Construction of Cyclohepta[*b*]indoles in the Total Synthesis of Indole Alkaloids

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Ne discere cessa.

Abstract

I In the first part, a brief overview about synthetic organic chemistry is given followed by a short debate why synthetic organic chemistry is still very important and why the profession of the synthetic chemist will not be supplanted by the field of synthetic biology.

II The second and main part of this work deals with the asymmetric construction of cyclohepta[*b*]indoles. Compounds exhibiting this structure motif display a broad spectrum of biological activities and are found in several natural products but have also attracted considerable interest from the pharmaceutical industry as potential therapeutics in recent years. The efficient preparation of highly functionalized and unsymmetrically substituted cyclohepta[*b*]indoles has become of central interest and, prior to this project, no enantioselective and comprehensive methodology to synthesize this structural motif was published in the literature.

This work presents several attempts to the synthesis of cyclohepta[*b*]indoles and the final strategy which utilizes the divinylcyclopropane-cycloheptadiene rearrangement in conjunction with the indole nucleus. Syntheses of numerous asymmetric indolylvinylcyclopropane derivatives and their transformation into cyclohepta[*b*]indoles are discussed, and the successful application of the developed methodology to the synthesis of (*S*)-SIRT1-inhibitor IV is presented.

With the methodology in hands, attention next turns to the synthesis of *Ervatamia* alkaloids. Several approaches to the total synthesis of 16-epimethuenine are discussed and their advantages and drawbacks are revealed. The final approach presents a robust, optimized, high-yielding and scalable asymmetric total synthesis of 16-epimethuenine.

III The transformation of 16-epimethuenine into several other natural products is presented thus underlining the optimized and asymmetric synthesis of diverse *Ervatamia* alkaloids. In addition, three compounds were evaluated in a bioassay in close collaboration with the Helmholtz Zentrum für Infektionsforschung in Braunschweig.

IV A minor part of this work deals with the approaches towards the synthesis of isoschizogamine. A general strategy is presented and syntheses of a precursor with a 3,6-dihydropyridin-2-one moiety for the synthesis of isoschizogamine are discussed. A final approach shows the synthesis of chiral γ-butenolides which are converted into the desired motif.

IV The last part covers a brief introduction into both marine dimeric bisindole alkaloids and bisindolylmaleimide alkaloids. General strategies for the synthesis of both cycloaplysinopsin A and dihydroarcyriacyanin A are discussed.

Keywords: total synthesis, divinylcyclopropane-cycloheptadiene rearrangement, *Ervatamia* alkaloids

Zusammenfassung

I Im ersten Teil wird ein kurzer allgemeiner Überblick über das Feld der synthetischen organischen Chemie gegeben, gefolgt von einer kurzen Erörterung, warum dieses Gebiet auch heutzutage noch einen hohen Stellwert besitzt und auch in naher Zukunft nicht vom Gebiet der synthetischen Biologie verdrängt werden wird.

II Der zweite und größte Teil dieser Arbeit beschäftigt sich mit der asymmetrischen Synthese von Cyclohepta[*b*]indolen. Zahlreiche Verbindungen mit diesem Motiv zeigen diverse biologische Aktivitäten und werden in zahlreichen Naturstoffen gefunden, doch auch von der pharmazeutischen Industrie wird dieses Motiv gerne benutzt. Eine effiziente und asymmetrische Synthese dieses Motivs ist von allgemein großer Bedeutung und war zu Beginn dieser Arbeit nicht literaturbekannt.

Diese Arbeit zeigt verschiedene Ansätze für die Synthese von Cyclohepta[*b*]indolen. Die finale Strategie beruht auf der Divinylcyclopropan-Umlagerung, welche den Indolkern inkludiert. Synthesen von zahlreichen asymmetrischen Indolylvinylcyclopropanderivaten und deren Transformationen in die zugehörigen Cyclohepta[*b*]indole werden diskutiert. Eine erste Anwendung der Methode wurde anhand der Syntheses des (*S*)-SIRT1 Inhibitors IV demonstriert.

Mit der Etablierung der Methode beginnt die Anwendung für die Synthese von *Ervatamia* Alkaloiden. Etliche Ansätze einer möglichen Synthese von 16-Epimethuenin werden auf ihre Vor- und Nachteile diskutiert. Der finale Weg zeigt eine robuste, optimierte und skalierbare Totalsynthese von 16-Epimethuenin mit durchweg hohen Ausbeuten.

III Die Transformation von 16-Epimethuenin in diverse andere Naturstoffe wird gezeigt. Dies unterstreicht die Effizienz und Durchführbarkeit der Methode in Hinblick auf die Synthese von *Ervatamia* Alkaloiden. Weiterhin wurden drei Verbindungen in biologischen Tests evaluiert; dies geschah in Kooperation mit dem Helmholtz Zentrum für Infektionsforschung in Braunschweig.

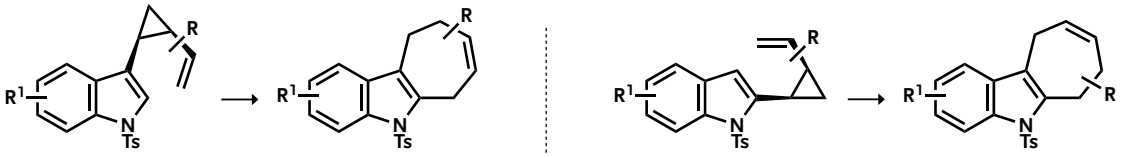
IV Ein kleiner Teil dieser Arbeit beschäftigt sich mit Ansätzen für die Synthese von Isoschizogamin. Eine allgemeine Strategie für die Synthese eines Vorläufers basierend auf 3,6-Dihydropyridin-2-on für die Synthese von Isoschizogamin wird aufgezeigt. Ein finaler Weg zeigt die Synthese chiraler γ-Butenolide, die in das gewünschte Motiv transformiert werden.

IV Der letzte Teil dieser Arbeit beschreibt sowohl eine kurze Einführung in marine dimere Bisindol-Alkaloide als auch Bisindolylmaleimid-Alkaloide. Allgemeine Strategien für die Synthesen von Cycloaplysinopsin A und Dihydroarcyriacyanin A werden diskutiert.

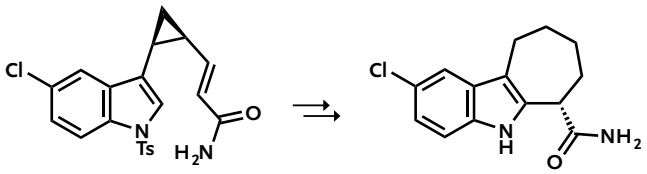
Stichworte: Totalsynthese, Divinylcyclopropan-Umlagerung, *Ervatamia* Alkaloide

Graphical Abstract

Methodology:

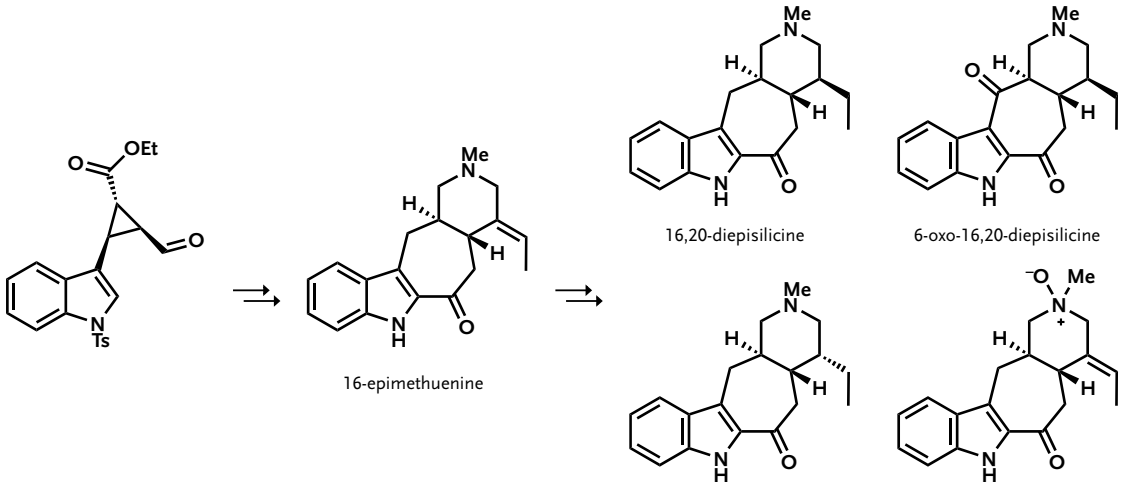


Synthesis of (*S*)-SIRT1 Inhibitor IV:



(*S*)-SIRT1 inhibitor IV

Total Syntheses of *Ervatamia* Alkaloids:



16-epimethuenine

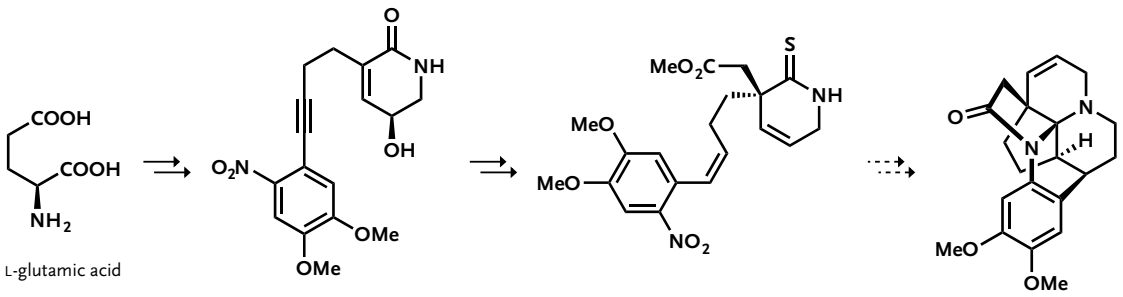
16,20-diepisilicine

6-oxo-16,20-diepisilicine

16-episilicine

16-epimethuenine-*N*-oxide

***En Route* to Isoschizogamine:**



L-glutamic acid

isoschizogamine

Scientific Contributions

Presentations

2016 **5. MINAS Symposium 2016**, Burg Warberg, Germany,
Talk: Total Syntheses of *Ervatamia* Alkaloids

2015 **Tetrahedron Symposium 2015**, Berlin, Germany,
Poster: Application of the Divinylcyclopropane Rearrangement to the Synthesis of Cyclohepta[*b*]indoles.

2013 **Winterfeldt Preis 2013**, Hannover, Germany,
Talk: The Divinylcyclopropane Rearrangement and its Application in the Total Synthesis of Indole Alkaloids.

2013 **Hochschule trifft Industrie 2013**, Basel, Switzerland,
Poster: A generalized approach and enantioselective gram-scale synthesis of (*S*)-SIRT1-inhibitor IV.

Publications

2017 E. Stempel, T. Gaich. Total Syntheses of *Ervatamia* Alkaloids. *(Manuscript in preparation.)*

2016 E. Stempel, T. Gaich, *Acc. Chem. Res.* **2016**, *49* (11), 2390–2402.
Cyclohepta[*b*]indoles: A Privileged Structure Motif in Natural Products and Drug Design.

2013 E. Stempel, P. Gritsch, T. Gaich, *Org. Lett.* **2013**, *15* (21), 5472–5475.
Enantioselective Synthesis of Cyclohepta[*b*]indoles: Gram-Scale Synthesis of (*S*)-SIRT1- Inhibitor IV.
Mentioned in *Synfacts*: "Synthesis of a SIRT1 Inhibitor", *Synfacts*, **2014**, *10*, 12.

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able to ignite everything (even dichloromethane) and to start a fire at any time in the lab, but everything went to normal after we equipped him with his own fire extinguisher. I thank Kostja for combining Russian military discipline with laboratory work and for completing the isoschizogamine team. I wish him all the best on finishing the synthesis of his natural product. We had a great time and I enjoyed you being my lab mates.

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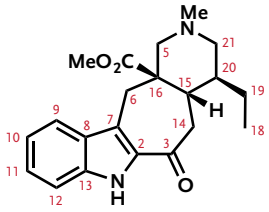
General Remarks

Within this dissertation numbering of the compounds relates to that reported for the ervitsine–ervatamine natural products (see below). In many cases for clarity, any atom mentioned in the text is numbered on the corresponding scheme, figure or table.

With regards to stereochemistry use of bold or dashed wedges indicates a single enantiomer, while bold or dashes lines indicates relative stereochemistry of a racemate. In case of plain drawn lines the configuration is unknown.



ervatamine

single enantiomer / absolute configuration

racemate / relative configuration

unknown configuration

Contents

Part I

Introduction

Constructing Nature's Molecules

1

The world is made of two parts, the full (pleres, stereon) and the empty, the vacuum (cenon, manon). The fullness is divided into small particles called atoms (atomon, that cannot be cut, indivisible). The atoms are infinite in number, eternal, absolutely simple; they are all alike in quality but differ in shape, order, and position. Every substance, every single object, is made up of those atoms, the possible combinations of which are infinite in an infinity of ways. The objects exist as long as the atoms constituting them remain together; they cease to exist when their atoms move away from one another. The endless changes of reality are due to the continual aggregation and disaggregation of atoms.

– Democritus, 5th century BC

Synthetic organic chemistry is the science of constructing complex molecules from more basic starting materials and reagents through formation and breaking of covalent bonds. It has developed to one of the most important branches of organic chemistry and can also be seen as powerful tool for other areas, that is biology, physics, materials science and medicine.

The field of organic synthesis can be divided into method oriented synthesis and target oriented synthesis(Chart 1-1).[1] The latter one is commonly referred to as total synthesis; a chemical synthesis of a target molecule—originally natural products—from relatively simple starting materials and reagents *via* a sequence of consecutive reactions in the most efficient way. The synthesis is based on a synthetic strategy which relies on the development of suitable synthetic methods and reagents. The field of method oriented synthesis is devoted to the development of new reagents, new catalysts, new bond forming strategies, new reaction and work-up procedures, in general to any innovation that can improve a synthetic procedure. The term *total synthesis* has evolved and target oriented synthesis also incorporates the field of designed molecules. Apart from natural bioactive compounds, target oriented synthesis covers also compounds

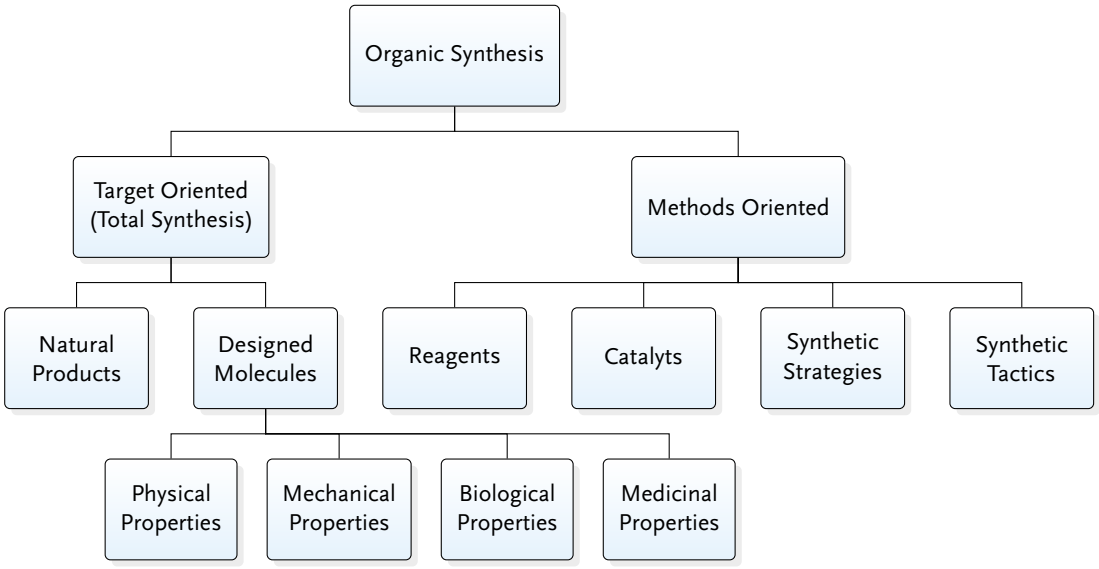


Chart 1-1. Organic synthesis in perspective.[1]

derived from rational design as potentially bioactive, compounds of commercial relevance, compounds with special physical or mechanical properties, or even compounds of theoretical interest. Examples for common and interesting targets are drugs, flavors, nutraceuticals, and new materials.

The field of organic synthesis can be traced back to ancient times, although it was not recognized as such. Most general chemistry and organic chemistry textbooks describe Friedrich Wöhler's synthesis of urea as the moment when modern organic chemistry was born.[2] It was 1828, when he obtained artificial urea (**1**) by treating silver cyanate with ammonium chloride.[3]

$$AgNCO + NH_4Cl \longrightarrow (NH_2)_2CO + AgCl \qquad (1\text{-}1)$$

This was a rather uncomplex synthesis but is seen as landmark. It was the first instance in which an inorganic substance was converted into an organic substance. This synthesis was followed by other milestones (Fig. 1-1). In 1845, Hermann Kolbe carried out the first organic compound synthesis, involving the formation of carbon-carbon and carbon-hydrogen bonds, using inorganic compounds. Pure carbon was transformed into carbon disulfide with iron sulphide which was transformed into carbon tetrachloride *via* chlorination, followed by pyrolysis to tetrachloroethylene and aqueous chlorination to trichloroacetic acid, and concluded with electrolytic reduction to acetic acid (**2**).[4] From today's perspective it was a rather complex synthesis for such a simple compound. It is noteworthy, that Kolbe used the word *synthesis* for the first time to describe the process of the construction of a compound from other substances.[5]

After syntheses of alizarin (**3**, 1869) by Carl Graebe and Carl Liebermann,[6] and indigo (**4**, 1878) by Adolf Baeyer[7] the probably most impressive total synthesis of the nineteenth century was that of (D)-glucose (**5**) by Emil Fischer in 1890.[8] It was the first molecule which

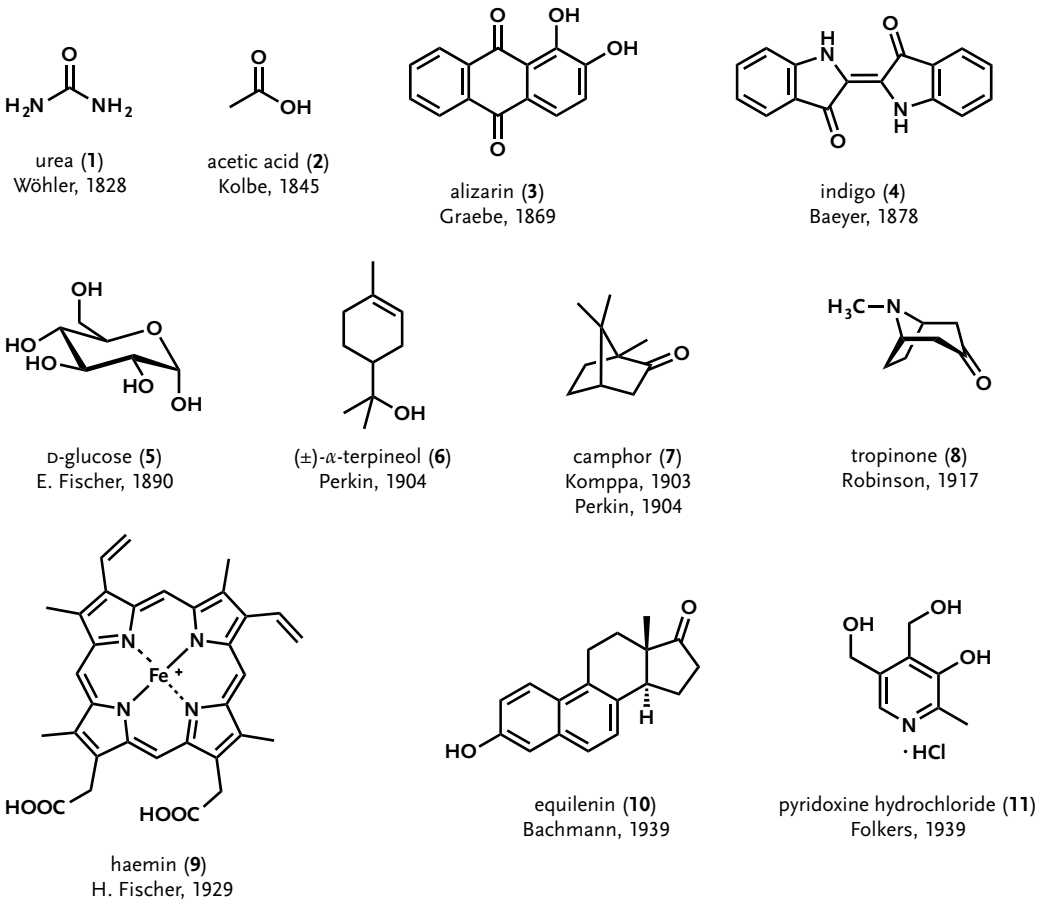


Figure 1-1. Selected milestones of early natural product total syntheses (1828–1939).[1]

contained stereochemical elements and the synthesis was remarkable for the complexity of the target. Emil Fischer was honored by the Nobel Prize for chemistry (1902) for "his work on sugar and purine syntheses". Other early landmark total syntheses of natural products were the synthesis of (±)-α-terpineol (**6**, W. H. Perkin, 1904),[9] camphor (**7**, G. Komppa, 1903; W. H. Perkin, 1904),[10] tropinone (**8**, R. Robinson, 1917),[11] haemin (**9**, H. Fischer, 1929),[12] equilenin (**10**, W. E. Bachmann, 1939),[13] and pyridoxine hydrochloride (**11**, K. Folkers, 1939).[14]

Although great achievements were gained, the field of total synthesis began flourishing after World War II and rapid development could be observed. It is due to two personalities who characterized the post World War II era that organic synthesis evolved so fast. It was in 1937 when R. B. Woodward became an assistant professor in the Department of Chemistry at Harvard University and the term total synthesis became a new meaning. One after another, several complex structures were synthesized and total synthesis progressed enormously. In 1956, Woodward said: *"Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."*[15] However, 25 years later, Woodward reported the first total synthesis of erythromycin A.[16] It was 1957, when young E. J. Corey took a sabbatical with the aid of a Guggenheim fellowship and went to Harvard University

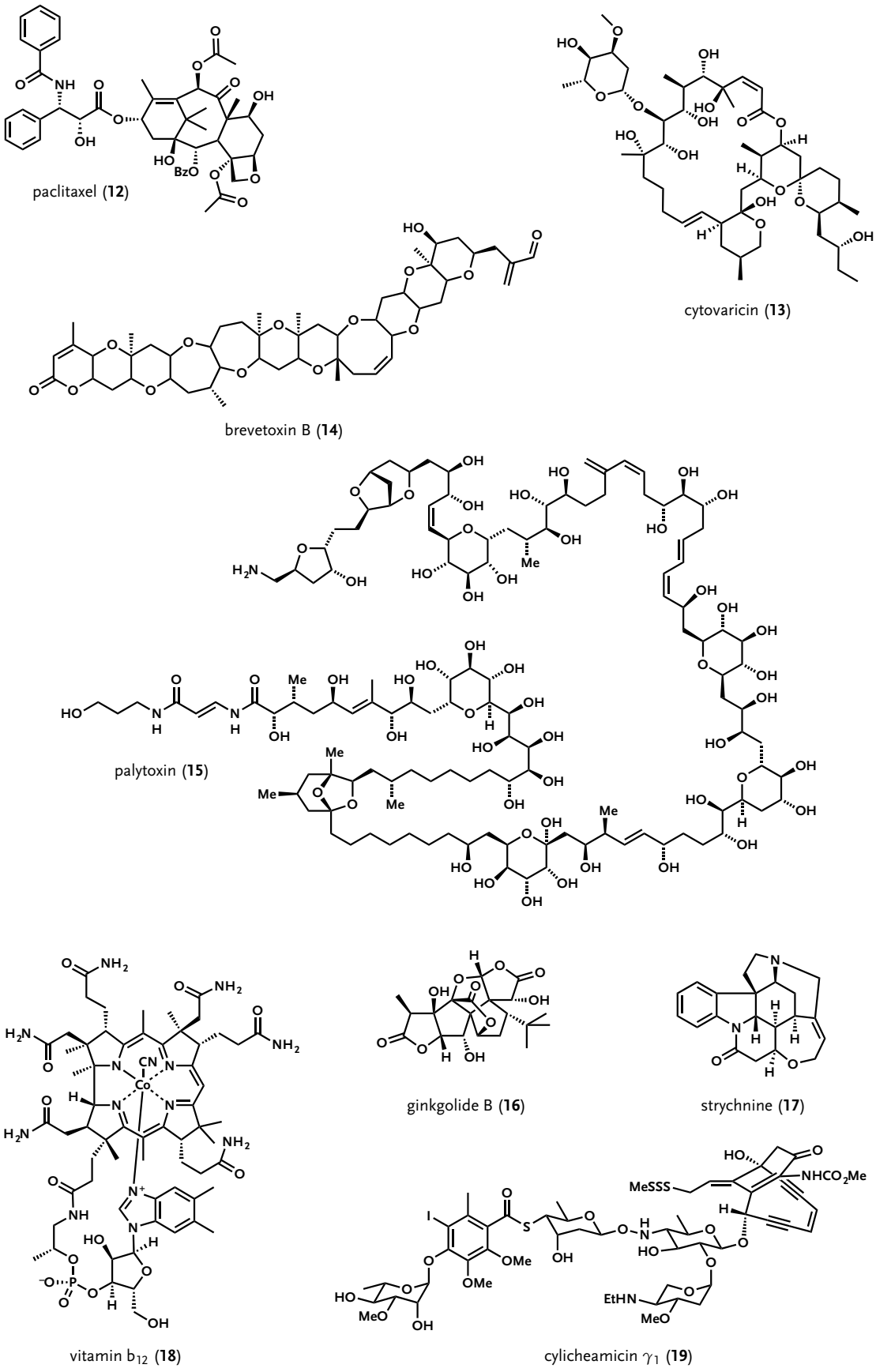
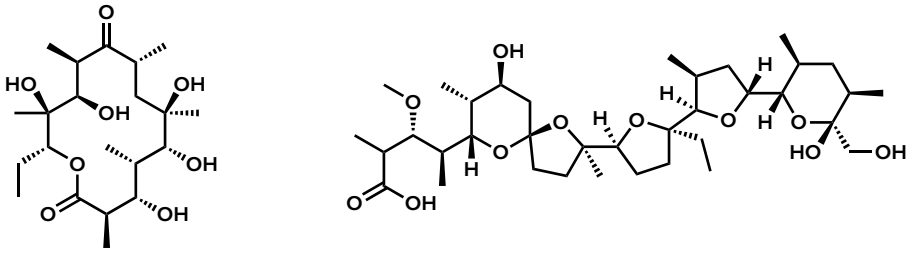


Figure 1-2. A couple of the most complex natural compounds which have been synthesized.

at the invitation of the world's best synthetic chemist at this time, R. B. Woodward.[17] Two years later, E. J. Corey himself became a full professor of chemistry at Harvard University. He introduced the concept of retrosynthetic analysis in 1961 with his synthesis of longifolene.[18] Combining his systematic approaches to total synthesis with the new tools of organic synthesis and analytical chemistry, E. J. Corey synthesized hundreds of natural and designed products.[5] R. B. Woodward won the Nobel Prize for chemistry in 1965 (*"for his outstanding achievements in the art of organic synthesis"*), E. J. Corey in 1990 (*"for his development of the theory and methodology of organic synthesis"*). Both personalities made organic synthesis to a powerful science and a fine art. A science and art which was carried on by numerous other chemists, and it was around 1980, when a new era began to rise and became apparent at the 6th International Symposium: "Synthesis in Organic Chemistry" (Cambridge, 1979).[19] R. B. Woodward was supposed to give a talk on his synthesis of erythronolide A (**20**, Fig. 1-3) but was struck down by a heart attack two weeks before and died prior to the arrival of medical help.[20] Over 50 co-workers contributed to the synthesis of **20**.[21] W. C. Still took his place and presented his synthesis of monensin (**21**, Fig. 1-3)—a compound, which exceeds erythronolide A in complexity but was completed by only two co-workers.[22] The audience became silent during this lecture. Everybody realized, that a new era has begun and from this point on, "only highly focused syntheses of complex natural products would make an impact on the organic chemistry community".[19]

Natural products provide the ultimate challenge to synthetic chemists and syntheses of numerous complex natural compounds have been accomplished (Fig. 1-2). The field of organic synthesis is nowadays advanced in such a way that it seems that the chemical synthesis of every natural product can be accomplished. The question is whether it can be made in a nice and practical way.



erythronolide A (**20**) monensin (**21**)

Figure 1-3. Structures of erythronolide A (**20**) and monensin (**21**).

The field of synthetic organic chemistry has evolved rapidly. For a long time, this powerful science has been used to construct compounds, most notably compounds from natural sources which are hard to obtain. But also the field of synthetic biology has evolved even faster than the field of organic chemistry and emerged as an alternative for the synthesis of organic molecules. In 2005, R. McDaniel and R. Weiss were even keen in such a way that they stated synthetic biology will replace chemical synthesis in the foreseeable future.[23]

This leads to the simple question: *"Why synthesize?"*.[1] There is no doubt, that synthetic biology enriches the syntheses of molecules and has the potential to shorten synthetic routes and reduce waste. However, there are more than enough reasons that synthetic chemistry will continue to dominate and that the demand for the profession of the synthetic chemist will not be supplanted by the field of synthetic biology.[24,25]

Total synthesis has long been seen as the epitome of the art. In the classical era, the reason to make complex molecules by total synthesis was often to confirm the molecular structure of a natural product. That motive have vanished thanks to powerful analytical techniques, especially X-ray crystallography and NMR spectroscopy. Another reason was because of the useful properties of quite a few natural products. Very often, it was cheaper to synthesize a natural product than to extract it from rare organisms. However, this purpose has changed nowadays. Today synthetic routes for advanced natural products are too complex to be used by the pharmaceutical industry. These compounds are basically the only ones which synthetic biology can compete with since evolution has optimized the biosynthesis of those products over time.[24] But total synthesis gives access to non-natural derivatives that also can have useful properties and helps in the discovery of new pharmaceutical relative compounds. Most of the relevant compounds for the pharmaceutical industry are based on non-natural molecular structures, ergo, enzymatic processes cannot be used for their synthesis; supposably, these compounds are even toxic to the organisms used in synthetic biology. The optimization of structures for superior properties is still carried out best by synthetic chemistry. Numerous chemical methods can do this in many different cases, and, in contrast to synthetic biology, these syntheses can often be developed and implemented in a competitive and short amount of time. But not only the pharmaceutical industry relies on synthetic chemistry. The global market demands molecules with particular physical properties which requires modern chemical branches like chemical biology or nanotechnology. However, these fields still depend on synthetic chemists since the required molecules contain motifs that are anything but natural. Once again, an enzymatic processes cannot necessarily be used for their whole synthesis. In summary, the demand for a complete total synthesis of a natural product is not given anymore. These compounds are basically the only ones which synthetic biology can compete. However, total syntheses of non-natural compounds or derivatives are still in demand; the field is as lively as ever and the supply of these molecules is best addressed by synthetic chemistry.

But there are far more reasons to decide to do synthetic chemistry and total synthesis of natural compounds. R. B. Woodward and E. J. Corey not only made synthetic chemistry to a powerful science, they also made an art out of it. To express it in Ball's words: *"Like architecture, chemistry deals in elegance in both design and execution."*[25] Natural products provide the ultimate challenge to synthetic chemists. Whereas non-natural compounds can be designed in a particular facile way to avoid synthetic difficulties, nature has no mercy on the synthetic chemist.[1] A good

[1] This paragraph relies on the essays of P. Ball (*Nature* **2015**, *528*, 327–329) and P. Baran (*Nature* **2012**, *492*, 188–189.), further reading is recommended. My opinion does not necessarily represent the general opinion of the synthetic community.

synthetic chemist values the challenge of synthesizing a naturally occurring substance and developing new synthetic chemistry which is required to solve the occurring synthetic problems. A great feeling arises, once a total synthesis of a natural product is conquered. However, this happens only rarely and most of the time, synthetic chemists have to cope with the inevitable disappointments. But after all, dealing with this disappointments and solving new problems day-to-day belongs to the process of the formation of a qualified synthetic chemist. Total synthesis of natural products is still ideal and will be for a long time to equip students with the practical skills that industry requires. The skill of synthesizing molecules remains the essential training for the next generation of chemists—combined with the sheer excitement of the endeavor.[1]

However, total synthesis of natural products also became a contest. It is not unusual, that natural products are synthesized, *"just because they are there"*.[25] Derek Lowe at Vertex Pharmaceuticals in Boston, Massachusetts, argues, that some groups pursue the goal of making gigantic natural products just for a publication in the end no one much cares about, often by utilizing chemistry everybody already knows, and by using a synthetic strategy which has been used several times before. Some people forgot about the art in total synthesis and often elegance is sacrificed for speed. In this day and age, statements like the one from S. Ley are very appreciated: *"I don't have to be first, the elegance of the approach is what interests me."*[26] As already mentioned before, the field of organic synthesis is nowadays advanced in such a way that the chemical synthesis of every natural product can be accomplished. The question is whether it can be made in a nice and practical way.

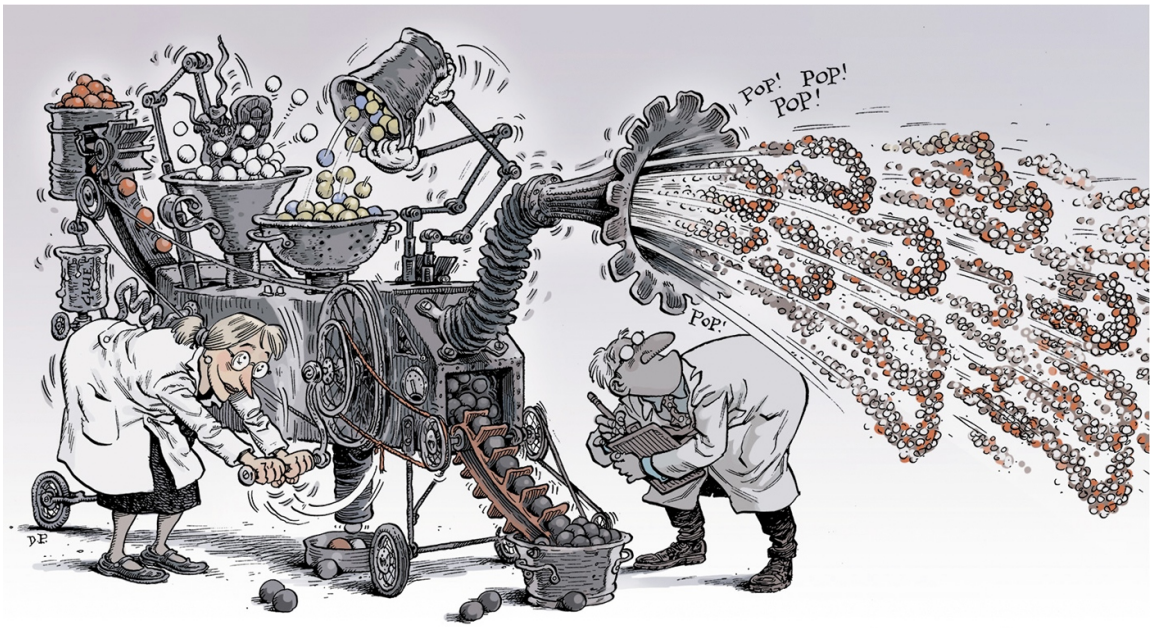


Figure 1-4. Modern synthetic chemistry? An illustration by David Parkins. (Reprinted by permission from Macmillan Publishers Ltd: *Nature* **2015**, *528*, 327–329, © 2016, license number: 4026100902360).

This discussion shall find some closing remarks from R. B. Woodward and E. J. Corey:

> "Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective."
>
> R. B. Woodward, *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1969**, *12*, 3.

> "I believe that chemical synthesis will make enormous contributions to human progress in the next century [...] However, those developments will not be fully realized without great and continuing advances in the central disciplines of chemistry. There is so much that remains to be discovered [...] that today's chemistry will seem archaic to a 22nd century chemist. I envy the young people in chemistry who will experience the excitement and pleasure of making the many discoveries of the next century of chemical research. Yet, at the same time, I worry about whether the younger generations of this country and the world will aspire to high creativity and persevere to achieve their impossible dreams."
>
> E. J. Corey, *J. Org. Chem.* **2004**, *69, 2917–2919.*

1.1 Natural Products and Pharmaceutical Industry

A lot of commercially available drugs against various diseases have been developed from isolated natural products. According to D. J. Newman and G. M. Cragg, one third of all small-molecule approved drugs from 1981–2014 are either pure natural products or natural product derivatives (Chart 1-2a).[29] Additional 5% are synthetic drugs which contain a pharmacophore from a natural product. One third of all all small-molecule approved drugs from 1981–2014 are absolute synthetic drugs. The remaining percentage are combinations of this classes which mimic a natural product. The whole database contains 1562 new approved drugs from 1981–2014, of which 1211 were small-molecule drugs.

"The simplest definition for a natural product is a small molecule that is produced by a biological source."[30] Natural products can be classified based on the chemical structure, on physiological activity, on taxonomy, or on biogenesis. In terms of synthetic chemistry, the classification occurs according to shared scaffolding elements. This leads to several structural classes, such as polyketides, peptides, terpenoids, and alkaloids. Natural products are derived from small monomeric building blocks of primary and secondary metabolic pathways. Organisms have evolved the ability to biosynthesize secondary metabolites although they are not essential for survival. This is argued to be due to the selectional advantages they obtain as a result of the functions of these compounds.[31]

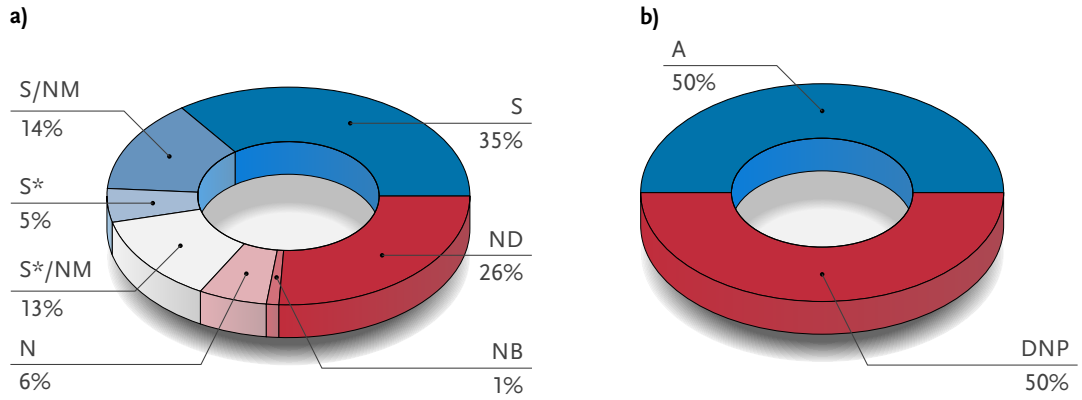


Chart 1-2. **a)** All small-molecule approved drugs 1981–2014, *n* = 1211. ■ S = absolute synthetic drug, ■ S/NM = absolute synthetic drug, but mimic of natural product, ■ S* = synthetic drug with a pharmacophore from a natural product, □ S*/NM = synthetic drug with a pharmacophore from a natural product, mimic of natural product, ■ N = unaltered natural product, ■ NB = botanical drug, ■ ND = natural product derivative. **b)** Source of pharmaceutical related or biological active natural products. ■ A = alkaloid, ■ DNP = other natural product class.

The term *alkaloid* originally derives from the concept of a compound being "alkali-like". These compounds contain at least one nitrogen atom and have a plant origin. As time went by, analytical techniques have developed enormously and structures became clearer thus requiring a more detailed definition of the the term *alkaloid*. The concept of being derived from amino acids together with the idea that the nitrogen should be in a heterocyclic ring were added. However, several alkaloids are known which do not fulfill this definition completely. Definitions for an *alkaloid* are proposed regularly, but none of these definitions is totally embracing.[32] Although the first alkaloid was isolated from man, (spermine phosphate in 1678 by van Leeuwenhoek), the best known sources of alkaloids are plants, fungi, bacteria, marine animals, and microorganisms. In 2001, G. A. Cordell and co-workers analyzed the NAPRALERT® database[2] and reported, that 50% of the natural products derived drugs were based on alkaloids (Chart 1-2b).[32] On the contrary, this analysis indicated only 26 900 known alkaloid structures out of about 150 000 characterized natural products, which is only 18% (Chart 1-3a). As a result of this, alkaloids play an important role in drugs and drug design. In addition, of the 21 120 alkaloids from higher plants, 2291 have been evaluated in a single bioassay (Chart 1-3b). 2361 have been evaluated in between two and ten bioassays. Only 167 alkaloids have been tested in more than 20 bioassays and one third of these alkaloids is pharmaceutically significant. More then three quarter of all alkaloids have never been subjected to any bioactivity study. As a result, only on very little amount of all alkaloids have contributed largely to the list of new chemical entities.

[2] NAPRALERT® is a relational database of natural products, including ethnomedical information, pharmacological/biochemical information on extracts of organisms in vitro, in situ, in vivo, in human (case reports, non-clinical trials) and clinical studies. Similar information is available for secondary metabolites from natural sources. At the date of Cordell's analysis, 150 000 scientific papers and reviews were included in NAPRALERT, representing organisms from all countries of the world, including marine and microorganisms.

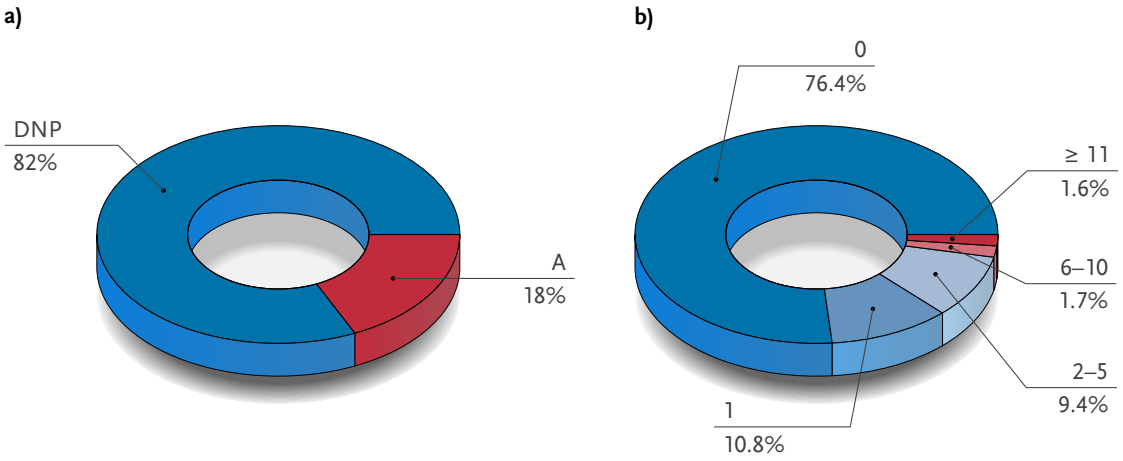


Chart 1-3. **a)** Classes of known natural products, n =150 000. ■ DNP = other natural product class, ■ A = alkaloid. **b)** The biological evaluation of alkaloids from higher plants (number of biological tests). ■ 0 biological tests, ■ 1 biological test, ■ 2–5 biological tests, ■ 6–10 biological tests, ■ ≥ 11 biological tests.

In summary, alkaloids have contributed in a significant way to the development of new drugs. By seeking for new bioactive molecules, alkaloids seem to be an ideal starting point. Of all known alkaloids, only a quarter has been evaluated at least once in a bioassay. Only a very small percentage of all known alkaloids have been seriously evaluated and one third of these alkaloids is pharmaceutically significant. Chances are very high to find new bioactive molecules by investigating unevaluated alkaloid natural products. The task for a synthetic chemist is therefore the ongoing investigation of total syntheses, but not only of alkaloids and their derivatives but all classes of natural products. This field equips chemists with the practical skills and the knowledge that industry requires.[3]

[3] Note: The analysis of G. A. Cordell dates back to 2001. In the meantime, the database contains over 200 000 entries. However, it is very likely, that the general conclusion of this paragraph has not changed.

Part II

Cyclohepta[*b*]indoles

The Cyclohepta[*b*]indole Motif

2

2.1 Introduction[1]

Seven-membered rings fused with an indole are termed cyclohepta[*b*]indoles. Compounds exhibiting this structure motif display a broad spectrum of biological activities, ranging from inhibition of adipocyte fatty-acid-binding protein (A-FABP), deacetylation of histones, inhibition of leukotriene production p53, anti-tuberculosis activities, and anti-HIV activities. These biological profiles are found in natural products containing the cyclohepta[*b*]indole motif, as well as in pharmaceuticals that contain this structure motif. Therefore, the biology of molecules derived from the skeleton of cyclohepta[*b*]indoles, as well as cyclopenta- and cyclohexa[*b*]indoles, has attracted considerable interest from the pharmaceutical industry as potential therapeutics in recent years. This is reflected by more than two dozen patents that have been issued in the last decade, solely based on the cyclohepta[*b*]indole structure motif. The efficient preparation of highly functionalized and unsymmetrically substituted cyclohepta[*b*]indoles has therefore become of central interest for synthetic organic chemists. Historically, this structure motif most often has been prepared by means of a Fischer indole synthesis. Although very robust and useful, this reaction poses certain limitations. Especially unsymmetrically functionalized cyclohepta[*b*]indoles are not suitable for a Fischer indole type synthesis, since product mixtures are inevitable. Therefore, novel methodologies to overcome these synthetic obstacles have been developed in recent years.

This chapter introduces all natural products and some pharmaceutical compounds exhibiting the cyclohepta[*b*]indole motif. The structural variability within cyclohepta[*b*]indole alkaloids in combination with the broad range of organisms where these alkaloids have been isolated

[1] Parts of this chapter have already been published as a review with the title "Cyclohepta[*b*]indoles: A Privileged Structure Motif in Natural Products and Drug Design" (E. Stempel, T. Gaich, *Acc. Chem. Res.* **2016**, *49*, 2390–2402. © 2016 American Chemical Society).[33] The content of the published review is not as thoroughly as this chapter: due to a word limitation some parts of this chapter are not part of the review or passages have been shortened.

from, strongly suggests that the cyclohepta[*b*]indole is somehow a "privileged" structure motif. The organisms producing these compounds range from evergreen trees (actinophyllic acid) to cyanobacteria (ambiguinines). The synthetic methodologies to construct these molecular scaffolds (natural and unnatural in origin) are in turn highlighted and discussed with regard to their potential to access highly functionalized and unsymmetrical cyclohepta[*b*]indoles, for which they specifically have been designed. The methods are classified with respect to reaction type and whether or not they are enantioselective. Finally, the syntheses of cyclohepta[*b*]indole natural products are presented, focusing on the construction of this structure motif in the course of the respective total synthesis.

2.2 Natural Products

2.2.1 Alkaloids

Several indole alkaloids exhibiting a cyclohepta[*b*]indole core are known (Fig. 2-1). Probably the best known natural product of this category is actinophyllic acid (**22**) which was isolated in 2005 by Carroll and co-workers[34] from the leaves of *Alstonia actinophylla* and possesses a complex unique skeleton which drew the attention of several synthetic groups. The alkaloid is an inhibitor of carboxypeptidase U/hippuricase.Three total syntheses have been accomplished to this day by Overman, Martin, and Kwon.[35–37]

Arcyriacyanin A (**23**) is a pigment from *Arcyria nutans*. It is a cytotoxic compound and inhibits protein kinase C and protein tyrosine kinase.[38,39] The green-blue bisindolylmaleimide is not only a cyclohepta[*b*]indole but also a cyclohepta[*cd*]indole and so far has been synthesized by two groups in the late 1990s.[40,41] The *cis*-dihydro modification dihydroarcyriacyanin A (**24**) has been found in the yellow sporangia of *Arcyria nutans*[42] and recently in the fruiting bodies of *Arcyria denudat*e and *Arcyria obvelata*.[43] The bisindole caulersin (**25**) has been isolated from the alga *Caulerpa serrulata* which naturally exists in the ocean around the Paracel Islands.[44] Compound **25** is an inhibitor of the multixenobiotic resistance (MXR) pump in algae and has been shown to act as plant growth regulator. Several syntheses have been published.[45–47] The most recent found natural products are exotines A (**26**) and B (**27**), two heterodimers of isopentenyl-substituted indoles and coumarin derivatives from *Murraya exotica*. Inhibitory effects on lipopoly-saccharide induced nitric oxide production in BV-2 microglial cells has been reported.[48] Aristolasol (**28**) and aristolasene (**29**) are two minor alkaloids from the aerial parts of *Aristotelia australasica* (Elaeocarpaceae).[49] These molecules have found very little attention up to now, no biological activities are known and one total synthesis of aristolasene (**29**) starting from 20-hydroxyhobartine has been published.[50]

A large group containing many alkaloids with a cyclohepta[*b*]indole skeleton can be found in the ambiguines which are structurally related to the hapalindoles.[51] To this date 17 different marine alkaloids have been found (ambiguines A–Q) of which 13 contain the cyclohepta[*b*]indole motif (ambiguines D–G and ambiguines I–Q, see Fig. 2-2). The earliest found marine alkaloids

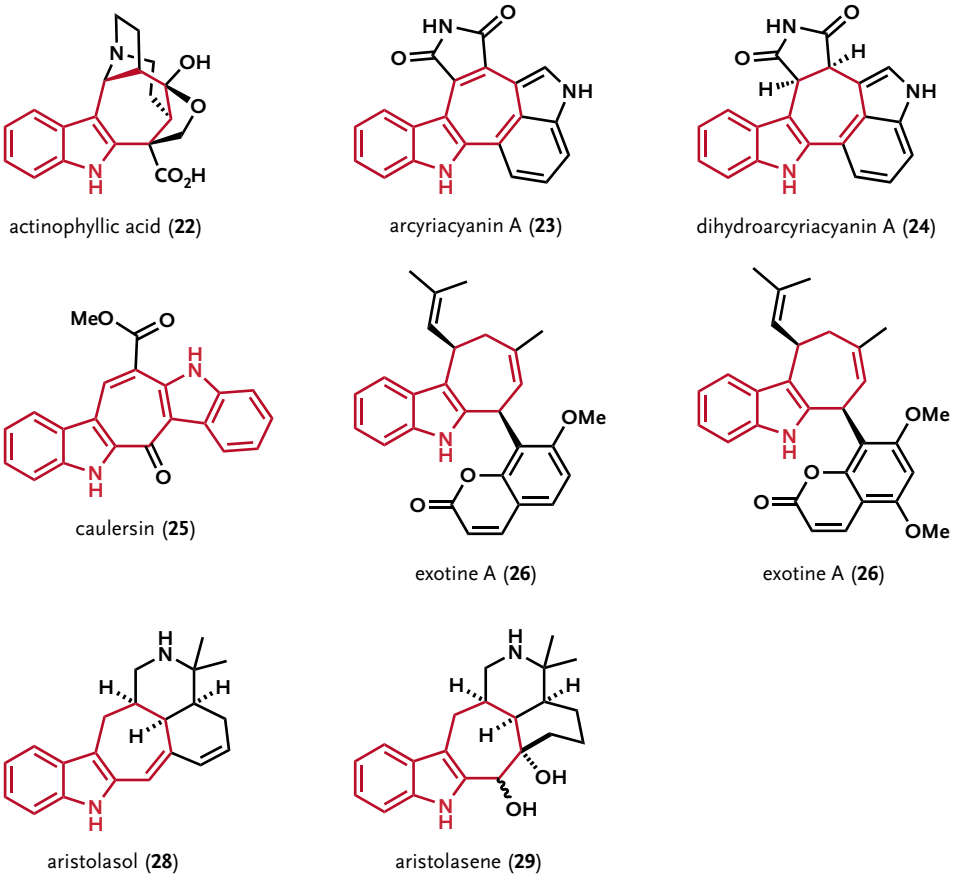


Figure 2-1. Natural products containing the cyclohepta[*b*]indole motif.

are ambiguine D isonitrile (**30**) from the terrestrial blue-green algae *Fischerella ambigua* and *Westiellopsis prolifica*, ambiguine E isonitrile (**31**) from terrestrial blue-green algae *Fischerella ambigua*, *Hapalosiphon hibernicus* and *Westiellopsis prolifica*, and ambiguine F isonitrile (**32**) from the terrestrial blue-green alga *Fischerella ambigua*.[52] All three alkaloids have antibiotic characteristics. The dechlorinated forms of ambiguines D and E (ambiguine J isonitrile (**35**) and ambiguine I isonitrile (**34**) have been extracted from cultured cyanobacterium *Fischerella* sp. but no biological activites are known.[53] Ambiguine G nitrile (**33**) has been isolated from the blue-green alga *Hapalosiphon delicatulus*.[54] No biological activities have been reported. In contrast to the other ambiguines, **33** possesses a nitrile instead of an isonitrile group. Ambiguines isonitriles K–O (**36–40**) were isolated from cultured cyanobacterium *Fischerella ambigua*. Ambiguine K isonitrile and ambiguine M isonitrile showed antibacterial activities against *M. tuberculosis*.[55] In 2010, two more alkaloids have been isolated from cultured cyanobacterium *Fischerella ambigua*.[56] Ambiguine P (**41**) is the first ambiguine which lacks an isonitrile or nitrile group and is also the only derivative bearing a hydroxyl group at C-15. Ambiguine Q nitrile (**42**) is the second congener with a nitrile instead of an isonitrile group. No noteworthy biological activities have been found. Although many derivatives of ambiguines with a cyclohepta[*b*]indole motif have been isolated, no total synthesis of ambiguines has been reported so far.

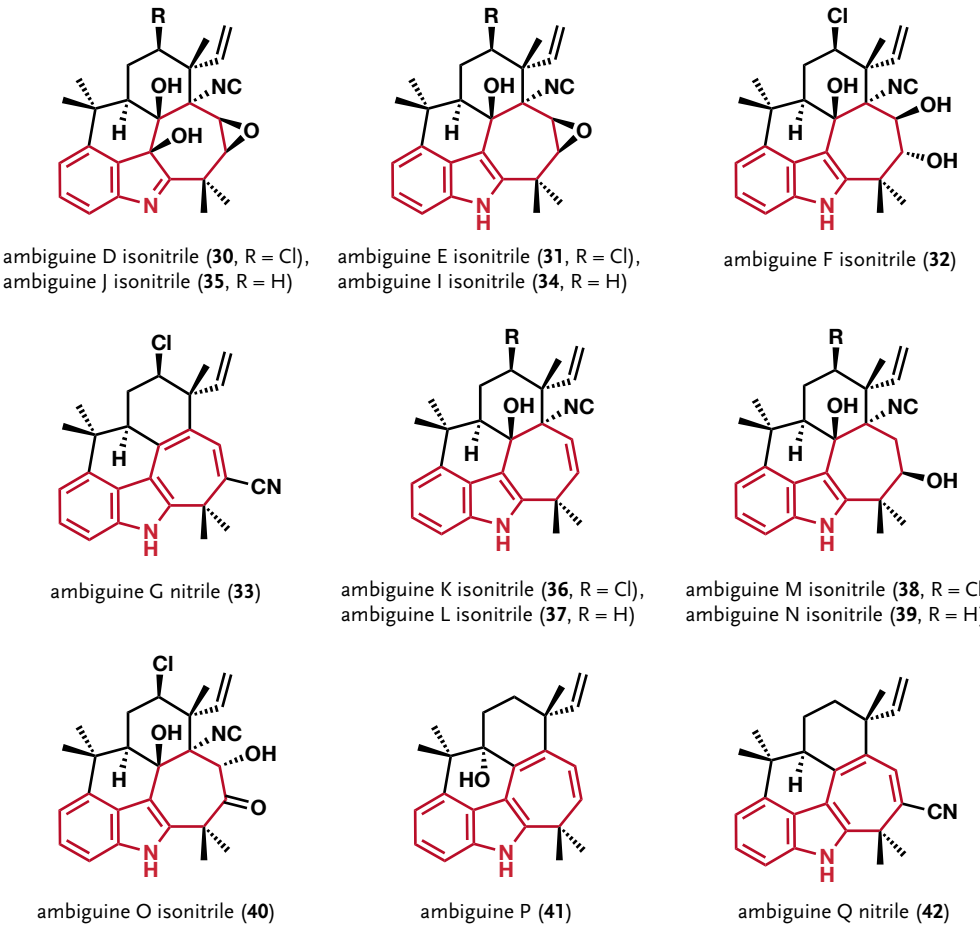


Figure 2-2. Ambiguines, a large group containing alkaloids with a cyclohepta[*b*]indole skeleton.

Another large group of alkaloids with a cyclohepta[*b*]indole skeleton are the ervitsine–ervatamine alkaloids (Fig. 2-3). Ervatamine (**43**) is the main alkaloid of the *Ervatamia* alkaloids which are corynanthean-type 2-acylindole alkaloids, but the side chain from the indole C-2 positions contains three linearly disposed carbon atoms and therefore lacks the characteristic tryptamine moiety.[57] Compound **43** was isolated from *Ervatamia orientalis* and *Ervatamia lifuana* (Apocynaceae),[58,59] and is a sodium channel blocker in nerve fibers and a local anesthetic blocker.[38] From the same sources 20-epiervatamine (**44**) and 19,20-didehydroervatamine (**52**) have been isolated.[58,59] 19,20-didehydro-N^1-methoxyervatamine (**53**) is an alkaloid from *Ervatamia malaccensis* (Apocynaceae),[60] 19,20-didehydro-5-oxoervatamine (**54**) has been isolated from leaves of *Tabernaemontana corymbosa* (Apocynaceae),[61] 19,20 didehydro-6α-hydroxyervatamine (**55**) and dehydroxyervataminol (**62**) are alkaloids from *Ervatamia divaricate*.[62] Decarboxylation of the ester at C-16 leads to the series of the methuenine–silicine alkaloids. Methuenine (**56**) is an alkaloid from *Ervatamia officinalis, Hazunta* spp., *Pterotaberna inconspicua*, and can also be isolated from the leaves and stem bark of *Ervatamia malaccensis*. It is an anticholinergic agent.[60,63–66] Also known is its 16-epimer (**57**),[60,65,67,68] its *N*-oxide (**58**),[65] its 16-epimer-*N*-oxide (**60**),[67] the 6-oxo derivative (**59**),[60,63,65] and the N^1-methoxy derivative (**61**).[60]

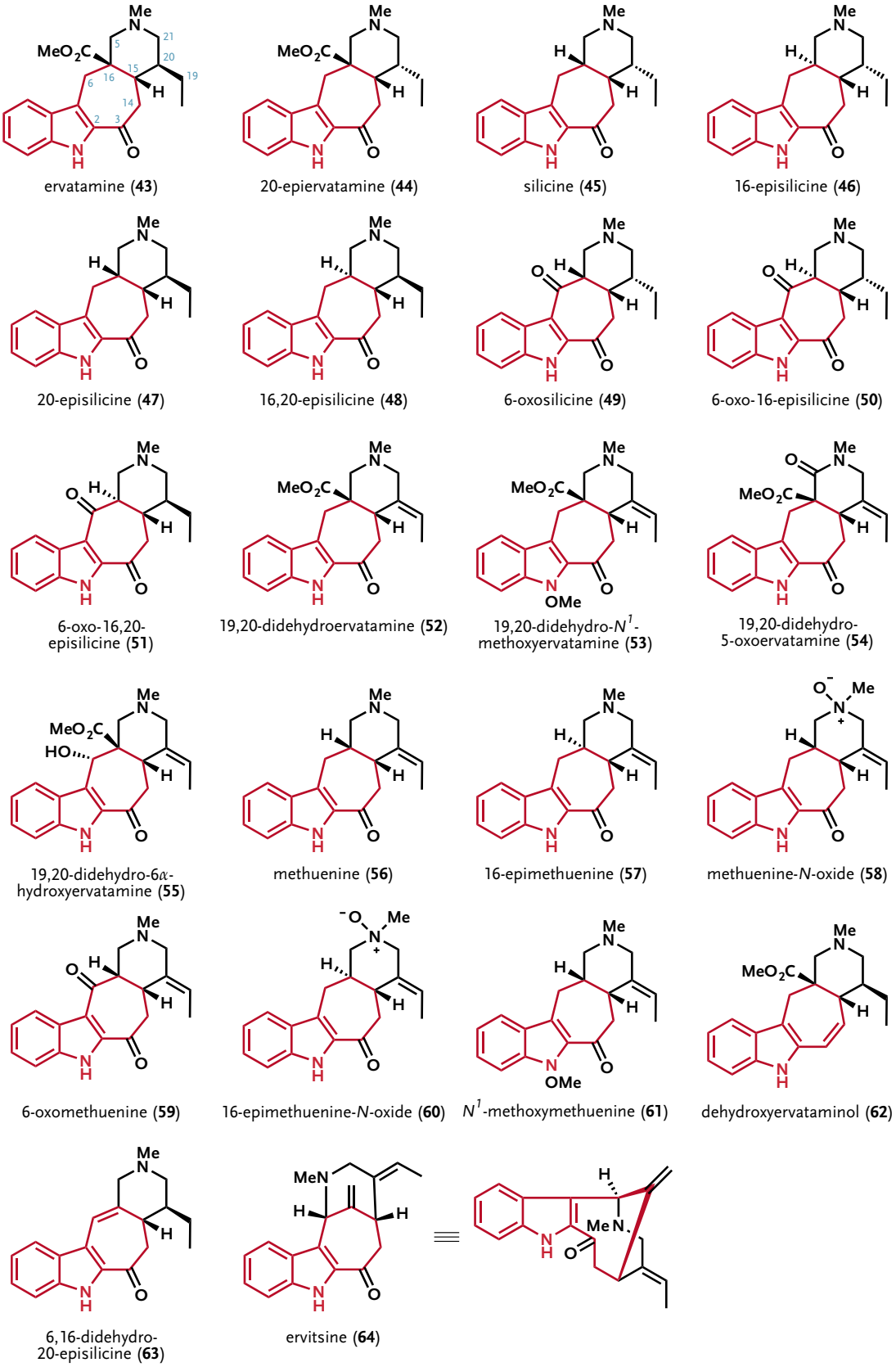


Figure 2-3. Ervitsine–ervatamine alkaloids.

Silicine (**45**) possesses an ethyl group at C-20 instead of an ethylidene function.[64,69–72] Seven further derivatives of **45** have been isolated: 16-episilicine (**46**),[73] 20-episilicine (**47**),[63,66] 16,20-episilicine (**48**),[66] 6-oxosilicine (**49**),[63,64,72] 6-oxo-16-episilicine (**50**),[64] 6-oxo-16,20-episilicine (**51**),[66] and 6,16-didehydro-20-episilicine (**63**).[66] Ervitsine (**64**) is a minor alkaloid from the root bark of *Pandaca boiteaui* (Apocynaceae).[74,75] It is the only member of this alkaloid family which has an additional link between C-5 and the C-7 and is therefore the only bridged alkaloid. Total syntheses of several members of the ervitsine–ervatamine alkaloids have been published.[76–78]

2.2.2 Non-natural Products with Biological Activities

Besides their widespread occurrence in natural products, cyclohepta[*b*]indoles exhibit a broad spectrum of biological activity and have attracted considerable interest from the pharmaceutical industry as potential therapeutics. Indole **65** is an active and selective compound (IC_{50} = 100 nM) for the inhibition of leukotriene B_4 (LTB_4) production which is implicated in numerous inflammatory and allergic diseases (Fig. 2-4).[79]

Compound **66** is a selective inhibitor of adipocyte fatty-acid binding protein (A-FABP, IC_{50} = 100 μM).[80] Consequences of the inhibition of A-FABP are a lower risk for hypertriglyceridemia, type 2 diabetes and coronary heart disease. The corresponding similar derivative based on a cyclohexa[*b*]indole core has shown lower activity.

Indole **68** shows large activity against Gram positive bacteria and good activity against Gram negative bacteria and high anti-tuberculosis activity with a minimum inhibitory concentration of 3.12 $\mu g \cdot ml^{-1}$. Similar compounds bearing a pyrazole or pyrimidine moiety instead of the isoxazole moiety have shown similar activities. In addition, it has been shown that the chlorine at the C-5 position of the indole is crucial for the activity.[81]

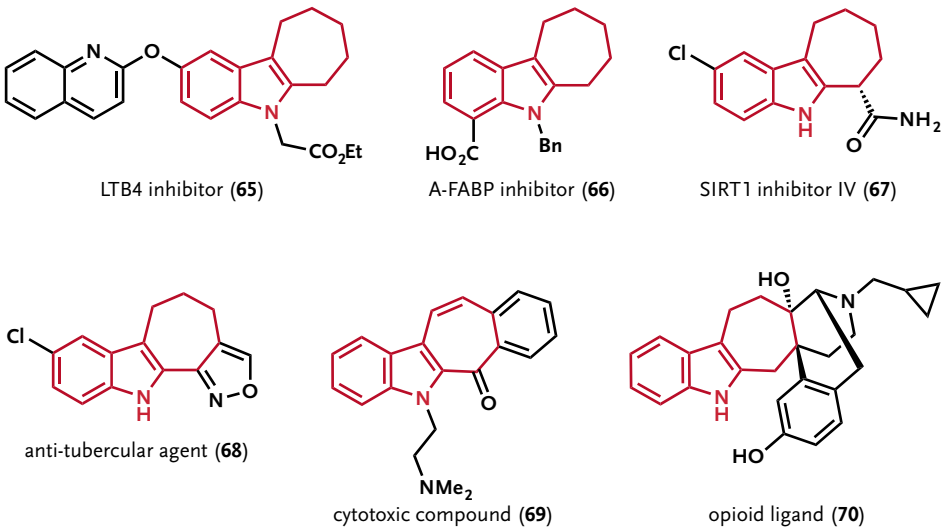


Figure 2-4. Non-natural products with a cyclohepta[*b*]indole.

The SIRT1-inhibitor IV (**67**) shows outstanding biological activity and is therefore heavily investigated. It belongs to a new class of histone deacetylase (HDAC) inhibitors and is involved in gene silencing via a new mode of action. Data shows that inhibition of SIRT1 enhances acetylation of p53. Compound **67** is one of the most potent compounds described (IC_{50} = 63 nM) representing a 500-fold improvement over previously reported inhibitors.[82] Enantioselective gram-scale synthesis of (*S*)-**67** has been reported.[83]

Furthermore, it has been shown that *N*-substituted 5,6-dihydrobenzo-[5,6]cyclohepta[*b*]indol-6-one derivatives like compound **69** are an interesting class of cytotoxic compounds and show activities against L1210 murine leukemia and HT29 cell lines.[84] Indole **70** is a novel opioid ligand with a *C*-homomorphinan skeleton and shows strong binding affinities for the δ receptor.[85]

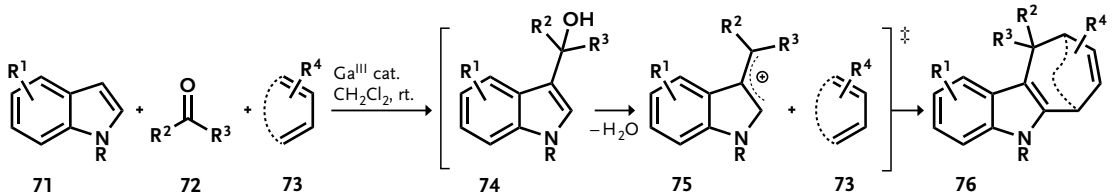
2.3 Methodologies for Construction of Cyclohepta[*b*]indoles

Cyclohepta[*b*]indoles are often prepared by means of the Fischer indoles synthesis. Although this reaction can be quite useful and satisfies the requirements of a modern indole synthesis, it possesses certain limitations.[86,87] Hence quite a few methodologies have been published for the construction of cyclohepta[*b*]indoles or derivatives respectively. In most cases pericyclic reactions have been used. Only publications with the aim of generation of this motif are covered. For more methodologies for general syntheses of carbocycle-fused indoles which are also suitable for the generation of cyclohepta[*b*]indoles further literature is recommended.[88–102]

2.3.1 *Via* Cycloaddition Reactions

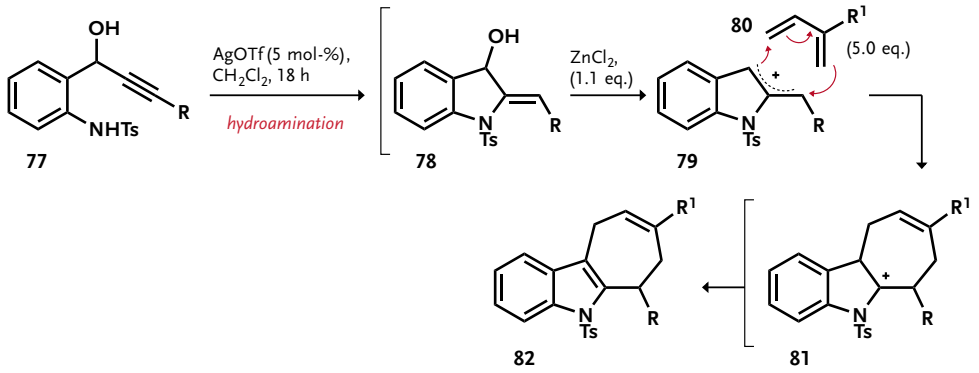
2.3.1.1 [4+3] Cycloaddition

One possibility for the formation of cyclohepta[*b*]indoles are [4+3] cycloaddition reactions, first published by J. Wu[87] and later in 2014 by Y. Li[103] and co-workers. In the work of J. Wu indole **71** reacts with an aldehyde or ketone to form indolyl alcohol **74** which generates corresponding indolyl cation **75** in the presence of a Lewis acid (Scheme 2-1). It was observed that especially gallium(III) bromide and gallium(III) triflate were effectively promoting this desired reaction. In addition, most gallium(III) salts—especially $Ga(OTf)_3$—are bench stable and therefore easy to handle. Once indolyl cation **75** is formed it reacts with diene **73** in a [4+3] cycloaddition



Scheme 2-1. Synthesis of cyclohepta[*b*]indoles *via* Ga(III) mediated [4+3] cycloaddition by J. Wu and co-workers (R = H, Me, Bn; R^1 = OMe, CO_2Me, halide; R^2 = H, alkyl; R^3 = alkyl, aryl; R^3 = alkyl, $(CH_2)_n$).[87]

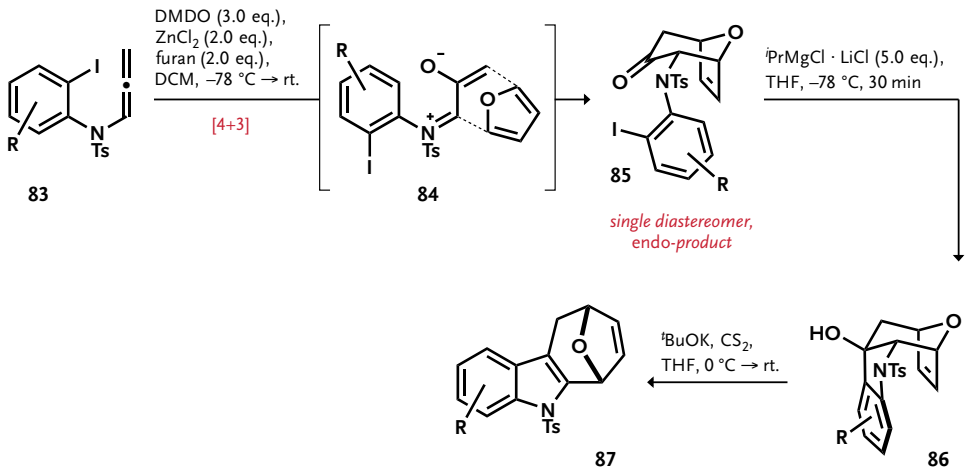
furnishing cyclohepta[*b*]indole **76**. It was the first time a [4+3] cycloaddition reaction has been described in which the 2π component is derived from indole. The scope of this gallium(III) mediated regio- and diastereoselective three-component [4+3] cycloaddition is quite broad and allows the access to several cyclohepta[*b*]indoles with different substitution patterns in one single step. Nevertheless, a major drawback is the formation of racemic products.



Scheme 2-2. Synthesis of cyclohepta[*b*]indoles *via* one pot hydroamination/[4+3] cycloaddition by Y. Li and co-workers (R = alkyl, aryl; R^1 = H, Me).[103]

Y. Li's strategy is also based on a [4+3] cycloaddition reaction but instead of using an indole, cyclohepta[*b*]indoles are furnished by means of Fischer base derivative **78** and various dienes (Scheme 2-2). For this purpose, **78** derives from silver(I) catalyzed intramolecular hydroamination reaction of *N*-tosyl protected hydroxypropynylaniline **77**. The 5-*exo-dig* ring closure was only effectively promoted by silver(I) triflate, neither $Pd(OAc)_2$ or AuCl were able to promote this cyclization. Next in line is the generation of cationic species **79** which was found to be promoted by $ZnCl_2$ in high yield. The *N*-tosyl protection seems to be crucial, using Boc or Bn protecting groups instead leads to complete recovery of starting material. By adding 5.0 equivalents of a diene, cationic species **79** undergoes [4+3] cycloaddition to furnish cyclohepta[*b*]indole **82**. In general, electron-rich dienes show better reactivity. Many substituents at the indole are tolerated, too. In conclusion, racemic cyclohepta[*b*]indoles are furnished *via* one pot tandem reaction containing hydroamination/[4+3].

R. P. Hsung and co-workers developed a different [4+3] cycloaddition strategy for the generation of aforesaid structure motif.[104] This approach starts with *N*-arylallenamides **88** which are subjected to Murray's reagent, zinc chloride and furan. This results in the formation of oxyallyl cation **84** which undergoes [4+3] cycloaddition with furan to afford cycloadduct **85** as a single diastereomer (Scheme 2-3). The yields for this transformation vary between 40% and 70%. With cycloadduct **85** in hand, indoline formation is accomplished *via* intramolecular Grignard reaction using $^{i}PrMgCl \cdot LiCl$ which yields in the generation of tertiary alcohol **86**. Transformation of the alcohol into the corresponding xanthate anion followed by elimination furnishes tetracyclic cyclohepta[*b*]indoles **87** in good yields. The required *syn*-relationship for the Chugaev elimination is given due to the diastereoselective attack of the Grignard reagent. In

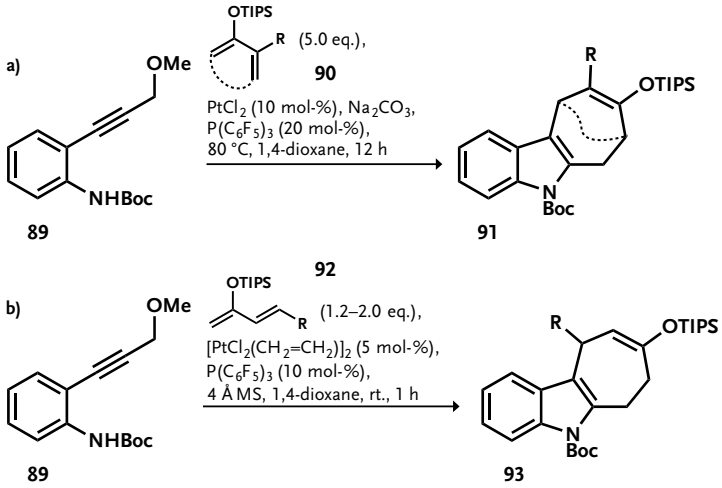


Scheme 2-3. Synthesis of cyclohepta[*b*]indoles *via* [4+3] cycloaddition–cyclization–elimination sequence by R. P. Hsung and co-workers (R = CO_2Me, halide).[104]

summary, this protocol allows rapid formation of racemic tetracyclic cyclohepta[*b*]indoles *via* a [4+3] cycloaddition reaction followed by intramolecular cyclization and Chugaev *syn*-elimination.

2.3.1.2 Formal [4+3] Cycloaddition

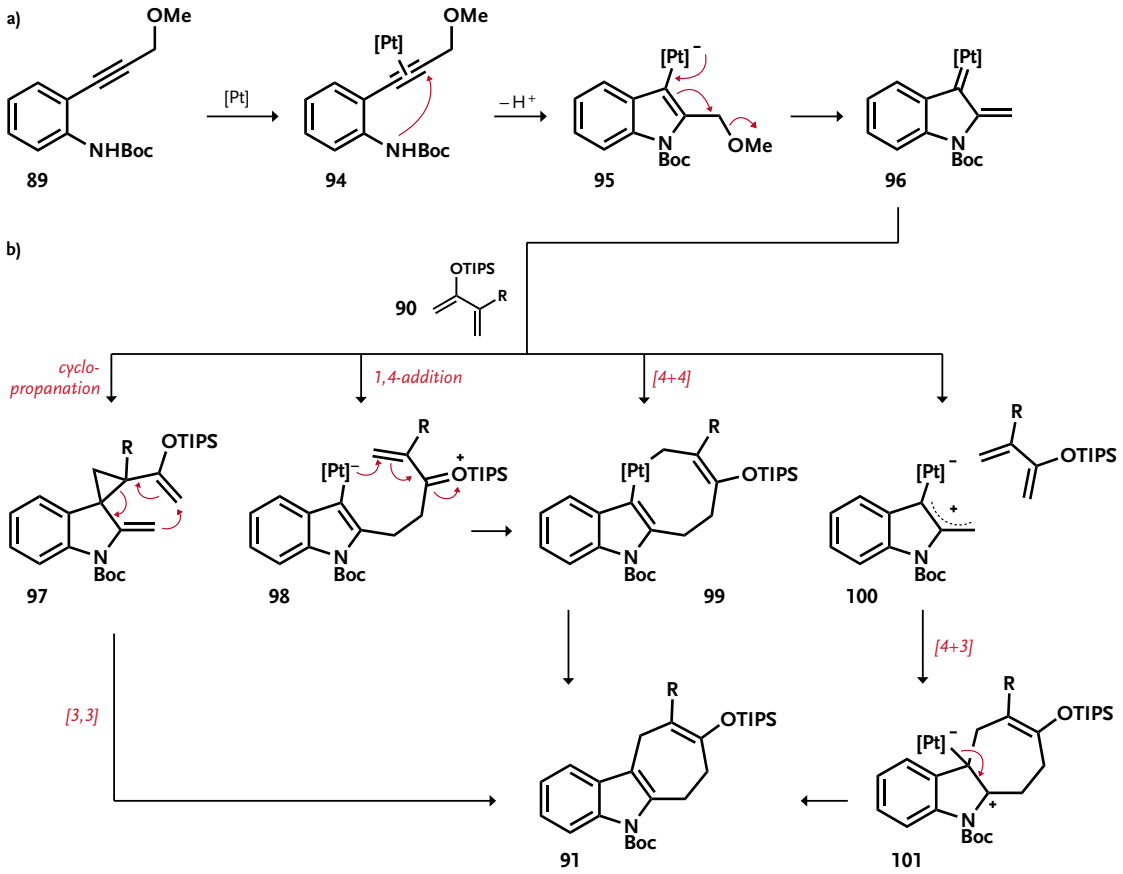
In 2013 the groups of W. Tang and N. Iwasawa published independently an almost identical protocol for the synthesis of cyclohepta[*b*]indoles using a metal-catalyzed intermolecular formal [4+3] cycloaddition reaction of vinyl Fischer carbenes with silyloxydienes.[105,106] Although the same type of reaction is described, different reaction mechanisms have been proposed. The protocol of W. Tang uses catalytic amounts of platinum(II) chloride whose reactivity is enhanced



Scheme 2-4. Syntheses of cyclohepta[*b*]indoles *via* a formal [4+3] cycloaddition reaction of vinyl Fischer carbenes and silyloxydienes. **a)** Protocol by W. Tang and co-workers (R = alkyl, aryl).[105] **b)** Protocol by N. Iwasawa and co-workers (R = alkyl, aryl).[106]

by the addition of electron-deficient tris(pentafluorophenyl)phosphine ligand in the presence of sodium carbonate in absolute 1,4-dioxane at 80 °C. Typical reaction times with 5.0 equivalents of silyloxydiene **90** are 12 hours (Scheme 2-4a). In some cases, the metal catalyst has been substituted with $[Rh(CO)_2Cl_2]$ in combination with $P[OCH(CF_3)_2]_3$ as ligand. The protocol of N. Iwasawa is quite similar, but differs in the amount of diene **92** (1.2–2.0 equivalents). Furthermore a slightly different platinum(II) catalyst is used ($[PtCl_2(C_2H_4)]_2$) and addition of 4 Å molecular sieves reduces the reaction time and temperature drastically compared to the methodology of W. Tang (1 h vs. 12 h, room temperature vs. 100 °C, see Scheme 2-4b).

Albeit it is a formal [4+3] cycloaddition reaction, different reaction mechanisms are proposed by the authors. Vinyl Fischer carbene **96** is formed in a metal catalyzed 5-*endo-dig* cyclization followed by elimination of methanol (Scheme 2-5a)[107] and several potential pathways for the cycloaddition with silyloxydiene **90** are proposed by the group of Tang. Cyclopropanation can afford Fischer base derivative **97** which undergoes divinylcyclopropane rearrangement to directly furnish cyclohepta[*b*]indole **91**, although there is no plausible justification for the divinylcyclopropane intermediate since different regioselectivity for the cyclopropanation had been reported before.[108,109] In addition, exclusive formation of *cis*-divinylcyclopropane **97** is

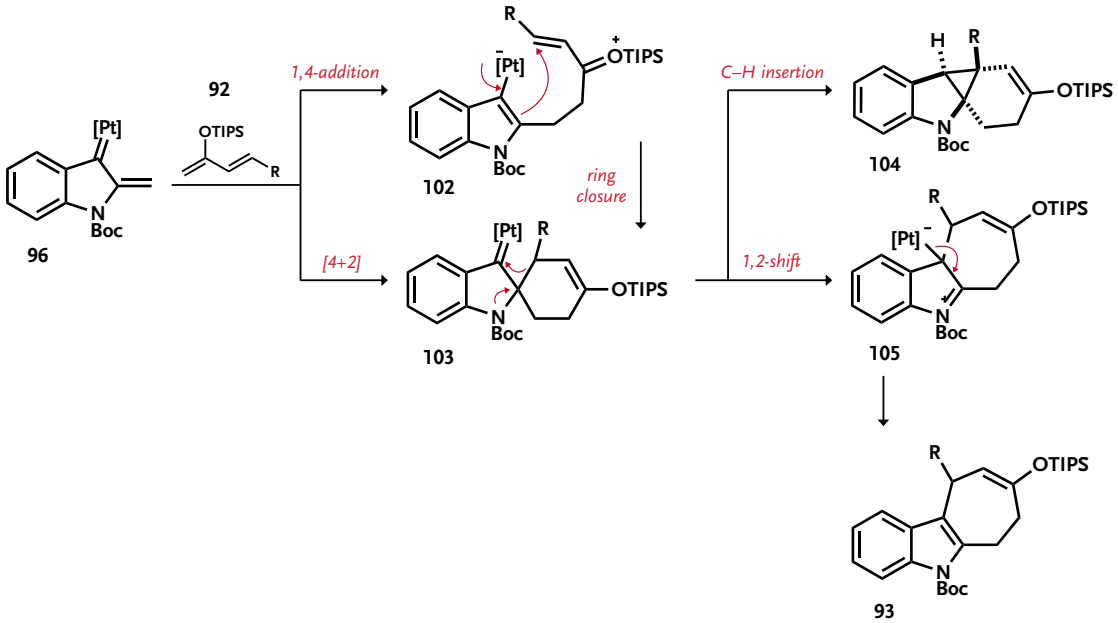


Scheme 2-5. **a)** Formation of vinyl Fischer carbene **96**. **b)** Proposed mechanisms for the formal [4+3] cycloaddition by W. Tang and co-workers.[105]

required for the sigmatropic rearrangement since *trans-cis*-isomerization usually occurs above 200 °C.[110] Furthermore the vinyl Fischer carbene can be attacked nucleophilicly by silyl enol ether **90** in a 1,4-manner followed by formation of metallacycle **99**. This metallacycle can also be furnished *via* concerted [4+4] cycloaddition reaction between **96** and silyl enol ether **90**. Reductive elimination gives cyclohepta[*b*]indole **91**. It can also be formed *via* concerted [4+3] cycloaddition reaction between **100** and silyloxydiene **90** and concomitant elimination of the metal (Scheme 2-5b).

Iwasawa *et al.* proposed a different mechanistic pathway due to the observation of the formation of a minor product (Scheme 2-6). Like the proposal of Tang it is assumed that vinyl Fischer carbene **96** is attacked nucleophilicly by silyl enol ether **92** in a 1,4-manner but ring closure occurs at the β-position of the metal to yield six-membered *spiro*-cyclic carbene intermediate **103**. Formation of **103** is also conceivable *via* [4+2] cycloaddition reaction between carbene **96** and silyloxydiene **92**. With electron donation from the nitrogen in mind 1,2-alkyl shift occurs at the carbene moiety forming *N*-acyliminium ion **105**. Regeneration of the metal catalyst furnishes cyclohepta[*b*]indole **93**. When using less electron-deficient phosphine ligands tetracyclic compound **104** has been observed as byproduct which is formed *via* insertion of the carbene intermediate **103** into the C–H bond. Further mechanistic studies have been carried out which support that the reaction proceeds through described mechanism.

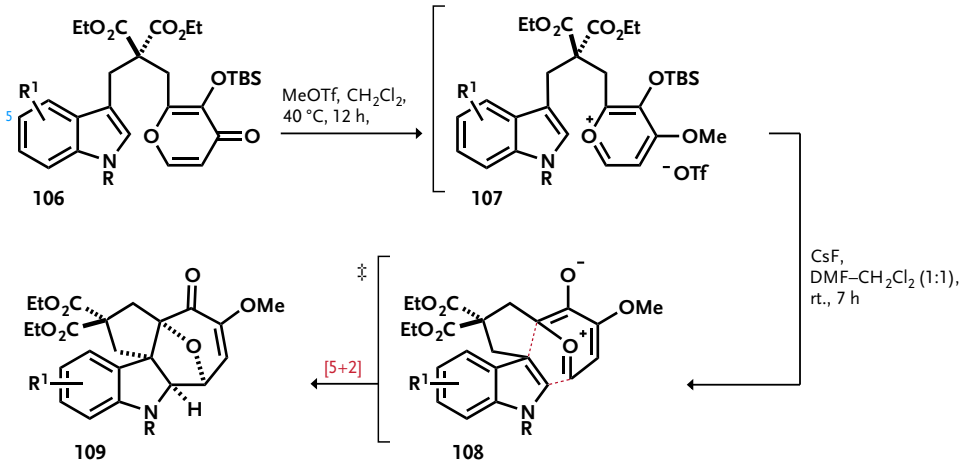
In conclusion, a unique method for an indole annulation/[4+3] cycloaddition sequence has been developed independently by the groups of Tang and Iwasawa. In both cases a highly regioselective formation of achiral cyclohepta[*b*]indoles *via* metal-catalyzed reaction of propargylic aniline derivatives and electron-rich dienes is described.



Scheme 2-6. Proposed mechanisms for the formal [4+3] cycloaddition by N. Iwasawa and co-workers.[106]

2.3.1.3 [5+2] Cycloaddition

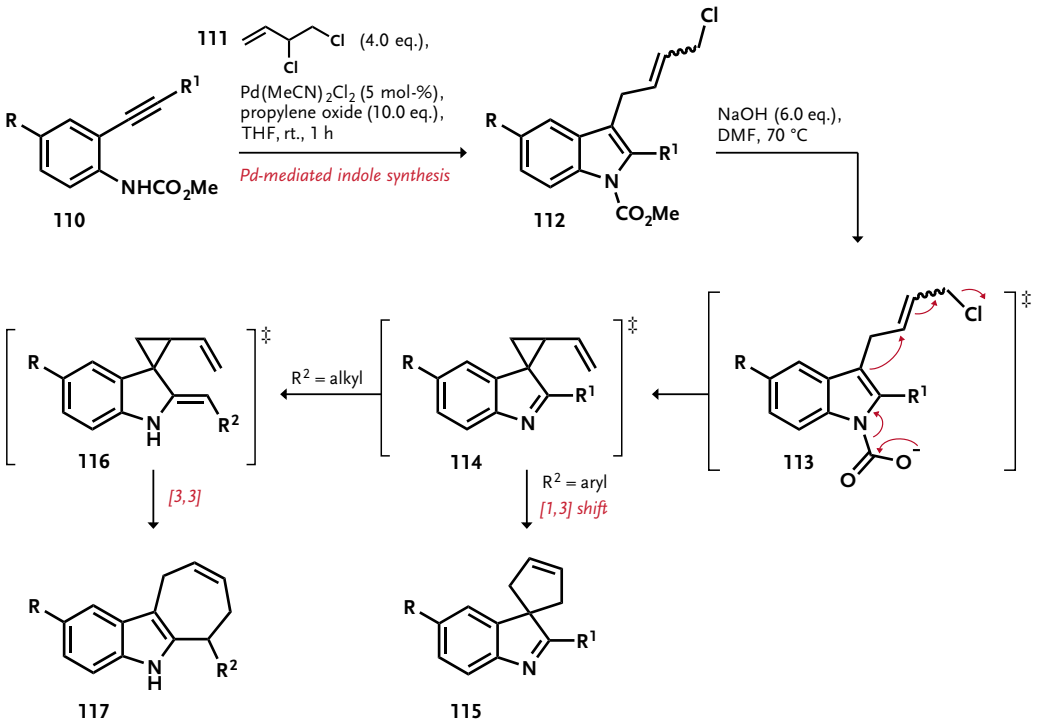
C. C. Li and co-workers elaborated a protocol for the construction of highly functionalized oxacyclohepta[*b*]indoles using a dearomative indole [5+2] cycloaddition reaction.[111] This work is inspired by the work of P. Wender's synthesis of seven-membered rings based on the generation and cycloaddition of 4-methoxy-3-oxidopyrylium intermediates.Wender:1991kx γ-Pyrone **106** is treated with a strong methylating reagent to form the methoxy pyrylium salt of kojic acid derivative **107** (Scheme 2-7). In accordance with P. Wender methyl triflate in dichloromethane is used in this case. When this salt in CH_2Cl_2/DMF is exposed to anhydrous caesium fluoride, generation of oxidopyrylium ylide **108** occurs and [5+2] cycloaddition proceeds smoothly at ambient temperature to give cycloadduct **109**. Exclusive production of the *endo* cycloaddition product is observed which has also been fortified by DFT calculations. The protocol allows the formation of a variety of indole systems with electron-withdrawing or electron-donating substituents at the indole-N^1 or the indole-C5 positions. Electronically mismatched oxidopyrylium ylides are also suitable. In summary, racemic oxacyclohepta[*b*]indoles are furnished *via* a novel dearomative intramolecular indole [5+2] cycloaddition using an oxidopyrylium ylide as 5π component and the indole C2–C3 bond as 2π unit with exclusive *endo* selectivity.



Scheme 2-7. Synthesis of cyclohepta[*b*]indoles *via* dearomative indole [5+2] cycloaddition reaction by C. C. Li and co-workers (R= H, Me, Ts, Bn, allyl; R^1 = H, OMe, halide).[111]

2.3.2 *Via* Sigmatropic Rearrangements

For more than 50 years the divinylcyclopropane rearrangement has been known for the generation of seven-membered rings and by the end of the 1970s the rearrangement has achieved synthetic utility and has been extensively applied to a number of syntheses of natural products.[110] Hence, it is not surprising that this variation of the Cope rearrangement has also been applied to syntheses of cyclohepta[*b*]indoles. The group of S. Sinha and co-workers developed a protocol using *in situ* generated Fischer base derivatives which undergo aforesaid rearrangement.[112] Alkynylaniline **110** is transformed into 2,3-disubsituted indole **112** with 4.0 equivalents

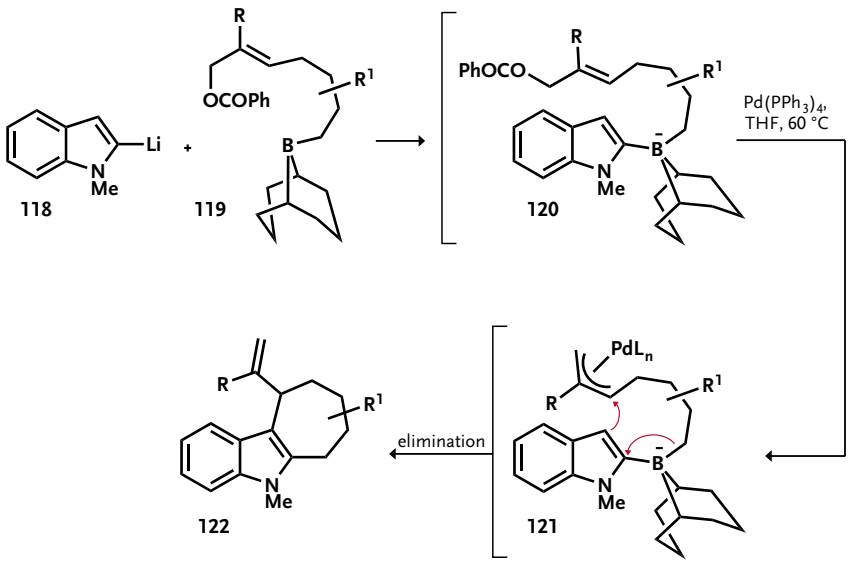


Scheme 2-8. Synthesis of cyclohepta[*b*]indoles *via in situ* generated divinylcyclopropyl Fischer base derivatives by S.Sinha and co-workers (R = H, halide, CF_3; R^1 = alkyl, aryl; R^2 = alkyl).[112]

of 3,4-dichloro-1-butene (**111**) in the presence of 5 mol % bis(acetonitrile)palladium(II) chloride and propylene oxide (Scheme 2-8). Treatment with sodium hydroxide leads to decarboxylation followed by intramolecular allylic alkylation in S_N2' manner to give **114**. Depending on the rest at the indole C-2 position different pathways are possible. If R^2 = aryl then vinylcyclopropane rearrangement takes place and spiroindole **115** is formed. In the case of R^2 = alkyl isomerization occurs forming divinylcyclopropane **116** which undergoes divinylcyclopropane rearrangement to furnish directly cyclohepta[*b*]indole **117**. This methodology allows simple formation of racemic cyclohepta[*b*]indoles bearing an alkyl rest at C-6 position.

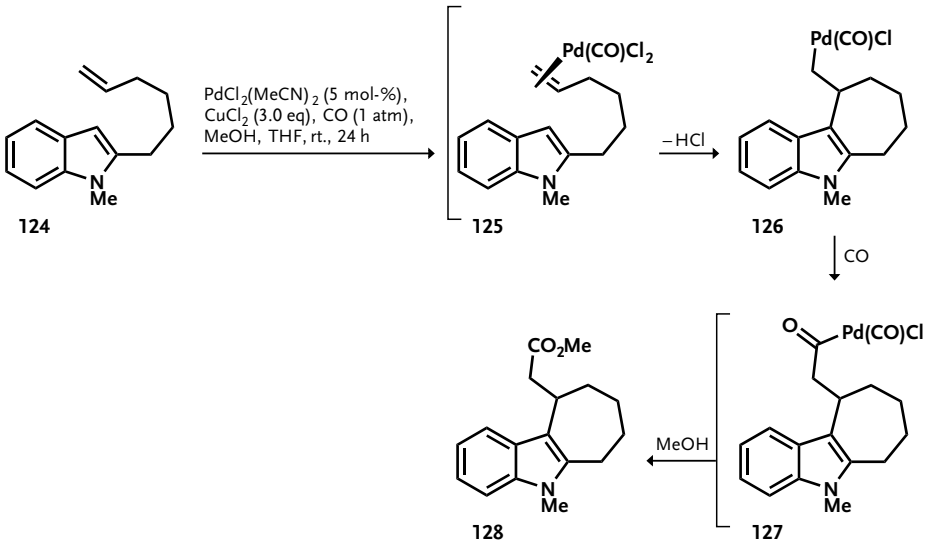
2.3.3 *Via* Palladium-Catalyzed Cyclization

Ishikura *et al.* developed a methodology for the synthesis of different cycloalka[*b*]indoles using several known concepts: the indole C-3 nucleophilicity, the 1,2-alkyl migration from boron to carbon, and the Tsuji-Trost allylic alkylation.[113] C-2 lithiated indole **118** is added to boron species **119** forming indolylborate **120** which is treated with a palladium(0) species. This leads to π-allyl cation **121** which is attacked by the indole core forming cycloalka[*b*]indoles **123** after reductive elimination and oxidative work-up whereupon rearomatization takes place (Scheme 2-9). In summary, this protocol describes the one-pot intramolecular cyclization for cycloalka[*b*]indoles *via* an intramolecular alkyl migration reaction using indolylborates.



Scheme 2-9. Pd-catalyzed intramolecular cyclization *via* alkyl migration process in indolylborates for the generation of cycloalka[*b*]indoles (R = H, Me; R^1 = H, alkyl).[113]

Widenhoefer and co workers published a protocol for a palladium(II)-catalyzed tandem cyclization/carboalkoxylation of alkenyl indoles.[114] Alkenyl indole **124** reacts with palladium(II) to furnish palladium-complexed olefin **125** which in turn undergoes carbopalladation (Scheme 2-10). This leads to the formation of halo acylpalladium species **127** which is transferred into methyl ester **128** with methanol. Regeneration of the catalyst is effected by copper(II) chloride. The use of palladium(II) catalysts is beneficial due to the reactivity of palladium(II) alkyl complexes towards carbon monoxide. Furthermore, B. Stoltz had already demonstrated the oxidative cy-

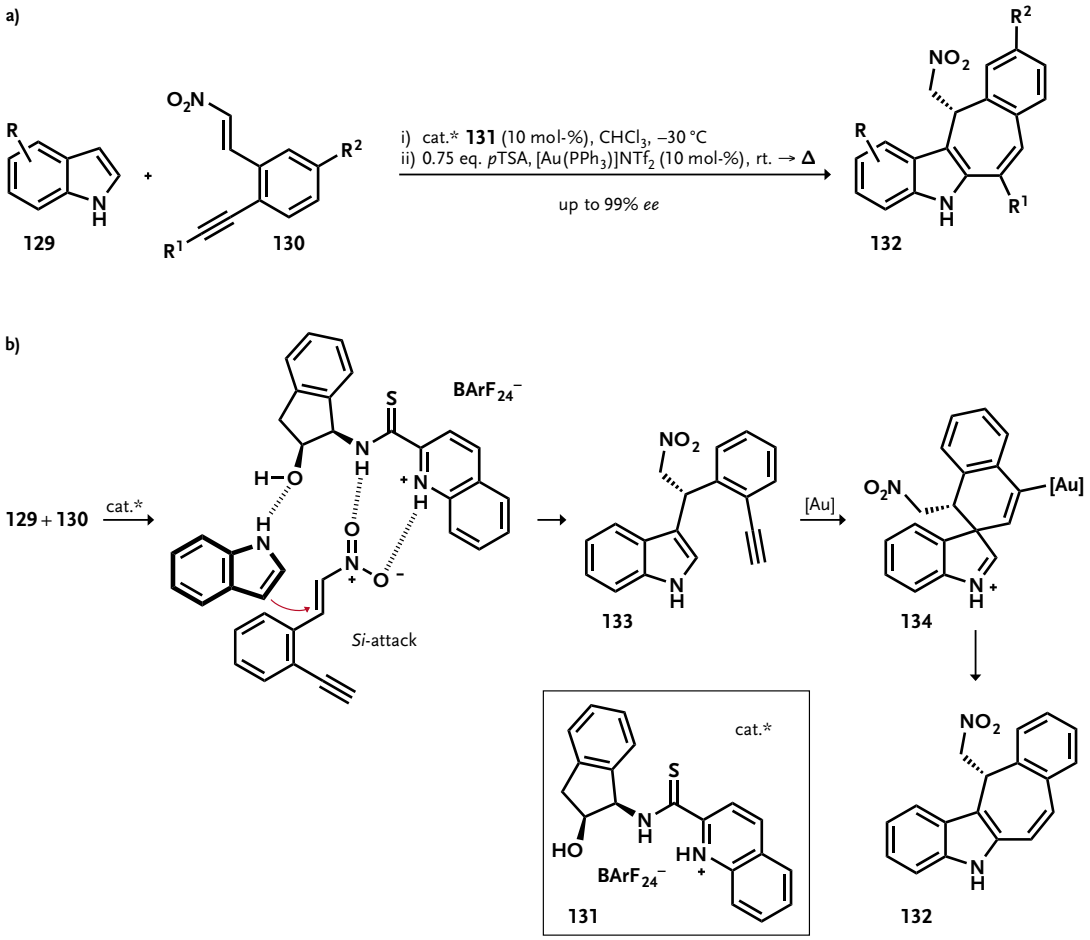


Scheme 2-10. Pd-catalyzed synthesis of cycloalka[*b*]indoles by Widenhoefer and co-workers..[114]

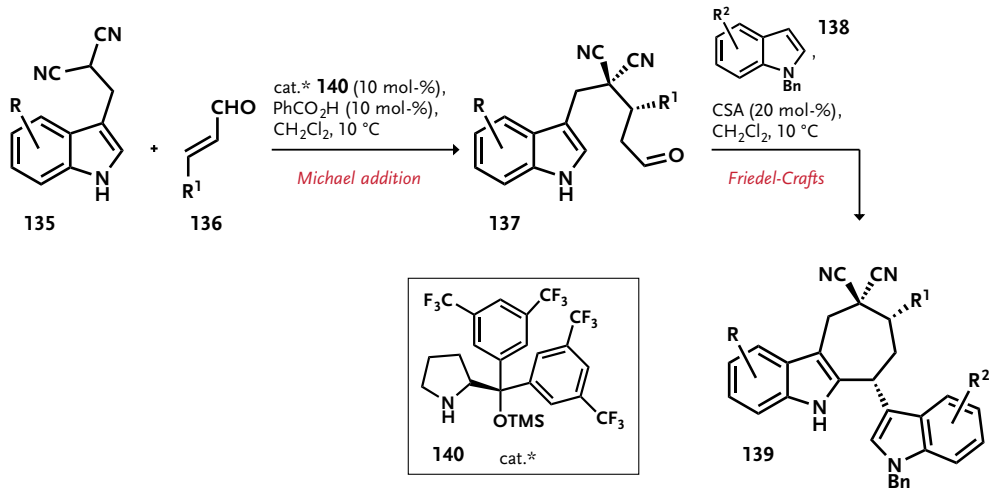
clization of alkenyl indoles catalyzed by palladium(II).[115] To sum up, this protocol allows an efficient palladium(II)-catalyzed formation of functionalized polycyclic indole derivatives.

2.3.4 Enantioselective Approaches

The methodologies presented so far furnish inherently racemic products or have not yet been developed in enantioselective manner. A combination of organo- and gold-based catalysis was the first enantioselective method published in 2011 by D. Enders and co-workers.[116] Indoles **129** react with ortho-alkyne substituted nitrostyrenes **130** in an organocatalytic Friedel-Crafts-type reaction catalyzed by thioamide-based organocatalyst **131** to form chiral C-3 substituted indoles which undergo concomitant gold-catalyzed cyclization yielding cyclohepta[*b*]indoles **132** (Scheme 2-11a). This protocol has two major drawbacks. In the first place only the formation of benzocyclohepta[*b*]indoles can be accomplished. Furthermore, it is limited to a nitromethyl group at C-12 of the cyclohepta[*b*]indoles albeit this group defines the stereochemistry. Nevertheless, this methodology provides rapid access to enantioenriched tetracyclic indole derivatives with



Scheme 2-11. **a)** Synthesis of cyclohepta[*b*]indoles *via* organo- and gold-based catalysis by D. Enders and co-workers. **b)** Mechanistic explanation for the stereochemical outcome (R= H, Me, OMe; R^1 = Ph, 3-tolyl; R^2 = H, F).[116]



Scheme 2-12. Organocatalytic synthesis of chiral cyclohepta[*b*]indoles by B.-C. Hong and co-workers (R = H, OMe, Br; R^1 = alkyl; R^2 = H, Me, OMe, CN, halide).[117]

an enantiomeric excess of up to 99%. The stereochemical outcome is explained in Scheme 2-11b. Bifunctional organocatalyst **131** forms hydrogen-bonding interactions with indole **129** and nitroolefin **130**. As a result, both reactions partners are preconfigured favoring *Si*-attack of indole **129** to give C-3 substituted indole **133**. Concomitant addition of π-acidic $[Au(PPh_3)]NTf_2$ activates the alkyne moiety favoring a second Friedel-Crafts-type 6-*endo-dig* cyclization to form spirocycle **134**. Indolenine–indole rearrangement furnishes cyclohepta[*b*]indole **132**.

B.-C. Hong *et al*. developed an analog protocol for the synthesis of cyclohepta[*b*]indoles.[117] Thus, α, β-unsaturated aldehyde **136** is activated by conversion into the corresponding Schiff base with L-proline derivative **140** and is attacked in a 1,4-manner by indolylalkyl malononitrile **135** from the *Re*-face (Scheme 2-12). The *Si*-face is shielded efficiently due to catalyst control which yields in an enantiomeric excess of ca. 90%. The resulting chiral aldehyde **137** subsequently reacts with Bn-protected indole **138** under Brønstedt-acidic conditions (20 mol % (+)-CSA) to give an iminium-activated cation which in turn is trapped by the unprotected indole in a Friedel-Crafts-type reaction. This results in the generation of cyclohepta[*b*]indoles **139** in moderate yields (ca. 60%) and diastereoselectivity (ca. 70:30 *syn*/*anti*). In summary, this one-pot strategy affords enantioenriched cyclohepta[*b*]indoles *via* tandem organocatalytic Michael addition/Friedel-Crafts alkylation reations. The reaction is indeed highly stereoselective; however, the diastereoselectivity is only moderate.

2.3.5 Brief Delineation of Other Methodologies

In the previous paragraphs, eleven methodologies for the synthesis of cyclohepta[*b*]indoles were discussed in detail. However, there are numerous more published methodologies which are going to be discussed very briefly. The reason for this parting is, that most of them are general syntheses of carbocycle-fused indoles which are also suitable for the generation of

cyclohepta[*b*]indoles, or are not as sophisticated as the aforementioned methodologies. At the very end, methodologies for the preparation of benzocyclohepta[*b*]indoles are delineated.[2]

In 1985, the group of Andrieux published an interesting approach for a hitherto unknown indole synthesis (Scheme 2-13).[118] Treatment of benzocyclobutenols (**141**) with hydrazoic acid in the presence of a Lewis acid leads to the corresponding benzocyclobutylazides (**142**). Acid-catalyzed rearrangement furnishes 2-substituted or cycloalka[*b*]indoles (**144**) in good yields. Although Andrieux described a very elegant indole synthesis, it has found practically no application. Only one publication from the group of U. Burger has made use of this approach.[119]

The group of Banwell published a Pd(0)-mediated Ullmann cross-coupling of *o*-halonitroarenes with α-haloenones. The cross-coupling products are converted into the corresponding cycloalka[*b*]indoles with hydrogen in the presence of palladium on charcoal (Scheme 2-14).[120]

The group of Arcadi published a double gold-catalyzed conjugate addition type reaction of indoles with α,β-enones (Scheme 2-15).[121] However, this gold-catalyzed reaction is not streoselective and furnishes a diastereomeric mixture of products. The group of Carbery published a very similar methodology but using an acid-mediated double Friedel-Crafts reaction to yield diastereomerically pure single products (Scheme 2-20).[122]

Willis *et al.* developed a new palladium-catalyzed route to *N*-functionalized indoles, in which the *N* fragments are introduced in a single-step cascade sequence onto an acyclic carbon framework (Scheme 2-16).[123]

Liu *et al.* published a methodology for the generation of 3,3-disubstituted indolenines starting from phenylhydrazine and a variety of α-branched aldehydes. Acid-mediated Wagner–Meerwein-type rearrangement yields 2,3-substituted indoles (Scheme 2-17).[124]

The group of Eilbracht published an interesting approach for the synthesis of α-branched aldehydes from olefins *via* Rh-catalyzed hydroformylation. The aldehydes are condensed with phenylhydrazine to give hydrazones in a one-pot procedure. Acid-promoted [3,3]-sigmatropic rearrangement yields 3,3-disubstituted indolenines, which in turn undergo a Wagner–Meerwein-type rearrangement to furnish 2,3-substituted indoles (Scheme 2-18).[125]

Barluenga *et al.* published a novel method for the construction of indole heterocycles using readily available starting materials, such as *o*-dihaloarenes and imines (Scheme 2-19).[126]

Kunick and König published syntheses of cycloalka[*b*]indoles *via* a modified Fischer indole synthesis (Schemes 2-21 and 2-23).[127,128]

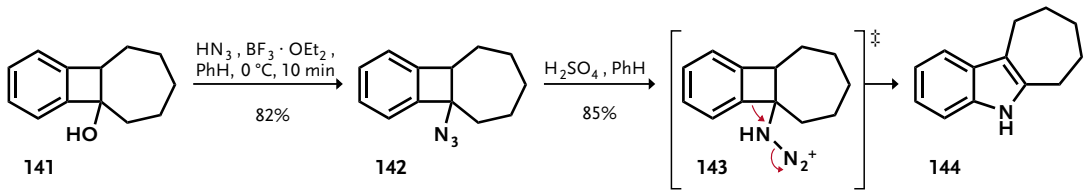
Driver and co-workers published a methodology which shows that rhodium carboxylate complexes, such as $[Rh_2(O_2CC_7H_{15})_4]$, can catalyze cascade reactions of β,β-disubstituted styryl azides to selectively produce 2,3-disubstituted indoles (Scheme 2-22). The formation of both cycloalka[*b*]indoles and benzo[*m*,*n*]cycloalka[*b*]indoles is described.[129] Two years later the same group demonstrated that iron(II) bromide promotes the tandem transformation of *ortho*-substituted aryl azides by C–H bond amination 1,2-migration reactions which furnishes both 2,3-disubstituted and cycloalka[*b*]indoles (Scheme 2-26).[130]

[2] In most cases, the schemes are labeled with the title of the particular publication in this subsection.

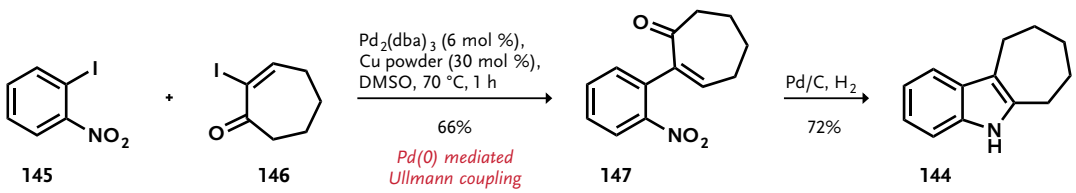
Novak *et al.* described an aza-Claisen rearrangement of (cycloalkylmethyl)benzeneamines (**166**, Scheme 2-24).[131] Aza–Claisen rearrangements usually require more harsh conditions than those required for the classic Claisen rearrangement of oxygenated substrates; this rearrangement usually occurs at 200–350 °C.[132] The process describes a Lewis acid catalyzed aza-Claisen rearrangement followed by an intramolecular aza–Alder–ene reaction to obtain cyclohepta[*b*]indoles (**168**).

The group of Messerle prepared a series of new pyrazolyl-1,2,3-triazolyl N–N' bidentate donor ligands. This ligands and their rhodium or iridium complexes were then applied to the synthesis of tricyclic indoles *via* tandem C–N and C–C bond formation reactions from hydroxyalkynylanilines (Scheme 2-25).[133]

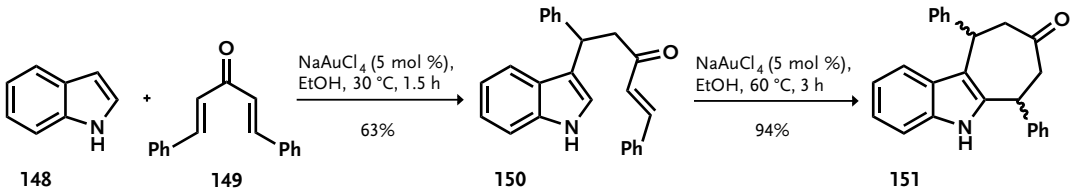
Cho *et al.* described a methodology for the preparation of ene-hydrazides (**174**) from enol triflates. This compounds undergo $ZnCl_2$-mediated Fischer indolization reaction to yield various cycloalka[*b*]indoles (Scheme 2-27).[134]



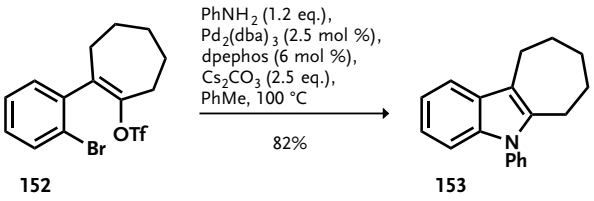
Scheme 2-13. Acid-catalyzed transformation of tertiary benzocyclobutylazides into cycloalka[*b*]indoles (Andrieux, 1985).[118]



Scheme 2-14. Synthesis of cycloalka[*b*]indoles *via* Pd(0)-mediated Ullmann cross-coupling of *o*-halonitroarenes with α-haloenones (Banwell, 2003).[120]



Scheme 2-15. Gold-catalyzed conjugate addition type reaction of indoles with α,β-enones (Arcadi, 2004).[121]



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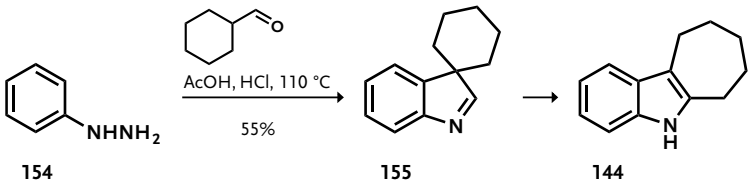
Scheme 2-16. Palladium-catalyzed tandem alkenyl and aryl C-N bond formation (Willis, 2005).[123]



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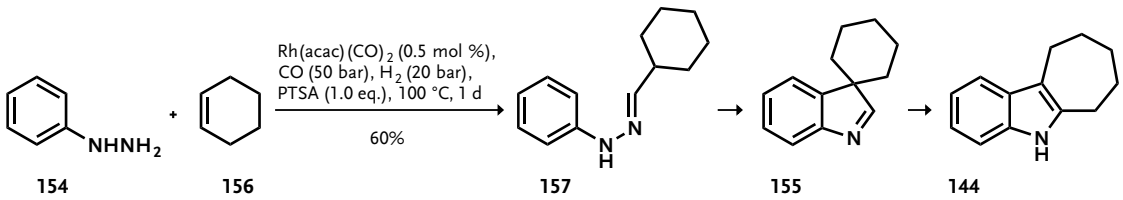
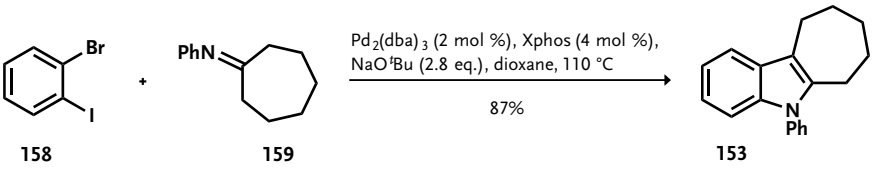
Scheme 2-17. Rearrangement of 3,3-disubstituted indolenines and synthesis of 2,3-substituted indoles (Liu, 2006).[124]



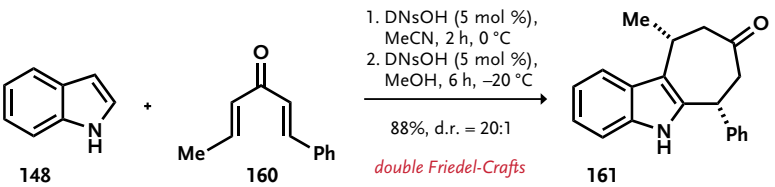
154 156 157 155 144

Scheme 2-18. Cyclohepta[*b*]indoles from olefins and hydrazines *via* tandem hydroformylation–Fischer indole synthesis and skeletal rearrangement (Eilbracht, 2006).[125]



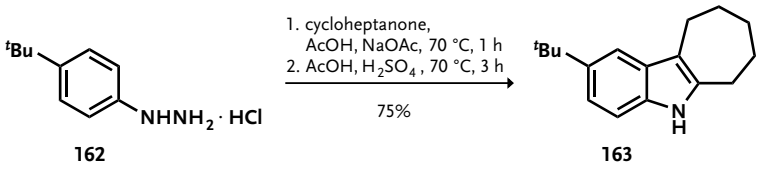
158 159 153

Scheme 2-19. The azaallylic anion as a synthon for Pd-catalyzed synthesis of heterocycles (Barluenga, 2007).[126]



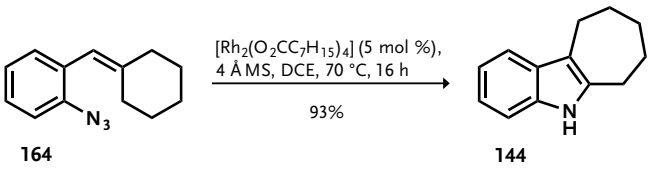
148 160 161

Scheme 2-20. Stereoselective double Friedel–Crafts alkylation of indoles with divinyl ketones (Carbery, 2009).[122]



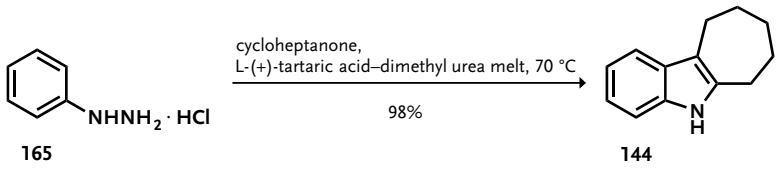
162 163

Scheme 2-21. Synthesis of 2-*tert*-butyl-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (Kunick, 2011).[127]



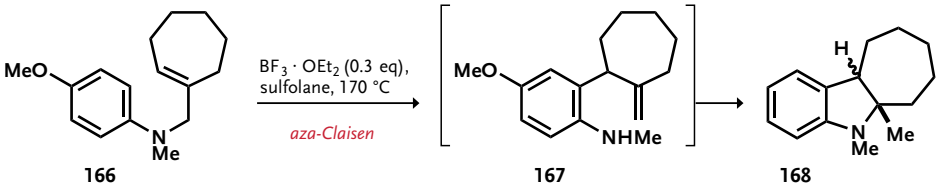
164 144

Scheme 2-22. Rhodium-catalyzed synthesis of cyclohepta[*b*]indoles from β,β-disubstituted stryryl azides (Driver, 2011).[129]



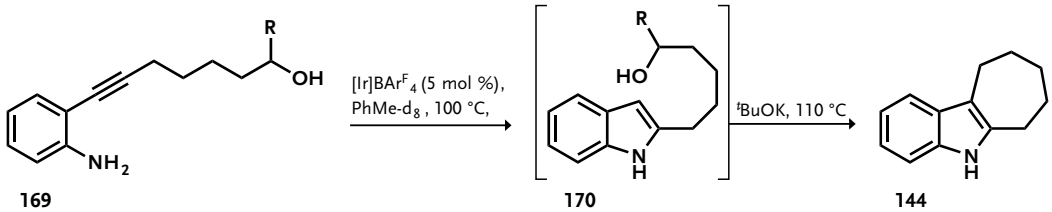
165 144

Scheme 2-23. Fischer indole synthesis of cyclohepta[*b*]indoles in low melting mixtures (König, 2012).[128]



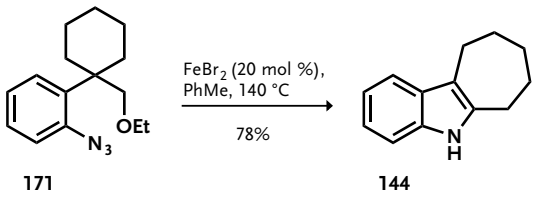
166 167 168

Scheme 2-24. Preparation of cycloheptano-indole derivatives (Novak, 2012).[131]



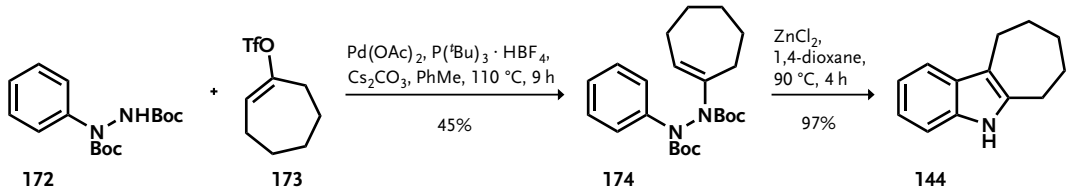
169 170 144

Scheme 2-25. Catalyzed tandem C–N/C–C bond formation for the synthesis of tricyclic indoles using Ir(III) pyrazolyl-1,2,3-triazolyl complexes (Messerle, 2012).[133]



171 144

Scheme 2-26. $FeBr_2$-catalyzed synthesis of cycloalka[*b*]indoles from aryl azides (Driver, 2013).[130]

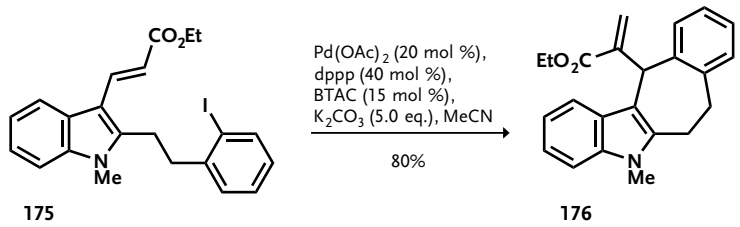


172 173 174 144

Scheme 2-27. Ene-hydrazide from enol triflate for the regioselective Fischer indole synthesis (Cho, 2014).[134]

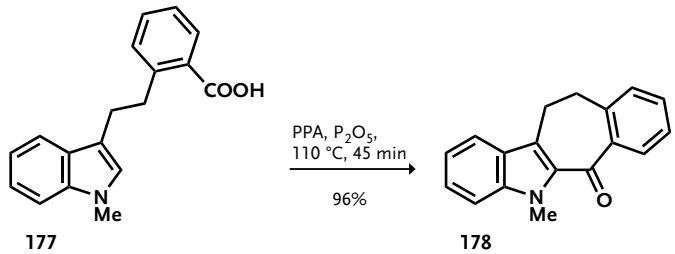
2.3.5.1 Benzocyclohepta[*b*]indoles

Almost all publications which deal with the formation of benzo[*m,n*]cyclohepta[*b*]indoles are using an indolyl aryl halide which is subjected to Heck reaction conditions to undergo an intramolecular ring closure (Schemes 2-28, 2-30, and 2-31).[135–137] J.-Y. Mérour used an indolyl benzoic acid derivative which undergoes intramolecular cyclization in the presence of a large excess of polyphosphoric acid and phosphorus pentoxide (Scheme 2-29).[84,138]



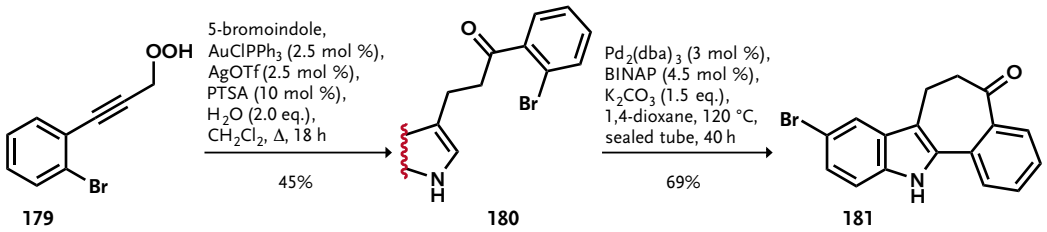
175 176

Scheme 2-28. Synthesis of benzo[4,5]cyclohepta[*b*]indole derivatives (Mérour, 1998).[135]

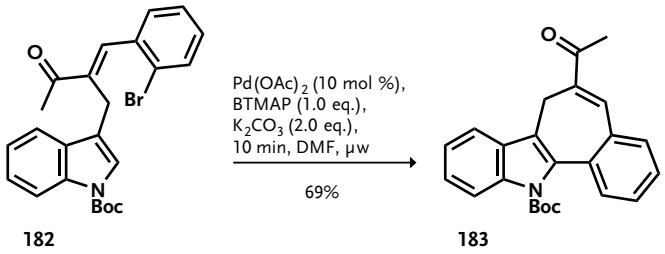


177 178

Scheme 2-29. Synthesis of benzo[5,6]cyclohepta[*b*]indole derivatives (Mérour, 1999, 2000).[84,138]



Scheme 2-30. Controlled gold-catalyzed reaction of propargylic hydroperoxides with phenols and palladium-catalyzed cyclization of β-aryl ketones (Alcaide, 2013).[136]



Scheme 2-31. Intramolecular Heck cyclization of aryl bromide **182** to synthesize benzo[6,7]cyclohepta[*b*]indole **183** (Phukan, 2015).[137]

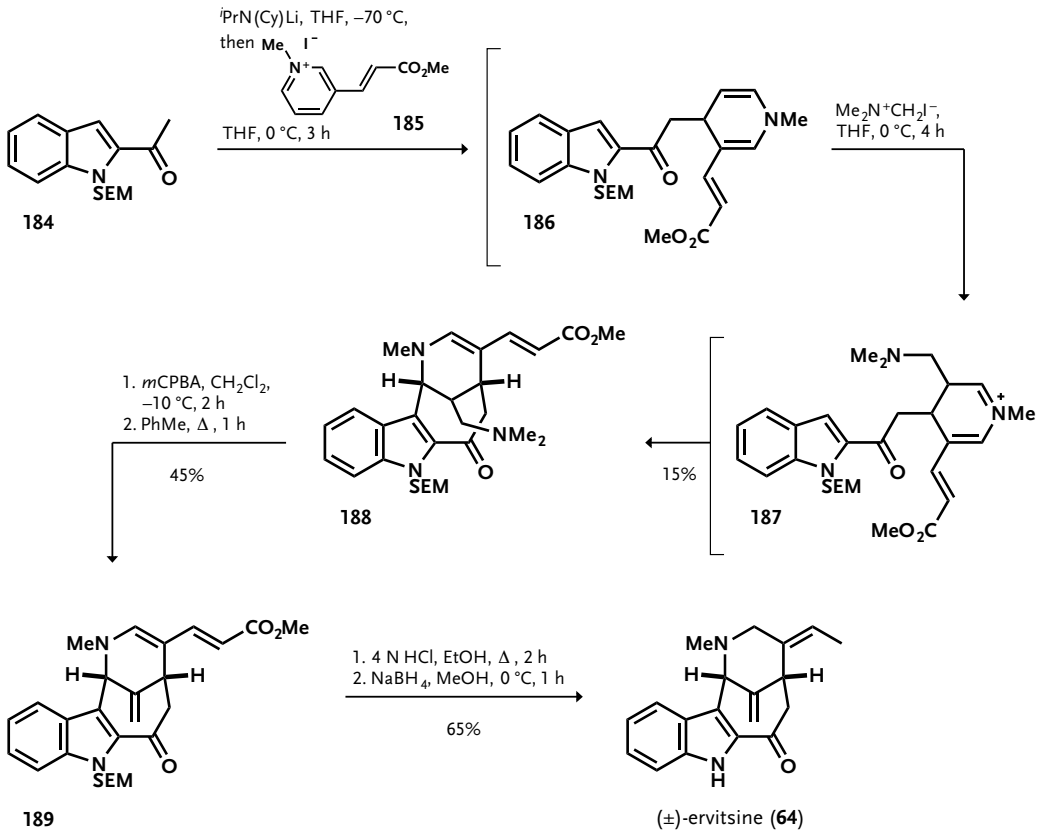
2.4 Syntheses of Natural Products

Total syntheses of several aforementioned natural products have been published (*cf.* Section 2.2). Hitherto actinophyllic acid (**22**) and ervitsine–ervatamine alkaloids have received the most attention from synthetic groups although the more readily accessible alkaloids arcyriacyanin A (**23**) and caulersin (**25**) have also been synthesized several times by different groups. Aristolasene (**29**) has been synthesized once starting from 20-hydroxyhobartine. No syntheses of aristolasol (**28**), exotines or ambiguines have been published to this day.

2.4.1 Synthesis of Ervatamia Alkaloids (J. Bosch)

2.4.1.1 Synthesis of (±)-Ervitsine

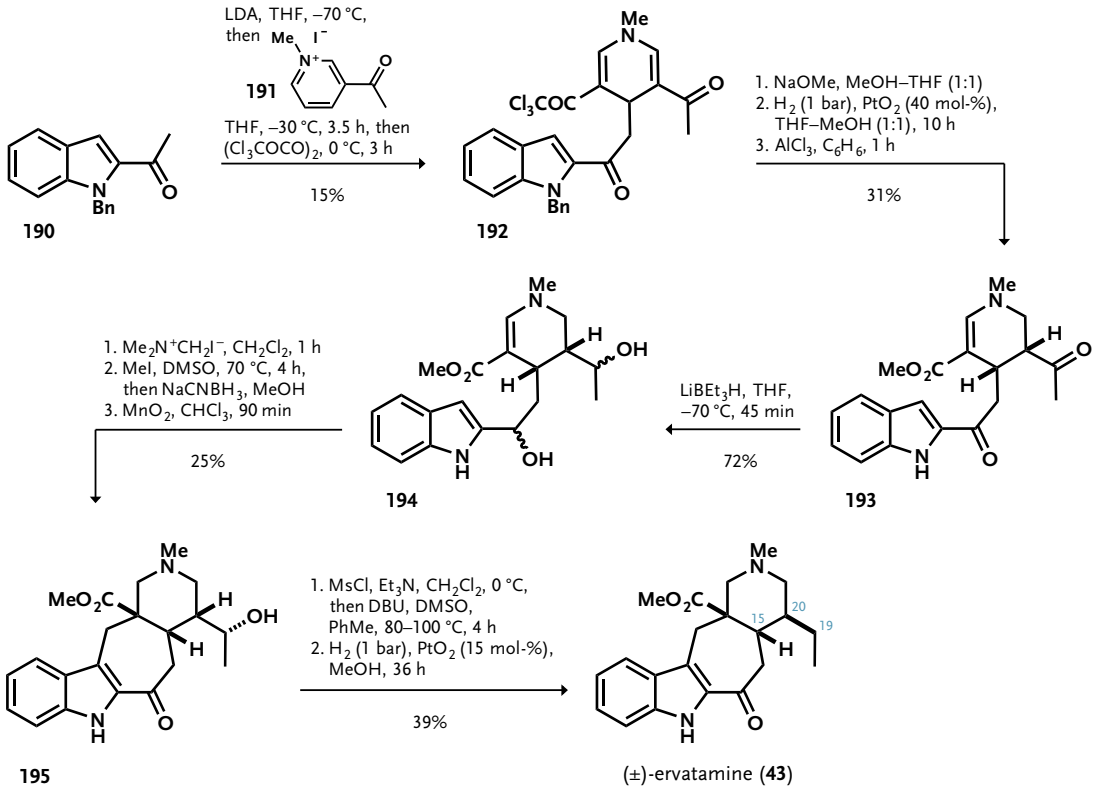
J. Bosch and co-workers published various syntheses of alkaloids of the ervitsine–ervatamine family. The first total synthesis of (±)-ervitsine was published in 1993 and was revised four years later.[78,139] It is a biomimetic synthesis utilizing 1,4-dihydropyridine and uses N^1-SEM protected 2-acetylindole (**184**) as starting material (Scheme 2-32). Its enolate reacts with pyridinium salt **185** and forms 1,4-dihydropyridine **186** followed by treatment with Eschenmoser's salt. This leads to iminium ion **187** which is trapped intramolecularly by the indole core yielding bridged system **188** in a one-pot three-step sequence with 15% overall yield. Although the yield of this sequence is poor it allows a rapid construction of the core structure. Oxidation of the dimethylamino moiety, followed by heating induced Cope elimination produces the



Scheme 2-32. Synthesis of (±)-ervitsine (**64**) by J.Bosch and co-workers.[78,139]

exomethylene group at C-16 in 45% yield. Subsequently, the tetracyclic product is subjected to acid-mediated decarboxylation followed by reduction with sodium borohydride. Under these conditions the protecting group is also cleaved to form (±)-ervitsine (**64**) in 65% yield. In this route, the construction of the cyclohepta[*b*]indole core is achieved *via* a Mannich reaction. An enantioselective approach of this route was used in the synthesis of (–)-N^1-methylervitsine employing a chiral *N*-methylpyridinium salt derived from (*S*)-*O*-methylprolinol.[140]

The total synthesis of (±)-ervatamine (**43**) was published by J. Bosch in 1997.[78] It profits from the same strategy as used in the total synthesis of (±)-ervitsine and is therefore also a biomimetic synthesis *via* a 1,4-dihydropyridine. The synthesis commences with the nucleophilic addition of the enolate of N^1-benzyl protected 2-acetylindole (**190**, Scheme 2-33) to 3-acylpyridinium salt **191** and trapping of the formed 1,4-dihydropyridine with trichloroacetic anhydride to give 2-acylindole **192** in moderate yield. The trichloroacetyl group is converted to the corresponding methyl ester and the 1,4-dihydropyridine moiety is reduced to the 1,2,3,4-tetrahydropyridine using H_2 and Adams's catalyst. Having the precognition that the benzyl group will cause problems at the end of the synthesis, the protecting group is cleaved using aluminium chloride in absolute benzene.[141] Prior to the biomimetic cyclization, reduction of the 2-acylindole carbonyl group is necessary as this moiety prevents successful aminoalkylation at the indole C-3 position. The resulting diol **194** is then treated with Eschenmoser's salt. After transformation of



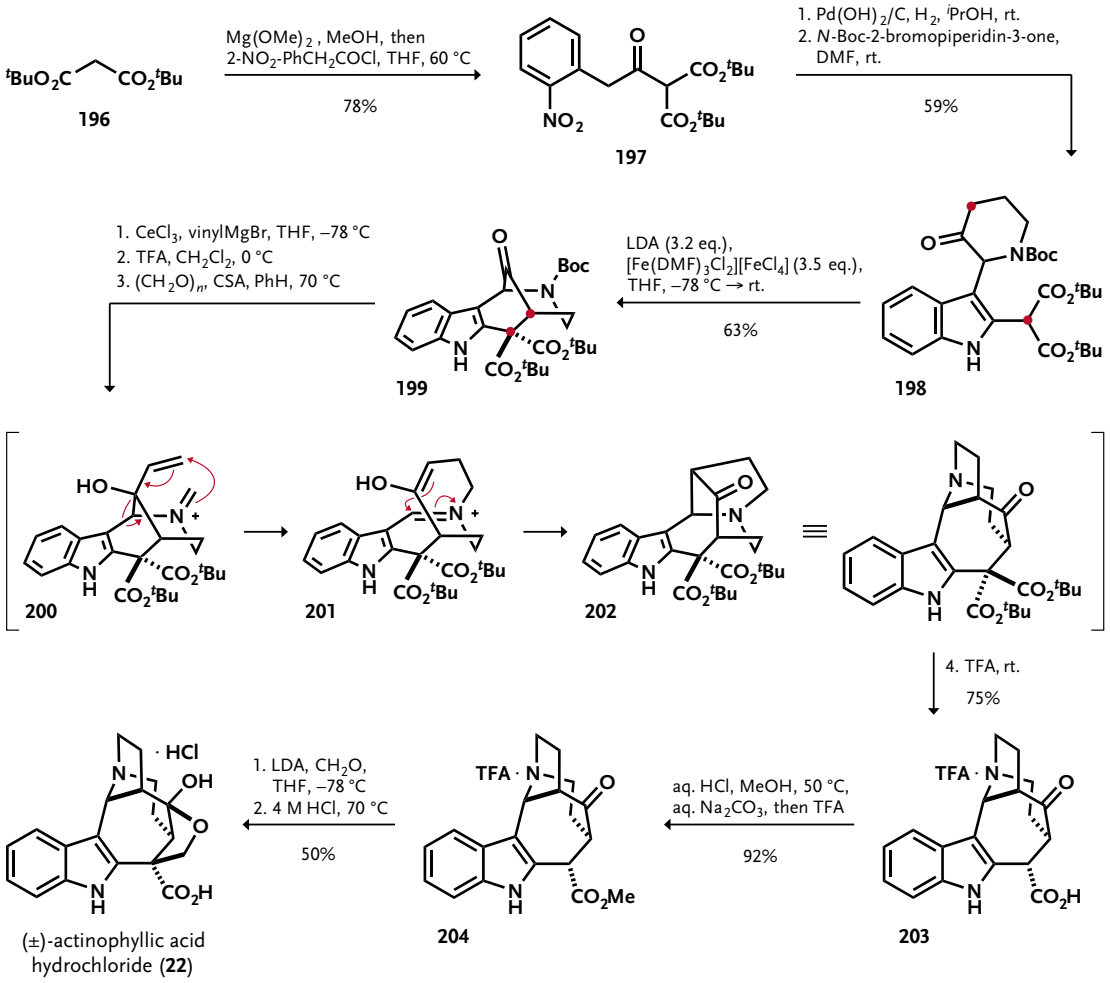
Scheme 2-33. Synthesis of (±)-ervatamine (**43**) by J. Bosch and co-workers.[78]

the gramine moiety into the corresponding methiodide under elevated temperatures, Hofmann elimination takes place and the system undergoes biomimetic cyclization. The resulting iminium salt is reduced using $NaCNBH_3$ and the tetracycle is chemoselectively oxidized to the ervatamine-type tetracyclic 2-acylindole **195** using MnO_2. Since the hydroxyethyl substituent at C-20 has to be *syn* to the adjacent proton at C-15, the alcohol moiety at C-19 is transferred into the corresponding mesylate followed by an *anti* elimination for the formation of an *E*-ethylidene double bond yielding (±)-19,20-didehydroervatmine (**52**), which is known to be convertible to (±)-ervatamine (**43**) *via* hydrogenation in the presence of Adams's catalyst.[142] In this synthesis, the formation of the cyclohepta[*b*]indole was achieved by gramine-type fragmentation reaction followed by intramolecular trapping of the putative iminium ion yielding the ervatamine-type tetracycle.

2.4.2 Synthesis of Actinophyllic Acid

2.4.2.1 Overman (2008)

The first total synthesis of (±)-actinophyllic acid (**22**) was published by L. Overman and co-workers in 2008 employing a concise sequence starting form di-*tert*-butyl malonate (**196**) which would allow production of gram quantities of the natural product.[143] The magnesium enolate of **196** reacts with *o*-nitrophenylacetyl chloride forming keto diester **197**, which in turn undergoes



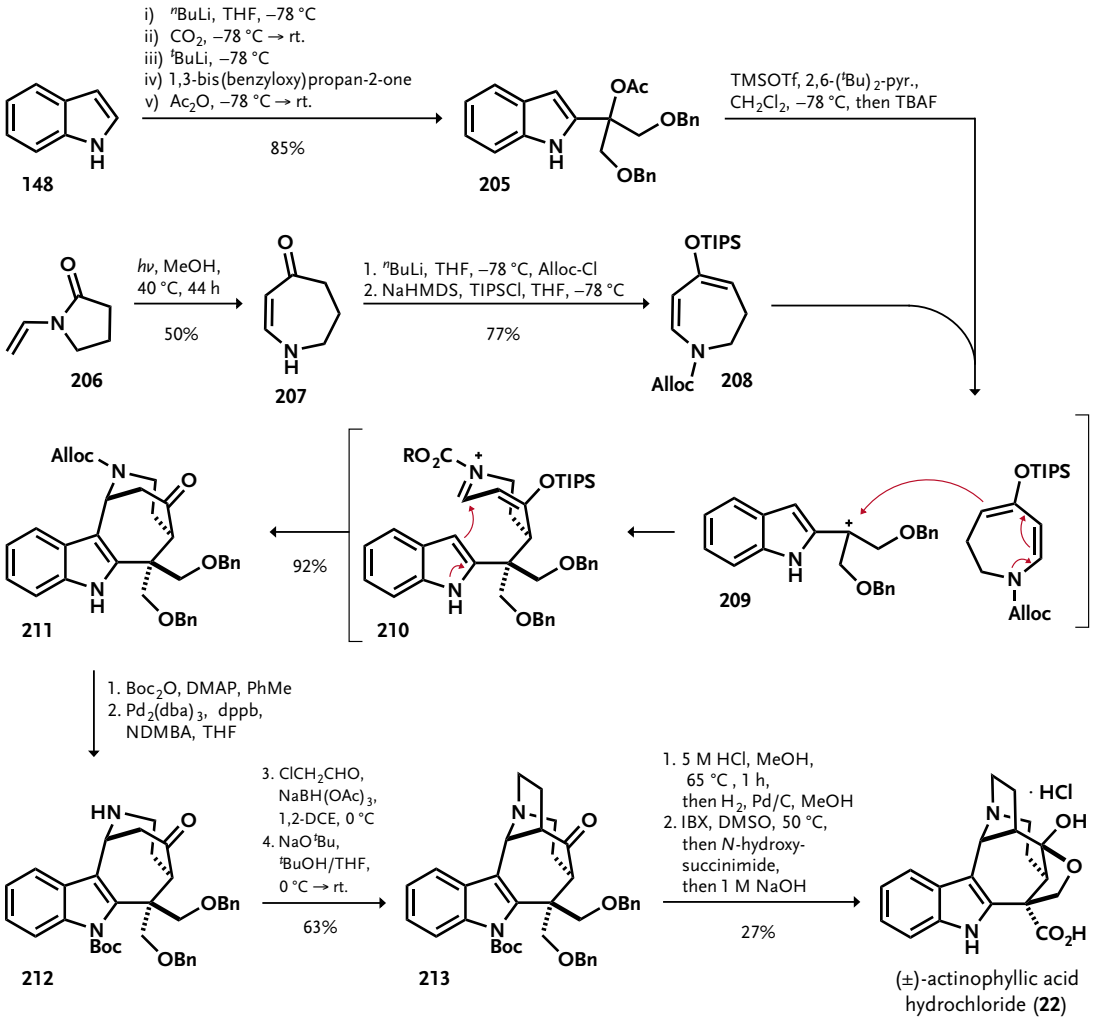
Scheme 2-34. Synthesis of (±)-actinophyllic acid hydrochloride (**22**) by Overman and co-workers.[143]

reductive cyclization to furnish an indole-2-malonate. Installation of a piperidin-3-one fragment at the C-3 position of the indole is simply achieved by the reaction of this indole with *N*-Boc-2-bromopiperidin-3-one in DMF obtaining indole **198**. Intramolecular oxidative coupling gives access to hexahydroazocino[4,3-*b*]indole **199**, the best results are obtained with a combination of LDA and $[Fe(DMF)_3Cl_2][FeCl_4]$, an easy prepared iron(III) chloride–dimethylformamide complex which has been elaborated for oxidative couplings of phenols and ketone enolates.[144,145] Although the yield is moderate, this optimized procedure allows formation of tetracyclic ketone **199** on scales up to 10 g in the presence of an unprotected indole. A vinyl rest is introduced by attack of the bridged ketone on the *Re* face followed by removal of the Boc protecting group. The liberated secondary amine reacts with paraformaldehyde at elevated temperatures to form iminium ion **200** which in turn undergoes a cationic 2-aza-Cope rearrangement and concomitant Mannich-type attack of the newly formed enol ether to iminium ion **201** to form pentacycle **202**. A similar aza-Cope/Mannich cascade has been carried out by L. Overman in the synthesis of strychnine and is a commonly used strategy.[146] Treatment of the crude product of this cascade

reaction with neat TFA gives (±)-actinophyllic acid precursor **203** in an overall yield of 75% from hexahydroazocino[4,3-*b*]indole **199**. Fischer esterification of the carboxylic acid to methyl ester **204** followed by treatment of its enolate with formaldehyde forms the tetrahydrofuran ring and gives (±)-actinophyllic acid methyl ester which is converted into the natural product **22** *via* acidic hydrolysis in 46% overall yield.

2.4.2.2 Martin (2013)

Five years after the first total synthesis of (±)-actinophyllic acid (**22**) by L. Overman and co-workers S. F. Martin and co-workers published a second synthesis using a cascade reaction of *N*-stabilized carbocations with π-nucleophiles to yield the tetracyclic skeleton of (±)-actinophyllic acid in one single step.[36] The required building blocks used in this cascade reaction are accessible in few steps from known compounds. For this purpose *N*-vinyl-2-pyrrolidinone (**206**) is converted into tetrahydroazepinone **207** *via* Norrish type I photorearrangement.[147] The enamine



Scheme 2-35. Synthesis of (±)-actinophyllic acid hydrochloride (**22**) by S. F. Martin and co-workers.[36]

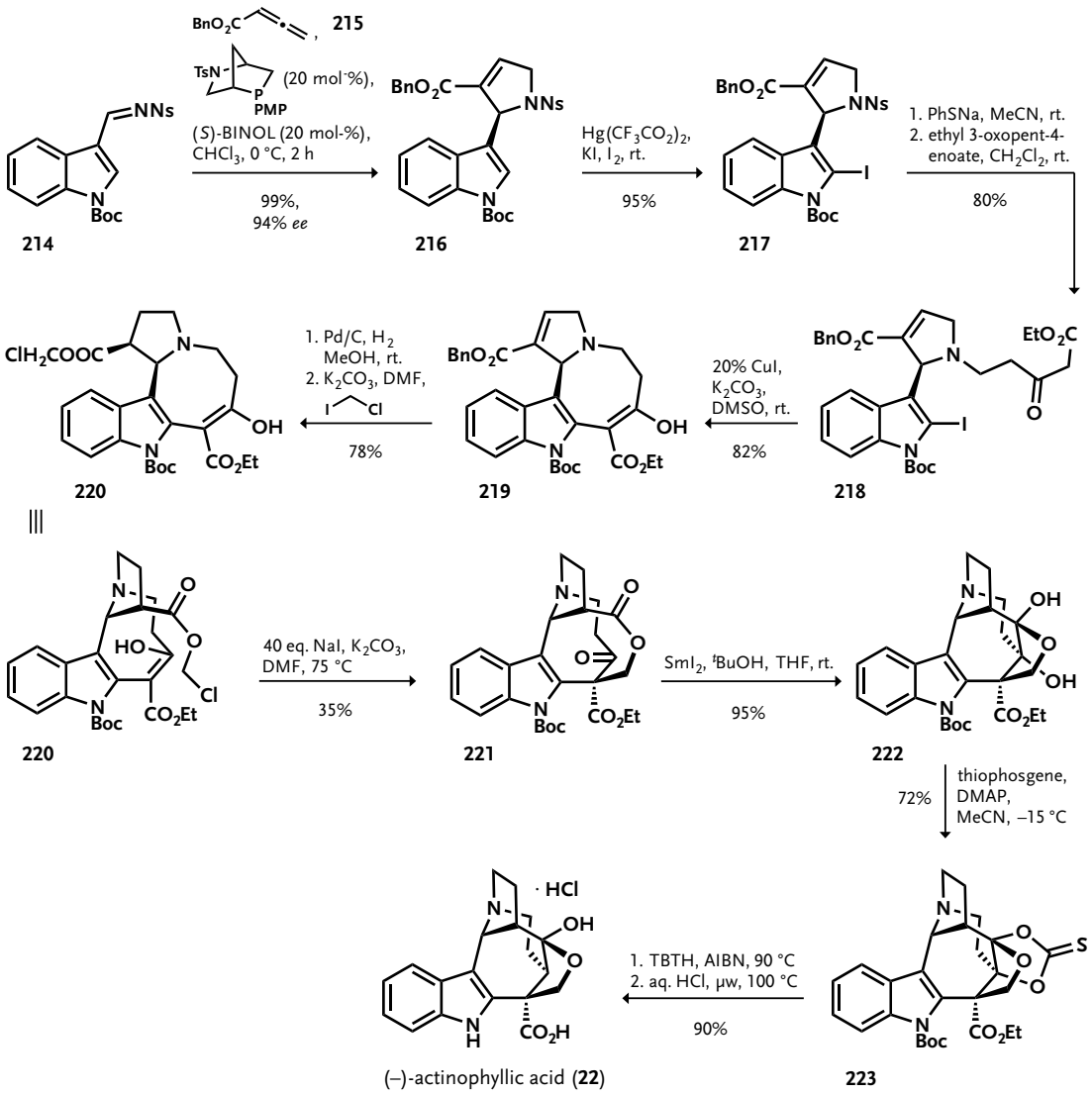
is protected with an Alloc group followed by formation of the corresponsding TIPS enol ether yielding dihydroazepinone **208** which is one building block for the cascade reaction. Indolyl acetate **205** is formed in a one-pot five-step sequence from indole (**148**) and is then treated with a Lewis acid to induce ionization of the tertiary acetate which is trapped by enamide **208**. The resulting *N*-acyliminium ion **210** is in turn trapped in a Mannich-type reaction by the indole core, furnishing the tetracyclic core of (±)-actinophyllic acid (**22**) in excellent yield. To avoid fragmentation by carbon-nitrogen scission, the indole nitrogen is protected with a Boc group. The Alloc protecting group is removed under palladium-catalyzed conditions in the presence of *N,N*-dimethylbarbituric acid to furnish the free amine **212** which in turn undergoes reductive amination with 2-chloroacetaldehyde. Treatment with base leads to displacement of the chloride and formation of bridged pyrrolidine **213**. Removal of all protecting groups leads to a spontaneous cyclization and formation of a hemiacetal. The remaining primary alcohol is oxidized to the corresponding carboxylic acid completing the synthesis of (±)-actinophyllic acid (**22**) in only ten steps from readily available compounds. The formation of the cyclohepta[*b*]indole core is achieved *via* the remarkable cyclization cascade of diene **208** and tertiary indolyl acetate **205**.

2.4.2.3 Kwon (2016)

Very recently, a third synthesis of (–)-actinophyllic acid (**22**) has been published by the group of O. Kwon.[37] The synthesis starts with a chiral phosphine-catalyzed [3+2] annulation between allenoate **215** and an indole sulfonylimine **214** (Scheme 2-36).[148,149] This reaction furnishes indole dihydropyrrole **216** in an almost quantitative yield and very good enantiomeric excess (94%). Mercury mediated installation of an iodine at the indole C-2 position, followed by the removal of the nosyl protecting group and direct alkylation of the generated secondary amine with ethyl 3-oxopent-4-enoate yields iodoketoester **218**. Subjecting the iodoketoester **218** to CuI in DMSO at ambient temperature furnishes azocane **219**. Simultaneous removal of the benzyl protecting group and *cis* hydrogenation is achieved with a high pressure of H_2 gas over Pd/C. Esterification of the resulting carboxylic acid with chloroiodomethane furnishes pyrrolidine **220**. Next in line is the formation of the tetrahydrooxocine moiety of the natural product; this is achieved *via* a modestly yielding alkylative lactonization. A SmI_2 mediated pinacol coupling furnishes the crucial cyclohepta[*b*]indole moiety and yields tetrahydrofuran **222** in an excellent yield. Radical dehydroxylation,[150] followed by global deprotection through the effect of aqueous HCl under microwave heating finally furnishes (–)-actinophyllic acid (**22**) in very good yield. The Kwon group constructed the cyclohepta[*b*]indole core of (–)-**22** *via* SmI_2 mediated intramolecular pinacol coupling between ketone and lactone subunits.

2.4.2.4 Partial Syntheses

Actinophyllic acid (**22**) has gained a lot of attention from the synthetic community. Since its isolation in 2005 by Carroll and co-workers[34] many groups have tried to synthesize this compound with its unprecedented architecture and great biomedical potential. Three total

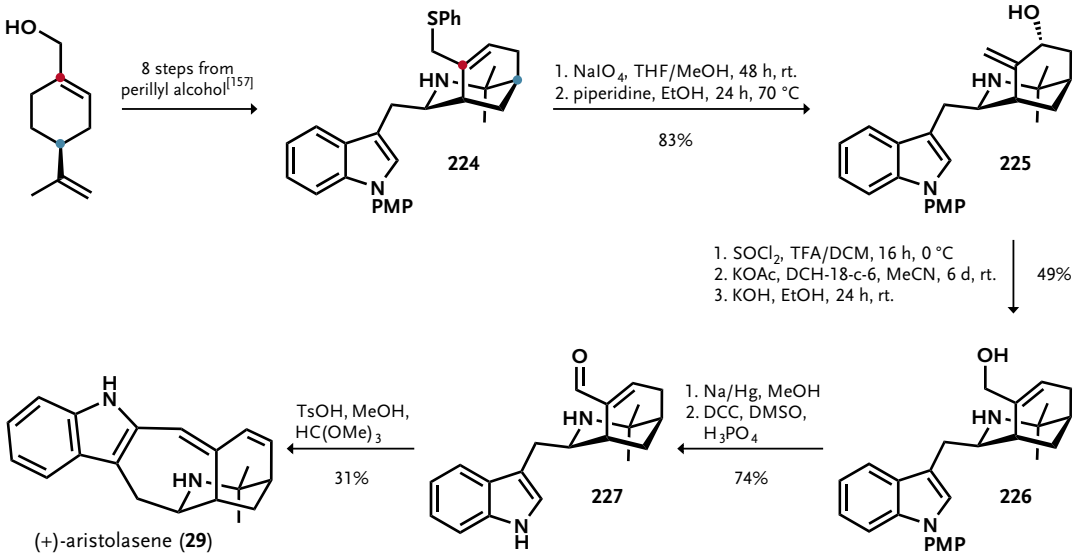


Scheme 2-36. Synthesis of (–)-actinophyllic acid hydrochloride (**22**) by O. Kwon and co-workers.[37]

syntheses have been published until today. Nevertheless, several other unfinished endeavors have been published by the groups of Coldham,[151] Maldonado,[152] Taniguchi,[153] Wood,[154] and Weinreb.[155] Our working group has also done some studies concerning the synthesis of (±)-**22**.[156] Due to incompleteness, these partial syntheses are not part of this dissertation.

2.4.3 Aristolasene (Borschberg, 1992)

H.-J. Borschberg published a synthesis of (+)-aristolasene (**29**) in 1992, among many other syntheses of *Aristotelia*-type alkaloids (Scheme 2-37).[50] All attemps to convert thiophenyl ether **224**—accessible in 8 steps from perillyl acohol[157]—into its corresponding aldehyde *via* a Pummerer reaction failed; instead the major product was indole-protected 18-*endo*-hydroxy-makomakine (**225**). This alcohol is treated with thionyl chloride which furnishes the rearranged



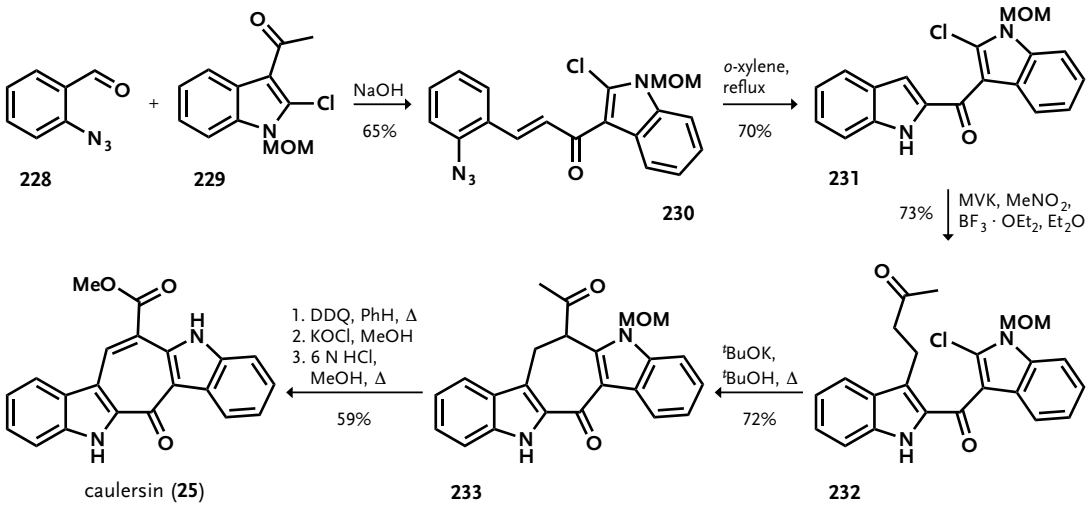
Scheme 2-37. Synthesis of (+)-aristolasene (**29**) by H.-J. Borschberg.[50]

allyl chloride which in turn is transformed into its corresponding alcohol **226** in two steps. Removal of the indole protecting group yields (–)-20-hydroxyboartine, which is transformed into (+)-aristolasene (**29**) in two additional steps in moderate yield. The cyclohepta[*b*]indole formation is achieved *via* a Pictet-Spengler-type reaction.

2.4.4 Caulersin

2.4.4.1 Fresneda (1999)

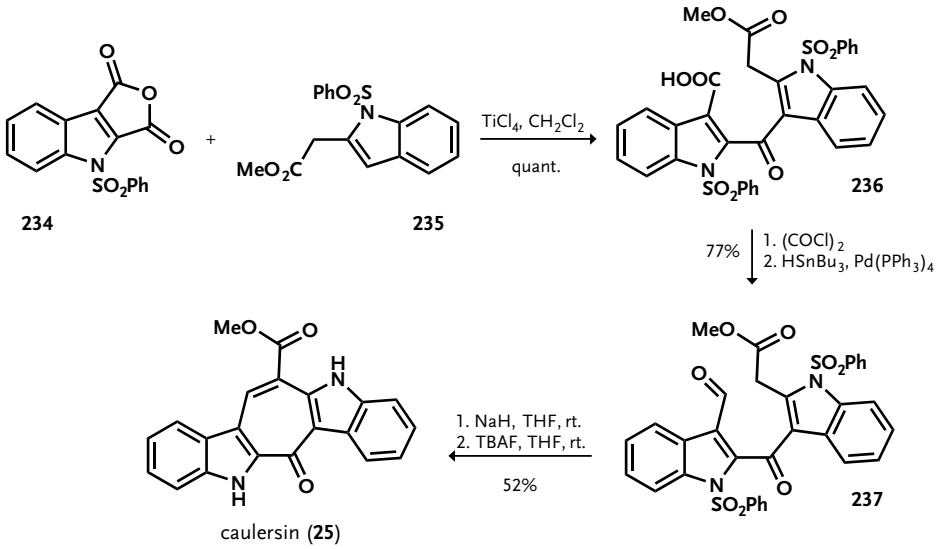
The first total synthesis of caulersin (**25**) was published by the group of Fresneda in 1999 (Scheme 2-38).[45] Aldol condensation between 2-azidobenzaldehyde (**228**) and *N*-protected 3-acetyl-2-chloroindole (**229**) in the absence of solvent yields chalcone **230**. The aryl azide is refluxed in *o*-xylene which furnishes bis(indole) **231**. Although the authors do not comment on this transformation, this reaction is a variant of the Hemetsberger-Knittel indole synthesis.[158] The mechanism of this indole synthesis is not entirely clear; the reaction is postulated to proceed *via* a highly electrophilic singlet nitrene species.[159] Lewis acid catalyzed Michael-type addition of bis(indolyl)ketone **231** to methyl vinyl ketone furnishes 3-oxoalkylated product **232** which is subjected to basic conditions and undergoes an intramolecular nucleophilic displacement of the chlorine atom *via* addition/elimination reaction to obtain **233**. Dehydrogenation with DDQ, followed by haloform reaction of the methyl ketone with potassium hypochlorite in methanol and removal of the indole protecting group under acidic conditions yields caulersin (**25**) in seven steps and 14% overall yield. The construction of the central seven-membered ring is based on an intramolecular nucleophilic substitution of 3-oxoalkylated product **232**.



Scheme 2-38. The first total synthesis of bis(indole) marine alkaloid caulersin (**25**) by Fresneda.[45]

2.4.4.2 Miki (2006)

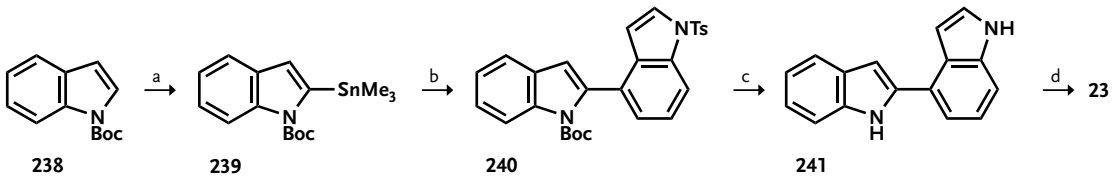
The second total synthesis of caulersin (**25**) was published by the group of Miki in 2006.[47] Lewis acid catalyzed reaction of *N*-protected indole-2,3-dicarboxylic anhydride **234** and methyl indolylacetate **235** affords 2-acylindole-3-carboxylic acid **236** in quantitative yield. The carboxylic acid is reduced to the corresponding aldehyde **237** in the presence of an ester and a ketone by converting the carboxylic acid to its acid chloride followed by tetrabutyltin hydride in the presence of $Pd(PPh_3)_4$. The construction of the central seven-membered ring is based on an intramolecular aldol condensation reaction. Final global deprotection affords caulersin (**25**) in five steps and 40% overall yield.



Scheme 2-39. Second total synthesis of bis(indole) marine alkaloid caulersin (**25**) by Miki.[47]

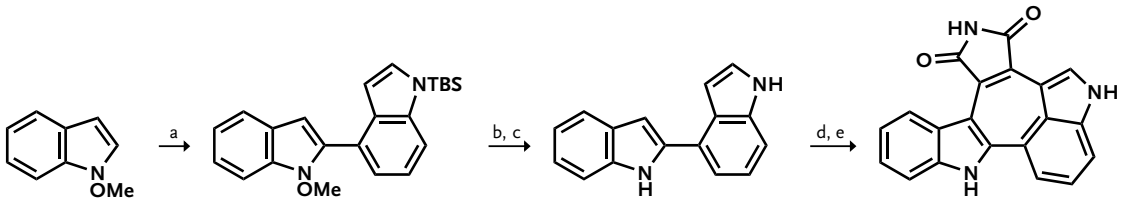
2.4.5 Arcyriacyanin A

Arcyriacyanin A (**23**) has been synthesized twice in the late 1990s by the groups of Steglich and Tobinaga, respectively.[40,41] Both strategies rely on palladium catalyzed cross-coupling reactions. Detailed information can be found in Section 15.1.



238 239 240 241

Scheme 2-40. Synthesis of arcyriacyanin A (Steglich, 1997).[40] Reagents and conditions: **a)** LDA, THF, –78 °C, 2 h, then Me_3SnCl, –78 °C → rt, 76%. **b)** *N*-tosyl-4-bromoindole, PhMe, 80 °C, $Pd(PPh_3)_4$, 20 h, 75% **c)** EtOH, 80 °C, 20% NaOH, 3 h, 68%. **d)** EtMgBr (2.0 eq.), THF, rt., then PhMe, 110 °C, 3,4-dibromomaleimide, 2 h, 41%.



242 243 241 arcyriacyanin A (**23**)

Scheme 2-41. Synthesis of arcyriacyanin A (Tobinaga, 1998).[41] Reagents and conditions: **a)** ^{n}BuLi, THF, –20 °C, 15 min, then Et_3B, –20 °C, 30 min, then $PdCl_2(PPh_3)_2$ (5 mol %), *N*-(*tert*-butyldimethylsilyl)-4-iodoindole, Δ, 4 h, 46%. **b)** TBAF, THF, 2 h, rt., 51%. **c)** Pd/C, MeOH, H_2 (1 atm), 2 h, 83%. **d)** MeMgBr, PhH, rt., 30 min, *N*-(*tert*-butyldimethylsilyl)-3,4-dibromomaleimide, Δ, 6 h, 16%. **e)** TBAF, THF, rt., 2 h, quant.

2.5 Conclusion

By far the biggest progress in methodology development has been made within the last decade. This coincides with the enhanced attention of pharmaceutical industry towards compounds exhibiting the cyclohepta[*b*]indole motif. However, up to date methods for enantioselective construction of cyclohepta[*b*]indoles are scarce. Among the completed ten total syntheses containing this structural motif, most of them—ervatamine (**43**), ervitsine (**64**), aristolasene (**29**), caulersin (**25**) and arcyriacyanin A (**23**); Schemes 2-32, 2-33, 2-37, 2-38, 2-40, and 2-41—date back to the 1990s. The total syntheses of actinophyllic acid (**22**, Schemes 2-34, 2-35, and 2-36) have been accomplished very recently. Analysis, especially of the most recent syntheses, reveals that the methodology development for the construction of cyclohepta[*b*]indoles of the last decade has so far not found its way into application in complex molecule synthesis. This is a very promising perspective, since further advancement can therefore be expected with regard to an efficient access to these compounds. Evermore, this shows the urgent demand for the development of synthetic methodologies involving the construction of cyclohepta[*b*]indoles, explicitly when

it comes to the development of methods for enantioselective construction of this privileged structural motif.

Cyclopropanes

3

3.1 Structure and Reactivity of Cyclopropanes

Cyclopropane, the smallest possible cycloalkane, was discovered in 1882 by A. Freund when trying to expand the Wurtz reaction to α,ω-dihaloalkanes.[160] He named the new compound trimethylene and—surprisingly—proposed the correct structure. Five years later G. Gustavson formed cyclopropane by using more manageable zinc instead of sodium.[161] While the cyclopropane ring is a highly strained entity, it is nonetheless found in a wide variety of naturally occurring compounds including terpenes, pheromones, fatty acid metabolites and unusual amino acids. Furthermore, its rigidity renders this group an attractive structural motif for the preparation of molecules with defined orientation of functional groups.[162]

Cyclopropane derivatives undergo a manifold of ring-opening reactions under the influence of a variety of chemical reagents (e.g., electrophiles, nucleophiles, radicals) or external physical forces (e.g., heat, light).[163] The C–C–C bond angles are 60°[164] and therefore considerably less than the ideal 109.5° for sp^3-hybridized orbitals which results in significant angular (Bayer) strain. Furthermore, cyclopropanes have additional torsional (Pitzer) strain as all hydrogens are eclipsed due to the coplanar arrangement of the carbon atoms (Fig. 3-1a).

The high reactivity is often rationalized by the relief of strain associated with ring opening. Though, the strain energies of cyclopropane and cyclobutane are similar: 27.5 and 26.5 kcal mol^{-1},

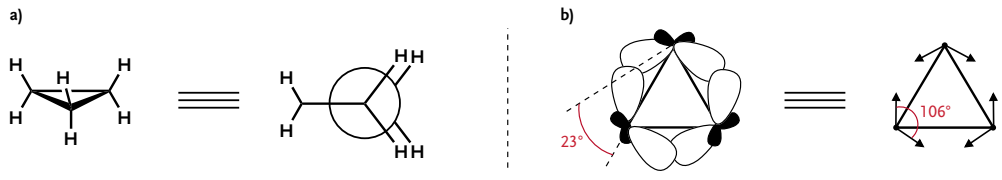


Figure 3-1. **a)** Cyclopropane. **b)** The Coulson-Moffitt model. Arrows denote directions of hybrid orbitals at the carbon atoms of cyclopropane.

respectively. Also, the required energy for the homolytic C–C cleavage is quite similar: 61.0 and 62.5 kcal mol^{-1}, respectively. Whereas the chemistry of cyclopropanes resembles that of a carbon-carbon double bonds, the chemistry of cyclobutanes does not. Therefore, the thermodynamical considerations alone are insufficient to explain the unusual reactivity of cyclopropanes.[163]

Several models try to describe the bonding situation in cyclopropanes. A popular description has been proposed by Coulson and Moffitt and describes the construction of the cyclopropane ring from three sp³-hybdridized CH_2-groups which make an angel of 106° with one another (Fig. 3-1b).[165,166] This results in about 20% less effective overlap than the C–C bond of ethane and for this reason, the bonds are often referred to as "banana bonded". The less effective overlap is also the source of the angular strain.

The Walsh model[167–169] proposes that cyclopropanes can be considered as an insertion of methylene into ethylene, therefore as being constructed from three sp²-hybdridized CH_2-groups, giving rise to the D_{3h} symmetric product. Thus, cyclopropanes have a significant sp² character and should react in analogy to olefins. The sp² hybrid orbitals are oriented towards the center of the cyclopropane ring (Fig. 3-2). As in the model of Coulson and Moffitt the angular strain is attributed to poor orbital overlap, too. Ψ_2 can be regarded as distorted π-bond which offers an explanation of the reactivity of cyclopropanes toward electrophilic reagents.[163,170]

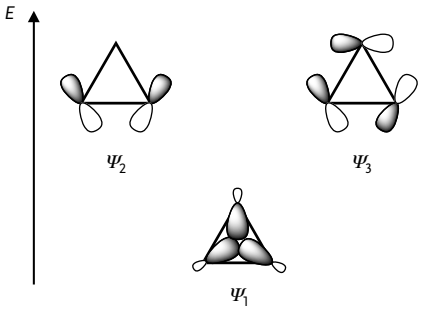


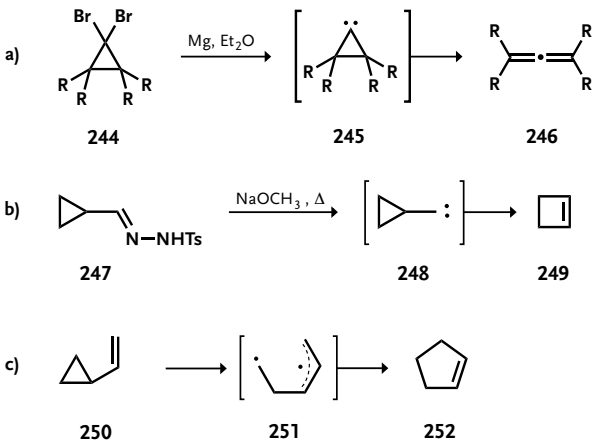
Figure 3-2. The Walsh model (basis set).

A property of cyclopropanes is that they are magnetically anisotropic but with the protons coming into resonance in their NMR spectra at unusually high field, typically 1 ppm upfield of the protons of an open-chain methylene group.

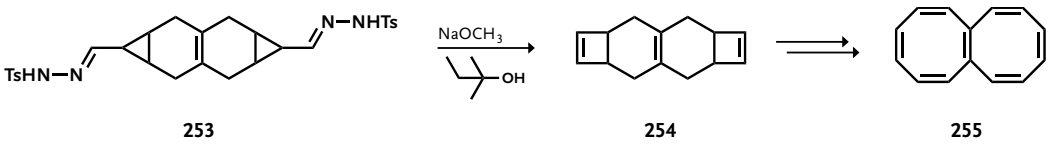
3.1.1 Thermal Ring Fission

There are four types of thermal cyclopropyl rearrangements which induce a ring fission: the cyclopropyl carbene rearrangement, the cyclopropylmethyl carbene rearrangement, the vinylcyclopropane rearrangement, and the divinylcyclopropane-cycloheptadiene rearrangement.

Treatment of *gem*-dihalocyclopropanes with magnesium results in the formation of a cyclopropyl carbenoid (*via* α-elimination) which undergoes a rearrangement (Scheme 3-1a). The product of this reaction is an allene and nowadays this reac-



Scheme 3-1. **a)** Cyclopropyl carbene rearrangement. **b)** Cyclopropylmethyl carbene rearrangement. **c)** Vinylcyclopropane rearrangement.



253 254 255

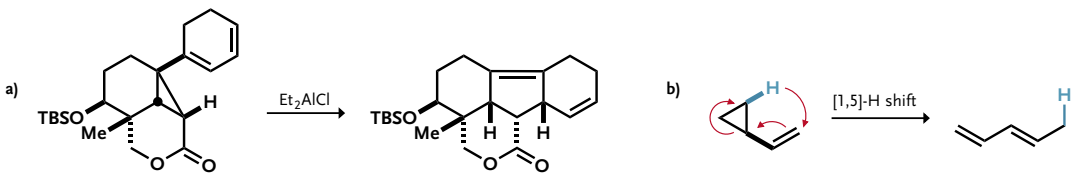
Scheme 3-2. Synthesis of octalene **255** *via* cyclopropylmethyl carbene rearrangement.[174]

tion is known as *Doering–LaFlamme allene synthesis*.[171,172] Alkyllithiums can also be used to generate allenes *via* cyclopropyl carbenoids (nowadays known as the *Skattebøl-Moore rearrangement*).[173,175b]

The generation of a carbene at a cyclopropylmethyl carbon results in a ring expansion through a 1,2-migration of the cyclopropyl C-C bond. This results in the formation of a cyclobutene (Scheme 3-1b).[163] Although this rearrangement has been used in the synthesis of octalene **255**[174] it is not as remarkble as the other types of rearrangements and has therefore not been widely used in syntheses of natural products.

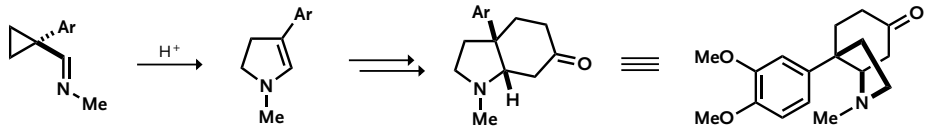
Cyclopropanes with adjactent π-systems have different chemical properties. Vinylcyclopropane **250** undergoes a rearrangement to yield cyclopentene **252** upon heating (Scheme 3-1c).[175] The activation energy for this process has been determined to be 49.7 kcal mol^{-1}.[176,177] The mechanism of this vinylcyclopropane rearrangement has been discussed extensively and involves biradical intermediates.[176–178] The rearrangement allows the preparation of functionalized cyclopentenes and has a great synthetical benefit since vinylcyclopropanes are readily accessible and cyclopentenes are important structural motifs in natural products. In the case of *trans*-alkylvinylcyclopropanes a 1,5-hydrogen shift (retro-ene reaction) can be a competing process but is controllable by temperature adjustment and sometimes can be reversible (Scheme 3-3b).[179] The vinylcyclopropane rearrangement strategy has been applied widely in the syntheses of complex natural products. In the synthesis of (±)-antheridium-inducing factor (A_{An}, 2) a vinylcyclopropane-cyclopentene rearrangement was a crucial step in the formation of the perhydrofluorene skeleton (Scheme 3-3a).[180]

A number of different functional groups can be introduced *via* this rearrangement at various positions, too. Under appropriate conditions, cyclopropanes in conjugation with an unsaturated functional group can also undergo this type of rearrangement. In this case it represents a heterocyclic variant of the vinylcyclopropane rearrangement. The acid-catalyzed thermal rear-



256 257 258 259

Scheme 3-3. **a)** A vinylcyclopropane rearrangement was a crucial step in the synthesis of (±)-antheridium-inducing factor (A_{An},2).[180] **b)** The a 1,5-hydrogen shift (retro-ene reaction) can be a competing process.



261 260 262

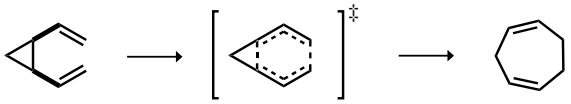
Scheme 3-4. The synthesis of mesembrine (**262**) by Stevens took advantage of the thermal rearrangement of cyclopropyl imines.[181]

rangement of cyclopropyl imines is a general method for the synthesis of Δ^2-pyrrolines **260**, which are useful compounds in the synthesis of alkaloids.[181,182]

3.1.1.1 Divinylcyclopropane-Cycloheptadiene Rearrangement

The most relevant rearrangement in the context of this work is the divinylcyclopropane-cycloheptadiene rearrangement (Scheme 3-5). It is a [3,3] sigmatropic rearrangement and is conceptually related to the Cope rearrangement but has the benefit of a thermodynamic driving force due to the release of ring strain. It involves the isomerization of a 1,2-divinylcyclopropane **263** into a cycloheptadiene **264** and was first discovered by E. Vogel in 1960.[175c] Vogel did not isolate divinylcyclopropane **263**, since, under the conditions he used for the formation, it rearranges rapidly to **265**. A decade later, divinylcyclopropane could be isolated for the first time and it was shown to rearrange to cycloheptadiene **265** with half-lives of approximately 90 s and 25 min at 35 °C and 11 °C, respectively.[183–185]

Its first synthetic application was in 1969 in the syntheses of (±)-dictyopterene C by G.Ohloff[186] and to this day it continues to be a useful approach since it provides a versatile, effective method for the construction of functionalized mono-, bi- and tricyclic substances (*cf.* Section 3.3).



263 264 265

Scheme 3-5. The divinylcyclopropane–cycloheptadiene rearrangement.

Only a *(Z)*-double bond geometry is observed in cycloheptadienes (Fig. 3-3) and *(E)*–cyclooctene is the smallest reported cyclic structure with a *trans* double bond that is stable at room temperature[190] The rearrangement proceeds in a concerted fashion *via endo*-boatlike transition state **267** where both vinyl groups are located above the cyclopropane. Only this transition state yields cycloheptadiene with the correct double bond geometry, whereas the chairlike transition state **270** and the *exo*-boatlike transition state **273** would yield *(Z,E)*- or even *(E,E)*-cycloheptadiens (**271** and **274**, respectively). The activation energy E_a for the rearrangement of **266** to **268** was established to be 19.0 kcal mol^{-1}.[183–185]

M. Zora has made an *ab initio* study about the transition structures and energetics for the rearrangement of *cis*-1,2-divinylcyclopropane, using the restricted Hartree-Fock and second-

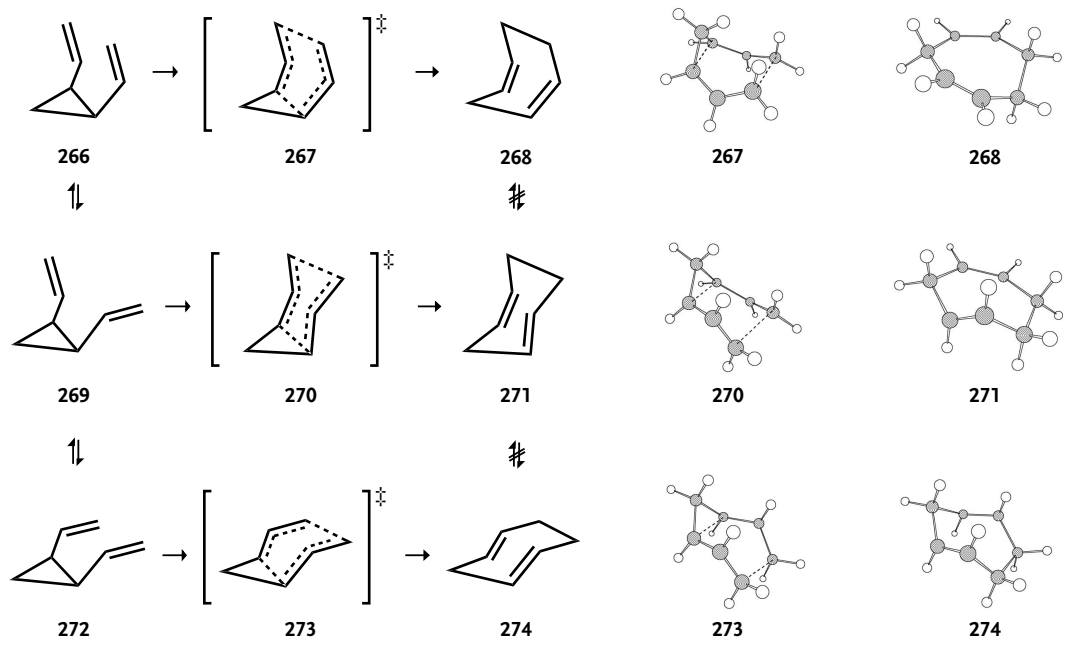


Figure 3-3. Transition states of the divinylcyclopropane-cycloheptadiene rearrangement: only *endo*-boat transition state **267** yields in *(Z,Z)*-cycloheptadiene **268**, highly unfavoured transition states **270** and **273** would yield virtually impossible *(Z,E)*- and *(E,E)*-cycloheptadiens **271** and **274**, respectively. The graphical structures are RHF/6–31G* optimized structures and show the particular transition state and the resulting cycloheptadiene.[187]

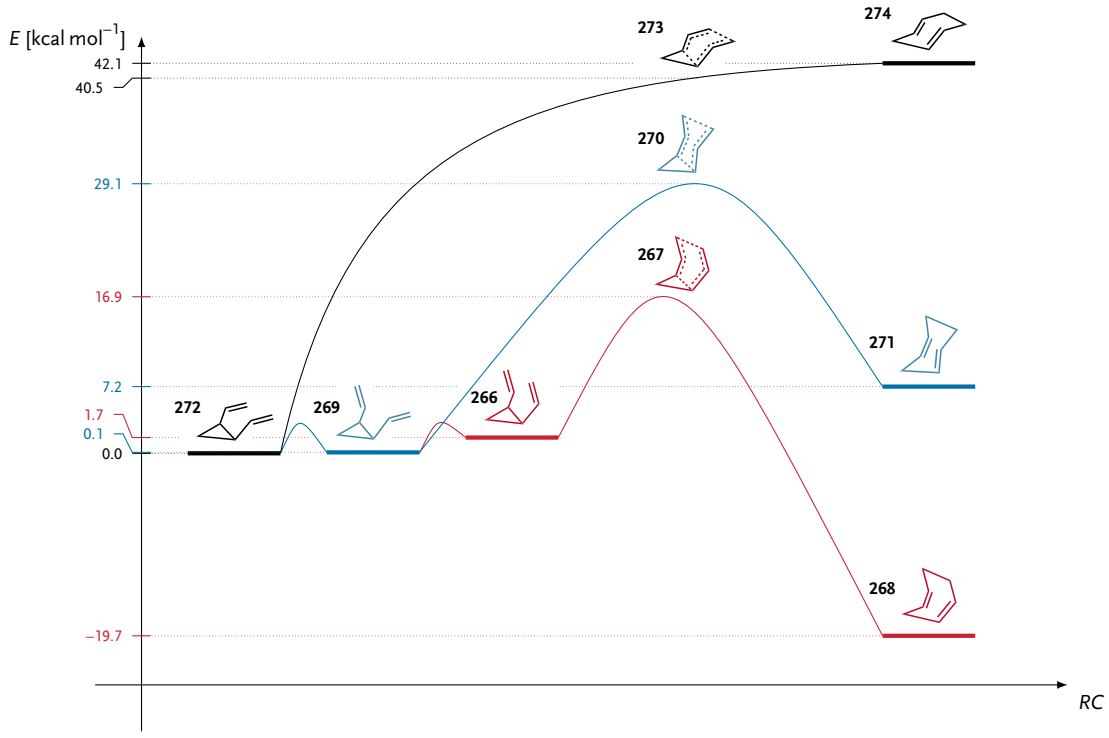
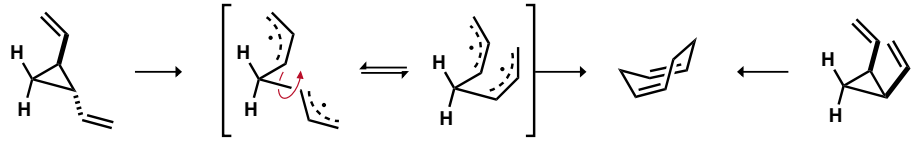


Figure 3-4. Energy diagram of cycloheptadiene formation *via* divinylcyclopropane-cycloheptadiene rearrangement. Energies are in kcal mol^{-1} and relative to that of **272**. All energy calculations used the second-order Møller-Plesset perturbation theory which is based on the Hartree-Fock method (MP2(full)6–31G*//RHF/6–31G*).[187–189] All values include zero-point vibrational energies.

order Møller-Plesset perturbation theory (MP2(full)6–31G*//RHF/6–31G*) and was the first to examine the formation of severely strained *(Z,E)*- and *(E,E)*-cycloheptadiens from these rearrangements (*cf.* Fig. 3-4).[187,189] The conversion of **272** into **269** and **266** is facile since the conformational energy barrier is 4.3 kcal mol^{-1} and 4.1 kcal mol^{-1} from **272** to **269** and from **269** to **266**, respectively. There is no direct conversion of **272** into **266**. The *endo*-boatlike transition state **267** has a calculated energy of activation of 16.9 kcal mol^{-1} which is in good agreement with the experimentally measured energy and is less strained than the chairlike and *exo*-boatlike transition states **270** and **273**, respectively. The formation of cycloheptadiene **268** is exothermic, whereas **271** and **274** are not energetically favorable due to increasing ring strain. It has to be noted, that the calculated relative energy of **273** is less than that of the resulting cycloheptadiene **274**. According to that, this conversion is effectively barrierless. This feature has also been observed in related systems.[191]

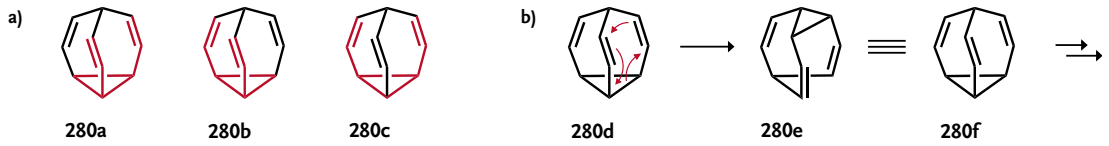
It is plausible that only *cis*-configured divinylcyclopropanes (**275**) are eligible for a [3,3] sigmatropic rearrangement (Scheme 3-6). For example, *cis* isomer **275** cyclizes already at ambient temperature or below. However, the *trans* configured counterparts (**276**) are usually thermodynamically more stable[175c] but rearrangement products are not directly formed since the required cyclic transition state cannot be adopted due to the absence of orbital overlap of the two π-bonds. Nevertheless, high temperature leads to the same rearrangement product **277** as it is obtained from the *cis* configured counterpart. The reason is a homolytic dissociation of the central linkage, to give *trans*-allyl biradical **278**.[192] Isomerization of the allyl groups enables the correct orbital geometry to perform a [3,3] sigmatropic rearrangement. To this day, it is not known whether only the isomerization occurs *via* a biradical mechanism or also the cyclization itself.



276 **278** **279** **277** **275**

Scheme 3-6. Radical isomerisation of *trans*-divinylcyclopropane.

A very special case of the divinylcyclopropane-cycloheptadiene rearrangement can be found in tricyclo[3.3.2.0^{2,8}] deca-3,6,9-triene, also named *bullvalene* (**280**, Scheme 3-7).[193] The bullvalene molecule is a cyclopropane with three vinyl arms conjoined at a methine group. Its molecular structure has the astonishing feature of having no permanent carbon–carbon bonds. All carbon atoms are bonded, or not bonded, to the same extent with every other carbon atom in the molecule, i.e., degenerated. Such molecules are named *fluxional* and this situation is the consequence of rapid Cope rearrangements. Its high-temperature proton NMR spectrum consists of exactly one sharp singlet at δ = 4.2 ppm and the ^{13}C spectrum shows only one sharp singlet at δ = 86.4 ppm. In total, there are $\frac{10!}{3}$ = 1 209 600 bonding possibilities. This explains why this structure is named *fluxional*.[194]



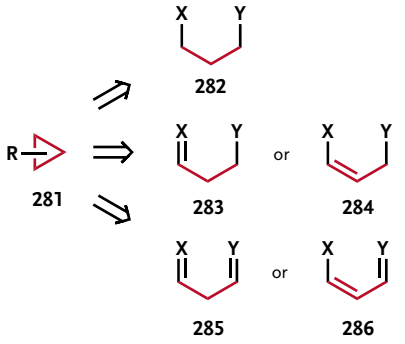
Scheme 3-7. **a)** Bullvalene (**280**) with highlighted Cope systems. **b)** One possible rearrangement: bullvalene rearranges to bullvalene. In total, there are $\frac{10!}{3}$ = 1 209 600 possibilities.[194]

3.2 Synthesis of Cyclopropanes

There are several methodologies for the generation of cyclopropanes. They can be classified into 1,3-cyclization reaction and [2+1] cycloaddition reactions. In the former case the cyclopropane ring is formed through the formation of a carbon–carbon bond in the immediate precursor, in the latter case two carbon–carbon bonds of the cyclopropane ring are formed in one preparative step. Several reviews for the construction of cyclopropanes have been published.[195–203]

3.2.1 Cyclopropanes *via* 1,3-Cyclization Reactions

1,3-Cyclizations are widely used for the construction of substituted cyclopropanes. In general, the three-membered ring can be formed as a result of a heterolytic or homolytic cleavage of two single bonds (**282** → **281**, Scheme 3-8), one single and one double bond (**283**/**284** → **281**), or two double bonds (**285**/**286** → **281**).

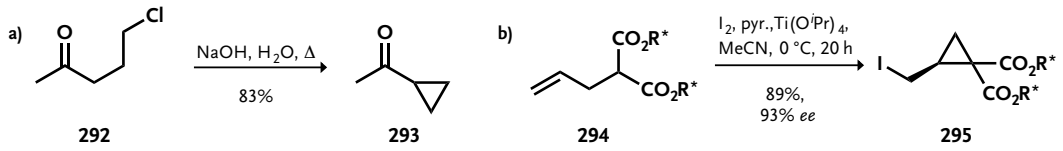


Scheme 3-8. Cyclopropanes from 1,3-cyclization reactions, a retrosynthetic view.

3.2.1.1 *Via* Cleavage of Two Single Bonds

The first synthesis of cyclopropane was discovered in 1882 by A. Freund when trying to expand the Wurtz reaction to α,ω-dihaloalkanes (*cf.* Section 3.1, see Scheme 3-9a).[160] Other quite similar examples for the generation of cyclopropanes *via* 1,3-cyclization reactions are presented in Schemes 3-9b and 3-9c, and show the synthesis of methylenecyclopropane

Scheme 3-9. **a)** Synthesis of cyclopropane by A. Freund (1882).[160] **b)** Synthesis of methylenecyclopropane from 2-methylallyl chloride (Boord, 1952).[204] **c)** Large scale synthesis of methylenecyclopropane (Salaün, 1977).[205]



Scheme 3-10. **a)** α-Cyclopropyl ketones from γ-haloketones.[206] **b)** Diastereoselective iodocarbocyclization reaction (R* = (–)-8-phenylmenthyl).[207]

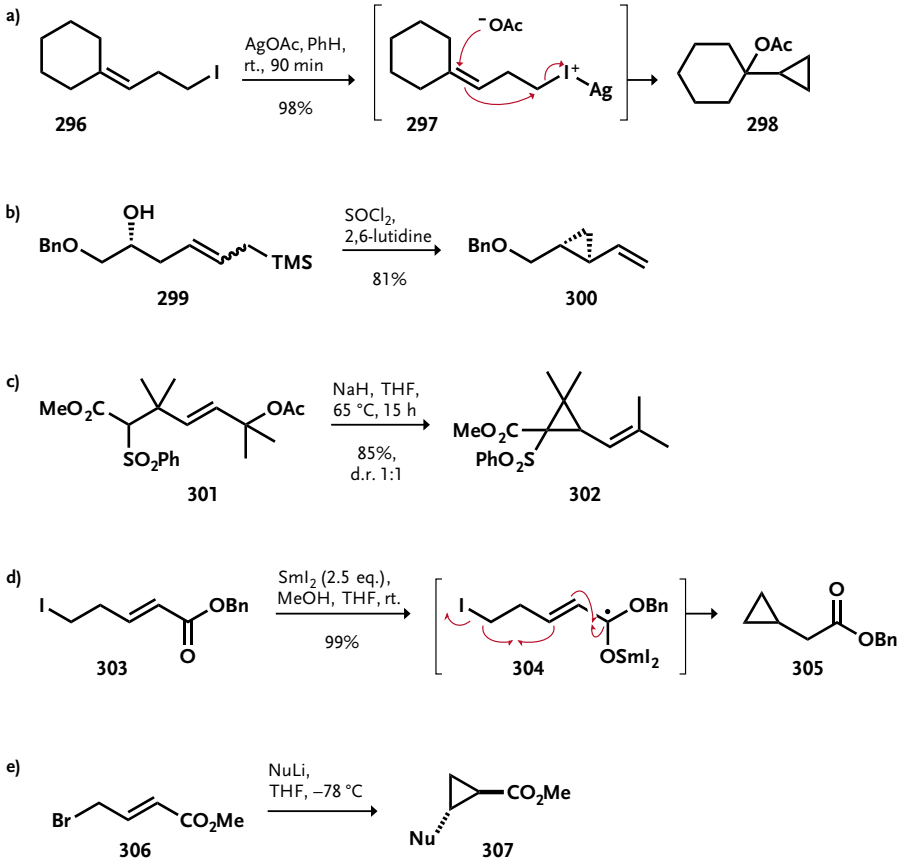
(**291**) starting from 2-methylallyl chloride (**289**). Small amounts of **291** were prepared by 1,3-dechlorination of dichloride **290** upon treatment with magnesium, large amounts were prepared by 1,3-dehydrochlorination of chloride **289**.

γ-Haloketones (**292**) are synthetically important building blocks for the synthesis of α-cyclopropyl ketones (**293**, Scheme 3-10a).[206] Treatment of this readily available compounds with aqueous sodium hydroxide leads smoothly to α-cyclopropyl ketones like **293**. This structure motif is often used in the synthesis of isoprenoids and other natural products. Taguchi *et al.* described the iodocarbocyclization of allylmalonate **294** using (–)-8-phenylmenthol as a chiral auxiliary which proceeded with high diastereoselectivity to give the iodomethylcyclopropane dicarboxylic ester **295** in 89% yield and 93% *ee* (Scheme 3-10b).

3.2.1.2 *Via* Cleavage of One Double Bond and One Single Bond

The rearrangement of homoallylic compounds into cyclopropylcarbinyl derivatives is a well known reaction and has received much attention from the synthetic community. Mangoni *et al.* described the synthesis of cyclopropylcarbinyl acetates (**298**) based on the reaction of homoallylic iodides (**296**) with silver(I) acetate in anhydrous media (Scheme 3-11a).[208] Taylor and co-workers described a similar intramolecular cyclization of homoallyl alcohol **299** bearing a silyl substituent (Scheme 3-11b).[209] Treatment with thionyl chloride under basic conditions leads to a homoallylic rearrangement. Similar to the Sakurai reaction,[213] the silyl group stabilizes the cyclopropylcarbinyl cation (beta-silicon effect); elimination of the silyl group leads to the formation of the vinyl cyclopropane **300**. *En route* to (±)-trans-chrysanthemic acid, Ficini *et al.* described a cyclopropane formation starting from sulfonylestser **301** (Scheme 3-11c).[210] Treatment with sodium hydride leads to a homoallylic carbanion, S_N2' substitution of the acetate group furnishes pentasubstituted cyclopropane **302** in a diastereomeric ration of 1:1. Guibé and co-workers described the formation of cyclopropylmethyl esters (**305**) from δ-iodo-α,β-unsaturated esters (**303**), with various substituents at the β- and γ-positions, in the presence of samarium diiodide and a proton source (Scheme 3-11d).[211] Another very common strategy is the use of the so-called MIRC[1] reaction (also known as Hassner–Ghera–Little MIRC reaction, *cf.* Scheme 3-11e).[212,214,215] This Michael initiated ring closure synthetic methodology is especially useful with sulfones and leads to the formation of β-substituted acceptor cyclopropanes. Formally, this reaction is a stereoselective [3+2] cycloaddition and is also applicable for the

[1] MIRC = Michael initiated ring closure

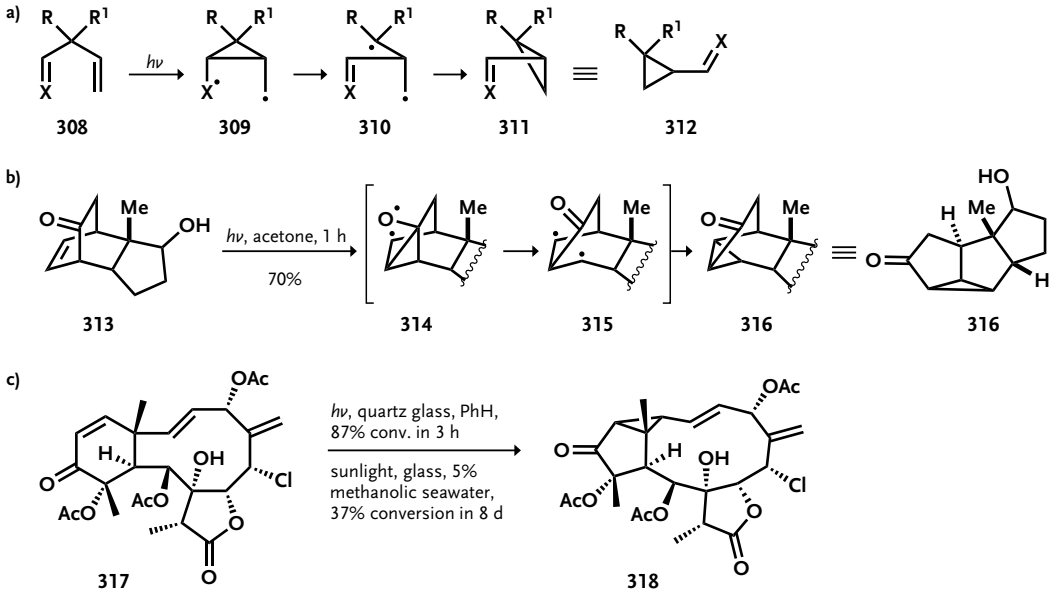


Scheme 3-11. **a)** Cyclopropylcarbinyl compounds from homoallylic iodides.[208] **b)** Vinylcyclopropanes from homoallylic alcohols.[209] **c)** *En route* to (±)-trans-chrysanthemic acid (Ficini, 1980).[210] **d)** Cyclopropane ring formation by an SmI_2 mediated cyclization of δ-halo-α,β-unsaturated esters.[211] **e)** MIRC reaction.[212]

formation of five-, six- and seven-membered rings. Enantioselective syntheses of MIRC reaction products starting from chiral sulfone imines have been described.[216]

3.2.1.3 *Via* Cleavage of Two Double Bonds

The photochemical rearrangement of 1,4-dienes to cyclopropane derivatives is known as di-pi-methane rearrangement, or oxa-di-pi-methane rearrangement if one of both π-systems is a carbonyl.[217] The main requirement then is that a carbon bears two π-moieties. The rearrangement product therefore, more generally, is a π-substituted cyclopropane. The very broad spectrum of types of organic molecules obtainable by the di-pi-methane rearrangement is remarkable and particularly useful in synthesis. More often than not, the photoproducts are not available by alternative routes.[217a] The biradical mechanisms is shown in Scheme 3-12a. The skeletal rearrangement where one of the two π-substituents is an aryl group is also possible and would yield aryl cyclopropanes. The (oxa-)di-pi-methane rearrangement has received much attention from the synthetic community and many syntheses with this skeletal rearrangement are described. Singh *et al.* irradiated tricyclic compound **313**, which is easy accessible from

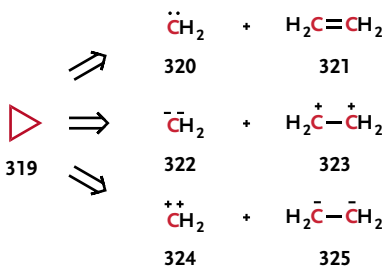


Scheme 3-12. **a)** Mechanism of the di-pi-methane rearrangement (X=CH_2) and oxa-di-pi-methane rearrangement (X=O).[217] **b)** *En route* to (±)-hirsutene *via* oxa-di-π-methane rearrangement (Singh, 2004).[218] **c)** Di-pi-methane rearrangement occurs naturally in some unique marine diterpenoids.[219]

salicyl alcohol in a few steps (Scheme 3-12b). The result is tetracyclic cyclopropane containing product **316** which would be difficult to synthesize by alternative routes.[218] Interestingly, this skeletal rearrangement occurs naturally in the that are unique marine diterpenoids interrelated by a naturally occuring di-pi-methane-rearrangement.[219] Look and co-workers showed, that irradiation of erythrolide B (**317**) under a variety of conditions yielded erythrolide A (**318**) as the sole product (Scheme 3-12c): irradiation of **317** in benzene in a quartz tube using a medium-pressure Hg lamp yielded **318** in 87% yield, irradiation of **317** in 5% methanolic seawater in a glass tube with sunlight yielded also **318** (37% conversion in 8 days).

3.2.2 Cyclopropanes *via* [2+1] Cyclization Reactions

In general, the formation of cyclopropanes *via* [2+1] cyclization reactions leads to reactions of methylene and ethylene fragments (Scheme 3-13). Homolytic or heterolytic cleavage of two carbon-carbon bonds of the three-membered ring gives two disconnection products: methylene and ethylene species (**320** + **321** → **319**). The unidirectional heterolytic fragmentation gives methylene 1,1-carbodianion and ethylene 1,2-carbodication (**322** + **323** → **319**), or methylene 1,1-carbodication and ethylene 1,2-carbodianion pairs (**324** + **325** → **319**). Although all methodologies in this section can be described with the coupling of the particular pairs from Scheme 3-13, it cannot be excluded that some reactions for the forma-



Scheme 3-13. Cyclopropanes from [2+1] cyclization reactions, a retrosynthetic view.

tion of cyclopropanes may be described more precisely by the recombination of the respective ion-radical species.

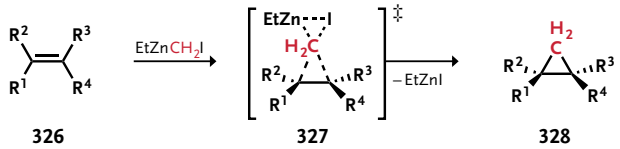
3.2.2.1 Simmons-Smith Cyclopropanation

In 1958, H. E. Simmons and R. D. Smith utilized diiodomethane in the presence of zinc-copper couple to convert unfunctionalized alkenes to cyclopropanes.[220,221] This transformation proved to be general and has become one of the most powerful methods of cyclopropane formation, since a wide range of alkenes is suitable for this reaction. Due to the electrophilic nature of the formed carbenoid **329** the rate of cyclopropanation is faster with more electron rich alkenes since these double bonds have a higher coefficient of the HOMO. The carbenoid Simmons-Smith reaction with isoprene confirms this theory: the reaction takes place on the double bond with the largest coefficient of the HOMO (Scheme 3-15).[170] However, in some cases steric hindrance of highly substituted alkenes can reduce the reaction rate.

Since the cyclopropane formation is a concerted process (*cf.* Scheme 3-14), it is a stereospecific reaction. In case of chiral substrates, the cyclopropanation is highly diastereoselective and occurs from the less hindered face of the double bond. If the alkene has functional groups containing heteroatoms (e.g., OH, OAc, OMe, OBn, NHR), the new methylene group adds stereoselectively to the same face of the double bond as the functional group.

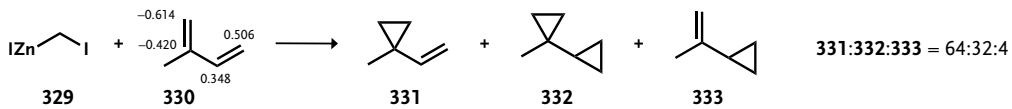
Nowadays, several modifications are known for the formation of the active reagent. The most popular modification uses diethylzinc with methylene iodide which gives highly reproducible results (Furukawa modificaion, Scheme 3-14).[222] Furthermore, there are two modifications for chemoselective cyclopropanation of allylic alcohols in the presence of other olefins and *vice versa*. The Molander modification uses iodomethylsamarium iodide ($Sm/Hg/CH_2I_2$)[223,224] for the chemoselective cyclopropanation of allylic alcohols in the presence of other olefins. Dialkyl(iodomethyl)aluminium ($^iBu_3Al/CH_2I_2$) exclusively cyclopropanates unfunctionalized olefins (Yamamoto modification).[225]

There are two different approaches for asymmetric Simmons-Smith cyclopropanations: either the use of cleavable chiral auxiliaries[226–228] or the addition of stoichiometric amounts of chiral



326 **327** **328**

Scheme 3-14. Simmons-Smith cyclopropanation (Furukawa modification).[220]



329 **330** **331** **332** **333**

331:**332**:**333** = 64:32:4

Scheme 3-15. The carbenoid Simmons-Smith reaction with isoprene. The values represent the Ψ_2-coefficients of isoprene.

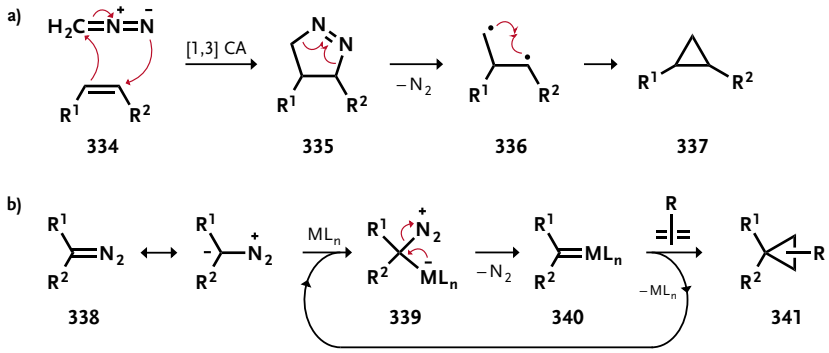
additives, such as dioxaborolanes (Charette asymmetric modification).[229] However, the latter approach is usually only suitable for allylic alcohols. It has often been used in syntheses of natural products, e.g. in the total synthesis of (+)-ambruticin by E. N. Jacobsen.[230]

3.2.2.2 Cyclopropanation *via* Diazo Compounds and *via* Metal Carbenoids

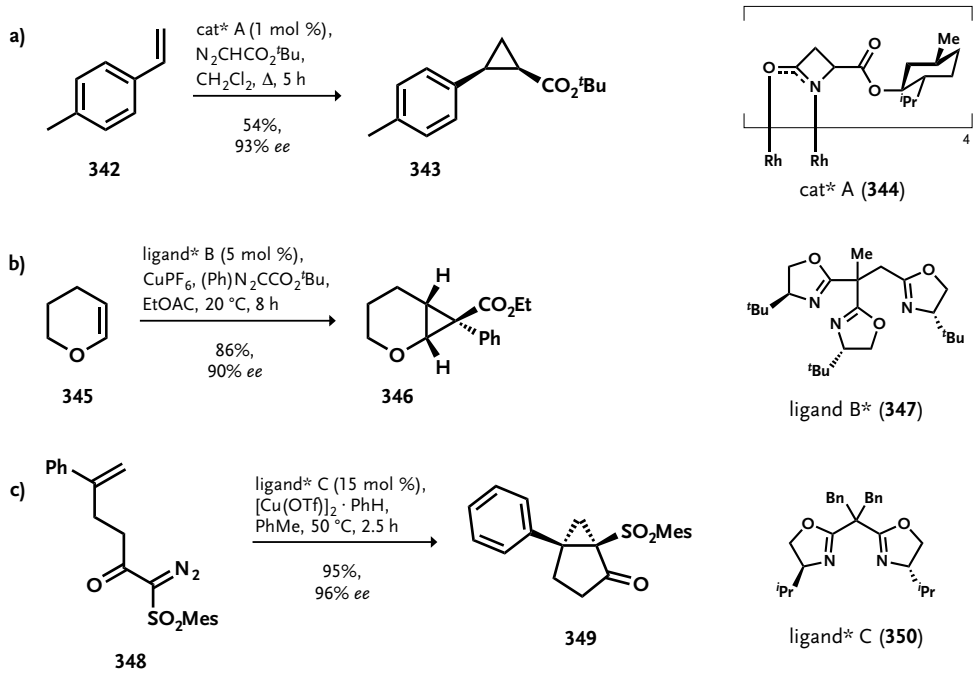
Certain diazo compounds can react with olefins to furnish cyclopropanes in a two-step manner (Scheme 3-16a). The first step involves a 1,3-dipolar cycloaddition to form pyrazoline **335** which then undergoes radical denitrogenation to yield cyclopropane **337**. The latter step occurs either photochemically or by thermal decomposition. The thermal route is also known as the Kishner cyclopropane synthesis.[231] The mechanism of decomposition has been studied but remains controversial, although it is assumed to proceed *via* a diradical species.[232]

More common is the cyclopropanation of olefins with a diazo compound under metal catalysis, which usually proceeds effectively in the presence of copper, palladium, and rhodium catalysts, but cyclopropanations with iron, nickel, and cobalt catalysts are also described. The general mechanism of this transformation is shown in Scheme 3-16b.[233] After formation of the α-diazomethyl organometallic intermediate **339**, elimination of nitrogen takes place to give metal-carbene complex **340**. The cyclopropanation of the olefin proceeds either by direct replacement of the metal or by formation of a metallacyclobutane intermediate which undergoes reductive elimination to afford cyclopropane **341**. The most likely active species in these transformation are copper(I),[234] palladium(0)[233c] and rhodium(II).[233a] However, copper(II) and palladium(II) salts can be used since they are reduced to the active copper(I) and palladium(0) species, respectively, with the diazo compound.

Literature contains a number of examples for the catalytic enantioselective cyclopropanation utilizing transition metal carbenoids generated from diazo compounds (Scheme 3-17). On the one hand, the use of chiral metal catalysts (e.g. **344**) is possible and usually leads to high *ee*'s. Doyle *et al.* used a new azetidine-ligated dirhodium(II) catalyst that possesses a L-menthyl ester attachment. This chiral Rh-catalyst provides a significant diastereocontrol and high enantio-



Scheme 3-16. **a)** Mechanism for the cyclopropanation using diazo compounds. **b)** Mechanism of the metal-catalyzed carbenoid cyclopropanation reaction.[233]

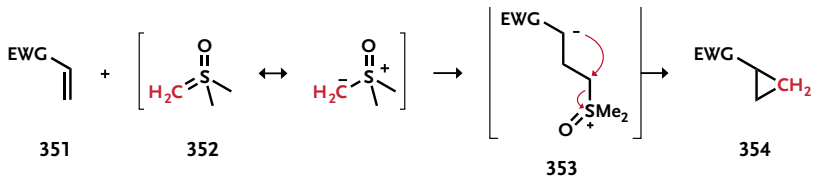


Scheme 3-17. Catalytic enantioselective cyclopropanation utilizing transition metal carbenoids generated from diazo compounds. **a)** *En route* to a cyclopropane-configured urea-PETT analogue (Doyle, 2002).[235] **b)** cyclopropanation of alkenes with aryldiazoacetates catalyzed by trisoxazoline/Cu(I).[236] **c)** Catalytic asymmetric intramolecular cyclopropanation reaction.[237]

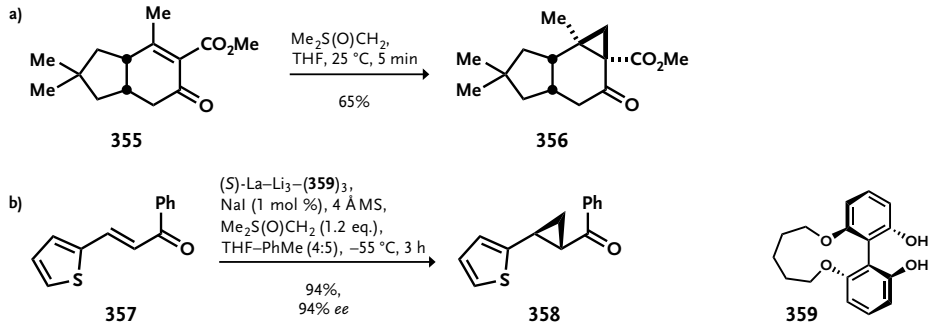
control for the formation of *cis*-cyclopropane products from reactions of substituted styrenes with diazo esters (Scheme 3-17a).[235] On the other hand, the use of common metal salts in combination with chiral ligands (e.g. **347** or **350**) is possible. Tang and co-workers published a highly enantioselective cyclopropanation of alkenes with phenyldiazoacetates catalyzed by $CuPF_6(CH_3CN)_4$/trisoxazoline (Scheme 3-17b).[236] Nakada and co-workers studied the catalytic asymmetric intramolecular cyclopropanation reactions of 5-aryl-1-diazo-1-mesitylsulfonyl-5-hexen-2-ones using BOX ligands (Scheme 3-17c).[237]

3.2.2.3 Sulfur Ylides: Corey-Chaykovsky reaction

Sulfonium and sulfoxonium ylides were first described by R. Kuhn in 1957,[238] but it were A. W. Johnson and E. J. Corey who saw its synthetic value and described syntheses of epoxides from the reaction of carbonyls and sulfur ylides.[239,240] The general reaction involves the addition of a



Scheme 3-18. Mechanism of the Corey-Chaykovsky reaction.



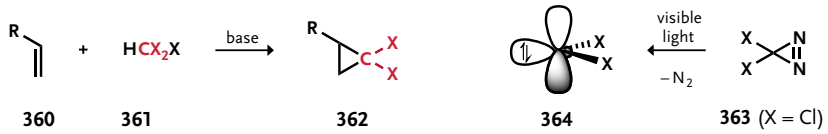
Scheme 3-19. **a)** From the total synthesis of (±)-isovelleral (Heathcock, 1992).[241] **b)** Catalytic asymmetric cyclopropanation of enones with dimethyloxosulfonium methylide promoted by a La–Li_3–(Biphenyldiolate)$_3$ + NaI complex.[242]

sulfur ylide to a ketone, aldehyde, imine, or enone to produce the corresponding 3-membered ring. Therefore, it can be used for the synthesis of epoxides, aziridines and cyclopropanes, respectively. For addition of sulfur ylides to enones, higher 1,4-selectivity is typically obtained with sulfoxonium reagents than with sulfonium reagents. This type of [2+1] cycloaddition has found widespread application in organic chemistry. The reaction proceeds *via* Michael addition of ylide **352** to an α,β-unsaturated compound followed by 1,3-cyclization of the betaine indermediate **353** to afford cyclopropane **354** (Scheme 3-18).[203]

The Corey-Chaykovsky reaction has received much attention from the synthetic community and numerous examples of application can be found in literature. C. H. Heathcock used this reaction in his synthesis of (±)-isovelleral (Scheme 3-19a).[241] A catalytic asymmetric cyclopropanation of enones with dimethyloxosulfonium methylide promoted by a La–Li_3–(Biphenyldiolate)$_3$ + NaI complex was described by M. Shibasaki (Scheme 3-19b).[242]

3.2.2.4 Halocarbene Equivalents

A highly effective method for cyclopropanation is to employ free carbenes, but the scope is limited because only few carbenes can be prepared conveniently and nearly all are unstable. Dihalocarbenes (**364**) are an exception and the preparation of heterosubstituted cyclopropanes with these carbenes was first documented by W. v. E. Doering in 1954 (Scheme 3-20).[243] A very effective way for the preparation of dihalocarbenes is the generation in a two-phase system upon treatment of the particular haloform species with concentrated aqueous lye in the presence of triethylbenzylammonium chloride. Only a small part of the generated carbene reacts with the

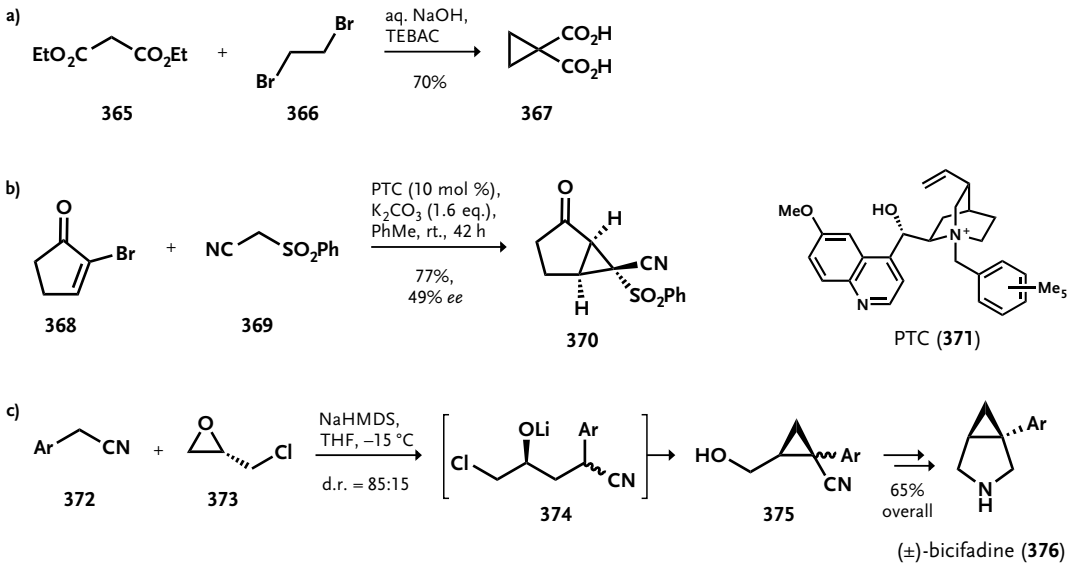


Scheme 3-20. Cyclopropanation *via in situ* formed dihalocarbene from methane trihalide. α-Elimination leads to an electrophilic carbene which reacts with the double bond with the largest coefficient in the HOMO (*cf.* Scheme 3-15).

water and the major part can be effectively trapped with an olefine.[244] Another effective way for the preparation of dichlorocarbene is the use of dichlorodiazirine, which is a nitrogenous precursor for dichlorocarbene. It is stable in the dark but decomposes into dichlorocarbene and nitrogen *via* photolysis.[245]

3.2.2.5 Cyclopropanes from 1,1-Carbodianions and 1,2-Carbodications

The unidirectional heterolytic fragmentation of cyclopropane can also give methylene 1,1-carbodianion and ethylene 1,2-carbodication (**322** + **323** → **319**, Scheme 3-13). An early example for this reaction dates back to 1884: W. Perkin described the preparation of diethyl cyclopropane-1,1-dicarboxylate from diethyl malonate (**365**) and 1,2-dibromoethane (**366**).[249] S. M. Danishefsky and co-workers described a similar reaction (Scheme 3-21a), but used aqueous caustic soda as a base and therefore yielded cyclopropane 1,1-dicarboxylic acid (**367**).[246] A more recent example has been published by Shioiri *et al.* and shows an asymmetric cyclopropanation reaction using chiral quaternary ammonium salts as the phase-transfer catalyst (Scheme 3-21b).[247] *En route* to (±)-bicifadine (**376**)—a potent inhibitor of both the serotonin and norepinephrine reuptake transporters—Xu and co-workers used an epoxy nitrile coupling (Scheme 3-21c).[248] Deprotonated nitrile **372** reacts with epichlorohydrin (**373**) to form intermediate **374**. The chlorine undergoes S_N2 displacement and the newly generated epoxide is attacked *in situ* by a second nitrile anion to give cyclopropane **375** which is transformed into (±)-**376** in two additional steps.

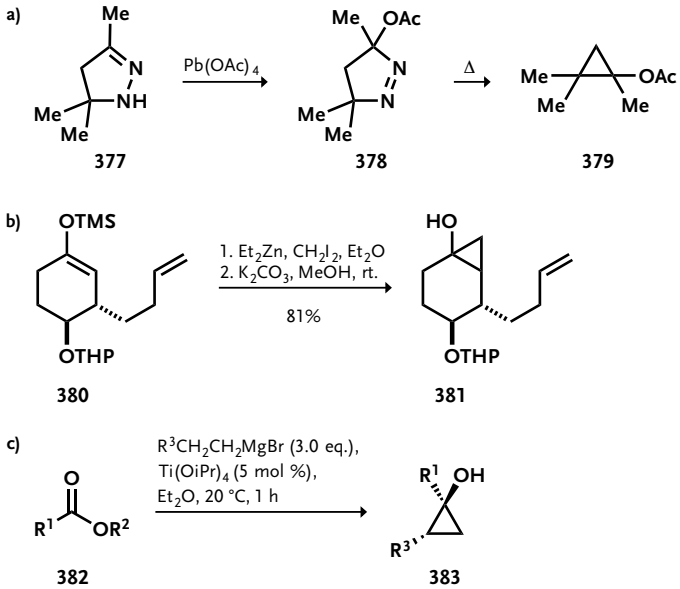


Scheme 3-21. **a)** Synthesis of cyclopropane 1,1-dicarboxylic acid.[246] **b)** Asymmetric cyclopropanation using chiral quaternary ammonium salts as the phase-transfer catalyst.[247] **c)** From the synthesis of (±)-bicifadine (Xu, 2006). Ar = *p*-MePh.[248]

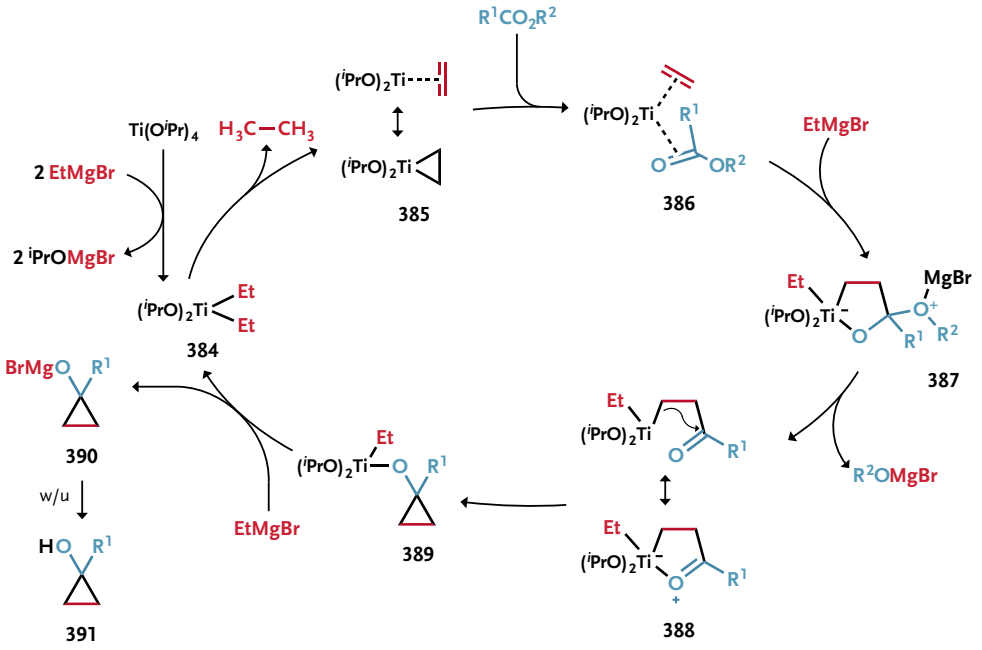
3.2.2.6 Cyclopropanes from 1,1-Carbodications and 1,2-Carbodianions: the Kulinkovich Reaction

An example for the synthesis of cyclopropanes from 1,1-carbodications and 1,2-carbodianions is the recently developed Kulinkovich reaction.[252] The reaction of carboxylic esters with alkylmagnesium bromide in the presence of titanium(IV) isopropoxide smoothly leads to the corresponding cyclopropanols (Scheme 3-22c). A synthesis of cyclopropyl derivatives is also possible *via* the pyrolysis of 3-acetoxy-1-pyrazolines (**378**) which are obtained by the action of lead tetraacetate on 2-pyrazolines (**377**, Scheme 3-22a),[250] or *via* Simmons-Smith cyclopropanation reaction of silyl enol ethers (Scheme 3-22b),[251] but these are not examples for the synthesis of cyclopropanes from 1,1-carbodications and 1,2-carbodianions.

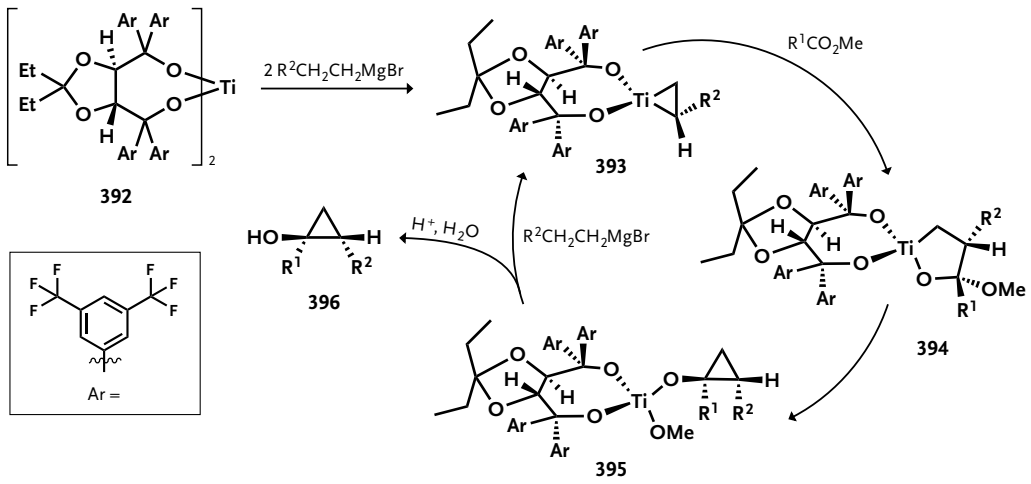
The mechanism of the Kulinkovich reaction is not trivial and is shown in Scheme 3-23.[220] Titanium(IV) isopropoxide is converted into the thermally unstable diethyltitanium intermediate **384** with two equivalents of ethylmagnesium bromide. This intermediate undergoes a β-hydride elimination followed by reductive elimination of ethane and forms titanacyclopropane **385**. This titanacyclopropane acts as a 1,2-dicarbanion equivalent when it reacts with the carboxylic ester and with an additional equivalent of ethylmagnesium bromide the titanacyclopropane-ester complex **386** is transformed into the oxatitanacyclopentane ate-complex **387**. The alkoxy group is eliminated as its magnesium salt, forming intermediate **388**. This undergoes cyclopropane formation and gives titanium cyclopropoxide **389** which undergoes alkylation at the titanium by ethylmagnesium bromide. Thus, the diethyltitanium intermediate is regenerated. The formed magnesium cyclopropoxide **390** is converted into the corresponding cyclopropyl alcohol upon



Scheme 3-22. Reactions for the synthesis of cyclopropanols and derivatives. **a)** Cyclopropyl acetates from the pyrolysis of 3-acetoxy-1-pyrazolines (Freeman, 1963).[250] **b)** Cyclopropanols *via* Simmons-Smith reaction of silyl enol ethers (Iwasawa, 1994).[251] **c)** Cyclopropanols from the reaction of carboxylic esters with alkylmagnesium bromide in the presence of titanium(IV) isopropoxide (Kulinkovich, 1989).[252]



Scheme 3-23. Mechanism of the Kulinkovich reaction.[220]



Scheme 3-24. Catalytic diastereoselective synthesis of *cis*-1,2-disubstituted cyclopropanols from esters.[254]

aqueous acidic work-up. In reactions with higher homologues than ethylmagnesium bromide, the formation of *cis*-1,2-disubstituted cyclopropyl alcohols occurs with high diastereoselectivity (usually 20:1 or higher, *cf.* Scheme 3-22c). The driving force for this high diastereoselectivity is explained by the relief of the steric strain at the titanium atom during the formation of the corresponding cyclopropanolates.[253]

A catalytic diastereoselective synthesis of *cis*-1,2-disubstituted cyclopropyl alchols from esters is also known with a TADDOL-based catalyst, developed by Corey and co-workers (Scheme 3-24).[254]

The Kulinkovich reaction is also known with carboxylic amides instead of esters, the reaction product is a cyclopropyl amine (de Meijere variation).[255] The substrate can also be a nitrile,

the reaction product in this case is again a cyclopropyl amine (Szymoniak variation).[256] Many intramolecular Kulinkovich reactions are known, making this reaction a very versatile tool in synthetic organic chemistry.[257–266]

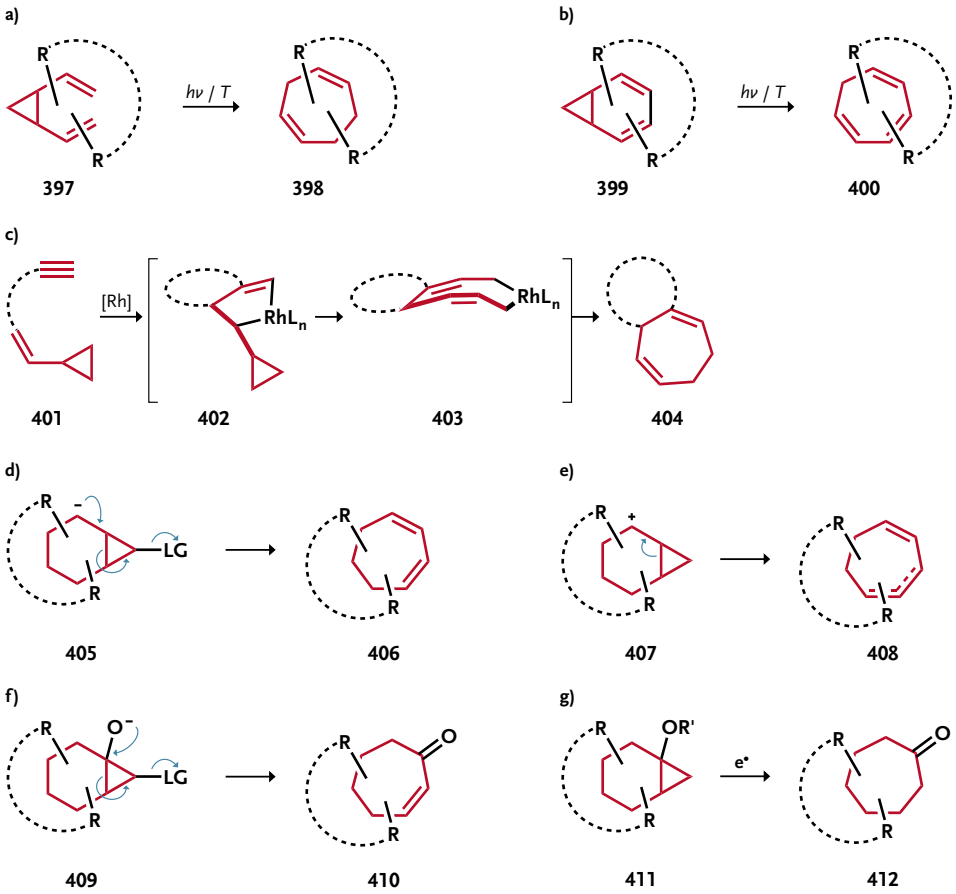
3.3 Cycloheptanes from Cyclopropane Precursors

Cycloheptanes can be synthesized by means of transformation of cyclopropane precursors and this strategy is widely used in the synthesis of natural products (Tab. 3-1).[2] The first person who demonstrably used a cyclopropane containing structure for the synthesis of a cycloheptane in a total synthesis was W. v. E. Doering in 1950.[267] A benzene solution of diazomethane was irradiated to furnish the cyclopropane product bicyclo[4.1.0]hepta-2,4-diene. The oxidation with 4% potassium permanganate produced a small amount of material which was identified as α-tropolone (Tab. 3-1, Entry 1). The divinylcyclopropane-cycloheptadiene rearrangement was not yet fully described at this time, but this synthesis used a special variant of the divinylcyclopropane-cycloheptadiene rearrangement: the Buchner ring expansion reaction which was already known since 1885.[268,269] The first application of the divinylcyclopropane-cycloheptadiene rearrangement in total synthesis was almost 20 years later; G. Ohloff used the rearrangement for the synthesis of (±)-dictyopterene C in 1969.[186]

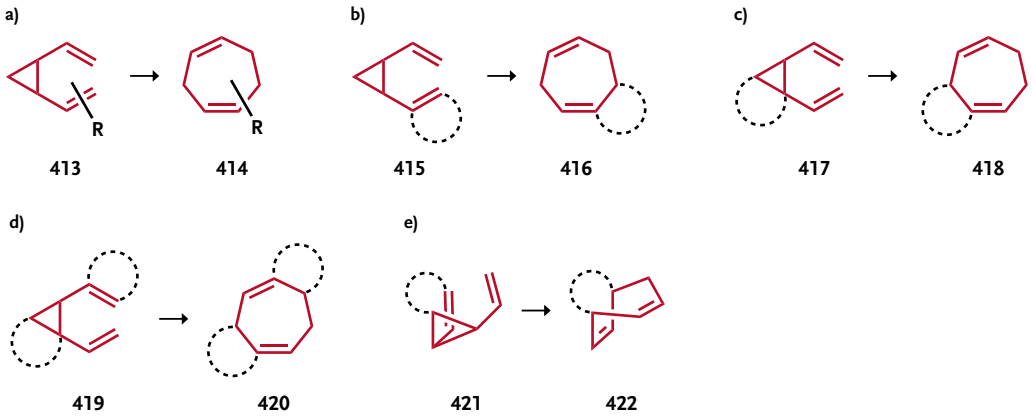
The table lists syntheses of carbocyclic natural compounds with seven-membered rings derived from cyclopropane precursors. The reactions can be divided in groups shown in Scheme 3-25. By far the largest part are cyclization reactions of divinylcyclopropane compounds (Scheme 3-25a, Entries 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 18, 24, 26, 29, 30, 32, 34, 39, 45, 49, 50, 51, 53, 54, 57, 60, and 61). 28 times the seven-membered ring construction occured by this intramolecular cyclization reaction. In addition, five syntheses of carbocyclic natural compounds with the application of the Buchner ring expansion reaction (Scheme 3-25b) are described (Entries 1, 2, 20, 25, and 27).

Due to the large amount of syntheses which used the divinylcyclopropane-cycloheptadiene rearrangement, a more detailed differentiation is taken into account (Scheme 3-26). The most simple outcome is a seven-membered ring with an attached alkyl chain (Scheme 3-26a). This was used in the synthesis of (±)-dictyopterene C (Entry 3, Ohloff, 1969),[186] (±)-ectocarpene (Entry 7, Schneider, 1980),[270] (+)-dictyopterene A and (+)-dictyopterene C' (Entry 11, Genet, 1985),[271] and (–)-dictyopterene C (Entry 12, Jaenicke, 1986).[272] All these natural products belong to a large number of constituents of marine brown algae, some of which exhibit remarkable physiological activities. Overman used the divinylcyclopropane-cycloheptadiene rearrangement for the generation of a monosubstituted cycloheptane in an early stage of the synthesis of (–)-scopadulcic acid A (Entry 26, 1999).[273] The same is true for the synthesis of 5-*epi*-vibsanin E (Entry 51, Williams, 2009).[274] Most often, the divinylcyclopropane-cycloheptadiene rearrangement is used for the synthesis of monoannulated cycloheptanes (Scheme 3-26b and Scheme 3-26c): synthesis

[2] Although the list in Tab. 3-1 is quite comprehensive, the author makes no claim to completeness.



Scheme 3-25. General strategies for the conversion of cyclopropane ring containing structures into cycloheptanes. **a)** *Via* divinylcyclopropane rearrangement. **b)** *Via* Buchner ring expansion reaction, a special case of the divinylcyclopropane rearrangement. **c)** *Via* [5+2] cycloaddition reaction. **d)** *Via* cyclopropyl activated precursors (i). **e)** *Via* cyclopropylcarbinyl activated precursors (i). **f)** *Via* cyclopropyl activated precursors (ii). **g)** *Via* cyclopropylcarbinyl activated precursors (ii). LG = leaving group.



Scheme 3-26. Different strategies for the use of the divinylcyclopropane rearrangement for the generation of different cycloheptane motifs. **a)** Monosubstituted cycloheptane. **b)** Monoannulated cycloheptane (alkene in ring). **c)** Monoannulated cycloheptane (cyclopropane in ring). **d)** Bisannulated cycloheptane. **e)** Bridged cycloheptane.

of (±)-damsinic acid (Entry 5, Wender, 1979),[275] (±)-β-himachalene (Entry 9, Piers, 1983),[276] phorbol related compounds (Entry 15, Wender, 1988),[277] (±)-tremulenolide A (Entry 24, Davies, 1998),[278] cyathin releated compound (Entry 30, Takeda, 2000),[279] (+)-frondosin B (Entry 45, Davies, 2008),[280] cyathane related compound (Entry 49, Sarpong, 2009),[281] guianolide related compound (Entry 50, Donaldson, 2009),[282] (±)-actinophyllic acid related compound (Entry 53, Wood, 2009),[154] (–)-bakerol (Entry 54, Sarpong, 2010),[283] and (+)-schisanwilsonene A (Entry 60, Echavarren, 2013).[284] There is only one example of the generation of a bisannulated cycloheptane (Scheme 3-26d) which was accomplished by Wender in the synthesis of a tigliane related compound (Entry 6, 1980).[285] The most advanced application of the divinylcyclopropane-cycloheptadiene rearrangement is for the generation of bridged cycloheptanes (Scheme 3-26e). The rearrangement provides a simple entry to more or less complex bridged structures and was applied in the synthesis of (±)-quadrone (Entry 10, Piers, 1985),[286] (±)-prezizaene (Entry 13, Piers, 1987),[287] sinularene (Entry 14, Piers, 1987),[288] tropane related compound (Entry 18, Davies, 1992),[289] (±)-isostemofoline (Entry 29, Kende, 1999),[290] (+)-gelsemine (Entry 32, Fukuyama, 2000, and Entry 34, Danishefsky, 2002),[291–293] (±)-clavubicyclone (Entry 39, Iguchi, 2006),[294,295] gelsemoxonine (Entry 57, Fukuyama, 2011),[296] and gelsenicine (Entry 61, Ferreira, 2015).[297]

The [5+2] cycloaddition reaction of vinylcyclopropanes and alkynes, as well as the divinylcyclopropane-cycloheptadiene rearrangement, affords 1,4-cycloheptadiene derivatives (Scheme 3-25c). This strategy for the construction of seven-membered rings has also been applied efficiently in the total synthesis of natural products. Pioneered by Wender, this reaction was also used and extended by other groups (Entries 28, 31, 33, 37, 43, and 44).

Other methodologies are the use of cyclopropyl activated precursors (Scheme 3-25d: Entries 4, 19, 42, 47, and 48; Scheme 3-25f: Entries 46 and 56) and cyclopropylcarbinyl activated precursors (Scheme 3-25e: Entries 8, 17, 22, 23, 52, 55, and 59; Scheme 3-25g: Entries 21, 35, 36, 38, and 58). In all four cases the formation of the seven-membered ring occurs *via* cyclohexane ring expansion reactions and not *via de novo* ring formation reactions like in the divinylcyclopropane-cycloheptadiene rearrangement or the [5+2] cycloaddition reaction.

Theses data indicates that cyclopropanes are widely used for the construction of seven-membered rings. Among all presented methodologies, the construction is mostly effected by intramolecular cyclization reactions and [5+2] cycloaddition reactions. Disconnections of carbon–carbon and carbon–heteroatom double bonds should be considered as strategic for retrosynthetic analysis.

Table 3-1. Examples for the synthesis of cycloheptane ring containing structures from cyclopropane precursors in total synthesis (1950–2015).

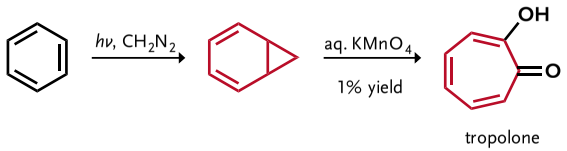
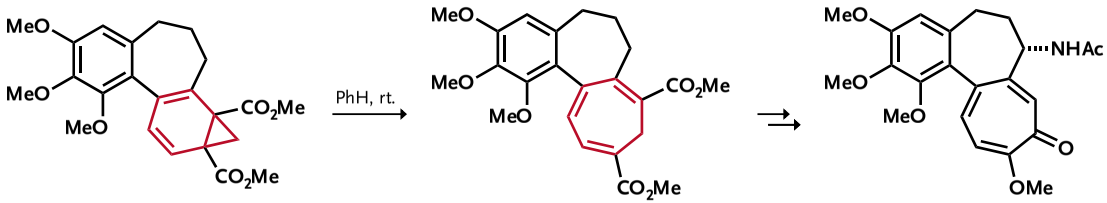
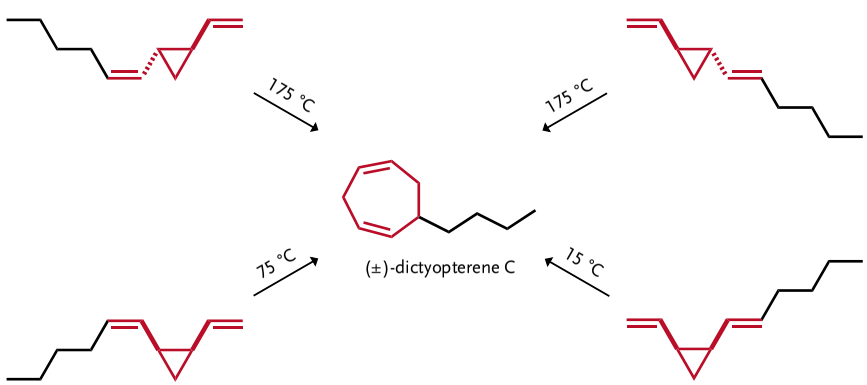
N°	Group (Year)	Transformation
1	Doering (1950)[267]	 tropolone
2	Eschenmoser (1959)[298]	 (±)-colchicine
3	Ohloff (1969)[186]	 (±)-dictyopterene C

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Table 3-1. *(continued)*

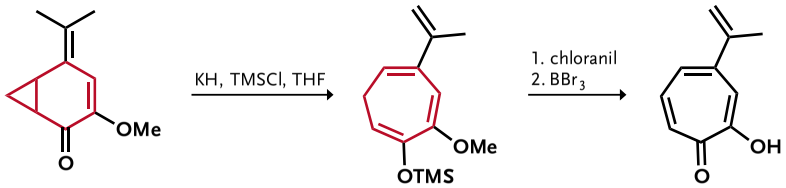
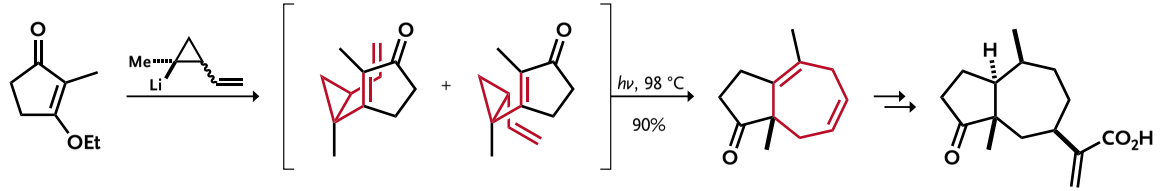
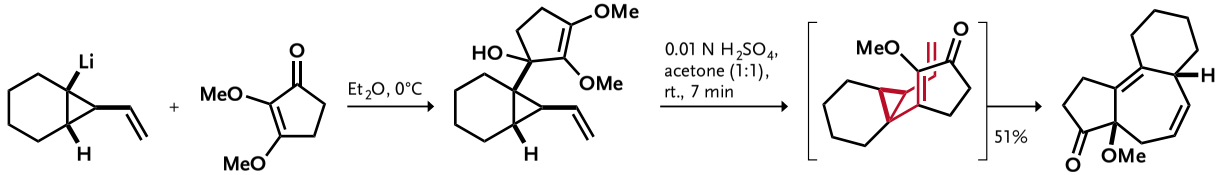
No	Group (Year)	Transformation
4	Evans (1978)[299]	 β-dolabrin
5	Wender (1979)[275]	 (±)-damsinic acid
6	Wender (1980)[285]	 tigliane related compound

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Table 3-1. *(continued)*

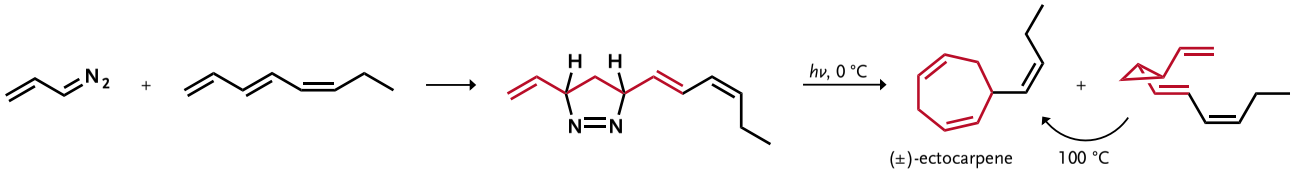
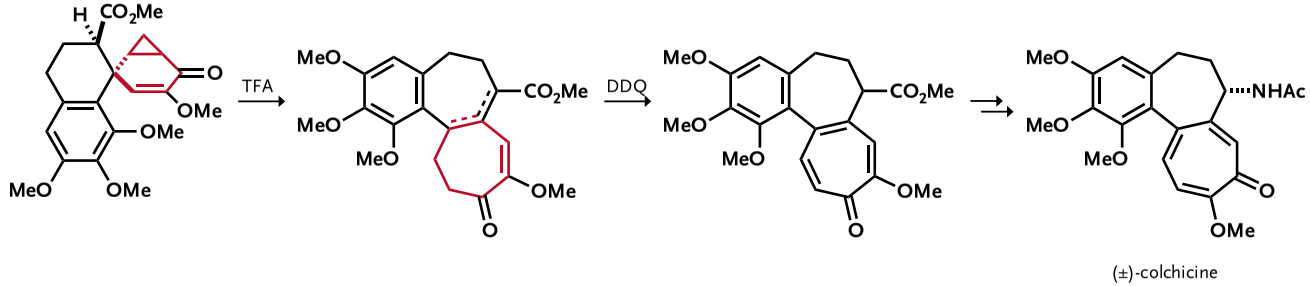
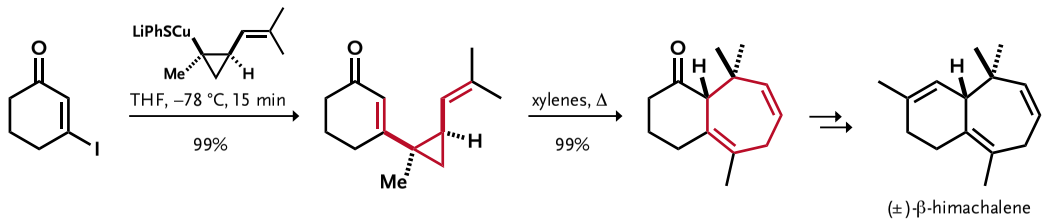
N°	Group (Year)	Transformation
7	Schneider (1980)[270]	
8	Evans (1981)[299,300]	
9	Piers (1983)[276]	

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Table 3-1. *(continued)*

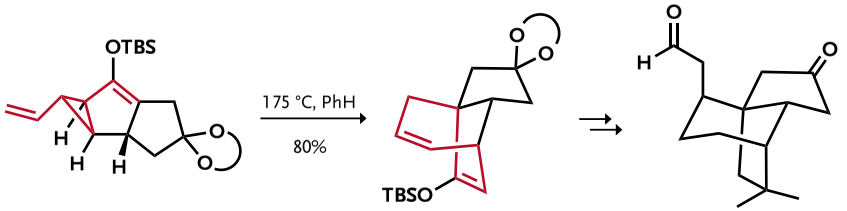
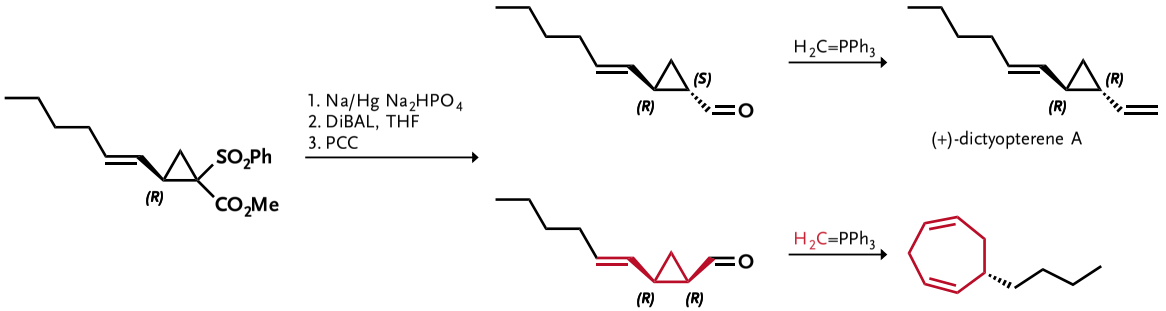
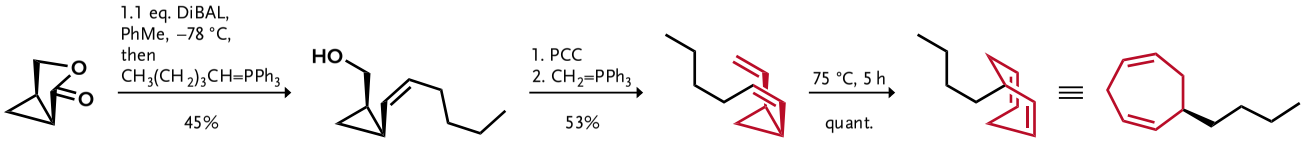
No	Group (Year)	Transformation
10	Piers (1985)[286]	 (±)-quadrone
11	Genet (1985)[271]	 (+)-dictyopterene A; (+)-dictyopterene C'
12	Jaenicke (1986)[272]	 (–)-dictyopterene C

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Table 3-1. *(continued)*

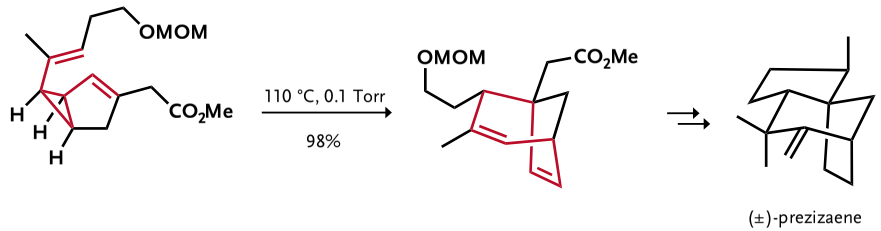
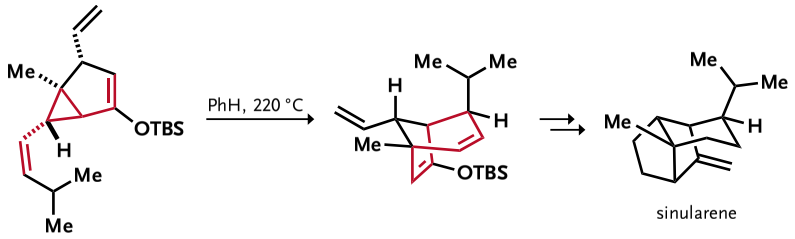
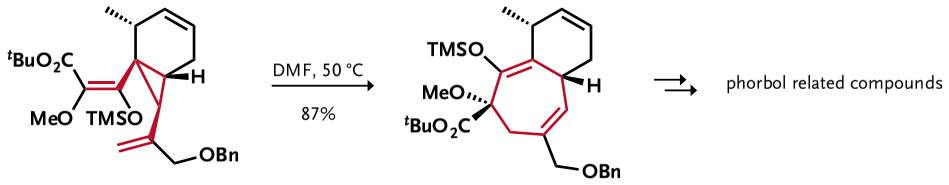
N°	Group (Year)	Transformation
13	Piers (1987)[287]	
14	Piers (1987)[288]	
15	Wender (1988)[277]	

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Table 3-1. *(continued)*

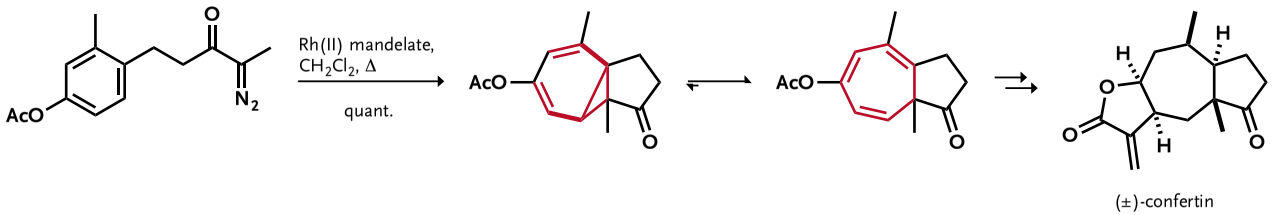
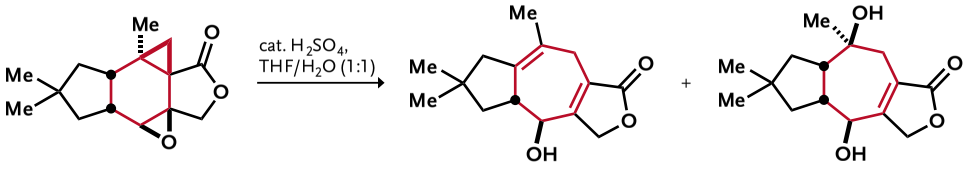
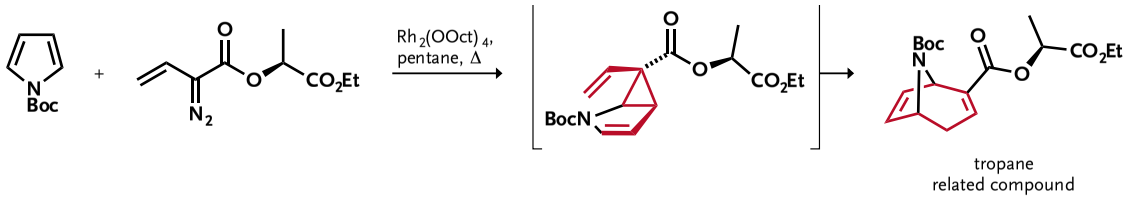
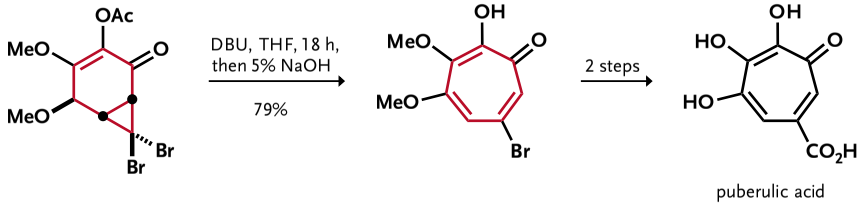
№	Group (Year)	Transformation
16	McKervey (1991)[301]	
17	Heathcock (1992)[302]	
18	Davies (1992)[289]	
19	Banwell (1993)[303]	

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Table 3-1. *(continued)*

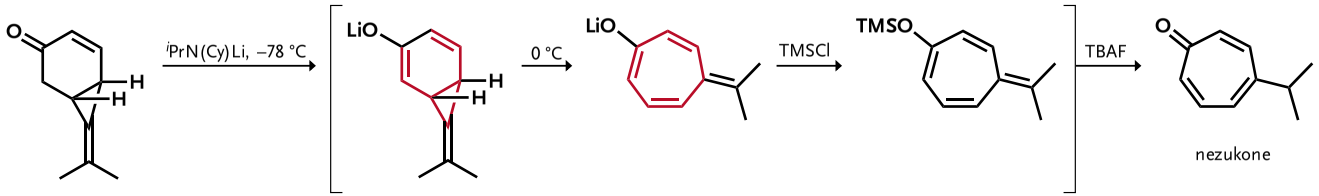
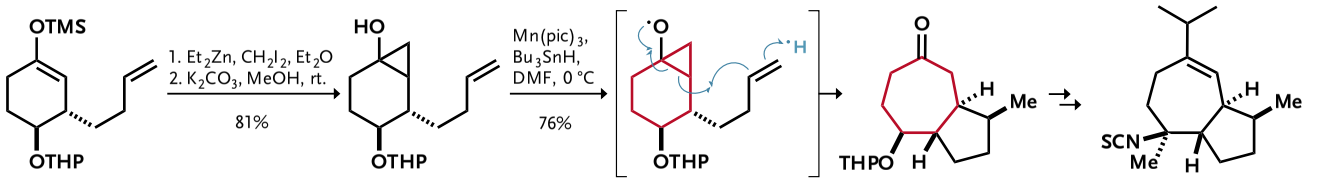
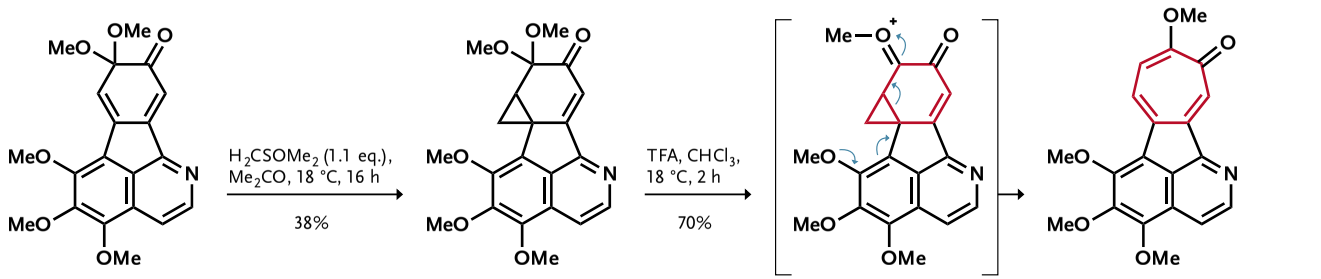
N°	Group (Year)	Transformation
20	Banwell (1993)[304]	 nezukone
21	Iwasawa (1994)[251]	 10-isothiocyanatoguaia-6-ene
22	Banwell (1994)[305]	 imerubrine

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Table 3-1. *(continued)*

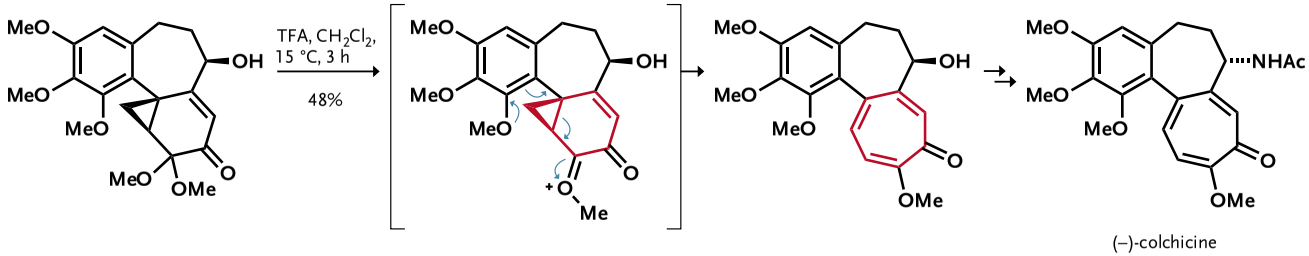
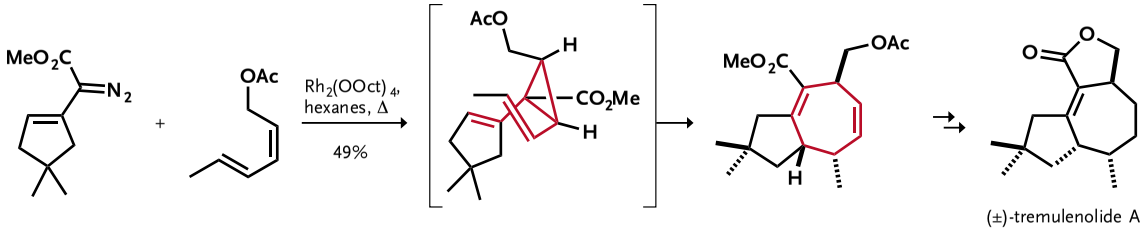
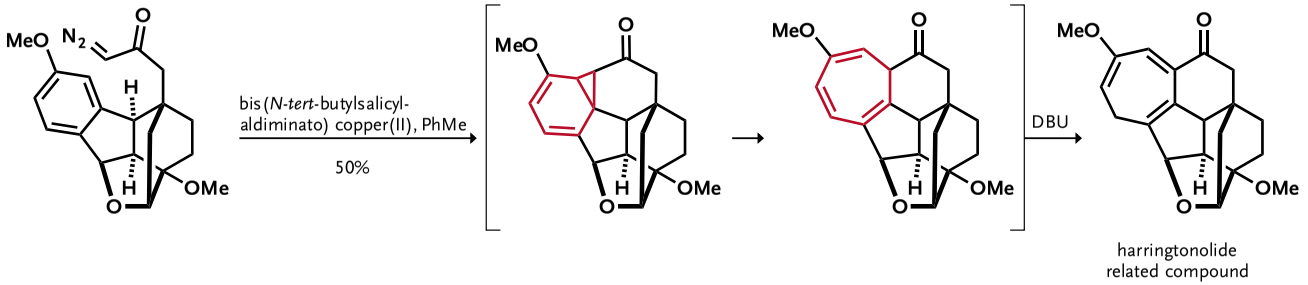
No	Group (Year)	Transformation
23	Banwell (1996)[306]	 (–)-colchicine
24	Davies (1998)[278]	 (±)-tremulenolide A
25	Mander (1998)[307,308]	 harringtonolide related compound

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Table 3-1. *(continued)*

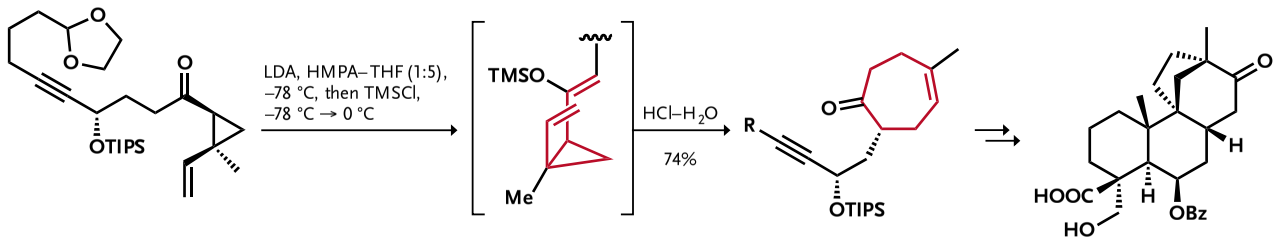
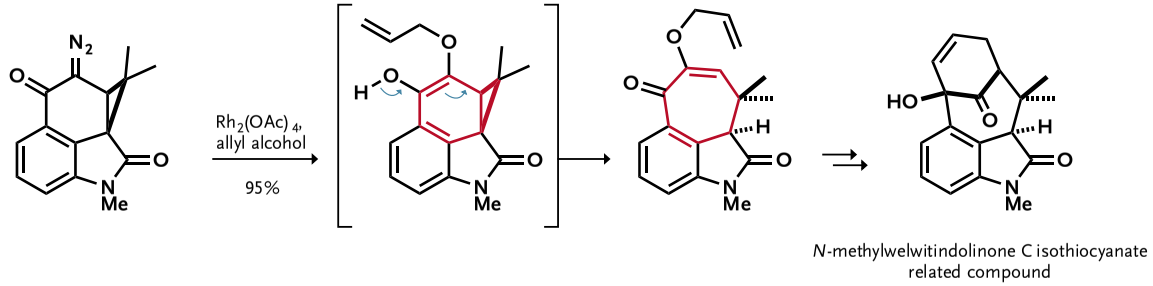
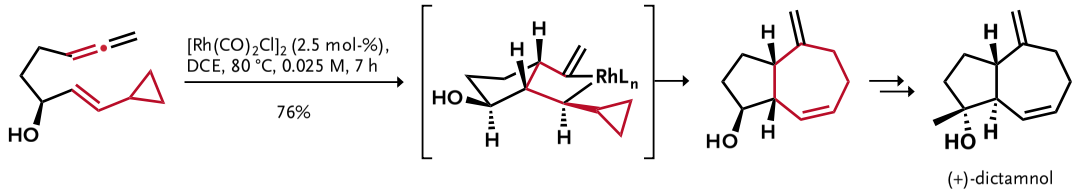
N°	Group (Year)	Transformation
26	Overman (1999)[273]	
27	Wood (1999)[309,310]	
28	Wender (1999)[311]	

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Table 3-1. *(continued)*

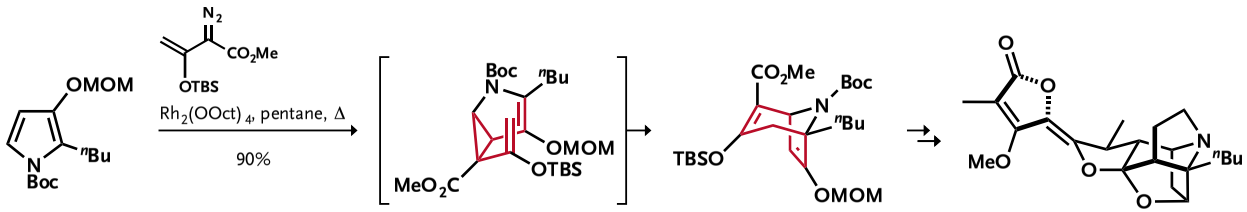
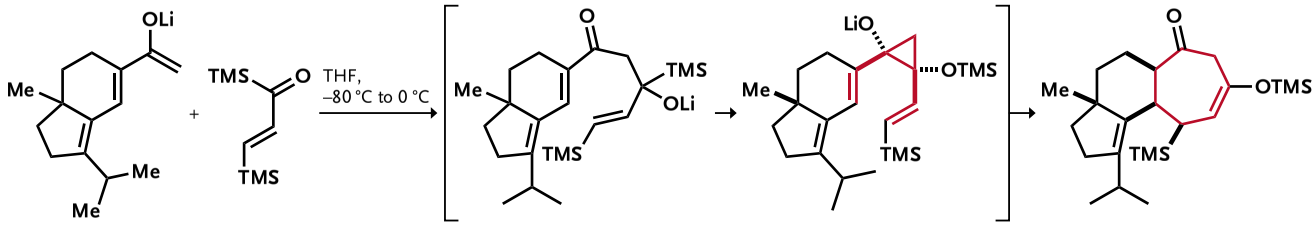
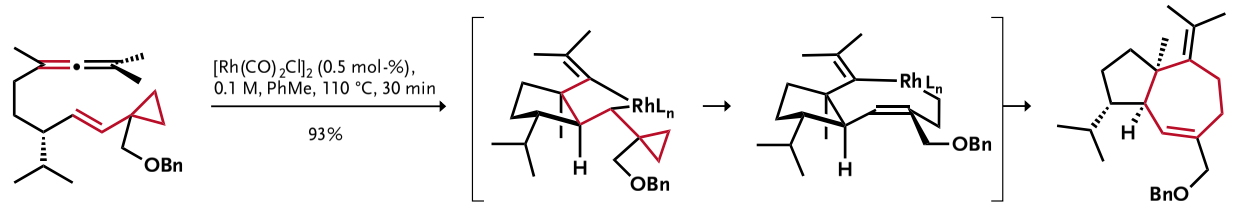
№	Group (Year)	Transformation
29	Kende (1999)[290]	 (±)-isostemofoline
30	Takeda (2000)[279]	 cyathin related compound
31	Wender (2000)[312]	 (+)-aphanamol I related compound

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Table 3-1. *(continued)*

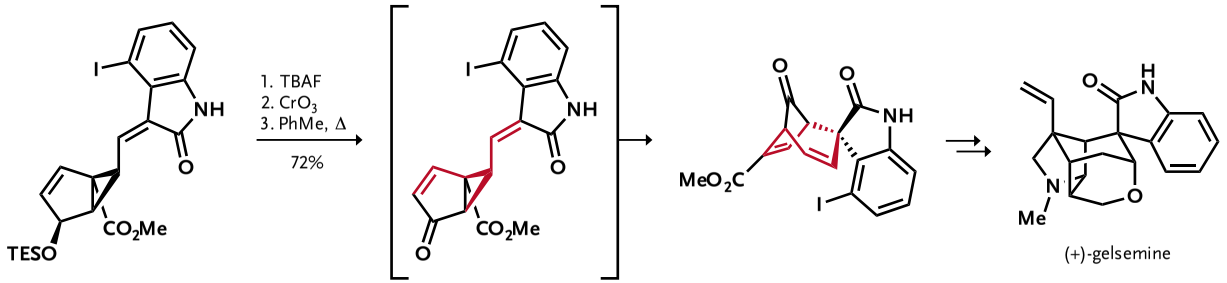
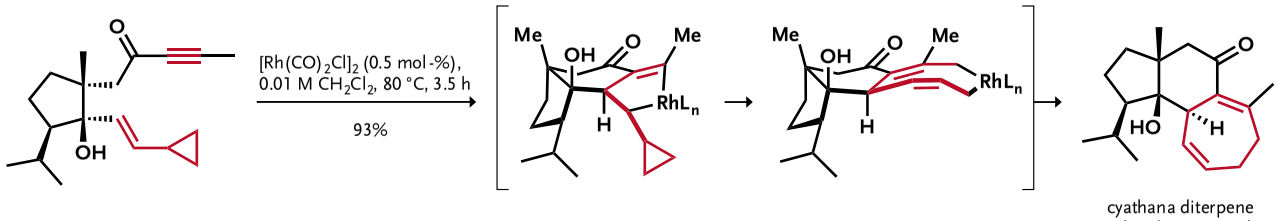
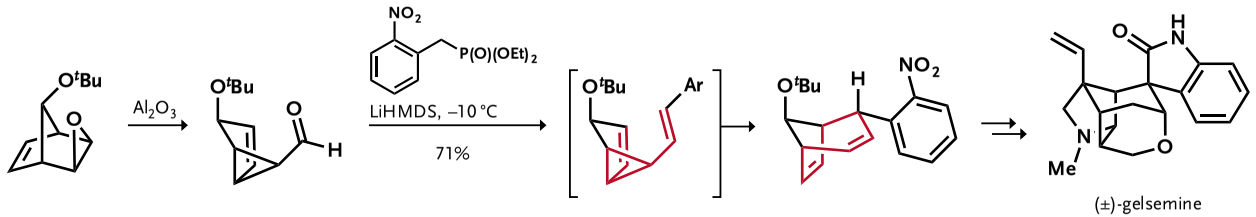
N°	Group (Year)	Transformation
32	Fukuyama (2000)[291]	
33	Wender (2001)[312]	
34	Danishefsky (2002)[292,293]	

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Table 3-1. *(continued)*

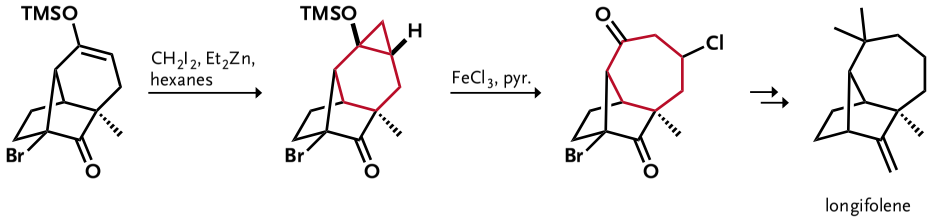
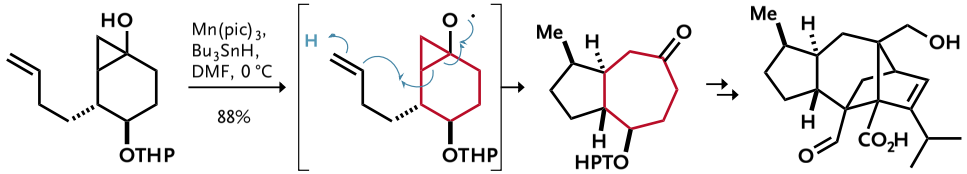
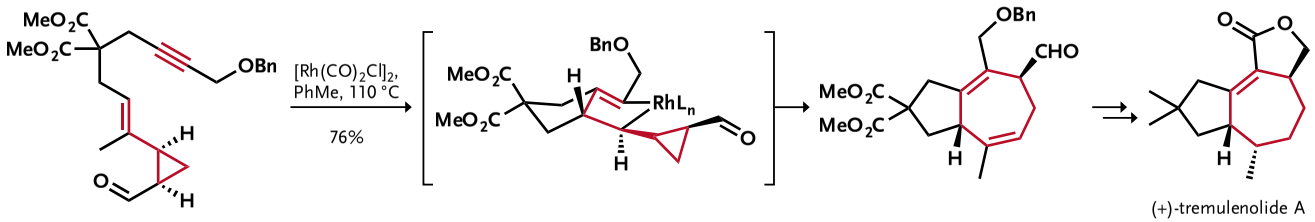
N°	Group (Year)	Transformation
35	Karimi (2003)[313]	 longifolene
36	Narasaka (2004)[314]	 (±)-sordaricin
37	Martin (2005)[315,316]	 (+)-tremulenolide A

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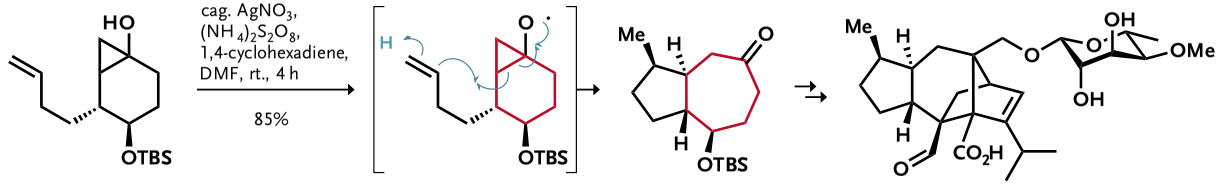
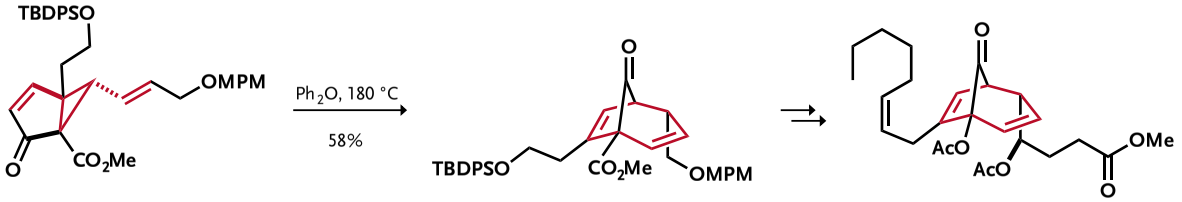
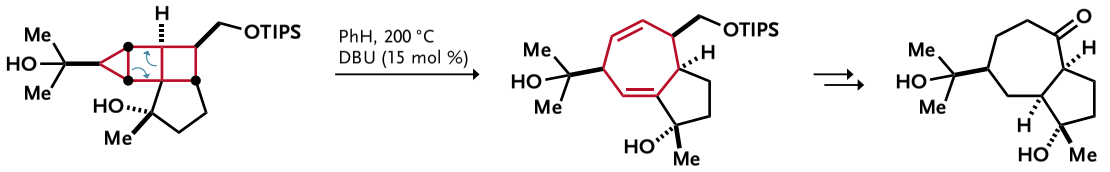
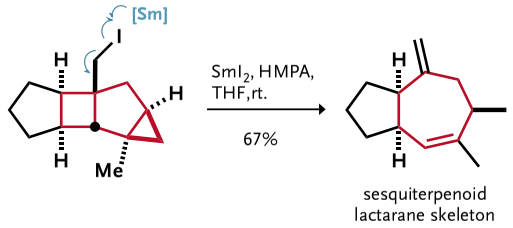
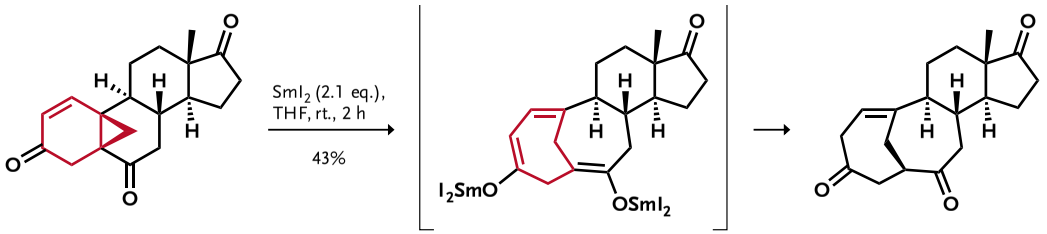
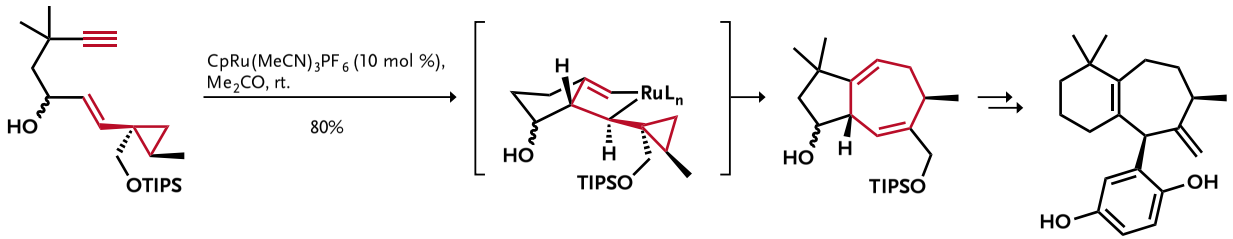
Table 3-1. *(continued)*

N°	Group (Year)	Transformation
38	Narasaka (2006)[317]	 (±)-sordarin
39	Iguchi (2006)[294,295]	 (±)-clavubicyclone
40	Snapper (2007)[318]	 (±)-pleocarpenone

(continued on next page...)

Table 3-1. *(continued)*

No	Group (Year)	Transformation
41	Lange (2007)[319]	 sesquiterpenoid lactarane skeleton
42	Schmalz (2007)[320]	 cyclocitrinol related compound
43	Trost (2007)[321]	 (+)-frondosin A

(continued on next page...)

Table 3-1. *(continued)*

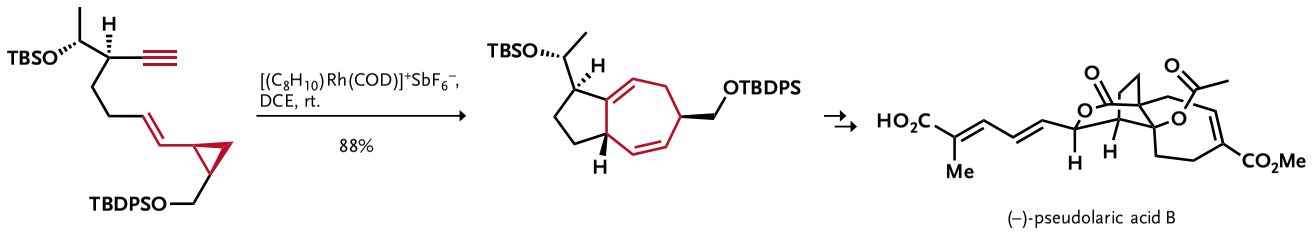
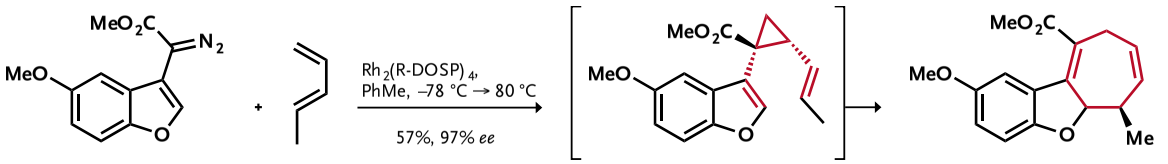
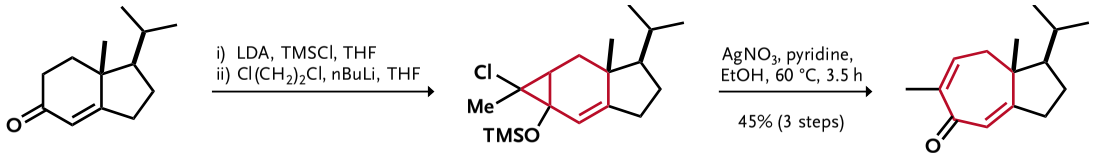
N°	Group (Year)	Transformation
44	Trost (2007)[322,323]	 (–)-pseudolaric acid B
45	Davies (2008)[280]	 (+)-frondosin B related compound
46	Danishefsky (2008)[324]	 tricholomalide A related compound

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Table 3-1. *(continued)*

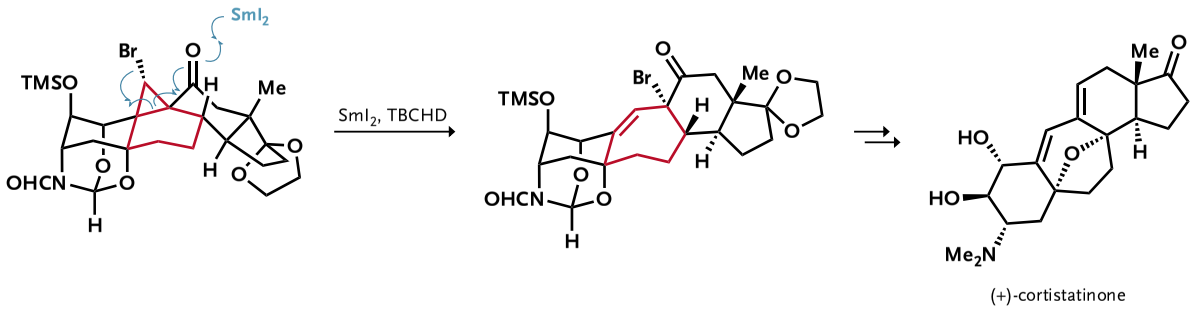
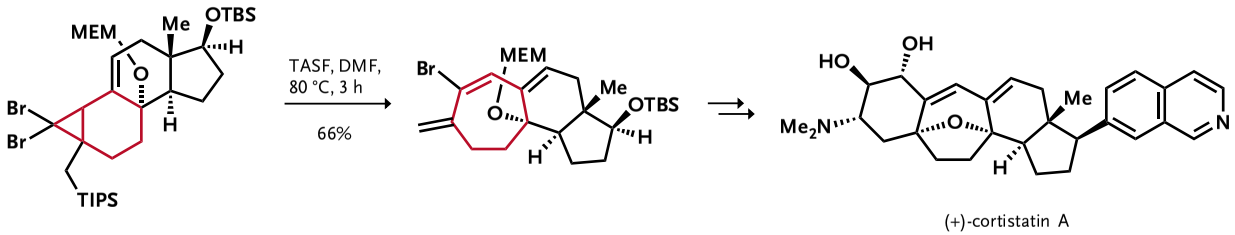
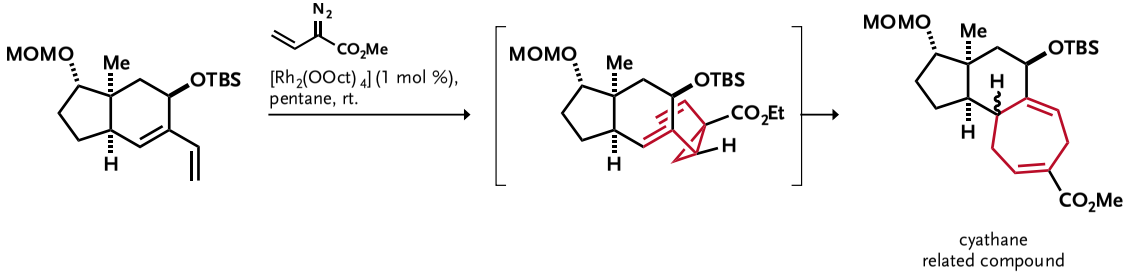
N°	Group (Year)	Transformation
47	Baran (2008)[325,326]	 (+)-cortistatinone
48	Shair (2008)[327]	 (+)-cortistatin A
49	Sarpong (2009)[281]	 cyathane related compound

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Table 3-1. *(continued)*

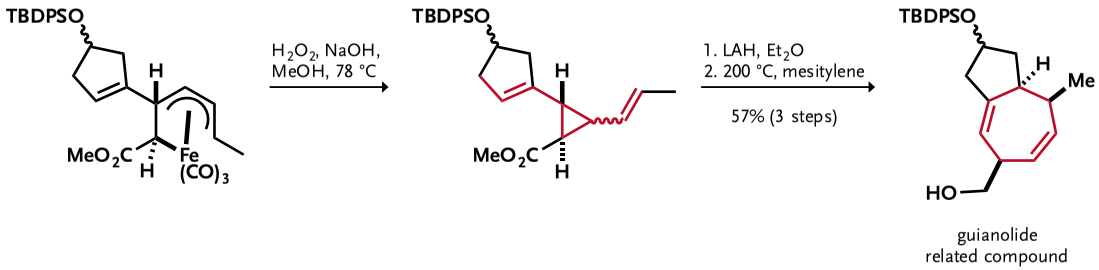
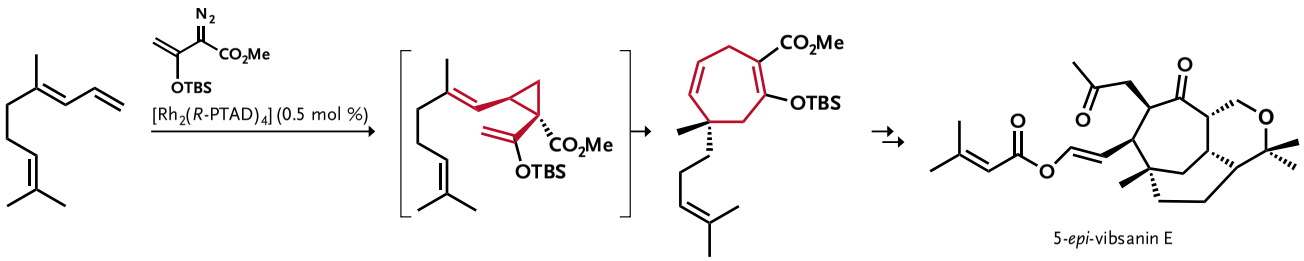
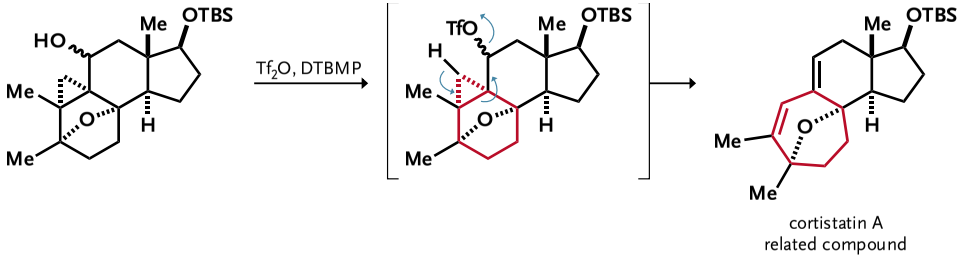
N°	Group (Year)	Transformation
50	Donaldson (2009)[282]	
51	Williams (2009)[274]	
52	Magnus (2009)[328]	

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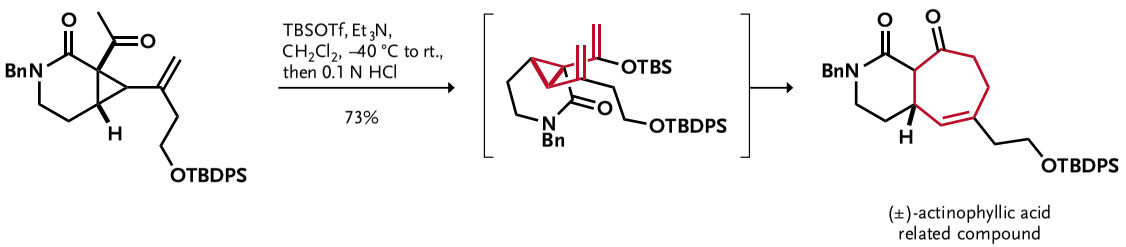
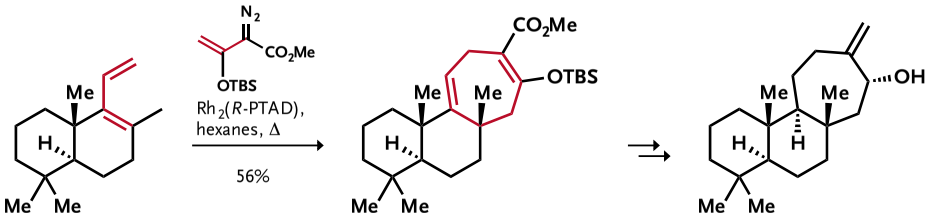
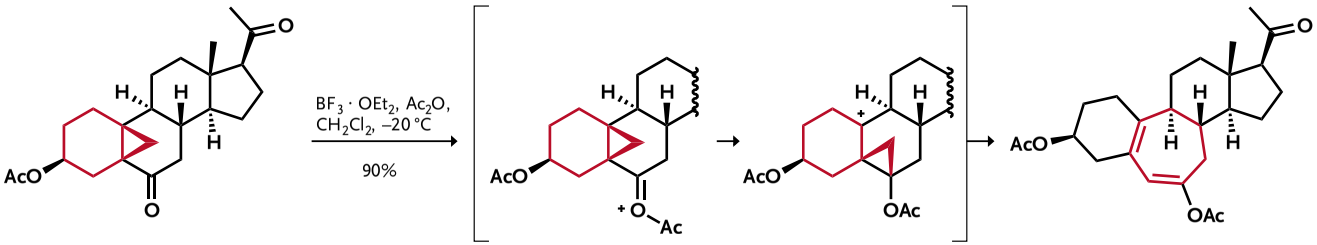
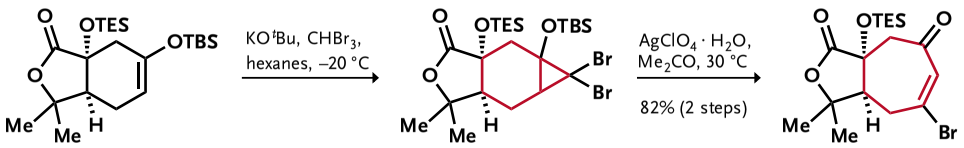
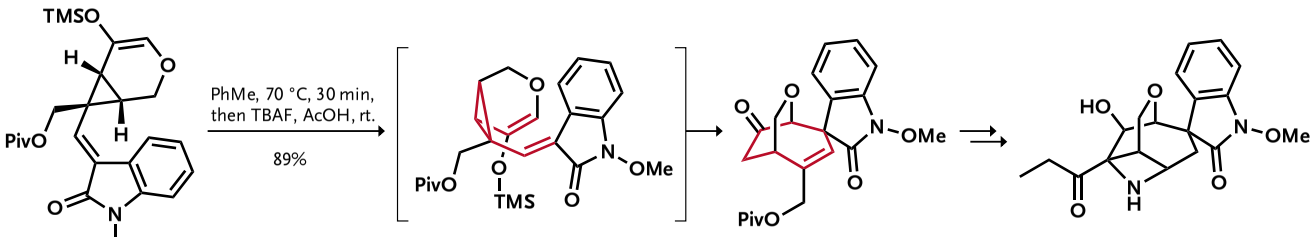
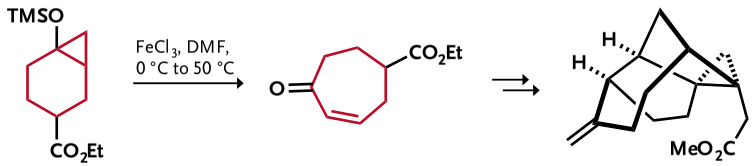
Table 3-1. *(continued)*

№	Group (Year)	Transformation
53	Wood (2009)[154]	 (±)-actinophyllic acid related compound
54	Sarpong (2010)[283]	 (–)-barekol
55	Schmalz (2011)[329]	 19-*nor*-B-*homo* steroid

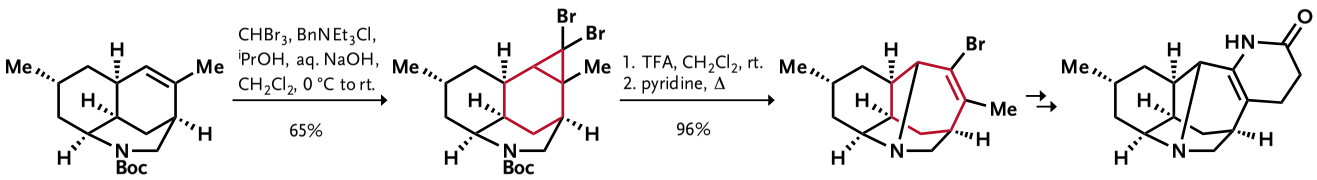
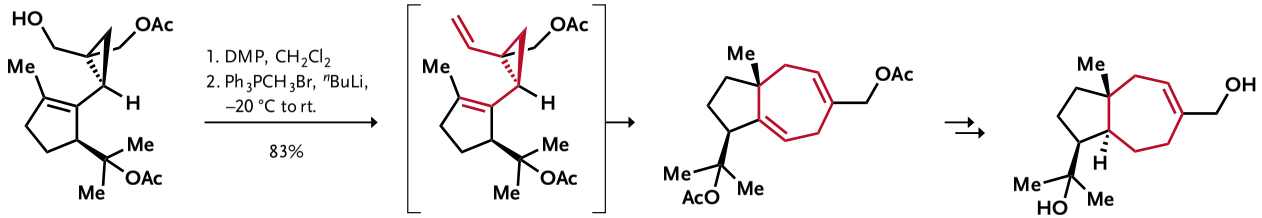
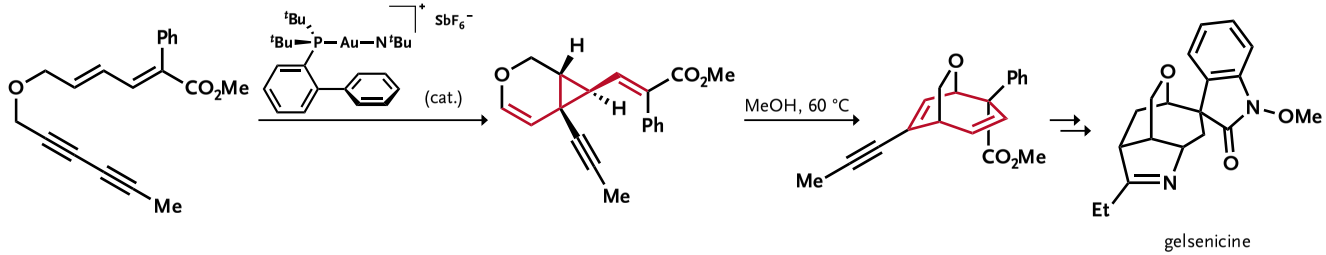
(continued on next page...)

Table 3-1. *(continued)*

N°	Group (Year)	Transformation
56	Yang (2011)[330]	 (±)-schindilactone A realated compound
57	Fukuyama (2011)[296]	 gelsemoxonine
58	Vanderwal (2012)[331]	 echinopine B

(continued on next page...)

Table 3-1. *(continued)*

№	Group (Year)	Transformation
59	Fukuyama (2013)[332]	 lyconadin A
60	Echavarren (2013)[284]	 (+)-schisanwilsonene A
61	Ferreira (2015)[297]	 gelsenicine

Ervatamia Alkaloids

4

4.1 General

A large group of alkaloids with a cyclohepta[*b*]indole skeleton are the ervitsine–ervatamine alkaloids (Fig. 4-1). The following text about this alkaloids in this Section 4.1 is merely a recap, for additional general information see Section 2.2.1, for total syntheses of *Ervatamia* alkaloids the author refers to Section 2.4.1.

Ervatamine (**43**) is the main alkaloid of the *Ervatamia* alkaloids which are corynanthean-type 2-acylindole alkaloids, but the side chain from the indole C-2 positions contains three linearly disposed carbon atoms and therefore lacks the characteristic tryptamine moiety.[57] Compound **43** was isolated from *Ervatamia orientalis* and *Ervatamia lifuana* (Apocynaceae),[58,59] and is a sodium channel blocker in nerve fibers and a local anesthetic blocker.[38] From the same sources 20-epiervatamine (**44**) and 19,20-didehydroervatamine (**52**) have been isolated.[58,59]

19,20-didehydro-N^1-methoxyervatamine (**53**) is an alkaloid from *Ervatamia malaccensis* (Apocynaceae),[60] 19,20-didehydro-5-oxoervatamine (**54**) has been isolated from leaves of *Tabernaemontana corymbosa* (Apocynaceae),[61] 19,20 didehydro-6α-hydroxyervatamine (**55**) and dehydroxyervataminol (**62**) are alkaloids from *Ervatamia divaricate*.[62]

Decarboxylation of the ester at C-16 leads to the series of the methuenine–silicine alkaloids. Methuenine (**56**) is an alkaloid from *Ervatamia officinalis*, *Hazunta* spp., *Pterotaberna inconspicua*, and can also be isolated from the leaves and stem bark of *Ervatamia malaccensis*. It is an anticholinergic agent.[60,63–66] Also known is its 16-epimer (**57**),[60,65,67,68] its *N*-oxide (**58**),[65] its 16-epimer-*N*-oxide (**60**),[67] the 6-oxo derivative (**59**),[60,63,65] and the N^1-methoxy derivative (**61**).[60] Silicine (**45**) possesses an ethyl group at C-20 instead of an ethylidene function.[64,69–72]

Furthermore, seven derivatives of silicine (**45**) have been isolated: 16-episilicine (**46**),[73] 20-episilicine (**47**),[63,66] 16,20-episilicine (**48**),[66] 6-oxosilicine (**49**),[63,64,72] 6-oxo-16-episilicine (**50**),[64] 6-oxo-16,20-episilicine (**51**),[66] and 6,16-didehydro-20-episilicine (**63**).[66]

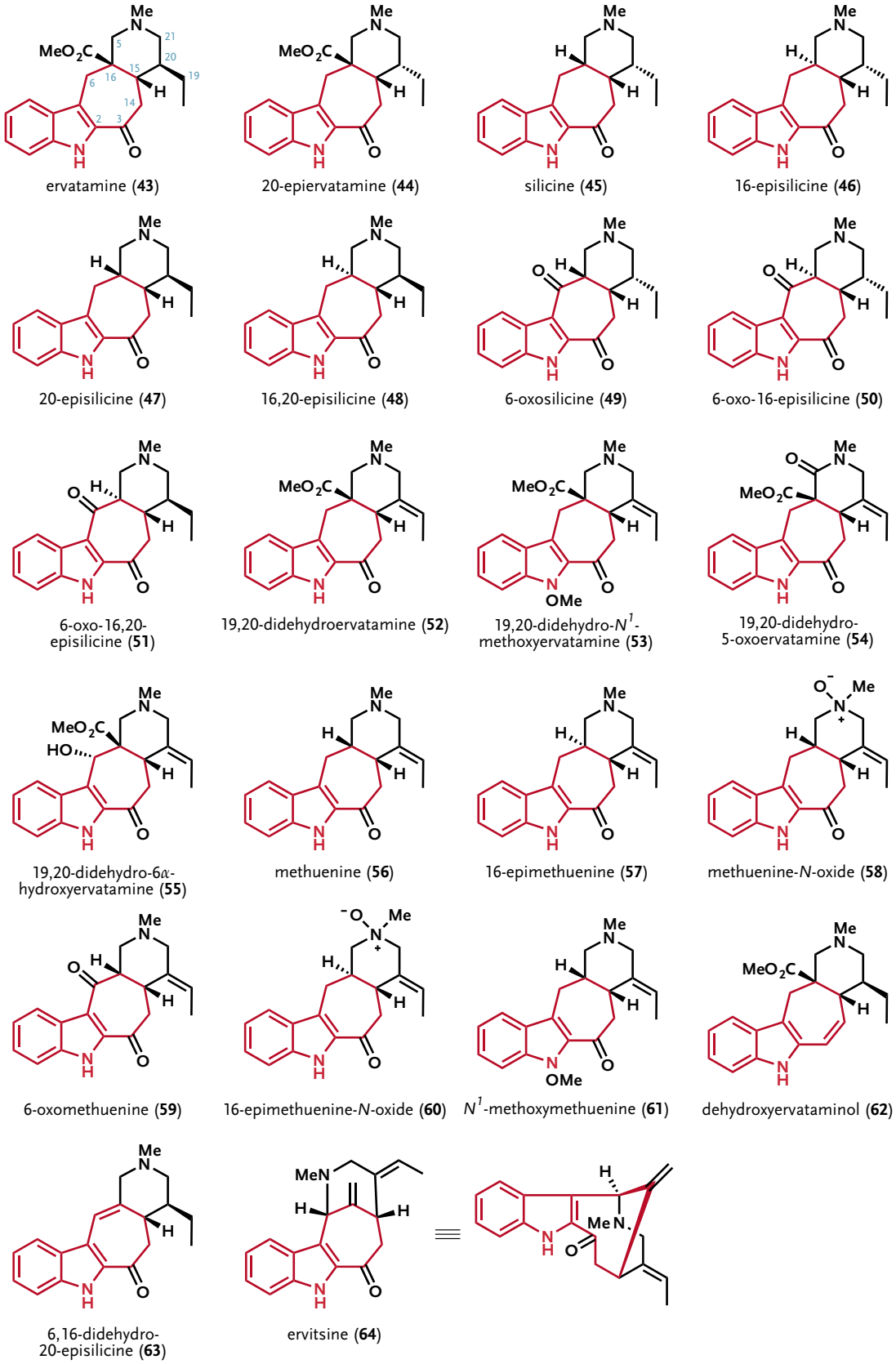


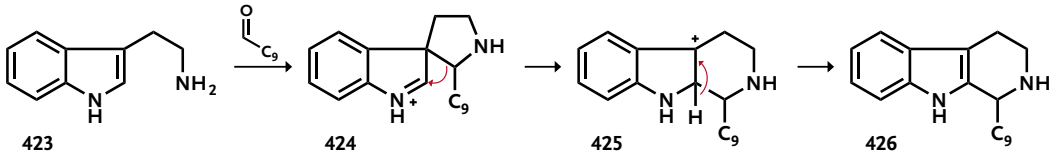
Figure 4-1. Ervitsine–ervatamine alkaloids.

Ervitsine (**64**) is a minor alkaloid from the root bark of *Pandaca boiteaui* (Apocynaceae).[74,75] It is the only member of this alkaloid family which has an additional link between C-5 and the C-7 and is therefore the only bridged alkaloid. Total syntheses of several members of the ervitsine–ervatamine alkaloids have been published (*cf.* Section 2.4.1).[76–78]

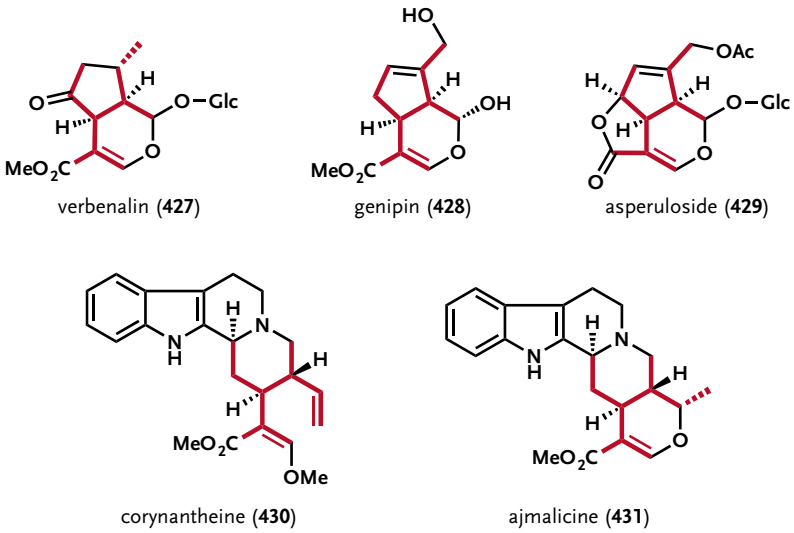
4.2 Monoterpene Indole Alkaloid Biosynthesis

The indole alkaloids comprise a diverse class of naturally occurring organic compounds, possessing the indole or indoline nucleus. Currently, the large and complex group of indole terpene alkaloids comprises over 2000 members and many of them possess biological activities.[333] Some of these alkaloids gained famousness even for average persons, e.g. strychnine, a convulsant poison, or lysergic acid, the diethylamide derivative of which is the powerful psychedelic drug LSD, known for its psychological effects similar to schizophrenia.

The majority of all these alkaloids is formally derived from a Pictet–Spengler reaction with an aliphatic aldehyde having nine or ten carbons (Scheme 4-1). In 1919, Perkin and Robinson were the first who suggested that the aromatic moiety is derived from tryptophan which underwent decarboxylation to tryptamine (**423**).[334] This was proven experimentally by Battersby *et al.*[335] The origin of the C_{10}-unit has been the subject of much speculation for many years.



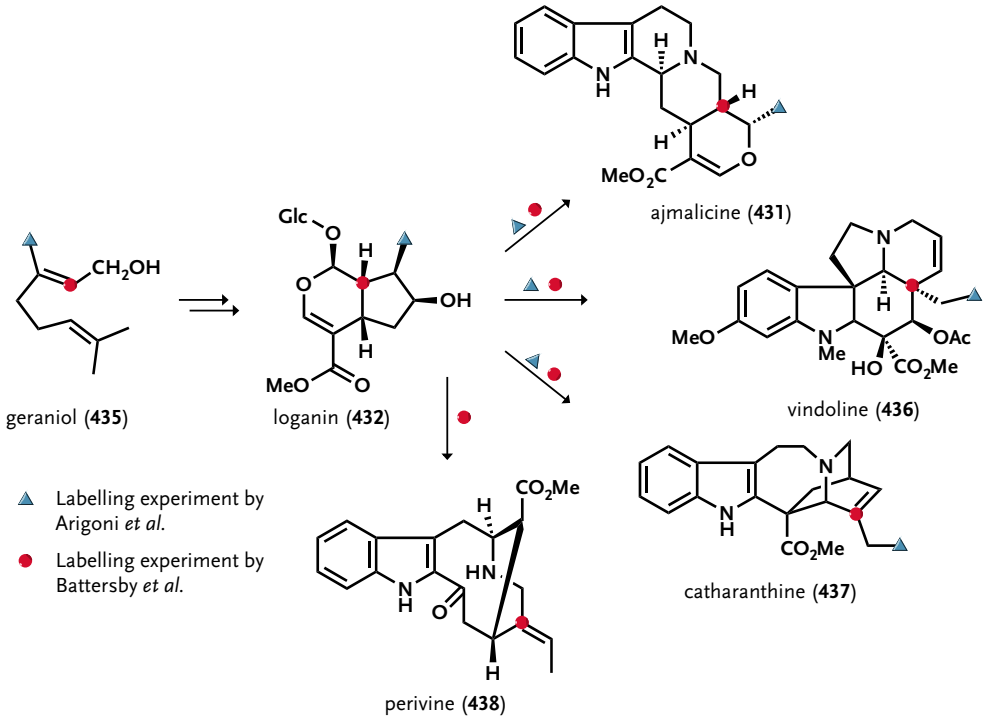
Scheme 4-1. The majority of the indole alkaloids is formally derived from a Pictet–Spengler reaction with an aliphatic aldehyde having nine or ten carbons.



verbenalin (**427**) genipin (**428**) asperuloside (**429**)

corynantheine (**430**) ajmalicine (**431**)

Figure 4-2. Similarity of some non-alkaloidal glycosides and the alkaloids corynantheine (**430**) and ajmalicine (**431**).

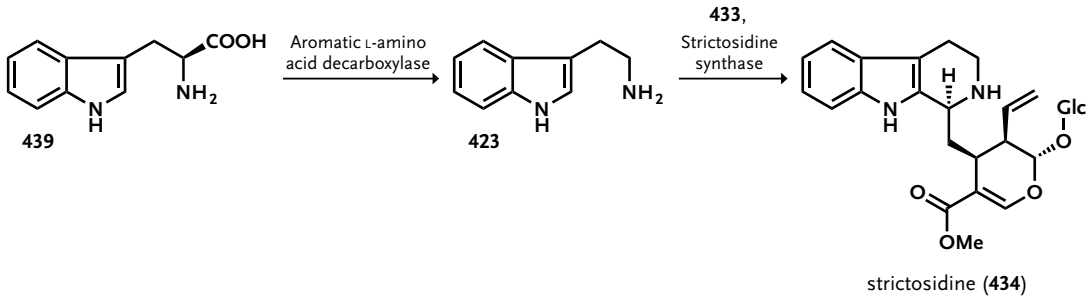


Scheme 4-2. Labelling experiments by Arigoni *et al.* and Battersby *et al.*[339–342]

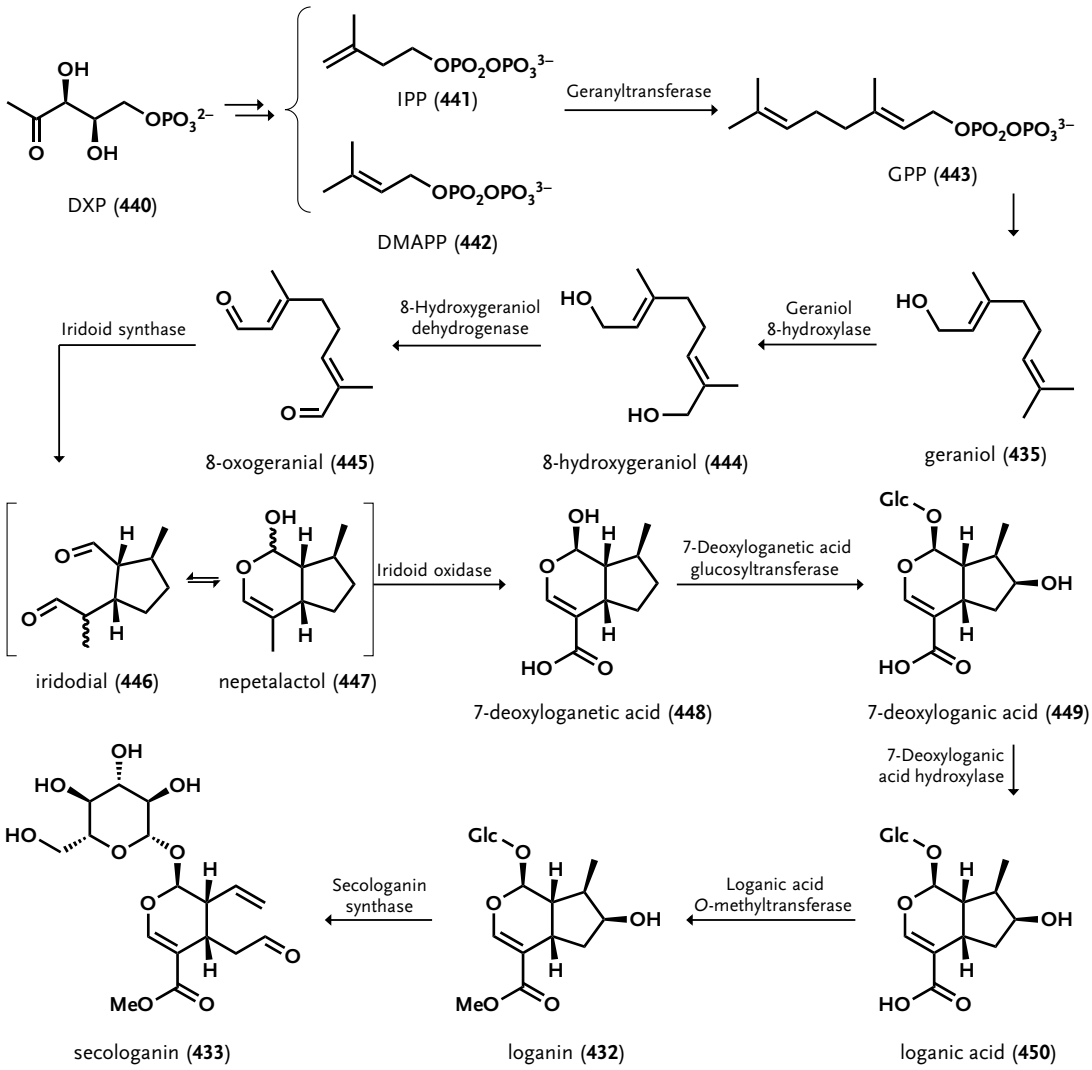
Based on similarities between several non-alkaloidal and non-nitrogenous glucosides such as verbenalin (**427**), genipin (**428**), and asperuloside (**429**) and the non-tryptophan moiety of some alkaloids such as corynantheine (**430**) and ajmalicine (**431**), R. Thomas and E. Wenkert suggested independently that they may have a common precursor (Fig. 4-2) and proposed that this precursor was formed from two mevalonate units.[336,337] In the following years, numerous feeding experiments followed to prove these statements including the incorporation of a mevalonate unit, the incorporation of geraniol derivatives, and the incorporation of iridoids.[57,338] Finally, after the elucidation of the structure of several iridoid terpenes, Arigori *et al.* and Battersby *etal.* independently fed *Vinca rosea* plants with ^{14}C-labeled loganin (**432**) and could observe the incorporation of ring-labelled loganin into a variety of indole alkaloids (Scheme 4-2).[339–342] Loganin (**432**) was thus proved to be a precursor of representative examples from the three major classes of indole alkaloids (*Yohimbe*, *Aspidosperma*, and *Iboga*).[338]

Nowadays it is known, that all terpene indole alkaloids are derived from tryptamine (**423**) and the iridoid terpene secologanin (**433**), forming the alkaloid strictosidine (**434**) by the enzyme Strictosidine synthase (STR, Scheme 4-3). Tryptamine itself arises from the decarboxylation of the amino acid tryptophan, promoted by the Aromatic L-amino acid decarboxylase, a pyridoxal phosphate dependent enzyme.[343,344] Thus, the suggestion of Perkin and Robinson from almost a century ago has been proven true.

Secologanin is a secoiridoid monoterpene synthesized from geranyl pyrophosphate (**443**) which in turn is synthesized from isopentenyl pyrophosphate (**441**) and dimethylallyl pyrophosphate (**442**, Scheme 4-4). Isopentenyl pyrophosphate is produced by either the mevalonate biosyn-



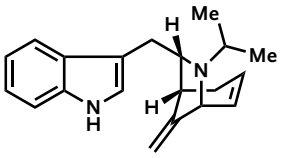
Scheme 4-3. First steps of the biosynthesis of terpene indole alkaloids.



Scheme 4-4. Biosynthesis of secologanin. IPP and DMAPP are synthesized by the non-mevalonate pathway from DXP.

thetic pathway or the triose phosphate/pyruvate pathway ("non-mevalonate pathway").[345,346] In the biosynthesis of secologanin, mevalonate was considered for a long time to be the exclusive precursor of isopentenyl diphosphate, but feeding studies of Contin *et al.* showed, that the non-

mevalonate pathway and not the mevalonate pathway was the major route for the biosynthesis of secologanin.[347] Therefore, isopentenyl pyrophosphate (**441**) derives from 1-deoxy-D-xylulose 5-phosphate (DXP, **440**). The enzyme Geraniol synthase (GES) transforms geranyl pyrophosphate (**443**) into geraniol (**435**)[348] which in turn is transformed into 8-hydroxygeraniol (**444**) by the enzyme Geraniol 8-hydroxylase (G80).[349] 8-Hydroxygeraniol (**444**) is a substrate for 8-Hydroxygeraniol dehydrogenase (8-HGO) which synthesizes 8-oxogeranial (**445**). **445** itself is a substrate for the Iridoid synthase (IS) which synthesizes *cis–trans*-iridodial (**446**) and *cis–trans*-nepetalactol (**447**). Iridodial (**446**) is then transformed into 7-deoxyloganetic acid (**448**) by the enzyme Iridoid oxidase (IO). **448** is a substrate for 7-deoxyloganetic acid glucosyltransferase (7-DLGT) which synthesizes 7-deoxyloganic acid (**449**). **449** is then transformed into loganic acid (**450**) by the enzyme 7-deoxyloganic acid hydroxylase (7-DLH). Loganic acid (**450**) is a substrate for the enzyme loganic acid *O*-methyltransferase (LAMT) for the production of loganin (**432**). Finally, **432** then becomes a substrate for the enzyme secologanin synthase (SLS) to form secologanin (**433**) which is incorporated in the synthesis of strictosidine (**434**), the key intermediate in the biosynthesis of numerous terpene indole alkaloids.[350]



peduncularine (**451**)

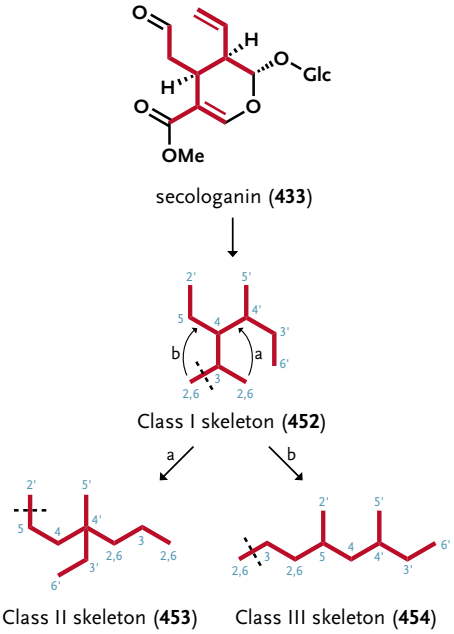
Figure 4-3. Peduncularine.

Plants of the genus *Aristotelia* produce about 30 indole alkaloids, the most important of which is peduncularine. It should be noted, that this indole alkaloids are a rare example for indole alkaloids which contain a monoterpenoid C_{10} part originating not from secologanin. The terpene moiety is divided by the *N*-atom into three (*N*-^{i}Pr) plus seven carbon atoms.[351,352]

4.2.1 Biogenetic Classification of Indole Alkaloids

The terpene indole alkaloids class of natural products comprises over 2000 members and includes a large number of different highly complex structures. The alkaloids can be divided in two units: the tryptophan unit and the non-tryptophan unit. Focussing on the non-tryptophan unit, the alkaloids can be readily assigned to five broad classes.[57,338] Usually, the terpenoid moiety contains ten carbons, but in some alkaloids of these classes only a nine carbon unit is found.

The first class includes alkaloids which contain the skeletal system of secologanin (**433**) in an unrearranged form (**452**, Scheme 4-5). These α- or β-condensation products can be found in several common types of indole alkaloids (Fig. 4-4), e.g. corynantheine (**430**, *Corynanthe* group), ajmalicine (**431**, *Ajmalicine*



Scheme 4-5. Class I, II, and III alkaloid skeletons.

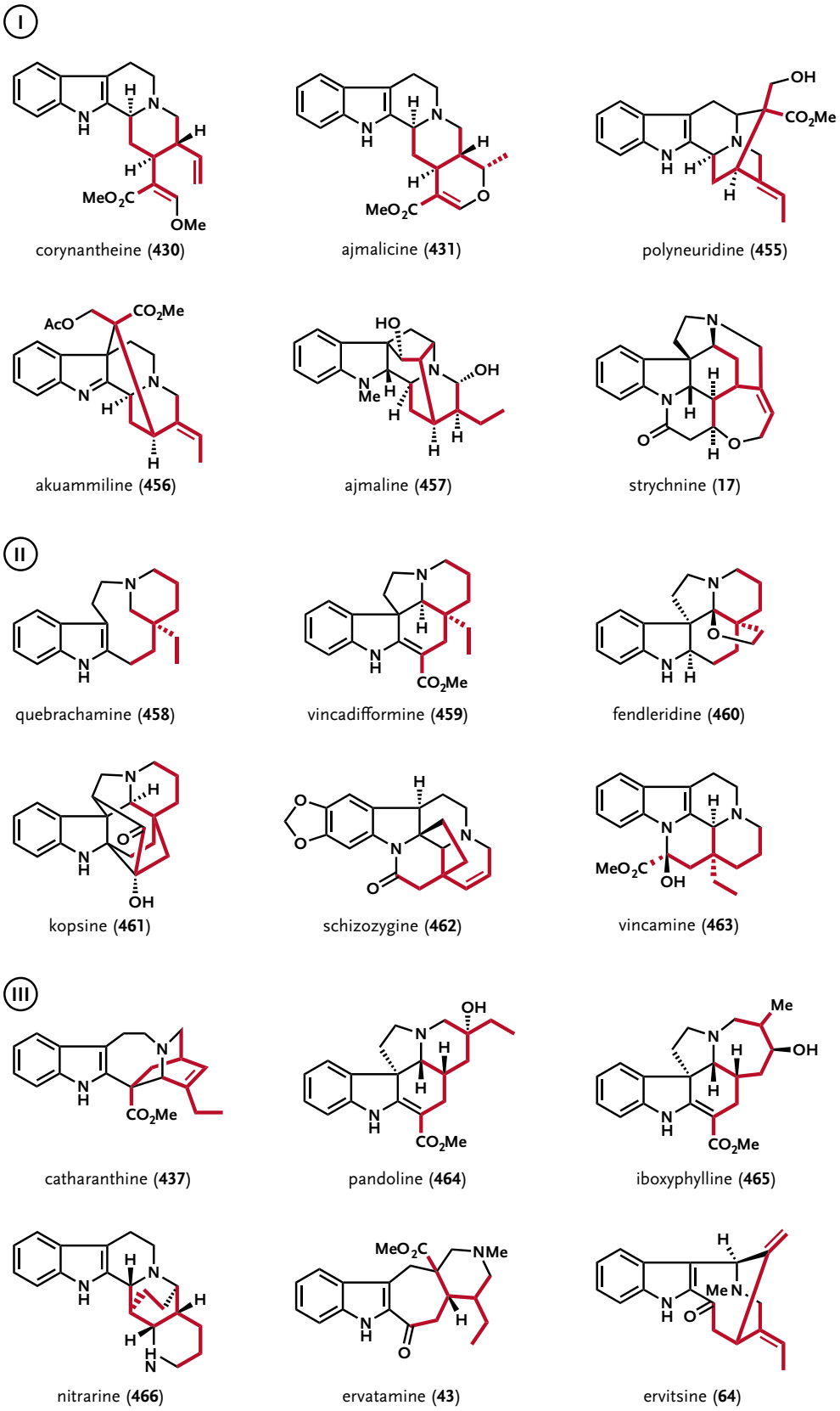


Figure 4-4. Examples for indole class I, II, and III alkaloids.

group), polyneuridine (**455**, *Sarpagine* group), akuammiline (**456**, *Picraline* group), ajmaline (**457**, *Ajmaline* group), and strychnine (**17**, *Strychnos* group).[1]

The second class of indole alkaloids does not contain the secologanin skeletal system in its original form. The carbon–carbond bond between C-3 and C-4 has been cleaved; instead a new bond between carbon C-{2,6} and carbon C-4 has been formed (Scheme 4-5, **452** → **453**). The rearrangement of the terpenoid moiety occurs after the condensation of tryptamine with secologanin (**433**). Examples for the second class of indole alkaloids (Fig. 4-4) are quebrachamine (**458**, *Quebrachamine* group), vincadifformine (**459**, *Aspidospermine* group), fendleridine (**460**, *Aspidoalbidine* group), kopsine (**461**, *Kopsine* group), schizozygine (**462**, *Schizozygine* group), and vincamine (**463**, *Vincamine* group).

The third class of indole alkaloids does not contain the secologanin skeletal system in its original form as well and is divided into two sub-groups. Again, the carbon–carbond bond between C-3 and C-4 has been cleaved, but in this case a new bond between carbon C-{2,6} and carbon C-5 has been formed (Scheme 4-5, **452** → **454**). The second sub-group contains terpene indole alkaloids which possess a novel C_{10} skeleton due to expansive rearrangement. Examples for the third class of indole alkaloids (Fig. 4-4) are catharanthine (**437**, *Iboga* group), pandoline (**464**, *Pandoline* group), iboxyphylline (**465**, *Ibophyllidine* group), nitrarine (**466**, *Nitramidine* group), ervatamine (**43**, *Ervatamia* group), and ervitsine (**64**, *Ervatamia* group).

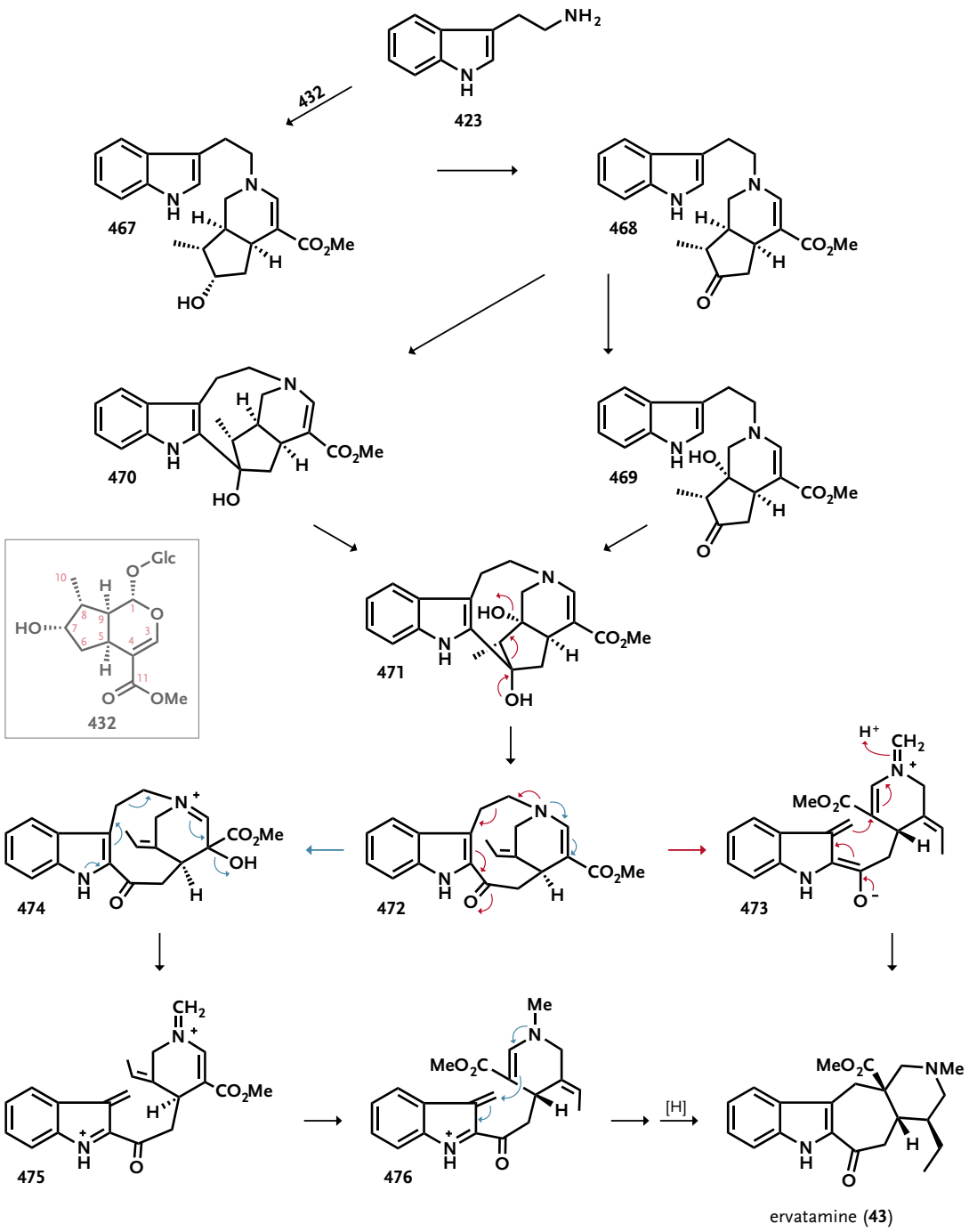
Due to their broad variety, the fourth and fifth classes are not going to be discussed in detail. The fourth class contains non-tryptophan indole alkaloids (carbazoles, etc.), non-isoprenoid tryptophan alkaloids, and indole alkaloids from fungi. The fifth class contains the bis-indole alkaloids.[338]

4.2.2 Biosyntheis of *Ervatamia* Alkaloids

Ervatamia alkaloids contains an indole nucleus, but the "backbone" from the indole 3-position to the basic nitrogen N_b contains three carbon atoms and is thus the product of a fairly extensive rearrangements. There are several hypothetical proposals from G. A. Cordell[57] and A.-U. Rahman,[338] but till this day no further studies for the elucidation of the biosynthesis have been made. Therefore, there is no "right" and "wrong" proposal, but from the author's point of view some proposals make more sense than others.

There are some general remarks which are to be considered: (i) an examination of the carbon skeleton of the non-tryptophan moiety of ervatamine (**43**) shows that the C_{10} skeleton is identical with that in secologanin (**433**), (ii) the indole 2-position is connected to C-7 of loganin (**432**) and a condensation reaction between an amine and the hemiacetal moiety of **432** may have taken place, (iii) it should be taken note of the point that the 19,20-dehydro species of *Ervatamia* alkaloids exists whereas the 18,19-dehydro species were not isolated. This may led to the assumption that the *Ervatamia* alkaloids may derived by reaction of tryptamine (**423**) and loganin **432**.

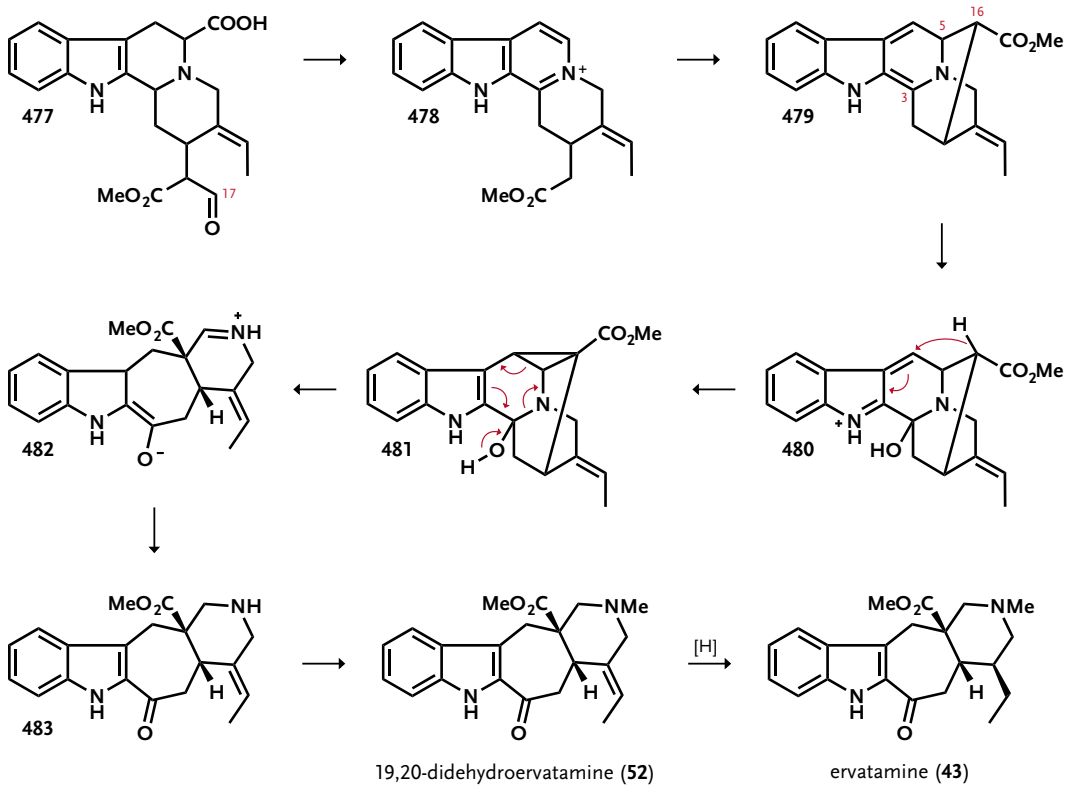
[1] The broad range of terpene indole alkaloids cannot be discussed within the scope of this section, only some important examples for each class are shown. For detailed information the author refers to specialized literature.[57,333,338]



Scheme 4-6. Biosynthesis of ervatamine (**43**) from tryptamine (**423**) and loganin (**432**).[57]

4.2.2.1 *Ervatamia* Alkaloids from Tryptamine

A potential biosynthesis starts from tryptamine (**423**) which undergoes a condensation reaction with the hemiacetal moiety of loganin (**432**) yielding indole terpenoide **467**. Attachment of C-7 of **432** to the indole 2-position is followed by a C-9 hydroxylation furnishing alkaloid **471**, which undergoes ring cleavage to afford the ethylidene group directly and install the indole



Scheme 4-7. Biosynthesis of ervatamine (**43**) from 5-carboxygeissoschizine (**477**).[57]

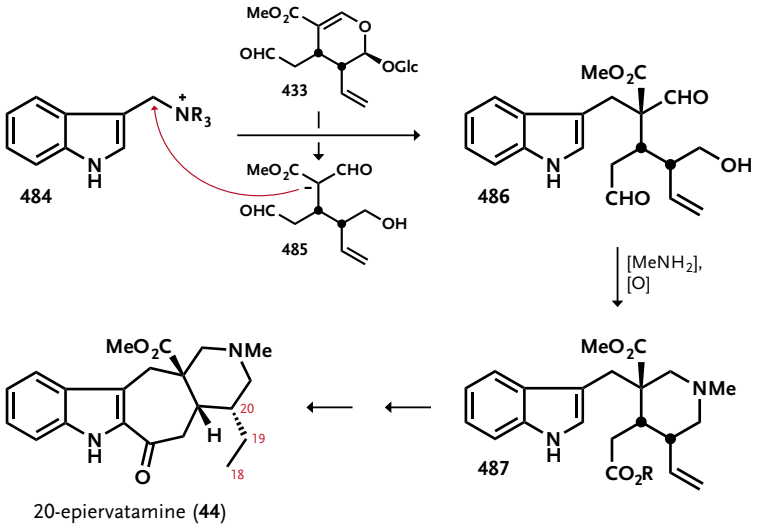
2-acyl moiety simultaneously. Compound **472** is possibly a key intermediate in this biogenetic proposal. It can turn into ervatamine (**43**) by fragmentation of the tryptamine bridge either *via* intermediate **473** or *via* intermediate **474** followed by cyclization to afford **43** as indicated in Scheme 4-6.

An alternative biogenetic proposal describes the biosynthesis of ervatamine (**43**) from 5-carboxygeissoschizine (**477**, Scheme 4-7).[57] Oxidative decarboxylation and loss of carbon C-17 followed by attachment of C-16 to C-5 leads to *Sarpagine* group like intermediate **479**. Oxidation at carbon C-3 followed by cyclopropane formation and cleavage as indicated affords **483** which is subsequently methylated. The primary product is 19,20-didehydroervatamine (**52**) which is converted into ervatamine (**43**).

Feeding ^{14}C-tryptophan and observing the remaining ^{14}C could lead to an evidence for the correctness of one of these proposals.

4.2.2.2 *Ervatamia* Alkaloids from Gramine Derivatives

As mentioned before the C_{10} skeleton of ervatamine (**43**) is identical with that in secologanin (**433**) and contains an extra carbon atom which is attached to the indole 3-position. It could therefore arise from the reaction of gramine derivatives (**485**) with **433** (Scheme 4-8).[338] This would lead to intermediate **485**. Formal condensation with methylamine and oxidation leads to

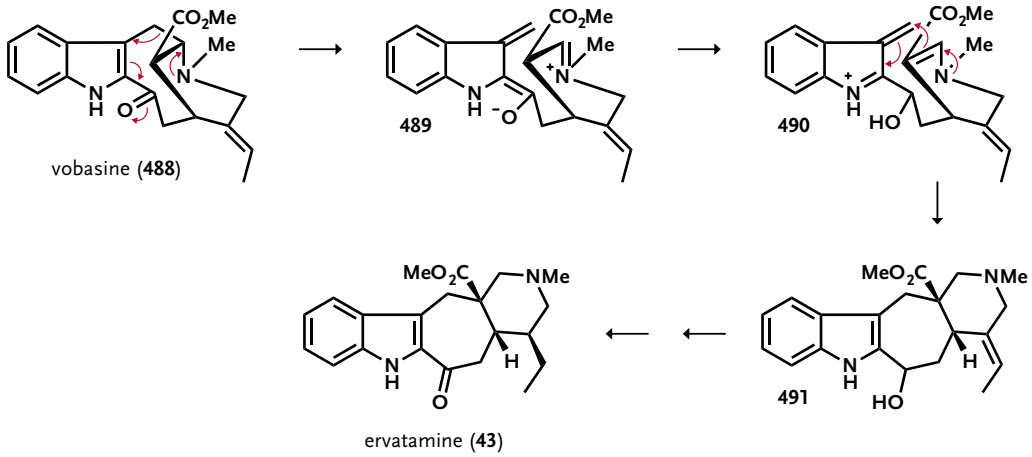


Scheme 4-8. *Ervatamia* alkaloids from gramine derivatives and secologanin.[338]

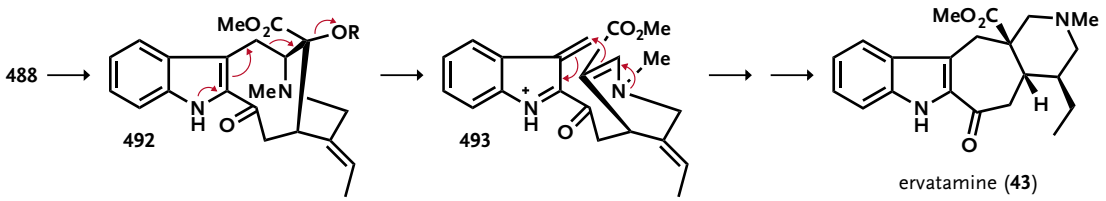
intermediate **485**. The ester moiety is attacked by the indole to form the indole 2-acyl moiety. This sequence would lead to 20-epiervatamine (**44**). Nevertheless, a drawback of this proposal is that the 19,20-dehydro species of *Ervatamia* alkaloids exists whereas the 18,19-dehydro species were never isolated.

4.2.2.3 *Ervatamia* Alkaloids from Vobasine Derivatives

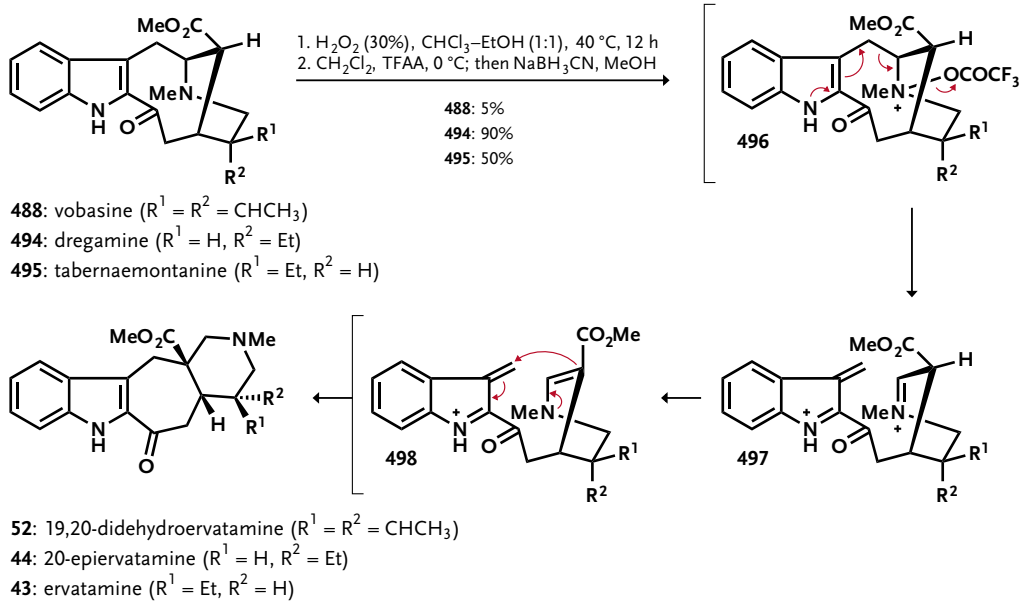
Another plausible proposal is that *Ervatamia* alkaloids can derive from vobasine derivatives as shown in Scheme 4-9. A fragmentation and reprotonation sequence leads to intermediate **490**. The iminium ion is then attacked intramolecularly by the enamine to afford 18,19-dehydro derivative **491** which is then transformed into ervatamine (**43**).



Scheme 4-9. Proposal for the biogenetic synthesis of ervatamine (**43**) from vobasine (**488**).[338]



Scheme 4-10. Another proposal for the biogenetic synthesis of ervatamine (**43**) from vobasine (**488**).



488: vobasine ($R^1 = R^2 = CHCH_3$)
494: dregamine (R^1 = H, R^2 = Et)
495: tabernaemontanine (R^1 = Et, R^2 = H)

52: 19,20-didehydroervatamine ($R^1 = R^2 = CHCH_3$)
44: 20-epiervatamine (R^1 = H, R^2 = Et)
43: ervatamine (R^1 = Et, R^2 = H)

Scheme 4-11. Conversion of diverse vobasine derivatives into *Ervatamia* alkaloids using a Polonovski-type sequence.[353]

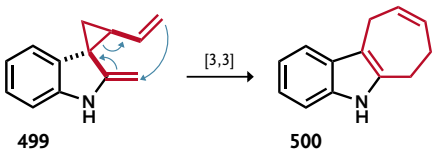
The author himself proposes a different biogenetic proposal for the synthesis of *Ervatamia* alkaloids from vobasine derivatives (Scheme 4-10). An oxidative process transforms vobasine (**488**) into vobasine derivative **492** which undergoes indicated fragmentation to afford compound **493**. The iminium ion is then attacked intramolecularly by the enamine to afford the 18,19-dehydro derivative which is then transformed into ervatamine (**43**).

Potier *et al.* have demonstrated the conversion of diverse vobasine derivatives into *Ervatamia* alkaloids using a Polonovski-type sequence (Scheme 4-11).[353] Vobasine (**488**) and the vobasine derivatives dregamine (**494**) and tabernaemontanine (**495**) were transformed into the corresponding *N*-oxide using hydrogen peroxide. These compounds were described as unstable and therefore directly treated with trifluoroacetic anhydride to induce the Polonvski-type rearrangement. This affords an analogous intermediate (**498**) to that which was proposed in some aforementioned biosynthetic proposals (Schemes 4-9 and 4-10). The iminium ion is then attacked intramolecularly by the enamine to afford *Ervatamia* alkaloids: (i) tabernaemontanine (**495**) was converted into ervatamine (**43**) in 50% yield, (ii) dregamine (**494**) was converted into 20-epiervatamine (**44**) in 90% yield, (iii) vobasine (**488**) was converted into 19,20-didehydroervatamine (**52**) in 5% yield. Some years later Potier *et al.* could demonstrate the successful rearrangement of

dregamine (**494**) into 20-epiervatamine (**44**) catalyzed by liver microsomes. This result may provide strong support for such a pathway and biogenetic filiation between alkaloids of the vobasine and ervatamine types. This may also led to the hypothesis of the modified Polonovski reaction being "biomimetic".[354]

5 Methodology

This chapter describes the development of a methodology for the synthesis of cyclohepta[*b*]indoles *via* sigmatropic rearrangement, that is a divinylcyclopropane-cycloheptadiene rearrangement. The central idea of this methodology is shown in Scheme 5-1: Fischer's base derivative **499** undergoes a divinylcyclopropane-cycloheptadiene rearrangement to afford cyclohepta[*b*]-indole **500**. Having the methodology in hands it should be applied to the total synthesis of diverse indole alkaloids from the ervatamine–ervitsine group. A small part of the development overlaps with the work which has been done in the course of the Master's thesis, therefore a small introduction at the beginning covers the work hitherto done and shows the most important transformations and intermediates to get a full understanding for the choice of the final strategy and the results.

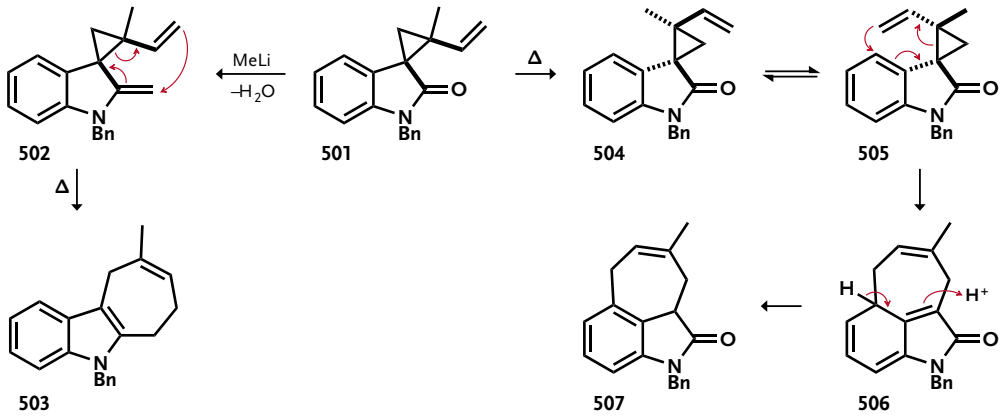


499 500

Scheme 5-1. General idea: indoline **499** undergoes a divinylcyclopropane-cycloheptadiene rearrangement to form cyclohepta[*b*]indole **500**.

5.1 Failed Strategies

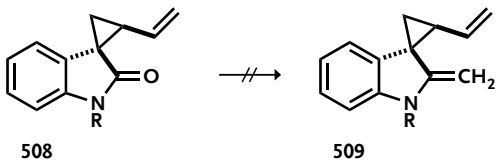
At the outset the feasibility of the proposed key step could be demonstrated. Model compound **501** was synthesized *via* rhodium catalyzed cyclopropanation reaction of isoprene and benzyl protected diazo isatine. The oxindole **501** could then be transformed into Fischer's base derivative **502** by addition of methyl lithium followed by dehydration. This affords the divinylcyclopropane system **502** (Scheme 5-2). Although the yields were exceedingly low for this transformation, upon heating **502** underwent smoothly a divinylcyclopropane rearrangement to yield cyclohepta[*b*]indole **503**. By reason of very low yields the work towards the cyclohepta[*b*]indoles *via* Fischer's base derivatives from oxindoles was discontinued. Additional work towards the optimization of this conversion were also not successful. However, when oxindole **501** was refluxed



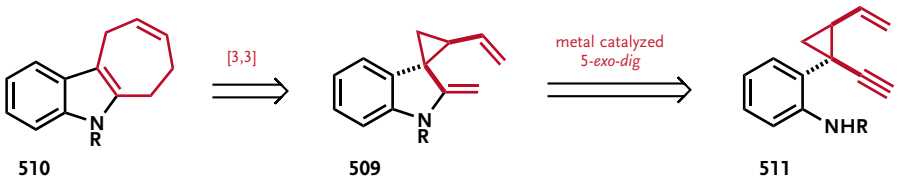
Scheme 5-2. Obtaining two different products from racemic cyclopropane **501**.

in high-boiling-point solvents, stereochemical scrambling at the cyclopropane moiety occurred (equilibrium between **504** and **505**). As a result the vinyl moiety has the correct geometry for a potential Cope rearrangement with the aromatic indole core. Indeed, the divinylcyclopropane rearrangement took place yielding cyclohepta[*cd*]indolone **507**. This transformation provided both the first experimental evidence for a possible enzyme-catalyzed sigmatropic process in the C-4 prenylation of indole alkaloids and the first direct C-C-bond forming cyclization which functionalizes the very unreactive C-4 indole position.[355] However, the formation of cyclohepta[*b*]indoles *via* divinylcyclopropane-cycloheptadiene rearrangement from Fischer's base derivatives required optimization work and a new strategy which does not rely on the transformation of oxindoles because various attempts for the transformation of 3,3-disubstituted oxindoles failed or proceeded with exceedingly low yield (Scheme 5-3).

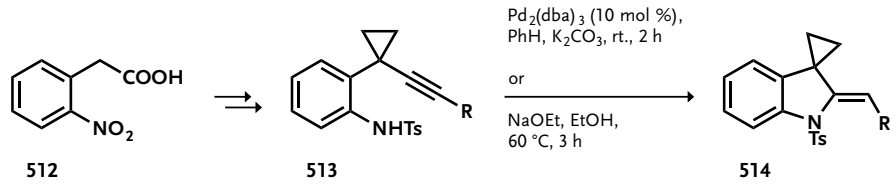
Another strategy should afford cyclohepta[*b*]indole precursor **509** *via* metal-catalyzed 5-*exo-dig* ring closure reaction (Scheme 5-4). In a first step, trisubstituted cyclopropane **511** was simplified to disubstituted cyclopropane **513** which was synthesized from 2-nitrophenylacetic acid. It



Scheme 5-3. Various attempts for the transformation of 3,3-disubstituted oxindoles failed or proceeded with exceedingly low yield.

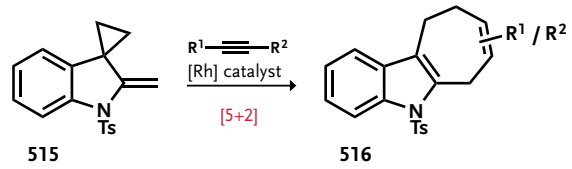


Scheme 5-4. Strategy: Fischer's base derivatives *via* metal-catalyzed ring closure.



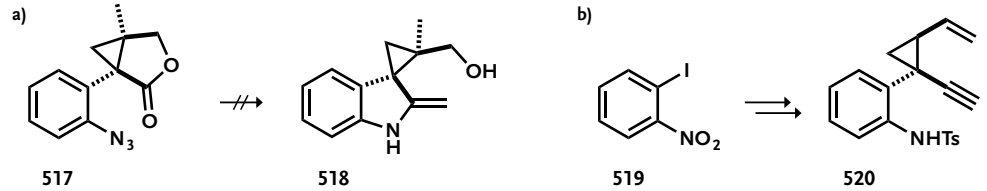
512 513 514

Scheme 5-5. Synthesis of Fischer's base derivatives.



515 516

Scheme 5-6. Attempts for a [5+2] cycloaddition reaction were not successful.



517 518 519 520

Scheme 5-7. **a)** Transformation of lactone **517** into Fischer's base derivative **518** was not successful. **b)** *o*-Iodonitrobenzene was converted into trisubstituted vinylcyclopropane **520**.

was elaborated that the desired 5-*exo-dig* cyclization could be accomplished either by metal catalysis using $Pd_2(dba)_3$ or by base-induced ring closure (Scheme 5-5). This methodology was applicable to both terminal alkynes and internal alkynes and produced the particular Fischer's base derivative in very good yield.

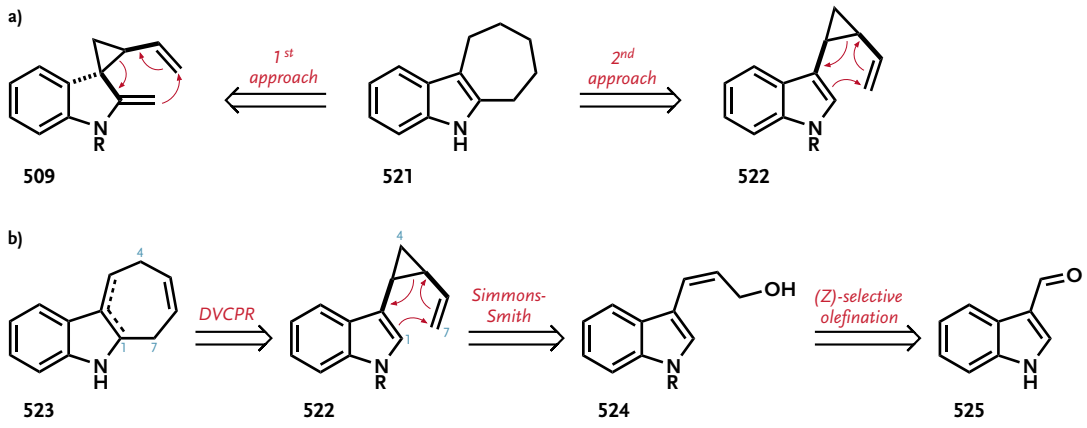
Although the synthesis of the discussed test system was just to demonstrate the ring closure and the formation of Fischer's base derivatives it was conceivable to use this compounds for the synthesis of cyclohepta[*b*]indoles anyway using the [5+2] cycloaddition of vinylcyclopropanes with alkynes. However, any attempt for a [5+2] cycloaddition reaction was not successful.

Albeit the synthesis of disubstituted cyclopropanes **509** was quite straightforward, the synthesis of trisubstituted vinylcyclopropane **520** was somewhat troublesome. On the one hand the conversion of bicyclo γ-lactone **517** into Fischer's base derivative **518** could not be managed (Scheme 5-7a). On the other hand *o*-iodonitrobenzene (**519**) was indeed successfully converted into trisubstituted vinylcyclopropane **520**, but this route turned out to be somewhat cumbersome (Scheme 5-7b). On account of this result, this route was not acceptable; although this route was potentially able to afford Fischer's base derivatives, it had no benefit over the finally established route for the synthesis of cyclohepta[*b*]indoles which is going to be discussed in the following sections.

5.2 Methodology: Cyclohepta[*b*]indoles from Indolylvinylcyclopropanes[1]

Many methodologies for the construction of cyclohepta[*b*]indoles have been described in Section 2.3 (p. 21). By far the biggest progress in methodology development has been made within the last decade. This coincides with the enhanced attention of pharmaceutical industry towards compounds exhibiting the cyclohepta[*b*]indole motif. Analysis especially of the most recent total syntheses of natural products which contains this structure motif reveals that the methodology development of the last decade has so far not found its way into application in complex molecule synthesis. This shows the urgent demand for the development of synthetic methodologies involving the construction of cyclohepta[*b*]indoles, explicitly when it comes to the development of methods for enantioselective construction of this privileged structure motif.

As already described at the beginning of this chapter (*cf.* p. 101) the central idea is the creation of cyclohepta[*b*]indoles *via* a sigmatropic rearrangement, that is a divinylcyclopropane-cycloheptadiene rearrangement (Scheme 5-1, p. 101). The first approach and its results were briefly discussed in Section 5.1, the focus now rests on the second approach (Scheme 5-8a). Since the synthesis of Fischer's base derivative **509** turned out to be somewhat troublesome, the idea was now to "move" the π-system: the indole C-3 position is not anymore part of the vinylcyclopropane moiety, but instead the whole vinylcyclopropane moiety is attached to the indole C-3 carbon (**522**, Scheme 5-8a, *2nd approach*). This movement can lead to a contingent drawback: whereas the divinylcyclopropane-cycloheptadiene rearrangement of Fischer's base derivative **509** affords an aromatic system, the rearrangement of **522** requires the loss of the aromaticity. At this point it was only possible to speculate about the successful outcome of this rearrangement since one π-system of the divinylcyclopropane belongs to an aromatic system. Literature examples for



Scheme 5-8. **a)** Comparison: 1st approach vs. 2nd approach. **b)** Retrosynthetic analysis of indolylvinylcyclopropane **522**, the precursor of cyclohepta[*b*]indole **523**.

[1] Parts of this section have already been published in a peer-reviewed journal: Enantioselective Synthesis of Cyclohepta[*b*]indoles: Gram-Scale Synthesis of (*S*)-SIRT1-Inhibitor IV. *Org. Lett.* **2013**, *15*, 5472–5475.[83,356] The content of the published article is not as thoroughly as this section and some passages have been shortened.

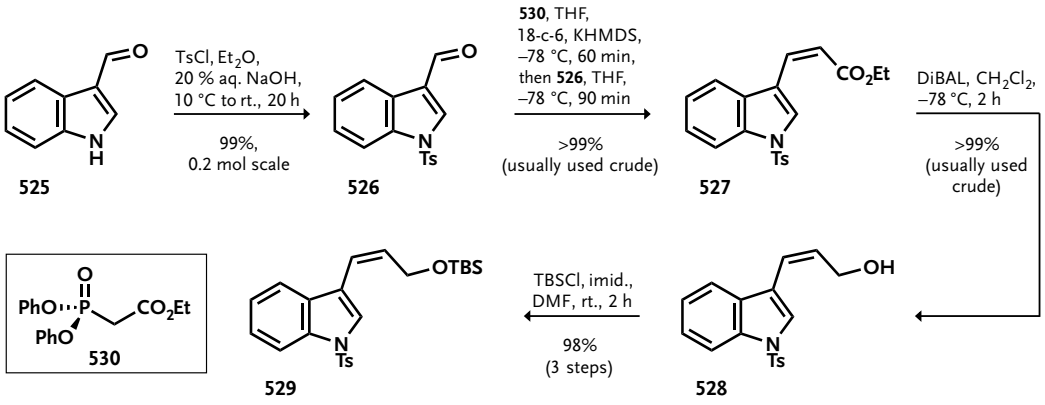
similar transformations are scarce; examples for the use of the C2–C3 indole bond as 2π unit in a sigmatropic rearrangement remains a *terra incognita*.

The retrosynthetic analysis for indolylvinylcyclopropane **522** is outlined in Scheme 5-8b. **522** derives from *(Z)*-allylic alcohol **524**, the disubstituted cyclopropane is planned to be installed *via* Simmons–Smith cyclopropanation reaction. *(Z)*-Allylic alcohol **524** in turn is accessible from indole-3-carbaldehyde (**525**), a compound which is inexpensive enough (100 €/100 g ≙ 145 €/mol)[2] to serve as starting compound for a synthetic route.

The choice of the indole protecting group is not trivial and the correct choice can be a key to a successful synthetic route. The protecting group should reduce the electron density in the heterocycle but also make it more stable towards oxidation. The decision was in favor of the toluenesulfonyl group. Arylsulfonyl groups are known to be highly effective protecting groups for a wide range of amine derivatives, indoles in particular, and are stable to most reaction conditions. Due to the robustness the removal can sometimes be troublesome, but a large amount of procedures—especially for the reductive removal—are described in literature.[357]

Starting from indole-3-carbaldehyde (**525**), the free nitrogen was tosyl protected (Scheme 5-9). Usual conditions (TsCl, Et_3N, CH_2Cl_2) provided aldehyde **526** already in good yield (84%). However, the yield could be optimized by using an aqueous biphasic system (20% aq. NaOH–Et_2O, 5:1) to afford aldehyde **526** in almost quantitative yield, even at 0.2 mol scale. Whereas the starting material **525** is air sensitive, aldehyde **526** is indefinitely bench-stable.

Modified Horner–Wadsworth–Emmons olefination reaction with phosphonate **530** (*Ando phosphonate*) afforded ester **527** with a *Z:E*-ratio >30:1 in almost quantitative yield, but the material was usually used crude for the next reactions. Crucial points were strongly dissociating conditions, that are the use of a potassium base (KHMDS) and the addition of 18-crown-6. Although usual literature procedures use 5.0 equivalents of the crown ether, it was worked out that 1.9 equivalents were sufficient and the addition of more equivalents of 18-crown-6 did not affect the very good *(Z)*-selectivity. The absence of a crown ether however drastically



Scheme 5-9. Synthesis of Simmons-Smith precursor **528**.

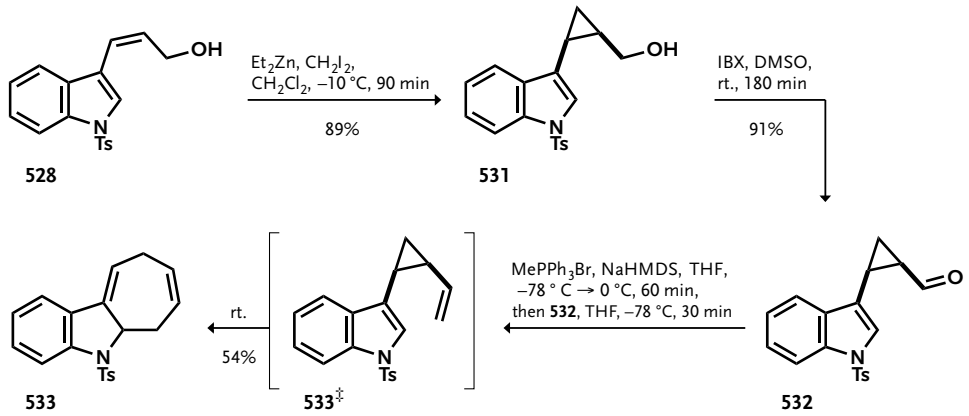
[2] http://www.abcr.de/shop/de/Indole-3-carboxaldehyde-98-26658.html (10/2016)

reduced the good *(Z)*-selectivity (only 3:1). There is no satisfying explanation for the *(Z)*-selectivity. Ando himself proposed that the use of electron-deficient phosphonates accelerates the elimination of the oxaphosphetane intermediates.[358] In addition, the methyl ester equivalent of α,β-unsaturated ester **527** was afforded *via* Still-Gennari olefination reaction using methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetate.[359] The olefination product was obtained in similar *Z:E*-selectivity (approx. 33:1), but the yield was only 82%; still a good yield for this transformation but not competitive to the quantitative yield of the Ando olefination.

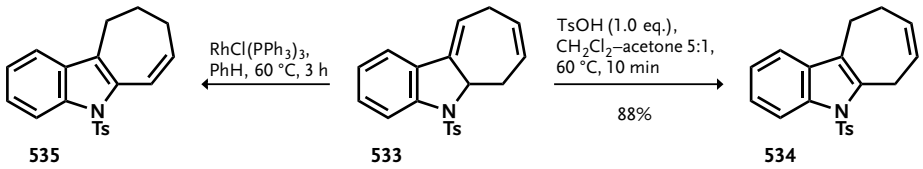
DiBAL reduction of α,β-unsaturated ester **527** afforded Simmons-Smith precursor **528** in quantitative yield. Allylic alcohol **528** was usually directly transformed into the corresponding TBS silyl ether **529** using usual protection conditions (TBSCl, imid., DMF). The 3-step sequence starting from aldehyde **526** usually afforded pure silyl ether **529** in 98% yield (1 to 35 mmol scale). Allylic alcohol **528**, required for the Simmons-Smith cyclopropanation, was usually obtained in 99% yield in a 2-step sequence.

Since the first approach (Scheme 5-8a) towards the synthesis of cyclohepta[*b*]indoles already included numerous cyclopropanations *via* Simmons–Smith reaction, the conditions for the transformation of allylic alcohol **528** into its cyclopropane derivative **531** (Scheme 5-10) were established quickly (2.2 eq. Et_2Zn, 4.4 eq. CH_2I_2, CH_2Cl_2, –10 °C, 1.5 h). Oxidation of the primary alcohol **531** with IBX afforded the corresponding aldehyde **532**. The key step in the synthesis of cyclohepta[*b*]indoles is a Wittig reaction/divinylcyclopropane-cycloheptadiene rearrangement cascade. Aldehyde **532** underwent olefination reaction to afford divinylcyclopropane **533**‡. Partial rearrangement already begun during the work-up and full rearrangement occurred after additional 2 h at ambient temperature yielding cyclohepta[*b*]indoline **533**. As it turned out, involving the indole moiety as a 2π-unit did not affect the successful outcome of this rearrangement.

A marginal drawback was that tautomerization to the indole did not occur spontaneously, even not during chromatography; the rearrangement product happened to be an indoline. Nonetheless, it could be shown that this product could be easily converted into the corresponding indole (Scheme 5-11). According to Spicer *et al.*,[360] treatment of indoline **533** with a catalytic



Scheme 5-10. Conversion of allylic alcohol **528** into cyclohepta[*b*]indoline **533**.

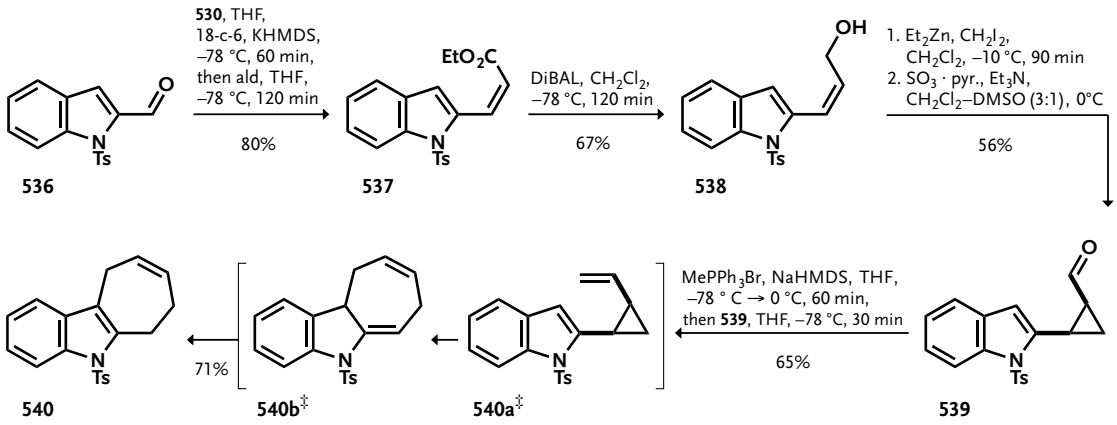


Scheme 5-11. Transformation of cyclohepta[*b*]indoline **533** into cyclohepta[*b*]indoles **534** and **535**.

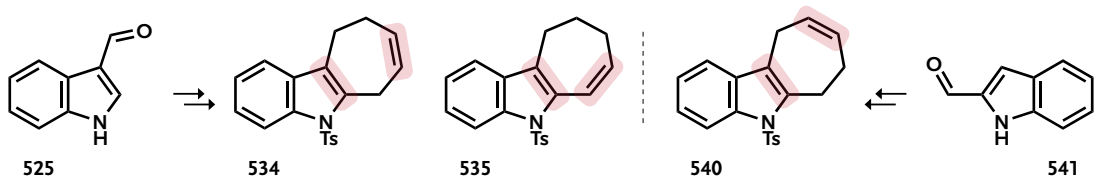
amount of *para*-toluenesulfonic acid in CH_2Cl_2 at ambient temperature smoothly furnished cyclohepta[*b*]indole **534**. However, this conditions were optimized by increasing the equivalents of *para*-toluenesulfonic acid (1.0 eq.), changing the solvent system (CH_2Cl_2 –acetone, 5:1) and temperature (T = 60 °C). These optimized conditions smoothly furnished cyclohepta[*b*]indole **534** in ten minutes in very good yield (88%). In addition, it could be shown, that treatment of indoline **533** with an equimolar amount of Wilkinson's catalyst {$RhCl(PPh_3)_3$} in benzene at 60 °C afforded a rearomatized product, too, but both double bonds were shifted in conjugation (**535**). Therefore, the marginal drawback was turned into an advantage, since indoline **533** can be transformed into two different cyclohepta[*b*]indoles.

5.2.1 Cyclohepta[*b*]indoles from 2-vinylcyclopropylindoles

After the methodology has been established, the idea was to repeat the route, but start with indole-2-carbaldehyde instead of indole-3-carbaldehyde. This work was then accomplished by my colleague Philipp J. Gritsch, but is mentioned here for the sake of completeness. The chemistry is pretty much the same as already shown for the synthesis of cyclohepta[*b*]indole **533** (Schemes 5-9 and 5-10) and requires no detailed explanation. Indole-2-carbaldehyde (**541**) is a commercially available compound. In contrast, indole-3-carbaldehyde (**525**) is not commercially available and had to be synthesized in a short sequence starting from ethyl indole-2-carboxylate.[361] Tosyl protected indole-2-carbaldehyde (**536**) was then transformed into *(Z)*-α,β-unsaturated ester **537** which in turn was reduced to the corresponding alcohol **538**. Simmons–Smith cy-



Scheme 5-12. Synthesis of cyclohepta[*b*]indole **540** from indole-2-carbaldehyde.



Scheme 5-13. Comparison of the different cyclohepta[*b*]indoles.

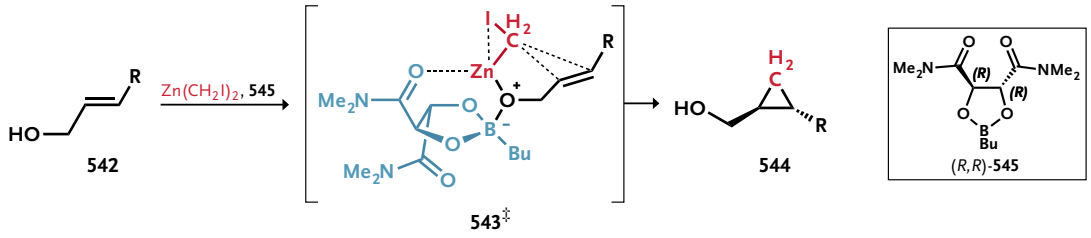
clopropanation followed by Parikh–Doering oxidation[362] furnished aldehyde **539**. The Wittig reaction/divinylcyclopropane-cycloheptadiene rearrangement cascade proceeded smoothly to yield directly cyclohepta[*b*]indole **540**, the tautomer **540b**‡has never been observed.

Comparing both synthetic routes leads to an interesting conclusion (Scheme 5-13): depending on either starting from indole-2-carbaldehyde (**541**) or indole-3-carbaldehyde (**525**) three different cyclohepta[*b*]indoles can be generated: 5,6,7,10-tetrahydrocyclohepta[*b*]indole (**540**), 5,6,9,10-tetrahydrocyclohepta[*b*]indole (**534**), and 5,8,9,10-tetrahydrocyclohepta[*b*]indole (**535**). The position of the olefinic moiety can be controlled specifically and therefore can be of use for successful synthetic planning.

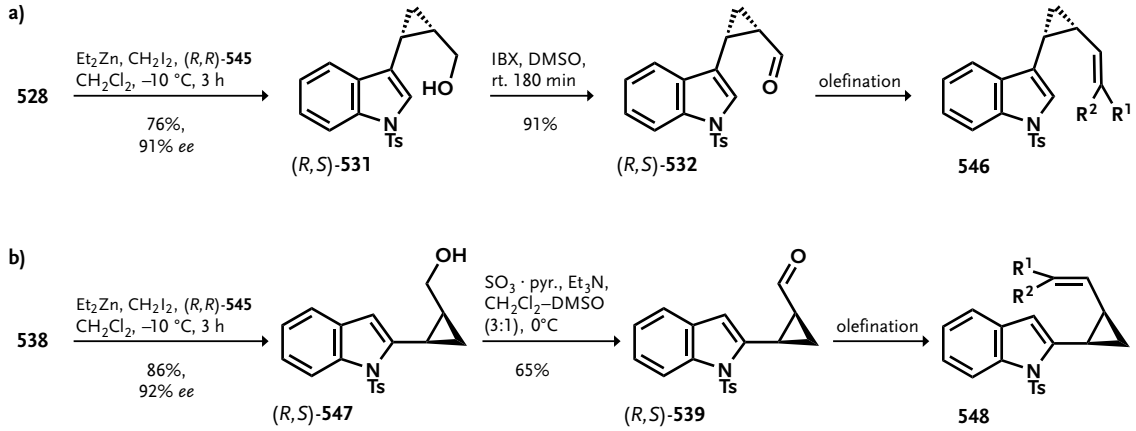
5.2.2 Asymmetric Synthesis of Cyclohepta[*b*]indoles

The described synthetic route for the synthesis of cyclohepta[*b*]indoles is ideally suited to be carried out in an asymmetric fashion. The Simmons–Smith cyclopropanation reaction can be rendered asymmetric by using a chiral boronic acid ester as a reagent, for this an allylic hydroxyl group is needed as a directing group.[363–367] *(Z)*-Indolyl allylic alcohol **528** fulfills this requirement.

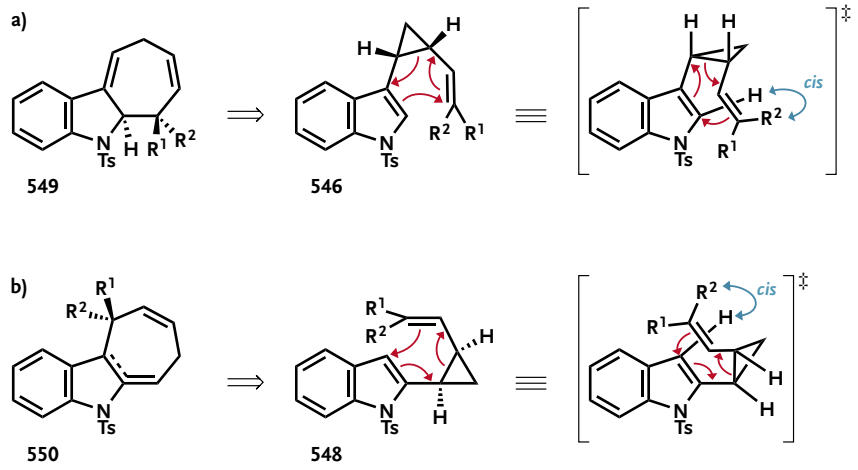
The asymmetric Charette–Juteau cyclopropanation reaction is shown in detail in Scheme 5-14. The chirality derives from dioxaborolane **545**, a simple amphoteric bifunctional ligand derived from (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartaric acid diamide. This ligand usually allows efficient chirality control for the Simmons–Smith cyclopropanation, furnishing cyclopropanes with an enantiomeric excess over 90% both for *trans*-substituted, *cis*-substituted, and trisubstituted olefins. It allows both the simultaneous chelation of the acidic Simmons–Smith reagent $\{Zn(CH_2I)_2\}$ and the basic allylic alcohol or its corresponding metal alkoxide (**543**‡). In addition, the chiral ligand can be easily removed and recovered from the organic reaction mixture.[363]



Scheme 5-14. Asymmetric cyclopropanation using chiral dioxaborolane **545**.



Scheme 5-15. Asymmetric cyclopropanations of allylic alcohols **528** and **538**. **a)** Indole-3-carbaldehyde series. **b)** Indole-2-carbaldehyde series.



Scheme 5-16. Chirality transfer in the divinylcyclopropane-cycloheptadiene rearrangement. **a)** Indole-3-carbaldehyde series. **b)** Indole-2-carbaldehyde series.

The developed methodology for the asymmetric cyclopropanation was first applied to allylic alcohol **528** (Scheme 5-15a). Reaction of **528** with Et_2Zn, CH_2I_2, and (*R,R*)-dioxaborolane **545** furnished cyclopropyl alcohol (*R,S*)-**531** in 76% yield. The enantiomeric excess was determined to be 91% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 30:70 ^{i}PrOH/hexanes, λ = 254 nm). IBX oxidation afforded aldehyde (*R,S*)-**532** which then can be transformed into different enantioenriched cyclohepta[*b*]indole precursors *via* olefination reactions. Same is true for the indole-2-carbaldehyde series. Asymmetric Charette–Juteau cyclopropanation reaction furnished cyclopropyl alcohol (*R,R*)-**547** (91% *ee*, determined *via* chiral HPLC analysis: AD-H, 1.0 ml min^{-1}, 30:70 ^{i}PrOH/hexanes, λ = 254 nm). Oxidation to the corresponding aldehyde (*R,S*)-**539** leads to the the starting compound for further different enantioenriched cyclohepta[*b*]indole precursors (**548**, Scheme 5-15b).

This divinylcyclopropane-cycloheptadiene rearrangement not only assembles the seven-membered ring, but due to orbital symmetry considerations,[368] chirality is transferred stereospecifi-

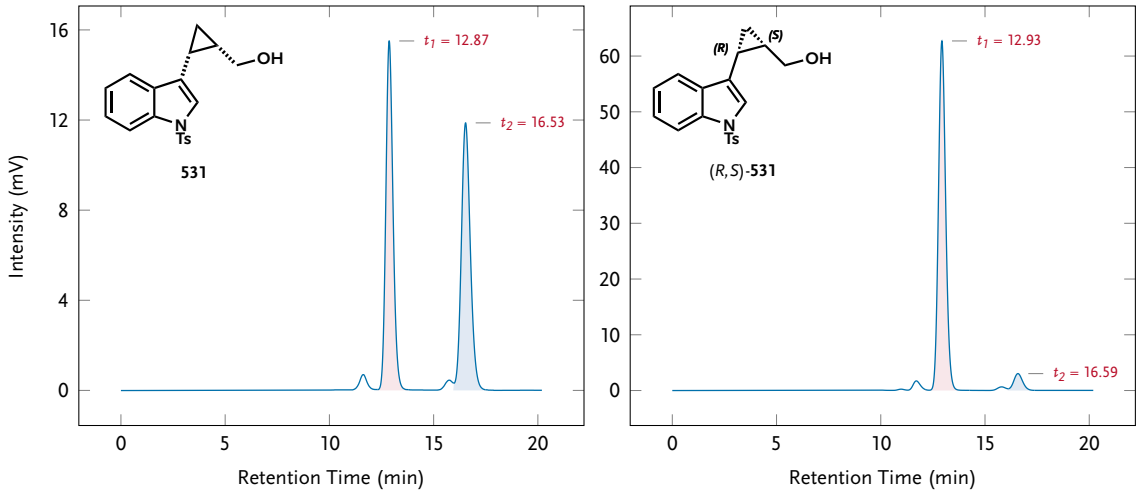


Figure 5-1. Chiral HPLC analysis of **531** (AD-H, 1.0 ml min^{-1}, 30:70 ^{i}PrOH/hexanes, $\lambda = 254$ nm), $ee = \frac{1507122-72013}{1507122+72013} = 90.9\%$.

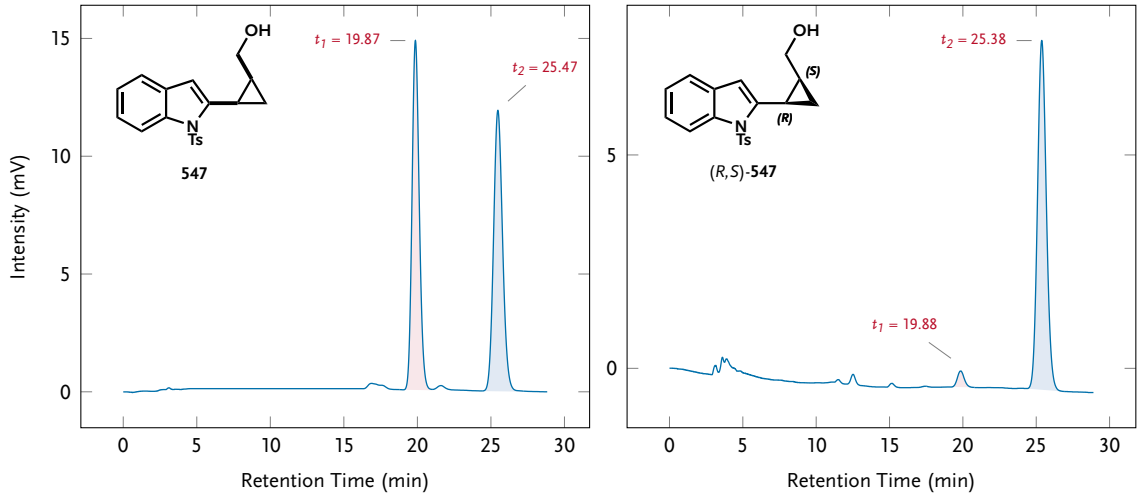


Figure 5-2. Chiral HPLC analysis of **547** (AD-H, 1.0 ml min^{-1}, 30:70 ^{i}PrOH/hexanes, $\lambda = 254$ nm), $ee = \frac{330467-12166}{330467+12166} = 92.9\%$.

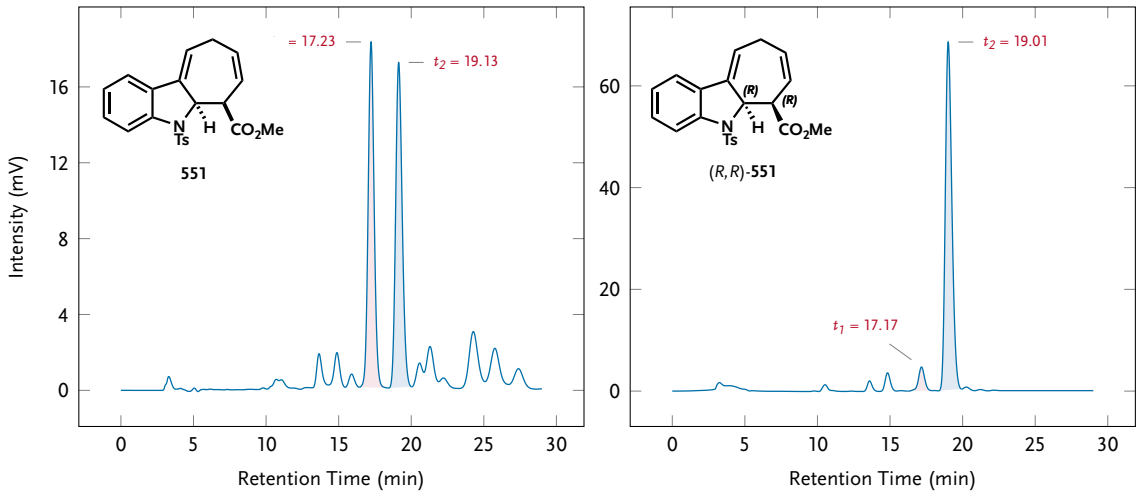
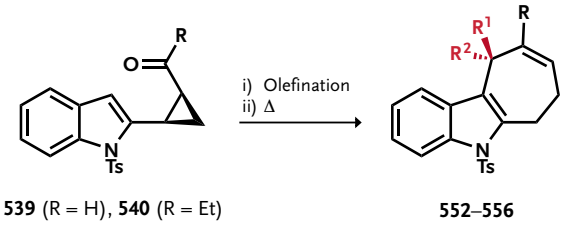


Figure 5-3. Chiral HPLC analysis of **551** (AD-H, 1.0 ml min^{-1}, 20:80 ^{i}PrOH/hexanes, $\lambda = 254$ nm), $ee = \frac{2143608-115067}{2143608+115067} = 89.8\%$.

cally from the cyclopropane ring to the benzylic positions, which are very labile and therefore difficult to access in a stereoselective way by other methods. The transfer of chirality for both 2- and 3-indole vinylcyclopropanes **546** and **548** is depicted in Scheme 5-16. In the case of 3-indole vinylcyclopropanes **546**, it can be clearly seen that R^2 and the indole C2-proton will adopt the *cis*-stereorelationship on the seven-membered ring. The relative configuration is therefore governed by the geometry of the double bond; hence, a *(Z)*-double bond will give the *cis*-compound, whereas the *(E)*-double bond will give the *trans*-compound. The same holds true for 2-indole vinylcyclopropanes **548**, but due to spontaneous aromatization in the course of the reaction, only one stereocenter is retained in the final product **550** (indicated with dashed line). The absolute stereochemistry in products **549** and **550** is governed by the stereocenters of the cyclopropane ring.

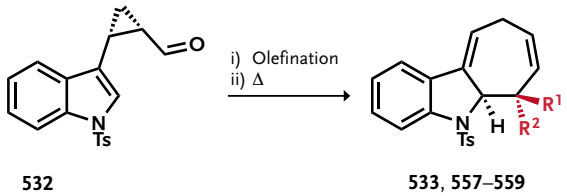
5.2.3 Extension of the Scope

To validate the concept and to explore the scope of the described domino sequence, a variety of olefins of type **546** (indole-3-cabraldehyde series) and **548** (indole-2-carbaldehyde series) were tested (Tables 5-1 and 5-2). These olefins derived from enantioenriched aldehydes **539** or **540**, respectively (Scheme 5-17), and aldehyde **532** (Scheme 5-18). The reaction turned out to be very robust, and tolerated a broad range of substituents (electron-rich and -deficient), which could be introduced at any position on the seven-membered ring. Even the formation of quaternary stereocenters was possible (Table 5-1, Entry 4, and Table 5-2, Entries 4 and 5). All Wittig adducts cyclized *in situ* to deliver cyclohepta[*b*]indoles in good to excellent yields. In all cases, the indoline product of the indole-2-carbaldehyde series was never observed, only the rearomatized product.



539 (R = H), **540** (R = Et) **552–556**

Scheme 5-17. Syntheses of cyclohepta[*b*]indoles, indole-2-carbaldehyde series, *cf.* Tab. 5-1.



532 **533**, **557–559**

Scheme 5-18. Syntheses of cyclohepta[*b*]indoles, indole-3-carbaldehyde series, *cf.* Tab. 5-2.

Table 5-1. Substrate scope of cyclohepta[*b*]indole synthesis (indole-2-carbaldehyde series).

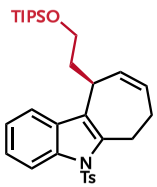
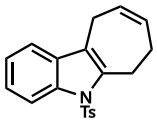
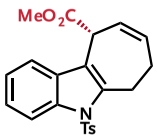
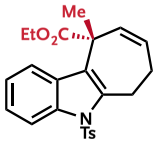
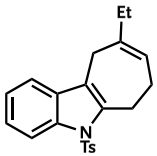
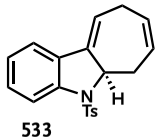
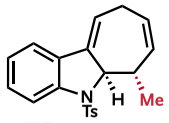
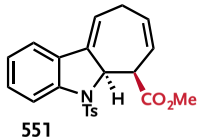
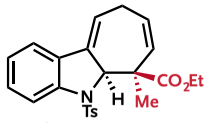
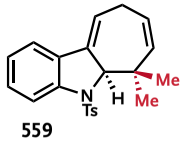
N°	Product	*T* [°C]	*t* [min]	*ee* [%]	yield [%]
1	 **552**	140	120	92	89
2	 **553**	rt.	60	—	71
3	 **554**	140	120	92	78
4	 **555**	140	180	89	65
5	 **556**	rt.	60	—	60

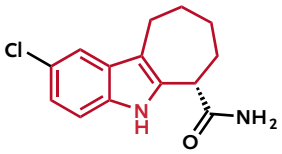
Table 5-2. Substrate scope of cyclohepta[*b*]indole synthesis (indole-3-carbaldehyde series).

N°	Product	*T* [°C]	*t* [min]	*ee* [%]	yield [%]
1	 **533**	rt.	60	89	54
2	 **557**	80	120	89	70
3	 **551**	80	180	89	76
4	 **558**	120	180	89	69
5	 **559**	120	180	89	73

It could be observed, that more substituted alkenes required a higher temperature and/or a prolonged reaction time. This becomes particularly apparent when comparing Tab. 5-2, Entries 1, 2, and 5. Whereas the rearrangement for the unsubstituted cyclohepta[*b*]indole **533** (derived from terminal alkene, **546**: $R^1 = R^2 = H$) took place at ambient temperature in 1.0 h, the rearrangement for monosubstituted cyclohepta[*b*]indole **557** (derived from disubstituted alkene, **546**: $R^1 = H$, $R^2 = Me$) required 2.0 h at 80 °C, and the rearrangement for *gem*-disubstituted cyclohepta[*b*]indole **559** (derived from trisubstituted alkene, **546**: $R^1 = R^2 = Me$) required an even higher temperature and prolonged reaction time (3.0 h, 120 °C). Notwithstanding this, all cyclohepta[*b*]indoles could be obtained in good to excellent yields.

5.3 Synthesis of (*S*)-SIRT1-inhibitor IV (**67**)

The cyclohepta[*b*]indole core, which occurs in a variety of indole alkaloids, is associated with a broad spectrum of biological profiles ranging from anti-inflammation and anti-aging to anti-tuberculosis activities (*cf.* Section 2.2.2 and Fig. 2-4, p. 20). Among the pharmaceutically active compounds based on this structure motif, around two dozen patents have been issued within the past decade.[369] The SIRT1-inhibitor IV (**67**) shows outstanding biological activity and is therefore being heavily investigated. It belongs to a new class of histone deacetylase (HDAC) inhibitors and is involved in gene silencing *via* a new mode of action. Data shows that inhibition of SIRT1 enhances acetylation of p53.[82,370] Compound **67** is one of the most potent compounds described, with IC_{50} values of 60–100 nM representing a 500-fold improvement over previously reported inhibitors.[82]



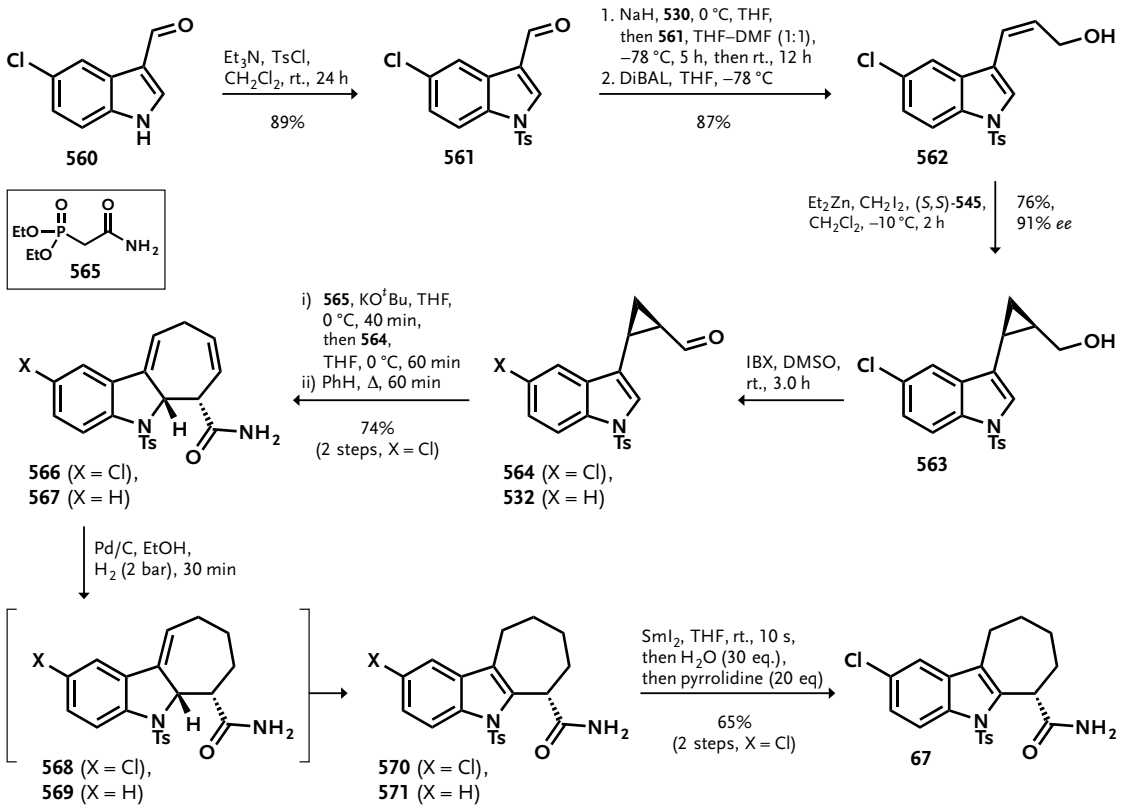
67

Figure 5-4. SIRT1-inhibitor IV.

This compound contains a single stereocenter and so far has only been synthesized as a racemate, which is separated by chiral HPLC. The two enantiomers differ drastically in their biological potency, with (*S*)-**67** (IC_{50} = 63 nM) being 365-fold more potent than (*R*)-**67** (IC_{50} = 23 µM), rendering an enantioselective access especially to the more potent (*S*)-**67** enantiomer utmost important.[82]

The synthesis of SIRT1-inhibitor IV (**67**) has been carried out in the style of the developed methodology and required only slightly modifications (Scheme 5-19). Starting from 5-chloro-indole-3-carbaldehyde (**560**, commercially available, 5 g/160 €[3]) the free nitrogen was tosyl protected under usual conditions (Et_3N, TsCl) to furnish aldehyde **561**. Ando olefination with phosphonate **530** and subsequent DiBAL reduction of the formed ester afforded *(Z)*-allylic alcohol **562** in 87% combined yield. Asymmetric Simmons–Smith cyclopropanation with dioxaborolane (*S,S*)-**545** gave cyclopropane **563** in good yield (76%). The enantiomeric excess was determined to be 91% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 25:75 ^{i}PrOH/hexanes, λ = 254 nm). IBX oxidation furnished aldehyde **564** and the enantiomeric excess was rechecked

[3] http://www.sigmaaldrich.com/catalog/product/aldrich/533076, (10/2016)



Scheme 5-19. Synthesis of (*S*)-SIRT1-inhibitor IV (**67**).

via chiral HPLC. In addition, NMR analysis showed only one single product which exluded potential racemization of the α-stereogenic center, which might occur during the oxidation process.

Next in line was the olefination/rearrangement tandem reaction sequence to afford cyclohepta[*b*]indoline **566**, which required some tuning. For this purpose, olefination of the 5-dechloro analogon **532** with phosphonate **565** were investigated. Finally, deprotonation of **565** with potassium *tert*-butoxide at 0 °C in THF for 40 min followed by the addition of aldehyde **532** and subsequent stirring in absolute refluxing benzene for 60 min afforded 5-dechloro analogon of cyclohepta[*b*]indoline **566**. Fortunately, these conditions could also be applied to 5-chloro aldehyde **564** and cyclohepta[*b*]indoline **566** was formed in 74% combined yield (from **563**).

The removal of the superfluous double bond was achieved with usual hydrogenation conditions (palladium on charcoal, ethanol, 2 bar H_2, 30 min) which were in turn first investigated on the 5-dechloro analogon **567**. Fortunately, it turned out that these conditions not only accomplished the reduction of the superfluous double bond but also caused the rearomatization of the second double bond. This was found out when the reaction mixture was stopped after 50% of the mentioned reaction time and both the indoline product **569** and the rearomatized indole product **571** could be observed on TLC and identified after separation and ^{1}H NMR analysis. Once again these conditions could be applied unmodified to the 5-chloro compound **566** to

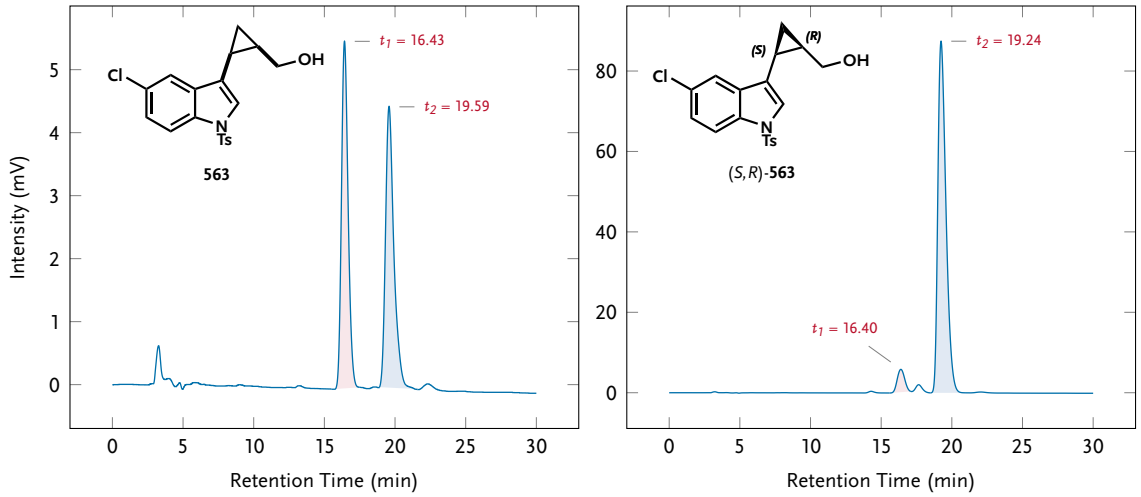


Figure 5-5. Chiral HPLC analysis of **563** (AD-H, 1.0 ml min^{-1}, 25:75 ^{i}PrOH/hexanes, λ = 254 nm), $ee = \frac{3675764-170225}{3675764+170225}$ = 91.1%.

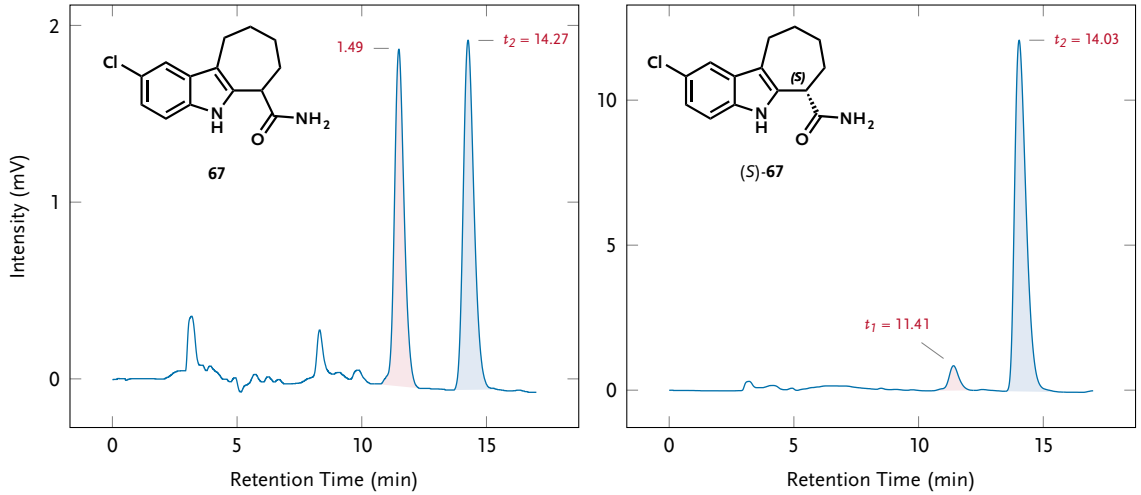


Figure 5-6. Chiral HPLC analysis of **67** (AD-H, 1.0 ml min^{-1}, 25:75 ^{i}PrOH/hexanes, λ = 254 nm), $ee = \frac{384796-18546}{384796+18546}$ = 90.8%.

furnish cyclohepta[*b*]indole **572** in 88% yield which usually was not purified but used crude for the final detosylation step. A potential dechlorination was not observed under these conditions.

The final step requires the removal of the protecting group. Several procedures for the detosylation of arenesulfonamides are described in literature.[371–377] Best results were obtained using a procedure of Hilmersson *et al.* who described an instantaneous deprotection of tosylamides with samarium diiodide.[378] This reaction requires a minimum amount of time and is usually directly quenched with an amine (pyrrolidine) and water. These conditions furnished (*S*)-SIRT1-inhibitor IV (**67**) with 91% *ee* and an overall yield of 28% (starting from commercially available aldehyde **560**) with complete retention of the labile stereocenter. It is important to note that even the exposure of **572** to magnesium and methanol did not result in racemization, as opposed to the treatment of the corresponding ester. For practical purposes it is important to note that the synthetic sequence requires only three purification steps and can be performed on a gram scale.

Towards the Total Synthesis of *Ervatamia* Alkaloids

6

6.1 General Strategy

Nature's way of synthesizing natural products is *via* privileged intermediates which in turn are generated from simple and basic building blocks (Fig. 6-1). The privileged intermediates are converted into different natural products with different bioindications. These conversions can include complex transformations, sometimes it is even not obvious that two different natural products have the same precursor. In some cases, a natural product itself can be a privileged intermediate. An example for a privileged intermediate is strictosidine (**434**, Section 4.2, p. 89) which derives from basic building block 1-deoxy-D-xylulose 5-phosphate (DXP, **440**).

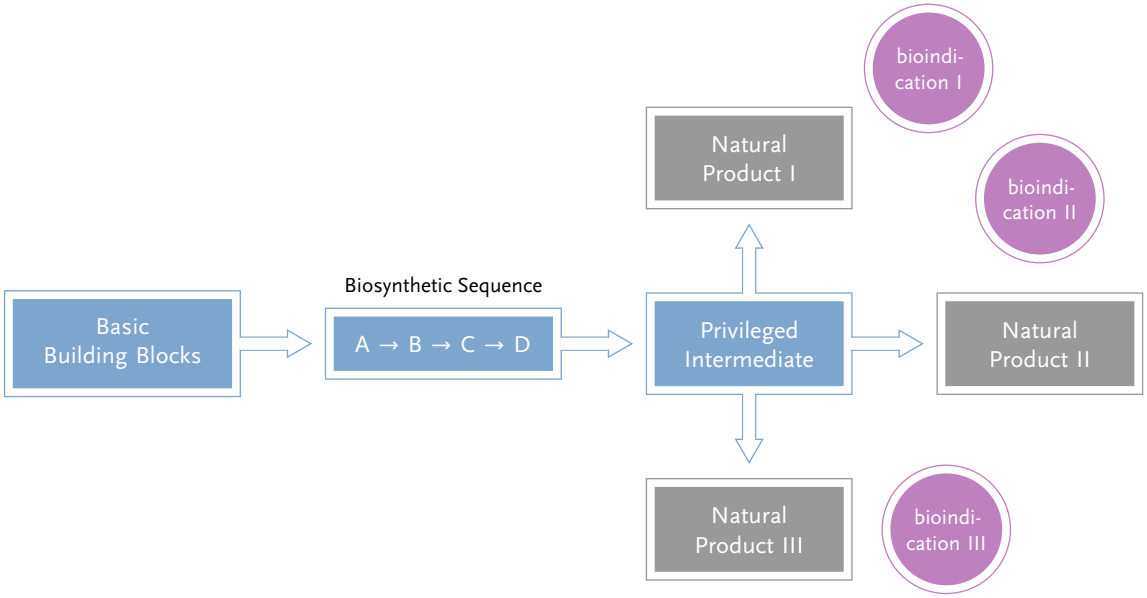


Figure 6-1. Biosynthetic sequence to a privileged intermediate.

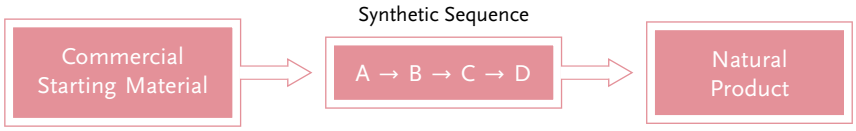


Figure 6-2. Usual synthetic strategy for the total synthesis of a natural product.

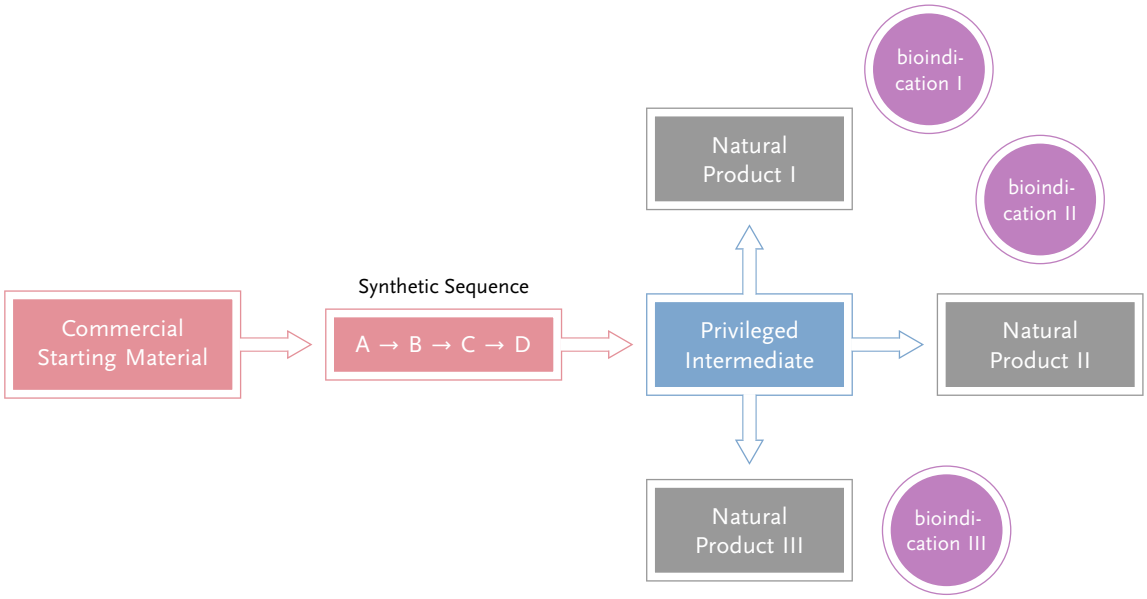
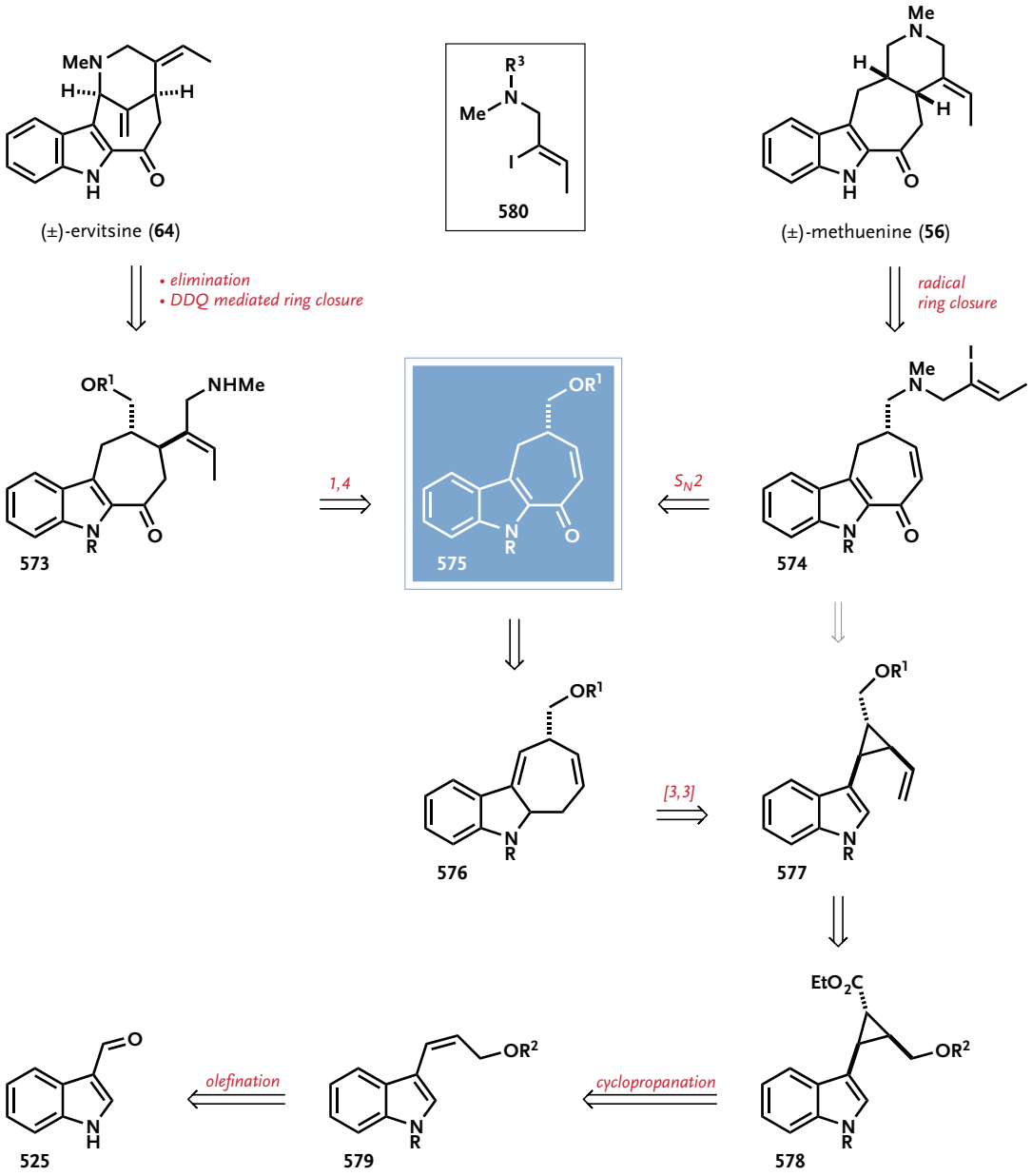


Figure 6-3. "Verbund"-synthesis.

On the contrary, classic total synthesis aims for one single target and the synthetic strategy is in most cases designed to exclusively furnish the desired target (Fig. 6-2). The so-called "Verbund"-synthesis tries to join both strategies (Fig. 6-3). The synthetic route is designed for the conversion of commercial available materials into a privileged intermediate which can be transformed into further different natural products. In the best case case scenario, this transformation requires only one single step. Admittedly, a biomimetic synthesis of indole monoterpene alkaloids allows a large amount of privileged intermediates since the biosynthetic pathways have been studied very well and various intermediates are known to be convertible into different natural products (*cf.* Section 4.2).

The first general retrosynthetic idea for the synthesis of *Ervatamia* alkaloids is shown in Scheme 6-1. Both (±)-ervitsine (**64**) and (±)-methuenine (**56**) derivatives can derive from target compound **575**. Transformation of **575** into (±)-ervitsine (**64**) occurs *via* 1,4-addition of a building block similar to **580** followed by a DDQ mediated ring closure. Similar late-stage ring-closing reactions are known from the literature, e.g. synthesis of (–)-tubifolidine (M. Shibasaki, 1998)[379] or synthesis of (±)-uleine (E. Ertürk, 2011).[380] On the contrary, methuenine (**56**) can be formed by displacement of the alcohol moiety of **575** followed by an intramolecular radical ring closure. Once more a building block similar to vinyl iodide **580** is required for the transformation making **580** a general building block for both synthetic approaches. Cyclohepta[*b*]indole **575** itself derives from cyclohepta[*b*]indoline **576** *via* rearomatization and allylic oxidation. The precursor of

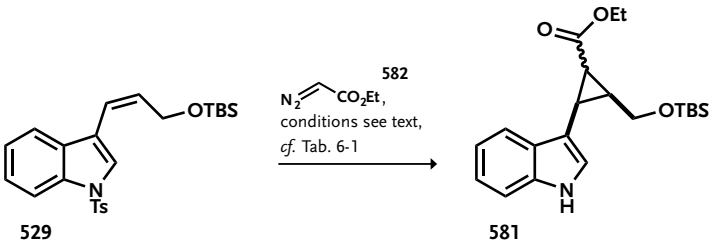


Scheme 6-1. Retrosynthetic analysis for *Ervatamia* alkaloids..

cyclohepta[*b*]indoline **576** is indolylvinylcyclopropane **577** which transformation into **576** *via* divinylcyclopropane-cycloheptadiene rearrangement has been discussed in Section 5.2. This transformation marks one key-step in this synthetic proposal and the elaborated methodology for this transformation has been successfully applied to several substrates. Straightforward transformations lead to trisubstituted cyclopropane precursor **578** which in turn derives from *(Z)*-allylic alcohol **579** *via* cyclopropanation using diazo compounds with metal catalysis. Starting material for the synthesis is aforementioned and commercially available indole-3-carbaldehyde (**525**).

6.2 First Approach

An important building block towards the synthesis of *Ervatamia* alkaloids is trisubstituted cyclopropane **581** (Scheme 6-2). Simmons–Smith cyclopropanation conditions were not applicable to this system but instead metal-catalyzed cyclopropanations with ethyl diazoacetate (**582**). Many trials were carried out to find optimal conditions for this transformation and the most important results are listed in Tab. 6-1.



Scheme 6-2. Cyclopropanation of allylic silyl alcohol **529** using ethyl diazoacetate with metal catalysis.

The most crucial point was the correct concentration of the starting material. First attempts used a concentration of 0.1 M for the starting material and additional 0.1 M for ethyl diazoacetate (**582**, equals to 0.05 M in total after complete addition). This resulted only in little formation of desired cyclopropane **581** and mostly furnished diethyl fumarate (*via* metal-catalyzed formation of to the dimer of **582**, exclusive formation of the *trans*-dimer; Tab. 6-1, Entries 1 and 2). By gradually decreasing the concentration of the starting material **529** and reducing the catalyst load from 6 mol % to 2 mol % it was found out that the cyclopropanation works best when dissolving the starting material only in a minimal amount of degassed CH_2Cl_2 (usually ≥2.0 M) followed by the addition of a diluted solution of ethyl diazoacetate in CH_2Cl_2 over 12 h (Entries 3 and 4).

Unfortunately, it was not possible to separate the cyclopropane product from diethyl fumarate and small amounts of this dimer were apparent in the NMR. The diastereomers were also not separable, the diastereomeric ratio was therefore determined *via* NMR analysis or after reduction of the ester to the corresponding alcohol which yielded two separable diastereomers. The correct assignment of both diastereomers is only possible *via* NMR analysis and is somehow not trivial. The best indicators are the coupling constants between the three cyclopropane protons. Since the starting material contains a *(Z)*-double bond, these two protons must consequently be *cis* configured in the cyclopropane product. Due to overlapping cyclopropane proton signals of the minor diastereomer, the analysis was only successful for the major formed diastereomer. According to the careful analysis, the major formed product was also the desired product where the ester moiety and the indole moiety have a *trans* relation (Fig. 6-4).

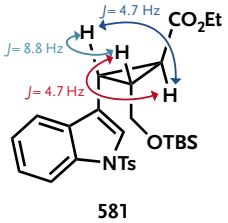


Figure 6-4. Assignment of the relative stereochemistry of the major diastereomer *via* examination of the cyclopropane proton coupling constants.

As to the metal, it turned out that copper catalyzed cyclopropanation furnished better results than rhodium catalyzed cyclopropanation in

Table 6-1. Cyclopropanation conditions for the generation of **581** (*cf.* Scheme 6-2).

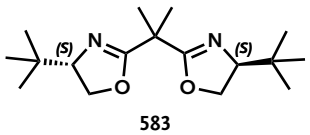
#	Conditions[7)]	Yield [%]	$\alpha:\beta$	*ee* [%]	Notes
1	CH_2Cl_2 (0.1 M), $Rh_2(OAc)_4$ (6 mol %), **582** (5.0 eq.) in CH_2Cl_2 (0.1 M), addition over 4 h, rt.	traces	—	—	1) 3)
2	CH_2Cl_2 (0.2 M), [Cu(OTf)] · PhH (5 mol %), **582** (1.5 eq.) in CH_2Cl_2 (0.2 M), addition over 4 h, rt.	traces	—	—	1) 3) 4)
3	CH_2Cl_2 (0.1 M), [Cu(OTf)] · PhH (2 mol %), **582** (2.5 eq.) in CH_2Cl_2 (0.2 M), addition over 10 h, rt.	32	3:1	—	1) 4)
4	CH_2Cl_2 (≥ 2 M, degas.), [Cu(OTf)] · PhH (2 mol %), **582** (5.0 eq.) in CH_2Cl_2 (0.1 M, degas.), addition over 12 h, rt.	76	3.2:1	—	2)
5	CH_2Cl_2 (≥ 2 M, degas.), [Cu(OTf)] · PhMe (2 mol %), **582** (5.0 eq.) in CH_2Cl_2 (0.1 M, degas.), addition over 12 h, rt.	68	2.8:1	—	2)
6	CH_2Cl_2 (≥ 2 M, degas.), [Cu(OTf)] · PhH (2 mol %), **582** (5.0 eq.) in PhH (0.1 M, degas.), addition over 12 h, rt.	15	—[5)]	—	2) 4) 6)
7	CH_2Cl_2 (≥ 2 M, degas.), $Rh_2(OAc)_4$ (2 mol %), **582** (5.0 eq.) in CH_2Cl_2 (0.1 M, degas.), addition over 12 h, rt.	45	1.1:1	—	2) 4)
8	hexanes (1.0 M), $CuSO_4$ (35 mol %), **582** (3.0 eq.) in hexanes (0.1 M), addition over 7.0 h, 105 °C	92	2:1	—	2)
9	CH_2Cl_2 (1.5 M, degas.), [Cu(OTf)] · PhH (1.5 mol %), BOX ligand **583** (3.3 mol %), **582** (6.0 eq.) in CH_2Cl_2 (0.1 M, degas.), addition over 12 h, rt. (1.5 g scale)	98	>30:1	43	2)
10	CH_2Cl_2 (1.5 M, degas.), [Cu(OTf)] · PhH (0.6 mol %), BOX ligand **583** (1.3 mol %), **582** (6.0 eq.) in CH_2Cl_2 (0.13 M, degas.), addition over 12 h, rt. (3.6 g scale)	96	>30:1	58	2)
11	CH_2Cl_2 (1.5 M, degas.), [Cu(OTf)] · PhH (2.5 mol %), BOX ligand **583** (5.5 mol %), **582** (6.0 eq.) in CH_2Cl_2 (0.13 M, degas.), addition over 12 h, rt. (6.0 g scale)	96	>30:1	60	2)

[1)] highly contaminated with ethyl diazoacetate dimer [2)] slightly contaminated with the dimer of ethyl diazoacetate [3)] many by-products [4)] no full conversion [5)] not determined [6)] contaminated with Buchner ring expansion product of benzene [7)] concentrations based on allylic silyl alcohol **529**

terms of yield and diastereomeric ratio ([Cu(OTf)] · PhH: 76% yield, $\alpha:\beta$ = 3.2:1; $Rh_2(OAc)_4$: 45% yield, $\alpha:\beta$ = 1:1; Entries 4 and 7). Copper(I) trifluoromethanesulfonate is commercially available as its benzene or toluene complex. In terms of reactivity no noteworthy differences have been observed. The benzene complex furnished cyclopropane **581** in slightly higher yield and diastereomeric ratio (Entries 4 and 5). The addition of of a diluted solution of ethyl diazoacetate in PhH instead of CH_2Cl_2 reduced the yield drastically. Apparently, the cyclopropanation of benzene is faster than the cyclopropanation of allylic silyl alcohol **529** since the Buchner ring expansion product of benzene has been obtained predominantly.

The yield of product **581** has been increased by the use of copper(I) sulfate (35 mol %) and the addition of a diluted solution of ethyl diazoacetate in hexanes to allylic silyl alcohol **529** in refluxing hexanes over 7.0 h (Entry 8). Albeit the diastereomeric ratio was slightly diminished in this case, this procedure allowed rapid access to multigram amounts of cyclopropane **581**.

The diastereomeric ratio could be improved drastically by using bisoxazoline ligands, **583** in particularly (Fig. 6-5).[381,382] Not only the desired product was furnished in a great diastereomeric ratio (α:β > 30:1) but also the yield was almost quantitative (at least 90%, usualy 96–98%, Entries 9–11). In addition, the use of bisoxazoline ligands for the metal-catalyzed cyclopropanation of olefins furnishes enantioenriched products. In accordance to literature different ligand ratios have been investigated and the best obtained enantiomeric ratio was 80:20 (Entry 11). At this point, no further investigations concerning the improvement of the enantiomeric excess have been carried out and this procedure was used to produce multigram amounts of almost diasteriomerically pure cyclopropane **581**.



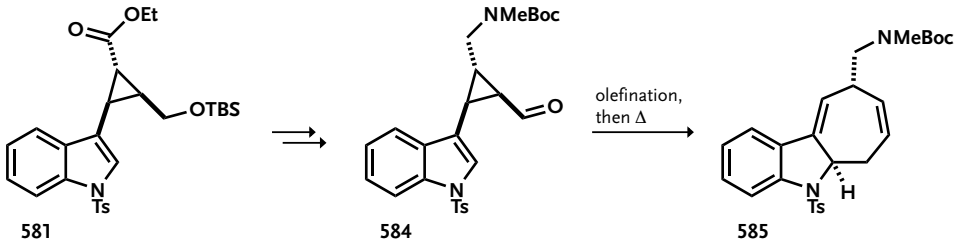
583

Figure 6-5. 2,2'-Isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline].

6.2.1 Towards Divinylcyclopropane Precursor **584**

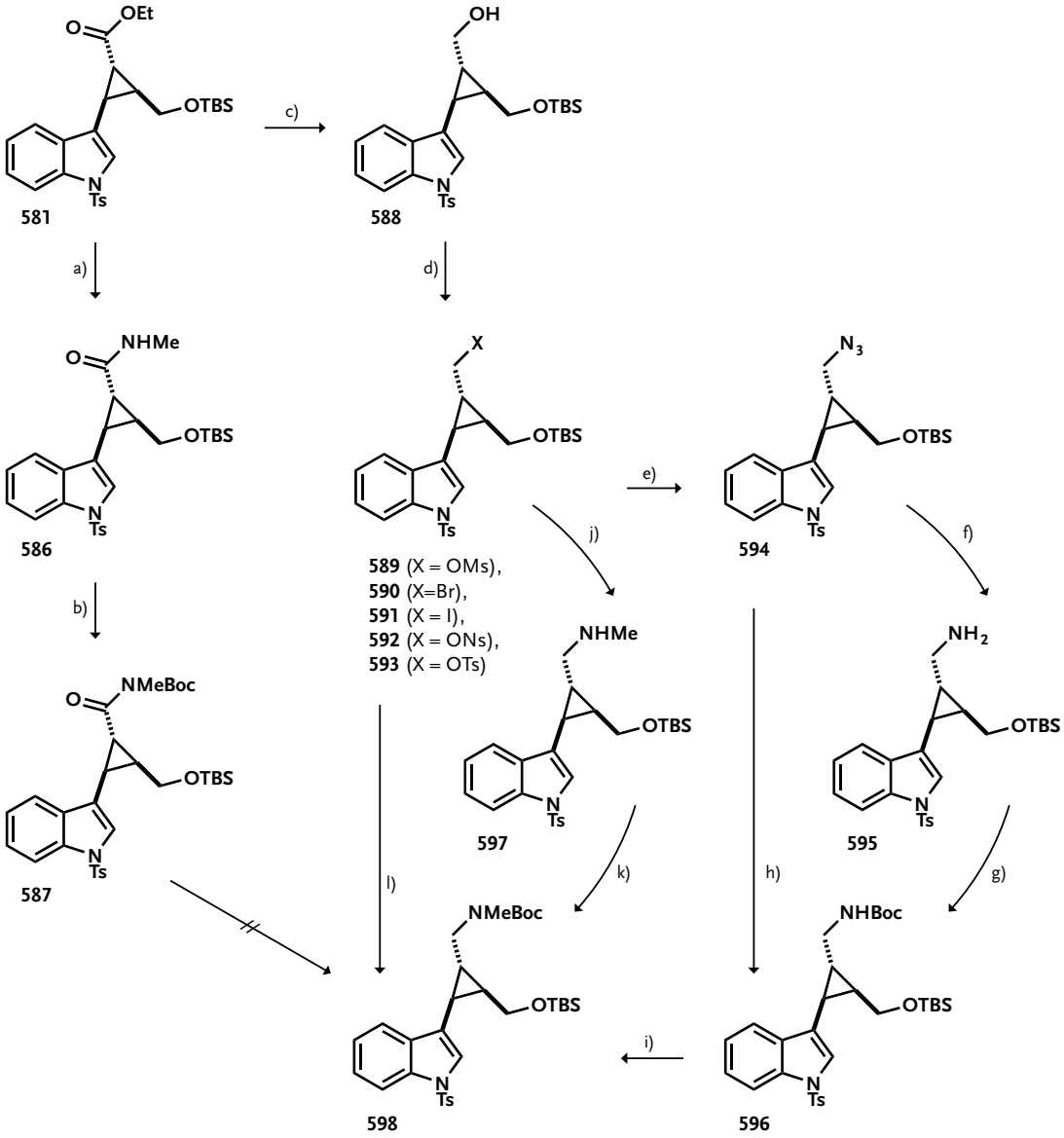
With trisubstituted cyclopropane product **581** in hand, attention next turned to the synthesis of divinylcyclopropane precursor **584** (Scheme 6-3)—an important building block towards the syntheses of *Ervatamia* alkaloids, the methuenine series in particular. Formally, this requires the transformation of the ester moiety into the corresponding Boc-protected methylamine which includes a lowering of the oxidation state. Many approaches towards this building block have been carried out to find the optimal conditions for this transformations (Scheme 6-4).

The most obvious conversion is the transformation of ester **581** into amide **586** followed by Boc protection and reduction. Treatment of ester **581** with 40% aqueous methylamine solution in methanol for 4 hours at 90 °C smoothly furnished secondary amide **586** in 70% yield. Boc protection with Boc_2O and a catalytic amount of DMAP afforded imide **587** in almost quantitative yield. However, this approach found an abrupt end when several reduction conditions ($NaBH_4$, $LiAlH_4$, LiTEBH) failed to transform imide **587** into the corresponding Boc-protected methylamine **598**. Therefore, ester **581** was first reduced to alcohol **588**. This reaction was not consistently reproducible with similar yields probably due to fumarate residues from the previ-



581 584 585

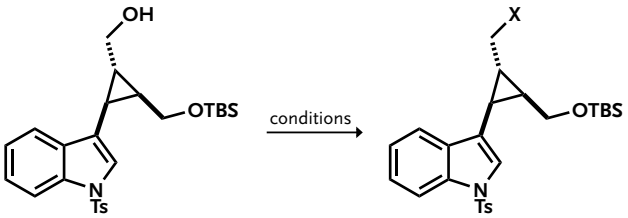
Scheme 6-3. Towards divinylcyclopropane precursor **584**.



Scheme 6-4. Reagents and conditions: **a)** $MeNH_2$ (40% aq.)–MeOH (2:1), 90 °C, 4.0 h, 70%. **b)** Boc_2O, DMAP, THF, rt., 15 min, 96%. **c)** DiBAL, CH_2Cl_2, –78 °C, 2 h, 34–70%; or $LiBH_4$, PhMe, 0 °C, 15 min, then 100 °C, 1.5 h, 66%. **d)** see text and Tab. 6-2. **e)** NaN_3, DMF, 50 °C, 60 min, 80% from **589** and 87% from **590**. **f)** PBu_3, THF–H_2O (10:1), rt., 3.0 h. **g)** Boc_2O, Et_3N, CH_2Cl_2, rt., 60 min **h)** H_2 (1 atm), Pd/C, Boc_2O, MeOH–THF (1:1), quant. **i)** MeI, NaH, DMF, 0 °C to rt., 3.0 h, 68% (3 steps). **j)** $MeNH_2$ (40% in MeOH), rt., 2.0 h. **k)** Boc_2O, Et_3N, rt., 10 min, 83% (from **588**). **l)** NHMeBoc, NaH, DMAc, 0 °C → rt., 2.0 h, 81% from **590** and 49% from **591**.

ous step. Several reduction conditions were investigated, best results were achieved both with DiBAL at –78 °C and $LiBH_4$ at 100 °C. With alcohol **588** in hand, transformations into several different derivatives were carried out (Tab. 6-2). Those derivatives which contains a potential leaving group were sometimes unstable and tended to elimination forming methylenecyclopropanes (X = I, ONs, and OTs). In most cases, these intermediates were used crude for the next step to circumvent stability issues. Compounds **589** (X = OMs), **590** (X = Br), and **591** (X = I) were then transformed into azide **594** using straightforward S_N2 conditions (NaN_3, DMF,

Table 6-2. Transformations of alcohol **588**.



#	Conditions	X	Product	Yield [%]
1	MsCl, Et_3N, CH_2Cl_2, 0 °C, 20 min	OMs	**589**	— [1]
2	CBr_4, PPh_3, CH_2Cl_2, 0 °C, 5 min	Br	**590**	— [1] [2] [3]
3	I_2, PPh_3, imid., PhH, rt., 5 min	I	**591**	— [1] [2] [3]
4	NsCl, Et_3N, CH_2Cl_2, 0 °C → rt., 120 min	ONs	**592**	62 [3]
5	TsCl, Et_3N, CH_2Cl_2, 0 °C → rt., 180 min	OTs	**593**	69 [3]
6	NaH, BnBr, DMF, 0°C → rt.	OBn	**599**	decomp.
7	NaH, PMBCl, THF, 0 °C → rt., 180 min	OPMB	**600**	32
8	NaH, MeI, THF, 0 °C → rt., 180 min	OMe	**601**	90

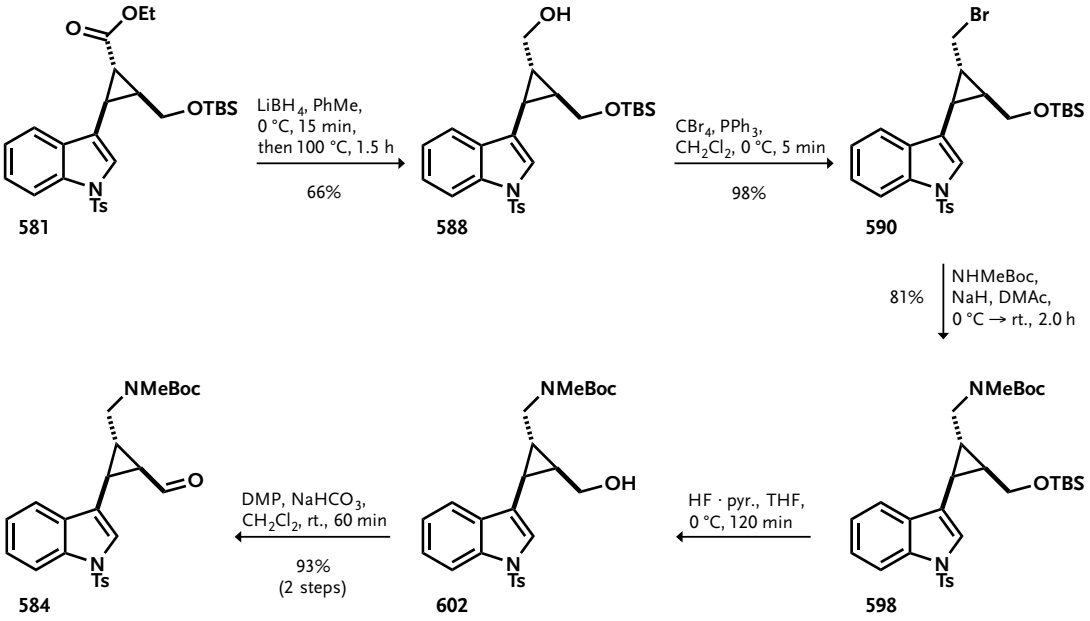
[1] used crude for the next step [2] short reaction time is crucial [3] unstable (tends to elimination)

50 °C). It turned out that mesylate **589** and bromide **590** were the most suitable compounds for this transformation furnishing azide **594** in more than 80% yield. Iodide **591** underwent the competing elimination reaction at elevated temperatures, no S_N2 reaction occurred at ambient temperature.

Azide **594** was then transformed into amine **595** *via* Staudinger reaction (PBu_3, THF–H_2O 10:1) and the labile amine was immediately converted into its corresponding Boc derivative **596**. Although this sequence proceeded with decent yield, this two-step sequence has been shortened and optimized. Hydrogenation of azide **594** over palladium on charcoal in MeOH–THF (1:1) in the presence of Boc_2O furnished directly amide **596** in almost quantitative yield which was methylated to afford the target compound **598**.

Since this synthetic route for Boc protected amine **598** contains quite a few transformations, a simpler access to **598** was investigated. Bromide **590**, and iodide **591** were treated with a methanolic solution of methylamine (40%) for 2 hours at ambient temperature to afford amine **597** which then was directly treated with Boc_2O in the presence of Et_3N to yield Boc protected amine **598**. Best yields were obtained with bromide **590** (83% over two steps). This procedure could even be reduced to a single-step reaction by treatment of bromide **590** with the sodium amide of NHMeBoc in dimethylacetamide. This afforded target compound **598** in 81% yield. Once again, best results were obtained with bromide **590**. Iodide **591** furnished target compound **598** in reduced yield, once again the competitive elimination reaction predominated.

A lot of synthetic routes for one and the same compound have been discussed. The final optimized sequence for amide **598** is shown in Scheme 6-5.

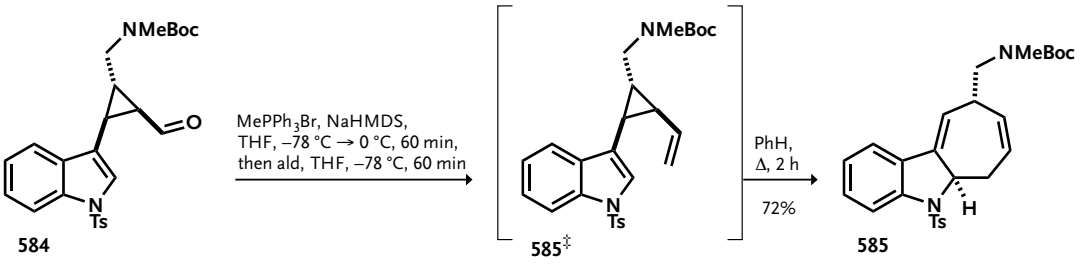


Scheme 6-5. Optimized synthetic sequence for amide **598** and conversion into the divinylcyclopropane precursor **584**.

With amide **598** in hand, attention next turned to the synthesis of divinylcyclopropane precursor **584** (Scheme 6-5). The silyl protecting group was removed with HF · pyr. in THF followed by subsequent oxidation of the primary alcohol to aldehyde **584** using Dess–Martin periodinane (**603**). This sequence afforded aldehyde **584** in 93% combined yield. Alcohol **602** could also be oxidized with IBX (**604**) in similar yields but prolonged reaction times. Parikh–Doering oxidation could also be used for alcohol **602**, but it was observed that under these conditions the stereochemistry at the α-carbon atom was scrambled and a diastereomeric mixture of **584** was obtained.

6.2.2 Cyclohepta[*b*]indoles from Divinylcyclopropane Precursor **584**

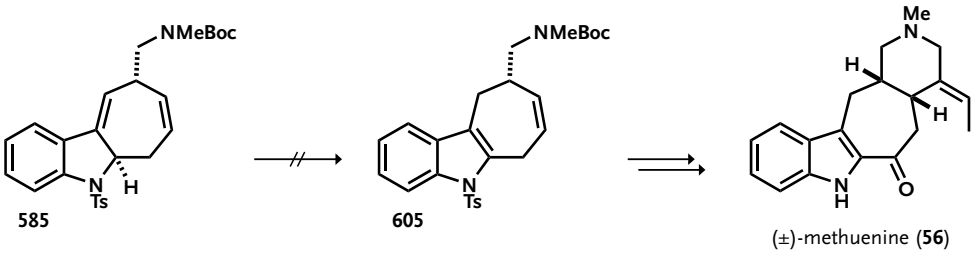
According to the developed methodology (Section 5.2), aldehyde **584** was converted into divinylcyclopropane compound **585**‡ *via* usual Wittig conditions. Quick work-up and subsequent stirring in refluxing benzene for additional 2 hours smoothly furnished cyclohepta[*b*]indoline **585** in



Scheme 6-6. Synthesis of cyclohepta[*b*]indole **585**.

72% yield. As expected, the additional rest at the cyclopropane had an effect on the rearrangement. Whereas the rearrangement for the unsubstituted cyclohepta[*b*]indole **533** (derived from terminal alkene, **546**: $R^1 = R^2 = H$; Scheme 5-15, p. 109) took place at ambient temperature in 1.0 h, the rearrangement of **585**‡ required increased temperatures and prolonged reaction times. However, in consideration of the fact that the steric hindrance has increased drastically due to the bulkiness of the attached substituent, the rearrangement proceeded in an adequate amount of time under moderate heating.

With cyclohepta[*b*]indoline **585** in hand, a significant building block towards the synthesis of *Ervatamia* alkaloids has been synthesized. More importantly, the generality of the methodology has been proven one more time. But unfortunately, the joy was short-lived. At this time it was observed, that several synthesized cyclohepta[*b*]indolines were not permanently stable and began to decompose after a short period of time, even below 0 °C. A simple workaround was to convert the cyclohepta[*b*]indolines into their corresponding cyclohepta[*b*]indoles, which has been already described in Section 5.2. The obtained cyclohepta[*b*]indoles seemed to be bench-stable for an indefinite period of time. At this point, it turned out that compound **585** was very acid-sensitive. Every attempt to rearomatize cyclohepta[*b*]indoline **585** under acidic conditions yielded in decomposition of the material (Scheme 6-7). It could be observed *via* TLC, that the Boc group was cleaved under the acidic conditions, but apparently the liberated secondary amine was not stable under these required conditions. Several attempts remained unsuccessful and led to the end of this synthetic route towards *Ervatamia* alkaloids.



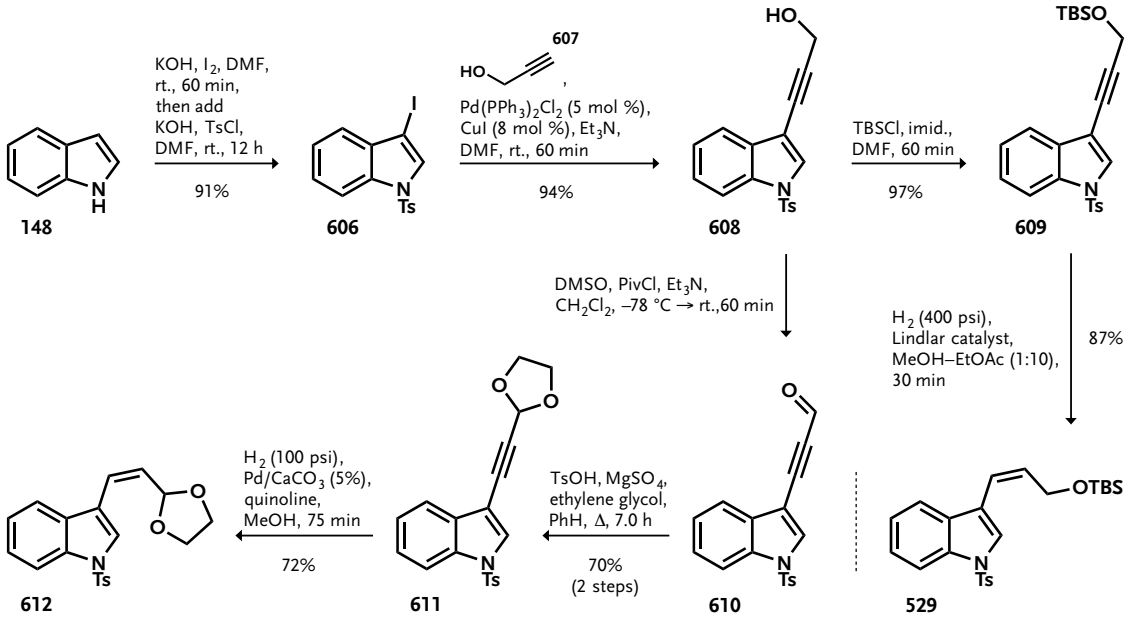
Scheme 6-7. Unsuccessful conversion of cyclohepta[*b*]indoline **585** into cyclohepta[*b*]indole **605**.

6.3 Variations

Since the first approach led to a dead end, several different synthetic proposals were taken into account. This section deals with the introduction of several intermediates *via* various synthetic routes which then will be referenced in subsequent sections. In addition, some variations for the synthesis of already presented or upcoming intermediates are discussed briefly.

6.3.1 Cyclopropanation Precursors *via* Hydrogenation of Alkynes

The divinylcyclopropane-cycloheptadiene rearrangement of indolylvinylcyclopropanes requires the indole moiety and the vinyl rest to be *syn*. As a consequence of this, the double bond geometry

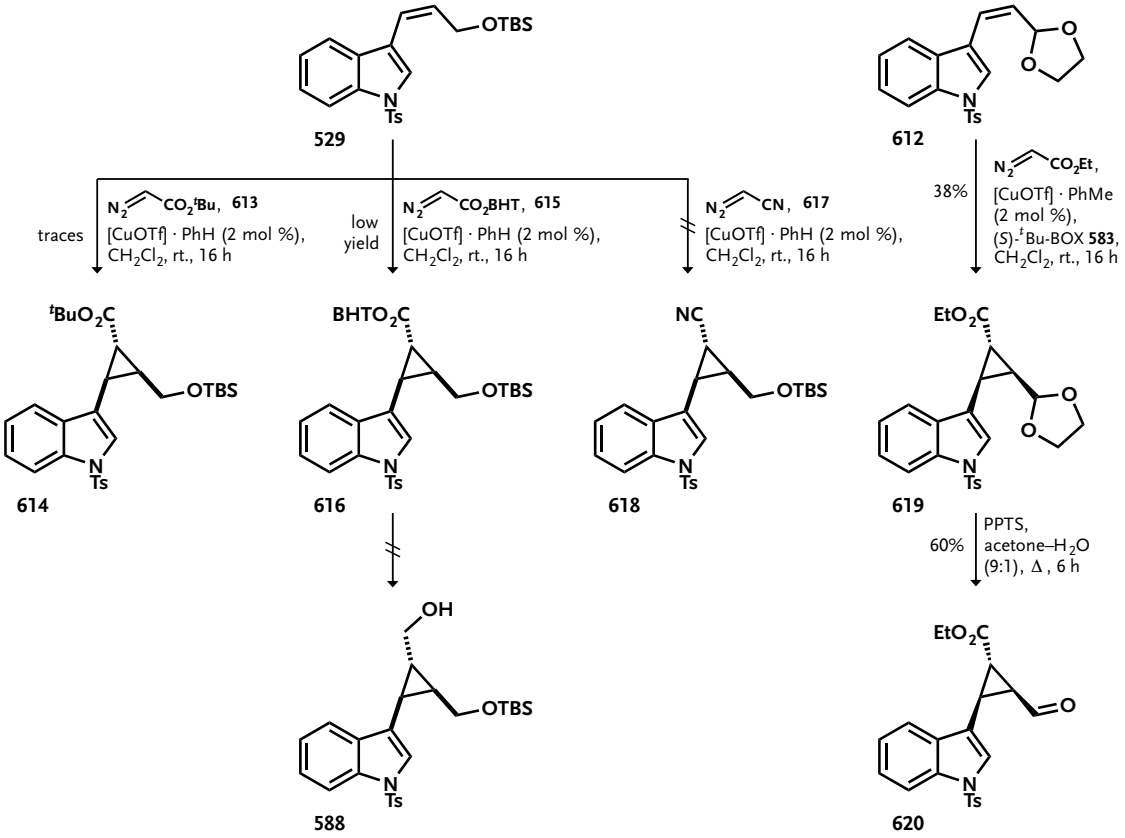


Scheme 6-8. Alternative route to (*Z*)-allylic silyl alcohol **529** and synthesis of acetal **612**.

of the cyclopropanation precursor has to be (*Z*). As shown before, this double bond geometry can be installed *via* Ando or Still–Gennari olefination (Section 5.2). An alternative approach is the *(Z)*-selective hydrogenation of alkynes such as propargylic alcohols **608** or **609**. Alcohol **608** is accessible *via* Sonogoshira coupling of propargyl alcohol (**607**) and *N*-tosyl-3-iodoindole (**606**),[383] the latter can be synthesized in one step from indole (**148**).[384] The hydrogenation of alkyne **608** was investigated, but all attempts failed and overreduction was observed. However, silyl protection of the free alcohol furnished propargylic silyl alcohol **609** which was successfully reduced to the corresponding *cis*-alkene **529** (400 psi H_2, Lindlar catalyst, MeOH–EtOAc 1:10, 30 min). Additionally, propargylic alcohol **608** was oxidized to the corresponding propynal derivative **610** *via* dimethyl sulfoxide pivaloyl chloride,[385] an alternative to the classical Swern oxidation.[362b] The aldehyde was then transformed to acetal **611** and hydrogenation over Pd/$CaCO_3$ (5%) with addition of quinoline furnished acrolein ethylene acetal derivative **612** in 50% overall yield (from propargylic alcohol **608**).

6.3.2 Cyclopropanation Variations

En route to the optimal conditions for the cyclopropanation of olefin **529** (Tab. 6-1, p. 121), several investigations concerning different cyclopropanation products were carried out (Scheme 6-9). Since ethyl diazoacetate (**582**) is commercially available and comparatively affordable it is quite common to use **582** as source for a diazo compound. The generation and handling of other diazo sources with a small molecular weight can sometimes be utterly cumbersome. Notwithstanding this, following diazo compounds were synthesized: diazoacetonitrile (**617**), 2,6-di-*tert*-butyl-4-methylphenyl 2-diazoacetate (BHT diazoacetate, **615**), and diazoacetone (**621**). Furthermore,



Scheme 6-9. Cyclopropanation variations.

tert-Butyl diazoacetate (**613**) was used as an additional commercially available diazo compound. Cyclopropanations with this diazo compounds were investigated.

tert-Butyl diazoacetate (**613**) and BHT diazoacetate (**615**) were chosen to investigate the influence of a bulky substituent to the *endo*/*exo* ratio of the cyclopropanation product. *tert*-Butyl diazoacetate (**613**) is known to undergo metal-catalyzed cyclopropanation reactions.[386–388] However, trisubstituted cyclopropane **614** was only formed in trace amounts. On the other hand, metal-catalyzed cyclopropanation of **529** with BHT diazoacetate (**615**) was fortunate, but (i) the yield was very low (< 10%), (ii) interestingly, the *endo*/*exo* ratio was about 1:1, and (iii) reduction of the bulky ester moiety to the corresponding alcohol **588** was unfruitful.

The cyclopropanation of olefin **529** with diazoacetonitrile (**617**) would lead to useful intermediate **618** due to the introduction of a masked amine. Unfortunately, there is only little knowledge about this diazo compound. Harada *et al*. have reported **617** to be highly explosive at high concentrations and disadvised to concentrate or isolate this diazo compound.[389] However, the 30 wt% solution of **617** in CH_2Cl_2 is not so dangerous. Although **617** has been synthesized successfully, several attempts to synthesize cyclopropane product **618** remained unfruitful.

Acrolein ethylene acetal derivative **612** was also an appropriate precursor for a metal-catalyzed cyclopropanation reaction with ethyl diazoacetate (**582**). In combination with BOX ligand **583**, enantioenriched trisubstituted cyclopropane **619** has been formed in decent yield. Once again

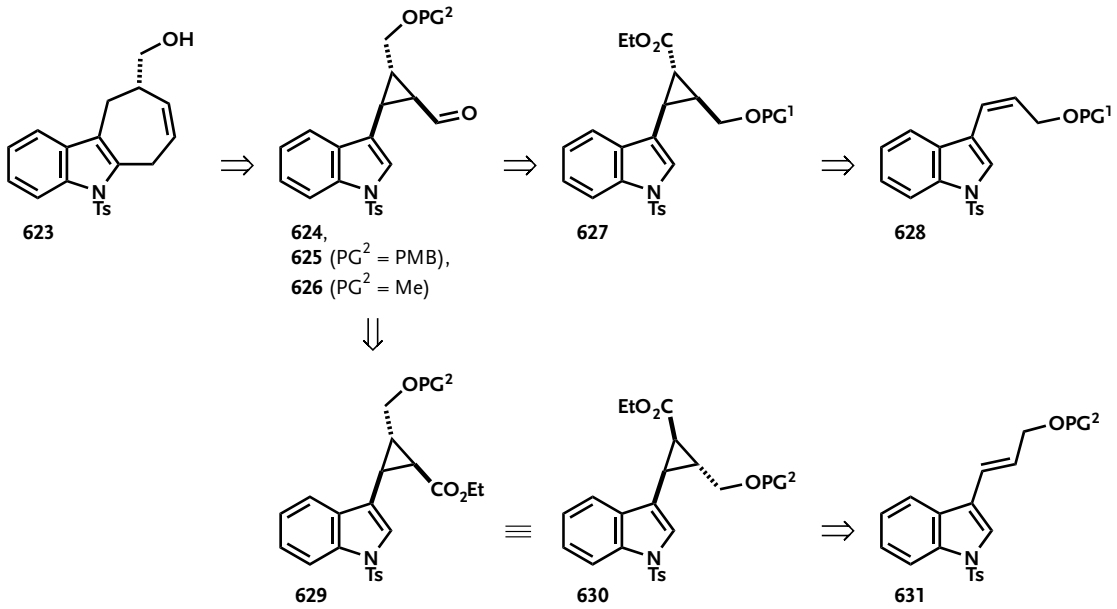
the diastereomeric ratio was excellent and formation of the all-*cis*-product was not observed. The acetal then was cleaved under aqueous acidic conditions to obtain aldehyde **622**. This intermediate becomes important at a later stage of the synthesis. The alternative synthesis and the use in a different approach is discussed later (Section 7.2, p. 153).

6.3.3 Cyclohepta[*b*]indoles from (*E*)-Olefins

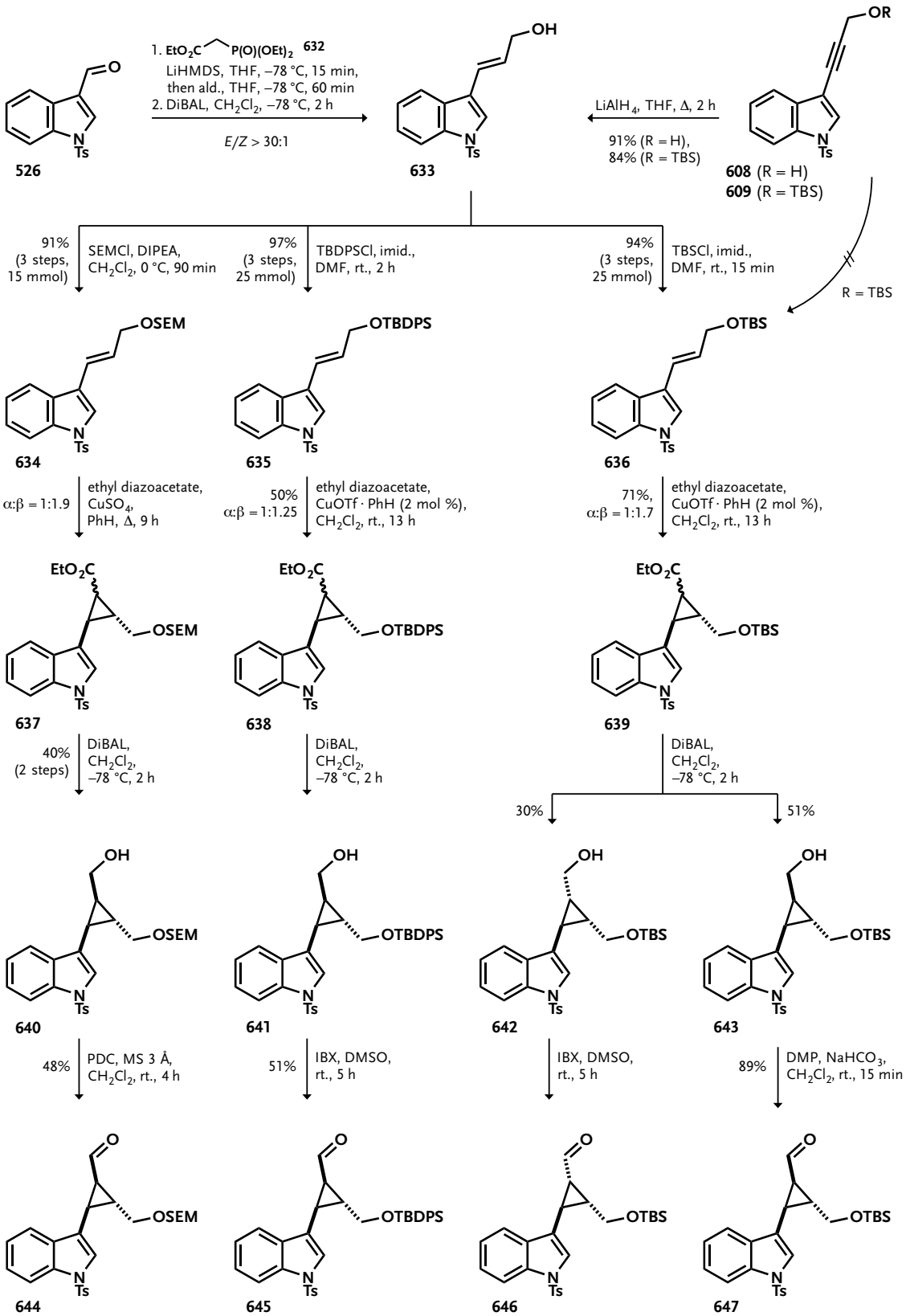
Since the first approach found an abrupt end due to rearomatization problems (p. 126), attention next turned to methanolyl-cyclohepta[b]indole **623** (Scheme 6-10) which is a precursor for both (±)-ervitsine (**64**) and (±)-methuenine (**56**, *cf.* Scheme 6-1, p. 119). The already established route *via* the cyclopropanation of *(Z)*-olefin **628** required only slight modifications. The ester moiety of cyclopropanation product **627** needs to be reduced to the corresponding alcohol **624** which requires protection. This is a real drawback since it necessitates another orthogonal protecting group. For this reason, only two intermediates of type **624** have been synthesized (*cf.* Tab. 6-2, p. 124): **625** (PG^2 = PMB) and **626** (PG^2 = Me).

Since the racemic cyclopropanation of *(Z)*-olefin **529** furnished the *endo*- and *exo*-product in a moderate ratio, it was worth to investigate the cyclopropanation of *(E)*-olefin **631**. In addition, according to Scheme 6-10 this approach would make the need for a second orthogonal protecting group for an alcohol functionality superfluous.

For this *N*-tosyl protected aldehyde **526** was reacted with triethyl phosphonoacetate (**632**) in the presence of LiHMDS followed by DiBAL reduction to obtain allylic alcohol **633** (Scheme 6-11). The ratio of *E*:*Z* here is over 30:1. Alternatively, **633** can be synthesized from the reduction of alkyne **608** with lithium aluminium hydride.[390,391] This reaction is completely *(E)*-selective.



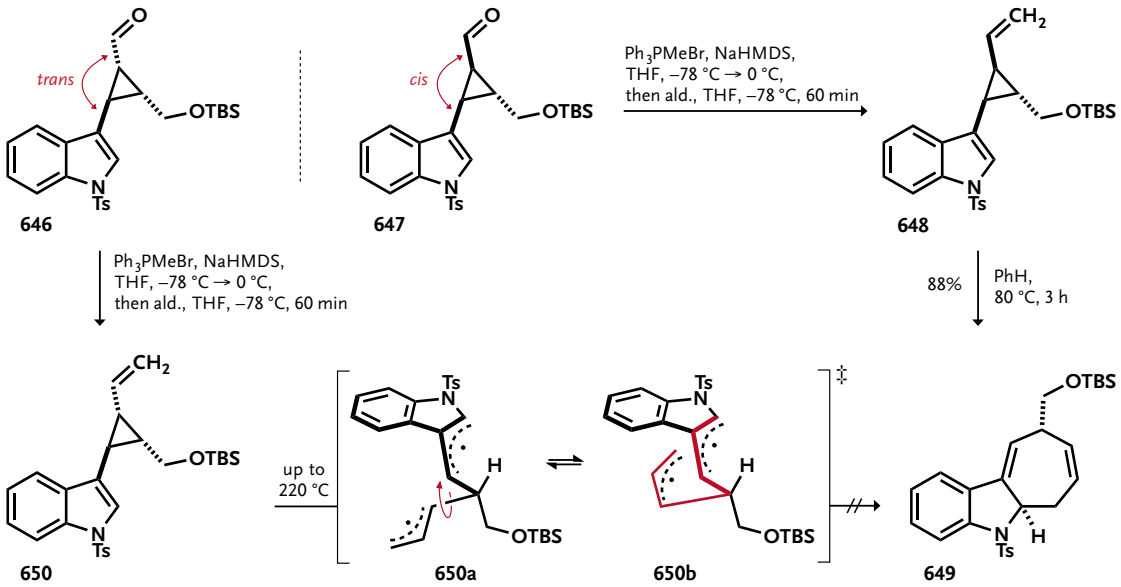
Scheme 6-10. Alternative approach to cyclohepta[*b*]indole **623**, a retrosynthetic analysis.



Scheme 6-11. Synthesis of four different cyclohepta[*b*]indole precursors **644**, **645**, **646**, and **647** from the cyclopropanation of (*E*)-allylic silyl alcohols **634**, **635**, and **636**.

Interestingly, the reduction of alkyne **609** furnished allylic alchol **633**, too, and not allylic silyl alcohol **636**. Although the TBS group is usually stable to reductive conditions, it is yet cleaved in this case. With allylic alcohol **633** in hands, protection with different silyl protecting groups (SEM, TBS, TBDPS) was carried out and all three silyl alcohols **634**, **635**, and **636** were obtained in excellent yield (91–97% over three steps). The primary reason for different protecting groups was the investigation of their influence during the cyclopropanation in terms of bulkiness and *endo*/*exo* ratio. In the case of TBS and TBDPS, usual conditions using 2 mol % [CuOTf] · PhH and an excess of ethyl diazoacetate (**582**) afforded trisubstituted cyclopropanes **638** and **639** in good to moderate yield. Surprisingly, the SEM group was cleaved under these conditions and no cyclopropanation took place. However, $CuSO_4$-mediated cyclopropanation with **582** in refluxing benzene afforded trisubstituted cyclopropane **637** in moderate yield. The *endo*- and *exo*-products were not separable at this stage, but DiBAL reduction of the ester moiety yielded two separable diastereomers in each case (**640**, **641**, **642**, and **643**). In all three cases the main diastereomer was also the desired one (that means, the methanolyl rest is *syn* to the indolyl rest). Surprisingly, best results were achieved with the smallest protecting group (SEM: α:β = 1:1.9, TBS: α:β = 1:1.7, TBDPS: α:β = 1:1.25). This concludes that olefins which contain a bulky group tend to produce the *exo*-product in higher yield. Finally, the primary alcohols were oxidized to obtain the corresponding aldehydes **644**, **645**, **646**, and **647** in moderate to good yields (48–89%).

With aldehydes **644**, **645**, **646**, and **647** in hand, attention next turned to the transformation of these aldehydes into the corresponding cyclohepta[*b*]indoles. This is shown exemplary for the transformation of aldehyde **647** (Scheme 6-12). Both diastereomers of this aldehyde were prepared (**646** and **647**). At first glance, only aldehyde **647** is an appropriate substrate for the upcoming divinylcyclopropane-cycloheptadiene rearrangement since it is plausible that only



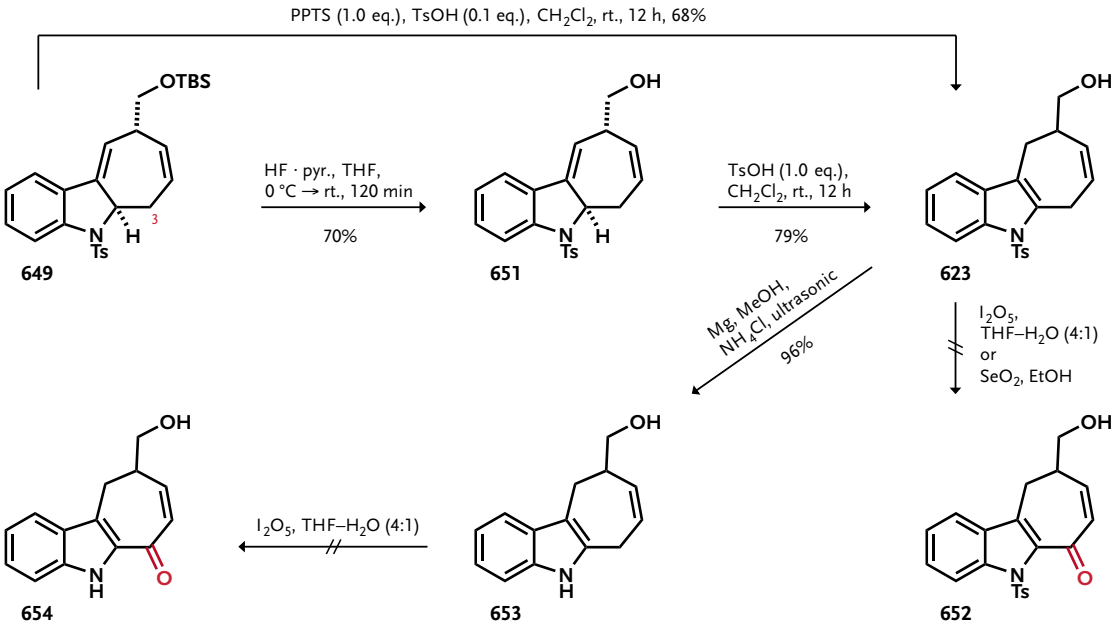
Scheme 6-12. Divinylcyclopropane-cycloheptadiene rearrangement of cyclohepta[*b*]indole precursor **647**.

cis-configured divinylcyclopropanes are eligible for a [3,3] sigmatropic rearrangement. The *trans*-configured counterparts usually cannot undergo a [3,3] sigmatropic rearrangement since the required cyclic transition state cannot be adopted due to the absence of orbital overlap of the two π-bonds. Nevertheless, high temperature can lead to the same product as it is obtained from the *cis* configured counterpart. The reason is a homolytic dissociation of the central linkage, to give a *trans*-allyl biradical. Isomerization of the allyl groups enables the correct orbital geometry to perform a [3,3] sigmatropic rearrangement. To this day it is not known whether only the isomerization occurs *via* a biradical mechanism or also the cyclization itself (*cf.* Scheme 3-6 on p. 52).[175c,192]

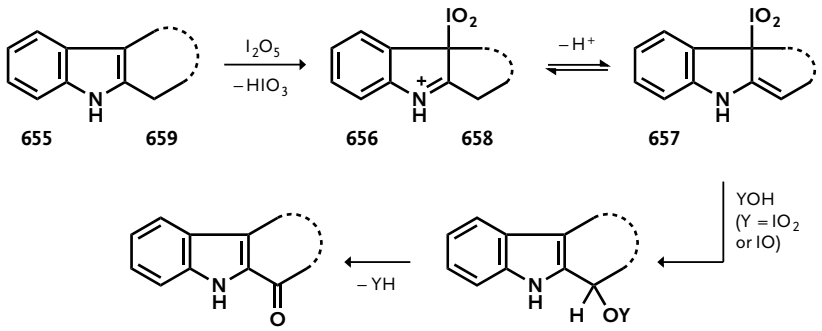
Aldehyde **647** was transformed into indolylvinylcyclopropane **648** which is stable at ambient temperature (Scheme 6-12). However, stirring in benzene at 80 °C for 3.0 h smoothly furnished cyclohepta[*b*]indoline **649** in very good overall yield (88%). The same sequence was repeated with the *trans*-configured counterpart **646**, but several attempts for the rearrangement of **650**—even heating up to 220 °C—remained unfruitful.

6.3.4 Generation of 2-Acylindoles — Oxidation (I)

With silyl protected methanolyl-cyclohepta[b]indoline **649** in hands, attention next turned to the synthesis of the 2-acylindole counterpart, that is the oxidation of the C-3 position (natural product counting, Scheme 6-13). The silyl protecting group was cleaved with hydrogen fluoride to obtain alcohol **651** which was subsequently treated with *p*-toluenesulfonic acid to afford methanolyl-cyclohepta[*b*]indole **623** in 55% combined yield. Alternatively, silyl compound **649** is treated with a catalytic amount of *p*-toluenesulfonic acid and an equimolar amount of pyri-



Scheme 6-13. Attempts for the synthesis of 2-acylindole **654**.

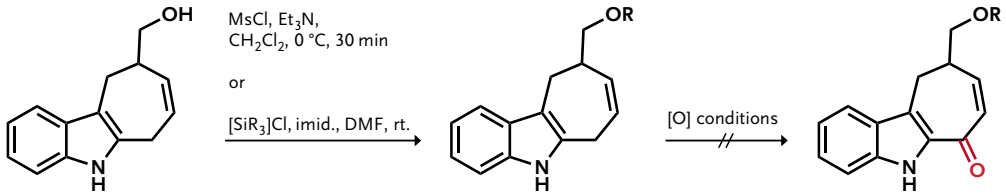


Scheme 6-14. Oxidation of cycloalkan[*b*]indoles with iodine pentoxide (I_2O_5).

dinium *p*-toluenesulfonate to obtain methanolyl-cyclohepta[*b*]indole **623** *via* desilylation and rearomatization in one single step in 68% yield.

There is only little knowledge about the direct oxidation of cycloalkan[*b*]indoles to their 2-acylindole counterparts. Basically the only effective methodology was published in 1987 by Yoshida *et al.* who described the oxidation of cycloalkan[*b*]indoles with iodine pentoxide (I_2O_5).[392] This methodology found some minor application in synthesis, e.g. in the synthesis of new NPY-1 antagonists.[393] The mechanism of this transformation is shown in Scheme 6-14. Quite recently, Banwell *et al.* published an oxidation using harsh conditions with PCC.[394] An unprotected indole is used in all cases. However, several attempts with *N*-tosyl protected compound **623** were carried out. But both iodine pentoxide and selenium dioxide turned out to be ineffective as starting material was recovered in all cases. Therefore, the tosyl group was cleaved using an excess of magnesium in methanol[395] and unprotected cyclohepta[*b*]indole **653** was obtained in almost quantitative yield. But again, several attempts for the oxidation remained unfruitful and 2-acylindole **654** was not obtained.

It might be a legitimate point that the unprotected alcohol may cause trouble during this oxidation process. Therefore, several protected derivatives were synthesized (Scheme 6-15). With derivatives **660**, **661**, and **662** in hands, several oxidative conditions were investigated



[O] Conditions:

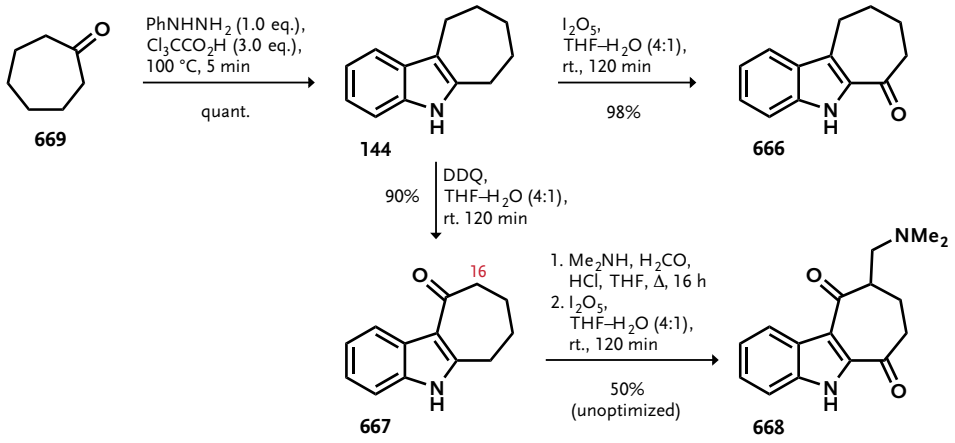
a) I_2O_5, THF–H_2O (4:1), rt.[392] **b)** PCC, CH_2Cl_2, rt. → Δ.[394] **c)** SeO_2, CH_2Cl_2 or EtOH, rt.

d) Ph_2Se_2, $PhIO_2$, C_6H_5N, 100 °C.[396,397] **e)** CrO_3 · 3,5-dimethylpyrazole, CH_2Cl_2, 0 °C.[398]

Scheme 6-15. Attempts for the synthesis of 2-acylindoles.

(see Scheme 6-15). To put it in a nutshell, not a single oxidation reaction was successful and 2-acylindoles **663**, **664**, or **665** were never obtained either due to inertness of the substrate to the applied conditions or due to rapid decomposition.

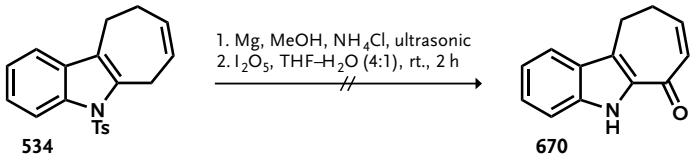
At this point, the generality of this oxidative sequence was questioned. For this reason, a simple test system was synthesized (Scheme 6-16). According to Bulman *et al.*,[399] cycloheptanone (**669**) was reacted with phenylhydrazine in the presence of trichloroacetic acid to obtain "naked" cyclohepta[*b*]indole **144** in quantitative yield. This compound was subjected to iodine pentoxide mediated oxidative conditions as before and 2-acylindole **666** was obtained in almost quantitative yield. To investigate if a late-stage oxidation would be possible, cyclohepta[*b*]indole **144** was transferred into 3-acylindole **667** with DDQ in aqueous THF.[400] Subsequent Mannich reaction with formaldehyde and dimethylamine[401] generates a compound similar to the *Ervatamia* alkaloids bearing an alkyl chain with a tertiary amine at C-16. This compound was oxidized with iodine pentoxide to the corresponding 2-acylindole **668** without difficulty.



Scheme 6-16. Test system for the synthesis of 2-acylindole derivatives.

No confirmed statements concerning the failed iodine pentoxide mediated oxidations in previous systems can be made. It is assumed, that the π-bond between C-15 and C-14 somehow prevents the successful oxidation of the C-3 position. This assumption is supported by the result of the unfruitful oxidation of simple cyclohepta[*b*]indole **534** (Scheme 6-17).

This results led to a general question: how to introduce an oxygen or an oxygen equivalent, respectively, before the divinylcyclopropane-cycloheptadiene rearrangement takes place? Attempts to this problem are described in the following two sections.



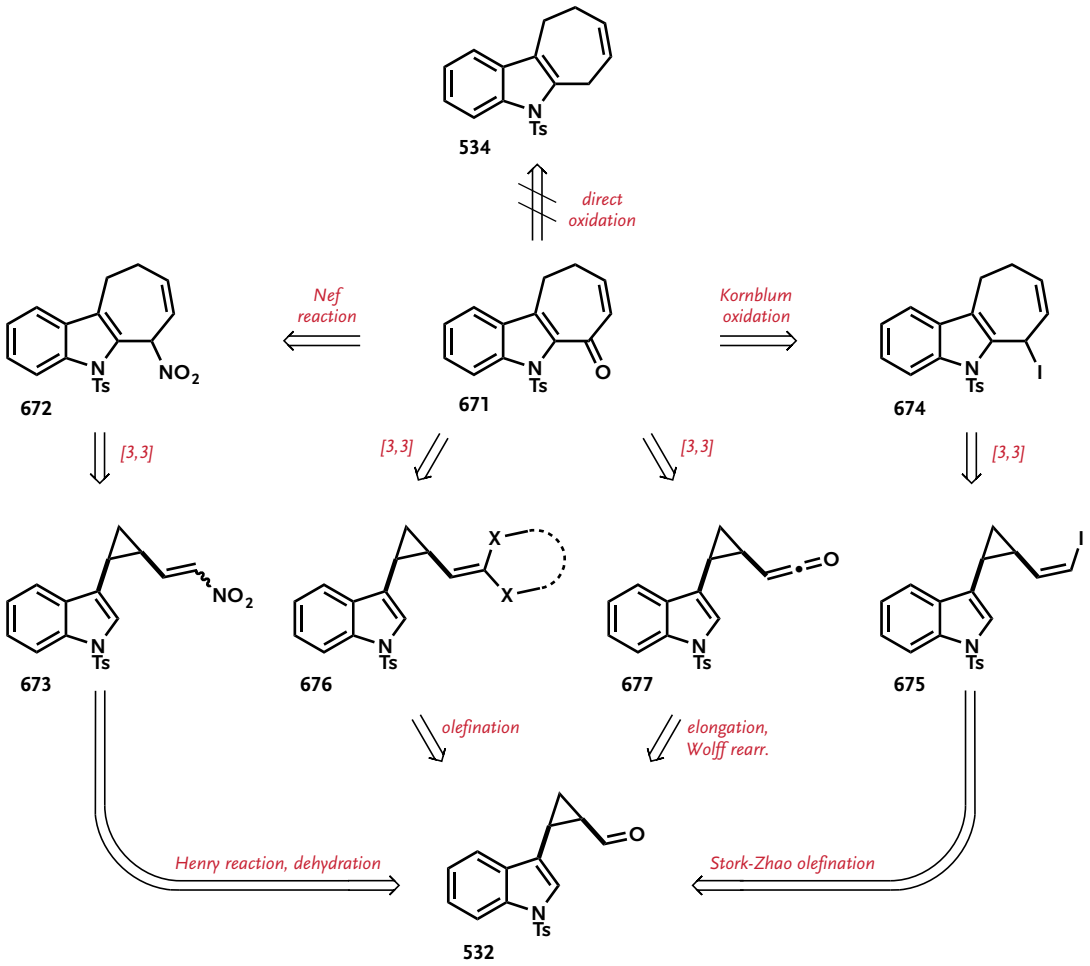
Scheme 6-17. Oxidation of simple cyclohepta[*b*]indole **534**.

6.4 Towards the Synthesis of 2-Acylindoles — Second Approach

Since the first approaches led to an end due to massive oxidation problems, the introduction of an oxygen or an oxygen equivalent, respectively, before the divinylcyclopropane-cycloheptadiene rearrangement takes place was taken into account. Since this section is for the most part about methodology development, the third rest at the cyclopropane was omitted consciously to simplify and accelerate the development.

Several possibilities are shown in Scheme 6-18. The keto functionality can derive from nitro compound **672** *via* Nef reaction.[402] Nitro compound **672** itself is the product of the divinylcyclopropane-cycloheptadiene rearrangement of olefin **673** which can be synthesized *via* Henry reaction[403] (and potential dehydration) from known aldehyde **532**.

Another possibility can be the Kornblum oxidation[404] (or more updated procedures with pyridine *N*-oxide[405]) of benzylic iodide **674**. The precursor **675** can again be synthesized from already known aldehyde **532** *via* Stork–Zhao olefination.[406]

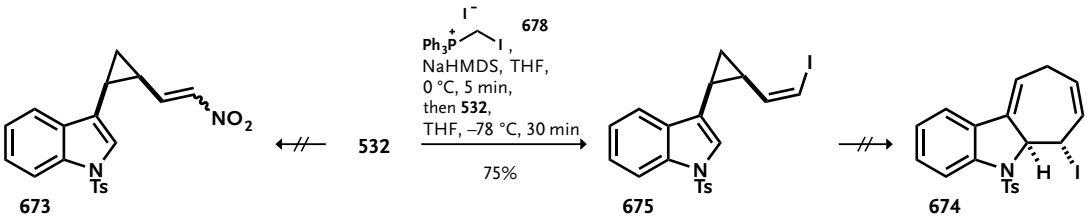


Scheme 6-18. New retrosynthetic analysis of 2-acylindoles.

A more direct way is the introduction of the keto functionality *via* ketene acetal **676** (X = S or O) or ketene **677**. Ketene acetal **676** derives from aldehyde **532** *via* olefination reaction as well as ketene **677**, which is accessible from aldehyde **532** *via* transformation into the corresponding α-diazo ketone followed by Wolff rearrangement.[407]

6.4.1 Approach *via* Henry Reaction and Stork–Zhao Olefination

Both the proposal from Scheme 6-18 for the Henry reaction and the proposal for the Stork–Zhao approach can be sum up in a very short way (Scheme 6-19). The transformation of aldehyde **532** into nitro olefin **673** was not successful. Instead the reaction of aldehyde **532** with the ylide of Stork–Zhao reagent **678** smoothly furnished *(Z)*-vinyl iodide **675** in 75% yield. But several attempts for the rearrangement of compound **675** to synthesize cyclohepta[*b*]indoline **674** remained unfruitful and led to decomposition of the material. Hence, attention turned to the generation of ketene acetals.

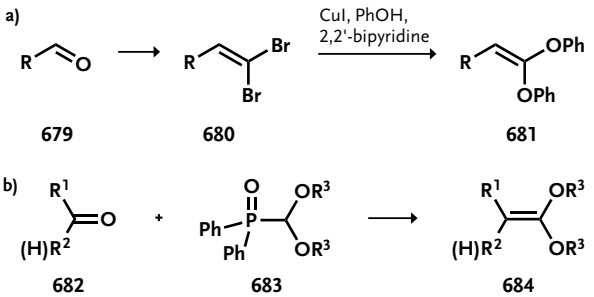


Scheme 6-19. Transformations of aldehyde **532**.

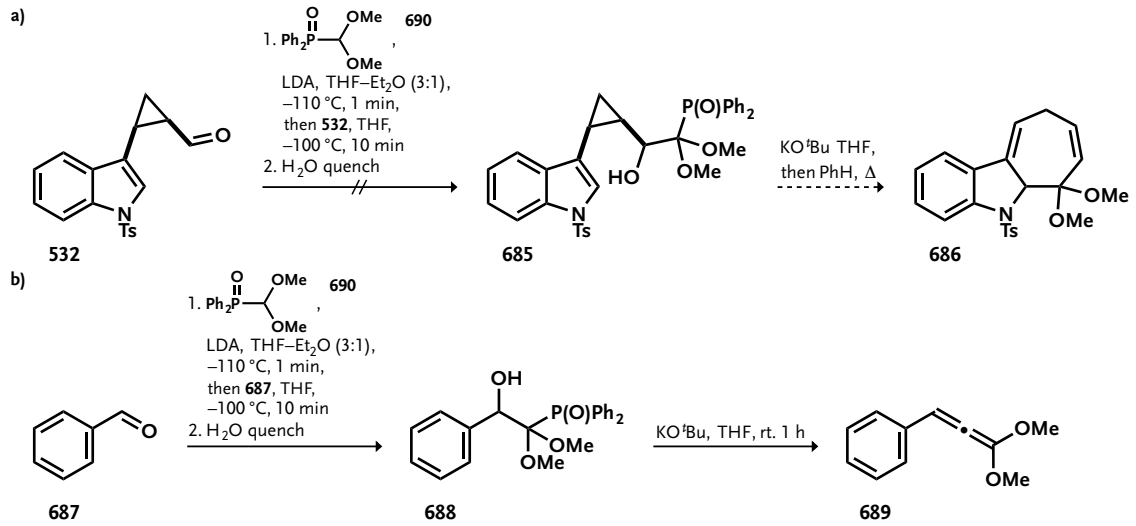
6.4.2 2-Acylindoles from the Divinylcyclopropane Rearrangement of Ketene Acetals

6.4.2.1 Ketene *O,O*-Acetals

The generation of ketene *O,O*-acetals is widely known and especially silyl ketene acetals have found widespread use in organic synthesis. However, literature for the synthesis of ketene *O,O*-acetals from aldehydes *via* homologation is scarce. Basically, there are only two methodologies reported: (i) a copper-catalyzed cross-coupling between 1,1-dibromoalkenes and phenols



Scheme 6-20. Transformation of carbonyls into their homologous ketene *O,O*-acetals.[408–410]



Scheme 6-21. Attempts for the generation of the homologous ketene *O,O*-acetal of aldehydes **532** and **687**.

(Scheme 6-20a),[408] and (ii) the conversion of aldehydes as well as ketones into their homologous ketene *O,O*-acetals by a Horner–Wittig reaction with dialkoxymethyl diphenylphosphine oxides (Scheme 6-20b).[409,410] Since the first methodology requires the previous transformation of the aldehyde into its 1,1-dibromoalkene derivative, only the Horner–Wittig reaction with dialkoxymethyl diphenylphosphine oxides was taken into account.

The Horner–Wittig protocol was then applied to aldehyde **532**. Deprotonation of dimethoxymethyl diphenylphosphine oxide (**690**) with LDA at –110 °C in THF–ether (3:1) smoothly furnished the ylide which was visible due to a bright yellow color of the anion. Nevertheless, several attempts for the reaction of this ylide with aldehyde **532** remained unfruitful and the formation of cyclohepta[*b*]indoline **686** could not be investigated (Scheme 6-21a). Due to the careful handling of phosphine oxide **690** and its ylide, similar reaction conditions were applied to the reaction with benzaldehyde (**687**) to check the generality of this Horner–Wittig reaction. The formation of intermediate **688** was observed and subsequent treatment with potassium *tert*-butoxide furnished ketene *O,O*-acetal **689** (Scheme 6-21b). Therefore, the formation of ketene *O,O*-acetal of aldehyde **532** was given up and attention next turned to the formation of ketene *S,S*-acetals of **532**.

6.4.2.2 Ketene *S,S*-Acetals

As for the synthesis for ketene *O,O*-acetals, the literature for the synthesis of ketene *S,S*-acetals from aldehydes *via* homologation is also very scarce. Juaristi *et al.* described the synthesis of (1,3-dithian-2-yl)diphenylphosphine oxide (**691**) and its application as Wittig–Horner/

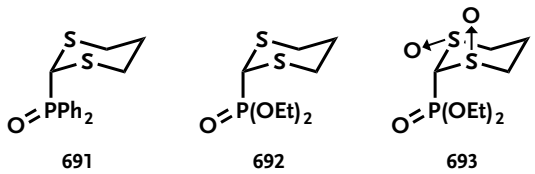
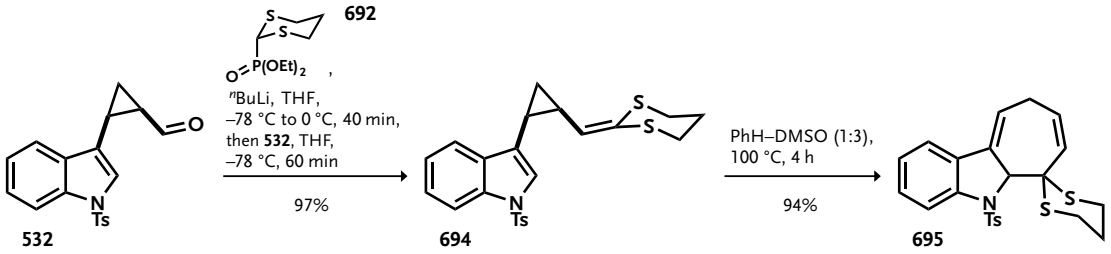


Figure 6-6. Reagents **691**, **692**, and **693**.



Scheme 6-22. Synthesis of ketene *S,S*-acetal **694** and its divinylcyclopropane-cycloheptadiene rearrangement product **695**.

Corey–Seebach reagent (Fig. 6-6).[411] Also known is its Horner–Wadsworth–Emmons/Corey–Seebach counterpart diethyl (1,3-dithian-2-yl)phosphonate (**692**, Fig. 6-6).[412] The latter reagent has an additional advantage since it is also known as its chiral sulfoxide counterpart **693**.[413]

Based on the protocol of Juaristi *et al.*, aldehyde **532** was reacted with the ylide of Horner–Wadsworth–Emmons/Corey–Seebach reagent **692** at –78 °C for 60 min and ketene *S,S*-acetal **694** was afforded in impressive yield (97%, Scheme 6-22). With **694** in hands, attention next turned to its divinylcyclopropane-cycloheptadiene rearrangement product. Usual conditions (refluxing benzene) afforded desired rearrangement product **695** very slowly. However, several attempts revealed, that the rearrangement product was afforded smoothly in benzene–dimethyl sulfoxide (1:3) at 100 °C in 4 h (94% yield).

With this good results in hands, attention next turned to the synthesis of trisubstituted cyclopropane ketene *S,S*-acetals. For this reason, aldehyde **584** was transformed into ketene *S,S*-acetal **696** in 80% yield using the same conditions as before (Scheme 6-23). However, ketene *S,S*-acetal **696** turned out to be very stable. Several attempts (listed in Tab. 6-3) for the divinylcyclopropane-cycloheptadiene rearrangement of **696** failed and cyclohepta[*b*]indoline **697** could not be obtained.

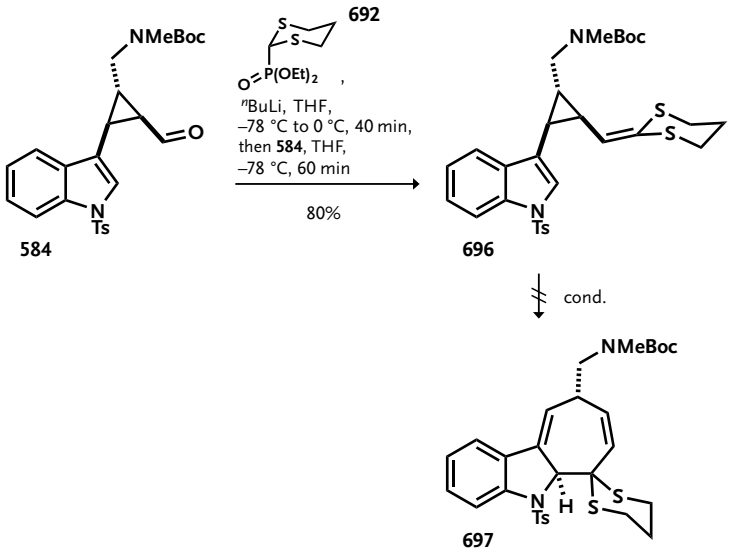
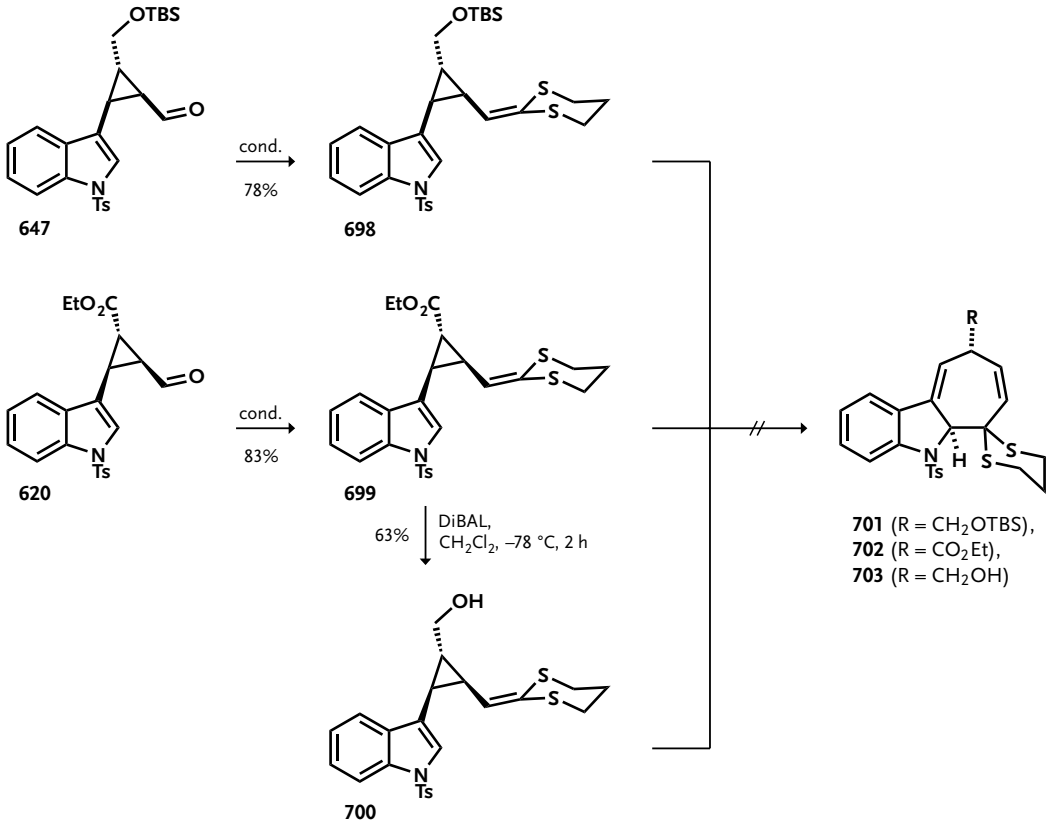


Table 6-3. Conditions (Scheme 6-23).

#	Conditions
1	PhH, 105 °C, 12 h [1]
2	PhH, 130 °C, 12 h [1]
3	PhH, 80 °C, μw [2]
4	$(CH_2OH)_2$, 205 °C, 2 h [2]
5	PhH–DMSO (1:3), 120 °C, 4 h [1]
6	PhMe–MeCN (1:1), 100 °C, 2 h [1]
7	dichlorobenzene, 160 °C, 60 min [1]
8	PhCN, 190 °C, 60 min [1]

[1] no reaction [2] decomposition

Scheme 6-23. Synthesis of ketene *S,S*-acetal **696** and attempts for its rearrangement.



Scheme 6-24. Syntheses of ketene *S,S*-acetals **698**, **699**, and **700** and failed attempts for the divinylcyclopropane-cycloheptadiene rearrangement of these compounds. Reagents and conditions: **692**, ^{n}BuLi, –78 °C → 0 °C, 40 min, then aldehyde **647**/**620**, THF, –78 °C, 60 min .

Having in mind, that the third additional substituent at the cyclopropane moiety is quite bulky due to the Boc group, several other derivatives were transformed into their ketene *S,S*-acetals followed by the divinylcyclopropane-cycloheptadiene rearrangement into the corresponding cyclohepta[*b*]indolines. The effect of a third substituent was investigated with these experiments. For this reason, ketene *S,S*-acetals **698** and **699** were synthesized from the corresponding aldehydes **647** and **620** (Scheme 6-24). In addition, the ester moiety of ketene *S,S*-acetal **699** was reduced to the corresponding primary alcohol **700** yielding three additional ketene *S,S*-acetals with various steric demand concerning the additional rest at the cyclopropane moiety. Compounds **698**, **699**, and **700** were subjected to most of the conditions listed in Tab. 6-3, but the rearranged products **701**, **702**, and **703** could not be obtained. The prior removal of the tosyl group did not affect this result.

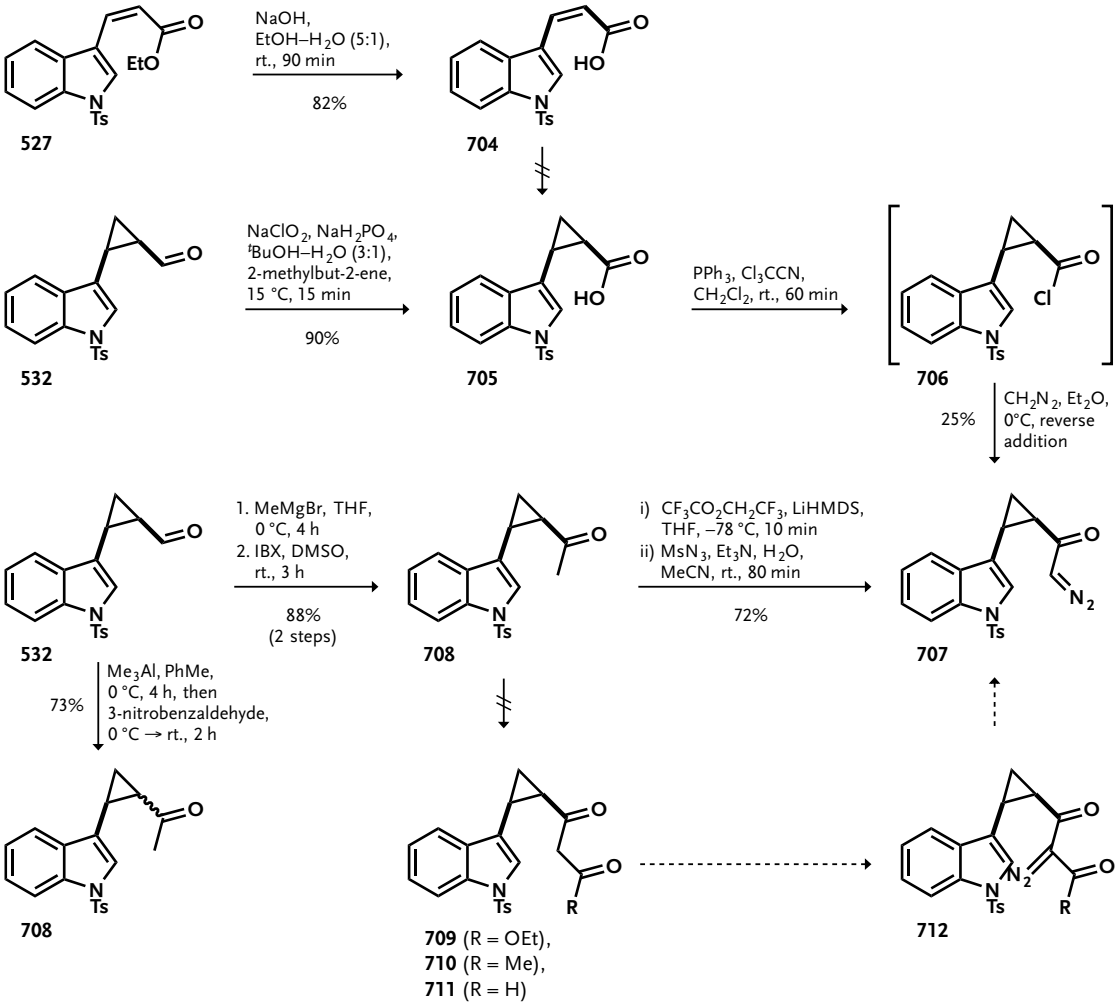
In summary, the generation of ketene acetals and the divinylcyclopropane-cycloheptadiene rearrangement of these compounds is possible and extends the developed methodology nicely. However, a main drawback is, that this extension only works with disubstituted cyclopropanes. Any attempt for the rearrangement of the trisubstituted counterparts fails.

6.4.3 2-Acylindoles from the Divinylcyclopropane Rearrangement of Ketenes

6.4.3.1 Disubstituted Cyclopropanes

Since the rearrangement of disubstituted cyclopropane ketene *S,S*-acetals proceeded smoothly but failed with the trisubstituted counterparts, attention next turned to the synthesis of α-diazo ketone **707** (Scheme 6-25). This compound can be transformed into the corresponding ketene **677** *via* Wolff rearrangement (*cf.* Scheme 6-18 on p. 135). The ketene derivatives are assumed to be highly reactive intermediates, giving a much higher overall reaction rate of the rearrangement in comparison to the ketene acetal counterparts.

The attempts to the synthesis are outlined in Scheme 6-25. Although the modified Simmons–Smith reaction of acrylic acid derivatives is known,[414] all attempts to convert carboxylic acid **704**—which is easy accessible from already known ester **527**—into the corresponding cyclopropane derivative **705** failed.[1] Therefore, well-known aldehyde **532** was oxidized to carboxylic

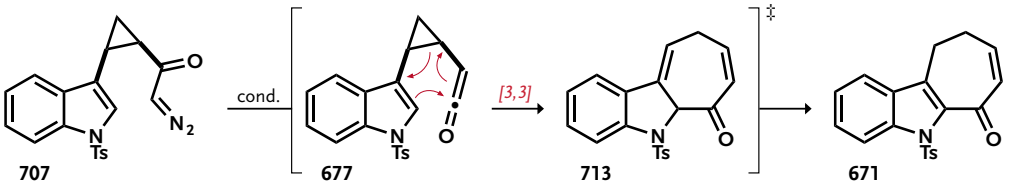


Scheme 6-25. Attempts to the synthesis of α-diazo compound **707**.

[1] Several attempts to the Corey-Chaykovsky reaction of α,β-unsaturated ester **527** and derivatives were not successful.

acid **705** *via* Pinnick–Lindgren oxidation in 90% yield.[415] **705** turned out to be very labile; temperatures above 30 °C (e.g. rotary evaporator) led to full decomposition of this compound. Therefore, careful handling during the reaction (reaction was carried out at 15 °C instead of ambient temperature) and the work-up (solvent evaporation at 15 °C) was necessary. Carboxylic acid **705** was then transformed into acid chloride **706** under mild and acid-free chlorination conditions with PPh_3 and CCl_3CN.[416,417] **706** turned out to be even more labile than its carboxylic acid precursor. Every attempt to purify this compound failed. Therefore, acid chloride **706** was prepared freshly and used crude in upcoming reactions. Reaction of **706** with freshly prepared diazomethane finally afforded α-diazo ketone **707** (reverse addition was crucial). However, the yield was very poor (25% over two steps) and no consistent reproduction was possible. Therefore, a new synthetic route was sought. For this reason, aldehyde **532** was transformed into the corresponding methyl ketone derivative **708** in a two-step Grignard addition/oxidation sequence. This compound could also be prepared in a nice single-step sequence *via* the addition of trimethylaluminium followed by the addition of 3-nitrobenzaldehyde (*in situ* oxidation *via* Oppenauer chemistry),[418,419] but unfortunately the stereochemistry at the α-carbon atom was scrambled under these conditions and a diastereomeric mixture of methyl ketone **708** was obtained. With **708** in hands, attention next turned to the formation of α-diazo ketone **707**. Direct diazo transfer to ketone enolates is usually not a feasible process, although highly stabilized β-dicarbonyl enolates do react with sulfonyl azide reagents to afford α-diazo ketones in good yield. Diazo transfer to simple ketones can be achieved, however, by employing an indirect deformylative diazo transfer strategy in which the ketone is first formylated under Claisen condensation conditions and then treated with a sulfonyl azide reagent.[420] This strategy was only successful with the Danheiser protocol for the generation of α-diazo ketones:[421] the lithium enolate of **708** was acylated by exposure to trifluoroethyl trifluoroacetate, the resulting α-trifluoroacetyl ketone was then treated with methanesulfonyl azide in acetonitrile containing one equivalent of water. This sequence afforded α-diazo ketone **707** in 72% combined yield. Next in line was the Wolff rearrangement/divinylcyclopropane-cycloheptadiene rearrangement tandem reaction of α-diazo compound **707** (Scheme 6-26). Wolff rearrangements can be induced under thermolytic, photolytic, and transition-metal-catalyzed conditions. Thermal conditions to induce rearrangement require heating to relatively high temperatures and therefore have limited use. The method of choice is often a transition-metal-catalyzed rearrangement since transition metals intensely lower the temperature for this reaction *via* stabilization of a metal-carbene intermediate. Some metals are known to build stable carbenes to such an extent as no rearrangement occurs; instead, non-Wolff products are obtained (primarily carbene insertion products). These metals include rhodium, copper, and palladium.[422] The most commonly used metal is silver and the most commonly used catalysts are silver benzoate, silver trifluoroacetate, and silver(I) oxide. Usually, these reactions are run in the presence of a weak base.

A similar tandem Wolff/Cope rearrangement sequence for the synthesis of fused carbocyclic skeletons have been published by B. Stoltz and R. Sarpong.[423] Therefore, their used conditions



Scheme 6-26. Wolff rearrangement/divinylcyclopropane-cycloheptadiene rearrangement tandem reaction for the synthesis of 2-acylindole **671** (conditions *see* Tab. 6-4).

were the first choice (10 mol % of AgOBz, Et_3N, THF, 45 °C, ultasonic, 30 min). Many products were generated with this protocol, but none of them could be identified as 2-acylindole **671** or **713**. Furthermore, several photochemical attempts were carried out (Tab. 6-4). Triplet sensitizers were not added since they are known to result in non-Wolff carbene by-products.[422] However, the formation of **671** or **713** could not be observed in both THF and CH_2Cl_2 as solvent. Finally, the rearrangement turned out to work best with a catalytic amount of silver(I) oxide (5 mol %) in THF at 60 °C in the absence of a weak base. These conditions directly furnished cyclohepta[*b*]indole **671** *via* ketene intermediate **677**; cyclohepta[*b*]indoline **713** was never observed.

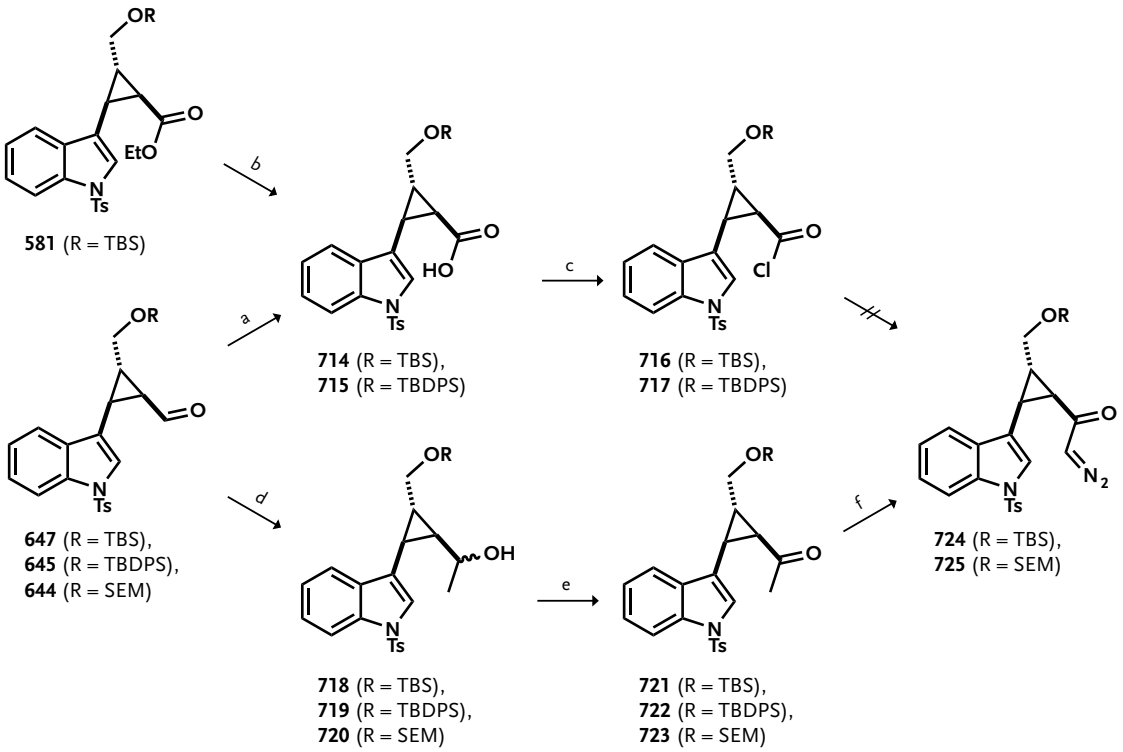
Table 6-4. Conditions for Scheme 6-26.

#	Conditions	Yield
1	AgOBz (0.1 eq.), Et_3N, 45 °C, ultrasonic	—
2	*hν* (254 nm), THF	—
3	*hν* (254 nm), CH_2Cl_2	—
4	AgTFA (0.1 eq.), Et_3N, THF, –30 °C → rt.	—
5	Ag_2O (5 mol %), THF, 60 °C, 2 h	84%

6.4.3.2 Trisubstituted Cyclopropanes

With 2-acylindole **671** in hands, attention next turned to the syntheses of the more challenging trisubstituted counterparts. Based on the *(E)*-olefin series (*cf.* Section 6.3.3), syntheses started either from already available aldehydes **647** (R = TBS), **645** (R = TBDPS), and **644** (R = SEM) or directly from cyclopropanation product **581** (R = TBS), see Scheme 6-27. Aldehydes **647** and **645** were transformed into their corresponding carboxylic acid derivatives **714** and **715** *via* Pinnick–Lindgren oxidation. Alternatively, this compound could also be obtained *via* saponification of ester **581** with potassium trimethylsilanolate.[424] Once again, this products turned out to be very labile and decomposition occurred above 30 °C (*cf.* Section 6.4.3.1). Notwithstanding this, **714** and **715** were subjected to mild and acid-free chlorination conditions with PPh_3 and CCl_3CN to obtain the corresponding acid chlorides **716** and **717**. With **716** and **717** in hands, several attempts for the formation of the α-diazo counterparts were carried out, but once again this reactions gave α-diazo compounds only in very low yield. Similar results were also obtained for the disubstituted cyclopropane counterparts (*cf.* Section 6.4.3.1).

Therefore, aldehydes **647** (R = TBS), **645** (R = TBDPS), and **644** (R = SEM) underwent Grignard addition reaction with MeMgBr to give alcohols **718**, **719**, and **720** followed by PDC oxidation



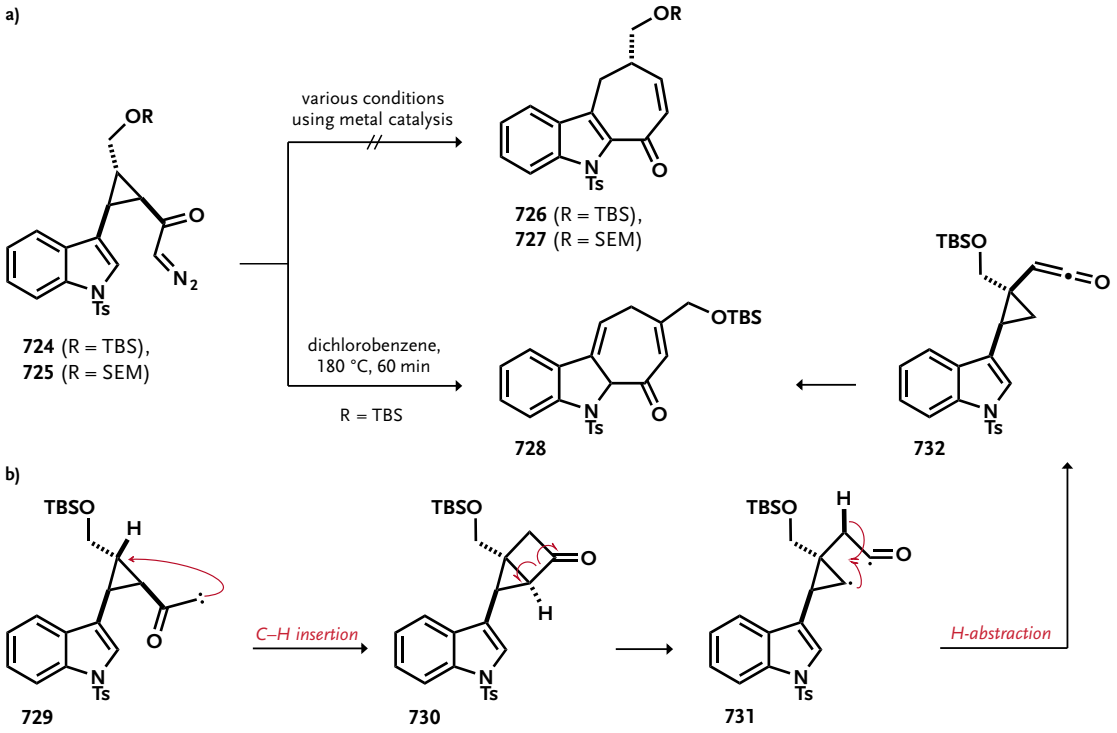
Scheme 6-27. Synthesis of α-diazo ketones **724** and **725**. Reagents and conditions: **a)** $NaClO_2$, NaH_2PO_4, ^tBuOH–H_2O (3:1), 2-methylbut-2-ene, 20 °C, 20 min (87% crude from **647**, 85% crude from **645**). **b)** TMSOK, THF, rt., 5.5 h (92% crude). **c)** PPh_3, Cl_3CCN, CH_2Cl_2, rt., 30 min. **d)** MeMgBr, THF, 0 °C, 60 min (80% from **647**, 62% from **645**, 93% from **644**). **e)** PDC, MS 3 Å, CH_2Cl_2, rt., 12 h (75% from **718**, — from **719**, 75% from **720**). **f)** (i) LiHMDS, THF, –78 °C, $F_3CCO_2CH_2CF_3$, 10 min, (ii) MsN_3, Et_3N, H_2O, MeCN, 60 min (56% brsm. from **721**, 51% from **723**) .

to the corresponding methyl ketones **721**, **722**, **723** (Scheme 6-27). With the aforementioned protocol for the synthesis of α-diazo ketones from methyl ketones from R. L. Danheiser, TBS and SEM derivatives **721** and **723** were transformed into α-diazo ketones **724** and **725** in moderate yields (56% and 51%, respectively). For a start, a single run of this synthetic sequence afforded enough material, to investigate the Wolff rearrangement/divinylcyclopropane-cycloheptadiene rearrangement tandem reaction (Scheme 6-28a and Tab. 6-5).

Table 6-5. Conditions for the attempts to the synthesis of 2-acylindoles **726** and **727**.

#	R =	Conditions	Product
1	TBS	Ag_2O, THF, 60 °C	— [1)]
2	TBS	Ag_2O, PhH, 60 °C	— [1)]
3	TBS	AgOBz (1.0 eq.), THF, 60 °C	— [1) + 2)]
4	TBS	AgOBz (1.0 eq.), Et_3N, THF, 60 °C	— [1) + 2)]
5	TBS	AgOBz (0.1 eq.), Et_3N, 45 °C, ultrasonic	— [2)]
6	TBS	*hν* (254 nm), THF	— [2)]

(continued on next page...)



Scheme 6-28. **a)** Attempts for the synthesis of 2-acylindoles **726** and **727** and actually obtained result **728**. **b)** Proposed mechanism for the outcome.

Table 6-5. *(continued)*

#	R =	Conditions	Product
7	TBS	*hν* (254 nm), CH_2Cl_2	— [2]
8	SEM	THF, 60 °C, Ag_2O	— [2]
9	SEM	$Rh_2(OAc)_4$, CH_2Cl_2, 50 °C, 3 min	— [2]
10	SEM	AgOBz (0.1 eq.), Et_3N, 45 °C, ultrasonic	— [2]
11	SEM	AgOAc (20 mol %), 1,2-dichloroethane, 50 °C	— [3]
12	SEM	AgTFA (20 mol %), 1,2-dichloroethane, 50 °C	— [2]
13	SEM	PhMe, 150 °C, 120 min	— [1] + [2]
14	TBS	dichlorobenzene, 180 °C, 60 min	**728**

[1] unidentified products (no plausible NMR spectrum, no correct mass)
[2] decomposition [3] recovered starting material

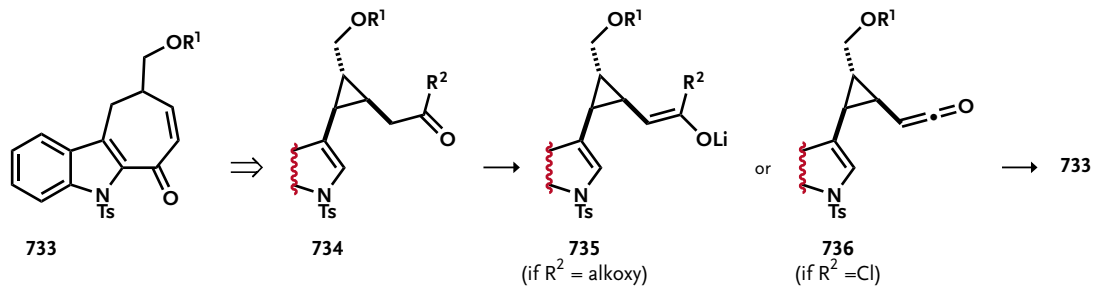
When the investigations concerning the Wolff rearrangement/divinylcyclopropane-cycloheptadiene rearrangement tandem reaction began it became apparent very quickly, that this transformation would be very cumbersome. Reaction conditions which afforded the 2-acylindole from disubstituted cyclopropanes (cat. Ag_2O, THF, 60 °C) yielded in decomposition of the material and the formation of many by-products which could not be identified both for the TBS and the

SEM series. Unfortunately, several other metal based or photochemical conditions also did not afford the desired products (*cf.* Tab. 6-5). Only in one case the formation of a defined product could be observed (Entry 14) and the outcome was very piquant. Heating in dichlorobenzene at 180 °C for 60 min did not afford 2-acylindole **726** but apparently regioisomeric compound **728** (Scheme 6-28a). This became clear after intense NMR analyses. Based on a similar observation (Padwa, 1988[425]), a proposed mechanism for this obscure transformation is shown in (Scheme 6-28b). After formation of carbene **729**, it is assumed that a carbene C–H insertion takes place and annelated cyclobutane **730** is formed. Under these reaction conditions, the cyclobutane ring is cleaved homolytically to give biradical **731**. Abstraction of a hydrogen yields ketene **732**. It should be pointed out, that this ketene is different to the ketene which arises from the Wolff rearrangement (*cf.* Scheme 6-26 on p. 142); the ketene is now attached to a different carbon atom, forming a geminal disubstituted cyclpropane which divinylcyclopropane-cycloheptadiene rearrangement yields observed product **728**.

Based on this results it is absolutely possible that the same sequence also occurs with the disubstituted cyclopropane series. But since no carbon atoms are labeled, the outcome appears to be identical either way.

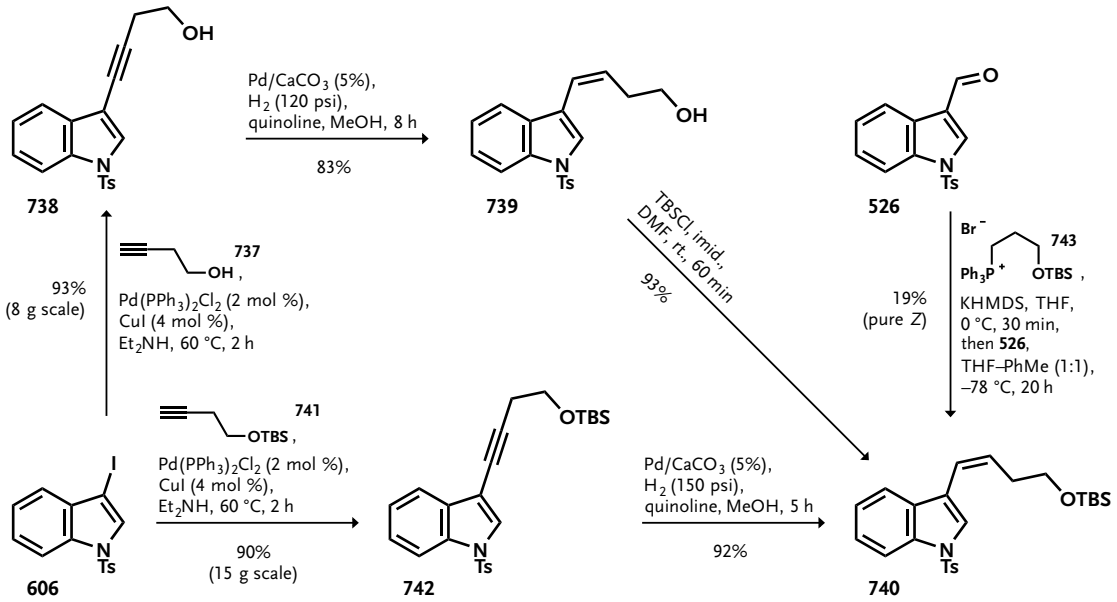
6.5 Third Approach: One Carbon Elongation[2]

After several α-diazo compounds were synthesized successfully, it turned out that the carbene intermediate underwent an unexpected rearrangement. Therefore, one last trial was to elongate the cyclopropane rest to yield cyclohepta[*b*]indole precursors like **734** (Scheme 6-29). This compound can be useful in two different points of view. On the one hand (R^2 = Cl) it can be transformed with an amine base into the corresponding ketene **736** (Wedekind's method).[426–428] This approach towards the ketene intermediate would furnish the ketene without a carbene intermediate, thus avoiding an undesirable rearrangement. On the other hand (R^2 = alkoxy), the enolate of this compound (**735**) can undergo a divinylcyclopropane-cycloheptadiene rearrangement. This rearrangement should even proceed at low temperatures as it has the driving force



Scheme 6-29. Retrosynthetic analysis: third approach.

[2] Work on the third approach was undertaken contemporaneously with the work which finally led to the final approach and the syntheses of *Ervatamia* alkaloids. Therefore, the investigation of several reactions of some advanced intermediates found a more or less abrupt end in favor to the final approach.

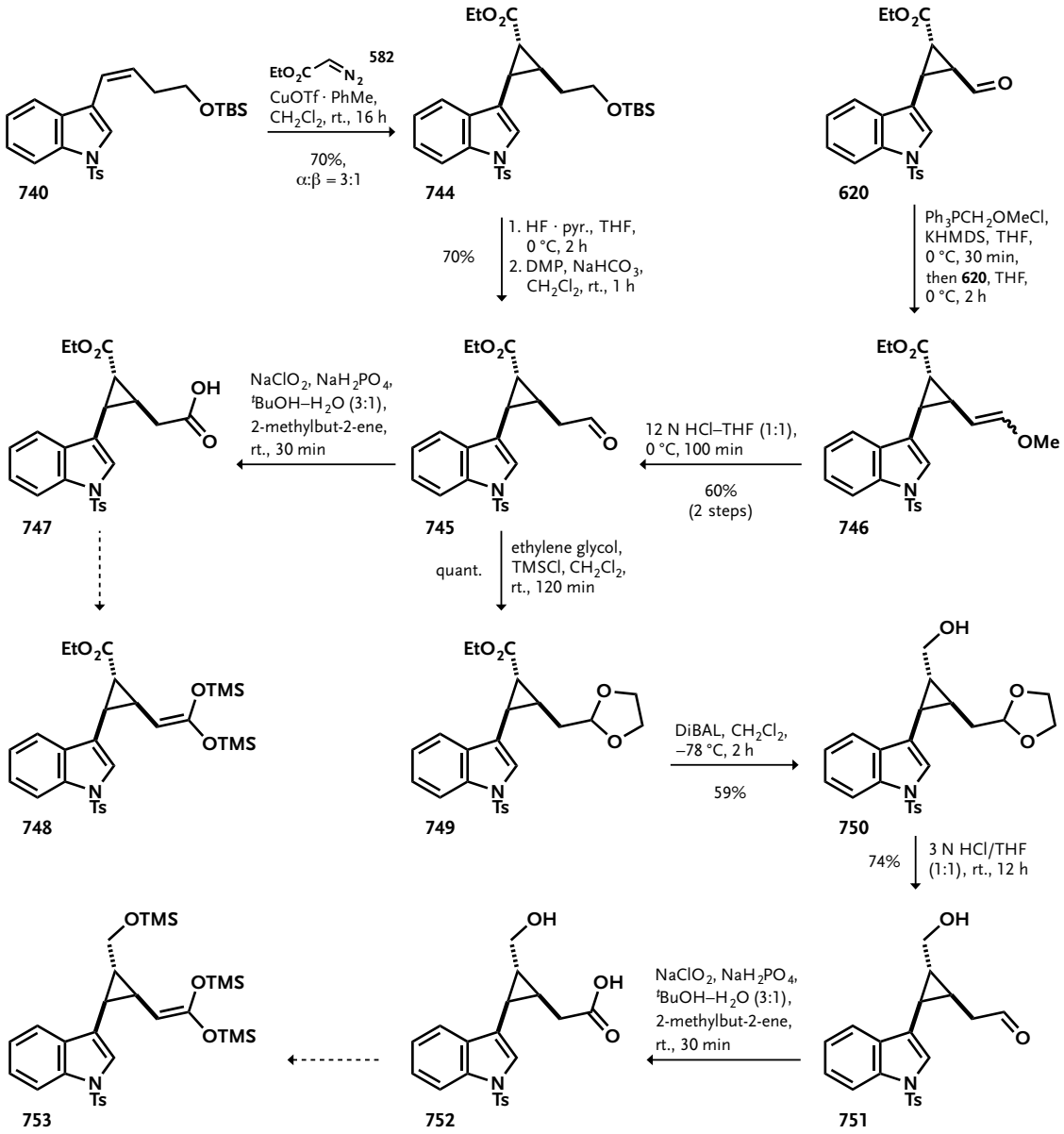


Scheme 6-30. Synthesis of (*Z*)-olefin **740**.

from the enolate. Several enolate driven divinylcyclopropane-cycloheptadiene rearrangement are known from literature (*cf.* Section 3.3).

En route to the synthesis of compounds like **734** the synthesis of *(Z)*-olefin **740** was carried out (Scheme 6-30). On the one hand, this olefin can be generated by a Wittig olefination from *N*-tosyl protected indole-3-carbaldehyde (**526**). The corresponding Wittig salt **743** was prepared, but it turned out that this reaction afforded olefin **740** only in low yield (19%). Since the coupling of alkynes to *N*-tosyl protected 3-iodoindole (**606**) has already been carried out successfully in a previous approach (Scheme 6.3.1 on p. 126), once again a coupling strategy was taken into account. Sonogashira coupling of **606** with 3-butyn-1-ol (**737**) afforded alkyne **738** in very good yield even at large scale. Modified hydrogenation conditions for the reduction of the alkyne to the corresponding *(Z)*-olefin **739** and subsequent silyl protection of the primary alcohol furnished compound **740** in 72% overall yield (from **606**). Alternatively, the Sonogashira coupling can also be carried out with silyl protected 3-butyn-1-ol **741**. This reaction afforded alkyne **742** in 90% yield. Subsequent hydrogenation furnished *(Z)*-olefin **740** in 83% overall yield.

Both the sequence *via* the coupling with 3-butyn-1-ol (**737**) and the sequence with the coupling of its silyl derivative **741** furnished more than enough material to investigate the upcoming cyclopropanation reaction. Pleasingly, the developed conditions for the cyclopropanation of olefin **529** (Tab. 6-1 on p. 121) could be applied to the cyclopropanation of olefin **740** yielding trisubstituted cyclopropane **744** in 70% yield (α:β = 3:1, work was continued only with the α-isomer), see Scheme 6-31. Removal of the silyl protecting group with hydrogen fluoride and subsequent oxidation of the primary alcohol with Dess–Martin periodinane (**603**) afforded aldehyde **745** in 70% yield. Alternatively, this aldehyde can be synthesized from aldehyde **620** *via* homologization with methoxymethylenetriphenylphosphine and subsequent hydrolysis



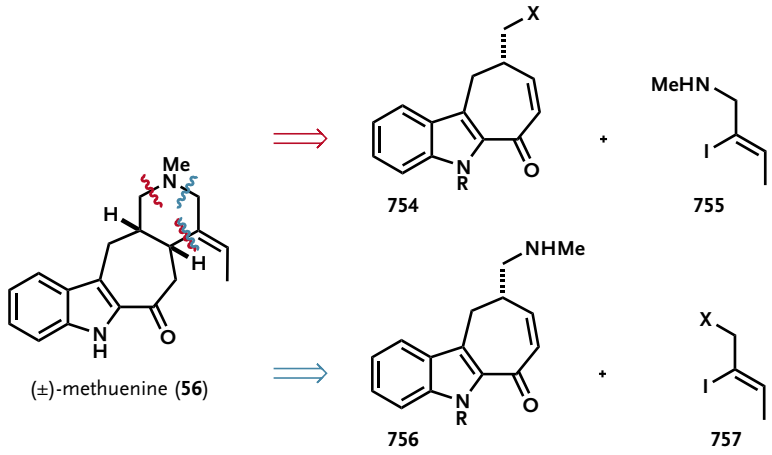
Scheme 6-31. Third approach: presentation of the most important reactions.

of the generated enol ether **746**. One the one hand, aldehyde **745** was transformed into the corresponding carboxylic acid **747** which served as precursor for enol ether **748**. On the other hand, the steric demand was decreased by the reduction of the ester moiety to the corresponding alcohol. Therefore, aldehyde **745** was converted into its acetal **749** followed by the reduction with DiBAL and subsequent treatment with acidic THF to obtain aldehyde **751** in 44% combined yield. Finally, Pinnick–Lindgren oxidation furnished carboxylic acid **752** which itself served as precursor for enol ether **753**.

As the fourth and final approach began to provide promising results, the work of this approach came to an end at this point and was no longer pursued.

6.6 Excursus: Syntheses of Vinyl Iodide Building Blocks

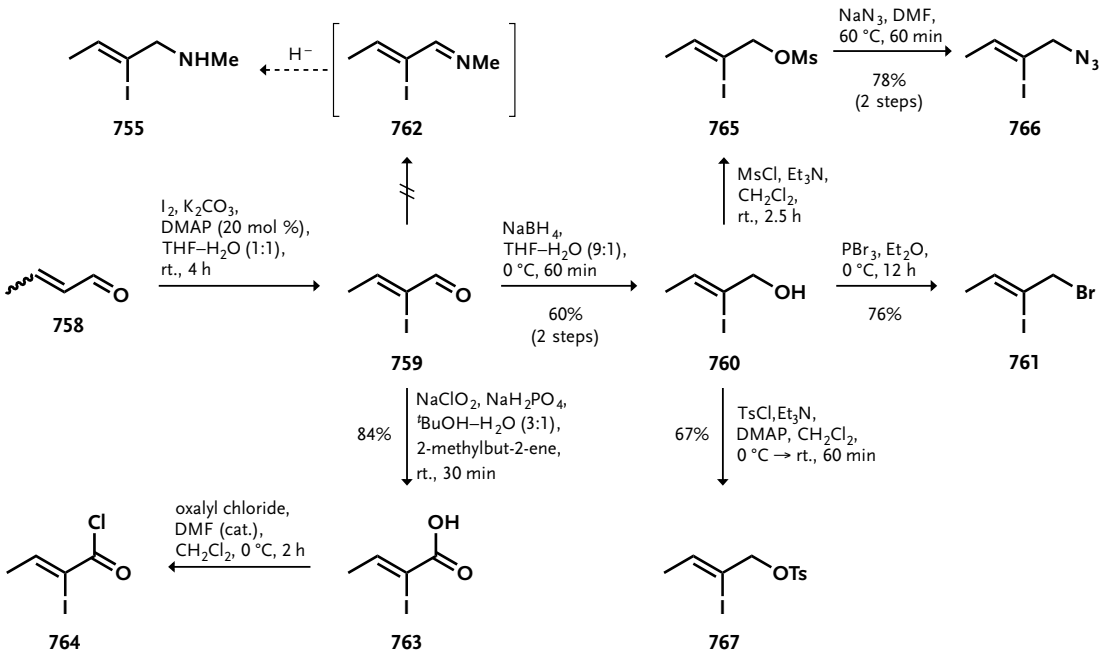
Starting with the upcoming sections an olefinic fragment plays an important role. All *Ervatamia* alkaloids (and also many other indole monoterpenoid alkaloids, *cf.* Section 4.2.1 on p. 92) have in common an characteristic terminal propene moiety; based on the whole alkaloid skeleton the olefin mostly is *(E)*-configured. In retrosynthetic view (Scheme 6-32) this leads to two different synthon pairs: cyclohepta[*b*]indole **754** and *(Z)*-iodo allylamine **755** (Disconnection 1), or cyclohepta[*b*]indole **756** and *(Z)*-iodo allyl halide **757** (Disconnection 2). The closure of the piperidine ring is planned to be done by a Heck coupling reaction as Heck couplings of vinyl halides and alkenes have proved to be useful for this fragment in the syntheses of *Strychnos* alkaloids,[429,430] including strychnine (**17**)[431–433] and minfiensine,[434] as well as in syntheses of sarpagine alkaloids,[435–437] strictamine[438–441] and approaches to the geissoschizine[442] and apogeissoschizine[443] skeletons. All these syntheses have in common the *(Z)*-iodo allyl halide building block **757**. By reason of its broad use one can think that smart and convenient procedures exist for the synthesis of this building block. Indeed, that is true nowadays due to a straightforward protocol for the α-iodination of croton aldehyde from 2005.[444] Before, it had to be synthesized in a cumbersome multistep procedure *via* stannane chemistry based on a protocol from 1981.[445] Whereas *(Z)*-iodo allyl halide **757** is a well-known building block, its amine counterpart **755** has not been investigated so far and no syntheses have been described in literature.



Scheme 6-32. Retrosynthetic disconnections.

The synthesis of (*Z*)-1-bromo-2-iodobut-2-ene (**761**) is shown in Scheme 6-33 and relies on the protocol of Krafft.[444] An isomeric mixture of crotonaldehyde (**758**) reacts with iodine and a catalytic amount of DMAP in basic aqueous THF. This reaction yielded vinyl iodide **759** and is proposed to follow a Baylis–Hillman type pathway. Straightforward reduction of the aldehyde followed by S_N2 displacement afforded pure *(Z)*-iodo allyl bromide **761** in 46% overall yield.

Furthermore, several additional building blocks containing the vinyl iodide motif were synthesized. Aldehyde **759** is oxidized to the corresponding carboxylic acid in 84% yield with the



Scheme 6-33. Syntheses of various intermediates which contains the vinyl iodide fragment.

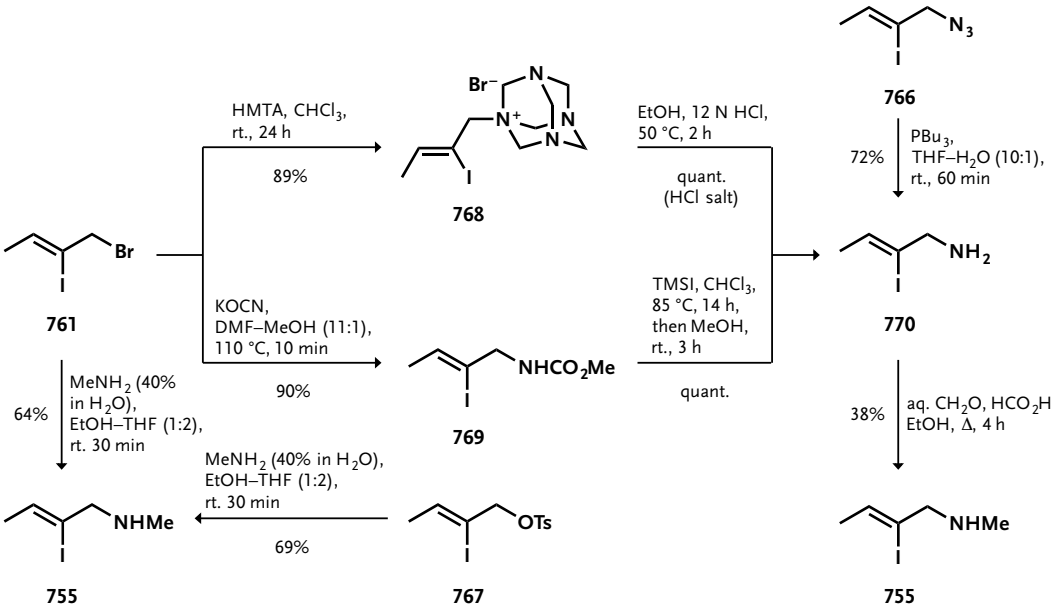
Pinnick–Lindgren protocol. This building block served for upcoming amidation reactions, as well as acid chloride **764** which usually was used crude.

Apart from the transformation of alcohol **760** into its corresponding bromide **761** it was also converted into its tosylate **767** and its mesylate **765** under usual conditions. The latter was then directly transformed into azide **766** in 78% combined yield.

The most straightforward way to synthesize the amine counterpart **755** is *via* reductive amination of *(Z)*-iodo crotonaldehyde **759** (Scheme 6-33). Numerous different protocols were carried out,[446–450] but unfortunately the formation of amine **755** was never observed and decomposition/polymerization took place thus taking other synthetic routes into account.

The synthesis of methylamine **755** required a lot of trials compared to its complexity and size, and numerous attempts remained fruitless. Dominant problems were often polyalkylation or even the formation of quaternary amine salts. In addition, all vinyl iodide building blocks turned out to be very base-labile thus forming the corresponding alkynes quite easily *via* elimination reaction.

In a first fruitful synthetic sequence (Scheme 6-34), allyl bromide **761** was reacted with hexamethylenetetramine and transformed into quaternary ammonium salt **768** which was hydrolyzed with ethanolic 12N hydrochloric acid furnishing allyl amine **770** in 89% combined yield. This reaction is known for over a century and is the so-called Delépine reaction which has general applications in the conversion of alkyl halides into primary amines.[451] **770** could also be synthesized from azide **766** *via* Staudinger reaction.[452] Alternatively, bromide **761** was transferred into carbamate **769**. For this, **761** was reacted with potassium cyanate in methanolic dimethyl formamide at 110 °C for 10 min—a very elegant way for the introduction of a nitrogen.[453] The



Scheme 6-34. Syntheses of methyl amine derivative **755**.

reaction of carbamate **769** with trimethylsilyl iodide in refluxing chloroform furnished primary amine **770** in 90% combined yield.

Finally, the only methylation protocol which furnished methylamine **755** was the Eschweiler–Clarke methylation—a special case of the Leuckart–Wallach reaction.[454] For this, primary amine **770** was reacted with an aqueous solution of formaldehyde and formic acid in refluxing ethanol. At least, this sequence afforded methyl amine **755** in moderate yield.

The most straightforward approach is the S_N2 displacement of bromine by methylamine. However, this transformation was accompanied by many problems (polyalkylation, alkyne formation *via* elimination, see above). Appropriate conditions for this transformation were obtained after extensive investigations: bromide **761** was reacted with an aqueous solution of methylamine (40%) in EtOH–THF (1:2) to afford methylamine **755** in 64% yield. Therefore, the solvent was a mixture of three components and every single component was required. The absence of one component led to the failure of this transformation. Slightly better yields were obtained with tosylate **767** (69%). Allyl methylamine **755** will play a major role in the synthesis of *Ervatamia* alkaloids.

Total Syntheses of *Ervatamia* Alkaloids

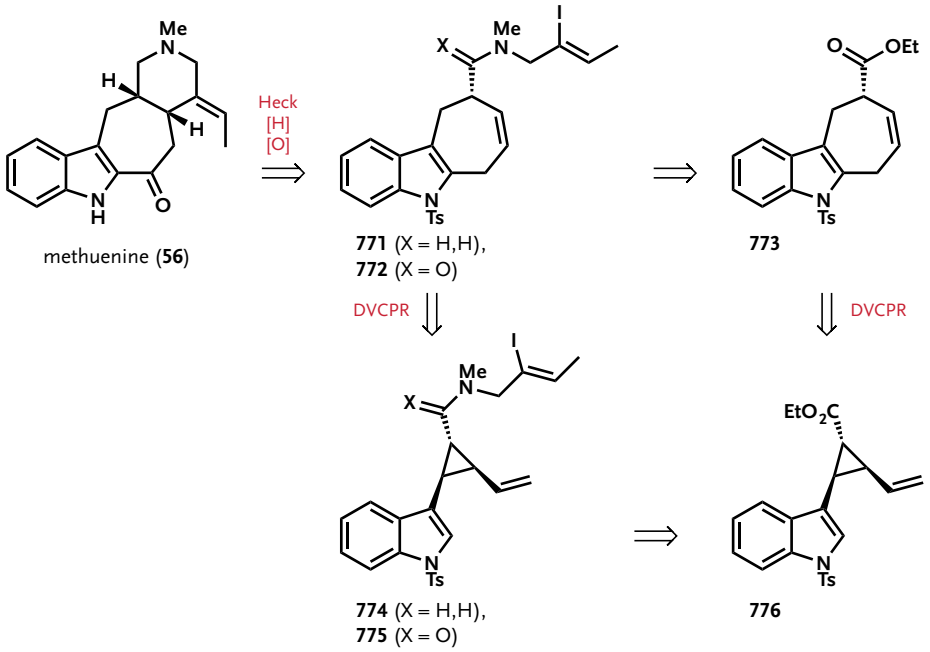
7

7.1 Preliminary Considerations

So far, many experiments and approaches have been carried out and in some points the systems became predictable concerning certain transformations. The forth and final approach towards the syntheses of *Ervatamia* alkaloids took the results of all approaches so far into account and following assumptions were made: (i) the crucial oxidation for the formation of the 2-acylindole moiety is one of the last steps after the piperidine ring has already been formed; (ii) the second 2π-unit of the divinylcyclopropane-cycloheptadiene rearrangement is a terminal alkene; (iii) installation of the vinyl iodide moiety is carried out very early in the synthesis (*cf.* retrosynthetic analysis in Scheme 7-1).

It was shown before, that the iodine pentoxide based oxidation was successfully carried out with different cyclohepta[*b*]indoles. It was indicated, that this oxidation did not afford the oxidation product when the cyclohepta[*b*]indole bore an additional double bond (Section 6.3.4 on p. 134), thus assuming that this oxidation is successful as soon as the piperidine ring has been formed.

In several preliminary studies it was shown, that substituted alkenes required harsher and prolonged reaction times for the divinylcyclopropane-cycloheptadiene rearrangement (Fig. 7-1). Whereas the simplest precursor **533**‡ rearranged at ambient temperature in one hour, the disubstituted counterpart **557**‡ required two hours at 80 °C and the trisubstituted counterpart **559**‡ even three hours at 120 °C. Trisubstituted cyclopropane **585**‡ which also bears a terminal olefin rearranged in two hours at 80 °C. On the contrary, disubstituted cyclopropane **694** which bears a dithiane at the olefinic moiety required four hours at 100 °C. This comparison shows very well, that additional substitutions at the cyclopropane are much more tolerated than additional substitutions at the olefinic moiety. This comparison also indicates, why the cyclohepta[*b*]indole product of precursor **696** was never obtained.



Scheme 7-1. Retrosynthetic analysis: final approach.

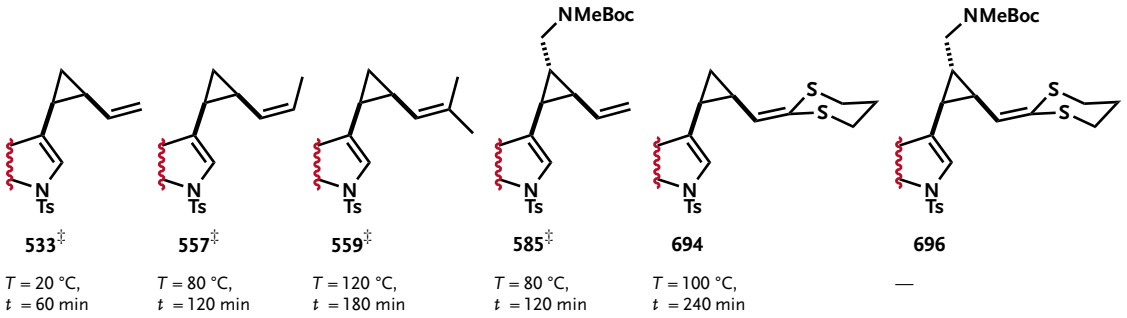
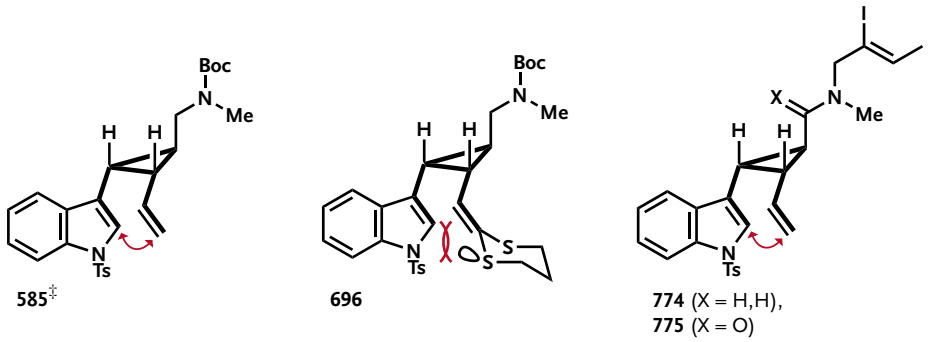


Figure 7-1. Comparison of different divinylcyclopropane-cycloheptadiene rearrangements in terms of temperature and reaction time.



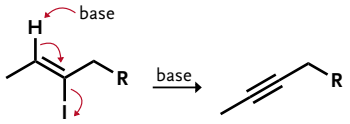
Scheme 7-2. Detailed view of selected divinylcyclopropanes.

Based on this facts, the installation of the vinyl iodide moiety is carried out very early in the new synthetic approach to avoid additional protections. Since divinylcyclopropane **585**‡ rearranged under appropriate conditions despite the bulky rest, it is assumed that derivatives bearing the vinyl iodide moiety and a terminal alkene (like **774** or **775**, see Fig. 7-2) will also rearrange smoothly to the corresponding cyclohepta[*b*]indole. Furthermore, it is assumed that the use of an amide (**775**, X = O) will yield in more robust compounds than the use of the corresponding amine (**774**, X = H,H). By reason of robustness and the knowledge, that the planned Heck coupling reaction for the formation of the piperidine ring can be troublesome with tertiary amines,[455] a late-stage reduction to the required amine is proposed.

7.2 Towards the Final Synthesis of *Ervatamia* Alkaloids

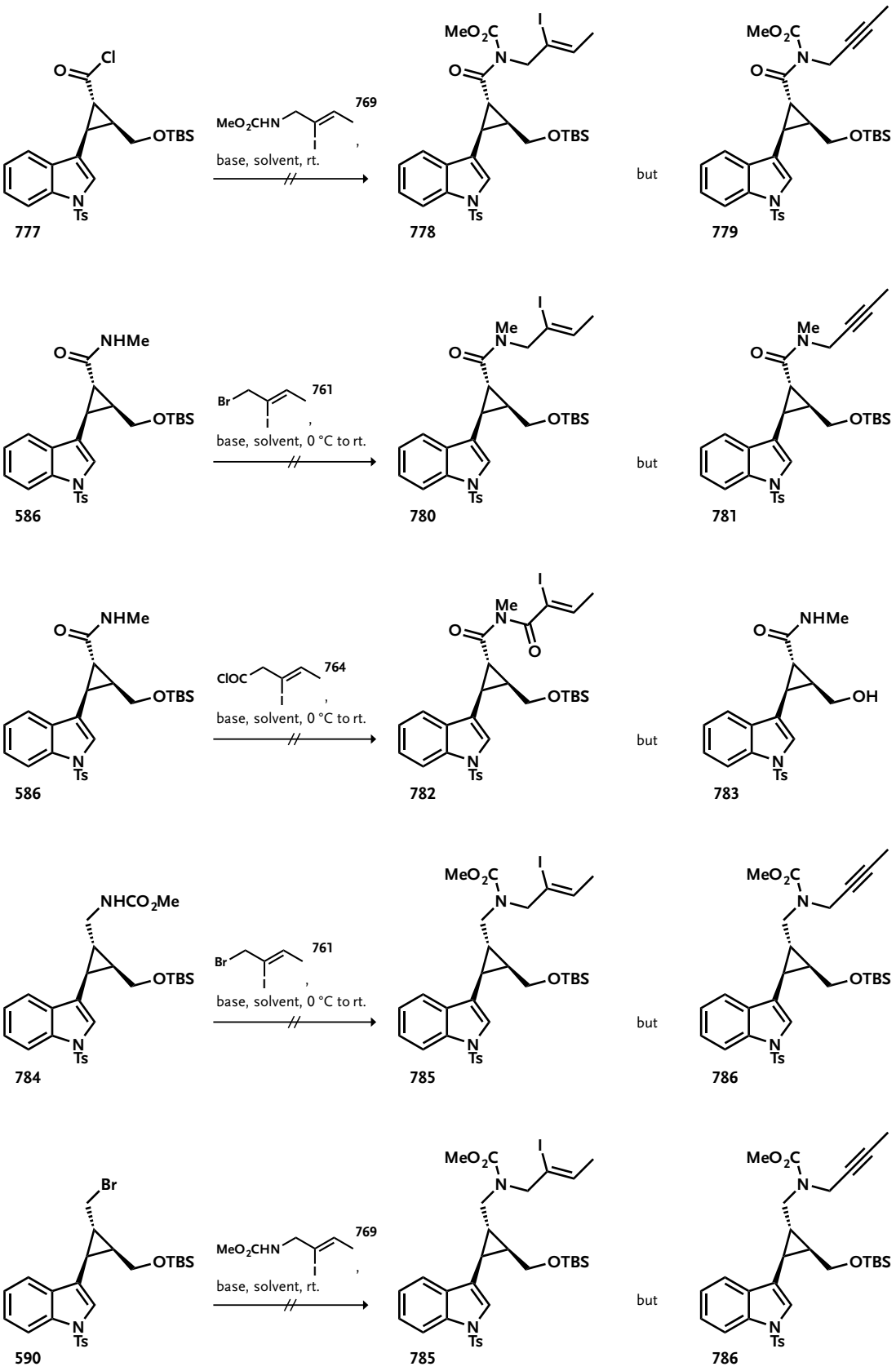
This section is a short description about important results which paved the way for the final synthetic route of *Ervatamia* alkaloids.

As already foreshadowed in Section 6.6, many vinyl iodide building blocks turned out to be very base-labile thus forming the corresponding alkynes quite easily *via* elimination reaction. This is shown in detail in Scheme 7-4. Indeed, the base-mediated coupling per se of carbamate **769** and cyclopropyl acid chloride **777** was successful, but the product turned out to be alkyne **779** and not vinyl iodide **778**. Several constellations were permuted. In almost all cases a similar result was obtained and alkyne formation was observed. Only the coupling of cyclopropyl carbamate **586** and acid chloride **764** was different; not only the coupling did not proceed but also the silyl protecting group was cleaved under this conditions thus yielding alcohol **783**. Therefore, the coupling was postponed at this stage and attention next turned to the rearrangement of divinylcyclopropane **776** (*cf.* Scheme 7-1 on p. 152).

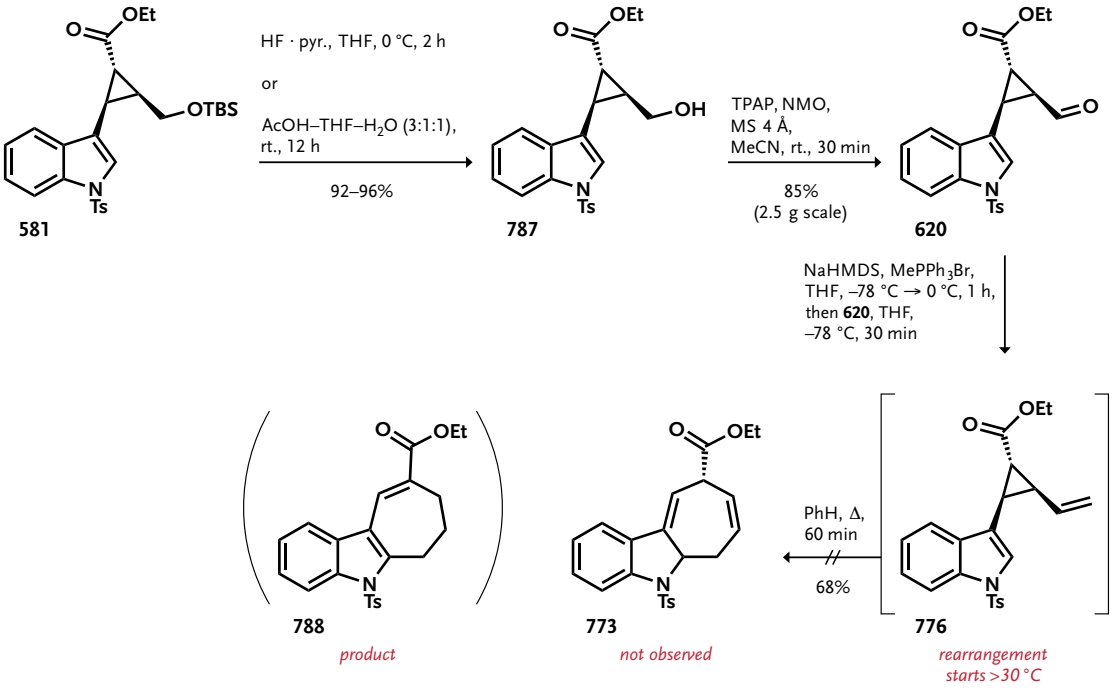


Scheme 7-4. Alkyne formation *via* elimination.

Enantioenriched cyclopropanation product **581** (*cf.* Section 6.2) was reacted with hydrogen fluoride in THF at 0 °C to remove the silyl protecting group and forming alcohol **787** (Scheme 7-5). Alternatively, the TBS ether was cleaved with acetic acid in aqueous THF at ambient temperature.[357,456] Both procedures furnished alcohol **787** in excellent yield. Next in line was the oxidation of the primary alcohol to the corresponding aldehyde. This transformation was best achieved using the Ley–Griffith oxidation;[457,458] the reaction with a catalytic amount of tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide afforded aldehyde **620** in 85% yield. Nowadays, this oxidation is carried out in CH_2Cl_2 in most cases. However, the original protocol was described in acetonitrile. And indeed, the yields for aldehyde **620** were 15% higher on average when using acetonitrile instead of CH_2Cl_2. With **620** in hands, Wittig reaction afforded the corresponding alkene. A partial rearrangement was already observed above 30 °C, full rearrangement occurred after one hour in refluxing benzene and the rearrangement product was obtained in 68% yield. However, NMR analysis revealed that the obtained product was not cyclohepta[*b*]indoline **773** but cyclohepta[*b*]indole **788**. Apparently, for once this compound



Scheme 7-3. Several attempts for the coupling of the cyclopropane and the vinyl iodide building blocks failed.

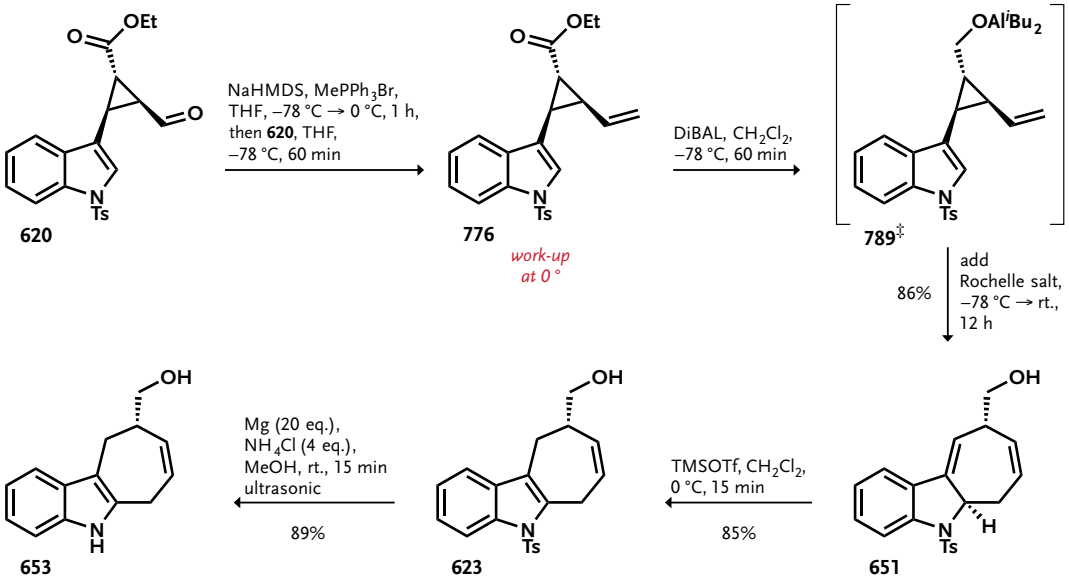


Scheme 7-5. Divinylcyclopropane-cycloheptadiene rearrangement of divinylcyclopropane **776**.

rearomatized spontaneously followed by double bond migration. This unusual transformation made the divinylcyclopropane-cycloheptadiene rearrangement of **776** useless. On the one hand, the position of the migrated double bond cannot be used in a practical way for the synthesis of *Ervatamia* alkaloids. On the other hand and far more important is the fact, that all stereochemical information has been lost since obtained product **788** lacks stereogenic centers.

The crucial idea was then to trap divinylcyclopropane **776** and transform it into other derivatives before the rearrangement takes place. This required some investigations and learning concerning the handling of compound **776** and its intermediates. As already mentioned, **776** starts to rearrange at about 300 K. To avoid any rearranged product, work-ups were carried out with ice-cold ether and the solvent was removed *in vacuo* at 0–5 °C. All operations had to be carried out quite quickly and upcoming transformations of divinylcyclopropane **776** required procedures which afford the appropriate derivative in a short amount of time at 0 °C or below.

In a first sequence divinylcyclopropane **776** was immediately cooled down to –78 °C after work-up and treated with diisobutylaluminium hydride at this temperature for 60 min (Scheme 7-6). To the formed aluminium species **789**‡ was added Rochelle salt and the reaction mixture was stirred for 12 h while warming up to ambient temperature. This furnished already completely rearranged product **651** in 83% overall yield (from aldehyde **620**). During some investigations on other cyclohepta[*b*]indolines it was observed, that the rearomatization step could be carried out with two equivalents of trimethylsilyl trifluoromethanesulfonate. And indeed, reaction of cyclohepta[*b*]indoline **651** with this reagent furnished cyclohepta[*b*]indole **623** after 15 min at 0 °C in 85% yield. In an additional step, removal of the tosyl group was carried out with



Scheme 7-6. Trapping the divinylcyclopropane intermediate.

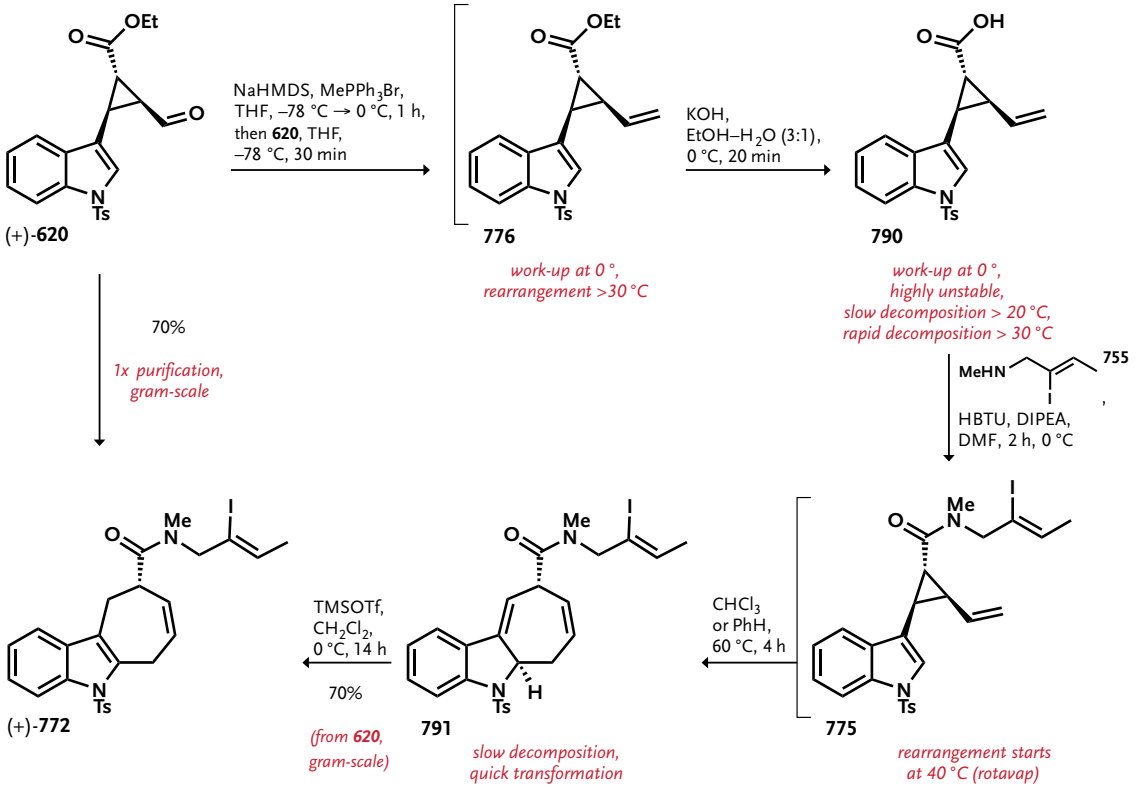
magnesium in methanol using ultrasonic.[395a] Indole **653** was obtained in 89% yield. *N*-Tosyl indole **623** and indole **653** served as backup compounds as they could be transformed very easily into the corresponding mesylate or bromide and subsequent S_N2 displacement to build the corresponding tertiary amine/vinyl iodide moiety (read more about the amine/amide problem above, Section 7.1).

With the knowledge of generating divinylcyclopropane-cycloheptadiene rearrangement products from trapped divinylcyclopropane **776**, attention next turned to a bold synthetic sequence which led to the total syntheses of *Ervatamia* alkaloids after all.

7.3 Total Synthesis of (+)-5-Oxoisomethuenine

7.3.1 Trapping of Divinylcyclopropane Intermediates

The total synthesis of (+)-5-oxoisomethuenine began with known enantioenriched aldehyde **620** (Scheme 7-7). Investigations led to a synthetic route, which transformed **620** into **772**. As described hitherto, **620** was transformed into divinylcyclopropane **776**. With appropriate knowledge about the handling of this compound and its upcoming derivatives, saponification of the ethyl ester afforded carboxylic acid **790**. As already observed with other intermediates (Section 6.4.3.1, p. 140), α-cyclopropyl carboxylic acid turned out to be be very labile; temperatures above 30 °C (e.g. rotary evaporator) led to full decomposition of this compound, decomposition even occurred partially at 20 °C. Once again, work-ups were carried out with ice-cold ether and the solvent was removed *in vacuo* at 0–5 °C. Several trials of the coupling of allyl amine **755** with an acid chloride resulted in alkyne formation or decomposition (Section 7.2). Therefore, an amide synthesis *via* coupling reagents was taken into account. To avoid decomposition of carboxylic acid **790**,



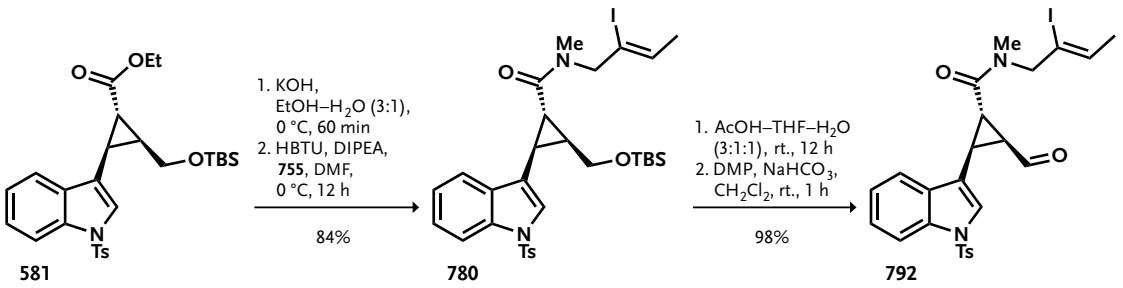
Scheme 7-7. Synthesis of crucial cyclohepta[*b*]indole derivative **772**.

the coupling should proceed at low temperatures. Best results for the coupling of amine **755** and **790** were achieved with HBTU and DIPEA in DMF. Pleasingly, this reaction was finished after two hours at 0 °C. The obtained divinylcyclopropane **775** was then subjected to benzene (or chloroform) and stirred four hours at 60 °C to afford cyclohepta[*b*]indoline **791**. Alternatively, **775** was stirred in toluene at 110 °C for just about 30 min to obtain the rearranged product. However, higher temperatures yielded in a diminished overall yield for this sequence. Cyclohepta[*b*]indoline **791** turned out to be somewhat unstable and decomposed slowly. Therefore, the crude mixture was usually subjected to rearomatization conditions (TMSOTf, CH_2Cl_2, 0 °C, 14 h) and cyclohepta[*b*]indole was furnished in 70% overall yield from aldehyde **620**.

It should be noted, that this sequence can be carried out in gram-scale and only one purification is necessary. However, it demands knowledge about the handling of occurring intermediates, especially ester **776**, carboxylic acid **790**, and amide **791**. In addition, simple building block **620** can be transformed into advanced intermediate **772** in just a day.

7.3.1.1 Variations

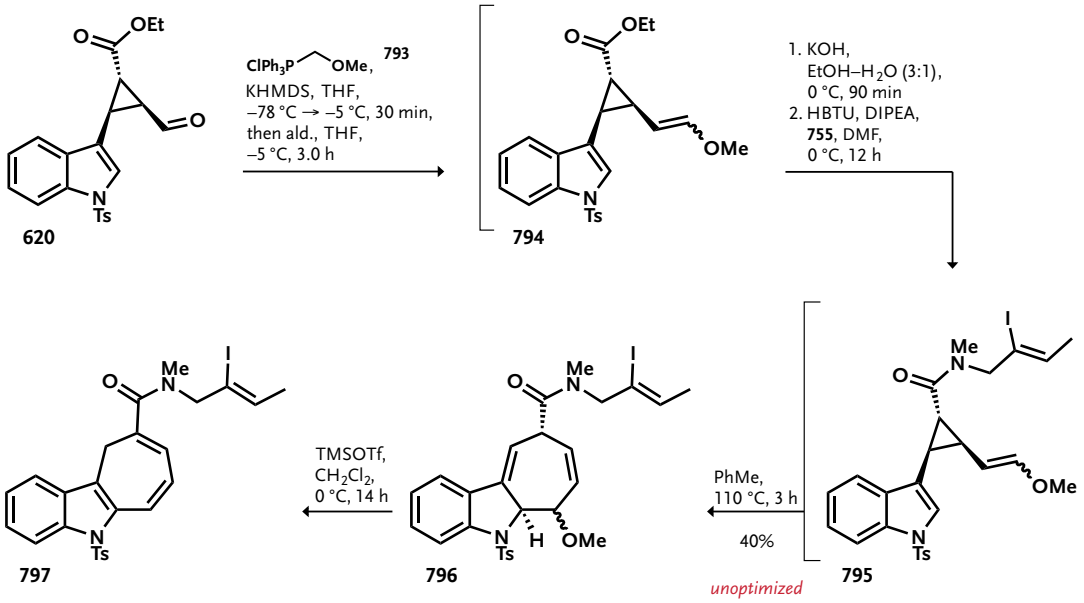
The synthetic route towards cyclohepta[*b*]indole **772** requires certain knowledge and experience about the handling of the intermediates. Therefore, it was tried to attach the vinyl iodide moiety before installing the second vinyl moiety *via* Wittig reaction by using identical chemical



Scheme 7-8. Alternative approach to aldehyde **792**.

operations. Enantioenriched cyclopropanation product **581** was therefore reacted with potassium hydroxide in aqueous ethanol at 0 °C for one hour to obtain the corresponding carboxylic acid (Scheme 7-8) which was immediately coupled with allyl amine **755** using the coupling reagent HBTU and DIPEA as base. This two-step sequence afforded α-cyclopropyl amide **780** in 84% overall yield. Removal of the silyl protecting group under acidic conditions and subsequent oxidation of the primary alcohol to the corresponding aldehyde with DMP furnished **792** in almost quantitative yield. Although this variation looked promising so far, the transformation into the methylene group *via* Wittig reaction followed by divinylcyclopropane-cycloheptadiene rearrangement gave cyclohepta[*b*]indoline **791** (*cf.* Scheme 7-7) only in moderate 52% yield.

In another trial, aldehyde **620** was converted into vinylmethoxyvinylcyclopropane **794** with methoxymethylenetriphenylphosphine ylide (Scheme 7-9). Similar to the first sequence, this intermediate was kept at low temperatures and transformed immediately to the carboxylic acid followed by amide formation using once again HBTU and DIPEA. The divinylcyclopropane-cycloheptadiene rearrangement proceeded in 3 h at 110 °C in toluene and afforded cyclohep-

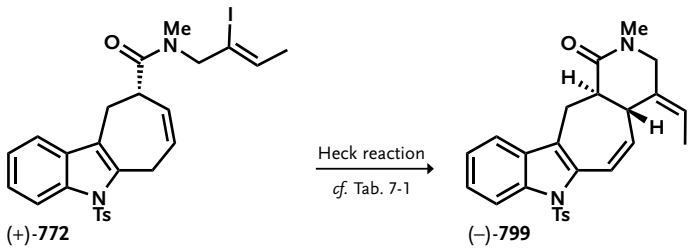


Scheme 7-9. Rearrangement of vinylmethoxyvinylcyclopropane **798**.

ta[*b*]indoline **796** in moderate 40% overall yield (unoptimized). However, this variation found and abrupt end when rearomatization conditions were applied to **796**. Treatment of **796** with TMSOTf in CH_2Cl_2 at 0 °C resulted not only in rearomatization but also in elimination of the methoxy group. This yielded cyclohepta[*b*]indole **797** and resulted in loss of not only the ketone surrogate but also the chirality.

7.3.2 Piperidine Ring Formation

Next in line was the Heck coupling reaction for the formation of the piperidine ring (Scheme 7-10). Extensive literature search was done in order to find Heck ring closing reactions on similar systems. Finally, best reactions conditions were found to be: $Pd(PPh_3)_4$ (10 mol %), K_3PO_4 (3.0 eq.), PhOH (25 mol %), Et_3N (5.0 eq.), PhMe (0.01 M), 110 °C, 2 h (Tab. 7-1, Entry 1). This conditions furnished the desired Heck product **799** in excellent yield (scale: 10 mg up to 1.5 g). However, formation of a by-product under these conditions was observed. Unfortunately, the separation of this by-product from the desired product was quite time-consuming. By exchanging $Pd(PPh_3)_4$ to $Pd_2(dba)_3$ and addition of DavePhos® the formation of the undesired by-product could be suppressed. However, the yield was about 20% lower than with $Pd(PPh_3)_4$. In addition, phenol was added as additive (25 mol %). Its positive role in some palladium-catalyzed arylations of ketone enolates has been observed by Buchwald.[459a] It is assumed, that the intermediacy of a palladium phenoxide (**800**, Scheme 7-11b) stabilizes an otherwise unstable intermediate and accounts for the beneficial effect of the added phenol.[455,459]



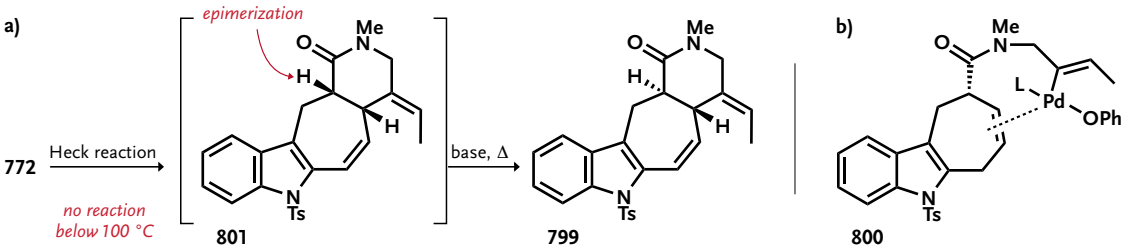
(+)-**772** (–)-**799**

Scheme 7-10. Heck coupling reaction for the formation of the piperidine ring.

Table 7-1. Heck coupling conditions for the formation of the piperidine ring (*cf.* Scheme 7-10).

#	Conditions	Scale	Yield [%]	Notes
1	$Pd(PPh_3)_4$ (10 mol %), K_3PO_4 (3.0 eq.), PhOH (25 mol %), Et_3N (5.0 eq.), PhMe (0.01 M), 110 °C, 2 h	10 mg 40 mg 120 mg 150 mg 500 mg 1500 mg	93 95 98 94 91 89	[1)]
2	$Pd_2(dba)_3$ (10 mol %), DavePhos® (20 mol %), K_3PO_4 (3.0 eq.), PhOH (25 mol %), Et_3N (5.0 eq.), PhMe (0.01 M), 110 °C, 2 h	100 mg 400 mg	78 73	—

[1)] formation of a by-product which was difficult to separate from the product



Scheme 7-11. **a)** Plausible explanation for the generation of a *trans*-fused piperidine ring. **b)** Role of the phenol additive.

The determination of the configuration of the annulated ring turned out to be quite cumbersome. ^{1}H NMR analysis could not reveal the relative configuration between protons H15 (double allylic proton) and H16 (α-amide proton, *cf.* Fig. 7-10 for numeration), due to the appearance of H15 as a very broad singlet. Measurements in different solvents could not circumvent this result. The relative configuration was finally revealed *via* NMR decoupling experiments. Decoupling is the process of removing specific kinds of *J*-coupling interactions in order to simplify a spectrum or identify which pairs of nuclei are involved in the *J*-coupling. Selected and characteristic spectra are shown in Figures 7-2 to 7-9 and the multiplicities and coupling constants for selected

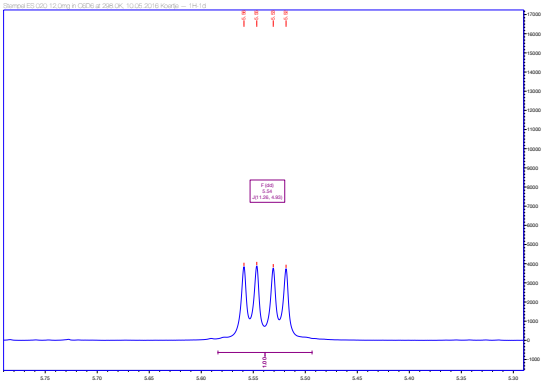


Figure 7-2. Detailed view of H14 NMR signal.

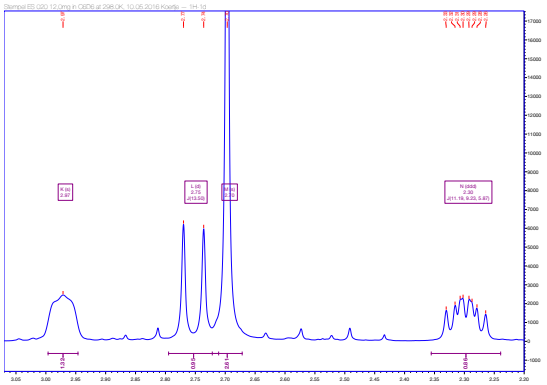


Figure 7-3. Detailed view of H15 and H16 NMR signals.

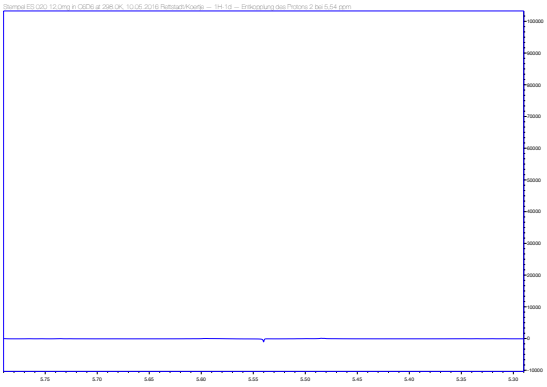


Figure 7-4. Detailed view of H14 NMR signal, decoupled at H14.

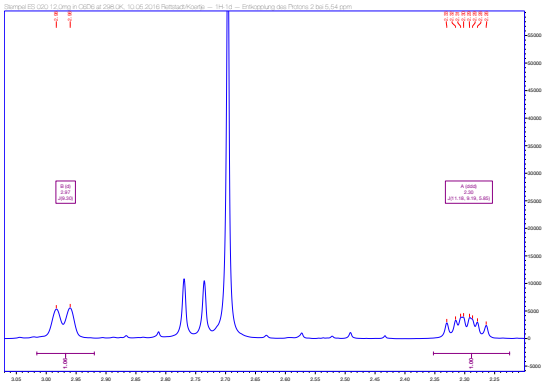


Figure 7-5. Detailed view of H15 and H16 NMR signals, decoupled at H14.

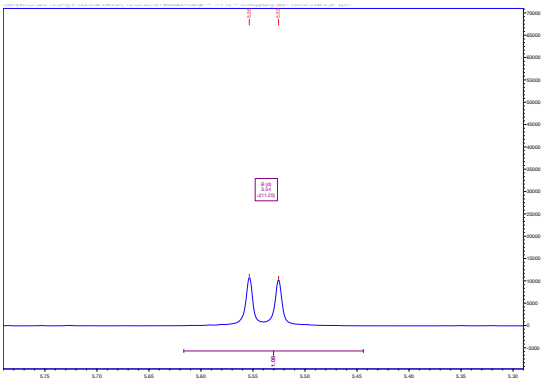


Figure 7-6. Detailed view of H14 NMR signal, decoupled at H16.

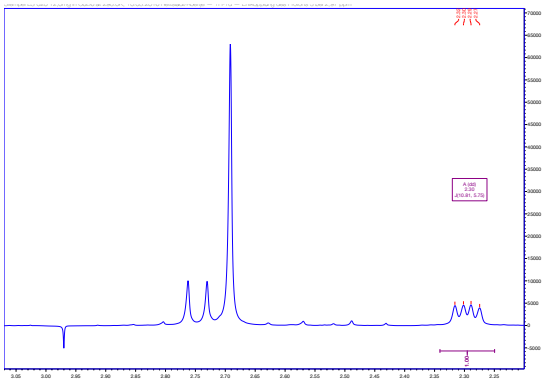


Figure 7-7. Detailed view of H15 and H16 NMR signals, decoupled at H15.

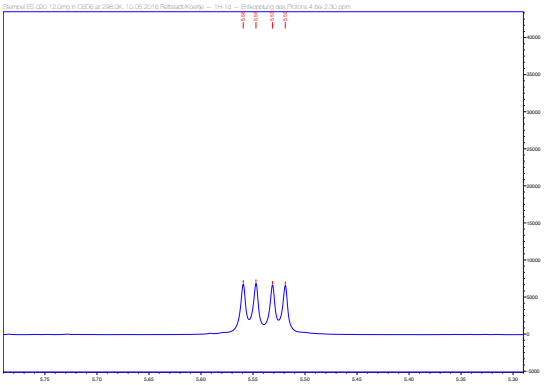


Figure 7-8. Detailed view of H14 NMR signal, decoupled at H15.

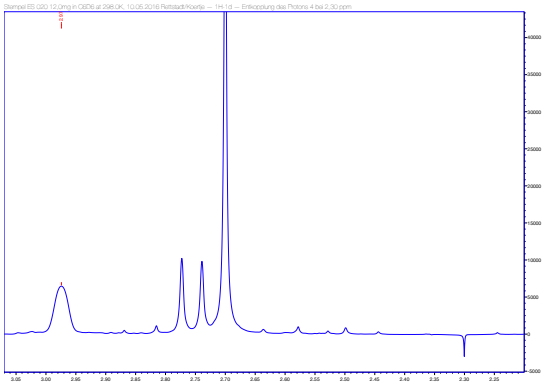


Figure 7-9. Detailed view of H15 and H16 NMR signals, decoupled at H16.

Table 7-2. Multiplicities and coupling constants for selected protons (*cf.* Fig. 7-10 for numeration), ▬ = decoupling of this proton took place.

#	H14		H15		H16	
	mult.	*J* [Hz]	mult.	*J* [Hz]	mult.	*J* [Hz]
1	dd	11.3, 4.9	br s	—	ddd	11.2, 9.2, 5.9
2	▬		d	9.2	ddd	11.2, 9.2, 5.9
3	d	11.3	▬		dd	10.9, 5.8
4	dd	11.3, 4.9	br s	—	▬	

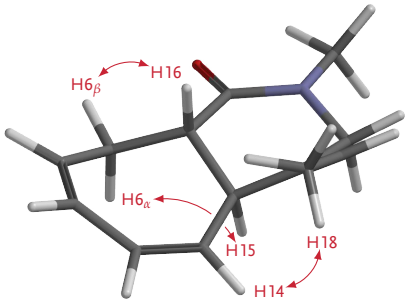


Figure 7-10. Calculated conformation of Heck product **799**, selected NOEs are highlighted.

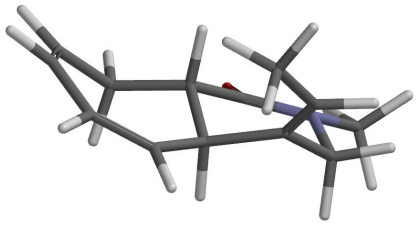


Figure 7-11. Calculated conformation of Heck product **799**, different viewing direction.

protons are listed in Tab. 7-2. This experiments revealed that $^{3}J_{H15,H16}$ = 9.2 Hz. This evidence supports the relative *trans*-configuration. The modeled *trans* conformer is shown in Figures 7-10 and 7-11 (the indole aromatic ring has been omitted for visibility reasons).

In addition, the conformation of the *cis*- and *trans*-configured products was modeled using a professional computational chemistry software (Spartan '09). Measurements of the dihedral angle ϕ of both conformers and comparison with the Karplus equation[460] supported the *trans* relationship ($\phi_{trans} = -174°$, $\phi_{cis} = 51°$). Furthermore, extended 1D-NOE studies were carried out. The results of this studies could not absolutely determine the relative configuration but were consistent with the decoupling experiments. In addition, the 1D-NOE experiments confirmed the *(E)*-configuration of the double bond, thus proving the double bond did not isomerize during the Heck coupling reaction. The absolute stereochemistry was then determined at the very end of the synthesis by comparing optical rotation signs of the synthesized natural products with the original natural products. The final results confirmed the NMR experiments and computational calculations.

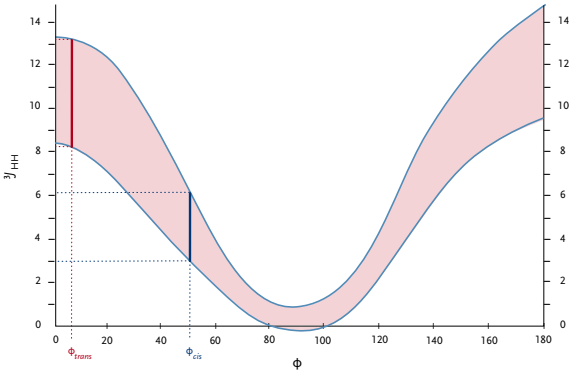


Figure 7-12. Graph of the Karplus relation.

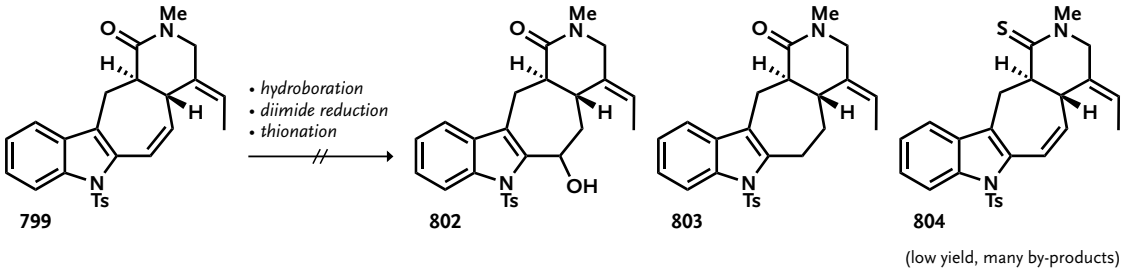
Based on precedent literature,[442,461,462] it was assumed that the ring closure will proceed in a *cis* fashion. Based on the obtained results concerning the *trans* relationship and the absolute stereochemistry, a plausible explanation for this outcome is shown in Scheme 7-11a (p. 160). This transformation required relatively high temperatures, no reaction occurred below 100 °C. Due to the excess of base, it is proposed that an epimerization at the α-amide carbon took place.

The complete tetracyclic skeleton as it occurs in the natural products have been generated. En route to isomethuenine (**57**, is equal to 16-epimethuenine) some minor transformations remained: (i) the reduction of the tertiary amide, (ii) reduction of the superfluous double bond, (iii) oxidation to the corresponding 2-acylindole, and (iv) removal of the protecting group.

7.3.3 Endgame

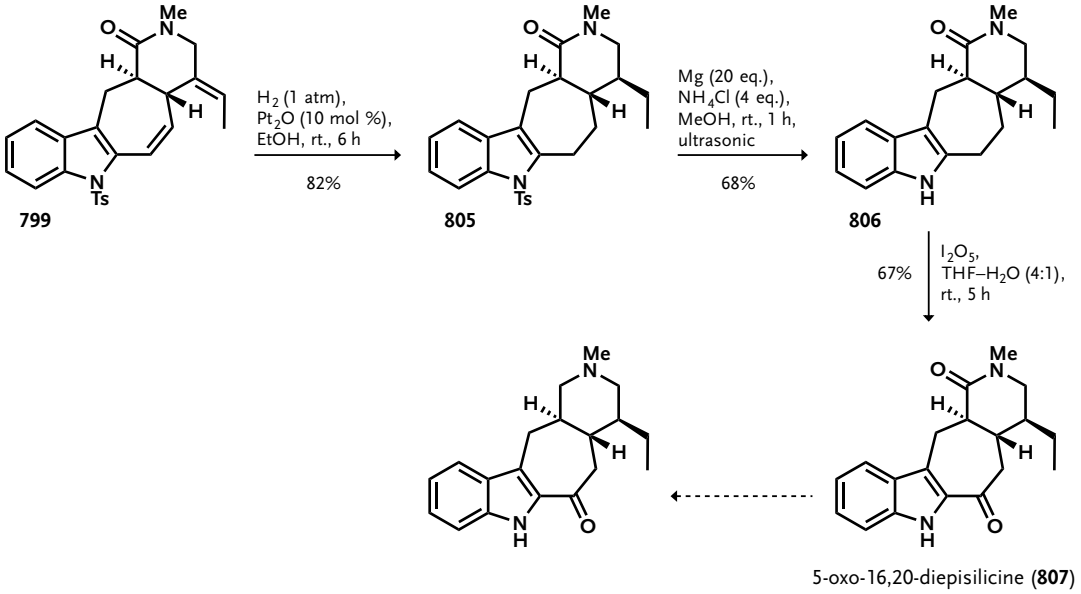
7.3.3.1 Total Synthesis of 5-Oxo-16,20-diepisilicine

With tetracycle **799** in hands, attention next turned to the regioselective reduction or conversion of the superfluous double bond. Several transformations were studied. The most important investigations are shown in Scheme 7-12. Neither the selective reduction of the double bond with diimide[463] nor its transformation into alcohol **802** *via* hydroboration was successful. In terms of an amide reduction, the amide moiety was transferred into thioamide **804**. However, thionation reactions with Lawesson's[464] reagent or Belleau's reagent[465] furnished thioamide **804** only in traces and the formation of many by-products was observed.



Scheme 7-12. Selected failed transformations of tetracycle **799**.

Since no regioselective reduction seemed possible, tetracycle **799** was hydrogenated at atmospheric pressure in the presence of Adams's catalyst.[74,142,466] Although **799** is almost insoluble in all common alcoholic solvents, hydrogenation was completed after 6 h in ethanol. As expected, both olefins have been reduced and compound **805** was obtained in 82% yield (Scheme 7-13). As



Scheme 7-13. Synthesis of 5-oxo-16,20-diepisilicine.

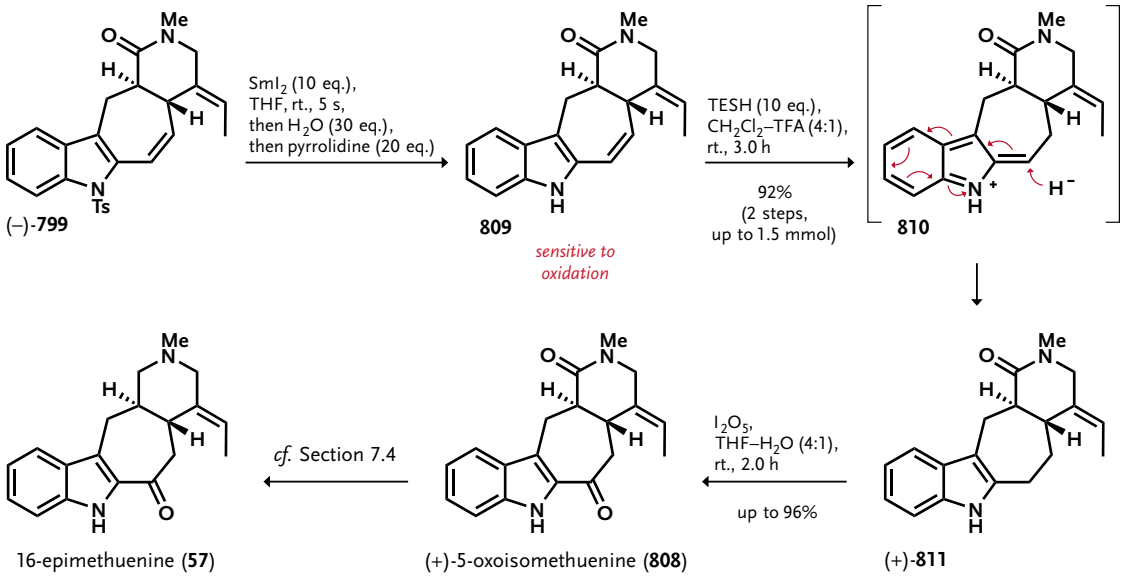
the oxidation to the 2-acylindole derivative with iodine pentoxide requires an unprotected indole, attention next turned to the removal of the tosyl group. Once again this was achieved with magnesium in methanol using ultrasonication. Due to solubility issues of the starting material, indole **806** was obtained in only moderate yield. Next in line was the crucial oxidation to the corresponding 2-acylindole derivative. Many approaches failed because of this crucial transformation. Although the oxidation with iodine pentoxide was successful on test systems (Scheme 6-16 on p. 134), oxidation products of real substrates could never be observed (*cf.* Section 6.3.4, p. 132). It was assumed, that the π-bond between C-15 and C-14 somehow prevented the successful oxidation of the C-3 position. This assumption was supported by the result of the unfruitful oxidation of simple cyclohepta[*b*]indole **534** (Scheme 6-17 on p. 134). Cyclohepta[*b*]indole **806** lacks this olefinic moiety and, pleasingly, reaction with iodine pentoxide smoothly furnished 5-oxo-16,20-diepisilicine (**807**) in 67% yield. Once again, this result supports the assumption that an additional olefinic moiety in the annulated cycloheptane prevents the successful oxidation.

The only remained transformation was the chemoselective reduction of the amide in the presence of the ketone at C-3 (basically, this moiety is more like a vinylogous amide than a ketone). A few attempts were carried out to achieve this transformation, but attention turned to the synthesis of (+)-5-oxoisomethuenine (**808**) as a regioselective reduction of the olefinic moieties was achieved. **808** is a more valuable derivative, since it can be reduced to 5-oxo-16,20-diepisilicine (**807**) anyway and additionally gives access to the methuenine-type alkaloids.

7.3.3.2 Total Synthesis of (+)-5-Oxoisomethuenine

All attempts to differentiate both double bonds came to nothing so far. Another idea was a differentiation based on the fact that one of both olefins is a benzylic double bond. Acid-mediated activation of this double bond should generate an iminium ion which could be trapped by a mild reducing agent. Literature examples for such an ionic reduction including an indole nucleus are scarce, only one example has been published (Sarpong, 2012).[467]

However, this transformation required the removal of the tosyl group at this stage as the strong electron-withdrawing group would probably prevent the planned activation and ionic reduction. Usual conditions with magnesium in methanol were not applicable since tetracycle **799** is almost insoluble in all common alcoholic solvents. Whereas the reduction with Adam's catalyst proceeded despite the poor solubility in methanol (Section 7.3.3.1), only traces of detosylated compound **809** could be observed with magnesium in methanol. Several procedures for the detosylation of arenesulfonamides are described in literature.[371–377] Best results were obtained using a procedure of Hilmersson *et al.* who described an instantaneous deprotection of tosylamides with samarium diiodide.[378] This reaction requires a minimum amount of time (literally not more than five seconds) and is usually directly quenched with an amine (pyrrolidine) and water. This protocol furnished indole **809** in probably quantitative yield (Scheme 7-14). The exact yield could not be determined, since indole **809** turned out to be very sensitive to oxidation and therefore was usually directly used in the next step.



Scheme 7-14. Total synthesis of (+)-5-oxoisomethuenine (**808**).

With indole **809** in hands, the protocol of Sarpong was applied (methanesulfonic acid, triethylsilane, DCE, 50 °C). Unfortunately, this protocol led to decomposition both at 50 °C and ambient temperature. Extended literature research was carried out[468] and conditions were chosen which are usually applied for the reduction of alcohols. Indole **809** was reacted with triethylsilane (10 eq.) in CH_2Cl_2 –TFA (4:1) at ambient temperature for 4 h. This protocol smoothly furnished tetracycle **811** *via* proposed iminium ion **810** in 92% combined yield (2 steps).

As already described in Section 7.3.3.1 towards the synthesis of 5-oxo-16,20-diepisilicine, the oxidation of indole **811** to the corresponding 2-acylindole was carried out with iodine pentoxide in aqueous THF at ambient temperature. This protocol smoothly furnished (+)-5-oxoisomethuenine (**808**) in up to 96% yield.[1]

The only remained transformation was the chemoselective reduction of the amide in the presence of the ketone at C-3 (basically, this moiety is more like a vinylogous amide than a ketone), which is described in the next section.

7.4 Total Synthesis of *Ervatamia* Alkaloids

The chemoselective reduction of amides in the presence of other more reactive reducible functional groups is a highly challenging transformation, and successful examples thereof are most valuable in synthetic organic chemistry. Only a limited amount of protocols have been described for such transformations (Fig. 7-13). Very common are protocols for the hydrosilylation of amides catalyzed by various platinum-group metals,[469] as well as iron,[470] zinc,[471] gold,[472] cobalt,[473] indium,[474] magnesium,[475] boron,[476] rhodium,[469a,477] ruthenium,[478] and quite

[1] It was observed, that this high yields were only observed with fresh iodine pentoxide. The yields dropped slightly from time to time with the ongoing use of this reagent.

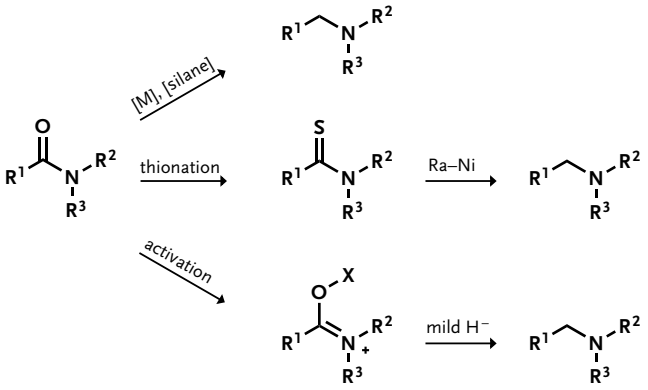
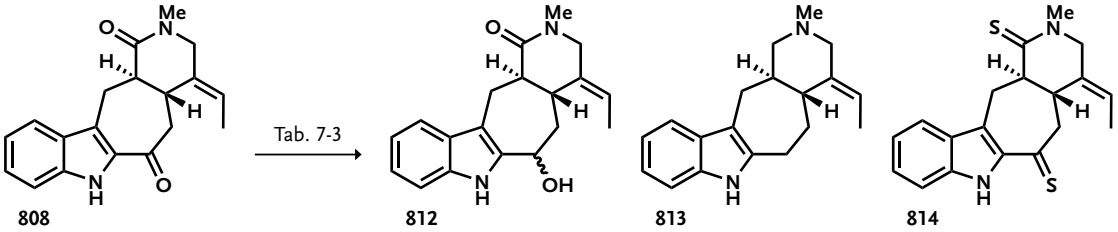


Figure 7-13. General concepts for the chemoselective reduction of amides.

recently molybdenum.[479] Another option is the transformation of the amide into the corresponding thioamide *via* thionation reagents (e.g. Lawesson's reagent[464] or Belleau's reagent[465]). Thioamides can then be selectively reduced *via* desulfurization with Raney nickel.[480] A third option is the activation of the amide carbonyl with strong activating agents, this yields an imidate cation which can be selectively reduced with mild hydrides (e.g. sodium cyanoborohydride). Protocols for the activation with Meerwein salts,[481] triflic anhydride,[482] and phosphorus oxychloride[483] are described.

Many protocols suggest chemoselectivity, but it is very often obvious that this is not the case. In addition, many protocols are described with very simple molecules thus keeping the reader in the dark about the tolerance and compatibility of many functional groups. Furthermore, in the case of 5-oxoisomethuenine (**808**), the protocol needs to distinguish between an amide and a vinylogous amide, thus demanding a very good chemoselectivity.



Scheme 7-15. Conversion of amide **808**, *cf.* Tab. 7-3 for conditions.

Table 7-3. Attempts for the reduction of amide **808**.

#	Conditions	Result	Ref.
1	Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, –78 °C to 0 °C, then $NaBH_3CN$, 0 °C → rt.	—[1)]	[482a]
2	Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, –78 °C to 0 °C, then TESH, 0 °C → rt.	—[1)]	[482a]
3	$BH_3 \cdot THF$, THF, 0 °C	—	[484,485]

(continued on next page...)

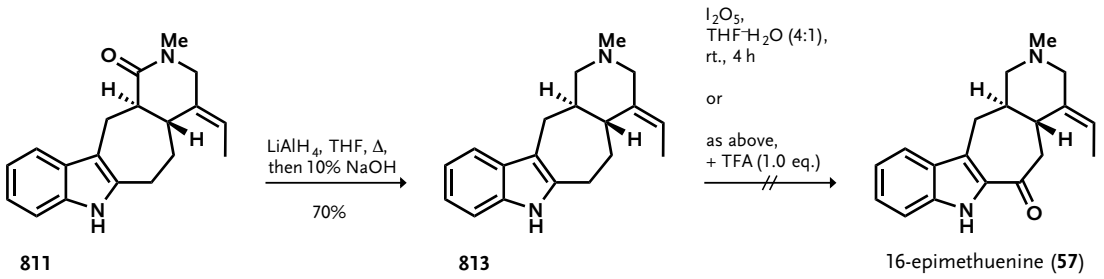
Table 7-3. *(continued)*

#	Conditions	Result	Reference
4	9–BBN (2.0 eq.), rt., 2 h	**813**	—
5	$RhH(CO)(PPh_3)_3$ (1 mol %), Ph_2SiH_2, rt., 12 h	—	[469a]
6	$Mo(CO)_6$ (5 mol %), TMDS (4.0 eq.), THF, 80 °C, 12 h	—	[479]
7	$Ru_3(CO)_{12}$ (1 mol %), TMDS (4.0 eq.), PhMe, 60 °C, 2 h	—[1)]	[478]
8	$Zn(OAc)_2$, $(EtO)_3SiH$, THF, 50 °C	—	[471a]
9	Me_3OBF_4, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, MS 4 Å, rt., 2 h, then $NaBH_3CN$, 0 °C	—	[481a,481d]
10	Et_3OBF_4, CH_2Cl_2, rt., 20 h, then NaBH4, MeOH, 0 °C	**812**	[481a,481b]
11	$H_2PtCl_6 \cdot 6\,H_2O$ (1 mol %), TMDS (5.0 eq.), PhMe, 75 °C	—[1)]	[469c]
12	Tf_2O (1.1 eq.), CH_2Cl_2, 0 °C, 30 min, then HEH (2.5 eq.), rt.	—[1)]	[482b]
13	Karstedt's catalyst (1 mol %), Ph_2SiH_2 (2.0 eq.), THF, 40 °C, 6 h	—	[469e]
14	$RhCl(PPh_3)_3$ (1 mol %), Ph_2SiH_2 (2.1 eq.), THF, rt., 12 h	—	[469a]
15	Et_2Zn (5 mol %), LiCl (10 mol %), TMDS, THF, rt., 6 h	—	[471c]
16	$TiCl_4$, $NaBH_4$, DME, rt., 14 h	**813**	[486]
17	$NaBH_4$, DMSO, MsOH, rt., 2 h	**812**	[487]
18	$POCl_3$, $NaBH_4$, EtOH, 0 °C, 60 min	**812**	[483]
19	Belleau's reagent, THF, 0 °C, 2 h	—	—
20	Lawesson's reagent, PhH, 100 °C, 1 h	**814**	—

[1)] decomposition

As listed in Tab. 7-3, a chemoselective reduction of amide **808** under a variety of conditions was not possible. An important drawback were the demanded concentrations for the metal-catalyzed hydrosilylation reactions. Very often a very high concentration for the successful reaction was required, typically the protocols are run with 1.0 M of solvent (based on the amide). Although the developed synthetic route can produce a considerable amount of amide **808**, the reduction attempts were usually run on scales between 2 mg and 10 mg; to make it clear, this means less than 40 µl of solvent even for the largest scale of 10 mg. Obviously, the reactions were carried out slightly more diluted which might have an effect to the reactivity. Other special reducing conditions furnished in some cases either alcohol **808** or indole **813** (Entries 4, 10, 16–18), thionation attempts afforded dithionated compound **814** (Entry 20).

At this point, plans for a chemoselective reduction were given up and attention next turned to three further synthetic attempts. In a first attempt, the order of synthetic transformations was changed. Amide **811**, which was obtained from the ionic reduction sequence, was first reduced to the corresponding tertiary amine **813** using lithium aluminium hydride in refluxing THF (Scheme 7-16). However, attempts for the oxidation to the corresponding 2-acylindole

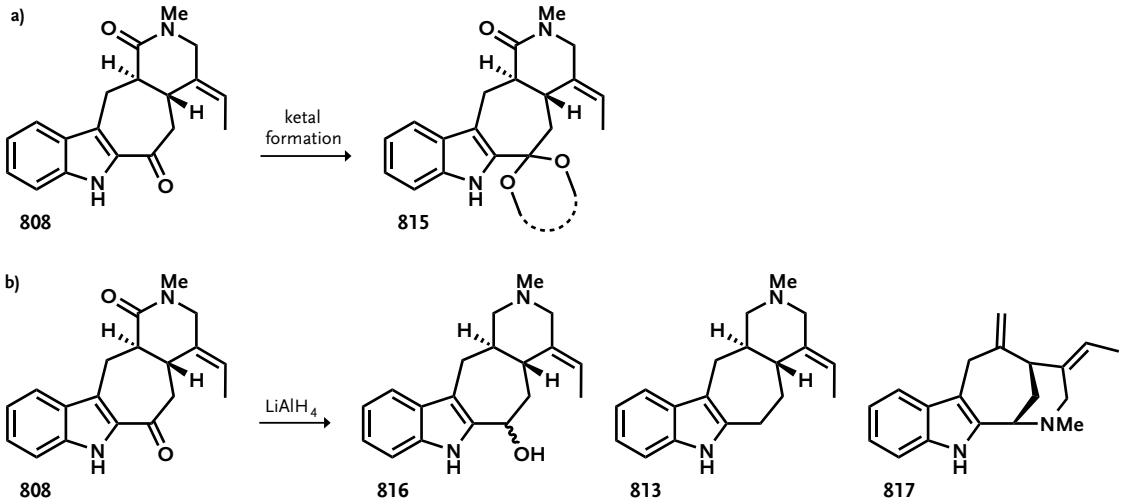


Scheme 7-16. Amide reduction followed by oxidation failed to furnish 16-epimethuenine (**57**).

failed once again. It was assumed, that the tertiary amine prevented the successful oxidation. Therefore, the reaction was repeated with the addition of one equivalent of TFA to block the tertiary amine but without any effect.

Next in line was the idea to mask the keto functionality *via* its transformation into a ketal (Scheme 7-17a). Surprisingly, literature examples for similar transformation are scarce and dated decades ago.[488] Several attempts to synthesize dioxolane derivative **815** afforded this compound only in traces.

A third option is to reduce (+)-5-oxoisomethuenine (**808**) under harsh conditions (Scheme 7-17). Needless to say, that the 2-acylindole moiety will be reduced under these conditions, too. As already mentioned, this moiety is more like a vinylogous amide than a ketone. Therefore, a hydride reduction under harsh conditions have not necessarily afford the desired product **816**; both completely reduced compound **813** and indole **817** with a rearranged skeleton are conceivable. Similar results were obtained by Bosch and co-workers en route to (–)-quebrachamine.[489] The final reduction and re-oxidation sequence is described in the next section.

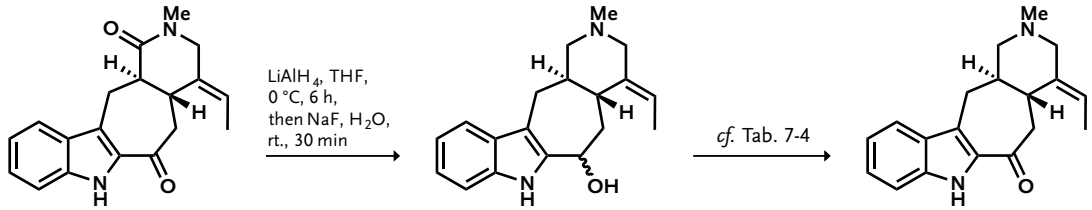


Scheme 7-17. Two additional possible attempts en route to *Ervatamia* alkaloids from amide **808**.

7.4.1 Total Synthesis of 16-Epimethuenine

(+)-5-oxoisomethuenine (**808**) was reduced with $LiAlH_4$ at 60 °C in THF in 1 h. However, LC–MS analysis revealed, that the resulted compound lacked both carbonyl functions ($[M + H]^+ = 281$). Same was true for the reduction with Red-Al®. Best results to obtain isomethueninol **816** were achieved with $LiAlH_4$ at 0 °C for 6 h followed by the addition of sodium fluoride (Scheme 7-18).[490] Several protocols for the benzylic oxidation to the corresponding 2-acylindole are known. Usually, this transformation is achieved by activated manganese dioxide,[78,491–495] pyridinium chlorochromate,[394] chromium trioxide,[496] *tert*-butyl hypochlorite,[497] or under Swern type conditions.[498] Best results for the conversion of alcohol **816** into 16-epimethuenine (**57**) were obtained with activated manganese dioxide (20.0 eq.) in chloroform at ambient temperature (Tab. 7-4, Entries 6 and 7). This reaction was accompanied by the formation of an unknown by-product and prolonged reaction times led to its predominated generation (Entry 5). The use of activated manganese dioxide in CH_2Cl_2 –THF (1:1) instead of chloroform led only to the formation of minimal amounts of the natural product (Entry 1).

With synthetic 16-epimethuenine (**57**) in hands, attention next turned to the comparison of synthetic analytical data with the analytical data from the isolation. **57** has been isolated five times: from *Hazunta modesta* (Potier, 1977, named "Alkaloid M"),[63] *Pterotabema inconspicua* (Le Men-Olivier, 1981),[67] *Tabernaemontana dichotoma* (Verpoorte, 1982),[68] *Pterotaberna inconspicua* (Bakana, 1984),[65] and *Ervatamia malaccensis* (Clivio, 1990).[60]



(+)-5-oxoisomethuenine (**808**) isomethueninol (**816**) 16-epimethuenine (**57**)

Scheme 7-18. Total synthesis of 16-epimethuenine (**57**).

Table 7-4. Conditions for the oxidation of alcohol **816** to 16-epimethuenine (**57**).

#	Conditions	Scale	Yield [%][1)]	Notes
1	MnO_2 (10 eq.), CH_2Cl_2 –THF (1:1), rt., 8 h	5 mg	traces	2)
2	PCC, CH_2Cl_2, rt.	5 mg	—	3)
3	oxalyl chloride, DMSO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, –45 °C	2 mg	30	4)
4	CrO_3, pyridine, rt., 5 min	4 mg	35	4)
5	MnO_2 (20 eq.), $CHCl_3$, rt., 7 h	6 mg	40	2)
6	MnO_2 (20 eq.), $CHCl_3$, rt., 4 h	25 mg	52	—
7	MnO_2 (20 eq.), $CHCl_3$, rt., 4 h	80 mg	70	—

[1)] combined yield with previous reduction [2)] formation of by-product predominated
[3)] decomposition [4)] with impurities

Table 7-5. 16-Epimethuenine: comparison of synthetic ^{1}H NMR data with isolation data.

H	16-Epimethuenine[60]			16-Epimethuenine[67]			16-Epimethuenine[68]			16-Epimethuenine[65]			"Alkaloid M"[63]			Synthetic (57)		
	ppm	mult.	*J* [Hz]	ppm	mult.	*J* [Hz]	ppm	mult.	*J* [Hz]	ppm	mult.	*J* [Hz]	ppm	mult.	*J* [Hz]	ppm	mult.	*J* [Hz]
5a	2.28–2.6	m														2.40–2.45	m	
5b	3.10–3.33	m														2.72–2.83	m	
6a	2.28–2.60	m														2.72–2.83	m	
6b	2.78–2.98	m														3.22	dd	17.5, 3.0
9	7.24	br d	8.3	7.6	br d	8.0	7.2–7.5	m		7.6–7.7	m		7.0–7.8	m		7.63	br d	8.1
10	6.89	dd	8.3, 7.3													7.13	ddd	8.0, 4.9, 3.1
11	7.16	dd	8.3, 7.3													7.37	m	
12	7.29	br d	8.3													7.37	m	
14a	2.28–2.60	m														2.89–2.95	m	
14b	3.47	m														2.72–2.83	m	
15	2.78–2.98	m														2.40–2.45	m	
16	2.28–2.60	m														2.89–2.95	m	
18	1.53	d	6.8	1.62	dd	7.2, 2.0	1.65	d	7.0	1.63	dd	6.5, 1.5	1.61	dd	—	1.63	dd	6.9, 1.6
19	5.66	q	6.8	5.45	q	7.0	5.53	q	7.0	5.47	q	6.5	5.4	q	—	5.46	q	6.8
21a	3.10–3.33	m														2.89–2.95	m	
21b	3.80–4.10	m														3.49	d	12.9
NMe	2.70	s		2.40	s		2.40	s		2.39	s		2.40	s		2.40	s	
NH	10.09	br s		9.10	br s		9.10	br s		9.10	br s		9.10	br s		8.98	br s	

[60] P. Clivio, B. Richard, M. Zeches, L. Le Men-Olivier, S. H. Goh, B. David, T. Sevenet, *Phytochemistry* **1990**, *29*, 2693–2696 [67] A. M. Morfaux, T. Mulamba, B. Richard, C. Delaude, *Phytochemistry* **1982**, *21*, 1767–1769 [68] P. Perera, G. Samuelsson, T. van Beek, R. Verpoorte, *Planta Med.* **1983**, *47*, 148–150 [65] P. Bakana, R. Dommisse, E. Esmans, R. Fokkens, L. Pieters, N. Nibbering, A. Vlietinck, *Planta Med.* **1984**, *50*, 331–334 [63] A.-M. Bui, M.-M. Debray, P. Boiteau, P. Potier, *Phytochemistry* **1977**, *16*, 703–706

Comparison of all reported data revealed, that it is not consistent at all. The most detailed analysis was reported by Clivio *et al.* and contains full ^{1}H and ^{13}C NMR data. The rest published only ^{1}H NMR data for the most characteristic signals: H9, H18, H19, NMe and NH (*cf.* Fig. 7-14). These four reports were very consistent among themselves and almost identical data for this protons were reported, whereas the reported data from Clivio *et al.* differed immensely from the rest. Interestingly, the synthetic data of 16-epimethuenine was not identical to Clivio *et al.* but in full accordance to the other four reports. Tab. 7-5 lists and compares the whole ^{1}H NMR data (reported and synthetic).

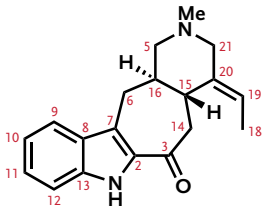


Figure 7-14. 16-Epimethuenine counting.

In addition, comparison of ^{13}C NMR data led to the same result. The synthetic data was in full accordance with reported data from Bakana *et al.* but differed from Clivio *et al.* (Tab. 7-6). Especially the olefinic signals of C19 (Clivio *et al.*: 131.0 ppm, synthetic: 122.6 ppm, Δ = −8.4 ppm) and C20 (Clivio *et al.*: 128.6 ppm, synthetic: 136.4 ppm, Δ = 7.8 ppm) differed immense.

Finally, comparison of IR data was also in full accordance with reported data (Tab. 7-7). The comparison of the $[\alpha]_D^{20}$ value is not significant, since the synthesis was started with 60% enantiomeric excess. Furthermore, the reported data is once again inconsistent (Tab. 7-8).

Table 7-6. 16-Epimethuenine: comparison of synthetic ^{13}C NMR data with isolation data (all values in ppm).

C	Ref. 60	Ref. 65	Synthetic (57)	Δ ppm (Ref. 60)	Δ ppm (Ref. 65)
2	131.0	131.7	132.0	1.0	0.3
3	191.6	192.6	193.5	1.9	0.9
5	55.4	56.9	58.4	3.0	1.5
6	29.6	30.8	31.2	1.6	0.4
7	119.9	121.3	122.4	2.4	1.1
8	127.1	127.8	128.2	1.1	0.4
9	120.1	121.2	121.4	1.3	0.2
10	120.7	120.3	120.4	–0.3	0.1
11	127.0	127.0	127.1	0.1	0.1
12	112.0	111.9	112.0	0.0	0.1
13	136.8	136.7	136.7	–0.1	0.0
14	45.7	43.7	47.3	1.6	3.6
15	36.2	37.6	38.8	2.6	1.2
16	35.7	37.4	38.0	2.3	0.6
18	12.9	12.9	13.0	0.1	0.1
19	**131.0**	125.2	122.6	**–8.4**	–2.6
20	**128.6**	133.8	136.4	**7.8**	2.6
21	54.3	55.4	57.0	2.7	1.6
NMe	42.3	46.8	45.1	2.8	–1.7

Table 7-7. 16-Epimethuenine: comparison of synthetic IR data with isolation data (all values in cm^{-1}).

Ref. 63	Ref. 67	Ref. 68	Ref. 65	Synthetic (57)	Note
3300	3300	3330	3280	3297	
				2920	
	2780	2850		2850	
1620	1625	1610	1645	1625	ketone
	1535			1537	
			1460	1450	
			1420	1430	
				1250	
			745	745	indole

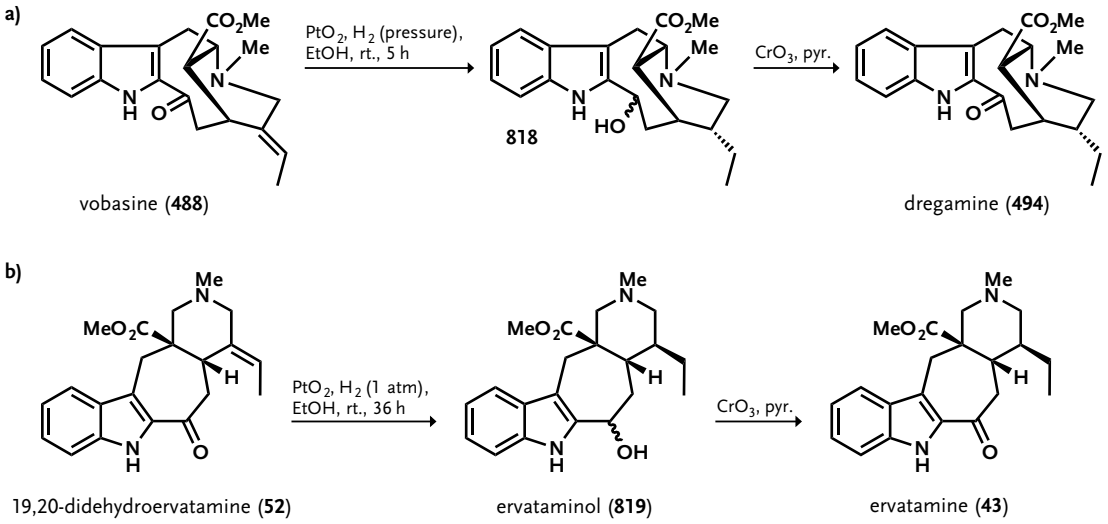
Table 7-8. 16-Epimethuenine: comparison of $[\alpha]_D^{20}$ values.

Ref. 68	Ref. 67	Ref. 63	Synthetic (57)
−178° ($c = 0.1$, $CHCl_3$)	−140° ($c = 1$, $CHCl_3$)	+137° ($c = 0.3$, EtOH)	−18° ($c = 0.1$, $CHCl_3$)

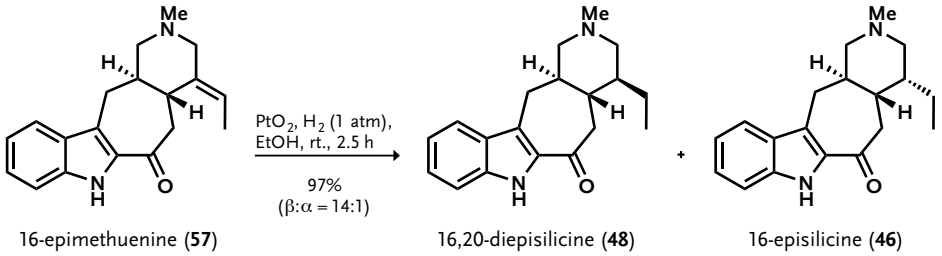
Due to several inconsistencies—especially the NMR data which on the one hand differed immense from Clivio *et al.* but on the other hand was in full accordance to Potier *et al.*, Le Men-Olivier *et al.*, Verpoorte *et al.*, and Bakana *et al.* for individual protons—additional 14 mg of pure 16-epimethuenine (**57**) were synthesized. This amount was sufficient for extended NMR studies. ^{1}H NMR, ^{13}C NMR, ^{1}H,^{1}H-COSY NMR, ^{1}H,^{13}C-HSQC NMR, ^{1}H,^{13}C-HMBC NMR, and ^{1}H,^{1}H-NOESY NMR in chloroform and dimethyl sulfoxide, respectively, have confirmed absolutely the correct structure of 16-epimethuenine (**57**). The *(E)*-geometry of the double bond have been confirmed definitively *via* ^{1}H,^{1}H-NOESY NMR (NOE correlations between H18 and H14). No crystal of high quality for an X-ray analysis could be obtained of synthetic 16-epimethuenine **57**. Therefore, **57** was transformed into its 2,4-dinitrophenylhydrazone derivative with Brady's reagent.[499] After all, the crystal quality of the 2,4-dinitrophenylhydrazone derivative was not sufficient for an X-ray analysis but its extended NMR analysis in pyridine once again confirmed the correct structure of 16-epimethuenine (**57**).

7.4.2 Total Syntheses of 16,20-diepisilicine and 16-episilicine

A final ultimate proof for the correctness would be the transformation of synthetic 16-epimethuenine (**57**) into its silicine derivative *via* hydrogenation of the double bond. If the obtained compound can be clearly identified as a silicine derivative, the precursor had to be 16-epimethuenine (**57**) unerringly. The conversion of 16-epimethuenine (**57**) into its silicine derivatives has not been described so far. However, similar transformation of other alkaloids have been reported, e.g. the conversion of vobasine (**488**) into dregamine (**494**, Scheme 7-19a),[500] or 19,20-didehydroervatamine (**52**) into ervatamine (**43**, Scheme 7-19b).[142] Both reports describe both the reduction of the olefinic moiety and the reduction of the 2-acylindole moiety. In both cases,



Scheme 7-19. **a)** Conversion of vobasine into dregamine.[500] **b)** Conversion of 19,20-didehydroervatamine into ervatamine.[142]



Scheme 7-20. Conversion of 16-epimethuenine in 16,20-diepisilicine and 16-episilicine.

the alcohol is re-oxidized to the corresponding 2-acylindole with chromium trioxide in pyridine. 16-epimethuenine **57** was hydrogenated under atmospheric pressure over a catalytic amount of Adams's catalyst in ethanol. Full consumption of the starting material was observed already after 2.5 h and NMR analysis revealed, that the 2-acylindole moiety remained untouched and that 16,20-diepisilicine (**48**) and 16-episilicine (**46**) have been formed in a ratio of 14:1. Extended NMR analysis of 16,20-diepisilicine (**48**) confirmed its correct structure.

16,20-diepisilicine (**48**) has been isolated once so far from *Ervatamia officinalis* (Yue, 2005).[66] The synthetic data of **48** was in full accordance with the reported isolation data. The obtained ^{1}H NMR data was almost identical to the reported one in all properties (Tab. 7-9). The synthetic compound could be definitely assigned to 16,20-diepisilicine. Due to the high favorable formation of the β-epimer, the α-epimer 16-episilicine (**46**) was produced only in traces. However, its NMR data was in accordance with the isolation data (Debray, 1975)[73] and with the data from the synthesis of (–)-16-episilicine from Bosch and co-workers.[501] Furthermore, the ^{13}C NMR data and IR data were in full accordance to the reported data, too (Tables 7-10 and 7-11). No discrepancies were observed.

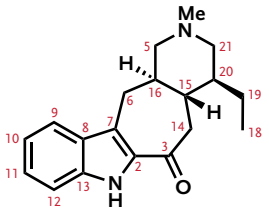


Figure 7-15. 16,20-Diepisilicine counting.

Table 7-9. 16,20-Diepisilicine: comparison of synthetic ^{1}H NMR data with isolation data.

H	16,20-Diepisilicine[66]			Synthetic (48)		
	ppm	mult.	*J* [Hz]	ppm	mult.	*J* [Hz]
5a	3.03	ddd	11.3, 4.3, 1.9	3.03	ddd	11.3, 4.4, 1.9
5b	1.82	dd	11.3, 11.3	1.82	dd	11.2, 11.2
6a	3.26	dd	17.4, 5.2	3.26	dd	17.3, 5.2
6b	2.80	dd	17.4, 8.8	2.80	dd	17.3, 8.8
9	7.64	dd	8.2, 0.6	7.63	dd	8.2, 1.0
10	7.13	ddd	8.2, 6.3, 1.7	7.13	ddd	8.1, 6.2, 1.8
11	7.32–7.36	m		7.32–7.38	m	
12	7.32–7.36	m		7.32–7.38	m	
14a	3.08	dd	16.8, 1.6	3.07	dd	16.9, 1.8
14b	2.62	dd	16.8, 9.6	2.62	dd	16.8, 9.6
15	1.37–1.45	m		1.35–1.42	m	
16	2.17–2.26	m		2.21	dtd	11.5, 9.4, 4.9
18	0.92	t	7.5	0.92	t	7.3
19a	1.71	dqd	14.1, 7.5, 2.2	1.71	dqd	15.1, 7.6, 2.3
19b	1.15–1.23	m		1.15–1.23	m	
20	1.42–1.50	m		1.42–1.50	m	
21a	2.99	ddd	11.2, 3.7, 1.9	2.98	ddd	11.4, 3.8, 2.0
21b	1.60	dd	11.2, 10.7	1.6	dd	10.9, 10.9
NMe	2.32	s		2.31	s	
NH	9.12	br s		9.00	br s	

[66] H. Zhang, J. M. Yue, *Helv. Chim. Acta* **2005**, *88*, 2537–2542

Table 7-10. 16,20-Diepisilicine: comparison of synthetic IR data with isolation data (all values in cm^{-1}).

Ref. 66	Synthetic (48)	Note
3313	3310	
2931	2927	
2875	2889	
2783	2791	
1620	1633	ketone
1576	1575	
1458	1458	
1335	1332	
1254	1255	
743	743	indole

These results clearly proved the correct structure of 16-epimethuenine (**57**). One the one hand, extensive 1D and 2D NMR analyses showed, that this data clearly belongs to the assigned structure. The *(E)*-geometry of the olefinic moiety have been demonstrated by the NOE correlations between H18 and H14. One the other hand, the conversion of **57** into 16,20-diepisilicine (**48**)

Table 7-11. 16,20-Diepisilicine: comparison of synthetic ^{13}C NMR data with isolation data (all values in ppm).

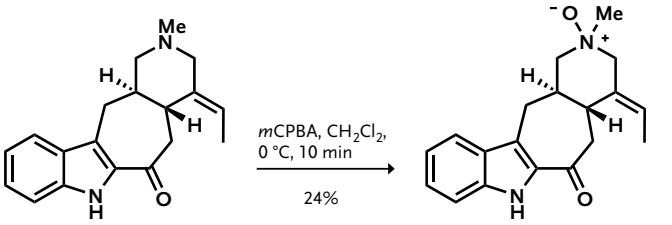
C	Ref. 66	Synthetic (48)	Δ ppm (Ref. 66)
2	132.0	132.2	0.2
3	193.4	193.5	0.1
5	63.4	63.6	0.2
6	29.8	30.0	0.2
7	122.2	122.4	0.2
8	127.7	127.9	0.2
9	120.8	121.0	0.2
10	120.0	120.2	0.2
11	126.6	126.8	0.2
12	111.9	112.1	0.2
13	136.6	136.8	0.2
14	47.0	47.3	0.3
15	40.4	40.7	0.3
16	41.0	41.3	0.3
18	11.3	11.5	0.2
19	24.4	24.6	0.2
20	42.4	42.6	0.2
21	60.7	61.0	0.3
NMe	46.3	46.5	0.2

and 16-episilicine (**46**) showed, that the precursor definitely had to be 16-epimethuenine (**57**). This leads to the result, that the reported data for **57** from Clivio *et al.* can not be correct. It is impossible to say, whether the group just made an unseen typo and printed the wrong values or actually did not isolate 16-epimethuenine (**57**) from the leaves and stem bark of *Ervatamia malaccensis* but a different alkaloid and misinterpreted the analytical data. In addition, this reported data was already not in accordance with previously reported data for **57** at the time of publication (1990).

7.4.3 Total Syntheses of Additional *Ervatamia* Derivatives

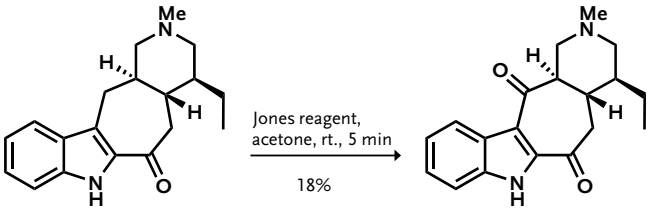
It was already shown, that 16-epimethuenine (**57**) was successfully transformed into two further natural products: 16,20-diepisilicine (**48**) and 16-episilicine (**46**). Furthermore, **57** was converted into another natural product: its *N*-oxide derivative 16-epimethuenine-*N*-oxide (**60**). For this purpose, 16-epimethuenine was reacted with *meta*-chloroperoxybenzoic acid for 10 min. TLC indicated the presence of two compounds, the least polar one being identical to 16-epimethuenine-*N*-oxide (**60**) after TLC separation (Scheme 7-21).[67]

In another run, 16,20-diepisilicine (**48**) was reacted with Jones reagent in acetone at ambient temperature for 5 min. This afforded 6-oxo-16,20-diepisilicine (**51**) in 18% yield (unoptimized) and spectral data was in accordance to literature (Scheme 7-22).[66] An alternative procedure



16-epimethuenine (**57**) 16-epimethuenine-*N*-oxide (**60**)

Scheme 7-21. Total synthesis of 16-epimethuenine-*N*-oxide (**60**), unoptimized yield.



16,20-diepisilicine (**48**) 6-oxo-16,20-diepisilicine (**51**)

Scheme 7-22. Total synthesis of 6-oxo-16,20-diepisilicine (**51**), unoptimized yield.

using IBX in EtOAc–DMSO (2:1) at 80 °C (according to Cook and co-workers)[502] could not afford **51**.

No further transformations and syntheses of additional *Ervatamia* natural products have been carried out. Some additional ideas are described in Section 8.1.

8 Outlook and Summary

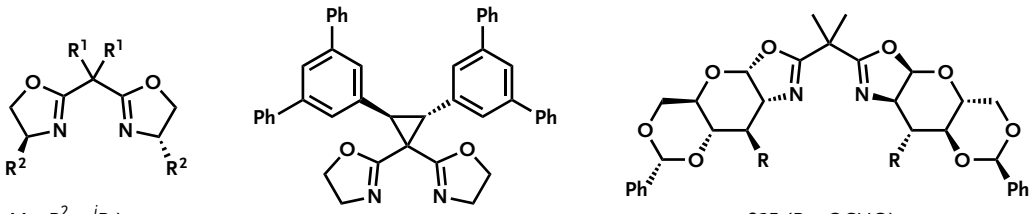
8.1 Outlook

Total syntheses of five *Ervatamia* alkaloids have been discussed. Two additional synthetic intermediates—(+)-5-oxoisomethuenine (**808**) and 16-epimethueninol (**816**), Section 7.4.1 on p. 169—have not been isolated so far from natural sources and therefore are not classified as natural products. However, there is a high probability that this might happen in the future since analogous derivatives from other *Ervatamia* alkaloids are known (Fig. 4-1 on p. 88).

Although the final approach described a fast and reliable synthesis of *Ervatamia* alkaloids, there is always room for improvement. Some proposals are discussed briefly in the upcoming sections.

8.1.1 Enantioselective Cyclopropanation

The cyclopropanation was carried out in an enantioselective fashion during the last approaches. The use of bisoxazoline ligand **583** improved the diastereomeric ratio drastically and led to the formation of almost one single diastereomer. In addition, the yield was almost quantitative. Usually, the use of bisoxazoline ligands for the metal-catalyzed cyclopropanation of olefins furnishes enantioenriched products. In accordance to literature different ligand ratios have been investigated. Unfortunately, the best obtained enantiomeric ratio was only 80:20 (Section 6.2, p. 120). Fortunately, a lot of protocols for asymmetric cyclopropanation reactions have been described in literature. An asymmetric transition-metal-catalyzed decomposition of diazoalkanes is known not only with copper, but also with cobalt, rhodium, ruthenium, iridium, palladium, and mercury.[503] Therefore, there are still lots of possibilities to raise the enantiomeric excess. Alternatively, the investigated cyclopropanation reaction could be continued to be carried out with copper but using other bisoxazoline ligands since many different bisoxazoline ligands are known (Fig. 8-1).



820 (R^1 = Me, R^2 = ^{i}Pr),
821 (R^1 = Me, R^2 = Ph)
822 (R^1 = 3,5-(^{t}Bu)$_2$C$_6$H$_3$CH$_2$, R^2 = ^{i}Pr)
823 (R^1 = Bn, R^2 = ^{i}Pr)

824

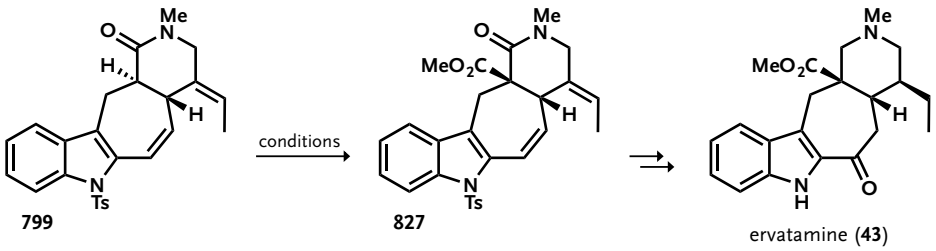
825 (R = OCHO),
826 (R = O_2CMe)

Figure 8-1. Structure of bisoxazoline ligands for asymmetric cyclopropanation reactions.

8.1.2 Approach to Ervatamine-type Alkaloids

Heck reaction furnished tetracycle **799** en route to 16-epimethuenine. This intermediate is ideally suited for the transformation to α-acyl amide **827** (Scheme 8-1). This compound is the precursor for all ervatamine-type alkaloids. For this purpose, several attempts for the conversion of **799** into **827** were carried out (Tab. 8-1). The potassium or lithium enolate, respectively, was reacted with methyl chloroformate or Mander's reagent (methyl cyanoformate/Zyklon A).[504] So far, no acylation could be achieved. Alternative attempts could use the LICKOR superbase[505] or phosphazene bases (Schwesinger bases)[506] for the enolate formation. Precedent literature examples for the α-acylation of α-disubstituted amides is scarce.[507–509] In addition, one protocol for the selective α-acylation of amides *via* dual reactivity of *O*-acylhydroxylamines toward zinc enolates has been described.[510]

With α-acyl amide **827** in hands, almost all *Ervatamia* alkaloids are accessible *via* the described synthetic approach towards the synthesis of 16-epimethuenine (**57**). Although **57** is accessible



799 → (conditions) → **827** → ervatamine (**43**)

Scheme 8-1. Attempts to the synthesis of compound **827**.

Table 8-1. Attempts for the synthesis of compound **827** (*cf.* Scheme 8-1).

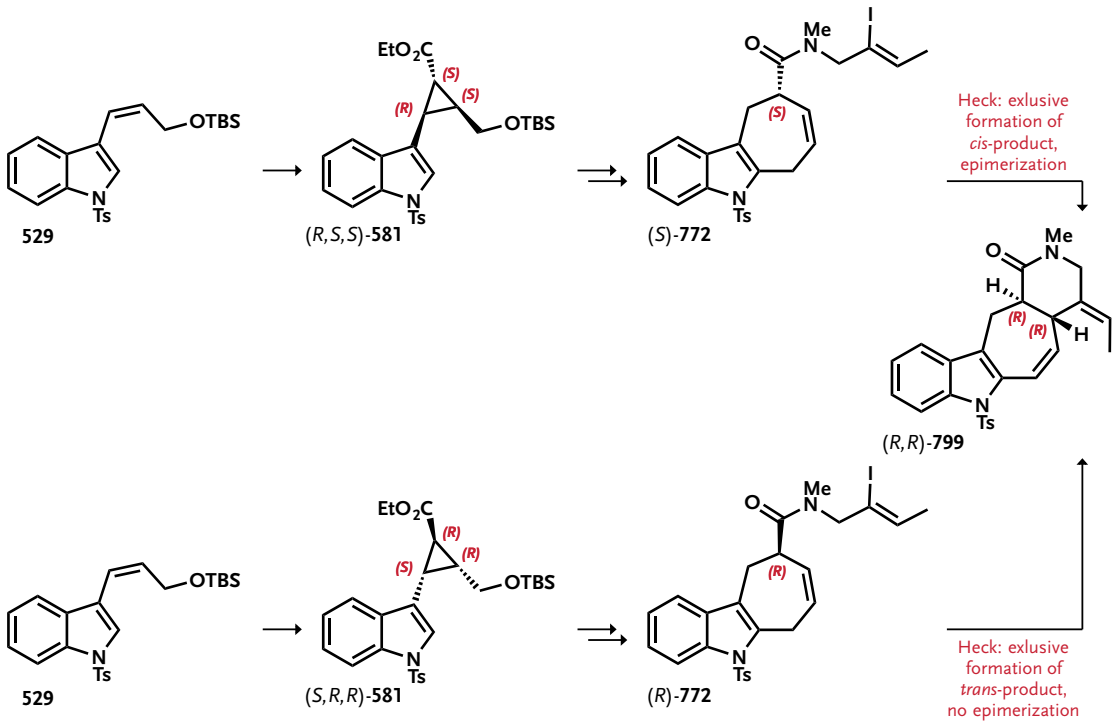
#	Conditions	Yield [%]
1	KHMDS, THF, –78 °C → 0 °C, then methyl chloroformate, THF, –78 °C	—[1)]
2	LDA, THF, HMPA, –78 °C → 0 °C, then Mander's reagent, THF, –78 °C	—[1)]
3	^{t}BuLi, THF, HMPA, –78 °C, then Mander's reagent, THF, –78 °C	—[1)]

[1)] no reaction

through the described route, this natural product and its epimer methuenine (**56**) could be synthesized from 19,20-didehydroervatamine (**52**), the direct precursor of ervatamine (**43**), thus making compound **827** an ideal privileged intermediate in terms of the "Verbund"-synthesis (Section 6.1).

8.1.3 Piperidine Ring Formation

Section 7.3.2 described the piperidine ring formation *via* Heck reaction. The reaction proceeded with excellent yield and furnished Heck product **799**. A plausible explanation for the formation of the *trans*-product has been described. However, this assumption has so far no evidence. This is also important for the knowledge of the absolute stereochemistry of the cyclopropanation product. The absolute stereochemistry was determined at the very end of the synthesis by comparing optical rotation signs of the synthesized natural products with the original natural products (assuming, the Heck reaction furnished the *cis*-product which epimerized under these conditions, *cf.* Section 7.3.2 on p. 159). Based on literature protocols, the absolute stereochemistry of the cyclopropanation product can be predicted in some cases. However, cyclopropanation reactions with determination of the absolute stereochemistry of compounds like vinylindole **529** are so far unprecedented, thus leading to a dubiety concerning the correct assignment of the stereochemistry. As shown in Scheme 8-2, the knowledge about the correct formation of tetracycle **799** is important to deduce the absolute stereochemistry of the cyclopropanation



Scheme 8-2. The knowledge about the correct formation of tetracycle **799** is important to deduce the absolute stereochemistry of the cyclopropanation product.

product. Depending on the style of the ring closure, two enantiomeric cyclopropanation products (*R*,*S*,*S*)-**581** and (*S*,*R*,*R*)-**581** can be the precursor. To investigate the piperidine ring formation, this reaction can be carried out under radical conditions (e.g. TBTH, AIBN, PhMe, Δ) instead of using a Heck coupling reaction.[511] The α-stereogenic center cannot epimerize under these conditions and the result should lead to a conclusion—assuming, that the same tetracyclic skeleton with identical ring sizes is formed under radical conditions. Future work on this project will hopefully clear all questions.

8.2 Résumé

This part of the thesis dealt with the cyclohepta[*b*]indole motif. This structural motif is found both in natural products and in pharmaceutical compounds. Nowadays, 43 natural products containing this particular motif are known, by far the biggest part of them are *Ervatamia* alkaloids (22 member) followed by *Ambigua* alkaloids (13 member). Several pharmaceuticals compounds are known and six of them have been presented. Cyclohepta[*b*]indoles are often prepared by means of the Fischer indoles synthesis. Although this reaction can be quite useful and satisfies the requirements of a modern indole synthesis, it possesses certain limitations. The efficient preparation of highly functionalized and unsymmetrically substituted cyclohepta[*b*]indoles has therefore become of central interest for synthetic organic chemists. For the construction of cyclohepta[*b*]indoles, eleven methodologies have been presented, additional 15 methodologies have been described shortly and additional four methodologies for the construction of benzocyclohepta[*b*]indoles have been shown. This makes 30 methodologies in total of which only two are capable of the asymmetric construction of this structure motif.

By far the biggest progress in methodology development has been made within the last decade. This coincides with the enhanced attention of pharmaceutical industry towards compounds exhibiting the cyclohepta[*b*]indole motif. Total syntheses of natural products with this motif have been presented and analysis especially of the most recent syntheses reveals that the methodology development of the last decade has so far not found its way into application in complex molecule synthesis (Fig. 8-2). Evermore, this showed the urgent demand for the development of synthetic methodologies involving the construction of cyclohepta[*b*]indoles, explicitly when it comes to the development of methods for enantioselective construction of this privileged structure motif.

The development of a methodology for the asymmetric construction of cyclohepta[*b*]indole *via* a divinylcyclopropane-cycloheptadiene rearrangement has been presented. For this purpose, Chapter 3 gave an overview about the cyclopropane motif, its syntheses and its role as a precursor in the synthesis of cycloheptanes. Starting from indole-3-carbaldehyde, several divinylcyclopropanes like **828** were synthesized and it was shown, that these compounds rearrange smoothly to the corresponding cyclohepta[*b*]indolines **829** (Scheme 8-3). Rearomatization could be carried out under acidic conditions or under metal-catalyzed conditions; whereas skipped dienes like **830** were formed under acidic conditions, metal-catalyzed conditions furnished conjugated dienes **833**.

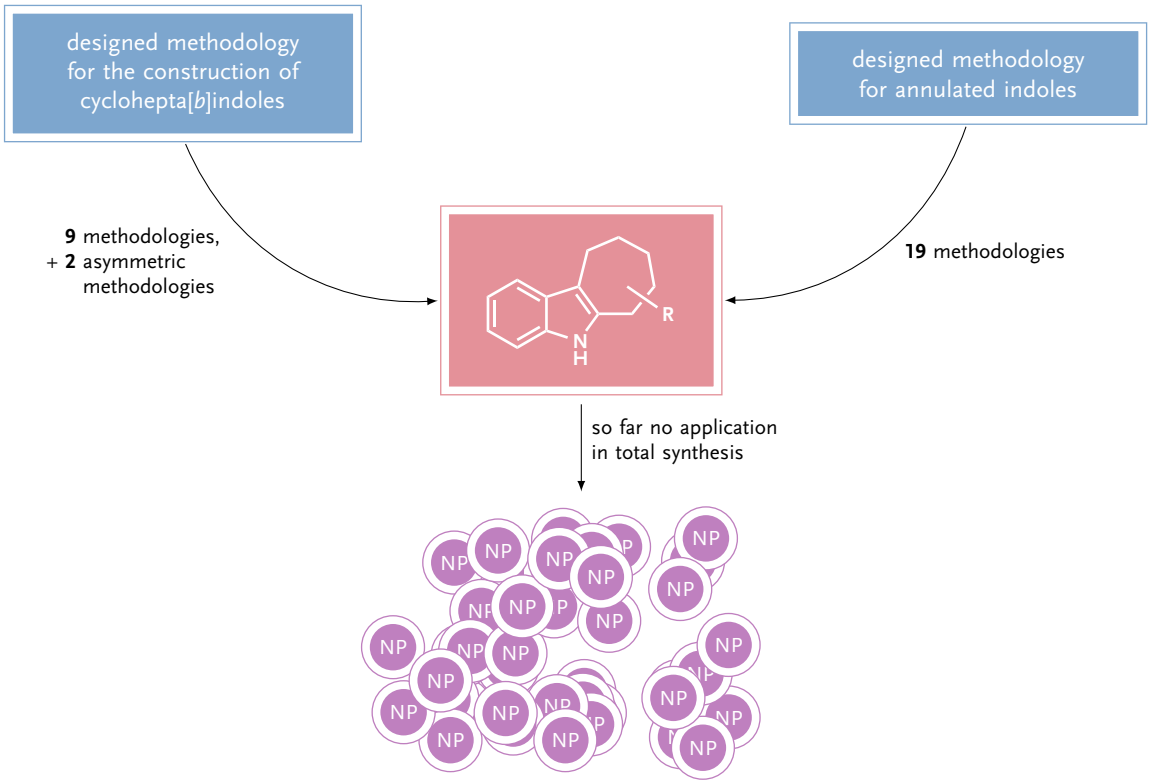
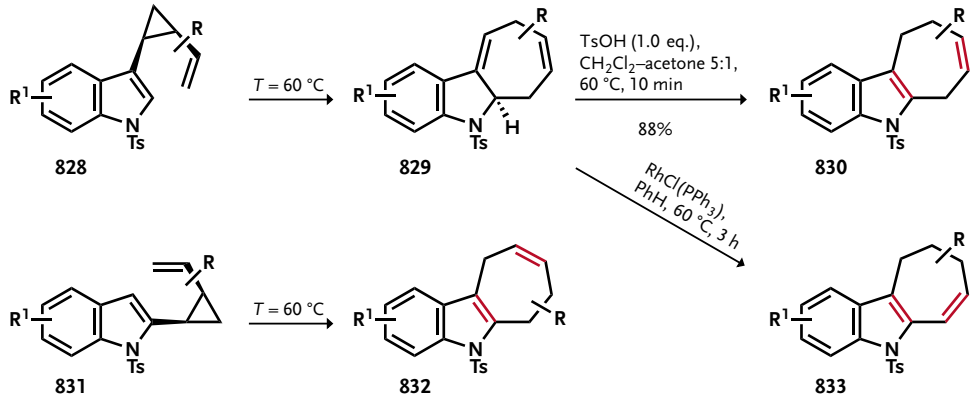
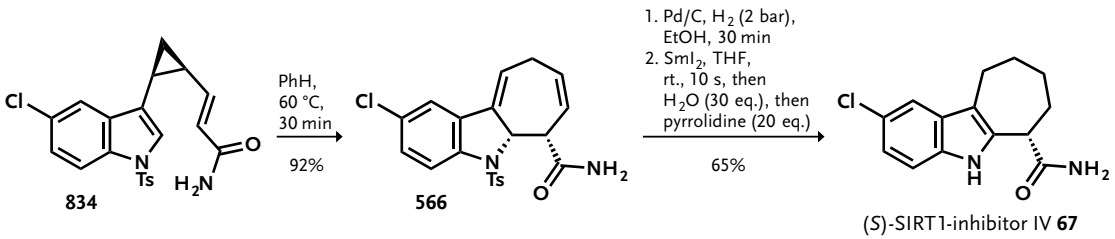


Figure 8-2. Reported methodologies for the construction of cyclohepta[*b*]indoles: status quo.

Divinylcyclopropanes **831** which were synthesized from indole-2-carbaldehyde yielded directly cyclohepta[*b*]indoles **832**. Comparing both synthetic routes leads to an interesting conclusion: depending on either starting from indole-2-carbaldehyde or indole-3-carbaldehyde, three different cyclohepta[*b*]indoles can be generated: 5,6,7,10-tetrahydrocyclohepta[*b*]indoles (**832**), 5,6,9,10-tetra-hydrocyclohepta[*b*]indoles (**830**), and 5,8,9,10-tetrahydrocyclohepta[*b*]indoles (**833**). The position of the olefinic moiety can be controlled specifically and therefore can be of use for



Scheme 8-3. Developed methodology for the construction of cyclohepta[*b*]indoles.



Scheme 8-4. Asymmetric total synthesis of (*S*)-SIRT1-inhibitor IV (**67**).

successful synthetic planning. The robustness of this methodology has been demonstrated by a broad scope, both for the indole-2-carbaldehyde and the indol-3-carbaldehyde series.

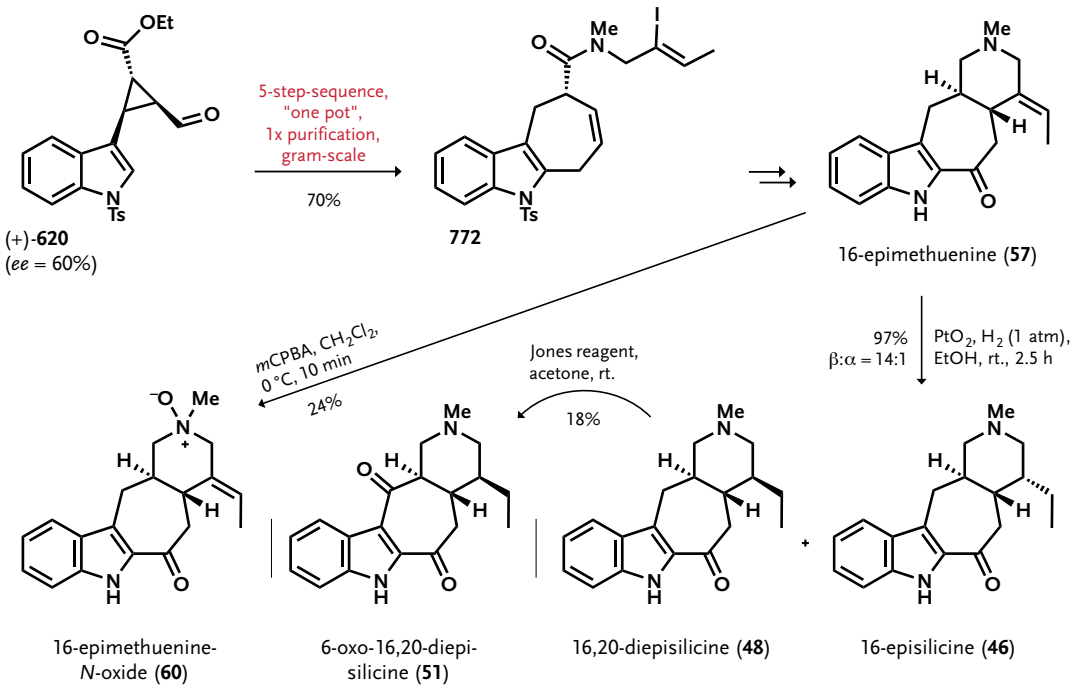
Finally, the methodology has been applied for the first enantioselective total synthesis of (*S*)-SIRT1-inhibitor IV (**67**, Scheme 8-4). (*S*)-**67** was furnished in 91% *ee* and and an overall yield of 28% (starting from commercially available 5-chloroindole-3-carbaldehyde). For practical purposes it is important to note that the synthetic sequence towards the synthesis of (*S*)-**67** requires only three purification steps and can be performed on a gram scale.

With the methodology in hands, attention next turned to the synthesis of *Ervatamia* alkaloids. For this purpose, a brief delineation about *Ervatamia* alkaloids and the biosynthesis of them has been given in Chapter 4. The synthesis planning was based on the concept of a "Verbund"-synthesis. Many approaches and variations have been described en route to *Ervatamia* alkaloids. Although all approaches worked fine with simplified test systems, their application to the "real" system which could lead to *Ervatamia* alkaloids was somehow cumbersome. Especially the divinylcyclopropane-cycloheptadiene rearrangements of ketenes and ketene acetals are noteworthy. Notwithstanding this, this approaches may not led to final synthesis of *Ervatamia* alkaloids but extend the developed methodology nicely. Having all this results in hand, the behavior of different systems under different conditions can be predicted very well now.

For the final approach, a synthetic route was designed to transform enantioenriched aldehyde **620** into cyclohepta[*b*]indole **772** (Scheme 8-5). This transformation was achieved *via* a smart sequence by trapping the divinylcyclopropane intermediate. The whole sequence is divided into five sub-steps; since many intermediates are instable and require direct conversion this transformation is more or less a "one-pot"[1] conversion. This sequence contains only one purification step and can be carried out in multigram scale. With cyclohepta[*b*]indole **772** in hands, piperidine ring formation was achieved *via* Heck coupling reaction which furnished the *trans*-fused annulated ring. This tetracycle was then transformed in four additional steps into the natural product 16-epimethuenine (**57**).

The total synthesis of 16-epimethuenine (**57**) contains 11 steps from literature known cyclopropane product **581** (and additional 5 steps from commercially available purchased chemicals),

[1] The author distances oneself from the term "one-pot". Although this term is very often used in publications, supplemental data reveals, that many intermediate steps require a quick work-up thus making the synthetic sequence not "one-pot". Many authors just take advantage of this term to reduce the overall step count.



Scheme 8-5. Total synthesis of 16-epimethuenine (**57**), 16,20-diepisilicine (**48**), 16-episilicine (**46**), 16-epimethuenine-*N*-oxide (**60**), and 6-oxo-16,20-diepisilicine (**51**).

only six intermediates require a purification. All steps have been optimized, thus yielding an overall yield of 29% (from literature known cyclopropanation product **581**). This overall yield is drastically reduced in the last step: the transformation of 5-oxoisomethuenine (**808**) into 16-epimethuenine (**57**) was carried out in moderate 61% yield. Notwithstanding this, this synthesis is an optimized and scalable asymmetric total synthesis and allows a rapid access to *Ervatamia* alkaloids. Many steps have also been carried out in multigram scale. For practical purposes it is important to note that the synthetic sequence towards the synthesis of 16-epimethuenine (**57**) can afford approximately 100 mg of pure natural product by starting with 1.0 g of olefin **529** in less than two weeks.

With synthetic 16-epimethuenine in hands, it turned out that the reported analytical data from several isolations was inconsistent. Four reports were very consistent among themselves and almost identical data for characteristic protons were reported, whereas the reported data from Clivio *et al.* differed immensely from the rest. Interestingly, the synthetic data of 16-epimethuenine (**57**) was not identical to Clivio *et al.* but in full accordance to the other four reports. Extensive 1D–NMR and 2D–NMR analysis and conversion of 16-epimethuenine (**57**) into 16,20-diepisilicine (**48**) and 16-episilicine (**46**) led to the result, that the reported data for **57** from Clivio *et al.* can not be correct. It is impossible to say, whether the group just made an unseen typo and printed the wrong values or actually did not isolate 16-epimethuenine (**57**) from the leaves and stem bark of *Ervatamia malaccensis* but a different alkaloid and misinterpreted the analytical data. In addition, this reported data was already not in accordance with previously reported data for **57** at the time of publication (1990).

16-Epimethuenine (**57**) was converted into four additional *Ervatamia* alkaloids. As already mentioned, **57** was converted into 16,20-diepisilicine (**48**) and 16-episilicine (**46**) *via* hydrogenation of the olefinic moiety. In addition, 16,20-diepisilicine (**48**) has been transformed into 6-oxo-16,20-diepisilicine (**51**) *via* Jones oxidation. Furthermore, 16-epimethuenine (**57**) was transformed into 16-epimethuenine-*N*-oxide (**60**) with *m*CPBA.

In summary, a smart, short, optimized, high-yielding and scalable synthesis of 16-epimethuenine (**57**) was described. Several transformations to further natural products have been demonstrated. Nevertheless, such a big project never comes to an end. Although this work has already accomplished a large part, some points still need more detailed investigations as discussed above: (i) the enantiomeric excess is only moderate and requires an optimization, (ii) this synthetic route is ideally suited for the synthesis of a privileged intermediate which can be transformed into all *Ervatamia* alkaloids, (iii) the mechanism of the Heck reaction was not fully clarified but this knowledge is crucial for the determination of the absolute configuration of the cyclopropanation product.

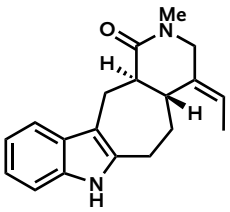
9 Addendum

9.1 Biological Assays

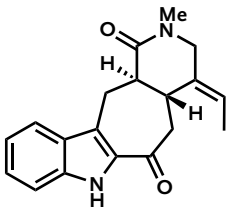
A selection of three compounds ((+)-3-deoxo-5-oxoisomethuenine (**811**), (+)-5-oxoisomethuenine (**808**), and (–)-16-epimethuenine (**57**), Fig. 9-1) was tested in growth inhibitory assays with the so-called ESKAPE panel that comprises the clinically relevant Gram-negative and Gram-positive bacterial pathogens *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. The activity of all compounds against Methicillin-resistant *S. aureus* (MRSA) and *E. faecium* was tested. In order to probe whether the compounds also affected eukaryotic cells, they were tested in a growth assay with the fungus *C. albicans* and in viability assays with four mammalian cell lines.

The cytotoxicity was determined using WST-1 cell proliferation assays. Targeting cell lines were L929 mouse fibroblast, KB-3-1 epidermoid cervix carcinoma, and MCF-7 breast cancer cell lines which were incubated for 5 days with the test substances. The acute toxicity was determined using the FS4-LTM conditionally immortalized human fibroblast cell line which was incubated for 24 hours with the test compounds.

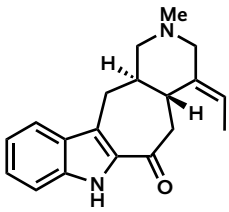
These tests were carried out at Helmholtz Zentrum für Infektionsforschung in Braunschweig by Bianka Karge under the supervision of Prof. Mark Brönstrup.



(+)-3-deoxo-5-oxoisomethuenine (**811**)



(+)-5-oxoisomethuenine (**808**)



(–)-16-epimethuenine (**57**)

Figure 9-1. Tested compounds.

9.1.1 Investigation of the Antimicrobial Activities

Table 9-1. Results antimicrobial activity in % growth, *E. coli*.

E. coli	**growth in %**									
Ciprofloxacin	–29	–29	–28	–28	–28	–26	–28	–29	–19	76
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01
811	96	101	102	96	103	103	103	108	105	97
808	94	102	100	99	104	103	103	104	107	102
57	95	98	98	96	102	100	102	102	108	98
DMSO	100	100	100	100	100	100	100	100	100	100
Ciprofloxacin	–28	–30	–29	–29	–29	–27	–28	–31	–13	78
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01

Table 9-2. Results antimicrobial activity in % growth, *P. aeruginosa*.

P. aeruginosa	**growth in %**									
Amikacin	–12	–12	–11	6	89	91	105	97	100	100
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	25.00	12.50	6.25	3.13	1.56	0.78	0.39	0.20	0.10	0.05
811	92	93	101	97	101	102	103	99	106	101
808	107	118	106	101	102	105	111	98	111	107
57	128	104	104	99	100	103	101	98	102	100
DMSO	100	100	100	100	100	100	100	100	100	100
Amikacin	–12	–12	–6	13	95	91	110	98	100	98
AB µg/ml	25.00	12.50	6.25	3.13	1.56	0.78	0.39	0.20	0.10	0.05

Table 9-3. Results antimicrobial activity in % growth. *A. baumannii*.

A. baumannii	**growth in %**									
Ciprofloxacin	–11	–11	–11	–10	–11	–7	–8	–1	34	78
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	10.00	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02
811	102	105	103	104	103	103	153	102	103	103
808	103	105	104	104	103	107	157	105	104	105
57	104	104	104	103	103	106	155	101	104	102
DMSO	100	100	100	100	100	100	100	100	100	100
Ciprofloxacin	–11	–12	–12	–11	2	–1	34	42	58	98
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01

Table 9-4. Results antimicrobial activity in % growth. *K. pneumoniae*.

K. pneumoniae	**growth in %**									
Ciprofloxacin	–9	–9	–9	–9	–9	–9	–9	–9	–9	73
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	10.00	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02
811	103	103	103	103	103	103	103	103	102	101
808	103	104	105	105	104	104	103	104	102	102
57	102	102	103	103	102	103	102	102	101	101
DMSO	100	100	100	100	100	100	100	100	100	100
Ciprofloxacin	–9	–9	–9	–9	–9	–9	–9	–2	97	99
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01

Table 9-5. Results antimicrobial activity in % growth. MRSA DSM.

MRSA DSM	**growth in %**									
Linezolid	–19	–18	–18	–19	–19	–27	1	72	119	105
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01
811	72	60	101	109	108	131	65	82	162	98
808	75	82	97	101	81	135	109	77	142	110
57	94	87	72	99	115	140	107	92	146	83
DMSO	100	100	100	100	100	100	100	100	100	100
Linezolid	6	–19	–18	–12	–20	–28	–5	26	86	126
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01

Table 9-6. Results antimicrobial activity in % growth. MRSA RKI.

MRSA RKI	**growth in %**									
Linezolid	–17	–17	–16	–17	–16	–12	18	99	104	102
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01
811	120	127	115	114	106	96	76	85	112	104
808	103	112	105	106	104	122	108	106	115	108
57	106	104	103	106	100	114	101	95	75	101
DMSO	100	100	100	100	100	100	100	100	100	100
Linezolid	–16	–17	–17	–16	–16	1	107	107	109	108
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01

Table 9-7. Results antimicrobial activity in % growth. *E. faecium*.

E. faecium	**growth in %**									
Ciprofloxacin	–15	–14	56	76	85	79	88	90	91	100
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02	0.01
811	94	99	100	101	100	105	107	108	104	107
808	100	105	102	104	104	108	112	111	112	111
57	103	106	105	102	102	104	105	106	94	106
DMSO	100	100	100	100	100	100	100	100	100	100
Ciprofloxacin	–8	–8	–21	54	68	82	89	93	93	99
AB µg/ml	10.00	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02

Table 9-8. Results antimicrobial activity in % growth. *C. albicans*.

C. albicans	**growth in %**									
Amphotericin B	–4	0	79	80	93	94	97	88	107	93
Compound µM	100.0	50.0	25.0	12.5	6.3	3.1	1.6	0.8	0.4	0.2
AB µg/ml	10.00	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04	0.02
811	134	140	123	104	105	104	94	102	94	61
808	111	112	103	89	82	95	92	64	77	57
57	130	110	107	98	104	101	84	86	87	83
Frichert F9	98	122	88	98	100	107	104	89	81	77
DMSO	100	100	100	100	100	100	100	100	100	100
Amphotericin B	–5	–5	–12	69	97	86	92	75	91	75
AB µg/ml	20.00	10.00	5.00	2.50	1.25	0.63	0.31	0.16	0.08	0.04

9.1.2 Cell Viability Tests

Table 9-9. Results of the cell viability tests.

			EC_{50} (µM)			
compound	**solvent**	**test concentration (µM)**	**L929**	**KB-3-1**	**MCF-7**	**FS4-LTM**
auranofin	DMSO	100 – 0.2	1.7	1.7	0.4	0.7
staurosporine	DMSO	50 – 0.1	—	< 0.1	< 0.1	< 0.1
staurosporine	DMSO	100 – 0.1	< 0.2	—	—	—
811	DMSO	100 – 0.2	> 100	5	10	4
808	DMSO	100 – 0.2	> 100	> 100	18	20
57	DMSO	100 – 0.2	> 100	> 100	100	67

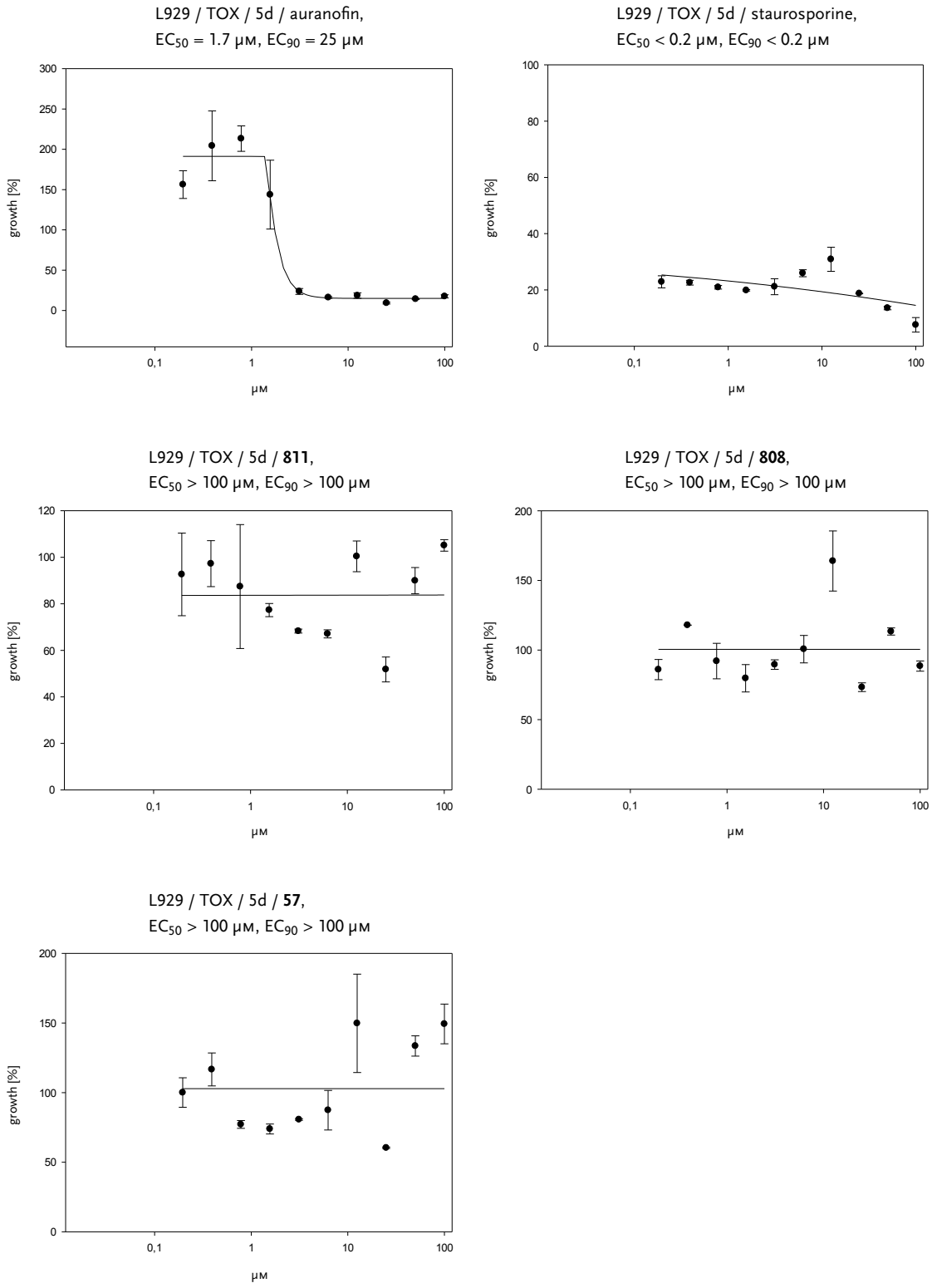


Chart 9-4. Cell viability test (L929).

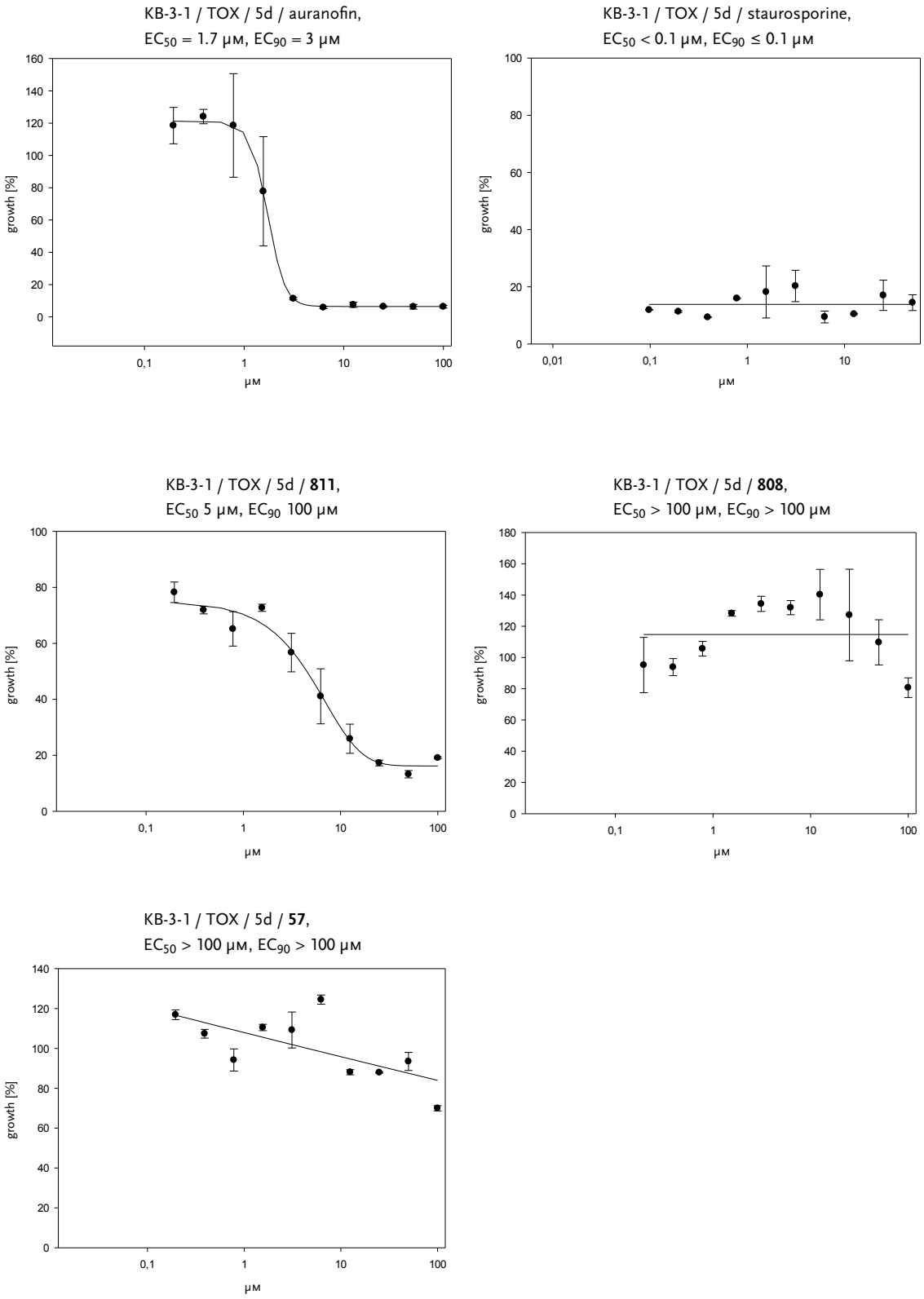
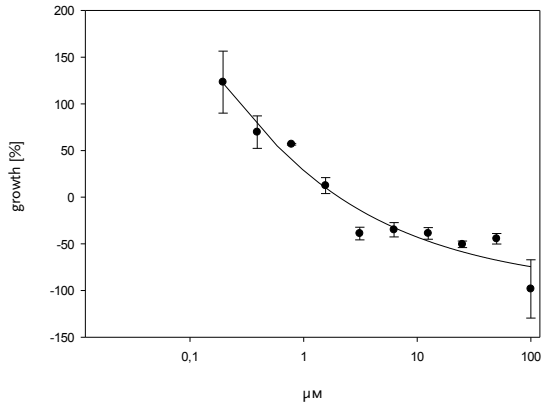
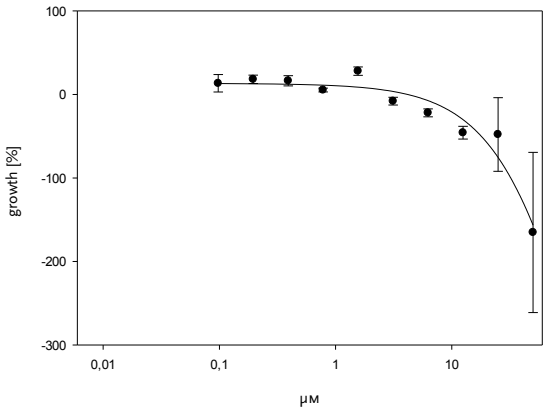


Chart 9-5. Cell viability test (KB-3-1).

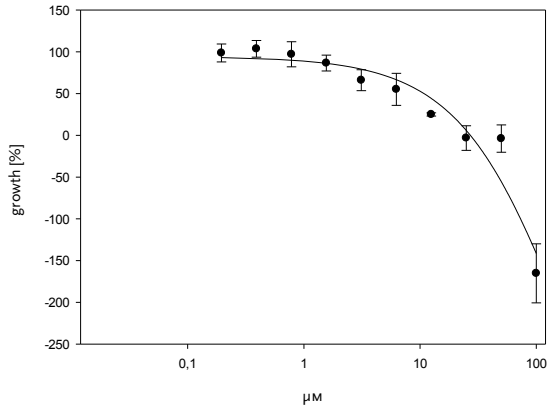
MCF-7 / TOX / 5d / auranofin,
EC_{50} = 0.4 µM, EC_{90} = 0.6 µM



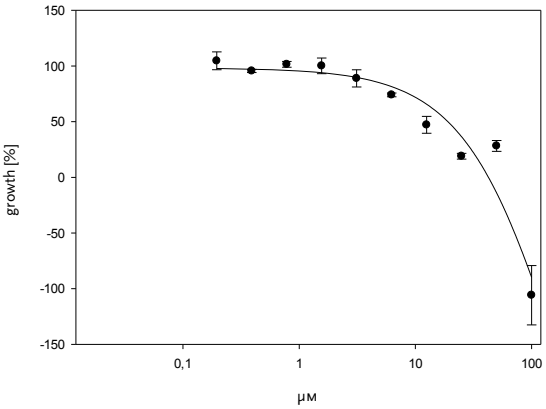
MCF-7 / TOX / 5d / staurosporine,
EC_{50} < 0.1 µM, EC_{90} < 0.1 µM



MCF-7 / TOX / 5d / **811**,
EC_{50} 10 µM, EC_{90} 55 µM



MCF-7 / TOX / 5d / **808**,
EC_{50} 18 µM, EC_{90} 36 µM



MCF-7 / TOX / 5d / **57**,
EC_{50} > 100 µM, EC_{90} > 100 µM

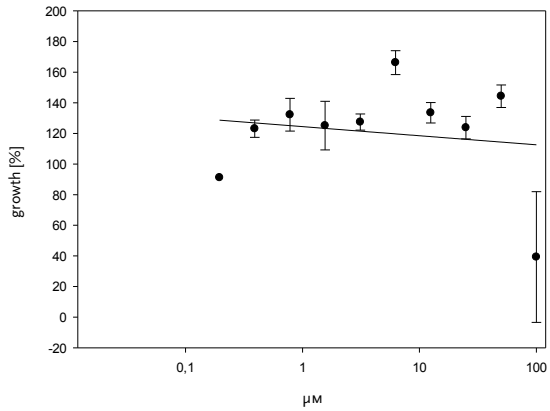
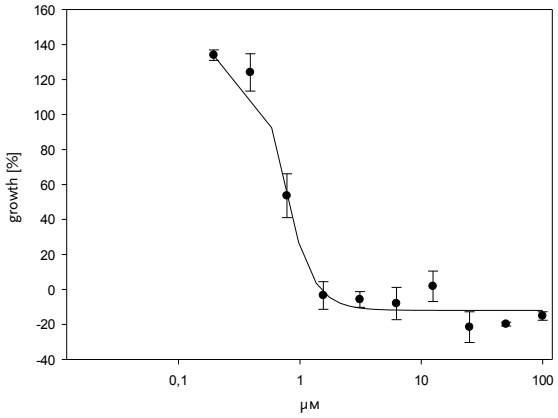
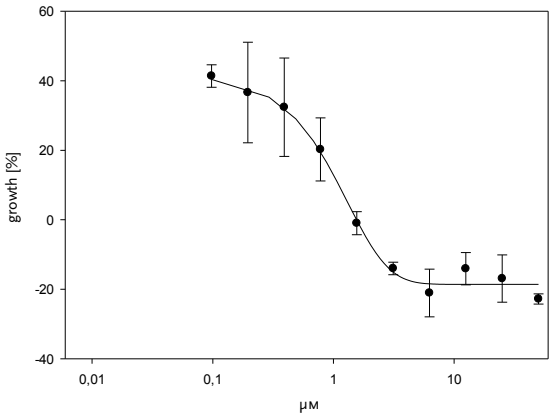


Chart 9-6. Cell viability test (MCF-7).

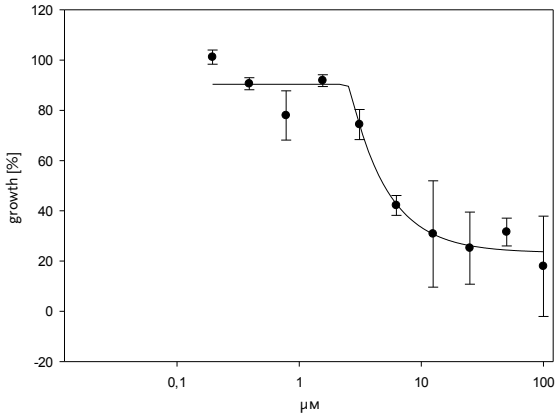
FS4-LTM / TOX / 24h / auranofin,
EC_{50} = 0.7 µM, EC_{90} = 1.2 µM



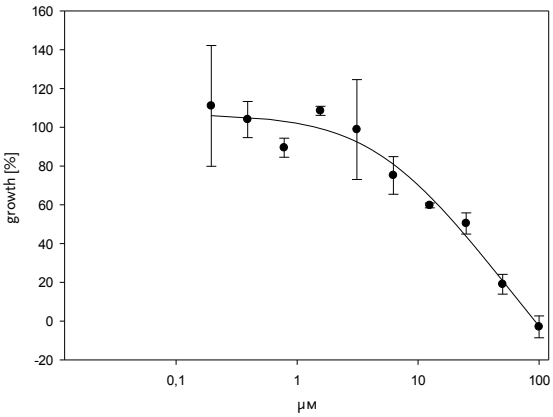
FS4-LTM / TOX / 24h / staurosporine,
EC_{50} < 0.1 µM, EC_{90} = 1 µM



FS4-LTM / TOX / 24h / **811**,
EC_{50} 4 µM, EC_{90} > 100 µM



FS4-LTM / TOX / 24h / **808**,
EC_{50} 20 µM, EC_{90} 69 µM



FS4-LTM / TOX / 24h / **57**,
EC_{50} 67 µM, EC_{90} ≥ 100 µM

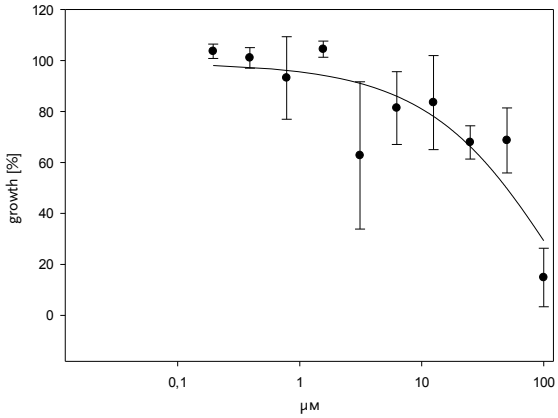


Chart 9-7. Cell viability test (FS4-LTM).

9.1.3 Short Discussion

Most alkaloids from the ervitsine–ervatamine group have never been evaluated in a bioassay. Ervatamine (**43**) is known to be a sodium channel blocker in nerve fibers and a local anesthetic blocker; methuenine (**56**) is known to be an anticholinergic agent (*cf.* Section 2.2.1).

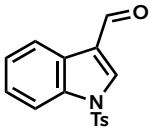
In these tests, (+)-3-deoxo-5-oxoisomethuenine (**811**), (+)-5-oxoisomethuenine (**808**), and (–)-16-epimethuenine (**57**, Fig. 9-1) were tested in growth inhibitory assays. In addition, the cytotoxicity was determined using WST-1 cell proliferation assays. No antimicrobial activity could be observed. Concerning the cytotoxic activities, **811** was found to be the most potent candidate and shows a fairly antiproliferative activity against human fibroblast cells and decent cytotoxic activities against epidermoid cervix carcinoma and breast cancer cell lines. **808** was also found to have moderate cytotoxic activities against breast cancer and human fibroblast cells. Interestingly, the natural product itself (**57**) was shown to be almost ineffective against the tested cell lines; only a weak cytotoxic activity against human fibroblast cells was determined. Further investigations are currently in progress.

10 Experimental

The experimental part follows the order of the particular sections and compounds are ordered by appearance. The general methods are described in Section A.1 on p. 353 and are valid for all other experimental parts in this thesis.

10.1 Experimental Part for Section 5.2

1-Tosyl-1*H*-indole-3-carbaldehyde (526).[512]

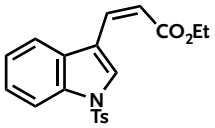


526

Indole-3-carbaldehyde (**525**, 29.4 g, 203 mmol, 1.0 eq.) was dissolved in Et_2O (1000 ml). Tosyl chloride (39.4 g, 203 mmol, 1.0 eq.) was added in one portion and the mixture was cooled to 0 °C. Sodium hydroxide (20% aq. solution, 200 ml) was added slowly. The ice-bath was removed and the reaction mixture was stirred for 18 h at ambient temperature (monitored by TLC). The mixture was filtered through a medium porosity sintered-glass funnel. The solid was repeatedly rinsed with ether and collected. The layers of the filtrate were separated and the aqueous layers were washed once with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The obtained solid was combined with the filtride. The combined solids were recrystallized from ethyl acetate to obtain title compound **526** as pale yellow solid[1] (60.0 g, 200 mmol, 99%). $R_f = 0.50$ (hexanes–EtOAc, 2:1). **M.p.** 220 °C (EtOH). **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta = 10.09$ (s, 1H), 8.25 (ddd, $J = 7.7, 1.5, 0.8$ Hz, 1H), 8.23 (s, 1H), 7.97 – 7.92 (m, 1H), 7.87 – 7.82 (m, 2H), 7.45 – 7.31 (m, 2H), 7.33 – 7.25 (m, 2H), 2.37 (s, 3H) ppm. **HRMS** (ESI): calcd. for $C_{16}H_{14}NO_3S$ $[M + H]^+$ 300.0694, found 300.0698. ▸ *NMR spectra on page 374.*

[1] Some batches were also colorless or pale rose, nevertheless the compound was always ≥ 99% pure according to NMR analysis.

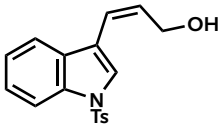
Ethyl (*Z*)-3-(1-tosyl-1*H*-indol-3-yl)acrylate (527).[513]



527

Ando phosphonate (**530**, 11.5 g, 36.0 mmol, 1.08 eq.) was dissolved in anhydrous THF (100 ml). 18-crown-6 (16.8 g, 63.5 mmol, 1.9 eq.) was added under argon and the resulting mixture was cooled down to –78 °C. KHMDS (0.7 M in THF, 50.4 ml, 35.3 mmol 1.06 eq.) was added dropwise over 20 min. After complete addition, the reaction mixture was stirred 15 min at –78 °C, then 15 min at 0 °C, then again cooled down to –78 °C. Aldehyde **526** (10.0 g, 33.4 mmol, 1.0 eq.) was dissolved in THF (60 ml, added small amount of CH_2Cl_2 for complete dissolution) and was then added dropwise to the reaction mixture over 15 min. After complete addition, the reaction mixture was warmed to –15 °C and stirred 1.5 h at this temperature (monitored by TLC). The reaction mixture was then quenched by the addition of sat. aq. NH_4Cl and extracted thrice with ether. Drying over $MgSO_4$ followed by the removal of the solvent *in vacuo* afforded title compound **527** as pale yellow oil which solidified below 10 °C (12.3 g, 33.3 mmol, >99%), which was analytically pure according to ^{1}H NMR. R_f = 0.55 (hexanes–EtOAc, 4:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 9.01 (s, 1H), 8.05 (dd, J = 6.9, 1.7 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 7.6, 1.5 Hz, 1H), 7.44 – 7.19 (m, 4H), 7.09 (d, J = 12.6 Hz, 1H), 6.04 (d, J = 12.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{20}H_{19}NNaO_4S$ $[M + Na]^+$ 392.0932, found 392.0934. ▸ *NMR spectra on page 374.*

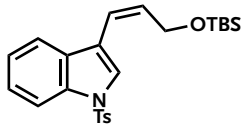
(*Z*)-3-(1-Tosyl-1*H*-indol-3-yl)prop-2-en-1-ol (528).



528

Ester **527** (2.40 g, 6.76 mmol, 1.0 eq.) was dissolved in absolute THF (60 ml) and cooled to –78 °C. To this solution DiBAL (1.0 M in hexanes, 16.9 ml, 16.9 mmol, 2.5 eq.) in toluene was added dropwise. The reaction was stirred for an additional hour at that temperature before it was cautiously quenched with sat. aq. Rochelle's salt and stirred at ambient temperature over night. The layers were separated and the aqueous phase was extracted two times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, and the solvents were removed under reduced pressure to yield crude (*Z*)-alcohol **528**, which was purified by flash column chromatography (ethyl acetate–hexanes, 1:2) to give title compound **528** as colorless oil (2.20 g, 6.72 mmol, 99%). R_f = 0.24 (hexanes–EtOAc, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.34 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.22 (d, J = 8.6 Hz, 2H), 6.57 (dt, J = 11.6, 0.9 Hz, 1H), 6.03 (dt, J = 11.4, 6.2 Hz, 1H), 4.45 (dd, J = 6.3, 1.7 Hz, 2H), 2.33 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.2, 135.2, 134.8, 132.5, 130.4, 130.1, 127.0, 125.2, 124.3, 123.6, 119.9, 119.6, 118.4, 113.8, 60.4, 21.7 ppm. **IR** (neat): 3013, 2252, 1738, 1438, 1367, 1218, 1039, 913, 751 cm^{-1}. **HRMS** (ESI): calcd. for $C_{18}H_{17}NNaO_3S$ $[M + Na]^+$ 350.0827, found 350.0826. ▸ *NMR spectra on page 375.*

(*Z*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-tosyl-1*H*-indole (529).

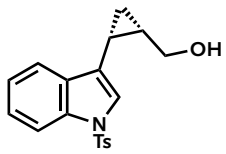


529

Alcohol **528** (2.00 g, 6.11 mmol, 1.0 eq.) was dissolved in anhydrous DMF (15 ml) at room temperature and imidazole (1.00 g, 14.7 mmol, 2.4 eq.) and TBSCl (1.01 g, 6.71 mmol, 1.1 eq.) were added sequentially. The reaction mixture was stirred for one hour at that temperature before it was diluted with water and extracted three times with Et_2O–pentane (1:1). The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure to give crude **529** as a colorless oil, which was subjected to flash column chromatography (pentane–ether, 9:1) to yield (2.64 g, 5.98 mmol, 98%) of desired **529**. R_f = 0.60 (pentane–ether, 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.7 Hz, 1H), 7.45 (s, 1H), 7.34 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.26 (td, J = 7.4, 1.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.51 (dq, J = 11.5, 1.7 Hz, 1H), 5.99 (dt, J = 11.8, 6.1 Hz, 1H), 4.42 (dd, J = 6.1, 1.7 Hz, 2H), 2.40 – 2.25 (m, 3H), 0.93 (s, 9H), 0.09 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.1, 135.3, 134.8, 133.7, 130.5, 130.0, 129.9, 126.9, 126.9, 125.1, 124.3, 123.5, 119.7, 118.7, 118.7, 113.7, 60.8, 58.1, 26.1, 21.7, 18.4, –5.0 ppm. **IR** (neat): 2939, 2856, 1455, 1173, 1087, 839, 771, 668 cm^{-1}. **HRMS** (ESI): calcd. for $C_{24}H_{31}NNaO_3SSi$ $[M + Na]^+$ 464.1692, found 464.1693.

▸ NMR spectra on page 376.

((1*S*,2*R*)-2-(1-Tosyl-1*H*-indol-3-yl)cyclopropyl)methanol (531).



531

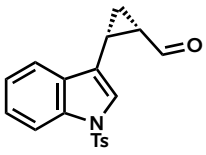
A solution of diethylzinc (1.0 M in hexanes, 644 µL, 644 µmol, 2.2 eq.) in 1.5 mL of anhydrous CH_2Cl_2 was cooled to –10 °C. Freshly distilled diiodomethane (105 µL, 1.29 mmol, 4.4 eq.) in 1.5 mL of anhydrous CH_2Cl_2 was added dropwise to this solution and stirred at –10 °C for 15 minutes. A white precipitate was formed to which (L)-dioxaborolane **545** (90.0 mg, 322 µmol, 1.1 eq.) was added dropwise. Upon addition the white precipitate disappeared and a clear solution was obtained. The reaction mixture was stirred for another 15 minutes at that temperature before alcohol **528** (100 mg, 290 µmol, 1.0 eq.) was added dropwise. The reaction mixture was warmed to 0 °C over one hour and then to ambient temperature over another two hours. Saturated aqueous NH_4Cl solution was added and the phases were separated. The aqueous phase was washed twice with ethyl acetate, the combined organic layers were dried over magnesium sulfate and the solvents were removed *in vacuo* to give crude cyclopropyl alcohol **531**, which was purified by flash column chromatography (ethyl acetate-hexanes, 1:2) to give 79 mg (220 µmol), 76% of desired **531**.

The enantiomeric excess was determined to be 91% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 30:70 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 16.6 min, t_R(major) = 12.9 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (dt, J = 8.3, 0.9 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.63 (ddd, J = 7.6, 1.4, 0.8 Hz, 1H), 7.35 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 3.47 (dd, J = 11.7, 5.9 Hz, 1H), 3.11 (dd, J = 11.7, 8.7 Hz, 1H), 2.32 (s, 3H), 2.08 (tdd, J = 8.3, 5.9, 1.4 Hz, 1H), 1.58 (qt, J = 8.5, 5.7 Hz, 1H), 1.13 (td, J = 8.3, 5.1 Hz, 1H), 0.98 (bs, 1H), 0.73 (q, J = 5.5 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.9, 135.4, 135.1, 131.7, 129.9, 126.7, 125.1, 124.0, 123.5, 120.9, 119.4, 113.9, 62.7, 21.6, 19.9, 10.8, 7.7 ppm. **IR** (neat): 3317, 2941, 2830, 1738, 1441, 1367, 1218, 1111, 1021, 667 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{17}NO_3S$ $[M + Na]^+$ 364.0983, found 364.0986. $[\alpha]_D^{20}$ = −69° (c = 0.46, $CHCl_3$). ▸ NMR spectra on page 377.

(1*S*,2*R*)-2-(1-Tosyl-1*H*-indol-3-yl)cyclopropane-1-carbaldehyde (532).



532

Alcohol **531** (258 mg, 0.69 mmol, 1.0 eq.) was dissolved in of anhydrous DMSO (3.0 ml) at ambient temperature. To this solution IBX (290 mg, 1.03 mmol, 1.5 eq.) was added in one portion. The reaction mixture was stirred at that temperature for three hours before it was diluted with ethyl acetate and extracted with water. The aqueous phase was washed with ethyl acetate twice, the combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. Crude aldehyde **532** was purified by flash column chromatography (ethyl acetate–hexanes, 1:4) to give 234 mg, 91% of aldehyde **532** as a pale yellow oil. The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 20:80 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 16.3 min, t_R(major) = 19.3 min. R_f = 0.70 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.64 (d, J = 6.2 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.54 (ddd, J = 7.7, 1.3, 0.7 Hz, 1H), 7.47 (d, J = 1.4 Hz, 1H), 7.32 (ddd, J = 9.3, 7.2, 1.3 Hz, 1H), 7.24 – 7.20 (m, 2H), 2.62 (tdd, J = 8.4, 7.1, 1.5 Hz, 1H), 2.33 (s, 3H), 2.22 (tdd, J = 8.3, 6.2, 5.3 Hz, 1H), 1.80 (dt, J = 7.1, 5.3 Hz, 1H), 1.64 (td, J = 8.1, 5.2 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.3, 145.2, 135.3, 135.1, 131.0, 130.0, 126.9, 125.4, 124.8, 123.7, 119.5, 118.6, 113.9, 28.2, 21.7, 16.7, 11.5 ppm. **IR** (neat): 3004, 2252, 1738, 1438, 1372, 1217, 1038, 917, 748 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{17}NO_3S$ $[M + Na]^+$ 362.0827, found 362.0828. $[\alpha]_D^{20}$ = +30° (c = 0.28, $CHCl_3$). ▸ NMR spectra on page 378.

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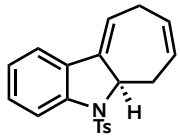
*General procedure for the Wittig reaction–divinylcyclopropane-cycloheptadiene rearrangement cascade of aldehyde **532** with non-stabilized Wittig ylides to give **533**, **557**, and **559**:*

2.4 eq. of the respective Wittig salt was dissolved in THF at a concentration of 0.2 M. The solution was cooled to –78 °C and NaHMDS (2.0 M in THF, 2.4 eq.) was added dropwise. The reaction mixture was stirred at that temperature for one hour before it was stirred at 0 °C for another 30 minutes. Then it was recooled to –78 °C and the aldehyde **532** (100 mg, 295 µmol, 1.0 eq.) in THF (0.3 M) was added dropwise to the mixture. The reaction was stirred another 30 minutes at that temperature before it was warmed to room temperature. After complete consumption of starting material the reaction mixture was quenched with sat. aq. NH_4Cl solution. The phases were separated and the aqueous phase was extracted two times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. Crude NMR indicated partial cyclization, therefore the crude product was heated to specified temperature in benzene until the TLC analysis showed complete consumption of

starting material. The solvent was removed under reduced pressure and the crude mixture was submitted to flash column chromatography to obtain pure cyclohepta[*b*]indolines **533**, **557**, and **559**.

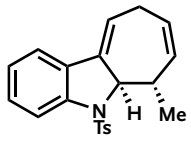
(*R*)-5-Tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole (533).



533

According to the general procedure (60 min at ambient temperature), cyclohepta[*b*]indoline **533** was obtained as pale yellow oil (54 mg, 159 µmol, 54%). R_f = 0.25 (hexanes–EtOAc, 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.75 (dt, J = 8.2, 0.8 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.30 – 7.21 (m, 2H), 7.23 – 7.16 (m, 2H), 7.04 (td, J = 7.5, 1.0 Hz, 1H), 6.07 (dddd, J = 7.4, 3.5, 2.7, 1.0 Hz, 1H), 5.76 (ddq, J = 12.0, 7.6, 2.2 Hz, 1H), 5.60 (ddddd, J = 12.2, 5.7, 3.3, 2.6, 1.0 Hz, 1H), 4.90 (dq, J = 11.0, 2.6 Hz, 1H), 3.14 (dp, J = 22.2, 3.1 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.95 – 2.79 (m, 1H), 2.59 – 2.44 (m, 1H), 2.35 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.2, 142.9, 140.3, 134.3, 129.8, 129.5, 129.2, 127.4, 127.2, 126.6, 124.4, 120.2, 116.4, 116.4, 65.0, 35.1, 29.3, 21.7 ppm. **IR** (neat): 2980, 2898, 2250, 1652, 1462, 1050, 913 cm^{-1}. **HRMS** (ESI): calcd. for $C_{20}H_{19}NNaO_2S$ $[M + Na]^+$ 360.1034, found 360.1035. $[\alpha]_D^{20}$ = +170° (c = 0.28, $CHCl_3$). ▸ NMR spectra on page 379.

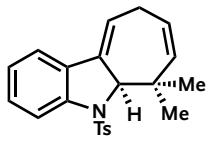
(5a*R*,6*S*)-6-Methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole (557).



557

According to the general procedure (2 h at 80 °C), cyclohepta[*b*]indoline **557** was obtained as pale yellow oil (72 mg, 206 µmol, 70%). The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 10:90 ^{i}PrOH/hexanes, λ = 254 nm): t_R(major) = 14.6 min, t_R(minor) = 16.1 min. R_f = 0.22 (hexanes–EtOAc, 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.69 (d, J = 8.1 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.25 – 7.15 (m, 2H), 7.11 – 7.00 (m, 3H), 6.05 (ddt, J = 8.1, 3.9, 1.4 Hz, 1H), 5.59 – 5.43 (m, 2H), 4.84 (dt, J = 10.5, 1.8 Hz, 1H), 3.03 (ddq, J = 20.4, 4.1, 1.9 Hz, 1H), 2.75 – 2.57 (m, 1H), 2.49 – 2.35 (m, 1H), 2.30 (s, 3H), 1.37 (d, J = 7.3 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.8, 143.4, 141.5, 134.7, 134.1, 131.2, 129.4, 128.8, 127.6, 125.5, 125.0, 120.4, 119.6, 117.4, 70.0, 37.0, 27.8, 21.7, 20.5 ppm. **IR** (neat): 3014, 1738, 1451, 1363, 1218, 1167, 756, 669 cm^{-1}. **HRMS** (ESI): calcd. for $C_{21}H_{21}NO_2S$ $[M + Na]^+$ 374.1191, found 374.1193. $[\alpha]_D^{20}$ = +212° (c = 0.86, $CHCl_3$). ▸ NMR spectra on page 380.

(*R*)-6,6-Dimethyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole (559).

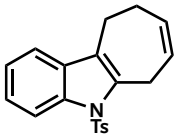


559

According to the general procedure (3 h at 120 °C, sealed tube), cyclohepta[*b*]indoline **559** was obtained as pale yellow oil (79 mg, 206 µmol, 734%). The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 10:90 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 9.2 min, t_R(major) = 12.0 min. R_f = 0.20 (hexanes–EtOAc, 5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.67 (dt, J = 8.1, 0.8 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.20 (ddd, J = 8.2, 7.4, 1.4 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.08 – 7.00 (m, 3H), 6.11 – 6.03 (m, 1H), 5.47 – 5.33 (m, 2H), 5.06 (t, J = 1.9 Hz, 1H), 2.98 (ddq, J = 20.2, 4.0, 1.9 Hz, 1H), 2.60 (ddd, J = 20.0,

8.2, 6.6 Hz, 1H), 2.29 (s, 3H), 1.37 (s, 3H), 0.75 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.8, 143.8, 140.0, 139.8, 133.8, 132.9, 129.3, 128.7, 127.7, 125.7, 122.9, 119.7, 119.6, 118.1, 72.2, 39.1, 29.4, 27.3, 22.9, 21.7 ppm. **IR** (neat): 2968, 1738, 1460, 1354, 1165, 911, 732, 662 cm^{-1}. **HRMS** (ESI): calcd. for $C_{22}H_{23}NO_2S$ $[M + Na]^+$ 388.1347, found 388.1344. $[\alpha]_D^{20} = -173°$ (c = 0.52, $CHCl_3$). ▸ NMR spectra on page 381.

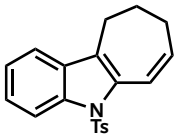
5-Tosyl-5,6,9,10-tetrahydrocyclohepta[b]indole (534).



534

Cyclohepta[*b*]indoline **533** (20.0 mg, 59.0 µmol, 1.0 eq.) was dissolved in CH_2Cl_2–acetone (5:1, *v/v*, 1.0 ml) and $TsOH \cdot H_2O$ (11.2 mg, 59.0 µmol, 1.0 eq.) was added in one portion. The reaction mixture was stirred 10 min at 60 °C (monitored by TLC) and was then diluted with ether (5 ml) and quenched by the addition of sat. aqueous $NaHCO_3$ (8 ml). The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash column chromatography (ethyl acetate–hexanes, 1:5) afforded pure aromatized cyclohepta[*b*]indole **534** as a colorless oil (17.6 mg, 52.0 µmol, 88%). R_f = 0.65 (hexanes–EtOAc, 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.21 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.34 (dd, J = 7.4, 1.1 Hz, 1H), 7.30 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 7.4, 1.4 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 5.95 (dtt, J = 11.1, 6.1, 1.6 Hz, 1H), 5.77 (dtt, J = 11.1, 5.5, 1.2 Hz, 1H), 3.96 (dt, J = 3.9, 1.5 Hz, 2H), 2.83 – 2.75 (m, 2H), 2.38 (ddt, J = 6.0, 4.6, 1.3 Hz, 2H), 2.32 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.6, 136.3, 136.2, 134.1, 131.8, 131.2, 129.8, 126.4, 126.1, 124.2, 123.5, 122.5, 117.9, 115.3, 26.9, 26.0, 23.1, 21.7 ppm. **IR** (neat): 3003, 2293, 1439, 1378, 1038, 917, 737 cm^{-1}. **HRMS** (ESI): calcd. for $C_{20}H_{19}NO_2S$ $[M + Na]^+$ 360.1034, found 360.1032. ▸ NMR spectra on page 382.

5-Tosyl-5,8,9,10-tetrahydrocyclohepta[*b*]indole (535).



535

Cyclohepta[*b*]indoline **533** (20.0 mg, 59.0 µmol, 1.0 eq.) was dissolved in anhydrous benzene (1.0 ml) and chloridotris(triphenylphosphane)rhodium(I) (54.6 mg, 59.0 µmol, 1.0 eq.) was added. The mixture was stirred for 3 h at 60 °C. NMR analysis of the crude mixture indicated the formation of title compound **535**. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.27 – 8.17 (m, 1H), 7.74 – 7.40 (m, 3H [overlapped by Wilkinson's catalyst]), 7.30 – 7.26 (m, 2H), 7.24 (d, J = 1.8 Hz, 1H), 7.22 – 7.14 (m, 2H), 6.46 (dt, J = 11.5, 1.7 Hz, 1H), 5.96 (dt, J = 11.1, 5.3 Hz, 1H), 3.43 – 3.28 (m, 2H), 2.44 (q, J = 5.7 Hz, 2H), 2.33 (s, 3H), 2.05 – 1.92 (m, 2H) ppm. **HRMS** (ESI): calcd. for $C_{20}H_{19}NNaO_2S$ $[M + Na]^+$ 360.1034, found 360.1036. ▸ NMR spectra on page 383.

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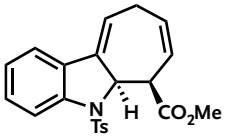
*General procedure for the Wittig reaction-divinylcyclopropane-cycloheptadiene rearrangement cascade of aldehyde **532** with stabilized Wittig ylides to give **551** and **558**:*

Aldehyde **532** (100 mg, 295 µmol, 1.0 eq.) was dissolved in benzene to give a 0.2 M solution.

To this solution 1.2 eq. of the respective stabilized ylides were added and heated to reflux until the TLC analysis showed complete consumption of starting material. The reaction time varied between one hour for compound **551** and six hours for compound **558**. The reaction mixture was cooled to room temperature, the solvents were removed *in vacuo*, and the crude product was submitted to flash column chromatography.

Methyl (5a*R*,6*R*)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (551).

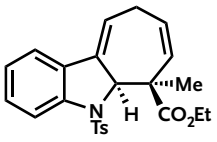


551

According to the general procedure, cyclohepta[*b*]indoline **551** was obtained as pale yellow oil (88 mg, 224 µmol, 76%). The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 20:80 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 17.2 min, t_R(major) = 19.0 min. R_f = 0.33 (hexanes–EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.74 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.31 – 7.16 (m, 4H), 7.04 (td, J = 7.5, 0.9 Hz, 1H), 6.03 (dtd, J = 7.2, 3.1, 1.0 Hz, 1H), 5.90 (ddt, J = 12.0, 8.0, 2.0 Hz, 1H), 5.81 (dt, J = 11.9, 4.2 Hz, 1H), 4.89 (qd, J = 3.2, 1.2 Hz, 1H), 4.30 (ddd, J = 8.2, 3.5, 2.0 Hz, 1H), 3.49 (s, 3H), 3.16 (dq, J = 23.1, 2.8 Hz, 1H), 3.00 (dt, J = 24.0, 5.8 Hz, 1H), 2.35 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.4, 144.3, 143.3, 137.2, 133.8, 130.9, 130.5, 129.8, 129.0, 127.4, 124.4, 124.1, 119.7, 116.1, 115.2, 65.0, 51.8, 49.7, 30.2, 21.6 ppm. **IR** (neat): 2953, 1737, 1354, 1165, 733, 664 cm^{-1}. **HRMS** (ESI): calcd. for $C_{22}H_{21}NO_4S$ $[M + Na]^+$ 418.1089, found 418.1089. $[\alpha]_D^{20}$ = −237° (c = 0.96, $CHCl_3$).

▸ NMR spectra on page 383.

Methyl (5a*S*,6*R*)-6-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxylate (558).



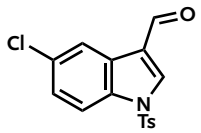
558

According to the general procedure, cyclohepta[*b*]indoline **558** was obtained as pale yellow oil (86 mg, 203 µmol, 69%). The enantiomeric excess was determined to be 89% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 18:82 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 13.5 min, t_R(major) = 14.0 min. R_f = 0.70 (hexanes–EtOAc, 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.20 (td, J = 7.8, 1.4 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.00 (td, J = 7.5, 1.0 Hz, 1H), 5.99 – 5.90 (m, 1H), 5.71 (dddd, J = 12.2, 5.4, 3.3, 1.0 Hz, 1H), 5.62 (dt, J = 12.2, 1.9 Hz, 1H), 4.96 (dt, J = 2.9, 1.4 Hz, 1H), 3.66 (dq, J = 10.8, 7.2 Hz, 1H), 3.46 (dq, J = 10.7, 7.1 Hz, 1H), 3.05 (dp, J = 22.5, 2.9 Hz, 1H), 2.89 (dt, J = 22.3, 6.0 Hz, 1H), 2.29 (s, 3H), 1.74 (s, 3H), 0.67 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.0, 144.6, 144.0, 138.1, 133.8, 133.7, 132.5, 129.3, 128.7, 127.7, 127.2, 125.3, 119.7, 119.4, 117.1, 70.4, 60.7, 51.3, 29.5, 25.3, 21.6, 13.4 ppm. **IR** (neat): 2975, 1723, 1459, 1354, 1165, 1025, 751, 667 cm^{-1}. **HRMS** (ESI): calcd. for $C_{24}H_{25}NNaO_4S$ $[M + Na]^+$ 446.1402, found 446.1400. $[\alpha]_D^{20}$ = +185° (c = 0.32, $CHCl_3$).

▸ NMR spectra on page 384.

10.2 Experimental Part for Section 5.3: Total Synthesis of (*S*)-SIRT1-inhibitor IV (**67**)

5-Chloro-1-tosyl-1*H*-indole-3-carbaldehyde (561).

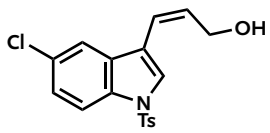


561

Commercial available 5-chloro-1*H*-indole-3-carbaldehyde (5.00 g, 27.8 mmol, 1.0 eq.) was suspended in CH_2Cl_2 (60 ml). To this mixture was sequentially added triethylamine (6.6 mL, 47.3 mmol, 1.7 eq.) and tosyl chloride (5.83 g, 30.6 mmol, 1.1 eq.) at room temperature. The reaction mixture was stirred for 24 hours, then concentrated to yield a brown powder, which was washed with CH_2Cl_2 then water and acetone yielding aldehyde **561** (8.27 g, 24.7 mmol, 89%) as a white amorphous powder. **^{1}H NMR** (400 MHz, DMSO) δ = 10.05 (s, 1H), 8.95 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 8.04 – 7.97 (m, 3H), 7.52 – 7.44 (m, 3H), 2.35 (s, 3H) ppm. **^{13}C NMR** (101 MHz, DMSO) δ = 186.7, 146.8, 139.5, 133.1, 132.8, 130.7, 129.8, 127.3, 127.1, 126.3, 121.0, 120.6, 115.0, 21.1 ppm. **IR** (neat): 3327, 2942, 2831, 1451, 1020 cm^{-1}. **HRMS** (ESI): calcd. for $C_{16}H_{12}ClNO_3S$ $[M + H]^+$ 334.0305, found 334.0310.

▸ NMR spectra on page 385.

(*Z*)-3-(5-Chloro-1-tosyl-1*H*-indol-3-yl)prop-2-en-1-ol (562).

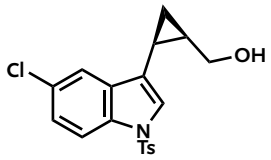


562

Sodium hydride (60% suspension in mineral oil, 340 mg, 8.53 mmol, 0.95 eq.) was suspended in THF (50 ml) and cooled to 0 °C. To this mixture ethyl 2-(diphenoxyphosphoryl)acetate (2.72 g, 8.53 mmol, 0.95 eq.) dissolved in THF (50 ml) was added dropwise and stirred at 0 °C until gas evolution had ceased. The yellow solution was cooled to –78 °C and aldehyde **561** (3.00 g, 8.98 mmol, 1.0 eq.) in THF–DMF (1:1, 50 ml) was added dropwise. The reaction was stirred at that temperature for five hours before it was slowly warmed to room temperature over night. The mixture was quenched with saturated NH_4Cl solution and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure to yield crude product, which was submitted to the next reaction without any further purification. The crude ester was dissolved in THF (50 ml) and cooled to –78 °C. To this solution DiBAL (1 M in PhMe, 22.5 mL, 2.5 eq.) was added dropwise. The reaction was stirred for one hour at –78 °C before it was quenched with sat. aq. Rochelle's salt. The mixture was extracted three times with ethyl acetate, the combined organic layers were dried over magnesium sulfate, and the solvents were removed under reduced pressure. The crude product was recrystallized from ethyl acetate–hexanes (1:1) to furnish allylic alcohol **562** (2.82 g, 7.81 mmol, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.91 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 1.6 Hz, 2H), 7.29 (dd, J = 8.8, 2.1 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 6.52 – 6.45 (m, 1H), 6.05 (dt, J = 11.4, 6.3 Hz, 1H), 4.41 (dd, J = 6.3, 1.7 Hz, 2H), 2.35 (s, 3H), 1.60 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.4, 134.8, 133.0, 132.8, 131.5, 130.0, 129.5, 126.8, 125.5, 125.3, 119.3, 119.3, 117.7, 114.7, 60.1, 29.3, 21.6 ppm. **IR** (neat): 3373,

1594, 1446, 1372, 1300, 1173, 1115, 810, 731, 669 cm^{-1}. **HRMS** (ESI): calcd. for $C_{18}H_{16}ClNO_3S$ $[M + Na]^+$ 384.0440, found 384.0437. ▸ *NMR spectra on page 386.*

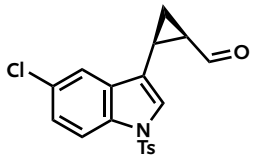
((1*R*,2*S*)-2-(5-Chloro-1-tosyl-1*H*-indol-3-yl)cyclopropyl)methanol (563).



563

A solution of diethylzinc (1.0 M in hexanes, 19.1 ml, 19.1 mmol, 2.2 eq.) in anhydrous CH_2Cl_2 (50 ml) was cooled to –10 °C. Freshly distilled diiodomethane (3.10 ml, 38.2 mmol, 4.4 eq.) in anhydrous CH_2Cl_2 (15 ml) was added dropwise to this solution and stirred for 15 minutes at –10 °C. A white precipitate was formed to which (D)-dioxaborolane **545** (2.60 g, 9.60 mmol, 1.1 eq.) was added dropwise. Upon addition the white precipitate disappeared and a clear solution was obtained. The reaction mixture was stirred for another 15 minutes at that temperature before alcohol **562** (3.14 g, 8.70 mmol, 1.0 eq.) was added in portions. The reaction mixture was warmed to 0 °C over one hour and then to ambient temperature over another two hours. Saturated aqueous NH_4Cl solution was added and the layers were separated. The aqueous phase was washed twice with ethyl acetate, the combined organic layers were dried over magnesium sulfate and the solvents were removed *in vacuo* to give crude cyclopropyl alcohol **563**, which was purified by flash column chromatography (ethyl acetate-hexanes, 1:2) to give 2.48 g (6.61 mmol, 76%) of desired **563**. The enantiomeric excess was determined to be 91% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 25:75 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 16.4 min, t_R(major) = 19.2 min. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.89 (d, J = 8.8 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.59 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 1.3 Hz, 1H), 7.27 (dd, J = 8.9, 2.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 3.45 (dd, J = 11.6, 6.1 Hz, 1H), 3.16 (dd, J = 11.6, 8.4 Hz, 1H), 2.34 (s, 3H), 2.04 – 1.98 (m, 1H), 1.56 (qt, J = 8.4, 5.9 Hz, 1H), 1.14 (td, J = 8.3, 5.1 Hz, 1H), 0.71 (q, J = 5.6 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.3, 135.0, 133.9, 133.2, 130.1, 129.5, 126.8, 125.4, 125.4, 120.5, 119.4, 115.1, 62.7, 21.7, 20.0, 10.8, 8.0 ppm. **IR** (neat): 3370, 1442, 1367, 1298, 1174, 1113, 1026, 802, 669 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{18}ClNNaO_3S$ $[M + Na]^+$ 398.0594, found 398.0597. $[\alpha]_D^{20}$ = −53° (c = 0.92, $CHCl_3$). ▸ *NMR spectra on page 387.*

(1*R*,2*S*)-2-(5-Chloro-1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carbaldehyde (564).



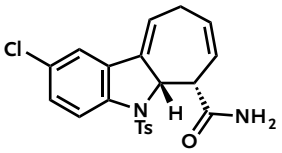
564

Alcohol **563** (2.20 g, 5.86 mmol, 1.0 eq.) was dissolved in anhydrous DMSO (20 ml) at ambient temperature. To this solution IBX (2.30 g, 8.21 mmol, 1.4 eq.) was added in one portion. The reaction mixture was stirred at that temperature for three hours before it was diluted with ethyl acetate and extracted with water. The aqueous phase was washed with ethyl acetate twice, the combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. An analytical sample of crude aldehyde **564** was purified by flash column chromatography (ethyl acetate–hexanes, 1:4) to give aldehyde **564** as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.73 (d, J = 5.7 Hz, 1H), 7.85 (dd, J = 8.8,

0.6 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.52 – 7.45 (m, 2H), 7.26 (dd, J = 8.8, 2.1 Hz, 1H), 7.24 – 7.21 (m, 2H), 2.56 (tdd, J = 8.4, 7.1, 1.4 Hz, 1H), 2.33 (s, 3H), 2.25 (tt, J = 8.3, 5.5 Hz, 1H), 1.79 (dt, J = 7.1, 5.3 Hz, 1H), 1.62 (td, J = 8.1, 5.2 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.6, 145.5, 134.8, 133.6, 132.3, 130.1, 130.1, 129.6, 126.8, 126.8, 126.2, 125.5, 119.2, 117.9, 115.0, 28.2, 21.7, 16.8, 11.5 ppm. **IR** (neat): 1703, 1444, 1369, 1300, 1175, 1135, 810, 669 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{16}ClNNaO_3S$ $[M + Na]^+$ 396.0437, found 396.0439. **$[\alpha]_D^{20}$ = −24°** (c = 1.3, $CHCl_3$).

▸ NMR spectra on page 388.

(5a*S*,6*S*)-2-Chloro-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-6-carboxamide (566).

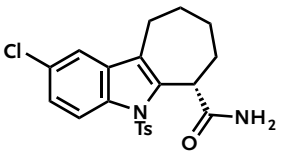


566

Phosphonoamide **565** (320 mg, 1.62 mmol, 1.1 eq.) was dissolved in THF (10 ml) at 0 °C. To this mixture potassium *tert*-butoxide (182 mg, 1.62 mmol, 1.1 eq.) was added in one portion. The reaction mixture was stirred for 40 minutes at that temperature before aldehyde **564** (550 mg, 1.47 mmol, 1.0 eq.) was added dropwise at 0 °C. The reaction was stirred for 30 minutes at 0 °C and further 30 minutes at room temperature before it was quenched with saturated NH_4Cl solution. The phases were separated extracted two times with ethyl acetate and the combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. The crude product was redissolved in benzene and heated at reflux for one hour. The mixture was cooled to room temperature the solvent was removed *in vacuo* and crude **566** was subjected to flash column chromatography (ethyl acetate–hexanes, 2:1) to give 457 mg (74% over two steps) of pure **566**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.65 (dd, J = 8.5, 0.6 Hz, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.25 – 7.21 (m, 2H), 7.20 – 7.14 (m, 2H), 6.06 (dddd, J = 5.5, 4.0, 2.9, 0.9 Hz, 1H), 5.94 – 5.77 (m, 3H), 5.25 (bs, 1H), 4.91 (p, J = 2.7 Hz, 1H), 4.16 – 4.08 (m, 1H), 3.12 (dt, J = 4.0, 1.6 Hz, 2H), 2.37 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.9, 145.0, 141.3, 134.4, 133.0, 132.3, 131.1, 130.6, 130.1, 129.1, 127.6, 125.0, 120.4, 118.3, 117.3, 66.1, 50.2, 30.7, 21.8 ppm. **IR** (neat): 3017, 1738, 1365, 1217 cm^{-1}. **HRMS** (ESI): calcd. for $C_{21}H_{19}ClN_2NaO_3S$ $[M + Na]^+$ 437.0703, found 437.0703. **$[\alpha]_D^{20}$ = +151°** (c = 0.88, $CHCl_3$).

▸ NMR spectra on page 389.

(*S*)-2-Chloro-5-tosyl-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-6-carboxamide (572).

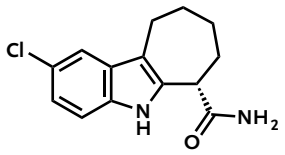


572

Tricycle **566** (457 mg, 1.09 mmol, 1.0 eq) was dissolved in ethanol (15 ml). Palladium on charcoal (10%, 40 mg) was added and the mixture was hydrogenated at 2 bar for 30 minutes. The palladium was filtered off and an analytical sample of **572** was purified for characterization. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.14 (d, J = 8.9 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 2.1 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.23 – 7.19 (m, 2H), 5.54 (bs, 1H), 5.38 (bs, 1H), 4.84 (dd, J = 5.4, 3.4 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.59 (ddd, J = 15.7, 11.9, 2.6 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.36 (s, 3H), 2.00 – 1.86 (m, 3H), 1.48 (ddt, J = 14.5,

10.1, 4.2 Hz, 1H), 1.34 (dtd, J = 14.5, 8.3, 7.6, 4.8 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.4, 137.2, 135.8, 135.0, 131.8, 130.1, 130.0, 129.7, 126.5, 125.2, 125.2, 118.6, 116.6, 43.7, 29.7, 26.6, 26.4, 23.8, 21.8 ppm. **IR** (neat): 3327, 2941, 2831, 1738, 1443, 1367, 1217, 1022 cm^{-1}. **HRMS** (ESI): calcd. for $C_{21}H_{21}ClN_2NaO_3S$ $[M + Na]^+$ 439.0859, found 439.0854. **$[\alpha]_D^{20}$ = +129°** (c = 0.62, $CHCl_3$). ▸ NMR spectra on page 390.

(*S*)-2-Chloro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-6-carboxamide [(*S*)-SIRT1-Inhibitor IV] (**67**).

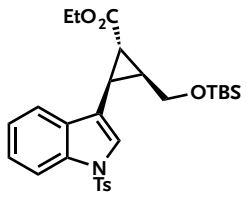


67

Crude **572** was added to samarium iodide (0.5 M solution in THF, 40 ml) at room temperature, then immediately water (30 eq.) and pyrrolidine (20 eq.) were added, and the reaction was quenched with saturated NH_4Cl solution. The phases were separated extracted two times with ethyl acetate and the combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure. Crude **67** was subjected to flash column chromatography (ethyl acetate–hexanes, 2:1) to afford (*S*)-SIRT1-inhibitor IV (**67**, 342 mg, 1.30 mmol, 65% over two steps). The enantiomeric excess was determined to be 91% by chiral HPLC analysis (AD-H, 1.0 ml min^{-1}, 75:25 ^{i}PrOH/hexanes, λ = 254 nm): t_R(minor) = 11.4 min, t_R(major) = 14.0 min. **^{1}H NMR** (400 MHz, MeOD) δ = 7.40 (dd, J = 2.1, 0.7 Hz, 1H), 7.22 (dd, J = 8.5, 0.6 Hz, 1H), 7.00 (dd, J = 8.6, 2.0 Hz, 1H), 3.85 (dd, J = 5.7, 2.8 Hz, 1H), 2.93 (ddt, J = 15.4, 4.1, 2.6 Hz, 1H), 2.69 (ddd, J = 15.6, 11.3, 2.4 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.00 – 1.92 (m, 2H), 1.91 – 1.80 (m, 2H), 1.56 (qd, J = 11.2, 10.4, 3.6 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, MeOD) δ = 177.4, 137.2, 135.1, 131.2, 125.4, 122.1, 118.3, 115.3, 112.8, 47.6, 31.9, 29.5, 28.9, 25.3 ppm. **IR** (neat): 2985, 1735, 1372, 1234, 1043, 930, 847, 789 cm^{-1}. **HRMS** (ESI): calcd. for $C_{14}H_{16}ClN_2O$ $[M + H]^+$ 263.0951, found 263.0959. **$[\alpha]_D^{20}$ = −46°** (c = 0.24, $CHCl_3$). ▸ NMR spectra on page 391.

10.3 Experimental Part for Section 6.2

Ethyl (1*S*,2*S*,3*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (581).



581

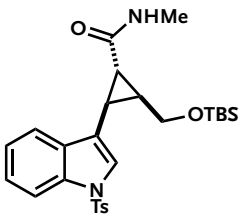
A flame-dried Schlenk tube was charged with [Cu(OTf)] · PhH (27.2 mg, 53 µmol, 1.5 mol %), (*S*)-^{t}Bu-BOX ligand **583** (34.1 mg, 116 µmol, 3.3 mol %), and olefine **529** (1.55 g, 3.51 mmol, 1.0 eq.) in the glove-box. The tube was flushed with argon and freeze-pump-thaw degassed CH_2Cl_2 (3.0 ml) was added. The reaction mixture was stirred 60 min at ambient temperature to produce a deep-green clear solution. A solution of ethyl diazoacetate (commercial, contains ≥13 wt. % dichloromethane; 2.2 ml, 21.0 mmol, 6.0 eq.) in freeze-pump-thaw degassed CH_2Cl_2 (20.0 ml) was added *via* syringe pump over 12 h at ambient temperature (N_2 evolution) at which the solution became orange. The solution was

filtered over a plug of celite to afford a clear yellow solution. The solvent was removed under reduced pressure to obtain crude **581** as yellow oil. Purification by flash column chromatography afforded pure cyclopropane **581** as pale yellow oil (1.82 g, 3.46 mmol, 98%) which solidified below 0 °C.

Note: Depending on the quality of the purification, the product always contains marginal amounts of fumaric acid diethyl ester. For this reason, cyclopropane **581** usually was subjected to the next step without purification. The enantiomeric excess was determined after cleavage of the silyl protecting group (*cf.* compound **787**, p. 250).

R_f = 0.70 (hexanes–EtOAc, 4:1, stains dark blue with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.42 (br s, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.21 (dd, J = 11.7, 7.7 Hz, 2H), 4.25 – 4.18 (m, 2H), 3.58 (dd, J = 11.0, 5.7 Hz, 1H), 3.23 (dd, J = 11.0, 8.4 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.32 (s, 3H), 2.11 (tt, J = 9.0, 5.1 Hz, 1H), 1.85 (t, J = 4.8 Hz, 1H), 1.33 – 1.29 (m, 3H), 0.78 (s, 9H), –0.20 (d, J = 24.4 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.9, 144.8, 135.2, 131.4, 129.8, 126.8, 124.9, 124.1, 123.2, 120.1, 118.3, 113.6, 60.9, 29.4, 25.9, 25.8, 23.4, 21.6, 21.3, 18.1, 14.3, –5.7 ppm. **IR** (neat): 3012, 2252, 1738, 1438, 1368, 1218, 750 cm^{-1}. **HRMS** (ESI): calcd. for $C_{28}H_{37}NNaO_5SSi$ $[M + Na]^+$ 550.2059, found 550.2059. **$[\alpha]_D^{20}$ = −32°** (c = 0.56, $CHCl_3$). ▸ *NMR spectra on page 392.*

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*-methyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxamide (586).



586

In a sealed tube, ester **581** (300 mg, 569 µmol, 1.0 eq.) was dissolved in MeOH (2.0 ml) and methylamine (40% aq. solution, 71 µl, 825 µmol, 1.45 eq.) was added. The sealed tube was heated for 4 h to 90 °C (monitored by TLC). The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated, the aqueous layer was extracted once with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed *in vacuo* and the crude was subjected to flash column chromatography (hexanes–EtOAc, 3:2) to obtain amide **586** as white foam (203 mg, 400 µmol, 70%). R_f = 0.25 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.23 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 1.3 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.04 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 6.52 (d, J = 8.1 Hz, 2H), 4.87 (q, J = 4.3 Hz, 1H), 3.54 (dd, J = 11.0, 5.8 Hz, 1H), 3.28 (dd, J = 11.0, 8.5 Hz, 1H), 2.82 (ddd, J = 9.0, 4.9, 1.4 Hz, 1H), 2.52 (d, J = 4.8 Hz, 3H), 2.32 (tdd, J = 8.8, 5.7, 4.6 Hz, 1H), 1.66 (s, 3H), 1.23 (td, J = 4.8, 1.4 Hz, 1H), 0.89 (s, 9H), –0.15 (d, J = 22.6 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{27}H_{36}N_2NaO_4SSi$ $[M + Na]^+$ 535.2063, found 535.2065. ▸ *NMR spectra on page 394.*

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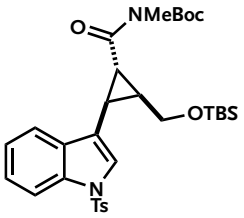
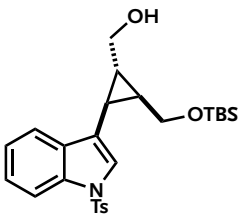
tert-Butyl (2-(((tert-butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carbonyl)(methyl)carbamate (587).



587

Amide **586** (25.0 mg, 49 µmol, 1.0 eq.) was dissolved in anhydrous THF (330 µl). Boc_2O (13.3 mg, 61 µmol, 1.25 eq.) and DMAP (1.2 mg, 10 µmol, 0.2 eq.) were added and the reaction mixture was stirred 15 min at ambient temperature. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated, the aqueous layer was extracted once with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed *in vacuo* and the crude was subjected to flash column chromatography to obtain title compound **587** as colorless oil (29.0 mg, 47 µmol, 96%). R_f = 0.85 (hexanes–EtOAc, 1:1, stains dark green with vanillin). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.01 – 7.90 (m, 1H), 7.80 – 7.70 (m, 2H), 7.62 – 7.52 (m, 2H), 7.32 (dd, J = 7.3, 1.4 Hz, 1H), 7.21 (td, J = 7.7, 1.5 Hz, 3H), 3.65 (dd, J = 10.9, 5.5 Hz, 1H), 3.31 – 3.21 (m, 2H), 3.20 (s, 3H), 2.69 (ddd, J = 9.0, 5.0, 1.4 Hz, 1H), 2.32 (s, 3H), 2.28 – 2.15 (m, 1H), 1.57 (s, 9H), 0.75 (s, 9H), –0.23 (d, J = 13.8 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{32}H_{44}N_2NaO_6SSi$ $[M + Na]^+$ 635.2587, found 635.2589. ▸ *NMR spectra on page 394.*

(2-(((tert-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methanol (588).

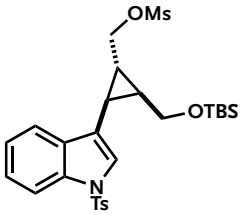


588

Racemic ester **581** (2.25 g, 4.26 mmol, 1.0 eq.) was dissolved in anhydrous toluene (13.5 ml) and cooled to 0 °C. $LiBH_4$ (4.0 M in THF, 2.66 ml, 10.7 mmol, 2.5 eq.) was added dropwise to the bright yellow solution. The reaction mixture was stirred 15 min at this temperature, then additional 2 h at 100 °C (the solution became colorless now). The reaction mixture was cooled to 0 °C, chloroform was added and subsequent 5% HCl. The layers were separated and the aqueous layer was washed once with chloroform. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 2:1 → 1:1) afforded pure alcohol **588** as colorless oil (1.37 g, 2.82 mmol, 66%). R_f = 0.20 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (dt, J = 8.3, 0.9 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.63 (ddd, J = 7.8, 1.3, 0.8 Hz, 1H), 7.36 (d, J = 1.4 Hz, 1H), 7.30 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 3.72 (d, J = 6.6 Hz, 2H), 3.49 (dd, J = 10.9, 5.9 Hz, 1H), 3.21 (dd, J = 10.9, 8.1 Hz, 1H), 2.31 (s, 3H), 1.98 (ddd, J = 8.8, 5.3, 1.4 Hz, 1H), 1.87 (br s, 1H), 1.43 (tdd, J = 8.5, 5.9, 5.1 Hz, 1H), 1.41 – 1.31 (m, 1H), 0.76 (s, 9H), –0.23 (d, J = 20.8 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.8, 135.4, 135.4, 132.0, 129.9, 126.8, 124.9, 124.0, 123.2, 120.3, 120.2, 113.6, 65.8, 62.1, 25.9, 25.4, 24.3, 21.6, 18.2, 16.6, –5.5, –5.6 ppm. **HRMS** (ESI): calcd. for $C_{26}H_{35}NNaO_4SSi$ $[M + Na]^+$ 508.1954, found 508.1957.

▸ *NMR spectra on page 395.*

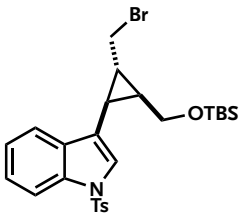
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl methanesulfonate (589).



589

Alcohol **588** (210 mg, 432 µmmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (4.3 ml) and cooled to 0 °C. Et_3N (120 µl, 865 µmol, 2.0 eq.) was added dropwise followed by the addition of MsCl (44 µl, 562 µmol, 1.3 eq.). The reaction mixture was stirred at this temperature for 20 min (monitored by TLC), then diluted with ether and quenched by the addition of sat. aq. NH_4Cl–NaCl (1:1). The aqueous layer was extracted twice with ether, the combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure to obtain mesylate **589** which was used crude for the next steps. $R_f = 0.48$ (hexanes–EtOAc, 3:2, stains with CAN and vanillin). **HRMS** (ESI): calcd. for $C_{27}H_{37}NNaO_6S_2Si$ $[M + Na]^+$ 586.1729, found 586.1730.

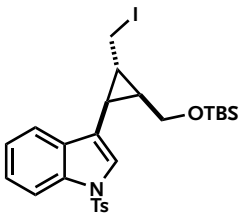
3-(2-(Bromomethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)-1-tosyl-1*H*-indole (590).



590

Alcohol **588** (120 mg, 247 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (4.8 ml) and cooled to 0 °C. Triphenylphosphine (130 mg, 494 µmol, 2.0 eq.) was added followed by tetrabromomethane (246 mg, 741 µmol, 3.0 eq.). The reaction mixture was stirred 5 min at 0 °C (prolonged reaction times lead to complete decomposition of the material), then diluted with ether and quenched by the addition of brine. The aqueous layer was washed once with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the material was subjected to a short filtration over a plug of silica (2 cm) to obtain bromide **590** (133 mg, 242 µmol, 98%) as colorless oil. This compound tended to rapid decomposition, therefore it was used quickly for the next steps. $R_f = 0.82$ (pentane–ether, 10:1). **HRMS** (ESI): calcd. for $C_{26}H_{34}BrNNaO_3SSi$ $[M + Na]^+$ 570.1110, found 570.1111.

3-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(iodomethyl)cyclopropyl)-1-tosyl-1*H*-indole (591).

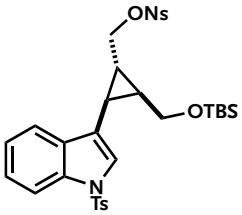


591

Alcohol **588** (57.0 mg, 117 µmol, 1.0 eq.) was dissolved in anhydrous benzene (800 µl). To this solution was added imidazole (20.0 mg, 293 µmol, 2.5 eq.) and PPh_3 (61.6 mg, 235 µmol, 2.0 eq.). The mixture was stirred until full dissolution of all components (slightly heating or ultrasonic may be necessary). Iodine (59.6 mg, 235 µmol 2.0 eq.) was dissolved in benzene (400 µl) to obtain a dark purple solution which was added dropwise to the reaction mixture. After complete addition, the reaction mixture was diluted with EtOAc and sat. aq. sodium thiosulfate was added. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over magnesium sulfate and the solvent was then removed under reduced pressure.

This afforded iodide **591** as orange oil which was directly used in the next steps due to its instability. R_f = 0.72 (hexanes–EtOAc, 15:1). **HRMS** (ESI): calcd. for $C_{26}H_{34}INNaO_3SSi$ $[M + Na]^+$ 618.0971, found 618.0976.

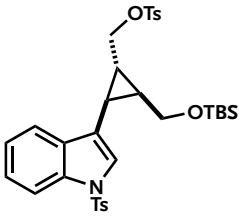
(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl 4-nitrobenzenesulfonate (592).



592

Alcohol **588** (37.0 mg, 76 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (800 µl) and cooled to 0 °C. Et_3N (21 µl, 152 µmol, 2.0 eq.) was added dropwise followed by the addition of nosyl chloride (21.9 mg, 99 µmol, 1.3 eq.). The reaction was stirred 30 min at 0 °C and 2 h at ambient temperature before diluted with EtOAc and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was then removed under reduced pressure. This afforded nosylate **592** (32.0 mg, 48 µmol, 62%) as orange oil which was directly used in the next steps due to its instability. R_f = 0.60 (hexanes–EtOAc, 3:2). **HRMS** (ESI): calcd. for $C_{32}H_{39}N_2O_8S_2Si$ $[M + H]^+$ 671.1917, found 671.1919.

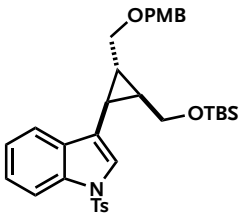
(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl 4-methylbenzenesulfonate (593).



593

Alcohol **588** (87.0 mg, 179 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (1.8 ml) and cooled to 0 °C. Et_3N (50 µl, 358, 2.0 eq.) was added dropwise followed by the addition of tosyl chloride (44.4 mg, 233 µmol, 1.3 eq.). The reaction was stirred 30 min at 0 °C and 2 h at ambient temperature before diluted with EtOAc and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was then removed under reduced pressure. This afforded tosylate **593** (79.0 mg, 123 µmol, 69%) as yellow oil which was directly used in the next steps due to its instability. **HRMS** (ESI): calcd. for $C_{33}H_{41}NNaO_6S_2Si$ $[M + Na]^+$ 662.2042, found 662.2044.

3-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(((4-methoxybenzyl)oxy)methyl)cyclopropyl)-1-tosyl-1*H*-indole (600).

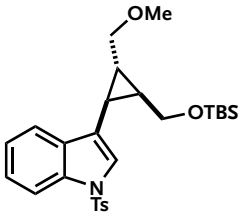


600

Alcohol **588** (115 mg, 237 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2.4 ml) and cooled to 0 °C. 4-Methoxybenzyl-2,2,2-trichloroacetimidate (148 µl, 710 µmol, 3.0 eq.) was added followed by the addition of triflic acid (1 drop). Stirring was continued at this temperature for 150 min (monitored by TLC). The reaction mixture was then diluted with EtOAc and quenched by the addition of pH 7.0 phosphate buffer. The aqueous layer was extracted twice with EtOAc and the combined organic layers were dried over sodium sulfate. After evaporation of the solvent, the crude residue was subjected to a quick flash column chromatography (hexanes–EtOAc, 2:1) to obtain pure PMB protected alcohol **600** (45.9 mg, 75.8 µmol, 32%) as pale yellow oil. $R_f = 0.20$ (hexanes–EtOAc, 3:2, stains excellent with CAN to give a blue-purple color). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (dt, J = 8.3, 0.9 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.63 (ddd, J = 7.8, 1.3, 0.7 Hz, 1H), 7.36 (d, J = 1.4 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.25 – 7.17 (m, 3H), 6.90 (d, J = 8.7 Hz, 2H), 4.62 (s, 2H), 3.81 (s, 3H), 3.72 (d, J = 6.6 Hz, 2H), 3.48 (dd, J = 10.8, 6.0 Hz, 1H), 3.23 (dd, J = 10.9, 8.1 Hz, 1H), 2.33 (s, 3H), 1.98 (ddd, J = 8.8, 5.3, 1.4 Hz, 1H), 1.48 – 1.41 (m, 1H), 1.37 (tt, J = 6.7, 5.4 Hz, 1H), 0.76 (s, 9H), –0.23 (d, J = 20.3 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{34}H_{43}NNaO_5SSi$ $[M + Na]^+$ 628.2529, found 628.2527.

▸ NMR spectra on page 396.

3-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(methoxymethyl)cyclopropyl)-1-tosyl-1*H*-indole (601).



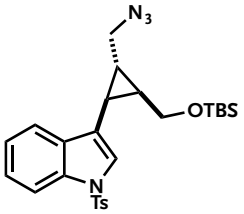
601

Alcohol **588** (56.0 mg, 115 µmol, 1.0 eq.) was dissolved in anhydrous THF (0.3 ml) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 13.8 mg, 346 µmol, 3.0 eq.) was added and the reaction was stirred 5 min at this temperature. Methyl iodide (43 µl, 692 µmol, 6.0 eq.) was then added and the reaction was stirred 15 min at 0 °C and additional 3 h at ambient temperature (monitored by TLC). The reaction mixture was diluted with chloroform and quenched by the addition of 1% HCl. The aqueous layer was washed once with chloroform and the combined organic layers were dried over sodium sulfate. After evaporation of the solvent, the crude residue was subjected to a quick flash column chromatography (hexanes–EtOAc, 4:1) to obtain pure methyl ether **601** (57.6 mg, 115 µmol, 90%). $R_f = 0.33$ (hexanes–EtOAc, 4:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.33 (d, J = 8.3 Hz, 1H), 8.21 (d, J = 1.7 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.59 – 7.51 (m, 1H), 7.23 – 7.19 (m, 1H), 7.13 – 7.08 (m, 1H), 6.50 (d, J = 8.2 Hz, 2H), 3.82 (dd, J = 11.2, 5.7 Hz, 1H), 3.62 (dd, J = 11.3, 9.0 Hz, 1H), 3.30 – 3.15 (m, 2H), 3.01 (s, 3H), 1.84 (td, J = 8.6, 1.7 Hz, 1H), 1.65 (s, 3H), 1.54 – 1.41 (m, 2H), 1.05 (s, 9H), 0.06 (s, 6H) ppm.[2] **HRMS** (ESI): calcd. for $C_{27}H_{37}NNaO_4SSi$ $[M + Na]^+$ 522.2110, found 522.2114.

▸ NMR spectra on page 397.

[2] signals in aromatic area are overlapped by C_6D_6 signal

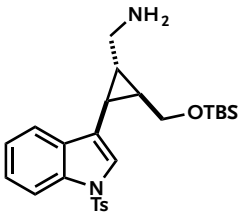
3-(2-(Azidomethyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)-1-tosyl-1*H*-indole (594).



594

Mesylate **589** (432 µmol, 1.0 eq.) was dissolved in anhydrous DMF (1.0 ml) and sodium azide (224 mg, 3.44 mmol, 8.0 eq.) was added in one portion. The reaction mixture was stirred for 120 min at 60 °C (monitored by TLC) before it was diluted with ether and quenched by the addition of water. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude azide **594** as a pale yellow oil which was quickly purified by a short flash column chromatography (hexanes–EtOAc, 10:11) and directly used for the next step. R_f = 0.73 (hexanes–EtOAc, 3:1). **HRMS** (ESI): calcd. for $C_{26}H_{34}N_4NaO_3SSi$ $[M + Na]^+$ 533.2019, found 533.2022.

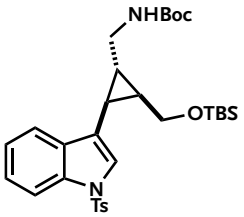
2-(((*tert*-Butyldimethylsilyl)oxy)methyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methanamine (595).



595

Azide **595** (179 mg, 350 µmol, 1.0 eq.) was dissolved in THF–H2O (10:1, 1.8 ml) and PBu_3 (90 µl, 368 µmol, 1.05 eq.) was added at ambient temperature and stirring was continued until TLC analysis showed complete consumption of starting material (4 h). The solvent was removed *in vacuo* and the residue was dissolved in benzene (2 ml), which in turn again was removed under reduced pressure. This sequence was repeated three times to obtain crude amine **595** as a pale yellow oil which was directly used for the next step without further purification. R_f = 0.05 (hexanes–EtOAc, 1:1, stains dark purple with ninhydrin). **HRMS** (ESI): calcd. for $C_{26}H_{37}N_2O_3SSi$ $[M + H]^+$ 485.2294, found 485.2296.

***tert*-Butyl ((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl)-carbamate (596).**



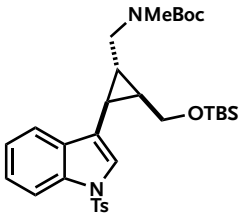
596

Variant 1: Crude amine **595** (350 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2.3 ml) and Et_3N (97 µl, 700 µmol, 2.0 eq.) was added dropwise at ambient temperature followed by the addition of Boc_2O (91.7 mg, 420 µmol, 1.2 eq.). The reaction mixture was stirred for 30 min at ambient temperature (monitored by TLC) before it was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude carbamate **596** as an orange oil which was directly used for the next step without further purification.

Variant 2: Crude azide **594** (234 mg, 458 µmol, 1.0 eq.) was dissolved in absolute MeOH–THF (1:1, 4.5 ml). Boc_2O (110 mg, 504 µmol, 1.1 eq.) followed by palladium on charcoal (10%,

56.5 mg, 0.053 mmol, 0.12 eq.) were added and the reaction mixture was hydrogenated ($p(H_2)$ = 1 atm) at ambient temperature for 60 min (monitored by TLC). The reaction mixture was filtered over a plug of celite to yield carbamate **596** in quantitative yield, which was directly used for the next step without further purification. **HRMS** (ESI): calcd. for $C_{31}H_{44}N_2NaO_5SSi$ $[M + Na]^+$ 607.2638, found 607.8342.

***tert*-Butyl ((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl)-(methyl)carbamate (598).**



598

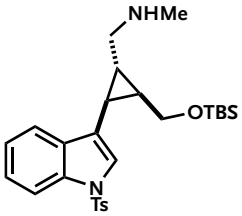
Variant 1: Carbamate **596** (175 mg, 350 µmol, 1.0 eq.) was dissolved in anhydrous DMF (0.8 ml) and the solution was cooled to 0 °C. NaH (60% in mineral oil, 14.7 mg, 368 µmol, 1.05 eq.) was added in one portion followed by the addition of methyl iodide (23 µl, 368 µmol, 1.05 eq.) and the solution was stirred 30 min at 0 °C and 150 min at ambient temperature. The reaction mixture was diluted with ether and quenched by the addition of water. The layers were separated and the aqueous layer was extracted thrice with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude *N*-methylcarbamate **598**. Purification by flash column chromatography (hexanes–EtOAc, 6:1) afforded pure *N*-methylcarbamate **598** as a colorless oil (143 mg, 238 µmol, 54% over five steps).

Variant 2: Crude amine **597** (121 mg, 242 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (1.6 ml) and Et_3N (67 µl, 484 µmol, 2.0 eq.) was added dropwise at ambient temperature followed by the addition of Boc_2O (63.4 mg, 290 µmol, 1.2 eq.). The reaction mixture was stirred for 30 min at ambient temperature (monitored by TLC) before it was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude carbamate **598** which was subjected to flash column chromatography (hexanes–EtOAc, 6:1) to afford pure *N*-methylcarbamate **598** as a colorless oil (120 mg, 205 µmol, 83% over three steps).

Variant 3: tert-Butyl methylcarbamate (**835**, 71.7 mg, 547 µmol, 2.0 eq.) was dissolved in anhydrous DMAc (0.7 ml) and cooled to 0 °C under an argon atmosphere. Sodium hydride (60% in mineral oil, 21.9 mg, 547 µmol, 2.0 eq.) was added and the reaction mixture was stirred 60 min at this temperature. A solution of bromide **590** (150 mg, 273 µmol, 1.0 eq.) in anhydrous DMAc (0.5 ml) was added to the reaction mixture and stirring was continued for additional 2 h at ambient temperature. The reaction mixture was diluted with ether and brine. The aqueous layer was extracted once with EtOAc and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the crude residue was subjected to flash column chromatography to obtain pure *N*-methylcarbamate **598** as a colorless oil (132 mg, 221 µmol, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 3.58 – 3.34 (m, 2H), 3.31 (br s, 1H), 3.19

(dd, J = 10.9, 8.2 Hz, 1H), 2.97 (s, 3H), 2.32 (s, 3H), 1.95 (ddd, J = 8.8, 5.4, 1.5 Hz, 1H), 1.48 (s, 9H), 1.26 (br s, 1H), 0.90 – 0.81 (m, 1H), 0.76 (s, 9H), –0.24 (d, J = 21.6 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.7, 135.3, 135.3, 131.9, 129.8, 126.8, 124.7, 123.7, 123.1, 120.1, 113.6, 79.5, 62.1, 34.4, 28.5, 28.4, 26.0, 26.0, 25.8, 21.5, 20.6, 18.1, 16.9, -5.7, –5.7 ppm. **IR** (neat): 3459, 2014, 2961, 1738, 1442, 1366, 1219, 1165, 1086, 986, 910, 838, 736 cm^{-1}. **HRMS** (ESI): calcd. for $C_{32}H_{46}N_2NaO_5SSi$ $[M + Na]^+$ 621.2794, found 621.2799. ▸ NMR spectra on page 397.

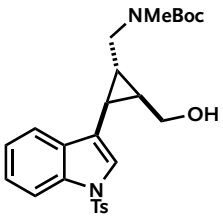
1-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-*N*-methylmethanamine (597).



597

Bromide **590** (133 mg, 242 µmol, 1.0 eq.) was dissolved in EtOH–THF (1:2, 0.7 ml) and cooled to 0 °C. Methylamine (40% aq. solution, 250 µl, 2.91 mmol, 12.0 eq.) was added and the reaction mixture was stirred 60 min at this temperature before it was diluted with ether and sat. aq. K_2CO_3. The phases were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure to yield amine **597** as pale yellow oil which was directly used in the next step. **HRMS** (ESI): calcd. for $C_{27}H_{38}N_2NaO_3SSi$ $[M + Na]^+$ 521.2270, found 521.2273.

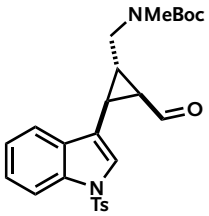
***tert*-Butyl ((2-(hydroxymethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl)(methyl)carbamate (602).**



602

A solution of TBS protected alcohol **598** (77.0 mg, 129 µmol, 1.0 eq.) in anhydrous THF (0.6 ml) was added dropwise to HF · pyr. (20% *w/w*, 0.6 ml) at 0 °C. The reaction mixture was stirred 60 min at 0 °C and 60 min at ambient temperature (monitored by TLC) before it was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether and once with ethyl acetate. The combined organic layers were extracted once with 1 M HCl and the organic layer was dried over magnesium sulfate. The solvents were removed under reduced pressure and the crude oil was purified by flash column chromatography (hexanes–EtOAc, 1:3) to obtain pure alcohol **602** as a colorless foam (56 mg, 116 µmol, 90%). R_f = 0.21 (hexanes–EtOAc, 1:3). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.30 – 7.21 (m, 1H), 7.22 – 7.17 (m, 2H), 3.45 (br s, 1H), 3.37 (d, J = 6.6 Hz, 2H), 3.27 – 3.13 (m, 1H), 2.97 (s, 3H), 2.33 (s, 3H), 2.07 – 1.96 (m, 1H), 1.57 – 1.50 (m, 1H), 1.47 (s, 9H), 1.39 – 1.29 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.1, 135.5, 135.2, 130.0, 126.8, 125.2, 124.0, 123.6, 119.4, 114.0, 79.8, 62.0, 28.6, 26.2, 21.7, 20.9, 17.0 ppm. **IR** (neat): 3314, 3014, 2958, 1740, 1438, 136, 1220, 1022, 909, 736 cm^{-1}. **HRMS** (ESI): calcd. for $C_{26}H_{32}N_2O_5S$ $[M + H]^+$ 507.1930, found 507.1928. ▸ NMR spectra on page 398.

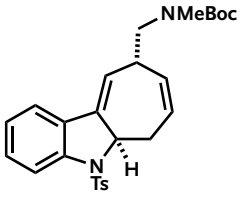
***tert*-Butyl ((2-formyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl)(methyl)carbamate (584).**



584

Alcohol **602** (56.0 mg, 116 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (0.6 ml) and sodium bicarbonate (97.5 mg, 1.16 mmol, 10.0 eq.) was added in one portion followed by the addition of Dess–Martin periodinane (73.5 mg, 173 µmol, 1.5 eq.). The suspension was stirred for 60 min at ambient temperature before the addition of sat. aq. $NaHCO_3$ quenched the reaction. Sat. aq. $Na_2S_2O_3$ was added and the solution was stirred 10 min at ambient temperature. The layers were separated and the aqueous phase was extracted thrice with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure to furnish crude title compound **584**. Purification by flash column chromatography (hexanes–EtOAc, 2:1) gave aldehyde **584** as white foam (54.9 mg, 114 µmol, 98%). R_f = 0.77 (hexanes–EtOAc, 1:1, stains dark red with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.76 (d, J = 5.8 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.50 (dt, J = 7.8, 1.0 Hz, 1H), 7.43 (d, J = 1.3 Hz, 1H), 7.31 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.23 (dd, J = 12.4, 8.0 Hz, 3H), 3.57 – 3.36 (m, 2H), 2.98 (s, 3H), 2.61 (br s, 1H), 2.38 (br s, 1H), 2.32 (s, 3H), 2.20 (br s, 1H), 1.47 (d, J = 5.3 Hz, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 198.8, 145.2, 135.2, 135.1, 130.0, 126.9, 125.4, 124.7, 123.7, 119.4, 113.9, 35.0, 34.0, 28.5, 24.4, 21.7 ppm. **IR** (neat): 2974, 1690, 1447, 1366, 1228, 1164, 1129, 981, 735, 670 cm^{-1}. **HRMS** (ESI): calcd. for $C_{26}H_{30}N_2O_5S$ $[M + H]^+$ 505.1773, found 505.1770. ▸ *NMR spectra on page 399.*

***tert*-Butyl methyl((5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indol-9-yl)methyl)carbamate (585).**



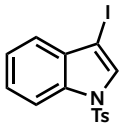
585

Methyltriphenylphosphonium bromide (71.2 mg, 199 µmol, 1.15 eq.) was dissolved in anhydrous THF (1.2 ml) and cooled to –78 °C under an argon atmosphere. NaHMDS (2.0 M in THF, 100 µl, 199 µmol, 1.15 eq.) was added dropwise and the reaction mixture was stirred 15 min at –78 °C, then 30 min at 0 °C and then again 5 min at –78 °C to obtain a bright yellow suspension. A solution of aldehyde **584** (83.7 mg, 173 µmol, 1.0 eq.) in anhydrous THF (0.5 ml) was added dropwise at –78 °C and the reaction mixture was continued stirring at this temperature for 60 min, then additional 20 min at ambient temperature. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The aqueous layer was extracted twice with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure, the crude was dissolved in benzene and was stirred 120 min at 80 °C (monitored by TLC). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (hexanes–EtOAc, 3.5:1) to afford cyclohepta[*b*]indoline **585** (60.2 mg, 125 µmol, 72%) as colorless oil. R_f = 0.77 (hexanes–EtOAc, 2:1, Wittig product, stains brown with vanillin). R_f = 0.71 (hexanes–EtOAc, 2:1, [3,3] product, stains brown with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.76 – 7.67 (m, 1H), 7.61 (d, J = 8.3 Hz, 2H), 7.20 (dd, J = 16.7, 7.9 Hz, 4H), 7.08 – 6.96 (m, 1H), 5.89 (s, 1H), 5.71 (dd, J = 12.1, 7.1 Hz, 1H), 5.38 (d, J = 12.8 Hz, 1H), 4.91 (d, J = 11.4 Hz, 1H), 3.43 (br s, 2H), 3.23 (dd, J =

13.3, 6.8 Hz, 1H), 3.00 (d, J = 23.9 Hz, 1H), 2.86 (s, 3H), 2.45 (dddd, J = 16.8, 11.4, 6.3, 3.1 Hz, 1H), 2.34 (s, 3H), 1.46 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$, 298 K) δ = 129.8, 127.3, 34.7, 28.6, 21.7 ppm. **^{13}C NMR** (126 MHz, $CDCl_3$, 328 K) δ = 143.9, 143.1, 139.9, 129.7, 129.6, 129.3, 129.1, 129.0, 127.2, 126.7, 124.2, 120.1, 116.3, 107.9, 79.7, 64.3, 61.5, 54.0, 37.9, 34.6, 29.6, 28.5, 28.4, 21.4, –0.9 ppm. **IR** (neat): 2972, 1686, 1461, 1359, 1161, 735, 665 cm^{-1}. **HRMS** (ESI): calcd. for $C_{27}H_{32}N_2NaO_4S$ $[M + Na]^+$ 503.1980, found 503.1988. ▸ NMR spectra on page 400.

10.4 Experimental Part for Section 6.3

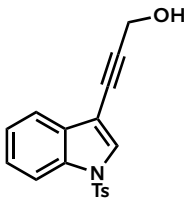
3-Iodo-1-tosyl-1*H*-indole (606).



606

Indole (11.7 g, 100 mmol, 1.0 eq.) was dissolved in absolute DMF (150 ml). Potassium hydroxide pellets (14.0 g, 250 mmol, 2.5 eq.) were added to this solution and stirring was continued at ambient temperature until full dissolution of all components. A solution of iodine (25.6 g, 101 mmol, 1.01 eq.) in absolute DMF (100 ml) was added dropwise to the reaction mixture at ambient temperature over 20 min. After complete addition, the reaction mixture was stirred for additional 60 min at this temperature. Once again, potassium hydroxide pellets (14.0 g, 250 mmol, 2.5 eq.) were added to the reaction mixture followed by the subsequent addition of tosyl chloride (40.0 g, 210 mmol, 2.1 eq.). The reaction mixture was stirred at ambient temperature for additional 18 h (monitored by TLC) and then divided into two parts. To each part 1500 ml of H_2O and 500 ml of ether were added. After separation of the layers, the aqueous layer was extracted thrice ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure to obtain a crude red residue. Title compound **606** was obtained after recrystallization from hexanes (36.0 g, 90.6 mmol, 91%) as a pale orange solid. R_f = 0.35 (hexanes–EtOAc, 15:1). **M.p.** 131 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 – 7.92 (m, 1H), 7.81 – 7.75 (m, 2H), 7.70 (s, 1H), 7.40 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 7.23 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.4, 134.9, 134.3, 132.4, 130.0, 129.8, 126.9, 125.7, 123.9, 122.0, 113.4, 66.9, 21.6 ppm. **HRMS** (ESI): calcd. for $C_{15}H_{12}INNaO_2S$ $[M + Na]^+$ 419.9531, found 419.9535. ▸ NMR spectra on page 404.

3-(1-Tosyl-1*H*-indol-3-yl)prop-2-yn-1-ol (608).[514]



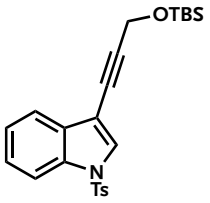
608

3-Iodo-1-tosyl-1*H*-indole (**606**, 795 mg, 2.0 mmol, 1.0 eq.), bis(triphenylphosphine)palladium(II) dichloride (64 mg, 90 µmol, 4.5 mol %) and copper(I) iodide (32 mg, 168 µmol, 8.4 mol %) were dissolved in anhydrous degassed DMF (5 ml). Et_3N (2.4 ml, 17 mmol, 8.5 eq.) and propargyl alcohol (140 µl, 2.4 mmol, 1.2 eq.) were added at ambient temperature and the reaction mixture was stirred 60 min at this temperature under an argon atmosphere (monitored by TLC). The reaction mixture was diluted with ether and sat. aq. NH_4Cl. The aqueous layer was separated and washed three additional times with ether. The combined organic

layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude was subjected to flash column chromatography (hexanes–EtOAc, 1.5:1 → 1:1) to obtain title compound **608** as white powder (612 mg, 1.88 mmol, 94%). R_f = 0.57 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (dt, J = 8.3, 0.9 Hz, 1H), 7.80 – 7.72 (m, 3H), 7.64 (ddd, J = 7.8, 1.3, 0.8 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.28 (ddd, J = 7.7, 7.2, 1.1 Hz, 1H), 7.18 (dd, J = 8.7, 0.7 Hz, 2H), 4.58 (s, 2H), 2.31 (s, 3H), 2.20 (br s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.5, 134.8, 134.2, 130.8, 130.1, 129.4, 127.0, 125.6, 123.9, 120.6, 113.6, 104.7, 91.8, 76.9, 51.8, 21.6 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{15}NNaO_3S$ $[M + Na]^+$ 348.0670, found 348.0669.

▸ NMR spectra on page 405.

3-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-yn-1-yl)-1-tosyl-1*H*-indole (609).

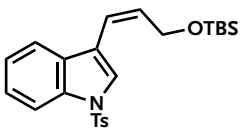


609

Alcohol **608** (8.13 g, 25.0 mmol, 1.0 eq.) was dissolved in anhydrous DMF (40 ml). Imidazole (4.26 g, 62.5 mmol, 2.5 eq.) and TBSCl (4.52 g, 30.0 mmol, 1.2 eq.) were added at ambient temperature and the reaction mixture was stirred 60 min at this temperature before it was diluted with brine and pentane–ether (1:1). The layers were separated and the aqueous layer was washed twice with pentane–ether (1:1). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The crude was subjected to flash column chromatography (hexanes–EtOAc, 7:1) to obtain title compound **609** as pale yellow powder (10.7 g, 24.3 mmol, 97%). R_f = 0.52 (hexanes–EtOAc, 7:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.00 – 7.92 (m, 1H), 7.81 – 7.73 (m, 2H), 7.71 (s, 1H), 7.65 – 7.58 (m, 1H), 7.40 – 7.23 (m, 3H), 4.65 – 4.50 (m, 2H), 2.35 (d, J = 0.6 Hz, 3H), 0.95 (s, 9H), 0.18 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_{24}H_{30}NO_3SSi$ $[M + H]^+$ 440.1716, found 440.1718.

▸ NMR spectra on page 406.

(*Z*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-tosyl-1*H*-indole (529).

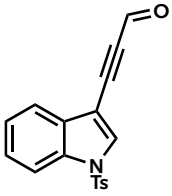


529

Alkyne **609** (120 mg, 273 µmol, 1.0 eq.) was dissolved in MeOH–EtOAc (1:10, 5 ml) and Lindlar catalyst (10 mol %) was added. The reaction mixture was stirred vigorously and hydrogenated (p = 400 psi) at ambient temperature for 30 min. The reaction mixture was filtered over a plug of silica to obtain title compound **529** as pale yellow oil (105 mg, 238 µmol, 87%). R_f = 0.60 (pentane–ether, 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 7.7 Hz, 1H), 7.45 (s, 1H), 7.34 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H), 7.26 (td, J = 7.4, 1.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.51 (dq, J = 11.5, 1.7 Hz, 1H), 5.99 (dt, J = 11.8, 6.1 Hz, 1H), 4.42 (dd, J = 6.1, 1.7 Hz, 2H), 2.40 – 2.25 (m, 3H), 0.93 (s, 9H), 0.09 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.1, 135.3, 134.8, 133.7, 130.5, 130.0, 129.9, 126.9, 126.9, 125.1, 124.3, 123.5, 119.7, 118.7, 118.7, 113.7, 60.8, 58.1, 26.1, 21.7, 18.4,

–5.0 ppm. **IR** (neat): 2939, 2856, 1455, 1173, 1087, 839, 771, 668 cm^{-1}. **HRMS** (ESI): calcd. for $C_{24}H_{31}NNaO_3SSi$ $[M + Na]^+$ 464.1692, found 464.1693. ▸ *NMR spectra on page 376.*

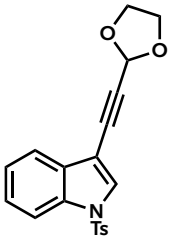
3-(1-Tosyl-1*H*-indol-3-yl)propiolaldehyde (610).



610

To anhydrous CH_2Cl_2 (1.0 ml) were added DMSO (82 µl, 1.14 mmol, 3.0 eq.) and pivaloyl chloride (94 µl, 762 µmol, 2.0 eq.) and the solution was cooled down to –78 °C under an argon atmosphere. The solution was stirred 15 min at this temperature, then a solution of alcohol **608** (124 mg, 381 µmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1.0 ml) was added dropwise. After consumption of the starting material (60 min), Et_3N (244 µl, 1.91 mmol, 5.0 eq.) was added and the reaction mixture was stirred additional 30 min at –78 °C and then additional 30 min at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain crude **610** which was directly used in the next step. $R_f = 0.50$ (hexanes–EtOAc, 3:1).

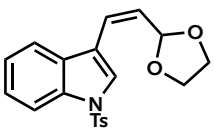
3-((1,3-Dioxolan-2-yl)ethynyl)-1-tosyl-1*H*-indole (611).



611

Crude aldehyde **610** (381 µmol, 1.0 eq.) was dissolved in anhydrous benzene (1.9 ml). Ethylene glycol (50 µl, 876 µmol, 2.3 eq.) and $TsOH \cdot H_2O$ (7.2 mg, 38 µmol, 0.1 eq.) were added. To this solution, some magnesium sulfate was added and the resulting suspension was refluxed for seven hours. The reaction mixture was cooled to ambient temperature, diluted with EtOAc and sat. aq. NH_4Cl was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain crude **611** which was filtered over a plug of silica to obtain purified dioxolane **611** (98.0 mg, 266 µmol, 70% over two steps), which was directly used in the next step. $R_f = 0.46$ (hexanes–EtOAc, 3:1). **HRMS** (ESI): calcd. for $C_{20}H_{17}NNaO_4S$ $[M + Na]^+$ 390.0776, found 390.0778.

(*Z*)-3-(2-(1,3-Dioxolan-2-yl)vinyl)-1-tosyl-1*H*-indole (612).



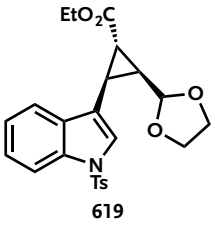
612

$Pd/CaCO_3$ (5%, 11.3 mg, 5 µmol, 2 mol %) was added to 1.8 ml of absolute methanol. Quinoline (24 µl, 200 µmol, 0.75 eq.) was added and the mixture was stirred vigorously at ambient temperature for 30 min (this step was crucial for the *poisoning* of the palladium). A solution of alkyne **611** (98 mg, 266 µmol, 1.0 eq.) was added and the reaction mixture was hydrogenated ($p(H_2)$ = 100 psi) at ambient temperature for 75 min (monitored by TLC). The reaction mixture was filtered over a plug of celite and the solvent was removed *in vacuo* to obtain crude diox-

olane **612** which was subjected to flash column chromatography (pentane–ether, 3:2) to afford pure dioxolane **612** (71.0 mg, 193 µmol, 72%) as a colorless oil. R_f = 0.43 (hexanes–EtOAc, 3:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.29 – 8.21 (m, 2H), 7.66 – 7.60 (m, 2H), 7.28 (dt, J = 7.9, 1.0 Hz, 1H), 7.02 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 6.50 (dt, J = 11.5, 1.1 Hz, 1H), 6.40 (dd, J = 8.7, 0.8 Hz, 2H), 6.01 (dd, J = 11.5, 6.6 Hz, 1H), 5.54 (dd, J = 6.6, 1.1 Hz, 1H), 3.61 – 3.55 (m, 2H), 3.41 – 3.36 (m, 2H), 1.59 (s, 3H) ppm. **HRMS** (ESI): calcd. for $C_{20}H_{19}NNaO_4S$ $[M + Na]^+$ 392.0932, found 392.0935.

▸ NMR spectra on page 406.

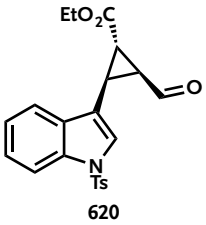
Ethyl (1*S*,2*S*,3*R*)-2-(1,3-dioxolan-2-yl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (619).



619

A flame-dried Schlenk tube was charged with [Cu(OTf)] · PhH (2.0 mg, 3.9 µmol, 1.5 mol %), (*S*)-^{t}Bu-BOX ligand **583** (1.3 mg, 4.3 µmol, 1.7 mol %), and olefine **612** (96.0 mg, 260 µmol, 1.0 eq.) in the glovebox. The tube was flushed with argon and freeze-pump-thaw degassed CH_2Cl_2 (0.5 ml) was added. The reaction mixture was stirred 60 min at ambient temperature to produce a deep-green clear solution. A solution of ethyl diazoacetate (commercial, contains ≥13 wt. % dichloromethane; 164 µl, 1.56 mmol, 6.0 eq.) in freeze-pump-thaw degassed CH_2Cl_2 (5.0 ml) was added *via* syringe pump over 12 h at ambient temperature (N_2 evolution) at which the solution became orange. The solution was filtered over a plug of celite to afford a clear yellow solution. The solvent was removed under reduced pressure to obtain crude **619** as yellow oil which was directly subjected to the next step due to large amounts of fumaric acid diethyl ester. R_f = 0.35 (hexanes–EtOAc, 3:1). **HRMS** (ESI): calcd. for $C_{24}H_{25}NNaO_6S$ $[M + Na]^+$ 478.1300, found 478.1301.

Ethyl (1*S*,2*S*,3*R*)-2-formyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (620).

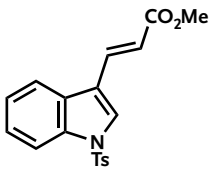


620

Crude dioxolane **619** (260 µmol, 1.0 eq.) was dissolved in acetone–H_2O (9:1, 7 ml) and pyridinium *p*-toluenesulfonate (65.3 mg, 260 µmol, 1.0 eq.) was added. The reaction mixture was refluxed for 6 h, then the solvent was evaporated and the residue was partitioned between EtOAc and bicarb. The layers were separated and the aqueous layer was washed once with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to yield crude aldehyde **620** which was subjected to flash column chromatography (hexanes–EtOAc, 1:1) to obtain pure aldehyde **620** as white foam (64.2 mg, 156 µmol, 60%). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.51 (d, J = 4.1 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 1.3 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 8.1 Hz, 2H), 3.93 (q, J = 7.1 Hz, 2H), 2.86 (dd, J = 9.1, 6.1 Hz, 1H), 2.68 (t, J = 5.3 Hz, 1H), 2.54 (dt, J = 9.1, 4.4 Hz, 1H), 1.62 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 194.7, 170.3, 144.7, 135.7, 135.7, 131.1, 129.9, 127.0, 125.6, 125.5, 123.8, 119.5, 116.0, 114.3, 61.4, 36.1, 25.5, 24.3, 21.0, 14.1 ppm. **IR** (neat): 1726, 1707, 1446, 1368, 1275,

1171, 1132, 1121, 1094, 976, 745, 667, 570, 536 cm^{-1}. **HRMS** (ESI): calcd. for $C_{22}H_{21}NNaO_5S$ $[M + Na]^+$ 434.1038, found 434.1044. $[\alpha]_D^{20}$ = +35.7° (c = 1.1, $CHCl_3$). ▸ NMR spectra on page 459.

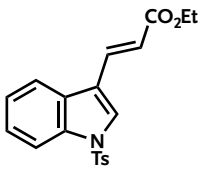
Methyl (*E*)-3-(1-tosyl-1*H*-indol-3-yl)acrylate (836).



836

General procedure: a solution of aldehyde **526** (1.0 eq.) and methyl (triphenylphosphoranylidene)acetate (1.0 eq.) in benzene (0.4 M) was refluxed for 6 h. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1) to obtain ester **836** in 92% yield (*E*/*Z* =5:1, separable). R_f = 0.43 (hexanes–EtOAc, 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (dt, J = 8.2, 0.8 Hz, 1H), 7.84 (s, 1H), 7.84 – 7.75 (m, 4H), 7.38 (td, J = 8.4, 7.9, 1.3 Hz, 1H), 7.32 (td, J = 7.7, 1.2 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 6.52 (d, J = 16.2 Hz, 1H), 3.82 (s, 3H), 2.35 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 167.6, 145.7, 136.0, 135.7, 134.9, 130.2, 128.6, 128.2, 127.1, 125.6, 124.2, 120.8, 118.2, 118.0, 118.0, 114.0, 51.9, 21.7 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{17}NNaO_4S$ $[M + Na]^+$ 378.0776, found 378.0780. ▸ NMR spectra on page 407.

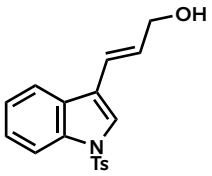
Ethyl (*E*)-3-(1-tosyl-1*H*-indol-3-yl)acrylate (837).



837

^{n}BuLi (2.5 M in hexanes, 9.72 ml, 24.3 mmol, 1.1 eq.) was added to anhydrous THF (50 ml) at –78 °C under an argon atmosphere. To this solution was added dropwise a solution of triethyl phosphonoacetate (4.9 ml, 24.3 mmol, 1.1 eq.) in anhydrous THF (10 ml). The resulting solution was stirred additional 15 min at –78 °C, then a solution of aldehyde **526** (6.60 g, 22.1 mmol, 1.0 eq.) in anhydrous THF (40 ml, in some cases a little amount of anhydrous CH_2Cl_2 was added to get a full dissolution of the aldehyde) was added dropwise. The resulting solution was stirred additional 120 min at –78 °C (monitored by TLC) before it was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. The residue can be purified by flash column chromatography (hexanes–EtOAc, 6:1) to obtain pure *(E)*-ester **837** in quantitative yield as pale yellow oil which solidified below 5 °C. Usually, it was used crude in the upcoming steps. R_f = 0.68 (hexanes–EtOAc, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (d, J = 8.1 Hz, 1H), 7.84 (s, 1H), 7.82 – 7.75 (m, 4H), 7.38 (td, J = 8.3, 7.8, 1.3 Hz, 1H), 7.31 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 6.51 (d, J = 16.1 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.34 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 167.2, 145.7, 135.7, 135.7, 134.9, 130.2, 128.5, 128.2, 127.1, 125.6, 124.2, 120.8, 118.5, 118.5, 118.3, 113.9, 60.7, 21.7, 14.5 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{20}NO_4S$ $[M + H]^+$ 370.1113, found 370.1115. ▸ NMR spectra on page 408.

(*E*)-3-(1-Tosyl-1*H*-indol-3-yl)prop-2-en-1-ol (633).

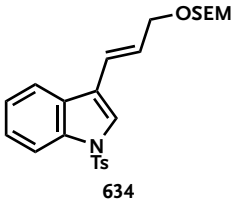


633

Ester **837** (12.8 g, 34.7 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (180 ml) and cooled to –78 °C. DiBAL (1.0 M in hexanes, 87.0 ml, 87.0 mmol, 2.5 eq.) was added dropwise and after complete addition the reaction mixture was stirred additional 2 h at –78 °C. Sat. aq. Rochelle's salt was added and the resulting suspension was diluted with CH_2Cl_2 and stirred vigorously for 16 h at ambient temperature. The layers were separated and the organic layer was extracted once with water and once with brine. The combined aqueous layers were then extracted thrice with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain title compound **633** as yellow solid (11.2 g, 34.2 mmol, 99%) which was analytically pure according to NMR analysis. R_f = 0.31 (hexanes–EtOAc, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.01 (d, J = 8.3 Hz, 1H), 7.74 (dd, J = 15.1, 8.1 Hz, 3H), 7.60 (s, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.69 (d, J = 16.1 Hz, 1H), 6.44 (dt, J = 16.1, 5.6 Hz, 1H), 4.35 (d, J = 5.2 Hz, 2H), 2.31 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.1, 135.5, 135.0, 130.0, 129.1, 126.9, 125.0, 124.0, 123.6, 121.6, 120.4, 120.1, 113.8, 63.9, 21.6 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{17}NNaO_3S$ $[M + Na]^+$ 350.0827, found 350.0830.

▸ *NMR spectra on page 409.*

(*E*)-1-Tosyl-3-(3-((2-(trimethylsilyl)ethoxy)methoxy)prop-1-en-1-yl)-1*H*-indole (634).



634

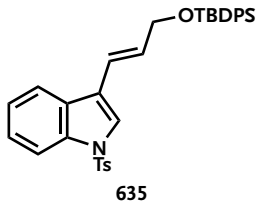
Crude alcohol **633** (15.3 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (50 ml) and cooled to 0 °C. To this solution SEMCl (95%, 4.28 ml, 22.9 mmol, 1.5 eq.) was added at which the solution turned dark red. Hünig's base (5.84 ml, 34.4 mmol, 2.25 eq.) was added dropwise over 10 min at 0 °C and the resulting solution was stirred for additional 10 min at this temperature, then additional 5.5 h at ambient temperature before it was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure to obtain crude title compound **634** which was subjected to flash column chromatography (hexanes–EtOAc, 8:1 → 6:1) to obtain pure SEM protected alcohol **634** as colorless oil (6.30 g, 13.8 mmol, 90% yield over three steps).

*Note: Caution! SEM protected alcohol **634** turned out to be a strong lachrymator and should only be handled in a well ventilated fume hood.*

R_f = 0.76 (hexanes–EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.01 (d, J = 8.2 Hz, 1H), 7.76 (t, J = 8.0 Hz, 3H), 7.62 (s, 1H), 7.40 – 7.31 (m, 2H), 7.33 – 7.24 (m, 1H), 7.23 (d, J = 7.9 Hz, 2H), 6.72 (dd, J = 16.1, 0.7 Hz, 1H), 6.39 (dt, J = 16.1, 6.0 Hz, 1H), 4.78 (s, 2H), 4.28 (dd, J = 6.1, 1.5 Hz, 2H), 3.75 – 3.65 (m, 2H), 2.35 (s, 3H), 1.05 – 0.95 (m, 2H), 0.05 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.2, 135.7, 135.2, 130.0, 129.1, 127.2, 127.0, 127.0, 125.1,

124.2, 123.6, 123.3, 120.5, 120.2, 113.9, 94.3, 68.3, 65.4, 21.7, 18.3, –1.2 ppm. **HRMS** (ESI): calcd. for $C_{24}H_{31}NNaO_4SSi$ $[M + Na]^+$ 480.1641, found 480.1640. ▸ NMR spectra on page 410.

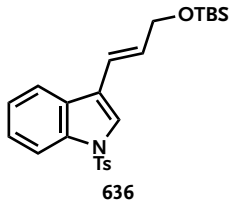
(*E*)-3-(3-((*tert*-Butyldiphenylsilyl)oxy)prop-1-en-1-yl)-1-tosyl-1*H*-indole (635).



635

Crude alcohol **633** (17.0 mmol, 1.0 eq.) was dissolved in anhydrous DMF (30 ml). Imidazole (2.90 g, 42.5 mmol, 2.5 eq.) and TBDPSCl (5.6 ml, 21.3 mmol, 1.25 eq.) were added at ambient temperature and the reaction mixture was stirred 60 min at this temperature before it was diluted with brine and pentane–ether (1:1). The layers were separated and the aqueous layer was washed twice with pentane–ether (1:1). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The crude was subjected to flash column chromatography (pentane–ether, 10:1) to obtain title compound **635** as pale yellow foam (9.38 g, 16.6 mmol, 97% over three steps). R_f = 0.60 (hexanes–EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.03 (dt, J = 8.3, 0.9 Hz, 1H), 7.83 – 7.71 (m, 6H), 7.71 – 7.63 (m, 1H), 7.58 (s, 1H), 7.49 – 7.33 (m, 7H), 7.32 – 7.23 (m, 1H), 7.23 (d, J = 7.9 Hz, 2H), 6.73 (dtd, J = 16.0, 1.9, 0.7 Hz, 1H), 6.36 (dt, J = 16.0, 4.8 Hz, 1H), 4.43 (dd, J = 4.9, 1.8 Hz, 2H), 2.35 (s, 3H), 1.14 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{34}H_{35}NNaO_3SSi$ $[M + Na]^+$ 588.2005, found 588.2007. ▸ NMR spectra on page 411.

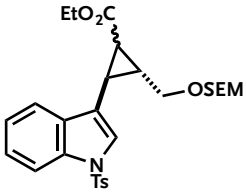
(*E*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-1-yl)-1-tosyl-1*H*-indole (636).



636

Crude alcohol **633** (14.4 g, 44.0 mmol, 1.0 eq.) was dissolved in anhydrous DMF (75 ml). Imidazole (7.49 g, 110 mmol, 2.5 eq.) and TBSCl (8.29 g, 55.0 mmol, 1.25 eq.) were added at ambient temperature and the reaction mixture was stirred 60 min at this temperature before it was diluted with brine and pentane–ether (1:1). The layers were separated and the aqueous layer was washed twice with pentane–ether (1:1). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The crude was subjected to flash column chromatography (pentane–ether, 10:1) to obtain title compound **636** as pale yellow foam (18.3 g, 41.5 mmol, 94% over three steps). R_f = 0.40 (pentane–ether, 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.33 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.67 (ddt, J = 16.0, 1.9, 1.0 Hz, 1H), 6.36 (dt, J = 16.0, 4.9 Hz, 1H), 4.37 (dd, J = 4.9, 1.7 Hz, 2H), 2.32 (s, 3H), 0.96 (s, 9H), 0.13 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.1, 135.6, 135.3, 130.6, 130.0, 129.4, 126.9, 125.0, 123.7, 123.6, 120.5, 120.4, 119.9, 113.9, 64.0, 26.1, 25.8, 21.7, 18.6, 14.3, –3.4, –5.0 ppm. **HRMS** (ESI): calcd. for $C_{24}H_{31}NNaO_3SSi$ $[M + Na]^+$ 464.1692, found 464.1692. ▸ NMR spectra on page 411.

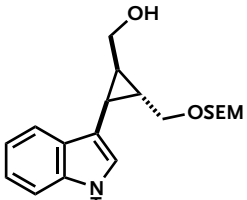
Ethyl-2-(1-tosyl-1*H*-indol-3-yl)-3-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)cyclopropane-1-carboxylate (637).



637

Olefine **634** (1.31 g, 2.86 mmol, 1.0 eq.) was dissolved in anhydrous benzene (4 ml) and anhydrous copper(I) sulfate (114 mg, 720 µmol, 25 mol %) was added. The resulting suspension was stirred under refluxing conditions and a solution of ethyl diazoacetate (commercial, contains ≥13 wt. % dichloromethane; 1.21 ml, 10.0 mmol, 3.5 eq.) in benzene (17 ml) was added *via* syringe pump over a period of 6 hours. After complete addition, the reaction mixture was refluxed additional 60 min. The reaction was cooled to ambient temperature and filtered over celite. A short flash column chromatography (hexanes–EtOAc, 5:1) was done to separate the obtained product **637** (inseparable *cis*/*trans*-mixture) which then was used directly in the next step. R_f = 0.51 (hexanes–EtOAc, 4:1). **HRMS** (ESI): calcd. for $C_{28}H_{37}NNaO_6SSi$ $[M + Na]^+$ 566.2009, found 566.2010.

(2-(1-Tosyl-1*H*-indol-3-yl)-3-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)cyclopropyl)-methanol (640).



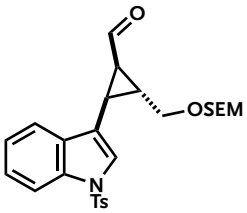
640

Crude ester **637** (2.86 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (15 ml) and cooled to –78 °C. DiBAL (1.0 M in hexanes, 8.6 ml, 3.0 eq.) was added dropwise and the reaction mixture was stirred for additional 2 h at –78 °C before quenched by the addition of sat. aq. Rochelle's salt. The resulting mixture was stirred vigorously over night. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The remained crude was subjected to flash column chromatography (hexanes–EtOAc, 2:1 → 1.5:1 → 1:1 → 1:2) to separate the diastereomeric alcohols. *Cis*-product **640** was obtained as colorless oil (706 mg, 1.41 mmol), the corresponding diastereomer was also obtained as colorless oil (373 mg, 743 mmol). The *endo*/*exo*-ratio of the cyclopropanation was therefore determined to be 1.9:1 and the combined yield was 38% over two steps. R_f = 0.22 (hexanes–EtOAc, 2:1, minor diastereomer, stains dark blue with vanillin). R_f = 0.15 (hexanes–EtOAc, 2:1, major diastereomer, stains dark blue with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$, major diastereomer) δ = 7.95 (dt, J = 8.3, 0.9 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.29 – 7.20 (m, 1H), 7.20 (d, J = 7.8 Hz, 2H), 4.74 (s, 2H), 3.73 – 3.57 (m, 4H), 3.45 (dd, J = 11.6, 6.3 Hz, 1H), 3.25 (dd, J = 11.6, 8.1 Hz, 1H), 2.32 (s, 3H), 2.01 (ddd, J = 8.7, 5.3, 1.4 Hz, 1H), 1.56 – 1.47 (m, 1H), 1.43 (tt, J = 6.4, 5.1 Hz, 1H), 0.98 – 0.92 (m, 2H), 0.01 (s, 9H) ppm. **^{1}H NMR** (400 MHz, $CDCl_3$, minor diastereomer) δ = 7.96 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.32 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.26 – 7.17 (m, 4H), 4.76 (s, 2H), 4.21 – 4.07 (m, 2H), 3.72 – 3.62 (m, 2H), 3.51 (dd, J = 11.9, 9.5 Hz, 2H), 2.33 (s, 3H), 1.77 – 1.69 (m, 1H), 1.64 (td, J = 9.3, 8.4, 5.1 Hz, 1H), 1.26 (t, J = 7.1 Hz, 1H), 1.01 – 0.92 (m, 2H), 0.04 (s, 9H) ppm. **HRMS** (ESI):

calcd. for $C_{26}H_{35}NNaO_5SSi$ $[M + Na]^+$ 524.1903, found 524.1908 (major diastereomer). **HRMS** (ESI): calcd. for $C_{26}H_{35}NNaO_5SSi$ $[M + Na]^+$ 524.1903, found 524.1905 (minor diastereomer).

▶ *NMR spectra on page 412.*

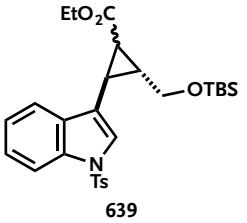
2-(1-Tosyl-1*H*-indol-3-yl)-3-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)cyclopropane-1-carbaldehyde (644).



644

Alcohol **640** (543 mg, 1.08 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (5.4 ml). Cornforth reagent (1.22 g, 3.45 mmol, 3.0 eq.) and molecular sieves (3 Å, 540 mg) were added. The resulting mixture was stirred 4 h at ambient temperature (monitored by TLC) before it was diluted with ether and filtered through a plug of silica (3 cm). The filtrate was reduced, diluted with ether and once again filtered through a plug of silica (3 cm). Evaporation of the solvent yielded aldehyde **644** (262 mg, 524 µmol, 48%) as yellow oil which was directly used in the next steps. R_f = 0.67 (hexanes–EtOAc, 2:1). **HRMS** (ESI): calcd. for $C_{26}H_{33}NNaO_5SSi$ $[M + Na]^+$ 522.1746, found 522.1752.

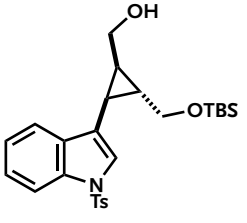
Ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (639).



639

A flame-dried Schlenk tube was charged with [Cu(OTf)] · PhH (23.2 mg, 45.2 µmol, 1.5 mol %) and olefine **636** (1.33 g, 3.01 mmol, 1.0 eq.) in the glovebox. The tube was flushed with argon and freeze-pump-thaw degassed CH_2Cl_2 (2.0 ml) was added. A solution of ethyl diazoacetate (commercial, contains ≥13 wt. % dichloromethane; 788 µl, 7.53 mmol, 2.5 eq.) in freeze-pump-thaw degassed CH_2Cl_2 (15.0 ml) was added *via* syringe pump over 12 h at ambient temperature (N_2 evolution) at which the solution became orange. The solution was filtered over a plug of celite to afford a clear yellow solution. The solvent was removed under reduced pressure to obtain crude **639** as yellow oil which was directly subjected to the next step. R_f = 0.64 (hexanes–EtOAc, 4:1). **HRMS** (ESI): calcd. for $C_{28}H_{37}NNaO_5SSi$ $[M + Na]^+$ 550.2059, found 550.2064.

(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methanol (643).



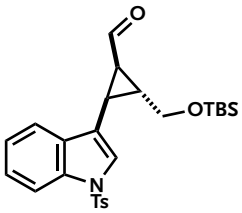
643

Crude ester **639** (3.01 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (16.0 ml) and cooled to –78 °C. DiBAL (1.0 M in hexanes, 7.5 ml, 7.5 mmol, 2.5 eq.) was added dropwise and stirring was continued for additional 2 h at –78 °C after complete addition. The reaction was quenched by the addition of sat. aq. Rochelle's salt and diluted with CH_2Cl_2. The suspension was stirred vigorously over night. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined

organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The remained crude was subjected to flash column chromatography (hexanes–EtOAc, 3:1 → 2:1) to separate the diastereomeric alcohols. *Cis*-product **643** was obtained as colorless oil (729 mg, 1.50 mmol), the corresponding diastereomer **642** was also obtained as colorless oil (438 mg, 902 µmol). The *endo/exo*-ratio of the cyclopropanation was therefore determined to be 1.7:1 and the combined yield was 80% over two steps. R_f = 0.11 (hexanes–EtOAc, 4:1, major diastereomer, stains dark blue with vanillin). R_f = 0.22 (hexanes–EtOAc, 4:1, minor diastereomer, stains dark blue with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$, major diastereomer) δ = 7.99 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.72 – 7.68 (m, 1H), 7.38 – 7.31 (m, 2H), 7.29 – 7.25 (m, 1H), 7.22 (d, J = 8.3 Hz, 2H), 3.84 (dd, J = 10.7, 5.5 Hz, 1H), 3.72 (dd, J = 10.7, 6.0 Hz, 1H), 3.54 (dd, J = 11.5, 6.0 Hz, 1H), 3.26 (dd, J = 11.5, 8.5 Hz, 1H), 2.35 (s, 3H), 2.04 (ddd, J = 8.6, 5.4, 1.3 Hz, 1H), 1.53 (tt, J = 8.6, 5.5 Hz, 1H), 1.37 (p, J = 5.5 Hz, 1H), 0.95 (s, 9H), 0.11 (d, J = 3.0 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$, major diastereomer) δ = 145.0, 135.5, 135.2, 131.9, 129.9, 129.7, 127.6, 126.8, 125.1, 124.1, 123.5, 120.3, 119.7, 114.0, 64.8, 62.2, 26.1, 26.0, 24.7, 24.4, 21.7, 18.4, 15.9, –5.1, –5.1 ppm. **^{1}H NMR** (400 MHz, $CDCl_3$, minor diastereomer) δ = 7.96 (d, J = 8.2 Hz, 1H), 7.73 (dd, J = 7.6, 1.1 Hz, 2H), 7.50 (ddd, J = 7.8, 1.3, 0.8 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.26 – 7.18 (m, 4H), 4.29 (dd, J = 11.4, 5.6 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.53 (ddd, J = 14.3, 11.9, 10.3 Hz, 2H), 3.27 (d, J = 10.6 Hz, 1H), 2.33 (s, 3H), 1.77 – 1.70 (m, 2H), 1.61 (ddt, J = 10.6, 8.4, 5.5 Hz, 1H), 0.94 (s, 9H), 0.14 (d, J = 5.2 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$, minor diastereomer) δ = 144.9, 135.3, 135.3, 131.0, 129.9, 126.9, 125.0, 123.3, 123.2, 121.8, 119.4, 113.9, 63.1, 62.4, 27.3, 26.6, 26.0, 21.7, 18.3, 17.7, –5.1, –5.4 ppm. **HRMS** (ESI): calcd. for $C_{26}H_{35}NNaO_4SSi$ $[M + Na]^+$ 508.1954, found 508.1954 (major diastereomer). **HRMS** (ESI): calcd. for $C_{26}H_{35}NNaO_4SSi$ $[M + Na]^+$ 508.1954, found 508.1957 (minor diastereomer).

▸ *NMR spectra on page 414.*

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carbaldehyde (647).



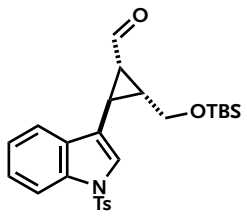
647

Alcohol **643** (716 mg, 1.47 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (7.4 ml). Dess–Martin periodinane (**603**, 782 mg, 1.84 mmol, 1.25 eq.) and $NaHCO_3$ (1.24 g, 14.7 mmol, 10.0 eq.) were added and the reaction mixture was stirred 15 min at ambient temperature (monitored by TLC). The reaction mixture was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting crude was subjected to flash column chromatography (hexanes–EtOAc, 6:1 → 4:1) to obtain aldehyde **647** (633 mg, 1.31 mmol, 89%) as white foam. R_f = 0.77 (hexanes–EtOAc, 2:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.78 (d, J = 6.1 Hz, 1H), 8.01 – 7.87 (m, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.64 – 7.54 (m, 1H), 7.44 (d, J = 1.4 Hz, 1H), 7.38 – 7.28 (m, 1H), 7.24 – 7.16 (m, 3H), 4.00 –

3.93 (m, 1H), 3.85 – 3.78 (m, 1H), 2.68 – 2.60 (m, 1H), 2.34 (s, 3H), 2.29 – 2.14 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_{26}H_{33}NNaO_4SSi$ $[M + Na]^+$ 506.1797, found 506.1799. ▸ *NMR spectra on page 418.*

*Note: Title compound **647** tended to decomposition, storage is recommended as solution in anhydrous benzene below –10 °C.*

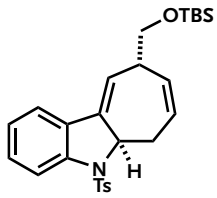
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carbaldehyde (646).



646

Alcohol **642** (1.20 g, 2.47 mmol, 1.0 eq.) was dissolved in anhydrous DMSO (5.0 ml). IBX (**604**, 1.04 g, 3.71 mmol, 1.5 eq.) was added and the reaction mixture was stirred at ambient temperature for five hours before it was diluted with ethyl acetate and extracted with water. The aqueous phase was washed with ethyl acetate twice, the combined organic layers were dried over magnesium sulfate and the solvents were removed under reduced pressure to obtain title compound **646** as white foam, which was directly used in the next step. R_f = 0.75 (hexanes–EtOAc, 3:1). **HRMS** (ESI): calcd. for $C_{26}H_{34}NO_4SSi$ $[M + H]^+$ 484.1978, found 484.1981.

9-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole (649).

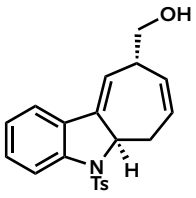


649

Methyltriphenylphosphonium bromide (923 mg, 2.58 mmol, 2.5 eq.) was dissolved in anhydrous THF (5.0 ml) and cooled to –78 °C under an argon atmosphere. NaHMDS (2.0 M in THF, 1.3 ml, 2.58 mmol, 2.5 eq.) was added dropwise and the reaction mixture was stirred 15 min at –78 °C, then additional 30 min at 0 °C and then again recooled to –78 °C to yield a bright yellow suspension. A solution of aldehyde **647** (500 mg, 1.03 mmol, 1.0 eq.) in anhydrous THF (2.0 ml) was added and the reaction mixture was stirred 60 min at –78 °C (monitored by TLC) and then additional 30 min at 0 °C. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with ether. The organic layers were combined, dried over magnesium sulfate and the solvent was removed *in vacuo*. TLC indicated, that partial rearrangement already took place. The crude was therefore dissolved in benzene and stirred 3 h at 80 °C to complete the rearrangement and afford cyclohepta[*b*]indoline **649** as white foam (437 mg, 907 µmol, 88%) after removal of the solvent. R_f = 0.74 (hexanes–EtOAc, 4:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.80 – 7.72 (m, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 1.8 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.05 (td, J = 7.5, 1.0 Hz, 1H), 6.10 – 6.01 (m, 1H), 5.74 (ddt, J = 12.0, 7.0, 2.4 Hz, 1H), 5.48 (d, J = 12.3 Hz, 1H), 4.96 (dd, J = 9.4, 7.0 Hz, 1H), 3.74 – 3.48 (m, 2H), 3.34 (br s, 1H), 3.00 (ddt, J = 16.7, 7.0, 3.4 Hz, 1H), 2.59 – 2.41 (m, 1H), 2.37 (s, 3H), 0.94 (s, 9H),

0.11 (d, J = 1.3 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{27}H_{35}NNaO_3SSi$ $[M + Na]^+$ 504.2005, found 504.2005. ▸ NMR spectra on page 419.

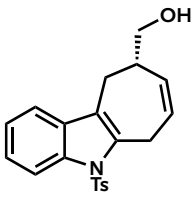
(5-Tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indol-9-yl)methanol (651).



651

A solution of crude cyclohepta[*b*]indoline **649** (385 µmol, 1.0 eq.) in anhydrous THF (2.0 ml) was added dropwise to HF · pyr. (20% *w/w*, 2.0 ml) at 0 °C. The reaction mixture was stirred 60 min at 0 °C and 60 min at ambient temperature (monitored by TLC) before it was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether and once with ethyl acetate. The combined organic layers were extracted once with 1 M HCl and the organic layer was dried over magnesium sulfate. The solvents were removed under reduced pressure and the crude oil was purified by flash column chromatography (hexanes–EtOAc, 2:1 → 1:1) to obtain pure alcohol **651** as a colorless oil (99.0 mg, 269 µmol, 70%). R_f = 0.18 (hexanes–EtOAc, 2:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.08 (dt, J = 8.2, 0.8 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.02 (ddd, J = 8.3, 7.3, 1.0 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.75 (td, J = 7.5, 1.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 2H), 5.84 (ddd, J = 3.8, 2.7, 1.3 Hz, 1H), 5.53 (ddt, J = 12.2, 7.3, 2.5 Hz, 1H), 5.30 – 5.19 (m, 1H), 5.14 (ddt, J = 11.4, 4.0, 2.4 Hz, 1H), 3.27 – 3.11 (m, 3H), 3.05 – 2.92 (m, 1H), 2.48 – 2.30 (m, 1H), 1.64 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 144.0, 143.9, 140.4, 135.1, 129.8, 129.6, 129.6, 128.9, 127.9, 127.5, 124.6, 120.7, 119.7, 117.0, 66.7, 64.9, 42.1, 35.1, 21.0 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{21}NNaO_3S$ $[M + Na]^+$ 390.1140, found 390.1141. ▸ NMR spectra on page 419.

(5-Tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indol-9-yl)methanol (623).



623

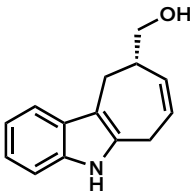
Variant 1: Cyclohepta[*b*]indoline **651** (15.0 mg, 40.8 µmol, 1.0 eq.) was dissolved in 400 µl of anhydrous CH_2Cl_2 and *p*-toluenesulfonic acid monohydrate (7.8 mg, 40.8 µmol, 1.0 eq.) was added. The reaction mixture was stirred over night at ambient temperature and then subjected to flash column chromatography (hexanes–EtOAc, 2:1 → 1:1) to obtain rearomatized cyclohepta[*b*]indole **623** as colorless oil (11.8 mg, 32.1 µmol, 79%).

Variant 2: Cyclohepta[*b*]indoline **649** (437 mg, 907 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (5.0 ml) and pyridinium *p*-toluenesulfonate (228 mg, 907 µmol, 1.0 eq.) was added to yield an orange solution. To this solution was added *p*-toluenesulfonic acid monohydrate (17.3 mg, 90.7 µmol, 10 mol %) at which point the solution turned dark green. The reaction mixture was stirred over night at 35 °C and then diluted with CH_2Cl_2 and quenched by the addition of sat. aq. $NaHCO_3$. The aqueous layer was extracted thrice with CH_2Cl_2, the combined organic layers were dried over sodium sulfate and the solvent was evaporated. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1 → 1:1) to obtain rearomatized cyclohepta[*b*]indole **623** as colorless oil (226 mg, 615 µmol, 68%). R_f = 0.22 (hexanes–EtOAc,

2:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.61 (dd, J = 8.8, 1.1 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.23 – 7.18 (m, 2H), 7.10 (td, J = 7.3, 1.0 Hz, 1H), 6.44 (d, J = 8.0 Hz, 2H), 5.62 (dddd, J = 10.3, 6.0, 4.0, 1.6 Hz, 1H), 5.53 (ddd, J = 11.4, 4.7, 2.3 Hz, 1H), 4.18 (dd, J = 20.4, 6.4 Hz, 1H), 3.89 (ddt, J = 20.5, 4.3, 2.1 Hz, 1H), 3.18 (dd, J = 10.3, 5.6 Hz, 1H), 3.07 (dd, J = 10.3, 7.2 Hz, 1H), 2.66 (dt, J = 14.9, 2.5 Hz, 1H), 2.51 – 2.29 (m, 2H), 1.61 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.7, 136.5, 136.0, 134.0, 132.6, 131.3, 129.9, 129.6, 126.8, 126.6, 126.4, 124.4, 123.6, 120.8, 117.9, 115.4, 66.3, 39.6, 27.2, 25.4, 21.7 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{21}NNaO_3S$ $[M + Na]^+$ 390.1140, found 390.1141.

▸ NMR spectra on page 421.

(5,6,9,10-Tetrahydrocyclohepta[*b*]indol-9-yl)methanol (653).

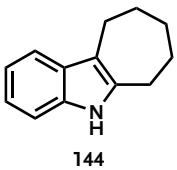


653

To cyclohepta[*b*]indole **623** (16.4 mg, 45 µmol, 1.0 eq.) in absolute MeOH (0.6 ml) was added NH_4Cl (8.5 mg, 159 µmol, 4.5 eq.) and magnesium turnings (17.2 mg, 706 µmol, 20.0 eq.). The reaction mixture was irradiated with ultrasonic at ambient temperature for 120 min before it was diluted with EtOAc and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over sodium sulfate and reduced *in vacuo*. The crude was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to obtain indole **653** as pale yellow foam (9.1 mg, 42.7 µmol, 96%). R_f = 0.24 (hexanes–EtOAc, 2:1, stains bordeaux with vanillin and bright red with Ehrlich's reagent). **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.61 – 7.54 (m, 1H), 7.30 – 7.18 (m, 2H), 7.10 – 7.03 (m, 1H), 6.32 (s, 1H), 5.77 (ddd, J = 11.3, 4.8, 2.4 Hz, 1H), 5.70 (dddd, J = 11.4, 6.3, 3.7, 1.5 Hz, 1H), 3.35 (dt, J = 10.8, 8.6 Hz, 2H), 3.26 (ddt, J = 21.4, 3.8, 2.0 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.83 (dd, J = 19.4, 6.2 Hz, 1H), 2.74 – 2.60 (m, 2H) ppm. **HRMS** (ESI): calcd. for $C_{14}H_{15}NNaO$ $[M + Na]^+$ 236.1051, found 236.1052.

▸ NMR spectra on page 422.

5,6,7,8,9,10-Hexahydrocyclohepta[*b*]indole (144).[399]

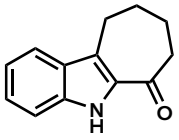


144

To phenylhydrazine (10.0 g, 92.5 mmol, 1.0 eq.) was added cycloheptanone (10.9 ml, 92.5 mmol, 1.0 eq.) and trichloroacetic acid (45.3 g, 277 mmol, 3.0 eq.) (caution, highly exothermic). The reaction mixture was carefully heated to 100 °C for 5 min. The mixture was cooled to ambient temperature and water was added. The mixture was filtered through a medium porosity sintered-glass funnel and the retentate was washed with an appropriate amount of water. Cyclohepta[*b*]indole **144** was obtained as pale rose solid in quantitative yield. **M.p.** 144 °C. **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.59 (ddt, J = 6.0, 3.4, 0.8 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.11 – 7.02 (m, 1H), 6.45 (br s, 1H), 2.84 – 2.68 (m, 2H), 2.41 – 2.30 (m, 2H), 1.76 – 1.60 (m, 4H), 1.62 – 1.51 (m, 2H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 136.9, 134.9, 130.1, 120.9, 119.4, 118.2, 113.8, 110.6, 32.2, 29.5, 29.2, 27.9, 25.1 ppm. **HRMS** (ESI): calcd. for $C_{13}H_{16}N$ $[M + H]^+$ 186.1283, found 186.1287.

▸ NMR spectra on page 423.

7,8,9,10-Tetrahydrocyclohepta[*b*]indol-6(5*H*)-one (666).[392]

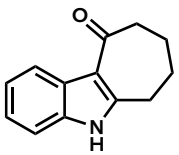


666

Cyclohepta[*b*]indole **144** (185 mg, 1.0 mmol, 1.0 eq.) was dissolved in THF–H_2O (4:1, 25.0 ml) and I_2O_5 (401 mg, 1.20 mmol, 1.2 eq.) was added. The resulting mixture was stirred 60 min at ambient temperature at which point the reaction mixture became dark orange. The solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and water. The layers were separated and the organic layer was additionally washed once with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine, respectively. Drying over sodium sulfate followed by flash column chromatography (hexanes–EtOAc, 5:1) afforded 6-oxo-cyclohepta[*b*]indole **666** as pale yellow solid (196 mg, 983 µmol, 98%). **M.p.** 147 °C. **^{1}H NMR** (400 MHz, C_6D_6) δ = 9.12 (br s, 1H), 7.51 (dd, J = 8.3, 1.1 Hz, 1H), 7.23 (ddd, J = 8.3, 6.9, 1.1 Hz, 1H), 7.09 – 7.05 (m, 2H), 2.71 – 2.67 (m, 2H), 2.57 – 2.53 (m, 2H), 1.53 (p, J = 6.1 Hz, 2H), 1.44 (ddt, J = 11.6, 8.0, 3.7 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 193.9, 137.1, 133.2, 128.5, 126.5, 123.8, 121.4, 120.1, 112.4, 43.0, 26.7, 25.7, 22.8 ppm. **HRMS** (ESI): calcd. for $C_{13}H_{13}NNaO$ $[M + Na]^+$ 222.0895, found 222.0898.

▸ *NMR spectra on page 424.*

6,7,8,9-Tetrahydrocyclohepta[*b*]indol-10(5*H*)-one (667).[515]

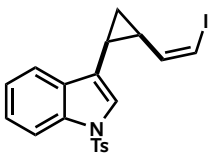


667

Cyclohepta[*b*]indole **144** (15.0 mg, 81 µmol, 1.0 eq.) was dissolved in THF–H_2O (9:1, 2.0 ml) and cooled to 0 °C. DDQ (36.8 mg, 162 µmol, 2.0 eq.) was added and the reaction mixture was stirred at this temperature for 2 h before it was diluted with CH_2Cl_2 and quenched by the addition of water. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain title compound **667** (14.4 mg, 97 µmol, 90%) as yellow solid. **M.p.** 218 °C. **HRMS** (ESI): calcd. for $C_{13}H_{13}NNaO$ $[M + Na]^+$ 222.0895, found 222.0898.

10.5 Experimental Part for Section 6.4

(*Z*)-3-(2-(2-Iodovinyl)cyclopropyl)-1-tosyl-1*H*-indole (675).



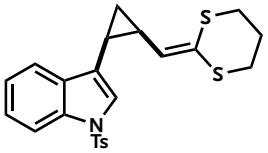
675

(Iodomethyl)triphenylphosphonium iodide (**678**, 620 mg, 1.17 mmol, 2.5 eq.) was dissolved in anhydrous THF (6.0 ml). NaHMDS (2.0 M in THF, 585 µl, 1.17 mmol, 2.5 eq.) was added dropwise at ambient temperature and stirred was continued for 5 min. The reaction mixture was then cooled to –78 °C and a solution of aldehyde **532** (159 mg, 468 µmol, 1.0 eq.) in anhydrous THF (2.5 ml) was added dropwise. After complete addition, the reaction mixture was stirred 30 min at –78 °C (monitored by TLC) and then additional 30 min at 0 °C before it was diluted with ether and quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue

was subjected to flash column chromatography (hexanes–EtOAc, 8:1) to obtain pure *(Z)*-vinyl iodide **675** (163 mg, 352 µmol, 75%) as colorless oil. R_f = 0.80 (hexanes–EtOAc, 2:1, stains dark blue with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.24 (dt, J = 8.3, 0.9 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.40 (dt, J = 7.8, 1.0 Hz, 1H), 7.32 (d, J = 1.4 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 6.45 (d, J = 8.1 Hz, 2H), 5.54 (dd, J = 7.5, 0.8 Hz, 1H), 4.99 (dd, J = 9.1, 7.5 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.75 (tdd, J = 8.2, 6.3, 1.5 Hz, 1H), 1.62 (s, 3H), 0.86 (td, J = 8.3, 4.9 Hz, 1H), 0.58 (dt, J = 6.3, 5.1 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 144.5, 140.7, 136.1, 136.0, 132.0, 129.8, 126.9, 125.4, 124.5, 123.7, 121.9, 120.4, 114.3, 80.2, 24.1, 21.0, 13.9, 12.0 ppm. **HRMS** (ESI): calcd. for $C_{20}H_{18}INNaO_2S$ $[M + Na]^+$ 486.0001, found 486.0005.

▸ NMR spectra on page 425.

3-(2-((1,3-Dithian-2-ylidene)methyl)cyclopropyl)-1-tosyl-1*H*-indole (694).



694

Diethyl (1,3-dithian-2-yl)phosphonate (**692**, 160 mg, 625 µmol, 4.0 eq.) was dissolved in anhydrous THF (0.5 ml) and cooled to –78 °C under an argon atmosphere. ^{n}BuLi (2.5 M in hexanes, 250 µl, 625 µmol, 4.0 eq.) was added dropwise to yield an bright yellow solution. The temperature was raised to 0 °C and the reaction mixture was stirred 40 min at this temperature. The reaction mixture was then cooled to –78 °C and a solution of aldehyde **532** (53 mg, 156 µmol, 1.0 eq.) in anhydrous THF (0.5 ml) was added dropwise. The resulting mixture was stirred 60 min at –78 °C (monitored by TLC), then additional 10 min at ambient temperature, and then diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The aqueous layer was extracted twice with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1) to obtain *S,S*-ketene acetal **694** as colorless oil (67.0 mg, 152 µmol, 97%). R_f = 0.72 (hexanes–EtOAc, 2:1, stains extensively with CAN). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.46 (ddd, J = 7.7, 1.4, 0.8 Hz, 1H), 7.20 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.15 – 7.09 (m, 3H), 5.06 (d, J = 9.1 Hz, 1H), 2.79 – 2.73 (m, 2H), 2.62 (dddd, J = 19.8, 13.3, 11.9, 5.9 Hz, 2H), 2.21 (s, 3H), 2.24 – 2.11 (m, 2H), 2.02 (dtd, J = 8.4, 6.8, 6.1, 4.4 Hz, 2H), 1.34 – 1.29 (m, 1H), 0.85 – 0.81 (m, 1H) ppm.[3] **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.8, 135.5, 135.2, 133.6, 131.9, 130.1, 130.0, 126.9, 126.8, 125.6, 124.9, 124.0, 123.3, 121.6, 120.0, 113.9, 30.6, 29.9, 25.4, 21.7, 18.8, 14.1, 13.1 ppm. **HRMS** (ESI): calcd. for $C_{23}H_{24}NO_2S_3$ $[M + H]^+$ 442.0969, found 442.0969.

▸ NMR spectra on page 426.

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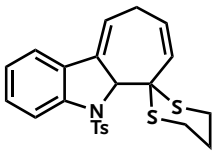
[3] One aromatic signal is missing due to overlapping with the solvent signal.

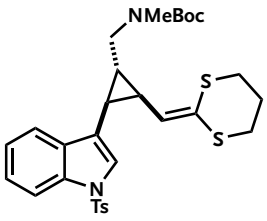
5-Tosyl-5a,9-dihydro-5*H*-spiro[cyclohepta[*b*]indole-6,2'-[1,3]dithiane] (695).



695

S,S-Ketene acetal **694** (40.0 mg, 90.6 µmol) was dissolved in PhH–DMSO (1:3, 4.0 ml) and was heated to 100 °C for 4 h (monitored by TLC). The solvent was removed *in vacuo* and the residue was subjected to a quick flash column chromatography (hexanes–EtOAc, 4:1) to afford pure cyclohepta[*b*]indole **695** as colorless oil (37.7 mg, 85.1 µmol, 94%) R_f = 0.71 (hexanes–EtOAc, 2:1, stains extensively with CAN). **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.98 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.04 – 6.97 (m, 1H), 6.88 (dd, J = 7.6, 1.4 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H), 6.48 (d, J = 8.0 Hz, 2H), 5.98 (dd, J = 12.2, 3.2 Hz, 1H), 5.87 (s, 1H), 5.64 (ddd, J = 8.2, 3.8, 2.0 Hz, 1H), 5.37 (ddd, J = 12.2, 7.9, 2.4 Hz, 1H), 3.97 – 3.86 (m, 1H), 2.94 – 2.82 (m, 1H), 2.60 (ddt, J = 14.1, 11.8, 3.9 Hz, 2H), 2.07 – 1.91 (m, 2H), 1.67 – 1.57 (m, 2H), 1.61 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 145.5, 143.6, 140.7, 134.6, 134.4, 133.6, 129.2, 128.7, 128.6, 128.2, 128.0, 126.1, 120.2, 120.1, 77.3, 51.1, 29.2, 28.8, 26.8, 24.1, 23.9, 21.0 ppm. **HRMS** (ESI): calcd. for $C_{23}H_{23}NNaO_2S_3$ $[M + Na]^+$ 464.0789, found 464.0791. ▸ *NMR spectra on page 428.*

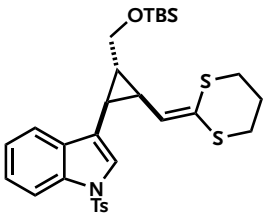
***tert*-Butyl ((2-((1,3-dithian-2-ylidene)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl)(methyl)carbamate (696).**



696

Diethyl (1,3-dithian-2-yl)phosphonate (**692**, 135 mg, 525 µmol, 2.5 eq.) was dissolved in anhydrous THF (0.4 ml) and cooled to –78 °C under an argon atmosphere. ^{n}BuLi (2.5 M in hexanes, 210 µl, 525 µmol, 2.5 eq.) was added dropwise to yield an bright yellow solution. The temperature was raised to 0 °C and the reaction mixture was stirred 30 min at this temperature to obtain an orange solution. The reaction mixture was then cooled to –78 °C and a solution of aldehyde **584** (101 mg, 210 µmol, 1.0 eq.) in anhydrous THF (0.4 ml) was added dropwise. The resulting mixture was stirred 45 min at –78 °C (monitored by TLC), then additional 10 min at ambient temperature, and then diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The aqueous layer was extracted twice with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes–EtOAc, 5:1 → 3:1) to obtain *S,S*-ketene acetal **696** as colorless oil (98.3 mg, 168 µmol, 80%). R_f = 0.59 (hexanes–EtOAc, 2:1, stains extensively with CAN). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.30 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.26 – 7.19 (m, 4H), 5.19 (d, J = 8.9 Hz, 1H), 3.50 (br s, 1H), 3.33 (dd, J = 14.5, 6.8 Hz, 1H), 2.97 (dtd, 3H), 2.87 (t, J = 5.9 Hz, 2H), 2.82 – 2.71 (m, 2H), 2.31 (s, 3H), 2.28 – 2.11 (m, 4H), 1.48 (s, 9H + 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 155.8, 144.9, 135.4, 135.1, 131.8, 131.7, 130.1, 126.8, 125.0, 123.9, 123.3, 119.8, 113.9, 79.8, 77.5, 52.1, 51.5, 34.8, 30.5, 29.8, 28.6, 25.8, 25.3, 24.8, 21.7, 19.7 ppm. **HRMS** (ESI): calcd. for $C_{30}H_{36}N_2NaO_4S_3$ $[M + Na]^+$ 607.1735, found 607.1741. ▸ *NMR spectra on page 429.*

3-(2-((1,3-Dithian-2-ylidene)methyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)-1-tosyl-1*H*-indole (698).

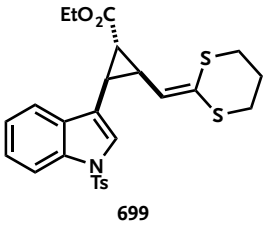


698

Diethyl (1,3-dithian-2-yl)phosphonate (**692**, 410 mg, 1.60 mmol, 4.0 eq.) was dissolved in anhydrous THF (2.0 ml) and cooled to –78 °C under an argon atmosphere. ^{n}BuLi (2.5 M in hexanes, 624 µl, 1.56 mmol, 3.9 eq.) was added dropwise to yield an bright yellow solution. The temperature was raised to 0 °C and the reaction mixture was stirred 30 min at this temperature to obtain an orange solution. The reaction mixture was then cooled to –78 °C and a solution of aldehyde **647** (193 mg, 400 µmol, 1.0 eq.) in anhydrous THF (1.0 ml) was added dropwise. The resulting mixture was stirred 45 min at –78 °C (monitored by TLC), then additional 10 min at ambient temperature, and then diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The aqueous layer was extracted twice with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1) to obtain *S,S*-ketene acetal **698** as colorless oil (183 mg, 312 µmol, 78%). R_f = 0.48 (hexanes–EtOAc, 4:1, stains extensively with CAN). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.03 – 7.88 (m, 1H), 7.80 – 7.60 (m, 3H), 7.39 – 7.12 (m, 5H), 5.26 (d, J = 8.0 Hz, 1H), 3.96 (dd, J = 10.7, 4.8 Hz, 1H), 3.63 (dd, J = 10.7, 6.4 Hz, 1H), 2.96 – 2.70 (m, 4H), 2.31 (s, 3H), 2.38 – 2.24 (m, 1H), 2.27 – 2.04 (m, 3H), 1.49 (t, J = 5.8 Hz, 1H), 0.93 (s, 9H), 0.10 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_{30}H_{39}NNaO_3S_3Si$ $[M + Na]^+$ 608.1759, found 608.1762.

▸ *NMR spectra on page 431.*

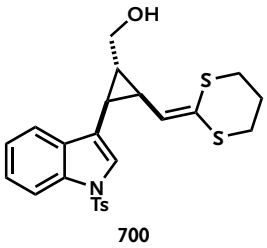
Ethyl 2-((1,3-dithian-2-ylidene)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (699).



699

Diethyl (1,3-dithian-2-yl)phosphonate (**692**, 69.8 mg, 272 µmol, 1.6 eq.) was dissolved in anhydrous THF (0.8 ml) and cooled to –78 °C under an argon atmosphere. ^{n}BuLi (2.5 M in hexanes, 102 µl, 255 µmol, 1.5 eq.) was added dropwise to yield an bright yellow solution. The temperature was raised to 0 °C and the reaction mixture was stirred 30 min at this temperature to obtain an orange solution. The reaction mixture was then cooled to –78 °C and a solution of racemic aldehyde **620** (70.0 mg, 170 µmol, 1.0 eq.) in anhydrous THF (0.5 ml) was added dropwise. The resulting mixture was stirred 180 min at –78 °C (monitored by TLC), then additional 15 min at ambient temperature, and then diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The aqueous layer was extracted twice with ether and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure to obtain crude *S,S*-ketene acetal **699** as pale yelow oil (71.9 mg, 140 µmol, 82%) which was directly used in the next steps. R_f = 0.55 (hexanes–EtOAc, 2:1, stain extensively with CAN, stains purple with vanillin). **HRMS** (ESI): calcd. for $C_{26}H_{28}NO_4S_3$ $[M + H]^+$ 514.1180, found 514.1183.

(2-((1,3-Dithian-2-ylidene)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methanol (700).

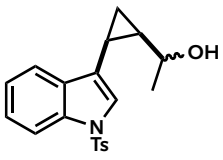


700

Ester **699** (37.0 mg, 72 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (0.4 ml) and cooled to –78 °C. DiBAL (1.0 M in hexanes, 180 µl, 180 µmol, 2.5 eq.) was added dropwise and the reaction mixture was stirred additional 2.0 h at –78 °C after complete addition. The reaction was diluted with CH_2Cl_2 and sat. aq. Rochelle's salt was added. The suspension was stirred vigorously for 60 min. The layers were separated and the aqueous layers was extracted once with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 1:1) to obtain pure alcohol **700** as white foam (21.4 mg, 45 µmol, 63%). R_f = 0.44 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.25 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 1.3 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 6.63 (d, J = 8.1 Hz, 2H), 5.43 (d, J = 8.9 Hz, 1H), 3.32 (dd, J = 11.2, 6.0 Hz, 1H), 3.26 (dd, J = 11.2, 6.3 Hz, 1H), 2.39 (ddd, J = 7.3, 5.0, 2.9 Hz, 2H), 2.28 (t, J = 6.0 Hz, 2H), 2.22 (td, J = 8.8, 5.0 Hz, 1H), 1.86 (ddd, J = 8.8, 5.8, 1.4 Hz, 1H), 1.67 (s, 3H), 1.54 (qd, J = 6.4, 1.4 Hz, 2H), 1.19 (p, J = 5.9 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 144.3, 144.1, 135.9, 135.8, 135.6, 135.6, 132.0, 131.4, 129.7, 129.6, 128.3, 127.9, 127.7, 127.2, 126.7, 126.6, 125.1, 124.9, 124.4, 124.3, 123.3, 123.3, 120.8, 120.5, 120.1, 120.0, 114.2, 114.1, 64.7, 64.3, 42.4, 33.6, 29.9, 29.3, 29.2, 27.0, 26.0, 24.9, 23.8, 23.5, 23.0, 20.8, 18.8, 18.7, 15.9 ppm.[4] **HRMS** (ESI): calcd. for $C_{24}H_{25}NNaO_3S_3$ $[M + Na]^+$ 494.0894, found 494.0895.

▸ *NMR spectra on page 431.*

1-(2-(1-Tosyl-1*H*-indol-3-yl)cyclopropyl)ethan-1-ol (838).



838

Aldehyde **532** (290 mg, 854 µmol, 1.0 eq.) was dissolved in anhydrous THF (4.2 ml) and the solution was cooled to 0 °C. Methylmagnesium bromide solution (3.0 M in ether, 356 µl, 1.07 mmol, 1.25 eq.) was added dropwise at 0 °C and the reaction mixture was stirred for 4 h at this temperature (monitored by TLC). The reaction was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain a diastereomeric mixture of alcohol **838** as pale yellow oil which was directly used in the next step. R_f = 0.40 (hexanes–EtOAc, 2:1, diastereomer I, stains blue with vanillin). R_f = 0.20 (hexanes–EtOAc, 2:1, diastereomer II, stains blue with vanillin).

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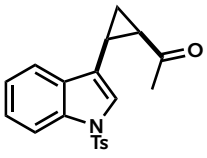
[4] Almost every signal appears twice.

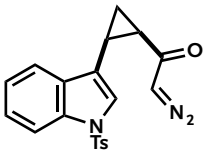
1-(2-(1-Tosyl-1*H*-indol-3-yl)cyclopropyl)ethan-1-one (708).



708

A crude diastereomeric mixture of alcohol **838** (854 µmol, 1.0 eq.) was dissolved in anhydrous DMSO (2.0 ml) and IBX (**604**, 420 mg, 1.5 mmol, 1.75 eq.) was added. The reaction mixture was stirred 4 h at ambient temperature (monitored by TLC) and then diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1) to obtain pure methyl ketone **708** as colorless oil (265 mg, 749 µmol, 88% over two steps). R_f = 0.40 (hexanes–EtOAc, 2:1, stains umber with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.89 (dt, J = 8.1, 0.9 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.53 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.36 (d, J = 1.1 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.23 – 7.18 (m, 3H), 2.60 – 2.47 (m, 2H), 2.31 (s, 3H), 1.92 (s, 3H), 1.76 (ddd, J = 7.2, 6.0, 4.8 Hz, 1H), 1.38 (ddd, J = 8.4, 7.5, 4.8 Hz, 1H) ppm. **HRMS** (ESI): calcd. for $C_{20}H_{19}NNaO_3S$ $[M + Na]^+$ 376.0983, found 376.0987. ▸ *NMR spectra on page 432.*

2-Diazo-1-(2-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)ethan-1-one (707).



707

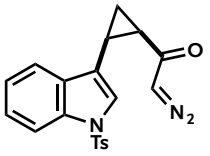
*Variant 1 (from aldehyde **532** via Pinnick–Lindgren oxidation and diazomethane):* Aldehyde **532** (147 mg, 433 µmol, 1.0 eq.) was dissolved in ^{t}BuOH (6.2 ml) at 25 °C and 2-methyl-2-butene (596 µl, 5.63 mmol, 13.0 eq.) was added. A solution of $NaClO_2$ (80%, 735 mg, 6.5 mmol, 15.0 eq.) and $NaH_2PO_4 \cdot 2\,H_2O$ (641 mg, 4.11 mmol, 9.5 eq.) in water (2.1 ml, ultrasonication may be required for complete dissolution of both salts) was added dropwise to the reaction mixture and stirring was continued for 30 min at ambient temperature (monitored by TLC). The reaction mixture was diluted with ether and brine was added. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure at 20 °C (important, higher temperatures led to rapid decarboxylation and decomposition) to obtain crude carboxylic acid **705** as white foam which was directly used in the next step. R_f = 0.15 (hexanes–EtOAc, 2:1, carboxylic acid, stains dark red with vanillin).

The crude carboxylic acid was taken up in anhydrous CH_2Cl_2 (0.5 ml) and triphenylphosphine (226 mg, 860 µmol, 2.0 eq.) was added in one portion at ambient temperature. Trichloroacetonitrile (86 µl, 860 µmol, 2.0 eq.) was added dropwise at which the color of the solution turned from yellow to dark orange. After 60 min (monitored by TLC), the reaction mixture was filtered over a plug of celite and the solvent was removed *in vacuo* to obtain acid chloride **706** was yellow oil. R_f = 0.75 (hexanes–EtOAc, 2:1, acid chloride, stains brownish blue with vanillin).

The crude acid chloride was dissolved in a small amount of ether and added dropwise to a solution of diazomethane (**839**, approx. 0.3 M, excess) at 0 °C. The ice-bath was removed and the reaction mixture was stirred for additional 12 h at ambient temperature. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to

obtain α-diazo compound **707** as yellow oil (37 mg, 97.5 µmol, 23% over three steps, contained impurities). R_f = 0.21 (hexanes–EtOAc, 2:1, stains purple with vanillin). **IR** (neat): 3106, 2100 (C=N_2), 1631, 1446, 1396, 1365, 1327, 1172, 1124, 1092, 748, 629 cm^{-1}. **HRMS** (ESI): calcd. for $C_{20}H_{17}N_3NaO_3S$ $[M + Na]^+$ 402.0888, found 402.0885.

2-Diazo-1-(2-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)ethan-1-one (707).[420]



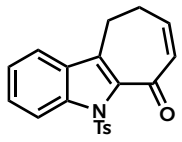
707

*Variant 2: from methyl ketone **708**:* Bis(trimethylsilyl)amine (62 µl, 299 µmol, 1.1 eq.) was dissolved in anhydrous THF (0.8 ml) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 120 µl, 299 µmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred 10 min at 0 °C before it was cooled down to –78 °C. A solution of methyl ketone **708** (96.0 mg, 272 µmol, 1.0 eq.) in anhydrous THF (0.6 ml) was added dropwise *via* syringe pump over a period of 15 min and the reaction mixture was stirred additional 60 min after complete addition at which point the solution turned dark red. 2,2,2-Trifluoroethyl 2,2,2-trifluoroacetate (**840**, 44 µl, 326 µmol, 1.2 eq.) was added quickly in one portion (important!) and the reaction mixture was stirred additional 10 min at –78 °C at which point the solution turned bright yellow. The solution was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. R_f = 0.49 (hexanes–EtOAc, 2:1, stains bright red with vanillin).

The intermediate was immediately dissolved in anhydrous MeCN (1.0 ml). H_2O (5 µl, 272 µmol, 1.0 eq.) and Et_3N (57 µl, 408 µmol, 1.5 eq.) were added at ambient temperature. A solution of MsN_3 (**841**, 36 µl, 408 µmol, 1.5 eq.) in anhydrous MeCN (1.0 ml) was added *via* syringe pump over a period of 30 min and the reaction mixture was stirred additional 50 min after complete addition (monitored by TLC). The reaction mixture was then diluted with ether and 10% NaOH was added. The layers were separated, the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to obtain pure α-diazo ketone **707** as yellow foam (74.5 mg, 196 µmol, 72%). R_f = 0.21 (hexanes–EtOAc, 2:1, stains purple with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.22 – 8.17 (m, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.65 (s, 1H), 7.37 – 7.32 (m, 1H), 7.15 – 7.02 (m, 2H), 6.63 (d, J = 7.6 Hz, 2H), 4.16 (br s, 1H), 1.96 – 1.86 (m, 1H), 1.68 (s, 3H), 1.73 – 1.65 (m, 1H), 1.52 – 1.41 (m, 1H), 0.86 – 0.78 (m, 1H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 144.3, 135.9, 135.8, 132.3, 129.8, 127.2, 125.9, 124.9, 123.3, 119.1, 118.0, 114.4, 27.6, 21.1, 17.9, 11.5 ppm. **IR** (neat): 3106, 2100 (C=N_2), 1631, 1446, 1396, 1365, 1327, 1172, 1124, 1092, 748, 629 cm^{-1}. **HRMS** (ESI): calcd. for $C_{20}H_{17}N_3NaO_3S$ $[M + Na]^+$ 402.0888, found 402.0885.

▸ *NMR spectra on page 433.*

5-Tosyl-9,10-dihydrocyclohepta[*b*]indol-6(5*H*)-one (671).

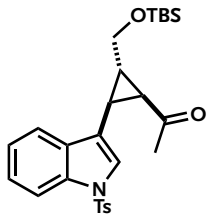


671

α-Diazo ketone **707** (15.0 mg, 39.5 µmol, 1.0 eq.) was dissolved in anhydrous THF (3.0 ml) and silver(I) oxide (0.5 mg, 2.0 µmol, 5 mol %) was added. The resulting suspension was stirred at 60 °C for 2 h, then filtered over celite. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography to afford cyclohepta[*b*]indolone **671** as white solid (11.7 mg, 33 µmol 84%). R_f = 0.55 (hexanes–EtOAc, 2:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.40 (dd, J = 8.5, 0.9 Hz, 1H), 8.33 – 8.28 (m, 2H), 7.29 (dt, J = 8.0, 1.0 Hz, 1H), 7.25 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.03 (ddd, J = 8.1, 7.1, 0.9 Hz, 1H), 6.76 (d, J = 8.2 Hz, 2H), 6.34 (dd, J = 10.8, 1.2 Hz, 1H), 5.85 (dt, J = 10.8, 6.2 Hz, 1H), 2.53 – 2.46 (m, 2H), 1.90 (dtd, J = 7.2, 6.1, 1.2 Hz, 2H), 1.80 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 191.2, 144.1, 138.6, 135.5, 129.5, 128.6, 128.2, 127.9, 123.6, 121.0, 120.4, 116.1, 42.5, 23.1, 21.2, 1.4 ppm.[5] **HRMS** (ESI): calcd. for $C_{20}H_{18}NO_3S$ $[M + H]^+$ 352.1007, found 352.1009.

▸ *NMR spectra on page 435.*

1-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)ethan-1-one (721).



721

Aldehyde **647** (530 mg, 1.10 mmol, 1.0 eq.) was dissolved in anhydrous THF (5.5 ml) and the solution was cooled down to 0 °C. Methylmagnesium bromide solution (3.0 M in ether, 500 µl, 1.42 mmol, 1.25 eq.) was added dropwise at 0 °C and the reaction mixture was stirred for 60 min at this temperature (monitored by TLC). The reaction was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain a diastereomeric mixture of alcohol **718** as pale yellow oil which was directly used in the next step. R_f = 0.31 (hexanes–EtOAc, 4:1, diastereomer I, stains dark blue with vanillin). R_f = 0.56 (hexanes–EtOAc, 4:1, diastereomer II stains dark blue with vanillin).

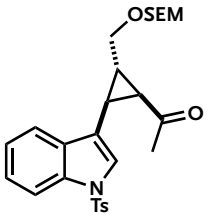
A crude diastereomeric mixture of alcohol **718** (1.10 mmol, 1.0 eq.) was dissolved in anhydrous DMSO (3.3 ml) and IBX (**604**, 560 mg, 2.0 mmol, 1.8 eq.) was added. The reaction mixture was stirred 2 h at ambient temperature (monitored by TLC) and then diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1) to obtain pure methyl ketone **721** as colorless oil (410 mg, 824 µmol, 75% over two steps). R_f = 0.60 (hexanes–EtOAc, 4:1 stains brown vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.89 (dt, J = 8.2, 1.1 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.56 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.35 (d, J = 1.1 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.21 – 7.18 (m, 3H), 3.87 (dd, J = 10.7, 4.5 Hz, 1H), 3.78 (dd, J = 10.7, 4.8 Hz, 1H), 2.59 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 2.48 (dd, J = 9.1, 5.3 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.31 (s, 3H), 1.96 (s, 3H),

[5] Some ^{13}C signals are overlapped by the solvent signal.

0.92 (s, 9H), 0.09 (d, J = 0.9 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 202.9, 144.7, 135.3, 135.1, 131.7, 130.0, 129.8, 129.8, 127.0, 126.9, 125.2, 124.7, 123.2, 119.1, 117.5, 113.9, 62.5, 33.0, 31.2, 27.4, 26.1, 26.0, 22.3, 21.7, 18.5, –5.1, –5.1 ppm. **HRMS** (ESI): calcd. for $C_{27}H_{35}NNaO_4SSi$ $[M + Na]^+$ 520.1954, found 520.1959.

▸ NMR spectra on page 436.

1-(2-(1-Tosyl-1*H*-indol-3-yl)-3-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)cyclopropyl)ethan-1-one (723).



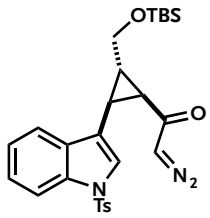
723

Aldehyde **644** (330 mg, 660 µmol, 1.0 eq.) was dissolved in anhydrous THF (3.3 ml) and the solution was cooled to 0 °C. Methylmagnesium bromide solution (3.0 M in ether, 660 µl, 1.98 mmol, 3.0 eq.) was added dropwise at 0 °C and the reaction mixture was stirred for 35 min at this temperature (monitored by TLC). The reaction was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain a diastereomeric mixture of alcohol **720** as pale yellow oil which was directly used in the next step. R_f = 0.10 (hexanes–EtOAc, 2.5:1, diastereomer I, stains dark purple with vanillin). R_f = 0.40 (hexanes–EtOAc, 2.5:1, diastereomer II stains dark purple with vanillin).

A crude diastereomeric mixture of alcohol **720** (318 mg, 620 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (3.1 ml). Cornforth reagent (696 mg, 1.85 mmol, 3.0 eq.) and molecular sieves (3 Å, 540 mg) were added. The resulting mixture was stirred 14 h at ambient temperature (monitored by TLC) before it was diluted with ether and filtered through a plug of silica (3 cm). The filtrate was reduced, diluted with ether and once again filtered through a plug of silica (3 cm). Evaporation of the solvent yielded crude ketone **723** which was purified *via* flash column chromatography (hexanes–EtOAc, 4:1) to afford pure title compound **723** as yellow oil (237 mg, 461 µmol, 75% over two steps). R_f = 0.50 (hexanes–EtOAc, 2.5:1 stains dark blue vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.20 (dt, J = 8.1, 0.9 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.67 (d, J = 1.2 Hz, 1H), 7.38 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.05 (td, J = 7.5, 1.1 Hz, 1H), 6.59 (d, J = 7.9 Hz, 2H), 4.60 (s, 2H), 3.65 (td, J = 8.1, 1.0 Hz, 2H), 3.48 (dd, J = 10.6, 5.7 Hz, 1H), 3.39 (dd, J = 10.6, 6.0 Hz, 1H), 2.42 (dq, J = 6.8, 5.8 Hz, 1H), 2.26 (ddd, J = 9.1, 6.8, 1.2 Hz, 1H), 2.06 (dd, J = 9.1, 5.3 Hz, 1H), 1.63 (s, 3H), 1.54 (s, 3H), 1.00 – 0.96 (m, 2H), 0.00 (s, 9H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 200.8, 144.2, 136.0, 135.8, 132.0, 129.9, 129.8, 128.6, 127.2, 126.1, 124.9, 123.4, 119.2, 117.5, 114.5, 95.1, 68.5, 65.5, 34.0, 30.7, 25.1, 23.2, 21.0, 18.3, –1.3 ppm. **HRMS** (ESI): calcd. for $C_{27}H_{35}NNaO_5SSi$ $[M + Na]^+$ 536.1903, found 536.1901.

▸ NMR spectra on page 438.

1-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)-2-diazoethan-1-one (724).



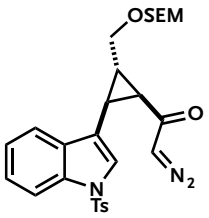
724

Bis(trimethylsilyl)amine (181 µl, 860 µmol, 1.1 eq.) was dissolved in anhydrous THF (2.2 ml) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 344 µl, 860 µmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred 10 min at 0 °C before it was cooled down to –78 °C. A solution of methyl ketone **721** (389 mg, 782 µmol, 1.0 eq.) in anhydrous THF (1.6 ml) was added dropwise *via* syringe pump over a period of 15 min and the reaction mixture was stirred additional 60 min after complete addition at which point the solution turned dark yellow. 2,2,2-Trifluoroethyl 2,2,2-trifluoroacetate (**840**, 126 µl, 938 µmol, 1.2 eq.) was added quickly in one portion (important!) and the reaction mixture was stirred additional 10 min at –78 °C at which point the solution turned bright yellow. The solution was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. R_f = 0.55 (hexanes–EtOAc, 4:1).

The intermediate was immediately dissolved in anhydrous MeCN (2.6 ml). H_2O (14 µl, 782 µmol, 1.0 eq.) and Et_3N (163 µl, 1.17 mmol, 1.5 eq.) were added at ambient temperature. A solution of MsN_3 (**841**, 101 µl, 1.17 mmol, 1.5 eq.) in anhydrous MeCN (3.0 ml) was added *via* syringe pump over a period of 30 min and the reaction mixture was stirred additional 60 min after complete addition (monitored by TLC). The reaction mixture was then diluted with ether and 10% NaOH was added. The layers were separated, the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 8:1) to obtain pure α-diazo ketone **724** as yellow oil (205 mg, 391 µmol, 56% brsm). R_f = 0.35 (hexanes–EtOAc, 4:1, stains purple with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.22 (dt, J = 8.3, 0.9 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.73 (s, 1H), 7.56 – 7.50 (m, 1H), 7.14 – 7.09 (m, 1H), 7.07 (td, J = 7.4, 1.3 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 4.25 (br s, 1H), 3.51 (d, J = 3.8 Hz, 2H), 2.44 – 2.33 (m, 2H), 1.92 (br s, 1H), 1.68 (s, 3H), 0.97 (s, 9H), 0.03 (d, J = 3.3 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 187.8, 171.1, 144.3, 135.9, 135.8, 132.3, 129.9, 129.9, 129.8, 128.6, 127.2, 125.9, 124.9, 123.4, 119.3, 117.7, 114.4, 62.5, 26.1, 26.1, 26.1, 21.1, 18.5, –5.2 ppm. **HRMS** (ESI): calcd. for $C_{27}H_{33}N_3NaO_4SSi$ $[M + Na]^+$ 546.1859, found 546.1857.

▸ *NMR spectra on page 439.*

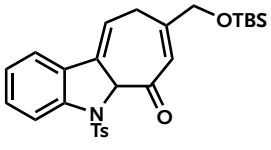
2-Diazo-1-(2-(1-tosyl-1*H*-indol-3-yl)-3-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)cyclopropyl)-ethan-1-one (725).



725

Bis(trimethylsilyl)amine (27 µl, 128 µmol, 1.2 eq.) was dissolved in anhydrous THF (0.3 ml) and cooled to 0 °C. ^{n}BuLi (2.5 M in hexanes, 51 µl, 128 µmol, 1.2 eq.) was added dropwise and the reaction mixture was stirred 10 min at 0 °C before it was cooled to –78 °C. A solution of methyl ketone **723** (55.0 mg, 107 µmol, 1.0 eq.) in anhydrous THF (0.2 ml) was added dropwise *via* syringe pump over a period of 15 min and the reaction mixture was stirred additional 60 min after complete addition at which point the solution turned brown. 2,2,2-Trifluoroethyl 2,2,2-trifluoroacetate (**840**, 19 µl, 139 µmol, 1.3 eq.) was added quickly in one portion (important!) and the reaction mixture was stirred additional 10 min at –78 °C at which point the solution turned bright yellow. The solution was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. R_f = 0.57 (hexanes–EtOAc, 3:1, stains light brown with vanillin). The intermediate was immediately dissolved in anhydrous MeCN (0.4 ml). H_2O (2 µl, 107 µmol, 1.0 eq.) and Et_3N (22 µl, 161 mmol, 1.5 eq.) were added at ambient temperature. A solution of MsN_3 (**841**, 14 µl, 161 mmol, 1.5 eq.) in anhydrous MeCN (3.0 ml) was added *via* syringe pump over a period of 30 min and the reaction mixture was stirred additional 60 min after complete addition (monitored by TLC). The reaction mixture was then diluted with ether and 10% NaOH was added. The layers were separated, the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1) to obtain pure α-diazo ketone **725** as yellow foam (30.0 mg, 55 µmol, 51%). R_f = 0.54 (hexanes–EtOAc, 3:1, stains dark brown with vanillin). **^{1}H NMR** (200 MHz, C_6D_6) δ = 8.28 – 8.13 (m, 1H), 7.79 (d, J = 8.3 Hz, 3H), 7.72 (s, 2H), 7.53 – 7.38 (m, 1H), 7.17 – 7.01 (m, 6H), 6.64 (d, J = 8.1 Hz, 2H), 4.60 (s, 2H), 4.24 (s, 1H), 3.74 – 3.56 (m, 2H), 3.60 – 3.33 (m, 2H), 2.52 (p, J = 5.7 Hz, 1H), 2.36 – 2.19 (m, 1H), 1.82 (s, 1H), 1.69 (s, 3H), 1.07 – 0.89 (m, 3H), 0.00 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{27}H_{33}N_3NaO_5SSi$ $[M + Na]^+$ 562.1808, found 562.1812. ▸ *NMR spectra on page 441.*

8-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-tosyl-5a,9-dihydrocyclohepta[b]indol-6(5*H*)-one (726).



726

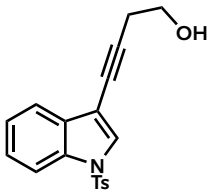
α-Diazo ketone **724** (14.0 mg, 26.7 µmol) was dissolved in dichlorobenzene (1.0 ml) and heated to 180 °C for 60 min. The reaction mixture was subjected to flash column chromatography (hexanes–EtOAc, 7:1) to obtain undesired title compound **726** as yellow oil which was additionally purified *via* HPLC. R_f = 0.52 (hexanes–EtOAc, 5:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.41 (d, J = 8.5 Hz, 1H), 8.37 – 8.30 (m, 2H), 7.58 (d, J = 7.9 Hz, 1H), 7.36 (s, 1H), 7.25 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.09 – 7.00 (m, 1H), 6.96 (s, 1H), 6.81 – 6.74

(m, 3H), 3.92 (d, J = 1.9 Hz, 2H), 2.53 – 2.50 (m, 1H), 1.95 – 1.87 (m, 1H), 1.81 (s, 3H), 1.00 (s, 9H), 0.05 (s, 6H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 191.2, 146.2, 144.0, 139.7, 138.7, 136.2, 129.5, 128.7, 127.4, 126.5, 123.7, 121.2, 116.2, 115.6, 94.5, 70.9, 65.6, 42.5, 30.2, 24.7, 21.2, 18.3, –1.3 ppm. **HRMS** (ESI): calcd. for $C_{27}H_{33}NNaO_4SSi$ $[M + Na]^+$ 518.1797, found 518.1792.

▸ NMR spectra on page 442.

10.6 Experimental Part for Section 6.5

4-(1-Tosyl-1*H*-indol-3-yl)but-3-yn-1-ol (738).

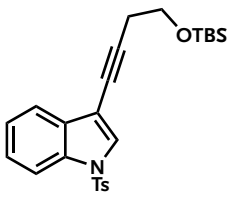


738

3-Iodo-1-tosyl-1*H*-indole (**606**, 8.20 g, 20.6 mmol, 1.0 eq.) was dissolved in diethylamine (41.3 ml) and the resulting solution was degassed (ultrasonication plus argon). $Pd(PPh_3)_2Cl_2$ (290 mg, 413 µmol, 2 mol %) and copper(I) iodide (161 mg, 826 µmol, 4 mol %) were added and the reaction mixture was heated to 60 °C. But-3-yn-1-ol (1.8 ml, 22.7 mmol, 1.1 eq.) was added and stirring was continued for 120 min (monitored by TLC). The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2. Silica was added and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2.5:1 → 1:1) to obtain pure alcohol **738** (6.49 g, 19.1 mmol, 93%) as white powder. R_f = 0.26 (hexanes–EtOAc, 3:1, stains bright orange with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (d, J = 8.4 Hz, 1H), 7.79 – 7.69 (m, 3H), 7.63 (d, J = 7.7 Hz, 1H), 7.35 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.28 (td, J = 7.5, 1.1 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 3.86 (t, J = 6.4 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.45 (br s, 1H), 2.28 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.3, 134.8, 134.1, 131.0, 130.0, 128.6, 126.8, 125.4, 123.7, 120.5, 113.6, 105.5, 91.2, 73.1, 61.2, 24.0, 21.5 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{17}NNaO_3S$ $[M + Na]^+$ 362.0827, found 362.0830.

▸ NMR spectra on page 443.

3-(4-((*tert*-Butyldimethylsilyl)oxy)but-1-yn-1-yl)-1-tosyl-1*H*-indole (742).



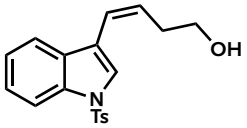
742

3-Iodo-1-tosyl-1*H*-indole (**606**, 15.0 g, 37.8 mmol, 1.0 eq.) was dissolved in diethylamine (68.7 ml) and the resulting solution was degassed (ultrasonication plus argon). $Pd(PPh_3)_2Cl_2$ (540 mg, 755 µmol, 2 mol %) and copper(I) iodide (294 mg, 1.51 mmol, 4 mol %) were added and the reaction mixture was heated to 60 °C. TBS-protected but-3-yn-1-ol (7.31 g, 39.7 mmol, 1.05 eq.) was added and stirring was continued for 90 min (monitored by TLC). The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2. Silica was added and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (pentane–ether, 20:1 → 15:1 → 10:1) to obtain pure alkyne **742** (15.4 g, 34.0 mmol, 90%) as off-white powder. R_f = 0.24 (pentane–ether, 20:1, stains orange with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.97 (dt, J = 8.3, 0.9 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.66 (s, 1H), 7.62 (ddd, J = 7.7, 1.4, 0.7 Hz, 1H), 7.34 (ddd, J = 8.4, 7.3, 1.4 Hz,

1H), 7.27 (ddd, J = 7.7, 7.2, 1.1 Hz, 1H), 7.22 – 7.18 (m, 2H), 3.85 (t, J = 7.0 Hz, 2H), 2.70 (t, J = 7.0 Hz, 2H), 2.32 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.3, 135.1, 134.3, 131.2, 130.0, 128.5, 127.0, 125.4, 123.7, 120.6, 113.7, 105.9, 91.7, 72.5, 62.0, 26.0, 24.2, 21.7, 18.5, –5.1 ppm. **HRMS** (ESI): calcd. for $C_{25}H_{32}NO_3SSi$ $[M + H]^+$ 454.1872, found 454.1873.

▸ NMR spectra on page 444.

(*Z*)-4-(1-Tosyl-1*H*-indol-3-yl)but-3-en-1-ol (739).

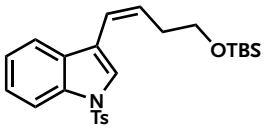


739

To anhydrous methanol (28.0 ml) was added $Pd/CaCO_3$ (5%, 141.1 mg, 66 µmol, 1.5 mol %) and quinoline (390 µl, 3.32 mmol, 0.75 eq.). The resulting suspension was stirred vigorously for 30 min at ambient temperature. Alkyne **738** (1.50 g, 4.42 mmol, 1.0 eq.) was added in one portion and the reaction mixture was hydrogenated ($p(H_2)$ =120 psi) at ambient temperature for 3 h. TLC analysis indicated, that only a small amount of material was hydrogenated to the alkane. The reaction mixture was filtered over celite and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to obtain pure *(Z)*-alcohol **739** (1.25 g, 3.66 mmol, 83%) as colorless oil. R_f = 0.15 (hexanes–EtOAc, 3:1, stains purple with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (dt, J = 8.3, 0.9 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.61 (s, 1H), 7.52 (dt, J = 7.5, 1.0 Hz, 1H), 7.33 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.24 – 7.19 (m, 2H), 6.56 (dtd, J = 11.4, 1.9, 1.0 Hz, 1H), 5.87 (dt, J = 11.4, 7.1 Hz, 1H), 3.81 (t, J = 6.4 Hz, 2H), 2.61 (qd, J = 6.4, 1.8 Hz, 2H), 2.33 (s, 3H), 1.56 (br s, 1H) ppm. **HRMS** (ESI): calcd. for $C_{19}H_{19}NNaO_3S$ $[M + Na]^+$ 364.0983, found 364.0983.

▸ NMR spectra on page 445.

(*Z*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)but-1-en-1-yl)-1-tosyl-1*H*-indole (740).



740

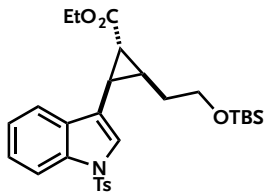
Variant 1 (via Wittig olefination): (3-((*tert*-Butyldimethylsilyl)oxy)propyl)triphenylphosphonium bromide (**743**, 4.00 g, 7.76 mmol, 1.72 eq.) was dissolved in anhydrous THF (26.0 ml) and cooled to –78 °C. KHMDS (0.5 M in PhMe, 15.2 ml, 7.60 mmol, 1.69 eq.) was added dropwise and the reaction mixture was then stirred additional 10 min at –78 °C, then 30 min at 0 °C and then again 10 min at –78 °C to yield a bright orange solution. A solution of aldehyde **526** (1.35 g, 4.51 mmol, 1.0 eq.) in anhydrous THF (14.0 ml) was added dropwise to the reaction mixture and stirring was continued for additional 70 min at –78 °C, then 3 h at –15 °C and then 18 h at ambient temperature. The reaction mixture was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 15:1) to obtain pure *(Z)*-olefine **740** as colorless oil (395 mg, 866 µmol, 19%).
*Variant 2 (via TBS protection of alcohol **739**):* To alcohol **739** (838 mg, 2.45 mmol, 1.0 eq.) in

anhydrous DMF (4.1 ml) was added TBSCl (444 mg, 2.95 mmol, 1.2 eq.) and imidazole (418 mg, 6.14 mmol, 2.5 eq.) at ambient temperature. The reaction mixture was stirred 2 h at this temperature. Ether and brine were added and the mixture was stirred 20 min vigorously. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were extracted once with water and once with brine, then dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 15:1)) to obtain pure **740** as colorless oil (1.03 g, 2.26 mmol, 92%).

*Variant 3 (via) hydrogenation of alkyne **742**:* To anhydrous methanol (7.0 ml) was added Pd/$CaCO_3$ (5%, 30.6 mg, 14 µmol, 1 mol %) and quinoline (34 µl, 287 µmol, 0.2 eq.). The resulting suspension was stirred vigorously for 30 min at ambient temperature. Alkyne **742** (652 mg, 1.44 mmol, 1.0 eq.) was added in one portion and the reaction mixture was hydrogenated ($p(H_2)$ =150 psi) at ambient temperature for 5 h. TLC analysis indicated, that only a small amount of material was hydrogenated to the alkane. The reaction mixture was filtered over celite and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (pentane–ether, 95:5) to obtain pure *(Z)*-olefine **740** (600 mg, 1.32 mmol, 92%) as colorless oil. R_f = 0.65 (hexanes–EtOAc, 9:1, stains pink with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.99 (dt, J = 8.3, 0.9 Hz, 1H), 7.79 – 7.75 (m, 2H), 7.58 (s, 1H), 7.52 (ddd, J = 7.8, 1.3, 0.7 Hz, 1H), 7.32 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.23 – 7.19 (m, 2H), 6.49 (dtd, J = 11.5, 1.8, 1.0 Hz, 1H), 5.87 (dt, J = 11.4, 7.0 Hz, 1H), 3.77 (t, J = 6.5 Hz, 2H), 2.54 (qd, J = 6.6, 1.9 Hz, 2H), 2.33 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.0, 135.4, 134.8, 131.1, 131.0, 130.0, 126.9, 125.0, 123.7, 123.4, 119.7, 119.2, 119.2, 113.7, 62.7, 60.5, 33.5, 26.1, 21.7, 21.2, 18.6, 14.4, –5.1 ppm. **HRMS** (ESI): calcd. for $C_{25}H_{33}NNaO_3SSi$ $[M + Na]^+$ 478.1848, found 478.1850.

▸ *NMR spectra on page 446.*

Ethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (744).



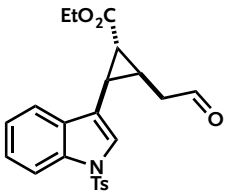
744

A flame-dried Schlenk tube was charged with [Cu(OTf)] · PhH (30.9 mg, 61 µmol, 2 mol %) and olefine **740** (1.40 g, 3.07 mmol, 1.0 eq.) in the glovebox. The tube was flushed with argon and freeze-pump-thaw degassed CH_2Cl_2 (2.0 ml) was added. A solution of ethyl diazoacetate (commercial, contains ≥13 wt. % dichloromethane; 1.1 ml, 10.8 mmol, 3.5 eq.) in freeze-pump-thaw degassed CH_2Cl_2 (15.0 ml) was added *via* syringe pump over 12 h at ambient temperature (N_2 evolution) at which the solution became orange. The solution was filtered over a plug of celite to afford a clear yellow solution. The solvent was removed under reduced pressure to obtain crude **744** as yellow oil which was subjected to flash column chromatography (pentane–ether, 95:5 → 90:10) to obtain pure cyclopropane **772** (880 mg, 1.62 mmol, 53%) as pale yellow oil (the diastereomer was obtained in 17% yield). R_f = 0.72 (hexanes–EtOAc, 4:1, minor diastereomer). R_f = 0.67 (hexanes–EtOAc, 4:1, major diastereomer). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.98 (dt, J = 8.3, 0.9 Hz, 1H), 7.77 –

7.73 (m, 2H), 7.60 (ddd, J = 7.7, 1.3, 0.8 Hz, 1H), 7.35 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.30 (d, J = 1.3 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.23 (d, J = 8.0 Hz, 2H), 4.28 (q, J = 7.2 Hz, 1H), 4.22 (qd, J = 7.2, 0.6 Hz, 2H), 3.51 (qt, J = 10.0, 6.3 Hz, 2H), 2.65 (ddd, J = 9.3, 4.9, 1.4 Hz, 1H), 2.35 (s, 3H), 1.94 (dddd, J = 9.3, 7.9, 6.2, 4.8 Hz, 1H), 1.88 (t, J = 4.8 Hz, 1H), 1.48 – 1.43 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 0.85 (s, 9H), –0.06 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.4, 145.0, 135.4, 135.3, 131.5, 130.0, 129.9, 126.9, 125.2, 123.9, 123.4, 119.8, 119.2, 113.9, 62.4, 61.0, 30.8, 26.0, 25.6, 25.2, 21.7, 21.6, 18.4, 14.4, –5.4 ppm. **HRMS** (ESI): calcd. for $C_{29}H_{39}NNaO_5SSi$ $[M + Na]^+$ 564.2216, found 564.2220.

▸ NMR spectra on page 447.

Ethyl 2-(2-oxoethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (745).



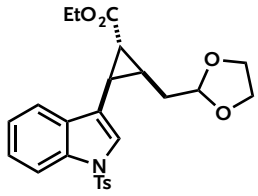
745

Variant 1: A solution of silyl alcohol **772** (275 mg, 510 µmol, 1.0 eq.) in anhydrous THF (2.5 ml) was added dropwise to HF · pyr. (20% *w/w*, 2.5 ml) at 0 °C. The reaction mixture was stirred 120 min at 0 °C and 20 min at ambient temperature (monitored by TLC) before it was diluted with EtOAc and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were extracted once with 1 M HCl and the organic layer was dried over magnesium sulfate. The solvents were removed under reduced pressure and the crude was dissolved in CH_2Cl_2 (2.6 ml). Dess–Martin periodinane (**603**, 270 mg, 638 µmol, 1.25 eq.) and $NaHCO_3$ (429 mg, 5.10 mmol, 10.0 eq.) were added and the reaction mixture was stirred 60 min at ambient temperature (monitored by TLC). The reaction mixture was diluted with CH_2Cl_2 and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting crude was subjected to flash column chromatography (hexanes–EtOAc, 3:1) to obtain aldehyde **745** (152 mg, 357 µmol, 70% over two steps) as white foam.

Variant 2: (Methoxymethyl)triphenylphosphonium chloride (195 mg, 570 µmol, 3.5 eq.) was dissolved in anhydrous THF (3.5 ml) and cooled to –78 °C. KHMDS (0.5 M in PhMe, 1.1 ml, 562 µmol, 3.45 eq.) was added dropwise and the resulting solution was stirred 10 min at –78 °C and additional 30 min at 0 °C to obtain a dark red solution. A solution of aldehyde **620** (67.0 mg, 163 µmol, 1.0 eq.) in anhydrous THF (1.0 ml) was added dropwise at 0 °C and the reaction mixture was stirred for 2 h at this temperature (monitored by TLC). The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl/5% HCl (2:1). The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were extracted once with brine and dried over sodium sulfate. The solvent was evaporated *in vacuo* (below 30 °C) and the residue was dissolved in THF (5.0 ml) and cooled to 0 °C. 12 N HCl/THF (1:1, 0.8 ml) were added dropwise at this temperature and stirring was continued for additional 100 min. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with EtOAc. The

combined organic layers were extracted once with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 3:1) to obtain aldehyde **745** (40.2 mg, 94 µmol, 58%) as white foam. R_f = 0.31 (hexanes–EtOAc, 3:1, CAN). **^{1}H NMR** (400 MHz, C_6D_6) δ = 9.35 (s, 1H), 8.34 (dt, J = 8.3, 0.9 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.69 (d, J = 1.4 Hz, 1H), 7.39 (dt, J = 7.8, 1.0 Hz, 1H), 7.24 (dd, J = 8.3, 1.3 Hz, 1H), 7.15 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 6.66 (dd, J = 8.7, 0.7 Hz, 2H), 3.99 – 3.88 (m, 2H), 2.72 (ddd, J = 19.1, 8.5, 0.6 Hz, 1H), 2.33 (ddd, J = 19.1, 5.9, 0.8 Hz, 1H), 2.07 – 1.99 (m, 2H), 1.74 (s, 3H), 1.64 – 1.51 (m, 1H), 1.01 (t, J = 7.1 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{23}H_{23}NNaO_5S$ $[M + Na]^+$ 448.1195, found 448.1193. ▸ *NMR spectra on page 448.*

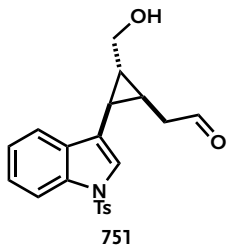
Ethyl 2-((1,3-dioxolan-2-yl)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (749).



749

Aldehyde **745** (212 mg, 498 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (1.2 ml) under an argon atmosphere. Ethylene glycol (2.5 ml, 44.8 mmol, 90 eq.) was added at ambient temperature followed by the addition of TMSCl (257 µl, 2.02 mmol, 4.05 eq.). The reaction mixture was stirred 2 h at this temperature, then diluted with CH_2Cl_2 and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure to obtain acetal **749** as colorless oil (234 mg, 498 µmol, quant.). R_f = 0.27 (hexanes–EtOAc, 3:1, CAN). **^{1}H NMR** (200 MHz, C_6D_6) δ = 8.22 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 1.3 Hz, 1H), 7.30 (dt, J = 7.7, 0.9 Hz, 1H), 7.20 – 7.06 (m, 1H), 6.97 (td, J = 7.5, 1.1 Hz, 1H), 6.48 (d, J = 8.4 Hz, 2H), 4.67 (t, J = 4.6 Hz, 1H), 4.00 (q, J = 7.1 Hz, 2H), 3.43 – 3.33 (m, 3H), 3.30 – 3.19 (m, 3H), 2.72 (ddd, J = 9.3, 4.9, 1.3 Hz, 1H), 2.26 – 2.06 (m, 1H), 1.96 (t, J = 4.8 Hz, 1H), 1.64 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{25}H_{27}NNaO_6S$ $[M + Na]^+$ 492.1457, found 492.1460. ▸ *NMR spectra on page 449.*

2-(2-(Hydroxymethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)acetaldehyde (751).



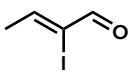
751

Ester **749** (234 mg, 498 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2.5 ml) and cooled to –78 °C. DiBAL (1.0 M in hexanes, 1.5 ml, 1.5 mmol, 3.0 eq.) was added dropwise and stirring was continued for additional 2 h at this temperature. The reaction mixture was diluted with CH_2Cl_2 and quenched by the addition of sat. aq. Rochelle's salt. The mixture was stirred vigorously for 6 h. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed once with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to a quick flash column chromatography to obtain alcohol **750** (125 mg, 292 µmol, 59%) as colorless oil which was dissolved in THF–HCl (3 N, 1:1, 2.0 ml). This mixture

was stirred 14 h at ambient temperature (monitored by TLC) and was the diluted with ether and carefully quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed once with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to a quick flash column chromatography (hexanes–EtOAc, 1:1) to obtain aldehyde **751** as colorless oil (63.2 mg, 165 µmol, 74%). R_f = 0.24 (hexanes–EtOAc, 1:1, stains dark blue with vanillin). **HRMS** (ESI): calcd. for $C_{21}H_{21}NNaO_4S$ $[M + Na]^+$ 406.1089, found 406.1089.

10.7 Experimental Part for Section 6.6

(*Z*)-2-Iodobut-2-enal (759).

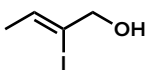


759

Crotonaldehyde (8.3 ml, 100 mmol, 1.0 eq.) was dissolved in THF–H_2O (1:1, 500 ml). Potassium carbonate (16.6 g, 120 mmol, 1.2 eq.), DMAP (2.44 g, 20.0 mmol, 0.2 eq.), and iodine (38.1 g, 150 mmol, 1.5 eq.) were added successively at ambient temperature. The reaction mixture was stirred at this temperature for 4 h, then diluted with EtOAc (1000 ml) and sat. aq. $Na_2S_2O_3$ (1000 ml). The mixture was divided in two parts and the aqueous layer of each part was washed once with 0.1 M HCl. The combined organic layers were concentrated to approximately 250 ml and were extracted once again with sat. aq. $Na_2S_2O_3$ and once with brine. The organic layer was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was usually directly used in the next step. A purification can be carried out by flash column chromatography (hexanes–EtOAc, 8:1). R_f = 0.60 (hexanes–EtOAc, 4:1, stains dark red with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.66 (d, J = 0.6 Hz, 1H), 7.28 (qd, J = 6.7, 0.6 Hz, 1H), 2.17 (d, J = 6.7 Hz, 3H) ppm. **HRMS** (ESI): calcd. for C_4H_5INaO $[M + Na]^+$ 218.9283, found 218.9285.

▸ NMR spectra on page 449.

(*Z*)-2-Iodobut-2-en-1-ol (760).

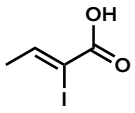


760

Crude aldehyde **759** (210 mmol, 1.0 eq.) was dissolved in THF–H_2O (9:1, 630 ml) and cooled to 0 °C (inner temperature). Sodium borohydride (3.97 g, 105 mmol, 0.5 eq.) was added in portions, keeping the inner temperature below 5 °C. After complete addition, the reaction mixture was stirred additional 40 min (monitored by TLC) at 0 °C. Water (600 ml) and EtOAc (600 ml) were added, the layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were extracted once with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 4:1 → 3:1) to obtain pure alcohol **760** as colorless oil (16.0 g, 81.0 mmol, 58% over two steps). R_f = 0.51 (hexanes–EtOAc, 4:1, stains teal blue with vanillin). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 5.96 (qt, J = 6.4, 1.3 Hz, 1H), 4.23 (d, J = 5.8 Hz, 2H), 2.48 – 2.32 (m, 1H), 1.78 (dt, J = 6.4, 1.2 Hz, 3H) ppm. **HRMS** (ESI): calcd. for C_4H_8IO $[M + H]^+$ 198.9620, found 198.9623.

▸ NMR spectra on page 450.

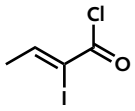
(*Z*)-2-Iodobut-2-enoic acid (763).



763

Aldehyde **759** (540 mg, 2.76 mmol, 1.0 eq.) was dissolved in ^{t}BuOH (10.3 ml) at 25 °C and 2-methyl-2-butene (2.9 ml, 27.6 mmol, 10.0 eq.) was added. A solution of monosodium phosphate dihydrate (1.29 g, 8.27 mmol, 3.0 eq.) and sodium chlorite (technical 80%, 3.11 g, 27.6 mmol, 10.0 eq.) in H_2O (3.4 ml, ultrasonication may be required for full dissolution, yields a yellow solution) was added and the reaction mixture was stirred additional 30 min at ambient temperature (monitored by TLC). The reaction mixture was diluted with ether and brine was added. The layers were separated and the aqueous layer was extracted thrice with EtOAc. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 1:1) to obtain pure carboxylic acid **763** as pale orange solid (490 mg, 2.31 mmol, 84%) R_f = 0.38 (hexanes–EtOAc, 1:1, stains red with vanillin). **M.p.** 115 °C (decomp.). **^{1}H NMR** (400 MHz, C_6D_6) δ = 11.81 (br s, 1H), 7.03 (q, J = 6.6 Hz, 1H), 1.39 (d, J = 6.7 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 169.1, 152.1, 95.8, 22.9 ppm. **HRMS** (ESI): calcd. for $C_4H_5INaO_2$ $[M + Na]^+$ 234.9232, found 234.9234. ▸ *NMR spectra on page 450.*

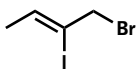
(*Z*)-2-Iodobut-2-enoyl chloride (764).



764

α-iodocarboxylic acid **764** (100 mg, 472 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (0.5 ml) and oxalyl chloride (45 µl, 519 µmol, 1.1 eq.) was added. To this orange solution was added one drop of DMF at ambient temperature. The solution turned immediately bright yellow and became bubbly. TLC analysis indicated, that the carboxylic acid has been complete transformed into the corresponding acid chloride after 30 min. The solvent was removed *in vacuo* and the residue was directly used in the next steps.

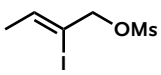
(*Z*)-1-Bromo-2-iodobut-2-ene (761).



761

Alcohol **760** (8.60 g, 43.4 mmol, 1.0 eq.) was dissolved in ether (80.0 ml) and cooled to 0 °C. Phosphorus tribromide (1.63 ml, 17.4 mmol, 0.4 eq.) was added dropwise and stirring was continued for 24 h. The reaction mixture was quenched by the addition of sat. aq. K_2CO_3 and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (pentane–ether, 10:1) afforded bromide **761** as colorless oil (8.60 g, 33.0 mmol, 76%) which was stored at –20 °C under an argon atmosphere. R_f = 0.56 (hexanes, pure, stains dark gray with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.04 (dtd, J = 7.4, 6.4, 1.0 Hz, 1H), 4.34 (t, J = 1.0 Hz, 2H), 1.79 (dt, J = 6.5, 1.0 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 136.1, 103.5, 43.5, 22.3 ppm. **HRMS** (ESI): calcd. for C_4H_6BrINa $[M + Na]^+$ 282.8595, found 282.8596. ▸ *NMR spectra on page 451.*

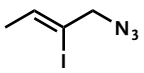
(*Z*)-2-Iodobut-2-en-1-yl methanesulfonate (765).



765

Alcohol **760** (10.9 g, 55.1 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (180 ml), cooled to 0 °C and triethylamine (11.5 ml, 82.6 mmol, 1.5 eq.) was added. A solution of freshly distilled methanesulfonyl chloride (6.4 ml, 82.6 mmol, 1.5 eq.) in CH_2Cl_2 (10.0 ml) was added *via* syringe pump over a period of 30 min and the reaction mixture was stirred additional 2 h at this temperatures. Sat. aq. NH_4Cl was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded crude mesylate **765** which was used in the next step without purification. $R_f = 0.18$ (hexanes–EtOAc, 4:1, stains with $KMnO_4$).

(*Z*)-1-Azido-2-iodobut-2-ene (766).

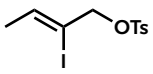


766

Crude mesylate **765** (55.1 mmol, 1.0 eq.) was dissolved in anhydrous DMF (110 ml) and sodium azide (28.6 g, 441 mmol, 8.0 eq.) was added. The resulting mixture was stirred at 60 °C for 60 min (monitored by TLC). The reaction mixture was diluted with chloroform and water (1000 ml) was added. The layers were separated and the aqueous layer was extracted twice with chloroform. The combined organic layers were extracted once with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 500:15) to obtain pure azide **766** as colorless oil (9.58 g, 43.0 mmol, 78%). $R_f = 0.34$ (hexanes, pure, stains with $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.96 (qdd, J = 6.5, 0.9 Hz, 1H), 4.09 (s, 2H), 1.82 (dd, J = 6.4, 1.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 134.9, 127.4, 62.6, 21.8 ppm. **HRMS** (ESI): calcd. for $C_4H_7IN_3$ $[M + H]^+$ 223.9685, found 223.9688. ▸ *NMR spectra on page 452.*

Note: Concerning the waste disposal, the excess of sodium azide is destroyed by titration of an aqueous solution of sodium azide containing a catalytic amount of $Na_2S_2O_3$ with an ethanolic solution of iodine (evolution of N_2!).

(*Z*)-2-Iodobut-2-en-1-yl 4-methylbenzenesulfonate (767).

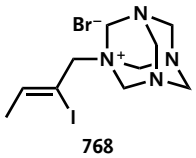


767

To a solution of alcohol **760** (800 mg, 4.04 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (10.0 ml) was added tosyl chloride (1.00 g, 5.25 mmol, 1.30 eq.) at 0 °C followed by the addition of DMAP (50 mg, 404 µmol, 0.1 eq.) and triethylamine (1.04 ml, 8.08 mmol, 2.0 eq.). The ice bath was removed and the reaction mixture was stirred at ambient temperature for 40 min. Sat. aq. NH_4Cl/1 N HCl (1:1) were added and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over magnesium sulfate. Evaporation of the solvent yielded crude tosylate **767** which was subjected to flash column chromatography (pentane–ether, 6:1) to afford pure tosylate **767** as white solid (952 mg, 2.70 mmol, 67%). $R_f = 0.58$ (hexanes–EtOAc, 4:1, stains with $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.82 – 7.76 (m, 2H), 7.36 – 7.31 (m, 2H), 6.02 (qt, J = 6.4, 1.1 Hz, 1H),

4.71 (p, J = 1.1 Hz, 2H), 2.44 (s, 3H), 1.71 (dt, J = 6.4, 1.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.1, 137.5, 133.3, 129.9, 128.2, 98.0, 77.5, 21.8, 21.7 ppm. **HRMS** (ESI): calcd. for $C_{11}H_{13}INaO_3S$ $[M + Na]^+$ 374.9528, found 374.9530. ▸ NMR spectra on page 453.

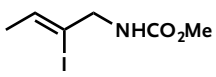
1-((Z)-2-Iodobut-2-en-1-yl)-1,3,5,7-tetraazaadamantan-1-ium bromide (768).



768

Bromide **761** (690 mg, 2.65 mmol, 1.0 eq.) was dissolved in anhydrous chloroform (4.0 ml) and hexamethylenetetramine (372 mg, 2.65 mmol, 1.0 eq.) was added in one portion. The resulting solution was stirred 24 h at ambient temperature (or alternatively 5 h at 75 °C). The white precipitate was filtered through a medium porosity sintered-glass funnel and the retentate was washed with chloroform and dried under high vacuum for several hours to obtain title compound **768** as white solid (940 mg, 2.34 mmol, 89%) which was directly used in the next step.

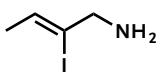
Methyl (*Z*)-(2-iodobut-2-en-1-yl)carbamate (769).



769

Bromide **761** (1.65 g, 6.32 mmol, 1.0 eq.) was dissolved in anhydrous DMF–MeOH (11:1, 23.0 ml) and potassium cyanate (1.74 g, 21.5 mmol, 3.4 eq.) was added in one portion. The resulting suspension was stirred at 110 °C (sealed tube) for 10 min. The reaction mixture was diluted with ether and brine was added. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to obtain crude carbamate **769** which was subjected to flash column chromatography (hexanes–EtOAc, 3:1) to afford pure carbamate **769** (1.45 g, 5.69 mmol, 90%) as white powder. R_f = 0.42 (hexanes–EtOAc, 3:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 5.40 (q, J = 6.4 Hz, 1H), 4.50 (br s, 1H), 3.76 (d, J = 6.3 Hz, 2H), 3.39 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 156.4, 131.8, 107.1, 53.1, 51.9, 21.5 ppm. **HRMS** (ESI): calcd. for $C_6H_{11}INO_2$ $[M + H]^+$ 255.9834, found 255.9835. ▸ NMR spectra on page 454.

(*Z*)-2-Iodobut-2-en-1-amine (770).



770

Variant 1: A stirred solution of quaternary amine **768** (343 mg, 855 µmol) in ethanol (3.0 ml) was added dropwise slowly into 12 N hydrochloric acid (1.5 ml) in the ice/water bath. Upon completion of the addition, the mixture was stirred at 50 °C for 2 h until a precipitate formed, then filtered through a medium porosity sintered-glass funnel to give title compound **770** · HCl as a white solid in quantitative yield.

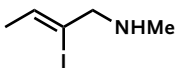
Variant 2: Trimethylsilyl iodide (770 µl, 5.41 mmol, 2.76 eq.) was added at ambient temperature to a solution of carbamate **769** (500 mg, 1.96 mmol, 1.0 eq.) in anhydrous chloroform (4.6 ml). The resulting solution was stirred at 85 °C (sealed tube) over night, then cooled to ambient temperature. Methanol (1.5 ml) was added carefully (exothermic!) and stirred additional 3.0 h at

ambient temperature. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (chloroform–methanol, 6:1 → 3:1) to afford pure amine **770** as brown solid (369 mg, 1.87 mmol, 96%).

Variant 3: Azide **766** (150 mg, 673 µmol, 1.0 eq.) was dissolved in THF–H_2O (10:1, 3.5 ml). PBu_3 (174 µl, 706 µmol, 1.05 eq.) was added dropwise at ambient temperature and the reaction was stirred 5 min at this temperature (monitored by TLC). Volatile components were evaporated *in vacuo* and by azeotropic distillation with benzene (5 times) to obtain title compound **770** as brown oil (95.5 mg, 485 µmol, 72%). R_f = 0.15 (chloroform–methanol, 6:1, stains intensively with ninhydrin). **^{1}H NMR** (400 MHz, MeOD) δ = 6.22 (q, J = 6.4 Hz, 1H), 3.93 (s, 2H), 1.82 (d, J = 6.3 Hz, 3H) ppm. **HRMS** (ESI): calcd. for C_4H_9IN $[M + H]^+$ 197.9780, found 197.9784.

▸ NMR spectra on page 455.

(*Z*)-2-Iodo-*N*-methylbut-2-en-1-amine (755).



755

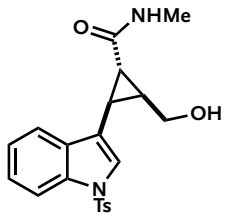
Methylamine (aq., 40% wt., 4.0 ml, 46.0 mmol, 12.0 eq.) was added to a solution of bromide **761** (1.00 g, 3.83 mmol, 1.0 eq.) in anhydrous THF–EtOH (2:1, 11.5 ml) at –7 °C. The resulting solution was stirred at this temperature for 45 min (monitored by TLC) and then diluted with ether. Brine was added, the layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (chloroform–methanol, 47:3) to afford methylamine **755** as pale yellow oil (515 mg, 2.44 mmol, 64%). R_f = 0.30 (chloroform–methanol, 15:1). **^{1}H NMR** (400 MHz, MeOD) δ = 5.89 (qt, J = 6.3, 1.2 Hz, 1H), 3.45 – 3.39 (m, 2H), 2.26 (s, 3H), 1.79 (d, J = 6.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, MeOD) δ = 133.8, 133.8, 63.3, 63.3, 33.9, 33.8, 33.8, 22.1, 22.1 ppm. **HRMS** (ESI): calcd. for $C_5H_{10}INNa$ $[M + H]^+$ 211.9936, found 211.9939.

▸ NMR spectra on page 456.

*Note: (i) The same sequence can be carried out with tosylate **767**, the yield is slightly higher (69%). (ii) Despite the purification, the compound decomposes rapidly (becomes dark brown after a short amount of time, even at –20 °C under an argon atmosphere, TLC analysis reveals several decomposition products). Therefore, methylamine **755** was usually freshly prepared and directly used as crude compound.*

10.8 Experimental Part for Section 7.2

2-(Hydroxymethyl)-*N*-methyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxamide (783).

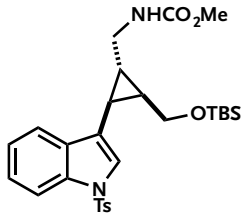


783

A solution of TBS protected alcohol **586** (116 mg, 226 µmol, 1.0 eq.) in anhydrous THF (1.1 ml) was added dropwise to HF · pyr. (20% *w/w*, 1.1 ml) at 0 °C. The reaction mixture was stirred 180 min at 0 °C (monitored by TLC) before it was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether and once with ethyl acetate. The combined organic layers were extracted once with 1 M HCl and the organic layer was dried over sodium sulfate. The solvents were removed under reduced pressure to obtain alcohol **783** as a white foam (90.1 mg, 226 µmol, quant.). R_f = 0.22 (EtOAc, pure). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.95 (dt, J = 8.2, 0.9 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 7.7 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.21 (d, J = 8.1 Hz, 2H), 5.89 (br s, 1H), 3.45 – 3.33 (m, 2H), 2.90 (d, J = 4.6 Hz, 3H), 2.72 (ddd, J = 9.1, 4.8, 1.3 Hz, 1H), 2.34 (s, 3H), 2.17 – 2.10 (m, 1H), 1.74 (t, J = 4.8 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.8, 145.3, 135.4, 135.1, 131.4, 130.1, 126.9, 125.4, 124.0, 123.8, 119.7, 118.9, 113.9, 61.1, 31.1, 28.3, 26.9, 25.6, 25.6, 21.7, 19.8 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{22}N_2NaO_4S$ $[M + Na]^+$ 421.1198, found 421.1199.

▸ NMR spectra on page 457.

Methyl ((2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropyl)methyl)-carbamate (784).

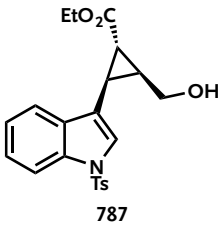


784

Crude amine **595** (515 µmol, 1.0 eq.) was dissolved in anhydrous THF (0.8 ml) and cooled to 0 °C. Triethylamine (145 µl, 1.05 mmol, 2.03 eq.) was added followed by the the dropwise addition of methyl chloroformate (41 µl, 531 µmol, 1.03 eq.). The reaction mixture was stirred for 14 h (0 °C → ambient temperature), TLC analysis revealed, that the amine has been fully consumed. The reaction mixture was diluted with EtOAc and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were extracted once with brine and dried over sodium sulfate. Evaporation of the solvent afforded carbamate **784** (190 mg, 350 µmol, 68%) after purification by flash column chromatography (hexanes–EtOAc, 3:1). R_f = 0.56 (hexanes–EtOAc, 2:1, stains bright purple with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.26 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.57 – 7.47 (m, 2H), 7.19 (dd, J = 7.5, 1.3 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 8.1 Hz, 2H), 4.47 (br s, 1H), 3.50 (s, 3H), 3.37 (dd, J = 10.9, 5.7 Hz, 1H), 3.16 – 3.06 (m, 1H), 3.03 (dd, J = 10.8, 8.5 Hz, 1H), 2.94 (dd, J = 14.4, 7.6 Hz, 1H), 1.69 (s, 3H), 1.60 (dd, J = 8.5, 5.1 Hz, 1H), 1.35 – 1.25 (m, 1H), 1.20 – 1.14 (m, 1H), 0.88 (s, 9H), –0.23 (d, J = 39.2 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{28}H_{39}N_2O_5SSi$ $[M + H]^+$ 543.2349, found 543.2346.

▸ NMR spectra on page 458.

Ethyl (1*S*,2*S*,3*R*)-2-(hydroxymethyl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (787).

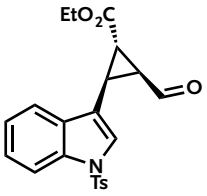


787

Crude enantioenriched silyl alcohol **581** from cyclopropanation (4.5 mmol, 1.0 eq.) was dissolved in AcOH–THF–H_2O (3:1:1, *v/v*, 50 ml) at ambient temperature. The resulting solution was stirred for 16 h at ambient temperature, then diluted with ether and carefully quenched by the addition of sat. aq. K_2CO_3. The layers were separated and the aqueous layer was extracted thrice with ether. The combined organic layers were extracted once with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes–EtOAc, 11:8) to afford pure alcohol **787** (1.71 g, 4.14 mmol, 92% over two steps) as white foam. The enantiomeric excess was determined to be 60% by chiral HPLC analysis (AD-H, 1.2 ml min^{-1}, 10:90 ^{i}PrOH/hexanes, λ = 254 nm): t_R(major) = 19.9 min, t_R(minor) = 25.5 min. R_f = 0.25 (hexanes–EtOAc, 1:1, stains dark blue with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.97 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.39 (d, J = 1.3 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.30 – 7.24 (m, 1H), 7.22 (d, J = 8.1 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.52 (dd, J = 11.7, 6.2 Hz, 1H), 3.29 (dd, J = 11.7, 8.2 Hz, 1H), 2.70 (ddd, J = 9.1, 4.9, 1.3 Hz, 1H), 2.34 (s, 3H), 2.21 – 2.13 (m, 1H), 1.97 (t, J = 4.8 Hz, 1H), 1.34 (d, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.7, 145.2, 135.4, 135.2, 131.1, 130.1, 126.9, 125.4, 124.3, 123.7, 119.5, 118.0, 114.0, 61.3, 61.0, 29.3, 23.6, 21.7, 21.1, 14.4 ppm. **IR** (neat): 3010, 1724, 1447, 1369, 1173, 1095, 1020, 748, 671, 575, 538 cm^{-1}. **HRMS** (ESI): calcd. for $C_{22}H_{23}NNaO_5S$ $[M + Na]^+$ 436.1195, found 436.1196. $[\alpha]_D^{20}$ = –22.8° (c = 1.03, $CHCl_3$). ▸ *NMR spectra on page 458.*

Note: Alternatively, the silyl protecting group can be cleaved with HF · pyr. (20% w/w). The yield is slightly higher (96%), but the simple treatment with acetic acid was preferred on larger scales.

Ethyl (1*S*,2*S*,3*R*)-2-formyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxylate (620).



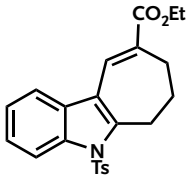
620

Alcohol **787** (2.50 g, 6.05 mmol, 1.0 eq.) was dissolved in anhydrous MeCN (12.1 ml). *N*-Methylmorpholine *N*-oxide (1.09 g, 9.29 mmol, 1.54 eq.), molecular sieves (4 Å, activated, 3.02 g), and tetrapropylammonium perruthenate (95.6 mg, 272 µmol, 4.5 mol %) were added successively at ambient temperature. The reaction mixture was stirred 30 min at this temperature (monitored by TLC). Silica was added and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (hexanes–EtOAc, 1:1) to afford pure aldehyde **620** (2.21 g, 5.37 mmol, 89%) as white foam. R_f = 0.32 (hexanes–EtOAc, 2:1, stains brownish purple with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.93 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 1.3 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.29 – 7.21 (m, 3H), 4.26 (q, J = 7.1 Hz, 2H), 3.12 (ddd, J = 9.3, 6.0, 1.4 Hz, 1H), 2.91 (dd, J = 6.0, 4.6 Hz, 1H), 2.79 (dt, J = 9.3, 4.7 Hz, 1H), 2.34 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 195.9, 170.4, 145.2, 135.0, 134.9, 130.4, 129.9, 126.8, 125.4, 124.9, 123.6, 119.2, 115.6, 113.8, 61.8, 35.9, 25.6, 24.0, 21.6, 14.2 ppm. **^{1}H NMR** (400 MHz,

C_6D_6) δ = 8.51 (d, J = 4.1 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 1.3 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 8.1 Hz, 2H), 3.93 (q, J = 7.1 Hz, 2H), 2.86 (dd, J = 9.1, 6.1 Hz, 1H), 2.68 (t, J = 5.3 Hz, 1H), 2.54 (dt, J = 9.1, 4.4 Hz, 1H), 1.62 (s, 3H), 0.95 (t, J = 7.2 Hz, 3H) ppm.[6] **^{13}C NMR** (101 MHz, C_6D_6) δ = 194.7, 170.3, 144.7, 135.7, 135.7, 131.1, 129.9, 127.0, 125.6, 125.5, 123.8, 119.5, 116.0, 114.3, 61.4, 36.1, 25.5, 24.3, 21.0, 14.1 ppm. **IR** (neat): 1726, 1707, 1446, 1368, 1275, 1171, 1132, 1121, 1094, 976, 745, 667, 570, 536 cm^{-1}. **HRMS** (ESI): calcd. for $C_{22}H_{21}NNaO_5S$ $[M + Na]^+$ 434.1038, found 434.1044. $[\alpha]_D^{20}$ = +35.7° (c = 1.1, $CHCl_3$).

▸ NMR spectra on page 459.

Ethyl 5-tosyl-5,6,7,8-tetrahydrocyclohepta[*b*]indole-9-carboxylate (788).



788

Methyltriphenylphosphonium bromide (243 mg, 680 µmol, 4.0 eq.) was dissolved in anhydrous THF (2.3 ml) and cooled to –78 °C under an argon atmosphere. NaHMDS (2.0 M in THF, 298 µl, 595 µmol, 3.5 eq.) was added dropwise and the reaction mixture was stirred 15 min at –78 °C, then additional 30 min at 0 °C and then again recooled to –78 °C to yield a bright yellow suspension. A solution of aldehyde **620** (70.0 mg, 170 µmol, 1.0 eq.) in anhydrous THF (0.9 ml) was added and the reaction mixture was stirred 60 min at –78 °C (monitored by TLC) and then additional 30 min at 0 °C. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with ether. The organic layers were combined, dried over magnesium sulfate and the solvent was removed *in vacuo*. TLC indicated, that partial rearrangement already took place. The crude was therefore dissolved in benzene and stirred 60 min at 60 °C to complete the rearrangement and afford unexpected cyclohepta[*b*]indole **788** as pale yellow oil (47.1 mg, 115 µmol, 68%). R_f = 0.56 (hexanes–EtOAc, 4:1, Wittig product, stains brown-gray with vanillin). R_f = 0.47 (hexanes–EtOAc, 4:1, [3,3] product, stains brown with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.26 – 8.21 (m, 1H), 7.79 (s, 1H), 7.68 – 7.61 (m, 3H), 7.36 – 7.28 (m, 2H), 7.21 (d, J = 7.5 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.38 (t, J = 6.0 Hz, 2H), 2.79 – 2.72 (m, 2H), 2.35 (s, 3H), 2.01 (dq, J = 8.2, 5.7 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 168.1, 145.3, 142.4, 136.5, 136.2, 132.1, 130.1, 129.8, 127.8, 126.5, 124.9, 123.9, 118.0, 116.3, 115.0, 61.0, 30.5, 29.1, 23.1, 21.8, 14.5 ppm. **IR** (neat): 3640, 3005, 2252, 1739, 1438, 1371, 1218, 1038, 916, 740 cm^{-1}. **HRMS** (ESI): calcd. for $C_{23}H_{24}NO_4S$ $[M + H]^+$ 410.1426, found 410.1429.

▸ NMR spectra on page 462.

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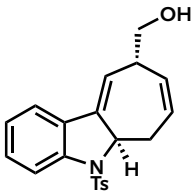
[6] One aromatic signal is overlapped by the solvent signal.

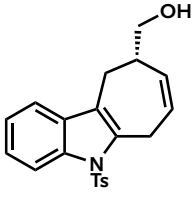
((5a*R*,9*R*)-5-Tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indol-9-yl)methanol (651).



651

Methyltriphenylphosphonium bromide (91.2 mg, 255 µmol, 1.5 eq.) was dissolved in anhydrous THF (0.9 ml) and cooled to –78 °C under an argon atmosphere. NaHMDS (2.0 M in THF, 128 µl, 255 µmol, 1.5 eq.) was added dropwise and the reaction mixture was stirred 15 min at –78 °C, then additional 30 min at 0 °C and then again recooled to –78 °C to yield a bright yellow suspension. A solution of aldehyde **620** (70.0 mg, 170 µmol, 1.0 eq.) in anhydrous THF (0.9 ml) was added and the reaction mixture was stirred 60 min at –78 °C (monitored by TLC) and then additional 30 min at 0 °C. The reaction mixture was diluted with precooled ether and quenched by the addition of ice-cold 5% HCl. The layers were separated and the aqueous layer was quickly extracted twice with precooled ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure (*at 10 °C or below, important*) to yield crude Wittig intermediate as a yellow foam which was quickly taken up in anhydrous CH_2Cl_2 (0.9 ml) and cooled to –78 °C. DiBAL (425 µl, 425 µmol, 2.5 eq.) was added dropwise and the resulting solution was stirred 60 min at –78 °C. The reaction was carefully quenched by the addition of sat. aq. Rochelle's salt at –78 °C. The reaction was transferred into a conical flask, diluted with CH_2Cl_2 and stirred vigorously at ambient temperature over night. TLC analysis indicated, that complete rearrangement took place. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 1.5:1) to obtain cyclohepta[*b*]indoline **651** as pale yellow foam (53.8 mg, 146 µmol, 86%). R_f = 0.56 (hexanes–EtOAc, 4:1, Wittig product, stains brown-gray with vanillin). R_f = 0.36 (hexanes–EtOAc, 1.5:1, DiBAL product, stains blue with vanillin). R_f = 0.33 (hexanes–EtOAc, 1.5:1, [3,3] product, stains brown with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.08 (dt, J = 8.2, 0.8 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.02 (ddd, J = 8.3, 7.3, 1.0 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.75 (td, J = 7.5, 1.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 2H), 5.84 (ddd, J = 3.8, 2.7, 1.3 Hz, 1H), 5.53 (ddt, J = 12.2, 7.3, 2.5 Hz, 1H), 5.30 – 5.19 (m, 1H), 5.14 (ddt, J = 11.4, 4.0, 2.4 Hz, 1H), 3.27 – 3.11 (m, 3H), 3.05 – 2.92 (m, 1H), 2.48 – 2.30 (m, 1H), 1.64 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 144.0, 143.9, 140.4, 135.1, 129.8, 129.6, 129.6, 128.9, 127.9, 127.5, 124.6, 120.7, 119.7, 117.0, 66.7, 64.9, 42.1, 35.1, 21.0 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{21}NNaO_3S$ $[M + Na]^+$ 390.1140, found 390.1141. ▸ *NMR spectra on page 419.*

(5-Tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indol-9-yl)methanol (623).

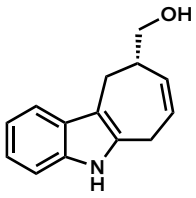


623

To a solution of cyclohepta[*b*]indoline **651** (87.0 mg, 237 µmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1.2 ml) was added trimethylsilyl trifluoromethanesulfonate (86 µl, 474 µmol, 2.0 eq.) dropwise at 0 °C. The solution was stirred 20 min at this temperature (monitored by TLC) at which the solution turned dark red. 1 N HCl was added, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were

dried over K_2CO_3 and the solvent was evaporated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to afford pure cyclohepta[*b*]indole **623** (74.0 mg, 201 µmol, 85%) as pale yellow foam. R_f = 0.35 (hexanes–EtOAc, 1.5:1, stains red with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.61 (dd, J = 8.8, 1.1 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.23 – 7.18 (m, 2H), 7.10 (td, J = 7.3, 1.0 Hz, 1H), 6.44 (d, J = 8.0 Hz, 2H), 5.62 (dddd, J = 10.3, 6.0, 4.0, 1.6 Hz, 1H), 5.53 (ddd, J = 11.4, 4.7, 2.3 Hz, 1H), 4.18 (dd, J = 20.4, 6.4 Hz, 1H), 3.89 (ddt, J = 20.5, 4.3, 2.1 Hz, 1H), 3.18 (dd, J = 10.3, 5.6 Hz, 1H), 3.07 (dd, J = 10.3, 7.2 Hz, 1H), 2.66 (dt, J = 14.9, 2.5 Hz, 1H), 2.51 – 2.29 (m, 2H), 1.61 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.7, 136.5, 136.0, 134.0, 132.6, 131.3, 129.9, 129.6, 126.8, 126.6, 126.4, 124.4, 123.6, 120.8, 117.9, 115.4, 66.3, 39.6, 27.2, 25.4, 21.7 ppm. **HRMS** (ESI): calcd. for $C_{21}H_{21}NNaO_3S$ $[M + Na]^+$ 390.1140, found 390.1141. ▸ *NMR spectra on page 421.*

(5,6,9,10-tetrahydrocyclohepta[*b*]indol-9-yl)methanol (653).

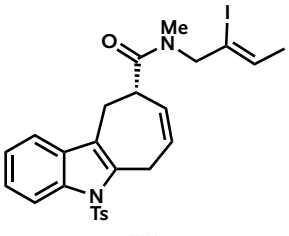


653

To cyclohepta[*b*]indole **623** (7.9 mg, 21.5 µmol, 1.0 eq.) in absolute methanol (0.4 ml) was added NH_4Cl (5.1 mg, 94.6 µmol, 4.4 eq.) and magnesium turnings (10.4 mg, 427 µmol, 20.0 eq.). The reaction mixture was irradiated with ultrasonic at ambient temperature for 120 min before it was diluted with EtOAc and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over sodium sulfate and reduced *in vacuo*. The crude was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to obtain indole **653** as pale yellow foam (4.4 mg, 20.6 µmol, 96%). R_f = 0.24 (hexanes–EtOAc, 2:1, stains bordeaux with vanillin and bright red with Ehrlich's reagent). **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.61 – 7.54 (m, 1H), 7.30 – 7.18 (m, 2H), 7.10 – 7.03 (m, 1H), 6.32 (s, 1H), 5.77 (ddd, J = 11.3, 4.8, 2.4 Hz, 1H), 5.70 (dddd, J = 11.4, 6.3, 3.7, 1.5 Hz, 1H), 3.35 (dt, J = 10.8, 8.6 Hz, 2H), 3.26 (ddt, J = 21.4, 3.8, 2.0 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.83 (dd, J = 19.4, 6.2 Hz, 1H), 2.74 – 2.60 (m, 2H) ppm. **HRMS** (ESI): calcd. for $C_{14}H_{15}NNaO$ $[M + Na]^+$ 236.1051, found 236.1052. ▸ *NMR spectra on page 422.*

10.9 Experimental Part for Section 7.3

(*S*,*Z*)-*N*-(2-Iodobut-2-en-1-yl)-*N*-methyl-5-tosyl-5,6,9,10-tetrahydrocyclohepta[*b*]indole-9-carboxamide (772).



772

Note: The experimental part for this compound is described in one single block, since all intermediates are highly instable and are directly used for the next transformation, cf. Section 7.3.

Part I: Methyltriphenylphosphonium bromide (95%, 912 mg, 2.55 mmol, 1.5 eq.) was dissolved in anhydrous THF (8.5 ml) and cooled to –78 °C under an argon atmosphere. NaHMDS (2.0 M in THF, 1.2 ml, 2.38 mmol, 1.4 eq.) was added dropwise and the

reaction mixture was stirred 15 min at –78 °C, then additional 30 min at 0 °C and then again recooled to –78 °C to yield an bright yellow suspension. A solution of aldehyde **620** (700.0 mg, 1.70 mmol, 1.0 eq.) in anhydrous THF (8.5 ml) was added and the reaction mixture was stirred 60 min at –78 °C (monitored by TLC) and then additional 30 min at 0 °C. The reaction mixture was diluted with precooled ether and quenched by the addition of ice-cold 5% HCl. The layers were separated and the aqueous layer was quickly extracted twice with precooled ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure (*at 10 °C or below, important*) to yield crude Wittig intermediate **776** as a yellow foam which was quickly subjected to the next step. R_f = 0.79 (hexanes–EtOAc, 5:2, stains brown with vanillin).

Part II: Crude ester **776** (1.70 mmol, 1.0 eq.) was dissolved in EtOH–H_2O (3:1, 40 ml) and cooled to 0 °C. Fine powdered potassium hydroxide (1.91 g, 34.0 mmol, 20.0 eq.) was added in portions and the resulting mixture was stirred 30 min at 0 °C (monitored by TLC). Precooled 1 M HCl was added until the acid precipitated (pH 1), then the mixture was diluted with ether. The layers were separated and the aqueous layer was quickly extracted once with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure (*at 10 °C or below, important*) to obtain crude carboxylic acid **790** as white foam. R_f = 0.17 (hexanes–EtOAc, 5:2, stains brown with vanillin).

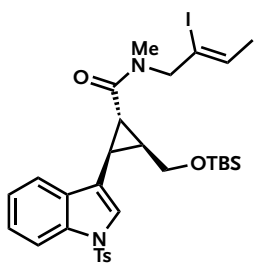
Part III: Crude carboxylic acid **790** (1.70 mmol, 1.0 eq.) was dissolved in anhydrous DMF (8.0 ml) and cooled to 0 °C. A solution of amine **755** (431 mg, 2.04 mmol, 1.2 eq.) in anhydrous DMF (2.5 ml) was added at 0 °C, followed by the addition of HBTU (774 mg, 2.04 mmol, 1.2 eq.) and DIPEA (1.2 ml, 6.80 mmol, 4.0 eq.). The resulting mixture was stirred 3 h at 0 °C (monitored by TLC) at which point the solution turned dark orange. The reaction mixture was diluted with ether and quenched by the addition of 10% citric acid. The layers were separated and the organic layer was extracted once with sat. aq. $NaHCO_3$ and brine, respectively. The aqueous layer containing the 10% citric acid was once again extracted with ether. The layers were separated and the organic layer was extracted once with sat. aq. $NaHCO_3$ and brine, respectively. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford crude divinylcyclopropane **775** as yellow oil. R_f = 0.40 (hexanes–EtOAc, 2:1, stains brown with vanillin).

Part IV: TLC analysis indicated, that partial rearrangement already took place during the evaporation process. Therefore, crude divinylcyclopropane **775** was taken up in benzene and stirred 3 h at 80 °C (monitored by TLC). The solvent was evaporated *in vacuo* to obtain crude cyclohepta[*b*]indoline **791** which turned out to be unstable and was therefore directly used in the next step. R_f = 0.33 (hexanes–EtOAc, 2:1, stains brown with vanillin). **HRMS** (ESI): calcd. for $C_{26}H_{28}IN_2O_3S$ $[M + Na]^+$ 575.0865, found 575.0865.

Part V: Crude cyclohepta[*b*]indoline **791** (1.70 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (8.5 ml) and cooled to 0 °C. Trimethylsilyl trifluoromethanesulfonate (620 µl, 3.40 mmol, 2.0 eq.) was added dropwise. The ice bath was removed and the reaction mixture was stirred 14 h (monitored by NMR) at ambient temperature. The reaction mixture was quenched by the

addition of 1 M HCl and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were dried over K_2CO_3. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 1.5:1) to obtain pure cyclohepta[*b*]indole **772** (666 mg, 1.19 mmol, 70% yield for the whole sequence starting from aldehyde **620**). R_f = 0.33 (hexanes–EtOAc, 2:1, stains brown with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.75 – 8.64 (m, 1H), 7.66 (dd, J = 15.1, 8.2 Hz, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.60 (d, J = 8.0 Hz, 2H), 6.21 – 6.07 (m, 1H), 5.89 – 5.76 (m, 1H), 5.37 (dq, J = 51.9, 6.1 Hz, 1H), 4.39 – 4.17 (m, 2H), 3.95 (dd, J = 48.0, 18.2 Hz, 2H), 3.63 – 3.50 (m, 1H), 3.34 – 3.13 (m, 2H), 2.80 (s, 1H), 2.44 (s, 2H), 1.76 (s, 3H), 1.61 (d, J = 6.3 Hz, 2H), 1.52 – 1.48 (m, 1H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 173.3, 172.7, 144.3, 144.2, 137.0, 136.8, 136.7, 132.9, 132.7, 132.7, 132.5, 132.3, 132.0, 131.9, 131.8, 129.8, 129.8, 127.6, 126.5, 124.8, 124.0, 121.2, 120.8, 118.5, 115.8, 115.7, 106.0, 105.8, 60.7, 58.0, 40.8, 40.6, 33.8, 33.2, 27.5, 27.1, 27.0, 26.7, 21.6, 21.4, 21.0 ppm.[7] **IR** (neat): 2918, 1645, 1452, 1398, 1367, 1350, 1168, 1089, 812, 747, 673, 575, 542, 500 cm^{-1}. **HRMS** (ESI): calcd. for $C_{26}H_{27}IN_2NaO_3S$ $[M + Na]^+$ 597.0685, found 597.0684. **$[\alpha]_D^{20}$ = +90.2°** (c = 0.5, $CHCl_3$). ▸ *NMR spectra on page 463.*

(1*S*,2*S*,3*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-*N*-((*Z*)-2-iodobut-2-en-1-yl)-*N*-methyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxamide (780).



780

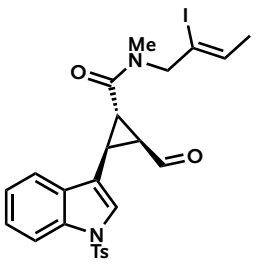
Enantioenriched ester **581** (108 mg, 204 µmol, 1.0 eq.) was dissolved in EtOH–H_2O (3:1, 4.7 ml) and cooled to 0 °C. Fine powdered potassium hydroxide (229 mg, 4.08 mmol, 20.0 eq.) was added in portions and the resulting mixture was stirred 60 min at 0 °C (monitored by TLC). Precooled 1 M HCl was added until the acid precipitated (pH 1), then the mixture was diluted with ether. The layers were separated and the aqueous layer was quickly extracted once with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure (*at 20 °C or below, important*) to obtain crude carboxylic acid as white foam which was directly taken up in anhydrous DMF (1.3 ml) and cooled to 0 °C. A solution of amine **755** (51.7 mg, 245 µmol, 1.20 eq.) in anhydrous DMF (0.2 ml) was added at 0 °C, followed by the addition of HBTU (92.9 mg, 245 µmol, 1.2 eq.) and DIPEA (142 µl, 816 µmol, 4.0 eq.). The resulting mixture was stirred 12 h at 0 °C at which point the solution turned dark orange. The reaction mixture was diluted with EtOAc and quenched by the addition of 10% citric acid. The layers were separated and the organic layer was extracted once with sat. aq. $NaHCO_3$ and brine, respectively. The aqueous layer containing the 10% citric acid was once again extracted with EtOAc. The layers were separated and the organic layer was extracted once with sat. aq. $NaHCO_3$ and brine, respectively. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford crude amide **780**. Purification by flash column chromatography (hexanes–EtOAc, 3:1) afforded pure title compound **780** (119 mg,

[7] The compound appears as two rotamers in a ratio of 1.1:1.9.

172 µmol, 84%) as pale yellow foam. R_f = 0.27 (hexanes–EtOAc, 2:1, carboxylic acid, stains dark red with vanillin). R_f = 0.65 (hexanes–EtOAc, 2:1, amide, stains dark orange with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 10.9, 7.8 Hz, 1H), 7.43 – 7.26 (m, 2H), 7.27 – 7.17 (m, 3H), 5.98 – 5.81 (m, 1H), 4.63 – 4.18 (m, 2H), 3.59 – 3.33 (m, 2H), 3.15 (s, 1.4H), 2.97 (s, 1.6H), 2.83 – 2.71 (m, 1H), 2.33 (s, 3H), 2.12 – 2.03 (m, 1H), 1.88 – 1.79 (m, 3H), 0.97 – 0.82 (m, 1H), 0.80 (d, J = 17.2 Hz, 9H), -0.04 – -0.23 (m, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.0, 171.7, 145.0, 135.4, 132.8, 131.9, 131.7, 130.0, 126.9, 126.9, 125.0, 123.9, 123.8, 123.4, 123.3, 120.3, 120.2, 119.3, 119.2, 113.7, 104.9, 61.6, 61.3, 61.3, 58.6, 34.9, 34.1, 29.5, 29.5, 26.0, 24.0, 23.2, 22.6, 21.9, 21.8, 21.7, 20.8, 20.5, 18.3, –5.3, –5.4 ppm.[8] **HRMS** (ESI): calcd. for $C_{31}H_{41}IN_2NaO_4SSi$ $[M + Na]^+$ 715.1499, found 715.1496.

▸ NMR spectra on page 464.

(1*S*,2*S*,3*R*)-2-formyl-*N*-((*Z*)-2-iodobut-2-en-1-yl)-*N*-methyl-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxamide (792).



792

Silyl alcohol **780** (100 mg, 144 µmol, 1.0 eq.) was dissolved in 1.4 ml of AcOH–THF–H_2O (3:1:1, *v/v*) an was stirred 12 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$ was added carefully. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure to yield crude alcohol which was directly taken up in CH_2Cl_2 (0.7 ml). Dess–Martin periodinane (**603**, 91.6 mg, 216 µmol, 1.5 eq.) and $NaHCO_3$ (121 mg, 1.44 mmol, 10.0 eq.) were added and the reaction mixture was stirred 60 min at ambient temperature (monitored by TLC). The reaction mixture was diluted with CH_2Cl_2 and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting crude was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to obtain aldehyde **792** (81.0 mg, 141 µmol, 98% over two steps) as white foam. **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.84 (dd, J = 27.9, 2.6 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.74 (dd, J = 8.3, 2.0 Hz, 2H), 7.64 (dd, J = 21.6, 1.3 Hz, 1H), 7.27 (dd, J = 16.7, 7.8 Hz, 1H), 7.13 – 7.07 (m, 1H), 6.99 (td, J = 7.6, 4.6 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 5.37 – 5.23 (m, 1H), 4.20 (d, J = 59.1 Hz, 1H), 3.65 (ddt, J = 79.0, 16.9, 1.7 Hz, 1H), 3.30 – 3.14 (m, 1H), 2.99 – 2.83 (m, 2H), 2.66 (s, 2H), 2.37 (s, 1H), 1.62 (d, J = 3.7 Hz, 3H), 1.51 (t, J = 5.6 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{25}H_{26}IN_2O_4S$ $[M + H]^+$ 577.0658, found 577.0658.

▸ NMR spectra on page 465.

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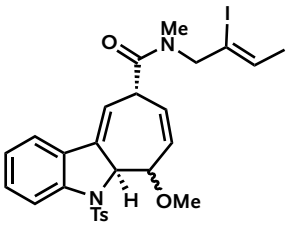
[8] The compound appears as two rotamers in a ratio of 1.4:1.6.

(5a*S*,9*R*)-*N*-((*Z*)-2-Iodobut-2-en-1-yl)-6-methoxy-*N*-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[*b*]indole-9-carboxamide (796).



796

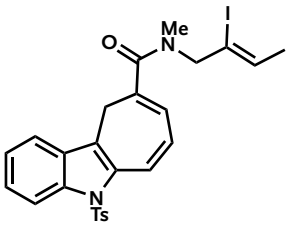
Part I: KHMDS (0.5 M in PhMe, 2.0 ml, 1.0 mmol, 3.3 eq.) was added dropwise to a solution of (methoxymethyl)triphenylphosphonium chloride (365 mg, 1.06 mmol, 3.5 eq.) in anhydrous THF (3.5 ml) at –78 °C. The resulting solution was stirred 10 min at –78 °C and additional 30 min at –5 °C to obtain a dark red solution. A solution of aldehyde **620** (125 mg, 304 µmol, 1.0 eq.) in anhydrous THF (1.0 ml) was added dropwise at –5 °C and the reaction mixture was stirred for 3 h at this temperature (monitored by TLC). The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl/5% HCl (2:1). The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were extracted once with brine and dried over sodium sulfate. The solvent was removed *in vacuo*. R_f = 0.31 (hexanes–EtOAc, 3:1, CAN).

Part II: The residue was directly taken up in EtOH–H_2O (6.8 ml, 3:1). Fine powdered potassium hydroxide (337 mg, 6.00 mmol, 20.0 eq.) was added in portions and the resulting mixture was stirred 90 min at ambient temperature (monitored by TLC). 1 M HCl was added until the acid precipitated (pH 1), then the mixture was diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure to obtain crude carboxylic acid as pale yellow foam. R_f = 0.19 (hexanes–EtOAc, 2:3, stains rose with vanillin).

Part III: The crude material was dissolved in anhydrous DMF (1.0 ml) and cooled to 0 °C. A solution of amine **755** (76.0 mg, 360 µmol, 1.20 eq.) in anhydrous DMF (1.0 ml) was added at 0 °C, followed by the addition of HBTU (137 mg, 360 µmol, 1.2 eq.) and DIPEA (209 µl, 1.20 mmol, 4.0 eq.). The resulting mixture was stirred 13 h at 0 °C at which point the solution turned dark orange. The reaction mixture was diluted with EtOAc and quenched by the addition of 10% citric acid. The layers were separated and the organic layer was extracted once with sat. aq. $NaHCO_3$ and brine, respectively. The aqueous layer containing the 10% citric acid was once again extracted with EtOAc. The layers were separated and the organic layer was extracted once with sat. aq. $NaHCO_3$ and brine, respectively. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford crude amide **780**. R_f = 0.70 (hexanes–EtOAc, 2:3, diastereomer I, stains pink with vanillin). R_f = 0.57 (hexanes–EtOAc, 2:3, diastereomer II, stains light brown with vanillin).

Part IV: The crude material was taken up in anhydrous toluene and stirred 3 h at 110 °C. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 1:1) to obtain title compound **796** as diastereomers which were directly used for the rearomatization step. R_f = 0.54 (hexanes–EtOAc, 1:1, diastereomer I, CAN). R_f = 0.48 (hexanes–EtOAc, 1:1, diastereomer II, CAN). **HRMS** (ESI): calcd. for $C_{27}H_{29}IN_2NaO_4S$ $[M + Na]^+$ 627.0790, found 627.0789.

(*Z*)-*N*-(2-Iodobut-2-en-1-yl)-*N*-methyl-5-tosyl-5,10-dihydrocyclohepta[*b*]indole-9-carboxamide (797).

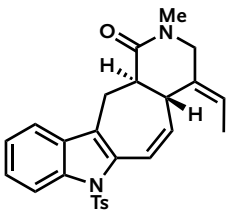


797

To a solution of crude cyclohepta[*b*]indoline **796** (300 µmol, 1.0 eq.) in anhydrous CH_2Cl_2 (1.5 ml) was added trimethylsilyl trifluoromethanesulfonate (150 µl, 826 µmol, 2.75 eq.) dropwise at 0 °C. The solution was stirred 12 h at this temperature (monitored by TLC) at which the solution turned dark red. 1 N HCl was added, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3 and the solvent was evaporated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to afford undesired cyclohepta[*b*]indole **797** (71.9 mg, 119 µmol, 40% from aldehyde **620**) as yellow oil. $R_f = 0.52$ (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, C_6D_6) $\delta = 8.58$ (d, $J = 8.4$ Hz, 1H), 7.62 – 7.54 (m, 3H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.22 (ddd, $J = 8.5, 7.3, 1.3$ Hz, 1H), 7.09 – 7.02 (m, 1H), 6.97 (s, 1H), 6.39 (d, $J = 8.1$ Hz, 2H), 5.57 (q, $J = 7.7$ Hz, 1H), 5.31 (q, $J = 6.2$ Hz, 1H), 4.00 (br s, 2H), 2.71 (d, $J = 7.2$ Hz, 2H), 2.60 (s, 3H), 1.58 (s, 3H), 1.50 (d, $J = 6.3$ Hz, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) $\delta = 190.0, 144.7, 138.8, 137.2, 135.3, 130.0, 129.6, 128.7, 127.0, 126.7, 126.4, 124.5, 123.7, 122.1, 120.1, 119.5, 116.1, 106.3, 60.1, 30.0, 21.6, 21.0, 14.2$ ppm. **HRMS** (ESI): calcd. for $C_{26}H_{25}IN_2NaO_3S$ $[M + Na]^+$ 595.0528, found 595.0530.

▸ *NMR spectra on page 466.*

(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-7-tosyl-3,4,4a,7,12,12a-hexahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-1(2*H*)-one (799).



799

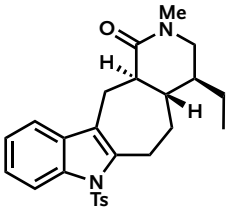
A flame-dried Schlenk tube was charged with vinyl iodide **772** (120 mg, 209 µmol, 1.0 eq.), phenol (4.9 mg, 52.3 µmol, 0.25 eq.), and K_3PO_4 (133 mg, 627 µmol, 3.0 eq.). The tube was evacuated and backfilled with argon. This was repeated three times, then $Pd(PPh_3)_4$ (24.2 mg, 20.9 µmol, 10 mol %) was added in the glovebox. Freeze-pump-thaw degassed anhydrous toluene (18.0 ml) was added and stirring was continued at 115 °C. TLC indicated the full conversion after 2.0 h, the reaction mixture was then cooled to ambient temperature. CH_2Cl_2 and sat. aq. $NaHCO_3$ were added, the layers were separated and the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 1:1) to obtain pure piperidine **799** (92.0 mg, 206 µmol, 98%) as white foam. $R_f = 0.24$ (hexanes–EtOAc, 2:3, stains bright orange with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) $\delta = 8.60$ (d, $J = 8.4$ Hz, 1H), 7.63 – 7.53 (m, 3H), 7.21 (t, $J = 8.5$ Hz, 2H), 7.01 (t, $J = 7.5$ Hz, 1H), 6.47 (d, $J = 8.4$ Hz, 2H), 5.55 (dd, $J = 11.3, 4.9$ Hz, 1H), 5.06 (qt, $J = 6.8, 1.7$ Hz, 1H), 3.55 (d, $J = 13.4$ Hz, 1H), 3.38 (dd, $J = 18.9, 5.8$ Hz, 1H), 3.21 (dd, $J = 18.8, 11.3$ Hz, 1H), 2.98 (br s, 1H), 2.76 (d, $J = 13.5$ Hz, 1H), 2.70 (s, 3H), 2.31 (ddd, $J = 11.2, 9.2, 5.9$ Hz, 1H), 1.63 (s, 3H), 1.29 (d, $J = 6.9$ Hz,

3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 170.9, 144.2, 137.5, 137.5, 136.5, 136.3, 132.6, 132.4, 129.5, 126.8, 125.9, 124.5, 124.0, 121.5, 120.4, 119.6, 116.2, 54.3, 43.2, 40.9, 34.1, 27.3, 21.0, 13.3, 1.4 ppm. **IR** (neat): 2920, 1651, 1452, 1365, 1171, 1089, 747, 704, 572, 500 cm^{-1}. **HRMS** (ESI): calcd. for $C_{26}H_{27}N_2O_3S$ $[M + H]^+$ 447.1742, found 447.1743. $[\alpha]_D^{20}$ = –15.9° (c = 1.0, $CHCl_3$).

▸ NMR spectra on page 467.

Note: (i) This procedure can also be carried out with $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol %) and DavePhos® (20 mol %) instead of $Pd(PPh_3)_4$. (ii) This procedure was carried out with up to 1500 mg of starting material with 90–98% yield.

(4*S*,4a*S*,12a*R*)-4-ethyl-2-methyl-7-tosyl-3,4,4a,5,6,7,12,12a-octahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-1(2*H*)-one (805).

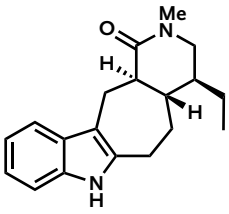


805

Olefine **799** (70.0 mg, 157 µmol, 1.0 eq.) was added to EtOH (1.6 ml, almost no dissolution). Adams's catalyst (7.1 mg, 31 µmol, 0.2 eq.) was added and the vigorous stirred reaction mixture was hydrogenated ($p(H_2)$ = 1 atm) at ambient temperature for 6 h. The mixture was filtered over celite and the solvent was removed under reduced pressure to obtain title compound **805** (58.0 mg, 129 µmol, 82%) as white solid (α:β = 1:10, according to NMR analysis). R_f = 0.34 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.62 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.19 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.50 (d, J = 8.1 Hz, 2H), 4.16 (dd, J = 16.1, 2.1 Hz, 1H), 3.59 (ddt, J = 16.8, 8.7, 1.6 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.70 (s, 3H), 2.61 (dd, J = 12.3, 5.4 Hz, 1H), 2.40 – 2.27 (m, 2H), 1.80 (td, J = 11.0, 2.1 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.65 (s, 3H), 1.18 – 1.07 (m, 2H), 1.08 – 1.01 (m, 1H), 0.92 – 0.77 (m, 2H), 0.58 (t, J = 7.4 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{26}H_{30}N_2NaO_3S$ $[M + Na]^+$ 473.1875, found 473.1879.

▸ NMR spectra on page 469.

(4*S*,4a*S*,12a*R*)-4-Ethyl-2-methyl-3,4,4a,5,6,7,12,12a-octahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-1(2*H*)-one (806).

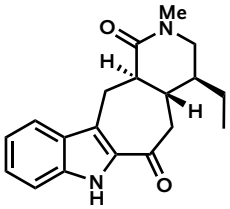


806

Tosylated indole **805** (48.0 mg, 107 µmol, 1.0 eq.) was dissolved in anhydrous methanol (1.8 ml) under argon atmosphere. Ammonium chloride (25.1 mg, 469 µmol, 4.40 eq.) and magnesium turnings (51.5 mg, 2.12 mmol, 20.0 eq.) were added. The reaction mixture was irradiated with ultrasonic at ambient temperature for 60 min (monitored by TLC). The reaction mixture was diluted with ether and sat. aq. NH_4Cl was added. The layers were separated and the aqueous layer was washed thrice with ether, then the aqueous layer was basified with K_2CO_3 and backwashed once with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to obtain a hardly soluble white solid which was dissolved in hot toluene and subjected to

flash column chromatography (hexanes–EtOAc, 1:1). This afforded title compound **806** as white solid (21.5 mg, 73 µmol, 68%). $R_f = 0.30$ (hexanes–EtOAc, 1:1, stains excellent with $KMnO_4$, stains dark red with Ehrlich's reagent). **HRMS** (ESI): calcd. for $C_{19}H_{25}N_2O$ $[M + H]^+$ 297.1967, found 297.1965.

(4*S*,4a*S*,12a*R*)-4-Ethyl-2-methyl-3,4,4a,7,12,12a-hexahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indole-1,6(2*H*,5*H*)-dione [5-oxo-16,20-diepisilicine] (**807**).

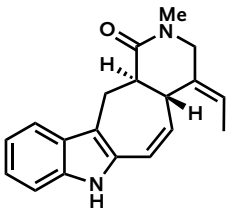


807

Indole **806** (34.0 mg, 115 µmol, 1.0 eq.) was dissolved in THF–H_2O (4:1, 2.9 ml) and I_2O_5 (45.9 mg, 138 µmol, 1.2 eq.) was added. The resulting mixture was stirred 5 h at ambient temperature (monitored by TLC) at which point the reaction mixture became dark orange. The solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and water. The layers were separated and the organic layer was additionally washed once with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine, respectively. Drying over sodium sulfate followed by flash column chromatography (EtOAc, pure) afforded 6-oxo-cyclohepta[*b*]indole **807** as yellow solid (24.0 mg, 77 µmol, 67%). $R_f = 0.15$ (hexanes–EtOAc, 1:2, stains bright yellow then brown with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta = 9.33$ (br s, 1H), 7.58 (d, $J = 8.2$ Hz, 1H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.14 (s, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 4.06 (dd, $J = 17.6$, 3.8 Hz, 1H), 2.88 (dd, $J = 17.6$, 11.3 Hz, 1H), 2.76 (s, 1H), 2.74 (s, 3H), 2.56 (dd, $J = 12.5$, 4.2 Hz, 1H), 2.34 (ddd, $J = 16.3$, 12.4, 6.4 Hz, 2H), 2.21 (dd, $J = 17.7$, 11.2 Hz, 1H), 1.45 (q, $J = 9.4$, 9.0 Hz, 1H), 1.11 (ddd, $J = 14.0$, 7.4, 3.5 Hz, 1H), 0.84 (dt, $J = 8.4$, 3.8 Hz, 1H), 0.73 (dt, $J = 14.6$, 7.4 Hz, 1H), 0.52 (t, $J = 7.4$ Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) $\delta = 191.9$, 170.9, 137.4, 132.5, 128.7, 126.9, 123.0, 121.9, 120.5, 112.3, 51.8, 47.1, 47.0, 39.7, 39.6, 35.2, 30.2, 23.6, 10.7 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{22}N_2NaO_2$ $[M + Na]^+$ 333.1579, found 333.1579.

▸ *NMR spectra on page 470.*

(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-3,4,4a,7,12,12a-hexahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-1(2*H*)-one (809).

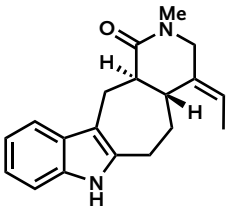


809

A solution of tosylated indole **799** (700 mg, 1.57 mmol, 1.0 eq.) in anhydrous degassed THF (5.0 ml) was added in one portion to a freshly prepared solution of SmI_2 (0.1 M in degassed THF, 157 ml, 15.7 mmol, 10.0 eq.) at ambient temperature. After complete addition, the reaction was stirred 5 s, then H_2O (850 µl, 47.1 mmol, 30.0 eq.) was added followed by the addition of pyrrolidine (2.57 ml, 31.4 mmol, 20.0 eq.). The reaction mixture immediately turned pale green and a white precipitate was formed. The mixture was diluted with EtOAc (200 ml) and 1 N HCl (400 ml) was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The aqueous layer was basified with K_2CO_3 and checked for product residues. The combined organic layers

were dried over sodium sulfate and the solvent was removed under reduced pressure to obtain crude indole **809** as a pale yellow solid. The product turned out to be very sensitive towards oxidation and therefore was directly used in the next step. R_f = 0.53 (hexanes–EtOAc, 1:2, stains pale red with vanillin, stains immediately bright yellow with CAN). **HRMS** (ESI): calcd. for $C_{19}H_{20}N_2NaO$ $[M + Na]^+$ 315.1473, found 315.1474.

(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-3,4,4a,5,6,7,12,12a-octahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-1(2*H*)-one (811).

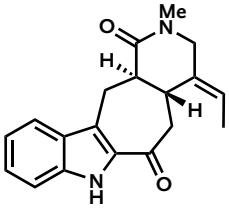


811

Crude indole **809** (1.5 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (60.0 ml) to yield a bright yellow solution. Trifluoroacetic acid (15.0 ml) was added after which the solution turned dark red. Triethylsilane (2.4 ml, 15.0 mml, 10.0 eq.) was added at ambient temperature and the resulting solution was stirred 3 h at this temperature (monitored by TLC) before it was carefully quenched by the addition of sat. aq. K_2CO_3. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over sodium sulfate the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (cyclohexane–EtOAc, 1:1) to obtain pure indole **811** (405 mg, 1.38 mmol, 92%) as white solid. R_f = 0.54 (hexanes–EtOAc, 1:2, stains bright pink with CAN). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.84 (s, 1H), 7.65 – 7.57 (m, 1H), 7.30 – 7.21 (m, 1H), 7.16 – 7.04 (m, 2H), 5.41 (qt, J = 7.0, 1.5 Hz, 1H), 4.12 (dq, J = 13.5, 1.5 Hz, 1H), 3.85 (dd, J = 16.1, 2.4 Hz, 1H), 3.28 (d, J = 13.3 Hz, 1H), 3.03 (ddd, J = 15.4, 13.2, 3.7 Hz, 1H), 3.01 (s, 3H), 2.91 (ddd, J = 15.8, 5.0, 3.2 Hz, 1H), 2.72 – 2.57 (m, 2H), 2.37 (ddd, J = 11.7, 9.3, 2.3 Hz, 1H), 2.06 (ddt, J = 13.9, 5.4, 2.5 Hz, 1H), 1.71 (dd, J = 11.5, 2.8 Hz, 1H), 1.66 (dd, J = 6.9, 1.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.5, 138.8, 135.9, 134.4, 129.4, 121.2, 120.1, 119.4, 118.3, 111.3, 110.3, 55.0, 47.0, 44.5, 34.4, 34.0, 28.4, 25.2, 13.6 ppm. **IR** (neat): 3273, 2930, 2855, 1635, 1487, 1464, 1435, 1398, 1312, 1056, 735 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{22}N_2NaO$ $[M + Na]^+$ 317.1630, found 317.1630. **$[\alpha]_D^{20}$ =** +14.9° (c = 1.0, $CHCl_3$).

▸ *NMR spectra on page 473.*

(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-3,4,4a,7,12,12a-hexahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indole-1,6(2*H*,5*H*)-dione [(+)-5-Oxoisomethuenine] **(808)**.



808

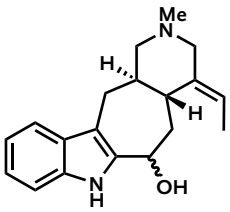
Indole **811** (25.0 mg, 84.3 µmol, 1.0 eq.) was dissolved in THF–H_2O (4:1, 2.1 ml) and I_2O_5 (33.8 mg, 101 µmol, 1.2 eq.) was added in one portion at ambient temperature. The reaction mixture was stirred 2 h at this temperature (monitored by TLC), before the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and methanol and silica was added. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (CH_2Cl_2 –MeOH, 40:1, or alternatively

hexanes–EtOAc, 1:1) to obtain pure title compound **808** as pale yellow solid (24.9 mg, 80.7 µmol, 96%). R_f = 0.57 (EtOAc, pure, stains bright yellow with CAN). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.94 (br s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.16 (ddd, J = 8.1, 5.7, 2.2 Hz, 1H), 5.49 (q, J = 6.9 Hz, 1H), 4.23 (d, J = 13.4 Hz, 1H), 4.00 (dd, J = 18.6, 3.4 Hz, 1H), 3.39 (d, J = 13.4 Hz, 1H), 3.23 – 3.08 (m, 2H), 3.07 (s, 3H), 2.94 (dd, J = 18.6, 12.0 Hz, 1H), 2.87 – 2.76 (m, 2H), 1.62 (d, J = 6.8 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 192.2, 171.7, 137.0, 135.4, 131.6, 128.5, 127.5, 122.9, 122.0, 121.4, 120.6, 111.9, 54.0, 48.1, 45.5, 36.1, 35.0, 28.0, 13.3 ppm. **IR** (neat): 3341, 2895, 1637, 162, 1573, 1539, 1485, 1436, 1402, 1332, 1311, 1247, 734 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{20}N_2NaO_2$ $[M + Na]^+$ 331.1422, found 331.1418. **$[\alpha]_D^{20}$ = +49.5°** (c = 1.0, $CHCl_3$).

▸ NMR spectra on page 475.

10.10 Experimental Part for Section 7.4

(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-1,2,3,4,4a,5,6,7,12,12a-decahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-6-ol [Isomethueninol] (**816**).

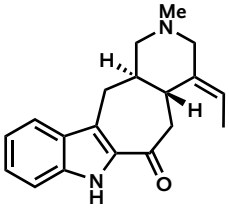


816

A solution of 5-oxoisomethuenine (**808**, 125 mg, 405 µmol, 1.0 eq.) in anhydrous THF (12.5 ml) was cooled to 0 °C and $LiAlH_4$ (2.4 M in THF, 2.35 ml, 13.9 eq.) was added dropwise. The solution turned bright yellow and stirring was continued for 5 h at ambient temperature (monitored by TLC) at which the solution was again colorless. The reaction mixture was cooled to 0 °C and benzene (15 ml) was added. To this solution was added sodium fluoride (1.0 g) followed by the careful addition of H_2O (0.4 ml, exothermic!). The ice bath was removed and the mixture was stirred vigorously for 20 min at ambient temperature. The mixture was filtered through a medium porosity sintered-glass funnel and the retentate was washed with an appropriate amount of chloroform. The solvent was removed *in vacuo* to obtain crude alcohol **816** as colorless foam which was directly used in the next step. R_f = 0.11 (cyclohexane–$CHCl_3$–Et_2NH, 12:6:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.71 (br s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.11 (dt, J = 23.4, 7.3 Hz, 2H), 5.41 (q, J = 7.3 Hz, 1H), 5.04 (dd, J = 11.2, 4.7 Hz, 1H), 3.76 – 3.59 (m, 1H), 3.41 (br d, J = 12.8 Hz, 1H), 2.94 – 2.86 (m, 1H), 2.86 – 2.70 (m, 2H), 2.50 – 2.38 (m, 1H), 2.36 (s, 3H), 2.30 – 2.19 (m, 2H), 2.15 (dd, J = 12.6, 4.5 Hz, 1H), 1.93 (dq, J = 40.1, 11.5, 10.8 Hz, 2H), 1.69 (d, J = 7.0 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{19}H_{25}N_2O$ $[M + H]^+$ 297.1967, found 297.1968.

▸ NMR spectra on page 476.

(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-1,3,4,4a,5,7,12,12a-octahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-6(2*H*)-one [16-Epimethuenine] (**57**).

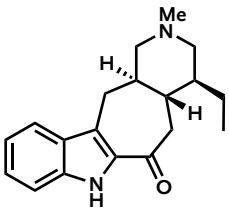


57

Crude alcohol **816** (400 µmol, 1.0 eq.) was dissolved in anhydrous chloroform (40.0 ml) and MnO_2 (696 mg, 8.00 mmol, 20.0 eq.) was added. The reaction mixture was stirred 4 h at ambient temperature (monitored by TLC) before it was filtered over celite. The retentate was washed with an appropriate amount of chloroform and the solvent was removed *in vacuo* to obtain crude title compound **57** which was subjected to flash column chromatography (cyclohexane–$CHCl_3$–Et_2NH, 12:6:1) to afford isomethuenine (82.0 mg, 279 µmol, 70% over two steps) as pale yellow solid. R_f = 0.28 (cyclohexane–$CHCl_3$–Et_2NH, 12:6:1, stains red with Ehrlich's reagent, stains excellent with $KMnO_4$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.98 (s, 1H), 7.63 (dd, J = 8.1, 0.9 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.13 (ddd, J = 8.0, 4.9, 3.0 Hz, 1H), 5.46 (q, J = 6.8 Hz, 1H), 3.49 (d, J = 12.9 Hz, 1H), 3.22 (dd, J = 17.5, 3.0 Hz, 1H), 2.93 (d, J = 4.5 Hz, 1H), 2.93 – 2.88 (m, 2H), 2.83 – 2.72 (m, 3H), 2.45 – 2.39 (m, 2H), 2.40 (s, 3H), 1.63 (dd, J = 6.9, 1.6 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 193.5, 136.7, 136.4, 132.0, 128.2, 127.1, 122.6, 122.3, 121.4, 120.4, 112.0, 58.4, 57.0, 47.3, 45.1, 38.8, 38.0, 31.2, 13.0 ppm. **^{1}H NMR** (400 MHz, DMSO) δ = 11.30 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.28 (ddd, J = 8.2, 6.8, 1.1 Hz, 1H), 7.05 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 5.37 (q, J = 6.8 Hz, 1H), 3.43 – 3.39 (m, 1H), 3.18 (dd, J = 17.4, 3.4 Hz, 1H), 2.99 (dd, J = 17.9, 12.1 Hz, 1H), 2.88 – 2.77 (m, 2H), 2.77 – 2.63 (m, 2H), 2.59 – 2.52 (m, 1H), 2.37 – 2.31 (m, 1H), 2.26 (s, 3H), 2.21 (d, J = 11.7 Hz, 1H), 1.60 (dd, J = 6.9, 1.4 Hz, 3H) ppm.[9] **^{13}C NMR** (101 MHz, DMSO) δ = 192.7, 137.4, 136.9, 131.9, 127.3, 126.0, 121.1, 121.0, 120.8, 119.4, 112.4, 58.1, 56.5, 46.9, 44.7, 37.8, 37.7, 30.2, 12.6 ppm. **IR** (neat): 3297, 2920, 2850, 1625, 1537, 1450, 1440, 1250, 745 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{23}N_2O$ $[M + H]^+$ 295.1810, found 295.1810. $[\alpha]_D^{20}$ = –18° (c = 1.0, $CHCl_3$).

▸ *NMR spectra on page 476.*

(4*S*,4a*S*,12a*R*)-4-Ethyl-2-methyl-1,3,4,4a,5,7,12,12a-octahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-6(2*H*)-one [16,20-Diepisilicine] (**48**).



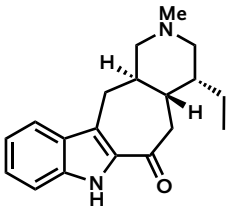
48

16-Epimethuenine (**57**, 30.0 mg, 102 µmol, 1.0 eq.) was dissolved in anhydrous ethanol (3.0 ml) and Adams's catalyst (3.0 mg, 13.2 µmol, 0.13 eq.) was added. The reaction mixture was hydrogenated ($p(H_2)$ = 1 atm) for 2.5 h at ambient temperature (monitored by TLC). The mixture was filtered over celite and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (cyclohexane–$CHCl_3$–Et_2NH, 12:6:1) to obtain 16,20-diepisilicine (**48**, 27.3 mg, 91.5 µmol, 90%) as yellow solid. R_f = 0.43 (cyclohexane–$CHCl_3$–Et_2NH, 12:6:1, stains with $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.00 (br s, 1H), 7.63 (dd, J = 8.2, 1.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.13 (ddd, J = 8.0, 6.2, 1.8 Hz, 1H), 3.26 (dd, J = 17.3, 5.2 Hz, 1H), 3.07 (dd, J = 16.8, 1.8 Hz, 1H),

[9] Two signal are partially overlapped by the solvent signals.

3.03 (ddd, J = 11.3, 4.4, 1.9 Hz, 1H), 2.99 (ddd, J = 11.3, 4.4, 1.9 Hz, 1H), 2.80 (dd, J = 17.3, 8.8 Hz, 1H), 2.62 (dd, J = 16.9, 9.6 Hz, 1H), 2.31 (s, 3H), 2.22 (ddt, J = 11.5, 9.4, 4.9 Hz, 1H), 1.82 (dd, J = 11.2, 11.2 Hz, 1H), 1.71 (dqd, J = 15.2, 7.6, 2.3 Hz, 1H), 1.60 (dd, J = 10.9, 10.9 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.42 – 1.35 (m, 1H), 1.23 – 1.14 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 193.5, 136.8, 132.2, 127.9, 126.8, 122.4, 121.0, 120.3, 112.1, 63.6, 61.0, 47.3, 46.5, 42.6, 41.3, 40.7, 30.0, 24.6, 11.5 ppm. **IR** (neat): 3310, 2927, 2889, 2791, 1633, 1575, 1458, 1332, 1255, 743 cm^{-1}. **HRMS** (ESI): calcd. for $C_{19}H_{25}N_2O$ $[M + H]^+$ 297.1967, found 297.1969. $[\alpha]_D^{20}$ = –20.0° (c = 0.3, $CHCl_3$). ▸ NMR spectra on page 481.

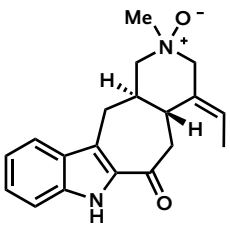
(4*R*,4a*S*,12a*R*)-4-ethyl-2-methyl-1,3,4,4a,5,7,12,12a-octahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indol-6(2*H*)-one [16-Episilicine] (**46**).



46

In the previous step, the 20-α-epimer 16-episilicine (**46**, 1.9 mg, 6.4 µmol, 7%) was also obtained as yellow solid. NMR analysis revealed a mixture of at least three different compounds. Purification by preparative chromatography (cyclohexane–$CHCl_3$–Et_2NH, 20:8:1) furnished title compound **46** (500 µg, 1.7 µmol, 2%) as pale yellow solid. R_f = 0.47 (cyclohexane–$CHCl_3$–Et_2NH, 12:6:1, stains with $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.77 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.15 (ddd, J = 8.0, 6.5, 1.4 Hz, 1H), 3.16 (dd, J = 16.4, 6.6 Hz, 1H), 2.96 (d, J = 11.1 Hz, 1H), 2.91 (d, J = 11.6 Hz, 1H), 2.85 (dd, J = 16.3, 6.5 Hz, 1H), 2.80 (d, J = 5.7 Hz, 2H), 2.24 (s, 3H), 2.20 – 2.13 (m, 1H), 1.86 (d, J = 11.0 Hz, 1H), 1.82 – 1.74 (m, 2H), 1.63 – 1.59 (m, 1H), 1.54 – 1.49 (m, 1H), 1.41 – 1.33 (m, 1H), 0.96 (t, J = 7.2 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{19}H_{25}N_2O$ $[M + H]^+$ 297.1967, found 297.1968. $[\alpha]_D^{20}$ = +62° (c = 0.05, $CHCl_3$). ▸ NMR spectra on page 483.

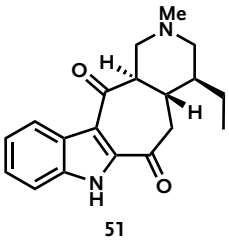
(4a*R*,12a*R*,*E*)-4-Ethylidene-2-methyl-6-oxo-1,2,3,4,4a,5,6,7,12,12a-decahydropyrido[3',4':4,5]cyclo hepta[1,2-*b*]indole 2-oxide [16-epimethuenine-*N*-oxide] (**60**).



60

16-Epimethuenine (**57**, 4.0 g, 13.6 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.8 ml) and *m*CPBA (75%, 3.1 mg, 13.6 µmol, 1.0 eq.) was added in one potion at ambient temperature and stirring was continued at this temperature for 15 min (monitored by TLC). The reaction mixture was quenched by the addition of sat. aq. K_2CO_3 and the layers were separated. The aqueous layer was extracted thrice with CH_2Cl_2 and the combined organic layers were dried over sodium sulfate. The solvent was removed under reduced pressure to obtain a pale yellow residue (1.0 mg, 24%). Comparison of the crude NMR data with literature revealed, that title compound **60** has been formed. No optimization or HPLC purification was carried out. R_f = 0.18 (EtOAc–iPrOH–Et_2NH, 85:15:5). **HRMS** (ESI): calcd. for $C_{19}H_{23}N_2O_2$ $[M + H]^+$ 311.1760, found 311.1759. $[\alpha]_D^{20}$ = +82° (c = 0.1, $CHCl_3$).

(4*S*,4a*S*,12a*R*)-4-Ethyl-2-methyl-1,3,4,4a,5,12a-hexahydropyrido[3',4':4,5]cyclohepta[1,2-*b*]indole-6,12(2*H*,7*H*)-dione [6-oxo-16,20-diepisilicine] (**51**).



51

16,20-Diepisilicine (**48**, 4.0 mg, 13.6 µmol) was dissolved in acetone (0.3 ml) and cooled to 0 °C and treated with Jones reagent (**842**). After stirring 5 min, the reaction mixture was diluted with CH_2Cl_2 and sat. aq. K_2CO_3 was added. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The solvent was evaporated and NMR analysis of the crude (0.8 mg, 2.6 µmol, 19%) revealed after comparison with literature, that 6-oxo-16,20-diepisilicine has been formed. No optimization or HPLC purification was carried out. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.25 (br s, 1H), 8.44 (dt, J = 8.3, 1.0 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.34 (ddd, J = 8.2, 6.3, 1.9 Hz, 1H), 3.61 (ddd, J = 11.6, 4.7, 1.8 Hz, 1H), 3.17 (d, J = 16.7 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.91 (td, J = 11.0, 4.4 Hz, 1H), 2.79 (dd, J = 16.7, 10.1 Hz, 1H), 2.35 (s, 3H), 1.91 (t, J = 11.5 Hz, 1H), 1.78 (q, J = 10.3 Hz, 1H), 1.75 – 1.59 (m, 2H), 1.55 – 1.49 (m, 1H), 1.24 – 1.12 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.4, 192.2, 136.0, 134.5, 127.5, 127.4, 125.0, 124.1, 118.2, 112.1, 60.7, 58.6, 57.6, 46.5, 44.0, 41.8, 37.5, 24.3, 11.5 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{23}N_2O_2$ $[M + H]^+$ 311.1760, found 311.1759. **$[\alpha]_D^{20}$** = –12° (c = 0.05, $CHCl_3$).

Part III

The Isoschizogamine Project

11 Schizozyganes

11.1 Introduction

Schizozyganes represent a small group of hexacyclic *N*-acyl indoline alkaloids. These alkaloids were isolated in 1963 from the twigs of *Schizozygia coffaeoides* Bail. (Apocynaceae) growing in tropical East Africa with schizozygine (**462**) being the main alkaloid (Fig. 11-1).[516] In Kenya this plant is used to treat several ailments: (i) the leaf extracts are used to treat ringworm, (ii) the steam from boiling the leaves is used to soothe inflamed eyes, (iii) the root extracts in combination with coconut oil were used for the treatment of sores on the skin. In addition, it was shown by R. M. Kariba and co-workers that theses extracts were fungitoxic to *Trichophyton mentagrophytes*, *Microsporum gypseum*, *Cladosporium cucumerinum*, and *Candida albicans*.[519]

Two pairs of minor alkaloids were also reported: schizogamine (**843**), schizogaline (**849**) and isoschizogamine (**845**), isoschizogaline (**846**).[517] The differences in physico-chemical properties between the pairs were ascribed to the epimeric stereochemistry at C-7. However, this turned

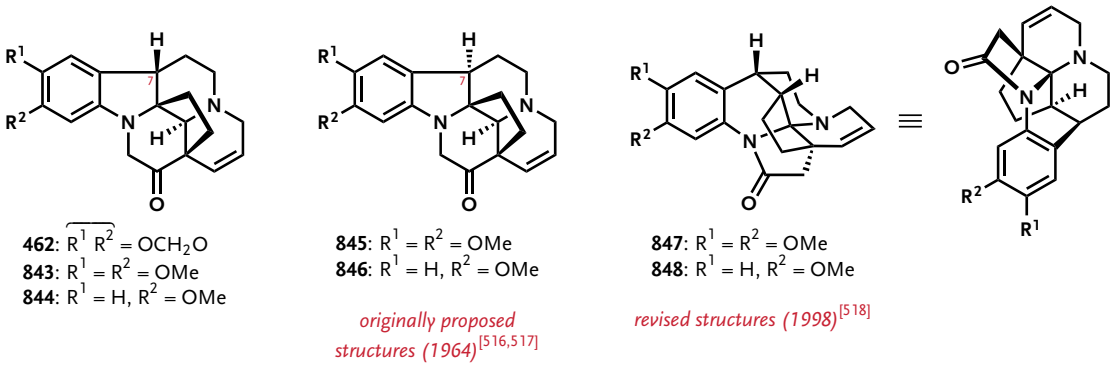


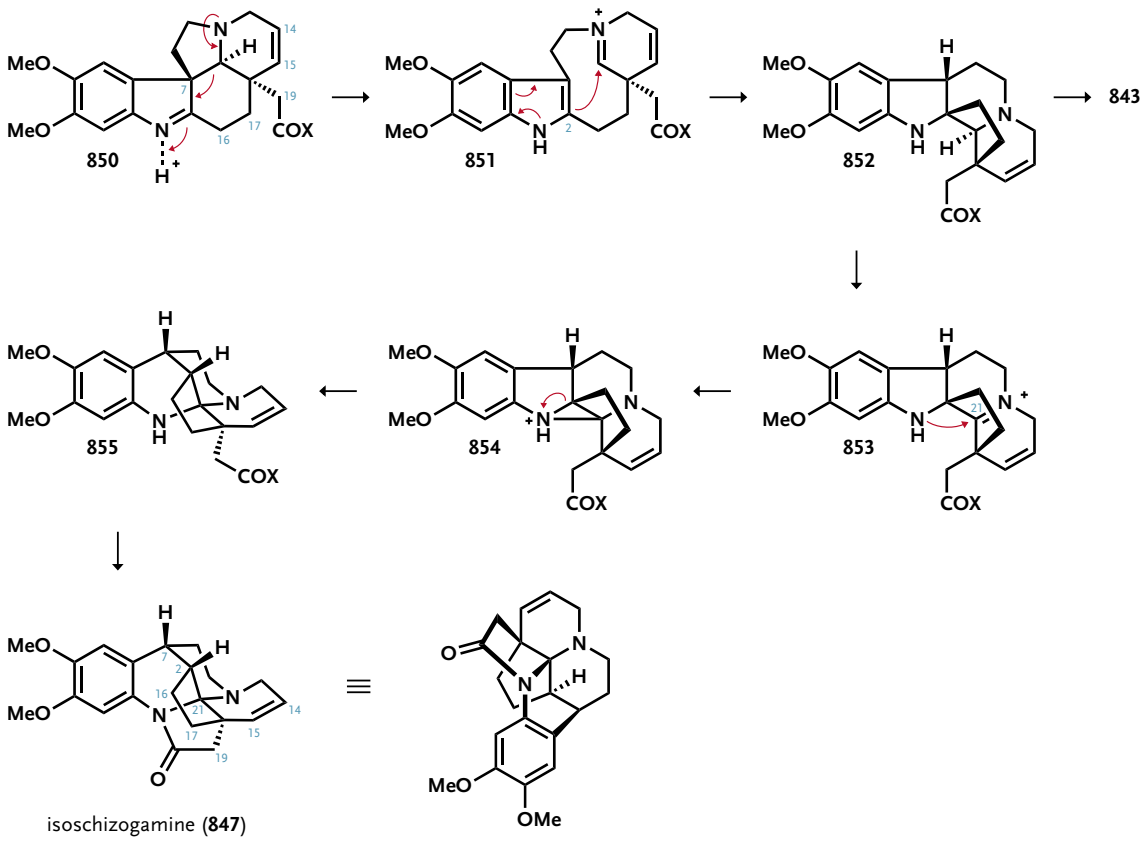
Figure 11-1. Schizozyganes from *Schizozygia caffaeoides*: (i) schizozygine (**462**), schizogamine (**843**), and schizogaline (**849**), (ii) originally proposed structures of isoschizogamine (**845**) and isoschizogaline (**848**),[516,517] (iii) revised structures of isoschizogamine (**847**) and isoschizogaline (**848**).[518]

out to be erroneous and a revised structure for isoschizogamine (**847**) and isoschizogaline (**848**) was published by J. Hájíček and co-workers based on up-to-date NMR analyses.[518] The absolute configuration of the iso-schizozygane alkaloids isoschizogamine (**847**) and isoschizogaline (**848**) was determined using vibrational circular dichroism (VCD) spectroscopy.[520,521]

11.2 Biosynthesis

It was anticipated that the skeleton of the schizozyganes could be biogenetically derived from the *Aspidosperma* alkaloid family (for further information, the author refers to Section 4.2, p. 89). Indeed, both groups of alkaloids have been found in the same plant species.[522]

J. Hájíček *et al.* reported a biosynthetic proposal[518] starting from alkaloid **850** (probably originated from the same biogenetic sequence as *Aspidosperma* alkaloid tabersonine) which undergoes rearrangement *via* indole iminium ion (Scheme 11-1). The newly formed azomethine ion is trapped by the indole *via* C-2 forming pentacycle **852**. This intermediate is the precursor for schizogamine (**843**). For the generation of its iso-derivative, dehydrogenation at C-21 takes place generating iminium **853** which is trapped by indoline nitrogen addition. This leads to



Scheme 11-1. Proposed biosynthesis of isoschizogamine (**847**).[518]

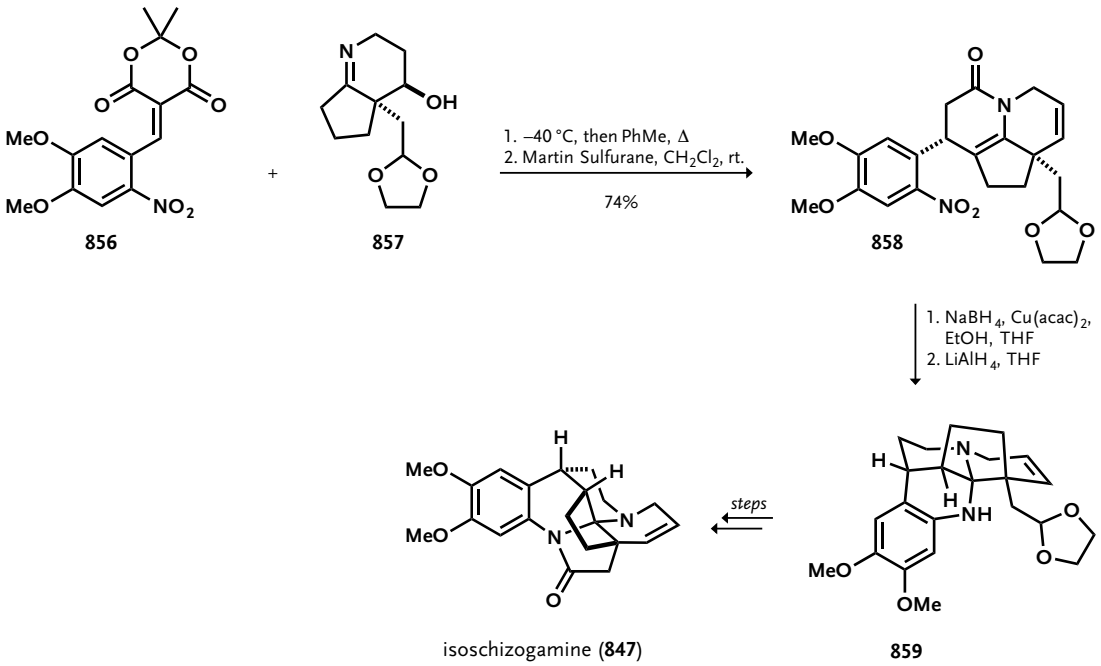
aziridine **854**. Subsequent reductive opening of the aziridine ring affords tetrahydroquinoline **855** which is finally transformed into hexacyclic isoschizogamine (**847**) *via* lactam formation.

11.3 Total Syntheses of Isoschizogamine (**847**)

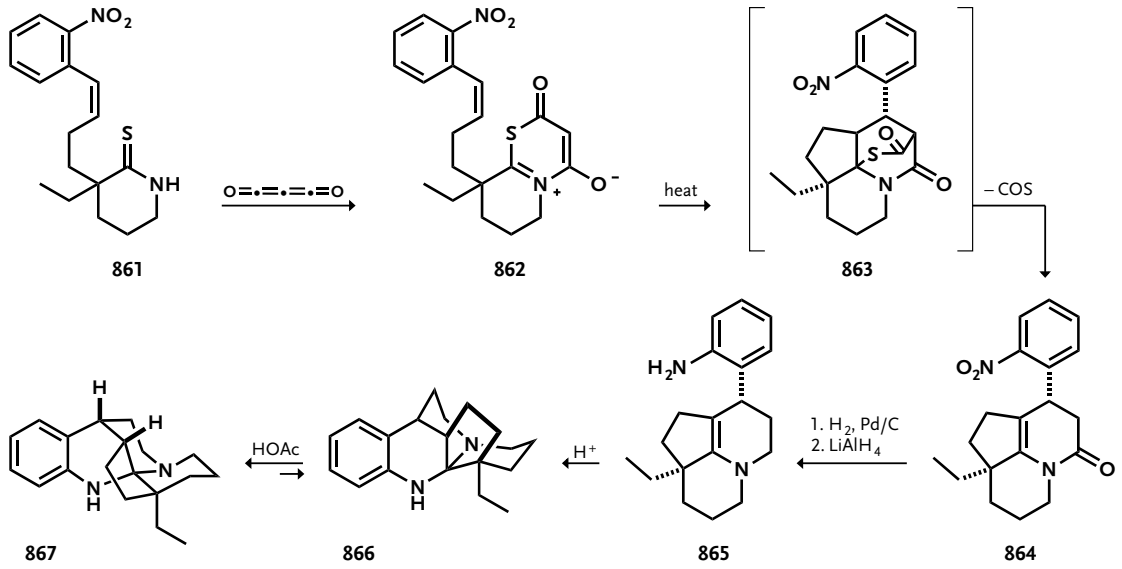
The structure of isoschizogamine (**847**) contains a unique [6,6,6,5]diazafenestrane system with an additional C2–C20 bridged five-membered ring. Additionally, the hexacyclic skeleton has a highly substituted tetrahydroquinoline unit with four contiguous stereogenic centers.

Isoschizogamine (**847**) has been synthesized five times so far. The first total synthesis of racemic **847** was published in 1999 by Heathcock *et al.*[523] (that was only one year, after the originally proposed structure has been revised by Hájíček and co-workers). The originally proposed absolute configuration *via* vibrational circular dichroism spectroscopy was later confirmed by the first asymmetric total synthesis of **847** by Fukuyama *et al.* in 2012.[524] Three additional asymmetric total syntheses of **847** have been published in 2015 by the groups of Qin,[525] Tokuyama,[526] and Zhu.[527]

In 1999, Heathcock *et al.* reported the first preparation of (±)-isoschizogamine (**847**).[523] The synthesis required eight steps from a readily available ketone starting material. The key transformations are shown in Scheme 11-2. Imine **860** underwent Michael addition to Meldrum's acid derivative **856** at –40 °C. This formed an intermediate which, upon heating in toluene, underwent a cyclization with concomitant loss of acetone and carbon dioxide. Final dehydration with Martin's sulfurane furnished tetrahydroquinolizinone **858** in 74% overall yield. The aromatic



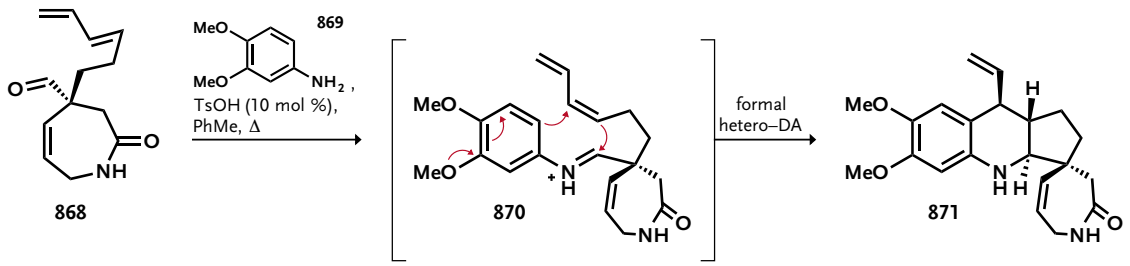
Scheme 11-2. Key transformations in the total synthesis of (±)-isoschizogamine (Heathcock, 1999).[523]



Scheme 11-3. An Approach to the isoschizozygane alkaloid core (Padwa, 2005).[528,529]

nitro group was then reduced to the corresponding aniline and subsequent reduction of the lactam carbonyl with lithium aluminium hydride gave aminal **859** as single diastereomer. **859** was transformed into (±)-isoschizogamine (**847**) in three additional steps finishing a landmark eight-step synthesis of this natural product.

Padwa and co-workers reported an approach to the isoschizozygane alkaloid core in 2005 (Scheme 11-3).[528] Thioamide **861** was reacted with carbon suboxide at ambient temperature to give isolable betaine **862** which, upon heating in toluene, underwent intramolecular 1,3-dipolar cycloaddition reaction to yield intermediate **863**. The resulting cycloadduct underwent loss of carbonyl sulfide followed by a hydrogen shift to give hexahydroquinolizinone **864**. Both the aromatic nitro group and the lactam carbonyl were reduced and treatment with acid furnished a 3:2-mixture of the diastereomeric aminals **866** and **867**. Treatment of either isolated isomer with acetic acid resulted in an equilibrated 1:6-mixture of **866** and **867** of which the latter one possessing the correct core skeleton of the isoschizozygane family of alkaloids. Padwa and co-workers reported a more detailed manuscript four years later[529] but a complete total synthesis of isoschizogamine (**847**) has not been published until today.

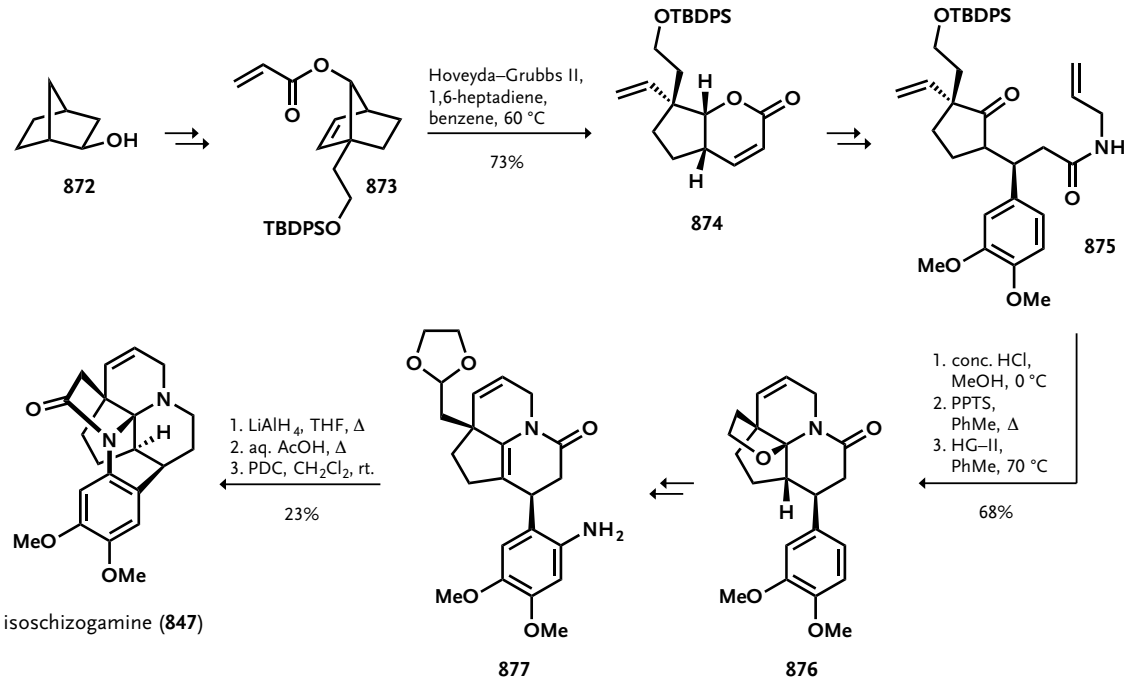


Scheme 11-4. Explorations on the asymmetric total synthesis of isoschizogamine (Zhou, 2007).[530]

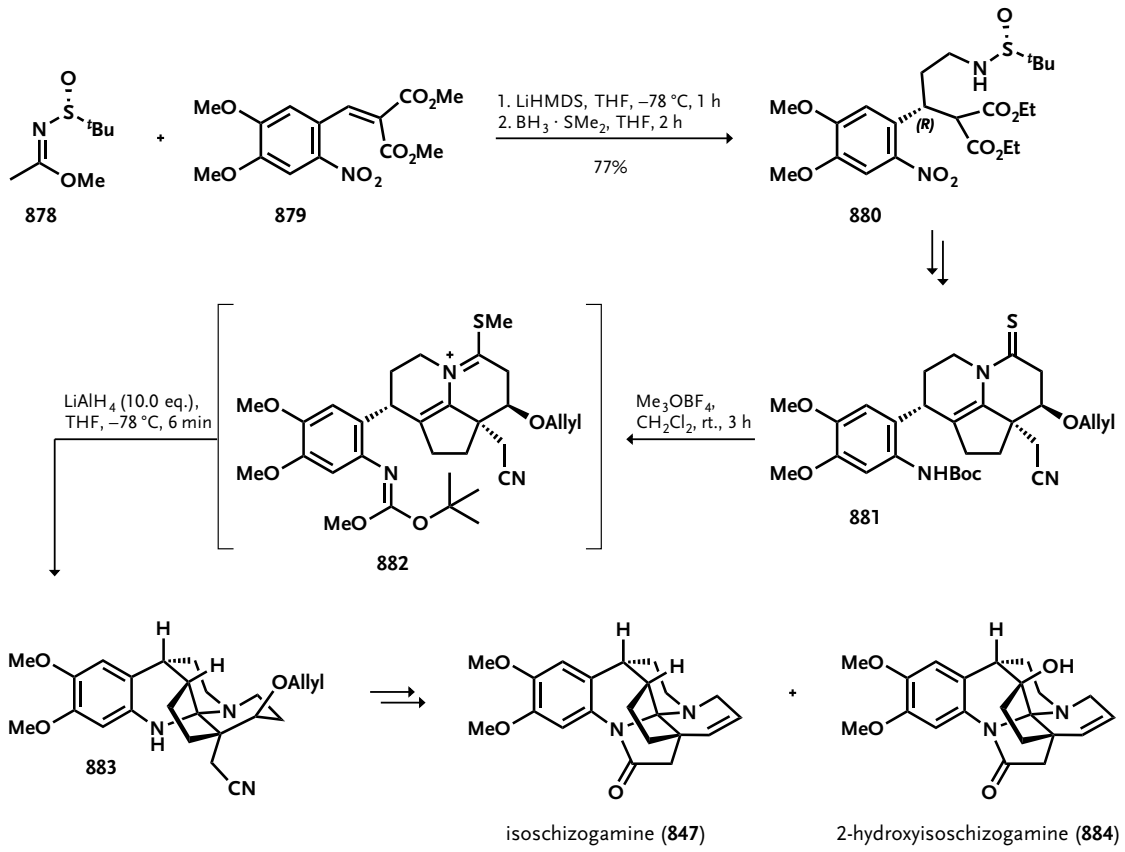
In 2007, Zhou and co-workers were the first to report an asymmetric approach towards the synthesis of (–)-isoschizogamine (**847**, Scheme 11-4).[530] ε-Lactam **868**, which was synthesized *via* an aza-Claisen rearrangement strategy,[531] was reacted with 4-aminoveratrole (**869**) and a catalytic amount of tosylic acid in refluxing toluene. This formed iminium ion **870** which *in situ* underwent a formal hetero Diels–Alder reaction to furnish highly functionalized tetrahydroquinoline product **871** which can be an intermediate in the synthesis towards isoschizogamine (**847**). However, no further approaches towards the total synthesis of **847** have been reported.

The first asymmetric total synthesis of isoschizogamine (**847**) was published by Fukuyama *et al.* in 2012 (Scheme 11-5).[524] Transformation of (+)-exo-norborneol (**872**) into bicyclic compound **873** was carried out by means of a Wagner–Meerwein rearrangement. Tandem metathesis constructed bicyclic lactone **874** which was transformed into ketone **875** in three steps. Acid-mediated cleavage of the TBDPS group, followed by treatment with PPTS in refluxing toluene, afforded a hemiaminal ether and subsequent metathesis furnished hexahydroquinoline **876** in 68% overall yield. This intermediate was transformed into Heathcock's key intermediate **876** in additional eight steps and (–)-isoschizogamine (**847**) was completed similar to Heathcock *et al.* in three steps.

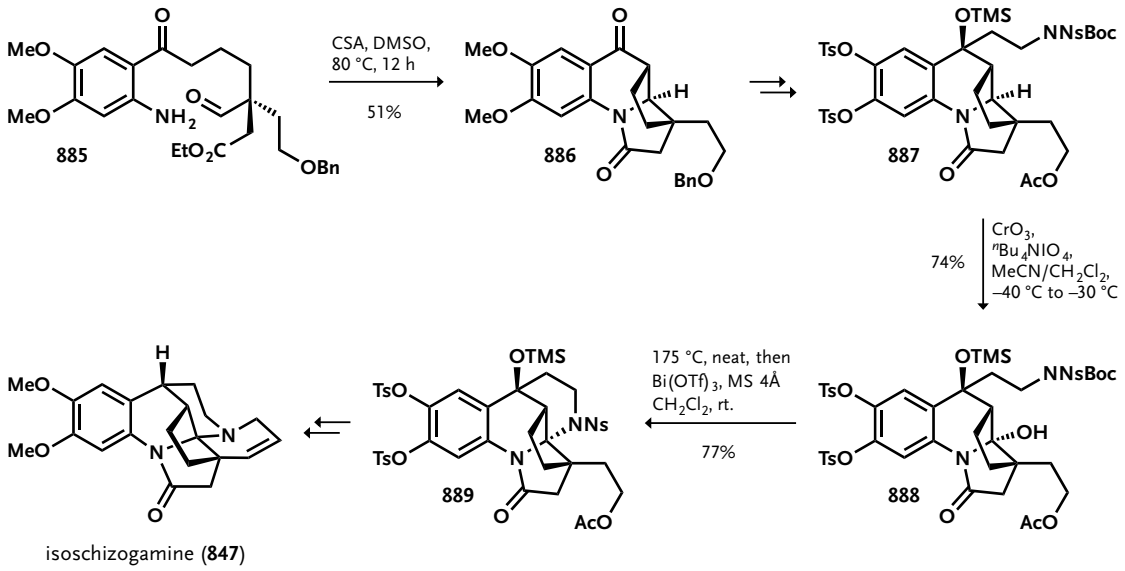
In late 2015, three asymmetric total syntheses of isoschizogamine (**847**) have been published. The synthesis of Qin and co-workers[525] employed two asymmetric Michael addition reactions to establish the chiral centers at C-7 and C-20. A key intermediate is thioamide **881** (a similarity to Heathcock's intermediate is once again obvious). The thioamide and amide functionalities were converted to a methylthioiminium cation and a methoxyl imidate group, respectively, using



Scheme 11-5. Key transformations in the total synthesis of (–)-isoschizogamine (Fukuyama, 2012).[524]



Scheme 11-6. Key transformations in the total synthesis of (–)-isoschizogamine and (–)-2-hydroxyisoschizogamine (Qin, 2015).[525]

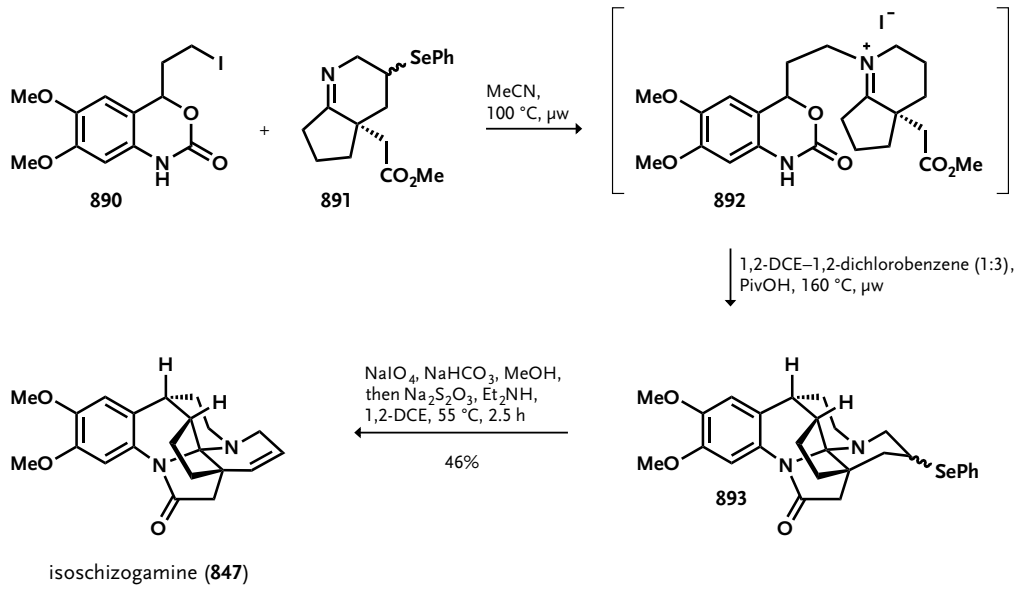


Scheme 11-7. Key transformations in the total synthesis of (–)-isoschizogamine (Tokuyama, 2015).[526]

Meerwein salt. This *in situ* prepared intermediate was then treated with lithium aluminium hydride at –78 °C to provide hexacyclic intermediate **883**. This intermediate is already very close to the natural product and was converted in several additional steps to (–)-isoschizogamine (**847**) and unnatural 2-hydroxyisoschizogamine (**884**).

In the synthesis of Tokuyama *et al.*,[526] chiral aldehyde **885** underwent an acid-mediated diastereoselective triple cyclization cascade including an intramolecular aldol condensation, aza–Michael addition, and lactamization in one-pot to provide the tetracyclic compound **886** as a single isomer (Scheme 11-7). **886** was then transformed into **887** in several steps. Chemoselective C–H oxidation at the position adjacent to the nitrogen atom afforded compound **888** which was heated to thermally remove the Boc group and subsequent treatment with bismuth triflate in the presence of molecular sieves constructed the cyclic aminal **889**. (–)-Isoschizogamine (**847**) was synthesized in eight additional steps.

One of the most elegant and short total syntheses of isoschizogamine (**847**) was reported by Zhu and co-workers (Scheme 11-8).[527] Carbamate **890** (accessible in four steps from 6-nitroveratraldehyde) was reacted with optically active selenoimine **891** (accessible in four steps from commercially available material) in acetonitrile at 100 °C (microwave) to afford iminium salt **892**. Pivalic acid was added and the resulting solution was once again heated to 160 °C for 30 minutes under microwave irradiation to give desired hexacyclic compound **893**. Oxidation of **893** to the selenoxide followed by a *syn* elimination afforded (–)-isoschizogamine (**847**) in 46% overall yield.



Scheme 11-8. Key transformations in the total synthesis of isoschizogamine (Zhu, 2015).[527]

11.4 Strategy and Retrosynthetic Analysis

Isoschizogamine (**847**) is a highly fused hexacyclic compound and contains a unique [6,6,6,5]diazafenestrane system, thus the two nitrogen atoms of these heterocycles form an aminal adjacent to a quaternary carbon. with an additional C2–C20 bridged five-membered ring (Fig. 11-2). Additionally, the hexacyclic skeleton has a highly substituted tetrahydroquinoline unit with four contiguous stereogenic centers and a pyrrolidinone moiety.

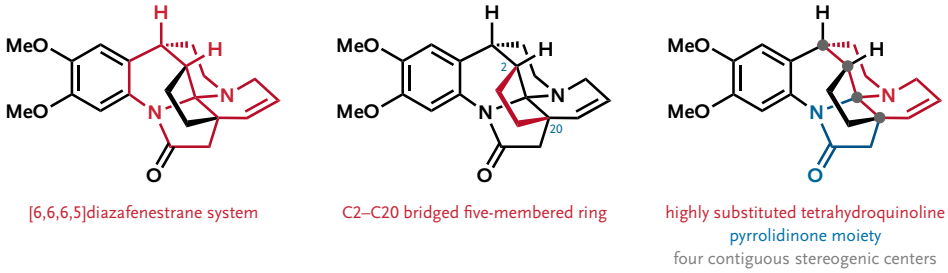
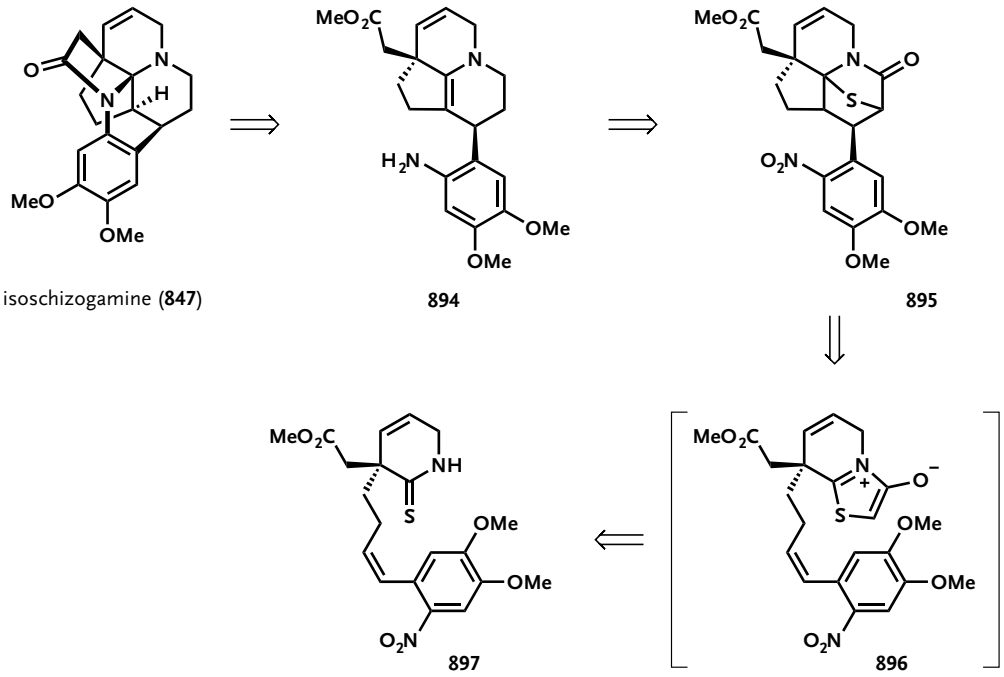
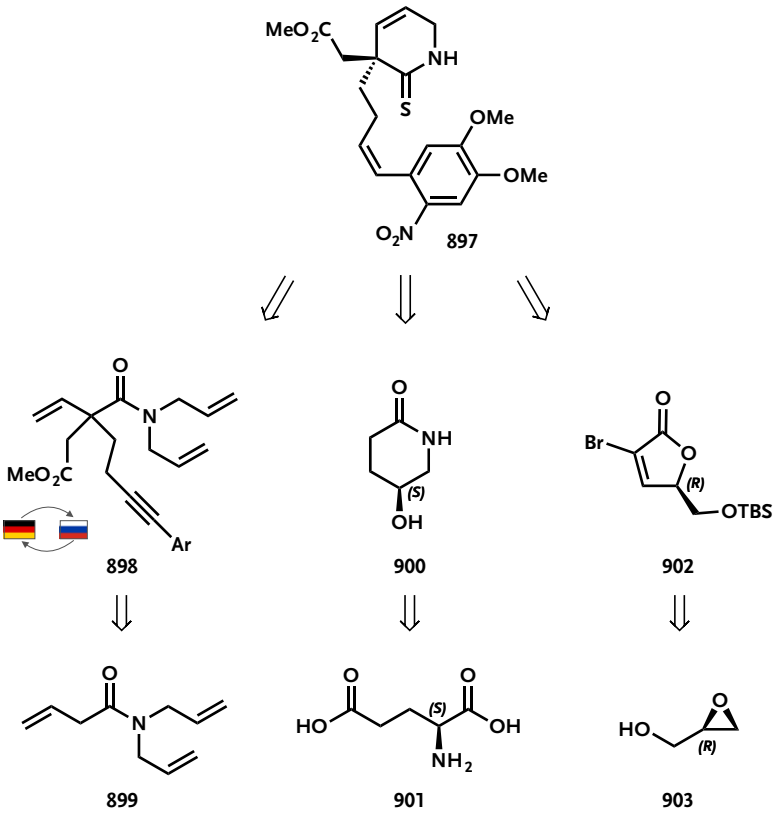


Figure 11-2. Analysis of the hexacyclic framework of isoschizogamine (**847**).

The strategy for the synthesis of isoschizogamine (**847**) is shown in Scheme 11-9. **847** is formed in an acid-mediated reaction from tetrahydroquinolizine **904** which in turns derives from epithioquinolizinone **895** *via* thioamide formation and desulfurization with Raney nickel. The formation of epithioquinolizinone **895** represents the key-step in this synthesis. It is planned to form **895** from α,α-disubstituted dihydropyridinethione **897** *via* substituted thioisomünchnone intermediate **896**. α,α-Disubstituted dihydropyridinethione **897** itself can be formed (i) from



Scheme 11-9. Retrosynthetic analysis (part I).



Scheme 11-10. Retrosynthetic analysis (part II).

amide **898** (racemic variant), (ii) from (*S*)-5-hydroxypiperidin-2-one (**900**, derived from L-**905**), or (iii) from γ-butenolide **902** (derived from glycidol **903**, Scheme 11-10). The first metathesis approach was carried out in cooperation with a Russian group colleague (Konnichiwa).

The key intermediate of this synthesis is planned to be the thioisomünchnone[534,535] derivative **896**. Thioisomünchnone is a trivial name for derivatives of either mesoionic compound thiazol-3-ium-4-olate (**919**) or thiazol-3-ium-5-olate (**920**, Fig. 11-3). There are several general ways for the generation of thioisomünchnones, all of them are based on thioamides. Potts *et al.* described the synthesis of thioisomünchnones *via* the reaction of bromoalkenoyl chlorides with thioamides (Scheme 11-11a).[533] Another possibility is the reaction of thioamides with diazo compounds, also first reported by Potts and co-workers (Scheme 11-11b).[532] Modern modifications of this procedure use metal catalysis (e.g. rhodium). A third option is the reaction of thioamides with oxirane-2,2-dicarbonitrile derivatives like **914**. The double loss of hydrogen cyanide forms ketene intermediate **917** which generates thioisomünchnone **918** as first reported by Baudy and co-workers (Scheme 11-11c).[536]

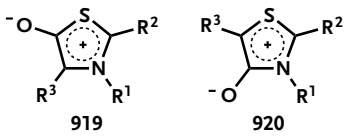
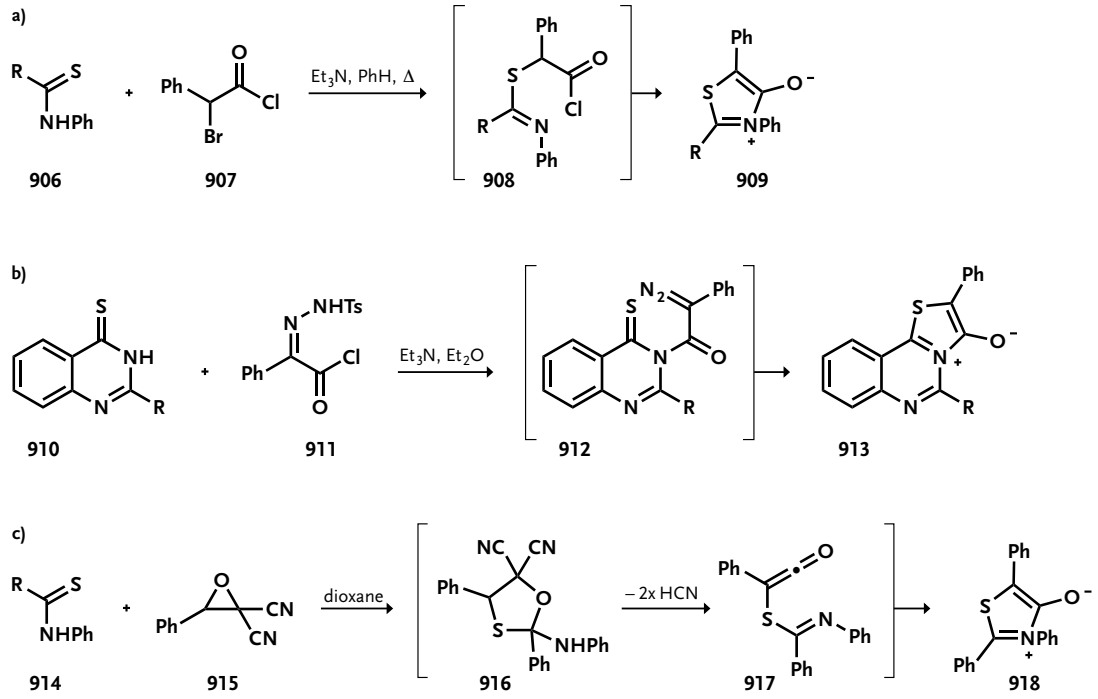


Figure 11-3. Thioisomünchnones.

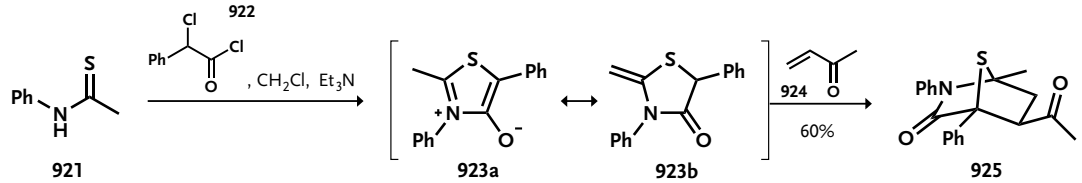


Scheme 11-11. Syntheses of thioisomünchnones.[532,533,536a,536b]

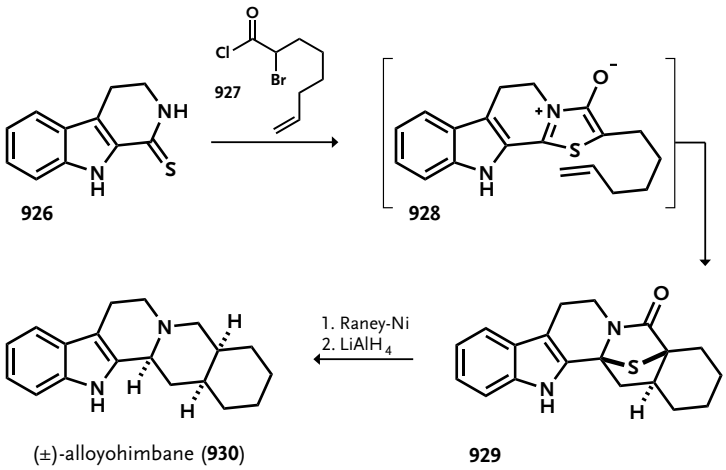
Isomünchnones and its sulfur counterpart thioisomünchnones have been applied frequently in diverse synthetic approaches and total syntheses[537–543] and several reviews have been published.[544–548]

Thioisomünchnones possess a masked thiocarbonylylide dipol which is stabilized through the nitrogen. This dipole allows this mesoionic compound to react remarkably with electron poor olefins thus undergoing 1,3-dipolar cycloadditions. Palacios *et al.* have demonstrated the general reactivity of 2-methyl thioisomünchnone with several α,β-unsaturated compounds. Thioisomünchnone **923** is generated from the reaction of thioamide **921** and chloroalkenoyl chloride **922** and reacts with the electron poor double bond of methyl vinyl ketone to furnish 2-aza-3-oxo-7-thiabicycle **925** (Scheme 11-12).[549]

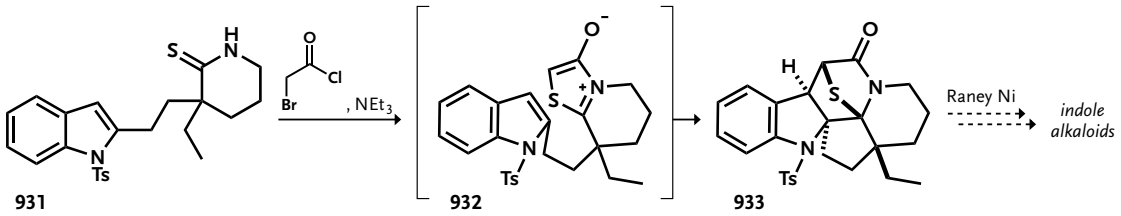
Padwa and co-workers demonstrated the feasibility of the 1,3-dipolar cycloaddition reaction of thioisomünchnones with olefins in a short total synthesis of yohimbanoid alkaloid (±)-alloyohimbane (**930**, Scheme 11-13). Thioisomünchnone dipole **928** was generated by the reaction of bromoalkenoyl chloride **927** with thioamide **926**. Subjection of thio-cycloadduct **929**



Scheme 11-12. Reactivity of 2-methyl thioisomünchnone.[549]



Scheme 11-13. Total synthesis of alloyohimbane (Padwa, 1998).[550]



Scheme 11-14. Group work.

to Raney nickel followed by further reduction using lithium aluminium hydride yielded (±)-alloyohimbane (**930**) in 24% overall yield.

Previous work in our group demonstrated the transformation of thioamide **931** into thioisomünchnone **932** and its intramolecular 1,3-dipolar cycloaddition reaction for the generation of cycloadduct **933**. This highly efficient method could be used for the synthesis of complex polycyclic *N*-heterocycles and was therefore chosen as key-step in the synthesis of isoschizogamine (**847**).

Approaches Towards the Synthesis of Isoschizogamine

12

These chapter describes three different approaches towards the synthesis of the thioisomünchnone precursor for the synthesis of isoschizogamine (**847**). This project was a side project on which work was carried out simultaneously to the primary cyclohepta[*b*]indole project. Work on this project found a more or less abrupt end when the cyclohepta[*b*]indole project began to produce promising results. In favor of the completion of the total syntheses of diverse natural products with the cyclohepta[*b*]indole motif, the work on this project was discontinued. The beginning of the first approach was carried out in cooperation with my group colleague Konstantin. Since the first approach found a quick end and was not relevant, the results of Konstantin have not found its way into this section.

12.1 Preface: The 3,6-Dihydropyridin-2-one Moiety

Although the 3,6-dihydropyridin-2-one motif seems very simple, its synthesis and the synthesis of its α,α-disubstituted derivatives should not be underestimated. The β,γ-unsaturated double bond turns this compound into a difficult to synthesize intermediate and literature concerning its synthesis is scarce. The unsubstituted dihydropyridinone is either synthesized by means of metathesis[551,552] or by the reaction of ammonia with vinyl acrylic acid.[553] However, the latter example produces the α,β-unsaturated compound as the major product. For the synthesis of α,α-disubstituted dihydropyridinones only four examples are reported in literature of which two are published in the context of isoschizogamine and use basically the same strategy.

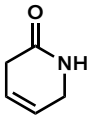
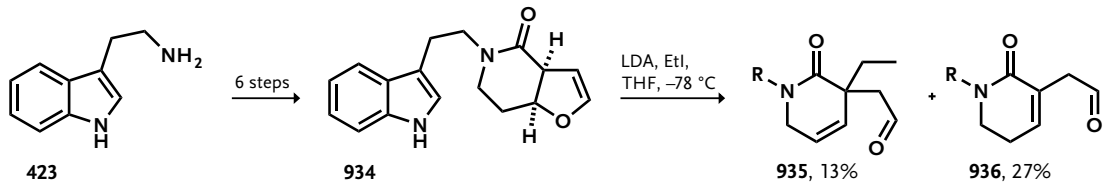
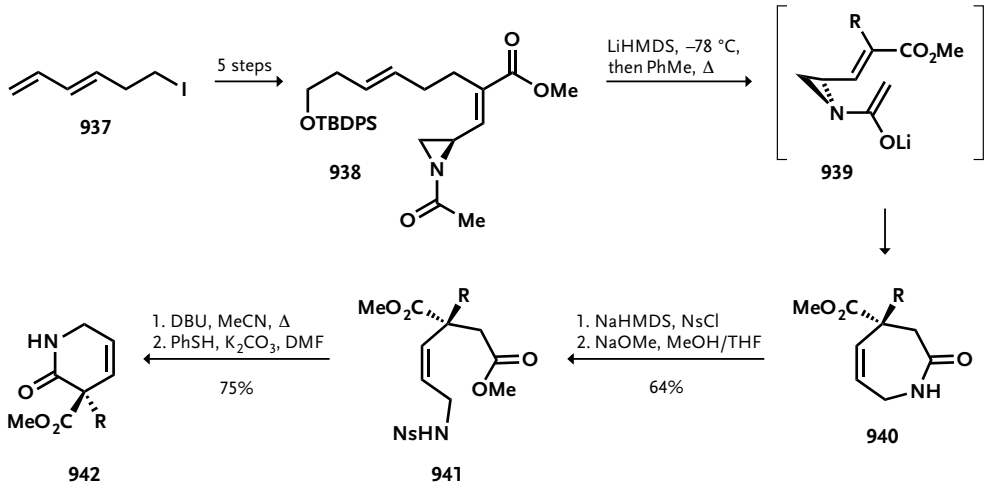


Figure 12-1. 3,6-Dihydropyridin-2-one.

Naito and co-workers reported the synthesis of furopyridone **934** in six steps starting from tryptamine (**423**, Scheme 12-1). Treatment of **934** with LDA (5.0 eq.) and ethyl iodide (10.0 eq.) furnished α,α-disubstituted lactam **935** in 13% yield. However, the major product was α,β-unsaturated lactam **936** (27%).



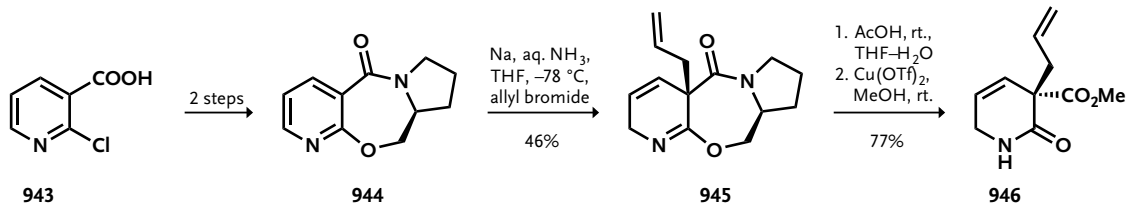
Scheme 12-1. Synthesis of α,α-disubstituted dihydropyridinone **935** (Naito, 1992). R = CH_2-CH_2-indole.[554]



Scheme 12-2. Synthesis of α,α-disubstituted dihydropyridinone **942** (Zhou, 2007), R = $(CH_2)_2-CH=CH-(CH_2)_2-$OTBDPS.[530]

Zhou and co-workers (*cf.* Section 11.3) reported the synthesis of vinyl *N*-acetylaziridine **938** in five steps from diene **937** (Scheme 12-2). Treatment of **938** with LiHMDS followed by heating in toluene furnished γ,δ-unsaturated ε-lactam **940** *via* [3,3]-sigmatropic rearrangement. Ring-opening-ring-closing sequence afforded α,α-disubstituted dihydropyridinone **942** in four additional steps in 48% overall yield. A similar strategy was also used by Padwa and co-workers in 2010 (*cf.* Section 11.3).[529]

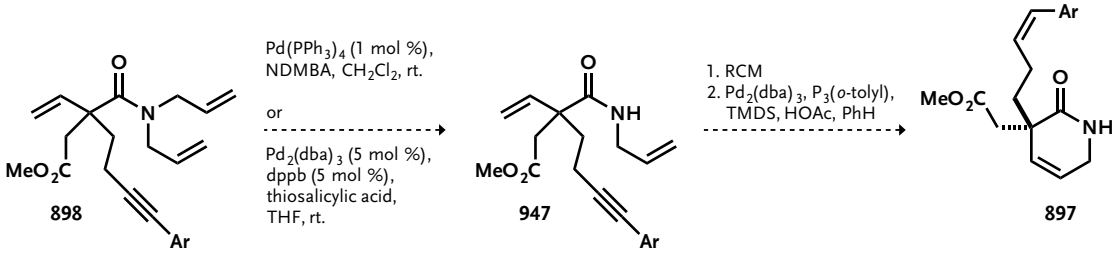
En route to (+)-vincadifformine (**459**), Pandey *et al.* reported the synthesis of optically active α,α-disubstituted dihydropyridinone **946**. 2-chloronicotinic acid (**943**) was transformed into nicotinic acid derivative **944**. Birch reduction-alkylation of **944** was only possible with the strong electrophillic allyl bromide and 2,5-dihydropyridine derivative **945** was obtained in moderate 46% yield. Acid-mediated ring opening followed by copper-mediated removal of the auxiliary furnished α,α-disubstituted dihydropyridinone **946** in two additional steps.



Scheme 12-3. Synthesis of α,α-disubstituted dihydropyridinone **946** (Pandey, 2011).[555]

12.2 The Metathesis Approach

The target compound in this approach is α,α-disubstituted amide **898** (Scheme 12-4). It was planned to form dihydropyridinone **897** *via* ring-closing metathesis. For this purpose, one allyl group can be selectively cleaved with either a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in the presence of *N,N*-dimethylbarbituric acid[556] or a catalytic amount of $Pd_2(dba)_3$ and a phosphine ligand (dppb) in the presence of thiosalicylic acid.[557] Both methodologies are known to remove selectively one allyl group from diallylamines. After the ring closure, the internal alkyne has to be reduced to the corresponding *(Z)*-alkene which is not trivial in the presence of an aromatic nitro group. However, according to Trost *et al.* this can be achieved once again with $Pd_2(dba)_3$ and a phosphine ligand (tri-*o*-tolylphosphine) with 1,1,3,3-tetramethyldisiloxane as the hydride donor.[558] α,α-Disubstituted amide **897** is the required precursor for the desired formation of the thioisomünchnone intermediate (Section 11.4).

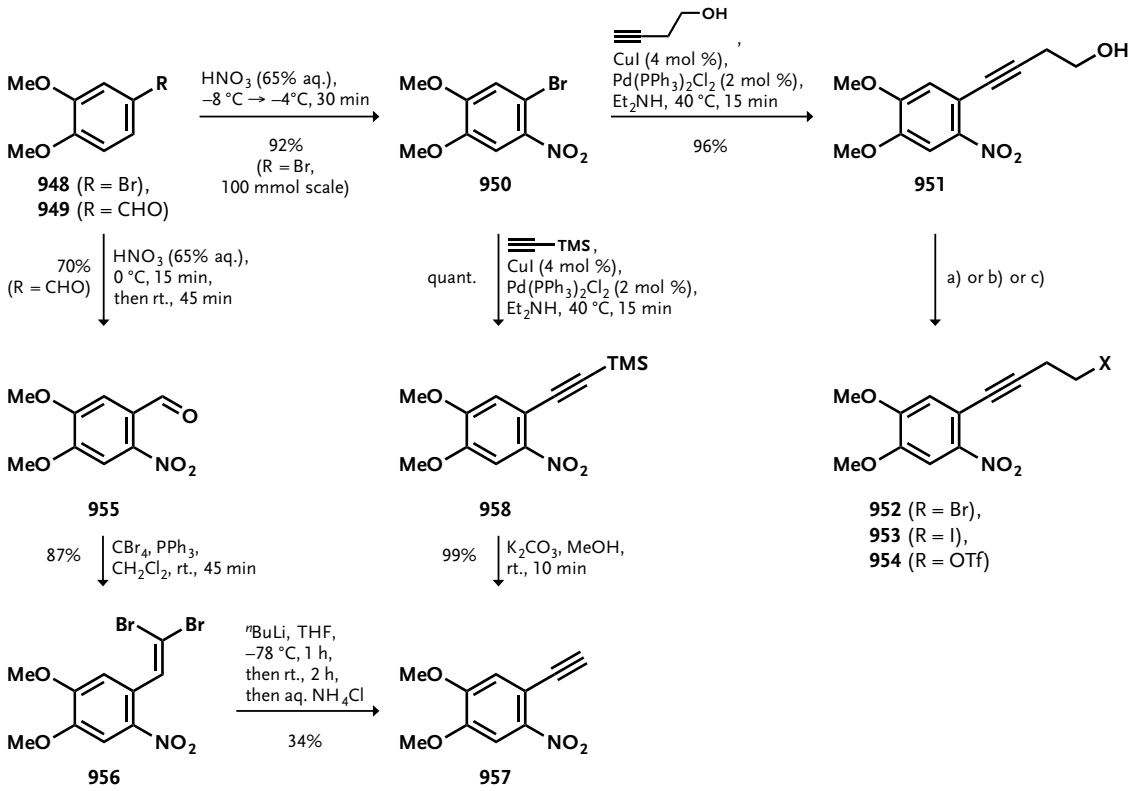


Scheme 12-4. Planned transformation of target compound **898** into key intermediate **897**.

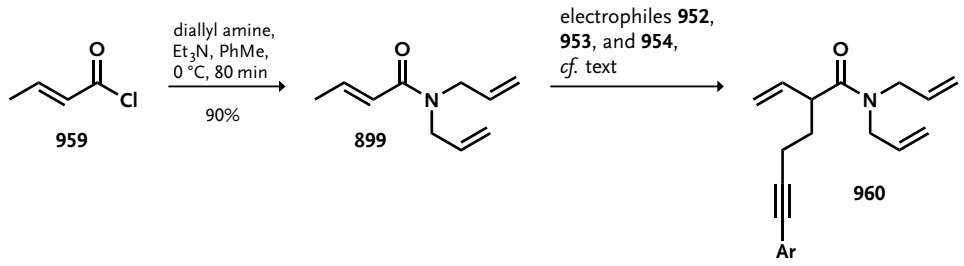
A variety of electrophiles and veratrol derivatives which are required for upcoming synthetic sequences have been synthesized. These are discussed at first (Scheme 12-5). 4-Bromoveratrole (**948**) was reacted with 65% aqueous nitric acid at –4 °C for 30 min to afford 4-bromo-5-nitroveratrole (**950**) in 92% yield. Sonogashira coupling with but-3-yn-1-ol afforded alkyne **951** in very good yield (96%). Alcohol **951** was then transformed into its corresponding bromide **952**, iodide **953**, and triflate **954** using standard procedures.

In a further sequence, veratraldehyde (**949**) was transformed into 6-nitroveratraldehyde (**955**) with 65% aqueous nitric acid. Conversion of the aldehyde into the 1,1-dibromoolefine **956** followed by Fritsch–Buttenberg–Wiechell rearrangement afforded terminal alkyne **957** in moderate yield (30%). In an alternative sequence, Sonogashira reaction of 4-bromo-5-nitroveratrole (**950**) with trimethylsilylacetylene afforded trimethylsilyl alkyne **958** in quantitative yield. The deprotection of the alkyne moiety was carried out with potassium carbonate in methanol and afforded terminal alkyne **957** in almost quantitative yield.

With electrophiles **952**, **953**, and **954** in hands attention next turned to the alkylation of crotonoyl diallylamide **899** (Scheme 12-6). **899** was synthesized from the reaction of crotonoyl chloride (**959**) with diallyl amine in toluene at 80 °C. The α-alkylation of amide **899** turned out to be quite cumbersome. Reaction of the lithium enolate of **899** (generated with either LiHMDS, LDA, or LiTMP) with aryl bromide **952**, aryl iodide **953**, or aryl triflate **954** at –78 °C did not

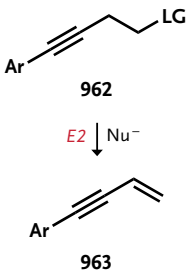


Scheme 12-5. Syntheses of diverse veratrol derivatives and electrophiles. Reagents and conditions: **a)** PBr_3, THF, 0 °C → rt., 12 h, 27%. **b)** PPh_3, imidazole, I_2, benzene, 2 min. **c)** Tf_2O, pyridine, CH_2Cl_2, –10 °C, 10 min, 88%.



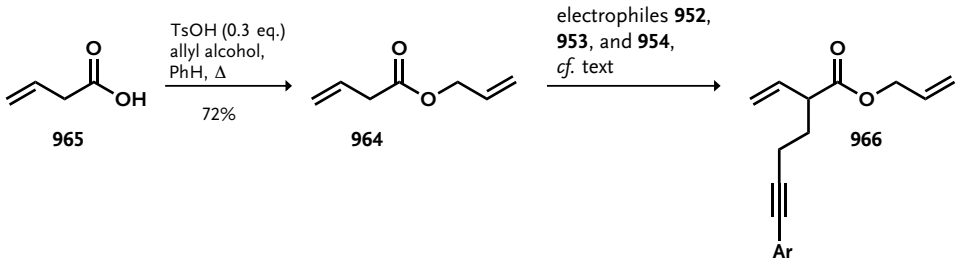
Scheme 12-6. Synthesis of crotonoyl diallylamide **961** and its reaction with various electrophiles.

form α-alkylated amide **960**. Instead, E2 elimination reaction took place and transformed the electrophiles into the corresponding aryl butenyne derivatives (*cf.* Scheme 12-7). Neither the addition of either DMPU or HMPA, nor the lowering of the reaction temperature to –100 °C did affect this result. Therefore, the α-alkylation of allyl but-3-enoate (**964**), which is easy accessible from vinylacetic acid, was investigated (Scheme 12-8) but similar results were obtained.

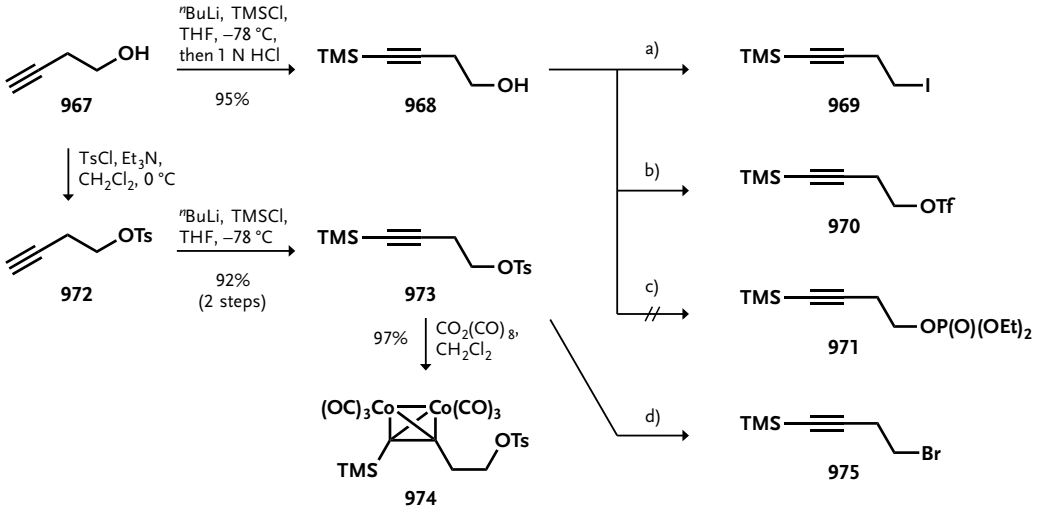


Scheme 12-7. E2 elimination reaction dominated over S_N2 displacement reaction.

As a result, compounds **952**, **953**, and **954** turned out to be great substrates for an elimination reaction but weak substrates for an S_N2 reaction. Therefore, the electrophiles have been modified and the aryl rest was



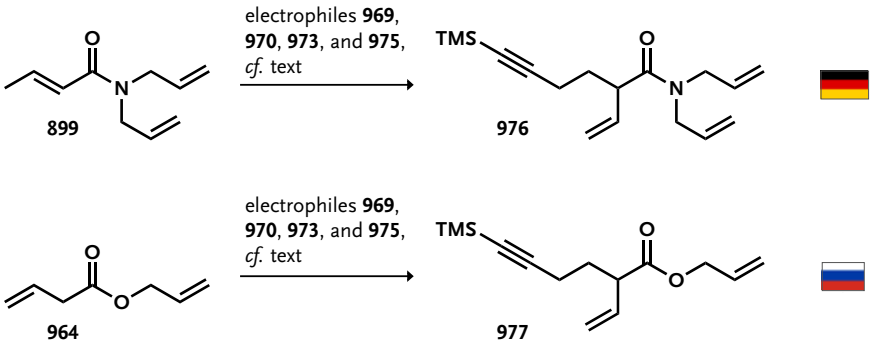
Scheme 12-8. Synthesis of allyl but-3-enoate (**964**) and its reaction with various electrophiles.



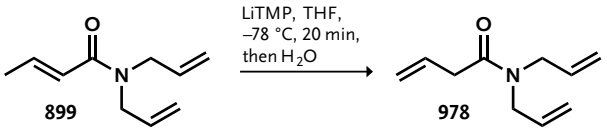
Scheme 12-9. Syntheses of various butynyl electrophiles. Reagents and conditions: **a)** PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C → rt., 16 h, 86%. **b)** Pyridine, diethyl chlorophosphate, 0 °C, decomposition. **c)** Pyridine, trifluoromethanesulfonic anhydride, 0 °C, 10 min, 81% **d)** LiBr (2.0 eq.), TBAI (2 mol %), acetone, rt., 12 h, 88%.

replaced by a trimethylsilyl group. Starting from but-3-yn-1-ol (**967**), a variety of electrophiles has been synthesized (Scheme 12-9). Treatment of **967** with an excess of ^{n}BuLi followed by the addition of an excess of chlorotrimethylsilane and subsequent work-up with 1 N HCl afforded protected alkyne **968** in 95% yield. The alcohol moiety was then converted into the corresponding iodide **969** and triflate **970** using standard procedures. Reaction of alcohol **968** with diethyl chlorophosphate led to decomposition and phosphate **971** was not obtained. In an alternative sequence, but-3-yn-1-ol (**967**) was converted into its corresponding tosylate **973** which was then subjected to ^{n}BuLi and chlorotrimethylsilane to furnish protected alkyne **973** in 92% yield. This compound was converted both to the corresponding bromide **975** with lithium bromide and to the cobalt-substituted alkyne **974** by the reaction with dicobalt octacarbonyl.

With this variety of electophiles in hands, attention next turned to the alkylation of diallylamide **899** (own work) and of ester **964** (group colleague, Scheme 12-10). Once again, lithium enolate of **899** (generated with either LiHMDS, LDA, or LiTMP) was reacted with bromide **975**, tosylate **973**, or iodide **969** but no reaction could be observed and only small amounts of the corresponding E2 product has been formed. To evaluate this result, the lithium enolate of **899** was generated with LiTMP and quenched by the addition of water (Scheme 12-11) to afford



Scheme 12-10. Alkylation of amide **899** and ester **964**.



Scheme 12-11. Formation of the anion of **899** and subsequent quench by H_2O.

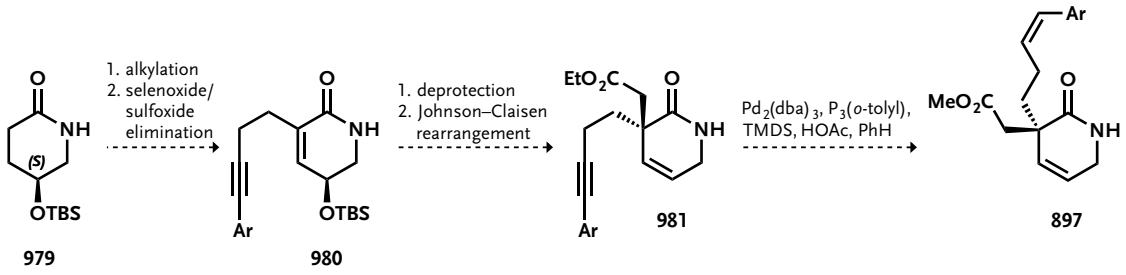
N,N-diallylbut-3-enamide (**978**) thus proving the formation of the anion. Alkylation product **976** could finally be generated with triflate **970** and the addition of HMPA (2.2 eq.). However, the yield was very low (<10%) thus making this transformation not feasible. Same was true for the alkylation of ester **964** (group colleague).

In summary, the alkylation of both the amide **899** and the ester **964** turned out to be very cumbersome. On the one hand, ethynylaryl compounds **952**, **953**, and **954** turned out to be unfavorable S_N2 substrates and were not suitable for an alkylation reaction due to the domination of the E2 elimination reaction. On the other hand, ethynylsilyl compounds **969**, **973**, and **975** were also not suitable for an alkylation reaction since no reaction with these substrates took place. Only the reaction with triflate **970** could generate traces of the desired compounds but this transformations were not feasible due to the low yield.

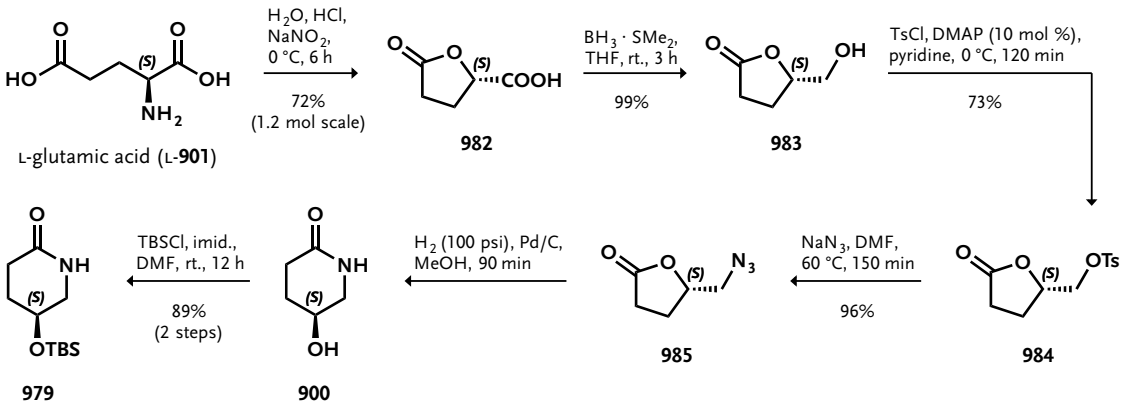
12.3 The Hydroxypiperidinone Approach

The second approach is based on a completely different strategy than the metathesis approach. The target compound in this approach is α,α-disubstituted amide **981** (Scheme 12-12). This compound can be easily transformed into amide **897** which is the required precursor for the desired formation of the thioisomünchnone intermediate (Section 11.4). However, in this approach α,α-disubstituted amide **981** derives from a 5-hydroxy-5,6-dihydropyridinone derivative (e.g. **980**) *via* a Johnson–Claisen rearrangement reaction. This leads to precursor **979**: TBS-protected (*S*)-5-hydroxypiperidin-2-one, a compound which can be synthesized in an enantiopure fashion from glutamic acid.

The synthesis of optically active lactam **979** is shown in Scheme 12-13 and is based on (*S*)-5-oxo-tetrahydrofuran-2-carboxylic acid (**982**)—a readily available and popular building block. First



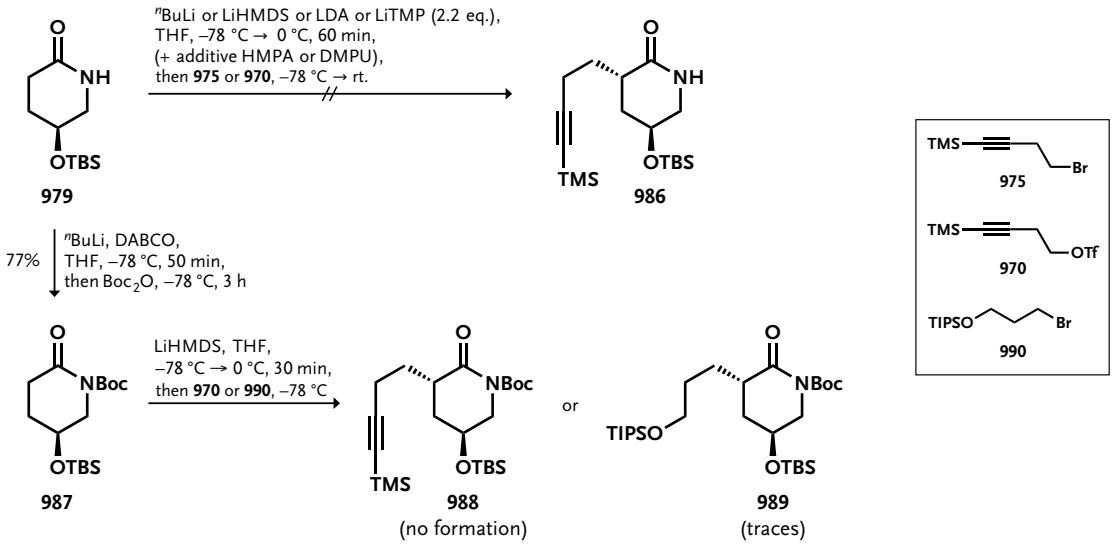
Scheme 12-12. Planned transformation of target compound **979** into key intermediate **897**.



Scheme 12-13. Synthesis of TBS-protected (*S*)-5-hydroxypiperidin-2-one.

introduced by K. Mori in 1975 in the synthesis of sulcatol[559] it has been used over 50 times in various syntheses.[560] Starting from L-glutamic acid, reaction with sodium nitrite in acidic medium at 0 °C for six hours smoothly furnished γ-carboxyl-γ-butyrolactone **982** in 72% yield.[559,561,562] This reaction can be carried out on large scales without difficulty (in this case 1.2 mol/180 g). The deamination of L-**901** proceeds *via* a diazonium ion. The choice of pathway, however, is not obvious and has been discussed.[563] Next in line was the generation of alcohol **983** *via* reduction of the carboxylic acid. There are many possibilities for this transformation. Originally obtained by reduction of the corresponding methyl ester, it was found out that the more convenient direct reduction of **982** with borane dimethyl sulfide gave almost quantitative distilled yields of alcohol **983** with full retention of configuration. **983** was then transformed into azide **985** in a two-step sequence *via* formation of tosylate **984** and subsequent displacement of the sulfonate group with sodium azide in *N,N*-dimethyl formamide.[564] Hydrogenation of azide **985** was then used for the generation (*S*)-(–)-piperidinol (**900**) which was directly converted into its TBS-protected counterpart **979** in 89% overall yield.[565]

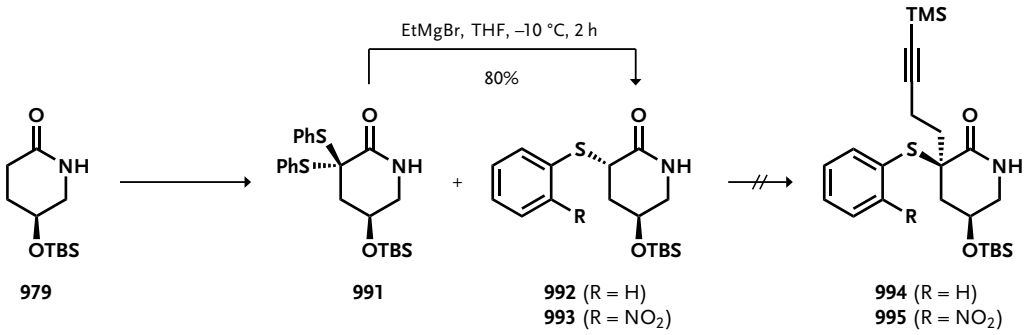
With TBS-protected (*S*)-(–)-piperidinol **979** in hands, attention next turned to the α-alkylation of this compound. Although some protocols for the α-alkylation of unprotected δ-valerolactam have been reported,[566] the α-alkylation of **979** remains a *terra incognita* and attempts for this alkylation are shown in Scheme 12-14. Once again, the alkylation turned out to be very cumbersome and can be summarized briefly. Several attempts for the reaction of optically active amide **979** with



Scheme 12-14. Several attempts for the alkylation of TBS-protected (*S*)-(–)-piperidinol (**979**).

at least two equivalents of either ^{n}BuLi, LiHMDS, LDA, or LiTMP followed by the addition of either electrophile **975** or **970** did not afford homopropargylic amide **986**. The addition of either HMPA or DMPU did not change this result. For this reason, the free amide was protected with a Boc group and alkylations of **987** were investigated. Reactions with either electrophile **975** or **970** were not successful and homopropargylic amide **988** was not formed. Only the reaction with electrophile **990** have generated alkylation product **989**—but only in trace amounts, thus making this route unfavorable.

On this account, it was planned to bring the sulfenylation step forward, thus changing the order of steps. Therefore, lactam **979** was transformed into different 3-(arylthio)piperidinones (Scheme 12-14, *cf.* Tab. 12-1). However, these transformations often produced the monosulfide compound **992** as the minor product and the formation of the bissulfide adduct **991** dominated. Addition of HMPA and prolonged reaction times below –70 °C finally afforded monosulfide compound **992** as the major product in 50% yield. Notwithstanding this, two protocols for the desulfenylation either by a Grignard reagent or by LDA/HMPA have been reported.[567,568]



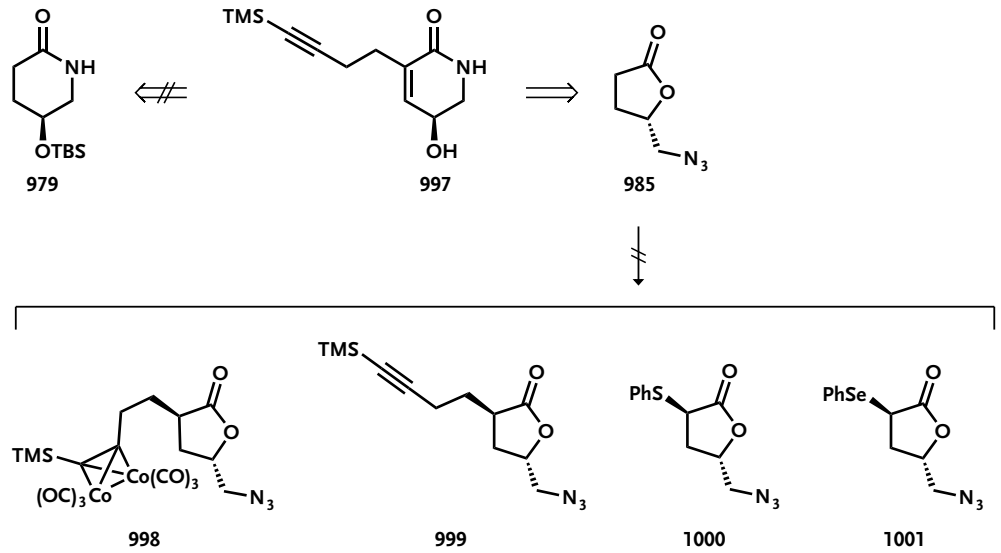
Scheme 12-15. Preparation of 3-(arylthio)piperidinones.

Table 12-1. Conditions for Scheme 12-15.

#	Conditions	991	992	993
1	^{n}BuLi (2.2 eq.), THF, –78 °C → 0 °C, 60 min, then PhSSPh, 2 h	28%	26%	—
2	^{n}BuLi (1.0 eq.), THF, –78 °C to 0 °C, 85 min, then TMSCl, 0 °C, 100 min, then –78 °C, addition of *N*-phenylthiophthalimide (**996**), KHMDS, –78 °C, 10 min, then rt., 45 min, then 5% HCl	99%	—	—
3	PhSSPh, KO^{t}Bu, THF, 75 °C, 16 h	82%	—	—
4	^{n}BuLi (2.2 eq.), THF, –78 °C to 0 °C, 80 min, then –78 °C, HMPA (3.5 eq.), PhSSPh, –78 °C, 14 h	10%	50%	—
5	^{n}BuLi (2.2 eq.), THF, –78 °C to 0 °C, 80 min, then –78 °C, 2-nitrobenzenesulfenyl chloride, –78 °C, 14 h	—	—	41%

Based on these protocosl, reaction of bissulfide adduct **991** with ethylmagnesium bromide in THF at –10 °C furnished the monosulfide compound **992** in 80% yield after two hours. In addition, lactam **979** was reacted with 2-nitrobenzenesulfenyl chloride. This furnished monosulfide compound **993** in 41% yield along with some decomposition products. With sulfide compounds **992** and **993** in hands, attention next turned to their alkylation and the formation of **994** or **995**, respectively. But once again, neither the generation of **994** nor **995** could be accomplished, thus bringing the attempts of the alkylation of lactam **979** to an end.

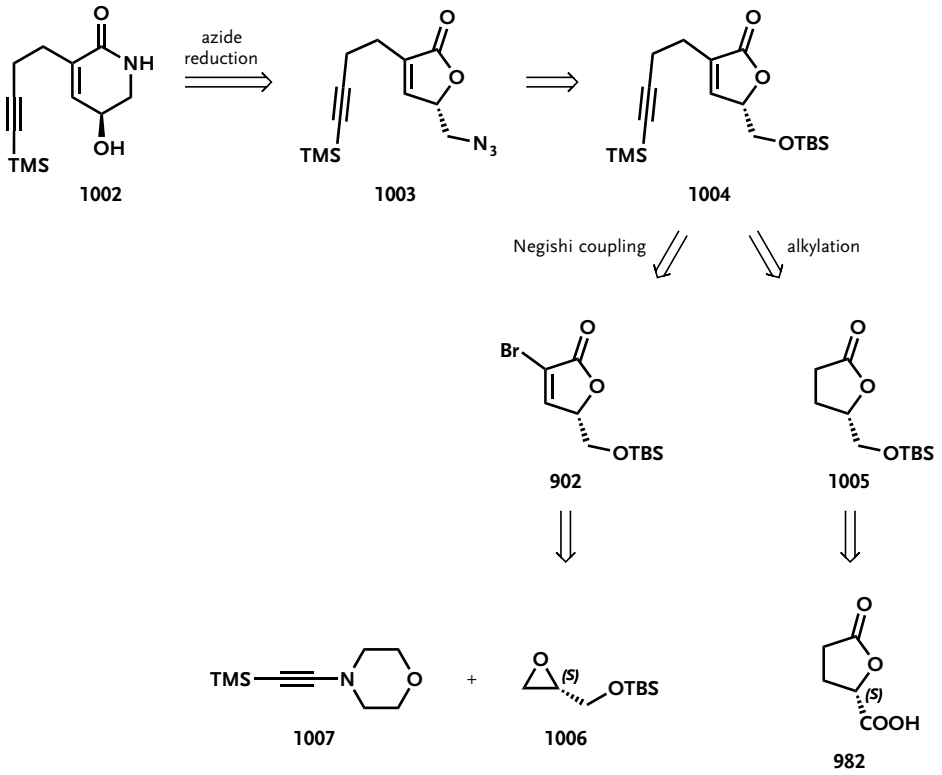
Since several attempts for the alkylation of lactam **979** and its derivatives failed, the retrosynthetic strategy was revised and the alkylation step was brought forward. Therefore, the α-alkylation of optically active azide **985** (Scheme 12-16, *cf.* Scheme 12-13) was investigated. However, this investigations were aborted as it turned out that azide **985** was not stable to strong basic conditions and decomposed very rapidly.



Scheme 12-16. Revised strategy.

12.4 The γ-Butenolide Approach

As a result from previous approaches, the synthesis of substituted dihydropyridinone **997** required a modified retrosynthetic strategy (Scheme 12-17). Therefore, **997** is synthesized from azide **1003** *via* reduction of the azide moiety and concomitant lactam formation. Compared to previous approaches, this reduction cannot be carried out *via* hydrogenation due to the present alkyne moiety. However, several other methodologies for the reduction of an azide to the corresponding amine are known:[569] this transformation can be carried out in the presence of thiols,[570–574] complex hydrides (e.g. butyltriphenylphosphonium tetrahydroborate **1008** as a selective reducing agent for reduction of organic azides),[575] boranes,[576–578] borohydrides[579,580] and phosphanes (Staudinger reaction),[581–587] to name but a few. Azide **1003** is planned to be synthesized from γ-butenolide **1004**. Two different approaches were envisioned for its synthesis: on the one hand **1004** can be synthesized from vinyl bromide **902** *via* Negishi coupling (this transition metal catalyzed cross-coupling reaction has been chosen since this reaction allows for the coupling of sp^3, sp^2, and sp carbons),[588,589] on the other hand it is available *via* alkylation/selenoxide elimination sequence from optically active lactone **1005**. Vinyl bromide **902** can be synthesized from glycidol derivative **1006** using a modified protocol of Movassaghi and Jacobsen who reported a direct method for the conversion of terminal epoxides into γ-butanolides.[590,591] Both stereoisomers of glycidol are commercially available, thus making



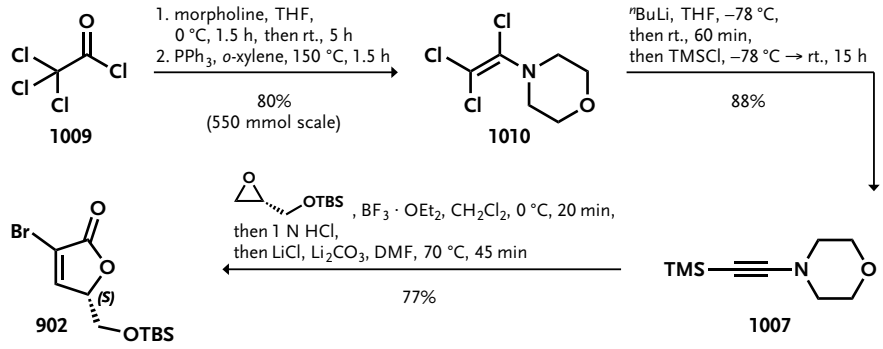
Scheme 12-17. New retrosynthetic analysis.

this approach enantioselective, too. Optically active lactone **1005** in turn is available from γ-carboxyl-γ-butyrolactone **982** (*cf.* Section 12.3) *via* reduction/silyl protection sequence.

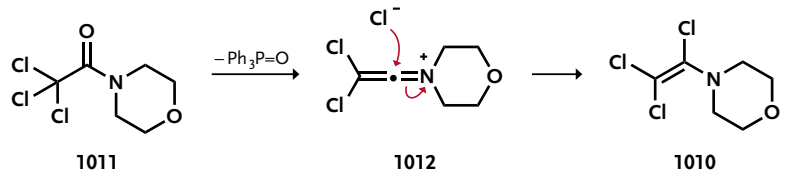
12.4.1 γ-Butenolides from Terminal Epoxides

In 2002, Movassaghi and Jacobsen reported a straightforward methodology for the generation of γ-butanolides from terminal epoxides.[590] By reason of the simple access to enantioenriched epoxides, this methodology found broad application in the synthesis of optically active γ-butanolides. The strategy is based on the use of 1-morpholino-2- trimethylsilyl acetylene (**1007**). The synthesis of this ynamine is shown in Scheme 12-18. Trichloroacetyl chloride (**1009**) was transformed into *N*-trichloroacetyl morpholine amide *via* the reaction with morpholine. This intermediate was then subjected to triphenylphosphine in refluxing *o*-xylene which led to a formal deoxygenation and the formation of desired *N*-trichlorovinyl morpholine (**1010**) in 80% yield. The suggested mechanism for this step is shown in Scheme 12-19 and is proposed to proceed *via* the attack of the keteniminium salt **1012**. Subjection of morpholine derivative **1010** to an excess of ^{n}BuLi followed by the addition of chlorotrimethylsilane furnished ynamine **1007** in 88% yield. The mechanism is proposed to proceed *via* a Fritsch–Buttenberg–Wiechell rearrangement followed by lithium-halogen exchange. Ynamine **1007** was then reacted with (*R*)-(+)-glycidol (**1006**), which was activated by boron trifluoride diethyl etherate, and an excess of *N*-bromosuccinimide followed by the treatment with lithium carbonate in DMF at 70 °C. This furnished γ-butenolide **902** in 77% yield.[591]

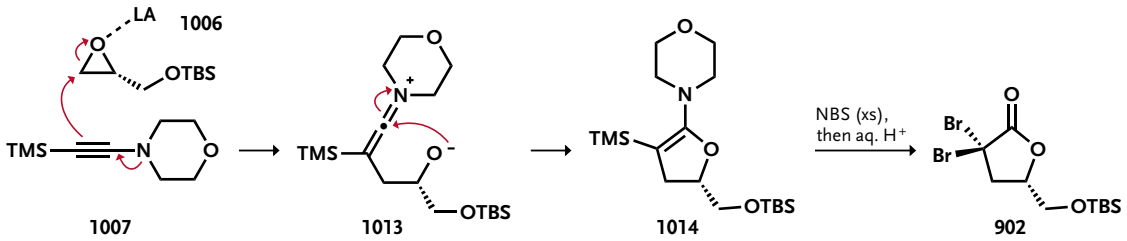
The mechanism for this reaction might not be obvious and the proposed mechanism is shown in Scheme 12-20. The reaction of ynamine **1007** and boron trifluoride diethyl etherate



Scheme 12-18. Synthesis of γ-butenolide **902** from ynamine **1007** and TBS-protected (*R*)-(+)-glycidol.



Scheme 12-19. Proposed mechanism for the generation of *N*-Trichlorovinyl morpholine.

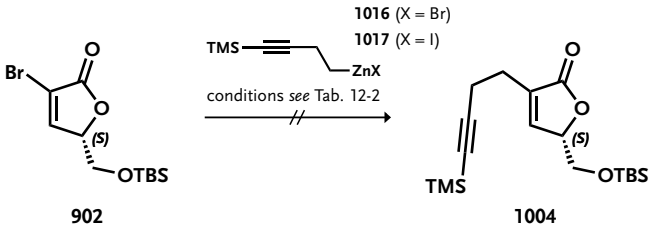


Scheme 12-20. Proposed mechanism for the formation of dibromo γ-butanolide **1015**.

allows the rapid and efficient conversion of terminal epoxide **1006** to the corresponding cyclic keteneaminal **1014** *via* the intramolecular attack of the keteniminium salt **1013**. Reaction with an excess of *N*-bromosuccinimide affords dibromo γ-butanolide **1015** which is then subjected to elimination conditions to yield γ-butenolide **902**.

With γ-butenolide **902** in hands, attention next turned to the Negishi coupling of homopropargylic zinc species **1017** or **1016**, respectively, to vinyl bromide **902** (Scheme 12-21). Negishi coupling reactions on similar γ-butenolide substrates have not been reported until today. Notwithstanding this, **902** was subjected to a variety of typical Negishi coupling conditions (Tab. 12-2). Unfortunately, coupling product **1004** has not been formed in any case. Therefore, attention next turned to the C–C-bond formation *via* Suzuki coupling which is also suitable for the coupling of sp^3 and sp^2 carbons.[592–594]

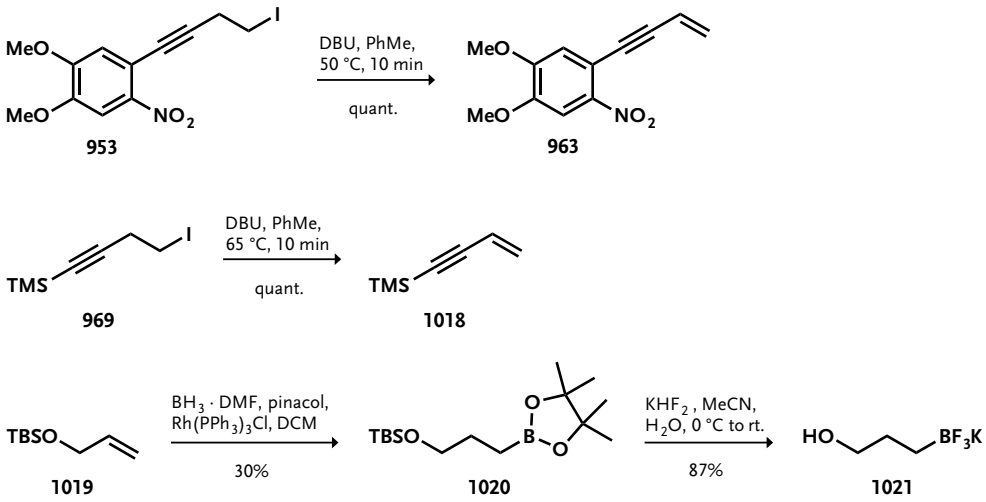
For this purpose, a variety of different precursors for a Suzuki coupling reaction have been synthesized (Scheme 12-22). The fact, that homopropargylic iodide **969** and especially aryl homopropargylic iodide **953** were poor S_N2 substrates (*cf.* Section 12.2) was utilized and both compounds were subjected to 1,8-diazabicyclo(5.4.0)undec-7-ene at elevated temperatures in



Scheme 12-21. Transformation of vinyl bromide **902** into γ-butenolide **1004** *via* Negishi coupling failed.

Table 12-2. Conditions for Scheme 12-21.

#	Conditions
1	**1017**, $PdCl_2(dppf) \cdot CH_2Cl_2$ (5 mol %), CuI (5 mol %), DMAc, 80 °C
2	**1016**, $PdCl_2(dppf) \cdot CH_2Cl_2$ (4 mol %), DMF, rt., 14 h
3	**1016**, $PdCl_2(dppf) \cdot CH_2Cl_2$ (2 mol %), THF, 0 °C → rt., 12 h
4	**1016**, $PdCl_2(dppf) \cdot CH_2Cl_2$ (4 mol %), DMF, rt., absence of light, 12 h
5	**1016**, $Pd(PPh_3)_4$ (3 mol %), Et_2O, rt., 12 h



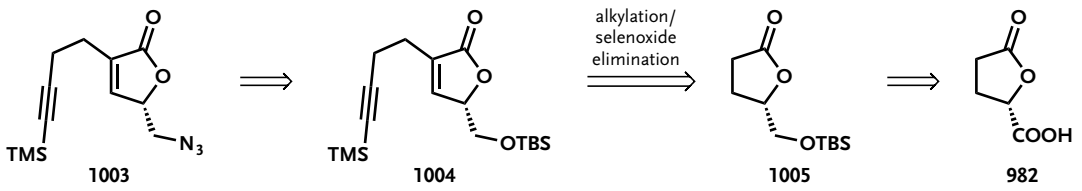
Scheme 12-22. Syntheses of various precursors for a Suzuki coupling reaction.

toluene. Enynes **963** and **1018**, respectively, were formed in less than ten minutes in quantitative yield. First prepared in 1960 by C. J. Willis,[595] organotrifluoroborate salts turned out to be versatile compounds in organic synthesis. They can be conveniently prepared from boronic acids and in general are air and moisture stable crystalline solids which can be synthesized on a multigram scale and purified by simple recrystallization.[596] Molander and co-workers demonstrated their use in metal-catalyzed cross-coupling reactions.[597,598] For this reason, organotrifluoroborate salt **1021** was prepared from TBS-protected allyl alcohol (**1019**) *via* boronic acid pinacol ester **1020** in 26% overall yield (unoptimized).

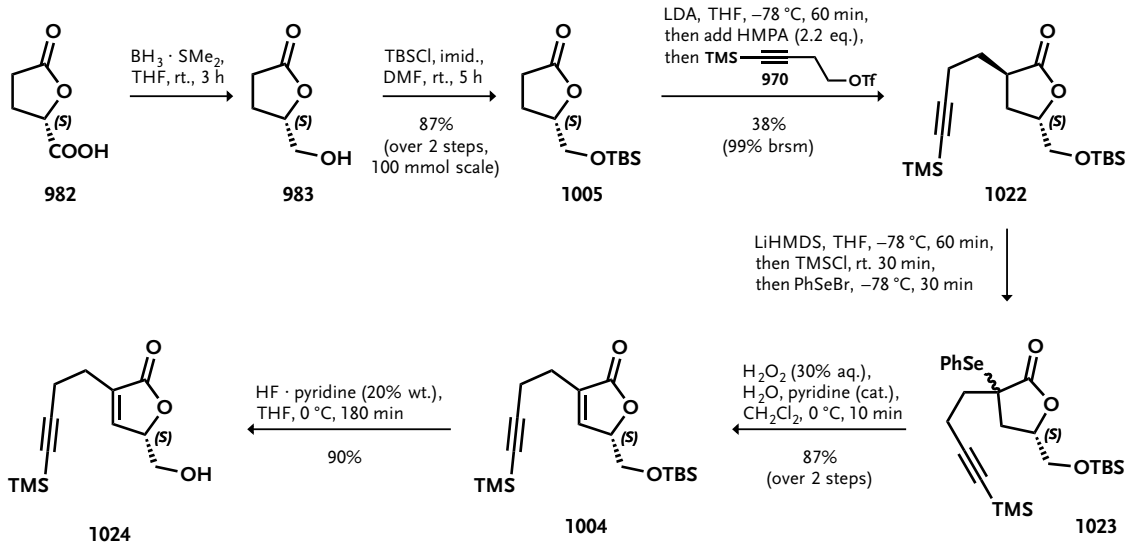
Although some unsuccessful trials concerning the Suzuki coupling of vinyl bromide **902** and precursors **963**, **1018**, and **1021** were carried out, this approach found an abrupt end based on results from a different approach towards γ-butenolide **1004** (*cf.* Section 12.4.2). It was found that upcoming transformations of γ-butenolide **1004** are not compatible with the existing double bond and therefore required its installation at a later stage of the synthesis, thus making this approach redundant.

12.4.2 γ-Carboxyl-γ-Butyrolactone Approach

As shown in Scheme 12-23, this retrosynthetic approach was designed to install the side chain in an alkylation reaction followed by the dehydrogenation *via* selenoxide elimination. Optically



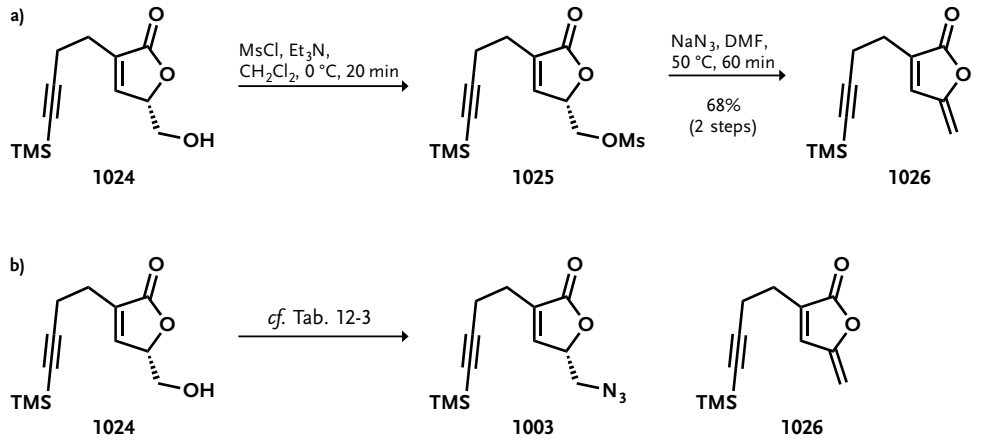
Scheme 12-23. Retrosynthetic analysis for the synthesis of γ-butenolide **1003**.



Scheme 12-24. Synthesis of optically active γ-butenolide **1024**.

active lactone **1005** in turn is available from γ-carboxyl-γ-butyrolactone **982** (*cf.* Section 12.3) *via* reduction/silyl protection sequence.

Reduction of γ-carboxyl-γ-butyrolactone **982** with borane dimethyl sulfide gave almost quantitative distilled yields of alcohol **983** which was transformed into its silyl counterpart **1005** in 87% yield using standard conditions (Scheme 12-24). Next in line was the α-alkylation with electrophile **970** which failed so many times in previous attempts. Notwithstanding this, deprotonation of lactone **1005** with LDA at –78 °C followed by the addition of HMPA (2.2 eq.) and electrophile **970** furnished product **1022** in 38% yield (99% brsm).[599] It should be noted that no reaction took place in the absence of HMPA. Also the substitution of either HMPA with DMPU or triflate **970** with its corresponding iodide (**969**) or bromide (**975**) did not generate desired compound **1022**. With **1022** in hands, attention next turned to the dehydrogenation of the ketone. Several methodologies are known for this transformation which can be achieved *via* sulfoxide elimination,[600,601] selenoxide elimination,[602] DDQ dehydrogenation,[603] dehydrogenation with methyl phenylsulfinate,[604] or Saegusa–Ito oxidation[605] to name but a few. Although many methodologies have been reported, this transformation still attracts researcher and leads to the design of new reagents particularly for this transformation, e.g. *N-tert*-butylbenzenesulfinimidoyl chloride[606] or a $Pd(TFA)_2$/4,5-diazafluorenone catalyst.[607] This approach focused on the selenoxide elimination. For this reason, lactone **1022** was reacted with LiHMDS at –78 °C followed by the addition of chlorotrimethylsilane. The *in situ* generated ketene silyl acetal was then reacted with phenylselenyl bromide to afford organoselenium species **1023** which was directly subjected to oxidative conditions (H_2O_2, cat. pyridine) to furnish α,β-unsaturated lactone **1004** in 87% combined yield. Finally, the silyl ether was cleaved with hydrogen fluoride in pyridine–THF to obtain alcohol **1024** in 90% yield, the alkyne protecting group remained untouched under these conditions.



Scheme 12-25. Attempts to the synthesis of azide **1003**.

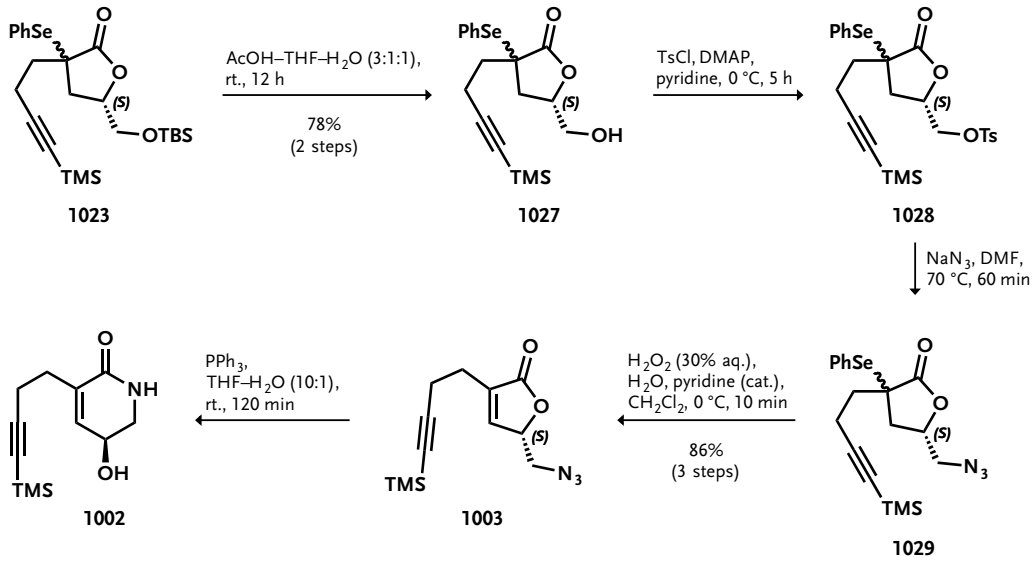
Table 12-3. Conditions for Scheme 12-25.

#	Conditions	Product	Yield [%]	Reference
1	TsCl, Et_3N, DMAP, CH_2Cl_2, rt., 20 min	**1026**	48	—
2	Tf_2O, pyridine, CH_2Cl_2, 0 °C , 20 min	**1026**	—[1)]	—
3	DPPA, DBU, PhH, 0 °C, 12 h	**1026**	50	[608]
4	PPh_3, DEAD, DPPA, THF, 0 °C	**1026**	—[1)]	[609]
5	PPh_3, DIAD, DPPA, PhMe, 0 °C	**1026**	—[1)]	[610,611]
6	PPh_3, DTBAD, DPPA, THF, 0 °C	**1026**	—[1)]	[612]

[1)] not determined

With alcohol **1024** in hands, attention next turned to its conversion to the corresponding azide **1003** (Scheme 12-25). For this reason, **1024** was converted into mesylate **1025** which was subjected to usual displacement conditions with sodium azide in *N,N*-dimethylformamide. However, the obtained product turned out to be UV active and analysis revealed, that desired azide **1003** was not formed; elimination product **1026** was generated instead as the single product. Alcohol **1024** was therefore converted into different leaving groups (tosyl and triflate, *cf.* Tab. 12-3, Entries 1–2) but under these conditions once again the elimination product **1026** was obtained as the single product in approximately 50% yield. Since approximately 50% of the starting material have been recovered, the reaction rate for the competitive elimination reaction seems to be much higher than for the deprotonation of the alcohol. Therefore, several direct conversions of alcohol **1024** into azide **1003** *via* Mitsunobu reaction[613] were carried out (*cf.* Tab. 12-3, Entries 3–6) but the generation of azide **1003** could be never observed and elimination product **1026** was formed in each case. Based on this results, the previous described approach with the generation of γ-butenolides from terminal epoxides was discontinued.

Since the transformation to the corresponding azide was not successful, it was planned to install the troublesome double bond after the formation of the azide. For this reason, organoselenium species **1023** was subjected to aqueous acidic tetrahydrofuran for 12 h which led to the

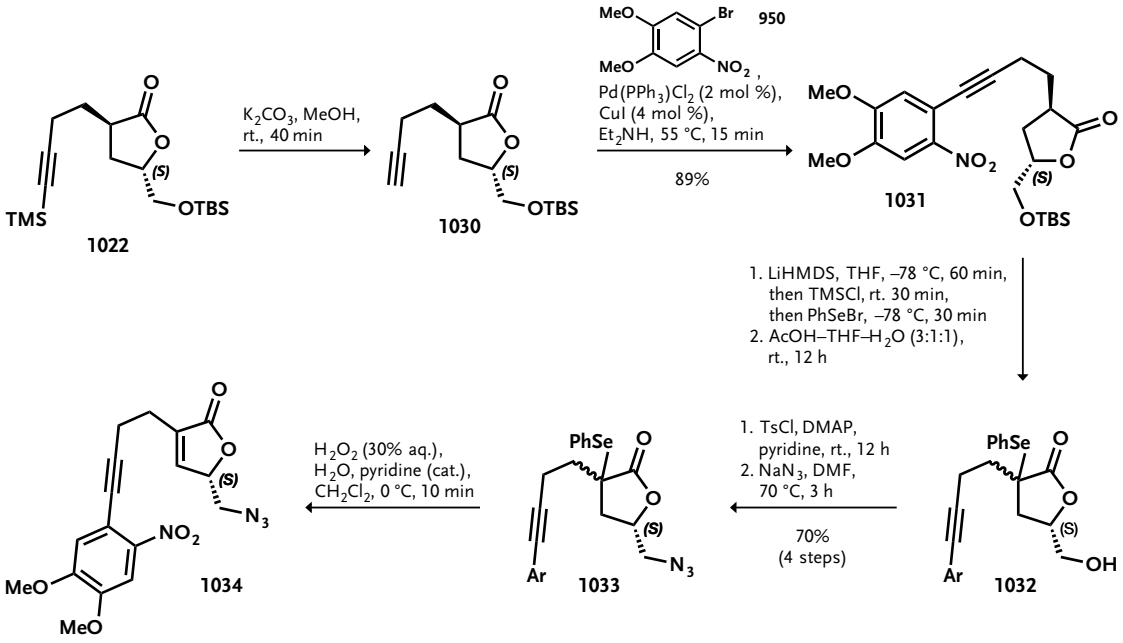


Scheme 12-26. New synthesis of azide **1003**.

cleavage of the TBS ether (Scheme 12-26). The liberated alcohol **1027** was then converted into the corresponding tosylate **1028** which was subjected to usual displacement conditions with sodium azide in *N,N*-dimethylformamide at 70 °C. Azide **1029** was formed after 60 min as single product which was taken up in dichloromethane and subjected to oxidative conditions (H_2O_2, cat. pyridine) to furnish α,β-unsaturated lactone **1003** in 86% overall yield (from alcohol **1027**). A small amount of azide **1003** was then subjected to Staudinger conditions (PPh_3, THF–H_2O 10:1) to obtain lactam **1002** thus demonstrating the general feasibility of this synthetic sequence.

Based on this results, the scope was extended by the additional installation of the required aryl moiety (Scheme 12-27). Silyl protected alkyne **1022** was subjected to potassium carbonate in methanol to liberate the terminal alkyne. Subsequent Sonogashira reaction of alkyne **1030** with 4-bromo-5-nitroveratrole (**950**) in diethylamine as solvent at 55 °C furnished lactone **1031** in 89% combined yield. Lactone **1031** was then reacted with LiHMDS at –78 °C followed by the addition of chlorotrimethylsilane. The *in situ* generated ketene silyl acetal was then reacted with phenylselenyl bromide to afford an organoselenium species which was directly subjected to aqueous acidic tetrahydrofuran for 12 h to cleave the TBS ether to afford alcohol **1032**. The alcohol was transformed into the corresponding tosylate and usual displacement conditions with sodium azide in *N,N*-dimethylformamide at 70 °C furnished azide **1033** in 70% overall yield. Finally, γ-butenolide **1034** was obtained after oxidation of the organoselenium species with **1035** and concomitant elimination.

The work on the these approaches was undertaken contemporaneously with the work on the synthesis of cyclohepta[*b*]indoles which finally led to the the syntheses of *Ervatamia* alkaloids (*cf.* Part II). In favor of the completion of the total syntheses of diverse natural products with the cyclohepta[*b*]indole motif, the work on this project was discontinued at this point. However, the general feasibility of the last approach has been demonstrated thus providing a synthetic



Scheme 12-27. Synthesis of γ-butenolide **1034**.

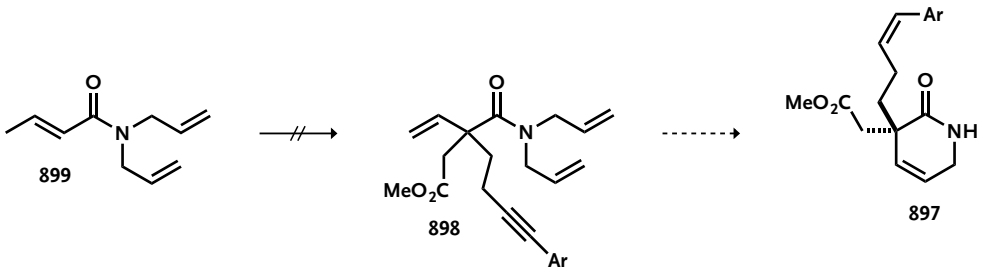
sequence for the generation of optically active lactam **1002** and γ-butenolide **1034** (Schemes 12-26 and 12-27) starting from enantiopure γ-carboxyl-γ-butyrolactone (**982**) which is accessible from L-glutamic acid.

12.5 Summary and Outlook

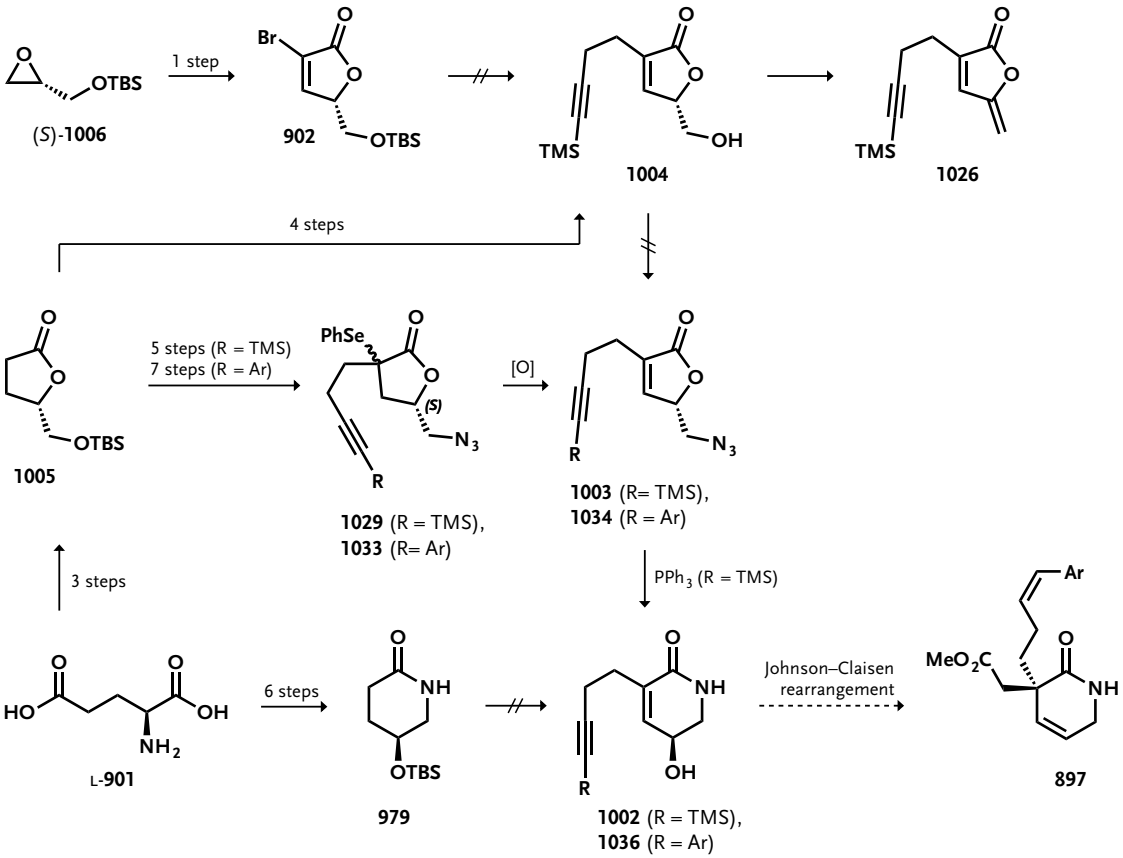
This part of the thesis dealt with three different approaches towards the synthesis of the key intermediate for the synthesis of isoschizogamine (**847**). The global catchword for these approaches seems to be *elimination*; some parts read like a textbook example for competitive reactions. Since this project was a side-project, this part was recapped not as detailed as the part about the cyclohepta[*b*]indoles on purpose although it turned out that this project required way more investigations than originally anticipated; only the most important results and dead-ends have been presented.

It was pointed out, that the synthesis of α,α-disubstituted 3,6-dihydropyridin-2-ones is not trivial and should not be underestimated. The first approach ("The Metathesis Approach", Scheme 12-28) found a quick end since the enolates formed from amides turned out to be moderate nucleophiles and in combination with the required electrophiles the E2 elimination reaction dominated over S_N2 displacement. Therefore, attention next turned to the second approach ("The Hydroxypiperidinone Approach", Scheme 12-29).

The target compound of this approach was dihydropyridinone **1036** which was planned to be transformed to key intermediate **897** *via* Johnson–Claisen rearrangement. TBS-Protected (*S*)-(–)-piperidinol **979** was synthesized in six steps from L-glutamic acid (**901**). This is a very robust



Scheme 12-28. The metathesis approach.



Scheme 12-29. Combined approaches towards dihydropyridinones **1002** and **1036**.

sequence and enantiopure **979** can be synthesized in multidecagram amounts in a short period of time. Since both enantiomers of glutamic acid are commercially available, this approach would allow the synthesis of either natural (–)-isoschizogamine (**1037**) or its unnatural antipode. However, the transformation of TBS-protected (*S*)-(–)-piperidinol **979** into dihydropyridinone **1036** was not successful. Therefore, L-glutamic acid (**901**) was converted into enantiopure lactone **1005** which could be converted into γ-butenolide **1004** in four additional steps. An additional approach towards γ-butenolide **1004** was envisioned *via* the sp^2–sp^3 cross-coupling of vinyl bromide **902** which is available from (almost) enantiopure glycidol derivative **1006** in one single step. Attempts for the cross-coupling were ineffective, but it turned out the transformation of alcohol **1004**

into the corresponding azide **1003** was not feasible anyway since elimination product **1026** has been formed in every case. Finally, azide **1003** was synthesized through the postponed oxidative elimination of organoselenium species **1029**. This sequence was also modified to the synthesis of organoselenium species **1033** (the aryl moiety is already installed) and its oxidative elimination to yield azide **1034**. Azide **1003** was shown to be transformed into desired dihydropyridinone **1002** *via* Staudinger reaction.

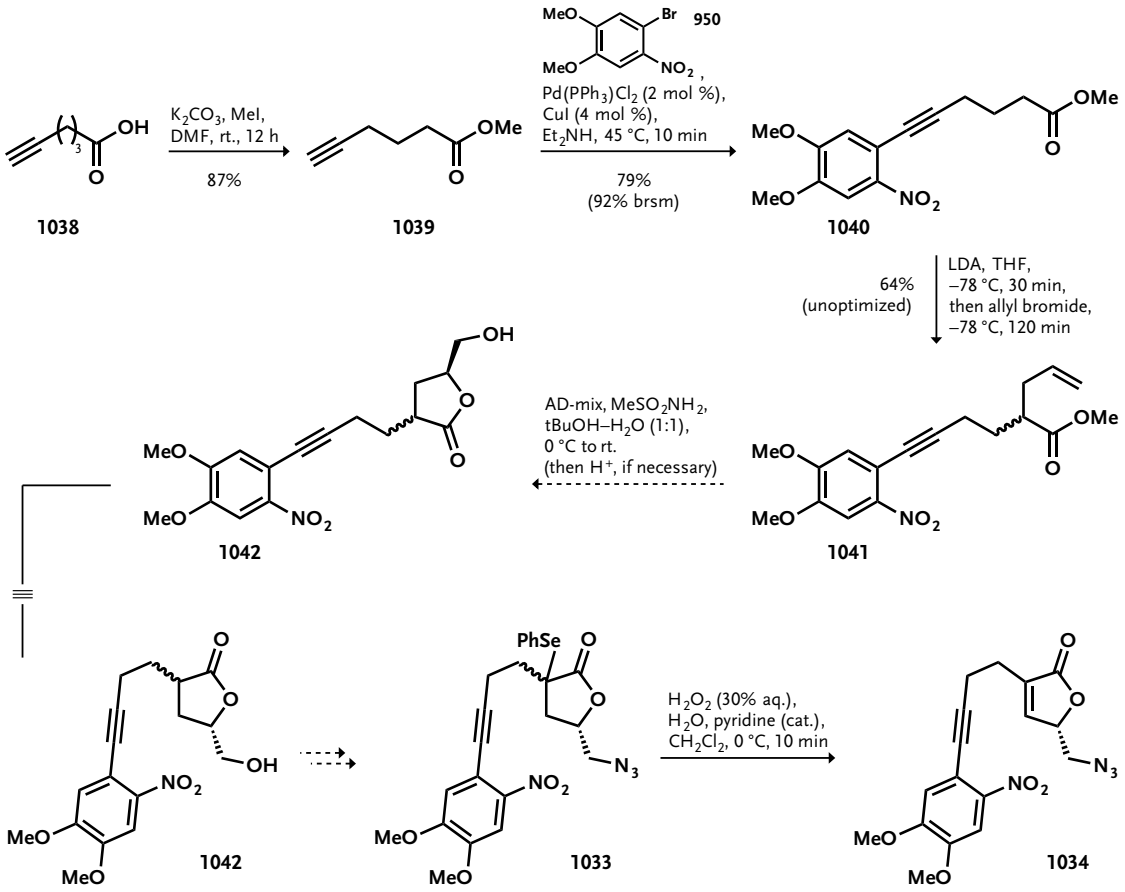
The work on the these approaches was undertaken contemporaneously with the work on the synthesis of cyclohepta[*b*]indoles which finally led to the the syntheses of *Ervatamia* alkaloids (*cf.* Part II). In favor of the completion of the total syntheses of diverse natural products with the cyclohepta[*b*]indole motif, the work on this project was discontinued at this point. However, the general feasibility of the last approach has been demonstrated thus providing a synthetic sequence for the generation of enantiopure lactam **1002** and γ-butenolide **1034** which are accessible from L-glutamic acid. Both enantiomers of glutamic acid are commercially available, thus allowing the synthesis of either natural (–)-isoschizogamine (**1037**) or its unnatural antipode.

12.5.1 Optimizations and Alternatives

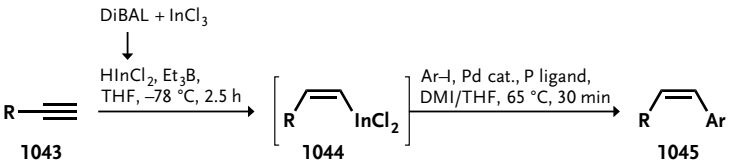
The final approach described a reliable synthesis of dihydropyridinone **1036**, but there is always room for improvement or coequal alternatives. Two proposals are discussed briefly.

It was shown, that γ-butenolide **1034** could be synthesized from azide **1033** which was shown to be available from lactone **1005** in seven steps. An alternative synthesis of azide **1033** is shown in Scheme 12-30 and was already partially carried out. Hex-5-ynoic acid (**1038**) was transformed into methyl hex-5-ynoate (**1039**) with methyl iodide and potassium carbonate. The terminal alkyne was then subjected to Sonogashira coupling conditions with aryl bromide **950** to obtain acetylene **1040** in 79% yield. Deprotonation with LDA followed by the addition of allyl bromide afforded γ,δ-unsaturated compound **1041** in moderate yield (this compound is also available from the reaction of allyl alcohol with the appropriate orthoester *via* Johnson–Claisen rearrangement). Either an Upjohn dihydroxylation[614] or a Sharpless asymmetric dihydroxylation[615] would lead to γ-hydroxymethyl-γ-butyrolactone **1042**. This compound is already an advanced intermediate and would require only a few transformations to afford azide **1033**. The asymmetric variant can be carried out either with commercially available AD-mix α or AD-mix β, thus allowing once again the synthesis of either natural (–)-isoschizogamine (**1037**) or its unnatural antipode.

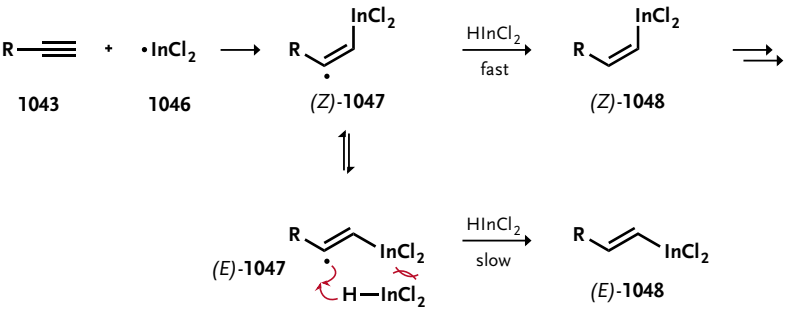
In addition, an optimization for the cross-coupling of aryl bromide **950** with diverse terminal alkynes is proposed. In 2003, Oshima and co-workers reported a triethylborane-mediated hydrogallation and hydroindation.[616] They also described a one-pot hydroindation/cross-coupling reaction (Scheme 12-31). It was shown, that the triethylborane-mediated hydroindation of alkynes proceeds in an *anti* manner to afford the corresponding (*Z*)-alkenylindium species (a rational explanation for this outcome is shown in Scheme 12-32). This method was used to employ unprotected alkynes as (*Z*)-alkenylmetal precursors and to synthesize either functionalized (*Z*)-alkenyl iodides or arylalkenes in a one-pot operation. This methodology can be applied



Scheme 12-30. Outlook for an alternative synthesis of γ-butenolide **1034**.



Scheme 12-31. One-pot hydroindation/cross-coupling reaction for the selective synthesis of (*Z*)-olefins from terminal alkynes and aryl halides (Oshima, 2003).[616]



Scheme 12-32. Proposed mechanism for the selective (*Z*) outcome.[616]

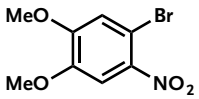
to a variety of alkynes and aromatic rings (electron-rich and electron-deficient). Although it was shown, that according to Trost *et al*. the reduction of the alkyne moiety in presence of an nitroarene can be achieved with $Pd_2(dba)_3$ and a phosphine ligand (tri-*o*-tolylphosphine) with 1,1,3,3-tetramethyldisiloxane as the hydride donor (*cf*. Section 12.2),[558] the method of Oshima and co-workers would simplify the synthesis and allow a more rapid access to the desired target compound.

13 Experimental

The experimental part follows the order of the particular sections and compounds are ordered by appearance. The general methods are described in Section A.1 on p. 353 and are valid for all other experimental parts in this thesis.

13.1 Experimental Part for Section 12.2

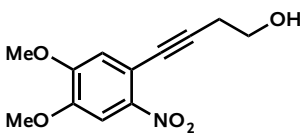
1-Bromo-4,5-dimethoxy-2-nitrobenzene [4-Bromo-5-nitroveratrole] (**950**).[617]



950

Nitric acid (65% aq., 250 ml) was cooled to –8 °C and 4-bromoveratrole (15.0 ml, 104 mmol) was added dropwise over 10 min. After complete addition, the mixture was stirred additional 20 min below –2 °C at which point a large amount of yellow precipitate has been formed. The reaction mixture was diluted with 1500 ml of ice-cold water and the mixture was filtered through a medium porosity sintered-glass funnel. The retentate was washed with an appropriate amount of water and collected. Recrystallization from ethanol furnished title compound **950** as yellow solid (25.1 g, 96 mmol, 92%). R_f = 0.73 (hexanes–EtOAc, 6:5, stains yellow with CAN). **M.p.** 124 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.54 (s, 1H), 7.09 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 152.9, 148.3, 141.8, 116.6, 109.1, 107.5, 56.8, 56.6 ppm. **HRMS** (ESI): calcd. for $C_8H_9BrNO_4$ $[M + H]^+$ 261.9715, found 261.9716. ▸ *NMR spectra on page 483.*

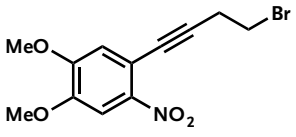
4-(4,5-dimethoxy-2-nitrophenyl)but-3-yn-1-ol (951).



951

Aryl bromide **950** (1.30 g, 4.96 mmol, 1.0 eq.) was dissolved in diethylamine (9.9 ml) and the resulting suspension was degassed using ultrasonication. Copper(I) iodide (38.6 mg, 198 µmol, 4 mol %) and bis(triphenylphosphine)palladium(II) dichloride (69.6 mg, 99 µmol, 2 mol %) were added under argon followed by the addition of but-3-yn-1-ol (385 µl, 4.96 µmol, 1.0 eq.). The resulting mixture was stirred 15 min at 50 °C (monitored by TLC), then silica was added and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 1:1 → 1:2) and title compound **951** was obtained as pale yellow solid (1.19 g, 4.74 mmol, 96%). R_f = 0.22 (hexanes–EtOAc, 6:5, stains with CAN). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.60 (s, 1H), 6.95 (s, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 3.85 (t, J = 6.0 Hz, 2H), 2.74 (t, J = 6.0 Hz, 2H), 2.32 (br s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 152.9, 148.6, 143.0, 115.4, 113.1, 107.6, 94.4, 79.0, 61.0, 56.6, 56.5, 24.5 ppm. **HRMS** (ESI): calcd. for $C_{12}H_{14}NO_5$ $[M + H]^+$ 252.0872, found 252.0874. ▸ NMR spectra on page 484.

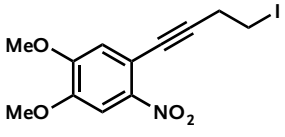
1-(4-Bromobut-1-yn-1-yl)-4,5-dimethoxy-2-nitrobenzene (952).



952

Alcohol **951** (56.0 mg, 223 µmol, 1.0 eq.) was dissolved in anhydrous THF (0.7 ml) and cooled to 0 °C. Phosphorus tribromide (21 µl, 223 µmol, 1.0 eq.) was added dropwise and the reaction mixture was stirred over night with the cooling bath slowly warming up to ambient temperature. The reaction was quenched by the addition of sat. aq. K_2CO_3 and extracted thrice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure to obtain bromide **952** as yellow oil (18.9 mg, 60.2 µmol, 27%) which was directly used in the next steps without further purification.

1-(4-Iodobut-1-yn-1-yl)-4,5-dimethoxy-2-nitrobenzene (953).

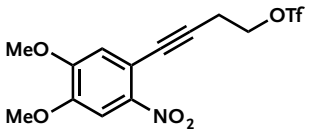


953

Alcohol **951** (78.0 mg, 310 µmol, 1.0 eq.) was dissolved in anhydrous benzene (2.1 ml). To this solution was added imidazole (52.8 mg, 776 µmol, 2.5 eq.) and PPh_3 (163 mg, 621 µmol, 2.0 eq.). The mixture was stirred until full dissolution of all components (slightly heating or ultrasonic may be necessary). Iodine (158 mg, 621 µmol 2.0 eq.) was dissolved in benzene (500 µl) to obtain a dark purple solution which was added dropwise to the reaction mixture. After complete addition, the reaction mixture was diluted with EtOAc and sat. aq. sodium thiosulfate was added. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over magnesium sulfate and the solvent was then removed under reduced pressure. This afforded iodide **953** as orange solid which was directly used in the next steps due to its instability. **^{1}H NMR** (200 MHz, $CDCl_3$,

crude) δ = 7.35 (s, 1H), 6.99 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.35 (td, J = 7.3, 0.9 Hz, 2H), 3.08 (td, J = 7.2, 0.9 Hz, 2H) ppm. **HRMS** (ESI): calcd. for $C_{12}H_{12}INNaO_4$ $[M + Na]^+$ 383.9709, found 383.9708. ▸ NMR spectra on page 485.

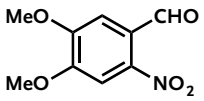
4-(4,5-Dimethoxy-2-nitrophenyl)but-3-yn-1-yl trifluoromethanesulfonate (954).



954

Alcohol **951** (163 mg, 649 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 and cooled to –10 °C. Pyridine (55 µl, 681 µmol, 1.05 eq.) was added followed by the addition of trifluoromethanesulfonic anhydride (115 µl, 681 µmol, 1.05 eq.). The reaction mixture was stirred for 10 min at –10 °C before quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude triflate **954** which was purified *via* filtration over a plug of silica (hexanes–EtOAc, 4:1) to afford triflate **954** as colorless oil (218 mg, 570 µmol, 88%). The compound was directly used in the next steps due to its instability. R_f = 0.74 (hexanes–EtOAc, 1:1). **HRMS** (ESI): calcd. for $C_{13}H_{13}F_3NO_7S$ $[M + H]^+$ 384.0365, found 384.0366.

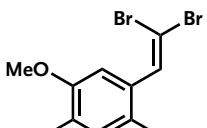
4,5-dimethoxy-2-nitrobenzaldehyde (955).[618]



955

Nitric acid (65% aq., 120 ml) was cooled to 0 °C and 3,4-dimethoxybenzaldehyde (20.0 g, 120 mmol) was added in portions over 10 min, keeping the temperature at 0 °C. After complete addition, the reaction mixture was stirred additional 15 min at 0 °C, then additional 45 min at ambient temperature. The reaction mixture was poured into 1000 ml of ice-cold water to precipitate the product which was collected by filtration through a medium porosity sintered-glass funnel. The retentate was washed with additional ice-cold water (1000 ml) and collected. Recrystallization from ethanol furnished title compound **955** as yellow solid (17.7 g, 83.8 mmol, 70%). **M.p.** 133 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.43 (s, 1H), 7.61 (s, 1H), 7.41 (s, 1H), 4.02 (d, J = 4.0 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 187.8, 153.4, 152.5, 144.0, 125.7, 109.9, 107.3, 56.9, 56.9 ppm. **HRMS** (ESI): calcd. for $C_9H_{10}NO_5$ $[M + H]^+$ 212.0559, found 212.0562. ▸ NMR spectra on page 486.

1-(2,2-Dibromovinyl)-4,5-dimethoxy-2-nitrobenzene (956).



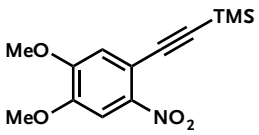
956

Tetrabromomethane (26.7 g, 80.5 mmol, 2.0 eq.) and triphenylphosphine (42.2 g, 161 mmol, 4.0 eq.) were dissolved in anhydrous CH_2Cl_2 (400 ml) to yield a bright dark red solution. 2-Nitro-4,5-dimethoxybenzaldehyd (**955**, 8.50 g, 40.3 mmol, 1.0 eq.) was added in portions at ambient temperature and stirring was continued for additional 45 min (monitored by TLC) after complete addition at this temperature. Water was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, the combined organic layers were once extracted

with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes–EtOAc, 6:1 → 4:1 → 2:1 → 1:1) to obtain 1,1-dibromoolefin **956** as pale red solid (12.9 g, 35.1 mmol, 87%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.78 (d, J = 0.7 Hz, 1H), 7.70 (s, 1H), 6.98 (d, J = 0.7 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 153.2, 149.0, 139.6, 134.9, 125.9, 112.8, 107.7, 92.3, 56.8, 56.6 ppm. **HRMS** (ESI): calcd. for $C_{10}H_9Br_2NNaO_4$ $[M + Na]^+$ 387.8796, found 387.8798.

▸ NMR spectra on page 487.

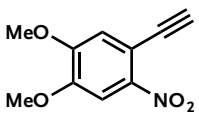
((4,5-Dimethoxy-2-nitrophenyl)ethynyl)trimethylsilane (958).



958

Aryl bromide **950** (5.70 g, 21.8 mmol, 1.0 eq.) was dissolved in diethylamine (43.5 ml) and the resulting suspension was degassed using ultrasonication. Copper(I) iodide (169 mg, 870 µmol, 4 mol %) and bis(triphenylphosphine)palladium(II) dichloride (305 mg, 435 µmol, 2 mol %) were added under argon followed by the addition of ethynyltrimethylsilane (3.3 ml, 23.3 mmol, 1.07 eq.). The resulting mixture was stirred 15 min at 40 °C (monitored by TLC) before it was diluted with EtOAc and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was washed once with EtOAc. The combined organic layers were dried over magnesium sulfate and then filtered over a plug of celite to obtain crude title compound **958** as brown solid in quantitative yield which was directly used in the next step. R_f = 0.62 (hexanes–EtOAc, 3:1, stains brown with vanillin). **HRMS** (ESI): calcd. for $C_{13}H_{18}NO_4Si$ $[M + H]^+$ 280.1005, found 280.1005.

1-Ethynyl-4,5-dimethoxy-2-nitrobenzene (957).



957

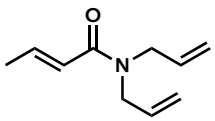
Variant 1: 1,1-dibromoolefin **956** (12.8 g, 34.9 mmol, 1.0 eq.) was dissolved in anhydrous THF (175 ml) and cooled to –78 °C. ^{n}BuLi (2.5 M in hexanes, 28.6 ml, 71.5 mmol, 2.05 eq.) was added dropwise and after complete addition the dark green solution was stirred 60 min at –78 °C and additional 120 min at ambient temperature. The reaction mixture was cooled down to –78 °C and quenched by the addition of sat. aq. NH_4Cl. The reaction mixture was diluted with ether and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1) to obtain pure acetylene **957** as off-white solid (2.42 g, 11.7 mmol, 34% yield)

Variant 2: Crude silyl acetylene **958** (21.8 mmol, 1.0 eq.) was dissolved in anhydrous methanol (30 ml) and potassium carbonate (6.03 g, 43.6 mmol, 2.0 eq.) was added at ambient temperature. The reaction mixture was stirred at 10 min at this temperature (monitored by TLC) before it was diluted with ether and quenched by the addition of water. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried

over sodium sulfate and the solvent was removed *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 3:1 → 2:1) to obtain acetylene **957** as off-white solid (4.45 g, 21.5 mmol, 99% over two steps). R_f = 0.54 (hexanes–EtOAc, 3:1, stains light brown with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.62 (s, 1H), 7.03 (s, 1H), 3.95 (s, 6H), 3.46 (s, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 152.8, 149.3, 143.4, 116.2, 111.5, 107.6, 83.9, 79.5, 56.7, 56.6 ppm. **HRMS** (ESI): calcd. for $C_{10}H_{10}NO_4$ $[M + H]^+$ 208.0610, found 208.0612.

▸ *NMR spectra on page 488.*

(*E*)-*N*,*N*-Diallylbut-2-enamide (899).[619]

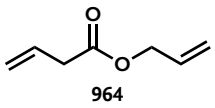


899

Triethylamine (34.0 ml, 246 mmol, 1.1 eq.) in anhydrous toluene (50 ml) was added to a solution of diallylamine (27.5 ml, 223 mmol, 1.0 eq.) in anhydrous toluene (400 ml) at 0 °C followed by the addition of a solution of crotonoyl chloride (21.4 ml, 223 mmol, 1.0 eq.) in anhydrous toluene (225 ml) over 30 min. The resulting mixture was stirred 40 min at 0 °C and then filtered to remove the triethylamine hydrochloride. The filtrate was concentrated to approximately 25% and chloroform was added and then filtered once again to remove the residual triethylamine hydrochloride. The filtrate was concentrated *in vacuo* and the residue was distilled (p = 4.5 Torr, 98–99 °C) to obtain amide **899** as colorless oil (33.2 g, 201 mmol, 90%). R_f = 0.42 (CH_2Cl_2 –EtOAc, 15:1, stains with $KMnO_4$). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 6.92 (dq, J = 15.0, 6.9 Hz, 1H), 6.15 (dq, J = 15.0, 1.7 Hz, 1H), 5.90 – 5.65 (m, 2H), 5.23 – 5.05 (m, 4H), 4.01 (br d, J = 6.0 Hz, 2H), 3.95 – 3.87 (m, 2H), 1.85 (dd, J = 6.9, 1.7 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{10}H_{16}NO$ $[M + H]^+$ 166.1232, found 166.1234.

▸ *NMR spectra on page 489.*

Allyl but-3-enoate (964).

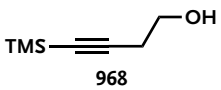


964

A mixture of vinylacetic acid (16.0 g, 186 mmol, 1.0 eq.), allyl alcohol (38.2 ml, 560 mmol, 3.0 eq.), and tosylic acid monohydrate (10.6 g, 56.0 mmol, 0.3 eq.) was heated in anhydrous benzene (100 ml) with azeotropic removal of water (Dean–Stark technique) for six hours. The reaction flask was attached to a distillation apparatus and ester **964** was obtained (p = 140 Torr, 89 °C) as colorless liquid (16.9 g, 134 mmol, 72%). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 6.02 – 5.79 (m, 1H), 5.37 – 5.06 (m, 2H), 4.56 (dt, J = 5.7, 1.4 Hz, 1H), 3.09 (dt, J = 6.9, 1.5 Hz, 1H) ppm. **HRMS** (ESI): calcd. for $C_7H_{10}NaO_2$ $[M + Na]^+$ 149.0578, found 149.0581.

▸ *NMR spectra on page 489.*

4-(Trimethylsilyl)but-3-yn-1-ol (968).



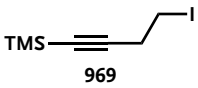
968

3-butyn-1-ol (7.35 g, 105 mmol, 1.0 eq.) was dissolved in anhydrous THF (500 ml) and cooled to –78 °C. A solution of ^{n}BuLi (2.5 M in hexanes, 88 ml, 220 mmol, 2.1 eq.) was added dropwise over 20 min and stirring was continued for 60 min at –78 °C. Chlorotrimethylsilane (28.0 ml, 220 mmol, 2.1 eq.) was added

dropwise at –78 °C and stirring was continued at this temperature for additional 30 min, then additional 45 min at –20 °C, and additional 45 min at ambient temperature (monitored by TLC). The reaction mixture was diluted with ether and quenched by the addition of 1 N HCl. The layers were separated and the aqueous layer was extracted thrice with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure to obtain alcohol **968** as colorless oil (14.2 g, 99.8 mmol, 95%) which was analytically pure according to NMR analysis. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.69 (t, J = 6.3 Hz, 2H), 2.48 (t, J = 6.4 Hz, 2H), 2.13 – 2.09 (m, 1H), 0.14 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 103.5, 87.0, 61.0, 24.3, 0.2 ppm. **HRMS** (ESI): calcd. for $C_7H_{15}OSi$ $[M + H]^+$ 143.0892, found 143.0890.

▸ NMR spectra on page 490.

(4-Iodobut-1-yn-1-yl)trimethylsilane (969).[620]

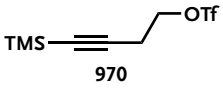


969

Alcohol **968** (900 mg, 6.33 mmol, 1.0 eq.), imidazole (818 mg, 12.0 mmol, 1.90 eq.), and triphenylphosphine (1.90 g, 7.24 mmol, 1.15 eq.) were dissolved in anhydrous CH_2Cl_2 (25 ml) and cooled to 0 °C. Iodine (1.84 g, 7.24 mmol, 1.15 eq.) was added in portions and stirring was continued for 16 h at 0 °C (monitored by TLC). The reaction mixture was diluted with water and extracted twice with pentane. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (pure pentane) to obtain iodide **969** as colorless oil (1.37 g, 5.43 mmol, 86%). R_f = 0.45 (pentane, pure). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.21 (td, J = 7.5, 0.9 Hz, 2H), 2.78 (td, J = 7.5, 0.9 Hz, 2H), 0.15 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 105.2, 86.9, 25.2, 1.1, 0.1 ppm. **HRMS** (ESI): calcd. for $C_7H_{14}ISi$ $[M + H]^+$ 252.9909, found 252.9911.

▸ NMR spectra on page 491.

4-(Trimethylsilyl)but-3-yn-1-yl trifluoromethanesulfonate (970).

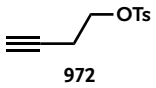


970

Alcohol **951** (1.10 g, 7.73 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 and cooled to 0 °C. Pyridine (655 µl, 8.12 mmol, 1.05 eq.) was added followed by the addition of trifluoromethanesulfonic anhydride (1.37 ml, 8.12 mmol, 1.05 eq.). The reaction mixture was stirred for 10 min at 0 °C before quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude triflate **970** which was purified *via* filtration over a plug of silica (pentane–ether, 10:1) to afford triflate **970** as colorless oil (1.71 g, 6.23 mmol, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.55 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H), 0.15 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_8H_{13}F_3NaO_3SSi$ $[M + Na]^+$ 297.0204, found 297.0208.

▸ NMR spectra on page 492.

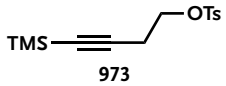
But-3-yn-1-yl 4-methylbenzenesulfonate (972).



972

To 3-butyn-1-ol (8.00 g, 114 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (100 ml) was added triethylamine (31.6 ml, 228 mmol, 2.0 eq.) and tosyl chloride (22.0 g, 116 mmol, 1.01 eq.) at 0 °C. The resulting mixture was stirred 10 min at 0 °C, then 12 h at ambient temperature before it was quenched by the addition of ice-cold water. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to obtain crude tosylate **972** which was directly used in the next step.

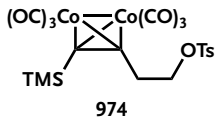
4-(Trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate (973).



973

Crude tosylate **972** (114 mmol, 1.0 eq.) was dissolved in anhydrous THF (160 ml) and cooled to –78 °C. A solution of ^{n}BuLi (2.5 M in hexanes, 50.0 ml, 125 mmol, 1.1 eq.) was added dropwise and stirring was continued for additional 60 min at –78 °C. Chlorotrimethylsilane (18.9 ml, 148 mmol, 1.3 eq.) was added dropwise over 25 min at –78 °C and stirring was continued for additional 12 h with the cooling bath slowly warming up to 5 °C. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried and the solvent was removed *in vacuo* to obtain crude tosylate **973** as brown oil which solidified below 0 °C after 24 h. Recrystallization from hexanes furnished title compound **973** as off-white solid (31.1 g, 105 mmol, 92% over two steps). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.85 – 7.73 (m, 2H), 7.39 – 7.29 (m, 2H), 4.07 (t, J = 7.3 Hz, 2H), 2.58 (t, J = 7.3 Hz, 2H), 2.44 (s, 3H), 0.11 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{14}H_{21}O_3SSi$ $[M + H]^+$ 297.0981, found 297.0980. ▸ *NMR spectra on page 492.*

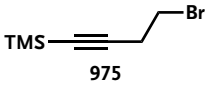
Bis(tricarbonylcobalt) complex of 4-(Trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate (974).



974

To a solution of tosylate **973** (192 mg, 648 µmol, 1.0 eq.) in CH_2Cl_2 (1.9 ml) was added dicobalt octacarbonyl (266 mg, 777 µmol, 1.2 eq.) in one portion at ambient temperature. After stirring for 30 min at that temperature, the reaction mixture was evaporated to dryness *in vacuo*. The crude product was purified by silica gel column chromatography (pentane–ether, 10:1) to obtain pure bis(tricarbonylcobalt) complex **974** (365 mg, 627 µmol, 97%) as brown solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.81 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.23 (t, J = 6.6 Hz, 2H), 3.24 (t, J = 6.7 Hz, 2H), 2.45 (s, 3H), 0.27 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{20}H_{20}Co_2NaO_9SSi$ $[M + Na]^+$ 604.9159, found 604.9163. ▸ *NMR spectra on page 493.*

(4-Bromobut-1-yn-1-yl)trimethylsilane (975).

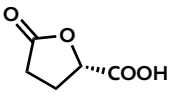


975

A mixture of tosylate **973** (23.7 g, 80.0 mmol, 1.0 eq.), lithium bromide (14.0 g, 161 mmol, 2.0 eq.) and TBAI (591 mg, 1.60 mmol, 2 mol %) in acetone (70 ml) was stirred at ambient temperature for 24 h. The mixture was diluted with pentane and water was added. The layers were separated and the aqueous layer was extracted twice with pentane. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (pure pentane) to obtain bromide **975** as colorless oil (14.4 g, 70.3 mmol, 88%). R_f = 0.40 (pentane, pure). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.41 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.5 Hz, 2H), 0.14 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 103.3, 87.1, 29.3, 24.4, 0.1 ppm. **HRMS** (ESI): calcd. for $C_7H_{13}BrNaSi$ $[M + Na]^+$ 226.9868, found 226.9870. ▸ NMR spectra on page 493.

13.2 Experimental Part for Section 12.3

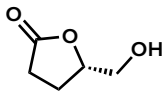
(*S*)-5-Oxotetrahydrofuran-2-carboxylic acid (982).



982

L-Glutamic acid (180 g, 1.22 mol, 1.0 eq.) was dissolved in H_2O (480 ml), cooled to 0 °C and conc. HCl (250 ml) was added to yield a white suspension. A solution of $NaNO_2$ (127 g, 1.84 mol) in H_2O (270 ml) was added dropwise at 0–5 °C under vigorous stirring over six hours. The pale yellow solution was stirred at ambient temperature overnight. Water was evaporated *in vacuo* to obtain a pale-yellow oil together with colorless crystals. This residue was stirred vigorously for 2 h with ethyl acetate (500 ml) and anhydrous sodium sulfate. The mixture was filtered through a medium porosity sintered-glass funnel and the filtrate was concentrated *in vacuo* to obtain a yellow oil which was kept below 0 °C overnight to induce solidification. The product was warmed up to ambient temperature and ether was added. The mixture was stirred 60 min at ambient temperature and additional five hours at 20 °C. The crystalline product was isolated by suction. The latter sequence was repeated two more times to furnish three batches of white crystalline product which were identical according to NMR analysis (115 g, 880 mmol, 72%). **M.p.** 74 °C. **^{1}H NMR** (200 MHz, MeOD) δ = 5.19 (br s, 1H), 5.08 – 4.93 (m, 1H), 2.74 – 2.46 (m, 3H), 2.41 – 2.20 (m, 1H) ppm. **^{13}C NMR** (101 MHz, MeOD) δ = 179.1, 173.4, 77.3, 27.8, 26.8 ppm. **IR** (neat): 3049, 2975, 2930, 1780, 1704 cm^{-1}. **HRMS** (ESI): calcd. for $C_5H_6NaO_4$ $[M + Na]^+$ 153.0164, found 153.0161. $[\alpha]_D^{20}$ = +11.2° (c = 5.0, MeOH). ▸ NMR spectra on page 494.

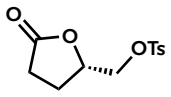
(*S*)-5-(Hydroxymethyl)dihydrofuran-2(3*H*)-one (983).


983

(*S*)-(+)-carboxylic acid (5.00 g, 38.4 mmol, 1.0 eq.) was dissolved in anhydrous THF (35 ml). $BH_3 \cdot SMe_2$ (4.2 ml, 44.2 mmol, 1.15 eq.) was added dropwise over 45 min at ambient temperature. After complete addition, the reaction mixture was stirred additional 3 h at this temperature (monitored by TLC). The mixture was cooled to 0 °C and methanol (50 ml) was carefully added. The solvents were removed *in vacuo* and the residue was redissolved in methanol. The solvent was again removed *in vacuo* and title compound **983** was obtained by Kugelrohr distillation as colorless oil (4.44 g, 37.9 mmol, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.60 (dddd, J = 7.5, 6.6, 4.6, 2.9 Hz, 1H), 3.85 (dd, J = 12.5, 2.9 Hz, 1H), 3.61 (dd, J = 12.6, 4.6 Hz, 1H), 3.21 (s, 1H), 2.67 – 2.43 (m, 2H), 2.24 (dddd, J = 12.8, 9.7, 7.6, 5.9 Hz, 1H), 2.11 (dddd, J = 12.8, 9.9, 8.0, 6.7 Hz, 1H) ppm. **HRMS** (ESI): calcd. for $C_5H_9O_3$ $[M + H]^+$ 117.0552, found 117.0554. $[\alpha]_D^{20}$ = +29.0° (c = 1.0, EtOH).

▸ NMR spectra on page 495.

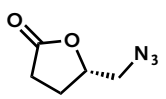
(*S*)-(5-Oxotetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (984).


984

(*S*)-Alcohol **983** (4.40 g, 37.9 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (25 ml) and cooled to 0 °C. Tosyl chloride (9.39 g, 49.3 mmol, 1.3 eq.) was added in portions followed by the addition of DMAP (463 mg, 3.79 mmol, 10 mol %). The reaction mixture was stirred 130 min at this temperature, then diluted with EtOAc and quenched by the addition of ice-cold 5% HCl. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo*. Recrystallization from EtOAc–Et_2O (1:1.5) afforded tosylate **984** as bright white powder (7.45 g, 27.6 mmol, 73%). R_f = 0.78 (EtOAc, pure). **M.p.** 83 °C. **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.76 – 7.69 (m, 2H), 6.76 (dt, J = 8.0, 0.7 Hz, 2H), 3.81 (dddd, J = 7.6, 6.7, 4.9, 3.2 Hz, 1H), 3.74 (dd, J = 11.0, 3.2 Hz, 1H), 3.61 (dd, J = 11.0, 4.9 Hz, 1H), 1.90 (ddd, J = 17.6, 9.6, 8.3 Hz, 1H), 1.85 (s, 3H), 1.67 (ddd, J = 17.8, 9.7, 8.3 Hz, 1H), 1.16 (dddd, J = 9.3, 8.2, 6.5, 5.3 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 175.2, 144.9, 133.4, 130.1, 128.2, 76.0, 70.3, 27.6, 23.1, 21.2 ppm. **HRMS** (ESI): calcd. for $C_{12}H_{15}O_5S$ $[M + H]^+$ 271.0640, found 271.0644. $[\alpha]_D^{20}$ = +48.2° (c = 1.0, $CHCl_3$).

▸ NMR spectra on page 496.

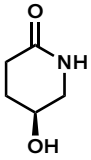
(*S*)-5-(Azidomethyl)dihydrofuran-2(3*H*)-one (985).


985

A mixture of tosylate **984** (1.30 g, 4.81 mmol, 1.0 eq.) and sodium azide (938 mg, 14.4 mmol, 3.0 eq.) was stirred 2.5 h at 60 °C (monitored by TLC). The solvent was removed under reduced pressure, the residue triturated with chloroform and filtered through a celite pad. The filtrate was concentrated to give crude **985** which was purified by silica gel column chromatography to obtain pure azide **985** (652 mg, 4.61 mmol, 96%) as colorless oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.62 (tdd, J = 7.1, 5.0, 3.7 Hz, 1H), 3.58 (dd, J = 13.3, 3.7 Hz, 1H), 3.42 (dd, J = 13.3, 5.0 Hz, 1H), 2.62 – 2.48 (m, 2H), 2.46 – 2.19

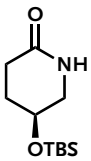
(m, 1H), 2.02 (dddd, J = 12.9, 10.0, 8.2, 6.9 Hz, 1H) ppm. **HRMS** (ESI): calcd. for $C_5H_7N_3NaO_2$ $[M + Na]^+$ 164.0436, found 164.0437. $[\alpha]_D^{20}$ = +89.2° (c = 2.0, $CHCl_3$). ▸ NMR spectra on page 497.

(*S*)-5-Hydroxypiperidin-2-one (900).


900

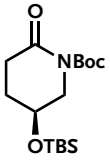
Azide **985** (9.00 g, 63.8 mmol) was dissolved in anhydrous methanol (160 ml) and Pd/C (10%, 160 mg) was added. The mixture was hydrogenated (p = 100 psi) at ambient temperature for 3.5 h. The mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The obtained product was usually used crude for the next step. In case of a purification, crude **900** was purified by alumina gel chromatography (chloroform–MeOH, 4:1) followed by a recrystallization from acetonitrile to yield pure **900** a bright white powder. **^{1}H NMR** (400 MHz, DMSO) δ = 7.30 (s, 1H), 3.85 (dq, J = 9.9, 3.7 Hz, 1H), 3.43 (qt, 1H), 3.26 – 3.12 (m, 1H), 3.05 – 2.88 (m, 1H), 2.23 (ddd, J = 17.5, 8.0, 6.5 Hz, 1H), 2.08 (dt, J = 17.5, 6.5 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.73 – 1.61 (m, 1H) ppm. **HRMS** (ESI): calcd. for $C_5H_{10}NO_2$ $[M + H]^+$ 116.0712, found 116.0715. $[\alpha]_D^{20}$ = –13.7° (c = 1.0, MeOH). ▸ NMR spectra on page 497.

(*S*)-5-((*tert*-Butyldimethylsilyl)oxy)piperidin-2-one (979).


979

Crude (*S*)-hydroxypiperidone **900** (63.8 mmol, 1.0 eq.) was dissolved in anhydrous *N,N*-dimethylformamide (315 ml) and cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (11.5 g, 76.5 mmol, 1.2 eq.) and imidazole (10.9 g, 159 mmol, 2.5 eq.) were added and the resulting mixture was stirred 15 min at this temperature, then additional 12 h at ambient temperature. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and silica was added. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (hexanes–EtOAc, 1:4) to obtain pure piperidinone **979** as colorless crystals (13.0 g, 56.7 mmol, 89% over two steps). **M.p.** 48 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.02 (br s, 1H), 4.03 (p, J = 4.7 Hz, 1H), 3.34 (ddd, J = 12.2, 4.0, 2.2 Hz, 1H), 3.13 (ddd, J = 12.1, 5.1, 2.5 Hz, 1H), 2.53 (dt, J = 17.7, 7.5 Hz, 1H), 2.26 (dt, J = 17.7, 6.1 Hz, 1H), 1.92 – 1.74 (m, 2H), 0.84 (s, 9H), 0.03 (d, J = 1.2 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{11}H_{24}NO_2Si$ $[M + H]^+$ 230.1576, found 230.1580. $[\alpha]_D^{20}$ = –65.0° (c = 0.2, $CHCl_3$). ▸ NMR spectra on page 498.

***tert*-Butyl (*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2-oxopiperidine-1-carboxylate (987).**

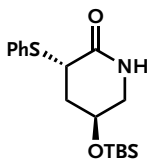

987

(*S*)-Lactame **979** (827 mg, 3.61 mmol, 1.0 eq.) was dissolved in anhydrous THF (30.0 ml) and DABCO (411 mg, 3.67 mmol, 1.02 eq.) was added. The mixture was cooled down to –78 °C and ^{n}BuLi (2.5 M in hexanes, 1.44 ml, 3.61 mmol, 1.0 eq.) was added dropwise. The mixture was stirred 50 min at this temperature, then a solution of Boc_2O (951 mg, 4.36 mmol, 1.21 mmol) in anhydrous THF (9.7 ml) was added in one portion at –78 °C. The reaction mixture was stirred additional three hours at this

temperature. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ at –78 °C, then ether was added and the layers were separated. The aqueous layer was extracted once and the combined organic layers were extracted thrice with sat. aq. NH_4Cl. The organic layer was dried over magnesium sulfate and the solvent w as removed *in vacuo*. The crude was subjected to flash column chromatography (hexanes–EtOAc, 6:4) to obtain pure title compound **987** as white solid. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.20 – 4.08 (m, 1H), 3.64 (br d, J = 4.3 Hz, 2H), 2.78 – 2.60 (m, 1H), 2.42 (dt, J = 17.2, 6.1 Hz, 1H), 2.01 – 1.77 (m, 2H), 1.52 (s, 11H), 0.88 (s, 9H), 0.08 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_{16}H_{31}NNaO_4Si$ $[M + Na]^+$ 352.1920, found 352.1921. $[\alpha]_D^{20}$ = +8.3° (c = 1.0, $CHCl_3$).

▸ NMR spectra on page 498.

(3*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-(phenylthio)piperidin-2-one (992).



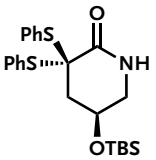
992

Variant 1: Amide **979** (760 mg, 3.31 mmol, 1.0 eq.) was dissolved in anhydrous THF (11.0 ml) and cooled to –78 °C. A solution of ^{n}BuLi (2.5 M in hexanes, 4.6 ml, 11.6 mmol, 3.5 eq.) was added dropwise and stirring was continued for additional 30 min at 78 °C, then 80 min at 0 °C. The mixture was recooled to –78 °C and HMPA (2.0 ml, 11.6 mmol, 3.5 eq.) was added in one portion. The mixture was stirred 20 min at this temperature, then a solution of diphenyl disulfide (796 mg, 3.64 mmol, 1.10 eq.) in anhydrous THF (1.5 ml) was added dropwise and stirring was continued at –78 °C for 14 h. The reaction was quenched at –78 °C by the addition of 1 N HCl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were extracted once with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The crude residue was subjected to flash column chromatography (hexanes–EtOAc, 1.5:1 → 1:1) to obtain both monothio compound **992** (514 mg, 1.52 mmol, 50%) and bisthio compound **991** (149 mg, 334 µmol, 10%) as white and yellow solid, respectively.

Variant 2: To a solution of bisthio compound **991** (40.0 mg, 89.7 µmol, 1.0 eq.) in anhydrous THF (0.6 ml) was added a solution of ethylmagnesium bromide (3.0 M in Et_2O, 54 µl, 162 µmol, 1.80 eq.) at –10 °C. After 2 h of stirring in the cold, the reaction mixture was quenched by the dropwise addition of 5% HCl and extracted thrice with ether. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave a residue that was purified by flash column chromatography on silica gel (hexanes–EtOAc, 1:1) to furnish monothio compound **992** (24.0 mg, 71.1 µmol, 80%) as white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.55 – 7.47 (m, 2H), 7.33 – 7.23 (m, 3H), 6.51 (br s, 1H), 4.18 (ddt, J = 6.7, 3.8, 2.2 Hz, 1H), 4.05 (dd, J = 9.2, 5.8 Hz, 1H), 3.39 (ddd, J = 12.3, 4.0, 1.8 Hz, 1H), 3.18 (dddd, J = 12.3, 4.4, 2.9, 1.5 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.07 – 1.94 (m, 1H), 0.86 (s, 9H), 0.04 (d, J = 7.1 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{17}H_{27}NNaO_2SSi$ $[M + Na]^+$ 360.1429, found 360.1430. $[\alpha]_D^{20}$ = –24.8° (c = 1.0, MeOH).

▸ NMR spectra on page 499.

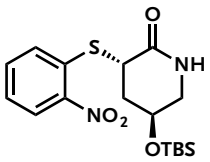
(*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,3-bis(phenylthio)piperidin-2-one (991).



991

To a solution of lactam **979** (155 mg, 676 µmol, 1.0 eq.) in anhydrous THF (2.4 ml) was added a solution of ^{n}BuLi (2.5 M in hexanes, 273 µl, 682 µmol, 1.01 eq.) at –78 °C. After complete addition the resulting solution was stirred 75 min at 0 °C. Chlorotrimethylsilane (96 µl, 745 µmol, 1.1 eq.) was added dropwise and the mixture was stirred additional 105 min at 0 °C. *N*-Phenylthiophthalimide (**996**, 380 mg, 1.49 mmol, 2.20 eq.) was added in one portion and the solution was cooled down to –78 °C. A solution of KHMDS (0.5 M in toluene, 3.0 ml, 1.49 mmol, 2.20 eq.) was added dropwise and the mixture was stirred 10 min at –78 °C, then additional 45 min at ambient temperature (monitored by TLC). The reaction was then quenched by the dropwise addition of 5% HCl and extracted thrice with EtOAc. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave a residue that was purified by flash column chromatography on silica gel (hexanes–EtOAc, 1.5:1) to furnish bisthio compound **991** (300 mg, 673 µmol, quant.) as yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.76 – 7.70 (m, 2H), 7.64 – 7.58 (m, 2H), 7.47 – 7.30 (m, 6H), 7.05 (br d, J = 4.3 Hz, 1H), 4.24 (tt, J = 9.9, 5.0 Hz, 1H), 3.28 (dddd, J = 11.8, 5.4, 4.5, 1.9 Hz, 1H), 2.86 (dd, J = 11.4, 9.6 Hz, 1H), 2.15 (ddd, J = 14.4, 4.6, 2.0 Hz, 1H), 2.12 – 2.06 (m, 1H), 0.79 (s, 9H), –0.04 (d, J = 15.8 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{23}H_{31}NNaO_2S_2Si$ $[M + Na]^+$ 468.1463, found 468.1462. ▸ *NMR spectra on page 499.*

(3*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((2-nitrophenyl)thio)piperidin-2-one (993).



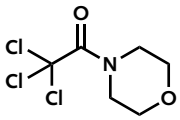
993

To a solution of lactam **979** (52.0 mg, 227 µmol, 1.0 eq.) in anhydrous THF (0.8 ml) was added a solution of ^{n}BuLi (2.5 M in hexanes, 199 µl, 499 µmol, 2.2 eq.) at –78 °C. The solution was stirred 20 min at this temperature and then additional 90 min at 0 °C. The solution was recooled to –78 °C and a solution of 2-nitrobenzenesulfenyl chloride (51.6 mg, 272 µmol, 1.20 eq.) in anhydrous THF (0.3 ml) was added. The resulting mixture was stirred 14 h at –78 °C, then quenched by the dropwise addition of 1 N HCl and extracted twice with EtOAc. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave a residue that was purified by flash column chromatography on silica gel (hexanes–EtOAc, 4:1 → 2:1) to furnish title compound **993** (36.1 mg, 94.3 µmol, 42%) as bright yellow solid. R_f = 0.37 (hexanes–EtOAc, 1.5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.32 (dd, J = 8.3, 1.4 Hz, 1H), 7.58 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.31 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 4.27 (p, J = 3.0 Hz, 1H), 3.90 (dd, J = 12.5, 3.1 Hz, 1H), 3.53 (d, J = 12.5 Hz, 1H), 2.95 (ddd, J = 18.4, 10.8, 7.9 Hz, 1H), 2.64 (dt, J = 18.0, 4.7 Hz, 1H), 2.05 (ddt, J = 7.9, 3.8, 2.4 Hz, 2H), 0.94 (s, 9H), 0.11 (d, J = 15.7 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_{17}H_{26}N_2NaO_4SSi$ $[M + Na]^+$ 405.1280, found 405.1283. ▸ *NMR spectra on page 500.*

Note: This compound has been synthesized only once. Based on the results, the use of ^{n}BuLi is not recommended, since the formation of butyl(2-nitrophenyl)sulfane has been observed. The use of LDA or an equal base should avoid the formation of this product and raise the yield.

13.3 Experimental Part for Section 12.4.1

2,2,2-Trichloro-1-morpholinoethan-1-one (1011).

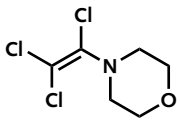


1011

Morpholine (100 ml, 1.14 mol, 2.08 eq.) was dissolved in anhydrous THF (300 ml) and cooled to 0 °C. A solution of trichloroacetyl chloride (100 g, 550 mmol, 1.0 eq.) in anhydrous THF (50 ml) was added dropwise over 90 min at 0 °C. The resulting milky white suspension was warmed up to ambient temperature for additional 5 h, then diluted with ether (300 ml) and quenched by the addition of 1 N HCl (100 ml). The layers were separated and the aqueous layer was extracted once with 1 N HCl, twice with sat. aq. $NaHCO_3$, and finally once with brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to provide title compound **1011** (122 g, 523 mmol, 95%) as white solid which was directly used for the next step. $R_f = 0.45$ (hexanes–EtOAc, 3:1, stains with $KMnO_4$). **^{1}H NMR** (200 MHz, $CDCl_3$) $\delta = 3.90 - 3.75$ (br s, 4H), 3.80 – 3.68 (m, 4H) ppm. **HRMS** (ESI): calcd. for $C_6H_8Cl_3NNaO_2$ $[M + Na]^+$ 253.9518, found 253.9522.

▸ NMR spectra on page 500.

***N*-Trichlorovinyl morpholine (1010).**

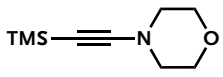


1010

Amide **1011** (122 g, 523 mmol, 1.0 eq.) was dissolved in *o*-xylene and triphenylphosphine (151 g, 575 mmol, 1.1 eq.) was added. The resulting solution was heated to 150 °C for 1.5 h. The reaction mixture was cooled to 125 °C, the reaction flask was equipped with a distillation apparatus and the solvent was removed under reduced pressure (100 Torr). The pressure was further reduced to 10 Torr to collect title compound **1010** as pale yellow oil (91.0 g, 420 mmol, 80% over two steps). **^{1}H NMR** (200 MHz, $CDCl_3$) $\delta = 3.79 - 3.71$ (m, 1H), 2.88 – 2.71 (m, 1H) ppm. **HRMS** (ESI): calcd. for $C_6H_8Cl_3NNaO$ $[M + Na]^+$ 237.9569, found 237.9570.

▸ NMR spectra on page 501.

4-((Trimethylsilyl)ethynyl)morpholine (1007).



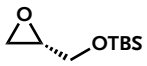
1007

N-Trichlorovinyl morpholine (**1010**, 24.6 g, 114 mmol, 1.0 eq.) was dissolved in anhydrous ether (290 ml) and cooled to –78 °C. A solution of ^{n}BuLi (2.5 M in hexanes, 100 ml, 250 mmol, 1.0 eq.) was added over 10 min and the resulting off-white suspension was gradually warmed to ambient temperature over 1 h. The solution was recooled to –20 °C and chlorotrimethylsilane (17.3 ml, 136 mmol, 1.2 eq.) was added dropwise and the mixture was allowed to warm to 23 °C. After 15 h, the suspension was diluted with hexanes and the solids were removed by filtration through a medium porosity sintered-glass funnel. The filtrate was concentrated and title compound **1007** was obtained by Kugelrohr distillation (18.3 g, 99.5 mmol, 88%) as colorless oil which solidified below 0 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta = 3.69 - 3.64$ (m, 4H), 3.09 – 3.03 (m, 4H), 0.12 (d, $J = 0.5$ Hz, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) $\delta = 108.7$, 66.1, 62.5, 51.7, 0.9 ppm. **HRMS** (ESI): calcd.

for $C_9H_{18}NOSi$ $[M + H]^+$ 184.1158, found 184.1155. ▸ NMR spectra on page 501.

Note: Storage in the freezer under an atmosphere of argon is possible for an indefinite period of time.

(*S*)-*tert*-Butyldimethyl(oxiran-2-ylmethoxy)silane (1006).

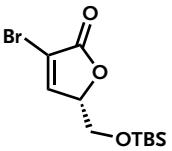


1006

A mixture of (*S*)-Glycidol (5.00 g, 67.5 mmol, 1.0 eq.), *tert*-butyldimethylsilyl chloride (13.2 g, 87.7 mmol, 1.3 eq.), and imidazole (7.35 g, 108 mmol, 1.6 eq.) in anhydrous *N,N*-dimethylformamide (40 ml) was stirred at 0 °C for 30 min, then additional 140 min at ambient temperature. Pentane–ether (1:1) and brine were added and the layers were separated. The aqueous layer was extracted once with pentane–ether (1:1) and the combined organic layers were dried over sodium sulfate. Evaporation of the solvent under reduced pressure and purification of the residue by flash column chromatography (pentane–ether, 50:1 → 10:1) provided pure title compound **1006** as colorless oil (12.4 g, 65.8 mmol, 98%). Alternatively, title compound **1006** can be purified *via* Kugelrohr distillation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.84 (dd, J = 11.9, 3.2 Hz, 1H), 3.64 (dd, J = 11.9, 4.8 Hz, 1H), 3.10 – 3.03 (m, 1H), 2.75 (dd, J = 5.1, 4.0 Hz, 1H), 2.62 (dd, J = 5.2, 2.7 Hz, 1H), 0.89 (s, 9H), 0.06 (d, J = 3.7 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_9H_{20}NaO_2Si$ $[M + Na]^+$ 211.1130, found 211.1132.

▸ NMR spectra on page 502.

(*S*)-3-Bromo-5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2(5*H*)-one (902).

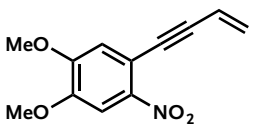


902

Ynamine **1007** (6.27 g, 34.2 mmol, 1.4 eq.) was dissolved in anhydrous CH_2Cl_2 (150 ml) and cooled to 0 °C. Boron trifluoride diethyl etherate (4.3 ml, 34.2 mmol, 1.4 eq.) was added dropwise followed by the addition of **1006** (4.60 g, 24.4 mmol, 1.0 eq.) at 0 °C. The dark orange solution was stirred 50 min at this temperature (monitored by TLC), then *N*-bromosuccinimide (13.0 g, 73.3 mmol, 3.0 eq.) was added at 0 °C and the reaction mixture was stirred additional 15 min at this temperature before it was diluted with CH_2Cl_2 and quenched by the addition of 5% HCl. The resulting mixture was stirred vigorously for 30 min at ambient temperature, then the layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were extracted once with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was dissolved in anhydrous *N,N*-dimethylformamide (50 ml). Lithium chloride (dried at 200 °C under vacuum, 5.18 g, 122 mmol, 5.0 eq.) and lithium carbonate (1.80 g, 24.4 mmol, 1.0 eq.) were added and the resulting mixture was heated to 70 °C for 20 min (monitored by TLC). The mixture was diluted with water and pentane–ether (1:1) was added. The layers were separated and the aqueous layer was extracted once with pentane–ether (1:1). The combined organic layers were extracted once with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 8:1) to obtain pure γ-butenolide **902** as pale yellow solid (5.78 g, 18.8 mmol, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 1.8 Hz, 1H), 4.99 (ddd,

J = 4.9, 4.1, 1.8 Hz, 1H), 3.91 (dd, J = 11.0, 4.1 Hz, 1H), 3.83 (dd, J = 11.0, 4.9 Hz, 1H), 0.85 (s, 9H), 0.05 (d, J = 3.6 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 168.4, 150.9, 113.9, 82.8, 62.6, 25.8, 18.2, –5.4, –5.4 ppm. **HRMS** (ESI): calcd. for $C_{11}H_{19}BrNaO_3Si$ $[M + Na]^+$ 329.0185, found 329.0188. $[\alpha]_D^{20}$ = –58° (c = 1.0, $CHCl_3$). ▸ NMR spectra on page 503.

1-(But-3-en-1-yn-1-yl)-4,5-dimethoxy-2-nitrobenzene (963).



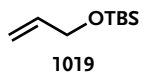
963

Iodide **953** (1.66 g, 4.60 mmol, 1.0 eq.) was dissolved in anhydrous toluene (10.0 ml) and DBU (755 µl, 5.06 mmol, 1.1 eq.) was added in one portion. The resulting solution was heated to 50 °C for 10 min (monitored by TLC). The reaction mixture was quenched by the addition of 5% HCl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 3:1) to provide enyne **963** (1.07 g, 4.59 mmol, quant.) as pale olive solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.63 (s, 1H), 6.97 (s, 1H), 6.07 (dd, J = 17.5, 11.2 Hz, 1H), 5.83 (dd, J = 17.5, 2.0 Hz, 1H), 5.64 (dd, J = 11.1, 2.0 Hz, 1H), 3.95 (d, J = 1.2 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 152.8, 148.9, 142.7, 128.8, 117.0, 115.4, 112.8, 107.7, 94.5, 86.1, 56.6, 56.5 ppm. **HRMS** (ESI): calcd. for $C_{12}H_{12}NO_4$ $[M + H]^+$ 234.0766, found 234.0762.

▸ NMR spectra on page 504.

*Note: Similar procedure was used for the generation of enyne **1018** from iodide **969**.*

(Allyloxy)(*tert*-butyl)dimethylsilane (1019).



1019

A mixture of ally alcohol (3.00 g, 51.7 mmol, 1.0 eq.), *tert*-butyldimethylsilyl chloride (9.34 g, 62.0 mmol, 1.2 eq.), and imidazole (8.79 g, 129 mmol, 2.5 eq.) in anhydrous *N,N*-dimethylformamide (86 ml) was stirred 18 h at ambient temperature. The reaction mixture was then diluted with pentane–ether (1:1) and water was added. The layers were separated and the aqueous layer was extracted once with pentane–ether (1:1). The combined organic layers were washed once with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (pentane–ether, 96:4) to provide silyl alcohol **1019** (8.88 g, 51.1 mmol, 99%) as colorless oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 5.92 (ddt, J = 17.1, 10.4, 4.5 Hz, 1H), 5.26 (dq, J = 17.1, 1.9 Hz, 1H), 5.08 (dq, J = 10.4, 1.8 Hz, 1H), 4.18 (dt, J = 4.5, 1.8 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_9H_{20}NaOSi$ $[M + Na]^+$ 195.1181, found 195.1184.

▸ NMR spectra on page 505.

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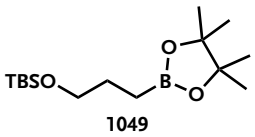
tert-Butyldimethyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane (1049).

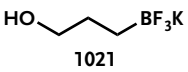


1049

Borane dimethyl sulfide (3.25 ml, 32.5 mmol, 1.0 eq.) was added dropwise to a solution of pinacol (3.84 g, 32.5 mmol 1.0 eq.) in anhydrous CH_2Cl_2 (3.3 ml) at 0 °C and the resulting solution was stirred for additional 60 min at this temperature. The cooling bath was removed and stirring was continued for additional 180 min at ambient temperature. The reaction mixture was recooled to 0 °C and a solution of silyl alcohol **1019** (2.8 g, 16.3 mmol, 0.5 eq.) in anhydrous CH_2Cl_2 (1.9 ml) was added followed by the addition of chloridotris(triphenylphosphane)rhodium(I) (15.0 mg, 16.3 µmol, 0.05 mol %). The reaction mixture was stirred 15 min at 0 °C and then 48 h at ambient temperature. The reaction mixture was diluted with water and the layer were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (pentane–ether, 95:5) to obtain boronate ester **1049** as colorless oil (1.43 g, 4.76 mmol, 30%) which was directly used for the next transformation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.56 (t, J = 6.8 Hz, 2H), 1.61 (dq, J = 8.1, 6.9 Hz, 2H), 1.23 (s, 12H), 0.88 (s, 9H), 0.76 (t, J = 7.9 Hz, 2H), 0.03 (s, 6H) ppm.

▸ *NMR spectra on page 505.*

Potassium 3-trifluoroboratopropan-1-ol (1021).



1021

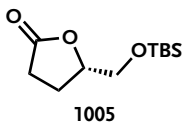
Boronate ester **1049** (1.40 g, 4.66 mmol, 1.0 eq.) was dissolved in anhydrous acetonitrile (23 ml) and cooled to 0 °C. Potassium bifluoride (1.13 g, 14.5 mmol, 3.1 eq.) was added in one portion followed by the dropwise addition of water (3.5 ml) over a period of 60 min at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 2.5 h at ambient temperature. Acetone was added and the suspension allowed to settle, then the solution decanted into a conical flask. The reaction flask was rinsed twice with MeOH and similarly decanted. The combined organics were filtered through a cotton plug and evaporated. The residue was taken up in water and washed four times with ethyl acetate. The aqueous layer was concentrated *in vacuo* and the residue was taken up in methanol and once again concentrated *in vacuo* to provide trifluoroborate salt **1021** as bright white solid (676 mg, 4.07 mmol, 87%) after drying for several hours under high vacuum. **^{1}H NMR** (400 MHz, MeOD) δ = 3.49 (t, J = 7.3 Hz, 2H), 1.52 (p, J = 7.4 Hz, 2H), 0.25 – 0.11 (m, 2H) ppm.

▸ *NMR spectra on page 506.*

Note: (i) Storage under argon at –18 °C. (ii) Caution! In this context, potassium bifluoride is a potential hydrogen fluoride source and should be handled with care.

13.4 Experimental Part for Section 12.4.2

(*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one (1005).

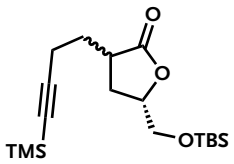


1005

Crude alcohol **983** (103 mmol, 1.0 eq.) was dissolved in anhydrous DMF (100 ml) and cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (20.2 g, 134 mmol, 1.3 eq.) and imidazole (17.6 g, 258 mmol, 2.5 eq.) were added in portions at 0 °C and stirring was continued for additional six hours (monitored by TLC). The reaction mixture was concentrated *in vacuo* to approximately 20%, then diluted with pentane–ether (1:1) and brine–H_2O (1:1). The layers were separated and the aqueous layer was extracted twice with pentane–ether (1:1). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to yield crude title compound **1005** which was subjected to flash column chromatography (pentane–ether, 30:1 → 15:1) to provide pure title compound **1005** (15.3 g, 66.4 mmol, 87% over two steps) as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.54 (ddt, J = 8.1, 5.1, 3.1 Hz, 1H), 3.82 (dd, J = 11.3, 3.2 Hz, 1H), 3.64 (dd, J = 11.3, 3.1 Hz, 1H), 2.56 (ddd, J = 17.5, 10.2, 7.3 Hz, 1H), 2.42 (ddd, J = 17.7, 10.1, 6.2 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 0.84 (d, J = 1.1 Hz, 9H), 0.03 (d, J = 3.3 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 177.6, 80.1, 64.9, 28.6, 25.8, 23.6, 18.3, –5.5, –5.5 ppm. **HRMS** (ESI): calcd. for $C_{11}H_{22}NaO_3Si$ $[M + Na]^+$ 253.1236, found 253.1240. $[\alpha]_D^{20}$ = +12.5° (c = 1.0, $CHCl_3$).

▸ NMR spectra on page 506.

(5*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl)dihydrofuran-2(3*H*)-one (1022).



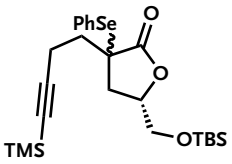
1022

^{n}BuLi (2.5 M in hexanes, 1.91 ml, 4.78 mmol, 1.1 eq) was added to a solution of diisopropylamine (732 µl, 5.21 mmol, 1.2 eq.) in anhydrous THF (10.4 ml) at –78 °C and the solution was stirred 60 min at –78 °C. A solution of lactone **1050** (1.00 g, 4.34 mmol, 1.0 eq.) and HMPA (1.7 ml, 9.55 mmol 2.20 eq.) in anhydrous THF (5.6 ml) was added over 20 min *via* syringe pump at –78 °C and the resulting solution was stirred for additional 2 h at this temperature. A solution of freshly prepared triflate **973** (1.37 g, 4.99 mmol, 1.15 eq.) in anhydrous THF (4.2 ml) was added dropwise at –78 °C and stirring was continued for 20 min at this temperature. The mixture was diluted with ether and quenched by the addition of 5% HCl. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to obtain crude title compound **1022** which was subjected to flash column chromatography (hexanes–EtOAc, 10:1 → 4:1) to provide recovered starting material (610 mg, 2.65 mmol) along with pure title compound **1022** (590 mg, 1.67 mmol, 38%, 99% brsm, diastereomeric ratio = 2:1) as colorless oil. R_f = 0.36 (hexanes–EtOAc, 8:1, stains with $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.53 (dq, J = 8.9, 3.0 Hz, 0.66H, major diastereomer), 4.45 (ddt, J = 10.0, 6.8, 3.8 Hz, 0.33H, minor diastereomer), 3.84 (ddd, J = 11.2, 5.4, 3.5 Hz, 1H), 3.69 (ddd, J = 14.2, 11.3, 3.4 Hz, 1H), 2.85

(qd, J = 9.5, 5.2 Hz, 0.66H, major diastereomer), 2.81 – 2.73 (m, 0.33H, minor diastereomer), 2.51 – 2.24 (m, 3H), 2.20 – 1.77 (m, 2H), 1.66 – 1.56 (m, 1H), 0.88 (s, 9H), 0.13 (d, J = 1.0 Hz, 9H), 0.07 (dd, J = 4.2, 2.1 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 179.4, 178.6, 105.7, 105.6, 85.9, 85.7, 78.6, 78.0, 65.2, 64.1, 39.8, 38.7, 30.6, 30.4, 30.1, 29.7, 26.0, 26.0, 25.8, 18.5, 18.4, 18.2, 18.2, 0.2, 0.2, –5.2, –5.3, –5.3, –5.4 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{35}O_3Si_2$ $[M + H]^+$ 355.2125, found 355.2125. ▸ *NMR spectra on page 507.*

Note: The yield was not significantly higher when stirring was carried out for longer than 20 min after the addition of triflate ***973****, e.g. 14 h at –78 °C provided title compound* ***1022*** *in 42% yield (66% brsm).*

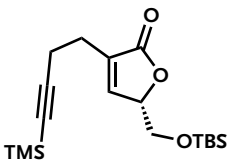
(5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(phenylselanyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl) dihydrofuran-2(3*H*)-one (1023).



1023

LiHMDS (1.0 M in THF, 328 µl, 328 µmol, 1.0 eq.) was added dropwise to a solution of lactone **1022** (104 mg, 293 µmol, 1.0 eq.) in anhydrous THF (1.0 ml) at –78 °C. The resulting mixture was stirred 60 min at this temperature, then chlorotrimethylsilane (47 µl, 366 µmol, 1.25 eq.) was added in one portion at –78 °C and the cooling bath was removed. The mixture was stirred 30 min at ambient temperature, then recooled to –78 °C. A solution of phenylselenyl bromide (104 mg, 440 µmol, 1.50 eq.) in anhydrous THF (0.5 ml) was added at this temperature and stirring was continued for additional 5 min (monitored by TLC). The dark orange reaction mixture was diluted with ether and water was added. The mixture was stirred vigorously at ambient temperature until the etheral layer became light yellow. Brine was added and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure to obtain crude organoselenium compound **1023** as yellow oil which was directly subjected to the oxidative elimination. R_f = 0.56 (hexanes–EtOAc, 8:1, stains intensely with $KMnO_4$, stains dark purple with vanillin).

(*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl)furan-2(5*H*)-one (1004).



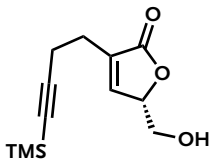
1004

Crude organoselenium species **1023** (290 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2.0 ml) and cooled to 0 °C. A solution of H_2O_2 (30%, 0.2 ml) in H_2O (0.4 ml) was added dropwise at this temperature followed by the addition of pyridine (one drop). The reaction mixture was stirred vigorously at 0 °C for 10 min (monitored by TLC) to obtain a colorless suspension. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under

reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 9:1) to obtain pure γ-butenolide **1004** (89.0 mg, 252 µmol, 87% over two steps) as colorless oil. R_f = 0.24 (hexanes–EtOAc, 9:1, stains dark olive with vanillin). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.23 – 7.19 (m, 1H), 4.93 (td, J = 5.1, 1.6 Hz, 1H), 3.87 (dd, J = 10.7, 4.8 Hz, 1H), 3.75 (dd, J = 10.7, 5.3 Hz, 1H), 2.55 – 2.44 (m, 4H), 0.87 (s, 9H), 0.13 (d, J = 0.5 Hz, 9H), 0.06 (d, J = 5.5 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.4, 147.2, 133.6, 105.5, 86.1, 81.6, 63.5, 25.9, 24.7, 18.4, 18.3, 0.2, –5.3, –5.3 ppm. **HRMS** (ESI): calcd. for $C_{18}H_{33}O_3Si_2$ $[M + H]^+$ 353.1968, found 353.1970.

▸ NMR spectra on page 508.

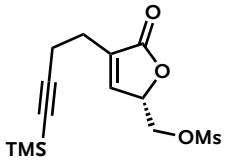
(*S*)-5-(Hydroxymethyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl)furan-2(5*H*)-one (1024).



1024

A solution of silyl alcohol **1004** (74.0 mg, 210 µmol, 1.0 eq.) in anhydrous THF (1.0 ml) was added to a solution of hydrogen fluoride pyridine (20% wt, 1.0 ml) at 0 °C and stirring was continued for three hours at this temperature (monitored by TLC). The reaction mixture was diluted with EtOAc and carefully quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were extracted with 1 N HCl to remove pyridine and dried over magnesium sulfate. The solvent was removed *in vacuo* to obtain title compound **1024** as colorless oil in quantitative yield which was directly subjected to the next step. R_f = 0.18 (hexanes–EtOAc, 1:1, stains brown with vanillin). **HRMS** (ESI): calcd. for $C_{12}H_{18}NaO_3Si$ $[M + Na]^+$ 261.0923, found 261.0922.

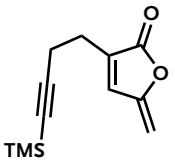
(*S*)-(5-Oxo-4-(4-(trimethylsilyl)but-3-yn-1-yl)-2,5-dihydrofuran-2-yl)methyl methanesulfonate (1025).



1025

Crude alcohol **1024** (210 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (2.1 ml) and cooled to 0 °C. Freshly distilled methanesulfonyl chloride (21 µl, 273 µmol, 1.3 eq.) and triethylamine (58 µl, 420 µmol, 2.0 eq.) were added and stirring was continued for 20 min at this temperature (monitored by TLC). The reaction as quenched by the addition of sat. aq. NH_4Cl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide crude mesylate **1025** as pale yellow oil which was directly subjected to the next step. R_f = 0.31 (hexanes–EtOAc, 1:1). **HRMS** (ESI): calcd. for $C_{13}H_{20}NaO_5SSi$ $[M + Na]^+$ 339.0698, found 339.0699.

5-Methylene-3-(4-(trimethylsilyl)but-3-yn-1-yl)furan-2(5*H*)-one (1026).

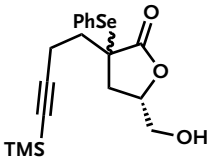


1026

A mixture of crude mesylate **1025** (210 µmol, 1.0 eq.) and sodium azide (50.5 mg, 777 µmol, 3.7 eq.) in anhydrous DMF (0.5 ml) was heated to 50 °C for 60 min (monitored by TLC). The reaction mixture was diluted with ether and brine and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were extracted once with brine. Drying over magnesium sulfate followed by the removal of the solvent under reduced pressure furnished crude title compound **1026** which was purified by flash column chromatography (hexanes–EtOAc, 9:1) to provide pure γ-butenolide **1026** (27.3 mg, 143 µmol, 68% over three steps) as colorless oil. R_f = 0.89 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 6.37 (dt, J = 1.4, 0.8 Hz, 1H), 4.81 – 4.74 (m, 1H), 4.23 – 4.16 (m, 1H), 2.30 – 2.23 (m, 2H), 2.23 – 2.15 (m, 2H), 0.26 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{12}H_{17}O_2Si$ $[M + H]^+$ 221.0998, found 221.0997.

▸ *NMR spectra on page 510.*

(5*S*)-5-(Hydroxymethyl)-3-(phenylselanyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl)dihydrofuran-2(3*H*)-one (1027).

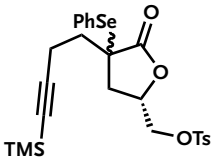


1027

Crude silyl alcohol **1023** (550 µmol) was stirred in AcOH–THF–H_2O (3:1:1, 11.0 ml) for 12 h at ambient temperature. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The residue was subjected to flash column chromatography (hexanes–EtOAc, 2:1 → 1:1) to obtain pure title compound **1027** as yellow oil (170 mg, 430 µmol, 78% over two steps). R_f = 0.44 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.63 (d, 2H), 7.48 – 7.41 (m, 1H), 7.38 – 7.32 (m, 2H), 4.57 (dddd, J = 10.2, 5.9, 4.4, 2.7 Hz, 1H), 3.92 (dd, J = 12.7, 2.7 Hz, 1H), 3.59 (dd, J = 12.7, 4.4 Hz, 1H), 2.61 – 2.39 (m, 3H), 2.18 (dd, J = 14.2, 5.9 Hz, 1H), 2.04 – 1.91 (m, 2H), 0.13 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{18}H_{25}O_3SeSi$ $[M + H]^+$ 397.0738, found 397.0735.

▸ *NMR spectra on page 511.*

((2*S*)-5-Oxo-4-(phenylselanyl)-4-(4-(trimethylsilyl)but-3-yn-1-yl)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (1028).

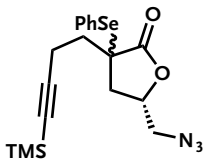


1028

Alcohol **1027** (75.0 mg, 190 µmol, 1.0 eq.) was dissolved in anhydrous pyridine (0.9 ml) and cooled to 0 °C. DMAP (2.3 mg, 19 µmol, 10 mol %) and tosyl chloride (39.0 mg, 199 µmol, 1.05 eq.) were added and the resulting mixture was stirred at 0 °C for 1 h, then additional 4 h at 40 °C (monitored by TLC). The reaction mixture was diluted with ether and quenched by the addition of 1 N HCl. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over magnesium sulfate and concentrated

in vacuo. The crude residue was directly subjected to the next step. **HRMS** (ESI): calcd. for $C_{25}H_{30}NaO_5SSeSi$ $[M + Na]^+$ 573.0646, found 573.0651.

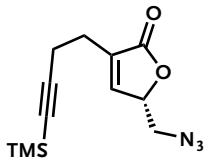
(5*S*)-5-(Azidomethyl)-3-(phenylselanyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl)dihydrofuran-2(3*H*)-one (1029).



1029

A mixture of crude tosylate **1028** (190 µmol, 1.0 eq.) and sodium azide (61.8 mg, 950 µmol, 5.0 eq.) in anhydrous DMF (0.6 ml) was heated to 70 °C for 60 min (monitored by TLC). The reaction mixture was cooled to ambient temperature and diluted with ether and water. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was directly subjected to the next step. **HRMS** (ESI): calcd. for $C_{18}H_{23}N_3NaO_2SeSi$ $[M + Na]^+$ 444.0622, found 444.0623.

(*S*)-5-(Azidomethyl)-3-(4-(trimethylsilyl)but-3-yn-1-yl)furan-2(5*H*)-one (1003).

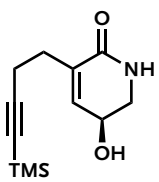


1003

Crude organoselenium species **1029** (190 µmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (1.2 ml) and cooled to 0 °C. A solution of H_2O_2 (30%, 107 µl) in H_2O (0.2 ml) was added dropwise at this temperature followed by the addition of pyridine (one drop). The reaction mixture was stirred vigorously at 0 °C for 10 min (monitored by TLC) to obtain a colorless suspension. The reaction mixture was diluted with ether and quenched by the addition of sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes–EtOAc, 5:1) to obtain pure γ-butenolide **1003** (43.0 mg, 163 µmol, 86% over three steps) as colorless oil. **^{1}H NMR** (200 MHz, C_6D_6) δ = 6.19 (d, J = 1.6 Hz, 1H), 4.12 (td, J = 5.3, 1.6 Hz, 1H), 2.65 (dd, J = 13.0, 4.7 Hz, 1H), 2.50 (dd, J = 13.0, 5.5 Hz, 1H), 2.27 (d, J = 2.0 Hz, 4H), 0.29 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{12}H_{17}N_3NaO_2Si$ $[M + Na]^+$ 286.0988, found 286.0991.

▸ *NMR spectra on page 511.*

(*S*)-5-Hydroxy-3-(4-(trimethylsilyl)but-3-yn-1-yl)-5,6-dihydropyridin-2(1*H*)-one (1002).

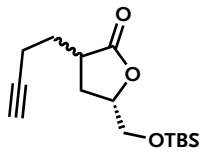


1002

Azide **1003** (22.0 mg, 83.5 µmol, 1.0 eq.) was dissolved in THF (technical, 0.4 ml), H_2O (40 µl) was added followed by the addition of triphenylphosphine (32.9 mg, 125 µmol, 1.5 eq.). The reaction mixture was stirred at ambient temperature for 2 h (monitored by TLC). Triethylamine (23 µl, 167 µmol, 2.0 eq.) was added at this temperature and stirring was continued for additional 2 h. Volatile components were evaporated *in vacuo* and by azeotropic distillation with benzene to obtain title compound **1002** as colorless oil along with trace amounts of the

imino-phosphorane adduct. The ^{1}H NMR spectrum of amide **1002** was determined from the crude mixture. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.13 (s, 1H), 4.97 (br s, 1H), 4.31 – 4.07 (m, 1H), 3.13 (dd, J = 13.9, 4.1 Hz, 1H), 2.89 (dd, J = 13.9, 5.7 Hz, 1H), 2.57 – 2.43 (m, 4H), 1.28 – 1.23 (m, 1H), 0.13 (s, 9H) ppm. **HRMS** (ESI): calcd. for $C_{12}H_{20}NO_2Si$ $[M + H]^+$ 238.1263, found 238.1267. **HRMS** (ESI): calcd. for $C_{30}H_{33}NO_2PSi$ $[M + H]^+$ 498.2018, found 498.2016 (imino-phosphorane adduct). $[\alpha]_D^{20}$ = –43.2° (c = 1.0, $CHCl_3$). ▸ NMR spectra on page 512.

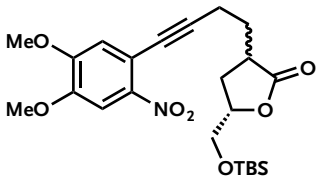
(5*S*)-3-(But-3-yn-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one (1030).



1030

Silyl protected alkyne **1022** (280 mg, 790 µmol, 1.0 eq.) was dissolved in anhydrous methanol (1.6 ml). Potassium carbonate (219 mg, 1.58 mmol, 2.0 eq.) was added at ambient temperature and stirring was continued for 90 min at this temperature (monitored by TLC). The reaction mixture was diluted with ether and sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The obtained residue was directly used in the next step without purification. R_f = 0.65 (hexanes–EtOAc, 3:1). **HRMS** (ESI): calcd. for $C_{15}H_{26}NaO_3Si$ $[M + Na]^+$ 305.1549, found 305.1548.

(5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(4-(4,5-dimethoxy-2-nitrophenyl)but-3-yn-1-yl)-dihydrofuran-2(3*H*)-one (1031).



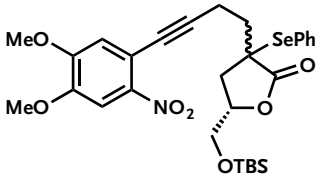
1031

Crude alkyne **1030** (790 µmol, 1.0 eq.) and aryl bromide **950** were dissolved in diethylamine (1.6 ml) and the resulting solution was degassed (ultrasonication plus argon). $Pd(PPh_3)_2Cl_2$ (11.1 mg, 16 µmol, 2 mol %) and copper(I) iodide (6.1 mg, 32 µmol, 4 mol %) were added and the reaction mixture was heated to 55 °C for 15 min (monitored by TLC). The mixture was diluted with ether and quenched by the addition of 1 N HCl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and concentration *in vacuo* provided crude title compound **1031** which was purified by flash column chromatography (hexanes–EtOAc, 4:1 → 2:1) to furnish pure **1031** (325 mg, 701 µmol, 89% over to steps) as diastereomeric mixture (diastereomeric ratio = 2:1) as yellow oil. The ^{1}H NMR spectra of both diastereomers were determined from the mixture. **^{1}H NMR** (400 MHz, C_6D_6, major diastereomer) δ = 7.34 (s, 1H), 6.77 (s, 1H), 4.02 (dq, J = 9.2, 3.3 Hz, 1H), 3.56 – 3.46 (m, 1H), 3.26 (dd, J = 11.1, 3.4 Hz, 1H), 3.13 (s, 3H), 3.05 (s, 3H), 2.96 (qd, J = 9.3, 6.5 Hz, 1H), 2.56 (dtd, J = 17.1, 6.9, 3.1 Hz, 1H), 2.39 (dt, J = 17.1, 6.9 Hz, 1H), 2.21 – 1.82 (m, 2H), 1.67 – 1.47 (m, 2H), 0.89 (s, 9H), 0.02 (d, J = 7.2 Hz, 6H) ppm. **^{1}H NMR** (400 MHz, C_6D_6, minor diastereomer) δ = 7.33 (s, 1H), 6.74 (s, 1H), 3.93 (ddt, J = 9.8, 6.6, 3.7 Hz, 1H), 3.56 – 3.46 (m, 1H), 3.35 – 3.29 (m, 1H), 3.11 (s, 3H), 3.06 (s, 3H), 2.69 (dtd, J = 11.6, 8.6, 6.0 Hz, 1H), 2.56 (dtd, J = 17.1, 6.9,

3.1 Hz, 1H), 2.39 (dt, J = 17.1, 6.9 Hz, 1H), 2.21 – 1.82 (m, 2H), 1.67 – 1.47 (m, 2H), 0.94 (s, 9H), 0.05 (d, J = 3.5 Hz, 6H) ppm. **^{13}C NMR** (101 MHz, C_6D_6, diastereomeric mixture) δ = 178.3, 177.5, 153.2, 149.2, 149.2, 143.6, 115.8, 115.7, 113.2, 107.8, 107.8, 96.0, 78.5, 78.5, 78.1, 77.5, 65.3, 64.3, 55.5, 55.4, 55.3, 39.4, 38.3, 30.3, 29.9, 29.8, 29.6, 26.1, 26.0, 18.4, 18.1, 18.1, -5.1, -5.3, -5.4, -5.5 ppm. **HRMS** (ESI): calcd. for $C_{23}H_{33}NNaO_7Si$ $[M + Na]^+$ 486.1924, found 486.1924.

▸ NMR spectra on page 513.

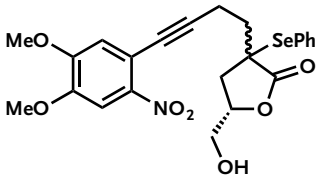
(5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(4-(4,5-dimethoxy-2-nitrophenyl)but-3-yn-1-yl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (1051).



1051

Lactone **1031** (92.5 mg, 200 µmol, 1.0 eq.) was dissolved in anhydrous THF (0.6 ml) and cooled to –78 °C. LiHMDS (1.0 M in THF, 279 µl, 279 µmol, 1.4 eq.) was added dropwise and the resulting solution was stirred 90 min at –78 °C. Chlorotrimethylsilane (46 µl, 359 µmol, 1.80 eq.) was added in one portion at –78 °C and stirring was continued at ambient temperature for 45 min. The mixture was recooled to –78 °C and a solution of phenylselenyl bromide (70.6 mg, 299 µmol, 1.50 eq.) in anhydrous THF (0.4 ml) was added dropwise. The mixture was stirred 30 min at –78 °C, then the dark orange reaction mixture was diluted with ether and water was added. The mixture was stirred vigorously at ambient temperature until the etheral layer became light yellow. Brine was added and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure to obtain crude organoselenium compound **1051** as yellow oil which was directly subjected to the next step without purification. **HRMS** (ESI): calcd. for $C_{29}H_{37}NNaO_7SeSi$ $[M + Na]^+$ 642.1402, found 642.1403.

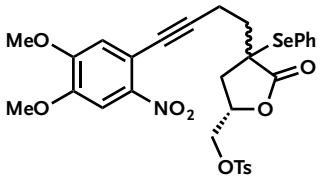
(5*S*)-3-(4-(4,5-dimethoxy-2-nitrophenyl)but-3-yn-1-yl)-5-(hydroxymethyl)-3-(phenylselanyl)-dihydrofuran-2(3*H*)-one (1032).



1032

Crude organoselenium silyl alcohol **1051** (200 µmol) was stirred in AcOH–THF–H_2O (3:1:1, 4.0 ml) for 12 h at ambient temperature. The reaction was quenched by the careful addition of sat. aq. $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was subjected to the next step without further purification. **HRMS** (ESI): calcd. for $C_{23}H_{23}NNaO_7Se$ $[M + Na]^+$ 528.0537, found 528.0541.

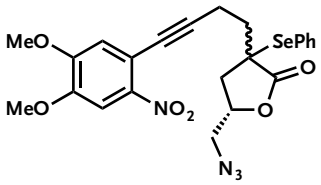
((2*S*)-4-(4-(4,5-dimethoxy-2-nitrophenyl)but-3-yn-1-yl)-5-oxo-4-(phenylselanyl)tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (1052).



1052

Crude alcohol **1032** (200 µmol) was dissolved in anhydrous pyridine (1.0 ml) and cooled to 0 °C. DMAP (2.4 mg, 20 µmol, 10 mol %) and tosyl chloride (40.1 mg, 210 µmol, 1.05 eq.) were added and the resulting mixture was stirred 12 h at ambient temperature. The reaction mixture was diluted with ether and quenched by the addition of 1 N HCl. The layers were separated and the aqueous layer was extracted once with ether. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was directly subjected to the next step without further purification. **HRMS** (ESI): calcd. for $C_{30}H_{29}NNaO_9SSe$ $[M + Na]^+$ 682.0626, found 682.0624.

(5*S*)-5-(Azidomethyl)-3-(4-(4,5-dimethoxy-2-nitrophenyl)but-3-yn-1-yl)-3-(phenylselanyl)-dihydrofuran-2(3*H*)-one (1033).

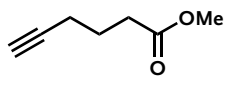


1033

A mixture of crude tosylate **1052** (200 µmol, 1.0 eq.) and sodium azide (65.0 mg, 1.00 mmol, 5.0 eq.) was heated to 70 °C for 180 min (monitored by TLC). The reaction mixture was diluted with ether and brine and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were extracted once with brine. Drying over magnesium sulfate followed by the removal of the solvent under reduced pressure furnished crude title compound **1033** which was purified by flash column chromatography (hexanes–EtOAc, 8:1) to provide pure azide **1026** (74.1 mg, 140 µmol, 70% over four steps) as diastereomeric mixture (diastereomeric ratio =2:1) as yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.86 – 7.83 (m, 1H), 7.67 – 7.55 (m, 4H), 7.39 – 7.35 (m, 1H), 6.95 (s, 1H), 5.19 (ddd, J = 5.8, 4.0, 1.9 Hz, 1H), 4.36 (dd, J = 12.0, 3.9 Hz, 1H), 4.23 (dd, J = 12.0, 5.9 Hz, 1H), 3.96 (s, 3H), 3.96 (s, 3H), 2.80 (td, J = 6.5, 2.5 Hz, 2H), 2.66 (t, J = 6.6 Hz, 2H), 2.40 – 2.26 (m, 1H), 2.26 – 2.11 (m, 1H) ppm. **HRMS** (ESI): calcd. for $C_{23}H_{23}N_4O_6Se$ $[M + H]^+$ 531.0783, found 531.0783. ▸ *NMR spectra on page 514.*

13.5 Experimental Part for Section 12.5

Methyl hex-5-ynoate (1039).

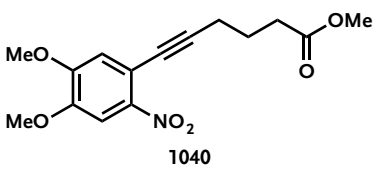


1039

Hex-5-ynoic acid (3.80 g, 33.9 mmol, 1.0 eq.) was dissolved in anhydrous *N,N*-dimethylformamide (25.0 ml). Methyl iodide (3.2 ml, 50.8 mmol, 1.5 eq.) and potassium carbonate (4.68 g, 33.9 mmol, 1.0 eq.) were added and the mixture was stirred for 12 h at ambient temperature. The mixture was diluted with ether and brine was added. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate and concentrated *in*

vacuo to provide methyl ester **1039** (3.71 g, 29.4 mmol, 87%) as colorless oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 3.64 (s, 3H), 2.43 (t, J = 7.4 Hz, 2H), 2.23 (tdd, J = 6.9, 2.6, 0.5 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.94 – 1.69 (m, 2H) ppm. **HRMS** (ESI): calcd. for $C_7H_{11}O_2$ $[M + H]^+$ 127.0759, found 127.0760. ▸ *NMR spectra on page 514.*

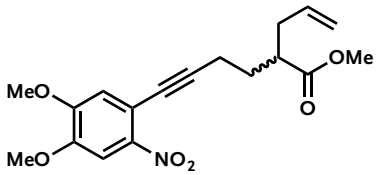
Methyl 6-(4,5-dimethoxy-2-nitrophenyl)hex-5-ynoate (1040).



1040

Aryl bromide **950** (650 mg, 2.48 mmol, 1.0 eq.) was dissolved in diethylamine (4.0 ml) and the resulting bright yellow solution was degassed (ultrasonication plus argon). $Pd(PPh_3)_2Cl_2$ (34.8 mg, 50 µmol, 2 mol %) and copper(I) iodide (19.3 mg, 99 µmol, 4 mol %) were added and the reaction mixture was heated to 45 °C. A solution of alkyne **1039** in diethylamine (1.0 ml) was added in one portion and stirring was continued at 45 °C for additional 10 min (monitored by TLC). The mixture was diluted with EtOAc and quenched by the addition of 1 N HCl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over magnesium sulfate and concentration *in vacuo* provided crude title compound **1040** which was purified by flash column chromatography (hexanes–EtOAc, 4:1) to furnish pure **1040** (600 mg, 1.95 mmol, 79%, 92% brsm) as dark orange oil. R_f = 0.48 (hexanes–EtOAc, 3:1, stains bright orange with vanillin). **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.31 (s, 1H), 6.67 (s, 1H), 3.32 (s, 3H), 3.07 (d, J = 5.0 Hz, 6H), 2.41 (t, J = 7.3 Hz, 2H), 2.34 (t, J = 6.9 Hz, 2H), 1.83 (p, J = 7.1 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 173.0, 153.1, 149.0, 128.6, 115.7, 113.2, 107.9, 96.4, 78.3, 55.4, 55.4, 51.1, 32.7, 24.0, 19.4 ppm. **HRMS** (ESI): calcd. for $C_{15}H_{17}NNaO_6$ $[M + Na]^+$ 330.0954, found 330.0951. ▸ *NMR spectra on page 515.*

Methyl 2-allyl-6-(4,5-dimethoxy-2-nitrophenyl)hex-5-ynoate (1041).



1041

A solution of ^{n}BuLi (2.5 M in hexanes, 183 µl, 457 µmol) was added to a solution of diisopropylamine (70 µl, 496 µmol, 1.25 eq.) in anhydrous THF (0.6 ml) at –78 °C and was stirred 60 min at this temperature. A solution of ester **1040** (122 mg, 397 µmol, 1.0 eq.) in anhydrous THF (1.2 ml) was added dropwise at –78 °C and the resulting solution was stirred 30 min at this temperature. Allyl bromide (52 µl, 596 µmol, 1.50 eq.) was added dropwise and the stirring was continued at –78 °C for 2 h. The reaction was then diluted with ether and quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (hexanes–EtOAc, 3:1) to furnish title compound **1041** (88.2 mg, 254 µmol, 64%) as colorless oil. R_f = 0.31 (hexanes–EtOAc, 3:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.60 (s, 1H), 6.94 (s, 1H), 5.76

(ddt, J = 17.1, 10.2, 7.1 Hz, 1H), 5.16 – 4.97 (m, 2H), 3.96 – 3.91 (m, 6H), 3.67 (s, 3H), 2.75 (q, J = 7.0 Hz, 1H), 2.52 (q, J = 7.4 Hz, 2H), 2.41 (dt, J = 14.8, 7.3 Hz, 1H), 2.32 (dt, J = 14.0, 6.8 Hz, 1H), 1.99 (dq, J = 14.6, 7.0 Hz, 1H), 1.83 (dq, J = 13.3, 6.9 Hz, 1H) ppm. **HRMS** (ESI): calcd. for $C_{18}H_{22}NO_6$ $[M + H]^+$ 348.1447, found 348.1448.

▸ NMR spectra on page 516.

Part IV

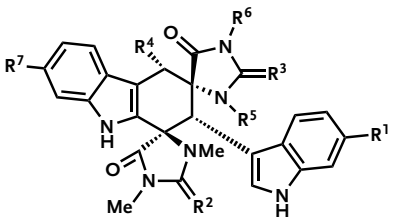
Minor Projects

Cycloaplysinopsin A

14

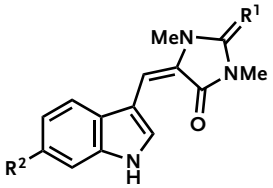
14.1 Marine Dimeric Bisindole Alkaloids

The bisindoles tubastrindoles A–C (**1053–1055**) with an hitherto unprecedented skeleton were isolated from the Japanese *Tubastraea* sp. stony coral collected in the Odomari area, Kagoshima Prefecture (Fig. 14-1).[621] The skeleton possesses a tetrahydrocarbazole core which is functionalized with two modified hydantoin (also known as glycolylurea) moieties and a second indole moiety. After further investigation of *Tubastraea* sp. the authors reported five new tubastrindoles D–H (**1056–1060**).[622] The authors primarily assumed that compounds **1053–1055** are biogenet-



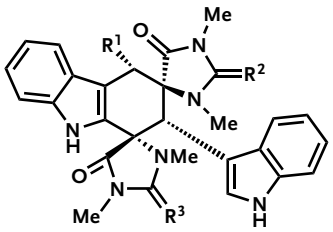
1053	R^1 = Br, R^2 = R^3 = NH, R^4 = R^7 = H, R^5 = R^6 = Me	tubastrindole A
1054	R^1 = R^4 = R^7 = H, R^2 = R^3 = NH, R^5 = R^6 = Me	tubastrindole B
1055	R^1 = R^4 = R^7 = H, R^2 = O, R^3 = NH, R^5 = R^6 = Me	tubastrindole C
1056	R^1 = Br, R^2 = O, R^3 = NH, R^4 = R^7 = H, R^5 = R^6 = Me	tubastrindole D
1057	R^1 = R^7 = H, R^2 = O, R^3 = NH, R^4 = OH, R^5 = R^6 = Me	tubastrindole E
1058	R^1 = Br, R^2 = NH, R^3 = O, R^4 = R^7 = H, R^5 = R^6 = Me	tubastrindole F
1059	R^1 = R^4 = R^7 = H, R^2 = NH, R^3 = O, R^5 = R^6 = Me	tubastrindole G
1060	R^1 = R^4 = R^7 = H, R^2 = R^3 = O, R^5 = R^6 = Me	tubastrindole H
1061	R^1 = R^7 = Br, R^2 = R^3 = NH, R^4 = H, R^5 = R^6 = Me	dictazoline A
1062	R^1 = R^7 = Br, R^2 = R^3 = NH, R^4 = R^5 = R^6 = H	dictazoline B
1063	R^1 = R^4 = R^5 = R^6 = H, R^2 = R^3 = NH, R^7 = Br	dictazoline C
1064	R^1 = R^4 = R^5 = H, R^2 = R^3 = NH, R^6 = Me, R^7 = Br	dictazoline D
1065	R^1 = R^4 = R^5 = R^7 = H, R^2 = R^3 = NH, R^6 = Me	dictazoline E

Figure 14-1. Aplysinopsin dimers tubastrindoles A–H (**1053–1060**) and dictazolines A–E (**1061–1065**).



1066	R^1 = NH, R^2 = H	aplysinopsin
1067	R^1 = O, R^2 = H	3'-deimino-3'-oxaplysinopsin
1068	R^1 = O, R^2 = Br	6-bromo-3'-oxoaplysinopsin

Figure 14-2. Aplysinopsin monomers **1066–1068**.



1069 $R^1 = H$, $R^2 = R^3 = O$ cycloaplysinopsin A
1070 $R^1 = OH$, $R^2 = R^3 = O$ cycloaplysinopsin B
1071 $R^1H = O$, $R^2 = R^3 = NH$ cycloaplysinopsin C

Figure 14-3. Aplysinopsin dimers **1069**–**1071**.

ically formed from an enzymatic Diels–Alder cycloadditon of two molecules of aplysinopsin (**1066**, Fig. 14-2), a natural product which also has been isolated from the same stony coral. However, all tubastrindoles have a very low optical purity; the absolute values of their optical rotations ranging from 1.4 to 14. This suggested that the dimers might be either artifacts formed during isolation or a naturally occurring mixture of enantiomers in almost equal ratios.

Shortly after the report of tubastrindoles A–C (**1053**–**1055**), Mancini and co-workers published two additional quasi-racemic bisindoles cycloaplysinopsin A (**1069**) and cycloaplysinopsin B (**1070**, Fig. 14-3), isolated from tropical Indo-Pacific (Comoros, Philippines) scleractinian corals of the family Dendrophylliidae.[623] HR-EI-MS data showed an intense retro-Diels–Alder fragmentation signal, corresponding to the molecular ion of 3'-deimino-3'-oxaplysinopsin (**1067**, Fig. 14-2). This led again to the proposition, **1069** is derived from the Diels–Alder reaction between two molecules of *(E)*-3'-deimino-3'-oxaplysinopsin (**1067**), followed by a double bond shift to establish the fused indole unit. However, attempts to form **1069** from synthetic *(E)*-**1067** under non-enzymatic conditions were not successful. Therefore, the authors concluded that a 'Diels–Alderase' enzyme an adventitious Diels–Alder catalyst present in the coral extracts triggers the dimerization. 'Diels–Alderase' enzymes are discussed controversially about whether nature uses the famous reaction to produce its own useful molecules. Some candidate natural 'Diels–Alderases' have been identified, but these have either been shown not to perform the reaction, or the evidence that they catalyze a Diels–Alder reaction is ambiguous. Quite recently Race and co-workers may have found the first *real* 'Diels–Alderase' enzyme in a bacterium called *Verrucosispora mari* originated from the Pacific seabed.[624]

Cycloaplysinopsin C (**1071**), a third aplysinopsin dimer, has been isolated from *Tubastraea* sp. collected from the archipelago of the Hanish Islands in Yemen together with the known alkaloids aplysinopsin (**1066**) and 6-bromo-3'oxo-aplysinopsin (**1068**) by Meyer and co-workers.[625]

The study of the secondary metabolites produced by the marine sponge *Smenospongia cerebriformis* has led to the isolation of two new bisindoles, dictazolines A (**1061**) and B (**1062**, Fig. 14-1).[626] Once again, the HR-EI-MS data of **1061** showed an intense signal corresponding to a retro-Diels–Alder aplysinopsin unit similar to the results of Mancini *et al.*[623]

In early 2010, the proposed biosynthetic origins of the aplysinopsin dimers took another twist. Further investigation of the extract of *Smenospongia cerebriformis* yielded three more bisindoles dictazolines C–E (**1063**–**1065**), along with the structurally unique cyclobutyl-containing bisin-

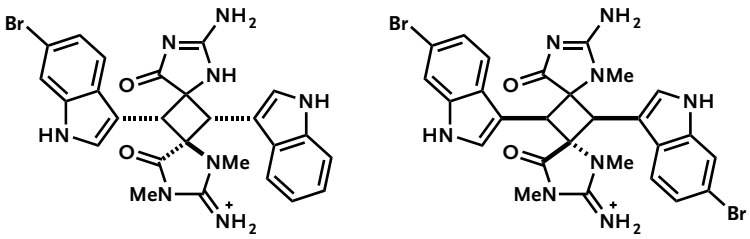
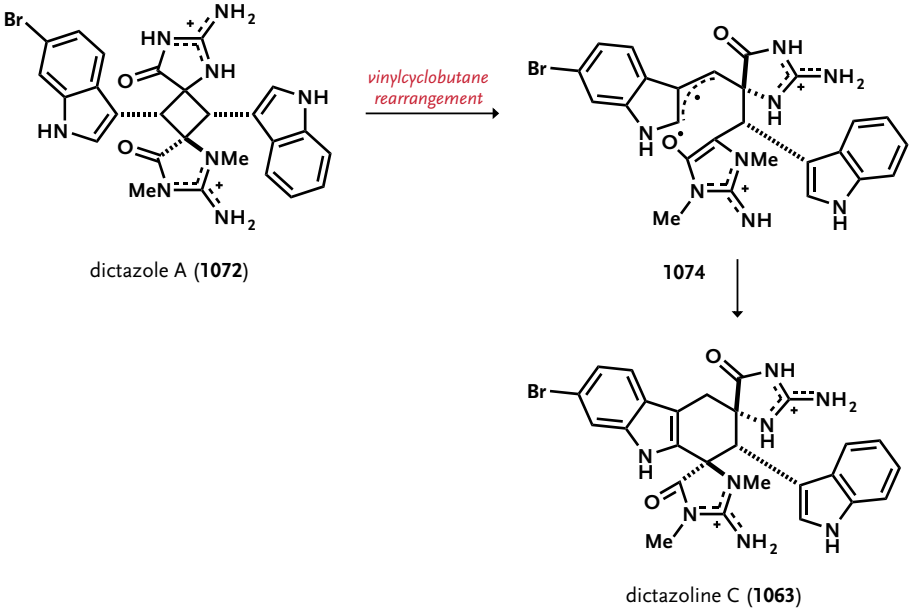


Figure 14-4. Dictazoles A (**1072**) and B (**1073**).

doles dictazoles A and B, **1072** and **1073**, respectively.[627] Using Baran's pioneering biomimetic total synthesis of ageliferin from the cyclobutane sceptrin as a guide,[628] Williams *et al.* suggested that the dictazoles are possible precursors to the corresponding dictazolines.[629] Specifically, it is assumed that dictazole A (**1072**) can be converted to dictazoline C (**1063**) *via* the vinylcyclobutane rearrangement,[630] as outlined in Scheme 14-1. Based on the work of Baran *et al.*, pure dictazole A (**1072**) was exposed to microwave irradiation at 200 °C in water for 1 min. A significant amount of dictazoline C (**1063**) was detected by LC-MS along with three monomeric aplysinopsins, which presumably arose from a retro-Diels–Alder reaction of **1072**. Due to the limited isolated amount of **1072**, the yield of this transformation has not been optimized, and the products have not been characterized by NMR.

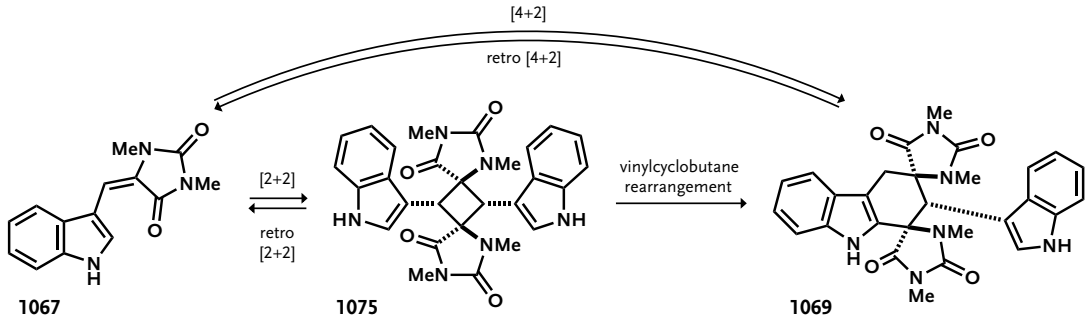


Scheme 14-1. Proposed biosynthesis of dictazoline C (**1063**) *via* vinylcyclobutane rearrangement of dictazole A (**1072**).

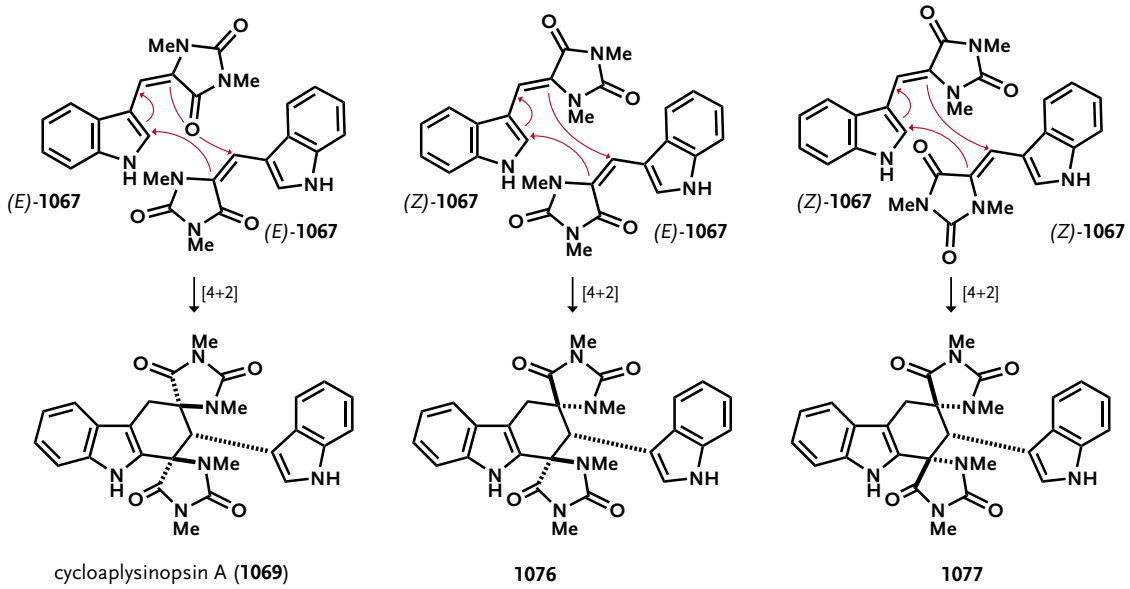
14.2 Investigations on the Synthesis of Cycloaplysinopsin A

Although the conclusions of Williams and co-workers are quite remarkable, they have led to even more unanswered questions. No work has been done for the conversion of the monomeric aplysinopsins to the corresponding cyclobutane dimer in a [2+2]-process. In addition, it is still unclear if the proposed vinylcyclobutane rearrangement to the cyclohexenyl dimer renders the Diels–Alder proposal obsolete, or if there is a biosynthetic cycle which includes more than one defined pathway (Scheme 14-2).

This work focuses on the attempts to the synthesis of cycloaplysinopsin A (**1069**) since it is one of the most simple aplysinopsin dimers: the indole core is not halogenated and it possesses two identical spiro-1,3-dimethylhydantoin moieties. The handling of hydantoin derivatives is more facilely than their diimino derivatives which possess a guanidine moiety. Careful consideration leads to the result that in the case of a potential Diels–Alder pathway as well as in the case of a



Scheme 14-2. Possible biosynthetic cycle of cycloaplysinopsin A (**1069**).

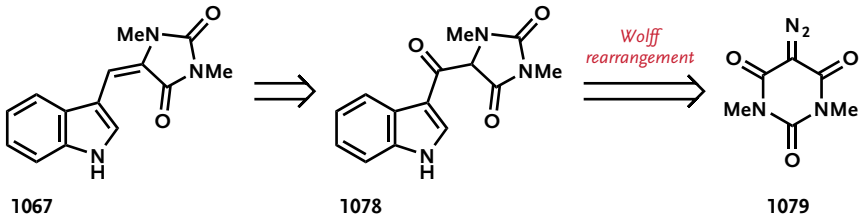


Scheme 14-3. The three different potential Diels–Alder products depending on the double bond geometry of the monomer. Only two *(E)*-configured double bonds will lead to cycloaplysinopsin A (**1069**).

potential [2+2]-pathway the product should derive from the same two identical *(E)*-configured aplysinopsin monomers (Schemes 14-2 and 14-3). In this case the aplysinopsin derivative is the known isolated alkaloid 3'-deimino-3'-oxaplysinopsin (**1067**, Fig. 14-2).

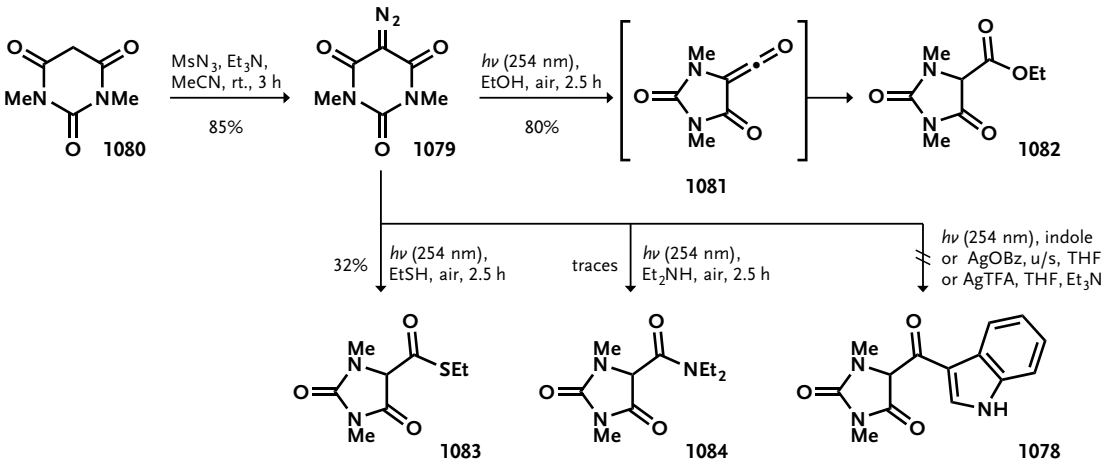
14.2.1 Synthetic Work

The crucial compound which is required for an examination of both compelling biosynthetic pathways (Scheme 14-2) through chemical synthesis is 3'-deimino-3'-oxaplysinopsin (**1067**). In the first retrosynthetic approach **1067** derives from 3-acylindole **1078** *via* reduction–elimination sequence. The formation of the 3-acylindole **1078** should be achieved *via* photochemically induced Wolff rearrangement of 5-diazo-1,3-dimethylbarbituric acid (**1079**).

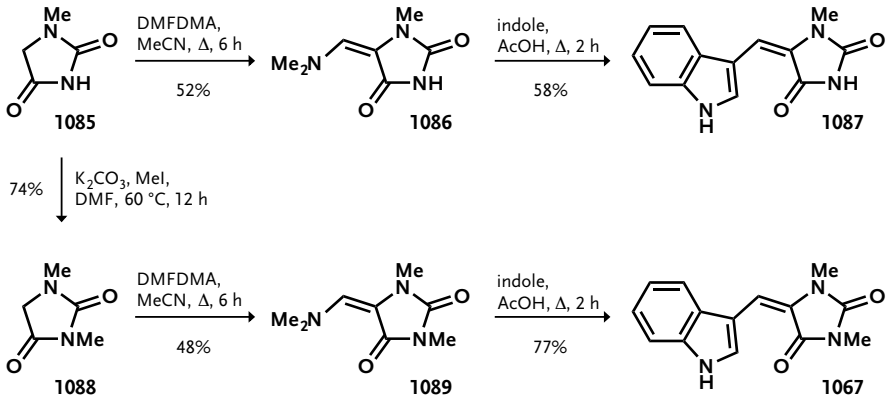


Scheme 14-4. First retrosynthetic approach towards the synthesis of **1067**.

Cyclic diazo compound **1079** was readily prepared by the diazotransfer reaction of *N,N*-dimethylbarbituric acid (**1080**) with methanesulfonyl azide in acetonitrile in 85% yield (Scheme 14-5).[631] Irradiation of **1079** in ethanol at λ = 366 nm did not induce a Wolff rearrangement and only starting material was recovered. However, irradiation of **1079** in ethanol at λ = 254 nm for 2.5 h under aerobic conditions yielded hydantoin **1082** *via* ketene **1081** in 80% yield.[632] But the repetition of this sequence with ethyl mercaptan instead of ethanol reduced the yield of hydantoin **1083** drastically and the use of diethylamine furnished hydantoin **1084** only in traces. Finally, the use of indole as a nucleophile was not successful at all; neither an irradiation at λ = 254 nm in aprotic solvents (acetonitrile, diethyl ether, dioxane) nor the use of metal catalysis



Scheme 14-5. Towards the synthesis of 3-acylindole **1078**.

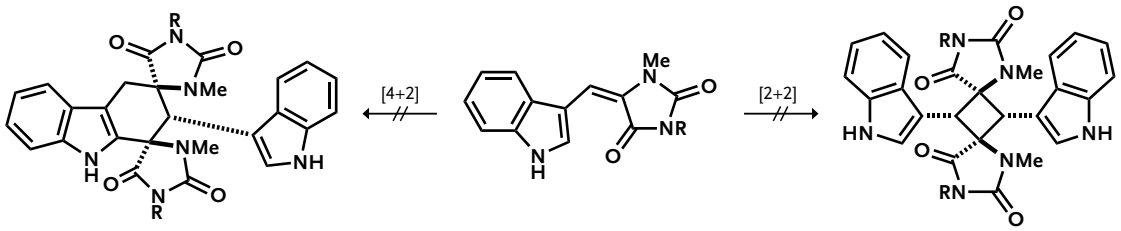


Scheme 14-6. Synthesis of aplysinopsin derivative **1087** and 3'-deimino-3'-oxaplysinopsin (**1067**).

(silver benzoate and/or silver trifluoroacetate, with ultrasonic or in the presence of a weak base) furnished 3-acylindole **1078**. Since the route *via* the Wolff rearrangement was not prosperous, a different strategy for the synthesis of aplysinopsin derivative **1067** was taken into account.

The new approach allows a quick access to aplysinopsin derivatives like **1087** or the known aplysinopsin monomer 3'-deimino-3'-oxaplysinopsin (**1067**). For this, 1-methylhydantoin (**1085**) was transformed with *N,N*-dimethylformamide dimethyl acetal into *(E)*-5-((dimethylamino)methylene)-1-methylhydantoin (**1086**) in 52% yield (Scheme 14-6). This compound was then coupled with indole under acidic conditions to furnish aplysinopsin derivative **1087** in 58% yield. In addition, 1-methylhydantoin (**1085**) was transformed to 1,3-dimethylhydantoin (**1088**) with iodomethane in the presence of K_2CO_3 in DMF at 60 °C for 12 h.[633] Repetition of the reaction sequence using *N,N*-dimethylformamide dimethyl acetal followed by indole led to 3'-deimino-3'-oxaplysinopsin (**1067**) in 27% overall yield. No attempts to optimize the overall yields of this sequence were made. Both **1087** and **1067** are characteristically bright yellow solids.

With aplysinopsin derivatives **1087** and **1067** in hand, several experiments concerning the [4+2]-products **1090** and **1069**, respectively, or the [2+2]-products **1091** and **1075**, respectively, have been conducted (Tab. 14-1). In no case a [4+2]-product was obtained, not even in slight amounts. No Diels–Alder product has been observed neither in refluxing toluene nor in refluxing



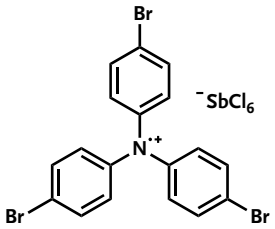
Scheme 14-7. There were no successful attempts concerning the conversion of aplysinopsin derivatives **1087** and **1067** into the [4+2]-products **1090** and **1069**, respectively, or the [2+2]-products **1091** and **1075**, respectively.

Table 14-1. Conditions for the conversion of **1087** and **1067** into the [4+2]-products **1090** and **1069**, respectively, or the [2+2]-products **1091** and **1075**, respectively.

#	Compound	Type	Conditions	Result
1	**1087**, **1067**	[4+2]	PhMe, 115 °C, 6 h	—
2	**1087**, **1067**	[4+2]	bromobenzene, 160 °C, 6 h	—
3	**1087**, **1067**	[4+2]	DMSO, 190 °C, 12 h	—
4	**1087**, **1067**	[4+2]	BnOH, 210 °C, 6 h	—
5	**1087**, **1067**	[4+2]	diethylene glycol, 250 °C, 10 h	—
6	**1087**, **1067**	[2+2]	*hν* (366 nm), PhH, 4 h	—
7	**1087**, **1067**	[2+2]	*hν* (254 nm), PhH, 4 h	—
8	**1087**, **1067**	[2+2]	*hν* (254 nm), acetone, 4 h	—
9	**1087**, **1067**	[2+2]	Ledwith–Weitz salt (10 mol-%), CH_2Cl_2, 0 °C	**1087**: decomp., **1067**: —
10	**1087**, **1067**	[2+2]	Ledwith–Weitz salt (10 mol-%), DMSO, 0 °C	**1087**: decomp., **1067**: —

bromobenzene nor in refluxing DMSO nor in refluxing benzyl alcohol. Even after treatment of compound **1087** for 10 h in refluxing diethylene glycol (250°C !) quantitative amounts of starting material have been recovered. The [4+2] experiments merely proved the high stability of these compounds.

For the construction of [2+2]-products **1091** and **1075** the aplysinopsin derivatives **1087** and **1067** were irradiated at different wavelengths (366 nm, 254 nm) and in different solvents (benzene, acetone). However, no formation of any [2+2]-product could be observed under these conditions and starting materials were completely recovered in all cases.

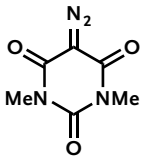


Ledwith–Weitz salt (**1092**)

Final attempts for the formation of the cyclobutane included radical-cation cycloadditions using the Ledwith–Weitz salt (**1092**).[634] Stable cation radical salts were first isolated in 1879 (*Wurster's Red* and *Blue*).[635] However, it took some decades to descry the true nature of these salts as monomeric species possessing both an unpaired electron and a single unit of positive charge.[636] These reagents are often used for radical-cation cyclodimerizations of electron-rich dienes and radical-cation Diels–Alder reactions of these dienes with electron-rich olefins.[637] A reactivity umpolung of the electron-rich diene *via* cation radical formation provides an effective and direct remedy for the absence of electron deficiency in these dienic systems. Despite the beneficial characteristics of these cation radical salts, the application in total synthesis is very rare. A recent use was in the total syntheses of kingianins A and D by the group of M. S. Sherburn.[638] Reaction of aplysinopsin derivative **1087** with **1092** (10 mol-%) at 0 °C led to decomposition both in CH_2Cl_2 and DMSO. Repetition with 3'-deimino-3'-oxaplysinopsin (**1067**) was also not successful; no reaction took place and the starting material was completely recovered. No further attempts were made to achieve the dimer formation of aplysinopsin derivatives.

14.3 Experimental

5-Diazo-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1079).

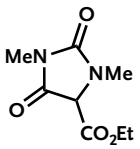


1079

1,3-dimethylbarbituric acid (1.64 g, 10.5 mmol, 1.0 eq.) was added to a flame-dried Schlenk tube. The reaction vessel was evacuated and flushed with argon. MeCN (21.0 ml) was added and after complete dissolution of the starting material MsN_3 (1.0 ml, 11.6 mmol, 1.1 eq.) was added dropwise followed by Et_3N (2.9 ml, 21.0 mmol, 2.0 eq.) and stirring was continued under Argon atmosphere for 3 h at ambient temperature (monitored by TLC). The mixture was diluted with 10% aq. NaOH and extracted thrice with CH_2Cl_2 (100 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield crude diazo compound **1079**. After recrystallization from benzene diazo compound **1079** was obtained as yellow solid (1.62 g, 8.90 mmol, 85% yield). R_f = 0.60 (hexanes–EtOAc, 1.5:1, UV active). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.28 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.2, 150.5, 71.7, 28.6 ppm. **HRMS** (ESI): calcd. for $C_6H_7N_4O_3$ $[M + H]^+$ 183.0518, found 183.0519. ▸ *NMR spectra on page 516.*

Notes: (i) Caution! Although I have never had any trouble with mesyl azide, it is potentially explosive! (ii) This reaction can also be done using p-*ABSA instead of* MsN_3 *yielding the same product over night with slightly diminished yield (64%).*

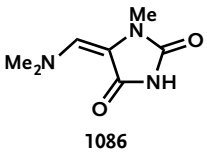
Ethyl 1,3-dimethyl-2,5-dioxoimidazolidine-4-carboxylate (1082).



1082

A flame dried quartz vessel was charged with a solution of diazo compound **1079** (14.3 mg, 78.5 µmol) in dry EtOH (40 ml). The vessel was flushed with air and then suspended horizontally under a UV lamp (Benda, 2×8 W, 254 nm). The mixture was irradiated for 150 min at room temperature and turned pale yellow in the course of time. TLC analysis showed complete consumption of starting material. The solvent was removed *in vacuo* to yield dioxoimidazolidine **1082** as a pale yellow oil (15.4 mg, 76.9 µmol, 98% yield) which was analytically pure according to NMR. R_f = 0.44 (hexanes–EtOAc, 1.5:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.53 (s, 1H), 4.37 – 4.26 (m, 2H), 3.03 (s, 3H), 3.00 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_8H_{13}N_2O_4$ $[M + H]^+$ 201.0875, found 201.0871. ▸ *NMR spectra on page 517.*

(*E*)-5-((Dimethylamino)methylene)-1-methylimidazolidine-2,4-dione (1086).



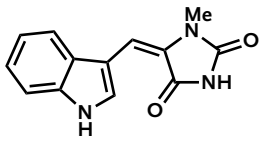
1086

A mixture of 1-methylhydantoin (5.0 g, 43.8 mmol, 1.0 eq.), *N,N*-dimethylformamide dimethyl acetal (97%, 8.61 g, 9.6 ml, 70.1 mmol, 1.6 eq.), and dry acetonitrile (145 ml) was heated under reflux for 6.0 h. The mixture was cooled down to ambient temperature and volatile components were evaporated *in vacuo* to obtain a yellow oil which was triturated with chloroform–hexanes (1:1, 145 ml). The precipitate was collected by filtration and washed with

chloroform–hexanes (1:1). Final drying under high vacuum yielded title compound **1086** as white solid (3.86 g, 22.8 mmol, 52% yield). R_f = 0.21 (hexanes–EtOAc, 1.5:1). **^{1}H NMR** (200 MHz, DMSO – d_6) δ = 10.34 (br s, 1H), 6.47 (s, 1H), 3.15 (s, 6H), 2.90 (s, 3H) ppm. **IR** (neat): 3150, 3008, 2802, 2720, 1687, 1485 cm^{-1}. **HRMS** (ESI): calcd. for $C_7H_{12}N_3O_2$ $[M + H]^+$ 170.0930, found 170.0933.

▸ NMR spectra on page 518.

(*E*)-5-((1*H*-Indol-3-yl)methylene)-1-methylimidazolidine-2,4-dione (1087).

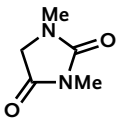


1087

Hydantoin **1086** (880 mg, 5.20 mmol, 1.0 eq.) and indole (609 mg, 5.20 mmol, 1.0 eq.) were dissolved in acetic acid (70 ml) and heated under reflux for 2.0 h. The mixture was cooled down to ambient temperature and volatile components were evaporated *in vacuo*. The residue was triturated with ethanol and the precipitate was collected by filtration. Final drying under high vacuum yielded aplysinopsin derivative **1087** as yellow solid (727.6 mg, 3.01 mmol, 58% yield). R_f = 0.43 (hexanes–EtOAc, 1:1, stains dark blue with Ehrlich's reagent). **^{1}H NMR** (400 MHz, DMSO) δ = 11.61 (s, 1H), 11.19 (s, 1H), 8.79 (d, J = 2.7 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.16 (dtd, J = 18.1, 7.1, 1.1 Hz, 2H), 6.68 (s, 1H), 3.19 (s, 3H) ppm. **^{13}C NMR** (101 MHz, DMSO – d_6) δ = 163.8, 153.4, 136.1, 129.0, 128.1, 126.1, 122.5, 120.3, 118.6, 112.4, 109.0, 107.9, 26.3 ppm. **IR** (neat): 3340, 3145, 3027, 2735, 1738, 1699, 1625, 1510 cm^{-1}. **HRMS** (ESI): calcd. for $C_{13}H_{12}N_3O_2$ $[M + H]^+$ 242.0930, found 242.0928.

▸ NMR spectra on page 519.

1,3-Dimethylimidazolidine-2,4-dione (1088).

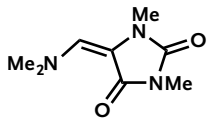


1088

To a suspension of 1-methylhydantoin (1.14 g, 10 mmol, 1.0 eq.) and K_2CO_3 (4.15 g, 30 mmol, 3.0 eq.) in abs. DMF (35 ml) was added MeI (1.9 ml, 30 mmol, 3.0 eq.) and the resulting mixture was stirred at 60 °C for 14 h. The reaction was quenched by the addition of 0.5 N HCl (400 ml) and extracted thrice with EtOAc (100 ml). The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexanes–EtOAc, 1:1) furnished 1,3-dimethylimidazolidine-2,4-dione (**1088**) as yellow oil (948 mg, 7.4 mmol, 74% yield). R_f = 0.30 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.79 (s, 2H), 2.92 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_5H_8N_2NaO_2$ $[M + Na]^+$ 151.0483, found 151.0482.

▸ NMR spectra on page 520.

(*E*)-5-((Dimethylamino)methylene)-1,3-dimethylimidazolidine-2,4-dione (1089).

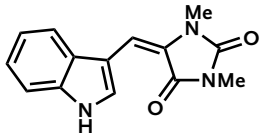


1089

1,3-Dimethylhydantoin (**1088**, 300 mg, 2.34 mmol, 1.0 eq.) was dissolved in absolute MeCN (8.0 ml), *N,N*-dimethylformamide dimethyl acetal (0.5 ml, 3.75 mmol, 1.6 eq.) was added and the resulting mixture was heated under reflux for 6.0 h and then additional 12.0 h at 80 °C. The mixture was cooled down to ambient temperature and volatile components were evaporated

in vacuo to obtain a yellow oil (208 mg, 1.14 mmol, 48% crude yield) which was used without purification in the next step. R_f = 0.61 (hexanes–EtOAc, 1:1).

(*E*)-5-((1*H*-Indol-3-yl)methylene)-1,3-dimethylimidazolidine-2,4-dione (1067).



1067

Crude hydantoin **1089** (208 mg, 1.14 mmol, 1.0 eq.) was dissolved in glacial acetic acid (16.0 ml) and indole (134 mg, 1.14 mmol, 1.0 eq.) was added in one portion. The resulting mixture was heated under reflux for 2.0 h. The mixture was cooled down to ambient temperature and volatile components were evaporated *in vacuo*. The residue was triturated with ethanol and the precipitate was collected by filtration. Final drying under high vacuum yielded 3'-deimino-3'-oxaplysinopsin (**1067**, 224 mg, 877 µmol, 77% yield) as a characteristic bright yellow solid. R_f = 0.59 (hexanes–EtOAc, 1:1, stains dark blue with Ehrlich's reagent). **^{1}H NMR** (400 MHz, DMSO) δ = 11.67 (s, 1H), 8.84 (d, J = 2.8 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.23 – 7.09 (m, 2H), 6.76 (s, 1H), 3.23 (s, 3H), 2.99 (s, 3H) ppm. **^{13}C NMR** (101 MHz, DMSO – d_6) δ = 161.9, 152.8, 135.6, 128.6, 127.7, 124.4, 122.1, 119.9, 118.2, 111.9, 108.5, 108.2, 26.2, 24.3 ppm. **HRMS** (ESI): calcd. for $C_{14}H_{13}N_3NaO_2$ $[M + Na]^+$ 278.0905, found 278.0907.

▸ *NMR spectra on page 520.*

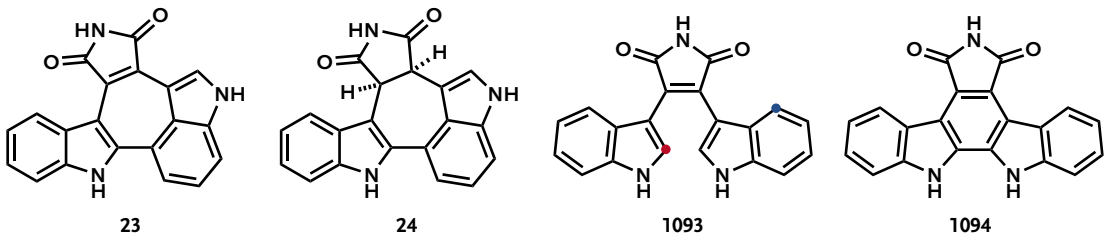
Dihydroarcyriacyanin A

15

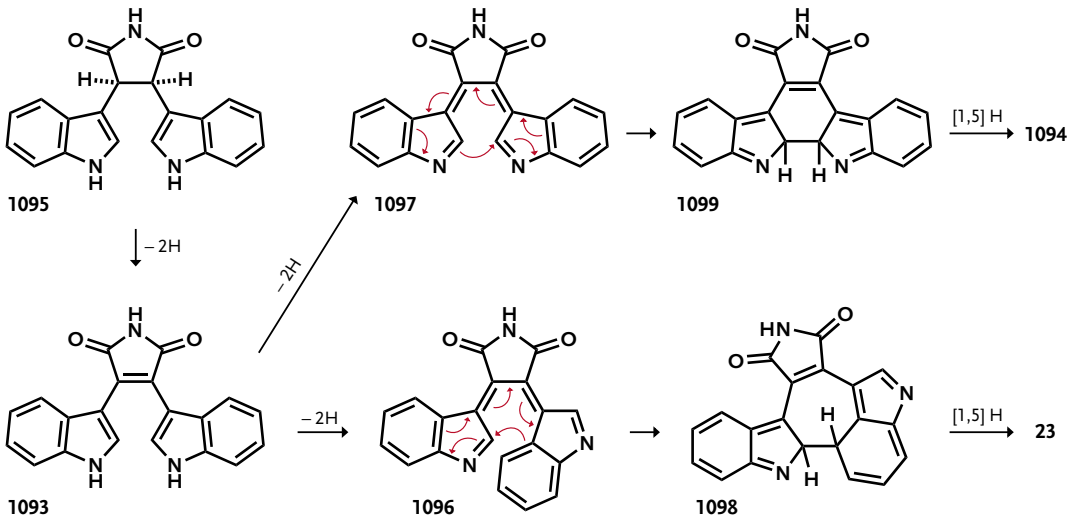
15.1 Bisindolylmaleimide Alkaloids

Arcyriacyanin A (**23**) is a bisindolylmaleimide alkaloid from *Arcyria nutans*.[42] It is a cytotoxic compound and inhibits protein kinase C and protein tyrosine kinase.[38,39] The green-blue bisindolylmaleimide is both a cyclohepta[*b*]indole and a cyclohepta[*cd*]indole and its structure can be formally derived from arcyriarubin A (**1093**) by connecting the two indoles at C-2 • and C-4' • (Scheme 15-1). It is isomeric to arcyriaflavin A (**1094**). The possible biosynthetic relationships of the *Arcyria* compounds are pretty apparent: it can be assumed that arcyriarubin A (**1093**) may be oxidatively cyclized either to arcyriaflavin A (**1094**) or to arcyriacyanin A (**23**), depending on the conformation of the starting compound (Scheme 15-2). The precursor of all *Arcyria* compounds is dihydroarcyriarubin A (**1095**) which is initially formed from two molecules of tryptophan. Double dehydrogenation would lead to either the intermediate **1096** or intermediate **1097** *via* arcyriarubin A (**1093**) and subsequently *via* electrocyclic ring closure followed by sigmatropic 1,5-hydrogen shifts to either the arcyriaflavins or the arcyriacyanin pigments **23** and **1094**.

The *cis*-dihydro modification dihydroarcyriacyanin A (**24**) has been found in the yellow sporangia of *Arcyria nutans*[42] and recently in the fruiting bodies of *Arcyria denudate* and *Arcyria*



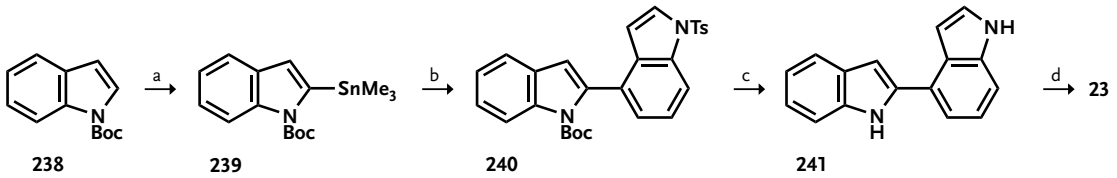
Scheme 15-1. u bisindolylmaleimide alkaloids: arcyriacyanin A (**23**), dihydroarcyriacyanin A (**24**), arcyriarubin A (**1093**), and arcyriaflavin A (**1094**).



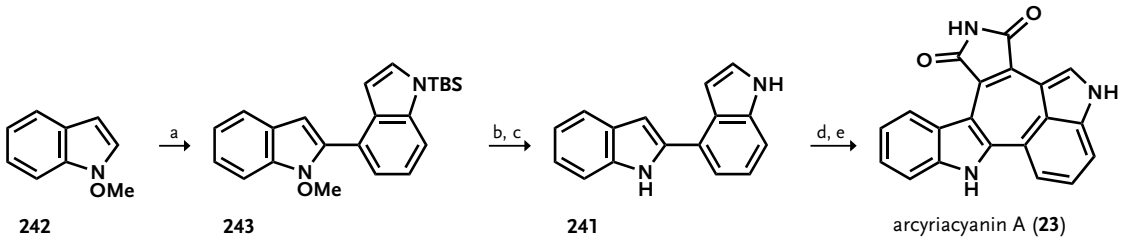
Scheme 15-2. Biosynthesis of the *Arcyria* compounds.

obvelata collected at Kōchi Prefecture, Japan.[43] It exhibits cytotoxic activity against Jurkat cells with an IC_{50} value of 7.0 µg/ml.

Arcyriacyanin A (**23**) has been synthesized twice in the late 1990s by the groups of Steglich and Tobinaga, respectively.[40,41] Both strategies rely on palladium catalyzed cross-coupling reactions. In the synthesis of the Steglich group, *N*-Boc-indole is stannylated at C2 to yield **239** (Scheme 15-3). 2,4'-Bisindole **241** is obtained *via* Stille coupling of the generated stannylindole **239** with *N*-tosyl-4-bromoindole followed by removal of the *N*-protecting groups. Finally, 3,4-



Scheme 15-3. Synthesis of arcyriacyanin A (Steglich, 1997). Reagents and conditions: **a)** LDA, THF, –78 °C, 2 h, then Me_3SnCl, –78 °C → rt, 76%. **b)** *N*-tosyl-4-bromoindole, PhMe, 80 °C, $Pd(PPh_3)_4$, 20 h, 75% **c)** EtOH, 80 °C, 20% NaOH, 3 h, 68%. **d)** EtMgBr (2.0 eq.), THF, rt., then PhMe, 110 °C, 3,4-dibromomaleimide, 2 h, 41%.

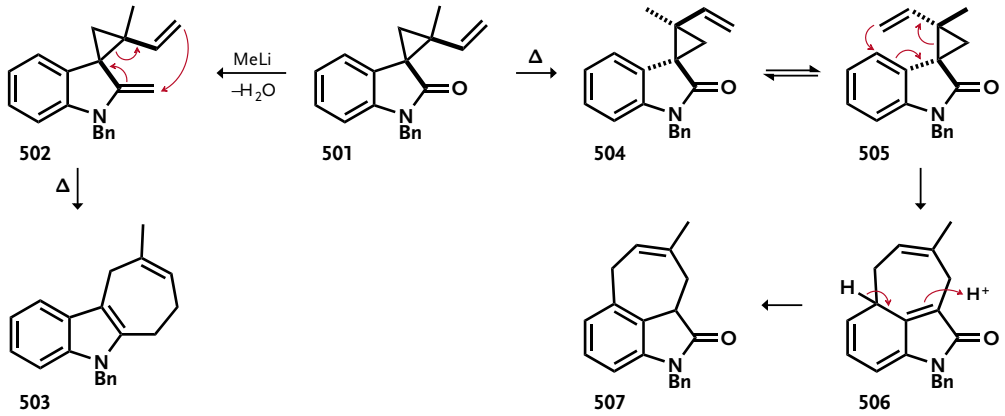


Scheme 15-4. Synthesis of arcyriacyanin A (Tobinaga, 1998). Reagents and conditions: **a)** ^{n}BuLi, THF, –20 °C, 15 min, then Et_3B, –20 °C, 30 min, then $PdCl_2(PPh_3)_2$ (5 mol %), *N*-(*tert*-butyldimethylsilyl)-4-iodoindole, Δ, 4 h, 46%. **b)** TBAF, THF, 2 h, rt., 51%. **c)** Pd/C, MeOH, H_2 (1 atm), 2 h, 83%. **d)** MeMgBr, PhH, rt., 30 min, *N*-(*tert*-butyldimethylsilyl)-3,4-dibromomaleimide, Δ, 6 h, 16%. **e)** TBAF, THF, rt., 2 h, quant.

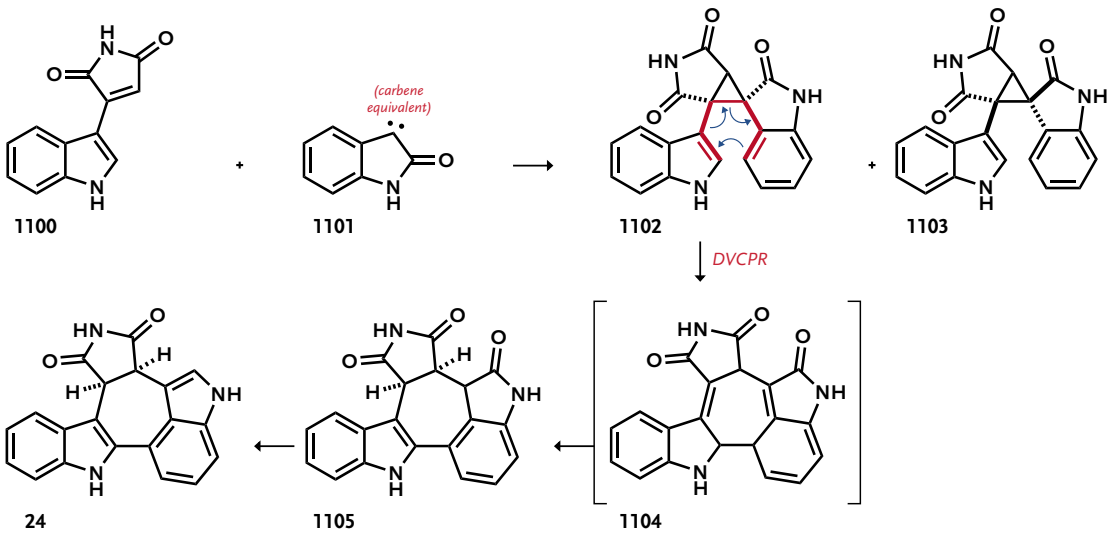
dibromomaleimide reacts with the bisbromomagnesium salt of **241** under refluxing conditions to furnish arcyriacyanin A (**23**) in 16% overall yield. The synthesis of Tobinaga *et al.* has basically the same final step but 2,4'-bisindole **241** is built up in a different fashion (Scheme 15-4). *N*-Methoxyindole is converted into triethyl-(1-methoxyindole-2-yl)borate and undergoes a Suzuki coupling with *N*-(*tert*-butyldimethylsilyl)-4-iodoindole to yield bis-*N*-protected 2,4'-bisindole **243** which in turn is converted into 2,4'-bisindole **241** in two additional steps.

15.2 Aims

A small amount of time was spent on the total synthesis of dihydroarcyriacyanin A (**24**). Technically, this molecule is not very challenging in a chemical point of view. Especially since already two groups have synthesized arcyriacyanin A (**23**) using the obvious synthons which were coupled *via* palladium catalyzed cross-coupling reactions (Section 15.1). At the beginning of my work towards the synthesis of cyclohepta[*b*]indoles an interesting reactivity was observed in our group by my co-workers. Oxindole **501** could be transformed into Fischer's base derivative **502** which in turn is a divinylcyclopropane system (Scheme 15-5). Although the yields were exceedingly low for this transformation, upon heating **502** underwent smoothly a divinylcyclopropane rearrangement to yield cyclohepta[*b*]indole **503**. By reason of very low yields the work towards the cyclohepta[*b*]indoles *via* Fischer's base derivatives was discontinued. However, when oxindole **501** was refluxed in high-boiling-point solvents, stereochemical scrambling at the cyclopropane moiety occurred (equilibrium between **504** and **505**). As a result the vinyl moiety has the correct geometry for a potential Cope rearrangement with the aromatic indole core. Indeed, the divinylcyclopropane rearrangement took place yielding cyclohepta[*cd*]indolone **507**. This transformation provided both the first experimental evidence for a possible enzyme-catalyzed sigmatropic process in the C-4 prenylation of indole alkaloids and the first direct C-C-bond forming cyclization which functionalizes the very unreactive C-4 indole position .[355]



Scheme 15-5. Obtaining two different products from racemic cyclopropane **501**.



Scheme 15-6. Intended synthesis of dihydroarcyriacyanin A (**24**): simultaneous construction of both a cyclohepta[*b*]indole and a cyclohepta[*cd*]indole *via* the divinylcyclopropane rearrangement.

To cut a long story short, depending on the stereochemistry of the vinyl group at the cyclopropyl moiety it is possible to construct both cyclohepta[*b*]indoles and cyclohepta[*cd*]indoles. The ultimate proof of concept would be the short total synthesis of dihydroarcyriacyanin A (**24**) as outlined in Scheme 15-6.

It was planned to cyclopropanate the double bond of the maleimide moiety of **1100**. For this purpose, a carbene equivalent like **1101** is required. Once the cyclopropanation took place the two diastereomers **1102** and **1103** are expected to be formed of which only *cis*-configured divinylcyclopropane **1102** is suitable for a [3,3] sigmatropic rearrangement. As depicted in Fig. 15-1, two different seven membered rings are formed simultaneously; whereas the labeled divinylcyclopropane **1102a** leads to a cyclohepta[*b*]indole the labeled divinylcyclopropane **1102b** furnishes the cyclohepta[*cd*]indole. The success of this reaction would be a great proof of concept of the methodologies which were developed by myself and co-workers.

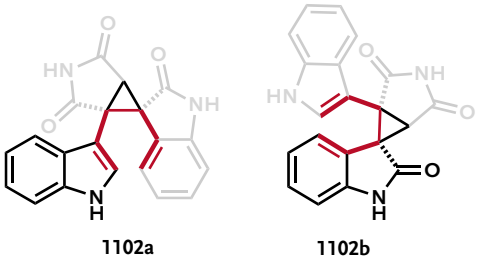
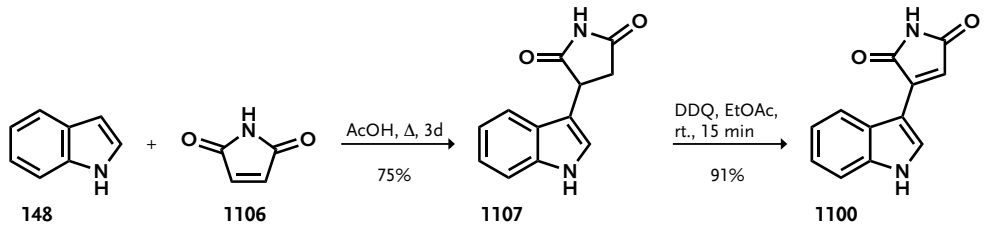


Figure 15-1. Different view of divinylcyclopropane **1102**: **1102a** yields in a cyclohepta[*b*]indole and **1102b** furnishes a cyclohepta[*[*cd]indole.

15.3 Synthetic Work

15.3.1 Synthesis of the Cyclopropanation Precursor

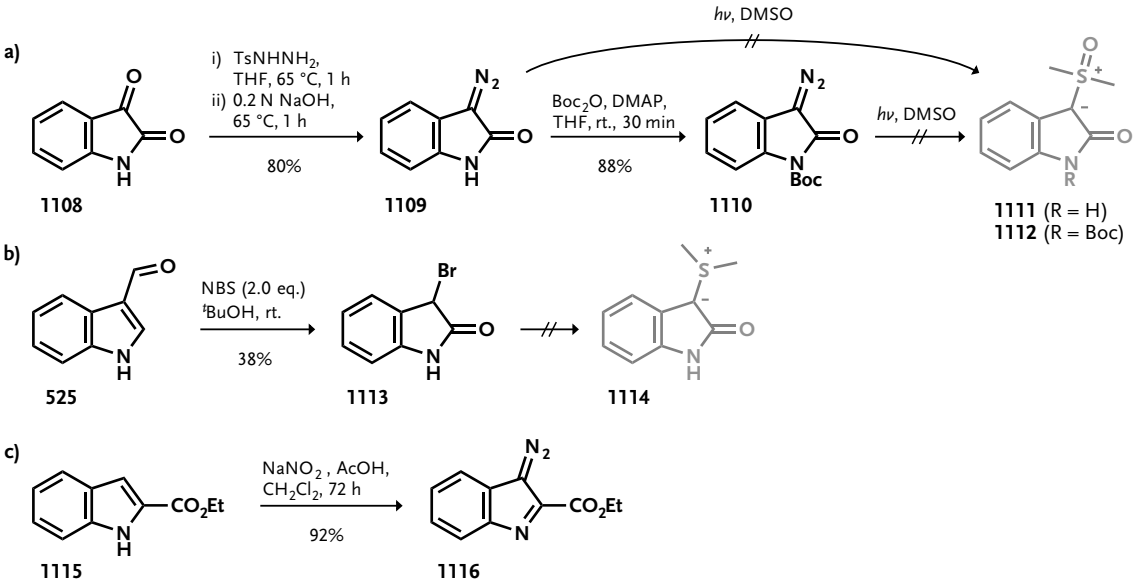
Building block **1100** is pretty simple and requires no explanation *in extenso*. It is simple accessible *via* the reaction of indole with maleimide followed by dehydrogenation with DDQ (Scheme 15-7).[639–641] The reaction rate could be increased enormously by changing the solvent from 1,4-dioxane to ethyl acetate (48 h *vs.* 15 min) in the latter reaction.[642]



Scheme 15-7. Synthesis of 3-(3-indolyl)maleimide (**1100**).

15.3.2 Synthesis of the Carbene Precursor

Diazo compounds are used as precursors to carbenes, which are generated by thermolysis, photolysis, or transformation into the corresponding metal-carbenoids. For this reason several diazo compounds have been prepared (Scheme 15-8). Diazoisatin (**1109**) is a popular building block and has been employed in several syntheses as carbene precursor *via* metal carbenoids.[643] It is easy accessible from isatin in a short two-step procedure *via* the isatin-3-*N*-tosylhydrazone in 80% yield.[644] The *N*-Boc derivative of **1109** has also been prepared (**1110**). In addition, it was assumed that 3-diazo-3*H*-indole-2-carboxylate (**1116**) could also act as a substrate since it is isoelectronic with α-diazocarbonyl compounds.[645] It is easily prepared by dropwise addition of glacial acetic acid to a mixture of ethyl indole-2-carboxylate (**1115**) and sodium nitrite. Although diazoisatin (**1109**) is known for its great stability,[646] diazo compound **1116** is known to decompose considerable exothermically when heated over 130 °C. Albeit the frequent use of diazo compounds in cyclopropanation reactions these reaction works best with electron-rich olefins. The cyclopropanation of electron-deficient double bonds usually requires different reagents, i.e., sulfur ylides. For this reason it was tried to synthesize sulfoxonium compounds **1111** and **1112**,

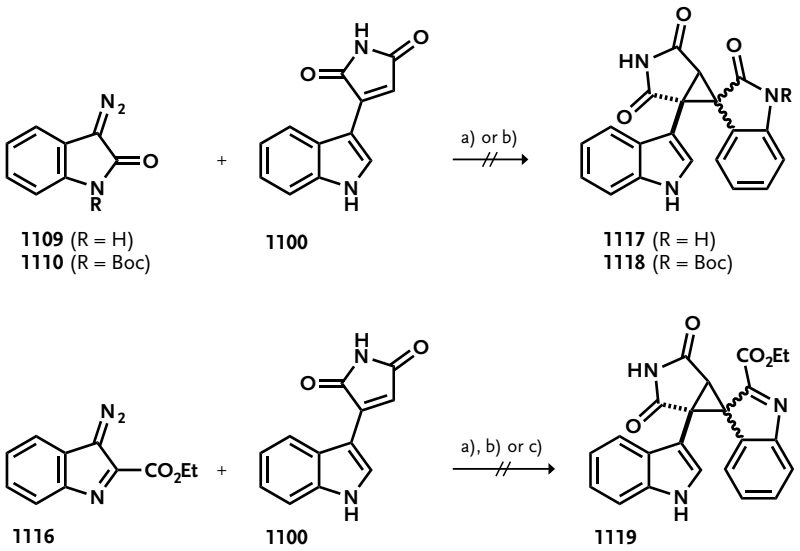


Scheme 15-8. Syntheses of different carbene precursors and sulfur ylides, respectively.

and sulfonium compound **1114**. Apparently, 3-sulfoxonium-oxindoles or 3-sulfonium-oxindoles are not literature known since no data was found to be available by a SciFinder® search. And indeed, although the synthesis of sulfoxonium ylides from α-diazo compounds is known under photochemical or metal catalysis conditions,[647,648] no reaction took place in the case of diazoisatins **1109** and **1110**. Also the synthesis of sulfonium ylide **1114** from α-bromo amide **1113** (accessible from indole-3-carbaldehyde with two equivalents of NBS in *tert*-butanol along with its dibromo compound in a 1:1 ratio) was not successful using several different conditions which were also used before for the generation of other sulfonium and sulfoxonium compounds starting from α-bromo carbonyl compounds. Therefore, only diazo compounds were used for further work.

15.3.3 Cyclopropanation of Maleimide **1100**

The cyclopropanation of aryl maleimide derivatives is known and is especially used in the pharmaceutical area.[649,650] In almost all cases the cyclopropanation is based on the Johnson–Corey–Chaykovsky reaction and cyclopropanation of maleimide derivatives using diazo compounds is very rare and only two examples are known.[649f,650a] In both cases metal carbenoid complexes are avoided and a Kishner cyclopropane synthesis[231b] is used instead. Having this literature results in hands, diazoisatins **1109** and **1110** were refluxed in toluene with maleimide derivative **1100** but no reaction took place even after 20 h (Scheme 15-9). Changing the solvent to xylene did not change this result; cyclopropanation products **1117** or **1118** could never be observed. Using the *N*-Boc derivative **1110** led to formation of remarkable amounts of **1109** by loss of the Boc group. The attempt to form a copper carbenoid with anhydrous cupric sulfate in refluxing hexanes yielded only in the formation of little amounts of the corresponding dimers of the

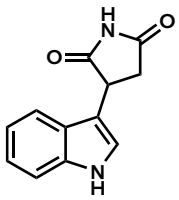


Scheme 15-9. Cyclopropanation attempts. Reagents and conditions: **a)** PhMe or xylenes, Δ. **b)** $CuSO_4$ (20 mol %), hexanes, Δ. **c)** $[Rh(OAc)_2]_2$ (5 mol %), PhH, 80 °C.

diazo compounds. However, cyclopropanation products **1117** or **1118** could never be observed. The same results were obtained when diazo compound **1116** was used instead. In addition, cyclopropanation *via* a rhodium carbenoid was also not successful so that any further attempts were discontinued at that point.

15.4 Experimental

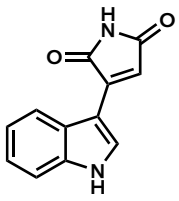
3-(1*H*-Indol-3-yl)pyrrolidine-2,5-dione (1107).



1107

A mixture of indole (4.00 g, 34.1 mmol, 1.0 eq.) and maleimide (3.31 g, 34.1 mmol, 1.0 eq.) was dissolved in glacial acetic acid (43 ml) and stirred at 125 °C for 3 d in a sealed tube (monitored by TLC). The reaction mixture was allowed to cool down to ambient temperature and the volatile components were evaporated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes–EtOAc, 1:1 → 1:2) to obtain pure title compound **1107** as an orange solid (5.50 g, 25.7 mmol, 75% yield). R_f = 0.28 (hexanes–EtOAc, 1:1). **^{1}H NMR** (400 MHz, DMSO) δ = 11.31 (s, 1H), 11.03 (s, 1H), 7.40 (dd, J = 18.1, 8.0 Hz, 2H), 7.33 (d, J = 2.4 Hz, 1H), 7.10 (ddd, J = 8.0, 6.8, 0.9 Hz, 1H), 7.00 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 4.33 (dd, J = 9.5, 5.3 Hz, 1H), 3.18 (dd, J = 18.0, 9.5 Hz, 1H), 2.77 (dd, J = 18.0, 5.3 Hz, 1H) ppm. **HRMS** (ESI): calcd. for $C_{12}H_{11}N_2O_2$ $[M + H]^+$ 215.0821, found 215.0825. ▸ *NMR spectra on page 522.*

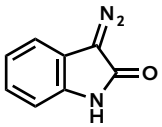
3-(1*H*-Indol-3-yl)-1*H*-pyrrole-2,5-dione (1100).



1100

Pyrrolidinedione **1107** (4.78 g, 22.3 mmol, 1.0 eq.) was dissolved in anhydrous ethyl acetate (450 ml). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (5.07 g, 22.3 mmol, 1.0 eq.) was added in one portion at ambient temperature and stirring was continued at this temperature for 15 min (monitored by TLC). The reaction was extracted twice with aq. sodium sulfite (10%, 500 ml) and once with brine (500 ml). The combined organic layers were dried over Na_2SO_4 and volatile components were evaporated *in vacuo*. Purification by flash column chromatography furnished title compound **1100** as a bright red solid (4.31 g, 20.3 mmol, 91% yield) which yields a bright yellow solution when dissolved in DMSO or chloroform. R_f = 0.66 (hexanes–EtOAc, 1:1, bright yellow spot on TLC, visible without stain or UV light). **^{1}H NMR** (400 MHz, DMSO) δ = 12.01 (s, 1H), 10.75 (s, 1H), 8.36 (d, J = 3.0 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.25 (ddd, J = 8.1, 7.1, 1.3 Hz, 1H), 7.20 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 6.79 (d, J = 1.3 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, DMSO–d_6) δ = 173.4, 173.2, 139.4, 136.6, 130.9, 125.6, 122.9, 121.4, 120.4, 115.2, 112.5, 105.3 ppm. **HRMS** (ESI): calcd. for $C_{12}H_8N_2NaO_2$ $[M + Na]^+$ 235.0483, found 235.0482. ▸ *NMR spectra on page 522.*

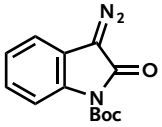
3-Diazoindolin-2-one (1109).


1109

Isatin (1.47 g, 10.0 mmol, 1.0 eq.) was dissolved in abs. THF (50 ml). Tosyl hydrazide (2.05 g, 11.0 mmol, 1.1 eq.) was added and the reaction mixture was stirred 60 min at 65 °C, then it was allowed to cool down to ambient temperature and was filtered through a medium porosity sintered-glass funnel. The solid was repeatedly rinsed with THF, then taken up in 0.2 N NaOH (100 ml), and stirred 60 min at 65 °C. The reaction mixture was extracted thrice with EtOAc and the combined organic layers were dried over $MgSO_4$. Volatile components were evaporated *in vacuo* and the residue was recrystallized from acetone to give diazo compound **1109** as red solid (1.27 g, 7.95 mmol, 80% yield). $R_f = 0.38$ (hexanes–EtOAc, 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$) $\delta = 9.03$ (s, 1H), 7.19 (d, $J = 7.7$ Hz, 1H), 7.16 (td, $J = 7.7$, 1.3 Hz, 1H), 7.08 (td, $J = 7.6$, 1.1 Hz, 1H), 7.01 (d, $J = 7.8$ Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) $\delta = 169.1$, 131.9, 125.7, 122.3, 118.5, 117.4, 110.8, 61.6 ($C{=}N_2$, very weak) ppm. **IR** (neat): 3449, 2120, 2090 ($C{=}N_2$), 1689, 1467, 1400, 1191 cm^{-1}. **HRMS** (ESI): calcd. for $C_8H_5N_3NaO$ $[M + Na]^+$ 182.0330, found 182.0331.

▸ NMR spectra on page 523.

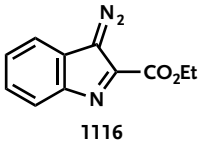
***tert*-Butyl 3-diazo-2-oxoindoline-1-carboxylate (1110).**


1110

Diazoisatin **1109** (466 mg, 2.93 mmol, 1.0 eq.) was dissolved in abs. THF (15.0 ml) and cooled to 0 °C. Boc_2O (767 mg, 3.51 mmol, 1.2 eq.) was added in one portion followed by the addition of DMAP (71.5 mg, 586 µmol, 0.2 eq.). The reaction was stirred 5 min at 0 °C, then the ice bath was removed and stirring was continued at ambient temperature for additional 30 min (monitored by TLC). Volatile components were evaporated *in vacuo* and the crude residue was purified by flash column chromatography (hexanes–EtOAc, 3:1) to furnish *N*-Boc protected diazoisatin **1110** as a brown solid (671 mg, 2.59 mmol, 88% yield). $R_f = 0.76$ (hexanes–EtOAc, 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta = 7.92 - 7.87$ (m, 1H), 7.25 – 7.14 (m, 3H), 1.65 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) $\delta = 165.0$, 149.1, 130.9, 126.2, 124.6, 117.7, 116.0, 115.7, 84.8, 60.5 ($C{=}N_2$, very weak), 28.2 ppm. **HRMS** (ESI): calcd. for $C_{13}H_{13}N_3NaO_3$ $[M + Na]^+$ 282.0855, found 282.0858.

▸ NMR spectra on page 524.

Ethyl 3-diazo-3*H*-indole-2-carboxylate (1116).


1116

Ethyl indole-2-carboxylate (5.0 g, 26.4 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (200 ml) and cooled to 0 °C. Sodium nitrite (16.4 g, 238 mmol, 9.0 eq.) was added in portions followed by dropwise addition of glacial acetic acid over 10 min (inner temp. < 5 °C). After complete addition the ice bath was removed and stirring was continued at ambient temperature. Although lots of precipitate has been already formed after 30 min, the reaction was stirred 72 h in total (monitored by TLC). After 48 h, two additional equivalents of sodium nitrite and glacial acetic acid,

respectively, were added to the reaction mixture. The reaction was poured into water (150 ml) and the layers were separated. The aqueous layer was extracted two additional times with CH_2Cl_2 (80 ml). The combined organic layers were extracted once with bicarb (150 ml) and dried over Na_2SO_4. Volatile components were evaporated *in vacuo* and the crude residue was purified by flash column chromatography (hexanes–EtOAc, 3:1 → 1:1) to yield diazo compound **1116** as a pale yellow solid (5.23 g, 24.3 mmol, 92% yield). R_f = 0.21 (hexanes–EtOAc, 4:1). **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.00 – 7.96 (m, 1H), 7.10 (ddd, J = 8.1, 7.2, 1.3 Hz, 1H), 7.02 (ddd, J = 7.8, 7.2, 1.1 Hz, 1H), 6.87 (ddd, J = 7.8, 1.3, 0.7 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 1.02 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6) δ = 162.0, 149.8, 147.2, 129.1, 126.1, 125.6, 124.3, 118.2, 72.3, 61.7, 14.1 ppm. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.04 – 7.92 (m, 1H), 7.60 – 7.49 (m, 1H), 7.43 – 7.31 (m, 2H), 4.50 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H) ppm. **^{1}H NMR** (200 MHz, DMSO) δ = 7.95 – 7.76 (m, 2H), 7.47 – 7.29 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{11}H_{10}N_3O_2$ $[M + H]^+$ 216.0773, found 216.0775.

▸ *NMR spectra on page 525.*

*Note: Caution! Studies indicate considerable exothermic decomposition when the pale yellow crystalline solid **1116** is heated over 130 °C.*

Part V

Appendix

Experimental Part for Reagents

A

A.1 General Methods

The general methods described in this section are also valid for all other experimental parts in this thesis (Section 10.1, Section 13.1, Section 14.3, and Section 15.4).

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Butyl refers to *n*-butyl and ether refers to diethyl ether unless otherwise stated. The terms hexanes and petroleum ether are used equally unless otherwise stated. Solvent mixtures were generally prepared in terms of volume ratios (v/v) unless otherwise stated. In the context of work-up, NH_4Cl, NaCl, $Na_2S_2O_3$, and $NaHCO_3$ refer to NH_4Cl (aq., sat.), NaCl (aq., sat.), $Na_2S_2O_3$ (aq., sat.) and $NaHCO_3$ (aq., sat.), respectively, unless otherwise stated.

All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grade. The applied petroleum ether fraction had a boiling point of 40–60 °C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Only tap water was used and aqueous solutions were prepared on site. All other solvents were HPLC grade unless otherwise stated.

Reactions were stirred magnetically or mechanically and monitored by thin layer chromatography with silica gel Merck® 60-F254 plates and visualized with ultraviolet radiation and by staining with either aqueous acidic potassium permanganate, aqueous acidic cerium molybdate, aqueous acidic vanillin, aqueous acidic dinitrophenylhydrazine, ninhydrin or aqueous acetic dimethylaminobenzaldehyde solutions. Flash column chromatography was performed with silica gel (0.04 – 0.063 mm, 240 – 400 mesh) under pressure. In some cases, alumina was used instead of

silica. Preparative thin layer chromatography was carried out using Macherey-Nagel, ADAMANT UV_{254}, Glass plates, silica 60. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated.

Concerning the work-up, no volumina for the solvents and aqueous solutions are stated in most cases unless it is important.

^{1}H, ^{13}C, DEPT, ^{1}H–^{1}H COSY, HMBC, HMQC, NOE, and NOESY NMR experiments were recorded in $CDCl_3$, C_6D_6, MeOD, DMSO–d_6, pyridine–d_5, toluene–d_8, or acetone–d_6 using either a Bruker Avance DPX-200 (200 MHz), AV-400 (400 MHz), DPX 400 (400 MHz), Ascend 400 Avance III HD (400 MHz), or DPX 500 (500 MHz) using the residual $CDCl_3$ peak (δ_H = 7.26 ppm, δ_C = 77.16 ppm), C_6H_6 peak (δ_H = 7.16 ppm, δ_C = 128.62 ppm), $(CD_3)_2CO$ peak (δ_H = 2.05 ppm, δ_C = 29.8, 206.3 ppm), MeCN peak (δ_H = 1.94 ppm, δ_C = 1.3, 118.3 ppm), and MeOH peak (δ_H = 3.34 ppm, δ_C = 49.86 ppm) as an internal standard.[651] Chemical shift, δ, is given in parts per million (ppm) and coupling constants, J, are given in Hertz (Hz) (s = singlet, d = doublet, t = triplet, q = quadruplet, p = pentett, m = multiplet, br = broad signal, or combination of these acronyms). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy.

NMR spectra were processed with Mestrelab Mnova 10 and 11. The baseline have been often corrected or smoothed *via* Whittaker Smoothing.[652]

High-performance liquid chromatography, HPLC, was run on either AlphaChrom using an AGILENT Prep SIL Scalat (4.6 × 250 mm, 5 µm or 21.2 × 250 mm, 10 µm) column or on a Merck-Hitachi HPLC System (L-7150 pump, L-7200 autosampler, L-7400 UV-detector, D-7000 Interface), with HPLC grade solvents and using UV detection (λ = 254, 280 nm) at ambient temperature.

High Resolution Mass Spectra, HRMS, were recorded on a Waters Micromass LCT Premier spectrometer (ESI).

IR measurements were carried out using Bruker Vector 22.

Melting points were determined on OptiMelt MPA 100 (Stanford Research Systems).

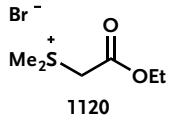
Compound names were either generated using ChemDraw® or looked up at catalogues of chemical suppliers.[1]

[1] In some cases the naming is not strict according to IUPAC and more friendly but still correct names were used, e.g., "2-iodoxybenzoic acid" instead of "1-hydroxy-1-oxo-1λ_5-benzo[*d*][1,2]iodaoxol-3(1*H*)-one".

A.2 Experimental[2]

A.2.1 Sulfur Ylides and Precursors

(Ethoxycarbonylmethyl)dimethylsulfonium bromide (1120).[653,654]

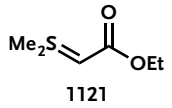


1120

A mixture of ethyl bromoacetate (10.3 g, 62.0 mmol 1.25 eq.) and dimethyl sulfide (2.97 g, 48.0 mmol, 1.0 eq.) were stirred in 20 ml of anhydrous acetone for 18 h at ambient temperature in the absence of light. The resultant precipitate was filtered through a medium porosity sintered-glass funnel, washed with an appropriate amount of cold acetone, and dried *in vacuo* for 12 h to furnish sulfonium salt **1120** as white solid in quantitative yield. R_f = 0.20 (DCM–MeOH, 95:5). **M.p.** 88 °C.

Note: Storage in the absence of light.

Ethyl 2-(dimethyl-λ_4-sulfaneylidene)acetate [EDSA] (**1121**).



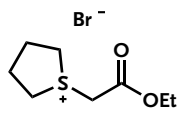
1121

Variant 1: The sulfur ylide **1121** was prepared by stirring a suspension of sulfonium salt **1120** (1.0 eq.) and sodium hydride (60% dispersion in mineral oil, 1.0 eq.) in anhydrous THF under an argon atmosphere at ambient temperature for 4.0 h. The voluminous white precipitate (sodium bromide) was removed by filtration using a Schlenk-frit and the filtrate was transferred to the relevant reaction mixture.

Variant 2 (according to Payne):[655] Sulfonium salt **1120** (1.63 g, 7.15 mmol) was dissolved in 6.0 ml of anhydrous CH_2Cl_2 and the suspension was stirred at 5 °C. Saturated aqueous potassium carbonate solution (5.0 ml) was added followed by 12 N NaOH (0.6 ml). The ice bath was removed and the reaction mixture was stirred at ambient temperature for additional 30 min. The phases were separated and the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3 (15 min), filtered, and concentrated *in vacuo* to furnish ylide **1121** as a pale yellow solid (95% crude yield) which usually was directly used in the next step. R_f = 0.21 (DCM–MeOH, 95:5).

Note: Storage is possible at –20 °C in a sealed bottle under an argon atmosphere.

(Ethoxycarbonylmethyl)tetrahydrothiophenium bromide (1122).



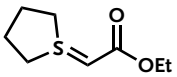
1122

A mixture of ethyl bromoacetate (15.1 g, 90.4 mmol 1.0 eq.) and tetrahydrothiophene (10.8 ml, 122 mmol, 1.35 eq.) were stirred in 30 ml of anhydrous acetone for 18 h at ambient temperature in the absence of light. The resultant precipitate was filtered through a medium porosity sintered-glass funnel and dried *in vacuo* for 12 h to furnish sulfonium salt **1122** as white solid in almost quantitative yield. R_f = 0.24 (DCM–MeOH, 95:5). **M.p.** 125 °C (decomp.).

Note: Storage in the absence of light.

[2] The experimental procedures for the reagents have no strict order of listing but are grouped by similarity where possible.

Ethyl 2-(tetrahydro-1λ_4-thiophen-1-ylidene)acetate (1123).

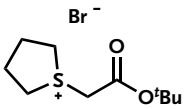


1123

Sulfonium salt **1122** (1.82 g, 7.15 mmol) was dissolved in 6.0 ml of anhydrous CH_2Cl_2 and the suspension was stirred at 5 °C. Saturated aqueous potassium carbonate solution (5.0 ml) was added followed by 12 N NaOH (0.6 ml). The ice bath was removed and the reaction mixture was stirred at ambient temperature for additional 30 min. The phases were separated and the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3 (15 min), filtered, and concentrated *in vacuo* to furnish ylide **1123** as a white solid in quantitative yield which usually was directly used in the next step. R_f = 0.25 (DCM–MeOH, 95:5). **M.p.** 55 °C (decomp.). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.03 (q, J = 7.2 Hz, 2H), 3.32 – 2.91 (m, 5H), 2.67 – 2.38 (m, 2H), 2.02 – 1.72 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H) ppm. ▸ NMR spectra on page 527.

Note: Storage is possible at –20 °C in a sealed bottle under an argon atmosphere.

(*tert*-Butoxycarbonylmethyl)tetrahydrothiophenium bromide (1124).

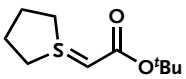


1124

A mixture of ethyl bromoacetate (15.0 g, 77.0 mmol 1.0 eq.) and tetrahydrothiophene (7.5 ml, 84.7 mmol, 1.1 eq.) were stirred in 26 ml of anhydrous acetone for 18 h at ambient temperature in the absence of light. The resultant precipitate was filtered through a medium porosity sintered-glass funnel, washed with an appropriate amount of cold acetone, and dried *in vacuo* for 12 h to furnish sulfonium salt **1124** as white solid in quantitative yield. R_f = 0.25 (DCM–MeOH, 95:5). **M.p.** 130 °C (decomp.). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.91 (s, 2H), 4.10 – 3.93 (m, 2H), 3.93 – 3.76 (m, 2H), 2.48 (td, J = 6.2, 3.5 Hz, 4H), 1.49 (s, 9H) ppm. ▸ NMR spectra on page 528.

Note: Storage in the absence of light.

***tert*-Butyl 2-(tetrahydro-1λ_4-thiophen-1-ylidene)acetate (1125).**



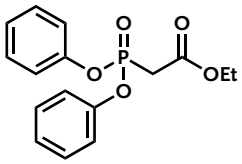
1125

Sulfonium salt **1124** (2.02 g, 7.15 mmol) was dissolved in 6.0 ml of anhydrous CH_2Cl_2 and the suspension was stirred at 5 °C. Saturated aqueous potassium carbonate solution (5.0 ml) was added followed by 12 N NaOH (0.6 ml). The ice bath was removed and the reaction mixture was stirred at ambient temperature for additional 30 min. The phases were separated and the aqueous layer was extracted thrice with CH_2Cl_2. The combined organic layers were dried over K_2CO_3 (15 min), filtered, and concentrated *in vacuo* to furnish ylide **1125** as a pale yellow solid in quantitative yield which usually was directly used in the next step. R_f = 0.25 (DCM–MeOH, 95:5). **M.p.** 37 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.19 – 3.65 (m, 1H), 3.24 – 2.82 (m, 4H), 2.45 (br s, 2H), 2.02 – 1.70 (m, 2H), 1.43 (s, 9H) ppm. ▸ NMR spectra on page 528.

Note: Storage is possible at –20 °C in a sealed bottle under an argon atmosphere.

A.2.2 Olefination Reagents and Precursors

Ethyl (Diphenylphosphono)acetate [Ando Reagent] (**530**).



530

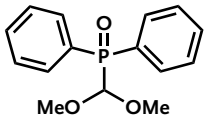
Variant 1 (according to Brückner):[656] A 1-L flame dried Schlenk flask was charged with sodium hydride (60% dispersion in mineral oil, 26.1 g, 392 mmol, 1.0 eq.), the flask was evacuated and flushed with argon. Anhydrous THF (300 ml) was added and the mixture was cooled down to 0 °C. Diphenyl phosphite (75.0 ml, 91.7 g, 392 mmol, 1.0 eq.) was added *via* syringe pump over a period of 3.0 h at 0 °C. After complete addition the reaction mixture was stirred an additional hour at 0 °C after which the reaction mixture became a clear orange solution. Subsequently ethyl bromoacetate (43.3 ml, 65.4 g, 392 mmol, 1.0 eq.) was added *via* syringe pump over a period of 150 min at 0 °C. The ice bath was removed and the reaction mixture was stirred for additional 14 h at ambient temp. The reaction mixture was diluted with ether and quenched by the addition sat. aq. NH_4Cl–H_2O (1:2, 150 ml). The layers were separated and the aqueous layer was extracted twice with ether (200 ml). The combined organic layers were dried over $MgSO_4$ and volatile components were evaporated *in vacuo*. The remaining orange oil was purified *via* flash column chromatography using hexanes–EtOAc (4:1 → 2:1 → 1:1 → 1:1.5) as eluent. Phosphonate **530** was obtained as a clear viscous oil (80.0 g, 250 mmol, 64% yield).

Variant 2: A 500-ml flame dried Schlenk tube was charged with a solution of diphenyl phosphite (28.7 ml, 35.1 g, 150 mmol, 1.0 eq.) in absolute CH_2Cl_2 (150 ml) and cooled to 0 °C. Ethyl bromoacetate (16.6 ml, 25.1 g, 150 mmol, 1.0 eq.) was added followed by the addition of Et_3N (50.0 ml, 36.7 g, 218 mmol, 1.45 eq.) over 15 min at 0 °C. After complete addition the reaction mixture was stirred additional 30 min at this temperature (formation of white precipitate), then the ice bath was removed and the reaction mixture was stirred additional 3.0 h at ambient temperature (monitored by TLC). The reaction was quenched by the addition of H_2O (100 ml), the layers were separated and the aqueous layer was extracted twice with ether (100 ml). The combined organic layers were dried over Na_2SO_4 and volatile components were evaporated *in vacuo*. The remaining orange oil was purified *via* flash column chromatography using hexanes–EtOAc (4:1 → 2:1 → 1:1 → 1:1.5) as eluent. Phosphonate **530** was obtained as a clear viscous oil (39.4 g, 123 mmol, 82% yield). R_f = 0.15–0.3 (hexanes–EtOAc, 4:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.40 – 7.13 (m, 10H), 4.23 (qd, J = 7.2, 0.6 Hz, 2H), 3.27 (d, J = 21.6 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H) ppm. **HRMS** (ESI): calcd. for $C_{16}H_{17}NaO_5P$ $[M + Na]^+$ 343.0711, found 343.0714.

▸ *NMR spectra on page 529.*

Note: (i) The own developed conditions seemed to be more convenient, even for the preparation of large amounts of phosphonate ***530****. (ii) Storage under argon at –20 °C.*

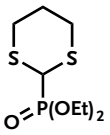
(Dimethoxymethyl)diphenylphosphine oxide (690).



690

Chlorodiphenylphosphine (9.0 ml, 11.0 g, 50.0 mmol, 1.0 eq.) was added dropwise to trimethyl orthoformate (5.5 ml, 5.31 g, 50.0 mmol, 1.0 eq., neat, caution: very exothermic) under an argon atmosphere at ambient temperature. The reaction mixture solidified and was then heated for 120 min at 110 °C (caution: large volumes of gas [MeCl] are produced). The reaction mixture was allowed to cool down to ambient temperature and the yellow solid was recrystallized from cyclohexane–toluene (1:2) to obtain title compound **690** as a white solid (12.0 g, 43.5 mmol, 87% yield). **M.p.** 83 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.00 – 7.78 (m, 4H), 7.58 – 7.36 (m, 6H), 4.92 (d, J = 7.8 Hz, 1H), 3.55 (s, 6H) ppm. ▸ *NMR spectra on page 529.*

Diethyl (1,3-dithian-2-yl)phosphonate (692).



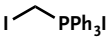
692

1,3-Dithiane (6.00 g, 50.0 mmol, 1.0 eq.) was dissolved in 150 ml of anhydrous benzene in a 250 ml flame dried Schlenk tube. NCS (6.70 g, 50.0 mmol, 1.0 eq.) was added in small portions at ambient temperature after which the reaction mixture was stirred for 24 h at this temperature under an argon atmosphere. Triethyl phosphite (10.3 ml, 60.0 mmol, 1.2 eq.) was then added dropwise at ambient temperature and the reaction mixture was stirred additional 4.0 h at 60 °C (monitored by TLC). The reaction mixture was allowed to cool down to ambient temperature and was filtered through a medium porosity sintered-glass funnel. The filtride was washed with an appropriate amount of cold ether and the filtrate was then concentrated under reduced pressure. The residue was triturated with cold ether to precipitate residues of succinimide which were again removed by filtration. Volatile components were evaporated *in vacuo* to obtain a yellow oil which was purified by flash column chromatography using cyclohexane–EtOAc (5:1) as eluent. Title compound **692** was obtained as colorless viscous oil (10.0 g, 39.1 mmol, 78% yield) which solidified below 10 °C. R_f = 0.40 (cyclohexane–EtOAc, 4:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.21 (pd, J = 7.1, 0.6 Hz, 4H), 3.53 (d, J = 19.4 Hz, 1H), 3.59 – 3.33 (m, 2H), 2.60 – 2.40 (m, 2H), 2.16 – 1.86 (m, 2H), 1.31 (td, J = 7.1, 0.7 Hz, 6H) ppm. **HRMS** (ESI): calcd. for $C_8H_{18}O_3PS_2$ $[M + H]^+$ 257.0435, found 257.0434.

▸ *NMR spectra on page 530.*

*Note: Phosphonate **692** is also accessible* via *the deprotonation of 1,3-dithiane followed by the addition of diethyl chlorophosphate, but the yields were low. In addition, diethyl chlorophosphate is a cholinesterase inhibitor and therefore highly toxic.*

(Iodomethyl)triphenylphosphonium iodide [Stork-Zhao Reagent] (**678**).



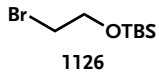
678

Triphenylphosphine (6.01 g, 22.9 mmol, 1.0 eq.) and diiodomethane (2.5 ml, 30.0 mmol, 1.3 eq.) were refluxed in anhydrous benzene (10 ml) in the absence of light under an argon atmosphere for 21.5 h. The reaction mixture was allowed to cool down to ambient temperature and the resultant precipitate was filtered through a medium

porosity sintered-glass funnel. The white solid was washed four times with anhydrous cold benzene (25 ml). The collected solid was dried under high vacuum for 18 h in the absence of light to obtain title compound **678** as a white solid (12.1 g, 22.8 mmol, quantitative yield). **M.p.** 228 °C (lit. 228 °C).

Note: The solid was transferred to an argon flushed amber-glass bottle and stored in a freezer.

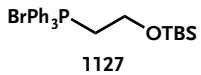
(2-Bromoethoxy)(*tert*-butyl)dimethylsilane (1126).



1126

To a solution of 2-bromoethanol (3.5 ml, 6.16 g, 49.3 mmol, 1.0 eq.) in anhydrous CH_2Cl_2 (20 ml) was added *tert*-butyldimethylsilyl chloride (8.17 g, 54.2 mmol, 1.1 eq.) followed by the addition of Et_3N (13.5 ml, 9.98 g, 98.6 mmol, 2.0 eq.) and DMAP (55.0 mg, 450 µmol, 1 mol %) at ambient temperature. The reaction mixture was stirred at this temperature for 15 h before it was diluted with pentane–ether (1:1) and quenched by the addition of H_2O. The layers were separated and the aqueous layer was extracted twice with pentane–ether (1:1, 40 ml). The combined organic layers were extracted once with brine, dried over $MgSO_4$ and volatile components were evaporated *in vacuo*. The residue was purified by flash column chromatography using pentane–ether (10:1) as eluent to obtain silane **1126** as clear colorless oil (11.0 g, 45.6 mmol, 94% yield). R_f = 0.80 (hexanes–EtOAc, 10:1, stains with $KMnO_4$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.88 (t, J = 6.5 Hz, 2H), 3.38 (t, J = 6.5 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 6H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 63.6, 33.3, 26.0, 18.4, –5.1 ppm. **HRMS** (ESI): calcd. for $C_8H_{19}BrNaOSi$ $[M + Na]^+$ 261.0286, found 261.0288. ▸ *NMR spectra on page 530.*

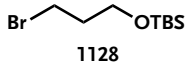
(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)triphenylphosphonium bromide (1127).



1127

Bromide **1126** (11.0 g, 45.6 mmol, 1.0 eq.) was refluxed with triphenylphosphine (12.0 g, 45.6 mmol, 1.0 eq.) in anhydrous benzene (30 ml) for 9.0 h (monitored by TLC). The reaction mixture was allowed to cool down to ambient temperature and the resultant precipitate was filtered through a medium porosity sintered-glass funnel. The white solid was washed four times with anhydrous cold benzene (15 ml). The collected solid was dried under high vacuum for 18 h to obtain title compound **1127** as a white solid (22.7 g, 45.4 mmol, quantitative yield). **^{1}H NMR** (200 MHz, MeOD) δ = 7.96 – 7.65 (m, 15H), 4.12 (t, J = 5.7 Hz, 1H), 4.01 (t, J = 5.7 Hz, 1H), 3.77 (dt, J = 11.5, 5.6 Hz, 2H), 0.73 (s, 9H), –0.10 (s, 6H) ppm. ▸ *NMR spectra on page 531.*

(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (1128).



1128

3-bromopropan-1-ol (93%, 8.0 ml, 12.8 g, 85.6 mmol, 1.0 eq.) was dissolved in anhydrous CH_2Cl_2 (300 ml). *tert*-Butyldimethylsilyl chloride (16.2 g, 107 mmol 1.25 eq.) was added in portions followed by addition of DMAP (1.05 g, 8.57 mmol, 0.1 eq.) and Et_3N (17.8 ml, 13.0 g, 128 mmol, 1.5 eq.) at ambient temperature. The reaction mixture was stirred at this temperature for 23 h before it was diluted with CH_2Cl_2

and quenched by the addition of 1 N H_2SO_4. The layers were separated and the organic layer was washed once with sat. aq. $NaHCO_3$, sat. aq. NH_4Cl, and brine, respectively. The organic layer was dried over $MgSO_4$ and volatile components were evaporated *in vacuo*. Purification by flash column chromatography (pentane–ether, 4:1) furnished silane **1128** as clear colorless oil (19.8 g, 78.2 mmol, 98% yield). R_f = 0.90 (pentane–ether, 3:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 3.73 (t, J = 5.7 Hz, 2H), 3.50 (t, J = 6.4 Hz, 2H), 2.02 (p, J = 6.0 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H) ppm. **^{1}H NMR** (200 MHz, DMSO) δ = 3.69 (t, J = 5.8 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.07 – 1.85 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_9H_{21}BrNaOSi$ $[M + Na]^+$ 275.0443, found 275.0447.

▸ NMR spectra on page 532.

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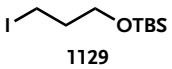
tert-Butyl(3-iodopropoxy)dimethylsilane (1129).

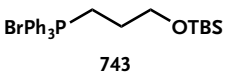


1129

Crude bromide **1128** (80.0 mmol, 1.0 eq.) was dissolved in anhydrous acetone (55 ml). Sodium iodide (3.00 g, 200 mmol, 2.5 eq.) was added in one portion and the reaction mixture was refluxed for 30 min (monitored by TLC, iodide **1129** is slightly more polar than bromide **1128**). The reaction mixture was allowed to cool down to ambient temperature, ether (200 ml) was added, and solids were removed by filtration through a medium porosity sintered-glass funnel. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (pentane–ether, 95:5 → 90:10) to yield iodide **1129** as light rose oil (17.2 g, 57.3 mmol, 77% yield over two steps). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 3.66 (t, J = 5.7 Hz, 2H), 3.28 (t, J = 6.7 Hz, 2H), 1.99 (tt, J = 6.7, 5.7 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H) ppm. **HRMS** (ESI): calcd. for $C_9H_{22}IOSi$ $[M + H]^+$ 301.0485, found 301.0484.

▸ NMR spectra on page 533.

(3-((tert-Butyldimethylsilyl)oxy)propyl)triphenylphosphonium bromide (743).

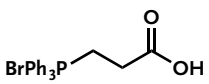


743

Silane **1128** (12.4 g, 49.0 mmol, 1.0 eq.) was heated with triphenylphosphine (96%, 13.4 g, 49.0 mmol, 1.0 eq.) in anhydrous benzene (33.0 ml) to 100 °C in a sealed tube for 3 d. Volatile components were evaporated *in vacuo* and the resultant solid was dried under high vacuum for 18 h to obtain title compound **743** as a white solid (25.0 g, 48.5 mmol, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.85 – 7.72 (m, 9H), 7.72 – 7.64 (m, 6H), 3.87 – 3.70 (m, 4H), 1.94 – 1.77 (m, 2H), 0.83 (s, 9H), 0.01 (s, 6H) ppm.

▸ NMR spectra on page 533.

(2-Carboxyethyl)triphenylphosphonium bromide (1130).



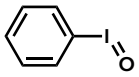
1130

Triphenylphosphine (98%, 13.4 g, 50.0 mmol, 1.0 eq.) and 3-bromopropionic acid (97%, 7.89 g, 50.0 mmol, 1.0 eq.) were refluxed in MeCN (19.2 ml) for 3 d (reaction progress was controlled by ^{1}H NMR). The solvent was removed *in vacuo* and the remained solid was recrystallized from MeCN to obtain carboxylic acid **1130** as white solid (19.9 g, 47.9 mmol, 96% yield). **^{1}H NMR** (400 MHz,

$CDCl_3$) δ = 10.89 (br s, 1H), 7.74 – 7.59 (m, 15H), 3.68 (dt, J = 12.7, 7.2 Hz, 2H), 2.90 (dt, J = 13.4, 7.5 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.0 (d, J = 13.8 Hz), 135.3 (d, J = 3.0 Hz), 133.5 (d, J = 10.1 Hz), 130.6 (d, J = 12.7 Hz), 117.3 (d, J = 86.7 Hz), 27.9 (d, J = 2.6 Hz), 18.7 (d, J = 55.1 Hz) ppm. ▸ NMR spectra on page 534.

A.2.3 Hypervalent Iodine Compounds

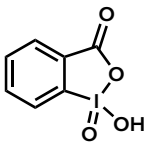
Iodosobenzene (1131).[657]



1131

A 250 ml flask was charged with (diacetoxyiodo)benzene (3.22 g, 10.0 mmol, 1.0 eq.) and 3 N NaOH (15.0 ml) was added dropwise over a period of 10 min with vigorous stirring. Stirring was continued for another 15 min after complete addition followed by standing for additional 45 min to complete the reaction. 10 ml of H_2O was added and the solid was filtered through a medium porosity sintered-glass funnel. The solid was collected and again dissolved in 20 ml of H_2O, was shaken properly and filtered through a medium porosity sintered-glass funnel. The latter sequence was repeated one more time. The collected white solid was dried under high vacuum for 12 h to obtain title compound **1131** as a fine-grained powder (1.58 g, 7.18 mmol, 72% yield). **M.p.** 205 °C (decomp.). *Note: Caution! Iodosobenzene explodes quite impressively when heated to 205 °C.*

2-Iodoxybenzoic acid [IBX] (**604**).[658]

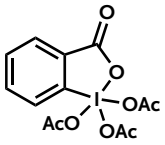


604

A 1-L two-neck round-bottom flasks was charged with Oxone® (181 g, 294 mmol, 1.45 eq.) and equipped with a mechanical stirrer. Water (650 ml) was added and after complete dissolution of Oxone®, 2-iodobenzoic acid (50.0 g, 202 mmol, 1.0 eq.) was added in one portion. The reaction mixture was heated until the inner temperature has reached 70 °C and from this point stirring was continued at this inner temperature for 3.0 h. The oil bath was removed, the reaction mixture allowed to cool down to ambient temperature, and was then stirred for 90 min at 0 °C. The resultant precipitate was filtered through a medium porosity sintered-glass funnel, the white solid was washed six times with H_2O (100 ml), and subsequently two additional times with acetone (100 ml). The collected white solid was dried under high vacuum for 18 h to obtain title compound **604** as a fine-grained powder (42.3 g, 151 mmol, 75% yield). **M.p.** 230 °C (decomp.). **^{1}H NMR** (400 MHz, DMSO) δ = 8.26 – 7.89 (m, 3H), 7.89 – 7.66 (m, 1H) ppm. **^{13}C NMR** (101 MHz, DMSO – d_6) δ = 167.6, 146.6, 133.5, 133.0, 131.4 (d, J = 9.9 Hz), 130.1, 125.0 ppm. ▸ NMR spectra on page 535.

Notes: (i) Caution! Although I could not observe any explosions while handling with IBX, even not when measuring the melting point, IBX is known to be explosive under impact or heating to >200 °C.[659] *(ii) This procedure was also reproducible on twice the scale (100 g of 2-iodobenzoic acid) yielding 85.1 g of IBX (75% yield).*

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one [Dess–Martin Periodinane] (**603**).[660]



603

To a suspension of IBX (43.0 g, 154 mmol, 1.0 eq.) in Ac_2O (170 ml) was added a catalytic amount of TsOH · H_2O (215 mg, 1.12 mmol, 0.75 mol %) and the reaction mixture was stirred at 80 °C for 2.0 h. The heating bath was then replaced with an ice bath and stirring was continued for additional 20 min. The resultant precipitate was filtered through a medium porosity sintered-glass funnel and the white solid was washed four times with anhydrous cold ether (25 ml). The collected white solid was dried under high vacuum for 18 h to obtain title compound **603** as a fine-grained powder (49.7 g, 117 mmol, 76% yield). **M.p.** 133 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.29 (dd, J = 7.4, 1.4 Hz, 2H), 8.08 (ddd, J = 8.5, 7.3, 1.6 Hz, 1H), 7.90 (td, J = 7.3, 1.1 Hz, 1H), 2.31 (s, 3H), 1.98 (s, 6H) ppm. ▸ *NMR spectra on page 536.*

A.2.4 Diazo Compounds and Precursors

Diazomethane (839).[661]

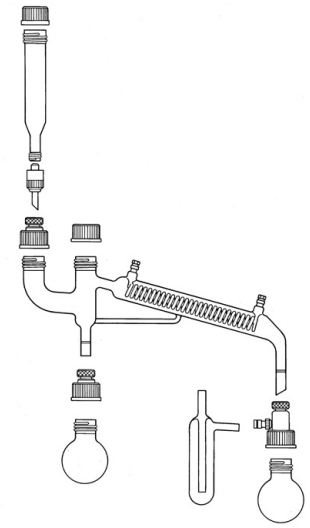


Figure 1-1. Apparatus for the safe generation of diazomethane.

Using an apparatus similar to Fig. 1-1, a solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamid (21.5 g, also known as *Diazald*®) in ether (130 ml) is slowly added over 20 min to a stirred solution of KOH (6.0 g) in 20 ml of water and 35 ml of 2-methoxyethanol which is heated to 50 °C. The solution turned yellow almost immediately and a solution of diazomethane in ether began to distill. The receiving flask which is attached to the distillation apparatus was cooled in an dry ice bath. After complete addition of Diazald®, additional ether (60 ml) was added dropwise and distillation was continued until the distillate was colorless. Using this procedure, diazomethane is obtained as approx. 0.3 M yellow solution in ether. *Notes: (i) Caution! Diazomethane is highly toxic and highly explosive. The operation must be carried out in a good hood with an adequate shield! The utmost care is essential in the preparation and use of this material! (ii) It is highly recommended that ground joints and sharp surfaces be avoided. Thus all glass tubes should be carefully fire-polished, connections should be made with rubber stoppers, and separatory funnels should be avoided, as should etched or scratched flasks.* Diazald® set with System 45™ compatible connections *glassware kit from Sigma-Aldrich (Z419761) was used.*[3]

[3] www.sigmaaldrich.com/catalog/product/aldrich/z419761, Fig. 1-1 has also been copied from this source.

2-Diazoacetonitrile (617).[662]

617

A two-necked round-bottom flask was charged with α-aminoacetonitrile bisulfite (2.73 g 13.0 mmol, 1.0 eq.), CH_2Cl_2 (13.0 ml) was added and the suspension was cooled down to –10 °C under an argon atmosphere. A solution of $NaNO_2$ (2.69 g, 39.0 mmol, 3.0 eq.) in water (4.0 ml) was added dropwise. After complete addition, the organic layer turned bright yellow and the suspension was stirred additional 45 min at –10 °C. The reaction mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed once with 1% aq. K_2CO_3 (10 ml) and the aqueous layers were backwashed with CH_2Cl_2 (20 ml). The combined organic layers were dried over K_2CO_3 and the volume was reduced to approx. 20 ml under reduced pressure (T = 20 °C). IR analysis confirmed the existence of a diazo group (ν = 2100 cm^{-1}). The bright yellow solution of 2-diazoacetonitrile in CH_2Cl_2 was used directly in subsequent reactions.

*Note: Caution! 2-Diazacetonitrile (**617**) has been reported to be highly explosive at high concentrations. The 30 wt% solution of **617** in CH_2Cl_2 is not so dangerous. It is important, that **617** can be used only in dilute solution: additionally, it must be avoided concentration and isolation of **617**, especially on a large scale.*[389]

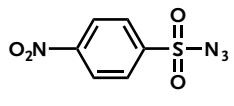
Methanesulfonyl azide (841).[421]

841

Sodium azide (4.26 g, 65.5 mmol, 1.5 eq.) was added in small portions over a period of 30 min to a solution of methanesulfonyl chloride (3.4 ml, 5.0 g, 43.7 mmol, 1.0 eq.) in absolute acetone (22.0 ml) at ambient temperature under argon. After complete addition, the suspension was stirred additional 90 min at this temperature. The mixture was filtered through a medium porosity sintered-glass funnel, and the salt (NaCl) was repeatedly rinsed with absolute acetone. Careful rotary evaporation of the filtrate followed by high vacuum for 2.0 h furnished azide **841** as colorless oil which solidified below 10 °C in 94% yield. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 3.25 (s, 3H) ppm. ▸ NMR spectra on page 536.

*Notes: (i) Caution! Like all sulfonyl azide derivaties, azide **841** is potentially explosive and should be handled with care. Especially never crack the solid but wait until the compound liquidates. (ii) Storage in the freezer is possible for an indefinite period of time.*

4-Nitrobenzenesulfonyl azide (1132).



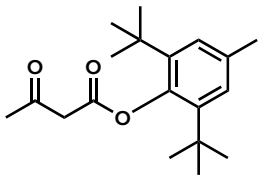
1132

Sodium azide (3.22 g, 49.6 mmol, 1.1 eq.) was dissolved in H_2O–acetone (1:1.6, 36 ml) and the resulting suspension was stirred vigorously. A solution of 4-nitrobenzenesulfonyl chloride (10.5 g, 45.1 mmol, 1.0 eq.) in acetone (24 ml) was added slowly at ambient temperature. After complete addition the resulting suspension was stirred additional 4.0 h at this temperature. Acetone was removed under reduced pressure (T = 20 °C) and the residue was extracted twice with CH_2Cl_2 (50 ml). The organic layers were combined, washed once with brine, and dried

over Na_2SO_4. Volatiles were removed *in vacuo* (T = 20 °C) and the residue was dried under high vacuum for 12 h to obtain azide **1132** as pale yellow solid (10.2 g, 44.8 mmol, 99% yield) which was stored under argon below –18 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.46 (dt, J = 9.1, 2.3 Hz, 2H), 8.16 (dt, J = 9.1, 2.3 Hz, 2H) ppm. ▸ NMR spectra on page 537.

*Note: Caution! Like all sulfonyl azide derivaties, azide **1132** is potentially explosive and should be handled with care.*

2,6-di-*tert*-Butyl-4-methylphenyl 3-oxobutanoate (1133).



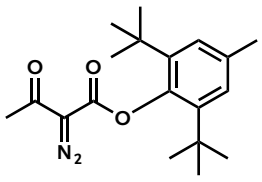
1133

In an opened round-bottom flask, 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (94%, 5.0 ml, 5.47 g, 36.2 mmol, 1.0 eq.) and dibutylhydroxytoluene (7.97 g, 36.2 mmol, 1.0 eq.) were heated in xylenes (8.0 ml) at 150 °C. The evolution of acetone became apparent within several minutes. After 100 min the oil bath was removed and volatile components were evaporated *in vacuo*. The residue was recrystallized from benzene to yield 1,3-dicarbonyl **1133** as white powder (8.58 g, 28.2 mmol, 78% yield). R_f = 0.85 (hexanes–EtOAc, 4:1, stains intensely dark blue with CAN). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.16 (s, 0.5H), 7.14 (s, 2H), 5.34 (s, 0.5H), 3.74 (s, 1H), 2.40 (s, 1.3H), 2.33 (s, 3H), 2.08 (s, 1.7H), 1.34 (d, J = 5.1 Hz, 18H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.2, 177.6, 173.4, 167.8, 145.5, 145.1, 142.4, 142.0, 135.1, 134.8, 127.3, 127.1, 90.6, 50.9, 35.4, 35.3, 31.6, 31.5, 30.9, 30.5, 21.7, 21.7, 21.6 ppm. **HRMS** (ESI): calcd. for $C_{19}H_{28}NaO_3$ $[M + Na]^+$ 327.1936, found 327.1936.

▸ NMR spectra on page 537.

*Note: **1133** appears as keto–enol tautomers, approx. 1:1 ratio.*

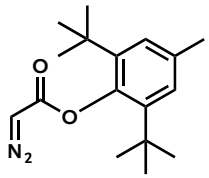
2,6-di-*tert*-Butyl-4-methylphenyl 2-diazo-3-oxobutanoate (1134).



1134

Dibutylhydroxytoluene[663] (5.51 g, 25.0 mmol, 1.0 eq.), NaOAc (211 mg, 2.6 mmol, 0.1 eq.) and *p*-ABSA (7.83 g, 32.6 mmol, 1.3 eq.) were dissolved in anhydrous acetonitrile (20 ml). The reaction mixture was refluxed and a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (94%, 6.9 ml, 50.0 mmol, 2.0 eq.) in anhydrous acetonitrile (5.0 ml) was added dropwise over a period of 30 min to the reaction mixture. After complete addition, the reaction mixture was refluxed for additional 10 h and then stirring was continued for additional two days at ambient temperature. The diazoacetoacetate product was isolated by adding NaOH (15% aq. solution) and extracting with ether, washing the ether extract with water and then drying the extract over $MgSO_4$. Evaporation of the ether left a brown oil that was subjected to acetyl cleavage. R_f = 0.70 (hexanes–EtOAc, 10:1).

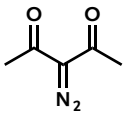
2,6-di-*tert*-Butyl-4-methylphenyl 2-diazoacetate (615).



615

The crude diazo compound **1134** was dissolved in 70 ml of acetonitrile and KOH (5% aq. solution, 70 ml) was added to the solution. The resulting mixture was stirred for 2 h at ambient temperature at which a yellow solid precipitated. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with water. The solid was dried *in vacuo* to obtain title compound **615** as a yellow solid. The yield can by increased by storage of the residual filtrate at –18 °C for several days (additional precipitation of deacetylated product). It was observed, that the yield varies between 25% and 75% (over two steps) and highly depends on the quality of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.12 (d, J = 0.8 Hz, 2H), 5.01 (br s, 1H), 2.32 (s, 3H), 1.36 (s, 18H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 142.6, 134.9, 127.2, 47.5 (C=N_2, very weak), 35.4, 31.7, 21.7 ppm. **IR** (neat): 2114, 1697, 1335, 1183, 1109, 915, 859, 733, 676 cm^{-1}. **HRMS** (ESI): calcd. for $C_{17}H_{24}N_2NaO_2$ $[M + Na]^+$ 311.1735, found 311.1735. ▸ *NMR spectra on page 538.*

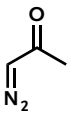
3-Diazopentane-2,4-dione (1135).



1135

Acetylacetone (2.0 g, 20.0 mmol, 1.0 eq.) was dissolved in absolute acetonitrile (100 ml) and *p*-ABSA (4.80 g, 20.0 mmol. 1.0 eq.) was added in one portion at ambient temperature. The reaction mixture was cooled down to 0 °C and Et_3N (8.3 ml, 60.0 mmol, 3.0 eq.) was added over 25 min at 0 °C. After complete addition the reaction mixture was stirred 30 min at 0 °C, then additional 60 min at ambient temperature (monitored by TLC). The white precipitate was removed *via* filtration and the filtrate were triturated with pentane–ether (1:1) and the precipitated white solids were again removed *via* filtration. Volatile components were removed *in vacuo* and the residue was purified *via* flash column chromatography (pentane–ether, 1:1) to obtain diazo **1135** as yellow oil (2.52 g, 20.0 mmol, quantitative yield). R_f = 0.35 (pentane–ether, 2:1). **^{1}H NMR** (200 MHz, C_6D_6) δ = 1.89 (s, 6H) ppm. ▸ *NMR spectra on page 539.*

1-Diazopropan-2-one (621).



621

Diazo **1135** (2.52 g, 20.0 mmol, 1.0 eq.) was stirred in 1 N NaOH–ether (1:1, 200 ml) at ambient temperature for 90 min (monitored by TLC). The layers were separated and the aqueous layer was washed four times with CH_2Cl_2 (10 ml). The combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure (T = 20 °C, p = 300 mbar) to obtain diazo **621** as yellow oil. IR analysis confirmed the existence of a diazo group (ν = 2104 cm^{-1}). R_f = 0.24 (pentane–ether, 2:1). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 5.25 (br s, 1H), 2.12 (s, 3H) ppm.

Note: Caution! If possible, avoid glass apparatus with ground joints and sharp surfaces.

A.2.5 Other Reagents

Samarium(II) iodide [Kagan's Reagent] (**1136**).[663]

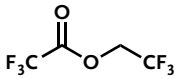
SmI_2
1136

Preliminary work: in the absence of light, commercial 1,2-diiodoethane was dissolved in ether and washed four times sat. aq. $Na_2S_2O_3$ and then once with brine. The solution was dried over Na_2SO_4, transferred into an amber round-bottom flask, and the solvent was removed *in vacuo*. The resulting bright white needles/plates were dried additional 30 min under high vacuum prior to use.

A flame-dried Schlenk tube was charged with samarium (451 mg, 3.0 mmol, 1.0 eq.) and freshly washed 1,2-diiodoethane (423 mg, 1.5 mmol, 0.5 eq.). The Schlenk tube was wrapped in tin foil and was evacuated and backfilled with argon (three times). Under an argon atmosphere, absolute THF (15.0 ml) was added at ambient temperature. After stirring for two minutes, the Schlenk tube was evacuated (carefully) one more time, backfilled with argon and stirred at least 12 h at ambient temperature. This procedure yields in an approx. 0.1 M deep blue solution of SmI_2. To get the exact concentration, the SmI_2 solution can be titrated following the procedure of Hilmersson[664] (reduction of 2-heptanone using mixtures of SmI_2, triethylamine, and water).

Note: Storage is possible for several days under argon in the absence of light. Re-titration is recommended.

2,2,2-Trifluoroethyl 2,2,2-trifluoroacetate (840).[665]



840

Trifluoroacetic anhydride (10.0 ml, 14.9 g, 70.8 mmol, 1.0 eq.) was mixed with 2,2,2-trifluoroethanol (5.0 ml, 6.63 g, 66.2 mmol, 0.94 eq.) at 0 °C under argon atmosphere. The clear reaction mixture was then refluxed for 8 h and left standing for additional 12 h at ambient temperature. $CaCO_3$ (7.09 g, 70.8 mmol, 1.0 eq.) was added at ambient temperature and the reaction mixture was stirred at this temperature for additional 60 min. The condenser was removed and a distillation apparatus was placed on the flask. Distillation (55 °C, 1 atm; distillation under argon atmosphere; collection of the product in a Schlenk tube) afforded ester **840** as colorless oil (11.7 g, 59.5 mmol, 84% yield) which was stored in a Schlenk tube under argon in a glove box. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.68 (q, J = 7.9 Hz, 2H) ppm.

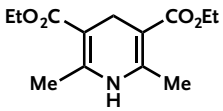
▸ NMR spectra on page 540.

CrO_3, aq. H_2SO_4 [Jones Reagent] (**842**).

CrO_3
aq. H_2SO_4
842

A typical procedure for the generation of Jones reagent is as follows: 6.7 g of CrO_3 were dissolved in 12.5 ml of H_2O. Using water cooling, 5.8 ml of conc. H_2SO_4 was added under stirring. The precipitate was dissolved by addition of a minimum amount of water. This yields in a dark red solution which was stored in the fridge.

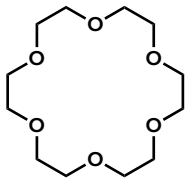
Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate [Hantzsch Ester] (**1137**).



1137

A 500 ml round-bottom flask was charged with ethyl acetoacetate (30.0 g, 231 mol, 1.0 eq.), urotropine (10.8 g, 76.8 mmol, 1/3 eq.) and ethanol (150 ml, undenaturated). The reaction mixture was stirred at ambient temperature and a solution of ammonium phosphate (17.2 g, 115 mmol, 0.5 eq.) in H_2O (30 ml) was added dropwise. After complete addition, the reaction mixture was stirred at 80 °C for 3.0 h. After cooling down to ambient temperature, the resultant precipitate was filtered through a medium porosity sintered-glass funnel, washed with an appropriate amount of cold water and then cold ethanol. The collected solid was dried under high vacuum for 18 h to obtain title compound **1137** as light orange solid (22.7 g, 89.4 mmol, 78% yield). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 5.27 (s, 1H), 4.15 (q, J = 7.1 Hz, 4H), 3.25 (s, 2H), 2.18 (s, 6H), 1.27 (t, J = 7.2 Hz, 6H) ppm. ▸ *NMR spectra on page 540.*

1,4,7,10,13,16-Hexaoxacyclooctadecane [18-crown-6] (**1138**).

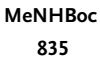

1138

18-crown-6 is commercially available and was never prepared. However, it often requires purification.

A round-bottom flask is charged with commercially available 18-crown-6 (25.0 g). Anhydrous acetonitrile (50 ml) is added and the flask is equipped with a calcium chloride drying tube. The resulting slurry is warmed up to 50 °C and stirred vigorously until all material was dissolved and a clear colorless solution is obtained. The oil bath was removed and the solution allowed to cool down to ambient temperature. The flask was flushed with argon and stored for 24 h in the freezer. The resultant precipitate was filtered through a medium porosity sintered-glass funnel under argon. The white solid was washed with anhydrous dry ice cold acetonitrile. The collected solid was dried under high vacuum with gentle heating (40 °C) for several hours to obtain 18-crown-6 as white powder (approx. 70% yield).

Note: Storage under argon below –10 °C.

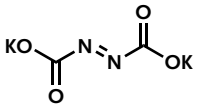
***tert*-Butyl methylcarbamate (835).**[666]


835

A 100 ml round-bottom flask was charged with di-*tert*-butyl dicarbonate (10.9 g, 50.0 mmol, 1.0 eq) and Amberlyst® 15 (hydrogen form, dry; 1.6 g). The mixture was cooled down to 0 °C and methylamine (40 wt. % in H_2O, 4.5 ml, 52.5 mmol, 1.05 eq.) was added dropwise (*strongly exothermic, large amounts of gas are produced*). After complete addition, the cooling bath was removed and the reaction mixture was stirred additional 5 min at ambient temperature. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with MeOH. Rotary evaporation of the filtrate followed by high vacuum for 1.0 h furnished carbamate **835** (6.01 g, 45.8 mmol, 92% yield) as clear colorless oil

which solidified below 10 °C. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 4.55 (s, 1H), 2.70 (d, J = 4.9 Hz, 3H), 1.41 (s, 9H) ppm. ▸ NMR spectra on page 541.

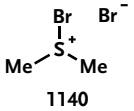
Potassium (*E*)-diazene-1,2-dicarboxylate (1139).[667]



1139

Potassium hydroxide (3.02 g, 53.8 mmol, 2.5 eq.) was dissolved in H_2O and cooled to 0 °C. Azodicarbonamide (2.50 g, 21.5 mmol, 1.0 eq.) was added in small portions at this temperature and vigorous stirring was continued for 30 min. A yellow solid precipitated. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with cold water, then with cold MeOH, and finally with cold ether. After short drying under high vacuum dicarboxylate **1139** was obtained as bright yellow solid (3.90 g, 20.1 mmol 93% yield).
Note: This reagent is used for the in situ generation of diimide $(NH)_2$.

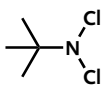
Bromodimethylsulfonium bromide (1140).



1140

A solution of bromine (32.0 g, 200 mmol, 1.0 eq.) in absolute CH_2Cl_2 (40.0 ml) was added to a solution of dimethyl sulfide (12.4 g, 200 mmol, 1.0 eq.) in absolute CH_2Cl_2 (40.0 ml). A yellow solid precipitated and the suspension was stirred for additional 30 min. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with cold ether. The collected solid was dried under high vacuum for 6.0 h to obtain bromide **1140** as yellow solid (40.0 g, 180 mmol 90% yield). **M.p.** 84 °C. **^{1}H NMR** (200 MHz, DMSO) δ = 2.54 (s, 6H) ppm. ▸ NMR spectra on page 541.

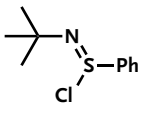
***N,N*-Dichloro-*tert*-butylamine (1141).**[668]



1141

A 1-L round-bottom flask equipped with a mechanical stirrer was charged with *tert*-butylamine (14.3 ml, 10.0 g, 137 mmol, 1.0 eq.) which was dissolved in CH_2Cl_2 (360 ml). Calcium hypochlorite (60%, 68.4 g, 287 mmol, 1.0 eq.) was added and the reaction mixture was cooled down to 0 °C. 3 M HCl (360 ml) was added over a period of 60 min at 0 °C and stirring at this temperature was continued for addition 2 h. Both layers became bright yellow. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (100 ml). The combined organic layers were extracted once with water and once with brine. Drying over Na_2SO_4 followed by solvent removal under reduced pressure (p > 200 mbar) yielded amine **1141** (17.8 g, 125 mmol, 92% yield) as bright yellow oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 1.38 (s, 9H) ppm. ▸ NMR spectra on page 542.
Note: Caution: a large amount of chlorine gas is produced during this reaction. The operation must be carried out in a good hood with adequate ventilation.

N-*tert*-Butylbenzenesulfinimidoyl chloride (1142).



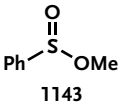
1142

A solution of *S*-phenyl thioacetate (16.5 g, 108 mmol, 1.0 eq.) in anhydrous benzene (55 ml) was added to a solution of *N,N*-Dichloro-*tert*-butylamine (16.2 g, 114 mmol, 1.05 eq.) in anhydrous benzene (55 ml). The reaction mixture was refluxed for 75 min and cooled down to ambient temperature. Volatile components were evaporated *in vacuo* and by azeotropic distillation with benzene (5 times) to obtain title compound **1142** as orange oil (22.7 g, 105 mmol, 97% yield) which partially solidified to a yellow solid by keeping it still or by cooling it below 0 °C. The product was used crude for follow-up reactions. If necessary, purification can be done *via* careful distillation (115 °C, 0.5 mmHg).[606] **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.19 – 8.08 (m, 2H), 7.65 – 7.57 (m, 3H), 1.58 (s, 9H) ppm.

▸ *NMR spectra on page 542.*

*Note: N-tert-Butylbenzenesulfinimidoyl chloride (**1142**) is a useful reagent for the oxidation of various alcohols to the corresponding carbonyl compounds and for the synthesis of α,β-unsaturated carbonyl compounds.*

Methyl benzenesulfinate (1143).[669]

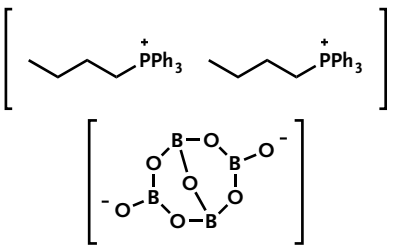


1143

Diphenyl disulfide (4.37 g, 20.0 mmol, 1.0 eq.) was dissolved in absolute MeOH (100 ml) and cooled to 0 °C. NBS (10.7 g, 60.0 mmol, 3.0 eq.) is added in portions at 0 °C and stirring was continued for additional 5 min at this temperature. The cooling bath was removed and the reaction mixture was stirred addition 30 min at ambient temperature. 300 ml of CH_2Cl_2 were added and the reaction mixture was washed twice with bicarb (300 ml) and once with water (300 ml). The organic layer was dried over Na_2SO_4, volatiles were removed under reduced pressure, and the residue was purified *via* flash column chromatography using hexanes–EtOAc (5:1) as eluent. Sulfinate **1143** was obtained as yellow oil (2.70 g, 17.3 mmol, 87% yield). **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 7.73 – 7.63 (m, 2H), 7.57 – 7.47 (m, 3H), 3.45 (s, 3H) ppm.

▸ *NMR spectra on page 543.*

Butyltriphenylphosphonium tetraborate [BTPPTB] (**1008**).[670]



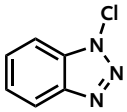
1008

To a solution of Butyltriphenylphosphonium bromide (20.0 g, 50.0 mmol, 1.0 eq.) in absolute MeOH (50.0 ml) was added $NaBH_4$ (1.89 g, 50.0 mmol, 1.0 eq.) in portions at ambient temperature. The mixture was stirred at this temperature for 36 h, very strong evolution of gas during the first 30 min was observed. The solvent was removed *in vacuo* which yielded a white sticky solid which was washed with H_2O (200 ml). The collected solid was dried under high vacuum for 24 h to yield tetraborate **1008** as white fluffy powder (15.6 g, 46.7 mmol, 93% yield). **M.p.** (°C.270) **^{1}H NMR**

(400 MHz, $CDCl_3$) δ = 7.84 – 7.71 (m, 9H), 7.72 – 7.61 (m, 6H), 1.70 – 1.46 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H) ppm.[4]

▸ NMR spectra on page 543.

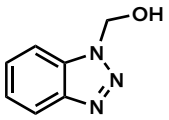
1-Chloro-1*H*-benzo[*d*][1,2,3]triazole (1144).[671]



1144

Commercial bleach (10% NaOCl, 64 ml, 96.0 mmol, 1.2 eq.) was added dropwise to a solution of benzotriazole (9.53 g, 80.0 mmol, 1.0 eq.) in 50% aqueous acetic acid (40 ml) at ambient temperature. After complete addition the reaction mixture was stirred additional 120 min at this temperature at which a white solid precipitated. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with water until the filtrate was neutral (approx. 300 ml). The collected solid was dried under high vacuum in the absence of light for 18 h to obtain title compound **1144** as white solid (11.7 g, 76.2 mmol, 95% yield) which was transferred to an argon flushed amber-glass bottle and stored in a freezer. **M.p.** 104 °C.

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)methanol (1145).[672]

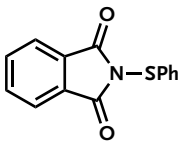


1145

A mixture of benzotriazole (6.00 g, 50.4 mmol, 1.0 eq.), formalin (38% in H_2O, 3.98 g, 3.7 ml, 1.0 eq.), glacial acetic acid (50 ml) and H_2O (100 ml) was slowly stirred at ambient temperature for 120 min. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was washed with ice-cold water. The collected solid was recrystallized from H_2O and dried 18 h *in vacuo* to obtain title compound **1145** as white solid (6.85 g, 45.9 mmol, 91% yield). **M.p.** 145 °C.

*Note: Benzotriazolylmethanol (**1145**) has proved to be a useful and versatile tool in synthesis since it generates* in situ *formaldehyde under anionic conditions.*[673]

2-(Phenylthio)isoindoline-1,3-dione (996).



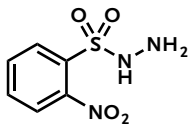
996

Phthalimide (14.7 g, 100 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (40.0 ml) and diphenyl disulfide (11.5 g, 52.5 mmol, 0.53 eq.) was added. The reaction mixture was heated until complete dissolution of all materials. After cooling down to ambient temperature (small amounts of materials re-precipitated) a solution of bromine (9.6 g, 3.1 ml, 60.0 mmol, 0.6 eq.) in acetonitrile (50.0 ml) was added over a period of 60 min at ambient temperature. After complete addition, the reaction mixture was stirred 2.0 h at this temperature. H_2O (100 ml) was added over a period of 30 min which started the precipitation of the product. After complete addition, the reaction mixture was cooled down to 0 °C and stirred additional 30 min for full precipitation. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was washed with a minimum amount of ice-cold water. The collected solid was dried *in vacuo* and complete removal of H_2O residues was achieved by azeotropic distillation with benzene (5 times). Drying

[4] CH_2–P signals diminished

under high vacuum for 18 h in the absence of light furnished phthalimide derivative **996** as a pale yellow fluffy solid (22.6 g, 88.5 mmol, 89% yield) which was transferred to an argon flushed amber-glass bottle and stored in a freezer. **M.p.** 158 °C (lit. 161 °C).[674] **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.92 (dd, J = 5.5, 3.1 Hz, 2H), 7.77 (dd, J = 5.5, 3.1 Hz, 2H), 7.61 – 7.55 (m, 2H), 7.34 – 7.28 (m, 3H) ppm. ▸ NMR spectra on page 544.

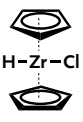
2-Nitrobenzenesulfonohydrazide [NBSH] (**1146**).[675]



1146

2-Nitrobenzenesulfonyl chloride (22.2 g, 100 mmol, 1.0 eq.) was dissolved in anhydrous THF (100 ml) and cooled down to –30 °C under an argon atmosphere. $N_2H_4 \cdot H_2O$ (12.2 ml, 12.5 g, 250 mmol, 2.5 eq.) was added dropwise to this solution. After complete addition, the dropping funnel was rinsed with anhydrous THF (5 ml) and the reaction mixture was stirred 30 min at –30 °C. EtOAc (200 ml) was added at –30 °C and the mixture was washed quickly five times with 10% ice-cold aqueous NaCl (150 ml). The organic layer was dried over Na_2SO_4 at 0 °C and filtered. The filtrate was added slowly (over 5 min) to hexanes (1200 ml) at ambient temperature. White solid precipitated immediately. After additional 15 min the mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with hexanes. The collected solid was dried *in vacuo* for 18 h to obtain hydrazide **1146** as a pale yellow solid (19.1 g, 88.0 mmol, 88% yield) which was transferred to an argon flushed amber-glass bottle and stored in a freezer. R_f = 0.20 (hexanes–EtOAc, 1:2). **M.p.** 94 °C (lit. 100 °C). **^{1}H NMR** (200 MHz, CD_3CN) δ = 8.14 – 8.00 (m, 1H), 7.93 – 7.74 (m, 3H), 6.92 (br s, 1H), 3.98 (br s, 2H) ppm. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 8.34 – 8.11 (m, 1H), 7.93 – 7.75 (m, 3H), 6.52 (br s, 1H) ppm. ▸ NMR spectra on page 544.

Chloridobis(η^5-cyclopentadienyl)hydridozirconium [Schwartz's reagent] (**1147**).[676]



1147

To zirconocene dichloride (1.46 g, 5.00 mmol, 1.0 eq.) in THF (12 ml) in a flame-dried Schlenk tube was added dropwise DIBAL (1.0 M in THF, 5.00 ml, 5.00 mmol, 1.0 eq.) at 0 °C. The resultant suspension was stirred for 45 min before the supernatant liquid was removed with a syringe. The white solid remaining in the tube was washed thrice with THF (5 ml). Solvent residues were removed *in vacuo* and the remaining solid was dried under high vacuum to provide $Cp_2Zr(H)Cl$ (**1147**) as white powder which was stored under argon atmosphere and below 0 °C.

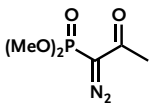
Bis(triphenylphosphine)palladium(II) dichloride (1148).

$Pd(PPh_3)_2Cl_2$
1148

Triphenylphosphine (5.56 g, 21.2 mmol, 2.2 eq.) was added to a solution of palladium(II) chloride (1.71 g, 9.64 mmol, 1.0 eq.) in 50 ml of benzonitrile and the reaction mixture was stirred at 180 °C under argon atmosphere. After 20 min, the heat source was removed and the reaction mixture was allowed to cool down slowly to room temperature.

The precipitated yellow solid was filtered off under argon atmosphere using a Schlenk frit and washed twice with ether. Extensive drying under high vacuum in the absence of light provided bis(triphenylphosphine)palladium(II) dichloride (**1148**) as a bright yellow solid (6.61 g, 9.42 mmol, 98%), which was stored in the glove box for use.

Dimethyl (1-Diazo-2-oxopropyl)phosphonate [Bestmann-Ohira Reagent] (**1149**).[677,678]



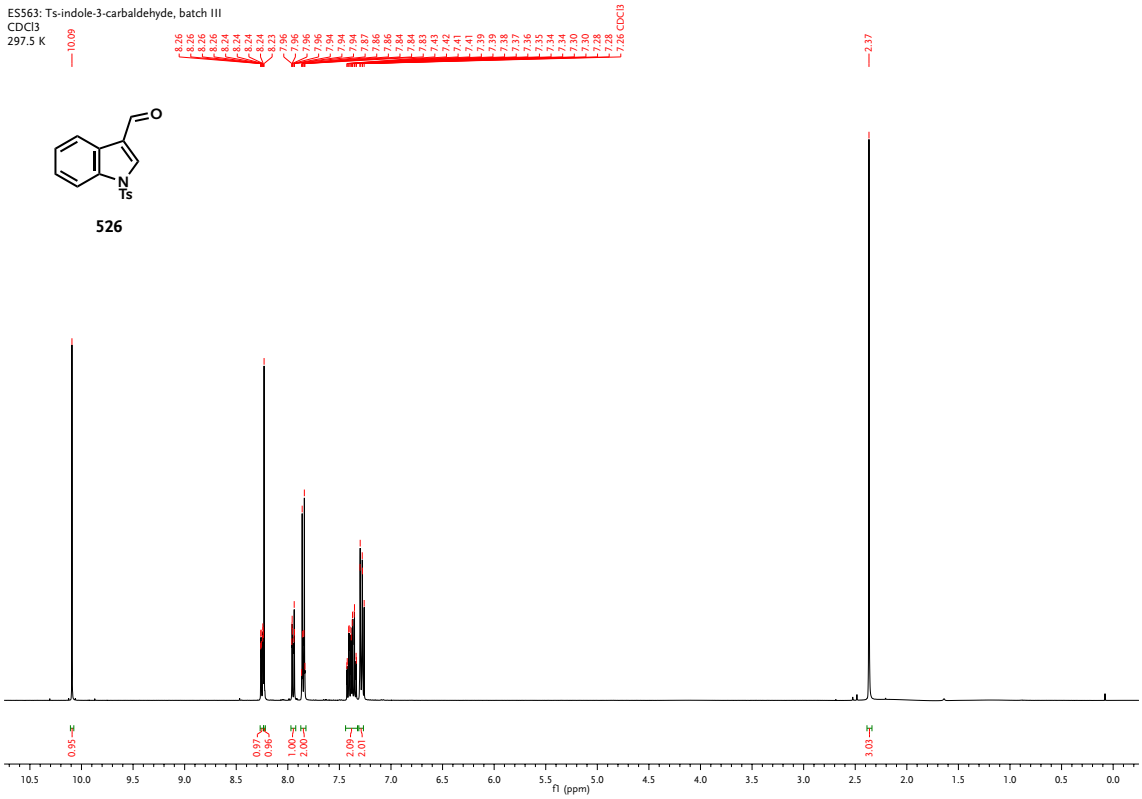
1149

General procedure: Stirring of a mixture of chloroacetone (1.0 eq.), potassium iodide (1.0 eq.), and trimethyl phosphite (1.0 eq.) in acetone–acetonitrile (6:5, 2.0 M) for 6 h at 20 °C and for 4 h at 50 °C in the air followed by simple filtration and distillation (83 °C, 0.04 mmHg) furnished dimethyl (2-oxopropyl)phosphonate as colorless liquid.

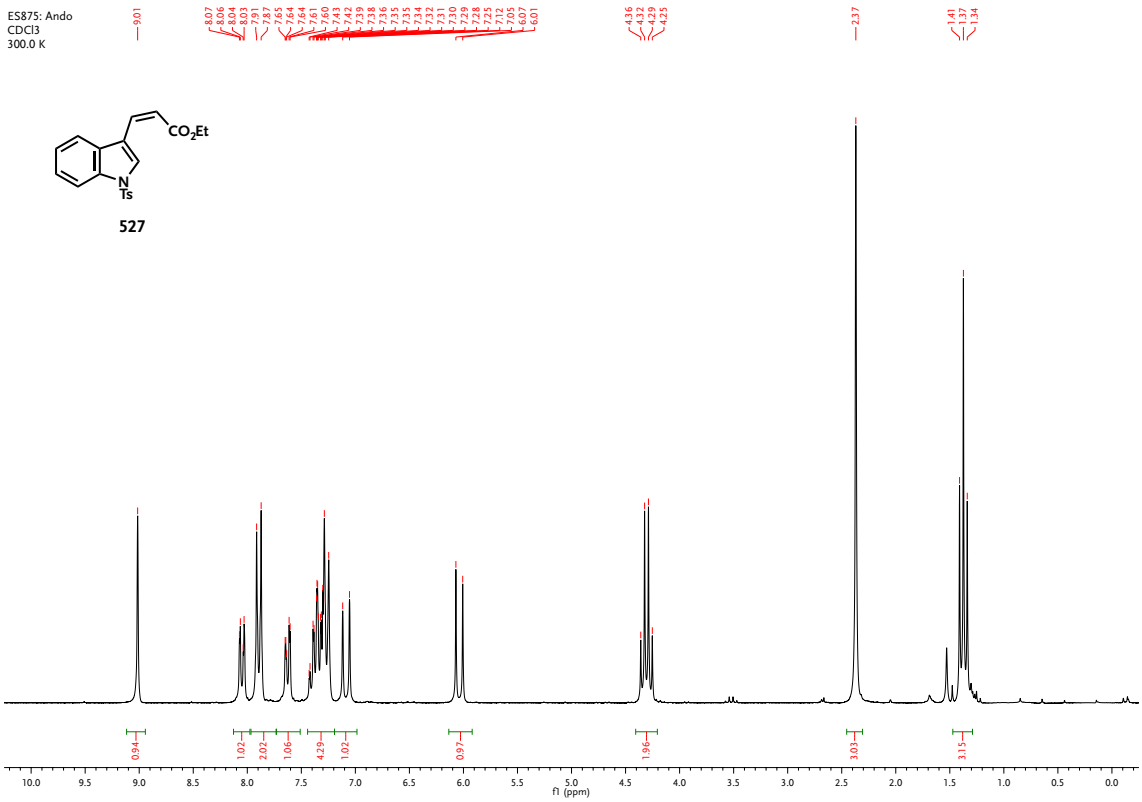
To an ice-cold solution of NaH (60% dispersion in mineral oil, 1.1 eq.) in anhydrous benzene–THF (3:1, 0.2 M) was added a solution of dimethyl (2-oxopropyl)-phosphonate (1.0 eq) in anhydrous benzene (1.0 M). The white suspension was stirred for 1 h at room temperature before a solution of 4-methylbenzenesulfonyl azide (**841**, 1.05 eq.) in anhydrous benzene (2.0 M) was added. The reaction mixture was stirred overnight at room temperature, then filtered over a plug of celite and concentrated *in vacuo* to obtain diazo **1149** as an orange oil. **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 3.80 (d, 6H), 2.22 (s, 3H) ppm. NMR data matches the reported.

NMR Spectra

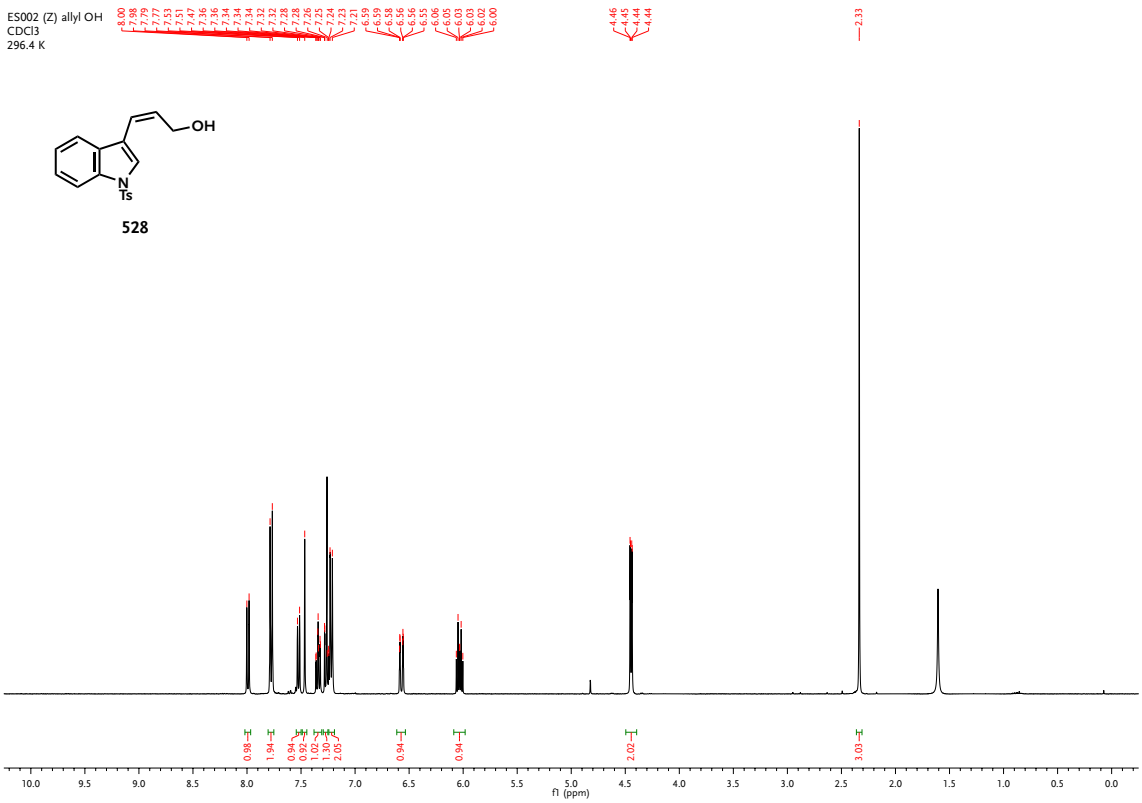
B



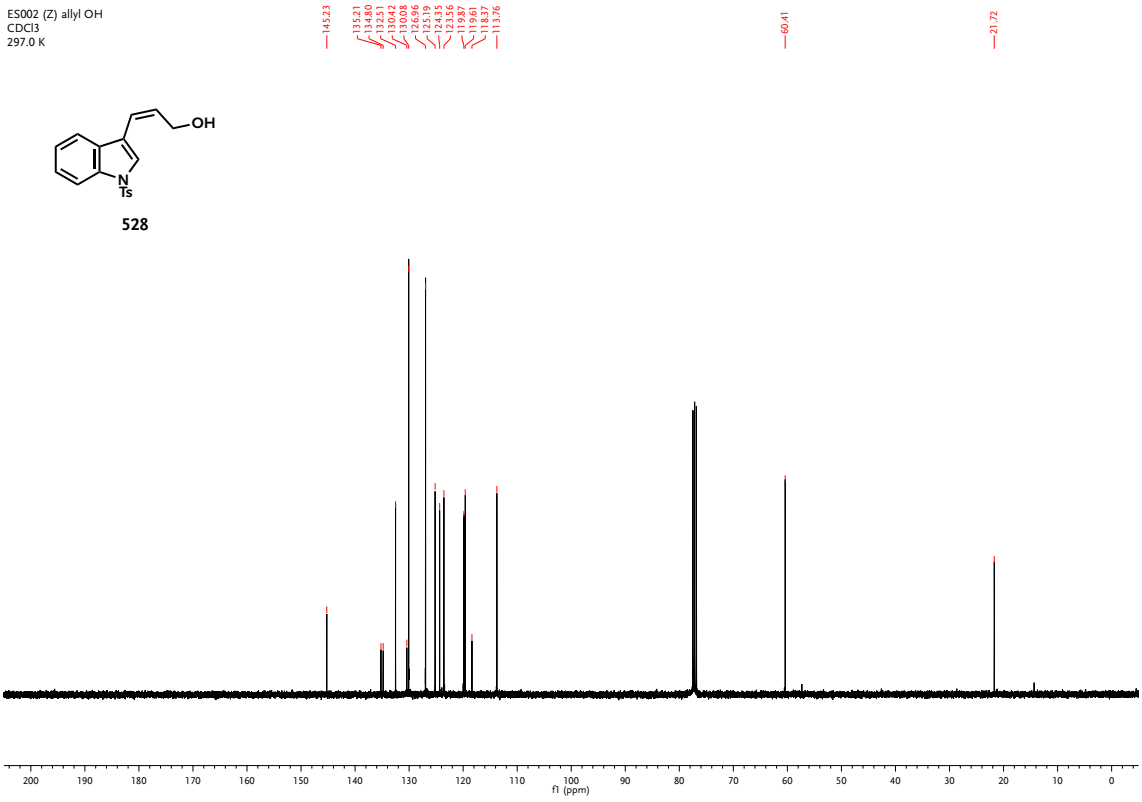
Spectrum B-1. ^{1}H-NMR spectrum for compound **526** *(experimental on page 195)*.



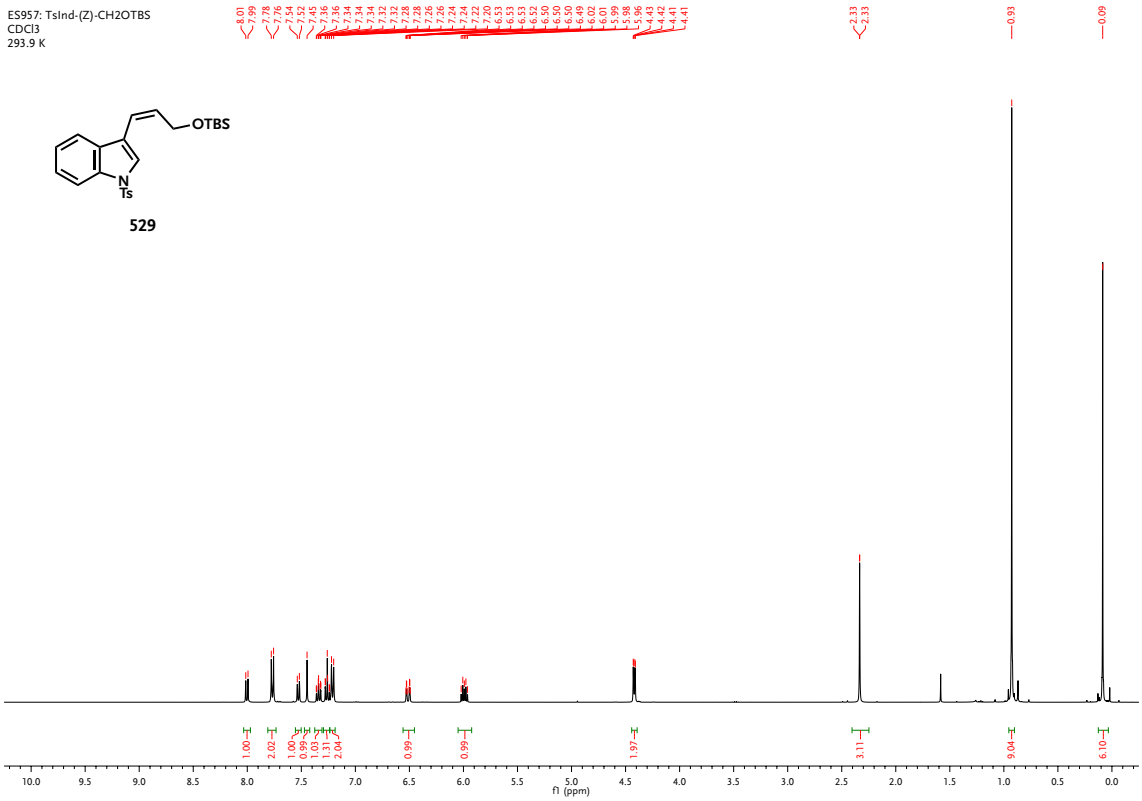
Spectrum B-2. ^{1}H-NMR spectrum for compound **527** *(experimental on page 196)*.



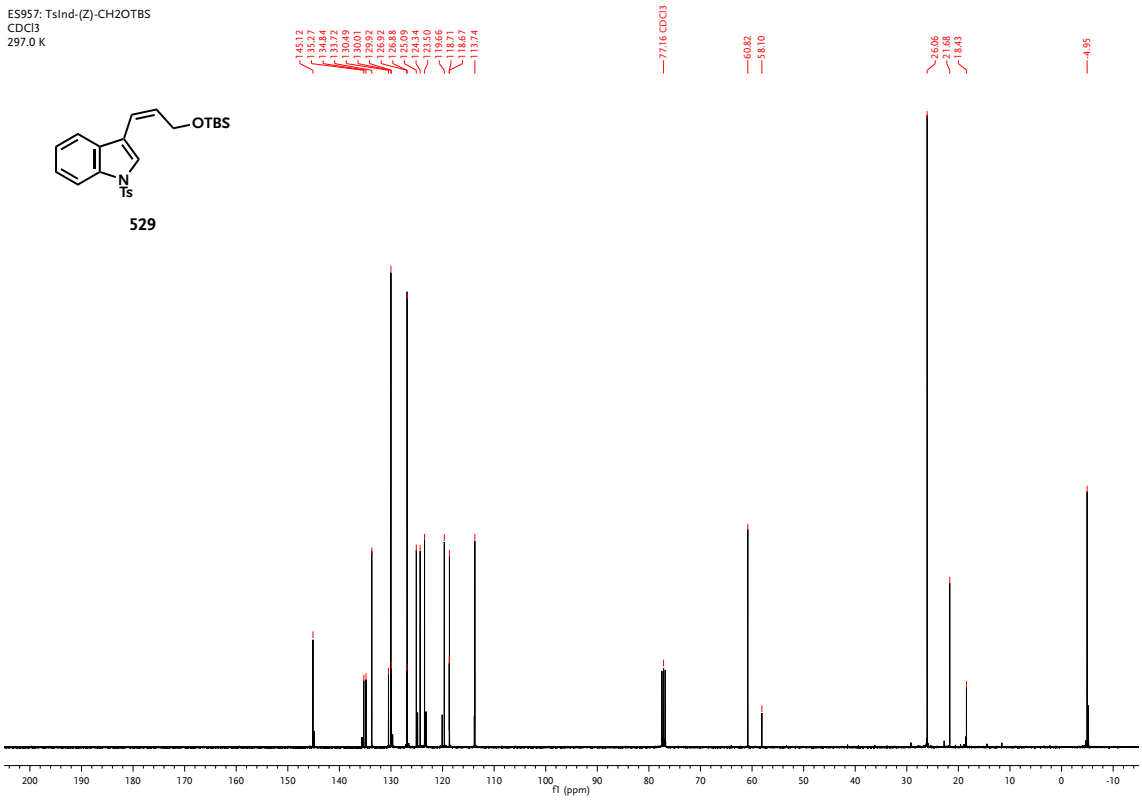
Spectrum B-3. ^{1}H-NMR spectrum for compound **528** *(experimental on page 196)*.



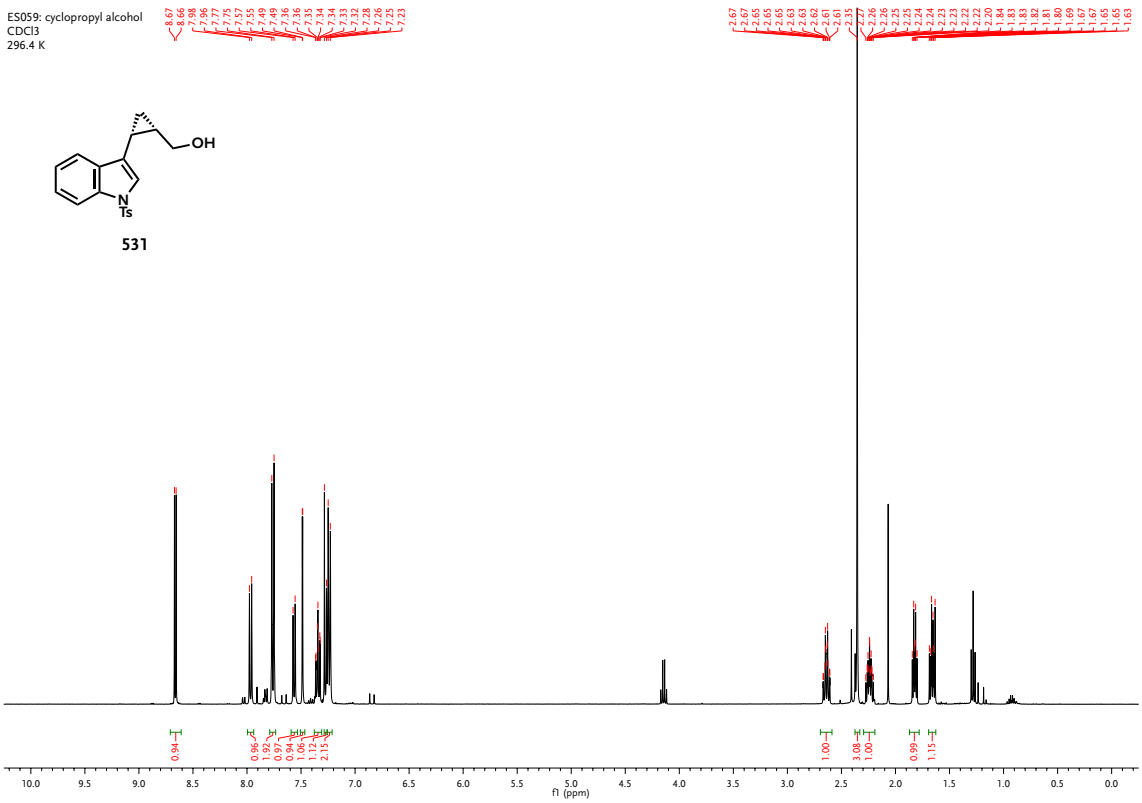
Spectrum B-4. ^{13}C-NMR spectrum for compound **528** *(experimental on page 196)*.



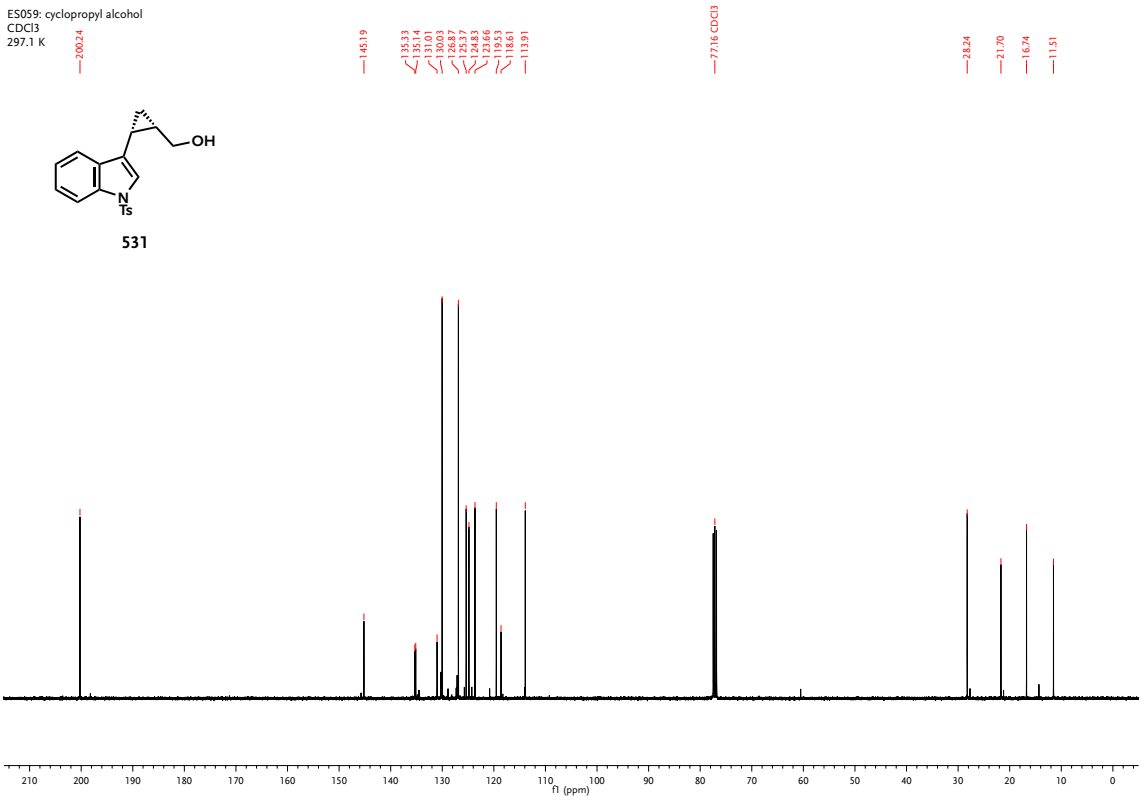
Spectrum B-5. ^{1}H-NMR spectrum for compound **529** *(experimental on page 197)*.



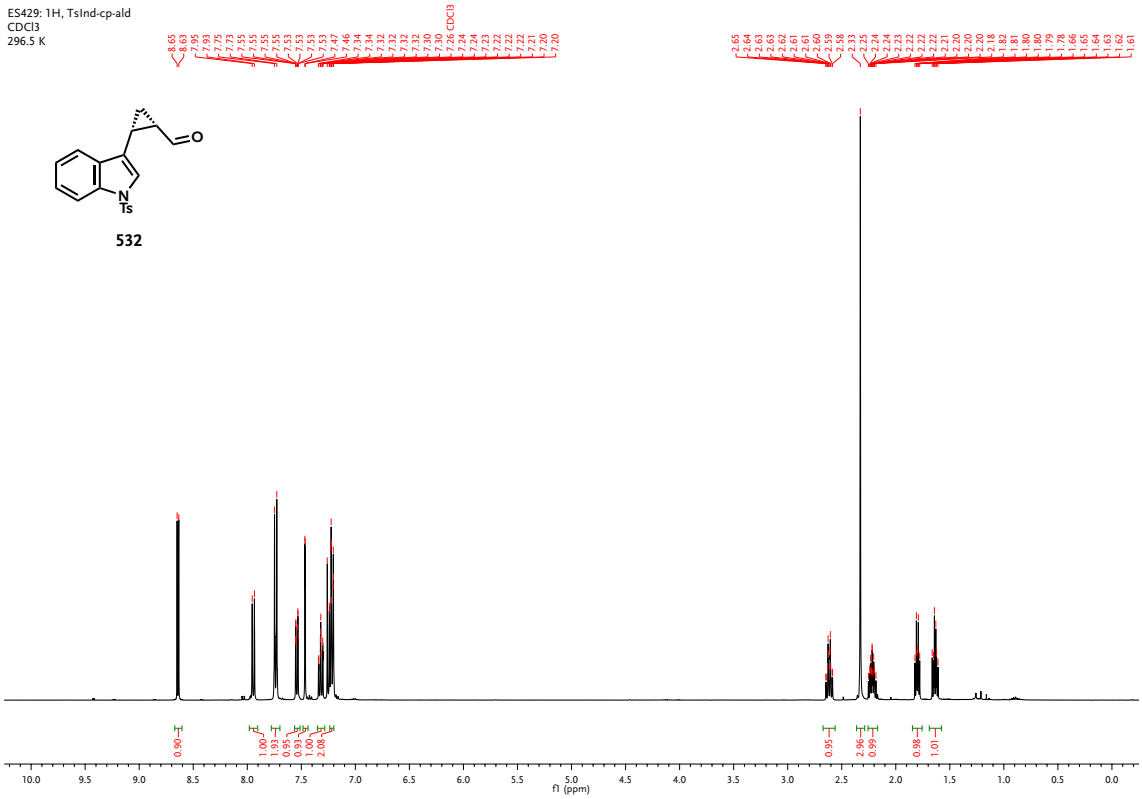
Spectrum B-6. ^{13}C-NMR spectrum for compound **529** *(experimental on page 197)*.



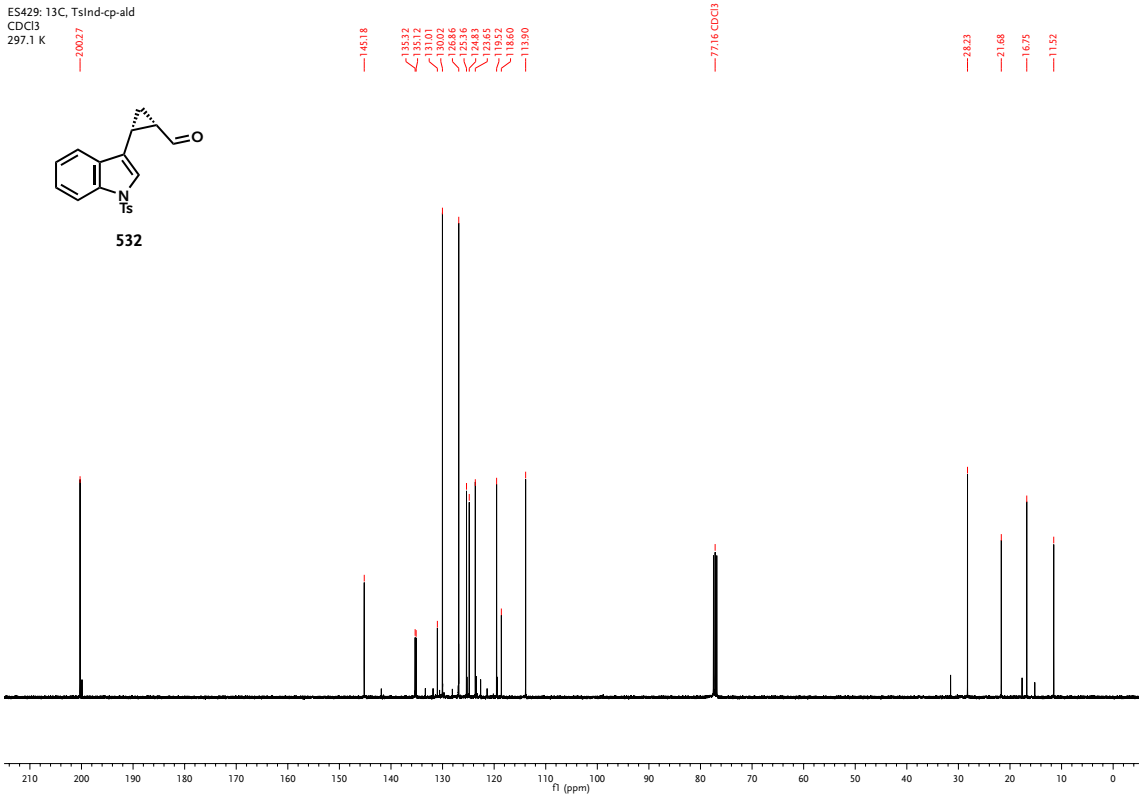
Spectrum B-7. ^{1}H-NMR spectrum for compound **531** *(experimental on page 197)*.



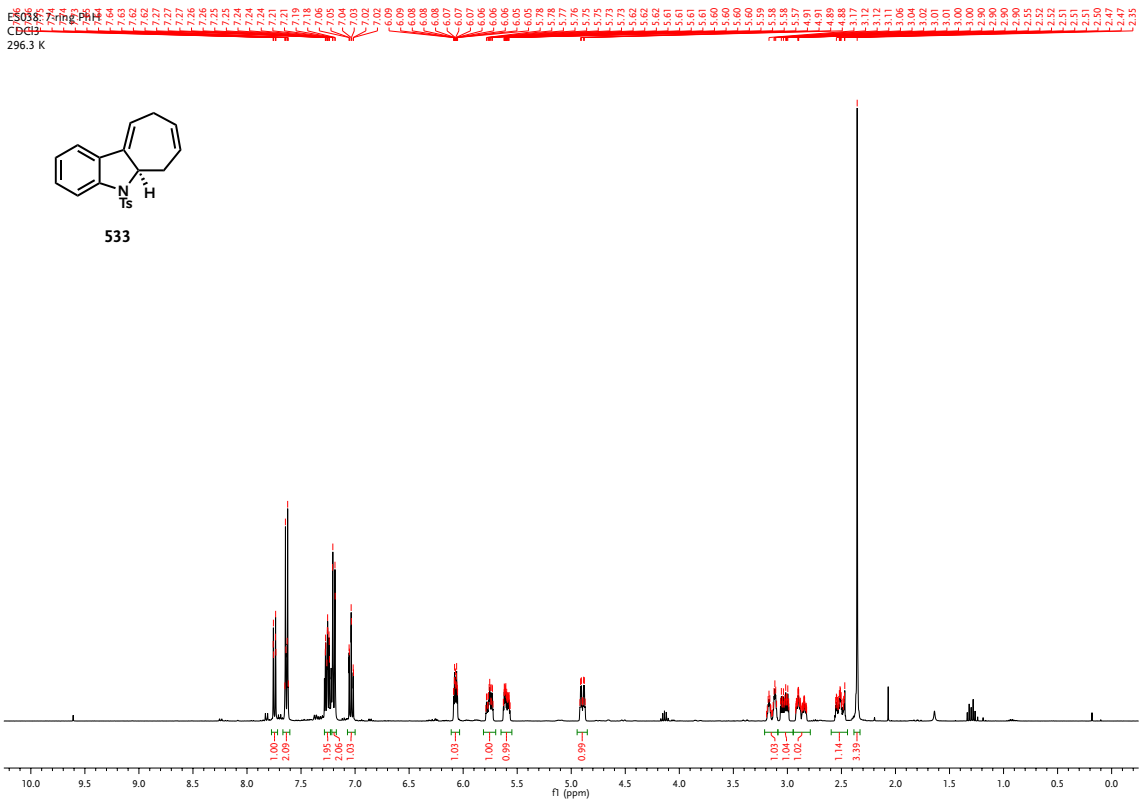
Spectrum B-8. ^{13}C-NMR spectrum for compound **531** *(experimental on page 197)*.



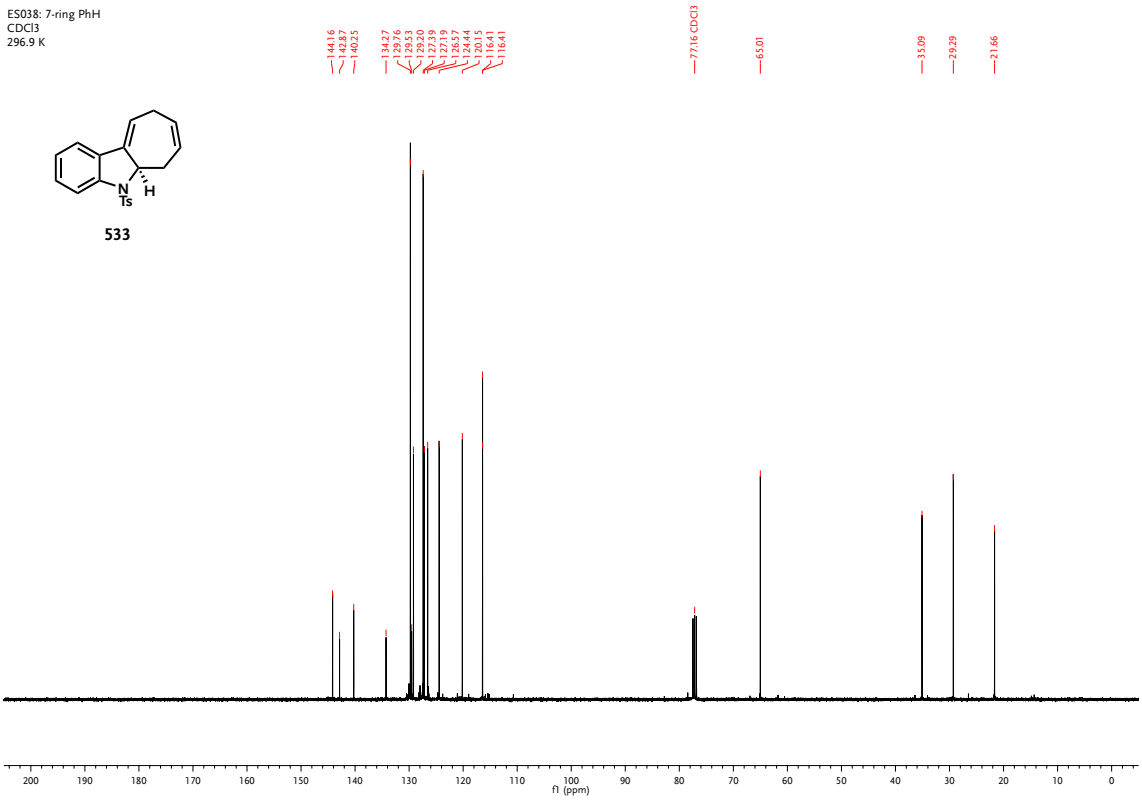
Spectrum B-9. ^{1}H-NMR spectrum for compound **532** *(experimental on page 198)*.



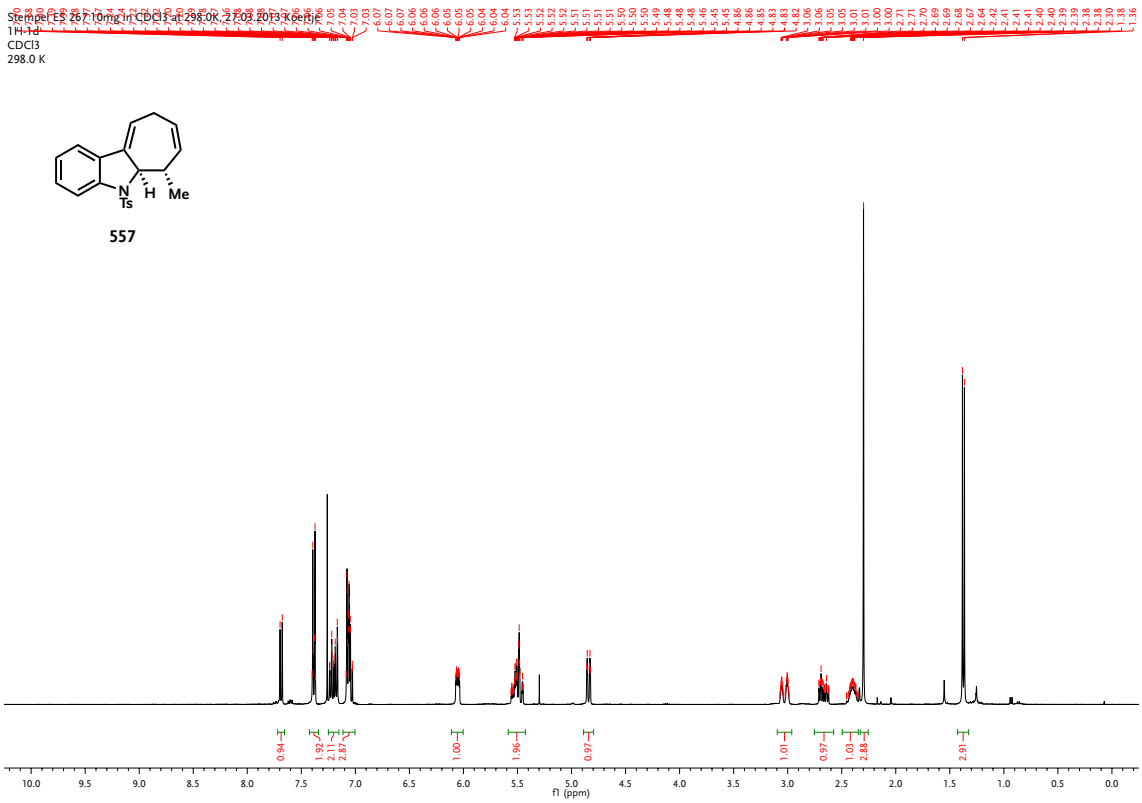
Spectrum B-10. ^{13}C-NMR spectrum for compound **532** *(experimental on page 198)*.



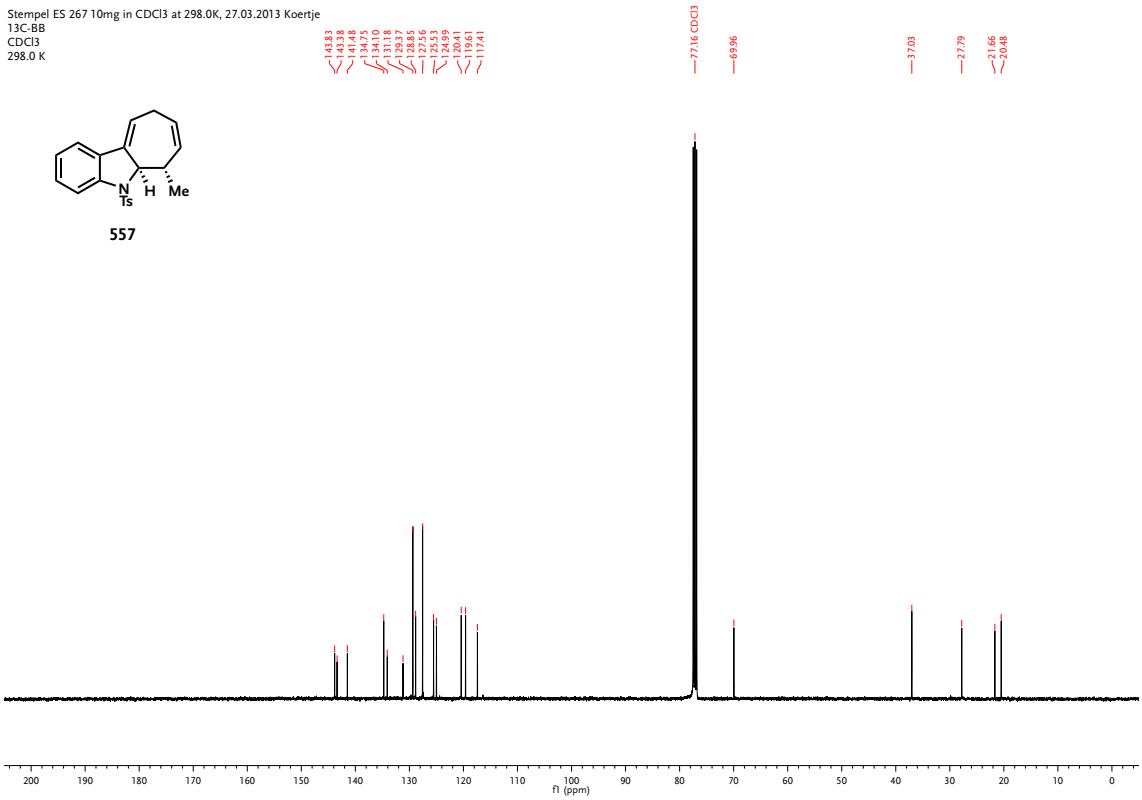
Spectrum B-11. ^{1}H-NMR spectrum for compound **533** *(experimental on page 199)*.



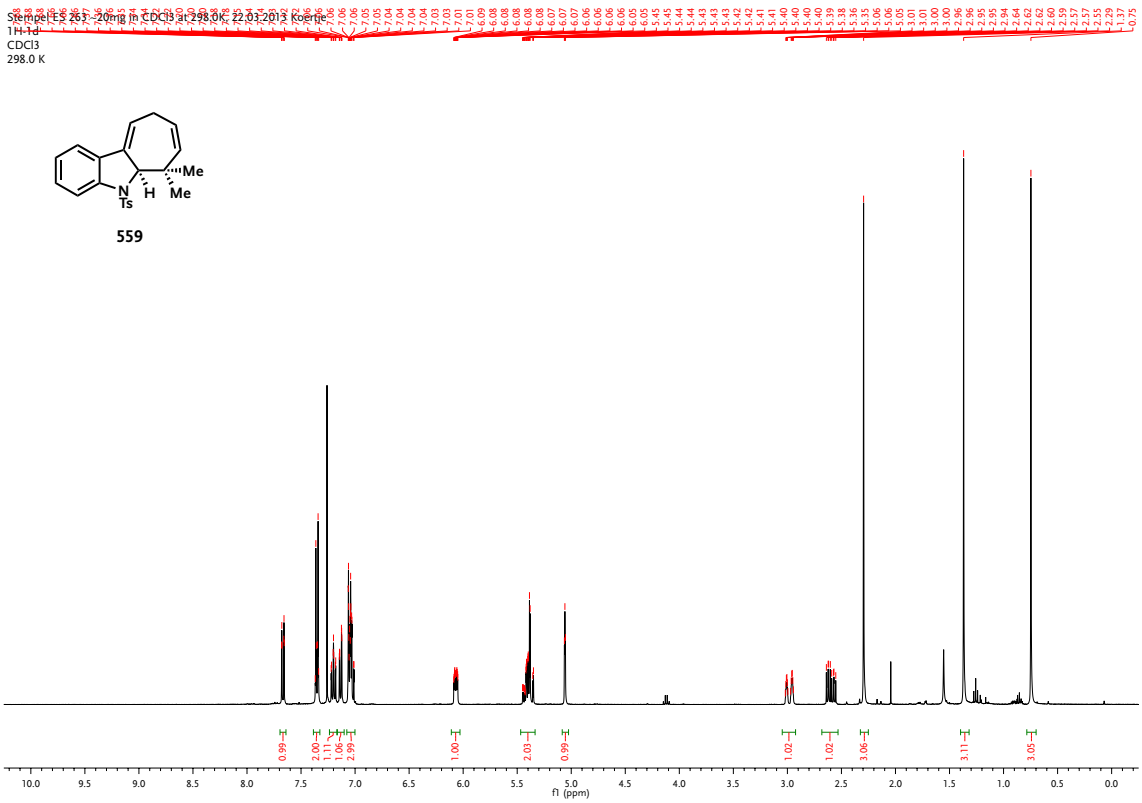
Spectrum B-12. ^{13}C-NMR spectrum for compound **533** *(experimental on page 199)*.



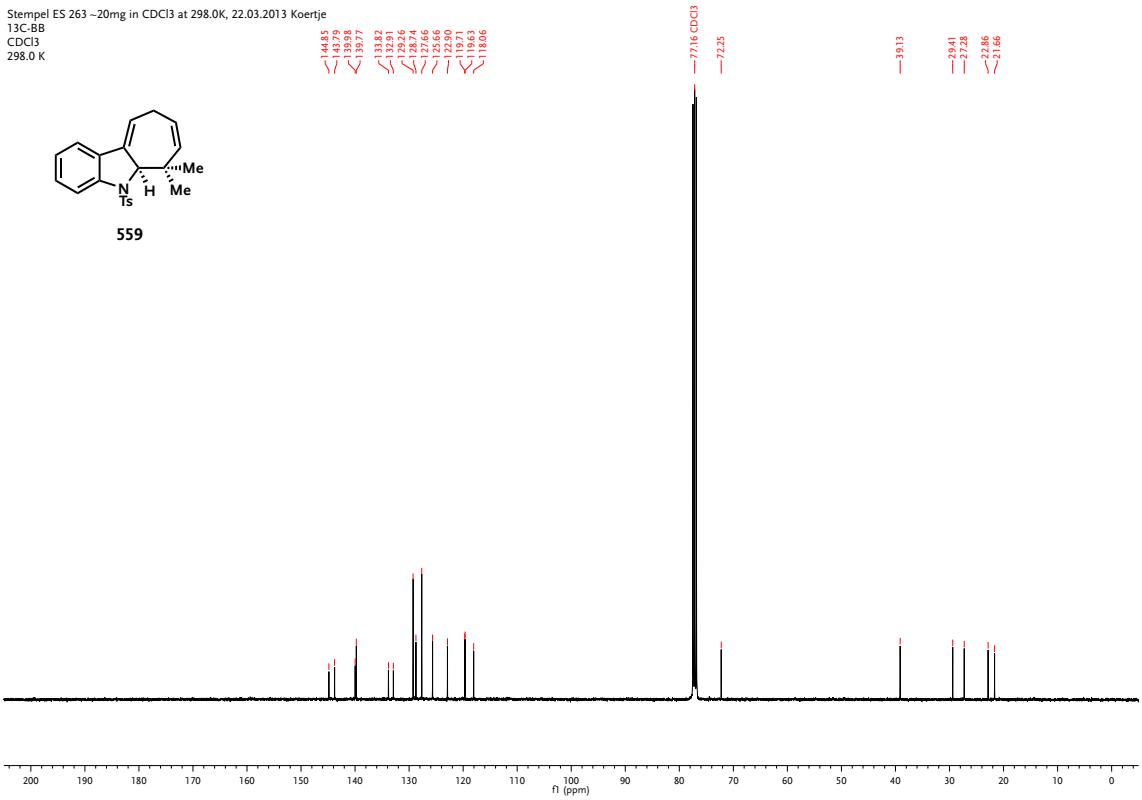
Spectrum B-13. ^{1}H-NMR spectrum for compound **557** *(experimental on page 199)*.



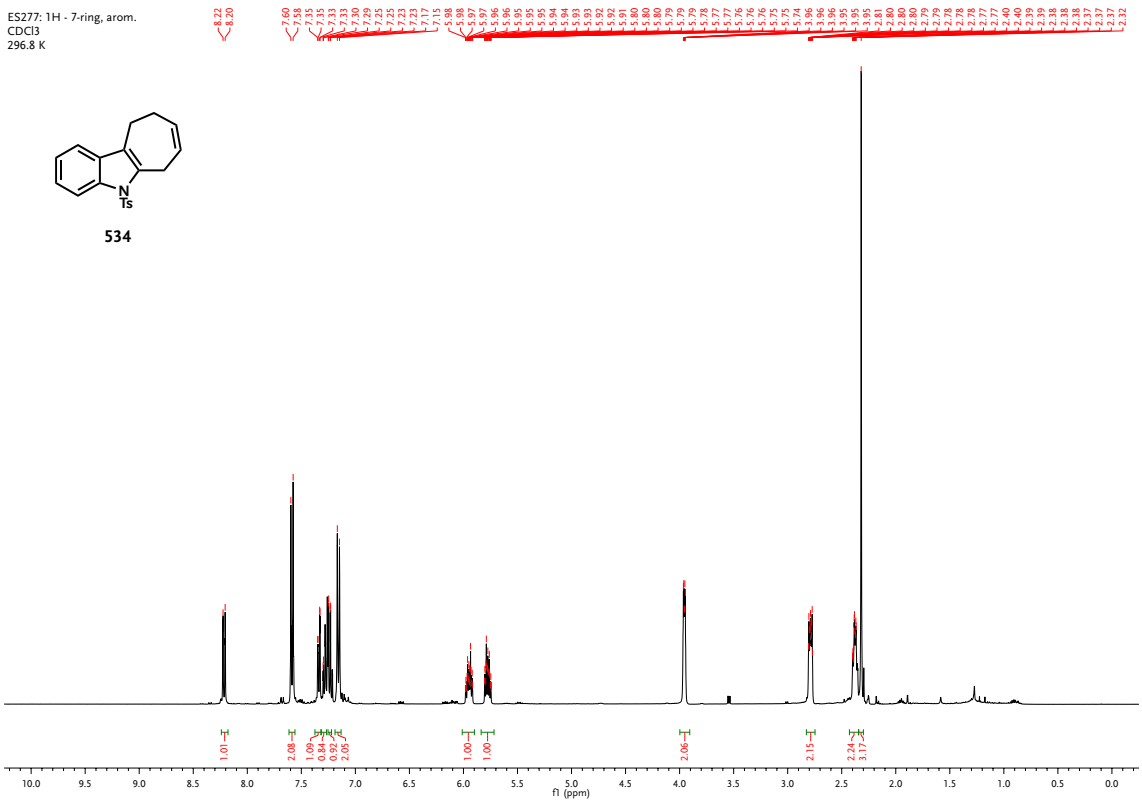
Spectrum B-14. ^{13}C-NMR spectrum for compound **557** *(experimental on page 199)*.



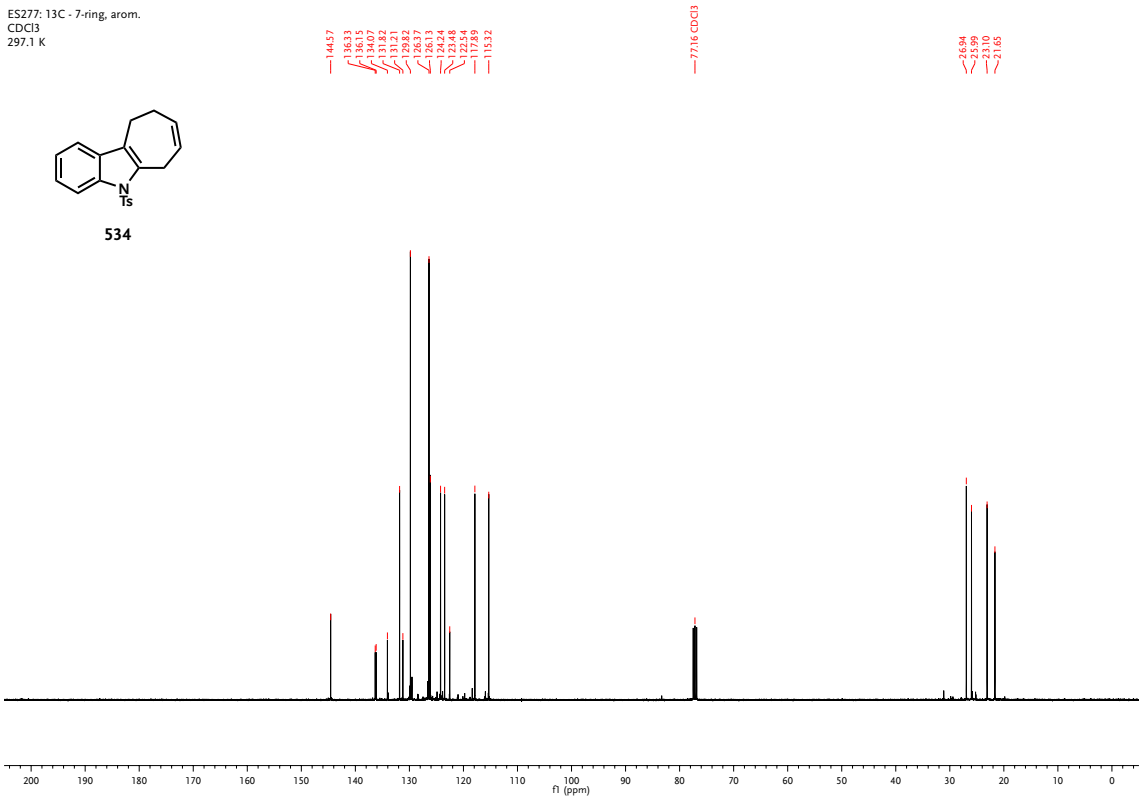
Spectrum B-15. ^{1}H-NMR spectrum for compound **559** *(experimental on page 199)*.



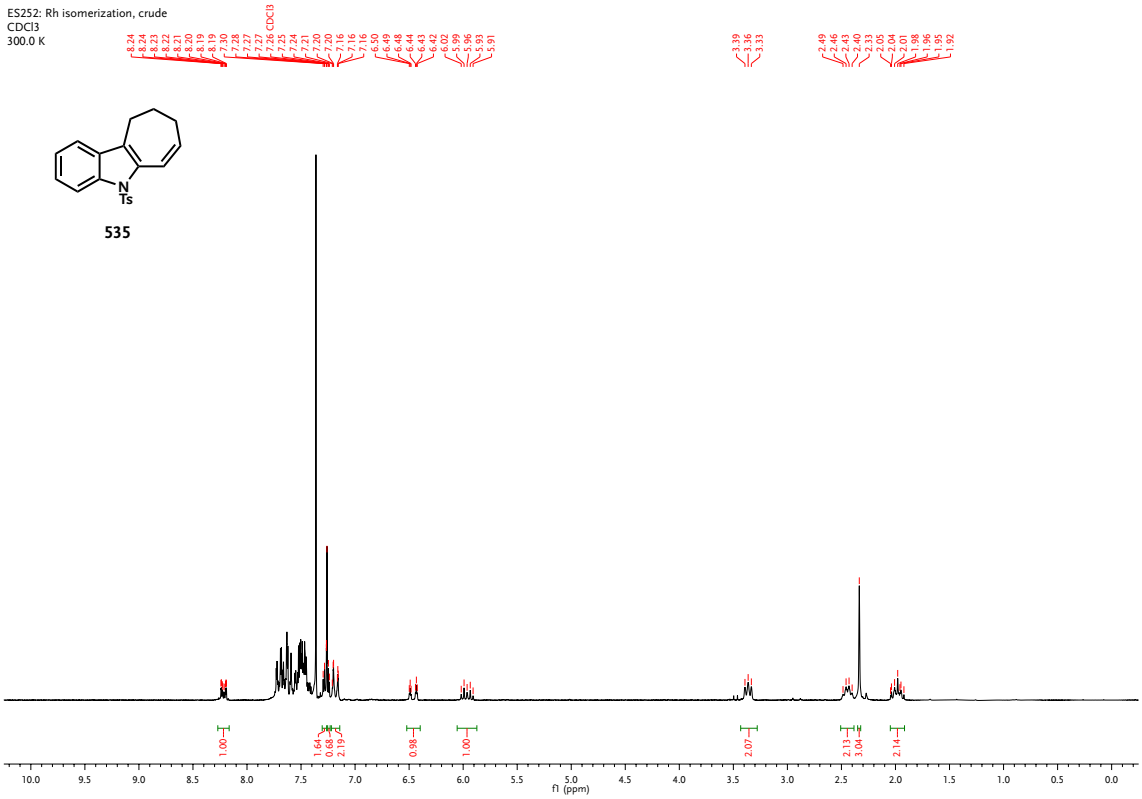
Spectrum B-16. ^{13}C-NMR spectrum for compound **559** *(experimental on page 199)*.



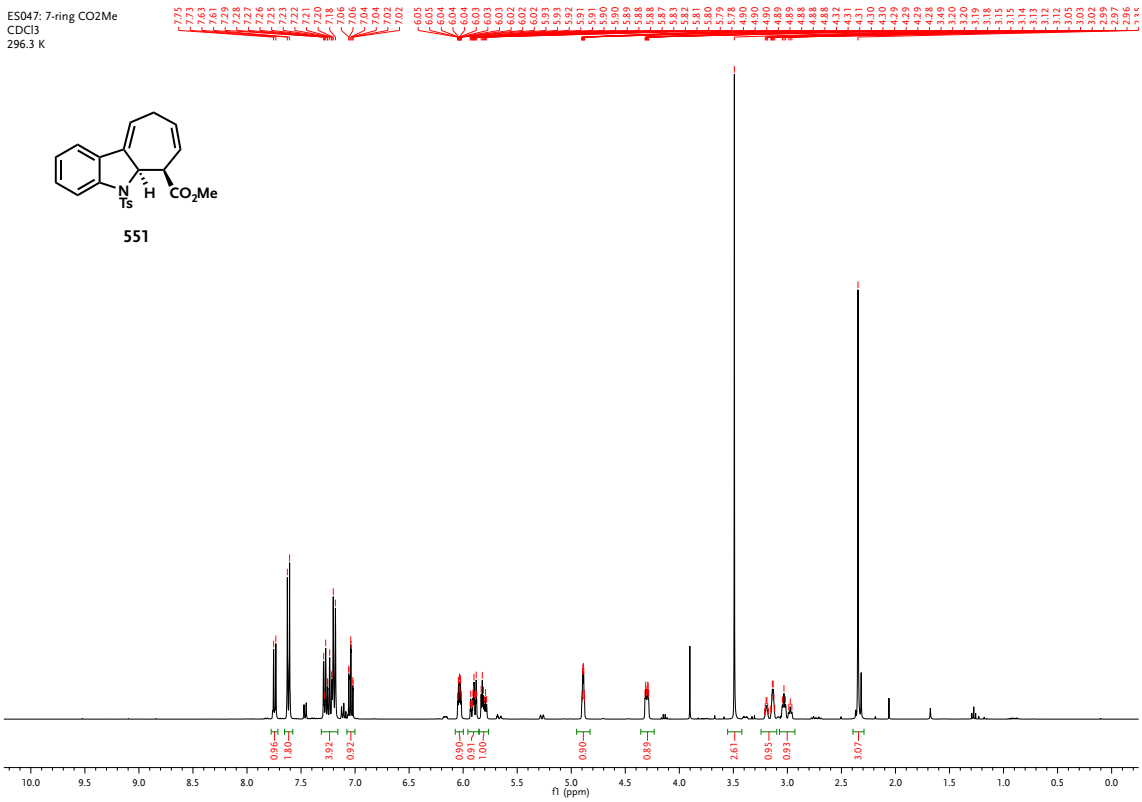
Spectrum B-17. ^{1}H-NMR spectrum for compound **534** *(experimental on page 200)*.



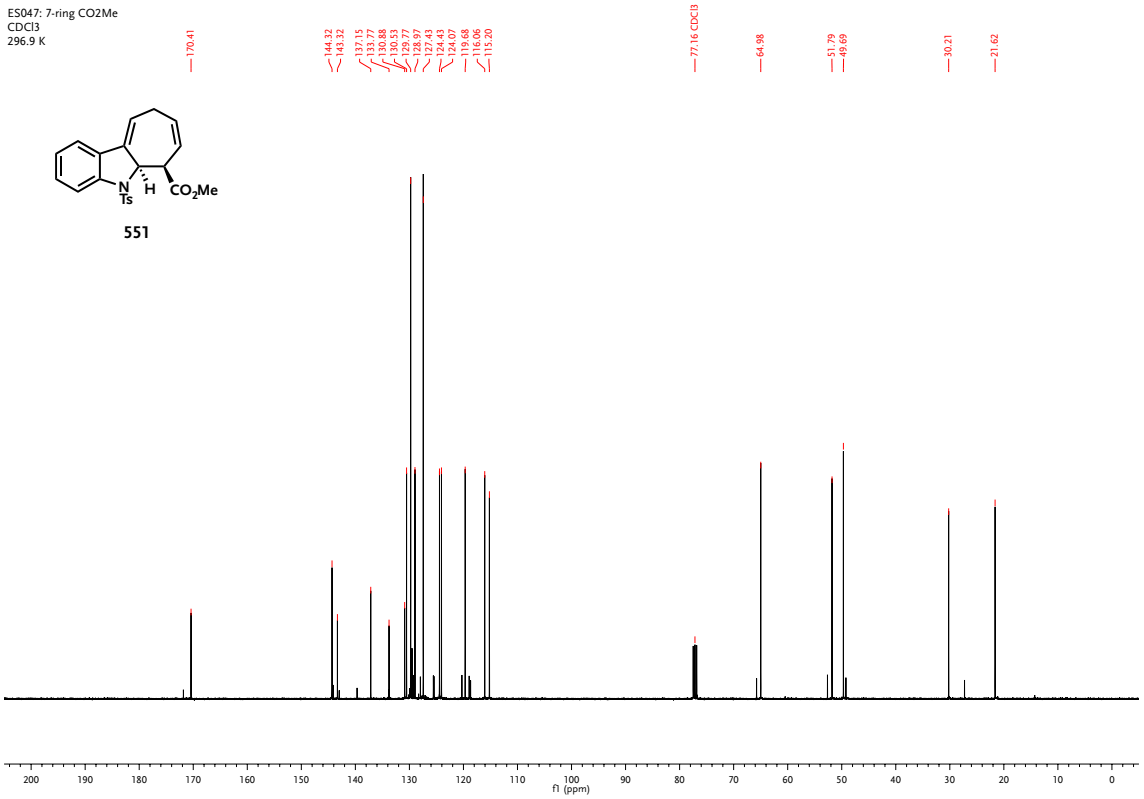
Spectrum B-18. ^{13}C-NMR spectrum for compound **534** *(experimental on page 200)*.



Spectrum B-19. ^{1}H-NMR spectrum for compound **535** *(experimental on page 200)*.

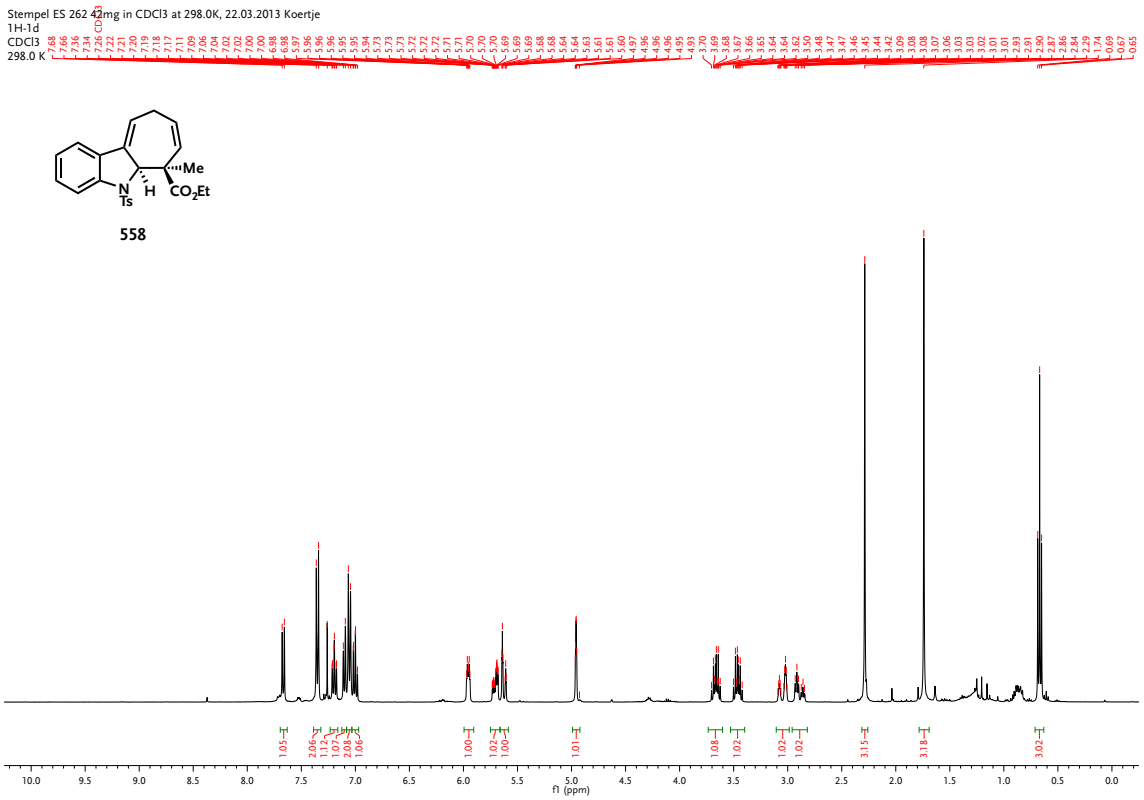


Spectrum B-20. ^{1}H-NMR spectrum for compound **551** *(experimental on page 201)*.



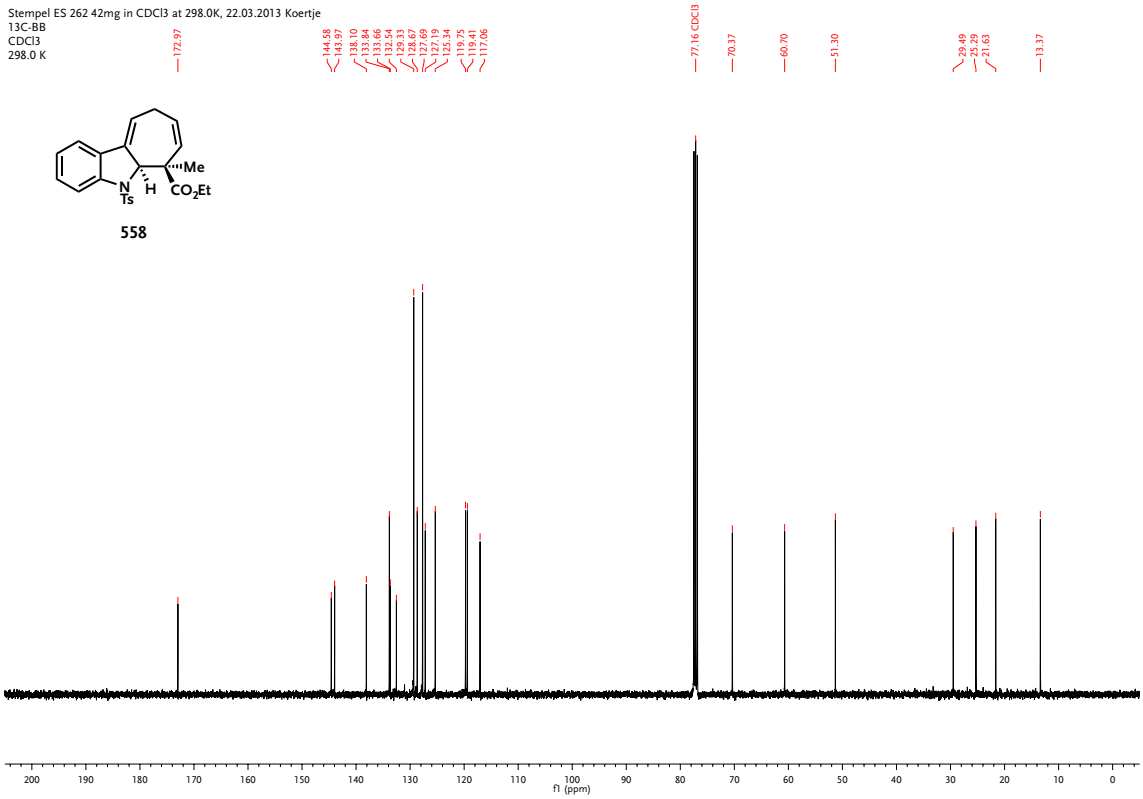
551

Spectrum B-21. ^{13}C-NMR spectrum for compound **551** *(experimental on page 201)*.

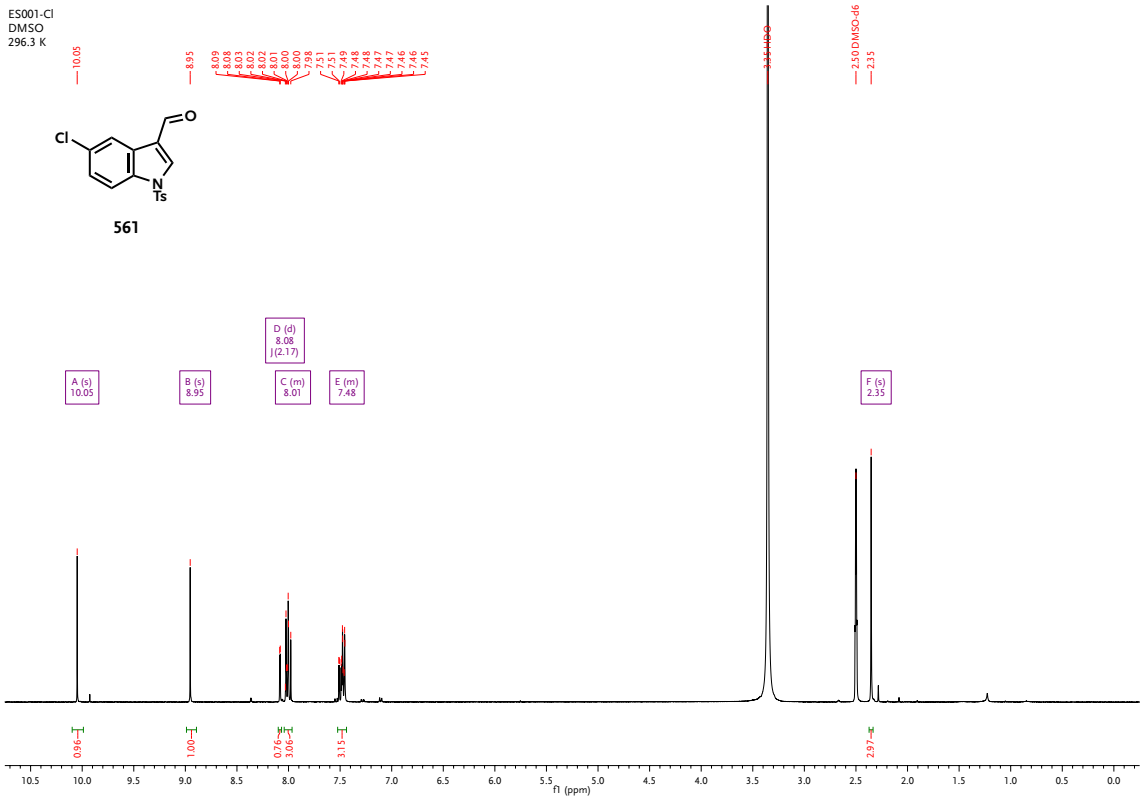


558

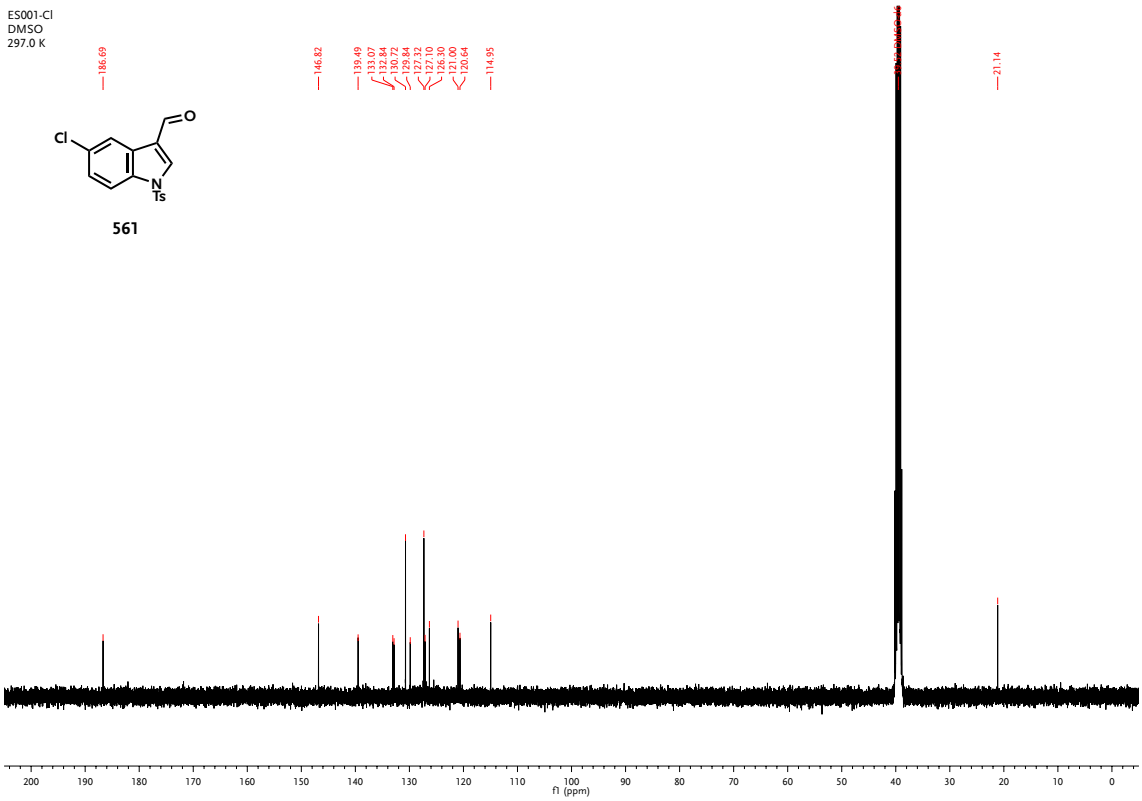
Spectrum B-22. ^{1}H-NMR spectrum for compound **558** *(experimental on page 201)*.



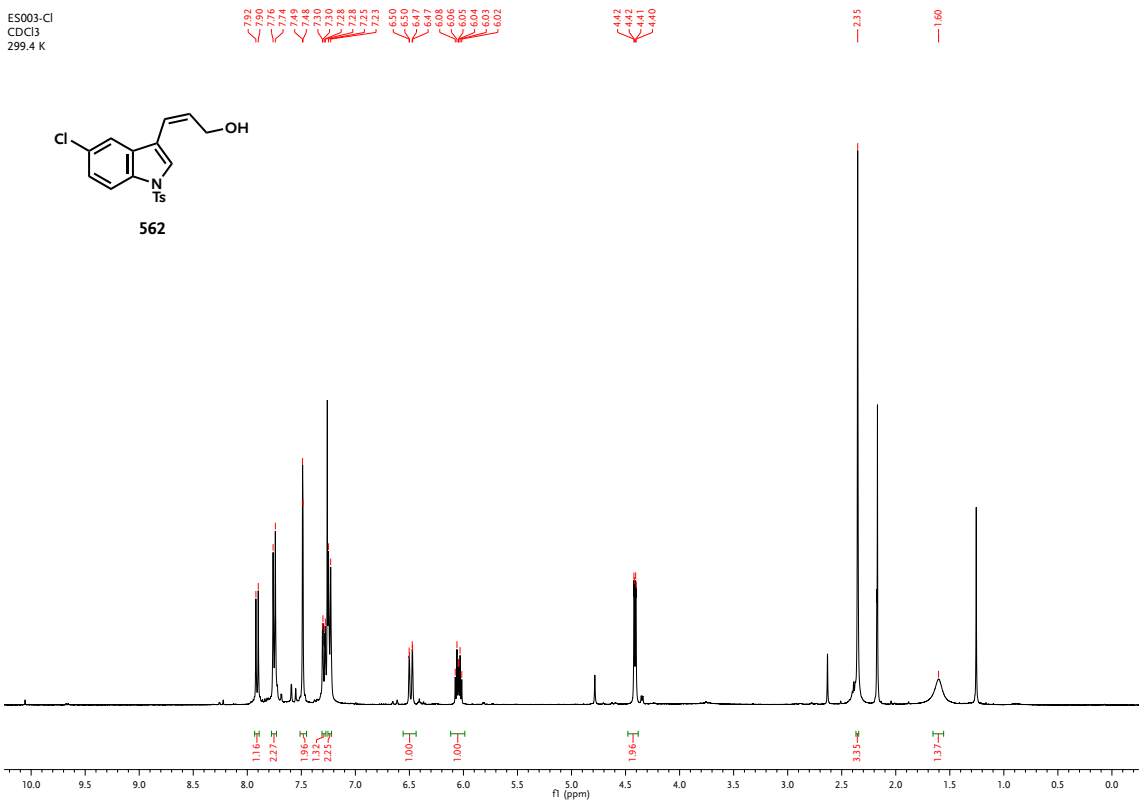
Spectrum B-23. ^{13}C-NMR spectrum for compound **558** *(experimental on page 201)*.



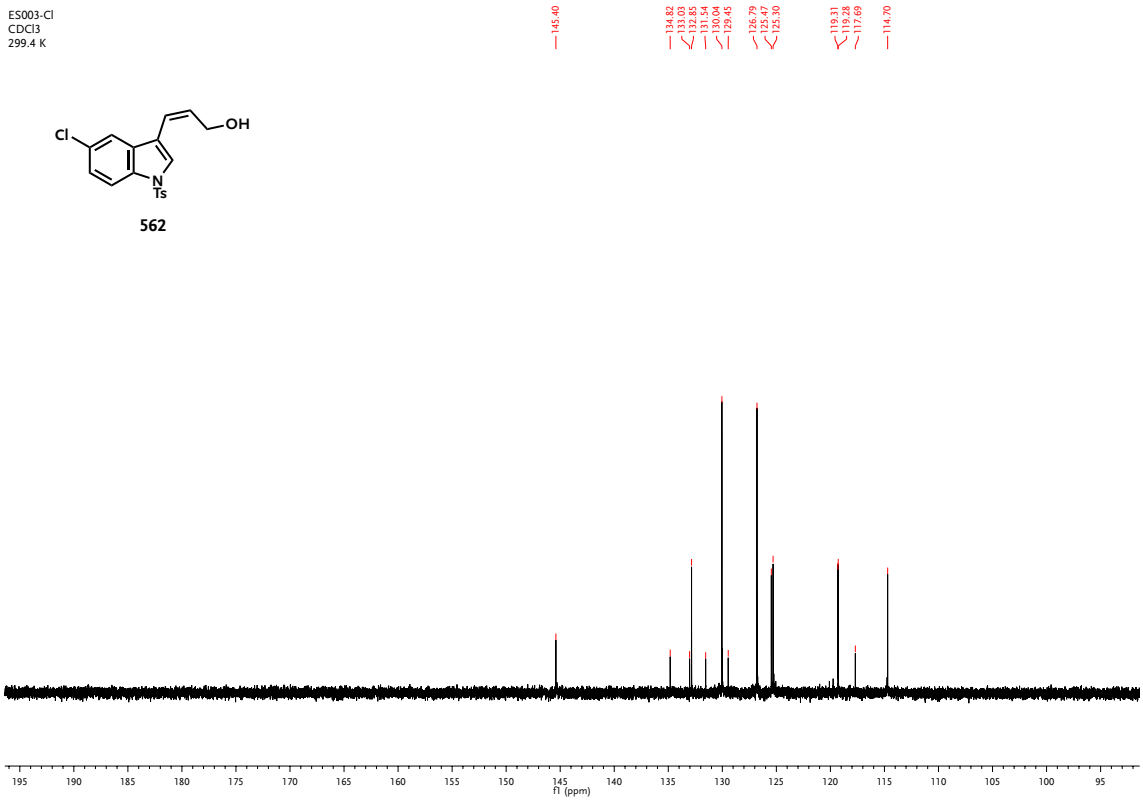
Spectrum B-24. ^{1}H-NMR spectrum for compound **561** *(experimental on page 202)*.



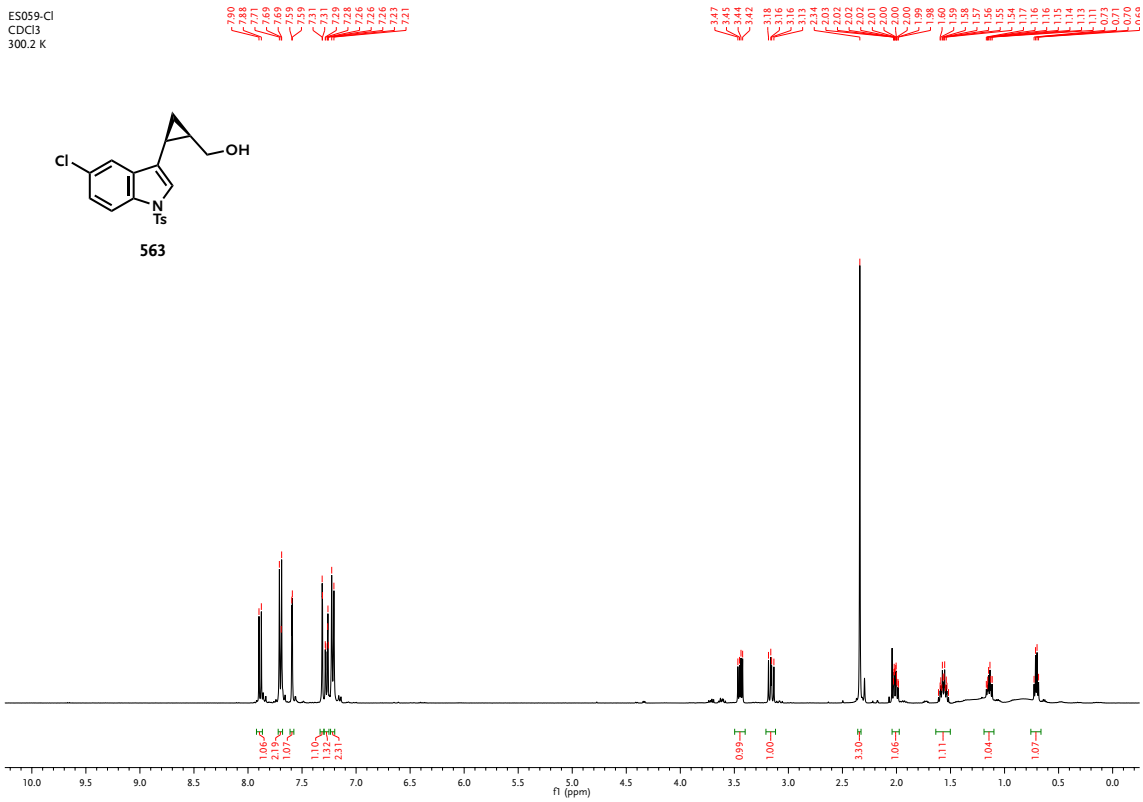
Spectrum B-25. ^{13}C-NMR spectrum for compound **561** *(experimental on page 202)*.



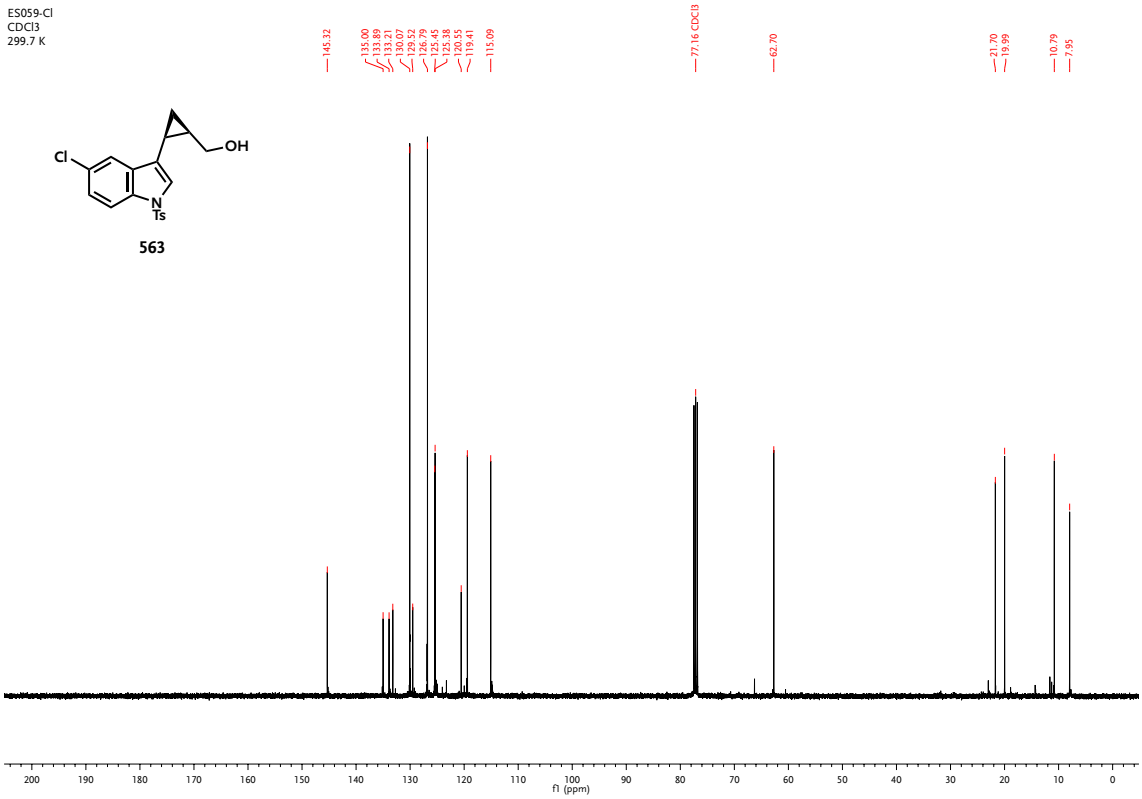
Spectrum B-26. ^{1}H-NMR spectrum for compound **562** *(experimental on page 202)*.



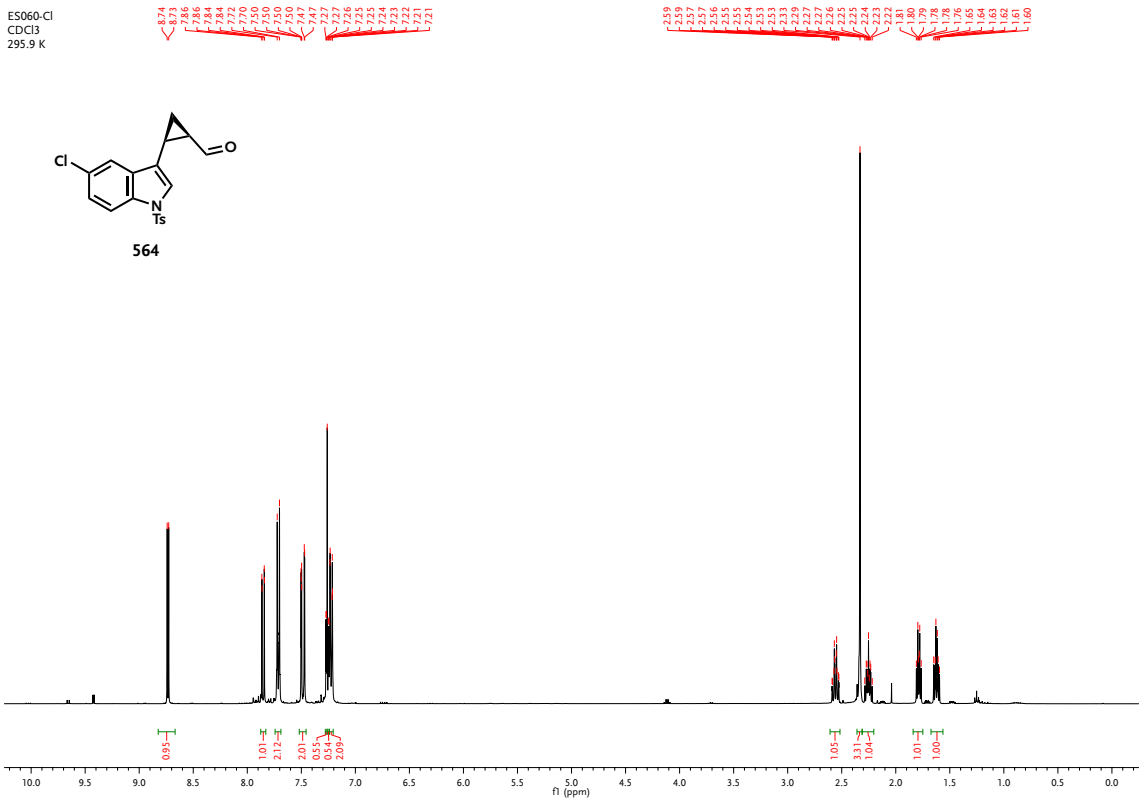
Spectrum B-27. ^{13}C-NMR spectrum for compound **562** *(experimental on page 202)*.



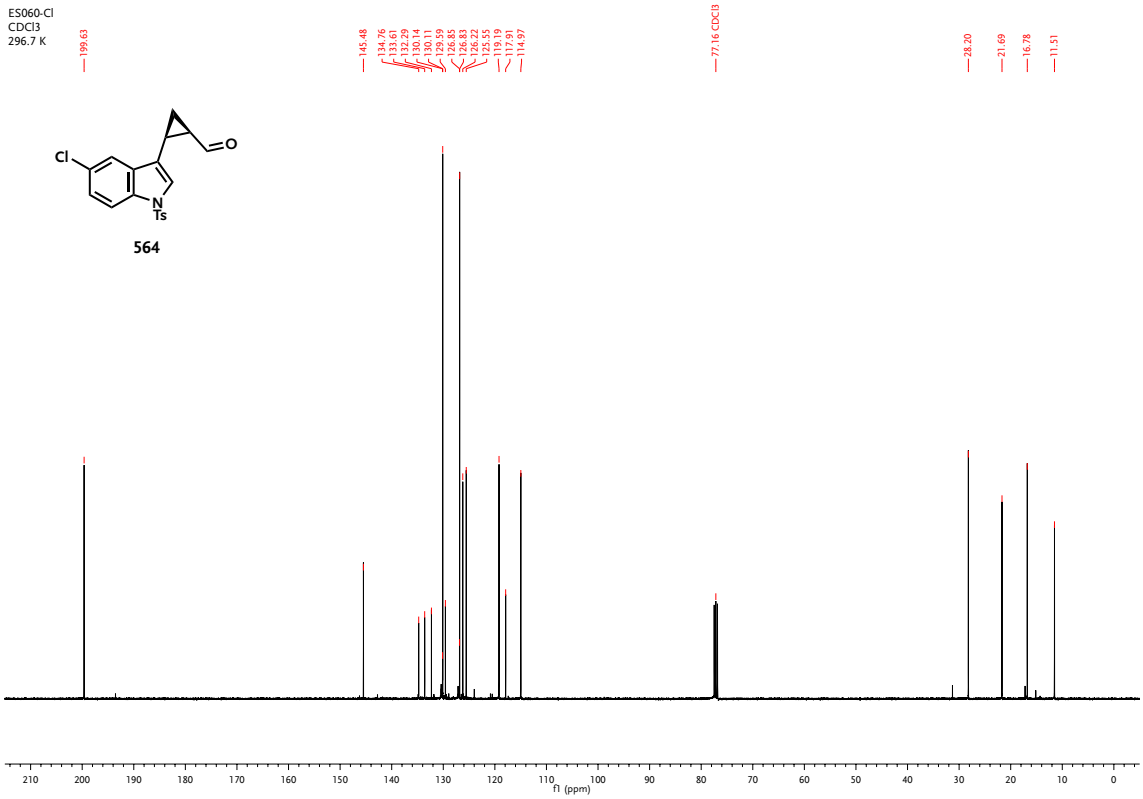
Spectrum B-28. ^{1}H-NMR spectrum for compound **563** *(experimental on page 203)*.



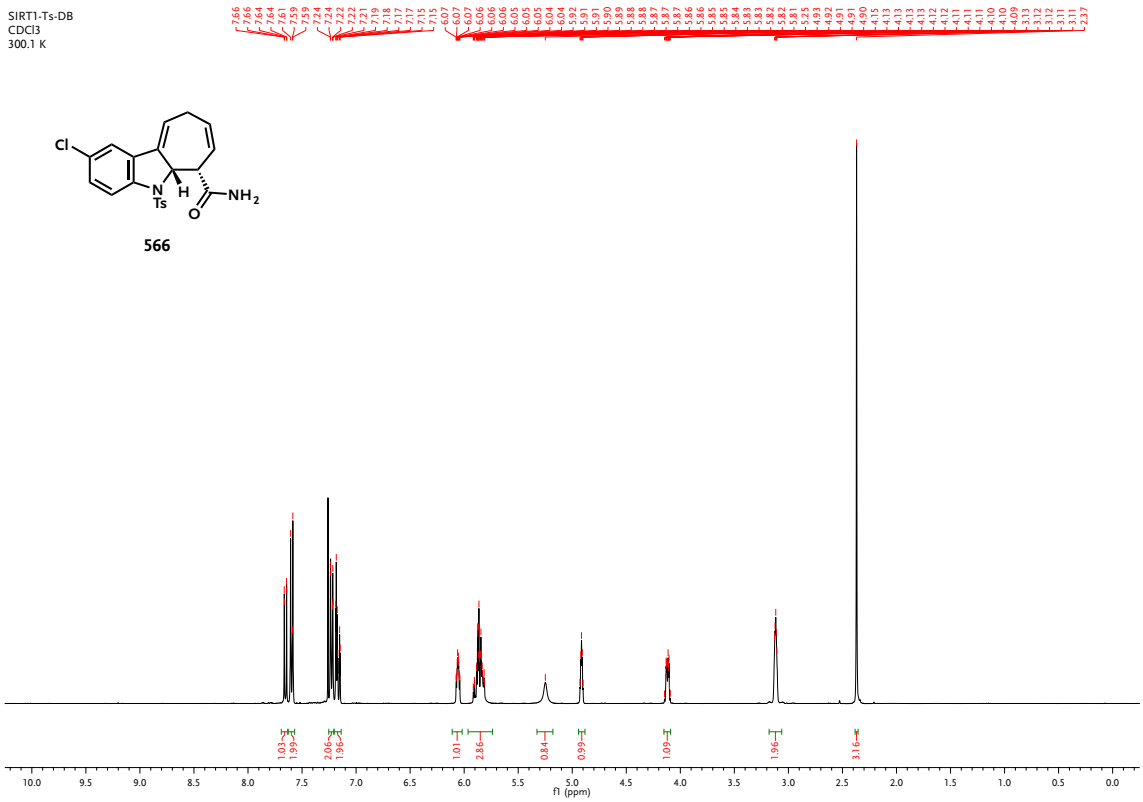
Spectrum B-29. ^{13}C-NMR spectrum for compound **563** *(experimental on page 203)*.



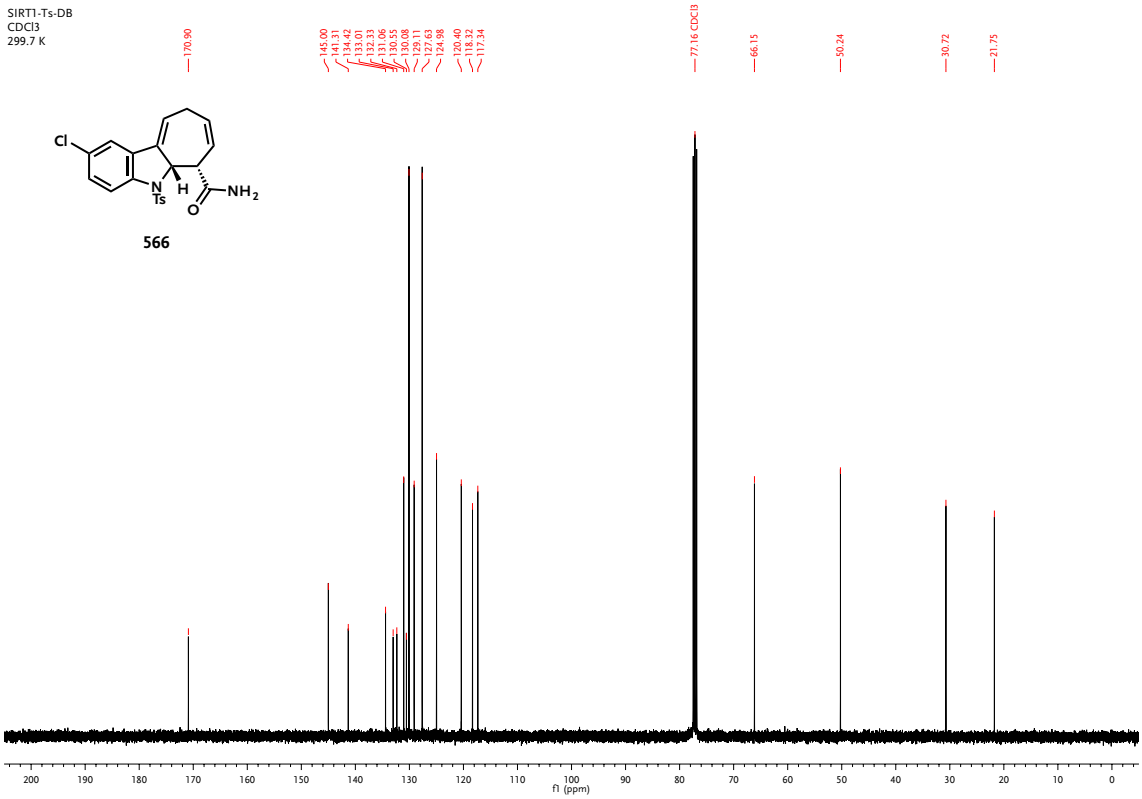
Spectrum B-30. ^{1}H-NMR spectrum for compound **564** *(experimental on page 203)*.



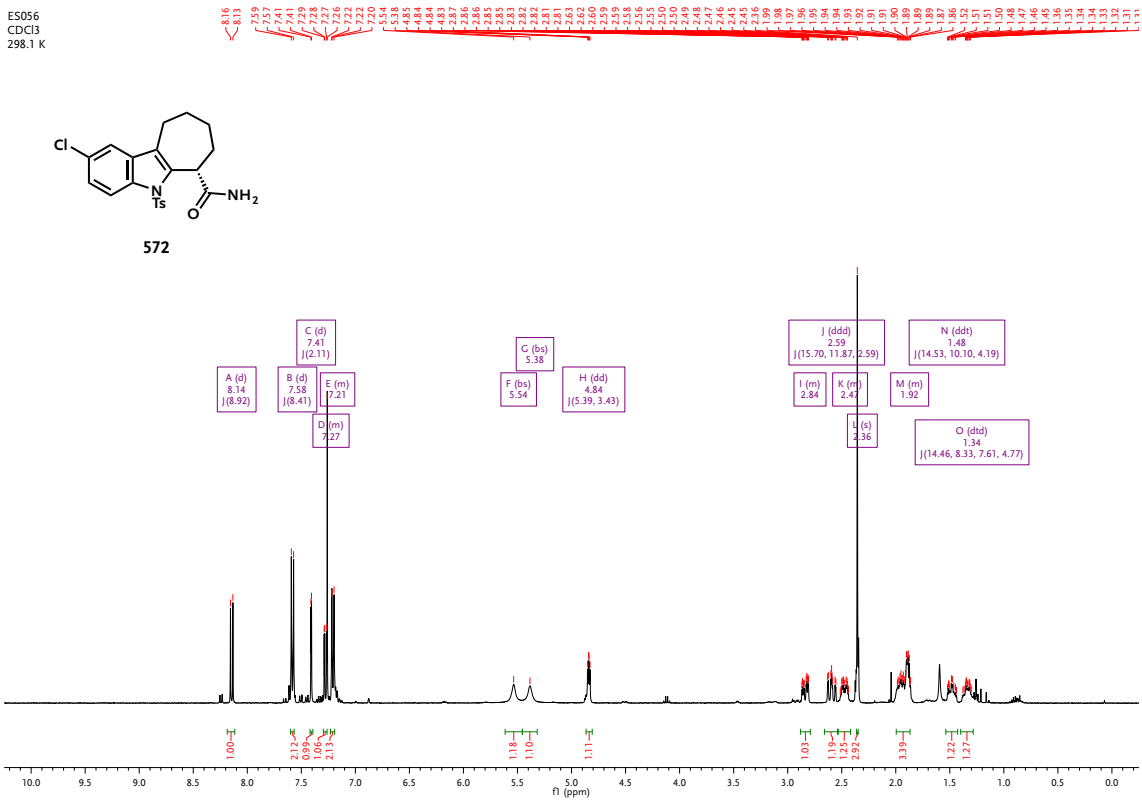
Spectrum B-31. ^{13}C-NMR spectrum for compound **564** *(experimental on page 203)*.



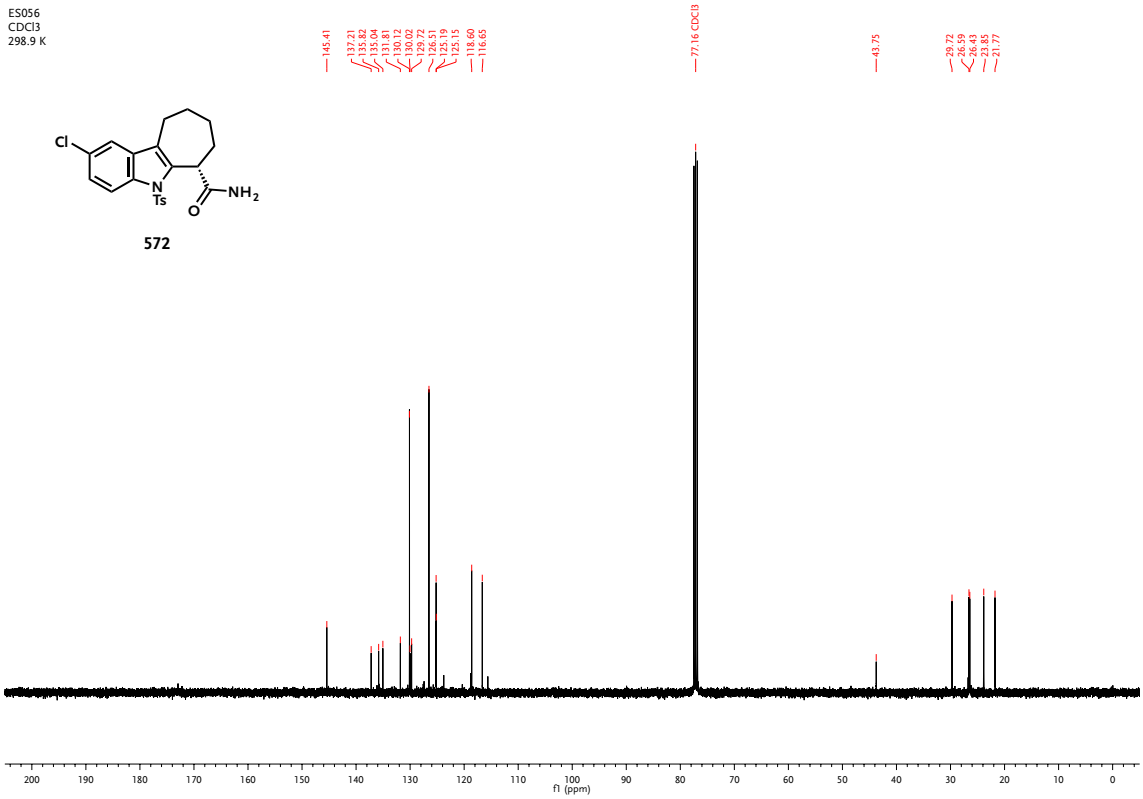
Spectrum B-32. ^{1}H-NMR spectrum for compound **566** *(experimental on page 204)*.



Spectrum B-33. ^{13}C-NMR spectrum for compound **566** *(experimental on page 204)*.

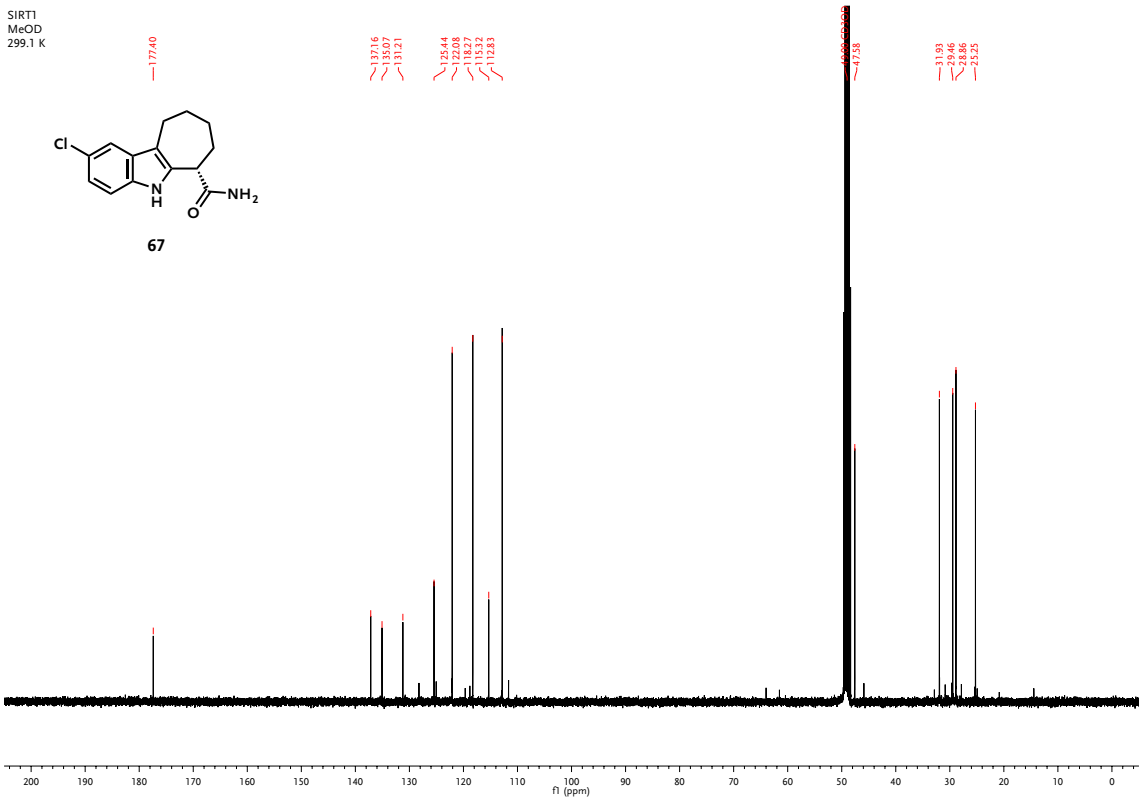


Spectrum B-34. ^{1}H-NMR spectrum for compound **572** *(experimental on page 204)*.

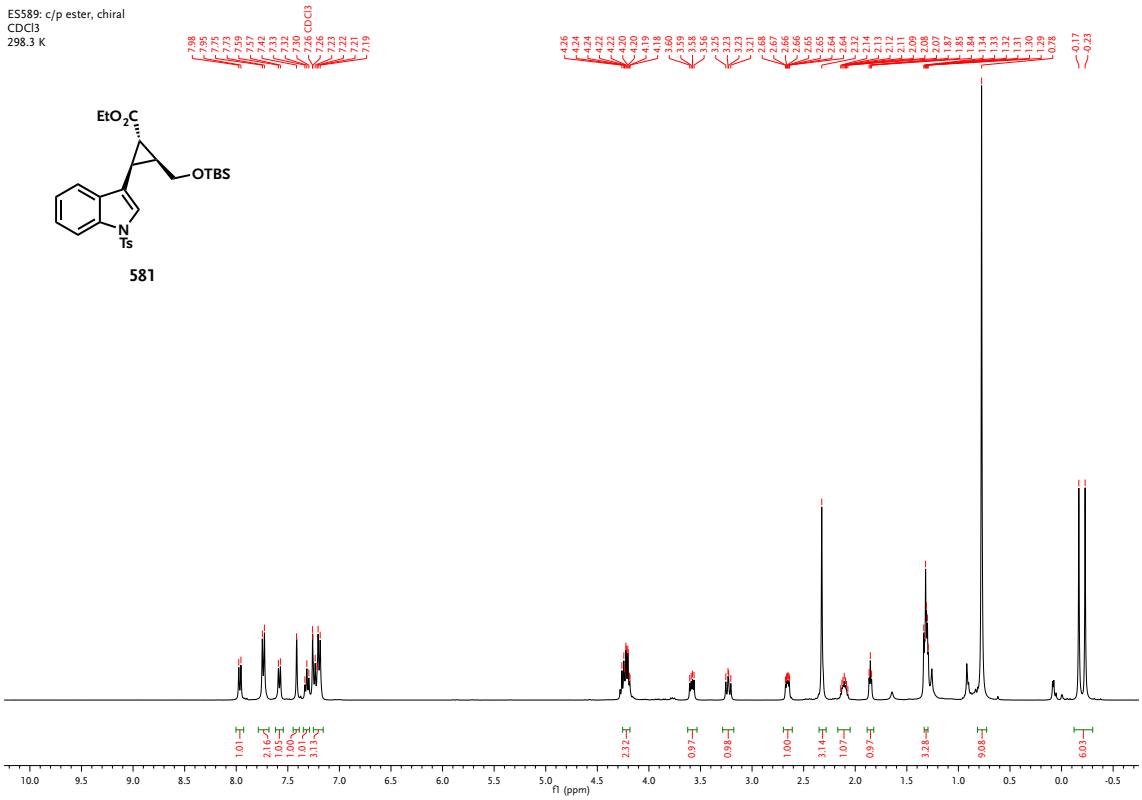


Spectrum B-35. ^{13}C-NMR spectrum for compound **572** *(experimental on page 204)*.

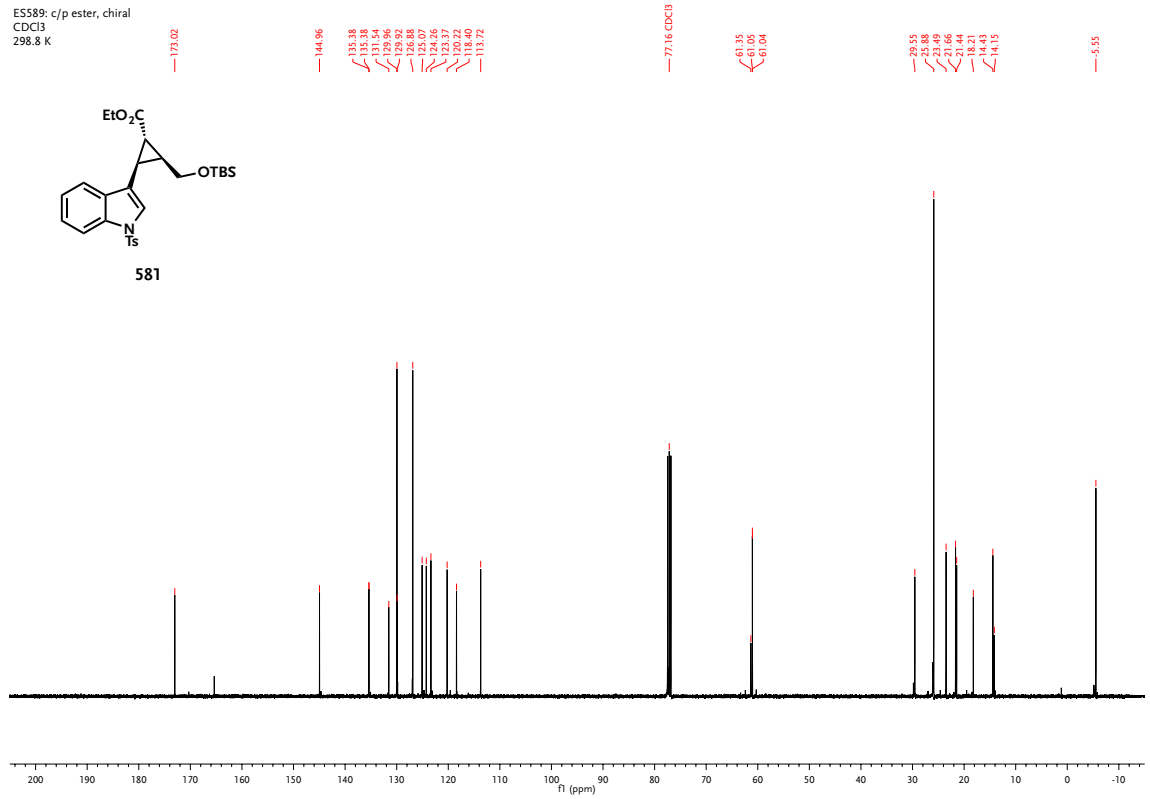
Spectrum B-36. ^{1}H-NMR spectrum for compound **67** *(experimental on page 205)*.



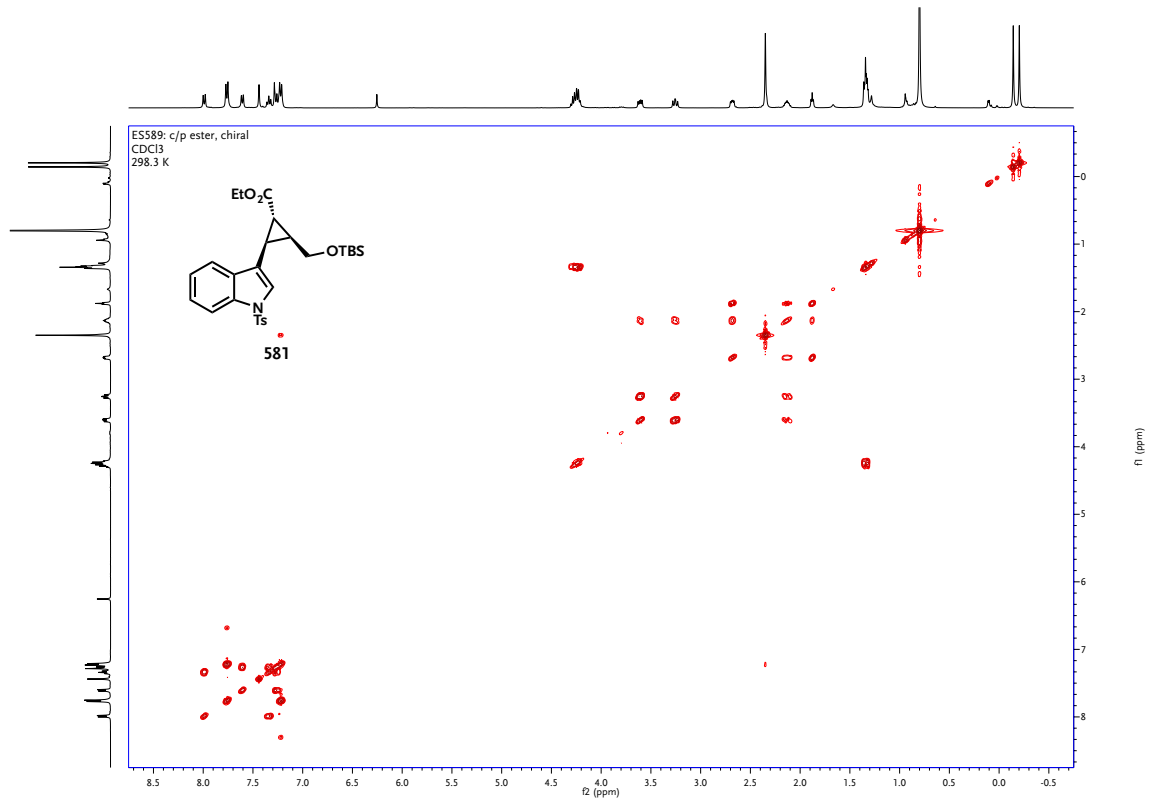
Spectrum B-37. ^{13}C-NMR spectrum for compound **67** *(experimental on page 205)*.



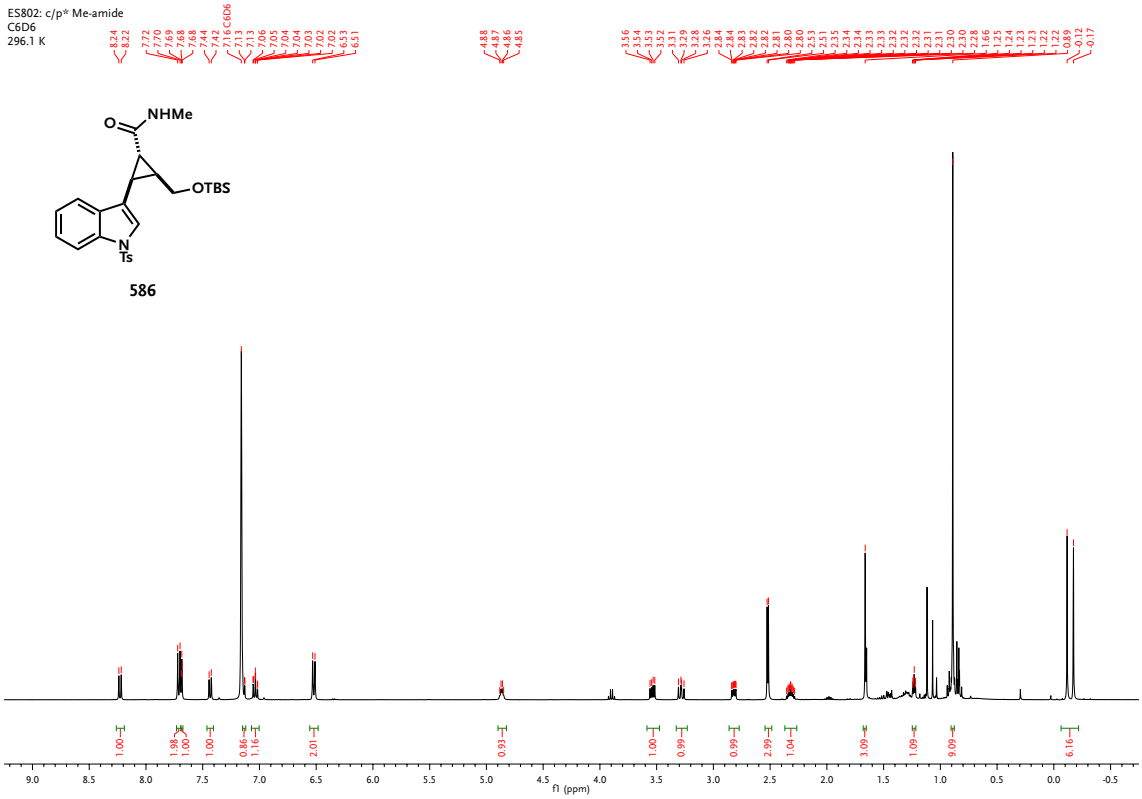
Spectrum B-38. ^{1}H-NMR spectrum for compound **581** *(experimental on page 205)*.



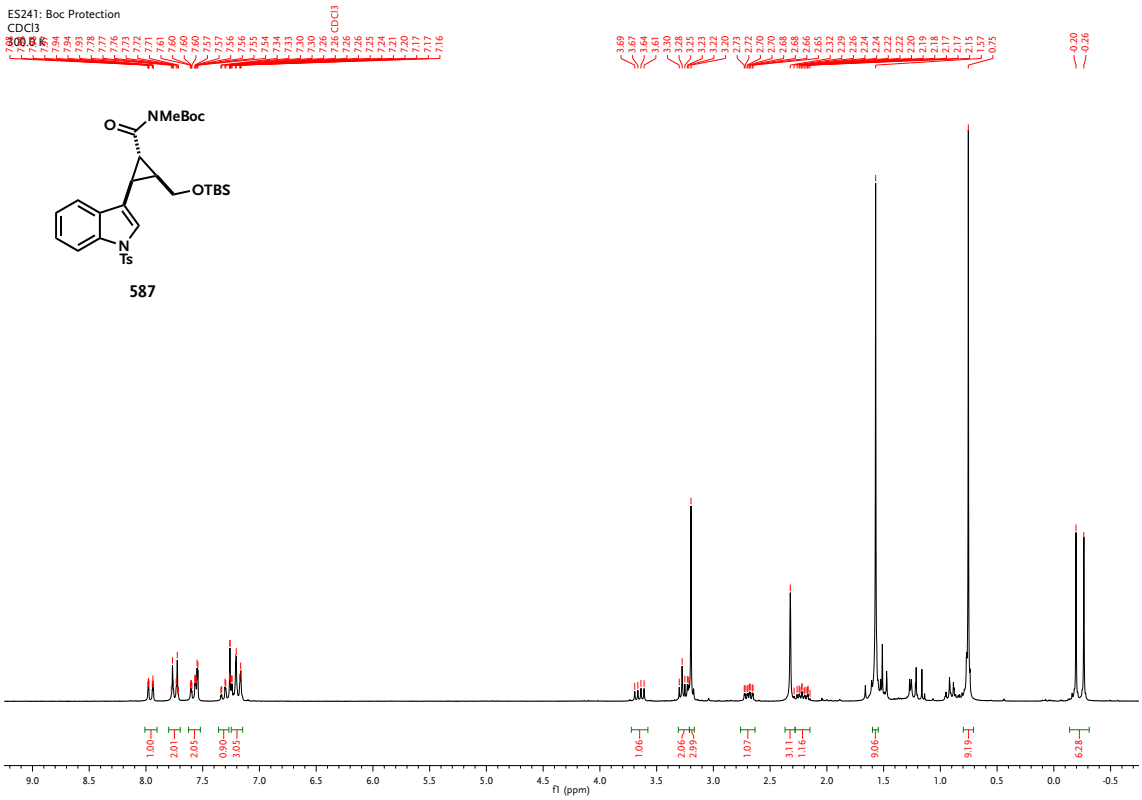
Spectrum B-39. ^{13}C-NMR spectrum for compound **581** *(experimental on page 205)*.



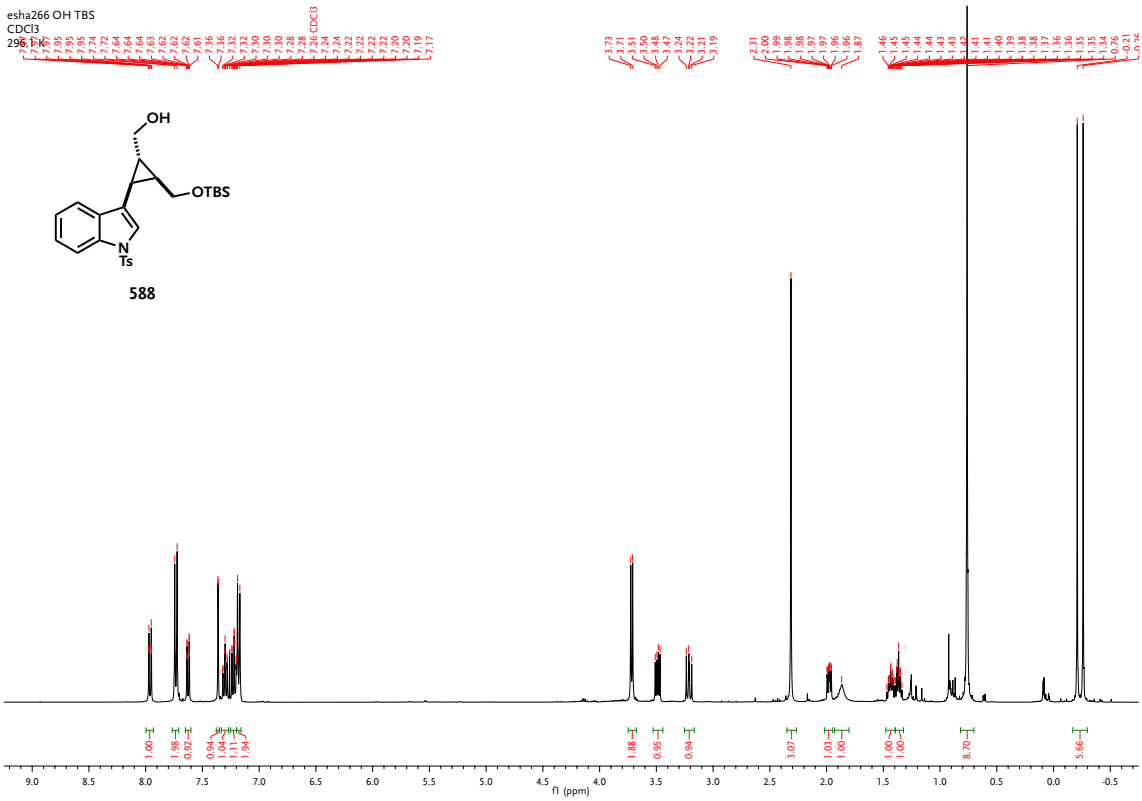
Spectrum B-40. COSY60 2D-NMR spectrum for compound **581** *(experimental on page 205)*.



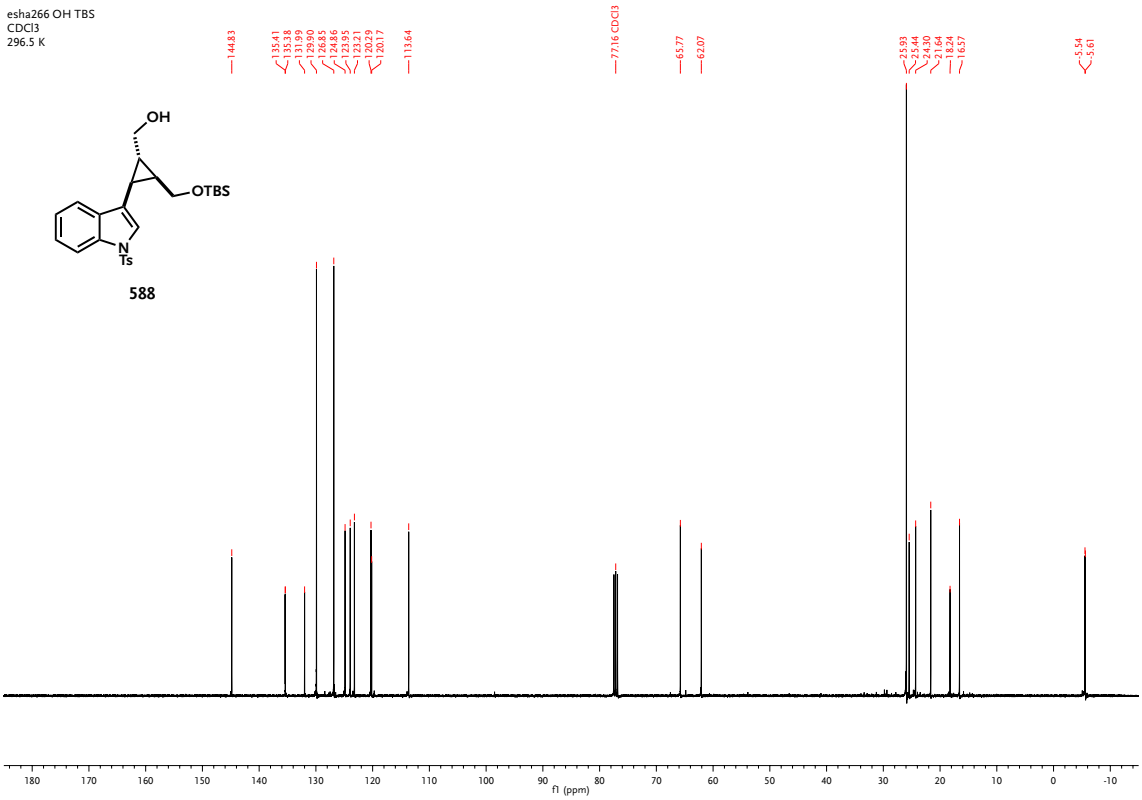
Spectrum B-41. ^{1}H-NMR spectrum for compound **586** *(experimental on page 206)*.



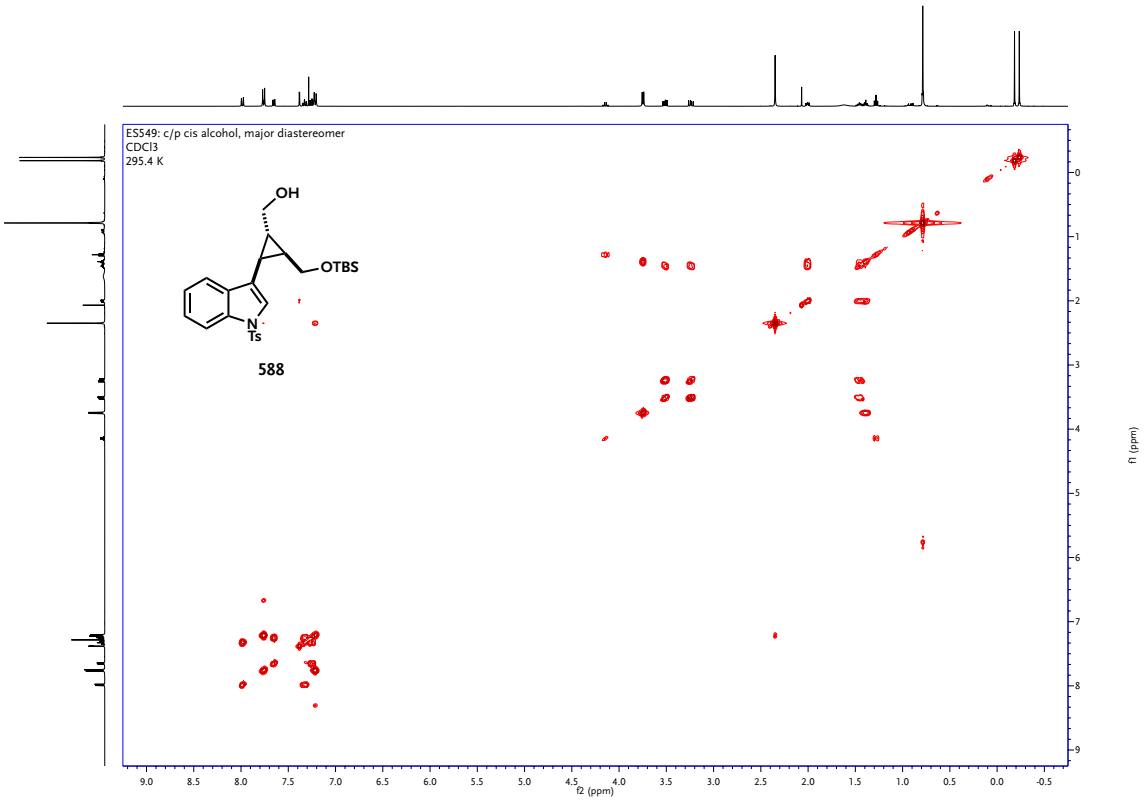
Spectrum B-42. ^{1}H-NMR spectrum for compound **587** *(experimental on page 207)*.



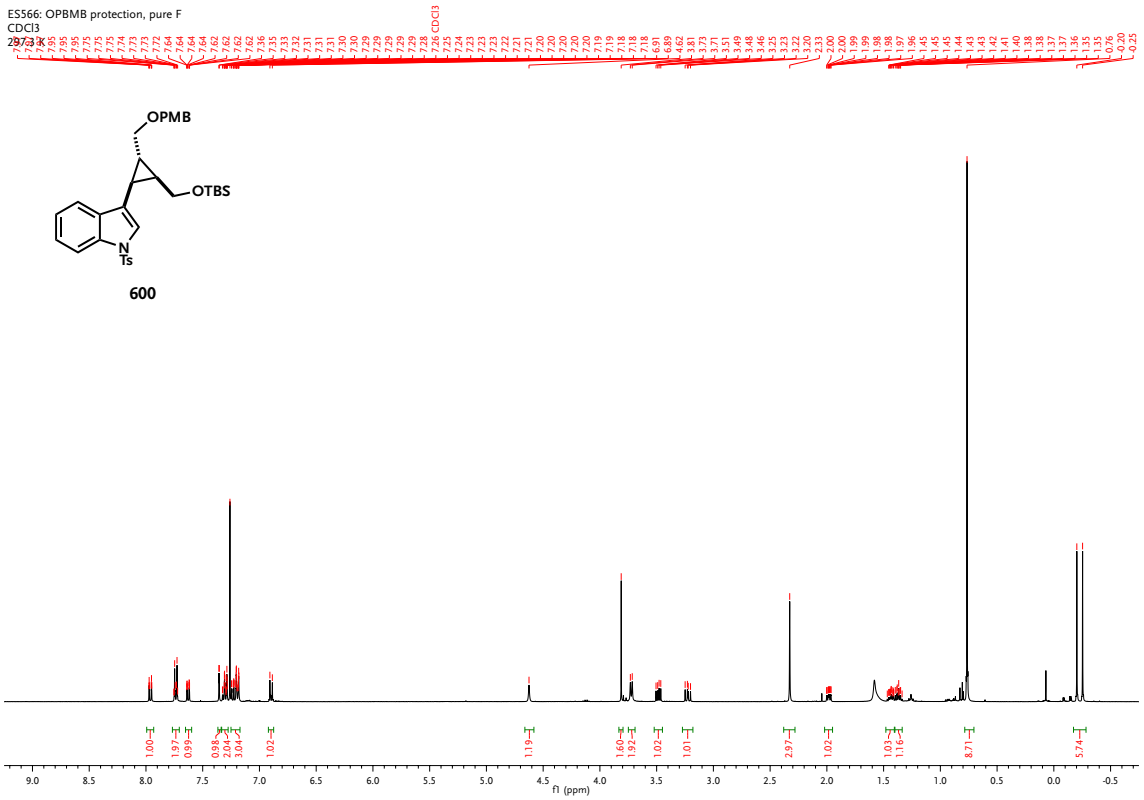
Spectrum B-43. ^{1}H-NMR spectrum for compound **588** *(experimental on page 207)*.



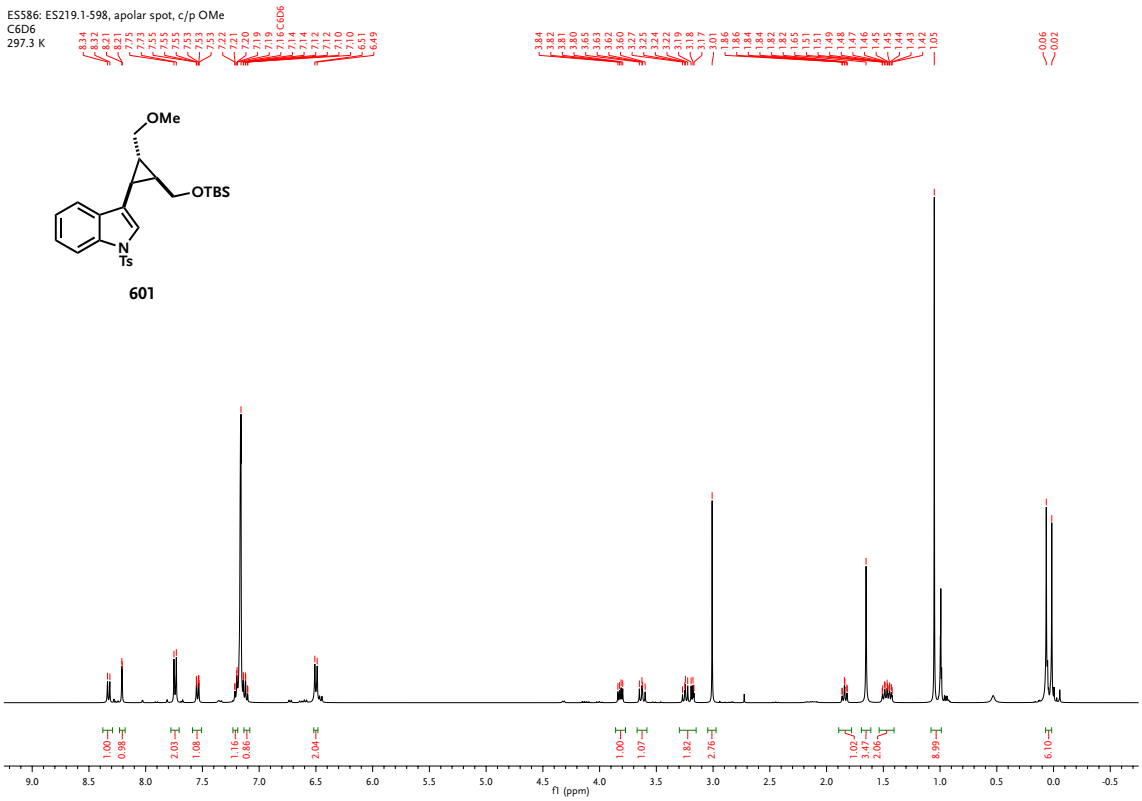
Spectrum B-44. ^{13}C-NMR spectrum for compound **588** *(experimental on page 207)*.



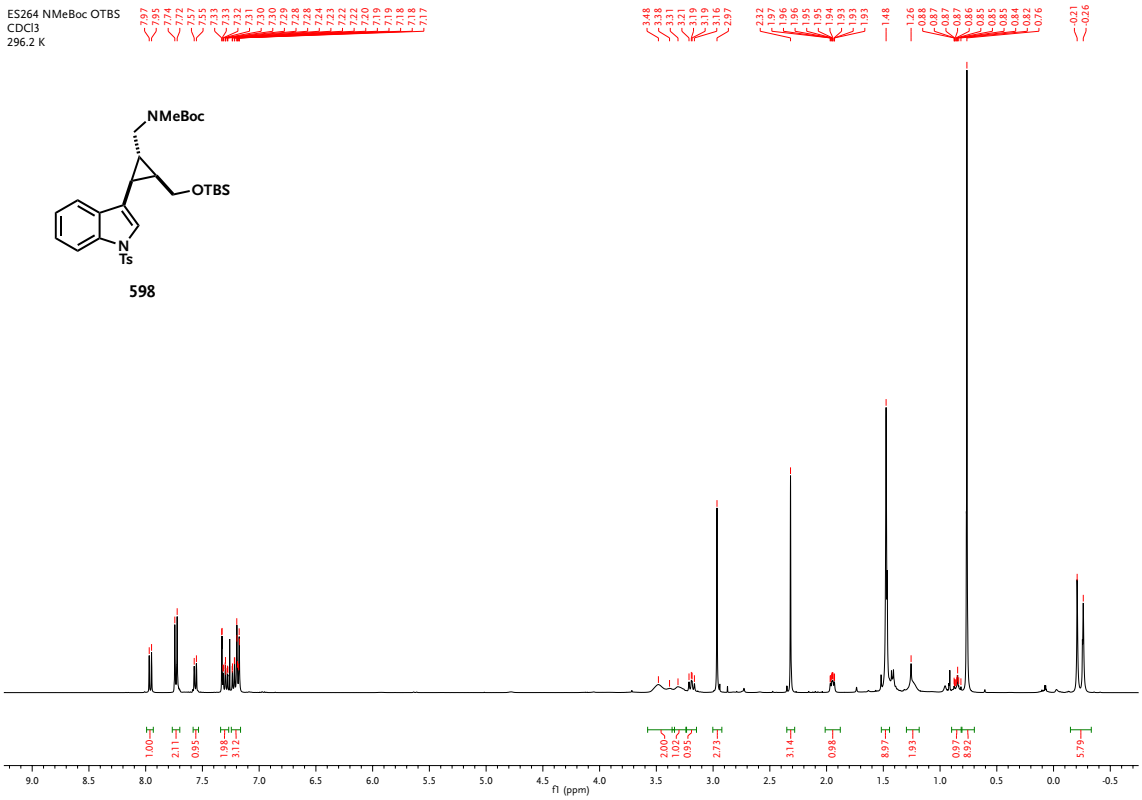
Spectrum B-45. COSY60 2D-NMR spectrum for compound **588** *(experimental on page 207)*.



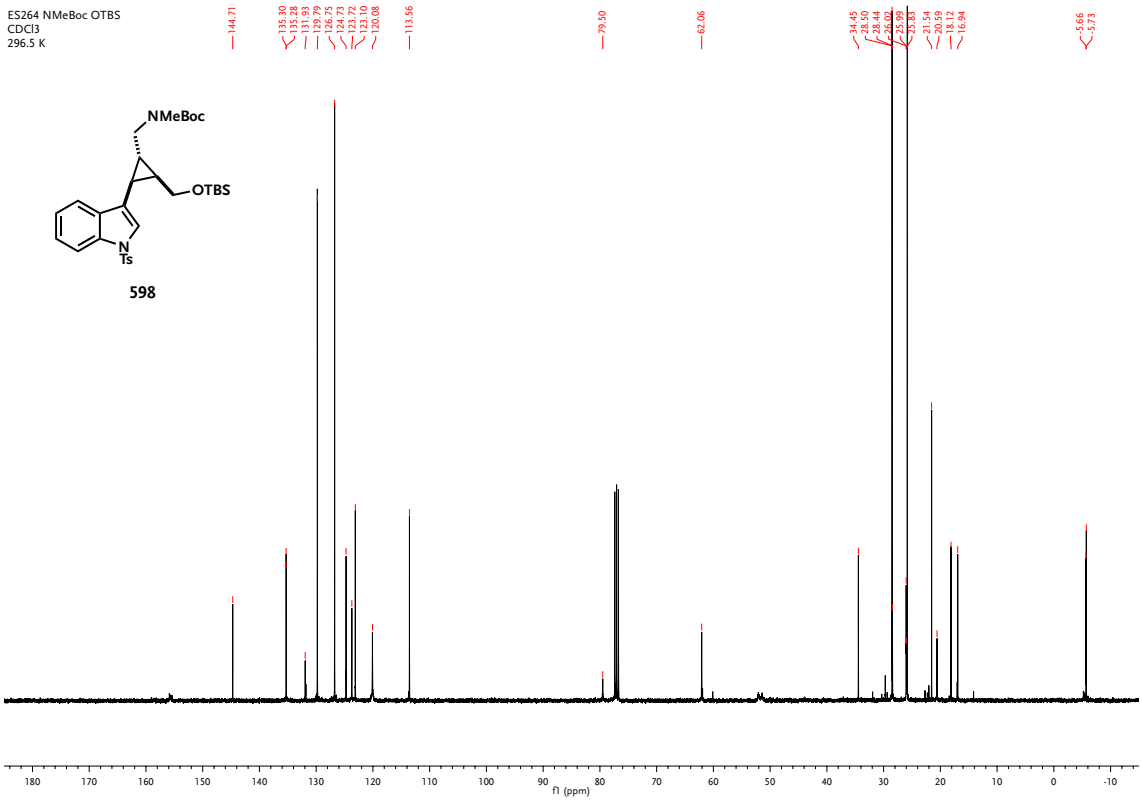
Spectrum B-46. ^{1}H-NMR spectrum for compound **600** *(experimental on page 210)*.



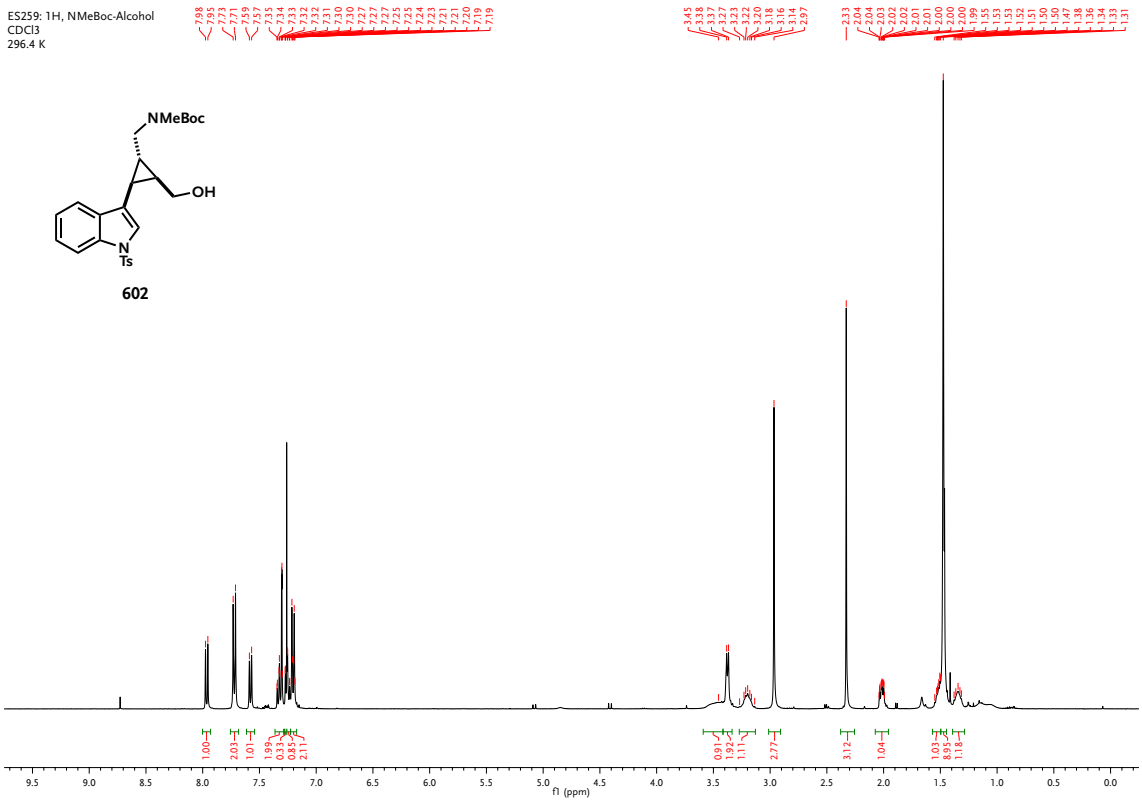
Spectrum B-47. [1]H-NMR spectrum for compound **601** *(experimental on page 210)*.



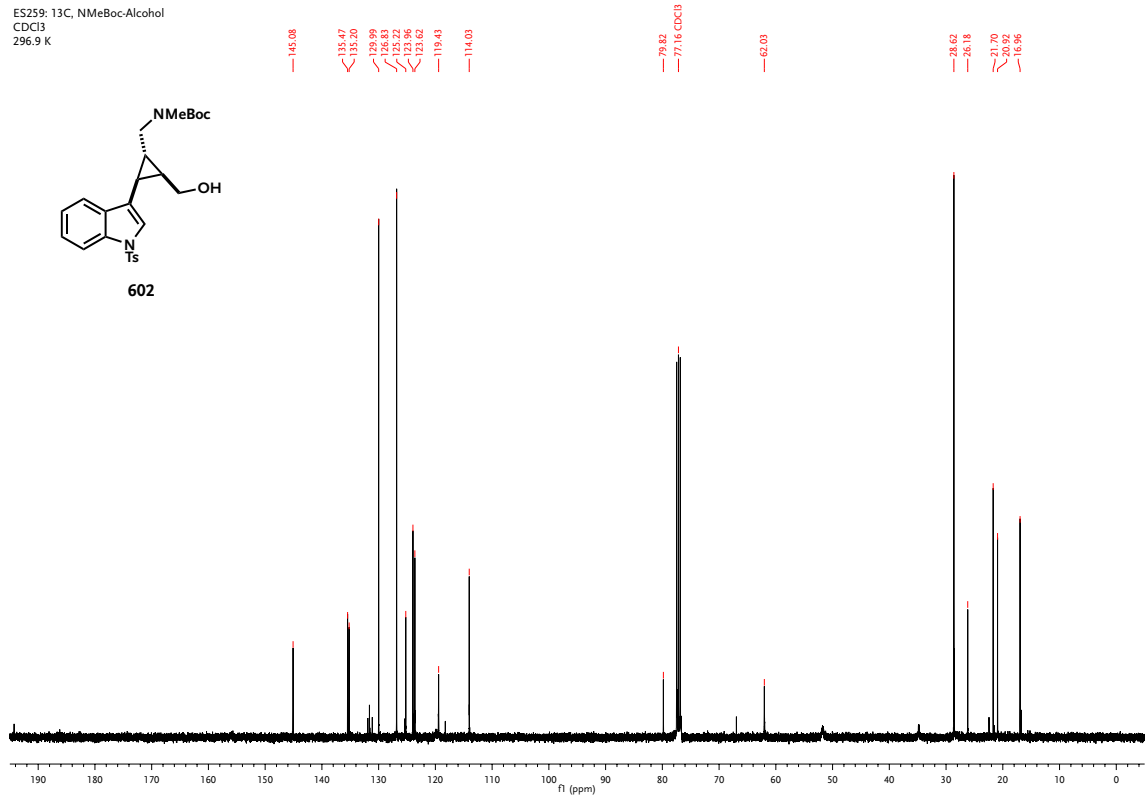
Spectrum B-48. [1]H-NMR spectrum for compound **598** *(experimental on page 212)*.



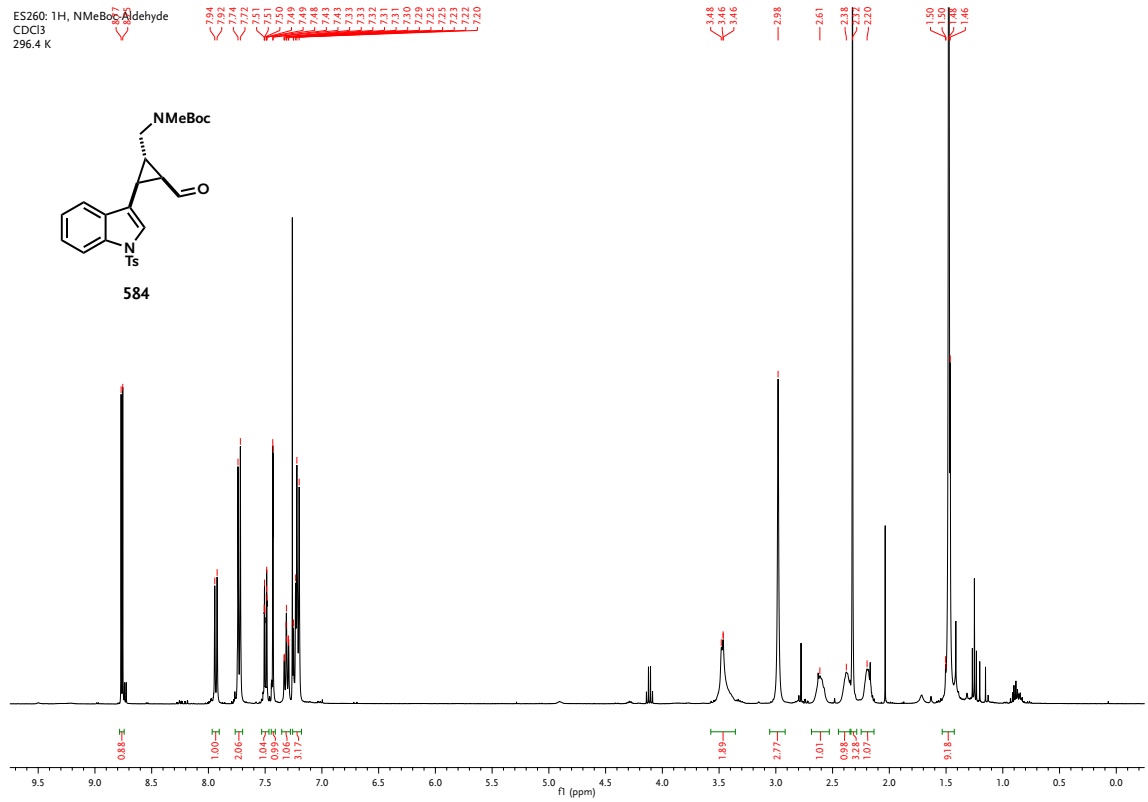
Spectrum B-49. ^{13}C-NMR spectrum for compound **598** *(experimental on page 212)*.



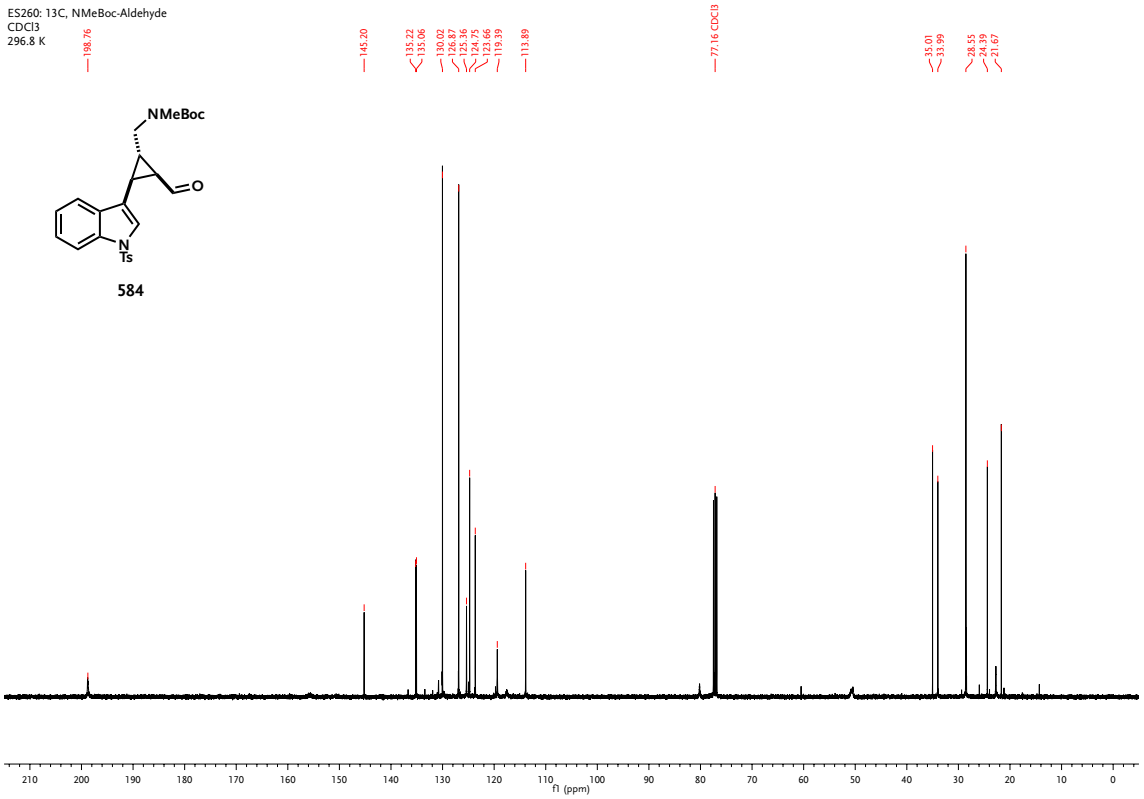
Spectrum B-50. ^{1}H-NMR spectrum for compound **602** *(experimental on page 213)*.



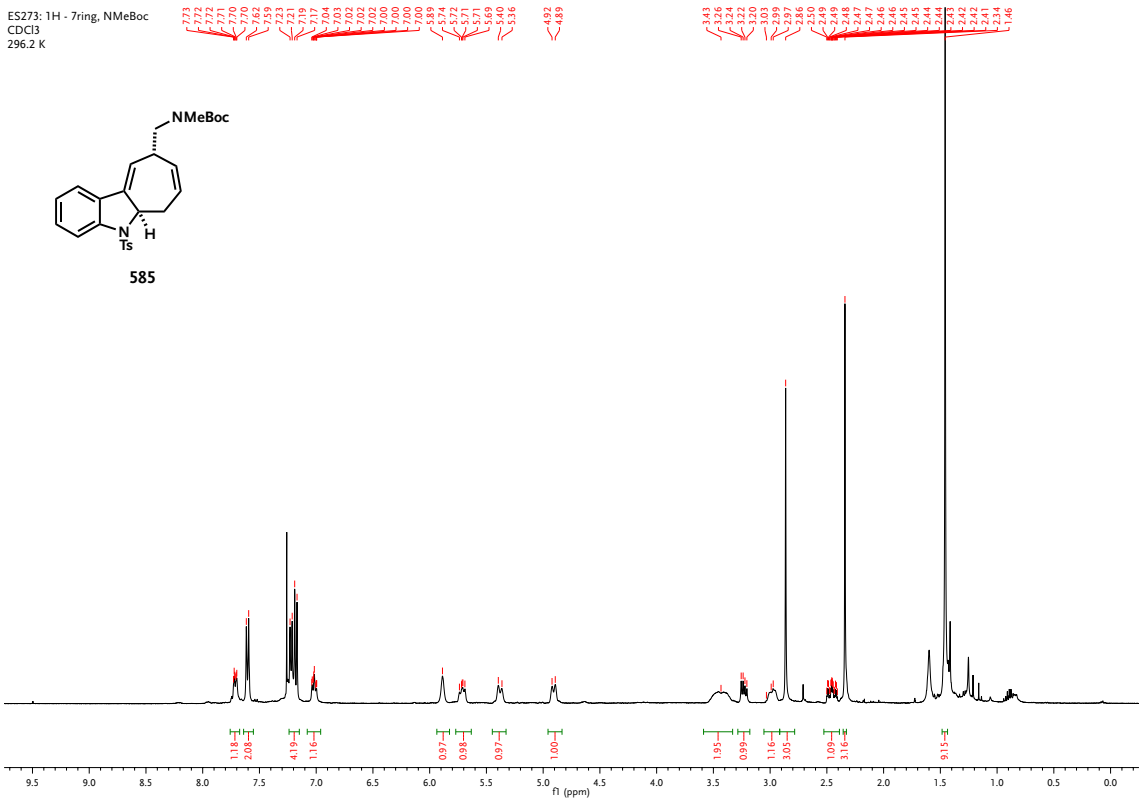
Spectrum B-51. ^{13}C-NMR spectrum for compound **602** *(experimental on page 213)*.



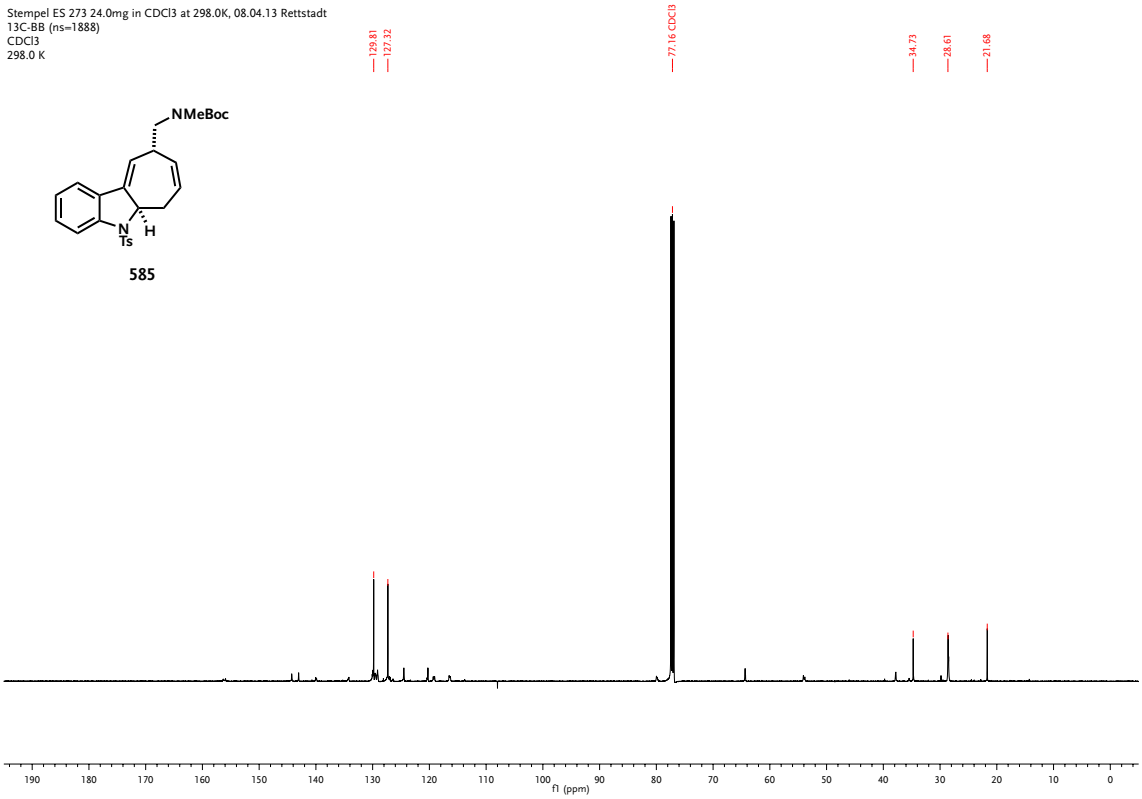
Spectrum B-52. ^{1}H-NMR spectrum for compound **584** *(experimental on page 214)*.



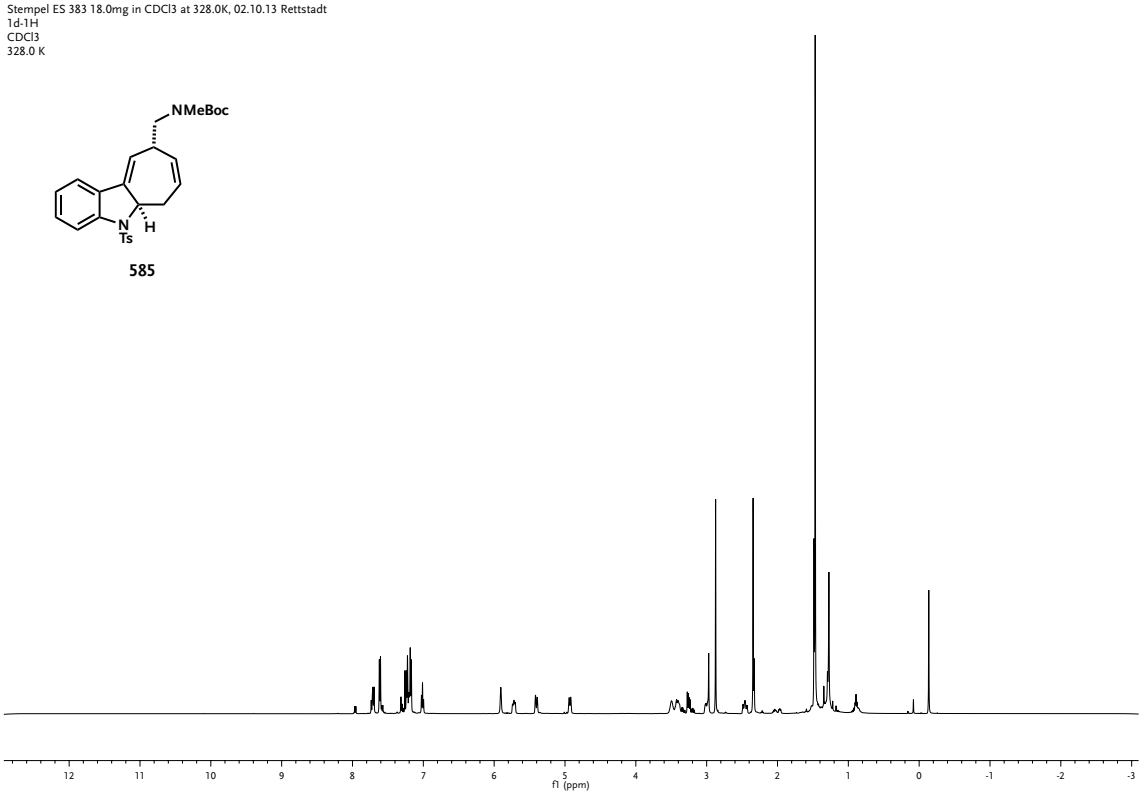
Spectrum B-53. ^{13}C-NMR spectrum for compound **584** *(experimental on page 214)*.



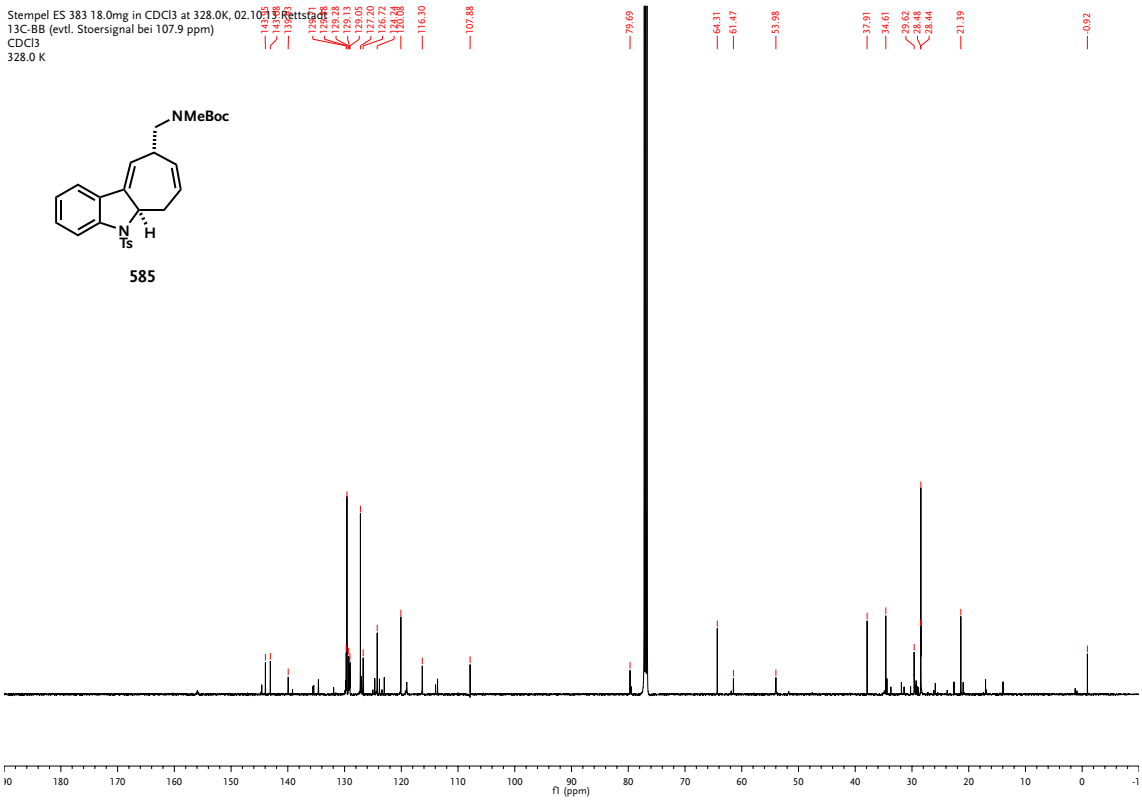
Spectrum B-54. ^{1}H-NMR spectrum for compound **585** *(experimental on page 214)*.



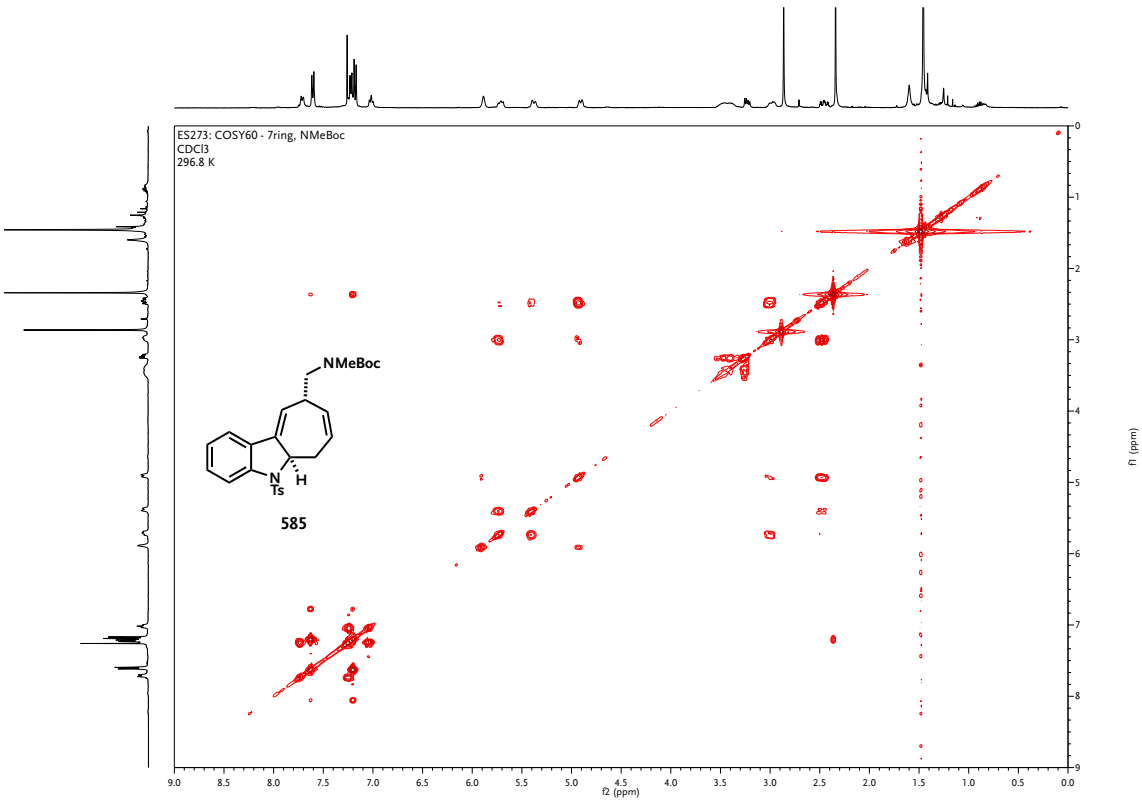
Spectrum B-55. ^{13}C-NMR spectrum for compound **585** *(experimental on page 214)*.



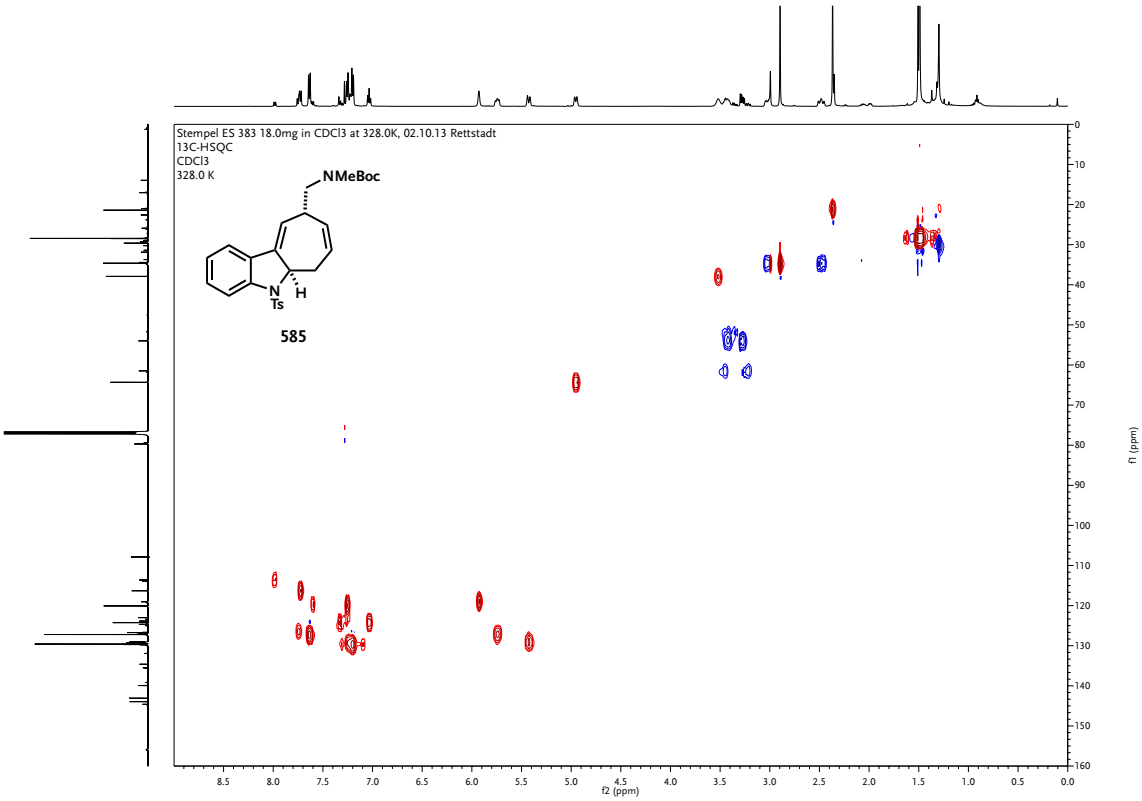
Spectrum B-56. ^{1}H-NMR spectrum for compound **585** *(experimental on page 214)*.



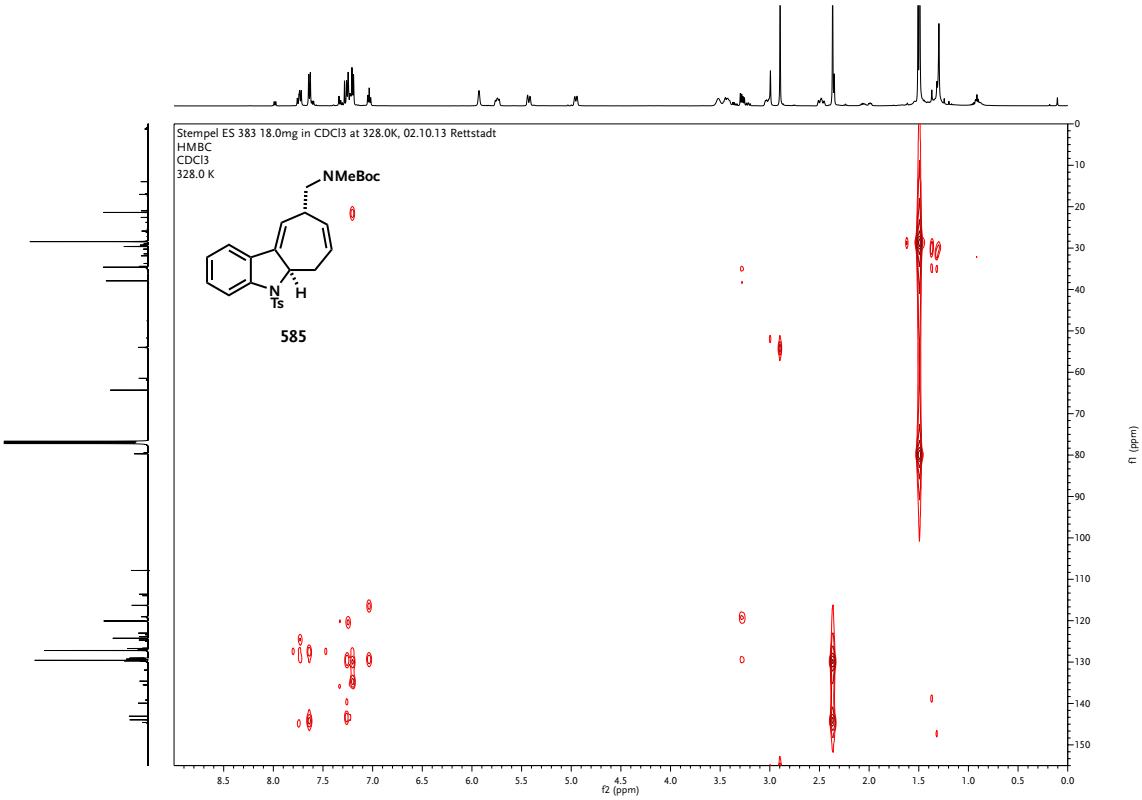
Spectrum B-57. ^{13}C-NMR spectrum for compound **585** *(experimental on page 214)*.



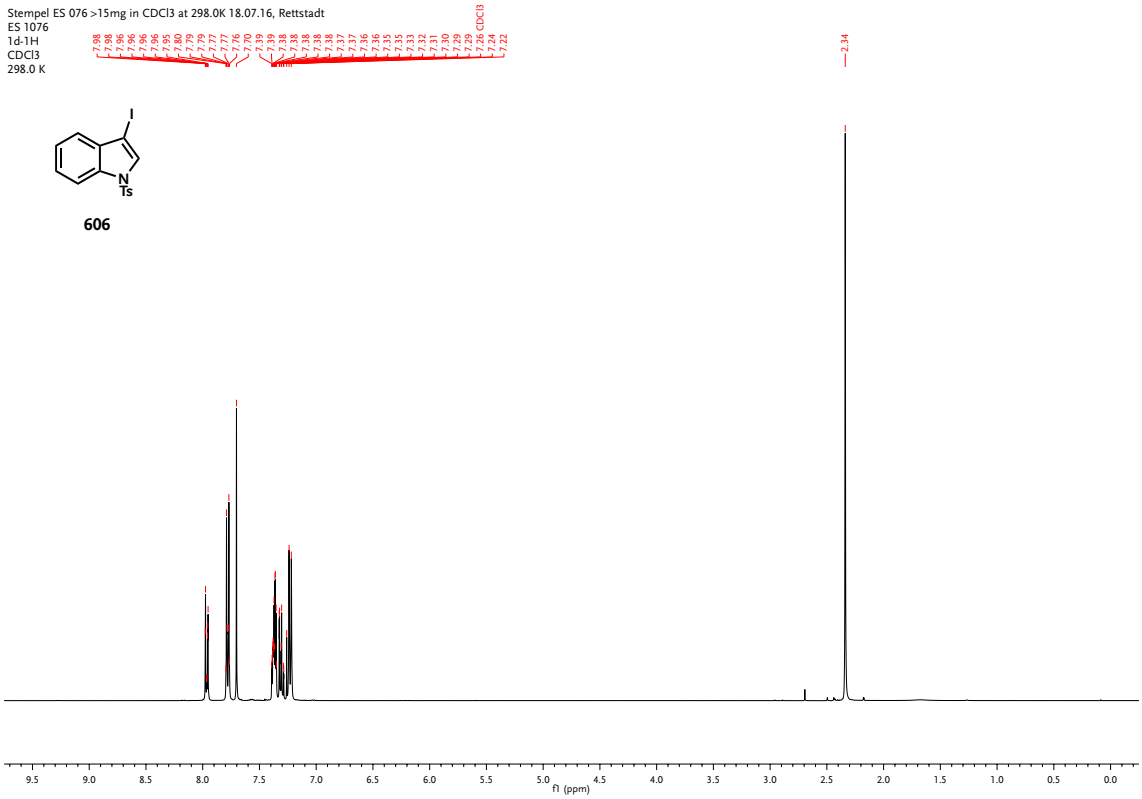
Spectrum B-58. COSY60 2D-NMR spectrum for compound **585** *(experimental on page 214)*.



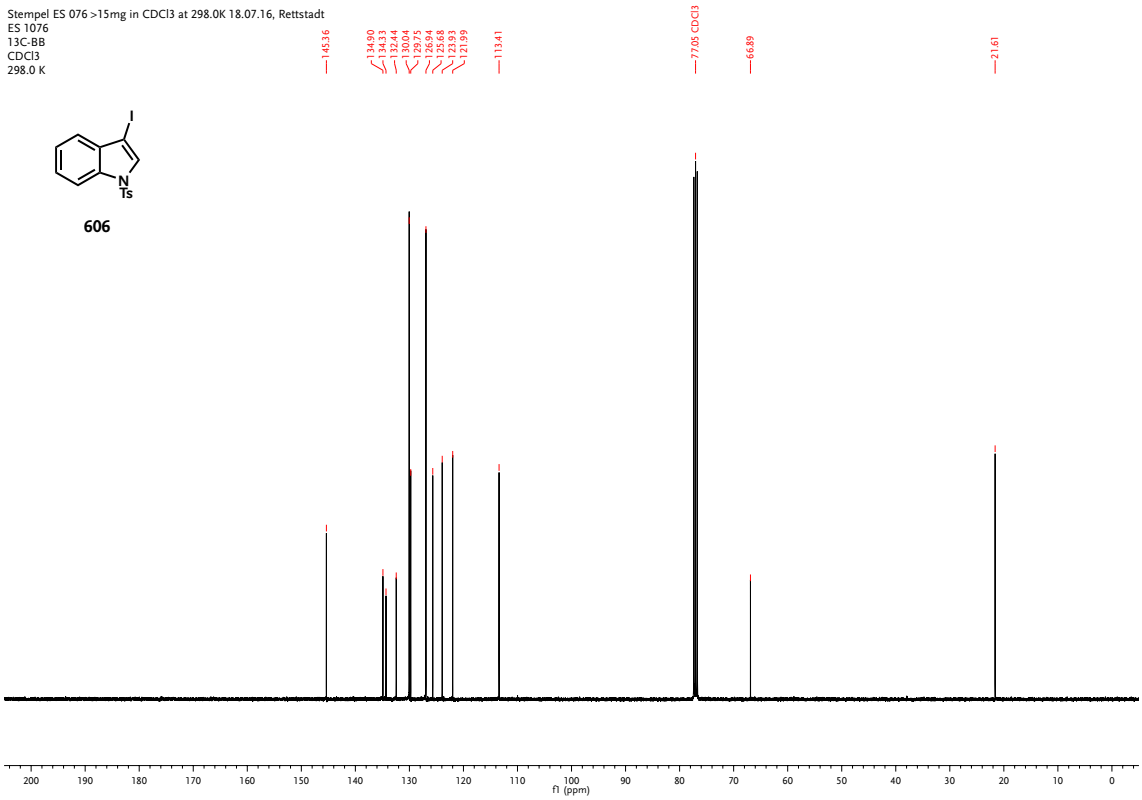
Spectrum B-59. HSQC 2D-NMR spectrum for compound **585** *(experimental on page 214)*.



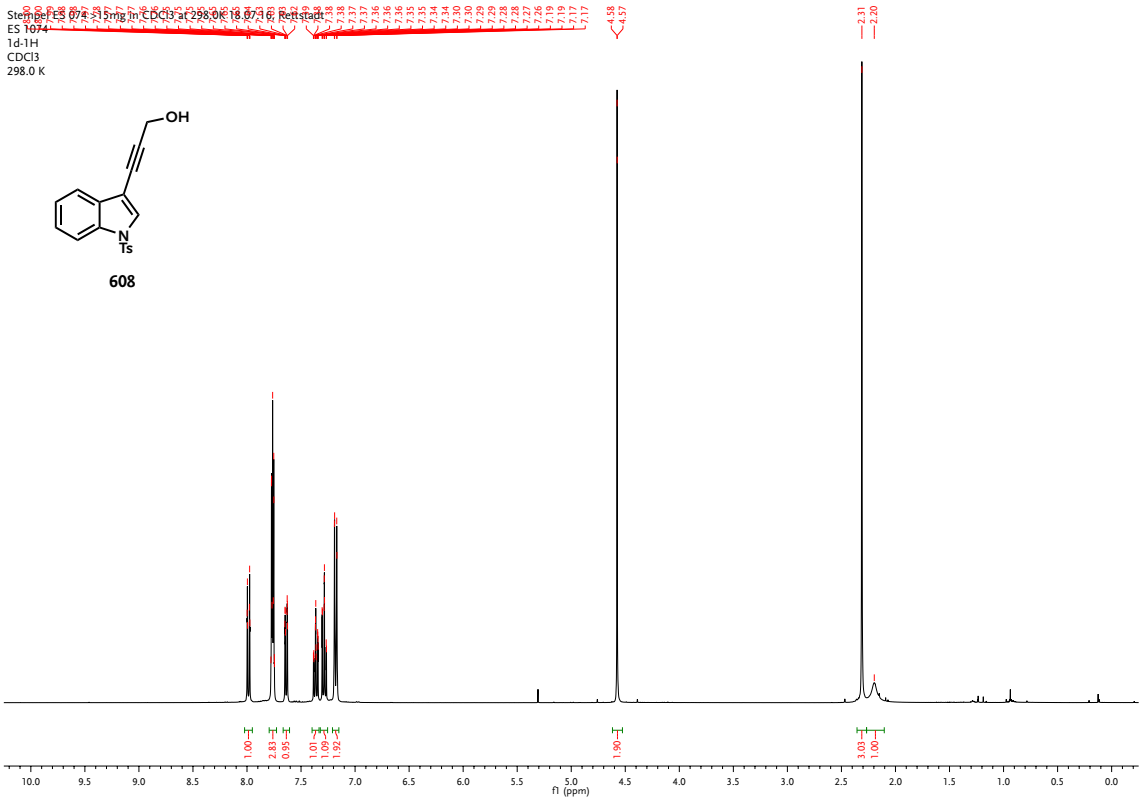
Spectrum B-60. HMBC 2D-NMR spectrum for compound **585** *(experimental on page 214)*.



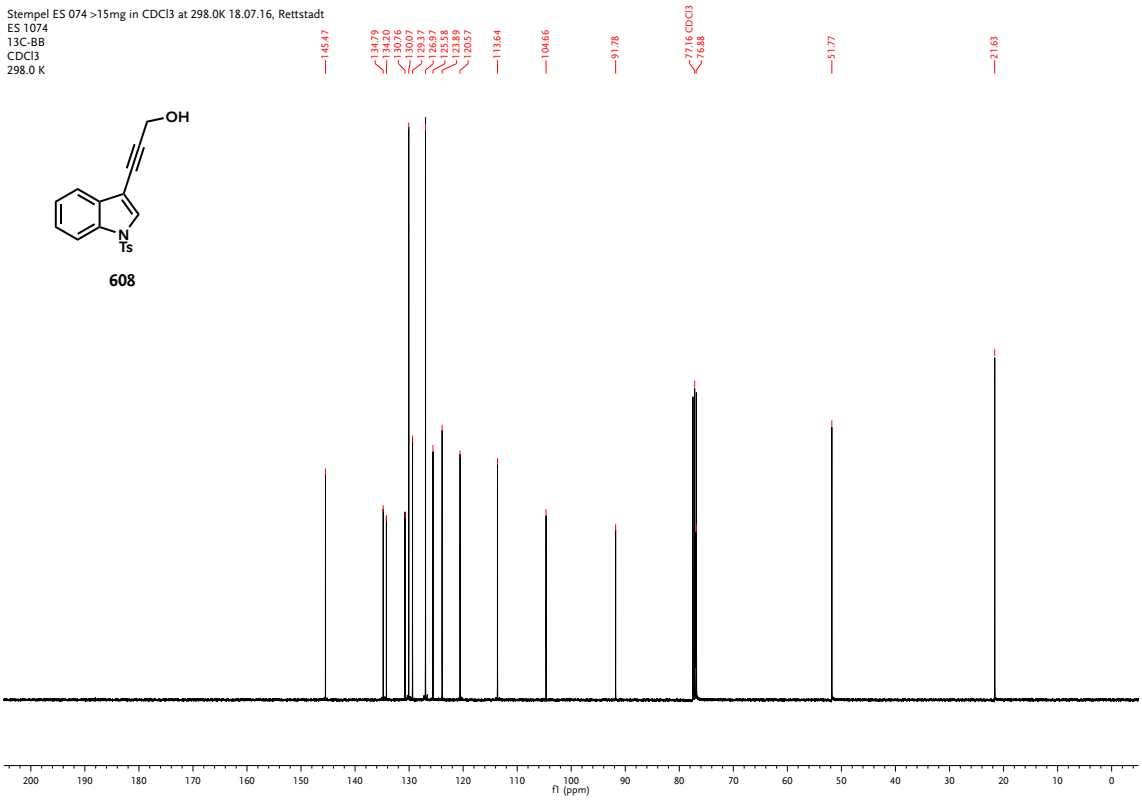
Spectrum B-61. ^{1}H-NMR spectrum for compound **606** *(experimental on page 215)*.



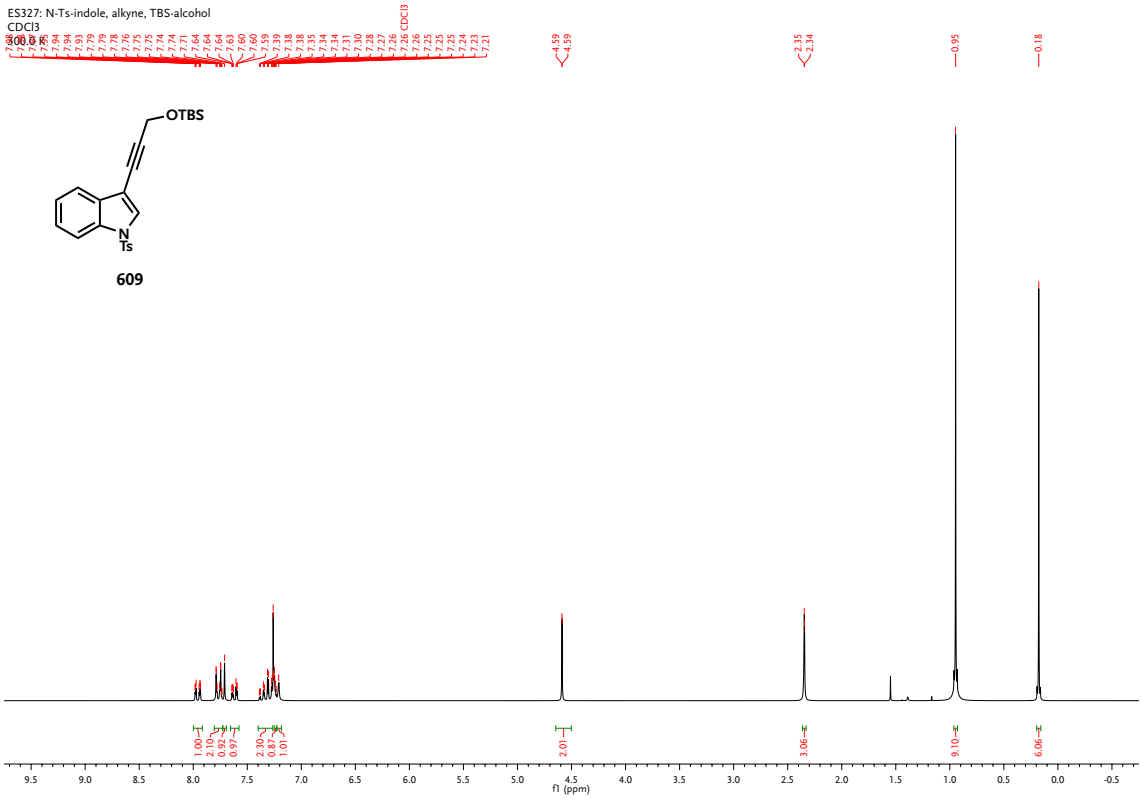
Spectrum B-62. ^{13}C-NMR spectrum for compound **606** *(experimental on page 215)*.



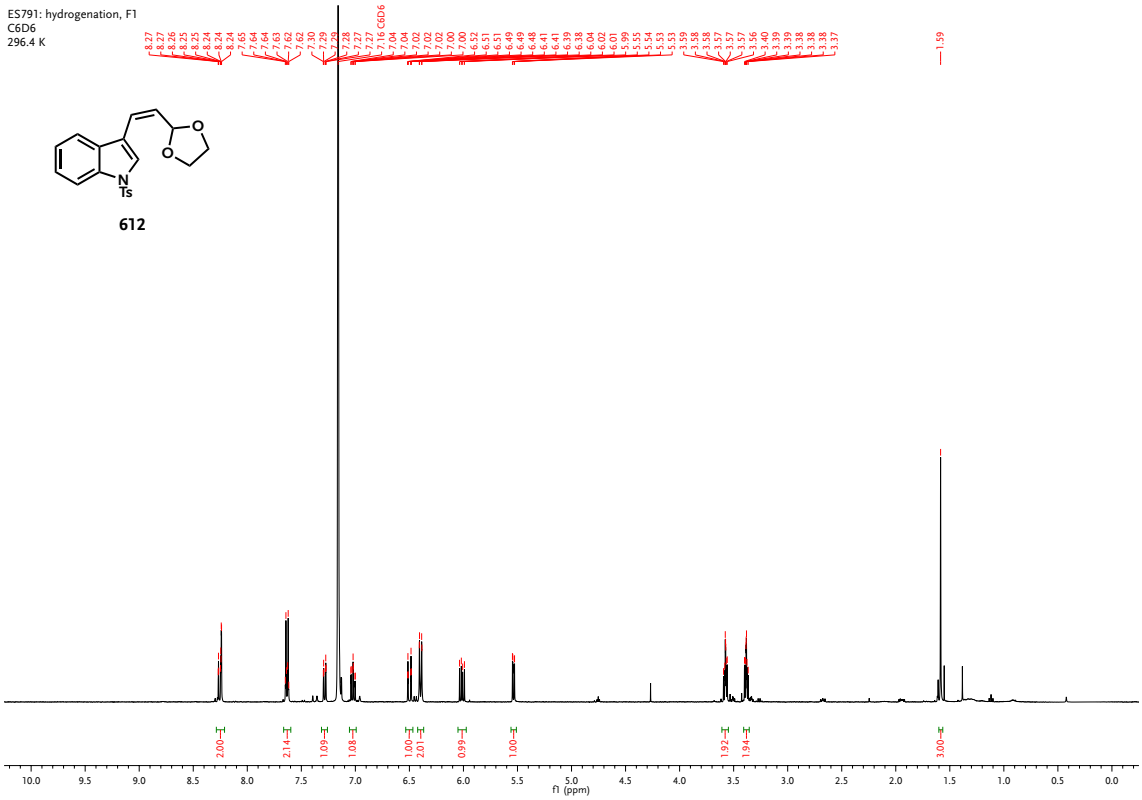
Spectrum B-63. ^{1}H-NMR spectrum for compound **608** *(experimental on page 215)*.



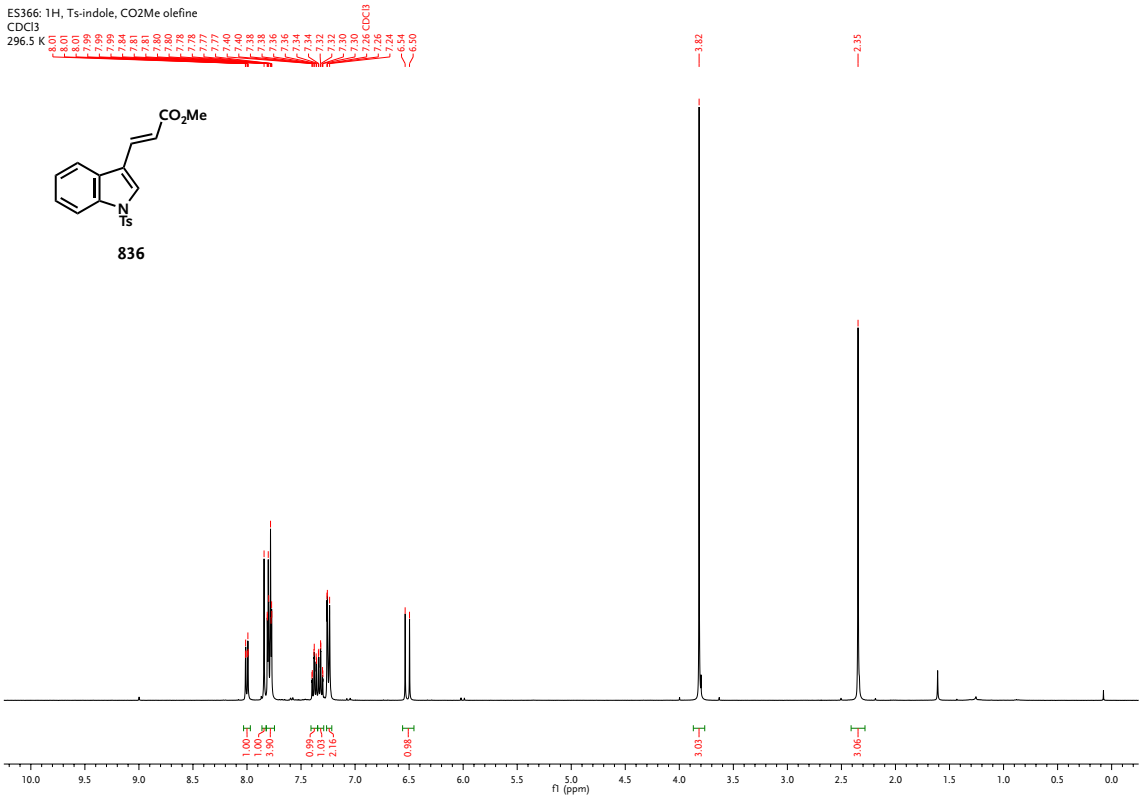
Spectrum B-64. ^{13}C-NMR spectrum for compound **608** *(experimental on page 215)*.



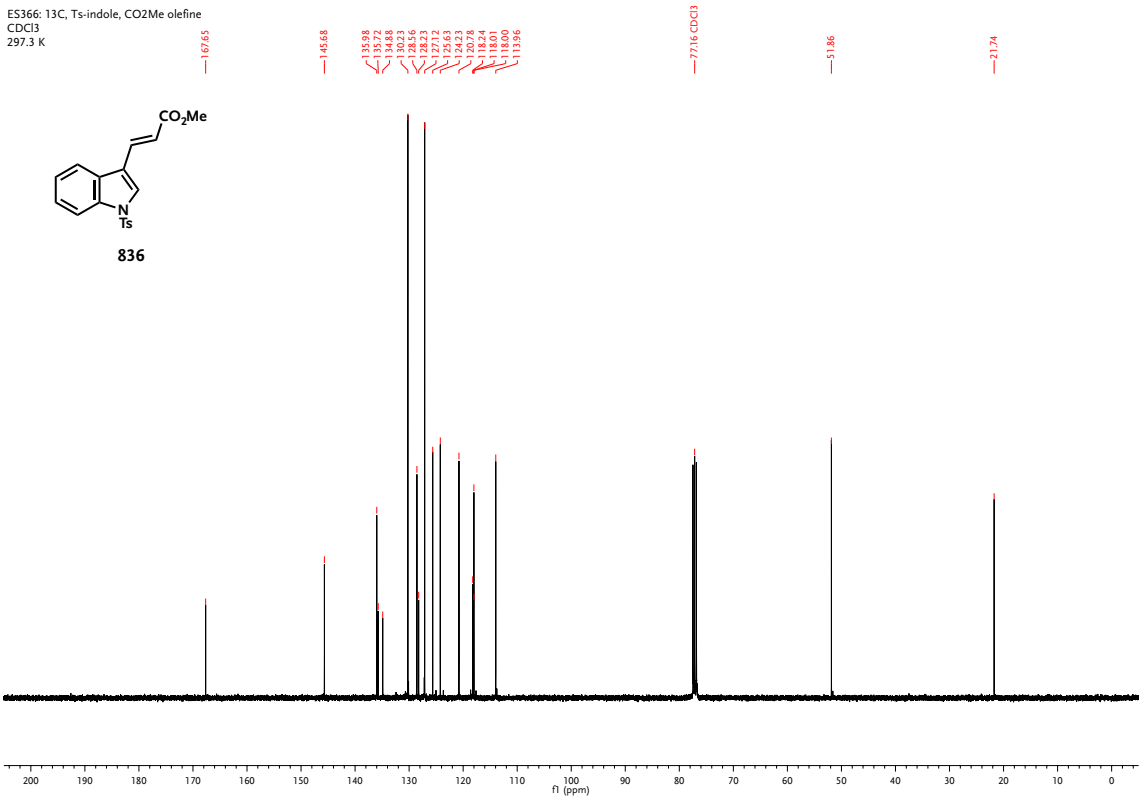
Spectrum B-65. ^{1}H-NMR spectrum for compound **609** *(experimental on page 216)*.



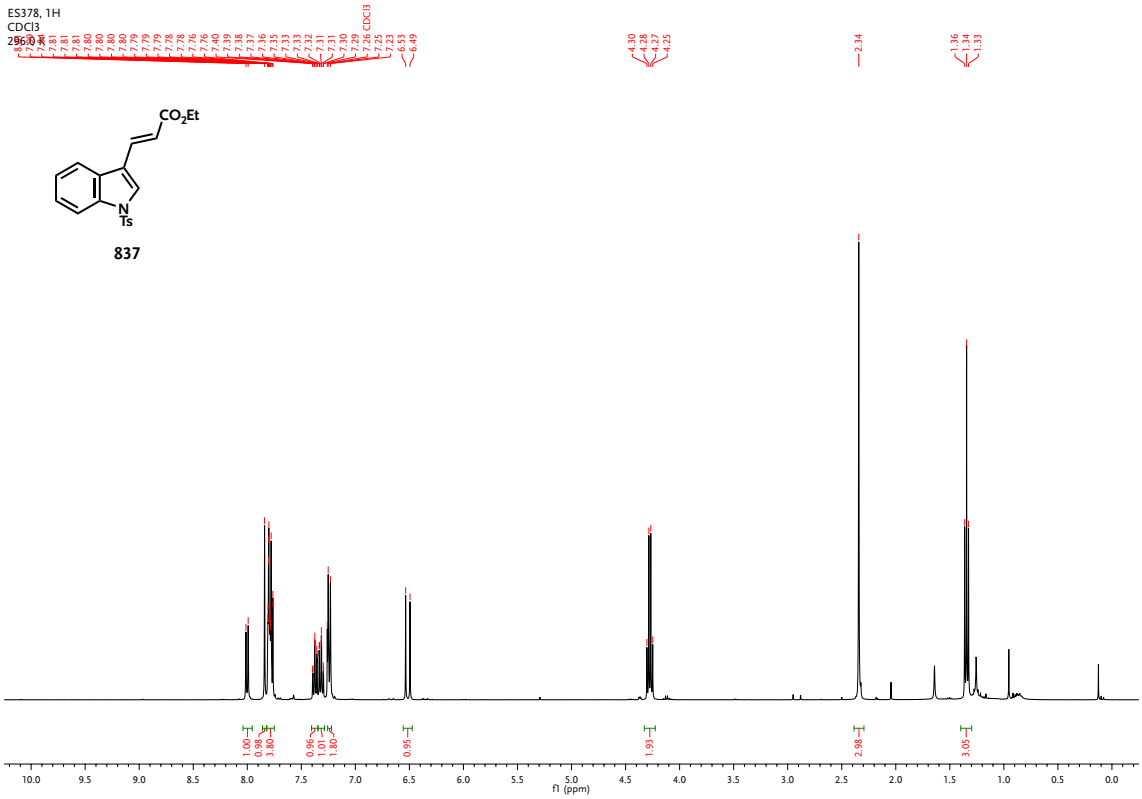
Spectrum B-66. ^{1}H-NMR spectrum for compound **612** *(experimental on page 217)*.



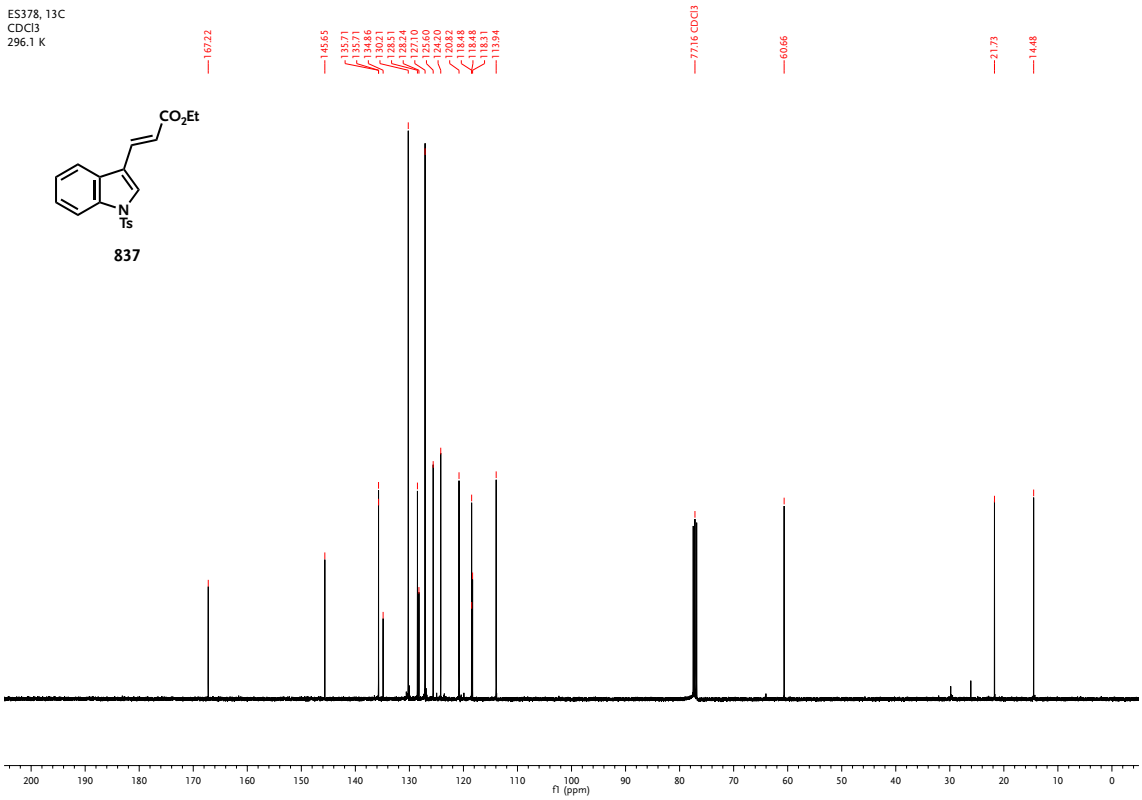
Spectrum B-67. [1]H-NMR spectrum for compound **836** *(experimental on page 219)*.



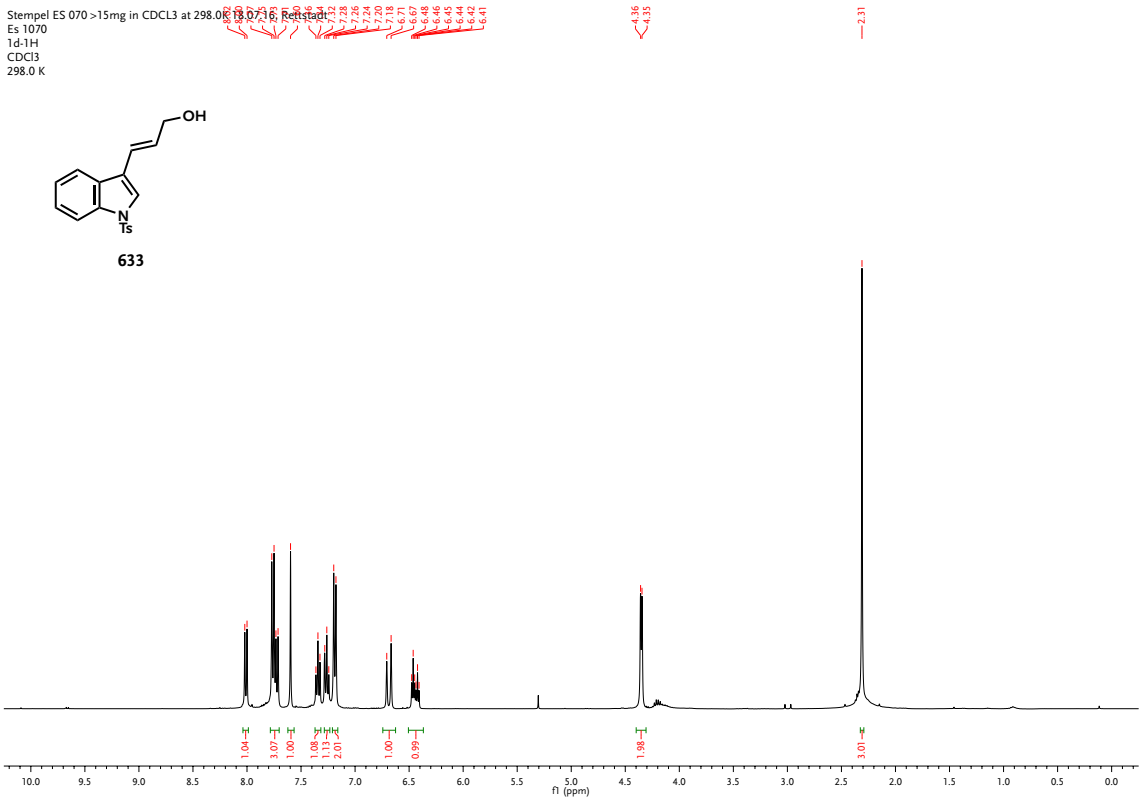
Spectrum B-68. [13]C-NMR spectrum for compound **836** *(experimental on page 219)*.



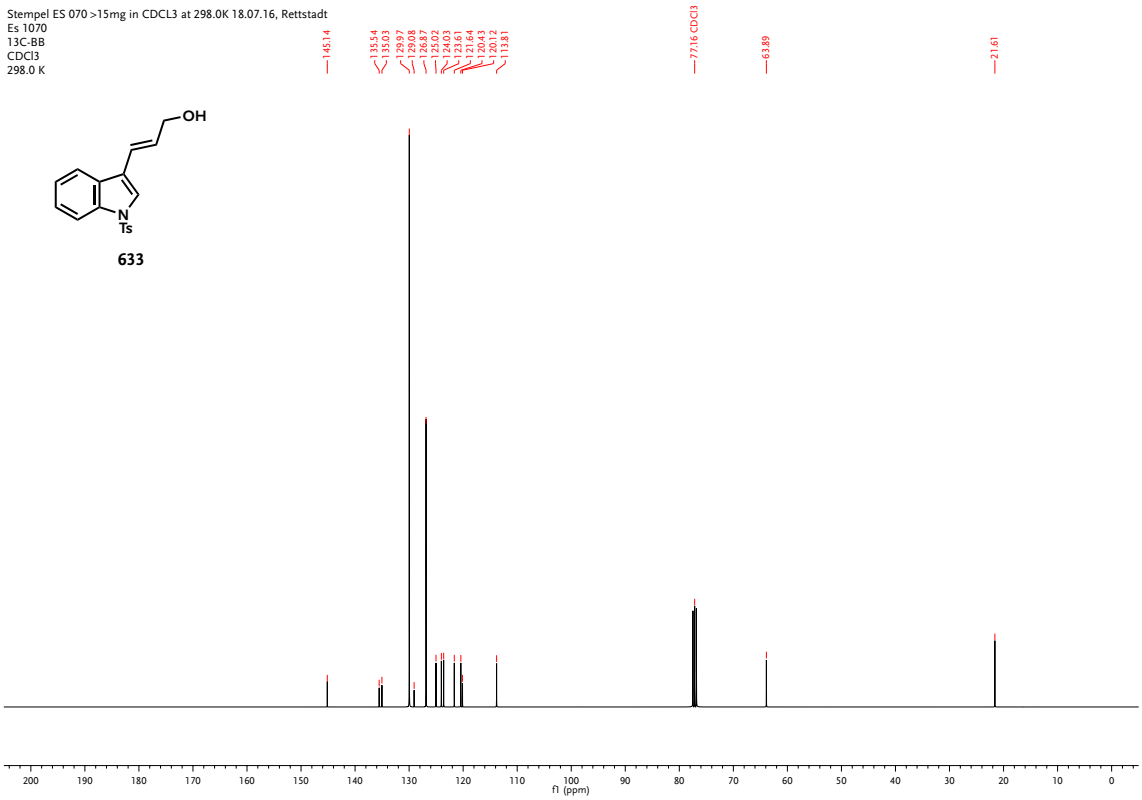
Spectrum B-69. ^{1}H-NMR spectrum for compound **837** *(experimental on page 219)*.



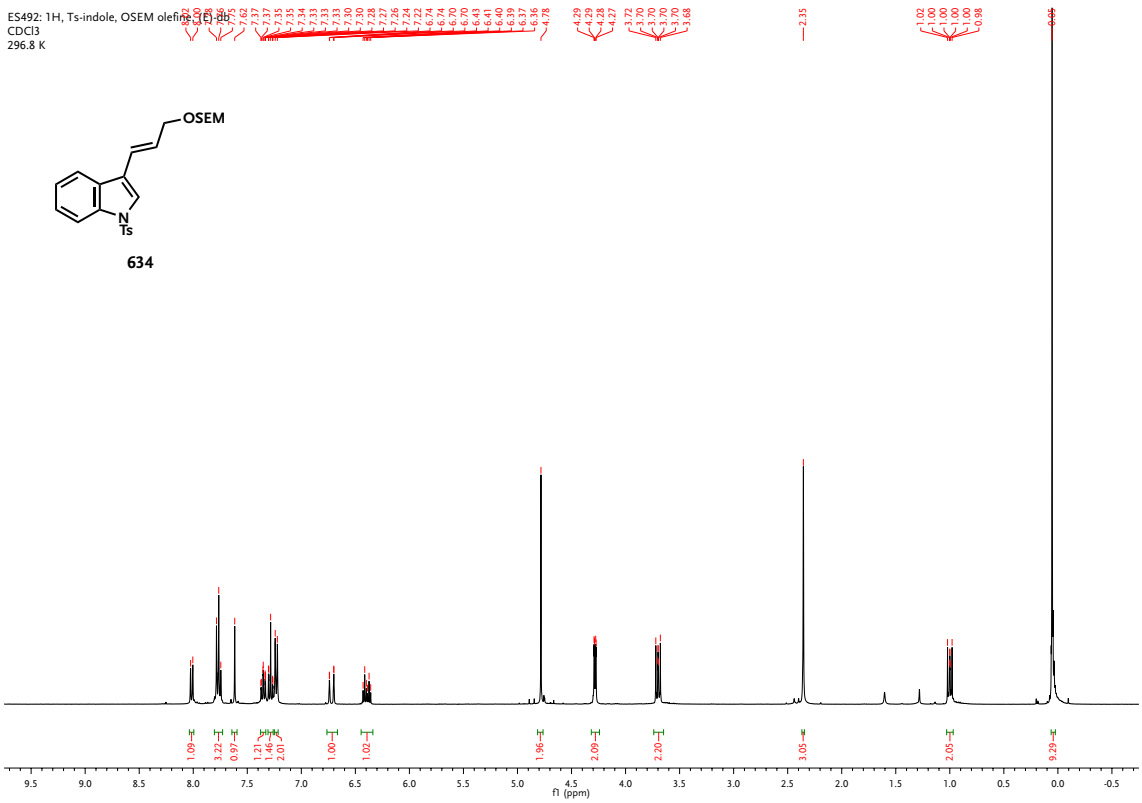
Spectrum B-70. ^{13}C-NMR spectrum for compound **837** *(experimental on page 219)*.



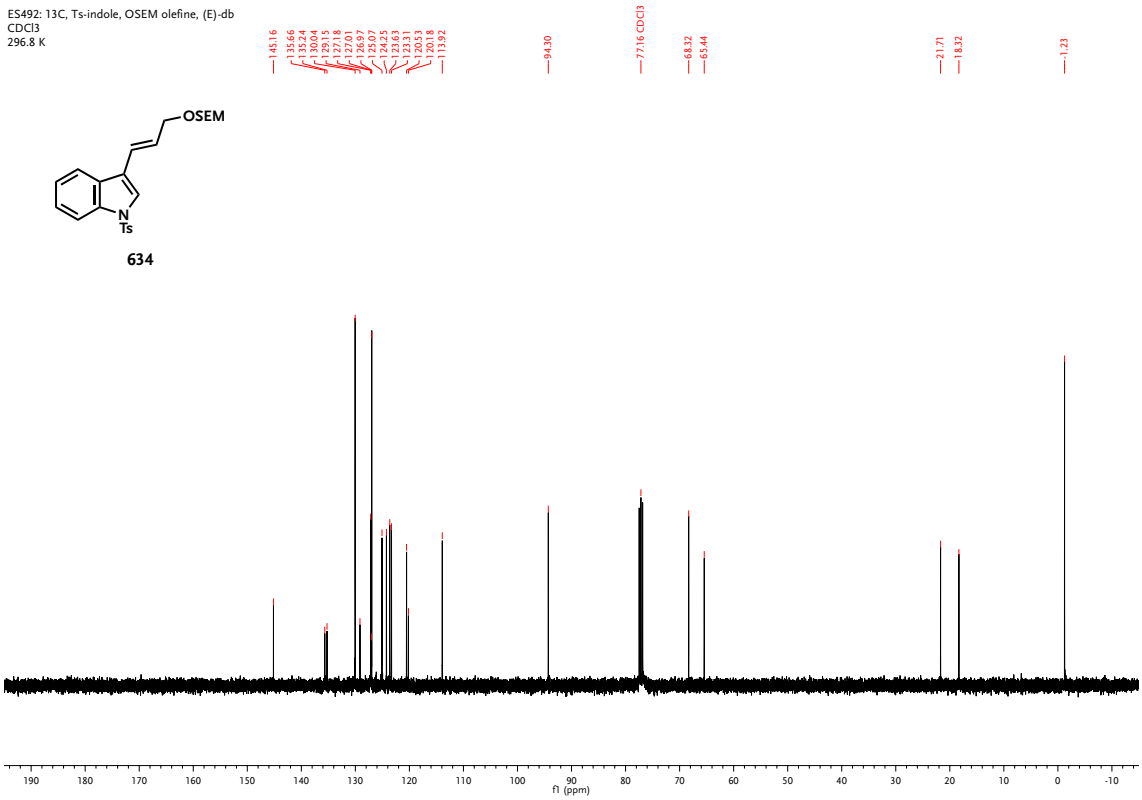
Spectrum B-71. ^{1}H-NMR spectrum for compound **633** *(experimental on page 220)*.



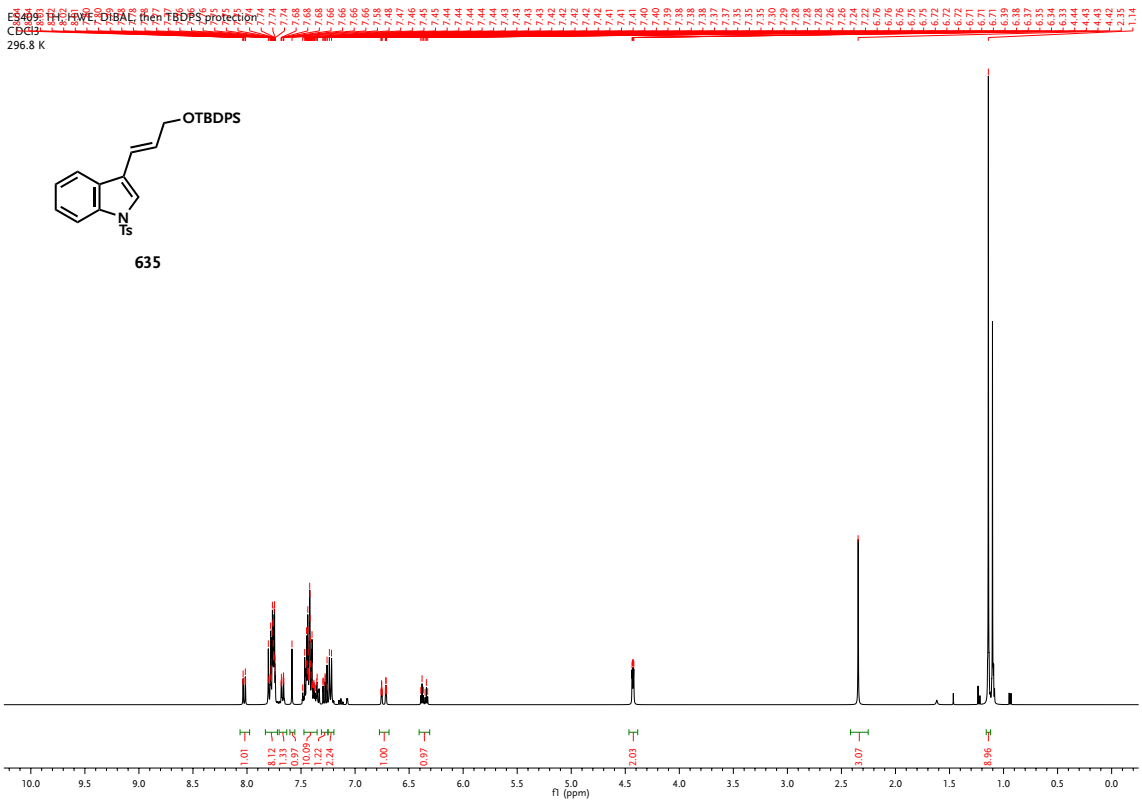
Spectrum B-72. ^{13}C-NMR spectrum for compound **633** *(experimental on page 220)*.



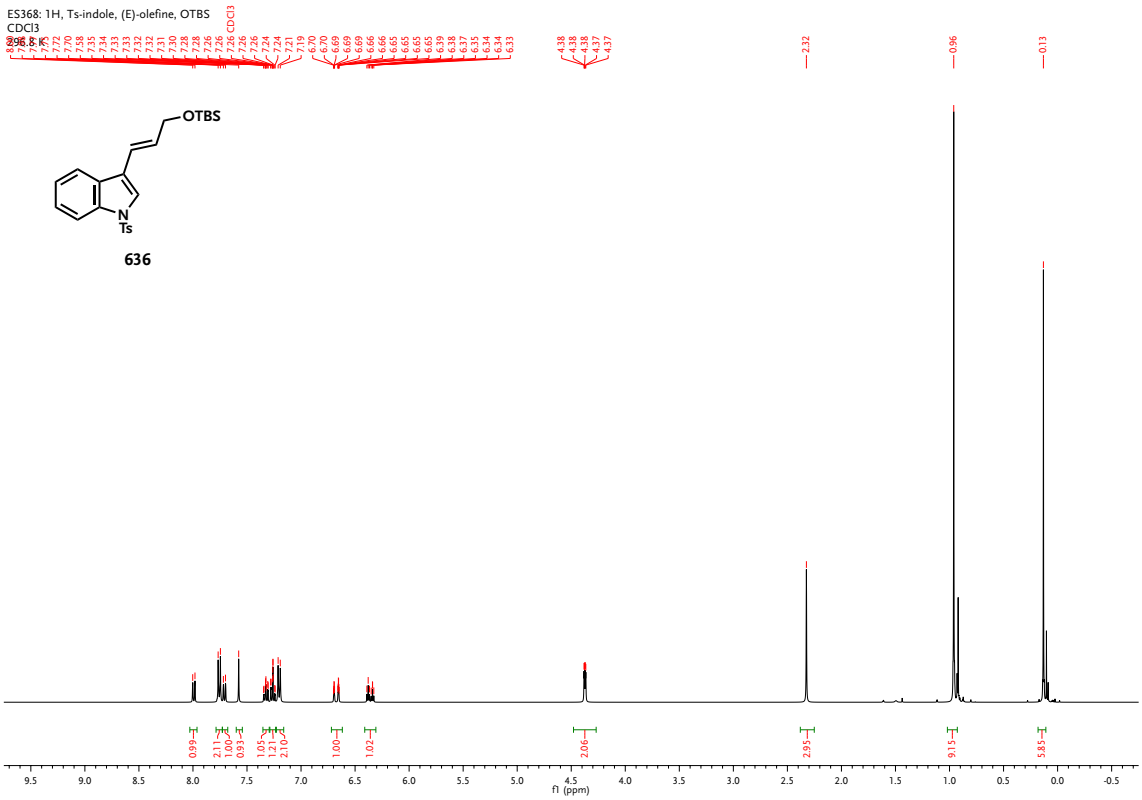
Spectrum B-73. ^{1}H-NMR spectrum for compound **634** *(experimental on page 220)*.



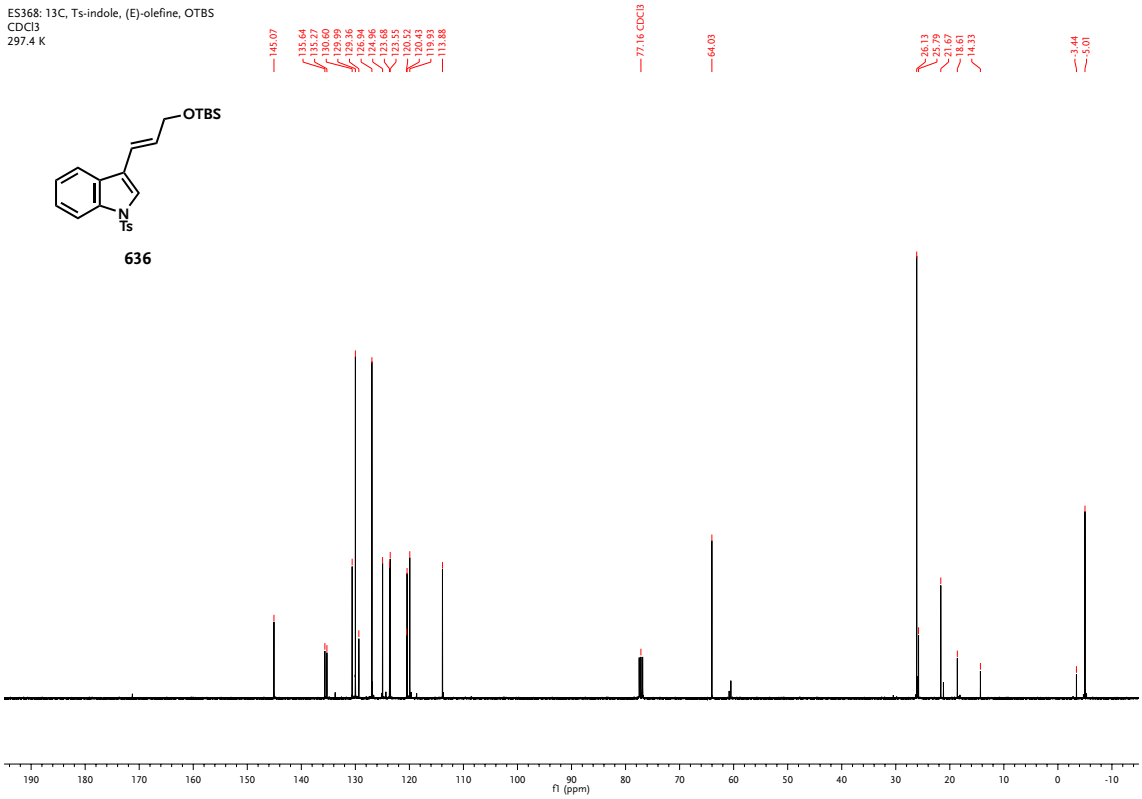
Spectrum B-74. ^{13}C-NMR spectrum for compound **634** *(experimental on page 220)*.



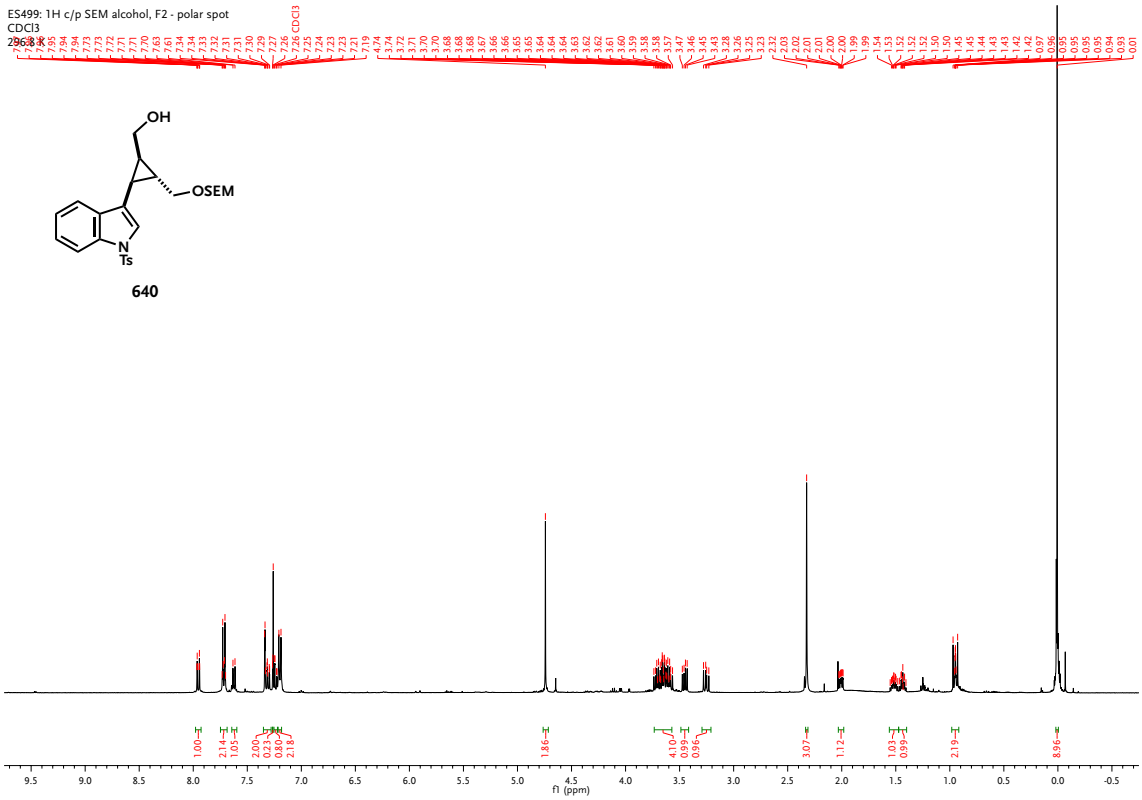
Spectrum B-75. [1]H-NMR spectrum for compound **635** *(experimental on page 221)*.



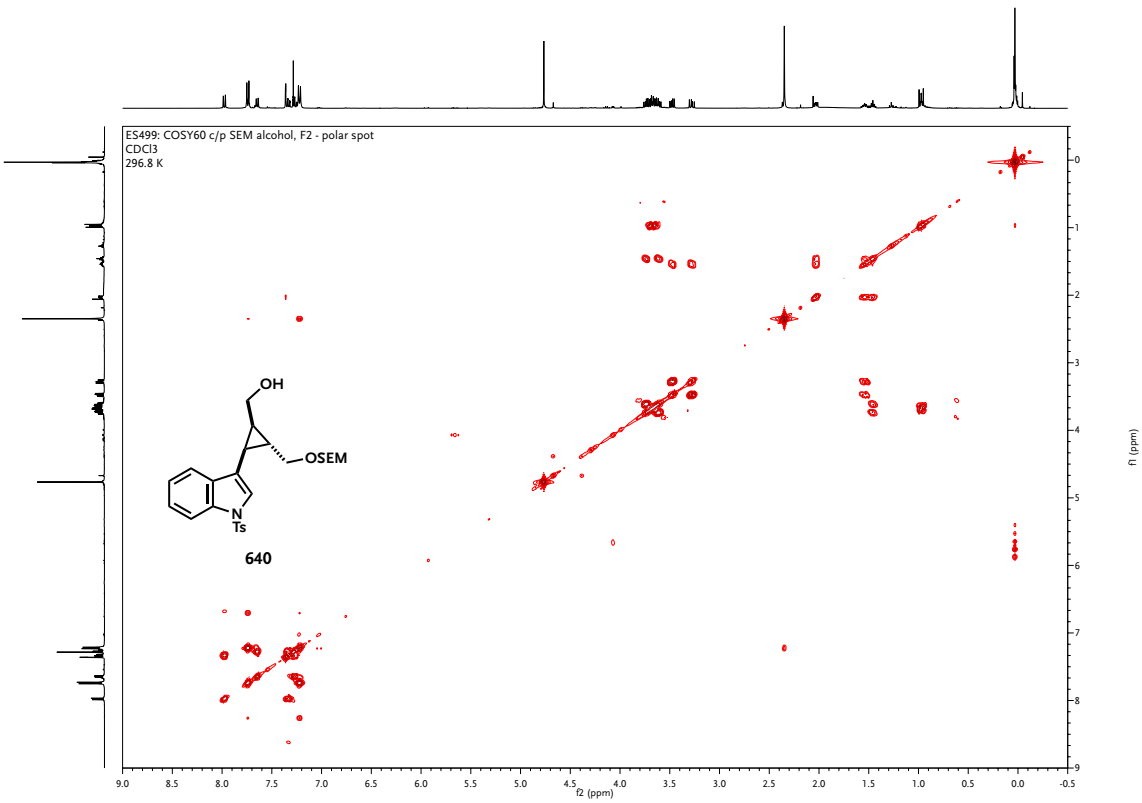
Spectrum B-76. [1]H-NMR spectrum for compound **636** *(experimental on page 221)*.



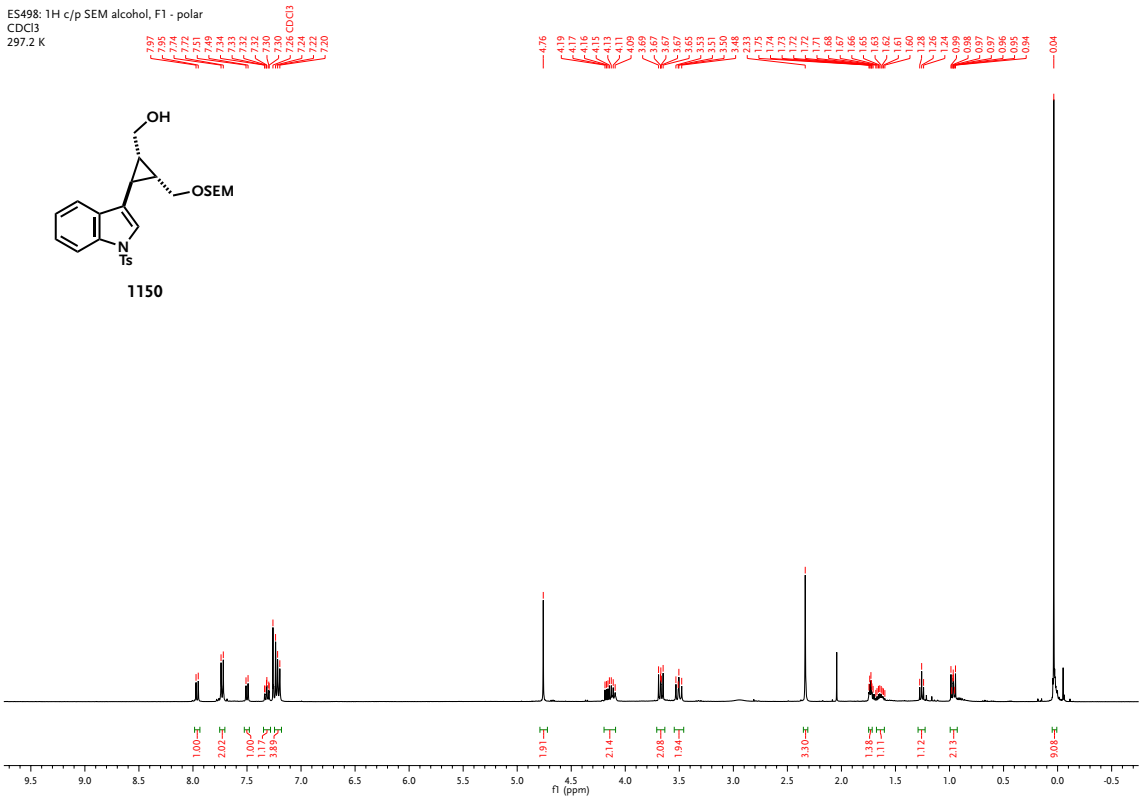
Spectrum B-77. ^{13}C-NMR spectrum for compound **636** *(experimental on page 221)*.



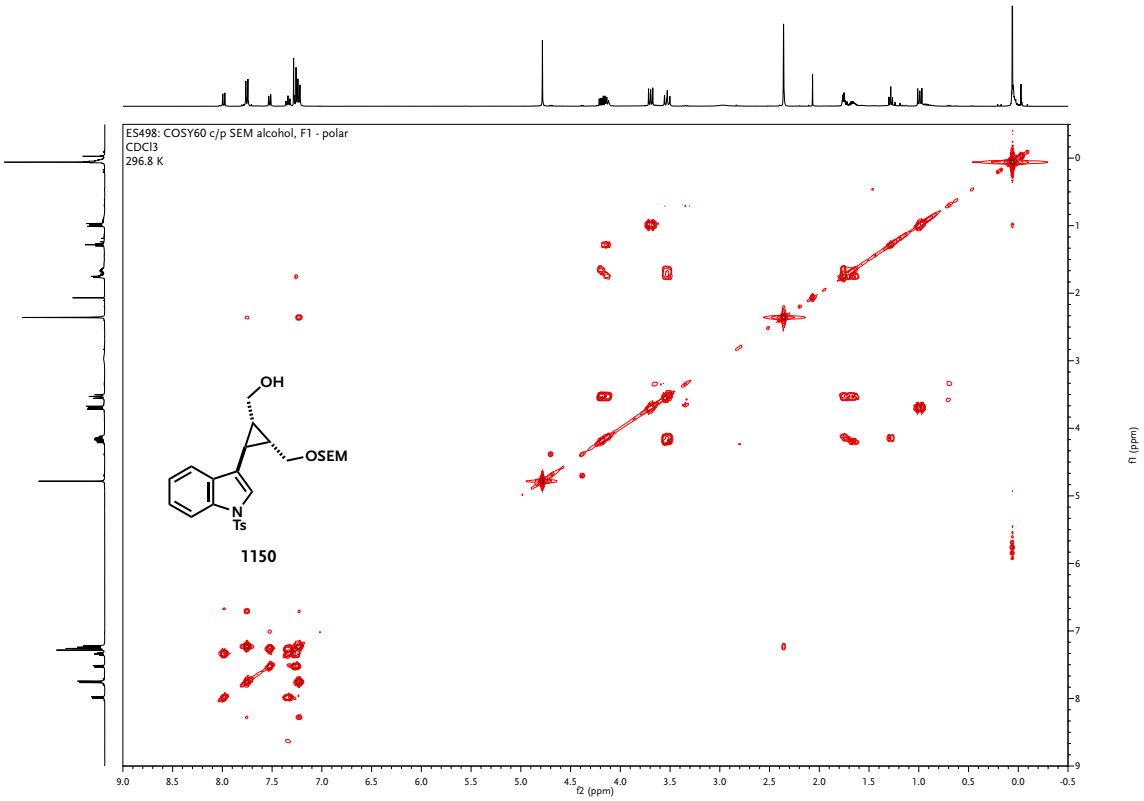
Spectrum B-78. ^{1}H-NMR spectrum for compound **640** *(experimental on page 222)*.



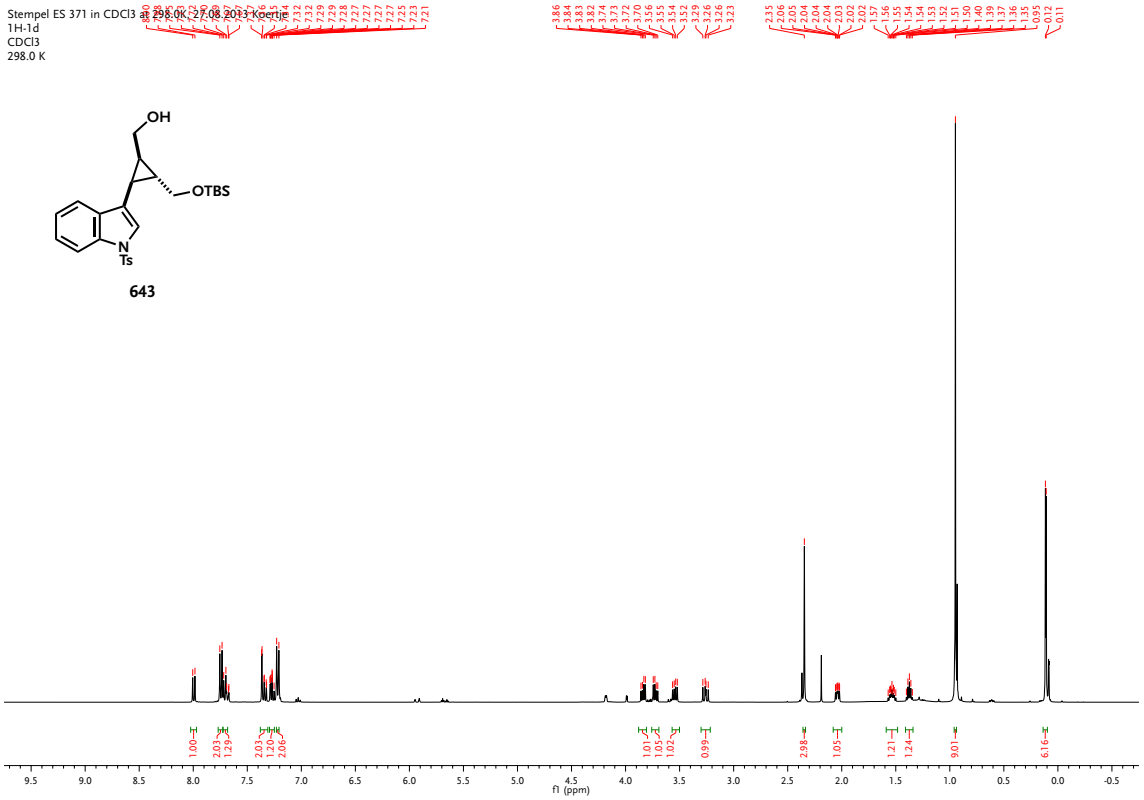
Spectrum B-79. COSY60 2D-NMR spectrum for compound **640** *(experimental on page 222)*.



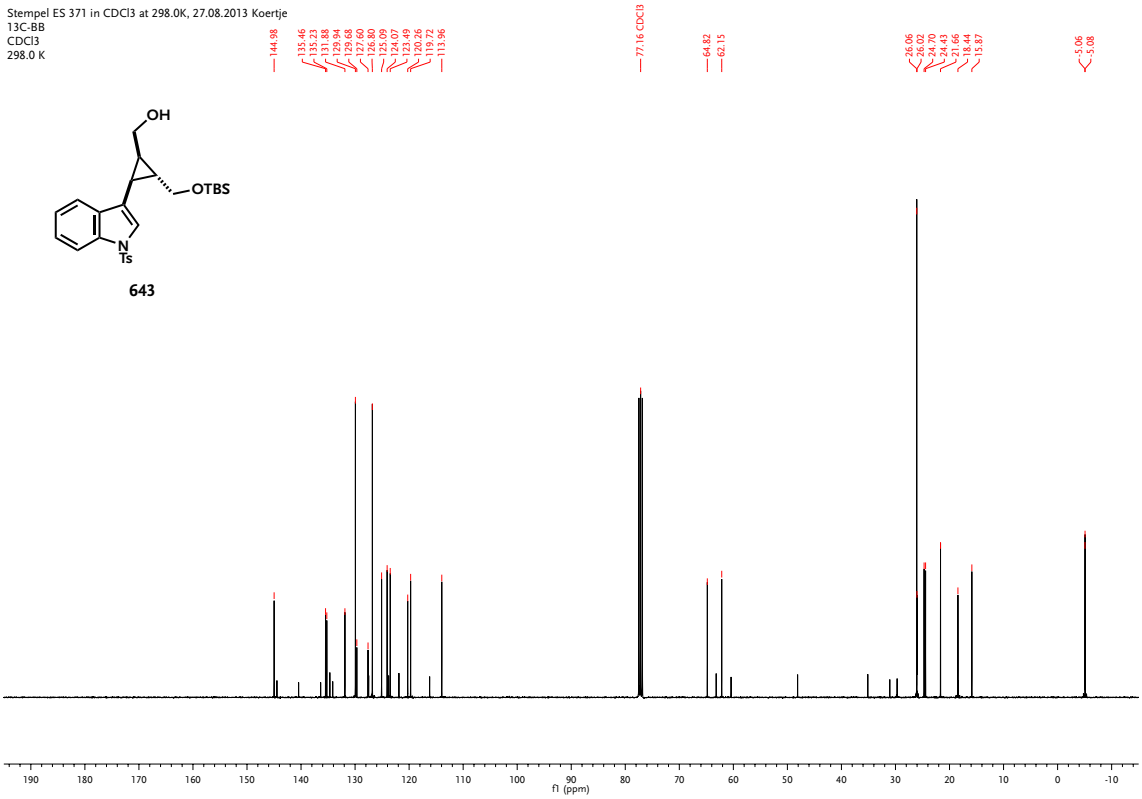
Spectrum B-80. ^{1}H-NMR spectrum for compound **1150** *(experimental on page 222)*.



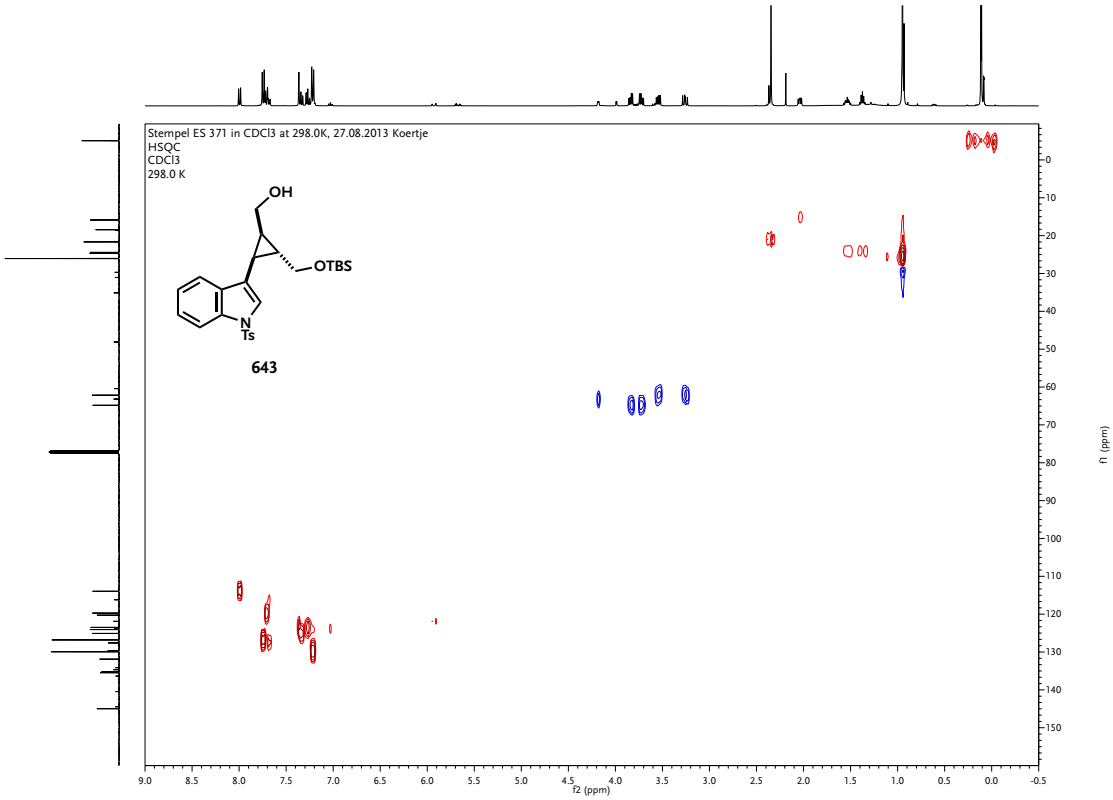
Spectrum B-81. COSY60 2D-NMR spectrum for compound **1150** *(experimental on page 222)*.



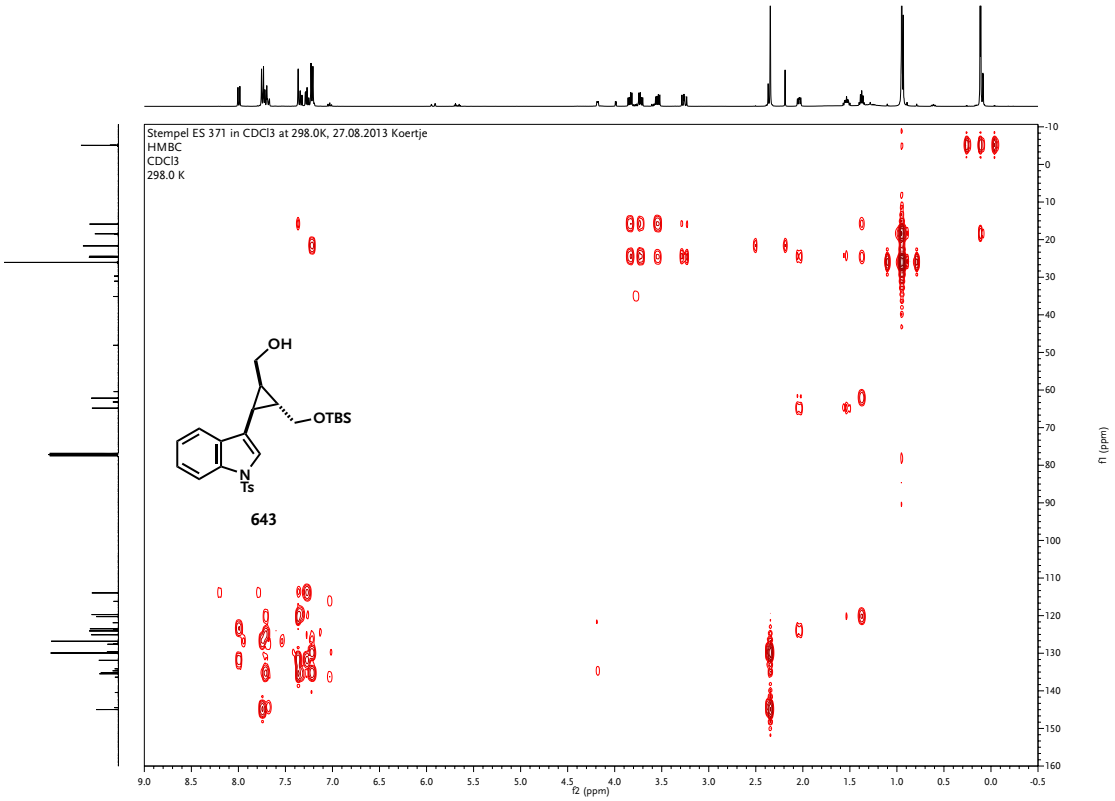
Spectrum B-82. ^{1}H-NMR spectrum for compound **643** *(experimental on page 223)*.



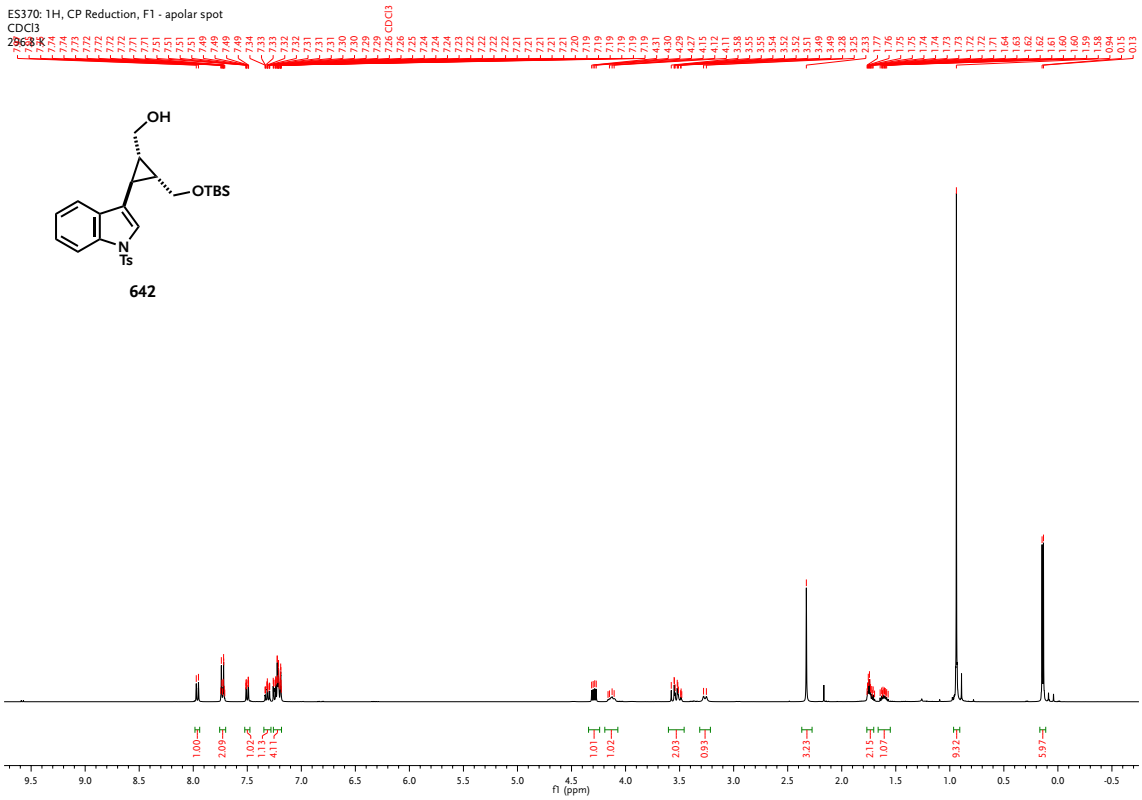
Spectrum B-83. ^{13}C-NMR spectrum for compound **643** *(experimental on page 223)*.



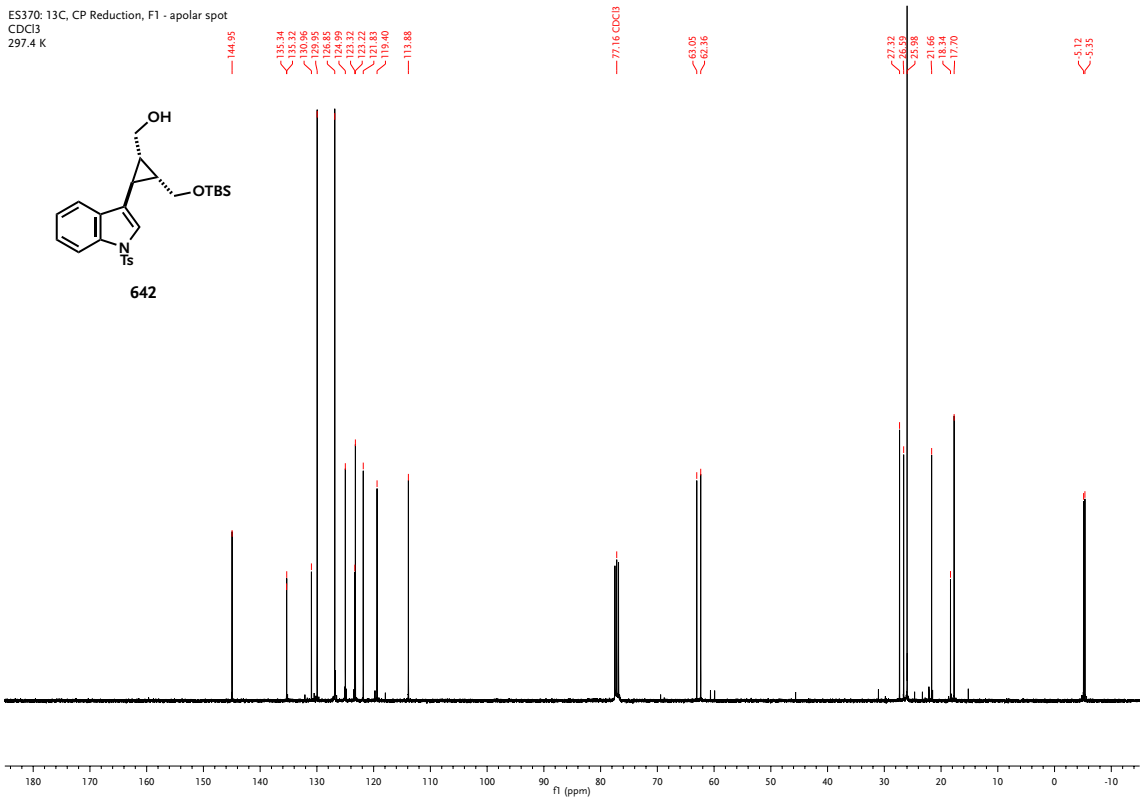
Spectrum B-84. HSQC 2D-NMR spectrum for compound **643** *(experimental on page 223)*.



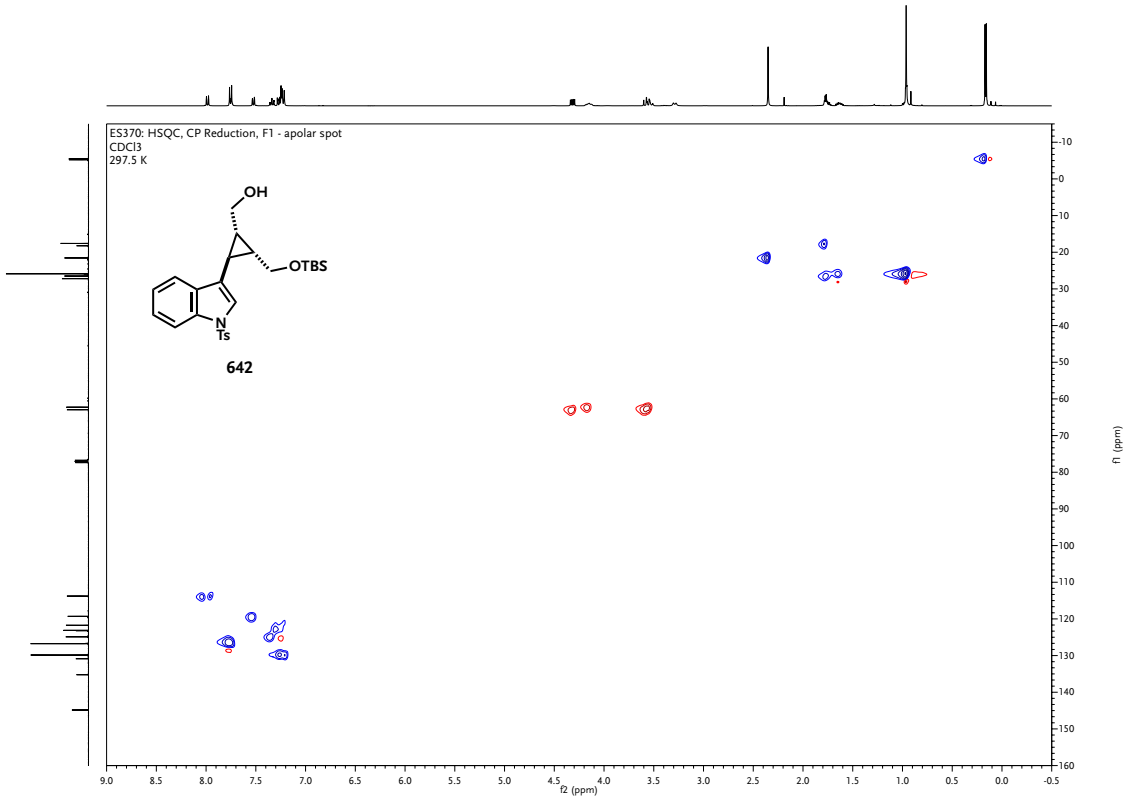
Spectrum B-85. HMBC 2D-NMR spectrum for compound **643** *(experimental on page 223)*.



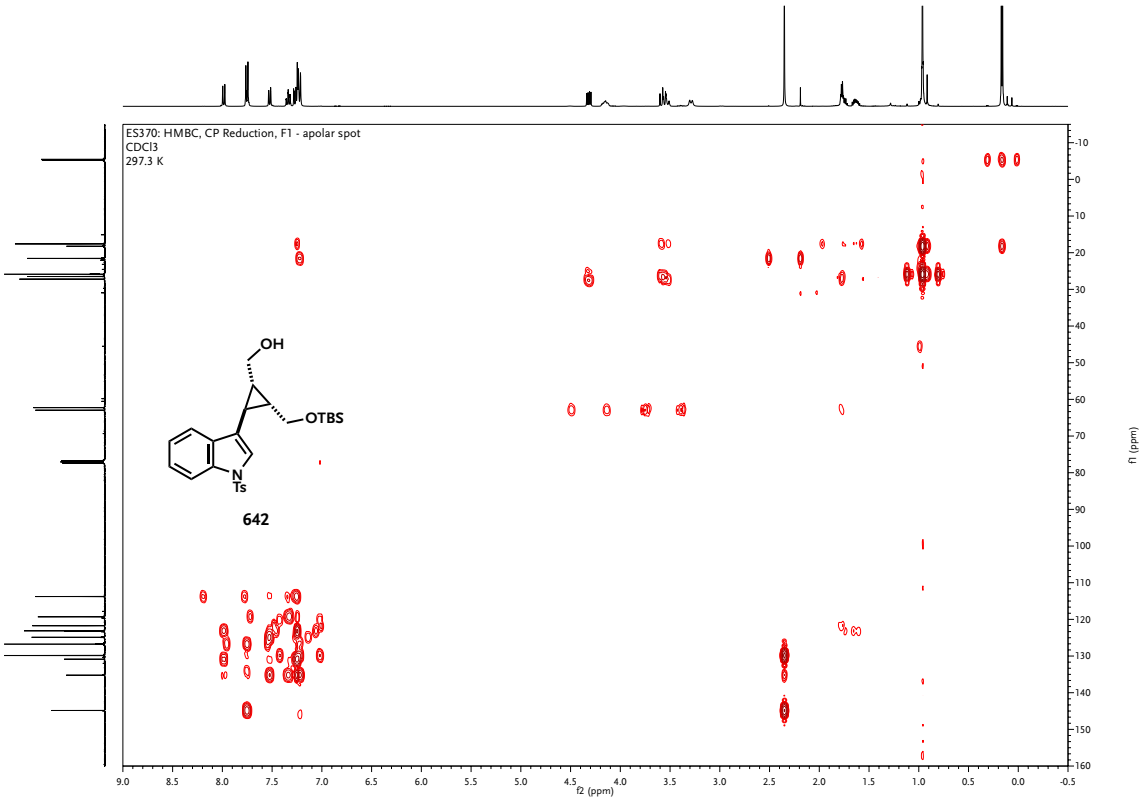
Spectrum B-86. ^{1}H-NMR spectrum for compound **642** *(experimental on page 223)*.



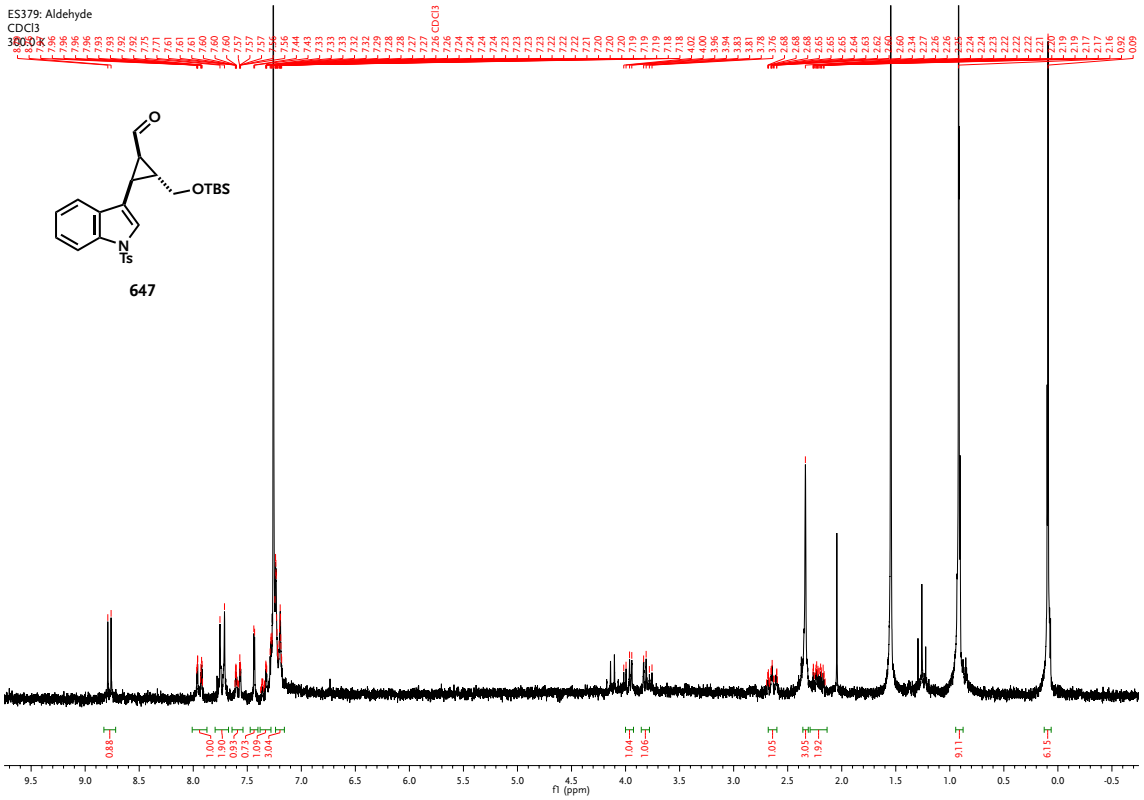
Spectrum B-87. ^{13}C-NMR spectrum for compound **642** *(experimental on page 223)*.



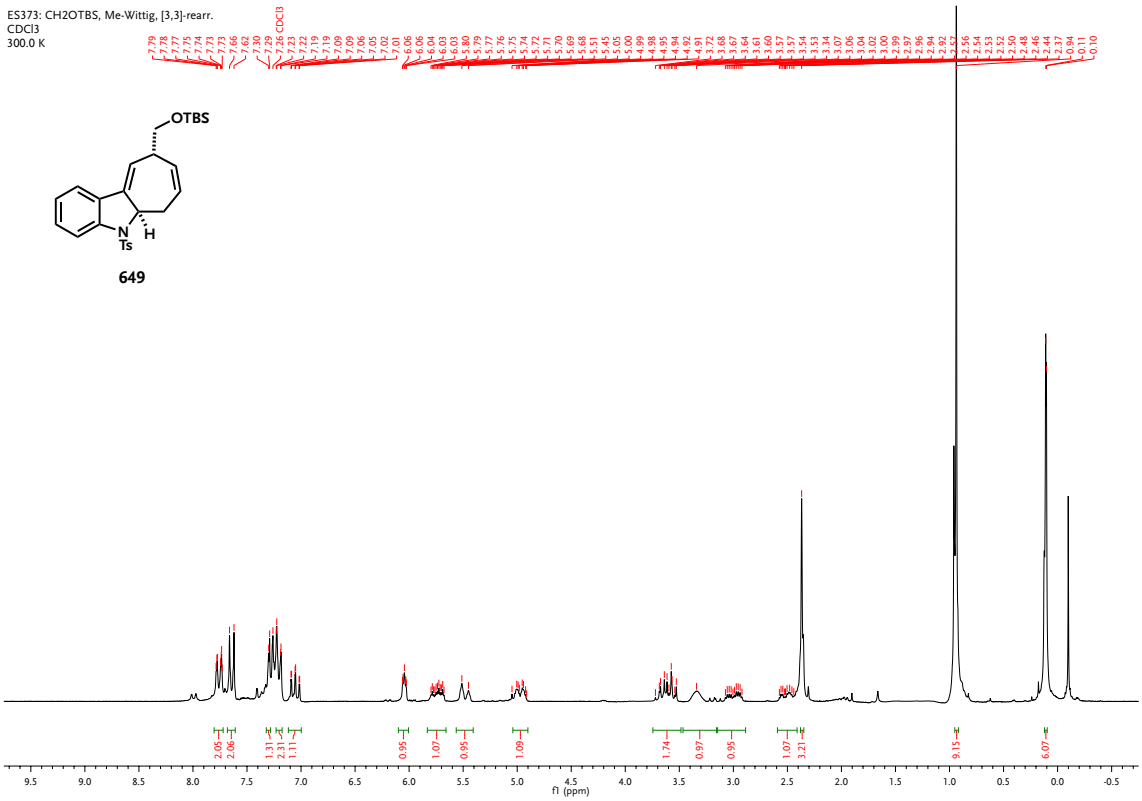
Spectrum B-88. HSQC 2D-NMR spectrum for compound **642** *(experimental on page 223)*.



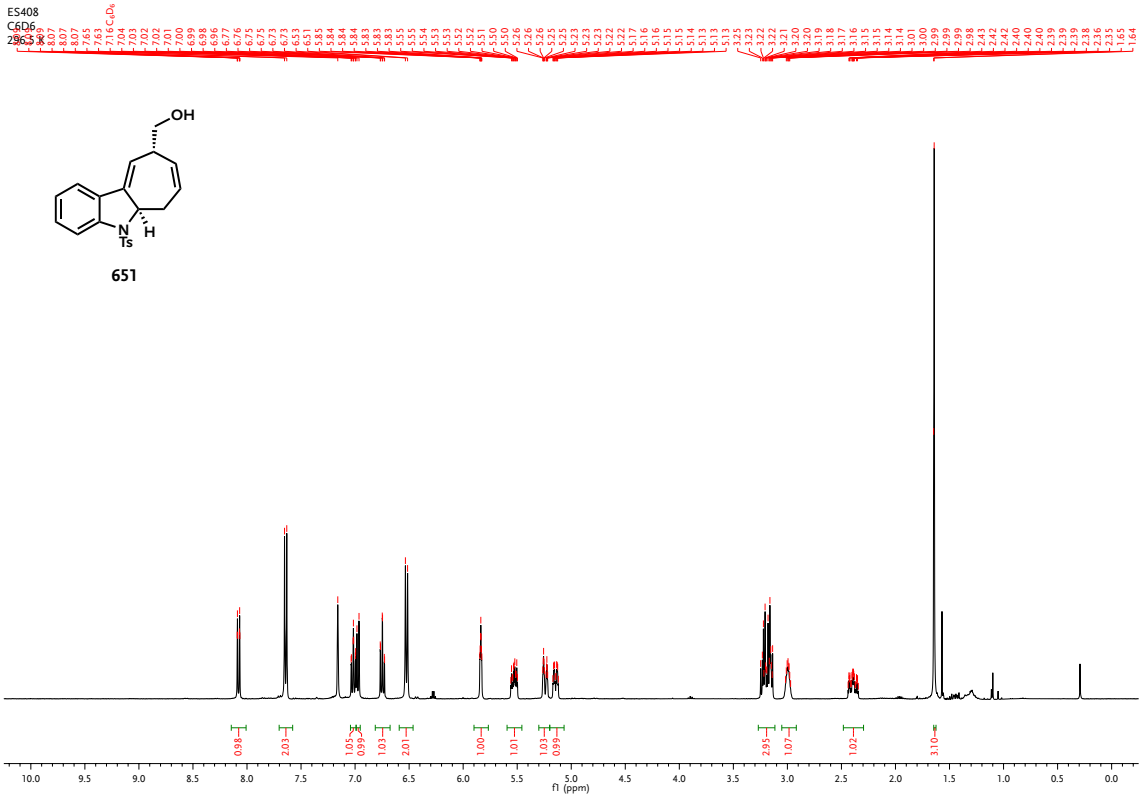
Spectrum B-89. HMBC 2D-NMR spectrum for compound **642** *(experimental on page 223)*.



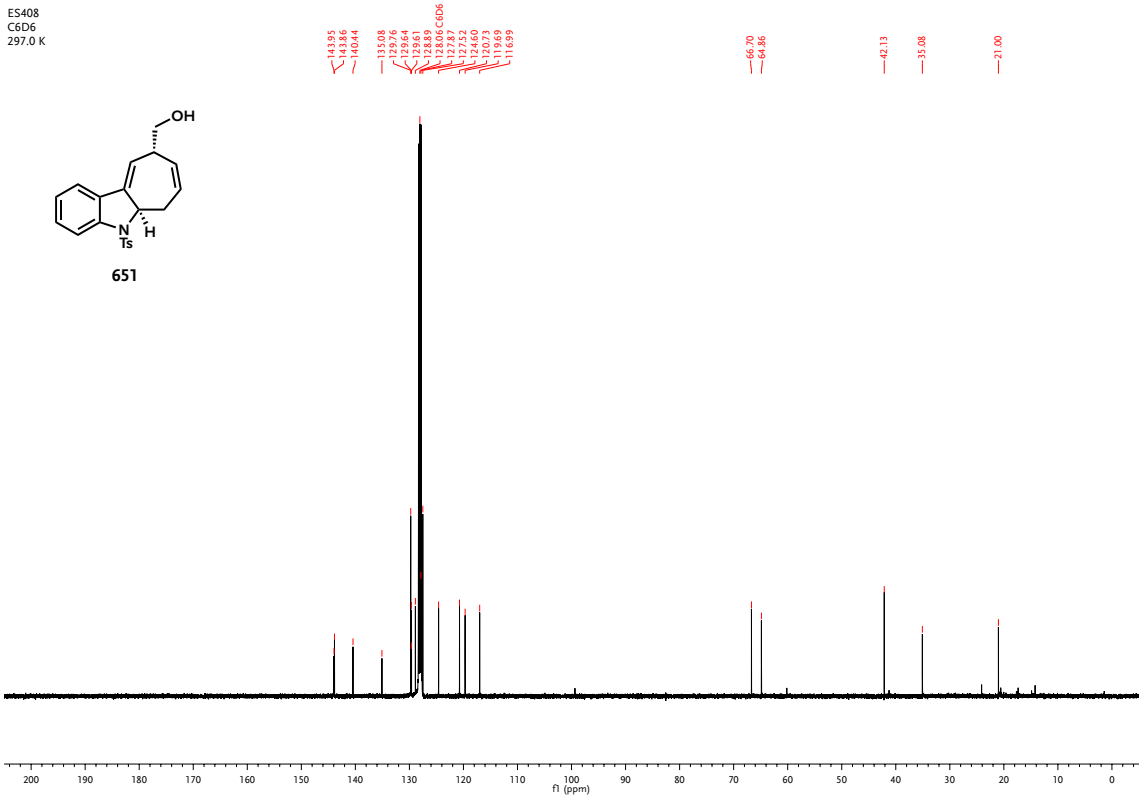
Spectrum B-90. ^{1}H-NMR spectrum for compound **647** *(experimental on page 224)*.



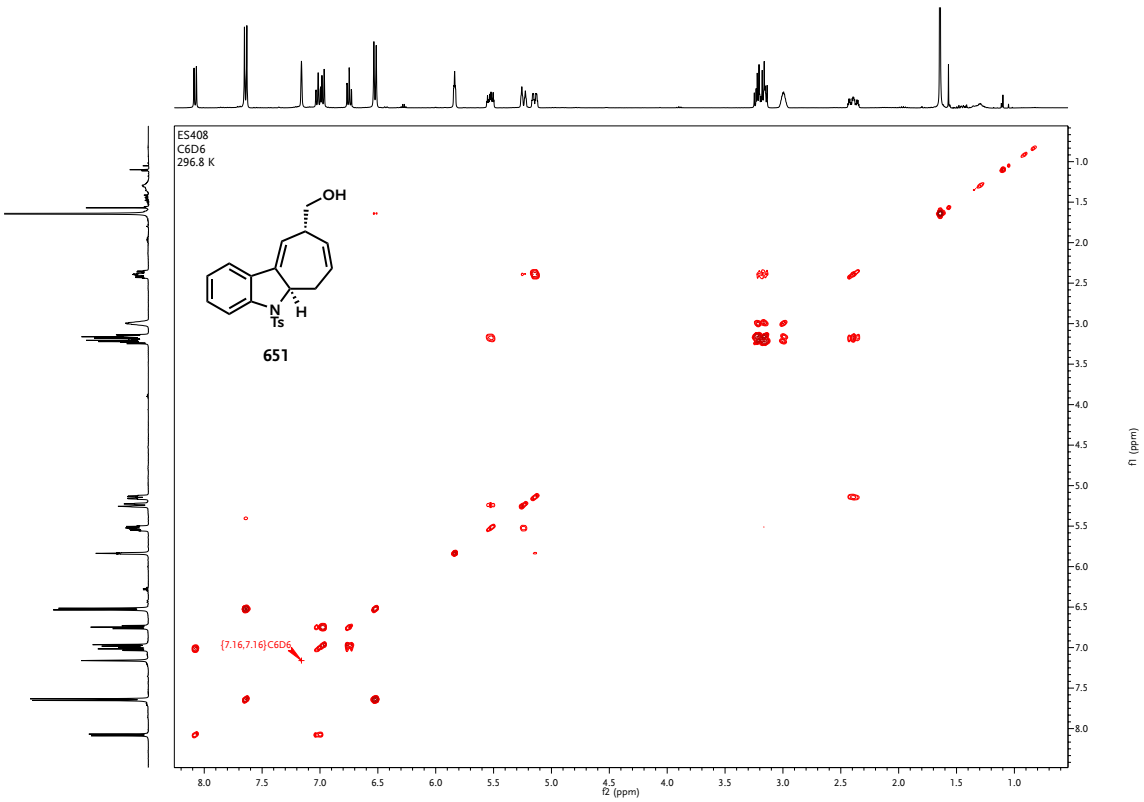
Spectrum B-91. [1]H-NMR spectrum for compound **649** *(experimental on page 225)*.



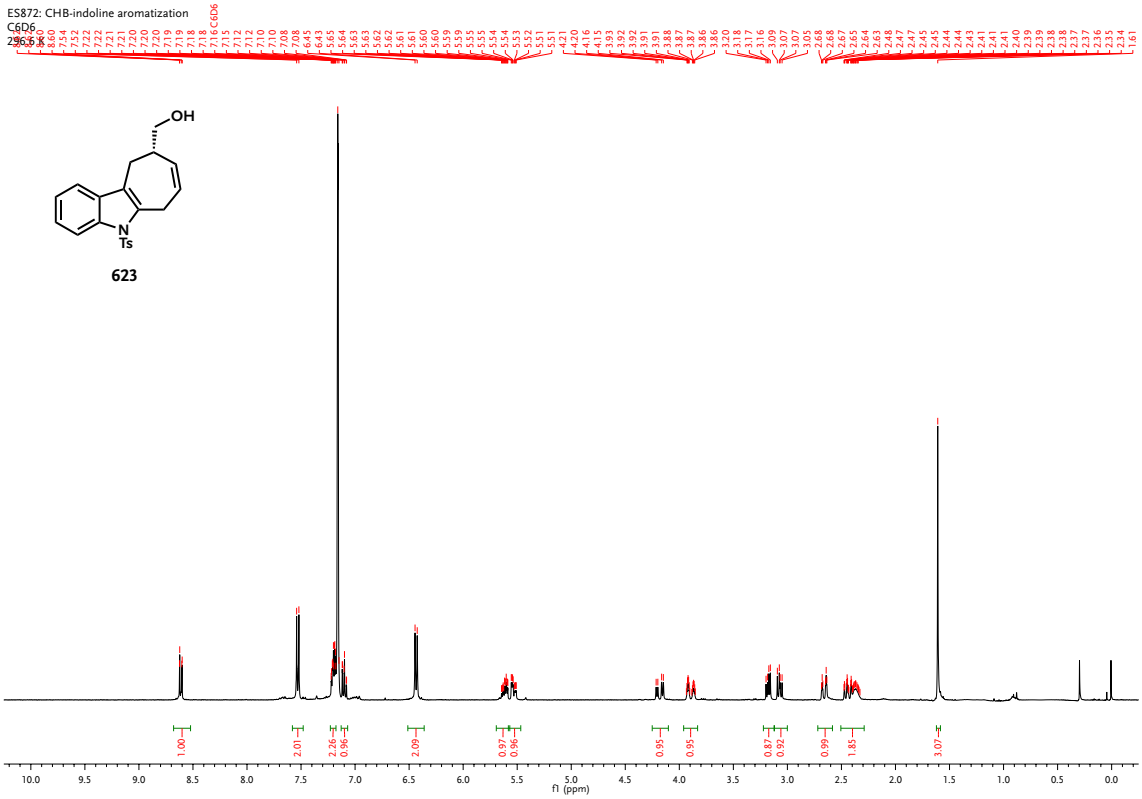
Spectrum B-92. [1]H-NMR spectrum for compound **651** *(experimental on page 226)*.



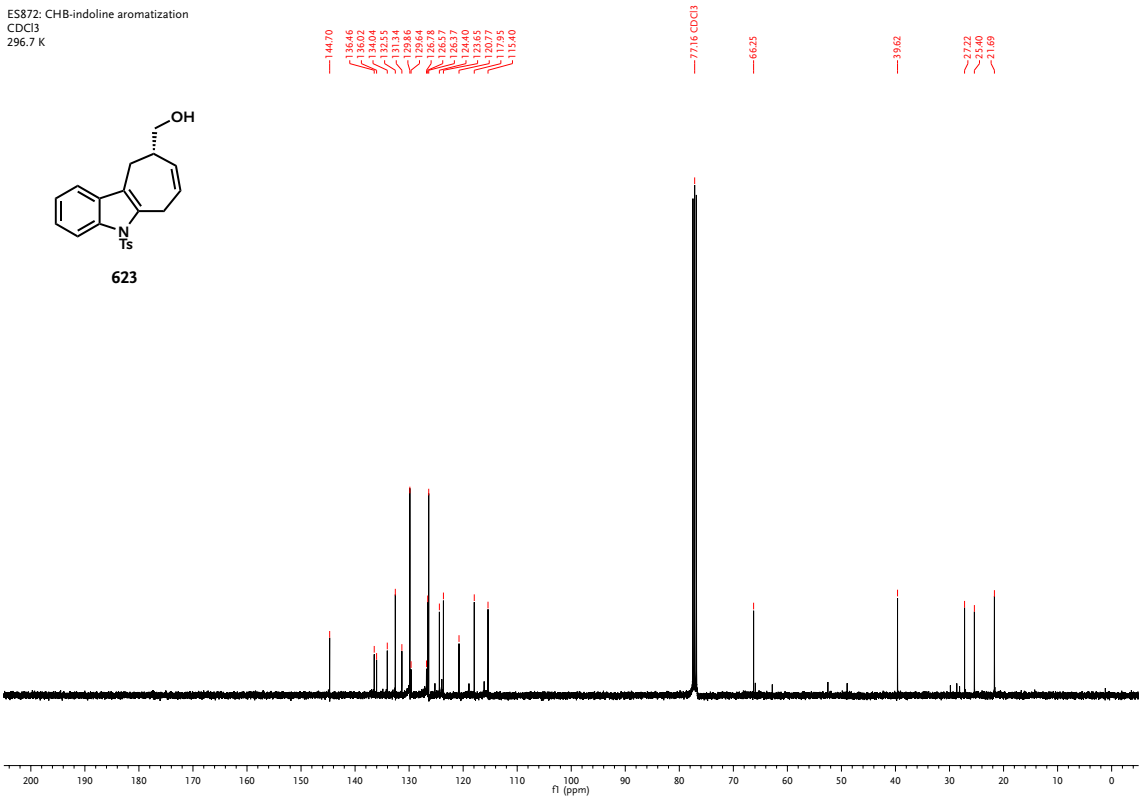
Spectrum B-93. ^{13}C-NMR spectrum for compound **651** *(experimental on page 226)*.



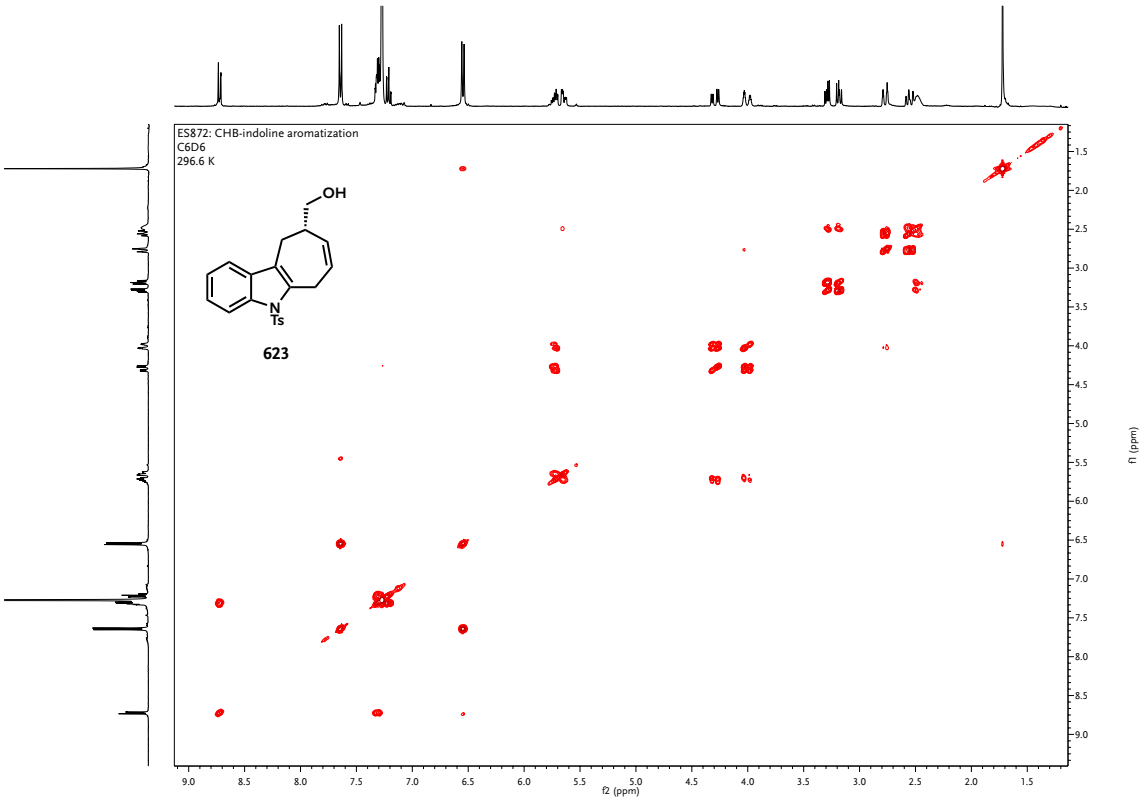
Spectrum B-94. COSY60 2D-NMR spectrum for compound **651** *(experimental on page 226)*.



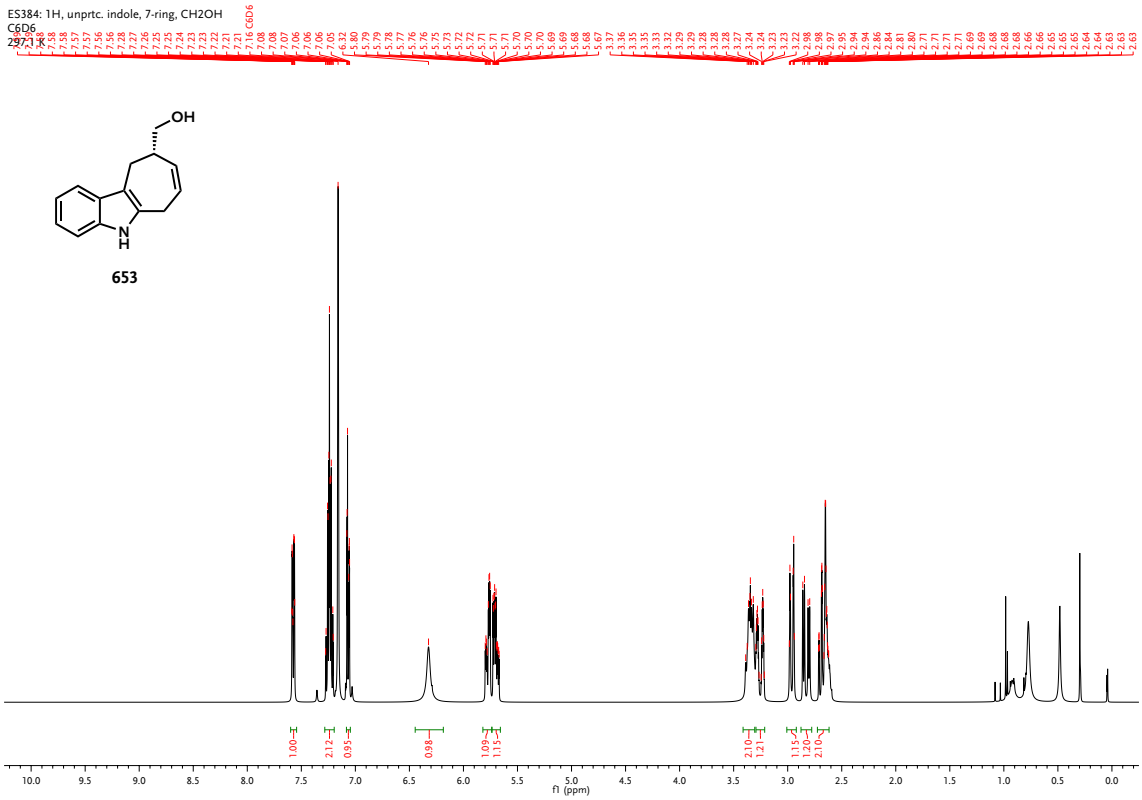
Spectrum B-95. ^{1}H-NMR spectrum for compound **623** *(experimental on page 226)*.



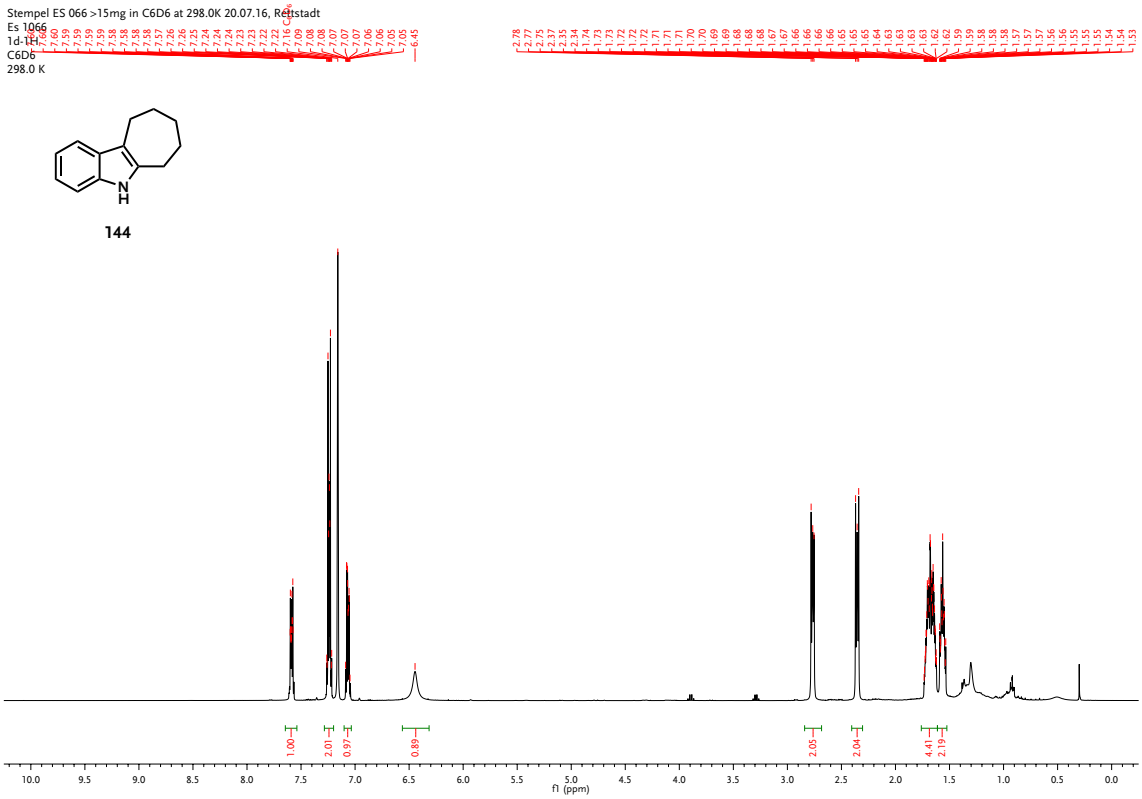
Spectrum B-96. ^{13}C-NMR spectrum for compound **623** *(experimental on page 226)*.



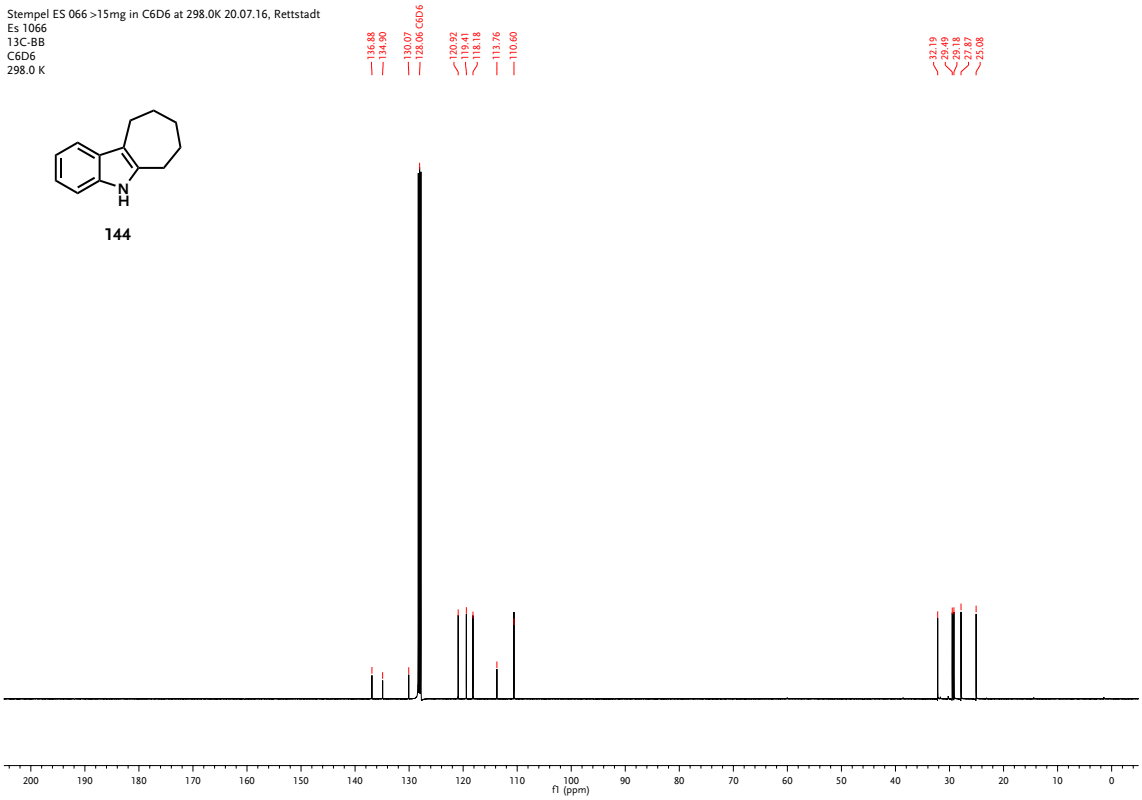
Spectrum B-97. COSY60 2D-NMR spectrum for compound **623** *(experimental on page 226)*.



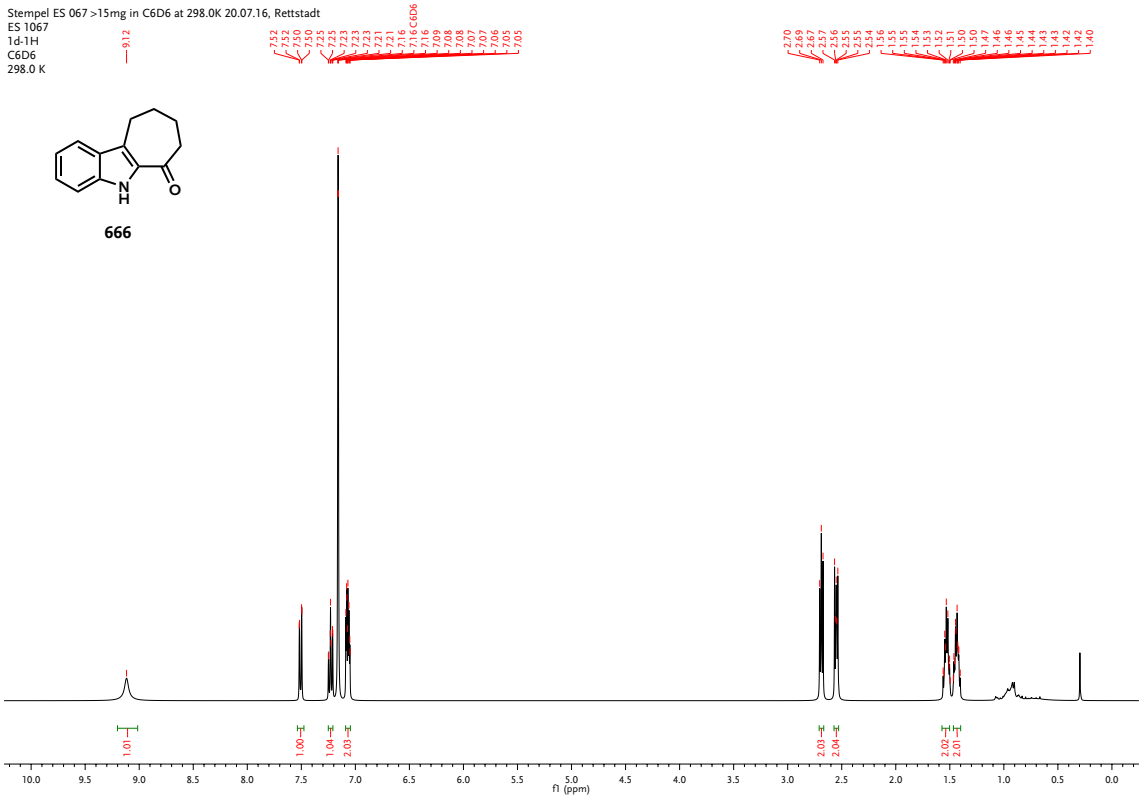
Spectrum B-98. ^{1}H-NMR spectrum for compound **653** *(experimental on page 227)*.



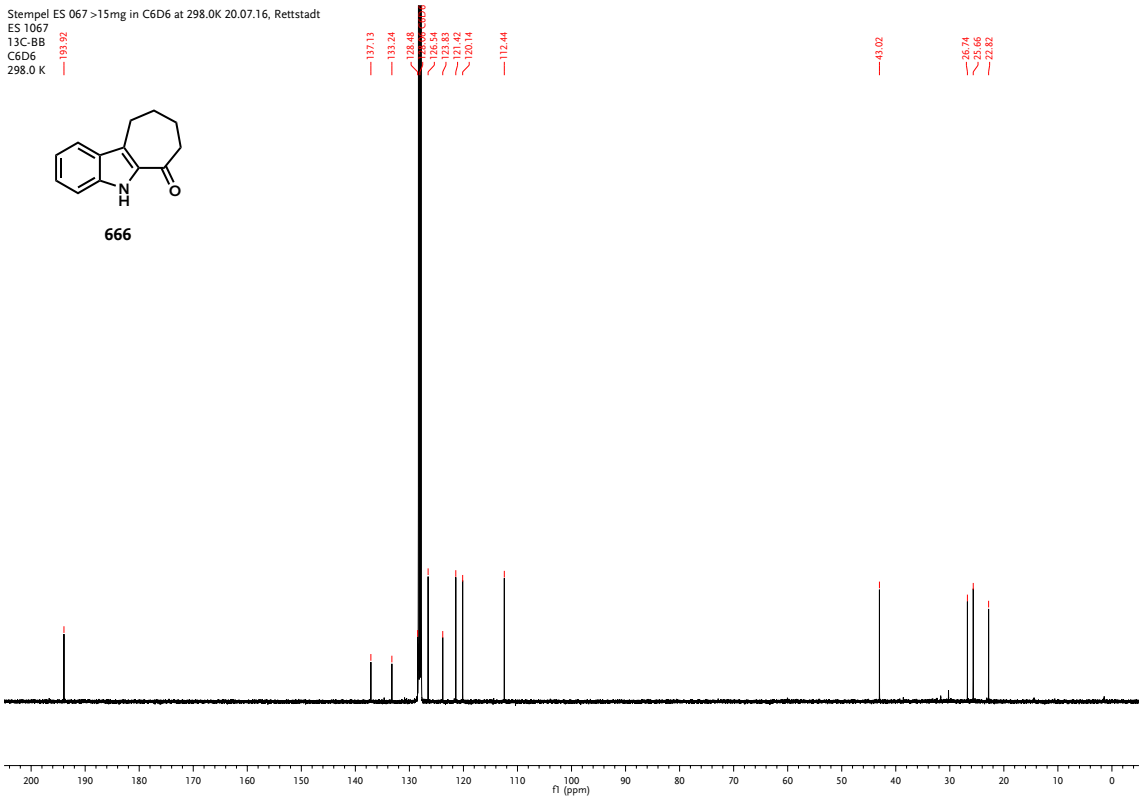
Spectrum B-99. ^{1}H-NMR spectrum for compound **144** *(experimental on page 227)*.



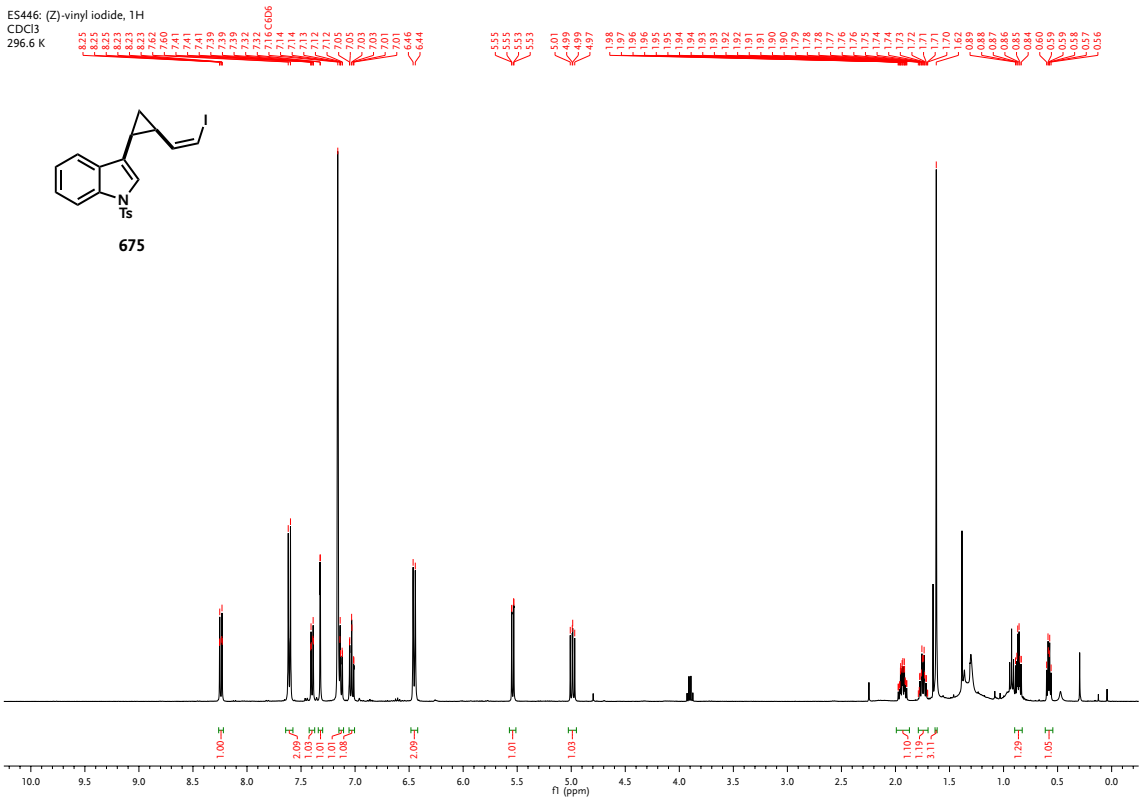
Spectrum B-100. ^{13}C-NMR spectrum for compound **144** *(experimental on page 227)*.



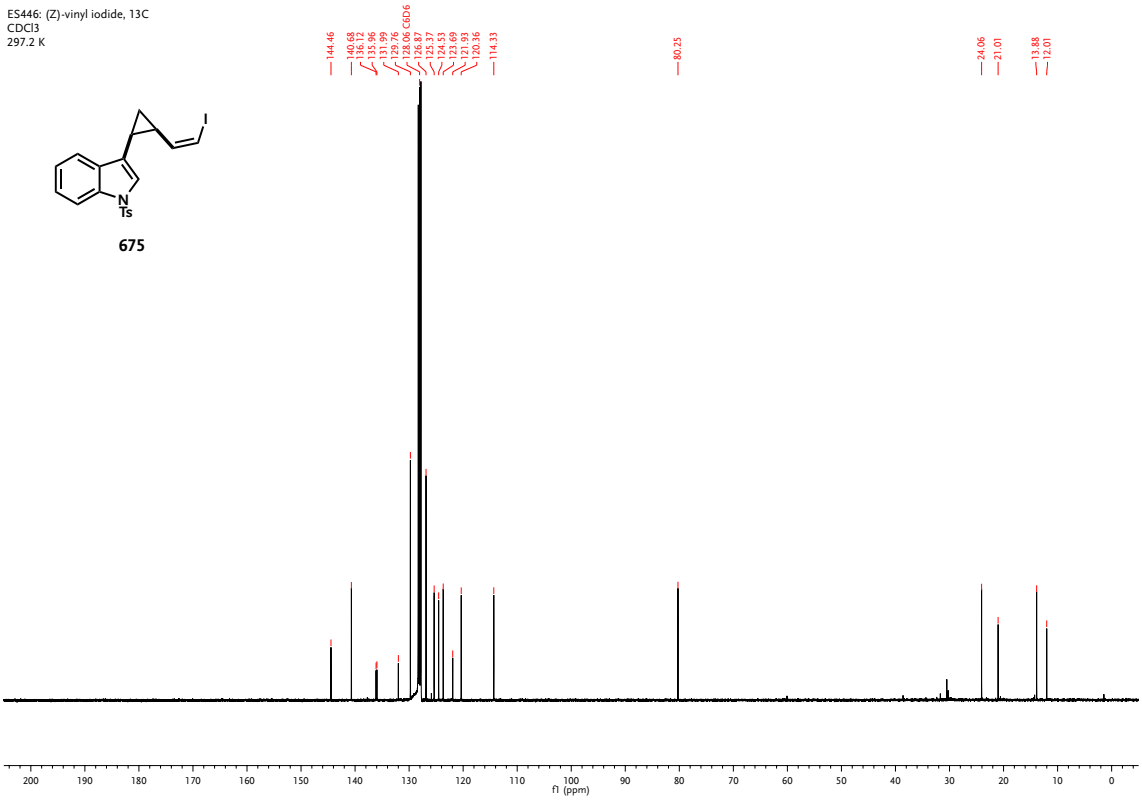
Spectrum B-101. ^{1}H-NMR spectrum for compound **666** *(experimental on page 228)*.



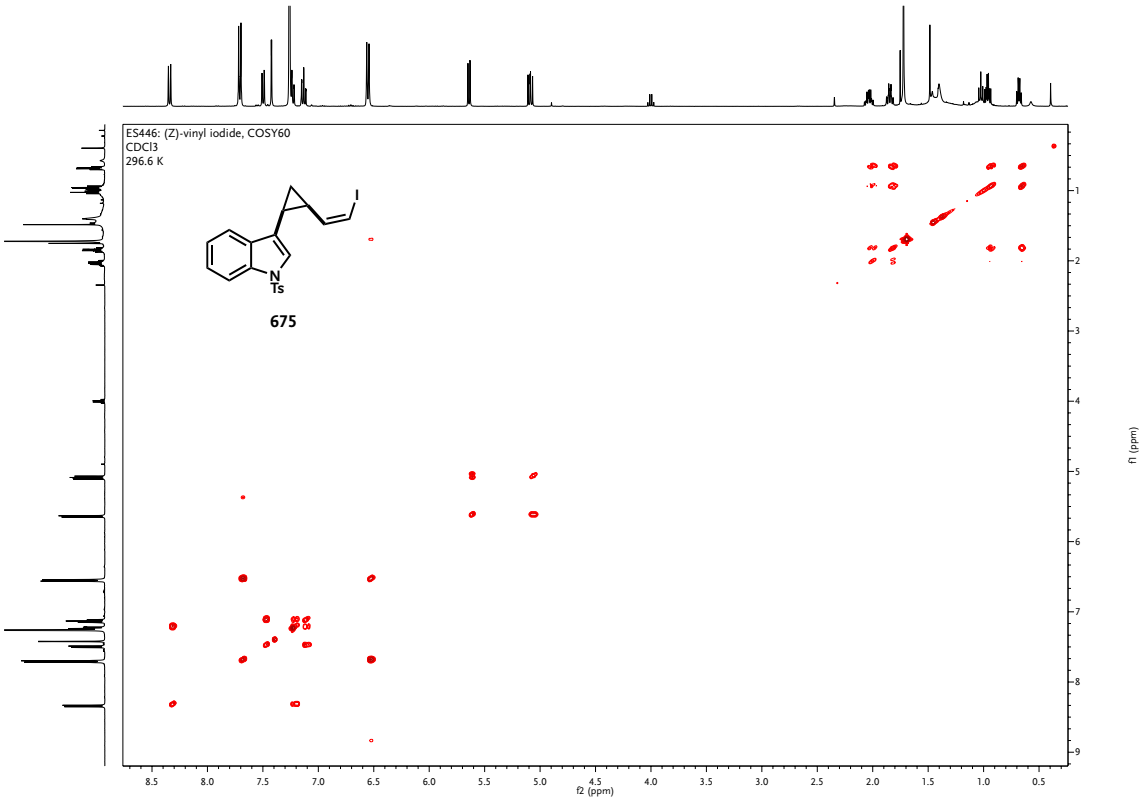
Spectrum B-102. ^{13}C-NMR spectrum for compound **666** *(experimental on page 228)*.



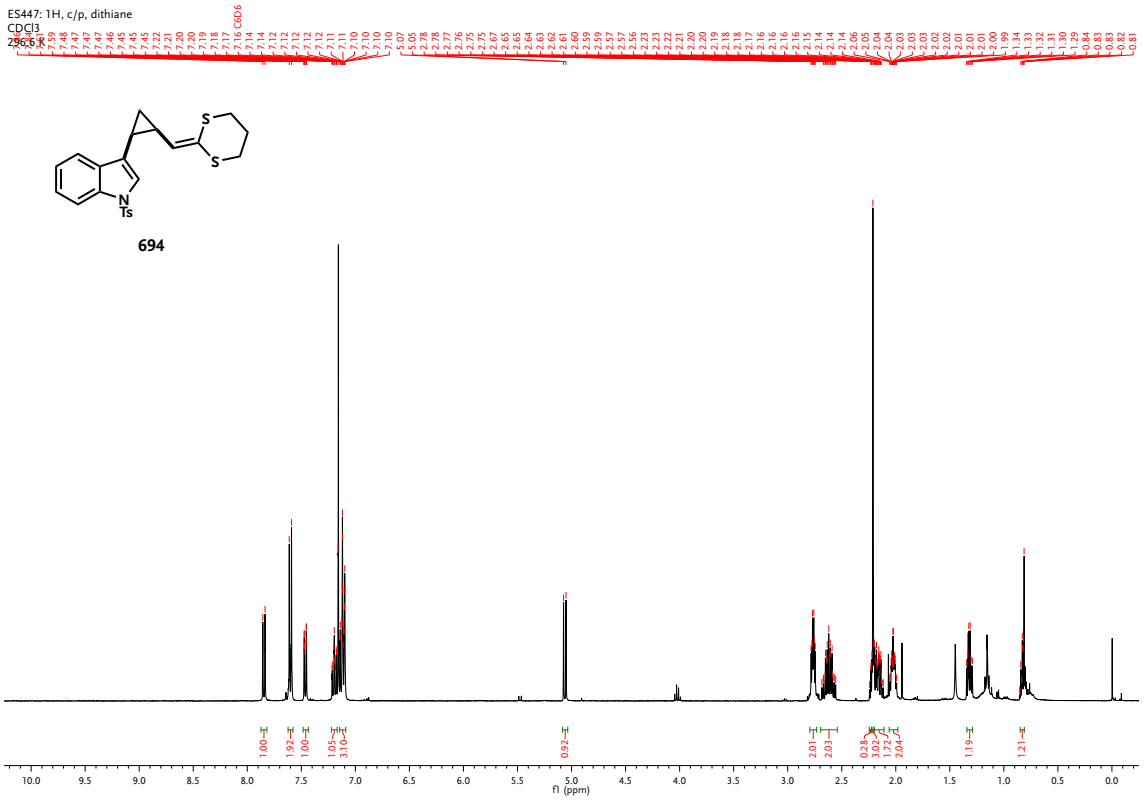
Spectrum B-103. ^{1}H-NMR spectrum for compound **675** *(experimental on page 228)*.



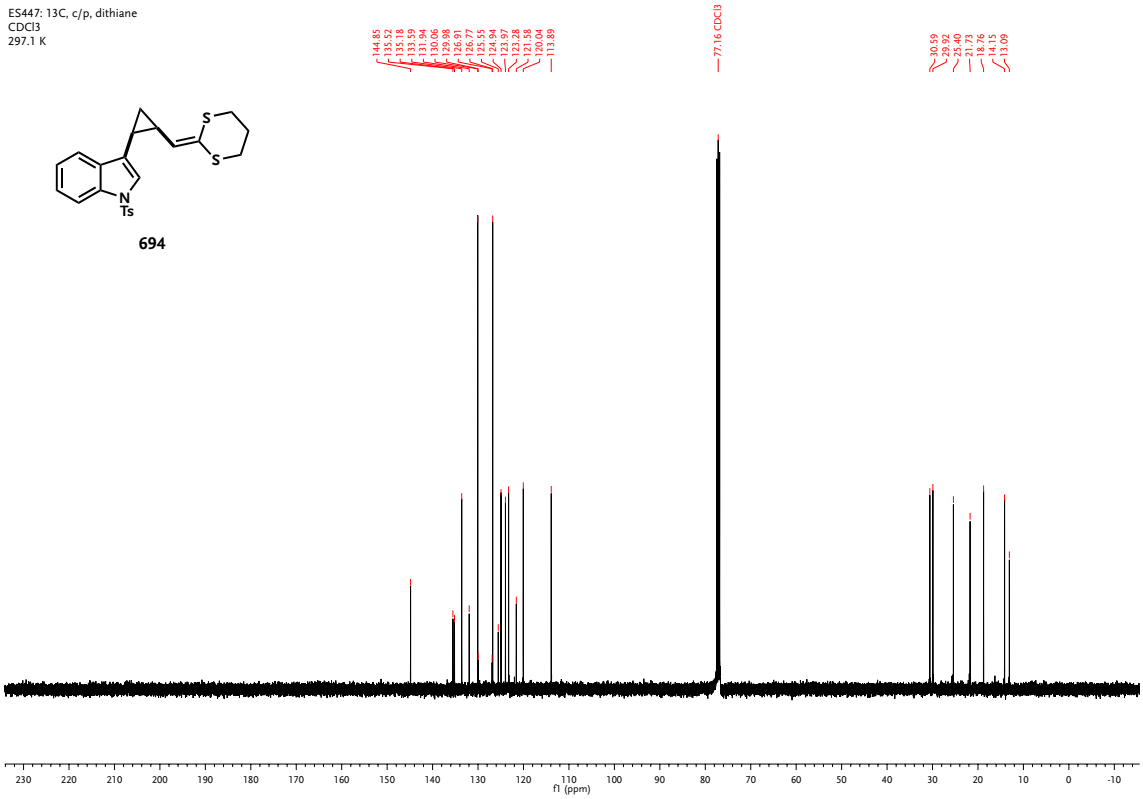
Spectrum B-104. ^{13}C-NMR spectrum for compound **675** *(experimental on page 228)*.



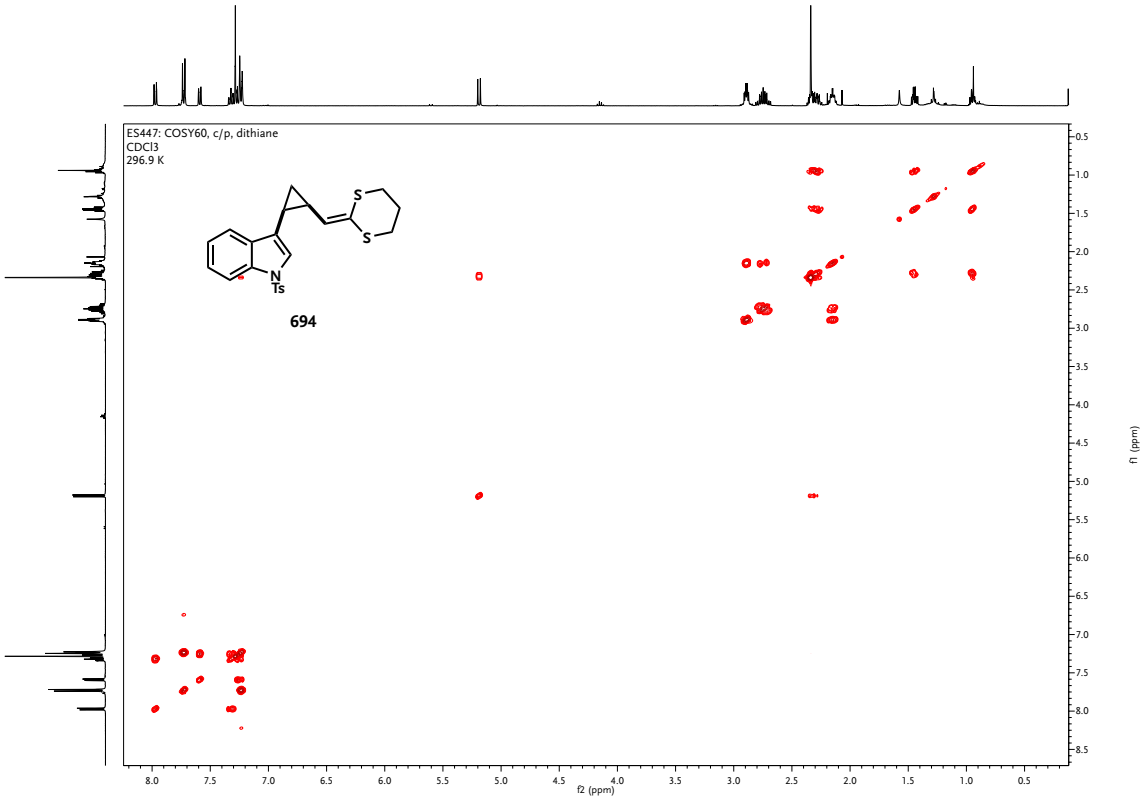
Spectrum B-105. COSY60 2D-NMR spectrum for compound **675** *(experimental on page 228)*.



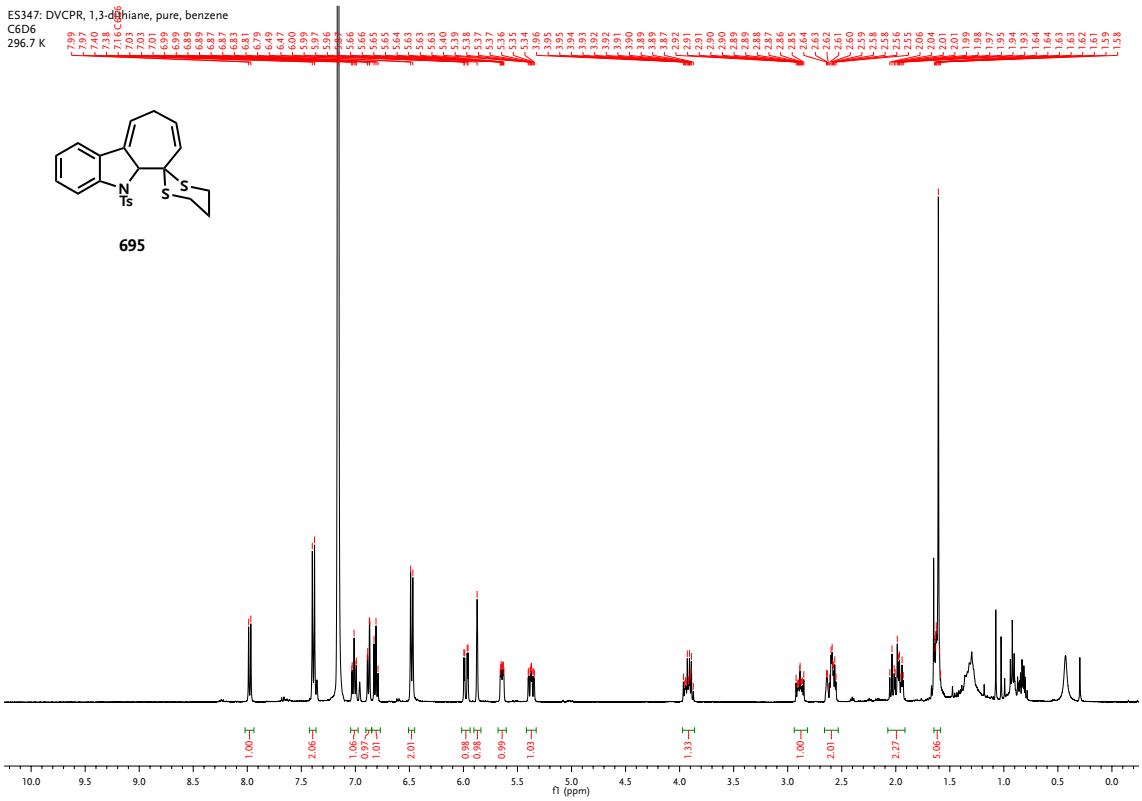
Spectrum B-106. ^{1}H-NMR spectrum for compound **694** *(experimental on page 229)*.



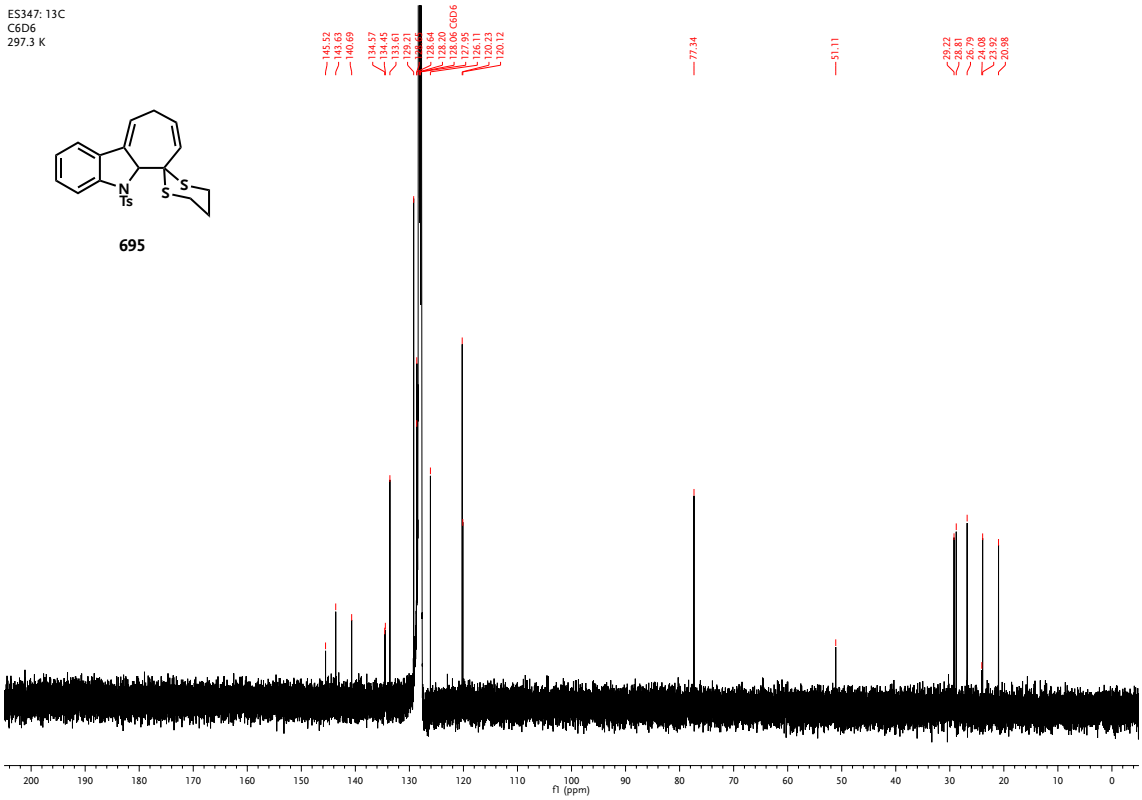
Spectrum B-107. ^{13}C-NMR spectrum for compound **694** *(experimental on page 229)*.



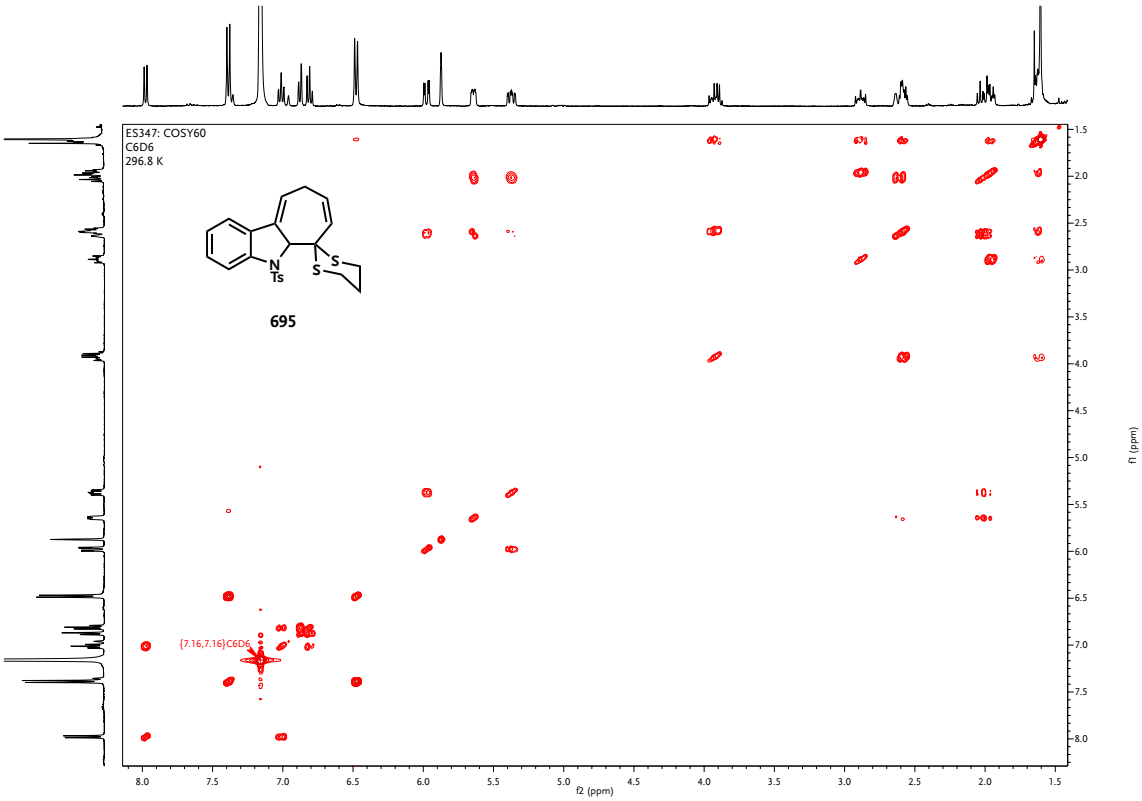
Spectrum B-108. COSY60 2D-NMR spectrum for compound **694** *(experimental on page 229)*.



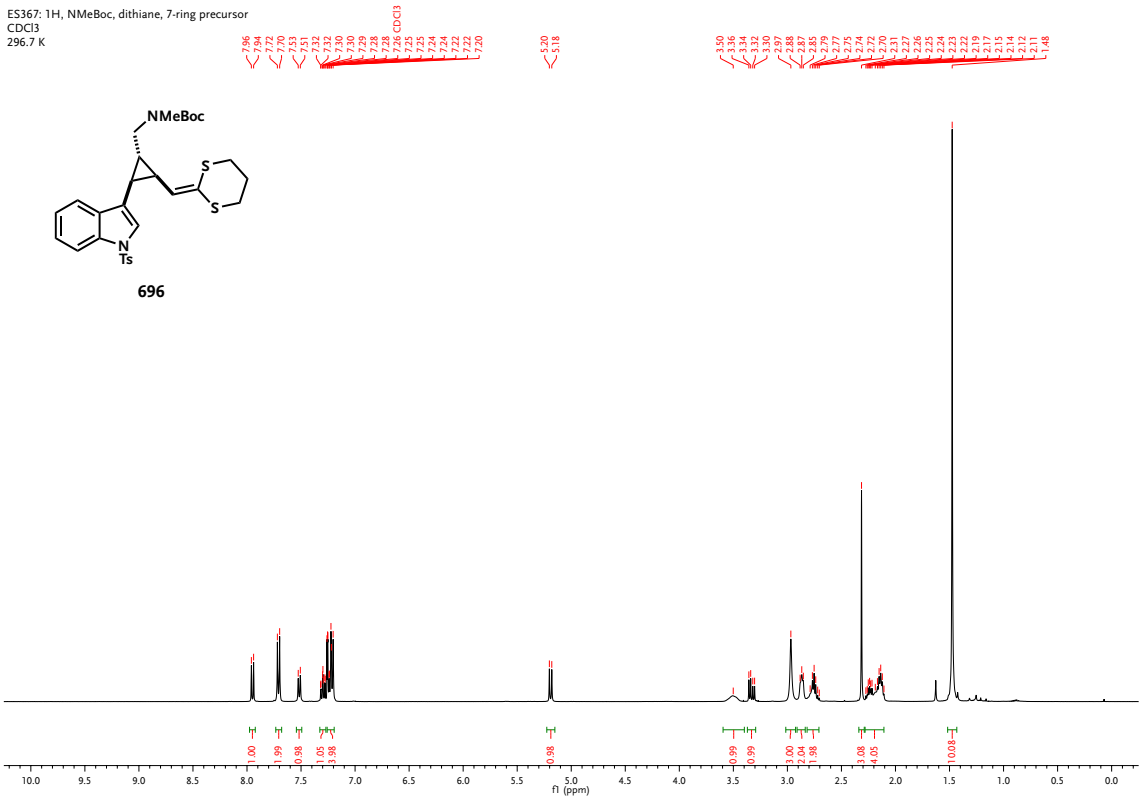
Spectrum B-109. ^{1}H-NMR spectrum for compound **695** *(experimental on page 230)*.



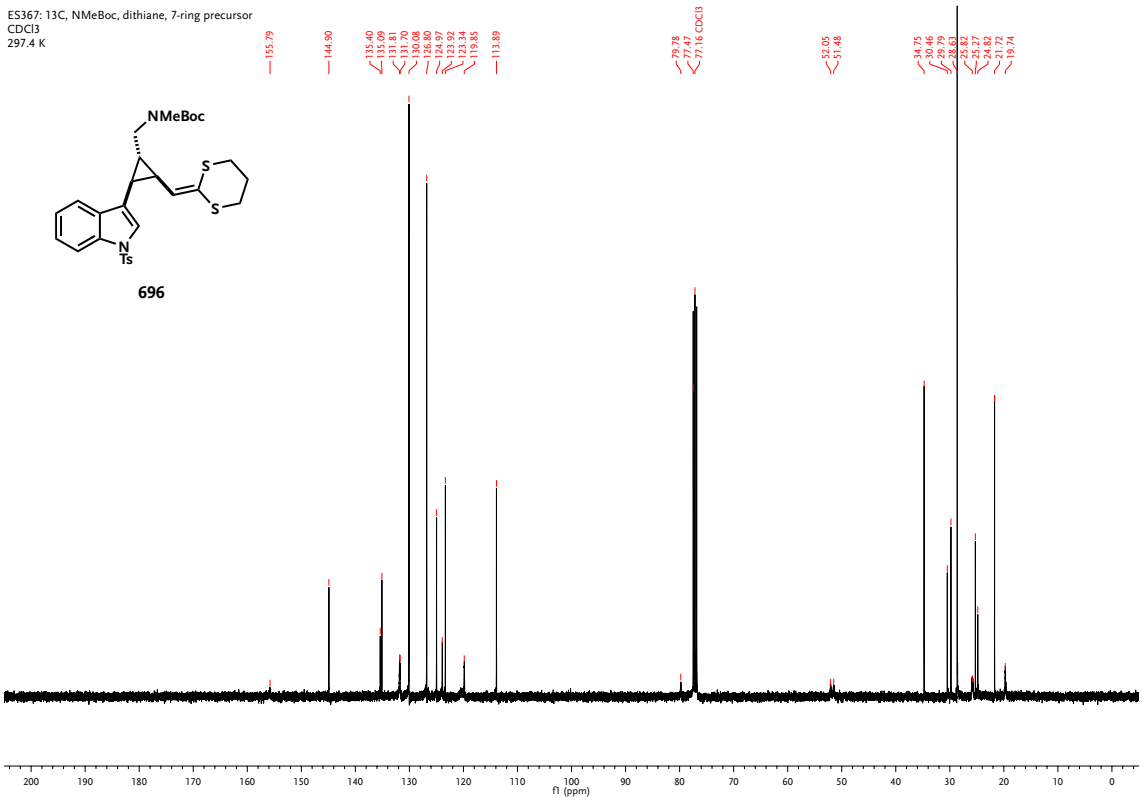
Spectrum B-110. ^{13}C-NMR spectrum for compound **695** *(experimental on page 230)*.



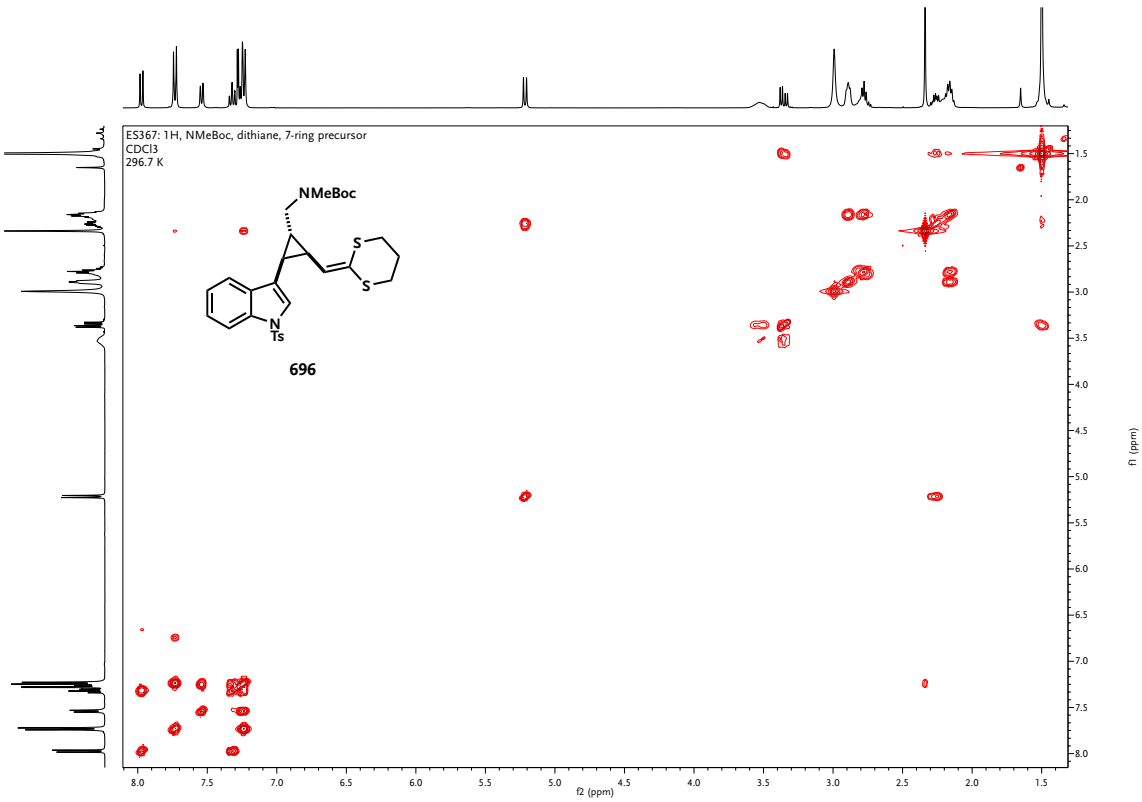
Spectrum B-111. COSY60 2D-NMR spectrum for compound **695** *(experimental on page 230)*.



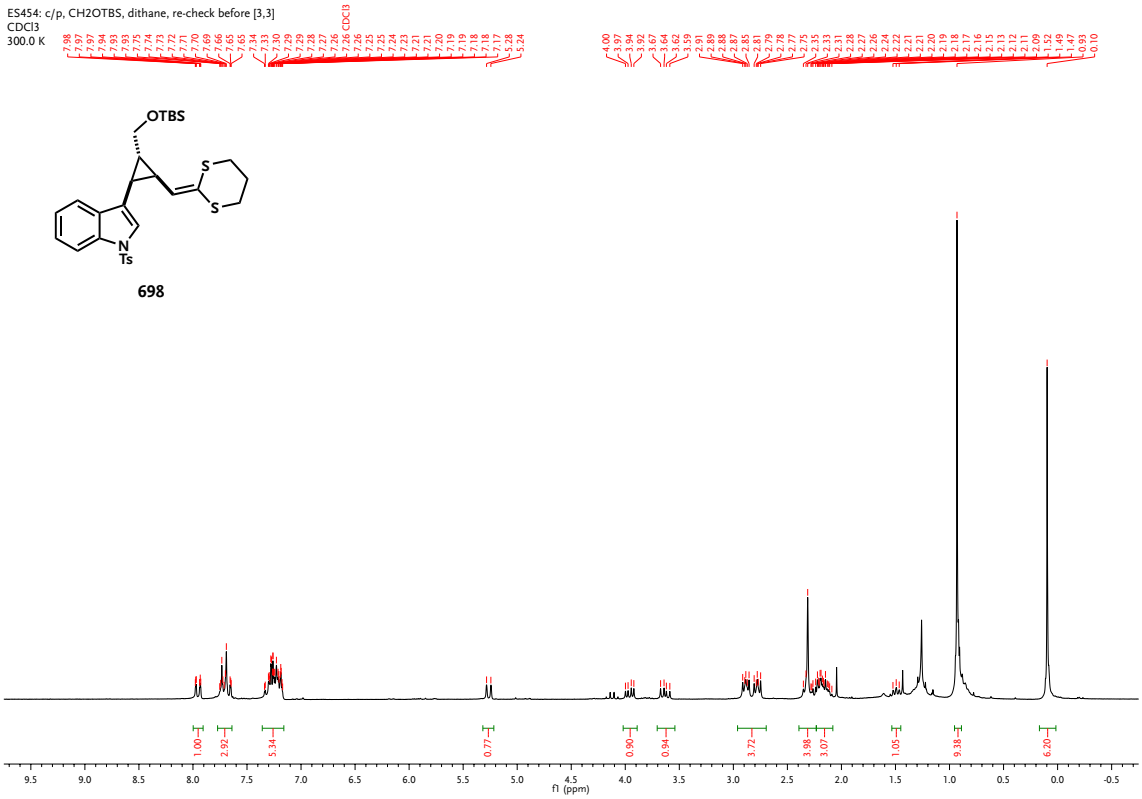
Spectrum B-112. ^{1}H-NMR spectrum for compound **696** *(experimental on page 230)*.



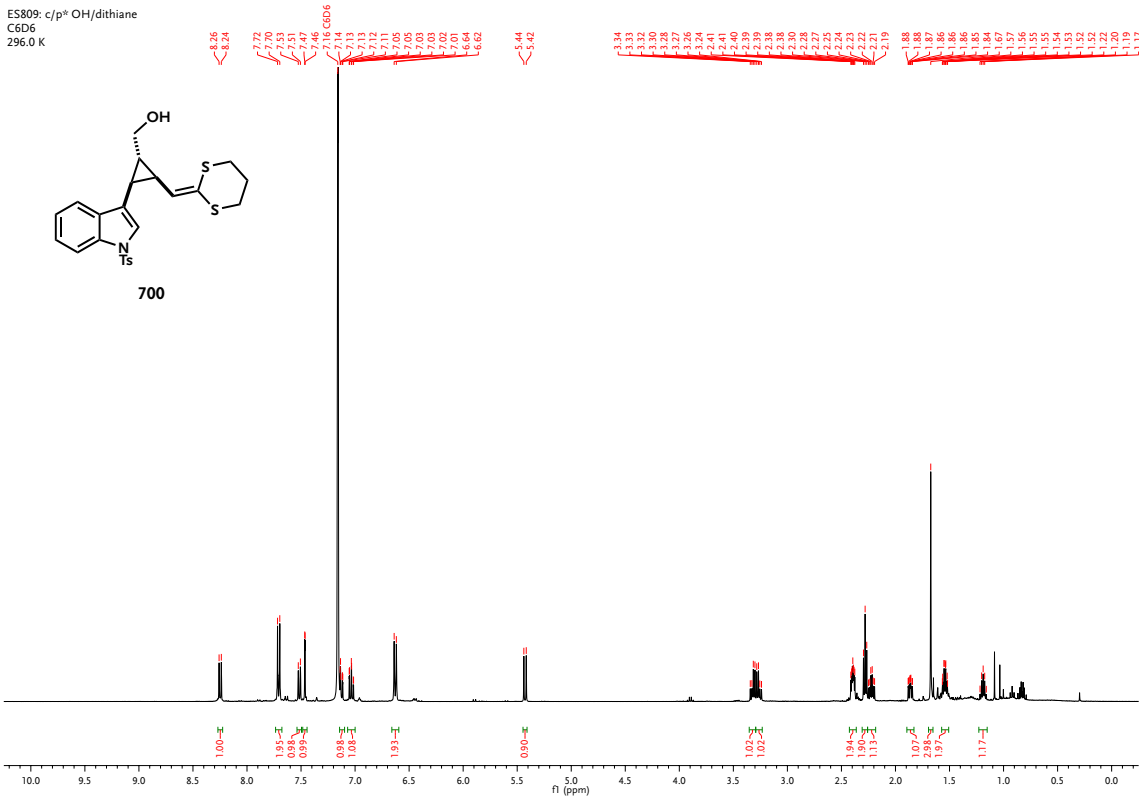
Spectrum B-113. ^{13}C-NMR spectrum for compound **696** *(experimental on page 230)*.



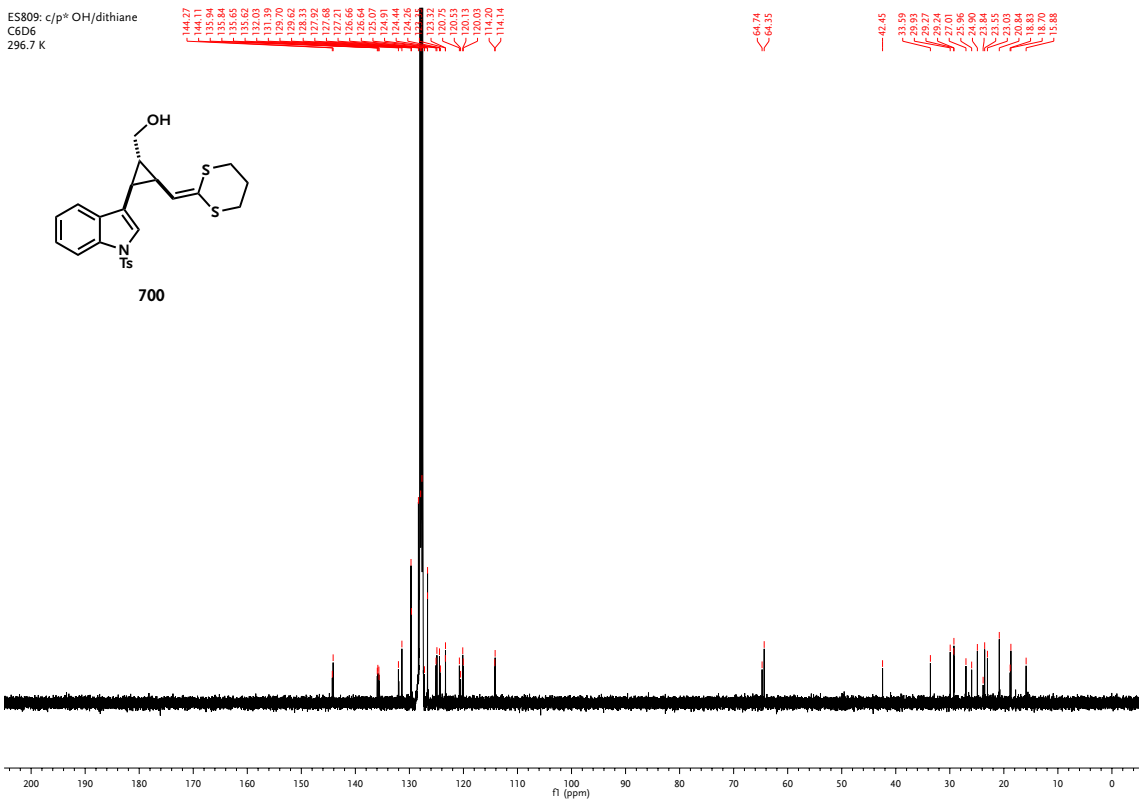
Spectrum B-114. COSY60 2D-NMR spectrum for compound **696** *(experimental on page 230)*.



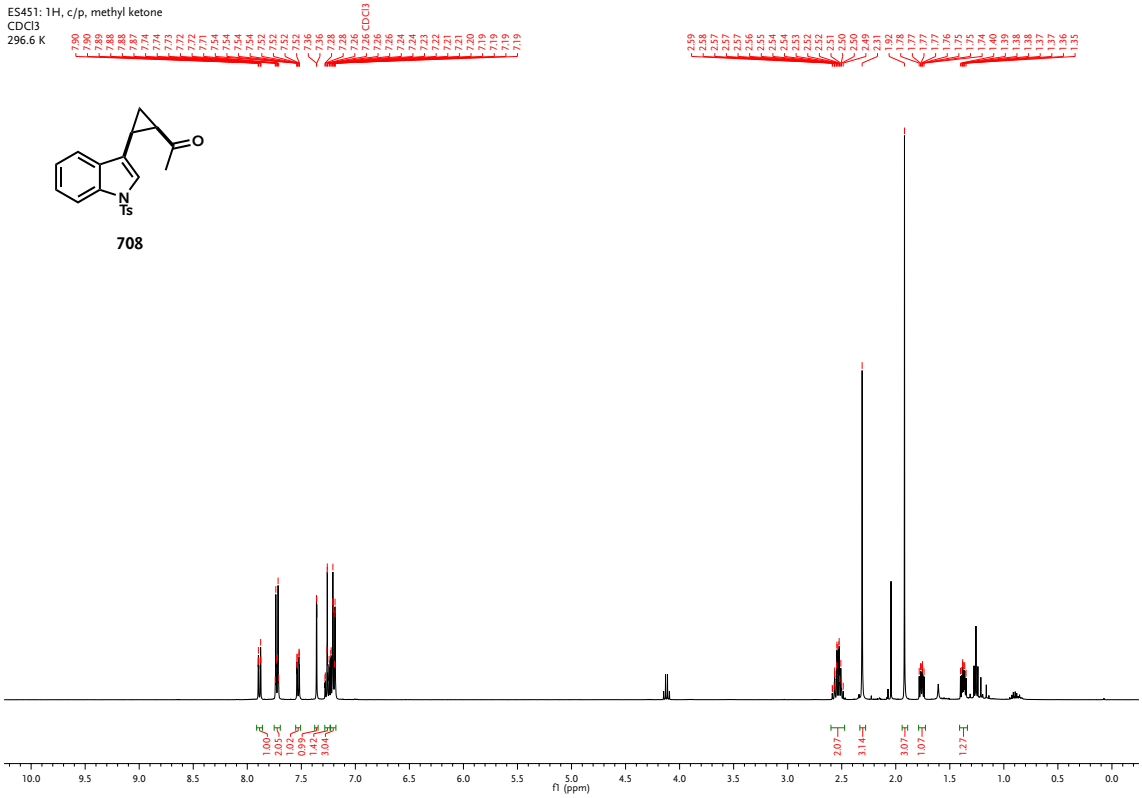
Spectrum B-115. [1]H-NMR spectrum for compound **698** *(experimental on page 231)*.



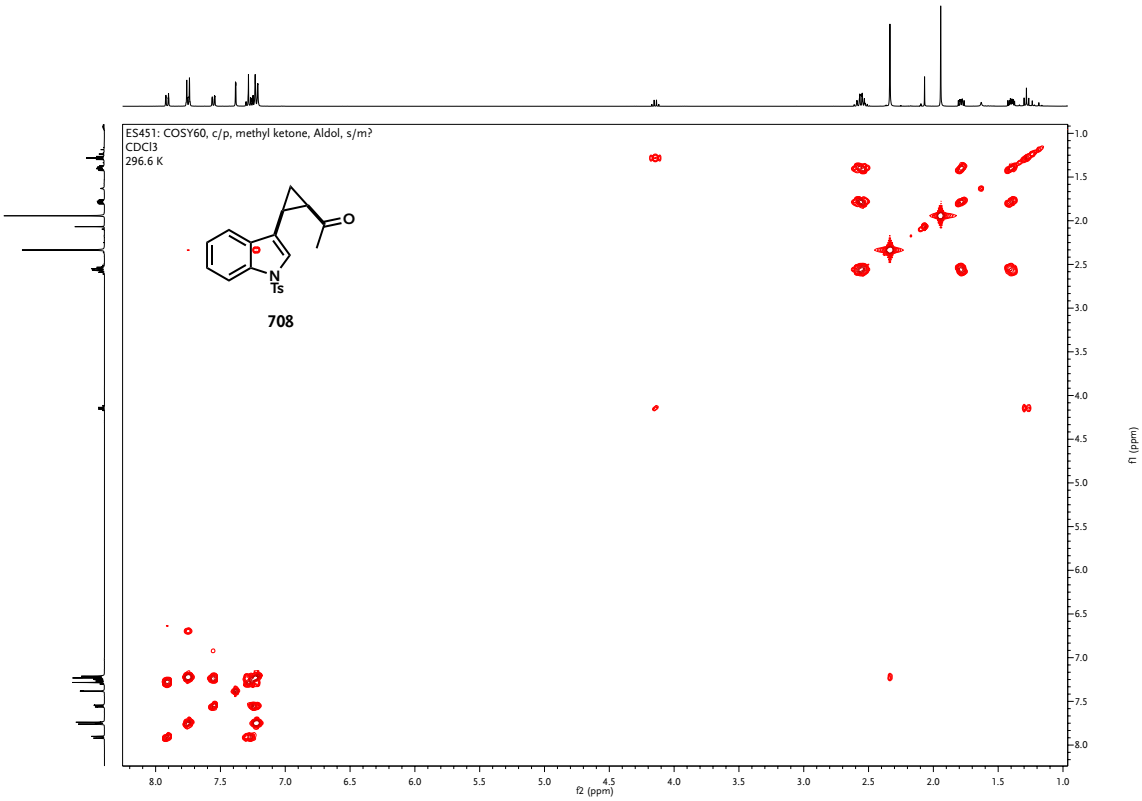
Spectrum B-116. [1]H-NMR spectrum for compound **700** *(experimental on page 232)*.



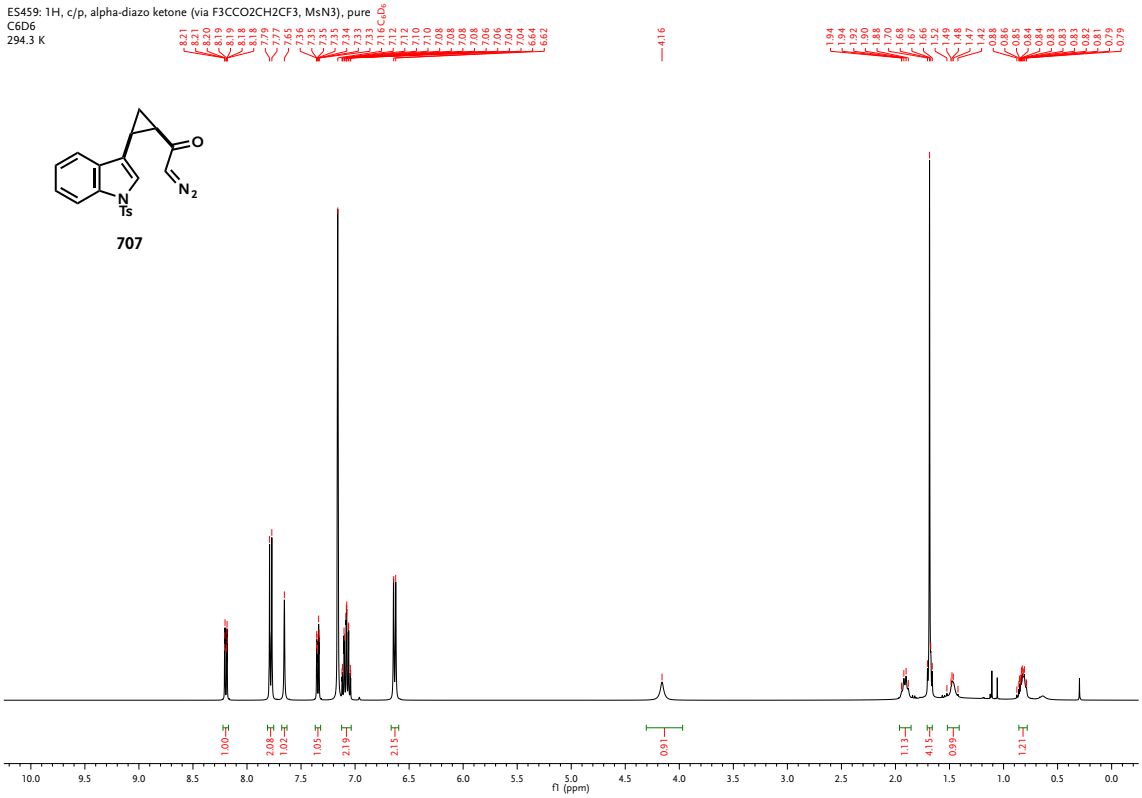
Spectrum B-117. ^{13}C-NMR spectrum for compound **700** *(experimental on page 232)*.



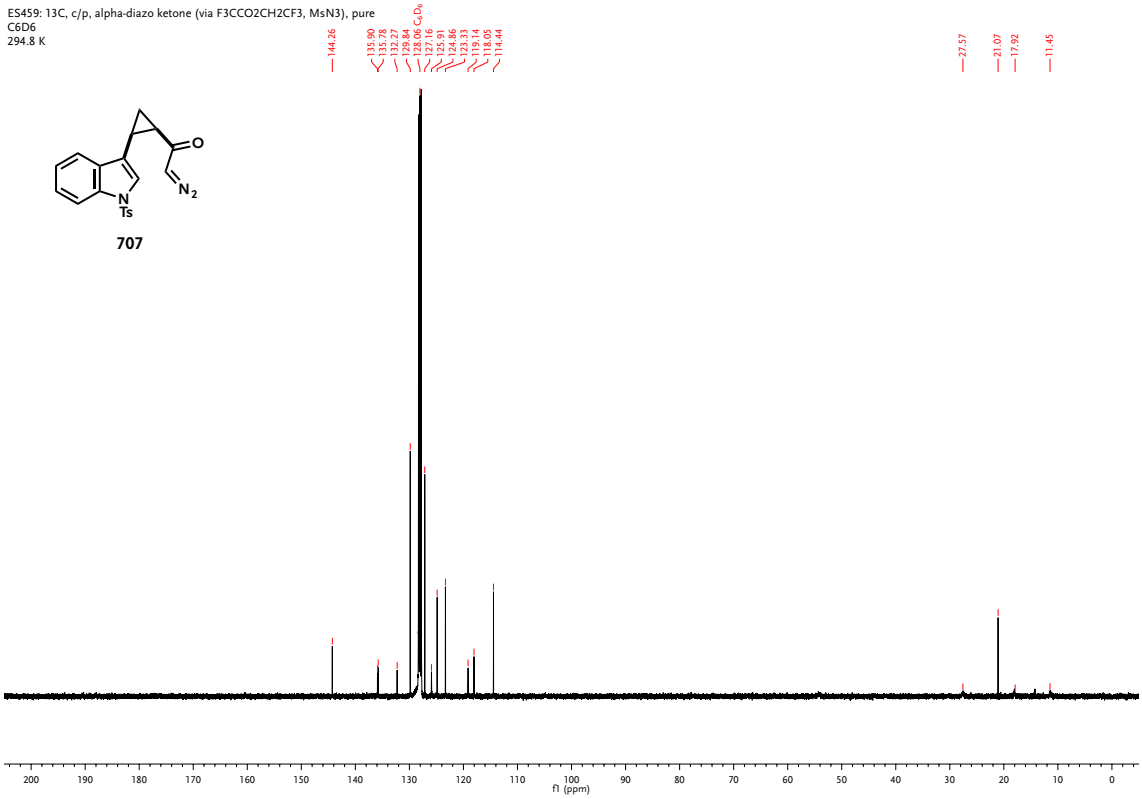
Spectrum B-118. ^{1}H-NMR spectrum for compound **708** *(experimental on page 233)*.



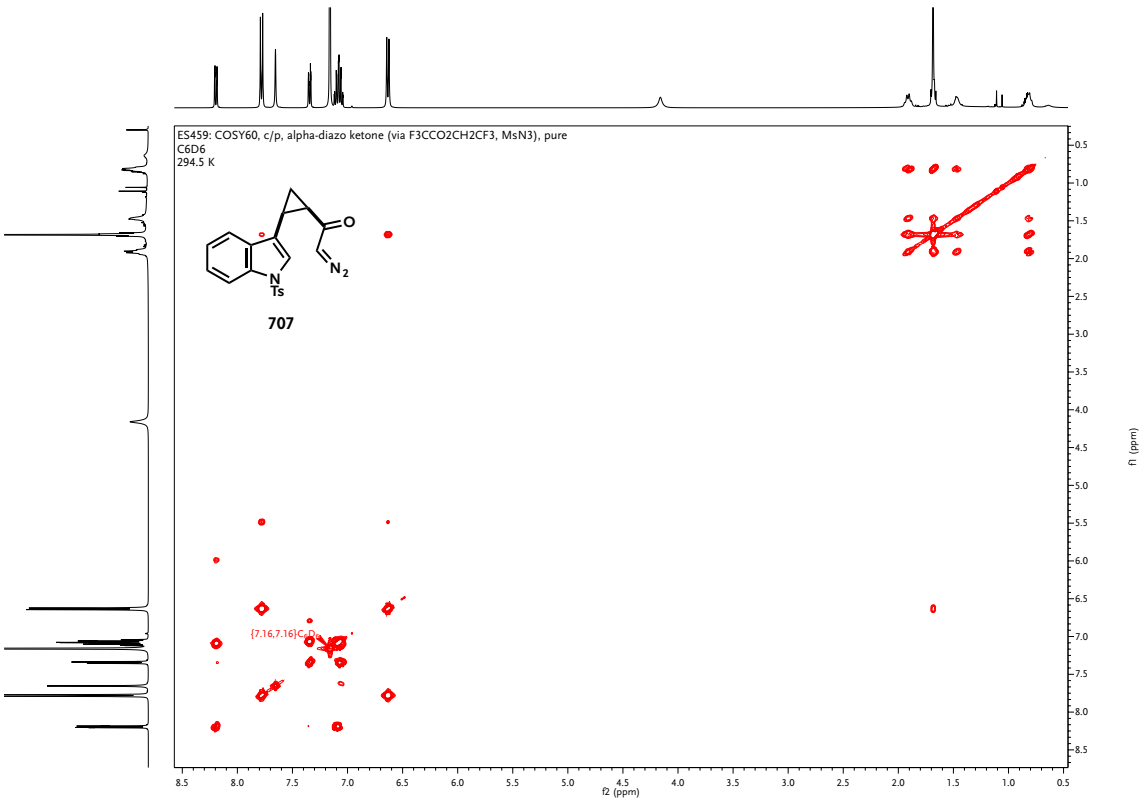
Spectrum B-119. COSY60 2D-NMR spectrum for compound **708** *(experimental on page 233)*.



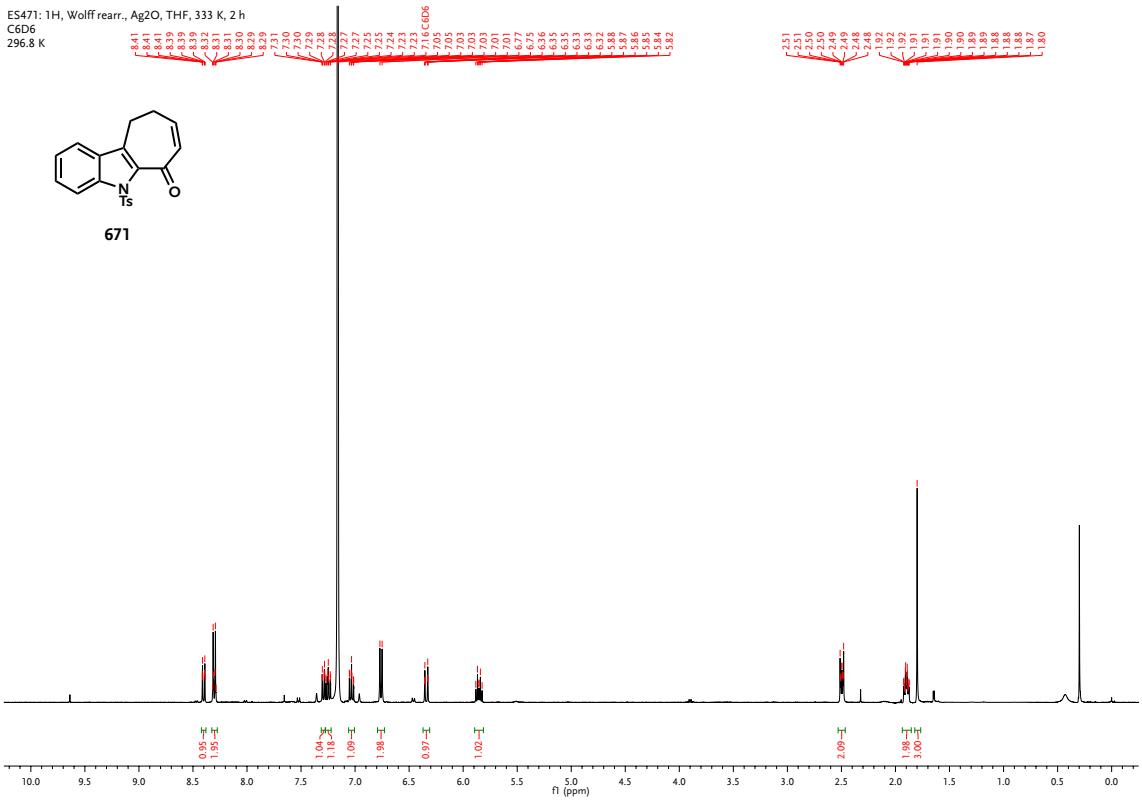
Spectrum B-120. ^{1}H-NMR spectrum for compound **707** *(experimental on page 233)*.



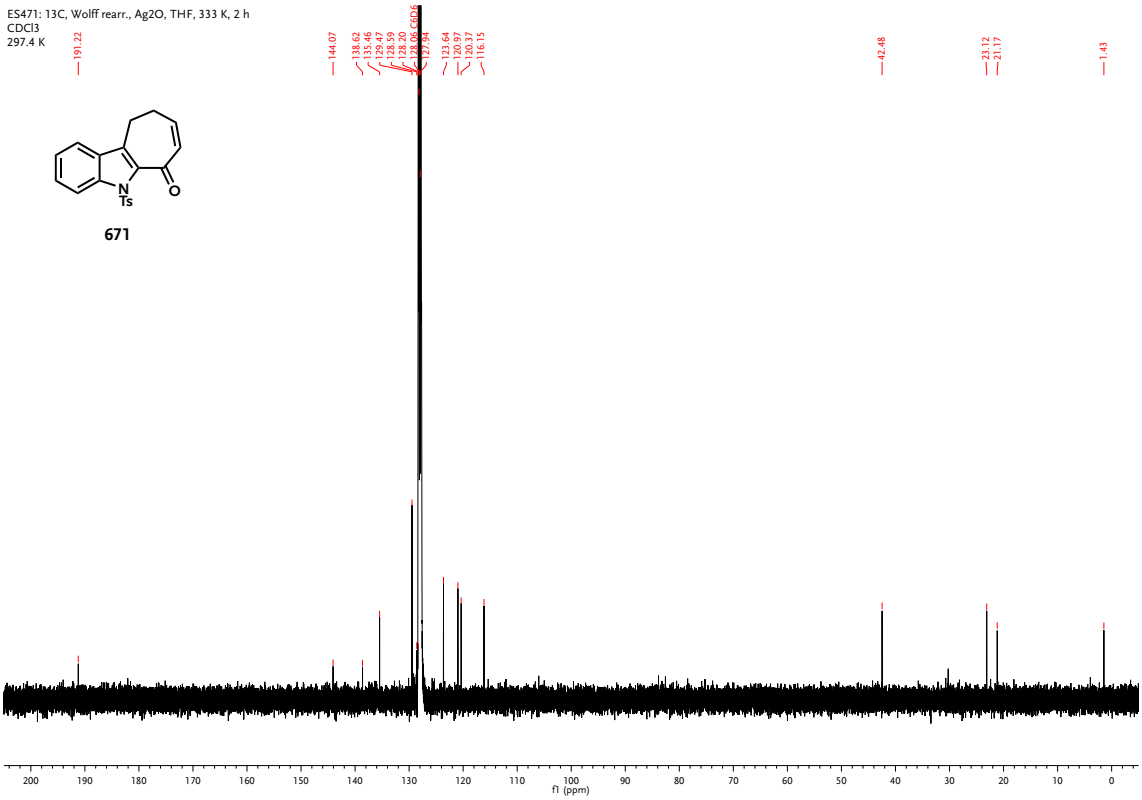
Spectrum B-121. ^{13}C-NMR spectrum for compound **707** *(experimental on page 233)*.



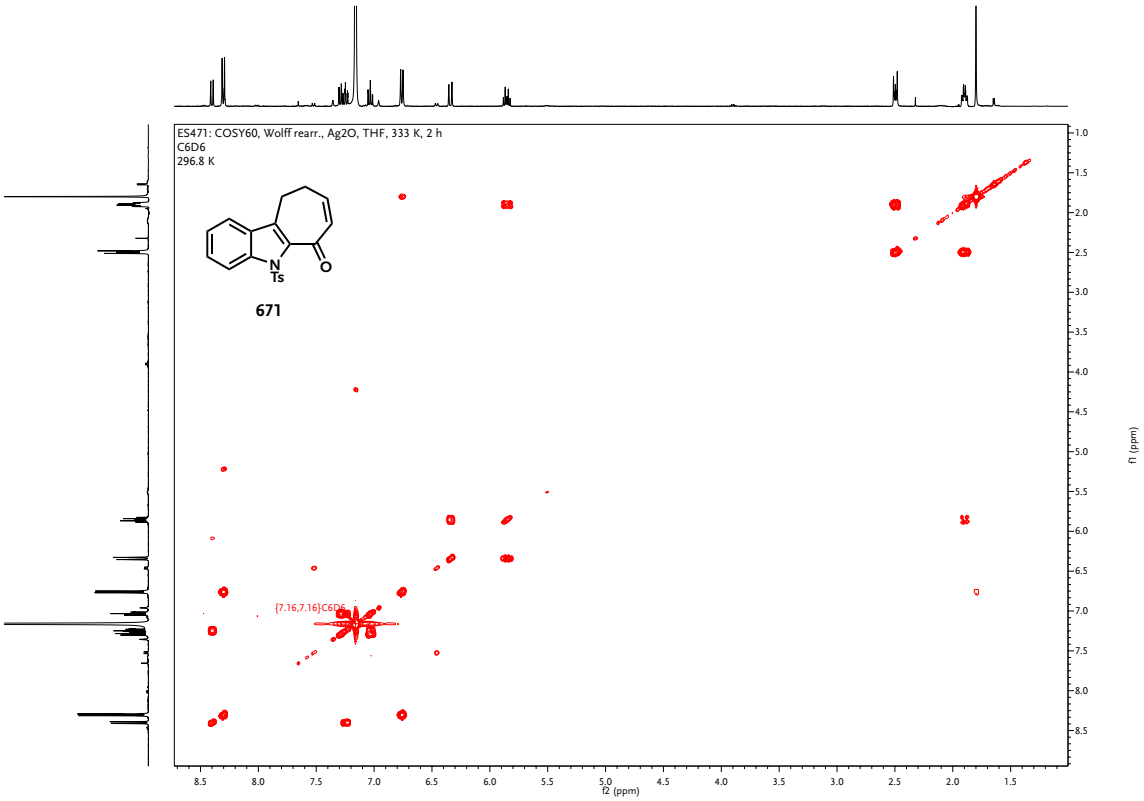
Spectrum B-122. COSY60 2D-NMR spectrum for compound **707** *(experimental on page 233)*.



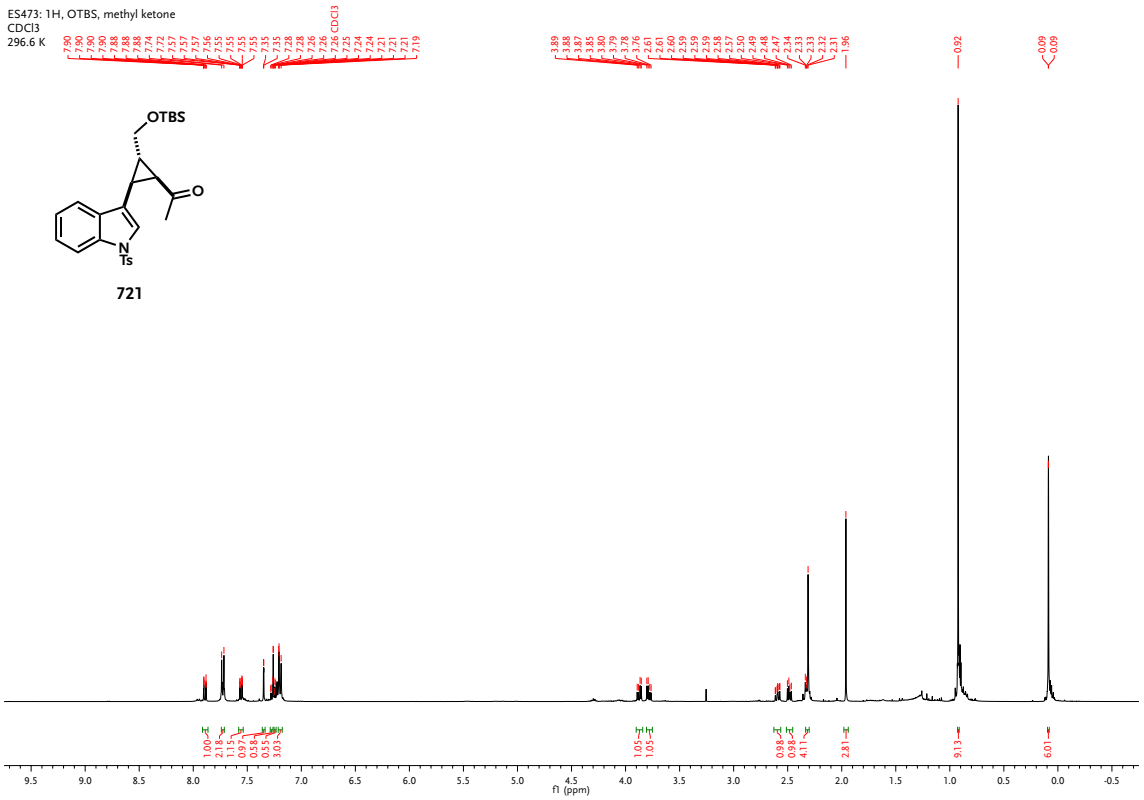
Spectrum B-123. ^{1}H-NMR spectrum for compound **671** *(experimental on page 235)*.



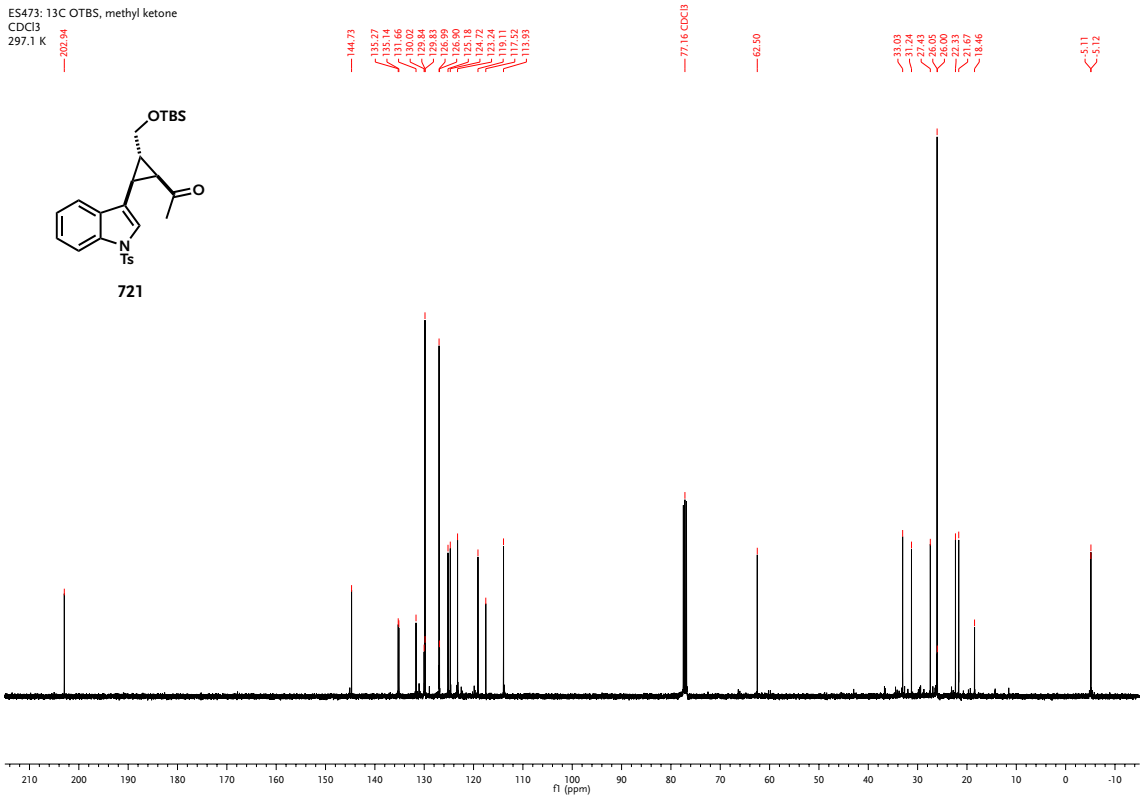
Spectrum B-124. ^{13}C-NMR spectrum for compound **671** *(experimental on page 235)*.



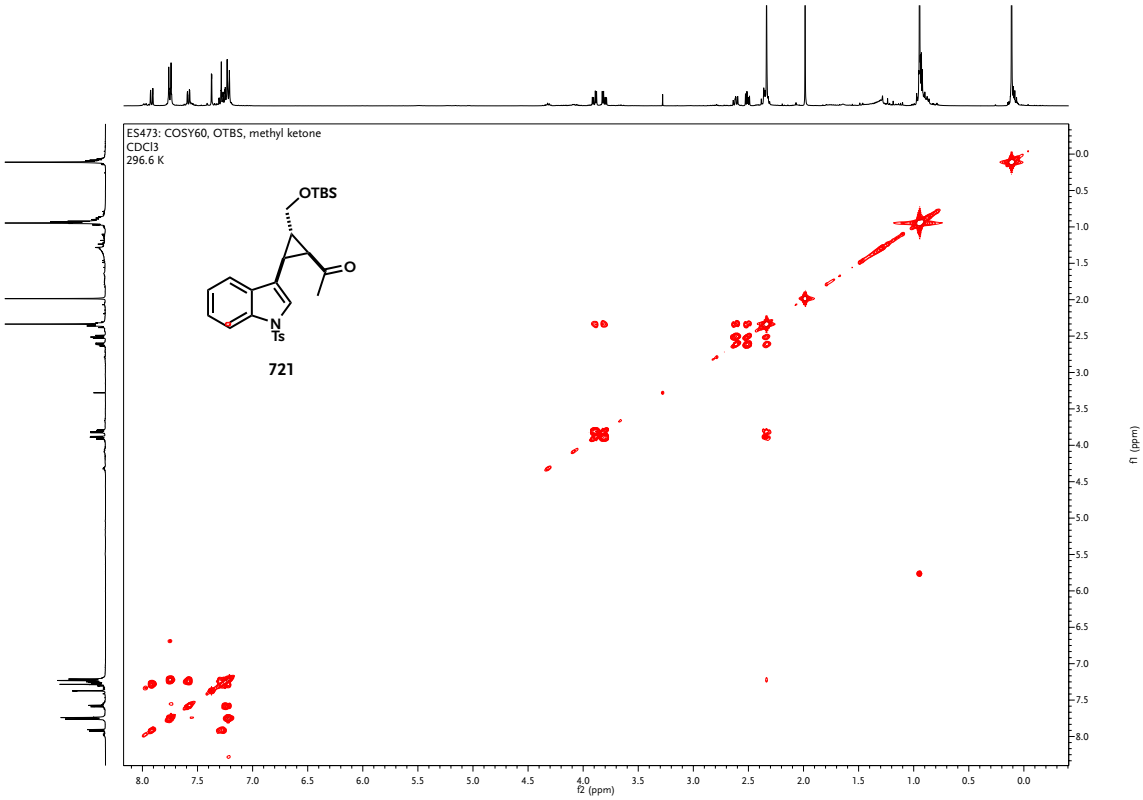
Spectrum B-125. COSY60 2D-NMR spectrum for compound **671** *(experimental on page 235)*.



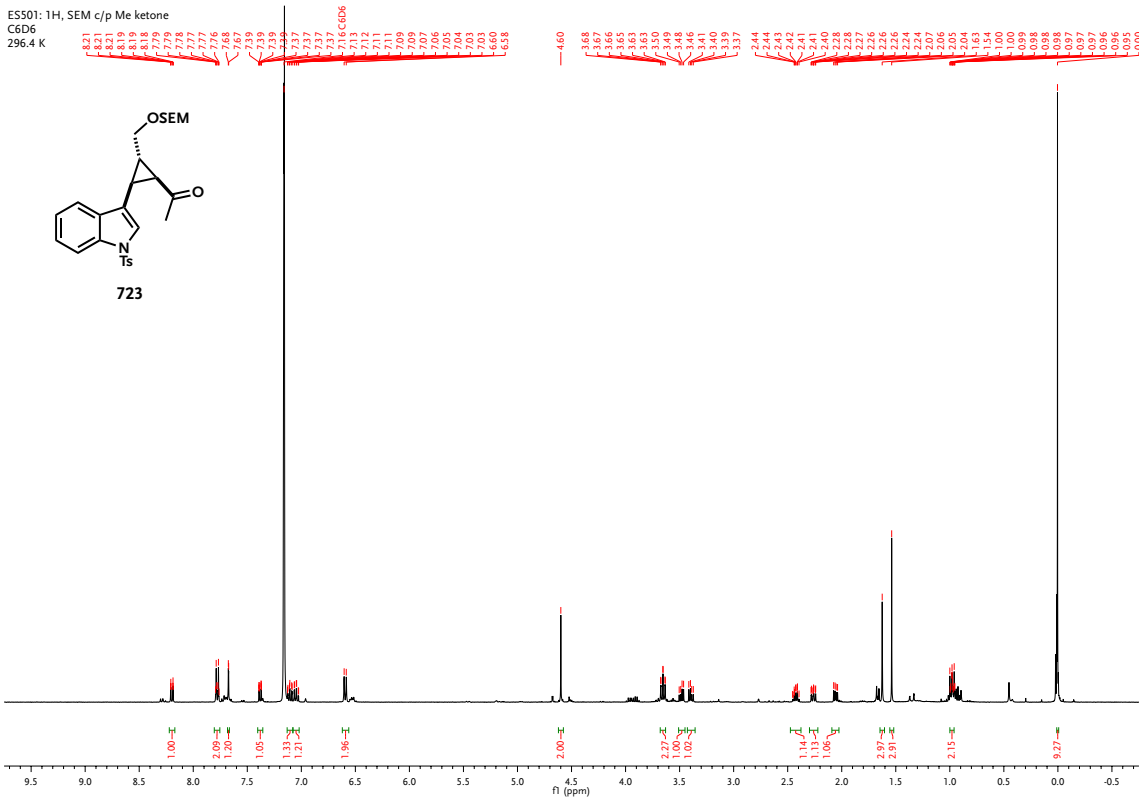
Spectrum B-126. ^{1}H-NMR spectrum for compound **721** *(experimental on page 235)*.



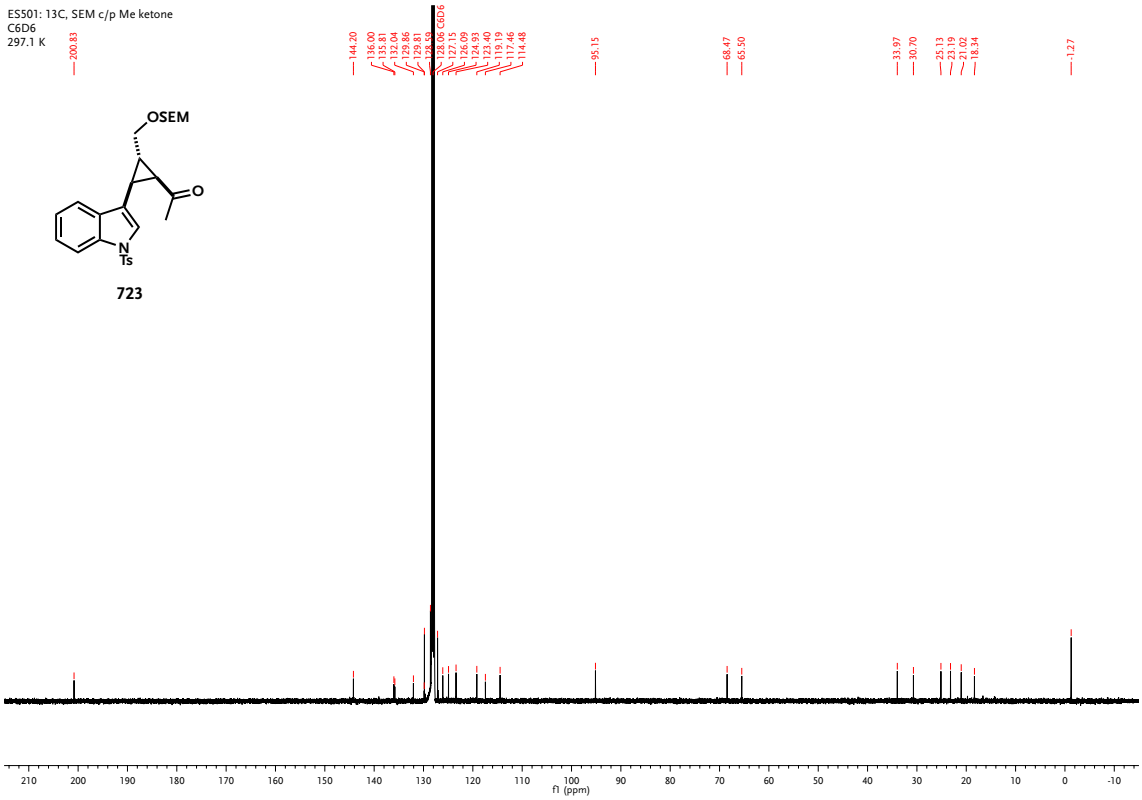
Spectrum B-127. ^{13}C-NMR spectrum for compound **721** *(experimental on page 235)*.



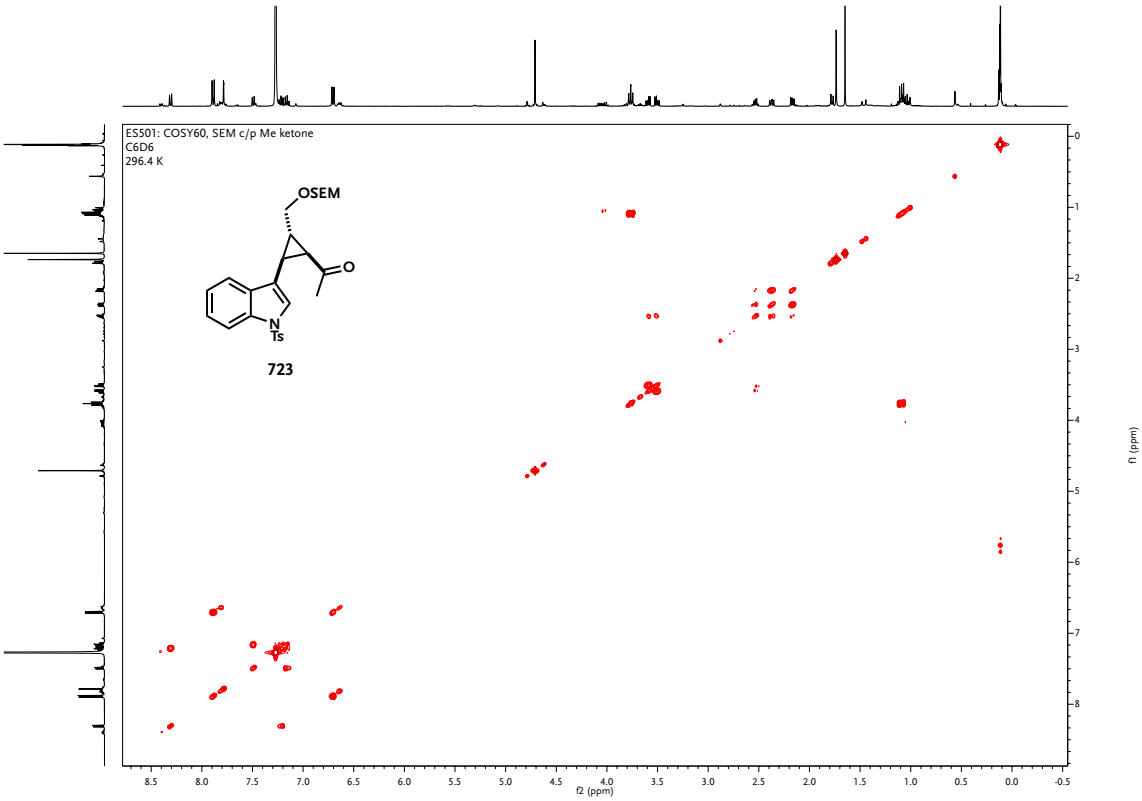
Spectrum B-128. COSY60 2D-NMR spectrum for compound **721** *(experimental on page 235)*.



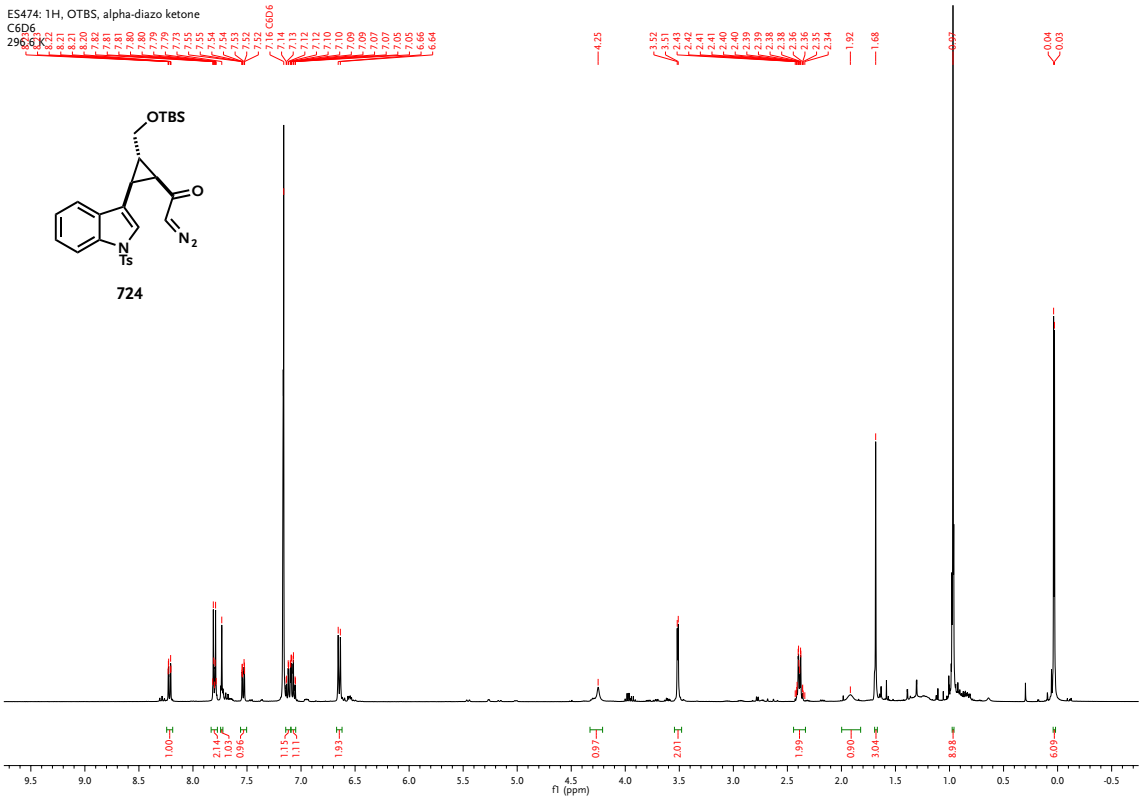
Spectrum B-129. ^{1}H-NMR spectrum for compound **723** *(experimental on page 236)*.



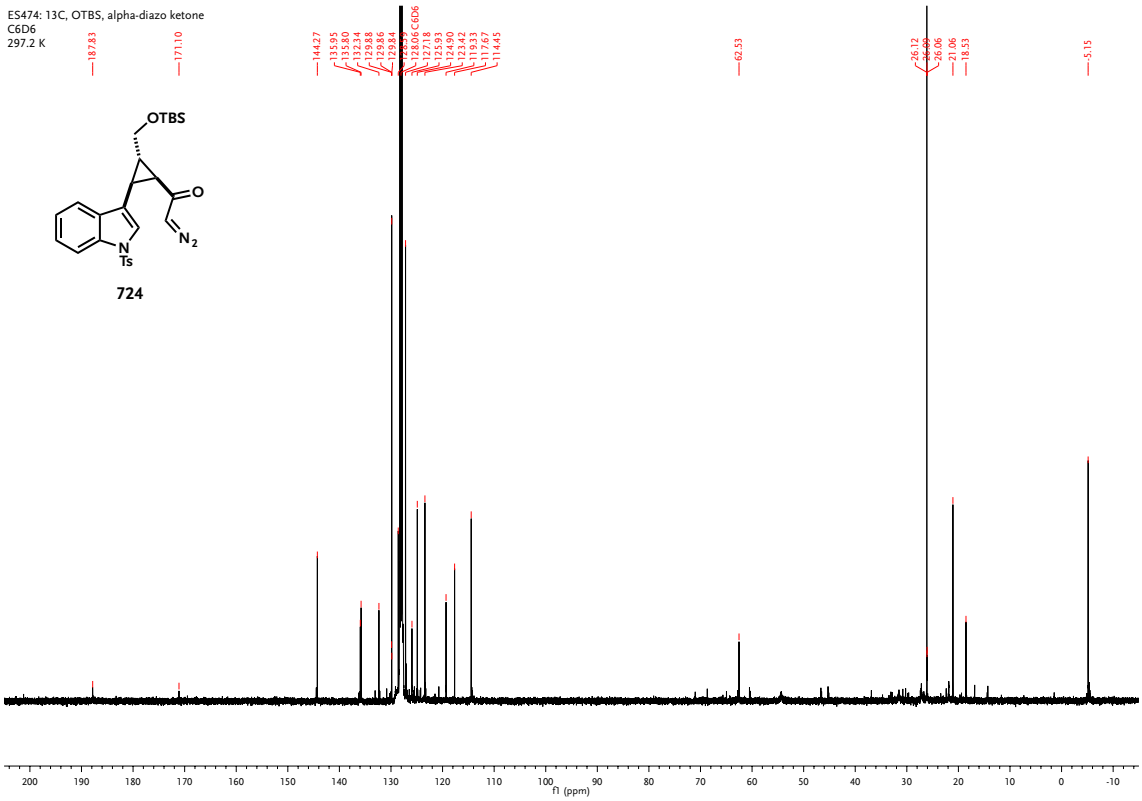
Spectrum B-130. ^{13}C-NMR spectrum for compound **723** *(experimental on page 236)*.



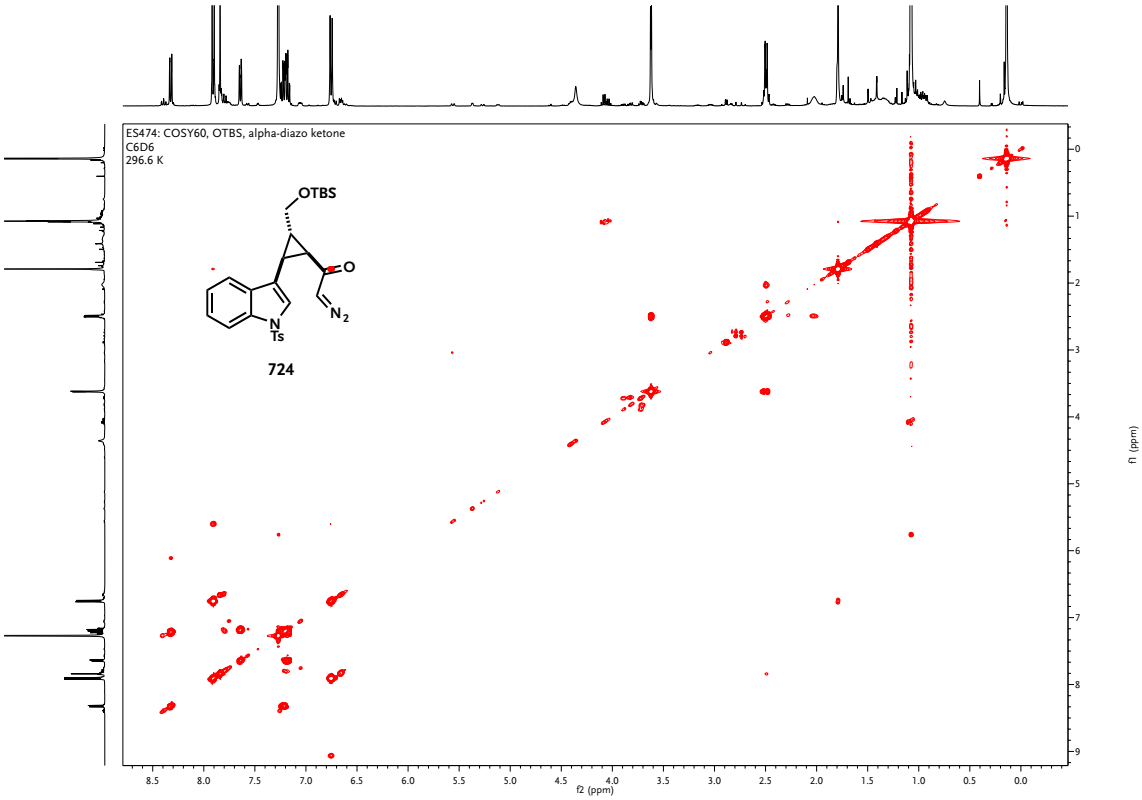
Spectrum B-131. COSY60 2D-NMR spectrum for compound **723** *(experimental on page 236)*.



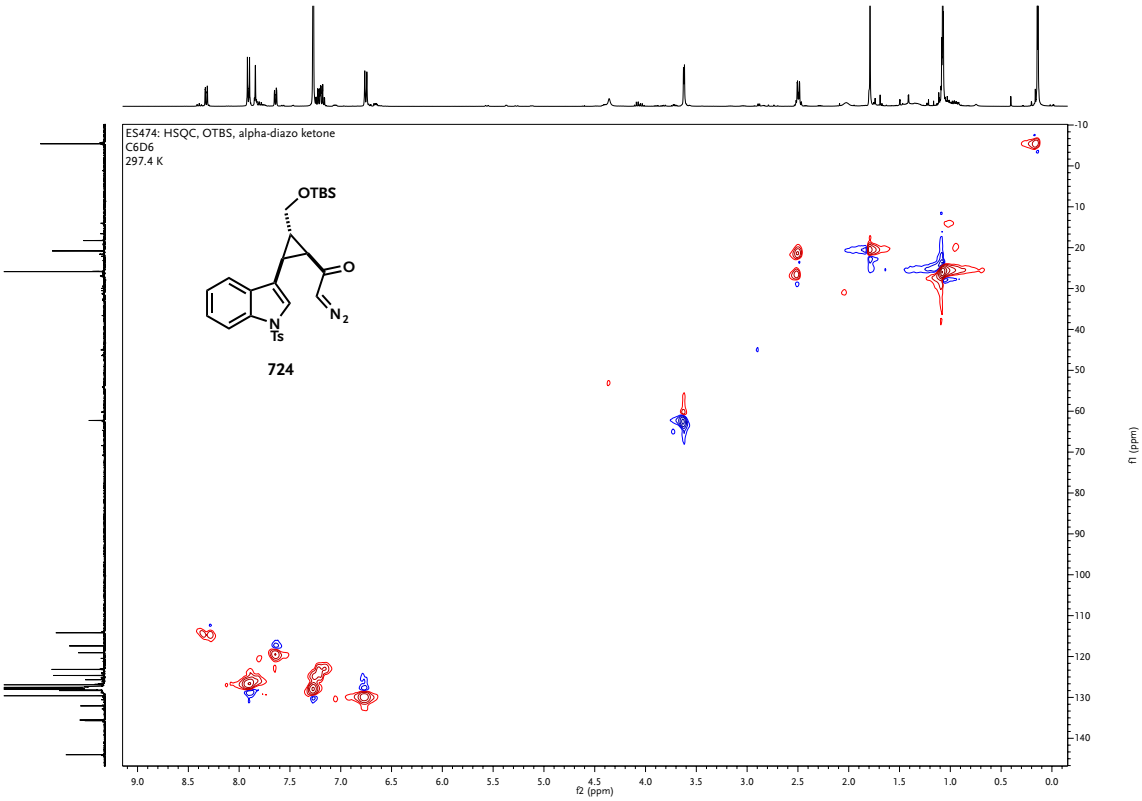
Spectrum B-132. ^{1}H-NMR spectrum for compound **724** *(experimental on page 237)*.



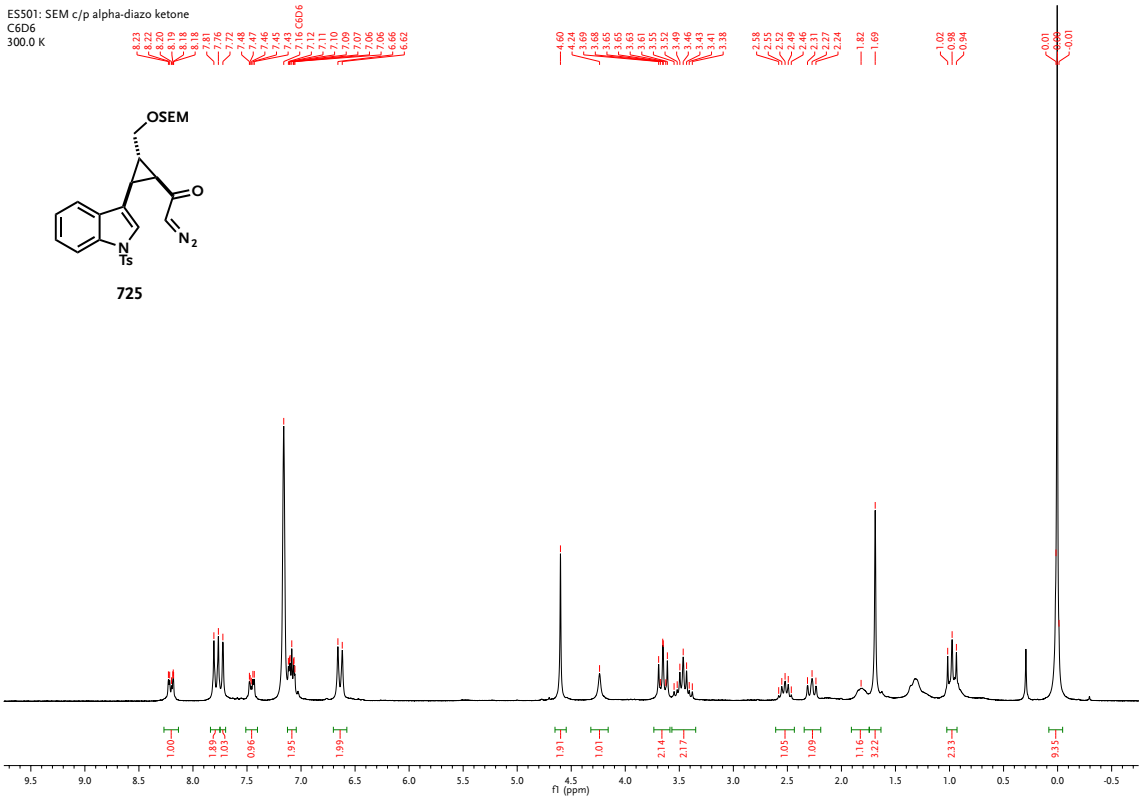
Spectrum B-133. ^{13}C-NMR spectrum for compound **724** *(experimental on page 237)*.



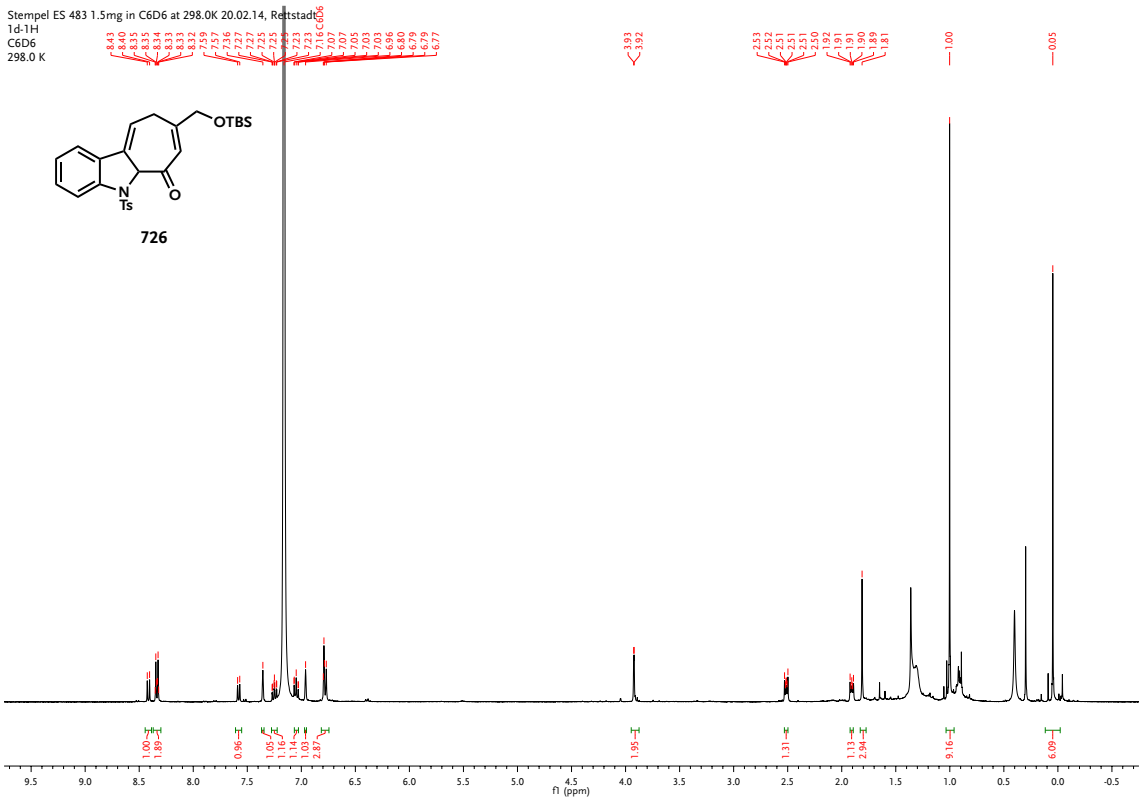
Spectrum B-134. COSY60 2D-NMR spectrum for compound **724** *(experimental on page 237)*.



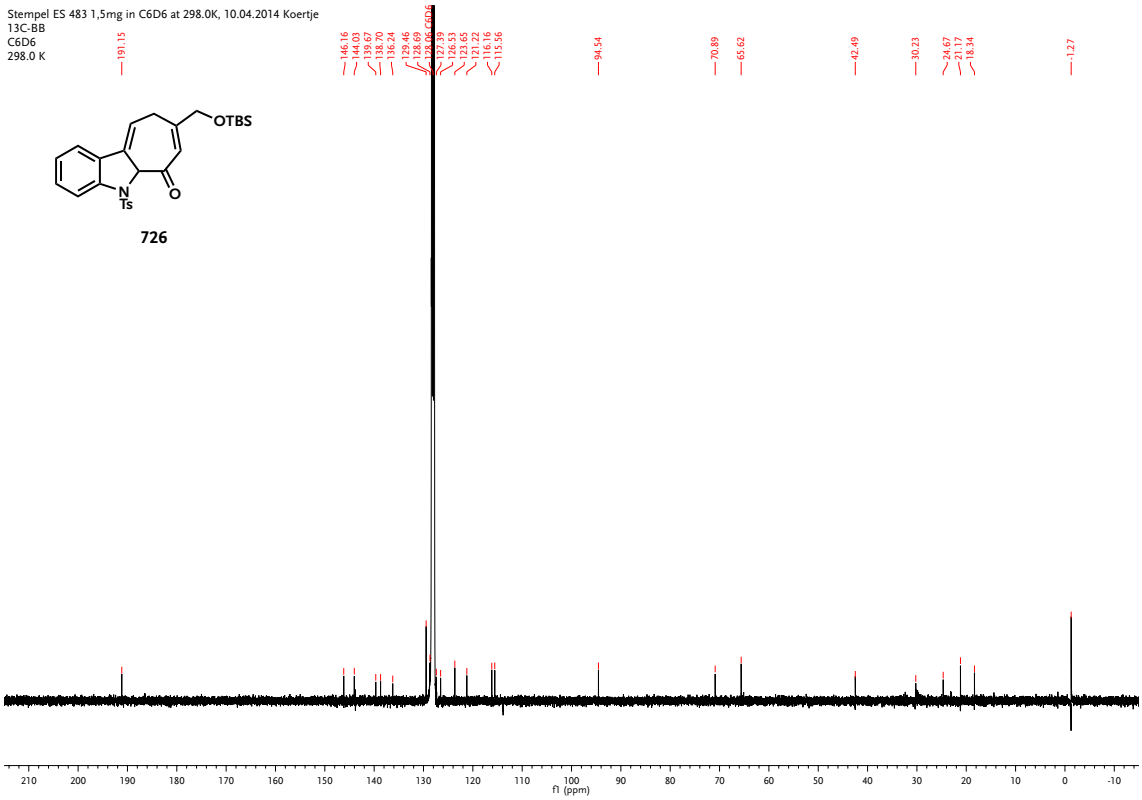
Spectrum B-135. HSQC 2D-NMR spectrum for compound **724** *(experimental on page 237)*.



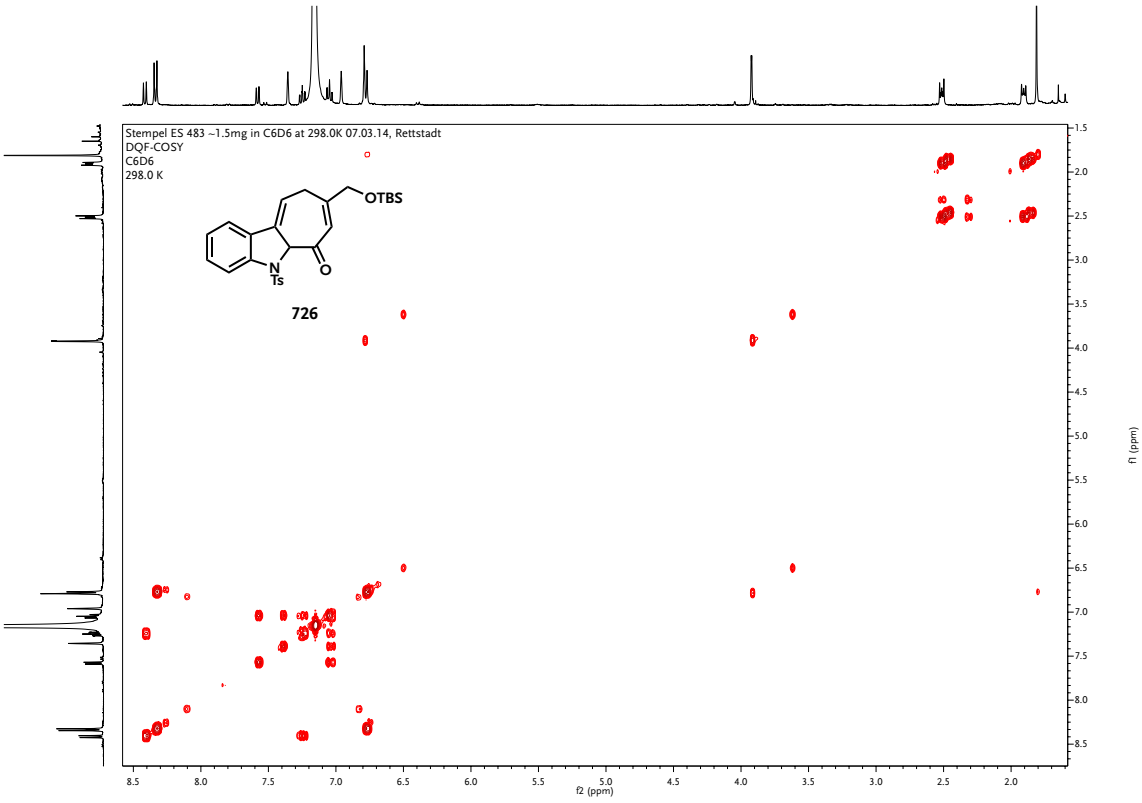
Spectrum B-136. ^{1}H-NMR spectrum for compound **725** *(experimental on page 238)*.



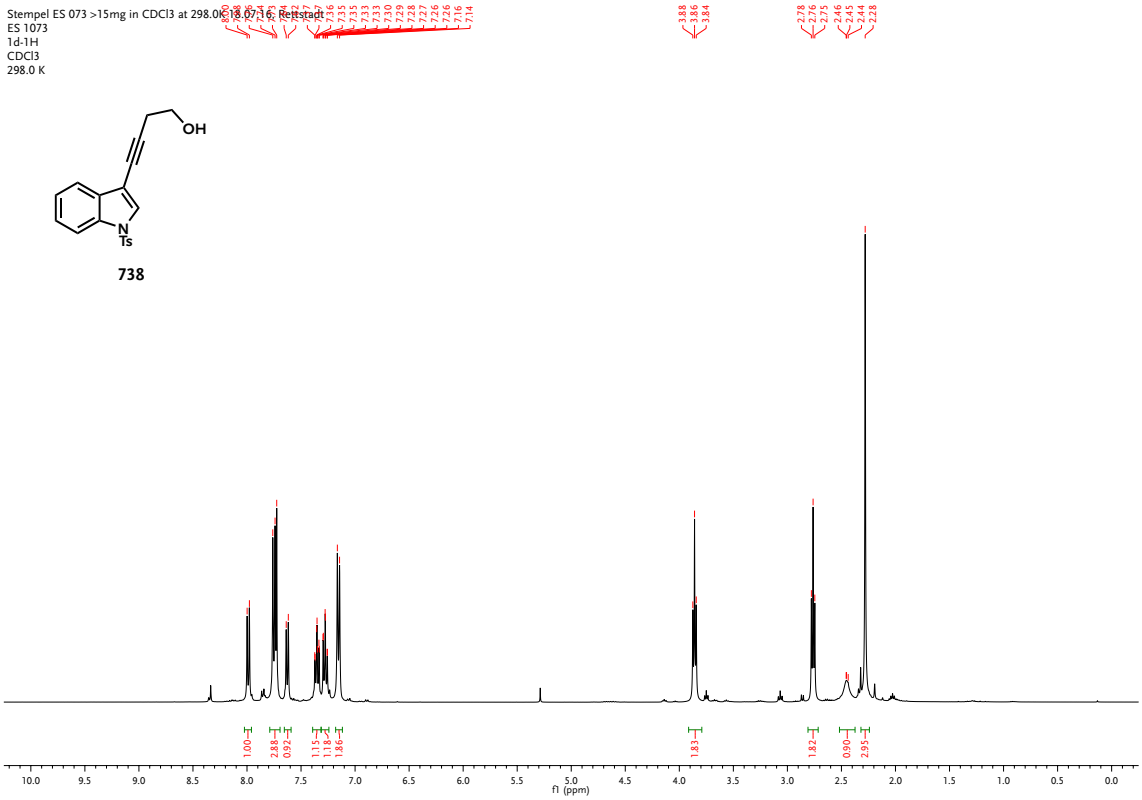
Spectrum B-137. ^{1}H-NMR spectrum for compound **726** *(experimental on page 238)*.



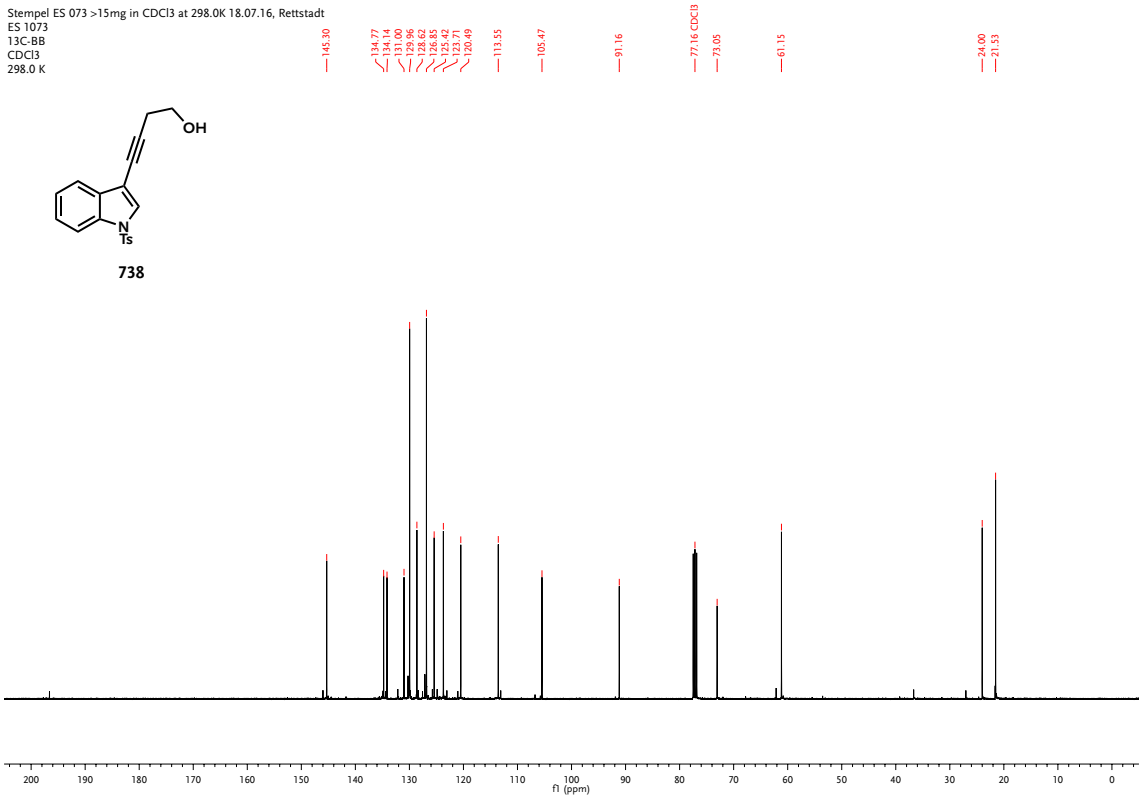
Spectrum B-138. ^{13}C-NMR spectrum for compound **726** *(experimental on page 238)*.



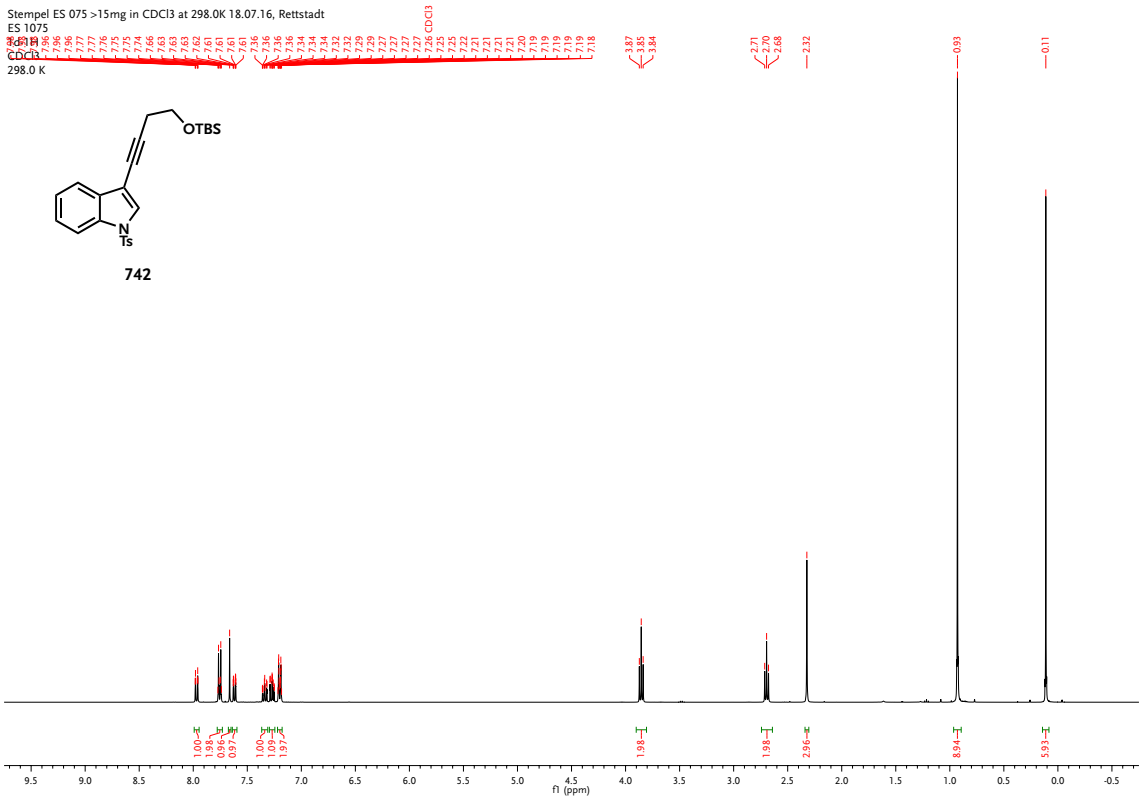
Spectrum B-139. COSY60 2D-NMR spectrum for compound **726** *(experimental on page 238)*.



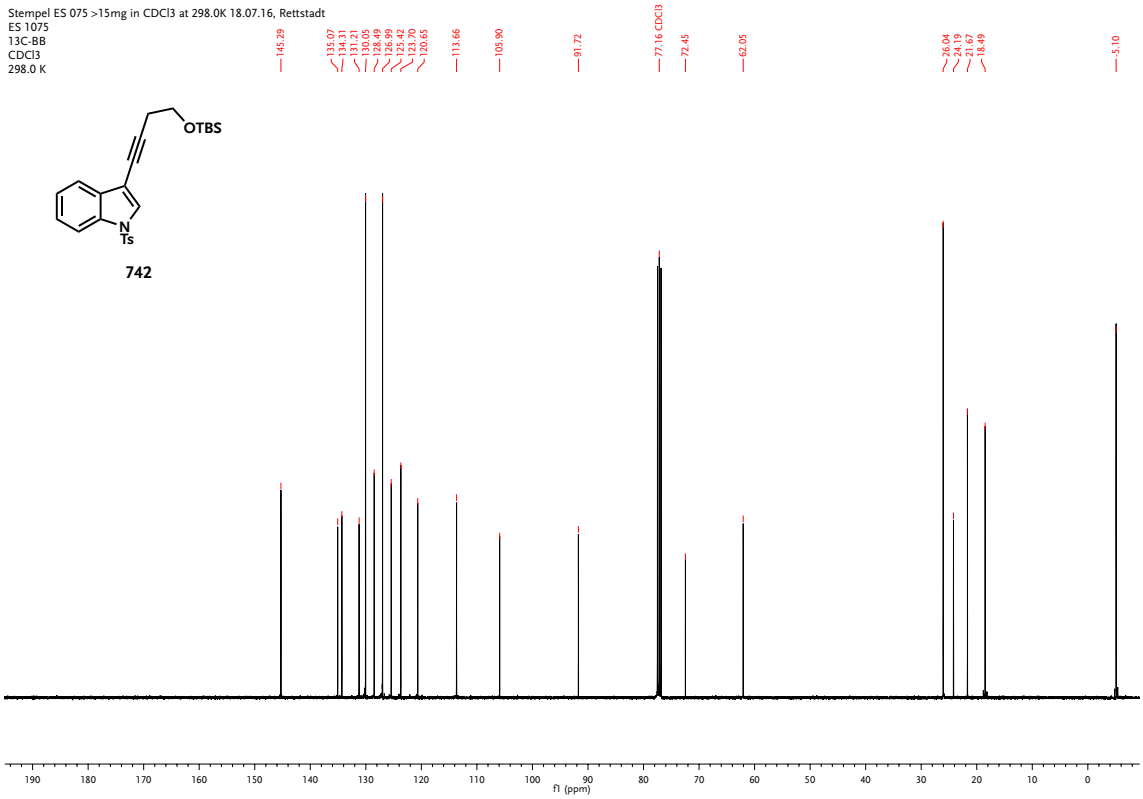
Spectrum B-140. ^{1}H-NMR spectrum for compound **738** *(experimental on page 239)*.



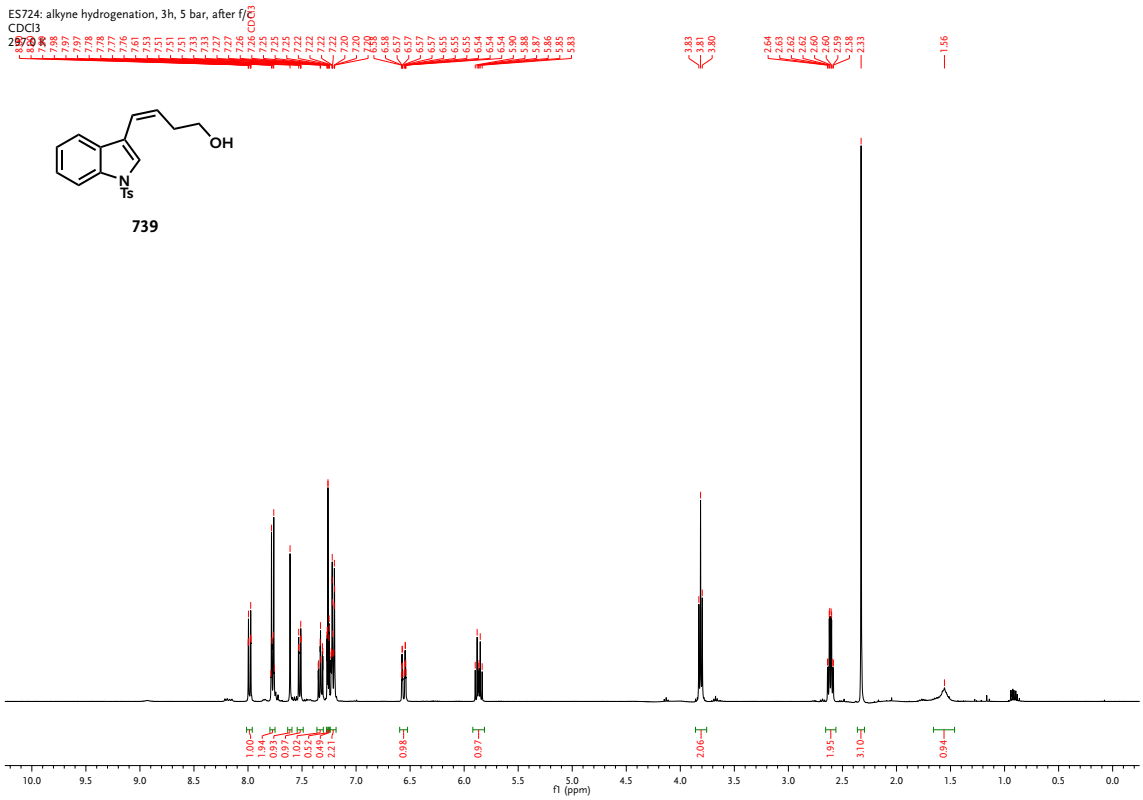
Spectrum B-141. ^{13}C-NMR spectrum for compound **738** *(experimental on page 239)*.



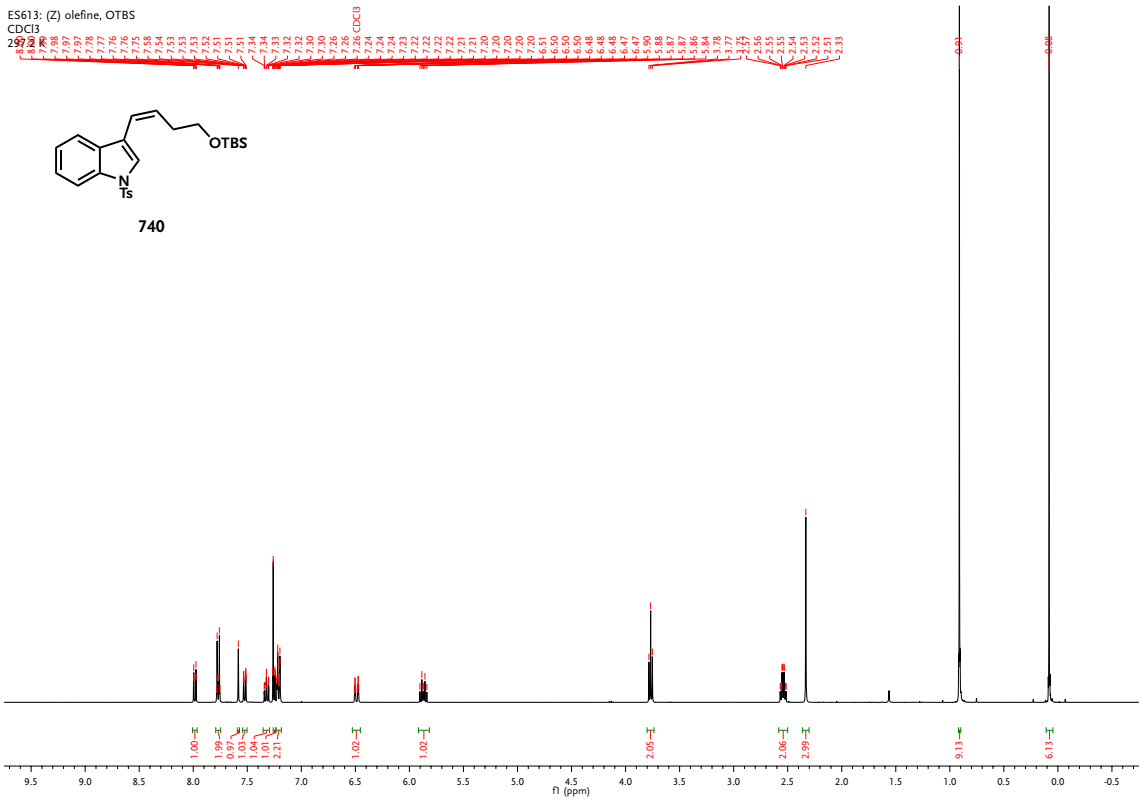
Spectrum B-142. ^{1}H-NMR spectrum for compound **742** *(experimental on page 239)*.



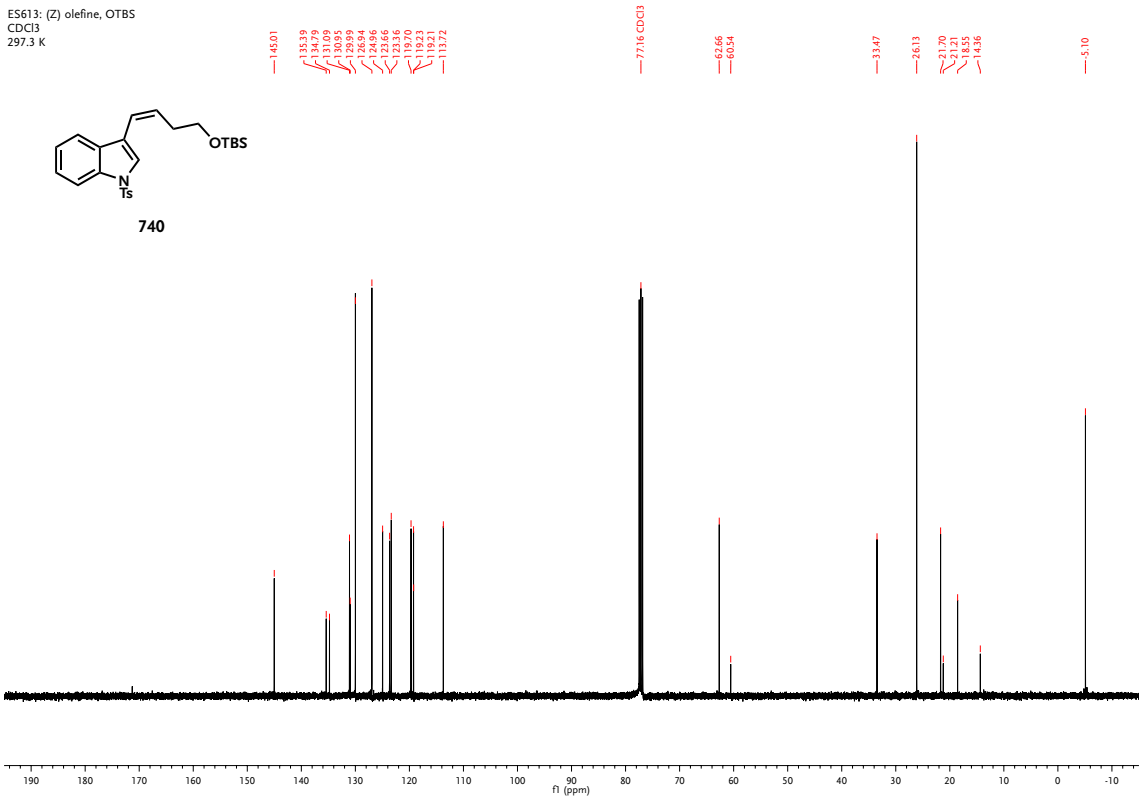
Spectrum B-143. ^{13}C-NMR spectrum for compound **742** *(experimental on page 239)*.



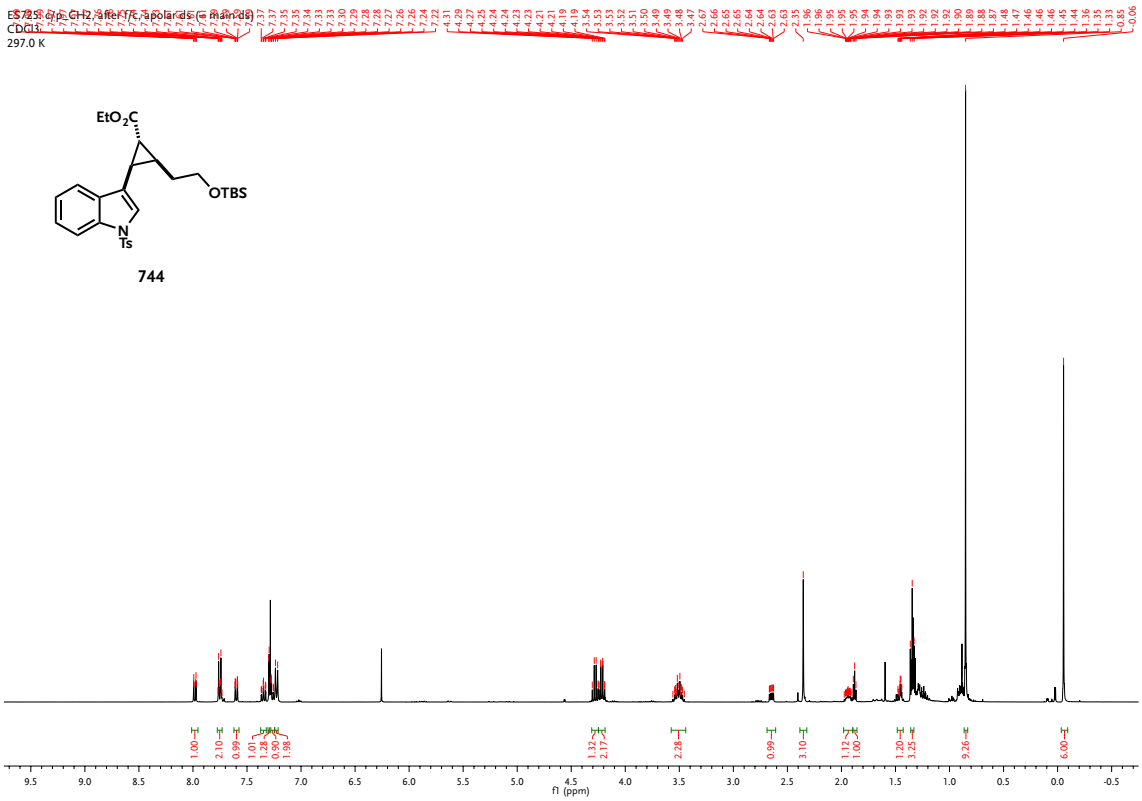
Spectrum B-144. ^{1}H-NMR spectrum for compound **739** *(experimental on page 240)*.



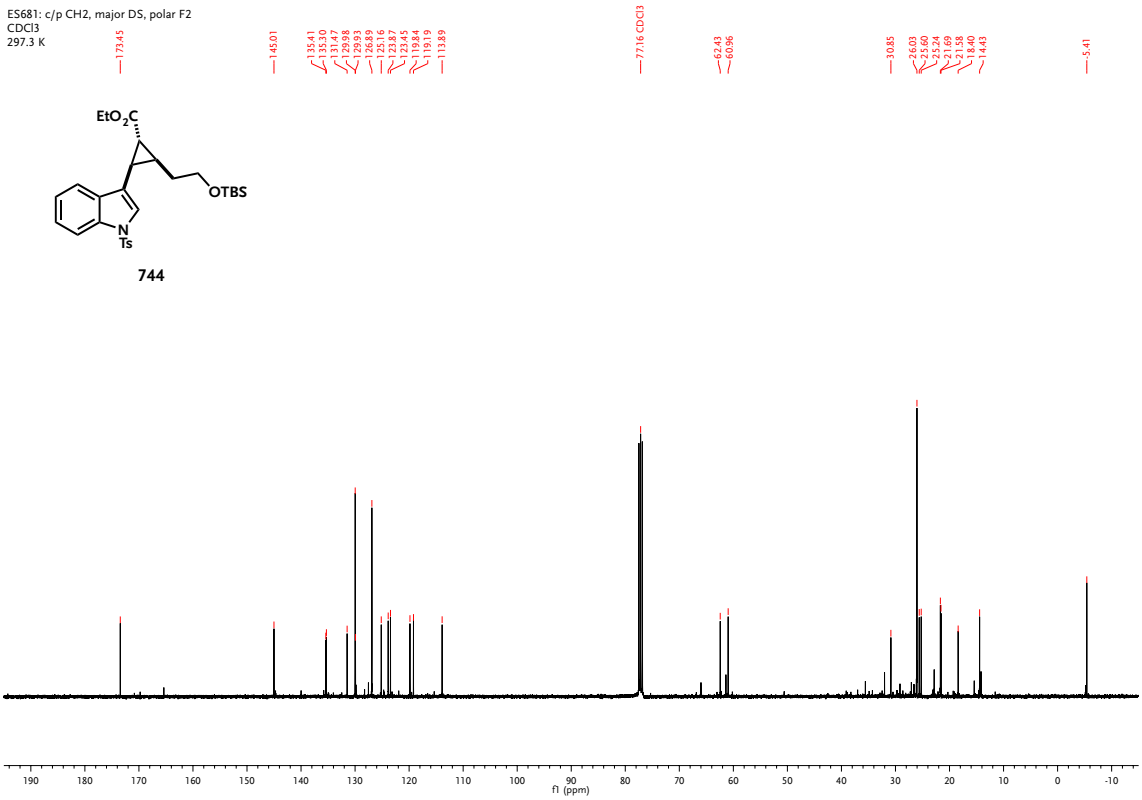
Spectrum B-145. ^{1}H-NMR spectrum for compound **740** *(experimental on page 240)*.



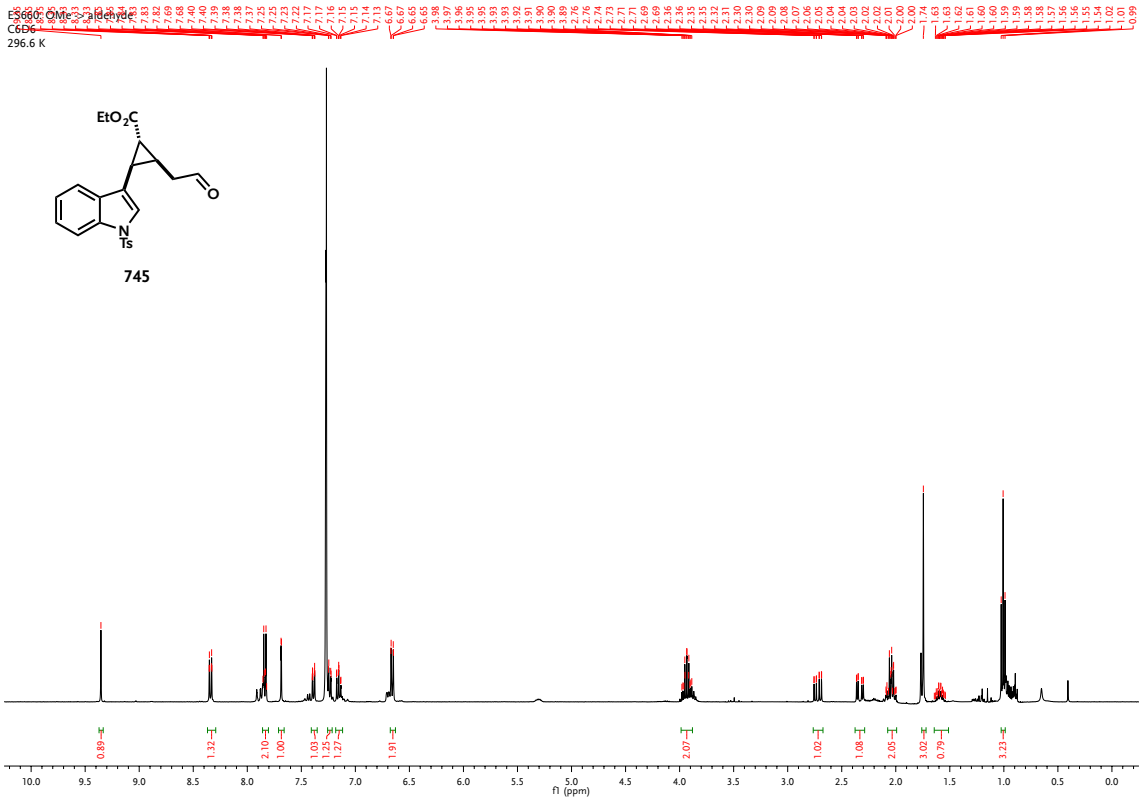
Spectrum B-146. ^{13}C-NMR spectrum for compound **740** *(experimental on page 240)*.



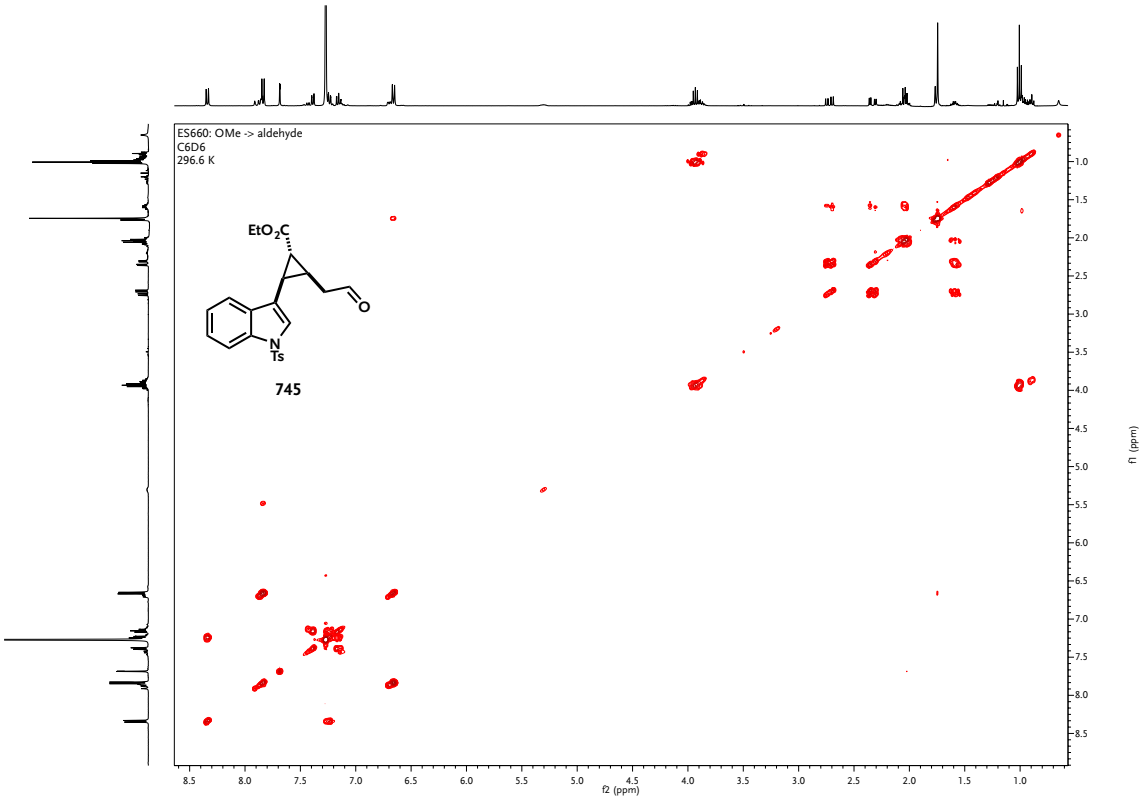
Spectrum B-147. [1]H-NMR spectrum for compound **744** *(experimental on page 241)*.



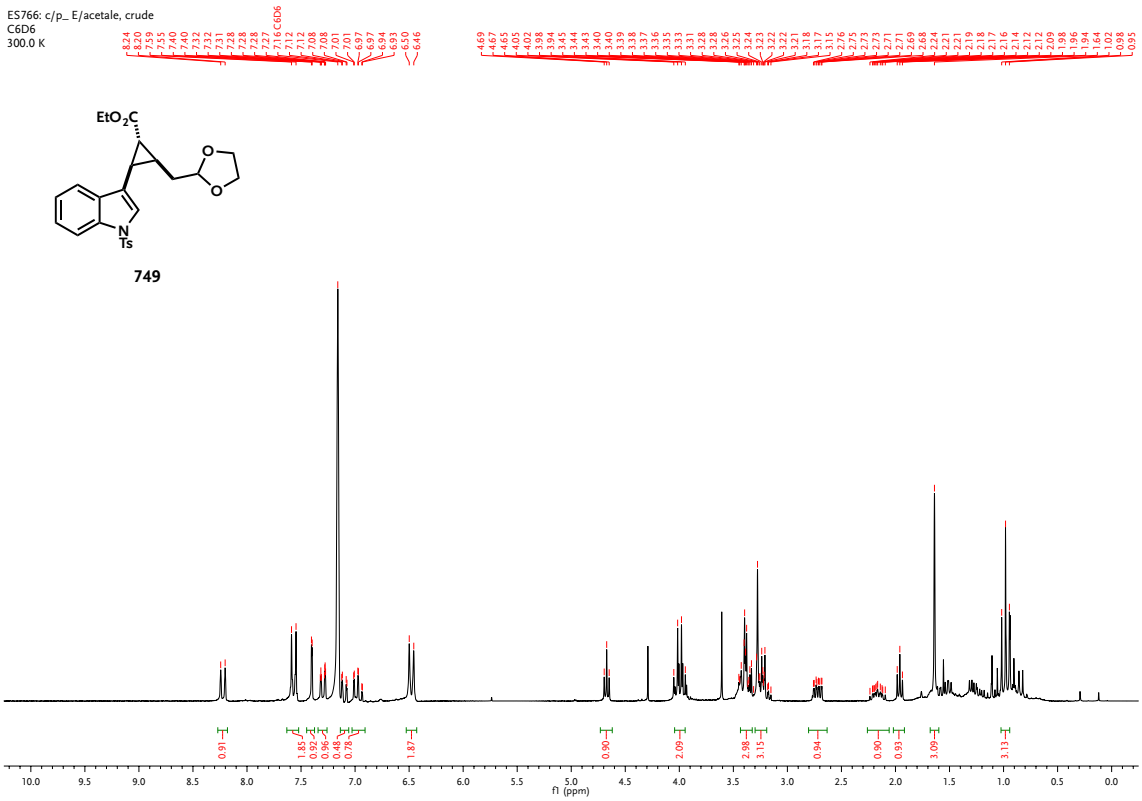
Spectrum B-148. [13]C-NMR spectrum for compound **744** *(experimental on page 241)*.



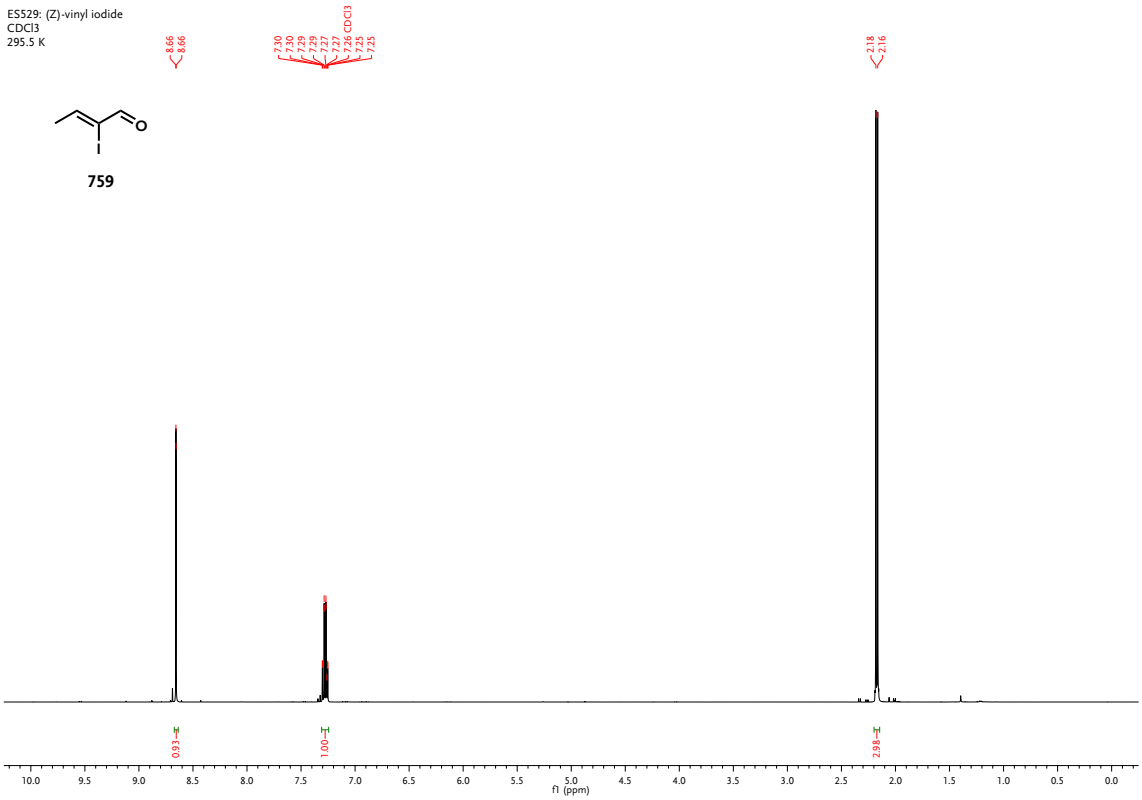
Spectrum B-149. ^{1}H-NMR spectrum for compound **745** *(experimental on page 242)*.



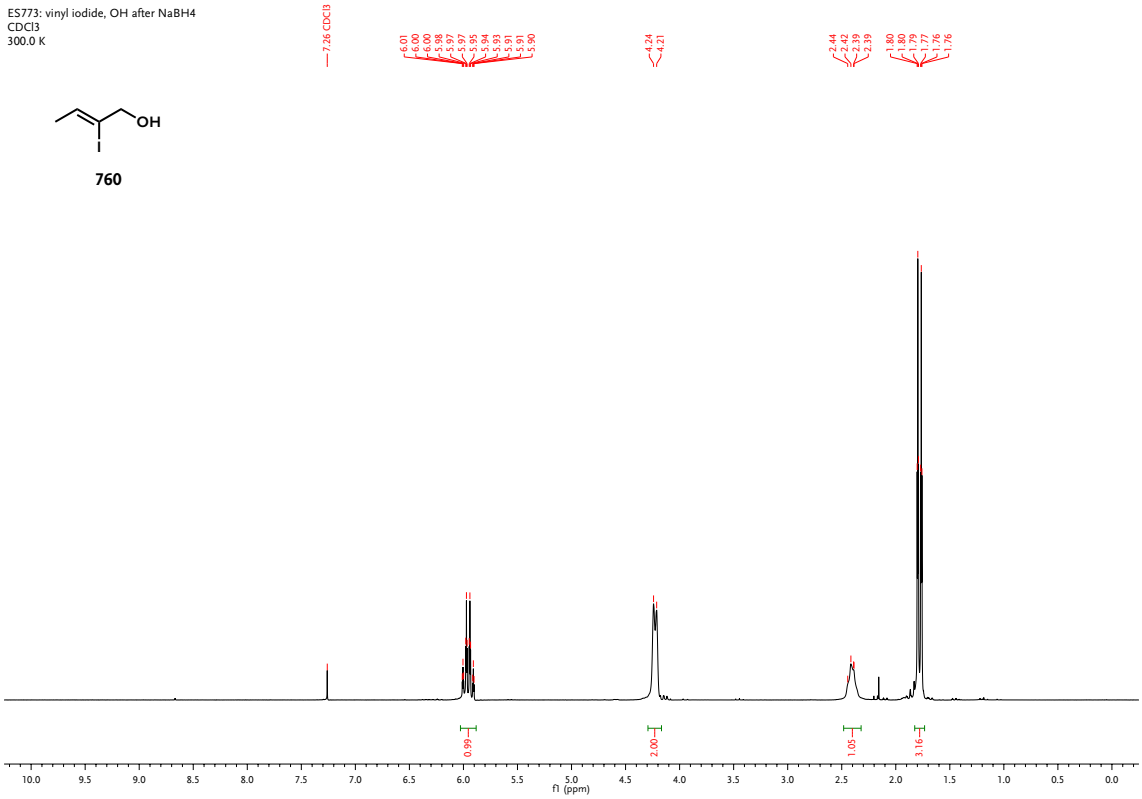
Spectrum B-150. COSY60 2D-NMR spectrum for compound **745** *(experimental on page 242)*.



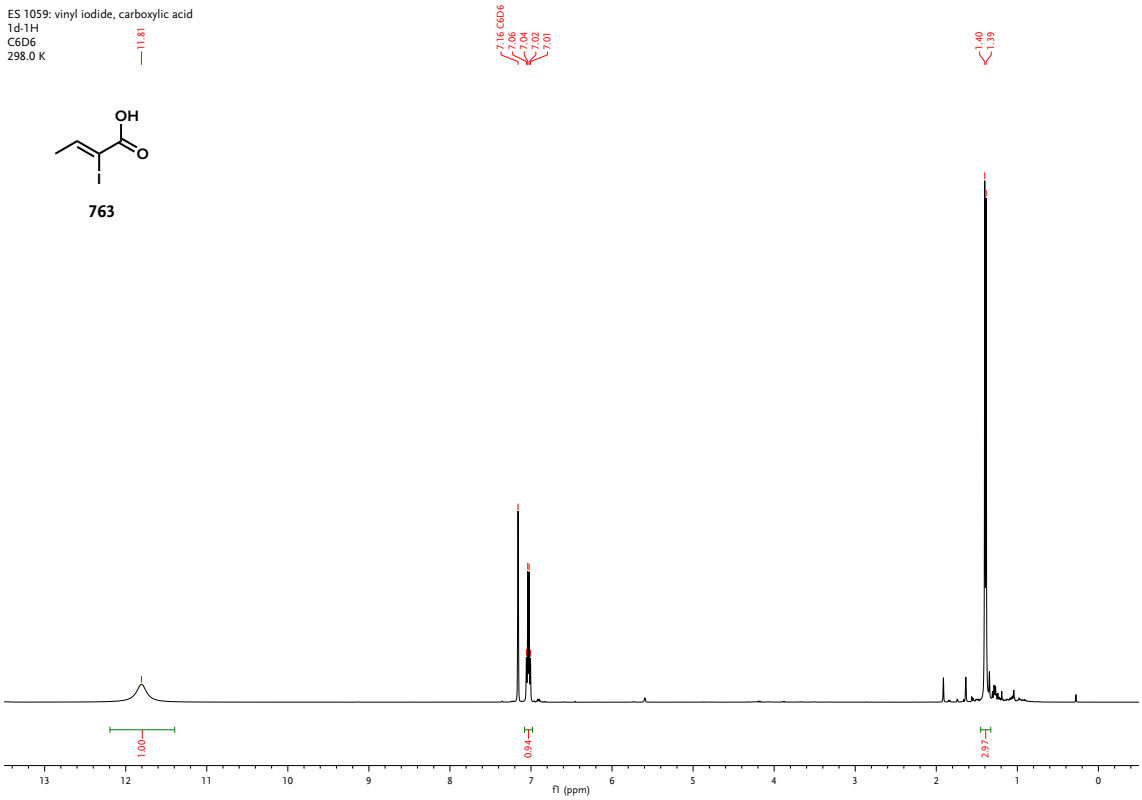
Spectrum B-151. [1]H-NMR spectrum for compound **749** *(experimental on page 243)*.



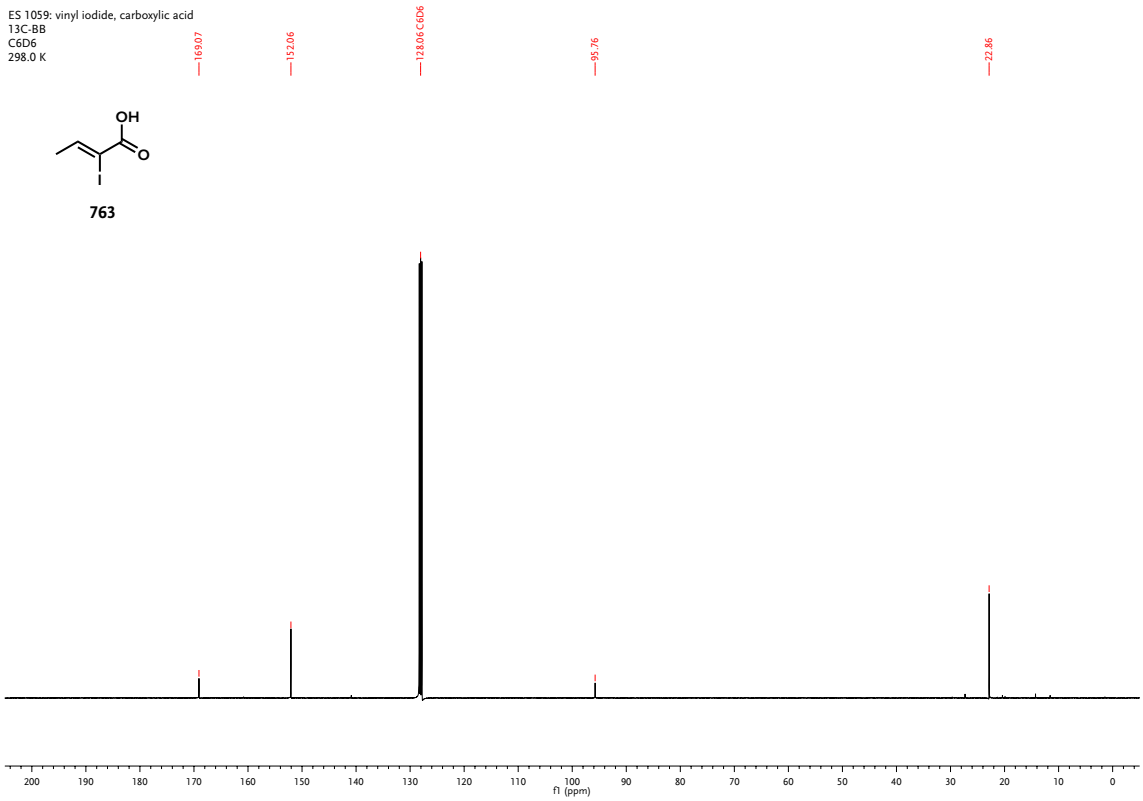
Spectrum B-152. [1]H-NMR spectrum for compound **759** *(experimental on page 244)*.



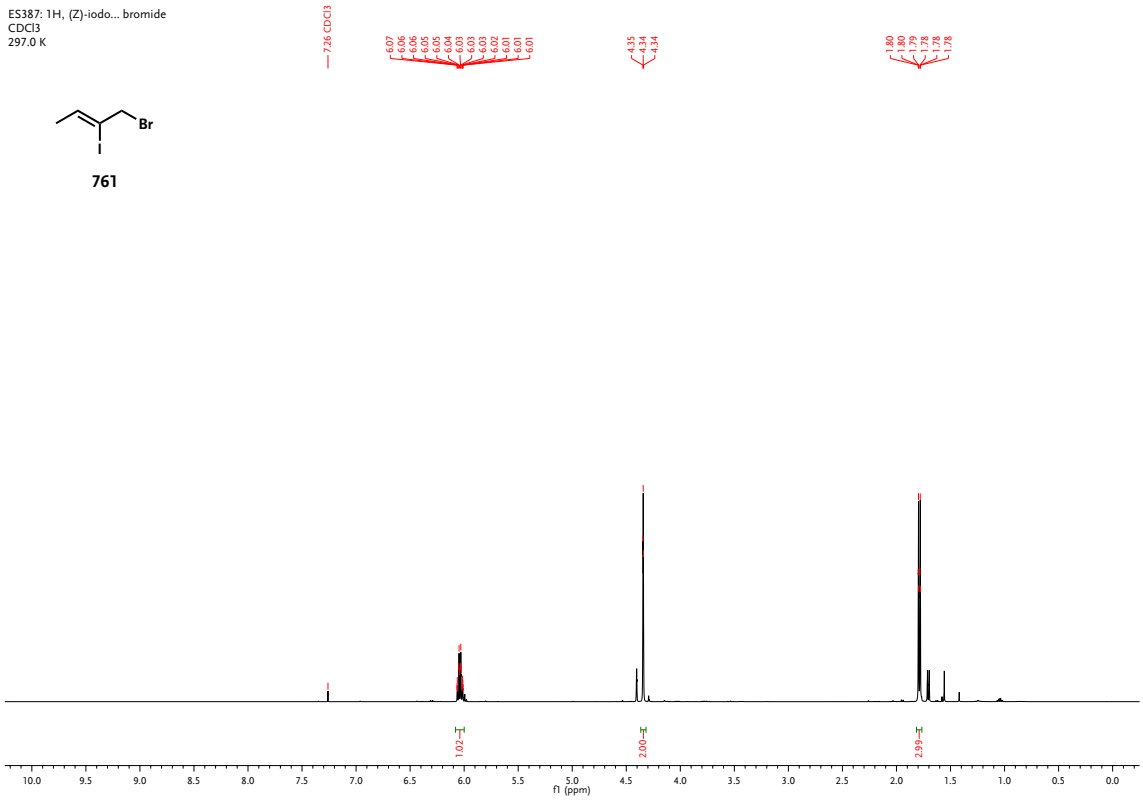
Spectrum B-153. ^{1}H-NMR spectrum for compound **760** *(experimental on page 244)*.



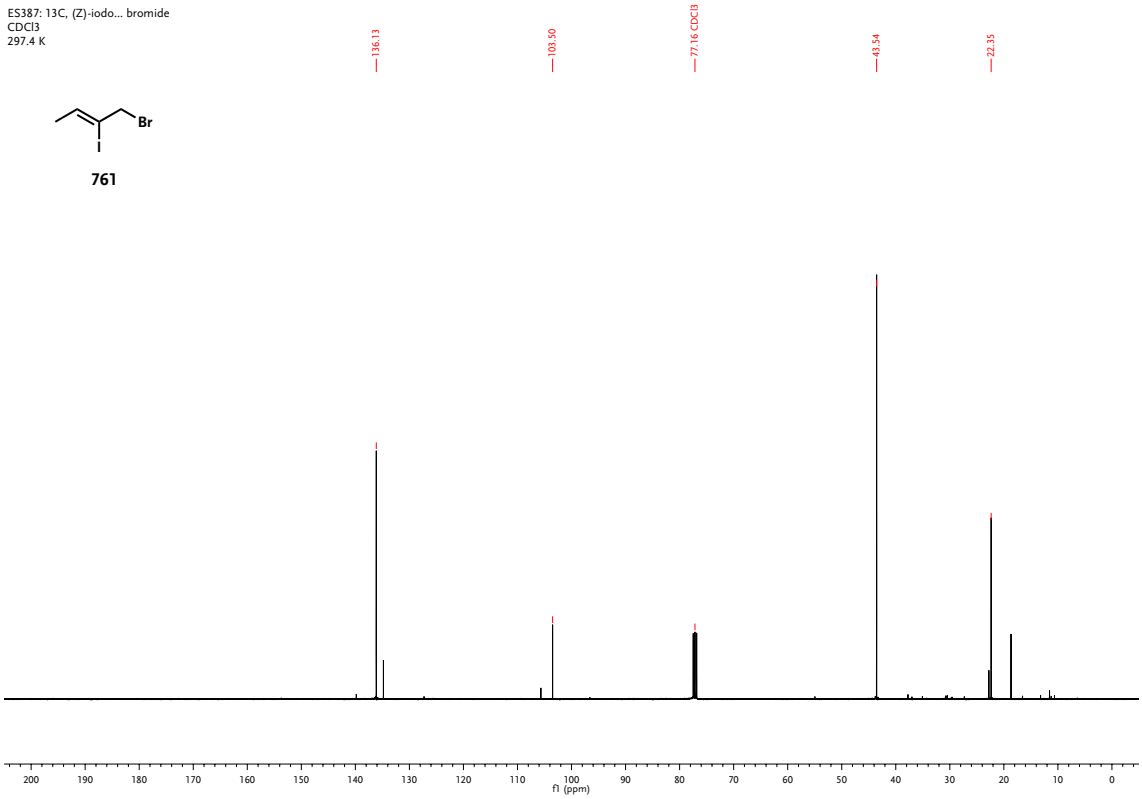
Spectrum B-154. ^{1}H-NMR spectrum for compound **763** *(experimental on page 245)*.



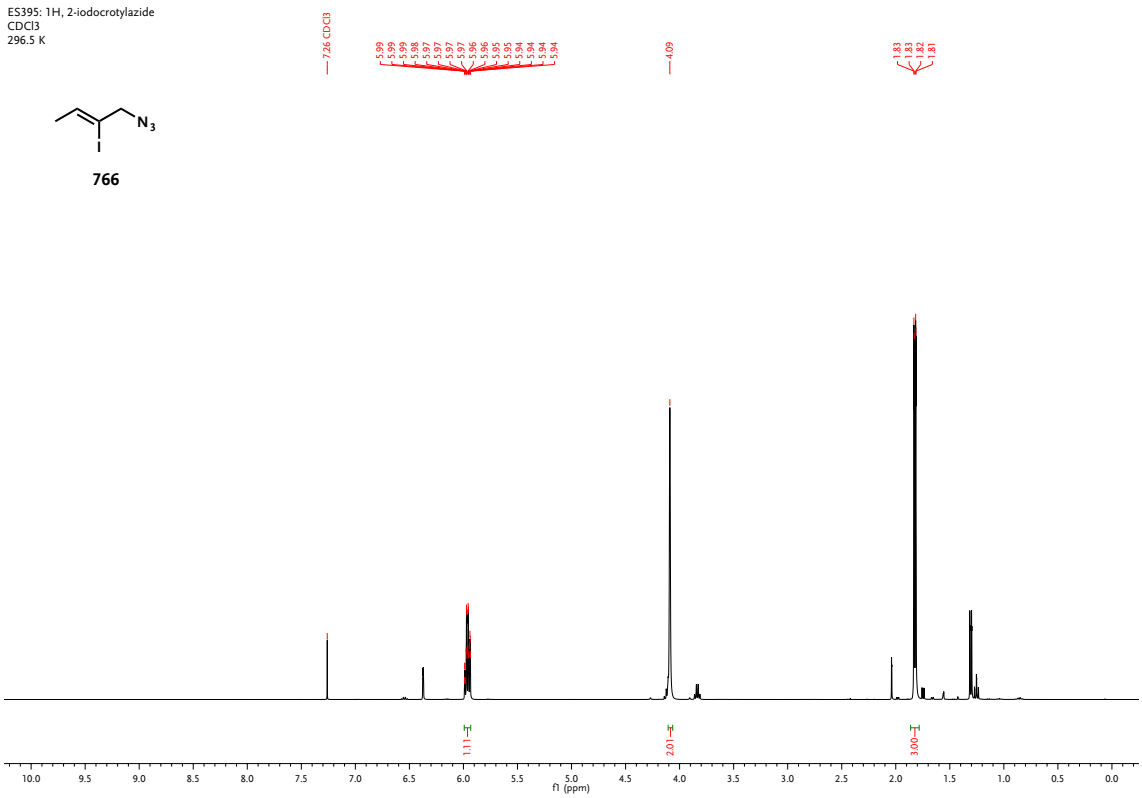
Spectrum B-155. ^{13}C-NMR spectrum for compound **763** *(experimental on page 245)*.



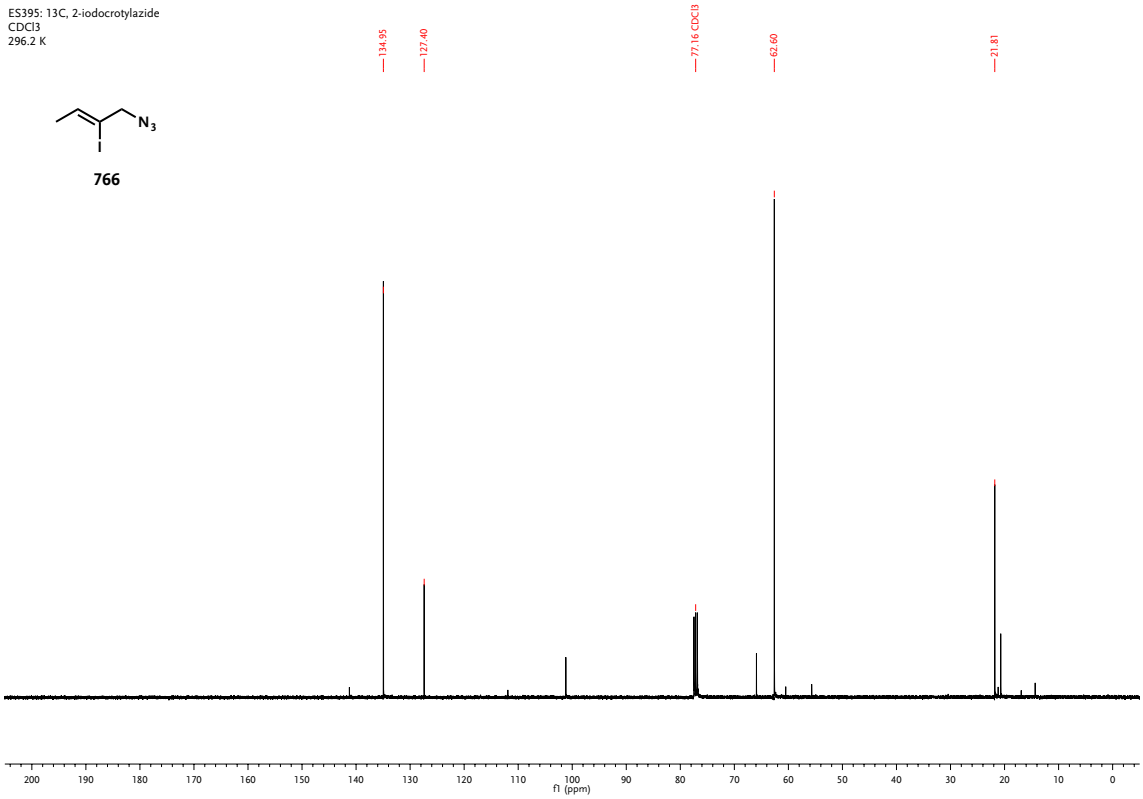
Spectrum B-156. ^{1}H-NMR spectrum for compound **761** *(experimental on page 245)*.



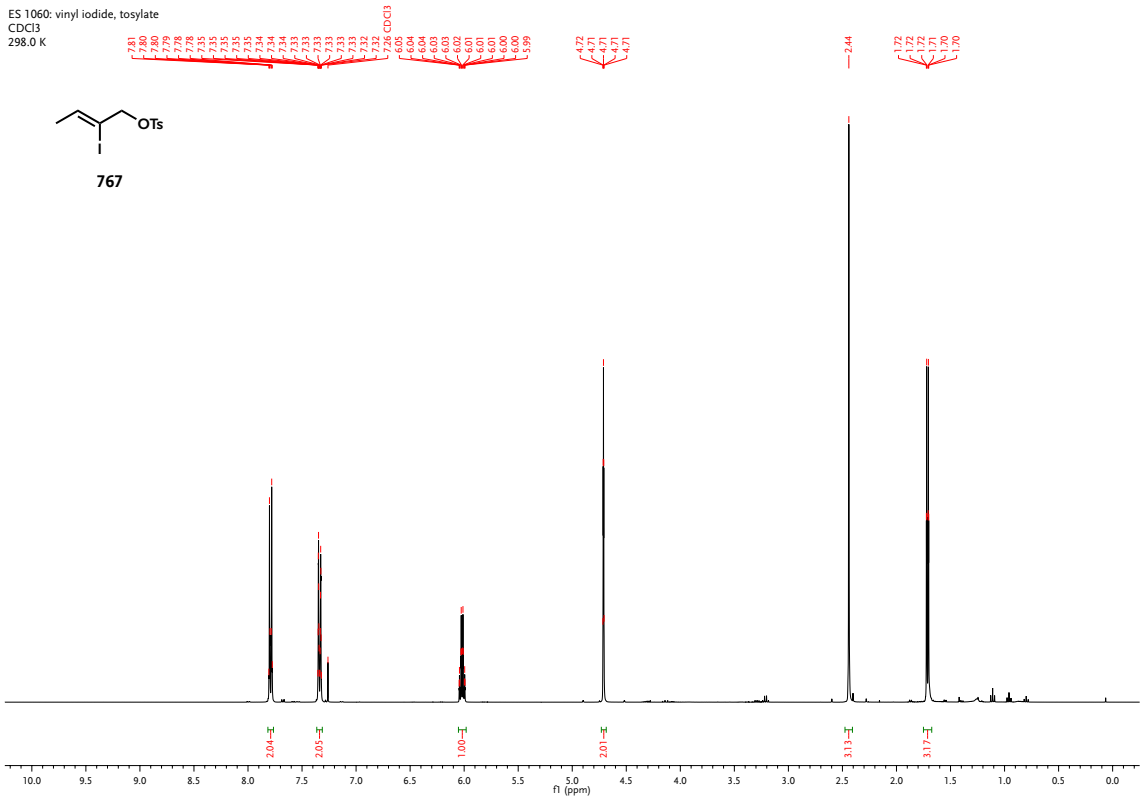
Spectrum B-157. ^{13}C-NMR spectrum for compound **761** *(experimental on page 245)*.



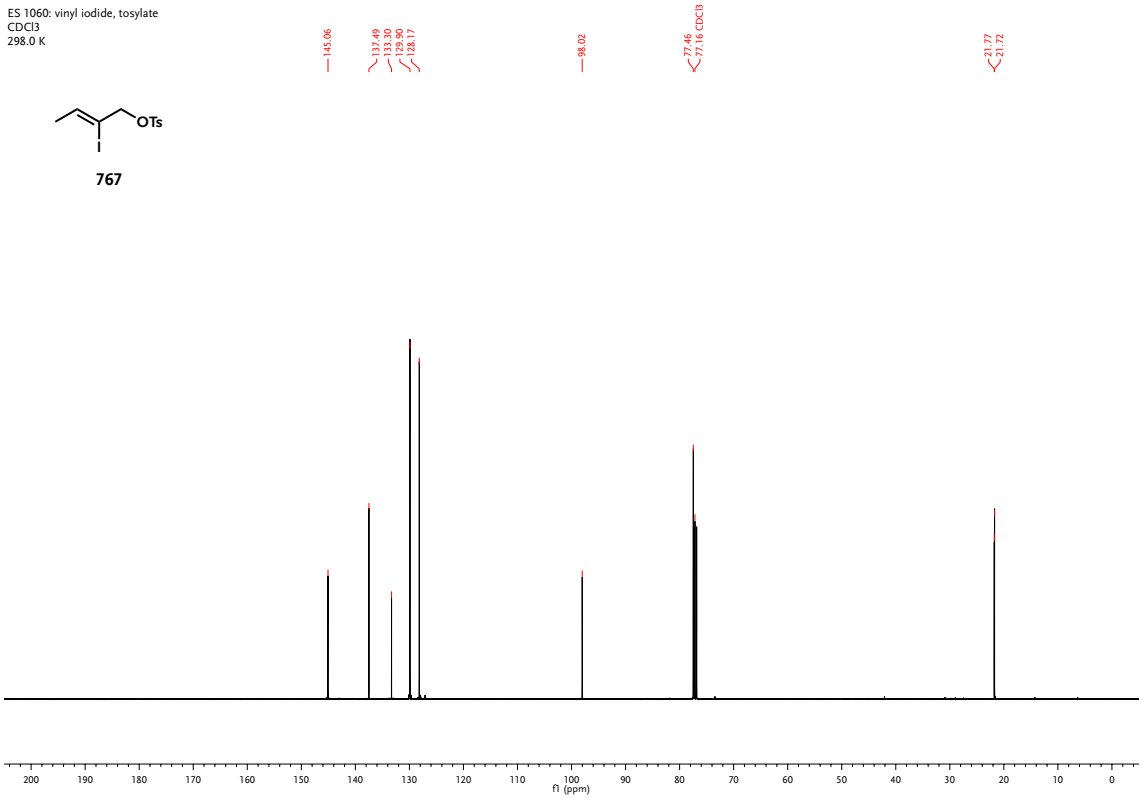
Spectrum B-158. ^{1}H-NMR spectrum for compound **766** *(experimental on page 246)*.



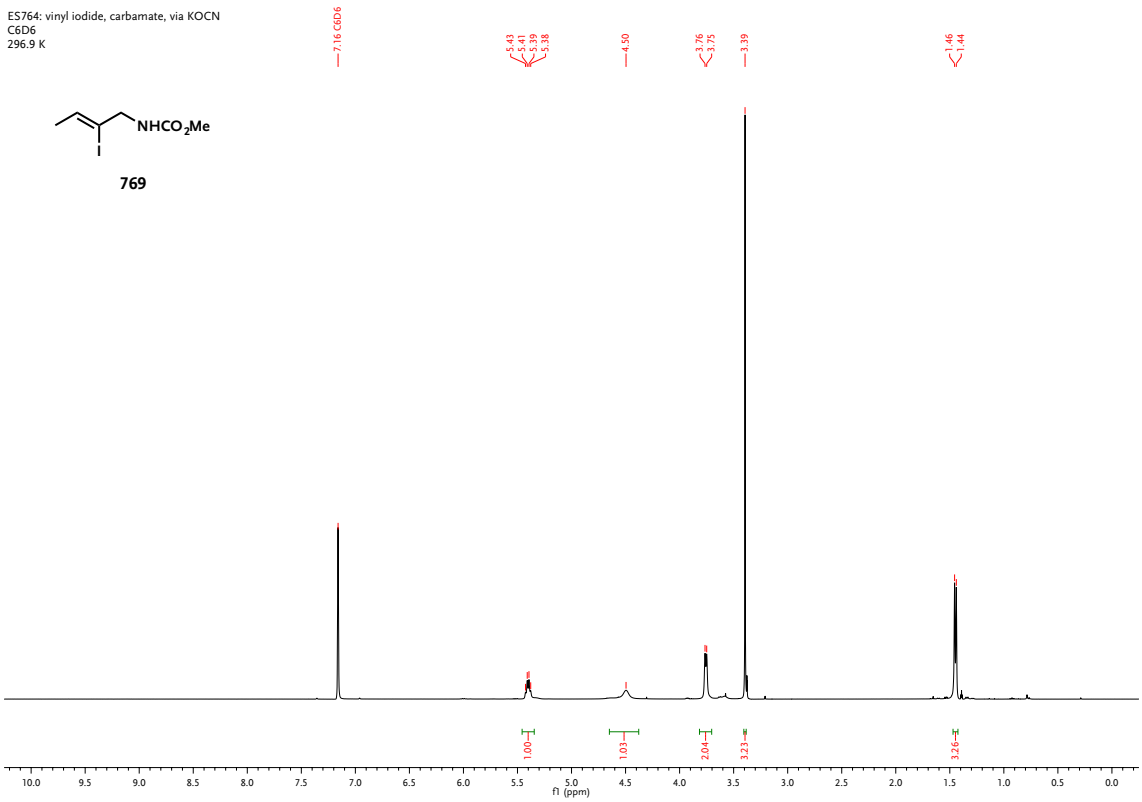
Spectrum B-159. ^{13}C-NMR spectrum for compound **766** *(experimental on page 246)*.



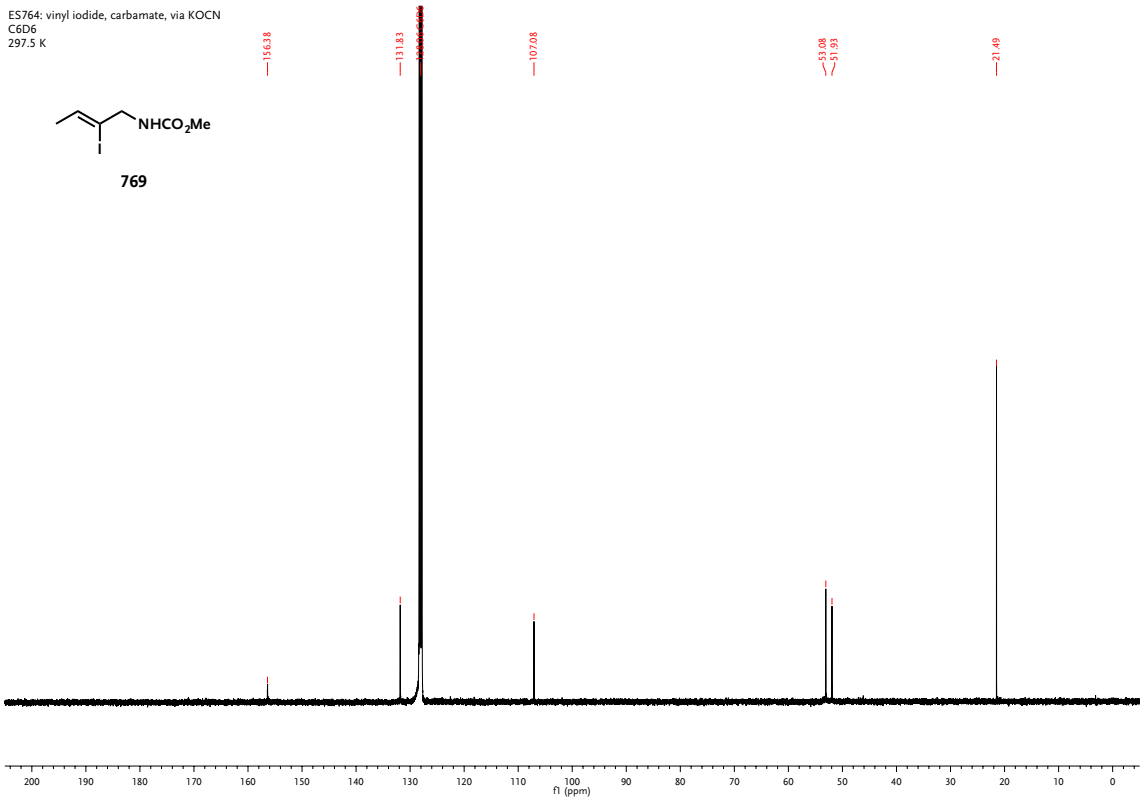
Spectrum B-160. ^{1}H-NMR spectrum for compound **767** *(experimental on page 246)*.



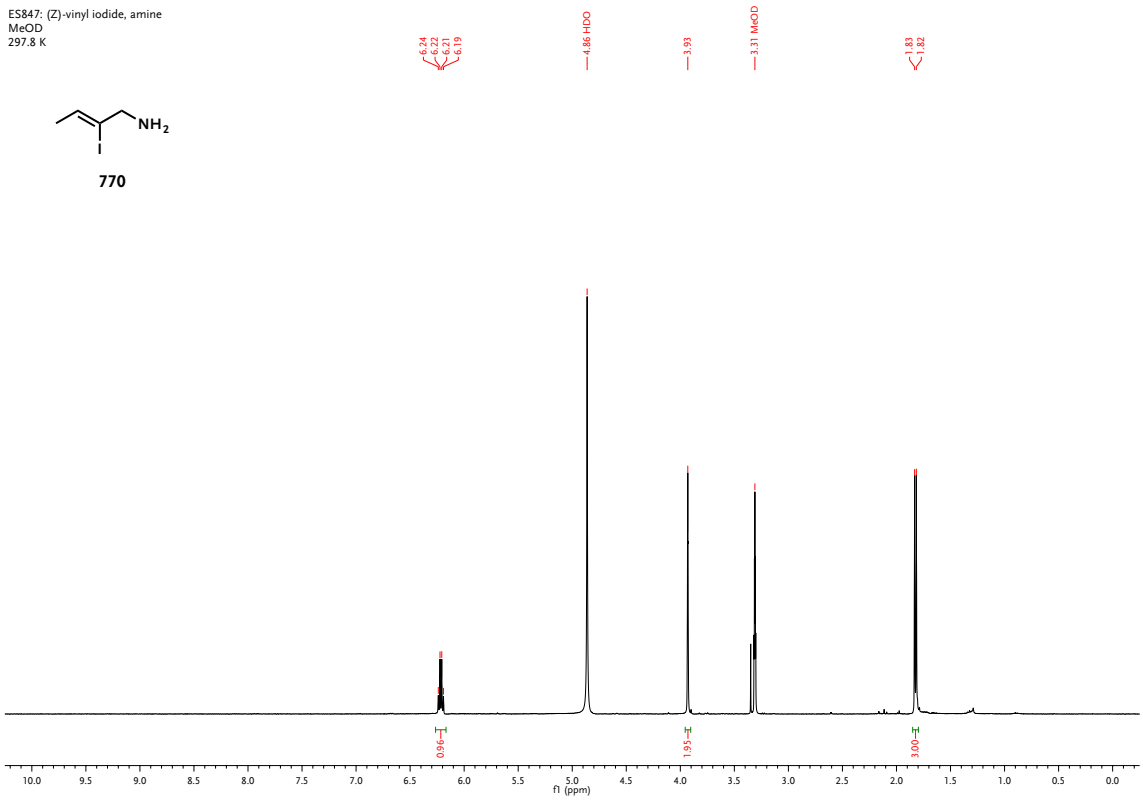
Spectrum B-161. ^{13}C-NMR spectrum for compound **767** *(experimental on page 246)*.



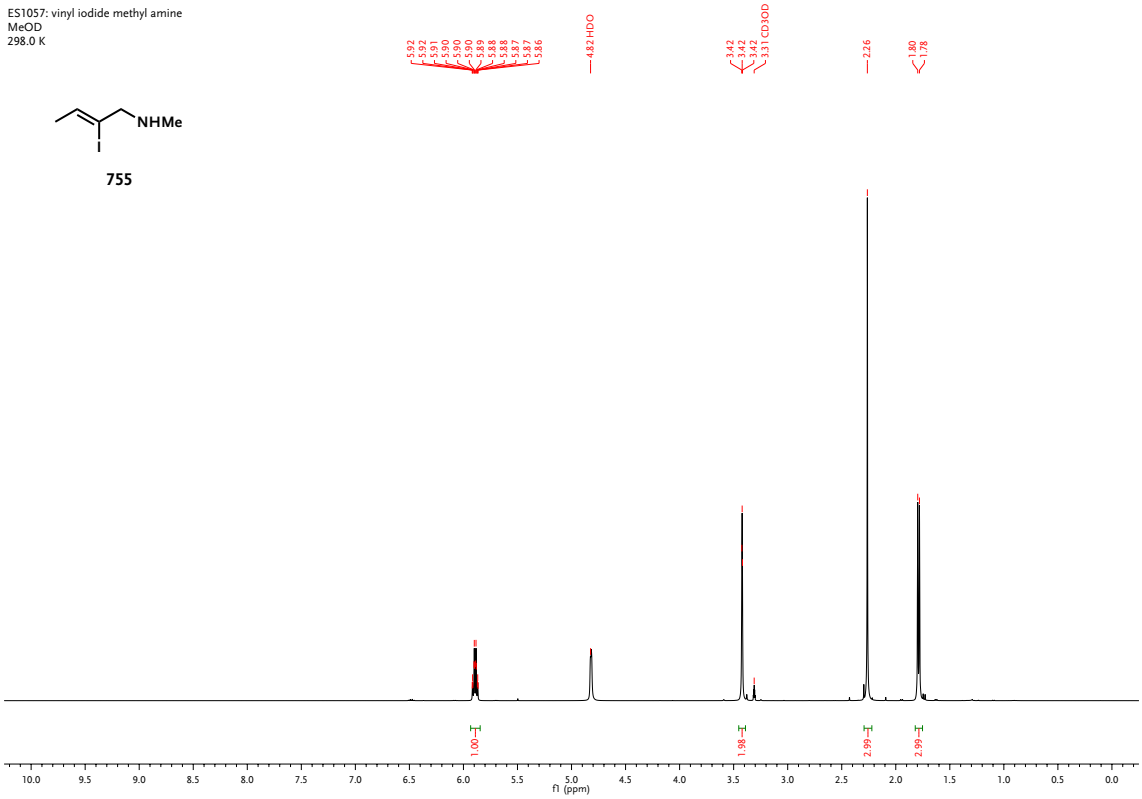
Spectrum B-162. ^{1}H-NMR spectrum for compound **769** *(experimental on page 247)*.



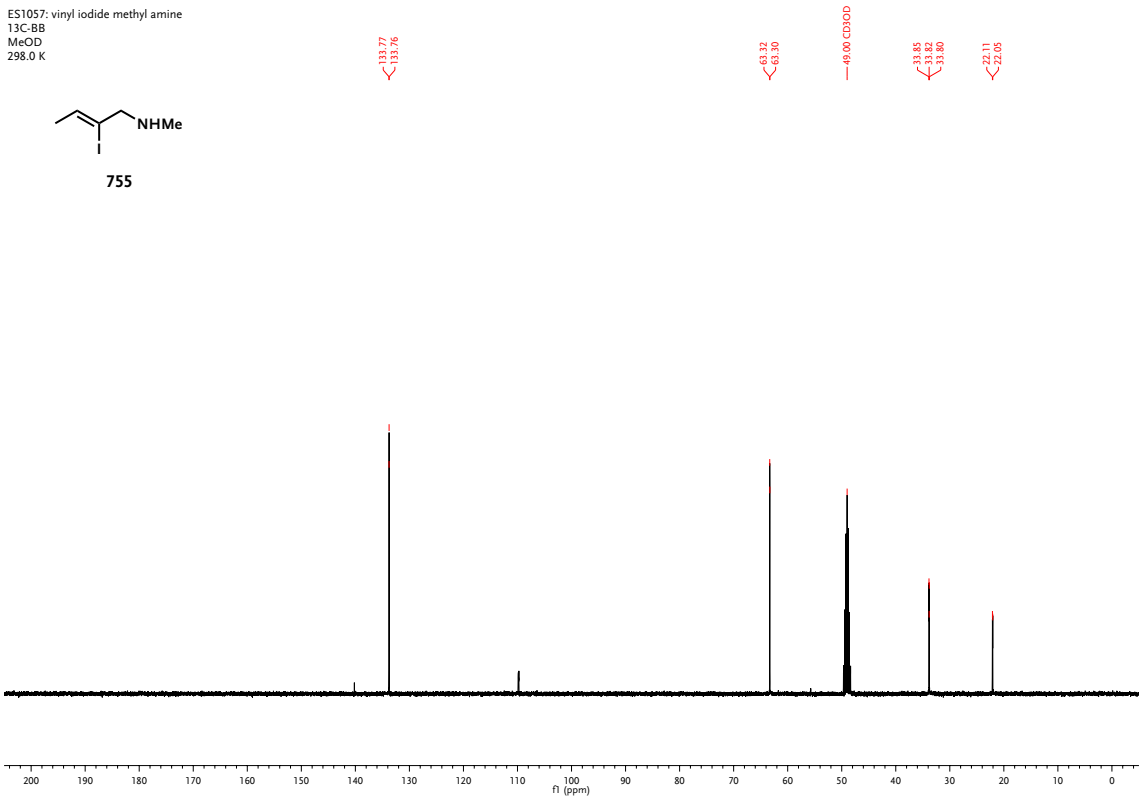
Spectrum B-163. ^{13}C-NMR spectrum for compound **769** *(experimental on page 247)*.



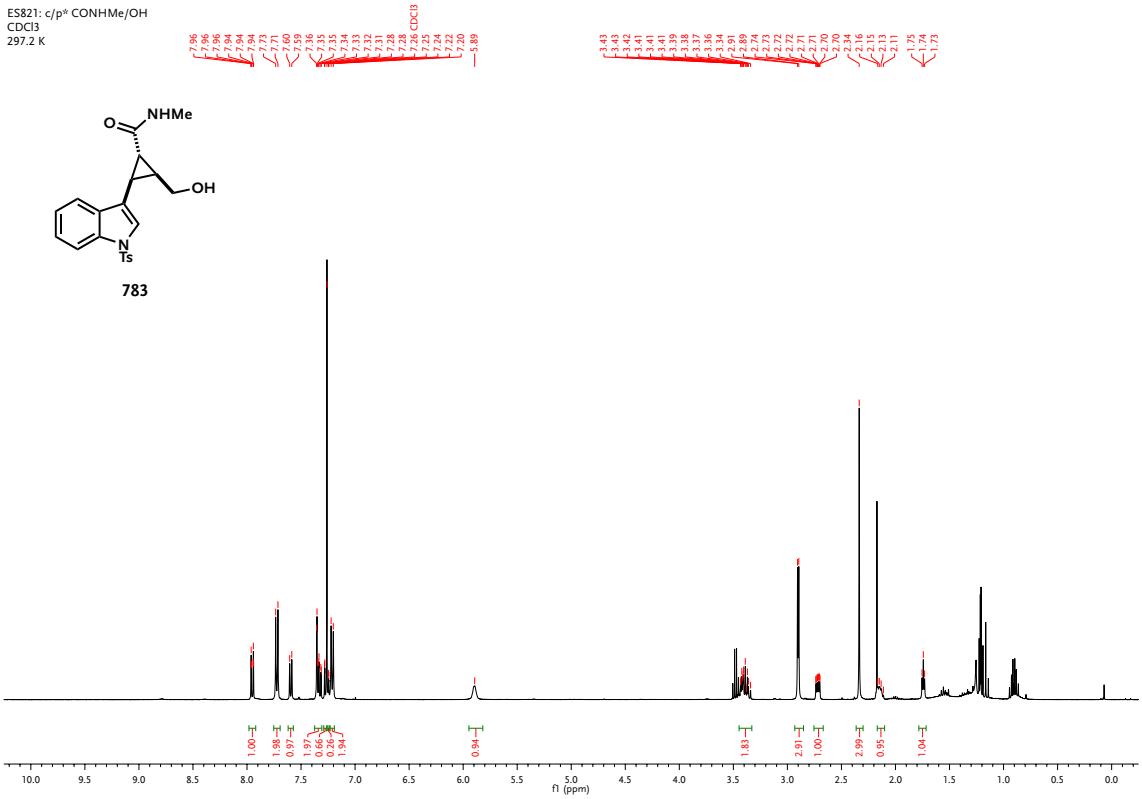
Spectrum B-164. ^{1}H-NMR spectrum for compound **770** *(experimental on page 247)*.



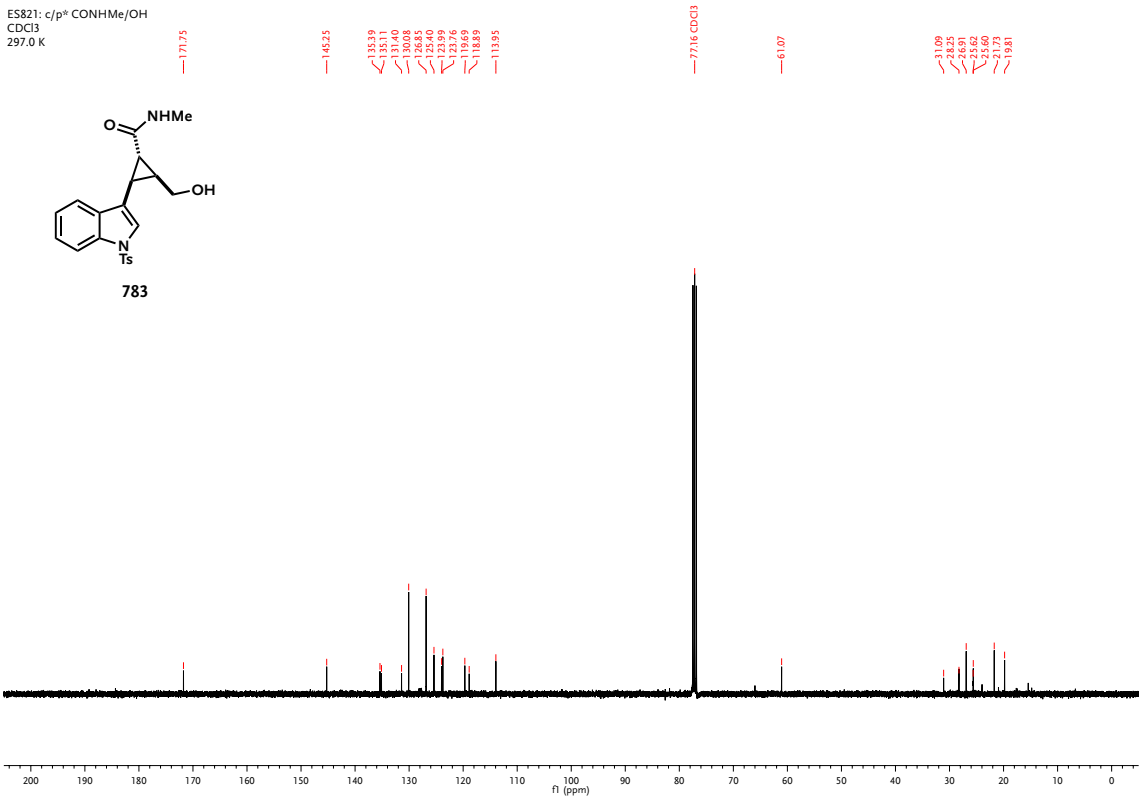
Spectrum B-165. ^{1}H-NMR spectrum for compound **755** *(experimental on page 248)*.



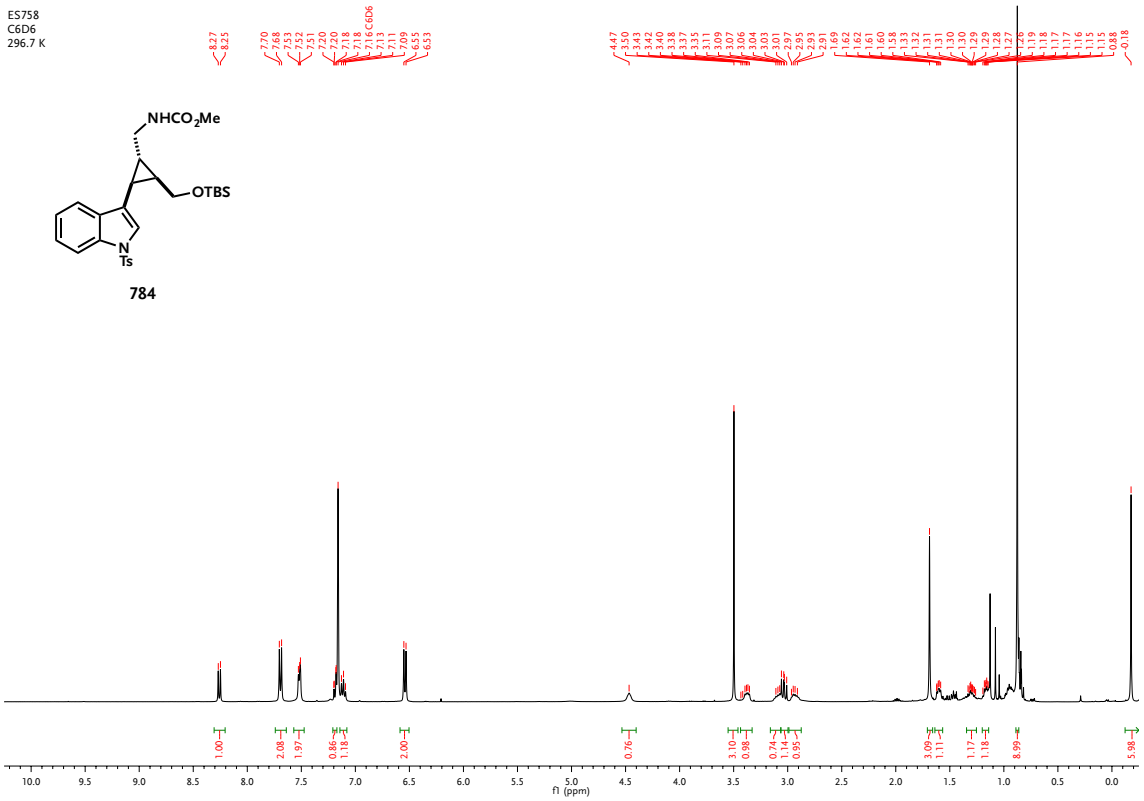
Spectrum B-166. ^{13}C-NMR spectrum for compound **755** *(experimental on page 248)*.



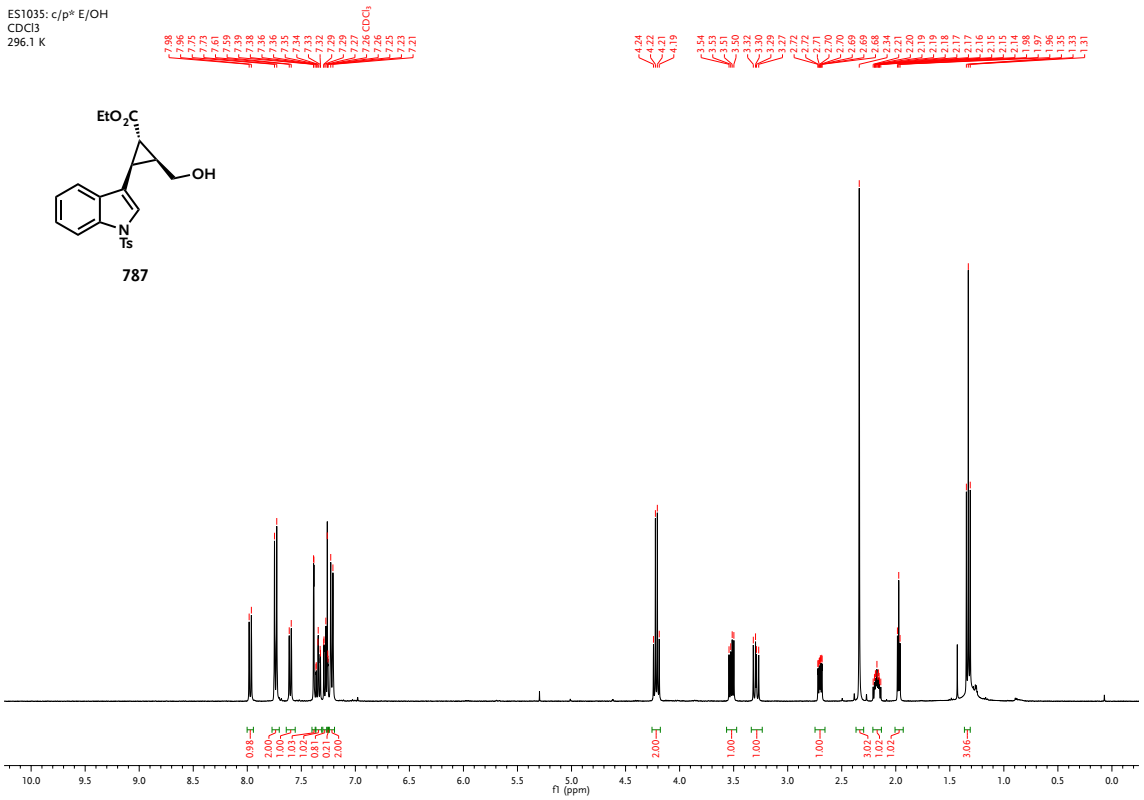
Spectrum B-167. [1]H-NMR spectrum for compound **783** *(experimental on page 249)*.



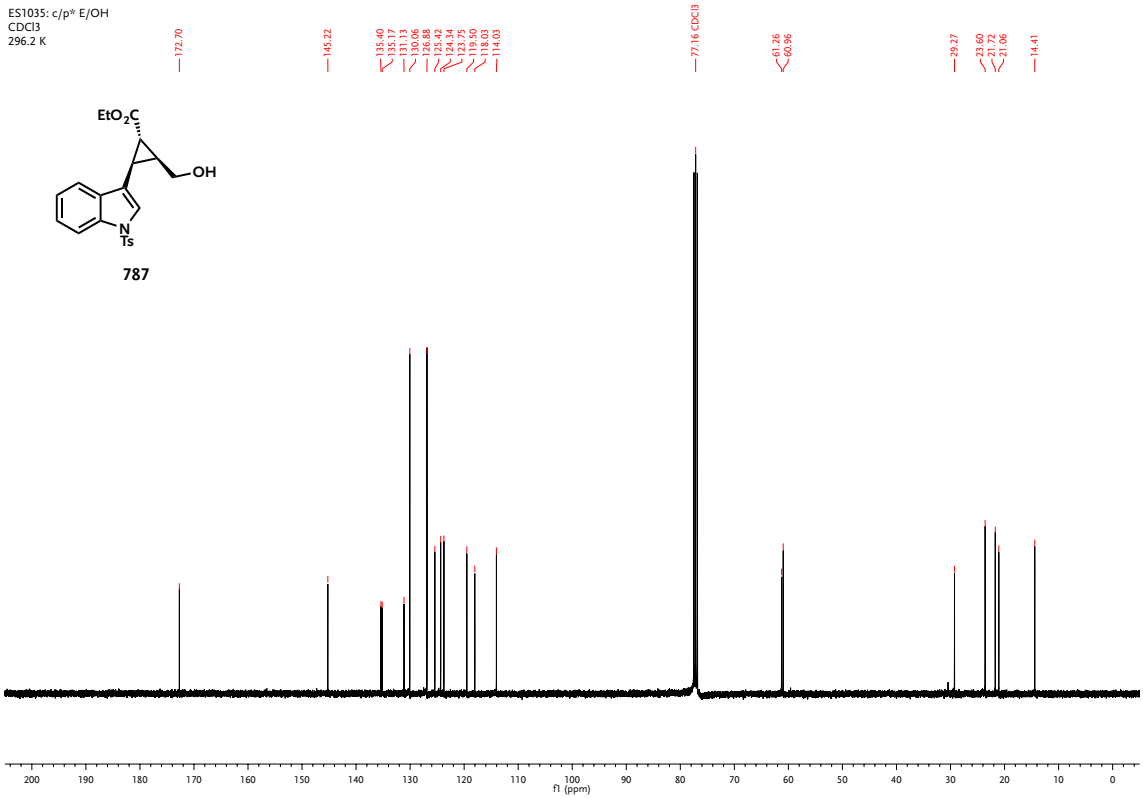
Spectrum B-168. [13]C-NMR spectrum for compound **783** *(experimental on page 249)*.



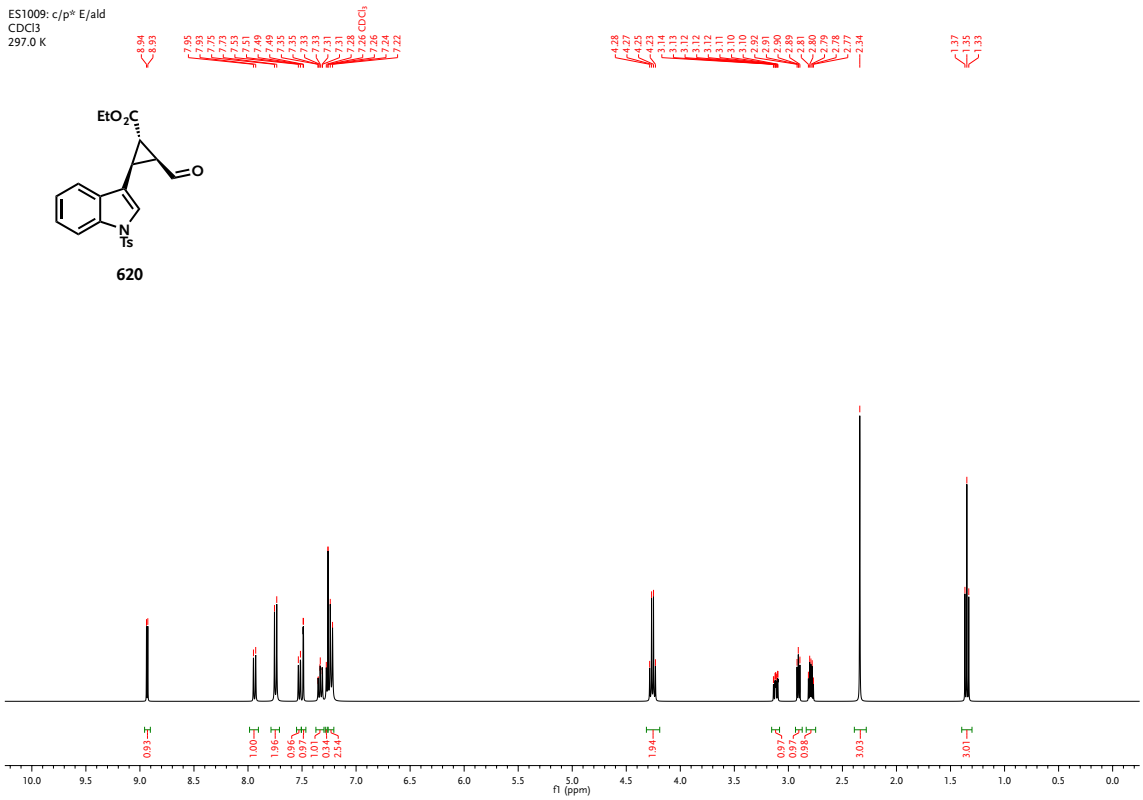
Spectrum B-169. ^{1}H-NMR spectrum for compound **784** *(experimental on page 249)*.



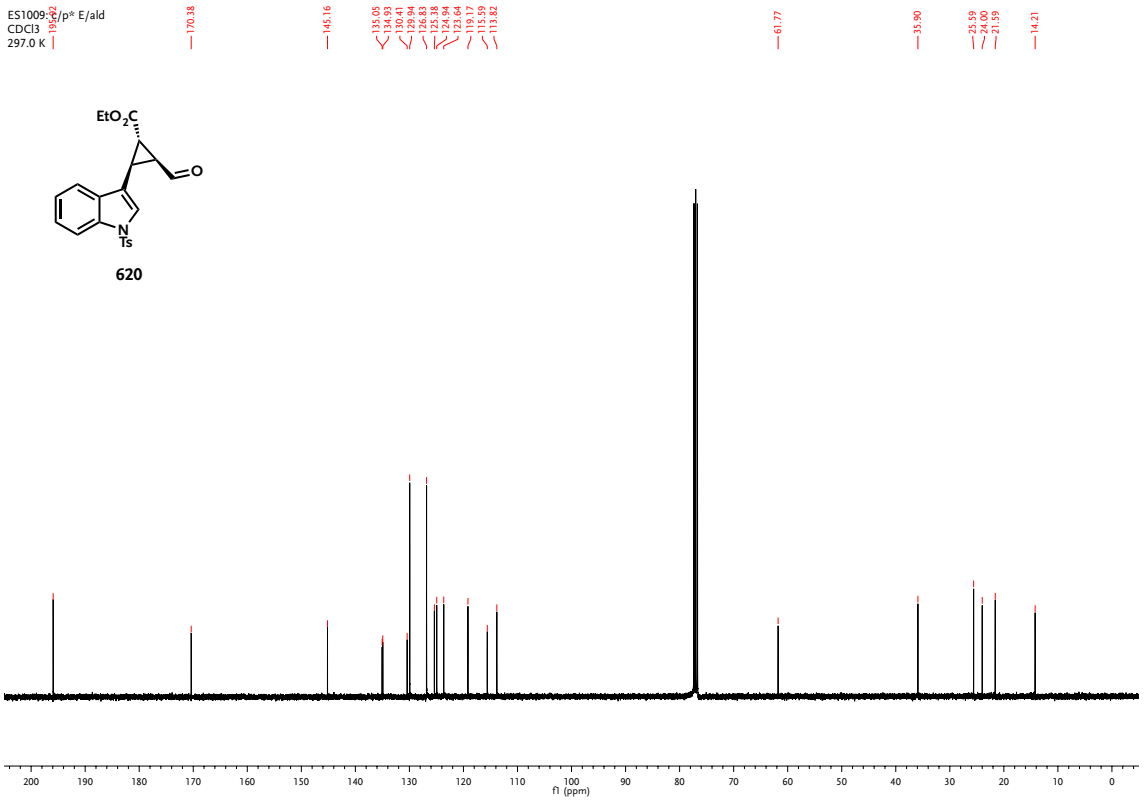
Spectrum B-170. ^{1}H-NMR spectrum for compound **787** *(experimental on page 250)*.



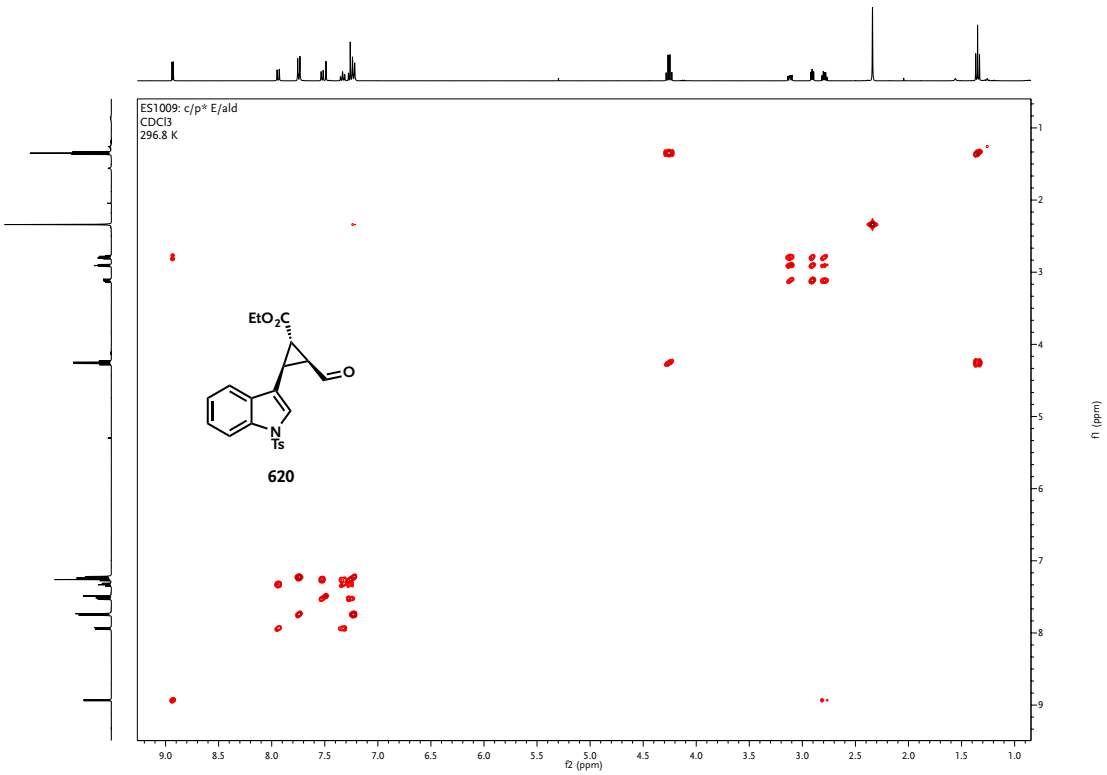
Spectrum B-171. ^{13}C-NMR spectrum for compound **787** *(experimental on page 250)*.



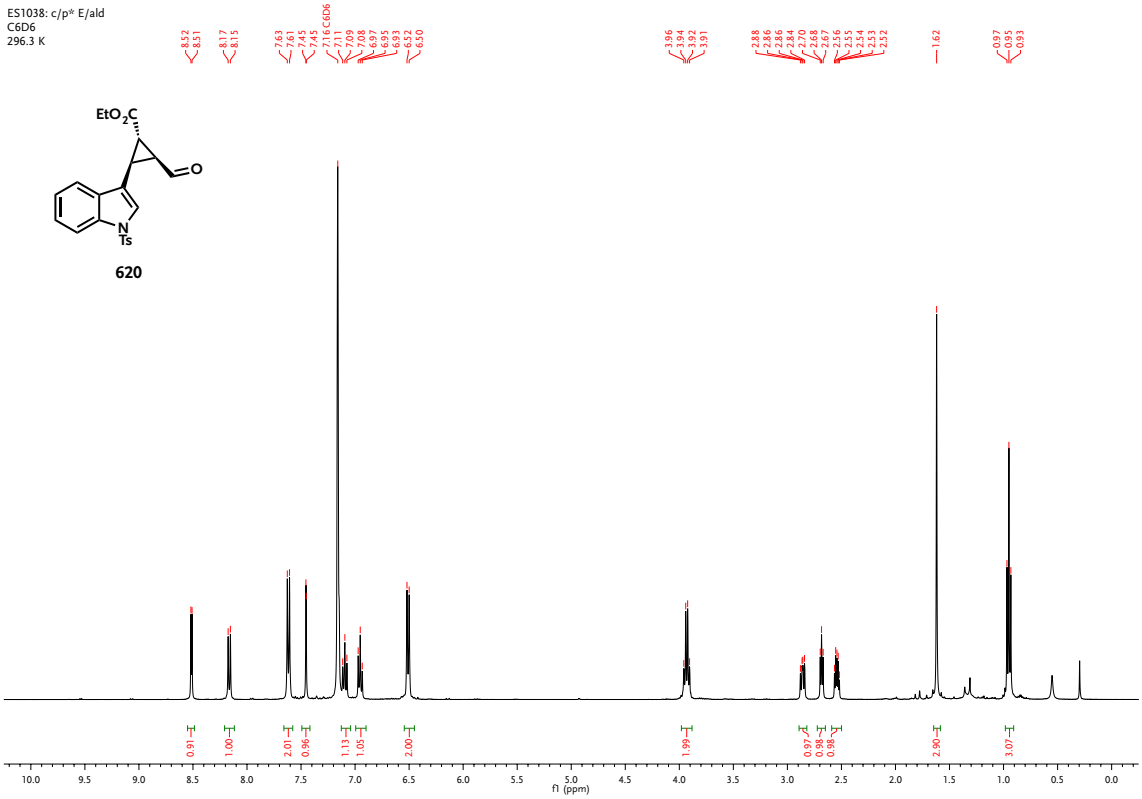
Spectrum B-172. ^{1}H-NMR spectrum for compound **620** *(experimental on page 250)*.



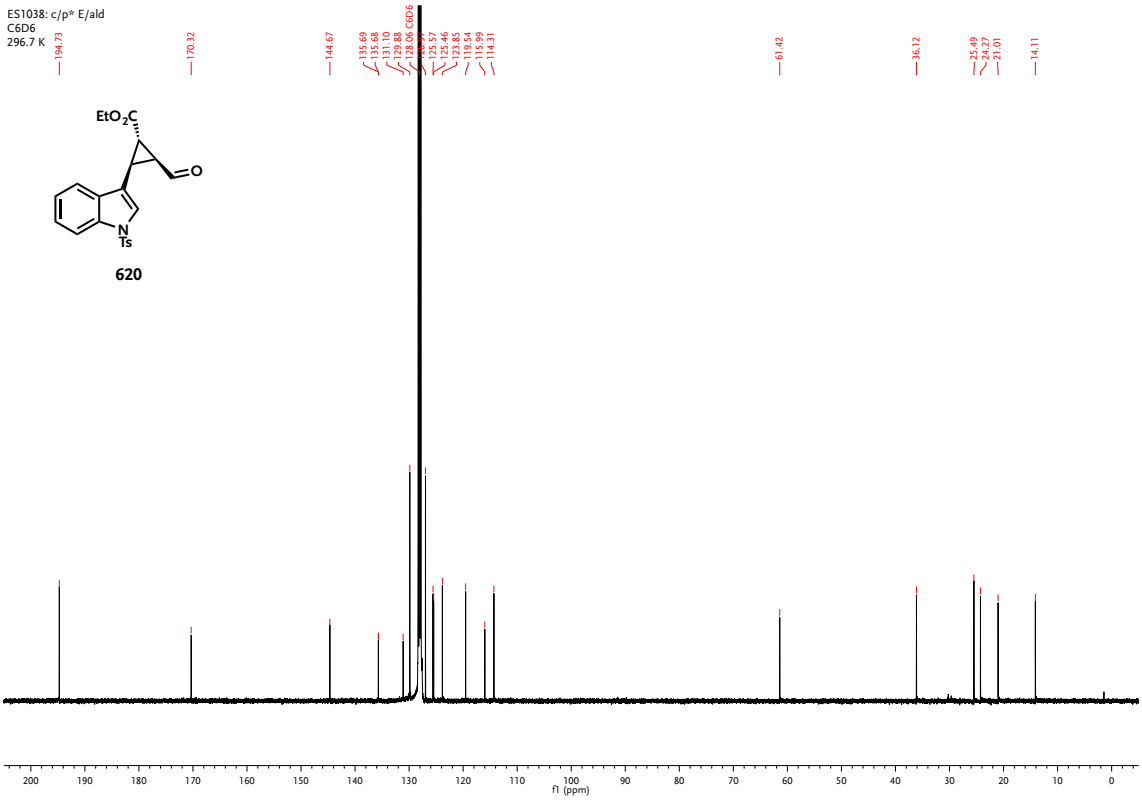
Spectrum B-173. ^{13}C-NMR spectrum for compound **620** *(experimental on page 250)*.



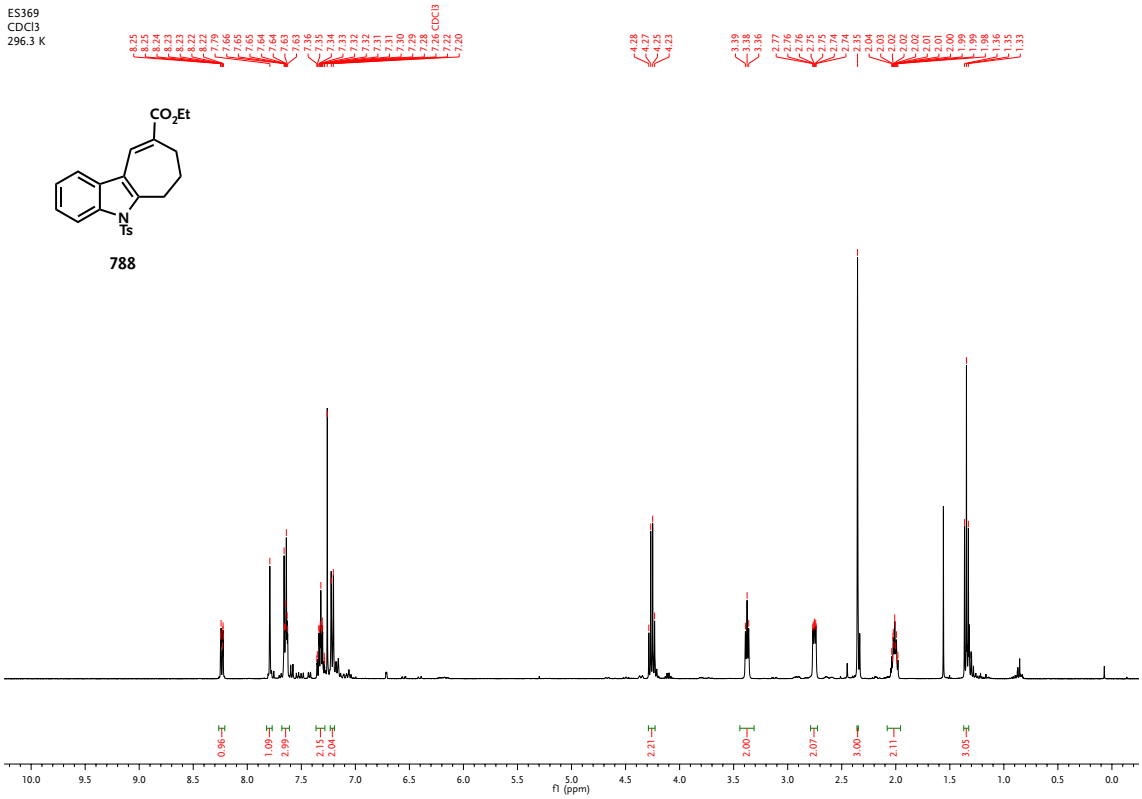
Spectrum B-174. COSY60 2D-NMR spectrum for compound **620** *(experimental on page 250)*.



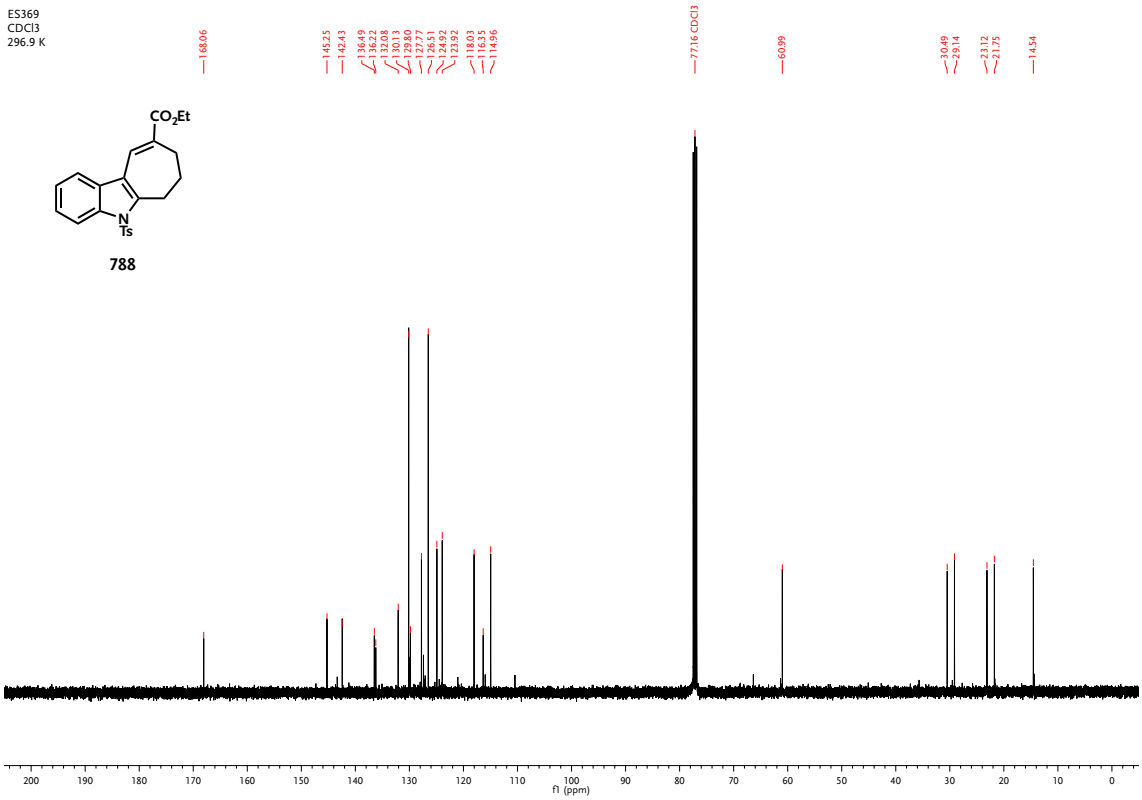
Spectrum B-175. ^{1}H-NMR spectrum for compound **620** *(experimental on page 250)*.



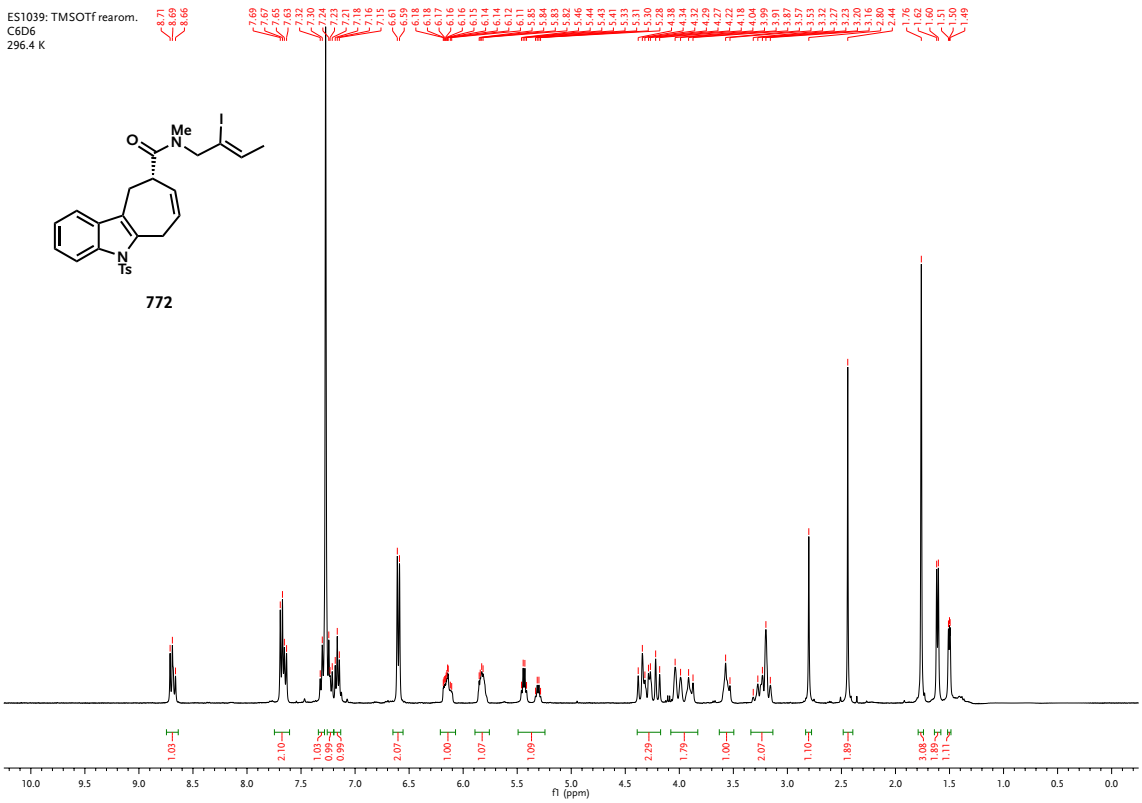
Spectrum B-176. ^{13}C-NMR spectrum for compound **620** *(experimental on page 250)*.



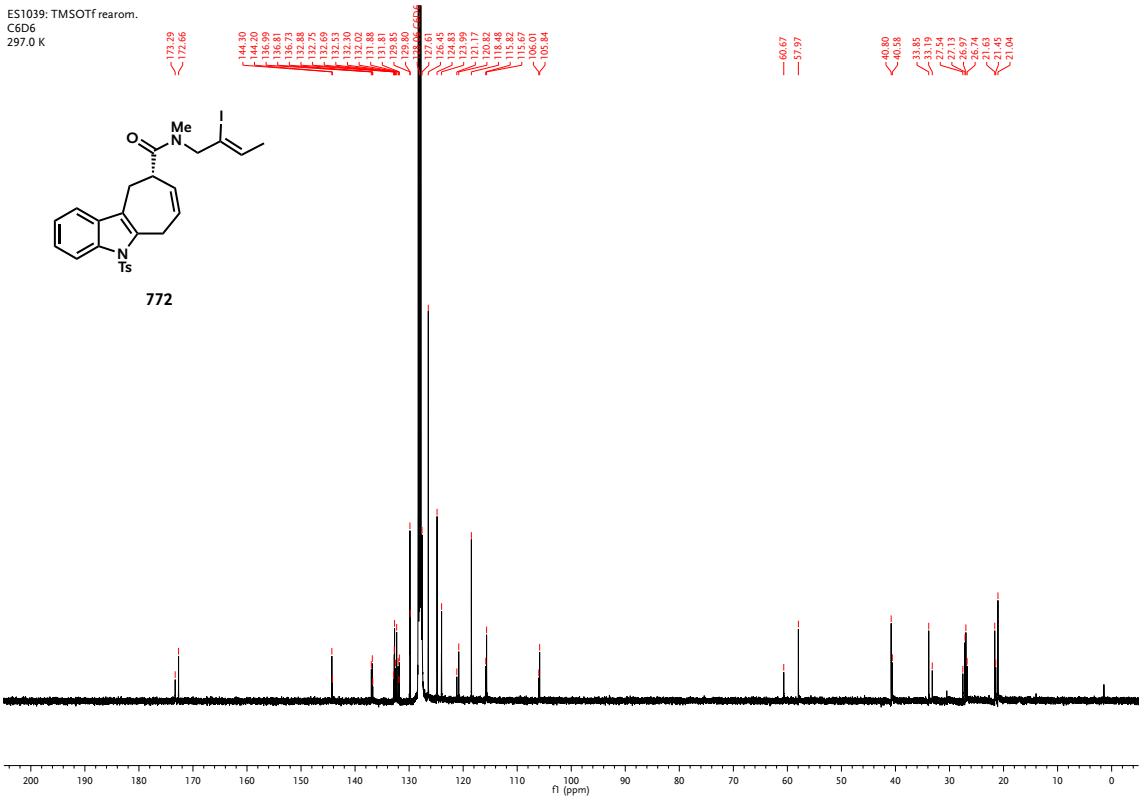
Spectrum B-177. [1]H-NMR spectrum for compound **788** *(experimental on page 251)*.



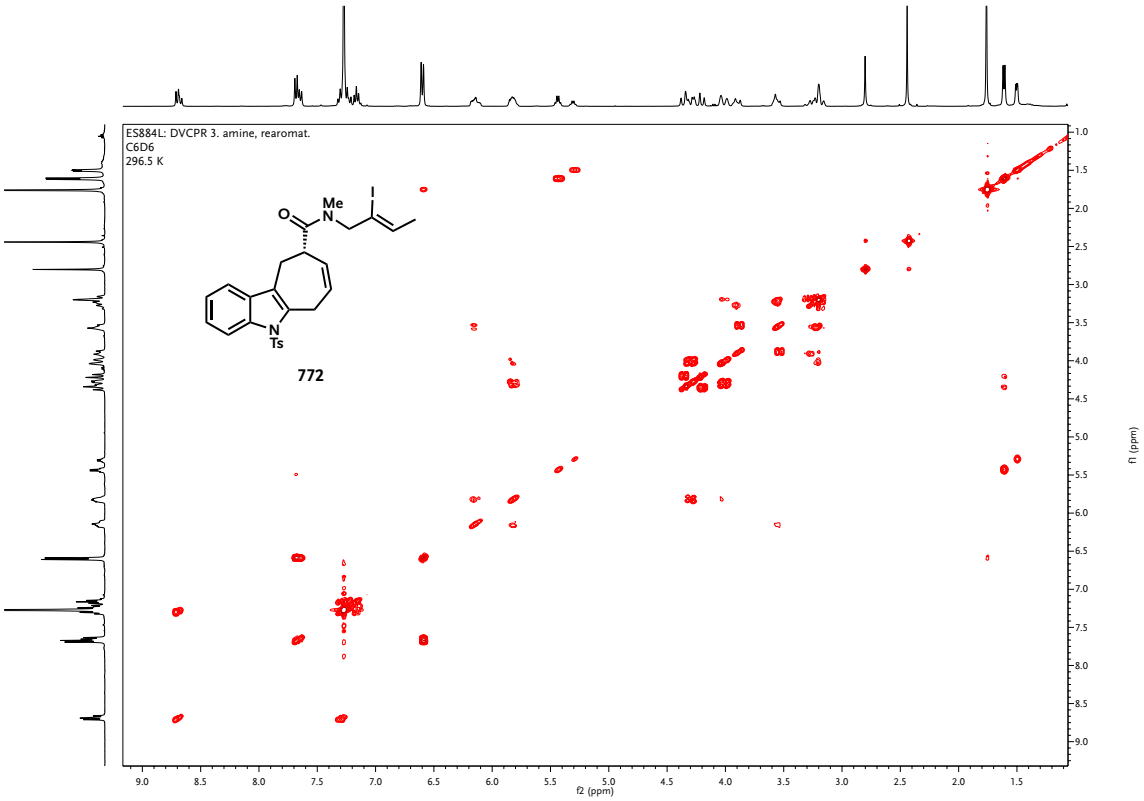
Spectrum B-178. [13]C-NMR spectrum for compound **788** *(experimental on page 251)*.



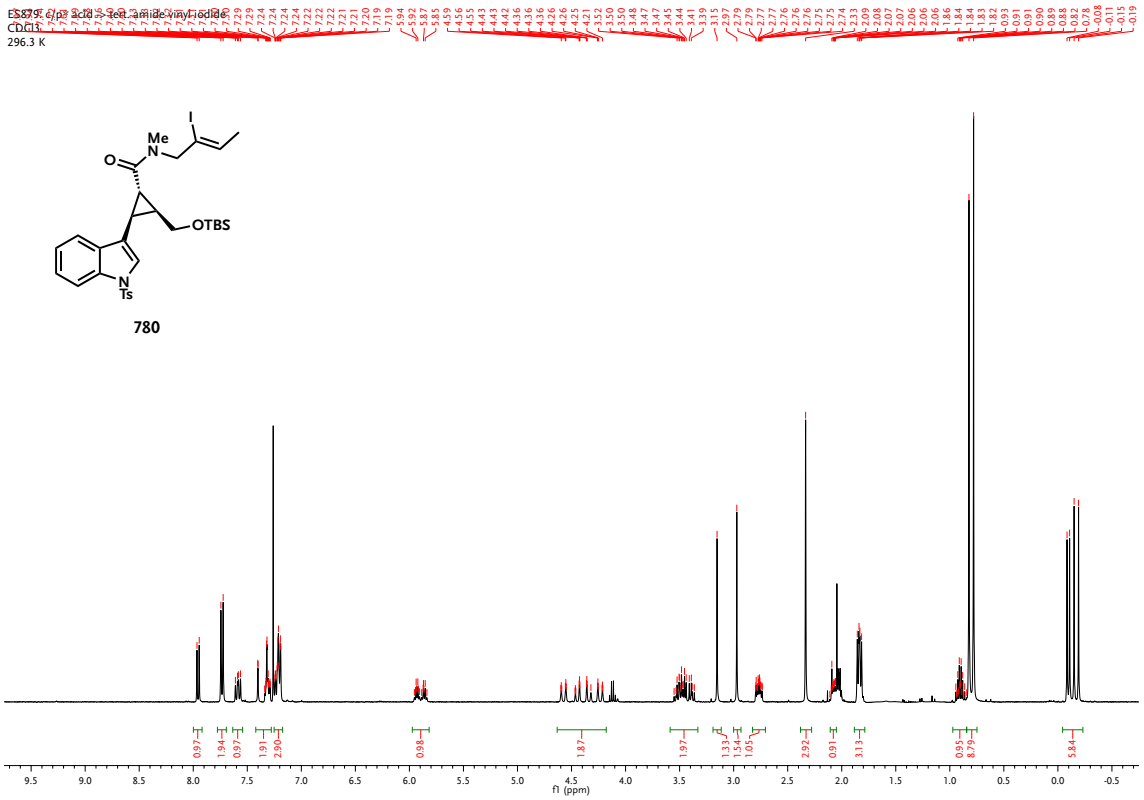
Spectrum B-179. ^{1}H-NMR spectrum for compound **772** *(experimental on page 253)*.



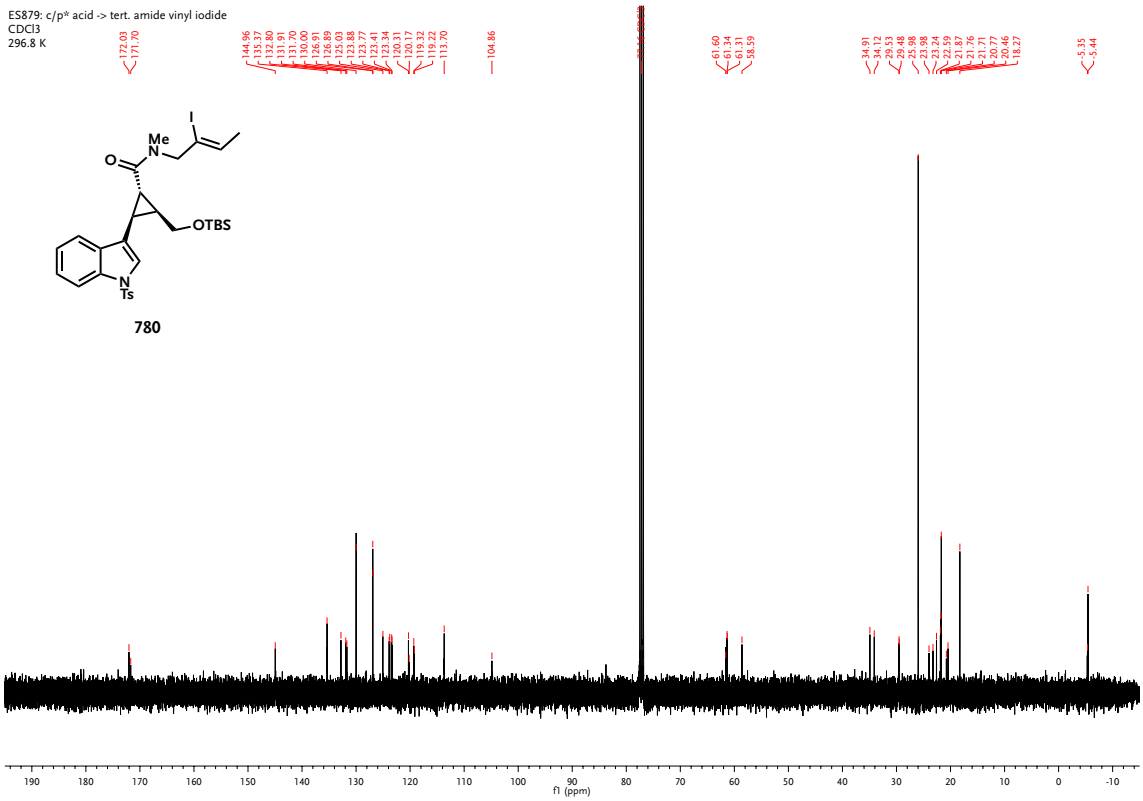
Spectrum B-180. ^{13}C-NMR spectrum for compound **772** *(experimental on page 253)*.



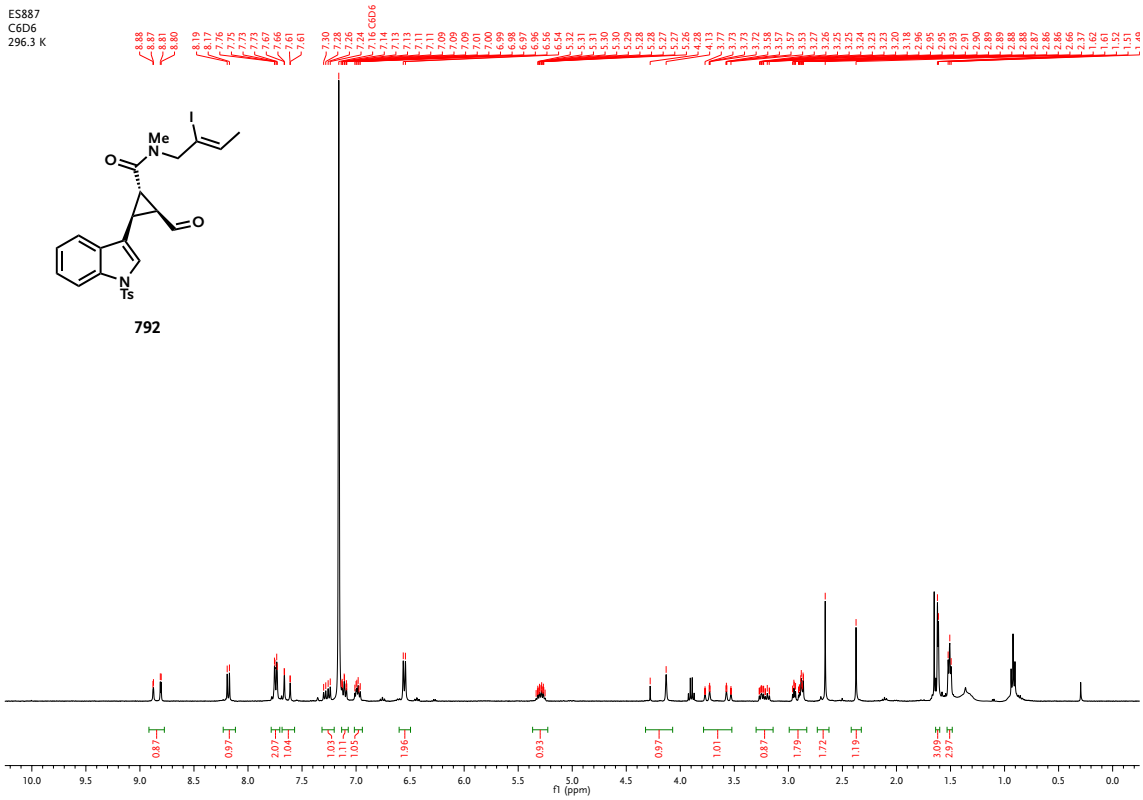
Spectrum B-181. COSY60 2D-NMR spectrum for compound **772** *(experimental on page 253)*.



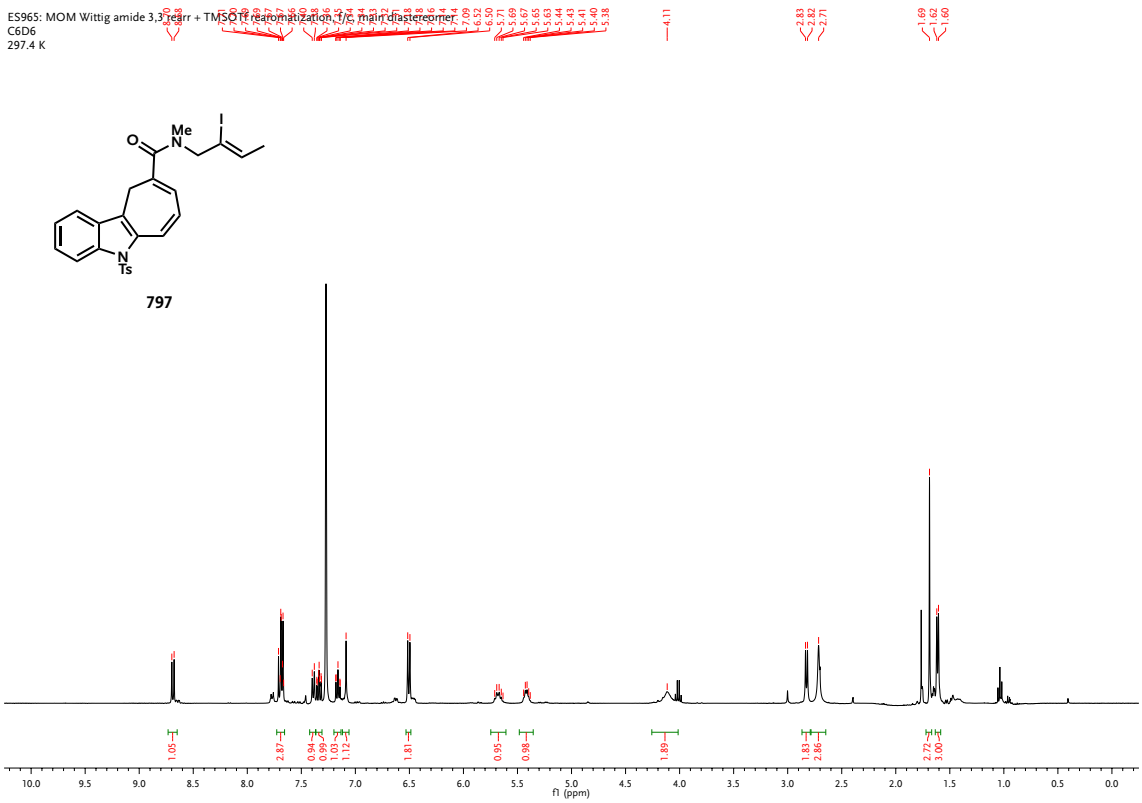
Spectrum B-182. ^{1}H-NMR spectrum for compound **780** *(experimental on page 255)*.



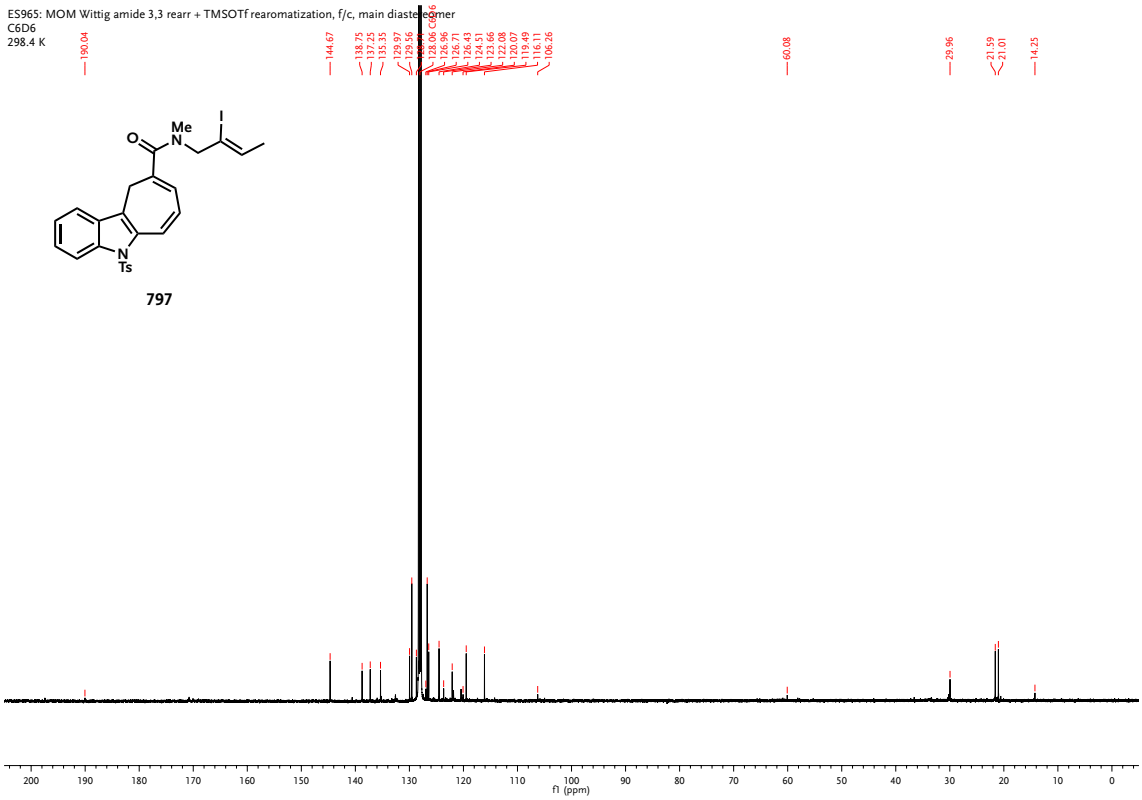
Spectrum B-183. ^{13}C-NMR spectrum for compound **780** *(experimental on page 255)*.



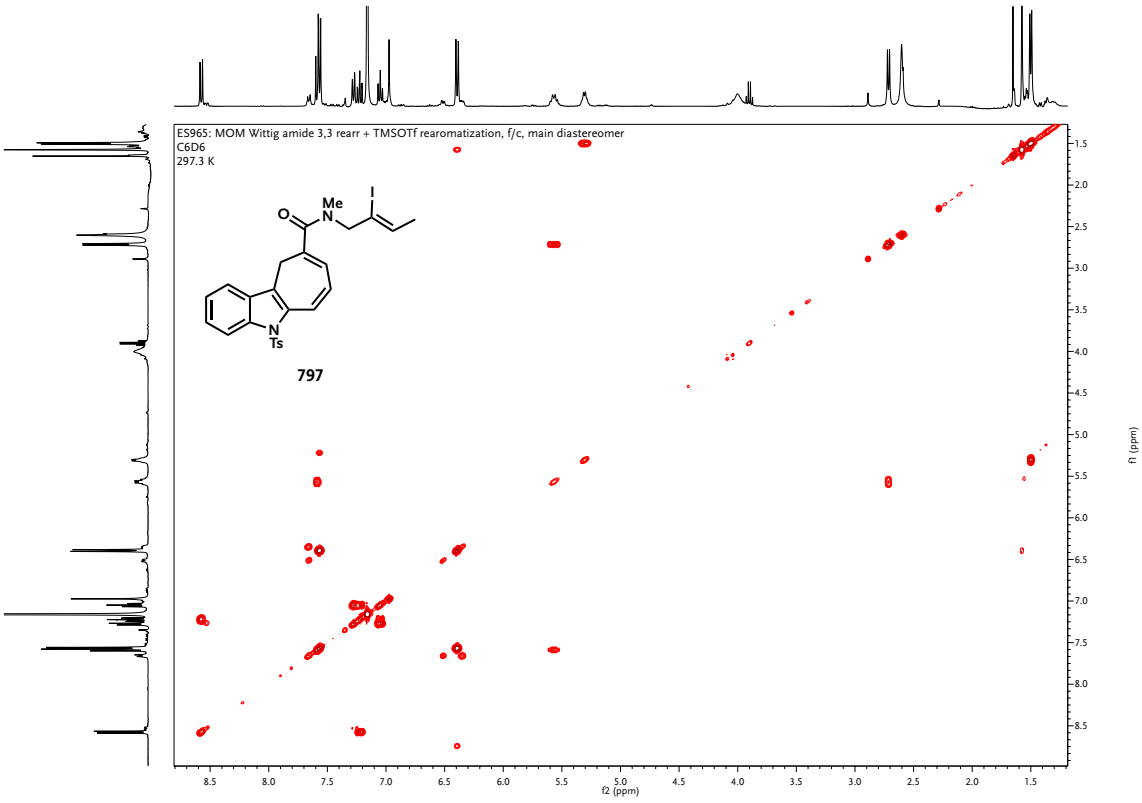
Spectrum B-184. ^{1}H-NMR spectrum for compound **792** *(experimental on page 256)*.



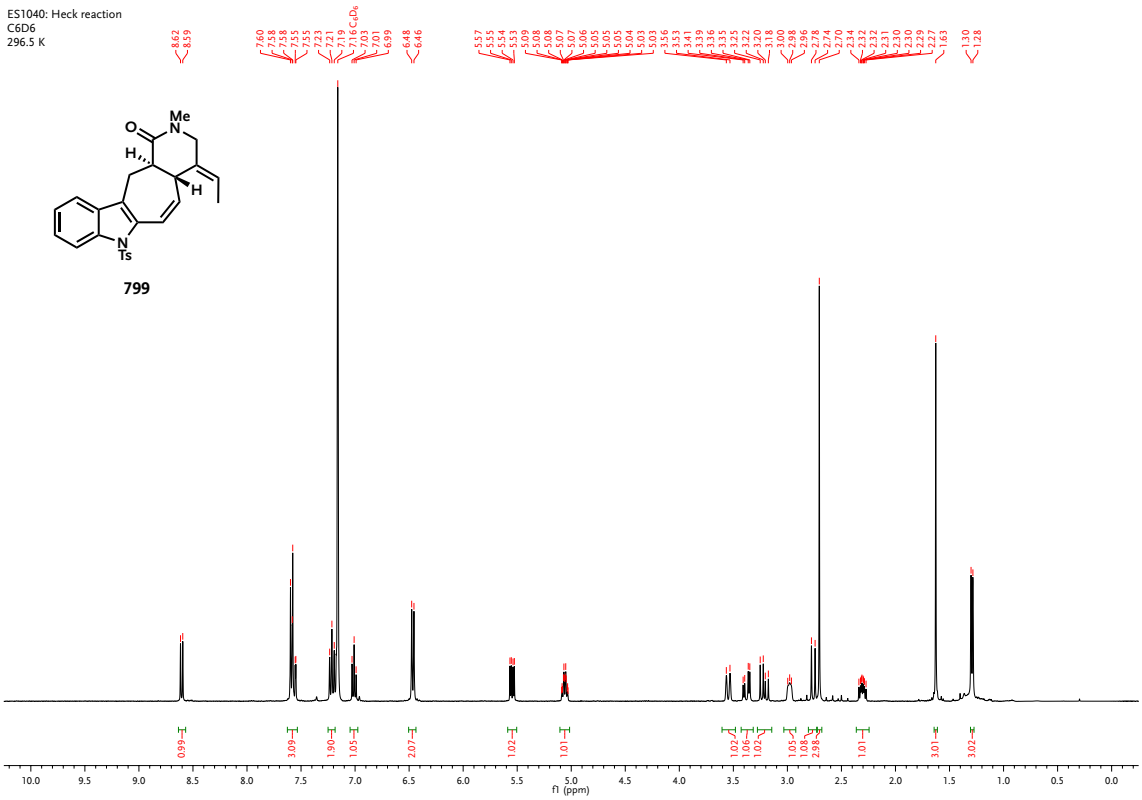
Spectrum B-185. ^{1}H-NMR spectrum for compound **797** *(experimental on page 258)*.



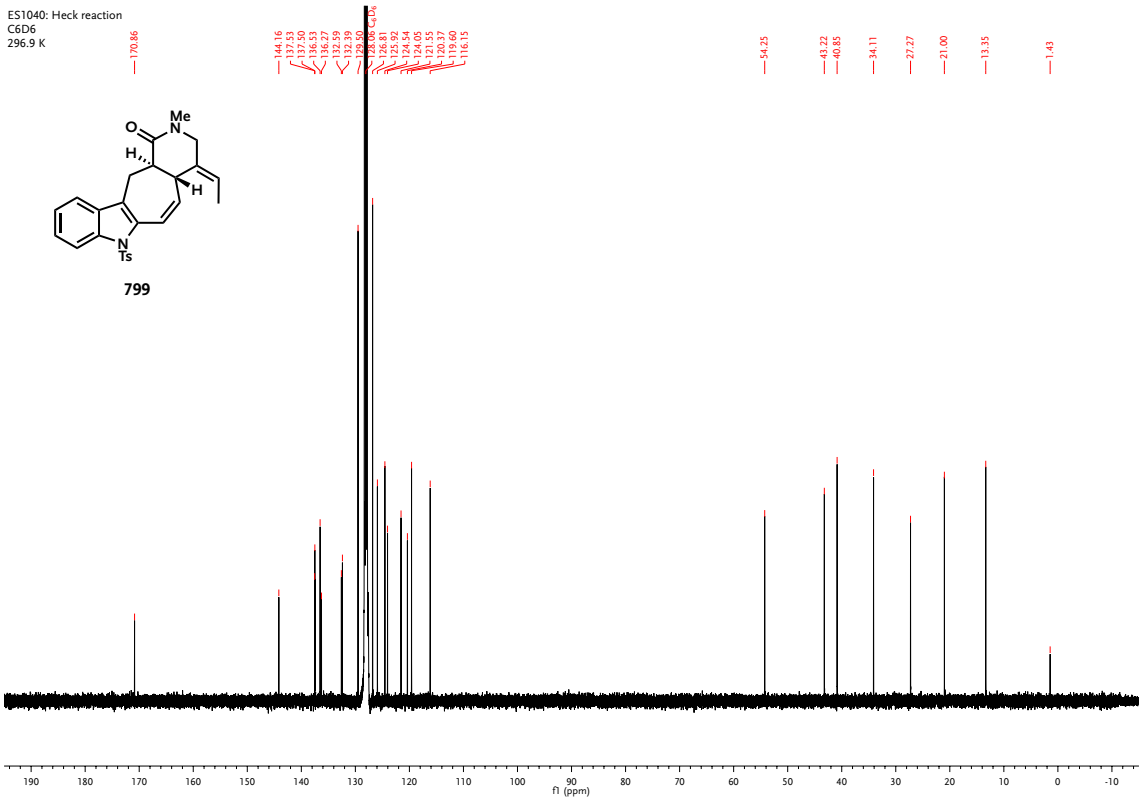
Spectrum B-186. ^{13}C-NMR spectrum for compound **797** *(experimental on page 258)*.



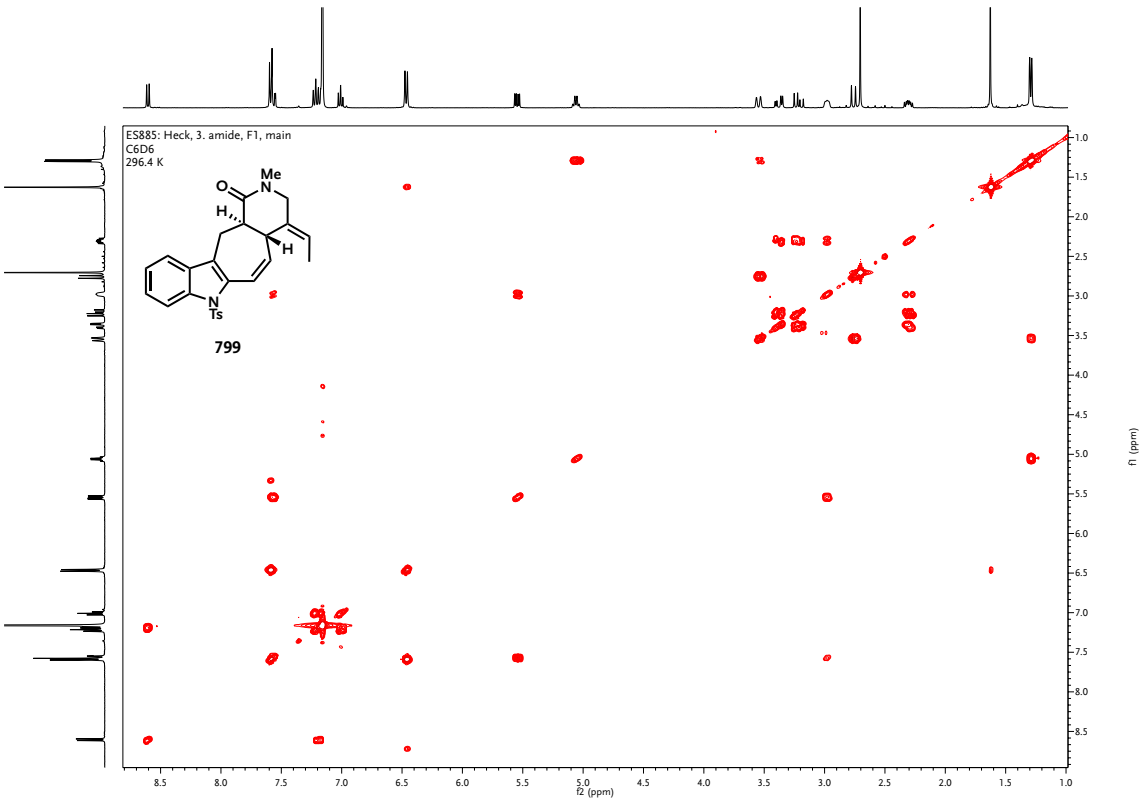
Spectrum B-187. COSY60 2D-NMR spectrum for compound **797** *(experimental on page 258)*.



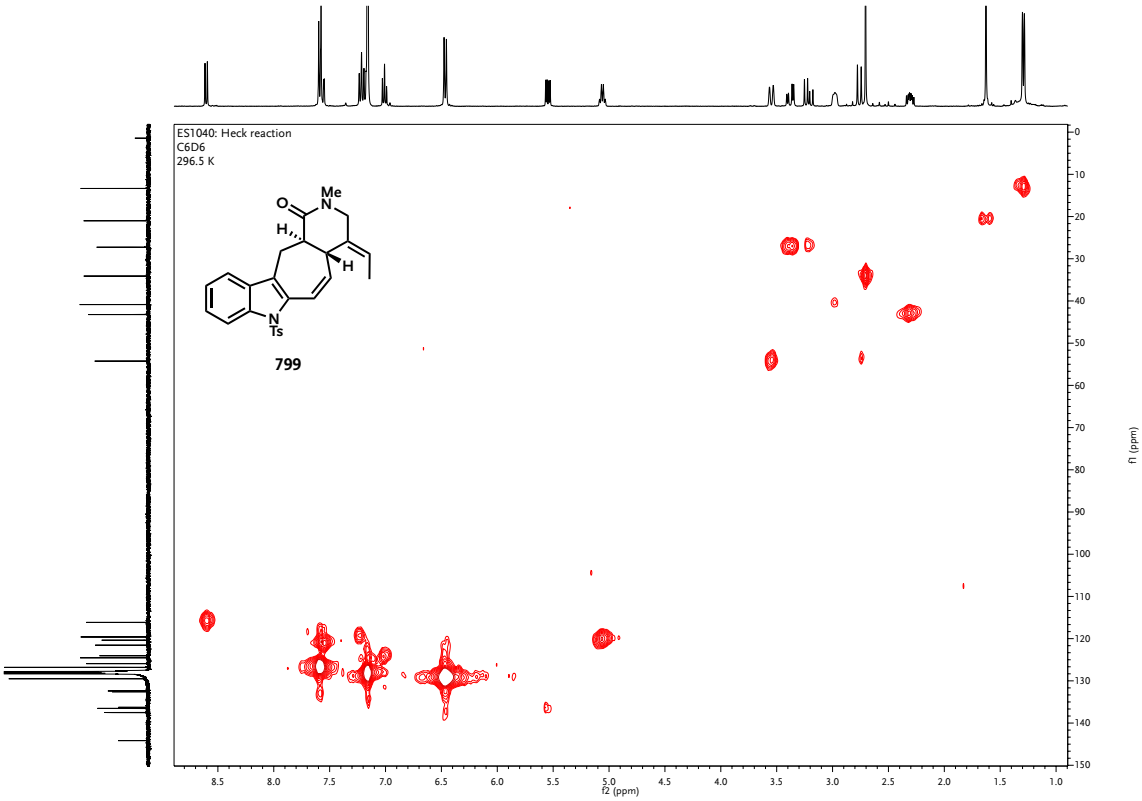
Spectrum B-188. ^{1}H-NMR spectrum for compound **799** *(experimental on page 258)*.



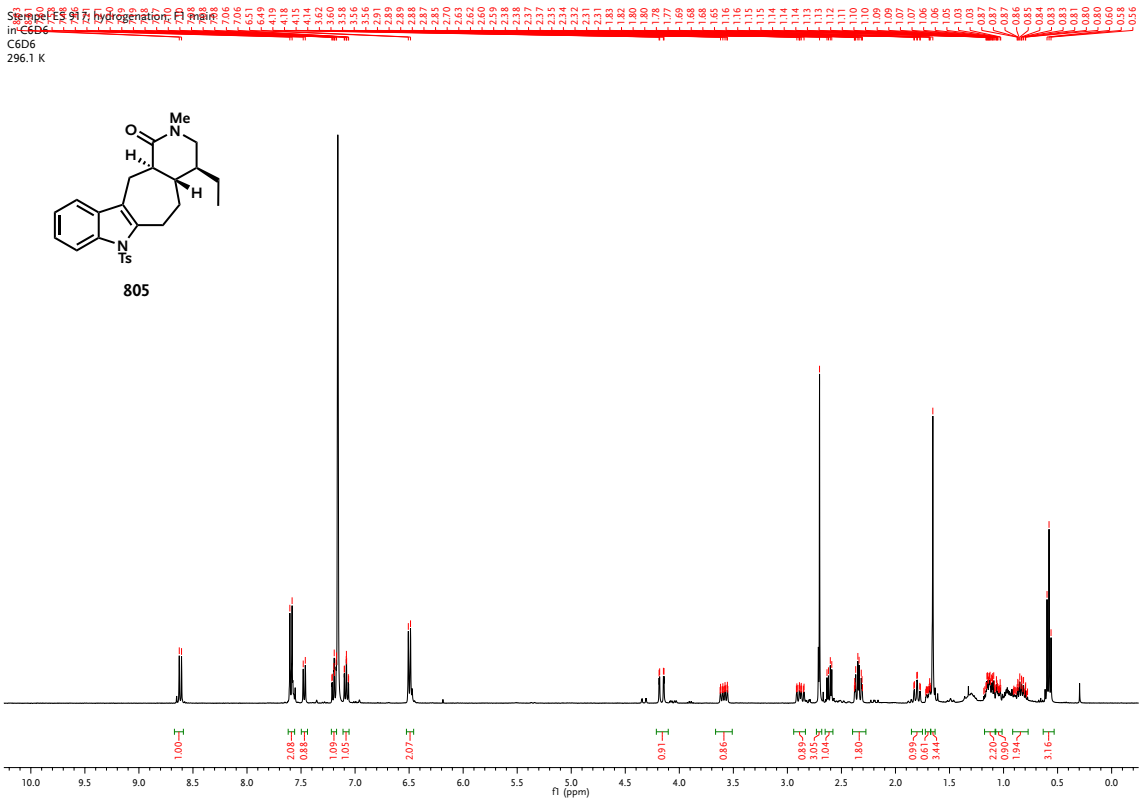
Spectrum B-189. ^{13}C-NMR spectrum for compound **799** *(experimental on page 258)*.



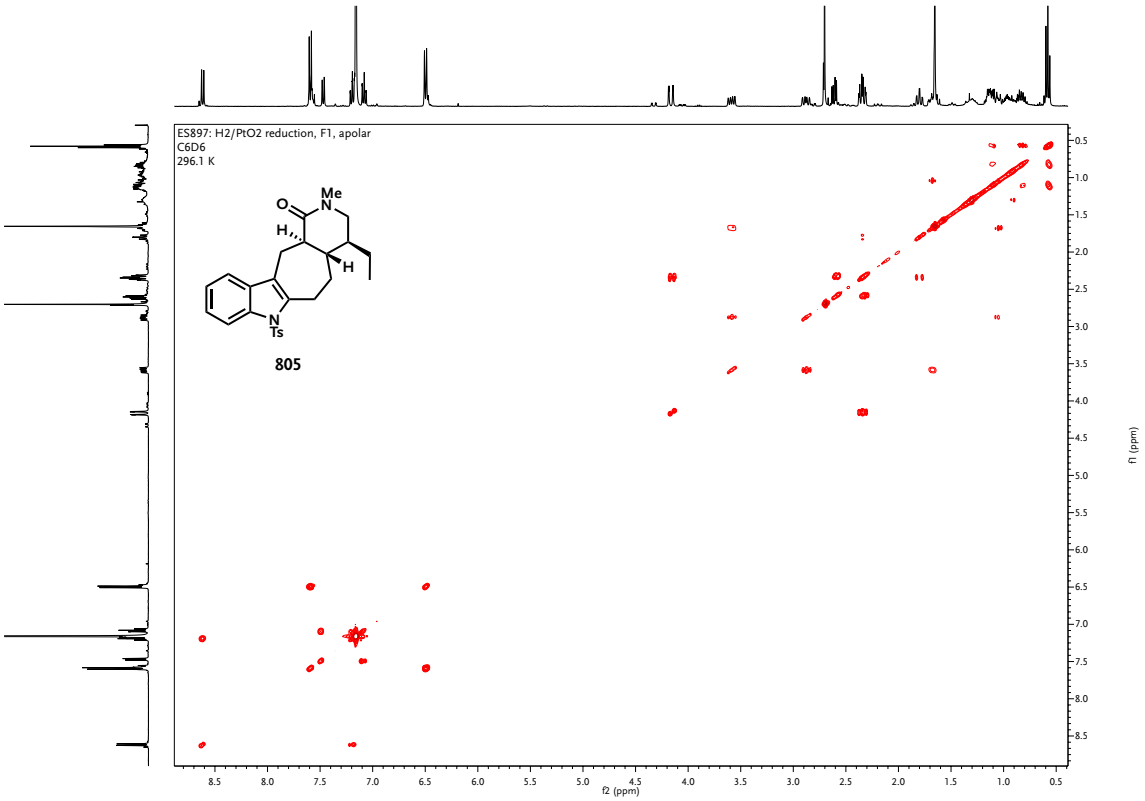
Spectrum B-190. COSY60 2D-NMR spectrum for compound **799** *(experimental on page 258)*.



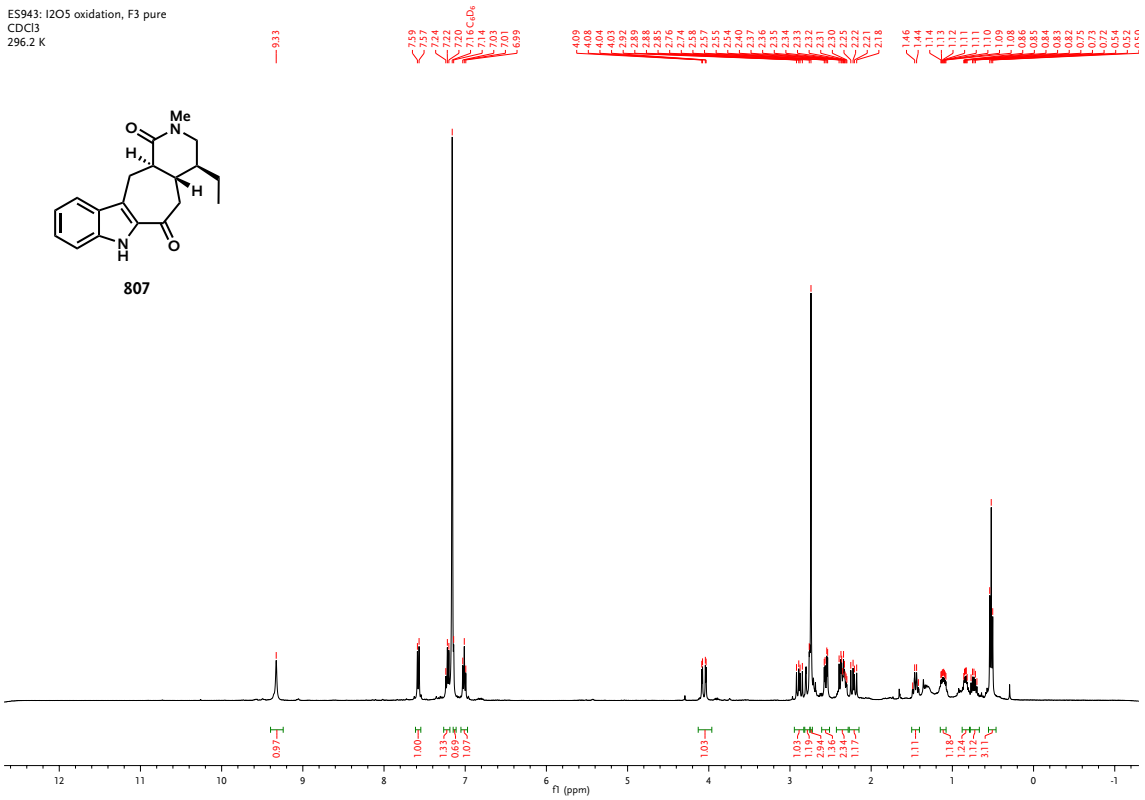
Spectrum B-191. HSQC 2D-NMR spectrum for compound **799** *(experimental on page 258)*.



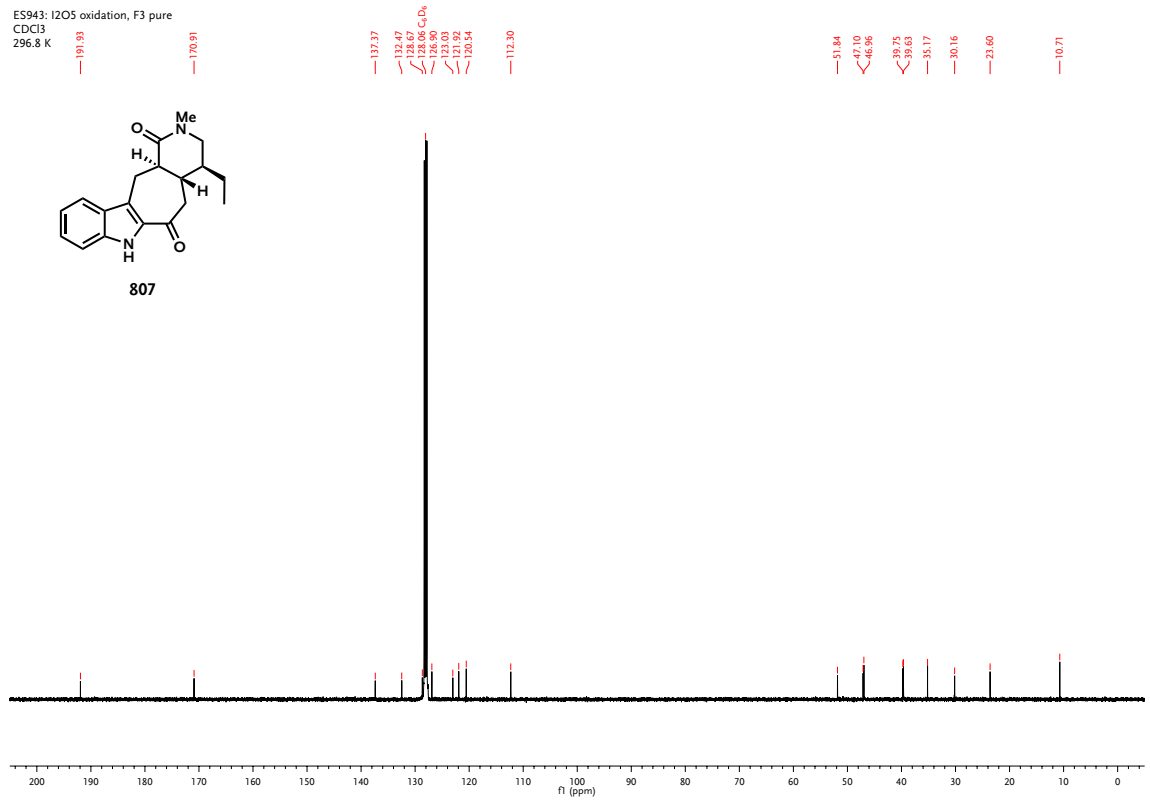
Spectrum B-192. ^{1}H-NMR spectrum for compound **805** *(experimental on page 259)*.



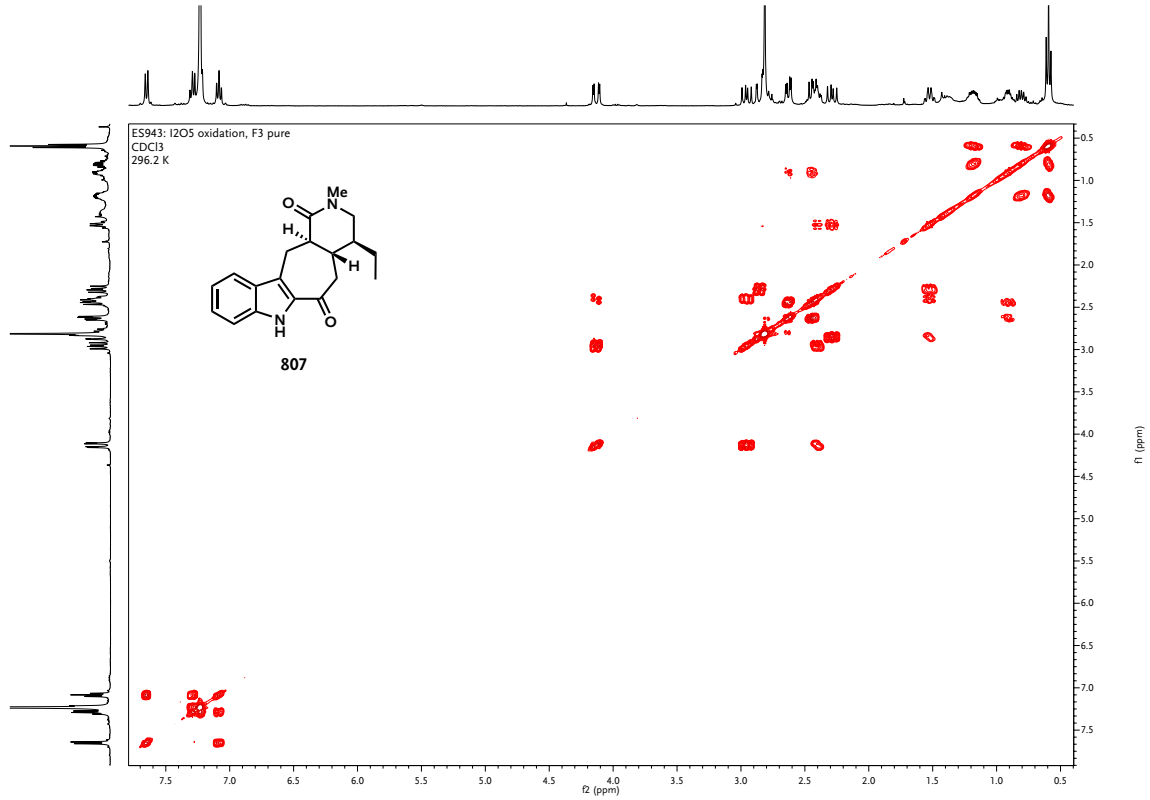
Spectrum B-193. COSY60 2D-NMR spectrum for compound **805** *(experimental on page 259)*.



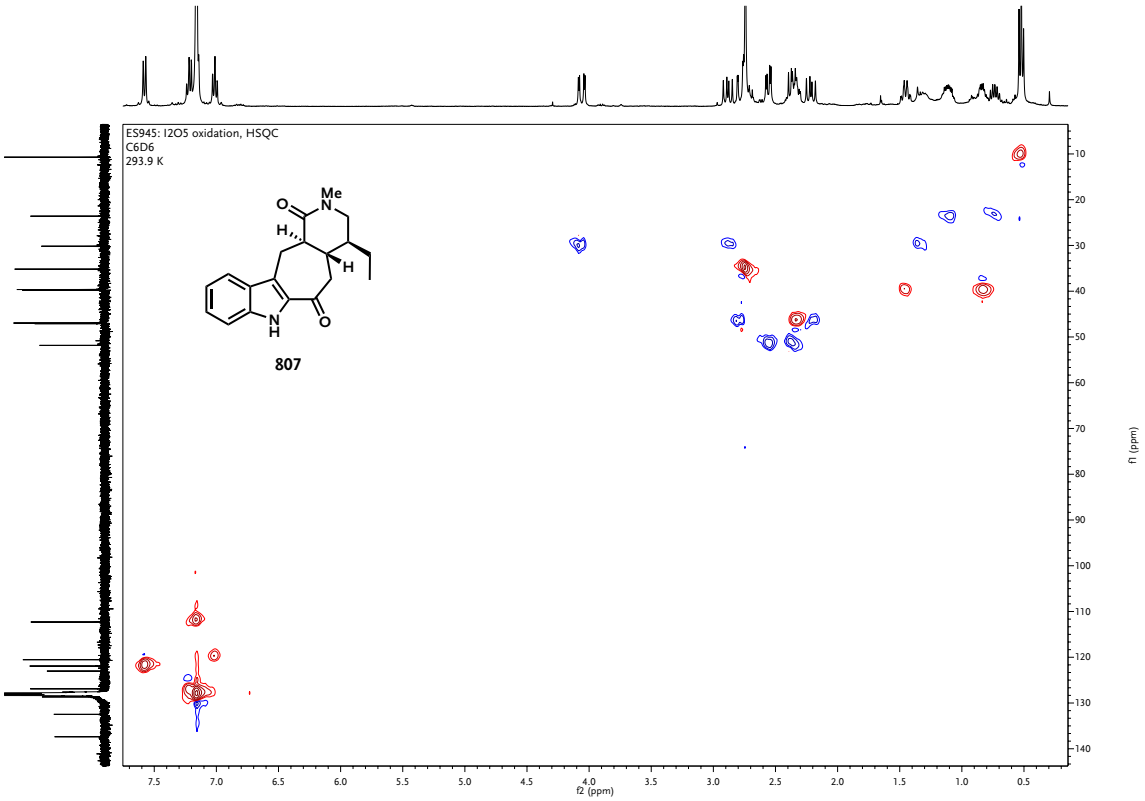
Spectrum B-194. ^{1}H-NMR spectrum for compound **807** *(experimental on page 260)*.



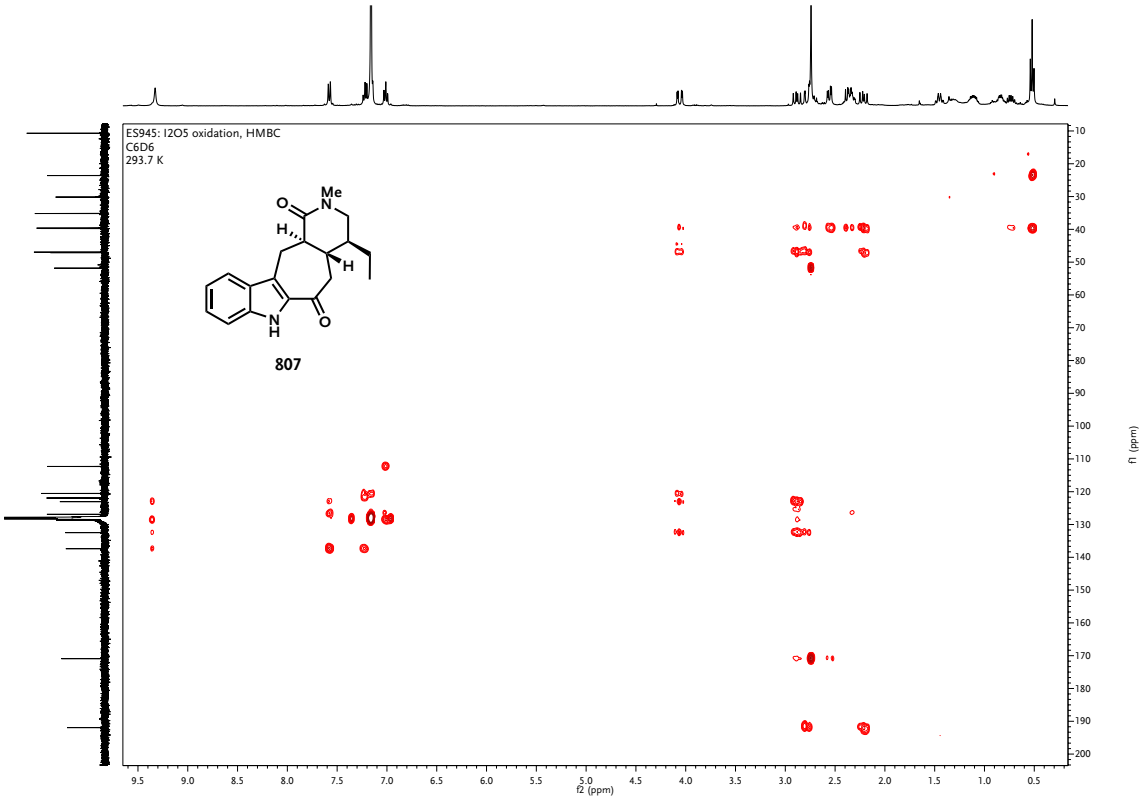
Spectrum B-195. ^{13}C-NMR spectrum for compound **807** *(experimental on page 260)*.



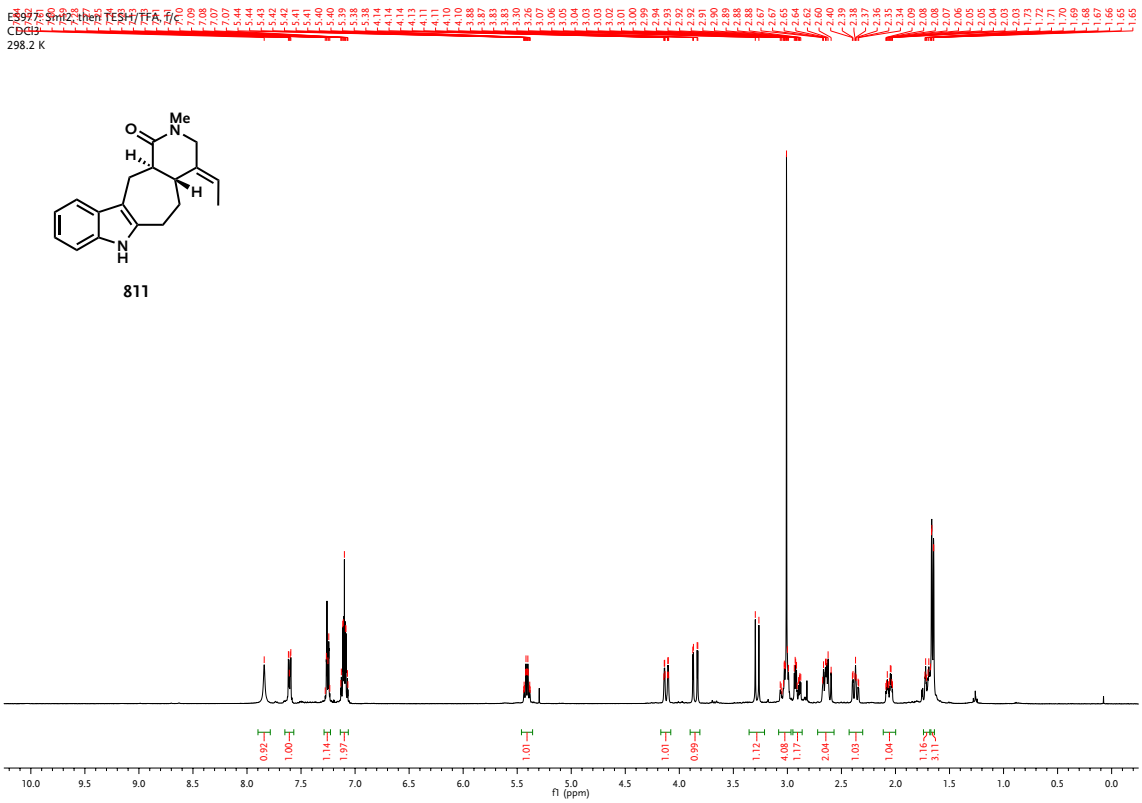
Spectrum B-196. COSY60 2D-NMR spectrum for compound **807** *(experimental on page 260)*.



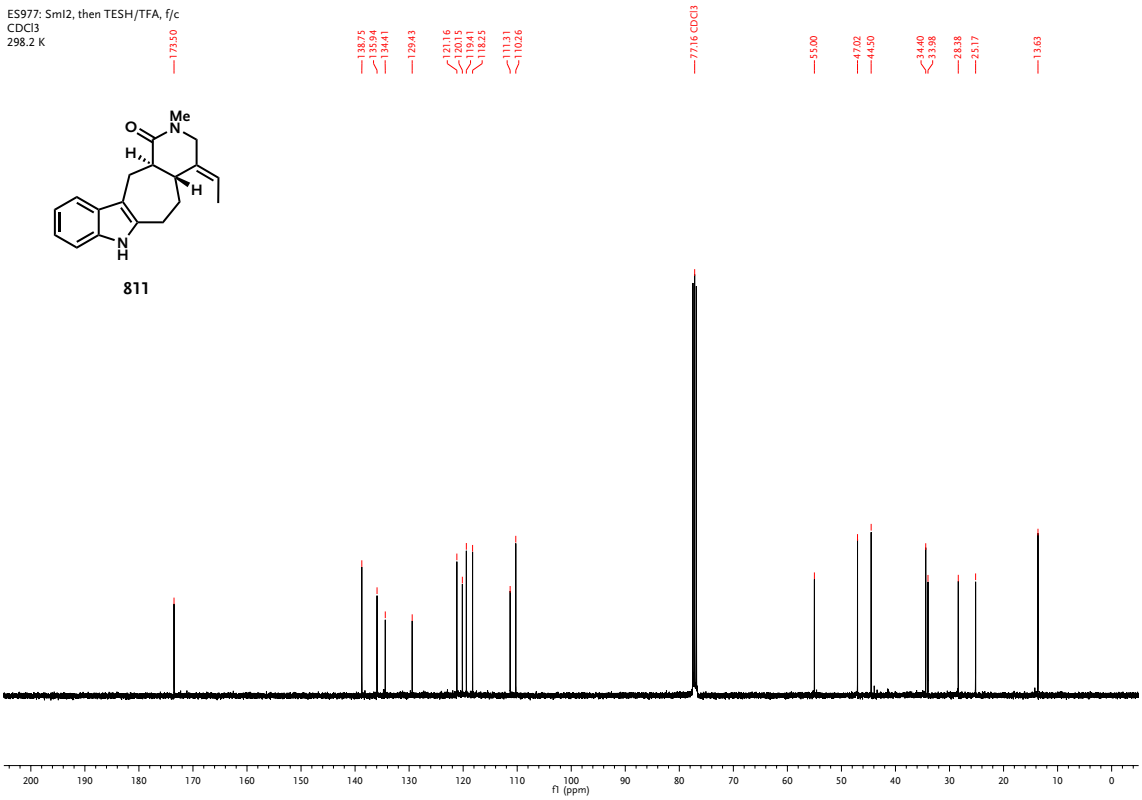
Spectrum B-197. HSQC 2D-NMR spectrum for compound **807** *(experimental on page 260)*.



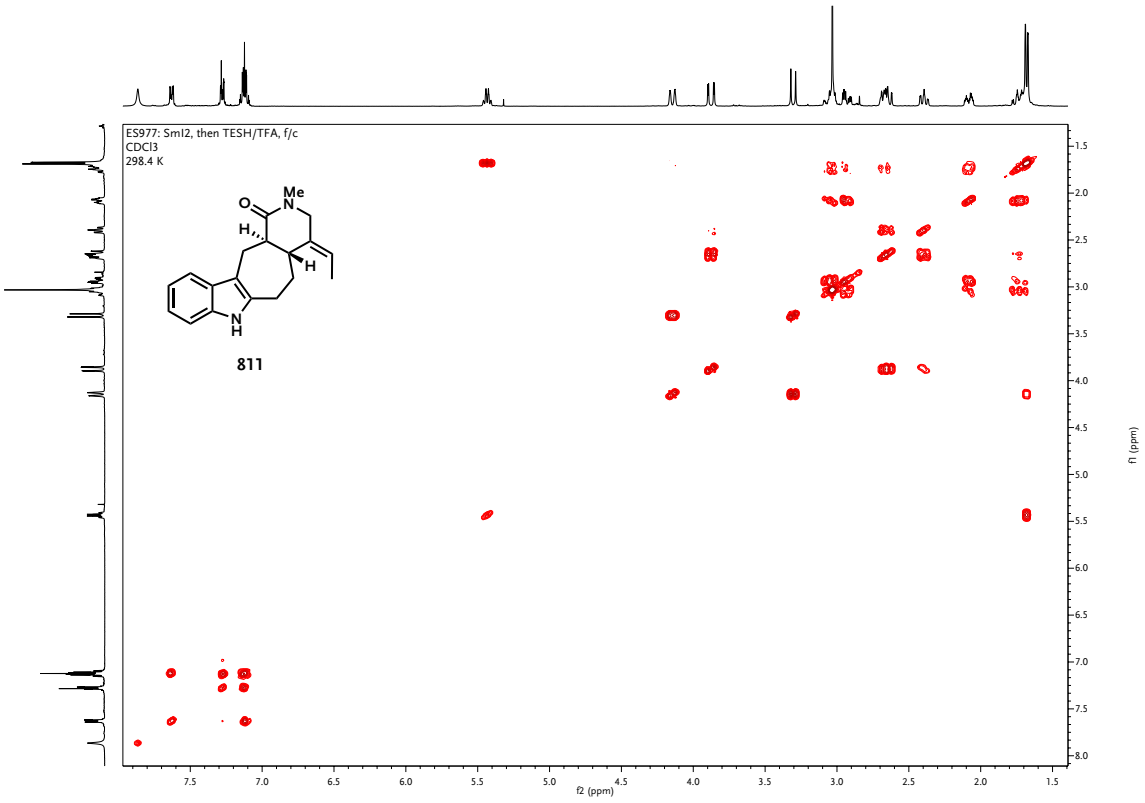
Spectrum B-198. HMBC 2D-NMR spectrum for compound **807** *(experimental on page 260)*.



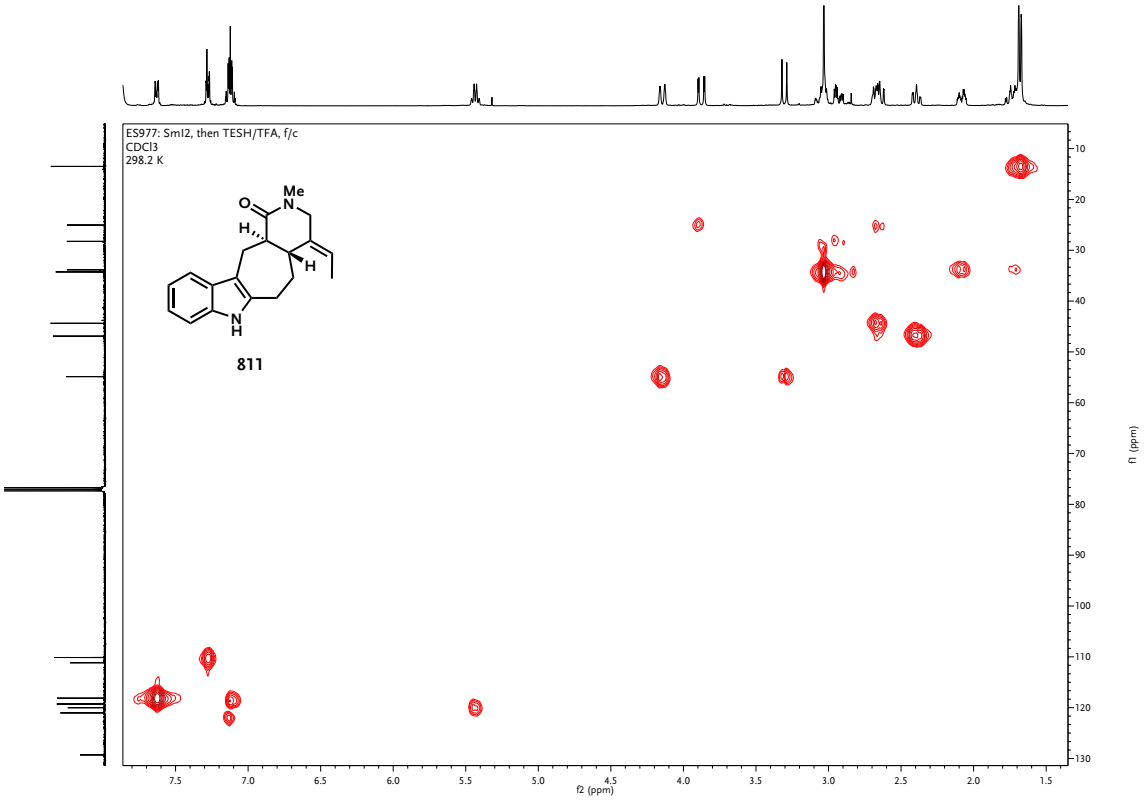
Spectrum B-199. [1]H-NMR spectrum for compound **811** *(experimental on page 261)*.



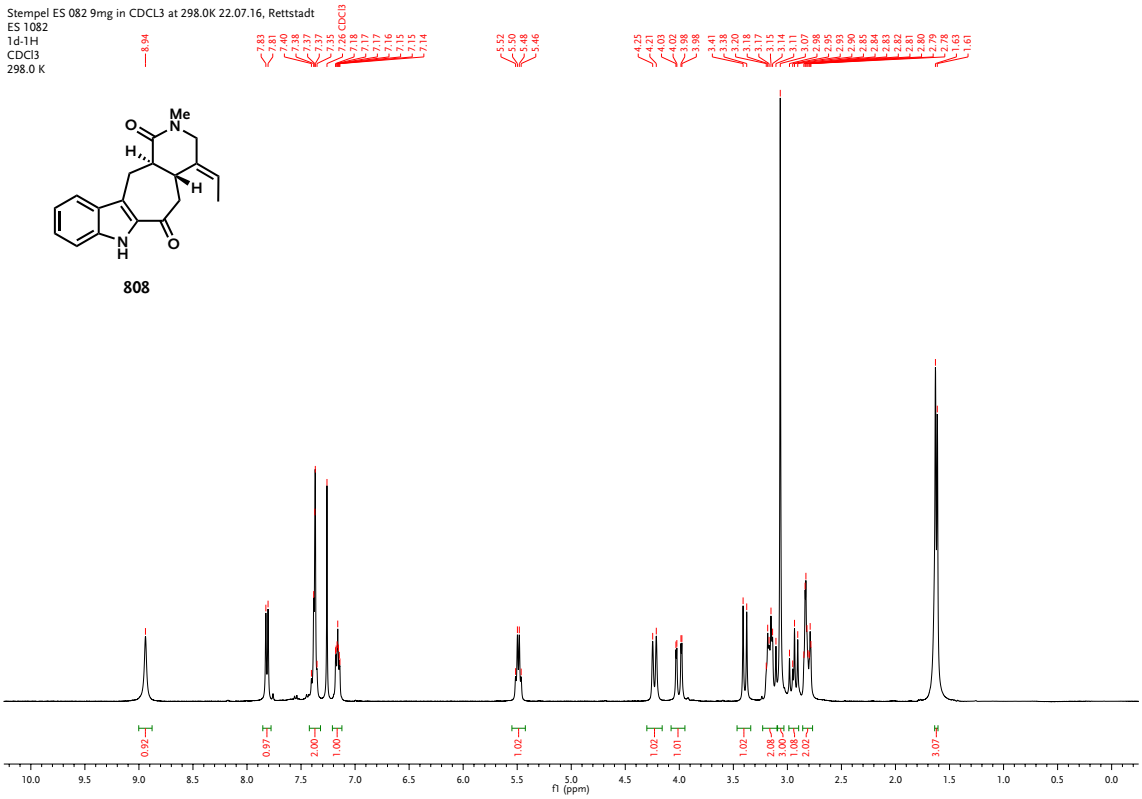
Spectrum B-200. [13]C-NMR spectrum for compound **811** *(experimental on page 261)*.



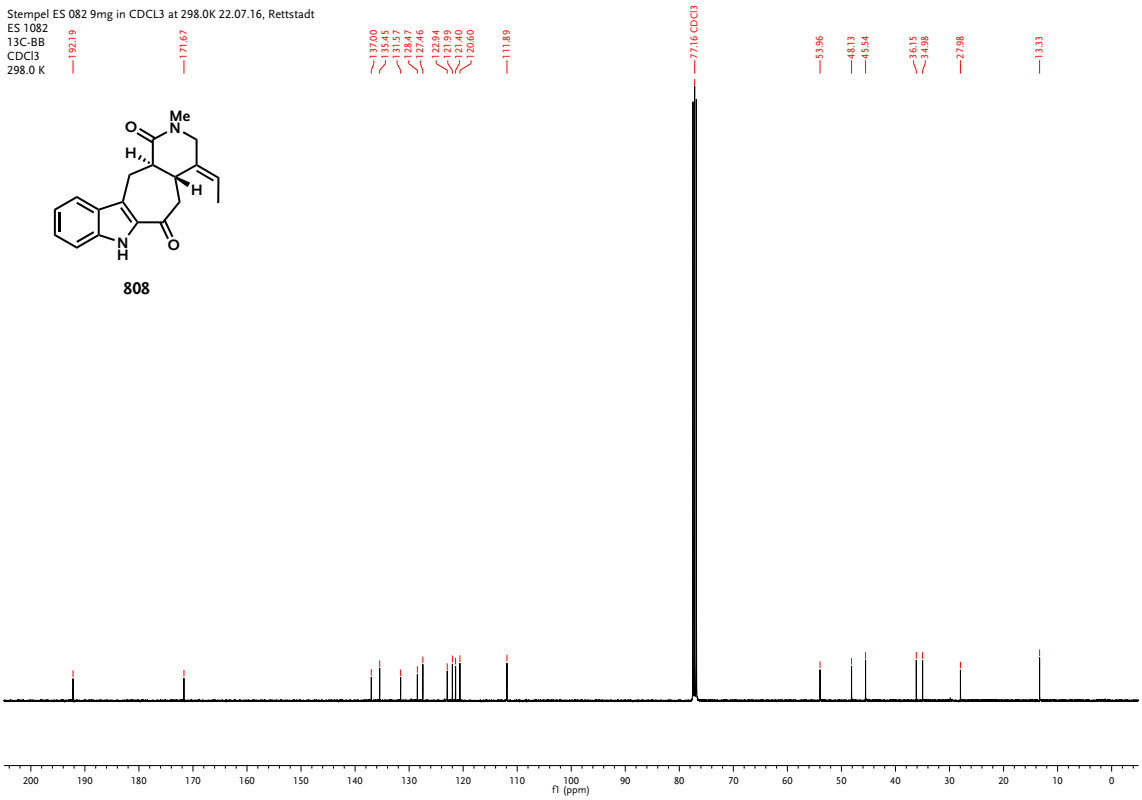
Spectrum B-201. COSY60 2D-NMR spectrum for compound **811** *(experimental on page 261)*.



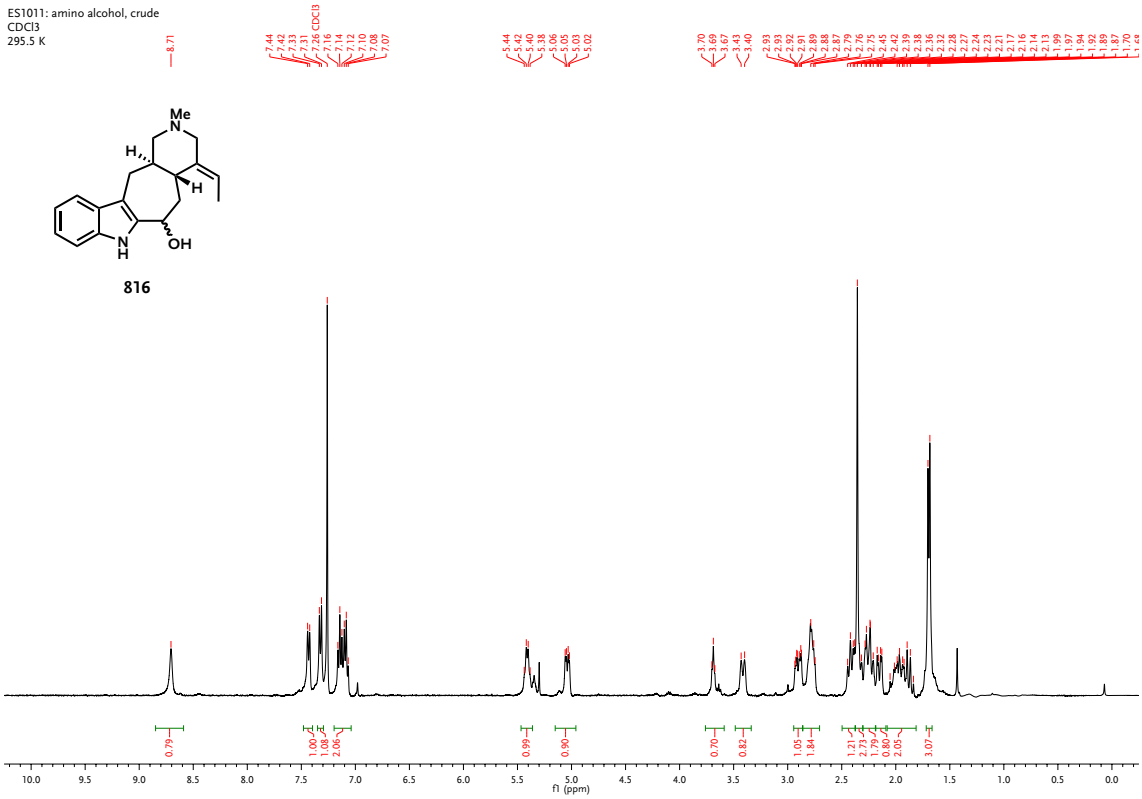
Spectrum B-202. HSQC 2D-NMR spectrum for compound **811** *(experimental on page 261)*.



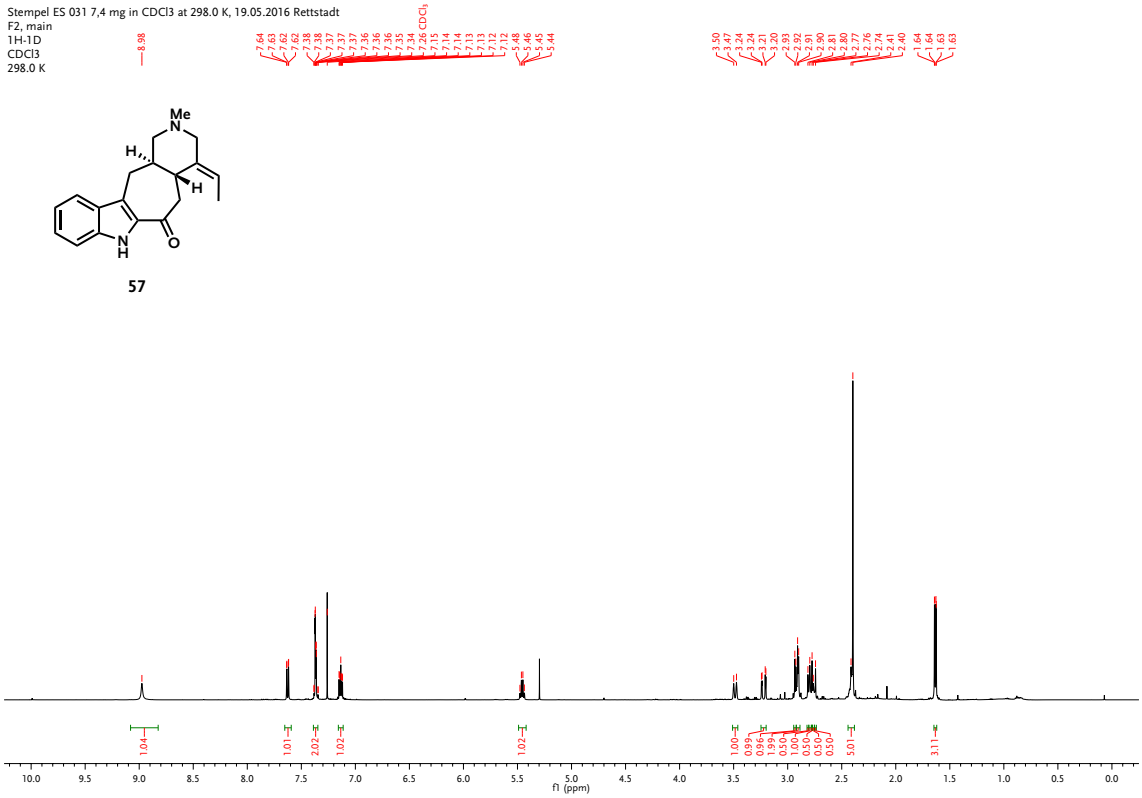
Spectrum B-203. [1]H-NMR spectrum for compound **808** *(experimental on page 261)*.



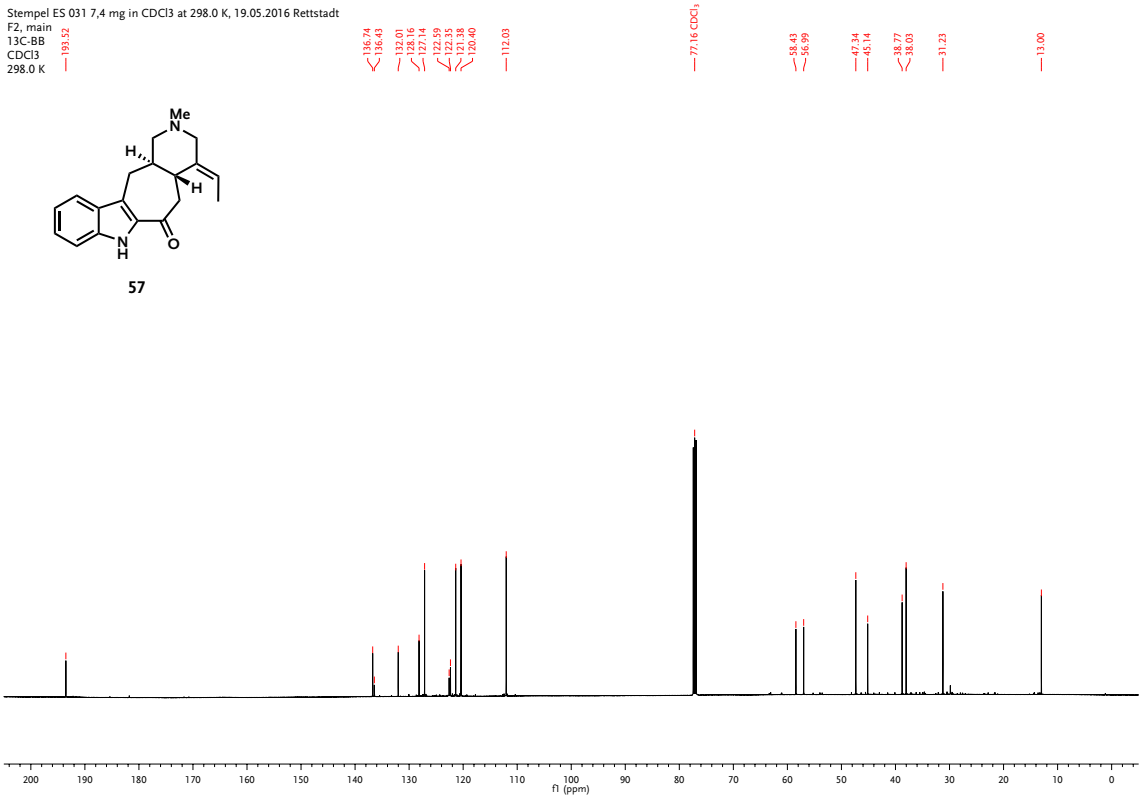
Spectrum B-204. [13]C-NMR spectrum for compound **808** *(experimental on page 261)*.



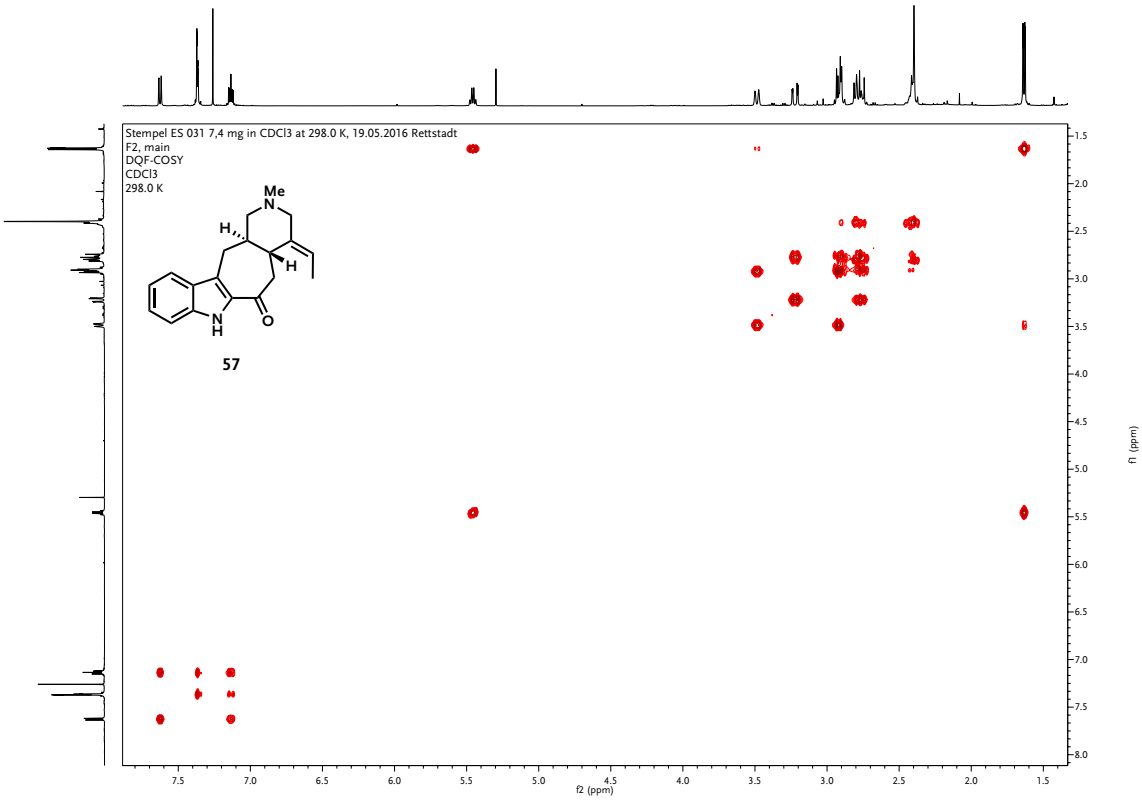
Spectrum B-205. ^{1}H-NMR spectrum for compound **816** *(experimental on page 262)*.



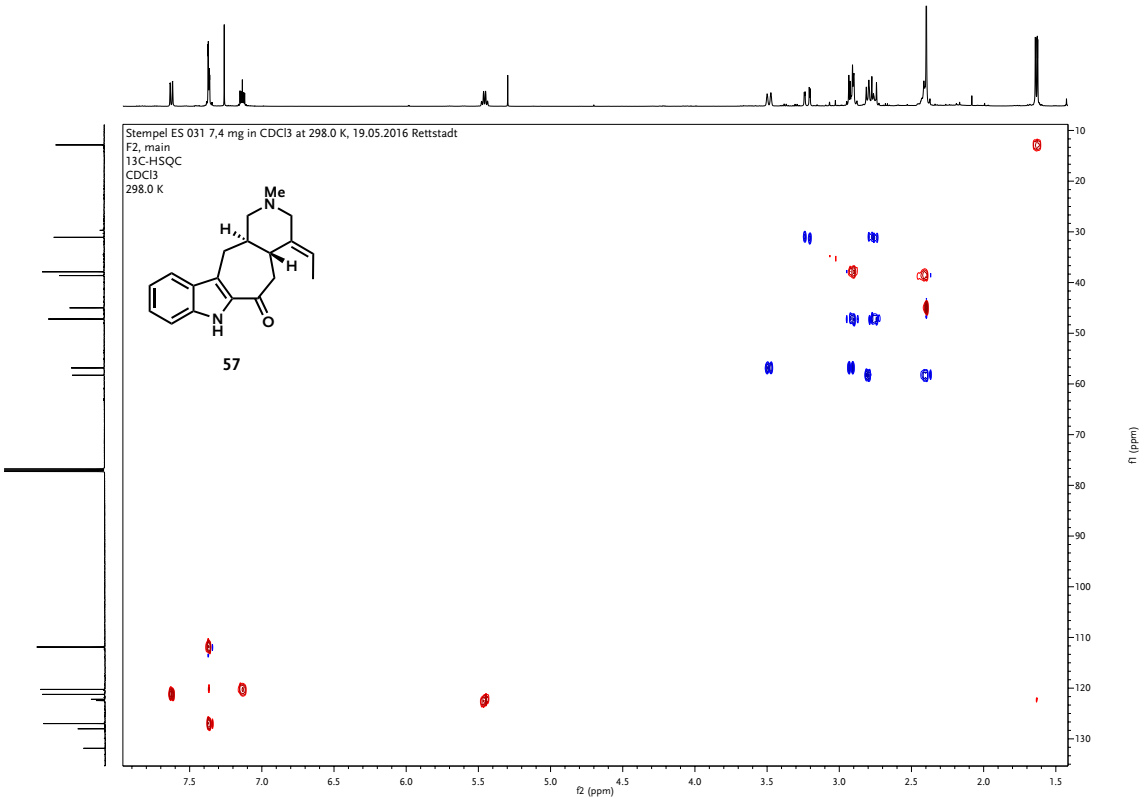
Spectrum B-206. ^{1}H-NMR spectrum for compound **57** *(experimental on page 263)*.



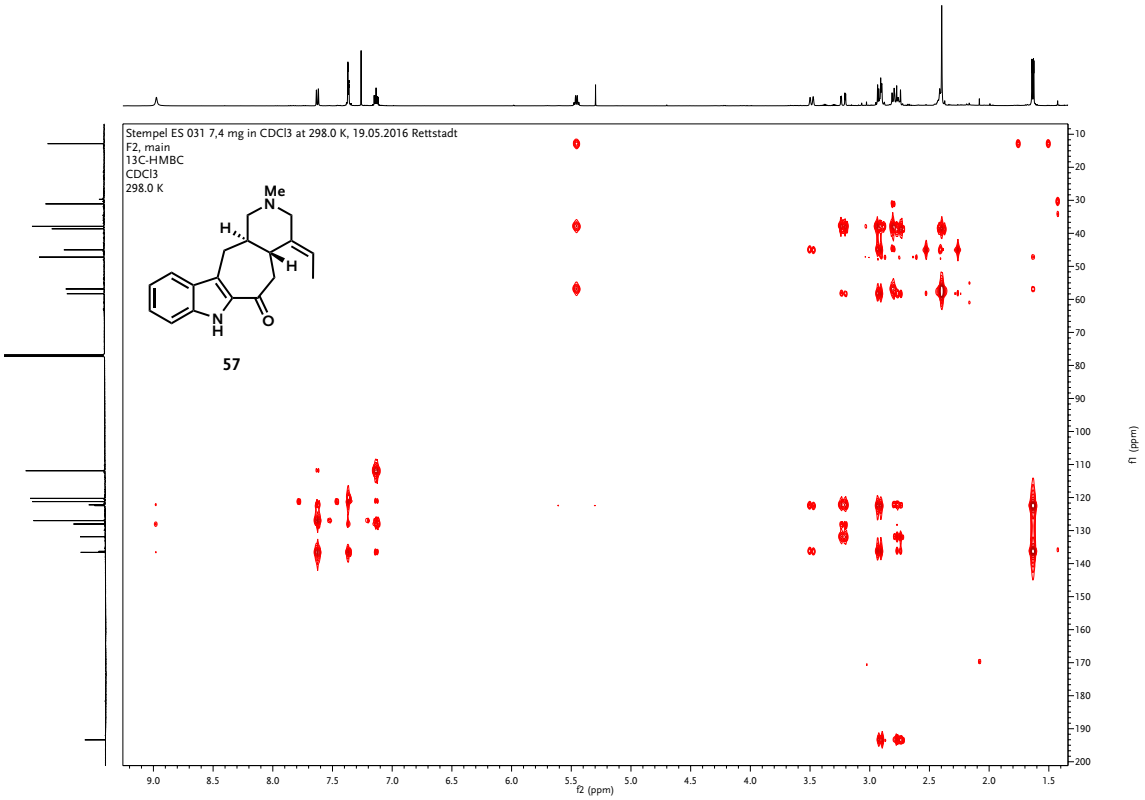
Spectrum B-207. ^{13}C-NMR spectrum for compound **57** *(experimental on page 263)*.



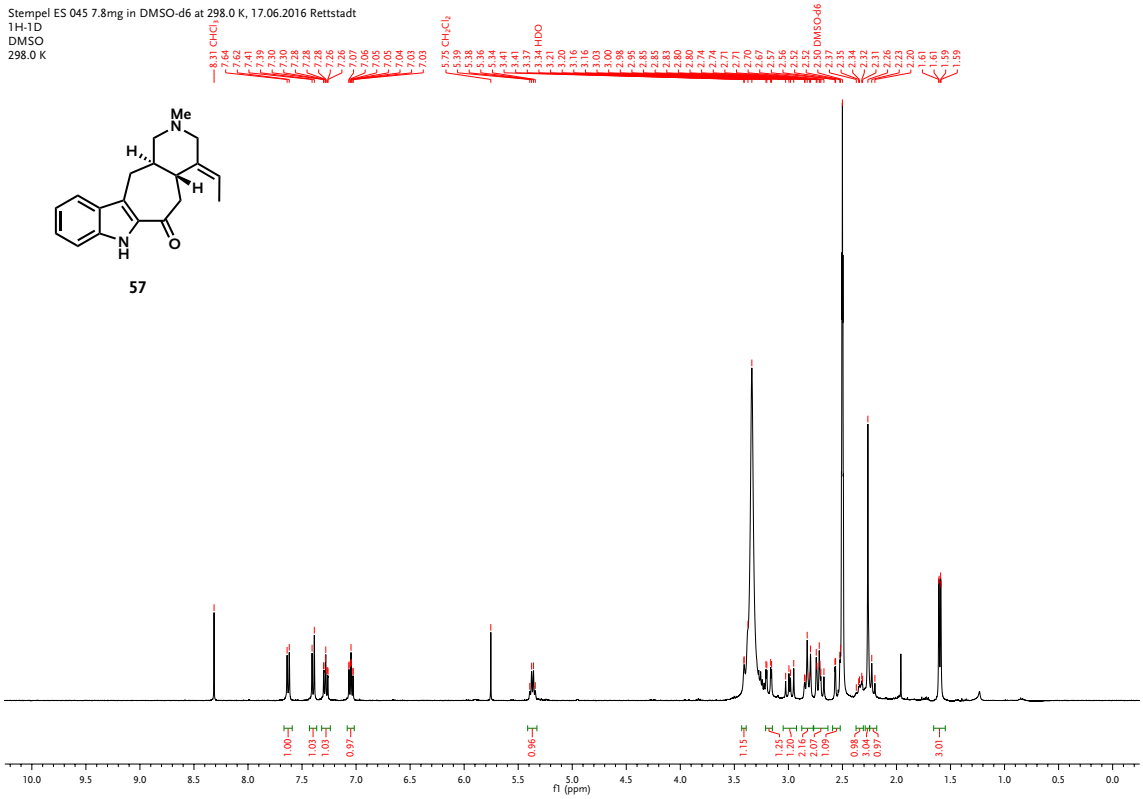
Spectrum B-208. COSY60 2D-NMR spectrum for compound **57** *(experimental on page 263)*.



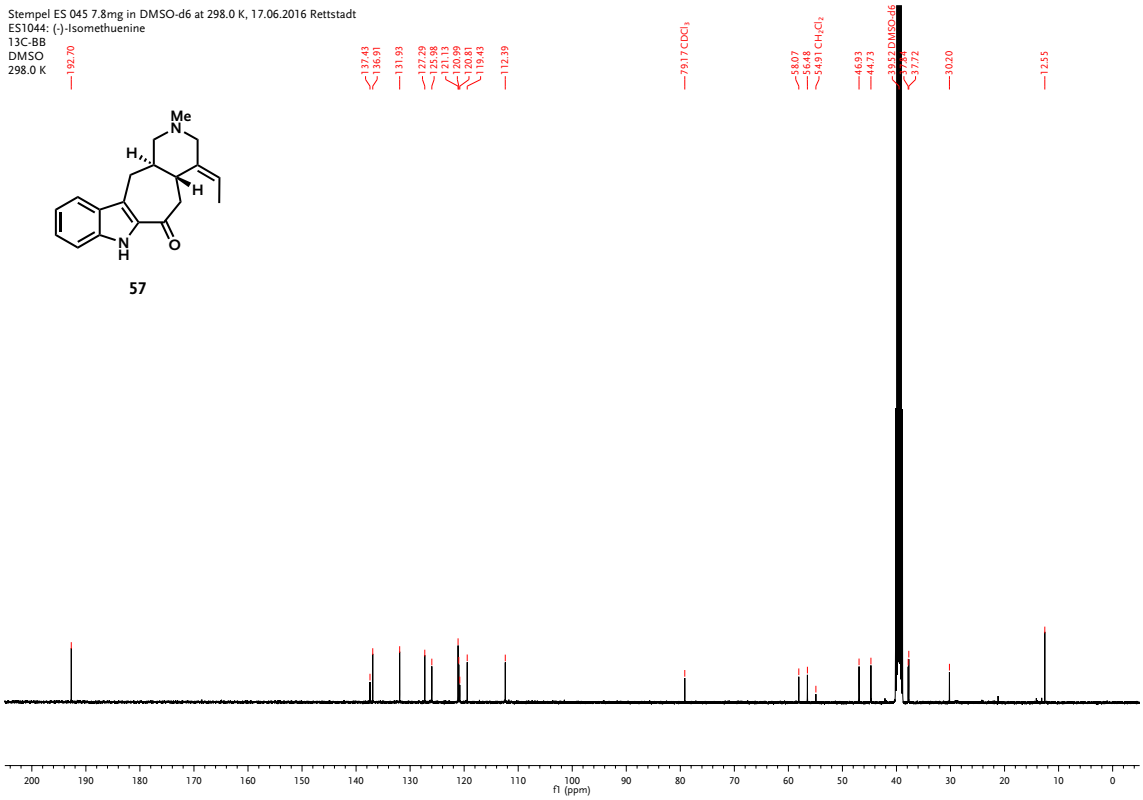
Spectrum B-209. HSQC 2D-NMR spectrum for compound **57** *(experimental on page 263)*.



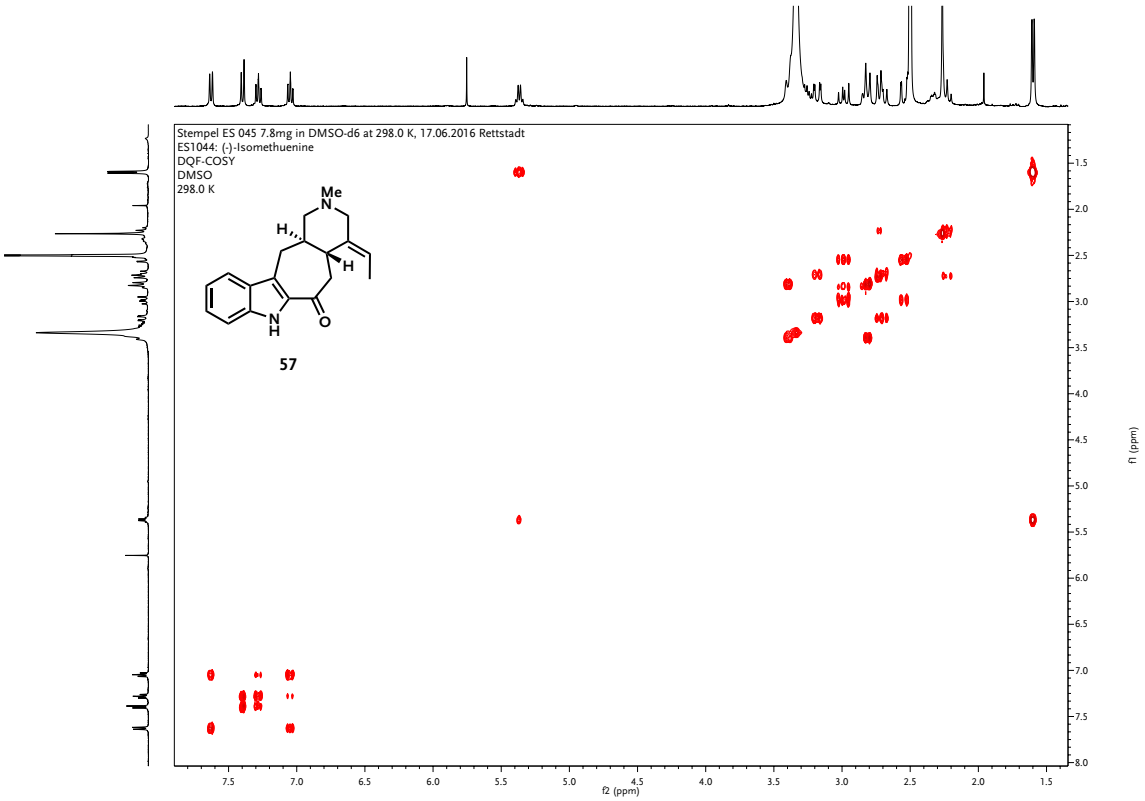
Spectrum B-210. HMBC 2D-NMR spectrum for compound **57** *(experimental on page 263)*.



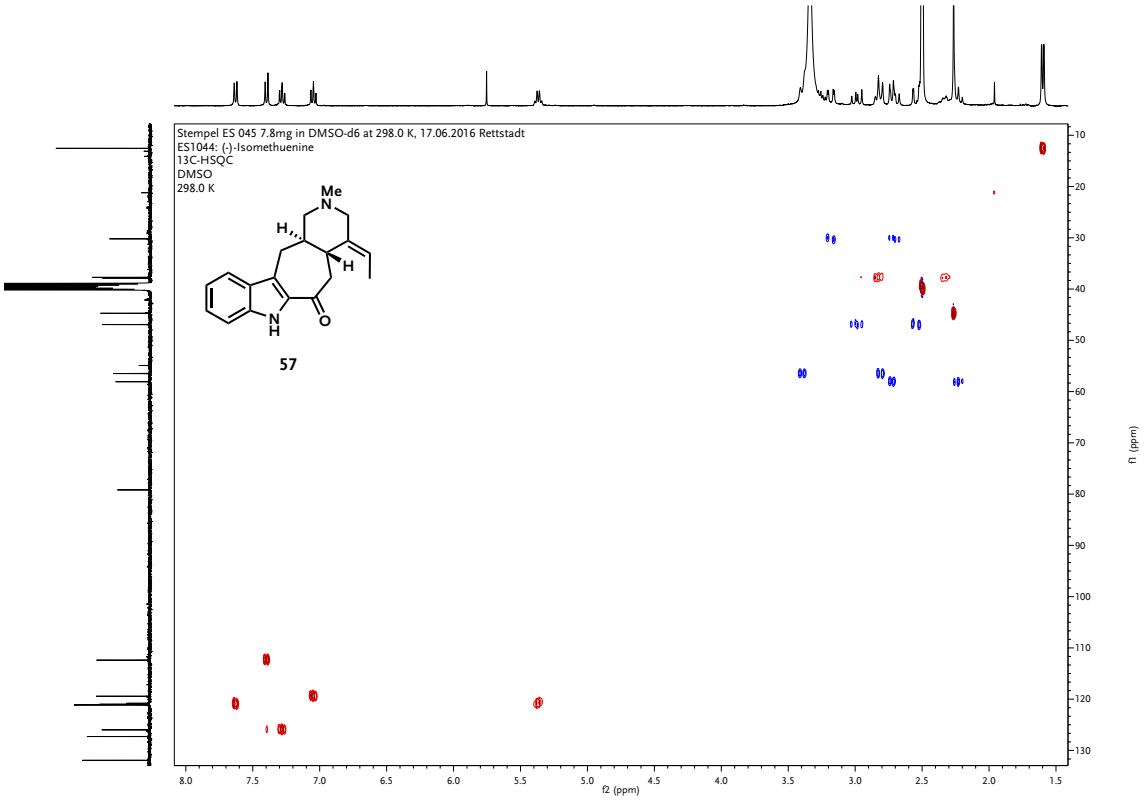
Spectrum B-211. ^{1}H-NMR spectrum for compound **57** *(experimental on page 263)*.



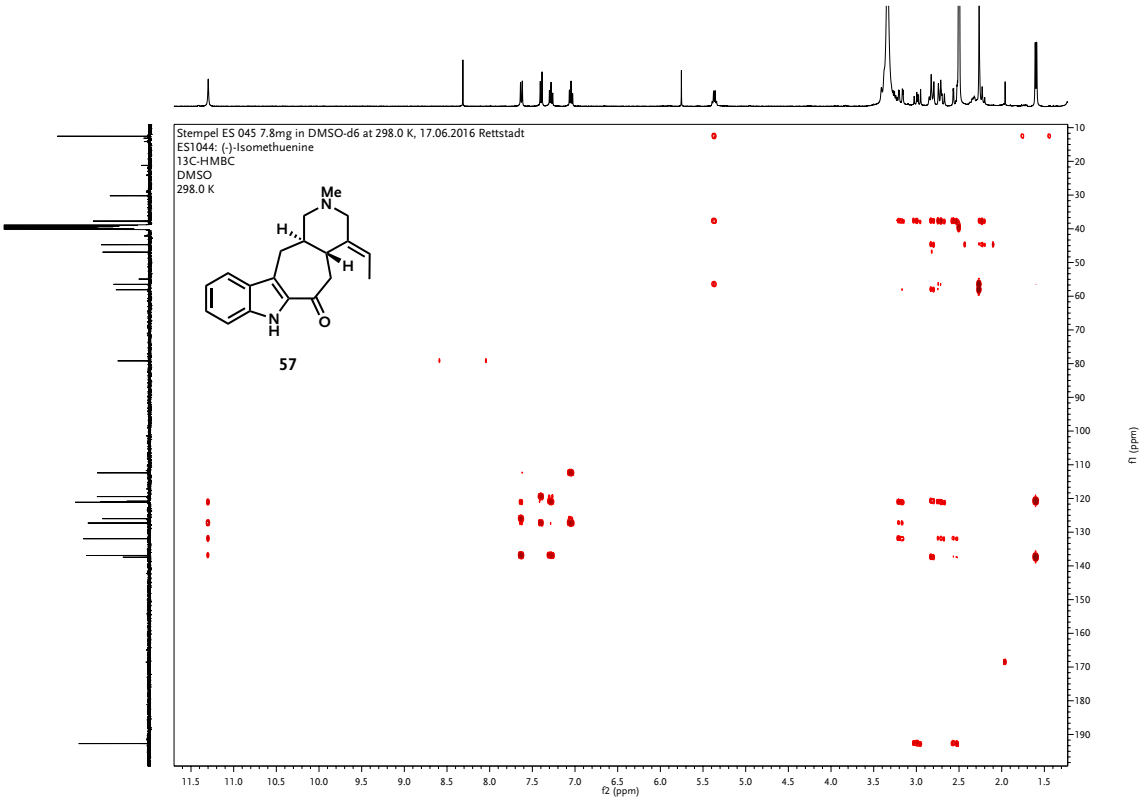
Spectrum B-212. ^{13}C-NMR spectrum for compound **57** *(experimental on page 263)*.



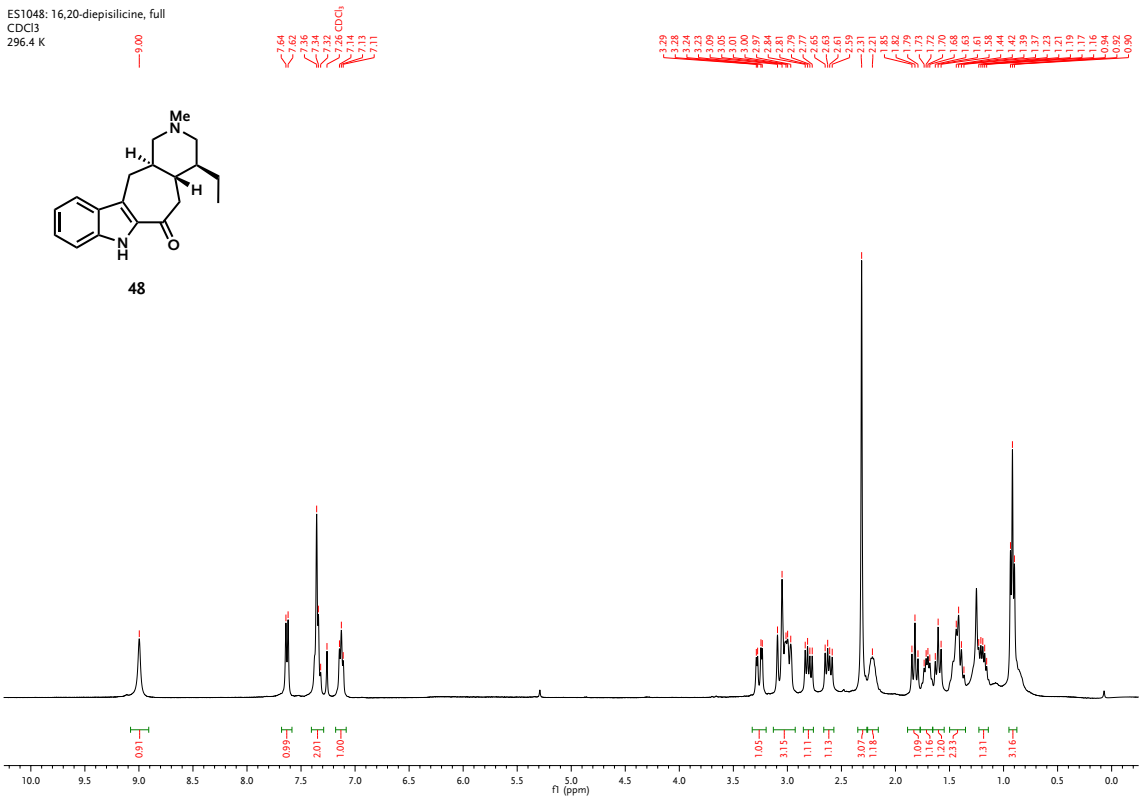
Spectrum B-213. COSY60 2D-NMR spectrum for compound **57** *(experimental on page 263)*.



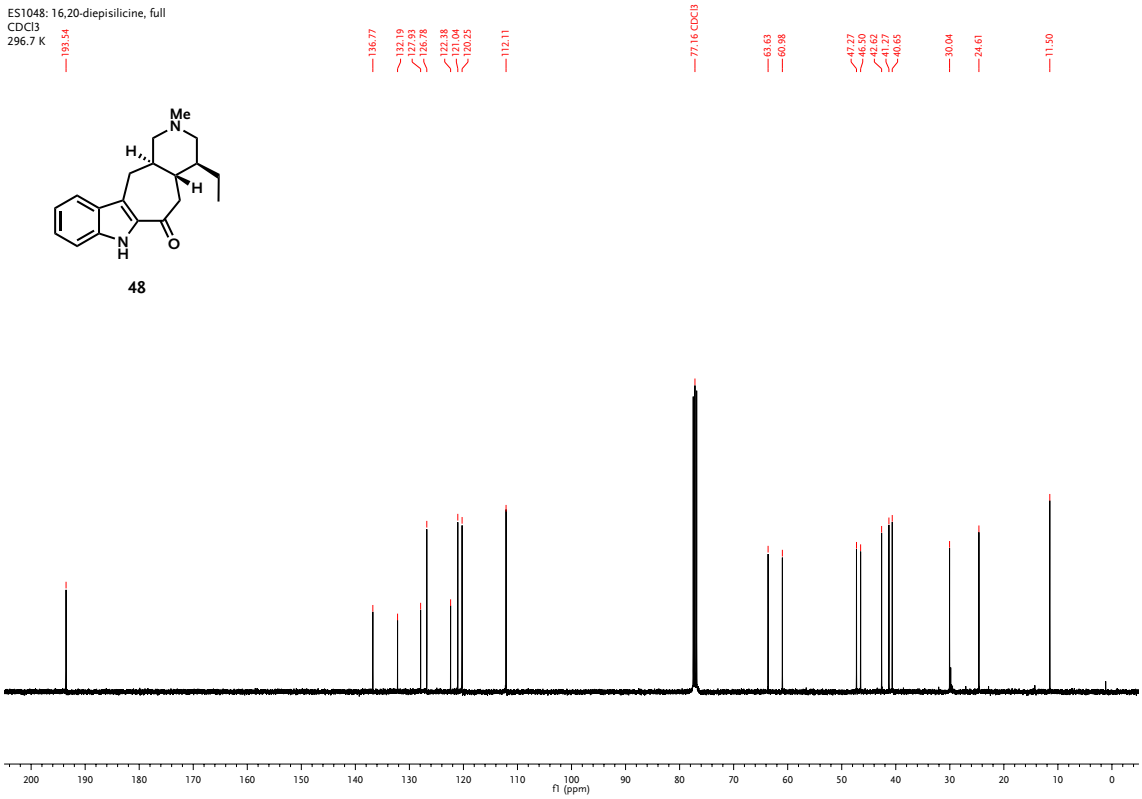
Spectrum B-214. HSQC 2D-NMR spectrum for compound **57** *(experimental on page 263)*.



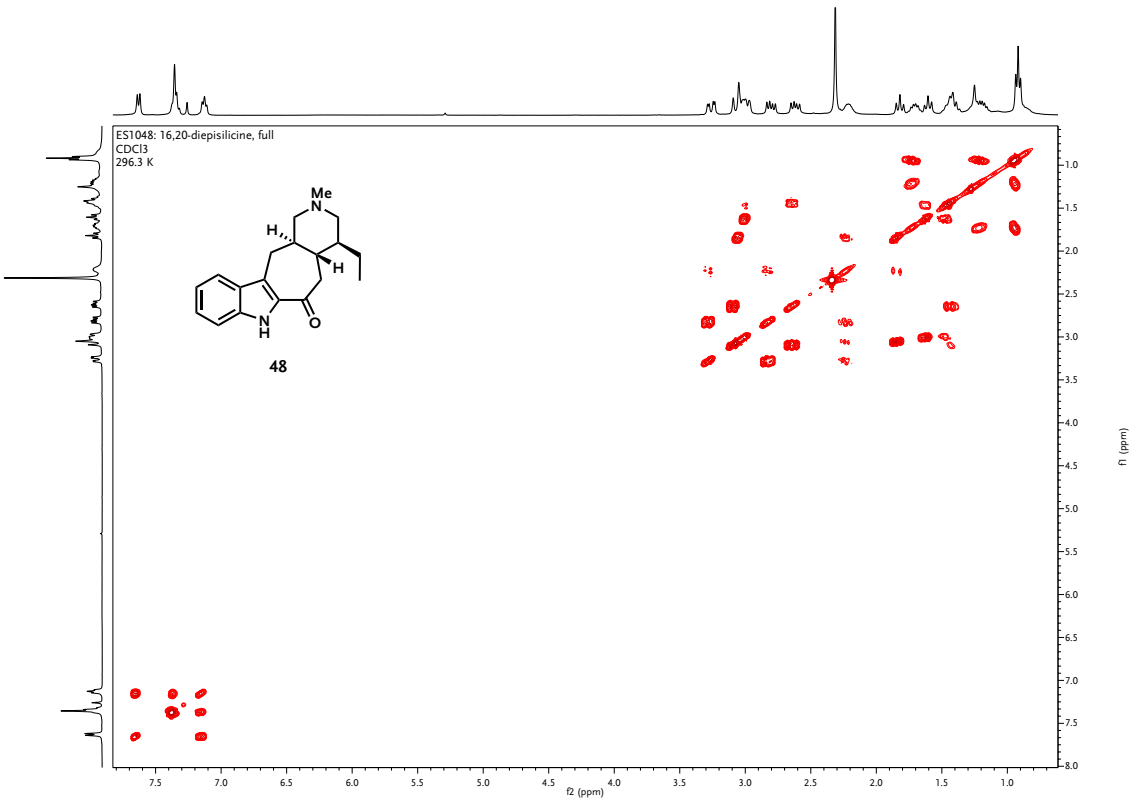
Spectrum B-215. HMBC 2D-NMR spectrum for compound **57** *(experimental on page 263)*.



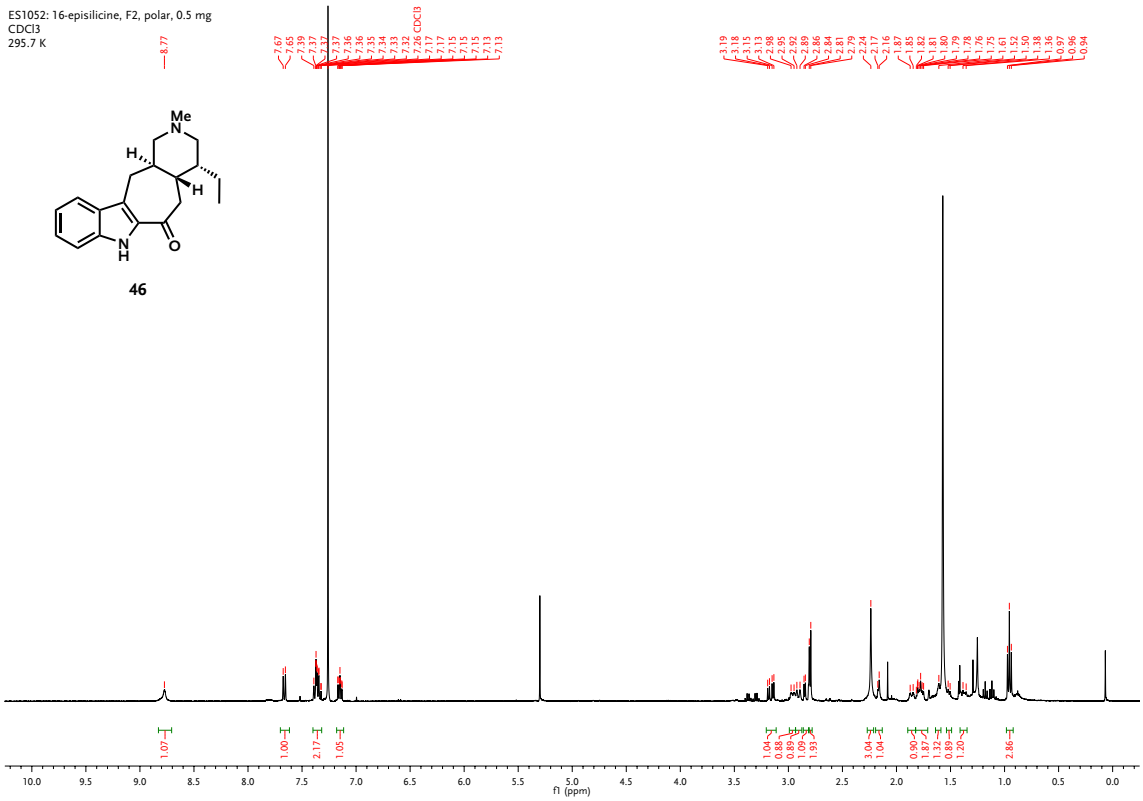
Spectrum B-216. ^{1}H-NMR spectrum for compound **48** *(experimental on page 263)*.



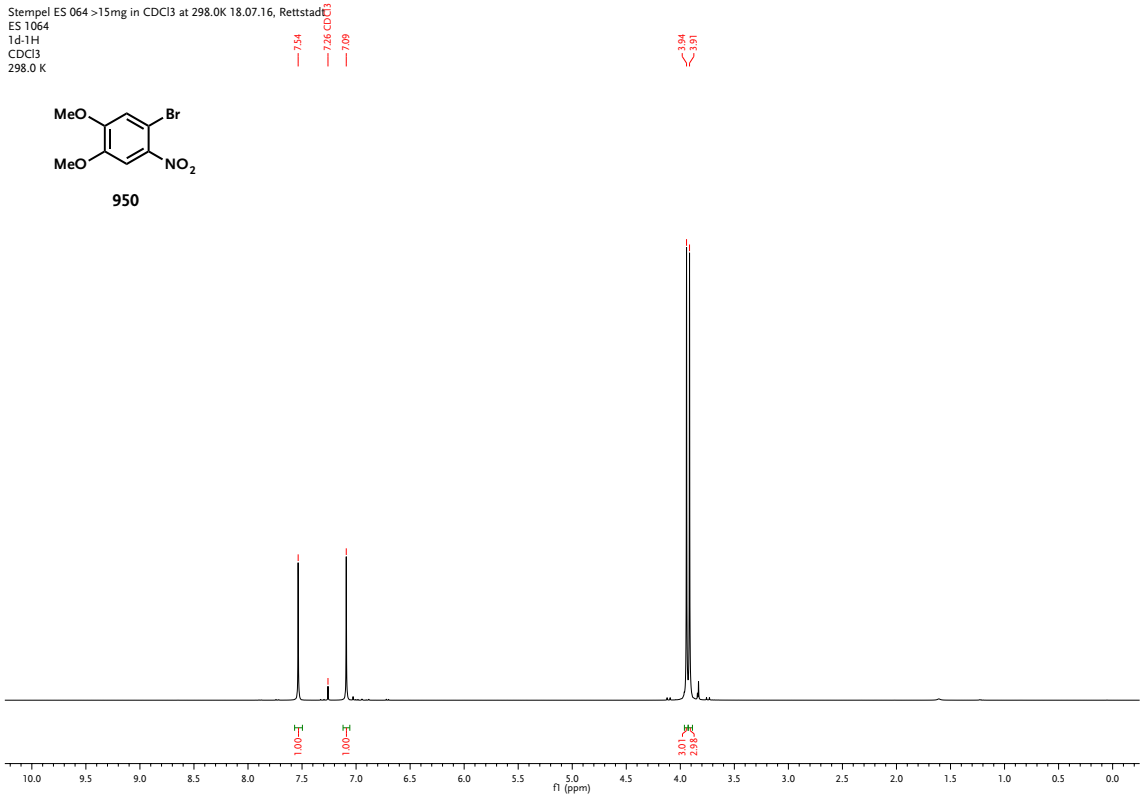
Spectrum B-217. ^{13}C-NMR spectrum for compound **48** *(experimental on page 263)*.



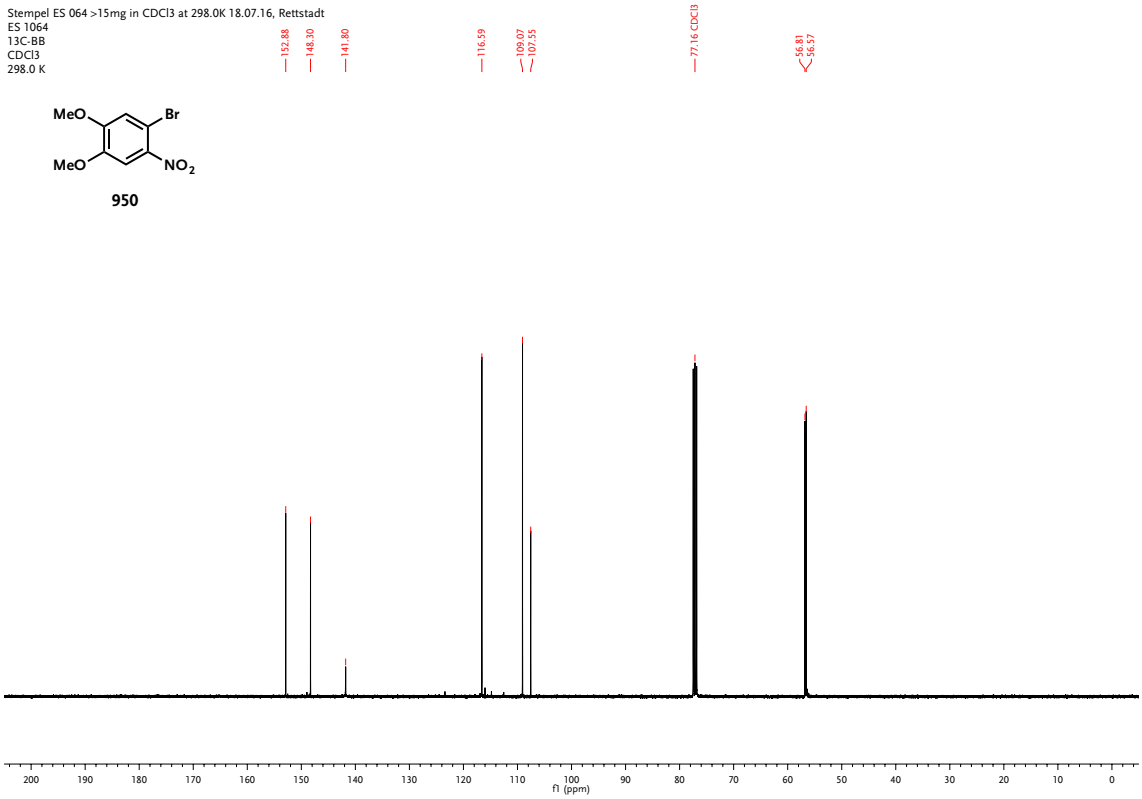
Spectrum B-218. COSY60 2D-NMR spectrum for compound **48** *(experimental on page 263)*.



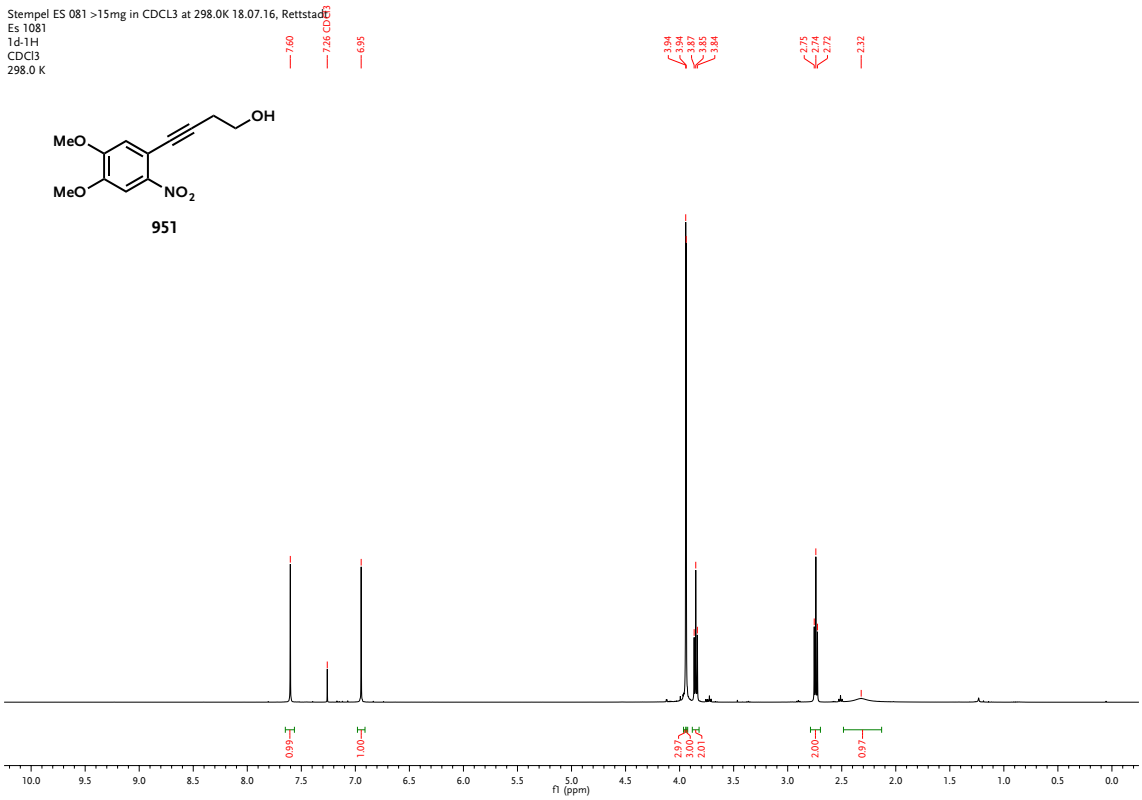
Spectrum B-219. ^{1}H-NMR spectrum for compound **46** *(experimental on page 264)*.



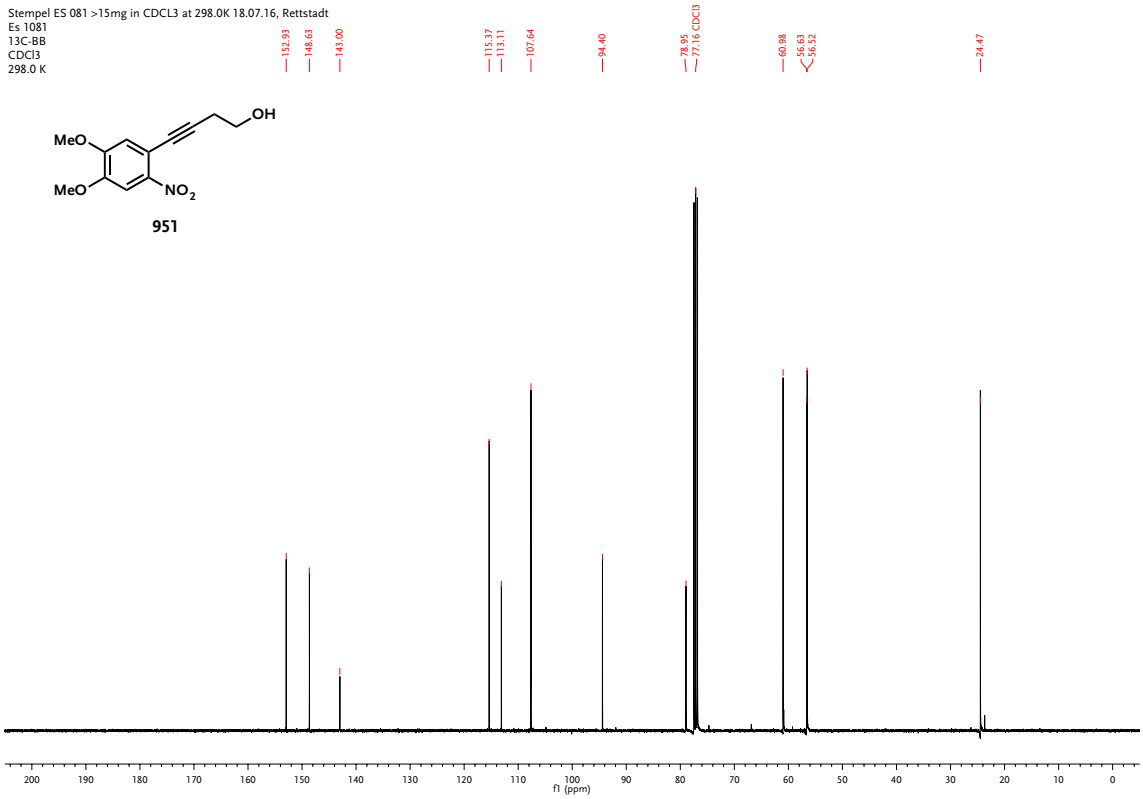
Spectrum B-220. ^{1}H-NMR spectrum for compound **950** *(experimental on page 303)*.



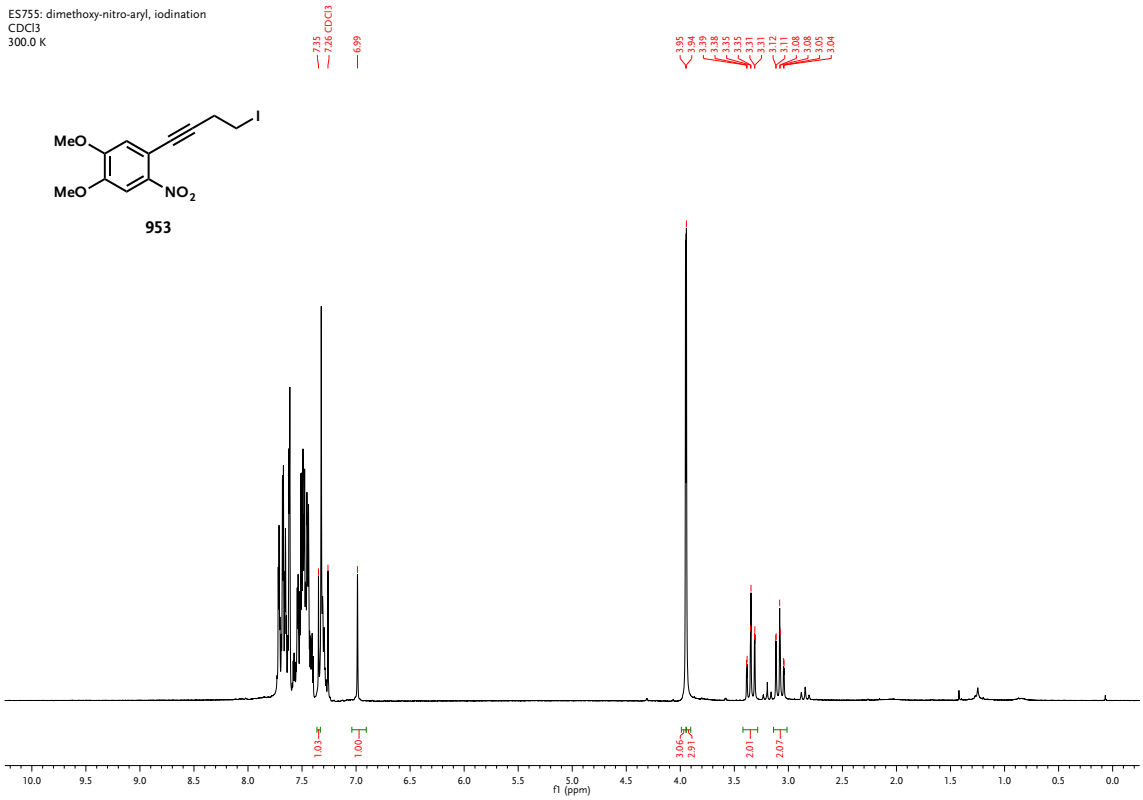
Spectrum B-221. ^{13}C-NMR spectrum for compound **950** *(experimental on page 303)*.



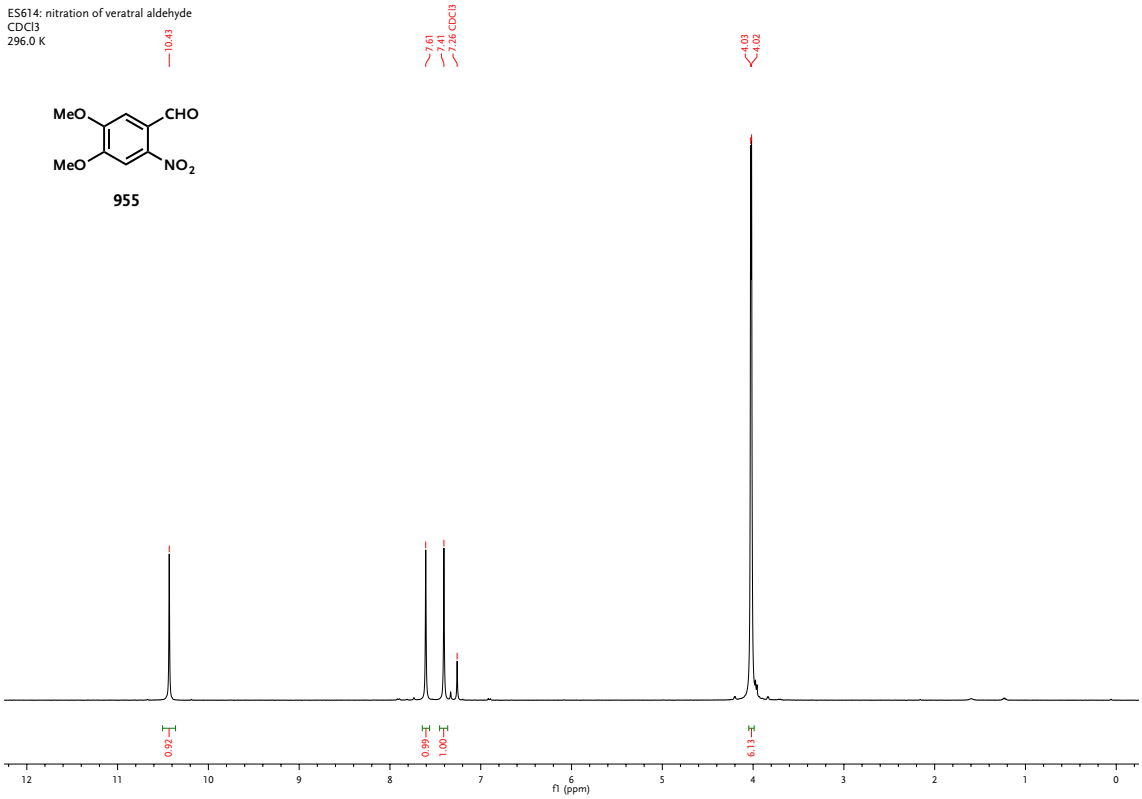
Spectrum B-222. ^{1}H-NMR spectrum for compound **951** *(experimental on page 304)*.



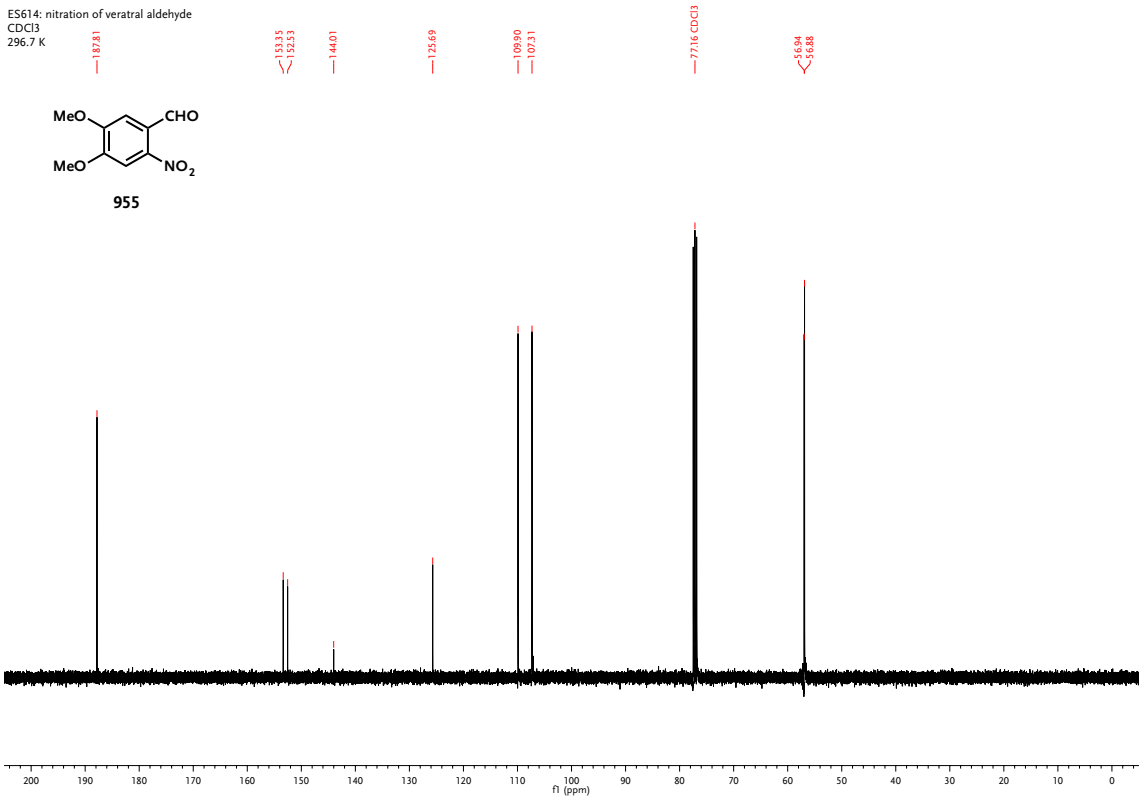
Spectrum B-223. ^{13}C-NMR spectrum for compound **951** *(experimental on page 304)*.



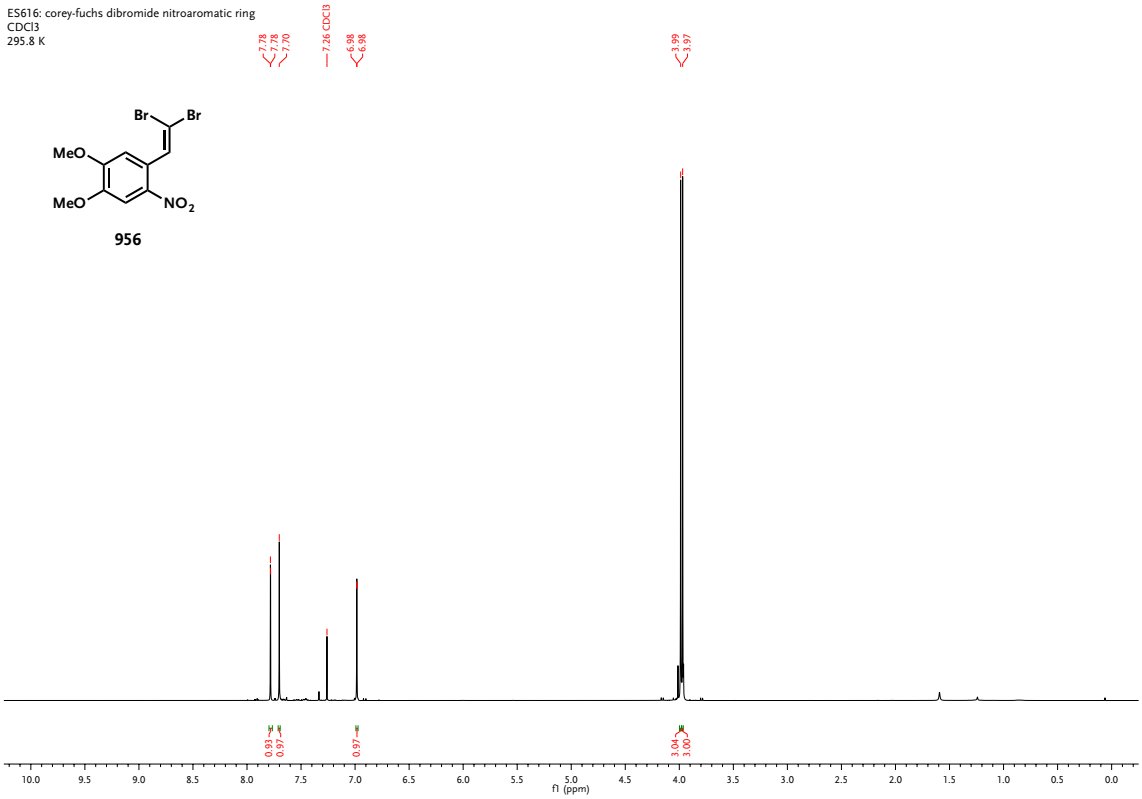
Spectrum B-224. ^{1}H-NMR spectrum for compound **953** *(experimental on page 304)*.



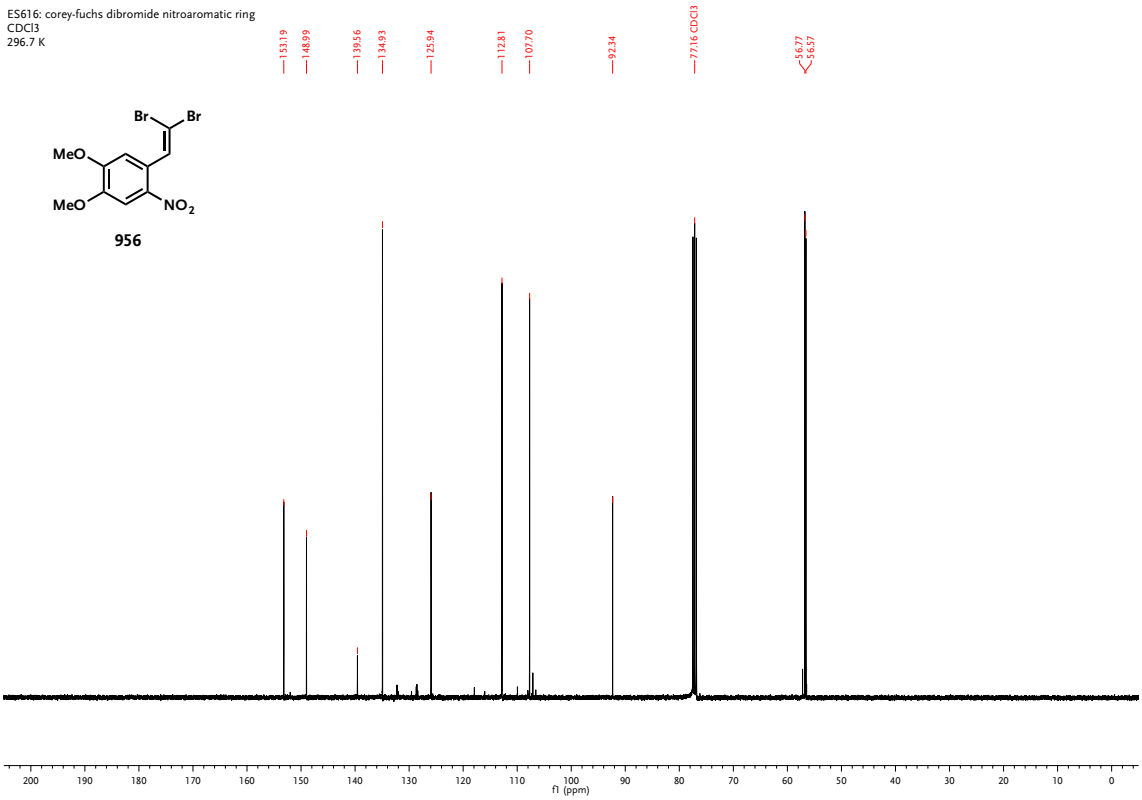
Spectrum B-225. [1]H-NMR spectrum for compound **955** *(experimental on page 305)*.



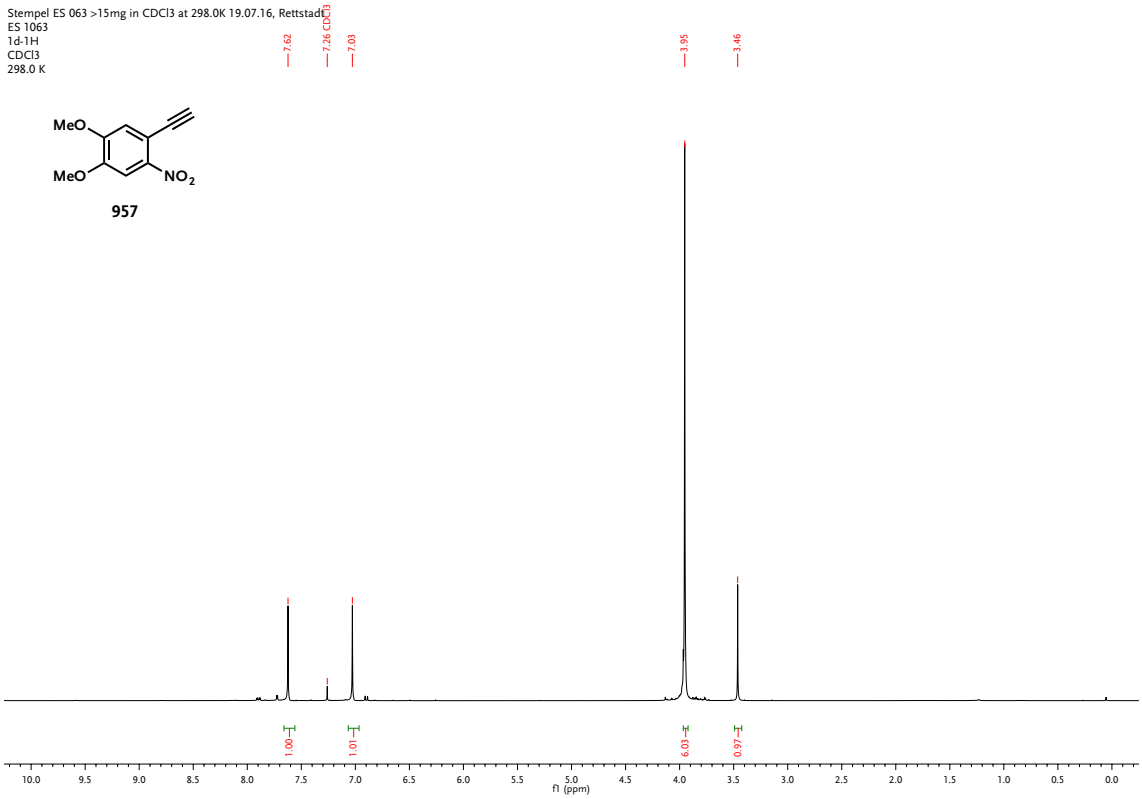
Spectrum B-226. [13]C-NMR spectrum for compound **955** *(experimental on page 305)*.



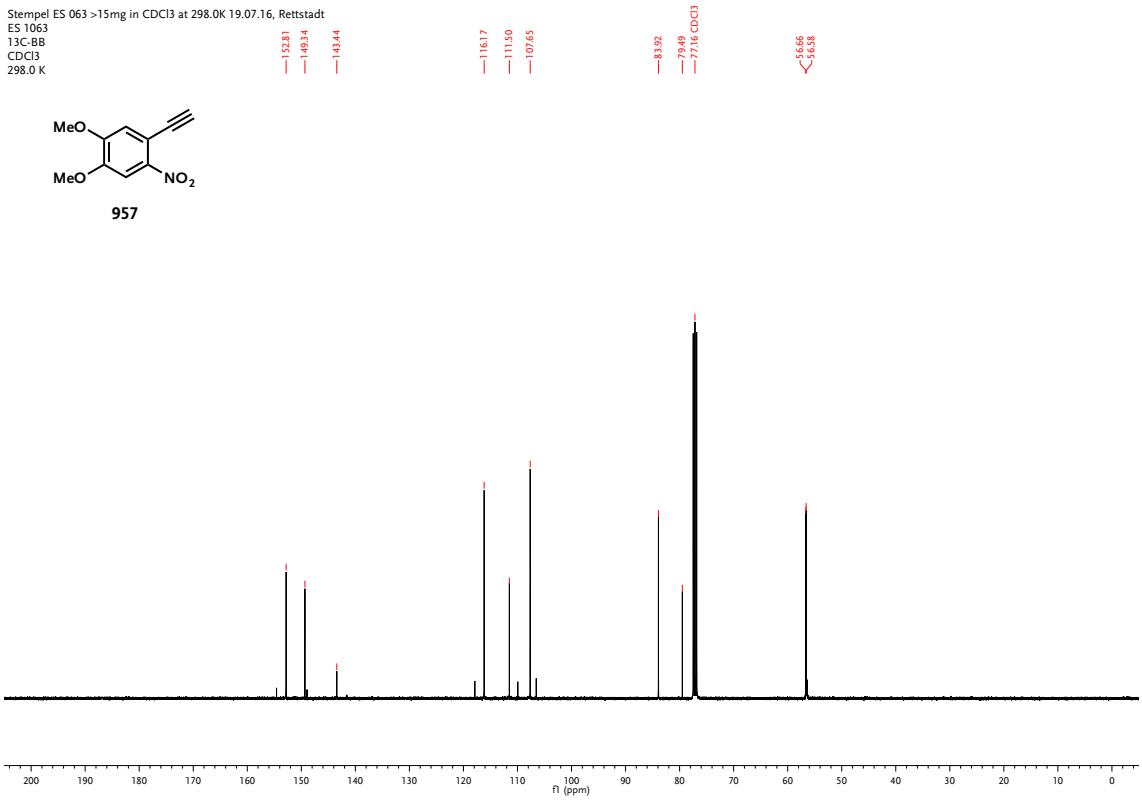
Spectrum B-227. [1]H-NMR spectrum for compound **956** *(experimental on page 305)*.



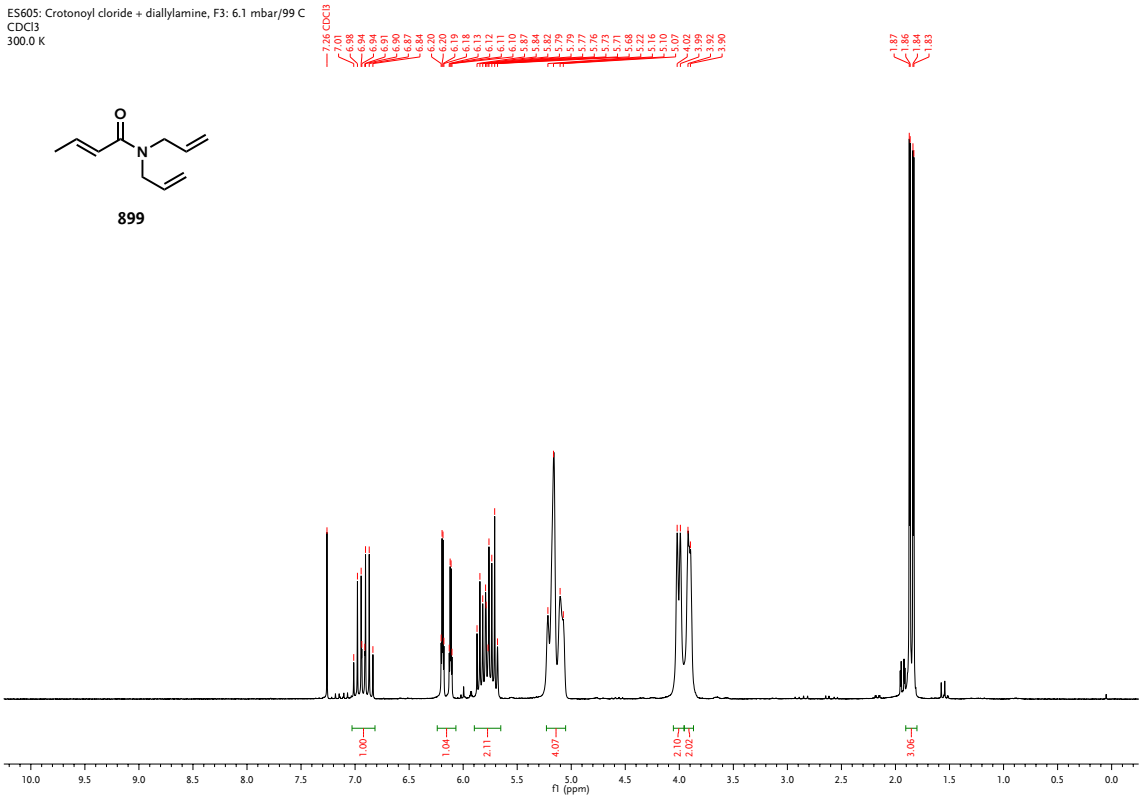
Spectrum B-228. [13]C-NMR spectrum for compound **956** *(experimental on page 305)*.



Spectrum B-229. ^{1}H-NMR spectrum for compound **957** *(experimental on page 306)*.

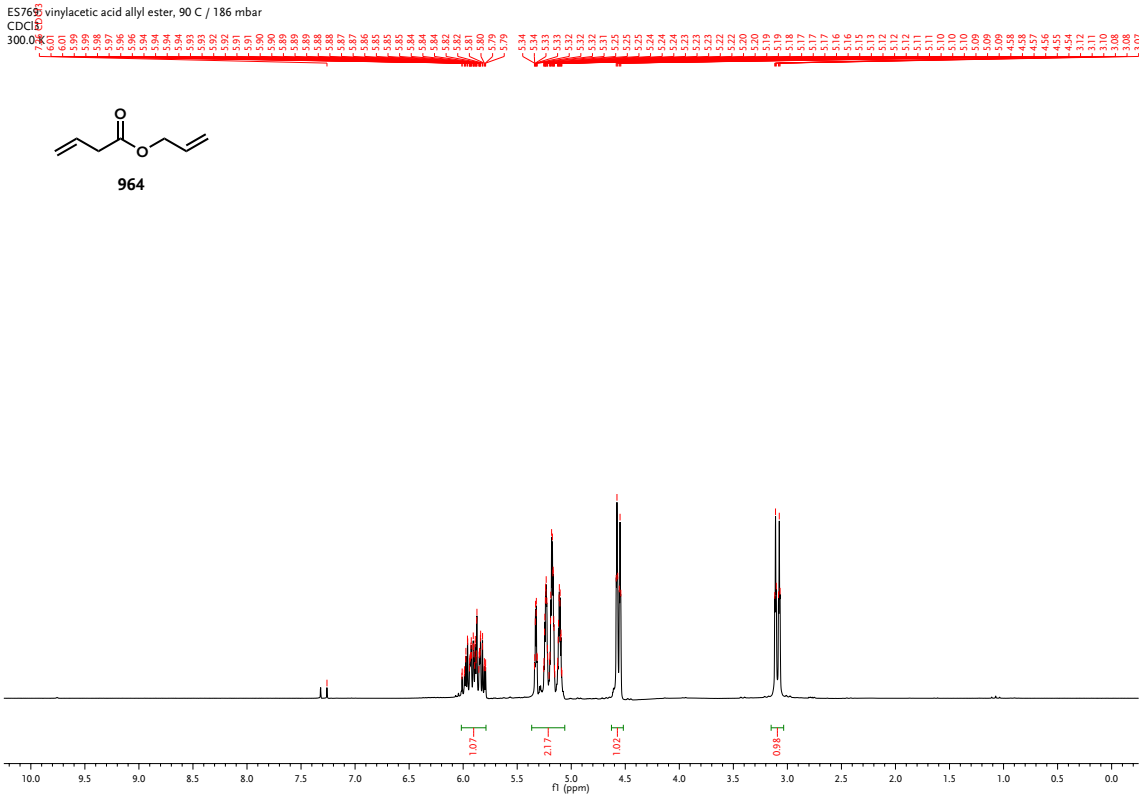


Spectrum B-230. ^{13}C-NMR spectrum for compound **957** *(experimental on page 306)*.



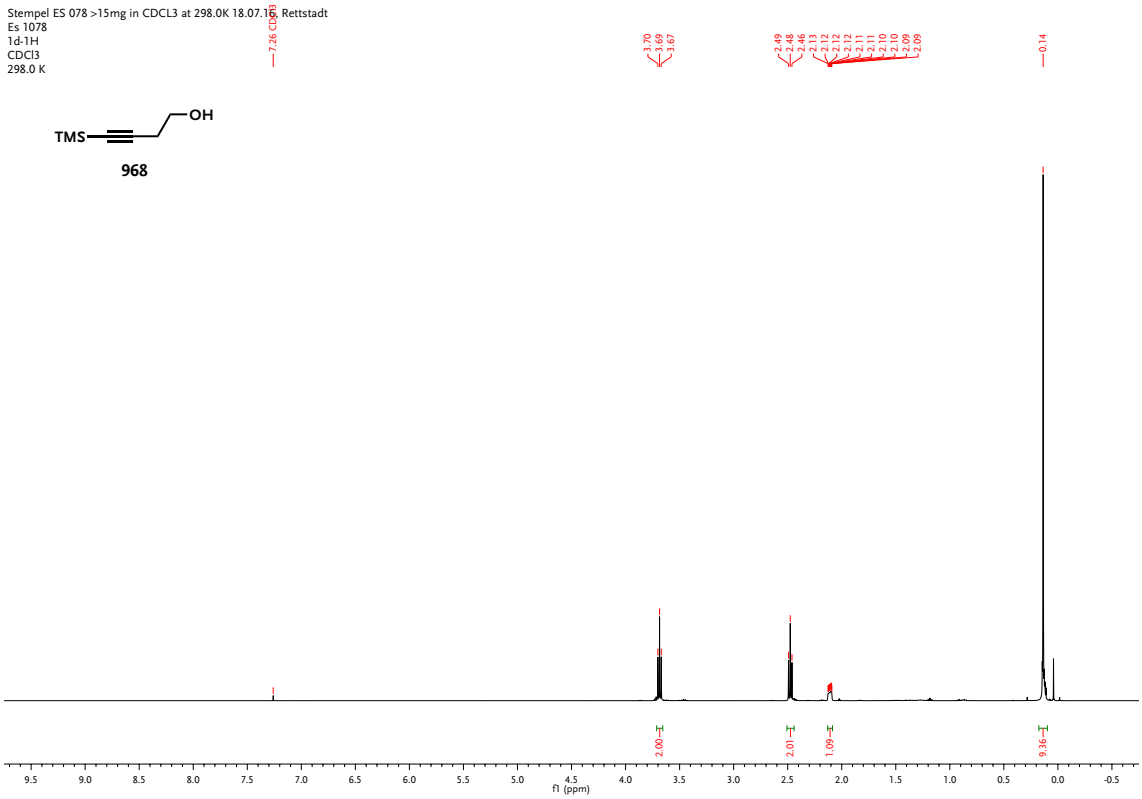
899

Spectrum B-231. [1]H-NMR spectrum for compound **899** *(experimental on page 307)*.

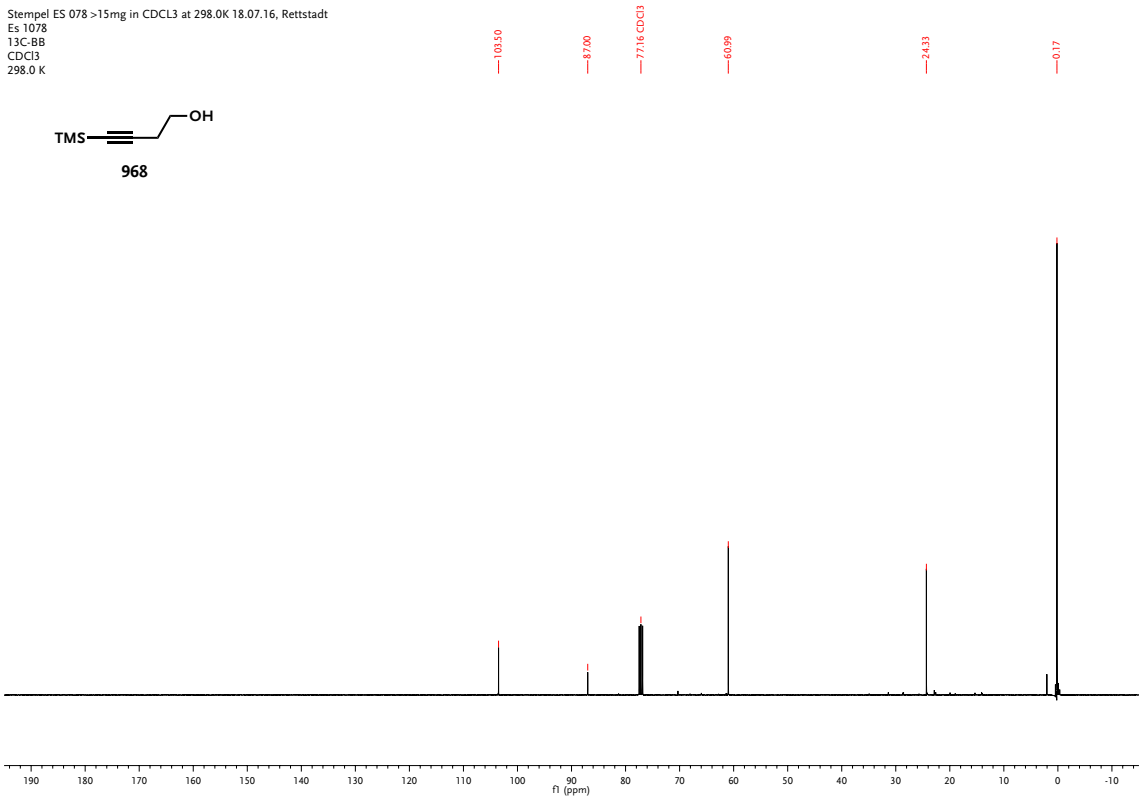


964

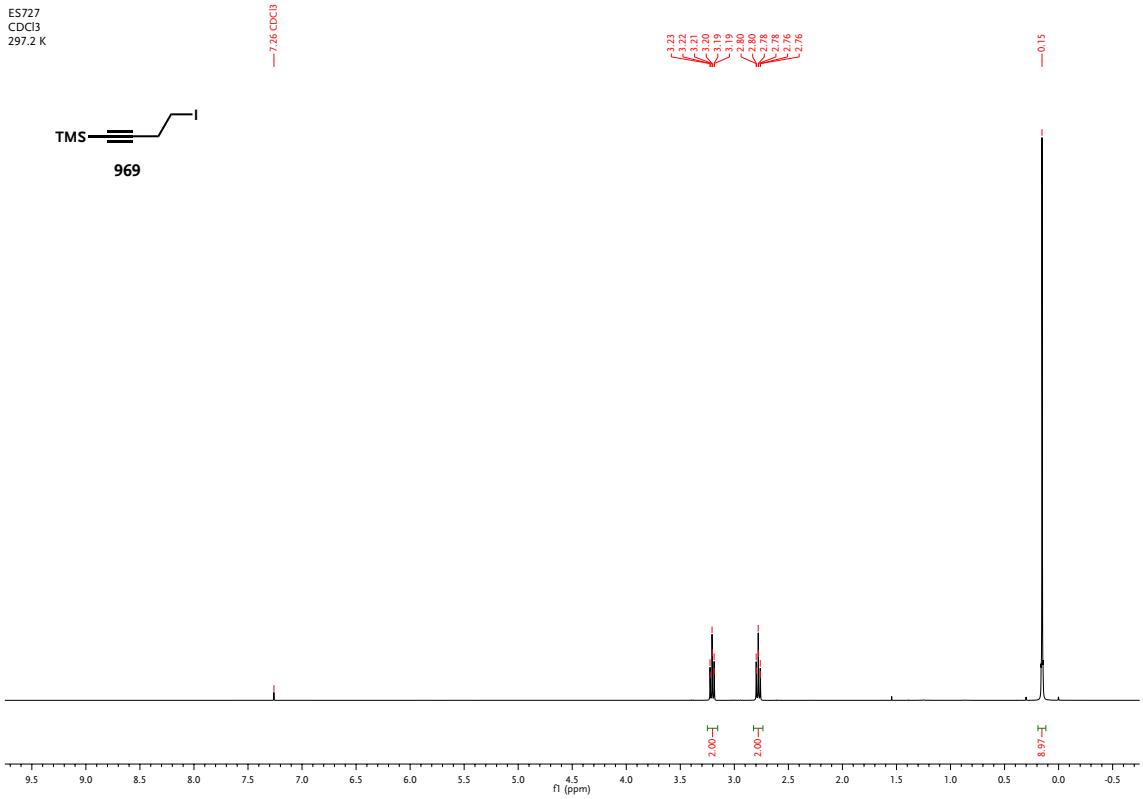
Spectrum B-232. [1]H-NMR spectrum for compound **964** *(experimental on page 307)*.



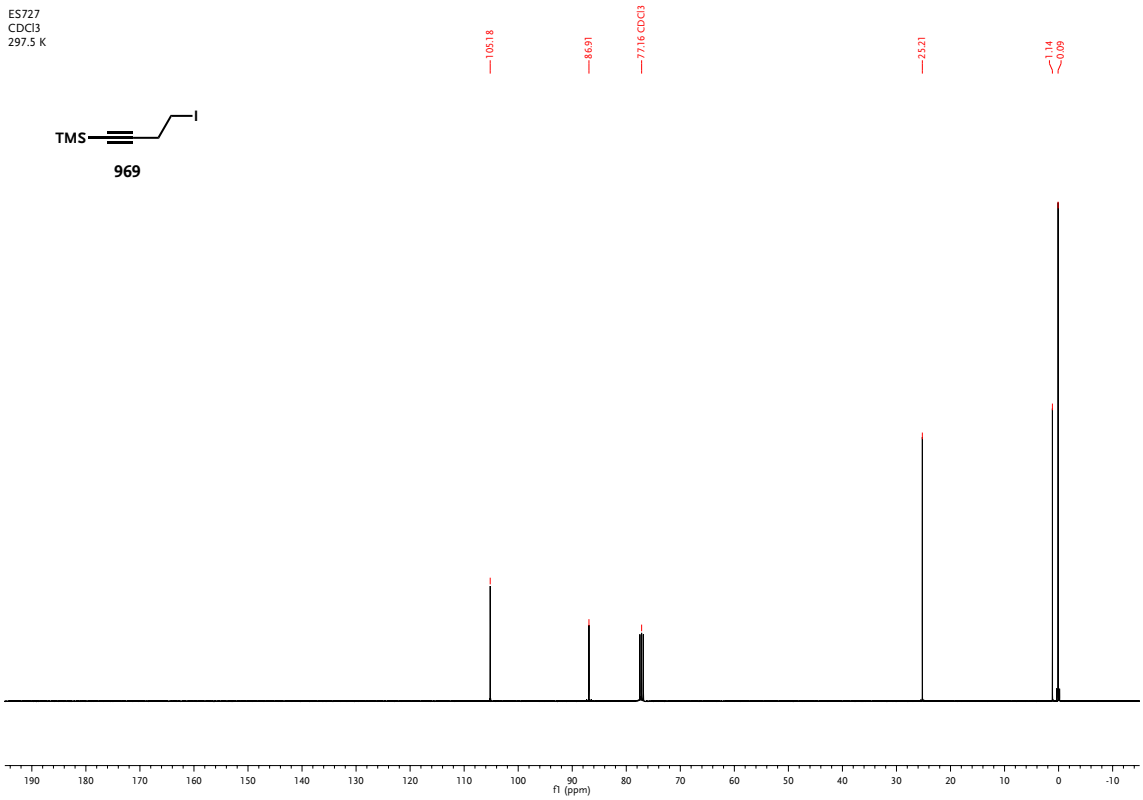
Spectrum B-233. ^{1}H-NMR spectrum for compound **968** *(experimental on page 307)*.



Spectrum B-234. ^{13}C-NMR spectrum for compound **968** *(experimental on page 307)*.

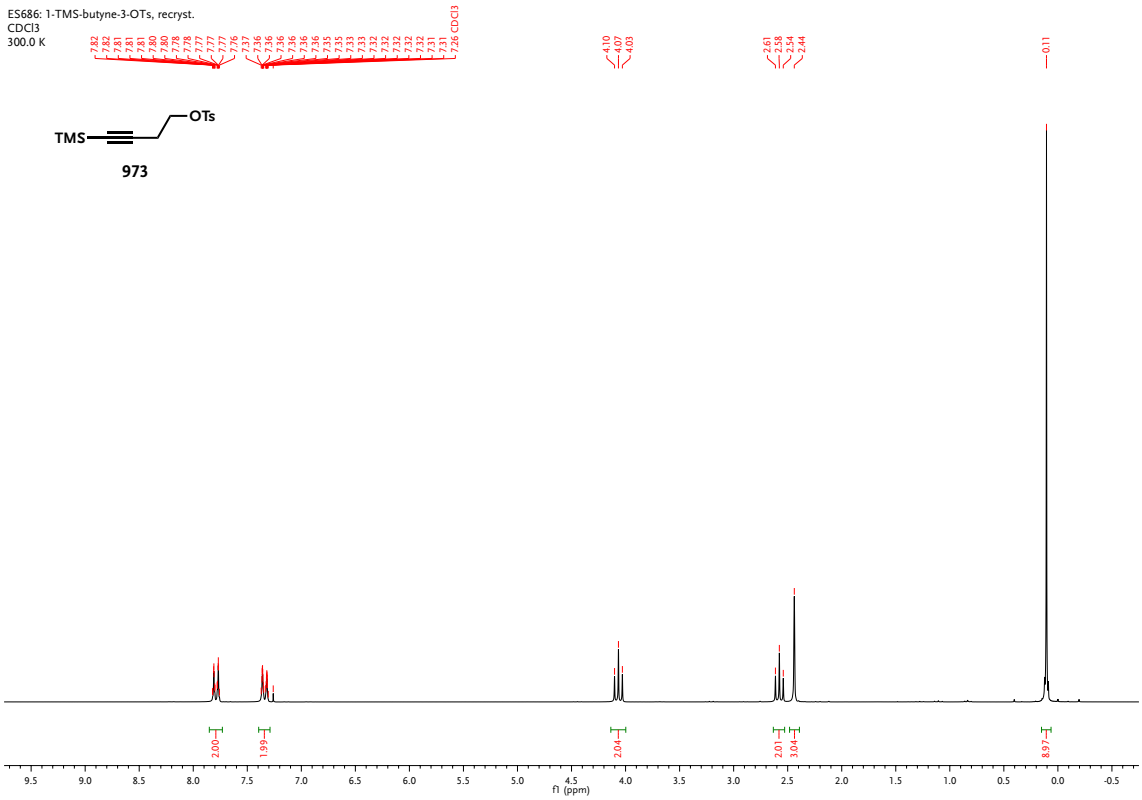


Spectrum B-235. ^{1}H-NMR spectrum for compound **969** *(experimental on page 308)*.

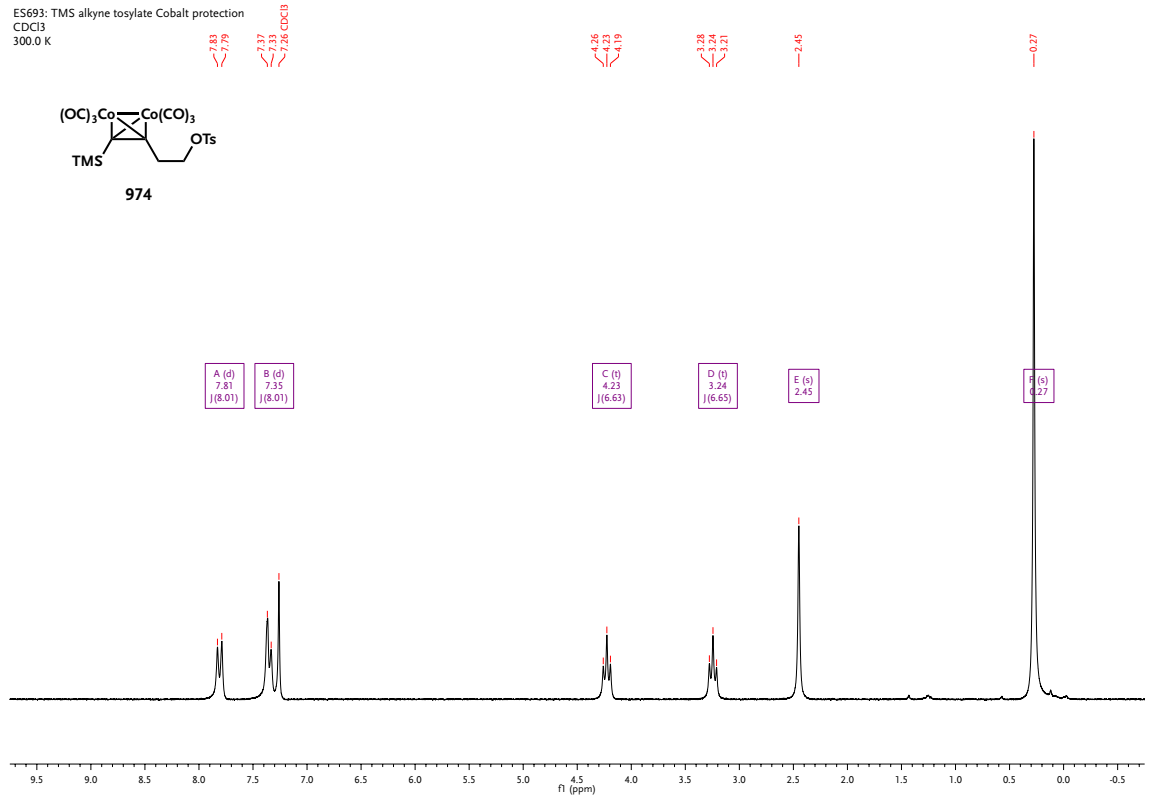


Spectrum B-236. ^{13}C-NMR spectrum for compound **969** *(experimental on page 308)*.

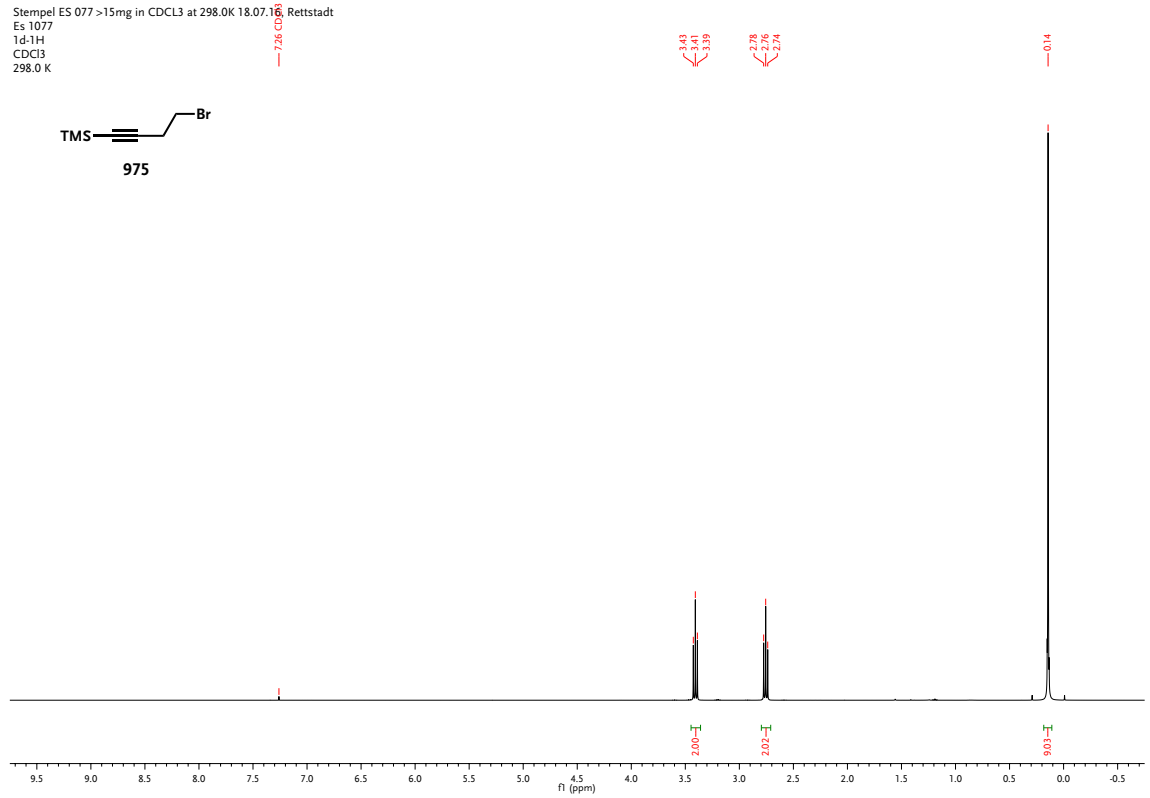
Spectrum B-237. ^{1}H-NMR spectrum for compound **970** *(experimental on page 308)*.



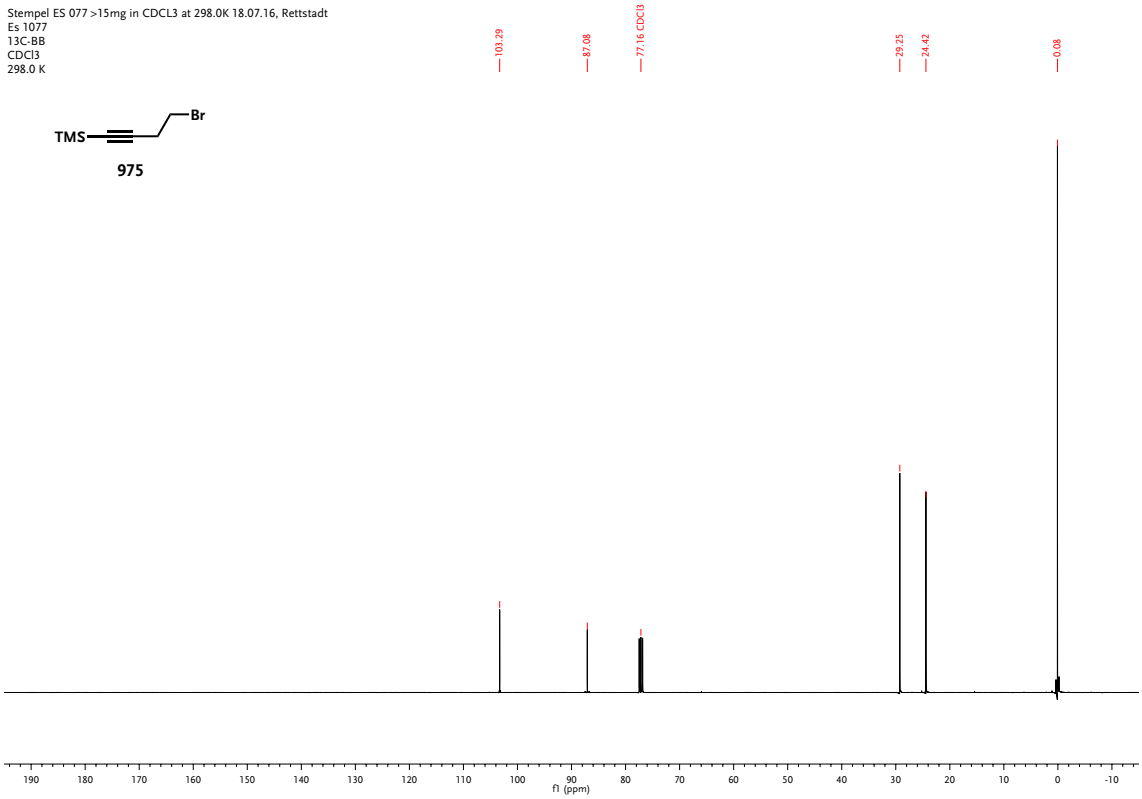
Spectrum B-238. ^{1}H-NMR spectrum for compound **973** *(experimental on page 309)*.



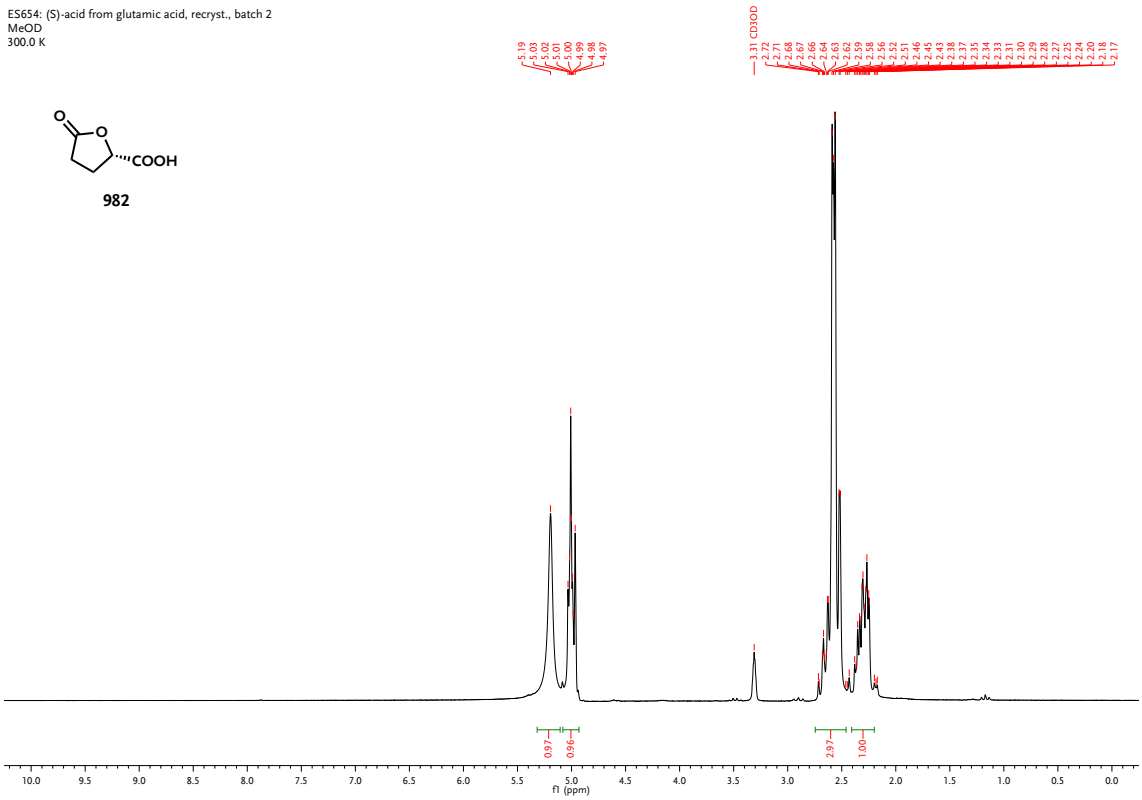
Spectrum B-239. ^{1}H-NMR spectrum for compound **974** *(experimental on page 309)*.



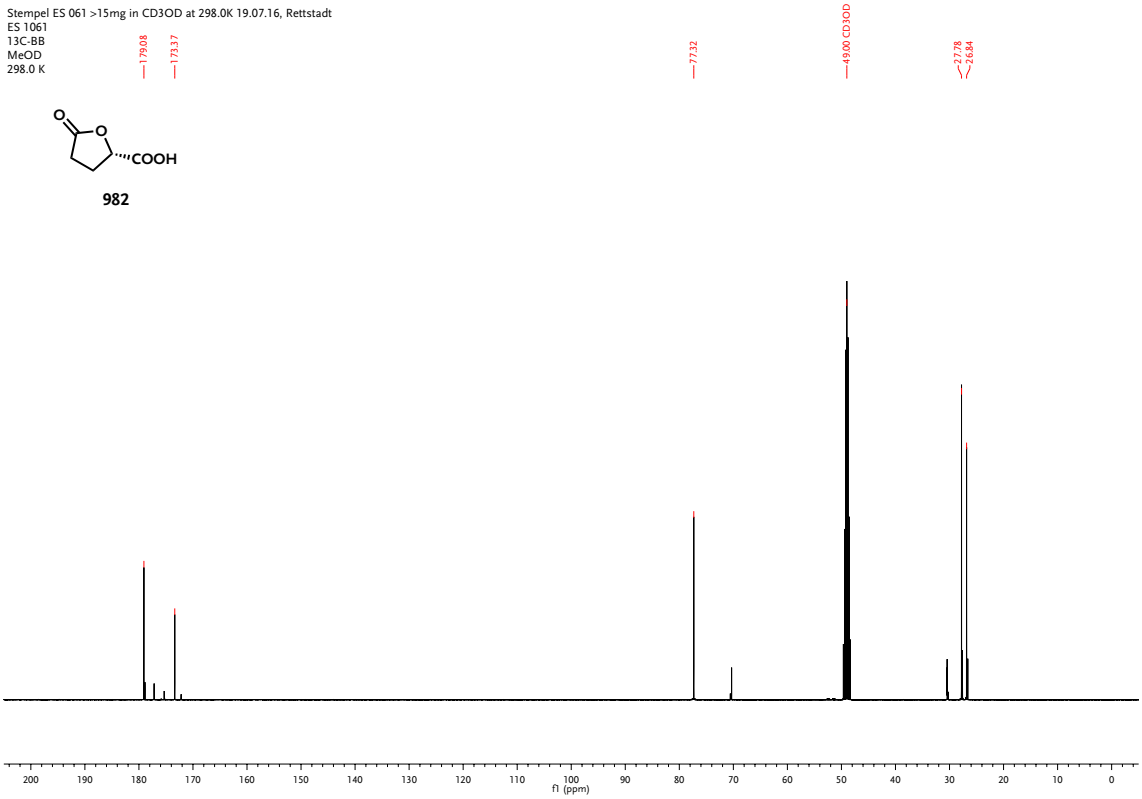
Spectrum B-240. ^{1}H-NMR spectrum for compound **975** *(experimental on page 310)*.



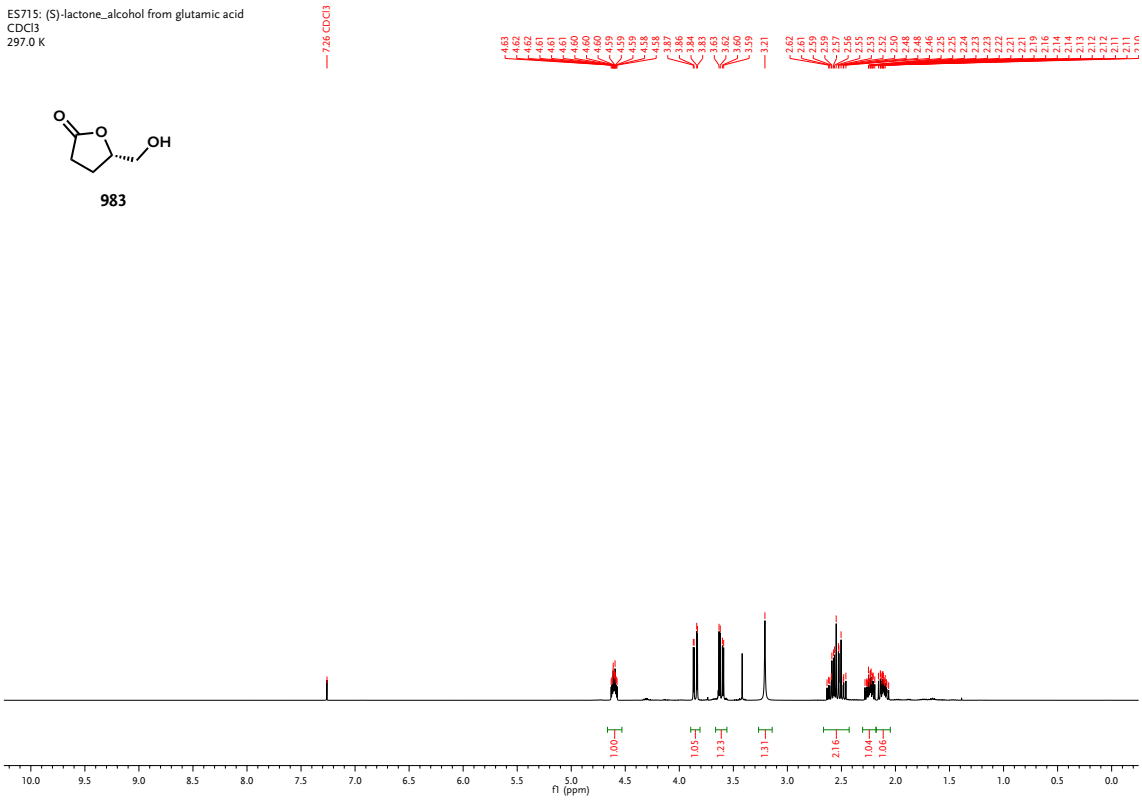
Spectrum B-241. ^{13}C-NMR spectrum for compound **975** *(experimental on page 310)*.



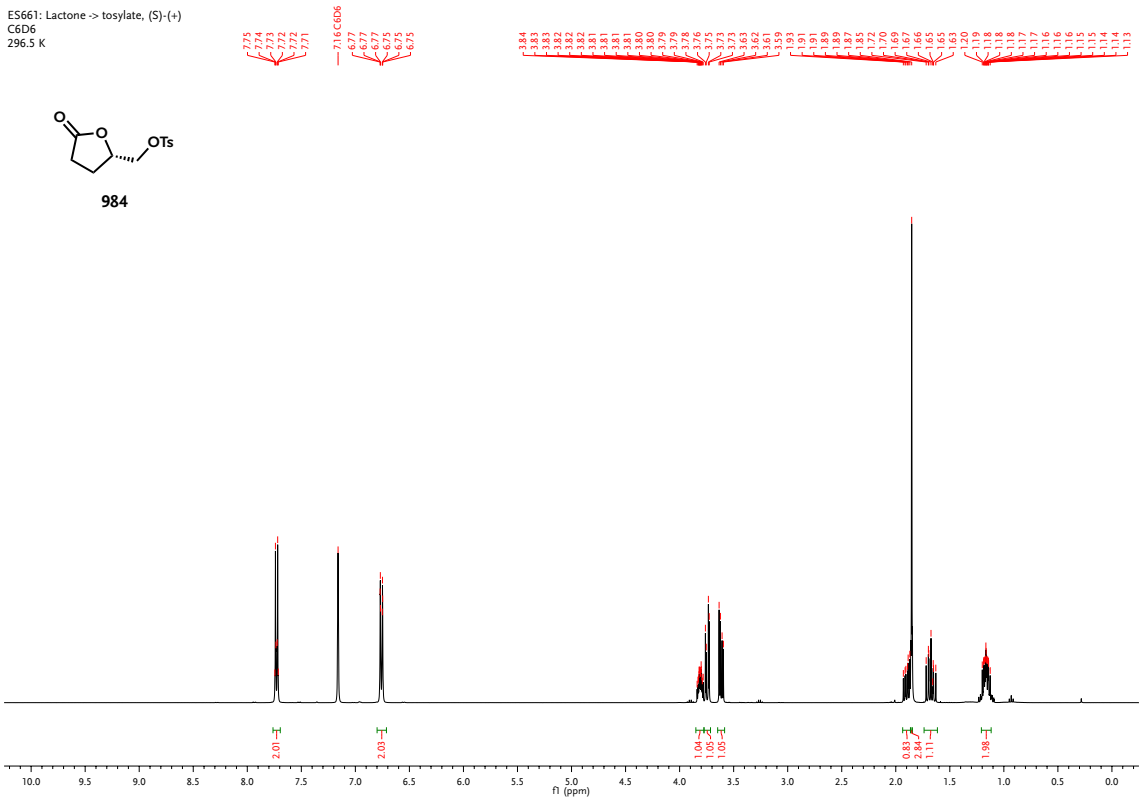
Spectrum B-242. ^{1}H-NMR spectrum for compound **982** *(experimental on page 310)*.



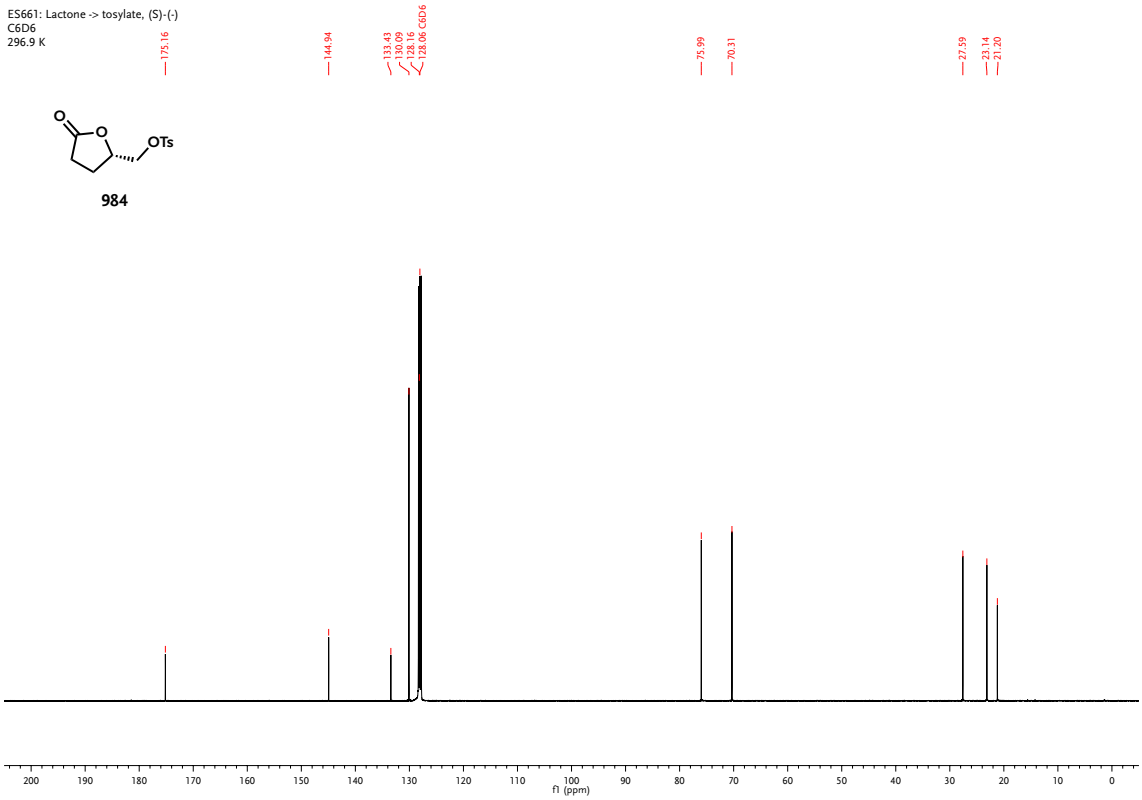
Spectrum B-243. ^{13}C-NMR spectrum for compound **982** *(experimental on page 310)*.



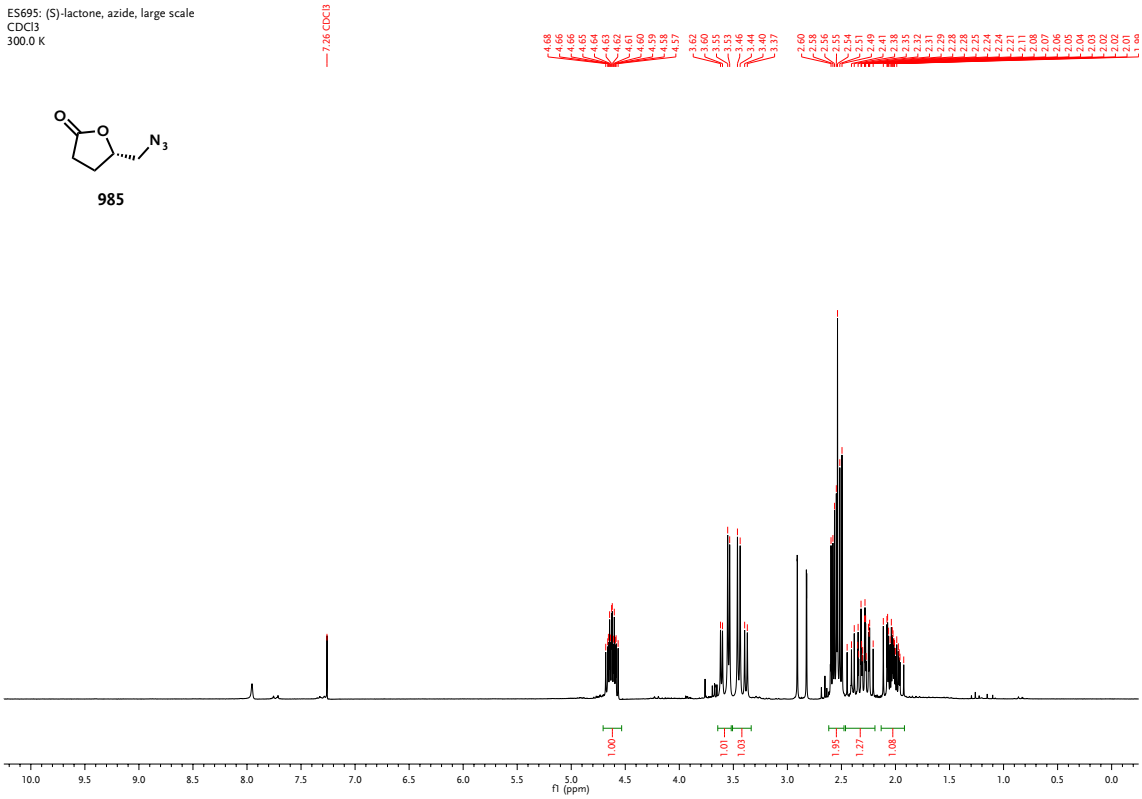
Spectrum B-244. ^{1}H-NMR spectrum for compound **983** *(experimental on page 311)*.



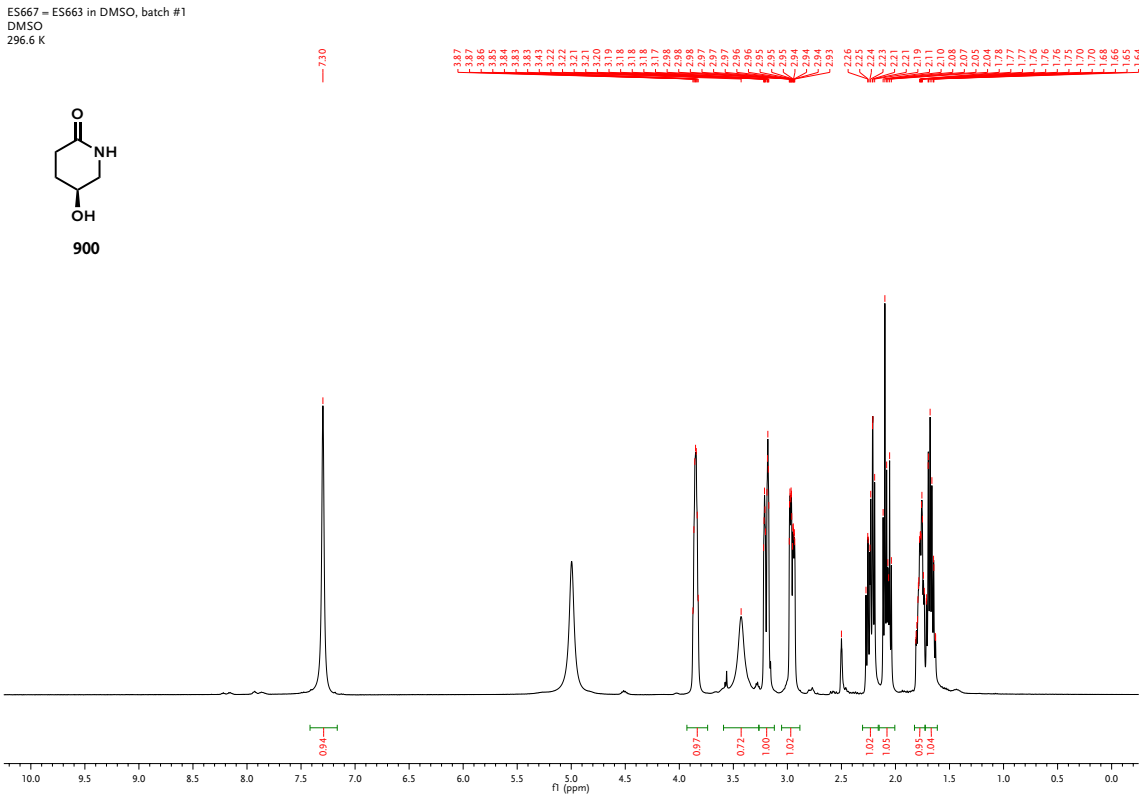
Spectrum B-245. ^{1}H-NMR spectrum for compound **984** *(experimental on page 311)*.



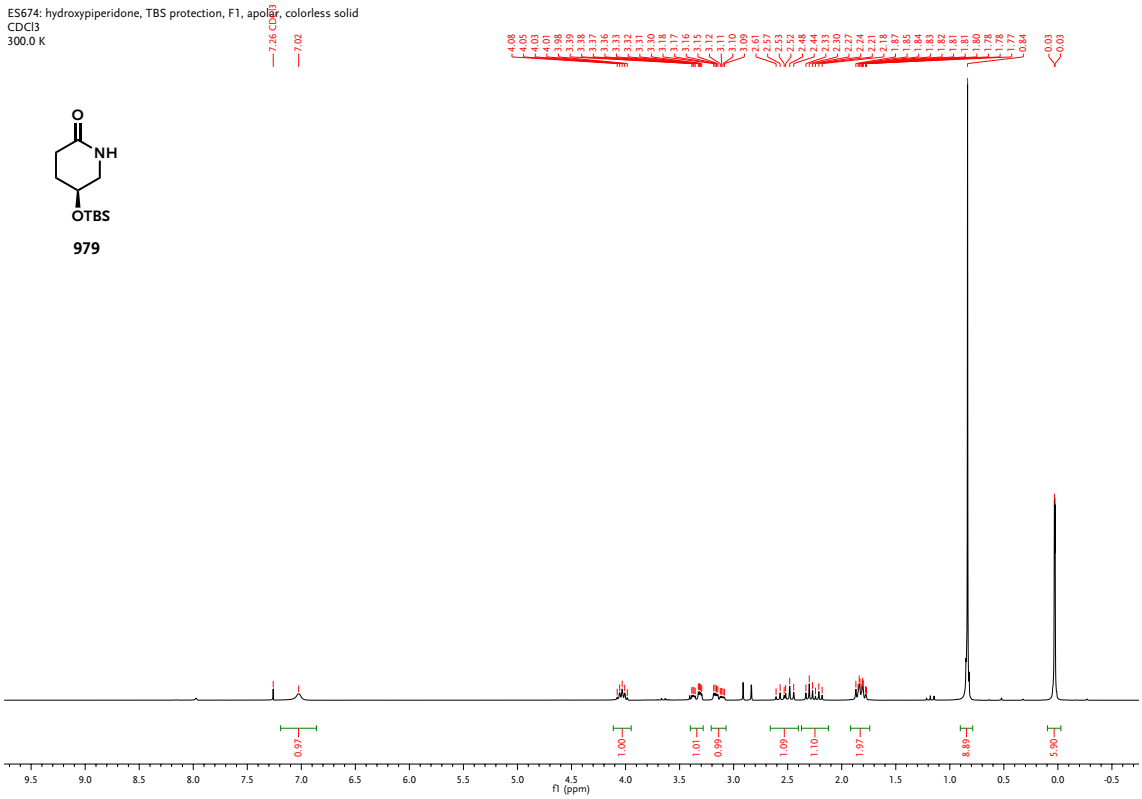
Spectrum B-246. ^{13}C-NMR spectrum for compound **984** *(experimental on page 311)*.



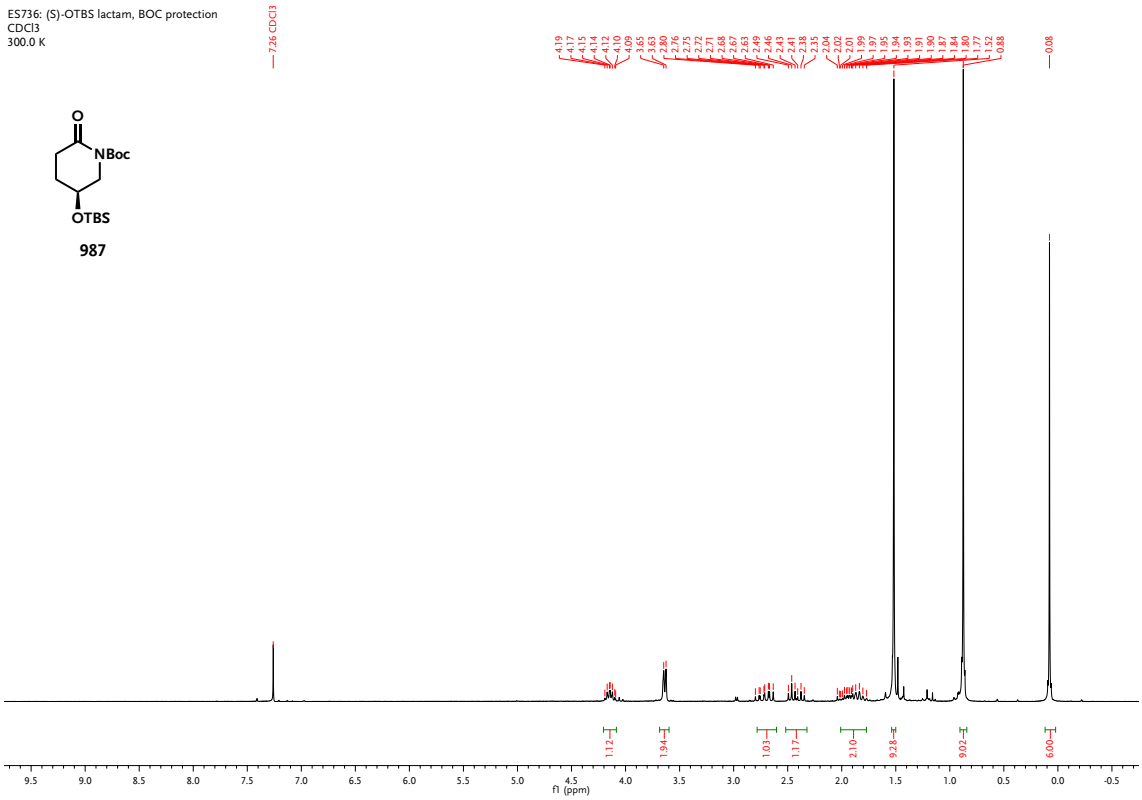
Spectrum B-247. ^{1}H-NMR spectrum for compound **985** *(experimental on page 311)*.



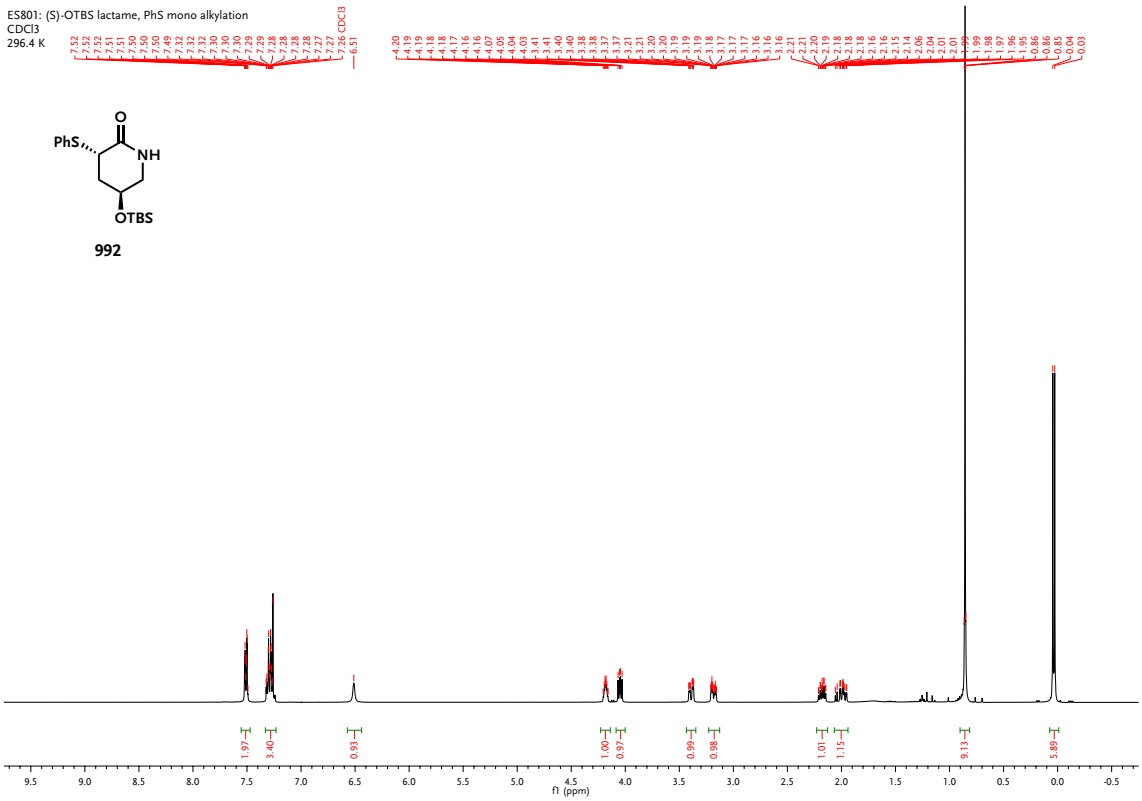
Spectrum B-248. ^{1}H-NMR spectrum for compound **900** *(experimental on page 312)*.



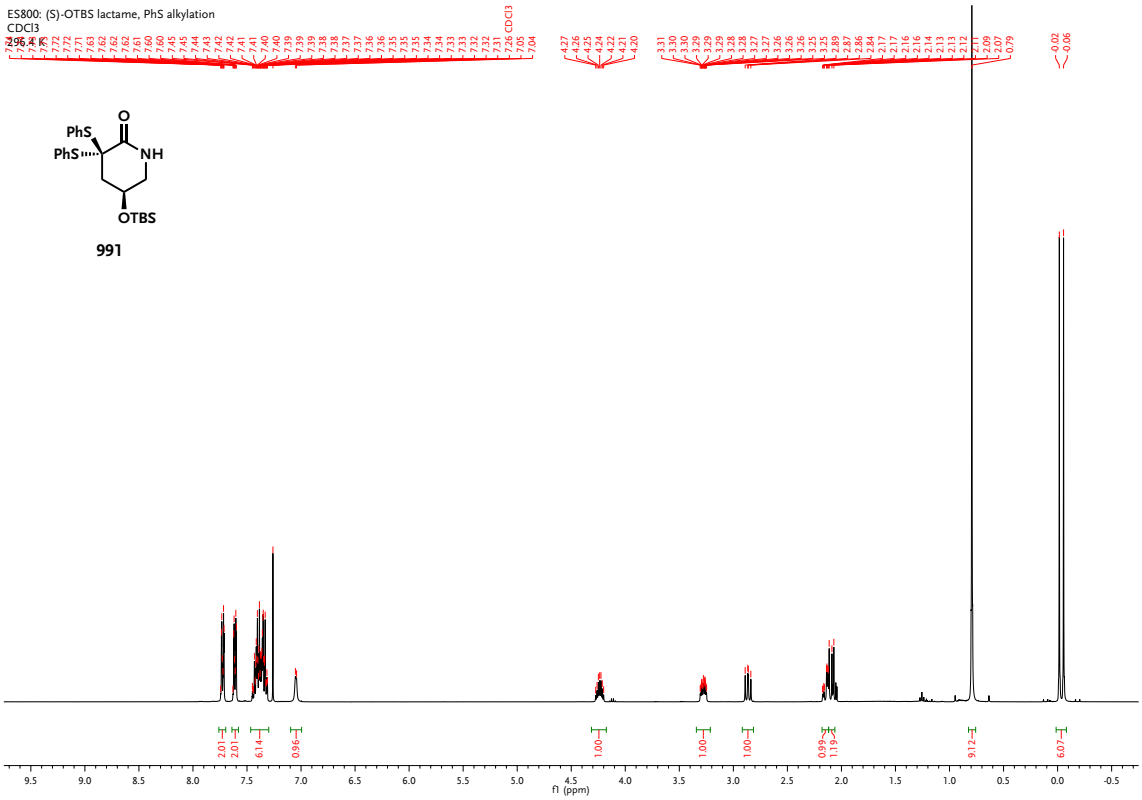
Spectrum B-249. ^{1}H-NMR spectrum for compound **979** *(experimental on page 312)*.



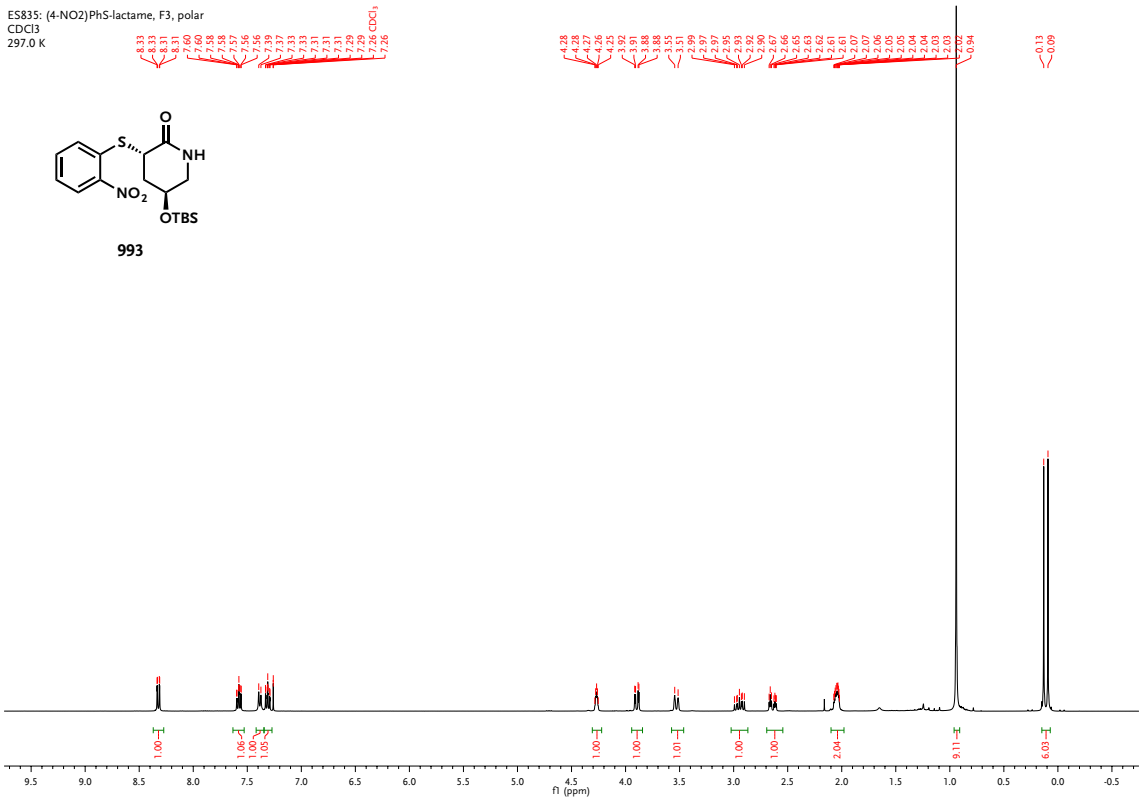
Spectrum B-250. ^{1}H-NMR spectrum for compound **987** *(experimental on page 312)*.



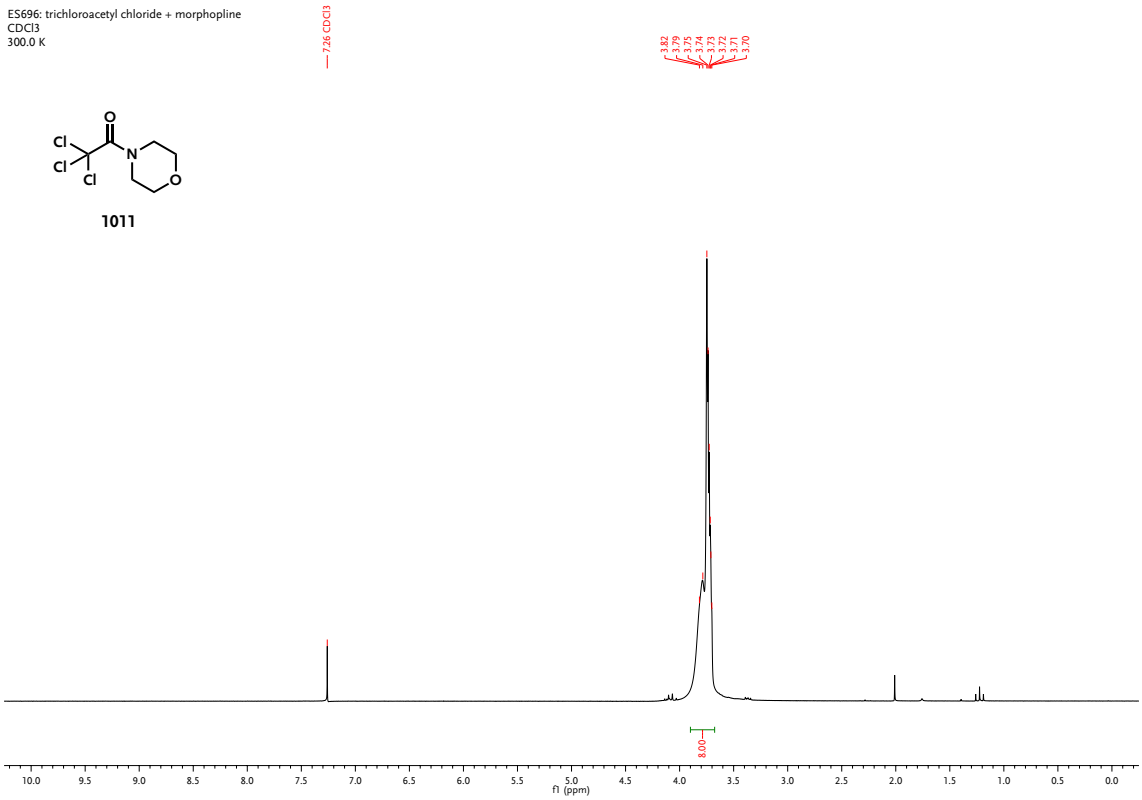
Spectrum B-251. ^{1}H-NMR spectrum for compound **992** *(experimental on page 313)*.



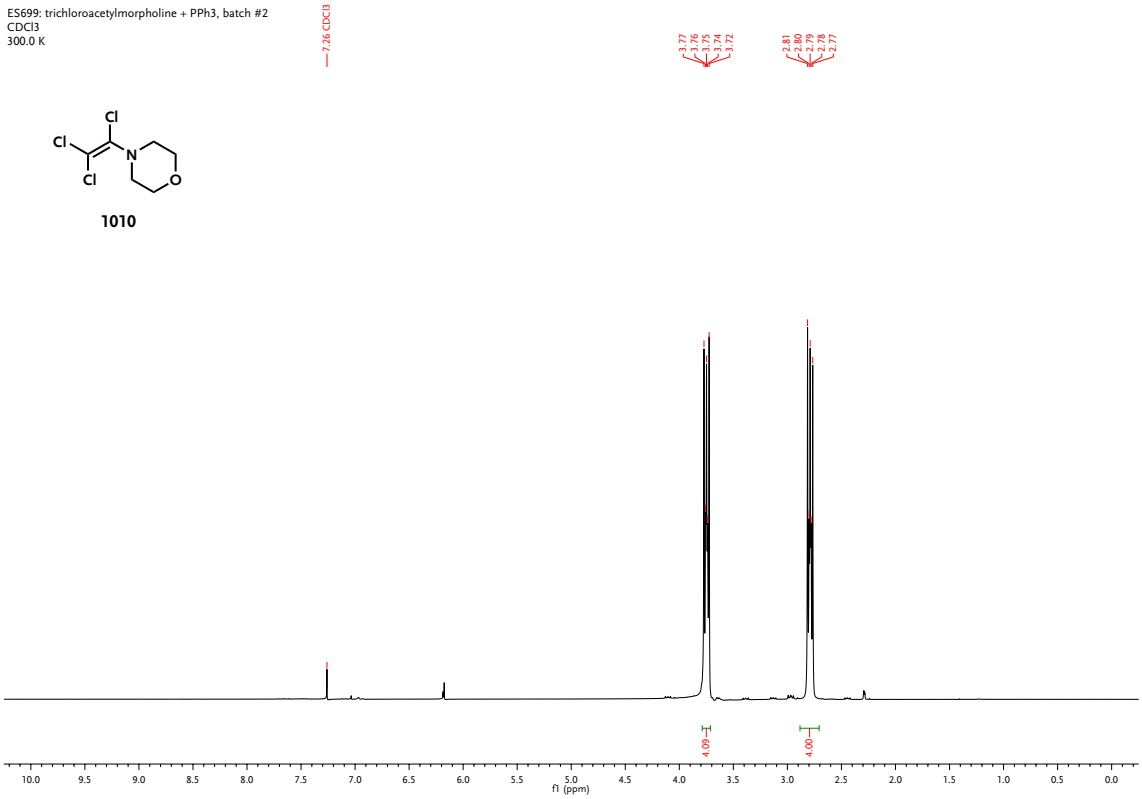
Spectrum B-252. ^{1}H-NMR spectrum for compound **991** *(experimental on page 314)*.



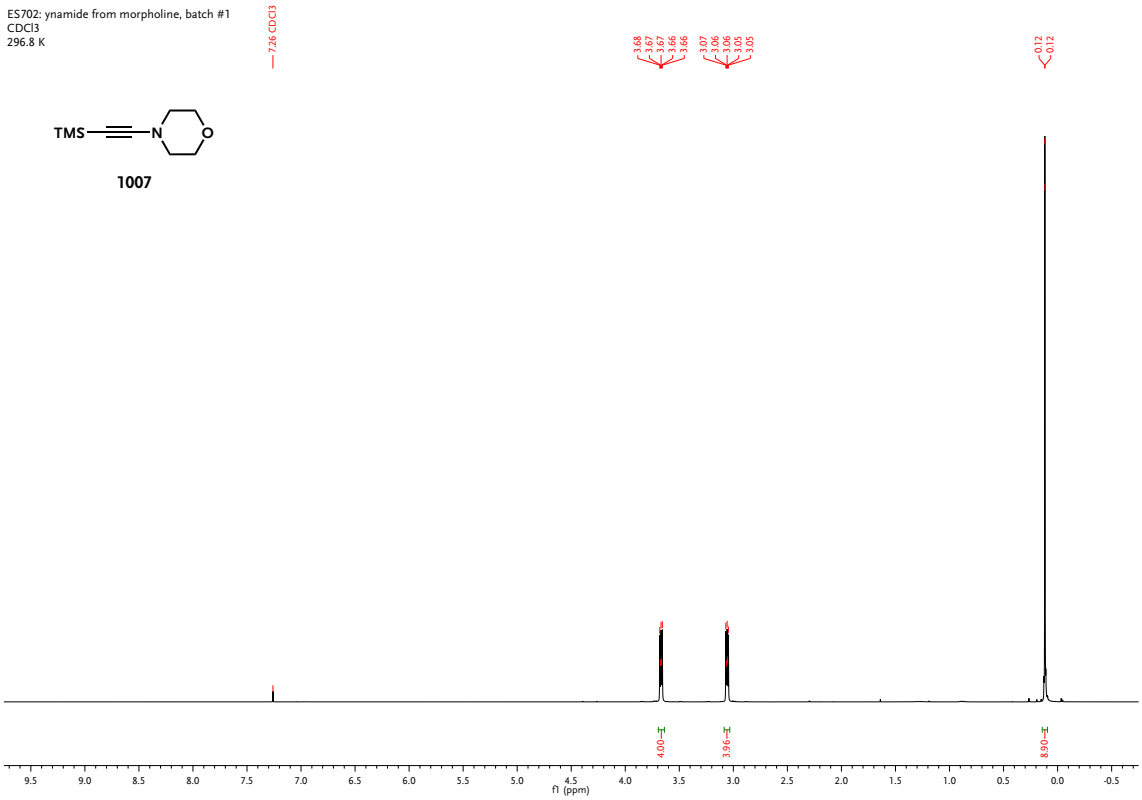
Spectrum B-253. ^{1}H-NMR spectrum for compound **993** *(experimental on page 314)*.



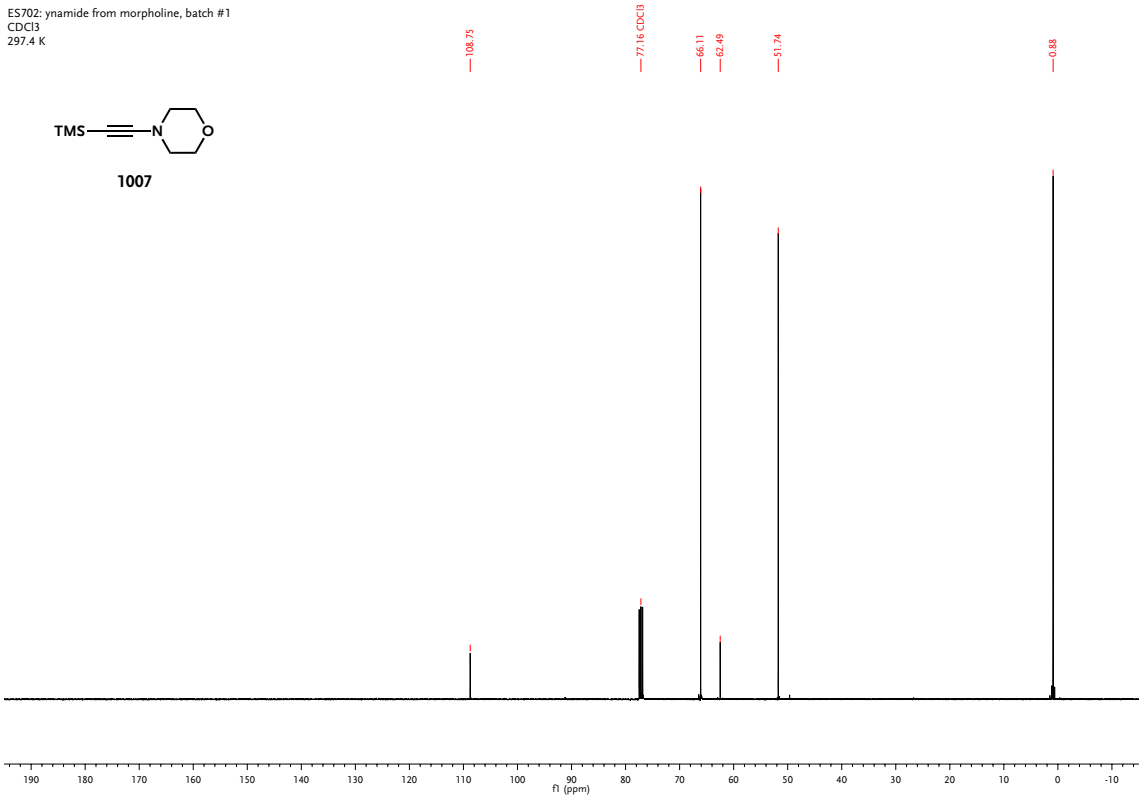
Spectrum B-254. ^{1}H-NMR spectrum for compound **1011** *(experimental on page 315)*.



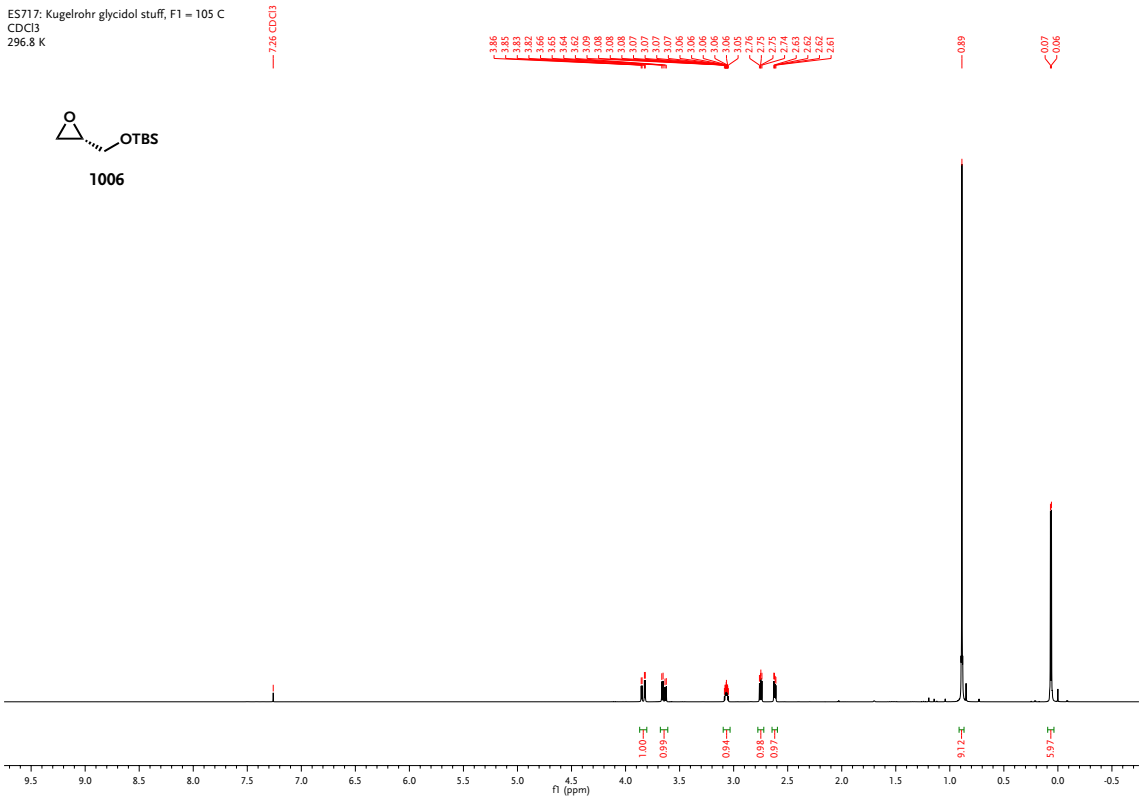
Spectrum B-255. [1]H-NMR spectrum for compound **1010** *(experimental on page 315)*.



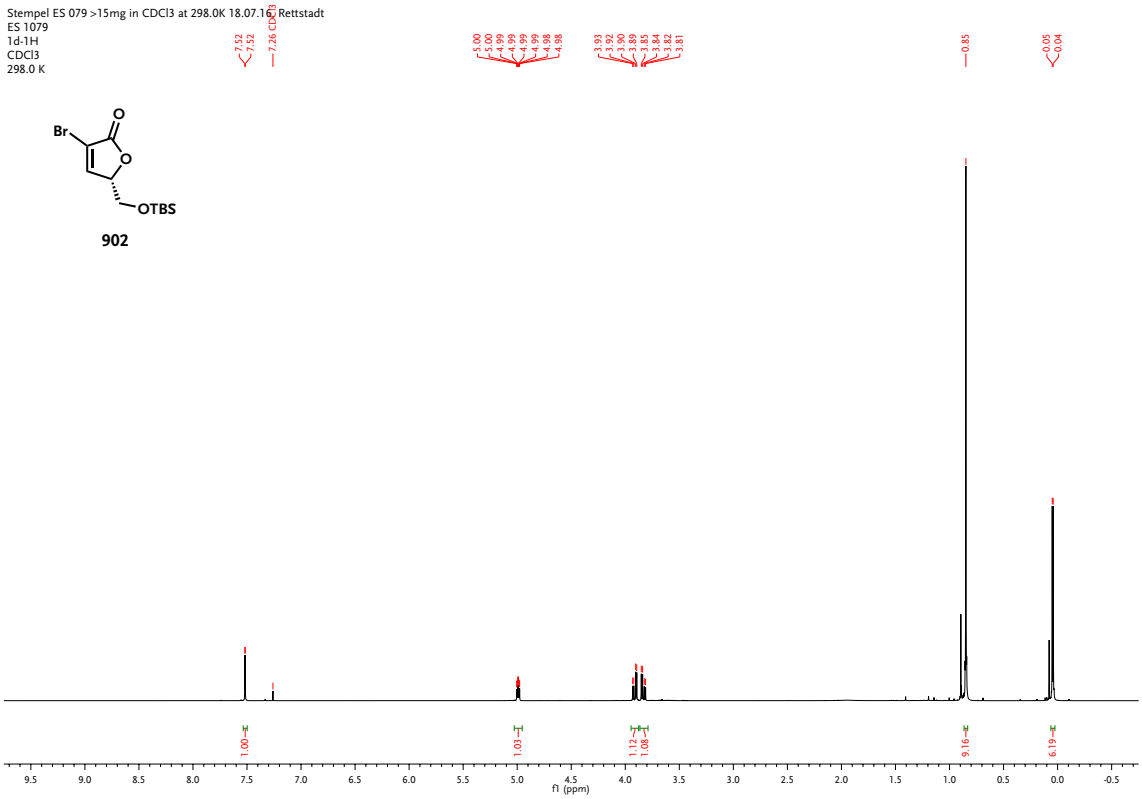
Spectrum B-256. [1]H-NMR spectrum for compound **1007** *(experimental on page 315)*.



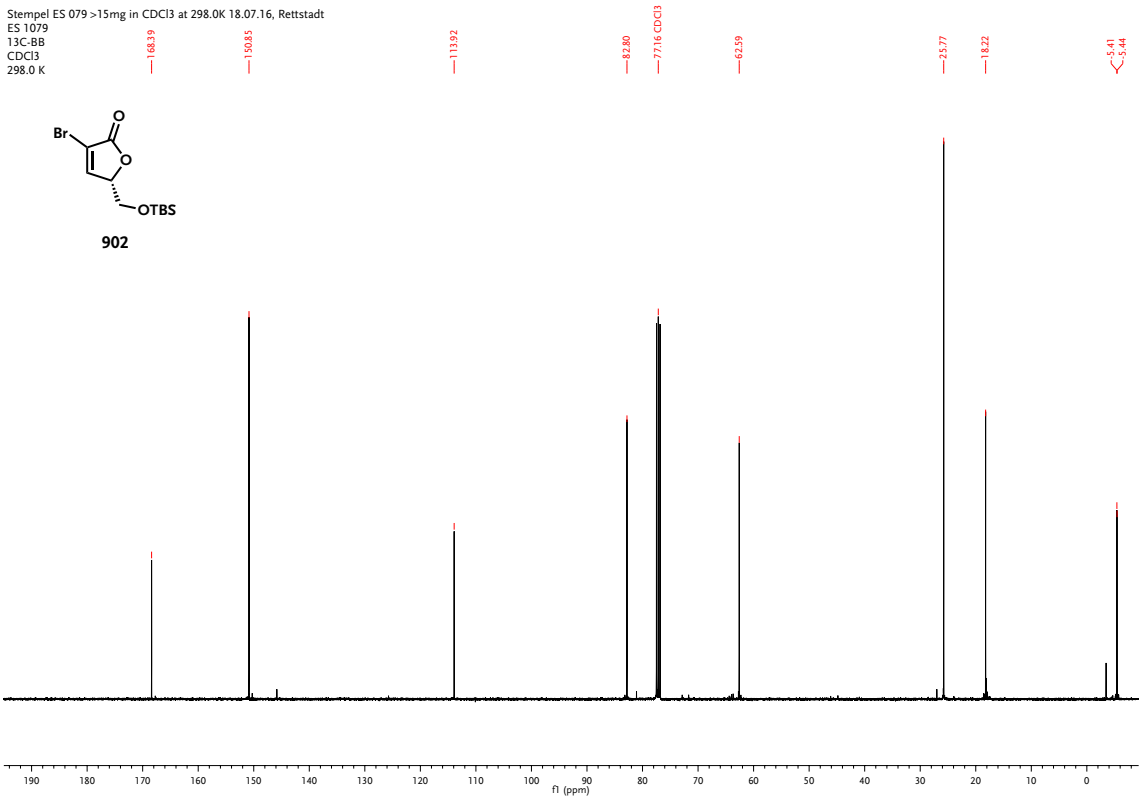
Spectrum B-257. ^{13}C-NMR spectrum for compound **1007** *(experimental on page 315)*.



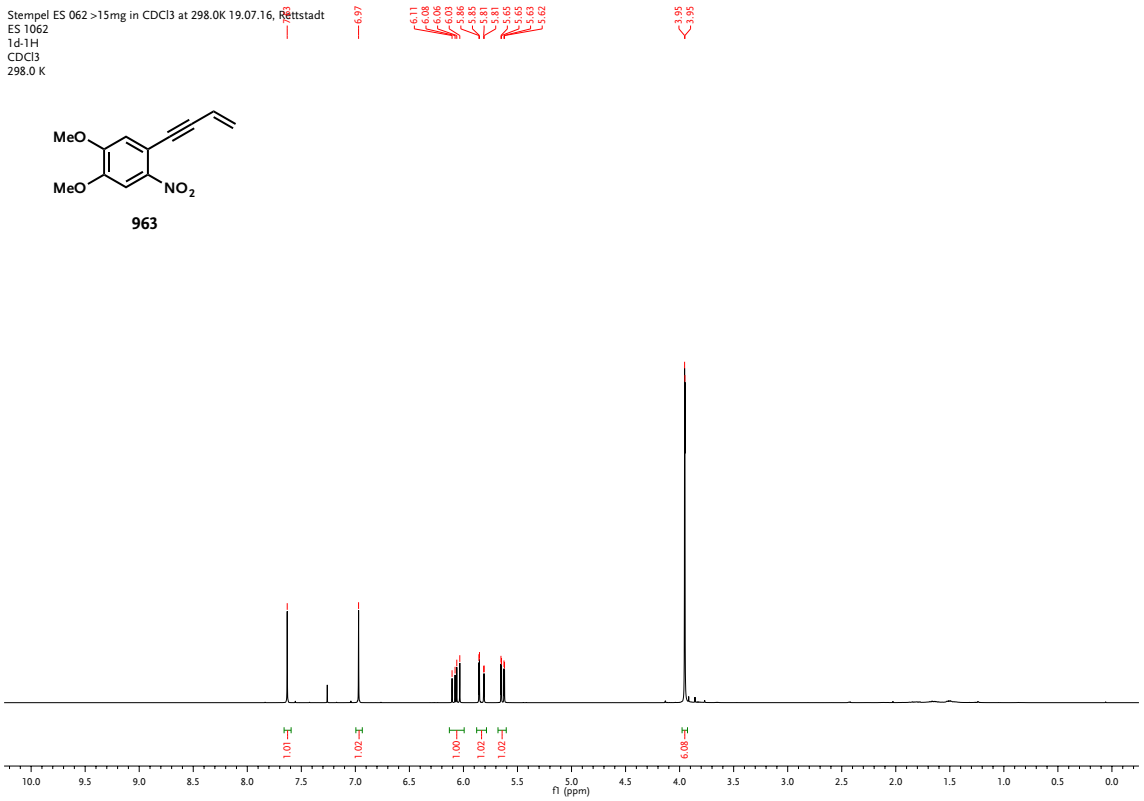
Spectrum B-258. ^{1}H-NMR spectrum for compound **1006** *(experimental on page 316)*.



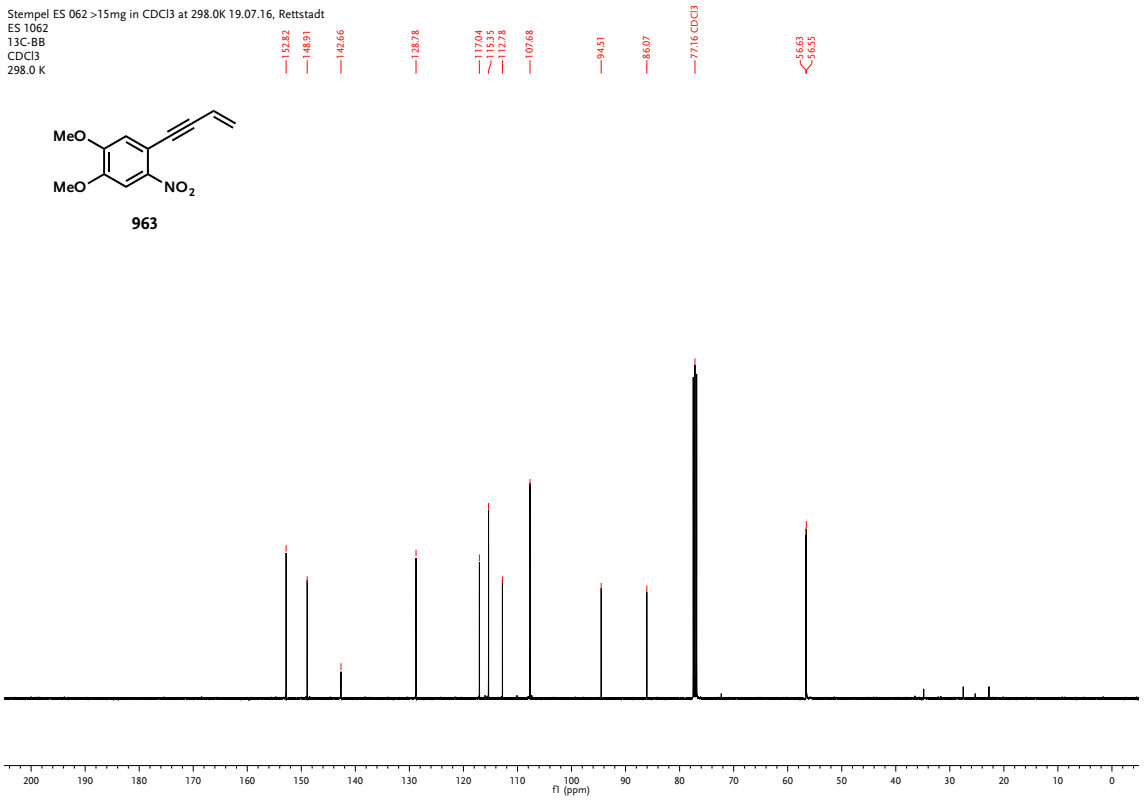
Spectrum B-259. [1]H-NMR spectrum for compound **902** *(experimental on page 316)*.



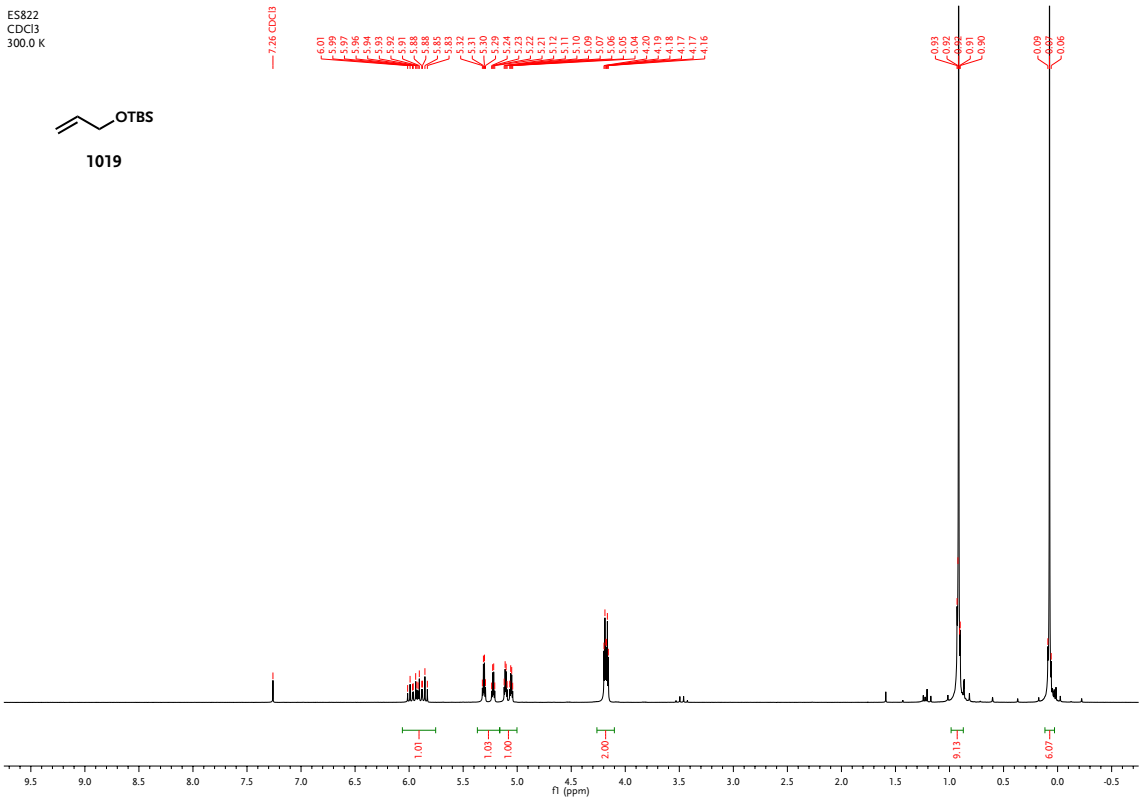
Spectrum B-260. [13]C-NMR spectrum for compound **902** *(experimental on page 316)*.



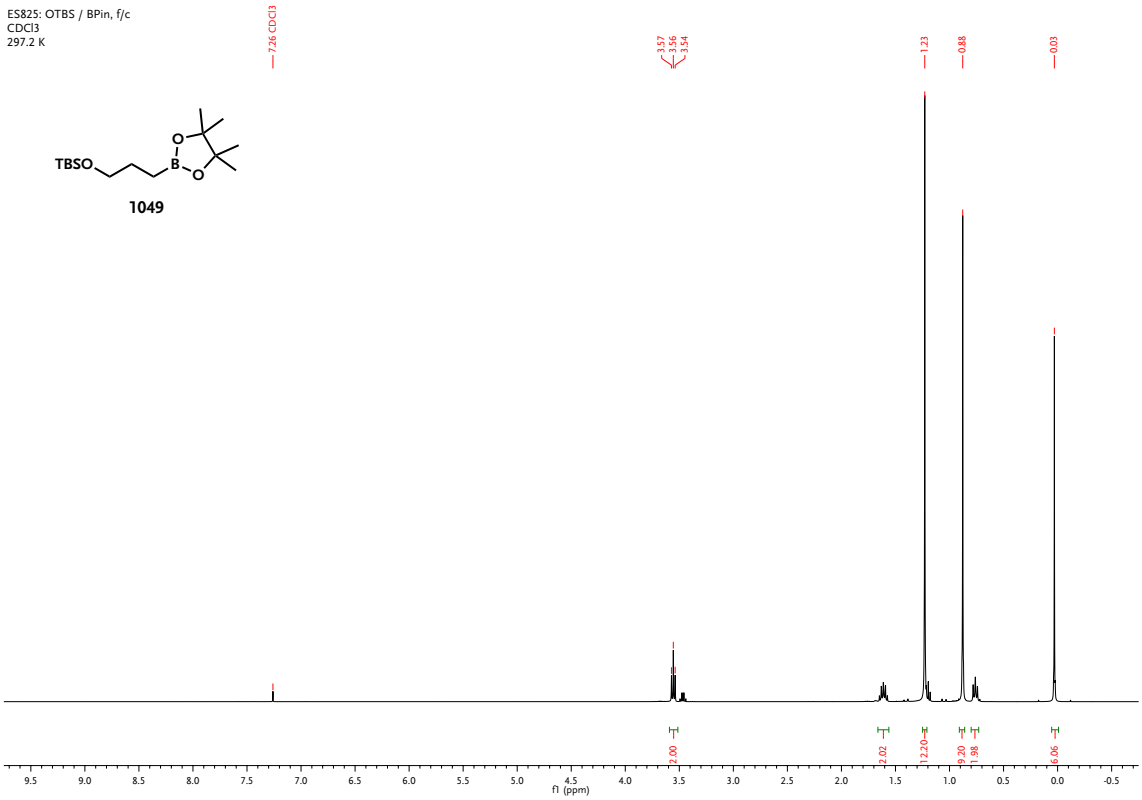
Spectrum B-261. [1]H-NMR spectrum for compound **963** *(experimental on page 317)*.



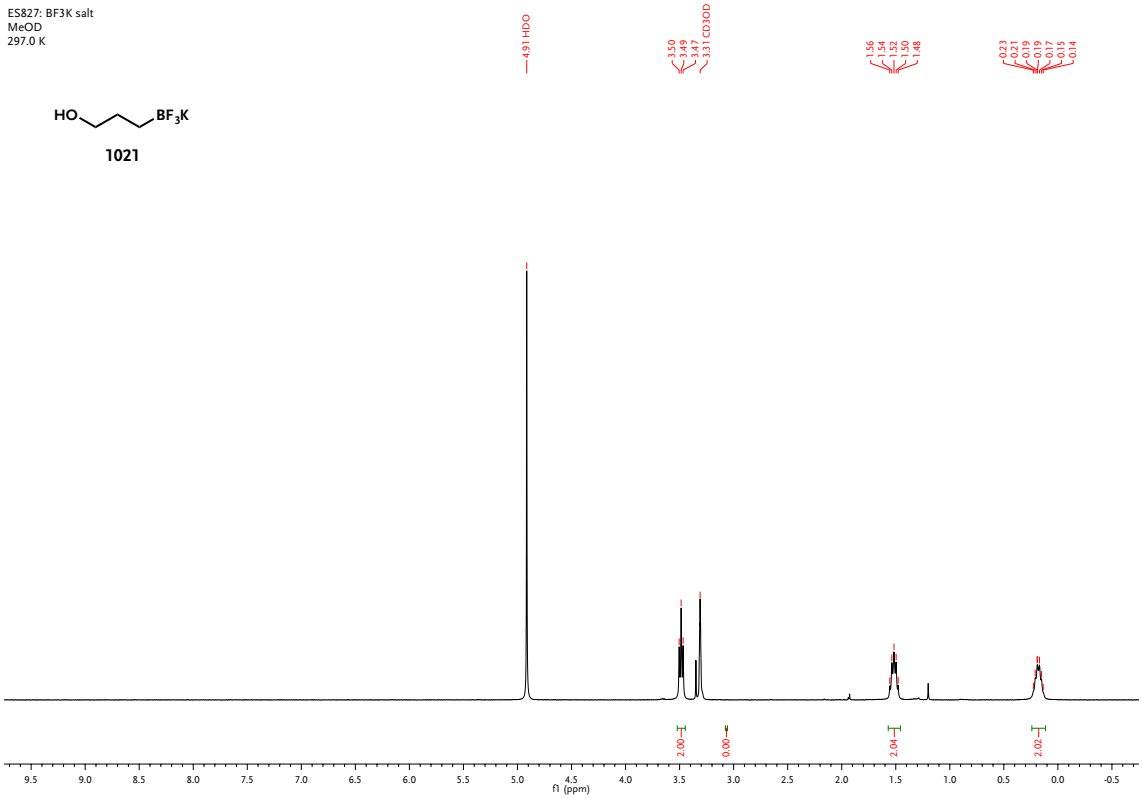
Spectrum B-262. [13]C-NMR spectrum for compound **963** *(experimental on page 317)*.



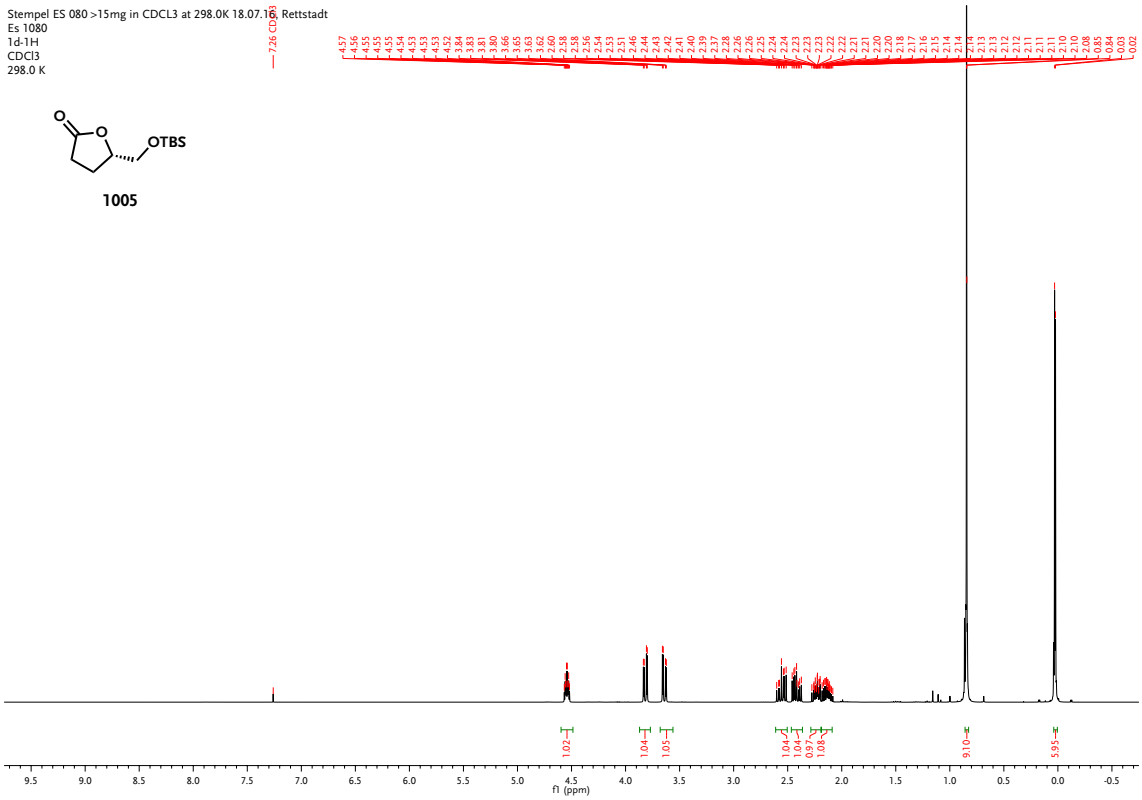
Spectrum B-263. ^{1}H-NMR spectrum for compound **1019** *(experimental on page 317)*.



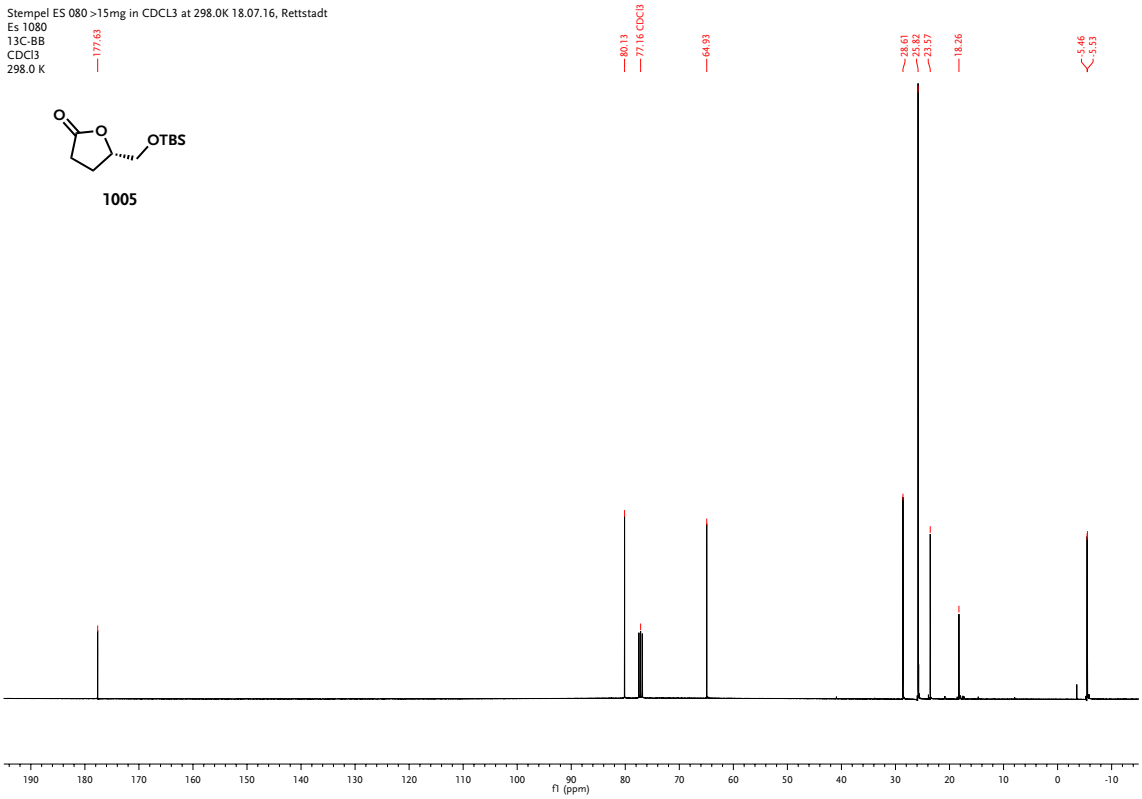
Spectrum B-264. ^{1}H-NMR spectrum for compound **1049** *(experimental on page 318)*.



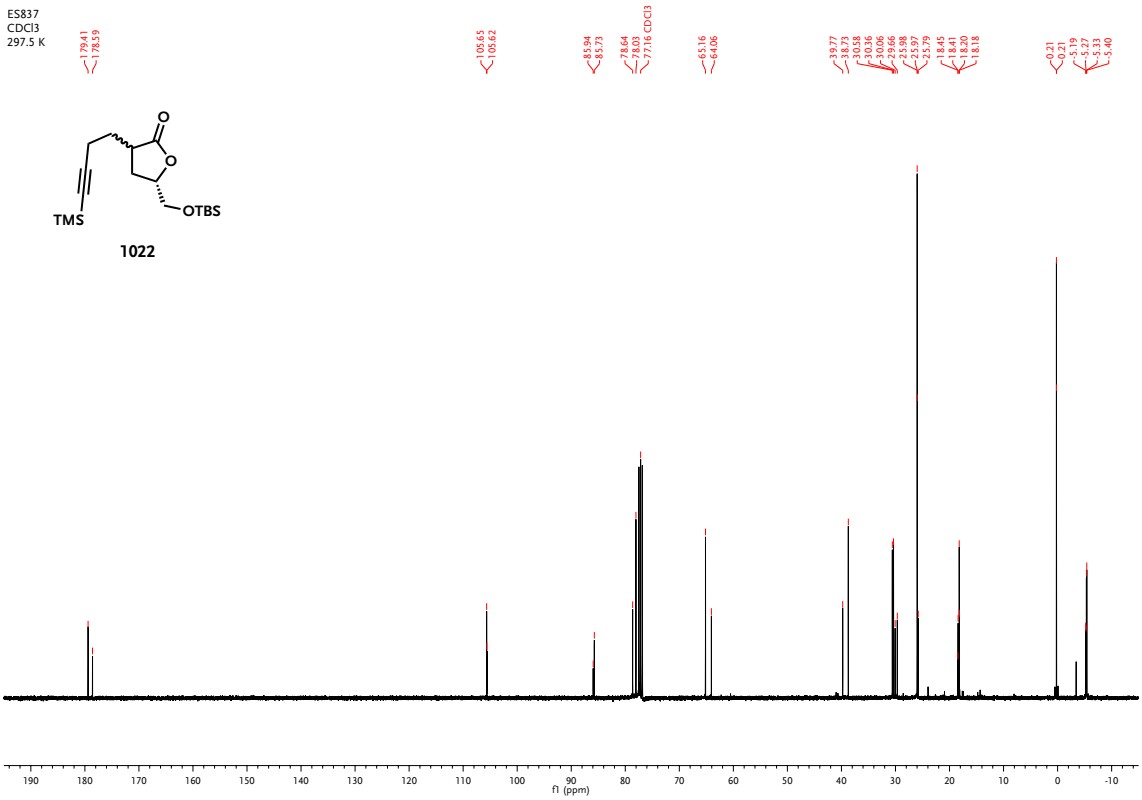
Spectrum B-265. ^{1}H-NMR spectrum for compound **1021** *(experimental on page 318)*.



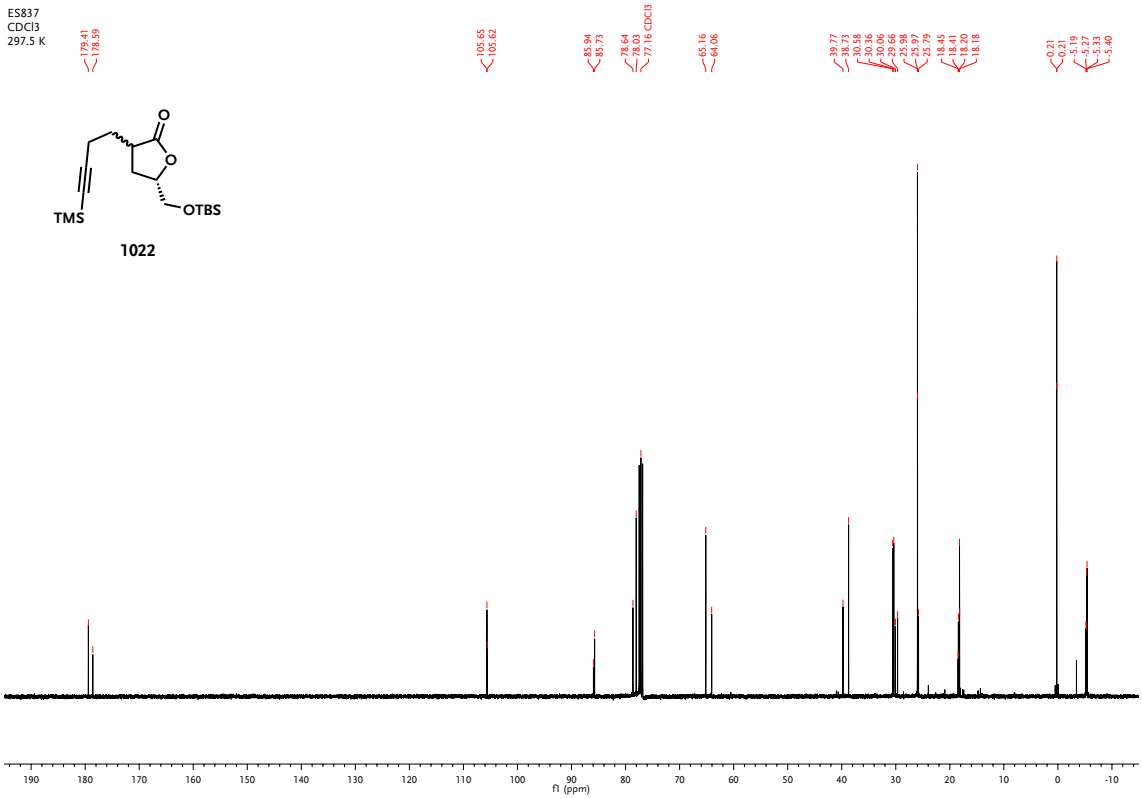
Spectrum B-266. ^{1}H-NMR spectrum for compound **1005** *(experimental on page 319)*.



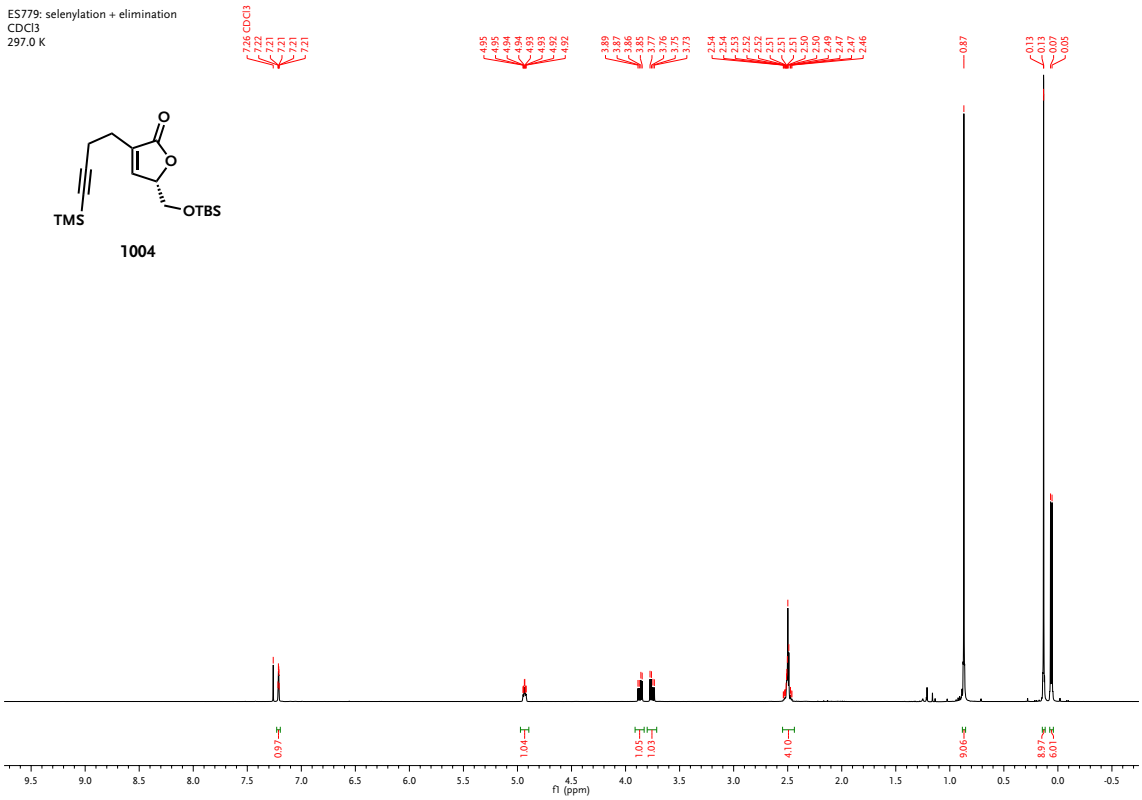
Spectrum B-267. ^{13}C-NMR spectrum for compound **1005** *(experimental on page 319)*.



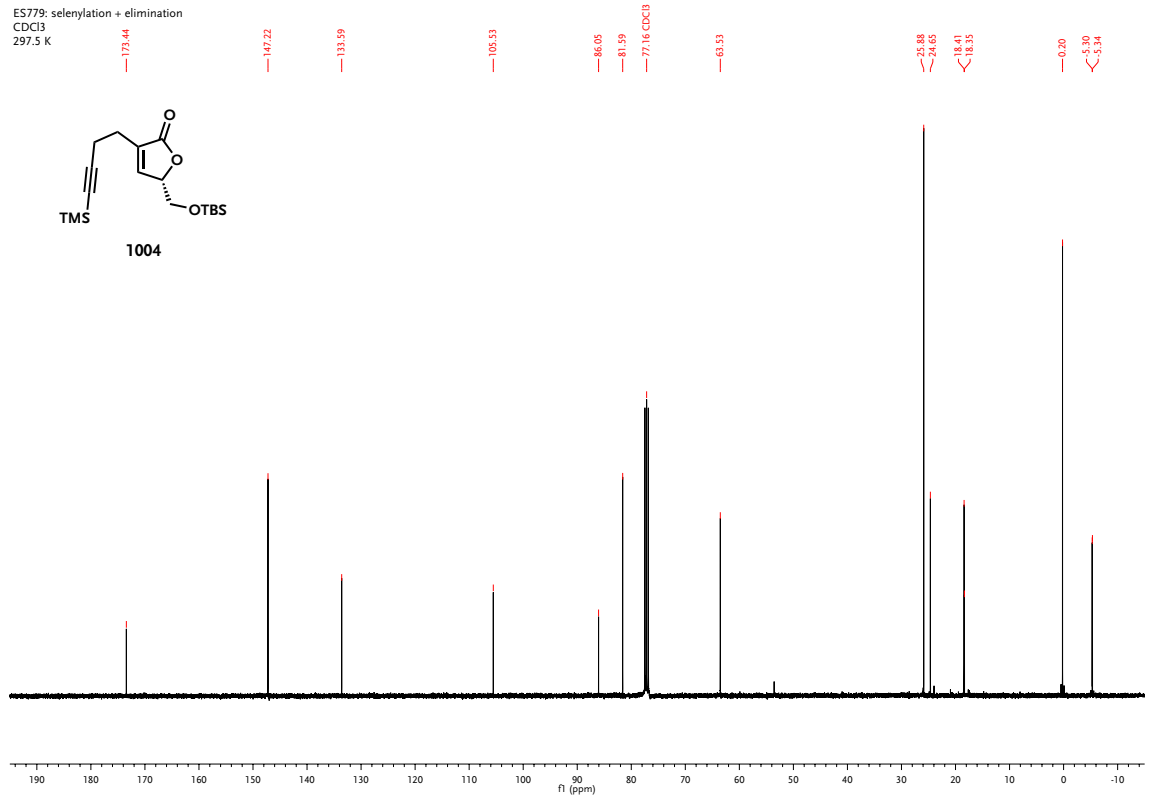
Spectrum B-268. ^{1}H-NMR spectrum for compound **1022** *(experimental on page 319)*.



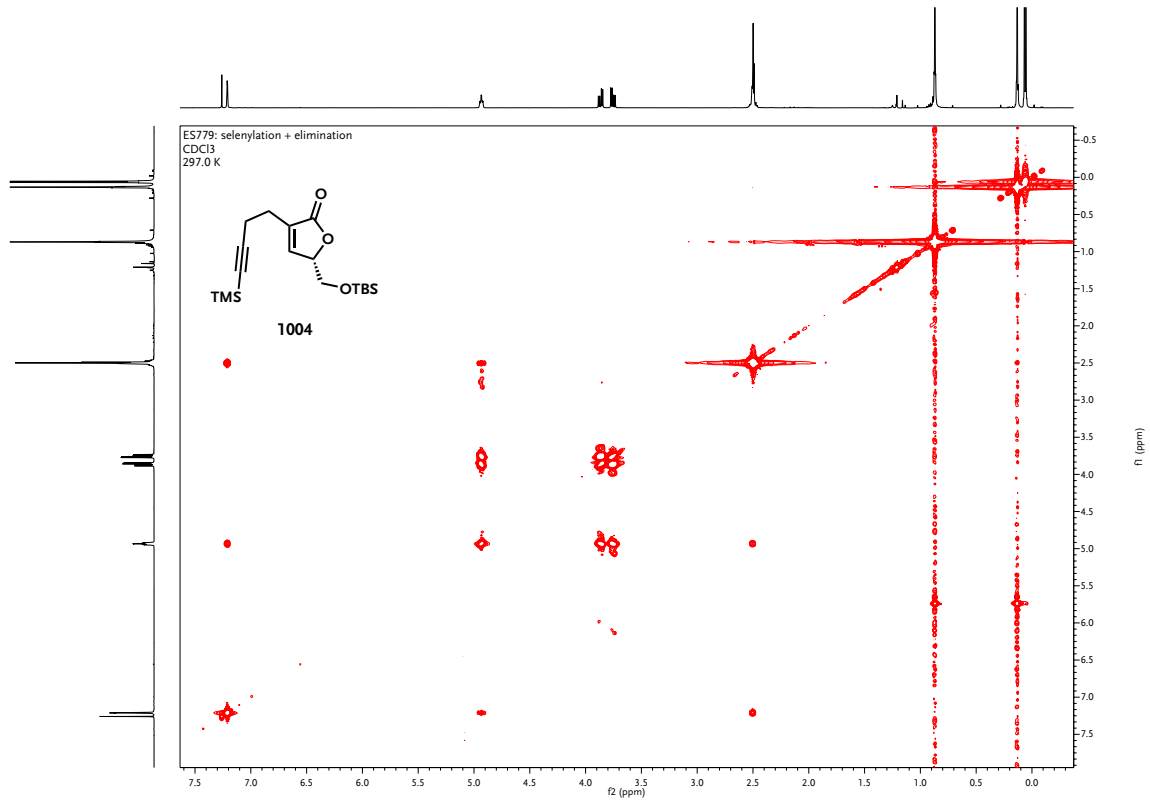
Spectrum B-269. ^{13}C-NMR spectrum for compound **1022** *(experimental on page 319)*.



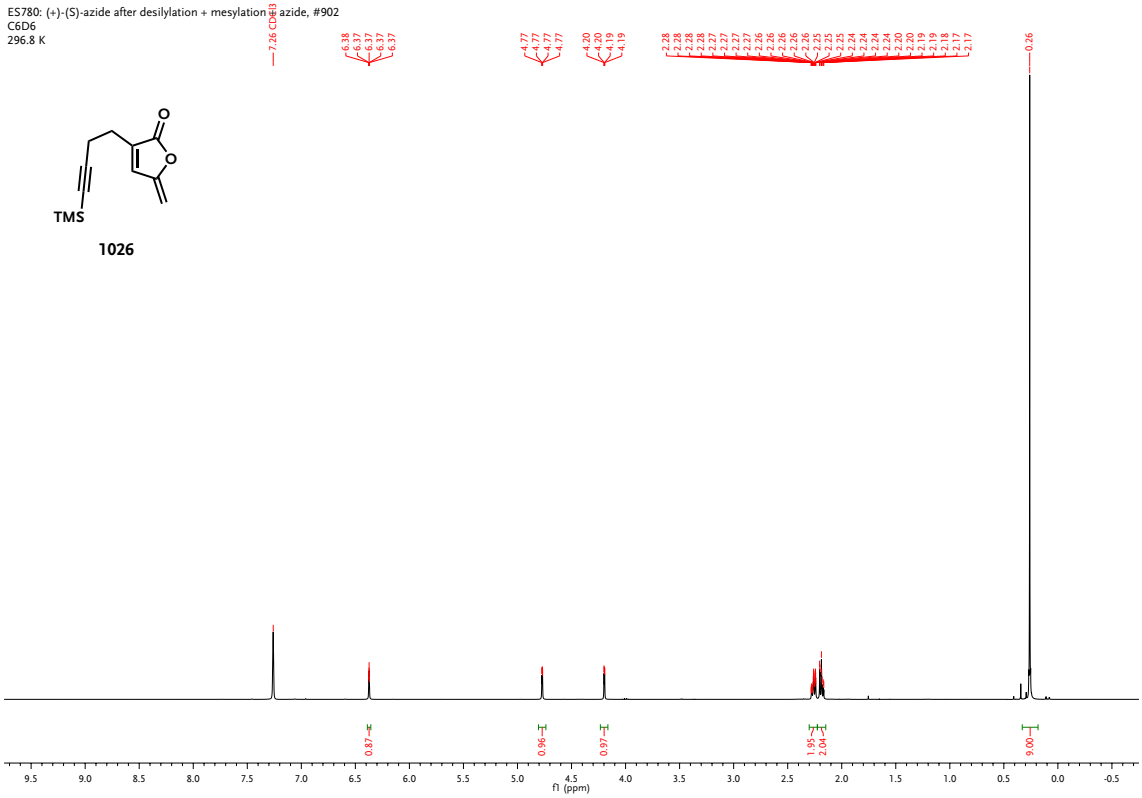
Spectrum B-270. ^{1}H-NMR spectrum for compound **1004** *(experimental on page 320)*.



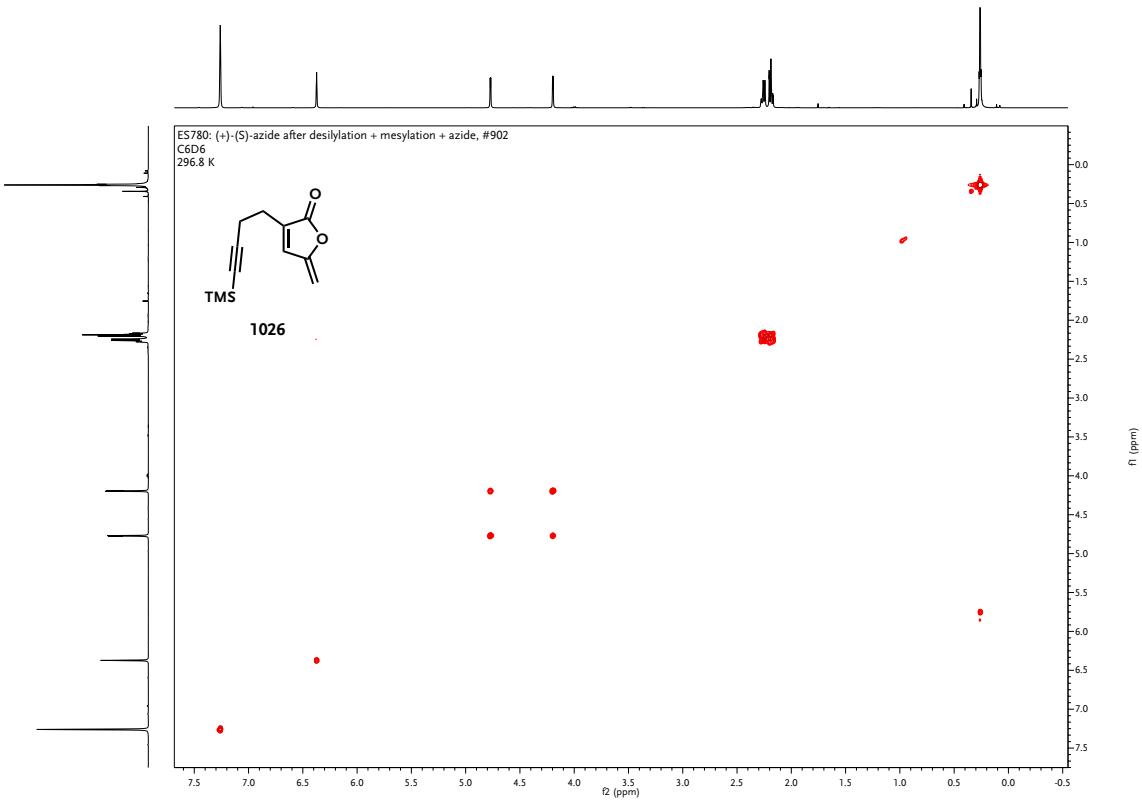
Spectrum B-271. ^{13}C-NMR spectrum for compound **1004** *(experimental on page 320)*.



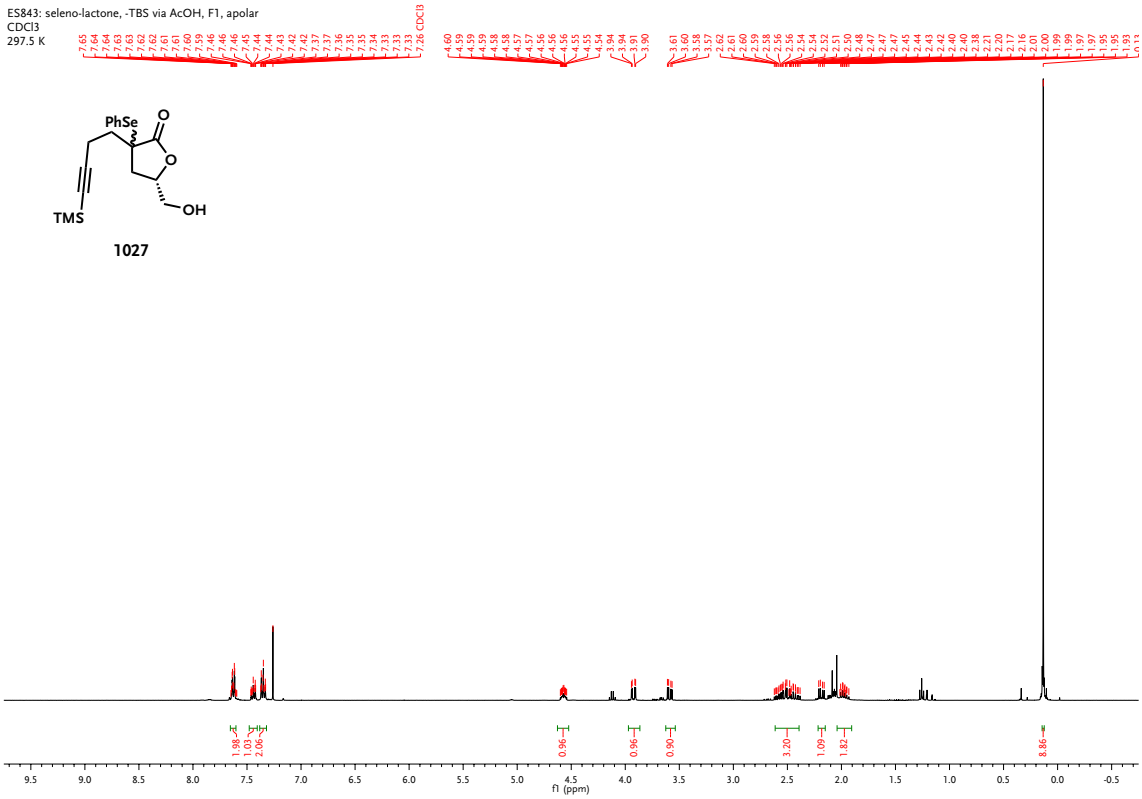
Spectrum B-272. COSY60 2D-NMR spectrum for compound **1004** *(experimental on page 320)*.



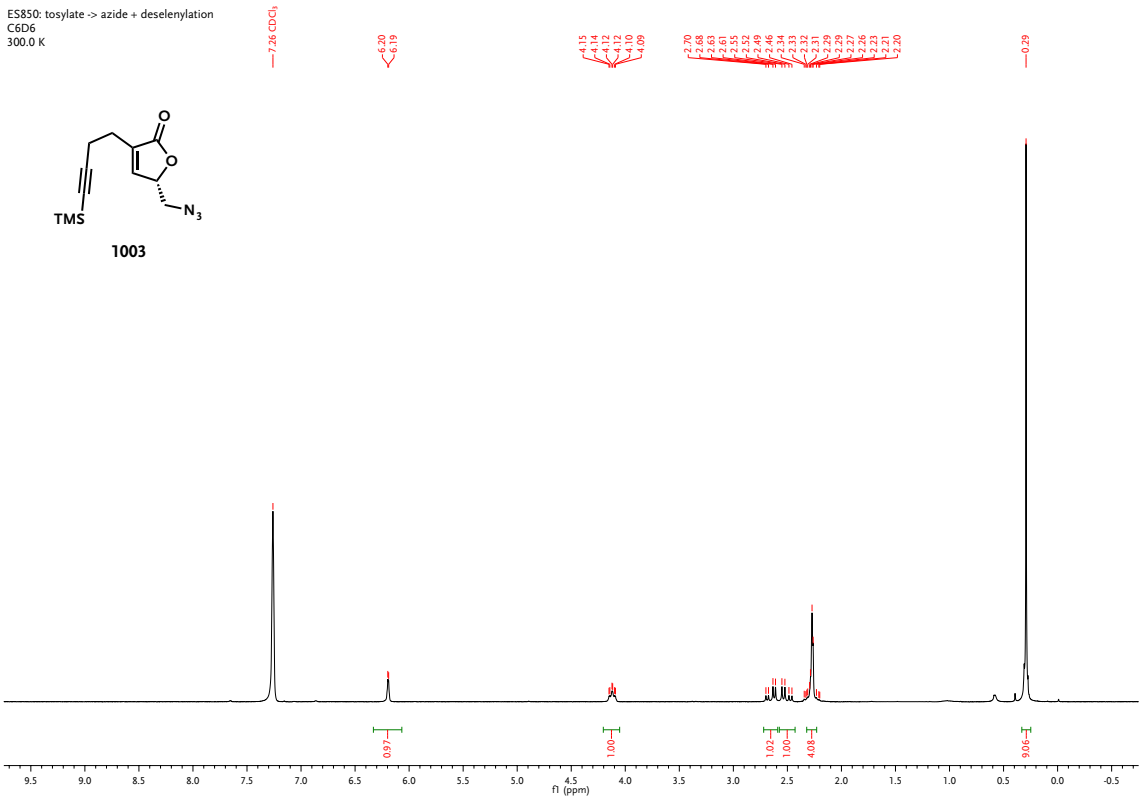
Spectrum B-273. ^{1}H-NMR spectrum for compound **1026** *(experimental on page 322)*.



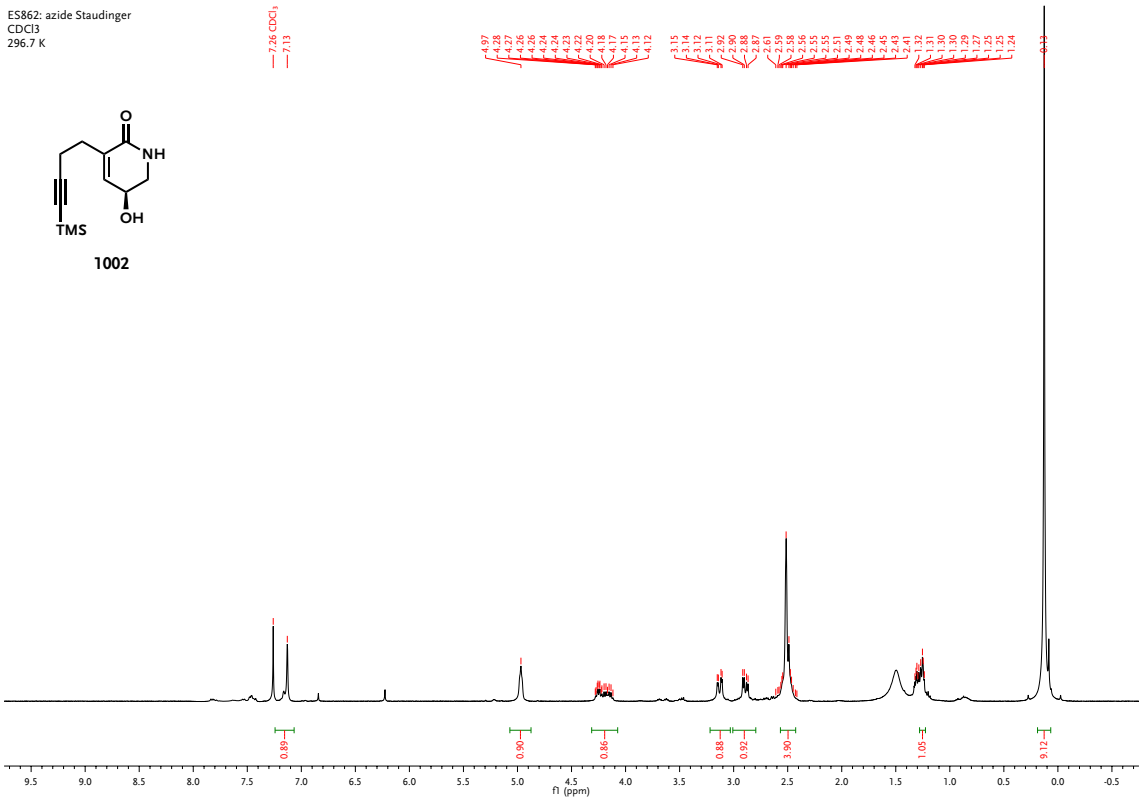
Spectrum B-274. COSY60 2D-NMR spectrum for compound **1026** *(experimental on page 322)*.



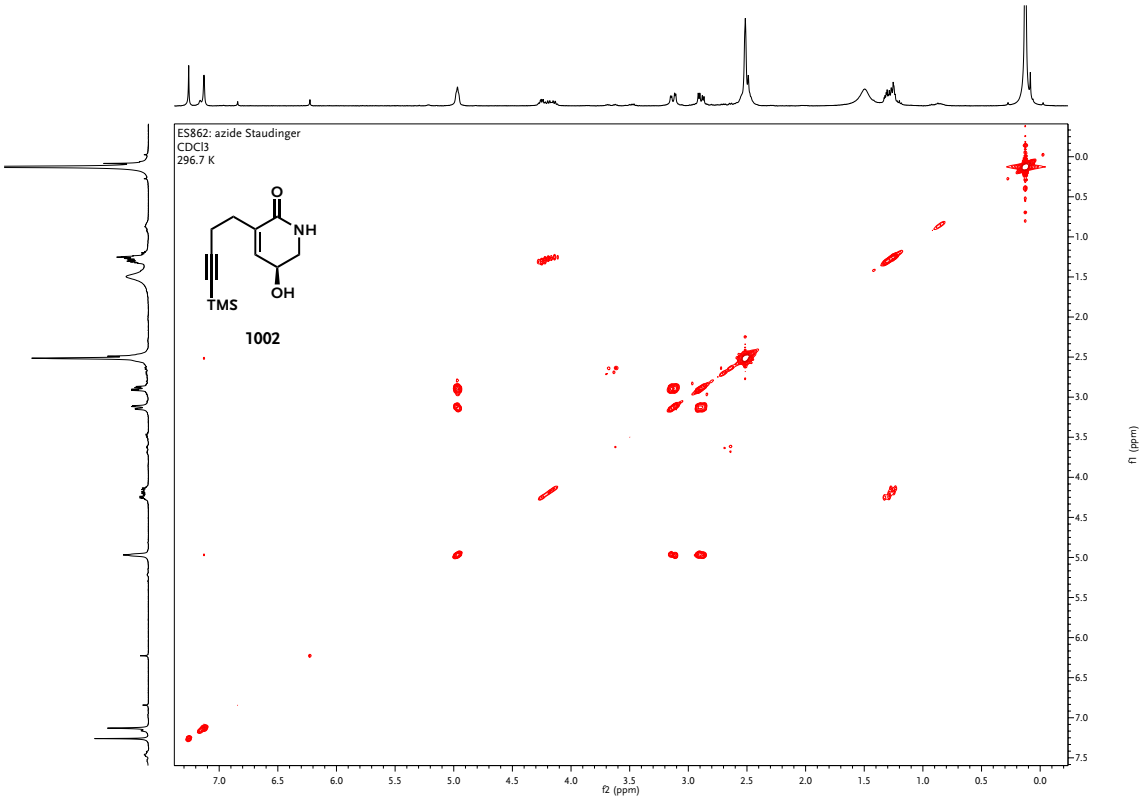
Spectrum B-275. ^{1}H-NMR spectrum for compound **1027** *(experimental on page 322)*.



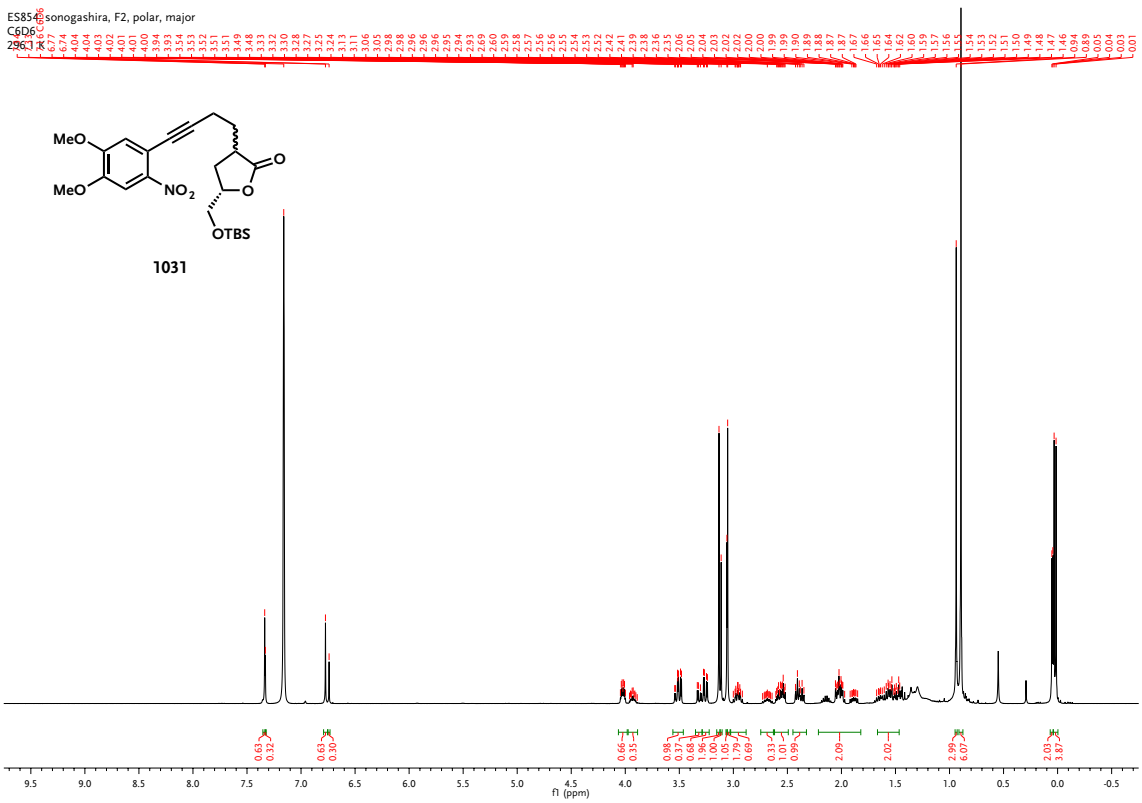
Spectrum B-276. ^{1}H-NMR spectrum for compound **1003** *(experimental on page 323)*.



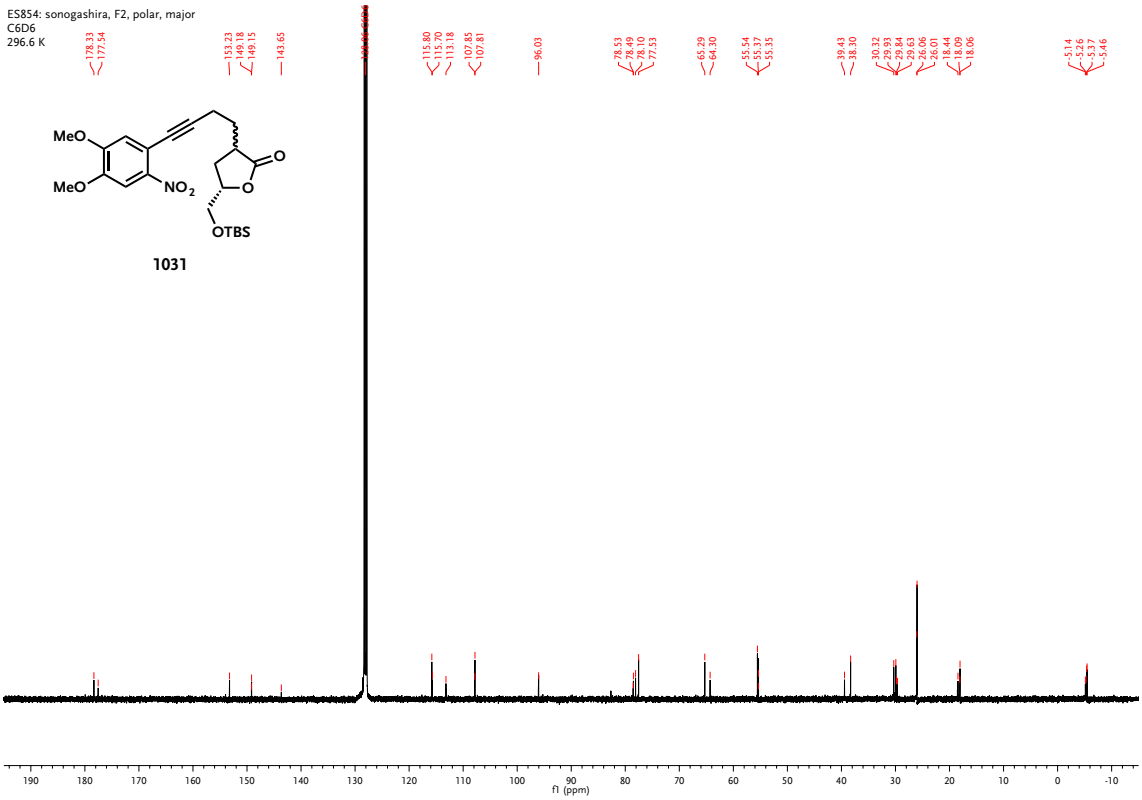
Spectrum B-277. ^{1}H-NMR spectrum for compound **1002** *(experimental on page 323)*.



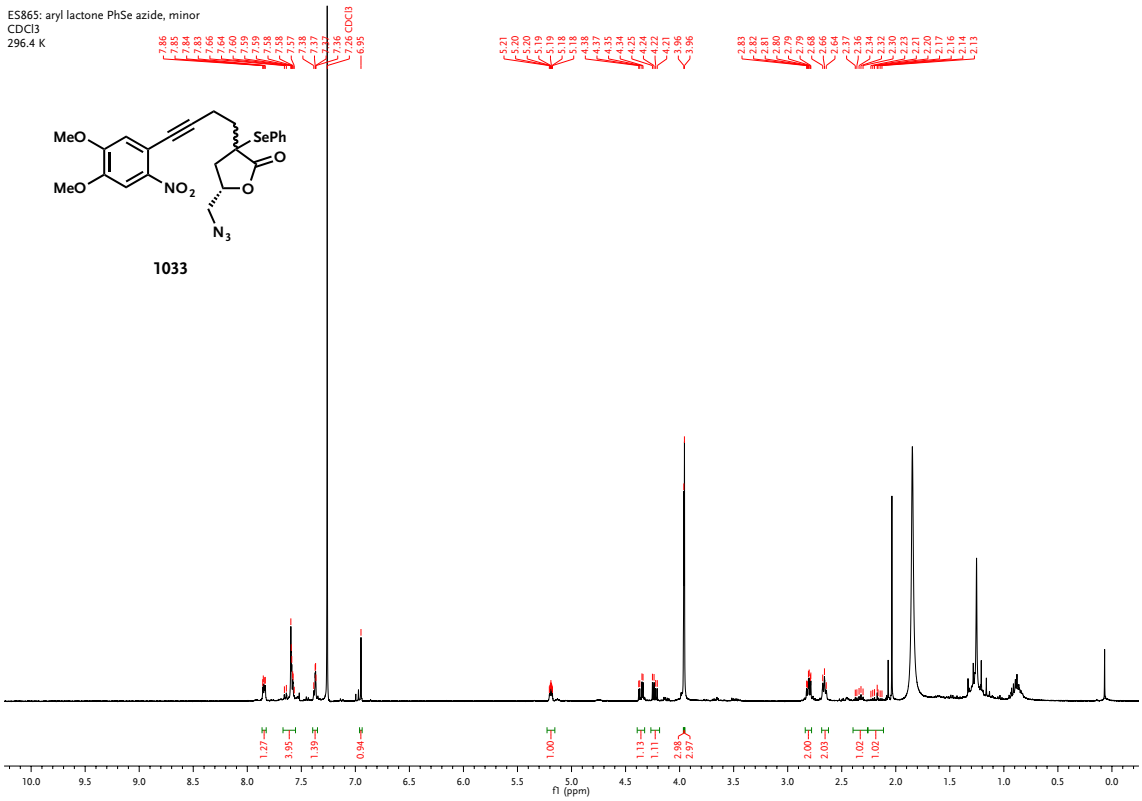
Spectrum B-278. COSY60 2D-NMR spectrum for compound **1002** *(experimental on page 323)*.



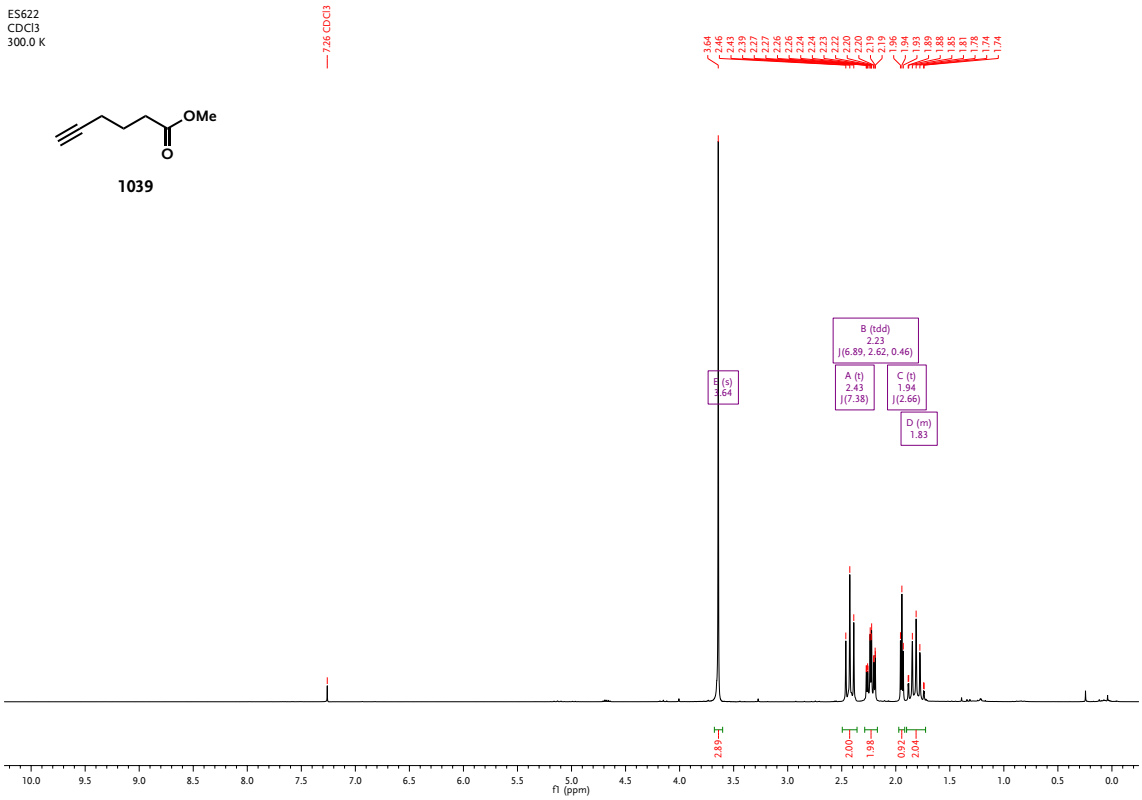
Spectrum B-279. [1]H-NMR spectrum for compound **1031** *(experimental on page 324)*.



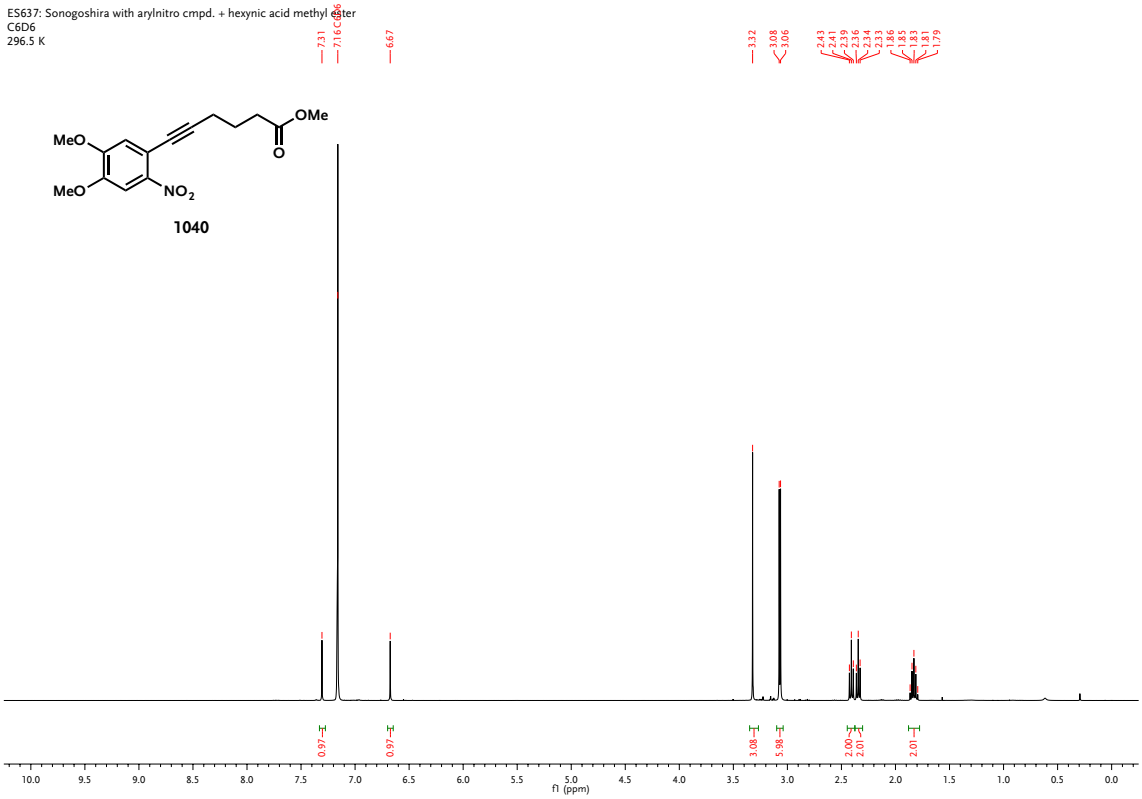
Spectrum B-280. [13]C-NMR spectrum for compound **1031** *(experimental on page 324)*.



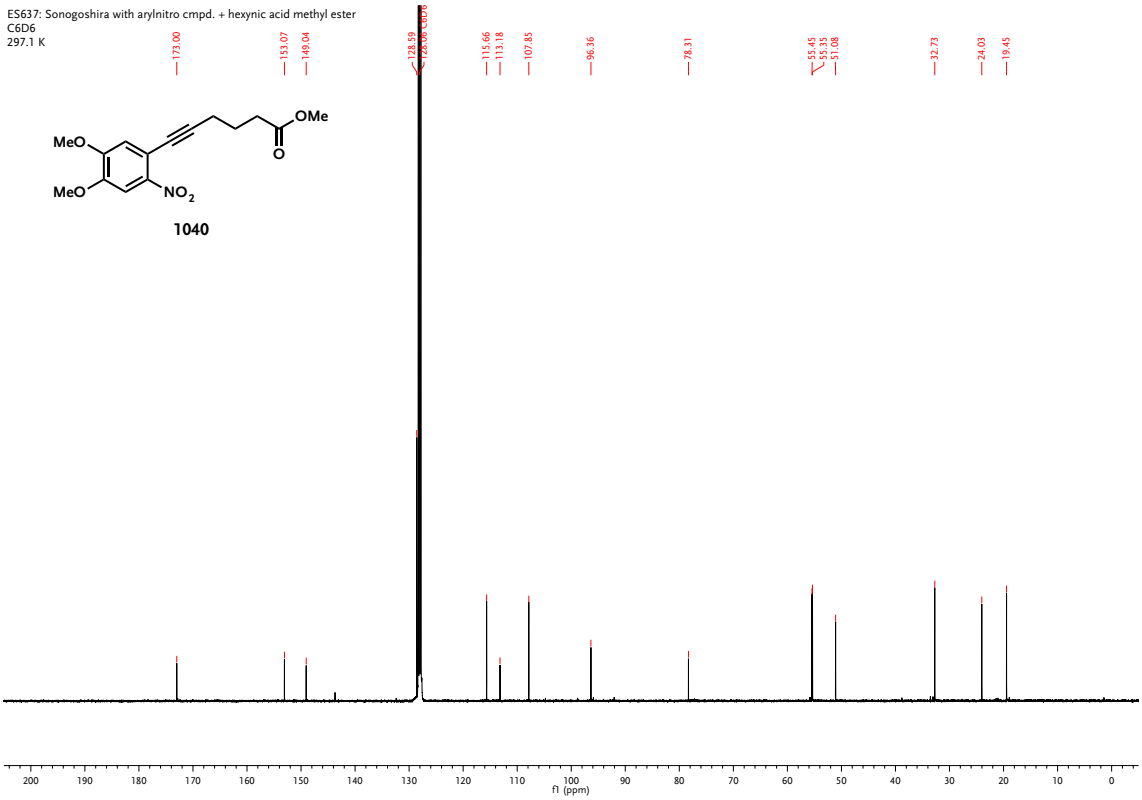
Spectrum B-281. ^{1}H-NMR spectrum for compound **1033** *(experimental on page 326)*.



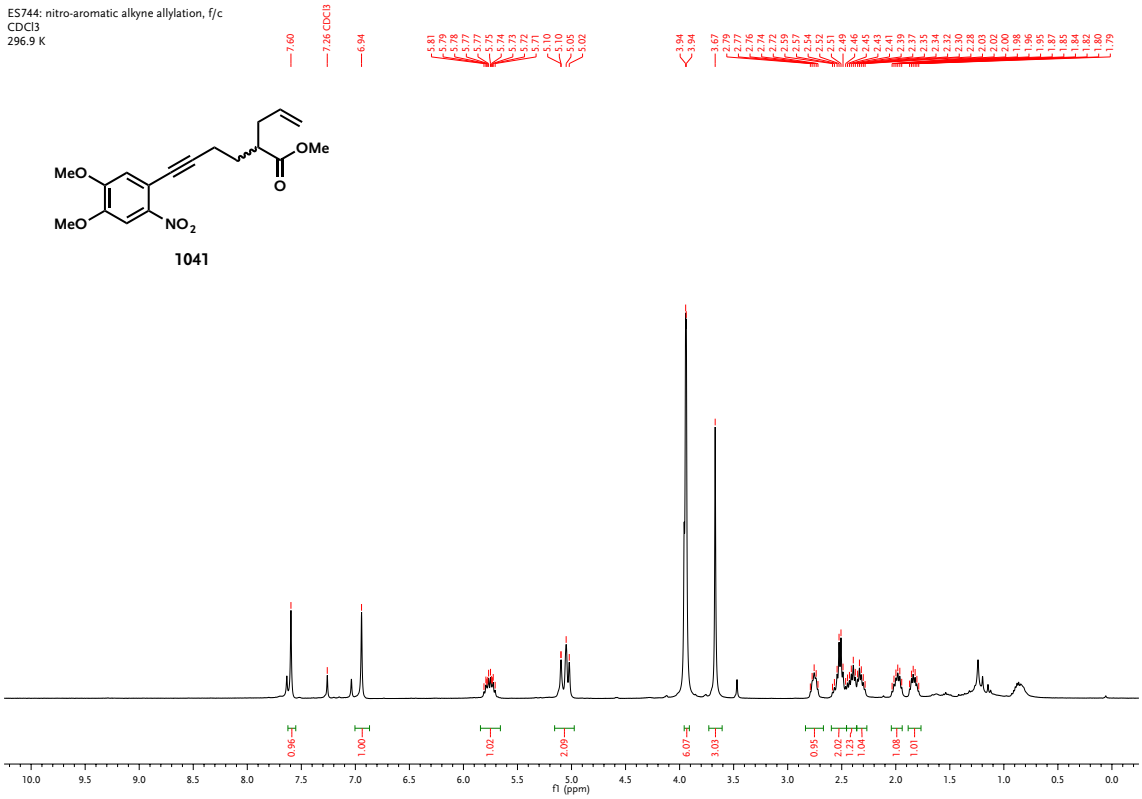
Spectrum B-282. ^{1}H-NMR spectrum for compound **1039** *(experimental on page 326)*.



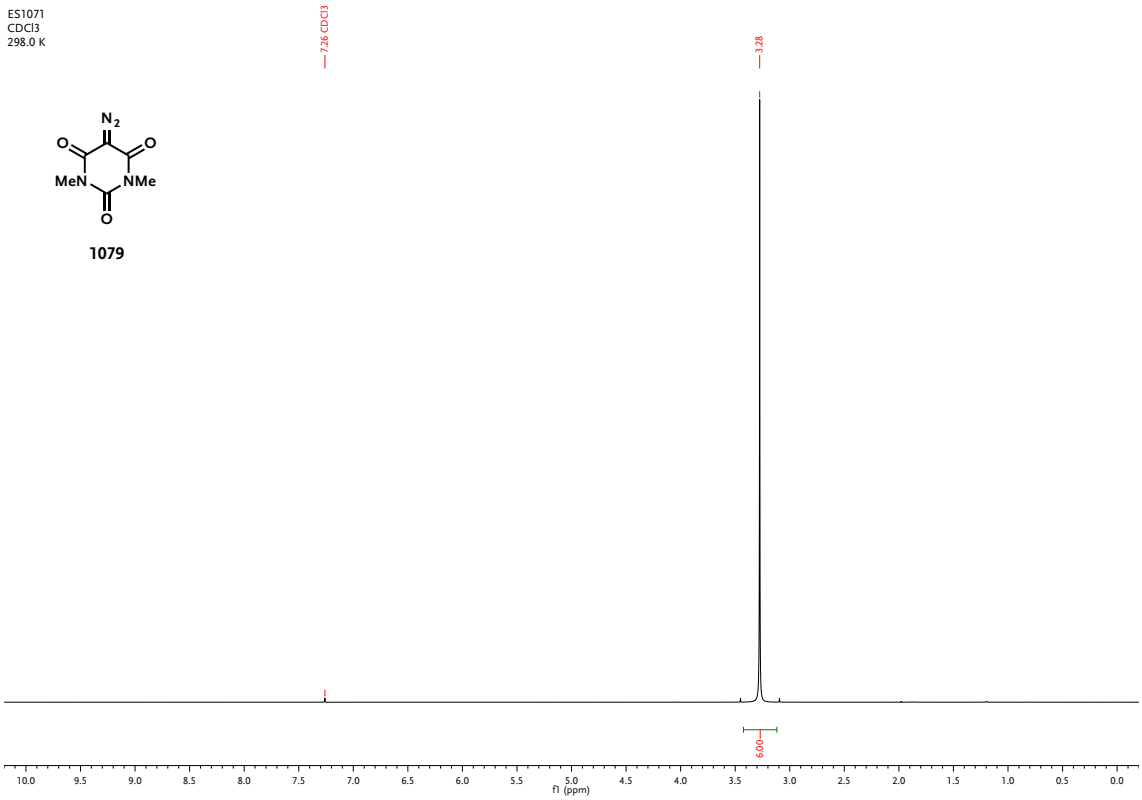
Spectrum B-283. [1]H-NMR spectrum for compound **1040** *(experimental on page 327)*.



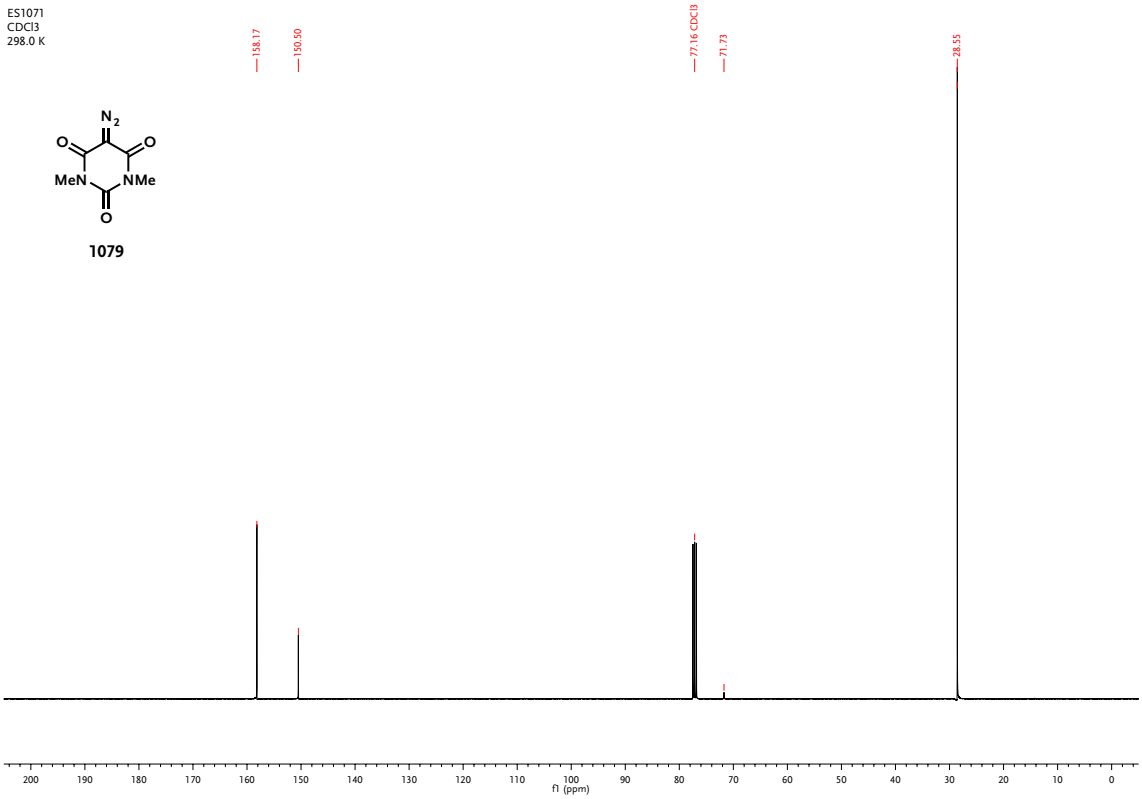
Spectrum B-284. [13]C-NMR spectrum for compound **1040** *(experimental on page 327)*.



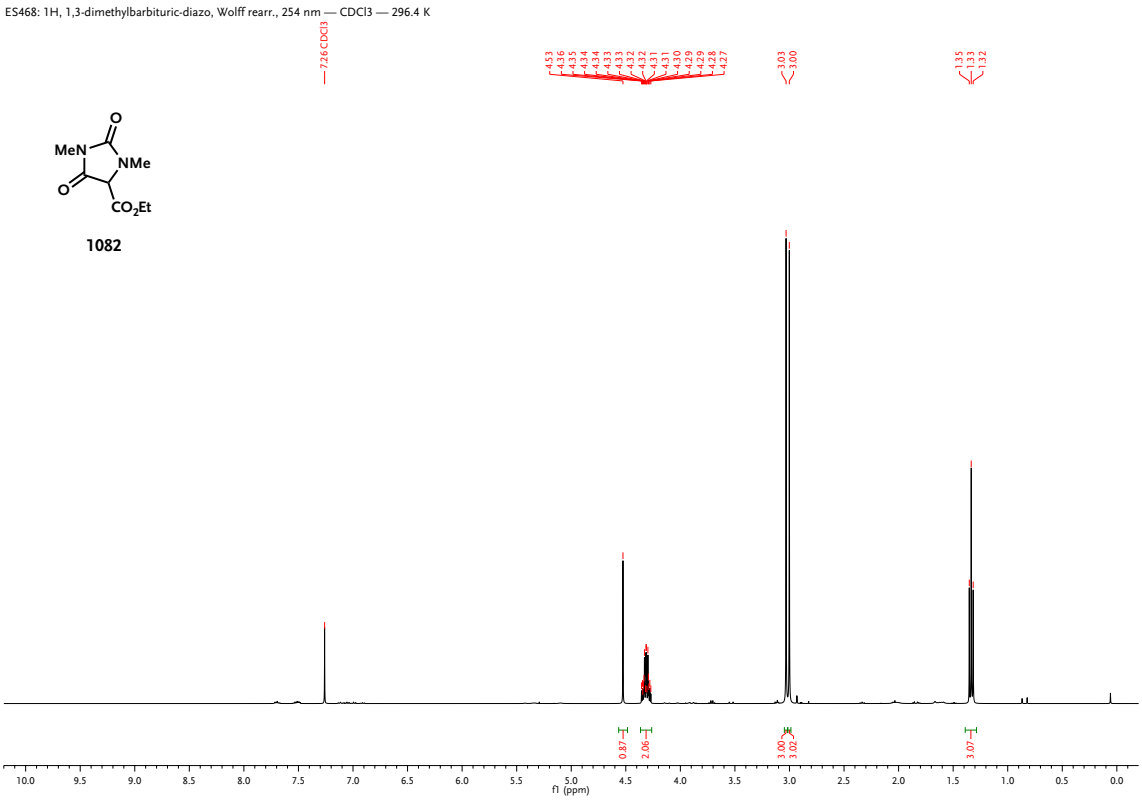
Spectrum B-285. ^{1}H-NMR spectrum for compound **1041** *(experimental on page 327)*.



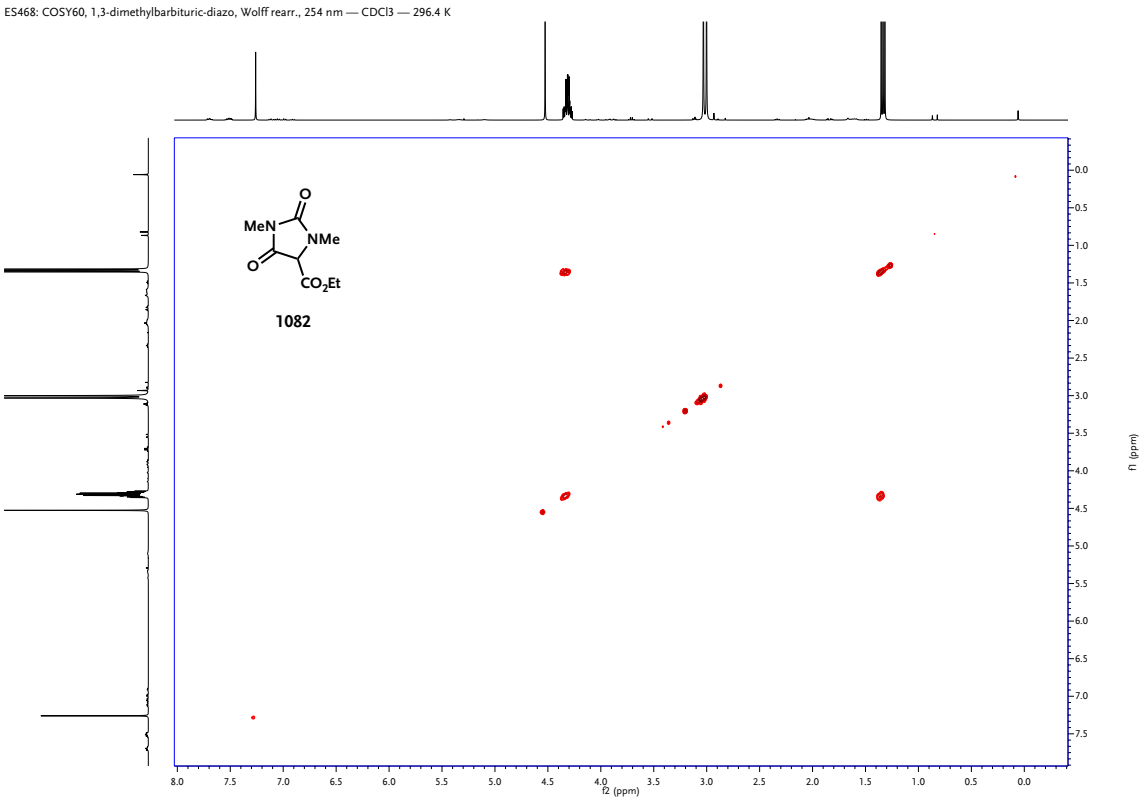
Spectrum B-286. ^{1}H-NMR spectrum for compound **1079** *(experimental on page 338)*.



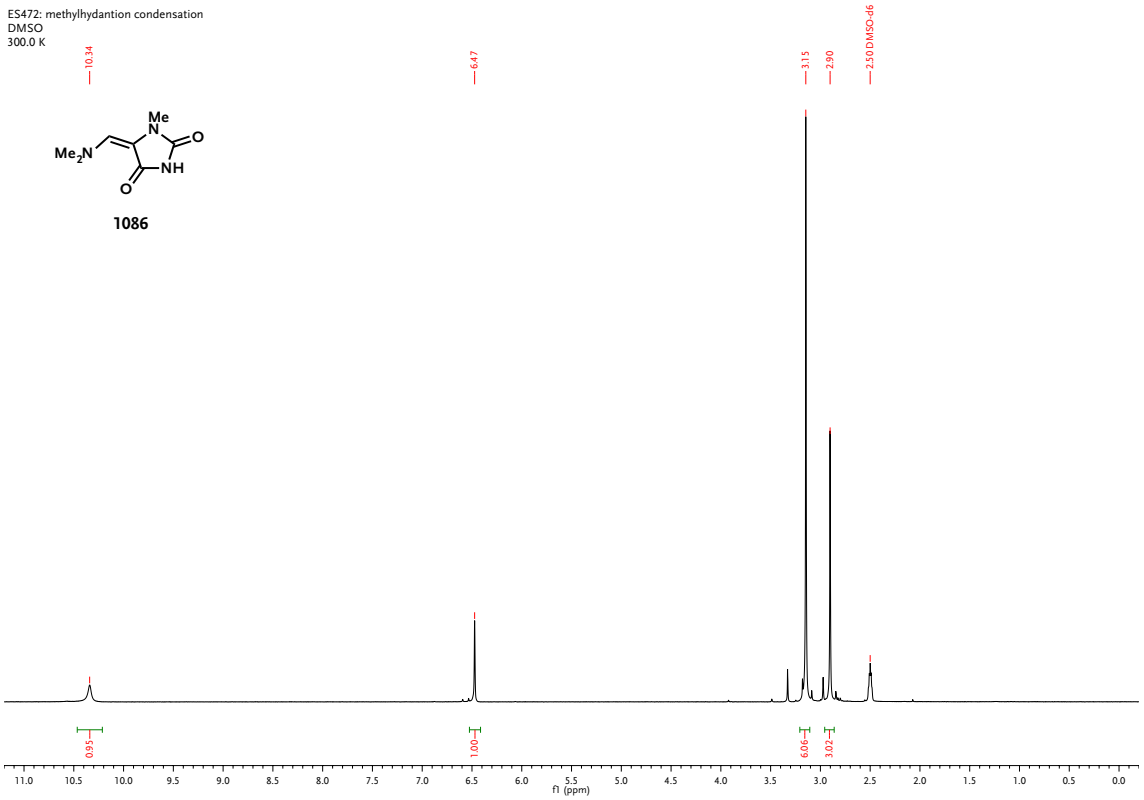
Spectrum B-287. ^{13}C-NMR spectrum for compound **1079** *(experimental on page 338)*.



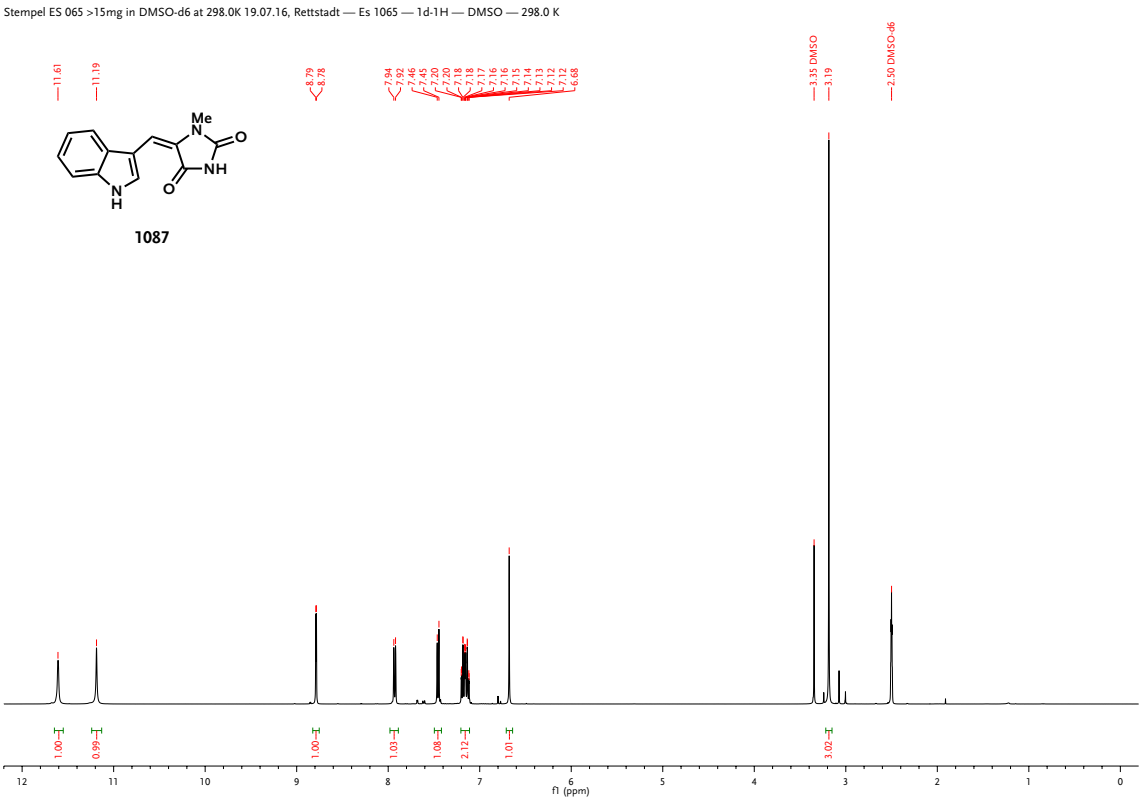
Spectrum B-288. ^{1}H-NMR spectrum for compound **1082** *(experimental on page 338)*.



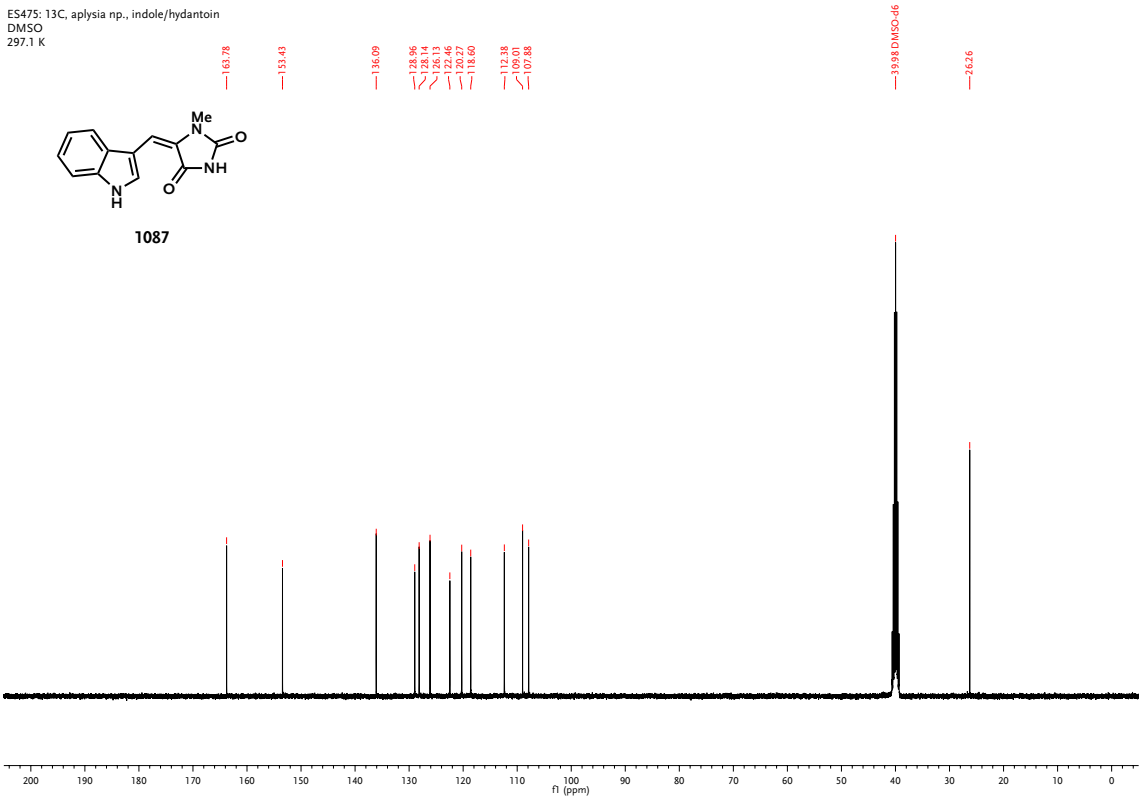
Spectrum B-289. COSY60 2D-NMR spectrum for compound **1082** *(experimental on page 338)*.



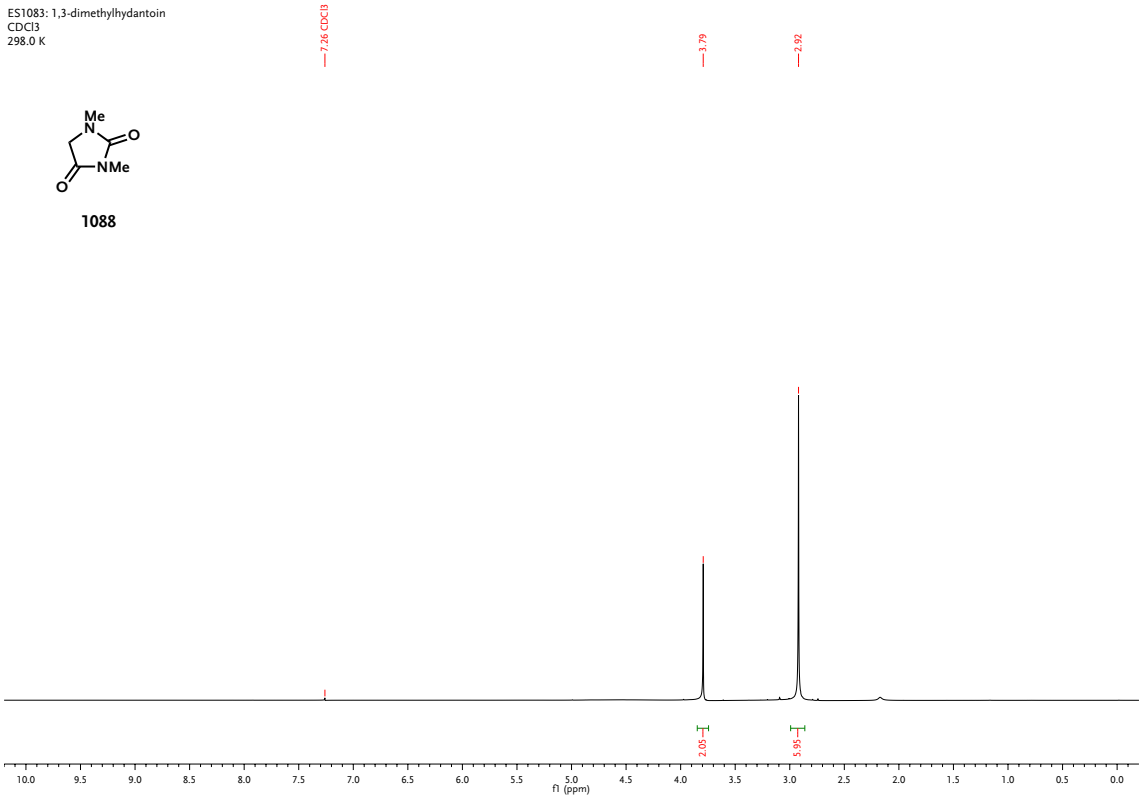
Spectrum B-290. ^{1}H-NMR spectrum for compound **1086** *(experimental on page 338)*.



Spectrum B-291. [1]H-NMR spectrum for compound **1087** *(experimental on page 339)*.

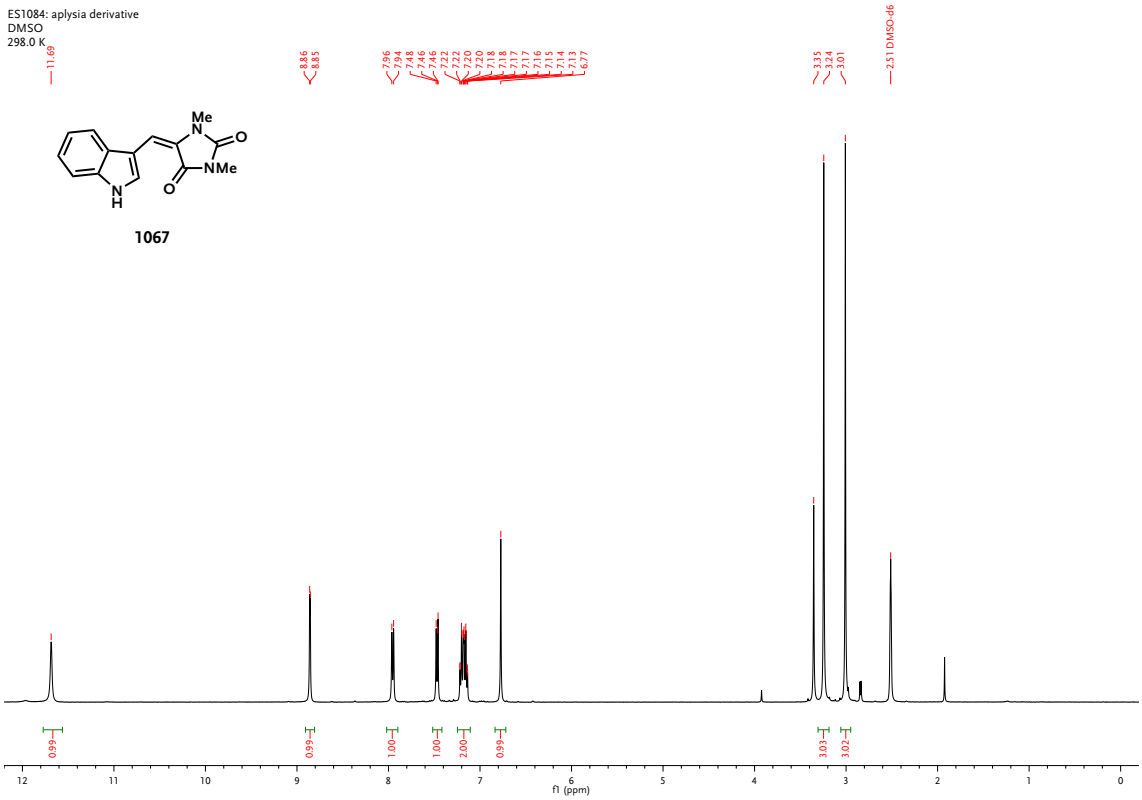


Spectrum B-292. [13]C-NMR spectrum for compound **1087** *(experimental on page 339)*.



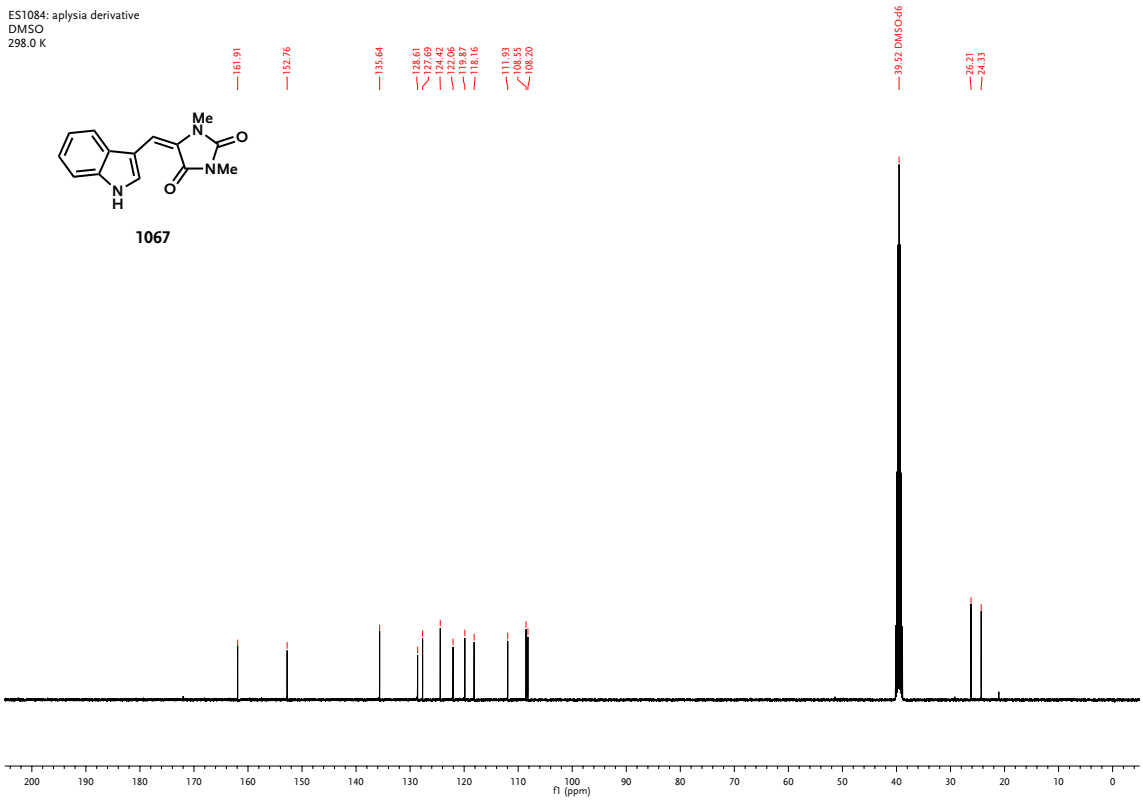
1088

Spectrum B-293. ^{1}H-NMR spectrum for compound **1088** *(experimental on page 339)*.

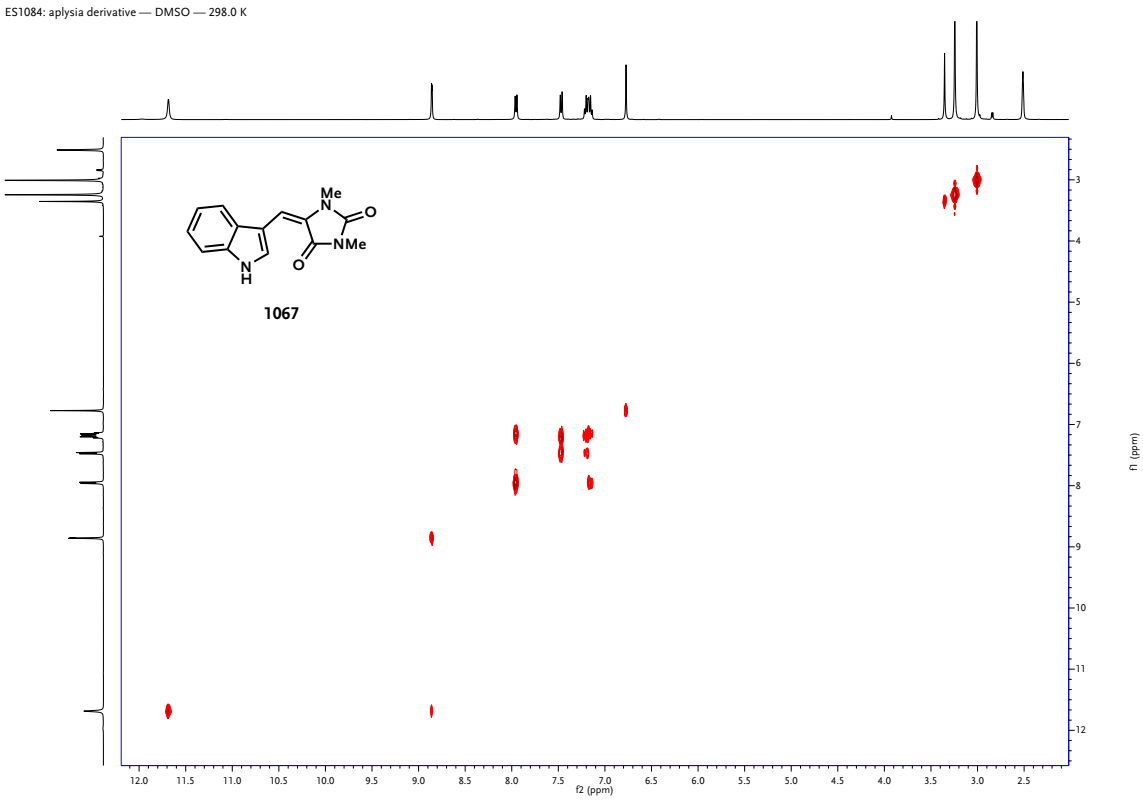


1067

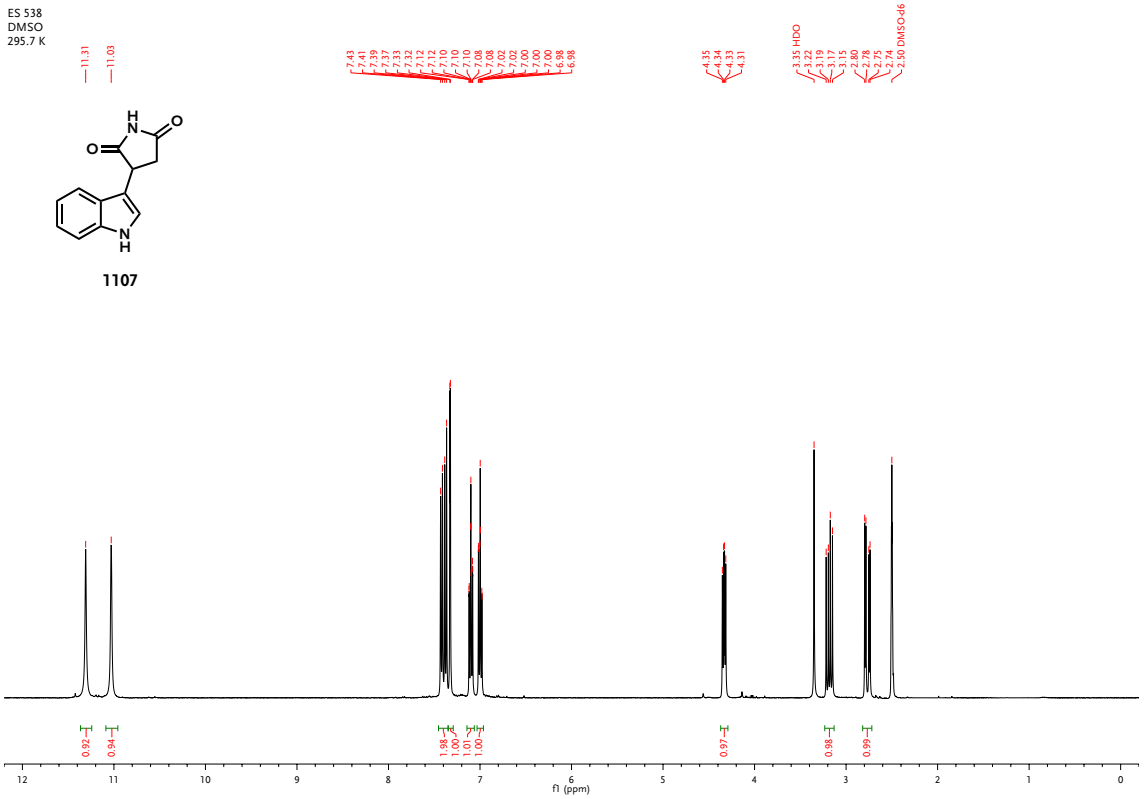
Spectrum B-294. ^{1}H-NMR spectrum for compound **1067** *(experimental on page 340)*.



Spectrum B-295. ^{13}C-NMR spectrum for compound **1067** *(experimental on page 340)*.

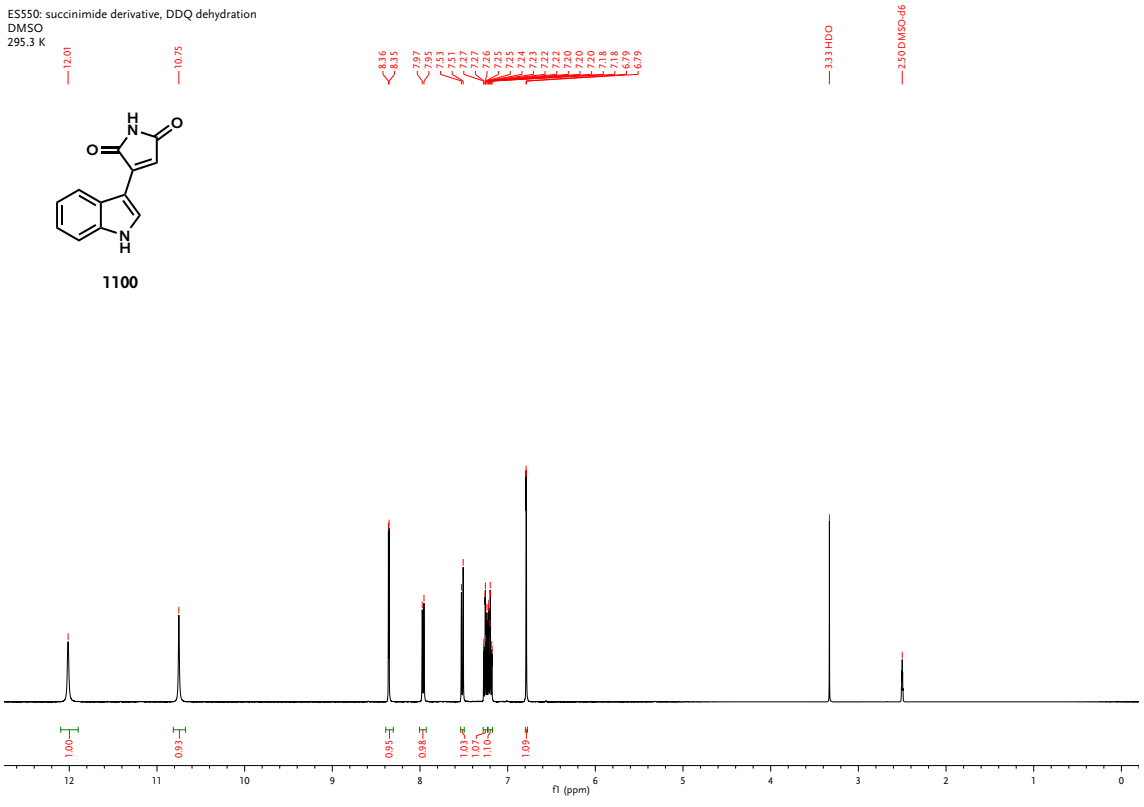


Spectrum B-296. COSY60 2D-NMR spectrum for compound **1067** *(experimental on page 340)*.



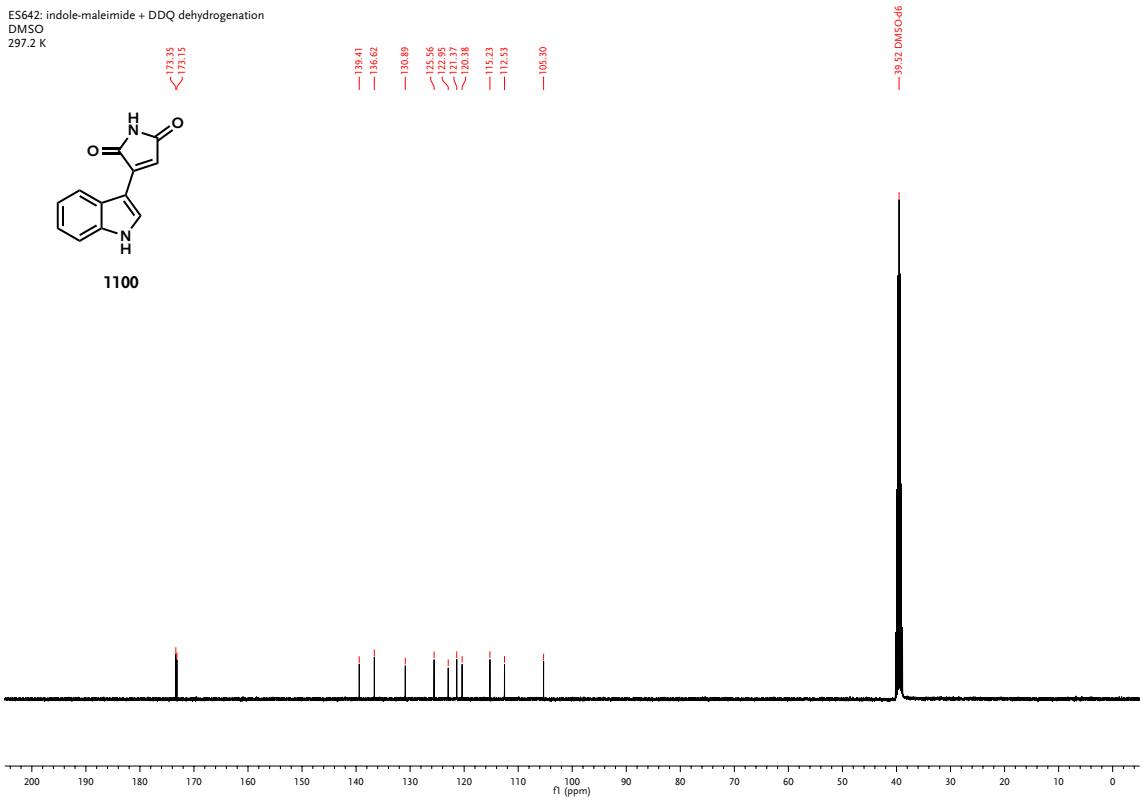
1107

Spectrum B-297. ^{1}H-NMR spectrum for compound **1107** *(experimental on page 347)*.

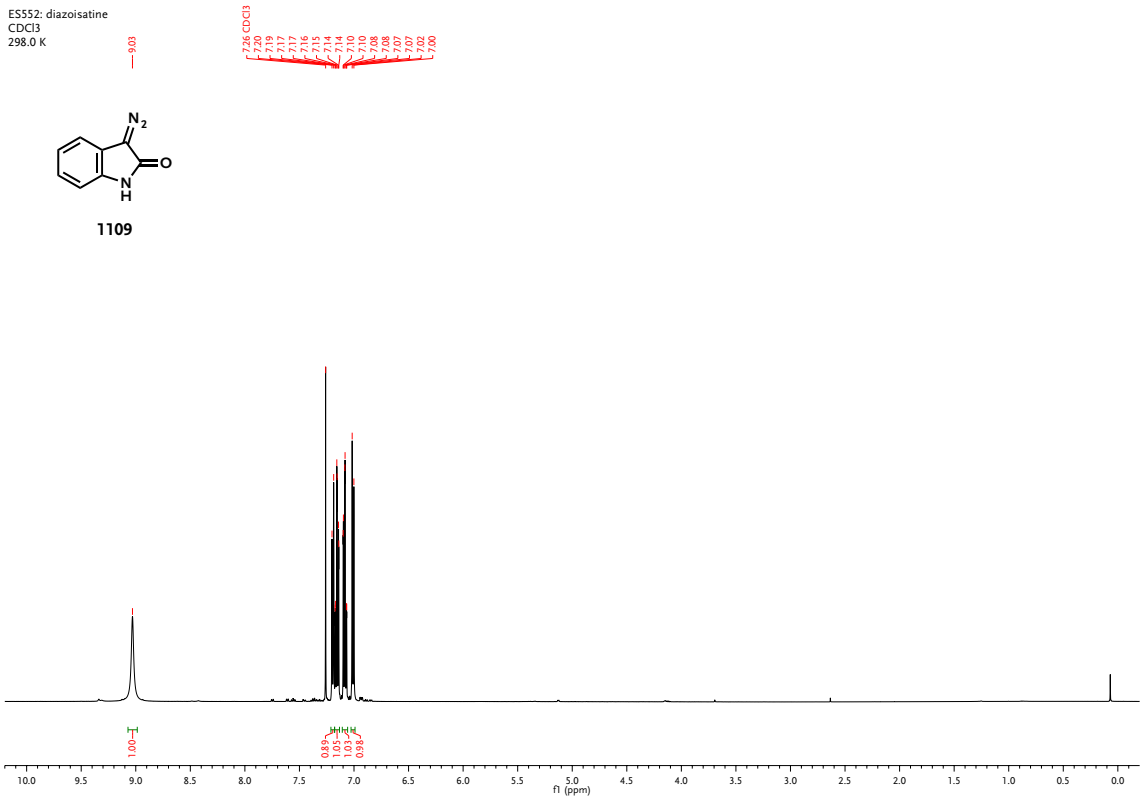


1100

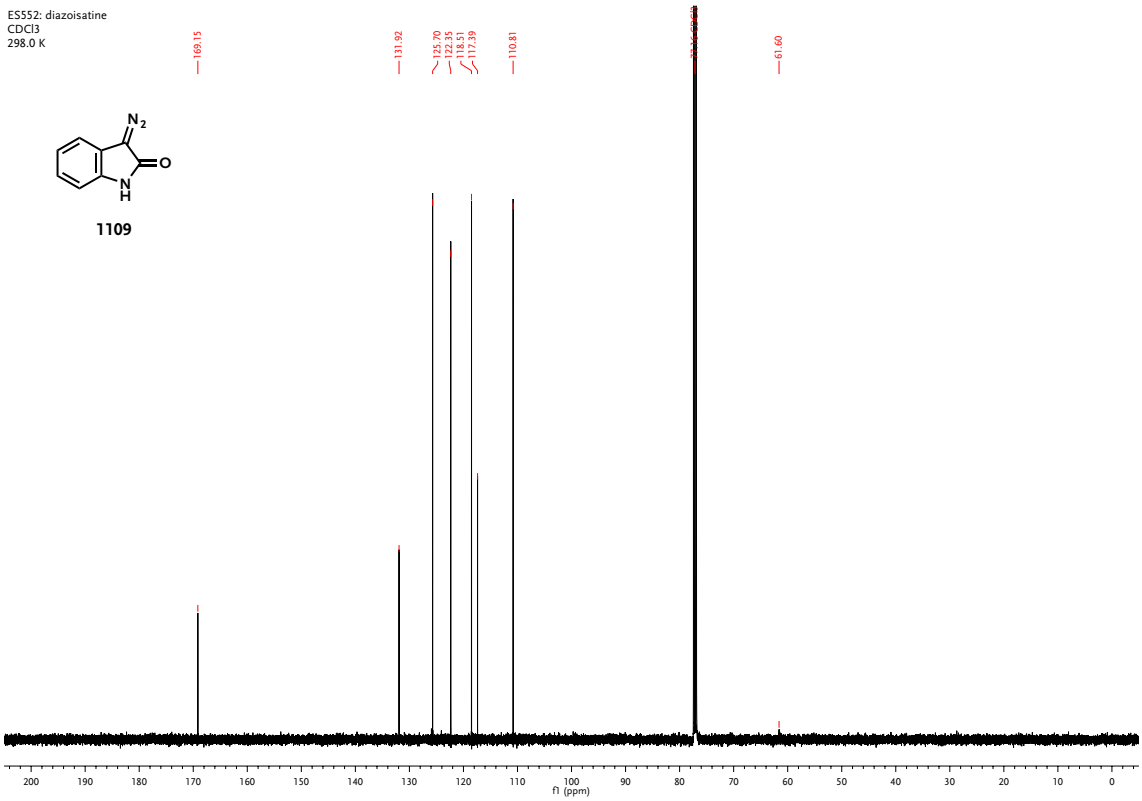
Spectrum B-298. ^{1}H-NMR spectrum for compound **1100** *(experimental on page 347)*.



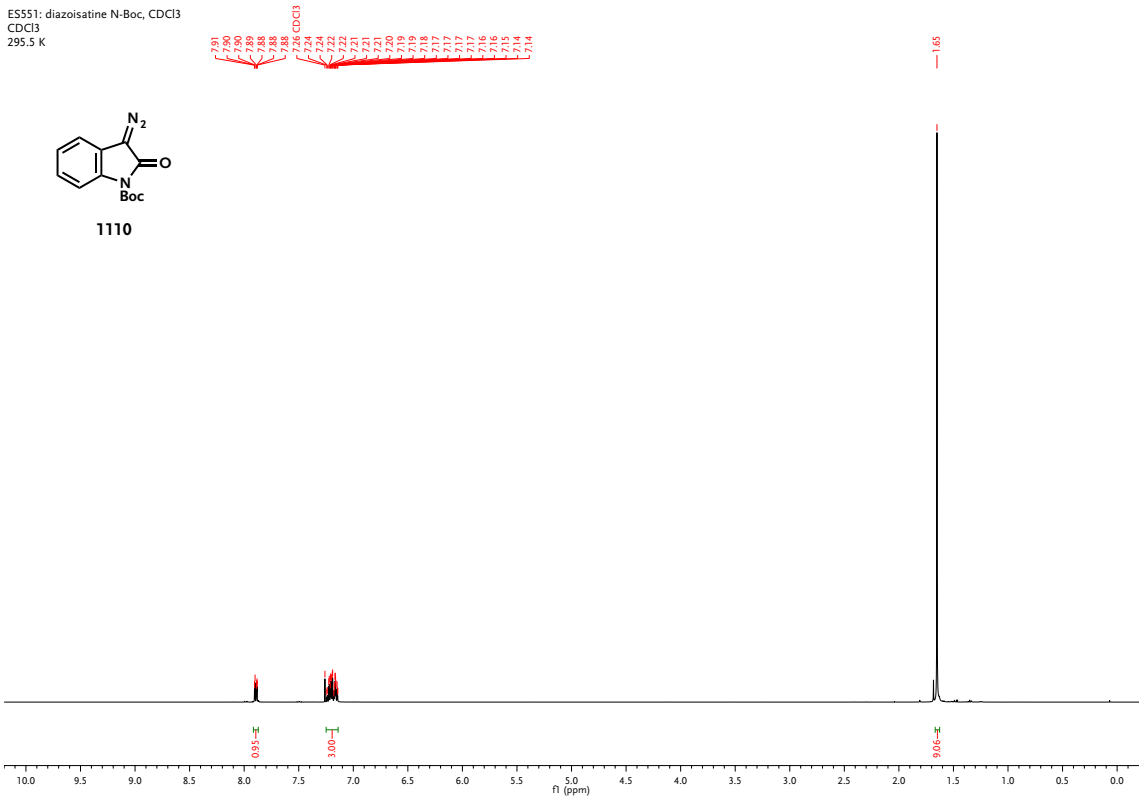
Spectrum B-299. ^{13}C-NMR spectrum for compound **1100** *(experimental on page 347)*.



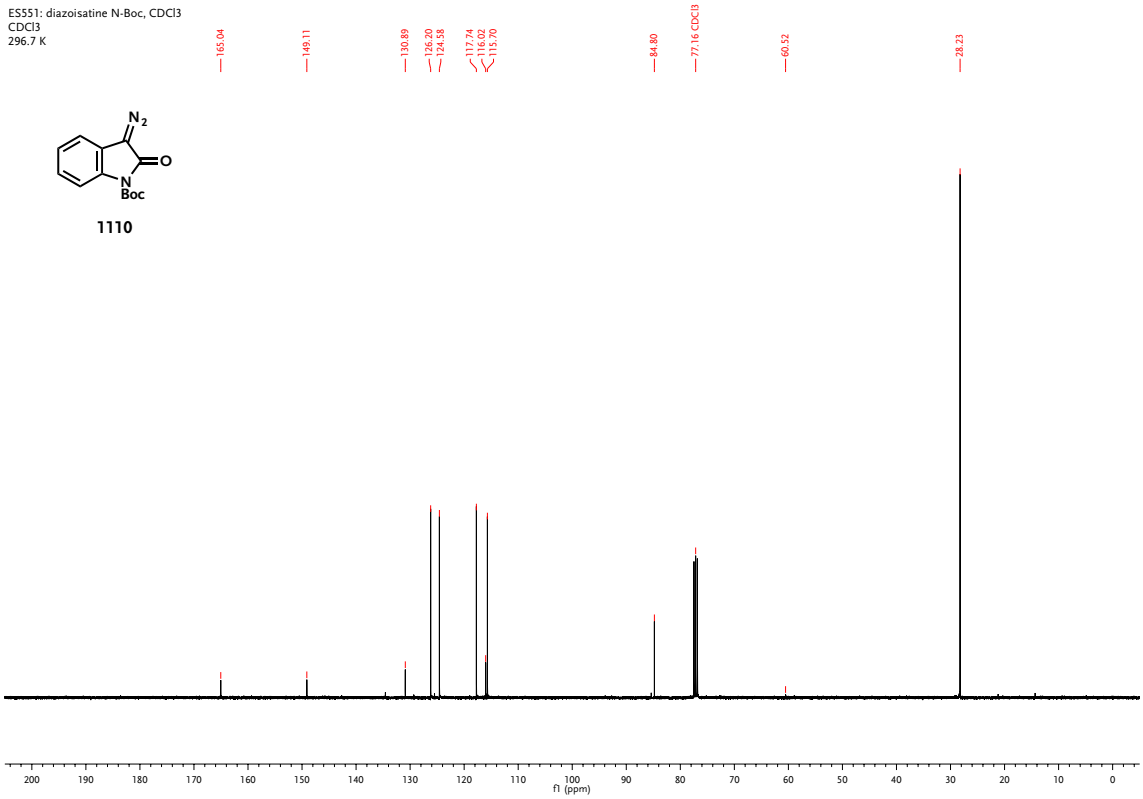
Spectrum B-300. ^{1}H-NMR spectrum for compound **1109** *(experimental on page 348)*.



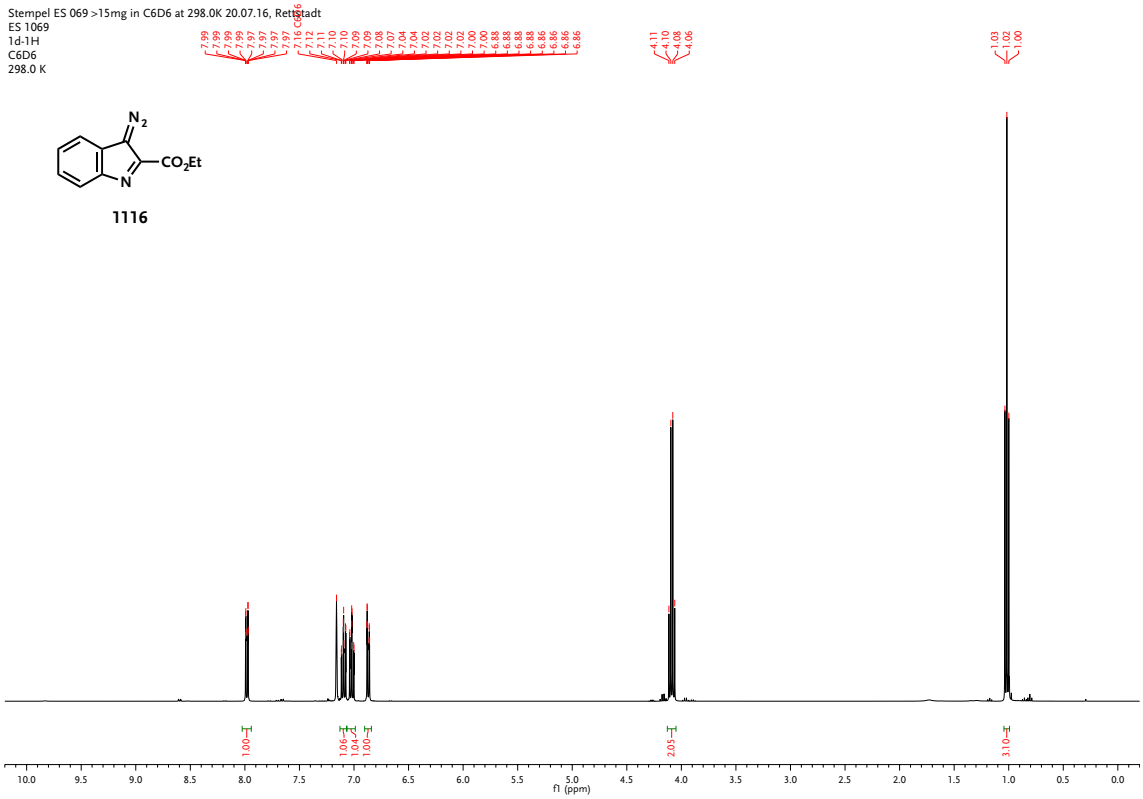
Spectrum B-301. ^{13}C-NMR spectrum for compound **1109** *(experimental on page 348)*.



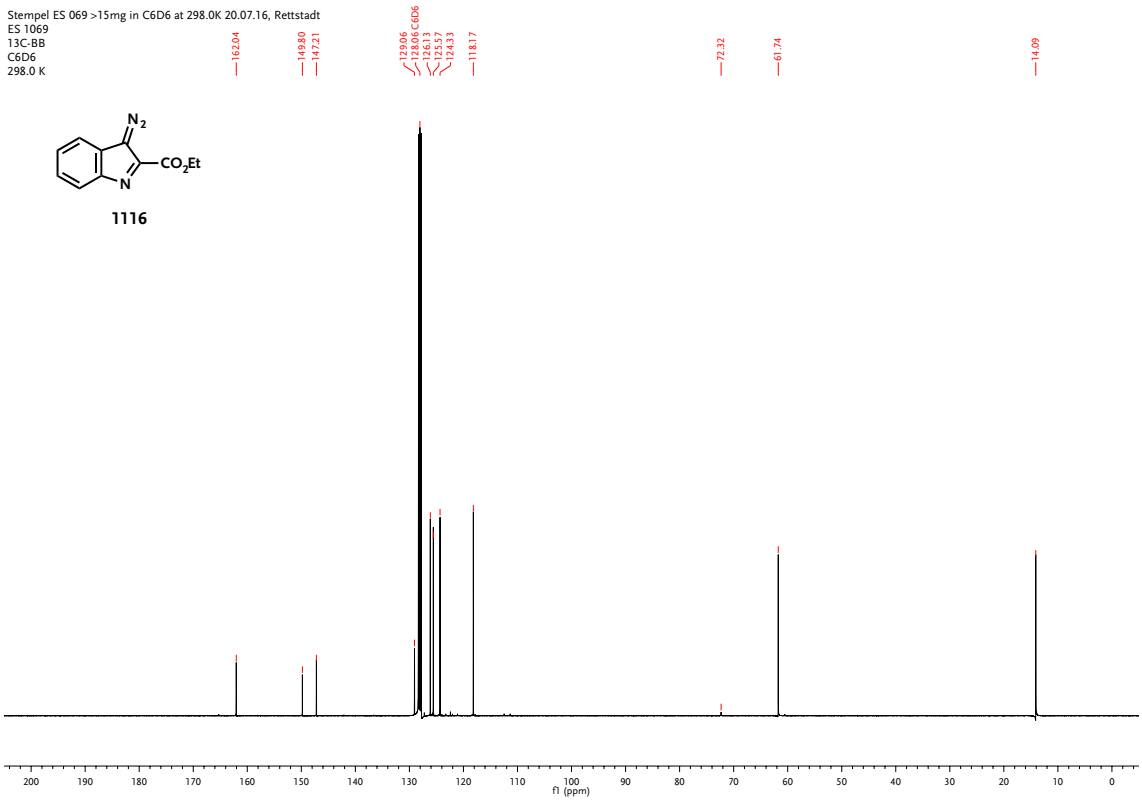
Spectrum B-302. ^{1}H-NMR spectrum for compound **1110** *(experimental on page 348)*.



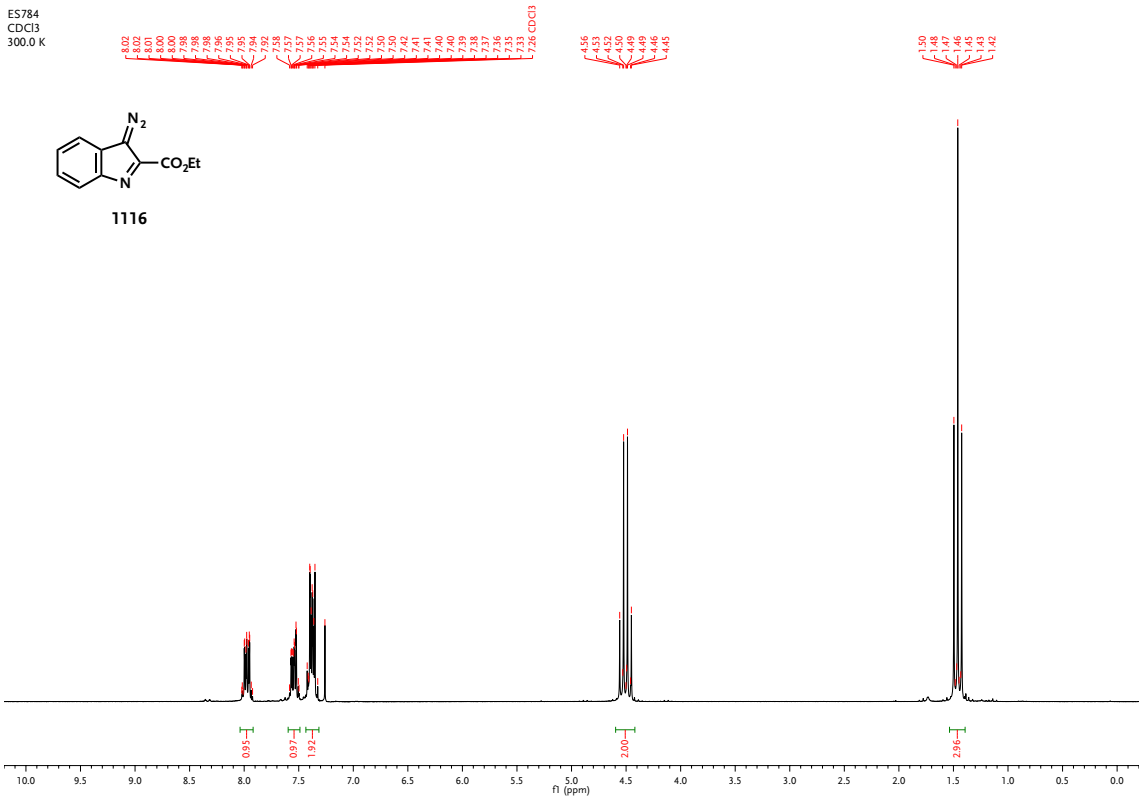
Spectrum B-303. ^{13}C-NMR spectrum for compound **1110** *(experimental on page 348)*.



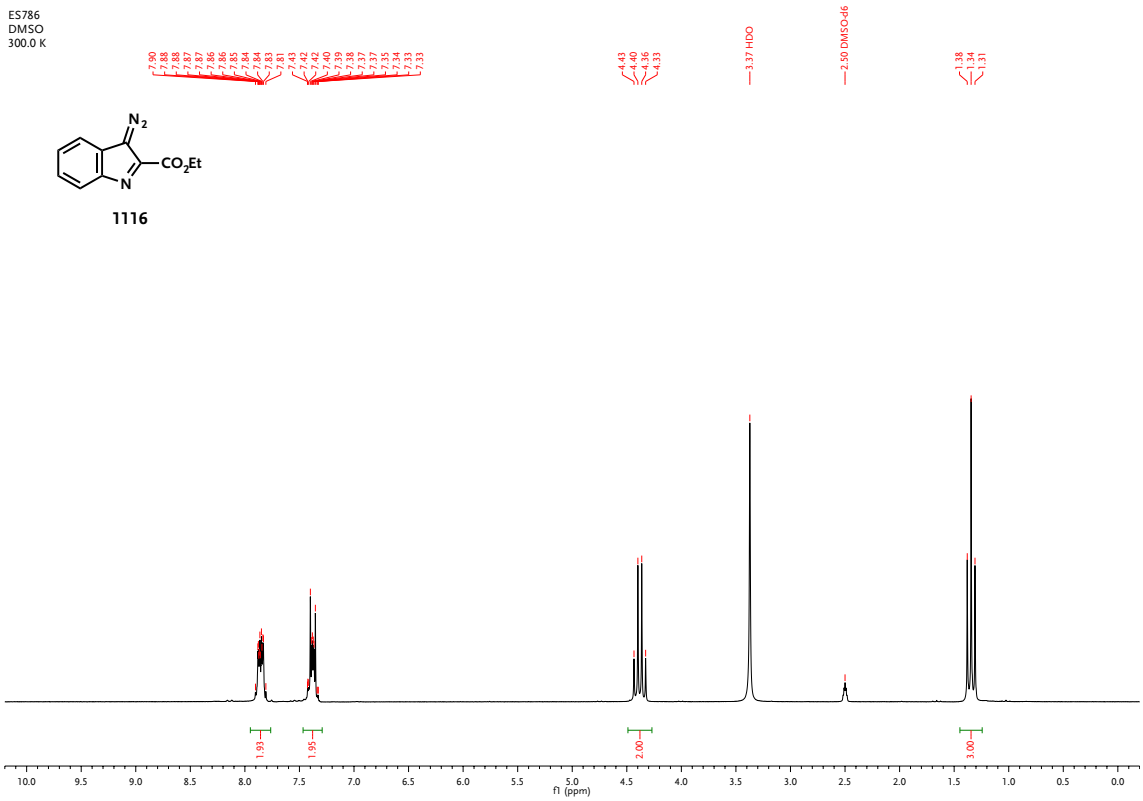
Spectrum B-304. ^{1}H-NMR spectrum for compound **1116** *(experimental on page 348)*.



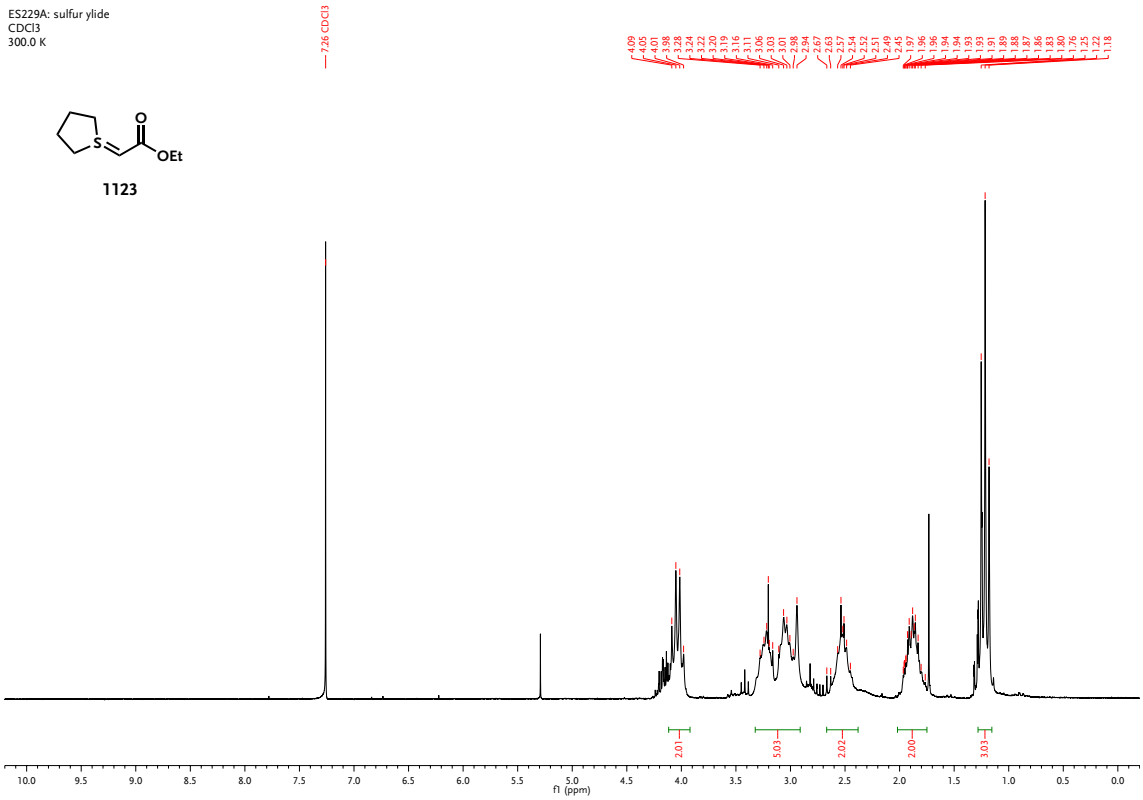
Spectrum B-305. ^{13}C-NMR spectrum for compound **1116** *(experimental on page 348)*.



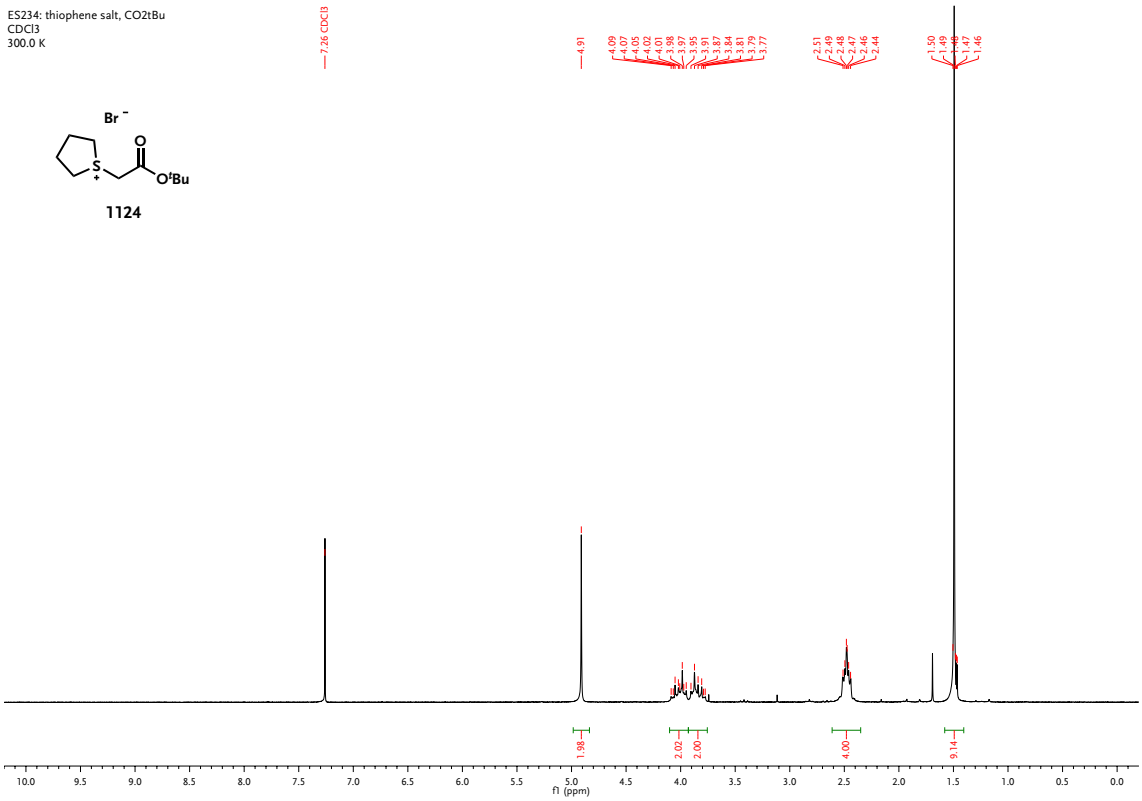
Spectrum B-306. ^{1}H-NMR spectrum for compound **1116** *(experimental on page 348)*.



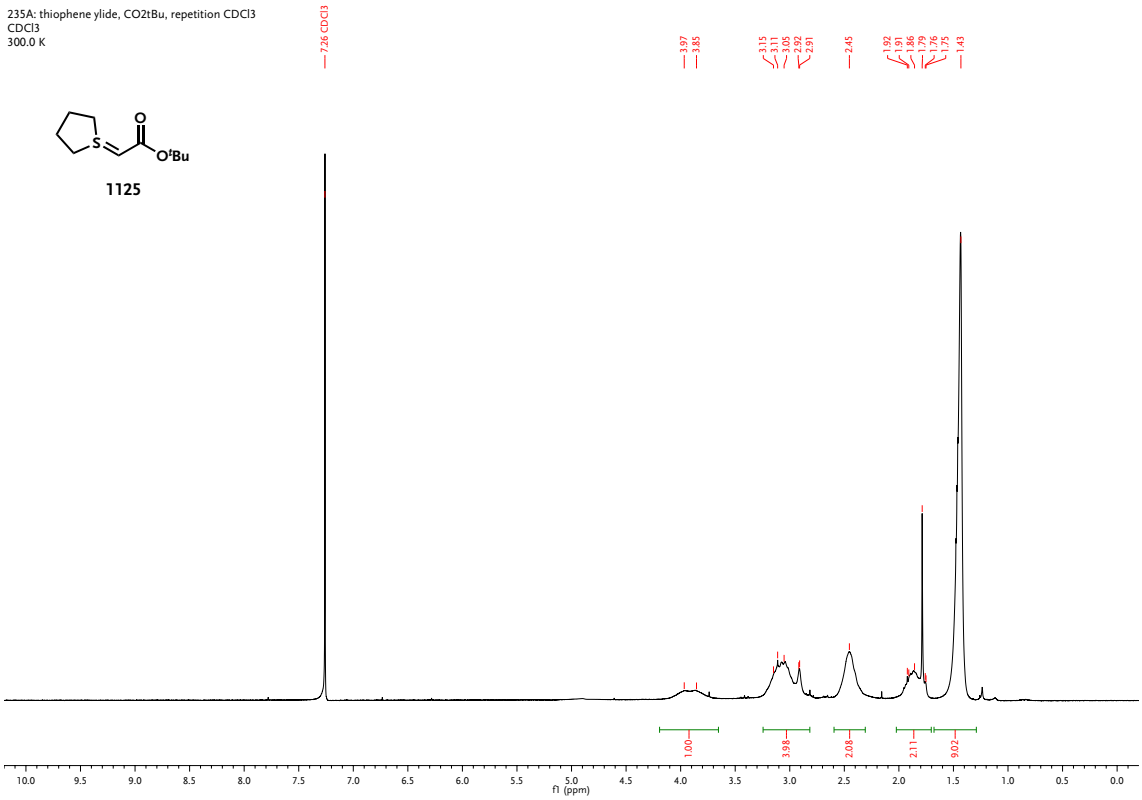
Spectrum B-307. ^{1}H-NMR spectrum for compound **1116** *(experimental on page 348)*.



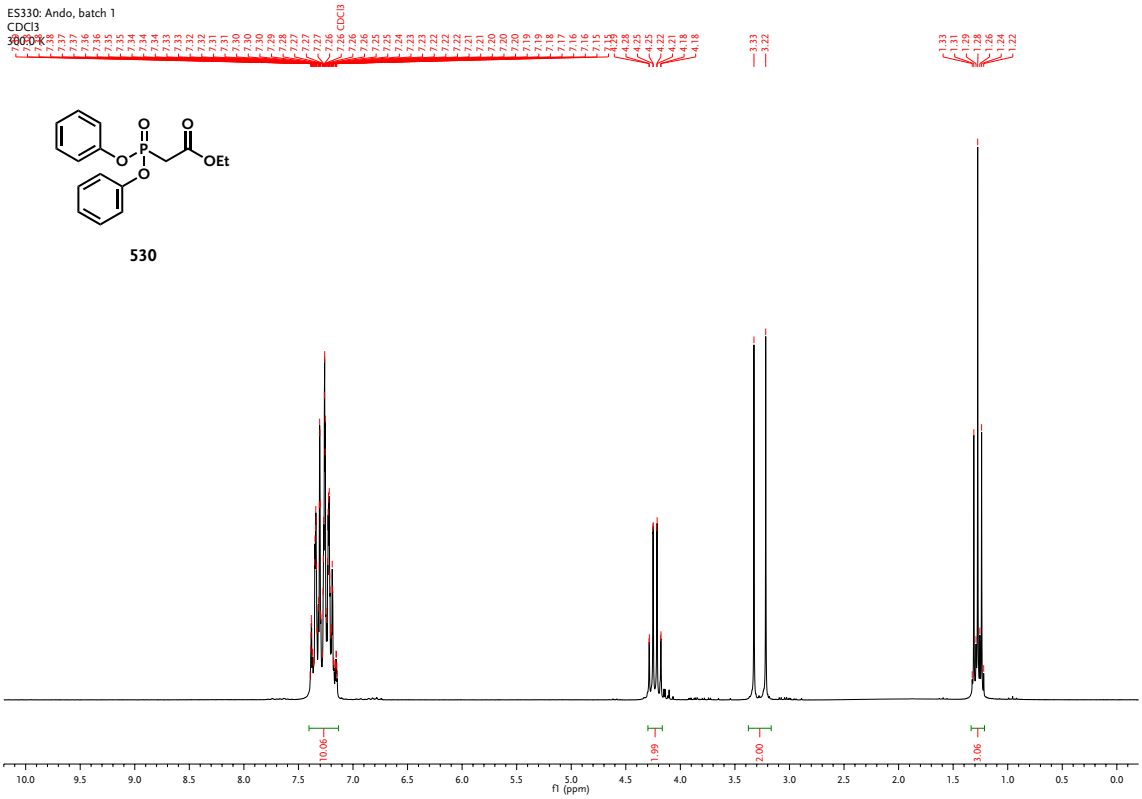
Spectrum B-308. ^{1}H-NMR spectrum for compound **1123** *(experimental on page 356)*.



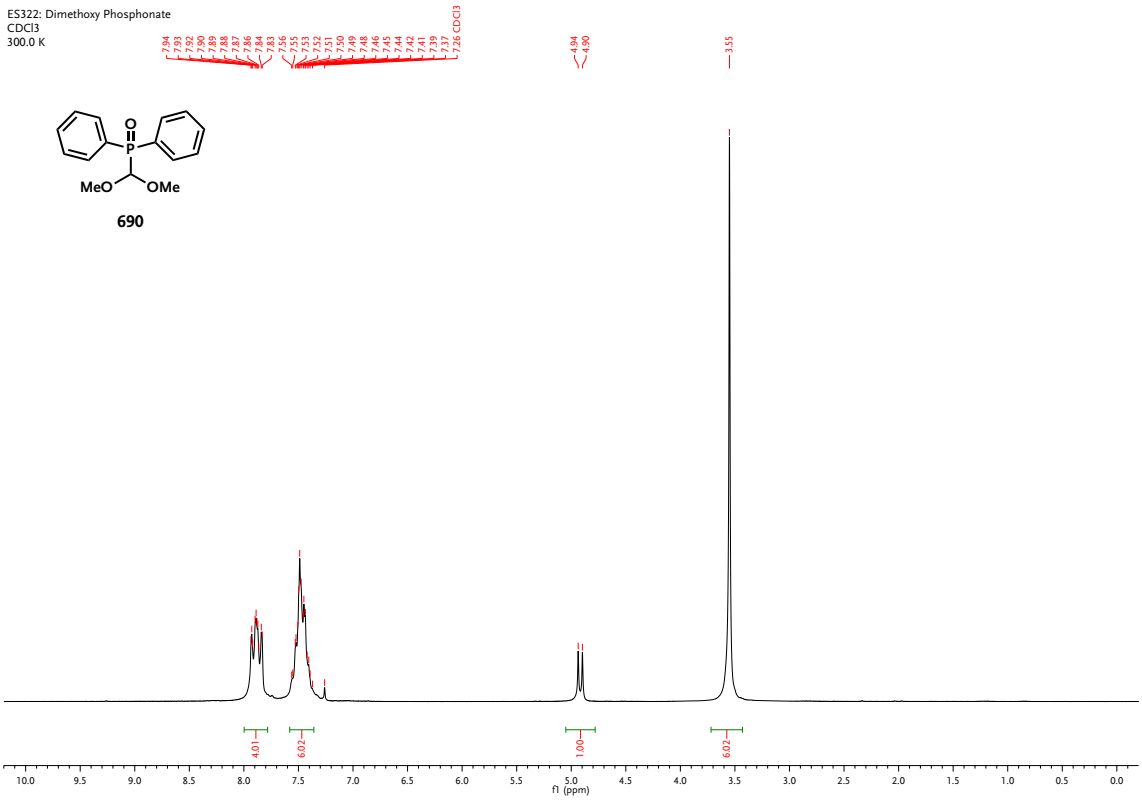
Spectrum B-309. ^{1}H-NMR spectrum for compound **1124** *(experimental on page 356)*.



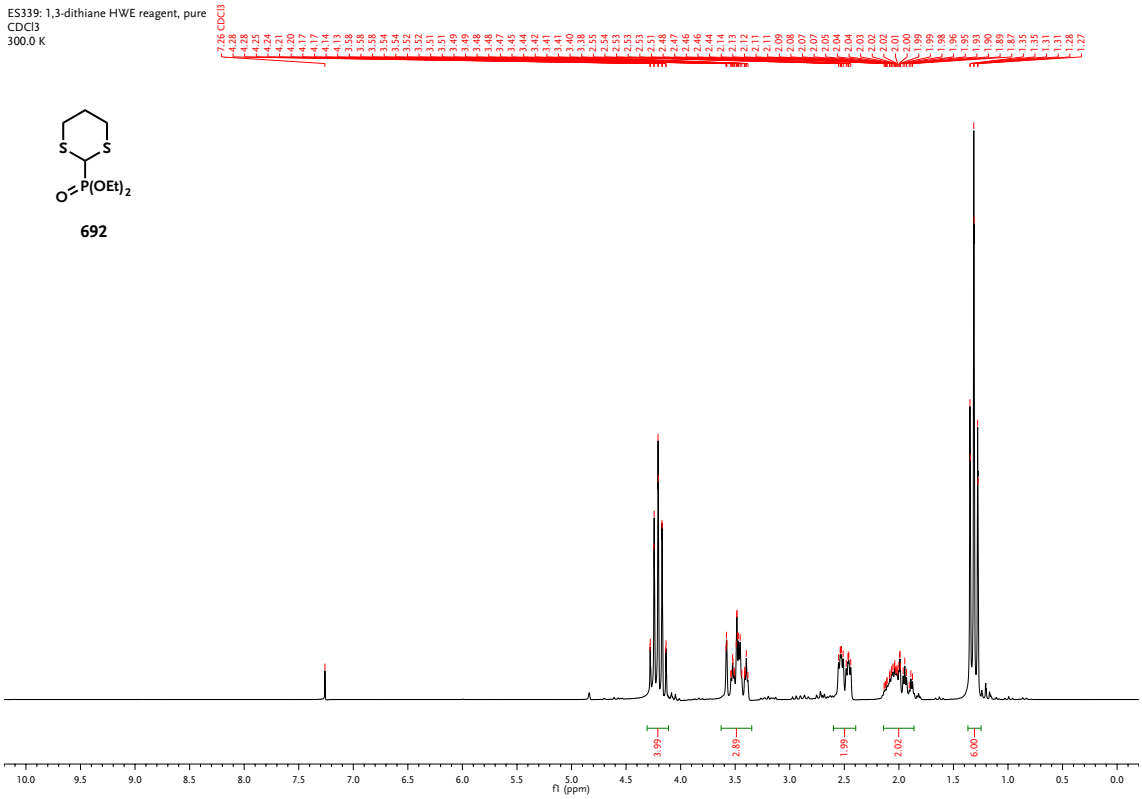
Spectrum B-310. ^{1}H-NMR spectrum for compound **1125** *(experimental on page 356)*.



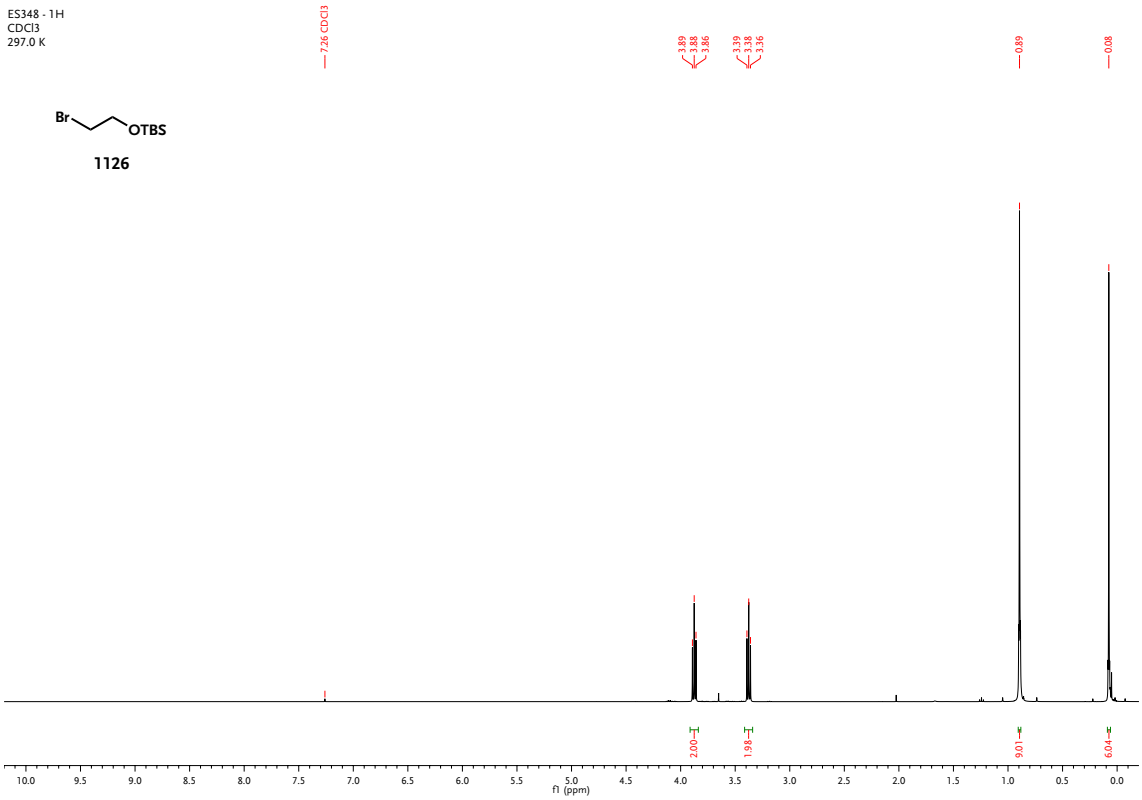
Spectrum B-311. ^{1}H-NMR spectrum for compound **530** *(experimental on page 357)*.



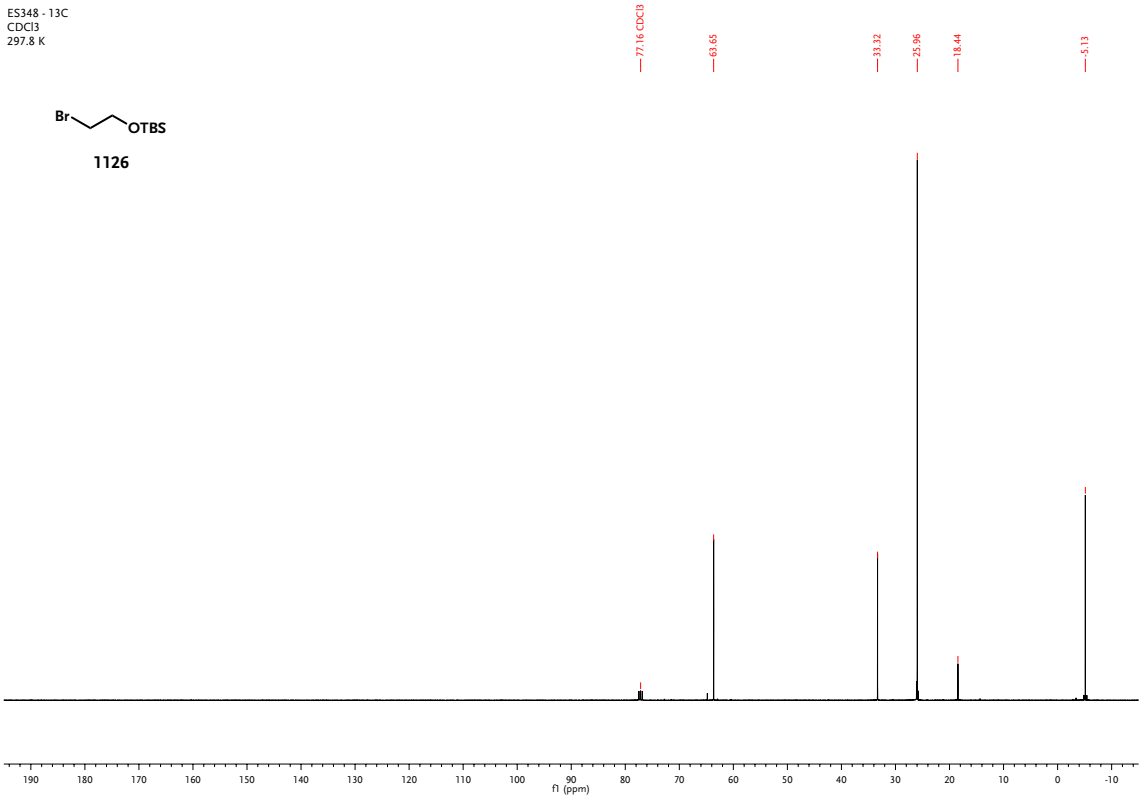
Spectrum B-312. ^{1}H-NMR spectrum for compound **690** *(experimental on page 358)*.



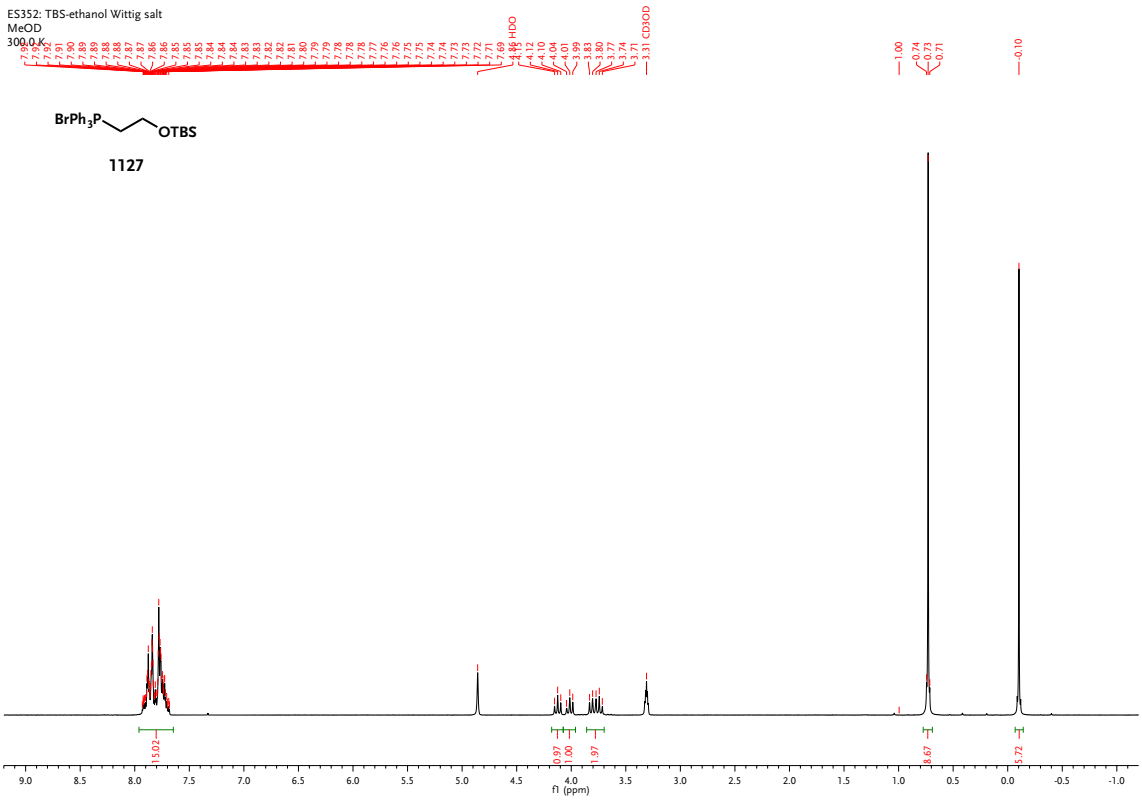
Spectrum B-313. ^{1}H-NMR spectrum for compound **692** *(experimental on page 358)*.



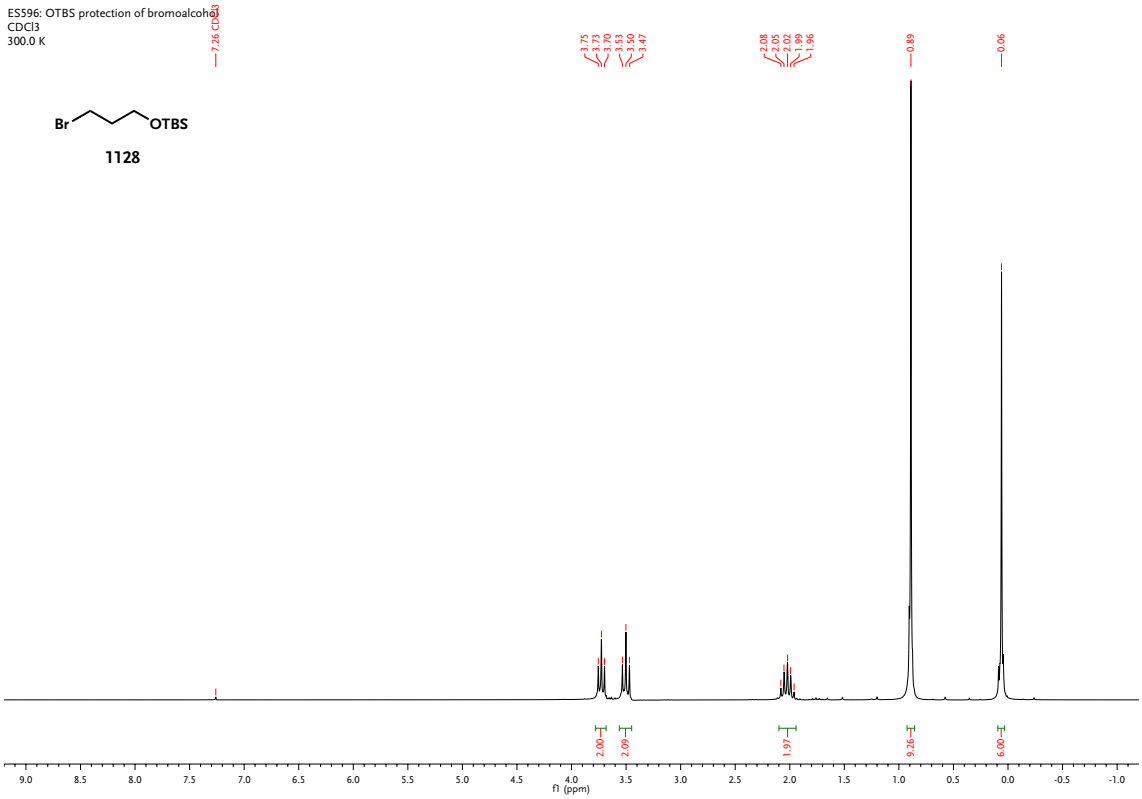
Spectrum B-314. ^{1}H-NMR spectrum for compound **1126** *(experimental on page 359)*.



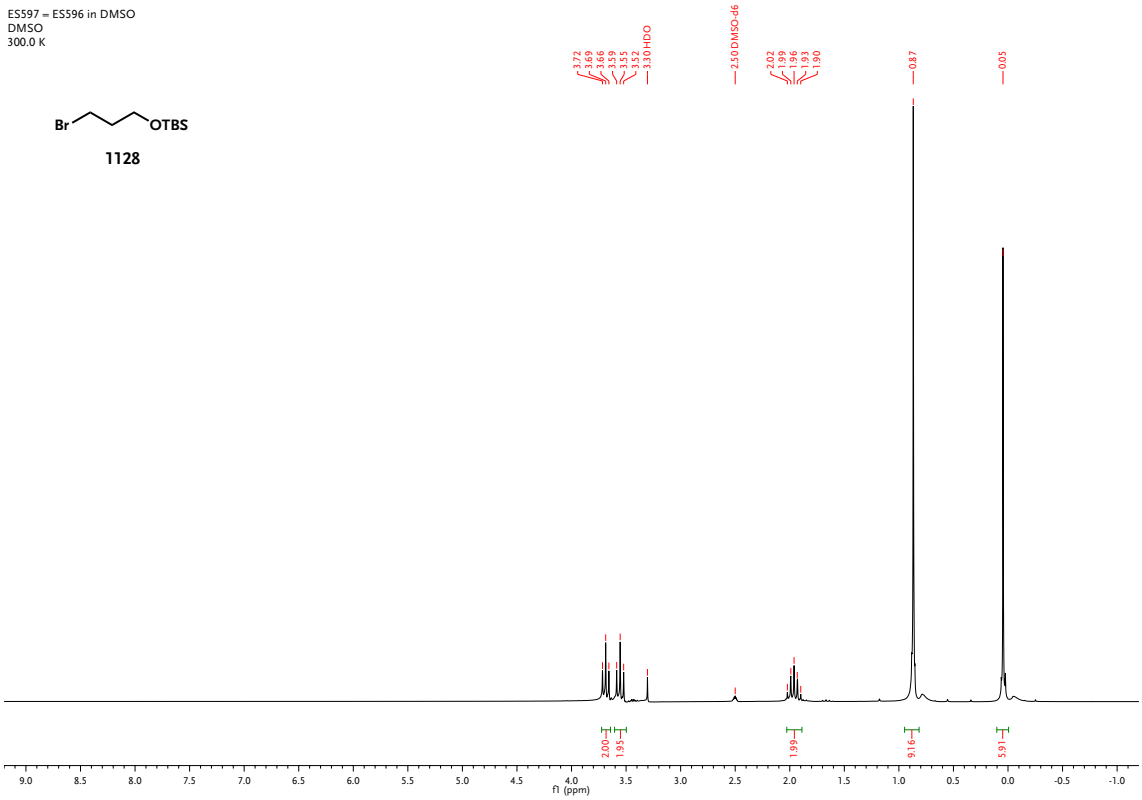
Spectrum B-315. ^{13}C-NMR spectrum for compound **1126** *(experimental on page 359)*.



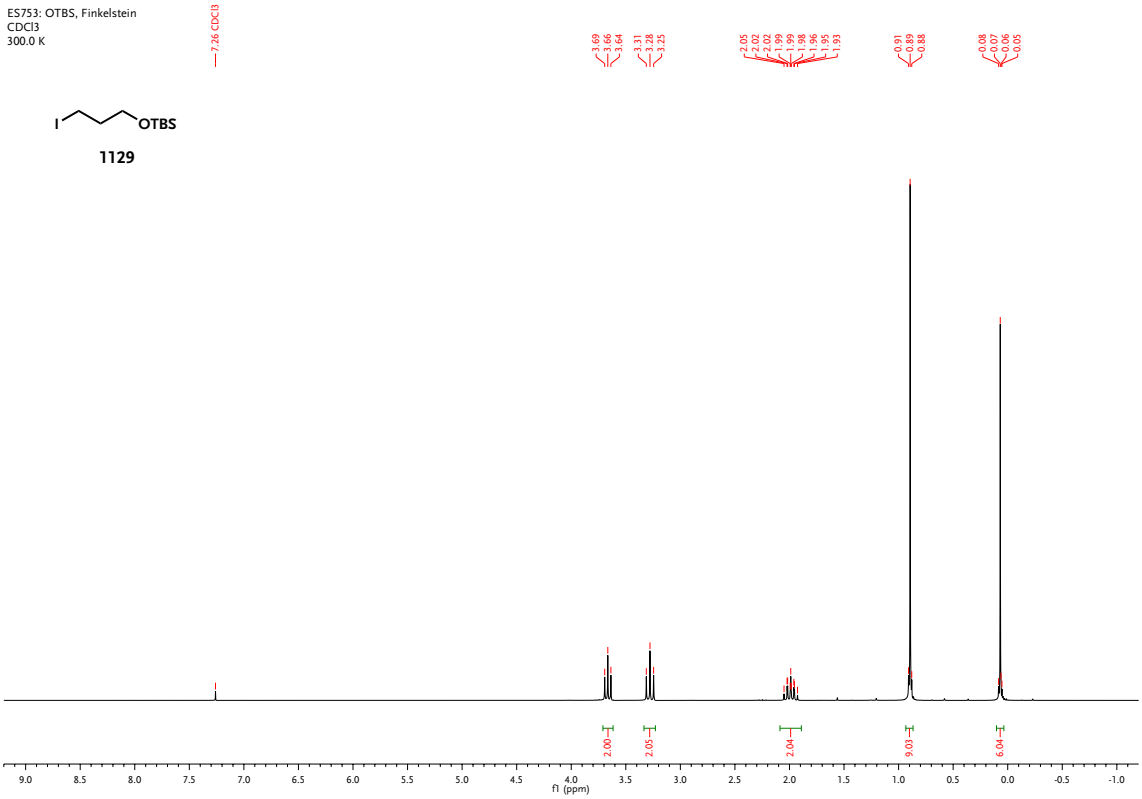
Spectrum B-316. ^{1}H-NMR spectrum for compound **1127** *(experimental on page 359)*.



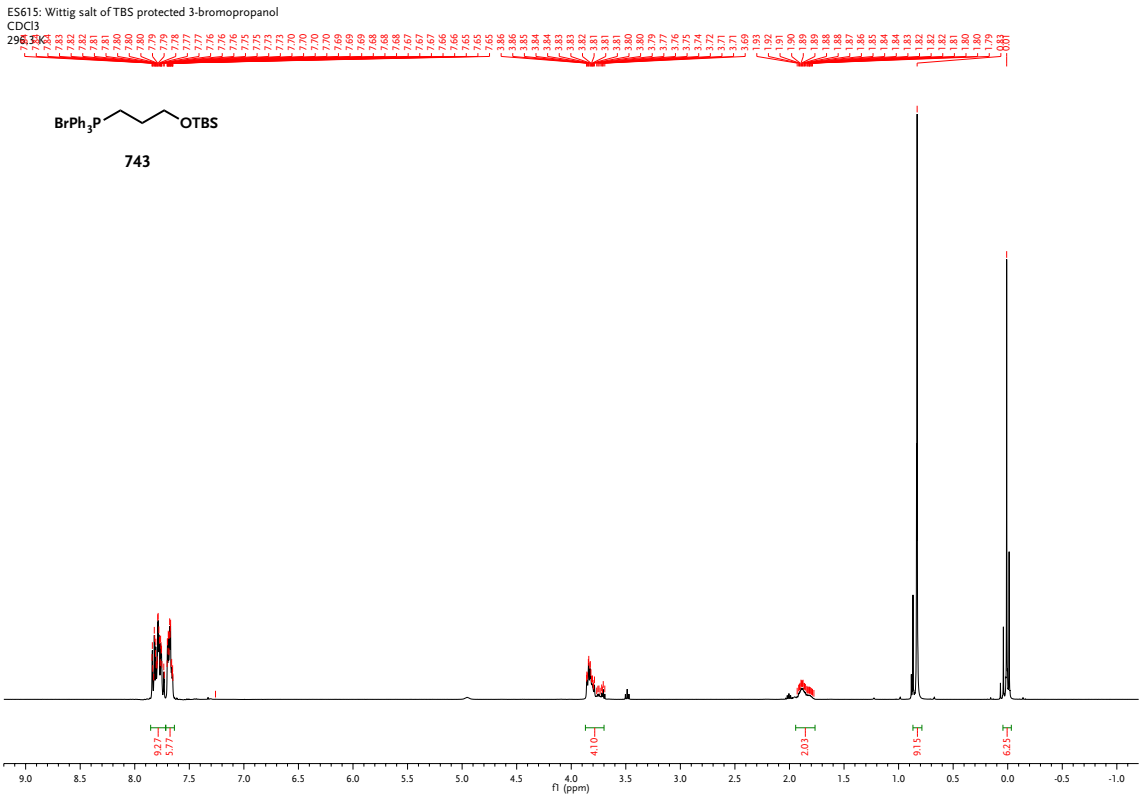
Spectrum B-317. ^{1}H-NMR spectrum for compound **1128** *(experimental on page 359)*.



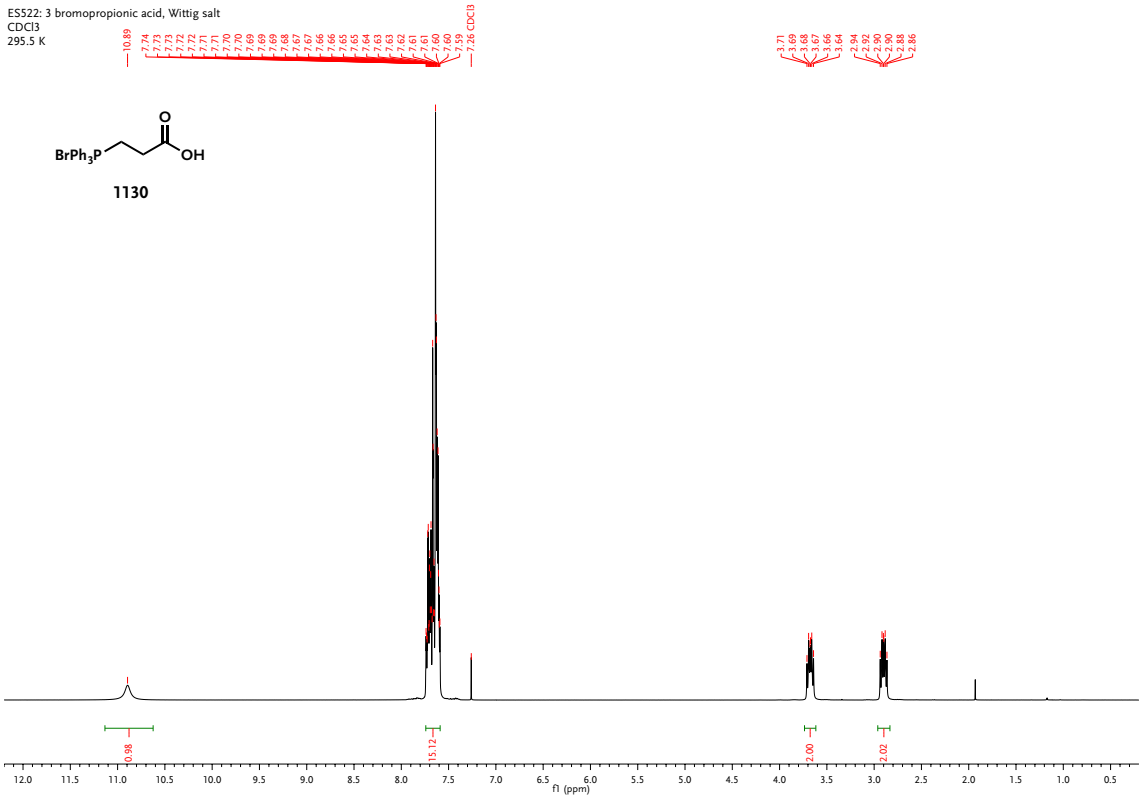
Spectrum B-318. ^{1}H-NMR spectrum for compound **1128** *(experimental on page 359)*.



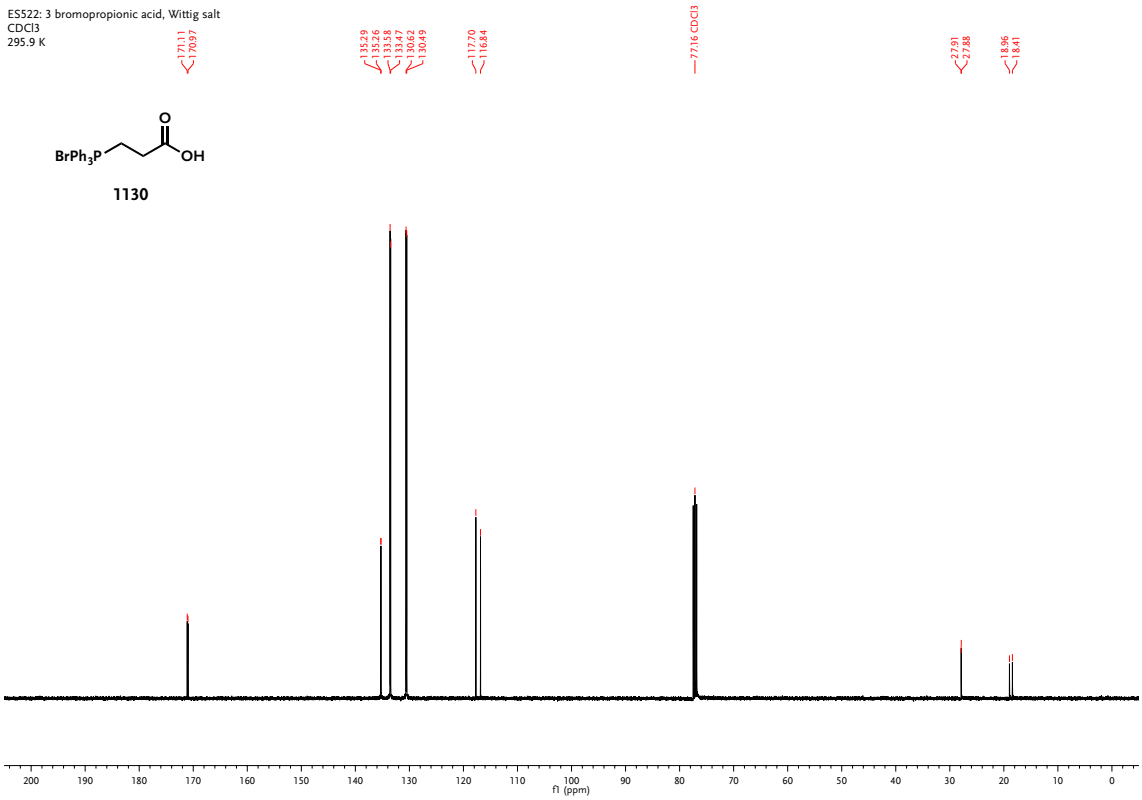
Spectrum B-319. [1]H-NMR spectrum for compound **1129** *(experimental on page 360)*.



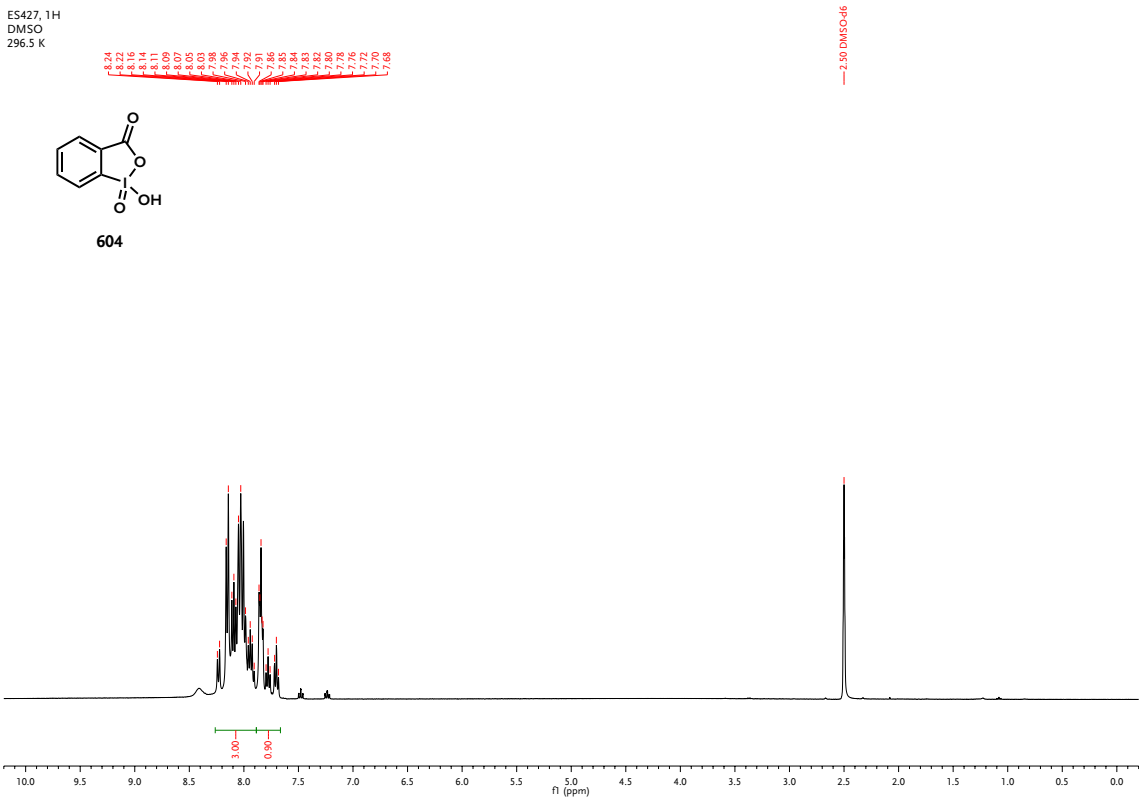
Spectrum B-320. [1]H-NMR spectrum for compound **743** *(experimental on page 360)*.



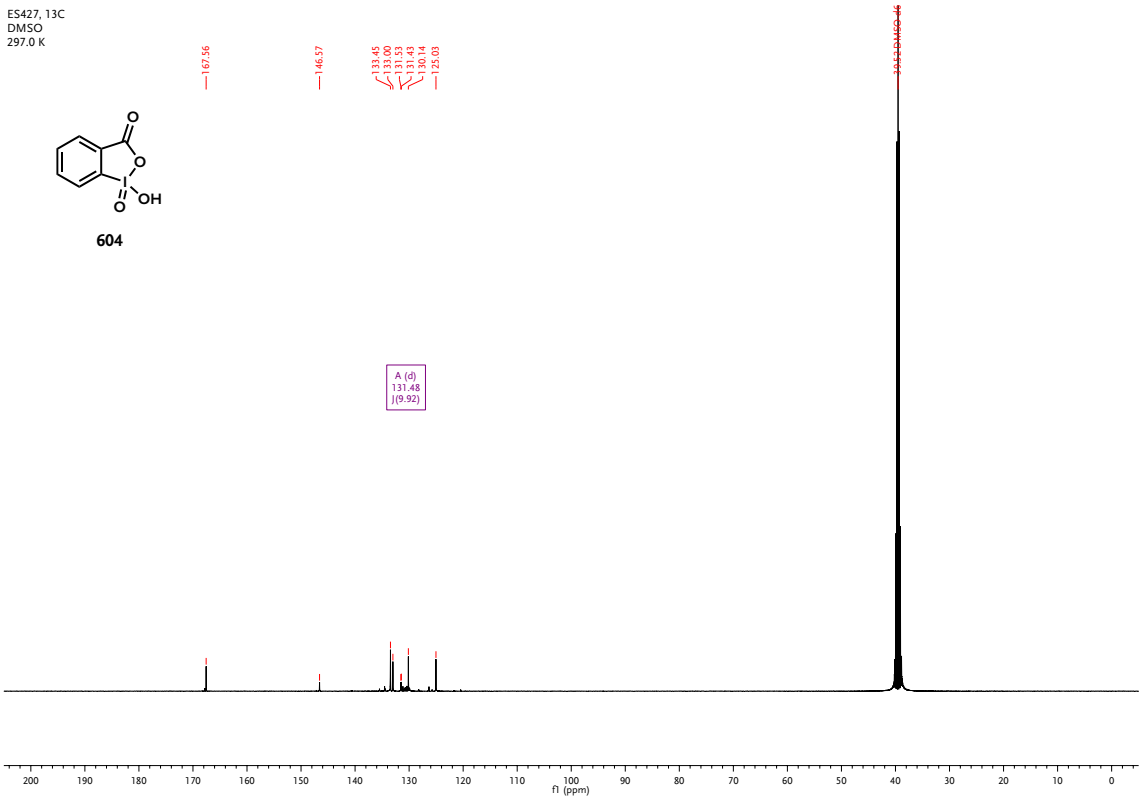
Spectrum B-321. ^{1}H-NMR spectrum for compound **1130** *(experimental on page 360)*.



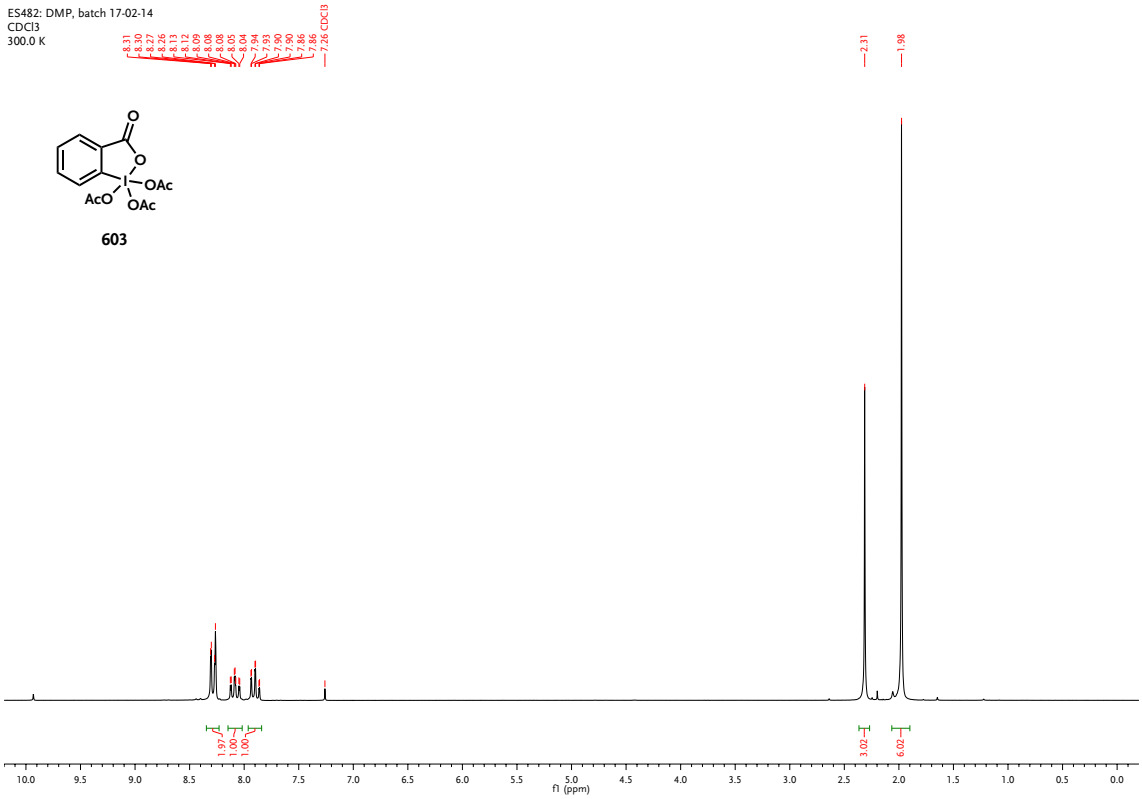
Spectrum B-322. ^{13}C-NMR spectrum for compound **1130** *(experimental on page 360)*.



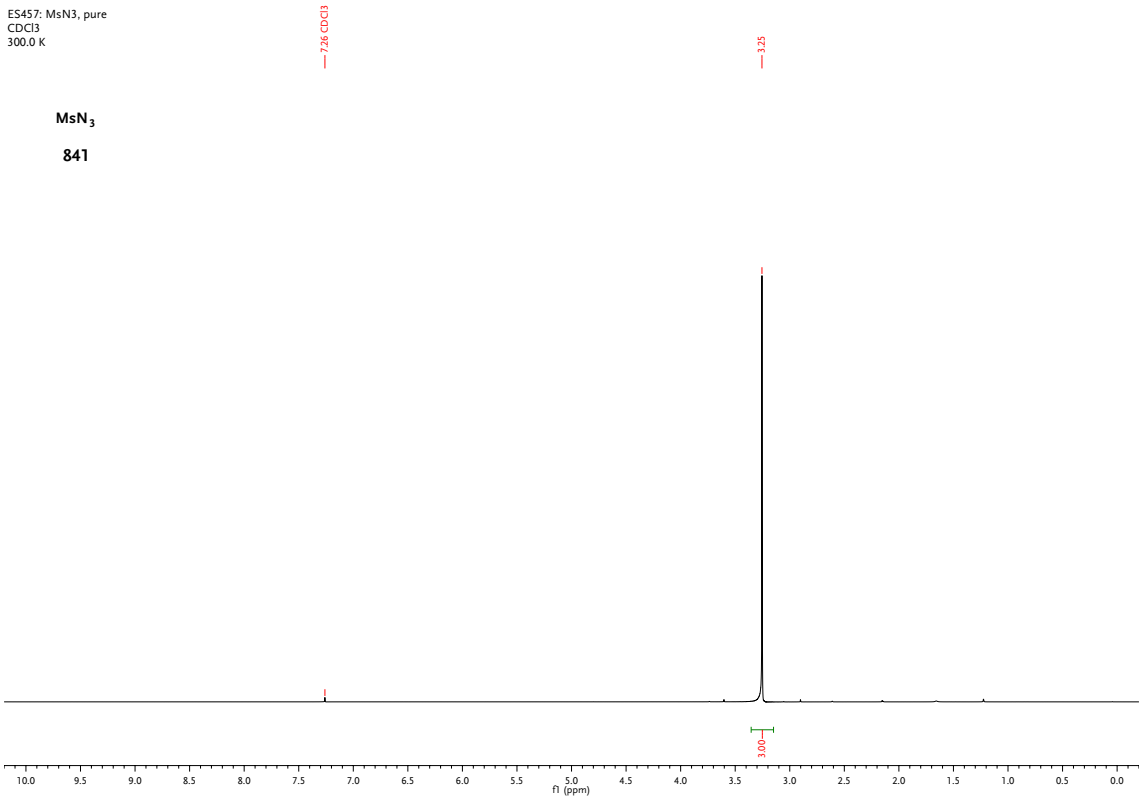
Spectrum B-323. ^{1}H-NMR spectrum for compound **604** *(experimental on page 361)*.



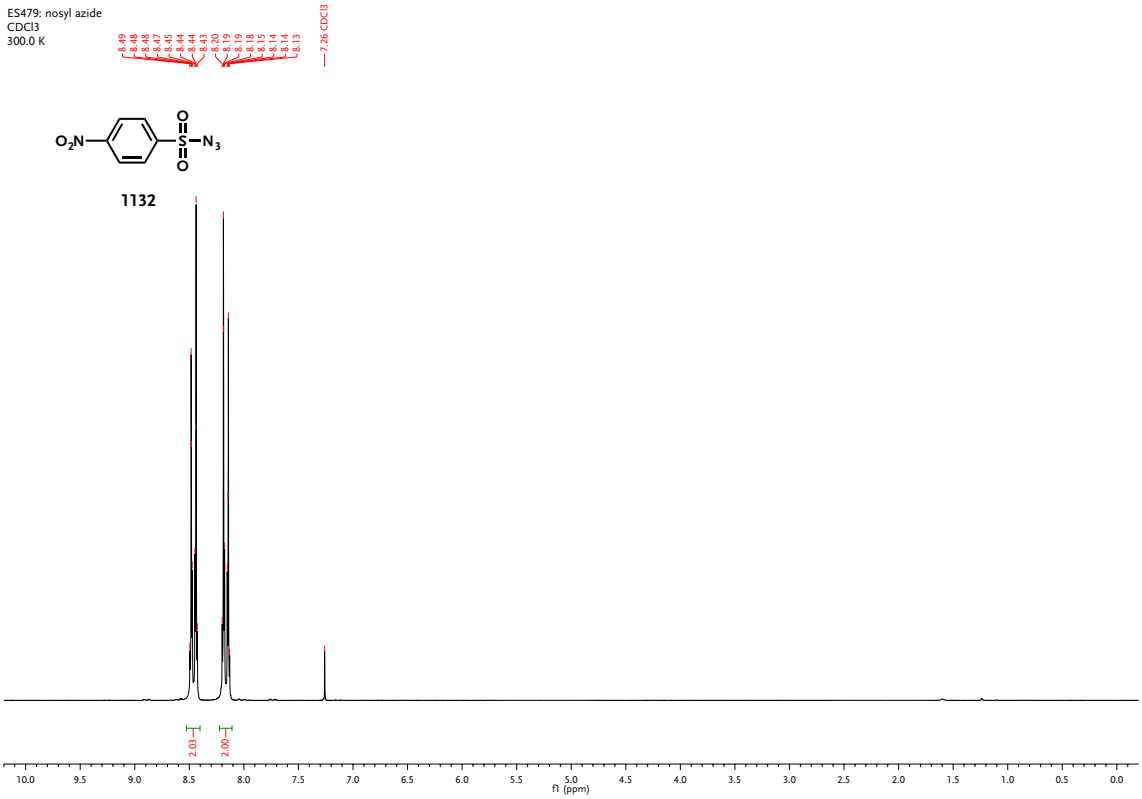
Spectrum B-324. ^{13}C-NMR spectrum for compound **604** *(experimental on page 361)*.



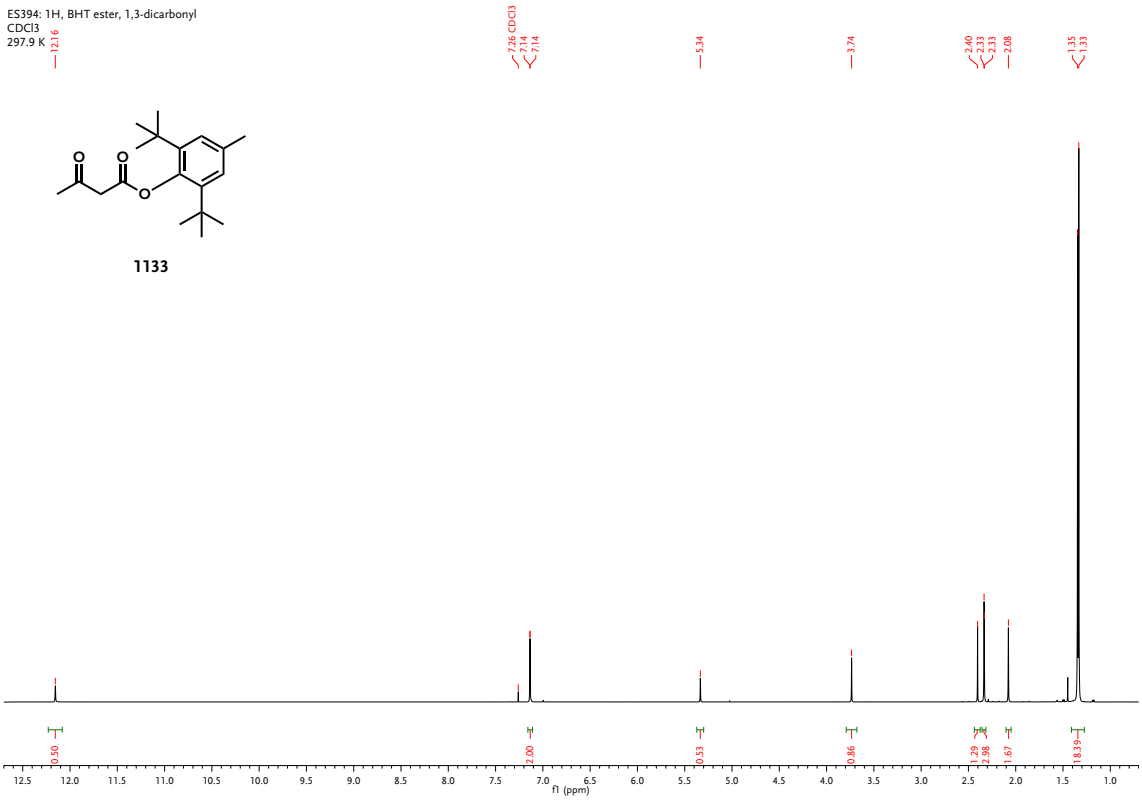
Spectrum B-325. ^{1}H-NMR spectrum for compound **603** *(experimental on page 362)*.



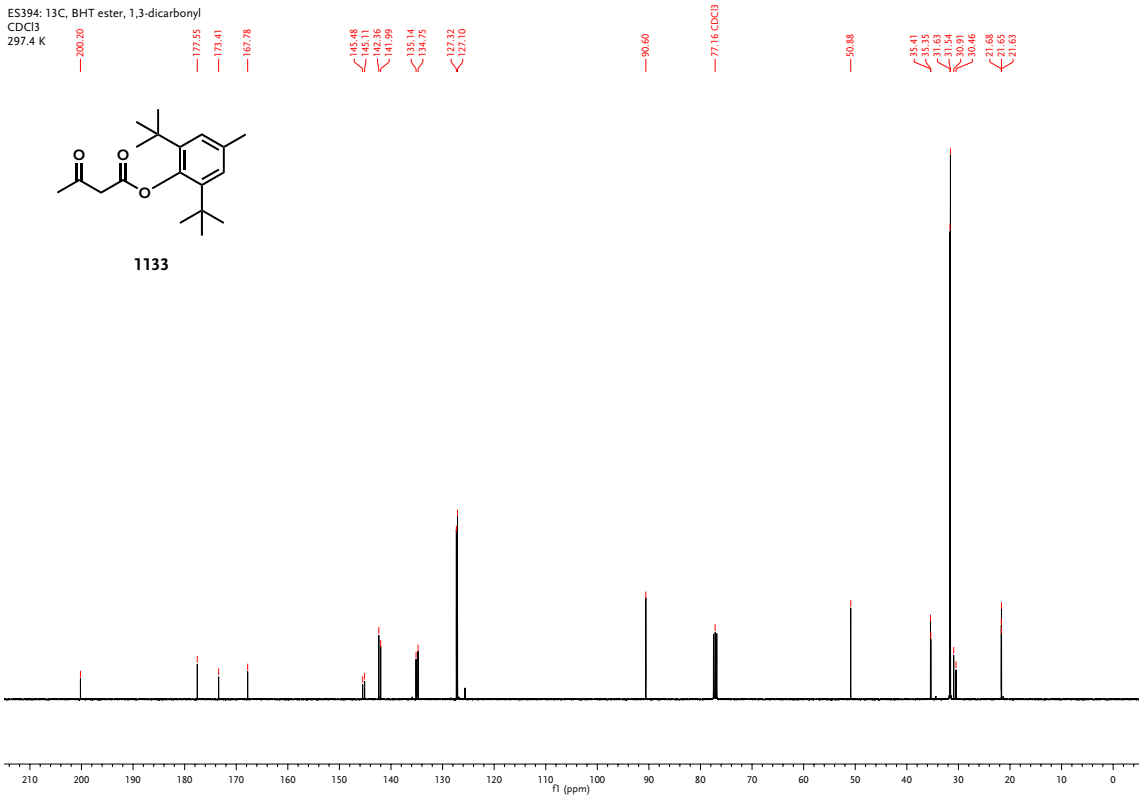
Spectrum B-326. ^{1}H-NMR spectrum for compound **841** *(experimental on page 363)*.



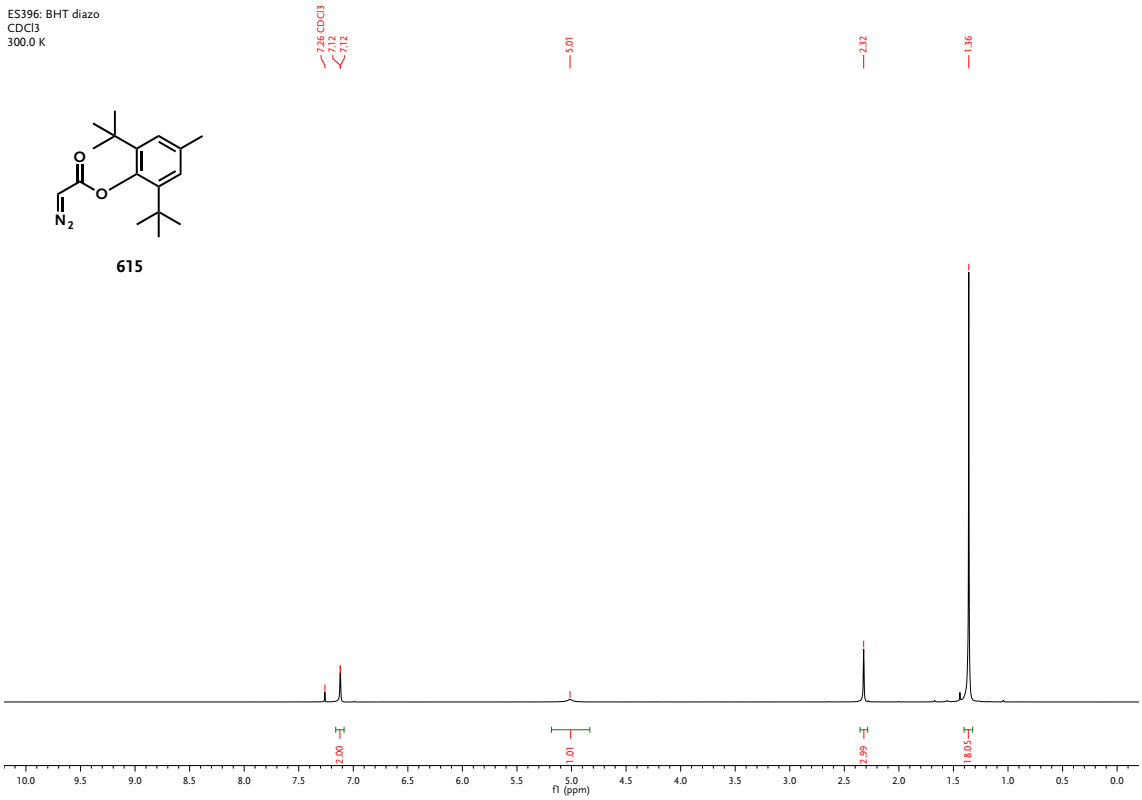
Spectrum B-327. [1]H-NMR spectrum for compound **1132** *(experimental on page 363)*.



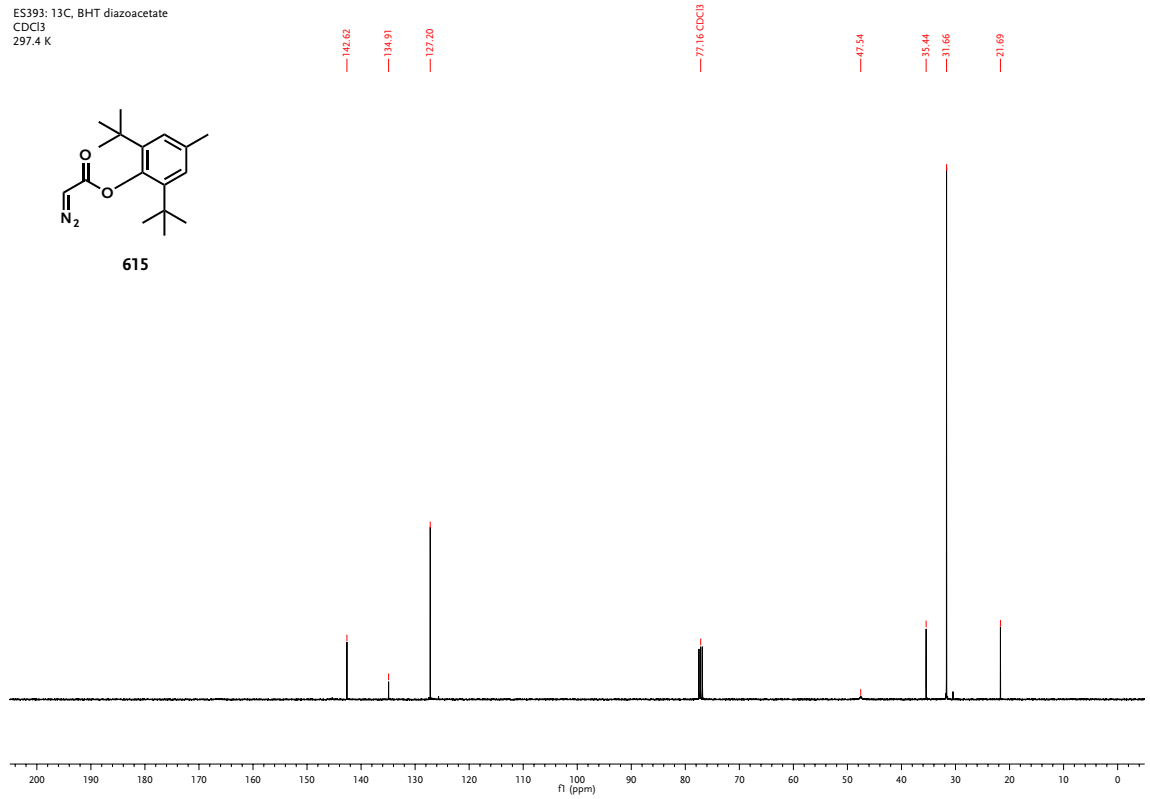
Spectrum B-328. [1]H-NMR spectrum for compound **1133** *(experimental on page 364)*.



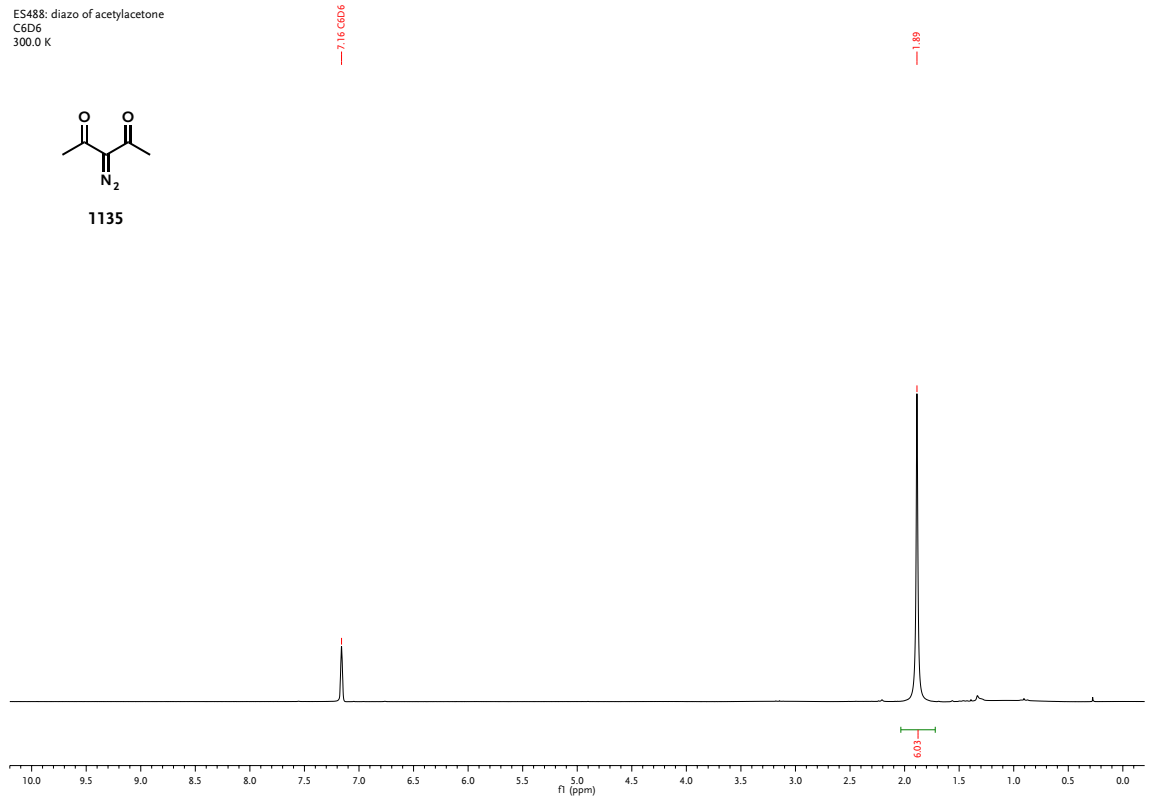
Spectrum B-329. ^{13}C-NMR spectrum for compound **1133** *(experimental on page 364)*.



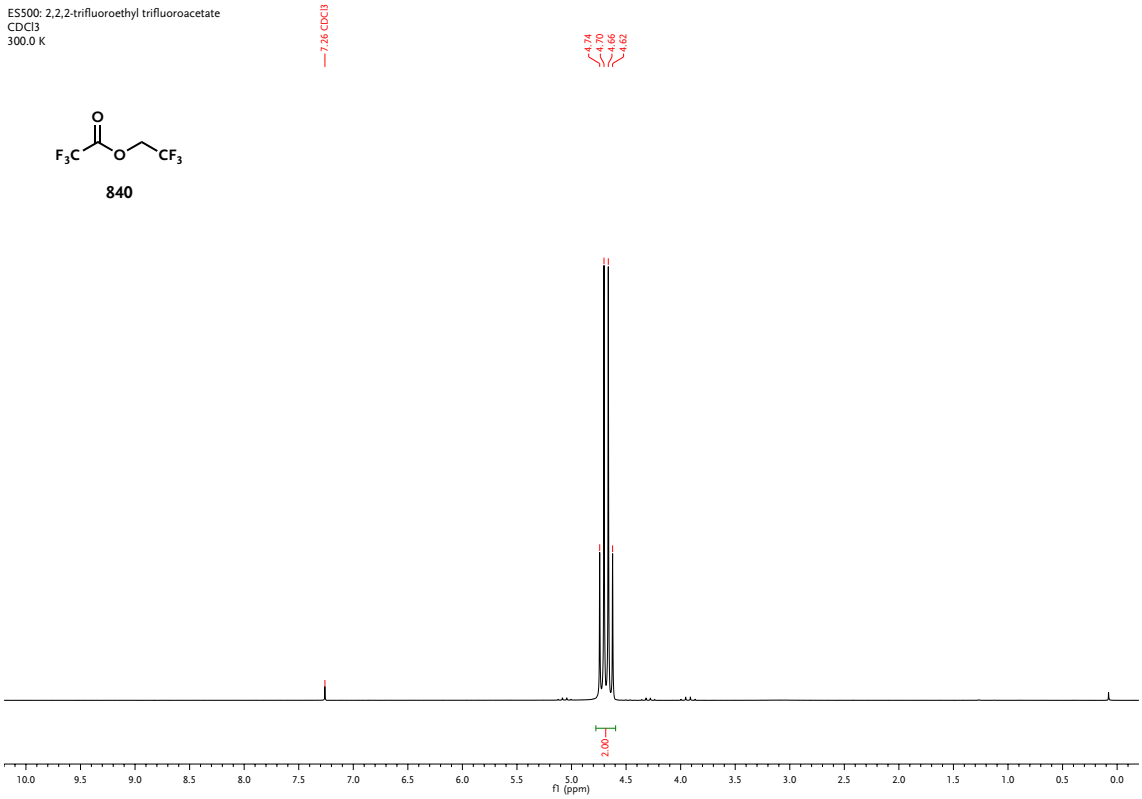
Spectrum B-330. ^{1}H-NMR spectrum for compound **615** *(experimental on page 365)*.



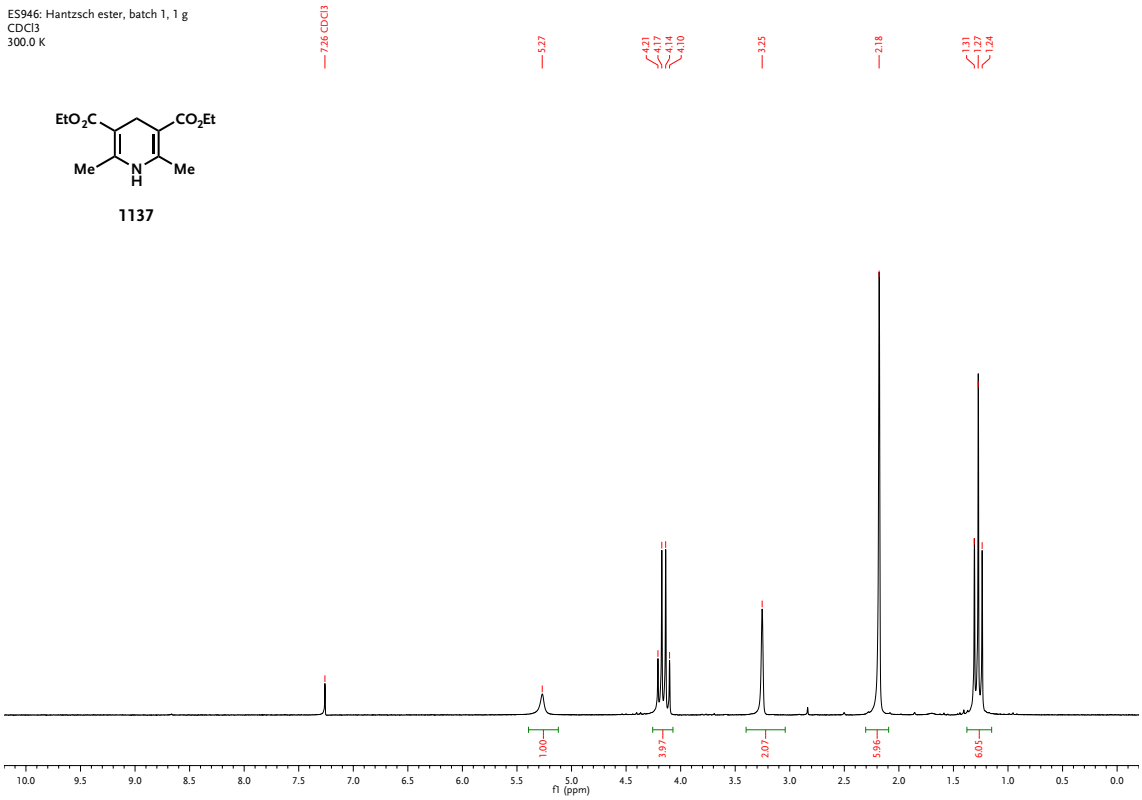
Spectrum B-331. ^{13}C-NMR spectrum for compound **615** *(experimental on page 365)*.



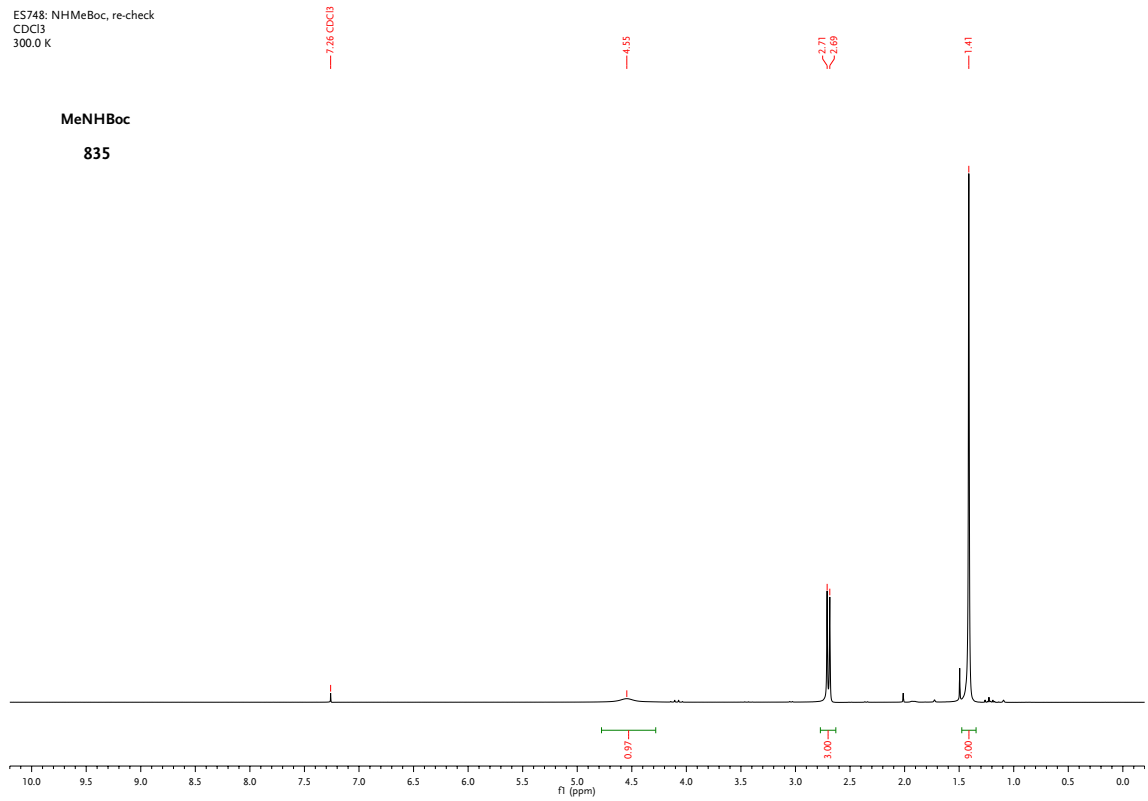
Spectrum B-332. ^{1}H-NMR spectrum for compound **1135** *(experimental on page 365)*.



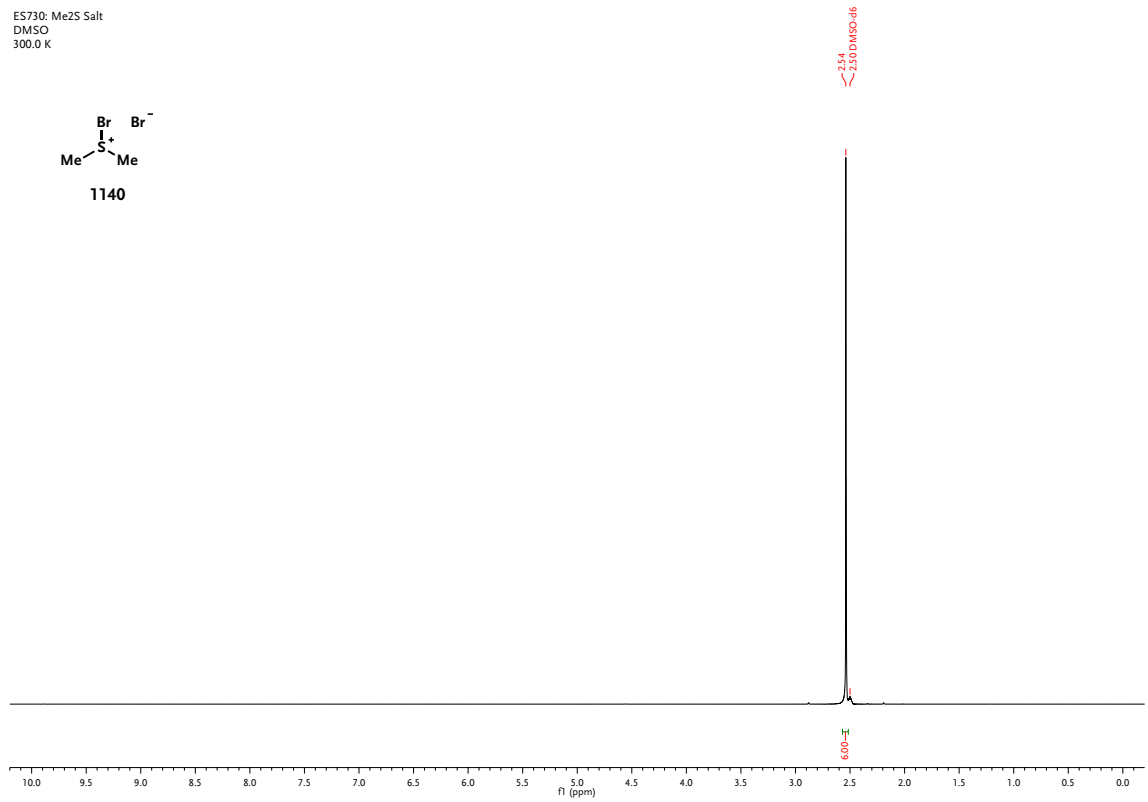
Spectrum B-333. ^{1}H-NMR spectrum for compound **840** *(experimental on page 366)*.



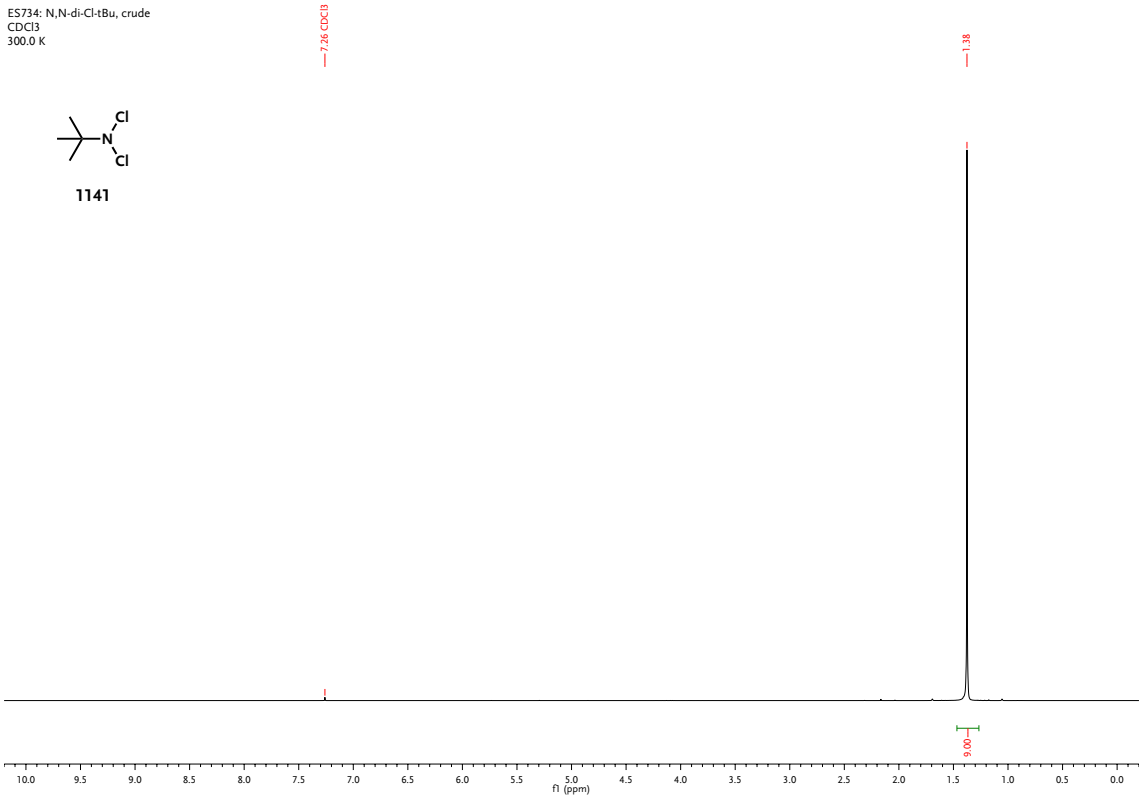
Spectrum B-334. ^{1}H-NMR spectrum for compound **1137** *(experimental on page 367)*.



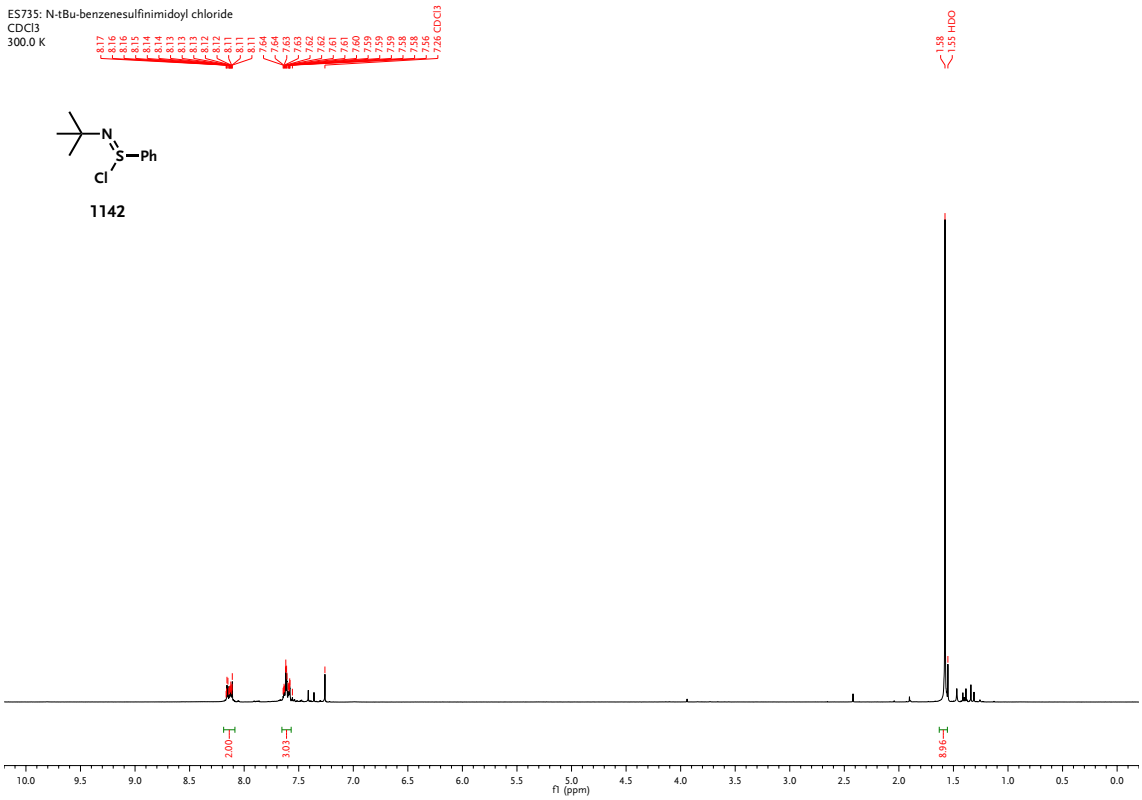
Spectrum B-335. ^{1}H-NMR spectrum for compound **835** *(experimental on page 367)*.



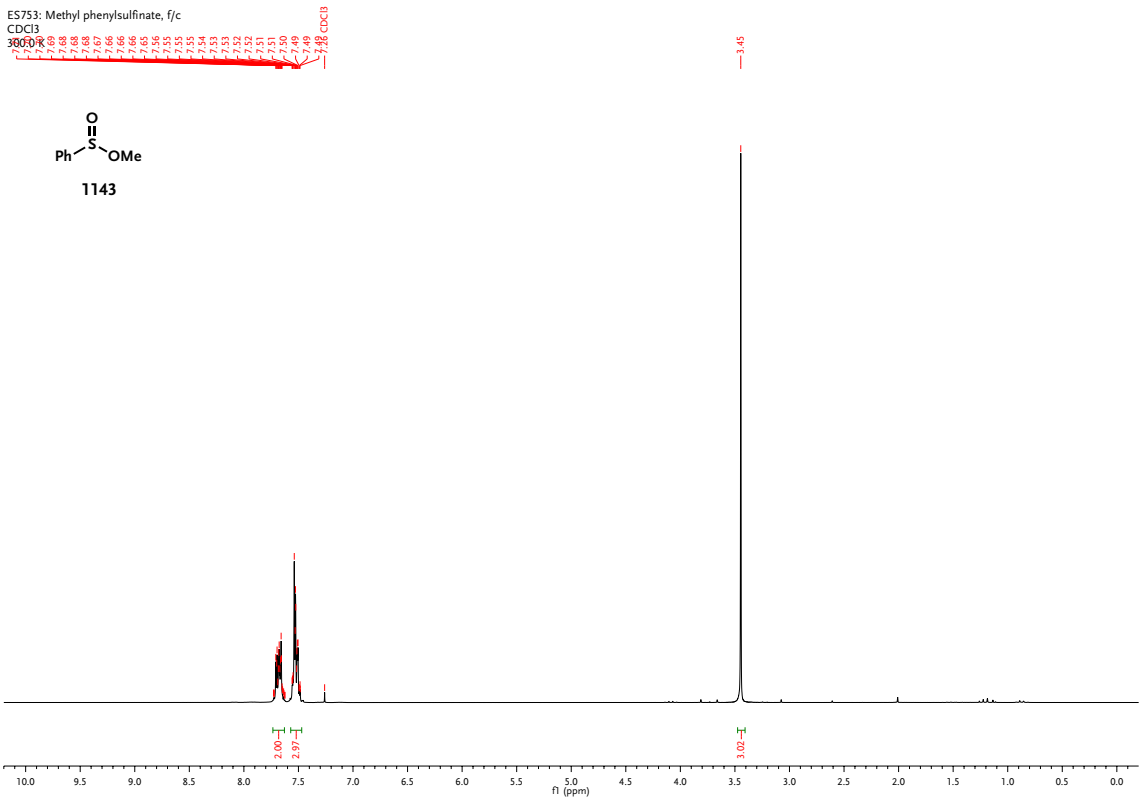
Spectrum B-336. ^{1}H-NMR spectrum for compound **1140** *(experimental on page 368)*.



Spectrum B-337. ^{1}H-NMR spectrum for compound **1141** *(experimental on page 368)*.

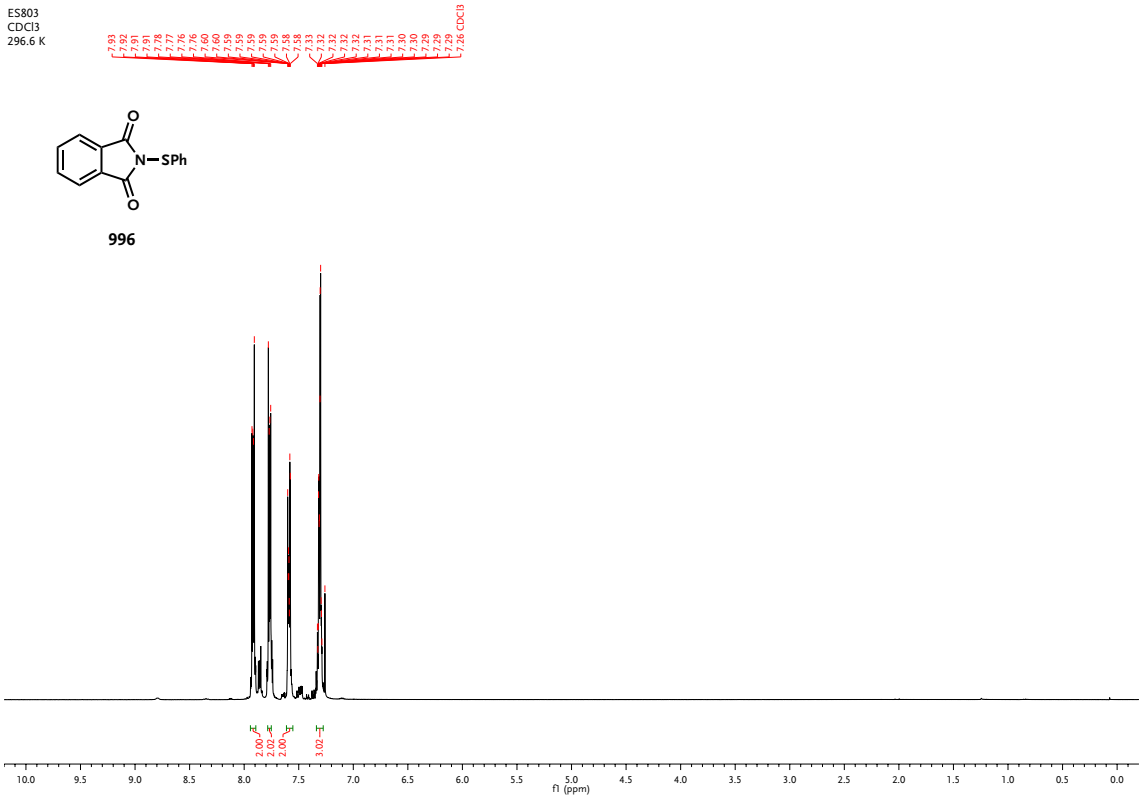


Spectrum B-338. ^{1}H-NMR spectrum for compound **1142** *(experimental on page 369)*.

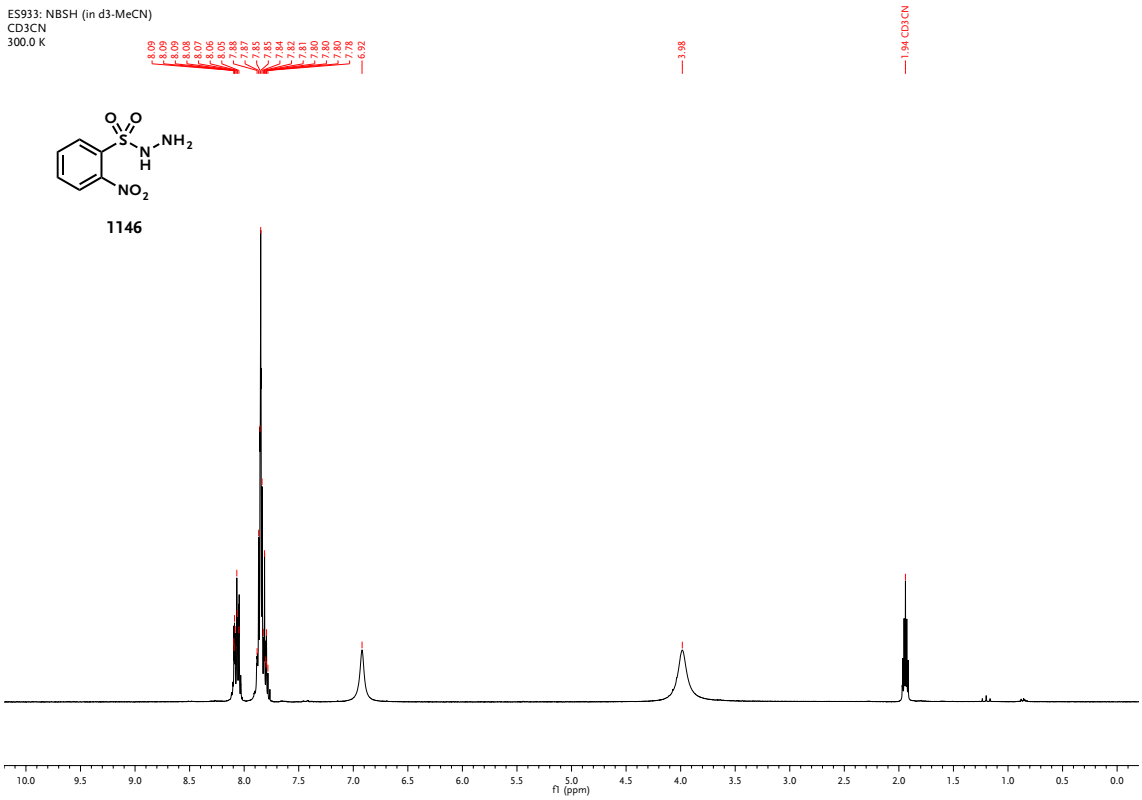


Spectrum B-339. [1]H-NMR spectrum for compound **1143** *(experimental on page 369)*.

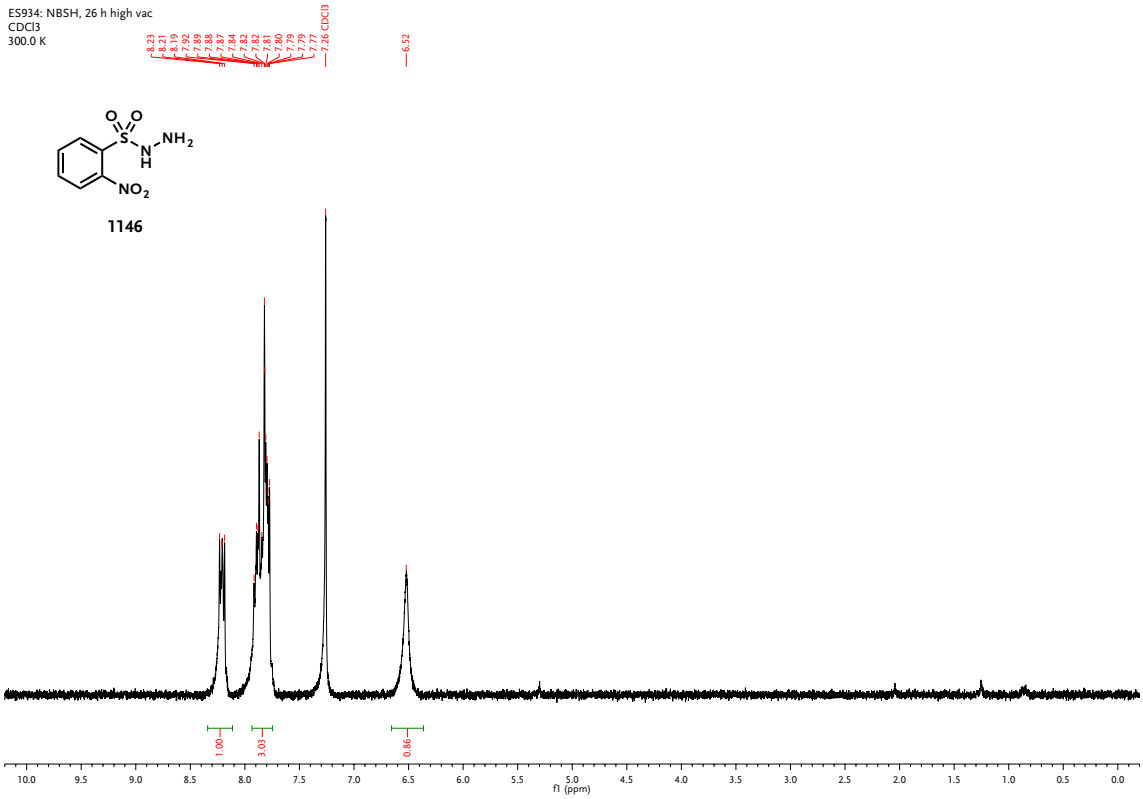
Spectrum B-340. [1]H-NMR spectrum for compound **1008** *(experimental on page 369)*.



Spectrum B-341. ^{1}H-NMR spectrum for compound **996** *(experimental on page 370)*.



Spectrum B-342. ^{1}H-NMR spectrum for compound **1146** *(experimental on page 371)*.



Spectrum B-343. ^{1}H-NMR spectrum for compound **1146** *(experimental on page 371)*.

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C

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List of Abbreviations

D

#	
#	entry
—	no reaction (in tables)
Δ	reflux
μw	microwave
18-c-6	18-crown-6
A	
abs.	absolute
Ac	acetyl
acac	acetylacetone
A-FABP	adipocyte fatty-acid binding protein
AIBN	azobisisobutyronitrile
Alloc	allyloxycarbonyl
aq.	aqueous
Ar	aryl
B	
$BArF_{24}$	tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate
BHT	butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
brsm	based on recovered starting material
Bu	butyl
BTAC	benzyltriethylammonium chloride
BTEAC	→ BTAC
BTMAP	benzyltrimethylammonium bromide
Bz	benzoyl
C	
CAN	ceric ammonium nitrate
cat.	catalyst
cat.	catalytic (in terms of amounts)
cf.	*confer* (compare to)
Cp	cyclopentadienyl
COD	1,5-cyclooctadiene
cond.	conditions
CSA	camphorsulfonic acid
cy	cyclohexyl
D	
d_n	deuteration degree
DABCO	1,4-diazabicyclo[2.2.2]octan
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DTBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	dichloroethane
DCH-18-c-6	dicyclohexano-18-crown-6
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
DEAD	diethyl azodicarboxylate

decomp.	decomposition
DIAD	diisopropyl azodicarboxylate
DiBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMAPP	dimethylallyl pyrophosphate
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMFDMA	*N*,*N*-dimethylformamide dimethyl acetal
DMI	1,3-dimethyl-2-imidazolidinone
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DNsOH	2,4-dinitrobenzenesulfonic acid
DOSP	*N*-(*p*-dodecylphenylsulfonyl)prolinato
dpephos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DVCPR	divinylcyclopropane rearrangement
DXP	1-deoxy-D-xylulose 5-phosphate

E

eq.	equivalent(s)
Et	ethyl
EWG	electron withdrawing group

G

GPP	geranyl pyrophosphate

H

HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HDAC	histone deacetylase
HEH	Hantzsch ester
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMTA	hexamethylenetetramine
HR-EI-MS	high resolution–electron ionization–mass spectrometry
HOMO	highest occupied molecular orbital

I

i	*iso*-
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
imid	imidazole
IPP	isopentenyl pyrophosphate
IUPAC	International Union of Pure and Applied Chemistry

L

L	ligand
LA	Lewis acid
LC–MS	liquid chromatography–mass spectrometry
LDA	lithium diisopropylamide
LiTEBH	lithium triethylborohydride (superhydride)
LG	leaving group
LSD	lysergic acid diethylamide
LTB_4	leukotriene B_4
LUMO	lowest unoccupied molecular orbital

M

M	molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
Mes	mesityl
MIRC	Michael initiated ring closure
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
MOM	methoxymethyl
MVK	methyl vinyl ketone

N

n	*normal*- (descriptor)
N	normal (concentration)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NDMBA	*N*,*N*-dimethylbarbituric acid
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Ns	nosyl (4-nitrobenzenesulfonyl)
Nu	nucleophile

O

O	octyl

P

p-ABSA	4-acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pic	3,4-pyridinedicarboxylate

PMP	*p*-methoxyphenyl
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTAD	(1-adamantyl)-(*N*-phthalimido)acetato
PTC	phase-transfer catalyst
*p*TSA	*p*-toluenesulfonic acid
pyr	pyridine

Q

quant.	quantitative

R

R	rest
Ra–Ni	Raney nickel
R_f	retardation factor
rt.	room temperature

S

s	*sec*-
SEM	2-(trimethylsilyl)ethoxymethyl
SIRT1	sirtuin-1

T

t	*tert*-
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAC	tetra-*n*-butylammonium chloride
TBAI	tetra-*n*-butylammonium iodide
TBAF	tetra-*n*-butylammonium fluoride
TBCHD	2,4,4,6-tetrabromo-2,5-cyclohexa dienone
TBDMS	→ TBS
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBTH	tributyltin hydride
TEBAC	→ BTAC
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
THP	tetrahydropyranyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMDS	1,1,3,3-tetramethyldisiloxane
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	tosyl (toluenesulfonyl)

W

w/u	work-up

X

xs	excess
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Index of Compounds

E

Mentioned in text

Experimental

NMR spectra

List of Schemes

F

List of Figures

G

List of Tables

H

List of Charts

Curriculum Vitae

J

Ph.D. Thesis

02/2013 – 07/2016 **Ph.D. Student**, Gottfried Wilhelm Leibniz Universität Hannover, Germany

Thesis title: Construction of Cyclohepta[*b*]indoles in the Total Synthesis of Indole Alkaloids

Supervisor: Prof. Dr. Tanja Gaich (now University of Konstanz)

Overall grade: summa cum laude

Master of Science

10/2010 – 12/2012 **Master course Medicinal and Natural Product Chemistry**, Gottfried Wilhelm Leibniz Universität Hannover, Germany.

Overall grade: graduation with distinction (1.2)

Master's thesis:
- The Divinylcyclopropane Rearrangement and its Application in the Total Synthesis of Indole Alkaloids
- supervised by Prof. Dr. Tanja Gaich (now University of Konstanz)
- overall grade: 1.0

International Experience

09/2011–03/2012 Research Stay with Prof. Steven V. Ley FRS, University of Cambridge, UK

Project: Azadirachtin – Studies Towards the Second Generation Synthesis of the Decalin Fragment

Bachelor of Science

10/2007–09/2010 **Bachelor course Chemistry**, Gottfried Wilhelm Leibniz Universität Hannover, Germany

Overall grade: good (2.2)

Bachelor's thesis:
- Synthesis of Asymmetric Epoxide Building Blocks Using the Shi Epoxidation for the Total Synthesis of Maltepolid E
- Dr. Evgeny Prusov / Helmholtz Centre for Infection Research, Braunschweig
- overall grade: 1.0