Development of a Total Synthesis of Cebulactams A1 and A2

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Helge Berneaud-Kötz, M. Sc.

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Referent:	Professor Dr. Andreas Kirschning
Korrefferent:	Professor Dr. Markus Kalesse
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"The chase is better than the catch." -
H. P. Baxxter

Kurzzusammenfassung

Helge Berneaud-Kötz

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Schlagwörter: Totalsynthese, marine Naturstoffe, Hochdruck-Diels-Alder-Reaktion, *ortho*-Chinonmethide, Olefinierungsreaktion, Wolfram-katalysierte Cykloisomerisierung.

Die Cebulactame A1 und A2 wurden im Jahr 2008 aus einem Extrakt der marinen Spezies *Saccharopolyspora cebuensis* isoliert. Sie bestehen aus einem 13-gliedrigen Makrolactam, einem Chroman Kern, fünf Stereozentren und einer Doppelbindung, die in Cebulactam A1 (*E*)-konfiguriert und in Cebulactam A2 (*Z*)-konfiguriert ist.

In der folgenden Arbeit werden zwei unterschiedliche Ansätze zu deren Totalsynthese beschrieben.

Der erste Weg konzentrierte sich auf eine Hochdruck-Diels-Alder-Reaktion in einer *de novo*-Konstruktion des aromatischen Kerns des Chromans, ausgehend von einem Dihydropyran, das mittels Aldolchemie und einer Wolfram-katalysierten Cycloisomerisierung synthetisiert wurde.

Der zweite Ansatz befasste sich mit *ortho*-Chinonmethid Chemie. Einerseits wird die Synthese des aromatischen Kerns und der Polyketidkette beschrieben, sowie deren Umsetzung in der ersten bekannten asymmetrischen katalytischen Oxa-6π-Elektrozyklisierungsreaktion. Zum anderen wird ein inverser Elektronenbedarfs-Hetero-Diels-Alder-Ansatz beschrieben, der als Schlüsselschritt zur Ermöglichung der Makrozyklisierung getestet wurde. In diesem Zusammenhang wurde der Vorläufer mit allen Kohlenstoffatomen von Cebulactam *via* einer intermolekularen Reformatsky-Reaktion synthetisiert.

Abstract

Helge Berneaud-Kötz

Development of a Total Synthesis of Cebulactams A1 and A2

Keywords: total synthesis, marine natural products, high pressure Diels-Alder reaction, *ortho*-quinone methide chemistry, olefination reaction, tungsten-catalyzed cycloisomerization.

The cebulactams A1 and A2 were isolated from an extract of the marine species *Saccharopolyspora cebuensis* in 2008. They consist of a 13-membered macrolactam, a chromane moiety, five stereocenters and a double bond, which is (*E*)-configured in cebulactam A1 and (*Z*)-configured in cebulactam A2.

In the following thesis, two distinctive approaches towards their total synthesis are described.

The first route focused on a high-pressure Diels-Alder reaction in a *de novo* construction of the aromatic core of the chromane, starting from a dihydropyran which was synthesized using aldol chemistry and a tungsten-catalyzed cycloisomerization.

The second approach evolved around *ortho*-quinone methide chemistry. On one hand the synthesis of the aromatic core and the polyketide chain are described, as well as their transformation in the first known asymmetrical catalytic oxa-6π-electrocyclization reaction. On the other hand, an inverse electron-demand hetero-Diels-Alder approach is described, which was tested as a keystep to enable macrocyclization. In that regard, the precursor with all carbon atoms of cebulactam was synthesized *via* an intermolecular Reformatsky reaction.

Contents

List of Abbreviations

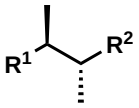
2,6-lutidine	2,6-dimethylpyridine
Ac	acetyl
Alloc	allyloxycarbonyl
B.C.	before christ
Bn	benzyl
brsm	based on recovered starting material
Bt	benzotriazole
*n*Bu	*n*-butyl
*s*Bu	*s*-butyl
*t*Bu	*tert*-butyl
CAN	ceric ammonium nitrate
CoA	coenzyme A
cod	cyclooctadienyl
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	days
DA	Diels-Alder
dba	dibenzylideneacetone
DBB	di-*tert*-butylbiphenyl
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	di*iso*propyl azodicarboxylate
DIBAl-H	di*iso*butylaluminium hydride
DIC	diisopropylcarbodiimide
DIPEA	*N,N*-di*iso*propylethylamine
DMAP	4-dimethylaminopyridine

DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
EA	ethyl acetate
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	equivalents
Et	ethyl
FDA	Food and Drug Administration
GCMS	gas chromatography mass spectrometry
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazane
HOBt	hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
IBX	2-iodoxybenzoic acid
Ipc	isopinocampheyl
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamine
LN	lithium naphthalenide
LUMO	lowest unoccupied molecular orbital
*m*CPBA	3-chloroperbenzoic acid
Me	methyl
Mes	mesitylene
min	minute
MOM	methoxymethyl
MS	molecular sieves
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile

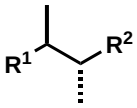
o/n	overnight
P	protecting group
PDC	pyridinium dichromate
PE	petroleum ether
PEPPSI	(3-chlorpyridyl)-(1,3-diisopropylimidazol-2-yliden)-palladium(II)-dichlorid
Ph	phenyl
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodine(III) ditrifluoroacetate
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
*i*Pr	*iso*-propyl
PT	5-phenyl-1H-tetrazole
*p*Ts	*para*-toluenesulfonyl
Py	pyridine
QTOF	quadrupole time-of-flight
QUINAP	1-naphthylisoquinoline
R	residue
R_f	retardation factor
SM	starting material
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TMEDA	*N,N,N,N*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
UV	ultraviolet

Preliminary Remarks

In the schemes and figures of the following thesis the following definition of absolute and relative stereochemistry is used. Wedged bonds show the absolute configuration of a stereocenter, whereas bar-typed bonds show the relative configuration of multiple stereocenters.

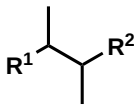


absolute stereochemistry

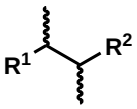


relative stereochemistry

Moreover, the use of single bonds indicates an indeterminate stereoconfiguration, while the use of wavy bonds describes the presence of a racemate.



indeterminate stereochemistry



racemate

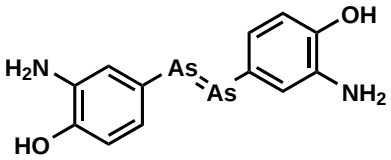
1 Introduction

1.1 Natural Products

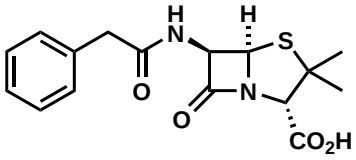
Organic synthesis is a rather new field of science, with the first syntheses dating back to the 1820s. At that time, Friedrich Wöhler succeeded to synthesize urea by heating of ammonium cyanate, which was prepared from silver cyanate and ammonium chloride. He thus managed to prepare *'animal'* compounds by the reaction of *'artificial'* starting materials.[1] This not only united organic and inorganic chemistry, which were then considered two separate disciplines, but also laid the foundation for modern biochemistry. Since then, people have been interested in the use of organic compounds to improve health. At the beginning of the 20th century, the first systematic studies on azo dyes and organoarsenic compounds by Paul Ehrlich gave rise to efforts to synthesize antibacterial organic compounds. Later, the first fully synthetic anitibiotic arsphenamine (**1**) was produced in Ehrlich's lab by Alfred Bertheim, enabling the treatment of *syphilis*, albeit with severe adverse effects.[2,3] Although the medicinal use of natural resources dates back to 2600 B.C., it was in 1929 that natural products entered the world of pharmacy, when Alexander Fleming published his work on a serendipitous find that contamination with the mold *penicillium notatum* on culture plates of *staphylococcus* resulted in lysis of the bacterium. After further investigation he also demonstrated that penicillin, the extract of the mold *penicillium*, which contains penicillin G (**2**, Figure 1.1), among others, exhibits inhibitory activity against a variety of bacteria.[4] It was thus reasoned that the fungus was producing an organic compound capable of repelling other bacteria for

1 F. Wöhler, *Ann. Phys.* **1828**, *87*, 253–256.
2 P. Ehrlich, A. Bertheim, *Berichte der Dtsch. Chem. Gesellschaft* **1912**, *45*, 756–766.
3 K. J. Williams, *J. R. Soc. Med.* **2009**, *102*, 343–348.
4 A. Fleming, *Br. J. Exp. Pathol.* **1929**, *10*, 226–236.

defensive purposes. This groundbreaking insight marked the beginning of modern natural product chemistry. Over the past 100 years, humankind has explored the broad library of bioactive natural compounds and used them for a variety medicinal applications, such as fighting infections and cancer, as well as cardiovascular diseases and multiple sclerosis.[5–7] In addition, the use of natural products as inspiration for the determination of lead structures to develop new artificial drugs has played a central role in the pharmaceutical industry.[8]



arsphenamine
1



penicillin G
2

Figure 1.1: Some of the first antibiotics, arsphenamine (**1**, originally published dimeric structure)[2] and penicillin G.[4]

One of natural products' success stories are the tetracyclines which mirror the evolution of medicinal chemistry (Figure 1.2).[9] This class of natural products consist of several compounds that were isolated and characterized in the 1940s and 50s bearing the tetracyclic pharmacophore (**3**). Oxytetracycline (**4**) is a naturally occuring polyketide that was first reported in 1950 and belongs to the first generation tetracyclines. It has bacteriostatic

5 D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*, 303–336.

6 D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2016**, *79*, 629–661.

7 M. Tintore, A. Vidal-Jordana, J. Sastre-Garriga, *Nat. Rev. Neurol.* **2019**, *15*, 53–58.

8 A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, I. Erdogan Orhan, M. Banach, J. M. Rollinger, D. Barreca, W. Weckwerth, R. Bauer, E. A. Bayer, M. Majeed, A. Bishayee, V. Bochkov, G. K. Bonn, N. Braidy, F. Bucar, A. Cifuentes, G. Donofrio, M. Bodkin, M. Diederich, A. T. Dinkova-Kostova, T. Efferth, K. El Bairi, N. Arkells, T.-P. Fan, B. L. Fiebich, M. Freissmuth, M. I. Georgiev, S. Gibbons, K. M. Godfrey, C. W. Gruber, J. Heer, L. A. Huber, E. Ibanez, A. Kijjoa, A. K. Kiss, A. Lu, F. A. Macias, M. J. S Miller, A. Mocan, R. Müller, F. Nicoletti, G. Perry, V. Pittalà, L. Rastrelli, M. Ristow, G. Luigi Russo, A. Sanches Silva, D. Schuster, H. Sheridan, K. Skalicka-Woźniak, L. Skaltsounis, E. Sobarzo-Sánchez, D. S. Bredt, H. Stuppner, A. Sureda, N. T. Tzvetkov, R. Anna Vacca, B. B. Aggarwal, M. Battino, F. Giampieri, M. Wink, J.-L. Wolfender, J. Xiao, A. Wai Kan Yeung, G. Lizard, M. A. Popp, M. Heinrich, I. Berindan-Neagoe, M. Stadler, M. Daglia, R. Verpoorte, C. T. Supuran, *Nat. Rev. Drug Discov.* **2021**, *201*, 200–216.

9 J. L. Markley, T. A. Wencewicz, *Front. Microbiol.* **2018**, *9*, 1058.

properties and is used as a broadband antibiotic. Early attempts to modify the tetracycline scaffolds of the natural precursors were hampered by the chemical instability of the 6-hydroxy group. In 1962 the first deoxygenation of that position supplied the semi-synthetic drug doxycycline (**5**).[10] The new analogue proved to have superior pharmacokinetic properties as well as an increased antibacterial activity compared to its parent compound. To this day it used to treat bacterial and certain parasital infections as well as being used as a malaria prophylactic.[11] The fully synthetic drug eravacycline (**6**) is a third-generation halogenated tetracycline. It has shown antibacterial activity against resistent pathogens in complicated intra-abdominal infections[12] and was therefore granted Fast Track designation by the FDA.[13]

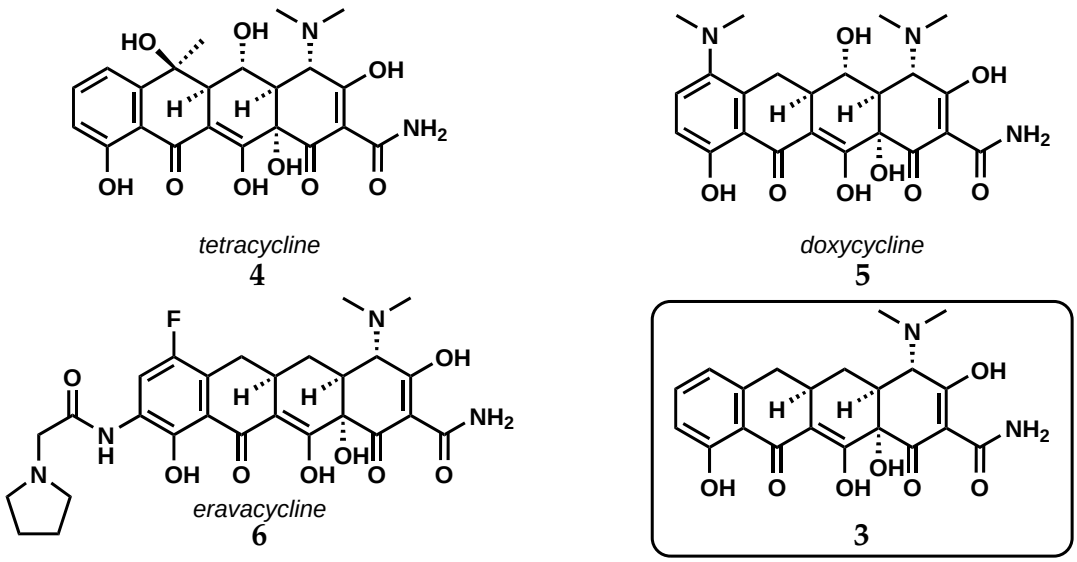


Figure 1.2: Bioactive tetracyclines and evolution of its scaffold.[9]

10 M. Schach von Wittenau, J. J. Beereboom, R. K. Blackwood, C. R. Stephens, *J. Am. Chem. Soc.* **1962**, *84*, 2645–2647.

11 B. A. Cunha, C. M. Sibley, A. M. Ristuccia, *Ther. Drug Monit.* **1982**, *4*, 115–135.

12 G. G. Zhanel, D. Cheung, H. Adam, S. Zelenitsky, A. Golden, F. Schweizer, B. Gorityala, P. R. Lagacé-Wiens, A. Walkty, A. S. Gin, D. J. Hoban, J. A. Karlowsky, *Drugs* **2016**, *76*, 567–588.

13 https://www.tphase.com/products/xerava/, 06.04.2021.

1.2 Marine Natural Products

One of nature's greatest resources is the ocean. Not only do they cover more than 70 % of Earth's surface, but they also harbor a gigantic reservoir of species that produce bioactive compounds, including marine microorganisms, phytoplankton, algae and sponges. In addition, it is estimated that microbes account for 70 % of the total marine biomass.[14] Each year, Natural Product Reports publishes a review of newly isolated marine compounds from the previous year, highlighting their bioactivity. In their recent publication[15], they report the isolation of 1490 new compounds for 2019. Because marine organisms have to be able to defend themselves in a highly dilute environment, the natural products they produce often have extremely high activity. The neurotoxin tetrodotoxin (**7**, Scheme 1.1) is one of the most potent non-protein toxins. It is found in a variety range of unrelated marine organisms, however, it is proposed that tetrodotoxin (**7**) is produced by a symbiotic bacterium that lives within the organism.[16] Accordingly, tetrodotoxin (**7**) is famously responsible for puffer fish poisoning alongside the east coast of asia.[17,18] Chemists have taken an interest in this marine compound not only for its high bioactivity and usage as a biochemical tool to study ion channel function[19], but even more so due to its intriguing structure, which was elucidated by three groups independently in 1964.[20–22] Cleaving the guanidine and the orthoester function, one can trace the tetracyclic structure of tetrodotoxin (**7**) back to highly functionalized cyclohexane **8**, which is a common intermediate in most published syntheses.[23] Efforts to elaborate a synthetic route towards the marine toxin peaked in 1972, when Kishi *et al*. published the first history-writing racemic total synthesis.[24,25] In their work, they constructed core cyclo-

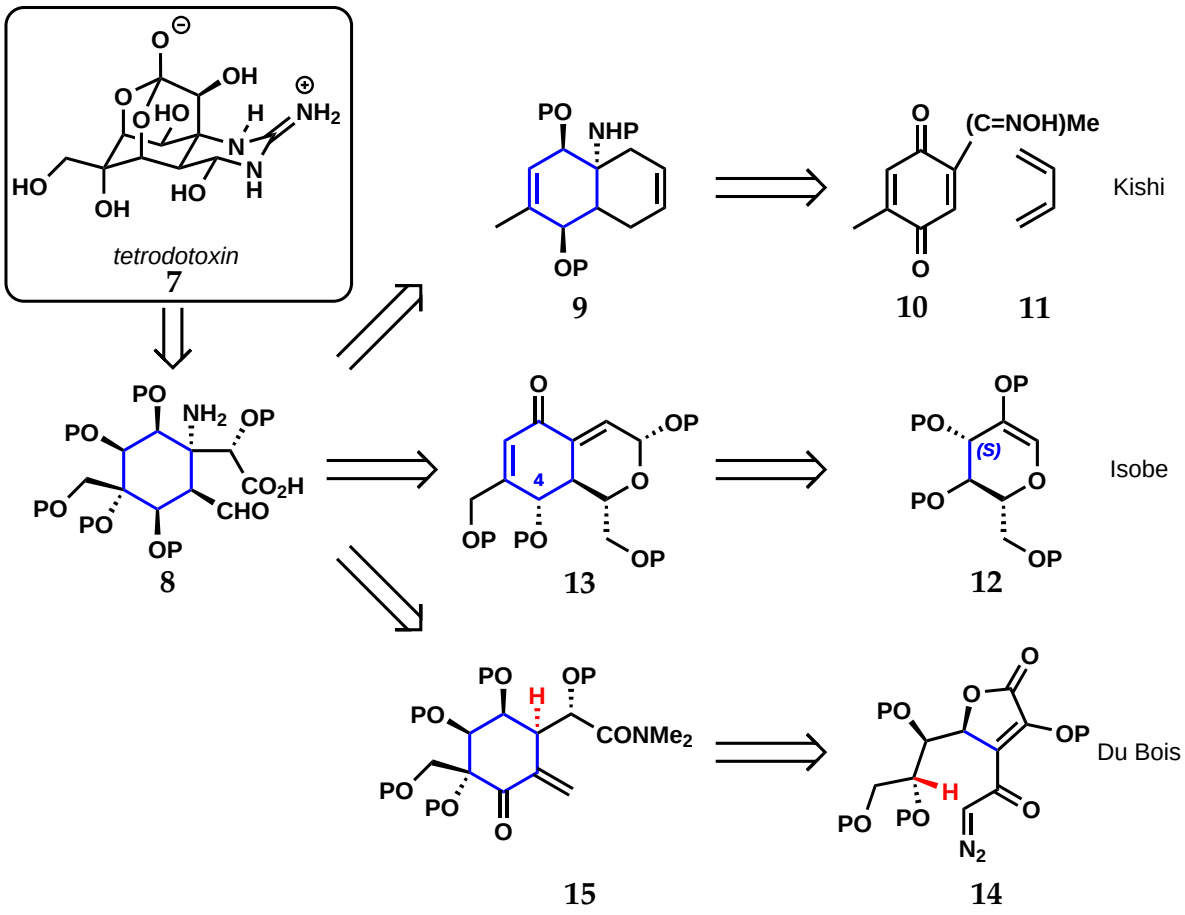
14 Y. M. Bar-On, R. Phillips, R. Milo, *PNAS* **2018**, *115*, 6506–6511.
15 A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers, M. Michèle, R Prinsep, *Nat. Prod. Rep.* **2021**, *38*, 362–413.
16 R. Chau, J. A. Kalaitzis, B. A. Neilan, *Aquat. Toxicol.* **2011**, *104*, 61–72.
17 N. Homaira, M. Rahman, S. P. Luby, M. Rahman, M. S. Haider, L. I. Faruque, D. Khan, S. Parveen, E. S. Gurley, *Am. J. Trop. Med. Hyg.* **2010**, *83*, 440–444.
18 Y. S. Yong, L. S. Quek, E. K. Lim, A. Ngo, *Case Rep. Med.* **2013**, *2013*.
19 J. E. Blankenship, *Perspect. Biol. Med.* **1976**, *19*, 509–526.
20 T. Goto, Y. Kishi, S. Takahashi, Y. Hirata, *Tetrahedron* **1965**, *21*, 2059–2088.
21 R. B. Woodward, *Pure Appl. Chem.* **1964**, *9*, 49–74.
22 K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sakai, C. Tamura, O. Amakasu, *Chem. Pharm. Bull.* **1964**, *12*, 1357–1374.
23 J. Chau, M. A. Ciufolini, *Mar. Drugs* **2011**, *9*, 2046–2074.
24 Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, *J. Am. Chem. Soc.* **1972**, *94*, 9217–9219.
25 Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, *J. Am. Chem. Soc.* **1972**, *94*, 9219–9221.

hexene **9** by a racemic Diels-Alder cycloaddition of quinone **10** and butadiene (**11**). The oxime group served as an electron-drawing group to achieve the desired regioselectivity and was later transformed to the crucial amine function by means of Beckmann rearrangement. Further functionalization of the six-membered ring and oxidative cleavage of the alkene led to an intermediate analogous to **8**, which was successfully transformed to tetradotoxin (**7**). It was around thirty years later, despite numerous attempts, that the first asymmetric synthesis was reported by Isobe *et al*.[26] Their approach was traced back to glucal **12** which was elaborated to enone **13**. The amine function was installed *via* an aza-michael addition, which was directed by the *syn* configured alcohol at the C-4 position. It was later inversed by an oxidation/reduction sequence to provide core structure **8**, which was further transformed to tetrodotoxin **7**. In 2003, another total synthesis was published by Du Bois *et al*.[27], in which an ex chiral pool approach utilizing two rhodium-catalyzed C-H-insertion reactions[1] was chosen. It commenced with the conversion of isoascorbic acid to diazo compound **14**, which was cyclized to cyclohexane **15** *via* the corresponding rhodium carbenoid. In the second key step, the amine function was implemented by a carbamate-directed C-H-insertion reaction. From there, only a few steps were necessary to finalize the tetrodotoxin **7** synthesis.

A further look into marine organisms shows that they are capable of producing structurally diversive compounds (Figure 1.3).[28] One example of an unusual natural product is arsenicin B (**16**), which was isolated by Tähtinen *et al*. in 2018 from the sponge *Echinochalina bargibanti* and shows strong microbial activity. It is the first known bio-originated compound to incorporate an arsenic-arsenic bond, making up its noradamantane-type structure.[29] Another new alkaloid, polyaurine B (**17**), was isolated from the indonesian tunicate *Polycarpa aurata* in 2019. This new natural product consists of a rare 1,2,4-thiadiazole ring, which's structure was identified by a combination of HRMS and NMR experiments.[30] Even though there are only few examples with naturally occuring thiadiazoles[31], it is a widely used heteroaromatic ring in the development of artifi-

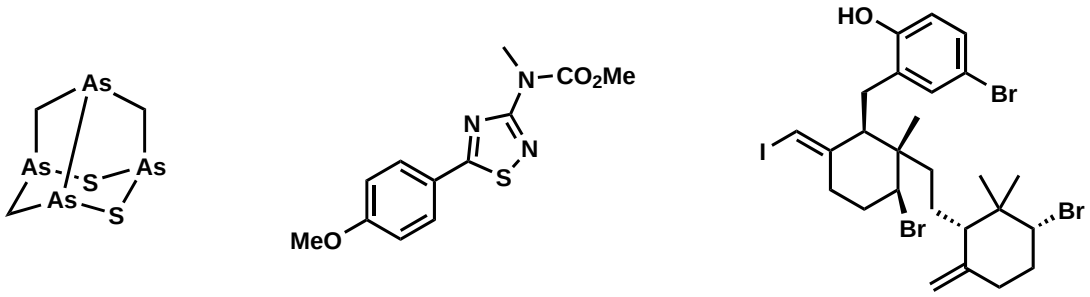
1 Participating hydrogen atoms are highlighted in red.

26 N. Ohyabu, T. Nishikawa, M. Isobe, *J. Am. Chem. Soc.* **2003**, *125*, 8798–8805.
27 A. Hinman, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511.
28 A. R. Carroll, B. R. Copp, R. A. Davis, R. A. Keyzers, M. R. Prinsep, *Nat. Prod. Rep.* **2020**, *37*, 175–223.
29 P. Tähtinen, G. Guella, G. Saielli, C. Debitus, E. Hnawia, I. Mancini, *Mar. Drugs* **2018**, *16*, 1–14.
30 M. Casertano, C. Imperatore, P. Luciano, A. Aiello, M. Y. Putra, R. Gimmelli, G. Ruberti, M. Menna, *Mar. Drugs* **2019**, *17*, 1–12.
31 C. D. Pham, H. Weber, R. Hartmann, V. Wray, W. Lin, D. Lai, P. Proksch, *Org. Lett.* **2013**, *15*, 2230–2233.



Scheme 1.1: Marine natural product tetradotoxin **7** and its chemically derived highly functionalized cyclohexane core structure, which serves as an advanced intermediate in most reported synthesis of the marine compound.

cial drugs.[32] An example of a marine meroditerpenoid is iodocallophycol E (**18**), which was isolated from the south pacific red alga *callophycus serratus*. It consists of a diterpenoid core which is highly halogenated, with an unusual vinyl iodide moiety. The natural product shows slight cytotoxicity against the promyelocytic leukemia cell line HL-60.[33]



arsenicin B **16** | *polyaurine B* **17** | *iodocallophycol E* **18**

Figure 1.3: Three newly isolated compounds, showcasing the structural diversity of marine natural products: arsenicin B (**16**), polyaurine B (**17**) and iodocallophycol E (**18**).

1.3 Cebulactam

Other marine natural products are the cebulactams A1 (**19a** and A2 **19b**, Figure 1.4). They owe their name to the philippinean island Cebu, where the sponge *Haliclona sp.* was found offshore. The bacterium *Saccharopolyspora cebuensis*, which was identified to live within the sponge, was examined in 2008 by Pimentel-Elardo *et al.*[34,35] Using HPLC-UV analysis of its extract they discovered two new natural products that had the same molecular mass by HRMS. Further 1D and 2D NMR studies suggested that both compounds have the same constitution, with small deviations of chemical shift and ^3J coupling constants on the alkene proton. NOE experiments unveiled that the

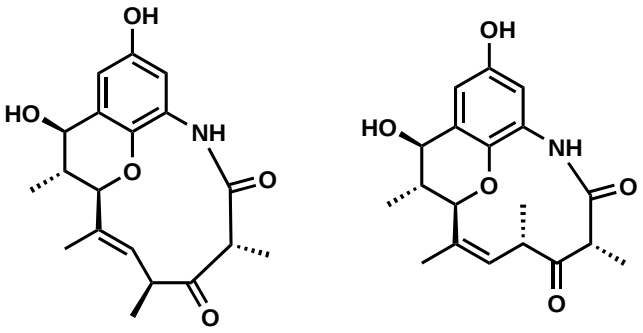
32 A. Tahghighi, F. Babalouei, *Iran. J. Basic. Med. Sci.* **2017**, *20*, 613–622.

33 V. H. Woolner, R. M. Gordon, J. H. Miller, M. Lein, P. T. Northcote, R. A. Keyzers, *J. Nat. Prod.* **2018**, *81*, 2446–2454.

34 S. M. Pimentel-Elardo, T. A. M. Gulder, U. Hentschel, G. Bringmann, *Tetrahedron Lett.* **2008**, *49*, 6889–6892.

35 S. M. Pimentel-Elardo, L. P. Tiro, L. Grozdanov, *Int. J. Syst. Evol. Microbiol.* **2008**, *58*, 628–632.

two identified compounds were the two stereoisomers cebulactam A1 (**19a**) and cebulactam A2 (**19b**), differing only in their double bond geometry. Their main structure consists of a 13-membered macrolactam, a chromane core, which is densely functionalized with a stereocenter on each pyran carbon, a 1,3-dicarbonyl moiety and two additional stereocenters in the polyketide chain. During preliminary experiments no antibiotic, antiparasitic or cytotoxic activity could be adressed to cebulactam A1 (**19a**) or cebulactam A2 (**19b**).[36]



cebulactam A1 **19a** *cebulactam A2* **19b**

Figure 1.4: The new marine natural products cebulactam A1 (**19a**) and cebulactam A2 (**19b**).[34]

Cebulactam belongs to the class of polyketide natural products, and is therefore biosynthesized by a polyketide synthase (PKS), as proposed by Pimentel-Elardo *et al*. (Figure 1.5).[36] The backbone is thus established from one large gene cluster. The biosynthesic pathway is initiated by the uptake of starting building block aminohydroxybenzoic acid (**20**) onto the acyl carrier protein (ACP) of the first module. Ketosynthase (KS) catalyzes the elongation by two carbon atoms, where methylmalonyl-CoA (**21**)[2] serves as the building block, providing a β-keto thioester. This step is iterated by a total of four times. Additionally, in each module, the oxidation state of the previous carbonyl function is manipulated by additional domains, such as keto reductase (KR) or dehydratase (DH). These manipulations lead to the stereoselective formation of a secondary alcohol (module 1 and 2) or an alkene (module 3), respectively. Termination of the biosynthesis is carried out be the thioesterase (TE), removing the cebulactam backbone from the terminal ACP. The

2 The newly added methylmalonyl-CoA building blocks **21** are highlighted in the color of the corresponding module

36 S. M. Pimentel-Elardo, PhD thesis, Julius-Maximilians-Universität Würzburg, **2008**.

cleavage of the thioester directly leads to the formation of an acid or the cyclized amine. Additional tailoring enzymes oxidize the benzene moiety to form the ether bridge of the chromane core and finalize the cebulactam A1 (**19a**) biosynthesis.[37]

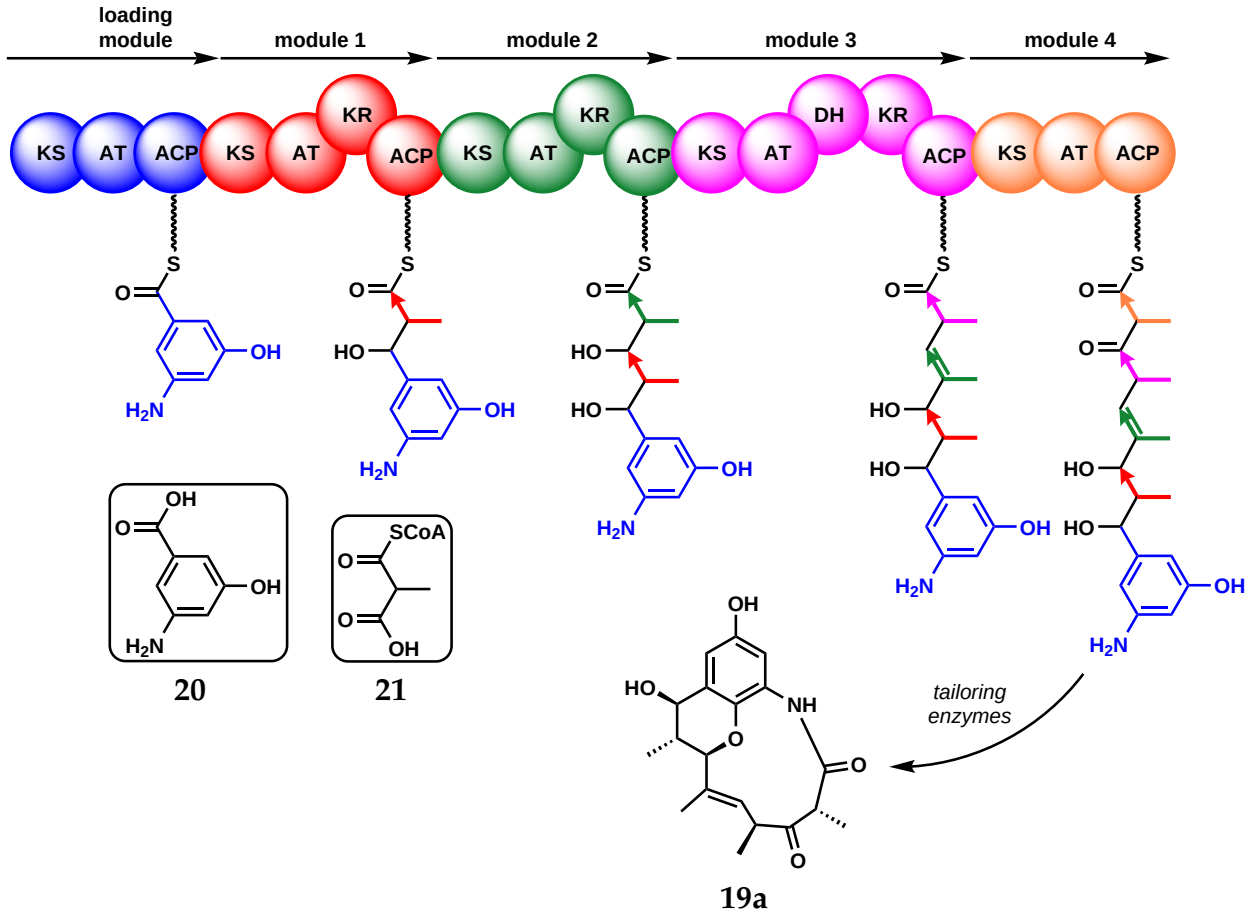


Figure 1.5: Proposed PKS biosynthesis of cebulactam A1 (**19a**).[34,37]

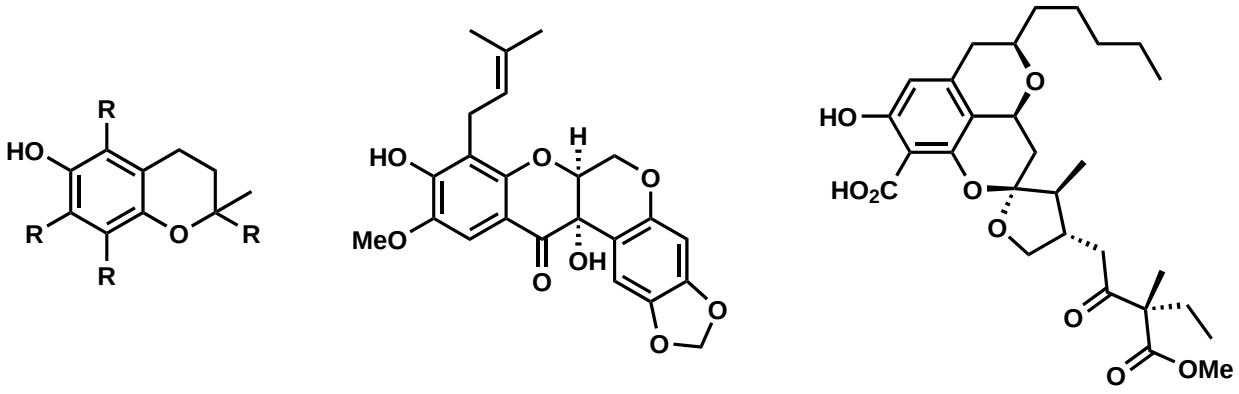
1.4 Chromanes and their Derivatives in Natural Products

The chromane structure is widely prevalent in natural products. They form the structural core of tocopherols, flavonoids as well as cannabinoids. Moreover, chromane derivatives such as coumarins, chromenes and chromane spiroketals play a pivotal role in medicinal

37 H. Berneaud-Kötz, Master Thesis, Leibniz Universität Hannover, **2017**.

chemistry.[38] The vitamin E class is essential in body function as it has a strong antioxidant effect, protecting cell membranes from reactive oxygen species by inhibiting free radical propagation. They consist of four tocopherols and four tocotrienols, all bearing the bioactive hydroxy-chromane substructure (**22**, Figure 1.6).[39] Another representative of the chromane-bearing natural products is caeruleanone C (**23**), a rotenoid from the fruits of *Millettia caerulea*, native to Myanmar, Thailand and Vietnam.[40] In Thai folkloric medicine, the stems and leaves of that plant are used to treat wound infection.[41] Its structure consists of a chromanone core which is *cis*-annulated to a second chromane ring. A famous example for a chromane spiroketal is berkelic acid (**24**), which was isolated in 2006 from an extremophile which evolved to live in the Berkeley Tar Pit, a flooded, highly acidic, former copper mine in Butte, Montana.[42] It exhibits selective anticancer activity against the human ovarian cell line OVCAR-3. In 2008 the structure was revised through total synthesis by Buchgraber *et al*.[43] In the following years, multiple finished syntheses were published on that molecule[44,45], with the latest being reported in 2021.[46]

38 E. Geist, H. Berneaud-Kötz, T. Baikstis, G. Dräger, A. Kirschning, *Org. Lett.* **2019**, *21*, 8930–8933.
39 R. Brigelius-Flohé, M. G. Traber, *FASEB J.* **1999**, *13*, 1145–1155.
40 L. Bueno Perez, L. Pan, U. Muñoz Acuña, J. Li, H.-B. Chai, J. C. Gallucci, T. N. Ninh, E. J. Carcache De Blanco, D. D. Soejarto, A. D. Kinghorn, *Org. Lett.* **2014**, *16*, 1462–1465.
41 E. F. Anderson, *Econ. Bot.* **1986**, *40*, 38–53.
42 A. A. Stierle, D. B. Stierle, K. Kelly, *J. Org. Chem.* **2006**, *71*, 5357–5360.
43 P. Buchgraber, T. N. Snaddon, C. Wirtz, R. Mynott, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2008**, *47*, 8450–8454.
44 X. Wu, J. Zhou, B. Snider, *Angew. Chem. Int. Ed.* **2009**, *48*, 1283–1286.
45 C. F. Bender, F. K. Yoshimoto, C. L. Paradise, J. K. De Brabander, *J. Am. Chem. Soc.* **2009**, *131*, 11350–11352.
46 H. G. Cheng, Z. Yang, R. Chen, L. Cao, W. Y. Tong, Q. Wei, Q. Wang, C. Wu, S. Qu, Q. Zhou, *Angew. Chem. Int. Ed.* **2021**, *60*, 5141–5146.



tocopherol substructure **22** | *caeruleanone C* **23** | *berkelic acid* **24**

Figure 1.6: Three examples for chromane-bearing natural products: tocopherol sub structure (**22**), caeruleanone C (**23**) and berkelic acid (**24**).

1.5 Preliminary Studies

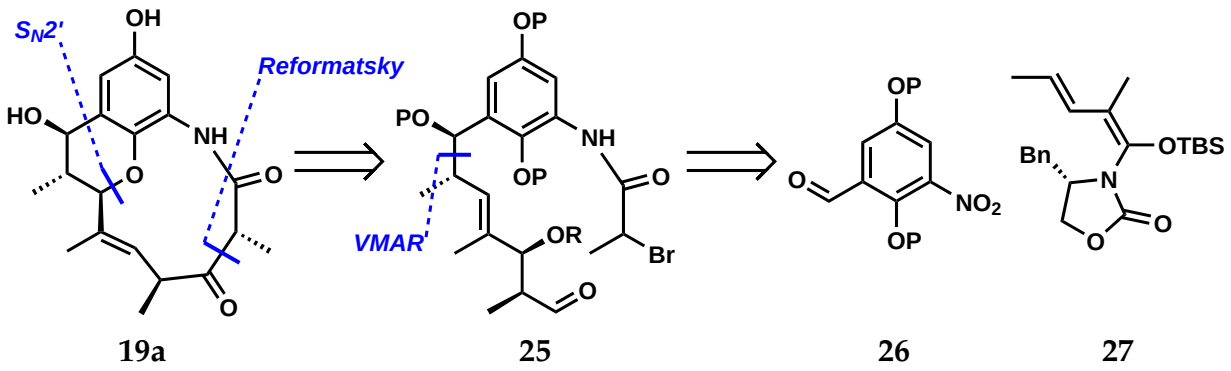
1.5.1 Total Synthesis by Yang and co-workers

In 2014 Yang *et al*. published a synthesis of cebulactam A1 **19a**.[47] Key steps in their transformation were a Reformatsky reaction to assemble the dicarbonyl moiety and a S_N2' reaction to forge the pyran ether, tracing the natural product back to aldehyde **25** (Scheme 1.2). This intermediate was planned to be synthesized by a vinylogous Mukaiyama aldol reaction (VMAR), leading to aldehyde **26** and chiral auxiliary **27**.

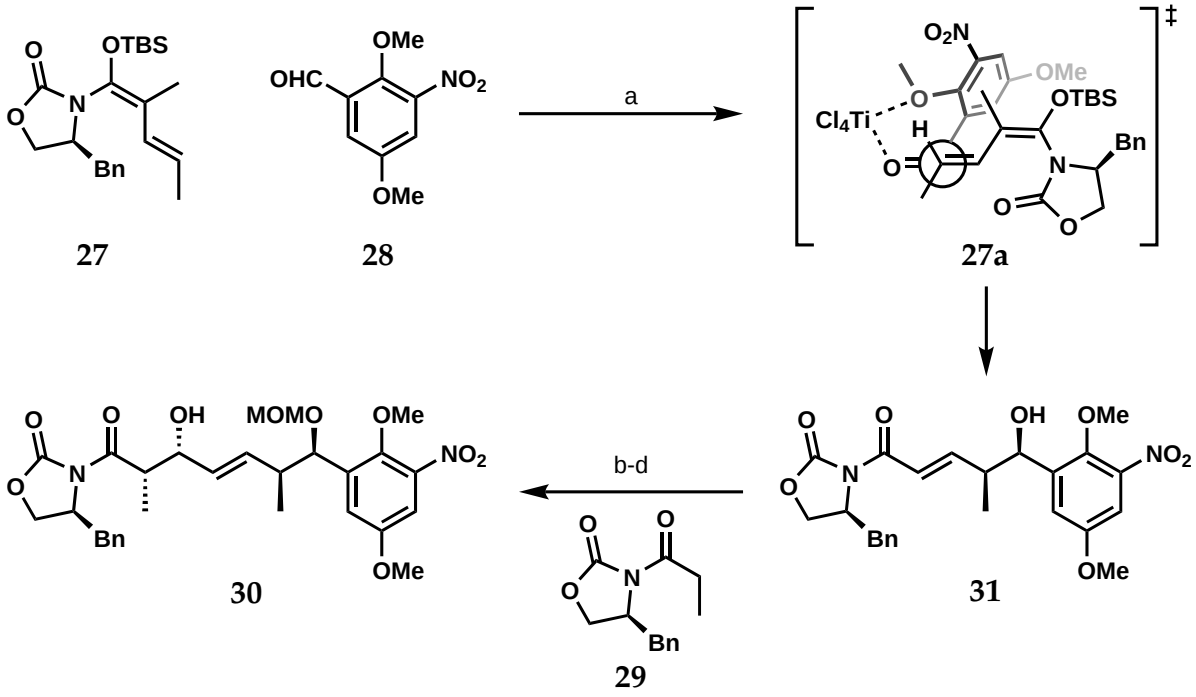
In the forward synthesis (Scheme 1.3), vinyl enol ether **27** and arene **28** were reacted with titanium(IV) chloride, forming the *syn* product as the major diastereomer *via* the proposed favored transition state **27a**, with a *dr* of 20:1. Protection of the resulting alcohol, followed by oxidation state manipulation and a subsequent aldol reaction with (*S*)-Evans auxiliary **29** gave rise to fragment **30**.

The synthesis continued with protection of the resulting alcohol, followed by nitro reduction to the corresponding aniline and allyl protection thereof (Scheme 1.4). A ceric ammonium nitrate mediated oxidative demethylation forged the hydroquinone which

47 S. Yang, Y. Xi, J. H. Chen, Z. Yang, *Org. Chem. Front.* **2014**, *1*, 91–99.

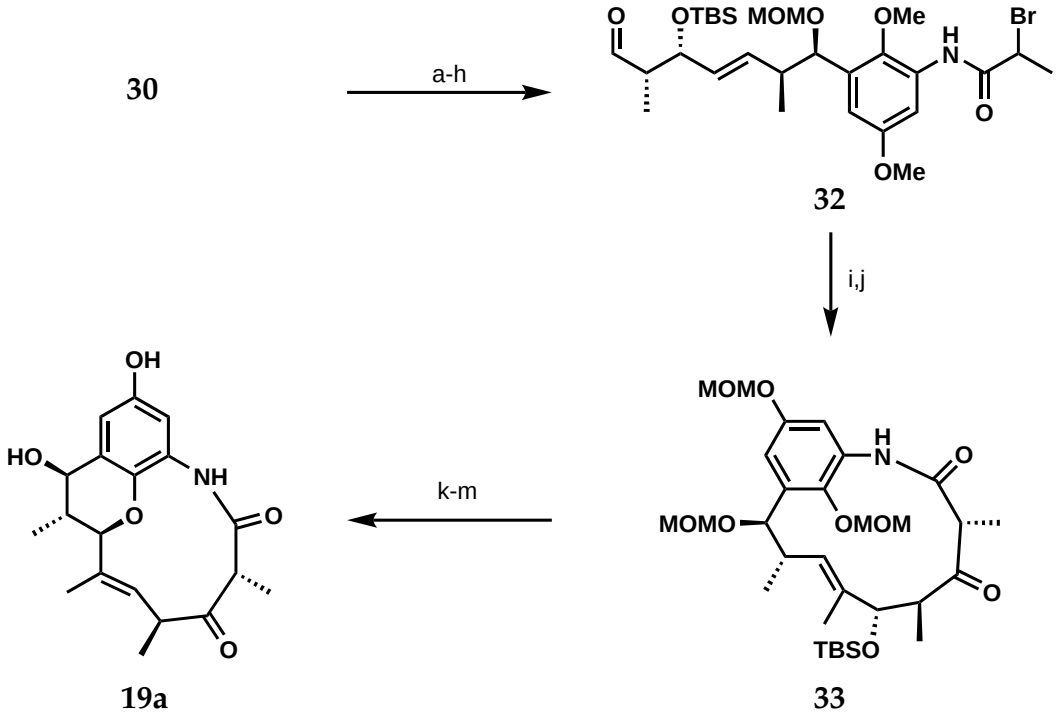


Scheme 1.2: Retrosynthetic approach towards cebulactam A1 (**19a**) as proposed by Yang *et al.*[47]



Scheme 1.3: VMAR and construction of the *ansa*-chain of cebulactam A1 (**19a**) as published by Yang *et al.*.[47] Conditions: a) $TiCl_4$, CH_2Cl_2, −78 °C to 0 °C, 92 %; b) DIPEA, MOMCl, CH_2Cl_2, rt, 96 %; c) DIBAl-H, CH_2Cl_2, −78 °C, 79 %; d) **29**, Et_3N, $n$$Bu_2BOTf$, THF, −78 °C to 0 °C, 85 %.

was bis-protected with methoxymethyl groups. Cleavage of the prior introduced allyl group under palladium(0) catalysis and reduction of the evans auxiliary, followed by acylation of the aniline with 2-bromopropionyl bromide forged α-bromo ketone **32**. Treatment with samarium(II) iodide led to formation of the samarium(III) enolate, which cyclized with the internal aldehyde to yield the aldol product. Oxidation using IBX led to corresponding dicarbonyl **33**. After silyl deprotection, reaction of the free secondary alcohol with triflic anhydride triggered an intramolecular S_N2 reaction to form the pyran ring with concomitant deprotection of the methoxymethyl group. From there, cebulactam A1 (**19a**) was obtained after one additional deprotection step to release the remaining phenol.



Scheme 1.4: Functional group manipulation and endgame of the cebulactam A1 (**19a**) synthesis of Yang *et al.*.[47] Conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 90 %; b) $NaBH_4$, S_8, THF, reflux, 87 %; c) AllocCl, pyridine, THF, 90 %; d) CAN *then* $Na_2S_2O_4$, MeCN, H_2O, rt; e) MOMCl, DIPEA, CH_2Cl_2, rt, 71 % (2 steps); f) $Pd(PPh_3)_4$, THF, 1,3-dimethylbarbituric acid, rt, 87 %; g) DIBAl-H, CH_2Cl_2, −78 °C *then* 2-bromopropionyl bromide; h) $NaHCO_3$, MeOH/CH_2Cl_2 (1:1), rt, 71 % (2 steps); i) SmI_2, THF, reflux, 84 %; j) IBX, DMSO, rt, 68 %; k) HF-pyridine, THF, rt, 71 %; l) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 71 %; m) *B*-bromocatechol borane, CH_2Cl_2, rt, 66 %.

1.5.2 Preliminary Studies in the Kirschning Group

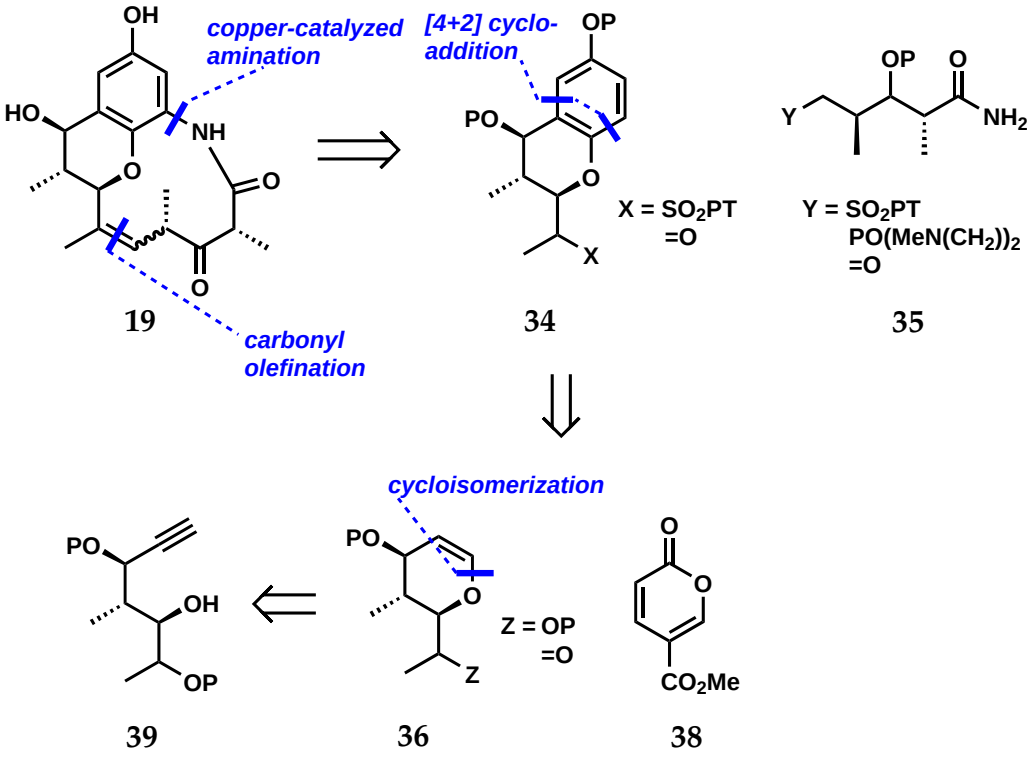
Cebulactam (**19**) has been a natural product of interest in the Kirschning group since 2010[37,48,49] due to its structural and biosynthetical similarities to the ansamycin natural products ansamitocin[50,51] and geldanamycin.[52,53] Retrosynthetically, we envisaged to dissect the target into two fragments of similar complexity. Therefore, chromane core **34** was planned to be disconnected from *ansa* chain **35** by a copper-catalyzed amination as well as a carbonyl olefination reaction. Polyketide chain **35** was planned to be synthesized by conventional aldol chemistry, whereas chromane **34** was to be obtained by a novel Diels-Alder approach, tracing back to pyran precursor **36**, which itself was planned to be accessed by a cycloisomerization of alkynol **37**. It is important to note, that this retrosynthetic approach allows for the installation of the double bond moiety at different stages of the synthesis, which was also the subject of a master thesis.[37]

The forward synthesis of east fragment **35** commenced from commercially available (*S*)-Roche ester (**40**. Silyl protection, followed by a reduction/oxidation sequence forged aldehyde **41**, which was converted to the Evans-aldol product using amide **42** under standard conditions. Further protection of the resulting alcohol, followed by reduction of the auxiliary amide led to formation of alcohol **43**.

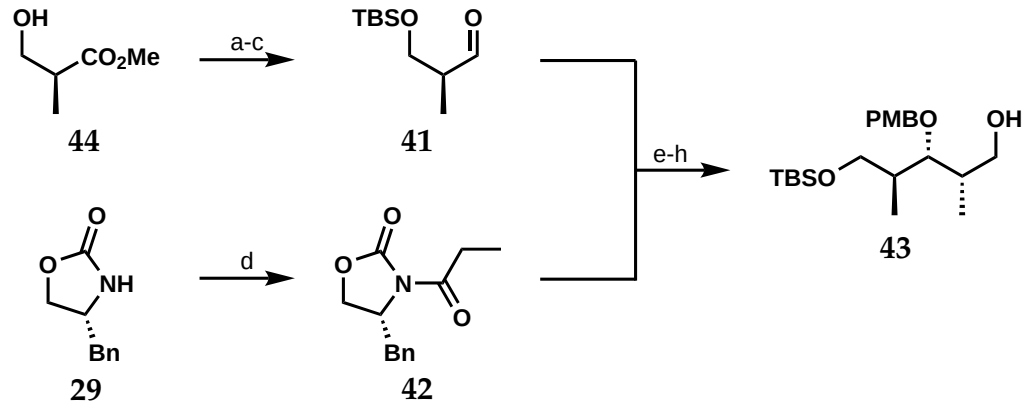
The chromane core synthesis began with a three step sequence, transforming L-ethyl lactate to ethyl ketone **45** *via* protection and Weinreb synthesis. Titanium(IV) chloride-mediated aldol reaction with propargyl aldehyde **46**, which itself was synthesized by formylation of terminal alkyne **47**, yielded hydroxyketone **48**. The *anti* conformation of diol **49** was established using the Evans-Saksena reduction, after which alkyne deprotection and selective silylation of the more accessible alcohol provided alkynol **49**. Photolysis in the presence of tungsten(VI) carbonyl cleanly led to ring-closure of pyran **50**.

With pyran **50** in hand, the olefination reaction to construct the alkene of cebulactam (**19**) was investigated. Accordingly, the secondary alcohol was reductively debenzylated, fol-

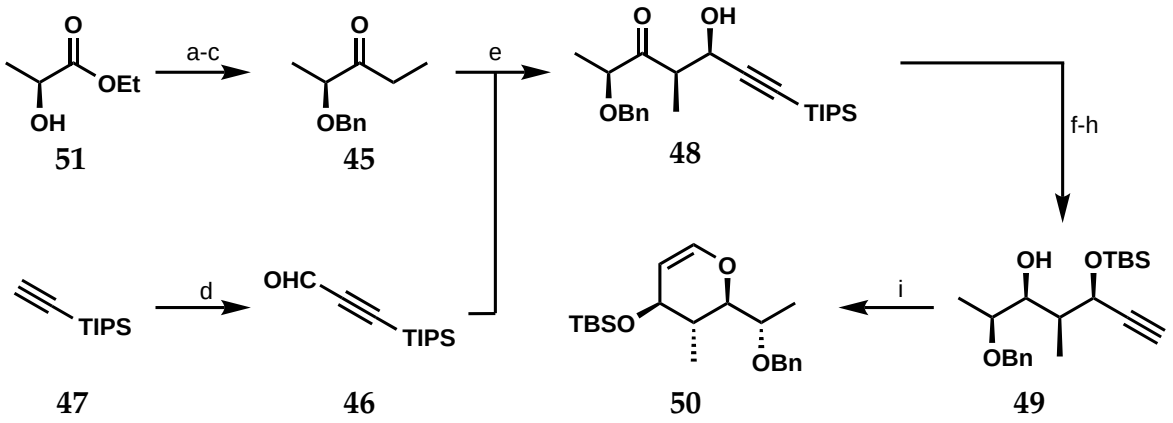
48 T. Baikstis, Master Thesis, Leibniz Universität Hannover, **2010**.
49 E. Geist, PhD thesis, Leibniz Universität Hannover, **2017**.
50 F. Taft, M. Brünjes, H. G. Floss, N. Czempinski, S. Grond, F. Sasse, A. Kirschning, *ChemBioChem* **2008**, *9*, 1057–1060.
51 A. Meyer, A. Kirschning, *Synlett* **2007**, *2007*, 1264–1268.
52 S. Eichner, H. G. Floss, F. Sasse, A. Kirschning, *ChemBioChem* **2009**, *10*, 1801–1805.
53 J. Hermane, S. Eichner, L. Mancuso, B. Schröder, F. Sasse, C. Zeilinger, A. Kirschning, *Org. Biomol. Chem.* **2019**, *17*, 5269–5278.



Scheme 1.5: Retrosynthetic approach towards cebulactam (**19**) as established by Geist *et al.*.[37,49]

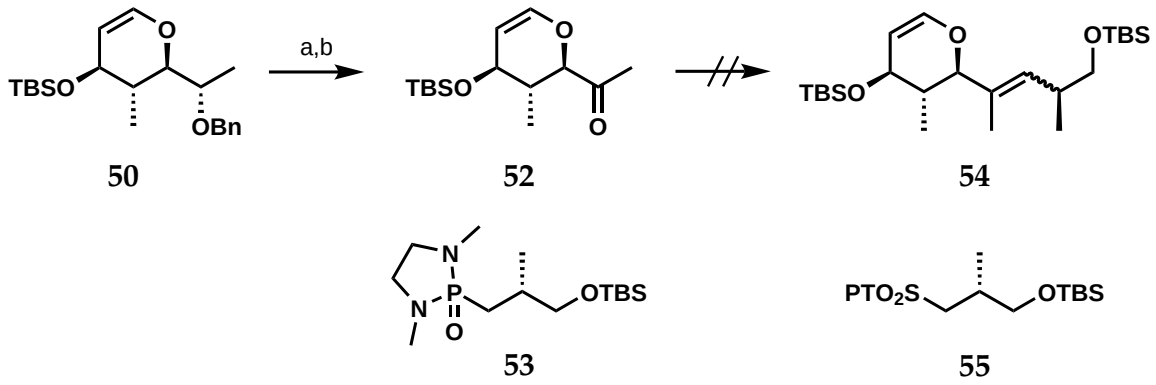


Scheme 1.6: Forward synthesis of alcohol **43**.[49] Conditions: a) TBSCl, imidazole, DMF, rt, *quant.*; b) BH_3·THF, rt, 95 %; c) Py·SO_3, DMSO, Et_3N, rt, 98 %; d) *n*BuLi, propionyl chloride, THF, −78 °C, 93 %; e) nBu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; f) PMB-trichloroacetimidate, $Sc(OTf)_3$, PhMe, rt, 71 % (2 steps); g) $LiBH_4$, MeOH, THF, 0 °C, 75 %; h) PDC; CH_2Cl_2, rt, 49 %.



Scheme 1.7: Forward synthesis of pyran **50**.[49] Conditions: a) pyrrolidine, rt; b) BnBr, Aliquat 336, NaOH, PhMe, rt, 60 % (2 steps); c) EtMgBr, THF, 0 °C, 89 %; d) *n*BuLi, DMF, THF, reflux, *quant.*; e) $TiCl_4$, DIPEA, CH_2Cl_2, −78 °C, 97 %, >10:1 *dr*; f) $NMe_4B(OAc)_3H$, MeCN/AcOH (1:1), −30 °C, 78 %; g) TBAF, THF, 50 °C, *quant.*; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; i) $W(CO)_6$, Et_3N, THF, *hν*, reflux, 82 %.

lowed by Dess-Martin oxidation to provide ketone **52**. Ungratifyingly, neither olefination with Hanessian's cyclophosphonamide **53** nor Julia-Kocienski reaction were able to provide alkene **54** in acceptable yields.



Scheme 1.8: Failed olefination attempts on pyran **52** using either Hanessian's phosphonamide **53** or Julia-Kocienski phenyltetrazole sulfone **55**.[37] Conditions: a) LiDBB, THF, 0 °C, 93 %; b) DMP, CH_2Cl_2, rt, 84 %.

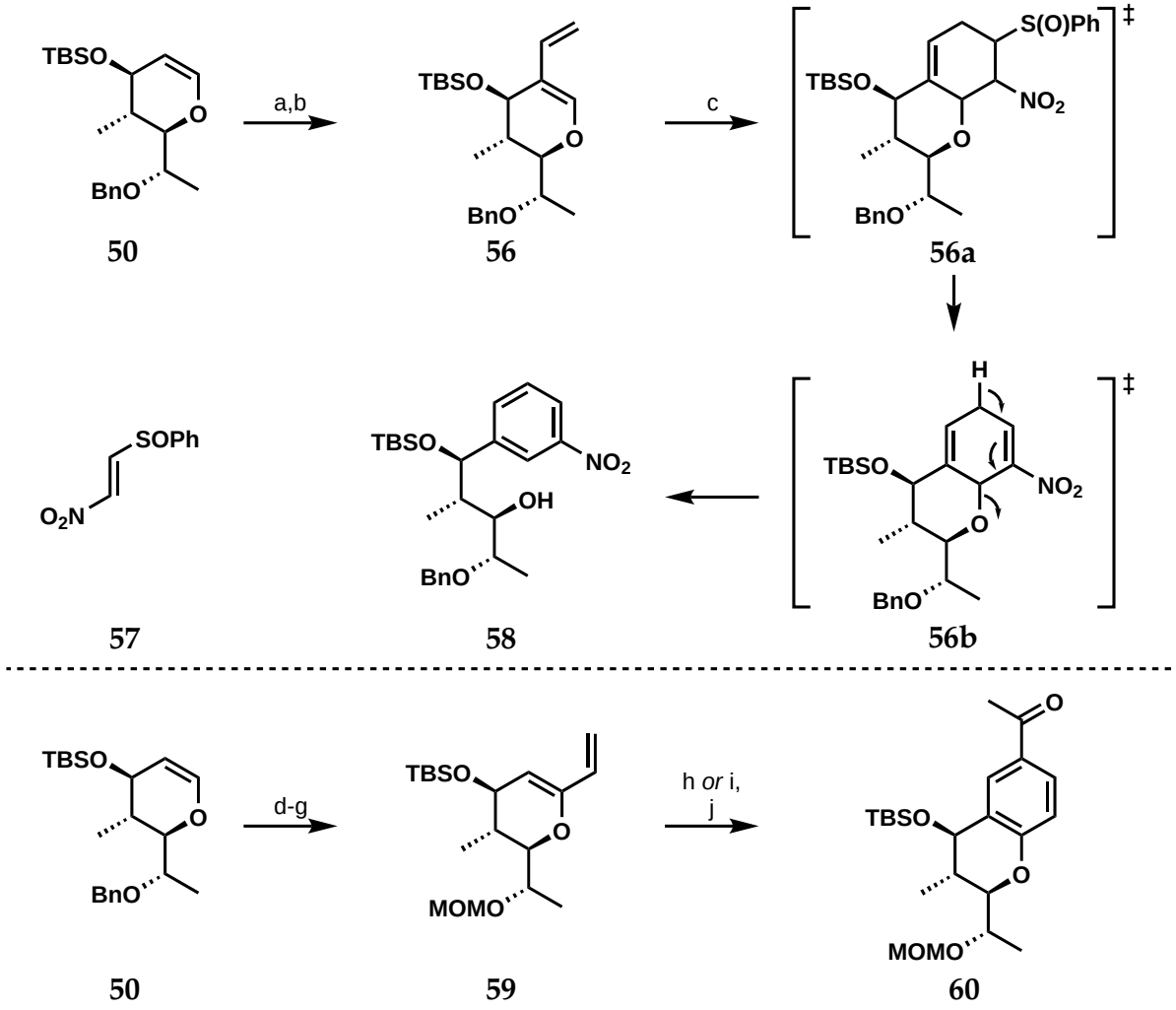
Due to the unsuccessful olefination on pyran **52**, the reaction reaction was planned to be investigated with the intact chromane core structure. Therefore, the Diels-Alder cycloaddition of pyran **50** was investigated.[38] Principally, three retrosynthetic scissions are

possible to provide the aromatic ring. The first approach that was investigated was the reaction of 2-vinyl pyran **56**, which itself was accessed from pyran **50** by bromination and Stille cross-coupling, with nitrosulfoxide **57**. Indeed, Diels-Alder reaction to cyclohexene **56a** took place, but to our dismay, the intermediate cycloaddition adduct underwent a double elimination and yielded the ring-opened nitroarene **58** *via* cyclohexadiene **56b** in one pot. Another retrosynthetic approach consisted of the Diels-Alder reaction of 1-vinyl pyran **59**. It was synthesized by deprotonation/iodination of enol ether **52** using *s*BuLi and a subsequent Stille coupling. Noteworthily, this reaction only took place after changing the benzyl protecting group to a methoxymethyl group. Diels-Alder reaction under either thermal or high pressure conditions with but-3-yn-2-one provided the corresponding diene, but only in preparatively unsatisfying yields. Nonetheless, DDQ oxidation succeeded and gave rise to chromane **60**, indicating that the oxidation step to form the aromatic should be generally feasible.

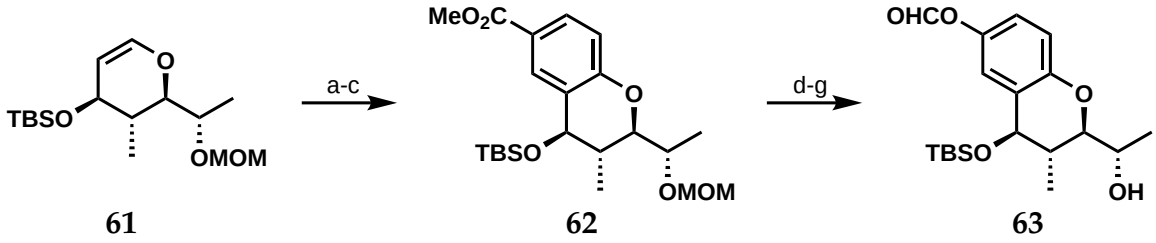
The last retrosynthetic route was the reaction of pyran **61** as the dienophile. Even though reaction with methyl 2-pyrone-5-carboxylate (**39**) did not take place under thermal or catalytic conditions, we found that high pressure conditions provided the desired cycloaddition adduct. The corresponding cyclohexadiene was obtained upon heating in toluene and extrusion of CO_2. Again, DDQ-mediated dehydrogenation gave rise to chromane **62** in good yield over three steps. After removal of the methoxymethyl group and a reduction/oxidation sequence to form the benzaldehyde, Bayer-Villiger oxidation usind *m*CPBA provided formyl protected phenol **63**.

With chromane **63** in hand, the olefination at this stage of the synthesis was examined. Therefore, the secondary alcohol was oxidized using Dess-Martin's periodinane, followed by deprotection of the formyl group and silylation of the resulting alcohol to yield ketone **64**. Unfortunately, neither olefination using phosphonamide **53** nor sulfone **65** led to any conversion of the starting ketone.

As carbonyl olefinations on neither pyran **52** nor chromane **64** lead to any conversion, we envisaged a switch of polarity to provide the desired alkene. Accordingly, alcohol **63** was substituted with 1-phenyl-1-*H*-tetrazole-5-thiol under Mitsunobu conditions, after which the phenol protecting group was exchanged with a silyl group under the same conditions as applied earlier. Oxidation to the sulfone with DMDO provided sulfone **68** which was then used to test the olefination with aldehyde **69**.

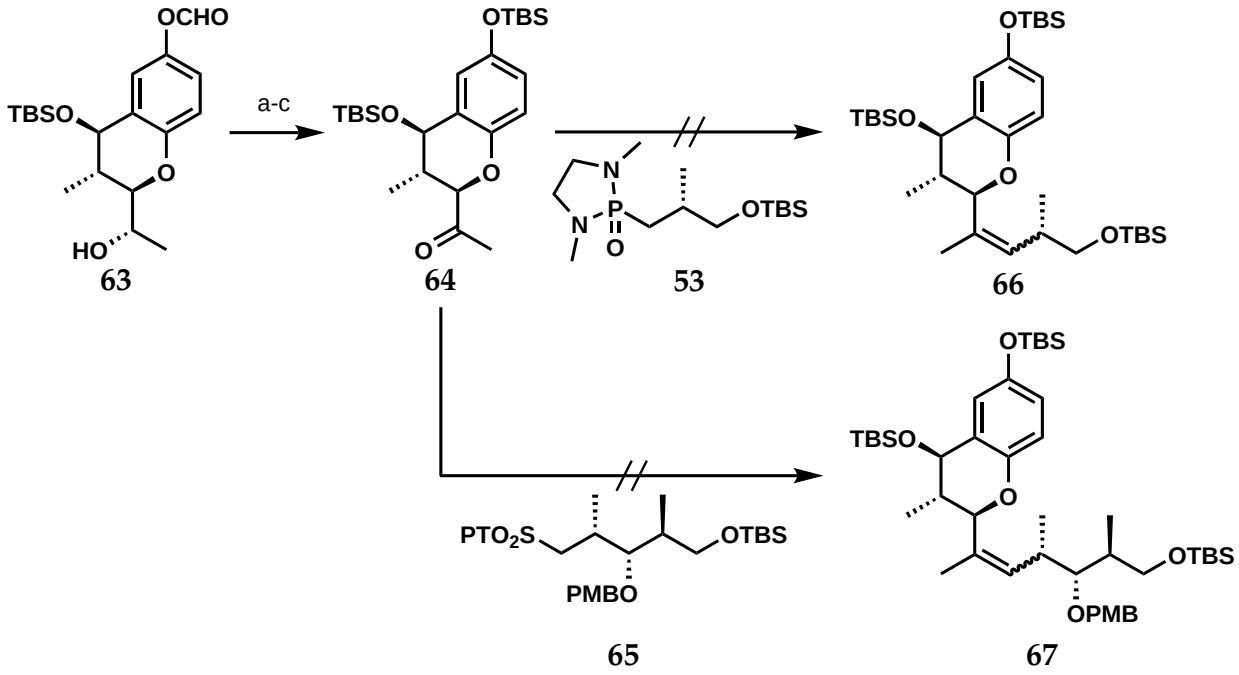


Scheme 1.9: Unsuccessful cycloadditions of the pyran moiety.[38,48,49] Conditions: a) Br_2, CH_2Cl_2, −78 °C *then* Et_3N, rt, 48 %; b) *n*$Bu_3SnCH{=}CH_2$, $Pd_2(dba)_2$, Ph_3As, THF, reflux, 47 %; c) **57**, PhMe, 60 °C, 67 %; d) LiDBB, THF, 0 °C, 93 %; e) MOMCl, DIPEA, rt, 97 %; f) *s*BuLi, CH_2I_2, −78 °C; g) PEPPSI*i*Pr, CsF, CuI, dioxane, *n*$Bu_3SnCH{=}CH_2$, rt, 93 %; h) but-3-yn-2-one, hydroquinone, PhH, reflux, 30 %; i) but-3-yn-2-one, PhH, 14 kbar, rt, 35 %; j) DDQ, CH_2Cl_2, rt, 70 %.



61 62 63

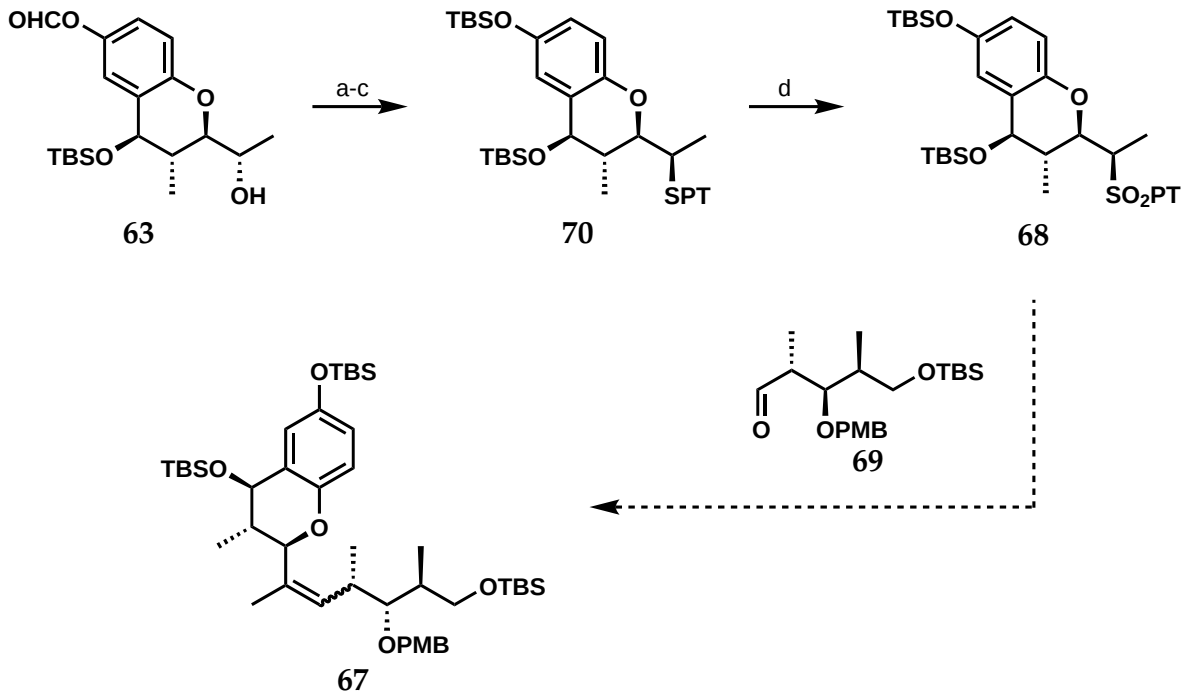
Scheme 1.10: Synthesis of the chromane core of cebulactam (**19**) and functional group manipulation to yield phenol **63**.[38,49] Conditions: a) **39**, PhH, 14 kbar, rt, 86 %; b) PhMe, 160 °C, 83 %; c) DDQ, CH_2Cl_2, rt, 90 %; d) Me_2S, *n*BuSH, $MgBr_2 \cdot Et_2O$, CH_2Cl_2, rt, 98 %; e) DIBAl-H, CH_2Cl_2, −78 °C; f) MnO_2, CH_2Cl_2, rt, 90 % (2 steps); g) *m*CPBA, CH_2Cl_2, reflux, 90 %.



63 64 53 66 65 67

Scheme 1.11: Failed olefination attempts on chromane **64**.[37,49] Conditions: a) DMP, CH_2Cl_2, rt, 80 %; b) K_2CO_3, MeOH, 0 °C, 89 %; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 56 %.

During the masters thesis, it was discussed that stability of the *in situ* formed sulfone is critical and that Barbier conditions led to formation of a product as indicated by LCMS, which unfortunately could not be isolated.

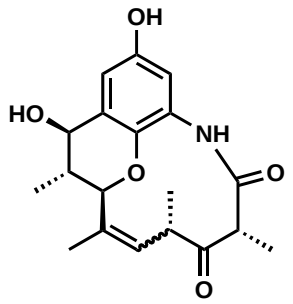


Scheme 1.12: Synthesis of Julia-Kocienski sulfone **68** and first attempts at the olefination reaction. Conditions: a) 1-phenyl-1-*H*-tetrazole-5-thiol, PPh_3, DIAD, THF, rt, 83 %; b) K_2CO_3, MeOH, rt; c) TBSOTf, 2,6-lutidine, rt, 78 %; d) DMDO, CH_2Cl_2, rt, 58 %.

2 Aim of the Thesis

The aim of this thesis is to find a synthetic access for the two marine natural products cebulactam A1 (**19a**) and cebulactam A2 (**19b**) (Figure 2.1), based on the previous work that has been carried out in the Kirschning group.[37,48,49] The syntheses shall commence from commercially available starting materials and be capable of providing the targets in an efficient and stereoselective fashion.

Although there is no bioactivity for cebulactam (**19**) known so far, its total synthesis would enable further bioactivity studies. Moreover, it could serve as a starting point for the development of total syntheses of other structurally similar compounds.



19

Figure 2.1: Target of the total synthesis: cebulactam A1/A2 (**19**).

3 Experimental Discussion

3.1 High Pressure Diels-Alder Route

3.1.1 Olefination on Chromane Moiety

Following the latest results and with the Julia-Kocienski reagent **68** in hand, further olefination reactions with aldehyde **69** were screened for positive results. As it was discussed earlier[37], Barbier type conditions led to the best results, as indicated by LCMS. Following that insight, the reaction was conducted under the same conditions. Using different bases that are known to be valid in Julia-Kocienski olefinations (KHMDS, LiHMDS, *n*BuLi and KH) did not lead to formation of the desired alkene. To dissect the reactivity of the substrate, a closer look into the stability of the intermediate anionic sulfone species was taken. As it turned out, deprotonation with 1.1 eq. KHMDS in THF at −78 °C over 3 min and subsequent termination by addition of deuterated MeOH led to formation of the α-deutero sulfone, proving that deprotonation is feasible and the anion is stable under the given conditions (Figure 3.1).

According to that result, treatment of sulfone **68** with KHMDS for 3 min in THF at −78 °C and subsequent addition of the aldehyde led to full conversion of the sulfone and yielded a new undesired compound **71** as the major product, as shown in Scheme 3.1.

A possible mechanism involves deprotonation of the aldehyde α-proton by the sulfur stabilized anion **68a**, followed by nucleophilic aromatic substitution at the tetrazole by the intermediate enolate **69a**. In that case, sulfur dioxide can be eliminated from the product with concomitant formation of a phenolate (Scheme 3.2). Nonetheless, the phenol degradation product could not been isolated.

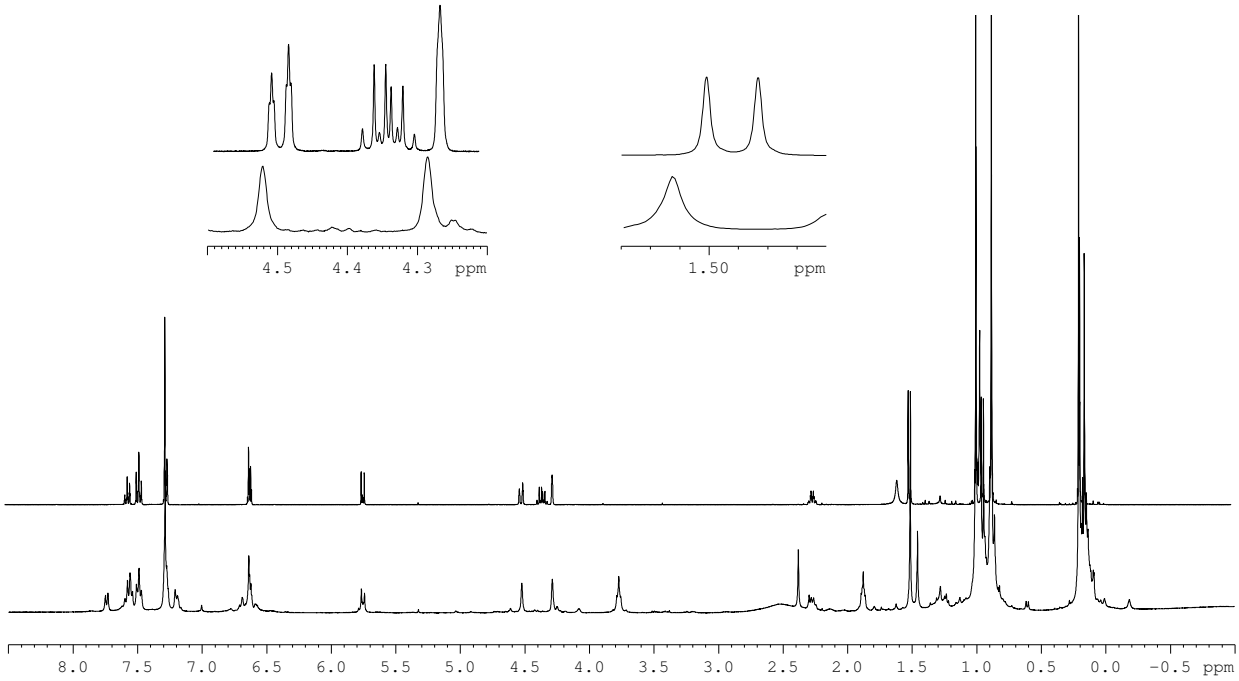
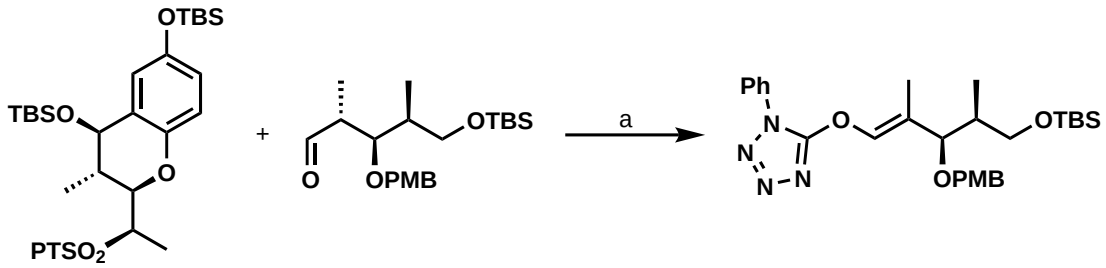
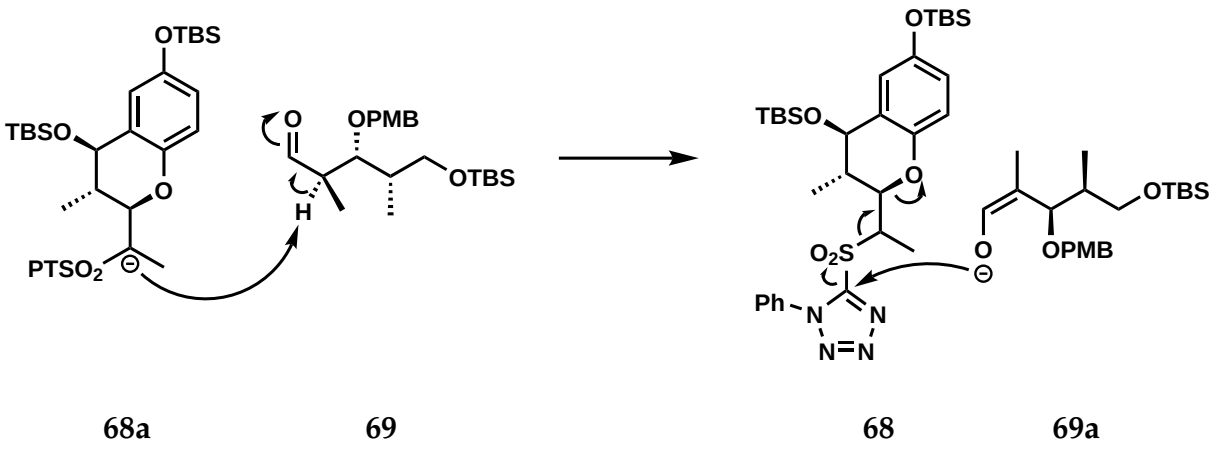


Figure 3.1: Comparison of the crude NMR-spectrum of the deuteration experiment (below) and the pure sulfone **68** (above). Top left: zoom onto the α-proton signal, which is not detected after deuteration; top right: zoom onto the proton signal of the adjacent methyl group, now displayed as a singlet.



68 **69** **71**

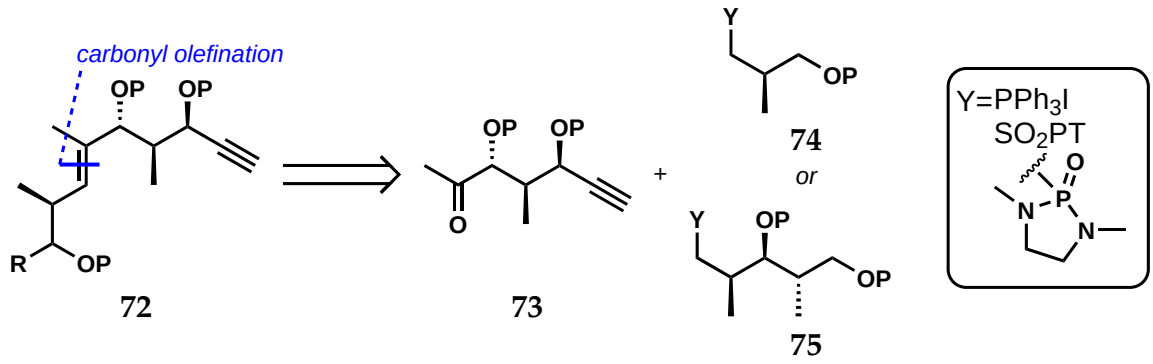
Scheme 3.1: Formation of the undesired enol ether **71**. Conditions: a) **68**, KHMDS, THF, −78 °C, 3 min *then* **69**, −78 °C, 30 min *to* rt, 1 h.



Scheme 3.2: A hypothetical mechanism for the formation of enol ether byproduct (**71**).

These results suggest that anion **68a** is sterically too hindered to react with aldehyde **69** as a nucleophile, but rather functioning as a base abstracting the α-proton which is more sterically accessible.

3.1.2 Olefination on Open Chain

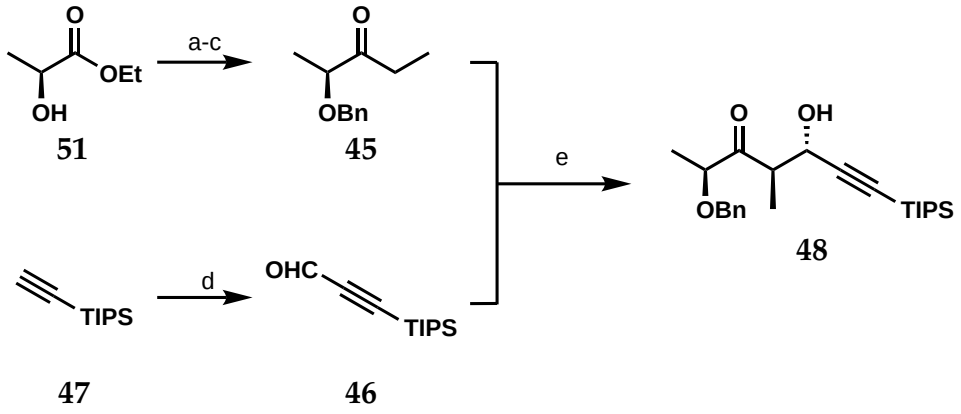


Scheme 3.3: Second generation retrosynthetic approach towards the olefination.

As the olefination did not succeed after the pyran moiety was constructed,[37] the coupling step before cyclizing the alkynol was examined. It was envisioned that alkene **72** could be synthesized by carbonyl olefination of ketone **73** and a suiting reaction partner **74** or **75**.

In that case, the former is easily accesible *via* the already established route[49] and the latter two by functional group manipulation of (*R*) or (*S*)-Roche ester, respectively (Scheme 3.3).

The ketones required for the olefination were synthesized analogous to the work of Geist.[49] Accordingly, L-ethyl lactate was transformed to ethyl ketone **45** in a three step sequence, consisting of pyrrolidine amide formation, benzylation of the free alcohol and subsequent substitution of the amide with ethylmagnesium bromide (Scheme 3.4). This step is remarkable, as it produces the ketone as opposed to the tertiary alcohol, resulting from the attack of the organometal species to the more electrophilic ketone. This observation is explained by the formation of a stable tetraedric hemiaminal, which only decomposes to the ketone upon workup.[54] Aldehyde **46** was prepared by formylation of silyl acetylene **76** under standard conditions. Afterwards, both compounds were connected in a substrate-controlled aldol reaction, providing hydroxy ketone **48** in excellent yield and stereoselectivity.

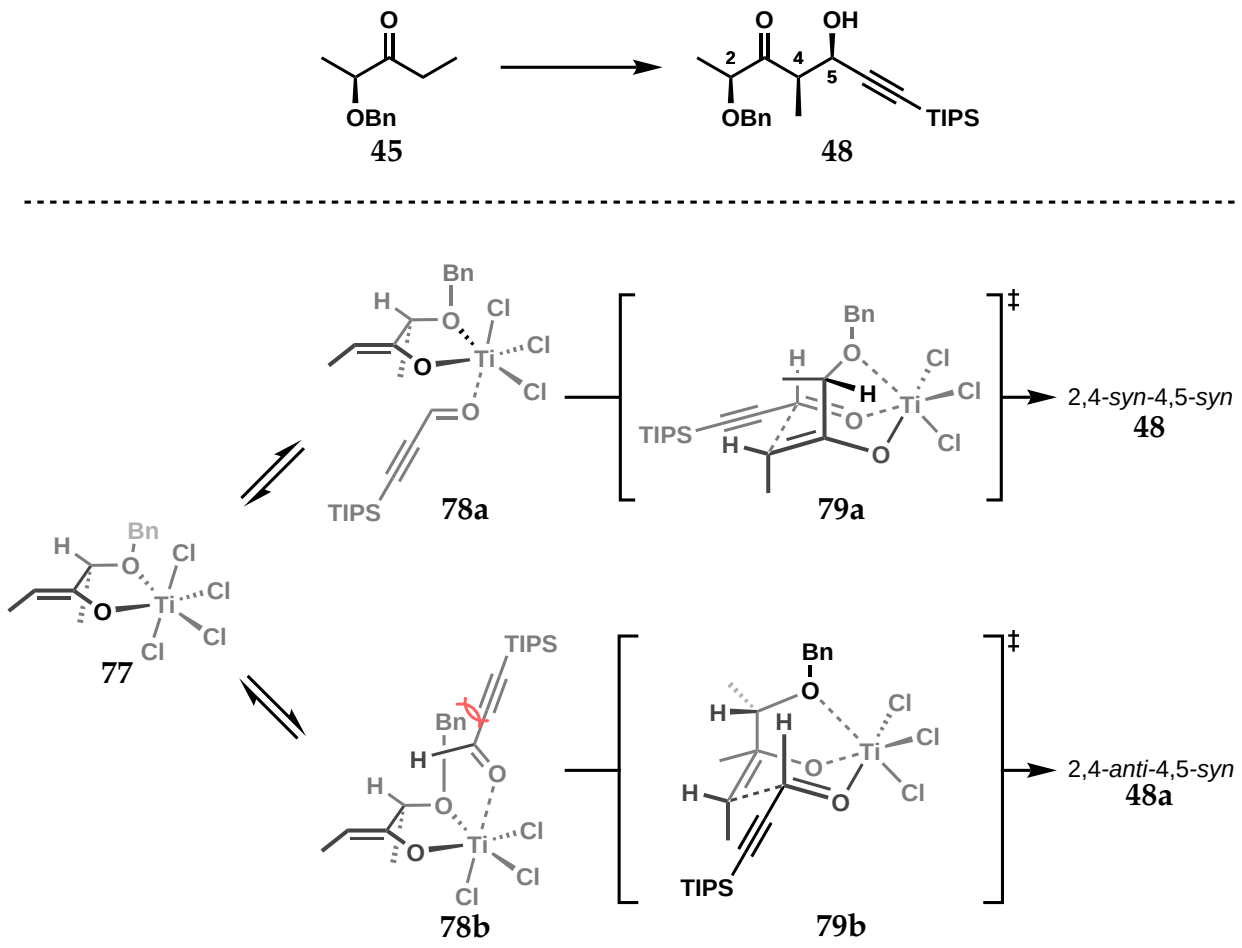


Scheme 3.4: Synthesis of the western fragment and titanium-mediated aldol reaction. Conditions: a) pyrrolidine, rt; b) BnBr, Aliquat 336, NaOH, PhMe, rt, 56 % (2 steps); c) EtMgBr, THF, 0 °C, 96 %; d) *n*BuLi, DMF, Et_2O, rt, 84 %; e) $TiCl_4$, DIPEA, CH_2Cl_2, −78 °C, 96 %, 12:1 *dr*.

Mechanistically, the stereochemical outcome of that transformation can be explained by a chair-like transition state. After formation of (*Z*)-enolate **77**, aldehyde **46** can approach the ligand sphere of the titanium metal from either face. When coordination takes place from the bottom face (**78a**), favorable transition state **79a** is formed, ultimately leading to

54 M. Ferreró, M. Galobardes, R. Martín, T. Montes, P. Romea, R. Rovira, F. Urpí, J. Vilarrasa, *Synthesis (Stuttg).* **2000**, 1608–1614.

formation of desired all *syn* aldol **48**. On the other hand, when aldehyde **46** is coordinated to the top face of the titanium center (**78b**), an unfavorable steric repulsion between the alkyne group and the benzyl group of the α-oxygen arises.[55]

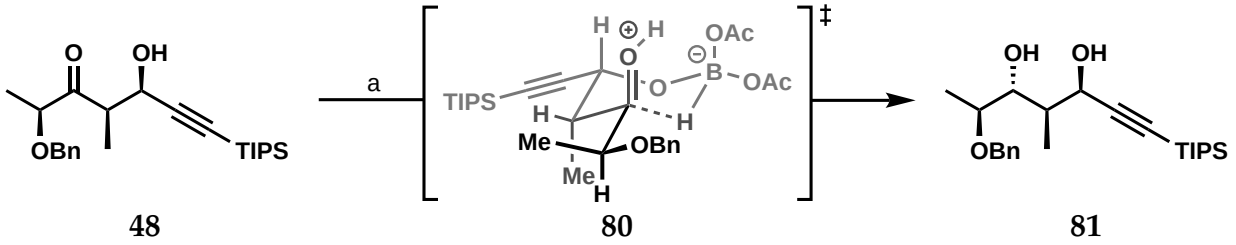


Scheme 3.5: Mechanism and transition states explaining the stereochemical outcome of the titanium-mediated aldol reaction of lactic acid derivative **45**, as proposed by Solsona *et al.*.[55]

In order to install the last remaining stereocenter of required carbonyls **73**, the β-hydroxy ketone moiety had to be reduced in an *anti*-selective fashion. Two widespread methods for this kind of transformation are the Evans-Tishchenko[56] and the Evans-Saksena[57] reductions, out of which the latter was chosen, as it was already investigated

55 J. G. Solsona, P. Romea, F. Urpí, J. Vilarrasa, *Org. Lett.* **2003**, *5*, 519–522.
56 D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
57 D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

for that substrate by Geist.[49] The selectivity is explained by chair transition state **80**, in which the hydride is delivered internally from the reducing agent. The carbonyl function is situated axially, as the more sterically hindered side chain occupies the equatorial position, confering the attack from the *Si*-face. As opposed to the reaction conditions discussed earlier, the transformation was performed using only a small excess of acetic acid instead of using it as a co-solvent. It was found that these conditions provided better conversion, as the initially reported ones led to a solidifying of the solvent mixture upon cooling. Naturally, this phenomenon was highly dependent on the concentration of the reaction, but nonetheless, even when employing a mechanical stirrer, yield and selectivity proved to be much worse than the ones reported by Geist.[49] Accordingly, the reaction was performed using the altered conditions, giving rise to stereotetrade **81** in excellent yield and selectivity.

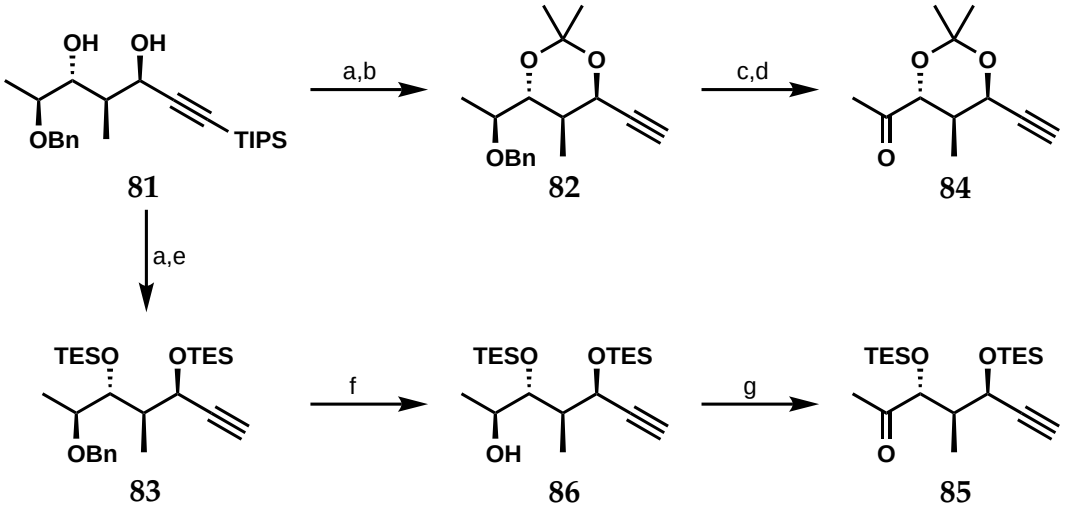


48 **80** **81**

Scheme 3.6: Mechanism and transition state explaining the stereochemical outcome of the Evans-Saksena *anti*-selective reduction of aldol **48**. Conditions: a) $NaB(OAc)_3H$, AcOH, MeCN, rt, 4.5 h, 93 %, 10:1 *dr*

With all required stereocenters in place, the protecting group strategy had to be decided. As these groups had to be stable to the debenzylation conditions, 1,3-acetonide and TES were chosen (Scheme 3.7). Consequently, the terminal alkyne was first liberated in good yield using TBAF and subsequent subjection of the resulting diol to 2,2-dimethoxypropane and catalytic amounts of CSA forged acetonide **82**. On the other hand, bis-silyl ether **83** was synthesized by treatment of the intermediate diol with TESOTf. Both compounds were reductively debenzylated using lithium naphthalenide, followed by Ley oxidation (**84**) or DMP oxidation (**85**) to form the corresponding ketones, respectively.

The nucleophiles were synthesized from (*R*)-Roche ester for the 3-carbon chain intermediates or (*S*)-Roche ester for the 5-carbon chain compounds, respectively. Synthesis of the shortened building blocks (Scheme 3.8) commenced with silylation of (*R*)-Roche ester (**87**)

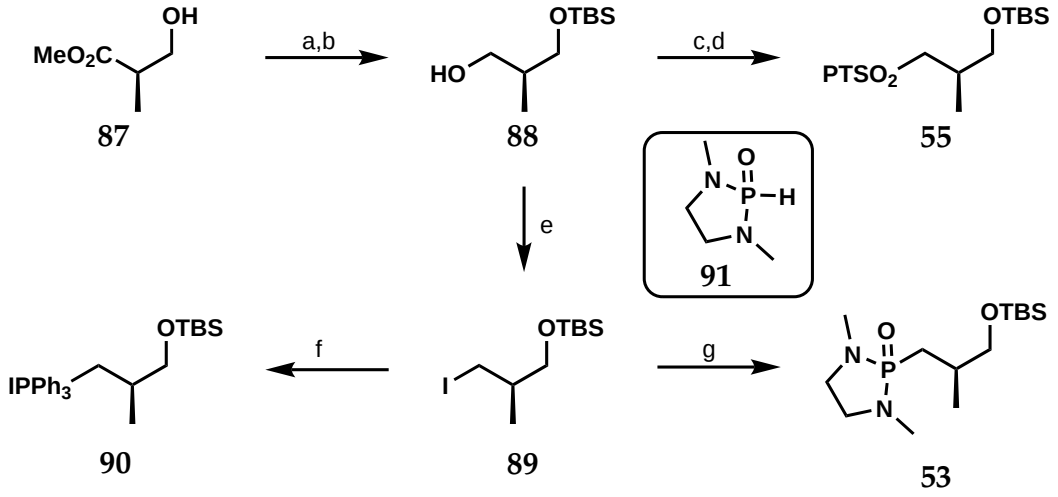


Scheme 3.7: Synthesis of the olefination ketones. Conditions: a) TBAF, THF, 50 °C, o/n, 86 %; b) 2,2-dimethoxypropane, CSA, neat, rt, o/n, 73 %; c) LN, THF, 0 °C, 30 min, 89 %; d) TPAP, NMO, CH_2Cl_2, rt, 3 h, 65 %; e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C *to* rt, 3 h, *quant.*; f) LN, THF, 0 °C, 30 min, 33 %; g) DMP, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 84 %.

under standard conditions, followed by borane reduction to give mono silylated diol **88**. Julia-Kocienski sulfone **55** was then installed by Mitsunobu reaction and subsequent oxidation using H_2O_2 under molybdenum catalysis. The phosphor-based reagents were prepared from iodide **89**, which itself was synthesized by Appel reaction of alcohol **88**. Subjection of iodide **89** to PPh_3 led to formation of Wittig salt **90**, whereas treatment with phosphoric diamide **91** under basic conditions led to formation of cyclic phosphonamide **53**, which was described by Hanessian and co-workers.[58,59]

The five carbon nucleophile syntheses commenced with (*S*)-Roche ester, which was protected, reduced and oxidized to aldehyde **41**, analogous to the synthesis established by Geist (Scheme 3.9).[49] The Evans-aldol[60,61] reaction with (*S*)-Bn-auxiliary **42** led to the stereoselective formation of stereotriade **92**, which can be explained with the Zimmerman-Traxler transition state.[62] First, the stereospecific formation of the (*Z*)-enolate is

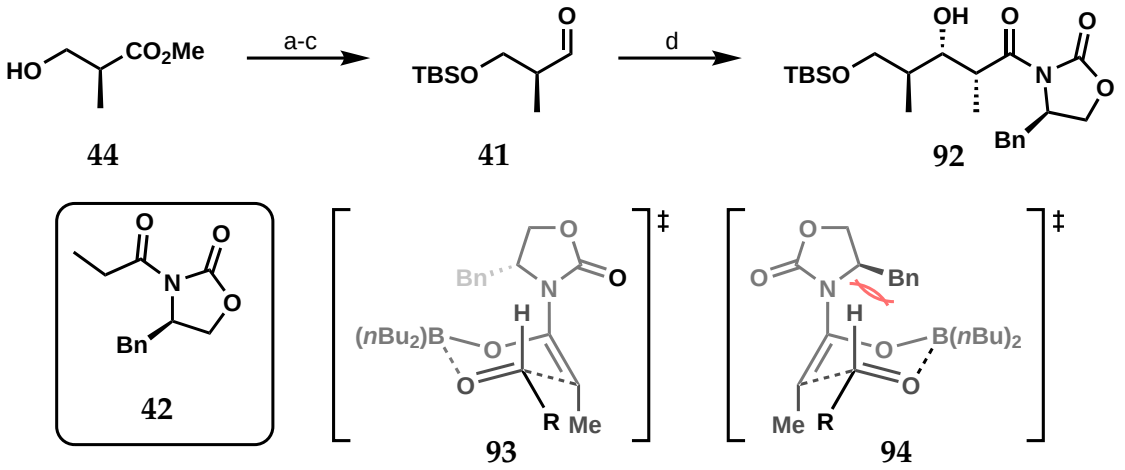
58 S. Hanessian, T. Focken, X. Mi, R. Oza, B. Chen, D. Ritson, R. Beaudegnies, S. Centre-Ville, *J. Org. Chem.* **2010**, *75*, 5601–5618.
59 S. Hanessian, T. Focken, R. Oza, *Org. Lett.* **2010**, *12*, 3172–3175.
60 D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123.
61 D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, 2127–2129.
62 H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.



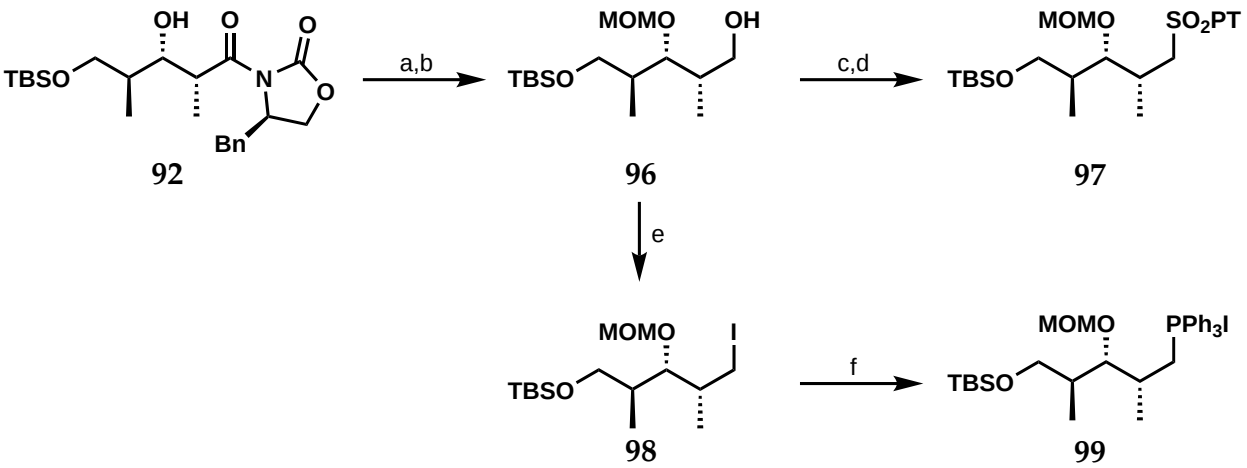
Scheme 3.8: Synthesis of the three carbon nucleophiles. Conditions: a) TBSCl, imidazole, DMF, rt, o/n, 95 %; b) BH_3·THF, THF, 0 °C *to* rt, o/n; c) PTSH, PPh_3, DIAD, THF, rt, o/n; d) $(NH_4)_6Mo_7O_{24}$·$4H_2O$, H_2O_2, rt, o/n, 46 % (3 steps); e) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C *to* rt, 3 h, 58 % (2 steps); f) PPh_3, neat, rt, o/n, *quant.*; g) **91**, NaH, THF/DMF (4:1), 0 °C *to* rt, o/n, 60 % (2 steps).

achieved by the reaction with $n$$Bu_2BOTf$ and Et_3N. Afterwards, nucleophilic attack onto aldehyde **41** results in the formation of a chair-like transition state, in which the carbonyl bond of the oxazolidinone faces in the opposite direction of the carbon-oxygen bond of the enolate, minimizing dipole interaction energy. Therefore, the rotation around the carbon-nitrogen bond is hampered, which results in a rigid favorable conformation, where one face of the enolate is sterically encumbered. Accordingly, attack of aldehyde **41** takes place from the more sterically accessible face (**93**). If the aldehyde was to attack from the other face, steric clash with the benzyl group would occur (**94**).

The chosen protecting group for the newly formed alcohol had to be compatible with further transformations that are planned for the synthesis, including the Diels-Alder chemistry and subsequent oxidation to the arene and have to be stable under conditions that selectively cleave primary TBS ether. With that in mind, the alcohol of Evans-aldol product **92** was protected by treatment with MOMCl and DIPEA, followed by $LiBH_4$-induced reductive cleavage of the auxiliary to yield alcohol **96** (Scheme 3.10). With that compound in hand, the Julia-Kocienski and Wittig reactivities were installed following the same procedures as were described for the three carbon nucleophiles (Scheme 3.8).

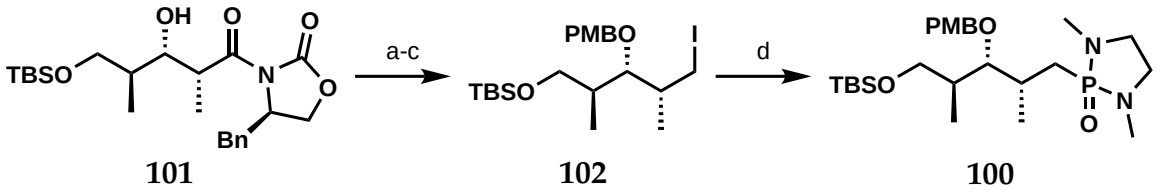


Scheme 3.9: Synthesis of aldehyde **41** and its Evans-Aldol reaction with transition states explaining the resulting stereochemistry. Conditions: a) TBSCl, imidazole, CH_2Cl_2, rt, o/n, 98 %; b) BH_3·THF, THF, rt, o/n, 54 %; c) $(COCl)_2$, DMSO, −78 °C, 30 min *then* **95**, −78 °C, 30 min *then* Et_3N, −78 °C, 30 min *to* rt, 1 h, 92 %; d) **42**, nBu$_2$BOTf, Et_3N, CH_2Cl_2, −78 °C *to* 0 °C, 80 min.



Scheme 3.10: Synthesis of the five carbon nucleophiles. Conditions: a) MOMCl, CH_2Cl_2/DIPEA (1:3), 0 °C *to* rt, o/n, 76 %; b) $LiBH_4$, THF/MeOH (20:1), 0 °C *to* rt, o/n, 76 %; c) PTSH, PPh_3, DIAD, THF, rt, o/n; d) *m*CPBA, CH_2Cl_2, rt, o/n, 67 % (2 steps); e) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C *to* rt, 3 h, 88 %; f) PPh_3, neat, rt, o/n, *quant.*.

Since substitution of the iodide **98** with phosphoric acid diamide **91** failed, the PMB protected alcohol was used, as it is a known substrate for the preparation of the phosphonamide **100**.[49] Accordingly, Evans-aldol product **92** was protected under the same conditions that were used by Geist.[49] The amide function of **101** was reduced using $LiBH_4$ to yield alcohol **43** and converted into iodide **102** by Appel reaction (Scheme 3.11). Subjection of that substrate to phosphoric diamide **91** and LiHMDS finalized the synthesis of five-carbon Hanessian nucleophile **100**.



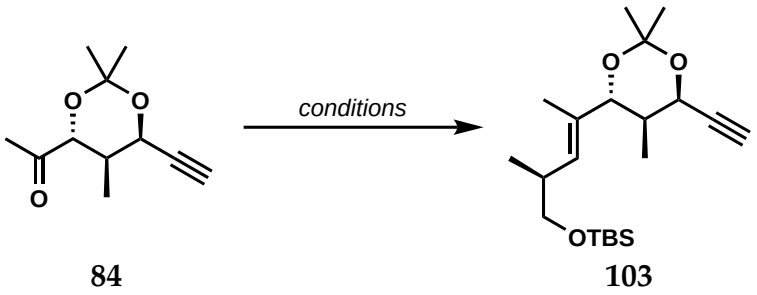
101 **102** **100**

Scheme 3.11: Synthesis of the PMB protected Hanessian nucleophile **100**. Conditions: a) PMB-trichloroacetimidate, $Sc(OTf)_3$, PhMe, rt, 48 h, 57 % (2 steps); b) $LiBH_4$, THF/MeOH (20:1), 0 °C *to* rt, 3 h, 75 %; c) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C *to* rt, o/n, 87 %; d) **91**, LiHMDS, THF, −78 °C, 30 min, *to* rt, o/n, 18 %, 55 % *brsm*.

With the ketones and the nucleophiles in hand, the olefination reaction was tested. First attempts focused on reactions of acetonide ketone **84** (Scheme 3.12). Indeed, pre-formation of the anion using Hanessians nucleophile **53** (entry 1) and reacting it with ketone **84** led to formation of the desired product **103**, albeit in low yields. On the contrary, neither reactions utilizing Julia-Kocienski sulfones **55** or **97** (entry 2 or 3) nor Wittig salt **99** (entry 4) led to successful olefination. In both cases epimerization of the ketone **84** was observed (entries 2, 3), whereas sulfone **97** led to no conversion and re-isolation of the starting materials.

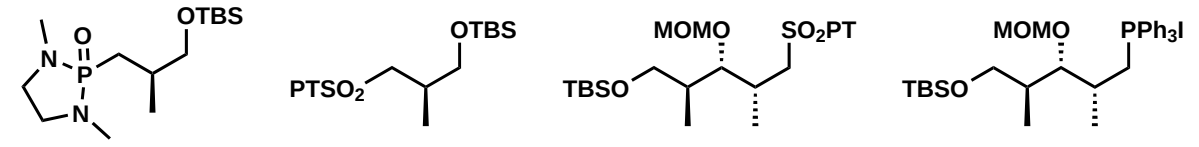
As cyclic phosphonamide **53** was the only substrate that led to olefination, a scale-up was attempted (entry 5). Unfortunately, increasing the scale diminished the yield and also led to increased epimerization of the ketone **84**. To overcome that problem, bases with higher steric demand as well as bases with different counterions were tested (entries 6, 7). In neither experiment, an increase of yields could be observed.

Since the acetonide protecting group leads to a conformationally rigid molecule, the use of an open chain ketone in the form of the bis-silyl ether **85** was used next as a coupling partner (Scheme 3.13). Olefinations using either phosphorus-based or sulfur-based nucleophiles always led to no conversion of the ketone under the previous elaborated



84 **103**

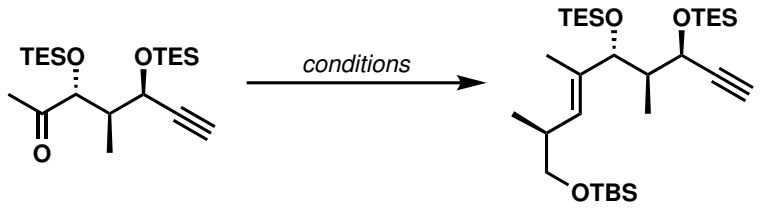
entry	nuc.	conditions	result
1	**53**	*n*-BuLi, THF, -78°C, 1h *then* **84**, -78°C, 1h *to* rt, 1h	18 %
2	**55**	KHMDS, THF, -78°C, 5min *then* **84**, -78°C, 30min *to* rt, o/n	*epi*-**84**
3	**97**	KHMDS, THF, -78°C, 5min *then* **84**, -78°C, 30min *to* rt, o/n	SM
4	**99**	*n*-BuLi, THF, -78°C, 15min *to* rt, 1h *then* **84**, -78°C, 30min *to* rt, o/n	*epi*-**84**
5	**53**	*n*-BuLi, THF, -78°C, 1h *then* **84**, -78°C, 1h *to* rt, 1h	4 % + *epi*-**84**
6	**53**	*t*-BuLi, THF, -78°C, 1h *then* **84**, -78°C, 1h *to* rt, 1h	12 % + *epi*-**84**
7	**53**	NaHMDS, THF, -78°C, 1h, 30min, 0°C *then* **84**, -78°C, 1h *to* rt, 1h	*epi*-**84**



53 **55** **97** **99**

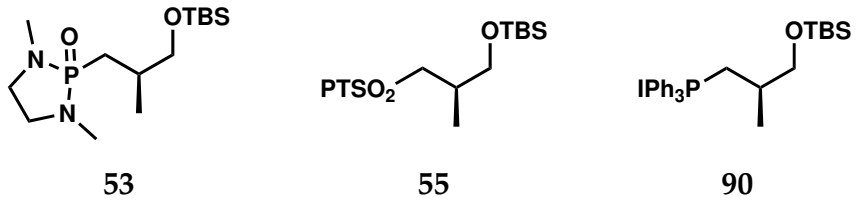
Scheme 3.12: Attempted olefinations using acetonide **84**.

conditions (entries 1 to 5). Efforts to use bulkier bases like *t*BuLi led to decomposition of the substrate (entry 6). Interestingly, the signal of the terminal alkyne proton could not be detected in the ^{1}H-NMR spectrum of the major product, suggesting that the nucleophile might have deprotonated that position, leading to decomposition of the substrate. Additionally, a reaction with NaH under refluxing conditions (entry 7) was tested. In that case, a complex mixture of compounds was obtained, which was not further characterized.

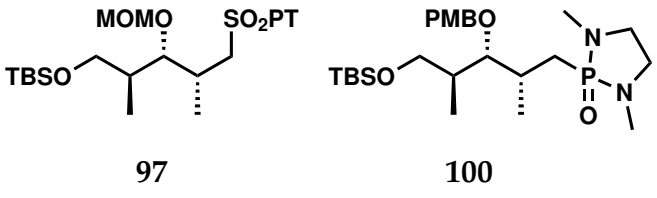


85 **104**

entry	nuc.	conditions	result
1	**53**	*n*BuLi, THF, -78°C, 1h *then* **85**, -78°C, 1 h	SM
2	**100**	*n*BuLi, THF, -78°C, 1h *then* **85**, -78°C, 1 h	SM
3	**55**	KHMDS, THF, -78°C, 1h *then* **85**, -78°C, 30 min *to* rt, o/n	SM
4	**97**	KHMDS, THF, -78°C, 1h *then* **85**, -78°C, 30 min *to* rt, o/n	SM
5	**90**	KHMDS, THF, 0°C, *to* rt, 1h *then* **85**, -78°C, 1 h *to* rt, o/n	SM
6	**53**	*t*BuLi, THF, -78°C, 1h *then* **85**, -78°C, 1 h	decomp.
7	**53**	NaH, THF, rt, 1h *then* **85**, reflux, 2 h	decomp.



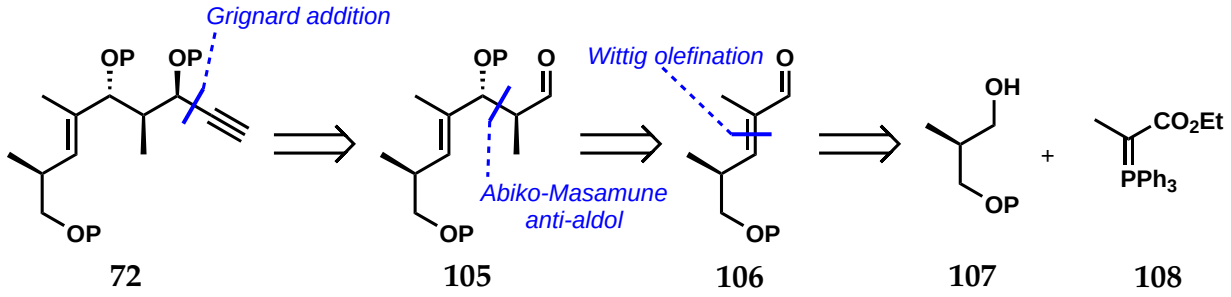
53 **55** **90**



97 **100**

Scheme 3.13: Attempted olefinations using bis-silyl ether **85**.

As olefination still did not occur in acceptable yields using the ketones **84** or **85**, a route which installs the double bond at an even earlier stage of the synthesis was developed (Scheme 3.14). It was envisioned that the terminal alkyne of **72** can be installed by Grignard-addition onto a carbonyl function. The stereocenters of the alcohol and the adjacent methyl group of **105** will be set by an *anti*-selective Abiko-Masamune aldol reaction.[63–65] The α,β-unsaturated aldehyde **106** will be prepared by Wittig reaction in a six step synthesis from commercially available (*R*)-Roche ester.[66,67]

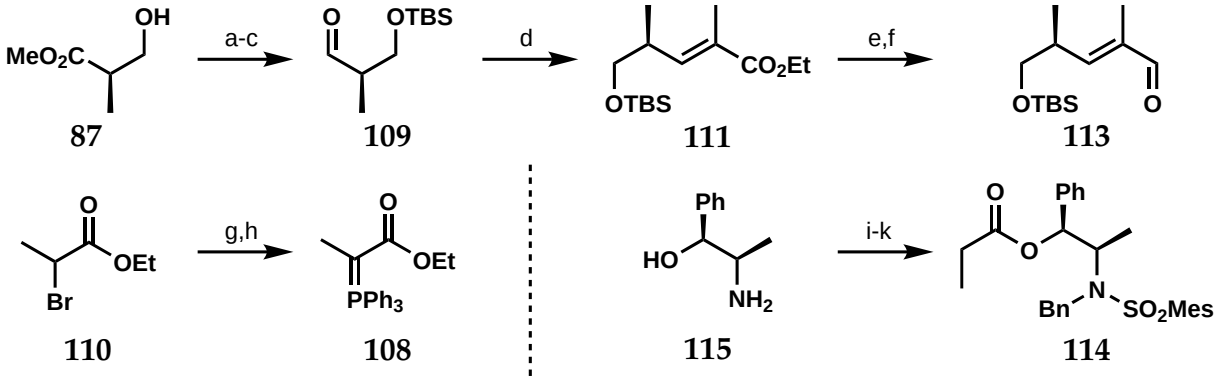


Scheme 3.14: Third generation retrosynthetic approach towards the olefination.

The forward synthesis commenced with TBS protection of (*R*)-Roche ester, followed by a reduction oxidation sequence to yield aldehyde **109** (Scheme 3.15). Subsequent treatment with Wittig reagent **108**, which is easily prepared in two steps from racemic ethyl 2-bromopropionate (**110**)[68], forged alkene **111** in good yield as a single diastereomer. Reduction of the resulting ester **111** using DIBAl-H led to formation of the corresponding alcohol **112**. It was crucial that the reaction progress was monitored closely and the reaction terminated as soon as the starting material was consumed since cleavage of the primary TBS group was observed as an undesired side-reaction. Accordingly, the yield dropped from 80 % to 68 % when increasing the scale from 230 mg to 8.0 g, due to increased addition time of the reductant. Swern oxidation of the resulting alcohol finalized the synthesis of aldehyde **113** which was used for the Abiko-Masamune aldol reaction.

63 S. Masamune, T. Sato, B. Kim, T. A. Wollmann, *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281.
64 A. Abiko, J. F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587.
65 T. Inoue, J. F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250–5256.
66 K. Matsui, B. Z. Zheng, S. I. Kusaka, M. Kuroda, K. Yoshimoto, H. Yamada, O. Yonemitsu, *Eur. J. Org. Chem.* **2001**, 3615–3624.
67 G. J. Florence, J. Wlochal, *Chem. Eur. J.* **2012**, *18*, 14250–14254.
68 S. E. Denmark, C. S. Regens, T. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776.

Required ethyl ketone **114** was prepared from commercially available (1*S*,2*R*)-norephedrine (**115**) in three steps by alkylation of the amine, followed by acylation of the alcohol.[65]

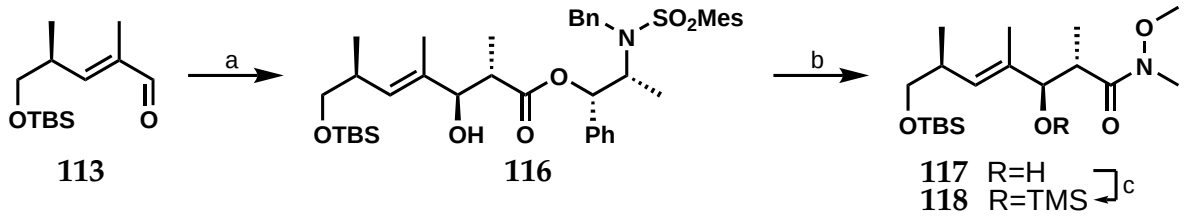


Scheme 3.15: Entry into the third generation route. Conditions: a) TBSCl, imidazole, DMF, rt, o/n; b) BH_3·THF, THF, 0 °C *to* rt, o/n; c) $(COCl)_2$, DMSO, −78 °C, 30 min *then* **88**, −78 °C, 30 min *then* Et_3N, −78 °C, 30 min *to* rt, 1 h; d) **108**, CH_2Cl_2, 2 d, rt, 68 % (4 steps); e) DIBAl-H, CH_2Cl_2, −78 °C, 30 min, 80 %; f) $(COCl)_2$, DMSO, −78 °C, 30 min *then* **112**, −78 °C, 30 min *then* Et_3N, −78 °C, 30 min *to* rt, 1 h, 97 %; g) PPh_3, neat, 50 °C, o/n; h) NaOH, CH_2Cl_2, H_2O, 0 °C *to* rt, 30 min, 94 % (2 steps); i) MesCl, Et_3N, CH_2Cl_2, 0 °C *to* rt, 2 h; j) BnBr, K_2CO_3, MeCN, 90 °C, o/n; k) propionyl chloride, pyridine, CH_2Cl_2, 0 °C *to* rt, 13 h, 77 % (3 steps).

With all the required compounds in hand, the Abiko-Masamune *anti*-aldol reaction which sets the desired stereochemistry of the methyl and hydroxy groups was engaged (Scheme 3.16).

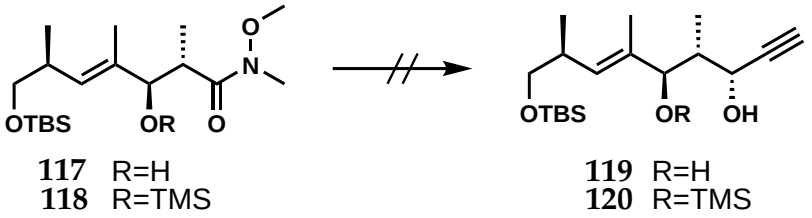
Accordingly, treatment of ethyl ketone **114** with Et_3N and freshly prepared Cy_2BOTf[69] formed the (*E*)-boron enolate which was reacted with aldehyde **113** to yield aldol product **116** in excellent yield and diastereoselectivity. Following a procedure by Menche and co-workers[70], Abiko ester was directly transformed into the Weinreb amide, which were envisioned to undergo nucleophilic substitution with ethynylmagnesium bromide to form the desired propargylic alcohols **119** or **120** (Scheme 3.17). Even though there is literature precedence for the substitution of a Weinreb amide with ethynylmagnesium

69 A. Abiko, *Org. Synth.* **2004**, *79*, 103–108.
70 J. Li, P. Li, D. Menche, *Synlett* **2009**, *1*, 2417–2420.



Scheme 3.16: *Anti*-aldol reaction and transformation to Weinreb amide **118**. Conditions: a) **114**, Et_3N, Cy_2BOTf, −78 °C, 30 min *then* **113**, −78 °C, 30 min, 85 %; b) *i*PrMgCl, THF, −20 °C, 10 min *then* *N,O*-dimethylhydroxylamine magnesium chloride, −20 °C, 2 h *to* −10 °C, 1 h, 45 %; c) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h, 65 %.

bromide[71–73], it was found that neither amide **117** nor **118** led to any conversion of the starting material to form the desired products. Efforts using a larger excess of nucleophile as well as elevated temperatures or the corresponding lithiate, which was generated *in situ* from 1,2-dibromoethan by treatment with 2 equivalents of LDA, either led to no conversion or to formation of the retro-aldol products.

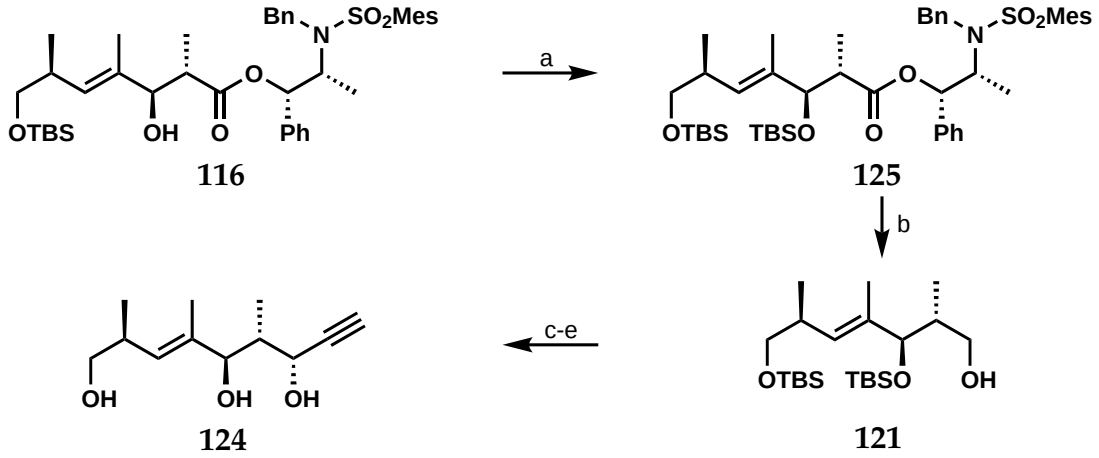


Scheme 3.17: Failed attempts at substituting the weinreb amide.

With the failed two step procedure for the substitution of the Abiko-ester a less step-economic protocol was developed (Scheme 3.18). Accordingly, protection of β-hydroxy alcohol **116** using TBSOTf and subsequent DIBAl-H reduction forged primary alcohol **121**. Again, keeping reaction time to a minimum was crucial to achieve good yields, since the primary TBS ether was labile under the given conditions. After oxidation of alcohol **121** to aldehyde **122** under Swern conditions, addition of ethynylmagnesium bromide in THF yielded desired propargylic aldehyde **123** in a 1:1 diastereomeric mixture with 73 % com-

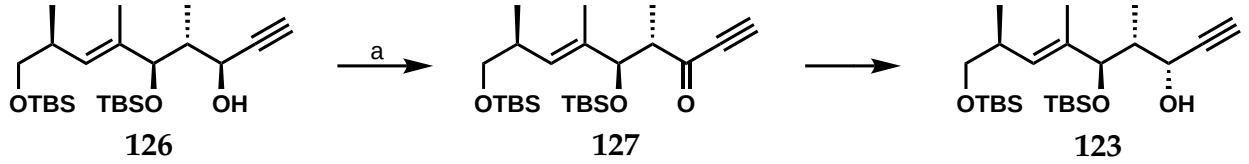
71 D. A. Evans, J. T. Starr, *J. Am. Chem. Soc.* **2003**, *125*, 13531–13540.
72 H. L. Shimp, G. C. Micalizio, *Tetrahedron* **2009**, *65*, 5908–5915.
73 B. M. Trost, C. E. Stivala, D. R. Fandrick, K. L. Hull, A. Huang, C. Poock, R. Kalkofen, *J. Am. Chem. Soc.* **2016**, *138*, 11690 –11701.

bined yield over two steps, which were separated by column chromatography. Deprotection of the two silyl ethers finalized the synthesis of triol **124**.



Scheme 3.18: Alternative route towards propargylic alcohol **124**. Conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h *to* rt, 30 min, 85 %; b) DIBAl-H, CH_2Cl_2, −78 °C, 10 min, 81 %; c) $(COCl)_2$, DMSO, −78 °C, 30 min *then* **121**, −78 °C, 30 min *then* Et_3N, −78 °C, 30 min *to* rt, 1 h; d) ethynylmagnesium bromide, THF, 0 °C, 1 h, 34 % (2 steps, single diastereomer); e) TBAF, THF, 50 °C, 2 h, 62 %.

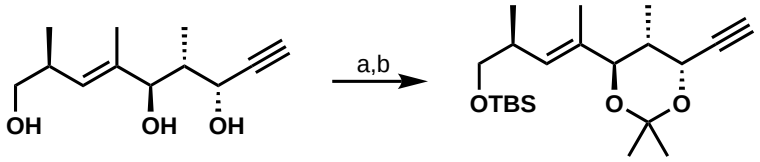
As a methodology to interconvert the undesired diastereomer **126** obtained from Grignard-addition into the desired one, an oxidation/reduction sequence, making use of an asymmetric ketone reduction, was investigated (Scheme 3.19). As it turned out, oxidation was faciliated using MnO_2 to yield the desired ketone **127**. Reducing that ketone using Noyori's transfer hydrogenation catalyst[74] did not lead to conversion of the starting material, whereas reduction using methyl-CBS-borane[75] did not occur with mentionable facial selectivity.



Scheme 3.19: Interconversion of the wrong diastereomer. Conditions: a) MnO_2, CH_2Cl_2, rt, o/n.

74 K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, 285–288.
75 E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

Additionally, to obtain insight about the stereochemistry which was set by the *anti*-aldol reaction as well as the Grignard-addition, the synthesized propargylalcohol **124** was converted to its acetonide (Scheme 3.20). Accordingly, subjection of triol **124** to 2,2-dimethoxypropane under acidic conditions led to selective protection of the diol, which was further silylated using TBSOTf to yield silyl ether **103**. Comparison of the product with the one prepared by olefination (Scheme 3.12) shows that they are identical, proving that the stereochemistry of the prepared compound is correct.



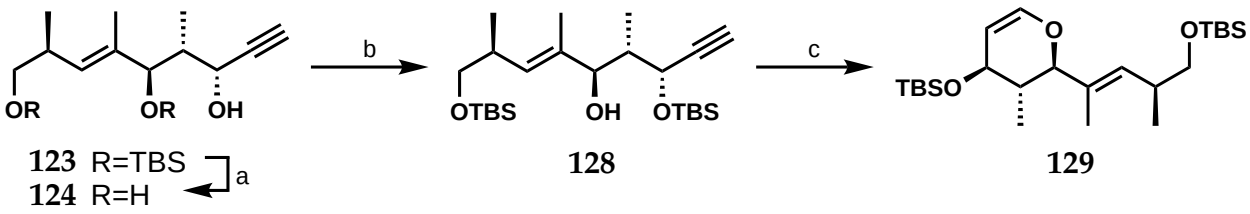
124 **103**

Scheme 3.20: Proof of stereochemistry by synthesis. Conditions: a) 2,2-dimethoxypropane, CSA, neat, rt, 2 h; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h, 39 % (2 steps).

Afterwards, the desilylation of bis-silyl ether **123** was optimized in regard to the workup, allowing the following silylation to take place without a purification step, leading to generally higher yields (Scheme 3.21).[76] To achieve the next transformation, crude diol **124** was treated with TBSOTf under basic conditions at −78 °C to yield bis-silyl ether **128** selectively. Subjecting this alkynol to the isomerization conditions established earlier led to formation of dihydropyran **129** in a formal 6-*endo-dig* cyclization in good yields.[49,77–79]

The proposed catalytic cycle is displayed in Scheme 3.22.[80] When irradiating a solution of tungsten hexacarbonyl in THF and Et_3N with UV light, an equilibrium between THF complex **130** and the catalytically active Et_3N complex **131** emerges. Moreover, these two complexes can undergo one additional ligand exchange, resulting in the formation of unactive species **132**. Therefore, a continuous exposure to the UV light source greatly increases the yield of the reaction. In an oxidative addition step of Et_3N complex **131** into the terminal carbon-hydrogen bond of alkyne **128**, alkynyl-tungsten species **128a** is formed. After a subsequent 1,3-hydride shift to vinylidene carbenoid **128b**, a highly

76 Y. Kaburagi, Y. Kishi, *Org. Lett.* **2007**, *9*, 723–726.
77 F. E. McDonald, H. Y. H. Zhu, S. Road, E V, *J. Am. Chem. Soc.* **1998**, *7863*, 4246–4247.
78 J. L. Bowman, F. E. McDonald, *J. Org. Chem.* **1998**, *63*, 3680–3682.
79 M. M. Gleason, F. E. McDonald, *J. Org. Chem.* **1997**, *62*, 6432–6435.
80 F. E. McDonald, K. S. Reddy, Y. Díaz, *J. Am. Chem. Soc.* **2000**, *122*, 4304–4309.

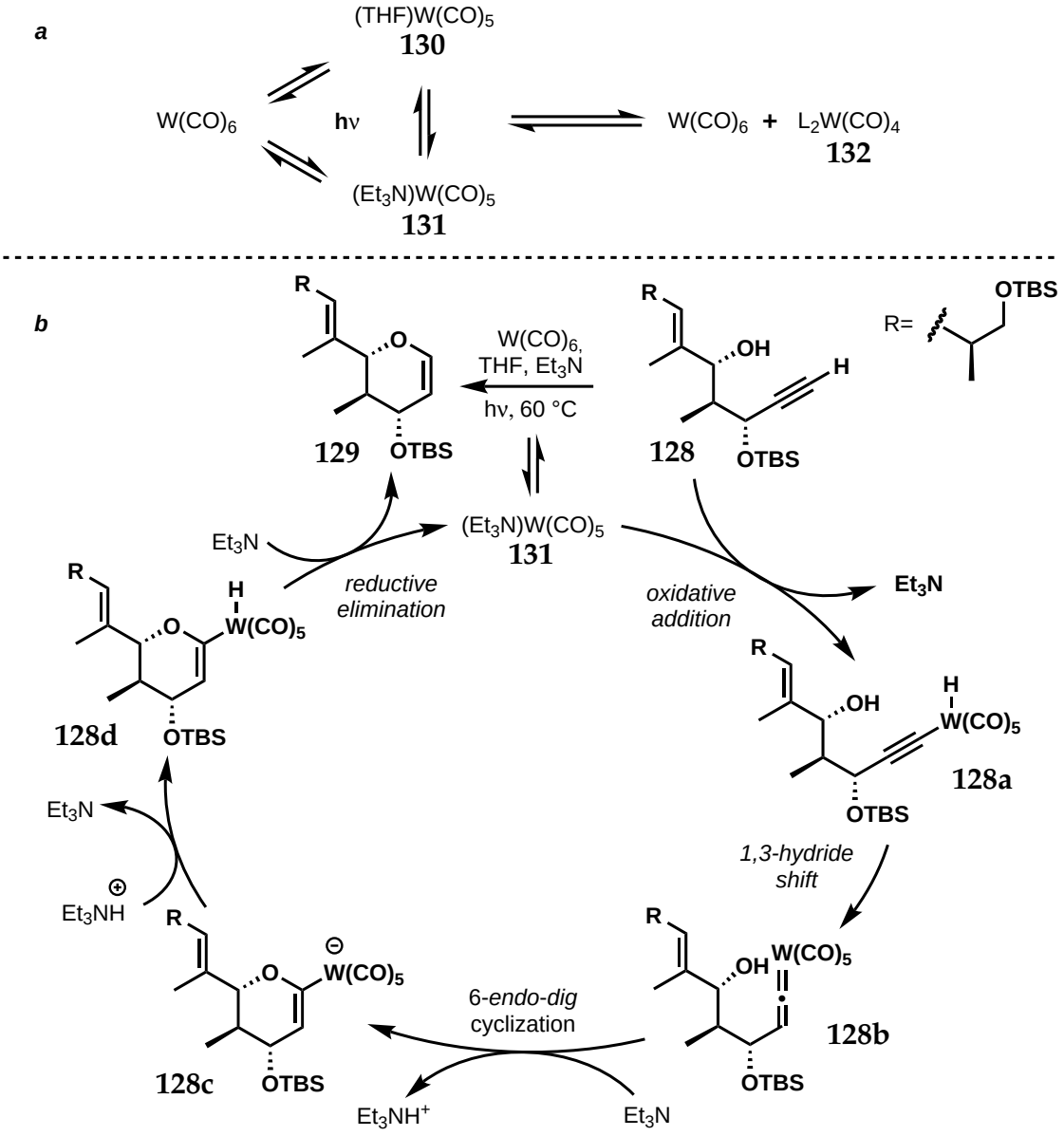


Scheme 3.21: Synthesis of the dihydropyran **129** by tungsten-catalyzed cycloisomerization. Conditions: a) TBAF, THF, 50 °C, 3 h; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h, 70 % (2 steps); c) $W(CO)_6$, Et_3N, THF, *hν*, 60 °C, 4 h, 80 %.

regioselective 6-*endo-dig* cyclization takes place at the terminal carbon. The resulting anionic tungsten species **128c** is protonated, forming oxocarbene **128d**, which undergoes reductive elimination to regenerate catalyst **131** and form dihydropyran **129**. Interestingly, if the reaction is performed in the abscence of Et_3N and with overstochiometric amounts of tungsten hexacarbonyl, the intermediate carbene **128d** can be isolated as a pure compound. Further reaction with Et_3N then results in formation of the product, albeit in lower yields compared to the one-step procedure.[81] Moreover, these carbene species **128b** can be transformed to different functionalities, for example into stannanes by reaction with nBu$_3$SnOTf.[78]

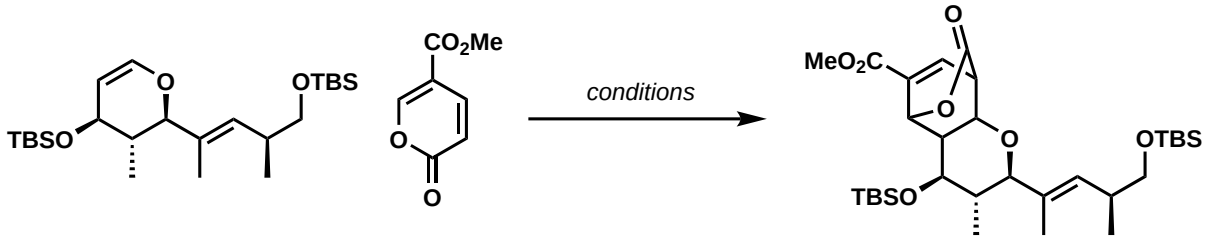
With the cycloaddition precursor **129** in hand, we were able to investigate the Diels-Alder reaction, having the alkene moiety of cebulactam already in place (Scheme 3.23). Despite extensive efforts, the cycloaddition could not be facilitated in isolable yields. In that regard, the earlier established high pressure conditions were tested first (entry 1). Applying a pressure of 14 kbar to a mixture of enol ether **129** and diene **39** in CH_2Cl_2 unfortunately only led to decomposition of dienophilic pyran **129**. As methyl coumalate **39** was reisolated in quantitative yields, a homo- or intramolecular reaction of pyran **129** in which diene **39** is not involved most likely takes place. Even though coumalate **39** is a well studied diene engaging in thermal Diels-Alder reactions[82–84], the formation of reaction product **133** was not observed. Under milder conditions no reaction took place, whereas an increase in temperature led to decomposition of starting enol ether **129**, as indicated in entry 3. Moreover, Lewis acid activation of coumalate **39** was investigated, even though

81 F. E. McDonald, H. Y. H. Zhu, *Tetrahedron* **1997**, *53*, 11061–11068.
82 G. A. Kraus, S. Wang, *RSC Adv.* **2017**, *7*, 56760–56763.
83 I. E. Markó, G. R. Evans, *Tetrahedron Lett.* **1993**, *34*, 7309–7312.
84 J. J. Lee, G. A. Kraus, *Tetrahedron Lett.* **2013**, *54*, 2366–2368.



Scheme 3.22: a) Isomerization equilibrium of $W(CO)_6$ in THF/Et_3N and formation and decay of the catalytically active complex **131**. b) Mechanism of the $W(CO)_6$-catalyzed cycloisomerization of alkynol **128** according to McDonald *et al.*.[80]

literature precendence on that mode of activation is scarce (entries 4 and 5).[85,86] It has to be noted that the work of Slack *et al*. focused on the use of $ZnBr_2$ as a Lewis acid utilizing methyl-2-oxo-2*H*-pyran-3-carboxylate as opposed to methyl-2-oxo-2*H*-pyran-5-carboxylate (**39**), allowing for easier Lewis acid coordination to the 1,3-dicarbonyl moiety of the diene. Carbaugh *et al*. argue that Lewis and Brønsted acid activation of methyl coumalate **39** proves hard due to competing Lewis basicity of the enol ether oxygen and the 5-carboxyl group of diene **129**. Nonetheless, they found that α-hydroxyacids lead to an increased yield in cycloaddition when reacting propargylic alcohols with methyl coumalate **39**. Unfortunately, both of these two described methods led to decomposition of dihydropyran **129**. A last reaction at high pressure conditions was attempted to increase the likelyhood of intermolecular reaction of the two Diels-Alder precursor (entry 6). Therefore, the reaction was carried out using a large excess of coumalate **39**. In that case, traces of the product **133** were observed by LC-MS but none could be isolated.



129 **39** **133**

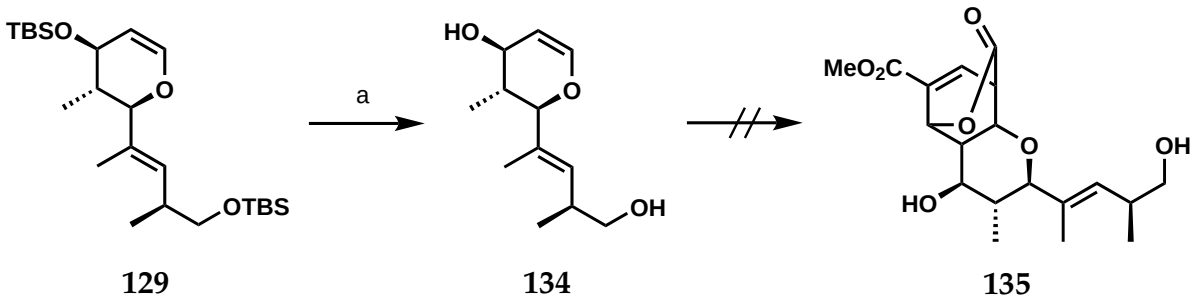
entry	conditions	result
1	CH_2Cl_2, 14kbar, 1 d	**129** decomposed, **39** recovered
2	MeCN, 100°C, o/n	recovered **129** and **39**
3	xylenes, 200°C, o/n	**129** decomposed, **39** recovered
4	$ZnBr_2$, CH_2Cl_2, 0°C, 3 h	**129** decomposed, **39** recovered
5	citric acid, EtOAc, 170°C, 3 d	**129** decomposed, **39** recovered
6	10 eq. of **5**, CH_2Cl_2, 14 kbar, 3 d	traces of **133** by LC-MS, not isolable

Scheme 3.23: Attempted Diels-Alder cycloaddition of dihydropyran **129** and methyl coumalate **39** under divergent conditions.

85 R. D. Slack, M. A. Siegler, G. H. Posner, *Tetrahedron Lett.* **2013**, *54*, 6267–6270.

86 A. D. Carbaugh, W. Vosburg, T. J. Scherer, C. E. Castillo, M. A. Christianson, J. Kostarellas, S. J. Gosai, M. S. Leonard, *Arkivoc* **2007**, *2007*, 43–54.

In order to overcome the limitations of the dihydropyran substrate **129**, the bulky TBS groups of the alcohols were removed, as steric hindrance was suspected to play a role in the reduced reactivity. Bis-silyl ether **129** was treated with TBAF to yield diol **134**, which was also tested in the Diels-Alder reaction (Scheme 3.23). Again, high pressure and thermal conditions were applied but the substrate **134** showed similar reactivity and both activation modes did not lead to formation of the desired product **135**. Under high pressure conditions the formation of an unsoluble polymer was observed.



129 **134** **135**

Scheme 3.24: Removal of the silyl protecting groups and attempted Diels-Alder reaction. Conditions: a) TBAF, THF, 50 °C, 2 h, 42 %.

With that Diels-Alder approach not leading towards the desired transformation, the strategy had to be changed entirely.

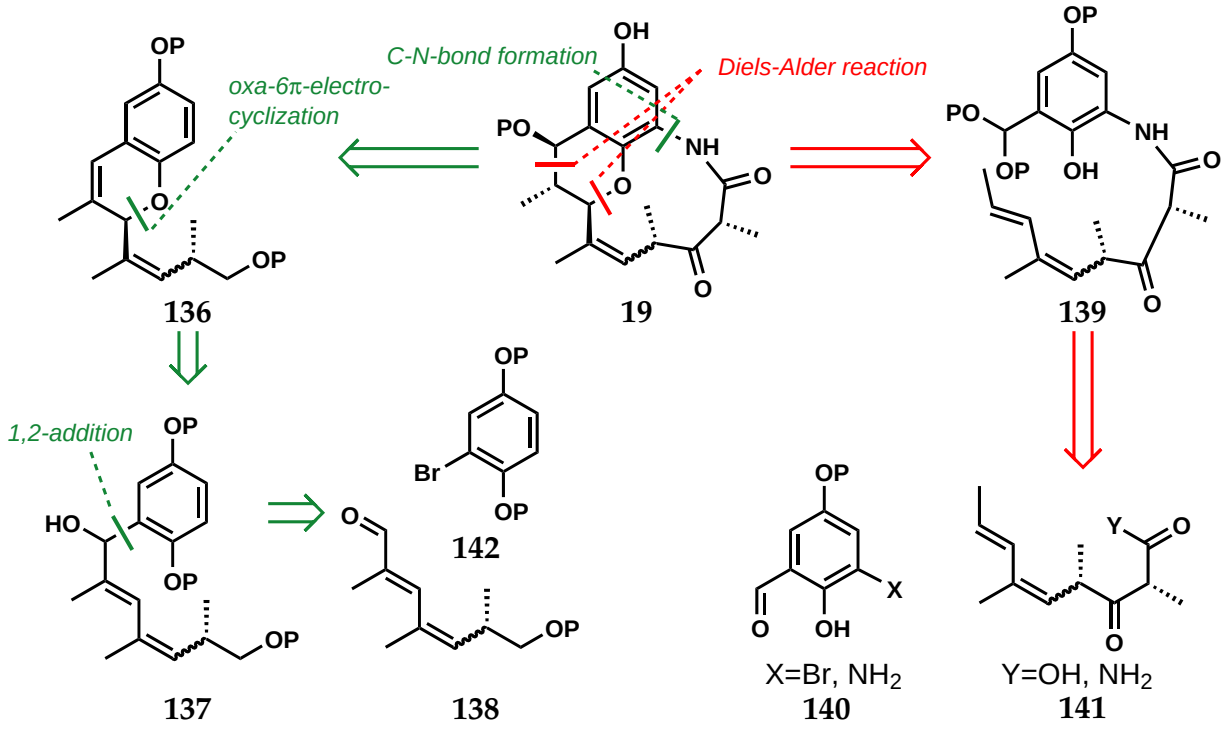
3.2 *ortho*-Quinone Methide Route

3.2.1 Retrosynthetic Considerations

All recent efforts of our group towards cebulactam (**19**) focused on Diels-Alder approaches that build the aromatic core of the chromane.[38,49] A conceptually different approach constitutes the reaction of an *ortho*-quinone methide (Scheme 3.25).[87–91] In that

87 C. D. Nielsen, H. Abas, A. C. Spivey, *Synthesis (Stuttg).* **2018**, *50*, 4008–4018.
88 N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160–9173.
89 M. S. Singh, A. Nagaraju, N. Anand, S. Chowdhury, *RSC Adv.* **2014**, *4*, 55924–55959.
90 T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210–9215.
91 W. J. Bai, J. G. David, Z. G. Feng, M. G. Weaver, K. L. Wu, T. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655–3664.

case, the retrosynthetic scission is not placed along the benzene ring but rather along the C-O-bond of the non-aromatic pyran moiety. Depending on the nature of the substrate, the *in situ* generated *ortho*-quinone methide reacts either in an oxa-6π-electrocyclization (highlighted in green) or in a Diels-Alder pathway (highlighted in red). In the former case, cebulactam **19** is traced back to electrocyclization product **136**, which arises from benzylic alcohol **137**, which can be prepared by 1,2-addition of an aryl-metalate onto aldehyde **138**. In the latter case, Diels-Alder precursor **139** can be accessed from arene **140** and carboxylic acid derivative **141** by either cross-coupling or peptide-coupling reactions.

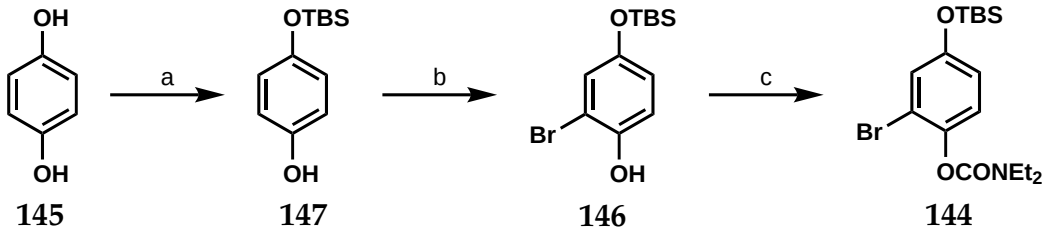


Scheme 3.25: Retrosynthetic considerations towards cebulactam **19** abusing *ortho*-quinone methide chemistry.

3.2.2 Electrocyclization Pathway

The first section deals with the electrocyclization pathway of an *ortho*-quinone methide. This reactivity requires an unsaturated system bearing a 6π moiety. In that case, electrocyclization is feasible, leading to re-aromatization. The synthesis towards chromene **143** was

inspired by the work of Dai *et al*. who made use of the same arene compound **144** as the *ortho*-quinone methide precursor (Scheme 3.26).[92] The synthesis of building block **144** commenced with mono silylation of hydroquinone **145** under standard conditions as described by Kranich *et al*.[93] An improved procedure for the bromination using $CaCO_3$ as base forged bromoarene **146** in good yield.[94] Subsequent acylation using diethylcarbamoyl chloride and 4-(dimethylamino)-pyridine finalized the synthesis of carbamate **144**.[92]



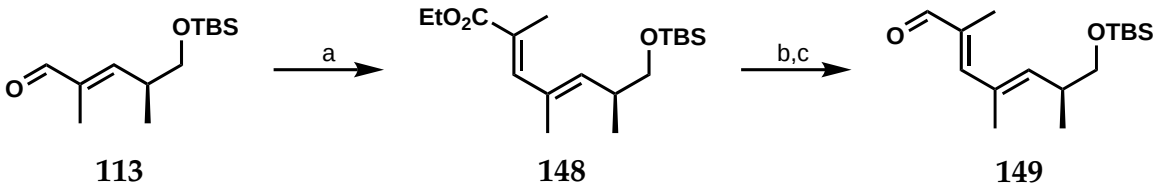
145 **147** **146** **144**

Scheme 3.26: Synthesis of the carbamate **144**. Conditions: a) TBSCl, imidazole, DMF, rt, o/n, 58 %; b) Br_2, $CaCO_3$, CH_2Cl_2, 0 °C, 2 h, 85 %; c) diethylcarbamoyl chloride, DMAP, pyridine, reflux, o/n, 43 %.

The aldehyde coupling partner required for the 1,2-addition was synthesized from earlier described aldehyde **113** by another Wittig reaction with ethyl 2-(triphenylphosphaneylidene)propanoate to yield double unsaturated ester **148** (Scheme 3.27). Oxidation state manipulation by means of DIBAl-H reduction and manganese dioxide oxidation forged aldehyde **149** in excellent yields.

Since this route suffers from several non-strategic reactions like oxidation state manpulations, some attempts to synthesize aldehyde **149** in a more direct manner were conducted. Unfortunately, the reaction of aldehyde **113** with 2-(triphenylphosphaneylidene)propanal did not lead to conversion of the starting material in a variety of solvents and different temperatures. Another approach for the direct chain-extension of aldehydes poses the Corey-Peterson olefination (Scheme 3.28).[95] This transformation relies on the lithiation of α-silylimine **150**, followed by nucleophilic attack on aldehyde **113** resulting in the formation of β-silanol **151**. Under acidic conditions the imine is protonated, allowing for

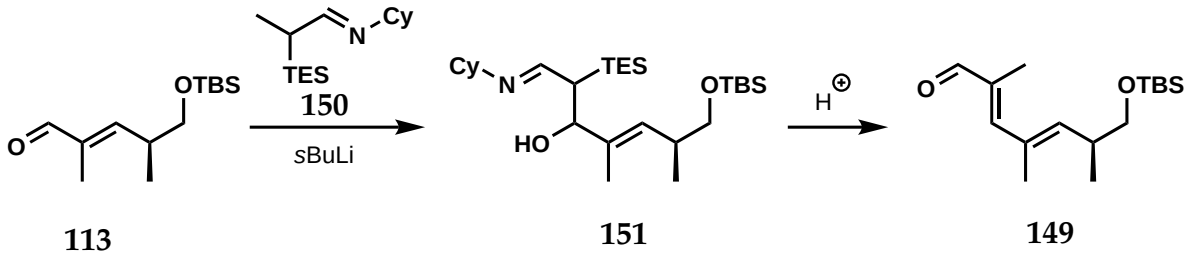
92 M. Dai, S. J. Danishefsky, *Tetrahedron Lett.* **2008**, *49*, 6610–6612.
93 R. Kranich, K. Eis, O. Geis, S. Mühle, J. Bats, H.-G. Schmalz, *Chem. Eur. J.* **2000**, *6*, 2874–2894.
94 R. Epple, C. Cow, Y. Xie, X. Wang, R. Russo, M. Azimioara, E. Saez, Compounds and Compositions as PPAR Modulators, **2005**.
95 E. J. Corey, D. Enders, M. G. Bock, *Tetrahedron Lett.* **1976**, *17*, 7–10.



113 **148** **149**

Scheme 3.27: Synthesis of the double unsaturated aldehyde **149** required for the oxa-6π-electrocyclization. Conditions: a) ethyl 2-(triphenylphosphaneylidene)propanoate, THF, reflux, o/n, 96 %; b) DIBAl-H, CH_2Cl_2, −78 °C, 15 min; c) MnO_2, CH_2Cl_2, rt, o/n, 90 % (2 steps).

Z to *E* isomerization which is followed by hydrolysis, liberating aldehyde **149**. Using the procedure of Zeng *et al.*[96] dienal **149** was prepared from aldehyde **113** as a single detected diastereomer, although in low yield and as a 4:1 mixture with unseparable starting material. Further optimization attempts and applying the same procedure to the synthesis of aldehyde **113** could reduce the stepcount for the synthesis of enal **149** from nine to five.



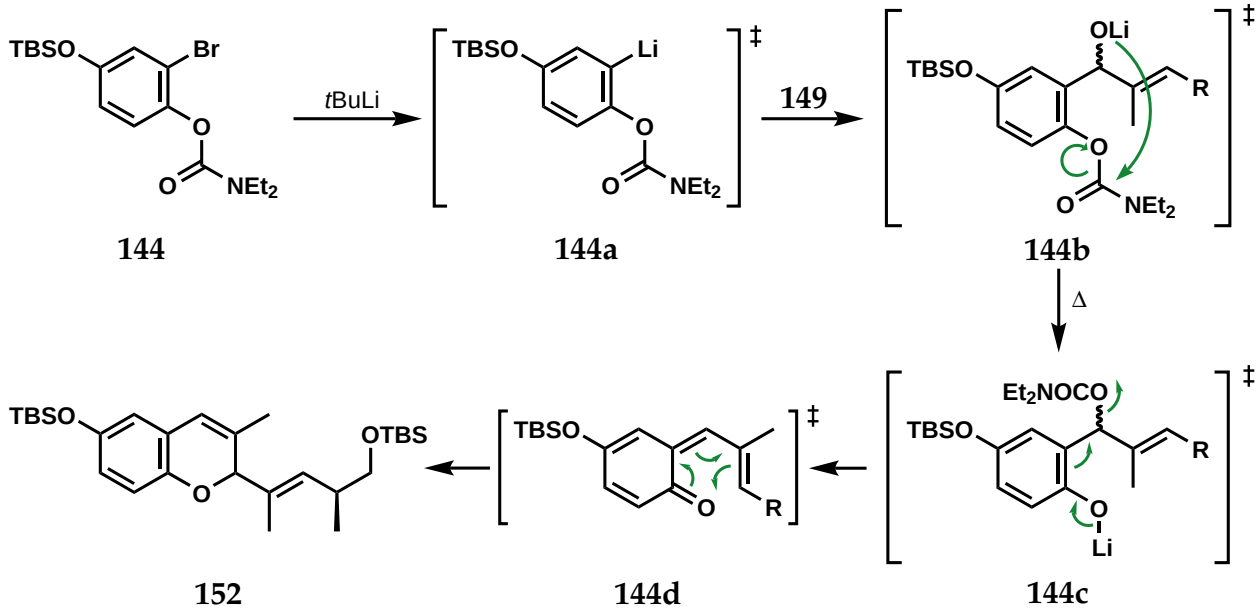
113 **151** **149**

Scheme 3.28: Corey-Peterson olefination of aldehyde **113**. Conditions: **150**, *s*BuLi, THF, −78 °C, 30 min *then* **113**, THF, to −20 °C, 1h *then* TFA, 0 °C, 1h *then* H_2O, 0 °C, 1h, 38 %.

With both precursors in hand we engaged into the fragment coupling and the following 6π-electrocyclization. As described by Dai *et al.*, the reaction proceeds in a stepwise manner (Scheme 3.29). First, treatment of bromoarene **144** with *t*BuLi induces lithium halogen exchange, giving rise to aryl lithiate **144a**. Upon addition of aldehyde **149**, nucleophilic attack at the carbonyl takes place forging benzylic alcoholate **144b**. When heated to reflux, migration of the carbamate group from the phenolate onto the more nucleophilic benzylic alcoholate takes place to yield **144c**, followed by extrusion of the carbamate group, giving rise to desired *ortho*-quinone methide intermediate **144d**.

96 X. Zeng, F. Zeng, E. I. Negishi, *Org. Lett.* **2004**, *6*, 3245–3248.

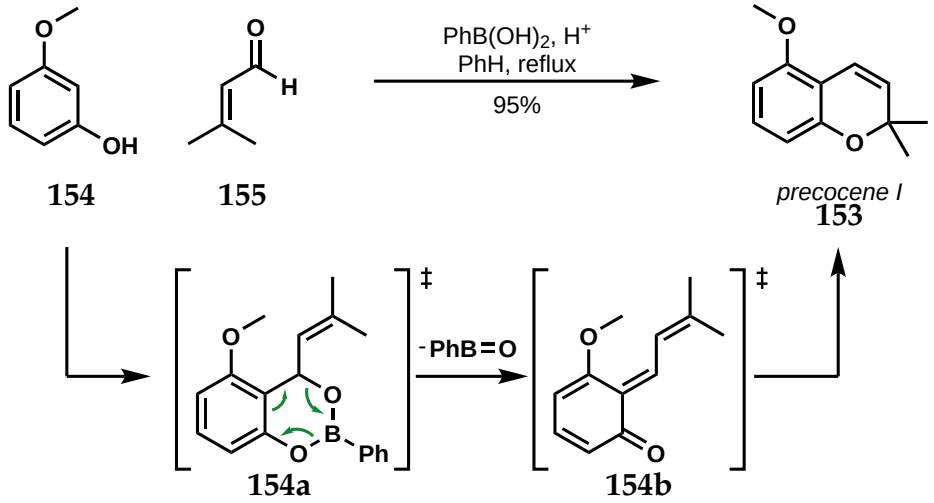
This system stabilizes to aromaticity by means of an oxa-6π-electrocyclization, resulting in the formation of chromene **152**.



Scheme 3.29: Mechanism of the 6π-electrocyclization of the *ortho*-quinone methide. Conditions: *t*BuLi, THF, −78 °C, 30 min *then* **149**, −78 °C, 30 min *then* 130 °C, o/n, 32 %, 1:1 dr.

Unfortunately, chromene **152** was obtained with almost no diastereomeric excess, indicating that the chiral methyl branching is positioned too remotely in order to influence the diastereomeric transition states. Moreover, the yield for the transformation was too low to be of preparative value. Optimizations involving changes in reaction temperatures as well as solvents or bases did not improve the yield. To further investigate the reaction, the cascade was disrupted by protodelithiation of benzylic alcoholate **144b**. Indeed, the alcohol was isolated with 79 % yield after purification. Subjecting that compound to basic conditions followed by heating the reaction again formed chromene **152**. This two step procedure yielded product **152** in a higher yield of 57 % over two steps. Nonetheless, this transformation was hard to reproduce. Since the reaction was carried out on a milligram scale, the higher yields might be explained by the inaccuracy of the balance, as all other attempts resulted in yields similar to the ones obtained in the one-step procedure. In order to overcome purification problems and issues involved in the weighing process, the optimization attempts were analyzed using integration of peaks in the ^{1}H-NMR-spectrum and comparing those to an internal standard.

Since this reaction pathway towards the chromene backbone did not yield respectable results, we focused on exploiting different reactivity. In the one-pot synthesis of precocene I (**153**) by Bissada *et al.*[97], 3-methoxyphenol (**154**) is reacted with crotonaldehyde **155** under Brønsted and boronic acid catalysis, leading to Friedel-Crafts product **154a**. The intermediate dioxaborin **154a** is then eliminated to yield *ortho*-quinone methide **154b**, which is stabilized through electrocyclization to give rise to chromene **153** (Scheme 3.30).



Scheme 3.30: One-pot synthesis of precocene I (**153**) by Bissada *et al.*.[97]

We envisaged this transformation to be applicable to our system by using 4-methoxyphenol (**156**) or silyl ether **147** as the nucleophile and aldehyde **149** as the electrophile (Scheme 3.31). After *ortho*-quinone methide formation, electrocyclization should give rise to chromenes **152** or **157**. Since the literature protocol did not lead to product formation (entry 1), the reaction was explored in crossover experiments using known test substrates. Accordingly, the reaction of arenes **158** and **147** with 2-hexenal (**159**) was conducted (entry 2). Additionally, the reaction of the required aldehyde **149** with 3-methoxyphenol (**154**) was carried out. In both cases, product formation was confirmed by isolation and spectroscopy, showcasing that both reaction partners are applicable in the desired transformation. Comparing the two systems, there are two major differences. Bissada *et al.* used 3-methoxyphenol (**154**) instead of 4-methoxyphenol (**156**). Even though both arenes should have a similar overall electronic excess, in the first arene the two electron-donating substituents are in a *meta*-relationship, greatly increasing the electron density at the carbon in-

97 S. Bissada, C. K. Lau, M. A. Bernstein, C. Dufresne, *Can. J. Chem.* **1994**, *72*, 1866–1869.

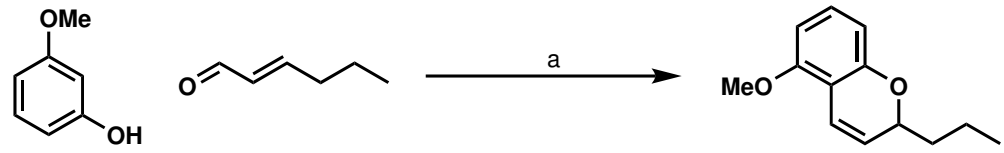
between and thus making it more reactive. In the latter case, there is no carbon where the electron-donating effects of both oxygen atoms match, therefore employing lower affinity for electrophilic substitution. Considering hexenal **159** used as the test substrate and aldehyde **149** required for the cebulactam synthesis, the main differences are the methyl branching in the 2-position, as well as the double unsaturated system in **149**. While the first mainly reduces the reactivity by hampering nucleophilic attack based on sterics, the latter changes the system electronically, making it less electrophilic due to increased stabilization of the partial positive charge at the carbonyl carbon.

In order to overcome the reduced reactivity, some optimization attempts were conducted. A simple increase in reaction temperature by changing the solvent to a higher boiling one did not lead to any conversion (entries 3 and 4). Increasing the boronic acid's Lewis acidity by introducing a nitro group on the benzene moiety also did not lead to conversion of the starting materials (entries 6 to 10). It is noteworthy that the nitrophenylboronic acid is insoluble in a wide range of polar solvents, thus hampering the reaction. Even though the annulation of phenol **154** and hexenal **159** did occur, the transformation proceeded much slower compared to the literature conditions. Inspired by the work of Lee *et al*.[98,99] the use of ethylenediamine diacetate (EDDA) was investigated (entries 11 and 12). In these publications EDDA was discovered to be an efficient catalyst for the electrocyclization of naphthols with unsaturated aldehydes. Its amphoteric properties allow acidic catalysis of the Friedel-Crafts alkylation while at the same time assisting in deprotonation of the phenol to form the desired *ortho*-quinone methide. Nonetheless, with the given reaction systems no formation of product was observed. Other catalysts that we attributed a similar reactivity to (entries 13 to 18) only led to decomposition of either the arene or the aldehyde.

As this mode of *ortho*-quinone methide formation also did not lead to satisfying yields, the acidic elimination of water from a salicyl alcohol derivative was investigated. Another hurdle that could be tackled by that strategy consisted of the almost non-existent stereoselectivity in the cyclization. Even though the asymmetric oxa-6π-electrocyclization is not described in the literature, the enantioselective Diels-Alder reaction of *ortho*-quinone methides[87] as well as asymmetric nucleophilic additions to *ortho*-quinone methides[90] have gained popularity in the last decade. Since *ortho*-quinone methides only show weak

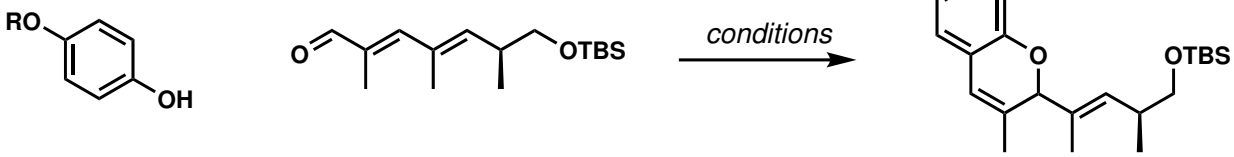
98 R. L. Yong, M. K. Yun, *Helv. Chim. Acta* **2007**, *90*, 2401–2413.
99 Y. R. Lee, Y. M. Kim, S. H. Kim, *Tetrahedron* **2009**, *65*, 101–108.

1)



154 **159** **160**

2)



147 R=TBS
158 R=Me

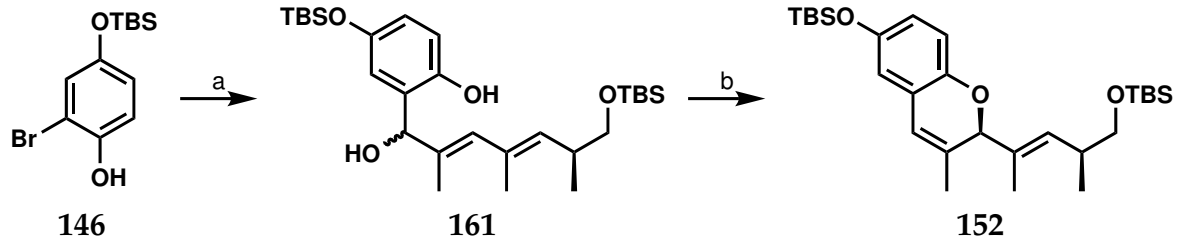
149

152 R=TBS
157 R=Me

entry	arene	aldehyde	conditions	result
1	**147/158**	**149**	$PhB(OH)_2$, prop. acid, PhH, reflux	no conversion
2	**147/158**	**159**	$PhB(OH)_2$, prop. acid, PhH, reflux	product isolated
3	**154**	**149**	$PhB(OH)_2$, prop. acid, PhH, reflux	product isolated
4	**147/158**	**149**	$PhB(OH)_2$, prop. acid, PhMe, reflux	no conversion
5	**147/158**	**149**	$PhB(OH)_2$, prop. acid, xylenes, reflux	no conversion
6	**147/158**	**149**	$pNO_2PhB(OH)_2$, prop. acid, PhMe, reflux	no conversion (insoluble)
7	**147**	**149**	$pNO_2PhB(OH)_2$, prop. acid, dioxane, reflux	no conversion (insoluble)
8	**147**	**149**	$pNO_2PhB(OH)_2$, prop. acid, DCE, reflux	no conversion (insoluble)
9	**147**	**149**	$pNO_2PhB(OH)_2$, prop. acid, xylenes, reflux	decomp. of **149**
10	**147**	**149**	$pNO_2PhB(OH)_2$, prop. acid, chlorobenzene, reflux	no conversion (insoluble)
11	**147/158**	**149**	ethylenediamine diacetate, $CHCl_3$, reflux	no conversion
12	**154**	**159**	ethylenediamine diacetate, $CHCl_3$, reflux	no conversion
13	**147/158**	**149**	$PhBCl_2$, $CHCl_3$, reflux	decomp. of **149**
14	**154**	**159**	$PhBCl_2$, $CHCl_3$, reflux	decomp. of **159**
15	**147/158**	**149**	PIDA, PhH, reflux	decomp. of **147/158**
16	**154**	**159**	PIDA, PhH, reflux	decomp. of **154**
17	**147/158**	**149**	PIFA, PhH, reflux	decomp. of both SM
18	**154**	**159**	PIFA, PhH, reflux	decomp. of both SM

Scheme 3.31: 1) Electrocyclization conditions employed by Bissada *et al.*. Conditions: a) $PhB(OH)_2$, $EtCO_2H$, PhMe, reflux; 2) translation into the system required for cebulactam A synthesis and optimization attempts.

interactions with chiral metal centers, most published examples make use of chiral Brønsted acid promoters, abusing protonated chiral *ortho*-quinone methide transition states. In order to achieve acidic activation, diol **161** had to be synthesized. This was accessed by the chemoselective 1,2-addition of a lithio *ortho*-lithiophenoxide onto aldehyde **149** (Scheme 3.32).[100] The chemoselectivity is exerted due to the higher nucleophilicity of the carbolithiate compared to the more stabilized lithiophenoxide. Accordingly, treatment of *ortho*-bromophenol **146** with an excess of *n*BuLi formed the dianion *in situ*, after which the aldehyde was added to the reaction to yield diol **161** in good yield after aqueous workup. The first attempts for the electrocyclization were attempted with commercially available (*R*)-BINOL-phosphoric acid (**162**) as a proof of concept. Indeed, reacting diol **161** with the acid in CH_2Cl_2 and a drying agent led to formation of chromene **152** in diastereomeric excess, which was analyzed by comparing the crude ^{1}H-NMR spectrum to the one obtained *via* the method of Dai *et al*. (Figure 3.2). It is noteworthy that the two obtained diastereomers were not identified. Spectroscopic methods to determine the isomers are limited since the C-5 proton does not have vicinal coupling partners, thus making analysis by ^3J-coupling-constants impossible. In order to confirm the stereoisomers, x-ray analysis would have to be applied. Therefore, it would be required to remove the *tert*-butyldimethylsilyl groups in order to increase crystallinity. Nonetheless, by switching from one chiral phosphoric acid to the other enantiomer, the stereochemical outcome of the reaction could be directed to yield either one of the two diastereomers selectively, as the substrate control in the transformation is negligible.



146 **161** **152**

Scheme 3.32: Synthesis of diol **161** required for the acid-promoted asymmetric electrocyclization reaction towards chromene **152**. Conditions: a) *n*BuLi, Et_2O, 0 °C, 30 min *then* **149**, Et_2O, −78 °C, 1 h, 76 %; b) (*R*)-BINOL-phosphoric acid (**162**), MS 5 Å, CH_2Cl_2, rt, 6 h, 35 %, 2.5:1 dr.

Nonetheless, two problems occured with the reaction. Firstly, the formation of an unseparable side-product was observed. Secondly, it appeared that the yields of the reaction

100 J. J. Talley, I. A. Evans, *J. Org. Chem.* **1984**, *49*, 5267–5269.

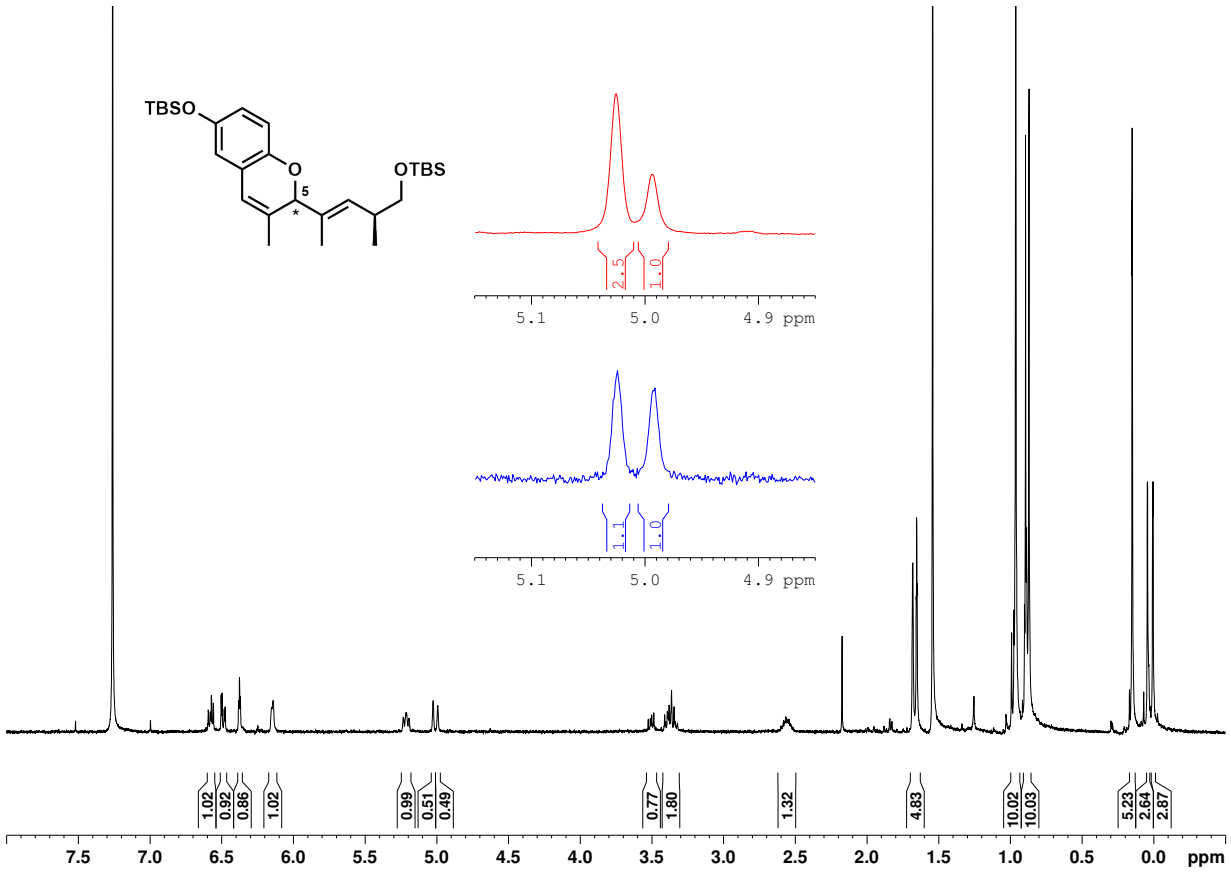
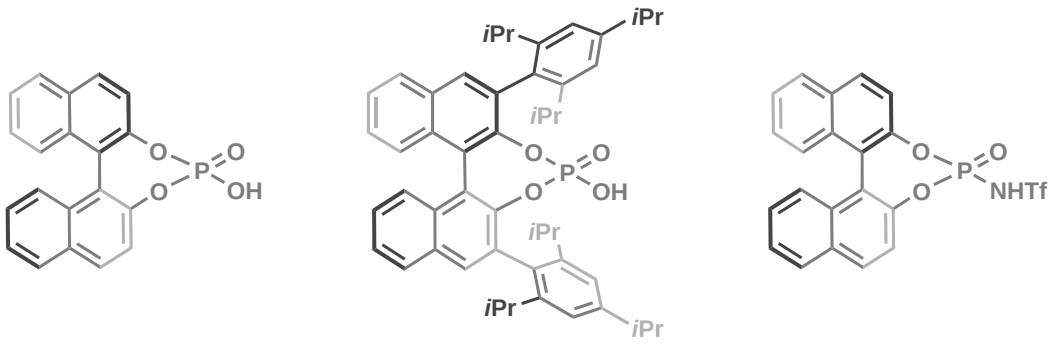


Figure 3.2: ^{1}H-NMR spectra of purified 1:1 diastereomeric mixture of chromene **152** and comparison of the 5-H singlets of the crude spectra obtained using chiral phosphoric acid (red) and of the purified 1:1 mixture (blue).

were, although full conversion of starting material took place, still poor. For those reasons, the yields in the upcoming screening reactions were determined by using an internal standard and integration of peaks in the ^{1}H-NMR spectra.

Phosphoric acids with an axially chiral binaphthyl backbone bearing bulky substituents in the 3-position were first introduced as catalysts in 2004 by Akiyama and Terada *et al.*[101,102] List *et al.*[103] established the BINOL-derived catalyst bearing two 2,4,6-tri*iso*-propyl-phenyl substituents in the 3-position, abbreviated as TRIP (**163**, Scheme 3.33). The high steric demand of the 3-substituents further increase the stereoselectivity in different types of acid catalyzed reactions.[104] Another class of catalysts, exceeding the acidity of the corresponding BINOL-based phosphates, are the *N*-triflylphosphoramides. By introduction of the electronwithdrawing triflylamide, the pKa value is estimatedly lowered from mildly acidic (1-2) to strongly acidic (-3 to -4).[105] All of these catalysts had to be prepared first and were then used in the electrocyclization.



162 **163** **164**

Scheme 3.33: Chiral phosphoric acids employed in the oxa-6π-electrocyclization.

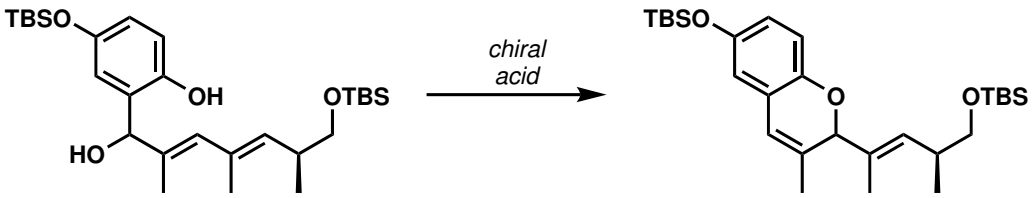
The generic conditions with simple BINOL-phosphate (**162**) yielded the product in moderate selectivity and yield (Scheme 3.34, entry 1). Surprisingly, the stereoselectivity exerted by (*R*)-TRIP (**163**) was inferior and, moreover, the reaction was much slower and also less yielding (entry 2). Changing to the more acidic N-triflylphosphoramide **164** increased the yield, but selectivity remained poor (entry 3). With the seemingly best cat-

101 T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568.
102 D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.
103 M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett* **2010**, 2189–2192.
104 R. Maji, S. C. Mallojjala, S. E. Wheeler, *Chem. Soc. Rev.* **2018**, *47*, 1142–1158.
105 M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116–13126.

alyst **162** identified, we started to investigate solvent effects. The choice had to be taken carefully, as some solvents could participate in a competing nucleophilic addition to the *ortho*-quinone methide intermediate. The solvent screen was conducted at room temperature and at elevated temperatures. In agreement with the Curtin-Hammett principle[106], the diastereoselectivity decreased as the temperature was increased. Moreover, higher temperatures typically led to higher yields for this transformation. Interestingly, some solvents led to a change in selectivity (entries 11, 15 and 17). Nonetheless, the first tested reaction conditions (entry 1) proved to be the most effective ones with regard to selectivity and yield. It should be noted that some experiments with different drying agents were conducted. In the literature molecular sieves ranging from powdered to pellets and 3 Å to 5 Å, as well as Dean-Stark traps, $MgSO_4$ and Celite^{TM} are used as drying agents in combination with chiral phosphoric acid catalyzed reactions.[107–110] Some of these conditions were tested for the given system but did not prove to have a statistically significant impact on the yield and diastereoselectivity and are thus not listed in the screening table.

As loss of *tert*-butyldimethylsilyl groups was a potential acid-catalyzed side reaction, the more acid-stable *tert*-butyldiphenylsilyl derivative **165** was synthesized (Scheme 3.35). Fluoride-induced silyl ether cleavage of aldehyde **149** followed by silylation with *tert*-butyldiphenylsilyl chloride and imidazole forged silyl ether **166** which was used in the 1,2-addition with *in situ* generated 2-lithio-4-methoxy-lithiophenoxide, which itself is accessible from 4-methoxyphenol (**158**). With this substrate in hand, 1,2-addition led to formation of diol **165** in 65 % yield. Nonetheless, reaction with chiral acid **162** also did not lead to an increase in yield nor selectivity, concluding that acid-lability of the silyl group is not the reason for low yields of this transformation.

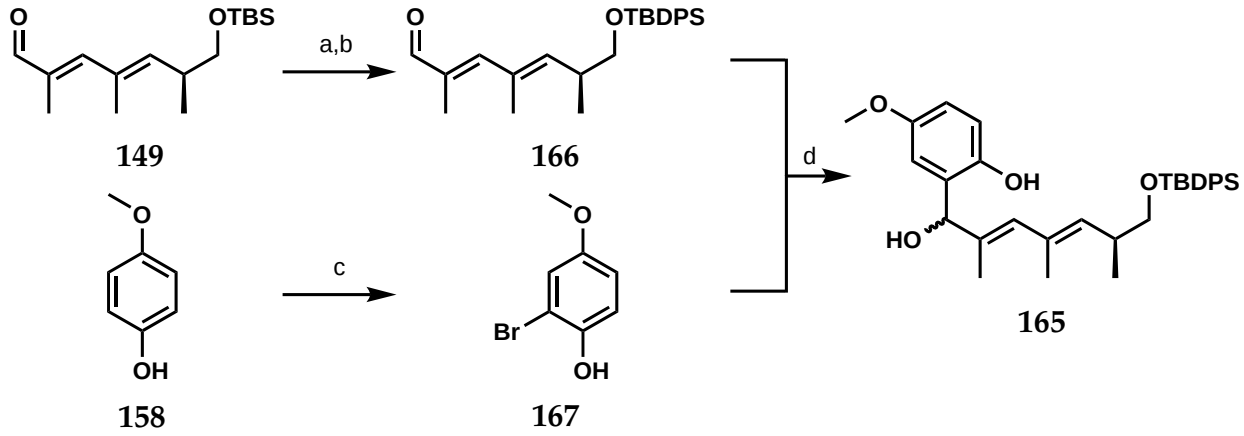
106 F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry Part A: Structure and Mechanisms*, Springer, **2007**.
107 J. Zhou, H. Xie, *Org. Biomol. Chem.* **2018**, *16*, 380–383.
108 Y. Xie, B. List, *Angew. Chem. Int. Ed.* **2017**, *56*, 4936–4940.
109 C. Yue, F. Na, X. Fang, Y. Cao, J. C. Antilla, *Angew. Chem. Int. Ed.* **2018**, *57*, 11004–11008.
110 Z. Lai, Z. Wang, J. Sun, *Org. Lett.* **2015**, *17*, 6058–6061.



161 **152**

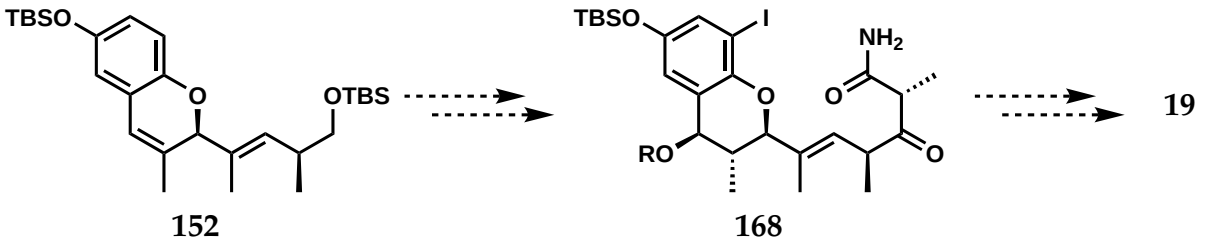
entry	conditions	result
1	**162**, CH_2Cl_2, MS 5Å, rt, o/n	2.5:1 *dr*, 35 %
2	**163**, CH_2Cl_2,MS 5Å, rt, o/n	1.5:1 *dr*, 16 %
3	**164**, CH_2Cl_2, MS 5Å, rt, o/n	1.7:1 *dr*, 30 %
4	**162**, THF, MS 5Å, rt, o/n	4 %
5	**162**, THF, MS 5Å, 110°C, o/n	1:1.1 *dr*, 15 %
6	**162**, DCE, MS 5Å, rt, o/n	1.5:1 *dr*, 30 %
7	**162**, DCE, MS 5Å, 80°C, o/n	1.2:1 *dr*, 35 %
8	**162**, PhMe, MS 5Å, rt, o/n	1:1 *dr*, 19 %
9	**162**, PhMe, MS 5Å, 80°C, o/n	1:1 *dr*, 39 %
10	**162**, MeCN, MS 5Å, rt, o/n	1:1 *dr*, 10 %
11	**162**, MeCN, MS 5Å, 80°C, o/n	1:1.2 *dr*, 34 %
12	**162**, DMF, MS 5Å, rt, o/n	trace
13	**162**, DMF, MS 5Å, 80°C, o/n	trace
14	**162**, EA, MS 5Å, rt, o/n	12 %
15	**162**, EA, MS 5Å, 80°C, o/n	1:1.1 *dr*, 31 %
16	**162**, acetone, MS 5Å, rt, o/n	trace
17	**162**, acetone, MS 5Å, 80°C, o/n	1:1.2 *dr*, 35 %
18	**162**, hexane, MS 5Å, rt, o/n	1.3:1 *dr*, 20 %
19	**162**, hexane, MS 5Å, 80°C, o/n	1.3:1 *dr*, 40 %
20	**162**, $CHCl_3$, MS 5Å, rt, o/n	1.6:1 *dr*, 30 %
21	**162**, $CHCl_3$, MS 5Å, 80°C, o/n	1.1:1 *dr*, 36 %

Scheme 3.34: Screening table for the optimization of the reaction towards chromene **152**.



Scheme 3.35: Synthesis of TBDPS-protected diol **165**. Conditions: a) TBAF, THF, 0 °C, 3 h; b) TBDPSCl, imidazole, CH_2Cl_2, rt, o/n, 93 % (2 steps); c) Br_2, CH_2Cl_2, 0 °C, 2 h, 63 %; d) *n*BuLi, Et_2O, 0 °C, 30 min *then* **166**, Et_2O, −78 °C, 1 h, 65 %.

With the material obtained from several optimization attempts the next backbone functionalizations were assessed (Scheme 3.36). These include the extension of the ansa chain by two carbons and introduction of the primary amide, halogenation of the arene as well as the stereo-, regio- and chemoselective hydrofunctionalization of the chromene double bond to introduce an oxygen surrogate. Strategically, the hydrofunctionalization and iodination should be carried out before introducing the primary amide and the 1,3-dicarbonyl moiety, since competing side-reactions might occur.



Scheme 3.36: Required functionalizations for the completion of the cebulactam (**19**) synthesis.

Hydroboration would be the most direct approach towards the alkene functionalization. Asymmetric versions for the transformations of styrenes to benzylic alcohols are

well-studied reactions. Most commonly, rhodium(I) catalytic systems[111–118] where a great amount of chiral ligands have been reported are used. In some cases chiral boron sources[119] as well as copper(I) systems[120] are applied. Moreover, asymmetric palladium catalyzed hydrosilylations[121–123] allow for the introduction of silanes that can be transformed to alcohols by Tamao-Fleming oxidation. Some other possible reactions leading to the desired benzylic alcohol include the radical Mukaiyama hydration[124], the radical Wacker oxidation[125] as well as the manganese(III) catalyzed olefin oxygenation[126,127], all of which suffer from not being asymmetric. Given the sheer mass of known rhodium-catalyzed hydroboration ligands, we decided to pick one that has been applied on a system that is closely related to chromene **152** and that additionally is commercially available. Accordingly, the hydroboration using the rhodium catalyst accessible from ligand exchange of (*R*)-QUINAP with $[Rh(cod)Cl]_2$ (**169**) and catecholborane was investigated (Scheme 3.37).[115] With the given system, hydroboration did not occur as no conversion of the starting material was observed (entry 1). It is known that vinyl arenes bearing substituents on the terminal position show decreased yield and stereoselectivity, nonetheless, even the trisubstituted aliphatic double bond remained untouched under the given conditions. In order to overcome the inherent low reactivity, the experi-

111 A. C. Maxwell, S. P. Flanagan, R. Goddard, P. J. Guiry, *Tetrahedron Asymmetry* **2010**, *21*, 1458–1473.
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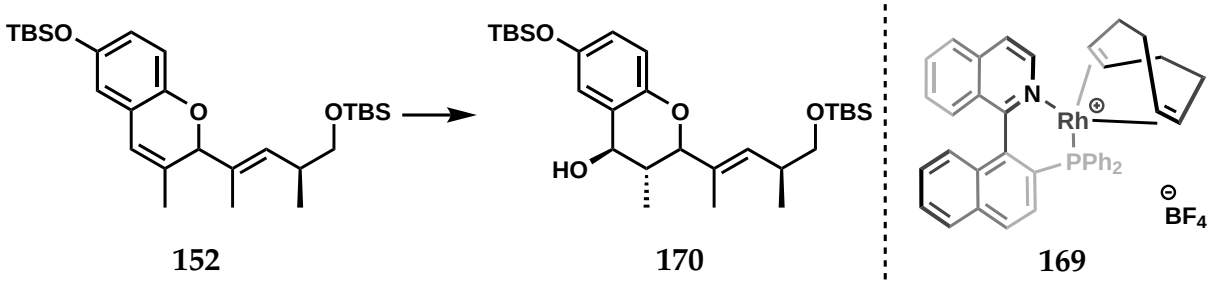
124 S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, 1071–1074.
125 F. Puls, H. J. Knölker, *Angew. Chem. Int. Ed.* **2018**, *57*, 1222–1226.
126 N. H. Lee, J. C. Byun, J. S. Baik, C. H. Han, S. bin Han, *Bull. Korean Chem. Soc.* **2002**, *23*, 1365–1366.
127 D. Ganapathy, J. R. Reiner, G. Valdomir, S. Senthilkumar, L. F. Tietze, *Chem. Eur. J.* **2017**, *23*, 2299–2302.

ment was repeated at elevated temperatures. At 60 °C and 80 °C no reaction took place, whereas the reaction at 100 °C led to desilylation of the primary alcohol. A possible mechanism follows rhodium(I) Lewis acid activation of the alcohol and subsequent hydride substitution of the alcohol on the silicon. A similar reaction is described in the literature for the desilylation of *tert*-butyldimethylsilyl ethers using borane dimethylsulfide complex and trimethylsilyl triflate.[128] Moreover, the hydroboration using (*R*)-IpcBH$_2$ was attempted.[119] It can conveniently be prepared by boron trifluoride etherate promoted liberation out of the commercially available and stable (*R*)-isopinocampheylborane tetramethylethylenediamine complex. The reaction was first attempted as described in the literature, where hydroboration is conducted at −30 °C, leading to no consumption of chromene **152** (entry 4). Increasing hydroboration temperature to room temperature led to decomposition of the starting material and only the Ipc-alcohol was isolated after oxidative workup (entry 5).



152 **170** **169**

entry	conditions	result
1	**169**, catecholborane, PhMe, rt, o/n	no conversion
2	**169**, catecholborane, PhMe, 60°C, o/n	no conversion
3	**169**, catecholborane, PhMe, 80°C, o/n	no conversion
4	**169**, catecholborane, PhMe, 100°C, o/n	loss of primary TBS
5	(*R*)-IpcBH$_2$, THF, -30°C, 2 h	no conversion
6	(*R*)-IpcBH$_2$, THF, rt, 2 h	decomposition

Scheme 3.37: Attempted hydroboration of chromene **152**.

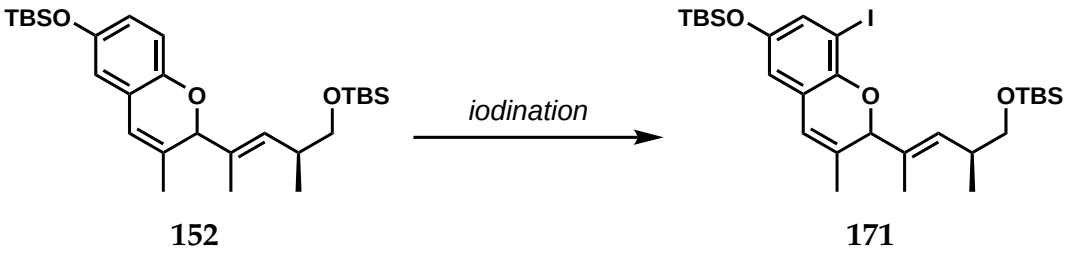
Another pending problem was the introduction of functionality at the aromatic core. Installing an iodide was envisaged to serve as an electrophilic handle enabling ring-closing Goldberg coupling, which is an established method in the syntheses of the related nat-

128 J. P. Michael, B. Bartels, R. Hunter, *Tetrahedron Lett.* **1991**, *32*, 1095–1098.

ural products ansamycin and geldanamycin.[129,130] This strategy was aimed at mainly because introduction of an amine *via* the corresponding nitro group seemed problematic due to harsh conditions of nitration. Two distinctly different approaches towards the halide are possible: electrophilic aromatic substitution using an electrophilic iodine species and deprotonation/lithiation followed by workup with iodine. Based on the work of Geist[49], the iodination using elemental iodide and silver(I) salts as lewis acid promoter were investigated first (Scheme 3.38). It was shown that the silver(I) triflate reaction led to decomposition of the starting material (entry 1), whereas adding sodium bicarbonate to the reaction shut down reactivity completely (entry 2). Using the silver(I) salt of trifluoroacetic acid also did not lead to conversion (entry 3), except for when used in large excess (entry 4). Iodination with *N*-iodosuccinimide led to loss of the TBS groups when used in DMF (entry 5). This is in accordance with the literature where iodine catalyzes desilylation when used in nucleophilic solvents.[92] Changing to the non-nucleophilic solvent CH_2Cl_2, the starting material decomposes to an unknown side-product (entry 6). Performing the second approach, deprotonation using *n*BuLi was tested (entry 7).[131,132] Under these conditions no conversion of starting material was observed whereas using *t*BuLi and a Lewis basic additive led to decomposition (entry 8).[133]

One of the reasons for the failure of the iodination might be the substitution pattern of the aromatic ring. The correct regioisomer was predicted to be formed by *ortho*-direction of the *O*-alkyl substituent. Even though the silyl ether also directs into its *ortho*-positions, these were anticipated to be unreactive due to steric congestion induced by the bulky silyl substituent. Nonetheless, in order to match the electronic effects of the substituents, the phenolic silyl ether was replaced by an acetate, thus making it electron-withdrawing (Scheme 3.39). A procedure for the selective cleavage of phenol silyl ethers over alkyl silyl ethers using potassium fluoride immobilized on aluminium(III) oxide was employed for the deprotection, yielding the product in low yield.[134] Subsequent acetylation using

129 G. Jürjens, A. Kirschning, *Org. Lett.* **2014**, *16*, 3000–3003.
130 H. L. Qin, J. S. Panek, *Org. Lett.* **2008**, *10*, 2477–2479.
131 C. Banzatti, N. Carfagna, R. Commisso, F. Heidempergher, L. Pegrassi, P. Melloni, *J. Med. Chem.* **1988**, *31*, 1466–1471.
132 H. Jiang, G. Ferrara, X. Zhang, K. Oniwa, A. Islam, L. Han, Y. J. Sun, M. Bao, N. Asao, Y. Yamamoto, T. Jin, *Chem. Eur. J.* **2014**, *21*, 4065–4070.
133 L. G. Heinz, O. Yushchenko, M. Neuburger, E. Vauthey, O. S. Wenger, *J. Phys. Chem. A* **2015**, *119*, 5676–5684.
134 J. S. Sawyer, E. A. Schmittling, *Tetrahedron Lett.* **1991**, 7207–7210.

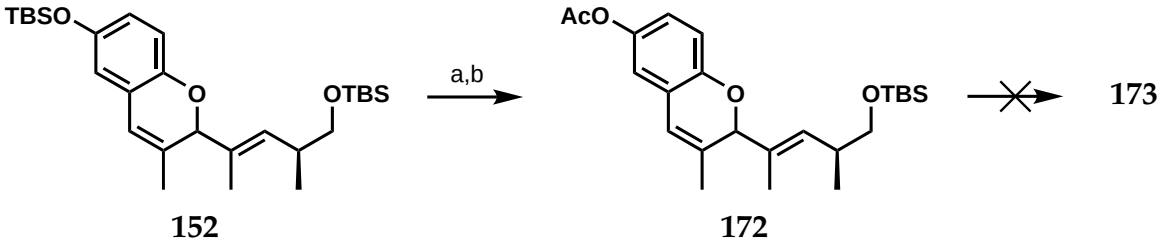


152 **171**

entry	conditions	result
1	I_2 (2.0eq), AgOTf (2.2eq), CH_2Cl_2, rt, o/n	decomposition
2	I_2 (2.0eq), AgOTf (2.2eq), $NaHCO_3$, CH_2Cl_2, rt, o/n	no conversion
3	I_2 (2.0eq), AgTFA (2.2eq), $NaHCO_3$, CH_2Cl_2, rt, o/n	no conversion
4	I_2 (5.0eq), AgTFA (6.0eq), $NaHCO_3$, CH_2Cl_2, rt, o/n	decomposition
5	NIS, DMF, rt, o/n	loss of TBS
6	NIS, CH_2Cl_2, rt, o/n	decomposition
7	*n*BuLi, THF, rt *then* I_2	no conversion
8	*t*BuLi, TMEDA, Et_2O, rt *then* I_2	decomposition

Scheme 3.38: Attempted iodination of chromene **152**.

acetyl chloride and pyridine forged acetate **172** in good yields. Nevertheless, iodination with neither *N*-iodosuccinimide in CH_2Cl_2 nor the iodine/silver(I) triflate system led to any conversion of the starting material.



152 **172**

Scheme 3.39: Protecting group exchange of chromene **152** and attempted iodination. Conditions a) $KF{\cdot}Al_2O_3$, MeCN, sonication, rt, 3 h, 22 %; b) AcCl, pyridine, CH_2Cl_2, 0 °C to rt, 3 h, 74 %.

Since not only the key step cyclization proved to only take place with major drawbacks in yield and reproducibility, but also the further functionalizations proved to be harder than expected, the current route was abandoned. Even though only a fragment of the literature known conditions for the hydrofunctionalization and iodination were tested, regenerat-

ing material to try out further conditions was unpractical. Some minor attempts to introduce a nitrogen bearing substituent at the aromatic core failed due to side reactions of the nitro group with *n*BuLi in the required 1,2-addition step.

3.2.3 Diels-Alder pathway

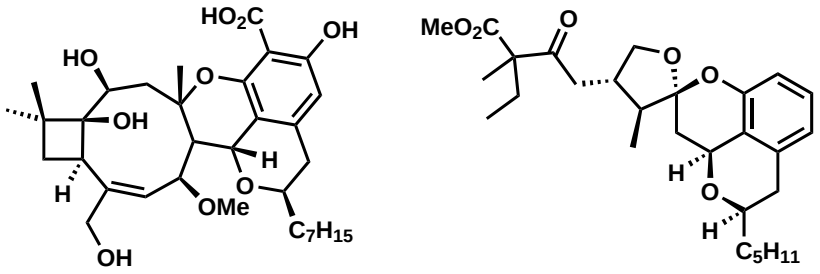
Diels-Alder reactions of *ortho*-quinone methides are a powerful tool in organic chemistry[87–91] and have been applied to the total syntheses of a variety of natural products like cytosporolide A (**174**)[135] and berkelic acid (**24**)[136] (Figure 3.3). Even though *ortho*-quinone methides count as electron-deficient dienes and match best with electron-rich alkenes to undergo inverse electron-demand hetero-Diels-Alder reactions, their high reactivity allows them to react with electron-deficient olefins as well. One drawback of *ortho*-quinone methide Diels-Alder reactions lies in the tendency of dimerization, thus requiring an excess of dienophile to allow for acceptable yields. In an intramolecular reaction this drawback can be overcome by using high dilution. One of the major advantages of applying this methodology to the cebulactam project consists of enabling the synthesis of a functionalized chromane core bearing a methyl-protected oxygen in the benzylic position, eliminating the need for hydrofunctionalization (Scheme 3.25). Moreover, the work of Lambert *et al*.[137] demonstrates that the use of a chiral acid allows for facial selectivity in the activation of aromatic *ortho*-hydroxydimethylacetals, which ultimately results in the diastereoselective formation of the hetero-Diels-Alder product. Therefore, we envisioned that the stereochemistry at the chromane core of cebulactam (**19**) could be set by this single reaction as well.

The aromatic core of cebulactam (**19**) was synthesized from 4-methoxyphenol (**158**) (Scheme 3.40). Formylation using magnesium dichloride and paraformaldehyde gave rise to 5-methoxysalicylaldehyde (**175**) in excellent yield and regioselectivity, which can be explained by a six-membered transition state in which the initially formed phenoxymagnesiumchloride **158a** reacts with a formaldehyde molecule, which itself is activated

135 K. I. Takao, S. Noguchi, S. Sakamoto, M. Kimura, K. Yoshida, K. I. Tadano, *J. Am. Chem. Soc.* **2015**, *137*, 15971–15977.

136 C. F. Bender, F. K. Yoshimoto, C. L. Paradise, J. K. De Brabander, *J. Am. Chem. Soc.* **2009**, *131*, 11350–11352.

137 C. D. Gheewala, J. S. Hirschi, W. H. Lee, D. W. Paley, M. J. Vetticatt, T. H. Lambert, *J. Am. Chem. Soc.* **2018**, *140*, 3523–3527.



cytosporolide A
174

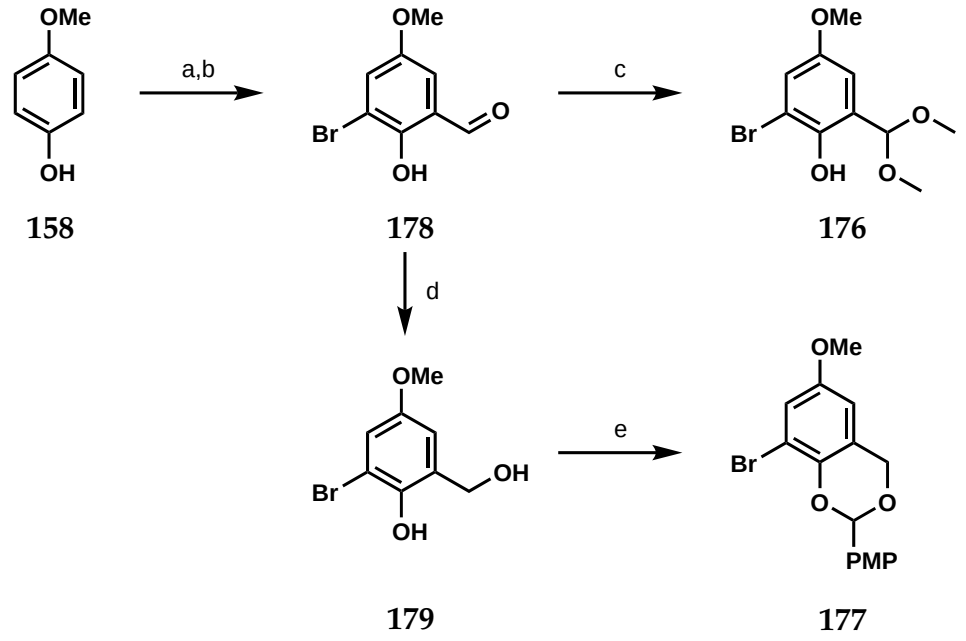
berkelic acid
24

Figure 3.3: Natural products synthesized by Diels-Alder reactions of *ortho*-quinone methides.

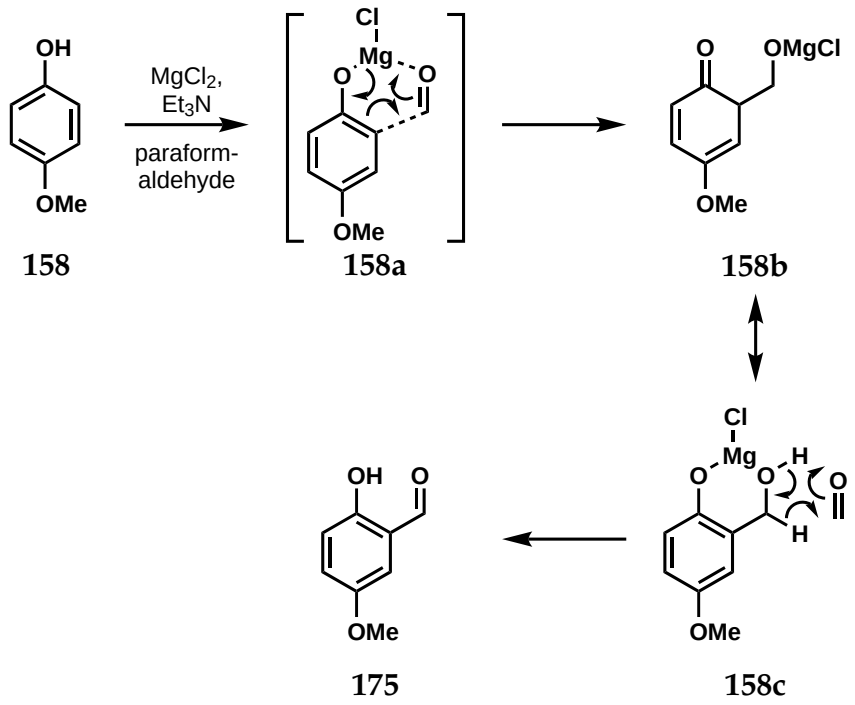
by the same magnesium atom (Scheme 3.41). After the Friedel-Crafts type alkylation, intermediately formed benzyl alcohol **158b** was oxidized by another molecule of formaldehyde to give rise to salicylaldehyde **175**,[138,139] which was brominated using bromine and sodium acetate.[140,141] With the halide in place as the electrophilic handle for the upcoming Goldberg coupling, the dimethyl acetal was prepared. Under standard conditions using trimethyl orthoformate product **176** was formed in good yield. Unfortunately, chromatography was not viable for purification, since decomposition to the aldehyde was observed. The same observation was made using Et_3N as an eluent additive, as well as using basic alumina as the stationary phase. Even though the amidation is known to work with free phenols[142], this functionality was anticipated to hamper the desired reactivity. Therefore, a two-step reduction/acetalization procedure was developed leading to formation of acetal **177**.

Next, the Goldberg coupling of the three bromoarenes **178**, **176** and **177** with acetamide as a test substrate was investigated (Scheme 3.42). The conditions examined first were the ones used by Geist[49], which are based on the work of Lv *et al*.[143] They found that ketoester **180** is a viable ligand for the copper(I)-catalyzed amidation of haloarenes. Accordingly, reaction of aryl bromides **178**, **176** and **177** with acetamide was carried out,

138 N. U. Hofsløkken, L. Skattebøl, *Acta Chem. Scand.* **1999**, *53*, 258–262.
139 D. J. Barrios Antúnez, M. D. Greenhalgh, C. Fallan, A. M. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2016**, *14*, 7268–7274.
140 E. M. McGarrigle, D. M. Murphy, D. G. Gilheany, *Tetrahedron Asymmetry* **2004**, *15*, 1343–1354.
141 G. Evano, J. V. Schaus, J. S. Panek, *Org. Lett.* **2004**, *6*, 525–528.
142 D. L. Clive, J. Peng, S. P. Fletcher, V. E. Ziffle, D. Wingert, *J. Org. Chem.* **2008**, *73*, 2330–2344.
143 X. Lv, W. Bao, *J. Org. Chem.* **2007**, *72*, 3863–3867.



Scheme 3.40: Synthesis of bromoarenes for the Goldberg coupling: a) paraformaldehyde, $MgCl_2$, Et_3N, THF, reflux, o/n, 93 %; b) Br_2, NaOAc, AcOH, rt, 1 h, 47 %; c) $CH(OMe)_3$, *p*TsOH·H_2O, MeOH, rt, o/n, 92 %; d) $NaBH_4$, EtOH, rt, 1 h; e) anisaldehyde dimethyl acetal, PPTS, CH_2Cl_2, rt, 1.5 h, 79 % (2 steps).

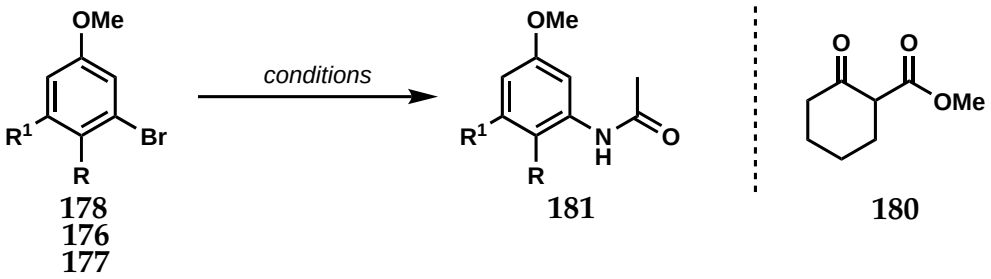


Scheme 3.41: Predicted mechanism of the formation of salicylaldehyde **175**.

unfortunately in all cases leading to no conversion of the starting material. Moreover, more conventional conditions employing *N,N*-dimethylethylenediamine as ligand and potassium carbonate as base were tested.[144] In that case, no conversion of the starting materials was observed again, leading us to the conclusion that the bromoarenes are too inert and do not participate in the oxidative addition.

Another alternative for the cebulactam fragment coupling would be the formation of the amide bond *via* peptide coupling reactions. This would require the presence of an amine at the arene, which can be conveniently implemented by electrophilic nitration followed by reduction. Salicylaldehyde **175** was nitrated according to a procedure by Barrios Antúnez *et al*. (Scheme 3.43).[139] Next, reduction of the nitro group was investigated. This transformation is a well-established reaction and can among others be performed using

144 G. Zhao, J. Wu, W. M. Dai, *Tetrahedron* **2015**, *71*, 4779–4787.



178
176
177

181

180

entry	conditions	result
1	acetamide, CuI, Cs_2CO_3, **180**, DMSO, reflux, o/n	no conversion
2	acetamide, CuI, K_2CO_3, DMEDA, dioxane, reflux, o/n	no conversion

Scheme 3.42: Attempted Goldberg couplings with bromoarenes.

hydrogen gas and a catalyst[145,146], as well as elemental metals in acidic medium.[147–149] Metal hydrides are usually not applied to this transformation as they tend to form azo compounds. Nonetheless, in the case of nitroarene **182** the reduction to the aniline could not be effected (Scheme 3.43). Using iron powder and acetic acid did not lead to any conversion (entry 1), whereas decomposition is observed when using more acidic conditions (entry 2). When zinc is used as the metal, again, decomposition takes place (entry 3). Under palladium catalysis and hydrogen atmosphere the formation of the dimethyl acetal of the aldehyde was observed (entry 4), whereas when using trifluoroacetic acid as an additive degradation occurs (entry 5). Using platinum dioxide as the hydrogenation catalyst forms traces of the product but purification proved challenging as big quantaties of degradated compounds were obtained (entry 6).

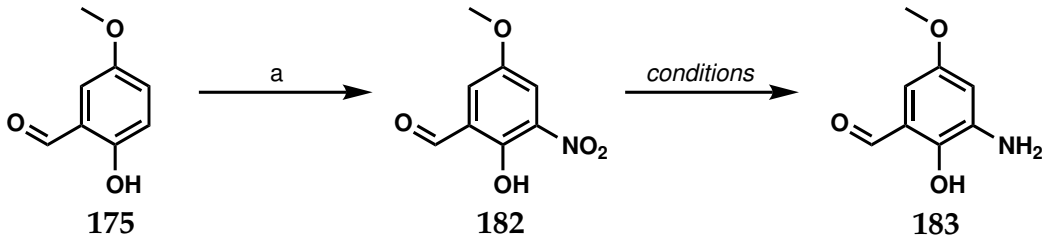
145 X. Lu, S. Wan, J. Jiang, X. Jiang, W. Yang, P. Yu, L. Xu, Z. Zhang, G. Zhang, L. Shan, Y. Wang, *Eur. J. Org. Chem.* **2011**, *46*, 2691–2698.

146 A. Amjad, J. A. Hunt, F. Kallashi, J. E. Kowalchik, D. Kim, C. Smith, P. Sinclair, R. Sweis, G. Taylor, C. Thompson, L. Chen, N. Quraishi, WO2007070173A2, **2007**.

147 M. Moeller, M. D. Norris, T. Planke, K. Cirnski, J. Herrmann, R. Müller, A. Kirschning, *Org. Lett.* **2019**, *21*, 8369–8372.

148 L. Lv, B. B. Snider, Z. Li, *J. Org. Chem.* **2017**, *82*, 5487–5491.

149 A. T. Garrison, Y. Abouelhassan, H. Yang, H. H. Yousaf, T. J. Nguyen, R. W. Huigens, *Med. Chem. Comm.* **2017**, *8*, 720–724.



175 **182** **183**

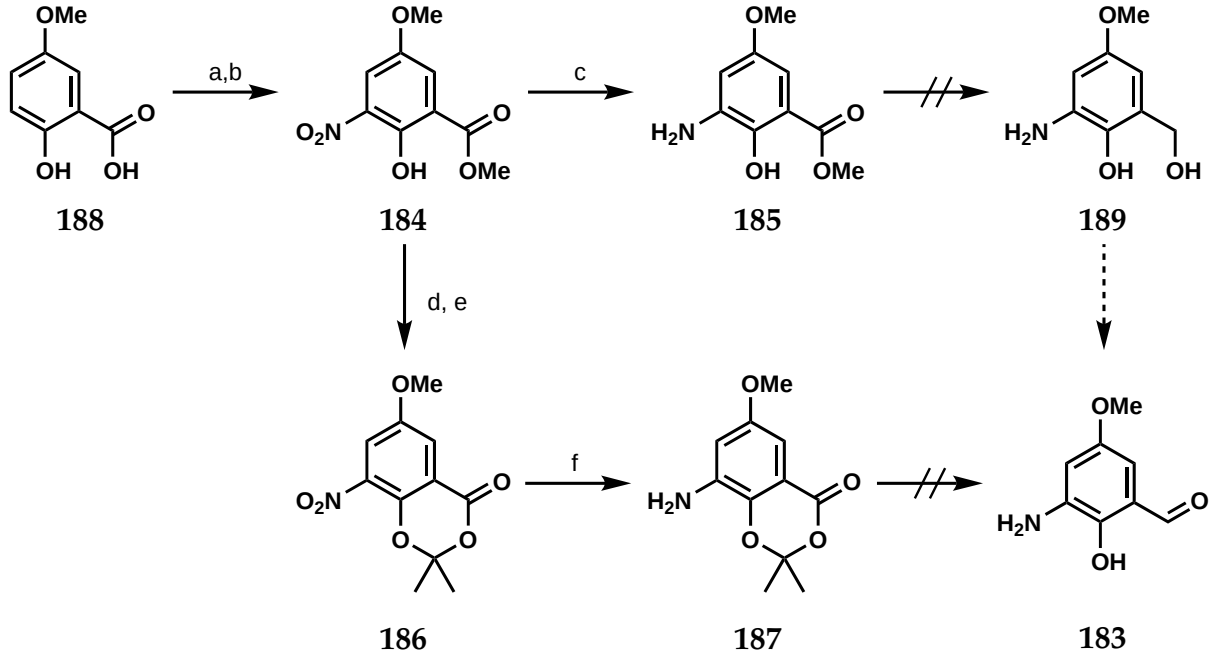
entry	conditions	result
1	Fe, EtOH, H_2O, AcOH, reflux, o/n	no conversion
2	Fe, EtOH, H_2O, HCl, reflux, 5h	decomposition
3	Zn, THF, EtOH, AcOH, reflux, o/n	decomposition
4	H_2, Pd/C, MeOH, rt, 2d	dimethyl acetal
5	H_2, Pd/C, TFA, MeOH, rt, 2d	decomposition
6	H_2, PtO_2-hydrate, THF, MeOH, rt, 1.5h	complex mixture

Scheme 3.43: Failed installation of the amino group onto the arene **175**: a) HNO_3, AcOH, 0 °C, 45 min, 64 %.

In order to overcome this problem, the route was slightly modified. The synthesis up to nitroarene **184** was performed as described in the literature[150,151] and platinum dioxide catalyzed hydrogenation gave rise to aniline **185** in quantitative yield. The synthesis of aldehyde **183** was planned to be finalized after a reduction of the ester followed by manganese dioxide oxidation. Unfortunately, subjecting ester **185** to DIBAl-H at −78 °C only resulted in decomposition. Another approach consisted of the protection of the salicylic acid moiety as an acetonide, the advantage being that it can be directly reduced to the salicylaldehyde.[152] In order to form that protection group, the ester would have to be hydrolyzed first. This was facilitated using lithium hydroxide in a mixture of THF and water. The following acetalization was performed with acetone in trifluoroacetic acid and trifluoroacetic anhydride as the water scavenging agent. The workup procedure proved to be crucial, as the product instantly decomposed to the starting material acid upon addition of water or sodium bicarbonate. Gratifyingly, all acidic components could be removed by concentration under reduced pressure, resulting in a slurry that could be worked up under aqueous conditions, leading to isolation

150 U. A. Carrillo-Arcos, S. Porcel, *Org. Biomol. Chem.* **2018**, *16*, 1837–1842.
151 L. Li, A. D. Abraham, Q. Zhou, H. Ali, J. V. O'Brien, B. D. Hamill, J. J. Arcaroli, W. A. Messersmith, D. V. LaBarbera, *Mar. Drugs* **2014**, *12*, 4833–4850.
152 N. Bajwa, M. P. Jennings, *J. Org. Chem.* **2006**, *71*, 3646–3649.

of acetonide **186** in 31 % yield alongside re-isolated starting material. Moreover, hydrogenation cleanly formed aniline **187** in good yield and purity. Unfortunately, reduction of the lactone only led to decomposition of the starting material and aldehyde **183** was not isolated. Nonetheless, aniline **187** could be a viable candidate for the coupling reaction, as well.



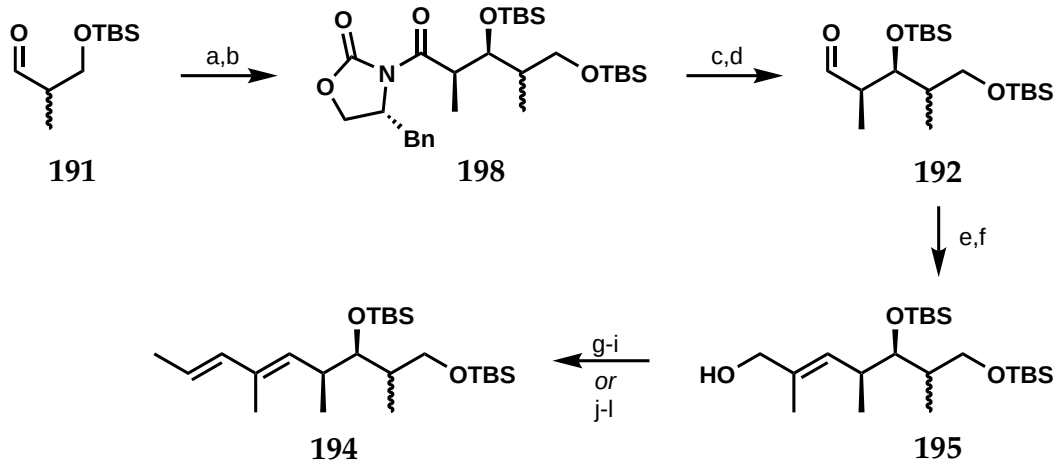
Scheme 3.44: Different approach towards aminosalicylaldehyde **183**: a) H_2SO_4, MeOH, reflux, o/n, 94 %; b) HNO_3, AcOH, 15 °C, 1 h, 89 %; c) PtO_2-hydrate, H_2 (1 atm), THF:MeOH (8:1), rt, 1.5 h, *quant.*; d) $LiOH \cdot H_2O$, THF:H_2O (4:1), 60 °C, o/n, 87 %; e) acetone, TFAA, TFA, 70 °C, o/n, 31 %, f) PtO_2-hydrate, H_2 (1 atm), THF:MeOH (8:1), rt, 1.5 h, 85 %.

To evaluate the peptide coupling, 1,3-dicarbonyl **190** had to be synthesized. A robust route utilizing well-established chemistry that would allow for the preparation of larger quantities of acid **190** without the requirement of difficult optimizations was chosen (Scheme 3.45). Accordingly, the synthesis commenced with the Evans-aldol reaction of the much cheaper, racemic aldehyde **191**, which is accessible by the same procedures as the one derived from the Roche ester. At a later stage in the synthesis, the stereocenter will be epimerized to the desired stereoisomer, as it is positioned inbetween two carbonyl groups, thus making the use of a single isomer obsolete. Silylation followed by a reduction/oxidation protocol forged aldehyde **192** in good overall yield. Wittig ole-

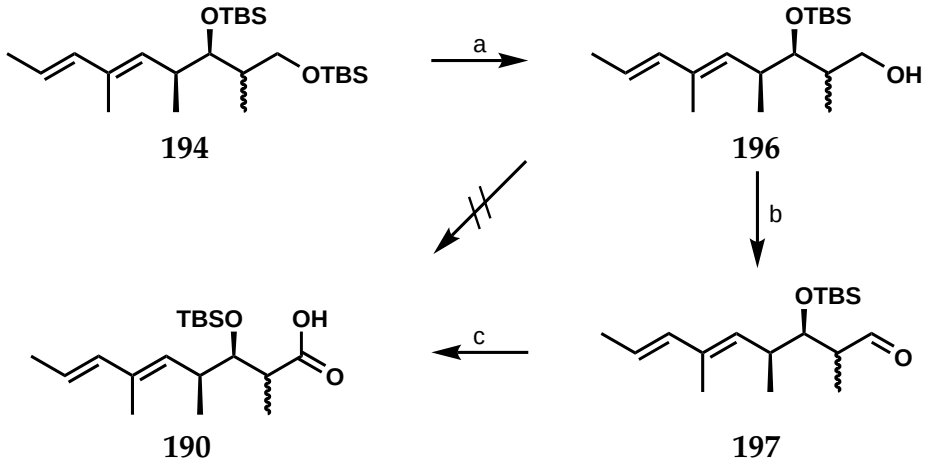
fination installed the unsaturated ester, which was transformed to aldehyde **193** by another reduction/oxidation sequence. Takai olefination[153] succeeded to install the vinyl iodide albeit in fairly low yield which likely resulted from preparative issues with the workup. Another Negishi cross-coupling finalized the synthesis of bis-silyl ether **194**.[154] Since the Takai olefination did not produce acceptable yields of product, alongside huge amounts of toxic waste, an optimized protocol was elaborated in which allyl alcohol **195** was brominated following standard Appel conditions. Insertion of tributylphosphine into the carbon-bromine bond led to formation of a phosphonium salt which was deprotonated *in situ* with dimsyl lithium and further reacted with acetaldehyde to furnish diene **194** in better yields and with improved reproducibility.[155] With the material in hand, the strategy to conclude the synthesis of the dicarbonyl had to be decided. It is noteworthy that 1,3-diols are not easily oxidized since the intermediates generally can participate in retro-aldol reactions leading to fragmentation. Alternatively, selective desilylation of the primary alcohol can be performed, followed by oxidation to the carboxylic acid. Even though this procedure would result in a longer route, problems arising from the Lewis basicity of the dicarbonyl moiety in the upcoming steps might be mitigated. Therefore, bis-silyl ether **194** was subjected to a catalytic amount of PPTS to liberate the primary alcohol selectively (Scheme 3.46). A following Swern oxidation forged the corresponding aldehyde which was oxidized by means of Pinnick oxidation to yield acid **190**. In order to achieve moderate yields, the protocol had to be optimized. Namely, a large excess of 2-methyl-but-2-ene as scavenger had to be employed, most likely due to the presence of the oxidation-sensitive diene moiety. Other scavengers like DMSO or resorcinol did not lead to improved yields nor did the use of other oxidation systems starting from the alcohol **196**. Jones reagent as well as PDC in DMF led to decomposition of the starting substrate, whereas aqueous TEMPO or Ley oxidations, as well as IBX/2-hydroxypyridine[156] proceeded to yield the aldehyde **197** but failed to accomplish further oxidation.

With aniline **187** and carboxylic acid **190** in hand, the coupling reaction to introduce the complete carbon backbone of cebulactam (**19**) was investigated. As amines and carboxylic acids do not condensate voluntarily at room temperature, activation methods for the latter have been studied for decades. One of the oldest methods to activate carboxylic

153 K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
154 Y. Huang, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2012**, *10*, 29–31.
155 D. Enders, J. L. Vicario, A. Job, M. Wolberg, M. Müller, *Chem. Eur. J.* **2002**, *8*, 4272–4284.
156 R. Mazitschek, M Marcel, A. Giannis, *Angew. Chem. Int. Ed.* **2002**, 4216–4218.



Scheme 3.45: Long route towards the polyketide chain fragment: a) (*R*)-Bn-Evans-auxiliary, *n*Bu2BOTf, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h *then* **191**, CH_2Cl_2, 0 °C, 1 h; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 68 % (2 steps); c) $LiBH_4$, MeOH, THF, 0 °C, 2.5 h, 75 %; d) DMP, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 78 %; e) ethyl 2-(triphenylphosphaneylidene)propanoate, THF, 70 °C, 72 h, 86 %; f) DIBAl-H, CH_2Cl_2, −78 °C, 5 min; g) MnO_2, CH_2Cl_2, rt, o/n, 79 % (2 steps); h) $CrCl_2$, CHI_3, THF, rt, 2 h, 22 %; i) $ZnBr_2$, MeMgBr, $Pd(PPh_3)_4$, THF, 0 °C to rt, o/n, 41 %; j) CBr_4, PPh_3, 2,6-lutidine, MeCN, 0 °C *to* rt, 15 min, 67 % (2 steps); k) P*n*Bu_3, MeCN, 0 °C, o/n; l) DMSO, *n*BuLi, PhMe, −78 °C, 1 h *then* acetaldehyde, rt, o/n, 73 % (2 steps).

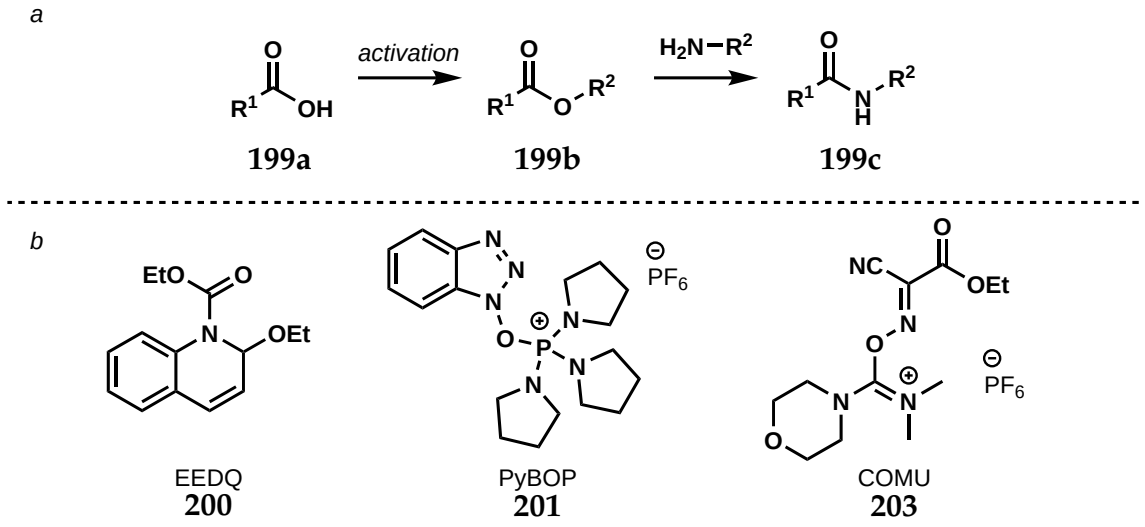


Scheme 3.46: Oxidation to carboxylic acid **190**: a) PPTS, EtOH, rt, 2d, 87 %; b) $(COCl)_2$, DMSO, −78 °C, 30 min *then* **112**, −78 °C, 30 min *then* Et_3N, −78 °C, 30 min *to* rt, 1 h; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, 0 °C *to* rt, 50 min, 66 % (2 steps).

acids poses the formation of an acyl chloride. One major disadvantage of that methodology lies in the acidity of reagents required for that transformation. Therefore, Sheehan developed a carbodiimide reagent that activates the carboxylic acid under neutral conditions, which was later used for the formation of the β-lactam ring of penicillin V in its landmark total synthesis.[157,158] Since then, a large bank of fine-tuned peptide coupling reagents has been developed enabling the reaction of sterically demanding and sensitive substrates. As depicted in Scheme 3.47, those reagents act as nucleophiles that are attacked by the carboxyl group of the acid **199a**. Now a good leaving group, an addition-elimination sequence of the amine on the carbonyl function of ester **199b** occurs to forge coupled amide **199c**. It was shown that additives like DMAP or HOBt may increase the reaction rate and suppress racemization. In that case, intermediate products **199b** are substituted to activated amides or esters, respectively, after which they undergo a second addition-elimination reaction to the desired amide **199c**.[159] The reaction of a carboxylic acid with the coupling reagent EEDQ (**200**)[160] results in the formation of an activated mixed ethoxycarbonyl anhydride, which readily reacts with amines. This proved to be a valuable methodology in the synthesis of cystobactamides in our group, where other reagents failed to faciliate the coupling of unreactive anilines.[147] The reagent PyBOP (**201**)[161] belongs to the class of phosphonium salts. Upon activation of the carboxylic acid, this reagent additionally liberates HOBt, which acts as a racemization suppressant additive. COMU (**202**)[162] is a coupling reagent that consists of an *O*-acyl urea moiety capable of activating a carboxylic acid. In that process, it releases Oxyma, an additive superior to HOBt as it poses a lower risk of explosion.[163]

Accordingly, several conditions to faciliate the reaction of aniline **187** and carboxylic acid **190** were tested (Scheme 3.48). When activating the latter by acyl chloride formation (entry 1), a complex mixture of products was observed, which was not further investigated. Both carbodiimide reagents EDC and DIC (entries 2 and 3) led to conversion of the acid, but again, a complex mixture of compounds was obtained. EEDQ-mediated coupling proceeded very slowly yet full consumption of the acid was observed (entry 4). Nonetheless, the isolated product proved to be ethyl ester **204**, whose formation can

157 J. C. Sheehan, G. P. Hess, *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068.
158 J. C. Sheehan, K. R. Henbry-Logan, *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263.
159 A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, *111*, 6557–6602.
160 B. Belleau, G. Malek, *J. Am. Chem. Soc.* **1968**, *90*, 1651–1652.
161 E. Frérot, J. Coste, A. Pantaloni, M. N. Dufour, P. Jouin, *Tetrahedron* **1991**, *47*, 259–270.
162 A. El-Faham, R. S. Funosas, R. Prohens, F. Albericio, *Chem. Eur. J.* **2009**, *15*, 9404–9416.
163 R. Subirós-Funosas, R. Prohens, R. Barbas, A. El-Faham, F. Albericio, *Chem. Eur. J.* **2009**, *15*, 9394–9403.

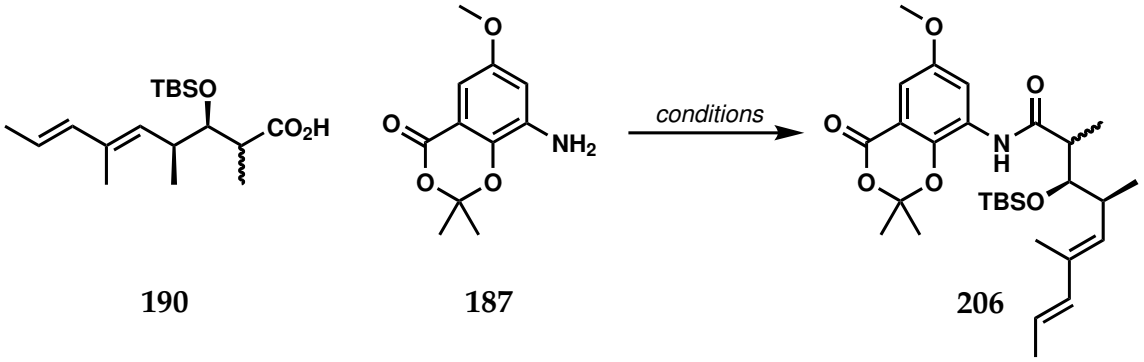


Scheme 3.47: a) General scheme of peptide coupling by activation of carboxylic acids; b) Modern coupling reagents EEDQ (**200**), PyBOP (**201**) and COMU (**203**).

be explained by the cleavage of the intermediately formed ethoxycarbonylanhydride by ethanol, which itself is released from EEDQ (**200**) upon activation of the acid **190**. When using HOBt in combination with EDC (entry 5) or PyBOP (**201**) (entry 6) as coupling reagents, benzotriazole ester **205** was isolated. These last results demonstrate that the acid is principally viable for the transformation, but that aniline **187** might not be reactive enough to substitute the active ester.

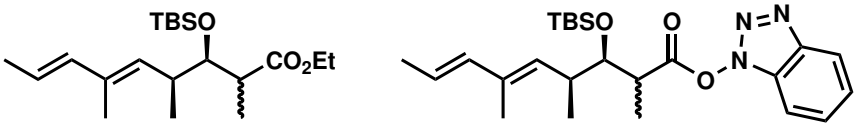
Fortunately, the aromatic core can be modified in order to increase the electron density at the nitrogen atom. Therefore, we decided to replace the ester function with a benzyl alcohol (Scheme 3.49). Thus, aldehyde **207** was reduced to diol **208** and protected as acetonide **209** under standard conditions and excellent yields. Nitro reduction using Adams' catalyst under atmospheric pressure of hydrogen gas forged aniline **210** in quantitative yield.[164] The following peptide coupling was achieved using COMU (**203**) to form amide **211** in decent yield. Unfortunately, the yields of this transformation were unconsistent. One of the major factors proved to be the purity of acid **190**, which was synthesized, purified and used immediately before setting up the peptide coupling reaction. Moreover, when scaling the reaction to preparatively useful amounts, the yield always proved to be below 20 %.

164 V. Voorhees, R. Adams, *J. Am. Chem. Soc.* **1922**, *44*, 1397–1405.



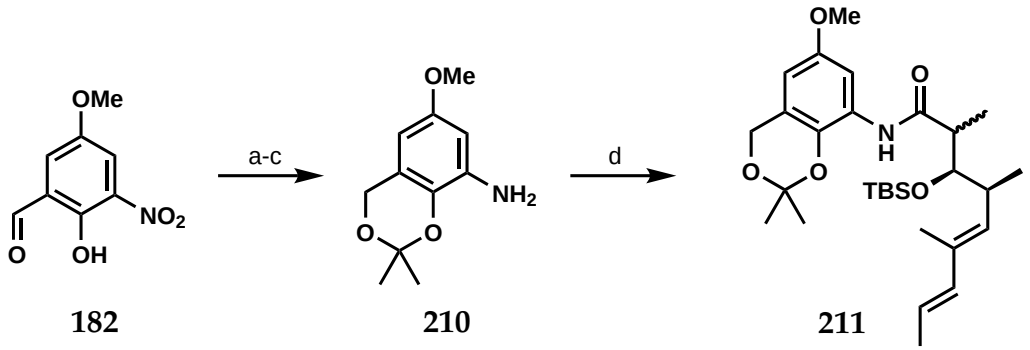
190 **187** **206**

entry	conditions	result
1	$POCl_3$, DIPEA, CH_2Cl_2, 0 °C, 10 min	complex mixture
2	EDC•HCl, DMAP, CH_2Cl_2, rt, o/n	complex mixture
3	DIC, CH_2Cl_2, rt, o/n	complex mixture
4	EEDQ, $CHCl_3$, 0 °C *to* rt, o/n	ethyl ester **204**, slow conversion
5	EDC•HCl, HOBt, CH_2Cl_2, rt, o/n	high conversion, Bt ester **205**
6	PyBOP, DIPEA, HOBt, DMF, rt, o/n	high conversion, Bt ester **205**



204 **205**

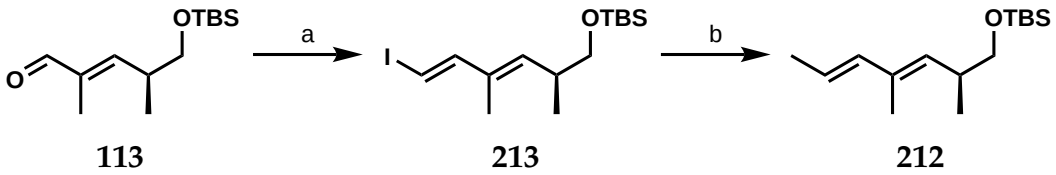
Scheme 3.48: Attempted peptide coupling of acid **190** and aniline **187**.



182 **210** **211**

Scheme 3.49: Synthesis of benzyl alcohol **210**: a) $NaBH_4$, MeOH, 0 °C *to* rt, 30 min, 96 %; b) 2,2-dimethoxypropane, *p*TsOH, Na_2SO_4, acetone, rt, o/n, 71 %; c) PtO_2-hydrate, H_2, 1 atm, THF:MeOH (8:1), rt, 1.5 h, *quant.*; d) **190**, COMU, DIPEA, DMF, 0 °C, 5 min *then* **210**, DIPEA, DMF, rt, o/n, 36 %.

As this coupling proved to be difficult, another strategy towards the same key intermediate **211** was developed. When inspecting the functionalized backbone, a 1,3-relationship between the amide and the alcohol can be observed, which is predestinated to be synthesized by aldol type chemistry. A viable approach is the formation of the amide bond by reaction of aniline **210** with an 2-haloacyl halide[47], followed by an intermolecular Reformatsky reaction with an aldehyde, ideally already bearing the complete diene system.[165,166] The required aldehyde was synthesized from silyl ether **212**, which itself is derived from aldehyde **113** (Scheme 3.50). Accordingly, Takai olefination allowed installation of the (*E*)-vinyl iodide in good selectivity[153], whereas Negishi cross-coupling with dimethyl zinc gave rise to diene **212** in excellent yield.[154]

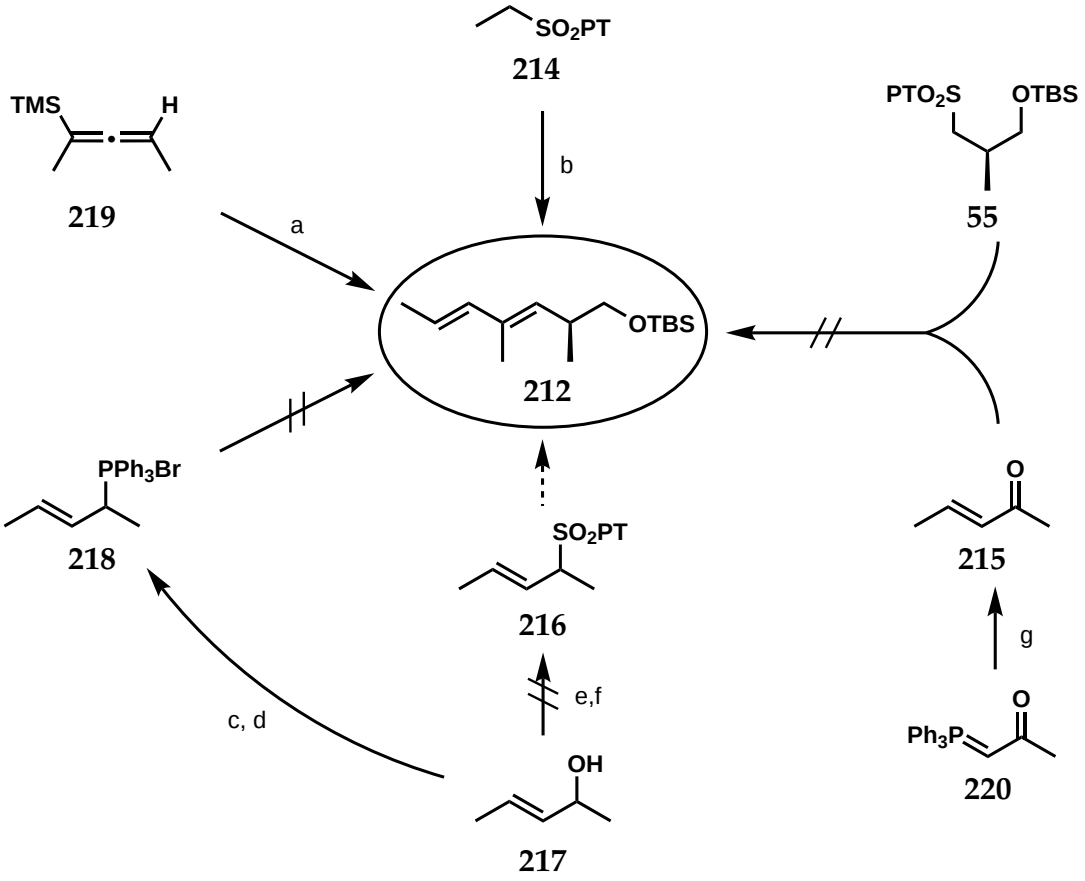


113 **213** **212**

Scheme 3.50: Synthesis of diene **212**: a) $CrCl_2$, CHI_3, THF, rt, 2 h; b) Me_2Zn, $Pd(PPh_3)_2Cl_2$, THF, 0 °C to rt, o/n, 88 % (2 steps).

In order to access key intermediate **212** in a more quick manner some direct retrosynthetic scissions were investigated (Scheme 3.51). The first approach focused on the replacement of the two-step Takai olefination Negishi cross-coupling procedure. Even though the yield and selectivity are good, both transformations rely on the use of highly toxic and expensive organometallic reagents. Especially in the case of the Takai olefination a high excess of chromium(II) has to be used in order to drive the reaction to completion. An alternative procedure uses the ethylsulfone **214** as olefination nucleophile to forge diene **212** in one step. Unfortunately, classic conditions using potassium hexamethyldisilazide in THF at low temperatures did not lead to conversion of the aldehyde.[167] An alternative procedure that is usually used for the methylenation under Julia-Kocienski conditions uses cesium carbonate as a base in THF:DMF under refluxing conditions.[168] Applying said conditions to the system of sulfone **214** and aldehyde **113** allows for the preparation of diene **212** albeit in low yield and with mediocre selectivity.

165 C. G. Nelson, T. R. Burke, *J. Org. Chem.* **2012**, *77*, 733–738.
166 M. Szostak, N. J. Fazakerley, D. Parmar, D. J. Procter, *Chem. Rev.* **2014**, *114*, 5959–6039.
167 P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26–28.
168 C. Aïssa, *J. Org. Chem.* **2006**, *71*, 360–363.

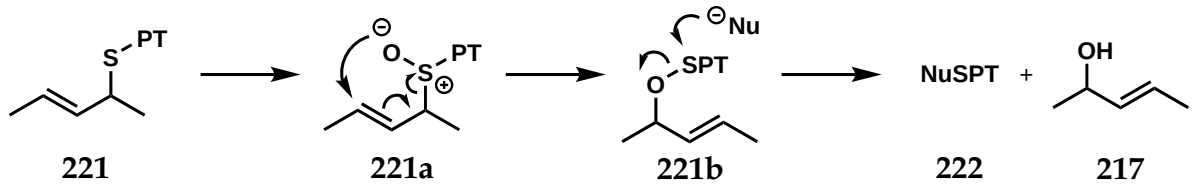


Scheme 3.51: Tested alternative approaches towards diene **212**: a) **109**, Cy_2BH, THF, 0 °C, 30 min to rt, 30 min, 64 % 3.5:1 dr; b) **113**, Cs_2CO_3, THF:DMF (3:1), reflux, o/n, 35 %, 5:1 dr; c) PBr_3, neat, −10 °C to rt, 2 h; d) PPh_3, MeCN, reflux, 4 h, 11 % (2 steps); e) PTSH, DIAD, PPh_3, THF, rt, o/n, 34 %; f) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, 0 °C, *decomposition*; g) acetaldehyde, CH_2Cl_2, reflux, 5 h, 53 %.

Another approach targeted the transformation of aldehyde **109** with a nucleophile capable of introducing the butadiene moiety. These include Wittig reagent **218**, Julia-Kocienski reagent **216** and trimethylsilylallene **219**. In the first case, the reaction was expected to form (*E*,*E*)-butadiene analogous to the work of Enders *et al*.[155] Nonetheless, the preparation of salt **218** proved difficult. Literature precendece for this compound is scarce and in all cases cites the work of Bartelt *et al*.[169] Unfortunately, neither a precise procedure for the preparation nor spectroscopic data are given. The allylic bromide was synthesized using phosphorus tribromide from corresponding allylic alcohol **217** which itself was accessed by Grignard-addition of methylmagnesium bromide onto crotonaldehyde. Reaction with triphenylphosphine then gave rise to Wittig reagent **218**. It was required to perform both steps of the salt formation in the absence of air since the product and intermediates were reported to be very hygroscopic.[169] Deprotonation of the Wittig salt with potassium *tert*-butoxide and reacting it with aldehyde **109** unfortunately did not lead to the desired product. Sulfone **216** was planned to arise from pentenol **217** as well. Mitsunobu reaction indeed formed thioether **221** alongside the undesired (*Z*)-isomer, which is supposedly formed by a competing S_N2' reaction of 1-phenyl-1*H*-tetrazole-5-thiol with the activated alcohol, yet oxidation to the desired sulfone **216** did not occur. The oxidant for this transformation had to be chosen carefully, since *meta*-chlorperbenzoic acid would be capable of oxidizing the double bond. The other standard method poses the molybdenum-catalyzed oxidation using H_2O_2 as stochiometric oxidant. In that case the formation of a derivative of the starting tetrazole of the Mitsunobu-transformation was isolated, indicating that it was cleaved from the pentene moiety during the reaction. A proposed mechanism involves a Mislow-Evans type rearrangement of intermediate sulfoxide **221a** after which the sulfenate **221b** species is cleaved from the pentene by a nucleophile (Scheme 3.52). Noteably, the byproduct was only characterized by ^{1}H-NMR spectroscopy, which does not allow for the identification of the oxidation state on the sulfur. Therefore, it is not clear if the sulfenate was cleaved by a hydroxide or by a different nucleophile.

The same retrosynthetic scission can be accomplished with changed polarity when using pentenone **215**, which is readily available by Wittig reaction of acetaldehyde and 1-(triphenylphosphoranylidene)-2-propanone.

169 R. J. Bartelt, P. F. Dowd, R. D. Plattner, D. Weisleder, *J. Chem. Ecol.* **1990**, *16*, 1015–1039.



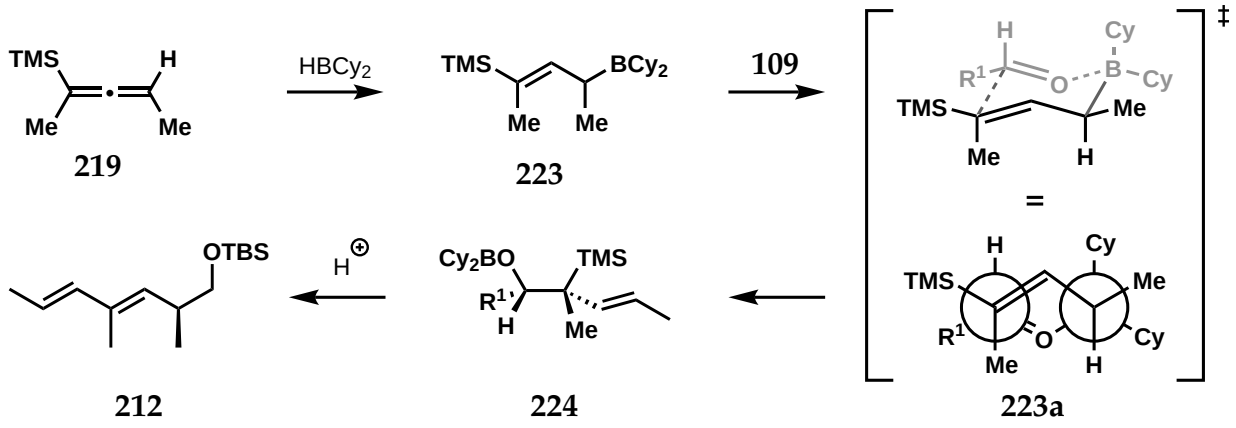
Scheme 3.52: Possible mechanism for the byproduct formation in the oxidation of thioether **221**.

The use of Julia-Kocienski reagent **55** should result in the formation of diene **212** in one step, while also making the synthesis more convergent. Unfortunately, neither under standard conditions employing potassium hexamethyldisilazide as base at low temperatures nor using cesium carbonate under refluxing conditions led to any conversion of the starting materials.

Lastly, the reaction with trimethylsilylallene **219** was investigated. The work of Wang *et al.*[170] focuses on the introduction of butadienes by a stepwise crotylation of an aldehyde with an *in situ* formed borane followed by a Peterson elimination. This method allows for the preparation of all four geometric isomers of the butadiene simply by deciding between 9-BBN and dicyclohexylborane as borylating reagent and choosing either basic *syn*-elimination or acid-promoted *anti*-elimination workup (Scheme 3.53). The authors suggest that borylation initially takes place at the less sterically hindered face of the allene to produce the (*Z*)-configured alkene, which quickly equillibrates by means of [1,3]-sigmatropic rearrangement to thermodynamically favored (*E*)-isomer **223**. Addition to aldehyde **109** leads to the formation of a chair transition state (**223a**) in which the rather small cyclohexyl substituents allow for the equatorial positioning of the methyl group, ultimately resulting in the formation of the (*E*)-double bond in silanol **224**. In case where 9-BBN is used as borylating agent, the methyl group adopts an axial position in the chair transition state, resulting in formation of the (*Z*)-double bond. Lastly, acidic workup facilitates the *anti*-elimination of silanol **224** to form diene **212** selectively and in good yield.

With quantitatively useful amounts of silyl ether **212** in hand, the Reformatsky cross-coupling was investigated (Scheme 3.54). First, amide **225** was synthesized by subjecting aniline **210** to 2-bromopropionyl bromide under basic conditions. Aldehyde **226** was ob-

170 R. R. Wang, Y. Gui Gu, C. Liu, *J. Am. Chem. Soc.* **1990**, *112*, 4424–4431.



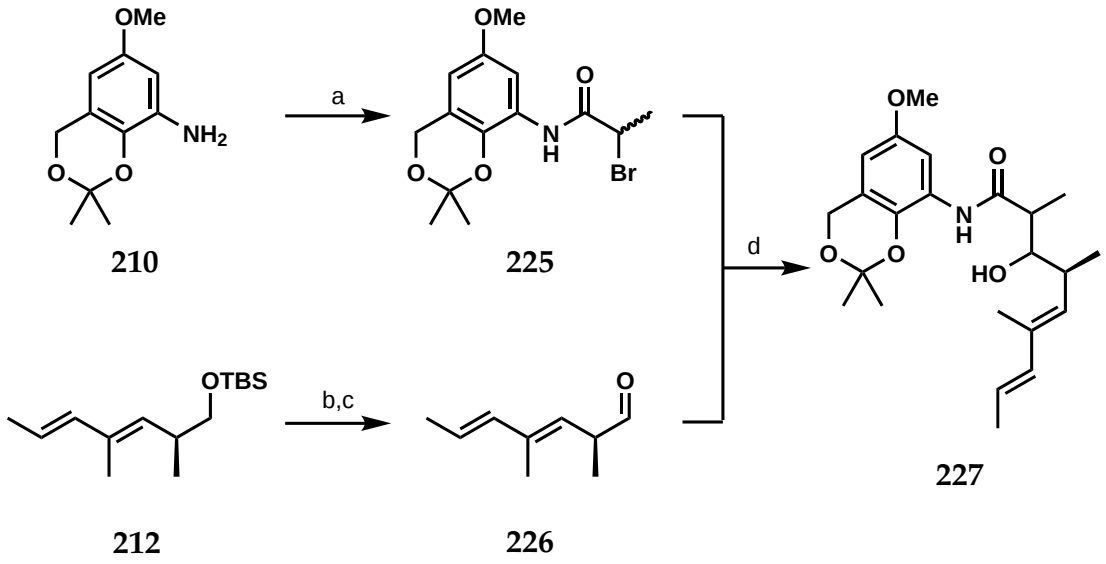
Scheme 3.53: Proposed mechanism for the Peterson reaction of trimethylsilylallene **219** with aldehyde **109**.

tained by desilylation of diene **212** with tetrabutylammonium fluoride, followed by IBX oxidation. It is noteworthy that the yield of the last transformation was rather low. Even though great effort went into the optimization of this reaction, where plenty different oxidation systems (TPAP, TEMPO, DMP, Cr(VI)-reagents, etc.) failed to produce the product, the yield could not be increased. Nonetheless, samarium iodide-mediated Reformatsky reaction formed coupled product **227** as a mixture of inconsequential diastereomers in quantitative yield.[171]1 Mechanistically, two one-electron reductions result in the formation of the Sm(III)-enolate of amide **225**, which then undergoes a nucleophilic attack onto aldehyde **226**. A competing side reaction, namely the pinacol homocoupling of aldehyde **226**, is suppressed as the formation of the required ketyl radical does not take place under cryogenic conditions. Protection of the resulting alcohol with silyl groups proved to be difficult, presumably due to steric hindrance. Therefore, it was decided to leave the alcohol unprotected, as no major problems involving a free alcohol function with the upcoming chemistry were anticipated.

The Diels-Alder reaction of *ortho*-quinone methides is regarded to take place under inverse electron-demand. This can be described with the frontier orbital theory (Scheme 3.55).[172] For a cycloaddition to occur, the electronic gap between HOMO and

1 The quality of the prepared SmI_2 solution proved to be crucial. Therefore, an optimized protocol utilizing samarium metal and iodine as the oxidant was chosen.[171]

171 M. Szostak, M. Spain, D. J. Procter, *J. Org. Chem.* **2012**, *77*, 3049–3059.
172 I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, **2010**.

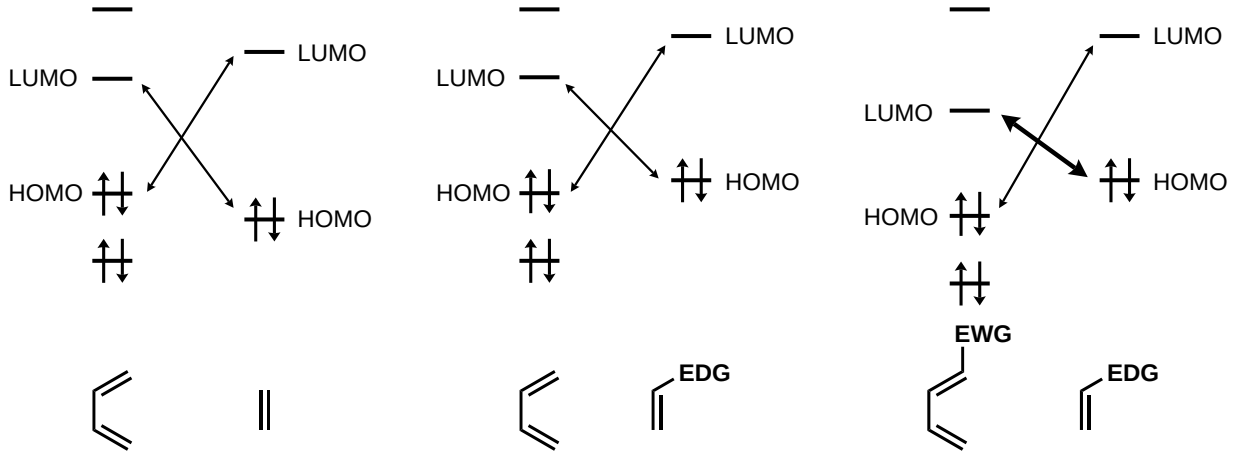


Scheme 3.54: Reformatsky reaction of aldehyde **226** with 2-bromo amide **225**: a) 2-bromopropionyl bromide, pyridine, CH_2Cl_2, 0 °C, 30 min, 88 %; b) TBAF, THF, rt, 30 min, 85 %; c) IBX, $NaHCO_3$, DMSO, rt, 2 h, 46 %; d) SmI_2, THF, −78 °C, 15 min, *quant*.

LUMO has to be sufficiently small. Generally, one can reason that electron-donating groups substantially raise the energy of the HOMO and slightly raise the energy of the LUMO, while electron-withdrawing groups slightly lower the energy of the HOMO and substantially lower the energy of the LUMO. Therefore, in the case with an unsubstituted diene and dienophile (left), no reaction occurs. Introducing an electron-donating group at the dienophile decreases the electronic gap, leading to the most favorable bond-forming interaction between the HOMO of the dienophile and the LUMO of the diene (middle). Nonetheless, the gap is still too large for cycloaddition to take place. A further decrease in energy separation of the $LUMO_{diene}/HOMO_{dienophile}$ pair by installment of an electron-withdrawing group onto the diene is required, allowing for Diels-Alder reaction to take place (right). As the p orbitals on oxygen atoms lie substantially lower in energy than those on carbon, the π molecular orbitals they form will inevitably have a lower-energy HOMO and LUMO. This is also the case for *ortho*-quinone methide hetero-Diels-Alder reactions. Therefore, the best orbital overlap is achieved when using electron-rich dienophiles.[137,173] Nonetheless, cycloadditions reacting *ortho*-quinone me-

173 M. P. Nguyen, J. N. Arnold, K. E. Peterson, R. S. Mohan, *Tetrahedron Lett.* **2004**, *45*, 9369–9371.

thides with neutral dienophiles have also been widely studied in the literature.[135,174]

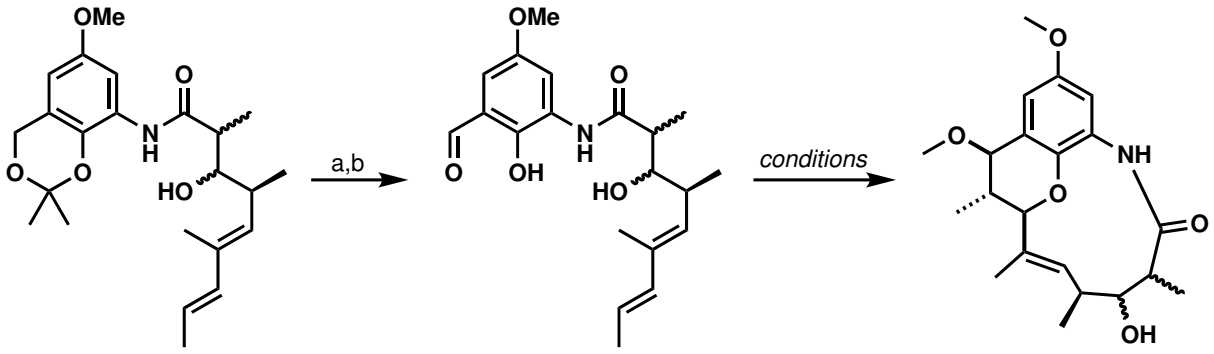


Scheme 3.55: Frontier orbital interactions involved in inverse electron-demand Diels-Alder reactions.[172]

To engage into the cycloaddition (Scheme 3.56), acetonide **227** was cleaved under acid catalysis after which manganese dioxide oxidation formed aldehyde **228** in good yield. It is noteworthy that the upcoming reaction was planned to be performed under asymmetric catalysis.[137] Therefore, a chiral Brønsted acid was supposed to be used to induce chirality into the transition state. Nonetheless, due to cost and time reasons, we first focused on the transformation using achiral catalysts.[175] The screening of the key step started with the same conditions that were prior used for the dimethyl acetal formation (entry 1). With these conditions it was already observed, that the dimethyl acetal seems to be unstable under aqueous workup conditions. Therefore, that intermediate could never be isolated and was only presumably formed, indicated by TLC analysis. Next, the reaction was tested at higher temperatures (entries 2 and 3)[135]. In that case, either aldehyde **228** was reisolated or the substrate decomposed. Another attempt focused on the use of benzene as solvent (entry 4). This change was supposed to favor the equilibrium of *ortho*-quinone methide formation and dimethylacetal formation, therefore potentially increasing the relative reaction rate of the cycloaddition. Yet again, decomposition was observed. The same applied to reduced equivalents of reagents (entry 5).

174 H. Miyazaki, K. Honda, M. Asami, S. Inoue, *J. Org. Chem.* **1999**, *64*, 9507–9511.
175 S. Inoue, M. Asami, K. Honda, H. Miyazaki, *Chem. Lett.* **1996**, 889–890.

In two cases, the use of rare earth triflates[173,176] (entries 6 and 7) was investigated, which also led to decomposition. Changing the Brønsted acid to trifluoroacetic acid[177,178] also did not improve the result of the transformation (entry 8).



227 **228** **229**

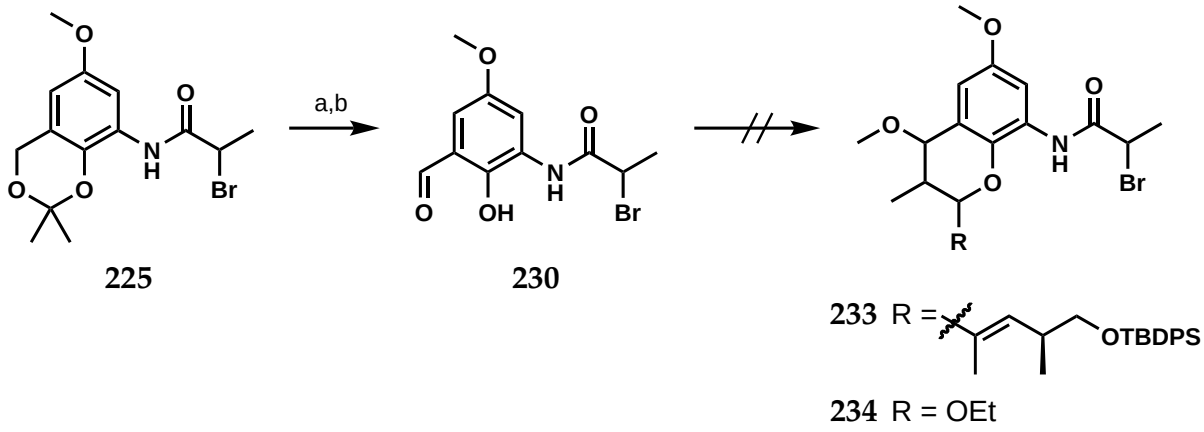
entry	conditions	result
1	$CH(OMe)_3$ (45), *p*TsOH (0.2), MeOH, rt, 2 h	full conv. to acetal, SM after workup
2	$CH(OMe)_3$ (45), *p*TsOH (0.2), MeOH, 60 °C, 2 h	full conv. to acetal, SM after workup
3	$CH(OMe)_3$ (45), *p*TsOH (0.2), MeOH, 70 °C, o/n	full conv. to acetal, decomp.
4	$CH(OMe)_3$ (45), *p*TsOH (0.2), PhH, rt, o/n	full conv. to acetal, decomp.
5	$CH(OMe)_3$ (1.2), *p*TsOH (0.2), PhH, rt, o/n	full conv. to acetal, decomp.
6	$CH(OMe)_3$ (2.0), $Yb(OTf)_3$ (0.05), CH_2Cl_2, 0 °C, 2 h	full conv. to acetal, decomp.
7	$CH(OMe)_3$ (2.0), $Bi(OTf)_3$ (0.05), MeCN, 0 °C, 2 h	full conv. to acetal, decomp.
8	$CH(OMe)_3$ (2.0), DCE:TFA (9:1), 0 °C, 2 h	full conv. to acetal, decomp.

Scheme 3.56: Synthesis of the Diels-Alder precursor and attempted cyclizations: a) *p*TsOH, MeOH, rt, 1 h, 68 %; b) MnO_2, CH_2Cl_2, rt, 3 h, 69 %. Employed equivalents are written in parenthesis.

As the intramolecular variant of the *ortho*-quinone methide Diels-Alder reaction did not lead to formation of any product, an intermolecular variant was tested. It is important to mention that regioselectivity issues for this transformation were anticipated, that were supposed to be mitigated by using the intramolecular variant. An approach to hamper reaction of the wrong π bond was to choose an alcohol protecting group that is sufficiently large enough to block an approach of the *ortho*-quinone methide to the more closely positioned double bond. Therefore, amide **225** was deprotected and oxidized to

176 J. S. Yadav, B. V. Reddy, C. Parisse, P. Carvalho, T. P. Rao, *Tetrahedron Lett.* **2002**, *43*, 2999–3002.
177 B. Sarmah, G. Baishya, N. Hazarika, P. J. Das, *Synlett* **2015**, *26*, 2151–2155.
178 K. Tanaka, M. Kishimoto, N. Ohtsuka, Y. Iwama, H. Wada, Y. Hoshino, K. Honda, *Synlett* **2019**, *30*, 189–192.

aldehyde **230** (Scheme 3.57). Using trimethyl orthoformate as methanol source as well as *para*-toluenesulfonic acid no Diels-Alder rection could be observed when employing either diene **231**, which was synthesized by protection of alcohol **232**, or the more electron-rich ethyl vinyl ether.

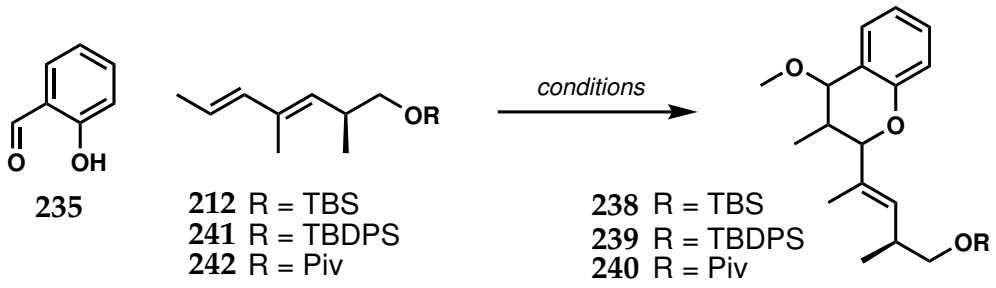


Scheme 3.57: Failed Diels-Alder reaction of aldehyde **230**: a) *p*TsOH, MeOH, rt, o/n, 86 %; b) MnO_2, CH_2Cl_2, rt, 2 h, 31 %.

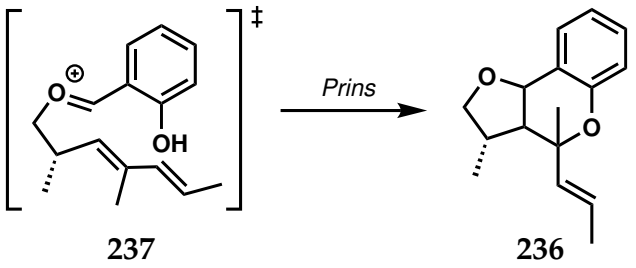
As the electron-donating nitrogen of the aniline, as well as the methoxy group were suspected to have a detrimental effect on the cycloaddition, the reaction was further investigated using salicyl aldehyde (**235**, Scheme 3.58). When reacting with TBS-protected alcohol **212**, the formation of tricyclic tetrahydrofuran **236** was observed (entry 1). This is in accordance with the literature[174,179], where free homoallylalcohols are used to form similar products. Mechanistically, this reaction has to be driven by a first desilylation, followed by an attack of the alcohol onto aldehyde **235** to form intermediate **237**. Subsequently, two different mechanisms can result in the formation of the product, where it is not quite clear which one is predominant. On one hand, a nucleophilic attack of the double bond onto the oxocarbenium ion, followed by a nucleophilic addition of the phenol to the resulting allylic cation can take place. On the other hand, loss of a proton and mesomerization leads to the formation of an *ortho*-quinone methide, which then participates in a [4+2] cycloaddition. Using the Lewis acid scandium triflate, the same product is observed (entry 2). Switching to the more acid-stable TBDPS protecting group hampers that reactivity, which results in no conversion of the starting materials (entry 3). It was suspected that when using methanol as an external nucleophile, a sim-

179 Y. Xie, B. List, *Angew. Chem. Int. Ed.* **2017**, *56*, 4936–4940.

ilar intermediate to **237** might be formed. A subsequent intermolecular Prins/Diels-Alder reaction should then forge the desired products **238**, **239** and **240** (entries 4 to 6). Unfortunately, in these cases no conversion of starting materials could be observed either.



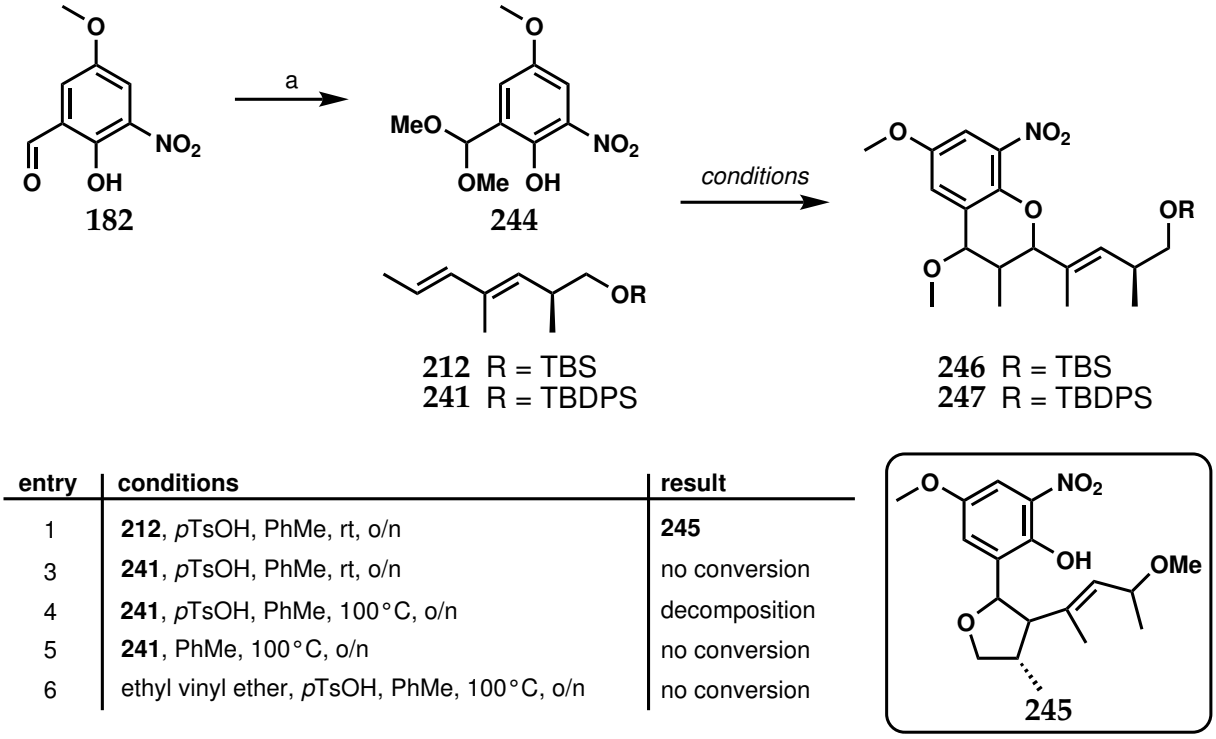
entry	conditions	result
1	**212**, $CH(OMe)_3$, *p*TsOH, PhMe, rt, o/n	**236**
2	**212**, $CH(OMe)_3$, $Sc(OTf)_3$, PhMe, rt, o/n	**236**
3	**241**, $CH(OMe)_3$, *p*TsOH, PhMe, rt, o/n	no conversion
4	**212**, MeOH, *p*TsOH, PhMe, rt, o/n	no conversion
5	**241**, MeOH, *p*TsOH, PhMe, rt, o/n	no conversion
6	**242**, MeOH, *p*TsOH, PhMe, rt, o/n	no conversion



Scheme 3.58: Attempted cycloaddition towards chromanes **238**, **239** and **243** and likely intermediate **237** in the formation of tetrahydrofuran **236**.

A more electron-deficient and more, in the context of cebulactam (**19**), synthetically useful *ortho*-quinone methide was nitroarene **182** (Scheme 3.59). To test various cycloaddition conditions, it was first transformed to stable dimethyl acetal **244** under standard conditions. The reaction with TBS-alcohol **212** led to formation of another Prins-type product **245** (entry 1). When employing TBDPS-diene **241**, no conversion was observed (entry 2). When heating the reaction to 100 °C, decomposition takes place (entry 4) or, in the case of absence of acid, no conversion was achieved (entry 5).

Moreover, reacting dimethyl acetal **244** with electron-rich ethyl vinyl ether also did not produce any product (entry 6).

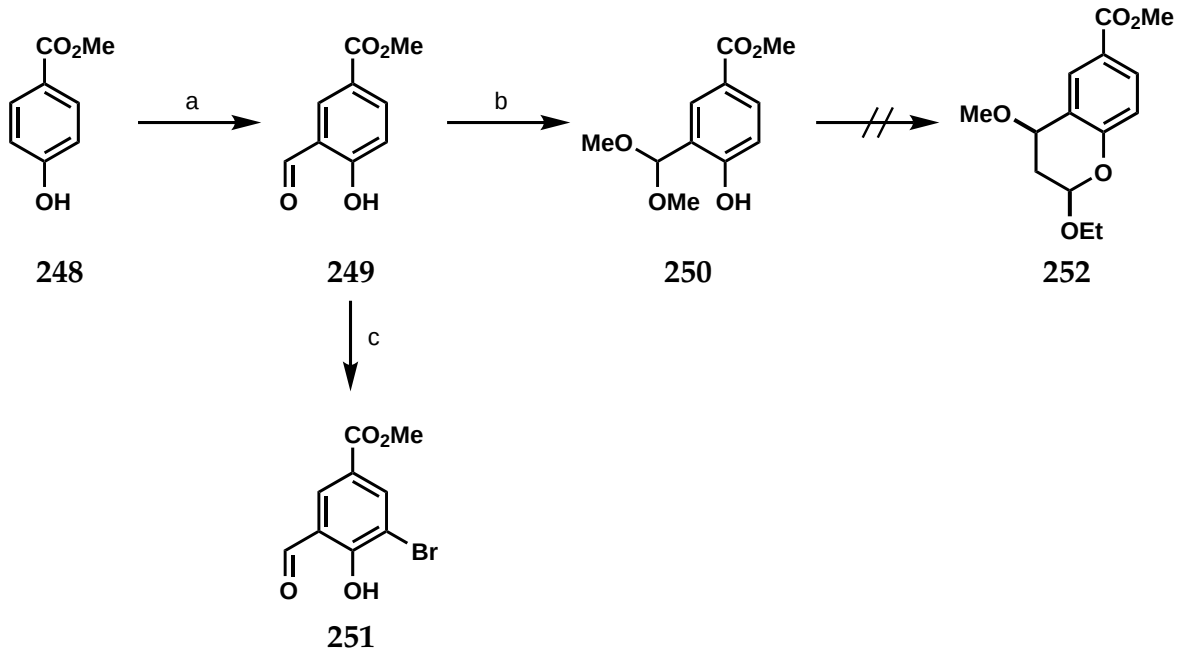


entry	conditions	result
1	**212**, *p*TsOH, PhMe, rt, o/n	**245**
3	**241**, *p*TsOH, PhMe, rt, o/n	no conversion
4	**241**, *p*TsOH, PhMe, 100 °C, o/n	decomposition
5	**241**, PhMe, 100 °C, o/n	no conversion
6	ethyl vinyl ether, *p*TsOH, PhMe, 100 °C, o/n	no conversion

Scheme 3.59: Attempted Diels-Alder reactions with nitroarene **244**. Conditions: a) $CH(OMe)_3$, *p*TsOH, MeOH, rt, 3 h, 77 %.

In order to further lower the energy of the LUMO, the methoxy group was replaced by an ester, which could later be transformed into a phenol by Bayer-Villiger oxidation, as shown earlier.[37,49] Thus, methyl 4-hydroxybenzoate (**248**) was formylated to give aldehyde **249** using the same conditions employed earlier.[138] Dimethyl acetal formation using catalytic amounts of lithium tetrafluoroborate forged arene **250** in quantitative yield.[180] Ungratifyingly, no Diels-Alder reaction with ethyl vinyl ether could be observed under acid catalysis. Moreover, it was not possible to nitrate aldehyde **249** under various tested conditions, employing nitric acid[181] as well as metal nitrates.[182,183] Fortunately, bromination took place with *N*-bromosuccinimide, givining rise to bromide **251**, another viable precursor for the cycloaddition.

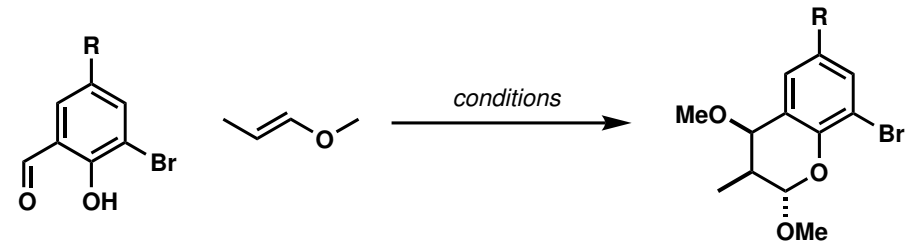
180 N. Hamada, K. Kazahaya, H. Shimizu, T. Sato, *Synlett* **2004**, 1074–1076.
181 R. Baker, J. L. Castro, *J. Chem. Soc. Perkin Trans I* **1990**, 47–65.
182 A. Srinivas, H. Akhila, M. Vydehi, *Eur. J. Biomed. Pharm.* **2016**, *3*, 409–416.
183 H. B. Sun, R. Hua, Y. Yin, *J. Org. Chem.* **2005**, *70*, 9071–9073.



Scheme 3.60: Synthesis of various methyl benzoate derivatives. Conditions: a) $MgCl_2$, Et_3N, paraformaldehyde, MeCN, reflux, o/n, 44 %; b) $CH(OMe)_3$, $LiBF_4$, MeOH, reflux, o/n, *quant.*; c) NBS, DMF, rt, 30 min, 84 %.

Next, the Diels-Alder reaction with bromides **178** and **251** was investigated (Scheme 3.61). Again, the ester substituted aldehyde **251** did not lead to formation of cycloaddition product **253** when treating with enol ether **254**, which was synthesized by isomerization of allyl methyl ether, and trimethyl orthoformate under acid catalysis (entry 1). Gratifyingly, when using methoxyarene **178**, under the same conditions, chromane **255** was obtained as a 1:3 mixture with starting aldehyde **178** and a 20:1 mixture of diastereomers (entry 2), as determined by integration of the ^{1}H-NMR signals. Stirring the reaction for an extended time of four days slightly increased the conversion and a 1:2.4 mixture of product and starting material was obtained (entry 3). Next, the reaction was performed at an elevated temperature in order to further increase the conversion (entry 4). Indeed, the product was obtained as a favorable 6.6:1 mixture with the starting material, but the *dr* dropped to 1:1.5. Lastly, the reaction was tested with isolation of the intermediate dimethyl acetal (entry 5). Though the dimethyl acetal was not stable enough for chromatography, it proved to be sufficiently unreactive for aqueous workup to be performed. The obtained crude mixture was immediately used for the reaction with enol ether **254**, now in the abscence of trimethyl orthoformate, to forge chromane **255** in good yield and selectivity. All attempts to react bromide **178** with a more suitable substrate of the architecture of diene **212**, unfortunately did not result in the formation of any cycloaddition products. It was thus reasoned that methoxy acetal **255** might be a viable intermediate in the cebulactam (**19**) synthesis, in which case the methoxy group has to be substituted in a chemistry resembling *C*-glycosilation.

With the Diels-Alder reaction producing sufficient quantities of chromane, the stereoselectivity has to be addressed. As an achiral catalyst was used, the resulting products have to be racemic mixtures, an optimization towards chiral acids will be performed when the downstream chemistry is established. Furthermore, as the next steps involve a substitution of the methoxy group of the acetal, the initial stereochemistry might play an important role if it takes place under S_N2 conditions, as opposed to a S_N1 mechanism. Therefore, as chromane **255** was not obtained as a solid and thus denying X-ray crystallography, the ^{3}J coupling-constants were compared to a compound that is literature known.[137] Generally speaking, the Diels-Alder reaction can produce two diastereomers, the *exo* and the *endo* products (**A** and **B**, respectively, Scheme 3.62). Nonetheless, when the Lambert group performed the Diels-Alder reaction with an E:Z mixture of the corresponding ethyl enol ether, they obtained the all *syn* product **E** as the sole diastereomer. Mechanistically, this could be explained by an *exo*-specific Diels-Alder reaction, followed



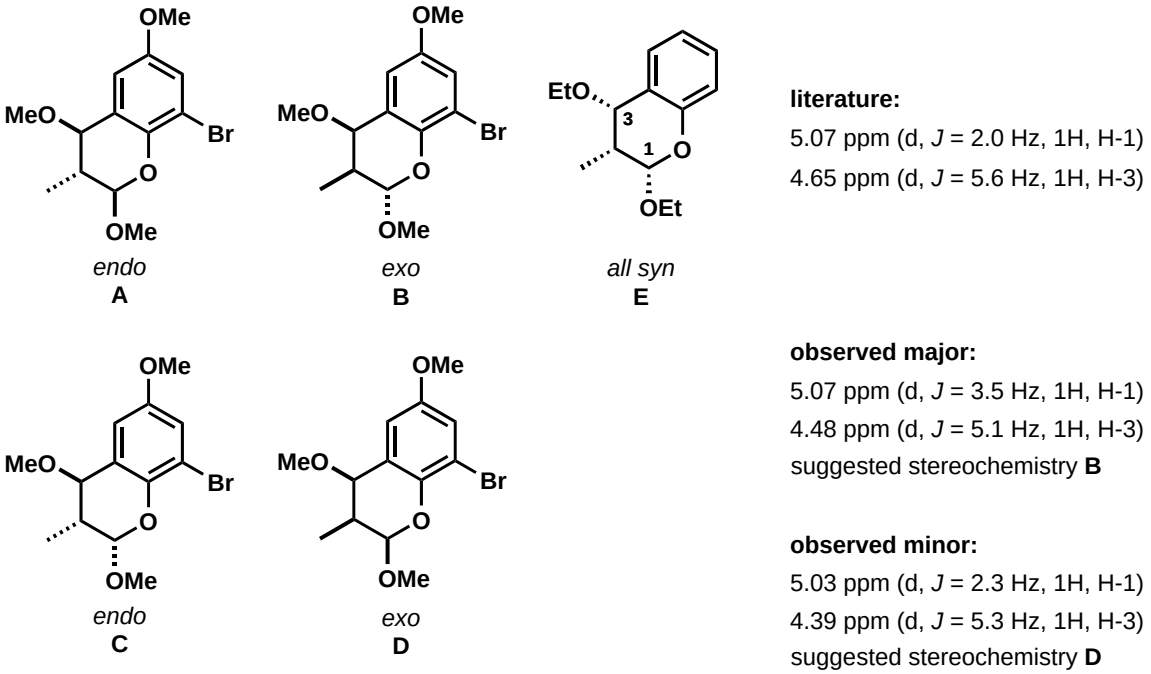
251 R = CO_2Me **254** **253** R = CO_2Me
178 R = OMe **255** R = OMe

entry	conditions	result
1	**251** (1.0), $CH(OMe)_3$ (1.2), *p*TsOH (0.2), PhMe, rt, o/n	no conversion
2	**178** (1.0), $CH(OMe)_3$ (1.2), *p*TsOH (0.2), PhMe, rt, o/n	**255:178** 1:3.0 (20:1 *dr*)
3	**178** (1.0), $CH(OMe)_3$ (1.2), *p*TsOH (0.2), PhMe, rt, 4 d	**255:178** 1:2.4 (20:1 *dr*)
4	**178** (1.0), $CH(OMe)_3$ (1.2), *p*TsOH (0.2), PhMe, 100 °C, 3 h	**255:178** 6.6:1 (1:1.5 *dr*)
5	**178** (1.0), $CH(OMe)_3$ (45) , *p*TsOH (0.3), MeOH, workup *then* **254** (3.0), *p*TsOH (0.2), PhMe, rt, o/n	88 % (20:1 *dr*)

Scheme 3.61: Diels-Alder reaction with bromoarenes **251** and **178**.

by an acid catalyzed epimerization of the C-1 stereocenter *via* the oxocarbenium species. Another explanation would be the loss of the double bond stereoinformation, only possible when the reaction takes place in a non-concerted manner. In that case, the reaction proceeds through an ionic intermediate that allows for rotation of a single bond, resulting in the formation of a different stereoisomer. The observed coupling-constants for the obtained minor product deviate only by 0.3 Hz compared to the ones reported in the literature, suggesting that this compound might be the all *syn* derivative **D**, formed by the previously provided mechanism. When comparing the coupling-constants of the major product one can observe that the H-3 proton coupling constant remains rather unchanged from the all *syn* product. Yet the H-1 coupling constant is 1.5 Hz larger, indicating that the stereochemistry between C-1 and C-2 is *anti*, thus suggesting structure **B**. This would correspond to the concertedly formed *exo* Diels-Alder product. In order to confirm the stereochemistry, derivatization to improve crystallinity that allow for X-ray crystallography have to be performed. Nonetheless, this would still prove as an useful substrate, as the stereoconfiguration at the benzylic position can be inverted by means of oxidation and asymmetric reduction.[74,75]

In order to increase the leaving group capability of the methoxy group of acetal **255**, it was planned to be converted into acetate **256**. In the literature, methyl glycosides are cleaved

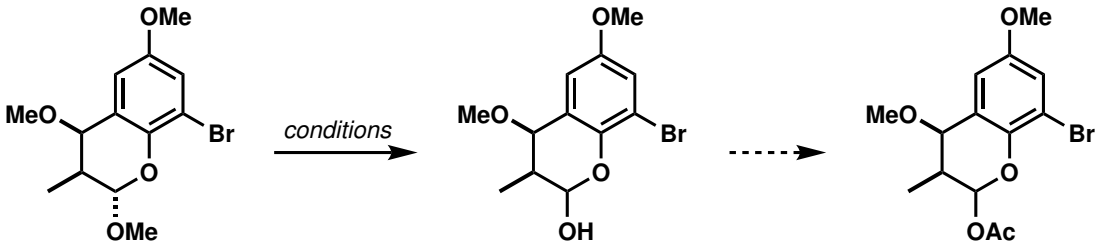


Scheme 3.62: Possible relative stereochemistry of obtained chromane **255** and comparison of ^3J-coupling constants with a literature known compound.[137]

by acid hydrolysis.[184–186] Nonetheless, when using *para*-toluenesulfonic acid (entry 1) or hydrochloric acid (entry 2), no conversion of starting material was observed. Another attempt focused on the use of titanium tetrachloride as Lewis acid (entry 3), where decomposition of the starting material was observed. Using sulfuric acid in acetic acid (entry 4), a complex mixture was obtained. One of the products present in the crude mixture was identified as aldehyde **178**, indicating that a *retro*-Diels-Alder reaction must have taken place.

Another approach to obtain alcohol **257** was to alter enol ether **258** (Scheme 3.64). When switched to benzyl ether **259**, the reaction yielded chromane **260** in decent yield albeit in lower diastereoselectivity. It is noteworthy, that it is not clear what the obtained diastereomers might be, as the ^3J-coupling-constants of the major and minor products are almost identical. With benzyl ether **260** in hand, the debenzylation was investigated.

184 G. Mehta, S. S. Ramesh, *Eur. J. Org. Chem.* **2005**, 2225–2238.
185 C. McDonnell, O. López, P. Murphy, J. G. Fernández Bolaños, R. Hazell, M. Bols, *J. Am. Chem. Soc.* **2004**, *126*, 12374–12385.
186 E. S. Han, D. Goleman, R. Boyatzis, A. Mckee, *J. Chem. Inf. Model.* **2019**, *53*, 1689–1699.

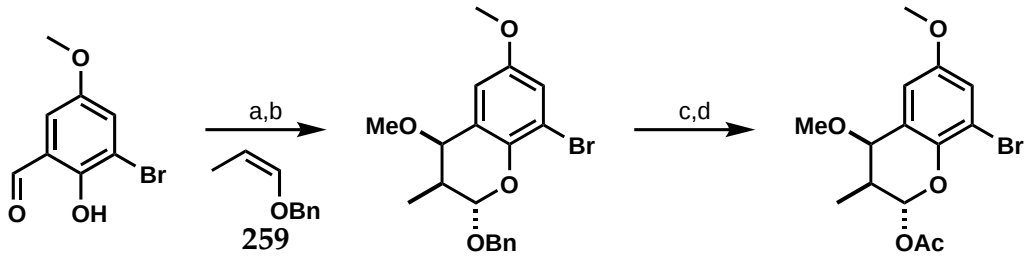


255 257 256

entry	conditions	result
1	*p*TsOH, acetone:water 1:1, rt, o/n	no conversion
2	THF:HCl (6M) 1:1, rt, o/n	no conversion
3	$TiCl_4$, PhMe, 0 °C, 2h *then* H_2O	decomposition
4	3M H_2SO_4, AcOH, 100 °C, 3 h	complex mixture, retro-DA

Scheme 3.63: Attempted hydrolysis conditions to obtain alcohol **257**.

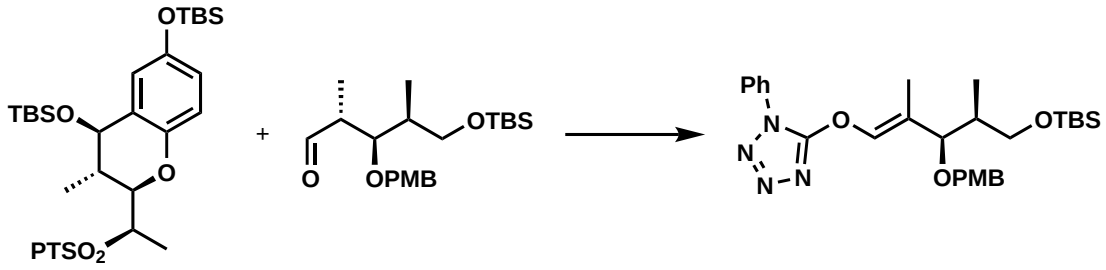
As the reduction of the bromide was a viable side-reaction, the use of birch conditions was dismissed. Moreover, when investigating hydrogenation conditions employing palladium catalysts, the formation of the methyl ether was observed, when performing the reaction in a THF:MeOH solvent system. Therefore, the reaction was conducted in pure THF, giving rise to stable hemiacetal **257** in good yield. Next, the hydroxy group was planned to be converted into the corresponding acetate. When employing standard basic conditions, the opening of the pyran-system was observed and the resulting thermodynamically favored phenolate was acetylated. Gratifyingly, when heating alcohol **257** in acetic anhydride, clean conversion to desired acetate **256** was observed. Interestingly, only a single diastereomer of acetate **256** was isolated, indicating that epimerization to the thermodynamically favored stereoisomer *via* mutarotation must have taken place.



Scheme 3.64: Diels-Alder reaction with benzyl ether **259**. Conditions: a) $CH(OMe)_3$, *p*TsOH, MeOH, rt, 4 h; b) **259**, *p*TsOH, PhMe, rt, 8 d, 80 %, 4.5:1 *dr*, (2 steps); c) H_2 (1 atm), Pd/C, THF, rt, 3 d, 63 % 1.6:1 *dr*; d) Ac_2O, neat, 75 °C, 2 h, 77 %, single diastereomer.

4 Summary and Future Directions

Firstly, the olefination reaction of the chromane moiety was examined. Therefore, the Julia-Kocienski olefination of the prior synthesized[37] advanced intermediates **68** and **69** was further investigated, with the result that alkene formation is not feasible and decomposition to enol ether **71** took place (Scheme 4.1).

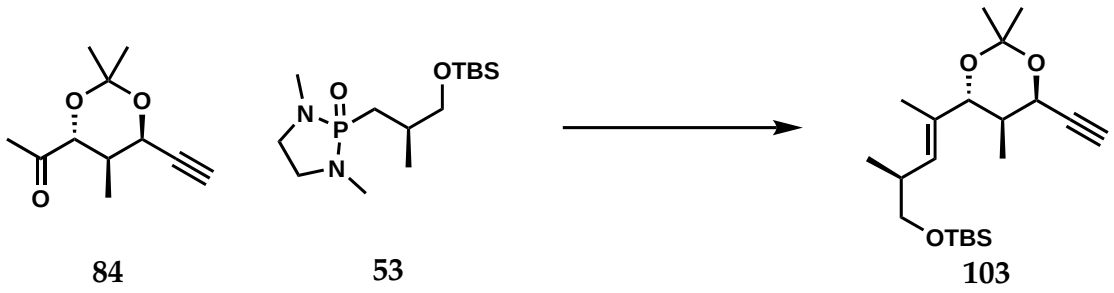


68 **69** **71**

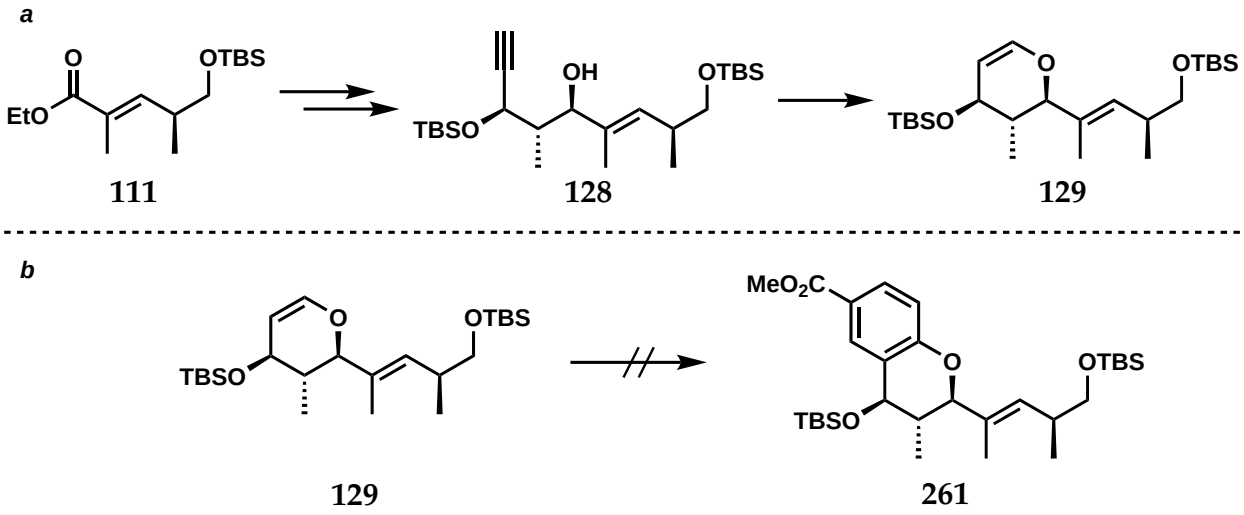
Scheme 4.1: Failed coupling of advanced intermediates **68** and **69**.

Afterwards the timing of the olefination in the synthesis was changed and two suitable ketones and a wide range of nucleophiles with either three or five carbon atoms were thus prepared. Even though formation of alkene **103** was observed when using acetonide **84** and Hanessian's cyclic phosphonamide **53**, the reaction did not provide preparative useful yields (Scheme 4.2)

A new strategy was developed in which the double bond was installed in the first key step of the synthesis. The follow-up chemistry was adapted and the carbon chain was extended with an *anti*-selective aldol reaction and organometal chemistry, providing alkynol **128**, which was photochemically cycloisomerized using a protocol of McDonalds *et al*. Unfortunately, Diels-Alder reaction of enol ether **129** did not lead to formation of the cycloaddition adduct, despite extensive optimization studies.

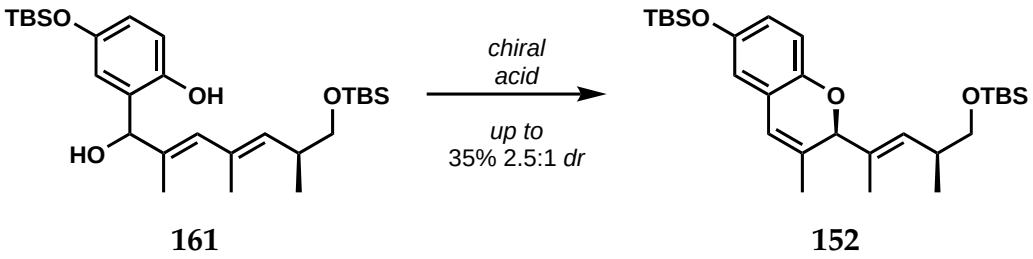


Scheme 4.2: Olefination reaction of ketone **84** to form alkene **103**.



Scheme 4.3: a) Synthesis of dihydropyran **129** *via* cycloisomerization of alkynol **128**; b) Failed Diels-Alder reaction of dihydropyran **129**.

Since these approaches did not lead to the desired results, an entirely new strategy towards the chromane core of cebulactam (**19**) based on *ortho*-quinone methide chemistry was developed. The first approach focused on an electrocylization path and chromene **152** was synthesized in few steps. Moreover, a prior unknown asymmetric method for the stereoselective formation of chromenes *via* electrocyclization was developed based on the use of chiral Brønsted acids (Scheme 4.4). Unfortunately, the yields and selectivities did not prove to be sufficient for the total synthesis purpose and, more importantly, the required downstream chemistry to functionalize the chromene core did not succeed.



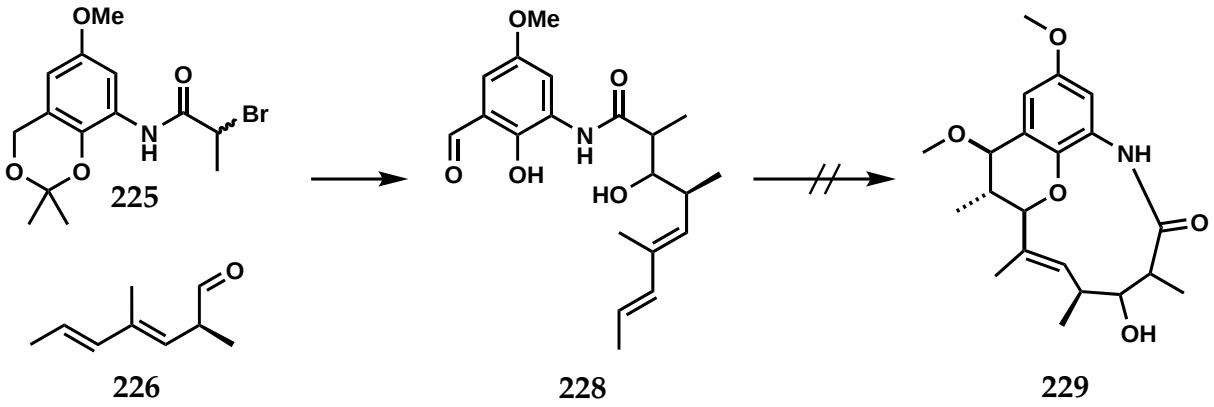
161 **152**

Scheme 4.4: First literature-known asymmetric oxa-6π-electrocyclization to form chromenes.

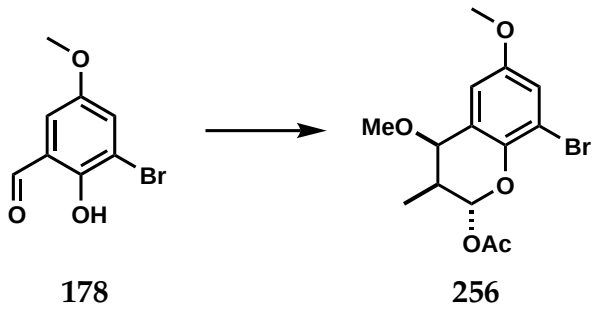
As *ortho*-quinone methides are also known to undergo Diels-Alder reactions, this approach was investigated for the synthesis of cebulactam (**19**). We envisioned that diene **228** could participate in a regioselective intramolecular cycloaddition that could be stereochemically controlled with the use of a chiral Brønsted acid (Scheme 4.5). Therefore, a new strategy to synthesize diene **228** was developed and the *ortho*-quinone methide formation/Diels-Alder cycloaddition cascade was investigated.

Moreover, inspired by the work of Lambert *et al.*[137], an intermolecular Diels-Alder approach was developed and the resulting acetal function was manipulated as to where it becomes a reactive carbon center, useful for substitution reactions. Unfortunately, the obtained stereochemistry is not yet determined.

In the future, the stereochemistry of intermolecular Diels-Alder product **260** has to be validated by single-crystal x-ray crystallography. If the configuration of the C-2 and C-3 substituents is indeed *syn*, the benzylic position has to be inverted at one point in the synthesis by means of oxidation and stereoselective reduction. Then, the cycloaddition has to be performed under chiral catalysis to yield enantioenriched Diels-Alder product **260**.

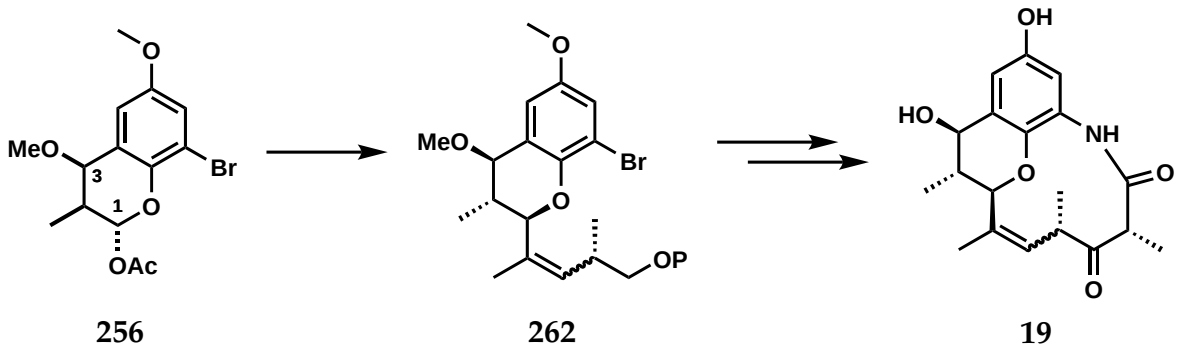


Scheme 4.5: Successful synthesis of cyclization precursor **228** and failed intramolecular Diels-Alder reaction to yield chromane **229**.



Scheme 4.6: Successful Diels-Alder reaction of aldehyde **178** and functional group manipulation to yield acetate **256**.

Moreover, a stereoselective substitution of acetate **256** has to be established in order to introduce the *ansa*-chain (Scheme 4.7). Stereoselectivity may be conferred *via* the benzylic alcohol, serving as either a directing group or as a steric shield, preventing the attack from the same face, depending on its actual configuration after the Diels-Alder reaction. Starting from alkene **262**, an amide coupling has to be developed in order to form the macrolactam of cebulactam (**19**). The synthesis would then be finalized by oxidation to the dicarbonyl and subsequent deprotection of the remaining alcohols to yield cebulactam (**19**).



256 **262** **19**

Scheme 4.7: Future directions for the synthesis of cebulactam (**19**) starting from prepared acetate **256**.

5 Experimental Procedures

5.1 General Procedures

Solvents and Reagents

All commercially available solvents and reagents were used as received (ACROS, ABCR, SIGMA-ALDRICH, TCI, ALFA). THF was freshly distilled from Na/benzophenone. Deuterated solvents for NMR were acquired from DEUTERO.

Chromatography

The silica gel used for manual flash column chromatography was acquired from MACHEREY-NAGEL (type 60 M, grain size 40 µm to 63 µm). Automated flash column chromatography was conducted with the flash purification system Sepacore® by BUCHI using prepacked cartridges (puriFlash® by INTERCHIM or chromabond® by MACHEREY-NAGEL). The eluents are given in parentheses.

Semi-preparative HPLC (<20 mg) was performed with a HPLC containg a fraction collector (Varian pro Star, Model 701) and pumps (Varian preStar, Model 218) by ALPHACHROM and a variable UV detector (proStar [λ = 248 nm]) along with a mass detector (MICROMASS type LCT) by WATERS. Separation was conducted through a RPC18 (Nucleodur®, 5 µm) column by MACHEREY-NAGEL.

Thin Layer Chromatography (TLC)

For TLC, aluminum plates coated with silica gel, type 60 F254 by MERCK, were used and the spots were visualized with UV light (λ = 248 nm) or alternatively by staining with vanillin or potassium permanganate solutions.

NMR-Spectroscopy

^{1}H NMR and ^{13}C NMR spectra were recorded with the DPX-400 (400 MHz), AVS-400 (400 MHz) and the Ultrashield 500 (500 MHz) by BRUKER at 298 K. The chemical shifts (δ) are reported in ppm and the calibration was conducted by using the residual proton peak of the solvent (CDCl3: δH = 7.26 ppm, δC = 77.16 ppm). The coupling constants *J* are reported in Hertz (Hz) and the multiplicities are described with the following abbreviations:
^{1}H-NMR: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, *brs* = broad signal.
^{13}C NMR: the multiplicities are corresponding to the non-decoupled spectra: s = quaternary C-atom, d = tertiary C-atom, t = secondary C-atom, q = primary C-atom.
If necessary, COSY, HMBC and HSQC experiments were conducted for full characterization.

Optical rotations

Specific optical rotation values $[\alpha]^{T}_{D}$ were measured with a PERKIN-ELMER Spectrum 341 polarimeter at λ = 589 nm (sodium D line) and the temperature T. The concentration c is given in 10 mg $\cdot$ ml^{-1}.

Mass Spectrometry

High resolution mass spectra (HRMS) were recorded with a MICROMASS LCT with a *lockspray* dual ion source in combination with a WATERS Alliance 2695 system. Injection was conducted in loop mode. Alternatively, a QTOF premier spectrometer (WATERS) in combination with a WATERS Acquity UPLC system was used. Ionisation was

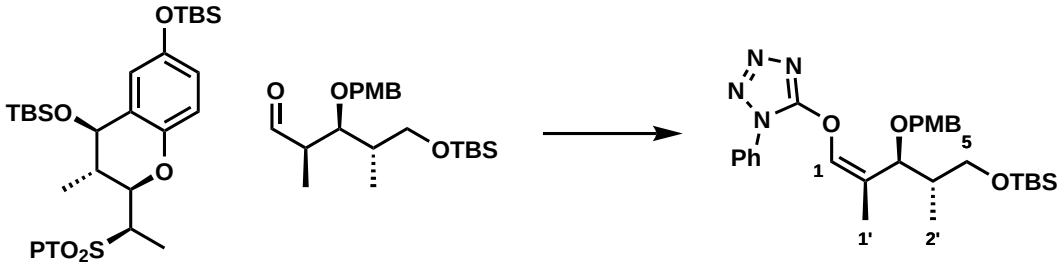
carried out *via* electrospray-ionisation (ESI). The calculated and the detected masses are reported.

High Pressure Reactions

High pressure reactions were conducted using a HOFER HP14 high pressure device. For the reaction, a teflon cylinder with a sealing stopper was used.

5.2 High Pressure Diels-Alder Route

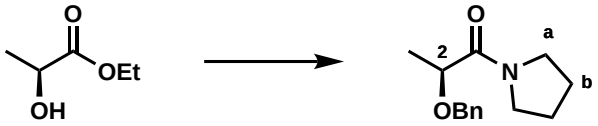
5-(((3*S*,4*S*,*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethylpent-1-en-1-yl)oxy)-1-phenyl-*1H*-tetrazole (71)



68 **69** **71**

To a solution of sulfone **68** (30 mg, 47 µmol, 1.00 eq.) in THF (0.6 ml) was added KHMDS (0.5 M in THF, 0.11 ml, 56 µmol, 1.20 eq.) dropwise at −78 °C. After stirring for 3 min a solution of aldehyde **69** (20 mg, 51 µmol, 1.10 eq.) in THF (0.4 ml) was added dropwise and stirring was continued for another 45 min. The reaction was allowed to warm to rt and then terminated by addition of a sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with a sat. NH_4Cl solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded the undesired enol ether **71** as the major product.
$\mathbf{R_f} = 0.70$ (PE:EA = 5:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.79 - 7.75 (m, 2H, Ph), 7.62 - 7.56 (m, 2H, Ph), 7.53 - 7.49 (m, 1H, Ph), 7.26 - 7.22 (m, 3H, Ph, 1-H), 6.88 - 6.84 (m, 2H, Ph), 4.42 (d, $J = 11.2$ Hz, 1H, -CH_2Ph), 4.20 (d, $J = 11.2$ Hz, 1H, -CH_2Ph), 4.20 (s, 3H, -OCH_3), 3.74 - 3.67 (m, 2H, H-5), 3.64 (d, $J = 9.6$ Hz, 1H, H-3), 1.94 - 1.84 (m, 1H, H-4), 1.74 (d, $J = 1.4$ Hz, 3H, H-1'), 0.9 (s, 9H, TBS), 0.81 (d, $J = 7.0$ Hz, 3H, H-2'), 0.04 (s, 6H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 159.3 (s, Ph), 158.7 (s, Ph), 137.5 (d, C-1), 133.2 (s, Ph), 130.5 (d, Ph), 129.9 (d, Ph), 129.5 (d, Ph), 129.5 (s, *tetrazole*), 122.2 (s, C-2), 122.0 (d, Ph), 113.9 (d, Ph), 80.1 (d, C-3), 70.1 (t, -CH_2Ph), 64.3 (t, C-5), 55.4 (q, -OCH_3), 37.9 (d, C-4), 26.1 (q, TBS), 18.5 (s, TBS), 14.0 (q, C-2'), 8.6 (q, C-1'), −5.2 (q, TBS), −5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{28}H_{40}N_4O_4Si$ $[M+Na]^+$: 547.2717, found 547.2719.

(*S*)-2-(Benzyloxy)-1-(pyrrolidin-1-yl)propan-1-one (263)

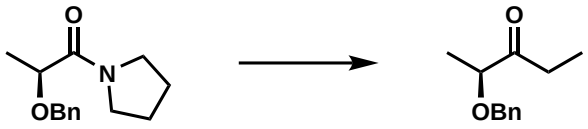


51 **263**

Pyrrolidine (30.6 ml, 372.5 mmol, 1.10 eq.) was cooled to 0 °C and L-ethyl lactate **51** (38.7 ml, 338.6 mmol, 1.00 eq.) was added via addition funnel. The resulting mixture was stirred for 10 min at 0 °C and then for another 2 d at rt after which it was concentrated under reduced pressure to yield the crude product. NaOH (47.3 g, 1.180 mol, 3.50 eq.) was suspended in toluene (100 ml) and cooled to 0 °C and a solution of the crude amide, Aliquat 336 (6.80 g, 16.90 mmol, 0.05 eq.) and BnBr (64.3 ml, 541.8 mmol, 1.60 eq.) in toluene (100 ml) was added dropwise. The reaction was stirred at rt overnight and then poured into Et_2O:H_2O (600 ml, 2:1). The phases were separated and the organic phase was washed with a 1 M HCl solution, a sat. $NaHCO_3$ solution and brine. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 2:1 to 100 % EA) yielded the pyrrolidineamide **263** (44.30 g, 209.2 mmol, 56 % over 2 steps) as a colorless oil.
$\mathbf{R_f} = 0.21$ (PE:EA = 1:1);
$[\alpha]^{28}_{\mathbf{D}} = -45.2°$ ($c = 0.75$; CH_2Cl_2); lit.:[49] $= -60.5°$;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.35 - 7.26 (m, 5H, Ph), 4.61 (d, $J = 11.8$ Hz, 1H, -CH_2Ph), 4.43 (d, $J = 11.8$ Hz, 1H, -CH_2Ph), 4.19 (q, $J = 6.7$ Hz, 1H, H-2), 3.56 - 3.37 (m, 4H, H-a), 1.93 - 1.76 (m, 4H, H-b), 1.42 (d, $J = 6.7$ Hz, 3H, H-3);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 170.9 (s, C-1), 137.9 (s, Ph), 128.5 (d, Ph), 128.1 (d, Ph), 127.9 (d, Ph), 74.9 (d, C-2), 71.1 (t, -CH_2Ph), 46.4 (t, C-a), 46.1 (t, C-a), 26.5 (t, C-b), 23.8 (t, C-b), 17.5 (q, C-3);
HRMS (ESI): m/z calc. for $C_{14}H_{19}NO_2$ [M+Na]$^+$: 256.1313, found: 256.1309.

The analytical data match those reported in the literature.[49]

(*S*)-2-(Benzyloxy)pentan-3-one (45)

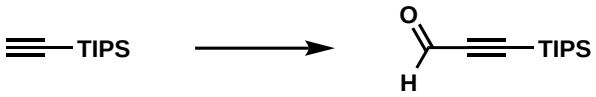


263 **45**

To a solution of amide **263** (30.00 g, 129.0 mmol, 1.00 eq.) in THF (300 ml) was added EtMgBr (3 M in THF, 42.9 ml, 129.0 mmol, 1.00 eq.) at −30 °C over 45 min and the solution was allowed to warm to rt over 1 h. The reaction was terminated by addition of a sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2) yielded ethyl ketone **45** (23.70 g, 123.8 mmol, 96 %) as a colorless oil.
$\mathbf{R_f} = 0.64$ (CH_2Cl_2);
$[\alpha]^{21}_{D} = -41.3°$ ($c = 1.00$; $CHCl_3$); lit.:[49] $= -36.5°$;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.38 - 7.27 (m, 5H, Ph), 4.55 (d, $J = 11.7$ Hz, 1H, -CH_2Ph), 4.50 (d, $J = 11.7$ Hz, 1H, -CH_2Ph), 3.95 (q, $J = 7.0$ Hz, 1H, H-2), 2.68 - 2.51 (m, 2H, H-4), 1.34 (d, $J = 7.0$ Hz, 3H, H-1), 1.06 (t, $J = 7.5$ Hz, 3H, H-5);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 213.7 (s, C-3), 137.8 (s, Ph), 128.6 (d, Ph), 128.0 (d, Ph), 127.9 (d, Ph), 80.7 (d, C-2), 72.0 (t, -CH_2Ph), 30.7 (t, C-4), 17.7 (q, C-1), 7.4 (q, C-5);
HRMS (ESI): m/z calc. for $C_{12}H_{16}O_2$ [M+Na]$^+$: 215.1048, found: 215.1048.

The analytical data match those reported in the literature.[49]

3-(Tri*iso*propylsilyl)propiolaldehyde (46)

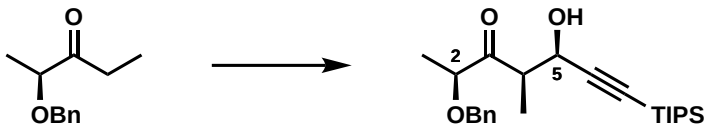


47 **46**

To a solution of tri*iso*propylsilylacetylene **47** (19.0 ml, 84.55 mmol, 1.00 eq.) in Et_2O (40 ml) was added dropwise *n*BuLi (2.5 M in hexane, 38.0 ml, 95.00 mmol, 1.10 eq.) at −78 °C. The reaction was stirred for 20 min at that temperature and then an additional 60 min at rt. Afterwards it was cooled back to −78 °C, DMF (7.6 ml, 98.10 mmol, 1.20 eq.) was added dropwise and it was allowed to warm to rt over 1 h. The reaction was acidified with 95 ml 2 M HCl and stirring was continued for another 2 h. After neutralization with a sat. $NaHCO_3$ solution the phases were separated and the aqueous phase was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE) yielded aldehyde **46** (14.90 g, 70.95 mmol, 84 %) as a red oil.
$\mathbf{R_f} = 0.20$ (PE);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.23 (s, 1H, C*H*O), 1.15 - 1.12 (m, 21H, TIPS).

The analytical data match those reported in the literature.[49]

(2*S*,4*R*,5*R*)-2-(Benzyloxy)-5-hydroxy-4-methyl-7-(tri*iso*propylsilyl)hept-6-yn-3-one (48)

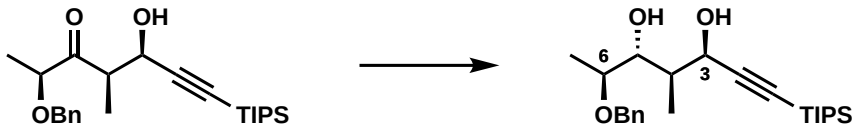


45 **48**

To a solution of ethyl ketone **45** (12.70 g, 66.20 mmol, 1.00 eq.) in CH_2Cl_2 (400 ml) was added dropwise at −78 °C $TiCl_4$ (8.0 ml, 72.82 mmol, 1.10 eq.) and then DIPEA (12.7 ml, 72.82 mmol, 1.10 eq.) and the resulting solution was stirred for 2.5 h at that temperature. Aldehyde **46** (19.5 g, 92.68 mmol, 1.40 eq.) in CH_2Cl_2 (20 ml) was added over 45 min and stirring was continued for 1 h. After addition of a sat. NH_4Cl solution at −78 °C the mixture was warmed to rt and the phases were separated. The aqueous phase was extracted with Et_2O, and the combined organic phases were washed with a sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded aldol **48** (26.40 g, 63.55 mmol, 96 %, 12:1 *dr*) as a colorless oil.
$\mathbf{R_f} = 0.15$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36 - 7.26 (m, 5H, Ph), 4.68 - 4.66 (m, 1H, H-5), 4.59 (d, $J = 11.6$ Hz, 1H, -CH_2Ph), 4.54 (d, $J = 11.6$ Hz, 1H, -CH_2Ph), 4.10 (q, $J = 6.9$ Hz, 2H, H-2), 3.24 - 3.17 (m, 1H, H-4), 2.96 (d, $J = 5.8$ Hz, 1H, -*OH*), 1.39 (d, $J = 6.9$ Hz, 3H, H-1), 1.30 (d, $J = 7.2$ Hz, 3H, H-1'), 1.09 - 1.05 (m, 21H, TIPS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 213.8 (s, C-3), 137.5 (s, Ph), 128.6 (d, Ph), 128.0 (d, Ph), 127.8 (d, Ph), 106.4 (s, C-6), 86.4 (s, C-7), 79.5 (d, C-2), 71.9 (t, -CH_2Ph), 63.6 (d, C-5), 47.8 (d, C-4), 18.6 (d, TIPS), 17.2 (q, C-1), 11.9 (q, C-1'), 11.2 (q, TIPS);
HRMS (ESI): m/z calc. for $C_{24}H_{38}O_3Si$ $[M+Na]^+$: 425.2488, found: 425.2488.

The analytical data match those reported in the literature.[49]

(3*R*,4*R*,5*R*,6*S*)-6-(Benzyloxy)-4-methyl-1-(tri*iso*propylsilyl)hept-1-yne-3,5-diol (81)

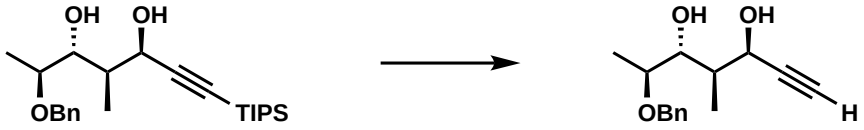


48 **81**

To a solution of hydroxyketone **48** (2.00 g, 4.80 mmol, 1.00 eq.) in MeCN (44 ml) was subsequently added $NaB(OAc)_3H$ (2.03 g, 9.60 mmol, 2.00 eq.) and dry AcOH (0.88 ml, 15.36 mmol, 3.20 eq.) and it was stirred for 4.5 h at rt. The reaction was terminated by addition of a sat. Rochelle's salt solution and it was stirred for another 15 min. The phases were separated and the aqueous phase was extracted with EA, the combined organic phases were washed with a sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded diol **81** (1.86 g, 4.46 mmol, 93 %, 10:1 *dr*) as a colorless oil.
$\mathbf{R_f} = 0.49$ (PE:EA = 5:1);
$[\alpha]^{23}_{\mathbf{D}} = -8.8°$ ($c = 1.00$; $CHCl_3$); lit.:[49] $= -7.6°$;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.38 - 7.28 (m, 5H, Ph), 4.60 - 4.52 (m, 2H, -CH_2Ph), 4.46 (d, $J = 2.6$ Hz, 1H, H-3), 4.23 (dd, $J = 9.5$, 2.9 Hz, 1H, H-5), 3.60 (dq, $J = 6.3$, 3.0 Hz, 1H, H-6), 2.00 - 1.92 (m, 1H, H-4), 1.19 (d, $J = 6.5$ Hz, 3H, H-7), 1.11 - 1.09 (m, 21H, TIPS), 0.90 (d, $J = 7.0$ Hz, 3H, H-1'');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 138.2 (s, Ph), 128.6 (d, Ph), 127.9 (d, Ph), 127.7 (d, Ph), 107.2 (s, C-1), 86.4 (s, C-2), 75.3 (d, C-6), 74.9 (d, C-5), 70.6 (t, -CH_2Ph), 67.9 (d, C-3), 39.6 (d, C-4), 18.8 (d, TIPS), 12.8 (q, C-1''), 12.6 (q, C-7), 11.3 (q, TIPS);
HRMS (ESI): m/z calc. for $C_{24}H_{40}O_3Si$ $[M+Na]^+$: 427.2644, found: 427.2647.

The analytical data match those reported in the literature.[49]

(3*R*,4*R*,5*R*,6*S*)-6-(Benzyloxy)-4-methylhept-1-yne-3,5-diol (264)

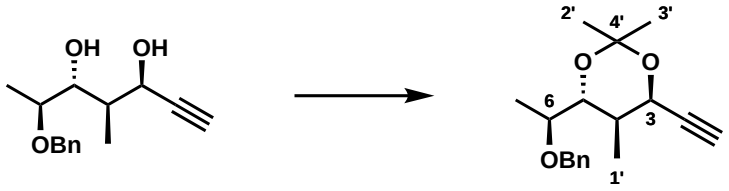


81 **264**

To a solution of hydroxyketone **81** (34.56 g, 85.42 mmol, 1.00 eq.) in THF (300 ml) was added TBAF (1 M in THF, 103 ml, 103.0 mmol, 1.20 eq.) dropwise at 0 °C after which the reaction was warmed to 50 °C overnight. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with a sat. $NaHCO_3$ solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 2:1) yielded the terminal alkyne **264** (18.30 g, 73.46 mmol, 86 %) as a colorless oil.
$\mathbf{R_f} = 0.32$ (PE:EA = 2:1);
$[\alpha]^{23}_{\mathbf{D}} = -7.6°$ ($c = 1.00$; $CHCl_3$); lit.:[49] $= -8.2°$;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 - 7.28 (m, 5H, Ph), 4.62 (d, $J = 11.8$ Hz, 1H, -CH_2Ph), 4.55 (d, $J = 11.8$ Hz, 1H, -CH_2Ph), 4.47 - 4.44 (m, 1H, H-5), 4.14 (dd, $J = 9.6$, 2.9 Hz, 1H, H-3), 3.62 (dq, $J = 3.0$, 6.3 Hz, 1H, H-6), 2.48 (d, $J = 2.2$ Hz, 1H, H-1), 2.00 - 1.92 (m, 1H, H-4), 1.19 (d, $J = 6.4$ Hz, 3H, H-7), 0.89 (d, $J = 7.0$ Hz, 3H, H-1'');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 138.2 (s, Ph), 128.6 (d, Ph), 128.0 (d, Ph), 127.8 (d, Ph), 83.3 (s, C-2), 75.4 (d, C-6), 75.0 (d, C-3), 74.0 (d, C-1), 70.8 (t, -CH_2Ph), 67.2 (d, C-5), 39.3 (d, C-4), 12.6 (q, C-1''), 12.4 (q, C-7);
HRMS (ESI): m/z calc. for $C_{15}H_{20}O_3$ [M+Na]$^+$: 271.1310, found 271.1310.

The analytical data match those reported in the literature.[49]

(4*R*,5*R*,6*R*)-4-((*S*)-1-(benzyloxy)ethyl)-6-ethynyl-2,2,5-trimethyl-1,3-dioxane (82)



264 **82**

To a solution of diol **264** (300 mg, 1.21 mmol, 1.00 eq.) in 2,2-dimethoxypropane (7 ml) was added CSA (28 mg, 0.12 mmol, 0.10 eq.) and the resulting solution was stirred overnight at rt. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1) yielded acetonide **82** (254 mg, 0.88 mmol, 73 %) as a colorless oil.

$\mathbf{R_f} = 0.55$ (PE:EA = 10:1);

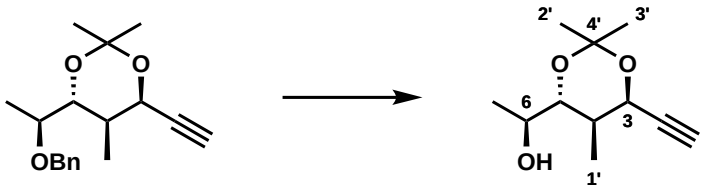
$[\alpha]^{23}_{\mathbf{D}} = -7.5°$ ($c = 1.00$; $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.37 - 7.27 (m, 5H, Ph), 4.68 - 4.52 (m, 3H, H-3, -CH_2Ph), 3.60 - 3.53 (m, 2H, H-5, H-6), 2.51 (d, $J = 2.6$ Hz, 1H, H-1), 2.02 - 1.94 (m, 1H, H-4), 1.48 (s, 3H, H-2'), 1.39 (s, 3H, H-3'), 1.22 (d, $J = 5.9$ Hz, 3H, H-7), 1.07 (d, $J = 7.0$ Hz, 3H, H-1');

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 138.8 (s, Ph), 128.5 (d, Ph), 127.8 (d, Ph), 127.7 (s, Ph), 101.0 (s, C-4'), 81.2 (s, C-2), 76.2 (d, C-5), 75.8 (d, C-6), 75.6 (d, C-1), 71.2 (t, -CH_2Ph), 63.2 (d, C-3), 36.0 (d, C-4), 27.0 (q, C-3'), 23.4 (q, C-2'), 15.5 (q, C-7), 14.1 (q, C-1');

HRMS (ESI): m/z calc. for $C_{18}H_{24}O_3$ $[M+Na]^+$: 311.1623, found 311.1627.

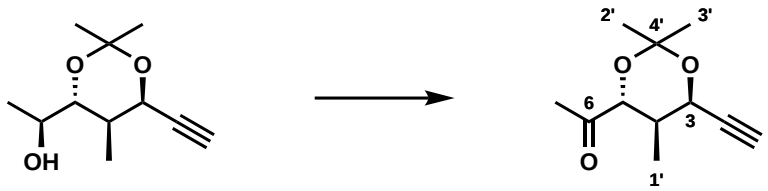
(*S*)-1-((4*R*,5*R*,6*R*)-6-Ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)ethan-1-ol (265)



82 **265**

To a solution of benzyl ether **82** (254 mg, 0.88 mmol, 1.00 eq.) in THF (3 ml) was added lithium naphthalenide (1 M in THF, 8.8 ml, 8.80 mmol, 10.0 eq.) dropwise at 0 °C. The resulting solution was stirred for 30 min and the reaction was terminated by addition of a sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded alcohol **265** (155 mg, 0.78 mmol, 89 %) as a colorless oil.
$\mathbf{R_f} = 0.18$ (PE:EA = 5:1);
$[\alpha]^{29}_{\mathbf{D}} = -11.2°$ ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.62 (dd, $J = 5.2$, 2.6 Hz, 1H, H-3), 3.94 - 3.86 (m, 1H, H-6), 3.64 (dd, $J = 8.7$, 3.1 Hz, 1H, H-5), 2.52 (d, $J = 2.2$ Hz, 1H, H-1), 2.09 (d, $J = 6.4$ Hz, 1H, -O*H*), 2.06 - 1.97 (m, 1H, H-4), 1.53 (s, 3H, H-2'), 1.39 (s, 3H, H-3'), 1.18 (d, $J = 6.6$ Hz, 3H, H-7), 1.04 (d, $J = 7.0$ Hz, 3H, H-1');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 101.0 (s, C-2), 81.1 (s, C-4'), 76.1 (d, C-1), 75.9 (d, C-5), 68.2 (d, C-6), 63.9 (d, C-3), 34.2 (d, C-4), 27.7 (q, C-3'), 23.6 (q, C-2'), 17.0 (q, C-7), 13.6 (q, C-1').

1-((4*R*,5*R*,6*R*)-6-Ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)ethan-1-one (84)



265 **84**

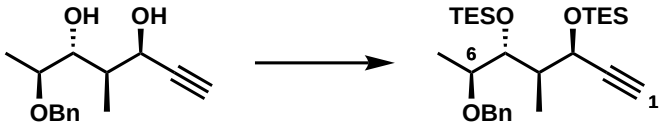
To a solution of alcohol **265** (100 mg, 0.50 mmol, 1.00 eq.) in CH_2Cl_2 (0.5 ml) was added molecular sieves (3 Å, 50 mg), TPAP (18 mg, 0.05 mmol, 0.10 eq.) and NMO (236 mg, 2.02 mmol, 4.00 eq.) and the mixture was stirred for 3 h at rt. After termination of the reaction by addition of a sat. $Na_2S_2O_3$ solution the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded ketone **84** (64 mg, 0.33 mmol, 65 %) as a colorless oil.

$\mathbf{R_f} = 0.55$ (PE:EA = 5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.70 (dd, $J = 5.2,\ 2.2$ Hz, 1H, H-3), 3.98 (d, $J = 9.2$ Hz, 1H, H-5), 2.56 (d, $J = 2.2$ Hz, 1H, H-1), 2.22 (s, 3H, H-7), 2.22 - 2.13 (m, 1H, H-4), 1.57 (s, 3H, H-2'), 1.43 (s, 3H, H-3'), 1.06 (d, $J = 6.6$ Hz, 3H, H-1');

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 207.5 (s, C-6), 101.0 (s, C-2), 80.7 (s, C-4'), 78.7 (d, C-1), 76.7 (d, C-5), 63.8 (d, C-3), 34.7 (d, C-4), 27.6 (q, C-3'), 26.1 (q, C-7), 23.8 (q, C-2'), 13.3 (q, C-1').

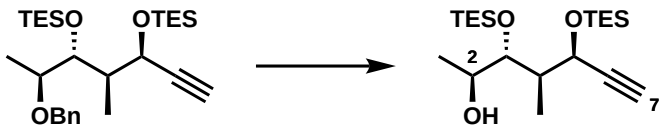
(5*R*,6*R*,7*R*)-5-((*S*)-1-(Benzyloxy)ethyl)-3,3,9,9-tetraethyl-7-ethynyl-6-methyl-4,8-dioxa-3,9-disilaundecane (83)



264 **83**

To a solution of diol **264** (1.00 g, 4.03 mmol, 1.00 eq.) in CH_2Cl_2 (8 ml) was added 2,6-lutidine (1.6 ml, 14.10 mmol, 3.50 eq.) and TESOTf (2.3 ml, 10.09 mmol, 2.50 eq.) dropwise at 0 °C and the resulting mixture was allowed to warm to rt over 3 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution the phases were separated and the aqueous phase was exracted with CH_2Cl_2. The combined organic phases were washed with a sat. $NaHCO_3$ solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded bis-silyl ether **83** (1.92 g, 4.03 mmol, *quant.*) as a colorless oil.
$\mathbf{R_f} = 0.72$ (PE:EA = 5:1);
$[\alpha]^{24}_{\mathbf{D}} = +17.6°$ ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36 - 7.23 (m, 5H, Ph), 4.64 (dd, $J = 5.4,\ 2.2$ Hz, 1H, H-2), 4.59 (d, $J = 12.0$ Hz, 1H, -OCH_2Ph), 4.42 (d, $J = 12.0$ Hz, 1H, -OCH_2Ph), 3.95 (dd, $J = 6.8,\ 4.6$ Hz, 1H, H-5), 3.54 (dq, $J = 4.9,\ 6.0$ Hz, 1H, H-6), 2.40 (d, $J = 2.4$ Hz, 1H, H-1), 1.76 - 1.67 (m, 1H, H-4), 1.16 (d, $J = 6.3$ Hz, 3H, H-1'), 0.99 - 0.91 (m, 21H, H-7, TES), 0.68 - 0.56 (m, 12H, TES);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 139.0 (s, Ph), 128.3 (d, Ph), 127.7 (d, Ph), 127.4 (s, Ph), 86.0 (d, C-1), 75.9 (d, C-6), 74.7 (d, C-5), 73.1 (s, C-2), 70.5 (t, -OCH_2Ph), 63.6 (d, C-3), 46.1 (d, C-4), 14.2 (q, C-1'), 10.5 (q, C-7), 7.2 (q, TES), 7.0 (q, TES), 6.9 (q, TES), 6.6 (t, TES), 5.4 (t, TES), 5.3 (t, TES);
HRMS (ESI): m/z calc. for $C_{27}H_{48}O_3Si_2$ $[M+Na]^+$: 499.3040, found 499.3039.

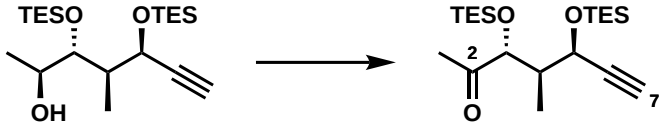
(2*S*,3*R*,4*R*,5*R*)-4-Methyl-3,5-bis((triethylsilyl)oxy)hept-6-yn-2-ol (86)



83 **86**

To a solution of benzyl ether **83** (1880 mg, 4.03 mmol, 1.00 eq.) in THF (5 ml) was added lithium naphthalenide (1 M in THF, 20.1 ml, 20.1 mmol, 5.00 eq.) dropwise at 0 °C. The resulting solution was stirred for 30 min and the reaction was terminated by addition of a sat. NH_4Cl solution. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 30:1 to 20:1) yielded alcohol **86** (500 mg, 1.29 mmol, 33 %) as a colorless oil.
$\mathbf{R_f} = 0.44$ (PE:EA = 10:1);
$[\alpha]^{25}_{\mathbf{D}} = +19.5°$ ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.65 (dd, $J = 4.4$, 2.2 Hz, 1H, H-5), 3.78 (q, $J = 6.1$ Hz, 1H, H-2), 3.68 (t, $J = 5.5$ Hz, 1H, H-3), 2.44 (d, $J = 2.2$ Hz, 1H, H-7), 1.88 - 1.79 (m, 1H, H-4), 1.59 (*brs*, 1H, -O*H*), 1.16 (d, $J = 6.2$ Hz, 3H, H-1), 1.03 (d, $J = 7.0$ Hz, 3H, H-1'), 0.98 (t, $J = 7.9$ Hz, 9H, TES), 0.97 (t, $J = 7.9$ Hz, 9H, TES), 0.74 - 0.60 (m, 12H, TES);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 85.3 (d, C-6), 77.7 (d, C-3), 73.7 (s, C-7), 68.3 (d, C-2), 63.9 (d, C-5), 46.2 (d, C-4), 18.9 (q, C-1), 9.8 (q, C-1'), 7.1 (q, TES), 7.0 (q, TES), 5.4 (t, TES), 5.3 (t, TES);
HRMS (ESI): m/z calc. for $C_{20}H_{42}O_3Si_2$ $[M+Na]^+$: 409.2570, found 409.2567.

(3*R*,4*R*,5*R*)-4-Methyl-3,5-bis((triethylsilyl)oxy)hept-6-yn-2-one (85)



86 **85**

To a solution of alcohol **86** (50 mg, 0.13 mmol, 1.00 eq.) in CH_2Cl_2 (5 ml) was added $NaHCO_3$ (32 mg, 0.39 mmol, 3.00 eq.) and DMP (274 mg, 0.65 mmol, 5.00 eq.) and the resulting suspension was stirred for 2 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution and a sat. $Na_2S_2O_3$ solution, the phases were separated and the aquoeus phase was extracted with EA. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded ketone **85** (42 mg, 0.11 mmol, 84 %) as a colorless oil.

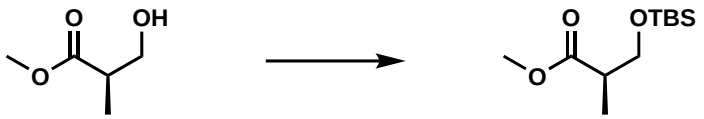
$\mathbf{R_f} = 0.66$ (PE:EA = 20:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.63 (dd, $J = 5.2$, 2.2 Hz, 1H, H-5), 4.07 (d, $J =$ 6.6 Hz, 1H, H-3), 2.45 (d, $J = 1.8$ Hz, 1H, H-7), 2.19 (s, 3H, H-1), 2.00 - 1.91 (m, 1H, H-4), 1.02 - 0.95 (m, 21H, H-1', TES), 0.74 - 0.61 (m, 12H, TES);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 212.1 (s, C-2), 84.9 (s, C-6), 79.6 (d, C-3), 73.7 (d, C-7), 62.3 (d, C-5), 45.6 (d, C-4), 26.1 (q, C-1), 10.4 (q, C-1'), 7.0 (q, TES), 6.9 (q, TES), 5.3 (t, TES), 4.9 (t, TES);

HRMS (ESI): m/z calc. for $C_{20}H_{40}O_3Si_2$ $[M+Na]^+$: 407.2414, found 407.2419.

Methyl (*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (266)



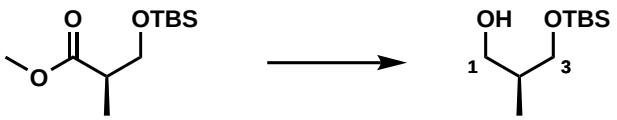
87 **266**

To a solution of TBSCl (5.74 g, 38.10 mmol, 1.50 eq.) and imidazole (2.59 g, 38.10 mmol, 1.50 eq.) in DMF (25 ml) was added (*R*)-Roche ester **87** (2.8 ml, 25.40 mmol, 1.00 eq.) and the resulting mixture was stirred overnight. After dilution with Et_2O (30 ml) and water (30 ml) the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1) yielded silyl ether **266** (5.60 g, 24.13 mmol, 95 %) as a colorless oil.
$\mathbf{R_f} = 0.47$ (PE:EA = 15:1);
$[\alpha]^{24}_{\mathbf{D}} = -20.0°$ ($c = 1.00$; $CHCl_3$); lit.:[187] $= -19.2°$;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.77 (dd, $J = 9.8$, 1 Hz, 6.8H, H_a-3), 3.69 - 3.62 (m, 4H, -OCH_3, H_b-3), 2.70 - 2.60 (m, 1H, H-2), 1.14 (d, $J = 7.0$ Hz, 3H, H-1'), 0.87 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 175.6 (s, C-1), 65.4 (t, C-3), 51.8 (q, -OCH_3), 42.7 (d, C-2), 25.9 (s, TBS), 13.6 (q, C-1'), -5.4 (q, TBS);
HRMS (ESI): m/z calc. for $C_{11}H_{24}O_3Si$ $[M+Na]^+$: 255.1392, found 255.1392.

The analytical data match those reported in the literature.[187]

187 G. E. Keck, R. L. Giles, V. J. Cee, C. A. Wager, T. Yu, M. B. Kraft, *J. Org. Chem.* **2008**, *73*, 9675–9691.

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (88)

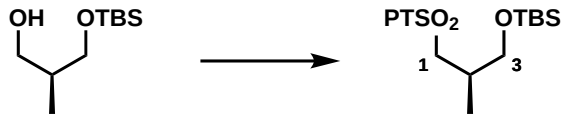


266 **88**

To a solution of methyl ester **266** (5.89 g, 25.40 mmol, 1.00 eq.) in THF (100 ml) was added $BH_3 \cdot THF$ (1 M in THF, 35.6 ml, 35.58 mmol, 1.40 eq.) at 0 °C *via* addition funnel and the resulting solution was stirred overnight at rt. After concentration under reduced pressure, the residue was re-dissolved in Et_2O (50 ml) and washed with water and with brine. It was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude alcohol **88** (5.43 g) as a colorless oil, which was used in the next step without further purification.
$\mathbf{R_f} = 0.34$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.74 (ddd, $J = 9.9,\ 4.4,\ 0.7$ Hz, 1H, H_a-3), 3.68 - 3.58 (m, 2H, H_a-1, H_b-3), 3.54 (dd, $J = 10.0,\ 8.1$ Hz, 1H, H_b-3),2.00 - 1.89 (m, 1H, H-2), 0.90 (s, 9H, TBS), 0.83 (d, $J = 7.0$ Hz, 3H, H-1'), 0.07 (s, 6H, TBS).

The analytical data match those reported in the literature.[49]

(*R*)-5-((3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropyl)thio)-1-phenyl-*1H*-tetrazole (55)



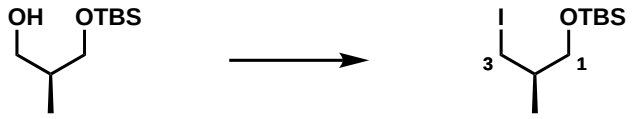
88 **55**

To a solution of crude alcohol **88** (5.43 g, 25.40 mmol, 1.00 eq.), PPh_3 (9.982 g, 38.10 mmol, 1.50 eq.) and PTSH (6.782 g, 38.10 mmol, 1.50 eq.) in THF (100 ml) was added DIAD (7.5 ml, 38.10 mmol, 1.50 eq.) and the resulting solution was stirred overnight at rt. After concentration under reduced pressure, the residue was re-dissolved in EtOH (100 ml) and a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.57 g, 1.27 mmol, 0.05 eq.) in H_2O_2 (30 wt% in H_2O, 31.1 ml, 304.6 mmol, 12.0 eq.) was added *via* pipette. The resulting solution was stirred overnight at rt and then diluted with CH_2Cl_2 (100 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded the sulfone **55** (4.65 g, 11.74 mmol, 46 % over 3 steps) as a colorless oil.
$\mathbf{R_f} = 0.36$ (PE:EA = 10:1);
$[\alpha]^{25}_{\mathbf{D}}$ = -3.9° ($c = 1.01$; $CHCl_3$); lit.:[188] $= -5.5°$;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.67 - 7.57 (m, 5H, Ph), 4.04 (dd, $J = 14.7,\ 4.8$ Hz, 1H, H_a-1), 3.71 (dd, $J = 10.0,\ 4.8$ Hz, 1H, H_b-1), 3.55 (dd, $J = 14.7,\ 7.5$ Hz, 1H, H_a-3), 3.50 (dd, $J = 10.0,\ 5.6$ Hz, 1H, H_b-3), 2.51 - 2.43 (m, 1H, H-2), 1.16 (d, $J = 6.8$ Hz, 3H, H-1'), 0.87 (s, 9H, TBS), 0.05 (s, 6H, TBS, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 154.2 (s, tetrazole), 133.2 (s, Ph), 131.6 (d, Ph), 129.8 (d, Ph), 125.3 (d, Ph), 66.3 (t, C-1), 58.7 (t, C-3), 31.3 (d, C-2), 26.0 (q, TBS), 18.4 (q, C-1'), 16.9 (s, TBS), -5.3 (q, TBS), -5.4 (q, TBS);
HRMS (ESI): m/z calc. for $C_{17}H_{28}N_4O_3SSi$ $[M+Na]^+$: 419.1549, found 419.1546.

The analytical data match those reported in the literature.[188]

188 T. Brandl, R. W. Hoffmann, *Eur. J. Org. Chem.* **2004**, 4373–4378.

(*R*)-*tert*-Butyl(3-iodo-2-methylpropoxy)dimethylsilane (89)

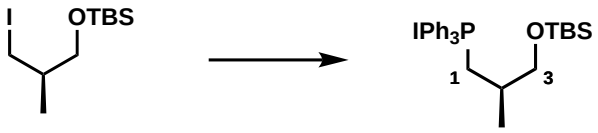


88 **89**

To a solution of iodine (18.48 g, 72.81 mmol, 3.00 eq.), PPh_3 (19.09 g, 72.81 mmol, 3.00 eq.) and imidazole (8.263 g, 121.3 mmol, 5.00 eq.) in CH_2Cl_2 (100 ml) was added crude alcohol **88** (5.43 g, 25.40 mmol, 1.00 eq.) in CH_2Cl_2 (25 ml) at 0 °C and the resulting solution was warmed to rt over 3 h. After termination of the reaction by addition of a sat. $Na_2S_2O_3$ solution and a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated on silica under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded iodide **89** (4.40 g, 14.01 mmol, 58 % over 2 steps) as a colorless oil.
$\mathbf{R_f} = 0.85$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.52 (dd, $J = 9.7,\ 4.8$ Hz, 1H, H_a-1), 3.40 (dd, $J = 9.8,\ 6.8$ Hz, 1H, H_b-1), 3.31 (dd, $J = 9.6,\ 5.1$ Hz, 1H, H_a-3), 3.25 (dd, $J = 9.4,\ 5.7$ Hz, 1H, H_b-3), 1.69 - 1.59 (m, 1H, H-2), 0.95 (d, $J = 6.6$ Hz, 3H, H-1'), 0.90 (s, sH, TBS), 0.06 (s, 6H, TBS).

The analytical data match those reported in the literature.[59]

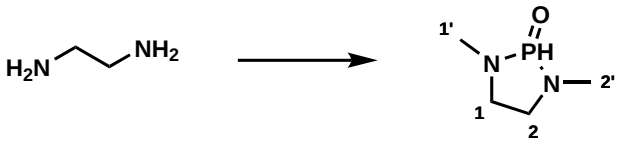
(*R*)-(3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropyl)triphenylphosphonium iodide (90)



89 **90**

A neat mixture of iodide **89** (500 mg, 1.59 mmol, 1.00 eq.) and PPh_3 (417 mg, 1.59 mmol, 1.00 eq.) was stirred at rt overnight. Wittig salt **90** (916 mg, 1.59 mmol, *quant.*) was obtained as a white solid without further workup or purification.
^{1}H-NMR (400 MHz, CD_3OD) δ [ppm] = 7.38 - 7.33 (m, 10H, Ph), 7.30 - 7.24 (m, 5H, Ph), 3.57 (dd, $J = 10.0,\ 5.2$ Hz, 1H, H_a-3), 3.45 (dd, $J = 10.0,\ 6.6$ Hz, 1H, H_b-3), 3.35 - 3.30 (m, 2H, H-1), 1.64 - 1.55 (m, 1H, H-2), 0.96 (d, $J = 6.6$ Hz, 3H, H-1'), 0.93 (s, 9H, TBS), 0.10 (s, 6H, TBS);
HRMS (ESI): m/z calc. for $C_{28}H_{38}OSiP$ $[M]^+$: 449.2430, found 449.2427.

1,3-Dimethyl-1,3,2-diazaphospholidine 2-oxide (91)

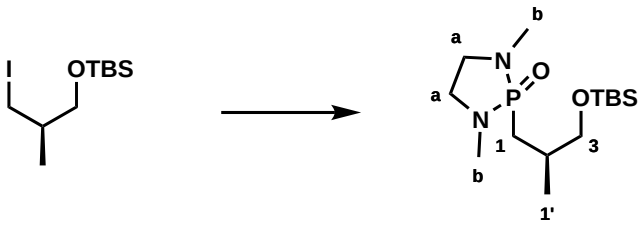


267 **91**

To a solution of *N,N*-dimethylethylenediamine **267** (8.07 ml, 75.00 mmol, 1.00 eq.) and Et_3N (41.7 ml, 300.0 mmol, 4.00 eq.) in toluene/THF (180 ml, 1:1) was added PCl_3 (6.54 ml, 75.00 mmol, 1.00 eq.) dropwise at 0 °C. The resulting solution was warmed to rt over 1 h and then re-cooled to 0 °C. Water (1.35 ml, 75.00 mmol, 1.00 eq.) was added and stirring was continued overnight at rt. Filtration through a small pad of $MgSO_4$ and concentration under reduced pressure yielded an oily residue which was re-dissolved in toluene/THF and filtered through Celite^{TM} after which crude phosphoric acid diamide **91** (4.56 g) was obtained as a yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.21 (d, $J = 603.7$ Hz, 1H, P*H*), 3.34 - 3.25 (m, 2H, H-1), 3.19 - 3.11 (m, 2H, H-2), 2.74 (s, 3H, H-1'), 2.71 (s, 3H, H-2').

The analytical data match those reported in the literature.[59]

(*R*)-2-(3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropyl)-1,3-dimethyl-1,3,2-diazaphospholidine 2-oxide (53)

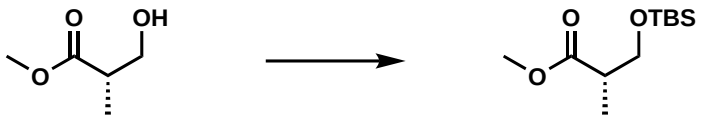


89 **53**

To a solution of iodide **89** (3.070 g, 10.00 mmol, 1.00 eq.) and phosphoric acid diamide **91** (3.14 g, 22.90 mmol, 2.30 eq.) in THF/DMF (50 ml, 4:1) was added NaH (60 % in mineral oil, 800.0 mg, 20.00 mmol, 2.00 eq.) portionwise at 0 °C. After warming to rt overnight, the reaction was terminated by addition of a sat. NH_4Cl solution and the phases were separated. The aqueous phase was extracted with EA and the combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EA to 10 % EtOH in EA) yielded phosphonamide **53** (1.930 g, 6.02 mmol, 60 % over 2 steps) as a colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.43 (ddd, J = 9.2, 6.1, 2.8 Hz, 1H, H_a-1), 3.35 (dd, J = 9.6, 6.6 Hz, 1H, H_a-3), 3.24 - 3.17 (m, 2H, H-a), 3.13 - 3.06 (m, 2H, H-a), 2.67 (d, J = 3.3 Hz, 3H, H-b), 2.65 (d, J = 2.9 Hz, 3H, H-b), 2.17 - 2.07 (m, 1H, H_b-1), 1.84 - 1.73 (m, 1H, H-2), 1.61 - 1.50 (m, 1H, H_b-3), 0.98 (d, J = 6.6 Hz, 3H, H-1'), 0.89 (s, 9H, TBS), 0.04 (s, 6H, TBS);
HRMS (ESI): m/z calc. for $C_{14}H_{33}N_2O_2SiP$ $[M+Na]^+$: 343.1947, found 343.1944.

The analytical data match those reported in the literature.[59]

Methyl (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (268)

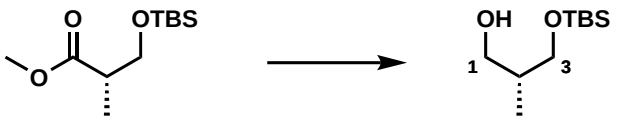


44 **268**

To a solution of TBSCl (1.34 g, 8.90 mmol, 1.05 eq.) and imidazole (0.69 g, 10.17 mmol, 1.20 eq.) in CH_2Cl_2 (8 ml) was added (*S*)-Roche ester **87** (1.00 g, 8.48 mmol, 1.00 eq.) and the resulting mixture was stirred overnight. After dilution with Et_2O (15 ml) and water (15 ml) the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1) yielded silyl ether **268** (1.93 g, 8.30 mmol, 98 %) as a colorless oil.
$\mathbf{R_f}$ = 0.47 (PE:EA = 15:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.77 (dd, J = 9.8, 1 Hz, 6.8H, H_a-3), 3.69 - 3.62 (m, 4H, -OCH_3, H_b-3), 2.70 - 2.60 (m, 1H, H-2), 1.14 (d, J = 7.0 Hz, 3H, H-1'), 0.87 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 175.6 (s, C-1), 65.4 (t, C-3), 51.8 (q, -OCH_3), 42.7 (d, C-2), 25.9 (s, TBS), 13.6 (q, C-1'), -5.4 (q, TBS);
HRMS (ESI): m/z calc. for $C_{11}H_{24}O_3Si$ [M+Na]$^+$: 255.1392, found 255.1392.

The analytical data match those reported for the enantiomer **266** earlier.

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (95)

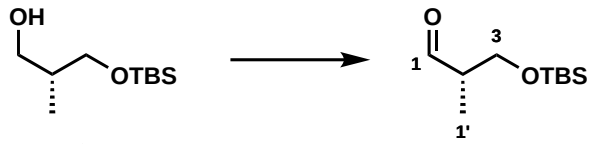


268 **95**

To a solution of methyl ester **268** (1.92 g, 8.29 mmol, 1.00 eq.) in THF (4 ml) was added $BH_3 \cdot THF$ (1 M in THF, 10.8 ml, 10.80 mmol, 1.30 eq.) at 0 °C *via* addition funnel and the resulting solution was stirred overnight at rt. After concentration under reduced pressure, the residue was re-dissolved in Et_2O (25 ml) and washed with water and with brine. It was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded alcohol **95** (0.91 g, 4.47 mmol, 54 %) as a colorless oil.
$\mathbf{R_f} = 0.34$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.74 (ddd, $J = 9.9,\ 4.4,\ 0.7$ Hz, 1H, H_a-3), 3.68 - 3.58 (m, 2H, H_a-1, H_b-3), 3.54 (dd, $J = 10.0,\ 8.1$ Hz, 1H, H_b-3),2.00 - 1.89 (m, 1H, H-2), 0.90 (s, 9H, TBS), 0.83 (d, $J = 7.0$ Hz, 3H, H-1'), 0.07 (s, 6H, TBS).

The analytical data match those reported in the literature.[49]

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal (41)

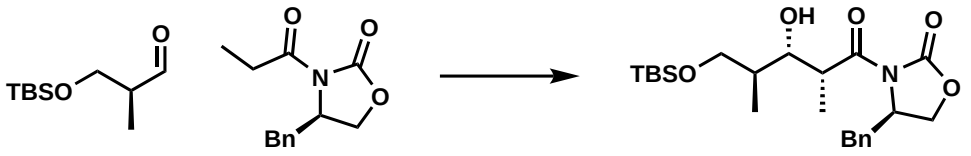


95 **41**

To a solution of oxalyl chloride (1.0 ml, 8.93 mmol, 2.00 eq.) in CH_2Cl_2 (9 ml) was added DMSO (1.3 ml, 17.86 mmol, 4.00 eq.) dropwise at −78 °C. After stirring for 30 min alcohol **95** (0.91 g, 4.47 mmol, 1.00 eq.) dissolved in CH_2Cl_2 (3 ml) was added dropwise and stirring was continued for another 30 min. Et_3N (3.7 ml, 26.80 mmol, 6.00 eq.) was added dropwise and after stirring for 30 min the reaction was allowed to warm to rt over 1 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a sat. NH_4Cl solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude aldehyde **41** (0.83 g, 4.11 mmol, 92 %) as a yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.74 (d, $J = 1.4$ Hz, 1H, H-1), 3.88 - 3.78 (m, 2H, H-3), 2.57 - 2.49 (m, 1H, H-2), 1.09 (d, $J = 7.0$ Hz, 3H, H-1'), 0.87 (s, 9H, TBS), 0.05 (s, 6H, TBS).

The analytical data match those reported in the literature.[49]

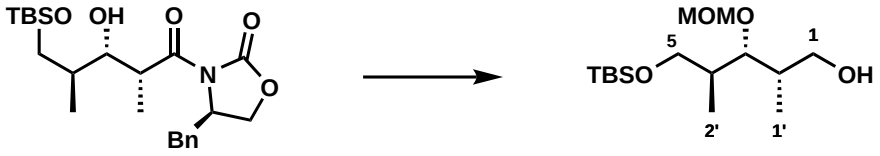
(*R*)-4-Benzyl-3-((2*R*,3*S*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylpentanoyl)oxazolidin-2-one (92)



41 **42** **92**

To a solution of (*S*)-Bn-Evans-auxiliary **42** (447 mg, 1.91 mmol, 1.20 eq.) in CH_2Cl_2 (5 ml) was added subsequently nBu$_2$BOTf (1 M in CH_2Cl_2, 2.1 ml, 2.07 mmol, 1.30 eq.) and Et_3N (0.37 ml, 2.71 mmol, 1.70 eq.) dropwise at −78 °C after which the reaction was warmed to 0 °C and stirred for 1 h. The reaction was cooled back to −78 °C and a solution of aldehyde **41** (307 mg, 1.60 mmol, 1.00 eq.) in CH_2Cl_2 (2 ml) was added dropwise. Stirring was continued for 20 min and the reaction was then warmed to 0 °C and stirred for 1 h. The reaction was terminated by addition of pH= 7 buffer solution, MeOH and H_2O_2 and stirred for 1 h at 0 °C. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 7:1) yielded a mixture of aldol **92** and (*S*)-Bn-Evans-auxiliary **42** (712 mg) as a colorless solid.

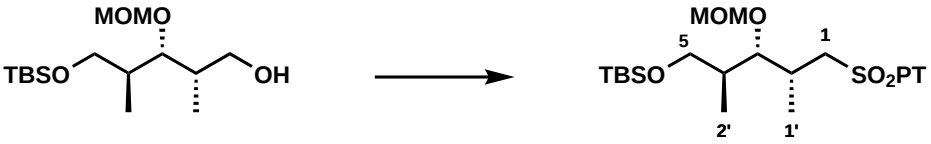
(2*S*,3*R*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-2,4-dimethylpentan-1-ol (96)



92 **96**

To a solution of alcohol **92** (2.00 g, 4.59 mmol, 1.00 eq.) in CH_2Cl_2/DIPEA (20 ml, 1:3) was added MOMCl (1.7 ml, 22.96 mmol, 5.00 eq.) at 0 °C and the reaction was allowed to warm to rt overnight. After termination of the reaction by addition of a sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded methoxymethyl ether **269** (1.80 g, 3.64 mmol, 82 %), which was dissolved in THF/MeOH (21 ml, 20:1). $LiBH_4$ (4 M in THF, 2.82 ml, 11.27 mmol, 3.00 eq.) was added dropwise at 0 °C and stirring was continued at rt overnight. After dilution with EA and termination of the reaction by addition of a sat. Rochelle's salt solution the mixture was stirred for another 2 h. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded alcohol **96** (0.88 g, 2.86 mmol, 76 % over 2 steps) as a colorless oil.
$\mathbf{R_f} = 0.24$ (PE:EA = 5:1).

5-(((2*R*,3*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-2,4-dimethylpentyl)thio)-1-phenyl-*1H*-tetrazole (97)



96 **97**

To a solution of alcohol **96** (200 mg, 0.65 mmol, 1.00 eq.), PPh_3 (256 mg, 0.98 mmol, 1.50 eq.) and PTSH (232 mg, 1.31 mmol, 2.00 eq.) in THF (4 ml) was added DIAD (0.2 ml, 0.98 mmol, 1.50 eq.) and the reaction was stirred at overnight at rt. After concentration on silica under reduced pressure the crude mixture was purified by column chromatography (PE:EA = 10:1) to yield the intermediate thioether (283 mg, 0.61 mmol), which was dissolved in CH_2Cl_2 (15 ml). *m*CPBA (77 %, 523 mg, 3.03 mmol, 5.00 eq.) was added in 3 portions over 2 h and the resulting solution was stirred at rt overnight. After concentration on silica under reduced pressure the crude mixture was purified by column chromatography (PE:EA = 10:1) to yield sulfone **97** (217 mg, 0.44 mmol, 67 % over 2 steps) as a colorless oil.

$\mathbf{R_f} = 0.62$ (PE:EA = 5:1);

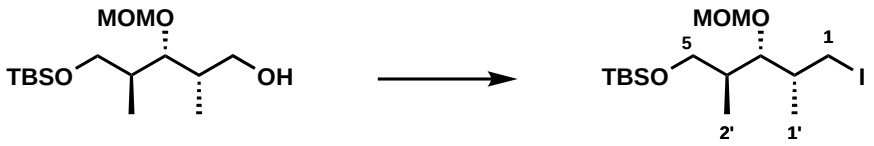
$[\alpha]^{31}_{D} = +33.6°$ ($c = 1.00$; $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.71 - 7.67 (m, 2H, Ph), 7.63 - 7.58 (m, 3H, Ph), 4.71 (d, $J = 6.6$ Hz, 1H, -OCH_2CH$_3$), 4.64 (d, $J = 6.6$ Hz, 1H, -OCH_2CH$_3$), 4.21 (dd, $J =$ 14.8, 5.2 Hz, 1H, H_a-5), 3.74 - 3.61 (m, 3H, H-3, H_b-5, H_a-1), 3.55 (dd, $J = 9.8$, 3.0 Hz, 1H, H_b-1), 3.41 (s, 3H, -OCH$_2$CH_3), 2.62 - 2.53 (m, 1H, H-4), 1.80 - 1.70 (m, 1H, H-2), 1.14 (d, $J = 7.0$ Hz, 3H, H-2'), 0.90 (d, $J = 7.2$ Hz, 3H, H-1'), 0.88 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 154.2 (s, *tetrazole*), 133.3 (s, Ph), 131.5 (d, Ph), 129.8 (d, Ph), 125.3 (d, Ph), 98.7 (t, -OCH$_2$OCH$_3$), 83.8 (d, C-3), 64.4 (t, C-5), 60.5 (t, C-1), 56.0 (-OCH$_2$OCH$_3$), 38.4 (d, C-4), 29.9 (d, C-2), 26.0 (q, TBS), 18.4 (s, TBS), 14.5 (C-1'), 13.7 (q, C-2'), -5.3 (q, TBS), -5.4 (q, TBS);

HRMS (ESI): m/z calc. for $C_{22}H_{38}N_4O_5Si$ $[M+Na]^+$: 521.2230, found 521,2231.

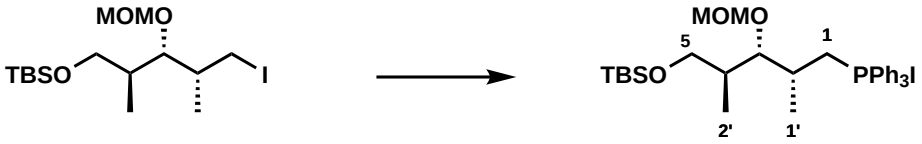
(5*S*,6*S*)-5-((*R*)-1-Iodopropan-2-yl)-6,9,9,10,10-pentamethyl-2,4,8-trioxa-9-silaundecane (98)



96 **98**

To a solution of PPh_3 (2261 mg, 8.62 mmol, 3.00 eq.), iodine (2139 mg, 8.62 mmol, 3.00 eq.) and imidazole (978 mg, 14.37 mmol, 5.00 eq.) in CH_2Cl_2 (25 ml) was added a solution of alcohol **96** (881 mg, 2.86 mmol, 1.00 eq.) in CH_2Cl_2 (10 ml) at 0 °C and stirring was continued at rt overnight. After dilution with Et_2O and termination of the reaction by addition of a sat. $NaHCO_3$ solution and a sat. $Na_2S_2O_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated on silica under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded iodide **98** (1054 mg, 2.53 mmol, 88 %) as a colorless oil.
$\mathbf{R_f} = 0.67$ (PE:EA = 5:1);
$[\alpha]^{30}_{\mathbf{D}} = +39.3°$ ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 4.69 (d, $J = 6.5$ Hz, 1H, -CH_2OCH$_3$), 4.66 (d, $J = 6.5$ Hz, 1H, -CH_2OCH$_3$), 3.64 (dd, $J = 9.8$, 4.7 Hz, 1H, H_a-5), 3.60 (dd, $J = 9.8$, 3.6 Hz, 1H, H_b-5), 3.55 (dd, $J = 8.6$, 2.4 Hz, 1H, H-3), 3.38 (s, 3H, -OCH$_2$OCH_3), 3.35 (dd, $J = 9.6$, 7.0 Hz, 1H, H_a-1), 3.2 (dd, $J = 9.6$, 6.7 Hz, 1H, H_b-1), 2.00 - 1.92 (m, 1H, H-2), 1.82 - 1.73 (m, 1H, H-4), 1.01 (d, $J = 7.4$ Hz, 3H, H-1'), 0.90 - 0.88 (m, 12H, H-2', TBS), 0.04 (s, 6H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 99.0 (t, -OCH$_2$CH$_3$), 83.4 (d, C-3), 64.7 (t, C-5), 56.1 (q, -OCH$_2$CH$_3$), 38.8 (d, C-2), 38.4 (d, C-4), 26.1 (q, TBS), 18.4 (s, TBS), 14.6 (q, C-1'), 14.5 (q, C-2'), 14.2 (t, C-1), -5.3 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{15}H_{33}IO_3Si$ [M+Na]$^+$: 439.1141, found 439.1143.

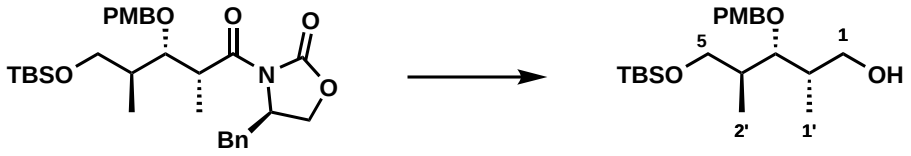
((2*R*,3*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-2,4-dimethylpentyl)-iodotriphenyl-γ^5-phosphane (99)



98 **99**

A solution of iodide **98** (100 mg, 0.24 mmol, 1.00 eq.) and PPh_3 (63 mg, 0.24 mmol, 1.00 eq.) in THF (1.5 ml) was stirred at rt overnight. Concentration under reduced pressure yielded crude Wittig salt **99** (163 mg, 0.24 mmol, *quant.*) as a colorless solid.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 - 7.30 (m, 15H, Ph), 4.72 (d, $J = 6.3$ Hz, 1H, -OCH_2OCH$_3$), 4.69 (d, $J = 6.3$ Hz, 1H, -OCH_2OCH$_3$), 3.69 - 3.56 (m, 3H, H-5, H-3), 3.41 (s, 3H, -OCH$_2$OCH_3), 3.38 (dd, $J = 9.6$, 7.4 Hz, 1H, H$_a$-1), 3.23 (dd, $J = 9.6$, 7.0 Hz, 1H, H$_b$-1), 2.02 - 1.95 (m, 1H, H-2), 1.84 - 1.76 (m, 1H, H-4), 1.04 (d, $J = 6.6$ Hz, 3H, H-1'), 0.93 - 0.91 (m, 12H, H-2', TBS), 0.07 (s, 6H, TBS).

(2*S*,3*R*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol (43)



101 **43**

To a solution of oxazolidinone **101**[1] (2.240 g, 4.03 mmol, 1.00 eq.) in THF/MeOH (21 ml, 20:1) was added dropwise $LiBH_4$ (4 M in THF, 4.2 ml, 8.46 mmol, 2.10 eq.) at 0 °C. After stirring for 3 h at that temperature the reaction was diluted with EA and terminated by addition of a sat. Rochelle's salt solution and the mixture was stirred for another 2 h. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded alcohol **43** (1.162 g, 3.04 mmol, 75 %) as a colorless oil.

$\mathbf{R_f} = 0.19$ (PE:EA = 5:1);

$[\alpha]^{24}_{D} = -2.8°$ ($c = 1.00$; $CHCl_3$), lit.: $[\alpha]^{24}_{D} = -3.4°$ ($c = 1.00$; $CHCl_3$)[49];

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.28 - 7.24 (m, 2H, Ph), 6.89 - 6.85 (m, 2H, Ph), 4.58 (d, $J = 10.9$ Hz, 1H, -OCH_2Ph), 4.49 (d, $J = 11.0$ Hz, 1H, -OCH_2Ph), 3.80 (s, 3H, -OCH_3), 3.74 (dd, $J = 10.1$, 5.0 Hz, 1H, H_a-5), 3.65 (dd, $J = 9.7$, 3.8 Hz, 1H, H_b-5), 3.59 - 3.53 (m, 3H, H-1, H-3), 1.95 - 1.85 (m, 2H, H-2, H-4), 1.77 (*brs*, 1H, -O*H*), 0.93 - 0.89 (m, 15H, H-1', H-2', TBS), 0.06 (s, 3H, TBS);

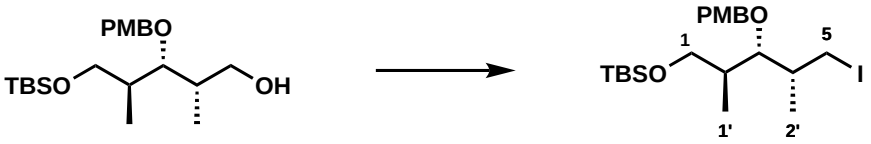
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 159.3 (s, Ph), 131.3 (s, Ph), 129.5 (d, Ph), 113.9 (d, Ph), 80.7 (d, C-3), 74.0 (t, -OCH_2OCH_3), 66.7 (d, C-1), 65.1 (C-5), 55.4 (q, -OCH_2CH_3), 38.5 (d, C-2), 37.4 (d, C-4), 26.1 (q, TBS), 18.5 (s, TBS), 14.6 (q, C-1'), 10.7 (q, C-2'), -5.2 (q, TBS), -5.3 (q, TBS);

HRMS (ESI): m/z calc. for $C_{21}H_{38}O_4Si$ $[M+Na]^+$: 405.2437, found 405.2444.

The analytical data match those reported in the literature.[49]

1 The starting material **101** was provided by Geist.[49]

tert-Butyl(((2*S*,3*S*,4*R*)-5-iodo-3-((4-methoxybenzyl)oxy)-2,4-dimethylpentyl)oxy)dimethylsilane (102)

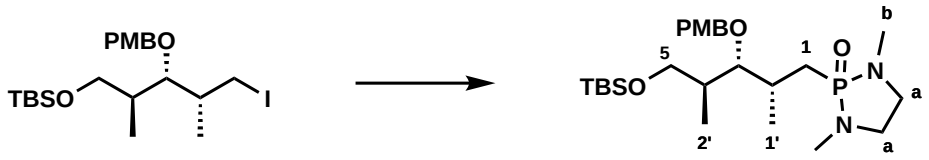


43 **102**

To a solution of PPh_3 (2.167 g, 8.27 mmol, 3.00 eq.), iodine (2.097 g, 8.62 mmol, 3.00 eq.) and imidazole (0.938 mg, 13.78 mmol, 5.00 eq.) in CH_2Cl_2 (25 ml) was added a solution of alcohol **43** (1.054 mg, 2.76 mmol, 1.00 eq.) in CH_2Cl_2 (10 ml) at 0 °C and stirring was continued at rt overnight. After dilution with Et_2O and termination of the reaction by addition of a sat. $NaHCO_3$ solution and a sat. $Na_2S_2O_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated on silica under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded iodide **102** (1.187 mg, 2.40 mmol, 87 %) as a colorless oil.
$\mathbf{R_f} = 0.81$ (PE:EA = 5:1);
$[\alpha]^{30}_{\mathbf{D}} = +25.9°$ ($c = 1.00$; $CDCl_3$), $[\alpha]^{24}_{\mathbf{D}} = +24.3°$ ($c = 1.00$; $CDCl_3$)[49];
^{1}H-NMR (400 MHz, $CHCl_3$) δ [ppm] = 7.37 - 7.22 (m, 2H, Ph), 6.90 - 6.85 (m, 2H, Ph), 4.62 (d, $J = 11.7$ Hz, 1H, -OCH_2Ph), 4.54 (d, $J = 11.3$ Hz, 1H, -OCH_2Ph), 3.81 (s, 3H, -OCH_3), 3.73 (dd, $J = 9.8,\ 5.0$ Hz, 1H, H_a-1), 3.66 - 3.62 (m, 1H, H_b-1), 3.56 (dd, $J = 8.9,\ 2.8$ Hz, 1H, H-3), 3.30 - 3.18 (m, 2H, H-5), 2.02 - 1.92 (m, 1H, H-4), 1.86 - 1.76 (m, 1H, H-2), 1.01 (d, $J = 6.9$ Hz, 3H, H-2'), 0.92 (s, 9H, TBS), 0.90 (d, $J = 7.5$ Hz, 3H, H-1'), 0.06 (s, 6H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 159.2 (s, Ph), 131.4 (s, Ph), 129.2 (d, Ph), 113.9 (d, Ph), 82.1 (d, C-3), 75.0 (t, -OCH_2Ph), 64.8 (t, C-1), 55.4 (q, -OCH_3), 39.1 (d, C-2), 39.0 (d, C-4), 26.1 (q, TBS), 18.4 (s, TBS), 14.7 (q, C-1'), 14.5 (q, C-2'), 14.3 (t, C-5), -5.2 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{21}H_{37}O_3ISi$ $[M+Na]^+$: 515.1454, found 515.1454.

The analytical data match those reported in the literature.[49]

2-((2*R*,3*S*,4*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethylpentyl)-1,3-dimethyl-1,3,2-diazaphospholidine 2-oxide (100)

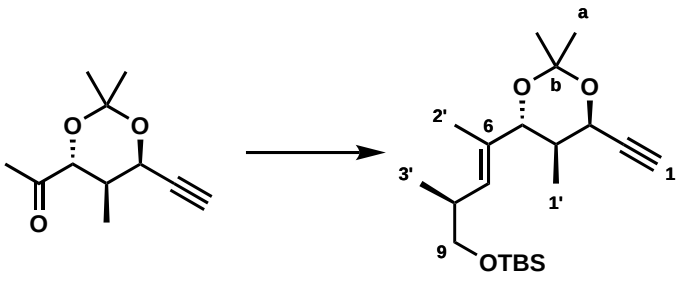


102 **100**

To a solution of iodide **102** (200 mg, 0.41 mmol, 1.00 eq.) and phosphoric acid diamide **91** (109 mg, 0.81 mmol, 2.00 eq.) in THF (2.8 ml) was added LiHMDS (1 M in THF, 0.8 ml, 0.81 mmol, 2.00 eq.) dropwise at −78 °C and it was stirred for 30 min after which the reaction was warmed to rt and stirring was continued overnight. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EA to 10 % EtOH in EA) yielded phosphonamide **100** (37 mg, 74 µmol, 18 %, 55 % *brsm*) as a colorless oil.
$[\alpha]^{30}_{D}$ = -3.5° (c = 1.00; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.28 - 7.22 (m, 2H, Ph), 6.89 - 6.84 (m, 2H, Ph), 4.59 (d, J = 11.1 Hz, 1H, -OCH_2Ph), 4.52 (d, J = 10.7 Hz, 1H, -OCH_2Ph), 3.79 (s, 3H, -OCH_3), 3.76 (dd, J = 10.3, 5.2 Hz, 1H, H_a-5), 3.61 (dd, J = 9.6, 3.0 Hz, 1H, H_b-1), 3.34 (dd, J = 9.0, 2.0 Hz, 1H, H-3), 3.23 - 3.01 (m, 4H, H-a), 2.65 (d, J = 1.8 Hz, 3H, H-b), 2.63 (d, J = 1.5 Hz, 3H, H-b), 2.03 - 1.72 (m, 5H, H-5, H-2, H-4), 0.99 (d, J = 6.6 Hz, 3H, H-1'), 0.93 - 0.87 (m, 12H, H-2', TBS), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 159.2 (s, Ph), 131.4 (s, Ph), 129.2 (d, Ph), 113.9 (d, Ph), 84.0 (d, J = 11.0 Hz, C-3), 74.8 (t, -OCH_2Ph), 65.0 (t, C-1), 55.4 (q, -OCH_3), 48.5 (d, J = 7.5 Hz, C-a), 48.3 (d, J = 8.0 Hz, C-a), 38.8 (d, C-4), 32.4 (d, J = 115.6 Hz, C-1), 32.3 (d, J = 5.0 Hz, C-b), 32.2 (d, J = 5.1 Hz, C-b), 30.7 (d, J = 3.8 Hz, C-2), 26.1 (q, TBS), 18.5 (s, TBS), 15.0 (q, C-2'), 14.8 (d, J = 6.4 Hz, C-1'), -5.2 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{25}H_{47}N_2O_4PSi$ $[M+Na]^+$: 521.2940, found 521.2945.

The analytical data match those reported in the literature.[49]

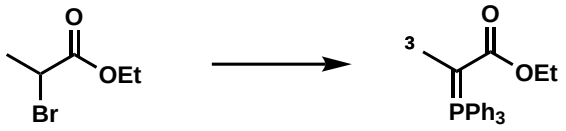
***tert*-Butyl(((*S*,*E*)-4-((4*R*,5*R*,6*R*)-6-ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylpent-3-en-1-yl)oxy)dimethylsilane (103)**



84 **103**

To a solution of phosphonamide **53** (30 mg, 92 µmol, 2.00 eq.) in THF (1 ml) was added *n*BuLi (54 µL, 87 µmol, 1.90 eq.) dropwise at −78 °C and the resulting mixture was stirred for 1 h. A solution of ketone **84** (9 mg, 46 µmol, 1.00 eq.) in THF (0.5 ml) was added dropwise and the reaction was stirred for 1 h at −78 °C after which it was allowed to warm to rt over 1 h. AcOH (0.1 ml) was added and stirring was continued for 5 min. After termination of the reaction by addition of a sat. $NaHCO_3$ solution the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded alkene **103** (3 mg, 8 µmol, 18 %) as a colorless oil.
$\mathbf{R_f} = 0.55$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.24 (dd, J = 9.2, 1.1 Hz, 1H, H-7), 4.71 (dd, J = 5.7, 2.4 Hz, 1H, H-3), 4.02 (d, J = 10.0 Hz, 1H, H-5), 3.45 - 3.34 (m, 2H, H-9), 2.65 - 2.56 (m, 1H, H-8), 2.53 (d, J = 2.6 Hz, 1H, H-1), 2.08 - 2.00 (m, 1H, H-4), 1.66 (d, J = 1.1 Hz, 3H, H-2'), 1.65 (s, 3H, H-a), 1.40 (s, 3H, H-a), 0.98 (d, J = 6.6 Hz, 3H, H-3'), 0.89 (s, 9H, TBS), 0.84 (d, J = 7.0 Hz, 3H, H-1'), 0.03 (s, 3H, TBS), 0.03 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 133.0 (s, C-6), 132.9 (d, C-7), 100.3 (s, C-b), 82.0 (s, C-2), 78.9 (d, C-5), 76.1 (d, C-1), 67.8 (t, C-9), 65.1 (d, C-3), 35.2 (d, C-8), 34.4 (d, C-4), 29.3 (q, C-a), 25.9 (q, TBS), 23.5 (q, C-a), 18.3 (s, TBS), 17.0 (q, C-3'), 13.2 (q, C-1'), 11.5 (q, C-2'), -5.3 (q, TBS), -5.4 (q, TBS);
HRMS (ESI): m/z calc. for $C_{21}H_{38}O_3Si$ $[M+Na]^+$: 389.2488, found 389.2484.

Ethyl 2-(triphenyl-γ^5-phosphaneylidene)propanoate (108)



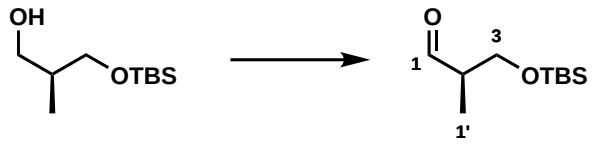
110 **108**

A mixture of bromide **110** (8.34 g, 46.10 mmol, 1.50 eq.) and PPh_3 (8.04 g, 30.70 mmol, 1.00 eq.) was stirred overnight at 50 °C. After cooling to rt, PE (30 ml) was added, the solid was crushed, filtered and washed with PE. After dissolving the salt in CH_2Cl_2 (15 ml) a solution of NaOH (2.51 g, 62.90 mmol, 2.05 eq.) in water (25 ml) was added dropwise at 0 °C. After warming to rt over 30 min the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine (5x), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude Wittig reagent **108** (10.50 g, 28.86 mmol, 94 %) as a yellow solid, which was used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.69 - 7.40 (m, 15H, Ph), 4.06 (q, $J = 7.3$ Hz, 2H, -OCH_2CH$_{3,\,minor}$), 3.71 (q, $J = 7.1$ Hz, 2H, -OCH_2CH$_{3,\,major}$), 1.62 (d, $J = 13.6$ Hz, 3H, H-3$_{major}$), 1.60 (d, $J = 14.3$ Hz, 3H, H-3$_{minor}$), 1.25 (t, $J = 7.0$ Hz, 3H, -OCH$_2$C$H_{3,\,minor}$), 0.46 (t, $J = 7.1$ Hz, 3H, -OCH$_2$C$H_{3,\,major}$).

The analytical data match those reported in the literature.[68]

(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal (109)

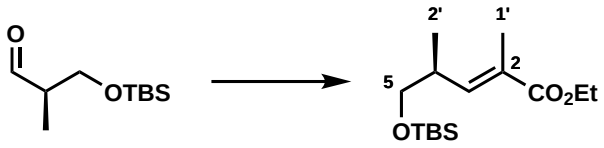


88 **109**

To a solution of oxalyl chloride (7.3 ml, 84.75 mmol, 2.00 eq.) in CH_2Cl_2 (84 ml) was added DMSO (12.0 ml, 169.5 mmol, 4.00 eq.) dropwise at −78 °C. After stirring for 30 min crude alcohol **88** (8.64 g, 42.37 mmol, 1.00 eq.) dissolved in CH_2Cl_2 (20 ml) was added dropwise and stirring was continued for another 30 min. Et_3N (35.4 ml, 254.2 mmol, 6.00 eq.) was added dropwise and after stirring for 30 min the reaction was allowed to warm to rt over 1 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a sat. NH_4Cl solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude aldehyde **109** (8.56 g) as a yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.74 (d, $J = 1.4$ Hz, 1H, H-1), 3.88 - 3.78 (m, 2H, H-3), 2.57 - 2.49 (m, 1H, H-2), 1.09 (d, $J = 7.0$ Hz, 3H, H-1'), 0.87 (s, 9H, TBS), 0.05 (s, 6H, TBS).

The analytical data match those reported in the literature.[66,67]

Ethyl (*S,E*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpent-2-enoate (111)

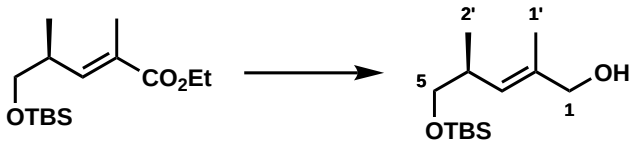


109 **111**

To a solution of aldehyde **109** (8.56 g, 42.37 mmol, 1.00 eq.) in CH_2Cl_2 (53 ml) was added phosphorane **108** (23.00 g, 63.56 mmol, 1.50 eq.) and the resulting solution was stirred at rt for 2 d. After concentration on silica, purification by column chromatography (PE:EA = 10:1) yielded alkene **111** (8.18 g, 28.81 mmol, 68 % over 4 steps) as a colorless oil.
$\mathbf{R_f} = 0.64$ (PE:EA = 10:1);
$[\alpha]^{29}_{\mathbf{D}}$ = -4.5° ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.55 (dd, J = 10.0, 1.5 Hz, 1H, H-3), 4.23 - 4.13 (m, 2H, -OCH_2CH$_3$), 3.49 (dd, J = 6.3, 0.7 Hz, 2H, H-5), 2.74 - 2.64 (m, 1H, H-4), 1.85 (d, J = 1.1 Hz, 3H, H-1'), 1.28 (t, J = 7.2 Hz, 3H, -OCH$_2$CH_3), 1.00 (d, J = 6.6 Hz, 3H, H-2'), 0.88 (s, 9H, TBS), 0.03 (s, 3H, TBS), 0.02 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 168.4 (s, C-1), 144.7 (d, C-3), 128.1 (s, C-2), 67.2 (t, C-5), 60.5 (t, -OCH$_2$CH$_3$), 36.4 (d, C-4), 26.0 (q, TBS), 18.4 (s, TBS), 16.4 (q, C-2'), 14.4 (q, -OCH$_2$CH$_3$), 12.8 (q, C-1'), -5.2 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{15}H_{30}O_3Si$ [M+Na]$^+$: 309.1864, found 309.1862.

The analytical data match those reported in the literature.[66,67]

(*S*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpent-2-en-1-ol (112)



111 **112**

To a solution of ester **111** (236 mg, 0.82 mmol, 1.00 eq.) in CH_2Cl_2 (10 ml) was added DIBAl-H (1 M in hexane, 2.8 ml, 2.80 mmol, 3.50 eq.) dropwise at −78 °C and the reaction was stirred for 30 min. After termination of the reaction by addition of MeOH, the mixture was diluted with EA and a sat. Rochelle's salt solution was added. After stirring for another 2 h, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded allyl alcohol **112** (185 mg, 0.66 mmol, 80 %) as a colorless oil.

$\mathbf{R_f} = 0$. (PE:EA = 10:1);

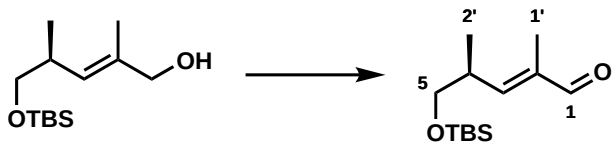
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.19 (dd, $J = 9.2,\ 1.1$ Hz, 1H, H-3), 4.00 (d, $J =$ 5.9 Hz, 2H, H-1), 3.45 (dd, $J = 9.8,\ 6.1$ Hz, 1H, H_a-5), 3.37 (dd, $J = 9.8,\ 7.2$ Hz, 1H, H_b-5), 2.64 - 2.53 (m, 1H, H-4), 1.69 (d, $J = 1.1$ Hz, 3H, H-1'), 1.28 (t, $J = 6.1$ Hz, 1H, -O*H*), 0.96 (d, $J = 6.6$ Hz, 3H, H-2'), 0.89 (s, 9H, TBS), 0.04 (s, 6H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 135.3 (s, C-2), 129.1 (d, C-3), 69.1 (t, C-1), 68.0 (t, C-5), 35.3 (d, C-4), 26.1 (q, TBS), 17.3 (q, C-2'), 14.1 (q, C-1'), -5.2 (q, TBS), -5.2 (q, TBS);

HRMS (ESI): m/z calc. for $C_{13}H_{28}O_2Si$ $[M+Na]^+$: 267.1756, found 267.1756.

The analytical data match those reported in the literature.[66,67]

(*S*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpent-2-enal (113)

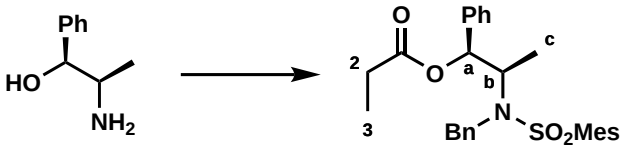


112 **113**

To a solution of oxalyl chloride (3.9 ml, 45.57 mmol, 2.00 eq.) in CH_2Cl_2 (44 ml) was added DMSO (6.4 ml, 91.15 mmol, 4.00 eq.) dropwise at −78 °C. After stirring for 30 min allyl alcohol **112** (5.56 g, 22.79 mmol, 1.00 eq.) dissolved in CH_2Cl_2 (20 ml) was added dropwise and stirring was continued for another 30 min. Et_3N (19.0 ml, 136.7 mmol, 6.00 eq.) was added dropwise and after stirring for 30 min the reaction was allowed to warm to rt over 1 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a sat. NH_4Cl solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded aldehyde **113** (5.32 g, 22.10 mmol, 97 %) as a colorless oil.
$\mathbf{R_f} = 0.59$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.40 (s, 1H, H-1), 6.32 (dd, $J = 9.6$, 1.5 Hz, 1H, H-3), 3.59 (dd, $J = 10.0$, 5.9 Hz, 1H, H_a-5), 3.54 (dd, $J = 9.8$, 6.5 Hz, 1H, H_b-5), 2.95 - 2.84 (m, 1H, H-4), 1.77 (d, $J = 1.1$ Hz, 3H, H-1'), 1.06 (d, $J = 6.6$ Hz, 3H, H-2'), 0.88 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 195.7 (d, C-1), 157.4 (d, C-3), 139.4 (s, C-2), 67.0 (t, C-5), 36.6 (d, C-4), 26.0 (q, TBS), 18.4 (s, TBS), 16.2 (q, C-2'), 9.6 (q, C-1'), -5.3 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{13}H_{26}O_2Si$ $[M+Na]^+$: 262.1600, found 262.1602.

The analytical data match those reported in the literature.[66]

(1*S*,2*R*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl propionate (114)



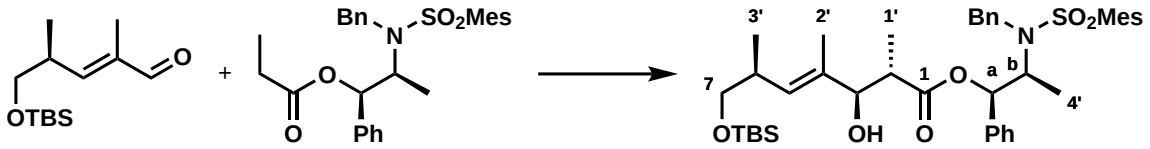
115 **114**

Auxiliary **114** was synthesized in three steps from commercially available (1*S*,2*R*)-norephedrine following a protocol by Abiko and co-workers.[65]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.38 - 7.19 (m, 8H, Ph), 6.98 - 6.88 (m, 4H, Ph), 5.86 (d, J = 3.7 Hz, 1H, H-a), 4.74 (d, J = 16.6 Hz, 1H, -CH_2Ph), 4.63 (d, J = 16.6 Hz, 1H, -CH_2Ph), 4.10 - 4.03 (m, 2H, H-2), 2.54 (s, 6H, *Mes*), 2.30 (s, 3H, *Mes*), 2.24 - 2.10 (m, 1H, H-b), 1.14 (d, J = 7.0 Hz, 3H, H-c), 1.04 (t, J = 7.6 Hz, 3H, H-3).

The analytical data match those reported in the literature.[65]

(1*R*,2*S*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl))-1-phenylpropyl (2*S*,3*R*,6*S*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4,6-trimethylhept-4-enoate (116)



113 **114** **116**

To a solution of (1*R*,2*S*)-auxiliary **114**[65] (5.00 g, 10.44 mmol, 1.00 eq.) in CH_2Cl_2 (50 ml) was added Et_3N (3.5 ml, 25.05 mmol, 2.40 eq.) and the solution was cooled to −78 °C. After addition of Cy_2BOTf (23.0 ml, 23.00 mmol, 2.20 eq.)[69] over 30 min the reaction was stirred for another 30 min. A solution of aldehyde **113** (3.03 g, 12.53 mmol, 1.20 eq.) in CH_2Cl_2 (10 ml) was added dropwise and stirring was continued for 30 min. After termination of the reaction by addition of a pH= 7 phosphate buffer, MeOH and H_2O_2 the reaction was stirred overnight at rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2, the combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded aldol product **116** (6.43 g, 8.91 mmol, 85 %) as a colorless foam.

$\mathbf{R_f} = 0.12$ (PE:EA = 10:1);

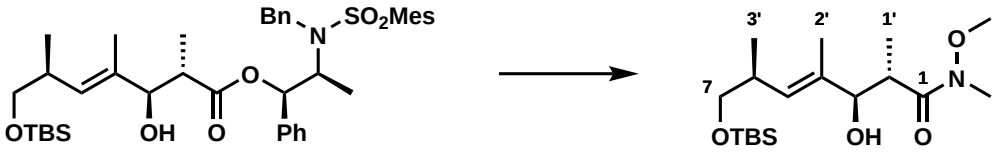
$[\alpha]^{29}_{\mathbf{D}} = -27.0°$ ($c = 1.00$; $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.38 - 7.33 (m, 2H, Ph), 7.28 - 7.15 (m, 4H, Ph), 6.92 - 6.81 (m, 4H, Ph), 5.81 (d, $J = 4.0$ Hz, 1H, H-a), 5.19 (dd, $J = 8.8$, 1.1 Hz, 1H, H-5), 4.83 (d, $J = 17.3$ Hz, 1H, -CH_2Ph), 4.63 (d, $J = 16.6$ Hz, 1H, -CH_2Ph), 4.09 - 4.03 (m, 2H, H-3, H-b), 3.39 (d, $J = 7.4$ Hz, 2H, H-7), 2.64 - 2.54 (m, 2H, H-2, H-6), 2.52 (s, 6H, *Mes*), 2.36 (d, $J = 3.3$ Hz, 1H, -O*H*), 2.29 (s, 3H, *Mes*), 1.64 (d, $J = 1.1$ Hz, 3H, H-2'), 1.15 (d, $J = 7.0$ Hz, 3H, H-4'), 0.94 (d, $J = 6.6$ Hz, 3H, H-1'), 0.94 (d, $J = 7.4$ Hz, 3H, H-3'), 0.88 (s, 9H, TBS), 0.02 (s, 3H, TBS), 0.01 (s, 3H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 174.9 (s, C-1), 142.7 (s, Ph), 140.4 (s, Ph), 139.0 (s, Ph), 138.5 (s, Ph), 134.1 (s, Ph), 133.7 (d, C-5), 133.7 (d, Ph), 132.3 (d, Ph), 128.5 (d, Ph), 128.4 (s, Ph), 128.0 (s, Ph), 127.7 (d, Ph), 127.2 (s, C-4), 125.9 (d, Ph), 80.5 (d, C-3), 78.4 (d, C-a), 67.9 (t, C-7), 57.0 (d, C-b), 48.4 (t, -CH_2Ph), 43.4 (d, C-2), 35.4 (d, C-6), 26.0 (q, TBS), 23.1 (q, *Mes*), 21.0 (q, *Mes*), 18.4 (s, TBS), 17.1 (q, H-3'), 14.4 (q, H-2'), 13.4 (q, H-4'), 10.8 (q,

H-1′), -5.2 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{41}H_{59}NO_6SSi$ [M+Na]$^+$: 744.3730, found 744.3734.

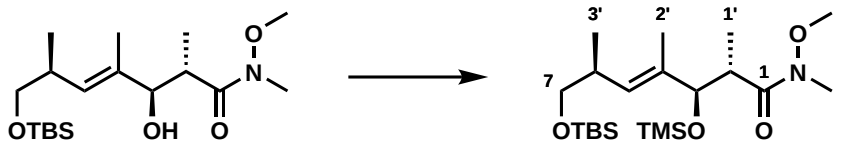
(2*S*,3*R*,6*S*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-*N*-methoxy-*N*,2,4,6-tetramethylhept-4-enamide (117)



116 **117**

To a solution of ester **116** (200 mg, 0.28 mmol, 1.00 eq.) in THF (0.9 ml) was added *i*PrMgCl (2 M in THF, 140 µL, 0.28 mmol, 1.00 eq.) dropwise at −20 °C. Meanwhile, a suspension of *N*,*O*-dimethylhydroxylaminmagnesium chloride was prepared by addition of *i*PrMgCl (2 M in THF, 2.8 ml, 5.54 mmol, 20.00 eq.) to a solution of *N*,*O*-dimethylhydroxylamine (268 mg, 2.78 mmol, 10.00 eq.) in THF (2.8 ml). After the substrate solution was stirred for 10 min, the suspension of the grignard reagent was added dropwise and stirring was continued for 2 h at −20 °C and afterwards for 1 h at −10 °C. The reaction was terminated by addition of a sat. NH_4Cl solution, the phases were separated. The aqueous phase was extracted with EA, the combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 2:1) yielded Weinreb amide **117** (45 mg, 0.13 mmol, 45 %) as a colorless foam.
$\mathbf{R_f} = 0.20$ (PE:EA = 2:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.22 (d, $J = 9.6$ Hz, 1H, H-5), 4.11 (dd, $J = 7.7$, 4.8 Hz, 1H, H-3), 3.73 (s, 3H, -OCH_3), 3.43 (dd, $J = 9.9$, 6.3 Hz, 1H, H_a-7), 3.43 (dd, $J = 9.9$, 6.3 Hz, 1H, H_b-7), 3.20 (s, 3H, -NCH_3), 3.17 - 3.06 (m, 1H, H-2), 2.81 (d, $J = 4.8$ Hz, 1H, -O*H*), 2.63 - 2.52 (m, 1H, H-6), 1.65 (d, $J = 1.1$ Hz, 3H, H-2′), 1.05 (d, $J = 7.4$ Hz, 3H, H-1′), 0.95 (d, $J = 7.0$ Hz, 3H, H-3′), 0.87 (s, 9H, TBS), 0.03 (s, 3H, TBS), 0.02 (s, 3H, TBS).

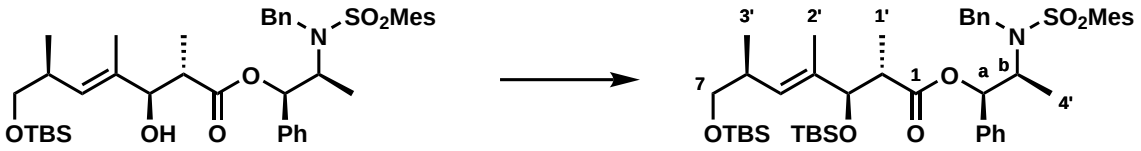
(2*S*,3*R*,6*S*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*,2,4,6-tetramethyl-3-((trimethylsilyl)oxy)hept-4-enamide (118)



117 **118**

To a solution of alcohol **117** (100 mg, 0.14 mmol, 1.00 eq.) in CH_2Cl_2 (3 ml) was subsequently added 2,6-lutidine (32 µL, 0.28 mmol, 2.00 eq.) and TMSOTf (38 µL, 0.21 mmol, 1.50 eq.) dropwise at −78 °C and stirring was continued for 1 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded a diastereomeric mixture of silyl ether **118** (72 mg, 0.09 mmol, 65 %, 3.3:1 **118**:**2-*epi*-118**) as a colorless foam.
$\mathbf{R_f} = 0.77$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.20 (d, $J = 9.2$ Hz, 1H, H-5_{d2}), 5.15 (d, $J = 9.6$ Hz, 1H, H-5_{d1}), 4.13 - 4.08 (m, 2H, H-3_{d1}, H-3_{d2}), 3.74 (s, 6H, -OC$H_{3,\,d1}$, -OC$H_{3,\,d2}$), 3.52 - 3.34 (m, 4H, H-7_{d1}, H-7_{d2}), 3.20 (s, 8H, , H-2_{d1}, H-2_{d2}, -NC$H_{3,\,d1}$, -NC$H_{3,\,d2}$), 2.61 - 2.51 (m, 2H, H-6_{d1}, H-6_{d2}), 1.61 - 1.58 (m, 6H, H-$2'_{d1}$, H-$2'_{d2}$), 0.95 (d, $J = 6.6$ Hz, 3H, H-$3'_{d1}$), 0.94 (d, $J = 6.6$ Hz, 3H, H-$3'_{d2}$), 0.90 (s, 9H, TBS_{d2}), 0.88 (s, 9H, TBS_{d1}), 0.86 (d, $J = 7.0$ Hz, 3H, H-$1'_{d1}$), 0.85 (d, $J = 6.6$ Hz, 3H, H-$1'_{d2}$), 0.05 - 0.01 (m, 30H, TBS_{d1}, TBS_{d2}, TMS_{d1}, TMS_{d2}).

(1*R*,2*S*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl (2*S*,3*R*,6*S*,*E*)-3,7-bis((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-4-enoate (125)



116 **125**

To a solution of alcohol **116** (1.54 g, 2.14 mmol, 1.00 eq.) in CH_2Cl_2 (10 ml) was subsequently added 2,6-lutidine (0.44 ml, 3.85 mmol, 1.80 eq.) and TBSOTf (0.69 ml, 2.99 mmol, 1.40 eq.) dropwise at 0 °C and stirring was continued for 2 h. The reaction was allowed to warm to rt over 30 min and after termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded silyl ether **125** (1.52 g, 1.82 mmol, 85 %) as a colorless oil.

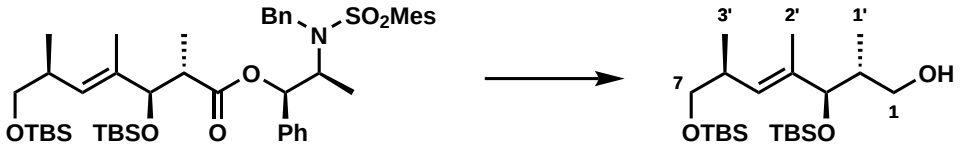
$\mathbf{R_f} = 0.45$ (PE:EA = 10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.46 - 7.41 (m, 2H, Ph), 7.33 - 7.25 (m, 3H, Ph), 7.19 - 7.13 (m, 1H, Ph), 7.10 - 7.04 (m, 2H, Ph), 6.89 (s, 2H, Ph), 6.69 - 6.65 (m, 2H, Ph), 5.66 (d, $J = 5.6$ Hz, 1H, H-a), 5.09 (dd, $J = 9.4$, 1.5 Hz, 1H, H-5), 4.93 (d, $J = 16.2$ Hz, 1H, -CH_2Ph), 4.39 (d, $J = 16.3$ Hz, 1H, -CH_2Ph), 4.09 (d, $J = 9.8$ Hz, 1H, H-3), 4.02 - 3.96 (m, 1H, H-b), 3.39 - 3.32 (m, 2H, H-7), 2.68 - 2.60 (m, 1H, H-2), 2.59 - 2.51 (m, 1H, H-6), 2.43 (s, 6H, *Mes*), 2.33 (s, 3H, *Mes*), 1.59 (d, $J = 1.0$ Hz, 3H, H-2'), 1.14 (d, $J = 7.2$ Hz, 3H, H-4'), 0.92 (d, $J = 6.7$ Hz, 3H, H-3'), 0.86 (s, 9H, TBS), 0.81 (s, 9H, TBS), 0.76 (d, $J = 7.2$ Hz, 3H, H-1'), 0.00 (s, 3H, TBS), -0,01 (s, 3H, TBS), -0.03 (s, 3H, TBS), -0.03 (s, 3H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 174.1 (s, C-1), 142.5 (s, Ph), 140.6 (s, Ph), 138.9 (s, Ph), 138.5 (s, Ph), 134.5 (s, Ph), 133.2 (d, C-5), 133.0 (d, Ph), 132.3 (d, Ph), 128.7 (d, Ph), 128.5 (s, Ph), 128.3 (s, Ph), 127.9 (d, Ph), 127.5 (s, C-4), 126.4 (d, Ph), 81.2 (d, C-3), 77.6 (d, C-a), 68.0 (t, C-7), 56.9 (d, C-b), 48.4 (t, -CH_2Ph), 44.5 (d, C-2), 35.3 (d, C-6), 26.1 (q, TBS), 26.0 (q, TBS), 23.0 (q, *Mes*), 21.0 (q, *Mes*), 18.4 (s, TBS), 18.3 (s, TBS), 16.7 (q, C-3'), 14.9 (q, C-4'), 14.6 (q, C-1'), 10.7 (q, C-2'), -4.6 (q, TBS), -4.7 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS);

HRMS (ESI): m/z calc. for $C_{47}H_{73}NO_6SSi_2$ $[M+Na]^+$: 858.4595, found 858.4401.

(2*R*,3*R*,6*S*,*E*)-3,7-bis((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylhept-4-en-1-ol (121)



125 **121**

To a solution of ester **125** (1592 mg, 1.90 mmol, 1.00 eq.) in CH_2Cl_2 (19 ml) was added DIBAl-H (1 M in hexane, 5.7 ml, 5.71 mmol, 3.00 eq.) at −78 °C and stirring was continued for 10 min. After dilution with EA the reaction was terminated by addition of MeOH and a sat. Rochelle's salt solution and stirred for another 2 h. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1) yielded alcohol **121** (644 mg, 1.54 mmol, 81 %) as a colorless oil.

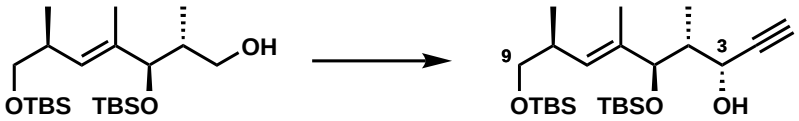
$\mathbf{R_f}$ = 0.36 (PE:EA = 10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.09 (d, J = 9.2 Hz, 1H, H-5), 3.80 (d, J = 10.0 Hz, 1H, H-3), 3.60 (t, J = 5.7 Hz, 2H, H-1), 3.41 (dd, J = 9.6, 6.3 Hz, 1H, H_a-7), 3.36 (dd, J = 9.6, 6.6 Hz, 1H, H_b-7), 2.96 (t, J = 5.7 Hz, 1H, -O*H*), 2.61 - 2.51 (m, 1H, H-6), 1.88 - 1.78 (m, 1H, H-2), 1.59 (d, J = 1.5 Hz, 3H, H-2'), 0.95 (d, J = 6.6 Hz, 3H, H-3'), 0.89 (s, 9H, TBS), 0.88 (s, 9H, TBS), 0.74 (d, J = 7.0 Hz, 3H, H-1'), 0.08 (s, 3H, TBS), 0.04 - 0.00 (m, 9H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 136.0 (s, C-4), 131.3 (d, C-5), 85.6 (d, C-3), 67.9 (t, C-7), 67.5 (t, C-1), 38.3 (d, C-2), 35.3 (d, C-6), 26.1 (q, TBS), 26.0 (q, TBS), 18.5 (s, TBS), 18.2 (s, TBS), 16.9 (q, C-3'), 14.4 (q, C-1'), 11.6 (q, C-2'), -4.1 (q, TBS), -5.0 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS);

HRMS (ESI): m/z calc. for $C_{22}H_{48}O_3Si_2$ $[M+Na]^+$: 439.3040, found 439.3040.

(3*R*,4*R*,5*R*,8*S*,*E*)-5,9-bis((*tert*-Butyldimethylsilyl)oxy)-4,6,8-trimethylnon-6-en-1-yn-3-ol (123)



121 **123**

To a solution of oxalyl chloride (0.6 ml, 7.05 mmol, 2.00 eq.) in CH_2Cl_2 (30 ml) was added DMSO (1.0 ml, 14.10 mmol, 4.00 eq.) dropwise at −78 °C. After stirring for 30 min alcohol **121** (1.41 g, 3.53 mmol, 1.00 eq.) dissolved in CH_2Cl_2 (5 ml) was added dropwise and stirring was continued for another 30 min. Et_3N (2.9 ml, 21.15 mmol, 6.00 eq.) was added dropwise and after stirring for 30 min the reaction was allowed to warm to rt over 1 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a sat. NH_4Cl solution, water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The oily residue was dissolved in THF (25 ml) and ethynylmagnesium bromide (0.5 M in THF, 21.0 ml, 10.58 mmol, 3.00 eq.) was added dropwise at 0 °C and stirring was continued for 1 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded a diastereomeric mixture of propargylic alcohols **123** (1.20 g, 2.72 mmol, 77 % combined, over 2 steps, 1:1 *dr*) as a colorless oil.

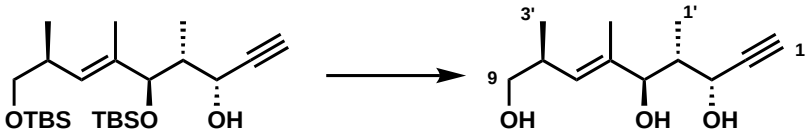
$\mathbf{R_f}$ = 0.45 (PE:EA = 10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.15 (dd, J = 9.3, 0.9 Hz, 1H, H-7), 4.49 (dd, J = 8.4, 2.5 Hz, 1H, H-3), 4.17 (d, J = 9.1 Hz, 1H, H-5), 4.13 (d, J = 8.4 Hz, 1H, -O*H*), 3.44 - 3.35 (m, 2H, H-9), 2.60 - 2.52 (m, 1H, H-8), 2.44 (d, J = 2.2 Hz, 1H, H-1), 2.06 - 1.97 (m, 1H, H-4), 1.60 (d, J = 1.3 Hz, 3H, H-2'), 0.96 (d, J = 6.7 Hz, 3H, H-3'), 0.90 (s, 9H, TBS), 0.88 (s, 9H, TBS), 0.81 (d, J = 7.0 Hz, 3H, H-1'), 0.14 - 0.13 (m, 3H, TBS), 0.04 - 0.02 (m, 9H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 135.2 (s, C-6), 132.5 (d, C-7), 83.9 (s, C-2), 83.4 (d, C-5), 73.6 (d, C-1), 67.9 (t, C-9), 66.3 (d, C-3), 40.6 (d, C-4), 35.4 (d, C-8), 26.1 (q, TBS), 26.1

(q, TBS), 18.5 (s, TBS), 18.2 (s, TBS), 16.8 (q, C-3′), 13.4 (q, C-1′), 11.5 (q, C-2′), -4.0 (q, TBS), -4.9 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS).

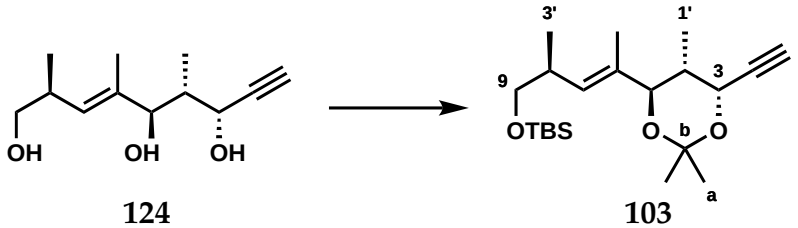
(2*S*,5*R*,6*R*,7*R*,*E*)-2,4,6-Trimethylnon-3-en-8-yne-1,5,7-triol (124)



123 **124**

To a solution of bis-silyl ether **123** (227 mg, 0.41 mmol, 1.00 eq.) in THF (2 ml) was added TBAF (1 M in THF, 2.0 ml, 2.05 mmol, 5.00 eq.) and the resulting mixture was stirred at 50 °C for 2 h. After completion of the reaction as judged by TLC, Dowex exchange resin (1500 mg), $CaCO_3$ (650 mg) and MeOH (4 ml) were added and the suspension was stirred for 1 h after which it was filtered over Celite^{TM} and concentrated to yield crude triol **124** (90 mg) as a colorless oil.
$\mathbf{R_f} = 0.22$ (PE:EA = 1:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.25 (dd, $J = 9.3,\ 1.0$ Hz, 1H, H-7), 4.53 (*brs*, 1H, H-3), 4.26 (d, $J = 9.4$ Hz, 1H, H-5), 4.00 (*brs*, 1H, -O*H*), 3.49 (dd, $J = 10.4,\ 6.2$ Hz, 1H, H_a-9), 3.40 (dd, $J = 10.6,\ 7.3$ Hz, 1H, H_b-9), 2.71 - 2.61 (m, 1H, H-8), 2.49 (d, $J = 2.2$ Hz, 1H, H-1), 2.24 (*brs*, 1H, -O*H*), 2.14 - 2.05 (m, 1H, H-4), 1.69 (d, $J = 1.2$ Hz, 3H, H-2′), 0.99 (d, $J = 6.8$ Hz, 3H, H-3′), 0.84 (d, $J = 7.0$ Hz, 3H, H-1′);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 137.4 (s, C-6), 132.0 (d, C-7), 83.3 (s, C-2), 81.8 (d, C-5), 74.0 (d, C-1), 67.8 (t, C-9), 66.8 (d, C-3), 39.9 (d, C-4), 35.3 (d, C-8), 16.9 (q, H-3′), 13.5 (q, H-1′), 11.5 (q, H-2′).

***tert*-Butyl(((*S*,*E*)-4-((4*R*,5*R*,6*R*)-6-ethynyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylpent-3-en-1-yl)oxy)dimethylsilane (103)**

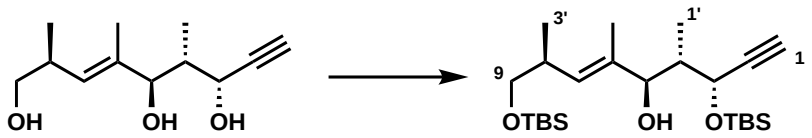


124 **103**

To a solution of triol **124** (9 mg, 42 µmol, 1 eq.) in 2,2-dimethoxypropane (1 ml) was added CSA (1 mg, 3 µmol, 0.30 eq.) and the reaction was stirred for 2 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1) yielded the intermediate acetonide (4 mg, 16 µmol) which was dissolved in CH_2Cl_2 (1 ml). 2,6-Lutidine (3 µL, 24 µmol, 1.50 eq.) and TBSOTf (4 µL, 20 µmol, 1.20 eq.) were added subsequently at −78 °C and the reaction was stirred for 1 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded alkene **103** (6 mg, 16 µmol, 39 % over 2 steps) as a colorless oil.

The analytical data completely match those reported on page 132.

(5*R*,6*S*,7*R*,10*S*,*E*)-5-ethynyl-2,2,3,3,6,8,10,13,13,14,14-undecamethyl-4,12-dioxa-3,13-disilapentadec-8-en-7-ol (128)



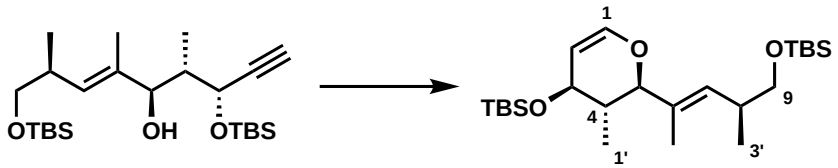
124 **128**

To a solution of crude triol **124** (90 mg) in CH_2Cl_2 (4 ml) was added 2,6-lutidine (142 µl, 1.23 mmol, 3.00 eq.) and TBSOTf (188 µl, 0.82 mmol, 2.00 eq.) dropwise at −78 °C and stirring was continued for 2 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 100:1 to 50:1) yielded a bis-silyl ether **128** (126 mg, 0.29 mmol, 70 %) as a colorless oil.

$\mathbf{R_f} = 0.34$ (PE:EA = 20:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.20 (d, $J = 9.6$ Hz, 1H, H-7), 4.70 (dd, $J = 2.9$, 2.2 Hz, 1H, H-3), 4.09 (dd, $J = 9.2$, 1.5 Hz, 1H, H-5), 3.47 - 3.36 (m, 3H, H-9, OH), 2.65 - 2.56 (m, 1H, H-8), 2.47 (d, $J = 2.2$ Hz, 1H, H-1), 1.97 - 1.88 (m, 1H, H-4), 1.65 (d, $J = 1.1$ Hz, 3H, H-2'), 0.99 (d, $J = 7.0$ Hz, 3H, H-3'), 0.94 (s, 9H, TBS), 0.91 (s, 9H, TBS), 0.83 (d, $J = 3$ Hz, 7.0H, H-1'), 0.21 (s, 3H, TBS), 0.17 (s, 3H, TBS), 0.06 - 0.05 (m, 6H, TBS).

tert-Butyl(((*S*,*E*)-4-((2*R*,3*S*,4*S*)-4-((_tert_-butyldimethylsilyl)oxy)-3-methyl-3,4-dihydro-2*H*-pyran-2-yl)-2-methylpent-3-en-1-yl)oxy)dimethylsilane (129)



128 **129**

To a solution of alkynol **128** (30 mg, 68 µmol, 1.00 eq.) THF (1.3 ml) was added $W(CO)_6$ (6 mg, 0.017 mmol, 0.25 eq.) and Et_3N (142 µl, 1.02 mmol, 15.0 eq.). The resulting solution was degassed in an ultrasonic bath for 30 minutes under argon atmosphere. Afterwards, the mixture was heated to 60 °C and irradiated with a UV mercury-lamp for 4 hours. The solution was filtered over Celite^{TM} and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 50:1) yielded dihydropyran **129** as a yellow oil (24 mg, 54 µmol, 80 %).

$\mathbf{R_f} = 0.56$ (PE:EA = 20:1);

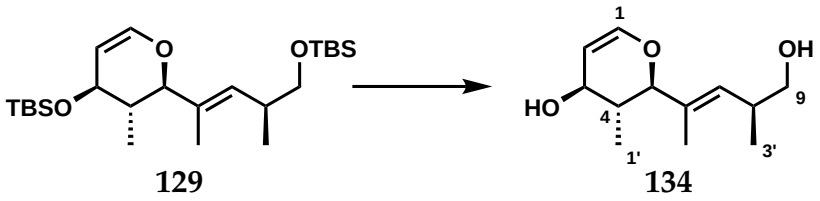
$[\alpha]^{24}_{D} = +74.1°$ ($c = 1.00$; $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.34 (dd, J = 6.2, 1.5 Hz, 1H, H-1), 5.24 (dd, J = 9.2, 1.3 Hz, 1H, H-7), 4.62 (dd, J = 6.3, 1.7 Hz, 1H, H-2), 3.99 (dt, J = 8.7, 1.6 Hz, 1H, H-3), 3.91 (d, J = 10.9 Hz, 1H, H-5), 3.43 (dd, J = 9.6, 6.3 Hz, 1H, H_a-9), 3.37 (dd, J = 9.6, 6.7 Hz, 1H, H_b-9), 2.66 - 2.56 (m, 1H, H-8), 1.89 - 1.79 (m, 1H, H-4), 1.63 (d, J = 1.2 Hz, 3H, H-2'), 0.98 (d, J = 6.7 Hz, 3H, H-3'), 0.91 (s, 9H, TBS), 0.89 (s, 9H, TBS), 0.82 (d, J = 6.7 Hz, 3H, H-1'), 0.10 (s, 3H, TBS), 0.09 (s, 3H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 144.2 (d, C-1), 134.4 (d, C-7), 132.9 (s, C-6), 105.8 (d, C-2), 87.1 (d, C-5), 70.5 (d, C-3), 67.9 (t, C-9), 37.6 (d, C-4), 35.4 (d, C-8), 26.1 (q, TBS), 26.0 (q, TBS), 18.5 (s, TBS), 18.3 (s, TBS), 17.1 (q, C-3'), 14.7 (q, C-1'), 11.0 (q, C-2'), -4.0 (q, TBS), -4.4 (q, TBS), -5.2 (q, TBS), -5.2 (q, TBS);

HRMS (ESI): m/z calc. for $C_{24}H_{48}O_3Si_2$ $[M+Na]^+$: 463.3040, found 463.3041.

(2R,3R,4S)-2-((S,E)-5-hydroxy-4-methylpent-2-en-2-yl)-3-methyl-3,4-dihydro-2H-pyran-4-ol (134)

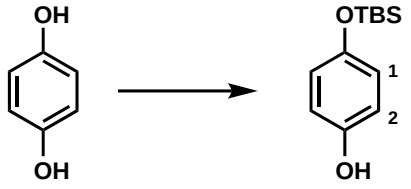


129 **134**

To a solution of silyl ether **129** (20 mg, 46 µmol, 1.00 eq.) in THF (0.9 ml) was added TBAF (230 µl, 0.23 mmol, 5.00 eq.) dropwise and the reaction was heated to 50 °C for 2 h. After completion of the reaction as judged by TLC, Dowex exchange resin (200 mg), $CaCO_3$ (100 mg) and MeOH (1 ml) were added and the suspension was stirred for 1 h after which it was filtered over Celite^{TM} and concentrated. Purification by column chromatography (PE:EA = 1:1) yielded diol **134** (4 mg, 18 µmol, 42 %) as a colorless oil.
$\mathbf{R_f} = 0.15$ (PE:EA = 1:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.41 (d, $J = 5.6$ Hz, 1H, H-1), 5.26 (d, $J = 9.2$ Hz, 1H, H-7), 4.75 (dd, $J = 6.3,\ 1.9$ Hz, 1H, H-2), 3.97 - 3.90 (m, 2H, H-3, H-5), 3.52 - 3.37 (m, 2H, H-9), 2.75 - 2.65 (m, 1H, H-8), 1.85 - 1.75 (m, 1H, H-3), 1.68 (d, $J = 1.1$ Hz, 3H, H-2'), 1.39 (d, $J = 1$ Hz, 7.8H, -OH), 1.30 (t, $J = 5.9$ Hz, 1H, -OH), 1.00 (d, $J = 6.6$ Hz, 3H, H-1'), 0.92 (d, $J = 7.0$ Hz, 3H, H-3').

5.3 *ortho*-Quinone Methide Route

4-((*tert*-Butyldimethylsilyl)oxy)phenol (147)



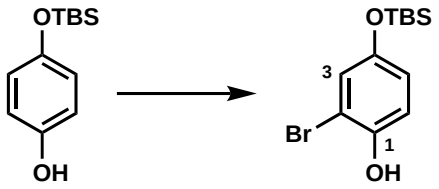
145 **147**

Silyl ether **147** (3.30 g, 14.71 mmol, 58 %) was synthesized following the protocol of Kranich *et al*.[93]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.73 - 6.67 (m, 4H, Ph), 4.52 (*brs*, 1H, OH), 0.97 (s, 9H, TBS), 0.16 (s, 6H, TBS).

The analytical data match those reported in the literature.[93]

2-Bromo-4-((*tert*-butyldimethylsilyl)oxy)phenol (146)



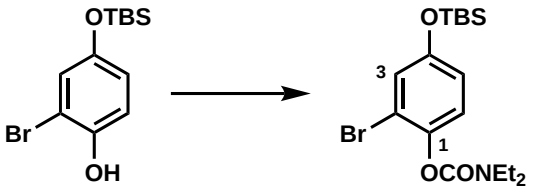
147 **146**

Bromoarene **146** (1.15 g, 3.79 mmol, 85 %) was synthesized following the protocol of Epple *et al*.[94]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.98 (d, $J = 3.0$ Hz, 1H, H-3), 6.90 (d, $J = 8.5$ Hz, 1H, H-6), 6.73 (dd, $J = 8.8,\ 2.9$ Hz, 1H, H-5), 5.16 (s, 1H, OH), 1.00 (s, 9H, TBS), 0.20 (s, 6H, TBS).

The analytical data match those reported in the literature.[93]

2-Bromo-4-((*tert*-butyldimethylsilyl)oxy)phenyl diethylcarbamate (144)



146 **144**

Carbamate **144** (4.95 g, 12.35 mmol, 43 %) was synthesized following the protocol of Dai *et al*.[92]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.05 (d, $J = 8.8$ Hz, 1H, H-6), 7.05 (d, $J = 2.6$ Hz, 1H, H-3), 6.75 (dd, $J = 8.7$, 2.8 Hz, 1H, H-5), 3.48 (q, $J = 7.7$ Hz, 2H, NEt_2), 3.38 (q, $J = 6.8$ Hz, 2H, NEt_2), 1.29 (t, $J = 6.8$ Hz, 3H, NEt_2), 1.21 (t, $J = 7.9$ Hz, 3H, NEt_2), 0.97 (s, 9H, TBS), 0.19 (s, 6H, TBS).

The analytical data match those reported in the literature.[92]

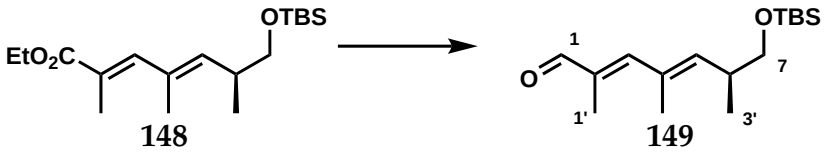
Ethyl (*S*,2*E*,4*E*)-7-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhepta-2,4-dienoate (148)

To a solution of aldehyde **113** (1.50 g, 6.19 mmol, 1.00 eq.) in THF (12 ml) was added ethyl 2-(triphenylphosphaneylidene)propanoate (3.36 g, 9.28 mmol, 1.50 eq.) and the reaction was heated to 60 °C overnight. The resulting suspension was concentrated on silica gel and purified by column chromatography (PE:EA = 35:1) to yield ester **148** (1.93 g, 5.91 mmol, 96 %) as a colorless oil.

$\mathbf{R_f} = 0.46$ (PE:EA = 20:1);

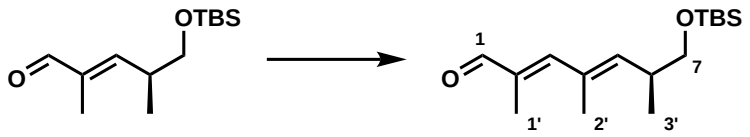
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.10 (s, 1H, H-3), 5.38 (d, $J = 9.6$ Hz, 1H, H-5), 4.20 (q, $J = 7.1$ Hz, 2H, OEt), 3.48 (dd, $J = 9.8,\ 6.4$ Hz, 1H, H_a-7), 3.43 (dd, $J = 9.8,\ 6.8$ Hz, 1H, H_b-8), 2.72 - 2.60 (m, 1H, H-6), 1.99 (d, $J = 1.1$ Hz, 3H, H-1'), 1.85 (d, $J = 1.1$ Hz, 3H, H-2'), 1.30 (t, $J = 7.2$ Hz, 3H, OEt), 0.98 (d, $J = 7.0$ Hz, 3H, H-3'), 0.88 (s, 9H, TBS), 0.03 (s, 3H, TBS), 0.03 (s, 3H, TBS).

(*S*,2*E*,4*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylhepta-2,4-dienal (149)



To a −78 °C solution of ester **148** (1.93 g, 5.91 mmol, 1.00 eq.) in CH_2Cl_2 (10 ml) was added pre-cooled to −78 °C DIBAl-H (1 M in hexane, 17.7 ml, 17.73 mmol, 3.00 eq.) dropwise. After stirring for 15 min the reaction was diluted with EA and terminated by addition of MeOH and a sat. Rochelle salt solution. After stirring for 1 h the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, fitlered and concentrated under reduced pressure. The crude allyl alcohol was dissolved in CH_2Cl_2 (46 ml) and MnO_2 (12.0 g, 138.5 mmol, 20.0 eq.) was added. The resulting suspension was stirred overnight and then filtered over Celite^{TM} and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 35:1) yielded unsaturated aldehyde **149** (1.76 g, 6.22 mmol, 90 % over 2 steps) as a colorless oil.
$\mathbf{R_f} = 0.42$ (PE:EA = 10:1);
$[\alpha]^{26}_{\mathbf{D}} =$ -20.2° ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.38 (s, 1H, H-1), 6.71 (s, 1H, H-3), 5.66 (d, J = 9.6 Hz, 1H, H-5), 3.48 (d, $J = 7.4$ Hz, 2H, H-7), 1.98 (d, $J = 1.1$ Hz, 3H, H-1'), 1.94 (d, $J = 1.1$ Hz, 3H, H-2'), 1.00 (d, $J = 7.0$ Hz, 3H, H-3'), 0.87 (s, 9H, TBS), 0.03 (s, 3H, TBS), 0.02 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 196.3 (d, C-1), 155.2 (d, C-3), 143.7 (d, C-5), 135.8 (s, C-2), 133.1 (s, C-4), 67.5 (t, C-7)), 36.2 (d, C-6), 26.0 (q, TBS), 18.4 (s, TBS), 16.8 (q, C-3'), 16.4 (q, C-1'), 10.8 (q, C-2'), -5.3 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{16}H_{30}O_2Si$ $[M+Na]^+$: 305.1913, found 305.1923.

(*S*,2*E*,4*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylhepta-2,4-dienal (149)

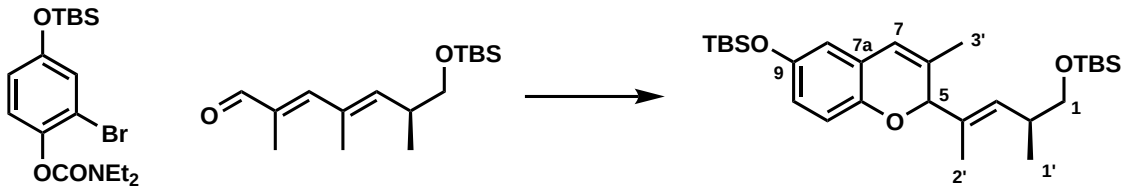


113 **149**

To a solution of silane **150** (136 mg, 0.54 mmol, 1.30 eq.) in THF (0.8 ml) was added *s*-BuLi (1.4 M in cyclohexane, 350 µl, 0.50 mmol, 0.20 eq.) dropwise at −78 °C and stirring was continued for 30 min after which aldehyde **113** (100 mg, 0.41 mmol, 1.00 eq.) in THF (0.4 ml) was added dropwise. The reaction was warmed to −20 °C and stirred for 1 h. Afterwards, the reaction was warmed to 0 °C and TFA (38 µl, 0.50 mmol, 1.20 eq.) were added and stirring was continued for 1 h after which water (0.6 ml) was added. After stirring for 1 h, the reaction was terminated by addition of a sat. $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded aldehyde **149** (44 mg, 0.16 mmol, 38 %) as a 4:1 mixture with starting material.

The analytical data match those reported on page 154.

tert-Butyl(((2*S*,*E*)-4-(6-((_tert_-butyldimethylsilyl)oxy)-3-methyl-2*H*-chromen-2-yl)-2-methylpent-3-en-1-yl)oxy)dimethylsilane (152)

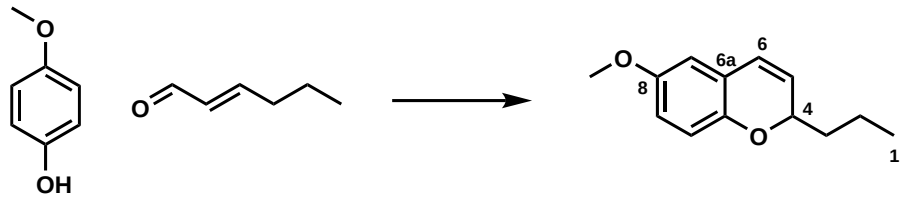


144 **149** **152**

To a solution of carbamate **144** (20 mg, 51 µmol, 1.10 eq.) in THF (1.2 ml) was added *t*-BuLi (1.7 M, 65 µl, 0.11 mmol, 2.40 eq.) dropwise at −78 °C and stirring was continued for 30 min after which a solution of aldehyde **149** (13 mg, 46 µmol, 1.00 eq.) in THF (0.9 ml) was added dropwise. After stirring for an additional 30 min the reaction was placed into a pre-heated 130 °C oil bath and stirred overnight at that temperature.[2] The reaction was terminated by addition of a sat. NH_4Cl solution and diluted with Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O, the combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:Et_2O = 50:1) yielded chromene **152** (7.2 mg, 15 µmol, 32 %, 1:1 *dr*) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f}$ = 0.81 (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.59 (d, J = 5.9 Hz, 1H, H-8_{d1}), 6.56 (d, J = 5.5 Hz, 1H, H-8_{d2}), 6.49 (dd, J = 8.7, 2.8 Hz, 1H, H-10), 6.39 - 6.36 (m, 1H, H-11), 6.17 - 6.13 (m, 1H, H-7), 5.24 - 5.19 (m, 1H, H-3), 5.03 (s, 1H, H-5_{d2}), 4.99 (s, 1H, H-5_{d1}), 3.53 - 3.32 (m, 2H, H-1), 2.61 - 2.51 (m, 1H, H-2), 1.69 - 1.64 (m, 6H, H-2', H-3'), 0.99 - 0.86 (m, 21H, H-1', TBS), 0.17 - 0.14 (m, 6H, TBS), 0.05 - 0.00 (m, 6H, TBS);
HRMS (ESI): m/z calc. for $C_{28}H_{48}O_3Si_2$ $[M+Na]^+$: 511.3040, found 511.3037.

2 Quick heating to high temperature was required as decomposition took place at rt.

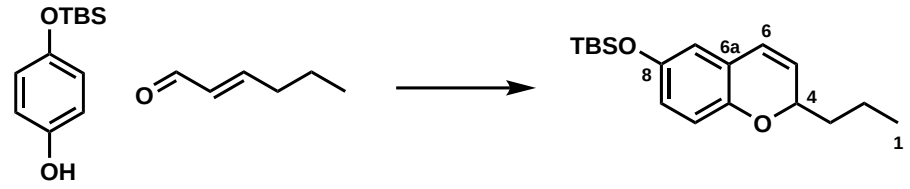
6-Methoxy-2-propyl-2*H*-chromene (270)



158 **159** **270**

To a solution of 4-methoxyphenol (**158**) (25 mg, 0.20 mmol, 1.00 eq.), (*E*)-2-hexenal (**159**) (47 µl, 0.40 mmol, 2.00 eq.) and $PhB(OH)_2$ (50 mg, 0.41 mmol, 2.03 eq.) in PhH (1 ml) was added propionic acid (3 µl, 40 µmol, 0.20 eq.) and the resulting mixture was heated under refluxing conditions overnight. The reaction was terminated by addition of water and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 30:1) yielded chromene **270** (15 mg, 73 µmol, 37 %) as a colorless oil.
$\mathbf{R_f} = 0.49$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.71 (d, $J = 8.8$ Hz, 1H, H-10), 6.65 (dd, $J = 8.5,\ 3.0$ Hz, 1H, H-9), 6.54 (d, $J = 2.9$ Hz, 1H, H-7), 6.36 (d, $J = 8.8$ Hz, 1H, H-6), 5.72 (dd, $J = 9.8,\ 3.5$ Hz, 1H, H-5), 4.81 - 4.75 (m, 1H, H-4), 3.75 (s, 3H, OMe), 1.84 - 1.73 (m, 1H, $H_{a\text{-}3}$), 1.65 - 1.42 (m, 3H, H_b, H-2), 0.95 (t, $J = 7.2$ Hz, 3H, H-1).

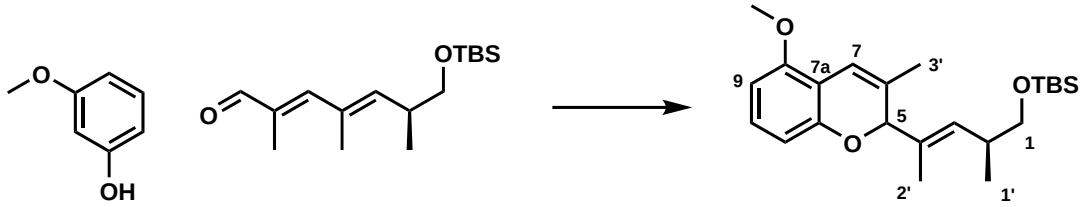
tert-Butyldimethyl((2-propyl-2_H_-chromen-6-yl)oxy)silane (271)



147 **159** **271**

To a solution of silyl ether **147** (45 mg, 0.20 mmol, 1.00 eq.), (*E*)-2-hexenal (**159**) (47 µl, 0.40 mmol, 2.00 eq.) and $PhB(OH)_2$ (50 mg, 0.41 mmol, 2.03 eq.) in PhH (1 ml) was added propionic acid (3 µl, 0.04 mmol, 0.20 eq.) and the resulting mixture was heated under refluxing conditions overnight. The reaction was terminated by addition of water and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 30:1) yielded chromene **271** (17 mg, 56 µmol, 28 %) as a colorless oil.
$\mathbf{R_f} = 0.66$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.66 (d, $J = 8.5$ Hz, 1H, H-10), 6.59 (dd, $J = 8.7$, 2.8 Hz, 1H, H-9), 6.48 (d, $J = 2.6$ Hz, 1H, H-7), 6.34 (d, $J = 9.9$ Hz, 1H, H-6), 5.71 (dd, $J = 10.0$, 3.3 Hz, 1H, H-5), 4.82 - 4.77 (m, 1H, H-4), 1.85 - 1.75 (m, 1H, H_a-3), 1.68 - 1.44 (m, 3H, H_b-3, H-2), 1.02 - 0.96 (m, 12H, H-1, TBS), 0.19 (s, 6H, TBS).

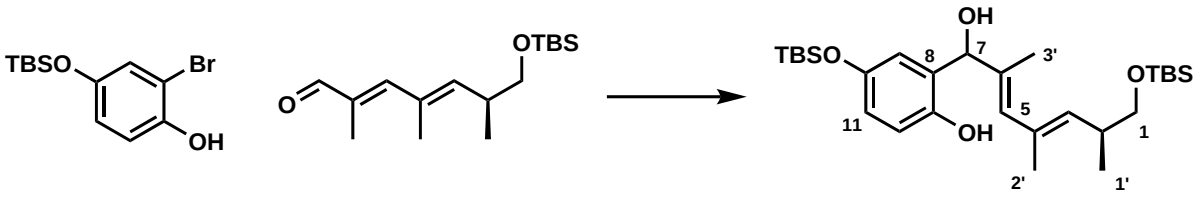
***tert*-Butyl(((2*S*,*E*)-4-(5-methoxy-3-methyl-2*H*-chromen-2-yl)-2-methylpent-3-en-1-yl)-oxy)dimethylsilane (272)**



154 **149** **272**

To a solution of 3-methoxyphenol (**154**) (16 mg, 0.13 mmol, 1.25 eq.), aldehyde **149** (29 mg, 0.10 mmol, 1.00 eq.) and $PhB(OH)_2$ (26 mg, 0.21 mmol, 2.05 eq.) in PhH (1 ml) was added propionic acid (2 µl, 0.02 mmol, 0.20 eq.) and the resulting mixture was heated under refluxing conditions overnight. The reaction was terminated by addition of water and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 30:1) yielded chromene **270** (16 mg, 43 µmol, 42 %, 1:1 *dr*) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.51$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.79 (d, $J = 8.5$ Hz, 1H, H-11), 6.40 - 6.32 (m, 2H, H-10, H-9), 6.20 - 6.16 (m, 1H, H-7), 5.29 - 5.23 (m, 1H, H-3), 5.10 (s, 1H, H_{d1}-5), 5.08 (s, 1H, H_{d2}), 3.77 (s, 3H, OMe), 3.61 - 3.37 (m, 2H, H-1), 2.65 - 2.54 (m, 1H, H-2), 1.68 (s, 6H, H-2', H-3'), 1.03 - 0.88 (m, 12H, H-1', TBS), 0.09 - 0.01 (m, 6H, TBS).

4-((*tert*-Butyldimethylsilyl)oxy)-2-((2*E*,4*E*,6*S*)-7-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-2,4,6-trimethylhepta-2,4-dien-1-yl)phenol (273)



146 **149** **273**

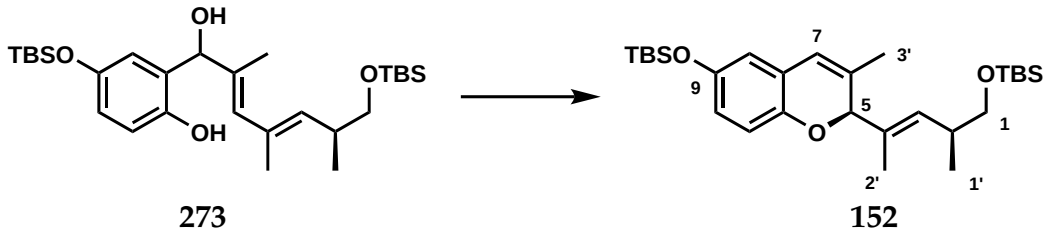
To a solution of bromoarene **146** (403 mg, 1.33 mmol, 1.50 eq.) in Et_2O (5.3 ml) was added *n*BuLi (1.6 M in hexane, 1.77 ml, 2.83 mmol, 3.20 eq.) dropwise at 0 °C. After stirring for 30 min the reaction was cooled to −78 °C and a solution of aldehyde **149** (250 mg, 0.89 mmol, 1.00 eq.) in Et_2O (4.4 ml) was added dropwise and stirring was continued for 60 min. The reaction was terminated by addition of a sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded an inconsequential mixture of diastereomers of diol **273** (339 mg, 0.67 mmol, 76 %) as a colorless oil.

Characterization of the diastereomeric mixture:

$\mathbf{R_f} = 0.15$ (PE:EA = 10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.69 (d, $J = 4.8$ Hz, 1H, OH), 6.73 - 6.63 (m, 2H, H-10, H-11), 6.45 (d, $J = 4.1$ Hz, 1H, H-9), 6.02 (s, 1H, H-5), 5.29 (s, 1H, OH), 5.13 (d, $J = 9.6$ Hz, 1H, H-3), 3.49 - 3.35 (m, 2H, H-1), 2.66 - 2.57 (m, 1H, H-2), 1.77 (s, 3H, H-2'), 1.75 (s, 3H, H-3'), 0.98 - 0.87 (m, 12H, H-1', TBS), 0.13 (s, 6H, TBS), 0.03 (s, 6H, TBS).

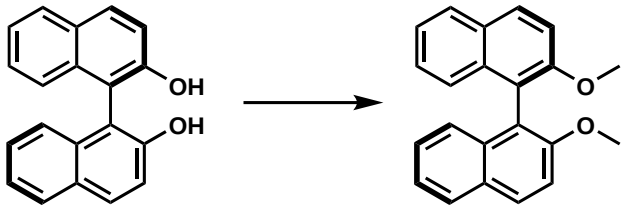
***tert*-Butyl(((*S*,*E*)-4-((*R*)-6-((*tert*-butyldimethylsilyl)oxy)-3-methyl-2*H*-chromen-2-yl)-2-methylpent-3-en-1-yl)oxy)dimethylsilane (152)**



To a solution of diol **273** (38 mg, 75 µmol, 1.00 eq.) in CH_2Cl_2 (3.7 ml) was added chiral acid **162** (1 mg, 4 µmol, 0.05 eq.) and MS (5 Å) (30 mg) and the suspension was stirred overnight. The reaction was terminated by addition of Na_2CO_3 and filtered. Purification by column chromatography (PE:Et_2O = 100:1) yielded chromene **152** (13 mg, 27 µmol, 35 %, 2.5:1 *dr*) as a colorless oil.

The analytical data match those reported on page 156.

(*R*)-2,2′-Dimethoxy-1,1′-binaphthalene (274)



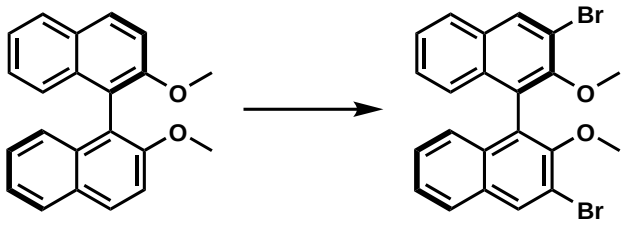
275 **274**

Dimethyl ether **274** (1.92 g, 6.10 mmol, 87 %) was synthesized following the protocol of Klussmann *et al*.[103]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.98 (d, $J = 8.84$ Hz, 2H, Ph), 7.87 (d, $J = 8.1$ Hz, 2H, Ph), 7.47 (d, $J = 9.2$ Hz, 2H, Ph), 7.32 (t, $J = 7.4$ Hz, 2H, Ph), 7.21 (t, $J = 7.7$ Hz, 2H, Ph), 7.11 (d, $J = 8.5$ Hz, 2H, Ph), 3.77 (s, 6H, OMe).

The analytical data match those reported in the literature.[103]

(*R*)-3,3′-Dibromo-2,2′-dimethoxy-1,1′-binaphthalene (276)



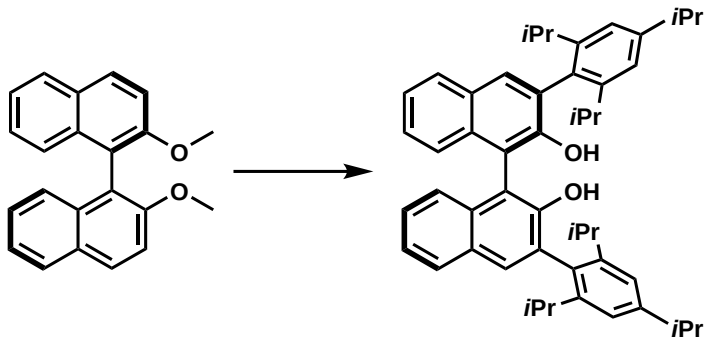
274 **276**

Dibromide **276** (1.32 g, 2.80 mmol, 46 %) was synthesized following the protocol of Klussmann *et al*.[103]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.30 (s, 2H, Ph), 7.85 (d, $J = 10.0$ Hz, 2H, Ph), 7.45 (t, $J = 7.7$ Hz, 2H, Ph), 7.30 (t, $J = 7.7$ Hz, 2H, Ph), 7.11 (d, $J = 8.5$ Hz, 2H, Ph), 3.54 (s, 6H, OMe).

The analytical data match those reported in the literature.[103]

(*R*)-3,3′-Bis(2,4,6-triisopropylphenyl)-[1,1′-binaphthalene]-2,2′-diol (277)

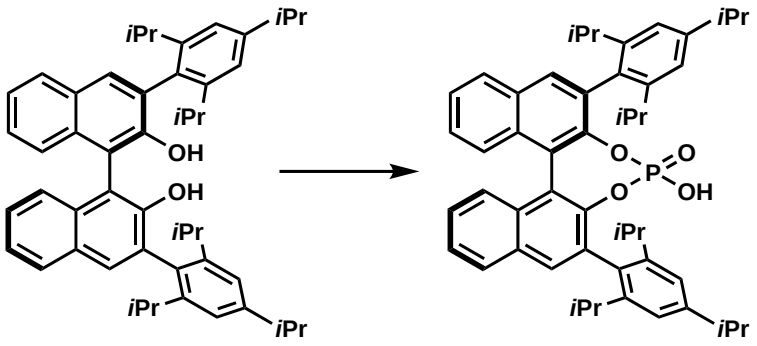


276 **277**

Substituted biaryl **277** (135 mg, 0.20 mmol, 92 % over 2 steps) was synthesized following the protocol of Klussmann *et al*.[103]
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.86 (d, $J = 8.1$ Hz, 2H, Ph), 7.39 - 7.26 (m, 6H, Ph), 7.12 (d, $J = 6.6$ Hz, 2H, Ph), 4.91 (s, 2H, OH), 2.95 (sept, $J = 6.9$ Hz, 2H, *i*Pr), 2.84 (sept, $J = 6.9$ Hz, 2H, *i*Pr), 2.68 (sept, $J = 6.4$ Hz, 2H, *i*Pr), 1.30 (d, $J = 7.0$ Hz, 12H, *i*Pr), 1.19 (d, $J = 6.6$ Hz, 6H, *i*Pr), 1.10 (d, $J = 7.0$ Hz, 6H, *i*Pr), 1.08 (d, $J = 7.0$ Hz, 6H, *i*Pr), 1.02 (d, $J = 6.6$ Hz, 6H, *i*Pr).

The analytical data match those reported in the literature.[103]

(*R*)-TRIP (163)



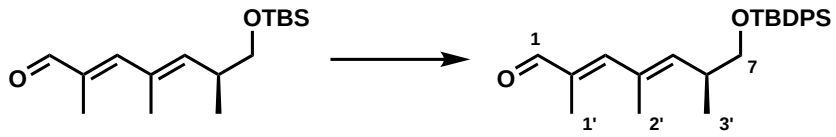
277 **163**

(*R*)-TRIP (**163**) (60 mg, 80 µmol, 42 %) was synthesized following the protocol of Klussmann *et al*.[103]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.89 (d, $J = 8.8$ Hz, 2H, Ph), 7.82 (s, 2H, Ph), 7.52 - 7.48 (m, 2H, Ph), 7.34 - 7.28 (m, 4H, Ph), 6.94 (s, 4H, Ph), 2.83 (sept, $J = 6.9$ Hz, 2H, *i*Pr), 2.62 - 2.51 (m, 4H, *i*Pr), 1.23 (d, $J = 4.8$ Hz, 6H, *i*Pr), 1.21 (d, $J = 5.5$ Hz, 6H, *i*Pr), 1.06 (d, $J = 6.2$ Hz, 6H, *i*Pr), 0.99 (d, $J = 6.6$ Hz, 6H, *i*Pr), 0.91 (d, $J = 6.6$ Hz, 6H, *i*Pr), 0.79 (d, $J = 6.2$ Hz, 6H, *i*Pr).

The analytical data match those reported in the literature.[103]

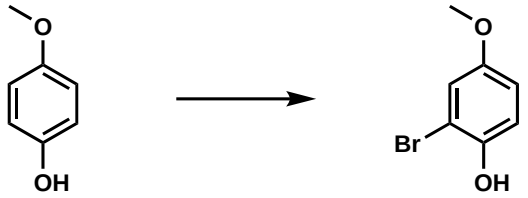
(*S*,2*E*,4*E*)-7-((*tert*-Butyldiphenylsilyl)oxy)-2,4,6-trimethylhepta-2,4-dienal (166)



149 **166**

To a solution of silyl ether **149** (210 mg, 0.74 mmol, 1.00 eq.) in THF (7.4 ml) was added TBAF (1 M in THF, 1.12 ml, 1.12 mmol, 1.50 eq.) dropwise at 0 °C and the reaction was stirred at rt for 3 h. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded the corresponding alcohol (107 mg, 0.64 mmol, 86 %) as a colorless oil. The obtained product was dissolved in CH_2Cl_2 (3.2 ml) and imidazole (65 mg, 0.95 mmol, 1.50 eq.) and TBDPSCl (198 µl, 0.76 mmol, 1.20 eq.) were added. Stirring was continued overnight after which the reaction was terminated by addition of water. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a sat. NH_4Cl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 30:1) yielded silyl ether **166** (240 mg, 0.59 mmol, 93 %) as a colorless oil.
$\mathbf{R_f} = 0.61$ (PE:EA = 10:1);
$[\alpha]^{22}_{\mathbf{D}} = -3.4°$ ($c = 1.00$; $CDCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.38 (s, 1H, H-1), 7.66 - 7.63 (m, 4H, TBDPS), 7.45 - 7.34 (m, 6H, TBDPS), 6.69 - 6.67 (m, 1H, H-3), 5.65 (d, $J = 9.6$ Hz, 1H, H-5), 3.58 (dd, $J = 9.7$, 6.3 Hz, 1H, H_a-7), 3.53 (dd, $J = 9.8$, 6.4 Hz, 1H, H_b), 2.82 - 2.71 (m, 1H, H-6), 1.93 (d, $J = 1.1$ Hz, 3H, H-1'), 1.92 (d, $J = 1.1$ Hz, 3H, H-2'), 1.05 - 1.02 (m, 12H, H-3', TBDPS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 196.4 (d, C-1), 155.2 (d, C-3), 143.9 (d, C-5), 135.8 (d, TBDPS, 2x), 135.7 (s, C-2), 133.8 (s, TBDPS), 133.8 (s, TBDPS), 133.2 (s, C-4), 129.8 (d, TBDPS), 129.8 (d, TBDPS), 127.8 (d, TBDPS), 127.8 (d, TBDPS), 68.2 (t, C-7), 36.12 (d, C-6), 27.0 (q, TBDPS), 19.4 (s, TBDPS), 16.9 (q, C-3'), 16.4 (q, C-1'), 10.8 (q, C-2');
HRMS (ESI): m/z calc. for $C_{26}H_{34}O_2Si$ $[M+Na]^+$: 429.2226, found 429.2227.

2-Bromo-4-methoxyphenol (167)



158 **167**

Bromoarene **167** (512 mg, 2.52 mmol, 63 %) was synthesized following the protocol of Baumgärtner *et al*.[189]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.01 (d, $J = 2.6$ Hz, 1H, H-3), 6.94 (d, $J = 8.8$ Hz, 1H, H-6), 6.80 (dd, $J = 9.2,\ 2.9$ Hz, 1H, H-5), 5.14 (s, 1H, OH), 3.75 (s, 3H, OMe).

The analytical data match those reported in the literature.[189]

189 K. Baumgärtner, A. L. Meza Chincha, A. Dreuw, F. Rominger, M. Mastalerz, *Angew. Chem. Int. Ed.* **2016**, *55*, 15594–15598.

2-((2*E*,4*E*,6*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-1-hydroxy-2,4,6-trimethylhepta-2,4-dien-1-yl)-4-methoxyphenol (165)

167 **166** **165**

To a solution of bromoarene **167** (75 mg, 0.37 mmol, 1.50 eq.) in Et_2O (1.5 ml) was added *n*BuLi (1.6 M in hexane, 490 µl, 0.79 mmol, 3.20 eq.) dropwise at 0 °C. After stirring for 30 min the reaction was cooled to −78 °C and a solution of aldehyde **166** (100 mg, 0.25 mmol, 1.00 eq.) in Et_2O (1.2 ml) was added dropwise and stirring was continued for 60 min. The reaction was terminated by addition of a sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1 to 7:1) yielded an inconsequential mixture of diastereomers of diol **165** (85 mg, 0.16 mmol, 65 %) as a colorless oil.

Characterization of the diastereomeric mixture:

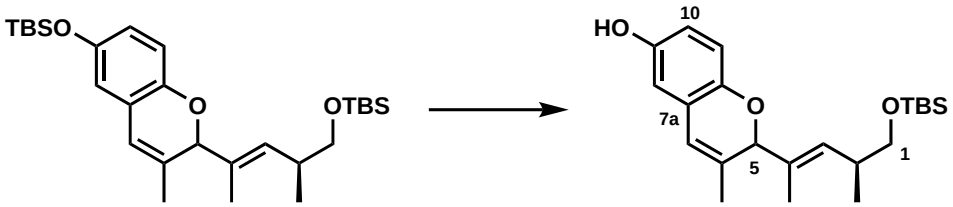
$\mathbf{R_f} = 0.06$ (PE:EA = 10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.68 - 7.63 (m, 4H, TBDPS), 7.44 - 7.33 (m, 6H, TBDPS), 6.80 (d, $J = 8.8$ Hz, 1H, H-12), 6.74 (dd, $J = 8.8$, 2.9 Hz, 1H, H-11), 6.53 (d, $J = 3.3$ Hz, 1H, H-9), 6.03 (s, 1H, H-5), 5.31 (d, $J = 2.6$ Hz, 1H, H-7), 5.17 (d, $J = 9.6$ Hz, 1H, H-3), 3.72 (s, 3H, OMe), 3.54 - 3.45 (m, 2H, H-1), 2.72 - 2.60 (m, 1H, H-2), 2.36 (d, $J = 2.6$ Hz, 1H, OH), 1.76 (d, $J = 1.1$ Hz, 3H, H-3'), 1.71 (d, $J = 1.1$ Hz, 3H, H-2'), 1.04 (s, 9H, TBDPS), 1.01 (d, $J = 7.0$ Hz, 3H, H-1');

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 152.8 (s, C-10), 149.9 (s, TBDPS), 149.9 (s, TBDPS), 135.7 (d, TBDPS), 135.6 (d, TBDPS), 135.0 (s, C-6), 134.7 (d, C-3), 134.6 (d, C-3), 133.9 (s, TBDPS), 132.1 (d, C-5), 132.1 (d, C-5), 131.9 (s, C-4), 131.9 (s, C-4), 129.6 (d, TBDPS), 129.5 (d, TBDPS), 127.6 (d, TBDPS), 125.1 (s, C-13), 125.1 (s, C-13), 117.8 (d, C-12), 117.8 (d, C-12), 114.0 (d, C-11), 114.0 (d, C-11), 113.6 (d, C-9), 113.5 (d, C-9), 81.6 (d, C-7), 68.4 (t, C-1), 55.7 (q, OMe), 35.7 (d, C-2), 26.9 (q, TBDPS), 19.3 (s, TBDPS), 17.3 (q, C-1'), 17.2 (q, C-1'), 17.1 (q, C-2'), 17.1 (q, C-2'), 13.7 (q, C-3');

HRMS (ESI): m/z calc. for $C_{33}H_{42}O_4Si$ [M+Na]$^+$: 553.2750, found 553.2766.

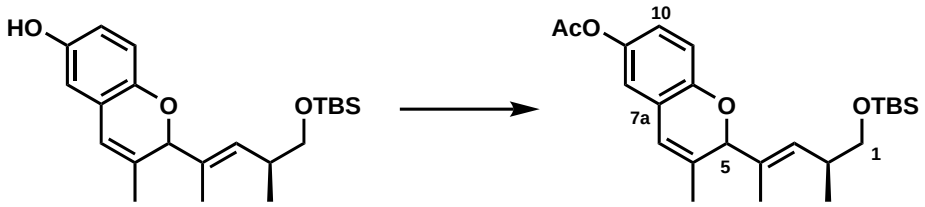
2-((*S*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylpent-2-en-2-yl)-3-methyl-2*H*-chromen-6-ol (278)



152 **278**

To a solution of silyl ether **152** (24 mg, 49 µmol, 1.00 eq.) in MeCN (0.5 ml) was added KF·Al_2O_3 (37 %, 23 mg, 0.15 mmol, 3.00 eq.) and the resulting suspension was sonicated for 3 h. The reaction was filtered over Celite^{TM} and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded a diastereomeric mixture of phenol **278** (4 mg, 11 µmol, 22 %) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.17$ (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.66 - 6.58 (m, 1H, H-11), 6.51 (dd, $J = 8.5$, 2.9 Hz, 1H, H-10), 6.43 - 6.40 (m, 1H, H-8), 6.19 - 6.15 (m, 1H, H-7), 5.27 - 5.21 (m, 1H, H-5), 5.06 - 5.01 (m, 1H, H-5), 4.47 - 4.44 (m, 1H, OH), 3.56 - 3.36 (m, 2H, H-1), 2.63 - 2.53 (m, 1H, H-2), 1.71 (d, $J = 1.1$ Hz, 3H, H-3'), 1.68 (d, $J = 1.1$ Hz, 3H, H-2'), 1.02 - 0.87 (m, 12H, H-1', TBS), 0.09 - 0.01 (m, 6H, TBS).

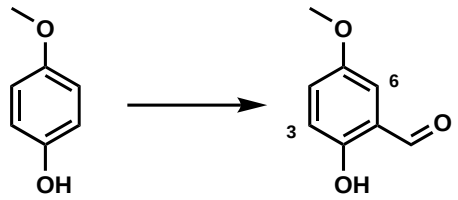
2-((*S*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylpent-2-en-2-yl)-3-methyl-2*H*-chromen-6-yl acetate (172)



278 **172**

To a solution of phenol **278** (4 mg, 11 µmol, 1.00 eq.) in CH_2Cl_2 (1 ml) was added pyridine (2 µl, 21 µmol, 2.00 eq.) and acetyl chloride (1 µl, 16 µmol, 1.50 eq.) at 0 °C and the solution was stirred for 2 h after which it was warmed to rt and stirring was continued for 1 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded a diastereomeric mixture of acetate **172** (3.3 mg, 8 µmol, 74 %) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f}$ = 0.46 (PE:EA = 10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.76 - 6.68 (m, 2H, H-11, H-10), 6.64 - 6.62 (m, 1H, H-8), 6.20 - 6.16 (m, 1H, H-7), 5.29 - 5.23 (m, 1H, H-3), 5.14 - 5.09 (m, 1H, H-5), 3.56 - 3.39 (m, 2H, H-1), 2.65 - 2.55 (m, 1H, H-2), 2.28 (s, 3H, OAc), 1.70 (d, J = 1.1 Hz, 3H, H-3'), 1.68 (d, J = 1.1 Hz, 3H, H-2'), 1.03 - 0.87 (m, 12H, H-1', TBS), 0.12 - 0.01 (m, 6H, TBS).

2-Hydroxy-5-methoxybenzaldehyde (175)



158 **175**

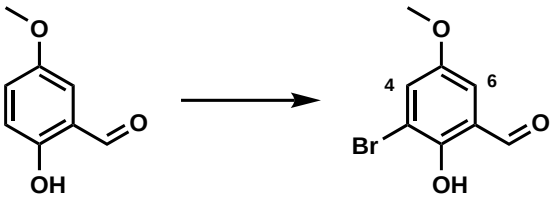
Benzaldehyde **175** (16.54 g, 108.7 mmol, 93 %) was synthesized following the procedure of Wang *et al*.[190]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 10.66 (s, 1H, OH), 9.86 (s, 1H, CHO), 7.14 (dd, $J = 9.2,\ 2.9$ Hz, 1H, H-4), 7.00 (d, $J = 3.3$ Hz, 1H, H-6), 6.93 (d, $J = 8.8$ Hz, 1H, H-3), 3.81 (s, 3H, OMe).

The analytical data match those reported in the literature.[190]

190 C. Wang, Y. Li, Y. Wu, Q. Wang, W. Shi, C. Yuan, L. Zhou, Y. Xiao, H. Guo, *Org. Lett.* **2018**, *20*, 2880–2883.

3-Bromo-2-hydroxy-5-methoxybenzaldehyde (178)



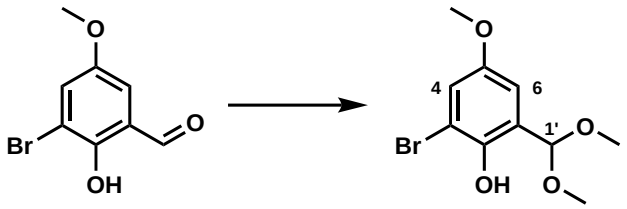
175 **178**

Bromoarene **178** (11.90 g, 51.50 mmol, 47 %) was synthesized following the procedure of Evano *et al*.[141]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 11.14 (s, 1H, OH), 9.86 (s, 1H, CHO), 7.44 (d, $J = 3.3$ Hz, 1H, H-4), 7.06 (d, $J = 3.3$ Hz, 1H, H-6), 3.85 (s, 3H, OMe).

The analytical data match those reported in the literature.[141]

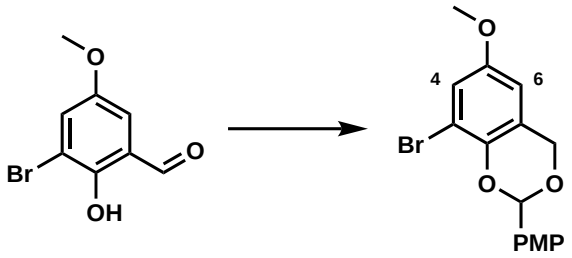
2-Bromo-6-(dimethoxymethyl)-4-methoxyphenol (176)



178 **176**

To a solution of benzaldehyde **178** (500 mg, 2.16 mmol, 1.00 eq.) in MeOH (22 ml) was added trimethyl orthoformate (10.6 ml, 97.38 mmol, 45.0 eq.) and *p*TsOH·H_2O (103 mg, 0.54 mmol, 0.25 eq.) and stirring was continued overnight. The reaction was diluted with EA and terminated by addition of a sat. $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with EA and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield dimethyl acetal **176** (550 mg, 1.99 mmol, 92 %) as a solid which was unstable to column chromatography conditions.
$\mathbf{R_f} = 0.29$ (PE:EA =20:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.88 (s, 1H, OH), 7.07 (d, $J = 2.9$ Hz, 1H, H-4), 6.79 (d, $J = 2.9$ Hz, 1H, H-6), 5.53 (s, 1H, H-1'), 3.75 (s, 3H, OMe), 3.39 (s, 6H, OMe).

2-Bromo-6-(hydroxymethyl)-4-methoxyphenol (177)



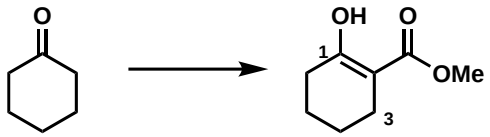
178 **177**

To a solution of benzyladehyde **178** (50 mg, 0.22 mmol, 1.00 eq.) in EtOH (2.2 ml) was added $NaBH_4$ (12 mg, 0.33 mmol, 1.50 eq.) at 0 °C and stirring was continued at rt for 1 h. The reaction was concentrated under reduced pressure and 1 M HCl was added and the resulting suspension was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield benzylic alcohol **179** as a colorless solid which was dissolved in CH_2Cl_2 (1 ml). Anisaldehyde dimethyl acetal (0.11 ml, 0.65 mmol, 3.00 eq.) and PPTS (16 mg, 65 µmol, 0.30 eq.) and MS 3 Å (50 mg) were added and stirring was continued for 1.5 h. The reaction was terminated by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA =20:1) yielded arene **177** (60 mg, 0.17 mmol, 79 %) as a colorless oil.

$\mathbf{R_f} = 0.49$ (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.58 (d, $J = 8.5$ Hz, 2H, Ph), 7.05 (d, $J = 3.7$ Hz, 1H, H-4), 6.98 (d, $J = 8.5$ Hz, 2H, Ph), 6.55 (d, $J = 3.3$ Hz, 1H, H-6), 5.14 (d, $J = 14.7$ Hz, 1H, CH_2Ph), 4.95 (d, $J = 15.1$ Hz, 1H, CH_2Ph), 3.86 (s, 3H, OMe), 3.78 (s, 3H, OMe).

Methyl 2-oxocyclohexane-1-carboxylate (180)



279 **180**

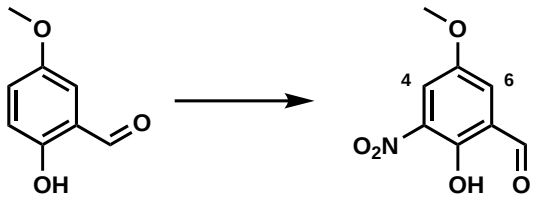
Ketoester **180** (1.15 g, 7.38 mmol, 73 %) was synthesized following the procedure of Saito *et al*.[191]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 12.16 (s, 1H, OH), 3.75 (s, 3H, OMe), 2.29 - 2.19 (m, 4H, H-3, H-6), 1.72 - 1.57 (m, 4H, H-4, H-5).

The analytical data match those reported in the literature.[191]

191 A. Saito, S. Zheng, M. Takahashi, W. Li, I. Ojima, T. Honda, *Synthesis (Stuttg).* **2013**, *45*, 3251–3254.

2-Hydroxy-5-methoxy-3-nitrobenzaldehyde (182)



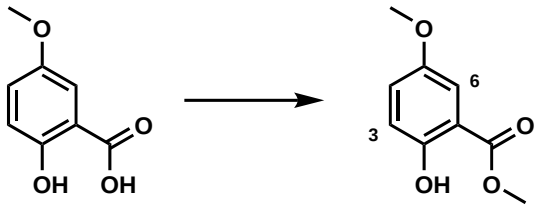
175 **182**

Nitroarene **182** (417 mg, 2.12 mmol, 64 %) was synthesized following the procedure of Barrios Antúnez *et al*.[139]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 10.91 (s, 1H, OH), 10.47 (s, 1H, CHO), 7.88 (d, $J = 3.3$ Hz, 1H, H-4), 7.74 (d, $J = 3.7$ Hz, 1H, H-6), 3.90 (s, 3H, OMe).

The analytical data match those reported in the literature.[139]

Methyl 2-hydroxy-5-methoxybenzoate (280)



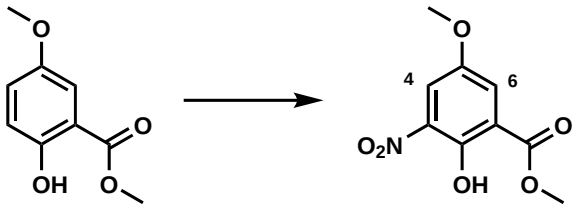
188 **280**

Methyl ester **280** (1.02 g, 5.62 mmol, 94 %) was synthesized following the procedure of Carillo-Arcos *et al*.[150]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 10.36 (s, 1H, OH), 7.29 (d, $J = 3.3$ Hz, 1H, H-6), 7.08 (dd, $J = 9.0$, 3.1 Hz, 1H, H-4), 6.92 (d, $J = 8.8$ Hz, 1H, H-3), 3.95 (s, 3H, OMe), 3.78 (s, 3H, OMe).

The analytical data match those reported in the literature.[150]

Methyl 2-hydroxy-5-methoxy-3-nitrobenzoate (184)

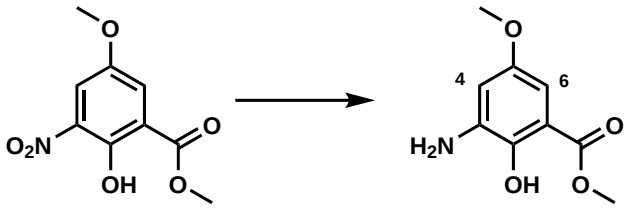


Nitroarene **184** (965 mg, 5.30 mmol, 89 %) was synthesized following the procedure of Li *et al.*[151]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 11.51 (s, 1H, OH), 7.76 (d, $J = 3.3$ Hz, 1H, H-4), 7.72 (d, $J = 3.7$ Hz, 1H, H-6), 4.03 (s, 3H, OMe), 3.87 (s, 3H, OMe).

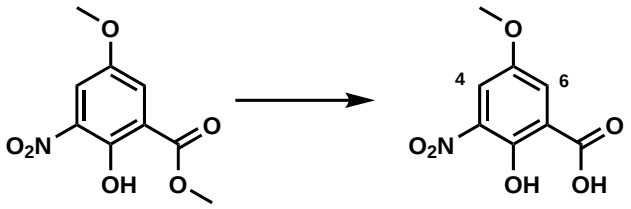
The analytical data match those reported in the literature.[151]

Methyl 3-amino-2-hydroxy-5-methoxybenzoate (185)



To a solution of nitroarene **184** (580 mg, 2.55 mmol, 1.00 eq.) in THF:MeOH (8:1, 20 ml) was added PtO_2-hydrate (72 mg, 0.26 mmol, 0.10 eq.) and H_2 was bubbled through the reaction for 10 min. An atmospheric pressure of H_2 was applied and the reaction was stirred for 1.5 h. The reaction was filtered over Celite^{TM} and concentrated under reduced pressure to yield aniline **185** (503 mg, 2.55 mmol, *quant.*) as a brown solid.
$\mathbf{R_f} = 0.66$ (PE:EA =1:1);
mp. 90 °C;
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 10.57 (s, 1H, OH), 6.70 (d, $J = 2.6$ Hz, 1H, H-4), 6.53 (d, $J = 2.6$ Hz, 1H, H-6), 3.98 - 3.93 (m, 5H, NH_2, OMe), 3.76 (s, 3H, OMe);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 171.1 (s, CO_2Me), 152.3 (), 145.1 (s, C-5), 137.0 (s, C-2), 111.1 (s, C-3), 108.4 (d, C-6), 100.0 (d, C-4), 55.8 (q, OMe), 52.4 (q, OMe).

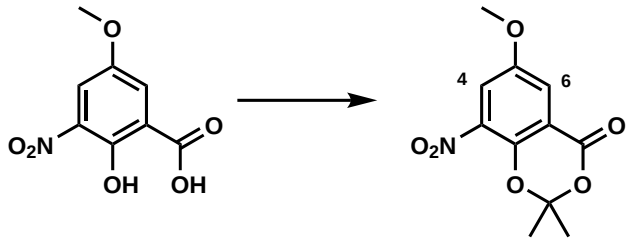
2-Hydroxy-5-methoxy-3-nitrobenzoic acid (281)



To a solution of methyl ester **184** (0.97 mg, 4.25 mmol, 1.00 eq.) in THF:H_2O (4:1, 8.5 ml) was added LiOH·H_2O (1.07 g, 25.49 mmol, 6.00 eq.) and the resulting suspension was heated to 60 °C overnight. The reaction was diluted with EA and adjusted to pH 2 with 2 M HCl. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield carboxylic acid **281** (0.79 g, 3.71 mmol, 87 %) as a yellow solid.
mp. 180 °C (lit.: 181 °C)[192];
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 10.89 (s, 1H, OH), 10.45 (s, 1H, CO_2H), 7.86 (d, $J = 3.4$ Hz, 1H, H-4), 7.72 (d, $J = 3.6$ Hz, 1H, H-6), 3.88 (s, 3H, OMe);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 188.23 (s, CO_2H), 152.2 (s, C-5), 151.3 (s, C-2), 126.3 (s, C-1), 123.1 (d, C-6), 115.3 (d, C-4), 56.5 (q, OMe).

192 A. Klemens, *Monatshefte fuer Chemie* **1913**, *33*, 1243–1254.

6-Methoxy-2,2-dimethyl-8-nitro-4H-benzo[d][1,3]dioxin-4-one (186)



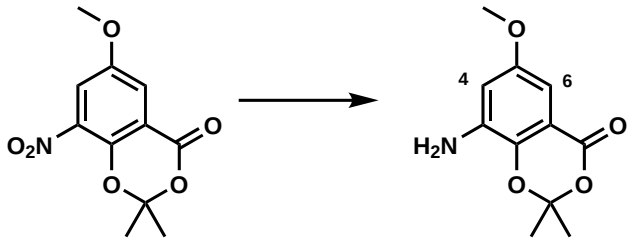
281 **186**

To a solution of acid **281** (200 mg, 0.94 mmol, 1.00 eq.) in TFAA (0.8 ml) and TFA (1.0 ml) was added acetone (0.32 ml, 4.32 mmol, 4.60 eq.) dropwise and the reaction was heated to 70 °C overnight. The reaction was concentrated under reduced pressure and redissolved in EA. A sat. $NaHCO_3$ solution was added and the phases were separated. The aqueous phase was extracted with EA and the combined organic phases were washed with a sat. $NaHCO_3$ solution and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield acetonide **186** (74 mg, 0.29 mmol, 31 %) as an orange solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.79 (s, 2H, H-4, H-6), 3.91 (s, 3H, OMe), 1.83 (s, 6H, Me);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 159.3 (s, CO_2R), 153.7 (s, C-5), 143.8 (s, C-2), 119.0 (d, C-4), 118.4 (d, C-6), 116.8 (s, O_2CMe_2), 108.1 (s, C-3), 56.6 (q, OMe), 26.0 (q, Me).

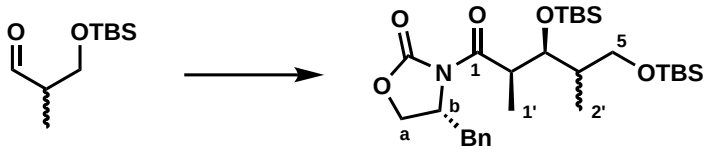
8-Amino-6-methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (187)



186 **187**

To a solution of nitroarene **186** (4 mg, 16 µmol, 1.00 eq.) in THF:MeOH (8:1, 150 µl) was added PtO_2-hydrate (0.5 mg, 2 µmol, 0.10 eq.) and H_2 was bubbled through the reaction for 10 min. An atmospheric pressure of H_2 was applied and the reaction was stirred for 1.5 h. The reaction was filtered over Celite^{TM} and concentrated under reduced pressure to yield aniline **187** (3 mg, 13 µmol, 85 %) as a colorless oil.
$\mathbf{R_f} = 0.196$ (PE:EA =3:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.83 (d, $J = 3.0$ Hz, 1H, H-6), 6.55 (d, $J = 2.6$ Hz, 1H, H-4), 3.90 - 3.84 (m, 2H, NH_2), 3.79 (s, 3H, OMe), 1.76 (s, 6H, Me).

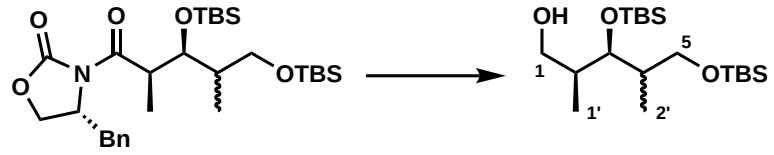
(4*R*)-4-Benzyl-3-((2*R*,3*S*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentanoyl)-oxazolidin-2-one (282)



191 **198**

To a solution of (*R*)-Bn-Evans-auxiliary (4.29 g, 18.38 mmol, 1.20 eq.) in CH_2Cl_2 (19 ml) was added subsequently $n$$Bu_2BOTf$ (1 M in CH_2Cl_2, 19.9 ml, 19.91 mmol, 1.30 eq.) and Et_3N (3.63 ml, 26.04 mmol, 1.70 eq.) dropwise at −78 °C after which the reaction was warmed to 0 °C and stirred for 1 h. The reaction was cooled back to −78 °C and a solution of aldehyde **191** (3.10 g, 15.32 mmol, 1.00 eq.) in CH_2Cl_2 (46 ml) was added dropwise. Stirring was continued for 20 min and the reaction was then warmed to 0 °C and stirred for 1 h. The reaction was terminated by addition of pH= 7 buffer solution, MeOH and H_2O_2 and stirred for 1 h at 0 °C. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 7:1) yielded a mixture of aldol and (*R*)-Bn-Evans-auxiliary as a colorless solid. The mixture was dissolved in CH_2Cl_2 (38 ml) and cooled to 0 °C. Subsequently, 2,6-lutidine (3.55 ml, 30.64 mmol, 2.00 eq.) and TBSOTf (4.58 ml, 19.91 mmol, 1.30 eq.) were added dropwise and stirring was continued for 30 min. The reaction was terminated by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded a diastereomeric mixture of silyl ether **198** (5.73 g, 10.42 mmol, 68 %) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f}$ = 0.36 (PE:EA =10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 - 7.22 (m, 5H, Ph), 4.68 - 4.61 (m, 1H, H-b), 4.22 - 3.95 (m, 5H, H-a, H-3, H-5), 3.43 - 3.36 (m, 1H, -CH_2Ph), 3.32 - 3.26 (m, 1H, H-2), 2.82 - 2.75 (m, 1H, -CH_2Ph), 1.85 - 1.67 (m, 1H, H-4), 1.27 - 1.24 (m, 3H, H-1'), 1.01 (d, J = 7.0 Hz, 3H, H-2'), 0.95 - 0.92 (m, 18H, TBS), 0.07 - 0.03 (m, 12H, TBS).

(2*S*,3*R*)-3,5-bis((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (283)



198 **283**

To a solution of amide **198** (5.73 g, 10.42 mmol, 1.00 eq.) in THF (52 ml) was added MeOH (1.27 ml, 31.25 mmol, 3.00 eq.) and $LiBH_4$ (4 M in THF, 5.73 ml, 22.92 mmol, 2.20 eq.) dropwise at 0 °C. The reaction was stirred for 2.5 h and was then diluted with Et_2O and terminated by addition of a sat. Rochelle salt solution and stirring was continued for 30 min. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1 to 10:1) yielded a diastereomeric mixture of alcohol **283** (2.95 g, 7.83 mmol, 75 %) as a colorless oil.

Characterization of the diastereomeric mixture:

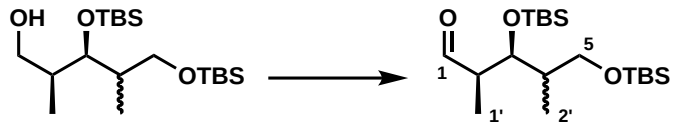
$\mathbf{R_f}$ = 0.35 (PE:EA =10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 3.95 - 3.38 (m, 5H, H-1, H-3, H-5), 2.02 - 1.88 (m, 2H, H-2, H-4), 0.95 - 0.85 (m, 24H, H-1', H-2', TBS), 0.14 - 0.06 (m, 12H, TBS).

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 74.39 (d, C-3), 74.38 (d, C-3), 66.7 (t, C-5), 66.6 (t, C-5), 66.1 (t, C-1), 65.7 (t, C-1), 40.5 (d, C-4), 40.2 (d, C-4), 38.8 (d, C-2), 37.8 (d, C-2), 26.2 (q, TBS), 26.1 (q, TBS), 26.1 (q, TBS), 26.0 (q, TBS), 18.5 (s, TBS), 18.4 (s, TBS), 18.4 (s, TBS), 18.3 (s, TBS), 14.2 (q, C-2'), 13.3 (q, C-2'), 12.3 (q, C-1'), 12.1 (q, C-1'), -4.0 (q, TBS), -4.1 (q, TBS), -4.2 (q, TBS), -4.3 (q, TBS), -5.2 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS), -5.3(q, TBS);

HRMS (ESI): m/z calc. for $C_{19}H_{44}O_3Si_2$ $[M+Na]^+$: 399.2727, found 399.2727.

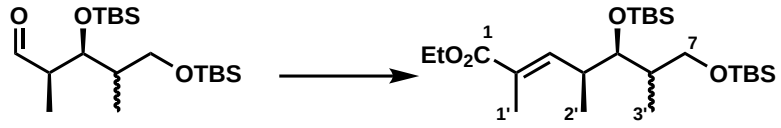
(2*R*,3*S*)-3,5-bis((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentanal (192)



283 **192**

To a solution of alcohol **283** (1.84 g, 4.78 mmol, 1.00 eq.) in wet CH_2Cl_2 (24 ml) was added $NaHCO_3$ (1.22 g, 14.61 mmol, 3.00 eq.) and DMP (5.16 g, 12.18 mmol, 2.50 eq.) at rt and stirring was continued for 2 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution and a sat. $Na_2S_2O_3$ the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded a diastereomeric mixture of aldehyde **192** (1.43 g, 3.19 mmol, 78 %) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.60$ (PE:EA =10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.87 (d, $J = 0.9$ Hz, 1H, H-1_{d1}), 9.71 (d, $J = 1.0$ Hz, 1H, H-1_{d2}), 4.25 - 4.21 (m, 1H, H-3), 3.62 - 3.39 (m, 2H, H-5), 2.62 - 2.46 (m, 1H, H-2), 1.91 - 1.71 (m, 1H, H-4), 1.11 (d, $J = 6.9$ Hz, 3H, H-2'$_{d2}$), 1.05 (d, $J = 6.9$ Hz, 3H, H-2'$_{d1}$), 0.94 - 0.80 (m, 21H, H-2', TBS), 0.10 - 0.00 (m, 12H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 205.6 (d, C-1), 205.3 (d, C-1), 72.2 (d, C-3), 72.0 (d, C-3), 65.4 (t, C-5), 64.8 (t, C-5), 51.8 (d, C-2), 50.0 (d, C-2), 40.6 (d, C-4), 39.3 (d, C-4), 26.1 (q, TBS), 26.0 (q, TBS), 18.4 (s, TBS), 18.4 (s, TBS), 18.4 (s, TBS), 18.3 (s, TBS), 13.8 (q, C-2'), 11.7 (q, C-2'), 9.6 (q, C-1'), 8.1 (q, C-1'), -3.9 (q, TBS), -4.1 (q, TBS), -4.2 (q, TBS), -4.4 (q, TBS), -5.2 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{19}H_{42}O_3Si_2$ [M+Na]$^+$: 397.2570, found 397.2570.

Ethyl (4*S*,5*R*,*E*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-enoate (284)



192 **284**

To a solution of aldehyde **192** (1.43 g, 3.82 mmol, 1.00 eq.) in THF (19 ml) was added ethyl 2-(triphenylphosphaneylidene)propanoate (2.08 g, 5.73 mmol, 1.50 eq.) and stirring was continued at 60 °C for 3 d. The reaction was concentrated on silica and purified by column chromatography (PE:EA = 10:1) to yield a diastereomeric mixture of ester **284** (1.50 g, 3.27 mmol, 86 %) as a colorless oil.

Characterization of the diastereomeric mixture:

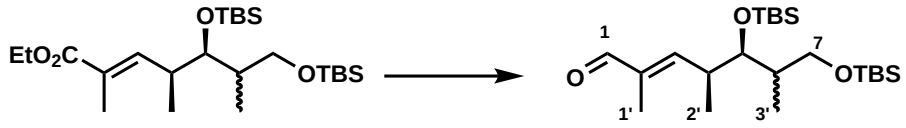
$\mathbf{R_f} = 0.61$ (PE:EA =10:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.71 - 6.67 (m, 1H, H-3_{d1}), 6.59 - 6.55 (m, 1H, H-3_{d2}), 4.18 (q, $J = 7.2$ Hz, 2H, OEt_{d1}), 4.18 (q, $J = 7.1$ Hz, 2H, OEt_{d2}), 3.74 - 3.35 (m, 3H, H-5, H-7), 2.74 - 2.62 (m, 1H, H-4), 1.89 - 1.78 (m, 4H, H-6, H-1'), 1.29 (t, $J = 7.1$ Hz, 3H, OEt_{d1}), 1.28 (t, $J = 7.2$ Hz, 3H, OEt_{d2}), 1.00 - 0.77 (m, 24H, H-2', H-3', TBS), 0.07 - 0.01 (m, 12H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 168.5 (s, C-1), 146.3 (d, C-3), 145.5 (d, C-3), 126.6 (s, C-2), 126.2 (s, C-2), 76.4 (d, C-5), 75.0 (d, C-5), 65.2 (t, C-7), 60.6 (t, OEt), 41.3 (d, C-6), 40.2 (d, C-6), 38.1 (d, C-4), 36.5 (d, C-4), 26.4 (q, TBS), 26.3 (q, TBS), 26.1 (q, TBS), 26.1 (q, TBS), 18.7 (s, TBS), 18.6 (s, TBS), 18.4 (s, TBS), 18.4 (s, TBS), 15.1 (q, C-3'), 14.5 (q, OEt), 14.4 (q, OEt), 13.8 (q, C-2'), 12.7 (q, C-1'), 12.6 (q, C-1'), -3.8 (s, TBS), -4.1 (s, TBS), -5.2 (s, TBS), -5.3 (s, TBS);

HRMS (ESI): m/z calc. for $C_{24}H_{50}O_4Si_2$ $[M+Na]^+$: 481.3145, found 481.1346.

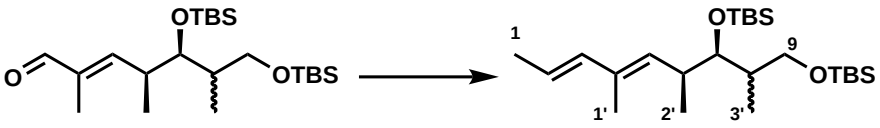
(4*S*,5*R*,*E*)-5,7-bis((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-enal (193)



284 **193**

To a solution of ester **284** (1.50 g, 3.27 mmol, 1.00 eq.) in CH_2Cl_2 (5.5 ml) at −78 °C was added to −78 °C pre-cooled DIBAl-H (1 M in hexane, 9.8 ml, 9.81 mmol, 3.00 eq.) and stirring was continued for 5 min. The reaction was diluted with EA, and terminated by addition of MeOH and a sat. Rochelle salt solution. After stirring for 2 h the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude alcohol was dissolved in CH_2Cl_2 (16 ml) and MnO_2 (7.10 g, 81.70 mmol, 25.0 eq.) was added. Stirring was continued overnight and the reaction was filtered over Celite^{TM} and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded a diastereomeric mixture of aldehyde **193** (1.08 g, 2.59 mmol, 79 % over 2 steps) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.29$ (PE:EA =20:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 9.39 (s, 1H, H-1_{d1}), 9.37 (s, 1H, H-1_{d2}), 6.46 (dd, $J = 10.3$, 1.5 Hz, 1H, H-3_{d1}), 6.30 (dd, $J = 10.3$, 1.1 Hz, 1H, H-3_{d2}), 3.81 - 3.35 (m, 3H, H-5, H-7), 2.95 - 2.84 (m, 1H, H-4), 1.89 - 1.59 (m, 4H, H-6, H-1'), 1.07 (d, $J = 5.9$ Hz, 3H, H-2'), 0.94 - 0.79 (m, 21H, H-3', TBS), 0.08 - 0.00 (m, 12H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 195.7 (d, C-1), 195.6 (d, C-1), 159.0 (d, C-3), 158.1 (d, C-3), 138.1 (s, C-2), 137.5 (s, C-2), 76.0 (t, C-7), 74.6 (t, C-7), 65.5 (d, C-5), 65.1 (d, C-5), 41.4 (d, C-6), 40.4 (d, C-6), 38.6 (d, C-4), 36.8 (d, C-4), 26.3 (q, TBS), 26.2 (q, TBS), 26.0 (q, TBS), 26.0 (q, TBS), 18.6 (s, TBS), 18.5 (s, TBS), 18.4 (s, TBS), 16.9 (q, C-3'), 15.4 (q, C-3'), 13.6 (q, C-2'), 10.7 (q, C-2'), 9.5 (q, C-1'), 9.4 (q, C-1'), -3.5 (q, TBS), -3.8 (q, TBS), -3.8 (q, TBS), -5.2 (q, TBS), -5.2 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): m/z calc. for $C_{22}H_{46}O_3Si_2$ $[M+Na]^+$: 437.2883, found 437.2882.

(5R)-2,2,3,3,6,9,9,10,10-Nonamethyl-5-((*S*,3*E*,5*E*)-4-methylhepta-3,5-dien-2-yl)-4,8-dioxa-3,9-disilaundecane (285)

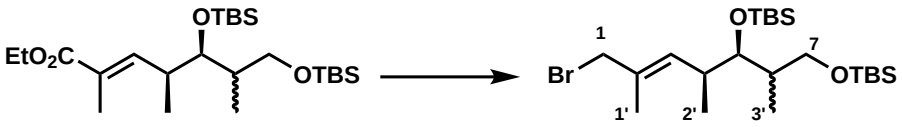


193 **285**

To a solution of $CrCl_2$ (355 mg, 2.89 mmol, 6.00 eq.) in THF (2.9 ml) was added a solution of aldehyde **193** (200 mg, 0.48 mmol, 1.00 eq.) and CHI_3 (570 mg, 1.45 mmol, 3.00 eq.) in THF (1.9 ml) and stirring was continued for 2 h. The reaction was diluted with EA and terminated by addition of a sat. $NaHCO_3$ solution, filtered and the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with water and with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 100:1) yielded a diastereomeric mixture of the vinyl iodide (56 mg, 0.10 mmol, 22 %) as a colorless oil. $ZnBr_2$ (234 mg, 1.04 mmol, 10.0 eq.) was suspended in THF (4.2 ml) and MeMgBr (3 M in Et_2O, 277 µl, 0.83 mmol, 8.00 eq.) was added dropwise at 0 °C and stirring was continued for 1 h at rt. After cooling the reaction to 0 °C a solution of vinyl iodide (56 mg, 0.10 mmol, 1.00 eq.) and $Pd(PPh_3)_4$ (24 mg, 20 µmol, 0.20 eq.) in THF (1.0 ml) was added added dropwise and stirring was continued at rt overnight. The reaction was diluted with Et_2O, the phases were separated and the organic phase was washed with a sat. NH_4Cl solution, a sat. $NaHCO_3$ solution and brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE) yielded the major diastereomer of diene **285** (18 mg, 42 µmol, 41 %) as a colorless oil.
$\mathbf{R_f}$ = 0.29 (PE:EA =20:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.05 (d, J = 17.7 Hz, 1H, H-3), 5.65 - 5.55 (m, 1H, H-2), 5.25 (d, J = 10.7 Hz, 1H, H-5), 3.64 (dd, J = 9.7, 5.7 Hz, 1H, H_a-9), 5.34 (dd, J = 5.3, 5.3 Hz, 1H, H-7), 3.4 (dd, J = 9.9, 7.4 Hz, 1H, H_b-9), 2.72 - 2.62 (m, 1H, H-6), 1.89 - 1.72 (m, 7H, H-1, H-8, H-1'), 0.99 - 0.89 (m, 24H, H-2', H-3', TBS), 0.09 - 0.02 (m, 12H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 136.4 (d, C-3), 134.8 (d, C-5), 131.9 (s, C-4), 122.4 (d, C-2), 77.6 (d, C-7), 65.4 (t, C-9), 41.3 (d, C-8), 35.8 (d, C-6), 26.3 (q, TBS), 26.1 (q, TBS), 18.6 (s, TBS), 18.5 (s, TBS), 18.4 (q, C-1), 16.8 (q, C-3'), 13.9 (q, C-2'), 12.8 (q, C-1'), -3.8 (q,

TBS), -3.8 (q, TBS), -5.2 (q, TBS), -5.2 (q, TBS);
HRMS (ESI): m/z calc. for $C_{24}H_{50}O_2Si_2$ [M+Na]$^+$: 449.3247, found 449.3253.

(5*R*)-5-((*S*,*E*)-5-Bromo-4-methylpent-3-en-2-yl)-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (286)

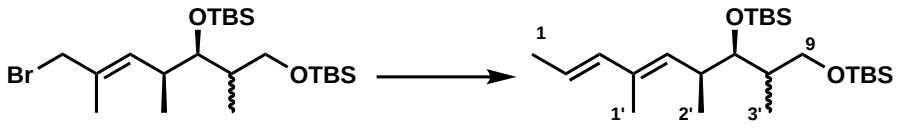


284 **286**

To a solution of ester **284** (1.50 g, 3.27 mmol, 1.00 eq.) in CH_2Cl_2 (5.5 ml) at −78 °C was added to −78 °C pre-cooled DIBAl-H (1 M in hexane, 9.8 ml, 9.81 mmol, 3.00 eq.) and stirring was continued for 5 min. The reaction was diluted with EA, and terminated by addition of MeOH and a sat. Rochelle salt solution. After stirring for 2 h the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude alcohol (1.50 g, 3.60 mmol, 1.00 eq.) was dissolved in MeCN (36 ml) and PPh_3 (2.93 g, 11.16 mmol, 3.10 eq.) was added. After the solids were dissolved, the solution was cooled to 0 °C and 2,6-lutidine (129 µL, 1.12 mmol, 0.31 eq.) and CBr_4 (4.89 g, 14.76 mmol, 4.10 eq.) were added. After warming to rt stirring was continued for 15 min and the reaction was terminated by addition of brine. The suspension was filtered and the filtrate was extracted with Et_2O. The combined organic phases were washed with a sat. $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 100:1 to 20:1) yielded a diastereomeric mixture of allylic bromide **286** (1.15 g, 2.39 mmol, 67 %) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.85$ (PE:EA =20:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.50 (d, $J = 10.0$ Hz, 1H, H-3_{d1}), 5.37 (d, $J = 9.9$ Hz, 1H, H-3_{d2}), 4.00 - 3.93 (m, 2H, H-1), 3.63 - 3.33 (m, 3H, H-5, H-7), 2.60 - 2.46 (m, 1H, H-4), 1.85 - 1.73 (m, 4H, H-6, H-1'), 0.95 - 0.87 (m, 24H, H-2', H-3', TBS), 0.06 - 0.02 (m, 12H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 135.9 (d, C-3_{d1}), 135.5 (d, C-3_{d2}), 130.6 (s, C-2_{d2}), 130.0 (s, C-2_{d1}), 75.2 (t, C-7), 65.6 (d, C-5_{d2}), 65.2 (d, C-5_{d1}), 42.0 (t, C-1_{d1}), 41.9 (t, C-1_{d2}), 41.3 (d, C-6_{d1}), 39.7 (d, C-6_{d2}), 37.5 (d, C-4_{d1}), 35.9 (d, C-4_{d2}), 26.2 (q, TBS), 26.1 (q, TBS),

26.0 (q, TBS), 25.9 (q, TBS), 18.2 (s, TBS), 18.4 (s, TBS), 18.3 (s, TBS), 18.2 (s, TBS), 17.4 (q, C-3′$_{d1}$), 15.9 (q, C-3′$_{d2}$), 14.9 (q, C-1′), 14.8 (q, C-1′), 13.5 (q, C-2′$_{d1}$), 10.6 (q, C-2′$_{d2}$), -3.6 (q, TBS), -4.0 (q, TBS), -4.0 (q, TBS), -5.2 (q, TBS), -5.3 (q, TBS), -5.3 (q, TBS);
HRMS (ESI): *m*/*z* calc. for $C_{22}H_{47}BrO_2Si_2$ $[M+Na]^+$: 501.2196, found 501.2194.

(5R)-2,2,3,3,6,9,9,10,10-Nonamethyl-5-((*S*,3*E*,5*E*)-4-methylhepta-3,5-dien-2-yl)-4,8-dioxa-3,9-disilaundecane (285)

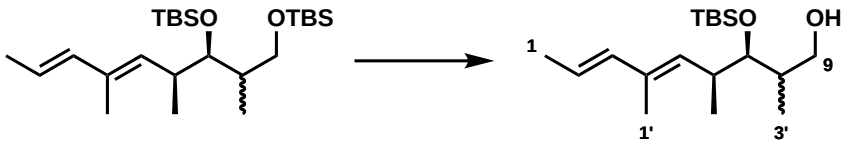


286 **285**

To a solution of bromide **286** (1.75 g, 3.64 mmol, 1.00 eq.) in MeCN (36 ml) was added freshly distilled PBu_3 (3.41 ml, 13.83 mmol, 3.80 eq.) at 0 °C and stirring was continued at that temperature overnight. The reaction was concentrated under reduced pressure and purified by column chromatography ($CHCl_3$:MeOH = 40:1) to yield the corresponding phosphonium salt (2.48 g) as a colorless solid. DMSO (5.17 ml, 72.78 mmol, 20.0 eq.) was dissolved in PhMe (48 ml) and *n*BuLi (1.6 M in THF, 11.4 ml, 18.20 mmol, 5.00 eq.) was added dropwise. After stirring for 45 min at rt, the solution was cooled to −78 °C and a solution of phosphonium salt (2.48 g, 3.64 mmol, 1.00 eq.) in PhMe (24 ml) was added dropwise and stirring continued for 1 h. Then, acetaldehyde (2.04 ml, 36.39 mmol, 10.0 eq.) was added dropwise and the solution was allowed to warm to rt overnight. The reaction was terminated by addition of a sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, fitlered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 100:1) yielded diene **285** (1.13 g, 2.65 mmol, 73 %) as a colorless oil.

The analytical data match those reported on page 188.

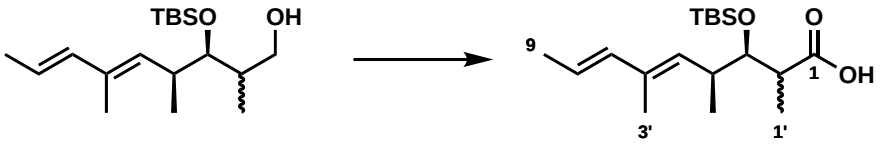
(3*R*,4*S*,5*E*,7*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylnona-5,7-dien-1-ol (196)



194 **196**

To a solution of bis-silyl ether **194** (548 mg, 1.28 mmol, 1.00 eq.) in EtOH (13 ml) was added PPTS (161 mg, 0.64 mmol, 0.50 eq.) and the reaction was stirred at rt for 2 d. After termination of the reaction by addition of a sat. $NaHCO_3$ solution the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded a diastereomeric mixture of alcohol **196** (350 mg, 1.12 mmol, 87 %) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.18$ (PE:EA =10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.05 (d, $J = 15.5$ Hz, 1H, H-3), 5.68 - 5.56 (m, 1H, H-2), 5.21 - 5.14 (m, 1H, H-5), 3.76 - 3.46 (m, 3H, H-7, H-9), 2.82 - 2-67 (m, 1H, H-6), 1.83 - 1.75 (m, 7H, H-8, H-1, H-1'), 1.06 - 0.99 (m, 6H, H-2', H-3'), 0.96 - 0.94 (m, 9H, TBS), 0.15 - 0.10 (m, 6H, TBS).

(3*R*,4*S*,5*E*,7*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylnona-5,7-dienoic acid (190)



196 **190**

To a solution of oxalyl chloride (97 µL, 1.13 mmol, 2.00 eq.) in CH_2Cl_2 (2.8 ml) was added DMSO (161 µL, 2.27 mmol, 4.00 eq.) at −78 °C and the reaction was stirred for 15 min. A solution of alcohol **196** (177 mg, 0.57 mmol, 1.00 eq.) in CH_2Cl_2 (2.0 ml) was added and stirring continued for another 30 min, after which Et_3N (0.47 ml, 3.40 mmol, 6.00 eq.) was added and the reaction was warmed to rt. After termination of the reaction by addition of a sat. NH_4Cl solution the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded the corresponding aldehyde (146 mg, 470.0 mmol, 83 %) as a colorless oil, which was immediately dissolved in *t*-BuOH (4.0 ml) and 2-methyl-2-butene (4.21 ml, 39.61 mmol, 100 eq.) was added and the reaction was cooled to 0 °C. A solution of $NaH_2PO_4 \cdot H_2O$ (437 mg, 3.17 mmol, 8.00 eq.) and $NaClO_2$ (214 mg, 2.38 mmol, 6.00 eq.) in H_2O (4.0 ml) was added dropwise *via* syringe pump (0.5 ml/min) and the reaction was warmed to rt over 50 min. After dilution with EA and termination of the reaction by addition of a pH 6 buffer solution, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1 to 5:1) yielded a diastereomeric mixture of carboxylic acid **190** (103 mg, 0.32 mmol, 80 %) as a colorless oil.

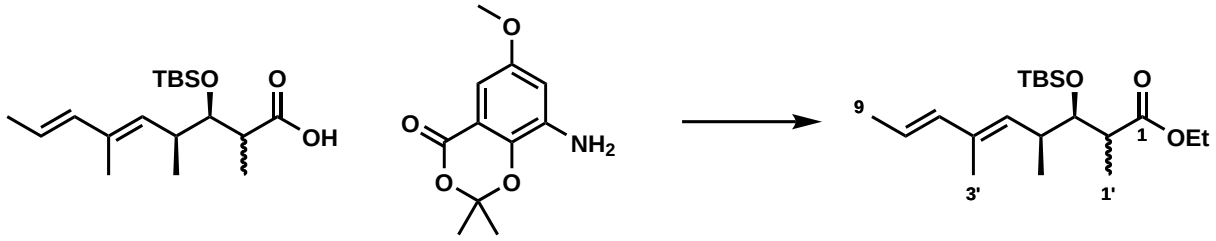
Characterization of the diastereomeric mixture:

$\mathbf{R_f}$ = 0.62 (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.06 - 5.95 (m, 1H, H-7), 5.66 - 5.56 (m, 1H, H-8), 5.16 (d, J = 10.3 Hz, 1H, H-5_{d1}), 5.09 (d, J = 10.0 Hz, 1H, H-5_{d2}), 3.93 (dd, J = 7.2, 3.5 Hz, 1H, H-3_{d1}), 3.72 (dd, J = 6.8, 3.5 Hz, 1H, H-3_{d2}), 2.77 - 2.58 (m, 2H, H-2, H-4), 1.79 - 1.71 (m, 6H, H-9, H-3'), 1.22 - 1.10 (m, 3H, H-2'), 1.00 - 0.97 (m, 3H, H-1'), 0.94 - 0.90 (m, 9H, TBS), 0.13 - 0.07 (m, 6H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 181.2 (s, C-1_{d1}), 179.4 (s, C-1_{d2}), 136.0 (s, C-7_{d1}), 135.9 (s, C-7_{d2}), 134.1 (d, C-6_{d2}), 133.7 (d, C-5_{d2}), 133.5 (d, C-6_{d1}), 132.8 (d, C-5_{d1}), 123.4 (d, C-8_{d2}), 123.3 (d, C-8_{d1}), 78.4 (d, C-3_{d2}), 77.3 (d, C-3_{d1}), 44.6 (d, C-4_{d2}), 43.8 (d, C-4_{d1}), 37.5 (d, C-2_{d1}), 36.7 (d, C-2_{d2}), 26.2 (q, TBS_{d1}), 26.1 (q, TBS_{d2}), 18.5 (s, TBS_{d1}), 18.4 (q, C-9_{d1}), 18.4 (s, TBS_{d2}), 17.6 (q, C-$1'_{d1}$), 17.1 (q, C-9_{d2}), 14.9 (q, C-$1'_{d2}$), 13.0 (C-$3'_{d2}$), 12.9 (q, C-$3'_{d1}$), 10.1 (q, C-$2'_{d1}$), 10.0 (q, C-$2'_{d2}$) -3.9 (q, TBS_{d1}), -4.0 (q, TBS_{d2}), -4.0 (q, TBS_{d1}), -4.2 (q, TBS_{d2});
HRMS (ESI): *m*/*z* calc. for $C_{18}H_{34}O_3Si$ $[M-H]^-$: 325.2199, found 325.2187.

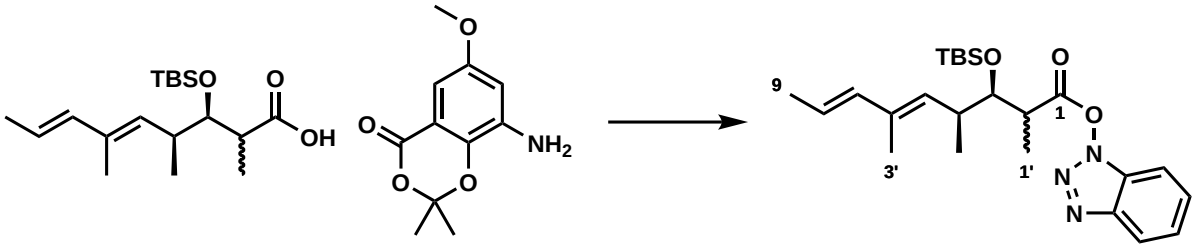
Ethyl (3*R*,4*S*,5*E*,7*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylnona-5,7-dienoate (204)



190 **187** **204**

To a solution of acid **190** (5.0 mg, 15 µmol, 1.00 eq.) and aniline **187** (4.1 mg, 18 µmol, 1.20 eq.) in $CHCl_3$ (0.8 ml) was added EEDQ (3.8 mg, 15 µmol, 1.00 eq.) at 0 °C and the reaction was warmed to rt overnight. The reaction was diluted with EA and terminated by addition of water, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded undesired ethyl ester **204** as a diastereomeric mixture.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.64$ (PE:EA =5:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.07 - 5.97 (m, 1H, H-7), 5.66 - 5.57 (m, 1H, H-8), 5.14 (d, $J = 10.0$ Hz, 1H, H-5), 4.35 - 4.29 (m, 2H, OEt), 3.94 (dd, $J = 7.7$, 3.0 Hz, 1H, H-3_{d1}), 3.84 (dd, $J = 7.0$, 4.4 Hz, 1H, H-3_{d2}), 2.78 - 2.56 (m, 2H, H-2, H-4), 1.79 - 1.73 (m, 6H, H-3', H-9), 1.38 - 1.33 (m, 3H, OEt), 1.18 (d, $J = 7.0$ Hz, 3H, H-$2'_{d1}$), 1.16 (d, $J = 7.0$ Hz, 3H, H-$2'_{d2}$), 1.01 (d, $J = 6.6$ Hz, 3H, H-$1'_{d1}$), 0.97 (d, $J = 6.6$ Hz, 3H, H-$1'_{d2}$), 0.90 (s, 9H, TBS), 0.08 - 0.03 (m, 6H, TBS).

1*H*-Benzo[d][1,2,3]triazol-1-yl (3*R*,4*S*,5*E*,7*E*)-3-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylnona-5,7-dienoate (205)



190 **187** **205**

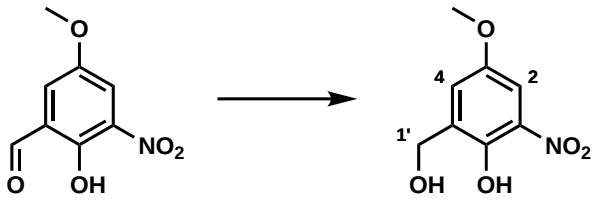
To a solution of acid **190** (5.0 mg, 15 µmol, 1.00 eq.) and aniline **187** (4.1 mg, 18 µmol, 1.20 eq.) in CH_2Cl_2 (0.8 ml) was added HOBt (0.9 mg, 6 µmol, 0.40 eq.) and EDC·HCl (12 mg, 61 µmol, 4.00 eq.) and the reaction was stirred at rt overnight. The reaction was terminated by addition of a pH 6 buffer solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded undesired benzotriazole ester **205** as a mixture of diastereomers.

Characterization of the diastereomeric mixture:

$\mathbf{R_f} = 0.74$ (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.11 - 8.07 (m, 1H, Ph), 7.59 - 7.51 (m, 1H, Ph), 7.48 - 7.40 (m, 2H, Ph), 6.11 (d, $J = 15.1$ Hz, 1H, H-7_{d1}), 6.09 (d, $J = 15.1$ Hz, 1H, H-7_{d1}), 5.73 - 5.61 (m, 1H, H-8), 5.30 - 5.24 (m, 1H, H-5), 4.12 (dd, $J = 7.2,\ 3.9$ Hz, 1H, H-3_{d1}), 3.96 (dd, $J = 8.1,\ 3.3$ Hz, 1H, H-3_{d2}), 3.28 - 3.16 (m, 1H, H-2), 3.05 - 2.96 (m, 1H, H-4_{d2}), 2.83 - 2.73 (m, 1H, H-4_{d1}), 1.87 - 1.76 (m, 6H, H-3', H-9), 1.46 - 1.41 (m, 3H, H-2'), 1.15 - 1.10 (m, 3H, H-1'), 0.96 (s, 9H, TBS), 0.18 - 0.09 (m, 6H, TBS).

2-(Hydroxymethyl)-4-methoxy-6-nitrophenol (208)



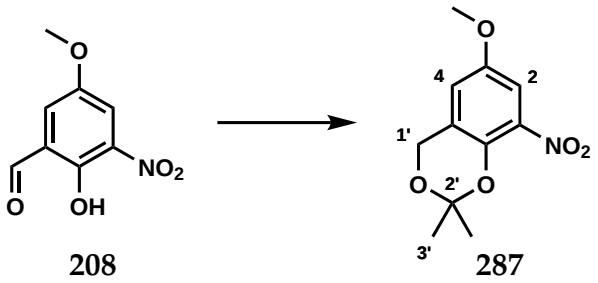
182 **208**

To a solution of aldehyde **182** (200 mg, 1.02 mmol, 1.00 eq.) in EtOH (5 ml) was added $NaBH_4$ (58 mg, 1.52 mmol, 1.50 eq.) at 0 °C and the reaction was allowed to warm to rt over 30 min. After concentration, the reaction was terminated by addition of a 1 M HCl solution. The residue was extracted with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield diol **208** (194 mg, 0.97 mmol, 96 %) as an orange solid.
mp. 118 °C (lit.: 106 °C)[193];
$\mathbf{R_f} = 0.71$ (PE:EA =1:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 10.73 (s, 1H, PhOH), 7.48 (d, $J = 2.9$ Hz, 2H, H-2), 7.38 (d, $J = 2.9$ Hz, 2H, H-4), 4.82 (d, $J = 6.3$ Hz, 1H, H-1'), 3.86 (s, 3H, OMe), 2.20 (t, $J = 6.5$ Hz, 1H, CH_2OH);
HRMS (ESI): m/z calc. for $C_8H_9NO_5Si$ $[M\text{-}H]^-$: 198.0402, found 198.0398.

The analytical data match those reported in the literature.[193]

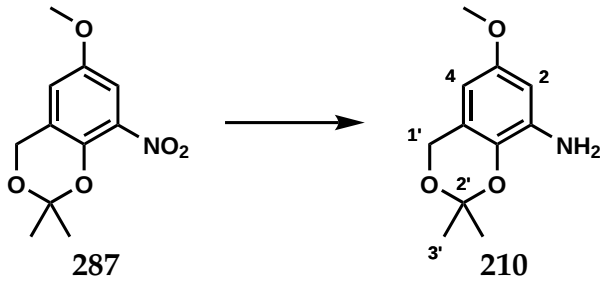
193 Y. Hayashi, M. Shoji, H. Ishikawa, J. Yamaguchi, T. Tamura, H. Imai, Y. Nishigaya, K. Takabe, H. Kakeya, H. Osada, *Angew. Chem. Int. Ed.* **2008**, *47*, 6657–6660.

6-Methoxy-2,2-dimethyl-8-nitro-4*H*-benzo[d][1,3]dioxine (287)



To a solution of diol **208** (100 mg, 0.50 mmol, 1.00 eq.) in acetone (1.6 ml) was added 2,2-dimethoxypropane (0.6 ml, 5.02 mmol, 10.0 eq.), Na_2SO_4 (263 mg, 1.86 mmol, 3.70 eq.) and *p*TsOH·H_2O (14 mg, 75 µmol, 0.15 eq.) at rt and the reaction was stirred overnight. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded acetonide **287** (85 mg, 0.36 mmol, 71 %) as a yellow solid.
$\mathbf{R_f}$ = 0.52 (PE:EA =3:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.34 (d, J = 2.9 Hz, 1H, H-2), 6.79 (d, J = 2.9 Hz, 1H, H-4), 4.87 (s, 2H, H-1'), 3.80 (s, 3H, OMe), 1.58 (s, 6H, H-3');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 152.0 (s, C-3), 140.3 (s, C-6), 123.3 (s, C-1), 116.7 (d, C-4), 108.8 (d, C-2), 101.2 (s, C-5), 60.7 (t, C-1'), 56.1 (q, OMe), 24.8 (q, C-3');
HRMS (ESI): m/z calc. for $C_{11}H_{13}NO_5$ $[M+Na]^+$: 262.0691, found 262.0690.

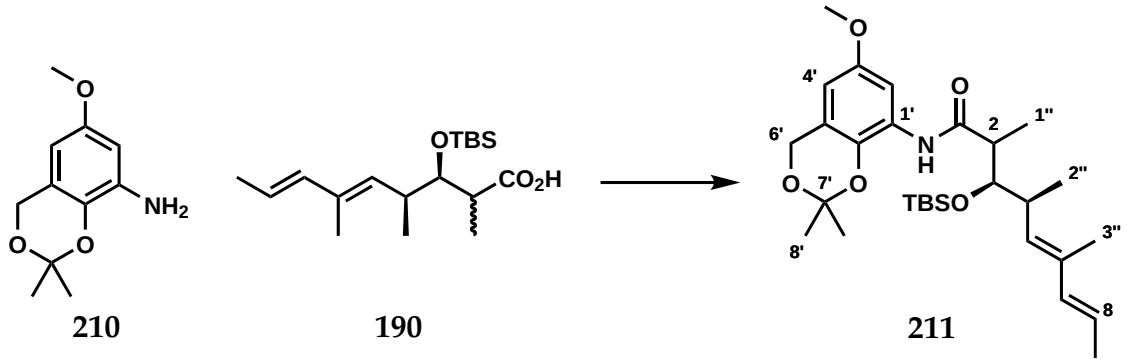
6-Methoxy-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-8-amine (210)



287 **210**

To a solution of nitroarene **287** (70 mg, 0.29 mmol, 1.00 eq.) in THF:MeOH (4:1, 2.5 ml) was added PtO_2-hydrate (17 mg, 59 µmol, 0.20 eq.) and H_2 was bubbled through the reaction for 10 min. An atmospheric pressure of H_2 was applied and the reaction was stirred for 1.5 h. The reaction was filtered over Celite^{TM} and concentrated under reduced pressure to yield aniline **210** (61 mg, 0.29 mmol, *quant.*) as a colorless solid.
mp. 59 °C;
$\mathbf{R_f} = 0.44$ (PE:EA =3:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.21 (d, $J = 2.8$ Hz, 1H, H-2), 5.93 (d, $J = 2.8$ Hz, 1H, H-4), 4.77 (s, 2H, H-1'), 3.71 (s, 3H, OMe), 1.54 (s, 6H, H-3');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 153.9 (s, C-3), 136.5 (s, C-6), 133.3 (s, C-1), 119.6 (s, C-5), 100.6 (d, C-2), 99.5 (s, C-2'), 97.8 (d, C-4), 61.2 (t, C-1'), 55.6 (q, OMe), 24.9 (q, C-3');
HRMS (ESI): m/z calc. for $C_{11}H_{15}NO_3$ $[M+Na]^+$: 232.0950, found 232.0953.

(3*R*,4*S*,5*E*,7*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-N-(6-methoxy-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-8-yl)-2,4,6-trimethylnona-5,7-dienamide (211)



210 **190** **211**

To a solution of carboxylic acid **190** (24 mg, 73 µmol, 1.00 eq.) in DMF (0.4 ml) was added DIPEA (16 µL, 87 µmol, 1.20 eq.) and COMU (37 mg, 87 µmol, 1.20 eq.) at 0 °C and the reaction was stirred for 5 min, after which TLC showed full conversion of the acid. Then, a solution of aniline **210** (30 mg, 0.15 mmol, 2.00 eq.) in DMF (0.4 ml) and DIPEA (25 µL, 0.15 mmol, 2.00 eq.) were added dropwise and the reaction was allowed to warm to rt overnight. After dilution with EA and termination of the reaction by addition of water, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a 1 M HCl solution, a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded amide **211** (14 mg, 26 µmol, 36 %) as a colorless oil.

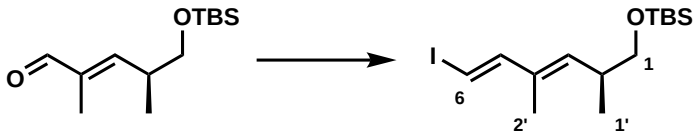
$\mathbf{R_f} = 0.65$ (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.00 - 7.95 (m, 2H, H-2, NH), 6.25 (d, $J = 2.8$ Hz, 1H, H-4'), 6.02 (dd, $J = 15.6$, 1.0 Hz, 1H, H-7), 5.62 - 5.53 (m, 1H, H-8), 5.20 (d, $J = 10.0$ Hz, 1H, H-5), 4.80 (s, 2H, H-6'), 3.91 (dd, $J = 7.2$, 4.0 Hz, 1H, H-3), 3.76 (s, 3H, OMe), 2.75 - 2.59 (m, 2H, H-2, H-4), 1.79 - 1.67 (m, 6H, H-9, H-3''), 1.55 (s, 6H, H-8'), 1.21 (d, $J = 7.5$ Hz, 3H, H-2''), 1.02 (d, $J = 6.7$ Hz, 3H, H-1''), 0.91 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.00 (s, 3H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 173.0 (s, C-1), 153.4 (s, C-3'), 136.1 (d, C-7), 134.0 (s, C-9'), 133.3 (s, C-1'), 133.1 (d, C-5), 127.9 (s, C-6), 123.2 (d, C-8), 119.3 (s, C-5'), 104.9 (d, C-2'), 104.3 (d, C-4'), 100.2 (s, C-7'), 78.4 (d, C-3), 61.0 (t, C-6'), 55.8 (q, OMe), 47.1 (d, C-2), 37.3 (d, C-4), 26.4 (q, C-8'), 26.3 (q, C-8'), 25.0 (q, TBS), 24.9 (q, TBS) 18.5 (s, TBS), 18.4 (q, C-9), 17.6 (q, C-2''), 12.9 (q, C-1''), 12.1 (q, C-3''), -3.9 (q, TBS), -4.0 (q, TBS);

HRMS (ESI): m/z calc. for $C_{29}H_{47}NO_5Si$ [M+Na]$^+$: 540.3121, found 540.3120.

***tert*-Butyl(((*S*,3*E*,5*E*)-6-iodo-2,4-dimethylhexa-3,5-dien-1-yl)oxy)dimethylsilane (213)**

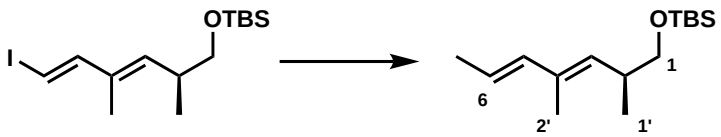


113 **213**

To a solution of $CrCl_2$ (1.44 g, 11.76 mmol, 6.00 eq.) in THF (11.8 ml) was added a solution of aldehyde **113** (475 mg, 1.96 mmol, 1.00 eq.) and CHI_3 (2.31 g, 5.87 mmol, 3.00 eq.) in THF (7.8 ml) dropwise and the resulting solution was stirred at rt for 2 h. After dilution with EA and termination of the reaction by addition of a sat. $NaHCO_3$ solution the suspension was filtered and the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 50:1) yielded a mixture of vinyl iodide **213** and CHI_3 (1.40 g) as a yellow solid[3].
$\mathbf{R_f} = 0.66$ (PE:EA =20:1);
$[\alpha]^{28}_{\mathbf{D}} = -7.1°$ ($c = 1.00$; $CHCl_3$);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.05 (dd, $J = 14.6,\ 0.7$ Hz, 1H, H-5), 6.17 (d, $J =$ 14.4 Hz, 1H, H-6), 5.29 (d, $J = 9.3$ Hz, 1H, H-3), 3.48 (dd, $J = 10.0,\ 6.2$ Hz, 1H, H_a-1), 3.43 (dd, $J = 9.7,\ 6.6$ Hz, 1H, H_b-1), 2.72 - 2.62 (m, 1H, H-2), 1.76 (d, $J = 1.2$ Hz, 3H, H-2'), 0.99 (d, $J = 6.7$ Hz, 3H, H-1'), 0.91 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 149.9 (d, C-5), 137.3 (d, C-3), 134.6 (s, C-4), 73.5 (d, C-6), 67.6 (t, C-1), 35.7 (d, C-2), 26.1 (q, TBS), 18.4 (s, TBS), 17.1 (q, C-1'), 12.4 (q, C-2'), -5.2 (q, TBS), -5.2 (q, TBS);

3 An aliquot was re-subjected to column chromatography and characterized, the next step was calculated assuming 100 % yield.

tert-Butyl(((*S*,3*E*,5*E*)-2,4-dimethylhepta-3,5-dien-1-yl)oxy)dimethylsilane (212)



213 **212**

To a solution of vinyl iodide **213** (718 mg, 1.96 mmol, 1.00 eq.) and $Pd(PPh_3)_2Cl_2$ (69 mg, 98 µmol, 0.05 eq.) in THF (7.8 ml) was added Me_2Zn (1.2 M in toluene, 1.96 ml, 2.35 mmol, 1.20 eq.) dropwise at 0 °C. The reaction was allowed to warm to rt overnight and then terminated by addition of water. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water and brine, dried over $MgSO_4$, fitlered and concentrated on silica under reduced pressure. Purification by column chromatography (PE:EA = 100:1) yielded diene **212** (440 mg, 1.73 mmol, 88 %) as a colorless oil.

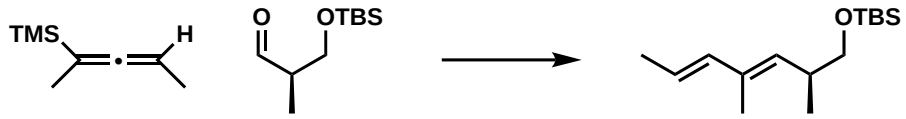
$\mathbf{R_f} = 0.57$ (PE:EA =50:1);

$[\alpha]^{30}_{\mathbf{D}} = +9.5°$ ($c = 1.00$; $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.08 (ddd, $J = 15.5, 1.5, 0.7$ Hz, 1H, H-5), 5.62 (dq, $J = 15.3, 6.6$ Hz, 1H, H-6), 5.14 (d, $J = 9.2$ Hz, 1H, H-3), 3.50 (dd, $J = 10.0, 5.9$ Hz, 1H, H_a-1), 3.37 (dd, $J = 9.8, 7.6$ Hz, 1H, H_b-1), 1.80 - 1.76 (m, 6H, H-2', H-7), 0.99 (d, $J = 6.6$ Hz, 3H, H-1'), 0.91 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 136.2 (d, C-5), 133.9 (s, C-4), 132.9 (d, C-3), 122.7 (d, C-6), 68.0 (t, C-1), 35.7 (d, C-2), 26.1 (q, TBS), 18.5 (s, TBS), 18.3 (q, C-7), 17.5 (q, C-1'), 13.0 (q, C-1'), -5.1 (q, TBS), -5.2 (q, TBS).

tert-Butyl(((*S*,3*E*,5*E*)-2,4-dimethylhepta-3,5-dien-1-yl)oxy)dimethylsilane (212)

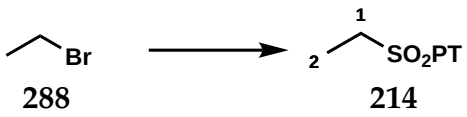


219 **109** **212**

To a solution of cyclohexene (112 µl, 1.11 mmol, 3.00 eq.) in THF (5.6 ml) was added $BH_3 \cdot Me_2S$ (53 µl, 0.56 mmol, 1.50 eq.) dropwise at 0 °C and the reaction was stirred for 1 h after which allene **219** (105 µl, 0.56 mmol, 1.50 eq.) was added dropwise and the resulting suspension was stirred for 3 h. Then a solution of aldehyde **109** (75 mg, 0.37 mmol, 1.00 eq.) in THF (1.9 ml) was added dropwise and stirring was continued for 30 min at 0 °C and then 30 min at rt. Concentrated H_2SO_4 (1 drop) was added and stirring was continued for 2 h after which 2 M NaOH and 30 % H_2O_2 were added. After stirring for an additional 20 min Et_2O was added and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE) yielded diene **212** (60 mg, 0.24 mmol, 64 % 3.5:1 *dr*) as a colorless oil.

The analytical data match those reported on page 202.

5-(Ethylsulfonyl)-1-phenyl-1*H*-tetrazole (214)



288 **214**

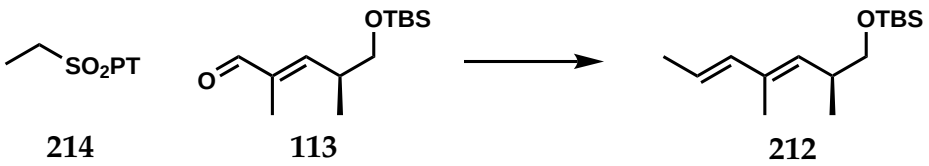
Sulfone **214** (3.87 g, 16.20 mmol, 59 %) was synthesized following a procedure by Merchant *et al*.[194]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.76 - 7.58 (m, 5H, Ph), 3.78 (q, $J = 7.4$ Hz, 2H, H-1), 1.55 (t, $J = 7.4$ Hz, 3H, H-2).

The analytical data match those reported in the literature.[194]

194 R. R. Merchant, J. T. Edwards, T. Qin, M. M. Kruszyk, C. Bi, G. Che, D. H. Bao, W. Qiao, L. Sun, M. R. Collins, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, P. Nuhant, P. S. Baran, *Science (80-.).* **2018**, *360*, 75–80.

tert-Butyl(((_S_,3_E_,5_E_)-2,4-dimethylhepta-3,5-dien-1-yl)oxy)dimethylsilane (212)

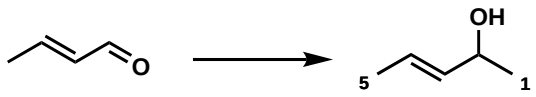


214 **113** **212**

A solution of aldehyde **113** (35 mg, 0.14 mmol, 1.00 eq.), sulfone **214** (67 mg, 0.29 mmol, 2.00 eq.) and Cs_2CO_3 (141 mg, 0.43 mmol, 3.00 eq.) in THF:DMF (3:1, 1.0 ml) was heated to 70 °C overnight. The reaction was terminated by addition of a sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE) yielded diene **212** (13 mg, 51 µmol, 35 % 5:1 *dr*) as a colorless oil.

The analytical data match those reported on page 202.

(*E*)-Pent-3-en-2-ol (217)



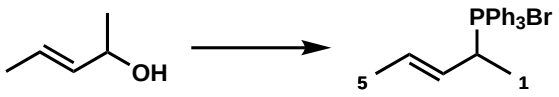
289 **217**

To a solution of freshly distilled crotonaldehyde **289** (5.00 g, 71.34 mmol, 1.00 eq., 77:1 (*E*):(*Z*)) in THF (71 ml) was added MeMgBr (3 M in Et_2O, 26.2 ml, 78.47 mmol, 1.10 eq.) dropwise at 0 °C. After stirring for 1 h the reaction was terminated by addition of a sat. NH_4Cl solution, the pahses were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and carefully concentrated under reduced pressure to yield alcohol **217** (2.85 g, 33.09 mmol, 46 %) as a colorless oil. No further purification of the compound was required.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.73 - 5.63 (m, 1H, H-3), 5.55 (ddq, J = 15.5, 6.6, 1.1 Hz, 1H, H-4), 5.55 (ddq, J = 15.5, 6.6, 1.1 Hz, 1H, H-4), 4.27 (q, J = 6.4 Hz, 1H, H-2), 1.71 (d, J = 5.9 Hz, 1H, H-5), 1.27 (d, J = 6.3 Hz, 1H, H-1).

The analytical data match those reported in the literature.[195]

195 J. B. Langlois, A. Alexakis, *Angew. Chemie - Int. Ed.* **2011**, *50*, 1877–1881.

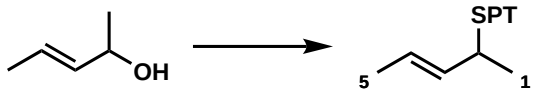
(*E*)-Bromo(pent-3-en-2-yl)triphenylphosphane (218)



217 **218**

To neat pentenol **217** (610 mg, 7.08 mmol, 1.00 eq.) was added PBr_3 (245 µl, 2.59 mmol, 0.37 eq.) dropwise at −10 °C and the reaction was allowed to sit without stirring at rt overnight. Dry hexane was added and the organic phase was transferred to a clean dry flask. This step was repeated three times. The combined hexane phases were concentrated under reduced pressure and then MeCN (7.0 ml) and PPh_3 (2.23 g, 8.50 mmol, 1.20 eq.) were added and the suspension was heated under refluxing conditions for 4 h. The supernatant was removed *via* syringe and the solid was washed with dry Et_2O and dried under reduced pressure to yield wittig salt **218** (307 mg, 0.75 mmol, 11 %) as an orange hygroscopic solid.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.06 - 8.00 (m, 6H, Ph), 7.78 - 7.69 (m, 9H, Ph), 6.52 - 6.41 (m, 1H, H-4), 6.28 - 6.17 (m, 1H, H-3), 5.24 - 5.15 (m, 1H, H-2), 1.65 - 1.61 (m, 3H, H-5), 1.44 (dd, $J = 19.0,\ 6.8$ Hz, 3H, H-1).

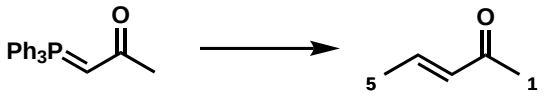
(*E*)-5-(Pent-3-en-2-ylthio)-1-phenyl-1*H*-tetrazole (221)



217 **221**

To a solution of pentenol **217** (1.00 g, 11.61 mmol, 1.00 eq.) in THF (23 ml) was added PPh_3 (4.57 g, 17.42 mmol, 1.50 eq.), PTSH (4.14 g, 23.22 mmol, 2.00 eq.) and DIAD (3.87 ml, 19.74 mmol, 1.70 eq.) and the reaction was stirred overnight. After termination of the reaction by addition of brine the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded thioether **221** (1.42 g, 3.90 mmol, 34 %) as a colorless oil.
$\mathbf{R_f} = 0.35$ (PE:EA =10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.60 - 7.53 (m, 5H, Ph), 5.87 - 5.77 (m, 1H, H-3), 5.56 (ddq, J = 15.2, 8.0, 1.6 Hz, 1H, H-4), 4.62 (dq, J = 6.8, 7.2 Hz, 1H, H-2), 1.70 - 1.67 (m, 3H, H-5), 1.60 (d, J = 7.0 Hz, 3H, H-1).

(*E*)-Pent-3-en-2-one (215)



220 **215**

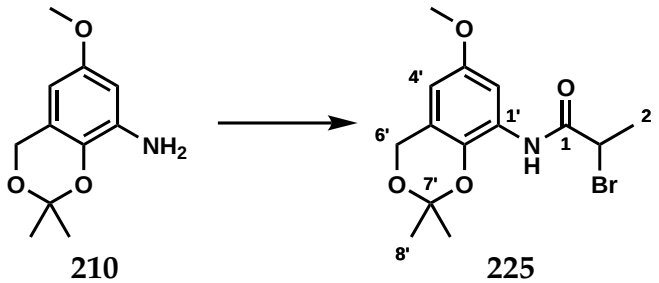
Pentenone **215** (1.40 g, 16.64 mmol, 53 %) was synthesized following the procedure of House *et al*.[196]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.81 (dq, $J = 15.7,\ 6.8$ Hz, 1H, H-4), 6.12 - 6.06 (m, 1H, H-3), 2.22 (s, 3H, H-1), 1.90 (dd, $J = 6.8,\ 1.7$ Hz, 3H, H-5).

The analytical data match those reported in the literature.[196]

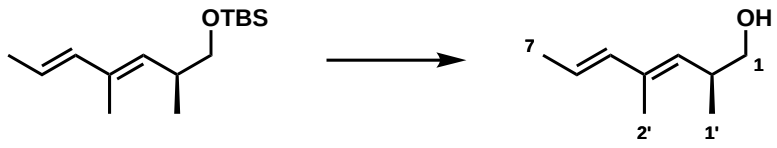
196 H. O. House, W. L. Respess, G. M. Whitesides, *J. Org. Chem.* **1966**, *31*, 3128–3141.

2-Bromo-*N*-(6-methoxy-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-8-yl)propanamide (225)



To a solution of aniline **210** (678 mg, 3.24 mmol, 1.00 eq.) and pyridine (800 µL, 8.10 mmol, 2.50 eq.) in CH_2Cl_2 (16 ml) was added 2-bromopropionyl bromide (560 µL, 4.86 mmol, 1.50 eq.) dropwise at 0 °C and stirring was continued for 30 min. After termination of the reaction by addition of water, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated on silica. Purification by column chromatography (PE:EA = 5:1) yielded amide **225** (986 mg, 2.87 mmol, 88 %) as a colorless solid.
mp. 97 °C;
$\mathbf{R_f}$ = 0.82 (PE:EA =3:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.56 (*brs*, 1H, NH), 7.92 (d, J = 3.2 Hz, 1H, H-4'), 6.30 (dt, J = 2.8, 0.6 Hz, 1H, H-2'), 4.80 (s, 2H, H-6'), 4.56 (q, J = 7.0 Hz, 1H, H-2), 3.76 (s, 3H, OMe), 2.0 (d, J = 7.5 Hz, 3H, H-3), 1.58 - 1.56 (m, 6H, H-8');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 167.1 (s, C-1), 153.4 (s, C-3'), 134.3 (s, C-9'), 127.1 (s, C-1'), 119.6 (s, C-5'), 105.1 (d, C-4'), 104.3 (d, C-4'), 100.5 (s, C-7'), 60.9 (t, C-6'), 55.9 (q, OMe), 45.6 (d, C-2), 24.9 (q, C-8'), 24.9 (q, C-8'), 23.1 (q, C-3);
HRMS (ESI): m/z calc. for $C_{14}H_{18}BrNO_4$ $[M+Na]^+$: 366.0317, found 366.0301.

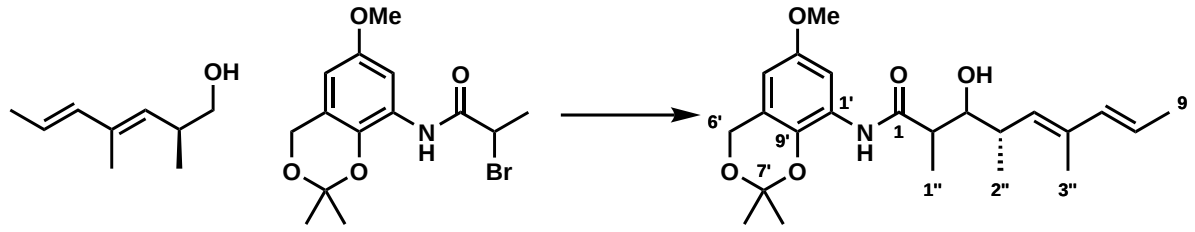
(*S*,3*E*,5*E*)-2,4-Dimethylhepta-3,5-dien-1-ol (232)



212 **232**

To a solution of silyl ether **212** (0.874 g, 3.43 mmol, 1.00 eq.) in THF (6.9 ml) was added TBAF (1 M in THF, 10.3 ml, 10.30 mmol, 3.00 eq.) dropwise at 0 °C. The reaction was allowed to warm to rt over 30 min and was then terminated by addition of a sat. NH_4Cl solution. The phases were separated and the aqeuous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 5:1) yielded alcohol **232** (0.49 mg, 2.92 mmol, 85 %) as a colorless oil.
$\mathbf{R_f} = 0.14$ (PE:EA =3:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.08 (d, $J = 17.7$ Hz, 1H, H-5), 5.69 - 5.57 (m, 1H, H-6), 5.10 (d, $J = 9.6$ Hz, 1H, H-3), 3.52 - 3.32 (m, 2H, H-1), 2.78 - 2.67 (m, 1H, H-2), 1.83 - 1.74 (m, 6H, H-7, H-2'), 8.96 (d, $J = 6.6$ Hz, 3H, H-1');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 135.9 (s, C-4), 135.7 (d, C-5), 132.1 (d, C-3), 123.5 (d, C-6), 68.0 (t, C-1), 35.7 (d, C-2), 18.3 (q, C-7), 17.1 (q, C-1'), 13.1 (q, C-2');
HRMS (EI): m/z calc. for $C_9H_{16}O$ $[M]^{\cdot+}$: 140.1201, found 140.1203.

(4*S*,5*E*,7*E*)-3-Hydroxy-*N*-(6-methoxy-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-8-yl)-2,4,6-trimethylnona-5,7-dienamide (227)



232 **225** **227**

To a solution of alcohol **232** (120 mg, 0.86 mmol, 1.10 eq.) in DMSO (8.6 ml) was added $NaHCO_3$ (719 mg, 8.56 mmol, 11.0 eq.) and IBX (719 mg, 2.57 mmol, 3.30 eq.) and the reaction was stirred at rt. After dilution with Et_2O and termination of the reaction by addition of a sat. $Na_2S_2O_3$ solution the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with a sat. $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, filtered and carefully concentrated under reduced pressure. Purification by column chromatography (pentane:Et_2O = 20:1) yielded aldehyde **226** (54 mg, 0.39 mmol, 46 %) as a colorless oil, which was immediately dissolved in THF (3.9 ml) and amide **225** (121 mg, 0.35 mmol, 1.00 eq.) was added. This solution was then added to a SmI_2 solution[171] (0.1 M in THF, 11.7 ml, 1.17 mmol, 3.30 eq.) dropwise at −78 °C. Stirring was continued for 15 min after which the reaction was diluted with EA and terminated by addition of a 1 M HCl solution. The phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with a sat. $Na_2S_2O_3$ solution, a sat. $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 3:1) yielded a diastereomeric mixture[4] of alcohol **227** (142 mg, 0.35 mmol, *quant.*) as a colorless oil.

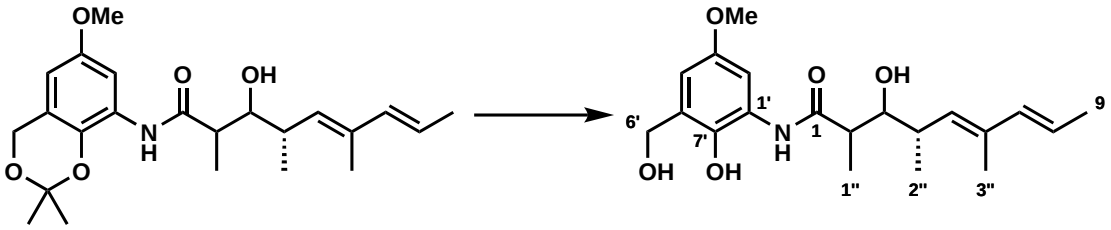
$\mathbf{R_f}$ = 0.62 (PE:EA =1:1);

^{1}H-NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.98 (d, J = 2.8 Hz, 1H, H-2'), 7.65 (*brs*, 1H, NH), 6.27 (d, J = 2.9 Hz, 1H, H-4'), 6.06 (dd, J = 15.8, 1.1 Hz, 1H, H-7), 5.58 (dq, J = 14.9, 6.9 Hz, 1H, H-8), 5.13 (d, J = 10.4 Hz, 1H, H-5), 4.79 (s, 2H, H-6'), 3.77 - 3.75 (m, 3H, OMe), 3.67 (d, J = 9.8 Hz, 1H, OH), 3.30 (dt, J = 9.1, 2.9 Hz, 1H, H-3), 2.65 - 2.54 (m, 2H, H-2, H-4),

4 An aliquot of the mixture was purified by HPLC for analytical purposes.

1.76 (dd, $J = 6.7,\ 1.5$ Hz, 3H, H-9), 1.62 (d, $J = 1.3$ Hz, 3H, H-3″), 1.52 (s, 3H, H_a-8′), 1.51 (s, 3H, H_b-8′), 1.41 (d, $J = 7.2$ Hz, 3H, H-1″), 1.10 (d, $J = 6.5$ Hz, 3H, H-2″);
^{13}C-NMR (125 MHz, $CDCl_3$) δ [ppm] = 175.2 (s, C-1), 153.4 (s, C-3′), 136.0 (d, C-7), 134.0 (s, C-9′), 133.9 (s, C-1′), 132.6 (d, C-5), 127.3 (s, C-6), 123.4 (d, C-8), 119.5 (s, C-5′), 104.8 (d, C-2′), 104.8 (d, C-4′), 100.4 (s, C-7′), 79.3 (d, C-3), 61.0 (t, C-6′), 55.9 (q, OMe), 44.0 (d, C-2), 38.7 (d, C-4), 24.9 (q, C-8′), 24.7 (q, C-8′), 18.3 (q, C-9), 17.8 (q, C-2″), 16.8 (q, C-1″), 13.1 (q, C-3″);
HRMS (ESI): m/z calc. for $C_{23}H_{33}NO_5$ $[M+Na]^+$: 426.2256, found 426.2252.

(4*S*,5*E*,7*E*)-3-Hydroxy-*N*-(2-hydroxy-3-(hydroxymethyl)-5-methoxyphenyl)-2,4,6-trimethylnona-5,7-dienamide (290)



227 **290**

To a solution of acetonide **227** (18 mg, 45 µmol, 1.00 eq.) in MeOH (0.45 ml) was added *p*TsOH·H_2O (8 mg, 45 µmol, 1.00 eq.) at rt and stirring was continued for 1 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 2:1) yielded a diastereomeric mixture[5] of diol **290** (11 mg, 30 µmol, 68 %) as a colorless oil.

$\mathbf{R_f}$ = 0.48 (PE:EA =1:1);

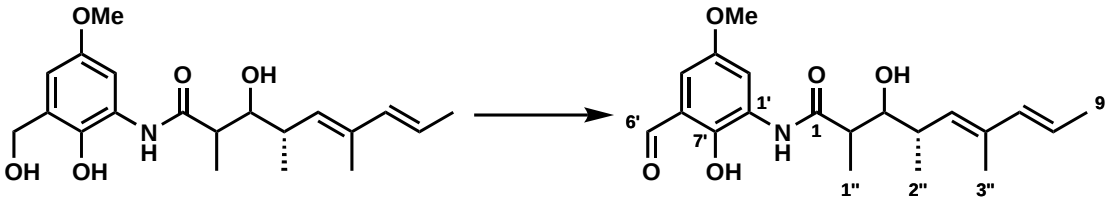
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.34 (s, 1H, PhOH), 8.13 (*brs*, 1H, NH), 7.05 (d, J = 2.9 Hz, 1H, H-2′), 6.55 (d, J = 3.0 Hz, 1H, H-4′), 6.05 (dd, J = 15.5, 1.1 Hz, 1H, H-7), 5.68 - 5.56 (m, 1H, H-8), 5.12 (d, J = 10.0 Hz, 1H, H-6), 4.77 (s, 1H, H_a-6′), 4.76 (s, 1H, H_b-6′), 3.75 (s, 3H, OMe), 3.39 (dt, J = 8.4, 3.5 Hz, 1H, H-3), 3.26 (d, J = 7.7 Hz, 1H, CHO*H*), 2.73 - 2.59 (m, 3H, H-2, H-4, CH_2O*H*), 1.78 - 1.74 (m, 3H, H-9), 1.66 (d, J = 1.1 Hz, 1H, H-3″), 1.39 (d, J = 7.4 Hz, 3H, H-1″), 1.09 (d, J = 6.6 Hz, 3H, H-2″);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 176.0 (s, C-1), 153.1 (s, C-3′), 140.3 (d, C-7), 135.9 (s, C-9′), 134.6 (s, C-1′), 131.7 (d, C-5), 128.9 (s, C-6), 126.5 (d, C-8), 123.8 (s, C-5′), 110.6 (d, C-2′), 106.5 (d, C-4′), 78.8 (d, C-3), 64.0 (t, C-6′), 56.0 (q, OMe), 44.0 (d, C-2), 38.1 (d, C-4), 18.4 (q, C-9), 17.4 (q, C-2″), 16.7 (q, C-1″), 13.1 (q, C-3″);

HRMS (ESI): m/z calc. for $C_{20}H_{29}NO_5$ $[M+Na]^+$: 386.1943, found 386.1933.

5 An aliquot of the mixture was purified by HPLC for analytical purposes.

(4*S*,5*E*,7*E*)-*N*-(3-Formyl-2-hydroxy-5-methoxyphenyl)-3-hydroxy-2,4,6-trimethylnona-5,7-dienamide (228)



290 **228**

To a solution of diol **290** (301 mg, 0.83 mmol, 1.00 eq.) in CH_2Cl_2 (41 ml) was added MnO_2 (1.44 g, 16.56 mmol, 20.0 eq.) at rt and stirring was continued for 3 h. The reaction was filtered over Celite^{TM} and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 3:1) yielded a diastereomeric mixture[6] of aldehyde **228** (205 mg, 0.57 mmol, 69 %) as a colorless oil.

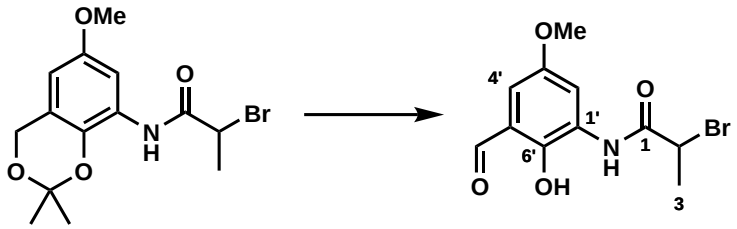
$\mathbf{R_f} = 0.56$ (PE:EA =1:1);

^{1}H-NMR (500 MHz, $CDCl_3$) δ [ppm] = 11.01 (s, 1H, PhOH), 9.85 (s, 1H, CHO), 8.40 (d, $J = 3.0$ Hz, 1H, H-2′), 8.05 (*brs*, 1H, NH), 6.79 (d, $J = 2.9$ Hz, 1H, H-2′), 6.04 (dd, $J = 15.4,\ 1.2$ Hz, 1H, H-7), 5.57 (dq, $J = 14.3,\ 7.0$ Hz, 1H, H-8), 5.13 (d, $J = 10.1$ Hz, 1H, H-5), 3.83 (s, 3H, OMe), 3.40 - 3.33 (m, 2H, H-3, CHO*H*), 2.68 - 2.60 (m, 2H, H-2, H-4), 1.76 (dd, $J = 6.6,\ 1.2$ Hz, 6.7H, H-9), 1.61 (d, $J = 1.4$ Hz, 3H, H-3″), 1.40 (d, $J = 7.0$ Hz, 3H, H-1″), 1.10 (d, $J = 6.6$ Hz, 3H, H-2″);

^{13}C-NMR (125 MHz, $CDCl_3$) δ [ppm] = 196.6 (s, CHO), 175.4 (s, C-1), 152.9 (s, C-3′), 144.8 (s, C-7′), 135.8 (d, C-7), 134.4 (s, C-6), 132.0 (d, C-5), 127.9 (s, C-5′), 123.7 (d, C-8), 119.3 (s, C-1′), 114.6 (d, C-2′), 110.2 (d, C-4′), 79.0 (d, C-3), 56.2 (q, OMe), 44.2 (d, C-2), 38.3 (d, C-4), 18.4 (q, C-9), 17.4 (q, C-2′), 16.6 (q, C-1′), 13.0 (q, C-3′).

6 An aliquot of the mixture was purified by HPLC for analytical purposes.

2-Bromo-*q*-(3-formyl-2-hydroxy-5-methoxyphenyl)propanamide (230)



225 **230**

To a solution of acetonide **225** (200 mg, 0.58 mmol, 1.00 eq.) in MeOH (2.9 ml) was added *p*TsOH·H_2O (110 mg, 0.58 mmol, 1.00 eq.) and stirring was continued at rt overnight. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 2:1) yielded diol **291** (152 mg, 0.50 mmol, 86 %) as a colorless solid, which was dissolved in CH_2Cl_2 (3.7 ml) and was added MnO_2 (652 mg, 7.50 mmol, 20.0 eq.) and stirring was continued at rt for 2 h. After filtration over Celite^{TM} and concentration under reduced pressure, purification by column chromatography (PE:EA = 5:1) yielded aldehyde **230** (47 mg, 0.12 mmol, 31 %) as a yellow solid.

mp. 124 °C;

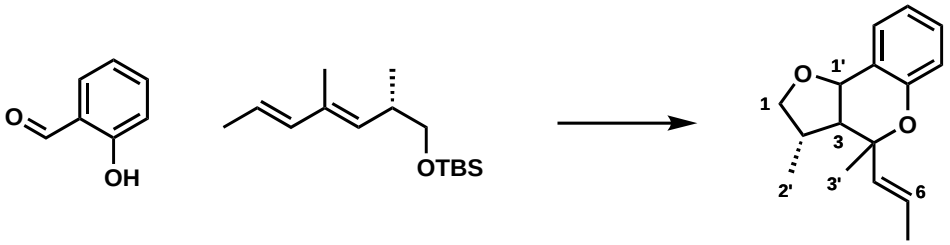
$\mathbf{R_f} = 0.79$ (PE:EA =1:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 11.11 (s, 1H, PhOH), 9.88 (s, 1H, CHO), 8.69 (*brs*, 1H, NH), 8.38 (d, $J = 2.6$ Hz, 1H, H-2'), 6.84 (d, $J = 3.7$ Hz, 1H, H-4'), 4.60 (q, $J = 7.0$ Hz, 1H, H-2), 3.86 (s, 3H, OMe), 2.00 (d, $J = 7.0$ Hz, 3H, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 197.5 (s, CHO), 167.6 (s, C-1), 152.9 (s, C-3'), 144.9 (s, C-7'), 127.6 (s, C-5'), 119.3 (s, C-1'), 114.2 (d, C-2'), 110.6 (d, C-4'), 56.2 (q, OMe), 44.9 (d, C-2), 22.3 (q, C-3);

HRMS (ESI): m/z calc. for $C_{11}H_{12}BrNO_4$ $[M+Na]^+$: 323.9847, found 323.9863.

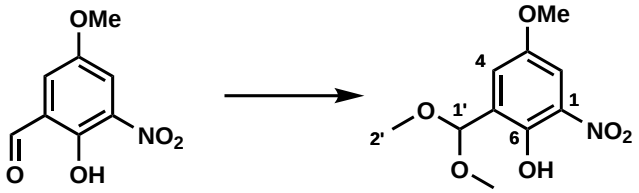
(3*S*)-3,4-Dimethyl-4-((*E*)-prop-1-en-1-yl)-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-c]chromene (236)



235 **212** **236**

To a solution of salicylaldehyde (**235**) (5 mg, 20 µmol, 1.00 eq.) and diene **212** (2.9 mg, 24 µmol, 1.20 eq.) in PhMe (0.4 ml) was added $CH(OMe)_3$ (2.6 µL, 24 µmol, 1.20 eq.) and *p*$TsOH \cdot H_2O$ (0.8 mg, 4 µmol, 0.20 eq.) and stirring was continued at rt overnight. After termination of the reaction by addition of water, the phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 15:1) yielded a diastereomeric mixture of undesired tetrahydrofuran **236** as the major product.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.49$ (PE:EA =5:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 - 7.31 (m, 1H, Ph), 7.19 - 7.14 (m, 1H, Ph), 6.96 - 6.88 (m, 1H, Ph), 6.84 - 6.79 (m, 1H, Ph), 5.69 - 5.51 (m, 2H, H-5, H-6), 4.99 (d, $J = 7.0$ Hz, 1H, H-1'$_{d1}$), 4.96 (d, $J = 7.0$ Hz, 1H, H-1'$_{d2}$), 3.82 (t, $J = 8.5$ Hz, 1H, H_a-1), 3.40 (dd, $J = 8.7$, 5.3 Hz, 1H, H_b-1), 2.40 - 2.29 (m, 1H, H-2), 1.72 (dd, $J = 6.6$, 1.5 Hz, 3H, H-7$_{d1}$), 1.63 (dd, $J = 6.1$, 1.3 Hz, 3H, H-7$_{d2}$), 1.43 (s, 3H, H-3'), 1.19 (d, $J = 7.0$ Hz, 3H, H-2').

2-(Dimethoxymethyl)-4-methoxy-6-nitrophenol (244)



182 **244**

To a solution of aldehyde **182** (36 mg, 0.18 mmol, 1.00 eq.) in MeOH (3.0 ml) was added *p*TsOH·H_2O (7 mg, 37 µmol, 0.20 eq.) and $CH(OMe)_3$ (0.2 ml, 1.83 mmol, 10.0 eq.) and stirring was continued at rt for 3 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were spearated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield dimethyl acetal **244** (34 mg, 0.14 mmol, 77 %) as a yellow solid.

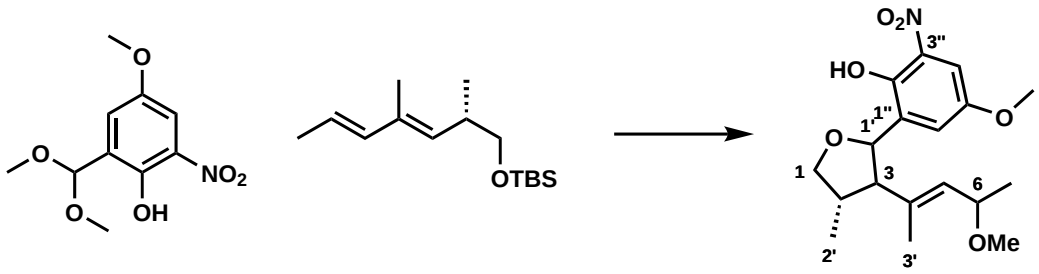
mp. 68 °C;

$\mathbf{R_f} = 0.61$ (PE:EA =3:1);

^{1}**H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 10.70 (s, 1H, PhOH), 7.54 - 7.51 (m, 2H, H-2, H-4), 5.69 (s, 1H, H-1'), 3.83 (s, 3H, OMe), 3.41 (s, 6H, H-3');

^{13}**C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 152.1 (s, C-3), 147.9 (s, C-6), 133.4 (s, C-5), 130.1 (s, C-1), 124.9 (d, C-4), 106.8 (d, C-2), 98.3 (d, C-1'), 56.2 (q, OMe), 54.2 (q, C-2');

2-((4*S*)-3-((*E*)-4-Methoxypent-2-en-2-yl)-4-methyltetrahydrofuran-2-yl)phenol (245)



244 **212** **245**

To a solution of dimethyl acetal **244** (5.0 mg, 20 µmol, 1.10 eq.) and diene **212** (4.3 mg, 18 µmol, 1.00 eq.) in PhMe (0.3 ml) was added *p*TsOH·H_2O (0.7 mg, 4 µmol, 0.20 eq.) and stirring was continued at rt overnight. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were spearated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded a diastereomeric mixture of undesired phenol **245** as the major product.

Characterization of the diastereomeric mixture:

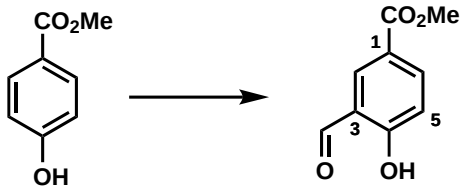
$\mathbf{R_f} = 0.41$ (PE:EA =5:1);

^{1}H-NMR (500 MHz, $CDCl_3$) δ [ppm] = 10.66 (s, 1H, $PhOH_{d1}$), 10.65 (s, 1H, $PhOH_{d2}$), 7.44 - 7.38 (m, 2H, Ph), 5.40 (d, $J = 7.5$ Hz, 1H, H-1'$_{d2}$), 5.32 (d, $J = 7.5$ Hz, 1H, H-1'$_{d2}$), 5.03 (dd, $J = 8.6,\ 0.8$ Hz, 1H, H-5$_{d1}$), ar4.84g1 (dd, $J = 8.6,\ 0.9$ Hz, 1H, H-5$_{d2}$), 4.41 - 4.37 (m, 1H, H-6), 3.85 - 3.77 (m, 4H, H_a-1, PhOMe), 3.53 - 3.48 (m, 1H, H_b-1), 3.06 (s, 3H, OMe_{d1}), 2.97 (s, 3H, OMe_{d2}), 2.91 (t, $J = 6.8$ Hz, 1H, H-3$_{d1}$), 2.81 (t, $J = 7.3$ Hz, 1H, H-3$_{d2}$), 2.49 - 2.41 (m, 1H, H-2), 1.50 (d, $J = 1.2$ Hz, 3H, H-3'$_{d2}$), 1.37 (d, $J = 1.3$ Hz, 3H, H-3'$_{d1}$), 1.15 (d, $J = 6.7$ Hz, 3H, H-7$_{d1}$), 1.13 (d, $J = 6.9$ Hz, 3H, H-7$_{d2}$), 0.89 (d, $J = 6.3$ Hz, 3H, H-2'$_{d2}$), 0.85 (d, $J = 6.5$ Hz, 3H, H-2'$_{d1}$);

^{13}C-NMR (125 MHz, $CDCl_3$) δ [ppm] = 152.1 (s, C-5''$_{d1}$), 152.1 (s, 5''$_{d1}$), 147.3 (s, C-2''$_{d1}$), 147.1 (s, C-2''$_{d2}$), 135.8 (s, C-4$_{d1}$), 135.4 (s, C-4$_{d2}$), 133.8 (s, C-3''$_{d1}$), 133.6 (s, C-3''$_{d2}$), 132.7 (s, C-1''$_{d1}$), 132.7 (s, C-1''$_{d2}$), 131.2 (d, C-5$_{d1}$), 130.1 (d, C-5$_{d2}$), 125.3 (d, C-6''$_{d1}$), 124.8 (d, C-6''$_{d2}$), 104.2 (d, C-4''$_{d1}$), 104.1 (d, C-4''$_{d1}$), 78.6 (q, OMe_{d1}), 78.1 (q, OMe_{d2}), 75.2 (t, C-1$_{d1}$), 75.0 (t, C-1$_{d2}$), 73.2 (d, C-6$_{d1}$), 73.1 (d, C-6$_{d2}$), 59.7 (d, C-1'$_{d1}$), 59.5 (d, C-1'$_{d2}$), 56.1 (q, $PhOMe_{d1}$), 56.1 (q, $PhOMe_{d2}$), 55.6 (d, C-3$_{d1}$), 55.4 (d, C-3$_{d2}$), 37.9 (d, C-2$_{d1}$), 37.3 (d,

C-2_{d2}), 21.0 (q, C-7_{d1}), 20.7 (q, C-7_{d2}), 17.7 (q, C-$3'_{d1}$), 17.6 (q, C-$3'_{d2}$), 17.1 (q, C-$2'_{d1}$), 15.8 (q, C-$2'_{d2}$).

Methyl 3-formyl-4-hydroxybenzoate (249)



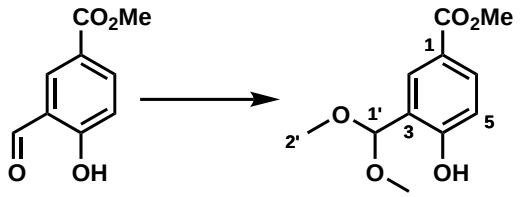
248 **249**

Aldehyde **249** (1.56 g, 8.66 mmol, 44 %) was synthesized following the protocol of Hofsløkken *et al*.[138]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 11.40 (s, 1H, PhOH), 9.96 (s, 1H, CHO), 8.33 (d, $J = 2.2$ Hz, 1H, H-2), 8.20 (dd, $J = 8.5,\ 1.8$ Hz, 1H, H-6), 7.04 (d, $J = 9.6$ Hz, 1H, H-5), 3.93 (s, 3H, CO_2Me).

The analytical data match those reported in the literature.[138]

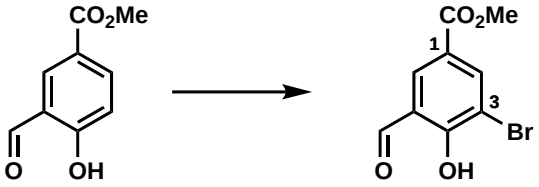
Methyl 3-(dimethoxymethyl)-4-hydroxybenzoate (250)



249 **250**

To a solution of aldehyde **249** (50 mg, 0.28 mmol, 1.00 eq.) in MeOH (0.4 ml) was added $LiBF_4$ (1 mg, 8 µmol, 0.03 eq.) and $CH(OMe)_3$ (40 µL, 0.36 mmol, 1.30 eq.) and the reaction was stirred under refluxing conditions overnight. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield dimethyl acetal **250** (68 mg, 0.28 mmol, *quant.*) as a white solid.
$\mathbf{R_f} = 0.23$ (PE:EA =5:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 8.59 (s, 1H, PhOH), 8.21 (d, $J = 1.8$ Hz, 1H, H-2), 8.06 (dd, $J = 8.5,\ 2.2$ Hz, 1H, H-6), 6.95 - 8.5 (m, 1H, H-5), 5.05 (s, 1H, H-1'), 3.51 (s, 3H, OMe), 2.83 (s, 6H, H-2').

Methyl 3-bromo-5-formyl-4-hydroxybenzoate (251)



249 **251**

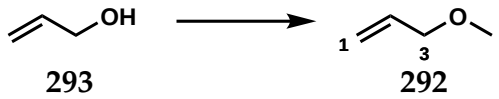
Bromoarene **251** (60 mg, 0.23 mmol, 84 %) was synthesized following the protocol of Kolesnikov *et al.*[197]

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 12.00 (s, 1H, PhOH), 9.91 (s, 1H, CHO), 8.45 (d, $J = 1.8$ Hz, 1H, H-2), 8.29 (d, $J = 1.8$ Hz, 1H, H-6), 3.94 (s, 3H, OMe).

The analytical data match those reported in the literature.[197]

197 A. Kolesnikov, S. Torkelson, T. Vojkvsky, 2 - ' 5 - (5-CARBAMIMIDOYL-1H-HETEROARYL)-6-HYDROXYBIPHENYL-3-YL! -CARBOXYLIC ACID DERIVATIVES AS FACTOR V I IA INHIBITORS, **2004**.

3-Methoxyprop-1-ene (292)



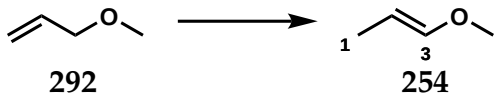
293 **292**

A solution of allyl alcohol (**293**) (25.5 g, 439.0 mmol, 1.00 eq.) and KOH (30.8 g, 548.8 mmol, 1.25 eq.) in DMSO (88 ml) was stirred for 1 h after which Me_2SO_4 (47.0 ml, 496.1 mmol, 1.13 eq.) was added dropwise. The reaction was heated to 60 °C and stirring was continued for 2 h. Afterwards, the product was distilled directly from the reaction to yield methyl allyl ether (**292**) (23.0 g, 319.0 mmol, 73 %) as a colorless oil.
bp. 45 °C (lit.: 43 °C[198])
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.93 (ddq, $J = 17.2,\ 10.4,\ 5.6$ Hz, 1H, H-2), 5.30 (dq, $J = 17.2,\ 1.7$ Hz, 1H, H_a-1), 5.21 (dq, $J = 10.4,\ 1.4$ Hz, 1H, H_b-1), 3.95 (dt, $J = 5.7,\ 1.4$ Hz, 2H, H-3), 3.37 (s, 3H, OMe).

The analytical data match those reported in the literature.[199]

198 G. H. Schmid, A. Modro, K. Yates, *J. Org. Chem.* **1977**, *42*, 871–875.
199 S. V. Ley, M. N. Tackett, M. L. Maddess, J. C. Anderson, P. E. Brennan, M. W. Cappi, J. P. Heer, C. Helgen, M. Kori, C. Kouklovsky, S. P. Marsden, J. Norman, D. P. Osborn, M. Á. Palomero, J. B. Pavey, C. Pinel, L. A. Robinson, J. Schnaubelt, J. S. Scott, C. D. Spilling, H. Watanabe, K. E. Wesson, M. C. Willis, *Chem. Eur. J.* **2009**, *15*, 2874–2914.

(*E*)-1-Methoxyprop-1-ene (254)



292 **254**

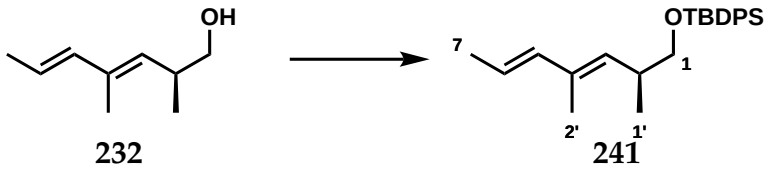
To a solution of allyl methyl ether (**292**) (5.00 g, 69.34 mmol, 1.00 eq.) in DMSO (12 ml) was added KOtBu (0.93 g, 8.32 mmol, 0.12 eq.) and stirring was continued at rt overnight. After distillation from the reaction mixture, vinyl ether **254** (3.30 g, 45.76 mmol, 66 %) as a colorless oil.
bp. 45 °C (lit.: 43 °C[200])
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.93 - 5.89 (m, 1H, H-1), 4.41 (q, $J = 6.7$ Hz, 1H, H-2), 3.62 (s, 3H, OMe), 1.60 (dd, $J = 6.8$, 1.7 Hz, 3H, H-3).

The analytical data match those reported in the literature.[201]

200 Roche Products, Novel acetals of alkadienic aldehydes, the manufacture thereof and conversion into a polyene aldehyde, **1956**.

201 T Tatsumi, K Hashimoto, H Tominaga, Y Mizuta, K Hata, M Hidai, Y Uchida, *J. Organomet. Chem.* **1983**, *252*, 105–112.

tert-Butyl(((_S_,3_E_,5_E_)-2,4-dimethylhepta-3,5-dien-1-yl)oxy)diphenylsilane (241)



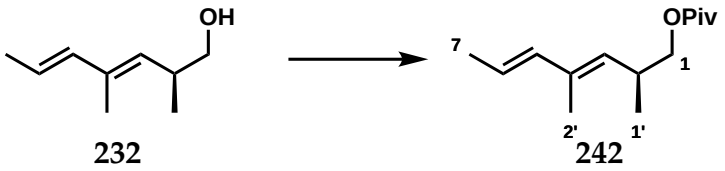
To a solution of alcohol **232** (40 mg, 0.29 mmol, 1.00 eq.) in CH_2Cl_2 (1.4 ml) was added imidazole (38 mg, 0.57 mmol, 2.00 eq.) and TBDPSCl (110 µL, 0.43 mmol, 1.50 eq.) and stirring was continued for 1 h at rt. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 50:1) yielded silyl ether **241** (92 mg, 0.24 mmol, 85 %) alongside silyl impurities as a colorless oil.

$\mathbf{R_f} = 0.92$ (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.68 - 7.64 (m, 5H, TBDPS), 6.06 - 6.00 (m, 1H, H-5), 5,57 (dq, $J = 15,2$, 6.6 Hz, 1H, H-6), 5.11 (d, $J = 9.2$ Hz, 1H, H-3), 3.51 (dd, $J = 9.7$, 5.9 Hz, 1H, H_a-1), 3.45 (dd, $J = 9.7$, 7.2 Hz, 1H, H_b-1), 2.75 - 2.64 (m, 1H, H-2), 1.75 (dd, $J =$ 6.8, 1.5 Hz, 3H, H-7), 1.66 (d, $J = 1.3$ Hz, 3H, H-2'), 1.05 (s, 9H, TBDPS), 1.02 (d, $J = 6.7$ Hz, 3H, H-1');

HRMS (ESI): m/z calc. for $C_{25}H_{34}OSi$ $[M+Na]^+$: 401.2277, found 401.2267.

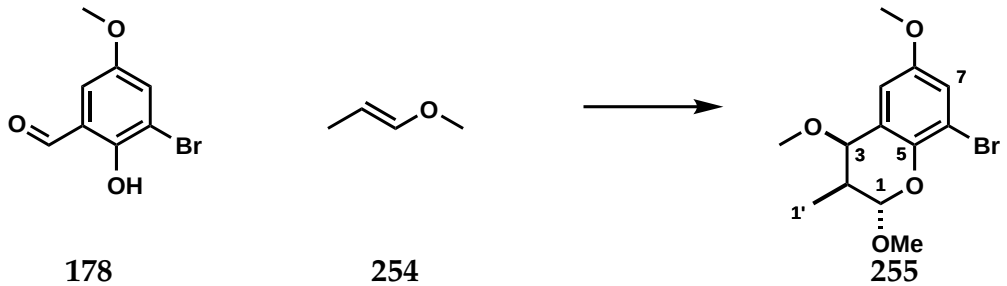
(*S*,3*E*,5*E*)-2,4-Dimethylhepta-3,5-dien-1-yl pivalate (242)



232 242

To a solution of alcohol **232** (70 mg, 0.50 mmol, 1.00 eq.) in CH_2Cl_2 (1 ml) was added pyridine (80 µL, 1.00 mmol, 2.00 eq.) and pivaloyl chloride (92 µL, 0.75 mmol, 1.50 eq.) and stirring was continued for 2 h at rt. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 30:1) yielded pivalate **242** (91 mg, 0.37 mmol, 74 %) as a colorless oil.
$\mathbf{R_f}$ = 0.57 (PE:EA =10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.05 (dd, J = 15.5, 1.1 Hz, 1H, H-5), 5.61 (dq, J = 15.3, 6.7 Hz, 1H, H-6), 5.11 (d, J = 9.4 Hz, 1H, H-3), 3.94 (dd, J = 10.7, 6.6 Hz, 1H, H_a-1), 3.83 (dd, J = 10.5, 7.2 Hz, 1H, H_b-1), 2.92 - 2.81 (m, 1H, H-2), 1.79 - 1.75 (m, 6H, H-2', H-7), 1.18 (s, 9H, Piv), 1.00 (d, J = 6.6 Hz, 3H, H-1');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 178.7 (s, Piv), 135.9 (d, C-5), 134.6 (s, C-4), 131.4 (d, C-3), 123.3 (d, C-6), 68.6 (t, C-1), 32.3 (s, Piv), 26.7 (q, Piv), 18.3 (q, C-7), 17.6 (q, C-1'), 12.9 (q, C-2');
HRMS (ESI): m/z calc. for $C_{14}H_{24}O_2$ $[M+Na]^+$: 247.1674, found 247.1674.

8-bromo-2,4,6-trimethoxy-3-methylchromane (255)



178 **254** **255**

To a solution of aldehyde **178** (1.00 g, 4.33 mmol, 1.00 eq.) in MeOH (43 ml) was added $CH(OMe)_3$ (21.3 ml, 194.8 mmol, 45.0 eq.) and pTsOH·H_2O (0.21 g, 1.08 mmol, 0.25 eq.) and stirring was continued at rt for 3 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude dimethyl acetal, which was immediately dissolved in PhMe (22 ml) and vinyl ether **254** (1.2 ml, 12.99 mmol, 3.00 eq.) and pTsOH·H_2O (0.17 g, 0.87 mmol, 0.20 eq.) were added and stirring continued at rt overnight. The reaction was terminated by addition of MeOH (22 ml) and $NaBH_4$ (0.16 g, 4.33 mmol, 1.00 eq.) was added. After 30 min the reaction was terminated by addition of a sat. $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with EA and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded chromane **255** (1.21 g, 3.83 mmol, 88 % over 2 steps) as a brown oil.

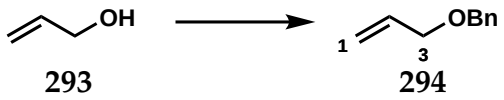
$\mathbf{R_f} = 0.47$ (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.02 (dd, J = 3.1, 0.5 Hz, 1H, H-7), 6.93 (dd, J = 3.0, 0.9 Hz, 1H, H-9), 5.05 (d, J = 3.5 Hz, 1H, H-1), 4.45 (d, J = 5.2 Hz, 1H, H-3), 3.76 (s, 3H, PhOMe), 3.50 (s, 3H, OMe), 3.46 (s, 3H, OMe), 2.4 (ddq, J = 7.0, 5.2, 3.5 Hz, 1H, H-2), 0.96 (d, J = 7.0 Hz, 3H, H-1');

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 154.1 (s, C-8), 141.7 (s, C-5), 124.9 (s, C-4), 118.5 (d, C-7), 112.3 (d, C-9), 110.6 (s, C-6), 103.9 (d, C-1), 74.3 (d, C-3), 56.9 (q, OMe), 56.2 (q, OMe), 56.0 (q, PhOMe), 32.8 (d, C-2), 10.1 (q, C-1');

HRMS (ESI): m/z calc. for $C_{14}H_{24}O_2$ $[M+H]^+$: 339.0208, found 339.0208.

((Allyloxy)methyl)benzene (294)



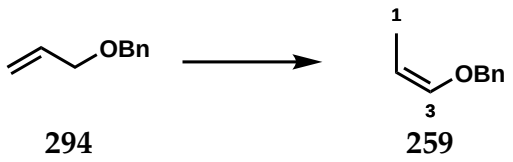
293 **294**

To a solution of allyl alcohol (**293**) (3.40 g, 58.47 mmol, 2.50 eq.) in THF (6 ml) was added NaH (60 % in mineral oil, 1.12 g, 28.06 mmol, 1.20 eq.) at 0 °C and the reaction was stirred for 1 h after which benzyl bromide (3.64 ml, 23.39 mmol, 1.00 eq.) was added dropwise. The reaction was heated to 75 °C and stirring was continued for 1 h. The reaction was terminated by addition of water and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 20:1) yielded benzyl ether **294** (2.20 g, 14.84 mmol, 64 %) as a colorless oil.
$\mathbf{R_f} = 0.54$ (PE:EA =10:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36 - 7.27 (m, 5H, Ph), 5.97 (ddq, $J = 16.8,\ 11.1,\ 5.6$ Hz, 1H, H-3), 5.32 (dq, $J = 17.3,\ 1.6$ Hz, 1H, H_a-1), 5.2 (dq, $J = 10.3,\ 1.5$ Hz, 1H, H_b-1), 4.53 (s, 2H, PhCH_2OR), 4.04 (dt, $J = 5.2,\ 1.5$ Hz, 1H, H-3).

The analytical data match those reported in the literature.[202]

202 L. Nielsen, T. Skrydstrup, *J. Am. Chem. Soc.* **2008**, *130*, 13145–13151.

(Z)-((Prop-1-en-1-yloxy)methyl)benzene (259)



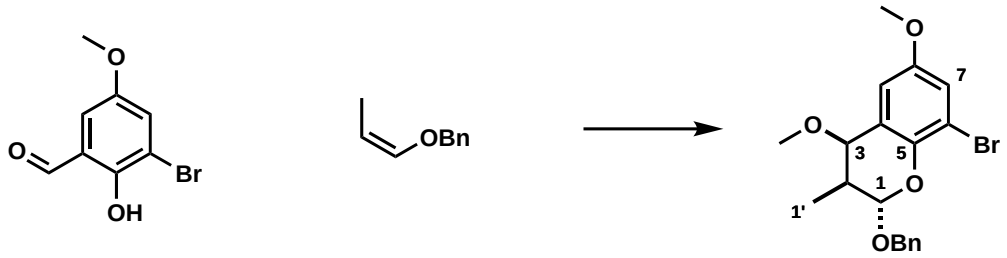
294 **259**

To a solution of benzyl allyl ether (**294**) (250 mg, 1.69 mmol, 1.00 eq.) in DMSO (1 ml) was added KOtBu (47 mg, 0.42 mmol, 0.25 eq.) and stirring was continued at rt overnight. The reaction was diluted with Et_2O and terminated by addition of a sat. NH_4Cl solution and the phases were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude vinyl ether **259** (150 mg, 1.01 mmol, 60 %) as a colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.39 - 7.28 (m, 5H, Ph), 6.03 (dq, $J = 6.2,\ 1.7$ Hz, 1H, H-3), 4.81 (s, 2H, PhCH_2OR), 4.45 (q, $J = 6.7$ Hz, 1H, H-2), 1.63 (dd, $J = 6.9,\ 1.8$ Hz, 3H, H-1).

The analytical data match those reported in the literature.[203]

203 Y. Motoyama, M. Abe, K. Kamo, Y. Kosako, H. Nagashima, *Chem. Commun.* **2008**, 5321–5323.

2-(Benzyloxy)-8-bromo-4,6-dimethoxy-3-methylchromane (260)



178 **259** **260**

To a solution of aldehyde **178** (500 mg, 2.16 mmol, 1.00 eq.) in MeOH (20 ml) was added $CH(OMe)_3$ (11.0 ml, 97.38 mmol, 45.0 eq.) and pTsOH·H_2O (103 mg, 0.54 mmol, 0.25 eq.) and stirring was continued at rt for 4 h. After termination of the reaction by addition of a sat. $NaHCO_3$ solution, the phases were separated and the aqueous phase was extracted with EA. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield crude dimethyl acetal, which was immediately dissolved in PhMe (8 ml) and vinyl ether **259** (963 mg, 6.50 mmol, 3.00 eq.) and pTsOH·H_2O (82 mg, 0.43 mmol, 0.20 eq.) were added and stirring continued at rt for 8 d. The reaction was terminated by addition of MeOH (8 ml) and $NaBH_4$ (82 mg, 2.17 mmol, 1.00 eq.) was added. After 30 min the reaction was terminated by addition of a sat. $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with EA and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded an unseparable diastereomeric mixture of chromane **260** (680 mg, 1.73 mmol, 80 %, 4.5:1 *dr*) as a brown oil.

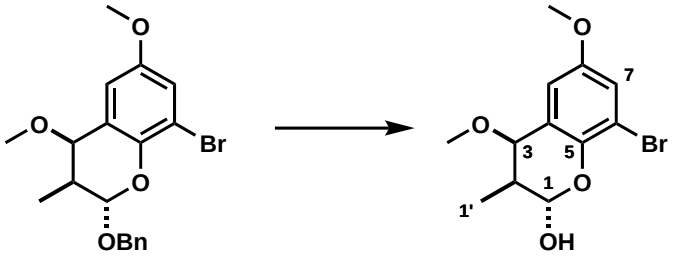
$\mathbf{R_f} = 0.53$ (PE:EA =5:1);

^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.36 - 7.27 (m, 5H, Ph), 7.04 (d, $J = 3.0$ Hz, 1H, H-7), 6.95 (d, $J = 2.96$ Hz, 1H, H-9), 5.07 (d, $J = 3.52$ Hz, 1H, H-1), 4.87 (d, $J = 11.9$ Hz, 1H, OCH_2Ph), 4.67 (d, $J = 12.0$ Hz, 1H, OCH_2Ph), 4.53 (d, $J = 5.0$ Hz, 1H, H-3), 3.77 (s, 3H, PhOMe), 3.47 (s, 3H, OMe), 2.49 - 2.40 (m, 1H, H-2), 0.94 (d, $J = 6.9$ Hz, 3H, H-1');

^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 154.1 (s, C-8), 141.7 (s, C-5), 137.3 (Bn), 128.6 (Bn), 128.3 (Bn), 128.1 (Bn), 128.0 (Bn), 125.0 (s, C-4), 118.5 (d, C-7), 112.4 (d, C-9), 110.6 (s, C-6), 101.5 (d, C-1), 74.4 (d, C-3), 69.9 (CH_2Ph), 56.9 (OMe), 56.0 (PhOMe), 32.8 (d, C-2), 10.2 (q, C-1');

HRMS (ESI): m/z calc. for $C_{19}H_{21}O_4Br$ [M+Na]$^+$: 415.0521, found 415.0523.

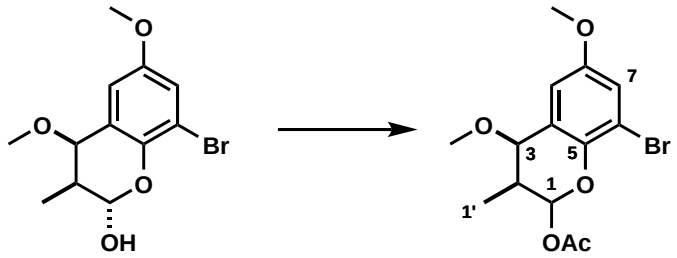
8-Bromo-4,6-dimethoxy-3-methylchroman-2-ol (257)



260 **257**

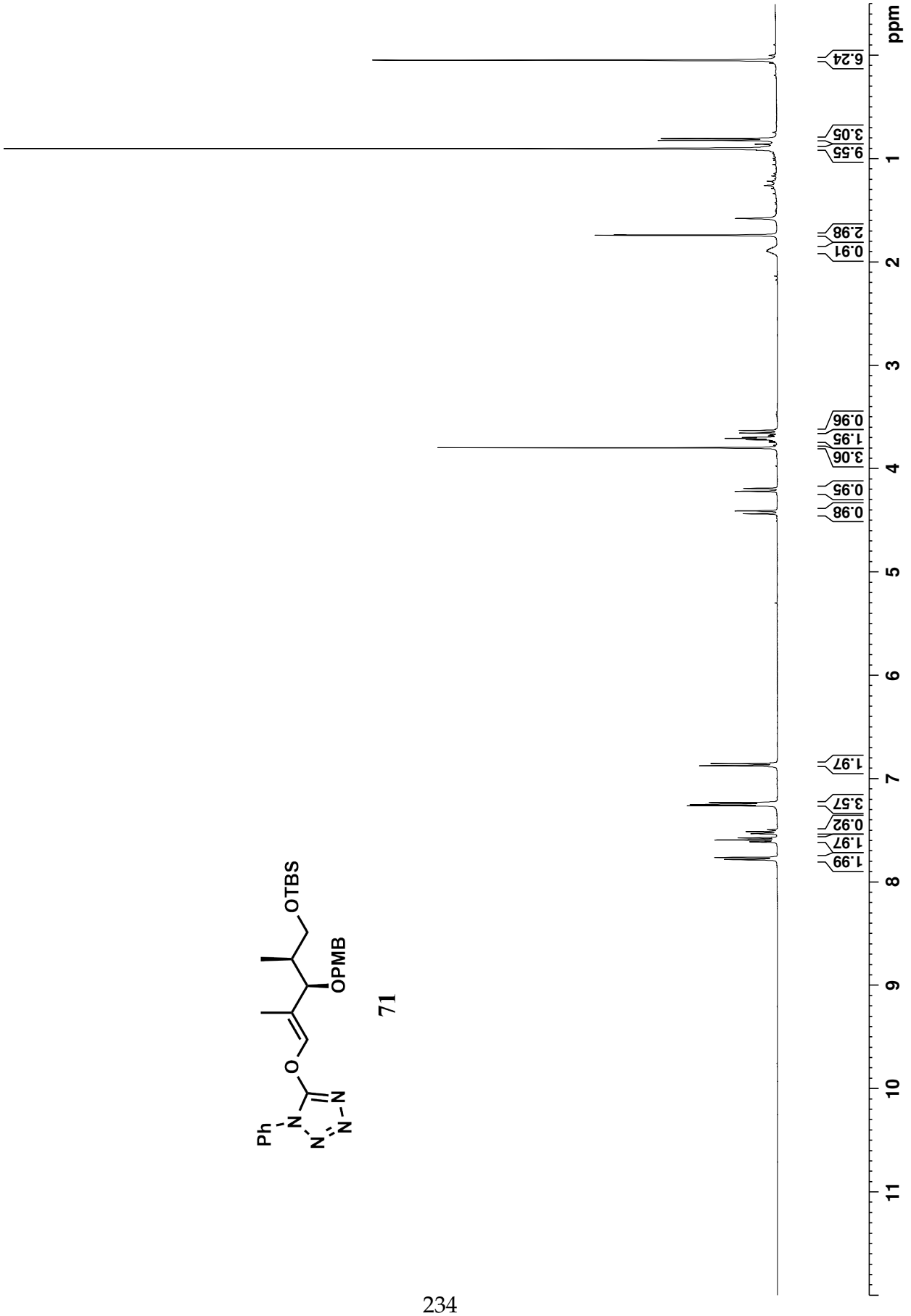
To a solution of benzyl ether **260** (670 mg, 1.70 mmol, 1.00 eq.) in THF (6 ml) was added Pd/C (10 %, 181 mg, 0.17 mmol, 0.10 eq.) and H_2 was bubbled through the reaction for 10 min. An atmospheric pressure of H_2 was applied and the reaction was stirred for 3 d. The reaction was filtered over Celite^{TM} and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded an unseparable diastereomeric mixture of hemiacetal **257** (327 mg, 1.08 mmol, 63 %, 1.6:1 *dr*) as a colorless oil.
Characterization of the diastereomeric mixture:
$\mathbf{R_f} = 0.33$ (PE:EA =5:1);
textbf^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.14 (d, $J = 2.9$ Hz, 1H, H-7_{d2}), 7.04 (d, $J = 2.9$ Hz, 1H, H-7_{d1}), 6.91 (d, $J = 3.3$ Hz, 1H, H-9_{d1}), 6.67 (d, $J = 2.9$ Hz, 1H, H-9_{d2}), 5.65 (d, $J = 11.8$ Hz, 1H, OH_{d2}), 5.54 (t, $J = 4.2$ Hz, 1H, OH_{d1}), 5.44 (ddd, $J = 11.5$, 2.5, 1.0 Hz, 1H, H-1_{d2}), 4.45 (d, $J = 4.4$ Hz, 1H, H-1_{d1}), 4.1 (dd, $J = 2.8$, 0.9 Hz, 1H, H-3_{d2}), 3.77 (s, 3H, $PhOMe_{d2}$), 3.76 (s, 3H, $PhOMe_{d1}$), 3.47 (s, 3H, OMe_{d1}), 3.40 (s, 3H, OMe_{d2}), 3.13 (d, $J = 4.1$ Hz, 1H, H-3_{d1}), 2.42 - 2.34 (m, 1H, H-2_{d1}), 2.30 - 2.23 (m, 1H, H-2_{d2}), 1.34 (d, $J = 7.7$ Hz, 3H, H-$1'_{d2}$), 0.99 (d, $J = 7.0$ Hz, 3H, H-$1'_{d1}$);
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 153.9 (s, C-8_{d2}), 152.8 (s, C-8_{d1}), 142.7 (s, C-5_{d1}), 142.1 (s, C-5_{d2}), 124.3 (s, C-4_{d2}), 121.6 (s, C-4_{d1}), 119.5 (d, C-7_{d1}), 118.6 (d, C-7_{d2}), 115.6 (d, C-9_{d1}), 112.7 (d, C-9_{d2}), 111.7 (s, C-6_{d1}), 110.3 (s, C-6_{d2}), 97.4 (d, C-1_{d2}), 97.2 (d, C-1_{d1}), 78.1 (d, C-3_{d1}), 74.5 (d, C-3_{d2}), 57.5 (q, OMe_{d1}), 57.0 (q, OMe_{d2}), 56.1 (q, $PhOMe_{d1}$), 56.0 (q, $PhOMe_{d2}$), 35.7 (d, C-2_{d1}), 33.9 (d, C-2_{d2}), 12.5 (q, C-$1'_{d1}$), 10.4 (q, C-$1'_{d2}$).

8-Bromo-4,6-dimethoxy-3-methylchroman-2-yl acetate (256)



A solution of alcohol **257** (85 mg, 0.28 mmol, 1.00 eq.) in Ac_2O (1.4 ml) was heated to 75 °C for 2 h. After cooling to rt, the reaction was terminated by addition of water. The phases were separated and the aqeuous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:EA = 10:1) yielded a single diastereomer of acetate **256** (74 mg, 0.21 mmol, 77 %) as a colorless oil.
$\mathbf{R_f} = 0.46$ (PE:EA =5:1);
^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm] = 7.04 (d, $J = 3.2$ Hz, 1H, H-7), 6.88 (d, $J = 3.0$ Hz, 1H, H-9), 6.38 (d, $J = 2.5$ Hz, 1H, H-1), 4.42 (d, $J = 5.0$ Hz, 1H, H-3), 3.76 (s, 3H, PhOMe), 3.52 (s, 3H, OMe), 2.56 - 2.48 (m, 1H, H-2), 2.17 (s, 3H, Ac), 1.05 (d, $J = 7.2$ Hz, 3H, H-1'');
^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm] = 169.7 (s, Ac), 154.3 (s, C-8), 142.1 (s, C-5), 123.7 (s, C-4), 119.1 (d, C-7), 113.0 (d, C-9), 110.6 (s, C-6), 93.2 (d, C-1), 75.7 (d, C-3), 57.8 (q, OMe), 56.0 (q, PhOMe), 33.3 (d, C-2), 21.3 (q, Ac), 7.3 (q, C-1');
HRMS (ESI): m/z calc. for $C_{14}H_{17}O_5Br$ $[M+Na]^+$: 367.0157, found 367.0151.

6 Attachments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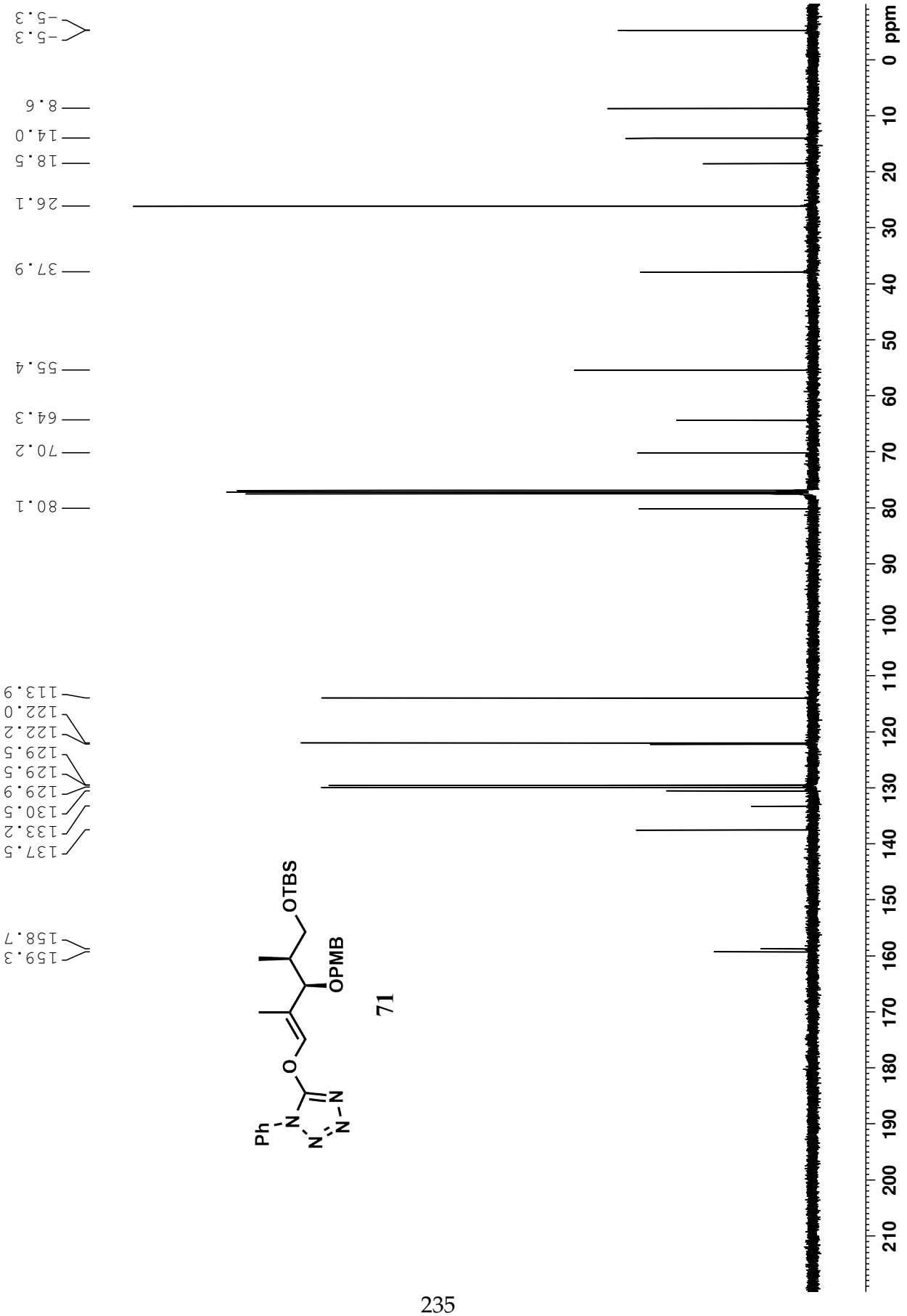
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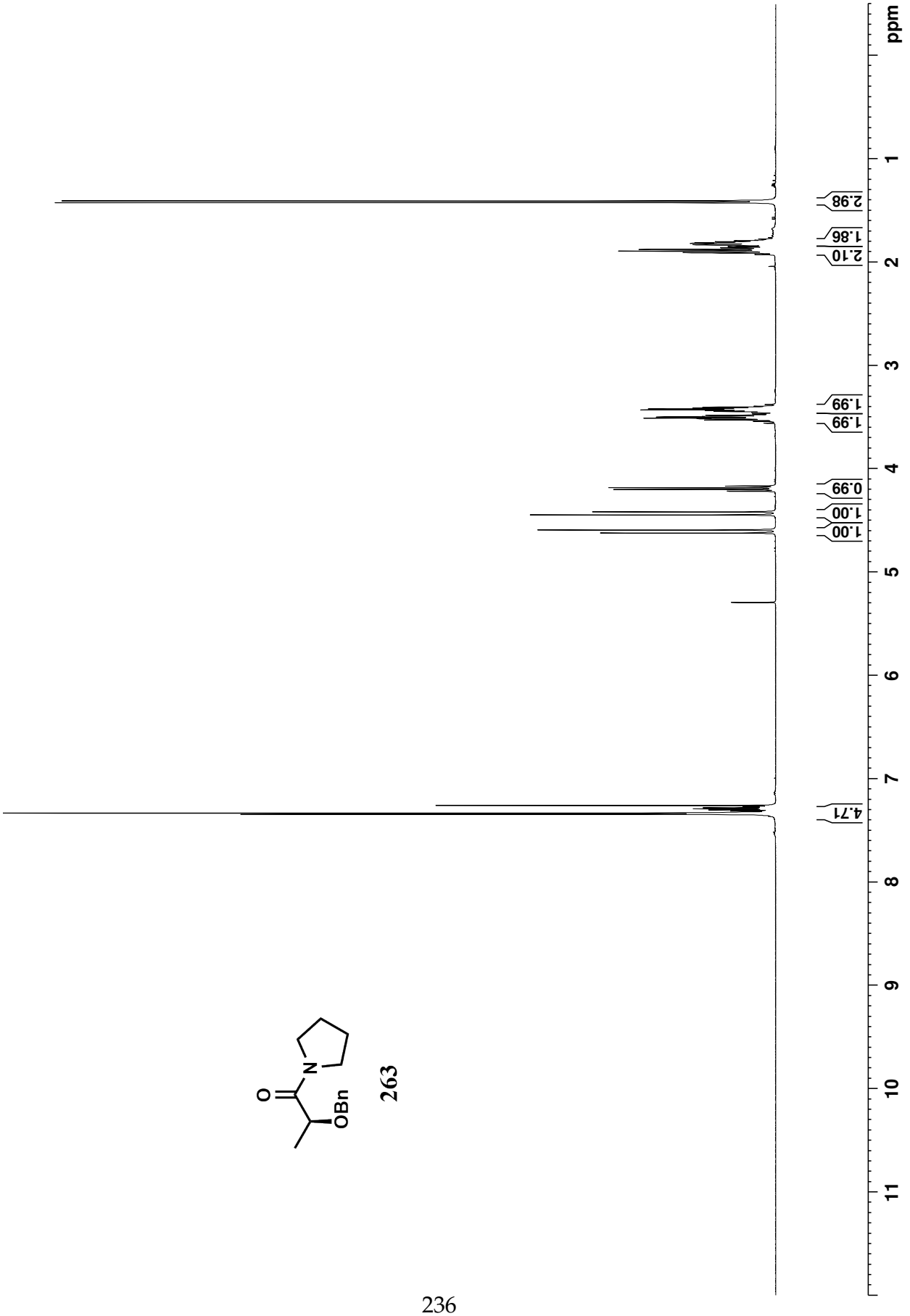

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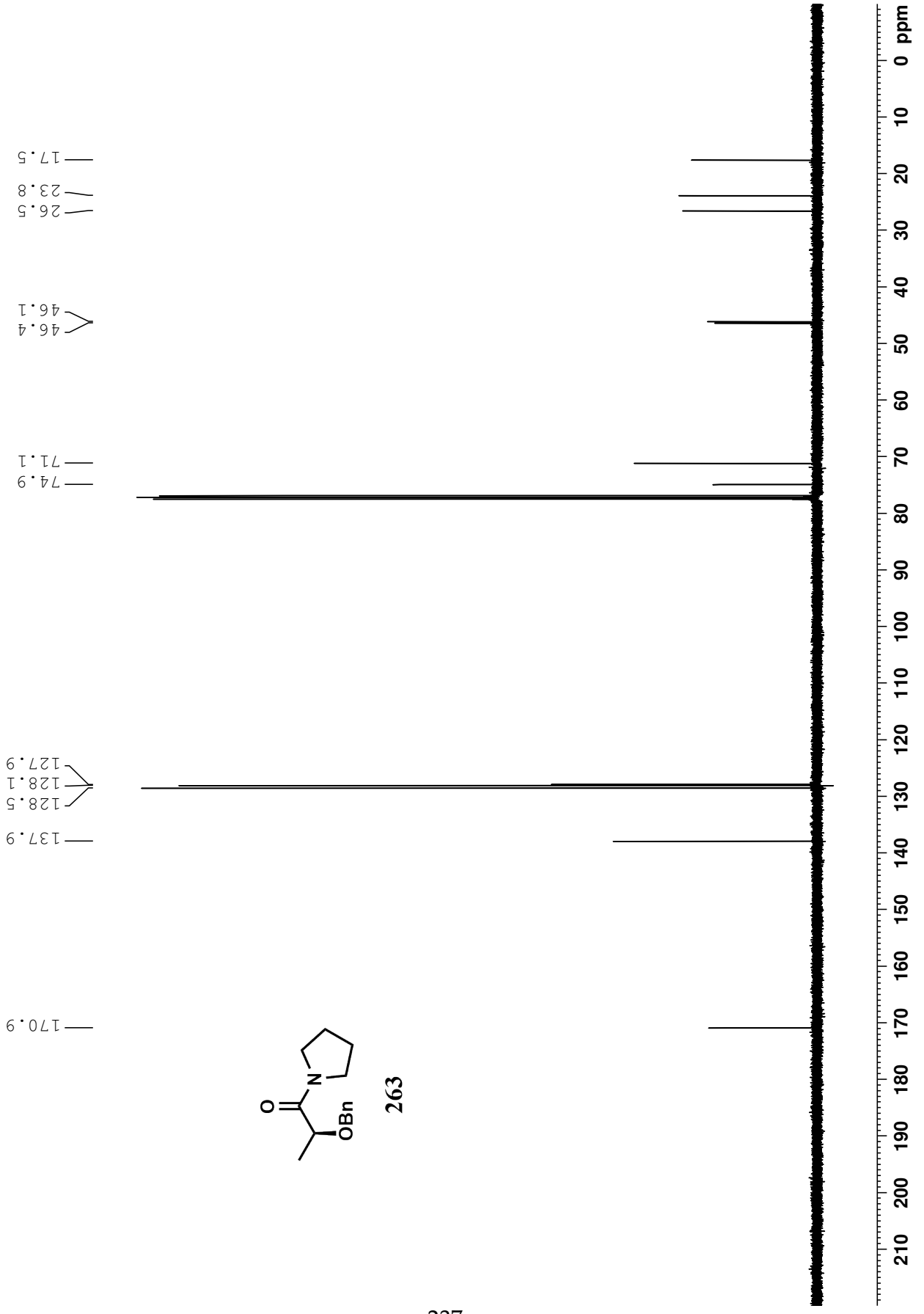
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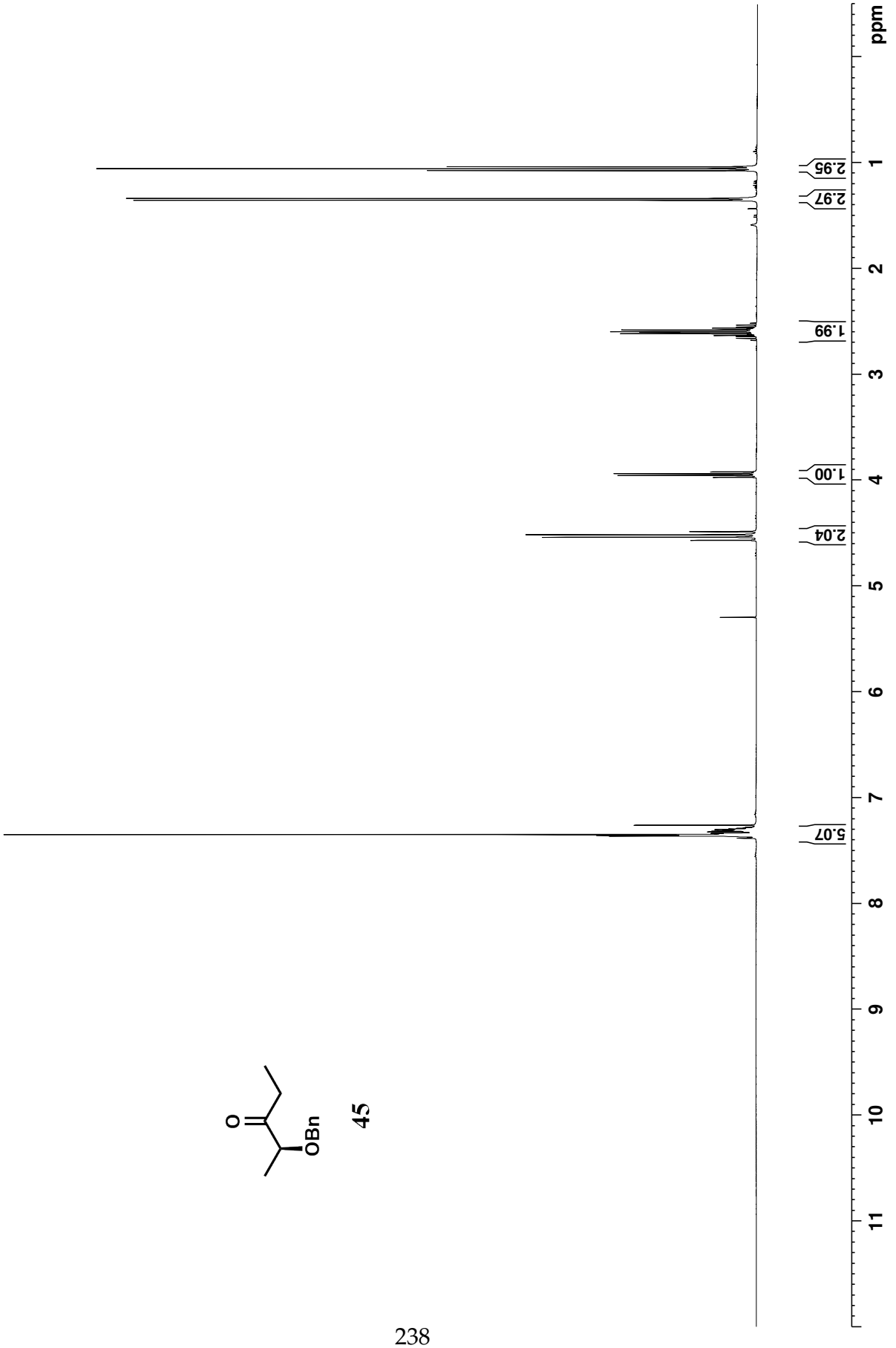
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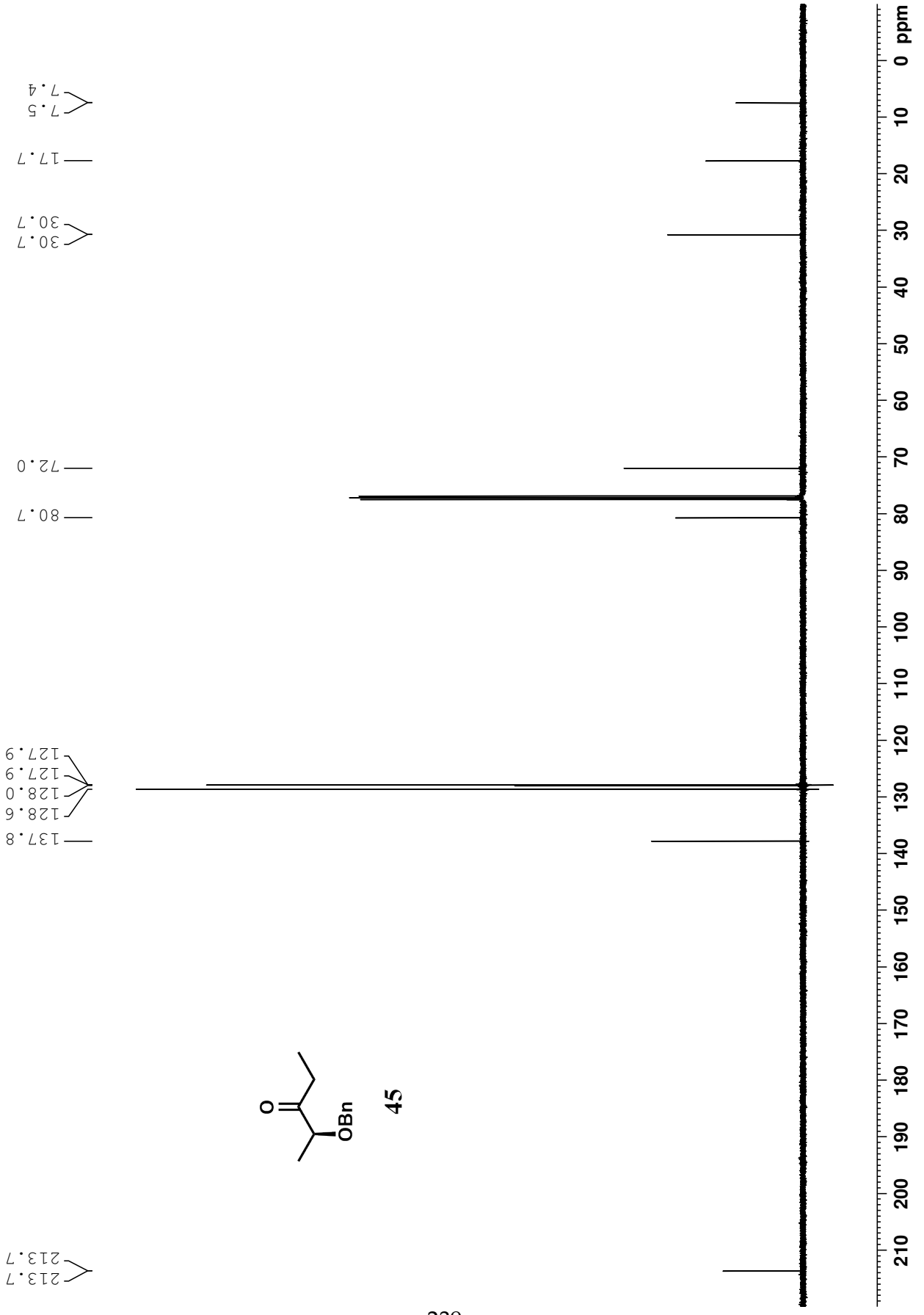
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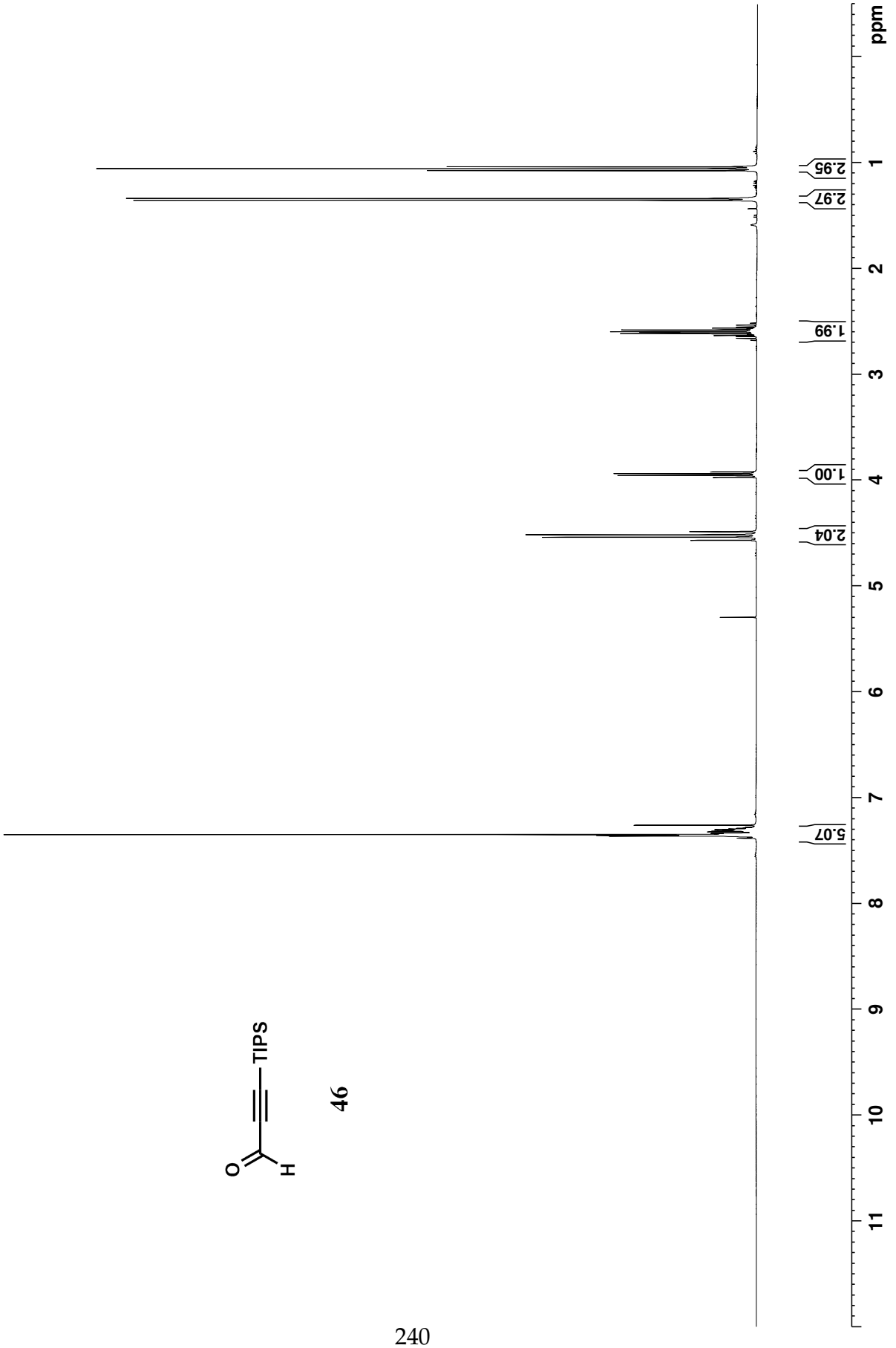

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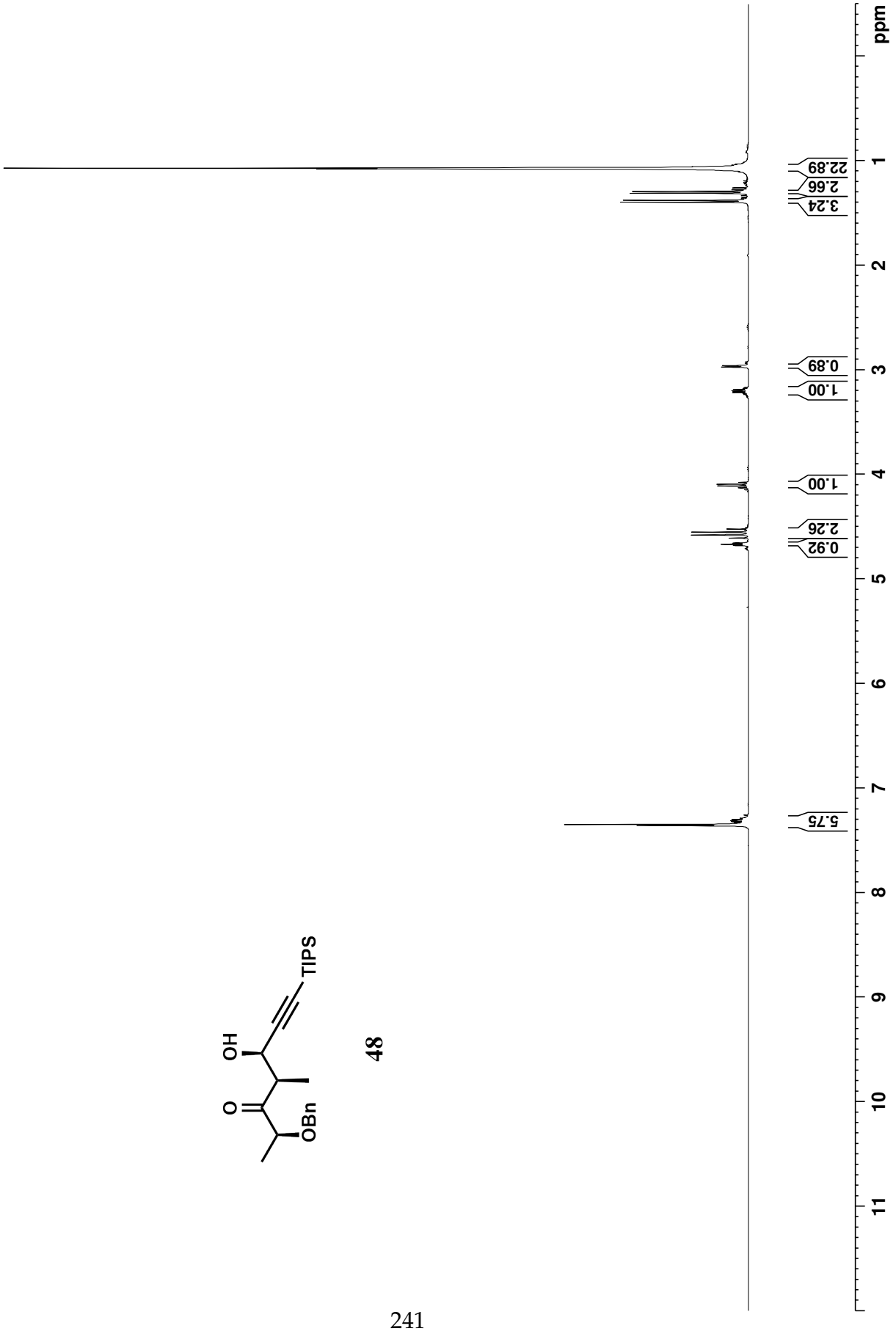
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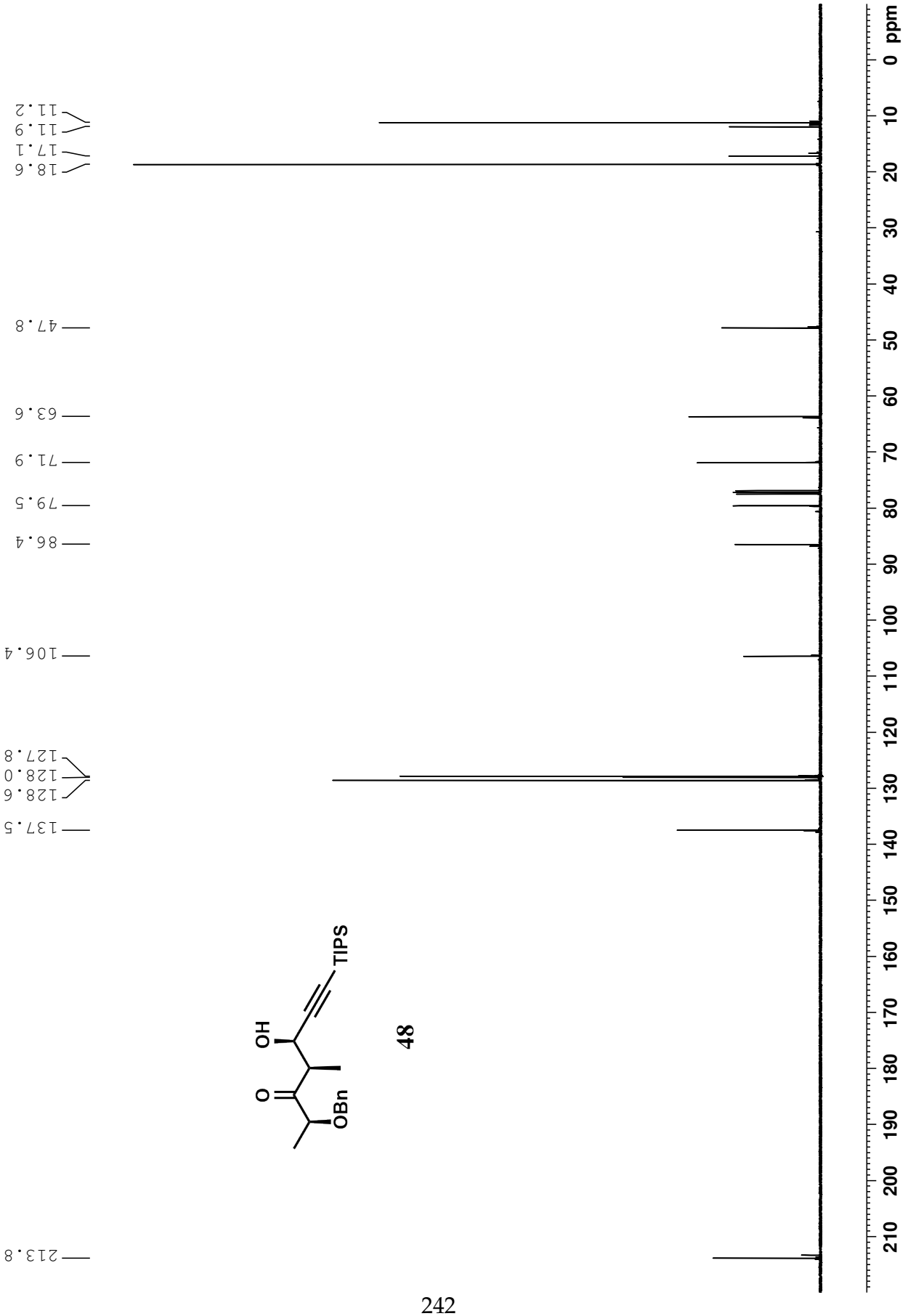
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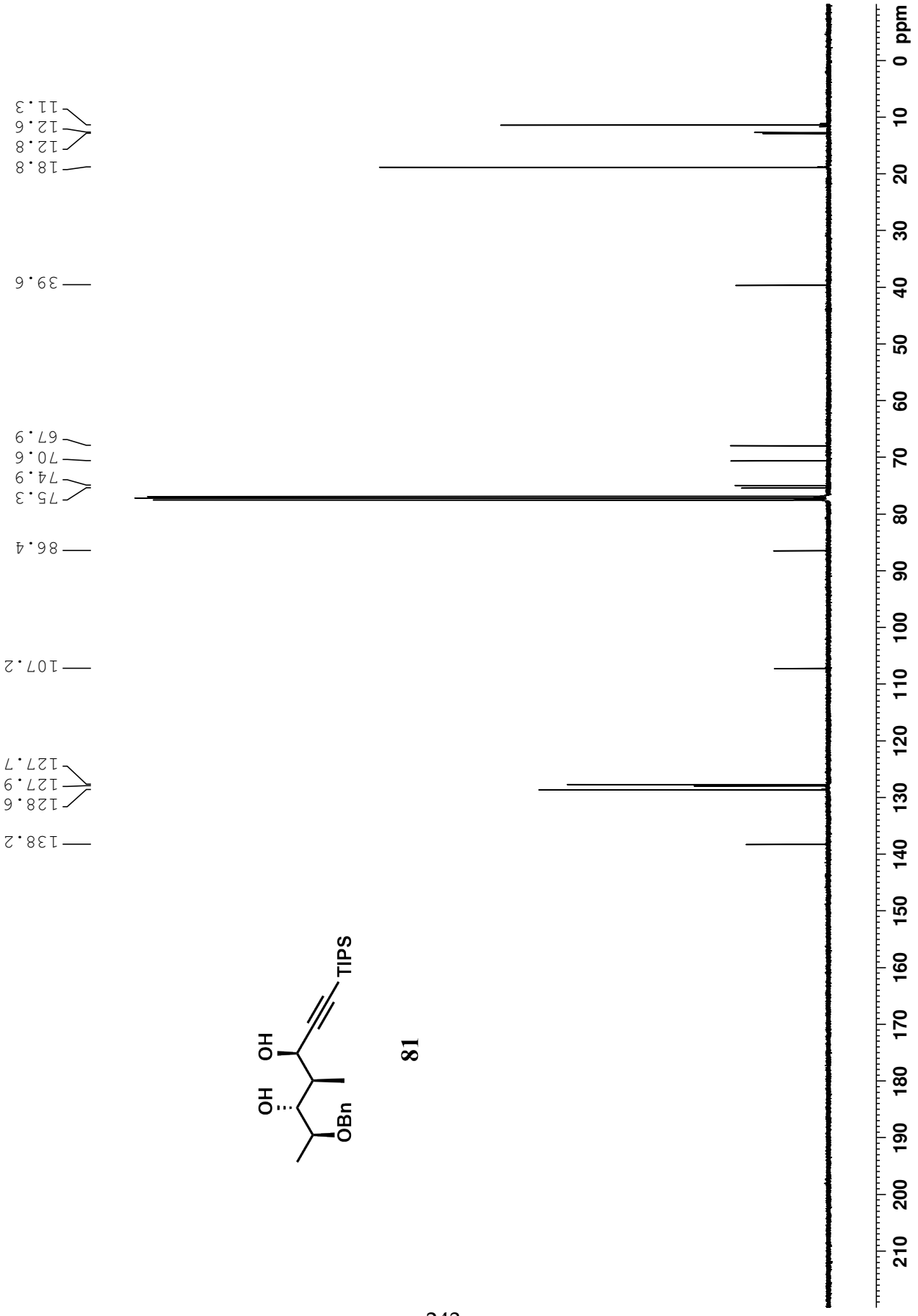
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TIPS

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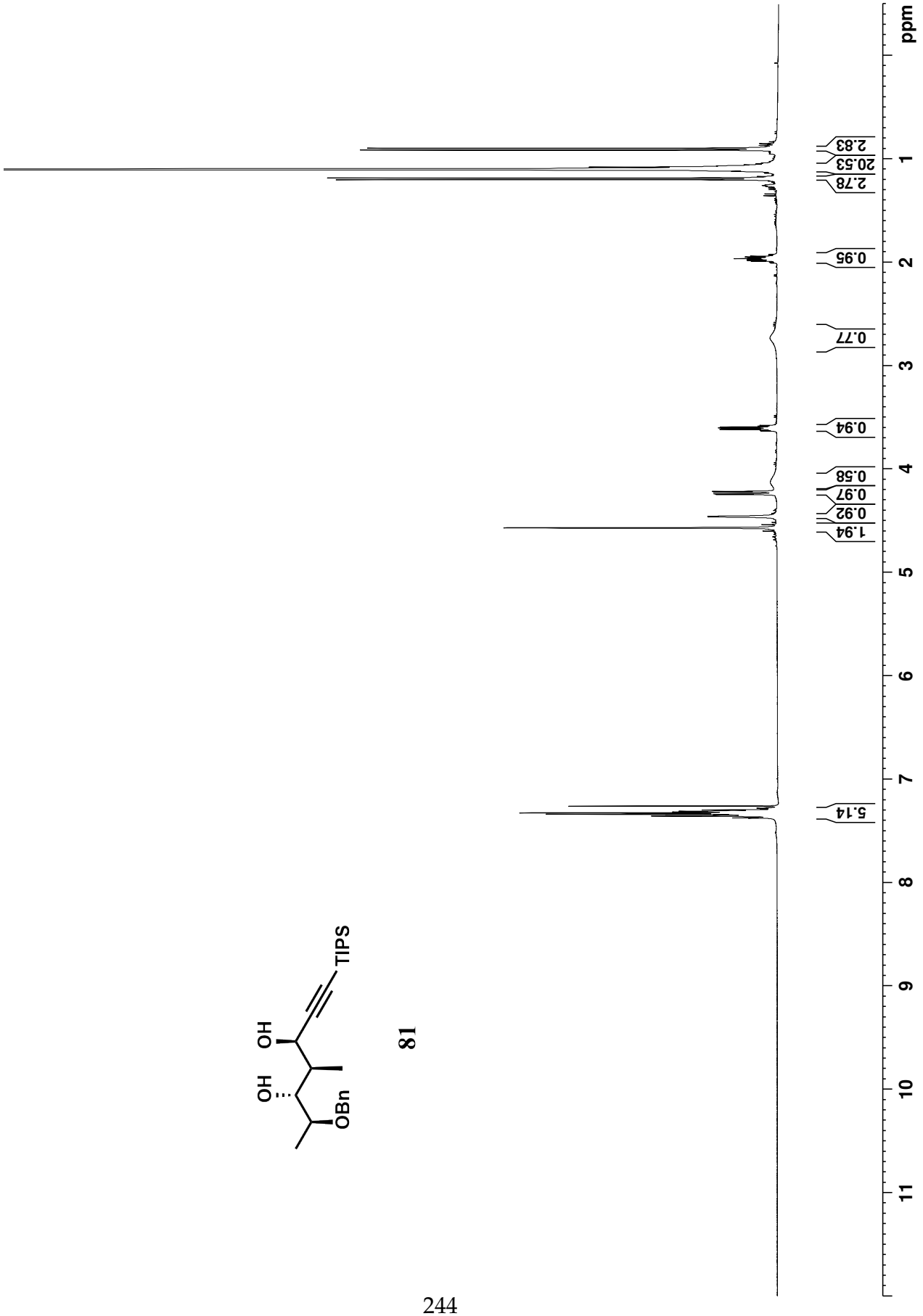
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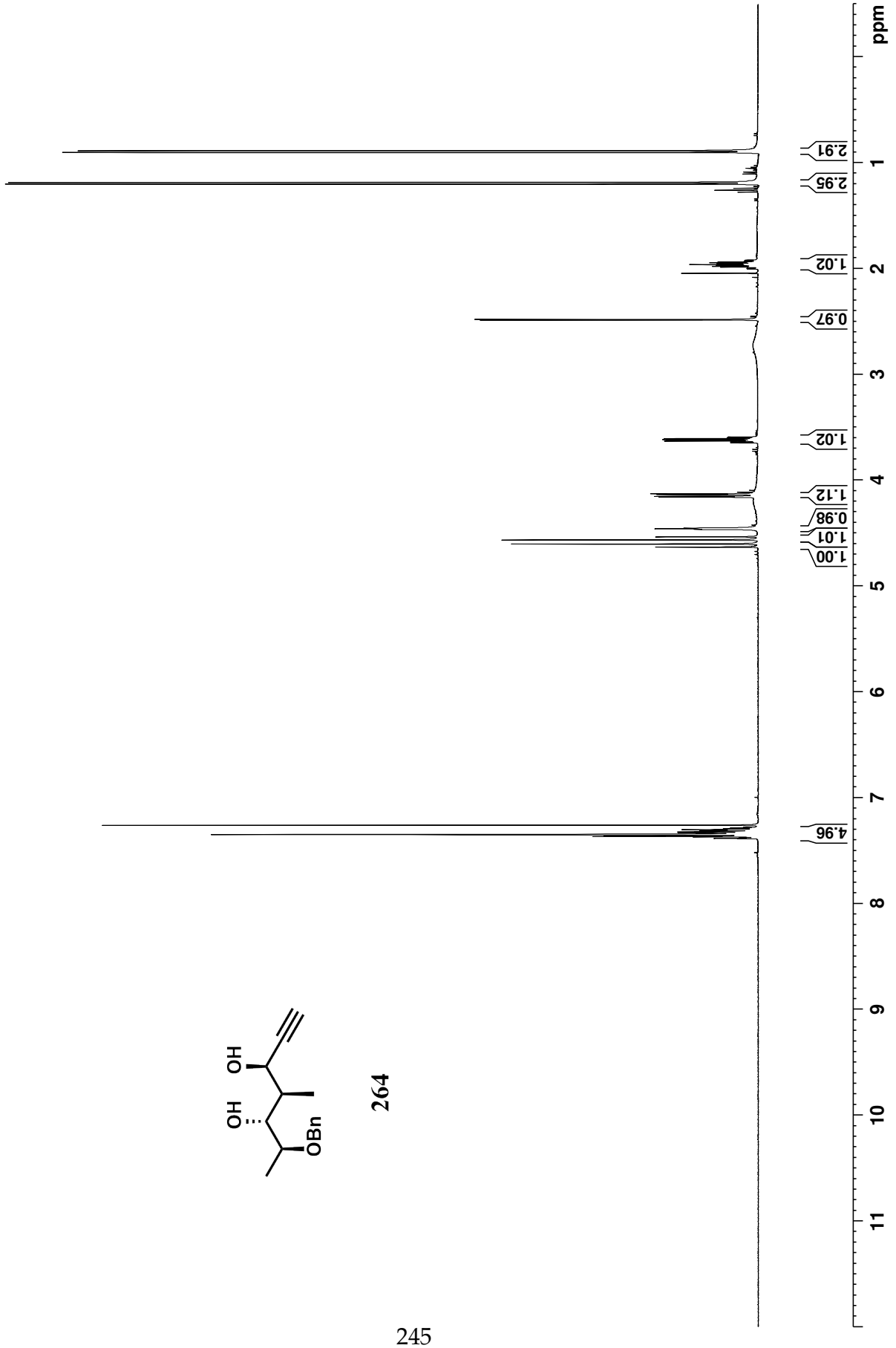
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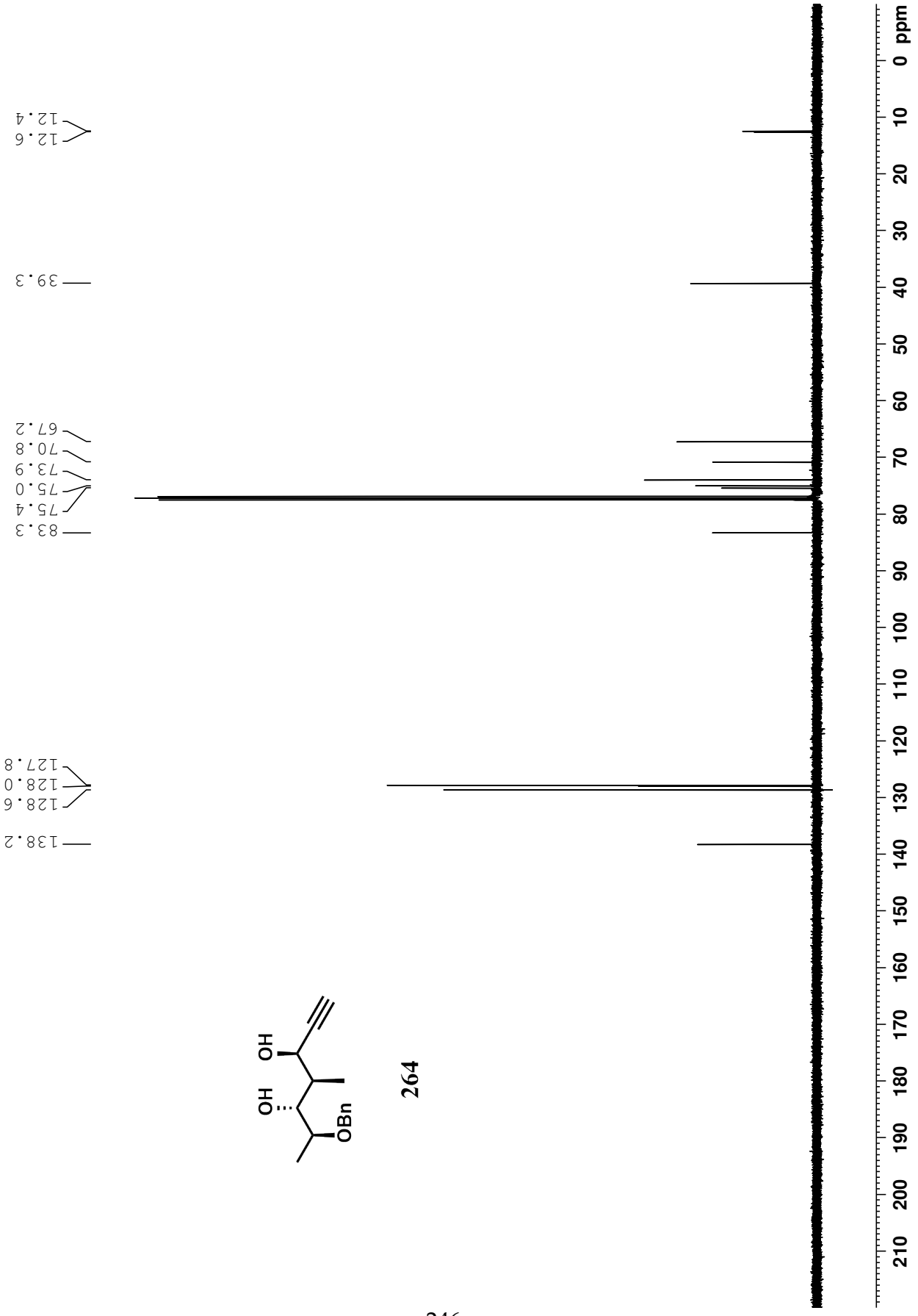
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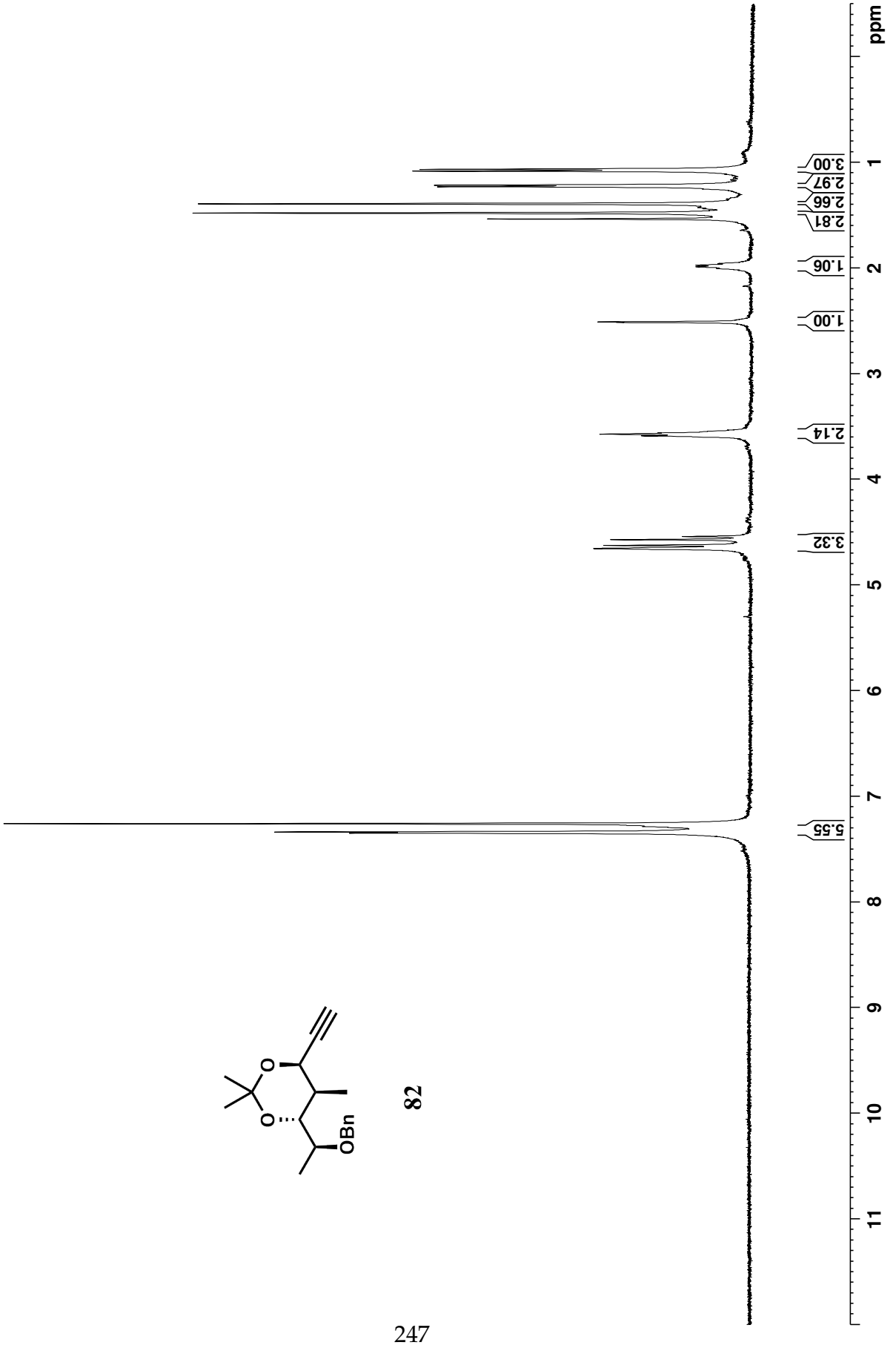

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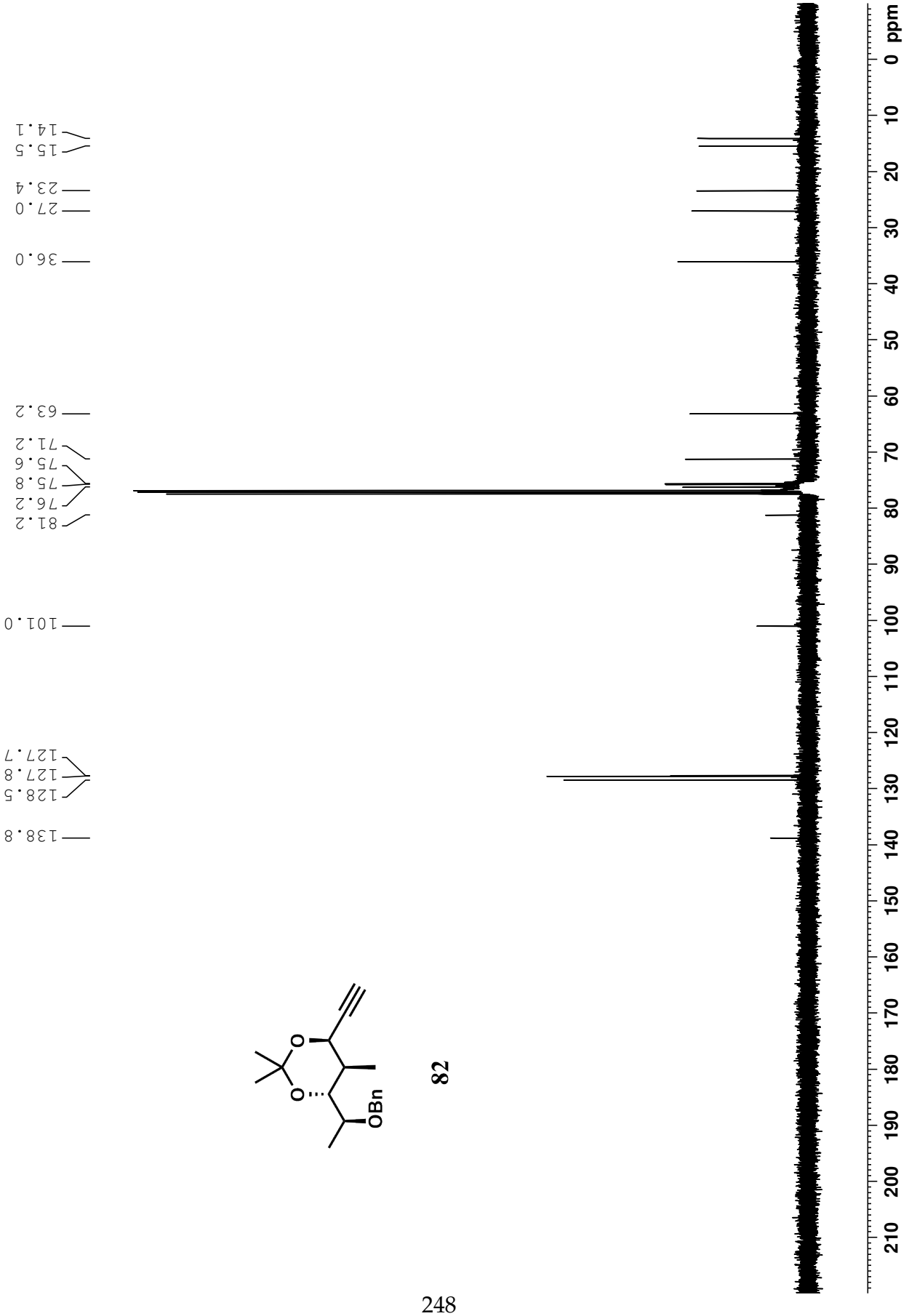
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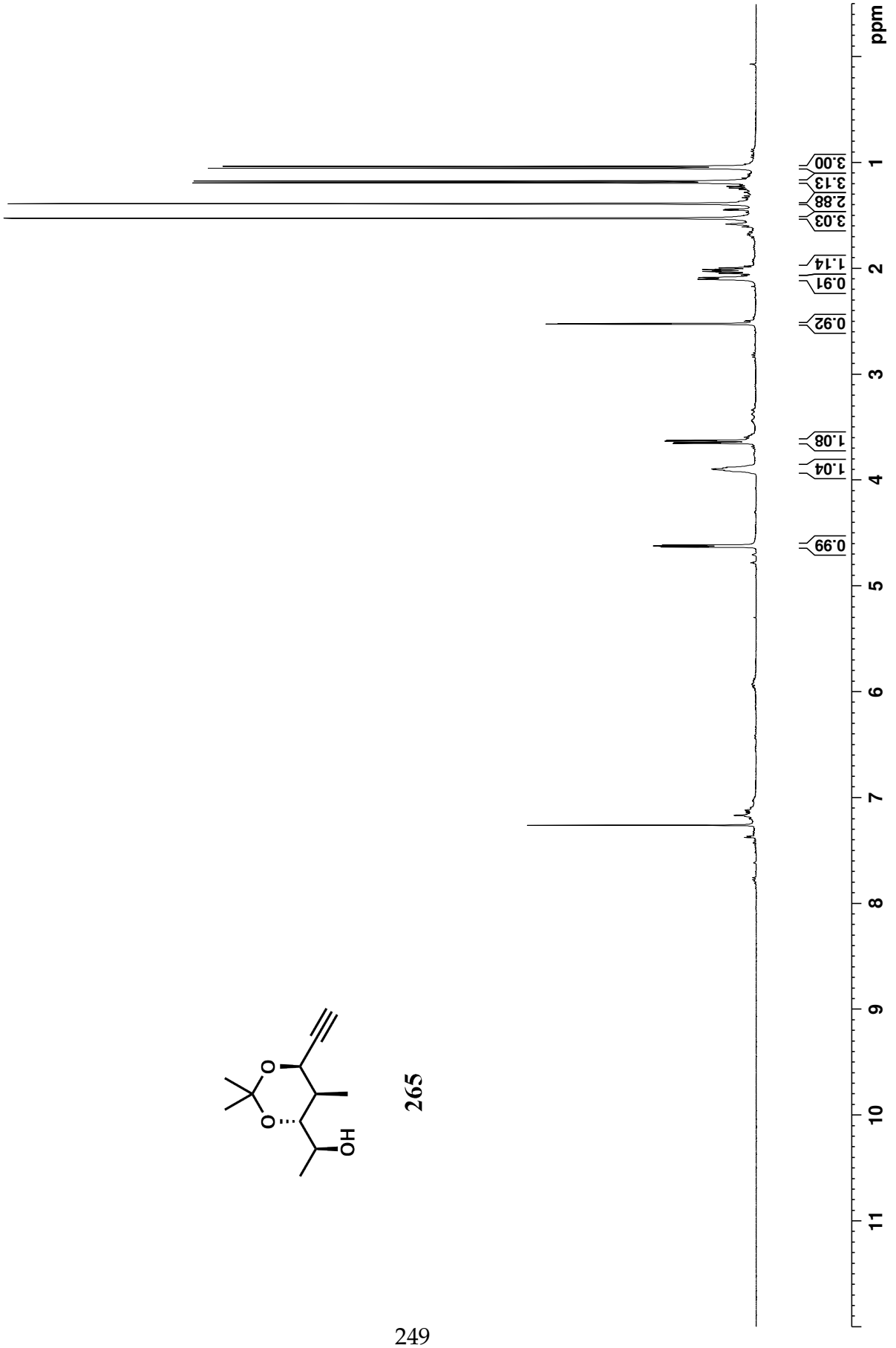
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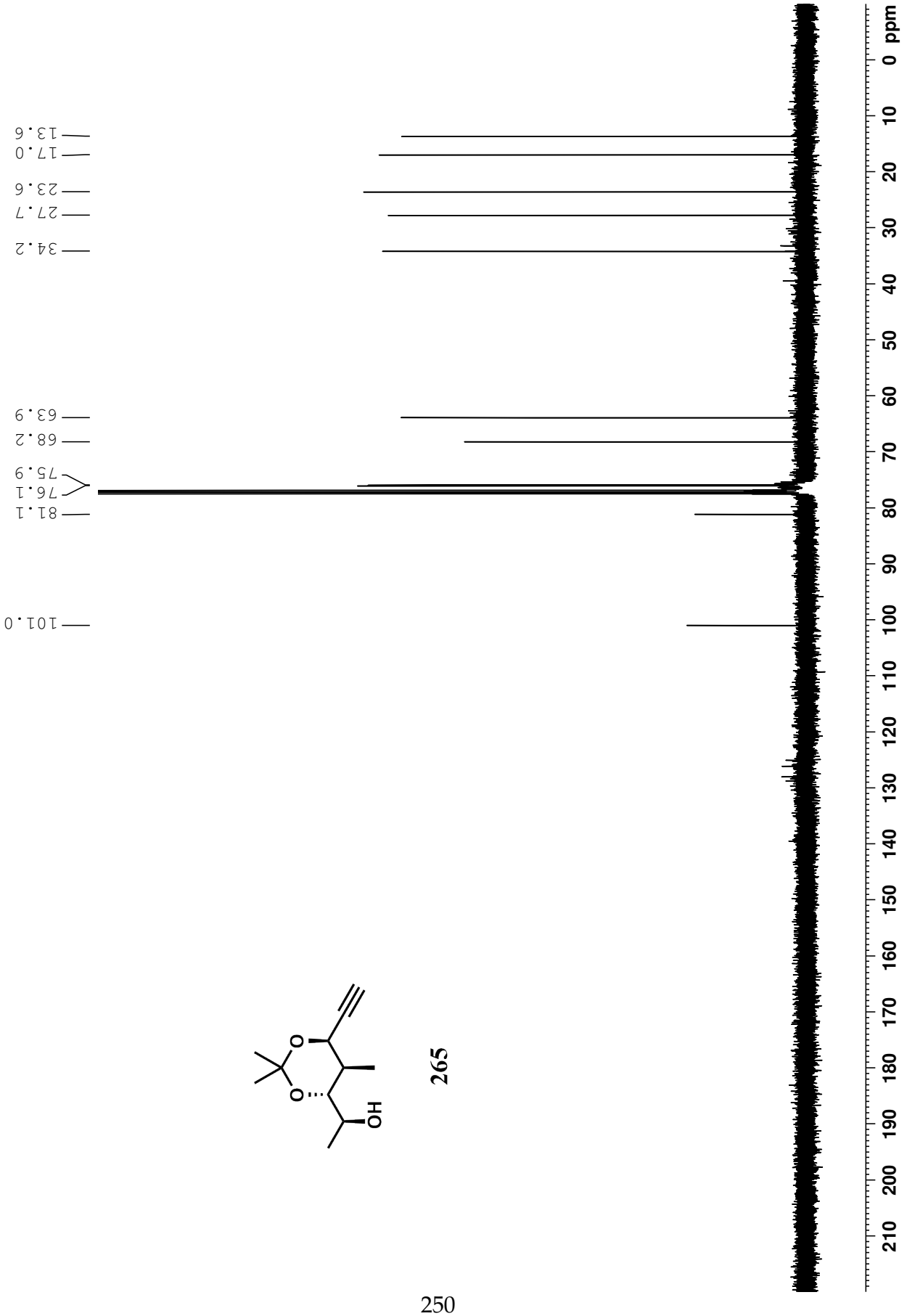
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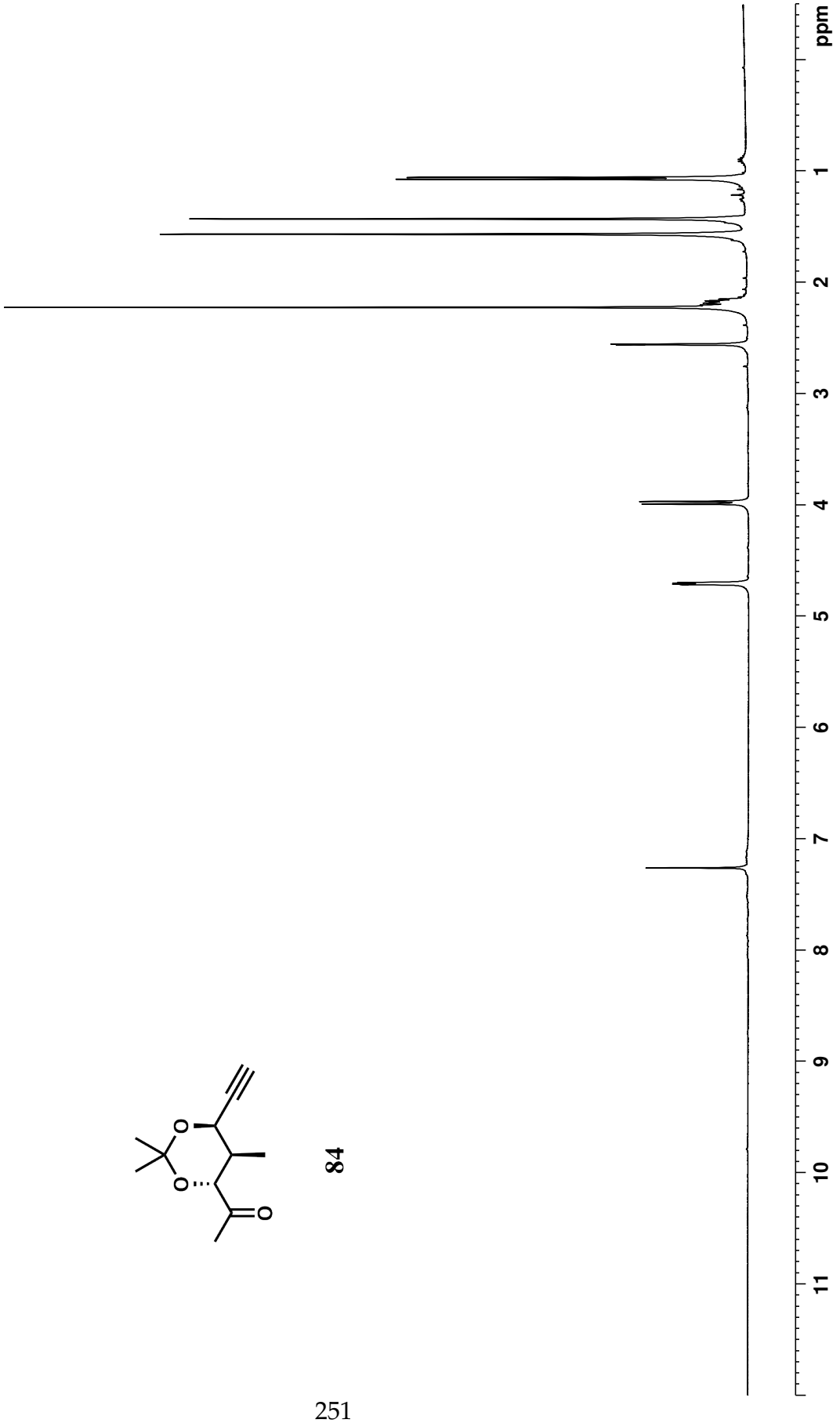

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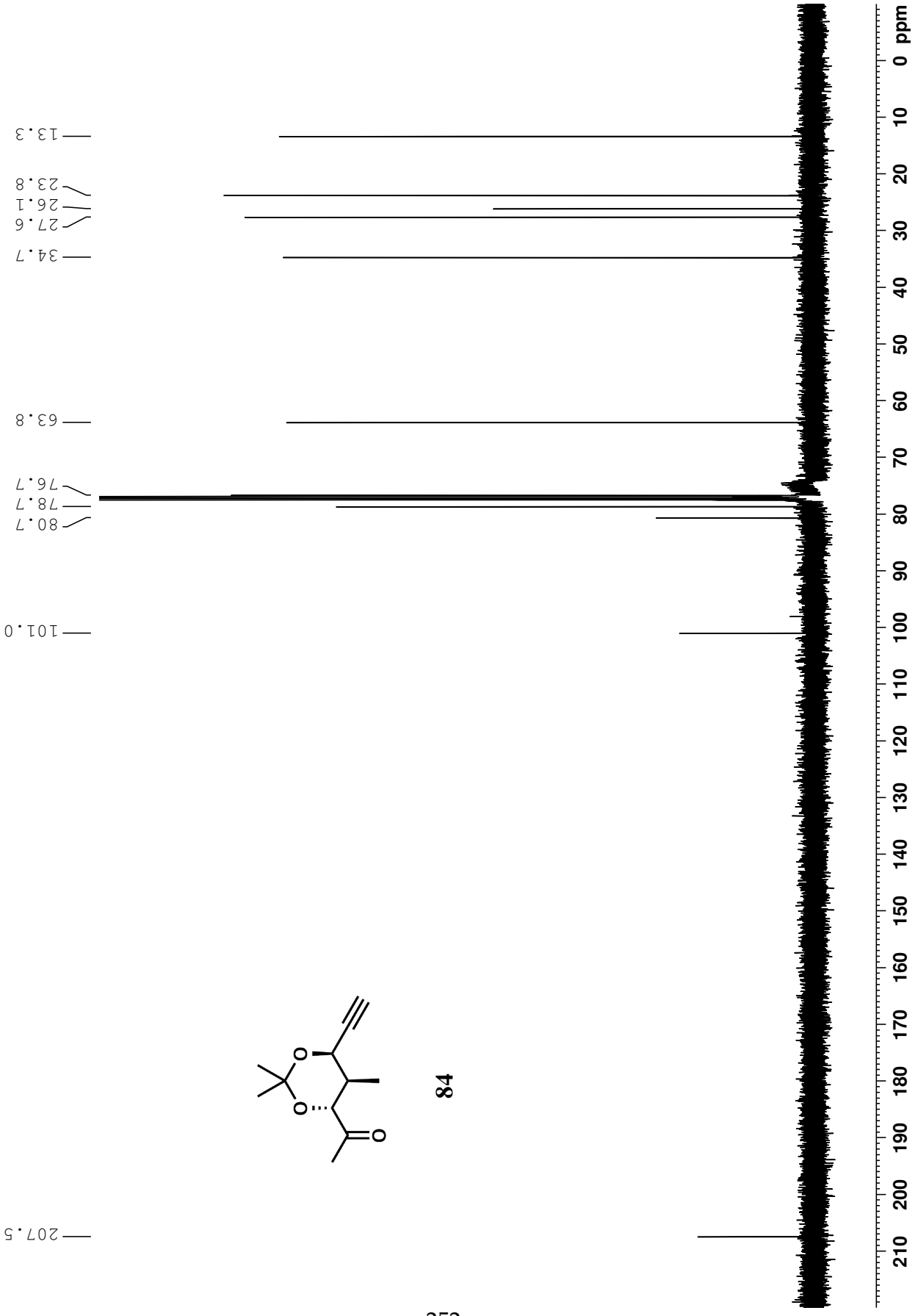
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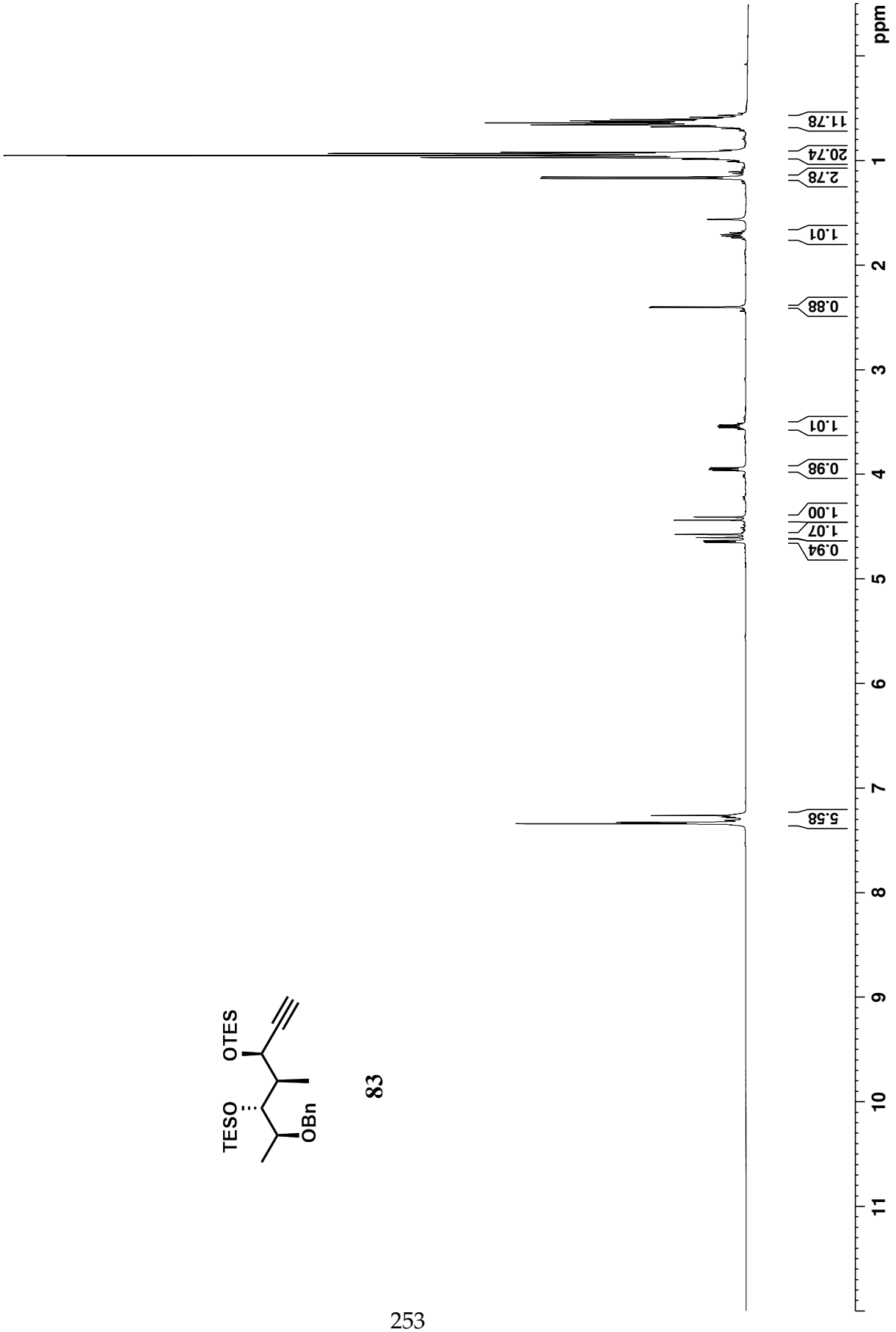
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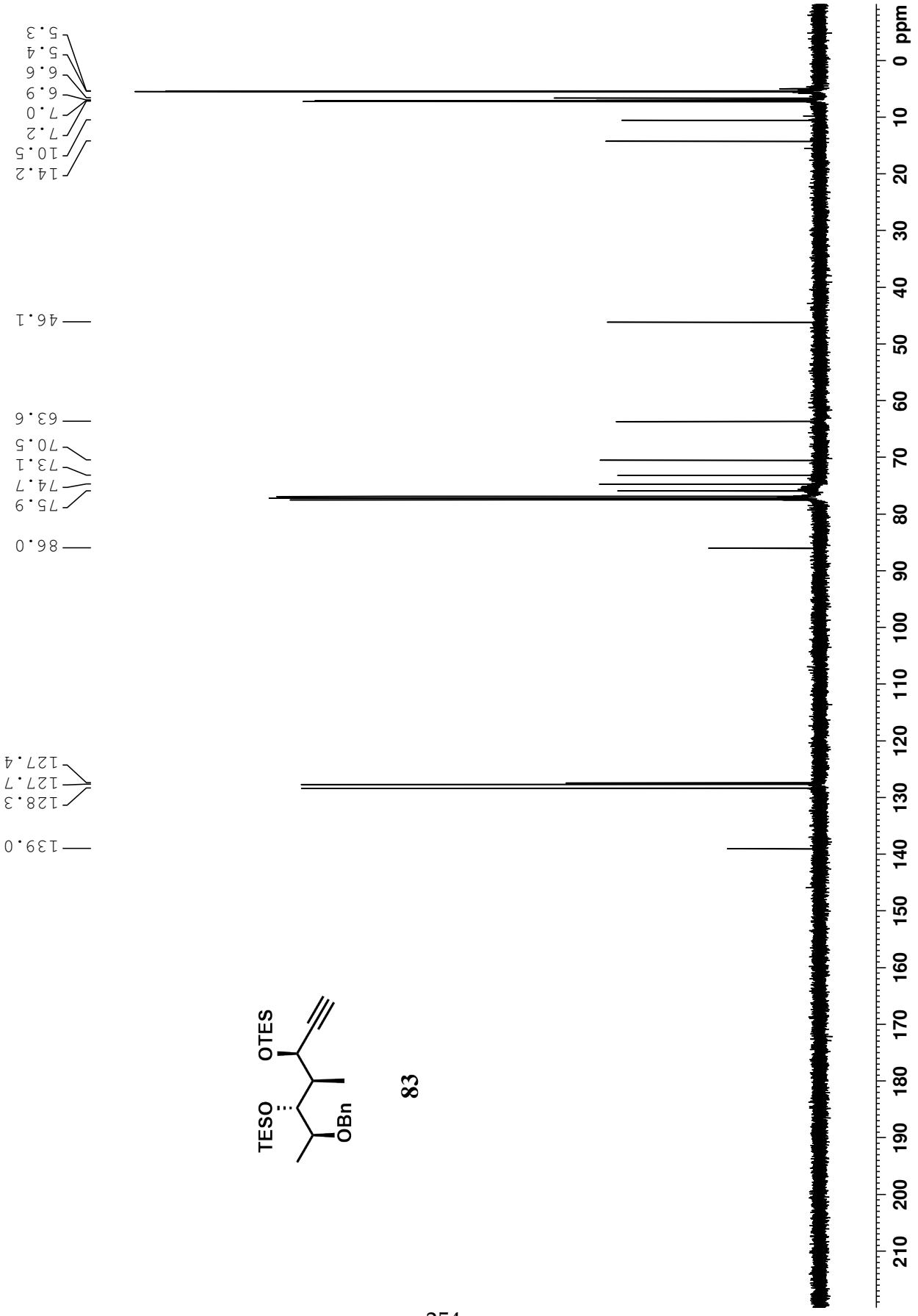
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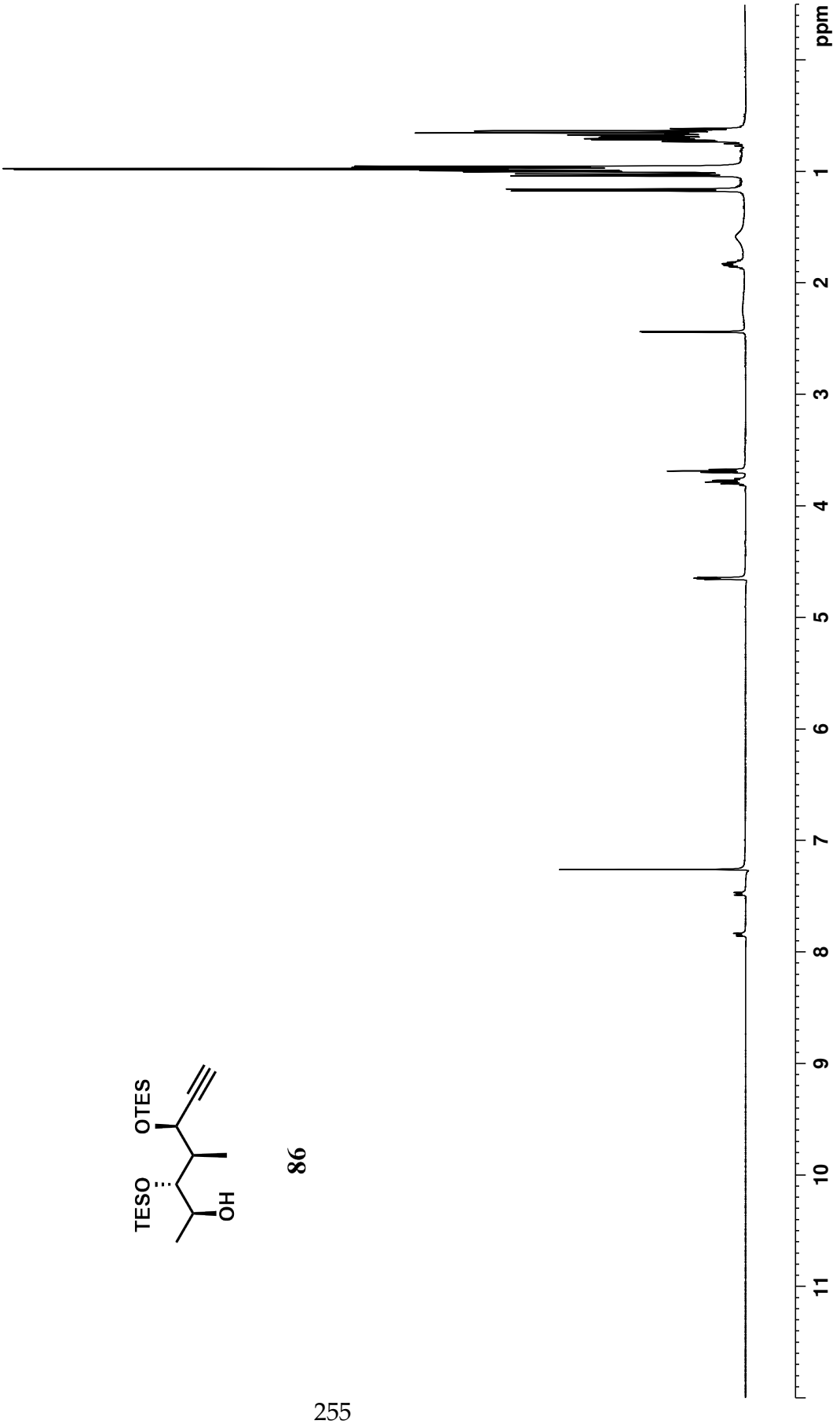
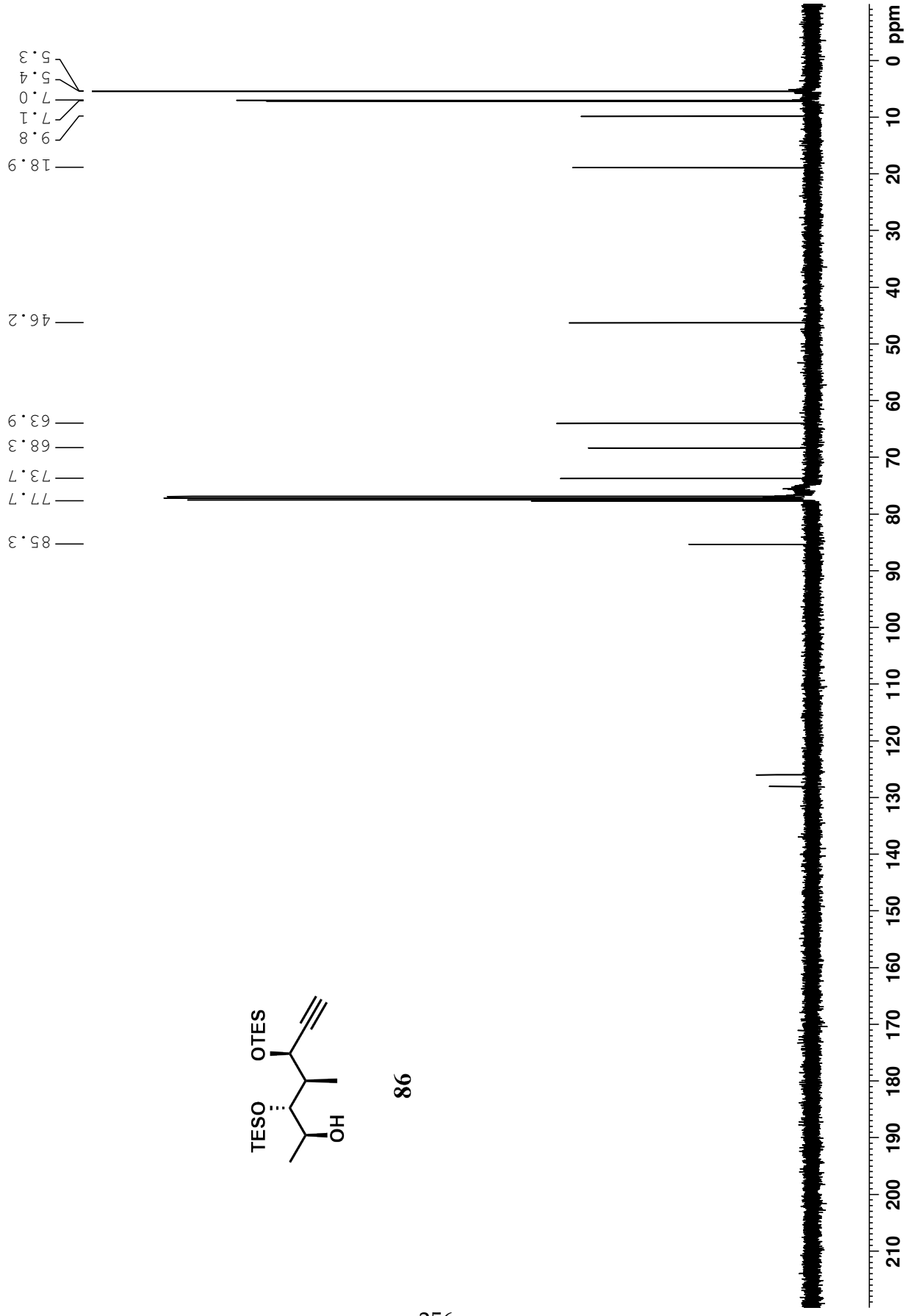
5.4
6.6
6.9
7.0
7.2
10.5
14.2
46.1
63.6
70.5
73.1
74.7
75.9
86.0
127.4
127.7
128.3
139.0
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OTES
TESO
OBn

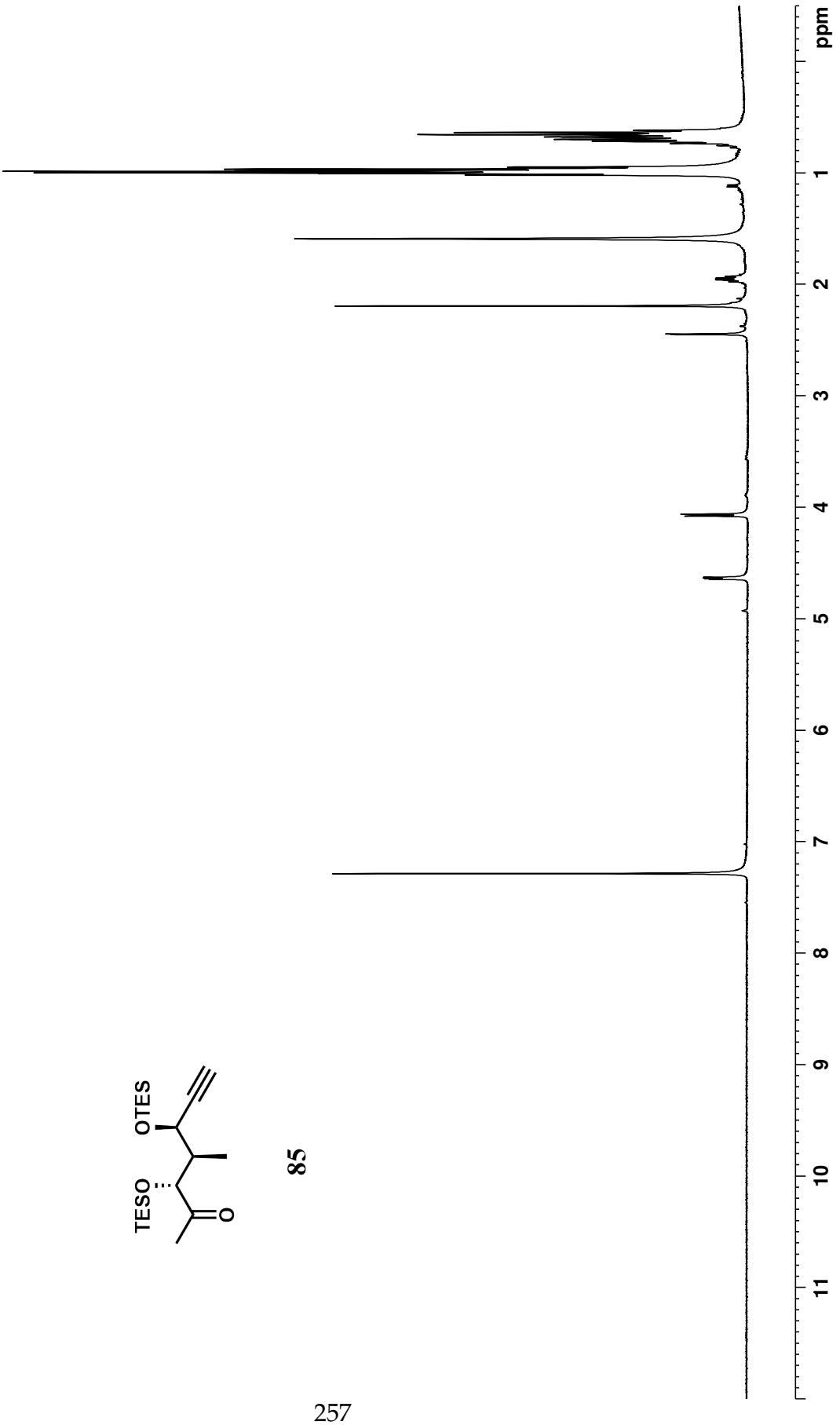
83



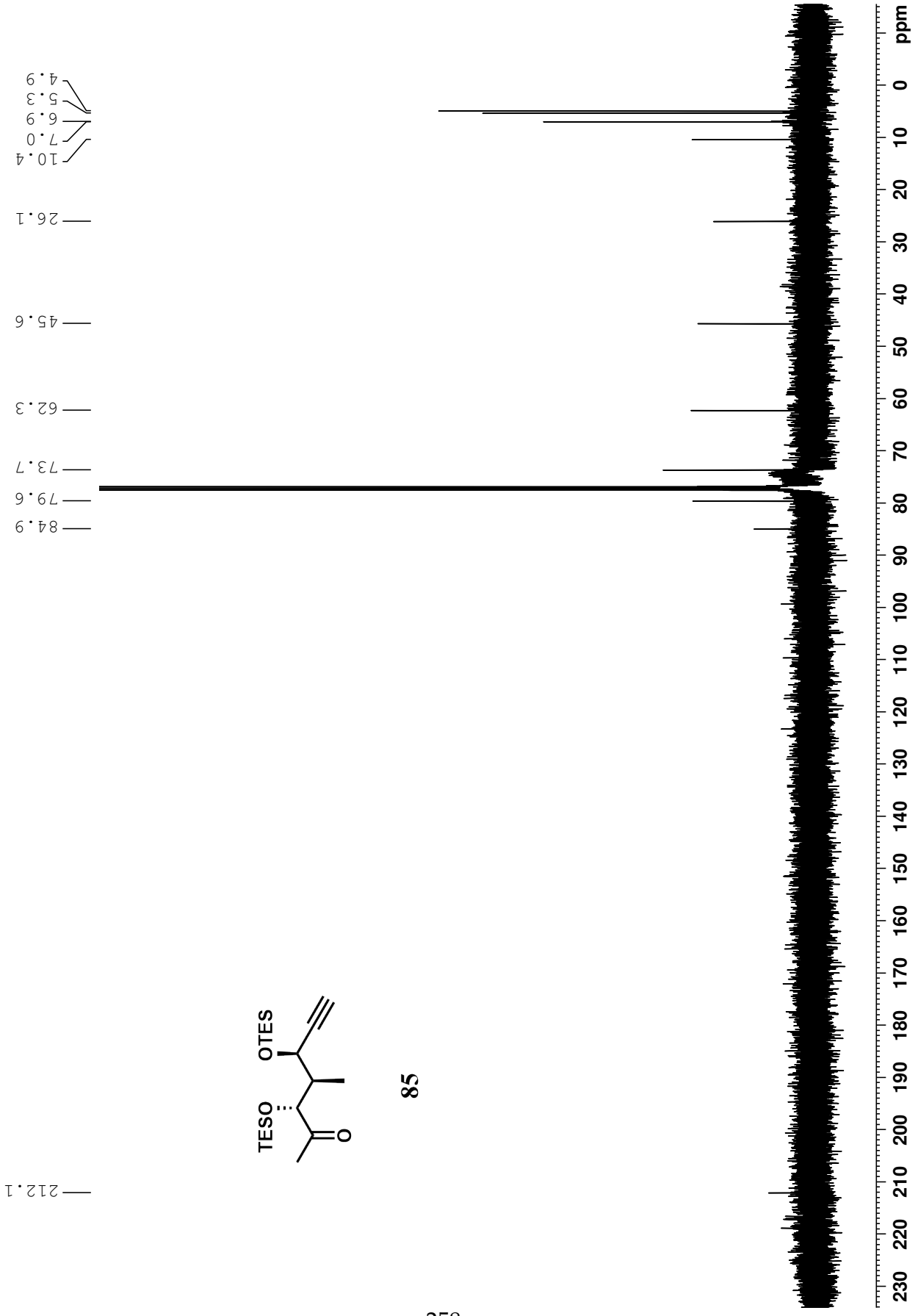
86


5.3
5.4
7.0
7.1
9.8
18.9
46.2
63.9
68.3
73.7
77.7
85.3
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OTES
TESO
OH

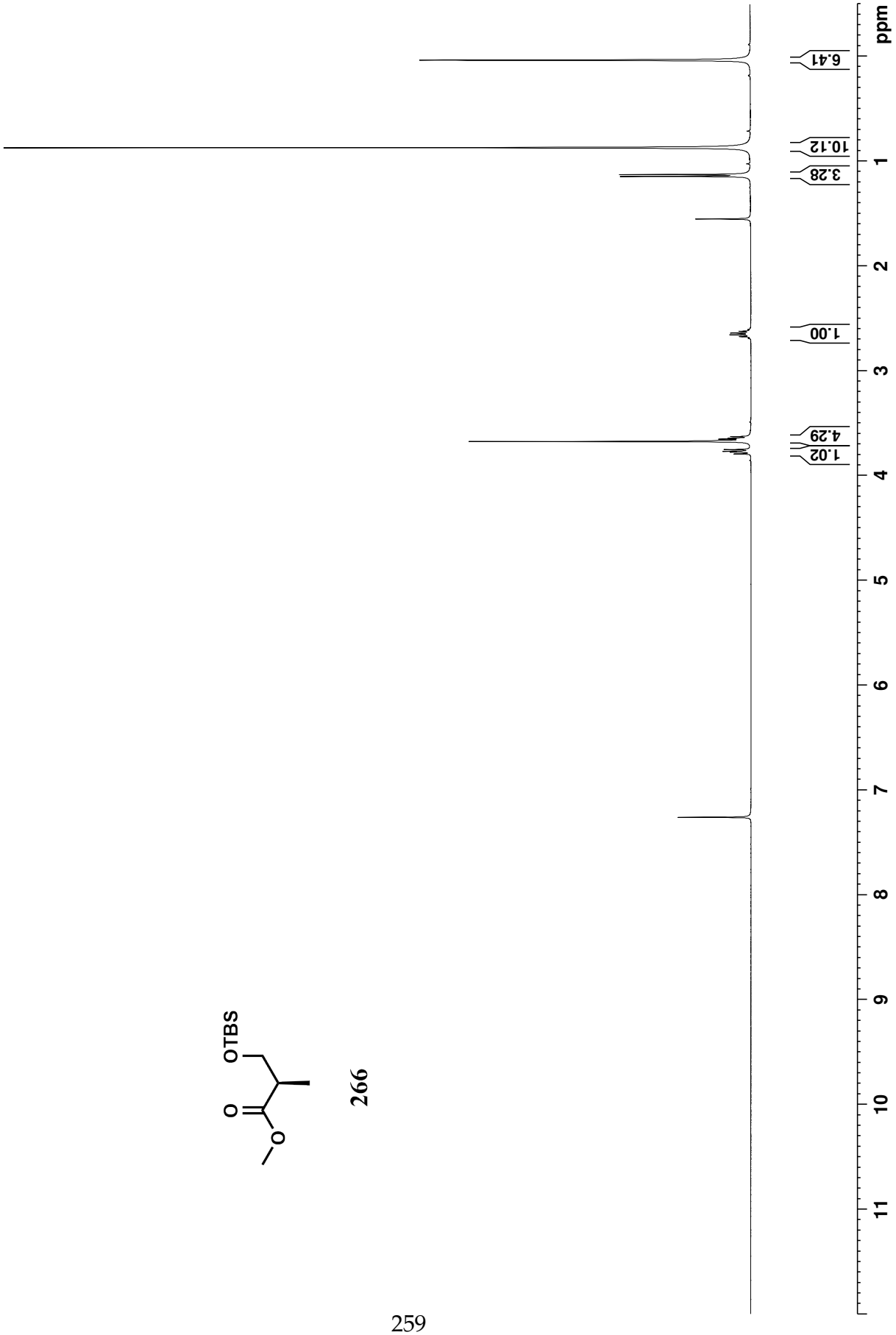
86

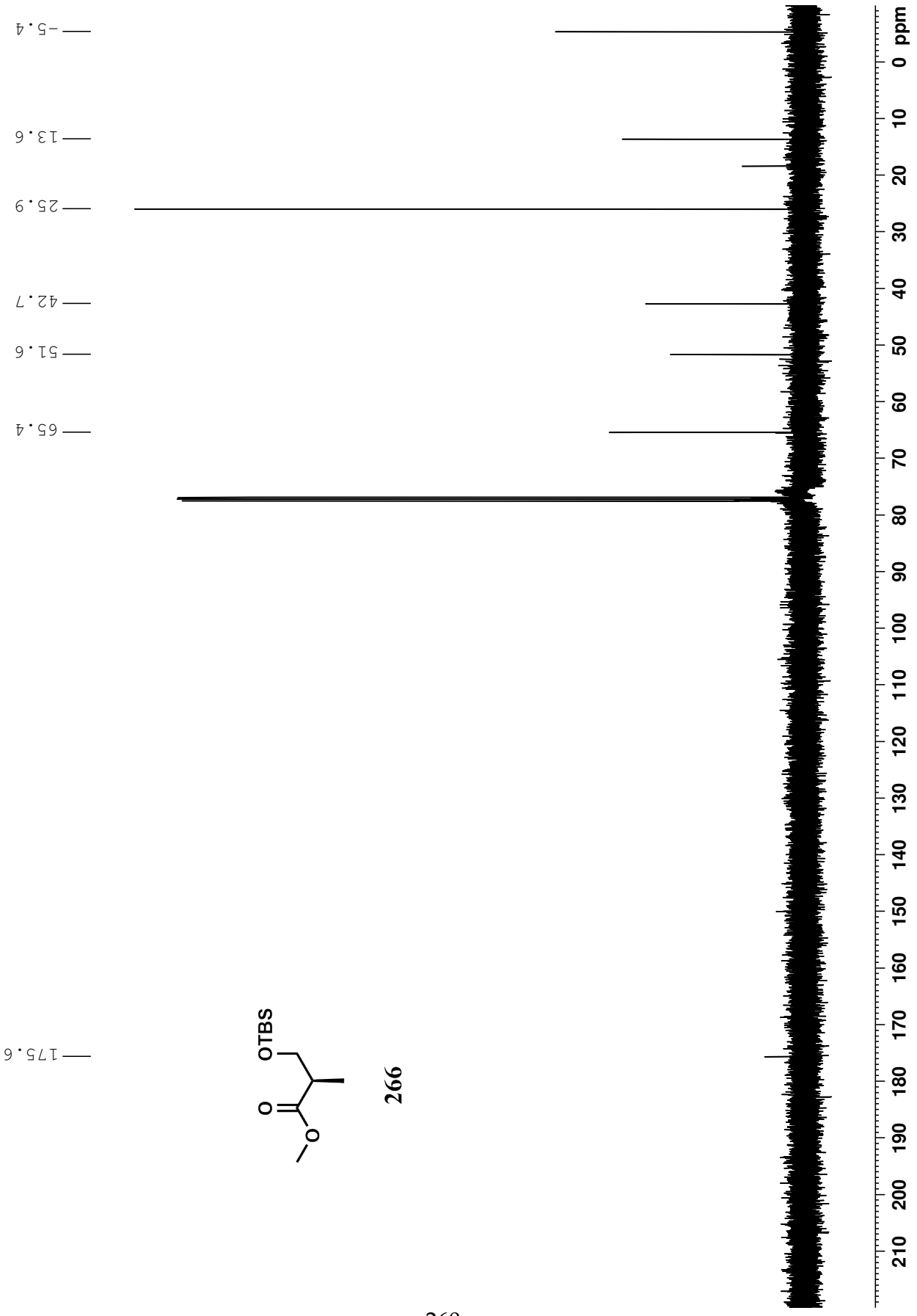


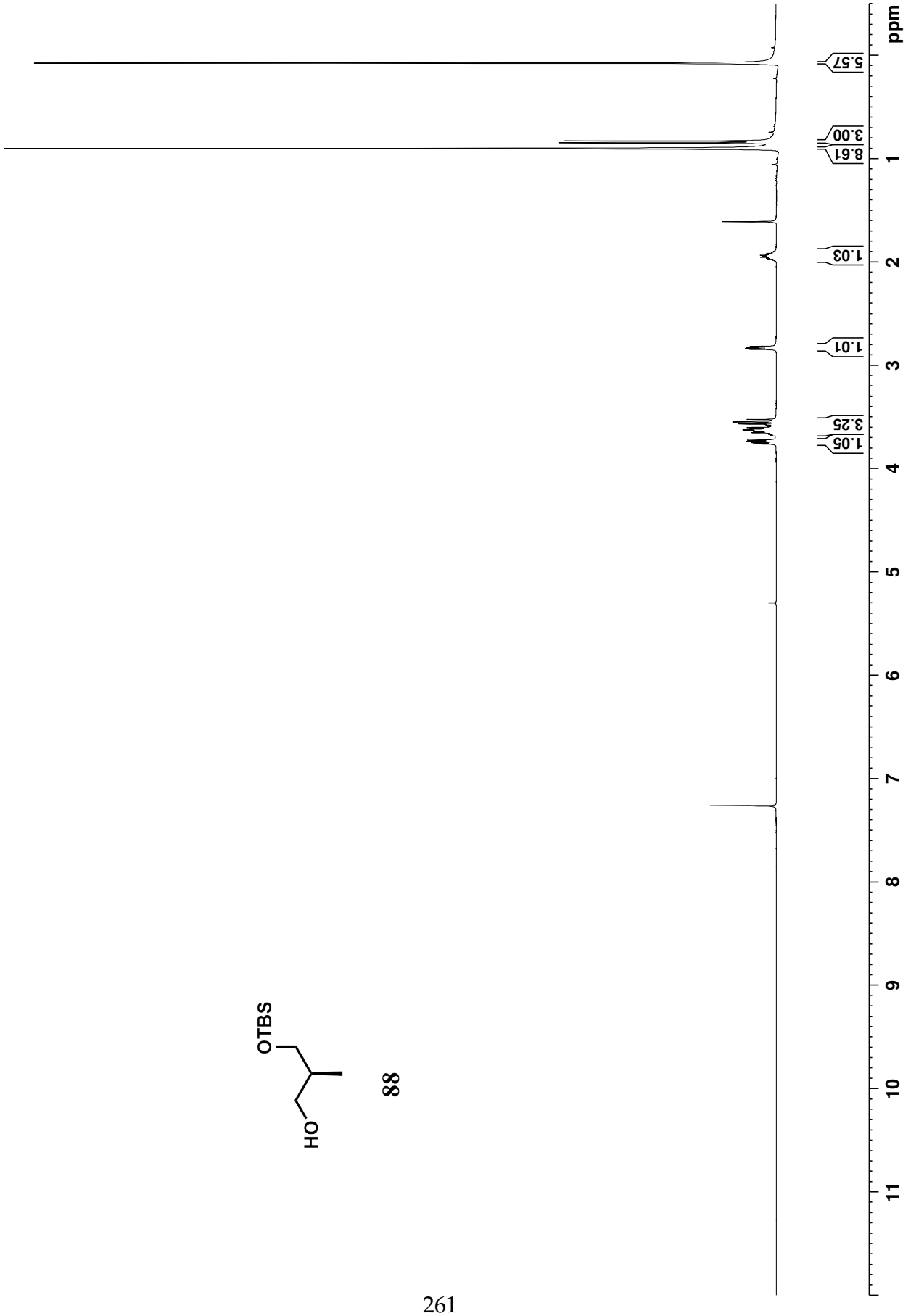
85

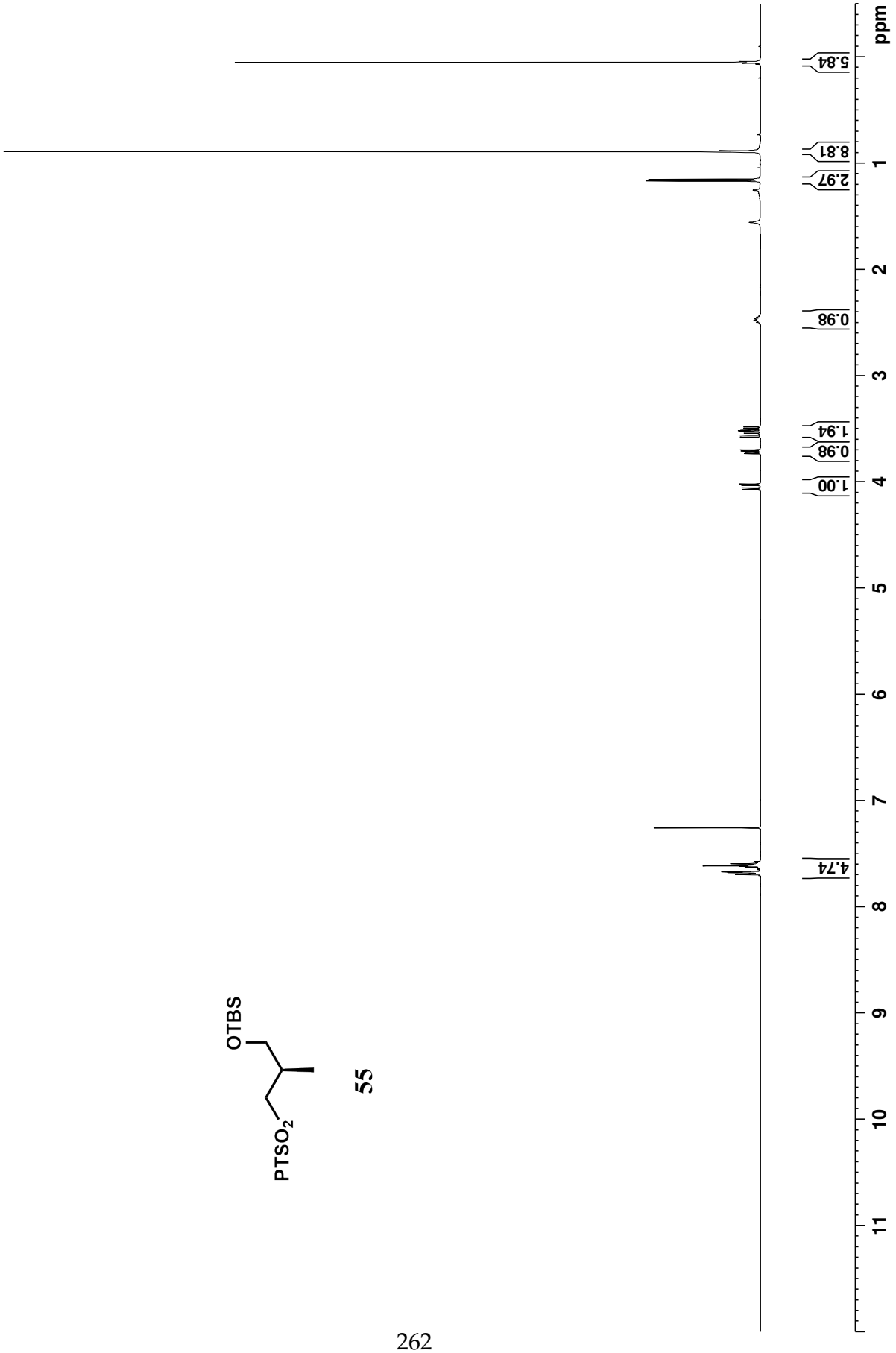

212.1
84.9
79.6
73.7
62.3
45.6
26.1
10.4
7.0
6.9
5.3
4.9
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
TESO
OTES
O

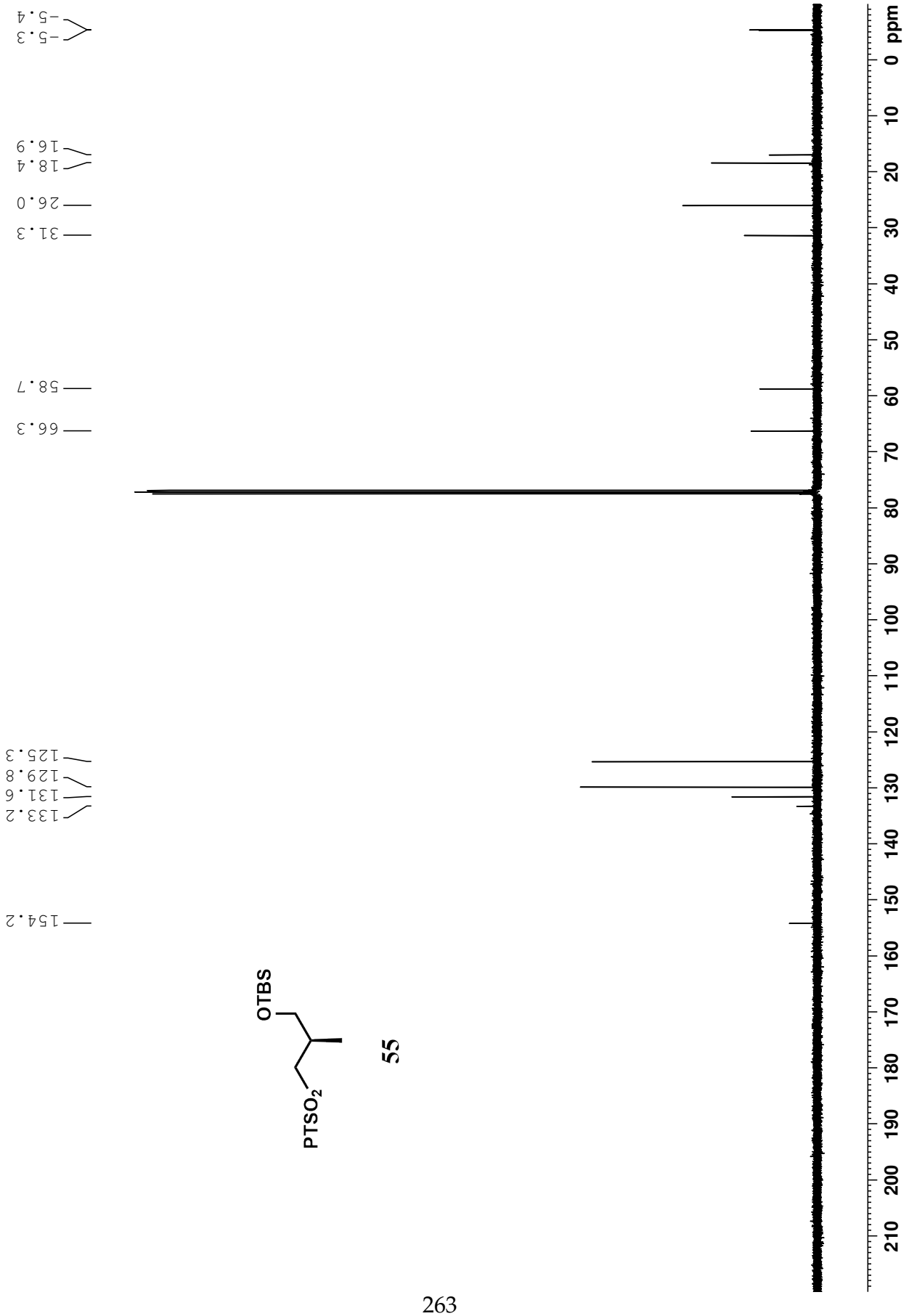
85

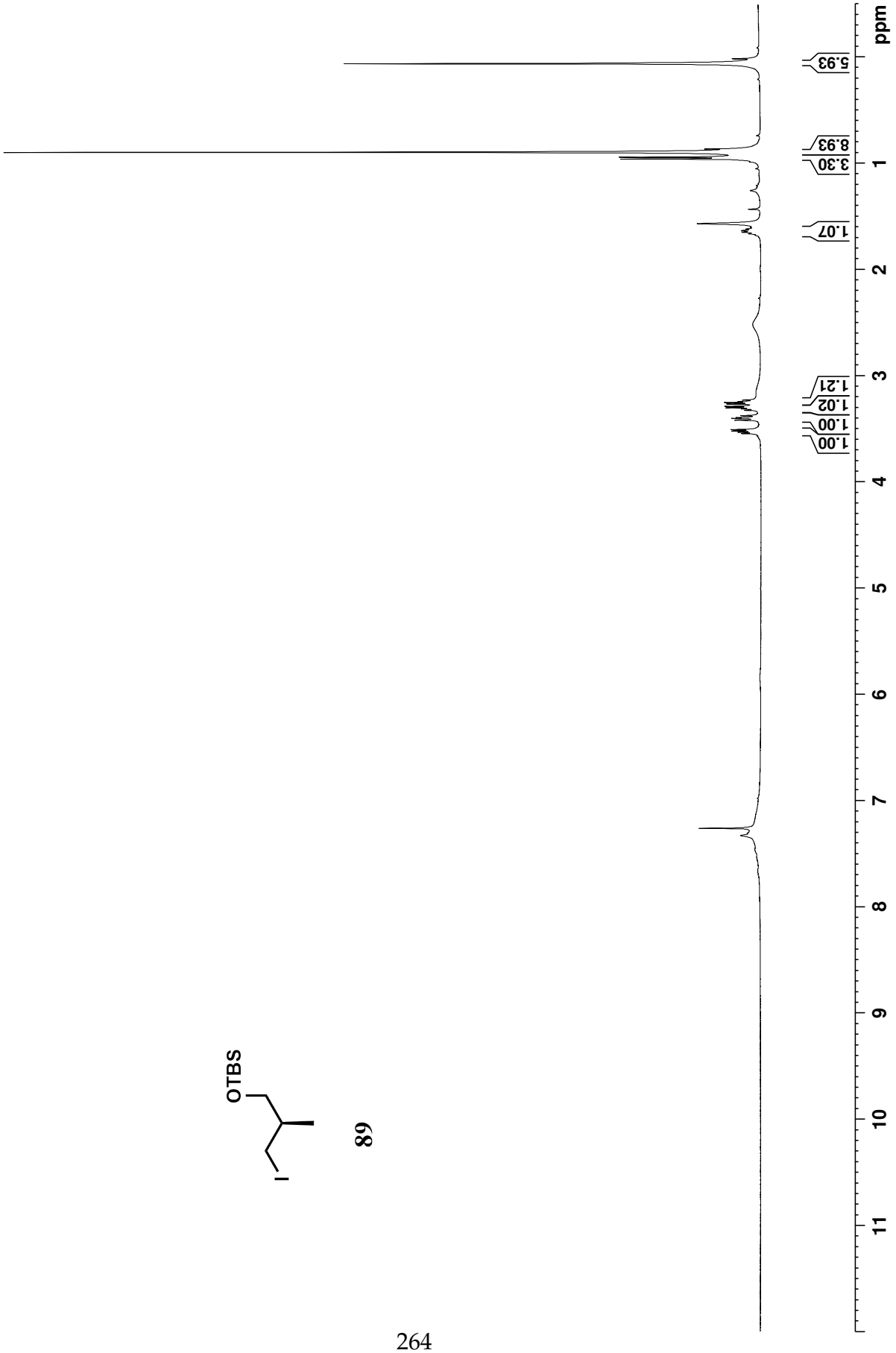

6.41
10.12
3.28
1.00
4.29
1.02
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
O
O
266

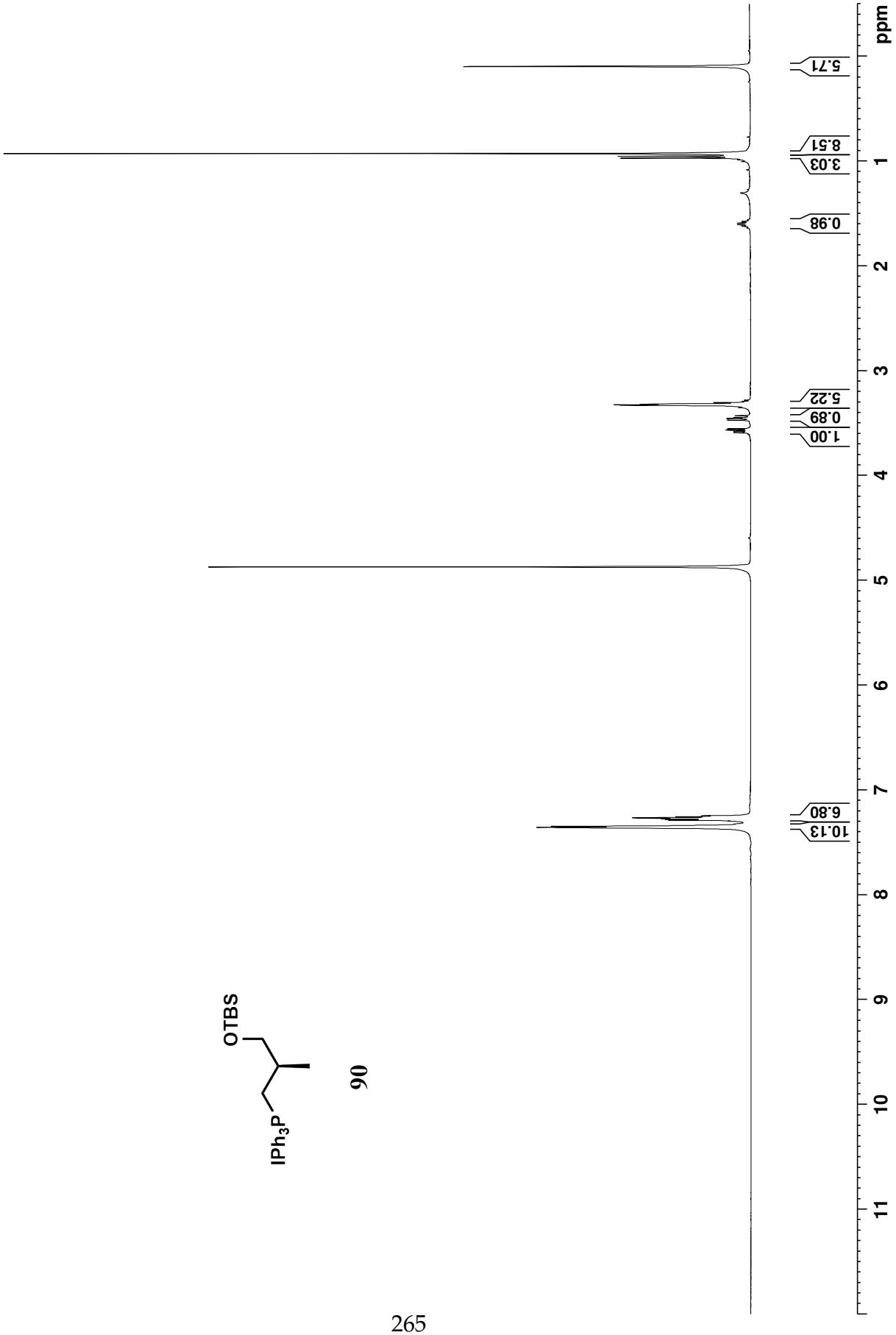

-5.4
13.6
25.9
42.7
51.6
65.4
175.6
OTBS
O
O
266
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

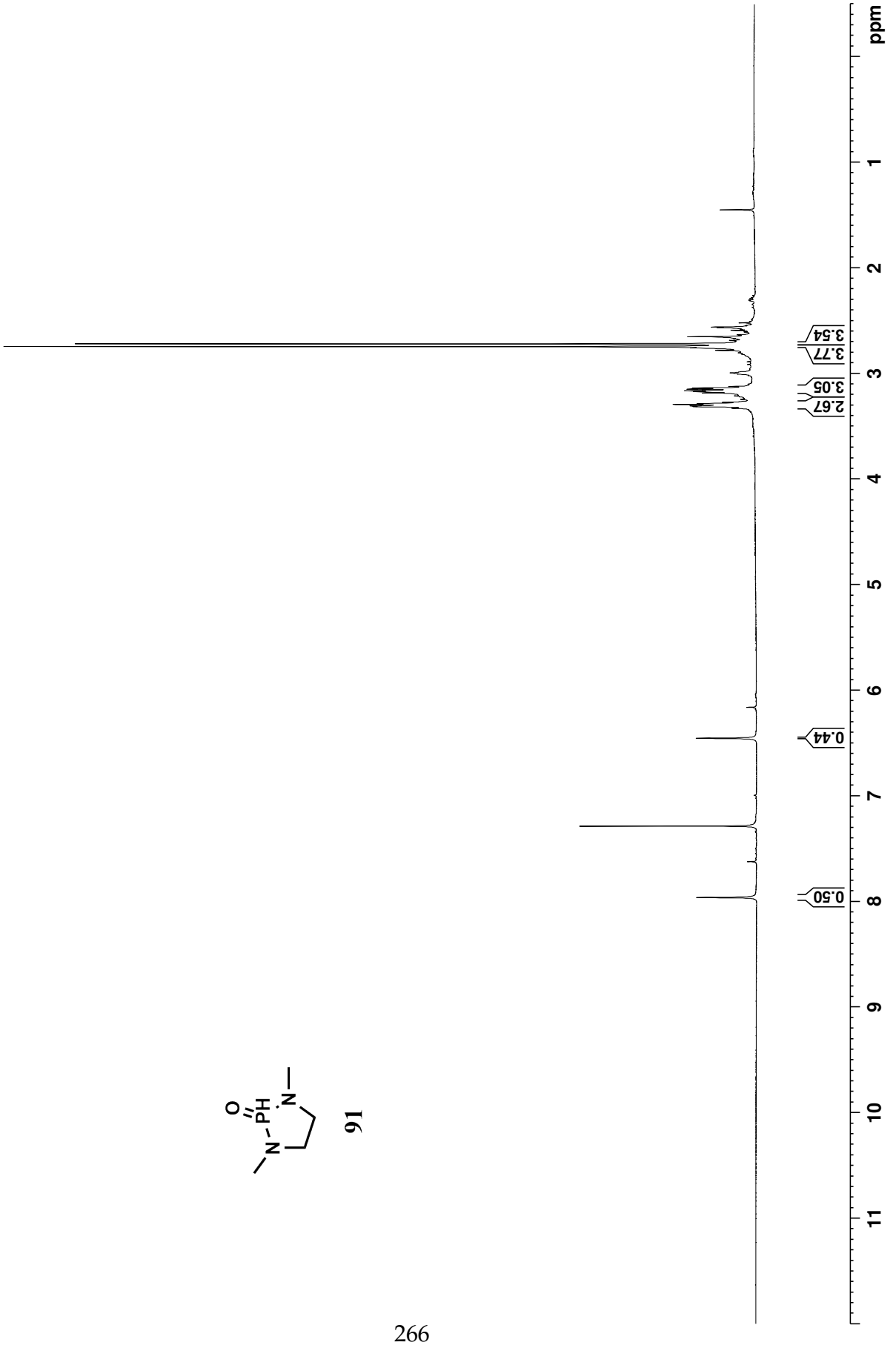

OTBS
HO
88
5.57
3.00
8.61
1.03
1.01
3.25
1.05
ppm
1
2
3
4
5
6
7
8
9
10
11


OTBS
PTSO2
55
5.84
8.81
2.97
0.98
1.94
0.98
1.00
4.74
ppm

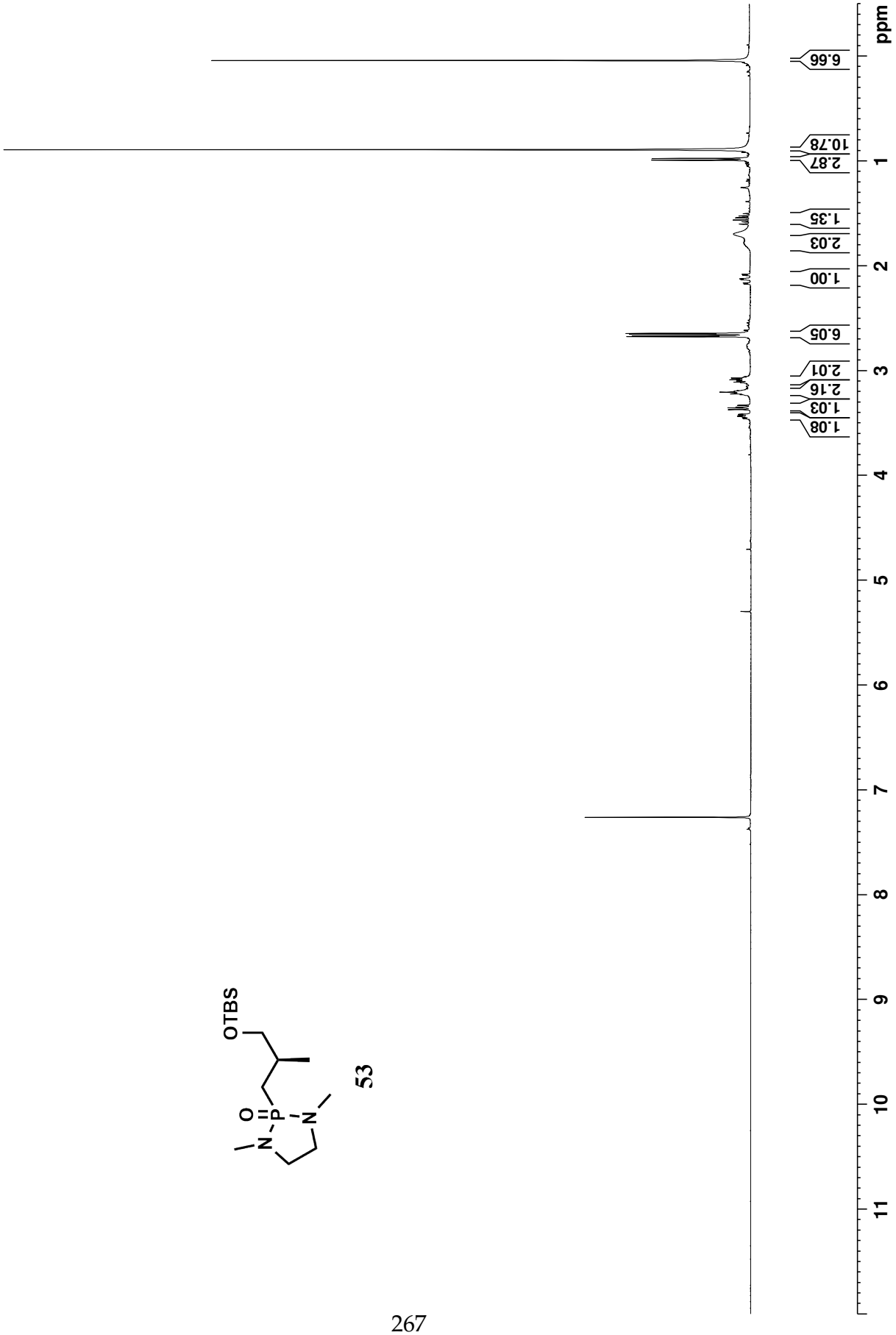

-5.4
-5.3
16.9
18.4
26.0
31.3
58.7
66.3
125.3
129.8
131.6
133.2
154.2
OTBS
PTSO2
55
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

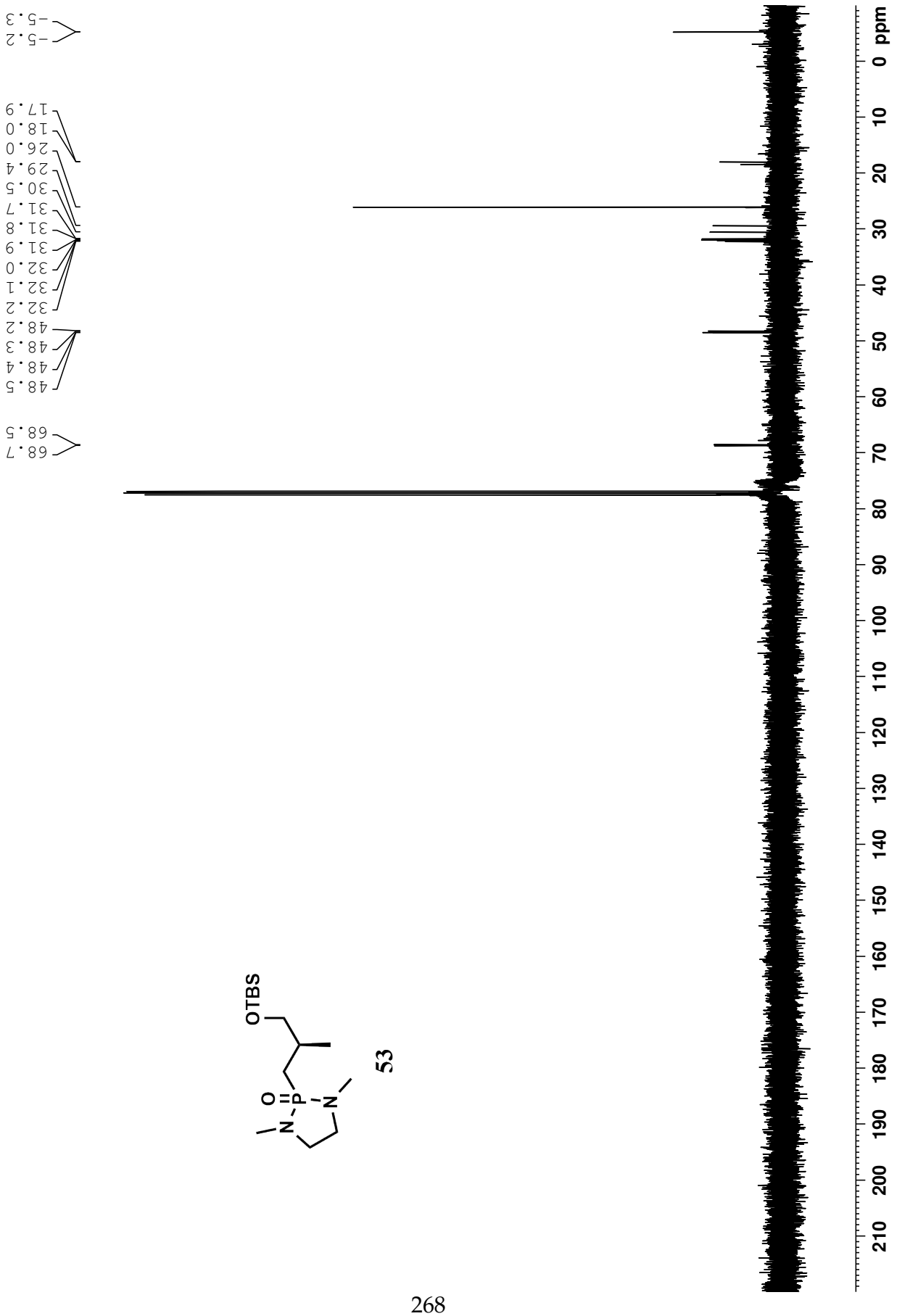

OTBS
I
89
5.93
8.93
3.30
1.07
1.21
1.02
1.00
1.00
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11

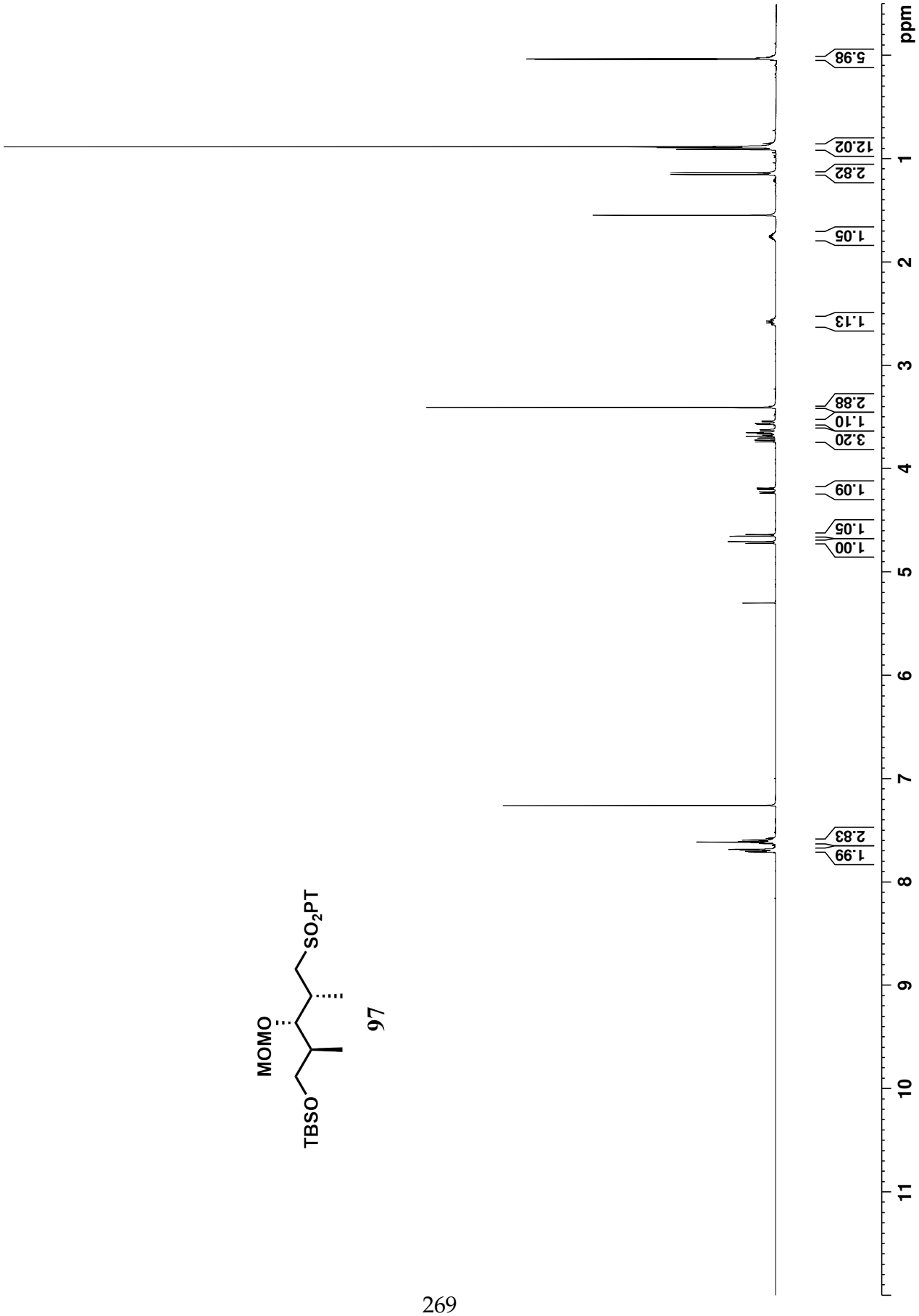

OTBS
IPh3P
90
5.71
8.51
3.03
0.98
5.22
0.89
1.00
6.80
10.13
ppm



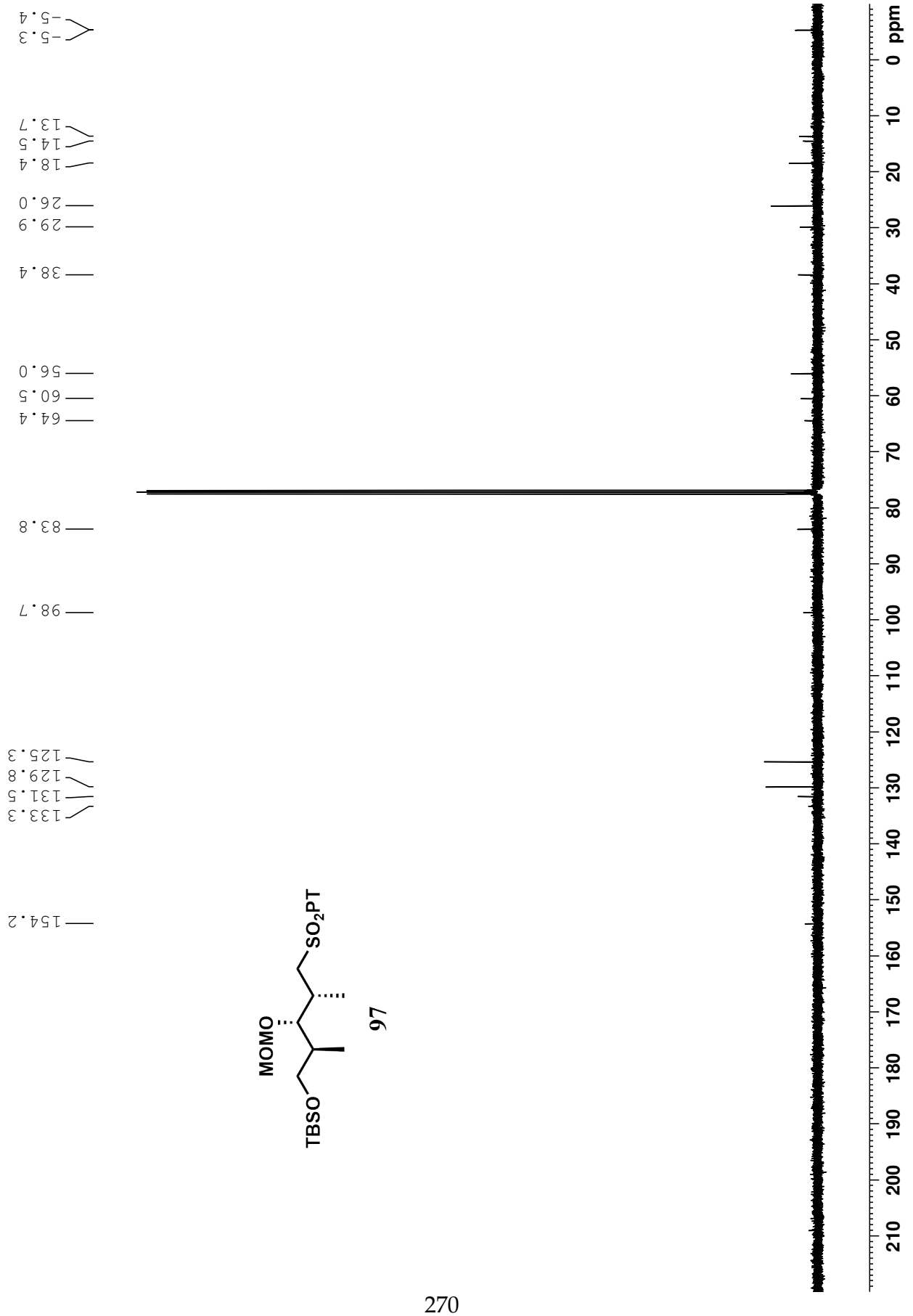
91

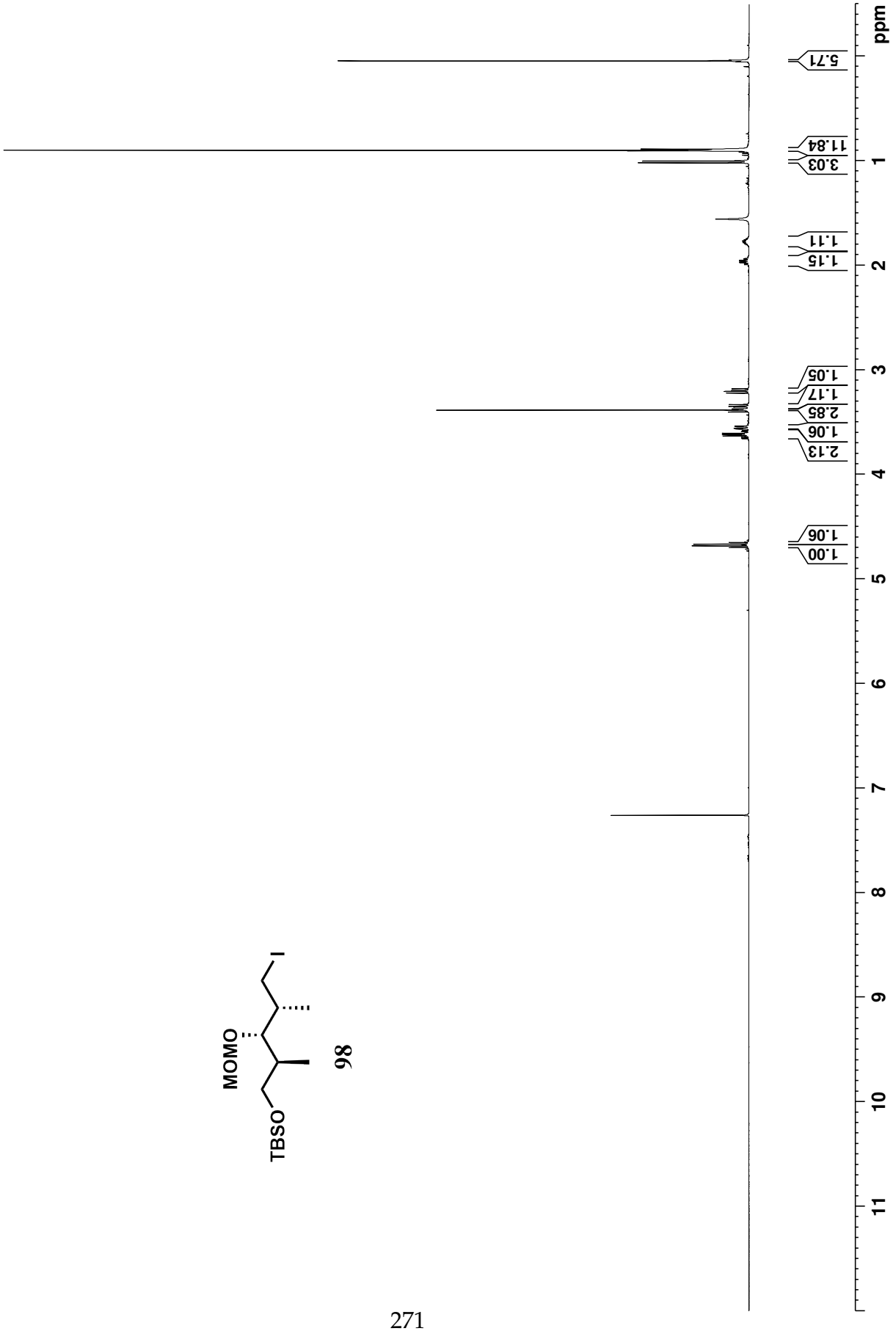

6.66
10.78
2.87
1.35
2.03
1.00
6.05
2.01
2.16
1.03
1.08
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
O
P
N
N
53


-5.3
-5.2
17.9
18.0
26.0
29.4
30.5
31.7
31.8
31.9
32.0
32.1
32.2
48.2
48.3
48.4
48.5
68.5
68.7
OTBS
O
P
N
N
53
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

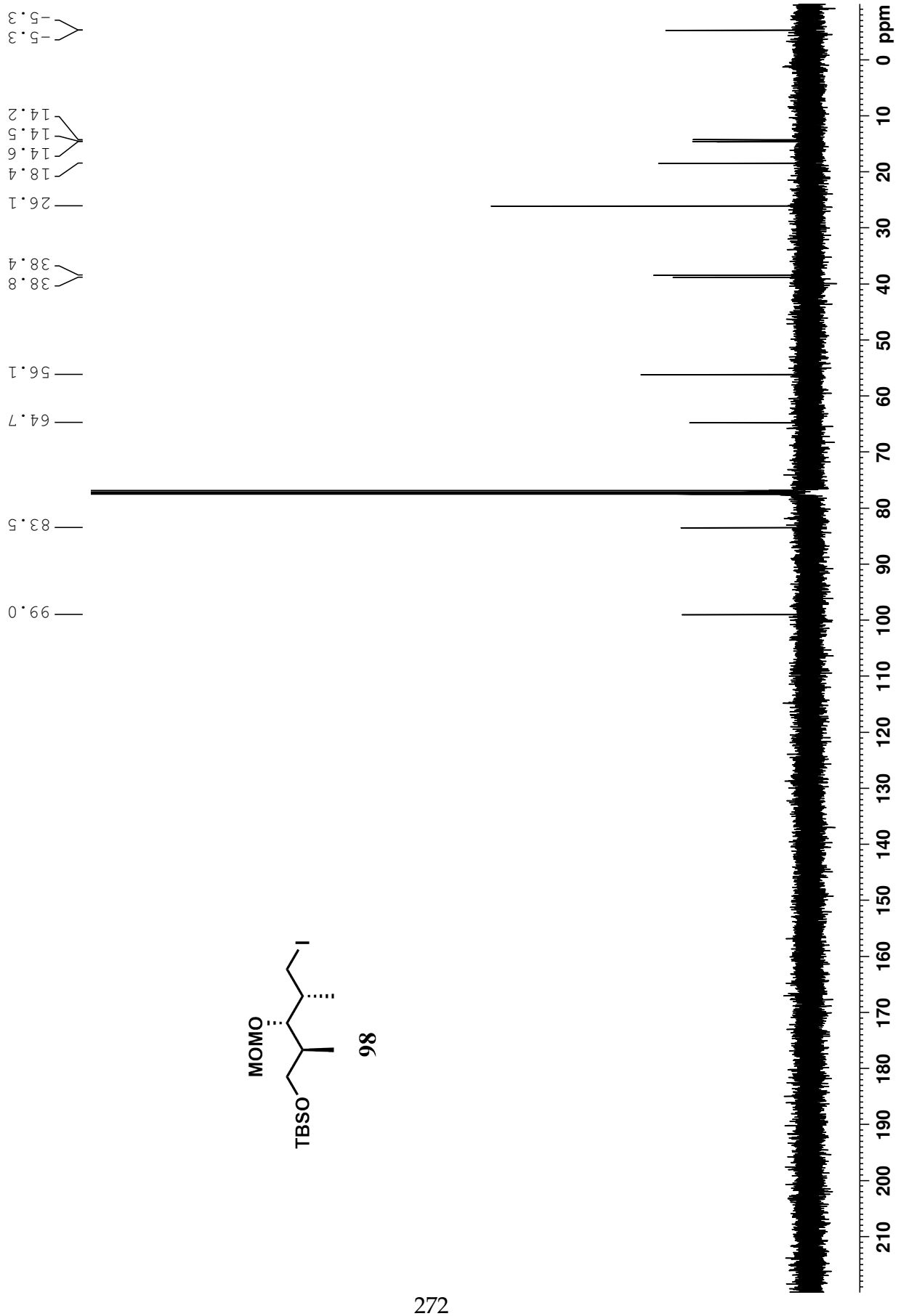

5.98
12.02
2.82
1.05
1.13
2.88
1.10
3.20
1.09
1.05
1.00
1.99
2.83
ppm
1
2
3
4
5
6
7
8
9
10
11
MOMO
TBSO
SO2PT

97

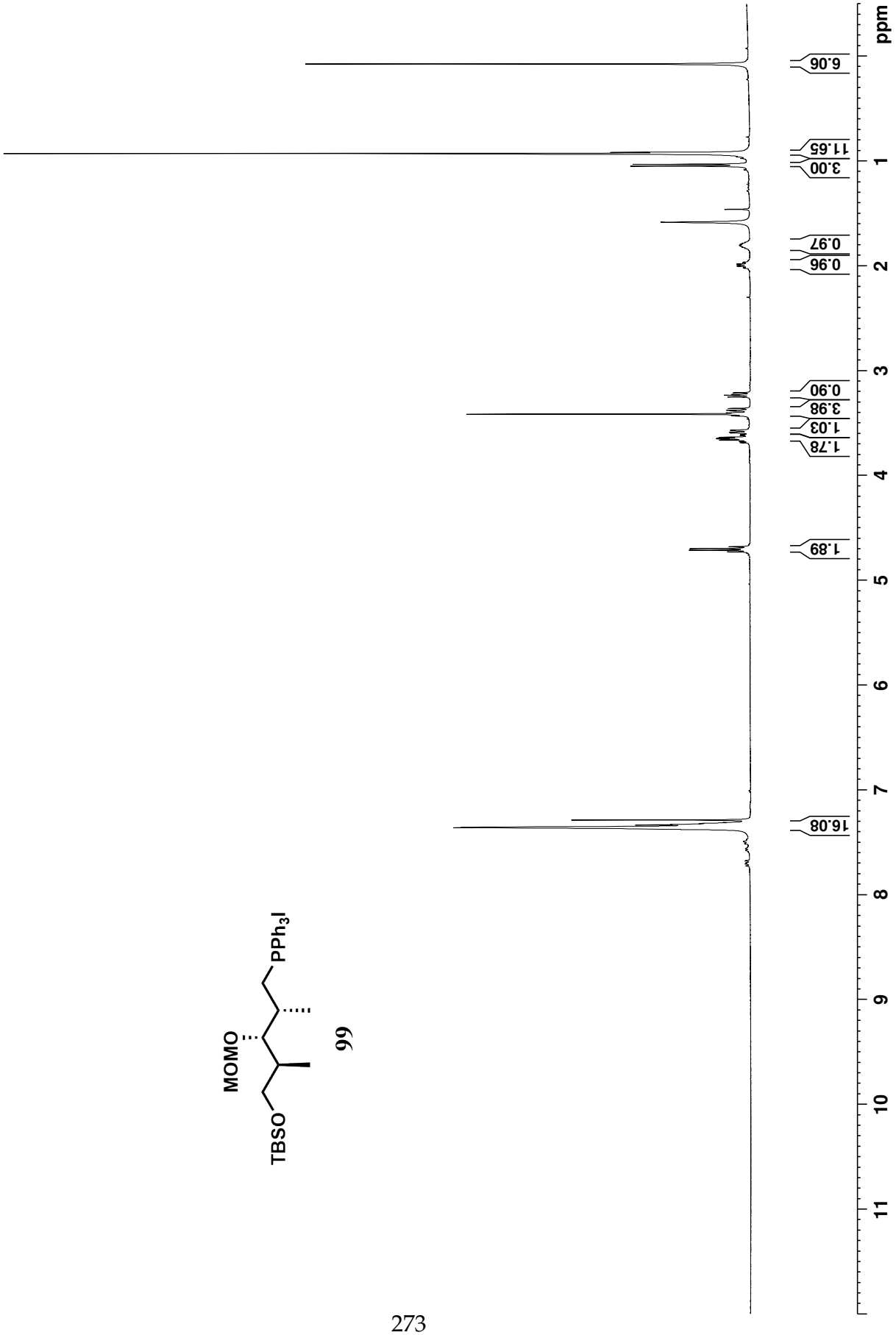

-5.4
-5.3
13.7
14.5
18.4
26.0
29.9
38.4
56.0
60.5
64.4
83.8
98.7
125.3
129.8
131.5
133.3
154.2
MOMO
TBSO
SO2PT
97
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

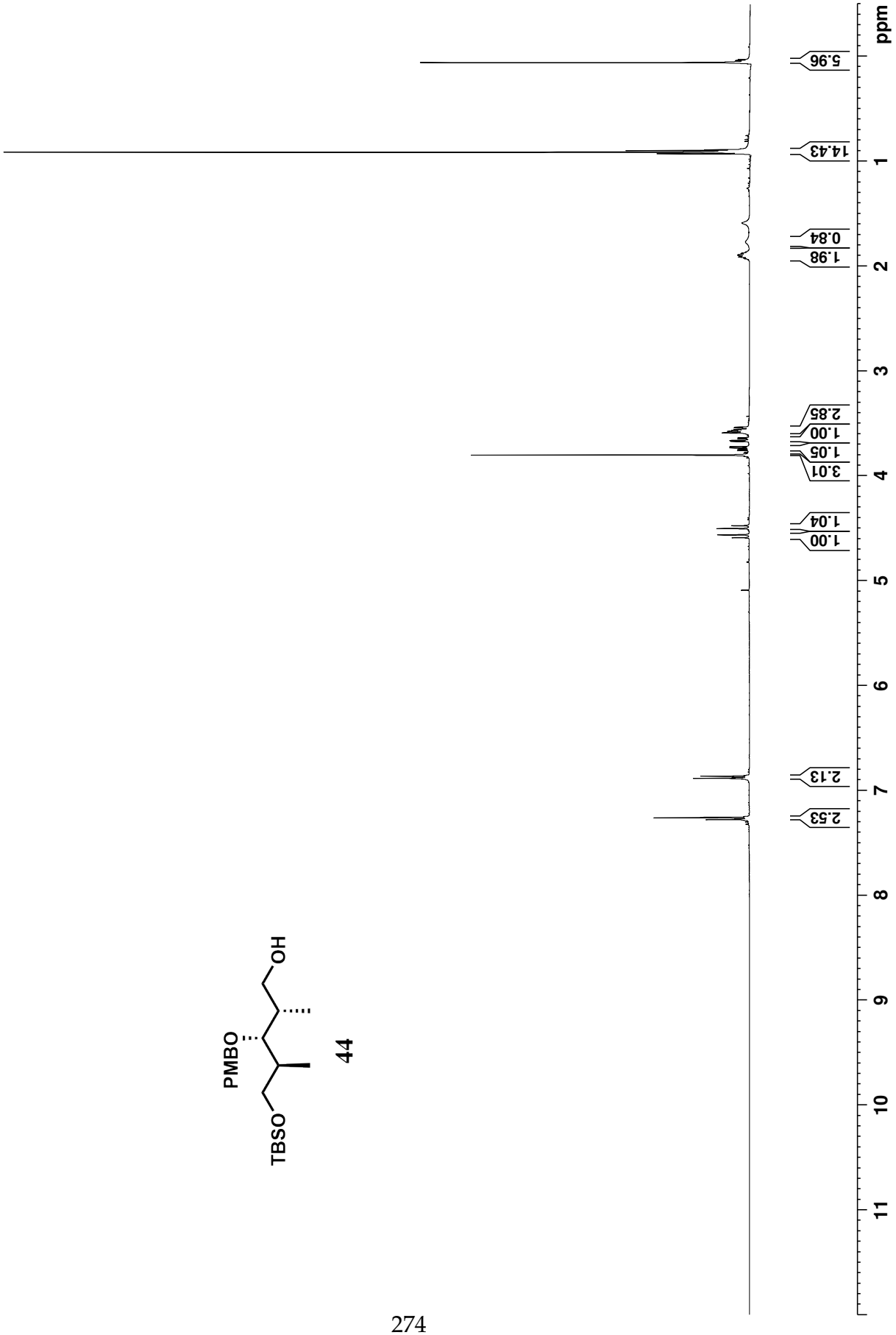

5.71
11.84
3.03
1.15
1.11
1.05
1.17
2.85
1.06
2.13
1.06
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
MOMO
TBSO
I

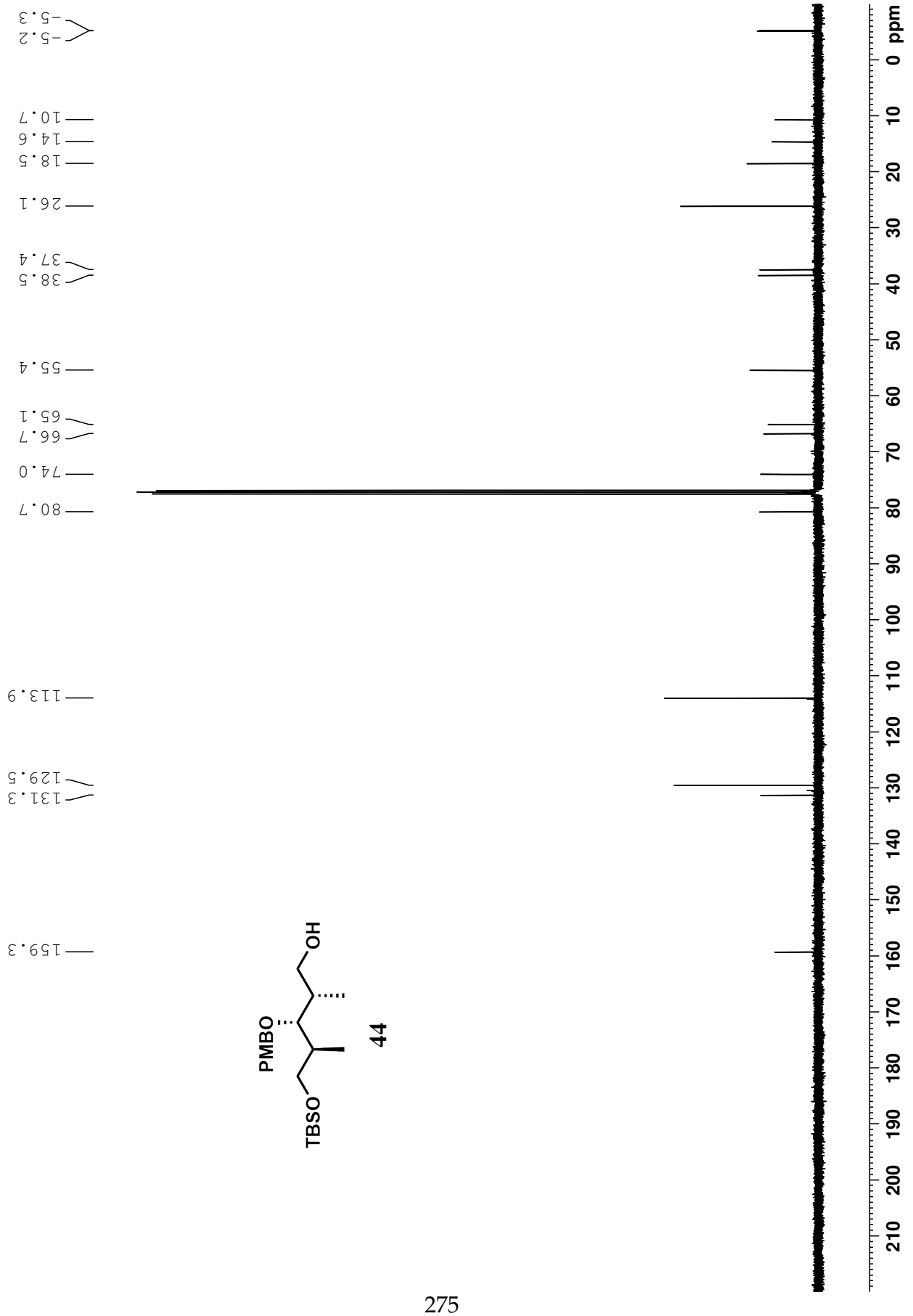
98

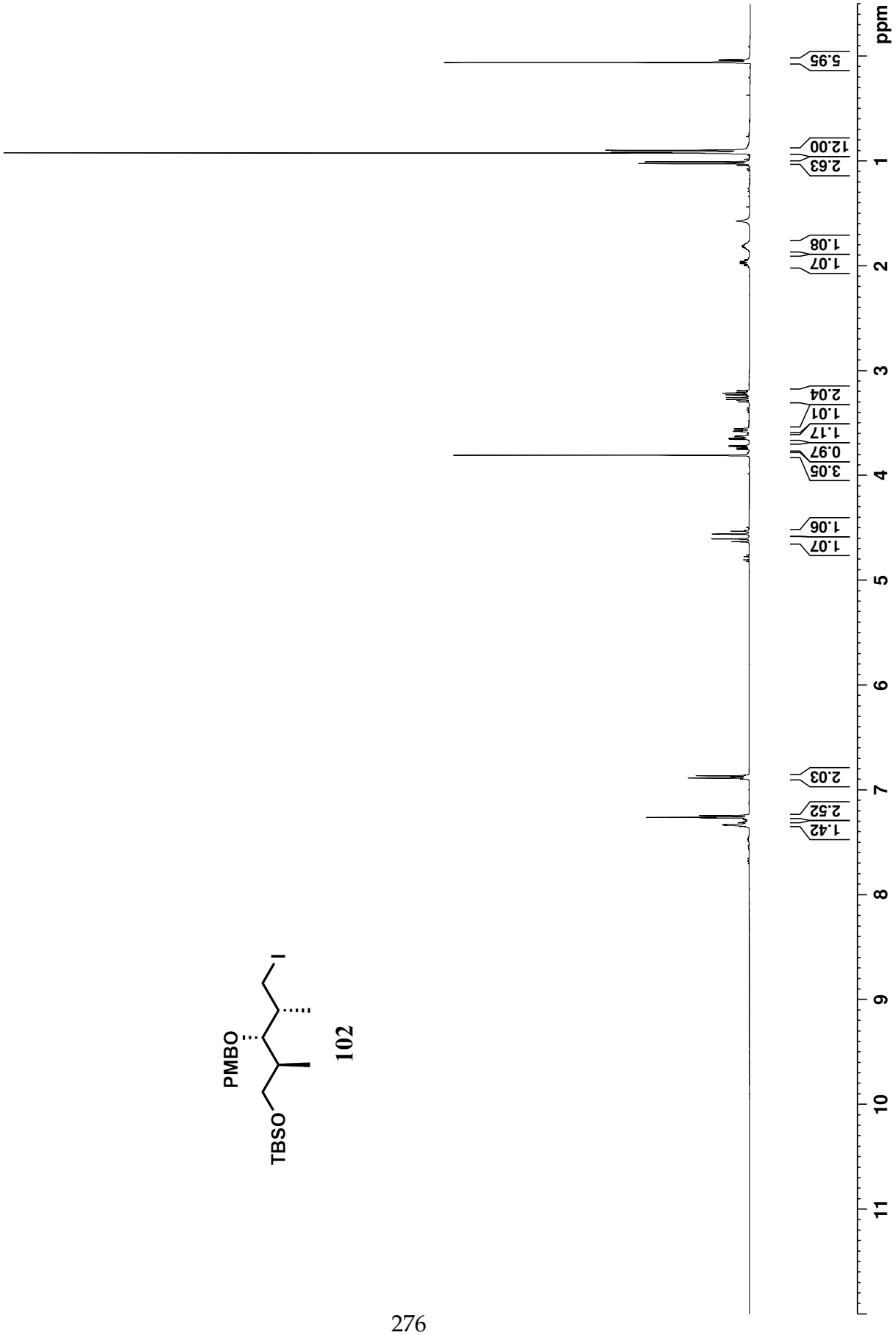

-5.3
-5.3
14.2
14.5
14.6
18.4
26.1
38.4
38.8
56.1
64.7
83.5
99.0
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
I
MOMO
TBSO

98

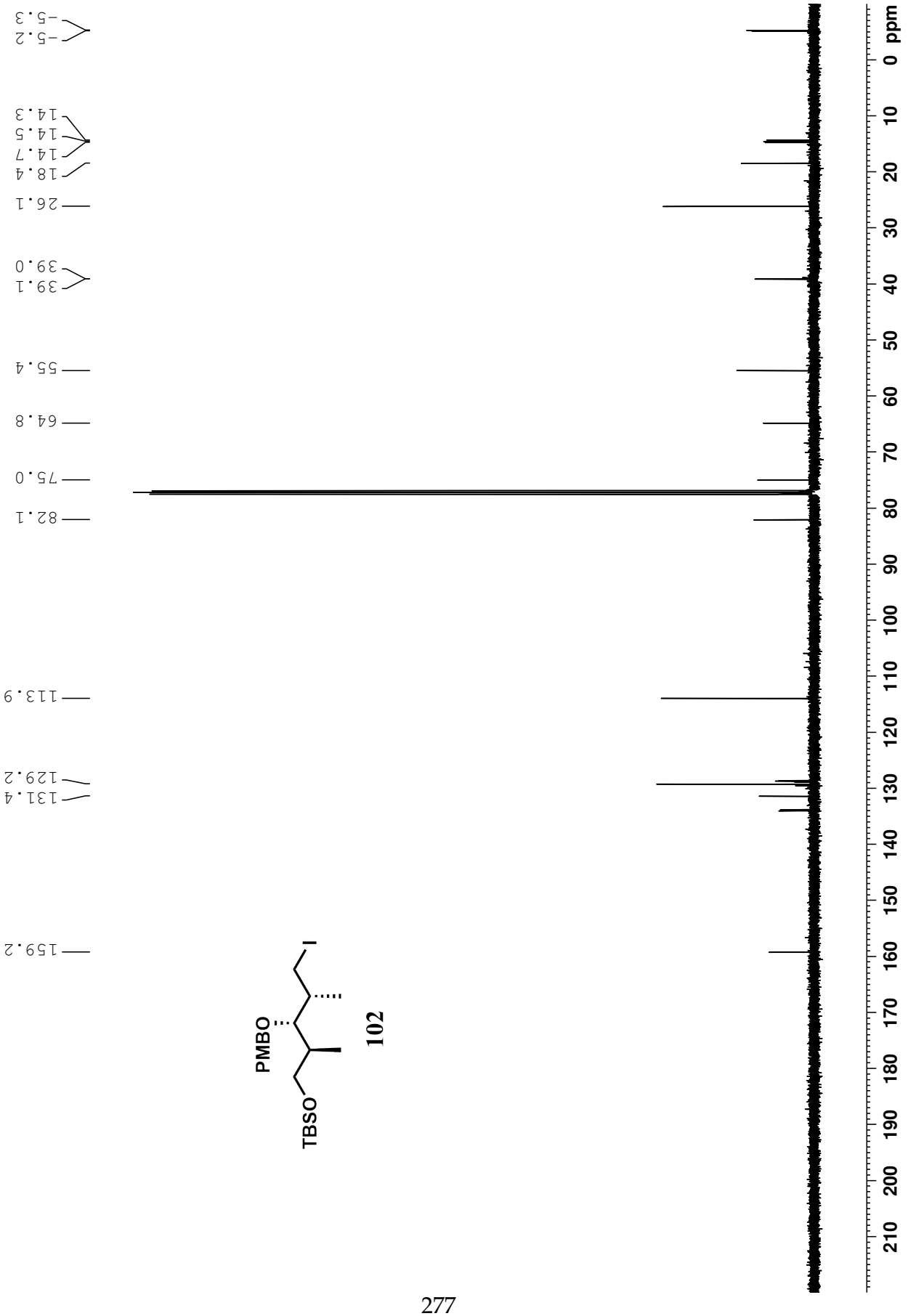

MOMO
TBSO
PPh3I
99
6.06
11.65
3.00
0.97
0.96
0.90
3.98
1.03
1.78
1.89
16.08
ppm

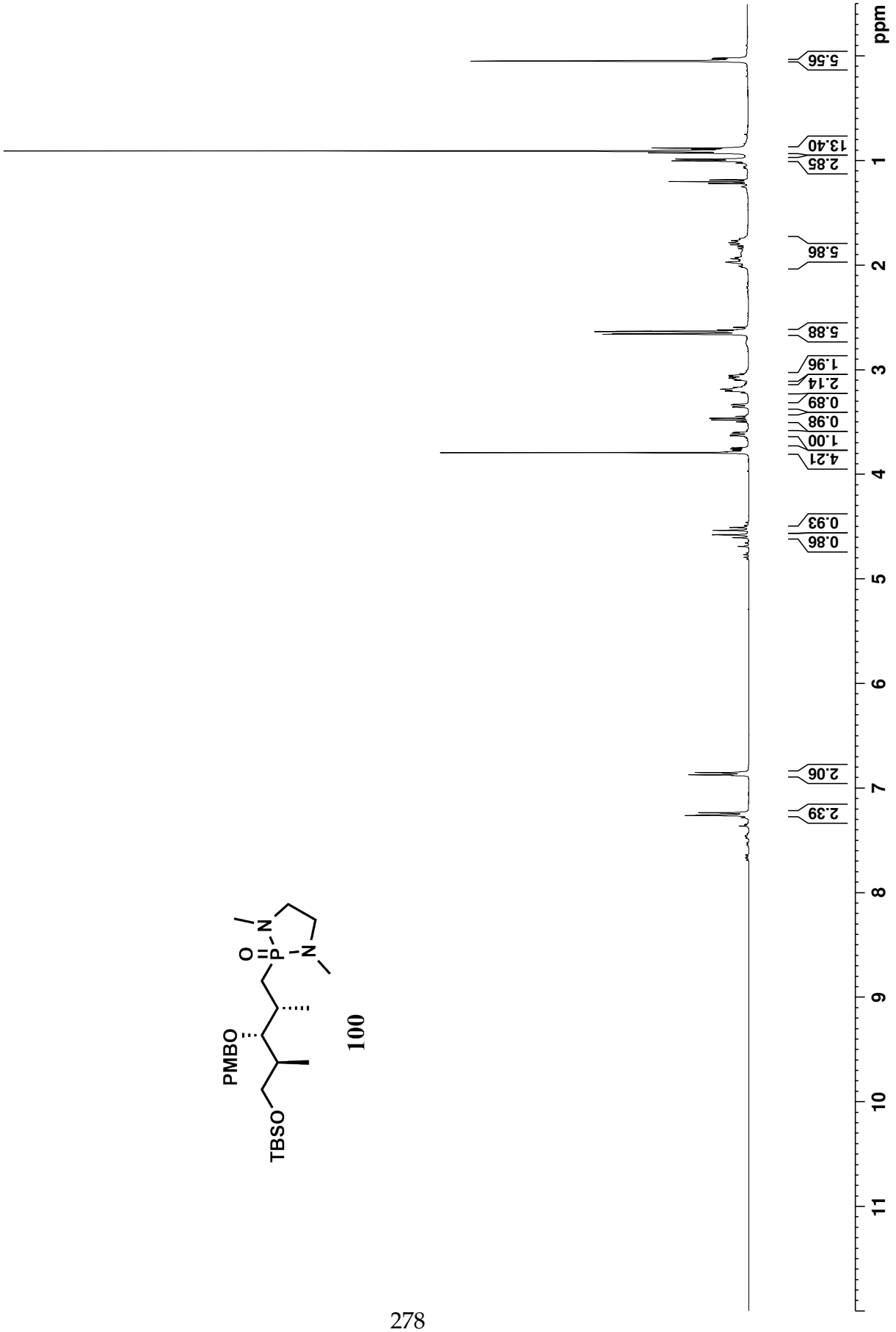

5.96
14.43
0.84
1.98
2.85
1.00
1.05
3.01
1.04
1.00
2.13
2.53
ppm
1
2
3
4
5
6
7
8
9
10
11
OH
PMBO
TBSO
44


-5.3
-5.2
10.7
14.6
18.5
26.1
37.4
38.5
55.4
65.1
66.7
74.0
80.7
113.9
129.5
131.3
159.3
PMBO
OH
TBSO
44
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

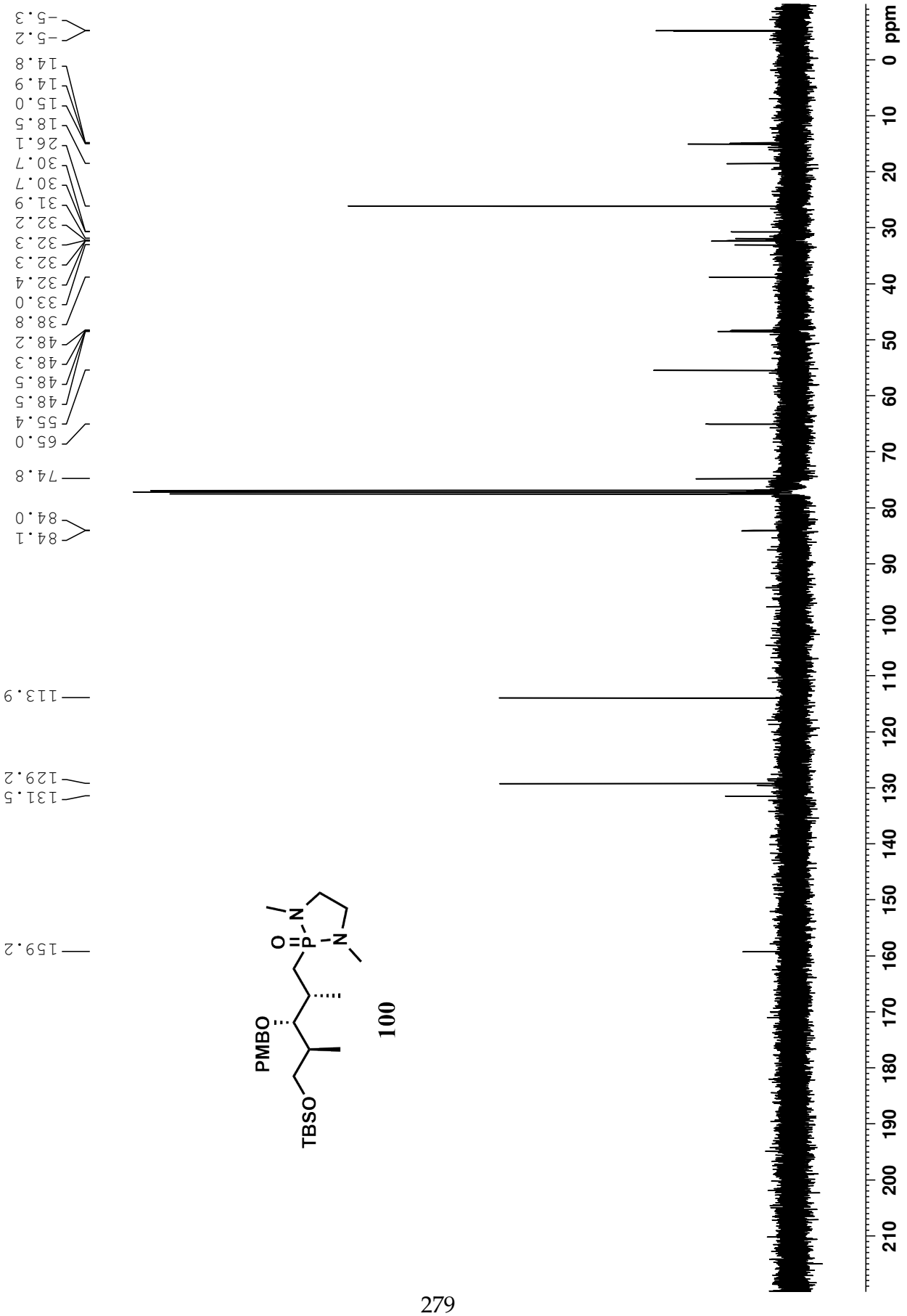

5.95
12.00
2.63
1.08
1.07
2.04
1.01
1.17
0.97
3.05
1.06
1.07
2.03
2.52
1.42
ppm
1
2
3
4
5
6
7
8
9
10
11
PMBO
TBSO
I

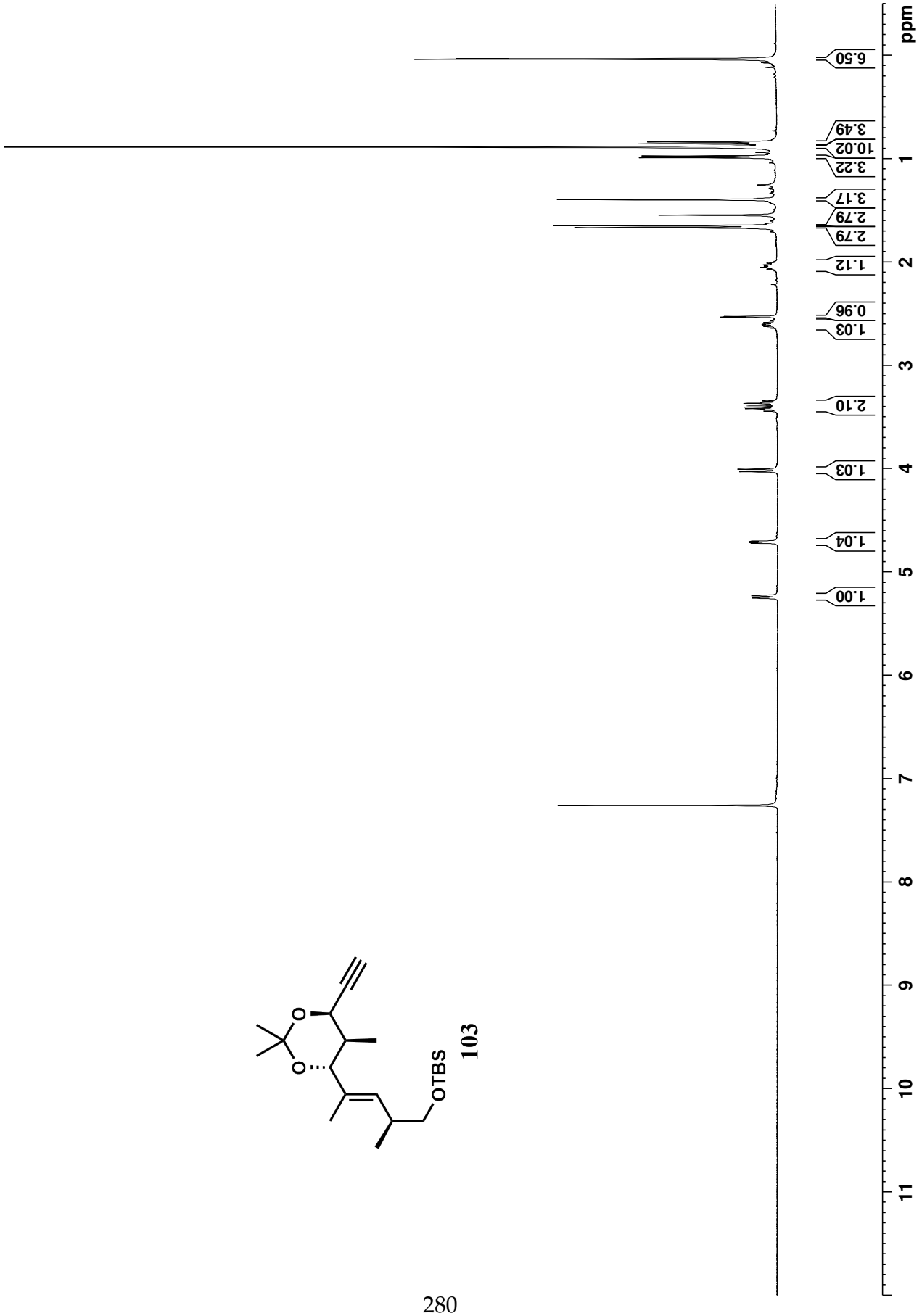
102


-5.3
-5.2
14.3
14.5
14.7
18.4
26.1
39.0
39.1
55.4
64.8
75.0
82.1
113.9
129.2
131.4
159.2
PMBO
TBSO
I
102
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

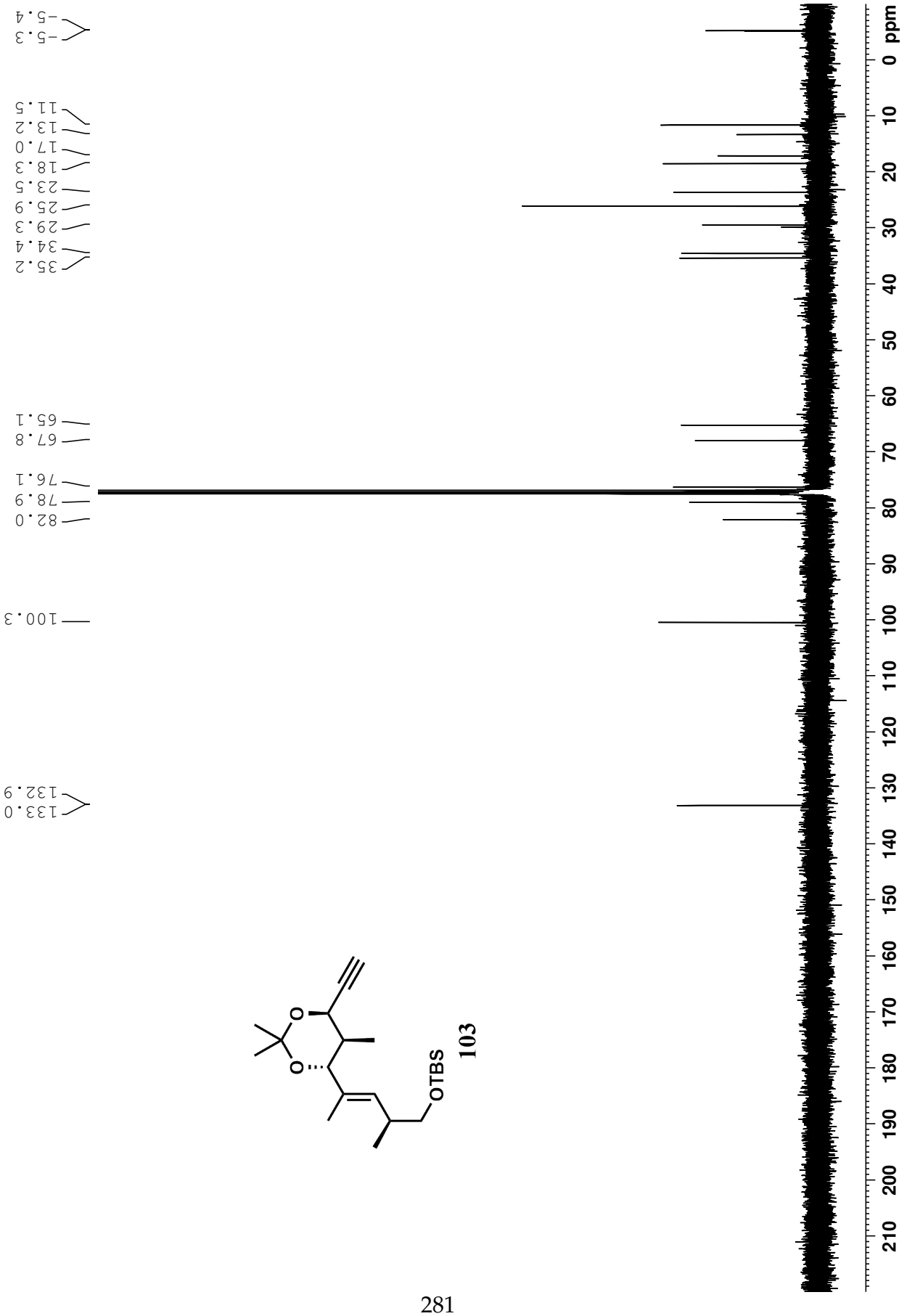

ppm
1
2
3
4
5
6
7
8
9
10
11
5.56
13.40
2.85
5.86
5.88
1.96
2.14
0.89
0.98
1.00
4.21
0.93
0.86
2.06
2.39
PMBO
TBSO
O
P
N
N

100

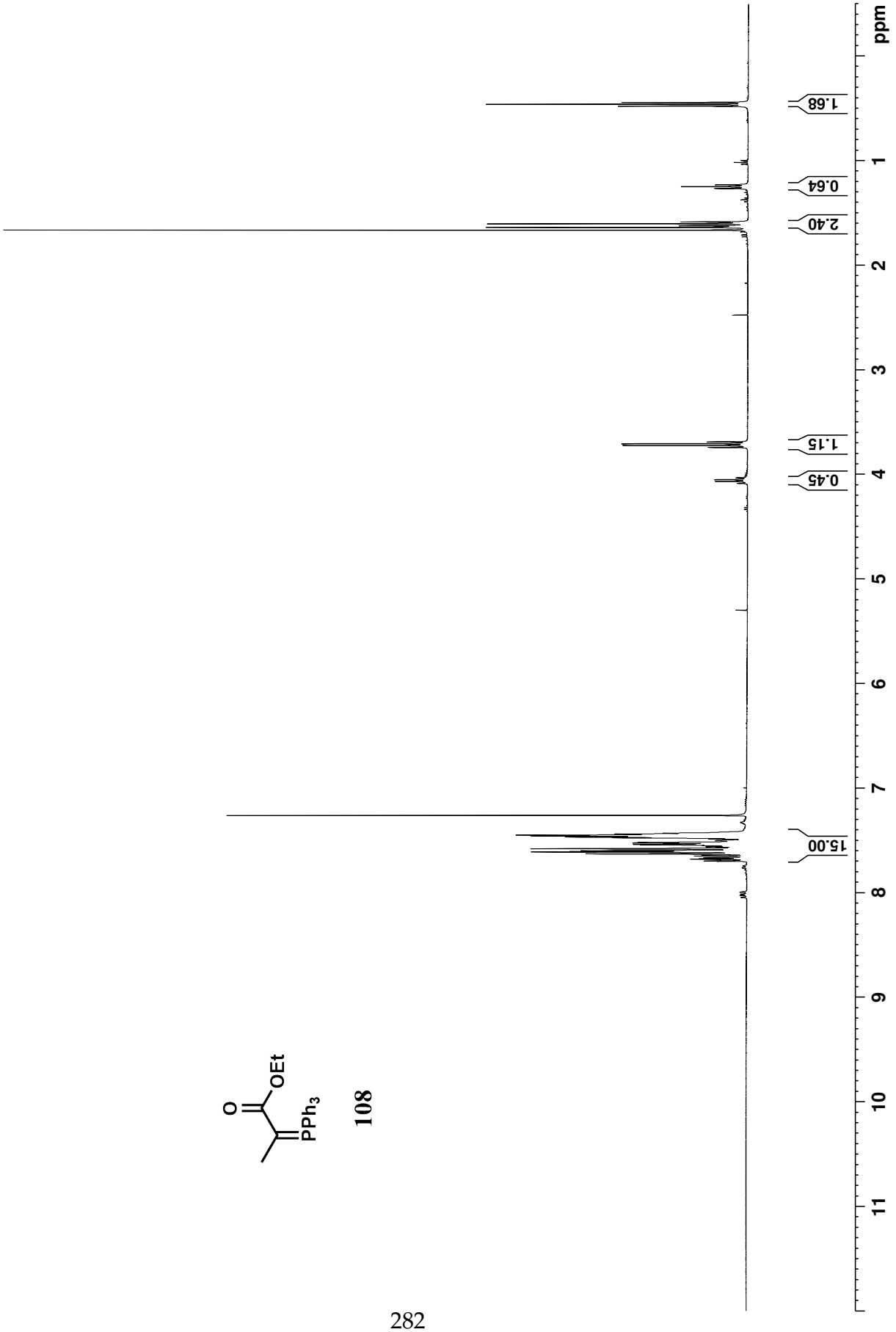

-5.3
-5.2
14.8
14.9
15.0
18.5
26.1
30.7
30.7
31.9
32.2
32.3
32.3
32.4
33.0
38.8
48.2
48.3
48.5
48.5
55.4
65.0
74.8
84.0
84.1
113.9
129.2
131.5
159.2
PMBO
TBSO
O
P
N
N
100
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


6.50
3.49
10.02
3.22
3.17
2.79
2.79
1.12
0.96
1.03
2.10
1.03
1.04
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
O
O
OTBS

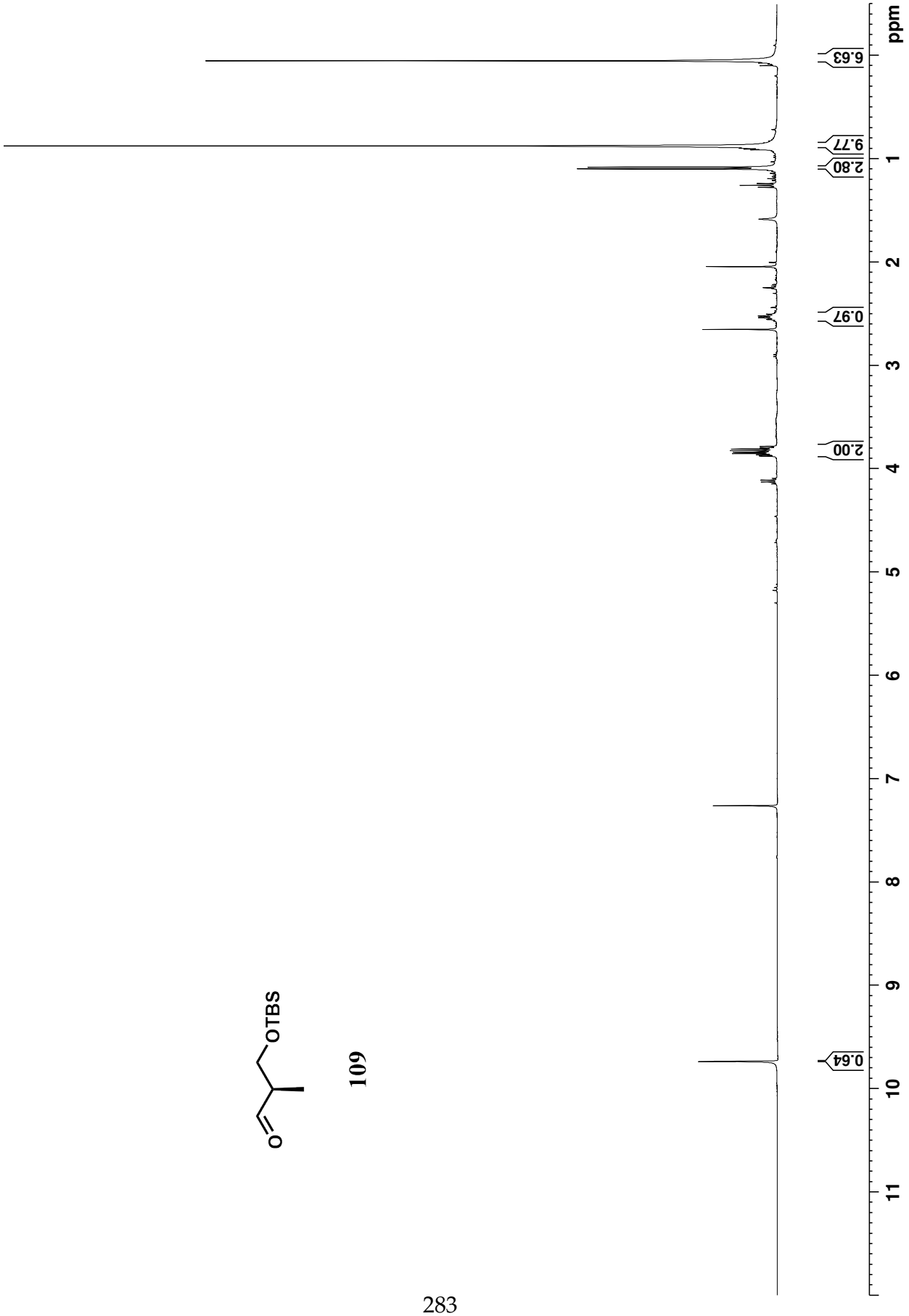
103


-5.4
-5.3
11.5
13.2
17.0
18.3
23.5
25.9
29.3
34.4
35.2
65.1
67.8
76.1
78.9
82.0
100.3
132.9
133.0
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
O
OTBS

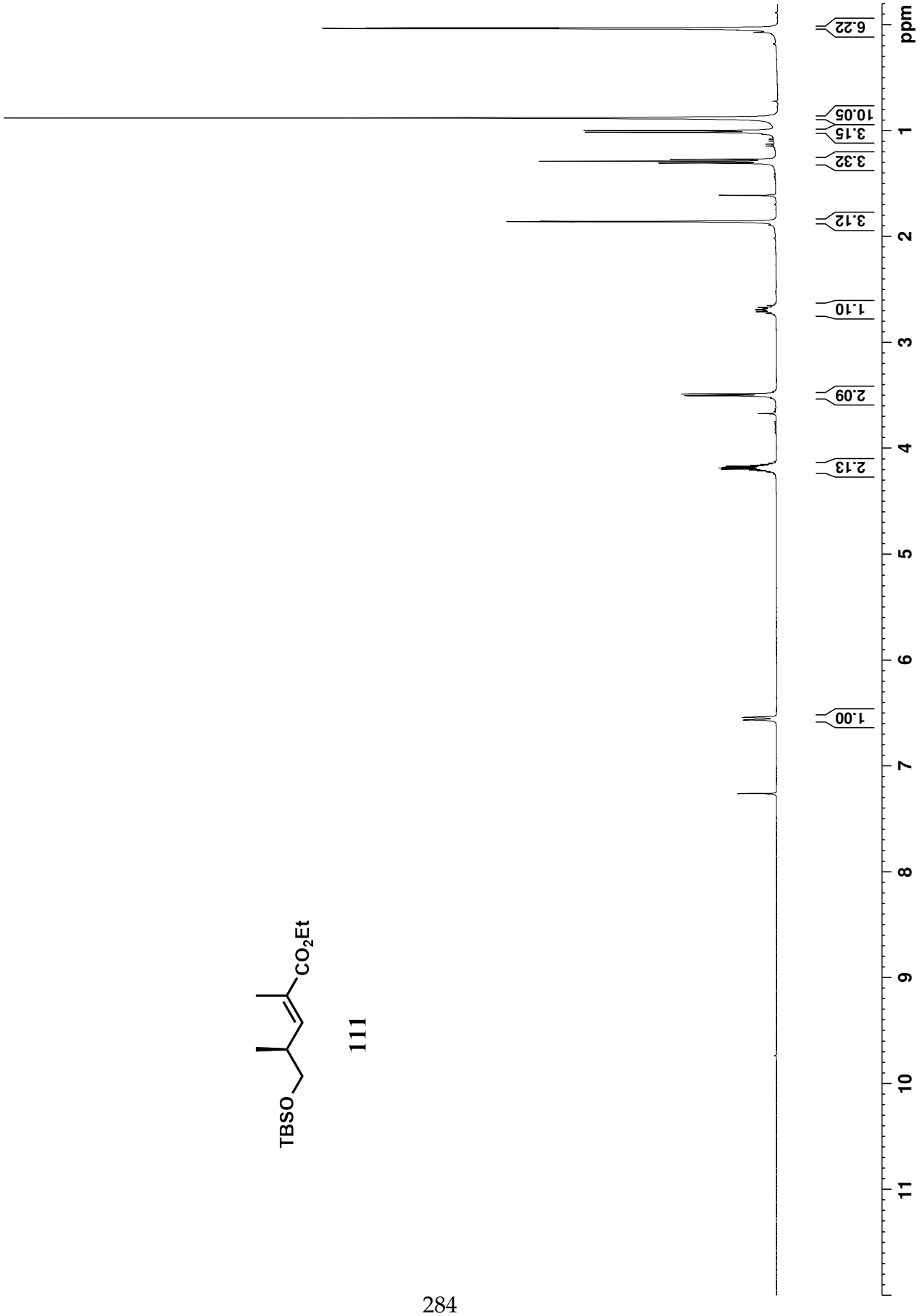
103



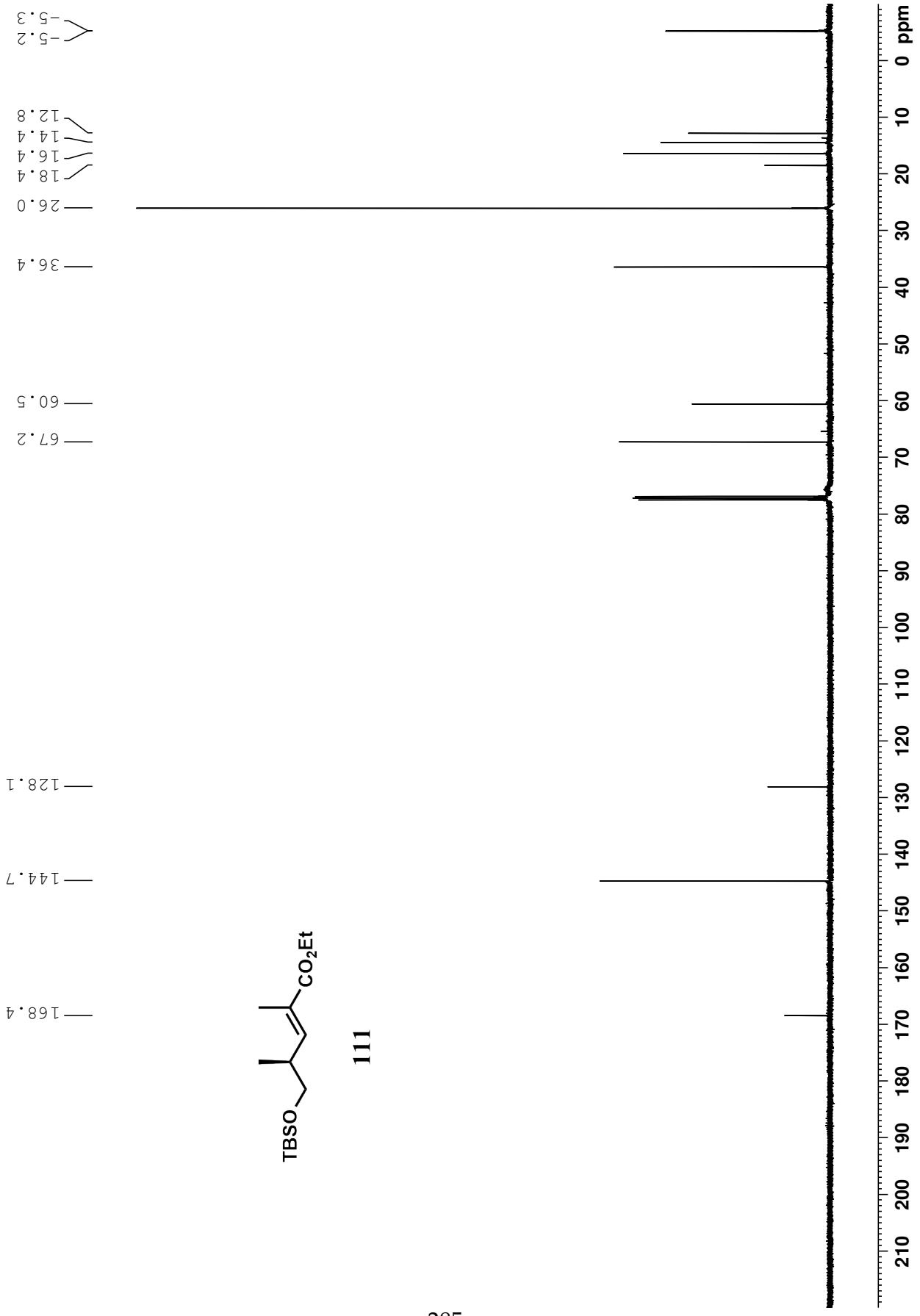
108

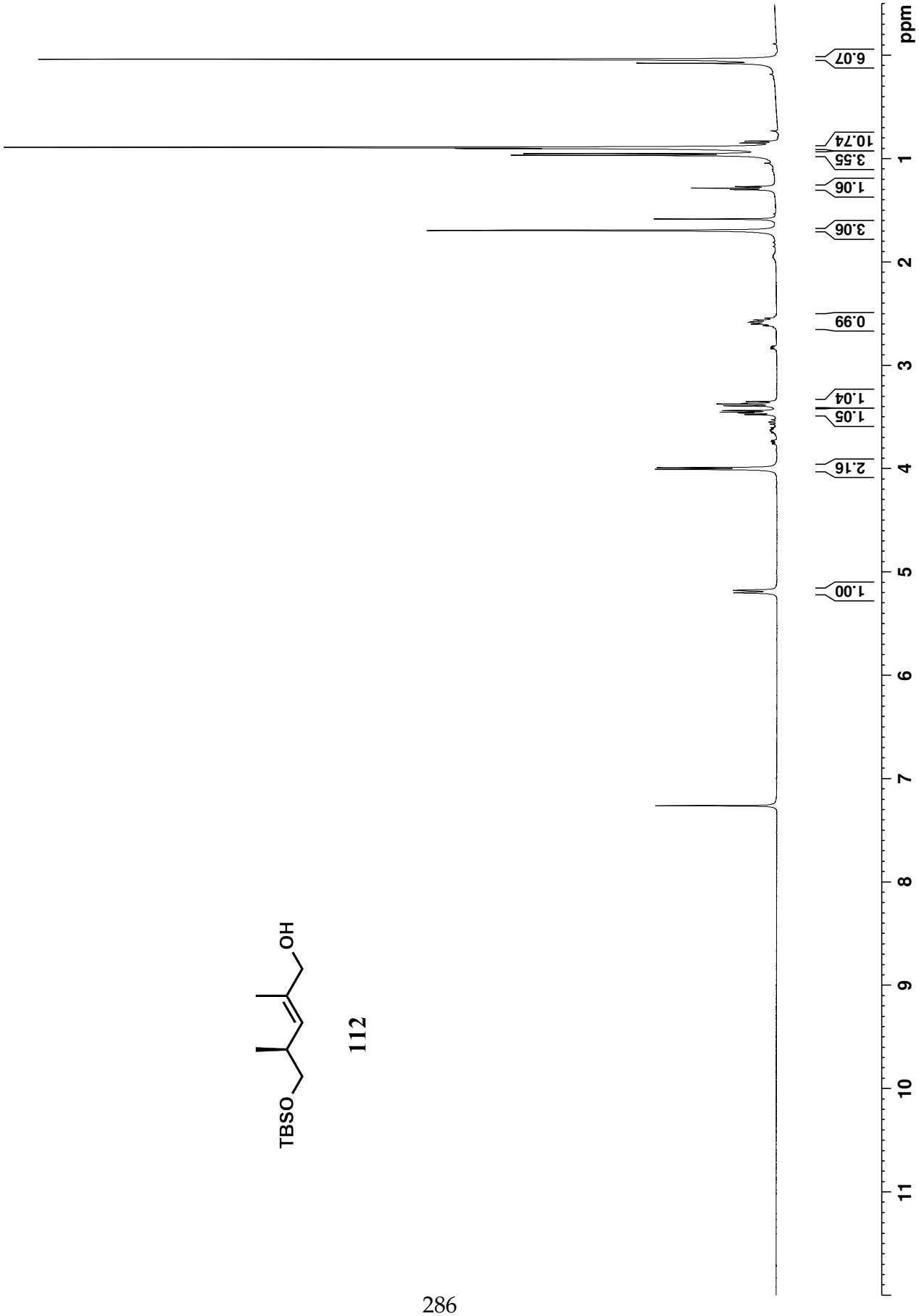


109

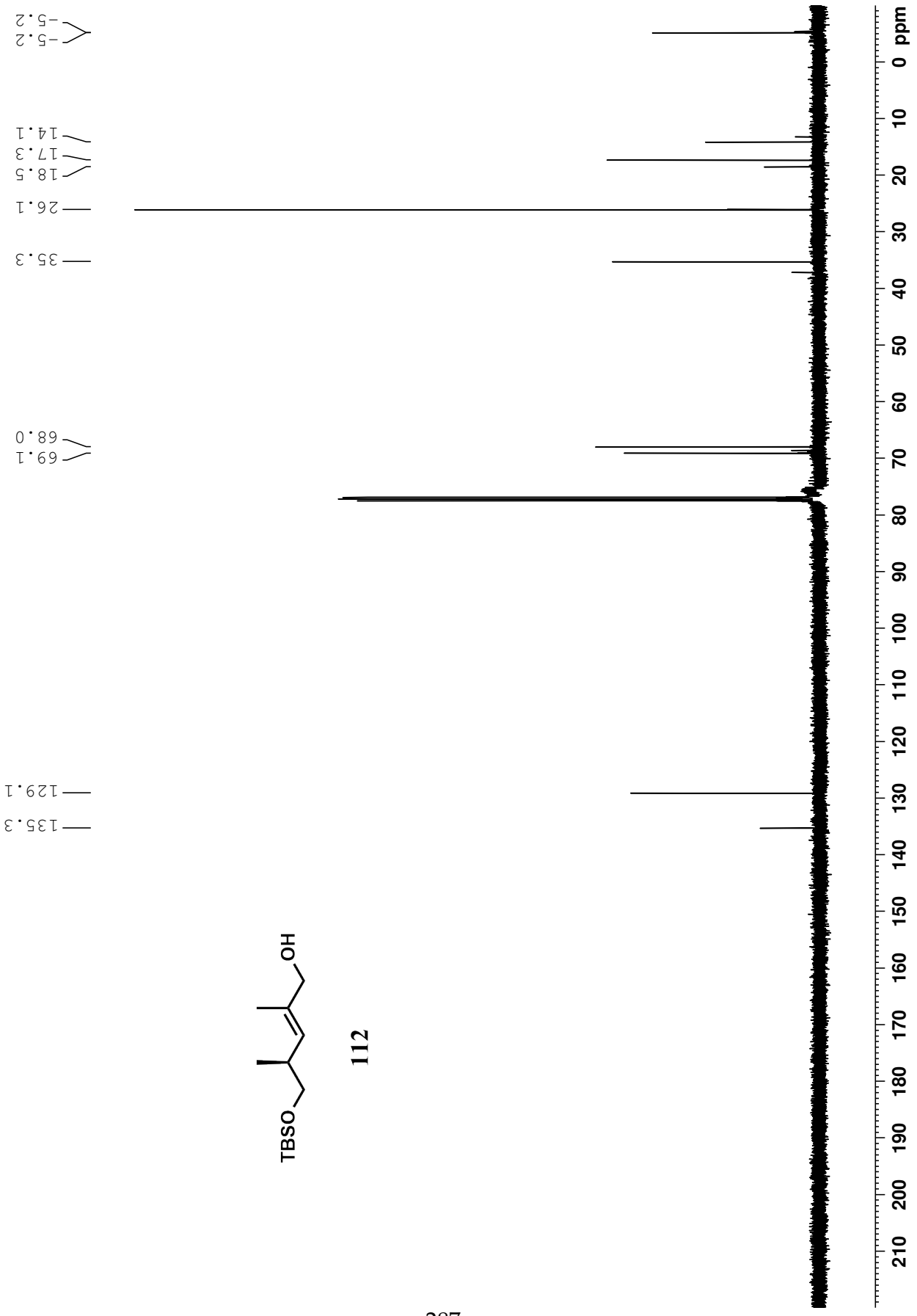

6.22
10.05
3.15
3.32
3.12
1.10
2.09
2.13
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
TBSO
CO2Et

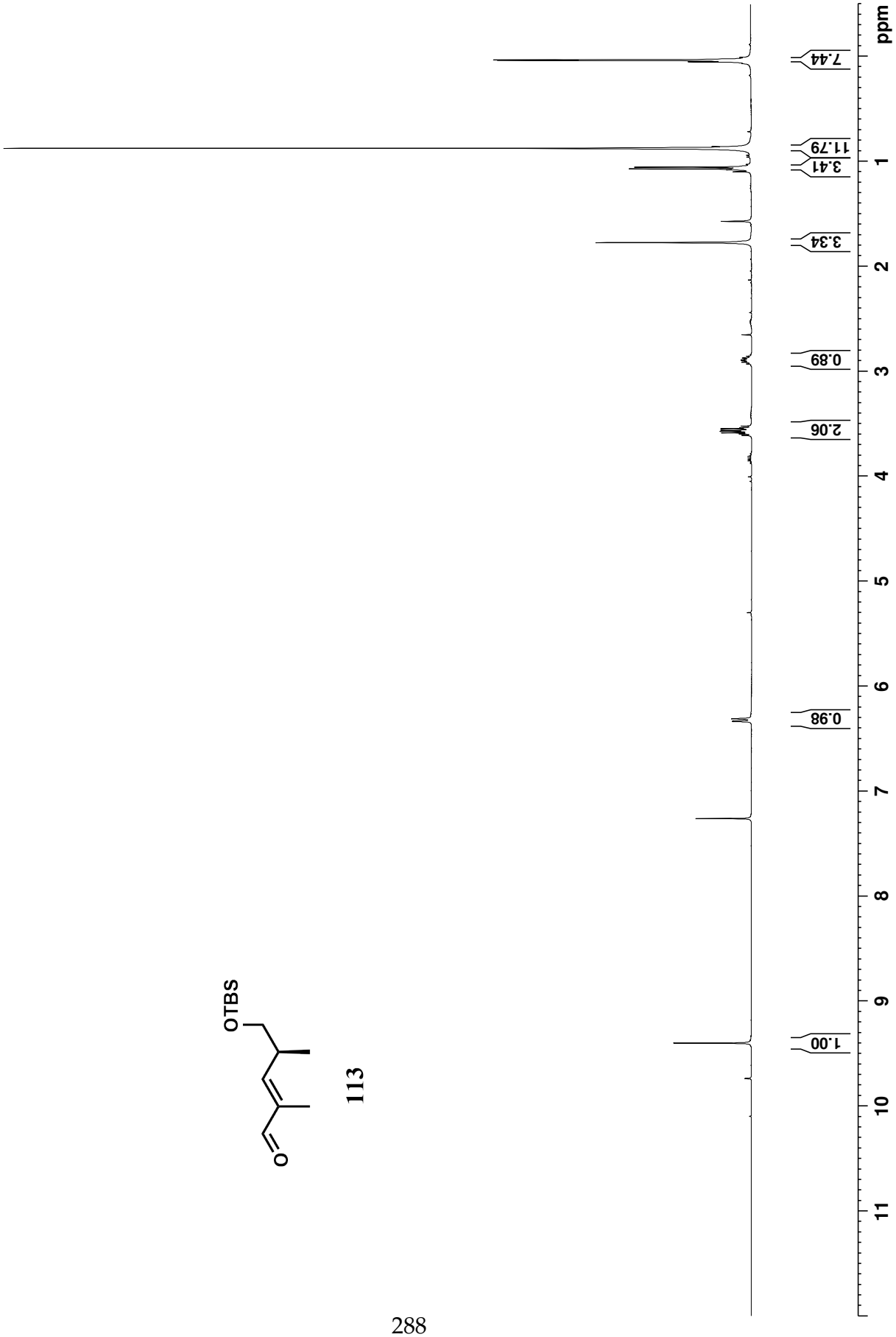
111

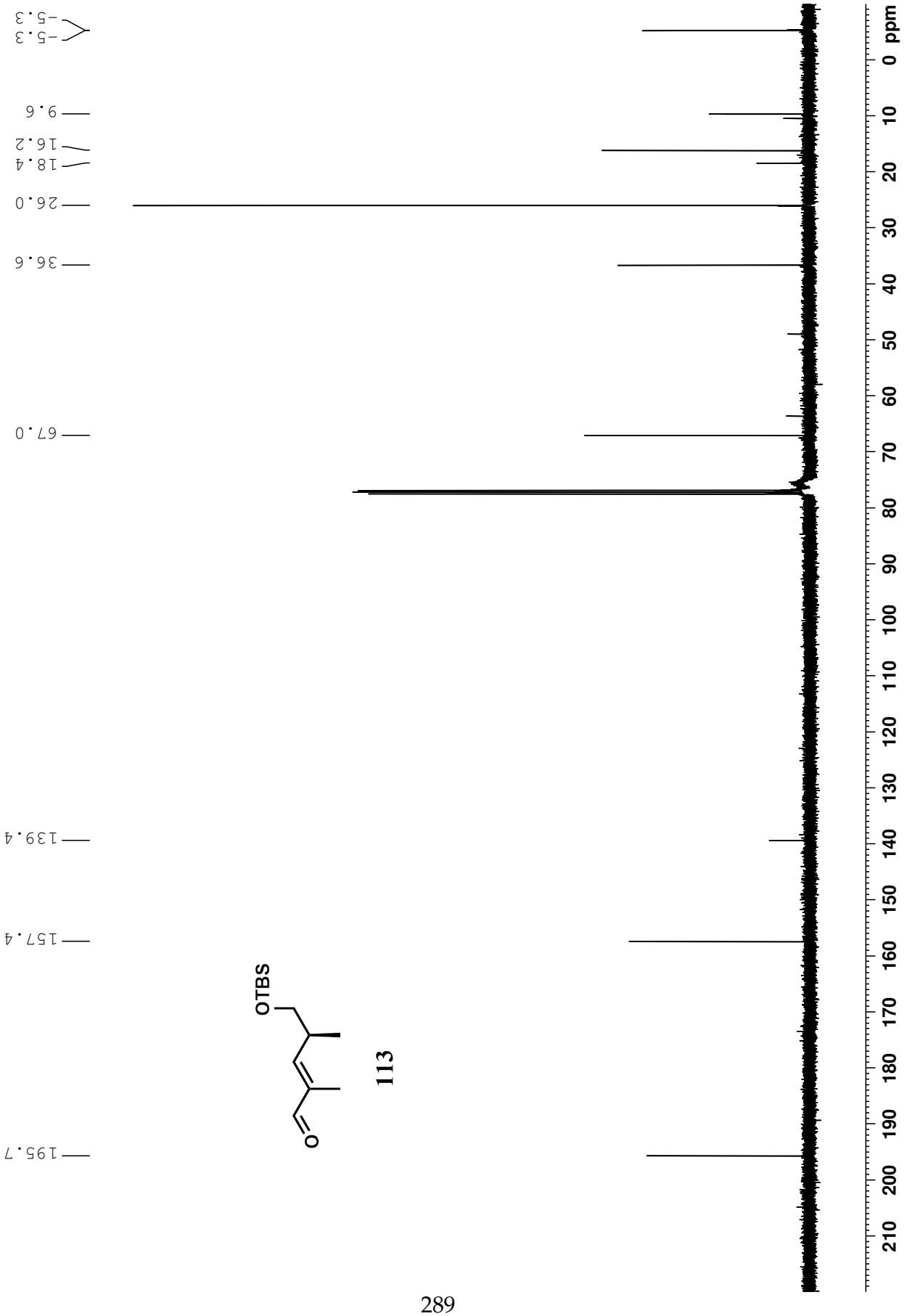

-5.3
-5.2
12.8
14.4
16.4
18.4
26.0
36.4
60.5
67.2
128.1
144.7
168.4
TBSO
CO2Et
111
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

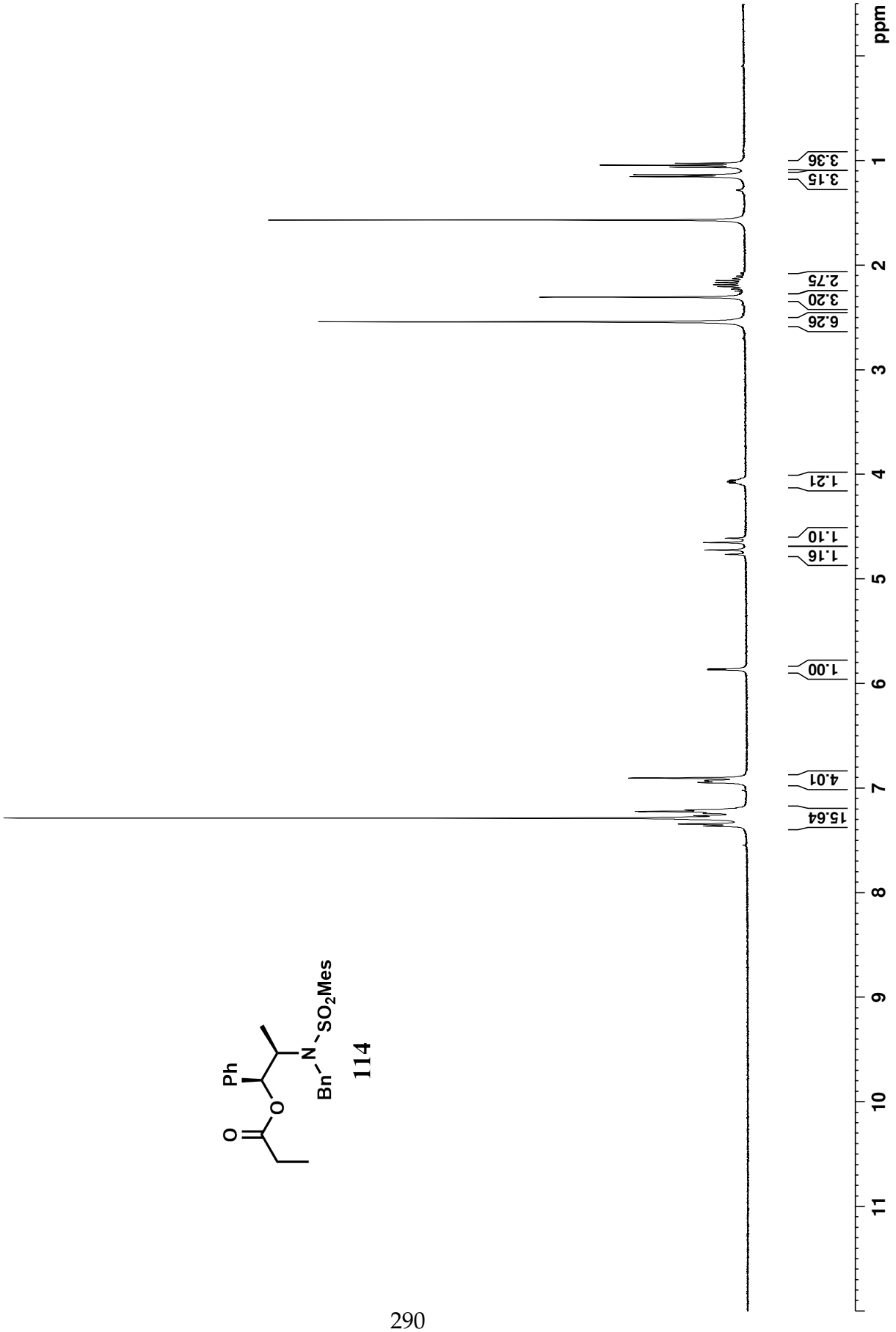

6.07
10.74
3.55
1.06
3.06
0.99
1.04
1.05
2.16
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
OH
TBSO

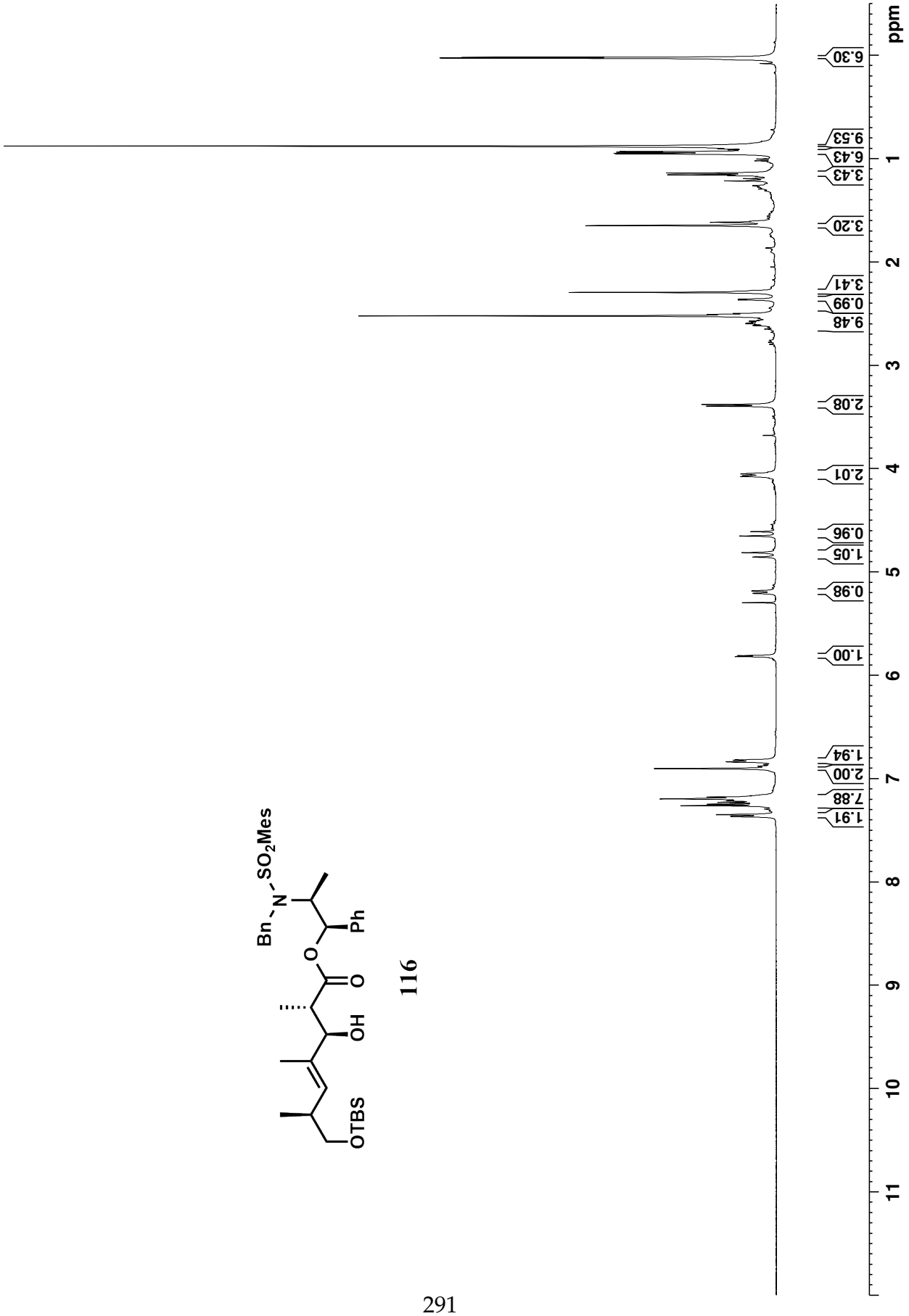
112

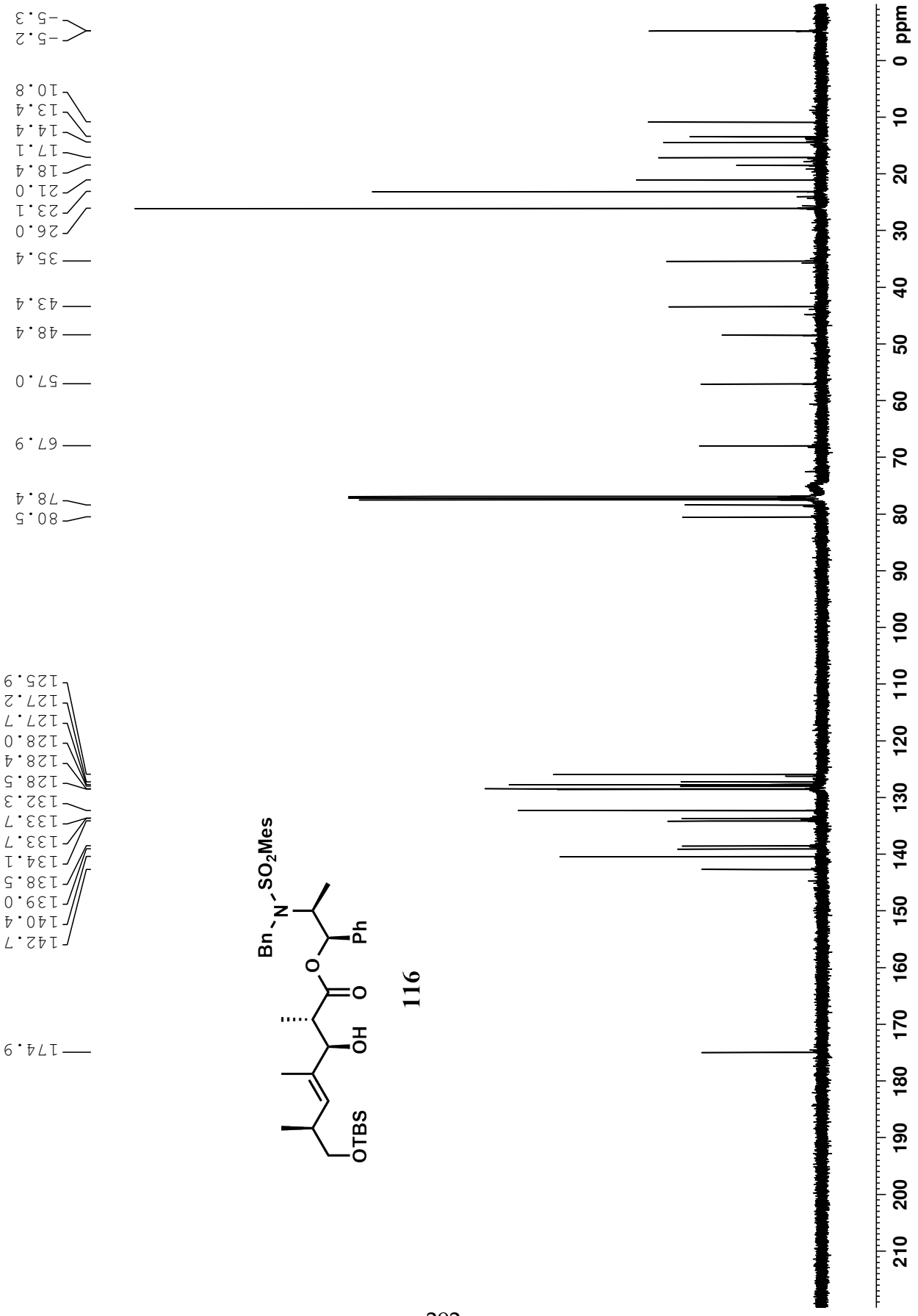

-5.2
-5.2
14.1
17.3
18.5
26.1
35.3
68.0
69.1
129.1
135.3
TBSO
OH
112
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

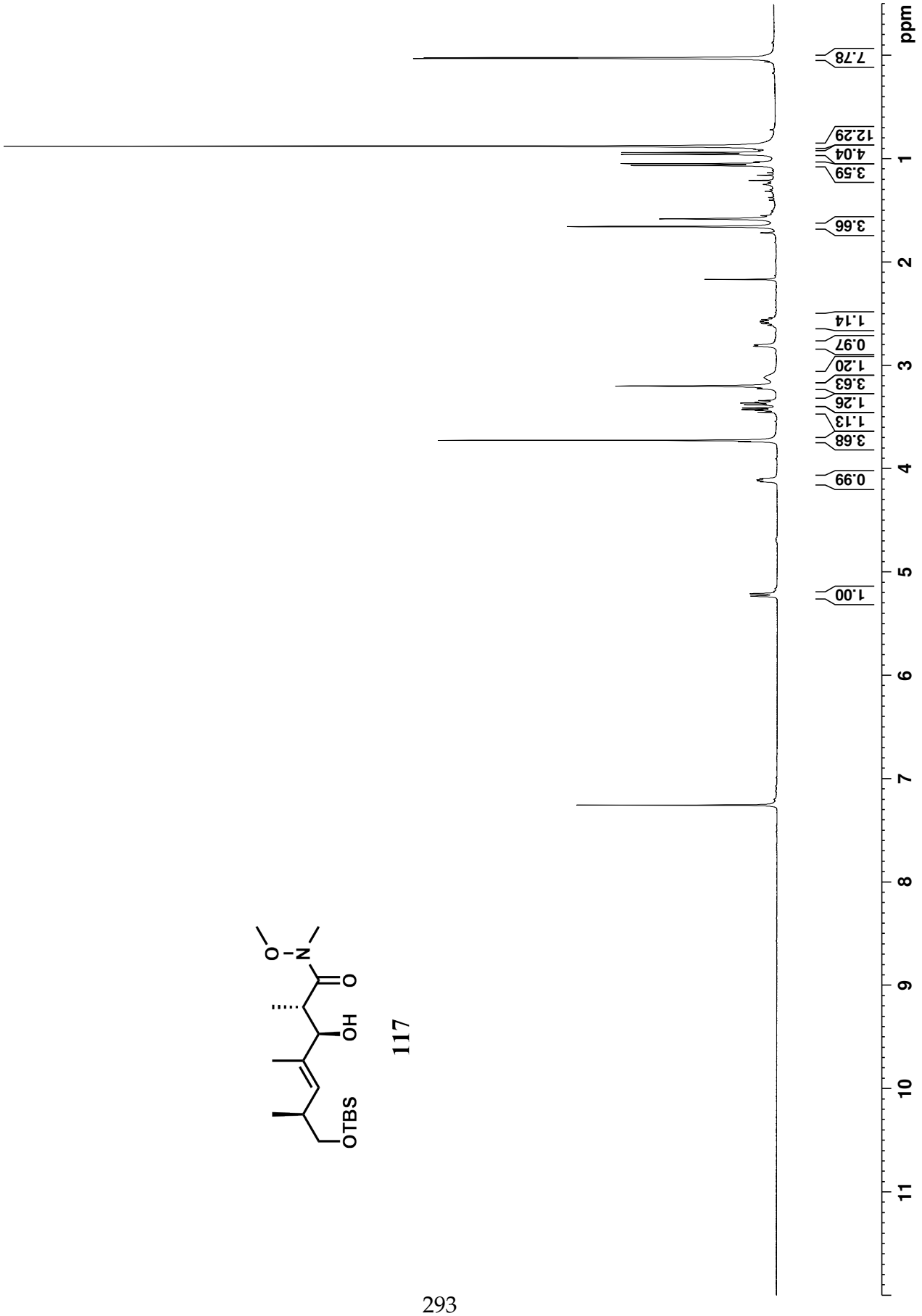

OTBS
O
113
7.44
11.79
3.41
3.34
0.89
2.06
0.98
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11


-5.3
-5.3
9.6
16.2
18.4
26.0
36.6
67.0
139.4
157.4
195.7
OTBS
O
113
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

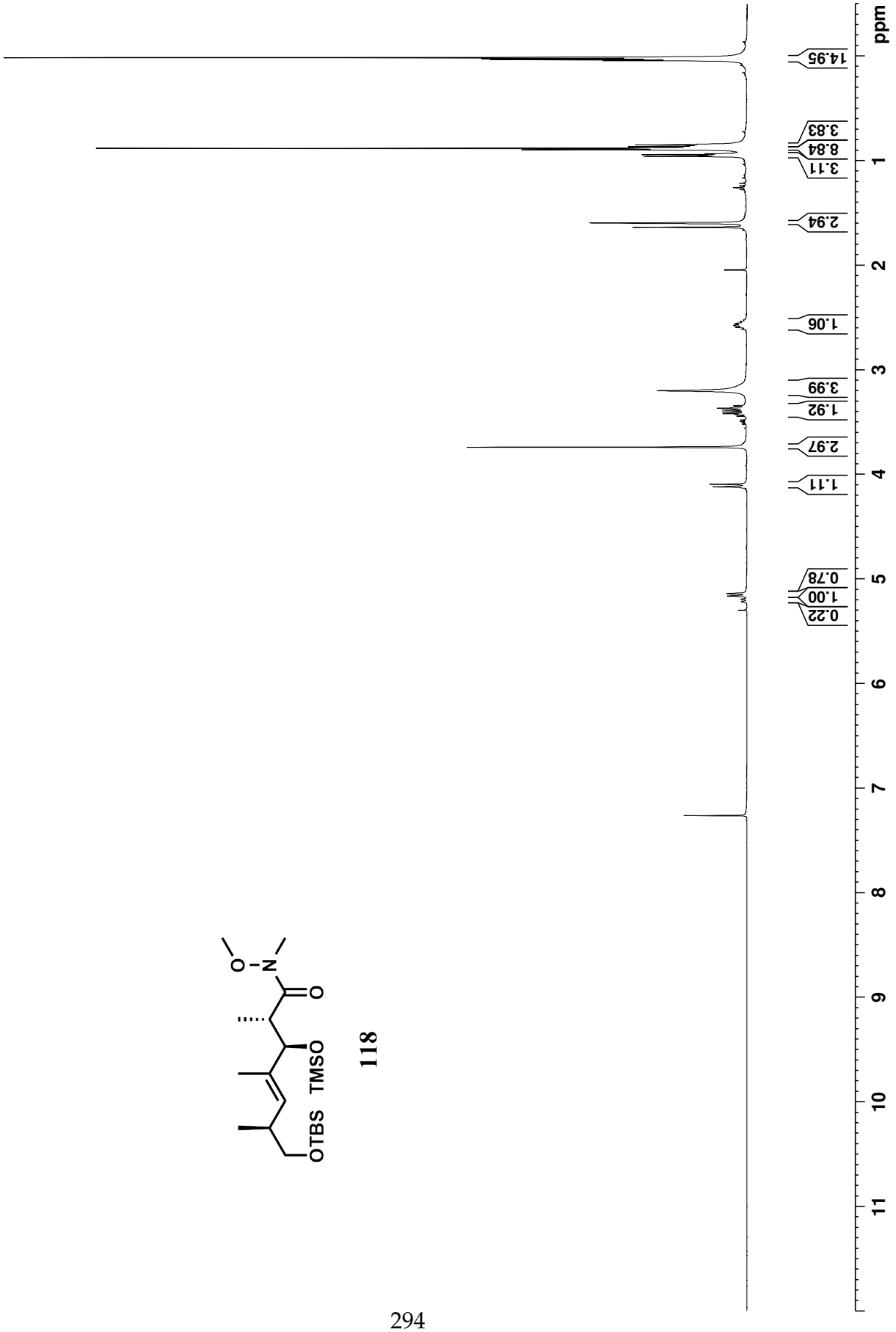

ppm
1
2
3
4
5
6
7
8
9
10
11
3.36
3.15
2.75
3.20
6.26
1.21
1.10
1.16
1.00
4.01
15.64
Ph
O
O
N
Bn
SO2Mes
114


Bn
N
SO2Mes
O
O
Ph
OH
OTBS
116
6.30
9.53
6.43
3.43
3.20
3.41
0.99
9.48
2.08
2.01
0.96
1.05
0.98
1.00
1.94
2.00
7.88
1.91
ppm
1
2
3
4
5
6
7
8
9
10
11

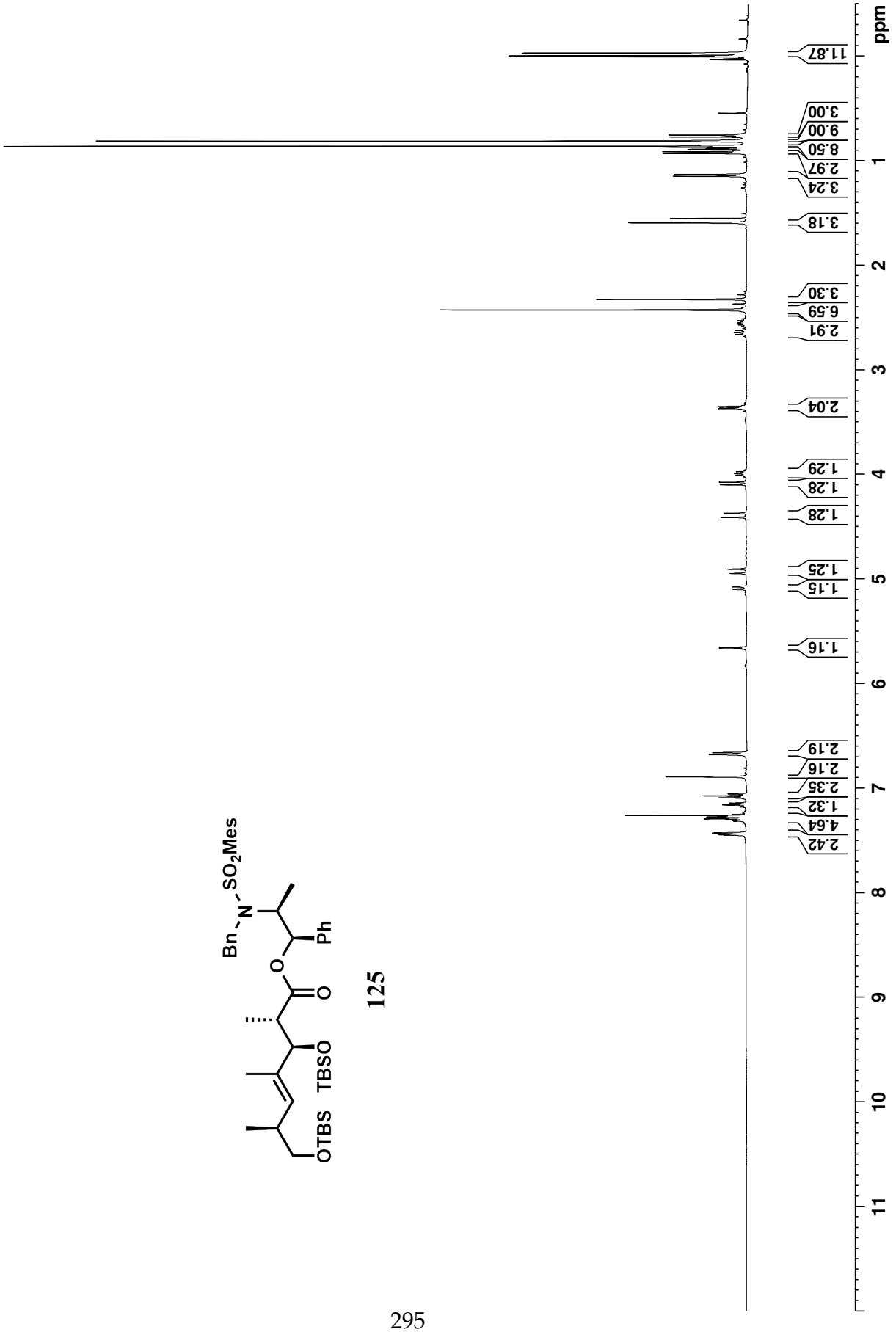

-5.3
-5.2
10.8
13.4
14.4
17.1
18.4
21.0
23.1
26.0
35.4
43.4
48.4
57.0
67.9
78.4
80.5
125.9
127.2
127.7
128.0
128.4
128.5
132.3
133.7
133.7
134.1
138.5
139.0
140.4
142.7
174.9
Bn
N
SO2Mes
Ph
O
O
OH
OTBS
116
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


7.78
12.29
4.04
3.59
3.66
1.14
0.97
1.20
3.63
1.26
1.13
3.68
0.99
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
O
N
O
O
OH
OTBS

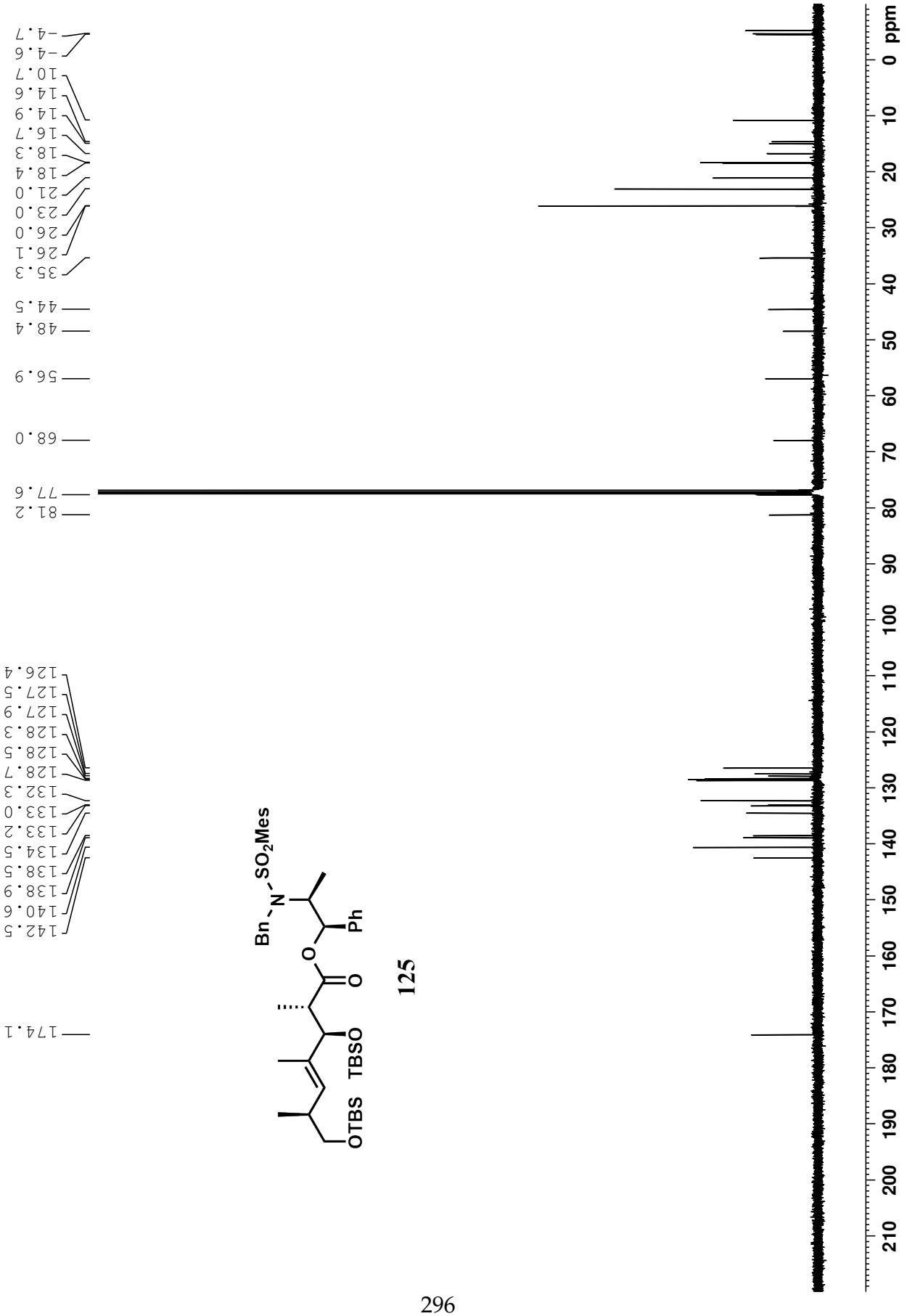
117

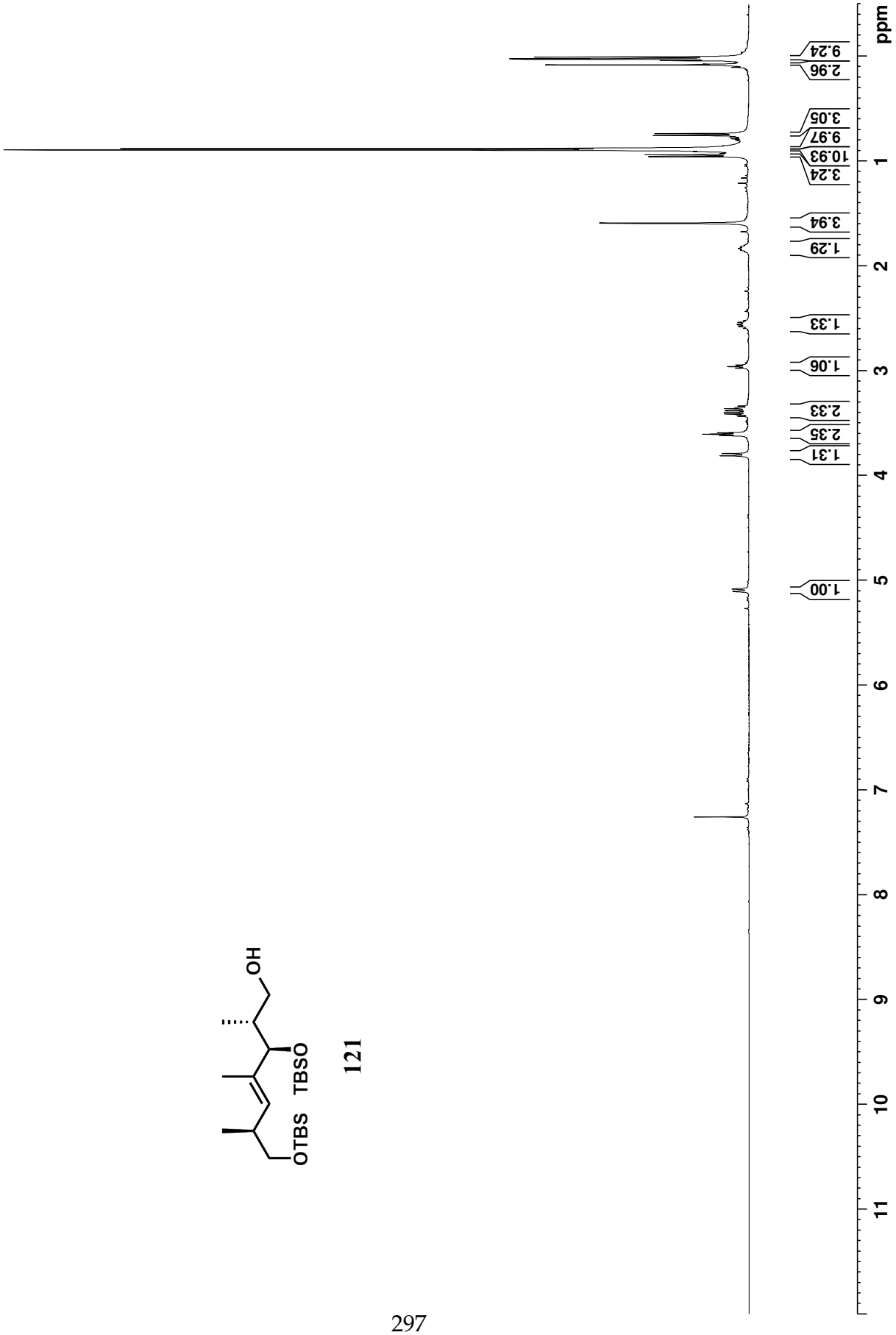

14.95
3.83
8.84
3.11
2.94
1.06
3.99
1.92
2.97
1.11
0.78
1.00
0.22
ppm
1
2
3
4
5
6
7
8
9
10
11
O
N
O
O
TMSO
OTBS

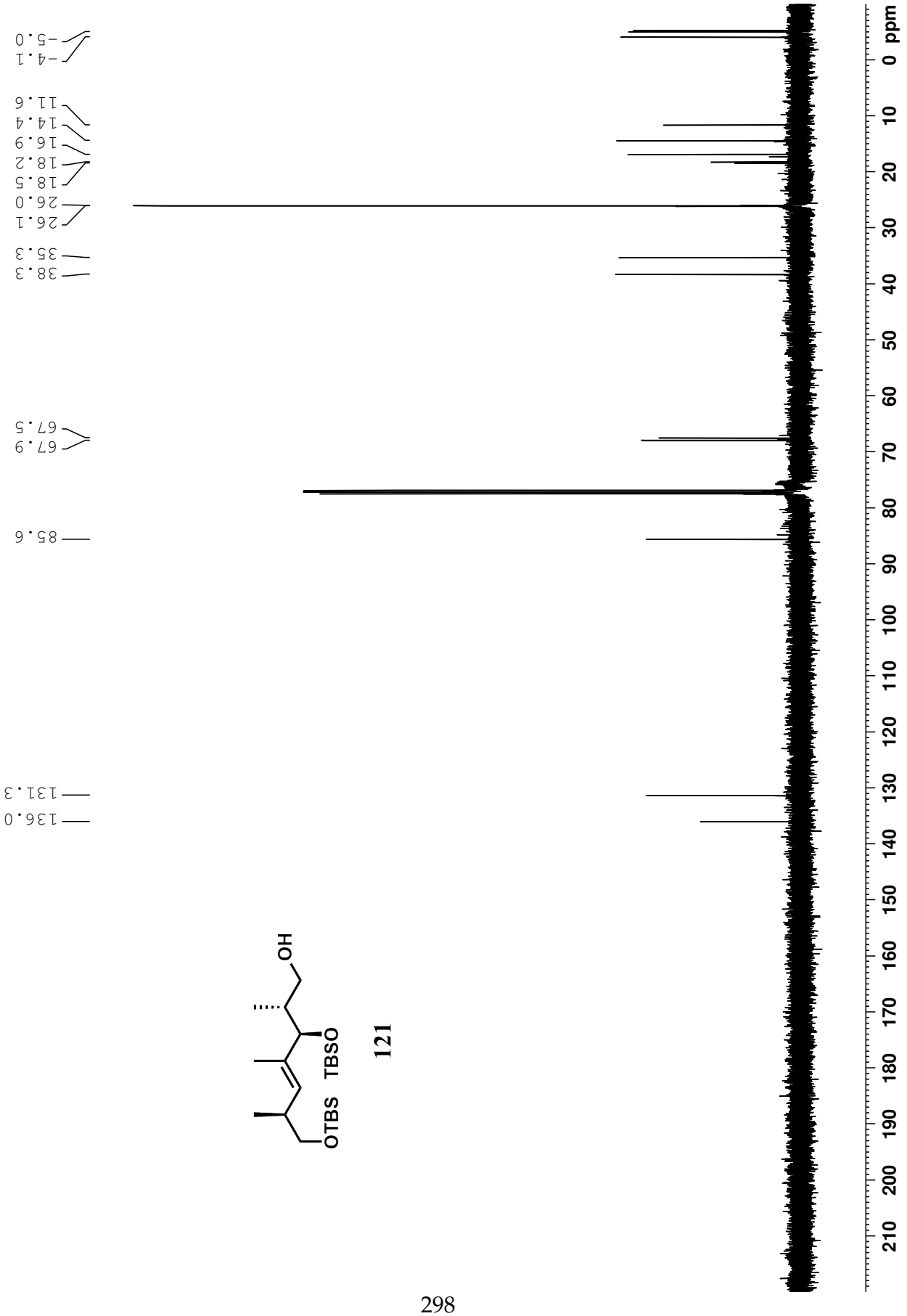
118


11.87
3.00
9.00
8.50
2.97
3.24
3.18
3.30
6.59
2.91
2.04
1.29
1.28
1.28
1.25
1.15
1.16
2.19
2.16
2.35
1.32
4.64
2.42
ppm
1
2
3
4
5
6
7
8
9
10
11
Bn
N
SO2Mes
Ph
O
O
TBSO
OTBS

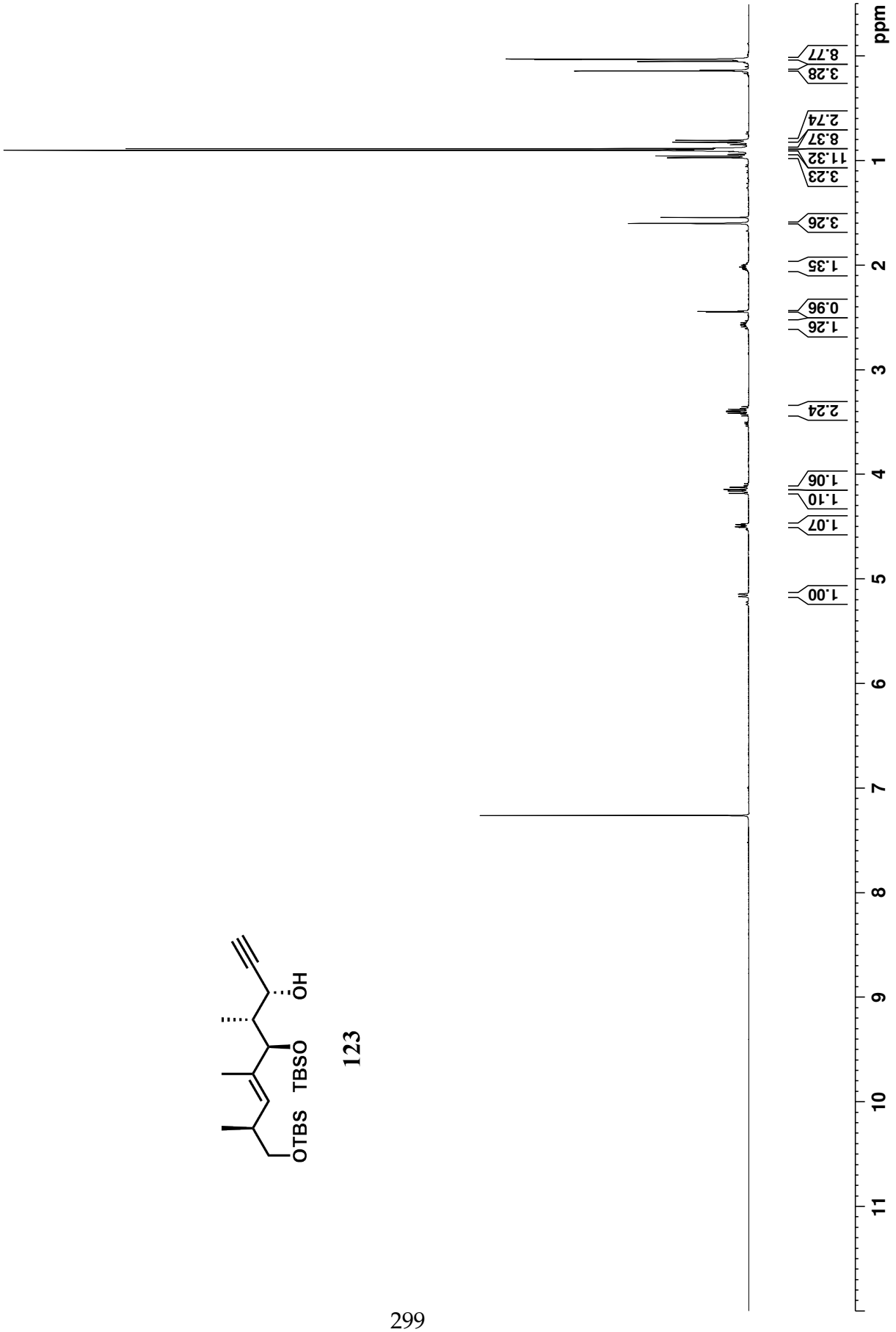
125


-4.7
-4.6
10.7
14.6
14.9
16.7
18.3
18.4
21.0
23.0
26.0
26.1
35.3
44.5
48.4
56.9
68.0
77.6
81.2
126.4
127.5
127.9
128.3
128.5
128.7
132.3
133.0
133.2
134.5
138.5
138.9
140.6
142.5
174.1
Bn
N
SO2Mes
O
O
Ph
TBSO
OTBS
125
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

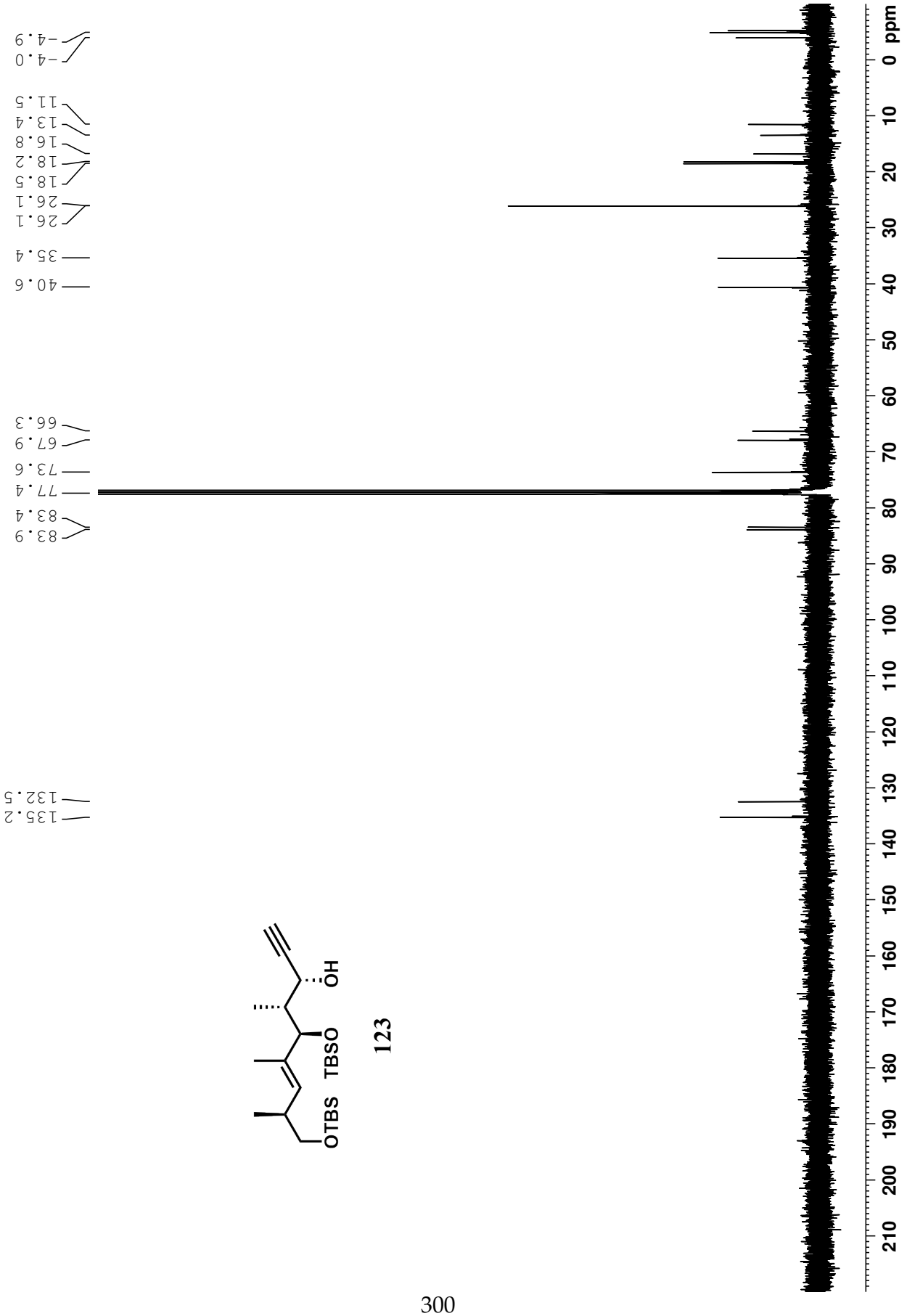

OH
TBSO
OTBS
121
9.24
2.96
3.05
9.97
10.93
3.24
3.94
1.29
1.33
1.06
2.33
2.35
1.31
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11

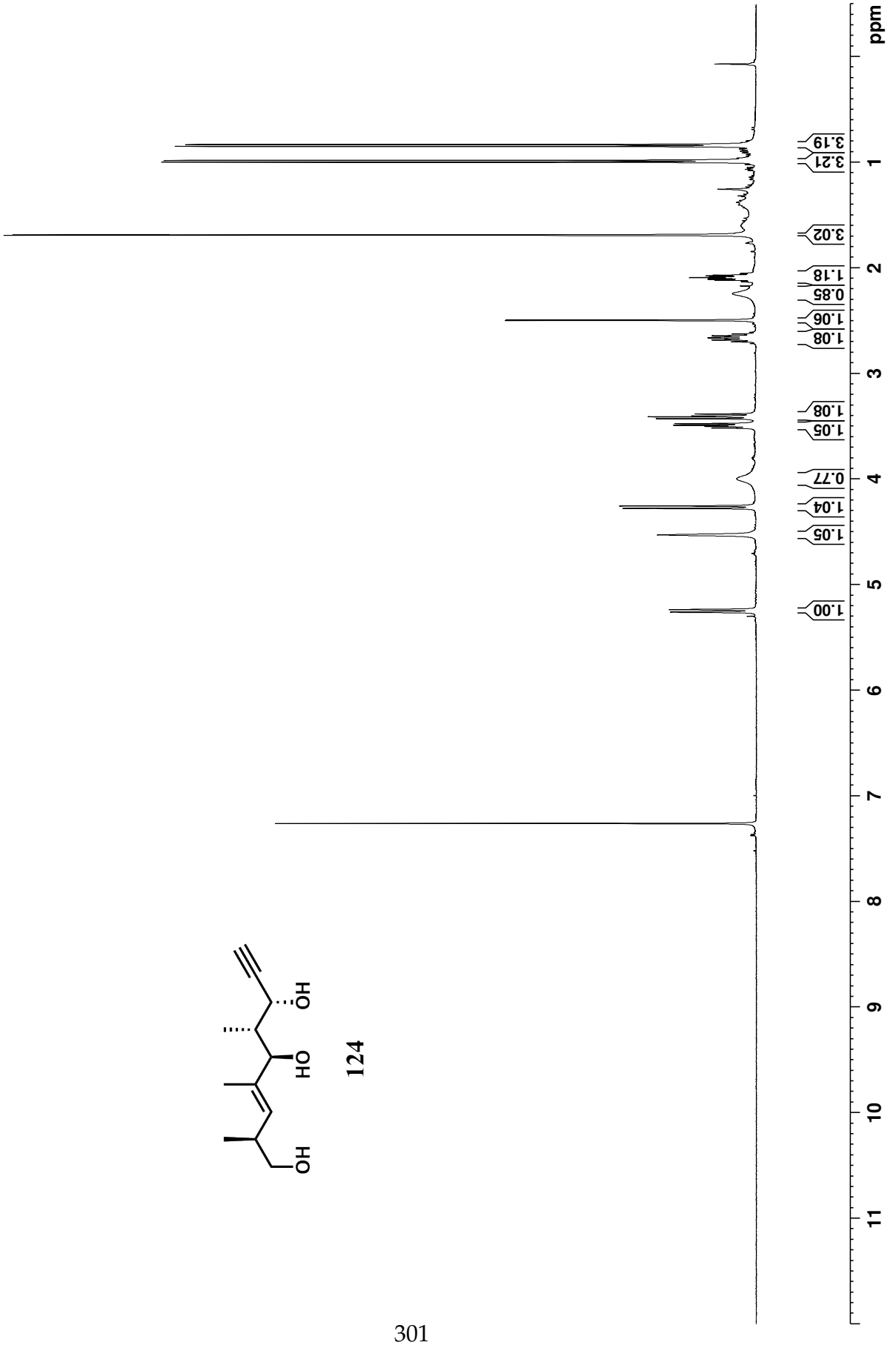

-5.0
-4.1
11.6
14.4
16.9
18.2
18.5
26.0
26.1
35.3
38.3
67.5
67.9
85.6
131.3
136.0
OH
TBSO
OTBS
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

121

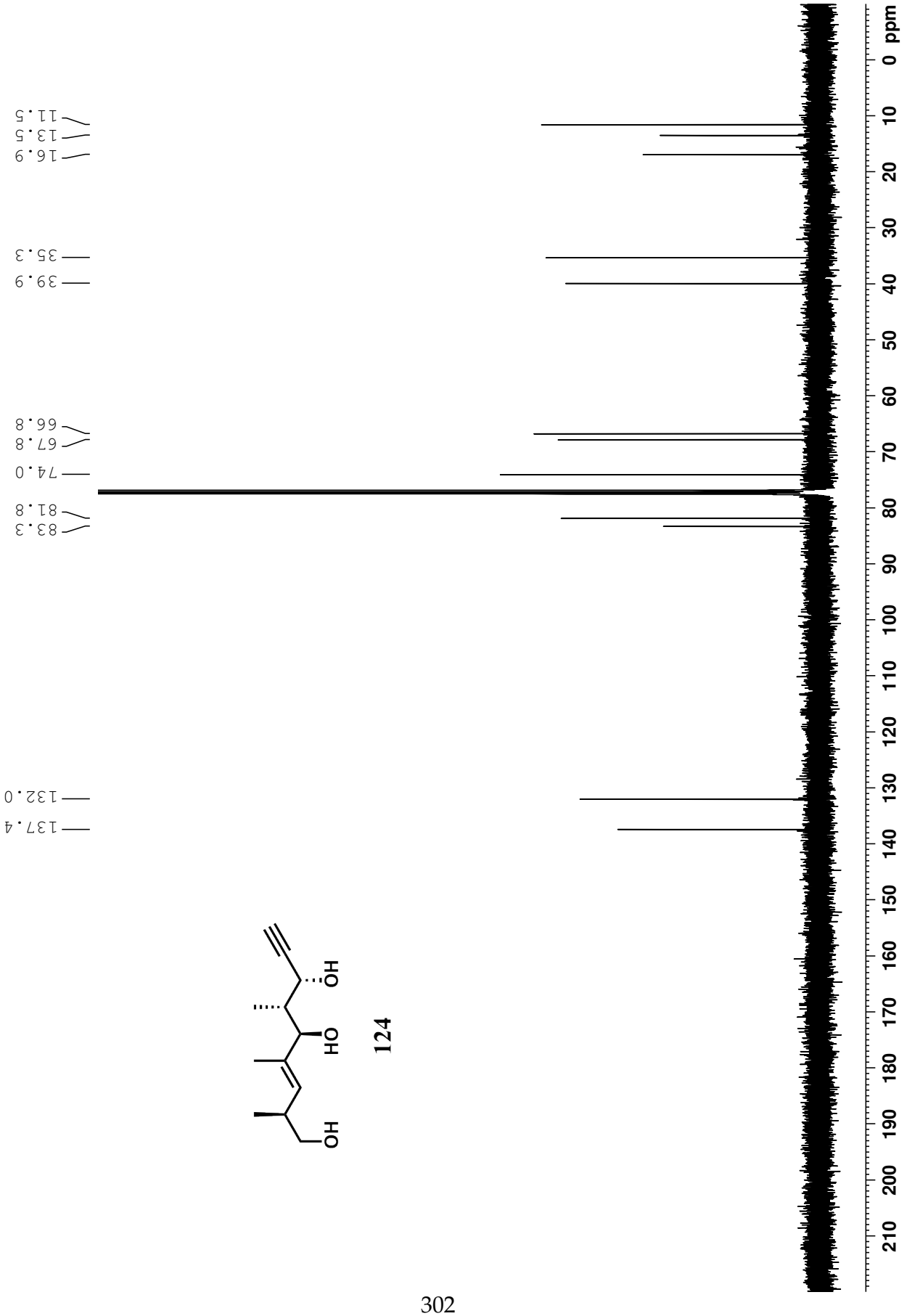

8.77
3.28
2.74
8.37
11.32
3.23
3.26
1.35
0.96
1.26
2.24
1.06
1.10
1.07
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
TBSO
OH

123

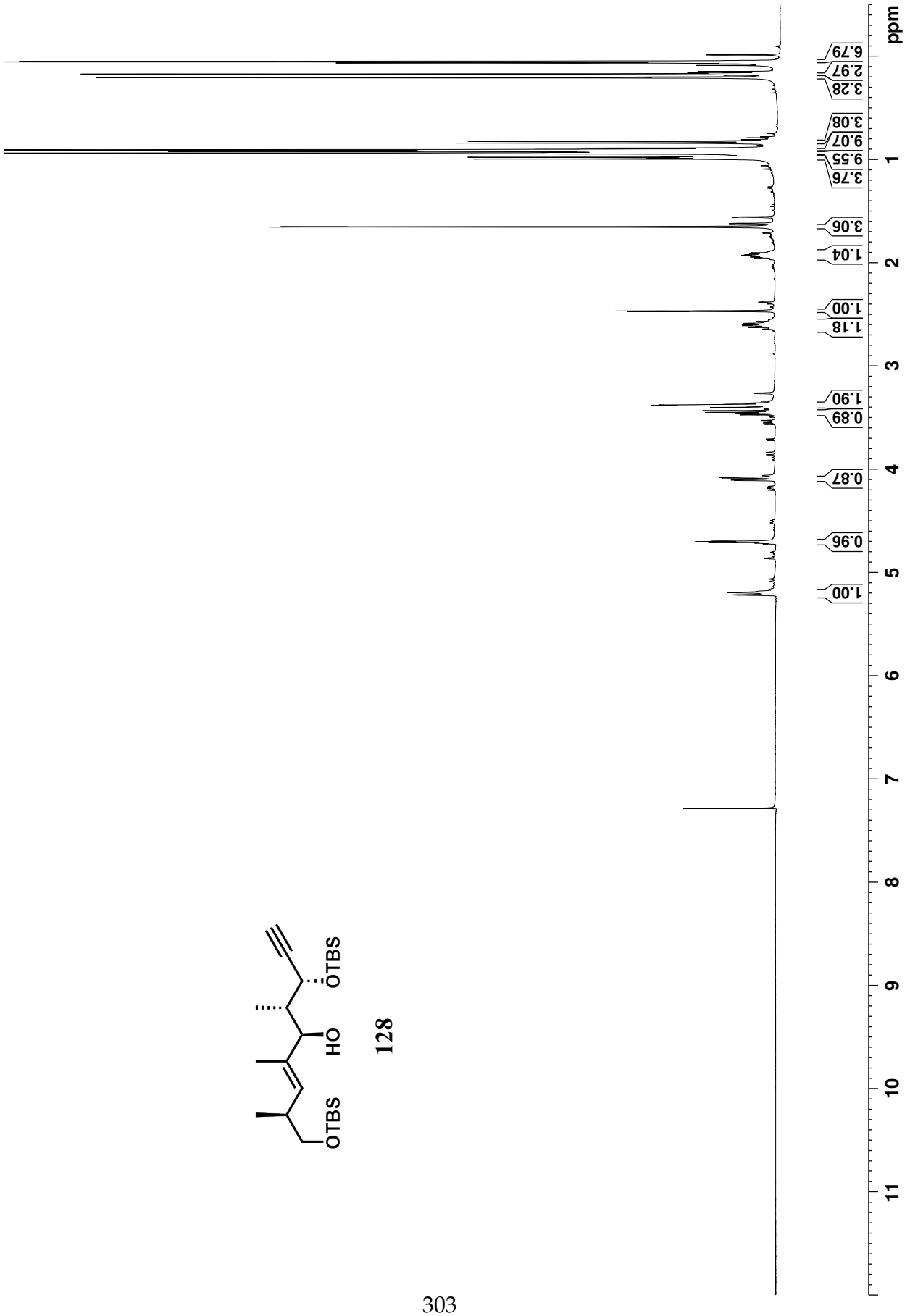

-4.9
-4.0
11.5
13.4
16.8
18.2
18.5
26.1
26.1
35.4
40.6
66.3
67.9
73.6
77.4
83.4
83.9
132.5
135.2
OTBS
TBSO
OH
123
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

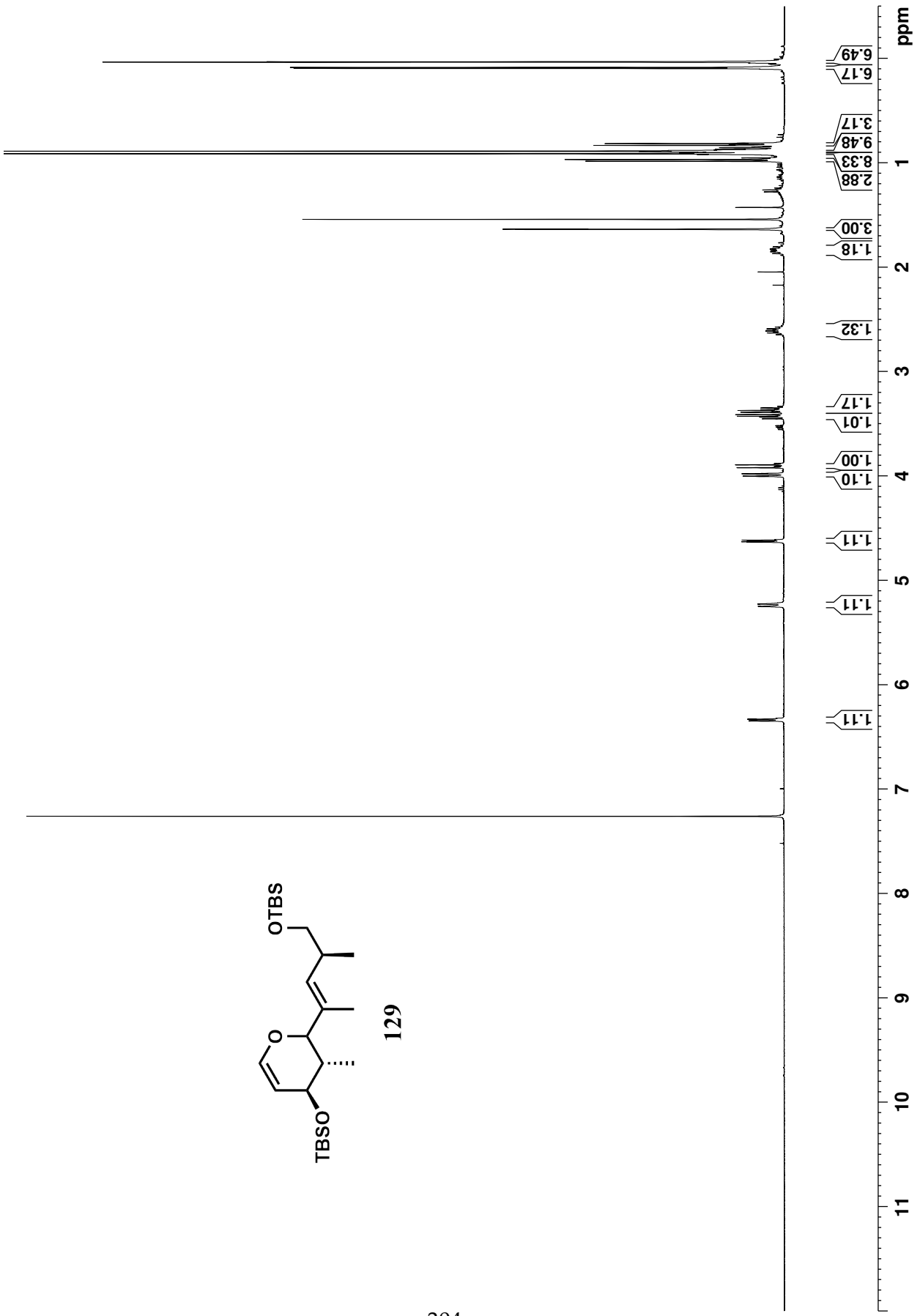

ppm
1
2
3
4
5
6
7
8
9
10
11
3.19
3.21
3.02
1.18
0.85
1.06
1.08
1.08
1.05
0.77
1.04
1.05
1.00
HO
OH
OH

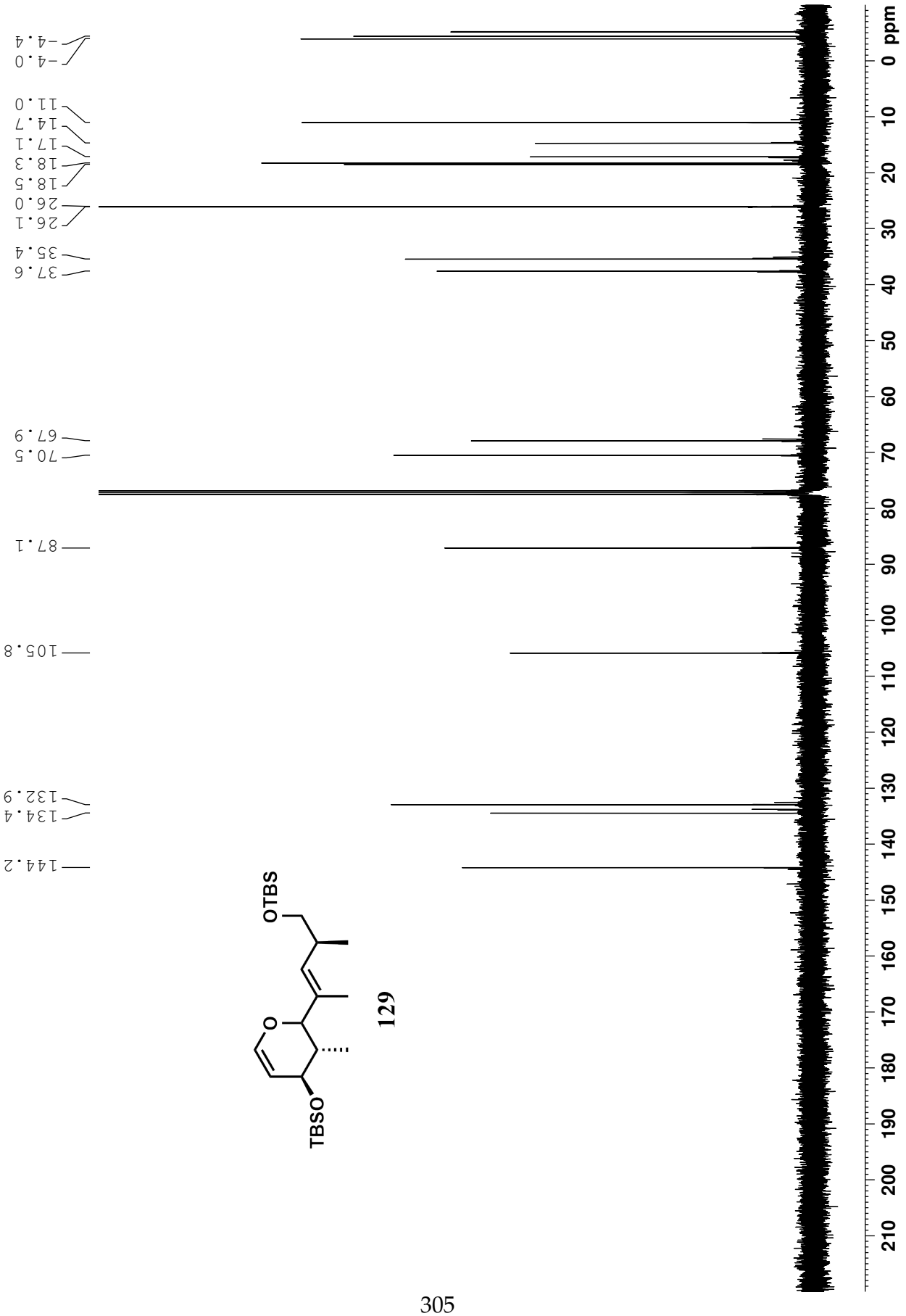
124

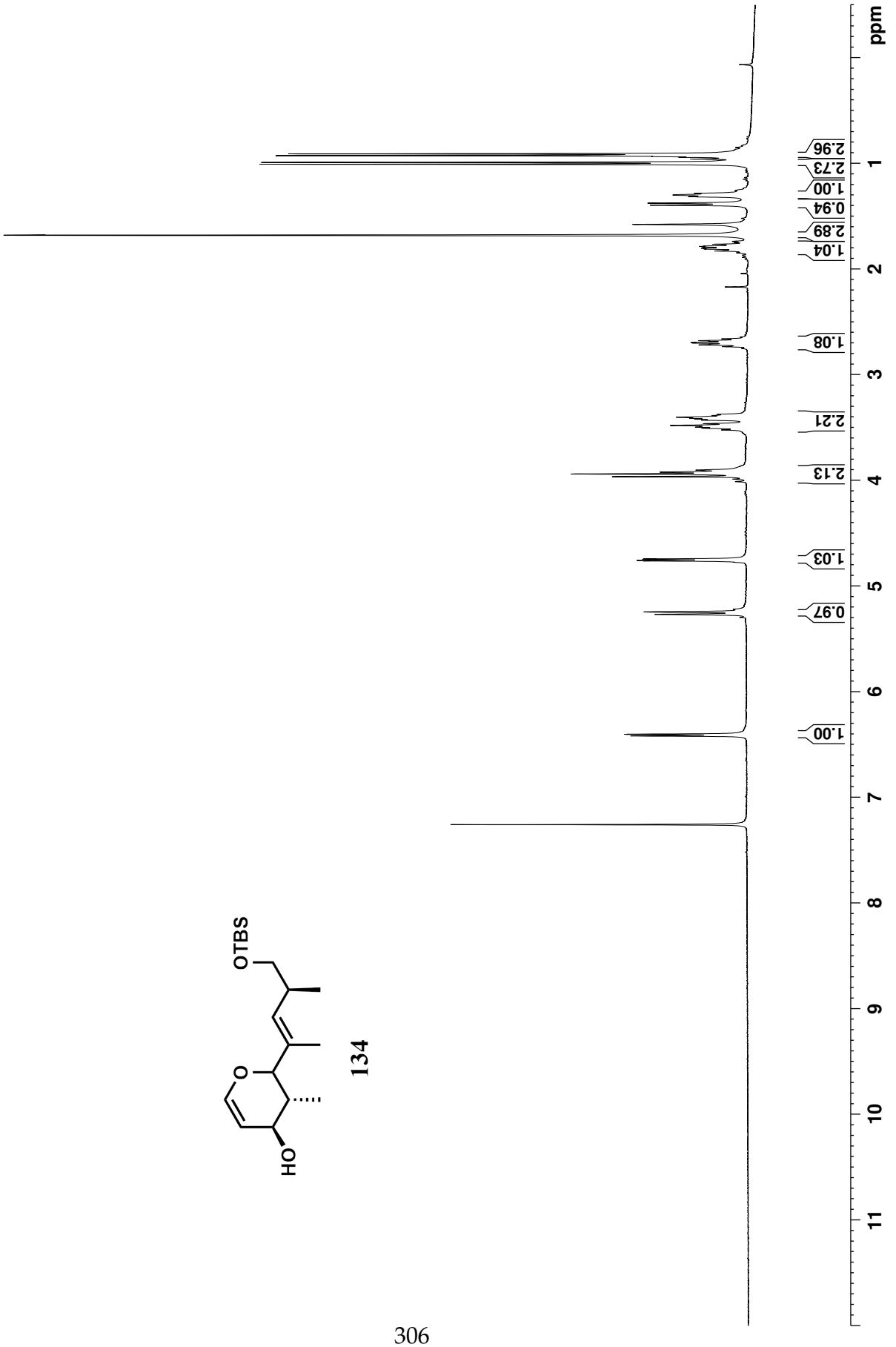

137.4
132.0
83.3
81.8
74.0
67.8
66.8
39.9
35.3
16.9
13.5
11.5
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
HO
OH
OH

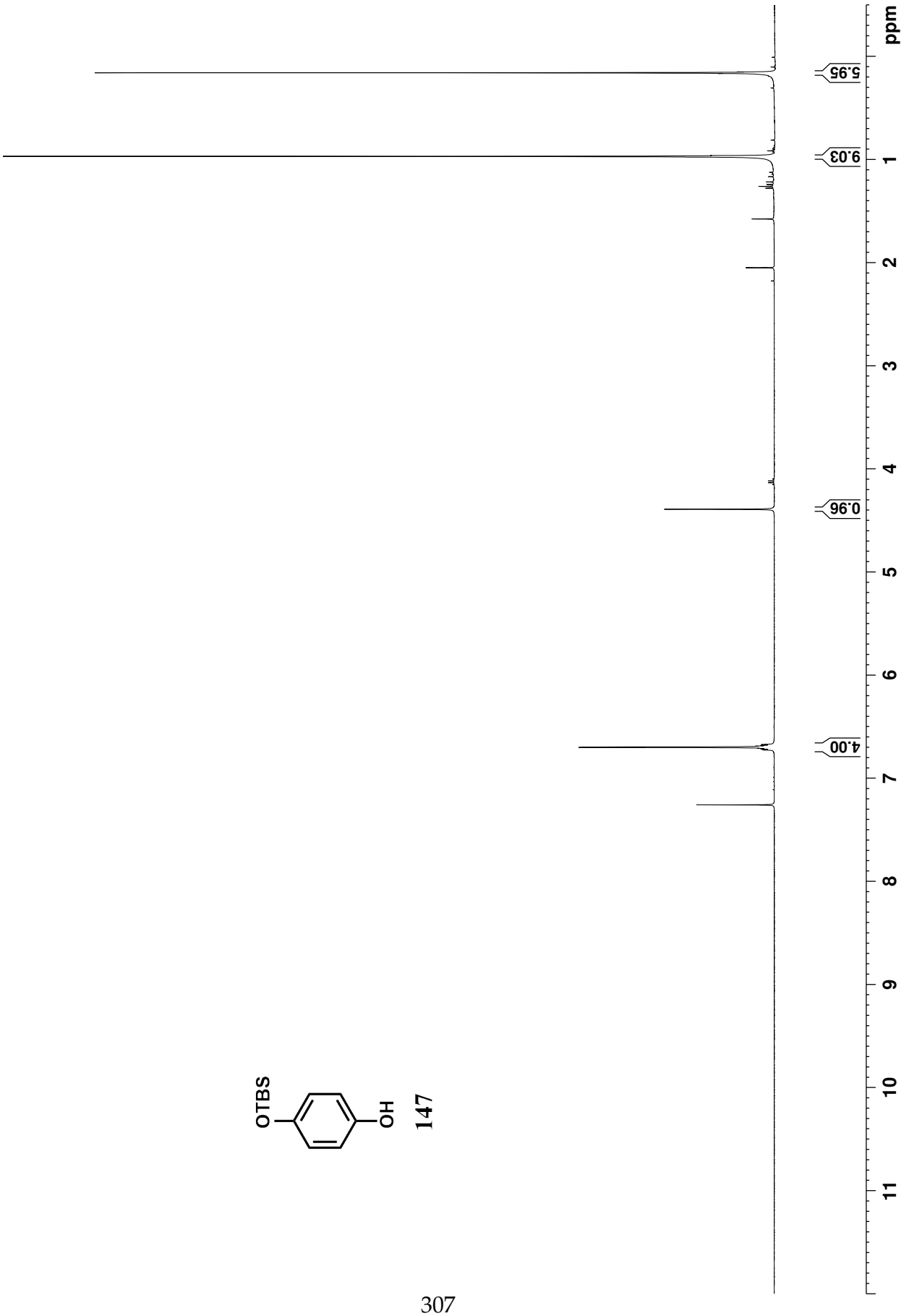
124

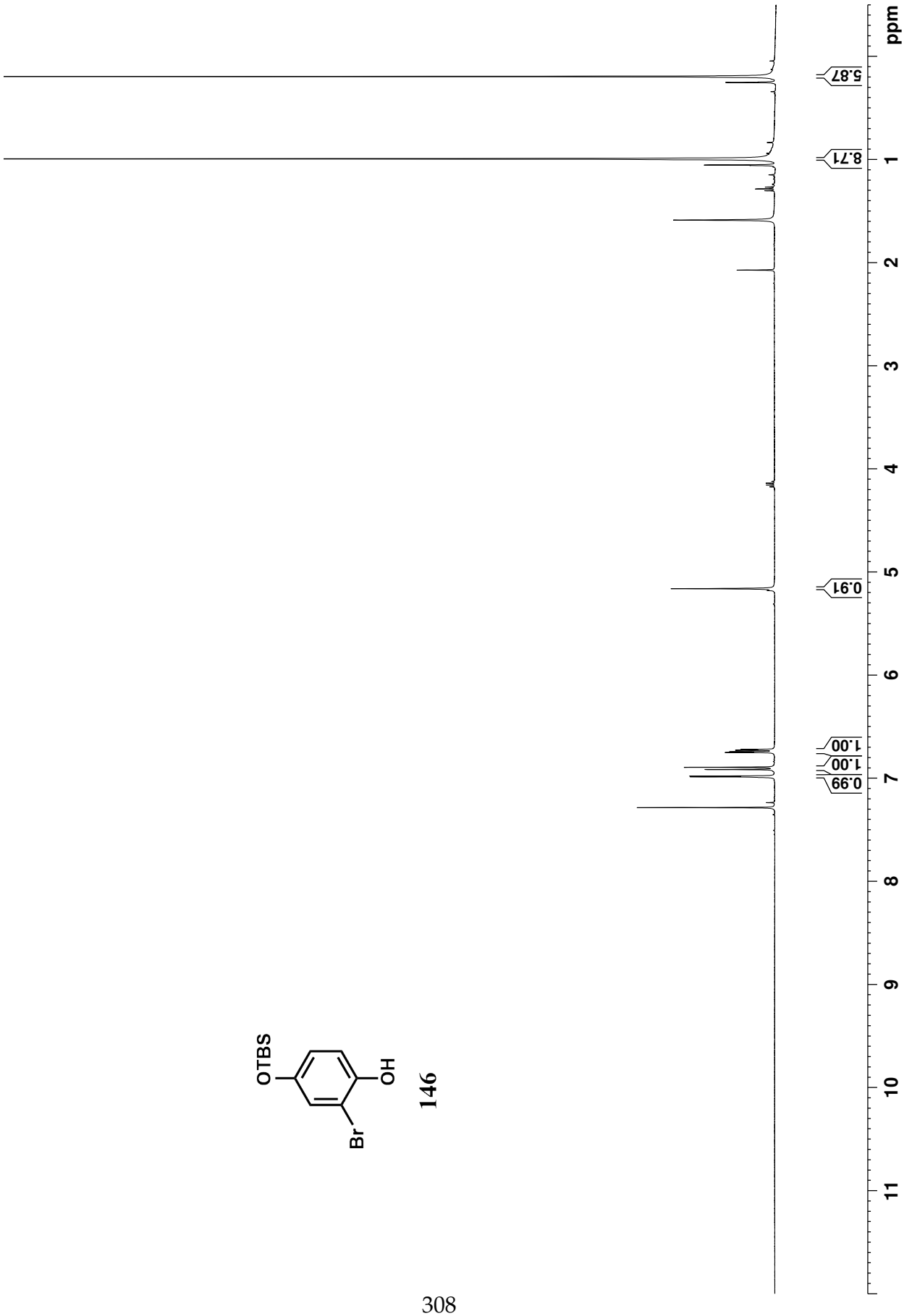

OTBS
HO
OTBS
128
6.79
2.97
3.28
3.08
9.07
9.55
3.76
3.06
1.04
1.00
1.18
1.90
0.89
0.87
0.96
1.00
ppm


OTBS
O
TBSO
129
6.49
6.17
3.17
9.48
8.33
2.88
3.00
1.18
1.32
1.17
1.01
1.00
1.10
1.11
1.11
1.11
ppm
1
2
3
4
5
6
7
8
9
10
11

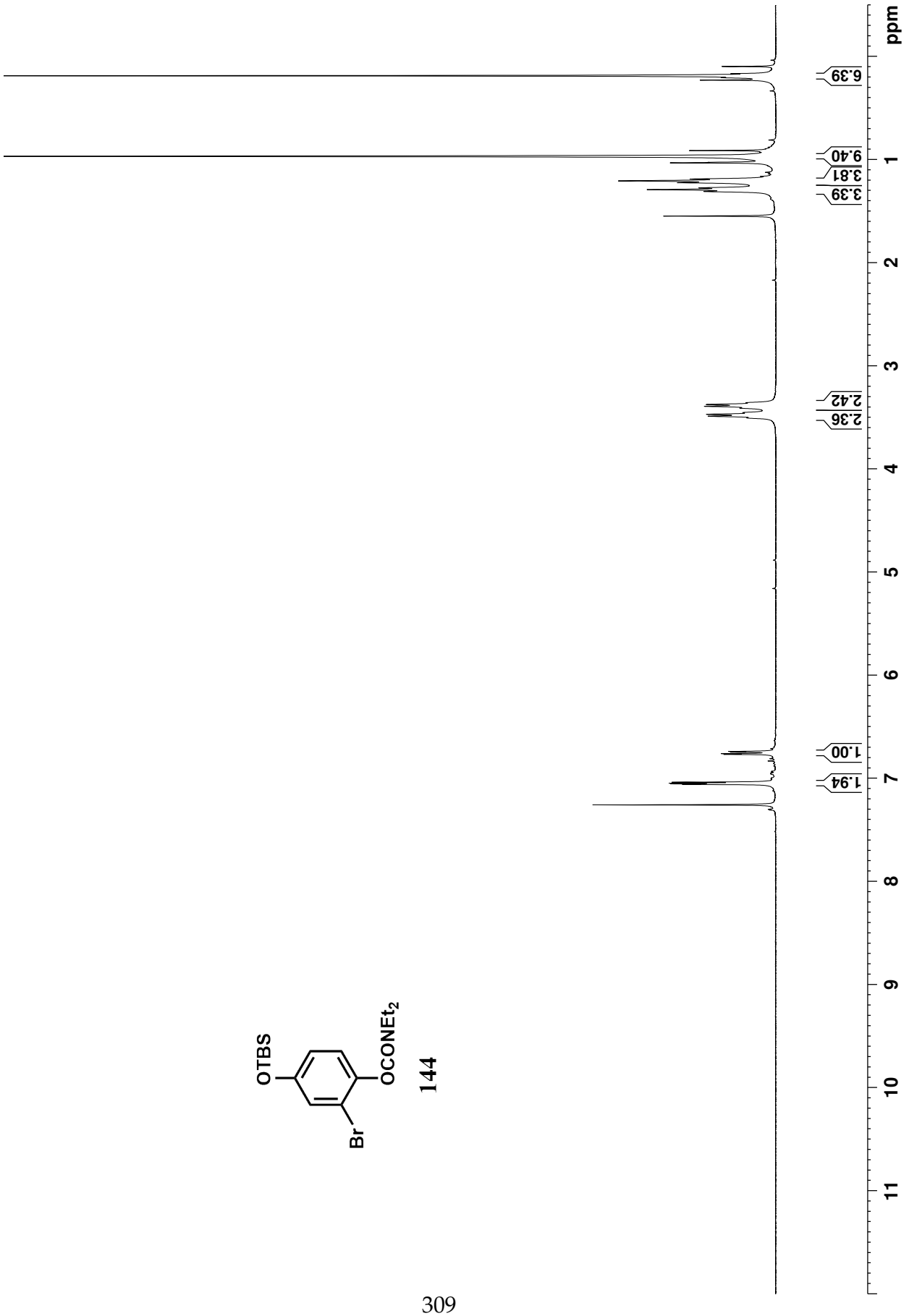

-4.4
-4.0
11.0
14.7
17.1
18.3
18.5
26.0
26.1
35.4
37.6
67.9
70.5
87.1
105.8
132.9
134.4
144.2
OTBS
TBSO
O
129
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

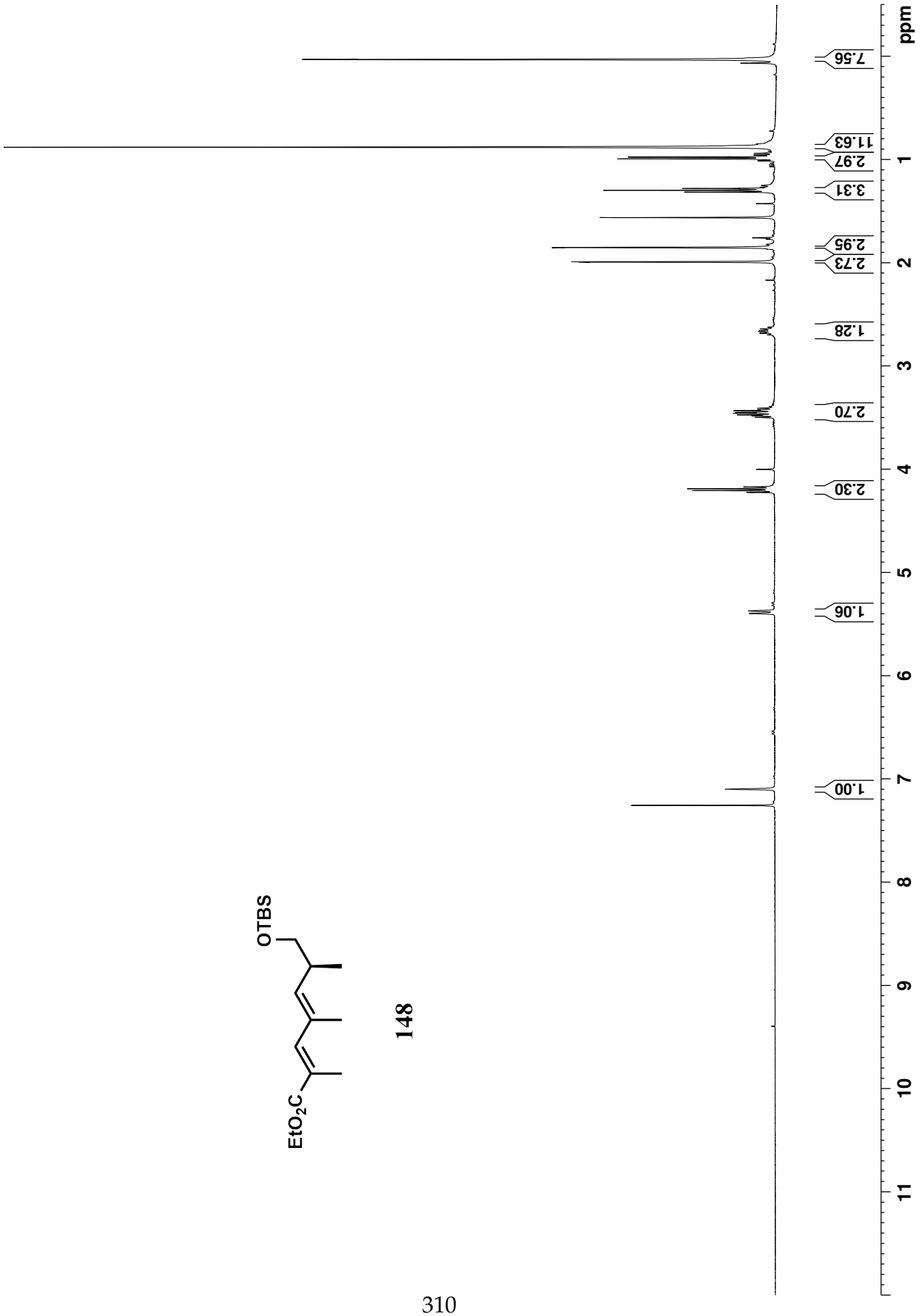

OTBS
O
HO
134
ppm
1
2
3
4
5
6
7
8
9
10
11
2.96
2.73
1.00
0.94
2.89
1.04
1.08
2.21
2.13
1.03
0.97
1.00

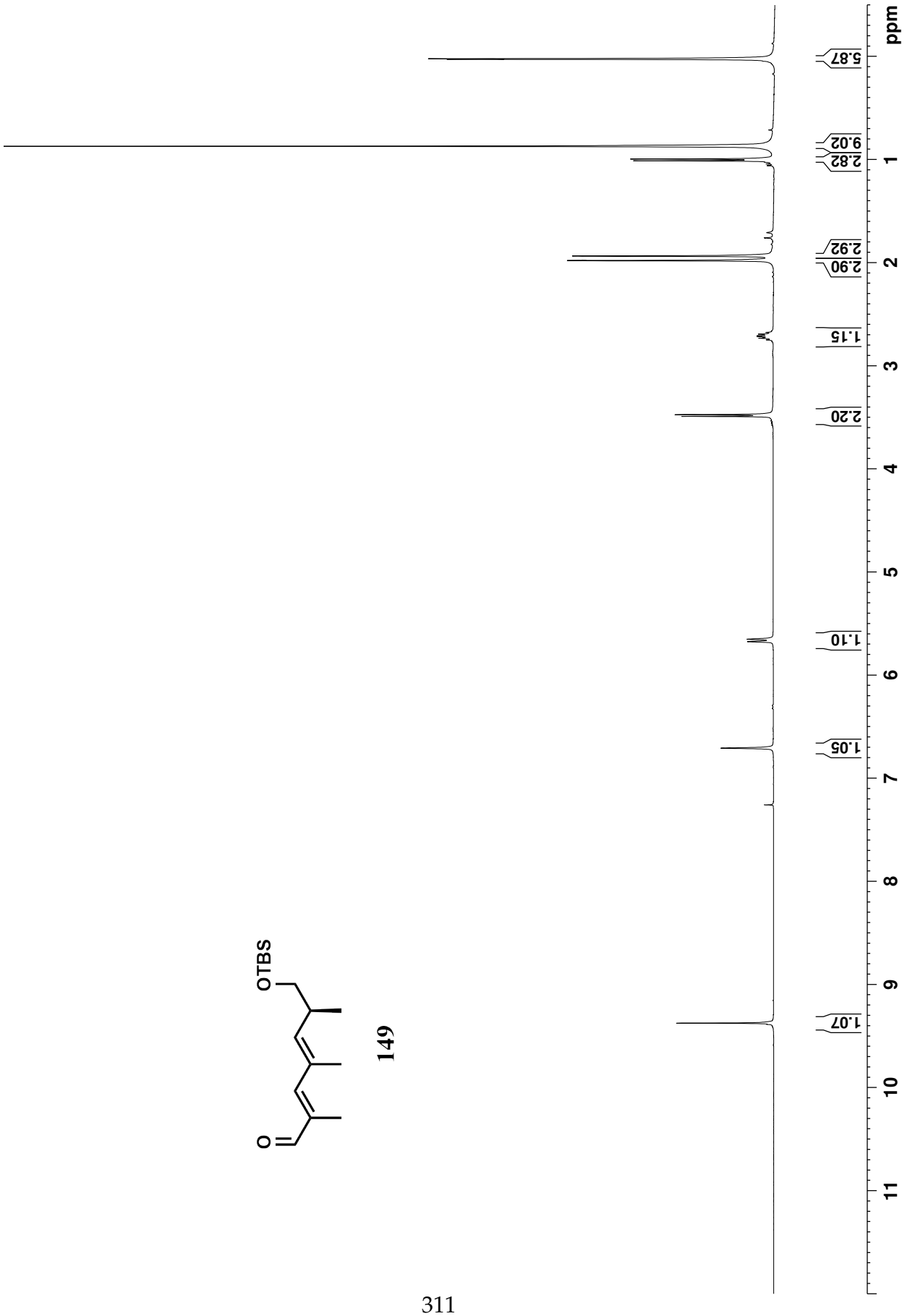

OTBS
OH
147
5.95
9.03
0.96
4.00
ppm
1
2
3
4
5
6
7
8
9
10
11

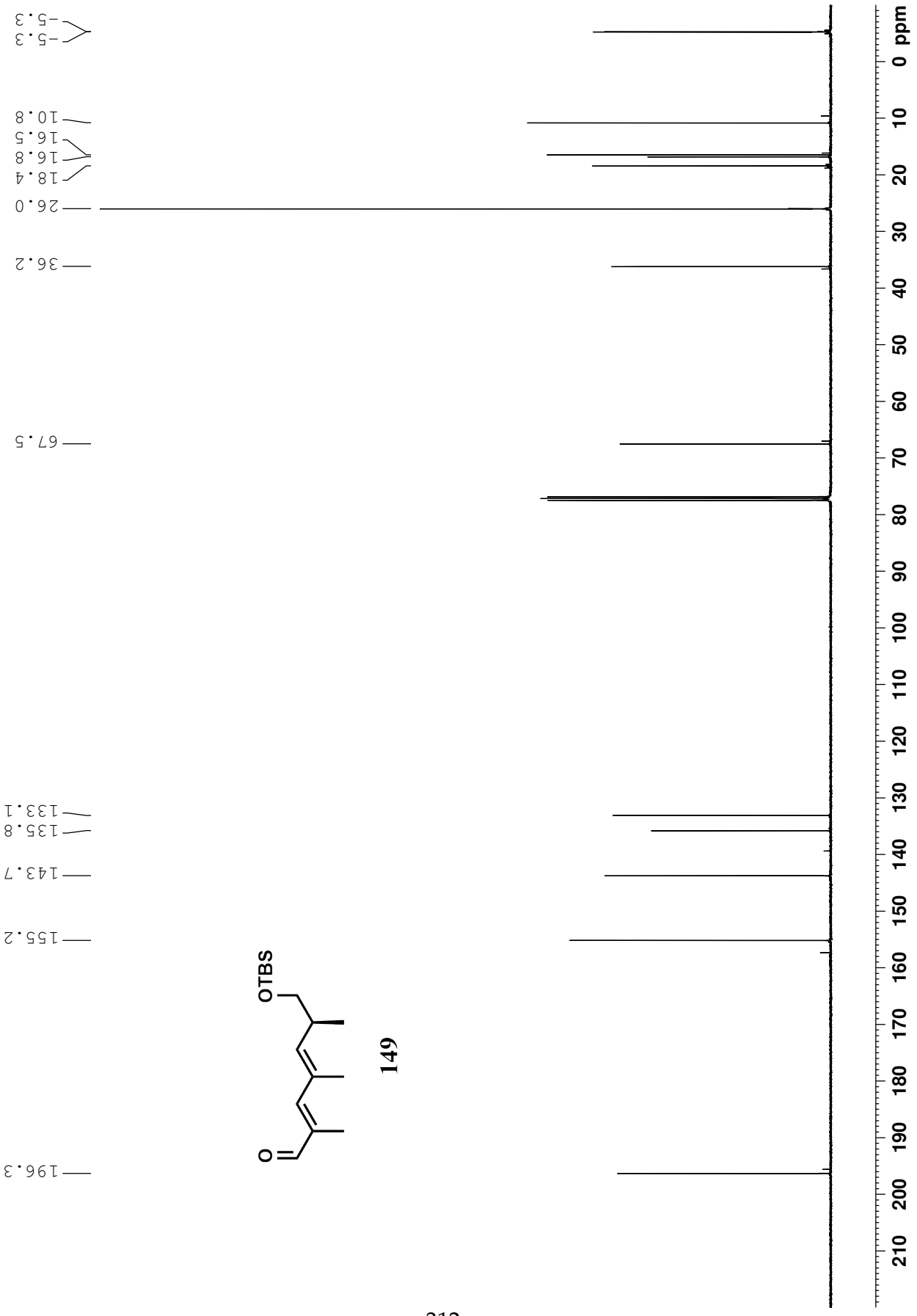


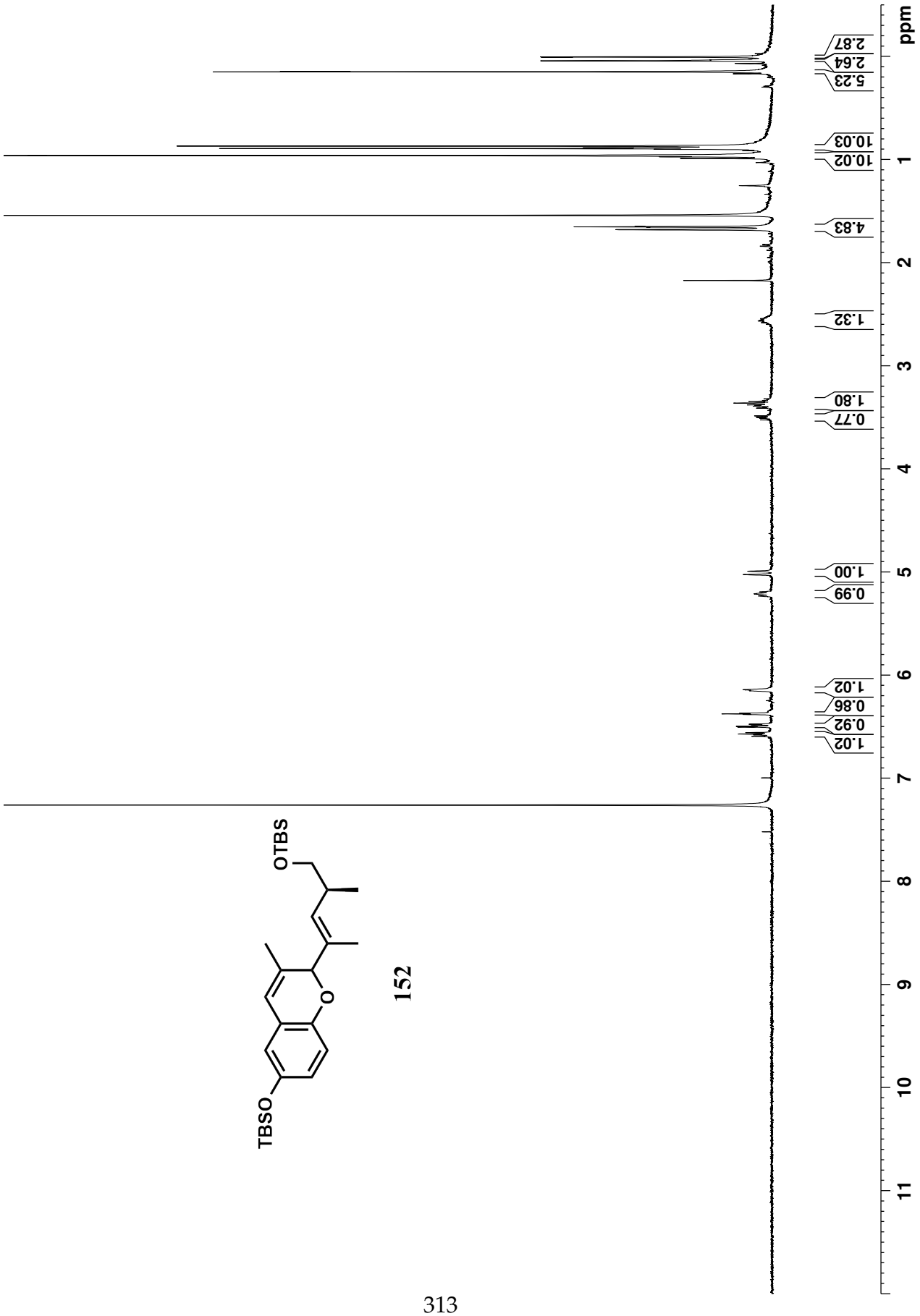
146

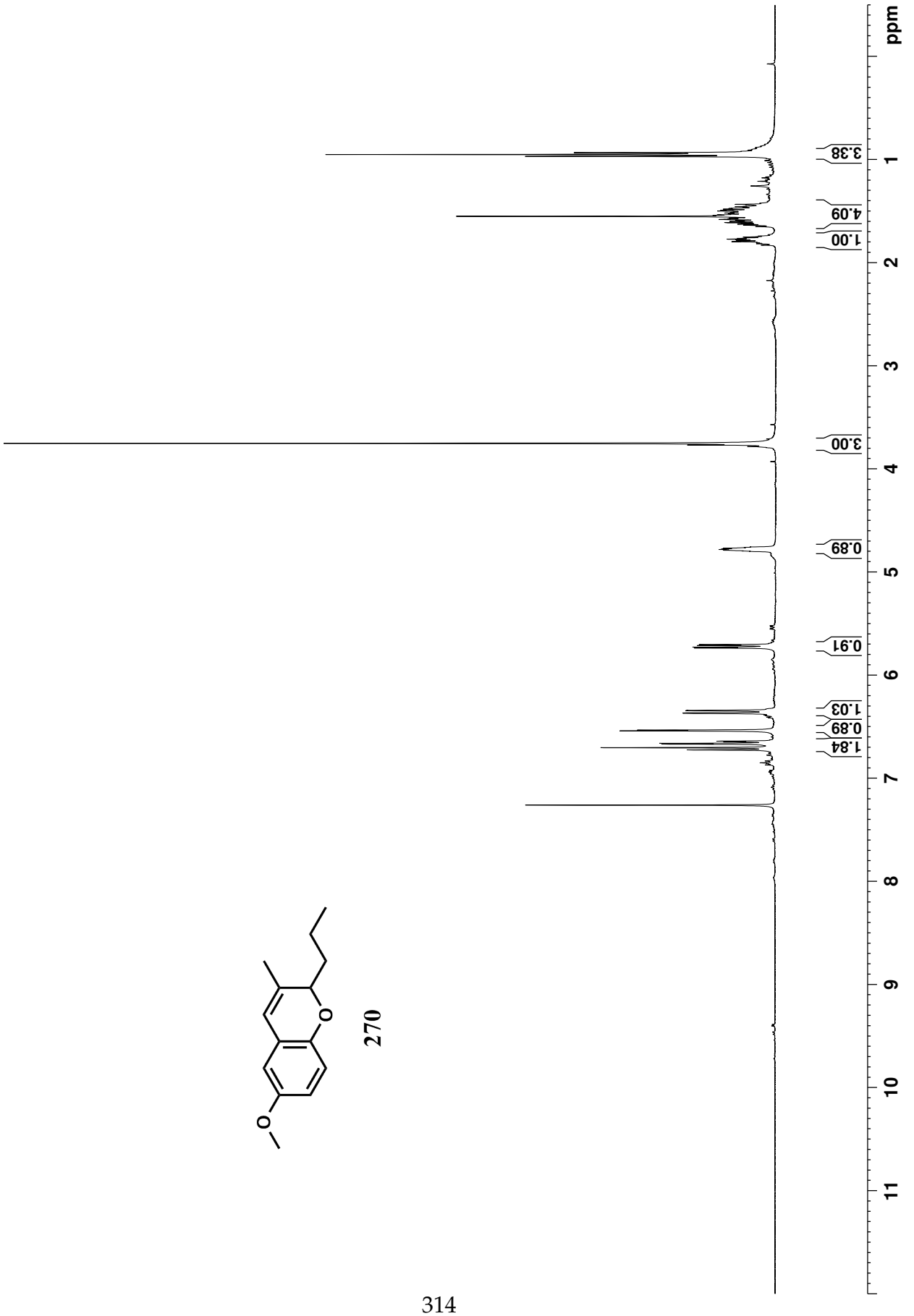

ppm
6.39
9.40
3.81
3.39
2.42
2.36
1.00
1.94
OTBS
OCONEt2
Br
144

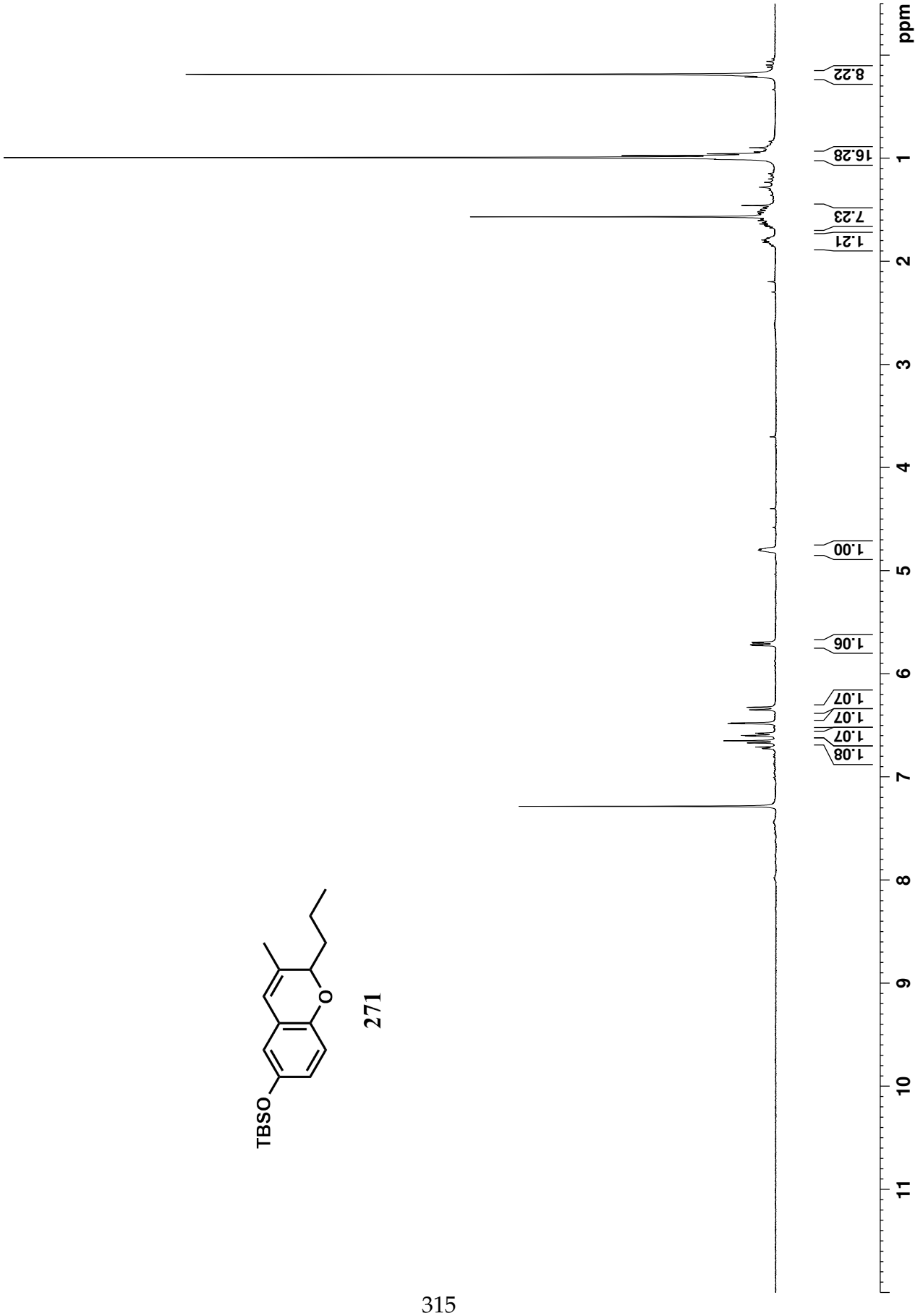

OTBS
EtO2C
148
7.56
11.63
2.97
3.31
2.95
2.73
1.28
2.70
2.30
1.06
1.00
ppm


OTBS
O
149
5.87
9.02
2.82
2.92
2.90
1.15
2.20
1.10
1.05
1.07
ppm
1
2
3
4
5
6
7
8
9
10
11

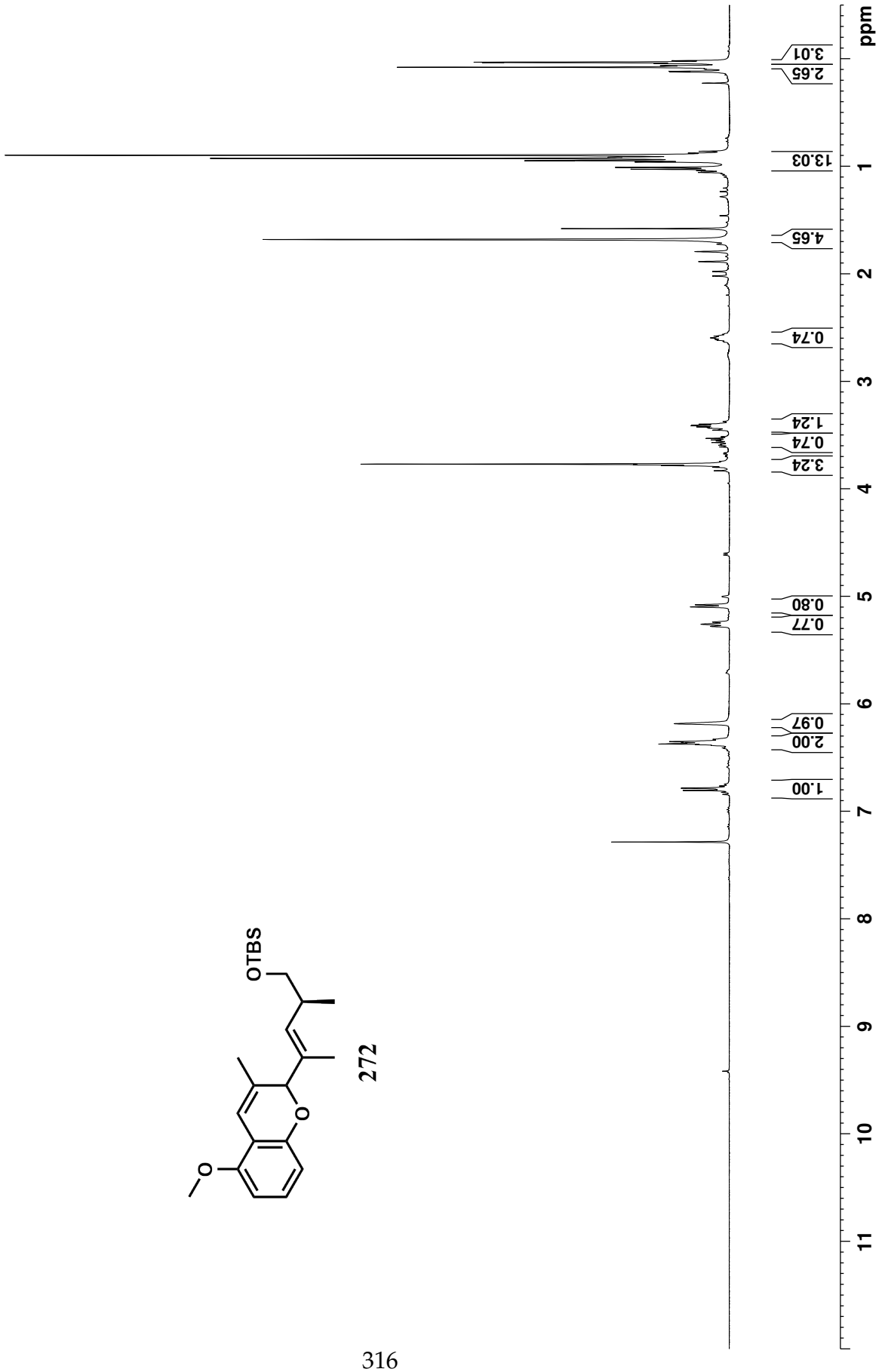

-5.3
-5.3
10.8
16.5
16.8
18.4
26.0
36.2
67.5
133.1
135.8
143.7
155.2
196.3
OTBS
O
149
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

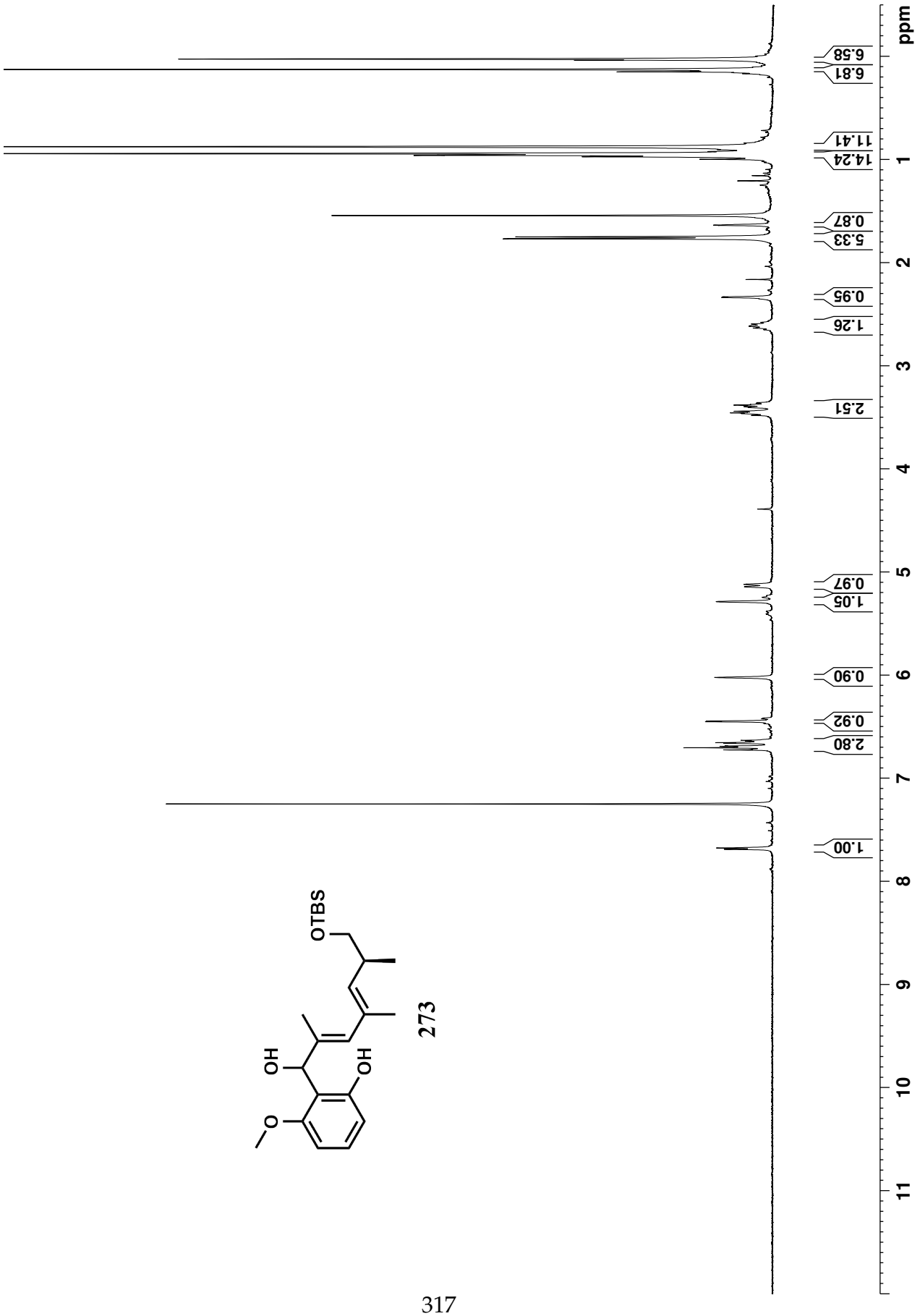

OTBS
TBSO
O
152
2.87
2.64
5.23
10.03
10.02
4.83
1.32
1.80
0.77
1.00
0.99
1.02
0.86
0.92
1.02
ppm
1
2
3
4
5
6
7
8
9
10
11

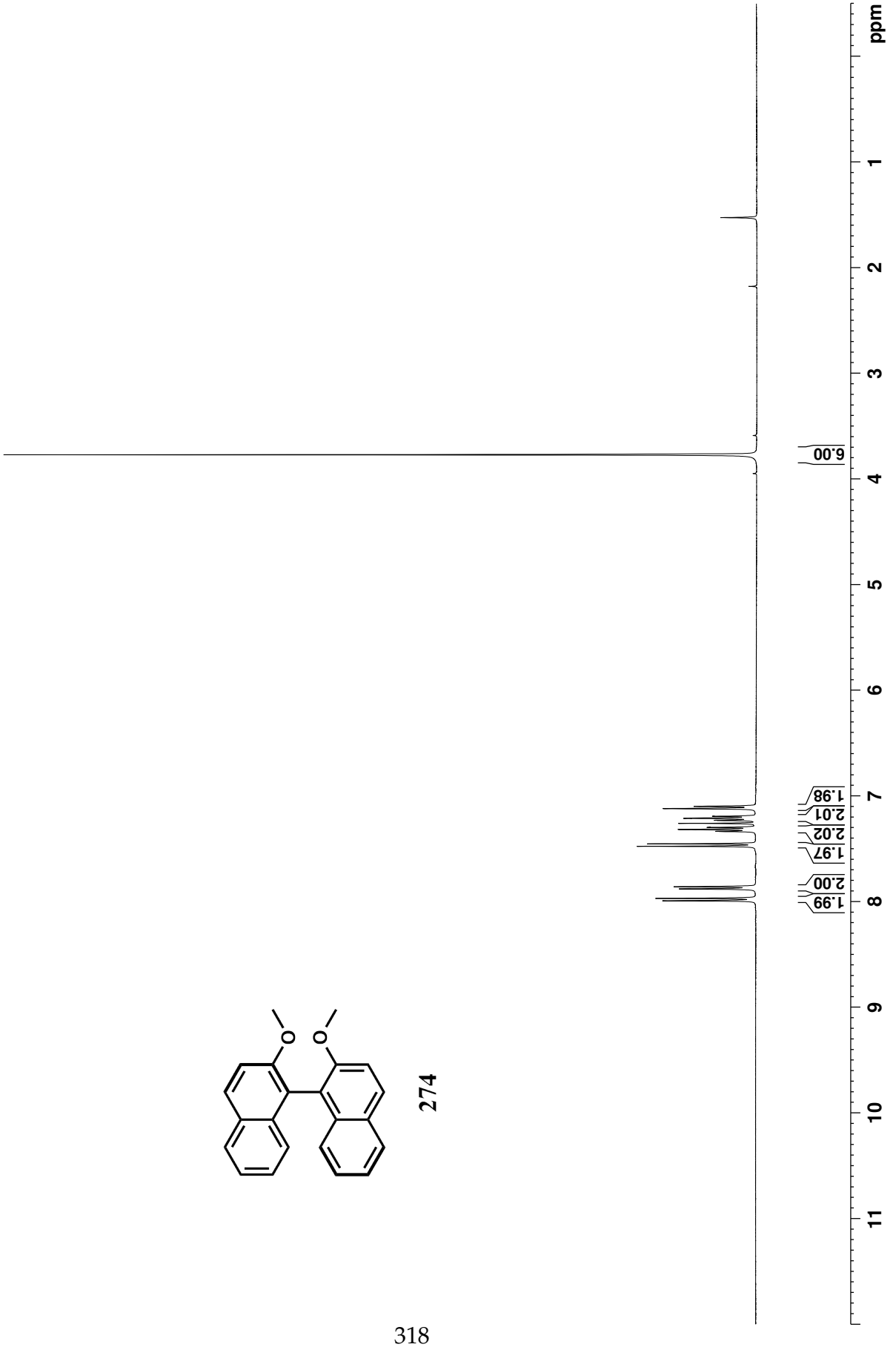

ppm
1
2
3
4
5
6
7
8
9
10
11
3.38
4.09
1.00
3.00
0.89
0.91
1.03
0.89
1.84
O
O
270


8.22
16.28
7.23
1.21
1.00
1.06
1.07
1.07
1.07
1.08
ppm
1
2
3
4
5
6
7
8
9
10
11
TBSO
O

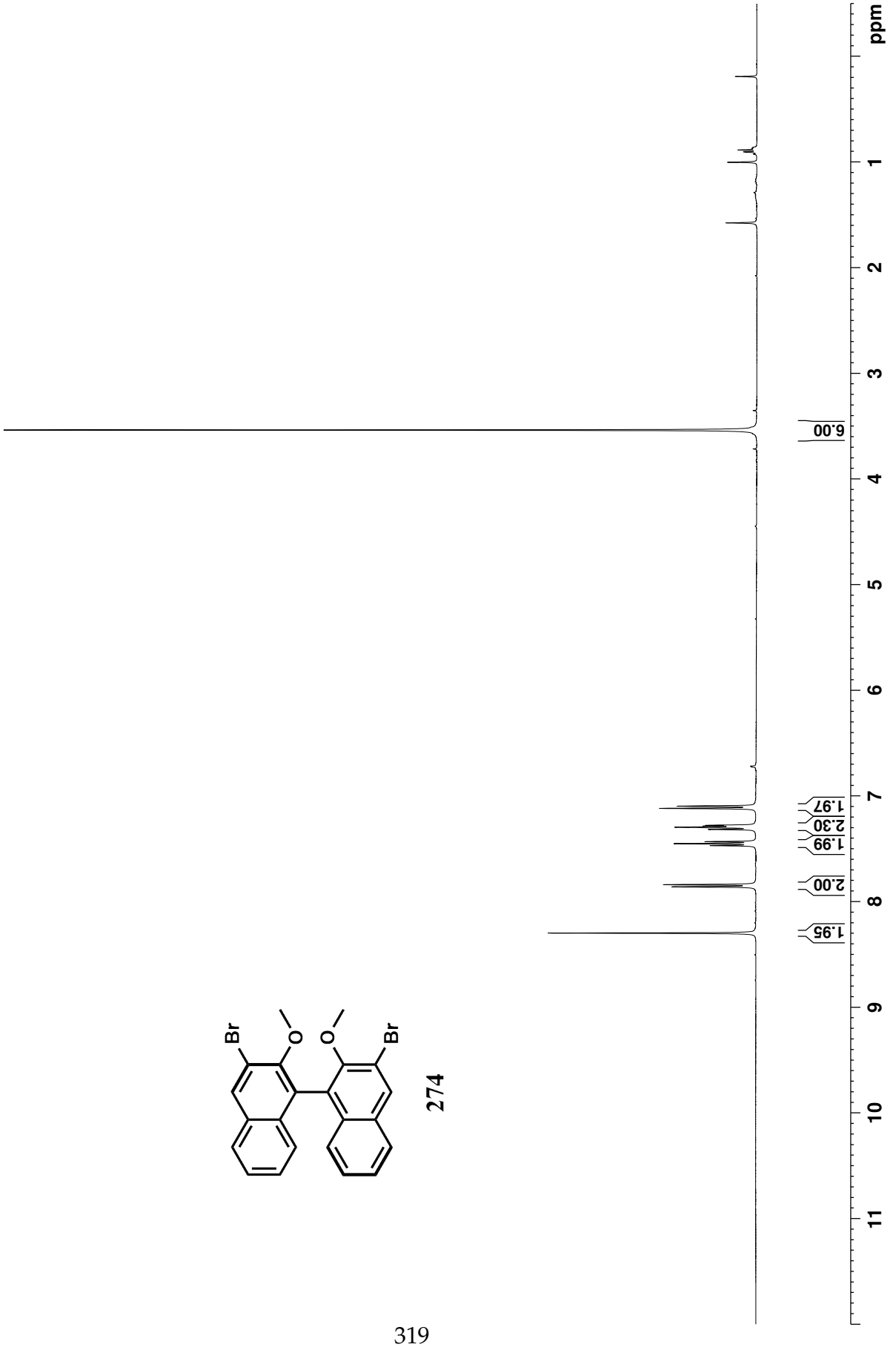
271


ppm
3.01
2.65
13.03
4.65
0.74
1.24
0.74
3.24
0.80
0.77
0.97
2.00
1.00
OTBS
O
O
272

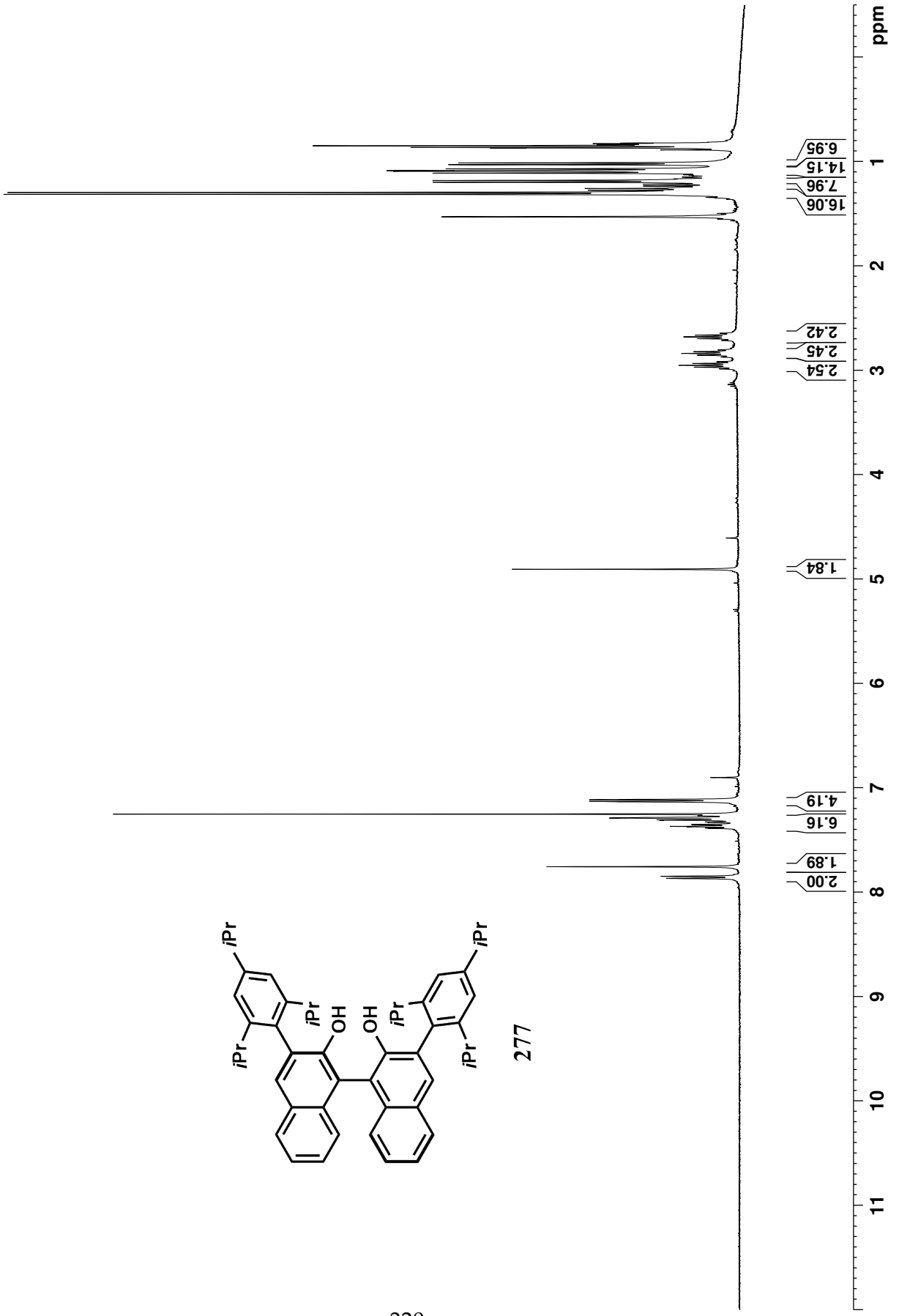

OTBS
OH
OH
O
273
6.58
6.81
11.41
14.24
0.87
5.33
0.95
1.26
2.51
1.05
0.97
0.90
0.92
2.80
1.00
ppm

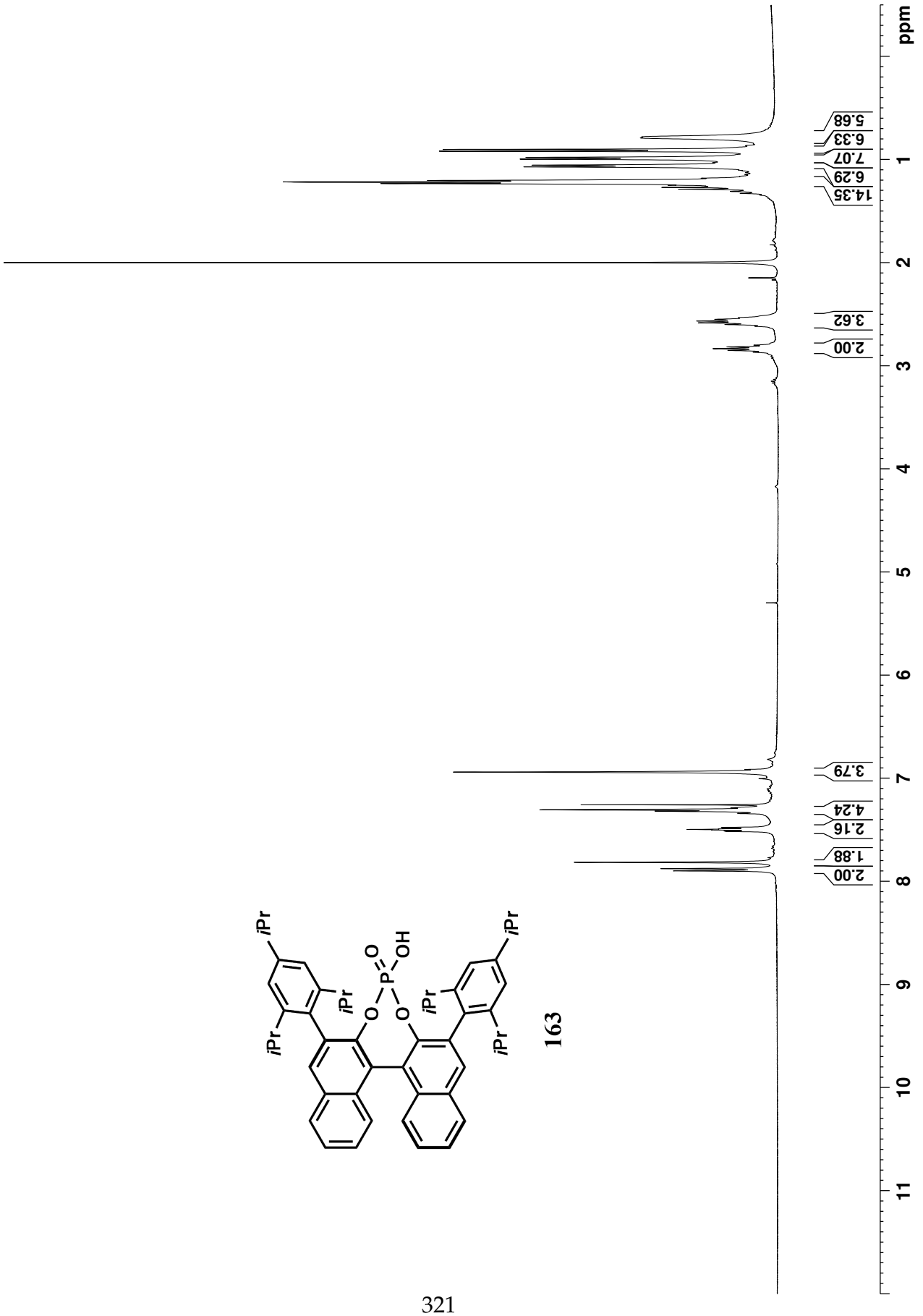


274

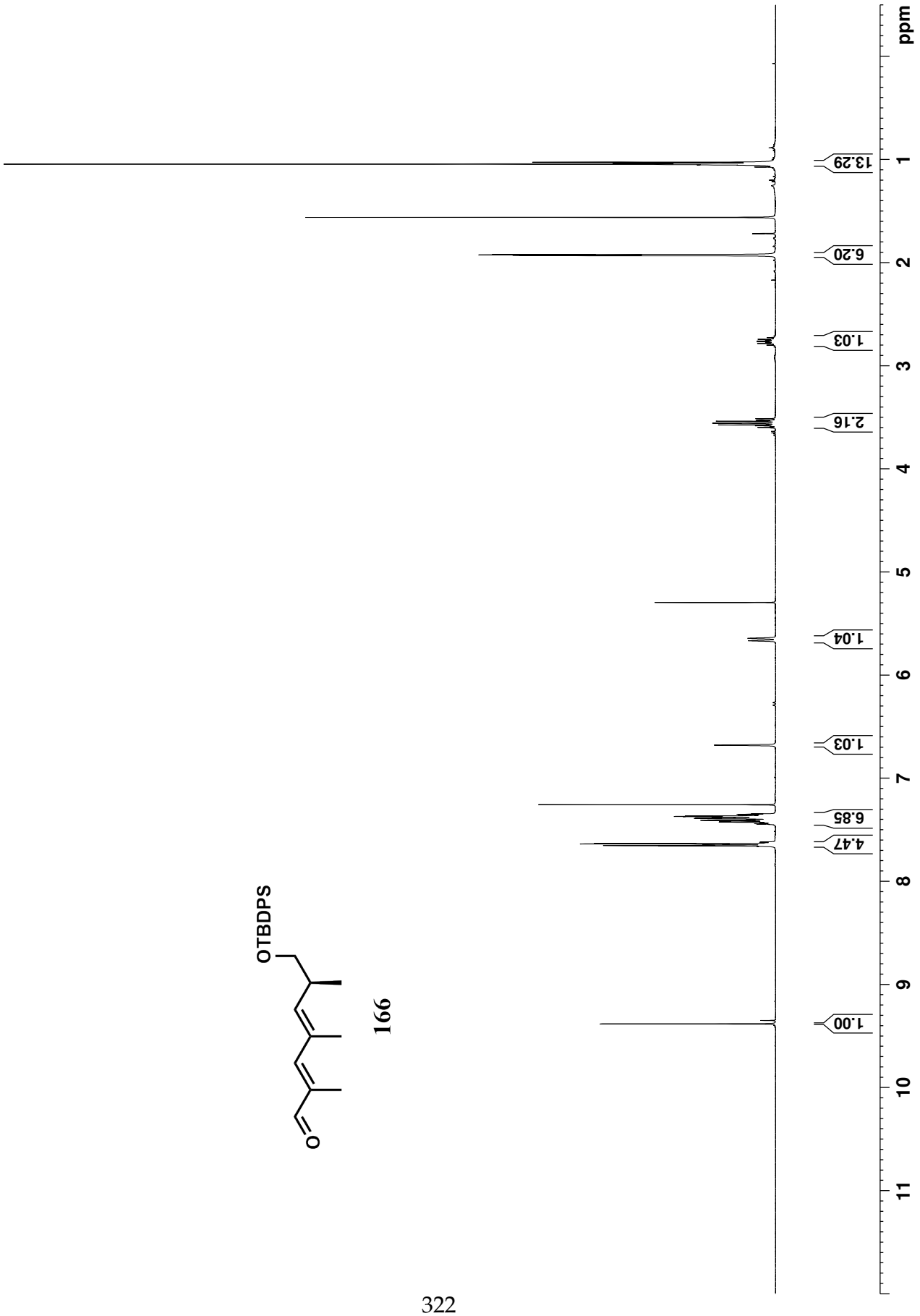


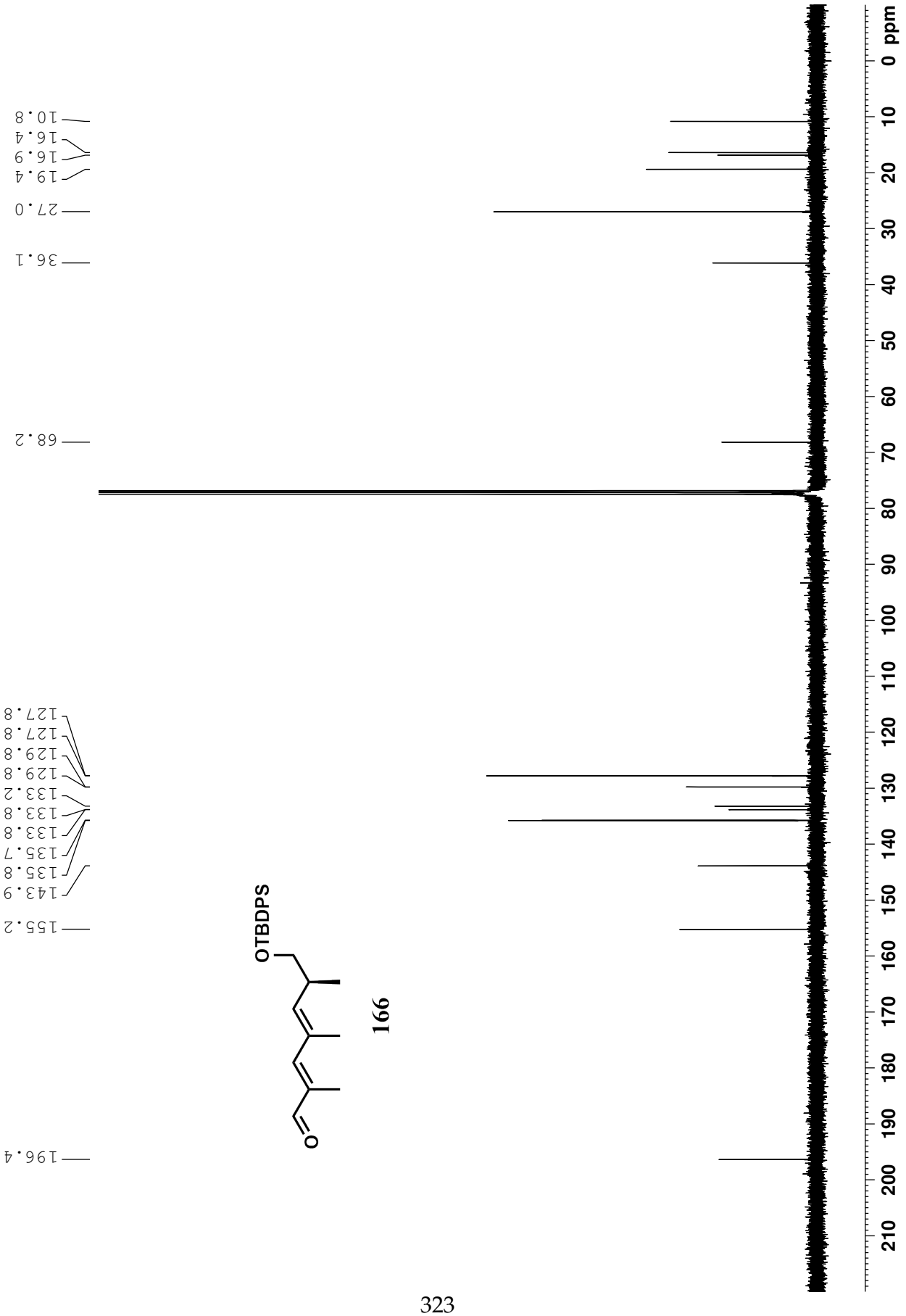
274

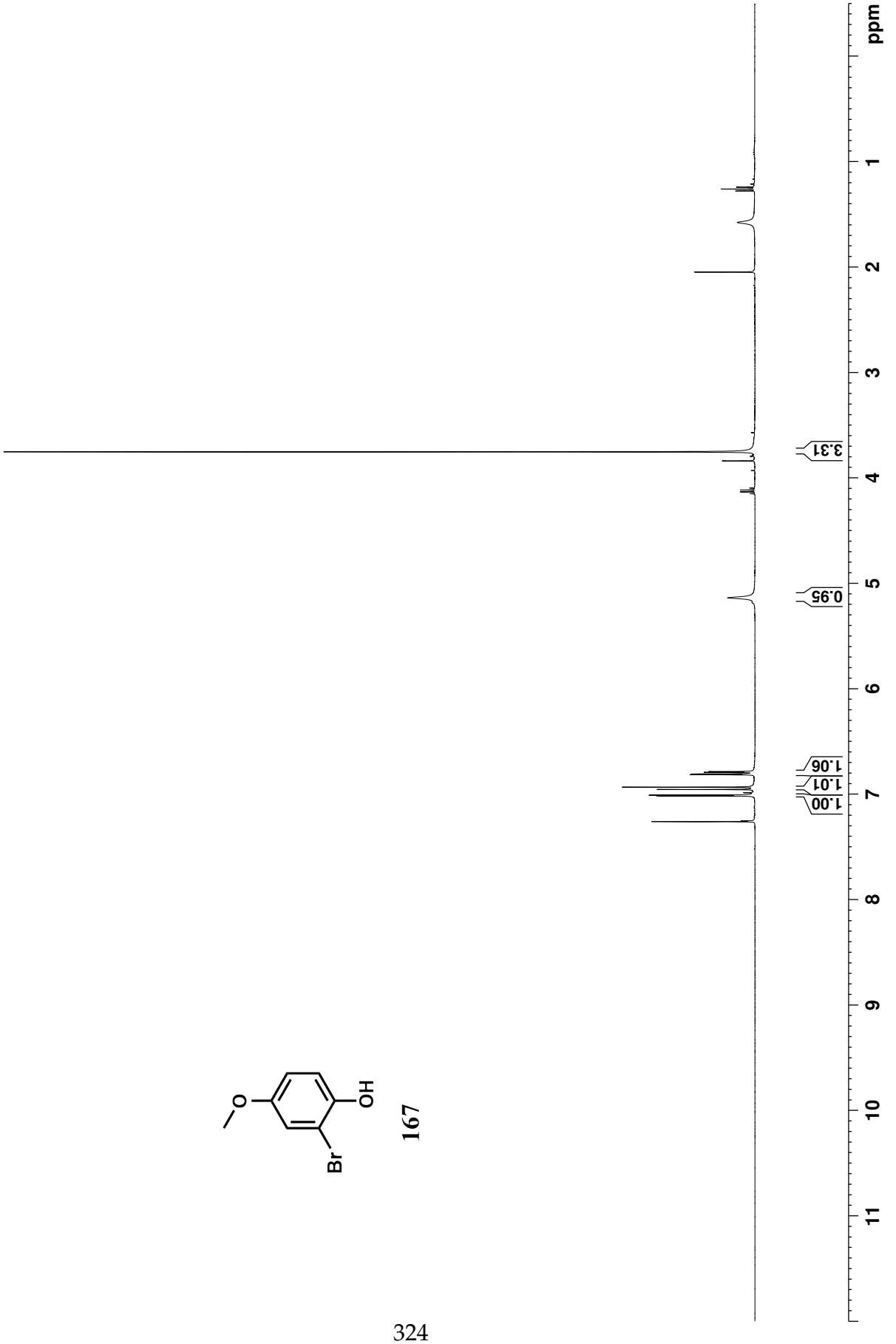

ppm
1
2
3
4
5
6
7
8
9
10
11
6.95
14.15
7.96
16.06
2.42
2.45
2.54
1.84
4.19
6.16
1.89
2.00
iPr
iPr
OH
OH
iPr
iPr
277


ppm
1
2
3
4
5
6
7
8
9
10
11
5.68
6.33
7.07
6.29
14.35
3.62
2.00
3.79
4.24
2.16
1.88
2.00
iPr
iPr
iPr
iPr
iPr
iPr
O
O
P
O
OH

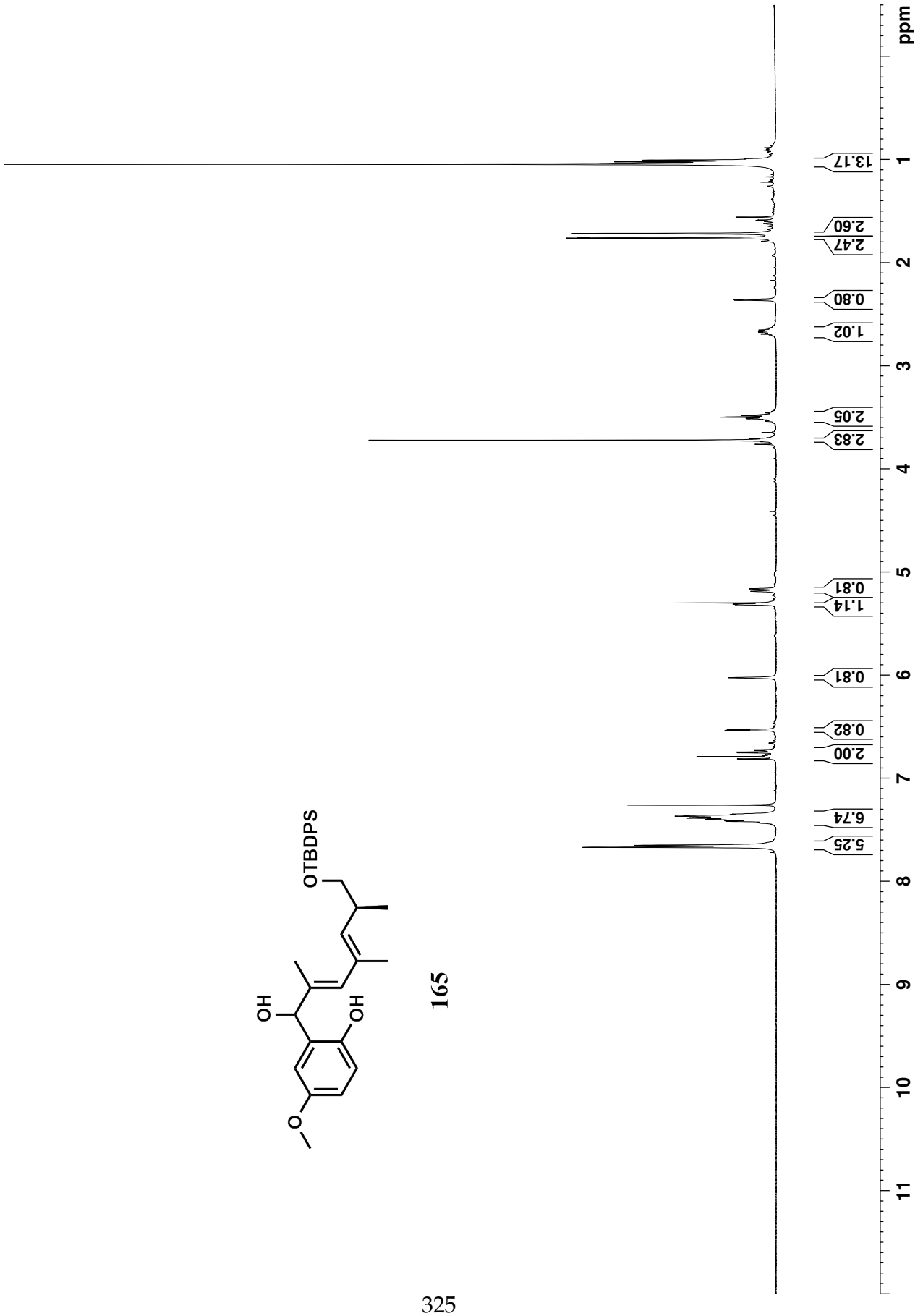
163


OTBDPS
O
166
13.29
6.20
1.03
2.16
1.04
1.03
6.85
4.47
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11

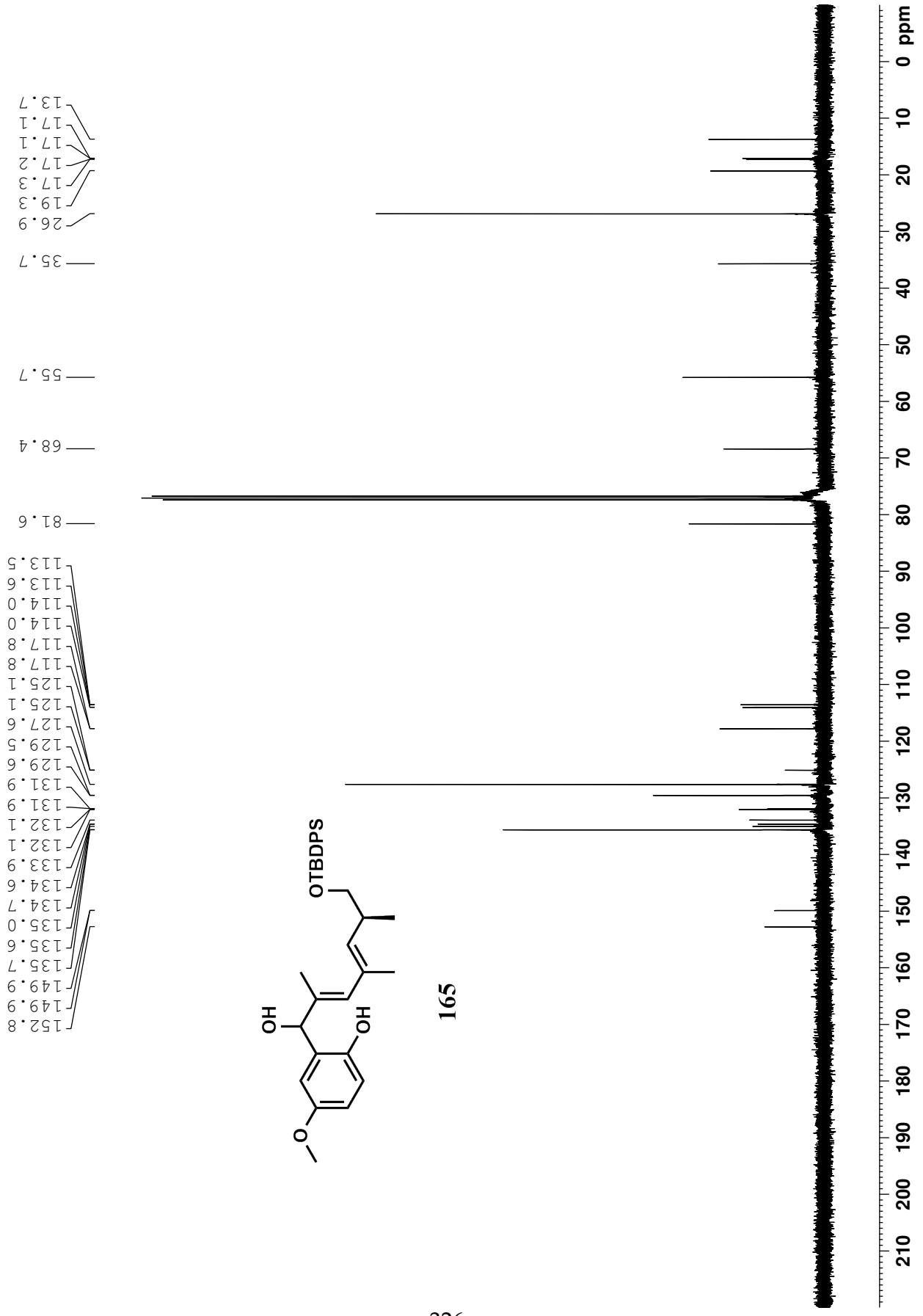

196.4
155.2
143.9
135.8
135.7
133.8
133.8
133.8
133.2
129.8
129.8
127.8
127.8
68.2
36.1
27.0
19.4
16.9
16.4
10.8
OTBDPS
O
166
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

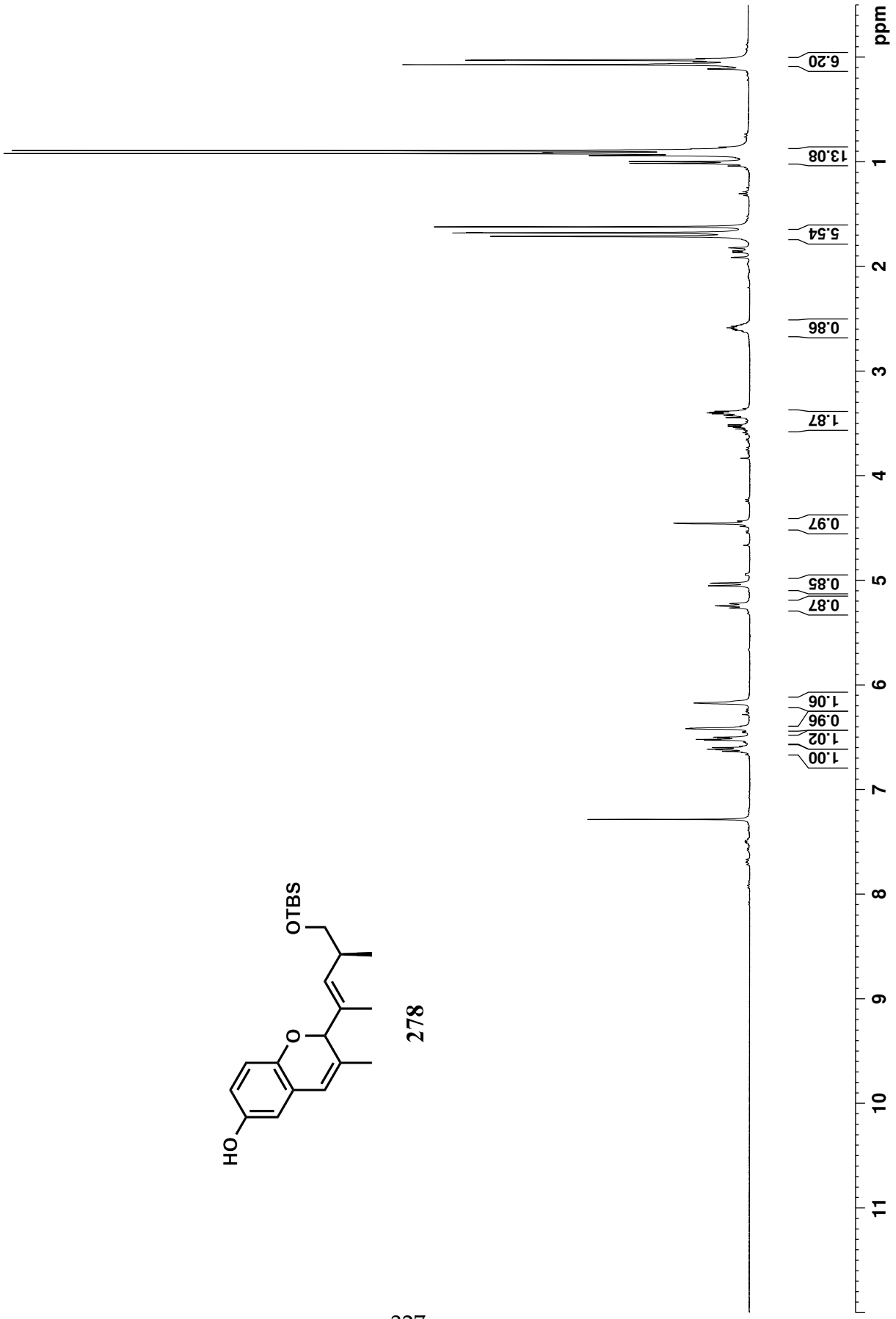


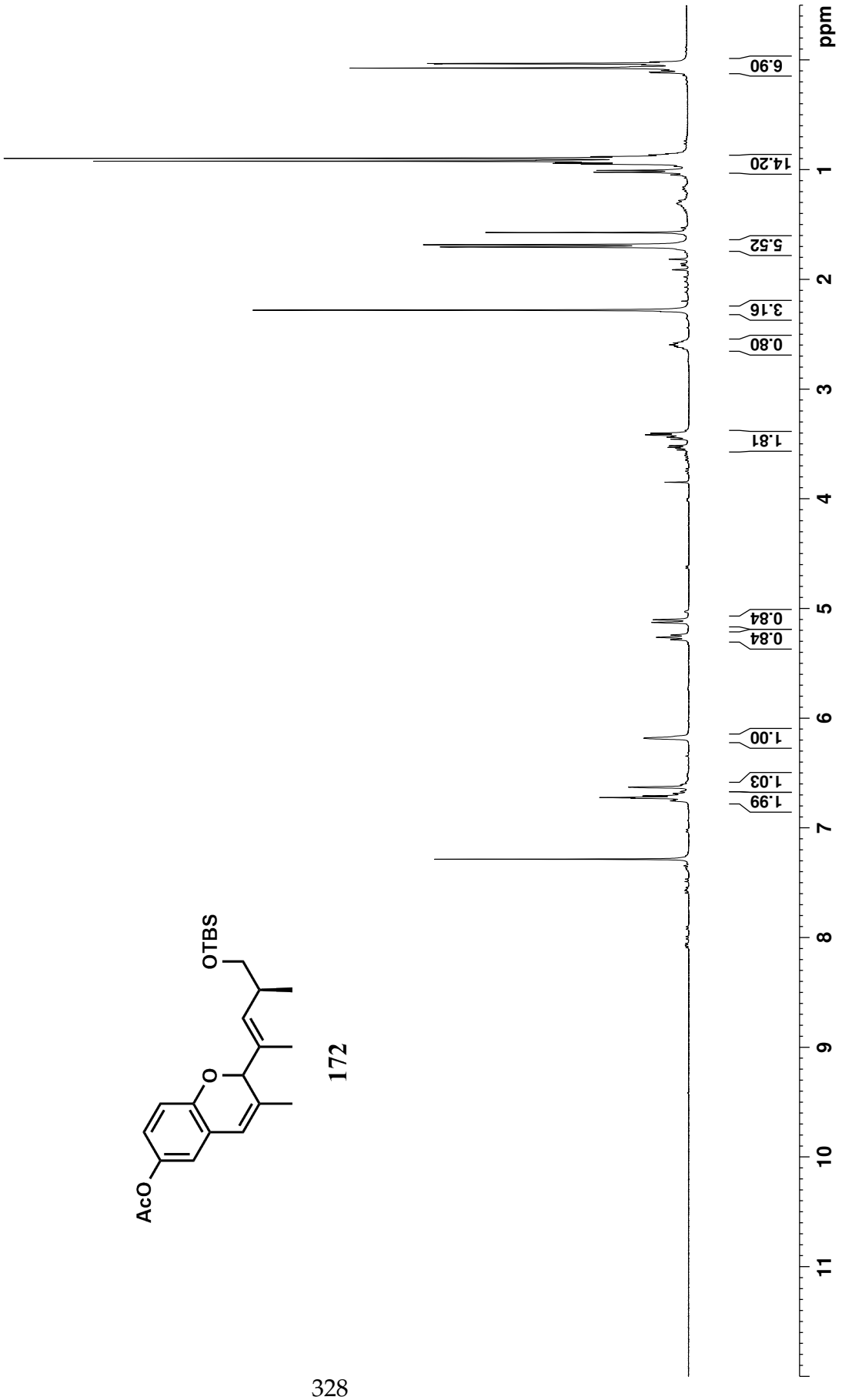
167


ppm
1
2
3
4
5
6
7
8
9
10
11
13.17
2.60
2.47
0.80
1.02
2.05
2.83
0.81
1.14
0.81
0.82
2.00
6.74
5.25
OTBDPS
OH
OH
O

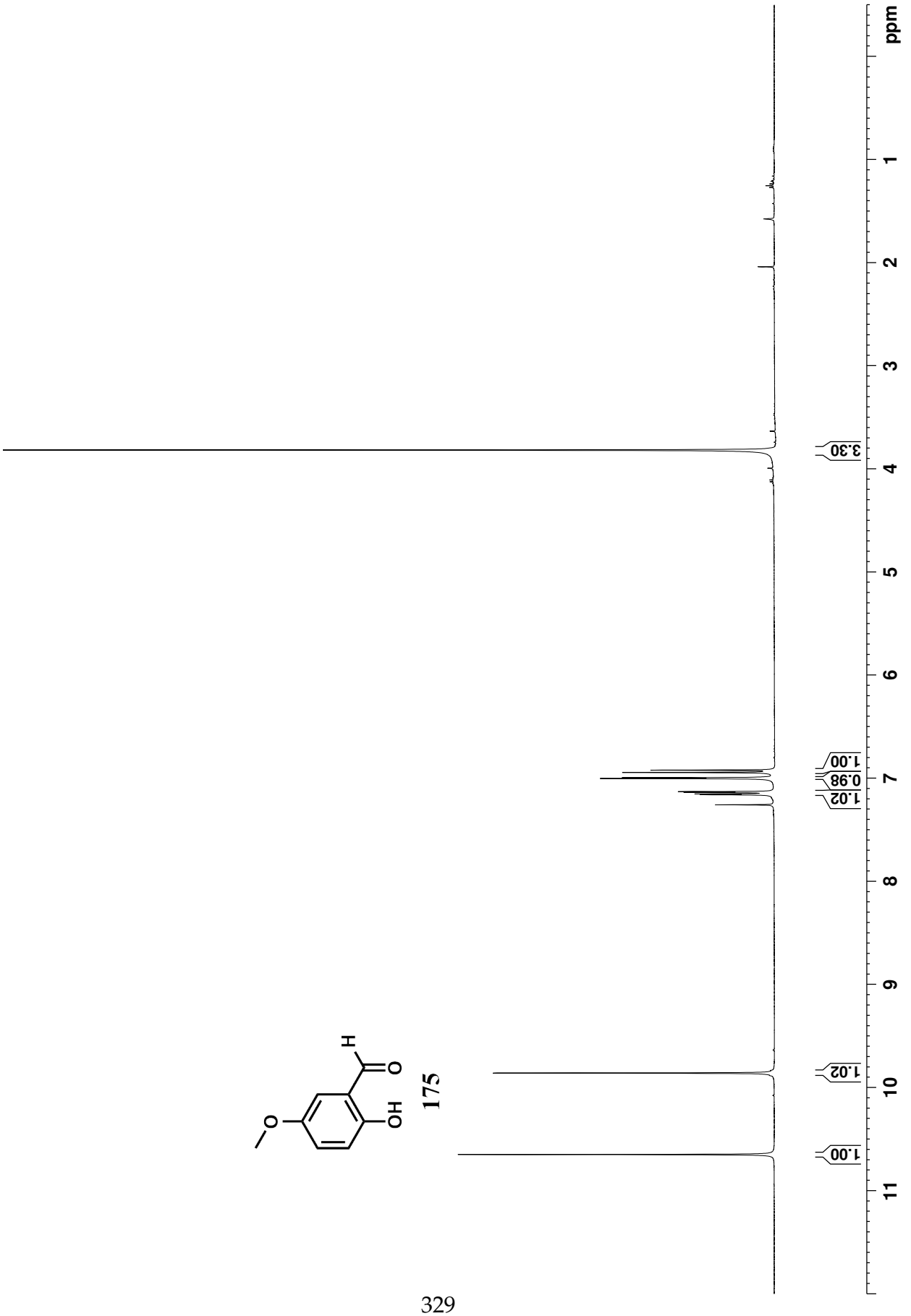
165

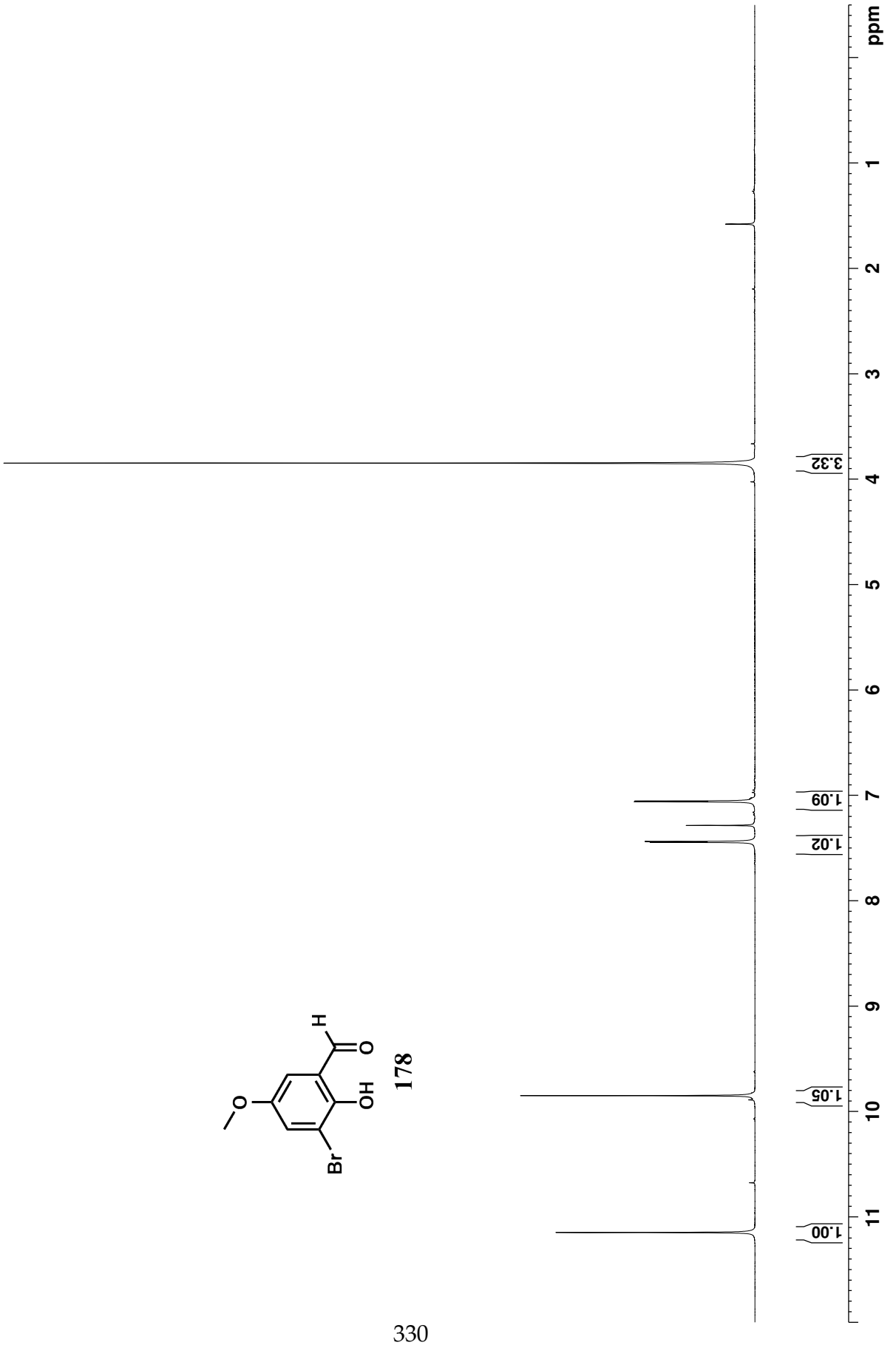

152.8
149.9
149.9
135.7
135.6
135.0
134.7
134.6
133.9
132.1
132.1
131.9
131.9
129.6
129.5
127.6
125.1
125.1
117.8
117.8
114.0
114.0
113.6
113.5
81.6
68.4
55.7
35.7
26.9
19.3
17.3
17.2
17.1
17.1
13.7
OTBDPS
OH
OH
O
165
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


OTBS
HO
O
278
6.20
13.08
5.54
0.86
1.87
0.97
0.85
0.87
1.06
0.96
1.02
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11

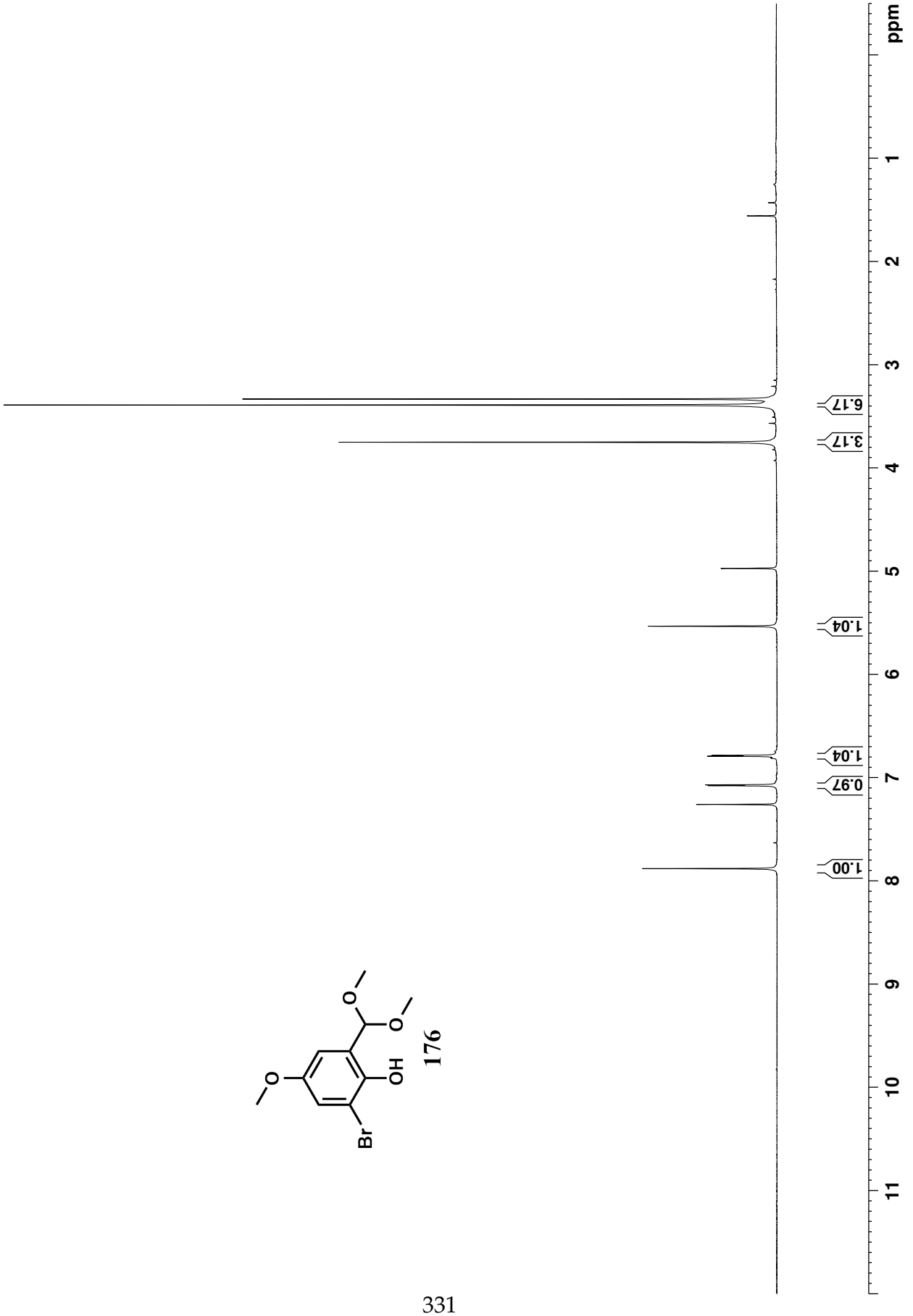

ppm
1
2
3
4
5
6
7
8
9
10
11
6.90
14.20
5.52
3.16
0.80
1.81
0.84
0.84
1.00
1.03
1.99
OTBS
O
AcO

172

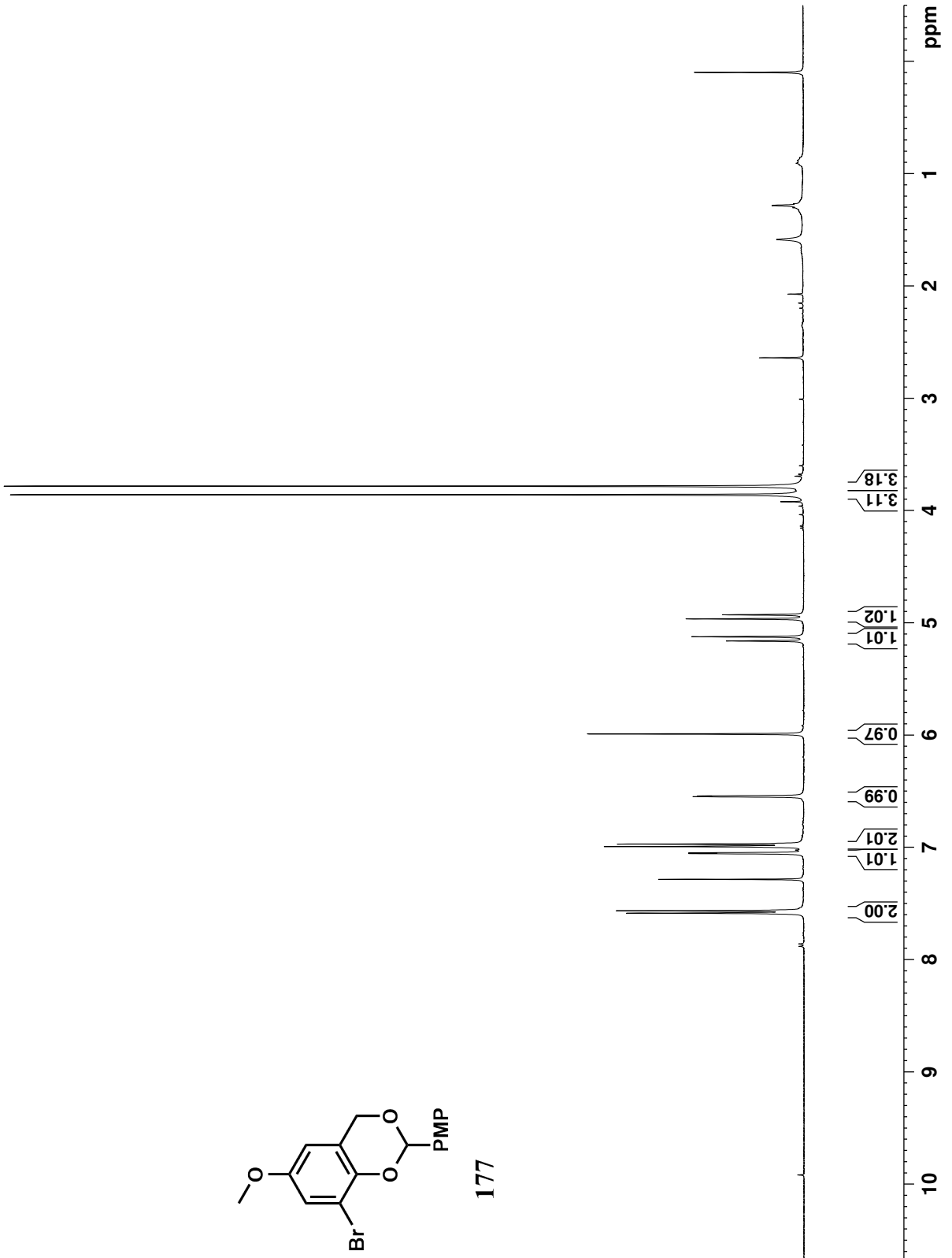

ppm
1
2
3
4
5
6
7
8
9
10
11
3.30
1.00
0.98
1.02
1.02
1.00
O
H
O
HO
175



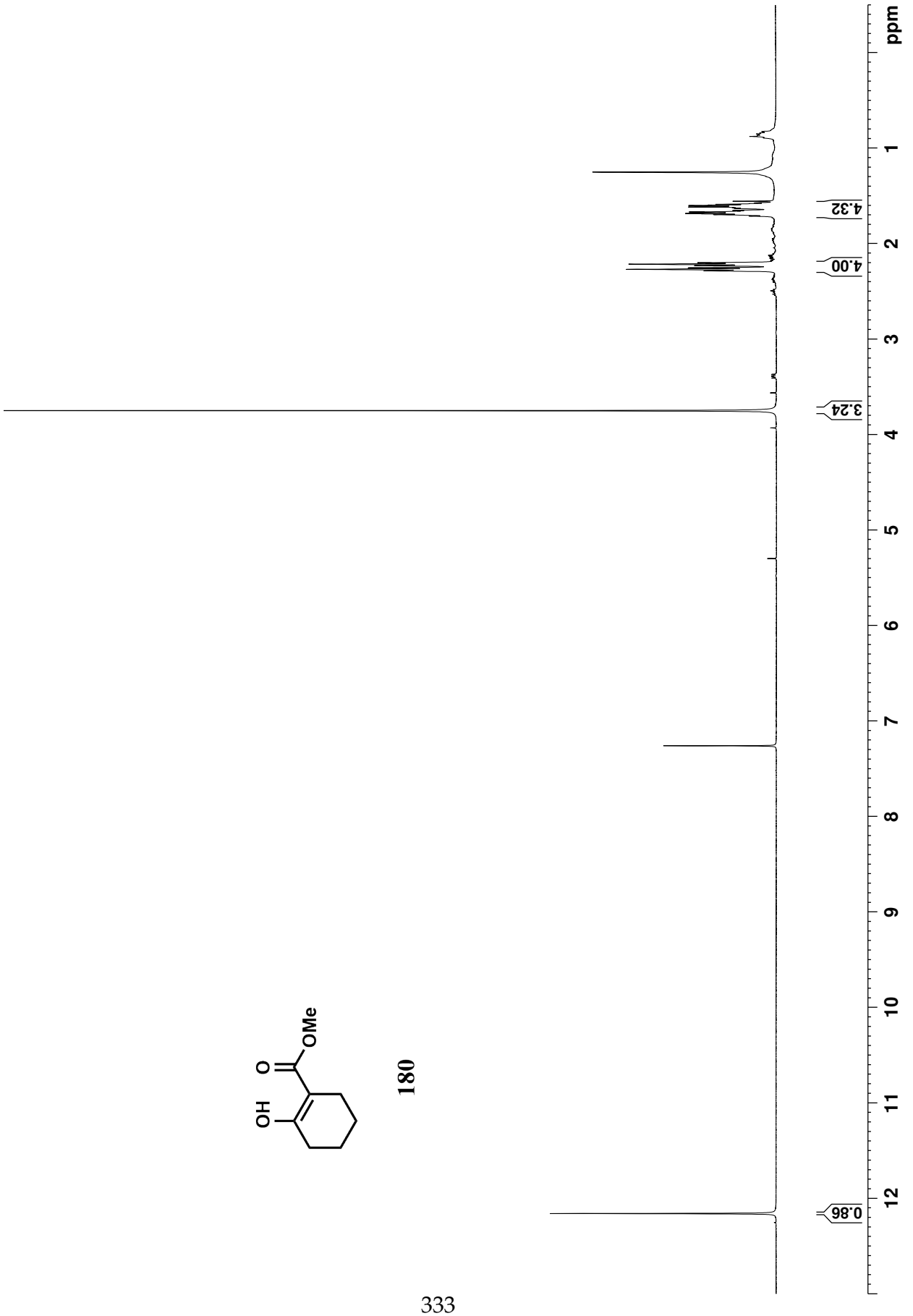
178



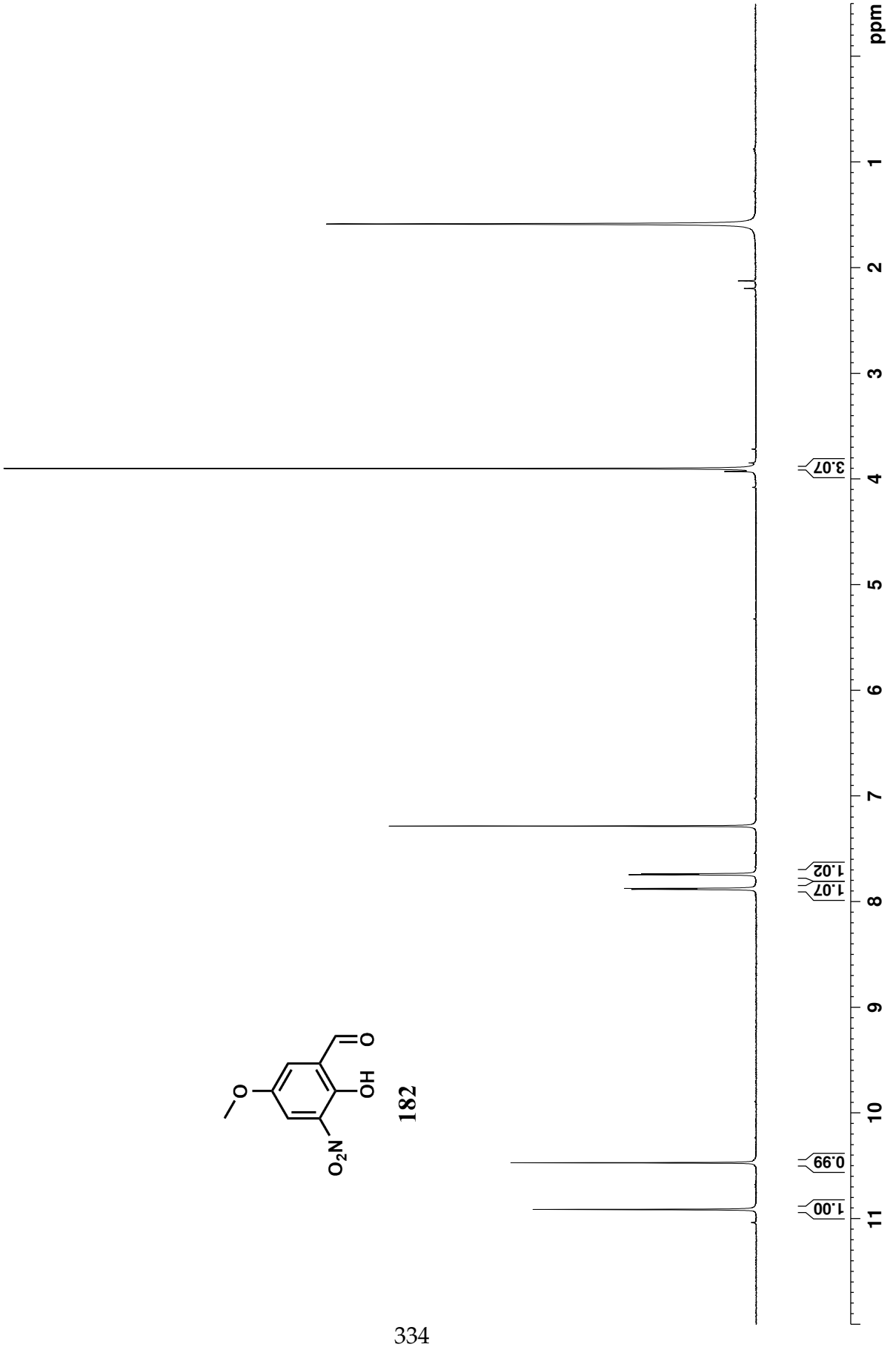
176


ppm
1
2
3
4
5
6
7
8
9
10
11
3.18
3.11
1.02
1.01
0.97
0.99
2.01
1.01
2.00
O
O
PMP
O
Br

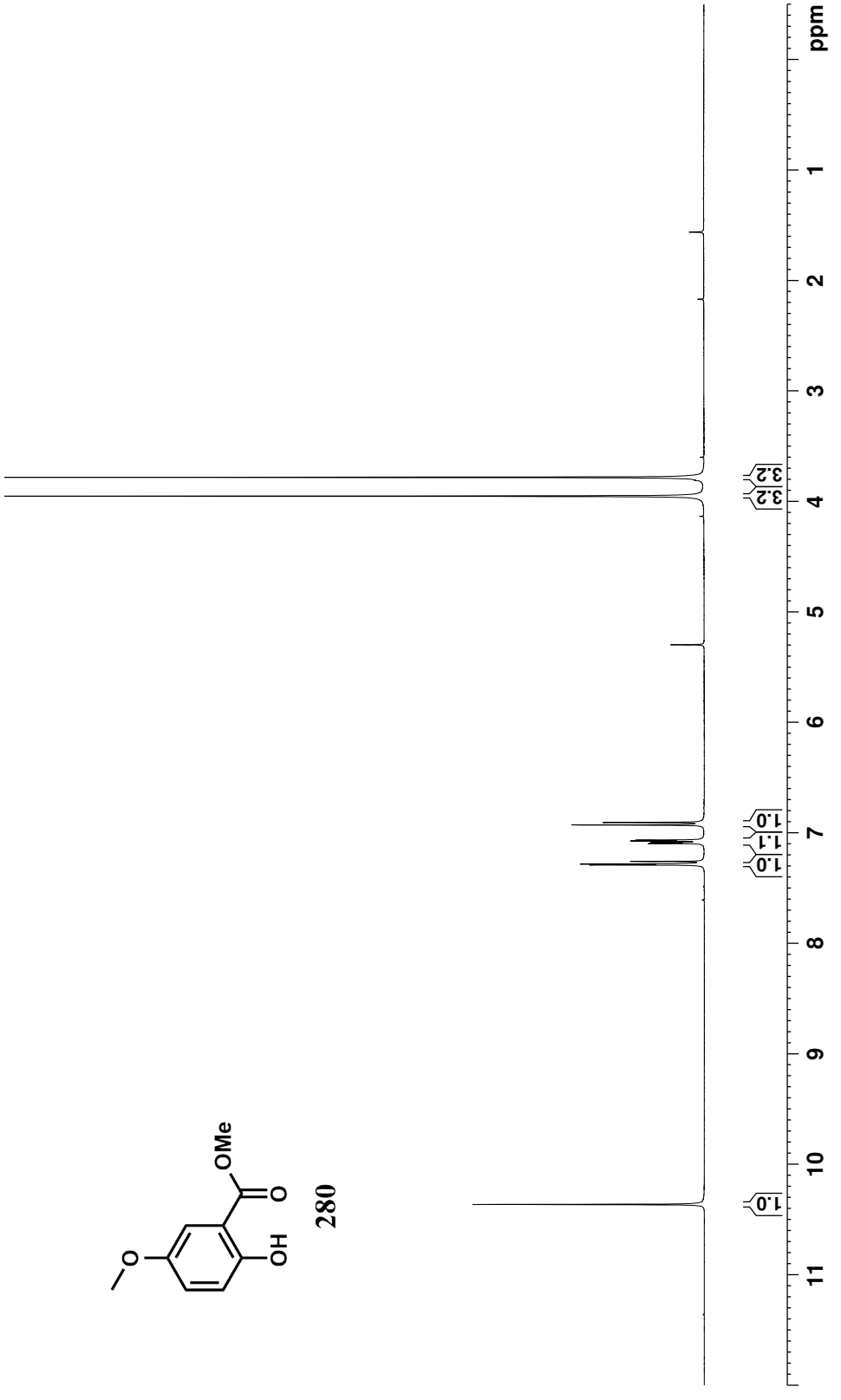
177

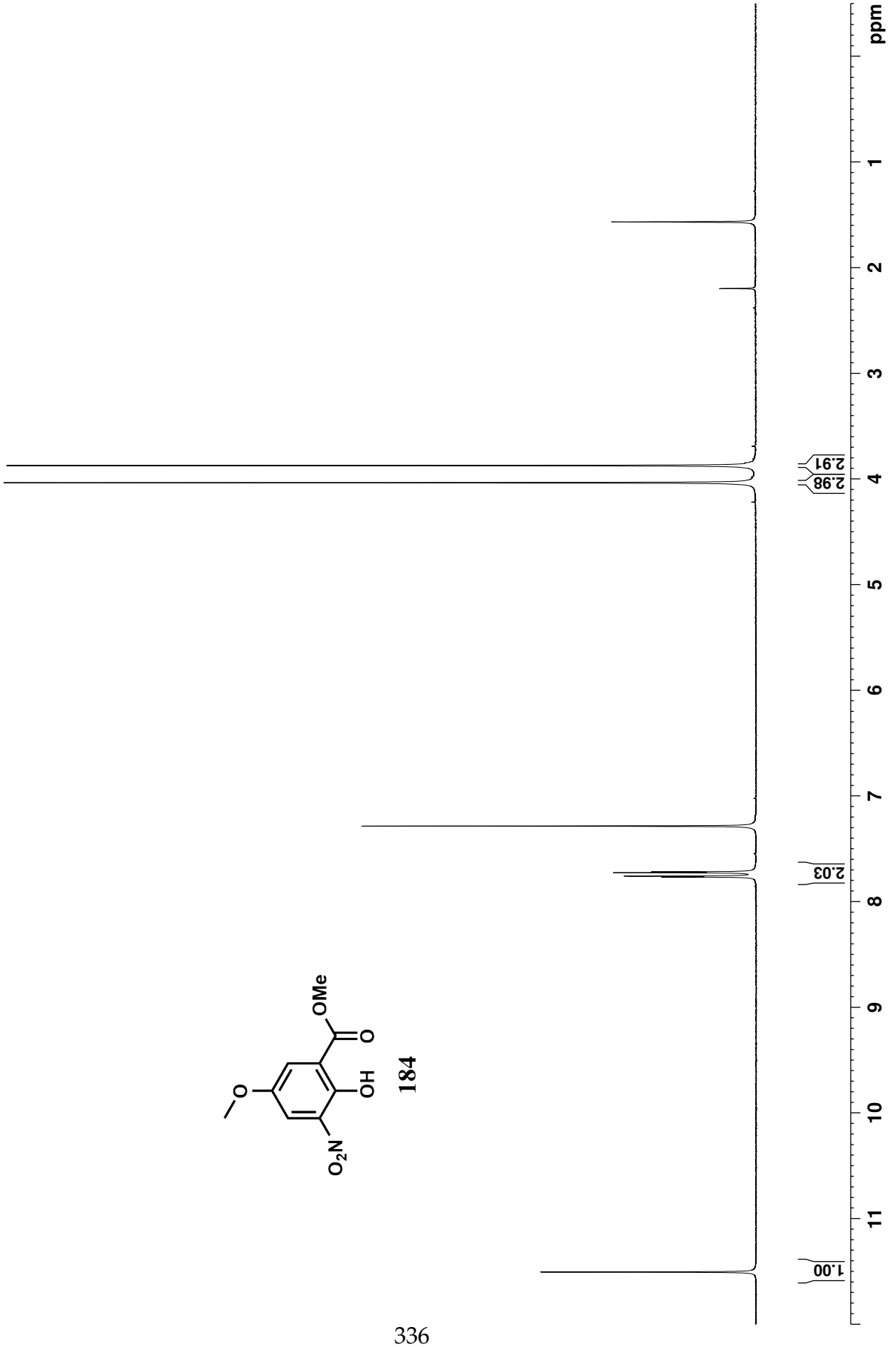


180

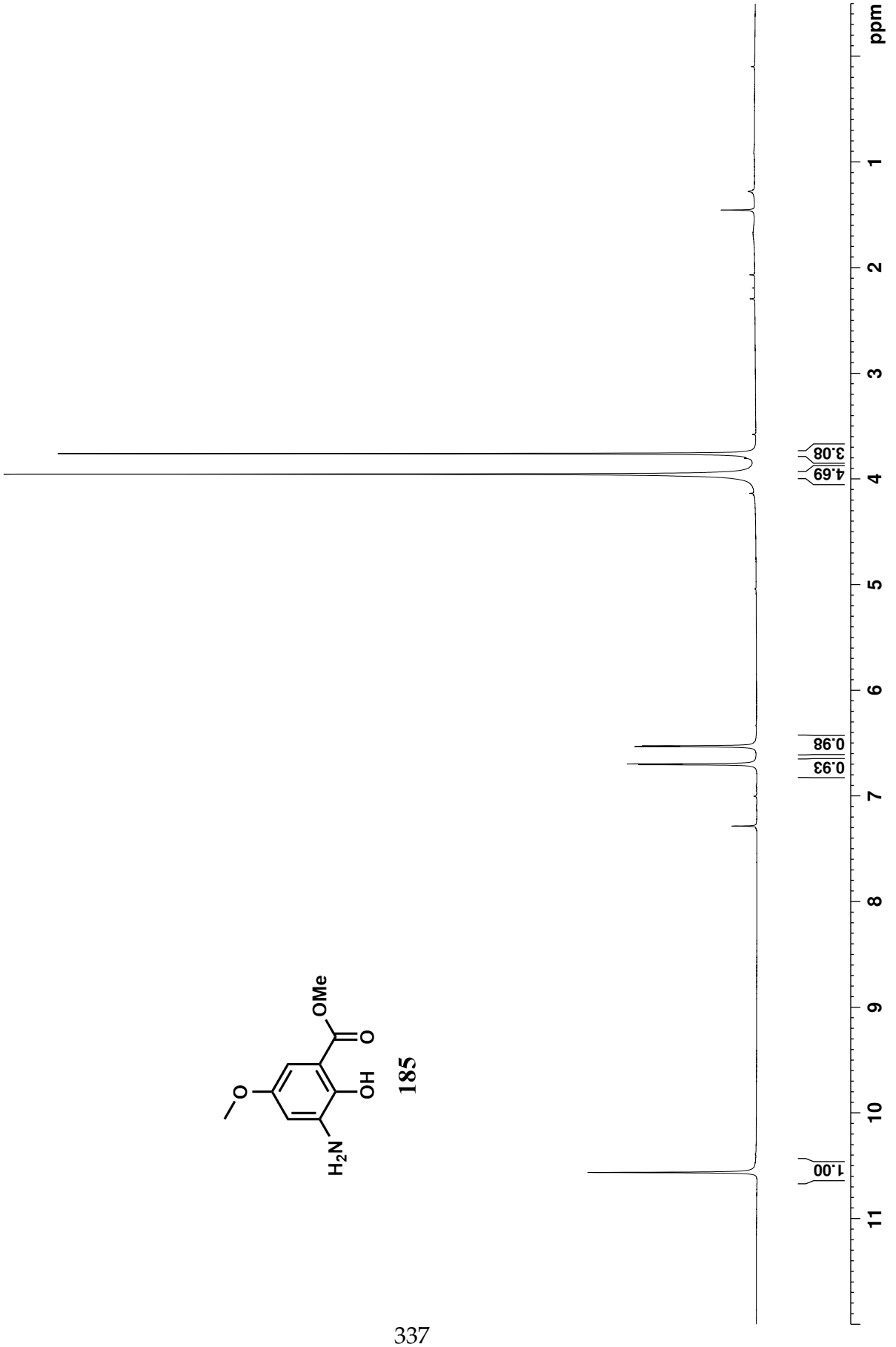


182

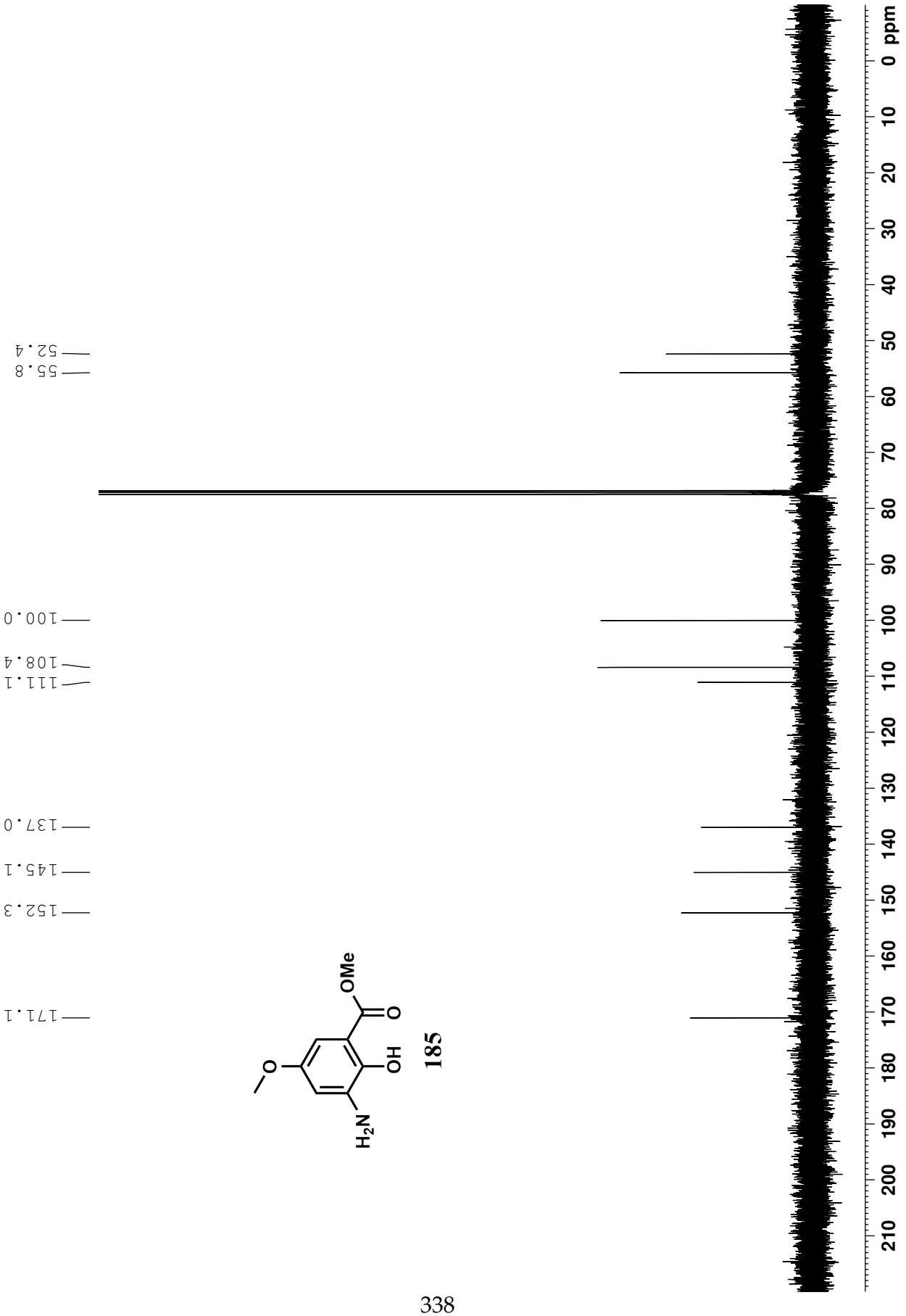

ppm
1
2
3
4
5
6
7
8
9
10
11
3.2
3.2
1.0
1.1
1.0
1.0
OMe
O
OH
O
280

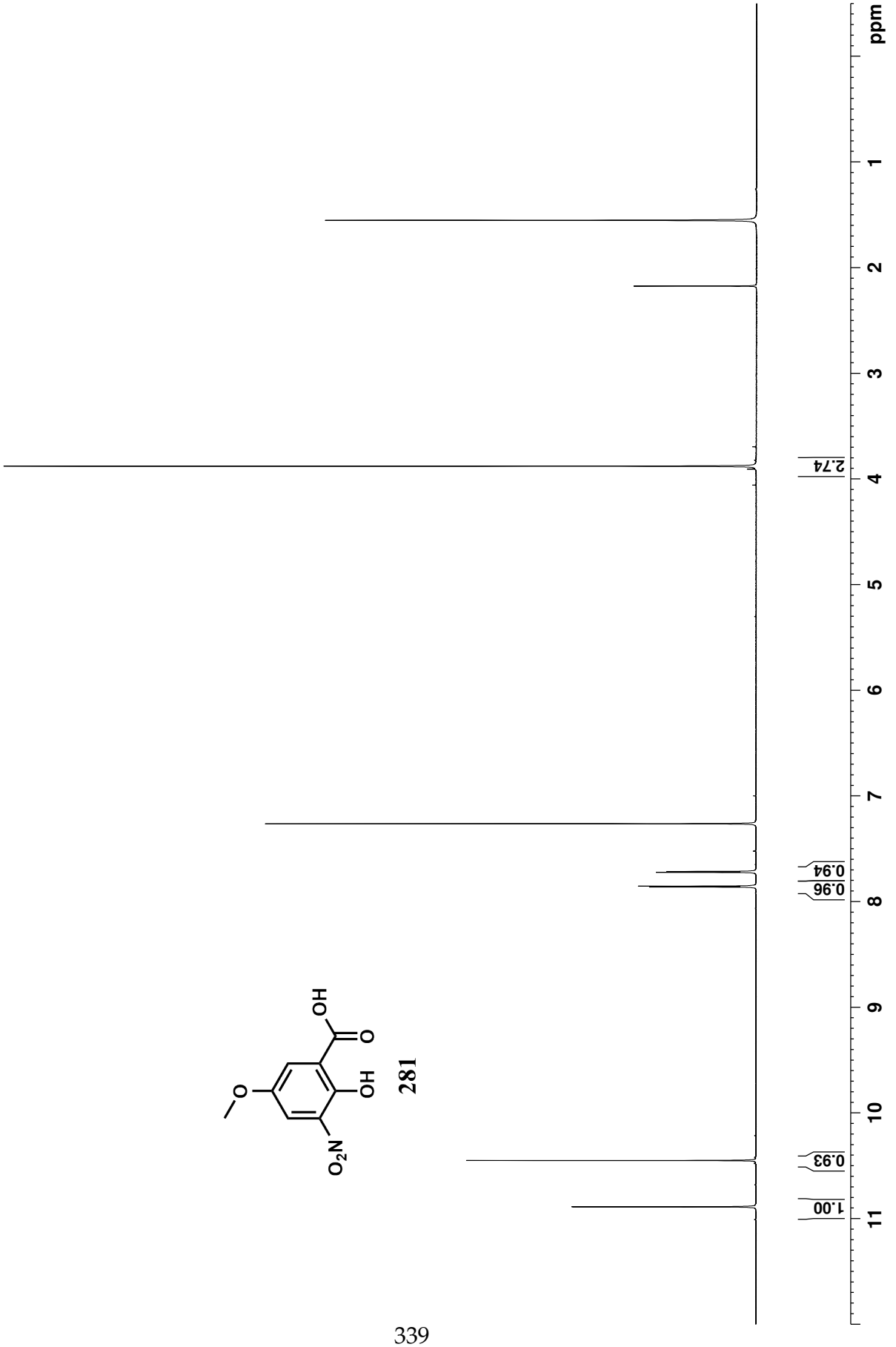


184

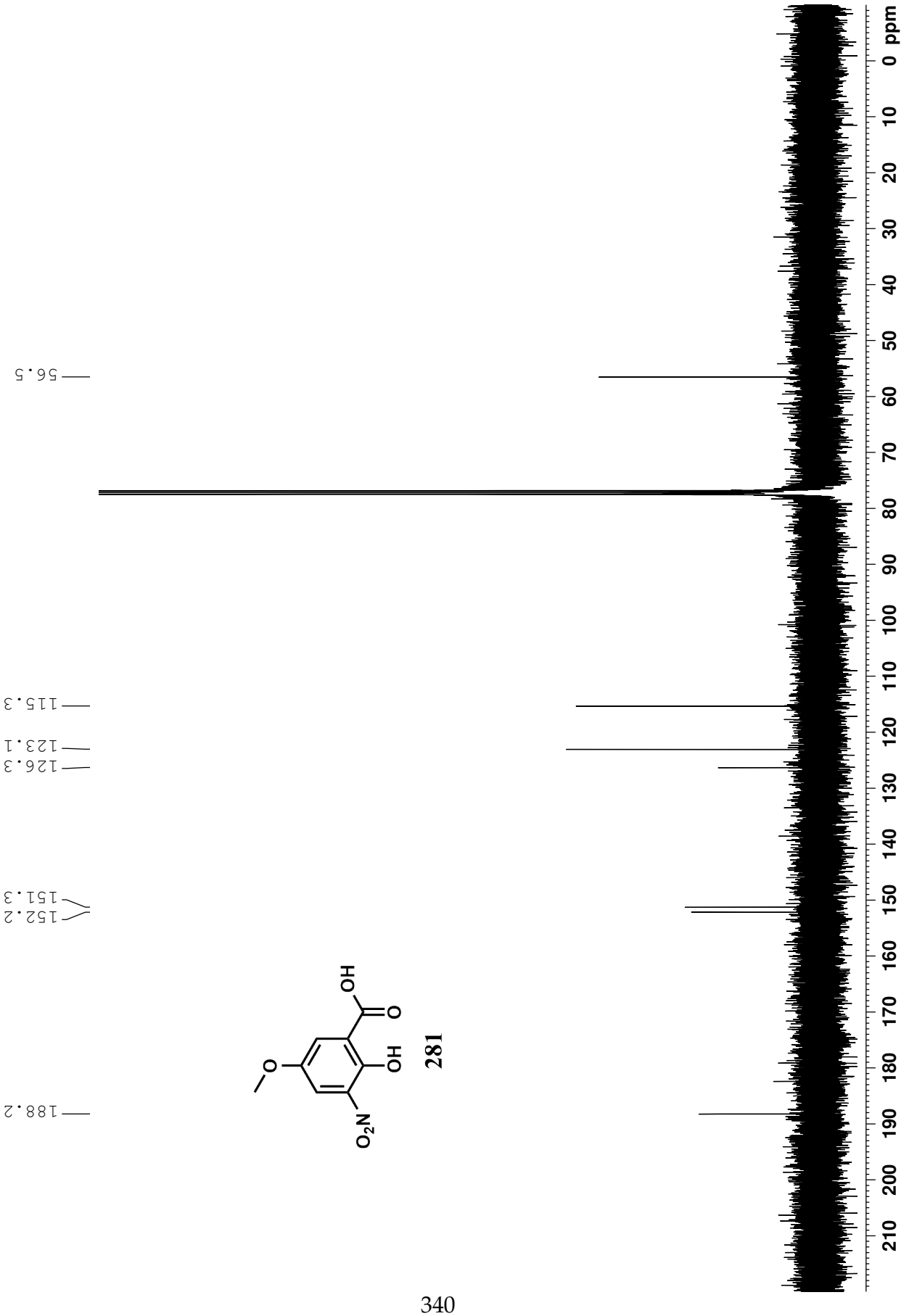


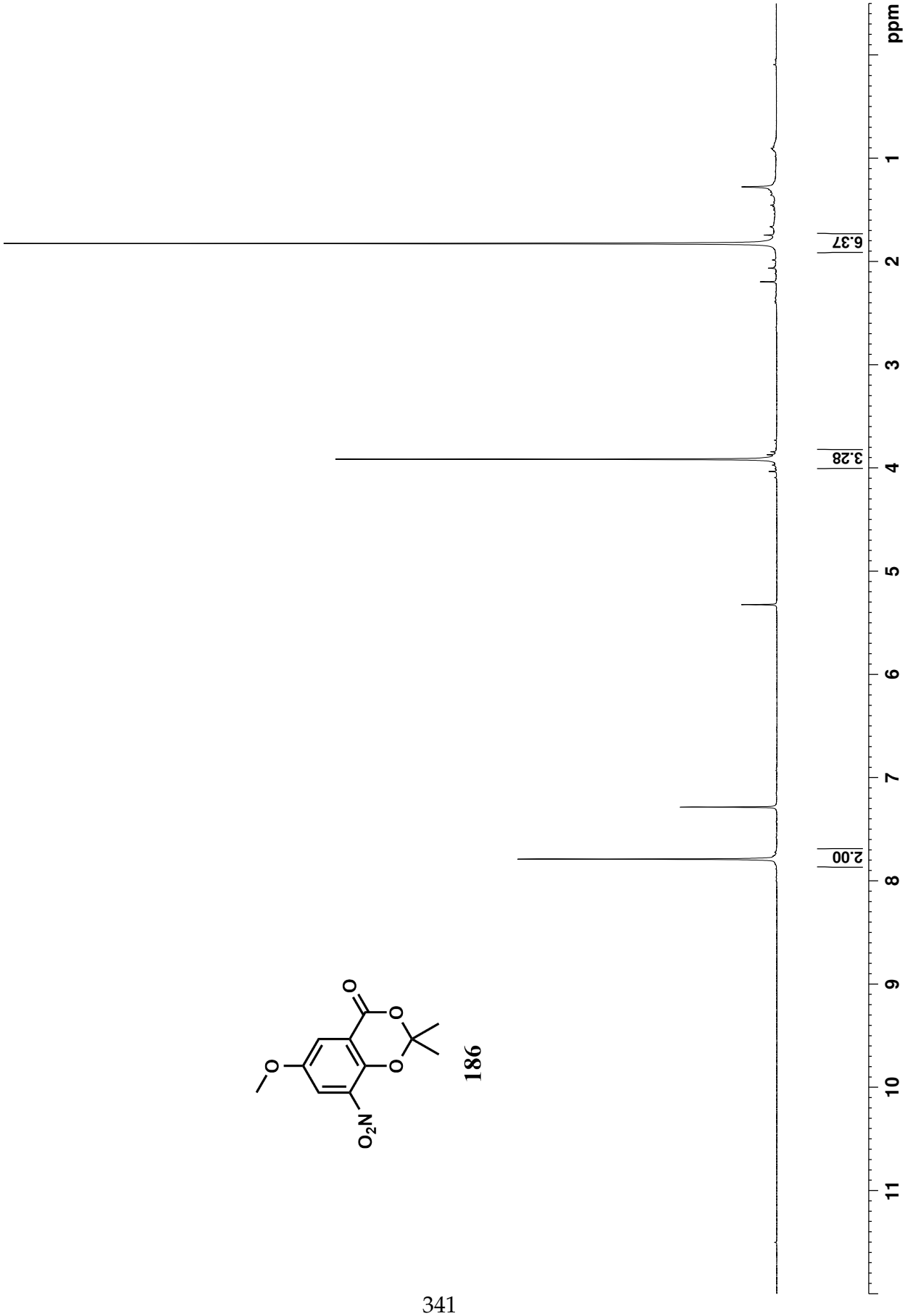
185


52.4
55.8
100.0
108.4
111.1
137.0
145.1
152.3
171.1
OMe
O
OH
O
H2N
185
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

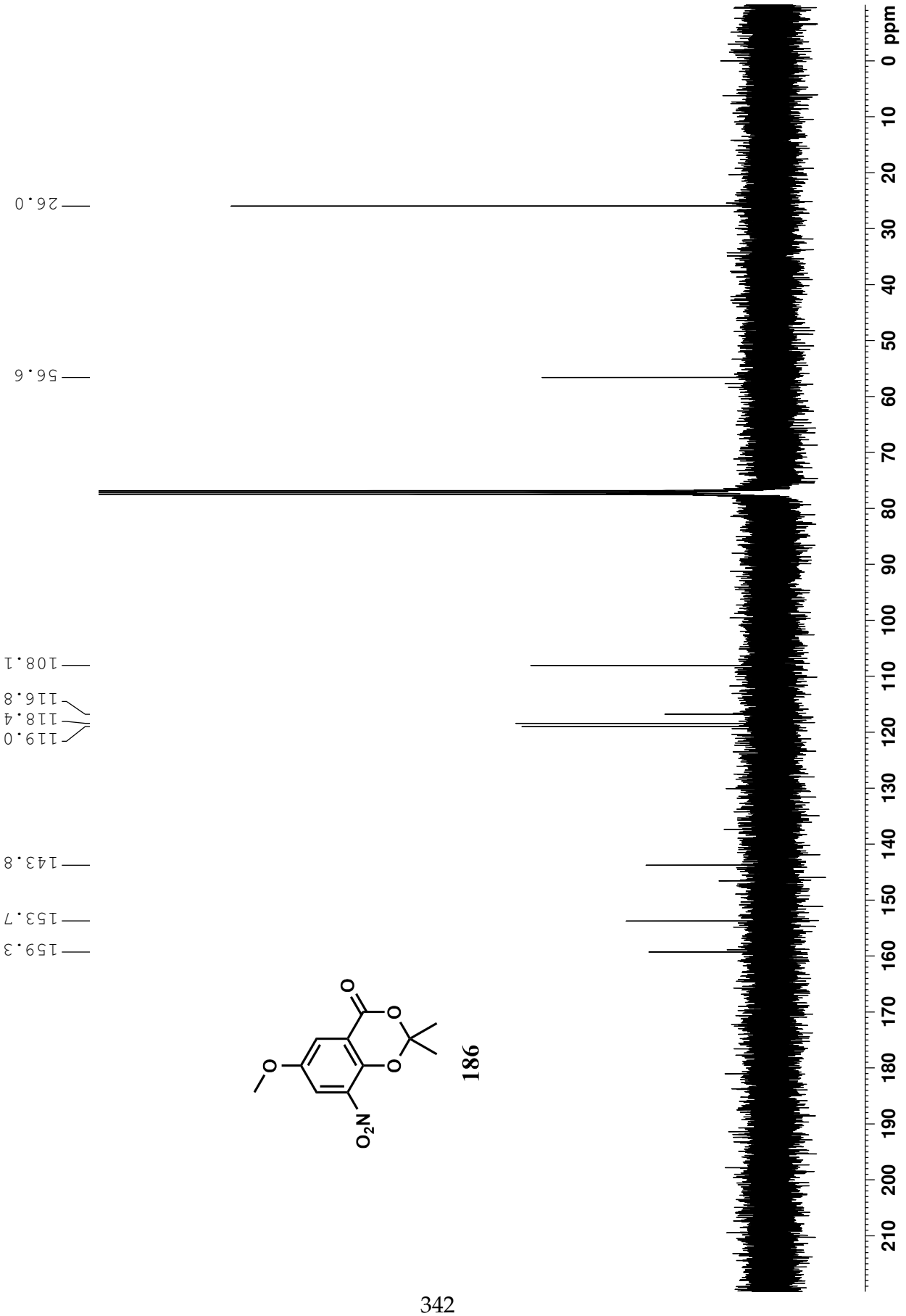


281

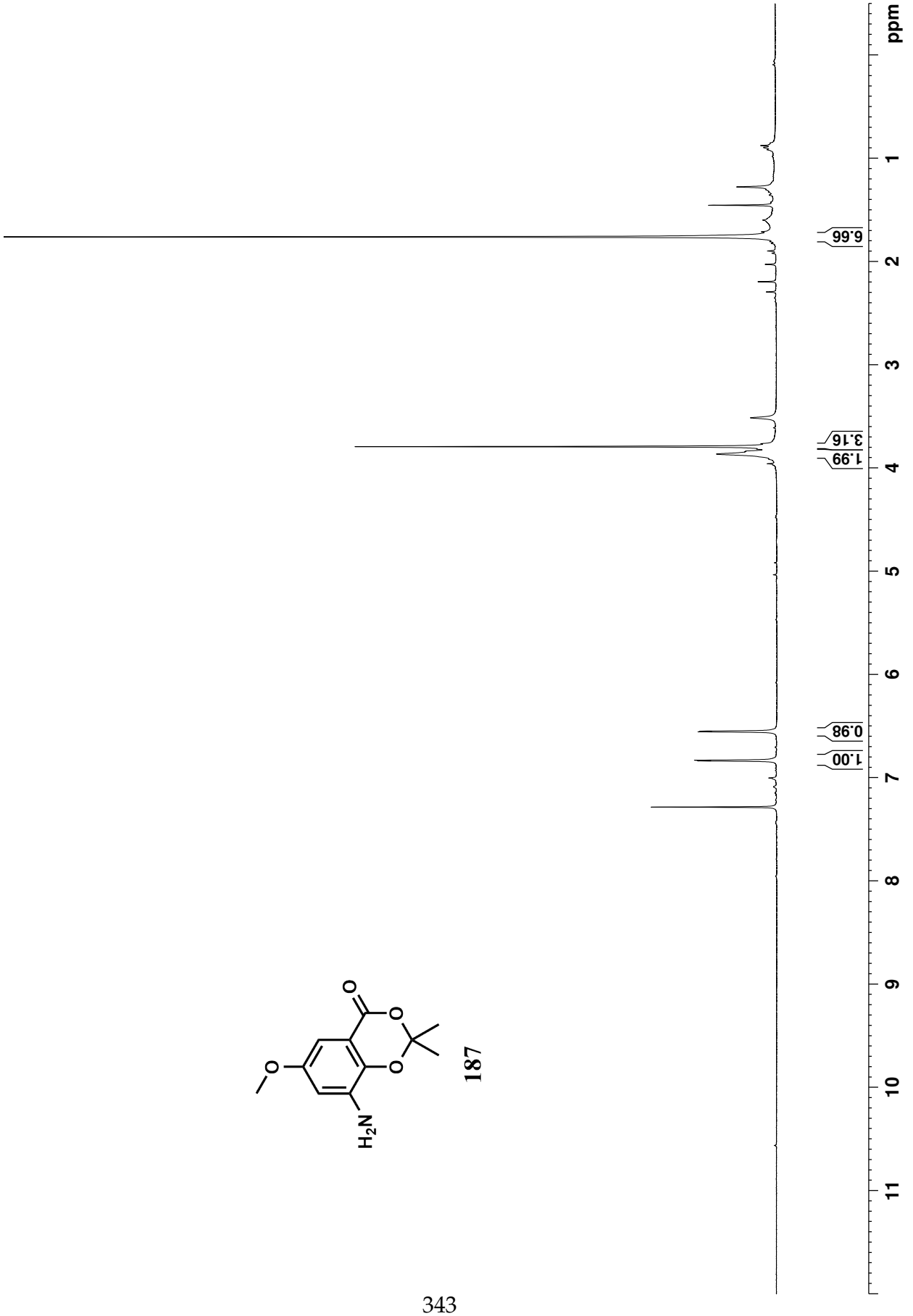

56.5
115.3
123.1
126.3
151.3
152.2
188.2
OH
O
OH
O
O2N
281
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210



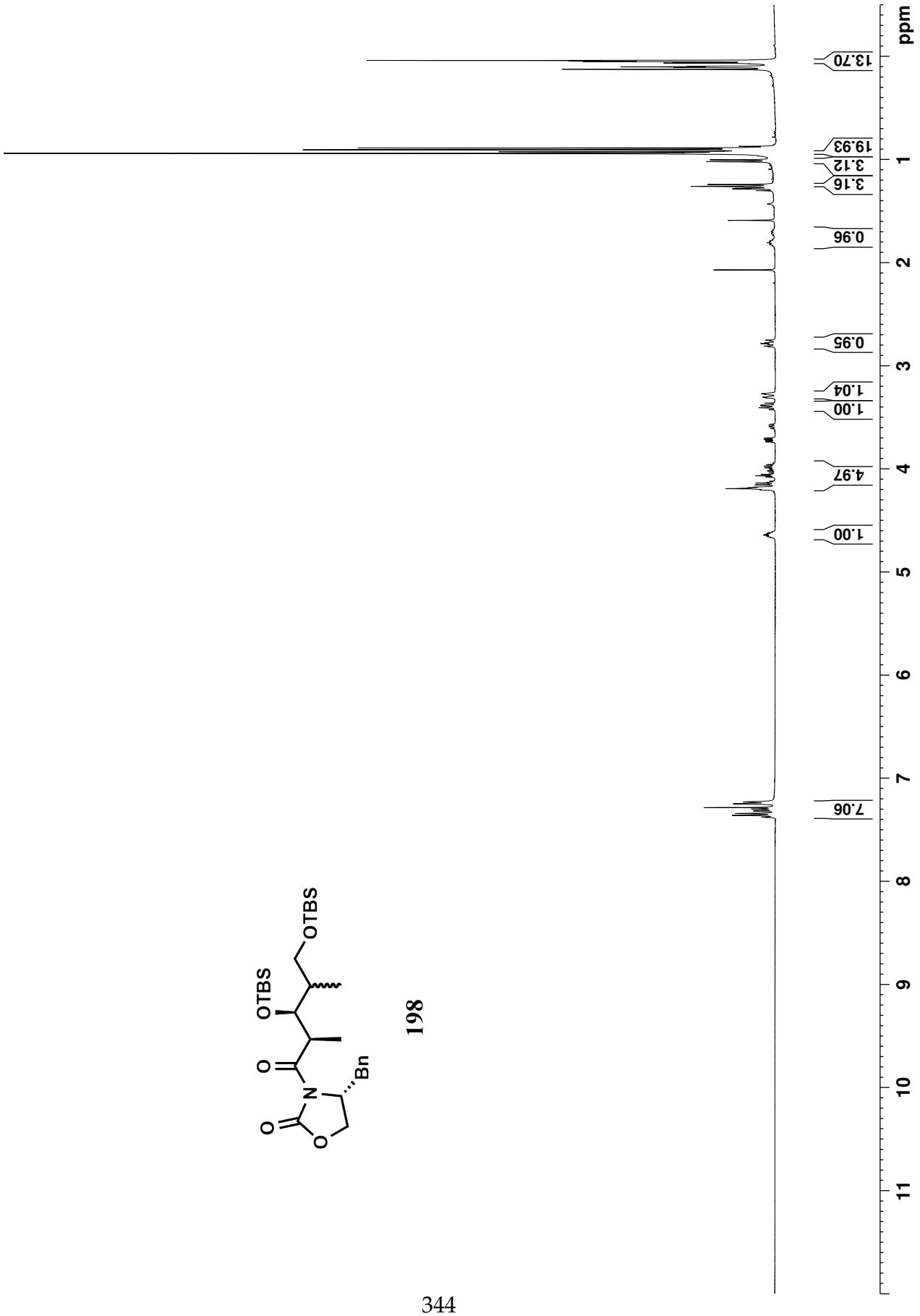
186


26.0
56.6
108.1
116.8
118.4
119.0
143.8
153.7
159.3
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
O
O
O
O2N

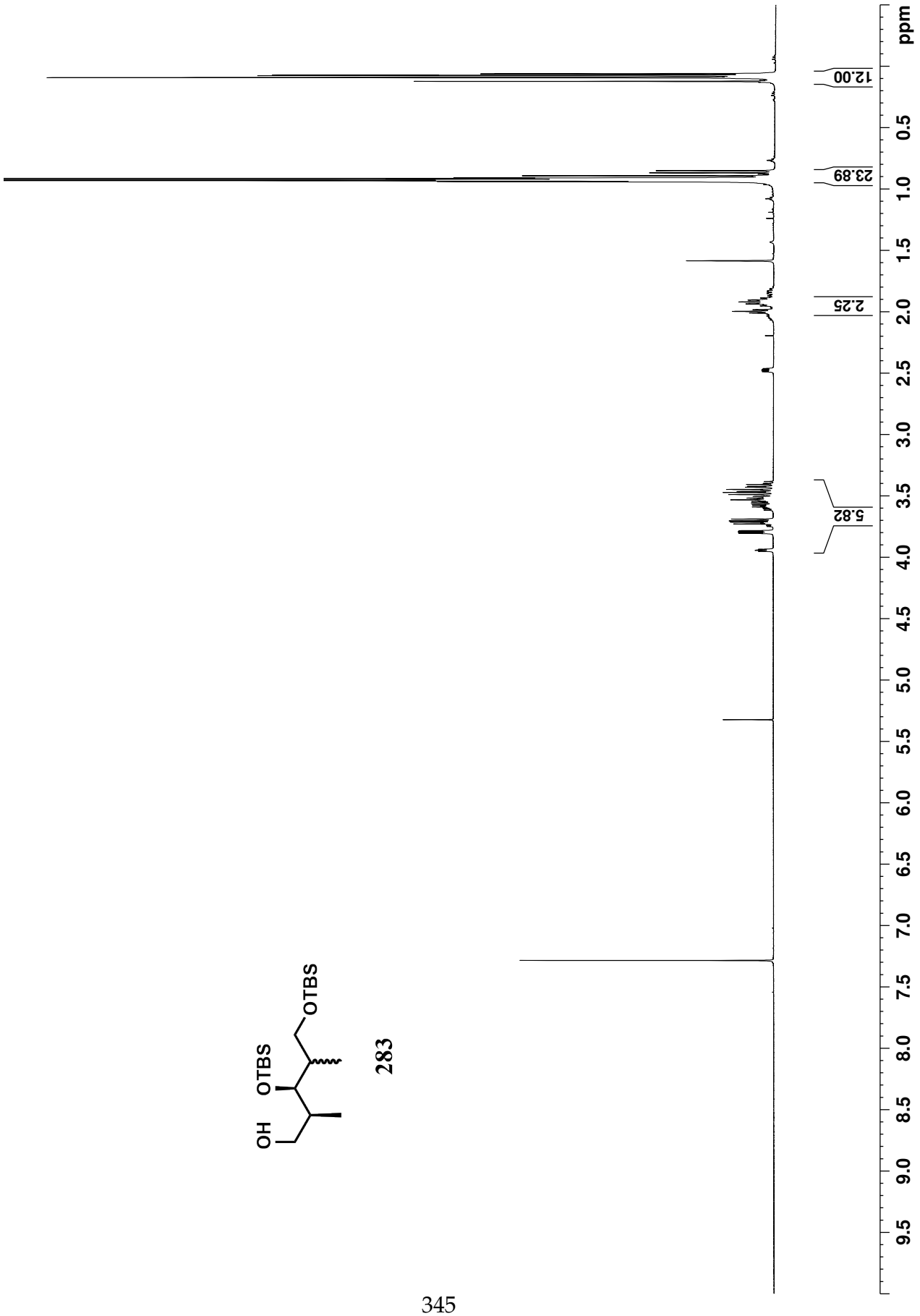
186

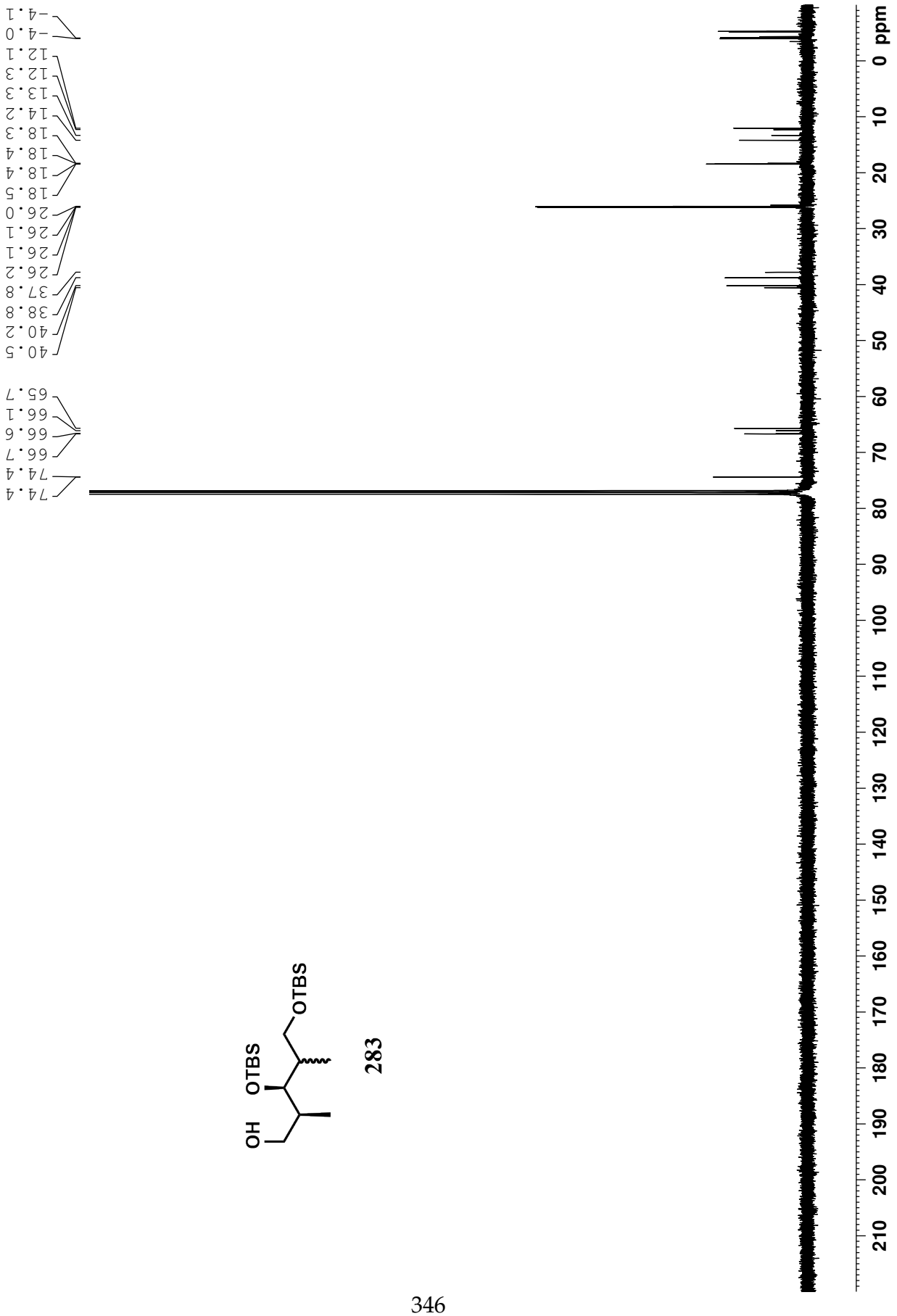


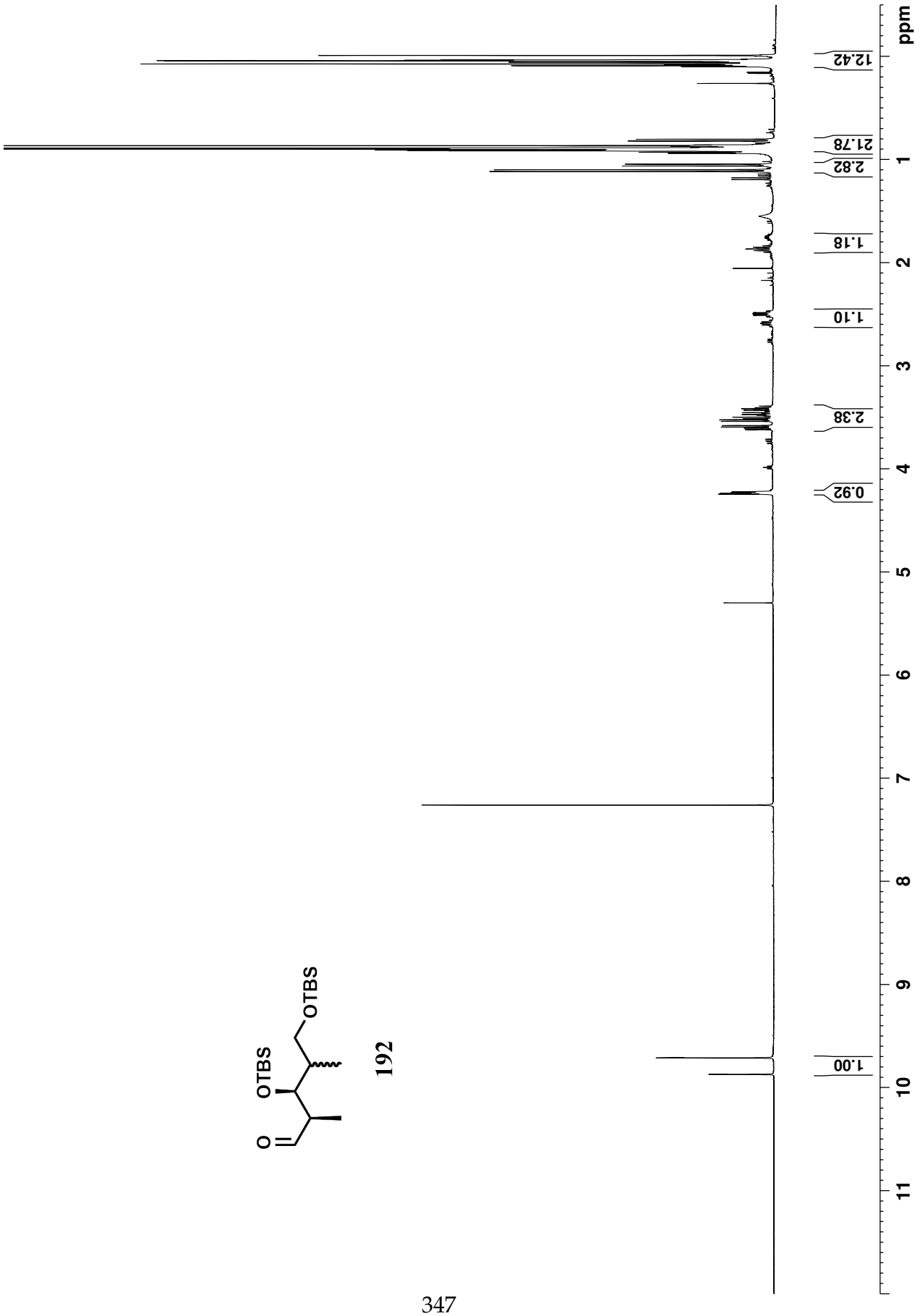
187


13.70
19.93
3.12
3.16
0.96
0.95
1.04
1.00
4.97
1.00
7.06
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
OTBS
O
N
Bn
O
O

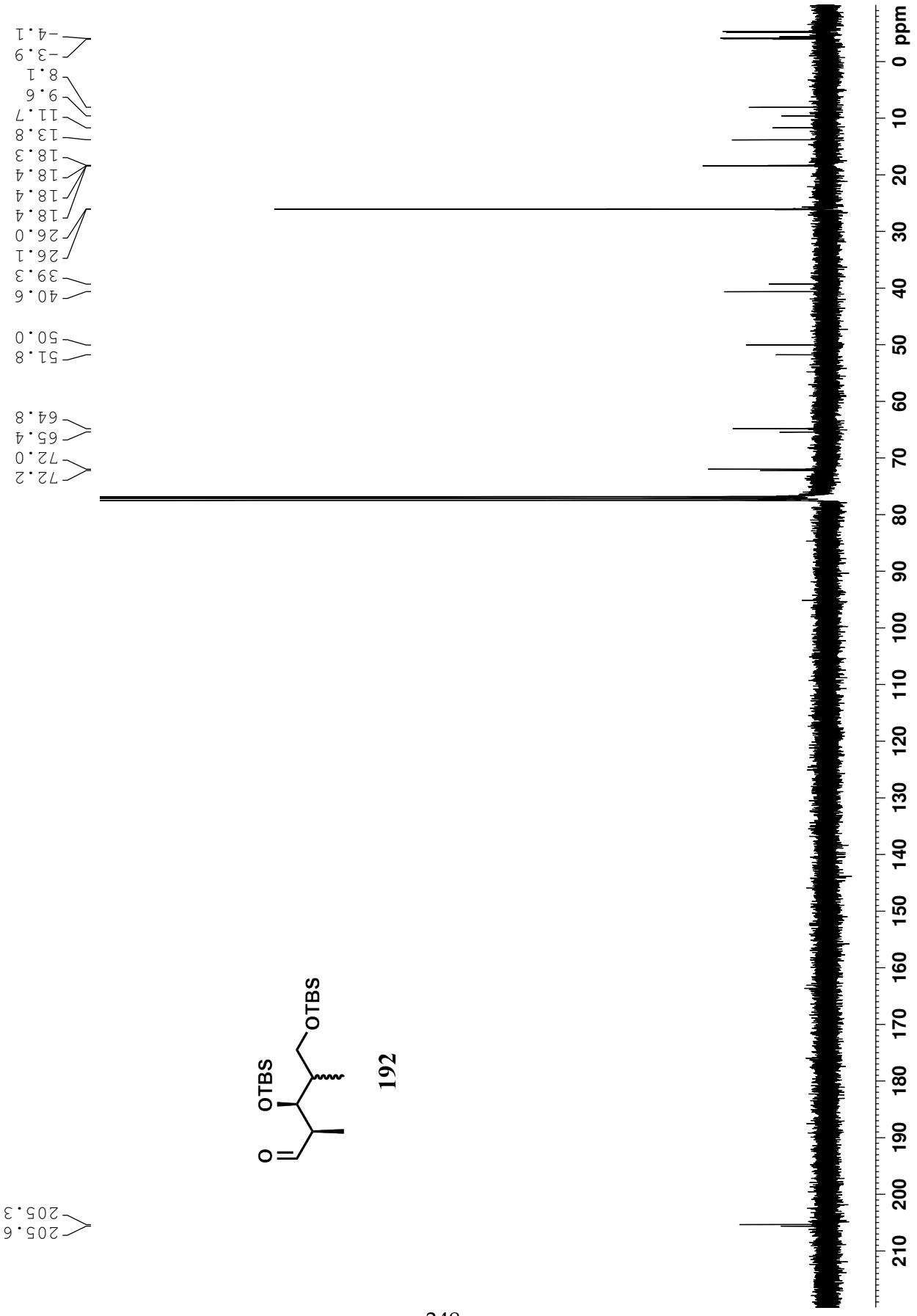
198

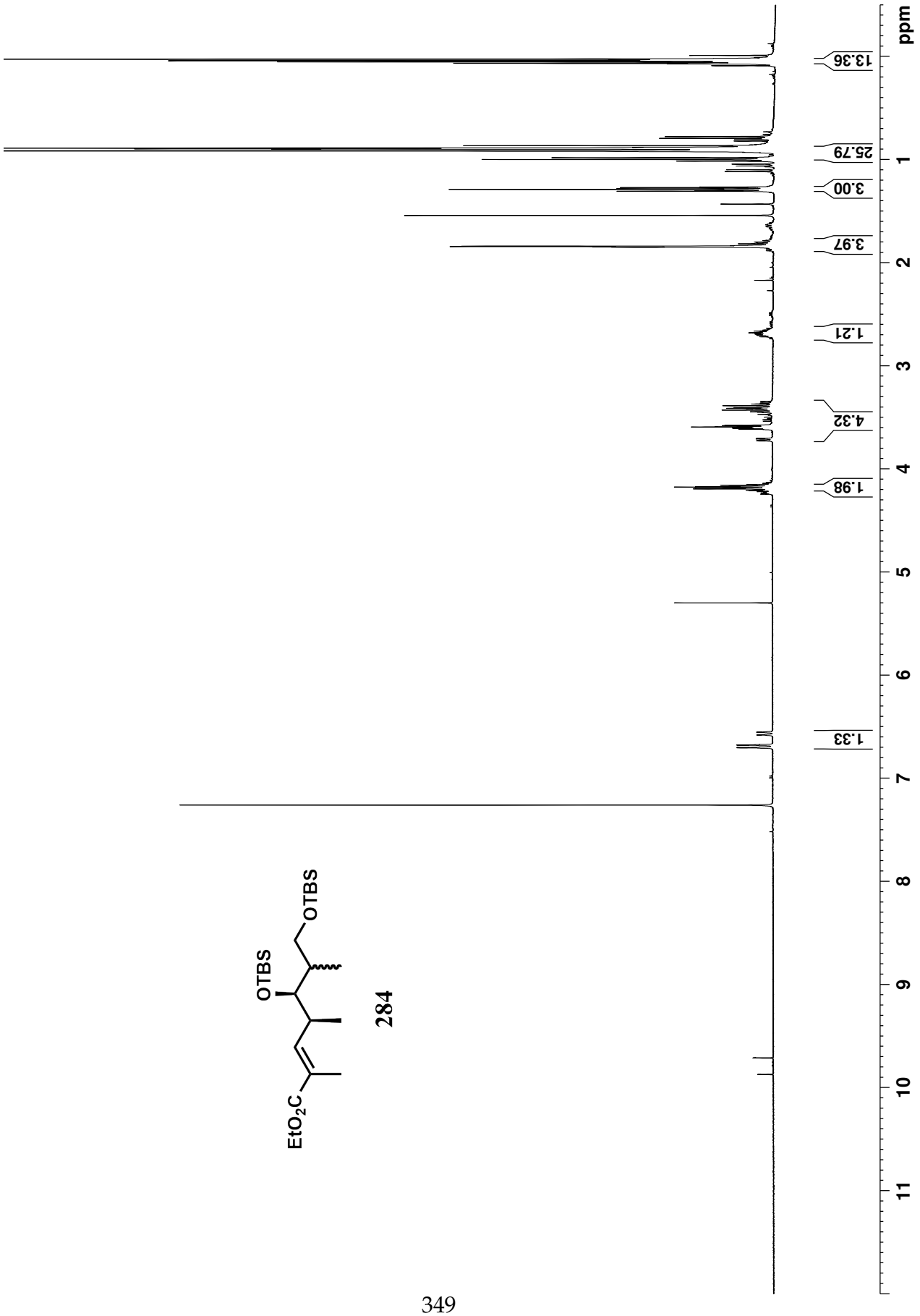

12.00
23.89
2.25
5.82
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
OTBS
OTBS
OH
283

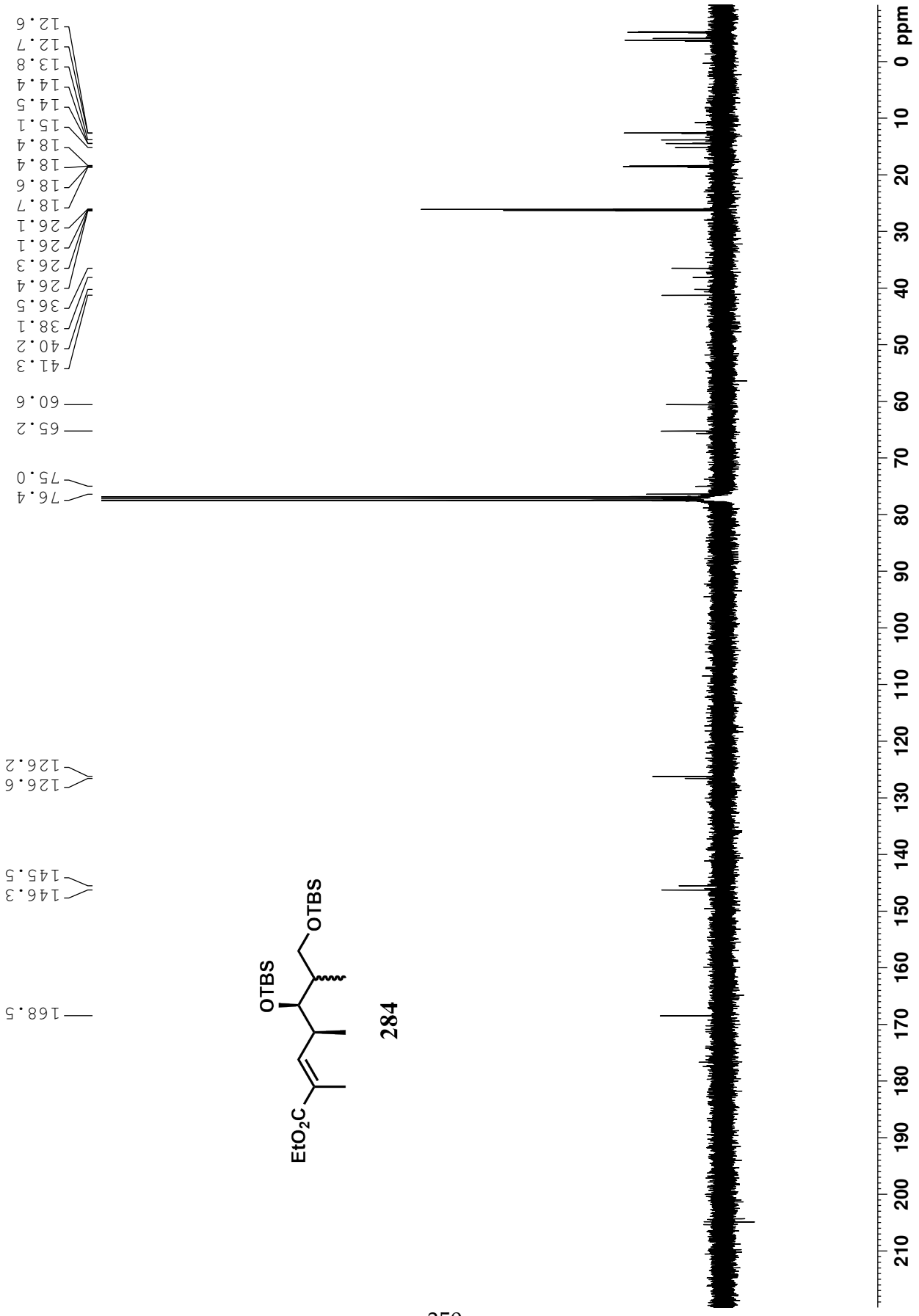

-4.1
-4.0
12.1
12.3
13.3
14.2
18.3
18.4
18.4
18.5
26.0
26.1
26.1
26.2
37.8
38.8
40.2
40.5
65.7
66.1
66.6
66.7
74.4
74.4
OH
OTBS
OTBS
283
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

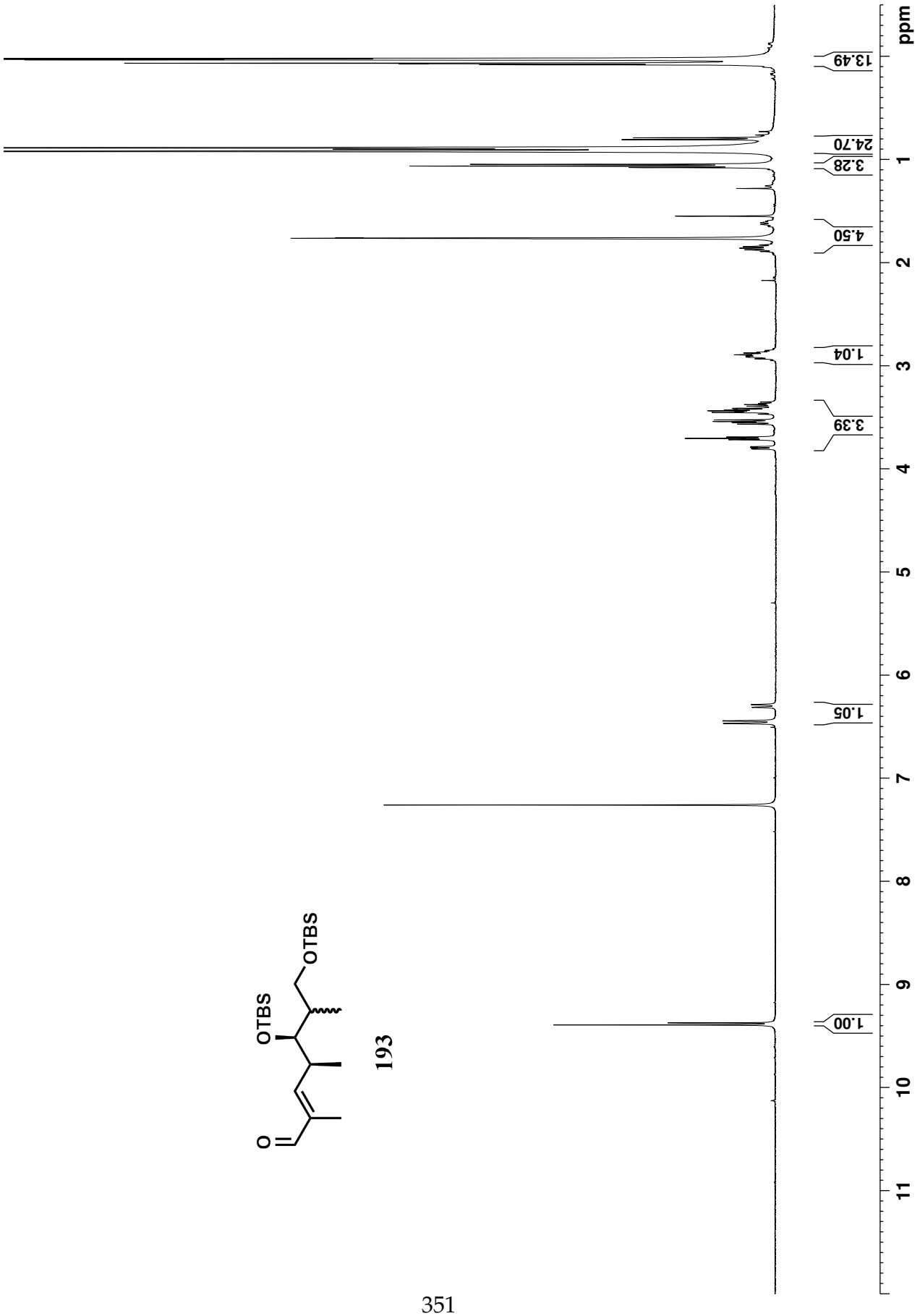

12.42
21.78
2.82
1.18
1.10
2.38
0.92
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
OTBS
O

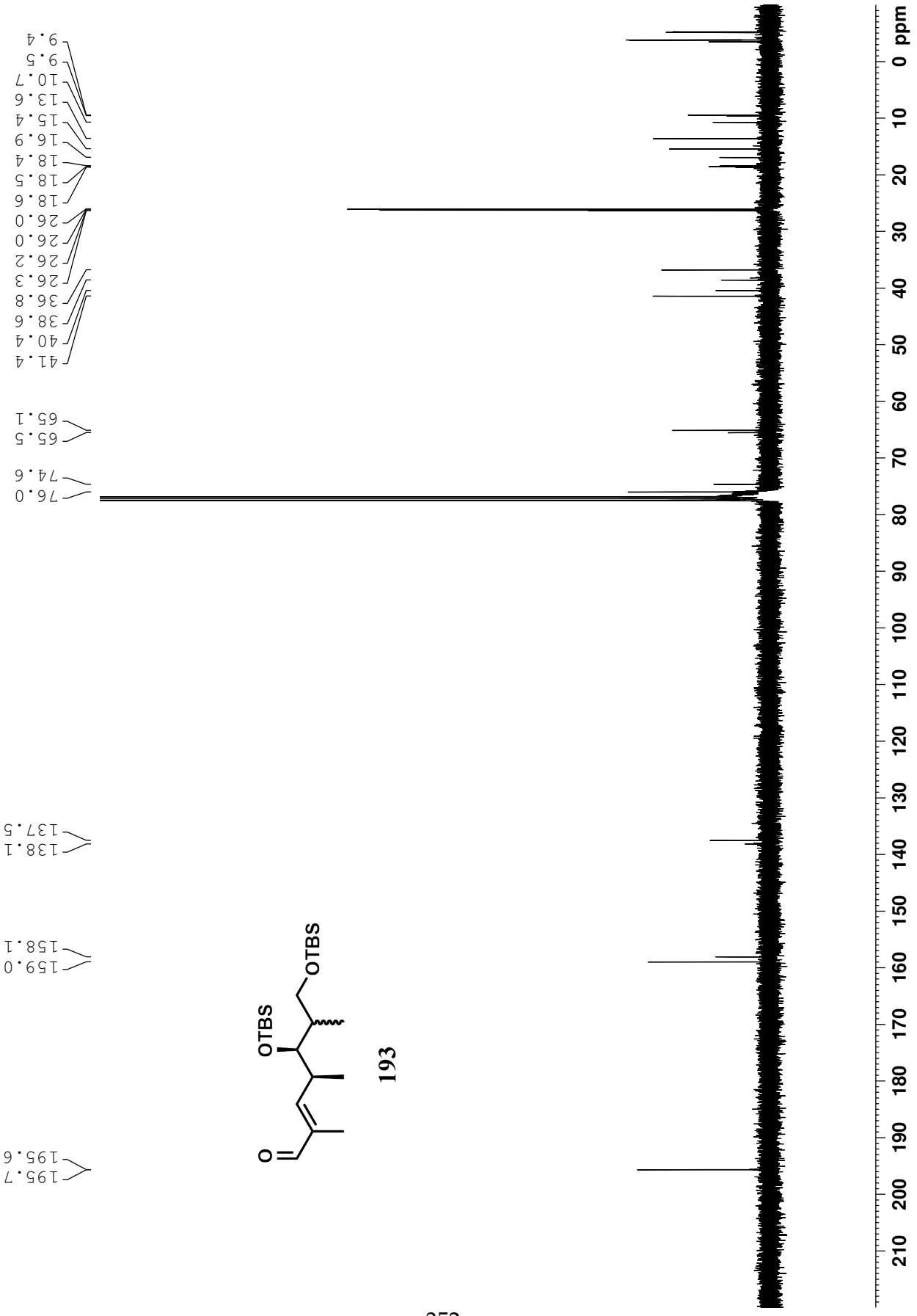
192

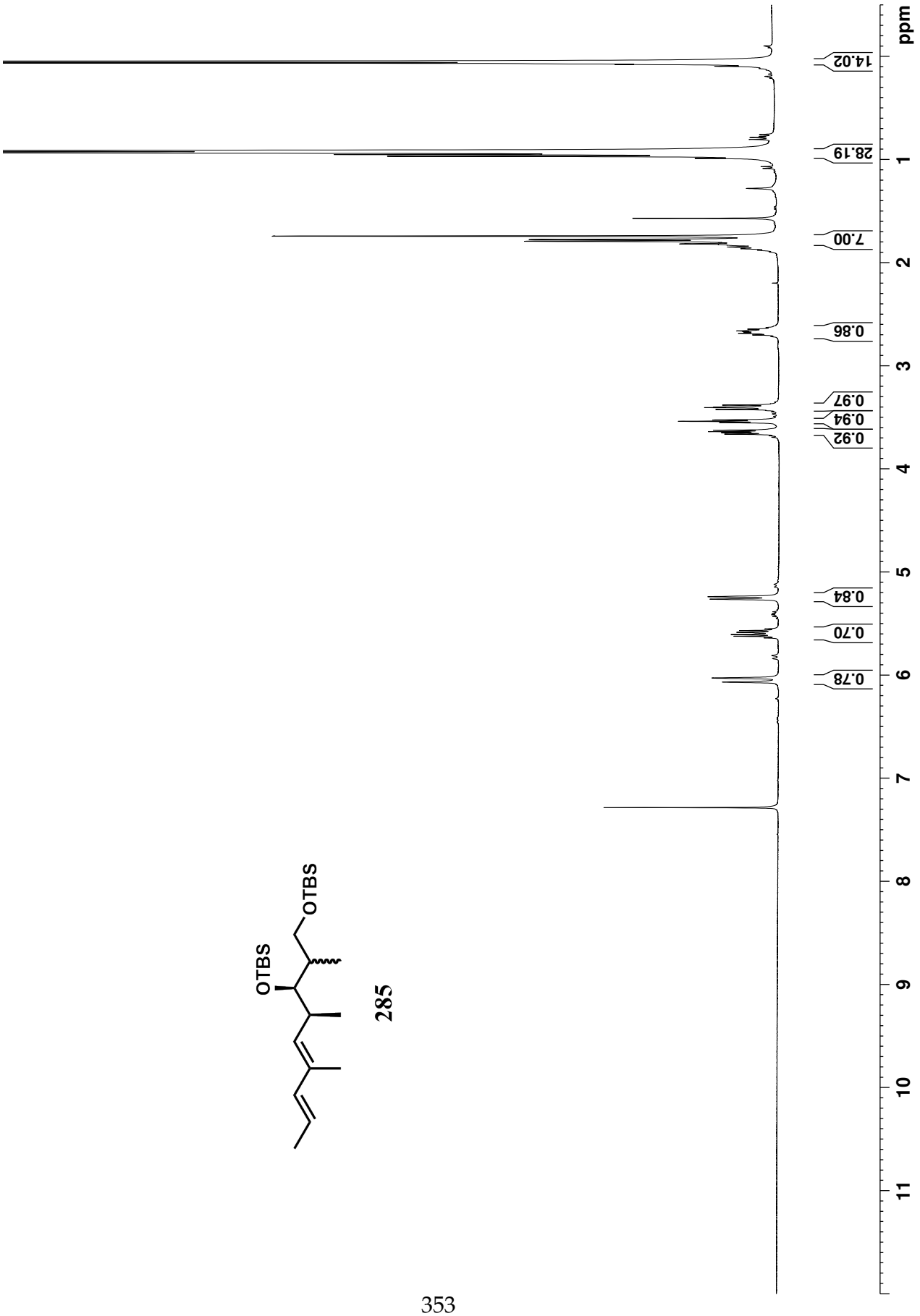

205.6
205.3
72.2
72.0
65.4
64.8
51.8
50.0
40.6
39.3
26.1
26.0
18.4
18.4
18.4
18.3
13.8
11.7
9.6
8.1
-3.9
-4.1
OTBS
OTBS
O
192
0 ppm

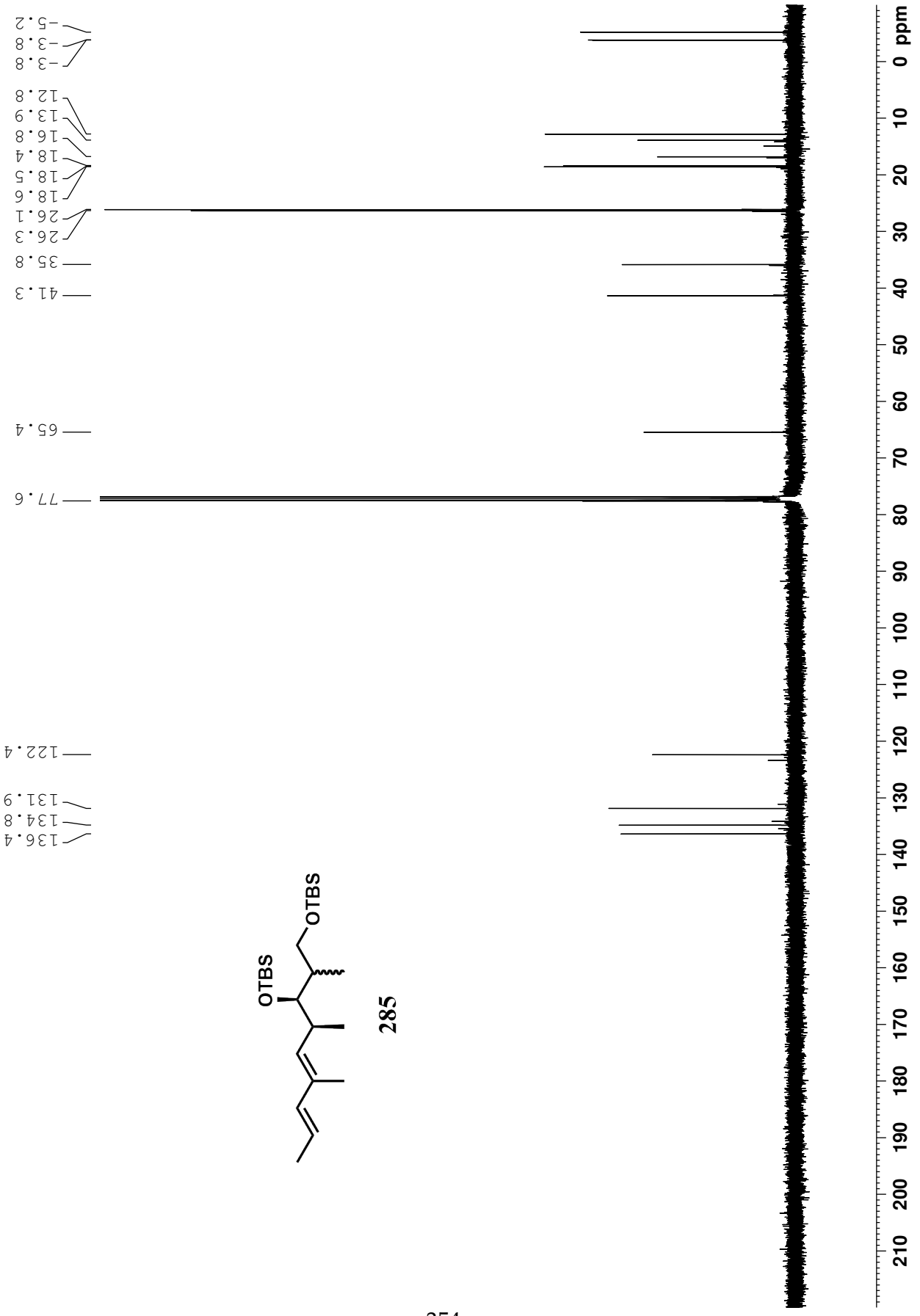

13.36
25.79
3.00
3.97
1.21
4.32
1.98
1.33
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
OTBS
EtO2C
284

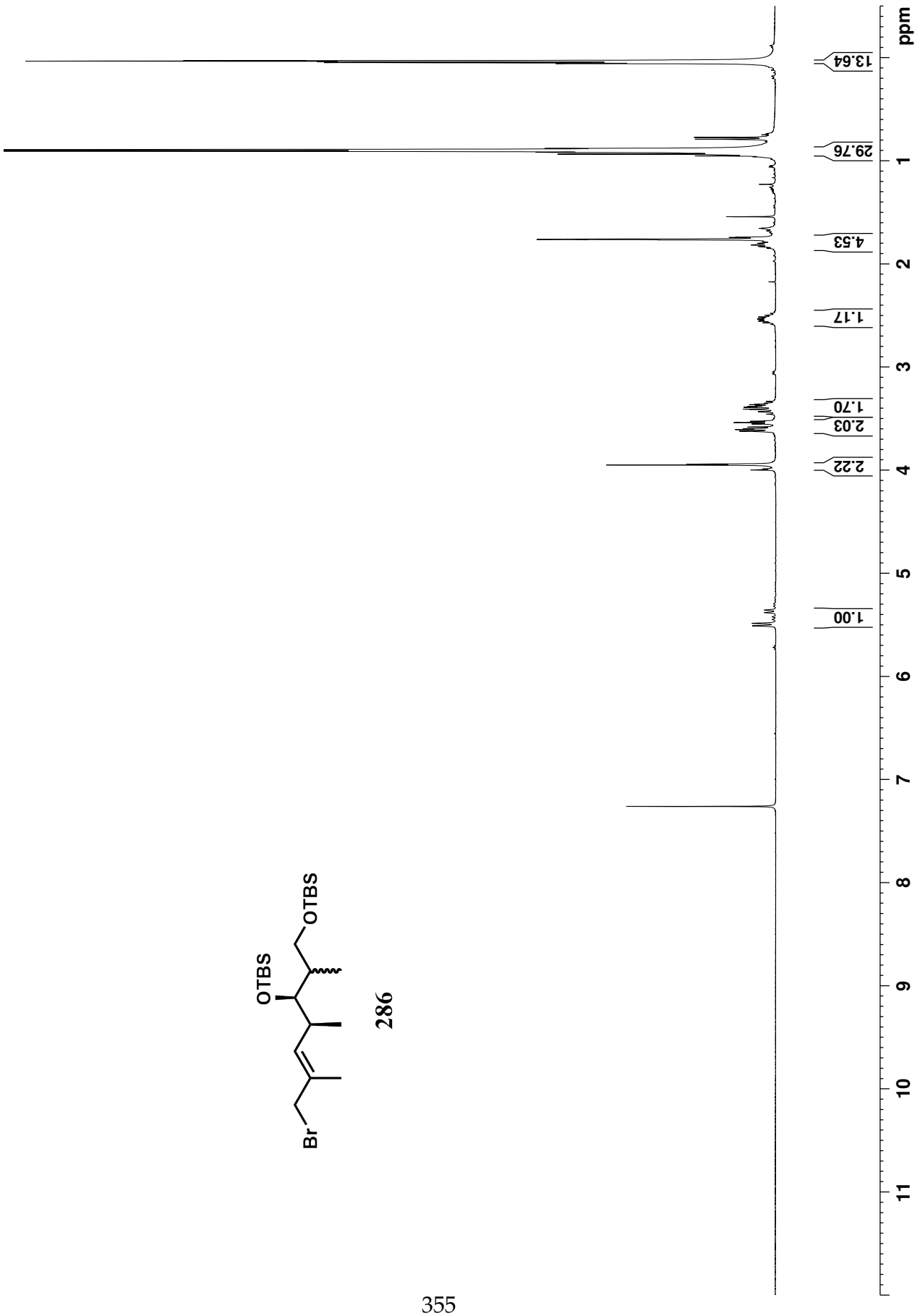

12.6
12.7
13.8
14.4
14.5
15.1
18.4
18.4
18.6
18.7
26.1
26.1
26.3
26.4
36.5
38.1
40.2
41.3
60.6
65.2
75.0
76.4
126.2
126.6
145.5
146.3
168.5
OTBS
OTBS
EtO2C
284
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


OTBS
OTBS
O
193
13.49
24.70
3.28
4.50
1.04
3.39
1.05
1.00
ppm

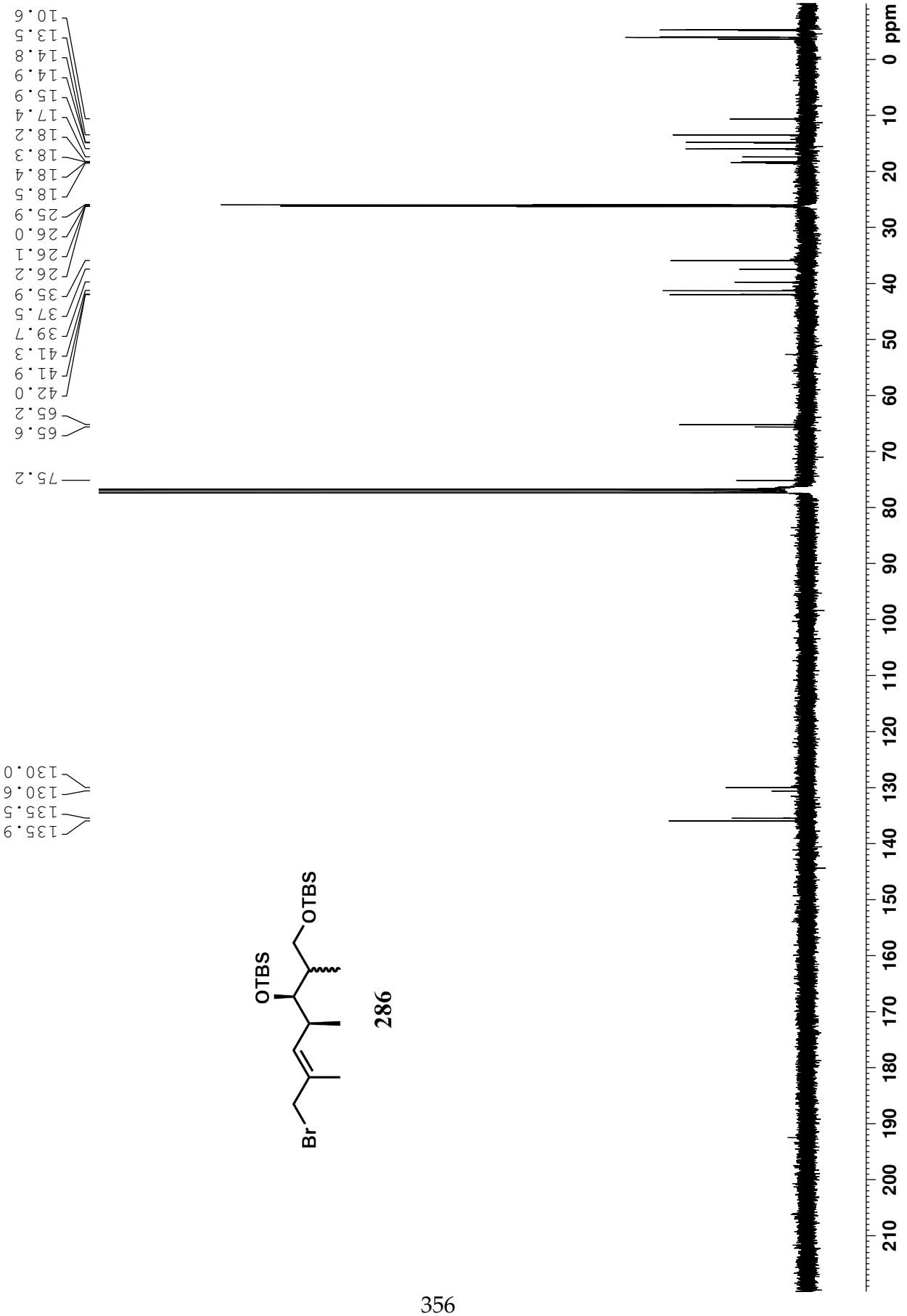

9.4
9.5
10.7
13.6
15.4
16.9
18.4
18.5
18.6
26.0
26.0
26.2
26.3
36.8
38.6
40.4
41.4
65.1
65.5
74.6
76.0
137.5
138.1
158.1
159.0
195.6
195.7
OTBS
OTBS
O
193
0 ppm

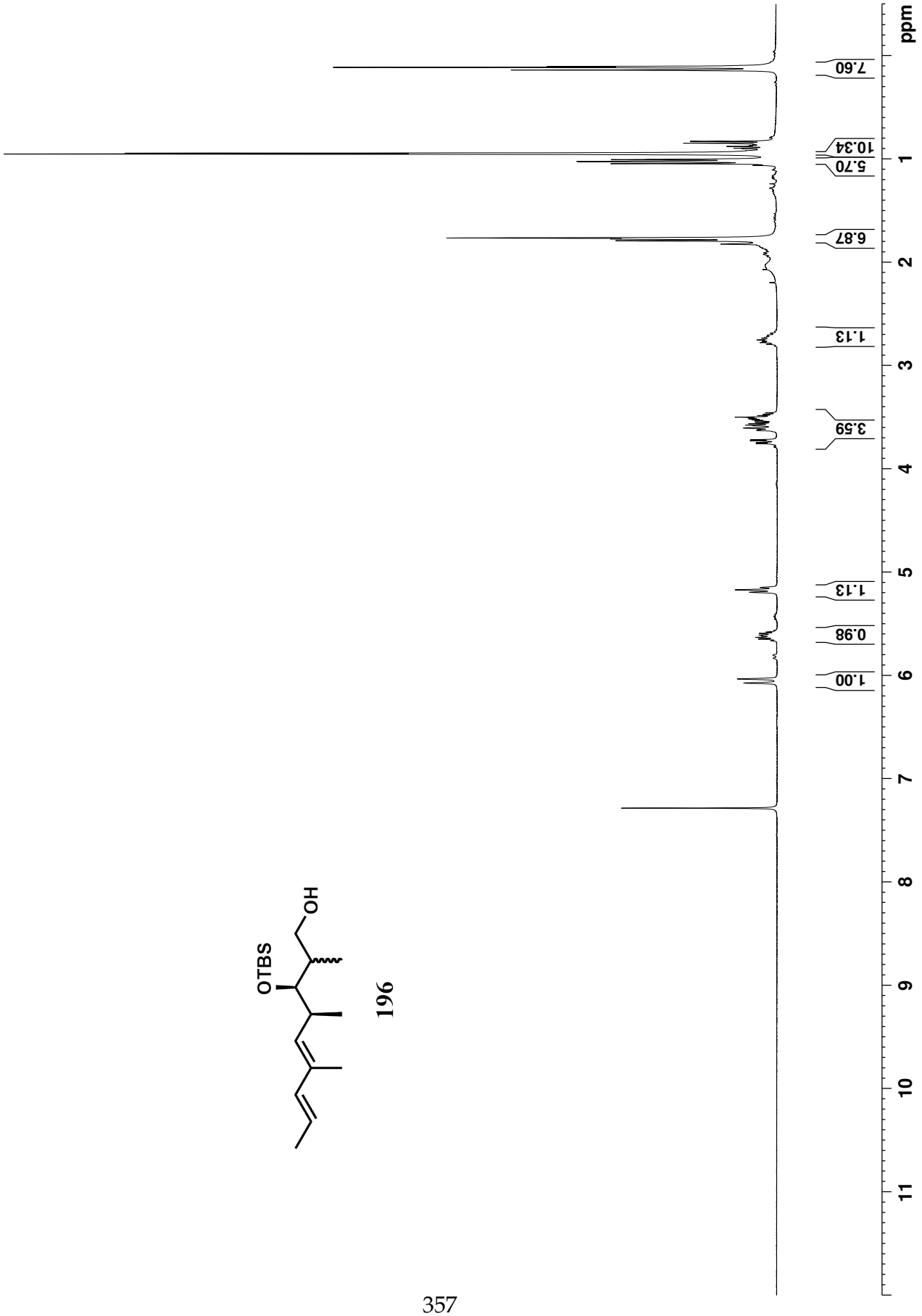

14.02
28.19
7.00
0.86
0.97
0.94
0.92
0.84
0.70
0.78
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
OTBS
285

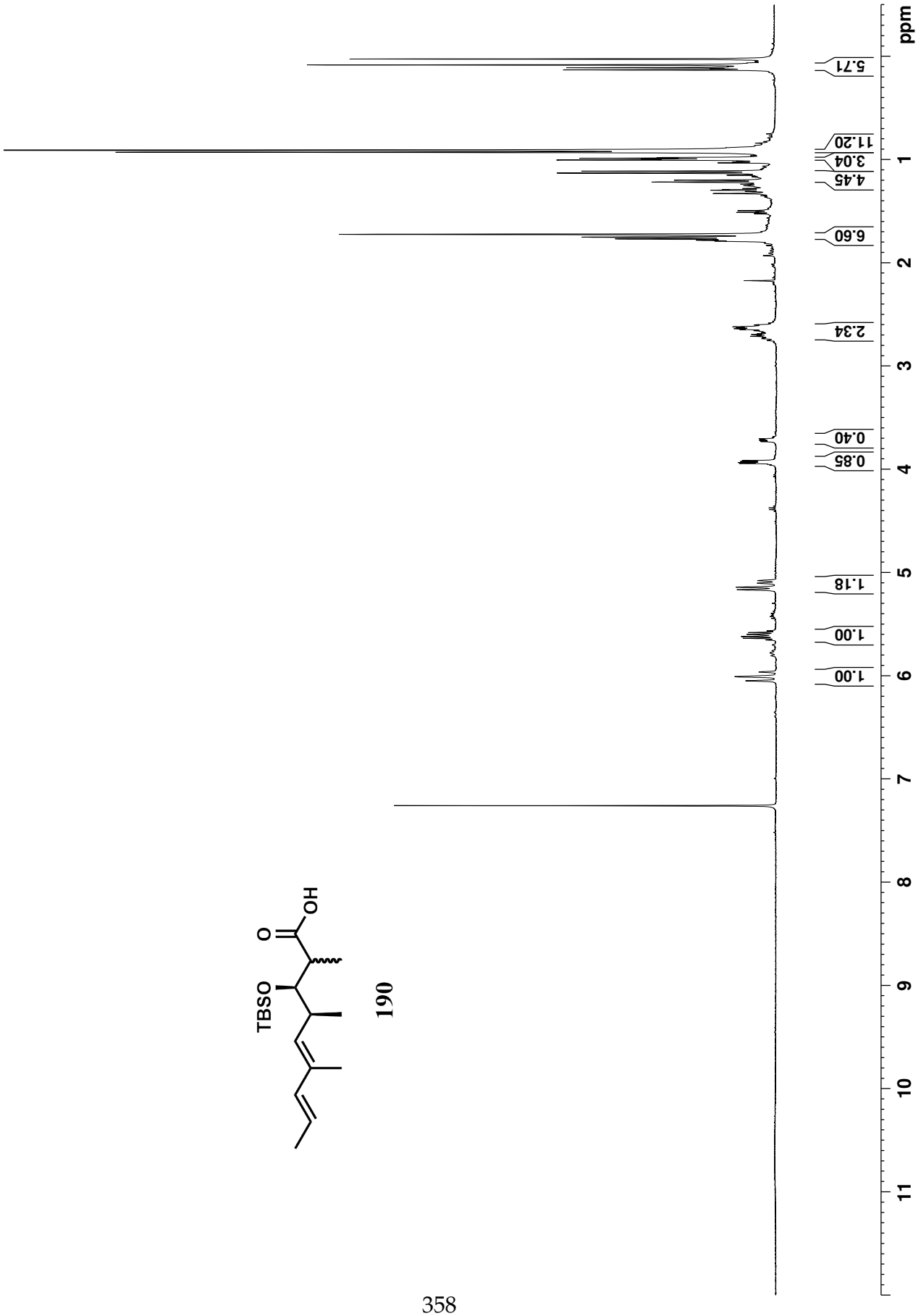

-5.2
-3.8
-3.8
12.8
13.9
16.8
18.4
18.5
18.6
26.1
26.3
35.8
41.3
65.4
77.6
122.4
131.9
134.8
136.4
OTBS
OTBS
285
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


13.64
29.76
4.53
1.17
1.70
2.03
2.22
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
OTBS
Br

286

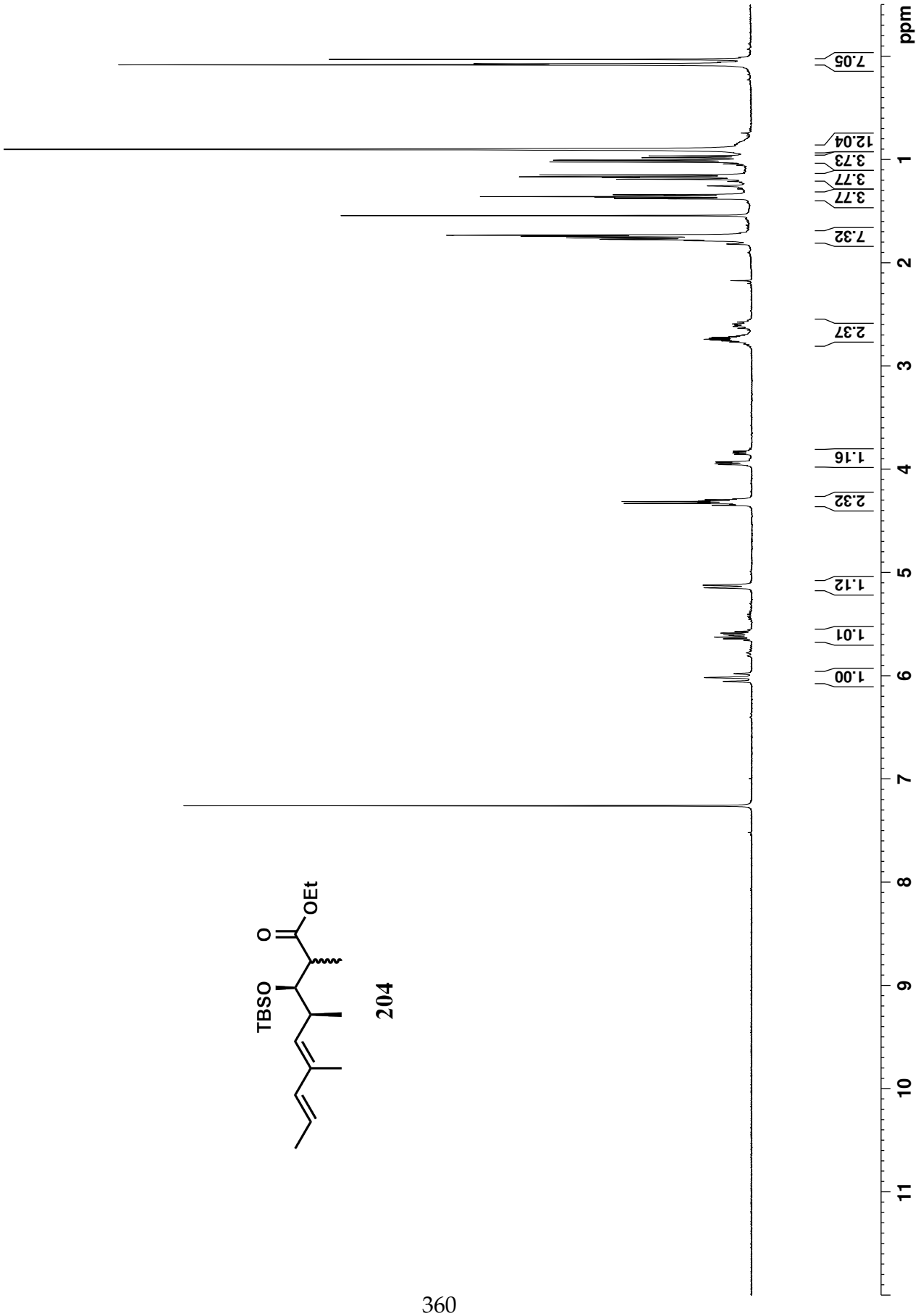

OTBS
OTBS
Br
286
135.9
135.5
130.6
130.0
75.2
65.6
65.2
42.0
41.9
41.3
39.7
37.5
35.9
26.2
26.1
26.0
25.9
18.5
18.4
18.3
18.2
17.4
15.9
14.9
14.8
13.5
10.6
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

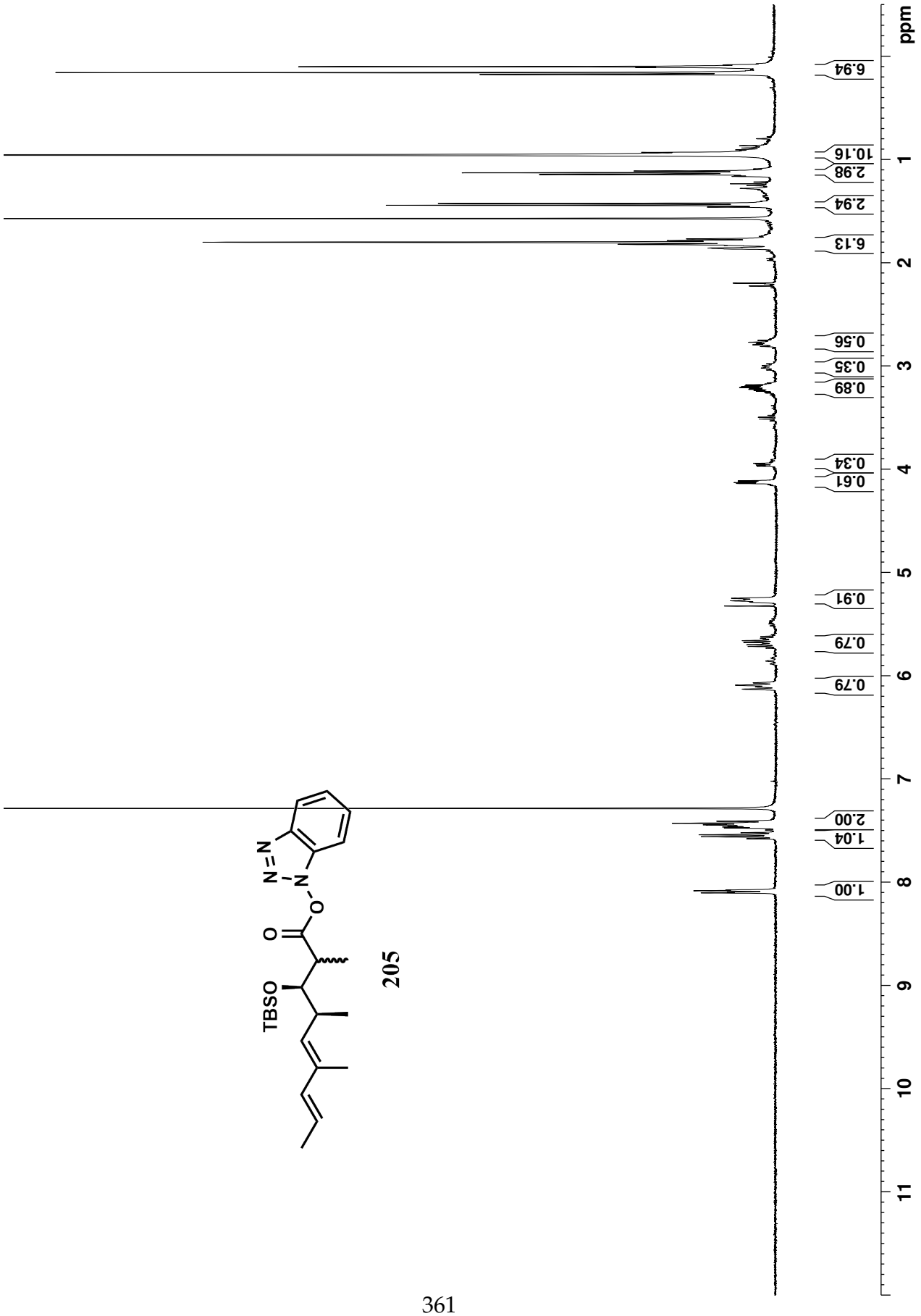

7.60
10.34
5.70
6.87
1.13
3.59
1.13
0.98
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
OH
196

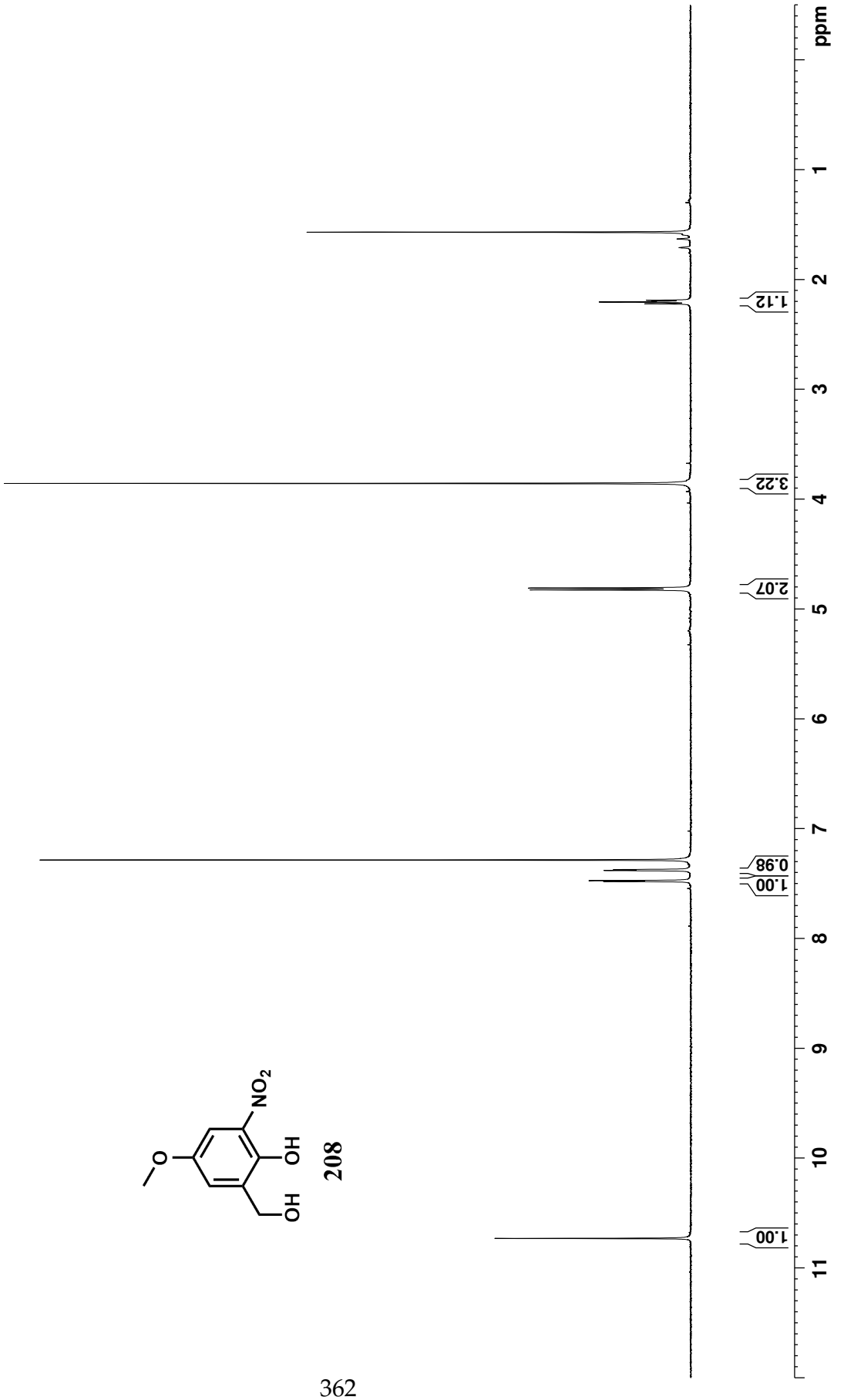

ppm
1
2
3
4
5
6
7
8
9
10
11
5.71
11.20
3.04
4.45
6.60
2.34
0.40
0.85
1.18
1.00
1.00
TBSO
O
OH

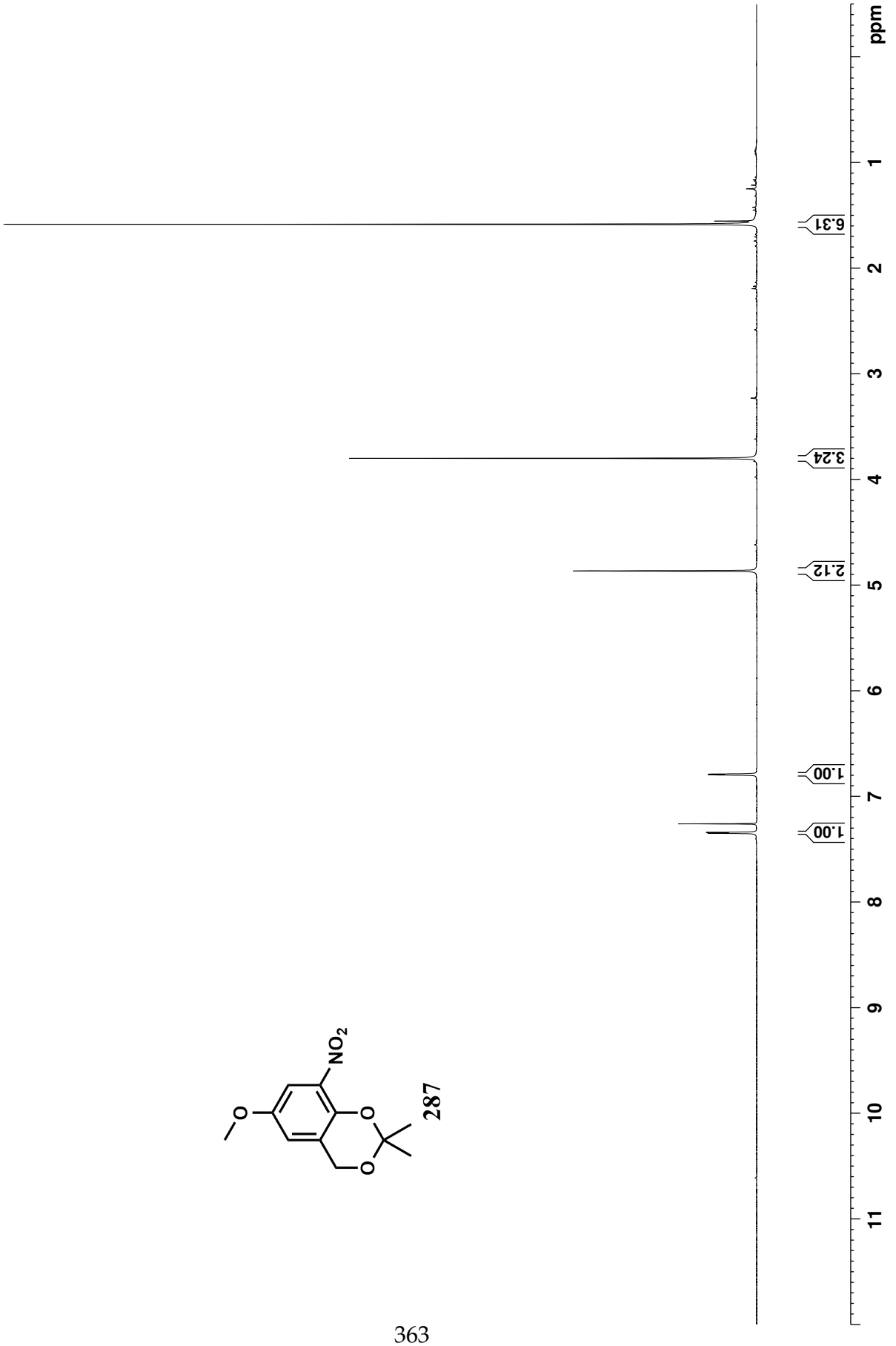
190

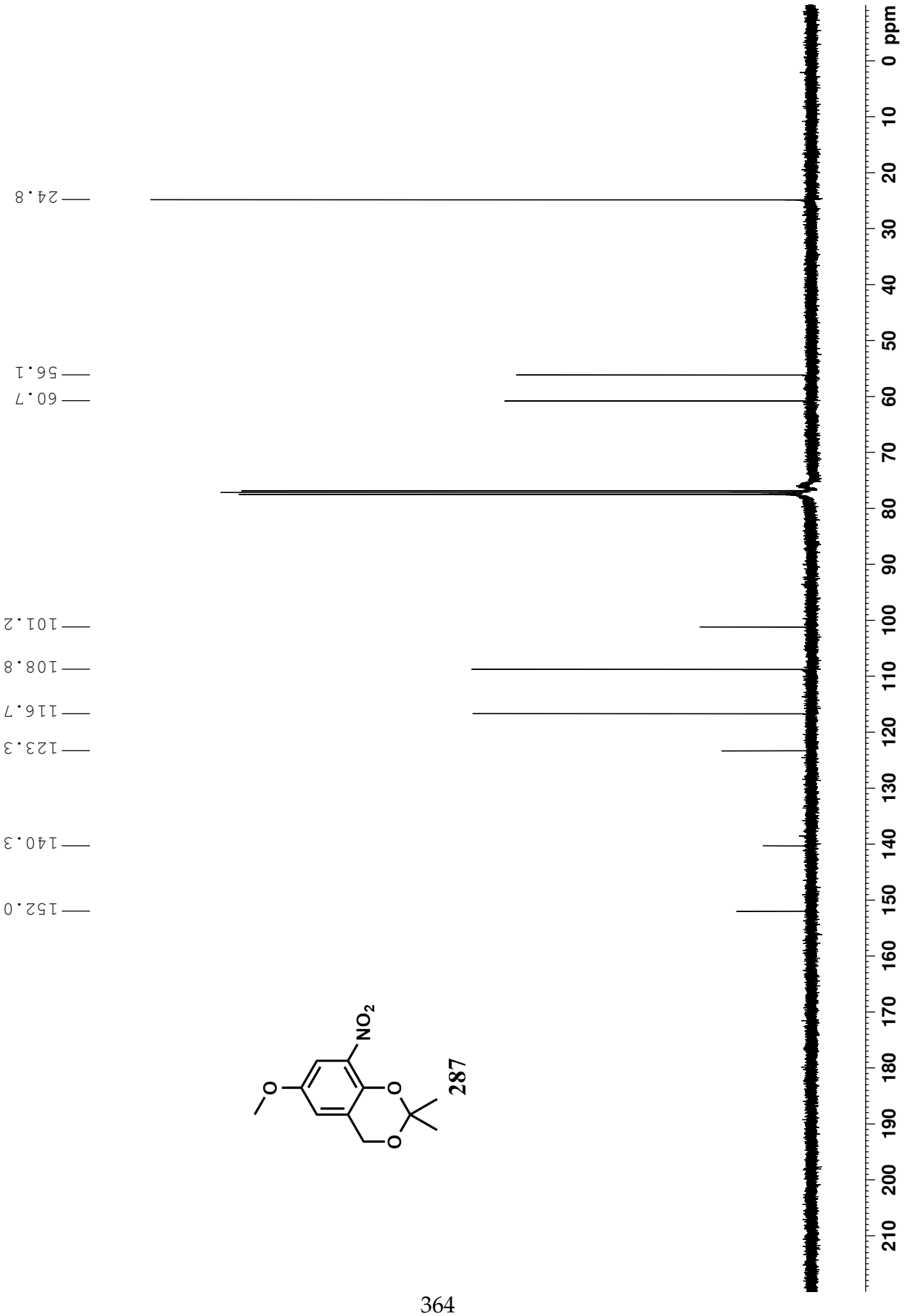

-3.9
10.0
10.1
12.9
13.0
14.9
17.1
17.6
18.4
18.4
18.5
26.1
26.2
36.7
37.5
43.8
44.6
77.4
78.4
123.3
123.4
132.8
133.5
133.7
134.1
135.9
136.0
179.4
181.2
TBSO
O
OH
190
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

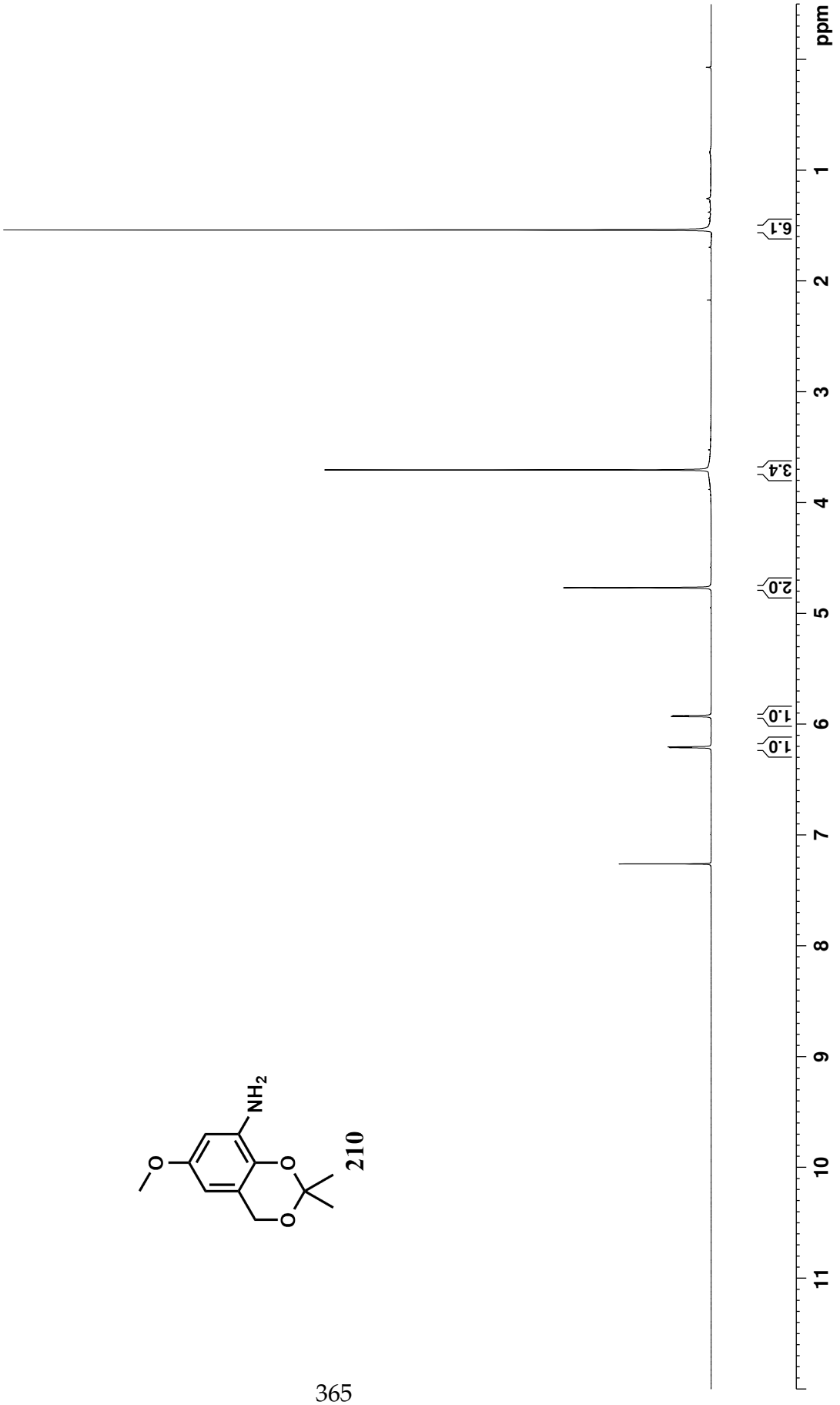

7.05
12.04
3.73
3.77
3.77
7.32
2.37
1.16
2.32
1.12
1.01
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
TBSO
O
OEt
204


6.94
10.16
2.98
2.94
6.13
0.56
0.35
0.89
0.34
0.61
0.91
0.79
0.79
2.00
1.04
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
TBSO
O
O
N
N
205

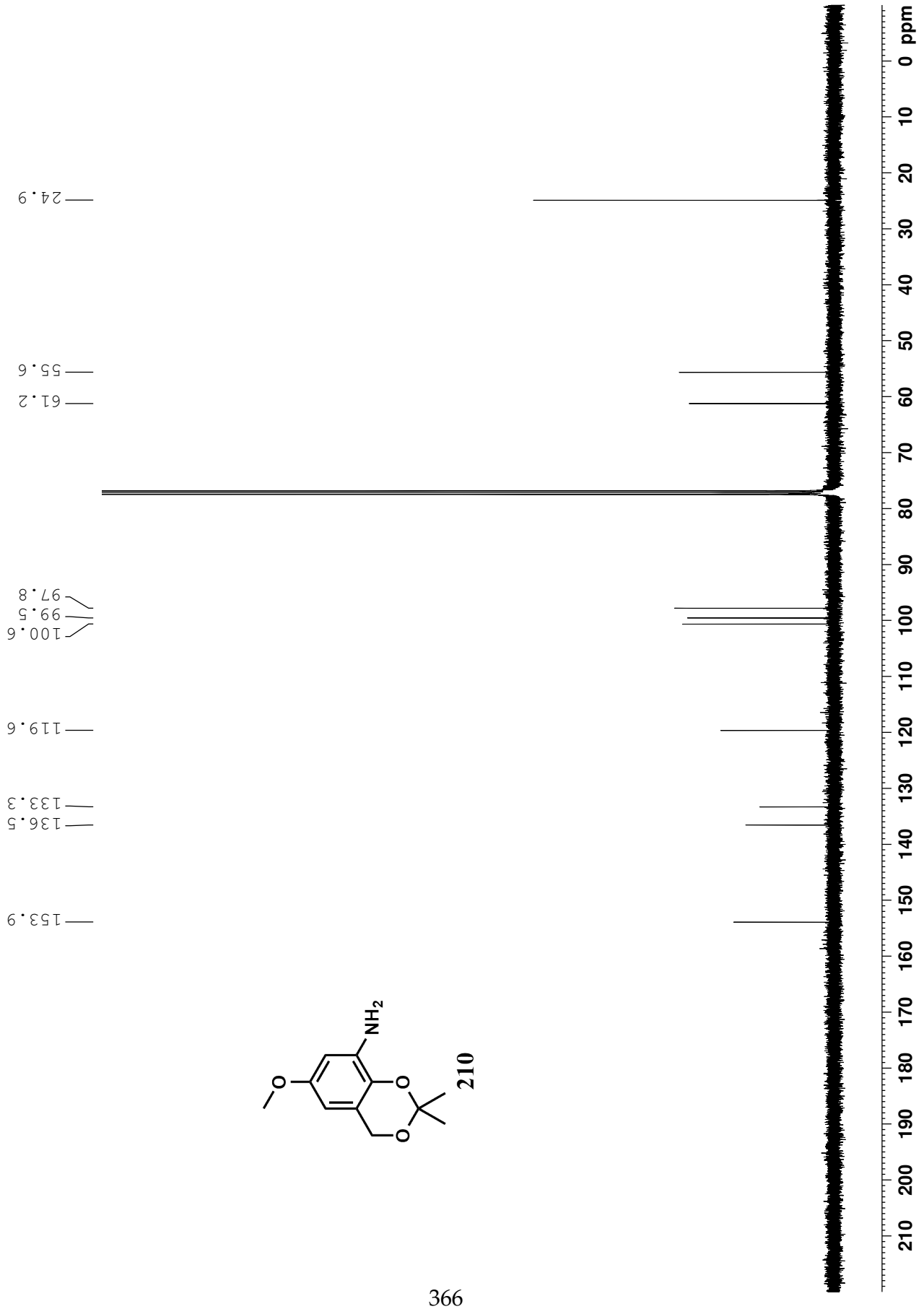

ppm
1
2
3
4
5
6
7
8
9
10
11
1.12
3.22
2.07
0.98
1.00
1.00
NO2
OH
OH
O
208

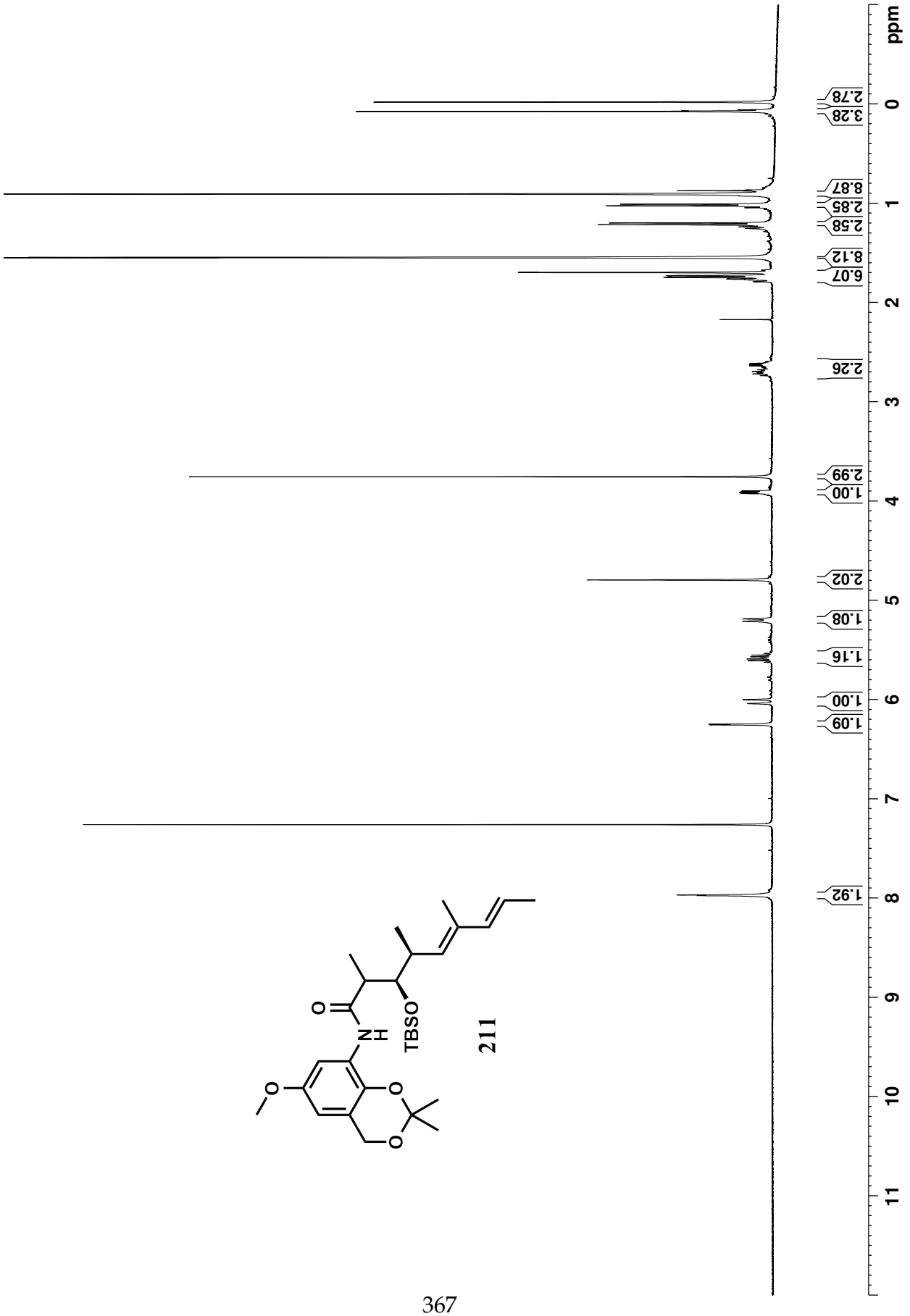

ppm
1
2
3
4
5
6
7
8
9
10
11
6.31
3.24
2.12
1.00
1.00
NO2
O
O
O
287

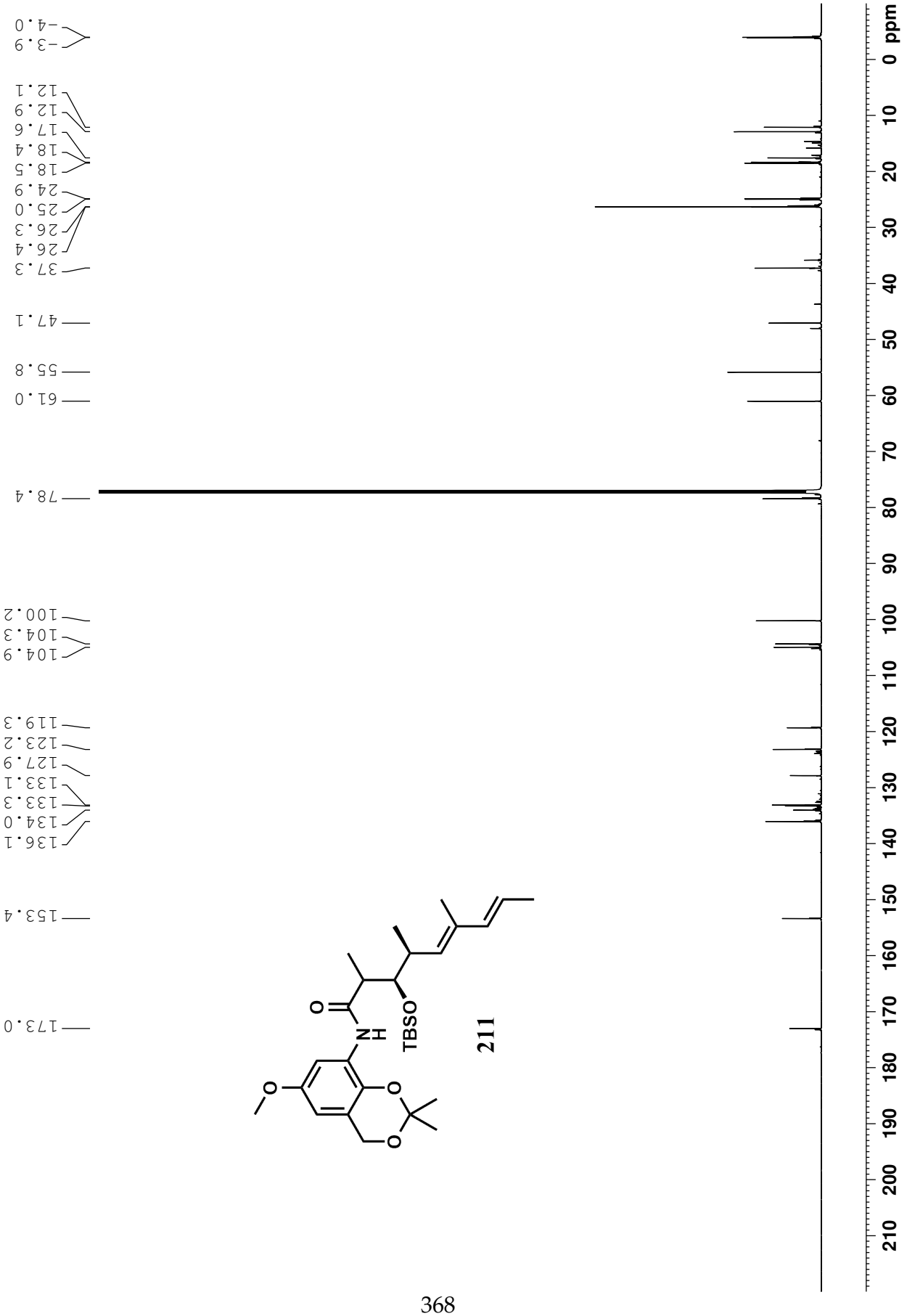

24.8
56.1
60.7
101.2
108.8
116.7
123.3
140.3
152.0
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
NO2
O
O
O
287

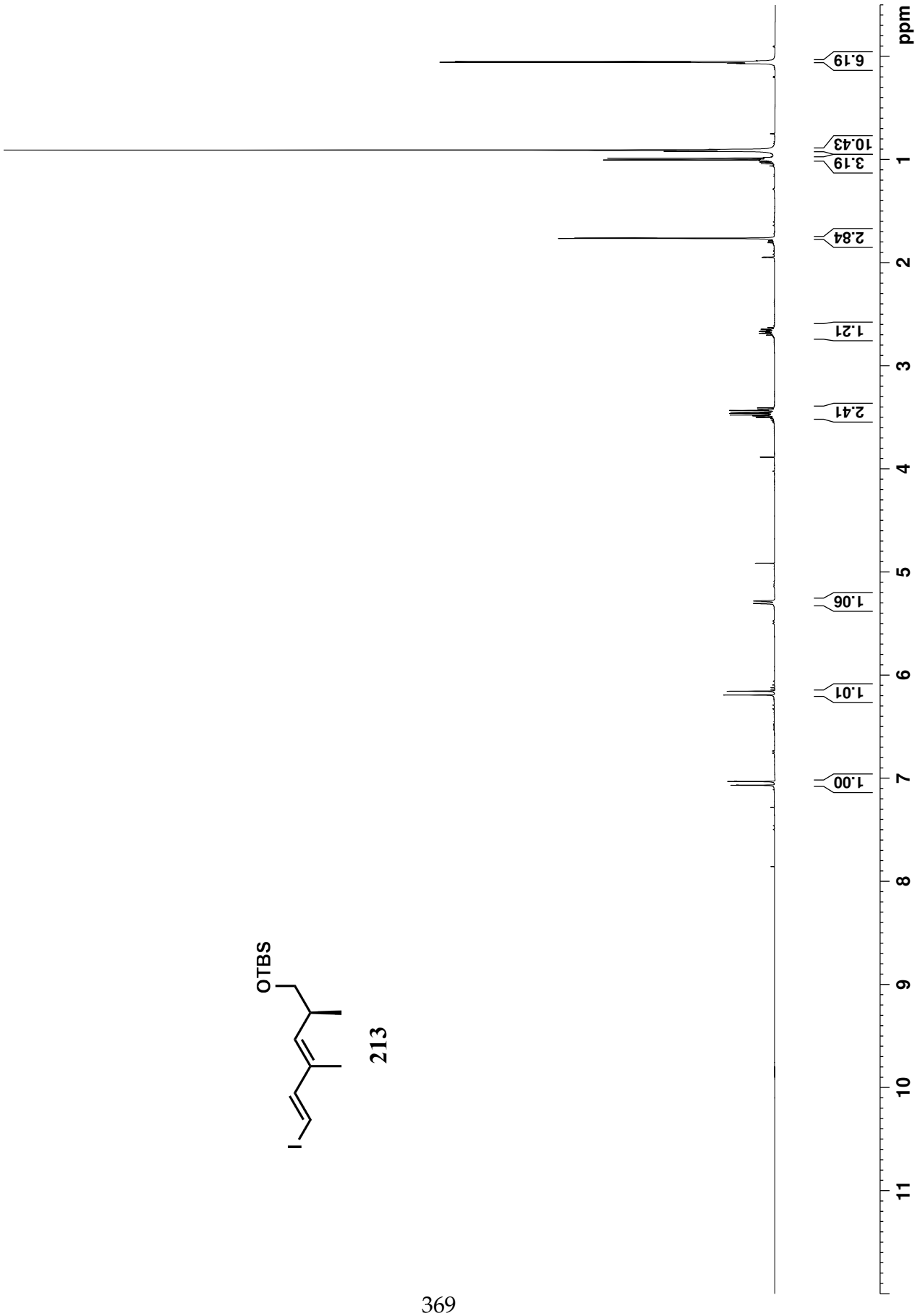


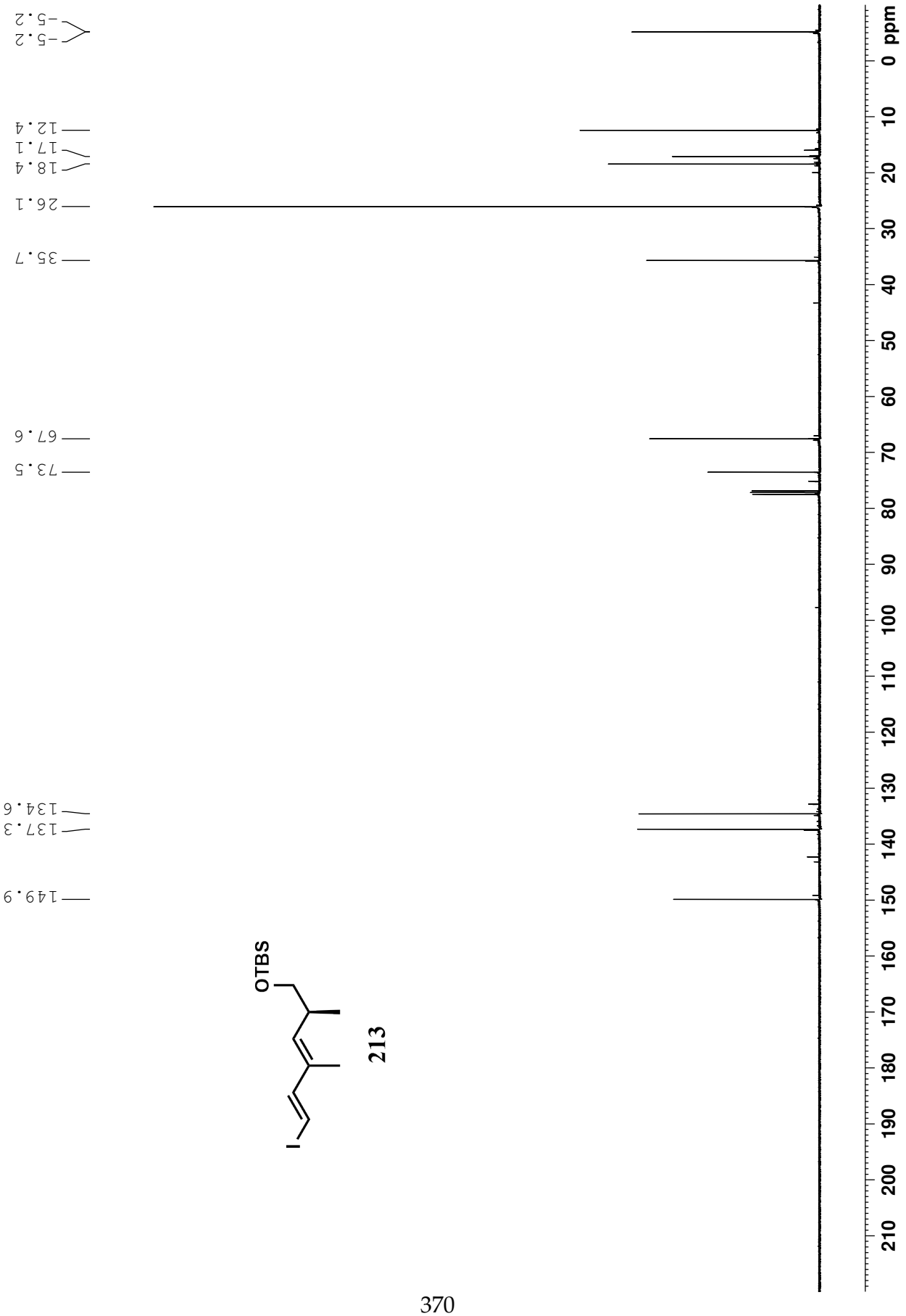
210

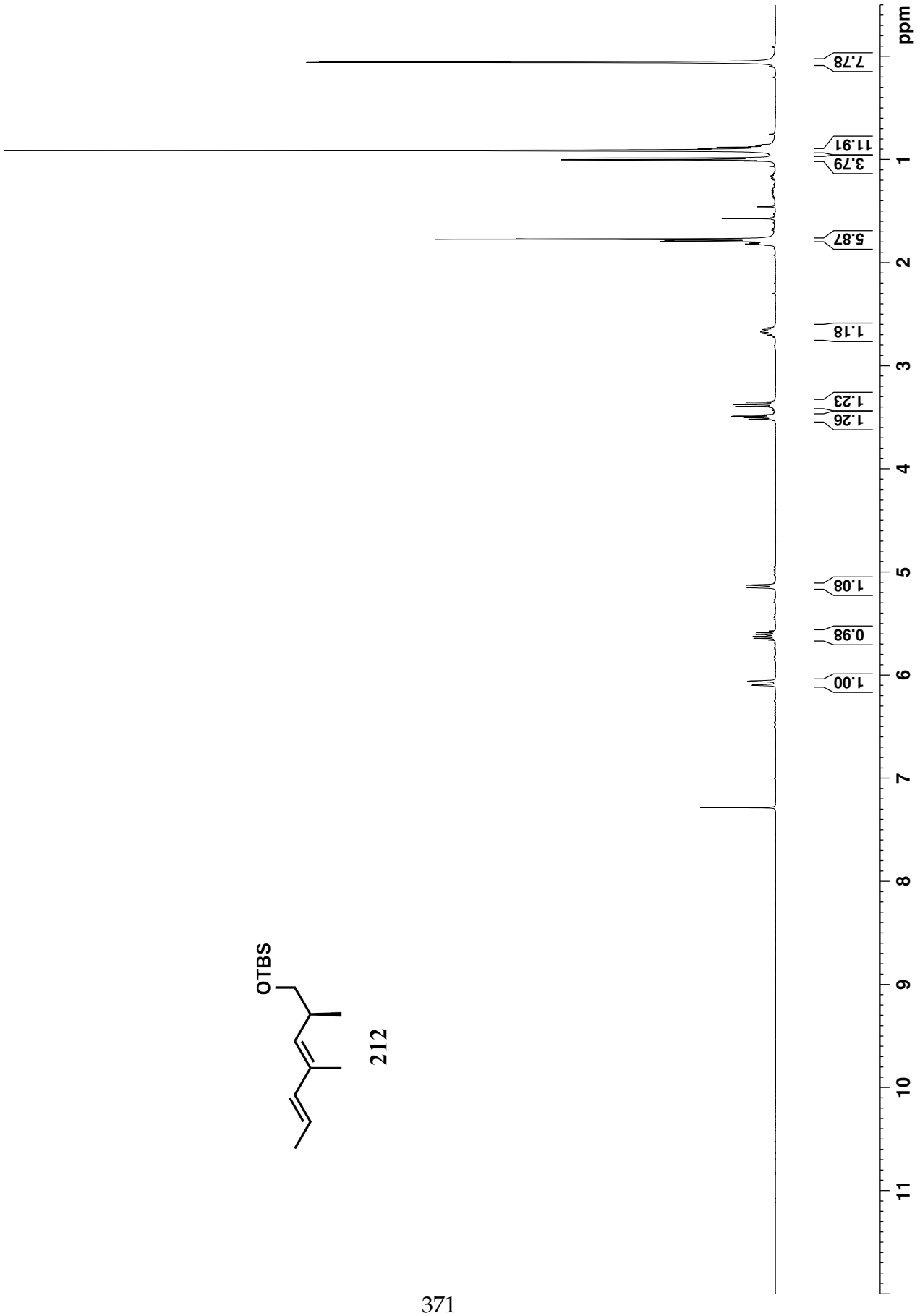

24.9
55.6
61.2
97.8
99.5
100.6
119.6
133.3
136.5
153.9
NH2
O
O
O
210
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

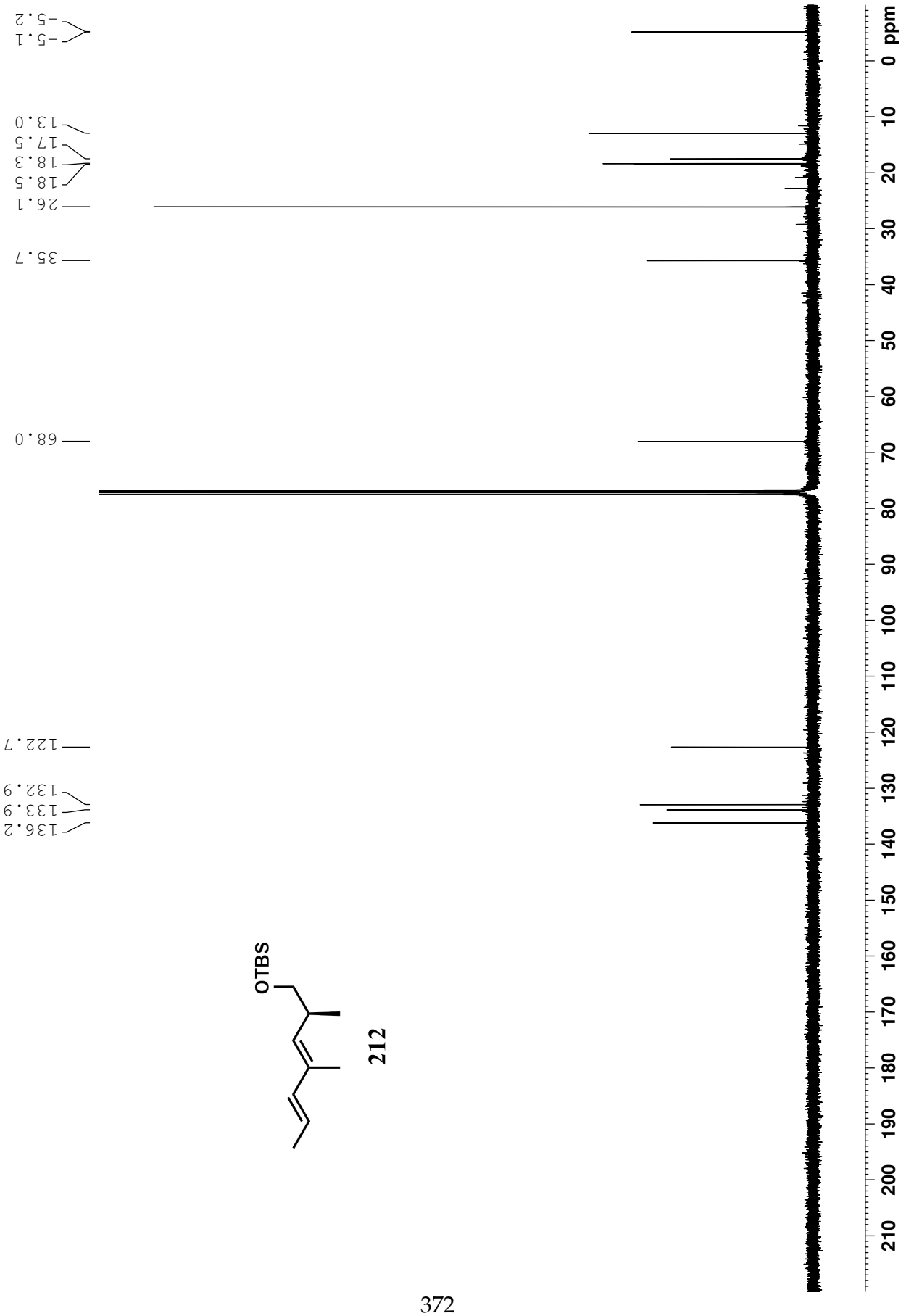

ppm
0
1
2
3
4
5
6
7
8
9
10
11
2.78
3.28
8.87
2.85
2.58
8.12
6.07
2.26
2.99
1.00
2.02
1.08
1.16
1.00
1.09
1.92
O
N
H
TBSO
O
O
O
O
211

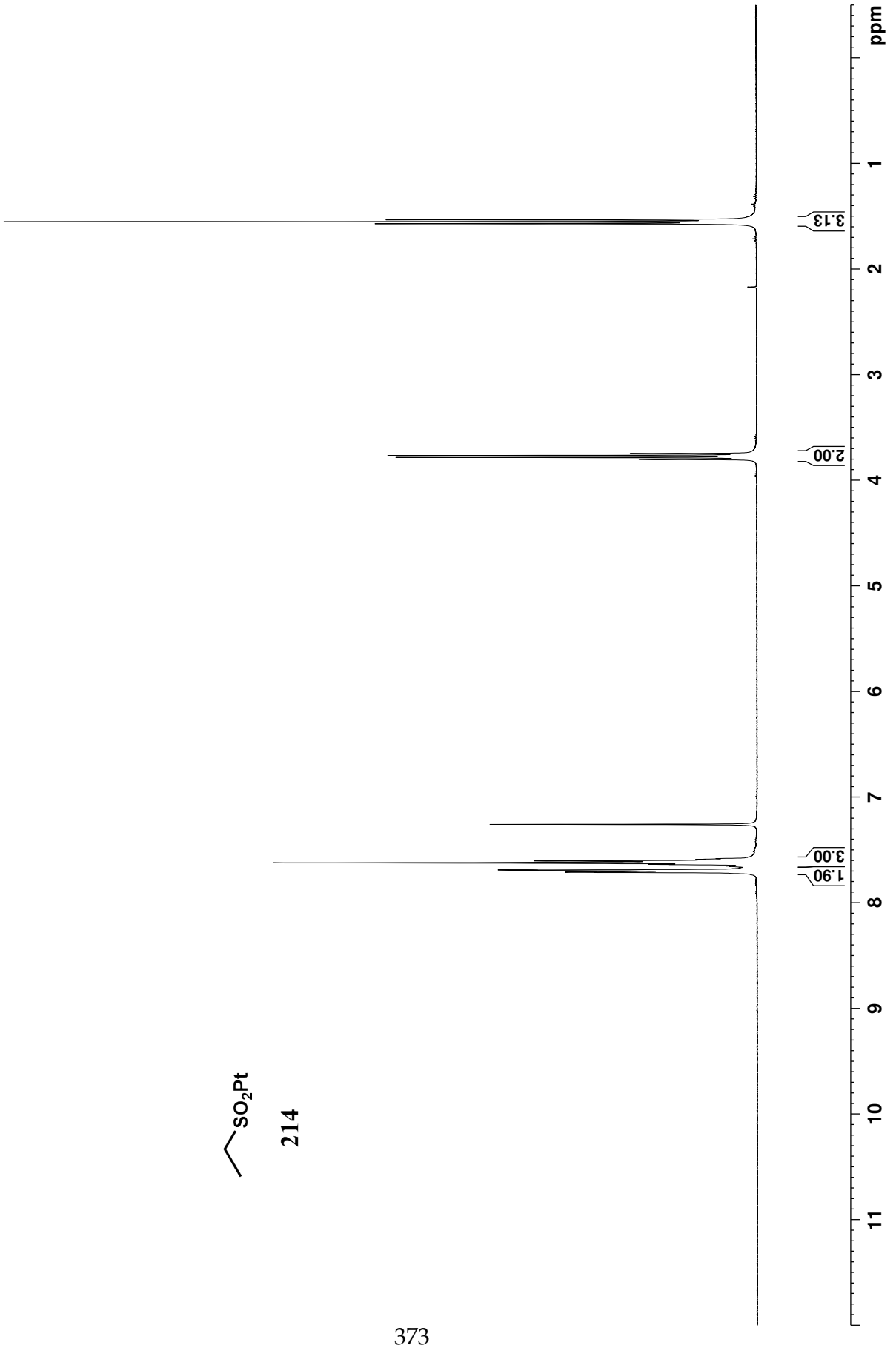

-4.0
-3.9
12.1
12.9
17.6
18.4
18.5
24.9
25.0
26.3
26.4
37.3
47.1
55.8
61.0
78.4
100.2
104.3
104.9
119.3
123.2
127.9
133.1
133.3
134.0
136.1
153.4
173.0
O
N
H
TBSO
O
O
O
211
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

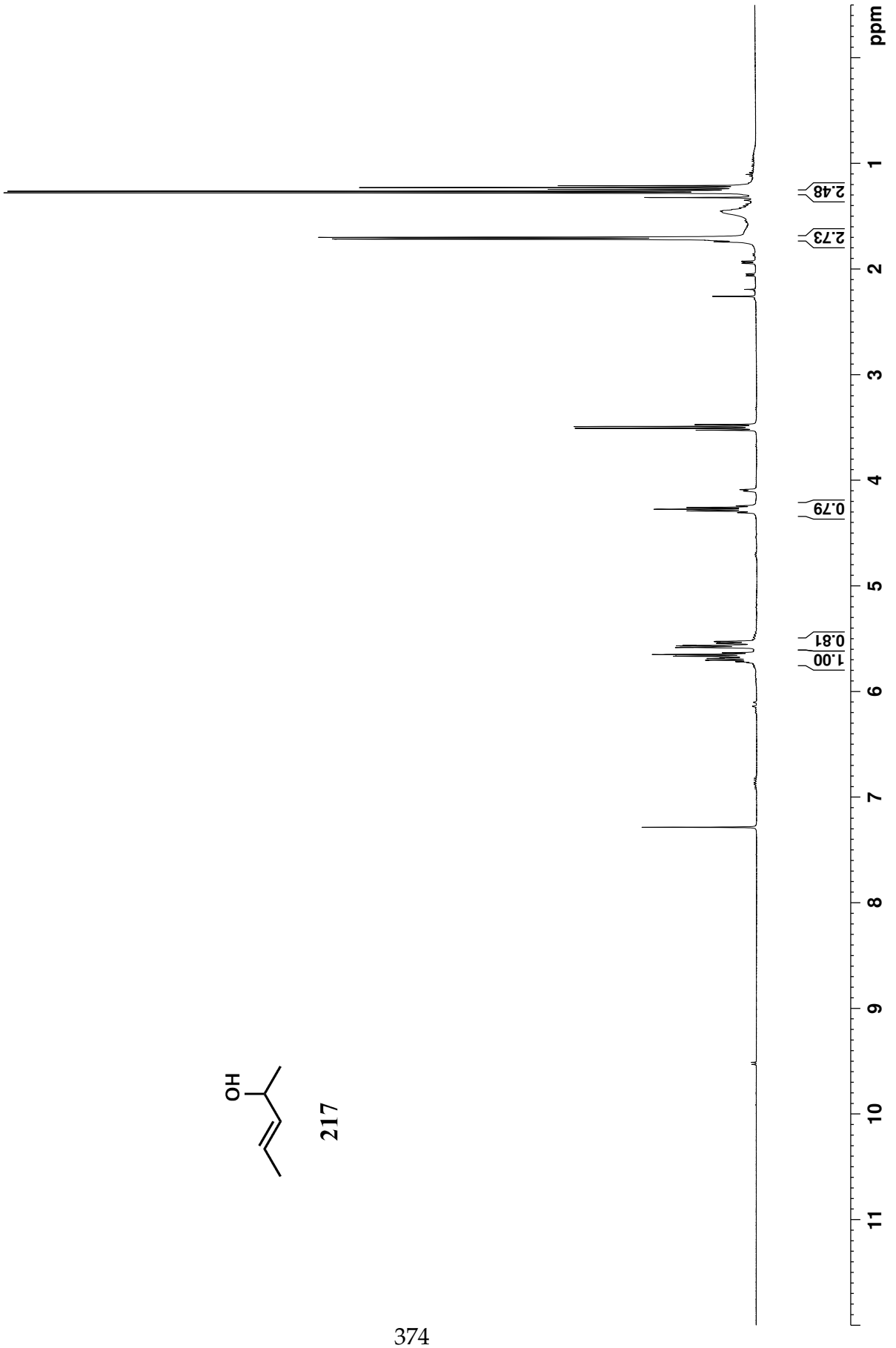

OTBS
213
6.19
10.43
3.19
2.84
1.21
2.41
1.06
1.01
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11


-5.2
-5.2
12.4
17.1
18.4
26.1
35.7
67.6
73.5
134.6
137.3
149.9
OTBS
213
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

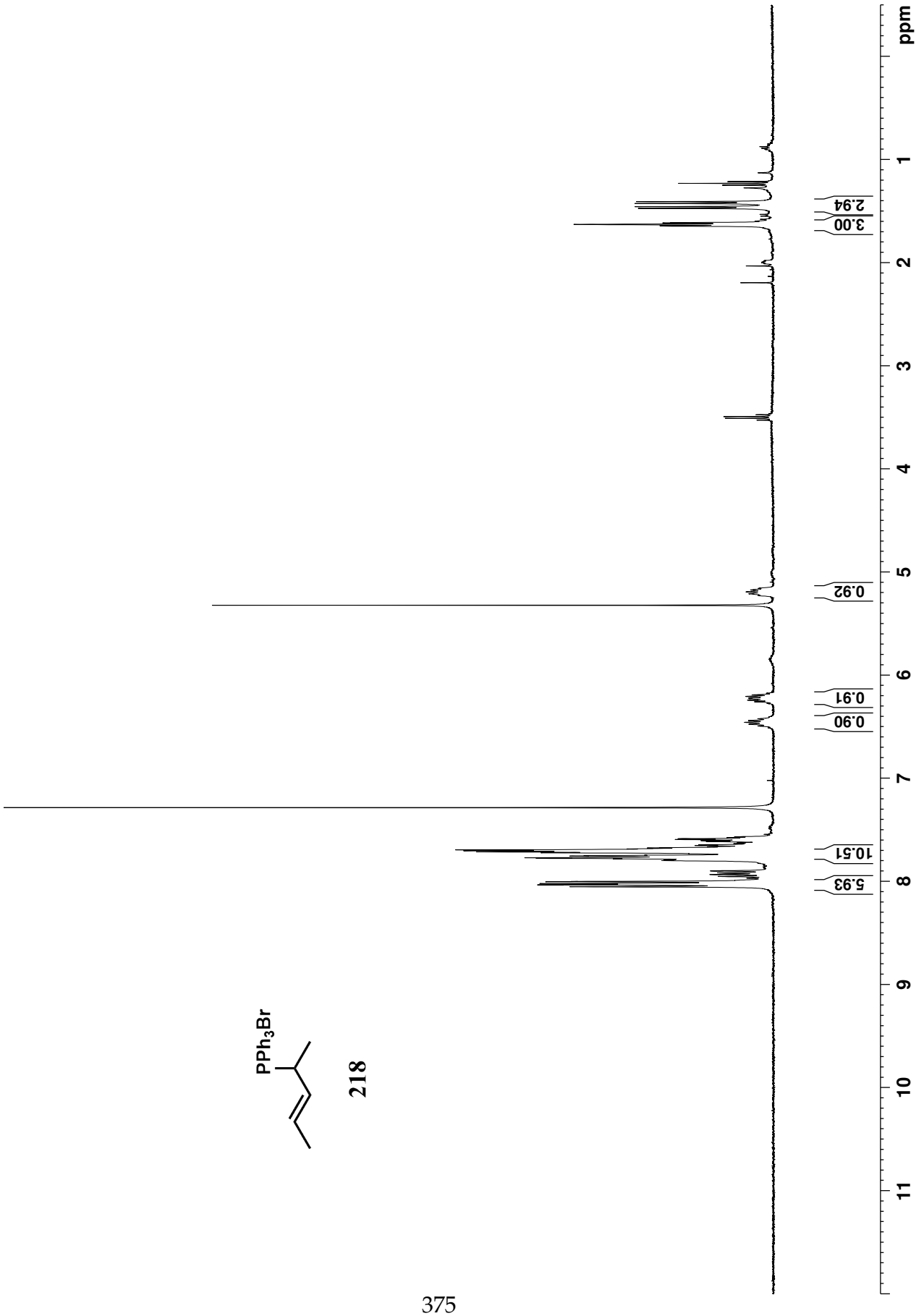

7.78
11.91
3.79
5.87
1.18
1.23
1.26
1.08
0.98
1.00
ppm
1
2
3
4
5
6
7
8
9
10
11
OTBS
212

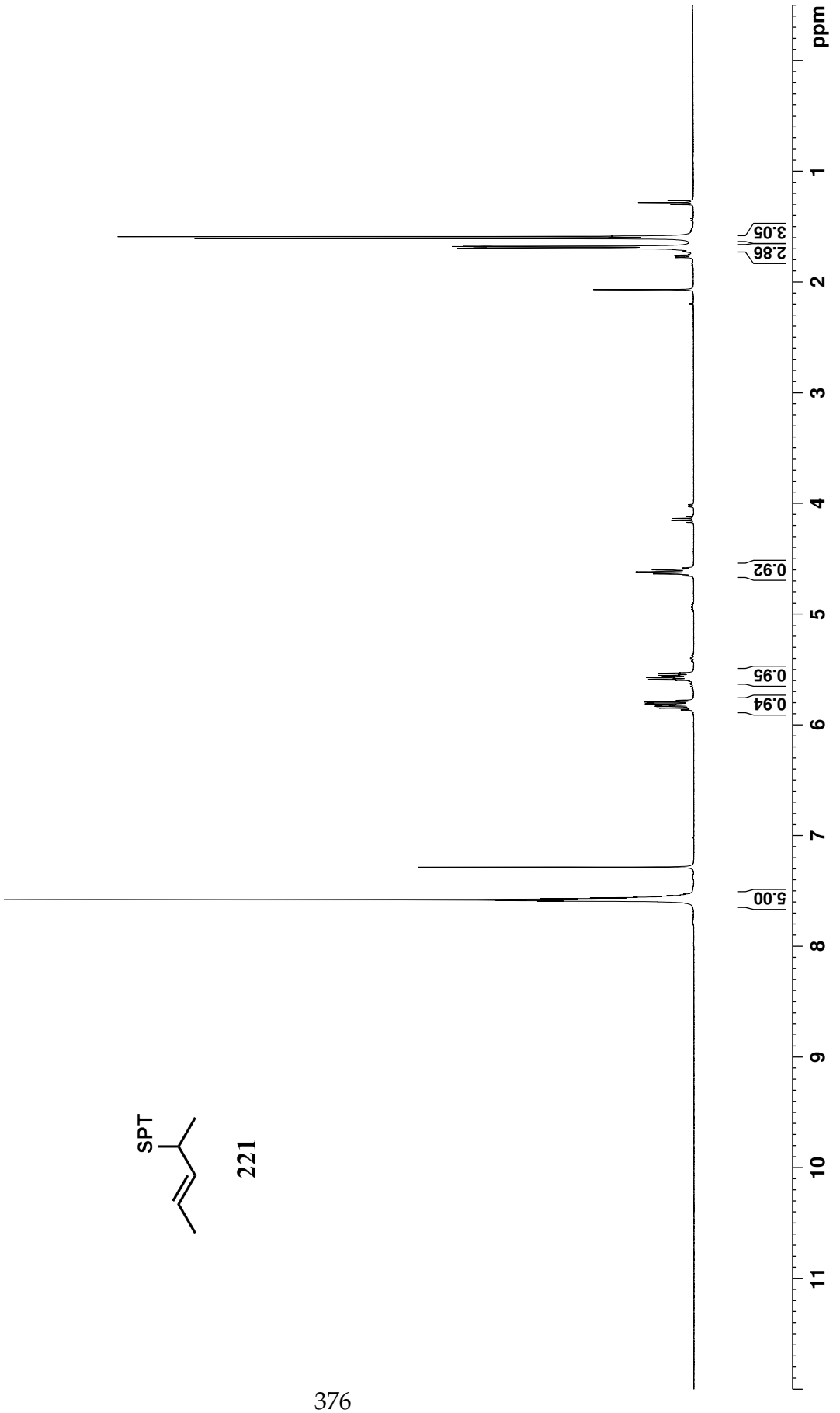

-5.2
-5.1
13.0
17.5
18.3
18.5
26.1
35.7
68.0
122.7
132.9
133.9
136.2
OTBS
212
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

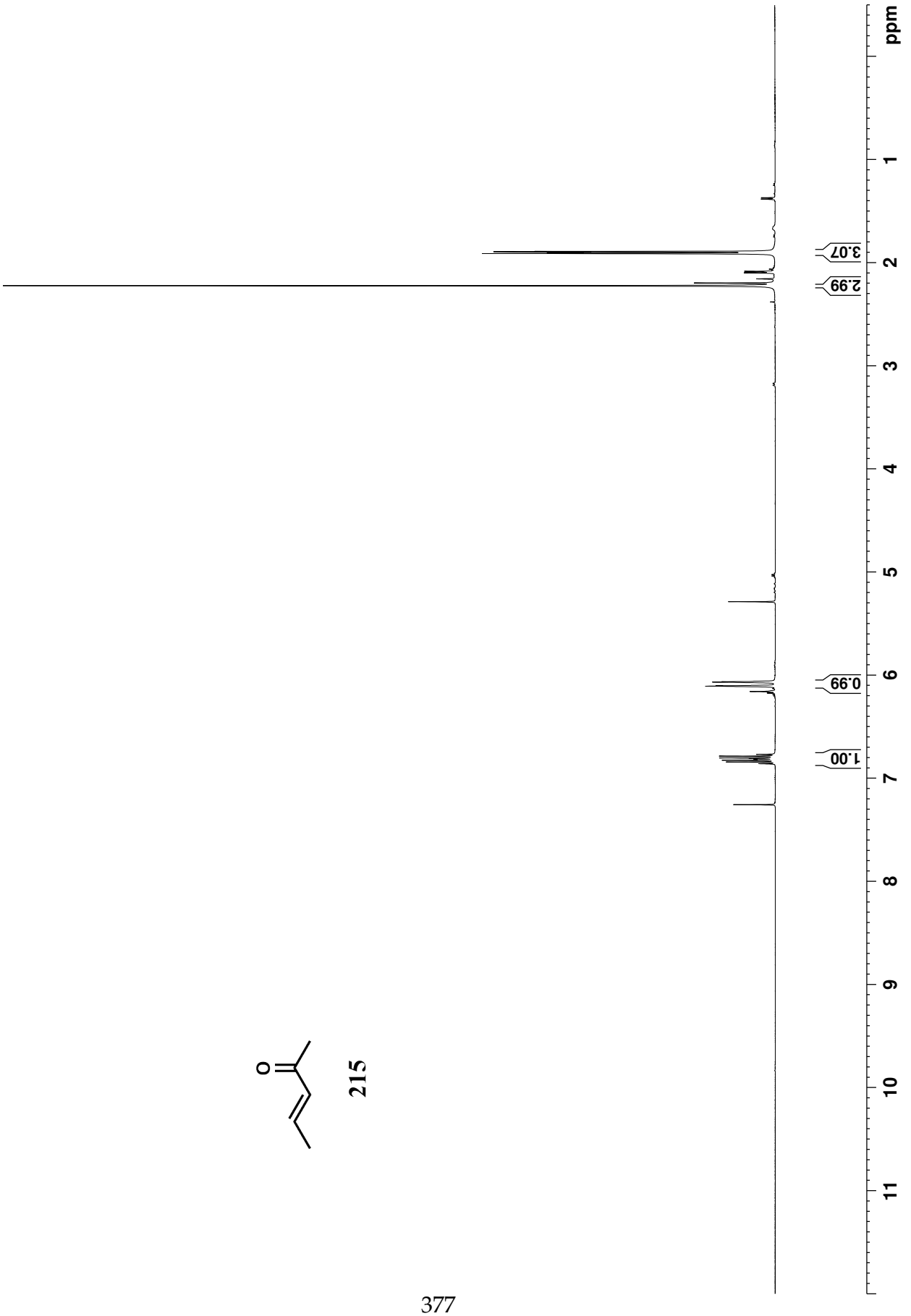

SO2Pt
214
3.13
2.00
3.00
1.90
ppm
1
2
3
4
5
6
7
8
9
10
11

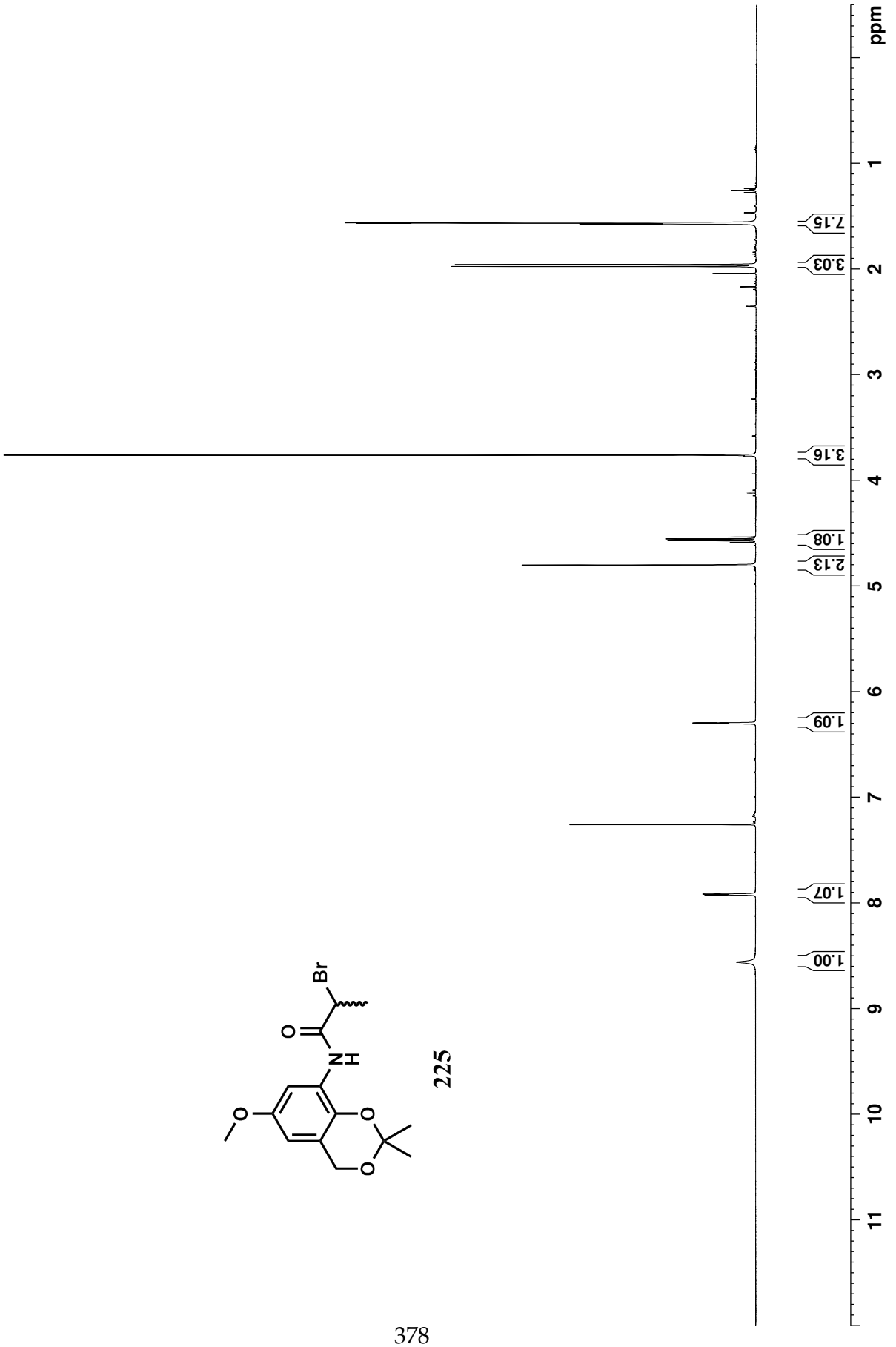


217

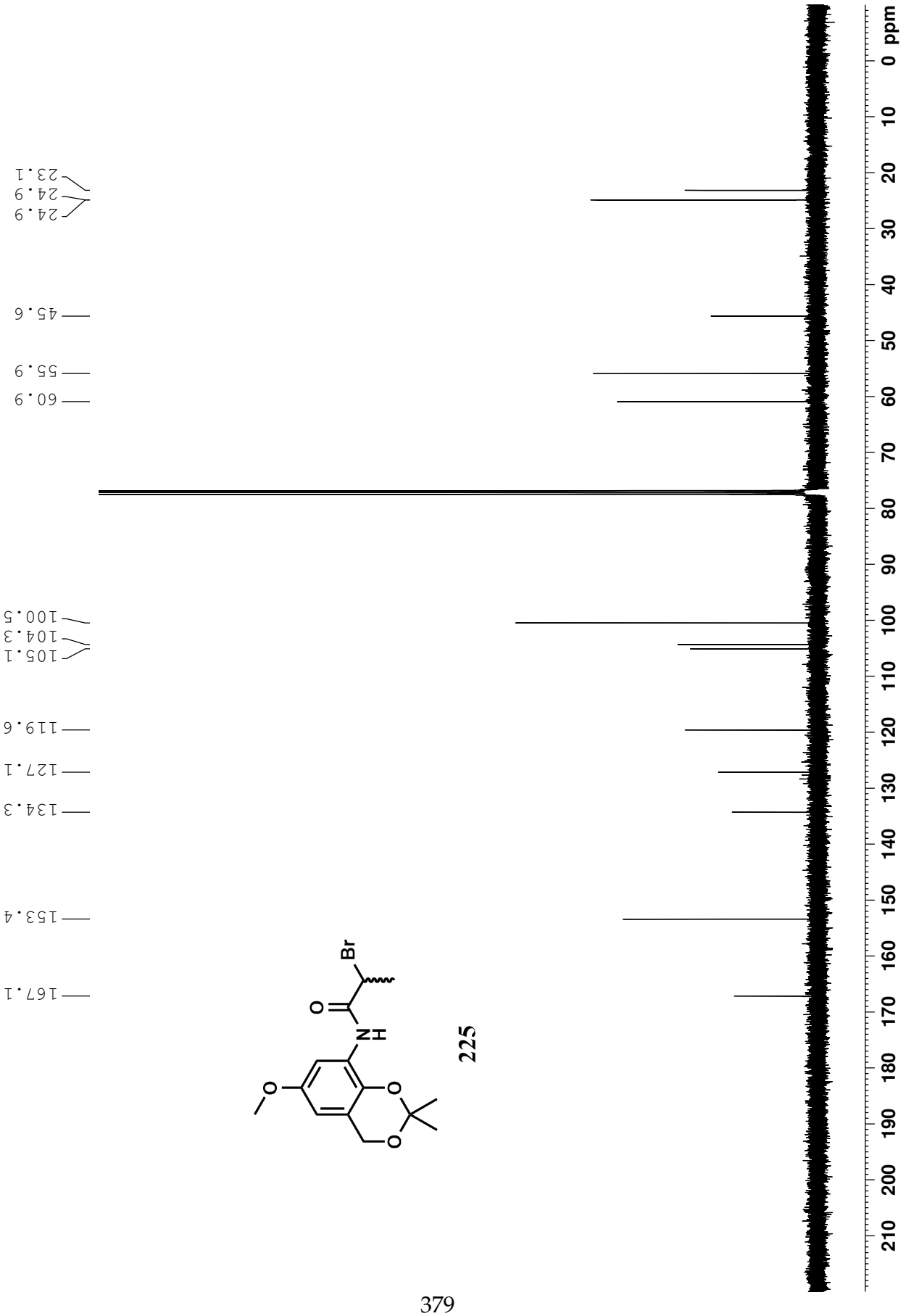

PPh3Br
218
2.94
3.00
0.92
0.91
0.90
10.51
5.93
ppm

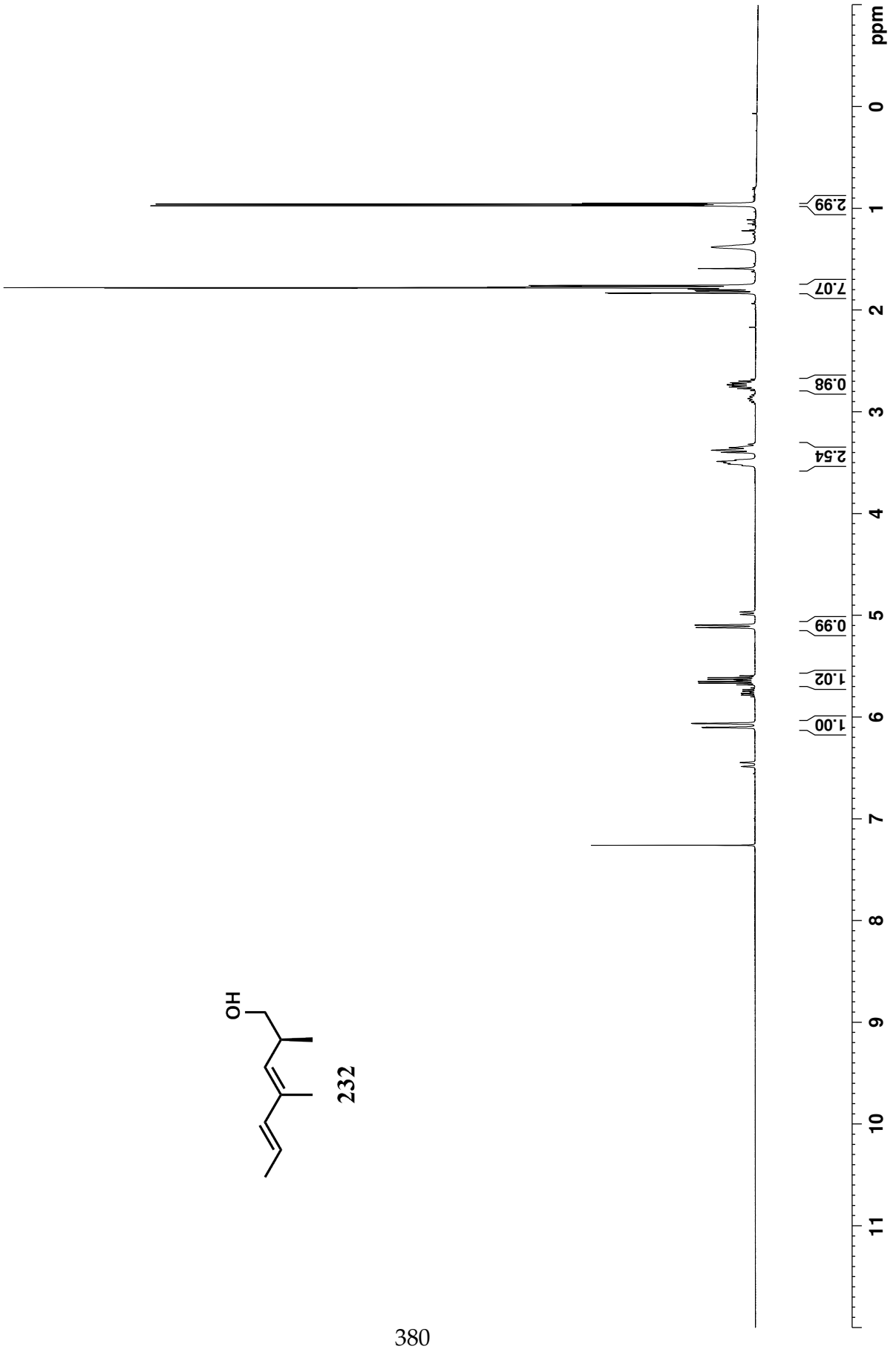

SPT
221
5.00
0.94
0.95
0.92
2.86
3.05
ppm

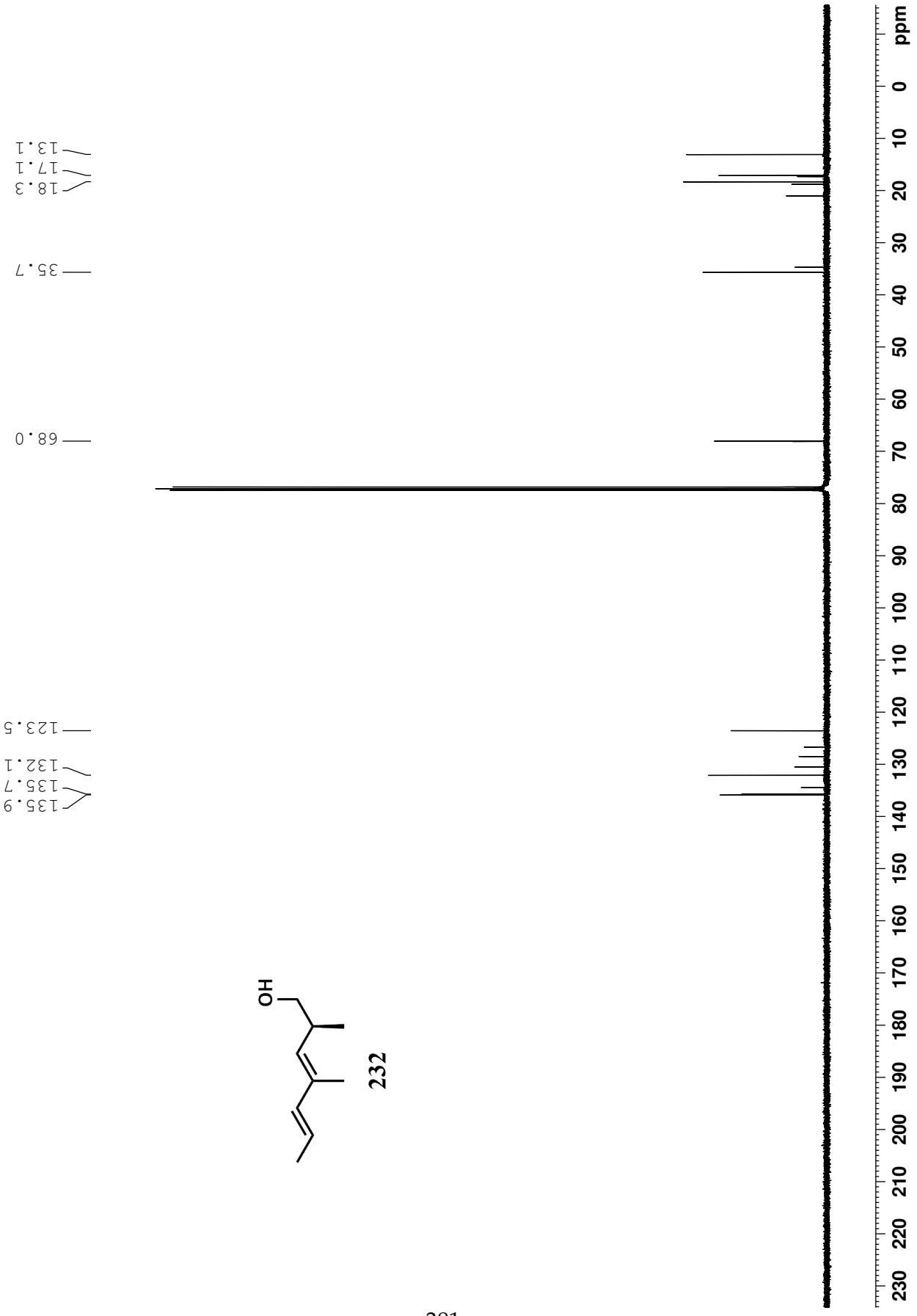

ppm
1
2
3
4
5
6
7
8
9
10
11
3.07
2.99
0.99
1.00
O
215



225


23.1
24.9
24.9
45.6
55.9
60.9
100.5
104.3
105.1
119.6
127.1
134.3
153.4
167.1
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
Br
O
N
H
O
O
O
225


ppm
0
1
2
3
4
5
6
7
8
9
10
11
2.99
7.07
0.98
2.54
0.99
1.02
1.00
OH
232


13.1
17.1
18.3
35.7
68.0
123.5
132.1
135.7
135.9
OH
232
ppm
0
10
20
30
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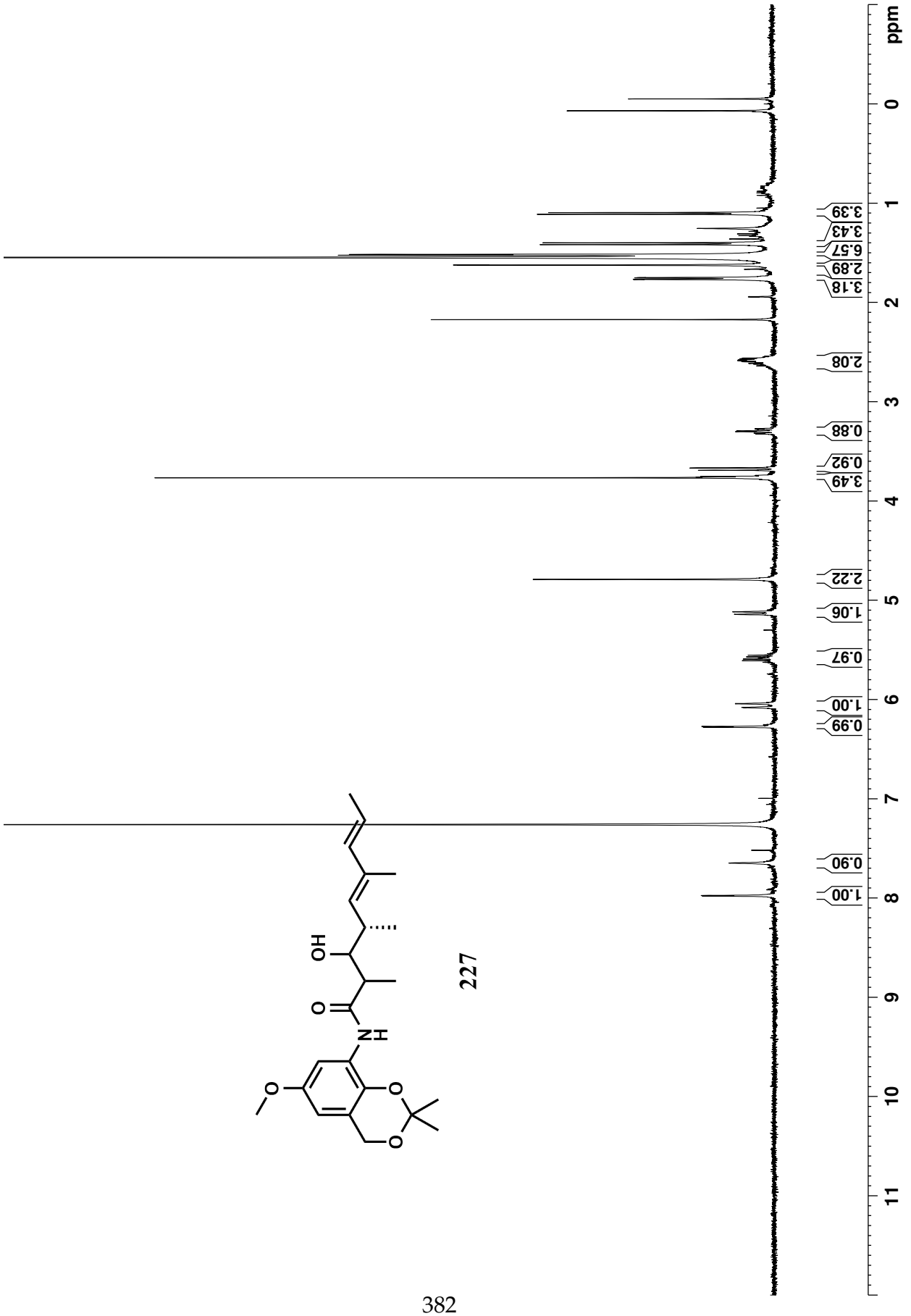
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11
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6.57
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3.18
2.08
0.88
0.92
3.49
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1.00
0.99
0.90
1.00
227
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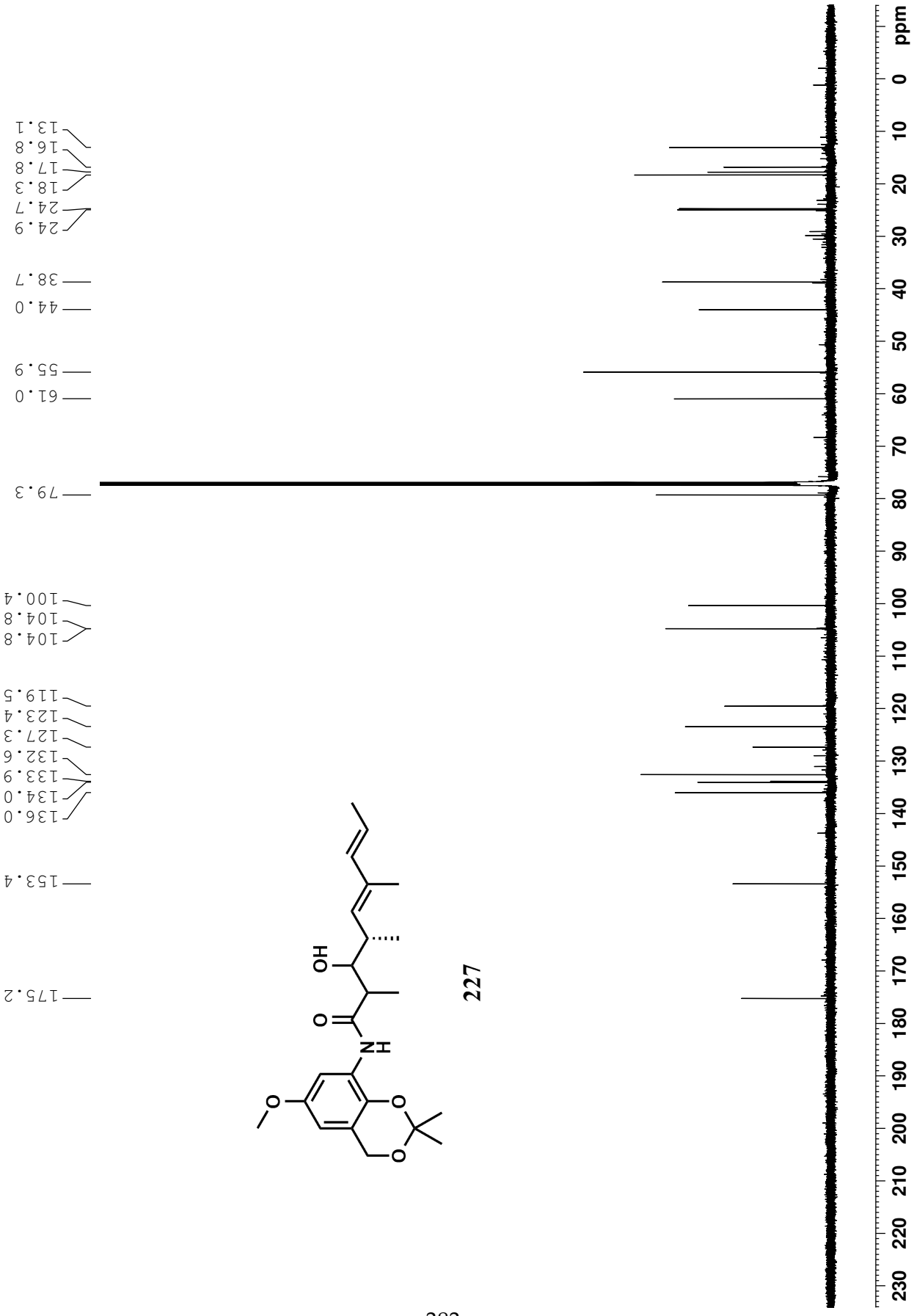
OH
N
H
O
O
O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123.4
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104.8
100.4
79.3
61.0
55.9
44.0
38.7
24.9
24.7
18.3
17.8
16.8
13.1
ppm
0
10
20
30
40
50
60
70
80
90
100
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160
170
180
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200
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OH
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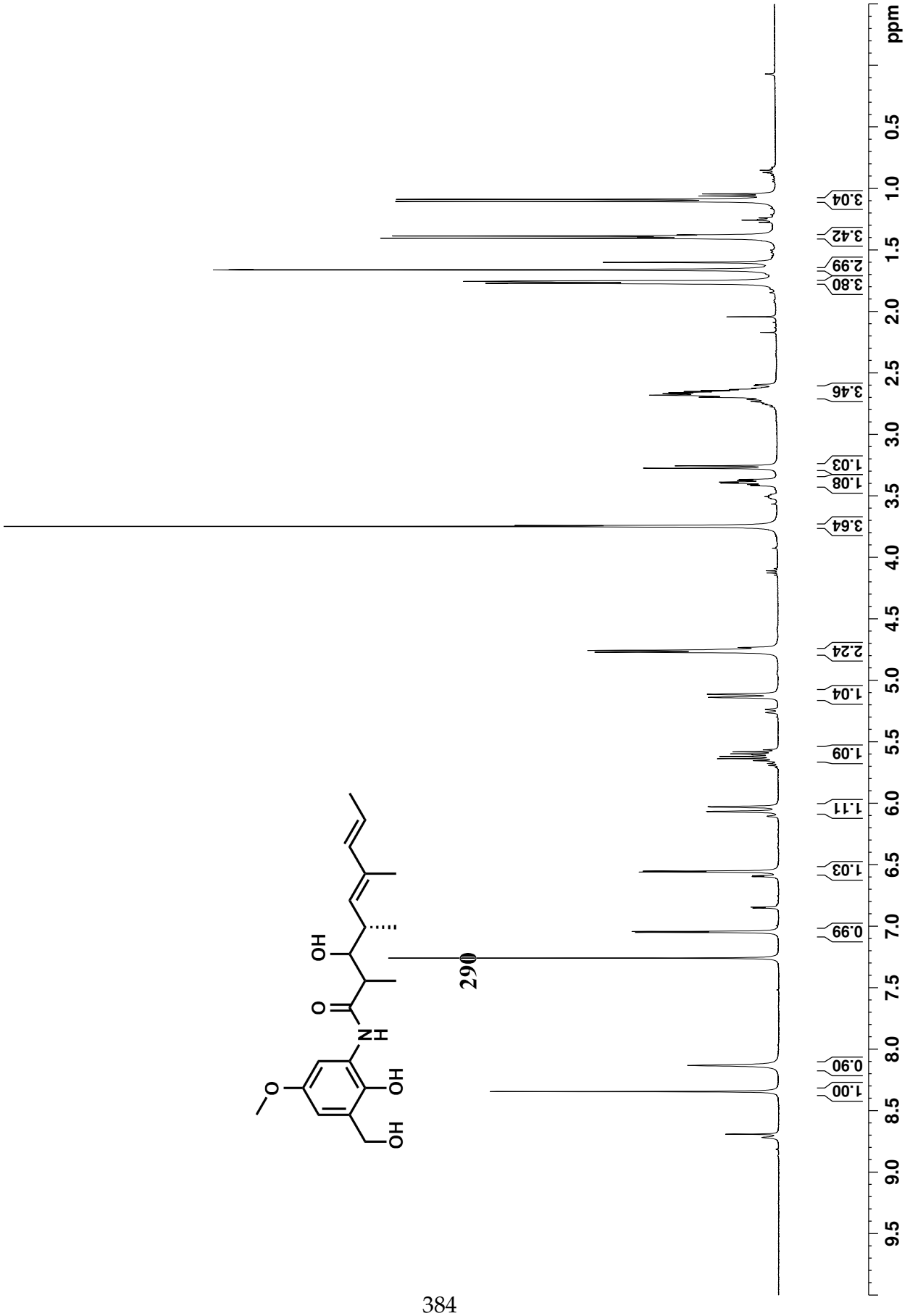
N
H
O
O
O
227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1.03
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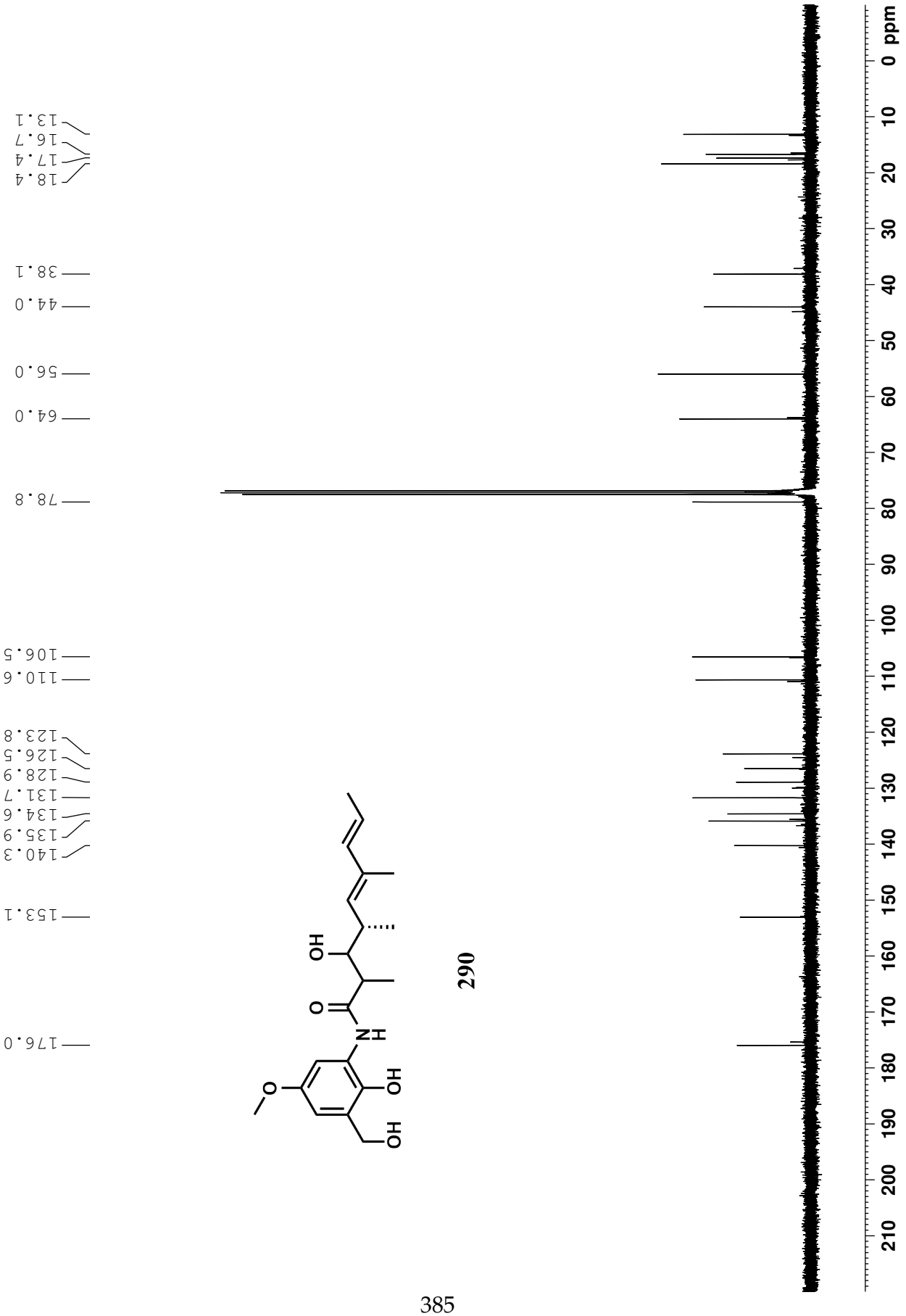
0.90
1.00
ppm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64.0
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110.6
123.8
126.5
128.9
131.7
134.6
135.9
140.3
153.1
176.0
OH
O
N
H
O
OH
OH
290
0 ppm
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200
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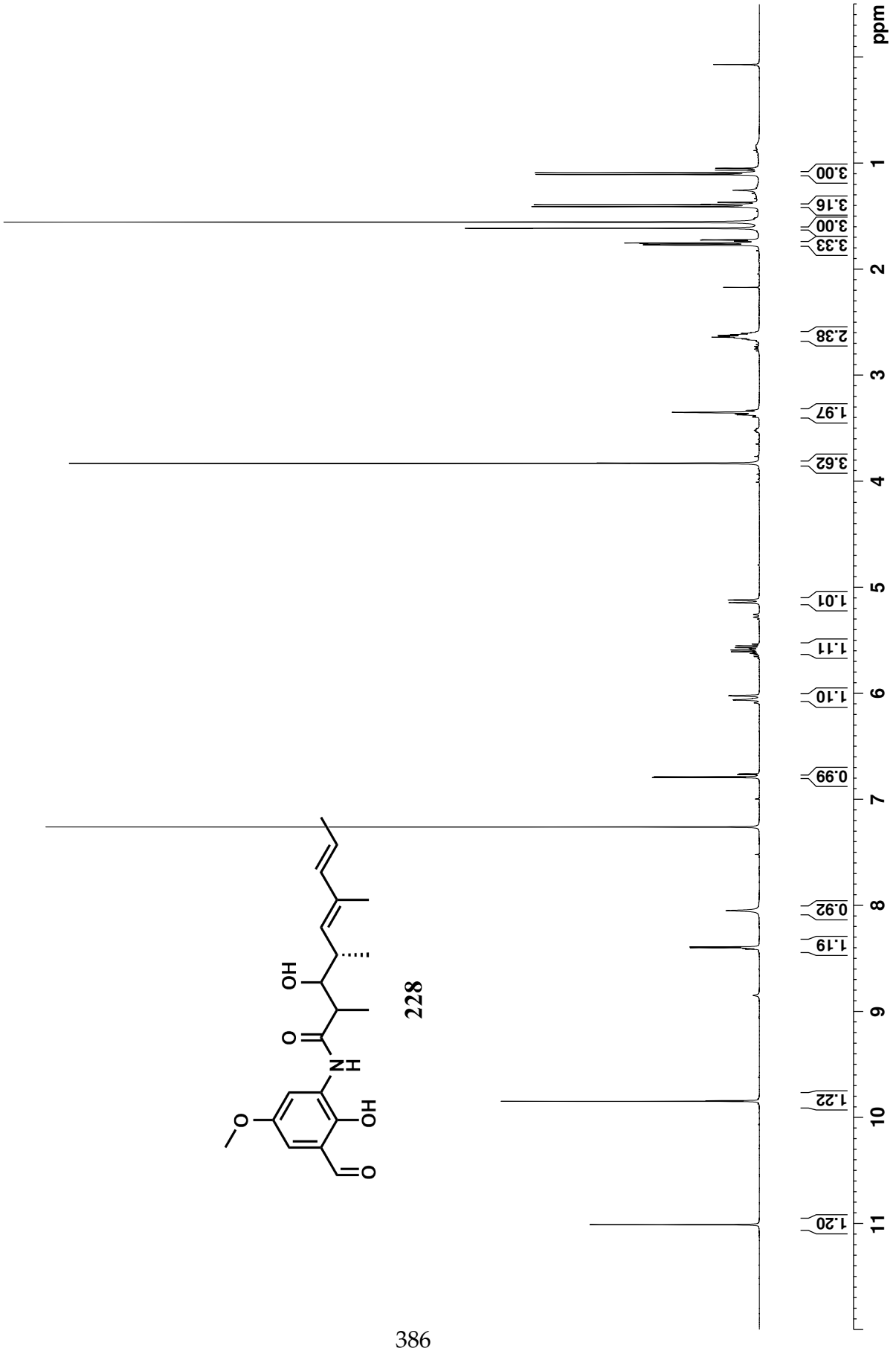
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0.92
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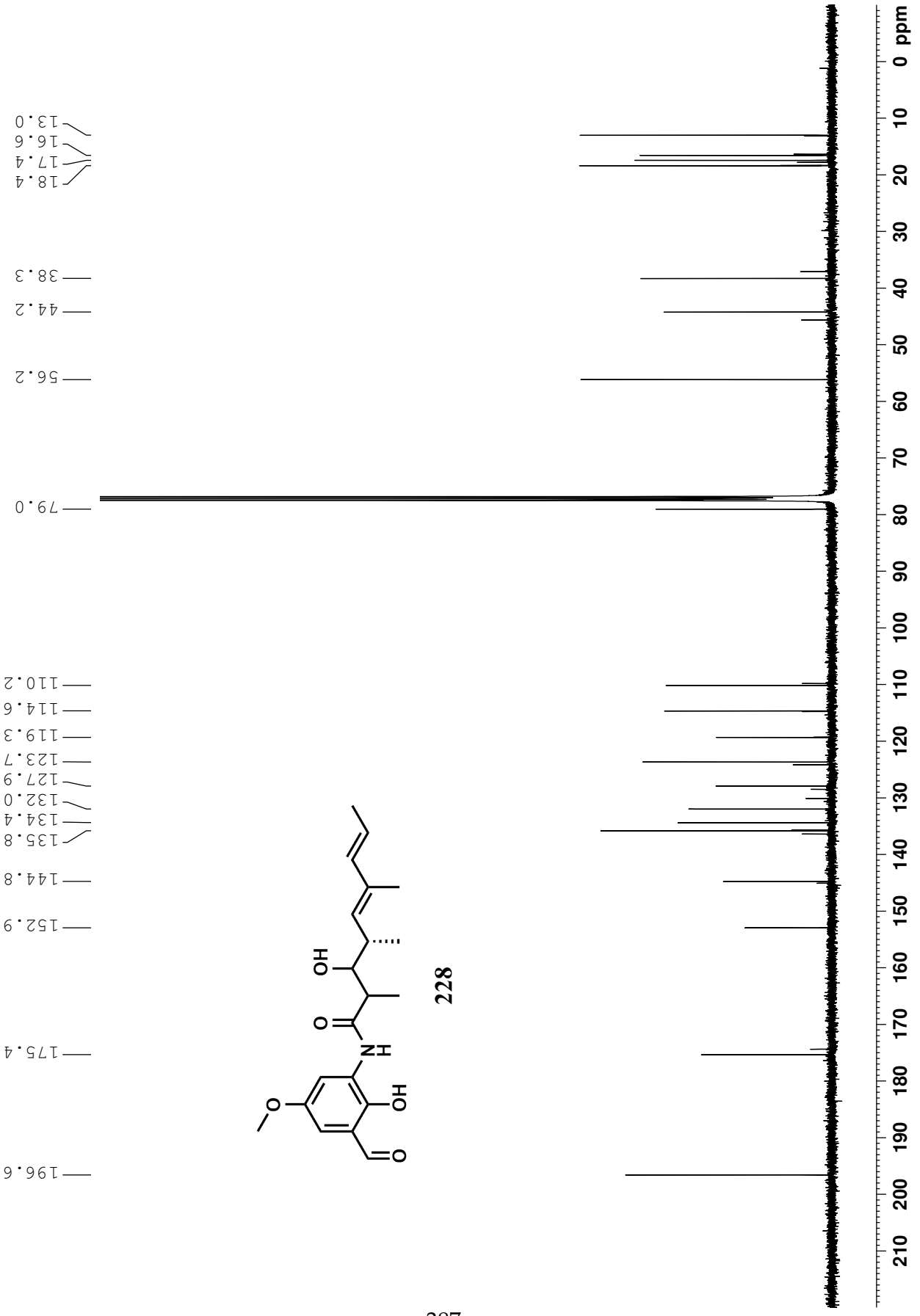
1.22
1.20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56.2
79.0
110.2
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123.7
127.9
132.0
134.4
135.8
144.8
152.9
175.4
196.6
0 ppm
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20
30
40
50
60
70
80
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140
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170
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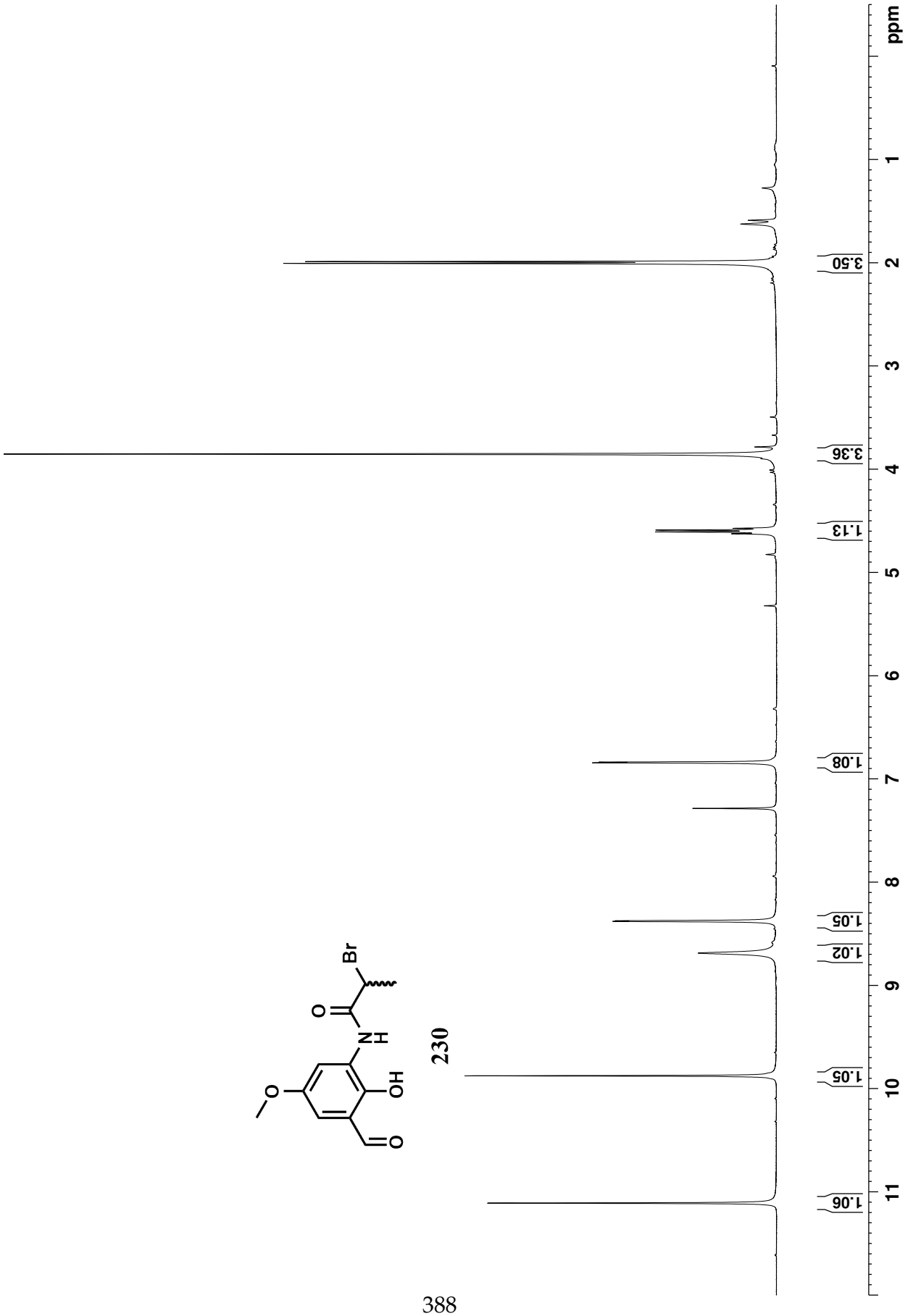
NH
OH
O
O
228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1.02
1.05
1.06
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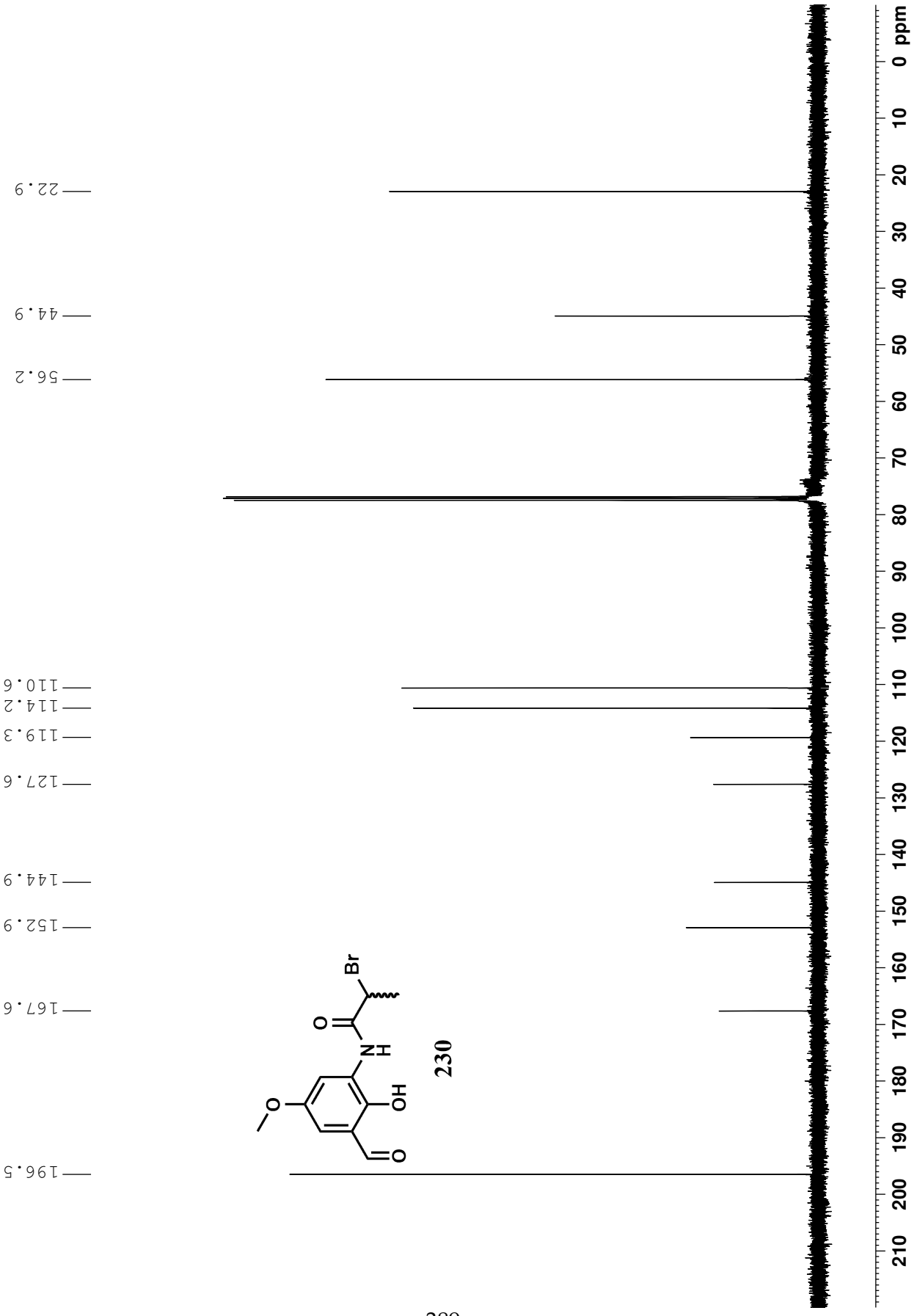
H
O
OH
O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44.9
56.2
110.6
114.2
119.3
127.6
144.9
152.9
167.6
196.5
Br
O
N
H
OH
O
O
230
0 ppm
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20
30
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50
60
70
80
90
100
110
120
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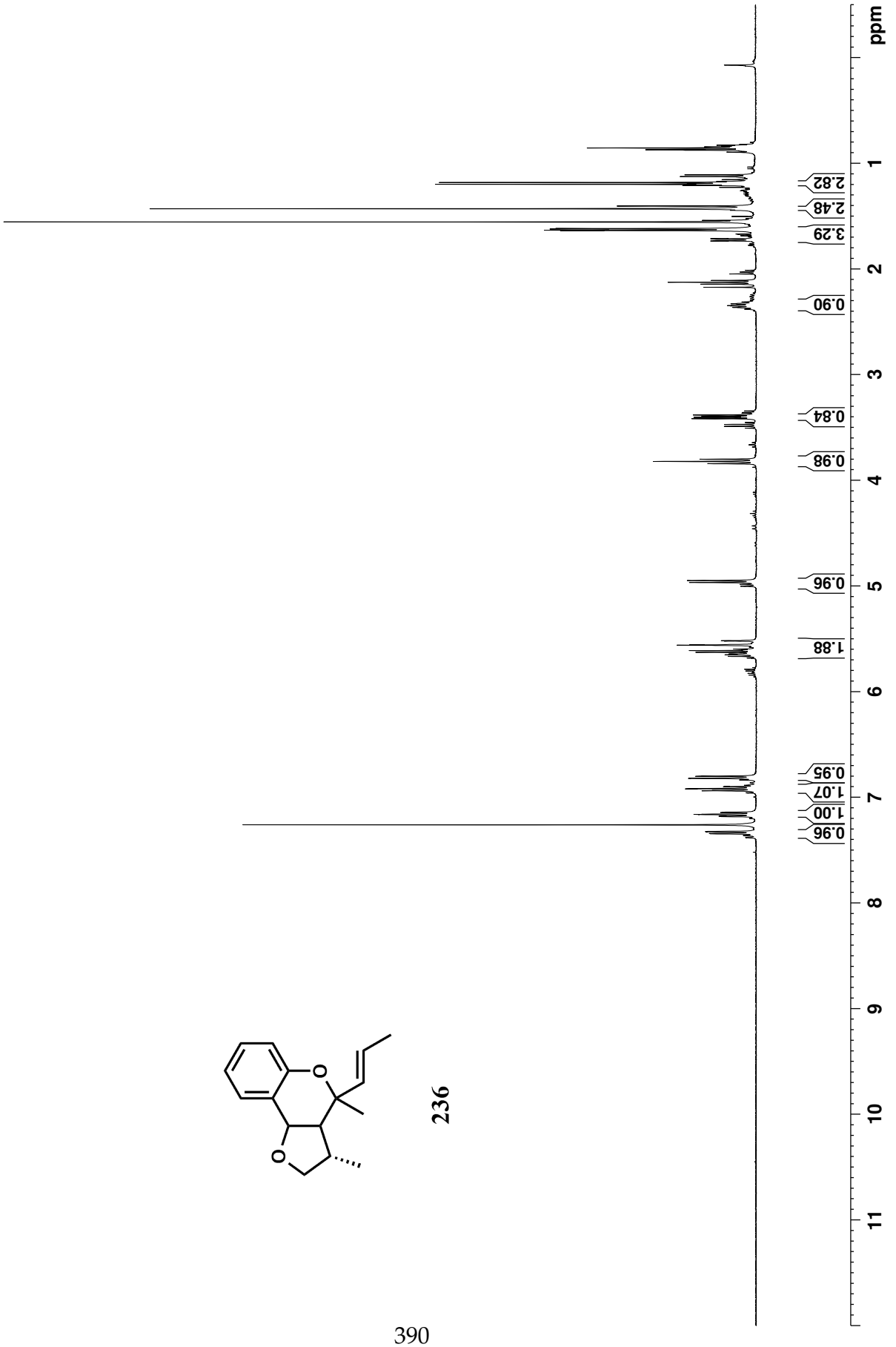
140
150
160
170
180
190
200
210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8
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10
11
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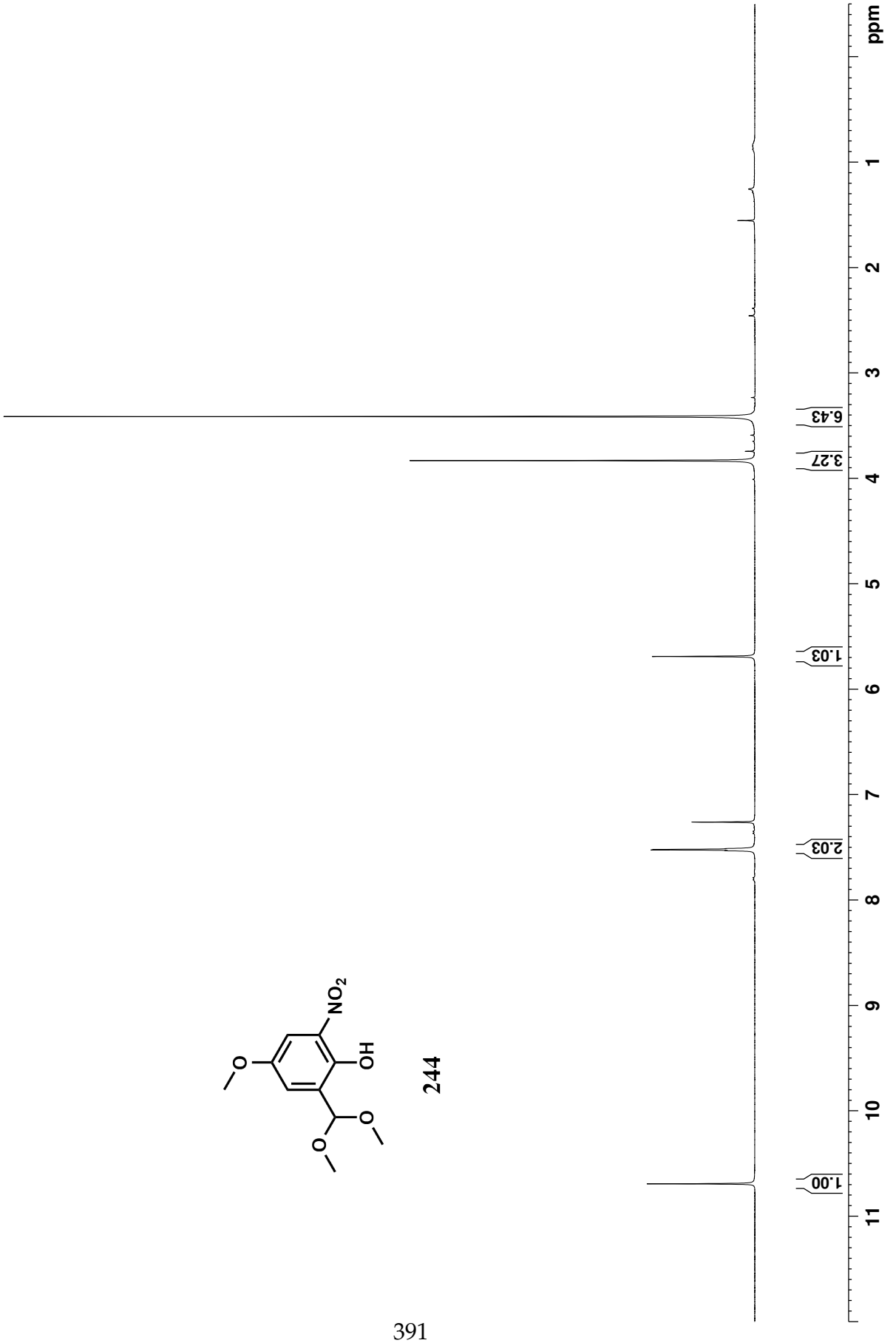
0.96
1.88
0.95
1.07
1.00
0.96

236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4
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1.03
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1.00
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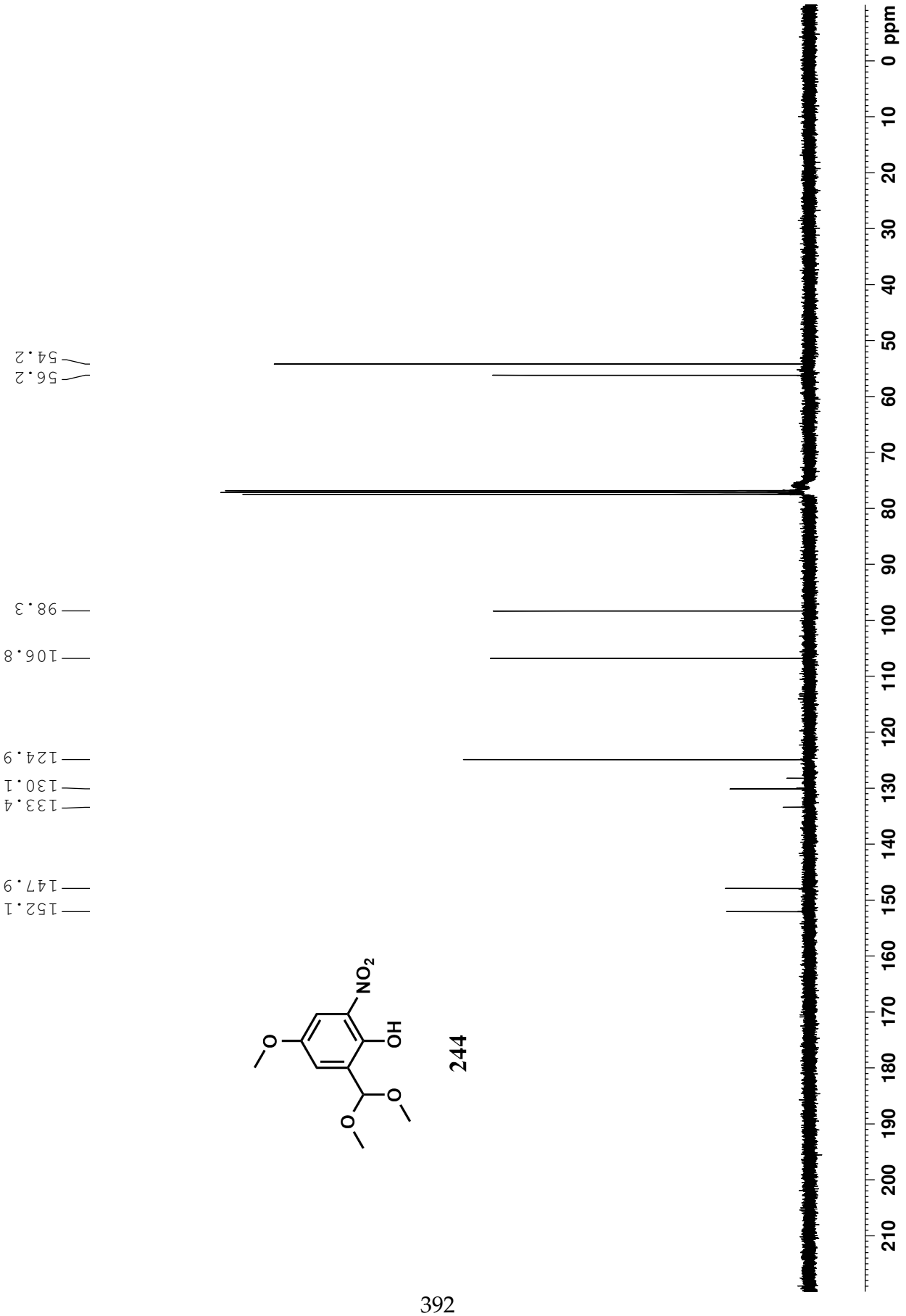
OH
O
O
O
244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56.2
98.3
106.8
124.9
130.1
133.4
147.9
152.1
0 ppm
10
20
30
40
50
60
70
80
90
100
110
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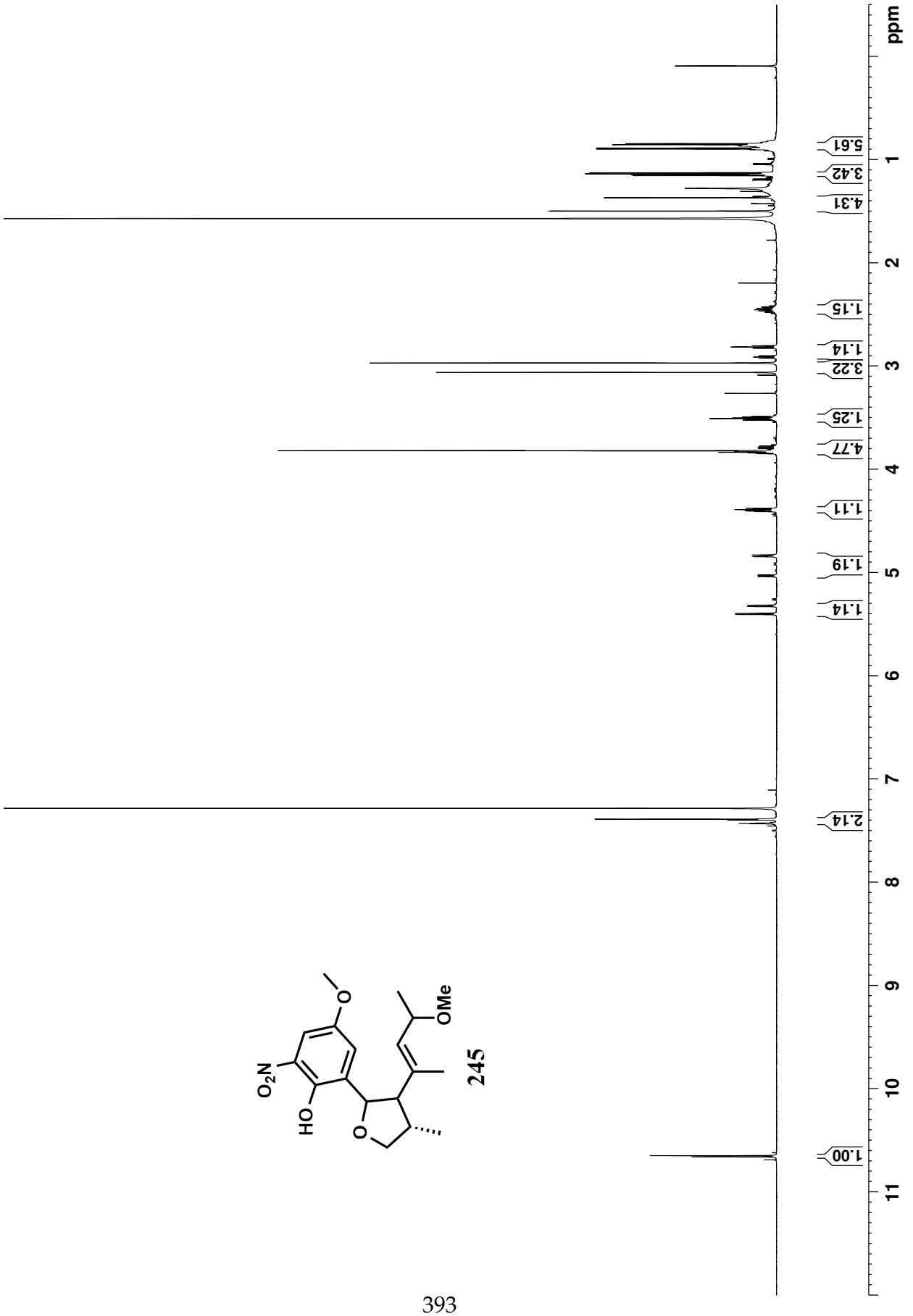
130
140
150
160
170
180
190
200
210
NO2
OH
O
O
O
O
244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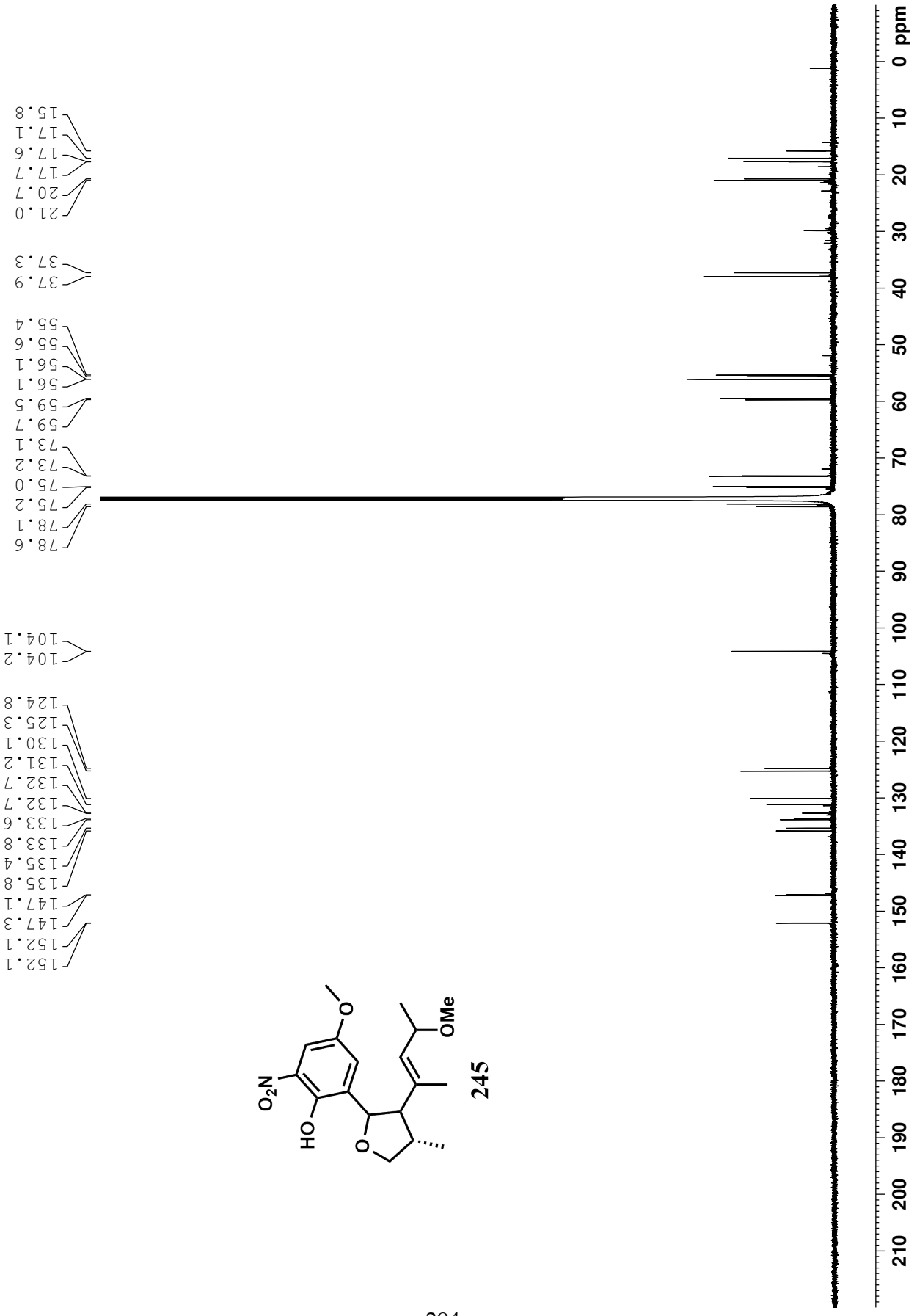
3.22
1.25
4.77
1.11
1.19
1.14
2.14
1.00
O2N
HO
O
OMe
245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152.1
147.3
147.1
135.8
135.4
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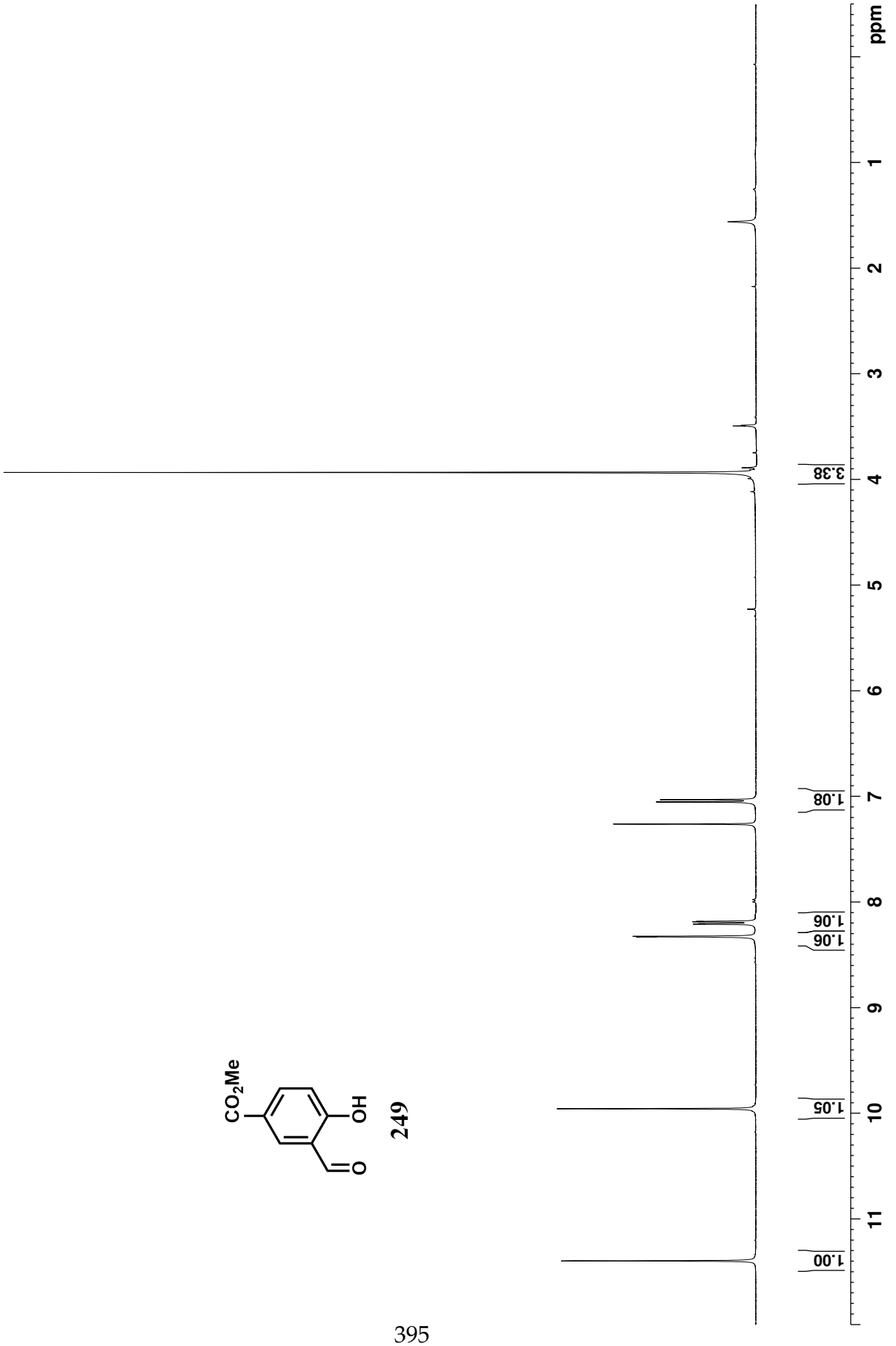
133.6
132.7
132.7
131.2
130.1
125.3
124.8
104.2
104.1
78.6
78.1
75.2
75.0
73.2
73.1
59.7
59.5
56.1
56.1
55.6
55.4
37.9
37.3
21.0
20.7
17.7
17.6
17.1
15.8
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O2N
HO
O
OMe
245



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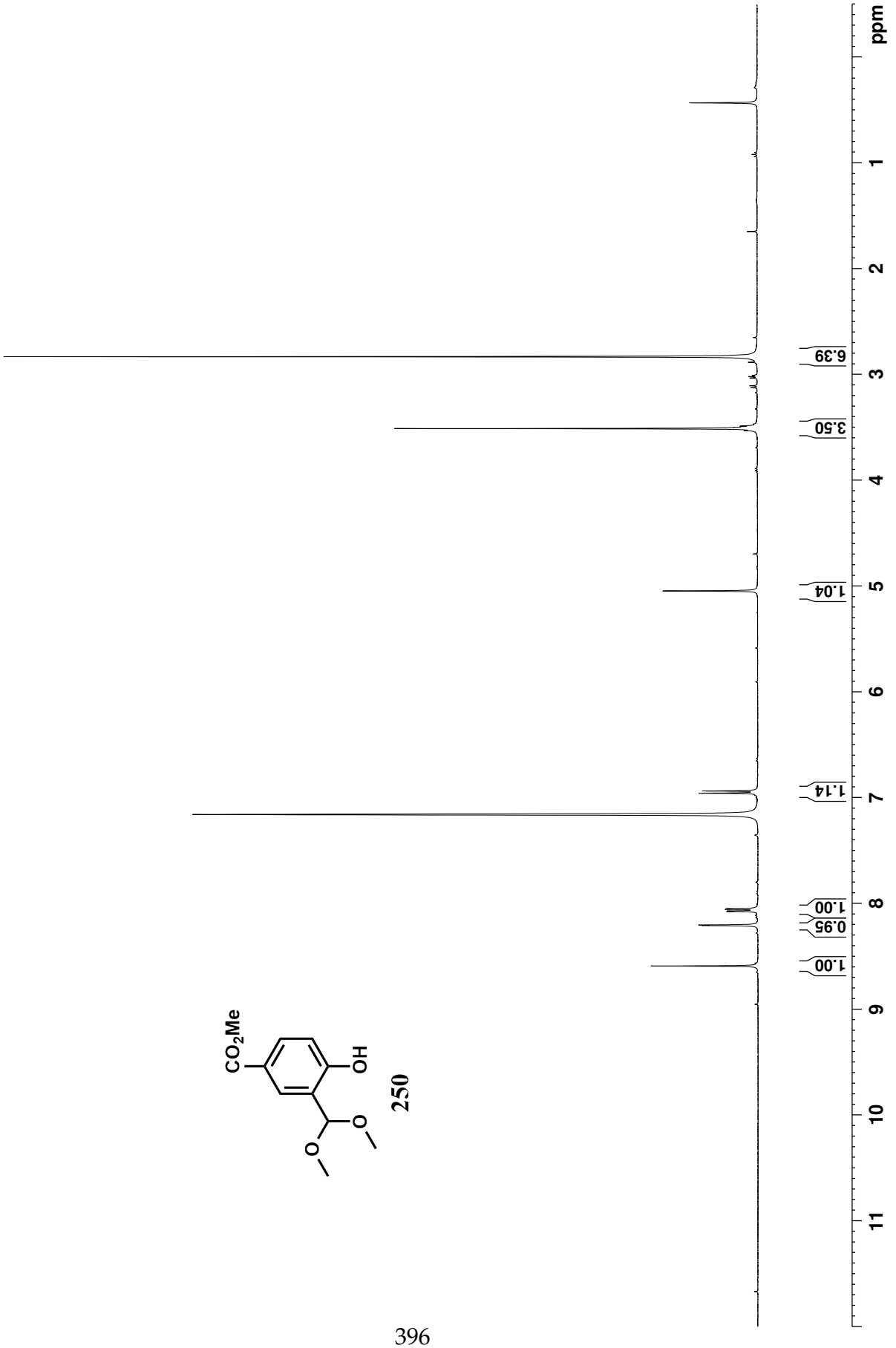
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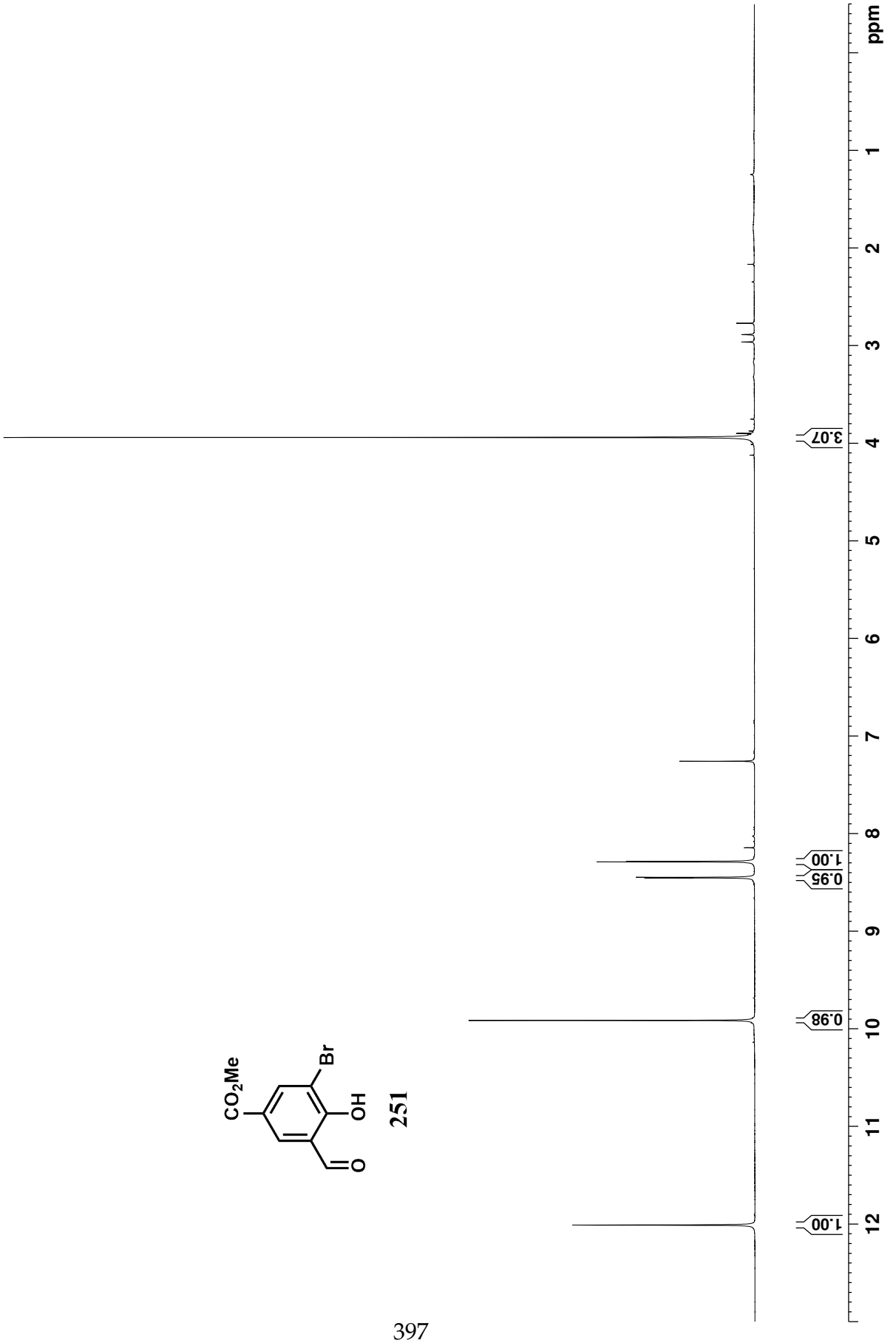
1.00
CO2Me
OH
O
O
250



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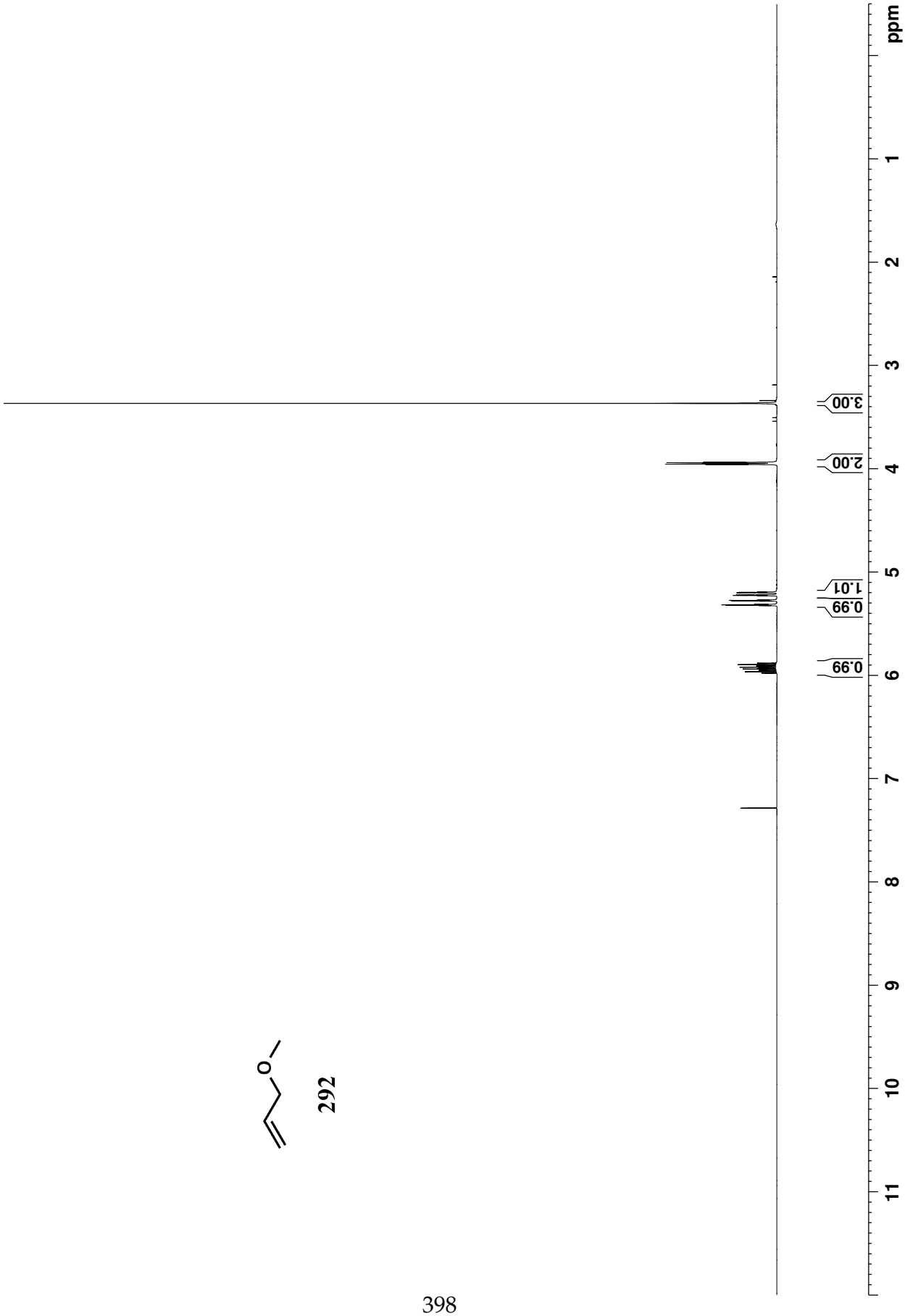

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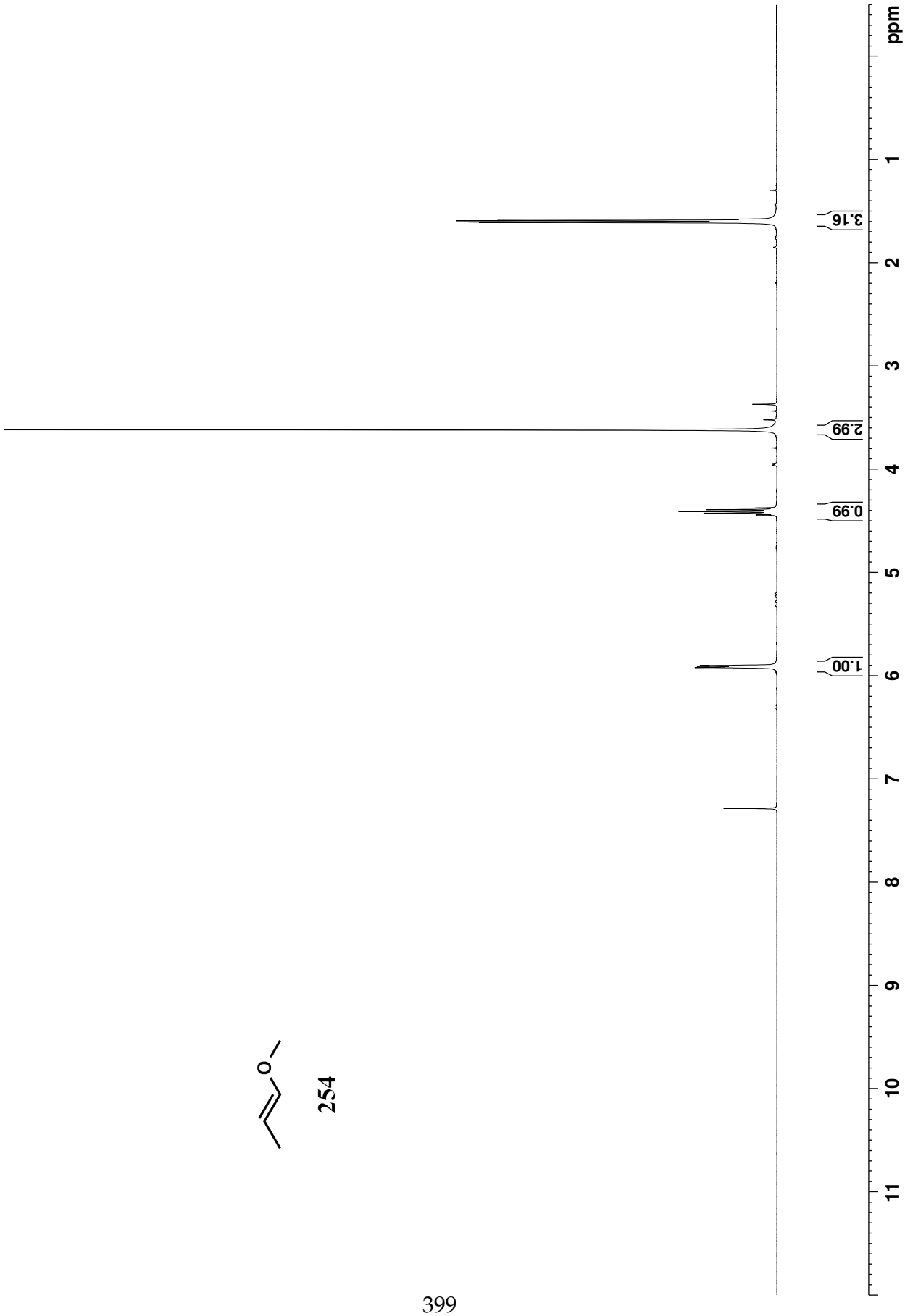
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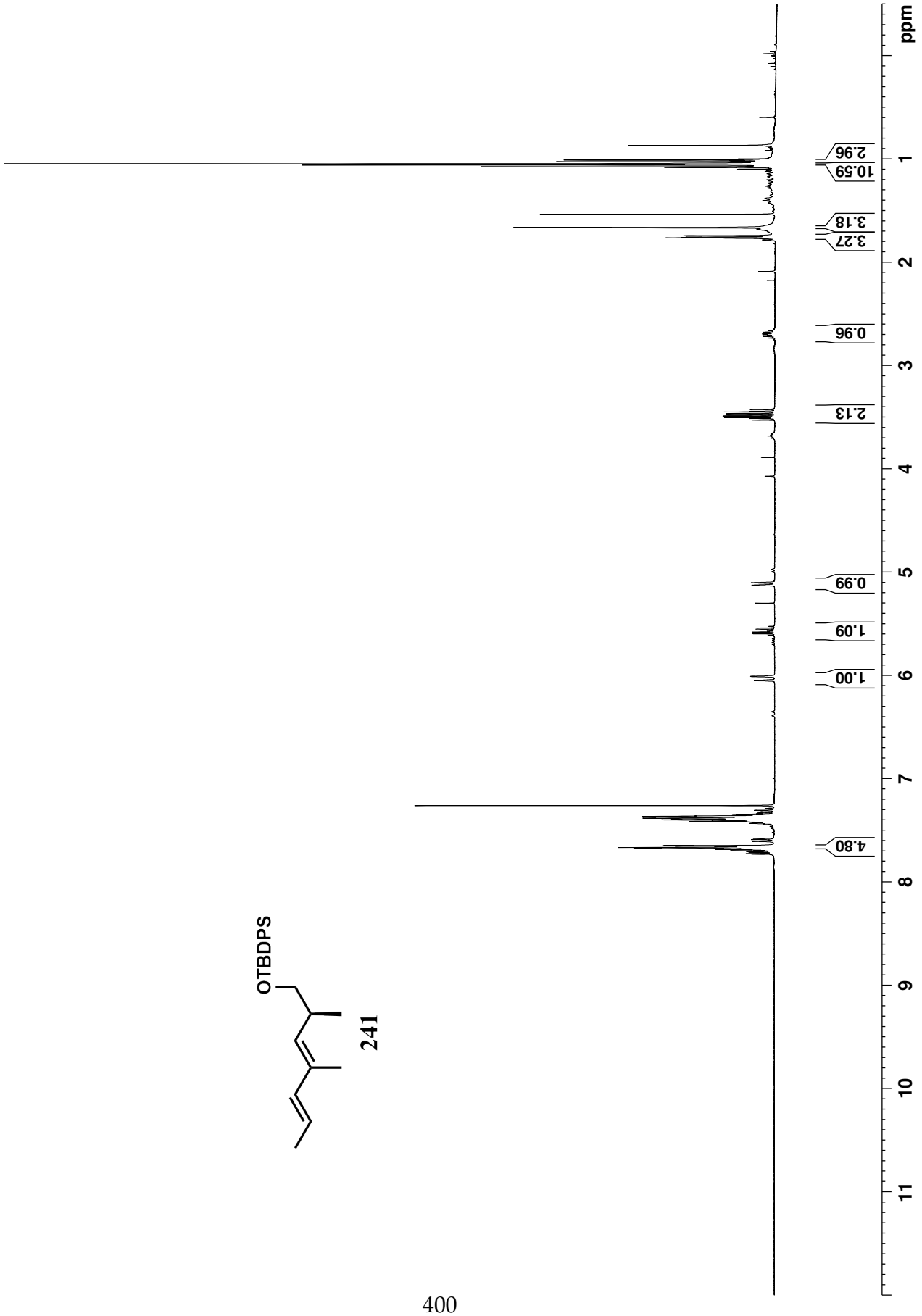
O
254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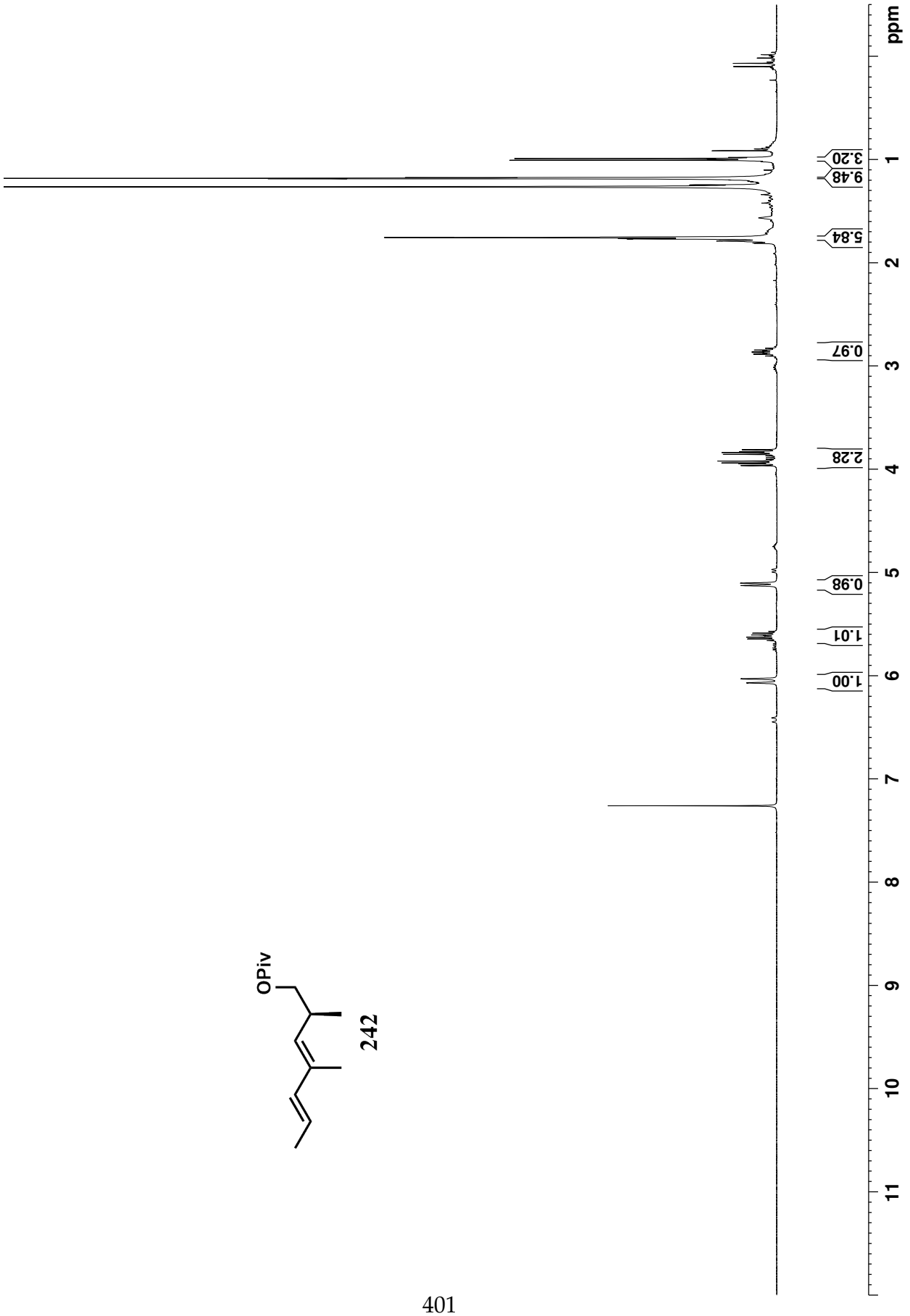
ppm


OPiv
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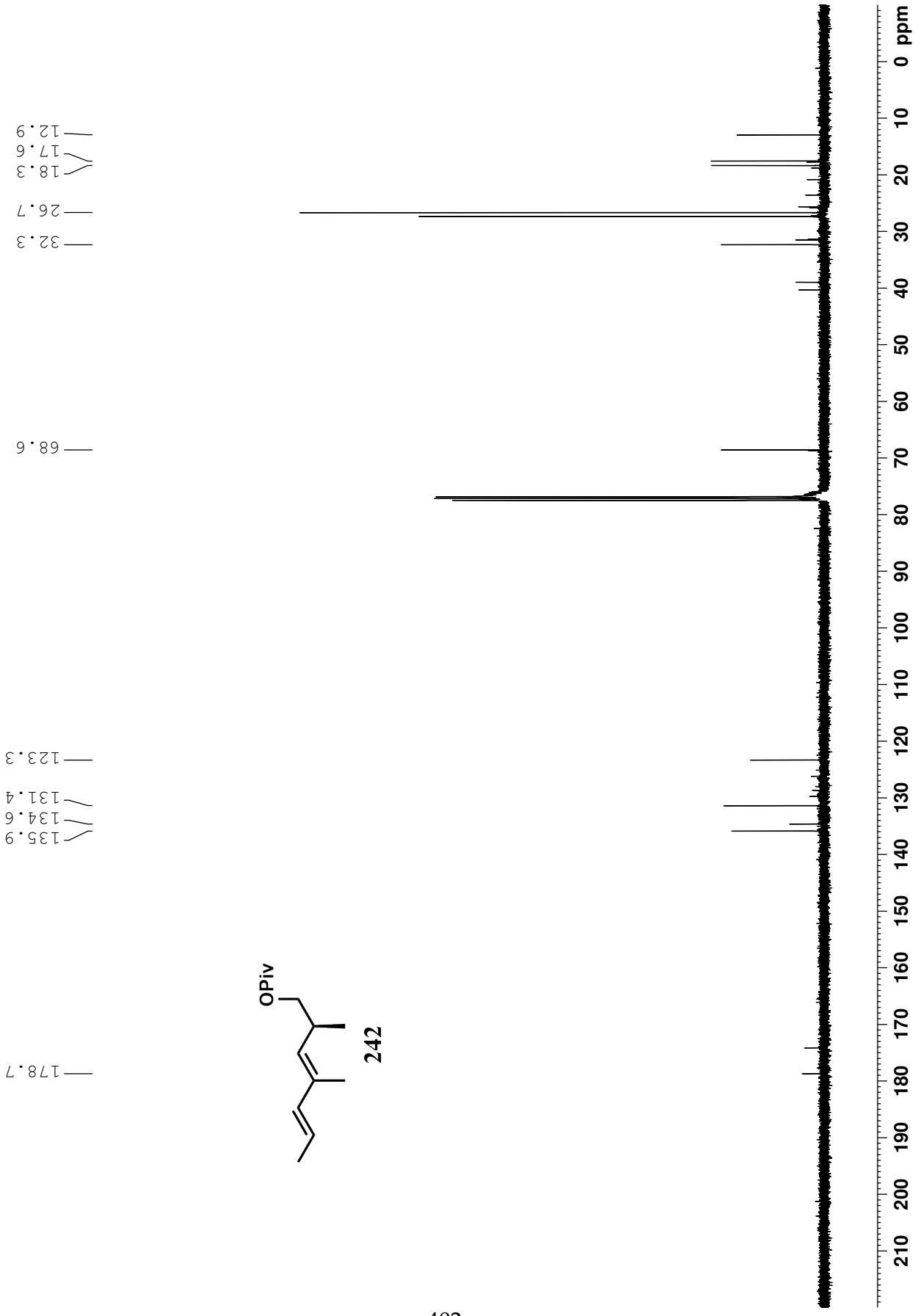
1.00
ppm


178.7
135.9
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131.4
123.3
68.6
32.3
26.7
18.3
17.6
12.9
OPiv
242
0 ppm
10
20
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60
70
80
90
100
110
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140
150
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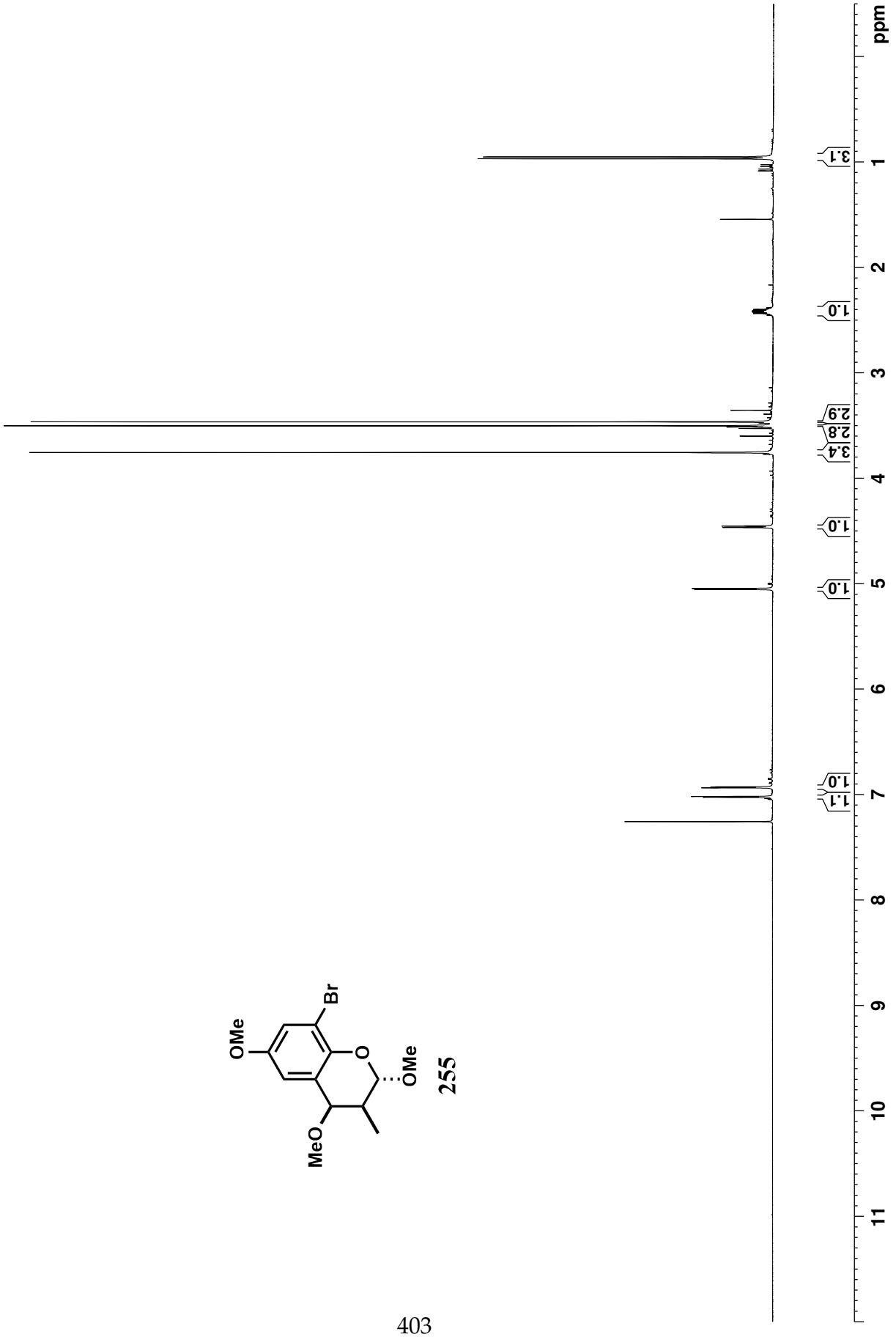
180
190
200
210



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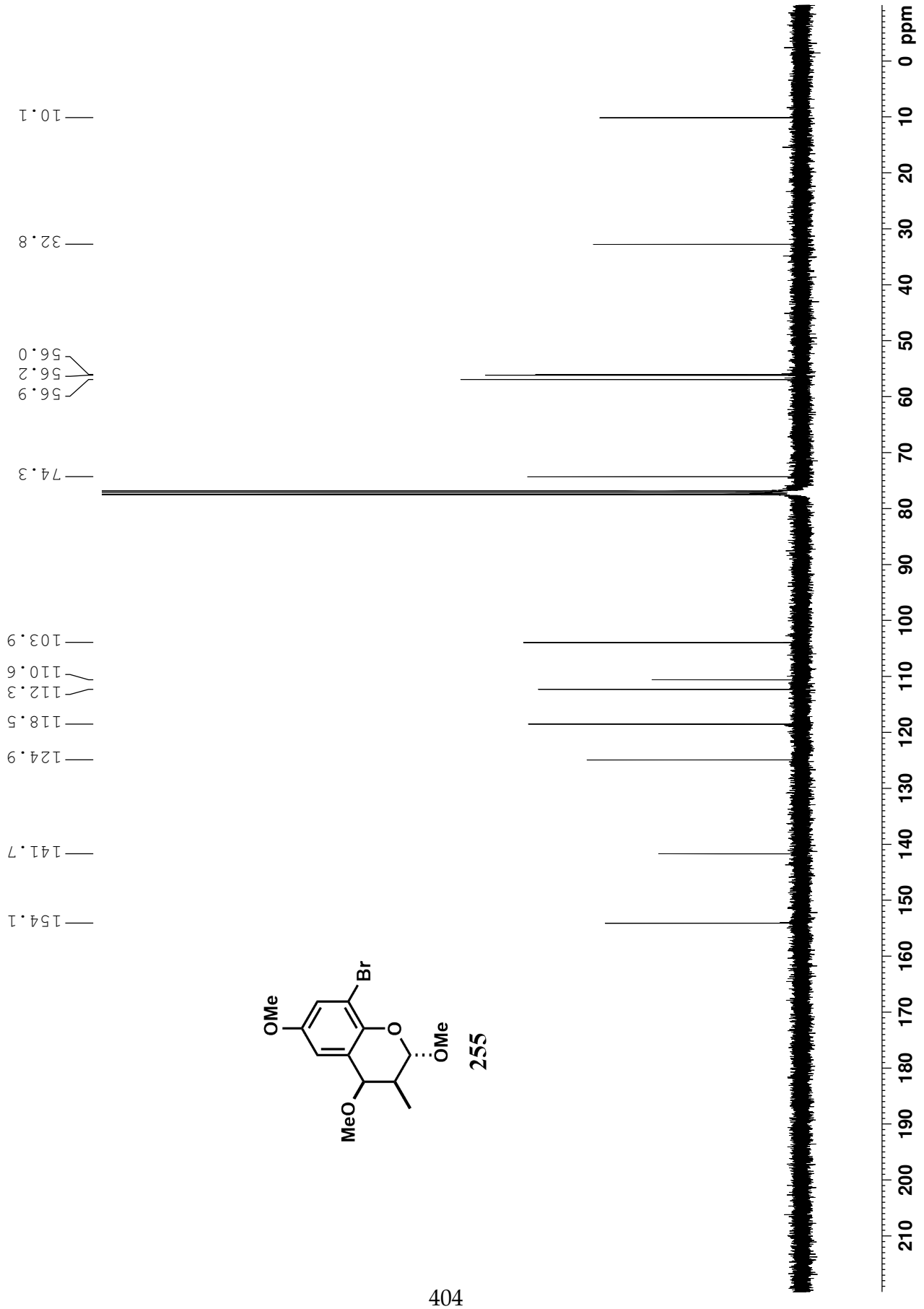
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56.9
74.3
103.9
110.6
112.3
118.5
124.9
141.7
154.1
OMe
Br
O
OMe
MeO
255
0 ppm
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60
70
80
90
100
110
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140
150
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180
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200
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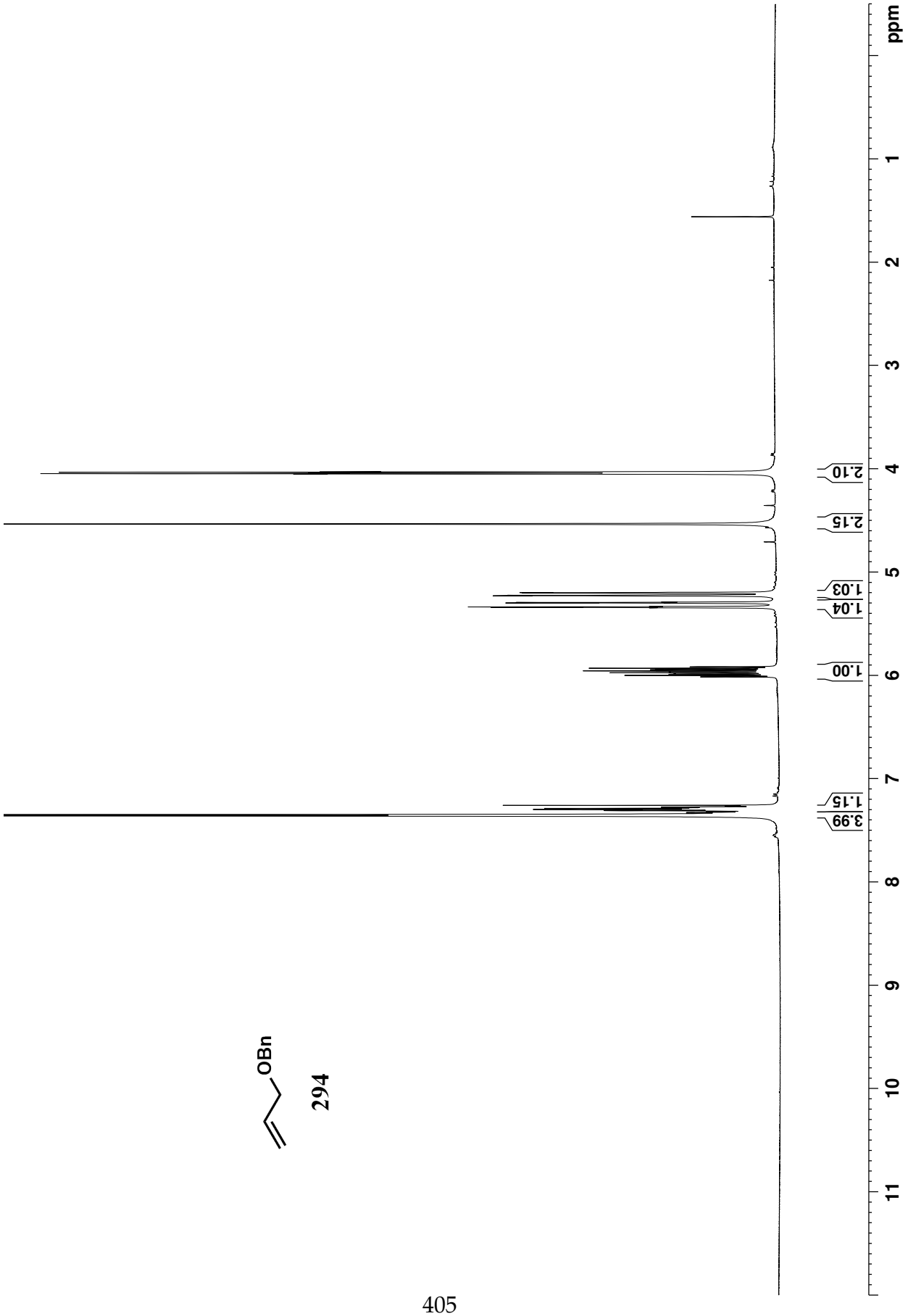
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1.04
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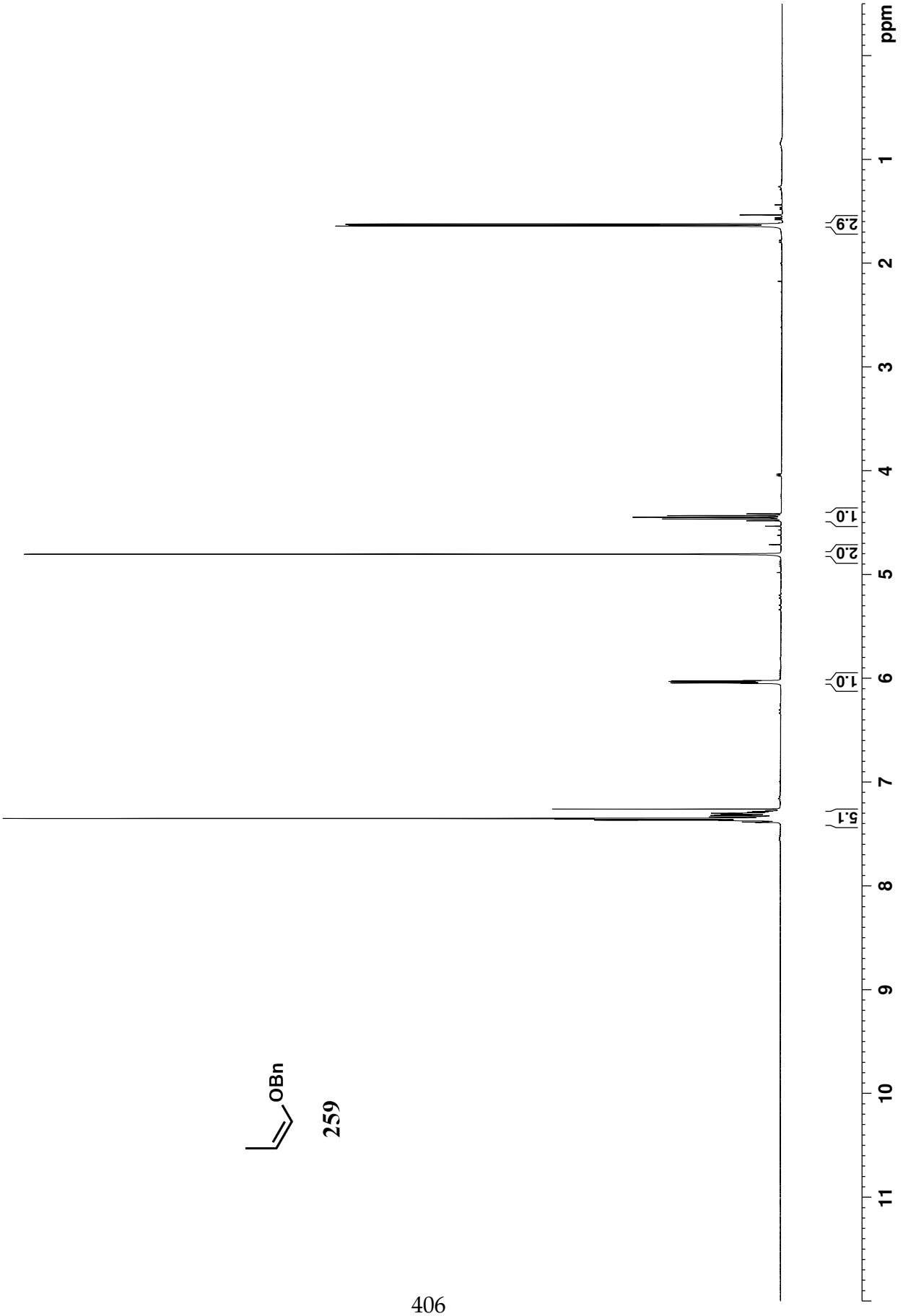
1.15
3.99
ppm


OBn
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1.0
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ppm
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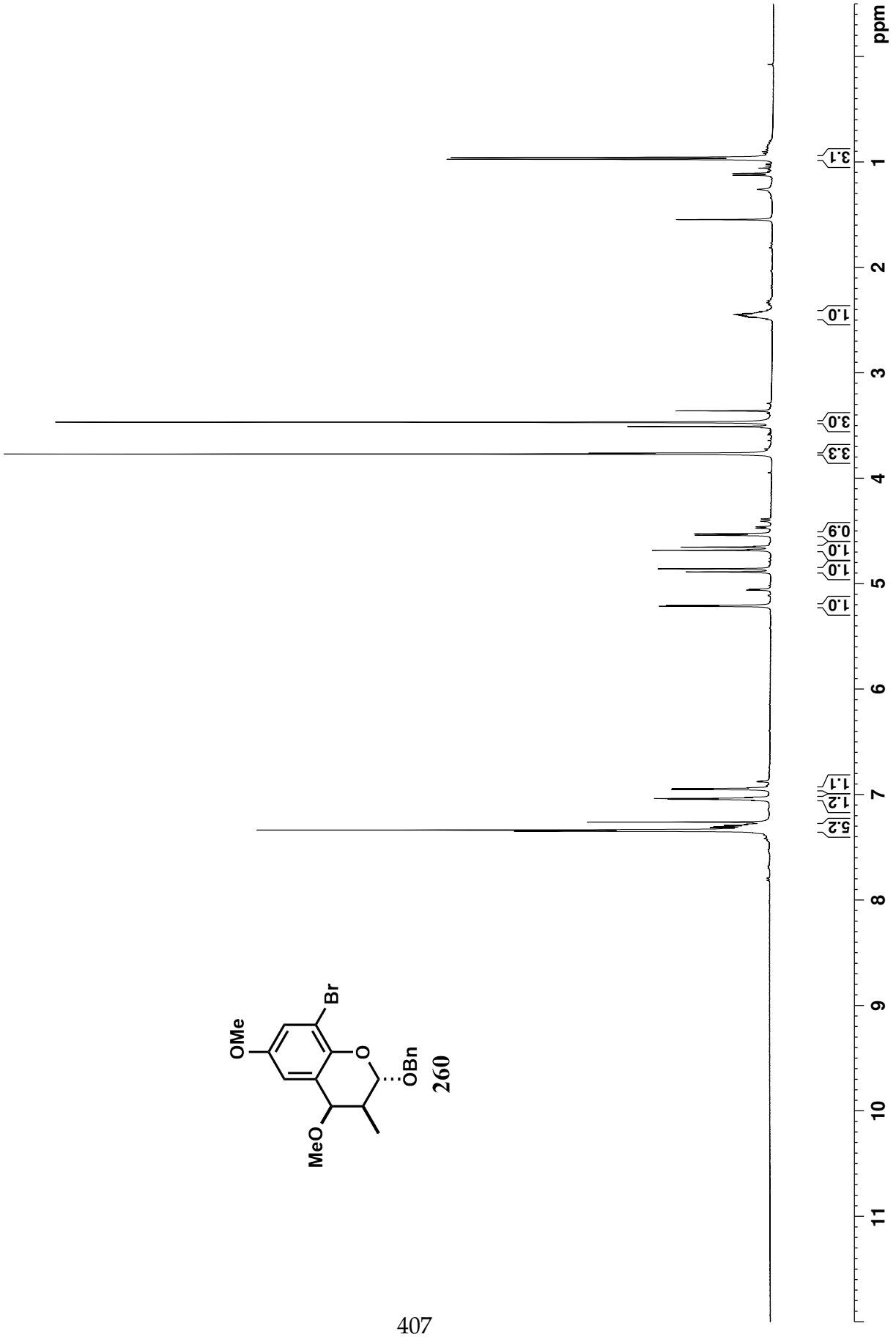
8
9
10
11


ppm
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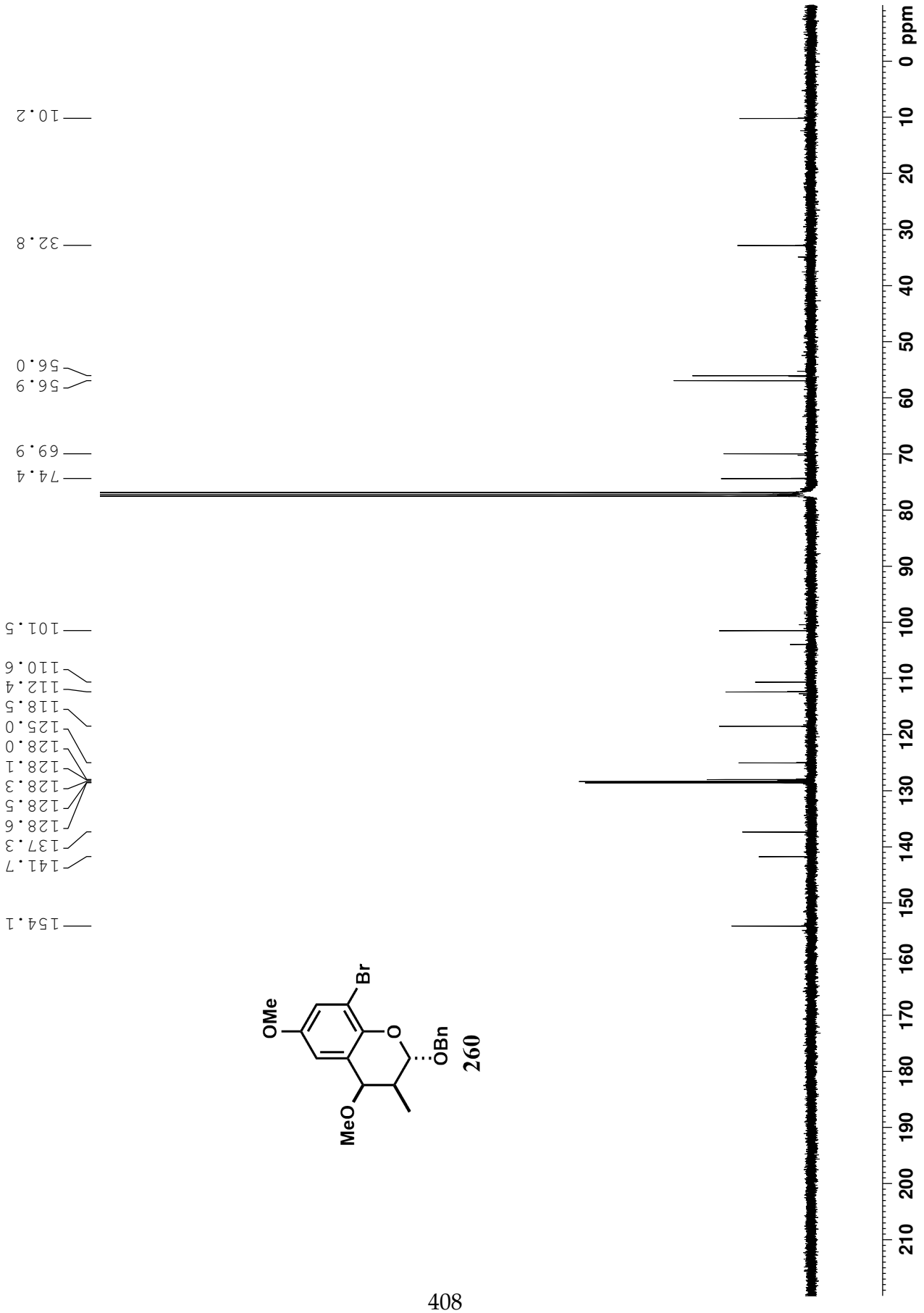
1.0
1.0
1.1
1.2
5.2
Br
OMe
O
OBn
MeO
260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128.3
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118.5
112.4
110.6
101.5
74.4
69.9
56.9
56.0
32.8
10.2
0 ppm
10
20
30
40
50
60
70
80
90
100
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130
140
150
160
170
180
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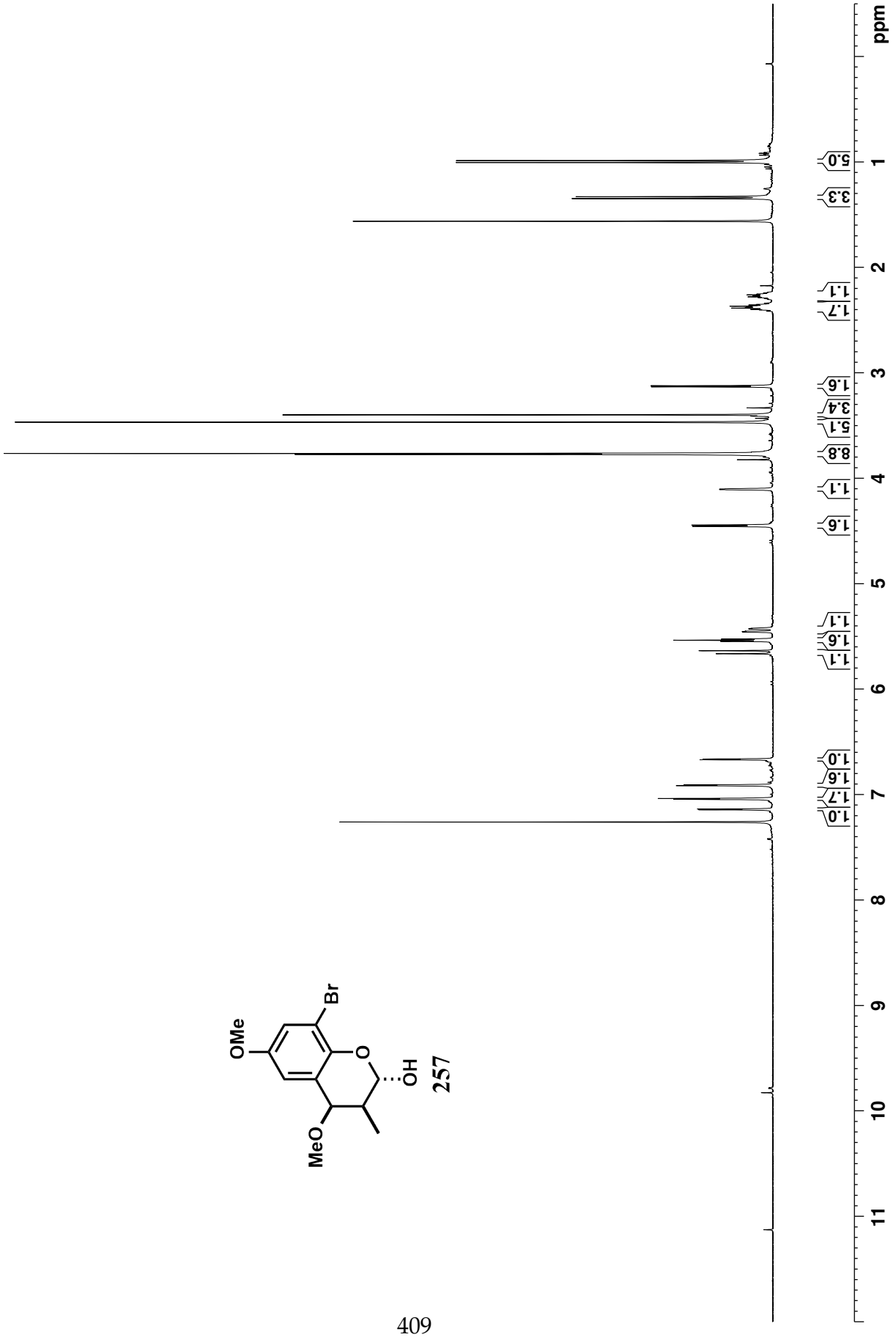
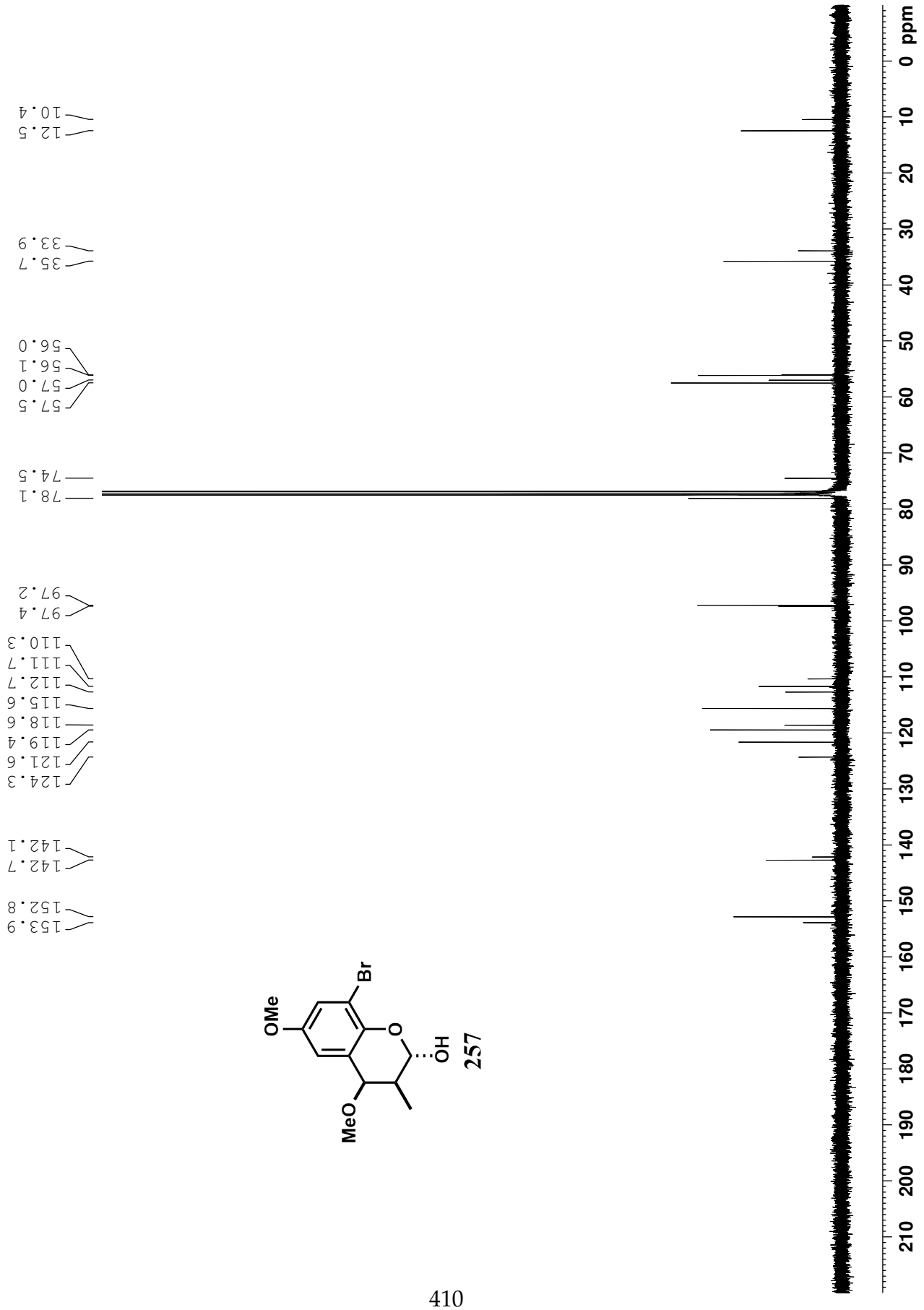
200
210
OMe
Br
O
OBn
MeO
260


Br
OMe
O
OH
MeO
257
ppm
1 2 3 4 5 6 7 8 9 10 11
5.0
3.3
1.1
1.7
1.6
3.4
5.1
8.8
1.1
1.6
1.1
1.6
1.1
1.0
1.6
1.7
1.0


153.9
152.8
142.7
142.1
124.3
121.6
119.4
118.6
115.6
112.7
111.7
110.3
97.4
97.2
78.1
74.5
57.5
57.0
56.1
56.0
35.7
33.9
12.5
10.4
0 ppm
10
20
30
40
50
60
70
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140
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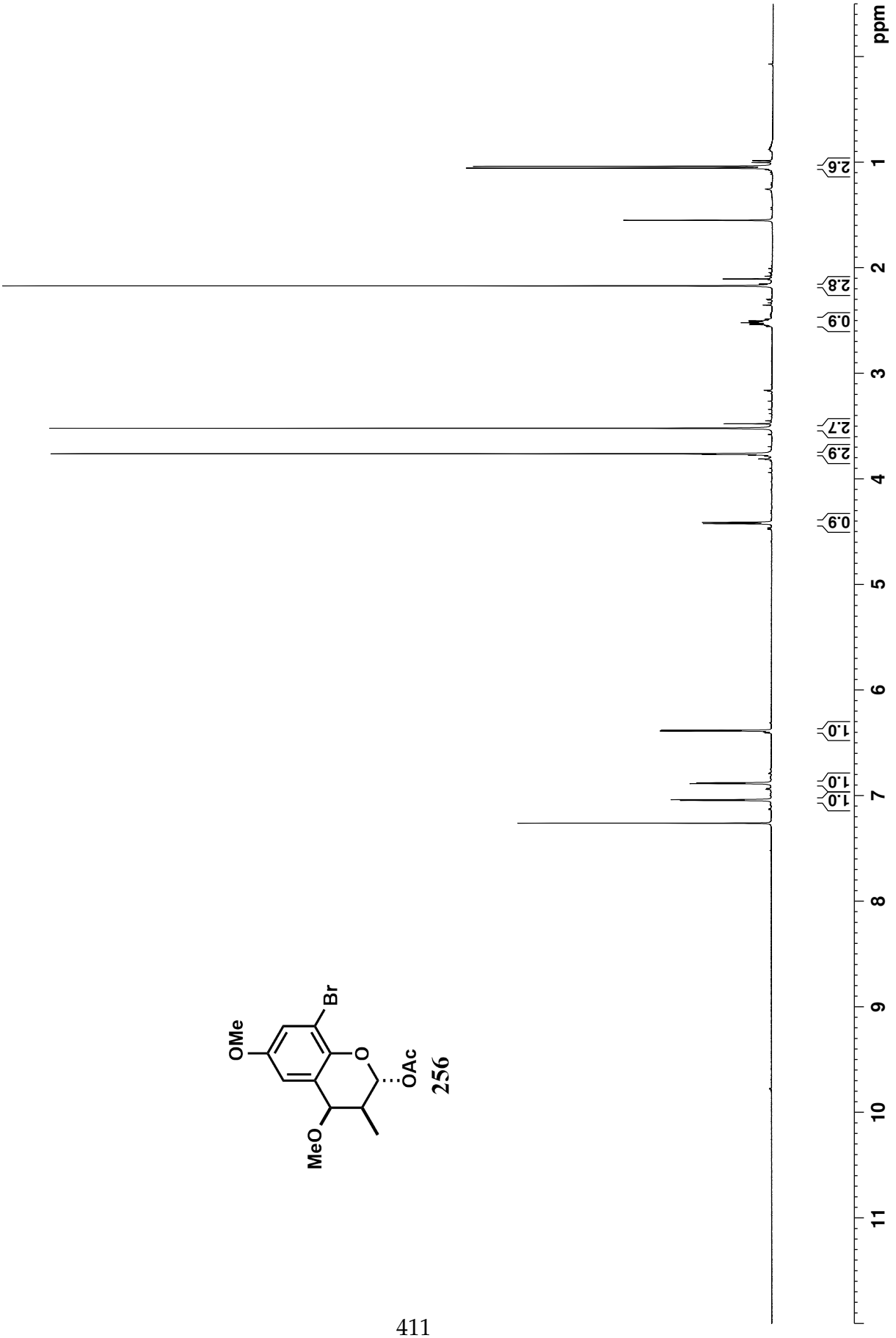
O
OH
MeO
257



256


169.7
154.3
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123.7
119.1
113.0
110.6
93.2
75.7
57.8
56.0
33.3
21.3
7.3
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
OMe
Br
O
OAc
MeO
256

Danksagung

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Lebenslauf

Persönliche Daten

Name	Helge Berneaud-Kötz
Geburtsdatum/-ort	23.02.1992 in Hamburg, Deutschland
Staatsangehörigkeit	Deutsch
Familienstand	ledig

Akademischer Werdegang

Januar 2018 - Mai 2021	**Promotionsstudium** an der Gottfried Wilhelm Leibniz Universität Hannover im Arbeitskreis von Prof. Dr. Andreas Kirschning, Thema: *„Development of a Total Synthesis of Cebulactams A1 and A2“*.
November 2017	M.Sc. Chemie, Gottfried Wilhelm Leibniz Universität Hannover (Note: *mit Auszeichnung*).
Mai 2017 - November 2017	Masterarbeit an der Gottfried Wilhelm Leibniz Universität Hannover im Arbeitskreis von Prof. Dr. Andreas Kirschning, Thema: *„Studies on the Total Synthesis of Cebulactam“*.
Oktober 2016 - April 2017	Forschungspraktikum an der University of California, Berkeley, USA im Arbeitskreis von Dr. Tom Maimone, Thema: *„Synthesis of new etoposide derivatives“*.
April 2015 - November 2017	Studium M.Sc. Chemie an der Gottfried Wilhelm Leibniz Universität Hannover.
Oktober 2011 - September 2014	Studium B.Sc. Chemie an der Gottfried Wilhelm Leibniz Universität Hannover, (Note: *gut*).
Juni 2011	Abitur, Humboldtschule Hannover, Hannover, Deutschland

Konferenzen/Poster Präsentationen

1. Poster Präsentation, ORCHEM, Deutschland, Berlin **2018**.
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Publikationen

1. E. Geist, H. Berneaud-Kötz, T. Baikstis, A. Kirschning *Org. Lett.* **2019**, *21*, 8930-8933.