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Synthesis of Desepoxy-Tedanolide C

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Dedicated to Prof. Steven V. Ley on the occasion of his 75th birthday

Abstract: The synthesis of desepoxy-tedanolide C was accomplished and provided experimental evidence on the configuration of tedanolide C. The reported chemical shifts and coupling constants point to a configuration different from the published structure and analogous to the structures of the other members of this family of natural products. The key step is a Kiyooka aldol protocol for the stereoselective synthesis of the tertiary alcohol flanked by three additional oxygenated carbon atoms. Furthermore, two additional aldol reactions and a Julia–Kocienski olefination were used to assemble the carbon framework.

The tedanolides[1] are a group of natural products isolated from marine sources which exhibit remarkable biological activities in the pM range (tedanolide (**1**): ED_{50} at 26.2 pM in lymphocytic leukemia cell lines; 13-deoxytedanolide (**2**) IC_{50} at 0.16 pM against P388 murine leukemia cell lines). The inhibition of translation was identified as their prime biological target and has initiated vital synthetic activities towards the synthesis of Tedanolide (**1**) itself as well as 13-deoxytedanolide (**2**) and desepoxyisotedanolide (**6**).[2] The latest additions to this family of natural products were the candidaspongolides (**3**)[3] and tedanolide C[4] (Figure 1).

Tedanolide C was isolated by the group of Chris M. Ireland from marine sponge *Ircinia sp.* collected in Milne Bay, Papua New Guinea. It shows a remarkable cytotoxic profile against HCT-116 cells at 95.3 nM. Like tedanolide and 13-deoxytedanolide it could serve as an inhibitor of protein biosynthesis. The

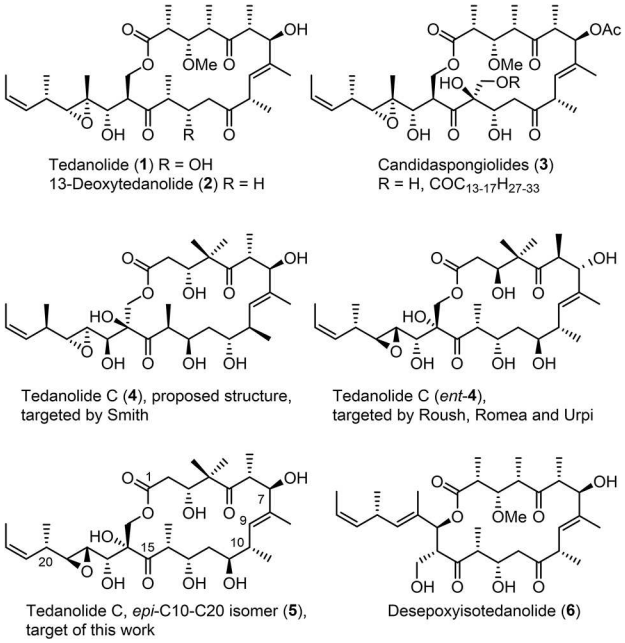

Figure 1. Members of the tedanolide family.

configuration of tedanolide C was determined based on coupling constants in combination with molecular modeling. This led to a putative structure which resembles the relative configuration of the southern and eastern part of tedanolide (C10-C23), albeit as its enantiomeric structure. The northern part, however, parallels the absolute configuration of tedanolide. The rational for the proposed deviation of tedanolide C in comparison to tedanolide argues that a 9.2 Hz coupling constant between H-9 and H-10 would support an eclipsed conformation and that only the proposed structure was in accordance with computationally generated isomers. On the other and the coupling constant for the corresponding protons of tedanolide were reported to be in the same range (Schmitz:[1d] 10.8 Hz, Kalesse:[2g] 8.5 Hz, Smith:[2c] 10.1 Hz, Roush:[2i] 9.6 Hz). Due to the fact that the configuration would significantly deviate from tedanolide even though a biosynthetic relationship is likely and the computationally proposed structure involves an eclipsed orientation of the protons H-9 and H-10, we used instead **5** as our target molecule for the synthesis of tedanolide C as the configurations resemble those of the other members of this family. Smith and his group targeted the putative structure of tedanolide C (**4**),[5] whereas the groups of Roush,[6] Romea and Urpi[7] used the enantiomer (*ent*-**4**) as their synthetic target.

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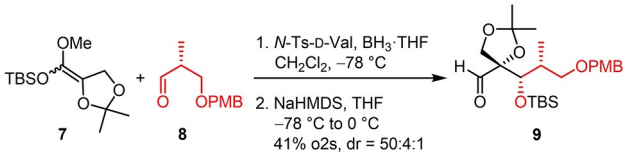
Our interest in this family of natural products was initiated by their extraordinary biological activity, the challenge of constructing a polyketidal natural product with a wide variety of sites which could hamper its synthesis due to retro-aldol processes and/or eliminations and finally because this group of natural products features a rare macrolactone comprising a primary alcohol.

Our synthesis uses a Kiyooka aldol protocol as the key step which we deliberately developed for this synthesis and which constructs the motif containing the tertiary alcohol and the three adjacent oxygenated carbon atoms selectively (Scheme 1).[8] For the synthesis of tedanolide C (**5**), we used aldehyde **8**,[8a,9] which is derived from Roche ester and builds up a matched situation with the oxazaborolidinone from *N*-Ts-D-Val as the employed Lewis acid. This step sets up the tertiary alcohol as well as the configuration at C14. The secondary alcohol at C15 will be oxidized later to its corresponding ketone but is carried through the synthesis in order to prevent retro-aldol processes and eliminations.

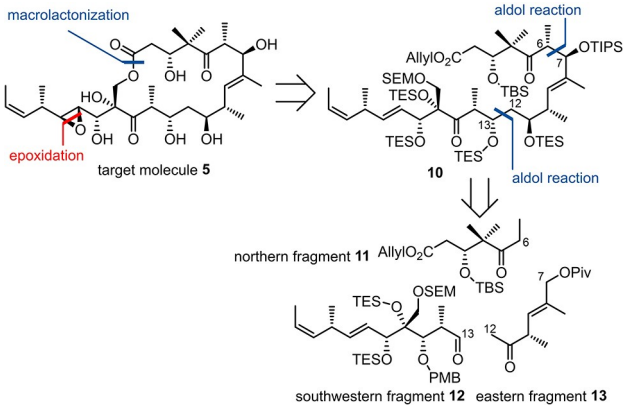
With the state of knowledge of successful tedanolide syntheses and the apparent success of aldol disconnections in these endeavors we also took advantage of two aldol disconnections between C6-C7 and C12-13, respectively (Scheme 2). The aldol disconnection between C6 and C7 has the advantage that it would provide the desired C5 keto carbonyl group. The C12-C13 disconnection requires an anti-selective reduction of the hydroxyl ketone. Finally, a macrolactonization would deliver the desired framework.

The synthesis commenced with carboxylic acid **15** which is accessible in 5 steps from readily available starting materials.[10] Generation of allyl ester **11** could be accomplished in 78% yield (Scheme 3). For the synthesis of eastern fragment **13** (Scheme 4) a vinylogous Mukaiyama aldol reaction provides intermediate **18**[11] which is TBS-protected, reduced and transformed to its pivalate **19**. Overall, the synthesis of the northern **11** and eastern segment **13** can be obtained rapidly through 6 or 5 steps, respectively. The synthesis of the southwestern part of tedanolide C however, was the subject of intensive investigations as it not only holds the tertiary alcohol but additionally required transformations on the adjacent, pseudo neopentylic positions (C15 and C17).

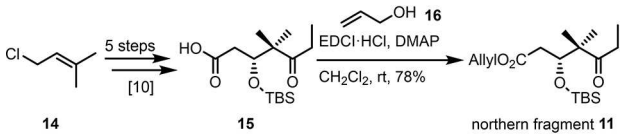
We started the synthesis with the above described Kiyooka protocol (Scheme 1) to generate the tertiary alcohol. The so-obtained product was protected as its PMP-acetal **21**,[8b] which in turn was cleaved by DIBAL-H reduction and the primary alcohol was Piv-protected (Scheme 5). TBAF deprotection of the mixed acetal liberated aldehyde **22** which was used in the stereoselective addition of vinyl magnesium bromide to generate allylic alcohol **24**. The configuration was assigned via its corresponding acetonide[12] (supporting information) and is consistent with Cram chelation control.[13] This set the stage for olefination with segment **28** which was obtained through an olefination of Roche ester (**20**) and subsequent generation of the Julia-Kocienski sulfone. For joining both segments, allylic alcohol **24** was dihydroxylated and subjected to diol cleavage with PIDA in acetone/water. The so-obtained aldehyde **29** was subjected to the above mentioned Julia–Kocienski olefination[14] to generate compound **30** in an *E*:*Z* ratio of ≥95:5. The next steps were committed to establish the appropriate protecting group assembly that would allow for the macrocyclization as well as for setting the appropriate oxidation states in the C11 to C15 region of the southwestern hemisphere. Here we will only cover the combination that was finally successful. The trials and errors that ultimately led to this route will be reported elsewhere. First, the acetonide imbedding the tertiary alcohol had to be cleaved as the primary alcohol needs to be selectively liberated for the macrolactonization. This was achieved in good



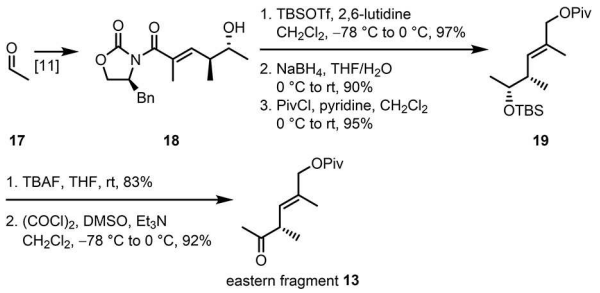
Scheme 1. Pivotal Kiyooka aldol step in the synthesis of tedanolide C (o2s = over 2 steps).



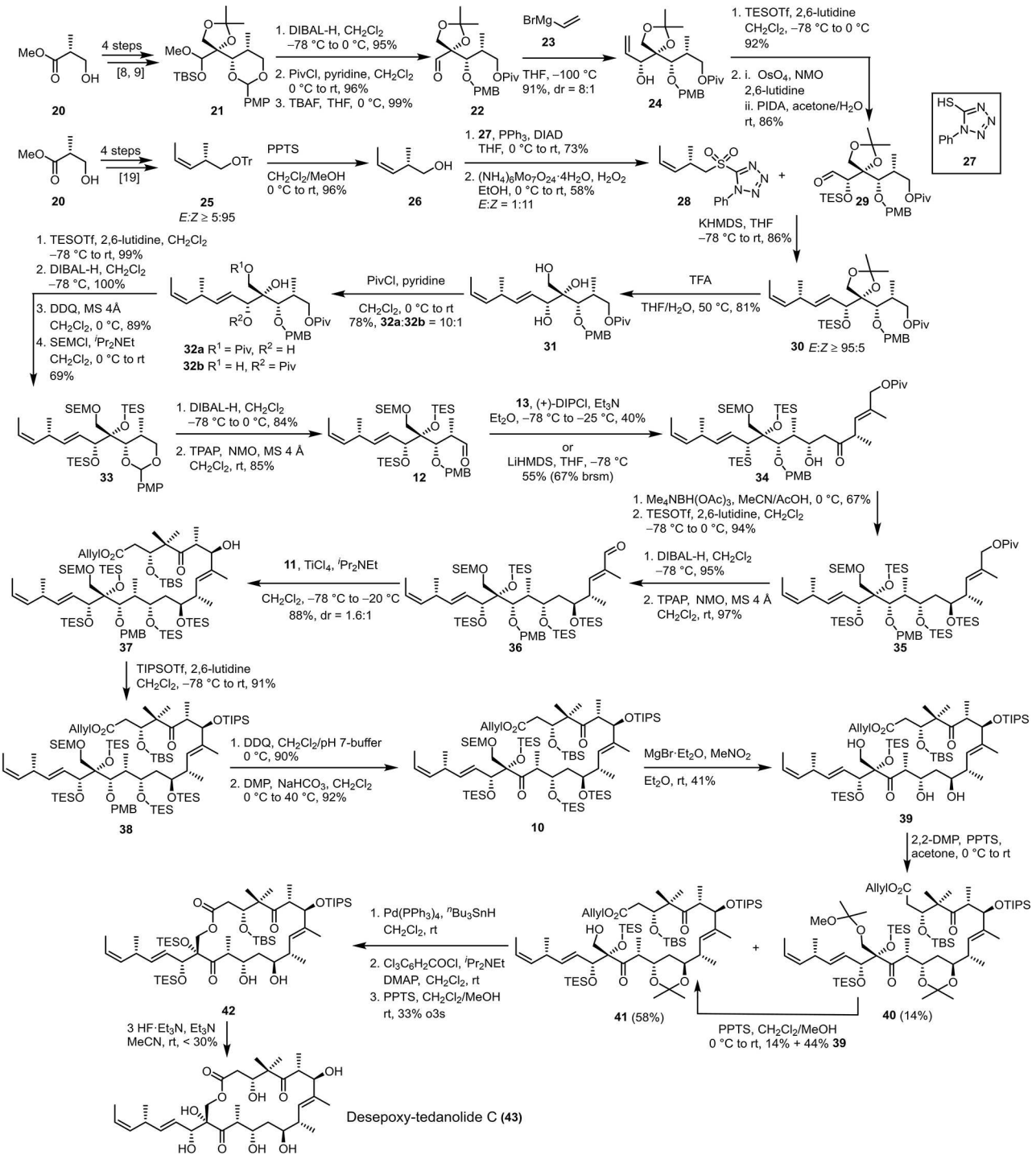
Scheme 2. Retrosynthetic analysis of tedanolide C (**5**).



Scheme 3. Synthesis of northern fragment **11**.



Scheme 4. Synthesis of eastern fragment **13**.



Scheme 5. Synthesis of desepoxy-tedanolide C (**43**) (o3 s = over three steps).

yields with TFA with the allylic TES-ether being simultaneously cleaved. The primary alcohol at C13 was Piv-protected in order to liberate both primary alcohols at the same time. Then, the allylic alcohol at C17 and the tertiary alcohol were both TES-protected, both Piv-groups were reductively removed and the alcohol at C13 was transformed to its PMP-acetal with DDQ. Finally, the only hydroxyl group unprotected was the one that is required for the macrolactonization which then was protected as its SEM-ether **33**. A DIBAL-H reduction liberated the primary alcohol at C13 and oxidation with TPAP[15] provided the desired aldehyde **12** for the aldol reaction with eastern fragment **13**. This aldol reaction was achieved with either DIPCl (40%) or LiHMDS (55%) and generated a single isomer **34**. The subsequent *anti*-selective reduction was accomplished with the Evans–Saksena protocol[16] in 67% yield. The newly generated secondary alcohol was TES-protected and the Piv-group reduc-

tively removed. TPAP oxidation set the stage for the second aldol reaction. This was put into practice with $TiCl_4$ in quite goods yields (88%) but with only a modest selectivity of 1.6:1 for the desired isomer. Nevertheless, both isomers could be separated and the desired one was TIPS-protected (**38**). At this stage, all carbons were assembled and we decided to establish the carbonyl group at C15 prior to ring closure.

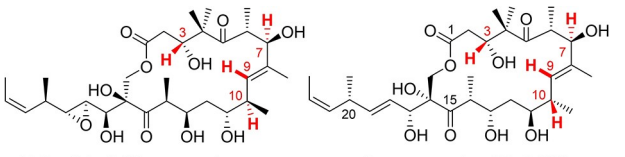
Again, in other protecting group combinations this proved to be a non-trivial task and here we only present the successful route. DDQ and DMP provided the carbonyl group in very good yields (90%, 92%) and treatment with $MgBr_2$ in $MeNO_2$[17] liberated the primary alcohol. During cleavage of the SEM-ether, the TES groups at C11 and C13 were removed as well and the latter were re-protected as acetonide **41**. Finally, a palladium-catalyzed cleavage of the allyl ester followed by a Yamaguchi lactonization[18] provided the macrolactone of tedanolide C. Eventually, global deprotection was achieved in two steps with PPTS and $HF{\cdot}Et_3N$.

Unfortunately, the material was not stable in MeOH and it slowly decomposed (retro-aldol products) while ^{13}C-NMR spectra of deseopxy-tedanolide C (**43**) were taken. However, the ^{1}H-NMR and HSQC/HMBC spectra recorded are in good agreement with the ones reported from isolated tedanolide C. In particular the chemical shift and coupling constant of the C9 and C10 protons are indicative as they were part of the argumentation for the proposed structure. The rational for the proposed structure took aid from computational studies which proposed an eclipsed conformation around this part of the molecule and served in part as a rational for the configuration of the southern part opposite as compared to the other congeners of the tedanolide family. Since desepoxy-tedanolide C (**43**) with the opposite configuration in the southern part shows the same coupling constant, one can safely argue that also this configuration can produce the chemical shifts and coupling constants as observed for the natural product and the unusual configuration is not necessary to explain the NMR-spectra (Figure 2). Whether compound **5** also displays an eclipsed conformation or this coupling constant results from an *anti*-orientation cannot be concluded at this moment.

The good agreement of the NMR spectra points to a different configuration as originally published. On the other hand, the fact that the synthetic compound was sensitive to decomposition spreads some questions on this conclusion since we in general observe that macrolactones of natural products are quite stable and conformationally restricted to prohibit retro-aldol processes and elimination.

Even though our data support the configuration of tedanolide C as targeted herein, the synthesis of the originally proposed structure and its comparison with the spectra of the authentic material would further back up the structure assignment.

In summary, we have established the first synthetic access to the carbon framework of this complex member of the tedanolide family and have shown how the synthesis of the motif containing a tertiary alcohol can be successfully introduced. Further studies on the configurational assignment of tedanolide C are in progress and will be reported in due course.



Tedanolide C (**4**), proposed structure

Desepoxy-tedanolide C (**43**)

δ^1H [ppm]	δ^{13}C [ppm]	δ^1H [ppm]	δ^{13}C [ppm]
3: 4.14 (dd, *J* = 11.2, 2.8 Hz)	73.1	**3**: 4.15 (dd, *J* = 10.8, 3.1 Hz)	73.0
7: 4.06 (d, *J* = 9.2 Hz)	81.3	**7**: 4.06 (d, *J* = 9.6 Hz)	81.1
9: 5.18 (d, *J* = 9.2 Hz)	134.1	**9**: 5.19 (d, *J* = 9.4 Hz)	134.1
10: 2.20 (ddq, *J* = 9.2, 6.9, <1.0 Hz)	40.4	**10**: 2.21 (multiplett)	40.2

Figure 2. Comparison of indicative NMR signals.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Kiyooka aldol · polyketides · structure elucidation · tedanolie C · tertiary alcohol

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