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Synthetic Studies of Tedanolide, a Marine Macrolide Displaying Potent Antitumor Activity. Stereoselective Synthesis of the C(13)–C(23) Segment

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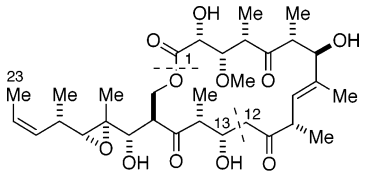
ABSTRACT



Tedanolide

A highly stereoselective synthesis of the C(13)–C(23) segment of tedanolide (1), an 18-membered macrolide isolated from the Caribbean sponge *Tedania ignis*, displaying significant cytotoxicity against KB and PS tumor cell lines, is described which involves two stereoselective epoxidations of regioisomeric trisubstituted double bonds and a stereospecific S_N2' methylation reaction of a *trans*-γ,δ-epoxy-*cis*-α,β-unsaturated ester as the key steps.

Tedanolide (**1**), a structurally complex 18-membered macrolide, was isolated from the Caribbean sponge *Tedania ignis* in 1984,[1] which was referred to as "fire sponge" because contact with the skin induced a localized burning sensation. Tedanolide (**1**) has demonstrated potent antitumor activity as well as cytotoxicity against KB and PS cell lines (ED_{50} values of 0.25 ng/mL and 16 pg/mL, respectively).[1] In 1991, 13-deoxytedanolide (**2**) was discovered from the Japanese sponge *Mycale adhaerens*, and **2** was also revealed to exhibit strong antitumor activity as well as significant cytotoxicity against P388 murine leukemia cells.[2]

These distinctive biological properties, combined with complex stereostructures, make the tedanolide macrolides extremely attractive targets for synthetic chemists,[3−10] and so far Smith[5a,5b] and very recently Roush[8a] have reported successful total syntheses of 13-deoxytedanolide (**2**). However, the synthesis of tedanolide (**1**) has been impeded owing

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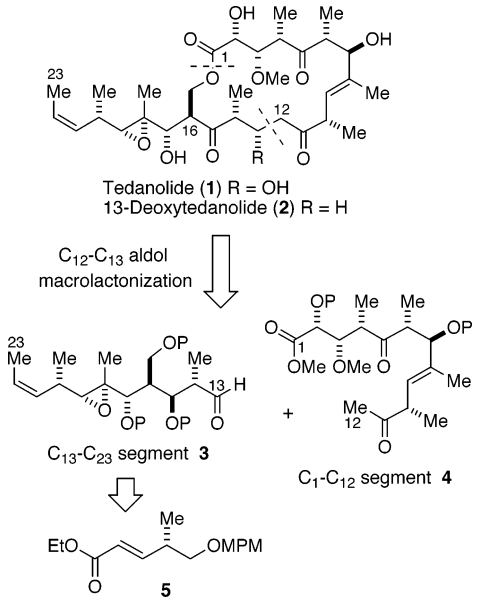
to its densely functionalized complex stereostructure, despite great synthetic efforts.

We set about synthetic studies of tedanolide (**1**) that aimed at developing an efficient synthetic route flexible enough to provide access to the tedanolide macrolides. Our retrosynthesis of tedanolide (**1**) is shown in Scheme 1.

Scheme 1. Retrosynthesis of Tedanolide (**1**)

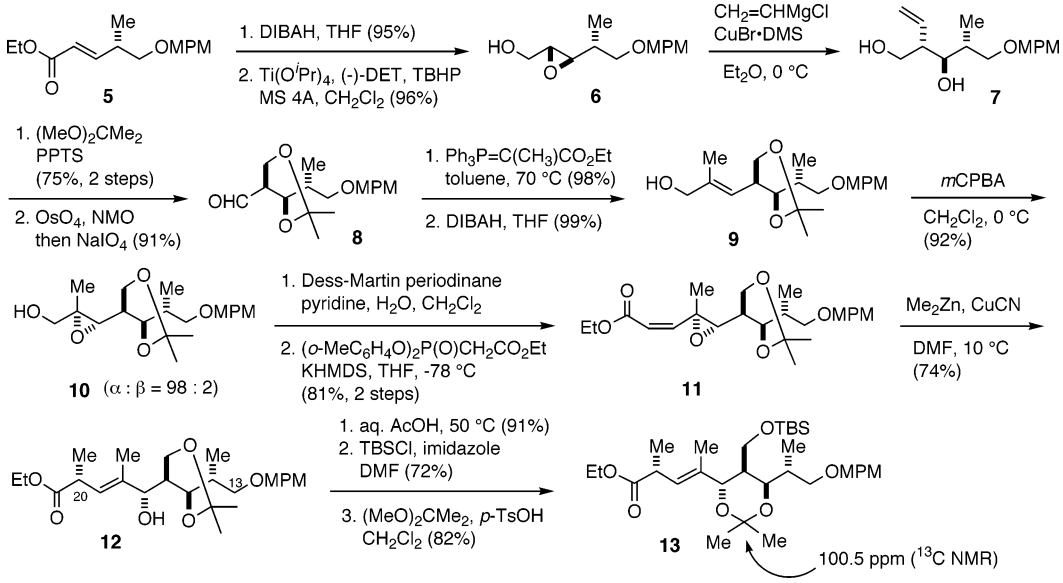


Namely, **1** was divided into the C(13)−C(23) segment **3** and the C(1)−C(12) segment **4**, and both segments were designed to connect by an aldol reaction at the C(12) and C(13) positions under Felkin−Anh control. We also designed a synthetic route for the C(13)−C(23) segment **3** starting from a chiral unsaturated ester **5**. We report herein the stereoselective synthesis of the C(13)−C(23) segment **3** having seven contiguous asymmetric carbon centers. The strategy is highlighted by two stereoselective epoxidation reactions of trisubstituted olefins and a stereospecific S_N2' methylation reaction of a *trans*-γ,δ-epoxy-*cis*-α,β-unsaturated ester[11] as the key steps.

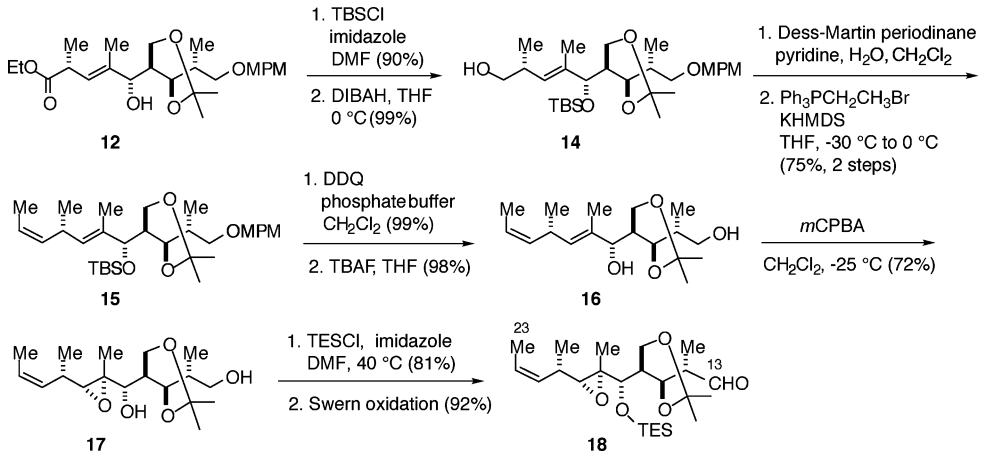
At first, the C(13)−C(21) polypropionate chain containing five stereogenic centers and a *trans*-trisubstituted double bond was elaborated according to Scheme 2. Thus, reduction of ester **5**[12] with DIBAH in THF furnished the allyl alcohol in 95% yield, which was then subjected to the Katsuki−Sharpless asymmetric epoxidation[13] resulting in the formation of the β-epoxy alcohol **6** (α/β = 5: 95) in 96% yield. Treatment of **6** with vinylmagnesium chloride and copper(I) bromide−dimethyl sulfide complex[14] in ether at 0 °C provided **7** stereoselectively. Interestingly, vinylmagnesium chloride was found to be much more effective than vinylmagnesium bromide in this substitution reaction. Protection of the resulting 1,3-diol as the acetonide followed by oxidative cleavage of the vinyl group using standard conditions furnished aldehyde **8** in 68% overall yield from **6**. Aldehyde **8** was then converted to the trisubstituted allyl alcohol **9** by a Wittig reaction with $Ph_3P{=}C(CH_3)CO_2Et$ in toluene followed by reduction of the ester with DIBAH in THF (97% yield for the two steps). Epoxidation of **9** with *m*-CPBA in CH_2Cl_2 at 0 °C gave the expected α-epoxy alcohol **10** with remarkably high stereoselectivity (α/β = 98:2) in 92% yield.

In turn, to introduce an α secondary methyl group at the C(20) position stereoselectively, we envisaged the use of the stereospecific S_N2' methylation reaction of γ,δ-epoxy-α,β-unsaturated esters recently developed in our laboratory.[11] For this purpose, the requisite *cis*-α,β-unsaturated ester **11** was synthesized by a two-step reaction sequence: (1) oxidation of the primary alcohol **10** with Dess−Martin periodinane[15] to the aldehyde and (2) Horner−Wadsworth−Emmons reac-

Scheme 2. Stereoselective Synthesis of the C(13)−C(21) Polypropionate Chain



Scheme 3. Stereoselective Synthesis of C(13)−C(23) Segment



tion with the Ando reagent (o-$CH_3C_6H_4O)_2P(O)CH_2CO_2Et$[16] and KHMDS in THF at −78 °C (81% yield for the two steps). The key S_N2' methylation reaction of **11** with Me_2Zn−CuCN reagent stereospecifically occurred in DMF, as we expected, giving rise to **12** as a single product in 74% yield.

It should be pointed out that other organocopper reagents, e.g., the Gilmann reagent[17] and Knochel's conditions,[18] were totally ineffective in this particular reaction. To confirm the stereochemistry of the product at this stage, **12** was transformed into acetonide **13** by the following reaction sequence: (1) removal of the acetonide in **12** by aq AcOH; (2) protection of the primary alcohol with TBSCl; (3) formation of isopropylidene acetal on the *anti*-1,3-diol moiety (54% for the three steps). As the acetal carbon in **13** appeared at δ 100.5 ppm in its ^{13}C NMR spectrum, the stereochemistry of the *anti*-1,3-diol was unequivocally confirmed.[19] This also proved the configuration of the secondary methyl group newly introduced at the C(20) position[20] as well as the stereochemistry of the previous trisubstituted epoxide **10**.

With the synthesis of the C(13)−C(21) polypropionate chain in hand, we focused on the conversion of **12** into the C(13)−C(23) segment **3** (Scheme 3). Namely, protection of the secondary hydroxyl group in **12** with TBSCl followed by reduction of the ester with DIBAH in THF produced the primary alcohol **14** in 89% yield. At this stage, the requisite terminal (*Z*)-olefin was installed by oxidation of alcohol **14** with Dess−Martin periodinane[15] followed by a Wittig reaction of the resulting aldehyde with $Ph_3PCH_2CH_3Br$ and KHMDS in THF (75% yield for the two steps). Removal of the MPM group in **15** with DDQ in CH_2Cl_2 and subsequent removal of the TBS group with TBAF furnished diol **16** in 98% yield. The crucial epoxidation of the allyl alcohol with *m*-CPBA occurred stereoselectively by the neighboring participation of the hydroxyl group, as we expected, giving rise to the α-epoxide **17** (α/β = 94: 6) in 72% yield. Finally, protection of two hydroxyl groups in **17** with TESCl followed by a Swern oxidation according to the Spur protocol[21] afforded the targeted C(13)−C(23) segment **18** in 75% yield.

In summary, we have achieved the straightforward, highly stereoselective synthesis of the C(13)−C(23) segment of tedanolide (**1**) through an original strategy based on acyclic stereocontrol without use of any aldol methodologies, in which two stereoselective epoxidations of regioisomeric trisubstituted double bonds and the stereospecific S_N2' methylation reaction of the *trans*-γ,δ-epoxy-*cis*-α,β-unsaturated ester **10** are involved as the key steps. Studies toward total synthesis of tedanolide (**1**) are in progress in our laboratory.

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Supporting Information Available: Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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