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Total Synthesis of (+)-13-Deoxytedanolide

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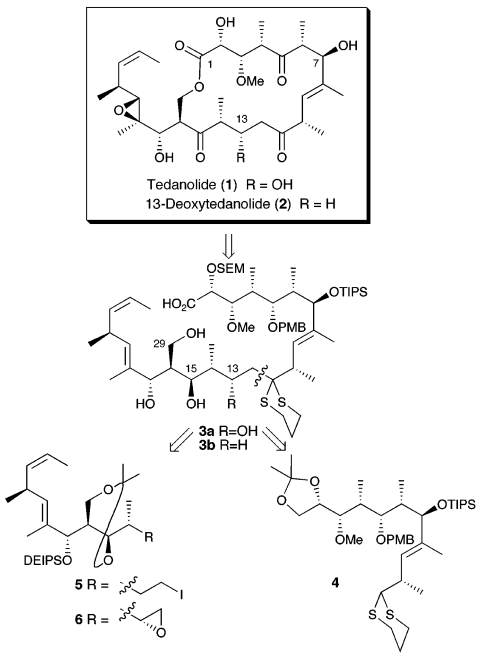
In 1984 Schmitz and co-workers reported the isolation and complete structural elucidation of (+)-tedanolide (**1**) from *Tedania ignis*, a Caribbean sponge.[1] Seven years later Fusetani and co-workers[2] disclosed a similar metabolite, (+)-13-deoxytedanolide (**2**), obtained from the Japanese sea sponge *Mycale adhaerens.* Importantly, these intricate 18-membered macrocycles exhibit significant antitumor activity.[2] Not surprisingly, this combination of architectural complexity and bioactivity has engendered wide interest on the part of the synthetic community.[3]

In 1995 we initiated a synthetic endeavor envisioned to exploit a unified strategy to construct both tedanolide (**1**) and 13-deoxytedanolide (**2**) from a common late-stage intermediate (Scheme 1). The potential instability of the trisubstituted epoxide, in conjunction with six epimerizable centers, and the fact that nearly every carbon of the backbone of the tedanolides is functionalized, demanded careful design of both the overall synthetic plan and an effective protecting group scenario.

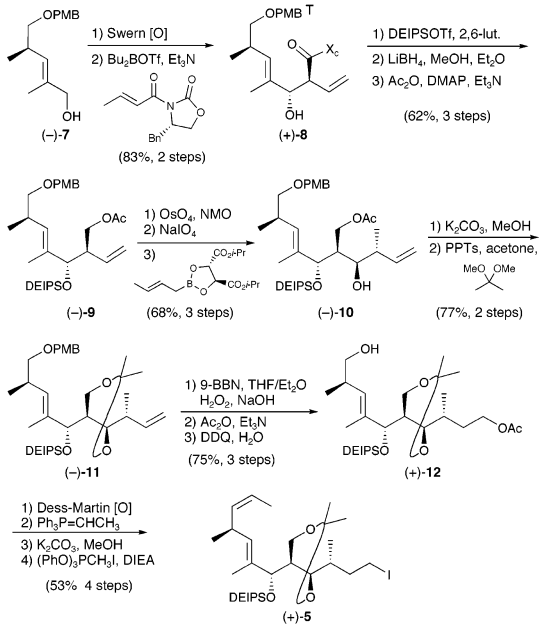
Scheme 1



Toward this end, we selected a strategy calling for a late stage, high-risk epoxidation of the C(18,19) trisubstituted olefin,[4] in conjunction with retention of the dithiane moiety until after macrocyclization to prevent potential ketalizations with the C(15) and C(29) hydroxyls. With this plan in mind, we envisioned **1** and **2** to arise from seco-acids **3a** and **3b**, which in turn would be available via union of dithiane **4**[5] respectively with epoxide **6** for tedanolide (**1**) and iodide **5** for 13-deoxytedanolide (**2**).

The synthesis of (+)-13-deoxytedanolide (**2**) began with known alcohol (−)-**7**[3e,f] (Scheme 2). Conversion to acetate (−)-**9** proved straightforward and proceeded in high overall yield (51%; five steps, Scheme 2).

Scheme 2



Although the trisubstituted olefin in (−)-**9** is certainly the more electron-rich olefin, we envisioned that the sterically less encumbered monosubstituted terminal olefin would permit selective oxidative cleavage to afford the aldehyde.[6] This indeed proved to be the case. Subsequent Brown crotylation[7] however, resulted in low yields due to difficulties experienced in the hydrolysis of the intermediate boronate. This hurdle was overcome with the Roush crotylation,[8] known to generate more labile boronate intermediates; exclusive formation of the desired alcohol (−)-**10** was obtained in excellent yield.[9] After conversion to alcohol (+)-**12**, Dess−Martin oxidation[10] furnished a readily epimerizable aldehyde, which was used without chromatographic purification in a highly *Z* selective Wittig olefination (>20:1), followed by saponification, and iodination.[11] No epimerization at C(20) was observed in the Wittig olefination.

With iodide (+)-**5** in hand, we turned to the construction of SEM ether (−)-**13** from dithiane (−)-**4**[5] and assembly of the carbon backbone of (+)-**2** (Scheme 3). Use of (−)-**13**, possessing the free hydroxyl would, upon successful union, afford (−)-**14**, comprising the fully elaborated backbone ready for direct conversion to the requisite carboxylic acid. This critical step was achieved by genera-

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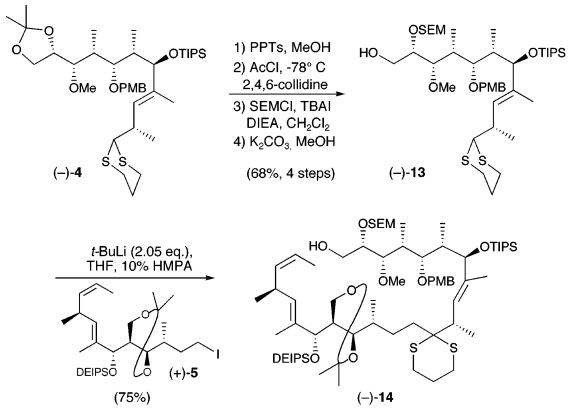
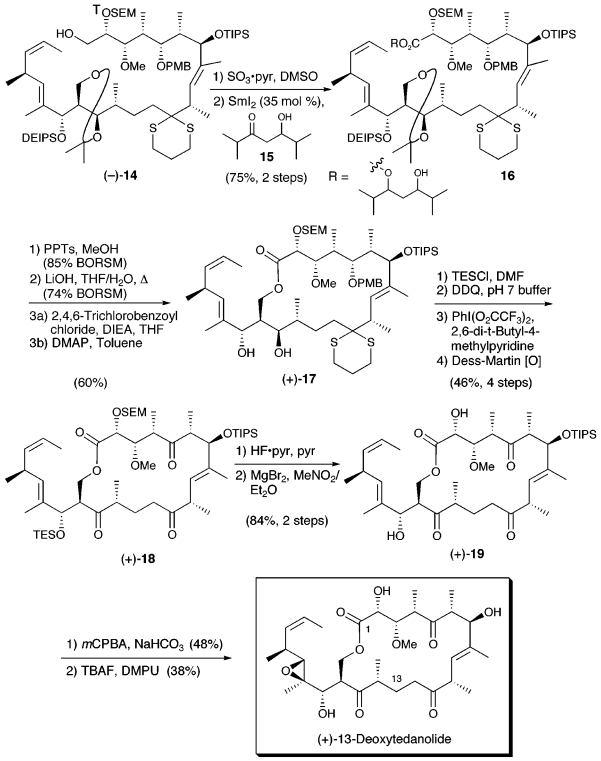
tion of the dianion of (−)-**13** with 2.05 equiv of *t*-BuLi, followed by addition of 1.1 equiv of iodide (+)-**5**; the yield was 75%.

Scheme 3



Access to the seco-acid (**3b**, Scheme 1) next called for the nontrivial conversion of the C(1) primary hydroxyl to the corresponding carboxylic acid in the presence of the oxidatively labile dithiane. Exhaustive screening of the standard arsenal of oxidants[12] proved unrewarding. We therefore turned to a novel use of the SmI_2-promoted Evans−Tishchenko *reduction*,[13] developed specifically for this synthesis (Scheme 4).[14] Pleasingly, Parikh−Doering oxidation of (−)-**14** to the corresponding aldehyde, followed by treatment with 35 mol % SmI_2 in the presence of β-hydroxy ketone **15**[13] afforded a diastereomeric mixture of ester **16**, effectively achieving *oxidation* at C(1) via an internal oxidation−reduction. Removal of the acetonide, as expected, led to concomitant loss of the diethylisopropylsily (DEIPS) group.[15] This event was not viewed as a problem as we anticipated that Yamaguchi macrolactonization[16] would prove highly selective for the C(29) primary hydroxyl, to furnish macrolactone (+)-**17**. In the event, hydrolysis of the ester[15] and macrocyclization afforded (+)-**17**. Silylation (TESCl) of the less hindered allylic alcohol, removal of both the PMB ether and dithiane, and Dess−Martin oxidation of the two free hydroxyls then led to triketone (+)-**18**. Upon sequential deprotection of the TES and SEM[17] ethers, the stage was set for the critical epoxidation of diol (+)-**19**. To our delight, treatment of (+)-**19** with *m*CPBA in the presence of $NaHCO_3$[3f,18] afforded the desired epoxide with excellent stereoselectivity (>15:1, 48% yield). Deprotection (TBAF, wet DMPU) completed the synthesis of (+)-13-deoxytedanolide (**2**), identical in all respects to an authentic sample (500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, HRMS, optical rotation, λ_{max}, TLC in three different solvent systems).

Scheme 4



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In summary the first total synthesis of the architecturally complex marine natural product (+)-13-deoxytedanolide (**2**) has been achieved via a highly convergent strategy.

Acknowledgment. We thank Professor Fusetani for supplying an authentic sample of (+)-**2**, and the National Institutes of Health (Institute of General Medical Sciences) for support (GM-29028).

Supporting Information Available: Spectroscopic and analytical data for compounds **2**, **5**, **8**−**14**, **17**−**19** and selected experimental procedures (PDF). This material is free of charge via the Internet at http://pubs.acs.org.

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