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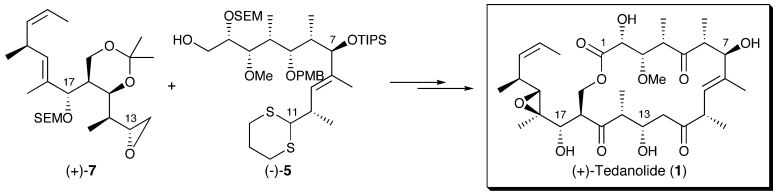

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Total Synthesis of (+)-Tedanolide

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Abstract: A convergent, stereocontrolled total synthesis of (+)-tedanolide (**1**), an architecturally complex marine antitumor macrolide, has been achieved in 31 steps (longest linear sequence). Highlights of the synthesis comprise a highly efficient dithiane union, followed by an Evans−Tishchenko "oxidation" to enable formation of the seco-ester in the presence of an oxidatively labile dithiane, a highly refined protecting group strategy, and a chemo- and stereoselective epoxidation at C(18,19).

Introduction

Tedanolide and the 13-deoxy-congener [(+)-**1** and (+)-**2**] comprise initial members of a small, architecturally intricate family of sponge metabolites, reported respectively by the Schmitz[1] and Fusetani[2] laboratories in 1984 and 1991 (Figure 1). Both display exceptionally potent antitumor activities with (+)-tedanolide (**1**), increasing the life span of mice implanted with lymphocytic leukemia by 23% at 1.5 μg/kg body weight,[3] and (+)-13-deoxytedanolide (**2**), lowering the growth rate of P388 tumors with a T/C value of 189% at a dose level of 0.125 mg/kg.[2] Although a detailed understanding of the mode of action remains unknown, Fusetani and co-workers[4] in an elegant study recently disclosed the binding site of (+)-13-deoxytedanolide (**2**) to be the 60S ribosomal subunit. A third equally potent congener, (+)-tedanolide C (**3**), bearing a different pattern of oxygenation and methylation, was recently described by Ireland and co-workers.[5]

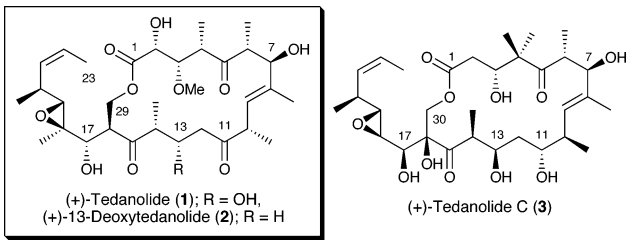

Figure 1. The tedanolide family of natural products.

From the synthetic perspective, (+)-tedanolide (**1**) comprises a significant challenge, given the four labile aldol units, a sensitive trisubstituted α-hydroxy epoxide, and a trisubstituted (*E*)-olefin encased in a 18-membered macrolide framework, punctuated with 13 stereogenic centers. Not surprisingly, the remarkable biological profile, in conjunction with the architectural complexity of (+)-**1** and (+)-**2**, has triggered considerable synthetic effort,[6] culminating in the first total synthesis of a tedanolide, namely (+)-13-deoxytedanolide (**2**) by our laboratory[7] in 2003, followed by a second total synthesis by Roush and co-workers[8] in 2005. More recently, Kalesse and co-workers[9] achieved the first total synthesis of (+)-tedanolide (**1**) exploiting a series of stereoselective aldol unions.

In keeping with our longstanding interest in the development of unified synthetic strategies for members of architecturally complex families of natural products, we initially devised a

(1) Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.
(2) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem.* **1991**, *56*, 4971.
(3) Schmitz, F. J.; Gunasekera, S. P.; Hossain, M. B.; van der Helm, D.; Yalamanchili, G. (1988) U.S. Patent Application 87−7347.
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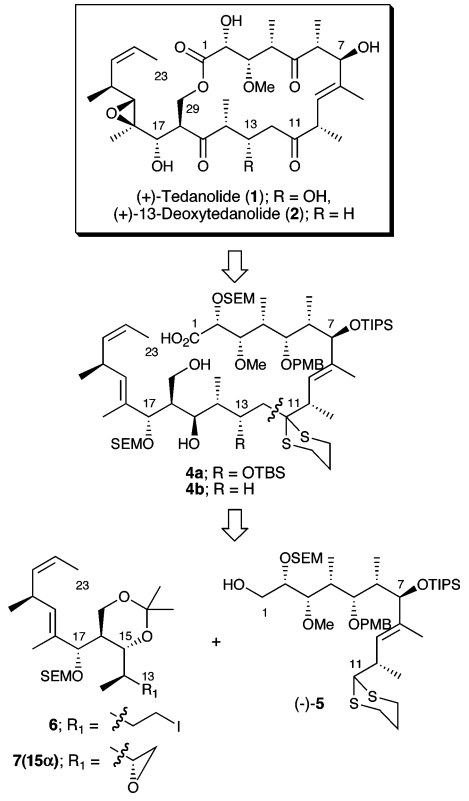
(7) (a) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (b) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042.
(8) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186.
(9) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038.

flexible approach envisioned to exploit a dithiane linchpin tactic[10] to access both (+)-tedanolide (**1**) and (+)-13-deoxytedanoilde (**2**) from a common advanced intermediate (*vide infra*). Having achieved the total synthesis of (+)-13-deoxytedanolide, we outline herein the culmination of this synthetic venture with an effective total synthesis of (+)-tedanolide (**1**).

Results and Discussions

Synthetic Analysis of (+)-Tedanolide (1). As with (+)-13-deoxytedanolide (**2**), our synthetic strategy for (+)-tedanolide (**1**) called for initial construction of the macrocyclic domain, with stereoselective installation of the C(18,19) epoxide late in the synthetic sequence to avoid the need to carry this potentially unstable functionality through various synthetic steps required for the construction of the complex backbone (Scheme 1). To

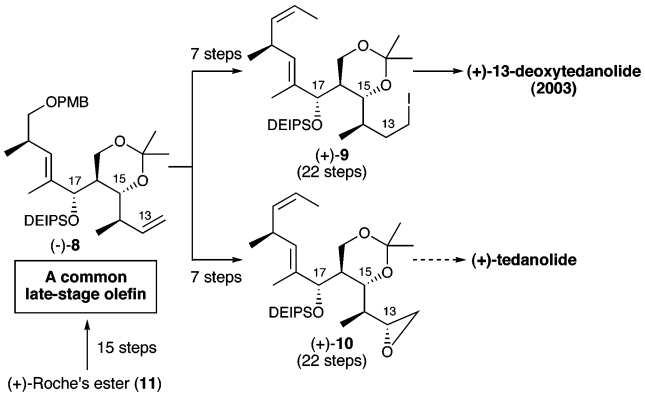
Scheme 1



this end, disconnection of (+)-tedanolide (**1**) at the macrolactone and C(11−12) linkage gave rise to a common C(1−11) dithiane (−)-**5**,[7a,b] and in the case of (+)-tedanolide (**1**), a C(13−23) epoxide **7**(**15**α). The 13-deoxy congener called for iodide **6** or a diastereomer thereof (*vide infra*). In the synthetic direction, we envisioned seco-acid **4a** to be available via addition of epoxide **7**(**15**α) to the dianion derived from dithiane (−)-**5**, followed by selective oxidation of the hydroxyl at C(1). Highlights of the late stage of the synthesis would then entail retention of the dithiane moiety until macrolactonization to prevent potential intramolecular ketalization between the C(15) and C(29) hydroxyl and ketone, respectively, as observed by Roush,[8] and installation of the requisite epoxide at the C(18,19) trisubstituted olefin.

In initiating the synthetic program for the tedanolides, we had outlined a unified synthetic strategy, anticipating that a common, late-stage olefin such as (−)-**8** would potentially serve as a precursor for iodide (+)-**9** and epoxide (+)-**10**, respectively, for (+)-13-deoxytedanolide (**2**) and (+)-tedanolide (**1**) (Scheme 2).[11] Although the first generation route to the southern hemisphere subunit (−)-**8** demonstrated the feasibility of

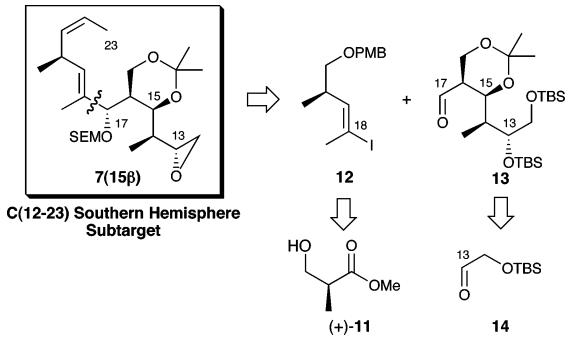
Scheme 2



utilizing an epoxide opening with a dithiane anion to construct the (+)-tedanolide (**1**) framework, this synthesis required 22 steps from the commercially available (*S*)-(+)-Roche's ester (**11**). The lengthy sequence resulted primarily from an unforeseen synthetic inefficiency; a seven-step protocol to convert olefin (−)-**8** to the terminal epoxide (+)-**10**.

Based on the lessons learned in our first generation synthesis of epoxide (+)-**10**, we therefore developed a second-generation strategy employing the alternative β-stereogenicity C(15), vis-à-vis the (+)-13-deoxytedanolide synthetic venture (Scheme 3). Importantly, the second-generation synthesis of the requisite

Scheme 3



epoxide [cf. **7**(**15**β)] for the dithiane coupling reaction was designed to produce this subunit efficiently and in suitable quantities to achieve the goal of (+)-tedanolide (**1**). Careful development of a viable protecting group strategy for the southern hemisphere also appeared prudent at this juncture. Indeed, the selection of the protecting groups for the C(15), C(17), and C(29) hydroxyls proved to be one of the most critical aspects of the (+)-tedanolide (**1**) synthetic venture. Further recognition of the allylic alcohol system at C(17) prompted construction of this structural array via a stereoselective union tactic. That is, disconnection of the C(17−18) σ-bond in **7**(**15**β) revealed vinyl iodide **12** and aldehyde **13**. In the synthetic sense this scenario would make construction of a C(12−23) subtarget considerably more convergent (Scheme 2). As with our (+)-13-deoxytedanolide (**2**) synthesis, the stereogenecity at C(15)

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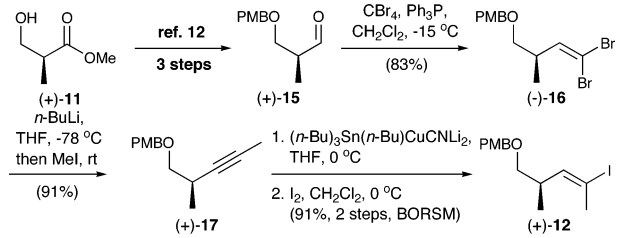
(11) Adams, C. M. Ph.D. Dissertation, University of Pennsylvania, 2003.

would be of no consequence, since the C(15) hydroxyl would eventually be oxidized to a ketone in the final product.

Elaboration of the C(18−21) Fragment: Vinyl Iodide (+)-12. Our point of departure for the construction of the C(18−21) (*E*)-vinyl iodide was known aldehyde (+)-**15**, prepared during the (+)-13-deoxytedanolide (**2**) synthesis (Scheme 4).[12] Aldehyde (+)-**15** was then converted to alkyne (+)-**17** via

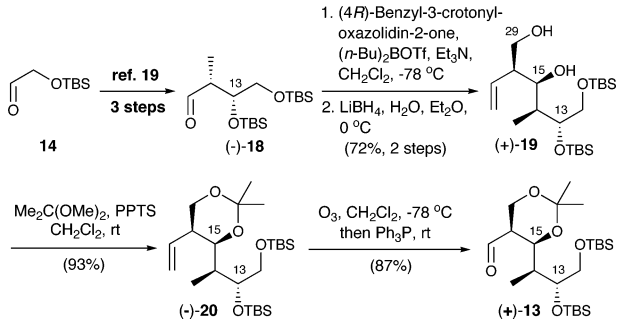
Scheme 4



Corey−Fuchs protocol[13] in 76% overall yield. To construct the key structural element of fragment (+)-**12**, the (*E*)-vinyl iodide moiety, we initially explored a palladium-catalyzed hydrostannylation approach,[14] followed by iodination; the result proved to be a mixture of regioisomeric vinyl iodides (6:1, 89%, BORSM[15]). Radical initiated hydrostannylation (AIBN, (*n*-Bu)$_3$SnH)[16] and hydrozirconation[17] resulted in similar selectivities. Pleasingly, however, stannylcupration of (+)-**17** employing the conditions of Pancrazi[18] and co-workers [i.e., 2 equiv of the mixed cyanocuprate (*n*-Bu)$_3$Sn(*n*-Bu)CuCNLi$_2$], followed by iodination afforded the desired (*E*)-trisubstituted vinyl iodide (+)-**12** as a single stereoisomer in excellent yield (91% over two steps, BORSM[15]), without compromise of regioselectivity. Fragment (+)-**12** was thus available in four steps and 69% overall yield from (+)-**15**.

Construction of the C(12−17) Fragment: Aldehyde (+)-13. Elaboration of aldehyde (+)-**13** began with known aldehyde (−)-**18**[19] bearing two contiguous stereogenic centers generated via a Brown asymmetric crotylboration[20] (Scheme 5). A *syn*-aldol condensation employing the Evans's crotonate imide,[21]

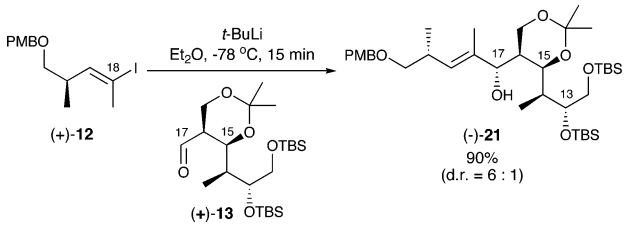
Scheme 5



followed by reductive-removal of the oxazolidinone then furnished homoallylic diol (+)-**19**, establishing the C(15) and C(16) stereogenic centers with excellent diastereoselectivity. The resulting C(15) and C(29) hydroxyls, which we anticipated could be readily differentiated during the macrolactonization event were protected as a cyclic ketal. Ozonolysis of the terminal olefin in (−)-**20** next provided aldehyde (+)-**13**, a substrate for the coupling reaction.

Construction of the C(12−23) Southern Hemisphere of (+)-Tedanolide (1). With both vinyl iodide (+)-**12** and aldehyde (+)-**13** in hand, we embarked on elaboration of the southern hemisphere epoxide (+)-**7**(**15**β) (Scheme 6). The coupling reaction was achieved by metal-halogen exchange of vinyl iodide (+)-**12** with *t*-BuLi in Et$_2$O at −78 °C, followed by the addition to aldehyde (+)-**13** to furnish predominantly the desired adduct (−)-**21**[22] as a diastereomeric mixture [6:1 at C(17)], in a combined yield of 90%. Importantly, the diastereomers could be separated chromatographically.

Scheme 6



The favorable stereochemical outcome of this substrate-controlled reaction can be understood in terms of transoid conformer **13**, that would minimize dipole−dipole interactions between carbonyl and the oxygens in the dioxolane ring, thereby leading to preferential nucleophilic attack from the less hindered face of the carbonyl group to furnish the α-isomer as a major diastereomer (Figure 2). This result is also consistent with a Cram−Felkin−Anh model.[23]

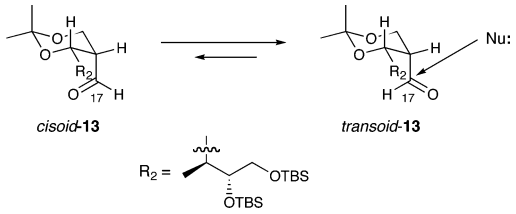


Figure 2. Conformational analysis of vinyl anion addition to C(17) aldehyde.

Completion of epoxide (+)-**7**(**15**β) was achieved in a straightforward fashion (Scheme 7). After separation, the C(17) hydroxyl group in (−)-**21** was protected as the SEM ether and the PMB group oxidatively removed to afford (−)-**22**. The

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(15) Based on recovered starting materials.
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(21) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.
(22) The absolute stereochemistry of the newly generated stereocenter in (−)-**21** was assigned by the modified Mosher ester analysis of the derived esters. For a complete discussion of the Mosher analysis for assignment of the stereochemistry of secondary alcohol, see: (a) Kusumi, T.; Fujita, Y.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2923. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
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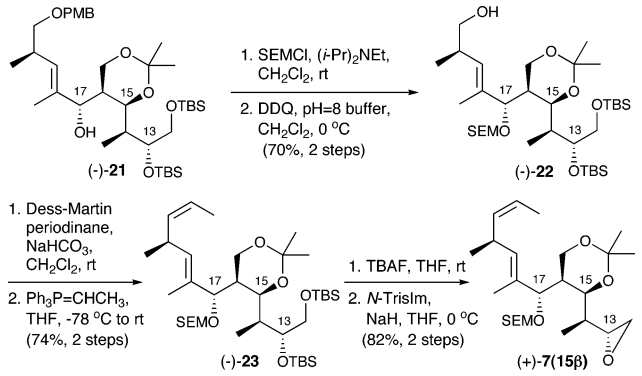
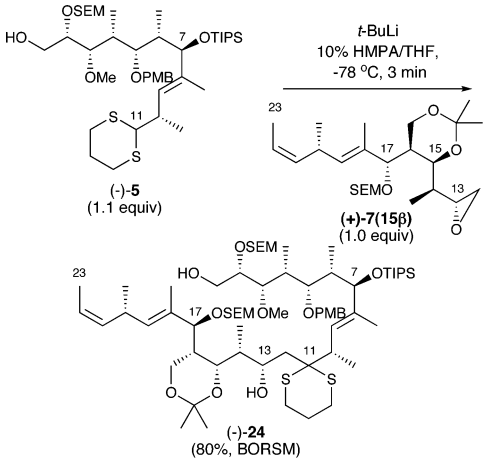
Scheme 7



required (*Z*)-olefin was then installed by Dess−Martin oxidation,[24] followed by Wittig ethylidenation of the resulting aldehyde, to yield (−)-**23**. Removal of both TBS groups, and in turn conversion of the resultant hydroxyl groups to the desired epoxide was achieved via the Fraser−Reid protocol,[25] thereby completing the construction of epoxide (+)-**7**(**15***β*). The overall sequence from (−)-**18** required 11 steps and proceeded in 22% overall yield.

Union of the Northern and Southern Hemispheres. Having secured scalable routes for both the preparation of (−)-**5** and (+)-**7**(**15***β*), we began to investigate assembly of the carbon framework of (+)-tedanolide (**1**). For the critical union, epoxide (+)-**7**(**15***β*) was added to the lithium dianion derived from the dithiane (−)-**5**, the latter generated by the Williams protocol[26] [e.g., *t*-BuLi in a 10% HMPA/THF solution] to furnish diol (−)-**24** in 80% yield (BORSM)[15] (Scheme 8). In contrast to

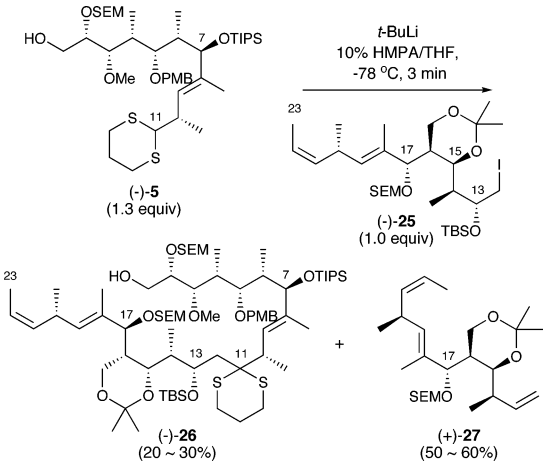
Scheme 8



relatively simple 1,3-dithianes, which readily undergo deprotonation with *n*-BuLi, metalation of structurally complex dithianes such as (−)-**5** often require a variety of stronger bases,[27] solvent additives, and time and temperature regimes. We have found that *t*-BuLi in a THF solution of HMPA at −78 °C comprises the optimal conditions for generation of the dianion corresponding to (−)-**5**. Addition of the electrophile immediately following metalation also proved important, since prolonged maintenance of the dianion at −78 °C results in loss of reactivity.

We also investigated iodide (−)-**25**, an equally attractive coupling partner, as an alternative coupling strategy to assemble the C(11−13) aldol unit in (+)-tedanolide (**1**) (Scheme 9). We

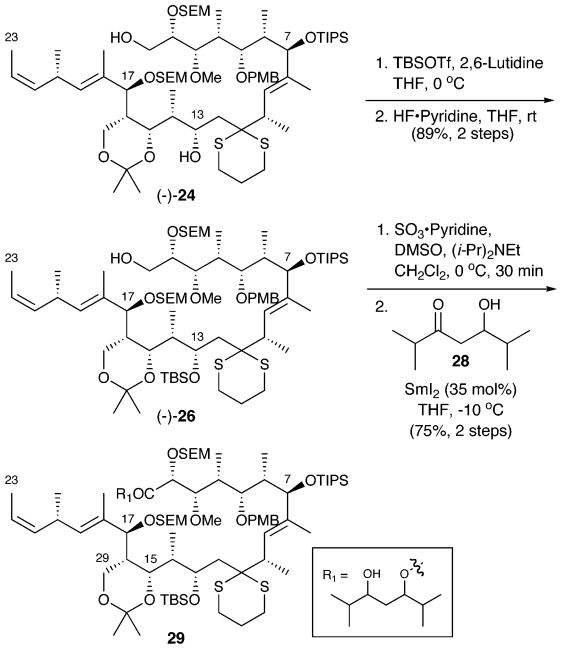
Scheme 9



reasoned that the union with dithiane (−)-**5** would prove to be a viable tactic, and in turn extend the utility of our dithiane coupling strategy. However, reaction of the lithium dianion derived from (−)-**5** with iodide (−)-**25**, under the same conditions that proved successful with epoxide (+)-**7**(**15***β*), led predominantly to elimination product (+)-**27** (50−60%), in conjunction with a low yield of the desired adduct (−)-**26** (20−30%). Although the desired tedanolide framework was obtained, adventitious formation of the elimination product prohibited further investment in this route.

Construction of Macrocycle (+)-31. Having achieved the critical union, and thereby the complete carbon skeleton of (+)-tedanolide (**1**), we next addressed oxidation of the primary hydroxyl to the requisite seco-acid for subsequent macrocyclization. To this end, bis-silylation of (−)-**24**, followed by selective removal of the primary TBS ether employing HF•pyridine in THF furnished (−)-**26** (Scheme 10). Access to the

Scheme 10



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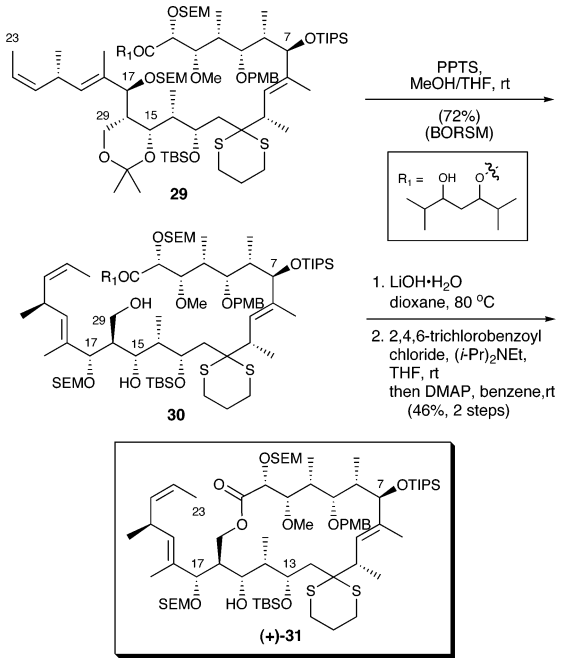
seco-acid would now require the nontrivial conversion of the primary hydroxyl to the corresponding seco-acid in the presence of the oxidatively labile dithiane. For this conversion we turned to the SmI_2-promoted Evans−Tishchenko "oxidation",[28,29] a protocol developed specifically for this transformation in our 13-deoxytedanolide synthesis.[7a,b] Toward this end, Parikh−Doering[30] oxidation of (−)-**26** provided the corresponding aldehyde, which upon treatment with SmI_2 in the presence of β-hydroxy ketone **28**[28,29] furnished a diastereomeric mixture of esters (**29**), effectively achieving oxidation at C(1) in 75% yield over two steps.

Acid-catalyzed methanolysis (PPTS, MeOH) of the C(15, 29) acetonide in **29** furnished the diol in good yield (72%, BORSM) (Scheme 11). At this juncture, the presence of two

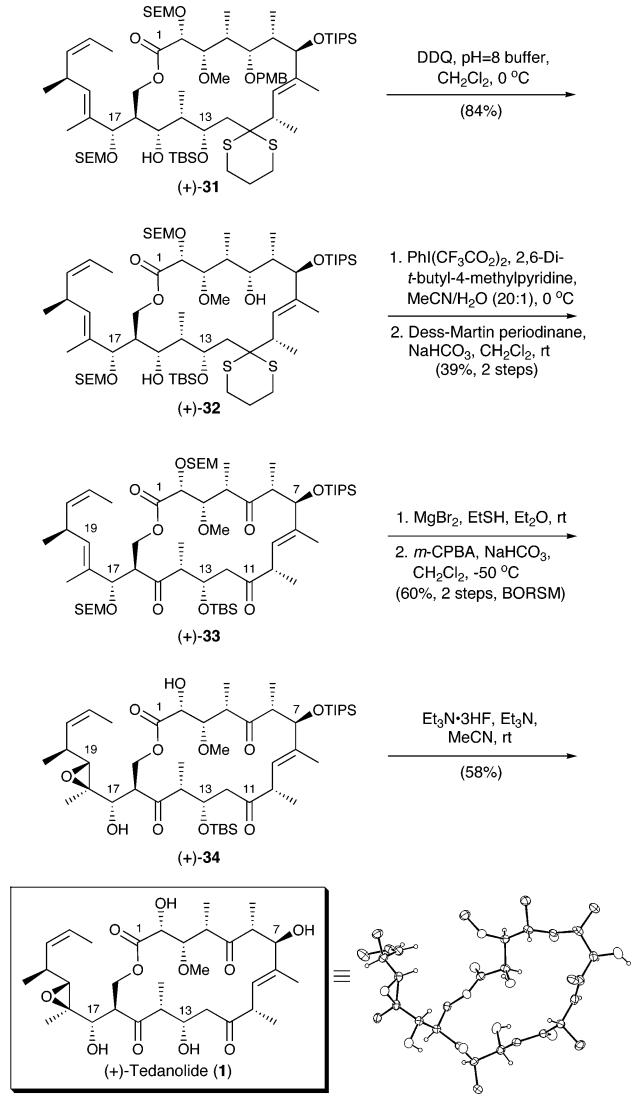
Scheme 11



hydroxyl groups was not viewed as an issue, as we anticipated that Yamaguchi lactonization[31] would prove highly chemoselective for the C(29) primary hydroxyl as in the 13-deoxytedanolide synthesis, thereby affording the desired macrolactone. This indeed proved to be the case. However, an initial attempt at saponification of the resultant triol-ester **30**, employing KOH at room temperature, only proceeded with low conversion. Use of LiOH in dioxane/H_2O at reflux, followed by the macrocyclization employing the Yamaguchi protocol was more effective, affording the desired macrocycle (+)-**31** in an acceptable yield of 46% over two steps.

Completion of the (+)-Tedanolide (1) Total Synthesis. Having achieved the crucial macrocyclization, we turned to final elaboration of (+)-tedanolide (**1**). The PMB group was removed oxidatively using DDQ to produce diol (+)-**32** in good yield (84%) (Scheme 12). Removal of the dithiane with $PhI(CF_3CO_2)_2$ employing the Stork[32] protocol followed by Dess−Martin

Scheme 12



oxidation[24] of the two free hydroxyls then led to triketone (+)-**33**.[33] Next, the desired diol was cleanly obtained in high yield (85%), employing the conditions of Kim[34] ($MgBr_2$, EtSH), known to remove selectively the SEM group in the presence of the TIPS and TBS silyl ethers. Hydroxyl-directed epoxidation[35] employing *m*-CPBA buffered with $NaHCO_3$,[7a,b] which had proven successful in our total synthesis of (+)-13-deoxytedanolide (**2**), furnished the desired epoxide (+)-**34** as a single diastereomer (70%, BORSM). Global deprotection exploiting Et_3N•3HF and Et_3N as described by Roush,[8] completed the total synthesis of (+)-tedanolide (**1**), identical in all respects (i.e., 500 MHz ^1H and 125 MHz ^{13}C NMR,[36] HRMS, chiroptical properties, and single crystal[37] X-ray analysis) to the data reported for the natural and the Kalesse synthetic (+)-tedanolide (**1**).[1,9]

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(33) Alternatively, *N*-iodosuccinimide (NIS) was also explored for the removal of dithiane in (+)-**32** but showed no improvement (20% overall yield from (+)-**32**).
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(36) Synthetic sample was found to undergo decomposition in $CDCl_3$ during a ^{13}C NMR experiment, but is stable in C_6D_6.
(37) Crystallization during an NMR experiment in C_6D_6 yielded crystals suitable for X-ray analysis.

Summary

Stereocontrolled total syntheses of both (+)-tedanolide (**1**) and the 13-deoxy congener (**2**), exploiting a unified dithiane linchpin strategy, have now been achieved. Highlights of this synthetic venture include the development of Evans−Tishchenko "oxidation" to generate a seco-ester in the presence of oxidatively labile dithiane, a highly refined protecting group strategy, and the stereocontrolled epoxidation at C(18,19). As for the total synthesis of (+)-tedanolide (**1**), the longest linear sequence comprised 31 steps and proceeded in 0.31% overall yield from (*S*)-(+)-glyceraldehyde acetonide.

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

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