ORGANIC LETTERS

1999
Vol. 1, No. 8
1249−1252

Synthesis of Tedanolide and 13-Deoxytedanolide. Assembly of a Common C(1)–C(11) Subtarget

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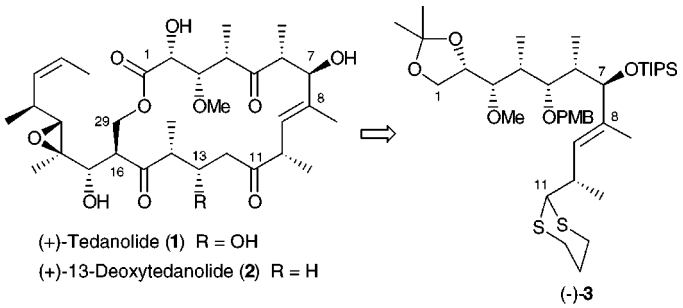
Received August 9, 1999

ABSTRACT



In this Letter we describe a synthetic strategy and an efficient assembly of a common C(1)–C(11) subtarget, (–)-3, for (+)-tedanolide (1) and (+)-13-deoxytedanolide (2), architecturally complex marine macrolides displaying potent antitumor activity. Key elements of the synthesis include two iterations of the Evans aldol protocol to construct the C(1)–C(6) moiety and a stereocontrolled vinyl anion addition to generate the C(8,9) trisubstituted olefin incorporating stereogenicity at C(7). Alkylation with a model epoxide demonstrates that (–)-3 is a competent dithiane for further elaboration of the macrolide skeleton.

In 1984 Schmitz and co-workers[1] isolated (+)-tedanolide (**1**), a structurally complex 18-membered macrolide, from *Tedania ignis*, a prevalent Caribbean sponge commonly referred to as "fire sponge" due to the sensation induced upon human contact.[2,3] The relative and absolute stereochemistry of **1** was determined by X-ray diffraction, exploiting the anomalous dispersion of oxygen.[1] More recently (1991), Fusetani and co-workers[4] disclosed the isolation and structural elucidation of the 13-deoxy congener (**2**) from the Japanese sponge *Mycale adhaerens*.

Tedanolide (**1**) displays in vitro cytotoxicity against KB and PS cell lines (ED_{50}'s: 0.25 ng/mL and 16 pg/mL, respectively)[1] and in vivo antitumor activity, increasing the lifespan of mice implanted with lymphocytic leukemia cells (23% at 1.56 μg/kg).[5] Deoxytedanolide (**2**) also displays significant antineoplastic activity (P388: T/C, 189%; 0.125 mg/kg).[4]

Tedanolide and deoxytedanolide represent unusual macrolides in that lactonization occurs at a primary hydroxyl instead of the customary secondary hydroxyl;[6] equally intriguing is the high level of oxygen functionality. Not surprisingly, this combination of structural complexity and antitumor activity has engendered considerable interest on the part of the synthetic community.[7] In this Letter, we outline a unified synthetic strategy and disclose an efficient

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(3) Yaffee, H. L. S. L.; Sturgardter, F. *Arch. Dermatol.* **1963**, *87*, 601.
(4) Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971.
(5) Schmitz, F. J.; Genasekera, S. P.; Hossain, M. B.; van der Helm, D.; Yalamanchili, G. U.S. Patent Application 87-7347 870127.
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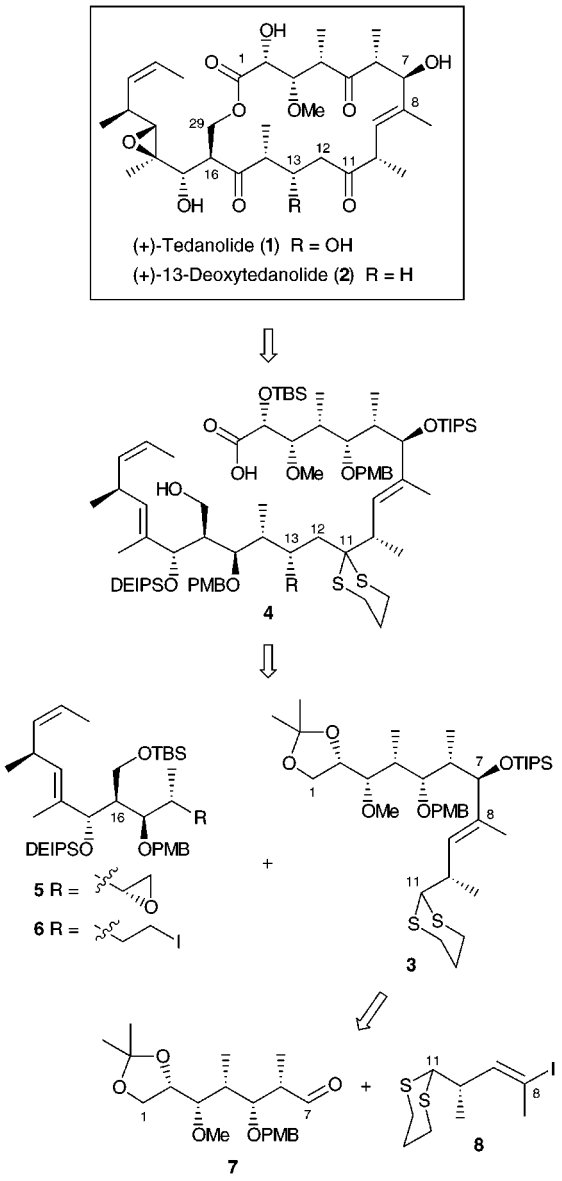
10.1021/ol9909233 CCC: $18.00
Published on Web 09/16/1999

assembly of a common advanced C(1)−C(11) subtarget (**3**) for tedanolide (**1**) and 13-deoxytedanolide (**2**).

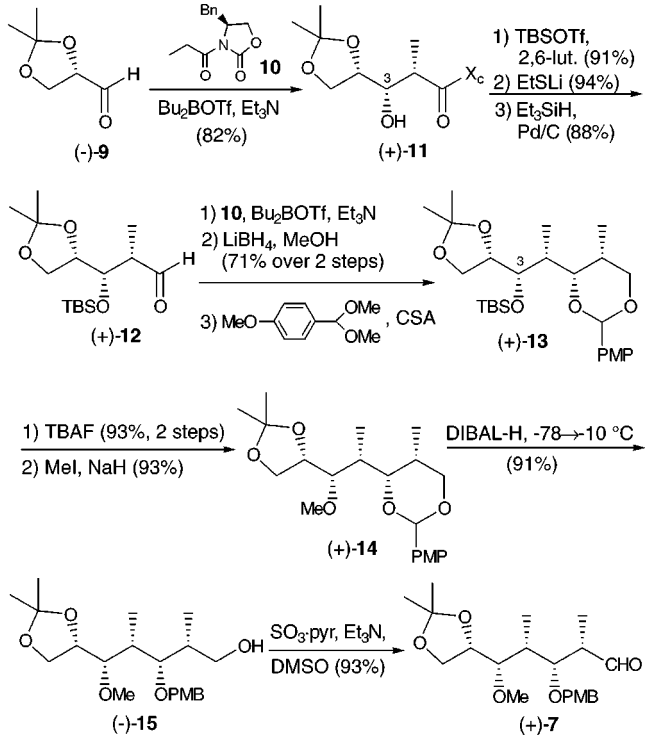
Scheme 1



Consistent with concurrent investigations on the utility of dithianes[8] as linchpins for complex molecule construction, disconnectionat the C(29) lactone and C(11,12) σ-bonds of **1** and **2** leads to dithiane **3**, a common subtarget for union with **5** for tedanolide (**1**) and with **6** for 13-deoxytedanolide (**2**). Further disconnection of **3** at C(7,8) yields aldehyde **7** and vinyl iodide **8**.

The synthesis of aldehyde **7** began with (*S*)-(−)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (**9**), available in three steps from ascorbic acid (Scheme 2).[9] Iterative Evans

Scheme 2



aldol[10] condensations incorporating silyl protection (TBSOTf/2,6-lutidine) and conversion via the thioester to aldehyde (+)-**12**[11] were followed by $LiBH_4$ reduction and acetal formation to furnish (+)-**13**.[11] Due to the observed lability of a methoxy group at C(3), we chose to forestall methylation of the C(3) hydroxyl in (+)-**11**[11] until after both the second Evans aldol and installation of the *p*-methoxyphenyl acetal. Removal of the silyl group at C(3) in (+)-**13** with TBAF and methylation (NaH, MeI) then provided (+)-**14**.[11]

Selective reduction of the acetal in (+)-**14** was initially accompanied by reduction of the acetonide (ca. 50%). This unanticipated process was eliminated by treatment with DIBAL-H (3 equiv) for *only* 15 min; adherence to this protocol furnished primary alcohol (−)-**15**[11] in excellent yield. Parikh−Doering oxidation (SO_3·pyr, DMSO, Et_3N) then completed the construction of aldehyde (+)-**7**.[11,12]

Turning to the synthesis of vinyl iodide (−)-**8**, Swern

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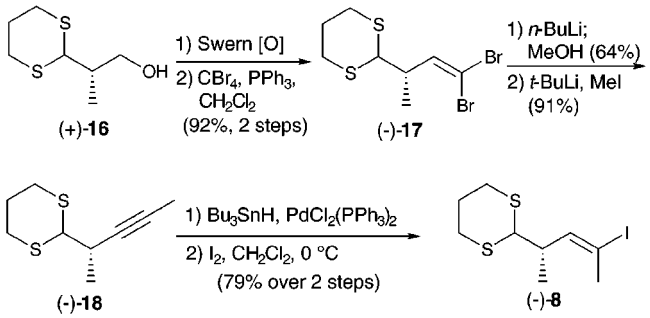
(11) The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

(12) Parikh, J. R.; von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

oxidation[13] of known alcohol (+)-**16**,[14] available in five steps from methyl (*S*)-(+)-3-hydroxyl-2-methylpropionate, was followed by the Corey−Fuchs[15] protocol (CBr_4/PPh_3) to furnish dibromide (−)-**17**[11] (Scheme 3). Conversion to the

Scheme 3

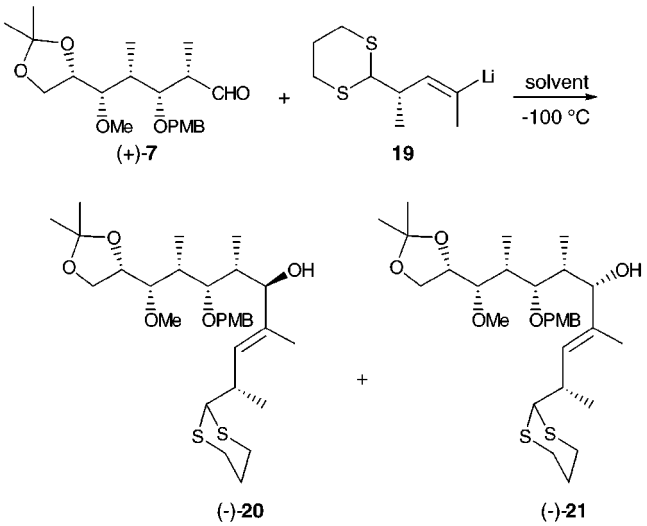


terminal alkyne (*n*-BuLi; −78 °C, THF) followed by alkylation with MeI led to (−)-**18**.[11] Attempts to generate alkyne (−)-**18** in one operation resulted at best in only modest yields. Hydrostannylation exploiting the conditions of Guibé[16] then furnished a mixture of (*E*)- and (*Z*)-vinylstannanes (6:1, 85% yield), separable by column chromatography.

Coupling the major (*E*)-vinylstannane with (+)-**7** (*n*-BuLi, −78 °C, THF) proved problematic. Quenching experiments employing MeOH-d_1 revealed that after 30 min at −78 °C transmetalation had proceeded only to 30% conversion; unfortunately, warming the metalation reaction mixture to −50 °C led to decomposition. To circumvent this problem, the stannane was converted to the corresponding vinyl iodide (I_2, CH_2Cl_2); metalation with *t*-BuLi at −78 °C followed by treatment with MeOH-d_1 demonstrated complete vinyl anion formation with no decomposition.

With efficient approaches to the requisite fragments available, treatment of vinyl iodide (−)-**8**[11] with *t*-BuLi at −78 °C for ca. 30 min, followed by low-temperature cannula addition to aldehyde (+)-**7** at −100 °C, led to a mixture of (−)-**20**[11] and (−)-**21**[11] (Scheme 4). With THF as solvent, a 2.7:1 mixture of **20** and **21** was obtained, favoring the desired isomer, (−)-**20**.[17] Less polar solvents (Et_2O and *tert*-butylmethyl ether) afforded improved selectivity, with best results (ca. 4:1) obtained with a 4:1 mixture of Et_2O and pentane; the yield in this case was 65%.

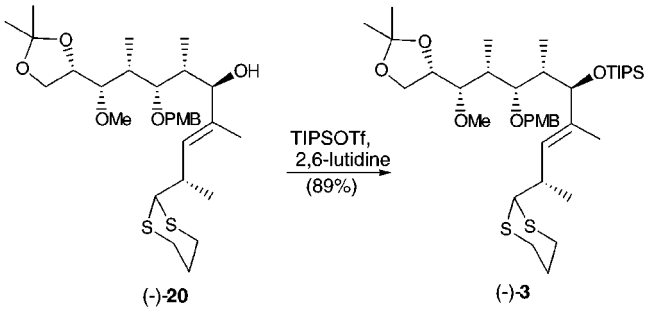
Scheme 4



Solvent	Ratio (20:21)	Yield
THF	2.7:1	58%
Et_2O	3.5:1	65%
t-Butylmethyl ether	3.5:1	43%
Et_2O/pentane (4:1)	4:1	65%

Final elaboration of subtarget **3** (Scheme 5) was achieved via treatment with TIPSOTf and 2,6-lutidine to provide silyl ether (−)-**3**.[11]

Scheme 5



Since the generation of highly oxygenated d^1 dithiane anions[18] can be capricious,[19] we decided to explore the coupling of (−)-**3** with a model epoxide (Scheme 6). To this end, treatment of (−)-**3** in THF at −78 °C with *t*-BuLi for 5 min followed by addition of benzyl (*S*)-(+)-glycidyl ether (−)-**22** provided (−)-**23**[11] in 78% yield, thereby demonstrating the viability of dithiane (−)-**3** as a linchpin.

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(17) The stereochemistry was determined via a combination of the Mosher ester analysis of secondary alcohols with application of the Kakisawa test (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092) and the Rychnovsky−Evans ^{13}C NMR 1,3-acetonide empirical correlation [Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511. Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.]
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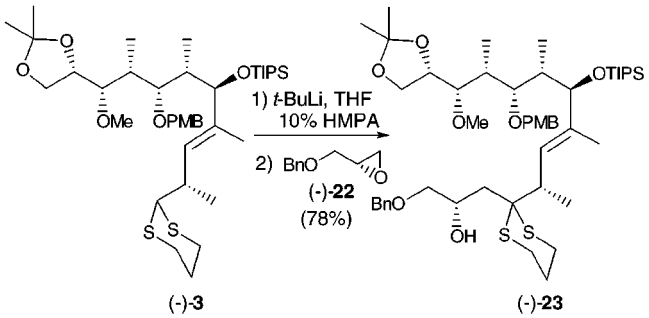
Scheme 6



In summary, we have developed an efficient synthesis of a common C(1)−C(11) dithiane (**3**) for tedanolide (**1**) and 13-deoxytedanolide (**2**) and demonstrated that this dithiane is a competent linchpin for future elaboration of the macrolide skeleton. The synthesis of (−)-**3**, requiring 13 steps, proceeded efficiently in 15% overall yield. Studies to assemble **5** and **6**, their union with (−)-**3**, and conversion to tedanolide (**1**) and 13-deoxytedanolide (**2**) continue in our laboratory.

Acknowledgment. Support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-29028 and by an American Chemical Society Division of Organic Chemistry Fellowship to S.A.L.

Supporting Information Available: Spectroscopic and analytical data for (+)-**11**, (+)-**12**, (+)-**13**, (+)-**14**, (−)-**15**, (+)-**7**, (−)-**17**, (−)-**18**, (−)-**8**, (−)-**20**, (−)-**21**, and (−)-**23** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9909233