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

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## 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<sup>1</sup> 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.<sup>2,3</sup> The relative and absolute stereochemistry of 1 was determined by X-ray diffraction, exploiting the anomalous dispersion of oxygen.<sup>1</sup> More recently (1991), Fusetani and co-workers<sup>4</sup> 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)<sup>1</sup> and in vivo antitumor activity, increasing the lifespan of mice implanted with lymphocytic leukemia cells (23% at 1.56  $\mu$ g/kg).<sup>5</sup> Deoxytedanolide (**2**) also displays significant antineoplastic activity (P388: T/C, 189%; 0.125 mg/kg).<sup>4</sup>

Tedanolide and deoxytedanolide represent unusual macrolides in that lactonization occurs at a primary hydroxyl instead of the customary secondary hydroxyl;<sup>6</sup> 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.<sup>7</sup> In this Letter, we outline a unified synthetic strategy and disclose an efficient

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



Consistent with concurrent investigations on the utility of dithianes<sup>8</sup> as linchpins for complex molecule construction, disconnectionat the C(29) lactone and C(11,12)  $\sigma$ -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).<sup>9</sup> Iterative Evans



aldol<sup>10</sup> condensations incorporating silyl protection (TBSOTf/ 2,6-lutidine) and conversion via the thioester to aldehyde (+)- $12^{11}$  were followed by LiBH<sub>4</sub> reduction and acetal formation to furnish (+)-13.<sup>11</sup> 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.<sup>11</sup>

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<sup>11</sup> in excellent yield. Parikh–Doering oxidation (SO<sub>3</sub>·pyr, DMSO, Et<sub>3</sub>N) then completed the construction of aldehyde (+)-7.<sup>11,12</sup>

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

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<sup>(9)</sup> Hubschwerlen, C. Synthesis 1986, 962.

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<sup>(11)</sup> The structure assigned to each new compound is in accord with its infrared, 500-MHz <sup>1</sup>H NMR, and 125-MHz <sup>13</sup>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<sup>13</sup> of known alcohol (+)-**16**,<sup>14</sup> available in five steps from methyl (*S*)-(+)-3-hydroxyl-2-methylpropionate, was followed by the Corey–Fuchs<sup>15</sup> protocol (CBr<sub>4</sub>/PPh<sub>3</sub>) to furnish dibromide (-)-**17**<sup>11</sup> (Scheme 3). Conversion to the



terminal alkyne (*n*-BuLi; -78 °C, THF) followed by alkylation with MeI led to (–)-**18**.<sup>11</sup> Attempts to generate alkyne (–)-**18** in one operation resulted at best in only modest yields. Hydrostannylation exploiting the conditions of Guibé<sup>16</sup> 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<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>); 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**<sup>11</sup> 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**<sup>11</sup> and (-)-**21**<sup>11</sup> (Scheme 4). With THF as solvent, a 2.7:1 mixture of **20** and **21** was obtained, favoring the desired isomer, (-)-**20**.<sup>17</sup> Less polar solvents (Et<sub>2</sub>O and *tert*-butylmethyl ether) afforded improved selectivity, with best results (ca. 4:1) obtained with a 4:1 mixture of Et<sub>2</sub>O and pentane; the yield in this case was 65%.



Solvent	Ratio (20:21)	Yield
THF	2.7:1	58%
Et <sub>2</sub> O	3.5:1	65%
t-Butylmethyl ether	3.5:1	43%
Et <sub>2</sub> O/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**.<sup>11</sup>



Since the generation of highly oxygenated  $d^1$  dithiane anions<sup>18</sup> can be capricious,<sup>19</sup> 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**<sup>11</sup> in 78% yield, thereby demonstrating the viability of dithiane (-)-**3** as a linchpin.

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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 mac-

rolide 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.

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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