Communication

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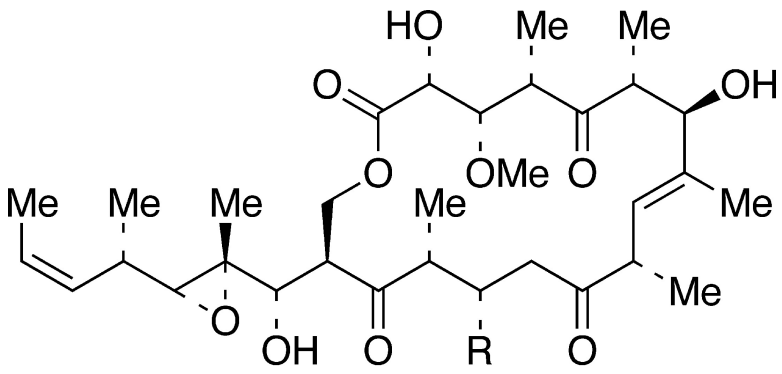
J. Am. Chem. Soc., **2005**, 127 (17), 6186-6187• DOI: 10.1021/ja050729d • Publication Date (Web): 09 April 2005



R = OH; tedanolide (**1**)
R = H; 13-deoxytedanolide (**2**)

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Published on Web 04/09/2005

Total Synthesis of (+)-13-Deoxytedanolide

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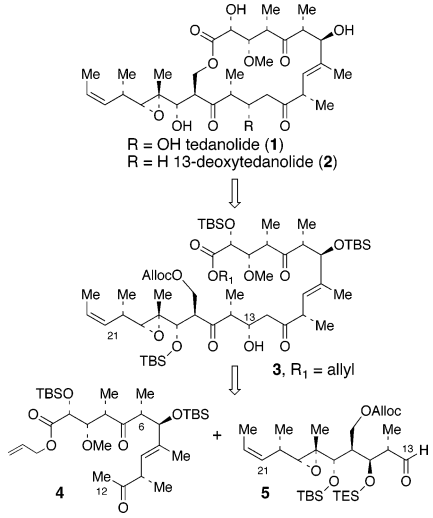
Tedanolide (**1**), was isolated in 1984 by Schmitz and co-workers from the Carribean sponge *Tedania ignis.*[1] In 1991, a closely related macrolide, 13-deoxytedanolide (**2**), was isolated from *Mycale adhaerens* by Fusetani and co-workers.[2] Both compounds display potent cytotoxicity against various cancer cell lines, and present considerable challenges as targets for total synthesis.[3−14] Smith and co-workers have recently published the first total synthesis of 13-deoxytedanolide.[10]

We have pursued a strategy that we anticipated would permit the total synthesis of both **1** and **2** from a common precursor **3** (Scheme 1).[15,16] We planned to assemble the complete carbon skeletons of **1** and **2** and to set the stereochemistry of the C(13)−OH (needed for **1**) through a stereoselective methyl ketone aldol reaction of ketone **4** and aldehyde **5**. After considerable experimentation, we elected to protect the C(1) acid of **4** as an allyl ester and the C(16) hydroxymethyl group of **5** as an allyl carbonate (Alloc), so that both units could be deprotected simultaneously prior to macrolactonization. Although we have thus far been unable to elaborate the aldol coupling product **4** and **5** to tedanolide (vide infra), we have successfully utilized these intermediates in a total synthesis of 13-deoxytedanolide (**2**), which is described herein.

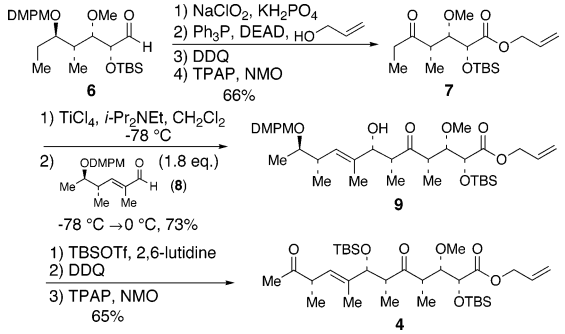
Methyl ketone **4** was synthesized as summarized in Scheme 2. Ethyl ketone **7** was prepared in four steps from known aldehyde **6**[16] in 66% yield, via chlorite oxidation of the aldehyde,[17] Mitsunobu esterification of the resulting carboxylic acid,[18] deprotection of the DMPM ether,[19] and TPAP oxidation of the resulting alcohol.[20] The aldol reaction of **7** and known aldehyde **8**[16] was best performed by exposure of **7** to $TiCl_4$ and *i*-Pr_2NEt for 8 min at −78 °C prior to addition of **8** (−78 °C with warming to 0 °C).[21] The targeted aldol **9** was obtained in 73% yield (10:1 ds). However, longer exposure of **7** to $TiCl_4$ and *i*-Pr_2NEt consistently led to low yields (30%) of **9**. Elaboration of aldol **9** to methyl ketone **4** proceeded in 65% over three standard transformations.

Synthesis of the Alloc-protected aldehyde fragment **5** proved more challenging (Scheme 3). The Alloc group could not be installed directly at the stage of **10** due to its incompatibility with subsequent olefin oxidative cleavage steps. Therefore, the primary alcohol of **10**[15] was initially protected as a bromoethyl carbonate (BEC), via treatment with 2-bromoethyl chloroformate. Subsequent oxidative cleavage of the olefin and asymmetric crotylboration using (*S,S*)-**11**[22] in toluene at −78 °C provided **12** in 71% yield over four steps. Protection of the free hydroxyl group of **12** as a TES ether, dihydroxylation of the vinyl group, and temporary protection of the resulting diol as bis-α-methoxyacetates then provided **13** as a ca. 5:1 mixture of diol diastereomers in 83% yield. It was necessary to functionalize the C(13) olefin prior to installing the C(21−22) (*Z*)-olefin, again due to problems encountered in attempts to cleave the terminal vinyl group in the presence of the C(21−22) (*Z*)-olefin (data not shown). Deprotection of the PMB ether of **13** and oxidation of the resulting alcohol with the Dess−Martin periodinane reagent[23] gave a highly sensitive β,γ-epoxyaldehyde. Treatment of the crude aldehyde with ethylidene(triphenyl)-phosphorane then provided **14** with >20:1 selectivity. Next, subjection of **14** to $H_2C{=}CHCH_2OMgBr$ in Et_2O−THF at 23 °C effected simultaneous cleavage of the labile methoxyacetates and trans-esterification of the bromoethyl carbonate to the targeted Alloc

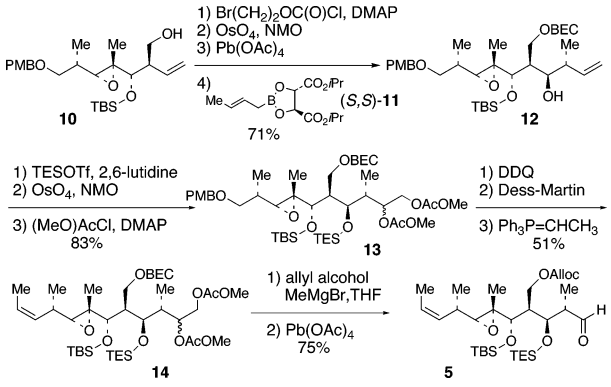
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Methyl Ketone **4**

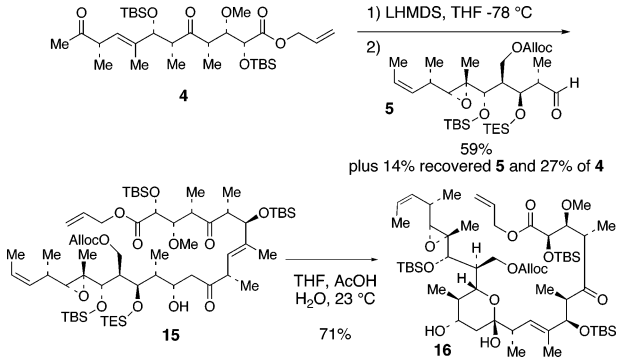


Scheme 3. Synthesis of Aldehyde **5**

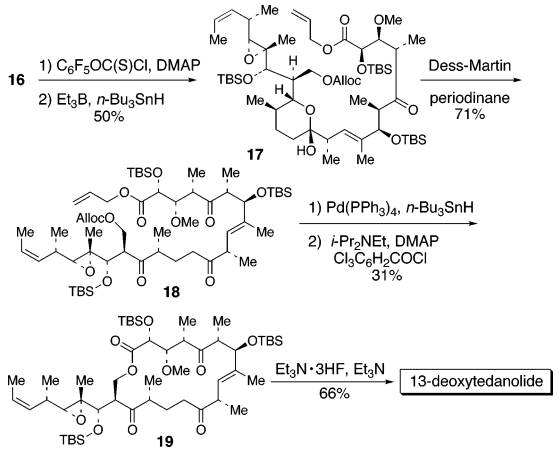


10.1021/ja050729d CCC: $30.25

Scheme 4. Fragment Assembly Aldol Reaction



Scheme 5. Completion of the Total Synthesis



unit. Finally, oxidative cleavage of the resulting diol provided the targeted aldehyde **5** in 75% yield over two steps.

Unification of the two fragments was accomplished by conversion of **4** (1.1 equiv) to the lithium enolate (LHMDS, THF, −78 °C) followed by addition of **5** (1.0 equiv). This provided aldol **15** as a single diastereomer in 59% yield (Scheme 4).[24] However, numerous attempts to elaborate **15** to tedanolide have been thwarted owing to the strong propensity for formation of pyran intermediates (cf., **16**) whenever C(15)−OH is deprotected. Hemiketal **16** has proven to be remarkably inert with respect to ring opening to the acyclic hydroxy ketone isomer, as all attempts to intercept the (minor) hydroxy ketone tautomer with oxidants (to obtain the C(11,15)-dione), or reagents designed to trap the C(11)-carbonyl, have been completely unsuccessful.

Although we have been unable to utilize **16** in a synthesis of tedanolide, this intermediate has proven useful for completion of a total synthesis of 13-deoxytedanolide. We postulated that removal of C(13)−OH might slightly destabilize the hemiketal with respect to the acyclic δ-hydroxy ketone tautomer, based on the precepts of the Thorpe−Ingold effect.[25] In the event, conversion of **16** to the corresponding C(13)-pentafluorophenylthiocarbonate,[26] followed by treatment with Et_3B and n-Bu_3SnH,[27] provided hemiketal **17** in 50% yield for the two steps (Scheme 5). Although the δ-hydroxy ketone tautomer of **17** was not observed spectroscopically, oxidation of **17** to the triketone **18** could now be accomplished in 71% yield by using the Dess−Martin periodinane.[23] Deprotection of the allyl ester and Alloc protecting groups by using $Pd(PPh_3)_4$ and n-Bu_3SnH[28] and subsequent modified-Yamaguchi macrolactonization[29] of the seco acid intermediate afforded the penultimate intermediate **19** in 31% over these two steps. Finally, deprotection of the three TBS ethers of **19** with $Et_3N{\cdot}(HF)_3$ and Et_3N[30,31] (thereby generating $Et_3N{\cdot}(HF)_2$ in situ) provided (+)-13-deoxytedanolide in 66% yield. Synthetic 13-deoxytedanolide was identical in all respects (^1H NMR, ^{13}C NMR, HRMS, IR, optical rotation) with an authentic sample.

Our continuing studies on the synthesis of tedanolide itself will be reported in due course.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (GM 38436), and a Bristol-Myers Squibb Graduate Fellowship to L.D.J. We thank Professors Fusetani and Matsunaga for supplying an authentic sample of 13-deoxytedanolide.

Supporting Information Available: Experimental procedures and NMR data for selected intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA050729D