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Synthesis of a Fully Functionalized Protected C1–C11 Fragment for the Synthesis of the Tedanolides

Michael E. Jung* and Christopher P. Lee

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

jung@chem.ucla.edu

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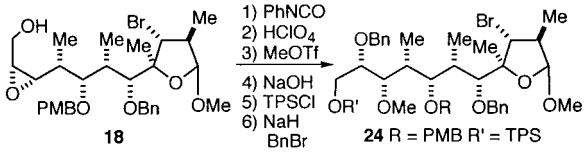
ABSTRACT



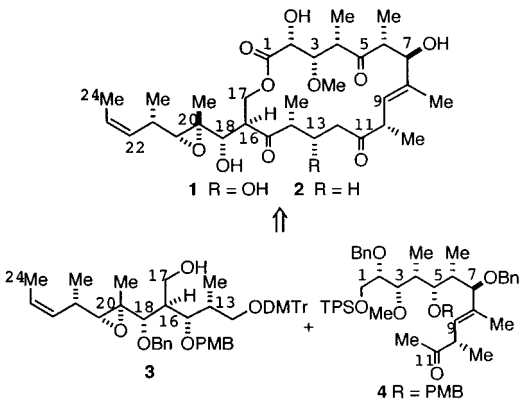
The use of several non-aldol aldol processes allows one to prepare a fully functionalized and completely protected C1–C11 fragment that should be useful for the total synthesis of the tedanolides.

The highly cytotoxic macrolide tedanolide (**1**, R = OH) was isolated by Schmitz and co-workers in 1984 from the Caribbean sponge *Tedania ignis*,[1] while the analogous cytotoxic compound 13-deoxytedanolide (**2**, R = H) was isolated from the Japanese sponge *Mycale adhaerens* by Fusetani and co-workers in 1991.[2] Because of their potent antitumor activity and their complex structures, the tedanolides **1** and **2** have generated considerable synthetic work,[3] including that of our group, which has used the non-aldol aldol process[4] in our approach to these molecules.

The straightforward retrosynthetic disconnection of the tedanolide skeleton by cleavage at the lactone moiety and at the C12−C13 bond affords the intermediates **3** and **4**, which could be combined in the forward sense by either an aldol reaction of the aldehyde derived from **3** (for tedanolide **1**) or an alkylation of the tosylate derived from **3** (for deoxytedanolide **2**) followed by removal of protecting groups, oxidation, and macrolactonization (Scheme 1). Recently we discussed our approach to the C1−C11 fragment **4**, in which the key step was a non-aldol aldol process.[5]

Thus, the epoxy mesylate **6** bearing a lactol methyl ether (prepared in several steps from the commercially available hydroxy ester **5**) underwent the desired non-aldol aldol

Scheme 1



(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) (a) Yonemitsu, O. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 946. (b) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 185. (c) Matsushima, T.; Mori, M.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (d) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (e) Matsushima, T.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, *6*, 780. (f) Liu, J.-F.; Abiko, A.; Pei, Z. H.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (g) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361. (h) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (i) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249.

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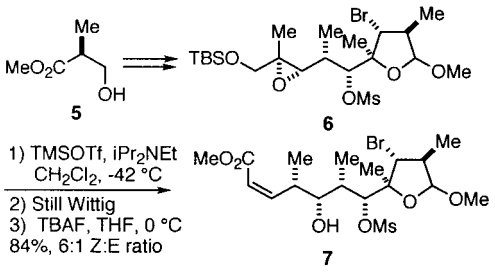
rearrangement on treatment with TMSOTf and Hunig's base to give the desired aldehyde, which was then converted into the hydroxy ester **7** in very good overall yield and selectivity (Scheme 2). We now report the conversion of this hydroxy

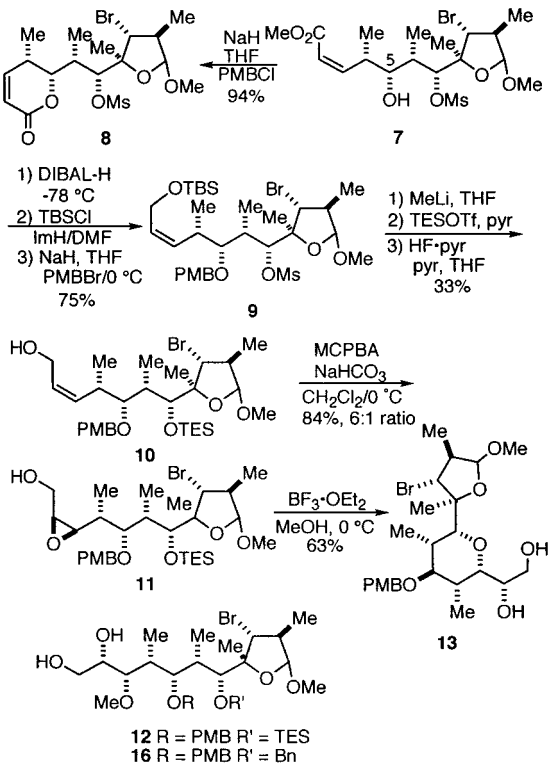
Scheme 2



ester into the fully functionalized protected C1−C11 fragment **24** for the synthesis of the tedanolides.

Since the natural products have a ketone at C5, the hydroxyl group at C5 of **7** must eventually be transformed into a ketone. For this reason, it would be advantageous to protect this alcohol with an orthogonal protecting group such as a PMB ether. Unfortunately, the usual procedure of PMB ether formation (PMBCl, NaH, THF) afforded the lactone **8** in 94% yield (Scheme 3). We opted instead for a three-step

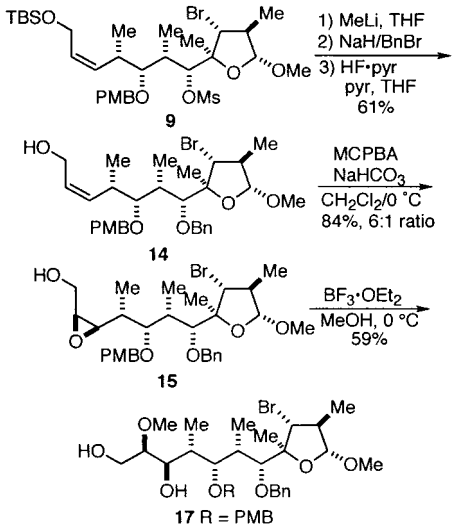
Scheme 3



route, namely, reduction of the *Z*-enoate of **7** using DIBAL-H, regioselective protection of the primary hydroxyl group as its TBS ether, and final protection of the secondary alcohol as its PMB ether **9** in 75% yield. The installation of the last two stereocenters in the C1−C11 fragment of tedanolide required removal of the mesylate protecting group of **9**, which was accomplished by a slight modification of our earlier route, namely, using methyllithium in THF,[4e,6] to give the alcohol, which was then protected as the triethylsilyl (TES) ether.[7] The steric hindrance of the secondary TES ether allowed for selective removal of the primary TBS ether to give the alcohol **10** in modest overall yield. MCPBA epoxidation of **10** occurred stereoselectively to give epoxide **11** in 84% yield and a 6:1 diastereomeric ratio.[8] The diastereoselectivity is the result of allylic 1,3 strain and the directing ability of the PMB ether. We hoped to open the epoxide with methanol to furnish the desired diol **12**, since Sharpless has reported the formation of 1,2-diols from epoxy alcohols in the presence of $Ti(OiPr)_4$ using a variety of nucleophiles including alcohols.[9] However, we observed no reaction of **11** with methanol, even at reflux. Several other Lewis and Bronsted acids were investigated, but none gave the desired product. When the Lewis acid was changed to BF_3 etherate,[10] TES deprotection exposed a free hydroxyl group that readily cyclized to provide the tetrahydropyran **13** in 63% yield. Thus, as seen in our earlier synthesis,[4e] a somewhat nucleophilic oxygen atom (even a silyl ether) six atoms away from a developing positive charge leads to cyclization.

We therefore decided to look at other ether protecting groups that might be less likely to participate in cyclizations of this sort (Scheme 4). The TBS ether **9** was converted via

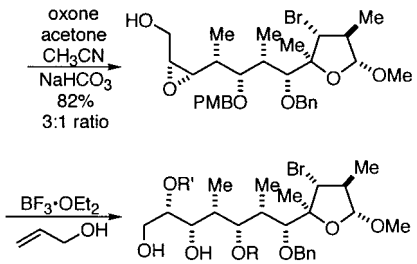
Scheme 4



a similar three-step route into the benzyl ether **14** in 61% overall yield. Kishi epoxidation again produced mainly the desired epoxide **15**. This benzyl ether epoxide could now be opened with methanol in the presence of BF_3 etherate to

give a methoxy diol in 59% yield. However, surprisingly, the desired 1,2-diol **16** was not obtained, but rather the unexpected 1,3-diol **17**.[11] Thus the steric hindrance of the chain outweighs that of the hydroxymethyl group, and no directing effect of the alcohol was observed with BF_3. We hypothesized that if we added another alcohol such as benzyl or allyl alcohol to the diastereomeric epoxide, then after methylation and removal of the benzyl or allyl group, the desired methoxy diol would be produced (in a sense using benzyl or allyl alcohol as a surrogate for water). The allylic alcohol **14** was epoxidized with DMDO (formed in situ from oxone and acetone) to give a 3:1 ratio favoring the desired syn epoxide **18** (Scheme 5). Opening with benzyl alcohol

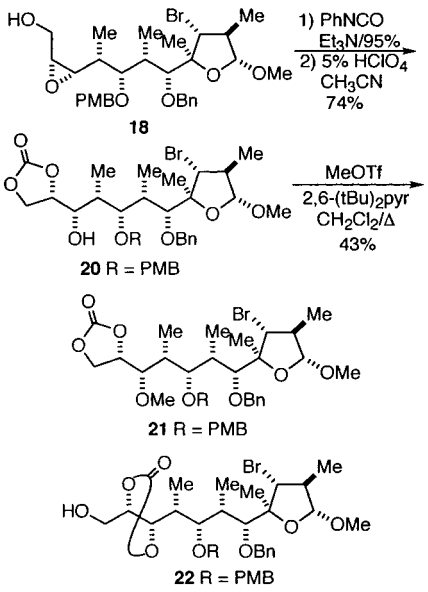
Scheme 5



was unsuccessful, but we were able to form the allyloxy diol **19** from **18** on treatment with allyl alcohol and BF_3 etherate.[12] However, because of the low yield we discontinued this route.

The solution to the formation of the desired methoxy diol involved an intramolecular strategy.[13] Thus the nucleophilic carbamate was attached to the hydroxyl group of **18** by treatment with phenyl isocyanate in 95% yield (Scheme 6). Treatment of this carbamate with 5% $HClO_4$ in acetonitrile[14]

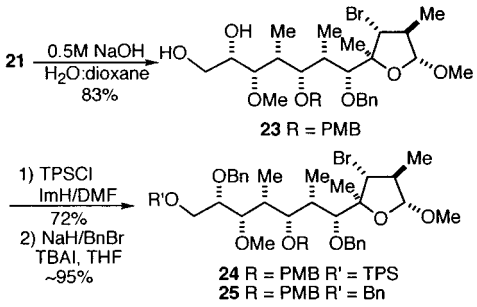
Scheme 6



gave the desired carbonate **20** in 74% yield.[15] No methyl lactol ether deprotection was observed during the acidic hydrolysis step. Formation of the anion of the alcohol of **20** with NaH, even in the presence of methyl iodide or triflate,[16] gave only the product of carbonate migration **22** rather than the desired methyl ether **21**. However, alkylation with methyl triflate in the presence of the very hindered base 2,6-di-*tert*-butylpyridine in refluxing dichloromethane furnished the desired methyl ether **21** in 43% yield.

To prepare the compound for regeneration of the trisubstituted alkene and methyl ketone formation, we first had to adjust the protecting groups. Basic hydrolysis of the carbonate **21** provided the diol **23** in 83% yield (Scheme 7). A *tert*-

Scheme 7



butyldiphenylsilyl (TPS) ether was then attached to the primary alcohol in 72% yield, allowing the secondary alcohol to be protected as its benzyl ether to give **24** in 50% yield, along with the bisbenzyl ether formed presumably as a result

(4) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208 and references therein. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) D'Amico, D. C. Ph.D. Thesis, UCLA, Los Angeles, CA, 1995. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307. (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343. (g) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663. (h) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (i) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669.

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(6) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V.; Wietzke, R. *Synth. Commun.* **1995**, *25*, 3109.

(7) The alcohol is too hindered to allow easy introduction of the TBS ether.

(8) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4343. Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4347.

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(10) Liu, Y.-J.; Chu, T.-Y.; Engel, R. *Synth. Commun.* **1992**, *22*, 2367.

(11) The position of the methyl ether was determined by constructing two derivatives, the cyclic carbonate, which had the characteristic IR stretch of a six-membered carbonate (1755 cm^{-1}), and the *p*-methoxybenzylidene acetal formed by oxidative cyclization with DDQ, which showed the expected NOE between 1,3 diaxial protons.

(12) The structure of **19** was again inferred, since the cyclic carbonate formed from it had the characteristic IR stretch of a six-membered carbonate (1748 cm^{-1}).

(13) (a) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691. (b) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31.

(14) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1705.

(15) The IR spectrum of **20** showed an absorption at 1798 cm^{-1}, indicative of a five-membered carbonate.

(16) (a) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050. (b) Jung, M. E.; Nichols, C. J. *Tetrahedron Lett.* **1998**, *39*, 4615.

of some hydrolysis of the TPS ether prior to or during the benzylation. Further reactions of **24**, namely, reductive debromination and formation of the methyl ketone to produce **4** are currently underway in our laboratories.

In conclusion, we have developed a good method for the preparation of a fully functionalized protected C1−C11 fragment for the synthesis of the tedanolides in several steps from the commercially available hydroxy ester **5**.

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

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