

Concerning the Synthesis of the
Tedanolide C(13)–C(23) Fragment via
Anti-Aldol Reaction

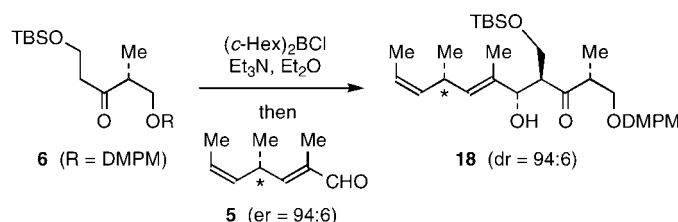
Joshua R. Dunetz and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458

roush@scripps.edu

Received March 10, 2008

ABSTRACT



Synthesis of C(13)–C(23) aldehyde **4**, an important intermediate in a planned total synthesis of tedanolide, is described. The stereoselectivity of the key anti-aldol reaction of aldehyde **5** and ketone **6** (en route to **4**) perfectly tracks the enantiomeric purity of **5**. It is demonstrated that aldehyde **24**, a precursor of **5**, undergoes facile epimerization during a Swern oxidation and stabilized ylide olefination sequence.

Tedanolide (**1**), isolated from the Caribbean fire sponge *Tedania ignis* in 1984 by Schmitz and co-workers, displays potent cytotoxicity against various cancer cell lines (ED₅₀ = 250 pg/mL against human nasopharynx carcinoma; ED₅₀ = 16 pg/mL against lymphocytic leukemia) and causes cell arrest in the S phase.¹ The closely related macrolide, 13-deoxytedanolide (**2**), was isolated from the Japanese sponge *Mycale adhaerens* in 1991 by Fusetani and co-workers and demonstrates high cytotoxicity against P388 murine leukemia cells (IC₅₀ = 94 pg/mL).² The impressive biological activities and structural complexities of the tedanolides have inspired our laboratory³ and others^{4–12} to pursue their synthesis. Kalesse (2006)^{4a,b} and Smith (2007)^{5a} recently reported total syntheses of tedanolide, and a few years earlier, Smith

(2003)^{5c,d} and our laboratory (2005)^{3a} reported total syntheses of the 13-deoxy congener, **2**.

(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.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971.

(3) (a) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186. (b) Roush, W. R.; Newcom, J. S. *Org. Lett.* **2002**, *4*, 4739. (c) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95.

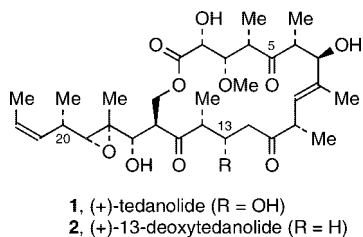
(4) (a) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *Chem. Eur. J.* **2008**, *14*, 2232. (b) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038. (c) Hassfeld, J.; Eggert, U.; Kalesse, M. *Synthesis* **2005**, 1183. (d) Ehrlich, G.; Kalesse, M. *Synlett* **2005**, 655. (e) Hassfeld, J.; Kalesse, M. *Synlett* **2002**, 2007.

(5) (a) Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957. (b) Cho, C.-G.; Kim, W.-S.; Smith, A. B., III. *Org. Lett.* **2005**, *7*, 3569. (c) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042. (d) Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (e) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249.

(6) (a) Jung, M. E.; Zhang, T.-h. *Org. Lett.* **2008**, *10*, 137. (b) Jung, M. E.; Yoo, D. *Tetrahedron Lett.* **2008**, *49*, 816. (c) Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543. (d) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (e) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719. (f) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (g) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129.

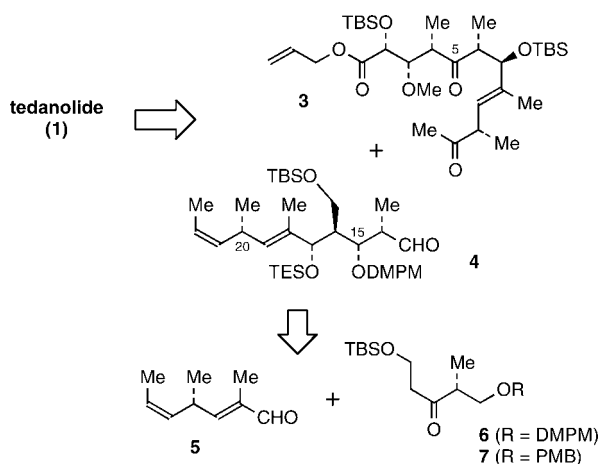
(7) (a) Wong, C.-M.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 4485. (b) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 6001. (c) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223.

(8) (a) Matsui, K.; Zheng, B.-Z.; Kusaka, S.-i.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. *Eur. J. Org. Chem.* **2001**, 3615. (b) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.-i.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441. (c) Matsushima, T.; Nakajima, N.; Zheng, B.-Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855. (d) Zheng, B.-Z.; Maeda, H.; Mori, M.; Kusaka, S.-i.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J.-i. *Chem. Pharm. Bull.* **1999**, *47*, 1288. (e) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.-i.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (f) Matsushima, T.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.-i.; Yonemitsu, O. *Synlett* **1999**, 780. (g) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.-i.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (h) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385.

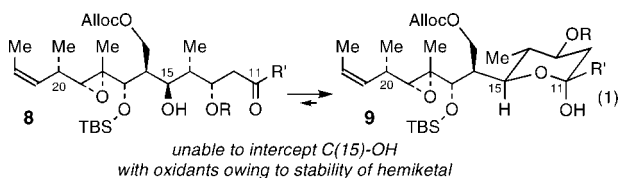


We are pursuing a strategy toward the synthesis of tedanolide in which the carbon skeleton is assembled in a convergent fashion via the aldol reaction of ketone **3**^{3a} and aldehyde **4** (Scheme 1). Our selection of **4** was based on

Scheme 1. Retrosynthetic Approach to Tedanolide



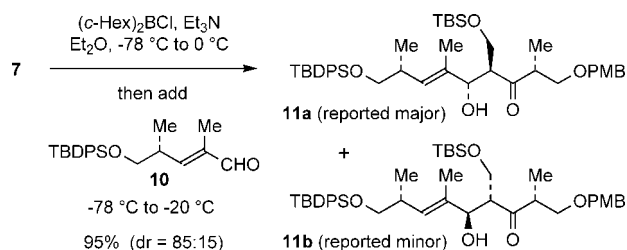
previous results from our laboratory in which we were unable to oxidize late-stage hydroxy intermediates (e.g., **8**) to the requisite C(15)-carbonyl owing to the remarkable stability of hemiketal **9** (eq 1). We hypothesized that inversion of the C(15)-(R)-alcohol stereochemistry of our first-generation intermediates (see **8**) to the (*S*)-configuration in **4** would destabilize the corresponding hemiketal via increased 1,3-diaxial interactions, thereby permitting C(15)-oxidation.^{13,14}



In planning our synthetic approach to **4** (Scheme 1), we were intrigued by the possible anti-aldol coupling of aldehyde

5 and ketone **6** using conditions developed by Paterson.¹⁵ This transformation would set the C(16)- and C(17)-stereocenters in a single operation through a transition state believed to minimize oxygen lone pair interactions between the enol borinate and benzyl ether.^{15b} We were encouraged by a report from Loh and co-workers that enol borinates derived from β -siloxy ethyl ketones participate in the anti-aldol reaction under Paterson's conditions without β -elimination of the siloxy substituent. Indeed, Loh reported 85:15 selectivity for the aldol coupling of ketone **7** and aldehyde **10** (Scheme 2).^{7c} In addition, during the preparation of this

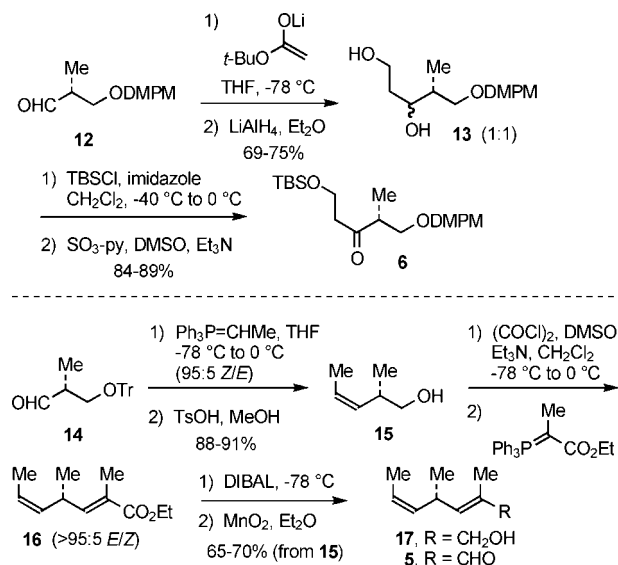
Scheme 2. Loh's Anti-Aldol Reaction of β -Siloxy Ketone **7**^{7c}



manuscript, Kalesse and co-workers reported 2:1 diastereoselectivity for the anti-aldol reaction of ketone **7** and aldehyde **5**.^{4a}

Both ketone **6** and aldehyde **5** are available in easily scalable routes (Scheme 3). Addition of the lithium enolate

Scheme 3. Syntheses of Ketone **6** and Aldehyde **5**



of *tert*-butyl acetate to aldehyde **12**¹⁶ and subsequent LiAlH₄ reduction of the ester afforded 1,3-diol **13**. Selective silylation of the primary alcohol followed by Parikh–Doering oxidation¹⁷ led to the targeted ketone **6**. The synthesis of aldehyde **5**^{4a,d} began with the Wittig olefination of aldehyde **14** and

(9) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, 39, 1873.

(10) Iwata, Y.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005**, 7, 2341.

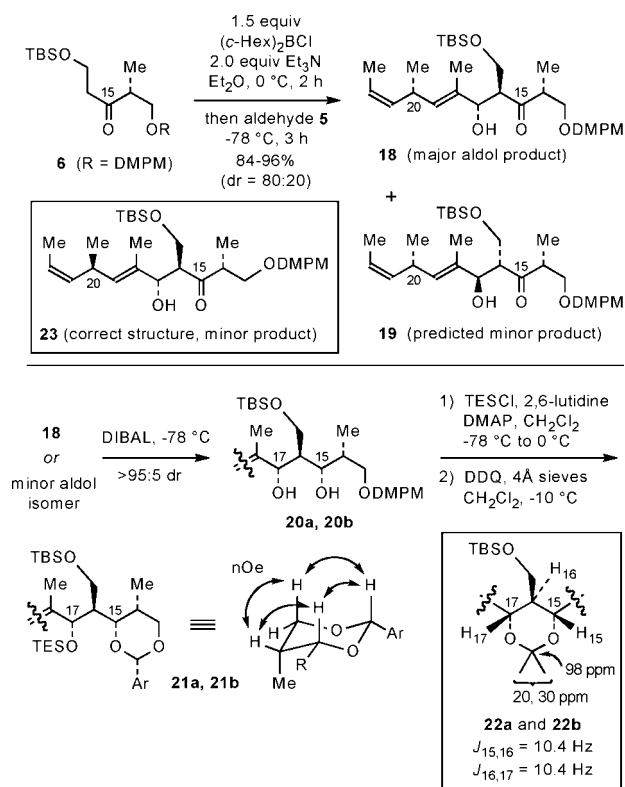
(11) (a) Taylor, R. E.; Hearn, B. R.; Ciavarrri, J. P. *Org. Lett.* **2002**, 4, 2953. (b) Taylor, R. E.; Ciavarrri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, 39, 9361.

(12) (a) Nyavanandi, V. K.; Nadipalli, P.; Nanduri, S.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2007**, 48, 6905. (b) Nyavanandi, V. K.; Nanduri, S.; Dev, R. V.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2006**, 47, 6667.

cleavage of the trityl ether. Swern oxidation¹⁷ of **15** and subsequent treatment of the β,γ -unsaturated aldehyde with the stabilized ylide $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$ gave the unsaturated ester **16** with excellent selectivity. DIBAL reduction of the ester followed by oxidation of the derived primary alcohol with MnO_2 provided the requisite aldehyde **5**.

Our initial exploration of the anti-aldol reaction of aldehyde **5** and ketone **6** under conditions developed by Paterson (treatment of **6** with 1.5 equiv of $(c\text{-Hex})_2\text{BCl}$ and 2.0 equiv of Et_3N in Et_2O at 0 °C and then addition of **5** at -78 °C) led to **18** as the major of two diastereomers with 80:20 selectivity (Scheme 4). Based on the aforementioned studies

Scheme 4. Anti-Aldol Reaction of Ketone **6** and Aldehyde **5**



by Loh^{7c} (and also as reported by Kalesse^{4a} after our work was completed), we expected **19** to be the minor aldol adduct. However, Mosher ester analysis¹⁸ of both aldol products revealed that *both have identical (S)-configurations* for the C(17)-alcohols. 1,3-Reduction of the two β -hydroxy ketones with DIBAL (>95:5 dr) afforded 1,3-diols **20a** and **20b**. The 1,3-syn diol stereochemistry in both **20a** and **20b** was

assigned by conversion to acetonides **22a** and **22b**; both acetals displayed identical coupling constants of $J_{15,16} = J_{16,17} = 10.4$ Hz, and the ^{13}C data of both acetonides were also consistent with the indicated 1,3-syn stereochemistry (analysis in CDCl_3).¹⁹ Selective silylation of the allylic alcohols of **20a,b** followed by treatment of the mono-TES ethers with DDQ provided benzylidene acetals **21a** and **21b** (deriving from the major and minor aldols, respectively). ^1H NOE analysis of these compounds revealed that the C(14)-methine and benzylidene acetal protons are syn and that the C(14)-H is equatorial in both **21a** and **21b**. Thus, the major and minor products from the aldol reaction of **5** and **6** have identical stereochemistry at C(14)–C(17)—both are anti-aldol products with (*S*)-stereochemistry at C(17)-OH.

It was clear from these results that the minor aldol product is not **19**, as originally assumed. Instead, we considered that C(20)-epimer **23** might be the minor aldol product. This structure would arise if epimerization of the bisallylic stereocenter of aldehyde **5** occurred during its synthesis. This hypothesis was consistent with our observation that only a single diastereomer is formed from the aldol reaction of ketone **6** with methacrolein (not shown). Furthermore, Mosher ester analysis of primary alcohol **17**, the immediate precursor of aldehyde **5**, revealed this intermediate to be *an 80:20 ratio of epimers at the C(20) bisallylic stereocenter* (Figure 1). This evidence confirmed our deduction that the C(20)-epimer **23** is the minor aldol diastereomer, and not compound **19** as suggested by previous studies.^{4a,7c}

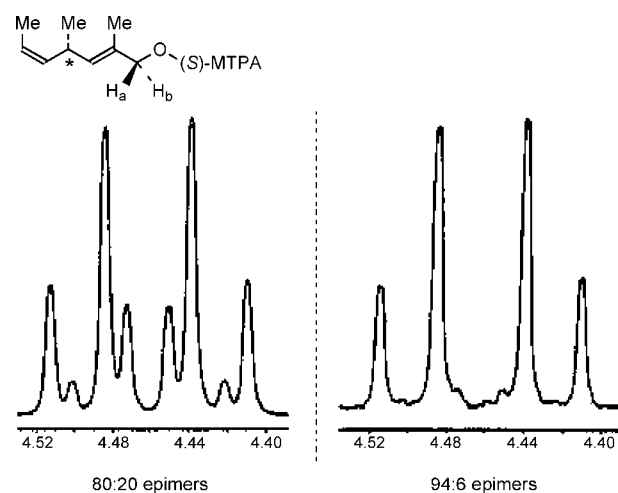


Figure 1. ^1H NMR spectra (400 MHz, C_6D_6) of the H_a and H_b protons of Mosher esters derived from alcohol **17**, the immediate precursor to aldehyde **5**.

It seemed most likely that epimerization of C(20) was occurring during the conversion of alcohol **15** (>95:5 er as

(13) Julian, L. D. Studies toward the total synthesis of the tedanolides: Total synthesis of 13-deoxytedanolide. Ph.D. thesis, University of Michigan, 2005.

(14) While this work was in progress, Kalesse reported experimental evidence for this hypothesis (refs 4a and 4b).

(15) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, 30, 7121. (b) Mechanistic discussion: Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, 49, 685.

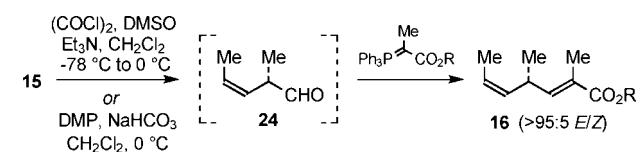
(16) Prepared in analogous fashion to the known *p*-methoxybenzyl-protected Roche aldehyde: Organ, M. G.; Wang, J. J. *Org. Chem.* **2003**, 68, 5568.

(17) For a review, see: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(18) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512.

(b) For a useful explanation and examples of Mosher ester analysis, see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, 113, 4092.

(19) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, 31, 9.

Table 1. Optimization of the Oxidation–Olefination Sequence

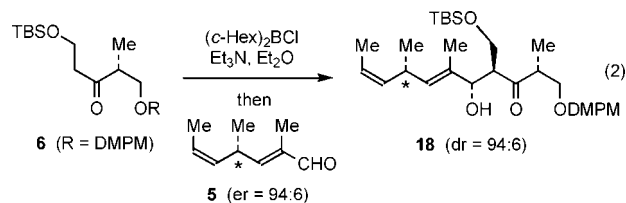
entry	oxidation	ylide addition	olefination	enant ratio ^a
1	Swern	one-pot, R = Et	rt	80:20
2	Swern	one-pot, R = Me	rt	80:20
3	Swern	one-pot, R = Me	$0\text{ }^\circ\text{C}$	85:15
4	Swern	two-pot, R = Me	$0\text{ }^\circ\text{C}$	90:10
5	Dess–Martin	one-pot, R = Me	rt	90:10
6	Dess–Martin	two-pot, R = Me	rt	90:10
7	Dess–Martin	one-pot, R = Me	$0\text{ }^\circ\text{C}$	94:6
8	Dess–Martin	one-pot, R = Me	$-20\text{ }^\circ\text{C}$	94:6

^a Determined by DIBAL reduction of ester **16** and Mosher ester analysis of the resulting alcohol **17** (as shown in Figure 1).

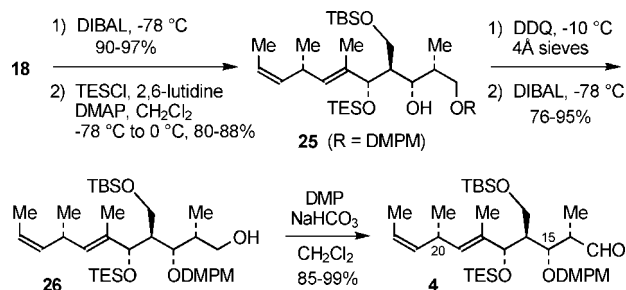
determined by Mosher ester analysis) to the α,β -unsaturated ester **16**. This was confirmed by the studies summarized in Table 1. We had originally employed a one-pot reaction sequence²⁰ in which alcohol **15** was oxidized by using the Swern protocol (DMSO, $(\text{COCl})_2$, CH_2Cl_2 , Et_3N , -78 to $0\text{ }^\circ\text{C}$), followed by addition of the stabilized ylide, $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{R}$ (R = Me, Et), directly to the Swern reaction mixture before the mixture was allowed to warm to room temperature (entries 1 and 2). The isomeric purity at C(20) was determined by DIBAL reduction of ester **16** and Mosher ester analysis of the derived alcohol **17**. Epimerization of C(20) was somewhat suppressed by maintaining the olefination reaction at $0\text{ }^\circ\text{C}$ (entry 3), and further improvement was realized (90:10 *er*) when isolated aldehyde **24** (by extractive workup of the Swern oxidation) was treated with $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Me}$ in a two-pot sequence (entry 4). Ultimately, the best results were obtained when the oxidation of **15** was performed by using Dess–Martin periodinane²¹ (entries 5–8). In this way, **16** was obtained with optimal enantiomeric purity of 94:6 (entries 7 and 8).

When aldehyde **5** (prepared from **16** of 94:6 *er*) was used in the anti-aldol reaction with **6**, a 94:6 mixture of aldol diastereomers **18** and **23** was obtained (eq 2). It is striking that the selectivity of the anti-aldol reaction tracks perfectly with the enantiomeric purity of alcohol **17**.

The synthesis of the C(13)–C(23) fragment **4** was completed in five steps. Reduction of **18** with DIBAL



afforded a *syn*-1,3-diol with excellent selectivity that was silylated at the allylic alcohol position. The dimethoxybenzyl group of **25** was then transferred to the internal C(15)-OH through a sequence involving benzylidene acetal formation with DDQ, followed by regioselective acetal reductive opening with DIBAL. Finally, Dess–Martin oxidation of alcohol **26** furnished the targeted C(13)–C(23) aldehyde **4** (Scheme 5).

Scheme 5. Completion of the C(13)–C(23) Fragment **4**

Further progress toward completion of the total synthesis of tetanolide will be reported in due course.

Acknowledgment. Support from the National Institutes of Health (GM 38436) is gratefully acknowledged.

Note Added after ASAP Publication. Due to a production error, the reference to eq 2 was incorrectly printed as eq 5 in the version published ASAP April 19, 2008; the corrected version was published ASAP April 23, 2008. In addition, the formula for $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{R}$ was corrected in the version published May 8, 2008.

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

OL800546G

(20) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

(21) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.