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

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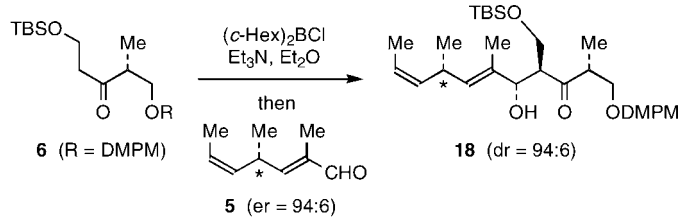
ABSTRACT



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 (ED_{50} = 250 pg/mL against human nasopharynx carcinoma; ED_{50} = 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 (IC_{50} = 94 pg/mL).[2] The impressive biological activities and structural complexities of the tedanolides have inspired our laboratory[3] 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**.

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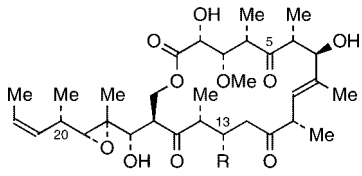
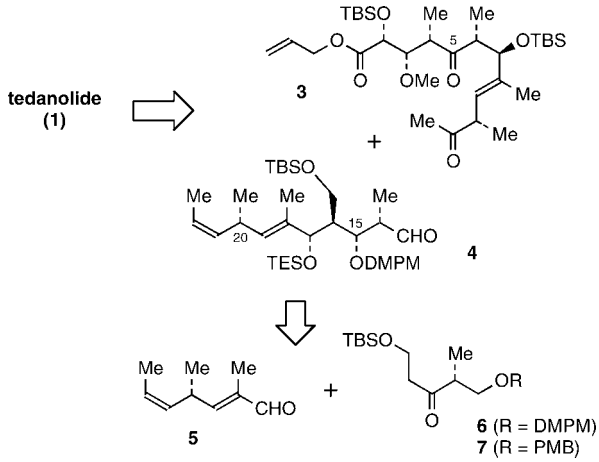


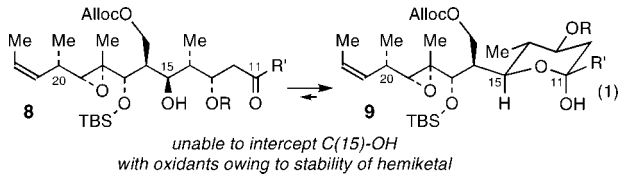
1, (+)-tedanolide (R = OH)
2, (+)-13-deoxytedanolide (R = H)

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



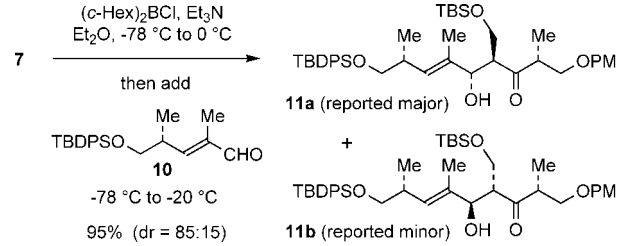
previous results from our laboratory in which we were unable to oxidize late-stage hydroxy intermediates (e.g., **8**) to the requisite C(15)-carbonyl owing to the remarkable stability of hemiketal **9** (eq 1). We hypothesized that inversion of the C(15)-(*R*)-alcohol stereochemistry of our first-generation 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]



unable to intercept C(15)-OH with oxidants owing to stability of hemiketal

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

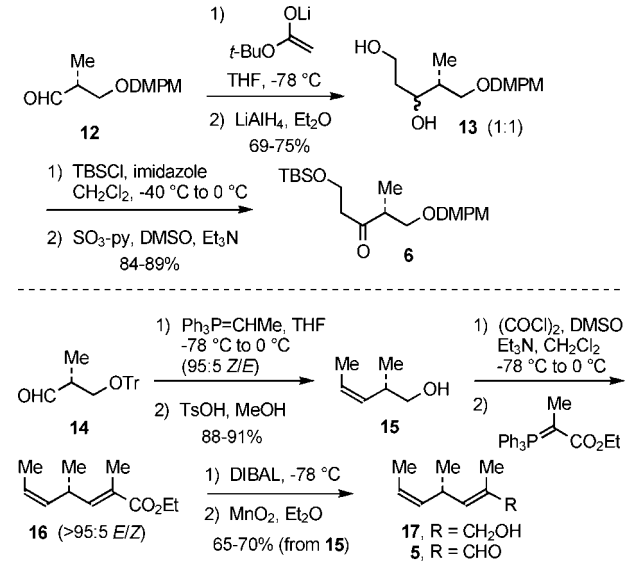
Scheme 2. Loh's Anti-Aldol Reaction of β-Siloxy Ketone **7**[7c]



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 $LiAlH_4$ reduction of the ester afforded 1,3-diol **13**. Selective silylation of the primary alcohol followed by Parikh−Doering oxidation[17] led to the targeted ketone **6**. The synthesis of aldehyde **5**[4a,d] began with the Wittig olefination of aldehyde **14** and

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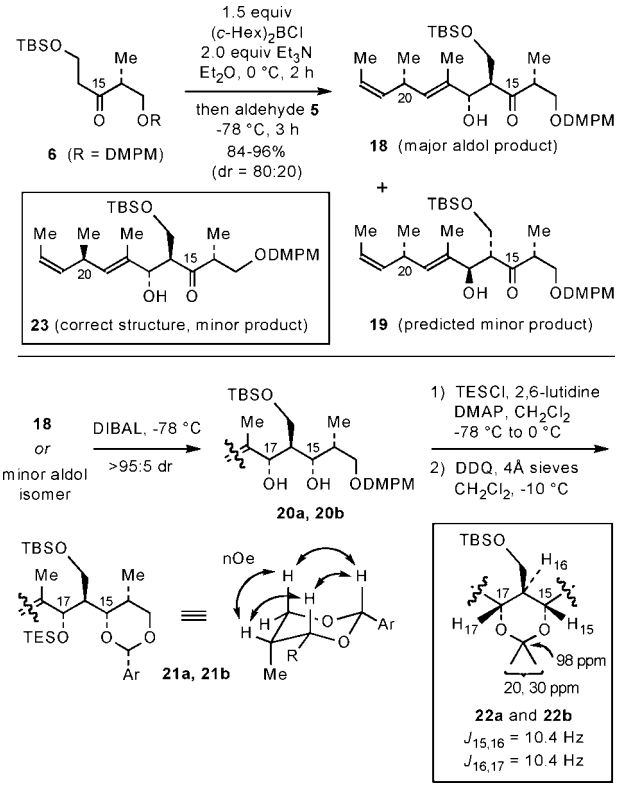
cleavage of the trityl ether. Swern oxidation[17] of **15** and subsequent treatment of the β,γ-unsaturated aldehyde with the stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ gave the unsaturated ester **16** with excellent selectivity. DIBAL reduction of the ester followed by oxidation of the derived primary 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 $(c\text{-Hex})_2BCl$ 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 analysis[18] 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]

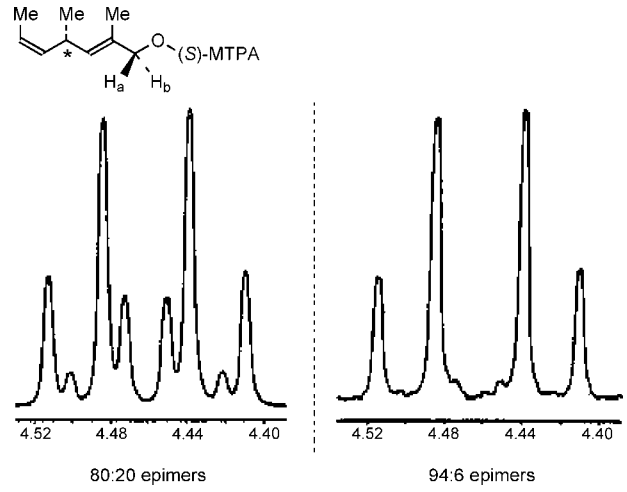


Figure 1. ^1H NMR spectra (400 MHz, C_6D_6) of the H_a and H_b protons of Mosher esters derived from alcohol **17**, the immediate precursor to aldehyde **5**.

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).

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(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.

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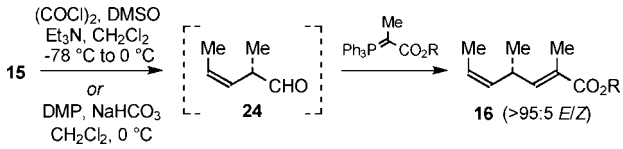
Table 1. Optimization of the Oxidation−Olefination Sequence



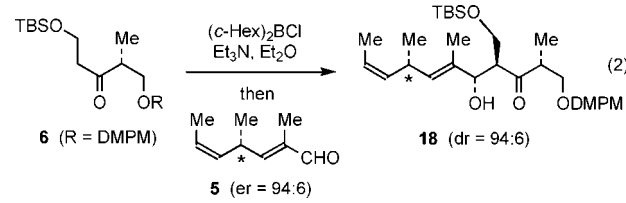
entry	oxidation	ylide addition	olefination	enant ratio[a]
1	Swern	one-pot, R = Et	rt	80:20
2	Swern	one-pot, R = Me	rt	80:20
3	Swern	one-pot, R = Me	0 °C	85:15
4	Swern	two-pot, R = Me	0 °C	90:10
5	Dess−Martin	one-pot, R = Me	rt	90:10
6	Dess−Martin	two-pot, R = Me	rt	90:10
7	Dess−Martin	one-pot, R = Me	0 °C	94:6
8	Dess−Martin	one-pot, R = Me	−20 °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 sequence[20] in which alcohol **15** was oxidized by using the Swern protocol (DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 to 0 °C), followed by addition of the stabilized ylide, $Ph_3P{=}C(Me)CO_2R$ (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 °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 $Ph_3P{=}C(Me)CO_2Me$ in a two-pot sequence (entry 4). Ultimately, the best results were obtained when the oxidation of **15** was performed by using Dess−Martin periodinane[21] (entries 5−8). In this way, **16** was obtained with optimal enantiomeric purity of 94:6 (entries 7 and 8).

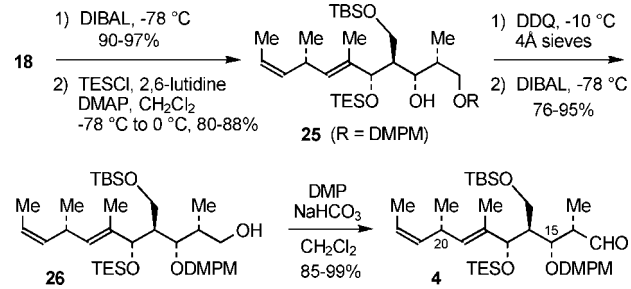
When aldehyde **5** (prepared from **16** of 94:6 er) was used in the anti-aldol reaction with **6**, a 94:6 mixture of aldol diastereomers **18** and **23** was obtained (eq 2). It is striking that the selectivity of the anti-aldol reaction tracks perfectly with the enantiomeric purity of alcohol **17**.

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 tedanolide will be reported in due course.

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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 $Ph_3P{=}C(Me)CO_2R$ 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.

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