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Synthesis of the C_1–C_{12} Fragment of the Tedanolides. Aldol–Non-Aldol Aldol Approach

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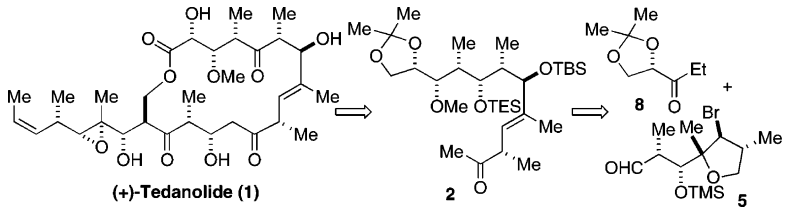
ABSTRACT

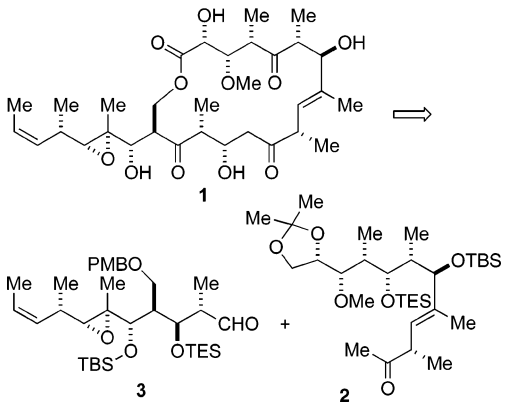


The combination of highly stereoselective non-aldol aldol and aldol processes allows the preparation of the completely protected C_1–C_{12} fragment 2 of the novel macrocyclic cytotoxic agent tedanolide 1.

Tedanolide **1** was isolated by Schmitz and co-workers in 1984 from the Caribbean sponge *Tedania ignis*.[1] The macrolide demonstrates high cytotoxicity, displaying ED_{50}'s of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Due to its powerful antitumor activity and structural features (an 18-membered macrocyclic lactone with a polypropionate skeleton, an internal trisubstituted *E* olefin, and 13 stereocenters), tedanolide has generated considerable synthetic interest,[2] including that of our group, which has used the non-aldol aldol process[3] in our approach to this molecule.

Disconnecting the tedanolide backbone in a retrosynthetic analysis is straightforward, beginning with cleavage at the lactone moiety and scission at the C_{12}−C_{13} bond to generate the precursors **2** and **3** (Scheme 1). Recently, we published

Scheme 1



a synthesis of the fully functionalized protected C_1−C_{11} fragment using sequential non-aldol aldol reactions.[3] However, several additional steps were necessary to prevent some problems[4] in the non-aldol aldol reaction. Therefore, we wanted to develop an approach that would construct this key

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(2) (a) Total synthesis of tedanolide: Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038. (b) Synthetic study of tedanolide: Iwata, Y.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005**, *7*, 2341. Ehrlich, G.; Kalesse, M. *Synlett* **2005**, 655. Hassfeld, J.; Kalesse, M. *Synlett* **2002**, 2007. Roush, W. R.; Newcom, J. S. *Org. Lett.* **2002**, *4*, 4739. Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002**, *4*, 2953. Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 6001. Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223. Smith, A. B.; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95.

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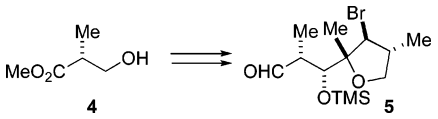
intermediate **2** via a much more convergent route. Herein, we report an efficient approach to the fragment **2**.

The synthesis of **2** began with the commercially available optically pure ester **4**. We prepared the optically pure aldehyde **5** in 13 steps by a method that we have described previously (Scheme 2).[3c] The aldehyde **5** has all the required

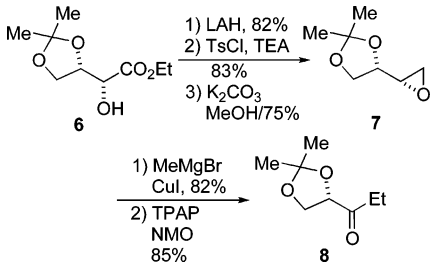
Scheme 2



chiral centers from C_5 to C_{11} of tedanolide. To synthesize the top fragment **2** efficiently, we decided to use the ketone **8** as a chiral equivalent of the C_1-C_4 fragment of tedanolide.

The ester **6** was prepared from commercially available L-ascorbic acid in more than 80% yield via the known three-step process, namely first diol protection with 2,2-dimethoxypropane, cleavage of the alkene with aqueous hydrogen peroxide, and final esterification with ethyl iodide.[5] After hydride reduction of the ethyl ester (82% yield), the resulting 3,4-*O*-isopropylidene-L-threitol was treated with *p*-TsCl to furnish in 83% yield the monotosylate, which on treatment with carbonate in methanol gave the epoxide **7**[6] in 75% yield (Scheme 3).

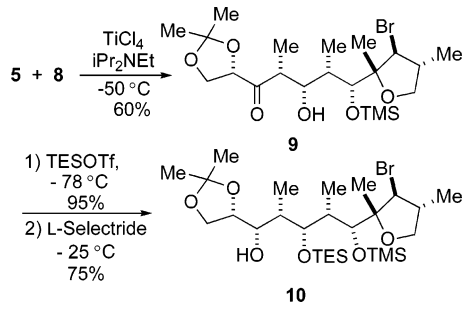
Scheme 3



Regioselective opening of the epoxide with methylmagnesium bromide in the presence of cuprous iodide provided the secondary alcohol in 82% yield from which the desired ketone **8** was obtained via TPAP−NMO oxidation in 85% yield.

We initially tried to combine the two fragments **5** and **8** using either lithium hexamethyldisilazide (LHMDS) or (n-Bu)$_2$BOTf/TEA[7] to generate the lithium and boron enolates of **8** respectively. Unfortunately, the aldol coupling of the boron enolate did not work at all and the ketone **8** was recovered completely while the aldehyde **5** decomposed under those conditions. With LHMDS, less than 10% of the desired product **9** was obtained. One possible reason for this low yield might be the rapid self-condensation of **8** during the formation of the lithium enolate. Quenching the reaction gave only the recovered aldehyde **5** with the ketone **8** being completely destroyed. The titanium enolate generated by treatment of **8** with $TiCl_4$ and Hunig's base in dichloromethane provided the best aldol coupling (Scheme 4). The

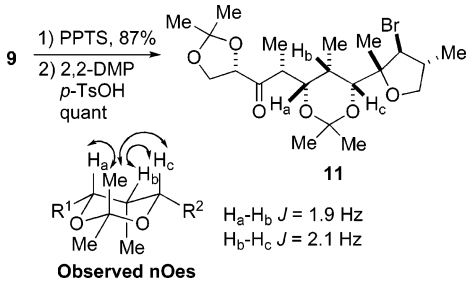
Scheme 4



chlorotitanium enolate generated was quenched with **5** after 3 min since longer reaction times led to a low yield of **9**, which is in line with Roush's report.[8] In this manner, a 60% yield of the single aldol product **9** was isolated. Protection of the alcohol as the TES ether followed by L-Selectride reduction of the ketone gave compound **10** having all of the required chiral centers. The selectivities of both the aldol coupling and the reduction[9] were complete and only one diastereomer was obtained in good yield.

To determine the stereochemistry of the two newly generated chiral centers from the aldol reaction, we carried out NMR experiments on several derivatives (Schemes 5 and

Scheme 5



6). First, the acetonide derivative **11** was synthesized by treatment of **9** with mild acid (PPTS) to deprotect the

(4) Although the simple non-aldol aldol reaction can be easily accomplished, the presence of an ethereal oxygen (including a silyl ether) five or six atoms away from the electrophilic tertiary site of the epoxide allows for attack of the oxygen atom before the internal hydride shift takes place.

(5) André, C.; Bolte, J.; Demuynck, C. *Tetrahedron: Asymmetry* **1998**, *9*, 1359.

(6) Sharma, G. V. M.; Cherukupalli, G. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1081.

(7) (a) Diáz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Peris, G.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 8130. (b) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 3211. (c) Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

(8) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186.

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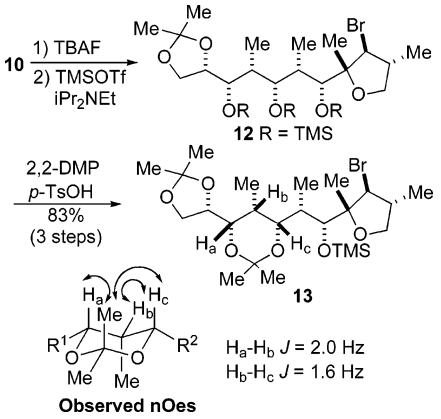
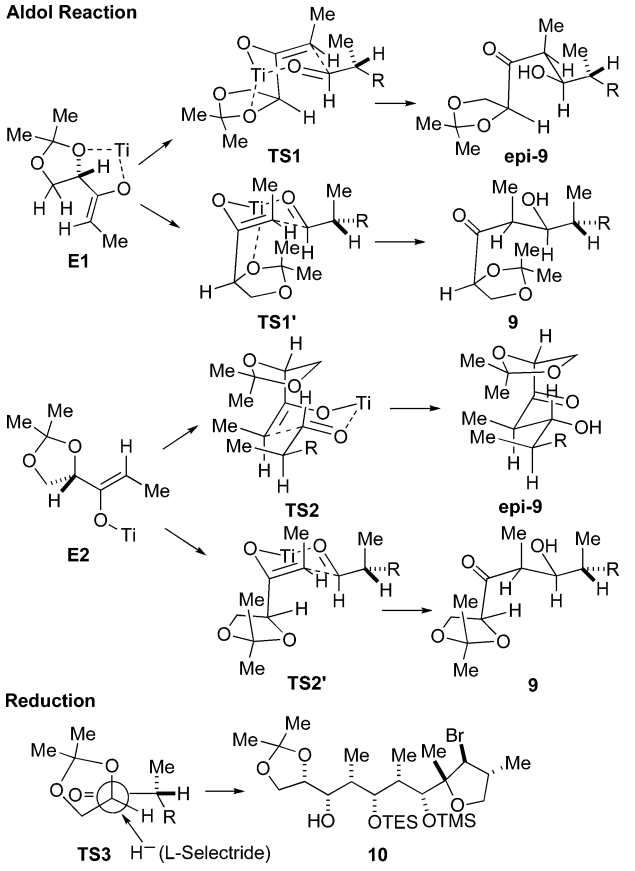
Scheme 6



trimethylsilyl group (since treatment with TBAF gave a mixture of epimerized and β-eliminated products presumably due to the basicity of the reagent). The diol was then converted to the acetonide **11**. The stereochemistry was confirmed via coupling constant analysis (small J_{ab} and J_{bc}) and NOE analysis as shown. Thus, the C_5 stereocenter could be assigned. Likewise, the selectivity at both C_4 from the aldol and at C_3 from the L-Selectride reduction was confirmed via a stereochemical analysis of the acetonide **13**, prepared in three steps from **10** (desilylation, followed by complete resilylation, and selective formation of the less hindered acetonide). NOE and coupling constant analysis was used to assign the structure of **13** as that shown. Thus both the aldol condensation and the reduction proceeded as expected to give **10**.

The closest analogy to this aldol reaction is from the work of Grée,[9] who reported that the corresponding iron enolate, or more likely the free enol,[10] generated by rearrangement of the allylic alcohol (prepared by addition of vinylmagnesium bromide to glyceraldehyde acetonide), gave a poorly selective 3:2 mixture of aldol products in contrast to the complete syn diastereoselectivity seen here. There are two reports of high anti diastereoselectivity in similar systems, namely Sulikowski[11] reported that treatment of an α'-trialkylsilyloxy ethyl ketone with LHMDS followed by addition of an aldehyde gave mainly the anti aldol products while Woerpel[12] described high anti diastereoselectivity in the reaction of an α'-alkyl-α'-alkoxy tin enolate with an aldehyde, both of which are in contrast to the syn diastereoselectivity seen here. Others have reported poor diastereoselectivity with similar α-silyloxy or α-alkoxy enolates.[13] We propose the following mechanism to explain the stereoselectivity of both the aldol reaction and the reduction (Scheme 7). The aldol transition structures derived from the

Scheme 7



enolate **E2** (**TS2** and **TS2′**) would be favored over those derived from **E1** (**TS1** and **TS1′**) since the five-membered chelate between the acetonide oxygen and the titanium places the titanium atom too far away from the aldehyde lone pair to allow for effective intramolecular activation via a Zimmerman−Traxler-type transition state. Thus, both **TS1** and **TS1′** are expected to be much higher in energy and therefore disfavored. Molecular mechanics calculations show that the nonchelated enolate **E2** prefers the conformation in which the acetonide and the enolate oxygen atoms are antiperiplanar. Of the two transition structures derived from that enolate, **TS2′** is clearly favored over **TS2** and thereby leads to the observed product **9**. A similar argument has been proposed for a similar aldol selectivity using an α-silyloxy ketone.[14] It is important to note that **TS2′** is favored even though there is a developing syn-pentane interaction in that transition state. In the reduction, a Felkin-Anh model with the alkoxy group controlling the direction of hydride attack via **TS3** would account for the stereoselectivity.[9]

The final elaboration of **10** into the target compound **2** began with methylation using Meerwein's reagent[15] (Scheme 8). Reductive ring opening was then effected using our earlier method[3e] with BuLi to give the desired *E* alkenol **14**. The

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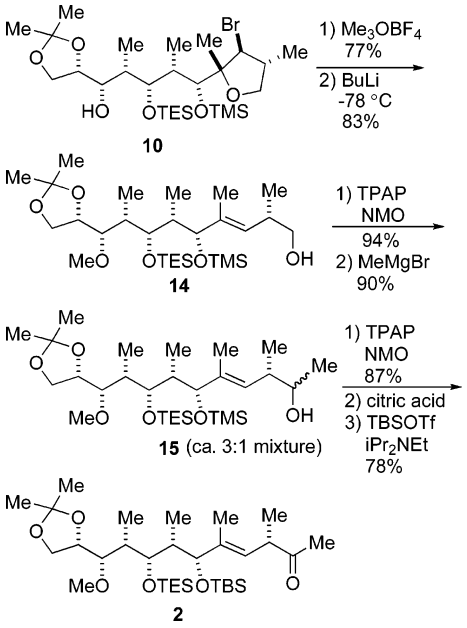
(15) Treatment of **10** with NaH and MeI afforded an unidentified product as the major product.

Scheme 8



primary alcohol was oxidized to the corresponding aldehyde using TPAP−NMO.[16] Addition of MeMgBr gave the allylic alcohol **15** as a 3:1 mixture of diastereomers; the stereochemistry of the major isomer was not determined. The desired ketone fragment having all the required methyl groups and oxygen atoms with the appropriate stereochemistry was prepared via a second TPAP−NMO oxidation. Since tedanolide has a ketone at C_5, the alkoxy group at C_5 of **15** must eventually be transformed into a ketone. Consequently, we decided to convert the TMS group at C_7 into a more stable TBS group to allow us to eventually deprotect the TES group selectively. This final conversion was achieved via treatment of the TMS ether with a catalytic amount of citric acid followed by reaction with TBSOTf and Hunig's base to provide the ketone **2**.

In conclusion, we have developed an efficient method for the preparation of a fully functionalized protected C_1-C_{12} fragment for the synthesis of the tedanolide using a combination of highly stereoselective non-aldol aldol and aldol reactions. In particular, the highly diastereoselective condensation of the enolate of **8** with aldehydes to give the all syn products is reported. Further developments toward the total synthesis of tedanolide will be published in due course.

Acknowledgment. We thank the NIH and NSF for generous support.

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

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