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Anti Aldol Selectivity in a Synthetic Approach to the C_1–C_{12} Fragment of the Tedanolides

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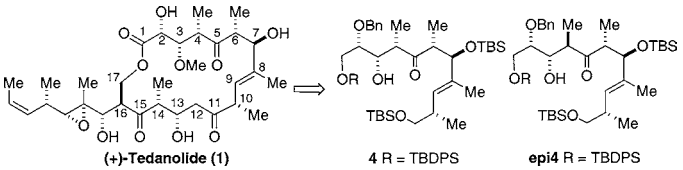
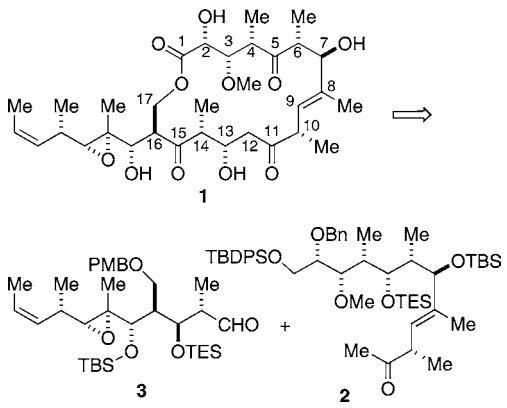
ABSTRACT



In a synthetic approach to the completely protected C_1–C_{12} fragment of the macrocyclic cytotoxic agent tedanolide 1, we carried out the tin-catalyzed Mukaiyama aldol reaction between the 2,3-dialkoxypropanal 5 and the silyl enol ether 6 derived from the ketone 7, which gave, unexpectedly, the anti aldol isomer, rather than the expected syn isomer 4, as the major diastereomer formed.

In 1984, Schmitz and co-workers[1] isolated tedanolide **1** from the Caribbean sponge *Tedania ignis* and reported that it showed very high cytotoxicity, with ED_{50} values of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Seven years later, Fusetani isolated 13-deoxytedanolide, which also displayed very potent cytotoxic effects.[2] Owing to its structural complexity and biological activity, tedanolide has generated considerable synthetic interest,[3] including two total syntheses and significant synthetic work. Over the past few years, we have employed the non-aldol aldol process[4] in several approaches to tedanolide and its analogues. By using a straightforward retrosynthetic disconnection of the tedanolide skeleton involving cleavage at the lactone moiety and scission at the C_{12}−C_{13} bond, we were able to generate the precursors

Scheme 1



2 and **3** (Scheme 1). Recently, we reported two approaches to the C_1−C_{12} fragment of tedanolide **2**, both of which used the non-aldol aldol process and either a highly stereoselective

(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) 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.

(4) (a) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (b) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719. (c) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (d) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (e) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663.

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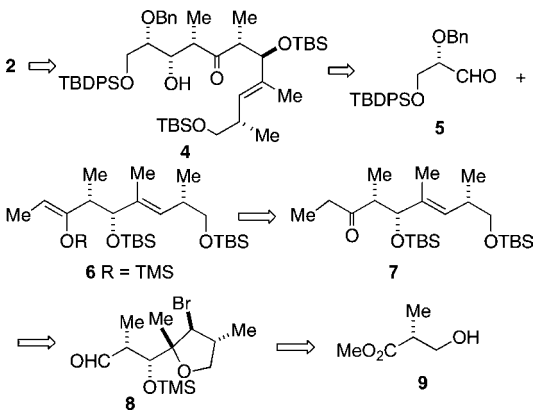
syn aldol reaction or a stereoselective vinyllithium addition coupled with a stereoselective hydroboration−protonation scheme.[5] While these routes are quite efficient, we nevertheless also investigated concurrently other possible routes to prepare the same "top half" fragment of tedanolide since this piece is a common intermediate for both tedanolide and 13-deoxytedanolide. We now report an attempted synthesis of this unit in which a novel anti-selective tin-catalyzed Mukaiyama aldol reaction was revealed.[6]

We thought that **2** could be prepared in a few steps from the silyl ether **4**, which could be formed by a route using as the key constructive step the Mukaiyama aldol reaction between the 2,3-dialkoxypropanal **5** and the silyl enol ether **6**, the latter easily prepared from the ketone **7** (Scheme 2).

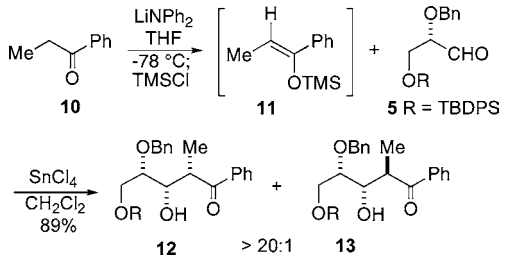
Scheme 2



Thus the commercially available optically pure ester **9** was converted in 13 steps to **8** by our earlier method. This ketone was prepared from the bromo-tetrahydrofurfuryl aldehyde **8**, the preparation of which we have reported previously,[4c] by a four-step route using straightforward chemistry.[7] The ketone **7** has all the carbons from C_4 to C_{11} and the three correct chiral centers at C_6, C_7, and C_{10} of tedanolide. To synthesize the top fragment **4** efficiently, a syn selective aldol or Mukaiyama aldol reaction of the enolate or the enol ether derived from **7**, e.g., **6**, with the aldehyde **5** was required. The results of our study of that condensation follow.

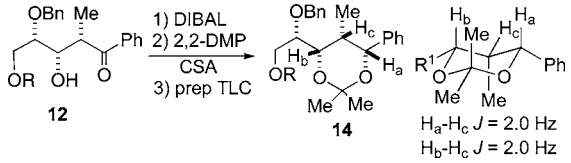
Before proceeding with the reaction of the enol ether **6** of the complex ketone **7** with the aldehyde **5**, we first examined the reaction of simpler ketones with **5**. Literature reports of such reactions of simple silyl enol ethers with α-alkoxy aldehydes indicated that, depending on the exact case and conditions, predominantly the syn aldol product was obtained.[8] Thus reaction of the known *Z*-trimethylsilyl enol ether **11**,[9] effected by treatment of ethyl phenyl ketone **10** with lithium diphenylamide and the silyl chloride, with the aldehyde **5** under Mukaiyama conditions, namely in the presence of stannic chloride in dichloromethane, afforded, in 89% yield, mainly the desired syn aldol diastereomer **12** with essentially none of the anti isomer **13** (Scheme 3). This

Scheme 3



result agrees well with the report of Reetz on a very similar system.[8b] The structure of **12** was proven (Scheme 4) by

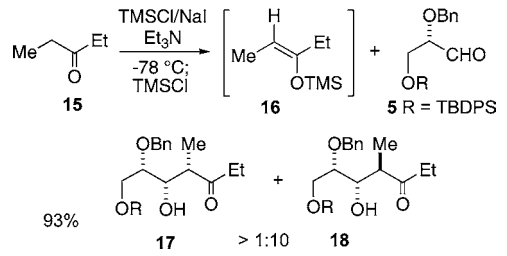
Scheme 4



reduction of the ketone with DIBAL to give a mixture of diols which were cyclized to the acetonide **14**, using 2,2-dimethoxypropane (DMP) and camphorsulfonic acid (CSA), which was purified by preparative TLC. The very small coupling constants of H_a and H_c and H_b and H_c (J = 2.0 Hz) in the proton NMR indicated that all three protons were cis and that we had indeed obtained the syn isomer **12**.[10]

However, when the known[11] *Z*-trimethylsilyl enol ether **16**, prepared from diethyl ketone **15** with trimethylsilyl iodide and triethylamine, was reacted under the same conditions with **5**, a 93% yield of a >10:1 ratio favoring the anti product **18** over the syn **17** (Scheme 5) was obtained. Thus the two analogous cases proceed to give the opposite diastereoselectivity. The structure of **18** was proven by the following

Scheme 5

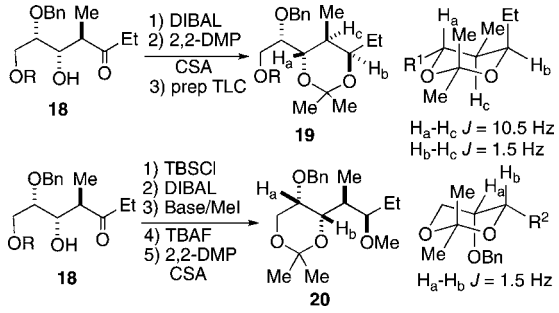


(5) (a) Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543−3546. (b) Jung, M. E.; Yoo, D. *Tetrahedron Lett.* In press.

(6) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. For reviews, see: (b) Chan, T.-H. Formation and Addition Reactions of Enol Ethers. In *Comp. Org. Synth.* **1991**, Ch. 2.3, 595. (c) Gennari, C. Asymmetric Synthesis with Enol Ethers. In *Comp. Org. Synth.* **1991**, Ch. 2.4, 629.

(7) Ethylmagnesium bromide was added to the aldehyde **8** followed by Dess−Martin oxidation to the ketone. Reductive ring-opening with zinc in acetic acid and silylation of the diol with TBSCl gave **7**.

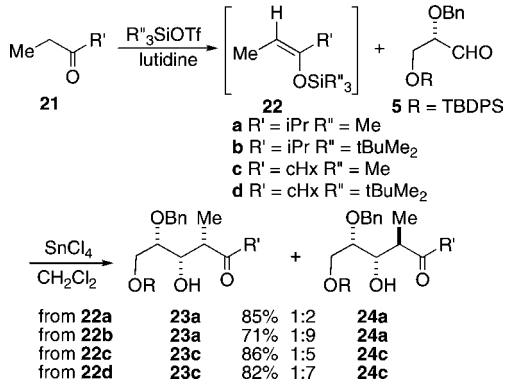
Scheme 6



two routes (Scheme 6). DIBAL reduction and acetonide formation with TLC separation afforded the acetonide **19**. Proton coupling analysis indicated that protons H_a and H_c were trans diaxial (J = 10.5 Hz) while protons H_b and H_c were cis (J = 1.5 Hz). The differences in the NMR spectra of **14** and **19** were very clear. The syn relationship between the benzyloxy group and the alcohol was shown by preparing the second acetonide **20** via first protection of the alcohol as the TBS ether, reduction of the ketone with DIBAL, and protection of the resulting alcohol as the methyl ether. Removal of the two silyl groups (TBAF), acetonide formation, and finally separation afforded **20**, in which protons H_a and H_b showed a small coupling (J = 1.5 Hz) therefore indicating they were cis.

Next, we investigated the condensation of the silyl enol ethers **22a**−**d** prepared from a series of ethyl alkyl ketones **21** with the aldehyde **5** in the presence of stannic chloride (Scheme 7). Whereas the TMS enol ether **22a** gave relatively

Scheme 7

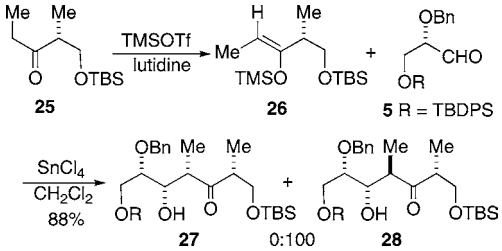


poor selectivity (1:2), the corresponding TBS enol ether **22b** gave a 1:9 ratio favoring the anti diastereomer **24a** in 71% yield. Likewise the cyclohexyl TMS enol ether **22c** furnished a 1:5 ratio favoring the anti isomer **24c** in 82% yield while the TBS enol ether **22d** gave a higher 1:7 ratio again favoring the anti isomer **24c**.

The structures of the two major diastereomeric products **24ac** were proven via the coupling constant analysis of the acetonides as described in detail above.

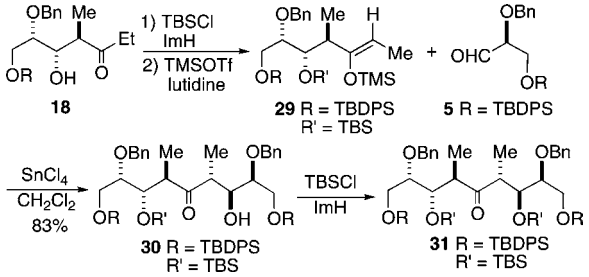
Interestingly, additional stereocenters in the ethyl ketone fragment do not disturb the anti selectivity. Thus the known[12] silyl enol ether **26**, prepared from the ketone **25**, reacted with the aldehyde **5** to give an 88% yield of only the anti diastereomer **28** (Scheme 8). Similarly treatment of the silyl

Scheme 8



enol ether **29**, derived from a two-step silylation of the ethyl ketone **18**, which was prepared as in Scheme 5, with the aldehyde **5** afforded only the anti diastereomer **30** in 83% yield (Scheme 9). The stereochemistry of **30** was easily

Scheme 9



assigned by silylation of the free alcohol to give the C_2-symmetric ketone **31**.

Finally, even though it was apparent that anti selectivity would be observed, nonetheless we tried the requisite key step for the synthesis of **4**, namely the Mukaiyama aldol condensation of the silyl enol ether **6** (prepared from the ketone **7**) with the aldehyde **5** in the presence of stannic chloride (Scheme 10). The condensation afforded, in 78% isolated yield, the anti diastereomer **32** as the major product, which is the epimer of the desired syn diasteromer **4** at C4.

The following reasons may be postulated for the observed selectivity. Theoretical calculations indicate that the two *Z*

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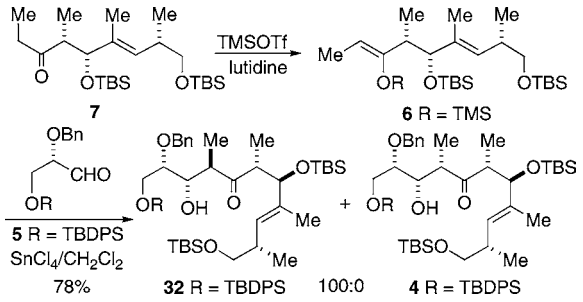
(10) Extensive decoupling experiments were carried out to ensure the identity of the indicated protons in all the acetonides.

(11) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2088.

(12) Denmark, S. E.; Fujimori, S.; Pham, S. M. *J. Org. Chem.* **2005**, *70*, 10823.

Scheme 10



transition states suggested by Heathcock,[8a] namely the *Z*-A[3] and the *Z*-S[1] transition states, have very different energies depending on whether the substituent is an ethyl or a phenyl group. Thus B3LYP/6-31G(d) level calculations[13] give the differences shown in Figure 1, specifically the anti transition

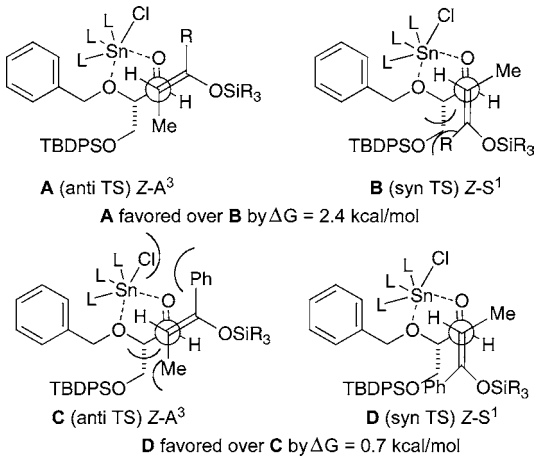


Figure 1. Energy Differences of Possible Transition States.

state **A** (Heathcock's *Z*-A[3]) is calculated to have a lower ΔG than that of the opposite syn transition state **B** (Heathcock's *Z*-S[1]) by roughly 2.4 kcal/mol. That energy difference is in good agreement with the product ratios observed. However the situation changes with the phenyl substituent: the syn transition state **D** is calculated to have a lower ΔG than that of the opposite anti transition state **C** by roughly 0.7 kcal/mol. Here, although the magnitude of the energy difference does not correspond to the ratio seen (all syn), the trend is at any rate in the right direction. Compared to **A**, the syn TS **B** is disfavored, mainly due to repulsion between the alkyl group R and the chiral C2 carbon of the aldehyde. However, the reasons for the smaller difference in energy between the phenyl substituted case, **D** and **C**, are less obvious. From a careful examination of the transition structures, it can be seen that in **C**, the silyl enol ether rotates from a perfectly staggered conformation to avoid interaction between the phenyl and a chloride on the tin, which introduces steric repulsion between the methyl and again the chiral C2 carbon of the aldehyde. This causes this normally favored transition state now to be higher in energy than its syn counterpart. Further theoretical studies will be needed to gain more insight into this difference.

In conclusion, we have observed a novel change in the diasteroselectivity of the tin-catalyzed Mukaiyama aldol reaction between an α-alkoxy aldehyde and the *Z* trialkylsilyl enol ether of ethyl ketones from completely syn when the opposite group is phenyl to mainly or completely anti when the opposite group is alkyl. This effect is seen even when the opposite group is a relatively large alkyl unit and has additional alkyl or oxygen stereocenters. Finally, we have carried out theoretical calculations which provide some rationale for this novel switch in the diastereoselectivity. Further developments toward the total synthesis of tedanolide will be published in due course.

Acknowledgment. We thank Professor Ken Houk and Joann Um (UCLA) for the theoretical calculations. We thank the NIH and NSF for generous support.

Supporting Information Available: Experimental procedures and spectral data (proton and carbon NMR, IR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) These calculations were done on a simpler model system where the enol silyl ether was replaced by an enol, the OTBDPS group by an OH, and the OBn by an OMe group with the R group being ethyl (R = Et).