Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 816–819
Tetrahedron Letters

Synthesis of the C_1–C_{12} fragment of the tedanolides. Selective hydroboration–protonation of allylic alcohol approach

Michael E. Jung *, Dongwon Yoo

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

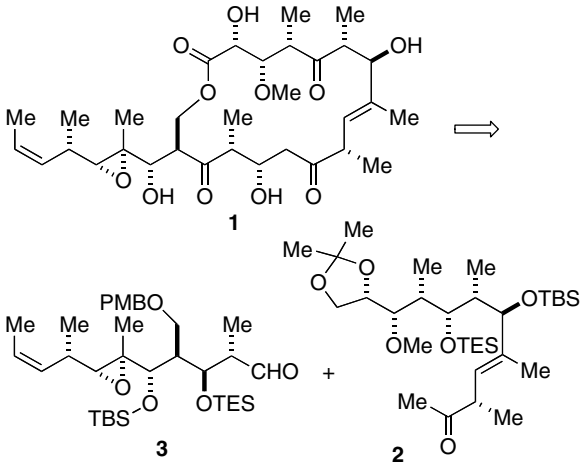
Received 8 October 2007; revised 27 November 2007; accepted 29 November 2007
Available online 4 December 2007

Abstract

The combination of highly stereoselective vinyllithium addition and hydroboration–protonation of the resulting allylic alcohol permits the preparation of the completely protected C_1–C_{12} fragment **2** of the novel macrocyclic cytotoxic agent tedanolide **1**.

Schmitz et al. isolated tedanolide **1** in 1984 from the Caribbean sponge *Tedania ignis*[1] and reported that it displayed very high cytotoxicity, with ED_{50}'s of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Several years later Fusetani reported the isolation of 13-deoxytedanolide, which also had very potent cytotoxic effects.[2] Due to its structural complexity and biological activity, tedanolide has generated considerable synthetic interest,[3] including two total syntheses and significant synthetic work. Our group has used the non-aldol aldol process[4] in various approaches to this molecule over the last few years. Straightforward retrosynthetic disconnection of the tedanolide skeleton involves cleavage at the lactone moiety and scission at the C_{12}-C_{13} bond to generate precursors **2** and **3** (Scheme 1). We recently reported an approach to the C_1–C_{12} fragment of tedanolide **2** using both the non-aldol aldol process and a novel highly stereoselective syn aldol reaction in our approach to this molecule.[5] While this route is quite efficient, we also investigated at the same time other possible routes to the same 'top half' fragment of tedanolide since that piece is a common intermediate for both tedanolide and 13-deoxytedanolide. We now report the efficient preparation of the C_1–C_{12} fragment of tedanolide **2** from methyl (*R*) 3-hydroxy-2-methyl-butanoate **4** and ascorbic acid, which involves the highly stereoselective production of an allylic alcohol and its hydroboration–protonation to ultimately install the desired methyl group.

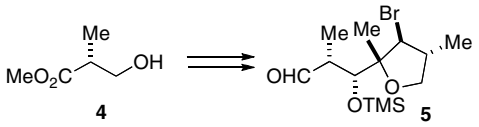
The synthesis of **2** began with the commercially available optically pure ester **4**. We prepared the optically pure aldehyde **5** in 13 steps by a method that we had described previously (Scheme 2).[4c] Aldehyde **5** has all the required chiral centers from C_5 to C_{11} of tedanolide with the C_8–C_9 alkene protected as a bromoether. To synthesize the top



Scheme 1.

* Corresponding author. Tel.: +1 310 825 7954; fax: +1 310 206 3722.
E-mail address: jung@chem.ucla.edu (M. E. Jung).

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.181

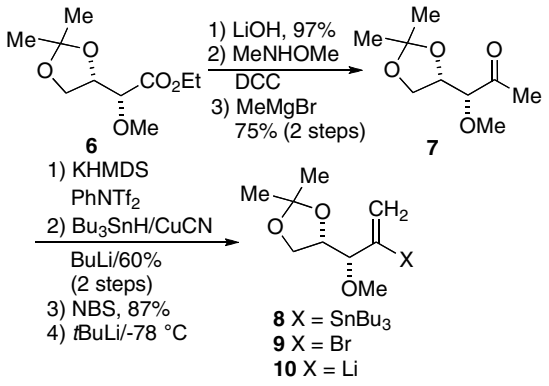


Scheme 2.

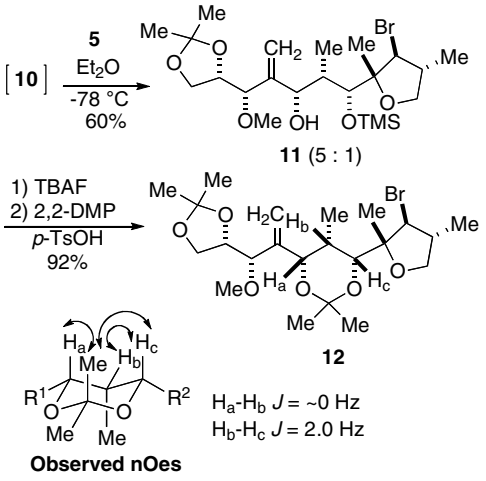
fragment **2** efficiently, we decided to use vinyllithium **10** (prepared from the corresponding vinylstannane **8** via bromide **9**) as a chiral equivalent of the C_1–C_4 fragment of tedanolide.

Ester **6** was prepared from commercially available L-ascorbic acid in more than 80% yield via the known 4-step process, namely first diol protection with 2,2-dimethoxypropane, cleavage of the alkene with aqueous hydrogen peroxide, esterification with ethyl iodide, and final methylation of the alcohol with silver oxide and methyl iodide.[6] The methoxy ester **6** was hydrolyzed to the acid (LiOH, 97%) and converted via the Weinreb amide into the methyl ketone **7** in 75% yield (Scheme 3). Ketone **7** was converted into vinylstannane **8** in 60% yield by treatment of the corresponding kinetic vinyl triflate with lithium tri-*n*-butylstannyl cuprate (prepared from tributyltin hydride, *n*-butyllithium, and copper cyanide).[7] Attempts to convert this vinylstannane into the corresponding organocuprate or vinyllithium using the higher order cyanodimethylcuprate (Me_2CuCN–Li_2) or *n*-butyllithium at 0 °C or −78 °C, respectively, did not give any significant exchange of tin for metal. Therefore vinylstannane **8** was converted into bromide **9** with NBS in 87% yield. The treatment of **9** with *tert*-butyllithium in diethyl ether at −78 °C quickly afforded the desired vinyllithium **10**, which was not isolated but used immediately.

The addition of **10** to aldehyde **5** in diethyl ether at −78 °C afforded an approximate 5:1 mixture of the two diastereomeric allylic alcohols in 60% yield (Scheme 4). The stereochemistry of major diastereomer of the mixture was assigned as the expected Cram–Felkin–Ahn product as follows. Fluoride-promoted removal of the silyl ether followed by treatment with 2,2-dimethoxypropane and acid gave acetonide **12**. The stereochemistry was confirmed



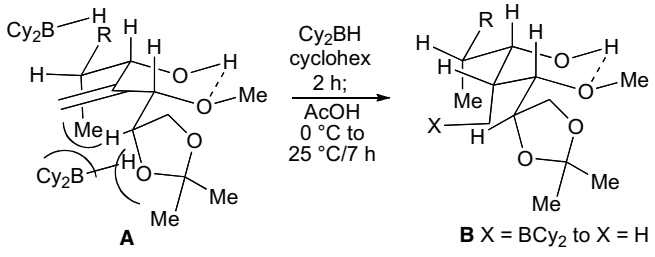
Scheme 3.



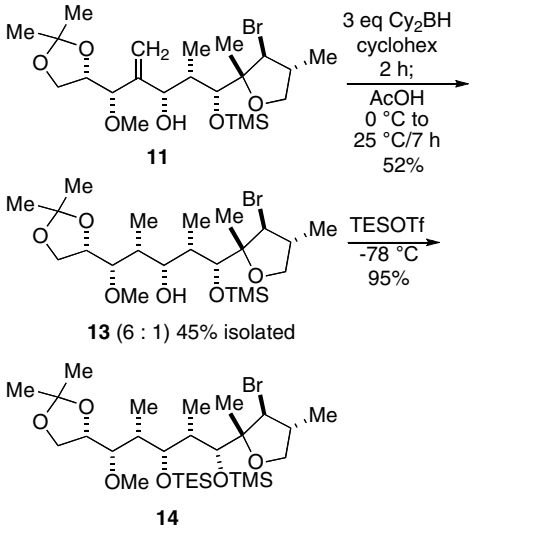
Scheme 4.

via coupling constant analysis (small J_{ab} and J_{bc}) and NOE analysis as shown. Thus the C_5 stereocenter could be assigned as shown.

The final step required for the synthesis of **2** was the selective hydroboration–protonation of the allylic alcohol. We required a very selective hydroboration of the acyclic alkene bearing both an allylic alcohol and an allylic ether along with mild protonation conditions, so that the acid sensitive functionalities of **11** (acetonide, tertiary ether) would survive. There have been several reports of the selective hydroboration of allylic alcohols[8] and amines[9] and varying mechanistic arguments to account for the stereoselectivity observed. We postulated that if the hydroboration was carried out in a very non-polar solvent, then the preferred reactive conformation of the allylic alcohol might be the cyclic hydrogen-bonded 6-membered ring **A** shown in Scheme 5. In this conformation, the top face of the alkene is less sterically hindered and thus more accessible to the large hydroborating agent, dicyclohexylborane. Thus hydroboration would occur from the top face as drawn to give the organoborane which would then be converted into the methyl group on protonation. For the protonation, Brown published a study that showed that the rate of protonation of trialkylboranes decreased as follows: Cy_2B–R > Sia_2B–R > ThxBH–R, with the latter two needing elevated temperatures (90–100 °C) while the first could



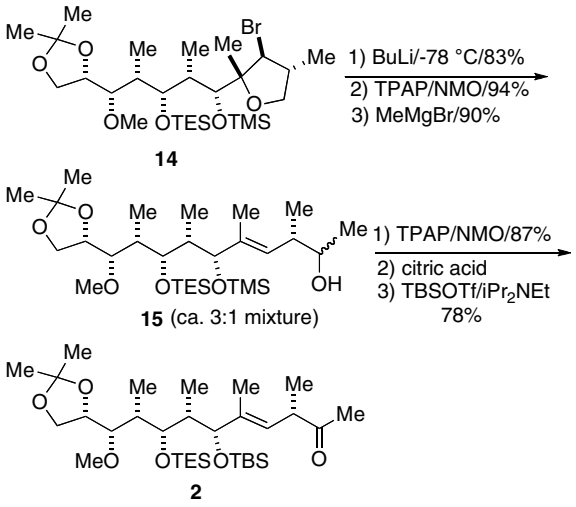
Scheme 5.



Scheme 6.

be carried out at 25 °C.[10] Therefore we chose to use dicyclohexylborane in the reaction with **11**.

Thus the treatment of a solution of the allylic alcohol **11** in cyclohexane with 3 equiv of dicyclohexylborane at 25 °C for 2 h followed by the addition of acetic acid and stirring at 0 °C with warming to 25 °C for 7 h afforded a 6:1 mixture of diastereomeric alcohols in 52% yield (Scheme 6). The major isomer **13** could be isolated in 45% yield by flash column chromatography.[11] It was readily converted into the triethylsilyl ether **14** in 95% yield by treatment with TESOTf at −78 °C. The stereochemistry of the newly created C_4 stereocenter was assigned by comparison of the bis-silyl ether **14** to an authentic sample prepared earlier via the aldol–non-aldol aldol route.[5] The stereochemistry of the authentic sample of **14** had been confirmed at a previous stage (when the methyl ether was still an alcohol) via the formation of an acetonide and the usual coupling constant and NOE analysis. Thus we have been able to set the two stereocenters at C_4 and C_5 via this combination of a Cram–Felkin–Ahn addition of a vinyllithium to aldehyde **5** followed by selective hydroboration–protonation.



Scheme 7.

The final elaboration of **14** into the target compound **2** was the same as we reported earlier (Scheme 7). Reductive ring opening[4e] of **14** with BuLi gave the desired *E* alkenol which was oxidized to the aldehyde and then methyl Grignard agent added to give the homoallylic alcohol **15** as a 3:1 mixture of diastereomers. 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 of **15**. 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 converted 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 the treatment of the TMS ether with a catalytic amount of citric acid followed by reaction with TBSOTf and Hunig's base to provide 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 a highly stereoselective Cram–Felkin–Ahn addition of vinyllithium **10** to aldehyde **5** followed by a highly stereoselective hydroboration–protonation of the resulting alkene **11**. Further developments toward the total synthesis of tedanolide will be published in due course.

Acknowledgment

We thank the National Science Foundation (CHE 0614591) for generous support of this work.

References and notes

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. Total syntheses of tedanolide: (a) Smith, A. B., III; Lee, D. *J. Am. Chem. Soc.* **2007**, *129*, 10957; Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, *128*, 14038; Synthetic studies on tedanolide: (b) Nyavanandi, V. K.; Nadipalli, P.; Nanduri, S.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2007**, *48*, 6905; Nyavanandi, V. K.; Nanduri, S.; Dev, R. V.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 6667; Wong, C.-M.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 4485; 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., III; 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.
5. Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543.

6. André, C.; Bolte, J.; Demuynck, C. *Tetrahedron: Asymmetry* **1998**, *9*, 1359.
7. (a) Suennemann, H. W.; Hofmeister, A.; Magull, J.; Banwell, M. G.; de Meijere, A. *Org. Lett.* **2007**, *9*, 517; (b) Hosoya, T.; Sumi, K.; Doi, H.; Wakao, M.; Suzuki, M. *Org. Biomol. Chem.* **2006**, *4*, 410; (c) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468; (d) Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025; (e) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795.
8. (a) Diaz, L. C.; Salles, A. G., Jr. *Tetrahedron Lett.* **2006**, *47*, 2213; (b) Jung, M. E.; Karama, U. *Tetrahedron Lett.* **1999**, *40*, 7907; (c) Knochel, P.; Lütjens, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1161; (d) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027.
9. (a) Sibi, M. P.; Li, B. *Tetrahedron Lett.* **1992**, *33*, 4115; (b) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758.
10. Brown, H. C.; Murray, K. J. *Tetrahedron* **1986**, *42*, 5497.
11. Attempted hydroboration of the corresponding trimethylsilyl or triethylsilyl ether of alcohol **11** under normal conditions gave back only the starting materials presumably due to increased steric hindrance around the alkene (possibly due to lack of coordination of the alcohol to the ether as shown in **A** which holds the molecule in a conformation favorable for reduction).