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Efficient Synthesis of the C_1–C_{11} Fragment of the Tedanolides. The Nonaldol Aldol Process in Synthesis

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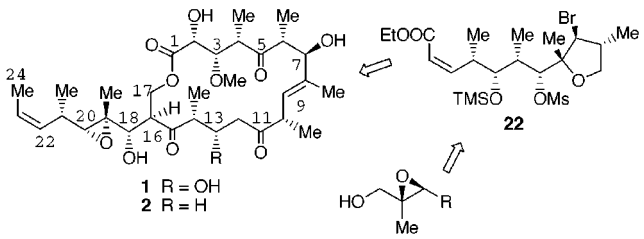
ABSTRACT



The nonaldol aldol process developed in our laboratories has been applied to the synthesis of a C_1–C_{11} fragment 22 of the novel macrocyclic cytotoxic agents tedanolide and 13-deoxytedanolide 1 and 2. The commercially available hydroxy ester 7 was converted in 24 steps into compound 22 using two nonaldol aldol reactions.

Since their isolation and characterization[1,2] in the mid 1980s and early 1990s, the cytotoxic marine macrocycles tedanolide **1** and 13-deoxytedanolide **2** have attracted a great deal of synthetic interest due to their strong biological activity and structural complexity.[3] Tedanolide **1** has shown ED_{50}'s of 250 pg/mL (vs the KB human carcinoma cell line) and 16 pg/mL (vs PS lymphocytic leukemia). Preliminary data also suggest that tedanolide **1** may induce terminal cell differentiation at the S phase at concentrations as low as 10 ng/mL, which offers the possibility of using it as a mechanism-based drug lead. 13-Deoxytedanolide **2**, on the other hand, has shown a T/C of 189% at a dose of 125 μg/kg vs p388 cell lines.[1,2] No mechanistic studies have been published for 13-deoxytedanolide **2** to date.

Structurally, both macrocycles are composed of an 18-membered macrocyclic lactone with a polypropionate skeleton, an internal trisubstituted *E* olefin, and 12 or 13 stereocenters, making their synthesis extremely challenging.

We now report our high yielding and highly stereoselective synthesis of the C_1−C_{11} fragment common to both tedanolide and 13-deoxytedanolide using the first practical synthetic application of the highly efficient nonaldol aldol methodolgy recently developed in our laboratories.[4] Using the nonaldol aldol transformation, it is possible to obtain highly enantio- and diastereospecific propionate units **6** via the Lewis acid

(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) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385. (b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Phar. Bull.* **1998**, *46*, 1335. (c) Liu, J. F.; Abiko, A.; Pei, Z.-H.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (d) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361. (e) Matsushima, T.; Mori, M.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Phar. Bull.* **1999**, *47*, 308. (f) Zheng, B. Z.; Maeda, H.; Mori, M.; Kusaka, S.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J. *Chem. Phar. Bull.* **1999**, *47*, 1288. (g) Matsushima, T.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780. (h) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (i) Smith, A. B., Lodise, S. A. *Abstracts of Papers*, 218th National Meeting of the American Chemical Society, New Orleans, LA, Aug 22−26, 1999; Amercian Chemical Society: Washington, DC, 1999; p 549. *Org. Lett.* **1999**, *1*, 1249.

(4) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208 and references therein. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) D'Amico, D. C. Ph.D. Thesis, UCLA, 1995. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307. (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343.

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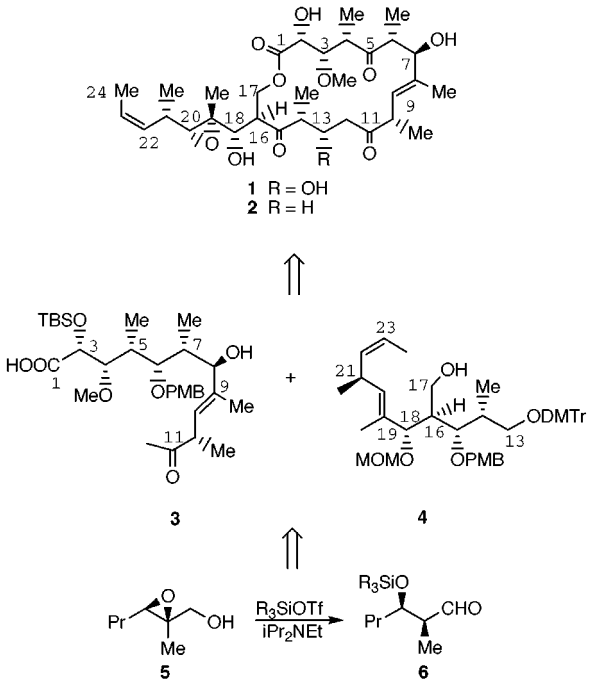
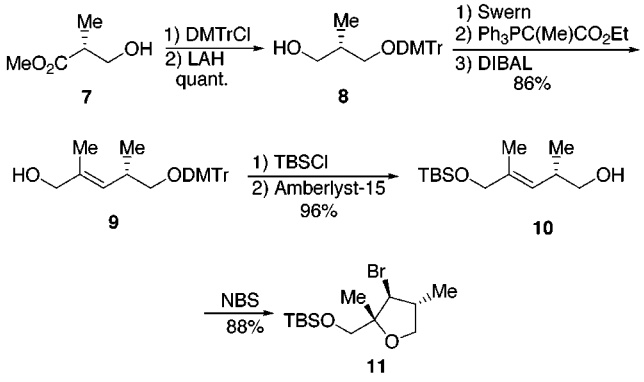
catalyzed rearrangement of chiral epoxy alcohols **5** without the use of chiral auxiliaries in the key step (obviously the step that produces the epoxy alcohols uses chiral reagents). Our convergent retrosynthetic analysis for the synthesis of both tedanolide and 13-deoxytedanolide called for the cleavage of the macrocyclic ring at the C_1-C_{17} ester functionality and the $C_{12}-C_{13}$ bond, generating the C_1-C_{12} fragment **3** and the $C_{13}-C_{24}$ fragment **4** (Scheme 1).

Scheme 1



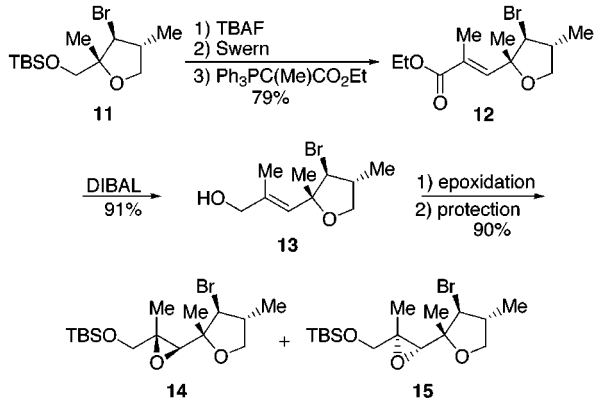
The synthesis of the top fragment **3** began with commercially available methyl *R* (−)-3-hydroxy-2-methylpropionate **7** (Scheme 2), which was protected with a dimethoxytrityl group (DMTr) and reduced to afford the monoprotected diol **8** in quantitative yield. Swern oxidation, followed by Wittig olefination,[5] and 1,2-reduction proceeded in good yield to produce the desired allylic alcohol **9**. TBS protection of alcohol **9** followed by DMTr group removal afforded the desired homoallylic alcohol **10** in excellent yield. NBS-promoted cyclization[6] of the free homoallylic alcohol onto the double bond generated the bromotetrahydrofuran **11** in good yield as a single diastereomer with the stereochemistry proven by NOE analysis. Our decision to proceed via the bromotetrahydrofuran functionality was based on previous results,[7] which demonstrated the utility of this protecting group as a masked homoallylic methyl ketone.

Scheme 2



Deprotection of the TBS ether **11**, followed by Swern oxidation and Wittig olefination, produced the desired *E*-conjugated ester **12** in good yield over three steps (Scheme 3). 1,2-Reduction of conjugated ester **12** afforded the expected allylic alcohol **13** in high yield as a single product. With the allylic alcohol **13** in hand, we attempted to take advantage of the stereochemical information present in the bromotetrahydrofuran ring to influence the stereochemical outcome of the epoxidation. Unfortunately, all of the substrate-controlled epoxidation conditions attempted yielded the undesired epoxide **14** as the major product. However, the use of Sharpless asymmetric epoxidation conditions[8] provided a 10:1 mixture of epoxides **14** and **15** with the desired epoxide **15** being the major diastereomer.

Scheme 3



Conditions	Ratio **14** : **15**
1) $VO(acac)_2$/*t*-BuOOH	2) TBSCl 2.3 : 1
1) *m*CPBA	2) TBSCl 6.7 : 1
1) TBSCl	2) *m*CPBA 6.2 : 1
1) L-(+) DIPT, $Ti(OiPr)_4$, *t*-BuOOH	2) TBSCl 1 : 10

(5) Fleck, F.; Schinz, H. *Helv. Chim. Acta* **1950**, *33*, 146.

(6) (a) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654. (b) Rychnovsky, S. D.; Barlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (c) Mihailovic, M. Lj.; Marinkovic, D. *J. Serb. Chem. Soc.* **1985**, *50*, 5. (d) Harding, K. E.; Tiner, T. H. Electrophilic Heteroatom Cyclizations. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. IV, p 363.

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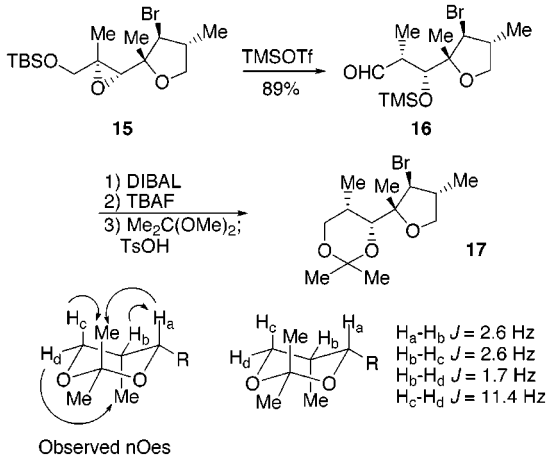
Crucial nonaldol aldol rearrangement of epoxide **15** provided the pivotal aldehyde aldol product **16** as a single diastereomer in excellent yield and without any need for purification (Scheme 4). The stereochemistry of the aldehyde

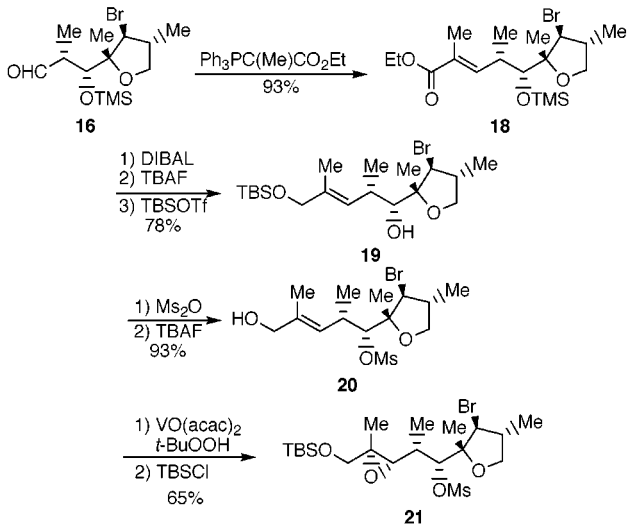
Scheme 4



16 was confirmed via NOE and *J*-value analysis of the acetonide derivative **17** which was readily prepared in three steps from aldehyde **16** (Scheme 4).

Wittig olefination of aldehyde **16** proceeded in excellent yield and with complete stereoselectivity to produce the *E*-conjugated ester **18** (Scheme 5). 1,2-Reduction, followed

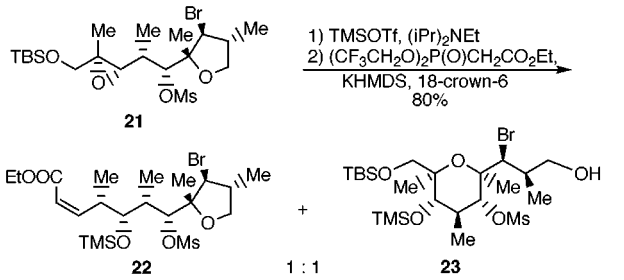
Scheme 5



by deprotection of the secondary silyl group and subsequent protection of the primary alcohol of the resulting diol, afforded the desired secondary alcohol intermediate **19** in good yield over three steps. Mesylation of the free secondary hydroxyl group followed by silyl group removal produced the required allylic alcohol **20** in excellent yield over both steps. Epoxidation of alcohol **20** under substrate-controlled conditions yielded, after silylation of the free hydroxyl, the desired epoxide **21** in 65% yield.

Once the desired epoxide **21** was in hand, the final nonaldol aldol rearrangement required to complete the C_1-C_{11} fragment of tedanolide was carried out (Scheme 6).

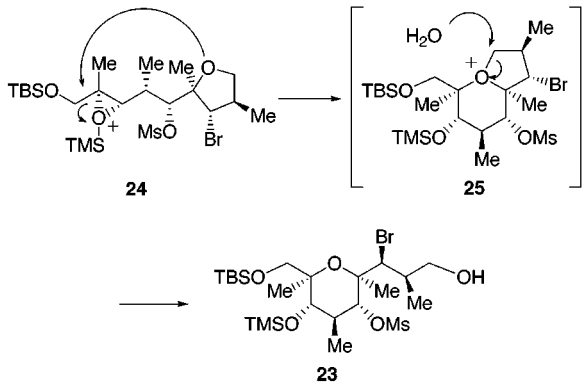
Scheme 6



Treatment of epoxide **21** with trimethylsilyl triflate, followed by Still−Wittig olefination conditions[9,10] afforded the desired C_1-C_{11} *Z*-conjugated ester **22** in 80% yield as a 1:1 mixture with the pyran derivative **23**.

Formation of the pyran side-product **23** was rationalized as originating from the attack of the tetrahydrofuran oxygen on the tertiary carbon of the activated epoxide **24** to generate the bicyclic intermediate **25**. Intermediate **25** is then hydrolyzed during aqueous workup to give the observed pyran **23** (Scheme 7).

Scheme 7



In conclusion, we have demonstrated the feasibility of using the nonaldol aldol methodology toward an efficient synthesis of tedanolide **1** and 13-deoxytedanolide **2**. With its ease of use, no purification requirements and no need for expensive chiral auxiliaries, we have shown that the nonaldol aldol methodology is a viable and economic alternative to

(9) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(10) We find that it is often advantageous to use the aldehydes immediately upon their formation rather than to isolate and try to purify them since one often observes some decomposition upon purification.

traditional asymmetric aldol methods. Further developments in our approach toward the total synthesis of tedanolide and 13-deoxytedanolide will be published in due course.

Acknowledgment. We thank the National Institutes of Health (CA-72684) for generous financial support. R.M. would like to thank the University of California President's Office for a fellowship.

Supporting Information Available: The NMR data and experimental procedures for compounds **8**−**23** are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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