Synthesis of the C13-C23 Segment of Tedanolide

Gunnar Ehrlich, Markus Kalesse*

Universität Hannover, Institut für Organische Chemie, Schneiderberg 1B, 30167 Hannover, Germany
Fax +49(511)7623011; E-mail: Markus.Kalesse@oci.uni-hannover.de

Received 3 December 2004

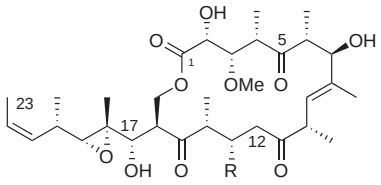
Abstract: The synthesis of the C13-C23 segment of tedanolide is described making use of orthogonal protecting groups in the construction of the carbon skeleton and for the selective liberation of hydroxyl groups in the endgame of the total synthesis.

Key words: tedanolide, natural product, aldol, protecting groups

Tedanolide[1] (**1**) and 13-deoxytedanolide (**2**) are polyketide natural products that were isolated from marine sources by Schmitz[1] and Fusetani[2], respectively (Figure 1). Their promising anti-tumor activity in combination with their limited availability prompted several research groups to investigate the synthetic access to these natural products.[3] The challenging structure has focused the retro-synthetic analyses to certain pivotal disconnection in such as the aldol coupling between the C1-C12 and the C13-C23 segment. Inspired by the fundamental contributions of Roush et al. on this transformation, we also chose the aldol connection to join both hemispheres of the molecule. In contrast to the Roush approach we decided to establish a C14-C15-*syn* configuration in the aldehyde segment, which requires a challenging Felkin-controlled aldol coupling. Recently, Smith et al. published the first total synthesis of 13-deoxytedanolide (**2**),[4] while the total synthesis of tedanolide still remains to be accomplished.

Based on the contributions from Roush et al. and Smith et al. we decided to perform the epoxidation as one of the latest steps in the synthesis. Additionally, we envisioned to protect the hydroxyl groups at C17 as the TBS ether and at C15 as PMB ether, respectively. In order to find the optimal protecting group for the primary alcohol we established a route that could be used for introducing either the MOM, MEM or SEM protecting groups. The correct choice of this protecting group seems to be one of the pivotal steps since it would have to tolerate the preceding transformations and should be removed under mild conditions prior to the macro lactonization.

We started from the Roche ester (**7**) by protecting with the acid labile trityl protecting group. Reduction with $LiAlH_4$ and subsequent Dess–Martin Oxidation provided the aldehyde which in turn was subjected to a Wittig olefination to establish the desired *Z*-configured double bond (*Z*/*E* = 93:7) (Scheme 1). Removal of the trityl group



R = OH, tedanolide **1**
R = H, 13-deoxytedanolide **2**

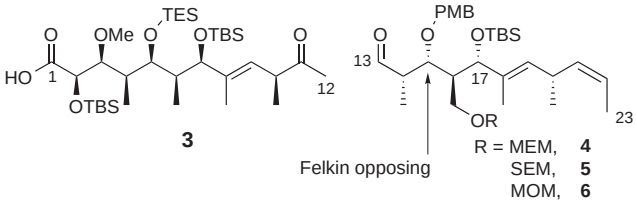
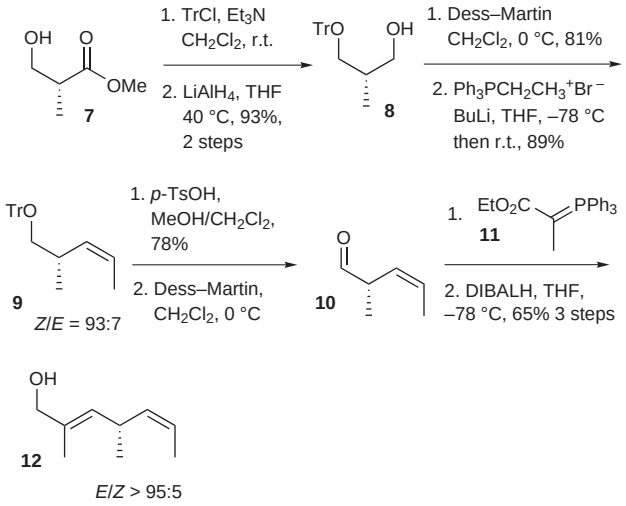


Figure 1 Retrosynthetic disconnection of tedanolide (**1**)

using *p*-TsOH followed by a sequence of Dess–Martin oxidation, olefination and reduction furnished allylic alcohol **12**.

Next we performed a MnO_2 oxidation of the allylic alcohol **12** and used the so-derived aldehyde for an aldol reaction with ethyl acetate. DIBALH reduction followed by protection of the primary alcohol as the TBS ether provided compound **14** that could be used in the aldol coupling with aldehyde **15**, also derived from the Roche ester **7**.

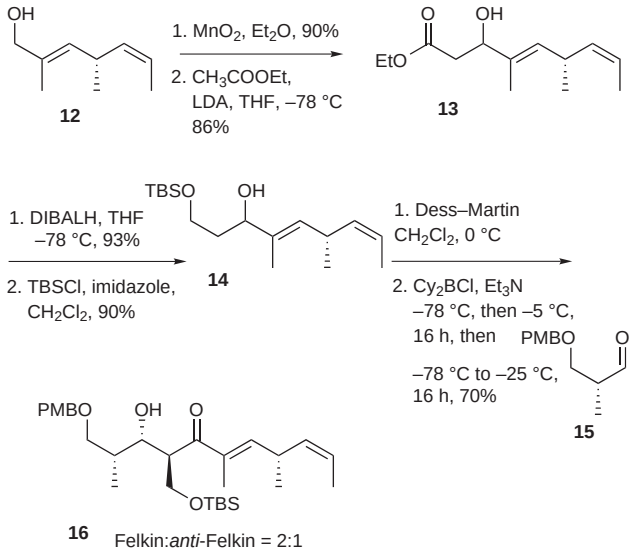


Scheme 1 Synthesis of allylic alcohol **12**

SYNLETT 2005, No. 4, pp 0655–0657
Advanced online publication: 22.02.2005
DOI: 10.1055/s-2005-862391; Art ID: G44504ST

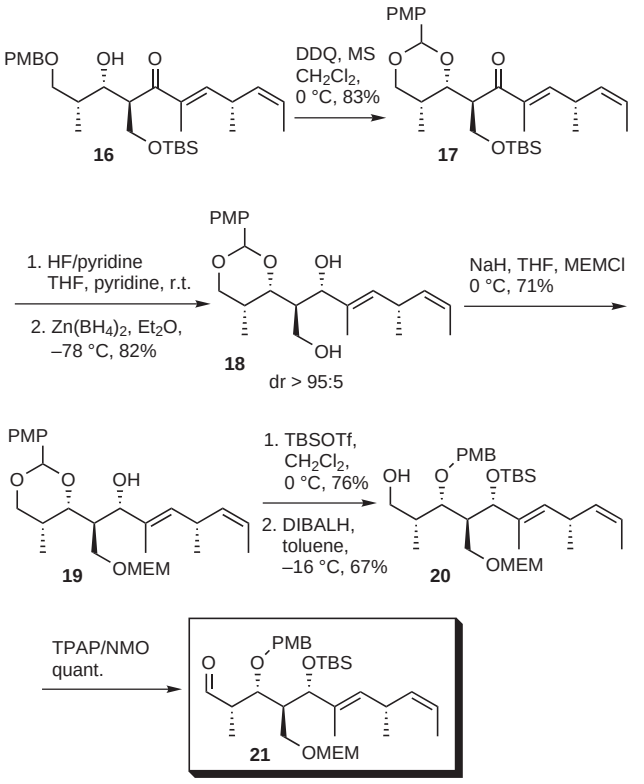
Dess–Martin oxidation and transformation to the bis-cyclohexyl boron enolate was accomplished prior to the *anti*-selective aldol reaction with aldehyde **15**. We could isolate the desired *anti*-aldol product from a 2:1 mixture of the Felkin and *anti*-Felkin product, respectively (Scheme 2).

In the end game of the synthesis we finally had to establish the appropriate positioning of protecting groups and had to set the desired configuration at C17.



Scheme 2 Synthesis of ketone **16**

Therefore the PMB group was oxidized with DDQ in the absence of water to provide PMP acetal **17**. Liberation of the primary hydroxyl with HF–pyridine allowed chelation controlled reduction of the keton with $Zn(BH_4)_2$ according to the work published by Yonemitsu.[3h] At this stage a variety of different protecting groups could be introduced. The 2-methoxyethoxymethyl protecting group was introduced by deprotonation with NaH and subsequent treatment with MEMCl. Finally, reductive acetal cleavage with DIBALH followed by TPAP oxidation furnished aldehyde **21**[5] for the aldol coupling with the western hemisphere of tedanolide (Scheme 3). The remaining aldol step and macrolactonization procedure towards the total synthesis of tedanolide will be reported in due course.



Scheme 3 Synthesis of the C13-C23 segment of tedanolide (**1**)

References

(1) Tedanolide was isolated from *Tedania ignis*: Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

(2) 13-Deoxytedanolide was isolated from *Mycale adhaerens*: 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. Pharm. Bull.* **1998**, *46*, 1335. (c) Liu, J.-F.; Abiko, A.; Pei, Z.; 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) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (f) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (g) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663. (h) Matsushima, T.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780. (i) Smith, A. B. III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. (j) Zheng, B.-Z.; Maeda, H.; Mori, M.; Kusaka, S.-i.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J. *Chem. Pharm. Bull.* **1999**, *47*, 1288. (k) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (l) Matsushima, T.; Nakajima, N.; Zheng, B.-Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855. (m) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.-I.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441. (n) Zheng, B.-Z.; Yamauchi, H.; Dei, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 1761. (o) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (p) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (q) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 6001. (r) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223. (s) Matsui, K.; Zheng, B.-Z.; Kusaka, S.-I.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. *Eur. J. Org. Chem.* **2001**, 3615. (t) Hearn, B. R.; Ciavarri, J. P.; Taylor, R. E. *Org. Lett.* **2002**, *4*, 2953.

(4) (a) Smith, A. B. III; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *J. Am. Chem. Soc.* **2003**, *125*, 350. (b) Smith, A. B. III; Adams, C. M.; Barbosa, S. A. L.; Degnan, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042.

(5) Spectroscopic analysis for **20**:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.30 (dq, *J* = 10.9 Hz, *J* = 6.6 Hz, 1 H), 5.25–5.21 (m, 2 H), 4.59 (s, 2 H), 4.55 (d, *J* = 11.2 Hz, 1 H), 4.36 (d, *J* = 11.2 Hz, 1 H), 4.12 (m, 1 H), 3.78 (s, 3 H), 3.77–3.73 (m, 1 H), 3.68–3.56 (m, 4 H), 3.49 (t, *J* = 4.6 Hz, 2 H), 3.47–3.42 (m, 1 H), 3.40–3.35 (m, 1 H), 3.34 (s, 3 H), 3.31 (dd, *J* = 9.7 Hz, *J* = 6.6 Hz, 1 H), 2.40 (br s, 1 H), 2.37–2.30 (m, 1 H), 2.13–2.03 (m, 1 H), 1.63–1.58 (m, 6 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.83 (s, 9 H), –0.02 (s, 3 H), –0.07 (s, 3 H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1 (s), 135.0 (d), 133.8 (s), 132.1 (d), 130.9 (s), 129.2 (d, 2 C), 121.8 (d), 113.7 (d, 2 C), 95.9 (t), 79.5 (d), 77.5 (d), 71.8 (t), 67.7 (t), 66.8 (t), 66.1 (t), 59.0 (q), 55.2 (q), 44.1 (d), 37.7 (d), 30.3 (d), 25.9 (q, 3 C), 21.0 (q), 18.1 (s), 13.0 (q), 12.9 (q), 12.2 (q), –4.3 (q), –5.1 (q).
HRMS (LC-MS, ESI): *m*/*z* calcd for $C_{33}H_{58}O_7SiNa^+$: 617.3850; found: 617.3864.
IR: 3455 (br), 3010 (w), 2956 (s), 2928 (s), 2888 (s), 2858 (s), 1613 (w), 1514 (m), 1463 (w), 1363 (w), 1301 (w), 1248 (s), 1174 (w), 1040 (ss), 837 (m), 776 (m), 740 (m) cm^{-1}.
$[\alpha]_D^{25}$ +21.9 (*c* 1.04, $CHCl_3$).