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Synthetic studies towards the total synthesis of tedanolide: formation of the C(13)–C(23) fragment

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Abstract—The C(13)–C(23) subunit of tedanolide was obtained using a boron-mediated aldol reaction as the key step to control the C_{16} and C_{17} stereocenters.

Tedanolide, an antitumor agent, was isolated from a prevalent Caribbean sponge *Tedania ignis* by Schmitz and co-workers[1] in 1984 and its structure was elucidated by means of X-ray analysis.[1] This antitumor macrolide features four labile aldol units, a side chain containing an α-epoxy alcohol, an 18-membered lactone and the crowded contiguous chiral centers from C_{16} to C_{19}, thus making the construction of this molecule one of the most difficult and challenging tasks for organic chemists. Tedanolide is highly cytotoxic,[1] exhibiting ED_{50} values of 250 pg/mL in KB cell lines and 16 pg/mL in PS cell lines. It also shows in vivo antitumor activity,[2] increasing the lifespan of mice implanted with lymphocytic leukemia cells (23% at 1.56 μg/kg). In view of its intricate architecture and biological activity, tedanolide has attracted extensive synthetic studies.[3–13] However, to date, there is still no reported total synthesis of this molecule. In this article, we present an efficient and stereoselective construction of fragment C(13)–C(23).

Our retrosynthetic analysis of tedanolide **1** is outlined in Fig. 1. Disconnection at the C_{29} lactone and between C_{12} and C_{13} produces subunits **2** C(13)–C(23) and **3** C(1)–C(12). The key step in our synthetic plan involves a boron-mediated aldol reaction developed by Paterson and co-workers[14] to construct fragment **2** with the desired stereochemistry.

Our synthesis commences with the preparation of ketone **5**. Ketone **5** was prepared from the readily available chiral aldehyde **I**[15] (Scheme 1). Aldol reaction of **I** with methyl acetate followed by DIBAL-H reduction provided alcohol **8** in 90% yield as a 55:45 mixture of two isomers. Selective protection of the primary alcohol with TBDMSCl in the presence of pyridine afforded **9** as a mixture of two isomers.[16] Finally, the target ketone **5** was obtained through Dess–Martin periodinane oxidation, amounting to 72% total yield over four steps.

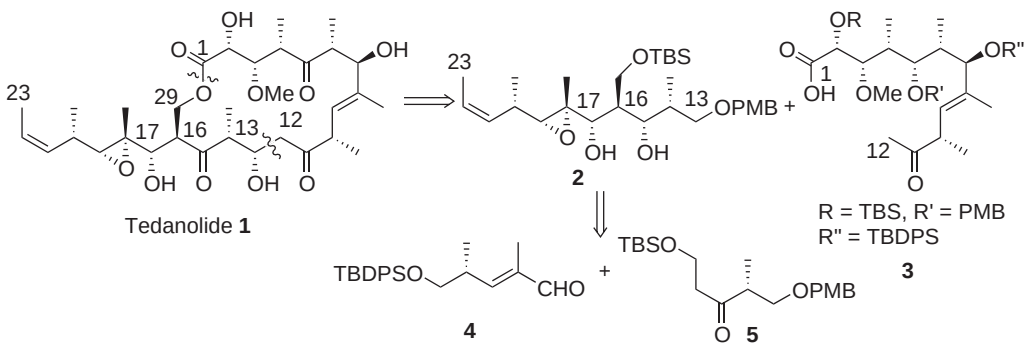

Figure 1.

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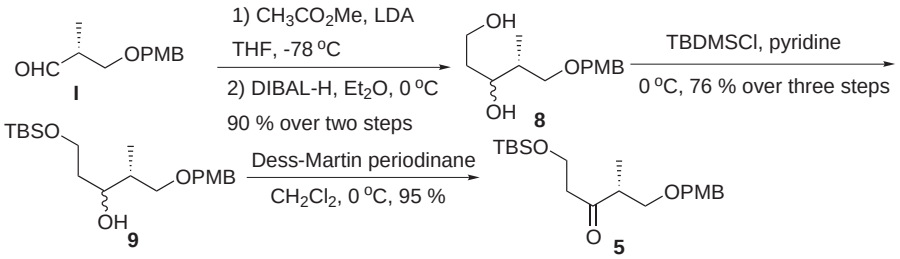
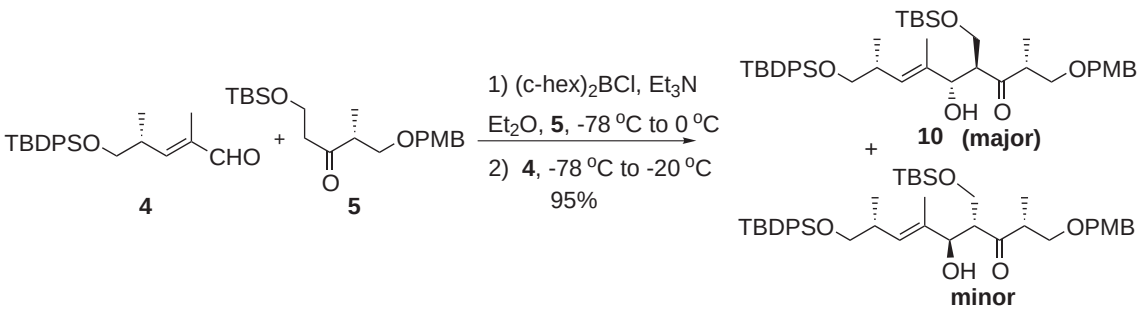
Aldehyde **4** was synthesized from the commercially available (*S*)-methyl 3-hydroxy-2-methylpropionate as reported in the literature.[14] With the two requisite fragments **4** and **5** in hand, we attempted the boron-mediated aldol reaction using Paterson's conditions.[14] As expected, the reaction proceeded smoothly and the aldol product was obtained in 95% yield as a mixture of two separable isomers (major:minor = 85:15) (Scheme 2).

In order to determine the relative stereochemistry of the major product, **10** was first selectively reduced to *syn* diol **11** as a >20:1 diastereomeric mixture using Et_2BOMe/$NaBH_4$,[17] which was then converted into acetonide **12** as well as the *p*-methoxybenzylidene acetal **13**. The configurations at C_{16} and C_{17} were confirmed by NOESY studies of *p*-methoxybenzylidene acetal **13** and *J* value analysis of acetonide **12** (Scheme 3). This result is also in accordance to the predicted stereochemistry based on the transition state proposed by Paterson.[14]

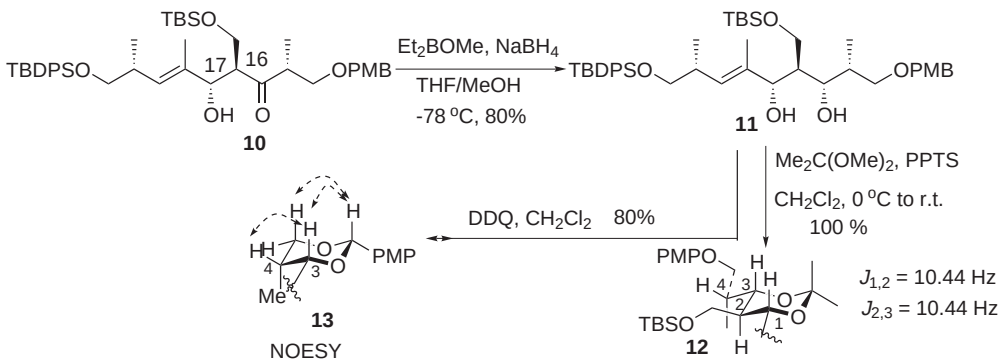
Further elaboration of fragment C(13)–C(23) commenced with selective removal of TBDPS from acetonide **12** (Scheme 4). In the presence of 10% NaOH/MeOH,[18] after refluxing for 8 h, only two-thirds of **12** was transformed into alcohol **14**. Prolonging the reaction time was found to result in cleavage of the TBS group. The alcohol **14** obtained was oxidized by Dess–Martin periodinane to aldehyde **15**. A Wittig reaction of **15** with unstablized $CH_3CH{=}PPh_3$ afforded **16** as a single isomer in 93% yield. To remove the acetonide group of **16**, we first tried a 1:1 mixture of 1 M HCl and THF at room temperature, but unfortunately, the reaction did not proceed and allowed only the recovery of the starting material. So we turned to Zn-$(NO_3)_2{\cdot}6H_2O$ which has been used to selectively cleave an acetonide group.[19] Fortunately, the reaction proceeded cleanly but with incomplete conversion of starting material. Efforts to raise the conversion yield by means of prolonging the reaction time failed due to the cleavage of the TBS group. After removal of ace-



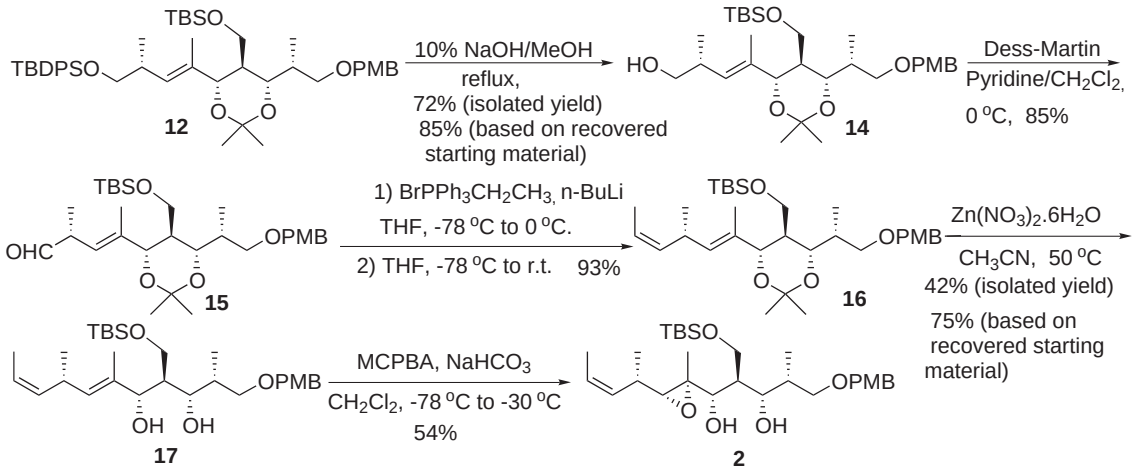
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

tonide, the diol **17** was treated with MCPBA in the presence of $NaHCO_3$ with CH_2Cl_2 as solvent. To our surprise, the epoxide product **2** was obtained in 54% isolated yield as a single isomer along with some unidentified by-products. The stereochemistry of the epoxide **2** was assigned on the basis of NOESY studies of the intramolecular epoxide opened product **18**.[20]

In conclusion, we have completed the construction of the C(13)–C(23) subunit **2**. Key features include the boron-promoted aldol reaction to control the configurations at C_{16} and C_{17} of tedanolide and hydroxy-directed epoxidation. The synthesis is highly convergent and practical. Assembly of subunit **3** and its combination with subunit **2** are in progress.

Acknowledgements

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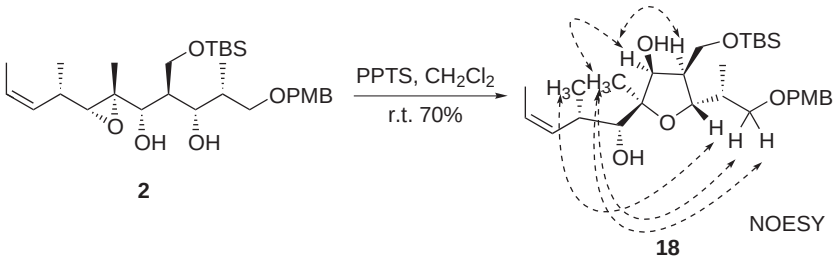
References

1. Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; Van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.
2. Schmitz, F. J.; Gunasekera, S. P.; Hossain, M. B.; Van der Helm, D.; Yalamanchili, G. US Patent. Application 87-7347 870127.
3. Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385.
4. Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Phar. Bull.* **1998**, *46*, 1335.
5. Liu, J. F.; Abiko, A.; Pei, Z.-H.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873.
6. Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361.
7. Matrushima, T.; Mori, M.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Phar. Bull.* **1999**, *47*, 308.
8. Zheng, B. Z.; Maeda, H.; Mori, M.; Kusaka, S.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J. *Chem. Phar. Bull.* **1999**, *47*, 1288.
9. Matsushima, T.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780.
10. Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95.
11. Smith, A. B.; Lodise, S. *Papers*, 218th National Meeting of the American Chemical Society, New Orleans, LA, Aug. 22–26, 1999; American Chemical Society: Washington, DC, 1999; p. 549. *Org. Lett.* **1999**, *1*, 1249.
12. Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669.
13. Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719.
14. Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182. Data for compound **2**: colorless oil, R_f 0.58 (*n*-hexane/EtOAc, 2:1); $[\alpha]_D^{31}$ +36 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): –0. 02 (d, $J=4.5$ Hz, 6H), 0.86 (s, 9H), 0.98 (d, $J=7.0$ Hz, 3H), 1.12 (d, $J=6.3$ Hz, 3H), 1.28 (s, 3H), 1.62 (d, $J=7.0$ Hz, 3H), 1.84–1.76 (m, 1H), 2.04–1.97 (m, 1H), 2.56–2.35 (m, 1H), 2.87 (d, $J=9.1$ Hz, 1H), 3.46–3.48 (m, 2H), 3.55–3.62 (m, 2H), 3.64 (d, $J=8.0$ Hz, 1H), 3.80 (s, 3H), 3.87 (br, 1H), 4.00 (dd, $J=2.4$, 8.0 Hz, 1H), 4.43 (s, 2H), 5.31–5.23 (m, 1H), 5.53–5.43 (m, 1H), 6.86 (d, $J=8.7$ Hz, 2H), 7.23 (d, $J=8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.2, 130.7, 130.4, 129.2, 124.5, 113.8, 76.9, 74.5, 73.4, 73.0, 66.5, 64.1, 61.7, 55.3, 44.8, 36.0, 31.7, 25.8, 18.8, 18.0, 13.2, 12.7, 10.6, –5.2, –5.5; HRMS (ESI) calcd for $C_{29}H_{50}NaO_6Si$ $[M+Na^+]$: 545.3282. Found: 545.3274; IR (neat) cm^{-1}: 3417, 3008, 2959, 2938, 2884, 2852, 1614, 1582, 1512, 1453, 1243, 1092, 828.
15. Walkup, R. D.; Kane, R. R.; Boatman, Jr., P. D.; Cunningham, R. T. *Tetrahedron Lett.* **1990**, *52*, 7587.
16. Ogilvie, K. K.; Schifman, A. L.; Penney, C. L. *Can. J. Chem.* **1979**, *57*, 2230.
17. Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

18. Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369.
19. Vijayasaradhi, S.; Singh, J.; Aidhen, I. S. *Synlett* **2000**, *1*, 110.
20. Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088. The intramolecular epoxide opening reaction was successfully carried out in CH_2Cl_2 in the presence of PPTS. The results from the NOESY experiment are shown in the diagram below.



2 **18**