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Enantioselective Synthesis of the Top Half of Tetronolide

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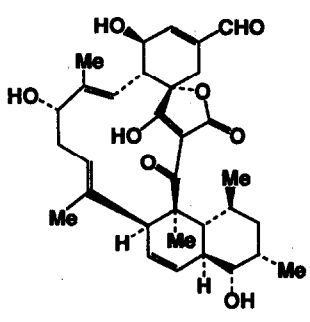
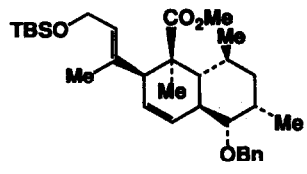
Abstract: A highly enantio- and diastereoselective synthesis of the top half spirotetronate subunit (**3**) of tetronolide is described.

Tetronolide (**1**) is the aglycone of the tetrocarcin group of anti-tumor antibiotics.[1] The structure of tetronolide was assigned by an X-ray analysis, and the absolute configuration was determined by Yoshii in a recent, pioneering total synthesis.[2,3] Tetronolide is related structurally to kijanolide and chlorothricolide,[4] which have also received considerable attention as synthetic targets.[5,6] In continuation of our efforts,[6] which includes the stereoselective synthesis of the octahydronaphthalene nucleus **2**,[6a] we now report a highly stereo- and enantioselective synthesis of the tetronolide top half spirotetronate substructure **3**, an intermediate in Yoshii's synthesis.[2,7] This synthesis features the highly exo-selective Diels-Alder reaction of triene **4** and the chiral dienophile (R)-**5**,[8] a reaction that we have also utilized in enantioselective syntheses of the kijanolide and chlorothricolide spirotetronate substructures.[6b,d]



tetronolide (**1**)



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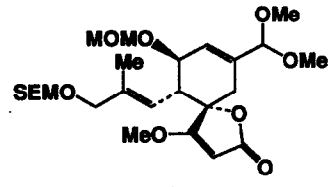
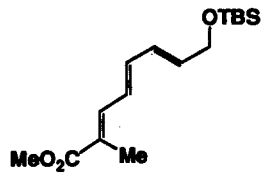
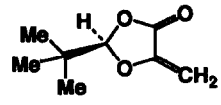


3



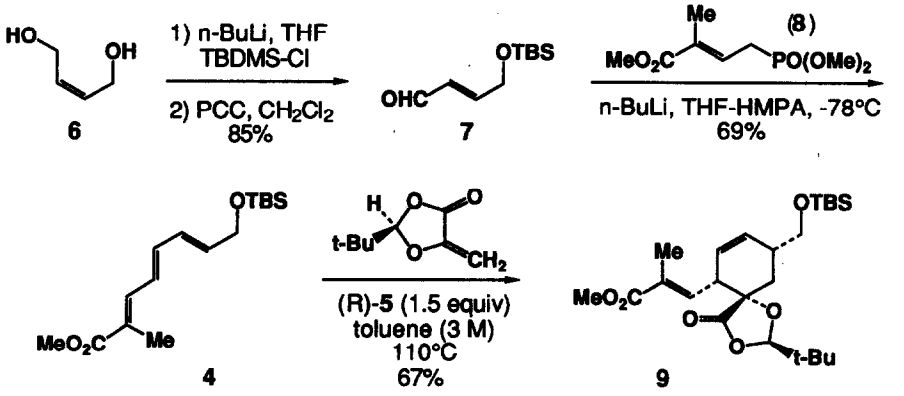
4



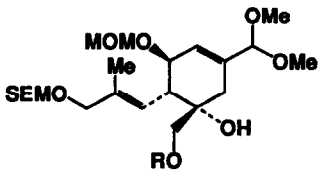
(R)-**5**

Our synthesis of **3** originates from the known enal **7**[9], which is easily prepared in two steps from cis-2-buten-1,4-diol (**6**) by selective monosilylation[10] and then PCC oxidation of the resulting allylic alcohol.[11] Treatment of **7** with the lithium anion of methyl γ-(dimethylphosphono)tiglate **8**[12] (generated at -78°C with n-BuLi) in a THF-HMPA solvent mixture (5 equiv of HMPA per equiv. of **8**) at -78°C to 23°C provided trienoate **4** in 69% yield.[13a] It is essential to use a polar aprotic solvent additive such as HMPA or DMPU in order to minimize the Michael addition of **8** to **7**, which is the major pathway in the absence of such additives. However, the yield of **4** is only 58% when the reaction is performed in the presence of 5 equiv. of DMPU, and consequently the THF-HMPA mixture is preferred.

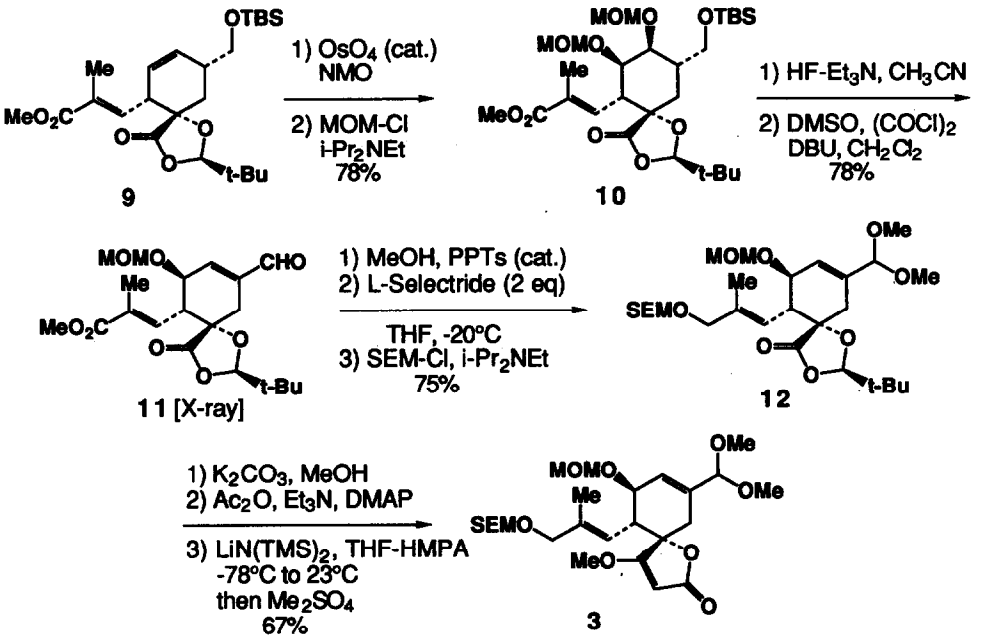
The key Diels-Alder reaction was performed by heating a mixture of **4** and 1.5 equiv. of (R)-**5** in toluene (3 M) at 110°C for 90 h. Under these conditions, the desired exo cycloadduct **9**[13a,b] ($[\alpha]_D^{24}$ -91.3° (c = 1.0, $CHCl_3$)) was obtained in 67% yield together with 5% of a second cycloadduct that tentatively has been assigned as the endo isomer, 14% of recovered **4**, and 5% of a mixture of products apparently resulting from the Diels-Alder dimerization of **4**. The reaction is faster at higher temperatures, but the yield of **9** is diminished owing to the increased rate of dimerization of **4**. Interestingly, no evidence for cycloadducts with reversed orientation of **4** and **5** was obtained, suggesting that the enoate substituent is a very powerful regiochemical directing element for this bimolecular Diels-Alder reaction.[6b,d,14]



Cis-dihydroxylation of **9** with catalytic OsO_4 and 1.0 equiv. of N-methylmorpholine oxide (NMO) proceeded with excellent β-face stereoselectivity.[15] Treatment of the resulting diol[13a,b] with MOM-Cl and iPr_2NEt in CH_2Cl_2 under standard conditions then provided **10**[13a,b] in 78% overall yield. The primary TBS ether was cleaved upon exposure to HF-Et_3N in CH_3CN, and the alcohol was oxidized by using a modified Swern protocol.[16] When this oxidation was preformed under standard conditions with Et_3N as the base, the β-alkoxy aldehyde was obtained as the major product with only minor amounts of enal **11**. However, by using the more basic DBU in place of Et_3N, enal **11**[13a,b] [m.p. 137-139°C; $[\alpha]_D^{22}$ +93.5° (c = 1.0, $CHCl_3$)] was obtained directly from the oxidation sequence in 78% yield from **10**. After protection of the aldehyde as a dimethyl acetal (MeOH, cat. PPTs, 92%), the unsaturated ester was selectively reduced by treatment with 2.2 equiv. of L-Selectride in THF at -20°C (86% yield). Protection of the resulting allylic alcohol as a SEM ether (SEM-Cl, i-Pr_2NEt, CH_2Cl_2, 23°C) then provided **12**[13a,b] ($[\alpha]_D^{23}$ +48.1° (c = 1.0, $CHCl_3$)) in 75% yield for the three step sequence from **11**. The enantiomeric purity of these intermediates deriving from **9** was determined to be ≥97% e.e. by Mosher ester analysis[18] of the subsequently prepared diol **13**.



13, R = H
14a, R = (R)-MTPA
14b, R = (S)-MTPA



The synthesis of spirotetronate **3** was completed by methanolysis of **12** with K_2CO_3 in MeOH, acylation of the resulting hydroxy methyl ester with acetic anhydride (excess) in the presence of DMAP and Et_3N in CH_2Cl_2, and then Dieckmann cyclization of the α-acetoxy ester ($LiN(TMS)_2$, THF-HMPA, -78°C, then warm the enolate solution to 23°C).[19] Addition of Me_2SO_4 directly to the reaction mixture[6b,d,7] then provided **3**[13a,b] (m.p. 65-66°C; $[\alpha]_D^{24}$ +134.3° (c = 2.80, $CHCl_3$)) in 67% overall yield. The spectroscopic properties of spirotetronate **3** were identical to those of an authentic sample ($[\alpha]_D^{23}$ +99.0° (c = 3.02, $CHCl_3$)) kindly provided by Professor Yoshii and Dr. Takeda.

In summary, we have developed efficient and highly diastereoselective syntheses of the tetronolide top half spirotetronate **3**. Our efforts to complete a tetronolide synthesis via the coupling of **2** and **3**, or their immediate precursors, will be reported in due course.

Acknowledgement. This research was supported by a grant from the National Institute of General Medical Sciences (GM26782). We are also grateful to the Sankyo Co. for providing financial support for K. K., to Mr. Richard J. Sciotti for preliminary studies on the synthesis of **9**, and to Professor Yoshii and Dr. Takeda of Toyama Medical and Pharmaceutical University for providing an authentic reference sample of **3**.

References

1. (a) Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2984. (b) Tamaoki, T.; Kasai, M.; Shirahata, K.; Tomita, F. *J. Antibiotics* **1982**, *35*, 979.
2. Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925.
3. Boeckman has recently reported considerable progress towards the total synthesis of tetronolide: (a) Boeckman, R K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091. (b) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Ibid.* **1991**, *32*, 4095.
4. (a) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. I* **1983**, 1497. (b) Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Helv. Chim. Acta* **1972**, *55*, 2094.
5. For leading references to studies on the synthesis of kijanolide and chlorothricolide: (a) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (b) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *Ibid.* **1990**, *55*, 2398. (c) Schmidt, R. R.; Hirsenkorn, R. *Liebigs Ann. Chem.* **1990**, 883. (d) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.
6. (a) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. (b) Roush, W. R.; Brown, B. B. *Ibid.* **1989**, *30*, 7309; the enantioselective synthesis of the kijanolide top half has been completed by using (R)-**5** in the originally reported sequence. (c) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192. (d) Roush, W. R.; Sciotti, R. J. *Tetrahedron Lett.* **1992**, in press.
7. Previous syntheses of tetronolide top half precursors: Matsuda, K.; Nomura, K.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1989**, 221 and ref. 3b.
8. (a) Enantioselective synthesis of (R)-**5**: Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380. See also: (b) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327. (c) Seebach, D.; Zimmermann, J. *Helv. Chim. Acta* **1987**, *70*, 1104.
9. Roush, W. R; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636.
10. For the selective monosilylation of symmetrical diols: (a) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, 49, 1772 (c.f., ref. 23 therein). (b) Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *Ibid.* **1984**, 49, 4674 (c.f., procedure for the syntheses of **49-51** therein). (c) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *Ibid.* **1986**, 51, 3388.
11. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
12. Pattenden, G.; Weedon, B. C. L. *J. Chem. Soc. C* **1968**, 1997.
13. (a) The spectroscopic properties (400 or 500 MHz ^{1}H NMR, IR, MS) of all new compounds are in agreement with the assigned structures. (b) A correct C,H analysis was obtained for this intermediate.
14. Representative examples of Diels-Alder reactions of trienes: (a) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. (b) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *Ibid.* **1978**, *100*, 7775. (c) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291. (d) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Ibid.* **1989**, *30*, 2233.
15. Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
16. (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) For a review of DMSO based oxidations: Tidwell, T. T. *Synthesis* **1990**, 857.
17. The stereochemistry of **11** was verified by X-ray crystal structure analysis. Details are provided in Report No. 92118 of the Indiana University Molecular Structure Center. Final residuals are R(F) = 0.0256 and R_w(F) = 0.0279. We thank Dr. John C. Huffman for performing this analysis.
18. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
19. Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.

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