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A MODULAR APPROACH TO MARINE MACROLIDE CONSTRUCTION. 1. AN ENANTIOCONTROLLED ROUTE TO THE C1-C12 (AB) SPIROACETAL SECTOR

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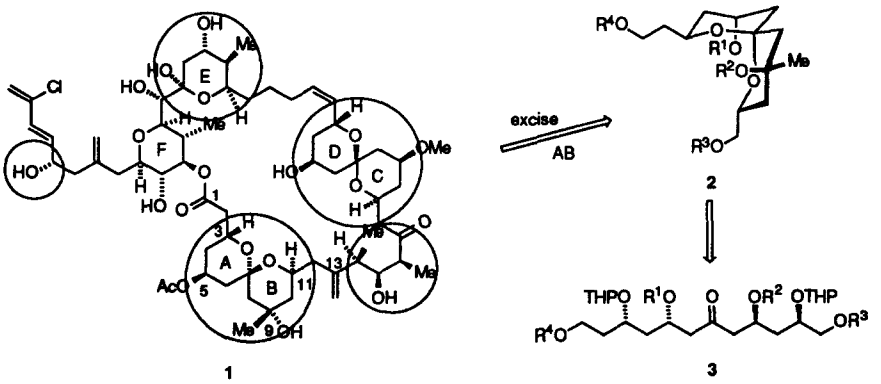
Abstract: A practical approach to a desymmetrized, enantiomerically pure AB spiroacetal ring component of altohyrtin A and its congeners is detailed. © 1997 Elsevier Science Ltd.

In early 1993, three research groups headed by Pettit,[1] Kitagawa,[2] and Fusetani[3] independently reported on the characterization of a new class of extremely potent antineoplastic macrocyclic lactones isolated from marine sponges. The major constituent in each study, spongistatin 1, altohyrtin A, and cinachyrolide A, was assigned the identical carbon framework in which two oxygenated spiroacetal units, a chlorinated carbinol side chain, and twenty-four stereogenic centers were prominently featured. The possibility remains open that all three macrolides are identical substances. However, since absolute stereochemistry has been deduced only for altohyrtin A,[2c,d] valid questions remain as to whether antipodal relationships exist in the sectors circled in **1**.[2d] Consequently, any synthetic approach to these scarce, exceptionally cytotoxic agents must incorporate an inherent capacity for accessing enantiomeric subunits as warranted.



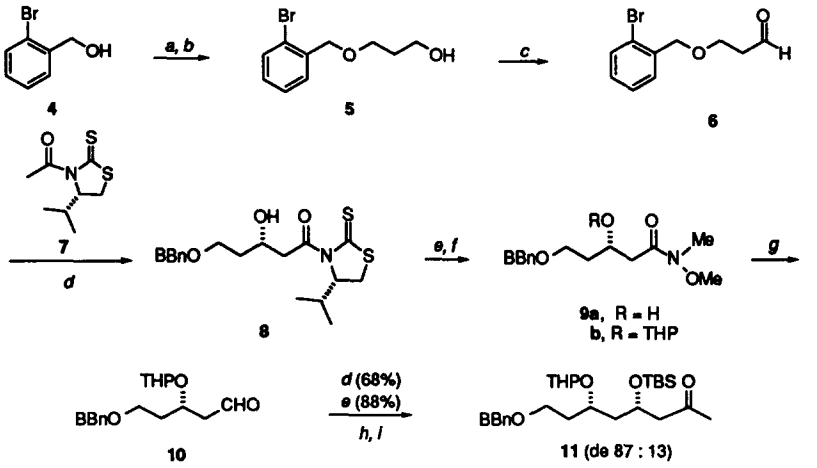
1 **2** **3**

The first objective of our studies was the AB sector of **1** with its thermodynamically advantaged double anomeric arrangement and equatorial disposition of those substituents positioned at C3 and C11. Preliminary reports by Heathcock[4] and by Paterson[5] have also

addressed this issue. However, their end products were either C_2-symmetric and inadequately functionalized, or substituted with identical side chains that cannot be distinguished for further elaboration. In contrast, the present approach provides a suitably desymmetrized, enantiomerically pure product, the antipode of which should be generatable with equal readiness. The key elements of our strategy centered about the expectation that stereocontrolled construction of **3** would be followed by the exclusive production of spiroacetal **2**.

Sequential allylation-hydroboration of commercially available *o*-bromobenzyl alcohol (**4**) provided **5** efficiently, particularly when recourse was made to sonication in the second step (Scheme 1). The ensuing oxidation of **5** delivered **6**, an aldehyde that we failed to obtain by direct Michael addition of **4** to acrolein. Condensation of **6** with **7** under Nagao's conditions[6] gave rise to a single detectable aldol, which was assigned the *S* configuration as in **8** on the basis of precedent. The optimal way to secure intermediate **10** involved the conversion of **8** to its Weinreb amide,[7] hydroxyl protection as the tetrahydropyranyl ether, and reduction with Dibal-H at -78 °C. Submission of **10** to the same protocol, but with TBS protection of the aldol and homologation to the methyl ketone gave rise to **11** in 55% overall yield for the four steps.

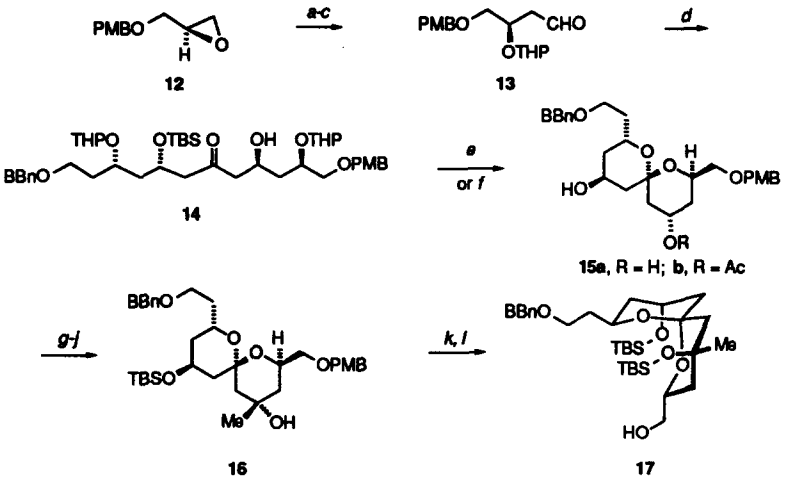
Scheme 1



[a] NaH, CH_2=$CHCH_2Br$, THF, rt, 4 h, 96%. [b] (1) 9-BBN, ultrasound, THF, rt, 3 h; (2) NaOH, H_2O_2, reflux, 1 h, 86%. [c] PCC/Celite, CH_2Cl_2, rt, 4 h, 76%. [d] (1) $Sn(OTf)_2$, N-ethylpiperidine, **7**, CH_2Cl_2, -50 to -40 °C, 4 h; (2) **6**, -78 °C, 4 h, 83%. [e] Me(MeO)NH·HCl, Me_3Al in toluene, CH_2Cl_2, -25 to 0 °C, overnight, 94%. [f] DHP, PPTS (cat), CH_2Cl_2, rt, 18 h, 97%. [g] Dibal-H, THF-hexanes, -78 °, 2 h, 96%. [h] TBSCl, imid, DMF, rt, 6 h, 99%. [i] MeMgBr, THF, Et_2O, -78 to 0 °C, 2 h, 92%.

Elaboration of the right-hand portion of **3** commenced with the *p*-methoxybenzyl ether of (*S*)-glycidol (*viz.*,**12**, 96% ee). Following conversion to **13** (Scheme 2), the two necessary building blocks were in hand. The stereogenicity of the chiral center that will result from their aldol coupling would appear at first glance to have little importance because of pending oxidation to the ketone level. Nonetheless, recourse was made to a highly (*S*)-diastereoselective reaction[8] in order to

Scheme 2



[a] CH_2=CHMgBr, CuI(cat), THF, -78 to 0 °C, 2 h, 85%. [b] DHP, PPTS (cat), CH_2Cl_2, rt, 5 h, 98%. [c] (1) OsO_4 (cat), NMO, THF-H_2O, rt, 1.75 h; (2) $NaIO_4$, THF-H_2O, rt, 1 h, 87%. [d] **11**, (-)-Ipc$_2$BCl, Et_3N, ether, 0 °C, 2 h; **13**, -78 °C, 4 h then -20 °C, 16 h, 89%. [e] BF_3•OEt_2, EtSH, CH_2Cl_2, -20 to 0 °C, 2 h, 60%. [f] (1) AcCl, py, C_6H_6, 4 h, rt, 95%; (2) BF_3•OEt_2, PhSH, CH_2Cl_2, -20 to 0 °C, 2 h, 60%. [g] TBSCl, imid, DMF, rt, 6 h, 95%. [h] Dibal-H, CH_2Cl_2, -78 °C, 3 h, 89%. [i] (*n*-Pr)$_4$NRuO$_4$, NMO 4 A MS, CH_2Cl_2, rt, 2 h, 91%. [j] MeMgBr, THF-Et_2O, -78 °C to rt, 2 h, 84%. [k] TBSOTf, (*i*-Pr)$_2$NEt, CH_2Cl_2, -70 to 0 °C, 2 h, 89%. [l] DDQ, CH_2Cl_2, pH 7 buffer, rt, 3 h, 90%.

simplify analysis and facilitate subsequent spirocyclization through hydrogen bonding. Quite unexpectedly, a number of accepted methods for the selective deprotection of THP groups in **14** did not lead to ring closure.[9] However, when recourse was made to the combination of boron trifluoride etherate and ethanethiol in CH_2Cl_2,[10] the desired transformation occurred with concomitant cleavage of the OTBS substituent to give **15a**. This diol was not considered to be serviceable because of an anticipated inability to distinguish between the pair of hydroxyl groups. In the long term, this event speaks to the need for appropriate replacement of the OTBS protecting group in **14**. However, with generous quantities of **14** in hand, advancement was made by acetylation prior to cyclization, this tactic affording **15b** in 60% yield.[11a] X-ray crystallographic analysis of this advanced intermediate (see Figure 1) confirmed that its absolute configuration was as expected.

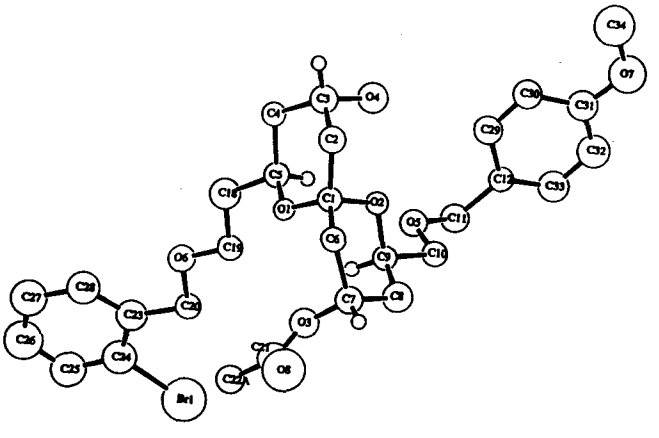


Figure 1. ORTEP drawing of **15b**.

Finally, silylation of **15b** made possible the acquisition of the B ring ketone which reacted with methylmagnesium bromide from the equatorial direction to give **16** (COSY and NOE analysis).[11b] Next to be addressed was protection of the tertiary hydroxyl as its *tert*-butyldimethylsilyl derivative and oxidative removal of the *p*-methoxybenzyl group. Both steps proceeded efficiently to provide the target compound **17**.

In summary, the convergent synthesis described herein makes available the C1-C12 spiroacetal sector of the marine macrolides in a manner that allows for direct chemical linkup to either side arm. Additionally, practical entry to the antipode of **17** is possible through alternative deployment of *R*-**7** and (*R*)-glycidol.

Acknowledgment. We thank the Eli Lilly Company for financial support.

References and Notes

1. (a) Pettit, G. R.; Chichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166. (c) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1805. (d) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605. (e) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271.
2. (a) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243. (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 2795. (c) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989. (d) Kobayashi, M.; Aoki, S.; Gato, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 2142.
3. Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.
4. Claffey, M. M.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 7646.
5. Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.
6. Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.
7. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
8. Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585.
9. Some of the methods examined were: Me_2AlCl, CH_2Cl_2, -25 °C to rt; $MgBr_2 \cdot Et_2O$, ether, rt; PPTS, MeOH, CH_2Cl_2, rt; and LiCl, DMSO, H_2O, 90 °C.
10. Nambiar, K. P.; Mitra, A. *Tetrahedron Lett.* **1994**, *35*, 3033.
11. (a) For **15b**: ^1H NMR (300 MHz, C_6D_6) δ 7.71 (d, J = 6 Hz, 1 H), 7.44 (d, J = 6 Hz, 1 H), 7.31 (d, J = 6 Hz, 2 H), 7.12 (t, J = 6 Hz, 1 H), 6.92 (d, J = 6 Hz, 2 H), 6.83 (t, J = 6 Hz, 1 H), 5.07 (m, 1 H), 4.55-4.25 (m, 3 H), 4.65 (d, J = 9 Hz, 2 H), 4.34 (d, J = 18 Hz, 2 H), 4.20-4.05 (br s, 1 H), 3.95 (q, J = 7.5 Hz, 1 H), 3.76-3.67 (m, 1 H), 3.40 (s, 3 H), 3.22 (t, J = 6 Hz, 1 H), 3.13 (dd, J = 12, 3 Hz, 1 H), 1.95 (s, 3 H), 2.05-1.65 (m, 7 H), 1.55 (d, J = 12 Hz, 1 H), 1.34 (td, J = 12, 4.5 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 170.1, 160.1, 139.1, 132.8, 131.1, 129.7, 129.4, 129.1, 128.0, 122.7, 114.5, 98.6, 73.4, 72.8, 72.7, 67.9, 66.9, 65.5, 64.7, 61.6, 55.1, 40.7, 39.0, 37.8, 36.7, 31.1, 21.6. (b) For **16**: ^1H NMR (300 MHz, C_6D_6) δ 7.58 (d, J = 6 Hz, 1 H), 7.33 (d, J = 6 Hz, 1 H), 7.23 (d, J = 6 Hz, 2 H), 7.05 (t, J = 6 Hz, 1 H), 6.82 (d, J = 6 Hz, 2 H), 6.73 (t, J = 6 Hz, 1 H), 4.64 (br s, 1 H), 4.52 (s, 2 H), 4.60-4.45 (m, 1 H), 4.38 (d, J = 6 Hz, 2 H), 4.45-4.25 (m, 1 H), 3.95-3.80 (m, 1 H), 3.65-3.45 (m, 3 H), 3.45-3.25 (m, 1 H), 3.32 (s, 3 H), 1.88 (d, J = 12 Hz, 1 H), 1.75-1.15 (m, 9 H), 1.23 (s, 3 H), 1.05 (s, 9 H), 0.10 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 160.0, 139.0, 132.9, 131.6, 129.8, 129.6, 129.1, 127.8, 123.0, 114.4, 99.3, 74.0, 73.6, 72.7, 68.3, 68.1, 66.4, 65.1, 63.0, 55.1, 47.4, 42.1, 41.5, 39.5, 36.5, 31.1, 26.5, 18.7, -4.2, -4.5.

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