Total Synthesis of Brevetoxin B. 1. CDEFG Framework


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With its imposing structure, brevetoxin B (1), produced by Gymnodinium breve,6 stands as an formidable challenge to synthetic chemists since its discovery and structural elucidation in 1981. Brevetoxin B's beautifully arranged molecular assembly includes 11 trans-fused rings, each containing an oxygen atom, with each fusion consisting of a C=C bond separating two adjacent ring oxygens and with all adjacent substituents flanking the oxygens placed syn to each other except on ring K. Its unprecedented architecture, its association with the “red tide” catastrophes,2 and its potent neurotoxicity and interference with the function of sodium channels attracted serious attention from chemists3 and biologists alike. We now wish to announce, in this and the following communication,6 the total synthesis of brevetoxin B (1) in its naturally occurring form.

Figure 1 outlines the strategic bond disconnections and retrosynthetic analysis of I. The adopted strategy benefited from convergency (oxocene disconnections) and synthetic technologies developed in these laboratories specifically for constructing oxocene4 and tetrahydropyran7 systems.

The construction of the CDEFG framework 4 described herein began with the previously reported intermediate 7 (Scheme 1).6 Swern oxidation of 7 followed by a Wittig reaction with the appropriate reagent furnished, in 99% overall yield, compound 9 via aldehyde 8. Hydrogenation of 9 and selective, acid-induced monodesilylation gave alcohol 10 in 97% overall yield. Oxidation of 11 in a sequential fashion using Swern and NaClO2 conditions resulted in carboxylic acid 12 (97%), which upon desilylation with TBAP led to 13 (91%). Lactonization of hydroxy acid 13 by the Yamaguchi method8 and enol triflate formation gave 15 via 14 in 84% overall yield. Generation of the higher order cuprate derived from the lithio derivative of iodide 17a,10 and 17b followed by coupling11 with triflate 15 and partial acid-induced orthoester hydrolysis resulted in formation of 18 via 16 (84% yield over two steps, ca. 2:1 ratio at C* in favor of the desired isomer, vide infra). Regio- and stereoselective hydroboration of 18 followed by oxidative workup and alkaline hydrolysis furnished hydroxy acid 19 in 73% overall yield. Finally, lactonizations10 of 19 and separation of the C* epimers afforded pure lactone 6 (60% yield, plus 25% of its C* methyl epimer), whose structure was determined by X-ray crystallographic analysis (see ORTEP drawing of a derivative10 of 6, Figure 2).

The fusion of the remaining three rings onto the DEFG system 6 was to afford the targeted poly cyclic framework 4 proceeded as depicted in Scheme 2. Thus, conversion of lactone 6 to its enol triflate (97%) followed by CrNi-mediated coupling12 with

(7) For preparation of and selected data for this compound, see the supplementary material.
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* Reagents and conditions: (a) 2.0 equiv of (COCl)2, 3.0 equiv of DMSO, CH2Cl2, -78 °C, then 7.0 equiv of Et3N, 0.5 h, 100%; (b) 2.0 equiv of TBSO(CH2)3PPh3, 1.5 equiv of NaHMDS, THF, 0 °C, 10 min, then 8, 0.5 h, 99%; (c) H2, 0.1 equiv of Pd/C (10%), 0.1 equiv of Na2CO3, EtOHac, 25 °C, 12 h, 100%; (d) 1.0 equiv of CSA, CH2Cl2/MeOH (1:1), 0 °C, 1 h, 97%; (e) 2.0 equiv of (COCl)2, 3.0 equiv of DMSO, CH2Cl2, -78 °C, then 7.0 equiv of Et3N, 0.5 h, 1.5 equiv of NaClO4, 2.0 equiv of NaH2PO4, 2.0 equiv of 2-methyl-2-butanone, i-Pr2NEt/H2O (2:1), 25 °C, 1 h, 97%; (f) 5.0 equiv of TBAF, THF, 65 °C, 8 h, 91%; (g) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et3N, THF, -78 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 90%; (h) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 2 h, then added to 1.5 equiv of TFA, decane), CH2Cl2, -78 °C, 5 min, 98%; (i) 1.7 equiv of Dess—Martin periodinane, CH2Cl2, 25 °C, 2 h, 85%; (j) 2.0 equiv of KH, THF, 25 °C, 2 h, 90%; (k) 1.3 equiv of DIBAL-H, CH2Cl2, -78 °C, 2 min, 99%; (l) 1.0 equiv of CSA, CH2Cl2/MeOH (2:1), 25 °C, 1 h, 100%; (m) 2.0 equiv of KH, THF, 25 °C, 2 h, 90%; (n) 2,5 equiv of DIBAL-H, CH2Cl2, -78 °C, 2 h, 98%; (o) 0.2 equiv of Ti(OiPr)4, 0.2 equiv of (+)-diethyl tartrate, 2.0 equiv of n-BuOH, 0 °C, 1 h, 89% (over two steps); (p) 1.5 equiv of TBAF-induced desilylation (100%).

* Reagents and conditions: (a) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 2 h, then 1.5 equiv of Ti(OPr)i, -78 to 25 °C, 97%; (b) 6.0 equiv of 20, 6.0 equiv of CrCl3, 0.02 equiv of Nicl2, DMF, 25 °C, ultrasound, 3 h, 66%; (c) 3.0 equiv of Cs2CO3, 0.0 equiv of KH (added over 5 h), Et3O, then 10.0 equiv of Mat, 25 °C, 89%; (d) 0.4 equiv of n-BuSnH, 0.1 equiv of AIBN, benzene, 80 °C, 67%; (e) 5.0 equiv of BH3*THF, -30 °C, then 25 equiv of 3 N NaOH, 50 equiv of 30% H2O2, 82%; (f) 2.0 equiv of TES/TOL, 2.5 equiv of 2,6-lutidine, CH2Cl2, -70 °C, 1 h, 96%; (g) 2.5 equiv of DIBAL-H, CH2Cl2, -78 °C, 5 min, 98%; (h) 1.7 equiv of Dess—Martin periodinane, CH2Cl2, 25 °C, 2 h, 85%; (i) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (j) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (k) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (l) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (m) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (n) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (o) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (p) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (q) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (r) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (s) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (t) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (u) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (v) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (w) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (x) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (y) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%; (z) 2.0 equiv of KH, THF, 25 °C, 2 h, 85%.

**Acknowledgment.** See following communication.3

**Supplementary Material Available.** See following communication.3

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**Figure 2.** ORTEP of the bis(tetramethylborate) derivative of 6.

**Scheme 1.** Construction of CDEFG Ring System 4

**Scheme 2.** Construction of CDEFG Ring System 4

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*yield via a stereoselective Michael-type reaction.14 Extension of the ester side chain via DIBAL-H reduction and phosphorane condensation furnished, via aldehyde 30 (97%), the α,β-unsaturated ester 31 (98%), which was reduced to allylic alcohol 32 (96%). Sharpless asymmetric epoxidation15 of 32 using (+)-DET as the chiral auxiliary gave the corresponding hydroxy epoxide (99% yield), which was further oxidized to the aldehyde and subjected to a Wittig reaction to afford terminal olefin 33 (96%). Coupling of the latter to the UK system 2 and the completion of the total synthesis of brevetoxin B (1) are described in the following communication.5,16

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**Communications to the Editor**

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(16) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

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