Total Synthesis of Brevetoxin B. 1. CDEFG Framework


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With its imposing structure, brevetoxin B (1), produced by Gonyaulax catenella, stood as a formidable challenge to synthetic chemists since its discovery and structural elucidation in 1981.1 Brevetoxin’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 oxygen atoms in such a way that the fused ring systems A—B and E—F are oriented similar 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 sparked serious attention from chemists3 and biologists4 alike. We now wish to announce, in this and the following communication,5 the total synthesis of brevetoxin B (1) in its naturally occurring form.

Figure 1 outlines the strategic bond disconnections and retrosynthetic analysis of 1. The adopted strategy benefited from convergency (oxocene disconnections) and synthetic technologys developed in these laboratories specifically for constructing oxocene6 and tetrahydropyran7 systems.

The construction of the CDEFG framework described herein began with the previously reported intermediate 7 (Scheme 1).8 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 11 via 10 in 97% overall yield. Oxidation of 11 in a sequential fashion using Swern and NaClO2 conditions resulted in the carboxylic acid 12 (97%), which upon deprotection with TBAF led to 13 (91%). Lactonization of hydroxy acid 13 by the Yamaguchi method9 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 17a10 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. 2.4:1 ratio at C* in favor of the desired isomer, vide infra). Regio- and stereoselective hydroboration of 18 followed by oxidative workup and alkali hydrolysis furnished hydroxy acid 19 in 73% overall yield. Finally, lactonization 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 derivative12 of 6, Figure 2).

The fusion of the remaining three rings onto the DEFG system 4 was achieved by the previously reported intermediate 7 (Scheme 1).8 Conversion of lactone 6 to its enol triflate (97%) followed by CrNi-mediated coupling13 with...
Scheme 1. Construction of DEFG Ring System 6

* 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) H₂O, 0.1 equiv of PSF (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 (OCOCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, -78 °C, then 7.0 equiv of Et₃N, 0.5 h, 1.5 equiv of NaClO₃, 2.0 equiv of NaH₂PO₄, 2.0 equiv of 2-methoxy-2-butanone, BuOH/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, 0 °C, 2 h, then added to 0.3 equiv of TBAF, THF, 25 °C, 3 h, 100%; (h) 0.1 equiv of Pd/C (10%), 0.1 equiv of Na₂CO₃, EtOAc, 0 °C, 30 min, 97%; (i) 2.0 equiv of (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, -20 °C, 5 h, 99%; (j) 1.2 equiv of NaHMDS, 1.5 equiv of 18-crown-6, 5.0 equiv of (MeO)₂P(Me)₂, THF, 0 °C, 0.5 h, then add 27, 3 h, 99%; (k) 1.0 equiv of CSA, CH₂Cl₂/MeOH (2:1), 25 °C, 1 h, 100%; (l) 2.0 equiv of KH, THF, 25 °C, 2 h, 90%; (m) 2.0 equiv of DIBAL-H, CH₂Cl₂, -78 °C, 2 min, then 3.0 equiv of MeOH, 97%; (n) 2.0 equiv of Ph₂PO(CH₂)₂CH₂Ph, THF, 0 °C, 0.5 h, then add 27, 3 h, 99%; (o) 1.0 equiv of CSA, CH₂Cl₂/MeOH (2:1), 25 °C, 1 h, 100%; (p) 5.0 equiv of SO₂pyridine, 10 equiv of DMSO, CH₂Cl₂, -78 °C, 2 min, 98%; (q) 2.0 equiv of Ti(OPr)₂, 0.2 equiv of (+)-diethyl tartrate, 2.0 equiv of Na₂CO₃, THF, 0 °C, 0.5 h, 97%; (r) 1.2 equiv of Na₂CO₃, 1.5 equiv of CH₃P(=O)Br⁻, THF, 25 °C, 1 h, 89% (over two steps), (s) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 100%.

Scheme 2. Construction of CDEFG Ring System 4

* Reagents and conditions: (a) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 3 h, then 1.5 equiv of Ti(OPr)₂, -78 °C, 97%; (b) 6.0 equiv of 20, 6.0 equiv of CrCl₂, 0.02 equiv of NiCl₂, DMF, 25 °C, ultrason; 3 h, 66%; (c) 1.0 equiv of Cs₂CO₃, 10.0 equiv of KH (added over 5 h), Et₂O, then 10.0 equiv of NaI, 25 °C, 89%; (d) 4.0 equiv of n-Bu₃SnH, 0.1 equiv of 18-crown-6, 5.0 equiv of NaOH, 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 TESOT, 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/DME, 0.2 equiv of 18-crown-6, 5.0 equiv of (MeO)₂P(=O)CH₂CH₂Me, THF, 0 °C, 0.5 h, then add 27, 3 h, 99%; (j) 1.0 equiv of CSA, CH₂Cl₂/MeOH (2:1), 25 °C, 1 h, 100%; (k) 2.0 equiv of KH, THF, 25 °C, 2 h, 99%; (l) 1.3 equiv of DIBAL-H, CH₂Cl₂, -78 °C, 2 min, then 3.0 equiv of MeOH, 97%; (m) 2.0 equiv of Ph₂PO(CH₂)₂Ph, CH₂Cl₂, 25 °C, 12 h, 98%; (n) 2.5 equiv of DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 96%; (o) 0.2 equiv of Ti(OPr)₂, 0.2 equiv of (+)-diethyl tartrate, 2.0 equiv of Na₂CO₃, THF, 0 °C, 0.5 h, 97%; (p) 1.2 equiv of Na₂CO₃, 1.5 equiv of CH₃P(=O)Br⁻, THF, 25 °C, 1 h, 89% (over two steps), (q) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 100%.

Figure 2. ORTEP of the bis(β-bromobenzyl) derivative of 6.

Aldolide 20b furnished alcohol 21 (66%, mixture of epimers), which was deoxygenated via xanthate 22 (89%) by the Barton method13 to afford 23 (67%). Regio- and stereoselective hydration of 23 via hydroboration/oxidation gave alcohol 24 (82%), which was silylated, leading to 25 (96%). A series of reactions involving DIBAL-H-mediated ester cleavage (98%), Dess—Martin oxidation (85%), honors—Emmons olefination (99%), and acid-induced selective desilylation (100%) afforded α,β-unsaturated ester 5 via 26, 27 and 28. Exposure of 5 to KH led to the formation of the CDEFG ring system 29 in 90% 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 (80% over two steps), and thence hydroxy epoxide 4 upon TBAF-induced desilylation (100%).

The elaboration of 4 to the AB CDEFG framework 3, the coupling of the latter to the IJK system 2 and the completion of the total synthesis of brevetoxin B (1) are described in the following communication.3

Acknowledgment. See following communication.

Supplementary Material Available: See following communication.

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