Total Synthesis of Brevetoxin B. 1. CDEFG Framework


Department of Chemistry, The Scripps Research Institute 10566 North Torrey Pines Road, La Jolla, California 92037

Department of Chemistry and Biochemistry University of California, San Diego 9500 Gilman Drive, La Jolla, California 92093

Received November 1, 1994

With its imposing structure, brevetoxin B (1), produced by Gymnodinium breve, stood as an 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 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 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 technologies developed in these laboratories specifically for constructing the oxygens placed adjacent ring oxygens and with all adjacent substituents flanking with each fusion consisting of a C—C bond separating two


Figure 1. Strategic bond disconnections and retrosynthetic analysis of brevetoxin B (1).
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 Et₂N, 0.5 h, 100%; (b) 2.0 equiv of TBSO(CH₂)₃PPh₃⁺, 1.5 equiv of NaHMDS, THF, 0 °C, 10 min, then 8, Et₂O, -120 °C -78 °C, 0.5 h, then 5.0 equiv of 17b, -78 — 30 °C, 0.5 h, then 25 equiv of 3 N NaOH, 50 equiv of 30% H₂PO₄, DME/H₂O/THF/HMPA (1:1:1), then 15, -78 — 0 °C, 2 h, 84%; (c) 0.3 equiv of TfaNPh, -78 — 25 °C, 93%; (d) 6.0 equiv of 17ft, 10.0 equiv of r-BuLi, 1.5 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 2 h, then added to 1.5 equiv of trichlorobenzoyl chloride, 1.5 equiv of Et₃N, THF, 0 °C, 2 h, then added to 1.5 equiv of TBAF, THF, 65 °C, 8 h, 91%; (e) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et₂N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 90%; (f) 5.0 equiv of TFA/TBSO, MeOH, 97%; (g) 2.0 equiv of Ph₃PCHC(O)Ph, 0 °C, 2 min, then 3.0 equiv of DIBAL-H, THF, 0 °C, 2 min, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 60% of 6, plus 25% of its C* epimer (after column chromatography).

Figure 2. ORTEP of the bis(p-bromobenzoyl) derivative of 6.

Scheme 2. Construction of CDEFG Ring System 4

**Reagents and conditions:** (a) 5.0 equiv of LiHMDS, 1.5 equiv of IMPA, THF, -78 °C, 2 h, then 1.5 equiv of TfNH₂, -78 — 25 °C, 97%; (b) 6.0 equiv of 20, 6.0 equiv of CrCl₂, 0.02 equiv of Nic, DMF, 25 °C, ultrasound, 3 h, 66%; (c) 3.0 equiv of CSA, 50.0 equiv of KH (added over 5 h), Et₂O, then 10.0 equiv of MeI, 25 °C, 89%; (d) 4.0 equiv of n-BuO,NH, 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 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/H₂O (2:1), 25 °C, 1 h, 100%; (j) 2.0 equiv of Ph₃PCHC(O)Ph, 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 Ph₂CHC(O)Et, CH₂Cl₂, 25 °C, 12 h, 98%; (o) 2.5 equiv of DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 95%; (p) 0.1 equiv of AIBN, benzene, 80 °C, 67%; (q) 1.3 equiv of DIBAL-H, CH₂Cl₂, -78 °C, 2 min, then 3.0 equiv of MeOH, 97%; (r) 2.0 equiv of Ph₂CHC(O)Et, CH₂Cl₂, 25 °C, 12 h, 98%; (s) 2.5 equiv of DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 95%; (t) 0.2 equiv of Ti(OPr)₄, 0.2 equiv of (+)-diethyl tartrate, 2.0 equiv of n-BuO,NH (5 N in decane), CH₂Cl₂, -20 °C, 5 h, 99%; (u) 5.0 equiv of SO₂pyridine, 10 equiv of Et₃N, CH₂Cl₂/DMSO (4:1), 0 °C, (v) 1.2 equiv of NaHMDS, 1.5 equiv of CH₂P(OMe)Br⁻, THF, 25 °C, 1 h, 80% (over two steps), (w) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 100%.

yield via a stereoselective Michael-type reaction. 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 epoxidation 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 (50% over two steps), and thence hydroxy epoxide 4 upon TBAF-induced desilylation (100%).

The elaboration of 4 to the ABCDEFG framework 3, the coupling of the latter to the IJK system 2 and the completion of the total synthesis of brevetoxicin B (1) are described in the following communication. Acknowledgment. See following communication. Supplementary Material Available: See following communication.

(16) All new compounds exhibit satisfactory spectroscopic and mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.