Brevetoxin B (1), a member of the "red tide"-associated class of marine neurotoxins,7 possesses a striking biological profile as a sodium channel modulator1 and a formidable molecular structure that includes 11 fused rings and 23 stereocenters. Several synthetic methods and schemes have been advanced toward the synthesis of this molecule,3,4 but to date, no total synthesis of brevetoxin B (1) or designed analogs have been reported. Herein we report the design and synthesis of a novel version of this compound, truncated brevetoxin B [AFGHIJK] (2), in which all the functionality within the natural compound is present, except for the internal rings BCDE (Figure 1). Such a design was considered important in that it could test the "length hypothesis" of the brevetoxins3,4 and provide useful information about their receptor.5,6

An attractive bond disconnection across the oxocene ring of 2 revealed two domains (3 and 4) that could be coupled in the synthetic direction via a Wittig reaction and cyclized to produce the desired poly cyclic framework.

This convergent synthesis began with the construction of intermediates 3 (Scheme 1) and 4 (Scheme 2). Swern oxidation of the alcohol 5a (Scheme 1) followed by addition of MeMgBr and subsequent reoxidation gave rise to ketone 6 in 94% overall yield. After desilylation, the liberated alcohol 7 was converted to the bromoacetate ester 8, which upon exposure to (MeO)3P at 180 °C afforded the phosphate 9 in 74% overall yield from 6. A modified Horner–Emmons1 reaction was then used for the ring closure of 9 to 10 (88%). Reduction of 10 to the corresponding dihydropyran 12 was achieved by sequential treatment with DIBALH and BF3·Et2O/Me3SiH via the intermediacy of lactol 11.

![Figure 1. Structure of truncated brevetoxin B [AFGHIJK] (3) and retrosynthetic analysis.](image-url)

**Scheme 1**

- **Reagents and conditions:**
  - (a) 2.0 equiv of (COCl)2, 3.0 equiv of imidazole, CH2Cl2, 25 °C, 0.5 h, 100%; (b) 2.0 equiv of MeMgBr, CH2Cl2, 0 °C, 0.5 h, 97%; (c) 2.0 equiv of (COCl)2, 3.0 equiv of pyridine, CH2Cl2, 25 °C, 12 h, 70%; (d) 10.0 equiv of Li, NH3, THF, -78 °C, 1.5 h, 100%; (e) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; (f) 2.0 equiv of LiCl, CH2CN, 25 °C, 3 h, 89%; (g) 1.5 equiv of DIBALH, CH2Cl2, -78 °C, 0.5 h, 98%; (h) 1.0 equiv of BF3·Et2O, 5.0 equiv of Et3SiH, CH2Cl2, -10 °C, 0.5 h, 97%; (i) 10.0 equiv of Li, NH3, THF, -78 °C, 1.5 h, 100%; (j) 1.1 equiv of TCI, 3.0 equiv of pyridine, CH2Cl2, 25 °C, 12 h, 70%; (k) 5.0 equiv of NaI, acetone, 60 °C, 12 h, 83%; (l) 1.5 equiv of TMS-iodimido, CH2Cl2, 25 °C, 0.5 h, 100%; (m) 3.0 equiv of PPh3, CH2CN, 65 °C, 1 h, 50%; (n) 2.0 equiv of PPh3, TMS = SiMe3, TaO = tolyl.

11 (95%). Debenzylation of 12 to the diol 13 followed by selective monosilylation and displacement with NaI of the primary tosylate 14 led to 15 in 58% overall yield. Finally, protection of the secondary alcohol in 15 as a TMS ether and treatment with PPh3 gave phosphonium salt 3 in quantitative yield.

The construction of aldehyde 4 commenced with diol 17 (Scheme 2), which was first protected as an acetonide and then...
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Scheme 2. Synthesis of the IJK Ring System 4

Reagents and conditions: (a) 3.0 equiv of CH₂—C(OMe)Me, 0.2 equiv of CSA, CH₂Cl₂, 25 °C, 4 h, 89%; (b) 2.0 equiv of TBAP, THF, 25 °C, 2 h, 97%; (c) 2.0 equiv of COCl₂, 3.0 equiv of DMSO, CH₂Cl₂, -78 °C, 0.5 h, then 7.0 equiv of Et₂N, 100%; (d) 2.0 equiv of Ph₂—CHO/Me₂Si, CH₂Cl₂, 25 °C, 5 h, 96% (E:E = 4:1); (e) H₂, Pd(0H)₄, THF, 25 °C, 40 h, 14 h, 100%; (f) 2.0 equiv of LiAlH₄, THF, 25 °C, 4 h, 92%; (g) 1.1 equiv of TPSCI, 2.0 equiv of Et₂N, 0.1 equiv of DMAP, CH₂Cl₂, 25 °C, 6 h, 95%; (h) 2.0 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH₂Cl₂, 0 °C, 0.5 h, 100%; (i) 0.2 equiv of CSA, 1.1 CH₂Cl₂/MeOH, 0 °C, 2 h, 97%; (j) 1.0 equiv of TBSCI, 2.0 equiv of imidazole, DMF, 0 °C, 1 h, 94%; (k) 1.5 equiv of NMO, 0.02 equiv of TPAP, CH₂CN, 25 °C, 1 h, 96%; (l) 3.0 equiv of BISH, 1.1 equiv of Zn(OTf)₂, CH₂Cl₂, 25 °C, 3 h (m) 0.2 equiv of CSA, MeOH, 25 °C, 1 h, 74% (over two steps); (n) 5.0 equiv of SO₂-pyridine, 5.0 equiv of Et₂N, 0 °C, 1.5 h, 92%. TBS = Si(OMe)₃, TPAP = tetrapropylammonium perruthenate.

converted via desilylation, oxidation, and a Wittig reaction to the unsaturated ester 19 (ca. 4:1 E:Z isomers, 83% overall yield) through aldehyde 18. Sequential treatment of 19 with H₂/Pd(OH)₄ and LiAlH₄ followed by selective silylation of the resulting hydroxyl groups furnished 23 in 87% overall yield. Removal of the acetone and selective protection of the primary alcohol, followed by oxidation of the secondary alcohol, provided the corresponding ketone 26 in 79% yield. Thiolactonization of 26 and hydrolytic-cleavage of the primary TBS ether afforded alcohol 27, which was oxidized to the requisite aldehyde 4 (68% overall yield).

Generation of the ylide from 23, followed by reaction with aldehyde 4, produced the Z-olefin 28 (Scheme 3) in 57% yield (based on 3). Desilyllation of 28, followed by AgClO₄-induced cyclization and desulfurization,3 provided oxocene 29 in 80% overall yield. Oxidation of 29 with PCC gave lactone 30 in 66% yield. Finally desilylation of 30, followed by oxidation and treatment of the resulting aldehyde 31 with Eschenmoser's salt10 secured, upon desilylation, the targeted 2 in 61% overall yield.

X-ray crystallographic analysis of 2 (mp 218 °C, from methanol/petroleum ether) confirmed its structure (sec ORTEP drawing, Figure 2).


Reagents and conditions: (a) 1.0 equiv of n-BuLi, 2.0 equiv of HMPA, THF, -78 °C, 1 h, 77%; (b) 0.2 equiv of PPTS, 1.1 CH₂Cl₂/MeOH, 25 °C, 1 h, 91%; (c) 4.0 equiv of AgClO₄, 2.0 equiv of NaHCO₃, SiO₂, 4 Å molecular sieves, CH₃NO₂, 25 °C, 30 h, 90%; (d) 4.0 equiv of Ph₂SnH, 0.1 equiv of AIIN, toluene, 100 °C, 2 h, 98%; (e) 4.0 equiv of PCC, CH₂Cl₂, 60 °C (sealed tube), 4 h, 66%; (f) 3.0 equiv of TBAP, THF, 25 °C, 13 h, 79%; (g) 3.0 equiv of Dess–Martin periodinane, CH₂Cl₂, 25 °C, 2 h, 100%; (h) 2.0 equiv of Me₂N—CH₂—CH₂⁺, 20 equiv of E₂N, CH₂Cl₂, 25 °C, 12 h, 79%; (i) HF-pyridine, CH₂Cl₂, 25 °C, 30 min, 97%. TBS = Si(OMe)₃, TPAP = Si(OMe)₃, TMS = SiMe₃.

Figure 2. ORTEP drawing of truncated brevetoxin B [AFGHIJK] 2.

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Supplementary Material Available: Characterization data for compounds 2 (including X-ray crystallographic parameters), 16, 27–30, and 32 (19 pages); listing of observed and calculated structure factors for 2 (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.