Total Synthesis of Truncated Brevetoxin B [AFGHIJK]


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Brevetoxin B (1),¹ a member of the "red tide"-associated class of marine neurotoxins,² possesses a striking biological profile as a sodium channel modulator³ 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,[4,5] 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 brevetoxins[6,7] and provide useful information about their receptor[s].⁸⁻¹⁰

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 polycyclic framework.

This convergent synthesis began with the construction of intermediates 3 and 4 (Scheme 2). Swern oxidation of the alcohol 5⁵ (Scheme 1) followed by addition of MeMgBr and subsequent reoxidation gave rise to ketone 6 in 94% overall yield. After destillation, the liberated alcohol 7 was converted to the bromoacetate ester 8, which upon exposure to (MeO)₂P at 180 °C afforded the phosphonate 9 in 74% overall yield from 6. A modified Horner–Emmons¹¹ reaction was then used for the ring closure of 9 to 10 (88%). Reduction of 10 to the corresponding dihydropropynol 12 was achieved by sequential treatment with DibalH and BF₃·EtO/O/Et₂SiH via the intermediacy of lactol

![Figure 1. Structure of truncated brevetoxin B [AFGHIJK] (2) and retrosynthetic analysis.](https://example.com/figure1)

### Scheme 1.¹ Synthesis of the AFG Ring System

![Diagram of the AFG Ring System](https://example.com/scheme1)

Reagents and conditions: (a) 2.0 equiv of (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, –78 °C, then 7.0 equiv of Et₃N, 1 h, 100%; (b) 2.0 equiv of MeMgBr, THF, 0 °C, 1 h, 96%; (c) 2.0 equiv of (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, –78 °C, then 7.0 equiv of Et₃N, 1 h, 98%; (d) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; (e) 2.0 equiv of Br₂·COCOCl, 4.0 equiv of pyridine, CH₂Cl₂, 0 °C, 5 h, 82%; (f) neat (MeO)₂P, 180 °C (sealed tube), 3 h, 90%; (g) 1.0 equiv of Ph₃P·CHNO₂, 2.0 equiv of LiCl, CH₂CN, 25 °C, 3 h, 88%; (h) 1.5 equiv of DibalH, CH₂Cl₂, –78 °C, 0.5 h, 98%; (i) 1.0 equiv of BF₃·EtO, 5.0 equiv of Et₂SiH, CH₂Cl₂, 10 °C, 0.5 h, 97%; (j) 2.0 equiv of Li·NH₃·THF, –78 °C, 1.5 h, 100%; (k) 1.0 equiv of TiCl₄, 3.0 equiv of pyridine, CH₂Cl₂, 25 °C, 12 h, 70%; (l) 5.0 equiv of NaI, acetone, 60 °C, 12 h, 83%; (m) 1.5 equiv of TMS-methylidene, CH₂Cl₂, 25 °C, 0.5 h, 100%; (n) 6.0 equiv of PPh₃, CH₂CN, 65 °C, 15 h, 100%; TBS = Si(2Me)₃, Bn = CH₃Ph, TMS = SiMe₃, Tt = tosylate.

11 95%. Debenzylation of 12 to the diol 13 followed by selective monotosylation 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 17⁴ (Scheme 2), which was first protected as an acetone and then...
Scheme 2* Synthesis of the JUK Ring System 4

* Reagents and conditions: (a) 3 equiv of CH₂=C(OH)Me, 0.2 equiv of CSA, CH₂Cl₂, 25 °C, 4 h, 89%; (b) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 97%; (c) 2.0 equiv of (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, -78 °C, 0.5 h, then 7.0 equiv of Et₃N, 100%; (d) 2.0 equiv of Ph₃P=CHCO₂Me, CH₂Cl₂, 25 °C, 5 h, 96% (E:Z = 4:1); (e) H₂, Pd(OH)₂, THF, 25 °C, 40 psi, 1 h, 61%; (f) 2.0 equiv of LIAH₂, THF, 25 °C, 4 h, 92%; (g) 1.1 equiv of TBSOT, 2.0 equiv of Et₃N, 0.1 equiv of DMAP, CH₂Cl₂, 25 °C, 6 h, 95%; (h) 2.0 equiv of TBSOT, 3.0 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, 87%; (j) 1.0 equiv of TBSOT, 2.0 equiv of imidazole, DMF, 0 °C, 1 h, 94%; (k) 1.5 equiv of NMO, 0.2 equiv of TPAP, CH₂CN, 25 °C, 1 h, 96%; (l) 3.0 equiv of EISH, 1.1 equiv of Zn(OAc)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 Et₃N, 1:1 CH₂Cl₂/DMSO, 0 °C, 1.5 h, 92%. TBS = Si₂Bu₂Me₃, TPS = Si₂Bu₂Me₂, BN = CH₃Ph, NMO = 4-methylmorpholine N-oxide, TPAP = tetrapropylammonium persulfate.

converted via diisylolation, 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)₂ and LiAlH₄ followed by selective silylation of the resulting hydroxyl groups furnished 23 in 87% overall yield. Removal of the acetonide 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 3, followed by reaction with aldehyde 4, produced the Z-olefin 28 (Scheme 3) in 57% yield (based on 3). Desilylation of 28, followed by AgClO₄-induced cyclization and desulfurization, 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 salt, 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 (see ORTEP drawing, Figure 2).

Truncated brevetroxin B [AFGHIJK] (2), lacking the BCDE ring segment of the parent compound (1), has a head-to-tail length of 20.4 Å as opposed to ca. 30 Å for 1. Biological studies with 2 revealed no binding to the brevetoxin B receptor, supporting the notion that the length of the molecule is crucial for biological activity. The described chemistry sets the stage for the total synthesis of the natural brevetroxin B (1) and for further chemical biology studies.

Scheme 3* Synthesis of Truncated Brevetoxin B (AFGHIJK) 2

* Reagents and conditions: (a) 1.0 equiv of n-BuLi, 2.0 equiv of HMPT, THF, -78 °C to 25 °C, 1 h, 97%; (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, CH₂Cl₂, 25 °C, 30 h, 90%; (d) 4.0 equiv of Ph₃P=CH₂, 0.1 equiv of AIBN, toluene, 100 °C, 2 h, 98%; (e) 8.0 equiv of PCC, CH₂Cl₂, 60 °C (sealed tube), 4 h, 66%; (f) 2.0 equiv of TBAF, THF, 25 °C, 13 h, 99%; (g) 3.0 equiv of Dess-Martin periodinane, CH₂Cl₂, 25 °C, 2 h, 100%; (h) 2.0 equiv of Me₂N=CH₂, 20 equiv of Et₃N, CH₂Cl₂, 25 °C, 12 h, 99%; (i) HF-pyridine, CH₂Cl₂, 25 °C, 30 min, 97%. TBS = Si₂Bu₂Me₃, TPS = Si₂Bu₂Me₂, NMO = 4-methylmorpholine N-oxide.

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.