Total Synthesis of Truncated Brevetoxin B [AFGHIJK]

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Brevetoxin B (1), a member of the “red tide”-associated class of marine neurotoxins,4 possesses a striking biological profile as a sodium channel modulator5 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,6 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 brevetoxins7 and provide useful information about their receptor.8

An attractive bond disconnection across the oxocene ring of 2 revealed two domains (3 and 4) that could be coupled in the receptor30,31 via a Wittig reaction and cyclized to produce the desired polycyclic framework.

This convergent synthesis began with the construction of intermediates 3 (Scheme 1) and 4 (Scheme 2). Swern oxidation of the alcohol 9 (Scheme 1) followed by addition of Me3SiBr 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 phosphonate 9 in 74% overall yield from 6. A modified Horner–Emmons9 reaction was then used for the Wittig reaction and cyclized to produce the desired polycyclic framework.

Reagents and conditions: (a) 2.0 equiv of (COCl)2, 3.0 equiv of BuLi, THF, 0 °C, 1 h, 97%; (b) 2.0 equiv of BrCH2COC1, 3.0 equiv of BuLi, THF, 0 °C, 1 h, 96%; (c) 2.0 equiv of (COCl)2, 3.0 equiv of BuLi, THF, 0 °C, 1 h, 98%; (d) 2.0 equiv of TBAF, THF, 25 °C, 1 h, 100%; (e) 2.0 equiv of BrCH2COC1, 3.0 equiv of BuLi, THF, 0 °C, 1 h, 98%; (f) 2.0 equiv of TBABF, THF, 25 °C, 2 h, 100%; (g) 2.0 equiv of LiCl, CH3CN, 25 °C, 3 h, 88%; (h) 1.5 equiv of DIBALH, CH2Cl2, -78 °C, 3 h, 90%; (i) 2.0 equiv of PPh3, CH2CN, 25 °C, 3 h, 88%; (j) 1.5 equiv of DBH, CH2Cl2, -78 °C, 0.5 h, 98%; (k) 1.0 equiv of BF3·Et2O, 0.5 equiv of Et3SiH, CH2Cl2, -10 °C, 0.5 h, 97%; (l) 1.0 equiv of Li, NH3·H2O, THF, -78 °C, 1.5 h, 100%; (m) 1.1 equiv of TiCl4, 3.0 equiv of pyridine, CH2Cl2, 25 °C, 12 h, 70%; (n) 1.0 equiv of Na, acetone, 60 °C, 12 h, 83%; (o) 1.5 equiv of TMSimidazole, CH2Cl2, 25 °C, 0.5 h, 100%; (p) 2.0 equiv of P2P2, CH3CN, 65 °C, 15 h, 100%; (q) 1.0 equiv of SiMe3, CH2Cl2, 25 °C, 15 h, 100%.

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

Scheme 1* Synthesis of the AFG Ring System 3

![Diagram of the synthetic pathway for truncated brevetoxin B](image)

*Reagents and conditions: (a) 2.0 equiv of (COCl)2, 3.0 equiv of DMSO, CH3Cl, -78 °C, then 7.0 equiv of Et3N, 1 h, 100%; (b) 2.0 equiv of Me3SiBr, THF, 0 °C, 1 h, 96%; (c) 2.0 equiv of (COCl)2, 3.0 equiv of DMSO, CH3Cl, -78 °C, then 7.0 equiv of Et3N, 1 h, 98%; (d) 2.0 equiv of TBABF, THF, 25 °C, 2 h, 100%; (e) 2.0 equiv of BrCH2COC1, 3.0 equiv of BuLi, THF, 0 °C, 1 h, 98%; (f) 2.0 equiv of BF3·Et2O, 0.5 equiv of Et3SiH, CH2Cl2, -10 °C, 0.5 h, 97%; (g) 1.0 equiv of Li, NH3·H2O, THF, -78 °C, 1.5 h, 100%; (h) 1.1 equiv of TiCl4, 3.0 equiv of pyridine, CH2Cl2, 25 °C, 12 h, 70%; (i) 1.0 equiv of Na, acetone, 60 °C, 12 h, 83%; (m) 1.5 equiv of TMSimidazole, CH2Cl2, 25 °C, 0.5 h, 100%; (p) 2.0 equiv of P2P2, CH3CN, 65 °C, 15 h, 100%.

**Scheme 2**

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

Scheme 1* Synthesis of the AFG Ring System 3

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*Reagents and conditions: (a) 2.0 equiv of (COCl)2, 3.0 equiv of DMSO, CH3Cl, -78 °C, then 7.0 equiv of Et3N, 1 h, 100%; (b) 2.0 equiv of Me3SiBr, THF, 0 °C, 1 h, 96%; (c) 2.0 equiv of (COCl)2, 3.0 equiv of DMSO, CH3Cl, -78 °C, then 7.0 equiv of Et3N, 1 h, 98%; (d) 2.0 equiv of TBABF, THF, 25 °C, 2 h, 100%; (e) 2.0 equiv of BrCH2COC1, 3.0 equiv of BuLi, THF, 0 °C, 1 h, 98%; (f) 2.0 equiv of BF3·Et2O, 0.5 equiv of Et3SiH, CH2Cl2, -10 °C, 0.5 h, 97%; (g) 1.0 equiv of Li, NH3·H2O, THF, -78 °C, 1.5 h, 100%; (h) 1.1 equiv of TiCl4, 3.0 equiv of pyridine, CH2Cl2, 25 °C, 12 h, 70%; (i) 1.0 equiv of Na, acetone, 60 °C, 12 h, 83%; (m) 1.5 equiv of TMSimidazole, CH2Cl2, 25 °C, 0.5 h, 100%; (p) 2.0 equiv of P2P2, CH3CN, 65 °C, 15 h, 100%.

**Scheme 2**

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Communications to the Editor

Scheme 2* Synthesis of the IJK Ring System 4

Scheme 3* Synthesis of Truncated Brevetoxin B [AFGHIJK] 2

*Reagents and conditions: (a) 3.0 equiv of CH₂CH₂(OH)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 (COCl)₂, 3.0 equiv of DMSO, CH₂Cl₂, -78 °C, 0.5 h, then 7.0 equiv of Et₂N, 100%; (d) 2.0 equiv of Ph₂C—CHO, CH₂Cl₂, 25 °C, 5 h, 96% (E/Z = 4:1); (e) H₂, Pd(OH)₂, THF, 25 °C, 40 min, 14 h, 100%; (f) 2.0 equiv of LIAH₄, THF, 25 °C, 4 h, 92%; (g) 1.1 equiv of TPSCI, 2.0 equiv of Et₂N, 1.0 equiv of H₂O, 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 equiv CH₂Cl₂/Meth, 0 °C, 2 h, 97%; (j) 1.0 equiv of TBSOTf, 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(OH)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 H₂O₂, 5.0 equiv of Et₂N, 1.1 equiv of Et₂N, 1.1 equiv CH₂Cl₂/DMSO, 0 °C, 1.5 h, 92%. TBS = Si(TBu)_2Me, TPS = Si(TBu)_2Ph, NMO = 4-methylmorpholine N-oxide, TPAP = tetrapropylammonium perruthenate.

*Reagents and conditions: (a) 1.0 equiv of n-BuLi, 2.0 equiv of HMPA, THF, -78 °C, 1 h, 97%; (b) 0.2 equiv of PPTS, 1.1 equiv CH₂Cl₂/Meth, 25 °C, 1 h, 91%; (c) 4.0 equiv of AgClO₄, 2.0 equiv of NaN₃CO₃, SiO₂, 4 Å molecular sieves, CH₂NO₂, 25 °C, 30 h, 90%; (d) 4.0 equiv of CH₂Cl₂/NH₃, 25 °C, 3 h, 95%; (e) 2.0 equiv of TBSOTf, 2.0 equiv of Na₂CO₃, 25 °C, 2 h, 100%; (f) 1.0 equiv of Dess–Martin periodinane, CH₂Cl₂, 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—T, 20 equiv of Et₂N, CH₂Cl₂, 25 °C, 12 h, 75%; (i) 1.0 equiv of Na₂CO₃, CH₂Cl₂, 25 °C, 30 min, 97%. TBS = Si(TBu)_2Me, TPS = Si(TBu)_2Ph, TMS = SiMe₃.