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Brevetoxin B (1), a member of the "red tide"-associated class of marine neurotoxins, possesses a striking biological profile as a sodium channel modulator 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, 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 and provide useful information about their receptor.

An attractive bond disconnection across the oxocene ring of 2 revealed two domains (3 and 4) that could be coupled in the receptor. Consideration of the brevetoxins and provide useful information about their receptor. 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 and provide useful information about their receptor.

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**Scheme 1. Synthesis of the AFG Ring System 3**

*Reagents and conditions: (a) 2.0 equiv of (COCl)₂, 3.0 equiv of Py, CH₂Cl₂, 0 °C, 5 h, 82%; (b) 2.0 equiv of Me₂N, CH₂Cl₂, -78 °C, then 7.0 equiv of Et₃SiH, 1 h, 98%; (c) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; (d) 2.0 equiv of BF₃·O₂Et, Et₂O, H₂, 0 °C, 98%; (e) 2.0 equiv of Br₂·MeOH, CO₂Me, 180 °C, 7 h, 98%; (f) neat (MeO)₂CCl₂, 65 °C, 15 h, 100%. TBS = SbBuMe₃, Bn = CH₂Ph, TMS = SiMe₃, TsO = OTs.*
Communications to the Editor

The acetonide and selective protection of the primary alcohol, ring segment of the parent compound (1), has a head-to-tail length treatment of the resulting aldehyde and hydrolytic cleavage of the primary TBS ether afforded alcohol followed by oxidation of the secondary alcohol, provided the

converted via desilylation, oxidation, and a Wittig reaction to the unsubstituted ether 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 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 desilylation, oxidation, and a Wittig reaction to the unsubstituted ether 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 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).

Truncated brevetoxin B (A[FGHIJK]) (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.4,12 for 1. Biological studies11 with 2 revealed no binding to the brevetoxin B receptor, supporting the notion that the length of the molecule is crucial for biological activity.13 The described chemistry sets the stage for the total synthesis of the natural brevetoxin B (1) and for further chemical biology studies.

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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.

† Reagents and conditions: (a) 3.0 equiv of CH2—CHO, MeOH, 25 °C, 4 h, 89%; (b) 2.0 equiv of TBAT, 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—CHO, CH2Cl2, 25 °C, 5 h, 96% (E/Z = 4:1); (e) H2, Pd(OH)2, THF, 25 °C, 40 h, 100%; (f) 2.0 equiv of LiAlH4, THF, 25 °C, 4 h, 92%; (g) 1.1 equiv of TPSiCl, 2.0 equiv of Et3N, 0.1 equiv of DMAP, CH2Cl2, 25 °C, 6 h, 95%; (h) 2.0 equiv of TBSOTf, 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, 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 SO3-pyridine, 5.0 equiv of Et3N, 1:1 CH2Cl2/DMSO, 0 °C, 1.5 h, 92%. TBS = Si(BuMe2)3, TPS = Si(BuPh2)3, TMS = SiMe3.

Scheme 2* Synthesis of the IJK Ring System 4

Scheme 3* Synthesis of Truncated Brevetoxin B [A[FGHIJK]] 2

Figure 2. ORTEP drawing of truncated brevetoxin B [A[FGHIJK]] 2.

* Reagents and conditions: (a) 1.0 equiv of n-BuLi, 2.0 equiv of HMPA, THF, -78 °C, 1 h, 97%; (b) 2.0 equiv of PPTS, 1:1 CH2Cl2/MeOH, 25 °C, 1 h, 91%; (c) 4.0 equiv of Ag2CO3, 2.0 equiv of Na2CO3, SiO2, 4 Å molecular sieves, CH3NO2, 25 °C, 30 h, 90%; (d) 4.0 equiv of Ph3SnH, 0.1 equiv of AlBN, toluene, 100 °C, 2 h, 99%; (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, 79%; (g) 3.0 equiv of Dess—Martin periodinane, CH2Cl2, 25 °C, 2 h, 100%; (h) 2.0 equiv of Me3N—CH2—I-, 20 equiv of Et3N, CH2Cl2, 25 °C, 12 h, 75%; (i) HpO2-pyridine, CH2Cl2, 25 °C, 30 min, 97%. TBS = Si(BuMe2)3, TPS = Si(BuPh2)3, TMS = SiMe3.