Total Synthesis of Truncated Brevetoxin B [AFGHIJK]

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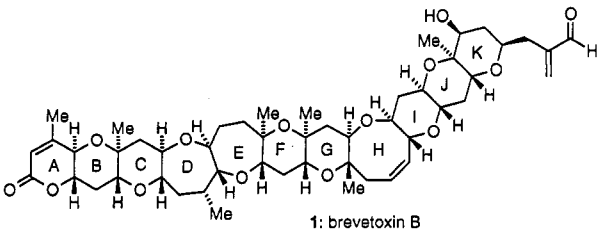
Received June 23, 1994

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 modulator[3] 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[3a,b] and provide useful information about their receptor.[3c-e]

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** (Scheme 1) and **4** (Scheme 2). Swern oxidation of the alcohol **5**[6] (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 phosphonate **9** in 74% overall yield from **6**. A modified Horner–Emmons[7] 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 $BF_3{\cdot}Et_2O/Et_3SiH$ *via* the intermediacy of lactol



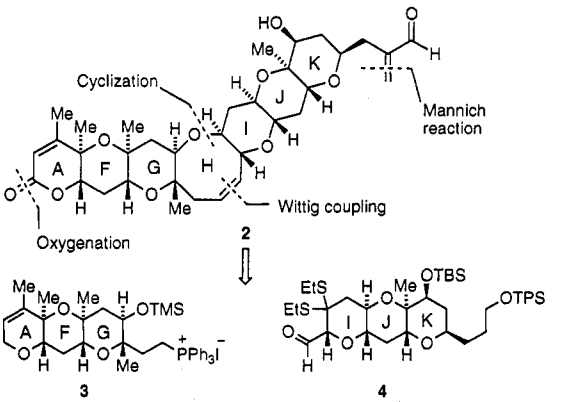
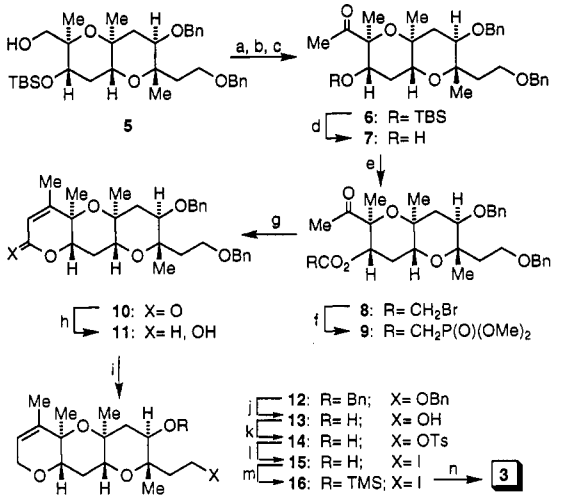


Figure 1. Structure of truncated brevetoxin B [AFGHIJK] (**2**) and retrosynthetic analysis.

Scheme 1.[a] Synthesis of the AFG Ring System **3**



[a] Reagents and conditions: (a) 2.0 equiv of $(COCl)_2$, 3.0 equiv of DMSO, CH_2Cl_2, −78 °C, then 7.0 equiv of Et_3N, 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, CH_2Cl_2, −78 °C, then 7.0 equiv of Et_3N, 1 h, 98%; (d) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 100%; (e) 2.0 equiv of $BrCH_2COCl$, 4.0 equiv of pyridine, CH_2Cl_2, 0 °C, 5 h, 82%; (f) neat $(MeO)_3P$, 180 °C (sealed tube), 3 h, 90%; (g) 2.0 equiv of $^iPr_2EtN$, 2.0 equiv of LiCl, CH_3CN, 25 °C, 3 h, 88%; (h) 1.5 equiv of DIBALH, CH_2Cl_2, −78 °C, 0.5 h, 98%; (i) 1.0 equiv of $BF_3{\cdot}Et_2O$, 5.0 equiv of Et_3SiH, CH_2Cl_2, −10 °C, 0.5 h, 97%; (j) 10.0 equiv of Li, NH_3, THF, −78 °C, 1.5 h, 100%; (k) 1.1 equiv of TsCl, 3.0 equiv of pyridine, CH_2Cl_2, 25 °C, 12 h, 70%; (l) 5.0 equiv of NaI, acetone, 60 °C, 12 h, 83%; (m) 1.5 equiv of TMS-imidazole, CH_2Cl_2, 25 °C, 0.5 h, 100%; (n) 8.0 equiv of PPh_3, CH_3CN, 65 °C, 15 h, 100%. TBS = Si^{t}BuMe$_2$, Bn = CH_2Ph, TMS = $SiMe_3$, TsO = 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 PPh_3 gave phosphonium salt **3** in quantitative yield.

The construction of aldehyde **4** commenced with diol **17**[8] (Scheme 2), which was first protected as an acetonide and then

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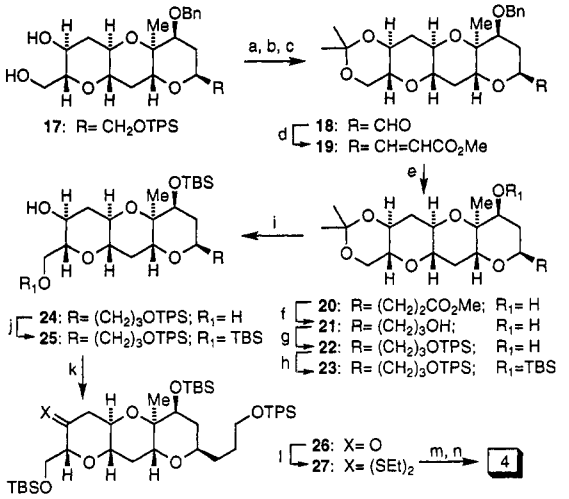
Scheme 2.[a] Synthesis of the IJK Ring System **4**



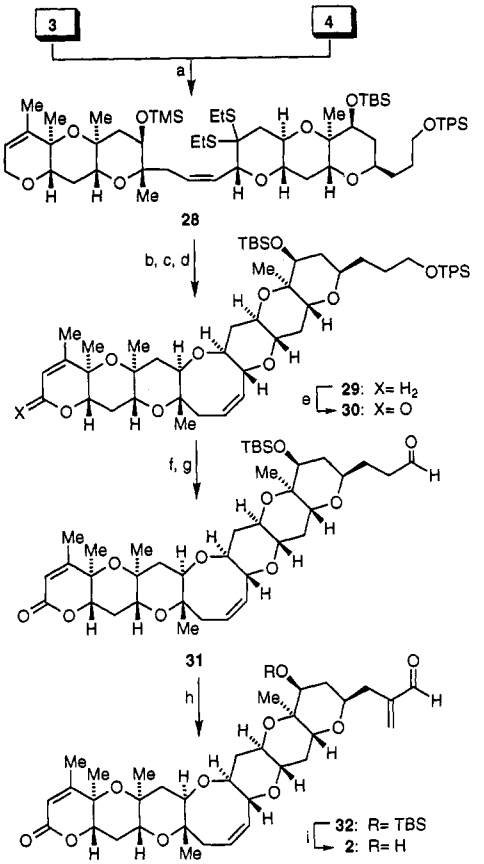
[a] Reagents and conditions: (a) 3.0 equiv of CH_2=C(OMe)Me, 0.2 equiv of CSA, CH_2Cl_2, 25 °C, 4 h, 89%; (b) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 97%; (c) 2.0 equiv of $(COCl)_2$, 3.0 equiv of DMSO, CH_2Cl_2, −78 °C, 0.5 h, then 7.0 equiv of Et_3N, 100%; (d) 2.0 equiv of Ph_3P=$CHCO_2Me$, CH_2Cl_2, 25 °C, 5 h, 96% (*E*:*Z* = 4:1); (e) H_2, $Pd(OH)_2$, THF, 25 °C, 40 psi, 14 h, 100%; (f) 2.0 equiv of $LiAlH_4$, THF, 25 °C, 4 h, 92%; (g) 1.1 equiv of TPSCl, 2.0 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 6 h, 95%; (h) 2.0 equiv of TBSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 100%; (i) 0.2 equiv of CSA, 1:1 CH_2Cl_2/MeOH, 0 °C, 2 h, 87%; (j) 1.0 equiv of TBSCl, 2.0 equiv of imidazole, DMF, 0 °C, 1 h, 94%; (k) 1.5 equiv of NMO, 0.02 equiv of TPAP, CH_3CN, 25 °C, 1 h, 96%; (l) 3.0 equiv of EtSH, 1.1 equiv of $Zn(OTf)_2$, CH_2Cl_2, 25 °C, 3 h; (m) 0.2 equiv of CSA, MeOH, 25 °C, 1 h, 74% (over two steps); (n) 5.0 equiv of SO_3·pyridine, 5.0 equiv of Et_3N, 1:1 CH_2Cl_2/DMSO, 0 °C, 1.5 h, 92%. TBS = Si^tBuMe_2, TPS = Si^tBuPh_2, Bn = CH_2Ph, NMO = 4-methylmorpholine *N*-oxide, 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 H_2/$Pd(OH)_2$ and $LiAlH_4$ 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. Thioketalization 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 $AgClO_4$-induced cyclization and desulfurization,[9] 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[10] 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 brevetoxin 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[1,3a] for **1**. Biological studies[11] with **2** revealed no binding to the brevetoxin B receptor, supporting the notion that the length of the molecule is crucial for biological activity.[3a,b] The described chemistry sets the stage for the total synthesis of the natural brevetoxin B (**1**) and for further chemical biology studies.

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



[a] Reagents and conditions: (a) 1.0 equiv of *n*-BuLi, 2.0 equiv of HMPA, THF, −78 → 25 °C, 1 h, 57%; (b) 0.2 equiv of PPTS, 1:1 CH_2Cl_2/MeOH, 25 °C, 1 h, 91%; (c) 4.0 equiv of $AgClO_4$, 2.0 equiv of $NaHCO_3$, SiO_2, 4-Å molecular sieves, CH_3NO_2, 25 °C, 30 h, 90%; (d) 4.0 equiv of Ph_3SnH, 0.1 equiv of AIBN, toluene, 100 °C, 2 h, 98%; (e) 8.0 equiv of PCC, CH_2Cl_2, 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, CH_2Cl_2, 25 °C, 2 h, 100%; (h) 2.0 equiv of Me_2N=$CH_2^+I^-$, 20 equiv of Et_3N, CH_2Cl_2, 25 °C, 12 h, 79%; (i) HF·pyridine, CH_2Cl_2, 25 °C, 30 min, 97%. TBS = Si^tBuMe_2, TPS = Si^tBuPh_2, TMS = $SiMe_3$.

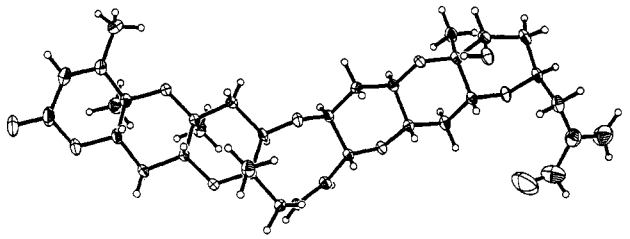


Figure 2. ORTEP drawing of truncated brevetoxin B [AFGHIJK] **2**.

Acknowledgment. We thank Drs. Raj Chadha, Gary Siuzdak, and Dee H. Huang for X-ray, mass, and NMR spectroscopic assistance. This work was financially supported by the National Institutes of Health and by fellowships from the Deutsche Forschungsgemeinschaft (J.T.), the Netherlands Organization for Scientific Research (NWO) (F.P.J.T.R.), UNITIKA Ltd. (M.S.), and Rhône Poulenc S. A. (E.U.).

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.

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