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 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 **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

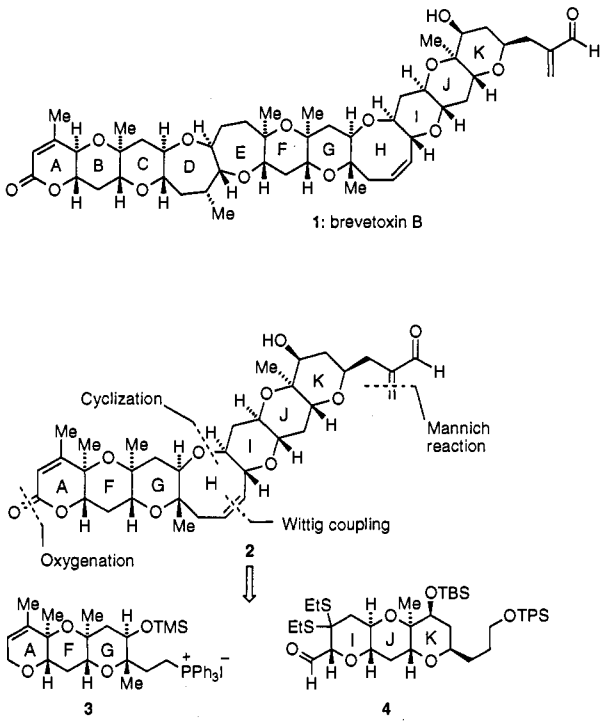
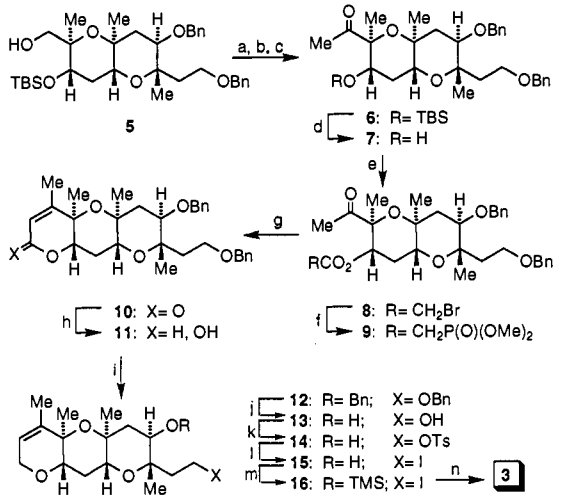


Figure 1. Structure of truncated brevetoxin B [AFGHIJK] (**2**) and retrosynthetic analysis.

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.

(1) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855.

(2) Shimizu, Y. *Pure Appl. Chem.* **1982**, *54*, 1973. Shimizu, Y. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, Chapter 1. Nakanishi, K. *Toxicon* **1985**, *23*, 473. *International Symposium on Red Tides*; Okaichi, T., Anderson, D. M., Nemoto, T., Eds.; Elsevier: New York, 1989. *Toxic Dinoflagellates*; Anderson, D. M., White, A. W., Baden, D. G., Eds.; Elsevier: New York, 1985.

(3) (a) Rein, K. S.; Baden, D. G.; Gawley, R. E. *J. Org. Chem.* **1994**, *59*, 2101. (b) Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G. *J. Org. Chem.* **1994**, *59*, 2107. (c) Baden, D. G.; Mende, T. J.; Szmant, A. M.; Trainer, V. L.; Edwards, R. A.; Roszell, L. E. *Toxicon* **1988**, *26*, 97. (d) Poli, M. A.; Mende, T. J.; Baden, D. G. *Mol. Pharmacol.* **1986**, *30*, 129. (e) Catterall, W. A. *Annu. Rev. Biochem.* **1986**, *55*, 953.

(4) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Oglivie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263. Nicolaou, K. C.; Prasad, C. V. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4988. Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040. Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335. Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666. Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6676. Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1362.

(5) For the total synthesis of the natural hemibrevetoxin B, see: Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935. Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558.

(6) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.

(7) Senfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

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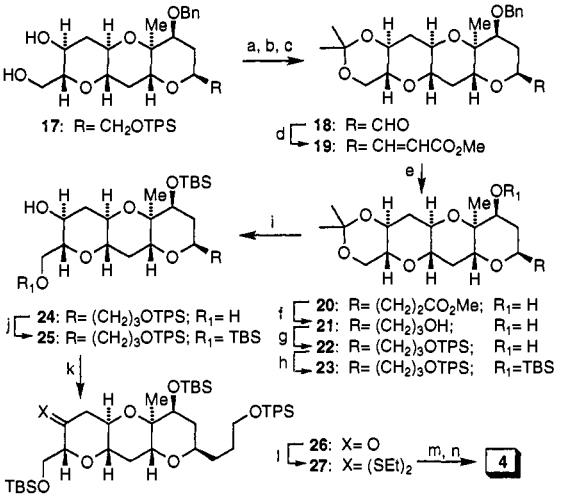
Scheme 2.[a] Synthesis of the IJK Ring System **4**



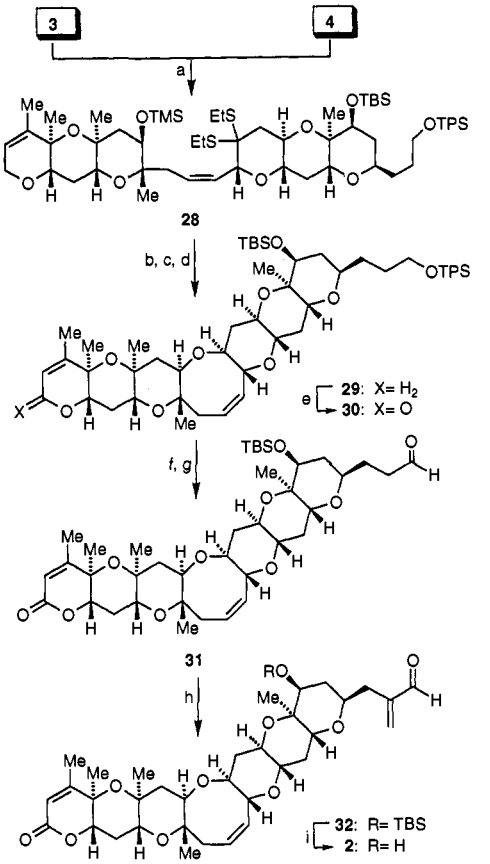
[a] Reagents and conditions: (a) 3.0 equiv of CH_2=C(OMe)Me, 0.2 equiv of CSA, CH_2Cl_2, 25 °C, 4 h, 89%; (b) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 97%; (c) 2.0 equiv of $(COCl)_2$, 3.0 equiv of DMSO, CH_2Cl_2, −78 °C, 0.5 h, then 7.0 equiv of Et_3N, 100%; (d) 2.0 equiv of Ph_3P=$CHCO_2Me$, CH_2Cl_2, 25 °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 = $SiMe_3$.

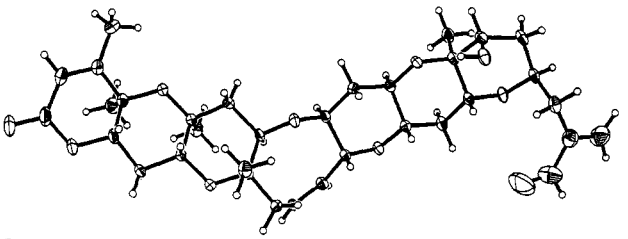


Figure 2. ORTEP drawing of truncated brevetoxin B [AFGHIJK] **2**.

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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.

(8) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682.
(9) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.
(10) Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, Y.; Sugihara, T.; Ogasawara, K. *Chem. Lett.* **1989**, *33*, 1283.
(11) We thank Professor D. G. Baden for these biological studies.