Total Synthesis of Brevetoxin B. 2. Completion

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In the preceding communication[1] we defined phosphonium salt **3** and aldehyde **2** (Figure 1) as key intermediates for the total synthesis of brevetoxin B (**1**) and described the construction of advanced intermediate **4** (Scheme 1) required for the synthesis of **3**. Herein we delineate the chemistry that led to the advancement of **4** to **3**, the coupling of **3** with **2**, and the completion of the total synthesis of brevetoxin B (**1**).

The initial task of completing the ABCDEFG ring framework of brevetoxin B from intermediate **4** proceeded as summarized in Scheme 1. Thus regio- and stereospecific epoxide opening[2] by the internal hydroxyl group of **4** under acid conditions afforded **5**, which was silylated to give **6** (76% over two steps). Ozonolysis of **6** led to the corresponding aldehyde **7**, which was reacted with MeMgCl, and the produced alcohol was oxidized (Dess−Martin) to afford methyl ketone **8** (91% overall yield).[3,4] Desilylation of the latter compound with TBAF followed by esterification with bromoacetyl chloride afforded bromo ester **10** via alcohol **9** in 73% overall yield. Arbuzov reaction of **10** with $(MeO)_3P$ then led to phosphonate **11**, which underwent intramolecular condensation with the carbonyl group under the influence of $^iPr_2EtN$−LiCl[5] to give lactone **12** (89% over two steps). Deoxygenation of the latter compound via a two-step reductive process (DIBAL-H followed by $BF_3{\cdot}Et_2O$−Et_3SiH) led to heptacyclic polyether **14** via compound **13** (93% overall). Finally, a conventional sequence (Li/liquid NH_3 induced debenzylation, selective monotosylation of the primary alcohol, iodide displacement, silylation, and reaction with Ph_3P) afforded the requisite phosphonium salt **3** (67% overall).[3,4] X-ray crystallographic analysis[6] of the crystalline iodide **18** (mp 192−193 °C, from acetonitrile) confirmed the stereochemistry of all asymmetric centers of the brevetoxin B ABCDEFG fragments shown in Scheme 1 (see ORTEP drawing, Figure 2).

The final stages of the total synthesis of brevetoxin B (**1**) are described in Scheme 2. The ylide generated from **3** reacted with aldehyde **2**[3] (TBS = ^{t}BuMe$_2$Si; TPS = ^{t}BuPh$_2$Si) to afford the *Z*-olefin **19**, which without further purification was selectively monodesilylated to furnish alcohol **20** in 75% overall yield. $AgClO_4$-induced[7] ring closure then secured the oxocene framework, while reductive desulfurization[7] and subsequent PCC oxidation completed the brevetoxin B skeleton (**22**) via the corresponding derivative **21** (72% overall). Selective desilylation of the primary alcohol, followed by oxidation to the aldehyde and treatment with Eschenmoser's salt,[8] furnished monosilylated brevetoxin B (**24**) in 57% yield (over three steps).

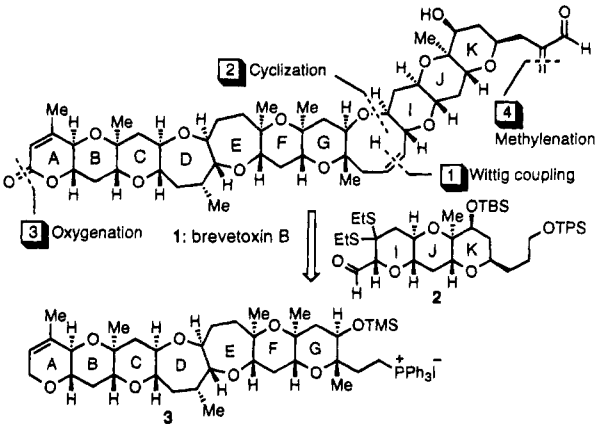
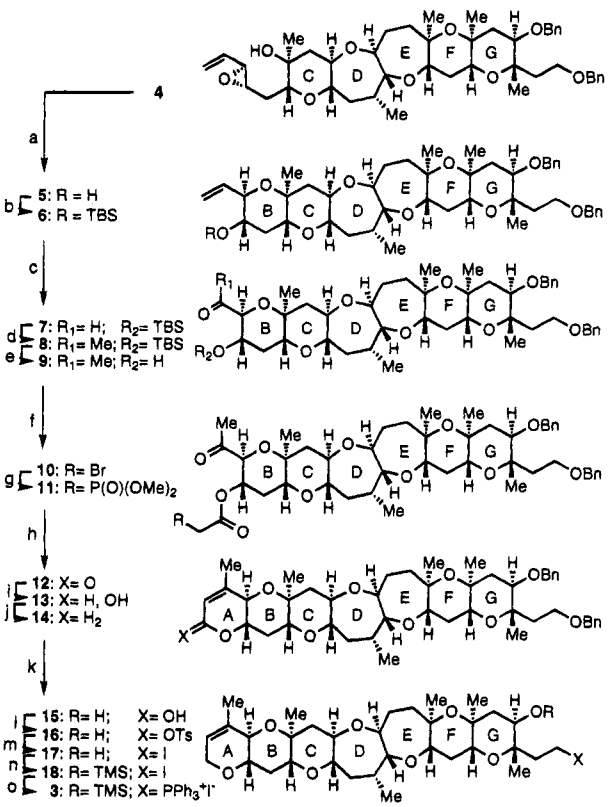


Figure 1. Strategic bond disconnections of brevetoxin B (**1**).

Scheme 1. Synthesis of the ABCDEFG Ring Fragment **3**



[a] Reagents and conditions: (a) 0.2 equiv of PPTS, CH_2Cl_2, 0 °C, 12 h; (b) 1.5 equiv of TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 76% (over two steps); (c) O_3, CH_2Cl_2, −78 °C, 1 min, then 2.0 equiv of Ph_3P, 0.5 h, 100%; (d) 2.0 equiv of MeMgCl, THF, 0 °C, 1 h, then 2.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 2 h, 91%; (e) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 90%; (f) 2.0 equiv of $BrCH_2COCl$, 4.0 equiv of pyridine, CH_2Cl_2, 0 °C, 20 min, 81%; (g) neat $(MeO)_3P$, 90 °C (sealed tube), 5 h; (h) 2.0 equiv of $^iPr_2EtN$, 2.0 equiv of LiCl, CH_3CN, 25 °C, 3 h, 89% (over two steps); (i) 1.5 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h; (j) 1.0 equiv of $BF_3{\cdot}Et_2O$, 5.0 equiv of Et_3SiH, CH_2Cl_2, −10 °C, 0.5 h, 93% (over two steps); (k) 10.0 equiv of Li, NH_3, −78 °C, 1.5 h, 92%; (l) 1.1 equiv of TsCl, 3.0 equiv of pyridine, CH_2Cl_2, 25 °C, 12 h, 79%; (m) 5.0 equiv of NaI, acetone, 60 °C, 5 h; (n) 1.5 equiv of TMS-imidazole, CH_2Cl_2, 25 °C, 0.5 h, 93% (over two steps); (o) 10.0 equiv of PPh_3, CH_3CN, 65 °C, 40 h, 99%.

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(6) We thank Dr. Raj Chadha of the Scripps Research Institute for this X-ray crystallographic analysis.
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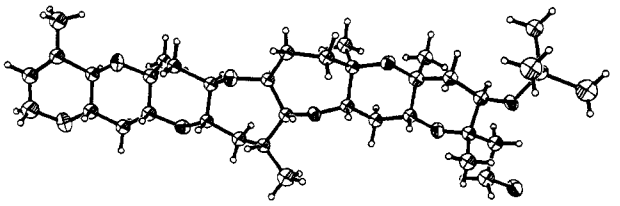
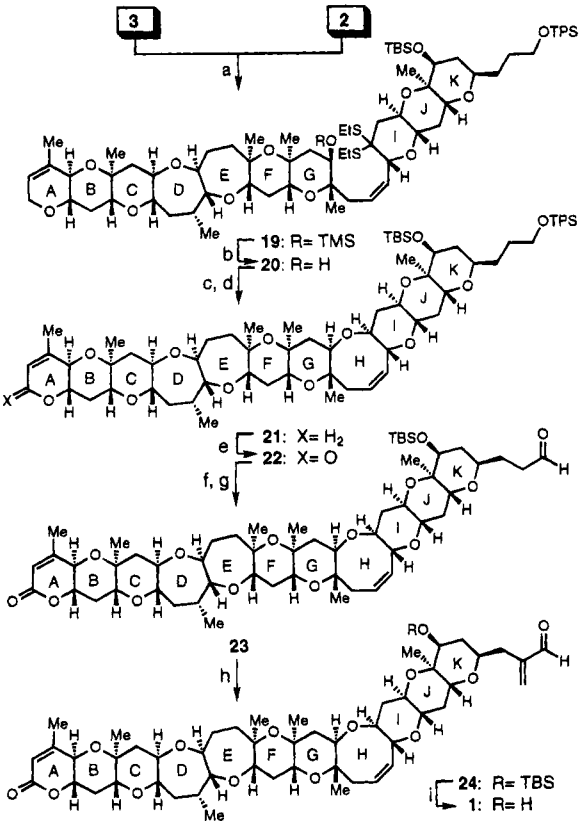


Figure 2. ORTEP drawing of **18**.

Scheme 2. Synthesis of Brevetoxin B (**1**)



[a] Reagents and conditions: (a) 1.0 equiv of *n*-BuLi, 2.0 equiv of HMPA, THF, −78 °C, then 1.5 equiv of **2**, 10 min; (b) 0.2 equiv of PPTS, CH_2Cl_2/MeOH (1:1), 25 °C, 1 h, 75% (over two steps); (c) 4.0 equiv of $AgClO_4$, 2.0 equiv of $NaHCO_3$, SiO_2, 4 Å molecular sieves, CH_3NO_2, 25 °C, 40 h, 85%; (d) 10.0 equiv of Ph_3SnH, 0.1 equiv of AIBN, toluene, 100 °C, 2 h, 100%; (e) 8.0 equiv of PCC, benzene, 80 °C, 3 h, 85%; (f) 1.0 equiv of TBAF, THF, 25 °C, 13 h, 69%; (g) 3.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 25 °C, 0.5 h, 100%; (h) 2.0 equiv of $Me_2N{=}CH_2{}^+I^-$, 20 equiv of Et_3N, CH_2Cl_2, 25 °C, 16 h, 83%; (i) HF·pyridine, CH_2Cl_2, 0 °C, 0.5 h, 91%.

Finally, deprotection of **24** with HF·pyridine generated brevetoxin B (**1**) in 91% yield. Synthetic **1** was identical with an authentic sample of natural brevetoxin B (TLC, HPLC, ^1H and ^{13}C NMR, IR, MS, $[\alpha]_D$, and mp).[9]

Accompanied by several discoveries and developments[10] in synthetic technology and strategy, the total synthesis of brevetoxin B (**1**) respresents a major advance in complex molecule construction.[11] Furthermore, the reported total synthesis now renders readily available designed compounds of the brevetoxin class for biological studies.[12]

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Supplementary Material Available: For preceding communication:[1] Schemes for the preparation of compounds **17a**, **20**, and bis(*p*-bromobenzoate) derivative of debenzylated **6**, selected physical data for compounds **14**, **6**, **23**, **24**, **5**, **29**, **30**, and **4**, and X-ray crystallographic data for the bis(*p*-bromobenzoate) derivative of debenzylated **6** (20 pages). For this communication: Listing of selected physical data for compounds **5**, **9**, **12**, **18**, **20**, **21**, **22**, **24**, and **1** and X-ray crystallographic data for compound **18** (24 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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(11) For a discussion of complex natural products syntheses, see: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, in press.

(12) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.