

Total Synthesis of Brevetoxin B. 2. Completion

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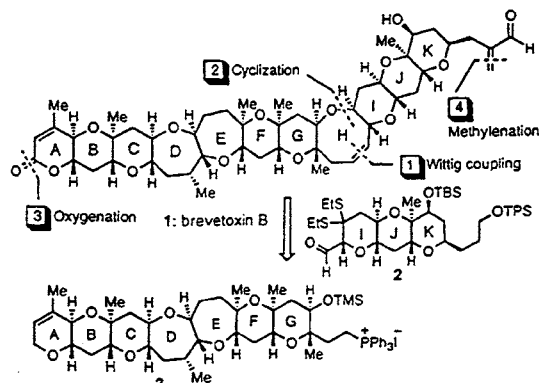
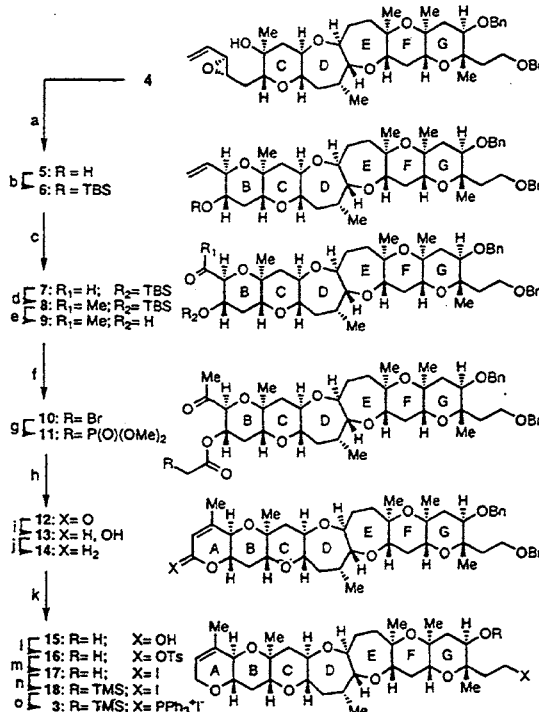
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In the preceding communication¹ we defined phosphonium salt **3** and aldehyde **2** (Figure 1) as key intermediates for the total synthesis of brevetoxin B (**1**) and described the construction of advanced intermediate **4** (Scheme 1) required for 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 opening² 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 ⁱPr₂EtN–LiCl⁵ to give lactone **12** (89% over two steps). Deoxygenation of the latter compound via a two-step reductive process (DIBAL–H followed by BF₃·Et₂O–Et₃SiH) led to heptacyclic polyether **14** via compound **13** (93% overall). Finally, a conventional sequence (Li/liquid NH₃ induced debenzoylation, selective monotosylation of the primary alcohol, iodide displacement, silylation, and reaction with Ph₃P) afforded the requisite phosphonium salt **3** (67% overall).^{3,4} X-ray crystallographic analysis⁶ 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 = ^tBuMe₂Si; TPS = ^tBuPh₂Si) to afford the Z-olefin **19**, which without further purification was selectively monodesilylated to furnish alcohol **20** in 75% overall yield. AgClO₄-induced⁷ ring closure then secured the oxocene

Figure 1. Strategic bond disconnections of brevetoxin B (**1**).Scheme 1. Synthesis of the ABCDEFG Ring Fragment **3**

Reagents and conditions: (a) 0.2 equiv of PPTS, CH₂Cl₂, 0 °C, 12 h; (b) 1.5 equiv of TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 1 h, 76% (over two steps); (c) O₃, CH₂Cl₂, –78 °C, 1 min, then 2.0 equiv of Ph₃P, 0.5 h, 100%; (d) 2.0 equiv of MeMgCl, THF, 0 °C, 1 h, then 2.0 equiv of Dess–Martin periodinane, CH₂Cl₂, 25 °C, 2 h, 91%; (e) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 90%; (f) 2.0 equiv of BrCH₂COCl, 4.0 equiv of pyridine, CH₂Cl₂, 0 °C, 20 min, 81%; (g) neat (MeO)₃P, 90 °C (sealed tube), 5 h; (h) 2.0 equiv of ⁱPr₂EtN, 2.0 equiv of LiCl, CH₃CN, 25 °C, 3 h, 89% (over two steps); (i) 1.5 equiv of DIBAL–H, CH₂Cl₂, –78 °C, 0.5 h; (j) 1.0 equiv of BF₃·Et₂O, 5.0 equiv of Et₃SiH, CH₂Cl₂, –10 °C, 0.5 h, 93% (over two steps); (k) 10.0 equiv of Li, NH₃, –78 °C, 1.5 h, 92%; (l) 1.1 equiv of TsCl, 3.0 equiv of pyridine, CH₂Cl₂, 25 °C, 12 h, 79%; (m) 5.0 equiv of NaI, acetone, 60 °C, 5 h; (n) 1.5 equiv of TMS–imidazole, CH₂Cl₂, 25 °C, 0.5 h, 93% (over two steps); (o) 10.0 equiv of PPh₃, CH₃CN, 65 °C, 40 h, 99%.

framework, while reductive desulfurization⁷ 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),

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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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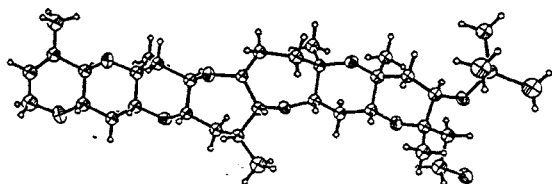
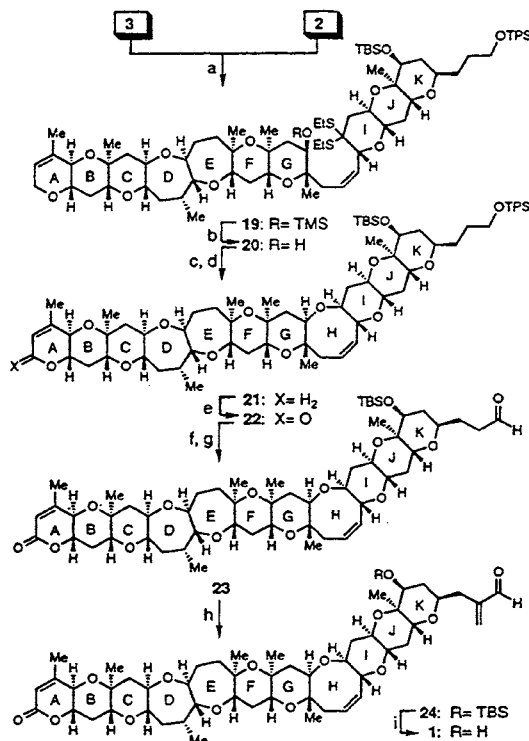


Figure 2. ORTEP drawing of 18.

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, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (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_2NO_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 $\text{Me}_2\text{N}=\text{CH}_2^+\text{I}^-$, 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 developments¹⁰ in synthetic technology and strategy, the total synthesis of brevetoxin B (1) represents 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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(12) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.