Total Synthesis of Brevetoxin B. 2. Completion


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Received November 1, 1994

In the preceding communication 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 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 treated with MeMgCl, and the produced alcohol was oxidized (Dess-Martin) to afford methyl ketone 8 (91% overall yield). Desilylation of the latter compound with TBAF followed by esterification with bromoacetyl chloride afforded bromo ester 10 via alcohol 9 in 73% overall yield. Arbusov reaction of 10 with (MeO)2P then led to phosphonate 11, which underwent intramolecular condensation with the carbonyl group under the influence of Pr3En-LiCl 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 polycyclic 14 via compound 13 (93% overall). Finally, a conventional sequence (Li/lIq quenched NH3 induced deprotection, selective mesylation of the primary alcohol, iodide displacement, silylation, and reaction with Ph3P) afforded the requisite phosphonium salt 3 (67% overall). X-ray crystallographic analysis 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 (TBS = BuMe2Si; TPS = BuPh2Si) to afford the Z-olefin 19, which without further purification was selectively monodesilylated to furnish alcohol 20 in 75% overall yield. AgClO4-induced ring closure then secured the oxocene framework, while reductive desulfurization and subsequent PCC oxidation completed the brevetoxin B skeleton (22) via the corresponding derivative 21 (72% overall). Selective deacetylation of the primary alcohol, followed by oxidation to the aldehyde and treatment with Eschenmoser’s salt furnished monomethylated brevetoxin B (24) in 57% yield (over three steps).
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Figure 2. ORTEP drawing of 18.

Scheme 2. Synthesis of Brevetoxin B (1)

* 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, CH₂Cl₂/MeOH (1:1), 25 °C, 1 h, 75% (over two steps); (c) 4.0 equiv of AgClO₄, 2.0 equiv of NaHCO₃, SiO₂, 4 Å molecular sieves, CH₂Cl₂, 25 °C, 40 h, 85%; (d) 10.0 equiv of PPh₃SnH, 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, CH₂Cl₂, 25 °C, 0.5 h, 100%; (h) 2.0 equiv of Me₂N⁺CH₃⁻, 20 equiv of BuN⁺, CH₂Cl₂, 25 °C, 16 h, 83%; (i) HF-pyridine, CH₂Cl₂, 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 ¹³C NMR, IR, MS, [α]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

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

Supplementary Material Available: For preceding communication1 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.

JA9435540


(9) We thank Drs. D. G. Baden and R. E. Gawley for a sample of natural brevetoxin B (1).


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