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Abstract: The second generation strategy for the total synthesis of brevetoxin B (1) is presented. According to this strategy, the heptacyclic [ABCDEF] phoshonium iodide 4 and the tricyclic [JK] aldehyde 3 were defined as the precursors for the brevetoxin B skeleton. The Yamaguchi lactonization was successfully applied for the formation of the [EFG] and [DEFG] lactones (15 — 7) and (29 — 6), respectively. The required appendage on ring [E] was efficiently introducted via a Mural coupling, involving addition of a higher order organocuprate derived from iodide 20 to the lactone-derived enol triflate 16 (16 — 25). The minor epimer of the resulting product 66 was then converted to the desired isomer 6c via disproportionation using an Ir(I) catalyst. A number of approaches were considered for further elaboration of lactone 6. Among them a convenient Cr/Ni-promoted coupling reaction was developed and applied to the introduction of the side chain on ring D. The scope and generality of this reaction was examined with a variety of aldehydes (e.g., 39, 59, and 62). Construction of 38 was thus achieved from vinyl triflate 36 and the ring B aldehyde 39. However, the projected intramolecular Michael addition (41 — 42) and reductive hydroxyl ketone cyclization (47 — 48) failed to yield ring C. Fattion cyclization afforded the pentacyclic lactone [CDEFG] (51 — 52), which resisted further useful functionalization. Using the more elaborate aldehyde 62, the Cr/Ni coupling reaction afforded allylic alcohol 64, which then served as a precursor to the pentacyclic lactol 80. The latter compound also resisted advanced to more elaborate intermediates, leading to abandonment of this approach and the formulation of a new strategy.

Introduction

In the preceding paper,1 we discussed first generation strategies toward the total synthesis of brevetoxin B (1, Scheme 1) and described the synthesis of several key intermediates required for a projected construction of the target molecule. The successes and failures in that campaign yielded information that led us to design a second generation of strategies toward brevetoxin B (1). In this article, we describe these new strategies which led to the successful construction of the DEFG region, containing the dioxepane system of the molecule and to the formulation of the third and final approach to brevetoxin B (1).2

Second Retrosynthetic Analysis and Strategy

Our original strategy toward brevetoxin B (1) postulated an optimally convergent route in which three equally complex fragments3a-c were to be constructed, coupled, and elaborated to form the oxocene and dioxepane regions of the molecule.4 The effectiveness and reliability of the hydroxy dialketal cyclization in forming the oxocene system coupled with the difficulties associated with the construction of the challenging dioxepane framework forced us to adopt the reverse approach in which the dioxepane region would be secured first. According to this newly evolved strategy, which was based on the retrosynthetic analysis of Scheme 1, the final ring closure would involve retro oxocene formation (1 — 2) defining hydroxy dioxetate 2 as a key advanced intermediate. The latter compound (2) was projected to be derived from aldehyde 3 and phosphonium salt 4 via a Wittig coupling reaction. Attempting to preserve as much convergency as possible in the scheme, intermediate 4 was disconnected as indicated on the structure, revealing fragments 5 (ring system B) and 6 (ring system DEF) as potential precursors. Both intermediates 5 and 6 were projected to arise from 2-deoxy-6-ribose (9). The latter fragment (6) would require, according to this plan, the intermediacy of tricycle 7 and bicycle 8. Both lactones 6 and 7 are disconnected by retro lactonization reactions, whereas bicyclic system 8 could be disconnected sequentially by two retro hydroxy epoxide cyclizations as shown in Scheme 1. Below, we describe first the construction of the DEFG lactone 6, and then a number of attempts to elaborate compound 6 further along the path toward brevetoxin B (1).

Construction of the DEFG Lactone 6

The plan for the construction of the DEFG lactone 6 required the synthesis and elaboration of the EFG tricyclic lactone 7 (Scheme 1). The latter compound (7) was prepared from the previously reported FG ring system 8 as shown in Scheme 2. Thus, Swern oxidation of 8 led to aldehyde 10 (100% yield) which was olefinated with the appropriate ylide (TBSO-

Scheme 2. Construction of the EFO Ring System 16

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(9) Tsushima, K.; Araki, K.; Murai, A. Chem. Lett. 1989, 5571. The synthesis of 10 proceeded in a straightforward manner from y-valerolactone (7) in order to allow the formation of the D ring. To this end, iodides 21 and 22 (both racemic, Table 1) were converted to their lithio derivatives by halogen–metal exchange (+-BuLi) and thence to the higher order cuprates RLi/Cu(2-thienyl)CNLi. 10 Proceedings will be described in a subsequent publication.

Recycling of Epimeric Lactone 6β to Lactone 6

Reagents and conditions: (a) 1.5 equiv of LHMDS, 1.5 equiv of HMPA, 2.0 equiv of PhSeBr, THF, -78—30 °C, 1 h; (b) 2.0 equiv of mCPBA, THF, 25 °C, 75% (2 steps); (c) 2.0 equiv of LHMDS, 2.0 equiv of HMPA, -78 °C, THF, 2 min; then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 80% (2 steps); (d) 2.0 equiv of LiOH, MeOH:H2O (4:1), 30 min, 100%; (e) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 90% of a 1:1 mixture of epimers; (e) 2.0 equiv of LiOH, MeOH:H2O (4:1), 30 min, 100%; (f) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et3N, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 1 h, 90% of a 1:1 mixture of 6 and 6β (separated by chromatography). COD = 1,5-cyclooctadiene, Cy = cyclohexyl.

Table 1. Synthesis of Extended Oxepenes 23-25

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodide</th>
<th>Product (yield (%), ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSO</td>
<td>Me</td>
</tr>
<tr>
<td>2</td>
<td>TBSO</td>
<td>Me</td>
</tr>
<tr>
<td>3</td>
<td>TBSO</td>
<td>Me</td>
</tr>
<tr>
<td>4</td>
<td>TBSO</td>
<td>Me</td>
</tr>
</tbody>
</table>

Scheme 3. Construction of Orthoester Iodide 20

Reagents and conditions: (a) 0.5 equiv of SOBr2, 0.05 equiv of ZnBr2, 55 °C, 42 h, then 1.0 equiv of 3-methyl-3-oxetanemethanol, 2.0 equiv of Et3N, 0.2 equiv of DMAP, CH2Cl2, 25 °C, 5 h, 20%; (b) 5.0 equiv of NaI, 0.1 equiv of 18-crown-6, acetone, 25 °C, 50 h, 90%; (c) 0.25 equiv of BF3·OEt2, -30 °C, 12 h, 70%.

Having attached the required appendage on ring E, the next task was hydroboration of the double bond of the oxepene system and construction of the second lactone comprising ring D. Scheme 4 details how this objective was achieved. Initial attempts to hydroborate compound 25 to the corresponding hydroxy methyl ester 31 (in which the double bond has been converted to the desired α-compound (6)). Scheme 5 outlines the chemistry used in this sequence. Thus, 6β was converted to its α,β-unsaturated counterpart (30) via phenylselenenylation—oxidation—syn-elimination (91% overall yield) and thence to the hydroxy methyl ester 31 (in which the double bond has been transformed to the desired α-compound (6)). Scheme 5 outlines the chemistry used in this sequence. Thus, 6β was converted to its α,β-unsaturated counterpart (30) via phenylselenenylation—oxidation—syn-elimination (91% overall yield) and thence to the hydroxy methyl ester 31 (in which the double bond has been converted to the desired α-compound (6)).
The reagents and conditions: (a) 0.2 equiv of CSA, MeOH/CH₂Cl₂ (1:1), 0 °C; (b) 3.0 equiv of PhCH₂Br, THF, 45 °C; (c) O₂, CH₂Cl₂, -78 °C, then PPh₃, 25 °C (90% overall yield).


Scheme 8a Failed Attempts To Construct the C Ring via Conjugate Addition

\[
\begin{array}{c}
\text{R}^1 \text{H} \\
\text{R}^2 \text{H} \\
\text{R}^3 \text{H} \\
\text{R}^4 \text{H} \\
\text{R}^5 \text{H}
\end{array}
\]

* Reagents and conditions: (a) 4.0 equiv of Dess-Martin periodinane, CH₂Cl₂, 3 h, 25 °C, 91%; (b) 2.0 equiv of TBABF, THF, 25 °C, 3 h, 93%.

Scheme 9a Failed Attempts To Construct the C Ring via Reductive Hydroxy Ketone Cyclization

\[
\begin{array}{c}
\text{R}^1 \text{H} \\
\text{R}^2 \text{H} \\
\text{R}^3 \text{H} \\
\text{R}^4 \text{H} \\
\text{R}^5 \text{H}
\end{array}
\]

* Reagents and conditions: (a) 10 equiv of KH, 5.0 equiv of CS₂, 25 °C, 2 h, then 20 equiv of Mel, 10 min, 76%; (b) 5.0 equiv of TBAF, THF, 25 °C, 3 h, 93%; (c) 5.0 equiv of NMO, CH₂Cl₂, 3 h, 91%; (d) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 95%; (e) 10 equiv of Ag₂CO₃/Celite, benzene, 80 °C, 2 h, 96%; (f) 2.0 equiv of TBAF, THF, 25 °C, 3 h, 96%; (g) 10 equiv of Ag₂CO₃/Celite, benzene, 80 °C, 2 h, 96%; Th = 2-thienyl.

At this juncture, it was decided that a linear strategy toward the BCDEFG ring system might prove more fruitful and, therefore, a number of approaches involving sequential building of rings C and B were explored. First to be attempted was the sequence shown in Scheme 10 in which the pentacyclic lactone 52 was to be utilized as a precursor for further elaboration. Thus, enol triflate 36 was coupled with the mixed higher order cuprate carrying the appropriate side chain (TBSO(CH₂)₃Cu(2-Th)CNLi)₂

The pentacyclic lactone 52 was to be utilized as a precursor for further elaboration. Thus, enol triflate 36 was coupled with the mixed higher order cuprate carrying the appropriate side chain (TBSO(CH₂)₃Cu(2-Th)CNLi)₂ furnishing oxepene 49 (82%) which was subjected to hydroboration-oxidation to give alcohols 50 and 50a (88%, ca. 6:1 mixture in favor of 50). Desilylation of the latter mixture of compounds (50 + 50a) gave a mixture of diols (51 and 51a, 93% total yield) which was subjected to Fetizon oxidation (Ag₂CO₃/Celite, Δ) furnishing a mixture of lactones (52 and 52a, 96% total yield). Attempts to elaborate this pentacyclic system gave mixed and discouraging results. For example, the corresponding triflate could only be obtained with difficulty and in low yield, whereas addition reactions to the corresponding thionolactone led to unsatisfactory mixtures of products. In order to circumvent these problems, more elaborate side chains were designed and coupled with the DEFG framework as described below.

Cr–Ni Coupling of the DEFG Lactone-Derived Enol Ether with Aldehydes and Further Attempts To Construct the ABCDEFG Ring System

In light of the difficulties encountered in functionalizing pentacyclic lactone 52 (Scheme 10), the fully functionalized side chain aldehydes 59 and 62 (Scheme 11) were considered as coupling partners. The latter compounds were synthesized by standard methods from d-mannitol (53) as summarized in Scheme 11. A number of second generation attempts to construct the ABCDEFG framework of brevetoxin B (L) from the DEFG system were then made. A new method of coupling

Scheme 11* Synthesis of Aldehydes 59 and 62

Reagents and conditions: (a) 2.1 equiv of PhCHO, 0.7 equiv of H2SO4, DMF, 25 °C, 3 days, 35%; (b) 2.3 equiv of Dess-Martin periodinane, CH2Cl2, reflux, 12 h, 90%, then toluene, 110 °C, 12 h, Soxhlet condenser; 4a MS, 90%; (c) 6.0 equiv of MeMgl (3.0 M in ether), 18 h, 92%; (d) H2, 0.1 equiv of 10% Pd(OH)2, AcOH, 25 °C, 48 h, 94%; (e) 2.5 equiv of Me3C(O)Me, 0.1 equiv of CSA, DMF, 80 °C, 15 min, 60%; (f) 1.0 equiv of MeI, THF, reflux, 12 h, 48%; (g) 4.0 equiv of TBSOTf, 7.0 equiv of 2,6-lutidine, 0.1 equiv of CSA and 0.1 equiv of 1.0 equiv of KHMDS, THF, 25 °C, 15 min, 60%; (h) 3.0 equiv of PivCl, 0.2 equiv of DMAP, pyridine, 25 °C, 5 h, 99%; (i) 3.0 equiv of PivCl, 0.2 equiv of DMAP, pyridine, 25 °C, 24 h, 100%; (j) 1.1 equiv of Pf(OAc)3, CH2Cl2, 25 °C, 15 min, 91%.

Table 2. Cr/Ni-Mediated Coupling of Aldehydes with Enol Triflate 36

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>product</th>
<th>(yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>58</td>
<td>5.0 equiv of aldehyde</td>
</tr>
<tr>
<td>59</td>
<td>58</td>
<td>6.0 equiv of Gr(CHO)2</td>
</tr>
<tr>
<td>59</td>
<td>58</td>
<td>0.02 equiv of N3S2</td>
</tr>
<tr>
<td>59</td>
<td>58</td>
<td>DMF, 25 °C, ultrasound</td>
</tr>
</tbody>
</table>

The plan for coupling product 63 (Table 2) called for the generation and elaboration of functionalized lactone 69 (Scheme 12) via deoxygenation, hydroboration, and Fetizon oxidation. The Barton deoxygenation19 63 —*  66 (54% overall yield) proceeded smoothly under the standard conditions via xanthate 65 as shown in Scheme 12. The resulting olefin 66 was then subjected to hydroboration, leading selectively to ketone 70, a compound with one carbon less than the anticipated lactone 69 (Scheme 12). This unusual outcome could be explained by the assumption of the initial intermediacy of 69 and its facile decarbonylation (~CO), under the reaction conditions, as indicated in the structure (Scheme 12). Having failed, once again, to reach our goal by this route, it was then decided to turn our attention to compound 64 (Table 2) and its chemistry.

The deoxygenation of secondary alcohol 64 proved sensitive, in that it was accompanied by two interesting migrations (Scheme 13). First, during xanthate formation, it was observed that upon addition of KH, an immediate migration of the alkyl group from the tertiary to the secondary oxygen was taking place, leading to an equilibrium in which the tertiary alcohol 71 (as the alkoxide) was by far the major component (Scheme 13). Fortunately, the low reactivity of the tertiary alkoxide derived from 64 toward CS2 allowed the latter compound to drive the unfavorable equilibrium in its direction by forming xanthate 72 (89% yield). Second, the n-Bu3SnH—AIBN-induced C—O bond cleavage was accompanied by double bond migration, leading to a mixture of products 73 (30%) and 74 (69%). The unwanted isomer 73 was fortunately convertible to the desired isomer 74 via Rh(PPh3)3Cl-induced double bond
migration back into the ring (40% yield), thus increasing the overall yield of the requisite oxepane.

The hydroxylation of compound 74 via the standard hydrogenation-oxidation protocol proceeded again regio- and stereo-selectively to afford, in 82% yield, pivaloate ester alcohol 75 (Scheme 14). Cleavage of the pivaloate group from the latter compound with DIBALH then furnished diol 76 (80% yield) which, however, resisted Petizon oxidation to the corresponding lactone. The latter failure is presumably due to steric hindrance provided by the tertiary center adjacent to this reaction site. A second route was then chosen in an attempt to form ring C via a stepwise approach. Thus, protection of the secondary alcohol in 75 as a triethylsilyl (TES) ether followed by DIBALH-induced removal of the pivaloate group and Dess-Martin oxidation gave aldehyde 79 via intermediates 77 and 78 in 80% overall yield (Scheme 14). Finally, treatment of 79 with 25 equiv of 3 N NaOH, 50 equiv of 30% H2O2, 82%; (c) 1.7 equiv of Dess-Martin periodinane, CH2Cl2, 25 °C, 2 h, 85%; (d) 0.2 equiv of CSA, MeOH/H2O (4:1), 2 h, 25 °C, 85% (single isomer, unassigned stereochemistry).

Attempts to fuse additional rings onto the DEFG ring system with suitable functionalities for framework extension, this goal remained elusive. A number of new tactics and strategies were developed, however. Among them, a convergent Cr/Ni-promoted coupling procedure of lactone-derived enol triflates and aldehydes proved quite general and applicable to a potential precursor of the ABCDEFG ring system of brevetoxin B (1). In the following article, we detail the successful construction of this advanced intermediate (4, Scheme 1) and the final stages of the strategy that led to the completion of the total synthesis of brevetoxin B (1).

**Experimental Section**

**General Techniques.** For a description of general techniques, see the preceding paper in this issue.1 NMR spectra were recorded on a Varian XL-300 instrument. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points (mp) are uncorrected and were recorded on a Thomas Hoover capillary melting point apparatus.

**Olefin 11.** A solution of DMF (13.0 mL, 168 mmol) in CH2Cl2 (200 mL) was treated with oxalyl chloride (11.0 mL, 126 mmol) at 0 °C. After stirring at 0 °C for 30 min, a solution of alcohol 8 (49.0 g, 83.8 mmol) in CH2Cl2 (100 mL) was added dropwise and the reaction mixture was allowed to warm to 0 °C. The mixture was diluted with ether (500 mL), washed...
with saturated aqueous ammonium chloride (300 mL), dried (MgSO4), and concentrated. The crude aldehyde was used for the next step without further purification. A mixture of 3-(tert-butyldimethylsilyl)-0xoyprop-1- tripheny1phosphonium iodide (83.8 g, 168 mmol) in THF (200 mL) was treated with sodium bis(triethoxysilyl)amide (125 mL of a 1.0 M solution in THF, 126 mmol) at 0 °C. The resulting orange solution was treated with aldehyde, followed by a solution of the aldehyde 10 (49.0, 38.3 mmol) in THF (100 mL) at 0 °C. After stirring at 0 °C for 20 min, the mixture was quenched with acetone (10 mL), diluted with ether (500 mL), washed with brine (200 mL), dried (MgSO4), and concentrated. Flash chromatography (silica, 5–20% ether in petroleum ether) gave olefin 11 (61.5 g, 83.3 mmol, 99%).

11: colorless oil; Rf = 0.64 (silica, 20% ether in petroleum ether); IR (film) νmax 2951 (s), 2933 (s), 2887 (m), 2858 (s), 1653 (w), 1464 (m), 1369 (m), 1254 (m), 1097 (s), 837 (s), 776 (m), 736 (m), 695 (m) cm⁻¹; [α]D +7.2 (c 1.0, CH2Cl2); 1H NMR (500 MHz, CDCl3) δ 7.35–7.28 (m, 10 H, ArH), 4.54–4.37 (m, 3 H, CH), 4.19–4.09 (m, 2 H, CH₂), 2.67–2.59 (m, 2 H, CH₂), 2.10 (dd, J = 11.5 Hz, 1 H, CH), 1.15 (s, 3 H, CH₃), 1.12 (s, 3 H, CH₃), 0.90 (s, 3 H, CH₃), 0.89 (s, 3 H, CH₃), 0.88 (s, 3 H, CH₃), 0.87 (s, 3 H, CH₃), 0.86 (s, 3 H, CH₃), 0.85 (s, 3 H, CH₃), 0.84 (s, 3 H, CH₃), 0.83 (s, 3 H, CH₃), 0.82 (s, 3 H, CH₃).

A mixture of the olefin 11 (61.5 g, 82.9 mmol), 10% Pd/C (6 g), and sodium carbonate (900 mg, 8.3 mol) in ethyl acetate (200 mL) was stirred under H₂ atmosphere for 12 h at 25 °C. The mixture was filtered through Celite and concentrated. The crude aldehyde was used for the next step.

Disilyl Ether 12: A mixture of the olefin 11 (61.5 g, 82.9 mmol), 10% Pd/C (6 g), and sodium carbonate (900 mg, 8.3 mol) in ethyl acetate (200 mL) was stirred under H₂ atmosphere for 12 h at 25 °C. The mixture was filtered through Celite and concentrated to give disilyl ether 12 (61.4 g, 82.9 mmol, 100%).

12: colorless oil; Rf = 0.64 (silica, 20% ether in petroleum ether); IR (film) νmax 3425 (m), 3062 (m), 2946 (s), 2874 (m), 1711 (s), 1456 (m), 1379 (s), 1275 (m), 1274 (m), 1173 (s), 1097 (s) cm⁻¹; [α]D +14.0 (c 1.0, CH2Cl2); 1H NMR (500 MHz, CDCl3) δ 7.35–7.28 (m, 10 H, Ar), 4.54–4.37 (m, 3 H, CH), 4.19–4.09 (m, 2 H, CH₂), 2.67–2.59 (m, 2 H, CH₂), 2.10 (dd, J = 11.5 Hz, 1 H, CH), 1.15 (s, 3 H, CH₃), 1.12 (s, 3 H, CH₃), 0.90 (s, 3 H, CH₃), 0.89 (s, 3 H, CH₃), 0.88 (s, 3 H, CH₃), 0.87 (s, 3 H, CH₃), 0.86 (s, 3 H, CH₃), 0.85 (s, 3 H, CH₃), 0.84 (s, 3 H, CH₃), 0.83 (s, 3 H, CH₃), 0.82 (s, 3 H, CH₃), 0.81 (s, 3 H, CH₃).
Ether (1 L), and washed with brine (500 mL). The organic layer was dried (MgSO₄, concentrated, and subjected to flash chromatography (silica, 10–20% ether in petroleum ether containing 1% of triethylamine) to give enol ether 20 (4.38 g, 0.14 mol, 70%).

**Enol Ether 25.** A solution of enol ether 20 (6.14 g, 19.7 mmol) in ether (75 mL) was treated with tert-butyl lithium (0.5 mL of a 2.0 M solution in THF, 1.0 mmol) at –78 °C. The mixture was allowed to warm to 5°C for 30 min. The mixture was washed with brine (2.0 mL), dried (MgSO₄), filtered, concentrated, and subjected to flash chromatography (silica, 10–20% ether in petroleum ether containing 1% of triethylamine) to give enol ether 25 (1.89 g, 2.79 mmol, 85%, 2:1 mixture of diastereoisomers).

**Enol Ether 26**. A solution of enol ether 25 (1.89 g, 2.79 mmol) in tetrahydrofuran (5 mL) was treated with sodium hydride (0.44 mmol) at 0 °C for 40 min. Sodium hydroxide (6.26 mL, 0.050 mmol) at –30 °C. After stirring for 12 h at –30 °C, the mixture was allowed to warm to 25 °C over 1 h. After stirring for 1 h at 25 °C, the mixture was reacted with water (500 mL), 16: colorless foam; Rf = 0.81 (silica, 50% ether in petroleum ether); IR (film) v max 2943 (m), 2872 (m), 1701 (s), 1421 (m), 1379 (m), 1280 (m), 1199 (m), 1080 (s), 992 (s), 840 (m), 738 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.31–7.07 (m, 10 H, ArH), 4.36–4.34 (m, 1 H, CH₂), 4.33 (s, 2 H, CH₂Ph), 4.32 (d, J = 11.6 Hz, 1 H, CH₃), 1.35 (s, 3 H, CH₃), 1.23 (s, 3 H, CH₃), 1.03 (d, J = 6.3 Hz, 2 H, oxetane CH₂), –0.02 (s, 3 H, CH₃); 13C NMR (125 MHz, CDCl₃) δ (major isomer) 162.2, 139.4, 139.3, 128.5, 128.3, 127.6, 127.5, 109.5, 102.9, 85.7, 78.7, 78.5, 77.1, 72.9, 72.5, 71.1, 66.4, 64.7, 41.6, 41.1, 41.0, 36.4, 34.8, 29.2, 28.1, 21.3, 19.7, 19.3, 18.6, 17.4, 13.6, 12.1; HRMS, calcd for C₁₉H₂₄O₅Na (M + H)+ 313.0301, found 313.0288.
Hydroxy Acid 29. A solution of trihydroxy ester 28 (2.4:1 mixture of diastereoisomers, 1.52 g, 2.13 mmol) in 1,2-dimethoxyethane (25 mL, 0.1M) was treated with lithium hydroxide hydrate (447 mg, 10.7 mmol) and stirred at 25 °C for 1 h. The reaction was quenched with water (50 mL) and the organic layer was washed with aqueous saturated sodium bicarbonate/sodium thiosulfate solution. The organic layer was dried (MgSO₄), filtered, and concentrated to give 29 (1.07 g, 1.90 mmol) as a mixture of 2.4:1 diastereoisomers. An oily residue was obtained on further purification. 4:0 (d, J = 6.9 Hz, 3 H, CH₃), 2.04 (d, J = 1.1 Hz, 3 H, CH₃), 0.84 (s, 3 H, CH₃). 

1H NMR (500 MHz, CDCl₃) δ (major isomer) 7.33–7.25 (m, 10 H, ArH), 4.45 (d, J = 11.6 Hz, 1 H, CH₃Ph), 3.96 (m, 1 H, OCH), 3.64–3.40 (m, 9 H, OCH), 3.34–3.27 (m, 1 H, CHHC(O)), 2.56 (dt, J = 10.5, 7.5 Hz, 1 H, CH), 2.12–1.98 (m, 5 H, CH₂), 1.92–1.74 (m, 4 H, CH₂), 1.62–1.49 (m, 3 H, CH₃), 1.30 (s, 3 H, CH₃), 1.25–1.20 (m, 1 H, CH), 1.14 (s, 3 H, CH₃), 1.12 (s, 3 H, CH₃), 0.75 (d, J = 6.9 Hz, 3 H, CH₃); 13C NMR (125 MHz, CDCl₃) δ 174.6, 138.4, 138.5, 128.2, 128.2, 127.6, 127.5, 127.4, 89.7, 83.6, 80.7, 73.9, 72.9, 72.6, 72.0, 70.0, 70.4, 69.6, 66.3, 65.9, 63.4, 50.3, 36.3, 35.9, 31.8, 31.7, 29.3, 29.0, 26.8, 21.4, 19.8, 17.5, 16.8, 15.7, 13.6; HRMS, calcd for C₂₉H₃₀O₇CaS (M + Cs⁺) 485.3214, found 485.3210.

Enol Triolate 36. A solution of lactone 6 (3.87 g, 6.63 mmol) and HMPA (2.3 mL, 13.1 mmol) in THF (100 mL) was treated with lithium bis(trimethylsilyl)amide (32.6 g, 0.10 M solution in THF, 32.6 mmol) at −78 °C. After stirring at −78 °C for 2 h, N-phenyl trifluoromethanesulfonamide (3.50 g, 9.80 mmol) was added and the mixture was allowed to warm to 25 °C over 1 h. After further stirring at 25 °C for 1 h, the reaction was quenched with water (50 mL), containing 1% of triethylamine) and extracted with ether (200 mL). The organic layer was dried (MgSO₄), filtered, and concentrated to give 36 (4.40 g, 6.07 mmol, 93%).

36: colorless foam, Rf = 0.83 (silica, 30% ether in petroleum ether); IR (film) νmax 3022, 2927, 1658, 1491, 1394, 1264, 1122, 1028 cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.27–7.22 (m, 10 H, ArH); 4.45 (d, J = 11.5 Hz, 1 H, CH₂Ph), 4.45–4.42 (m, 1 H, OCHOCO), 4.38 (d, J = 11.5 Hz, 1 H, CH₂Ph), 3.65–3.57 (m, 3 H, OCH₃), 3.37–3.31 (m, 2 H, OCH), 3.05 (dd, J = 10.5, 7.5 Hz, 1 H, OCH), 2.72 (tt, J = 14.0 Hz, 1 H, CHHC(O)), 2.58 (dd, J = 15.5, 13.0 Hz, 1 H, CHCC(OH)), 2.17 (dd, J = 11.5, 11.0 Hz, 1 H, CH₂), 1.92–1.80 (m, 2 H, CH₂), 1.88–1.72 (m, 4 H, CH₄), 1.69–1.63 (m, 1 H, CH), 1.51–1.41 (m, 2 H, CH₃), 1.31 (s, 3 H, CH₃), 1.24 (s, 3 H, CH₃), 0.77 (d, J = 6.5, 3 H, CH₃); 13C NMR (125 MHz, CDCl₃) δ 174.6, 138.4, 138.3, 128.3, 128.7, 127.7, 127.5, 91.3, 90.0, 82.0, 78.1, 73.8, 73.5, 71.0, 66.0, 40.3, 40.2, 39.3, 38.7, 33.0, 32.9, 29.0, 28.5, 21.0, 20.3, 19.3, 17.3; HRMS, calcd for C₂₉H₂₈O₅M (M + Cs⁺) 725.2454, found 725.2466.

Diketone 55. A solution of lactone 54 (15.0, 41.9 mmol) and Dess-Martin periodinane (40.0, 94.3 mmol) in CH₂Cl₂ (200 mL) was heated at 40 °C for 12 h. The mixture was diluted with ether (300 mL) and washed with aqueous saturated sodium bicarbonate/sodium thiosulfate solution (1:1, 300 mL). The organic layer was dried (MgSO₄), concentrated, and subjected to flash chromatography (silica, 20–50% of ethyl acetate in petroleum ether) to give 55 as its hydrate, which was vacuum-dried and stored at −20 °C under Ar. 

Diol 56. A solution of methyleneiodide (68.0 mL of a 3.0 M solution in ether, 256 mmol) was added to diketone 55 in four portions at 0 °C. The reaction was quenched with MeOH (10 mL), diluted with EtOAc (250 mL), and washed with aqueous saturated ammonium chloride (200 mL). The organic layer was dried (MgSO₄), concentrated, and subjected to flash chromatography (20–40% of ethyl acetate in petroleum ether) to give diol 56 (12.0 g, 31.2 mmol, 92%).

56: colorless crystals, mp 112–114 °C (toluene); Rf = 0.37 (silica, 50% ethyl acetate in petroleum ether); IR (film) νmax 2930 (m), 2933 (m), 2886 (m), 1455 (m), 1396 (m), 1096 (s), 1020 (s), 963 (m), 915 (m), 761 (m) cm⁻¹; 1H NMR (300 MHz,
Total Synthesis of Brevetoxin B. 2

**Coupling Product 64.** A mixture of enol triflate 36 (435 mg, 0.734 mmol), aldehyde 62 (11.1 g, 3.67 mmol), chromium(II) chloride (560 mg, 2.94 mmol), and nickel(II) chloride (2 mg, 0.015 mmol) in DCM (1 mL) was stirred at 25 °C for 30 min in an ultrasonic bath.

The resulting dark green suspension was diluted with ether (100 mL), filtered through Celite, washed with brine (2 × 50 mL), dried (MgSO₄), and filtered. Concentration and flash chromatography (silica, 10–30% ether in petroleum ether containing 1% triethylamine) gave the addition product 64 (425 mg, 0.454 mmol, 66%, 51% mixture of isomers). 64 (major isomer): colorless foam; Rf = 0.31 (silica, 10% ethyl acetate in benzene); IR (film) νmax 3456 cm⁻¹ (ω), 2954 cm⁻¹ (s), 2930 cm⁻¹ (s), 2858 cm⁻¹ (m), 1732 cm⁻¹ (s), 1389 cm⁻¹ (m), 1291 cm⁻¹ (m), 1148 cm⁻¹ (s), 1042 cm⁻¹ (s), 838 cm⁻¹ (m), 778 cm⁻¹ (m); [α]D 22 +12.0 (c 1.2, CHCl₃).

**Aldehyde 62.** A mixture of dipivaloate 61 (6.7 g, 10 mmol) and Ag₂O/Celite (50 mg in benzene (2 mL) was heated at 80 °C under acetate removal for water for 3 h. The resulting black suspension was filtered through Celite, concentrated, and subjected to preparative TLC (silica, 100% ether) to give hydroxy ketone 70 (5 mg, 82% yield, 80% purity).

**Hydroxy Ketone 70.** A mixture of triol 68 (7 mg, 0.01 mmol) and Ag₂O/Celite (50 mg in benzene (2 mL) was heated at 80 °C under acetate removal for water for 3 h. The resulting black suspension was filtered through Celite, concentrated, and subjected to preparative TLC (silica, 100% ether) to give hydroxy ketone 70 (5 mg, 82% yield, 80% purity).
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HRMS calcd for C_{11}H_{18}O_{10}SiCs (M + Cs^+) 1101.4419, found 1101.4446.

Xanthate 72. A solution of alcohol 64 (650 mg, 0.717 mmol) and carbodiimide (50 mg) was heated at 60 °C for 20 h. The xanthate 72 (166 mg, 0.192 mmol, 30%) 73: colorless foam; HRMS, calcd for C_{11}H_{18}O_{10}SiCs (M + Cs^+) 995.4469, found 995.4499.

Disilyl Ether 77. A solution of alcohol 75 (100 mg, 0.115 mmol) in THF (0.5 mL) was treated with BH_yTHF (0.58 mL of a 1.0 M solution in CH_2Cl_2, 4.48 mmol) at -78 °C. After the mixture was diluted with ether (2 x 10 mL), dried (MgSO_4), filtered, concentrated, and subjected to flash chromatography (silica, 10% ether in petroleum ether containing 1% triethylamine) to give the disilyl ether 77 (69 mg, 0.209 mmol, 94%) mixture of isomers. 72 (major isomer): colorless foam, R_f 0.68

Enol Ether 74. A solution of xanthate 72 (620 mg, 0.640 mmol), tri-n-butyltin hydride (690 μL, 2.25 mmol) and ether (250 mL) was heated at 80 °C for 3 h. The resulting mixture was treated with 3 N sodium hydroxide (1.5 mL) and flash chromatography (silica, 10-30% ether in petroleum ether) to give the alcohol 75 (82 mg, 0.093 mmol, 82%). 75: colorless foam; R_f 0.35 (silica, 10% ether in petroleum ether); IR (film) ν_3510 (w), 2935 (s), 2837 (s), 1727 (m), 1664 (w), 1548 (w), 1238 (m), 1085 (m), 1025 (m), 874 (m), 697 (m) cm^{-1}; [α]_D^20 +1.6 (c 1.0, CH_2Cl_2); 'H NMR (500 MHz, C_6D_6) 8 5.01 (t, J = 3.7 Hz, 1 H, CH), 4.07-4.02 (m, 1 H, OCH), 3.79-3.74 (m, 10 H, ArH), 2.23-2.16 (m, 2 H, CH), 2.14-2.08 (m, 2 H, CH), 1.76-1.68 (m, 4 H, CH), 1.39-1.28 (m, 9 H, f-Bu), 0.85 (d, J = 6.9 Hz, 3 H, CH_3), 0.23 (s, 2 H, 2 × Si); 13C NMR (125 MHz, CDCl_3) δ 175.4, 154.7, 153.4, 152.8, 128.5, 128.2, 127.5, 127.4, 125.8, 125.3, 108.1, 88.3, 88.1, 87.7, 77.5, 73.7, 74.2, 74.1, 73.4, 73.1, 71.0, 70.9, 66.4, 40.9, 40.8, 33.9, 31.0, 29.7, 28.6, 28.4, 27.5, 27.4, 26.6, 26.1, 26.0, 21.8, 20.6, 17.9, 14.8, -1.9, -2.3; HRMS, calcd for C_{11}H_{18}O_{10}SiCs (M + Cs^+) 1195.4469, found 1195.4499.

Disilyl Ether 77. A solution of alcohol 75 (1.03 g, 1.16 mmol) and 2,6-lutidine (338 mL 2.90 mmol) in CH_2Cl_2 (10 mL) was treated dropwise at 0 °C with triethyl(trifluoromethanesulfon)imide (787 μL, 3.46 mmol). After stirring at 0 °C for 30 min, the mixture was diluted with ether (250 mL), washed with aqueous saturated ammonium chloride (2 x 20 mL), and dried (MgSO_4). Filtration, concentration, and flash chromatography (silica, 10-30% ether in petroleum ether) gave the disilyl ether 77 (111.1 g, 1.12 mmol, 96%). 77: colorless oil; R_f 0.72 (silica, 30% ether in petroleum ether); IR (film) ν_3510 (w), 2987 (s), 2786 (s), 1729 (s), 1459 (s), 1356 (m), 1253 (m), 1071 (m), 835 (m), 733 (m), 697 (m) cm^{-1}; [α]_D^20 +23.6 (c 1.0, CH_2Cl_2); H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (m, 10 H, ArH), 6.05 (d, J = 9.9 Hz, 1 H, OCH), 4.46 (d, J = 4.2, 3.9 Hz, 2 H, CH_2), 3.75-3.65 (m, 5 H, OCH), 2.96-2.90 (m, 5 H, OCH), 2.52-2.49 (m, 1 H, CHOCCH_3), 2.38-2.37 (m, 1 H, OCH), 1.36-1.31 (m, 2 H, OCH), 1.22 (d, J = 11.7 Hz, 3 H, OCH), 1.33 (d, J = 11.7 Hz, 3 H, OCH), 0.63 (q, J = 6.9 Hz, 3 H, OCH), 0.14 (s, 3 H, SiCH_3), 0.09 (s, 3 H, SiCH_3); 'H NMR (500 MHz, CDCl_3) 8 7.87, 7.82, 7.74, 7.40, 7.34, 7.31, 7.12, 6.64, 47.0, 41.0, 40.9, 39.0, 30.6, 29.5, 28.8, 27.5, 26.2, 20.4, 18.4, 18.1, 17.8, -1.9, -2.0; HRMS, calcd for C_{11}H_{18}O_{10}SiCs (M + Cs+) 1195.4469, found 1195.4499.

Diethyl Alcohol 78. A solution of disilyl ether 77 (11.1 g, 1.12 mmol) in CH_2Cl_2 (10 mL) was treated with dichloroaluminum hydride (4.48 mL of a 1.0 M solution in CH_2Cl_2, 4.48 mmol) at -78 °C. After
stirring for 2 min at 78 °C the reaction was quenched with MeOH (2 mL). The mixture was diluted with EtOAc (300 mL), washed with aqueous saturated sodium potassium tartrate (100 mL), and dried (MgSO₄). Filtration, concentration, and flash chromatography (silica, 20 → 40% ether in petroleum ether) afforded the alcohol 78 (965 mg, 1.06 mmol, 95%). 78: colorless oil; Rf = 0.21 (silica, 30% ether in petroleum ether); IR (film) νmax 3504 (w), 2953 (m), 2876 (m), 1458 (m), 1382 (m), 1254 (m), 1070 (s), 834 (m), 733 (m), 697 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.24–7.20 (m, 1 H, CHO), 3.33–3.22 (m, 4 H, OCH), 3.05 (dd, J = 11.8, 3.6 Hz, 1 H, OCH), 2.84 (bs, 1 H, CHO), 2.10–1.92 (m, 2 H, CH), 1.82–1.64 (m, 10 H, CH), 1.47–1.37 (m, 3 H, CH₂), 1.32 (s, 3 H, CH₃), 1.25 (s, 3 H, CH₂), 1.19 (s, 3 H, CH₃), 1.03 (d, J = 7.0 Hz, 3 H, CH₃), 0.89 (s, 9 H, t-Bu) ppm; HRMS, calecl for C₉H₁₈O₃Si₂ (M + Cs⁺) 1043.4855, found 1043.4856.

Aldehyde 79. A solution of alcohol 78 (955 mg, 1.00 mmol) in CH₂Cl₂ (20 mL) was treated with Dess-Martin periodinane (1.78 g, 4.1 mmol), stirred at 25 °C for 3 h. The reaction was quenched with triethylamine (10 mL), concentrated, and subjected to preparative TLC (silica, 50% ether in petroleum ether) to give the aldehyde 79 (822 mg, 904 mmol, 86%). 79: colorless foam; Rf = 0.58 (silica, 50% ether in petroleum ether); IR (film) νmax 3504 (w), 2955 (m), 2877 (m), 1732 (m), 1462 (m), 1380 (m), 1254 (m), 1070 (s), 834 (m), 733 (m), 697 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 9.58 (s, 1 H, CHO), 7.32–7.23 (m, 10 H, ArH), 4.54 (d, J = 11.9 Hz, 1 H, CHO), 4.45 (s, 2 H, CH₂CHO), 4.35 (d, J = 7.0 Hz, 3 H, CH₃), 0.89 (s, 9 H, t-Bu) ppm; HRMS, calecl for C₉H₁₆O₂Si₂ (M + Cs⁺) 1025.0618, found 1025.0619.

Lactol 80. A mixture of silyl ether 79 (5 mg, 6 μmol) and camphorsulfonic acid (0.4 mg, 1 μmol) in MeOH/H₂O (10:1, 41) was stirred at 25 °C for 2 h. The reaction was quenched with triethylamine (10 mL), concentrated, and subjected to preparative TLC (silica, 50% ether in petroleum ether) to give the lactol 80 (4 mg, 5 μmol, 85%, single isomer). 80: colorless oil; Rf = 0.45 (silica, 50% ether in petroleum ether); IR (film) νmax 3504 (w), 2955 (m), 2877 (m), 1732 (m), 1462 (m), 1380 (m), 1254 (m), 1070 (s), 834 (m), 733 (m), 697 (m) cm⁻¹; 1H NMR (500 MHz, CDCl₃) δ 7.23–7.24 (m, 10 H, ArH), 4.73 (bs, 1 H, CHO), 4.55 (d, J = 11.6 Hz, 1 H, C(2)HPh), 4.46 (s, 2 H, CH₂Ph), 4.37 (d, J = 11.6 Hz, 1 H, C(1)HPh), 3.69–3.55 (m, 5 H, OCH), 3.45–3.32 (m, 2 H, OCH), 3.24–3.21 (m, 1 H, OCH), 3.08 (dd, J = 11.8, 3.6 Hz, 1 H, OCH), 2.84 (bs, 1 H, CHO), 2.10–1.92 (m, 2 H, CH), 1.82–1.64 (m, 10 H, CH), 1.47–1.37 (m, 3 H, CH₂), 1.32 (s, 3 H, CH₃), 1.25 (s, 3 H, CH₂), 1.19 (s, 3 H, CH₃), 1.03 (d, J = 7.0 Hz, 3 H, CH₃), 0.89 (s, 9 H, t-Bu) ppm; (H NMR (500 MHz, CDCl₃) δ 9.58 (s, 1 H, CHO), 7.32–7.23 (m, 10 H, ArH), 4.54 (d, J = 11.9 Hz, 1 H, CHO), 4.45 (s, 2 H, CH₂CHO), 4.35 (d, J = 7.0 Hz, 3 H, CH₃), 0.89 (s, 9 H, t-Bu) ppm; HRMS, calecl for C₉H₁₆O₂Si₂ (M + Cs⁺) 1025.0618, found 1025.0619.

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Supporting Information Available: Selected data for compounds 21–24, 26, 30–34, 37–41, 43–47, 49, 51–52, 54, 57–59, 63, 65–68, and 76 are provided as well as X-ray crystallographic data for compound 32, tables of anisotropic displacement coefficients and H atom coordinates, unit cell packing diagrams, stereoviews, and torsion angles and mean plane equations (45 pages); listing of structure factors (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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