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Contribution from the Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92039

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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 [ABCDEFG] phosphonium 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 introduced via a Murali 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 6θ was then converted to the desired isomer 6a via hydrogenation 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 hydroxy ketone cyclization (47 — 48) failed to yield ring C. Fetizon 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 advancement 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 fragments2−4 were to be constructed, coupled, and elaborated to form the oxocene and dioxepane regions of the molecule.1 The effectiveness and reliability of the hydroxy dithioketal 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 dithioketal 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 DEFG) 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 intermediary of tricycle 7 and bicyclo 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-
Nicolaou et al.


<table>
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<tr>
<th>R2</th>
<th>R1</th>
<th>CH(OH)2</th>
<th>CH2OH</th>
<th>CH2CO2H</th>
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<td>OH</td>
<td>CH2OH</td>
<td>CH(OH)2</td>
<td>CH2OH</td>
<td>CH2CO2H</td>
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Reagents and conditions: (a) 1.5 equiv of (COCl)2, 2.0 equiv of DMSO, CH2Cl2, -78 °C; then 5.0 equiv of EnN, 30 min, 100%; (b) 2.0 equiv of TBSO(CH2)3PPh+Tf-, 1.5 equiv of NaHMDS, THF, 0 °C, 10 min, then 8, 0.5 h, 99%; (c) H3, 10 wt % of Pd/C (10%), 0.1 equiv of NaSCN, EtOH, 25 °C, 12 h, 100%; (d) 1.0 equiv of CSA, CH2Cl2, MeCN (1:1), 0 °C, 1 h, 97%; (e) 2.0 equiv of (COCl)2, 3.0 equiv of S02Cl2, -78 °C, -78 °C, then 5.0 equiv of DMAP, DMSO, CH2Cl2, -78 °C, then 7.0 equiv of EnN, 0.5 h; 1.5 equiv of NaClO4, 2.0 equiv of NaHPO4, 2.0 equiv of 2-methyl-2-buene, t-BuOH:H2O (2:1), 25 °C, 1 h, 97%; (f) 5.0 equiv of TBAP, THF, 65 °C, 8 h, 91%; (g) 1.0 equiv of 2,4,6-trichlorobenzyl chloride, 1.5 equiv of EnN, THF, 0 °C, 2 h, then added to 5.0 equiv of DMAP, benzene (c = 0.05 mM), 80 °C, 3 h, 90%; (h) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, -78 °C, 2 h, then 1.5 equiv of PhN(Tf)2, -78 to 25 °C, 93%.

lactone 7. In preparation for the anticipated Murai coupling,6 lactone 7 was converted to its enol triflate 16 via enolization (LiHMDS) followed by quenching with PhN(Tf)2 (93% yield)7 (Scheme 2).

The next task was to attach an appropriate appendage on ring E in order to allow the formation of the D ring. To this end, iodides 21P and 22P (both racemic, Table 1) were converted to their lithium derivatives by halogen—metal exchange (t-BuLi) and thence to the higher order cuprates RLi/2-thienyl/CNL18 which coupled smoothly with the lactone-derived enol triflate 16 to afford extended oxepenes 23 (50% yield, ca. 1:1.4 ratio of epimers in favor of the wrong epimer at C*) and 24 (49% yield, ca. 1:1.5 ratio of epimers at C*), respectively (see Table 1, entries 1 and 2). In view of the lack of stereoselectivity in these coupling reactions the orthoester iodide 20 (Table 1 and Scheme 3) was prepared7,11 and utilized in the hope of improving the stereochimical outcome of the process. The synthesis of 20 proceeded in a straightforward manner from y-valeralactone 17 as outlined in Scheme 3. Its coupling to enol triflate 16 via the higher order cuprate reagent proved quite superior to the two previous cases, leading to 25 with an 85% total yield and with ca. 2:4:1 stereoselectivity in favor of the desired stereoisomer at C* (see Table 1). It should be noted at this point

(4) Iodide 21 was prepared from 1,4-butanediol in four steps: (a) 1.0 equiv of NaH, 1.0 equiv of TBSCI, THF, 25 °C; (b) 1.5 equiv of (COCl)2, 2.0 equiv of DMSO, -78 °C, then EnN; (c) 1.2 equiv of MeMgCl, -78 to 25 °C; (d) 1.4 equiv of t-BuLi, 1.0 equiv of PhP(Tf)2, 1.2 equiv of imidazole, benzene, 25 °C (64% overall yield).
(5) Iodide 22 was prepared from 1,4-butanediol in seven steps: (a-x-d) as for 21 (ref 3); (b) 1.0 equiv of CSA, CH2Cl2/CH3OH (1:1), 0 °C; (c) 3.0 equiv of SO2-pyridine, CH2Cl2/DMSO (1:1), 10 equiv of Bu3SnH, 30 °C; (d) 2.0 equiv of 1-ethylthioethanol, T3OH catalyse, benzene, 25 °C (55% over 3 steps).
that crucial to the observed stereoselectivity was the employment of the solvent system Et₂O:THF:HMPA (1:1:1) in the coupling reaction. The two diasteroisomers so obtained were carried through to a later stage as a mixture, where chromatographic separation and structural assignment became possible (lactone 6, vide infra).

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 hydroboration of the double bond, followed by intramolecular hydride delivery onto the adjacent orthoester carbon atom. To circumvent this problem, the orthoester 25 was partially hydrolyzed under mildly acidic conditions (PPTS, DME/H₂O, 25 ºC) to the dihydroxy ester 27 (100% yield) which now served to hydroborate to furnish, regio- and stereoselectively (after chromatography). COD = 1,5-cyclooctadiene, Cy = cyclohexyl.

In order to optimize the yield of the desired α-epimer 6, a process was developed whereby the β-epimer (6β) was 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 phenylselenenylenation—oxidation—syn-elimination (91% overall yield) and thence to the hydroxy methyl ester 31 (in which the double bond has...
migrated to the \( \gamma \)-position) by deconjugation with LiHMDS, 4.5 equiv of DMAP, \( \text{CH}_2\text{Cl}_2 \), 25 °C, 25 min, 72%.

The structural assignment of lactone 6 was secured by X-ray crystallographic analysis of its bis(p-bromobenzoate) derivative, which was chromatographically separated into its pure components.

Coupling of B and DEFG Ring Systems and Attempts To Construct the BCDEFG Framework

After securing the DEFG lactone 6, the plan called for its coupling to ring B aldehyde 39\(^{13} \) (Scheme 7). To this end, lactone 6 was converted to the thionolactone 33 (Scheme 7) by treatment with Lawesson’s reagent\(^{14} \) at 180 °C (68% yield) and thence to the vinylstannane 34 via sequential treatment with LDA, \( \text{n-Bu}_3\text{SnH} \), I(\( \text{CH}_3 \)), and 2,6-lutidine (50% overall yield).\(^{15} \) Conversion of 34 to the corresponding lithium reagent via tin–lithium exchange (\( \text{n-BuLi} \), HMPA, \( \text{THF} \), –78 °C) followed by addition of aldehyde 39 resulted in the formation of adduct 38 (40%, \( \text{a}:\text{b} \) and 2,6-lutidine (50% overall yield)) and 20% of 35; (d) 5.0 equiv of \( \text{HMPA} \), \( \text{THF} \), –78 °C, 20 min, then add 39, –78 °C, 20 min, 40% of 38 (6:1 mixture of isomers) and 20% of 35. Although the overall yield of converting 6 to the stannyl enol ether was significantly higher in the latter case, compounds 38 and 35 were obtained in the same yields (40 and 20%, respectively) as before. The above two methods of coupling were surpassed, however, in both efficiency and convenience, by a third approach, whose discussion will be deferred to a later section (vide infra).

Having secured coupling product 38, an attempt was made to construct ring C via an intramolecular Michael reaction as shown in Scheme 8. Thus, Dess-Martin oxidation of 38 led smoothly to enone 40 (91%) which was then transformed to the requisite hydroxy enone 41 by desilylation (TBAF, 93%). All attempts, however, to induce ring closure in 41 under basic or acidic conditions failed and, therefore, a second approach was explored.

According to the new alternative, outlined in Scheme 9, hydroxy ketone 45 was to serve as a precursor to the BCDEFG ring system 48 via a reductive cyclization process. The sequence leading to 47 involved initial deoxygenation of 38 via the Barton–McCombie two-step protocol\(^{19} \) (a) KH–CS\( \text{Me}_2 \), 2 h, then 2.0 equiv of \( \text{LiCl} \), \( \text{DMF} \), 14 h, 95%; (f) 2.0 equiv of \( \text{n-BuLi} \), 1.0 equiv of \( \text{HMPA} \), THF, –78 °C, 20 min, then add 39, –78 °C, 20 min, 40% of 38 (6:1 mixture of isomers) and 20% of 35.


\(^{13} \) Aldehyde 39 was prepared in three steps from intermediate 20, ref 3a: (a) 0.2 equiv of CSA, MeOH/\( \text{CH}_2\text{Cl}_2 \) (1:1), 0 °C; (b) 3.0 equiv of PhCH\( _2\text{Br} \), THF, 45 °C; (c) \( \text{Os}, \text{CH}_2\text{Cl}_2 \), –78 °C, then PF\( _3\text{H} \), 25 °C (90% overall yield).


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) to furnish oxepene 49 (82%) which was subjected to hydroboration—oxidation to give alcohols 50 and 50a (88%), ca. 6:1 mixture of isomers; (c) 1.5 equiv of TBAF, THF, 25 °C, 9 h; 93%; (d) 10 equiv of Ag2CO3/Celite, benzene, 80 °C, 2 h, 96%. Th = 2-thienyl.

The Cr—Ni coupling of the DEFG lactone-derived enol ether with aldehydes and further attempts to construct the ABCDEFG ring system were then made. A new method of coupling the ABCDEFG framework as described below.

* Reagents and conditions: (a) 2.0 equiv of HMPA, 5.0 equiv of TBSO(CH2)3Cu(2-Th-CN)Li, THF, 0 °C, 1 h, 92%; (b) 5.0 equiv of BHyTHF, THF, -30 °C, 14 h, then 10 equiv of 3 N NaOH, 20 equiv of H2O, 25 °C, 1 h, 90%; (c) 5.0 equiv of BHyTHF, THF, -30 °C, 12 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H2O2, 0 °C, 1 h, 76%; (d) 0.1 equiv of TPAP, 2.0 equiv of NMO, CH2CN, 25 °C, 1 h, 90%; (e) 1.2 equiv of TBAF, THF, 25 °C, 7 h, 95%; (f) 10 equiv of Ph3SiH, 1.2 equiv of TMSOTf, MeNO2, 0 °C, 1 h.

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

(R) 40: R » TBS

compound (45) with N-methylmorpholine N-oxide (NMO) in the presence of a catalytic amount (10%) of tetra-n-propylammonium peruthenate (TPAP)20 furnished ketone 46 (90%) which was desilylated (TBAF) to give the desired hydroxy ketone 47 in 95% yield. Again, however, all attempts to effect cyclization of 47 to 48 using a number of silanes and a variety of acid conditions proved unsuccessful (Scheme 9).

* Reagents and conditions: (a) 4.0 equiv of Dess-Martin periodinane, CH2Cl2, 3 h, 25 °C, 91%; (b) 2.0 equiv of TBAF, THF, 25 °C, 3 h, 93%; (c) 1.5 equiv of TBAF, THF, 25 °C, 3 h, 93%; (d) 10 equiv of Ag2CO3/Celite, benzene, 80 °C, 2 h, 96%. Th = 2-thienyl.

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 11.23 A number of second generation attempts to construct the ABCDEFG framework of brevetoxin B (1) from the DEFG system were then made. A new method of coupling

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

Scheme 9a Failed Attempts To Construct the C Ring via Reductive Hydroxy Ketone Cyclization
Scheme 11* Synthesis of Aldehydes 59 and 62

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>59</td>
<td>62</td>
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* Reagents and conditions: (a) 2.1 equiv of PhCHO, 0.7 equiv of HSO₃, 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 condensation; 4A MS, 90%; (c) 6.0 equiv of NaMeCl (3.0 M in THF), 0 °C, 1 h, 92%; (d) H₂, 0.1 equiv of 10% Pd(OH)₂, AcOH, 25 °C, 48 h, 94%; (e) 2.5 equiv of Me₃S(O), 0.1 equiv of CSA, DMF, 80 °C, 15 min, 60%; (f) 1.0 equiv of NaO₂, THF/H₂O (1:1), 72 h, 90%; (g) 4.0 equiv of TBSOTf, 7.0 equiv of 2,6-lutidine, 0.1 equiv of H₂SO₄, CH₂Cl₂, 25 °C, 48 h, 91%; (h) 3.0 equiv of PIVCl, 0.2 equiv of DMAP, pyridine, 25 °C, 24 h, 100%; (i) 1.1 equiv of Ph(OAc)₂, 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>
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<tbody>
<tr>
<td>59</td>
<td>62</td>
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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 condensation; 4A MS, 90%; (c) 6.0 equiv of NaMeCl (3.0 M in THF), 0 °C, 1 h, 92%; (d) H₂, 0.1 equiv of 10% Pd(OH)₂, AcOH, 25 °C, 48 h, 94%; (e) 2.5 equiv of Me₃S(O), 0.1 equiv of CSA, DMF, 80 °C, 15 min, 60%; (f) 1.0 equiv of NaO₂, THF/H₂O (1:1), 72 h, 90%; (g) 4.0 equiv of TBSOTf, 7.0 equiv of 2,6-lutidine, 0.1 equiv of H₂SO₄, CH₂Cl₂, 25 °C, 48 h, 91%; (h) 3.0 equiv of PIVCl, 0.2 equiv of DMAP, pyridine, 25 °C, 24 h, 100%; (i) 1.1 equiv of Ph(OAc)₂, CH₂Cl₂, 25 °C, 15 min, 91%.

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 deoxygenation⁵⁹ 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 enol alcohol 67 (72% yield), from which the triol 68 was generated upon acid hydrolysis (95% yield). Fetizon oxidation of 68, however, resulted in the unexpected formation of hydroxy 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 allyl 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-Bu₂SnH—ABN-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 hydroboration—oxidation protocol proceeded again regio- and stereo-selectively to afford, in 82% yield, pivalate ester alcohol 75 (Scheme 14). Cleavage of the pivalate 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-promoted coupling procedure of lactone-derived enol inflates the oxocene ring system as the last ring to be closed. A number of other relatives of 80 (e.g., methyl glycoside, 2,6-lutidine, CH₂Cl₂, -78 °C, 1 h, 96%; (c) 2.0 equiv of TESOTf, 2,5 equiv of 3 N NaOH, 50 equiv of 30% H₂O₂, 25 °C, 2 h, 85%; (d) 2.5 equiv of DIBALH, -78 °C, 10 min, 80%; (e) 1.7 equiv of Dess-Martin periodinane, CH₂Cl₂, 25 °C, 2 h, 85%: (f) 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 DEF_G 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 Bruker AMX-500 or AM-300 instruments. 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 DMSO (13.0 mL, 168 mmol) in CH₂Cl₂ (200 mL) was treated with oxalyl chloride (11.0 mL, 126 mmol) at -78 °C. After stirring at -78 °C for 30 min, a solution of alcohol 8 (49.0 g, 83.8 mmol) in CH₂Cl₂ (100 mL) was added dropwise and the mixture was stirred for an additional 30 min at -78 °C. Triethylamine (54 mL, 419 mmol) was added and the reaction mixture was allowed to warm to 0 °C. The mixture was diluted with ether (500 mL), washed

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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)oxypropyl-1-triphenylphosphonium iodide (83.8 g, 186 mmol) in THF (200 mL) was treated dropwise with sodium bis(trimethylsilyl)amide (126 mL of a 1.0 M solution in THF, 126 mmol) at 0°C. The resulting orange gum was treated dropwise with a solution of the aldehyde 10 (49.0 g, 38.8 mmol) in THF (100 mL) at 0°C. After stirring at 0°C for 20 min, the mixture was quenched with aqueous 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 (61.3 g, 83.0 mmol, 99%).

11: colorless oil; Rf = 0.64 (silica, 20% ether in petroleum ether); IR (film) νmax 2946 (m), 2871 (m), 1739 (s), 1679 (m), 1579 (m), 1461 (m), 1369 (m), 1245 (m), 1097 (s), 837 (s), 766 (m), 736 (m), 697 (m) cm⁻¹; [α]D +7.2 (c 1.0, CH2Cl2); H NMR (500 MHz, CDCl3) δ 7.35–7.25 (m, 10 H, ArH), 5.01–4.94 (m, 3 H, OCH), 2.65–2.62 (m, 2 H, CH), 2.13 (dd, J = 10.0, 5.5 Hz, 1 H, CHPh), 1.75–1.70 (m, 3 H, CH3), 1.18 (s, 3 H, CH3).

Disilyl Ether 12. A mixture of the olefin 11 (61.3 g, 82.9 mmol), 10% Pd/C (6.6 g, 50 wt%), and sodium carbonate (500 mg, 83.0 mmol) in ethyl acetate (200 mL) was stirred under H2 atmosphere for 12 h. The mixture was filtered through Celite and concentrated to give disilyl ether 12 (61.4 g, 82.9 mmol, 100%).

Disilyl ether: colorless oil; Rf = 0.64 (silica, 20% ether in petroleum ether); IR (film) νmax 2946 (m), 2871 (m), 1739 (s), 1679 (m), 1579 (m), 1461 (m), 1369 (m), 1245 (m), 1097 (s), 837 (s), 766 (m), 736 (m), 697 (m) cm⁻¹; [α]D +7.2 (c 1.0, CH2Cl2); H NMR (500 MHz, CDCl3) δ 7.35–7.25 (m, 10 H, ArH), 5.01–4.94 (m, 3 H, OCH), 2.65–2.62 (m, 2 H, CH), 2.13 (dd, J = 10.0, 5.5 Hz, 1 H, CHPh), 1.75–1.70 (m, 3 H, CH3), 1.18 (s, 3 H, CH3).

A solution of disilyl ether 12 (61.4 g, 82.9 mmol) and camphorsulfonic acid (19.3 g, 82.9 mmol) in CH2Cl2/methanol (11: 80 mL) at 0°C was stirred for 1 h at 0°C. The reaction was quenched with triethylamine (20 mL) and concentrated. Flash chromatography (silica, 5%–20% ether in petroleum ether) gave alcohol 13 (50.4 g, 80.4 mmol, 97%).

Carboxylic Acid 14. Oxalyl chloride (14.0 mL, 161 mmol) was added dropwise to a solution of DMSO (171 mL, 241 mmol) in CH2Cl2 (200 mL) at −78°C. After 10 min, a solution of alcohol 13 (50.4 g, 80.4 mmol) was added dropwise. Triethylamine (78.4 mL, 563 mmol) was added after stirring at −78°C for 1 h, and the reaction mixture was warmed to 0°C. The mixture was diluted with ether (500 mL), washed with aqueous saturated ammonium chloride (300 mL), dried (MgSO4), and concentrated. The crude ester was dissolved in tert-butyl alcohol/H2O (2.1, 150 mL) and treated with 2-methyl-2-buten (80.4 mL of a 2.0 M solution in THF, 161 mmol; NaH2PO4·2H2O (10.9 g, 121 mmol), and sodium chloride (10.9 g, 121 mmol) at 25°C. After 1 h, the reaction mixture was diluted with ethyl acetate (200 mL) and washed with 10% aqueous tartaric acid (2 × 100 mL). The water layer was re-extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were dried (MgSO4), concentrated, and chromatographed (silica, 50–100% ether in petroleum ether) to give carboxylic acid 14 (50.0 g, 78.0 mmol, 97%).

Hydroxy Acid 15. A mixture of carboxylic acid 14 (50.0 g, 78.0 mmol) and tetra-2-butylammonium fluoride (390 mL of a 1.0 M solution in THF, 390 mL) in THF (100 mL) was stirred at 65°C for 8 h. The reaction mixture was diluted with ethyl acetate and the combined organic layers were dried (MgSO4), concentrated, and chromatographed (silica, 50–100% ether in petroleum ether) to give hydroxy acid 15 (11.9 g, 71.0 mmol, 91%).

Hydroxy acid: colorless oil; IR (film) νmax 3446 (m), 2945 (m), 2871 (m), 1739 (s), 1679 (m), 1579 (m), 1461 (m), 1369 (m), 1245 (m), 1078 (s), 885 (s), 776 (m), 734 (m), 697 (m) cm⁻¹; [α]D +4.6 (c 1.0, CH2Cl2); H NMR (500 MHz, CDCl3) δ 7.34–7.26 (m, 10 H, ArH), 4.46 (d, J = 11.5 Hz, 1 H, CHPhH), 3.69 (d, J = 11.5 Hz, 1 H, CHPhH), 3.59 (m, J = 15.6, 5.6 Hz, 2 H, CH), 2.72 (dd, J = 11.0, 5.5 Hz, 1 H, CH), 1.31 (s, 3 H, CH3), 1.19 (s, 3 H, CH3).

Lactone 7. A solution of hydroxy acid 15 (50.2 g, 143 mmol) and triethylamine (2.0 mL, 14.3 mmol) in THF (100 mL) was treated dropwise with 2,4-dichlorobenzoyl chloride (2.4 g, 10.0 mmol) at 0°C. After 2 h, the reaction mixture was diluted with benzene (500 mL) and added dropwise over 1 h to a refluxing solution of NaN₃dimethyl-4-aminopyridine (3.81 g, 47.5 mmol) in benzene (1.5 L). After 3 h, the reaction was concentrated and the residue was diluted with ether (500 mL), washed with aqueous saturated ammonium chloride (200 mL), aqueous saturated sodium bicarbonate (200 mL), and brine (200 mL). The organic layer was dried (MgSO4), concentrated, and subjected to flash chromatography (silica, 50–70% ether in petroleum ether) to give lactone 7 (4.30 g, 8.60 mmol, 90%).

Lactone 7: colorless needles, mp 103 °C (ether/hexanes); [α]D +0.3 (c 1.0, CH2Cl2); H NMR (500 MHz, CDCl3) δ 7.33–7.28 (m, 10 H, Ar), 4.56 (d, J = 11.6 Hz, 1 H, CHPhH), 4.41 (d, J = 11.6 Hz, 1 H, CHPhH), 4.31 (d, J = 11.0, 5.5 Hz, 1 H, CHC(O)(O)), 3.66–3.59 (m, 9 H, 3 × CH2OCH2Ph and OCH), 3.35 (dd, J = 12.0, 3.8 Hz, 1 H, OCH), 2.65–2.62 (m, 2 H, CH(O)(O)), 2.13 (dd, J = 11.7, 5.1 Hz, 1 H, CH), 2.00–1.87 (m, 8 H, 1 × CH2, 1 × CH), 1.75–1.40 (m, 3 × CH3, 1 × CH2), 1.26 (s, 6 × CH3), 1.23 (s, 3 × CH3), 1.26 (MgSO4 125 Hz, CDCl3) δ 174.0, 138.3, 138.3, 128.2, 127.6, 127.3, 72.9, 72.8, 72.6, 72.4, 70.9, 65.9, 41.2, 40.1, 39.8, 34.0, 30.8, 22.4, 19.3, 18.3, 17.3; HRMS, calculated for C13H14O5Si (M + Cs) 569.1857, found 569.1997.


Nicolaou et al.
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 triflate 16 (2.10 g, 3.28 mmol). The mixture was diluted with ether (200 mL), washed with brine (20 mL), dried (MgSO₄), filtered, concentrated, and subjected to flash chromatography (silica, 50–70% ether in petroleum ether containing 1% of triethylamine) to give enol ester 27 (1.54 g, 2.22 mmol, 100%, 24:1 mixture of diastereoisomers).

**Lactone Derived Enol Triflate 16.** Lactone derivative 20 (1.55 g, 3.21 mmol) was treated with enol ether 16 (2.10 g, 3.28 mmol) in THF (25 mL). The mixture was stirred for 2 h at 25 °C. The reaction was quenched with triethylamine (10 mL), diluted with ether (200 mL), washed with aqueous saturated ammonium chloride (100 mL) and water (100 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), filtered, concentrated, and subjected to flash chromatography (silica, 50–70% ether in petroleum ether containing 1% of triethylamine) to give enol ester 27 (1.54 g, 2.22 mmol, 100%, 24:1 mixture of diastereoisomers).
Nicolaou et al.

...mmol) and stirred at 25 °C for 1 h. The mixture was acidified with 2 mM, 1726 (m), 1453 (m), 1381 (s), 738 (m), 698 (m) sodium bicarbonate (100 mL), and brine (100 mL). The organic layer concentrated and the residue was diluted with ether (300 mL) washed with aqueous saturated sodium bicarbonate/sodium thiosulfate. After heating at 110 °C for 12 h, the solution was cooled to 0 °C and the crystalline diketone was filtered off (14.6 g, 7.37 mmol, 50%).

Diketone 55. A solution of diketone 54 (15.0 g, 41.9 mmol) and Dess-Martin periodinane (40.0 g, 94.3 mmol) in CHCl₃ (200 mL) was heated at 40 °C for 2 h. The reaction was diluted with ethyl acetate (500 mL) and washed with aqueous saturated sodium bicarbonate (100 mL), and brine (100 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give 28 (2.82 mmol, 0.475 mmol, 25%).

Lactone 6. A solution of hydroxy acid 29 (2.14 mmol of diol) and triethylamine (0.19 mL, 1.10 mol) and triethylamine (3.76 mmol, 1.44 mol) in THF (10 mL) was treated dropwise with 2.46-trichloroacentonitrile (296 mL, 1.90 mmol) at 0 °C. After 2 h, the reaction mixture was diluted with benzene (600 mL) and added dropwise over 1 h to a refocusing solution of Na₂,N-dimethyl-4-aminoypyridine (1.39 g, 11.4 mmol) in benzene (400 mL). After 3 h, the reaction was concentrated and the residue was diluted with ether (300 mL) washed with aqueous saturated ammonium chloride (100 mL), aqueous saturated sodium bicarbonate (100 mL), and brine (100 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give the desired lactone 6 (767 mg, 1.14 mmol, 60%) and its epimer 6b (282 mg, 0.475 mmol, 25%).

6: colorless foam; Rf = 0.75 (silica, 80% ether in petroleum ether); IR (film) νmax 3187 (br.), νmax 1785 (s), νmax 1615 (m) cm⁻¹; H NMR (500 MHz, CDCl₃) δ 7.29-7.25 (m, 10 H, ArH); 4.46 (d, J = 11.6 Hz, 2 H, CH₂,CH₂CO₂) 3.65-3.55 (m, 2 H, OCH₂), 3.52-3.48 (m, 1 H, OCH₂), 2.00-1.53 (m, 11 H, CH), 1.27 (s, 3 H, CH₃), 1.25 (s, 3 H, CH₃), 1.24 (s, 3 H, CH₃), 0.93 (d, J = 6.9 Hz, 3 H, CH₃), 0.84 (s, 3 H, CH₃); 13C NMR (125 MHz, CDCl₃) δ (major isomer) 174.5, 138.4, 136.3, 128.2, 128.2, 127.6, 127.5, 127.4, 89.7, 87.8, 85.6, 70.7, 72.9, 72.6, 72.0, 70.4, 69.4, 66.3, 65.9, 63.0, 63.5, 53.9, 31.8, 29.3, 29.0, 26.8, 21.4, 19.8, 17.5, 16.8, 15.7, 13.6; HRMS, calcd for C₇₉H₇₀O₂₅S (M + Cs⁺) 1894.5479, found 1894.5453.

Enol Triflate 36. A solution of lactone 6 (3.87 g, 6.53 mmol) and HMPA (2.3 mL, 13.1 mmol) in THF (100 mL) was treated with lithium bis(trimethylsilyl)amide (3.26 g, 0.10 mol) in THF (32.6 mmol) at -78 °C. After stirring at -78 °C for 2 h, N-phenyl trifluoromethanesulfonimide (3.50 g, 28.80 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 hydroxy acid 29 (1.07 g, 6.53 mmol, 93%).

36: colorless foam, Rf = 0.83 (silica, 50% ether in petroleum ether); IR (film) νmax 2925 (m), 2875 (m), 1699 (m), 1421 (m), 1214 (m), 1139 (m), 1072 (s), 836 (s), 739 (m), 699 (m) cm⁻¹; [α]D²⁸ = -12.9 (c = 1, CH₂Cl₂); H NMR (500 MHz, CDCl₃) δ 7.27-7.07 (m, 10 H, ArH); 4.36 (d, J = 7.3, 1 H, CH₃CO₂); 4.34 (d, J = 11.6, 1 H, CH₂CO₂); 4.04 (d, J = 5.5 Hz, 1 H, OCH₂), 3.56-3.5 (m, 3 H, OCH₂), 3.44-3.38 (m, 1 H, OCH₂), 2.47-2.30 (m, 2 H, CH₂CO₂), 2.12 (d, J = 11.5, 4.9 Hz, 1 H, CH₂OCH₂), 2.16-1.67 (m, 11 H, CH), 1.28 (s, 3 H, CH₃); 13C NMR (125 MHz, CDCl₃) δ (major isomer) 174.7, 138.4, 136.3, 128.2, 128.2, 127.5, 127.4, 89.7, 87.8, 85.6, 70.7, 72.9, 72.6, 72.0, 70.4, 69.4, 66.3, 65.9, 63.0, 63.5, 53.9, 31.8, 29.3, 29.0, 26.8, 21.4, 19.8, 17.5, 16.8, 15.7, 13.6; HRMS, calcd for C₇₉H₇₀O₂₅S (M + Cs⁺) 1894.5479, found 1894.5453.
Total Synthesis of Brevetoxin B. 2

C. D. Clatworthy, J. W. P. Grant, and J. M. A. Vella


Coupling Product 64. A mixture of enol triflate 36 (435 mg, 0.734 mmol), aldehide 62 (11.1 g, 3.67 mmol), chromium(II) chloride (150 mg, 2.54 mmol), and nickel(II) chloride (2 mg, 0.015 mmol) is 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 concentrated. Concentration and flash chromatography (silica, 10–30% ether in petroleum ether containing 1% triethylamine) gave the addition product 64 (425 mg, 0.484 mmol, 66%, 51 mixture of isomers). 64 (major isomer): colorless foam; RT = 0.31 (silica, 10% ethyl acetate in benzene); IR (film) ν = 3546 (w), 2954 (w), 2856 (w), 1730 (m), 1670 (w), 1642 (m), 1253 (m), 1072 (s), 836 (m), 775 (m), 725 (m), 697 (m) cm⁻¹; [α]D = -153 (c 1.0, CHCl₃); ΔH NR (500 MHz, CDCl₃) δ 7.30–7.07 (m, 10 H, ArH), 5.16 (dd, J = 7.5, 1.5, 20 H, CHO), 4.37 (d, J = 11.5 Hz, 2 H, CH₂PH); 4.33 (d, J = 11.5 Hz, 1 H, CH₂OPiv), 4.19 (d, J = 11.5 Hz, 1 H, CH₂OPiv), 4.17–4.13 (m, 1 H, OCH), 4.13 (s, 1 H, CH(O)), 3.80–3.76 (m, 1 H, OCH), 3.67 (dd, J = 11.5, 5.5 Hz, 1 H, OCH), 3.65–3.61 (m, 1 H, OCH), 3.45 (dd, J = 12.0, 2.5 Hz, 1 H, OCH₃), 3.22 (dd, J = 9.0, 1.0 Hz, 1 H, CH₂O), 3.13 (d, J = 11.0 Hz, 2 H, CH₂CH₂); 1.79 (s, 2 H, CH₂O), 1.68–1.64 (m, 1 H, CH₂); 0.29 (silica, 1 H, Si(OCH₃)₂), 0.11 (s, 3 H, Si(CH₃)₃); [α]D (125 MHz, CDCl₃) δ 177.0, 157.1, 139.3, 139.2, 128.3, 128.2, 127.6, 127.5, 107.2, 87.3, 87.0, 84.1, 78.7, 77.9, 77.5, 76.9, 75.9, 73.8, 73.0, 72.8, 71.0, 69.3, 66.3, 41.0, 39.1, 36.2, 30.9, 29.7, 28.3, 27.4, 26.0, 23.3, 20.6, 18.2, 15.2, 3.2, –4.2, 2.8; HRMS, calcd for C₄₀H₇₈O₁₄Si₂ (M + H) + 810.4419, found 810.4462.

Hydrogen 70. A mixture of triol 68 (7 mg, 0.10 mmol) and Ag₂CO₃/Celite (50 mg in benzene) (2 mL) was heated at 80 °C under an atmosphere of hydrogen for 3 h. The resulting black suspension was filtered through Celite, concentrated, and subjected to preparative TLC (silica, 100% ether) to give hydrogen ketone 79 (5 mg, 0.02 mmol, 78%); colorless foam; Rf = 0.55 (silica, 100% ether); IR (film) ν = 3449 (m), 2934 (m), 2872 (2727 m), 1714 (1455 m), 1378 (m), 1007 (s), 737 (m), 698 (m) cm⁻¹; [α]D = -15.6 (0.2, CH₂CH₂); [α]D NR (500 MHz, CDCl₃) δ 7.33–7.24 (m, 10 H, ArH), 4.45 (d, J = 11.7 Hz, 1 H, CH₂OPiv), 4.46 (s, 2 H, CH₂O), 4.37 (d, J = 11.7 Hz, 1 H, CH₂OPiv), 3.65–3.54 (m, 5 H, OCH₃), 3.36–3.27 (m, 3 H, OCH), 3.07 (dd, J = 11.7, 3.8 Hz, 1 H, OCH); 2.81 (dd, J = 16.1, 3.0 Hz, H, CH₂OCH₂); 2.63 (dd, J = 16.0, 9.0 Hz, 1 H, CH₂OCOCH₂); 2.18 (s, 3 H, COCH₃), 2.10 (dd, J = 11.6, 5.2 Hz, 1 H, CH₂O), 2.01–1.90 (m, 4 H, CH₂O), 1.83–1.79 (m, 2 H, CH₂), 1.72 (q, J = 11.8 Hz, 1 H, CH); 1.67–1.50 (m, 4 H, CH₂), 1.39 (t, J = 11.4 Hz, 1 H, CH, 1.28 (s, 3 H, CH₃), 1.24 (s, 3 H, CH₃), 1.22 (s, 3 H, CH₃), 1.21 (s, 3 H, CH₃); [α]D NR (125 MHz, CDCl₃) δ 209.5, 183.5, 138.5, 128.3, 128.2, 127.7, 127.6, 127.5, 127.5, 107.2, 88.6, 86.5, 83.0, 80.1, 78.1, 75.2, 74.3, 73.3, 73.0, 71.0, 66.0, 48.4, 40.3, 40.2, 38.1, 38.0, 31.6, 31.2, 28.8, 28.7, 21.8, 20.1, 18.6, 17.5; HRMS, calcd for C₃₇H₇₆O₁₄Si₂ (M + H) + 783.2873, found 783.2874.

Tertiary Alcohol 71. A solution of alcohol 64 (20 mg, 23 μmol) in ether (200 μL) was treated with potassium hydride (5 mg of a 35% suspension in mineral oil) and stirred at 25 °C for 5 min. The mixture was diluted with ether (20 mL) and poured into aqueous saturated ammonium chloride (10 mL). The organic layer was dried (MgSO₄), filtered, concentrated, and subjected to preparative TLC (silica, 30% ether in petroleum ether) to give alcohol 71 (20 mg, 23 μmol, 100%); colorless foam; RT = 0.34 (silica, 10% ethyl acetate in benzene); IR (film) ν = 3510 (w), 2956 (w), 2855 (s), 1733 (w), 1641 (m), 1381 (m), 1281 (m), 1153 (s), 1075 (s), 838 (m), 737 (m), 685 (m) cm⁻¹; [α]D = -11.4 (c 1.0, CH₂Cl₂); [α]D NR (500 MHz, CDCl₃) δ 7.30–7.07 (m, 10 H, ArH), 5.13 (dd, J = 7.5, 2.5 Hz, 1 H, CH₂O), 4.37 (d, J = 11.5 Hz, 1 H, CH₂OPiv), 4.36 (d, J = 11.5 Hz, 1 H, CH₂OPiv), 4.18 (d, J = 11.5 Hz, 1 H, CH₂OPiv), 4.12–4.07 (m, 1 H, OCH), 3.88 (s, 2 H, CH₂O), 1.68–1.64 (m, 1 H, CH₂); 0.29 (silica, 1 H, Si(OCH₃)₂), 0.11 (s, 3 H, Si(CH₃)₃); [α]D (125 MHz, CDCl₃) δ 177.0, 157.1, 139.3, 139.2, 128.3, 128.2, 127.6, 127.5, 107.2, 87.3, 87.0, 84.1, 78.7, 77.9, 77.5, 76.9, 75.9, 73.8, 73.0, 72.8, 71.0, 66.0, 48.4, 40.3, 40.2, 38.1, 38.0, 31.6, 31.2, 28.8, 28.7, 21.8, 20.1, 18.6, 17.5; HRMS, calcd for C₃₇H₇₆O₁₄Si₂ (M + H) + 783.2873, found 783.2874.
Nicolaou et al.

2.56 mmol) in benzene (5 mL) was heated at 80 °C for 3 h. The desired enol ether 74 (370 mg, 0.43 mmol, 67%) and the exocyclic carbon disulfide (129 A'L, 2.15 mmol) in ether (2 mL) was stirred at 0 °C, 1.77–1.74 (1 m, 1 H, CH), 1.67 (bt, J = 10.8 Hz, 1 H, CH), 1.40 (s, 3 H, CH3). 1.35–1.30 (1 m, 1 H, CH) 1.29 (s, 3 H, CH3). 1.26 (s, 9 H, t-Bu); 1.23 (s, 3 H, CH3). 1.06 (s, 9 H, t-Bu); 0.85 (d, J = 6.9 Hz, 1 H, CH), 0.23 (s, 2 H, 1 × 2H); 2.475 (M) NMR (125 MHz, CDCl3) δ 75.4, 154.7, 134.9, 139.2, 128.5, 128.2, 127.6, 127.1, 108.1, 88.3, 81.1, 78.7, 77.5, 73.7, 74.2, 74.1, 73.4, 73.1, 71.0, 70.9, 66.4, 40.9, 40.8, 33.9, 30.1, 29.7, 28.6, 28.4, 27.5, 27.4, 26.6, 26.1, 26.0, 21.6, 20.8, 17.9, 14.8, −1.9, −2.3; HRMS, calef for C23H30O3SiC6 (M + C*) 995.4489, found 995.4489.

Alcohol 75. A solution of enol ether 74 (100 mg, 0.115 mmol) in THF (0.5 mL) was treated with BHF/THF (0.58 mL of a 1.0 M solution in THF, 0.58 mmol) at −30 °C and stirred at −30 °C for 14 h. The resulting mixture was treated with 3 N sodium hydroxide (1.5 mL) and 30% hydrogen peroxide (1.0 mL) and stirred for 1 h at 25 °C. The mixture was diluted with ether (2 × 50 mL), dried (MgSO4), filtered, and concentrated. Flash chromatography (silica, 20–40% ether in petroleum ether) gave the alcohol 75 (82 mg, 0.093 mmol, 82%). 75: colorless foam; Rf = 0.35 (silica, 50% ether in petroleum ether); IR (film) νou 3510 (w), 2955 (s), 2930 (s), 2857 (s), 1727 (s), 1664 (w), 1541 (s), 1420 (m), 1380 (m), 1280 (m), 1273 (m), 1082 (w), 734 (m), 697 (m) cm−1; [α]D +23.6 (c 1.0, CH2Cl2); 'H NMR (500 MHz, CDCl3) δ 7.32–7.24 (10 m, 1 H, ArH), 4.54 (d, J = 11.6 Hz, 1 H, CH), 4.45 (s, 2 H, CH2Ph), 4.36 (d, J = 11.6 Hz, 1 H, CH), 4.09 (d, J = 9.0 Hz, 1 H, CH); 3.96 (s, 3 H, OCH3); 1.69 (s, 3 H, t-Bu); 0.94 (d, J = 6.9 Hz, 1 H, CH), 2.03–1.79 (m, 7 H, CH2), 1.44 (s, 3 H, CH3); 1.39 (s, 3 H, CH3); 1.32–1.30 (m, 1 H, CH); 1.28 (s, 3 H, CH3), 1.26 (s, 3 H, CH3), 1.24 (s, 3 H, CH3), 1.20 (s, 9 H, t-Bu); 0.85 (d, J = 6.9 Hz, 1 H, CH), 0.23 (s, 2 H, 1 × 2H); 2.475 (M) NMR (500 MHz, CDCl3) δ 76.3, 73.8, 73.5, 71.0, 70.9, 66.4, 40.9, 40.8, 33.9, 30.1, 29.7, 28.6, 28.4, 27.5, 27.4, 26.6, 26.1, 26.0, 21.6, 20.8, 17.9, 14.8, −1.9, −2.3; HRMS, calef for C23H30O3SiC6 (M + C*) 995.4489, found 995.4489.

Disilyl Ether 77. A solution of alcohol 75 (1.03 g, 1.16 mmol) and 2,6-lutidine (338 mL, 2.90 mmol) in CH2Cl2 (10 mL) was treated dropwise at 0 °C with triethylsilyl trifluoromethanesulfonate (787 mL, 3.46 mmol). After stirring at 0 °C for 30 min, the mixture was diluted with ether (250 mL), washed with aqueous saturated sodium chloride (2 × 100 mL), and dried (MgSO4). Filtration, concentration, and flash chromatography (silica, 10–30% ether in petroleum ether) gave disilyl ether 77 (1.11 g, 1.12 mmol, 96%). 77: colorless oil; Rf = 0.72 (silica, 30% ether in petroleum ether); IR (film) νou 3510 (w), 2955 (s), 2876 (s), 1729 (s), 1459 (s), 1356 (m), 1253 (m), 1071 (m), 835 (m), 733 (m), 697 (m) cm−1; [α]D +23.6 (c 1.0, CH2Cl2); 'H NMR (500 MHz, CDCl3) δ 7.33–7.25 (10 m, 1 H, ArH), 4.55 (d, J = 11.6 Hz, 1 H, CH), 4.45 (s, 2 H, CH2Ph), 4.37 (d, J = 11.6 Hz, 1 H, CH), 4.05 (s, 3 H, OCH3); 1.69 (s, 3 H, t-Bu); 0.94 (d, J = 6.9 Hz, 1 H, CH), 2.03–1.79 (m, 7 H, CH2), 1.44 (s, 3 H, CH3); 1.39 (s, 3 H, CH3); 1.32–1.30 (m, 1 H, CH); 1.28 (s, 3 H, CH3), 1.26 (s, 3 H, CH3), 1.24 (s, 3 H, CH3), 1.20 (s, 9 H, t-Bu); 0.85 (d, J = 6.9 Hz, 1 H, CH), 0.23 (s, 2 H, 1 × 2H); 2.475 (M) NMR (500 MHz, CDCl3) δ 76.3, 73.8, 73.5, 71.0, 70.9, 66.4, 40.9, 40.8, 33.9, 30.1, 29.7, 28.6, 28.4, 27.5, 27.4, 26.6, 26.1, 26.0, 21.6, 20.8, 17.9, 14.8, −1.9, −2.3; HRMS, calef for C23H30O3SiC6 (M + C*) 1013.4354, found 1013.4354.
Total Synthesis of Breve toxin B. 2

J. Am. Chem. Soc., Vol. 117

Lactol 80. A mixture of silyl ether 79 (5 mg, 6 μmol) and camphorsulfonic acid (0.4 mg, 1 μmol) in MeOH/H2O (10 mL, 1:1) was stirred at 25 °C for 2 h. The reaction was quenched with triethylamine (10 μL), concentrated, and subjected to preparative TLC (silica, 50% ether in petroleum ether) to give the lactol 80 (4 mg, 5 μmol, 85%, single isomer).

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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.