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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 [JKK] 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 68 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. Fetzon 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 dioxpane 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 fragments3—6 were to be constructed, coupled, and elaborated to form the oxocene and dioxpane regions of the molecule.1 The effectiveness and reliability of the hydroxy diithioketal cyclization in forming the oxocene system coupled with the difficulties associated with the construction of the challenging dioxpane framework forced us to adopt the reverse approach in which the dioxpane 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 diithioketal 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 intermediacy 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-...
(CH$_3$)$_2$PPh$_2$"$^+$T", NaHMDS, Scheme 2) to afford the (Z)-olefin 11 in 99% yield. Catalytic hydrogenation of the double bond in 11 using 10% Pd/C and Na$_2$CO$_3$ gave the saturated compound 12 in 100% yield, while exposure of the latter compound (12) to CSA in CH$_3$OH at 0 °C allowed selective desilylation of the primary hydroxyl group to afford monosilyl ether 13 in 97% yield. Sequential oxidation of 13 with COCl$_2$ in THF, 65 °C, 8 h, 91%; (g) 1.05 equiv of 2,4,6-trichlorobenzyl chloride, 1.5 equiv of En$_3$N, 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, THF, −78 °C, then 7.0 equiv of En$_3$N, 0.5 h; 1.5 equiv of NaHMDS, 2.0 equiv of NaHPO$_4$, 2.0 equiv of 2-methyl-2-bune, r-BuOH:H$_2$O (2:1), 25 °C, 1 h, 97%; (i) 5.0 equiv of TBAF, THF, 65 °C, 8 h, 91%; (g) 1.05 equiv of 2,4,6-trichlorobenzyl chloride, 1.5 equiv of En$_3$N, 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 PhNIT$_2$, −78 to 25 °C, 93%.

lactone 7. In preparation for the anticipated Murai coupling, lactone 7 was converted to its enol triflate 16 via enolization (LiHMDS) followed by quenching with PhNIT$_2$ (93% yield) (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 21 and 22 (both racemic, Table 1) were converted to their lithio derivatives by halogen—metal exchange (f-BuLi) and thence to the higher order cuprates RLi/Cu(2-thienyl)CNLi. Iodides 21 and 22 proceeded in a straightforward manner from γ-valerolactone (1:1.5 ratio of epimers 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 orhoester iodide 20 (Table 1 and Scheme 3) was prepared and utilized in the hope of improving the stereochemical outcome of the process. The synthesis of 20 proceeded in a straightforward manner from γ-valerolactone 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 stereo-isomer at C* (see Table 1). It should be noted at this point that...
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>TBSOi</td>
<td>17 (60, ca 1:1 at C*)</td>
</tr>
<tr>
<td>2</td>
<td>TBSOi</td>
<td>20 (91, ca 1:1.4 at C*)</td>
</tr>
<tr>
<td>3</td>
<td>Me*</td>
<td>21 (60, ca 1:1.5 at C*)</td>
</tr>
<tr>
<td>4</td>
<td>Me*</td>
<td>22 (65, ca 2:1 at C*)</td>
</tr>
<tr>
<td>5</td>
<td>Me*</td>
<td>23 (50, ca 1:1.4 at C*)</td>
</tr>
<tr>
<td>6</td>
<td>Me*</td>
<td>24 (49, ca 1:1.5 at C*)</td>
</tr>
<tr>
<td>7</td>
<td>Me*</td>
<td>25 (85, ca 2:1 at C*)</td>
</tr>
</tbody>
</table>

*a* Reagents and conditions: (a) 6.0 equiv of RI, 10.0 equiv of t-BuLi, EtO, -120°C to -78°C, 0.5 h, then 5.0 equiv of Cu2(Th)(CN)LL, Me2, -78°C to 0°C, 2 h.

Scheme 4 Construction of Orthoester Iodide 20

![Scheme 4](image)

*a* 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·Et2O, -30°C, 12 h, 70%.

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 diastereoisomers 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 hydroxy methyl ester 26, which is presumably formed by initial oxidation—elimination (91% overall yield) and thence to the desired α-compound (6), were converted to the desired α-epimer 6 by treatment with 1.5 equiv of LiHMDS, 1.5 equiv of HMPA, 2.0 equiv of PhSeBr, THF, -78°C to 0°C, 1 h; (b) 2.0 equiv of mCPBA, THF, 25°C, 91% (2 steps); (c) 2.0 equiv of LiHMDS, 2.0 equiv of HMPA, -78°C, THF, 30 min; quench with MeOH, 94%; (d) H2, 0.2 equiv of Ir(COD)(Py)2PF6, CH2Cl2, 25°C, 15 min, 80% of a 1:1 mixture of epimers; (e) 2.0 equiv of LiOH, MeOH:THF: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, 3 h, 60% of 6, plus 25% of its β-epimer 6β (after column chromatography).

Scheme 5 Recycling of Epimeric Lactone 6β to Lactone 6

![Scheme 5](image)

*a* Reagents and conditions: (a) 1.5 equiv of LiHMDS, 1.5 equiv of HMPA, 2.0 equiv of PhSeBr, THF, -78°C to 0°C, 1 h; (b) 2.0 equiv of mCPBA, THF, 25°C, 91% (2 steps); (c) 2.0 equiv of LiHMDS, 2.0 equiv of HMPA, -78°C, THF, 30 min; quench with MeOH, 94%; (d) H2, 0.2 equiv of Ir(COD)(Py)2PF6, CH2Cl2, 25°C, 15 min, 80% of a 1:1 mixture of epimers; (e) 2.0 equiv of LiOH, MeOH:THF: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.

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-ungaturated counterpart (30) via phenylesselenenylation—oxidation—syn-elimination (91% overall yield) and thence to the hydroxy methyl ester 31 (in which the double bond has...
Nicolaou et al.

**Scheme 6** Synthesis of DEFG Lactone Derivative 32

**Scheme 7** Coupling of B Ring 39 with the DEFG Ring System

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* Reagents and conditions: (a) H2, 20 wt % of 10% Pd(OH)2/C, EtOAc, 25 °C, 48 h, 93%; (b) 3.0 equiv of p-bromobenzoyl chloride, LDA, n-BuLi, tin—lithium exchange (n-BuLi, HMPA, THF, -78 °C) and addition of 39, -78 °C, 20 min, 40% of 38 (6:1 mixture of isomers) and 20% of 35; (d) 5.0 equiv of LiHMDS, THF, -78 °C, 20 min, then add 39, -78 °C, 20 min, 5.0 equiv of 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. 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 dehydropyranolization (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.14 The sequence leading to 47 involved initial deoxygenation of 38 via the Barton—McCombie two-step protocol16 (a) KH—CS—Me (70%); (b) n-BuSnH—AIBN, A (75%) to afford compound 44 via xanthate 43 followed by hydroboration—oxidation of the resulting enol ether (44) leading, regio- and stereochemically, to alcohol 45 (76% yield). Finally, oxidation of the latter...
Reductive Hydroxy Ketone Cyclization

Scheme 8: Failed Attempts to Construct the C Ring via Conjugate Addition

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Scheme 9: Failed Attempts to Construct the C Ring via Reductive Hydroxy Ketone Cyclization

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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)23 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 Ketoxin oxidation (Ag2CO3/Celite, benzene, 80 °C, 2 h; 96%). Th = 2-thienyl.

Cr–Ni Coupling of the DEF System

Scheme 10: Preparation of the DEF System

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References:

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>63</td>
<td>58</td>
</tr>
<tr>
<td>60</td>
<td>64</td>
<td>61</td>
</tr>
</tbody>
</table>

Reagents and conditions: (a) 2.1 equiv of PhCHO, 0.7 equiv of H$_2$SO$_4$, DMF, 25 °C, 3 days, 35%; (b) 2.3 equiv of Dess-Martin periodinane, CH$_2$Cl$_2$, reflux, 12 h, 90%, then toluene, 110 °C, 12 h, Soxhlet condensation; 4A IR, 90%; (c) 6.0 equiv of MeMgl (3.0 M in THF), 0 °C, 1 h, 92%; (d) H$_2$, 0.1 equiv of 10% Pd(OH)$_2$, AcOH, 25 °C, 48 h, 94%; (e) 2.5 equiv of Me$_3$C(OMe)$_2$, 0.1 equiv of CSA, DMF, 80 °C, 15 min, 60%; (f) 1.0 equiv of NaIO$_4$, THF/H$_2$O (1:1), 72 h, 90%; (g) 4.0 equiv of TBSCl, 7.0 equiv of 2,6-lutidine, 0.1 equiv of CSA, DMF, 25 °C, 3 days, 35%; (h) 1.1 equiv of Pb(OAc)$_4$, CH$_2$Cl$_2$, 25 °C, 24 h, 100%; (i) 3.0 equiv of PivCl, 0.2 equiv of DMAP, pyridine, DMAP, 25 °C, 5 h, 99%; (j) H$_2$, 0.1 equiv of 10% Pd/C, AcOH, 25 °C, 2 h, then 20 equiv of Mel, 10 min, 90%; (k) 5.0 equiv of n-Bu$_3$SnH, 0.1 equiv of AIBN, benzene, 80 °C, 30 min, 60%; (l) 5.0 equiv of BH$_3$/THF, THF, −30 °C, 16 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H$_2$O$_2$, 0 °C, 1 h, 72%; (m) 0.3 equiv of CSA, MeOH, 25 °C, 5 h, 95%; (n) 20 equiv of Ag$_2$CO$_3$/Celite, benzene, 80 °C, 3 h, 82%.

The Barton deoxygenation$^{19}$ 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 acetolide 67 (72% yield), from which the triol 68 was generated upon acid hydrolysis (95% yield). Feltiz 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 Cs$_2$O allowed the latter compound to drive the unfavorable equilibrium in its direction by forming xanthate 72 (89% yield). Second, the n-Bu$_3$SnH−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(PPh$_3$)$_3$Cl-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, 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 Petzolt 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 methanol/H₂O (4:1) containing catalytic amounts of camphor-sulfonic acid (CSA) furnished lactol 80 in 85% yield as a single anomer (stereochemistry unassigned). However, all attempts to C-glycosidate the anomeric position of the latter compound (80) met with failure. For example, allyltrimethylsilane under a variety of conditions did not lead to the expected derivative 81. A number of other relatives of 80 (e.g., methyl glycoside, acetate) also resisted functionalization and, therefore, this approach was no longer pursued.

Conclusion

In this paper a number of second generation strategies toward brevetoxin B (1) are described. The main themes of these studies were developed around a retrosynthetic analysis which defined suitable ABCDEFG and UK ring systems as potential advanced intermediates for a convergent strategy and projected the oxocene ring system as the last ring to be closed. A successful synthesis of the DEFG ring framework, a precursor to the larger ABCDEFG ring system, was developed. Several methods for the elaboration of the latter compound to a more advanced intermediate were also explored. Despite the many 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 inflates the oxocene ring system as the last ring to be closed. A number of other relatives of 80 (e.g., methyl glycoside, acetate) also resisted functionalization and, therefore, this approach was no longer pursued.

Experimental Section

General Techniques. For a description of general techniques, see the preceding paper in this issue.

NMR spectra were recorded on a Brucker 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 (58.4 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
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, 168 mmol) in THF (200 mL) was treated dropwise with sodium bis(trimethylsilyl)amide (126 mL of a 0.1 M solution in THF, 126 mmol) at 0 °C. The resulting orange solution was treated dropwise with a solution of the aldehyde 10 (90.0 g, 38.8 mmol) in THF (100 mL) at 0 °C. After stirring at 0 °C for 20 min, the mixture was quenched with 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 (61.1 g, 83.0 mmol, 99%). 11: colorless oil; 

\[ \text{IR (film) } \nu \text{cm}^{-1}: \text{[a] } 22^\circ \text{D} +7.3 \text{ (c 1.0, CHCl}_3) \]

Camphorsulfonic acid (19.3 g, 82.9 mmol) in CH2Cl2/methanol (1:1, 200 mL) at — 78 °C. After 10 min, a solution of alcohol 13 (50.4 g, 80.4 mmol, 82%) was added dropwise. Triethylamine (78.4 mL, 563 mmol) and tetra-n-butylammonium fluoride (390 mL of a 1.0 M solution in THF, 390 mL) was stirred at 65 °C for 2 h. The reaction mixture was diluted with ether (500 mL) and washed with 2 M hydrochloric acid (300 mL). The water layer was re-extracted with ether acetic (4 × 100 mL) and the combined organic layers were dried (MgSO4), concentrated, and chromatographed (silica, 50–100% ether in petroleum ether) to give carboxylic acid 15 (50.0 g, 78.0 mmol, 97%). 15: colorless foam; 

\[ \text{IR (film) } \nu \text{cm}^{-1}: \text{[a] } 22^\circ \text{D} =-43.1 \text{ (c 1.0, CHCl}_3); \text{H NMR (500 MHz, CDCl}_3) \]

Hydroxy Acid 15. A mixture of carboxylic acid 14 (50.0 g, 78.0 mmol) and tetra-n-butylammonium fluoride (390 mL of a 1.0 M solution in THF, 390 mL) was stirred at 65 °C for 2 h. The reaction mixture was diluted with ether (500 mL) and washed with 2 M hydrochloric acid (300 mL). The water layer was re-extracted with ether acetic and the combined organic layers were dried (MgSO4), concentrated, and chromatographed (silica, 20–50% tetrahydrofuran in ether acetic) to give hydroxy acid 15 (41.1 g, 71.0 mmol, 91%). 15: colorless foam; 

\[ \text{IR (film) } \nu \text{cm}^{-1}: \text{[a] } 22^\circ \text{D} =-44.6 \text{ (c 1.0, CHCl}_3); \text{H NMR (500 MHz, CDCl}_3) \]

Lactone 7. A solution of hydroxy acid 15 (50.2 g, 14.3 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 N,N-dimethyl-4-aminopyridine (3.81 g, 47.5 mmol) in benzene (1.5 L). After 3 h, the mixture was concentrated and the residue was diluted with ether (500 mL), washed with aqueous saturated ammonium chloride (200 mL), saturated aqueous 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, 50%). 7: colorless needles, mp 103 °C (ether/hexanes); [a] 22°D = 0.38 (silica, 70% ether in petroleum ether); 

\[ \text{IR (film) } \nu \text{cm}^{-1}; \text{[a] } 22^\circ \text{D} =+0.9 \text{ (c 1.0, CHCl}_3); \text{H NMR (500 MHz, CDCl}_3) \]

Carboxylic Acid 14. Oxalyl chloride (14.0 g, 161 mmol) was added dropwise to a solution of DMSO (17.1 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 product 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, NaHPO4•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 (500 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%). 14: colorless foam; 

\[ \text{IR (film) } \nu \text{cm}^{-1}; \text{[a] } 22^\circ \text{D} =-14.1 \text{ (c 1.0, CHCl}_3); \text{H NMR (500 MHz, CDCl}_3) \]
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 18 (43.8 g, 0.14 mol, 70%). 

19: To a solution of enol triflate 18 (20.0 g, 0.07 mol) in THF (25 mL), n-BuLi (20.7 mL of a 1.7M solution in pentane) was added dropwise at −120 °C. After stirring at −120 °C for 30 min, the mixture was allowed to warm to −78 °C and lithium bis(trimethylsilyl)amide (42.5 mL of a 1.0 M solution in THF) at −78 °C. After stirring at −78 °C for 2 h, 4-nitrophenyl trifluoromethanesulfonylimide (4.61 g, 12.8 mmol) was added to the mixture, and stirring for 1 h at −25 °C, the reaction was quenched with water (500 mL). After stirring for 1 h at 25 °C, the mixture was allowed to warm to 25 °C over 1 h. After stirring for 1 h at 25 °C, the reaction was quenched with water (500 mL). The organic layer was dried (MgSO₄), filtered, concentrated, and subjected to flash chromatography (silica, 20-50% ether in petroleum ether containing 1% of triethylamine) to give iodide 19 (62.4 g, 0.20 mol, 20% over 2 steps). 

20: To a solution of iodide 19 (24.4 g, 0.200 mol), triethylamine (279 mL, 2.00 mol), and 3-methyl-3-oxetanemethanol (100 g, 1.00 mol) in CH₂Cl₂ at 0 °C. After stirring for 10 min, the mixture was quenched with triethylamine (10 mL), diluted with ether (200 mL), washed with aqueous saturated ammonium chloride (200 mL), and added dropwise to a solution of terr-butyllithium (20.7 mL of a 1.7M solution in pentane, 35.2 mmol) at −120 °C. After stirring at −120 °C for 30 min, the mixture was allowed to warm to −78 °C and lithium bis(trimethylsilyl)amide (42.5 mL of a 1.0 M solution in THF) at −78 °C. After stirring at −78 °C for 2 h, 4-nitrophenyl trifluoromethanesulfonylimide (4.61 g, 12.8 mmol) was added to the mixture, and stirring for 1 h at −25 °C, the reaction was quenched with water (500 mL). The organic layer was dried (MgSO₄), filtered, concentrated, and subjected to flash chromatography (silica, 20-50% ether in petroleum ether containing 1% of triethylamine) to give iodide 19 (62.4 g, 0.20 mol, 20% over 2 steps). 

20: A solution of enol ether 18 (20.0 g, 0.07 mol) in THF (25 mL) was treated with lithium bis(trimethylsilyl)amide (42.5 mL of a 1.0 M solution in THF) at −78 °C. After stirring at −78 °C for 2 h, 4-nitrophenyl trifluoromethanesulfonylimide (4.61 g, 12.8 mmol) was added to the mixture, and stirring for 1 h at −25 °C, the reaction was quenched with water (500 mL). The organic layer was dried (MgSO₄), filtered, concentrated, and subjected to flash chromatography (silica, 10-20% ether in petroleum ether containing 1% of triethylamine) to give enol triflate 18 (43.8 g, 0.14 mol, 70%).
4.37 (d, mixture was diluted with benzene (600 mL) and added dropwise over hydrochloric acid to pH 1 and the water layer was extracted with sodium bicarbonate (100 mL), and brine (100 mL). The organic layer was dried (MgSO₄), filtered, and concentrated to give hydroxy acid 29 (1.07 g, 37.7 mmol, 90%). 55: white solid, mp 184-186 °C (toluene); 56. A solution of lactone 6 (376 mg, 1.14 mmol) and triethylamine (397 mg, 3.85 mmol) in benzene (300 mL). After 3 h, the mixture was washed with aqueous saturated ammonium chloride (100 mL), aqueous saturated sodium thiosulfate (25 mL, 4:1) was treated with lithium hydroxide hydrate (447 mg, 10.7 mmol) at -78 °C. After stirring at -78 °C for 2 h, N-phenyl trifluoromethanesulfonylimide (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 Enol Triflate 36 (4.40 g, 6.07 mmol, 93%). 36: colorless foam, Rf 0.83 (silica, 30% ether in petroleum ether); IR (film) v 2952 (m), 2875 (m), 1699 (s), 1421 (m), 1214 (m), 1109 (s), 739 (m), 727 (s), 710 (m), 704 (s), 69.5, 64.3, 63.5, 36.5, 35.9, 31.8, 29.7, 29.3, 26.8, 21.4, 19.8, 17.5, 16.8, 15.7, 13.6; HRMS, calculated for C₉H₇O₃S (M + Cs+) 275.2454, found 275.2466.

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 (32.6 mL of a 1.0 M solution in THF, 32.6 mmol) at -78 °C. After stirring at -78 °C for 2 h, N-phenyl trifluoromethanesulfonylimide (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 Enol Triflate 36 (4.40 g, 6.07 mmol, 93%). 36: colorless foam, Rf 0.83 (silica, 30% ether in petroleum ether); IR (film) v 3051 (s), 2930 (m), 2872 (m), 1740 (s), 1452 (m), 1380 (s), 1274 (w), 1218 (s), 1118 (m), 1024 (s), 737 (m), 699 (s); HRMS, calculated for C₉H₇O₃S (M + Cs+) 275.2454, found 275.2466.
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 g, 0.015 mmol) in DMF (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%) in petroleum ether containing 1% triethylamine gave the addition product 64 (425 mg, 0.484 mmol, 69% of isomer) as a colorless foam (5). 64: IR (film) 3449 (m), 2934 (m), 2872 (m), 1714 (m), 1455 (m), 1378 (m), 1260 (s), 1148 (s), 1042 (s), 972 (s), 917 (s), 836 (m) cm⁻¹; [α]D₂₂ 3.4 (c 1.0, CH₂Cl₂); HRMS, calcd for C₃₀H₃₃N₅S (M) 783.2873, found 783.2874.

Hydroxy Ketone 70. A mixture of triol 68 (7 mg, 10 μmol) and Ag₂O/Celite (50 mg) in benzene (2 mL) was heated at 80 °C under anhydrous conditions 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) as a colorless foam; Rf = 0.24 (silica, 10% ethyl acetate in petroleum ether). 70: IR (film) 3439 (m), 2934 (m), 2872 (m), 1727 (s), 1714 (m), 1663 (s), 1577 (s), 1508 (s), 1415 (m), 1367 (m), 1323 (s), 1277 (s), 1269 (s), 1257 (m), 1135 (s), 1058 (s), 1004 (s), 836 (m), 774 (m) cm⁻¹; [α]D₁₀ 2.4 (c 0.5, CHCl₃); HRMS, calcd for C₃₀H₃₃N₅S (M) 783.2849, found 783.2844.

Dipivaloate 61. A solution of tetralin 60 (5.10 g, 11.6 mmol, N,N-dimethylethylamine (0.28 g, 2.3 mmol), and pivaloyl chloride (4.30 mL, 34.8 mmol) in pyridine (15 mL) was stirred at 25 °C for 24 h. The mixture was diluted with ether (200 mL), washed with aqueous saturated ammonium chloride (200 mL), and dried (MgSO₄). Filtration, concentration, and flash chromatography (silica, 30−50% ether in petroleum ether) gave dipivaloate 61 (6.70 g, 11.6 mmol, 100%). 61: colorless oil; Rf = 0.36 (silica, 10% ether in petroleum ether); IR (film) 2943 (m), 2930 (m), 2853 (m), 2716 (m), 2663 (m), 2636 (m), 2026 (m), 1995 (m), 1868 (m), 1865 (m), 1687 (s), 1534 (s), 1465 (m), 1421 (m), 1397 (m), 1284 (m), 1257 (m), 1152 (s), 1037 (m), 836 (s), 775 (m) cm⁻¹; [α]D₁₀ 2.3 (c 1.0, CHCl₃); HRMS, calcd for C₃₀H₃₃N₅S (M) 783.2849, found 783.2844.

Aldeyde 62. A solution of dipivaloate 61 (6.7 g, 11.7 mmol) in CH₂Cl₂ (25 mL) was treated with lead tetracetate (5.7 g, 12.9 mmol) and stirred at 25 °C for 15 min. The mixture was diluted with ether (100 mL), washed with aqueous saturated sodium bicarbonate (100 mL), and dried (MgSO₄). Filtration, concentration, and flash chromatography (silica, 10% ether in petroleum ether) gave the aldehyde 62 (6.40 g, 21.2 mmol, 91%). 62: colorless oil; Rf = 0.29 (silica, 10% ether in petroleum ether); IR (film) 2943 (m), 2930 (m), 2853 (m), 2716 (m), 2663 (m), 2636 (m), 2026 (m), 1995 (m), 1868 (m), 1865 (m), 1687 (s), 1534 (s), 1465 (m), 1421 (m), 1397 (m), 1284 (m), 1257 (m), 1152 (s), 1037 (m), 836 (s), 775 (m) cm⁻¹; [α]D₁₀ −11.6 (c 1.0, CHCl₃); HRMS, calcd for C₃₀H₃₃N₅S (M) 783.2849, found 783.2844.
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 25 °C with potassium hydride (1.43 g, 35.9 mmol, after washing with 3 N sodium hydroxide (1.5 mL) in THF, 0.58 mmol) at -30 °C and stirred at -30 °C for 14 h. The resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether containing 1% of triethylamine) gave the alcohol 75 (82 mg, 0.093 mmol, 82%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 30% ether in petroleum ether) gave the alcohol 76 (82 mg, 0.093 mmol, 82%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 77 (1.11 g, 1.12 mmol, 96%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 78 (1.07 g, 1.08 mmol, 99%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 79 (0.69 g, 0.71 mmol, 71%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 80 (0.31 g, 0.32 mmol, 32%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 81 (0.18 g, 0.19 mmol, 19%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 82 (0.08 g, 0.09 mmol, 9%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 83 (0.04 g, 0.04 mmol, 4%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 84 (0.02 g, 0.02 mmol, 2%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 85 (0.01 g, 0.01 mmol, 1%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 86 (0.00 g, 0.00 mmol, 0%). The alcohol was treated with 3 N sodium hydroxide (1.5 mL) at 25 °C and the resulting mixture was stirred with ether (2 × 50 mL), dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 10% ether in petroleum ether) gave the alcohol 87 (0.00 g, 0.00 mmol, 0%).
Total Synthesis of Brevetoxin B. 2

A mixture of silyl ether 79 (5 mg, 6 µmol) in acetonitrile (2 mL) was treated with Dess-Martin periodinane (1.78 g, 4.1 mmol, 95%). The mixture was stirred for 2 h at 25 °C. 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). Lactol 80 was purified by thin layer chromatography (silica, 50% ether in petroleum ether) followed by preparative TLC (silica, 20% ether in petroleum ether). The compound was then subjected to preparative flash chromatography (silica, 50% ether in petroleum ether) for the final purification. The compound was then subjected to preparative TLC (silica, 20% ether in petroleum ether) to obtain the final product.

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