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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 [JJK] 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 \( \rightarrow \) 7) and (29 \( \rightarrow \) 6), respectively. The required appendage on ring [E] was efficiently introduced via a Murai coupling, involving addition of a higher order organocuprate derived from iodide 20 to the lactone-derived enol triflate 16 (16 \( \rightarrow \) 25). The minor epimer of the resulting product 69 was then converted to the desired isomer 6a via hydrogenation using an Ir(1) 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 \( \rightarrow \) 42) and reductive hydroxy ketone cyclization (47 \( \rightarrow \) 48) failed to yield ring C. Fetizon cyclization afforded the pentacyclic lactone [CDEFG] (51 \( \rightarrow \) 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 fragments34–50 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 dithiolactone 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 \( \rightarrow \) 2) defining hydroxy dithiolactone 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-R-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-


(la) 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 PhNTF2 (93% yield)2 (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 211 and 222 (both racemic, Table 1) were converted to their lithio derivatives by halogen—metal exchange (t-BuLi) and then to the higher order cuprates RLi/Cu(2-thienyl)NCl10 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 prepared11 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 stereoisomer at C* (see Table 1). It should be noted at this point


(8) Iodide 21 was prepared from 1,4-butanediol in four steps: (a) 1.0 equiv of NaH, 1.0 equiv of TBSiCl, THF, 25 °C; (b) 1.5 equiv of (CICO)2, 2.0 equiv of DMSO, −78 °C, then Et3N; (c) 1.2 equiv of MeMgCl, −78−25 °C; (d) 1.4 equiv of I2, 1.0 equiv of PhPF, 1.2 equiv of imidazole, benzene, 25 °C (64% overall yield).

(9) Iodide 22 was prepared from 1,4-butanediol in seven steps: (a−d) as for 21 (see ref 8); (e) 1.0 equiv of CSA, CH2Cl2/MeOH (1:1), 0 °C; (f) 3.0 equiv of SO3/pyridine, CH2Cl2/DMSO (1:1), 10 equiv of Et3N, −30 °C; (g) 2.0 equiv of 1,2-ethanediol, THF, benzene, 25 °C (55% over 3 steps).


that crucial to the observed stereoselectivity was the employment of the solvent system Et$_2$O: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 secondary alcohol were accompanied by considerable amounts of the reduced product 26, which is presumably formed by initial 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:H$_2$O (1:1), 25 °C, 100%; (c) 2.0 equiv of H$_2$O, 25 °C, 91% (2 steps); (d) 2.0 equiv of LiHMDS, 25 °C, 40 min, then 10 equiv of 3 N NaOH, 20 equiv of 30% H$_2$O$_2$, 89%; (d) 2.0 equiv of LiOH, DME:H$_2$O (1:1), 25 °C, 1 h, 82%; (e) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et$_3$N, 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 4: Construction of the DEFG Ring System 6

Reagents and conditions: (a) 5.0 equiv of BH$_3$·THF, −30 °C, 17 h, then 25 equiv of 3 N NaOH, 50 equiv of 30% H$_2$O$_2$, 81%; (b) 0.3 equiv of PPTS, DME:H$_2$O (1:1), 25 °C, 100%; (c) 6.0 equiv of BH$_2$·THF, 0 °C, 40 min, then 10 equiv of 3 N NaOH, 20 equiv of 30% H$_2$O$_2$, 89%; (d) 0.5 equiv of SO$_2$Br$_2$, 0.05 equiv of H$_2$SO$_4$, −78 °C, THF, 30 min; quench with MeOH, 94%; (e) 2.0 equiv of LiHMDS, 2.0 equiv of PhSeBr, THF, −78−−−30 °C, 1 h; (f) 2.0 equiv of mCPBA, THF, 25 °C, 91% (2 steps); (g) 2.0 equiv of LiHMDS, 2.0 equiv of HMPA, −78 °C, THF, 30 min; quench with MeOH, 94%; (d) H$_2$, 0.2 equiv of Ir(COD)(Py)(Cy)$_2$PF$_6$, CH$_2$Cl$_2$, 25 °C, 15 min, 80% of a 1:1 mixture of epimers; (h) 2.0 equiv of LiOH, MeOH:H$_2$O (4:1), 30 min, 100%; (i) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et$_3$N, 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.

Scheme 5: Recycling of Epimeric Lactone 6β to Lactone 6

Reagents and conditions: (a) 1.5 equiv of LiHMDS, 1.5 equiv of HMPA, 2.0 equiv of Ph$_2$SbH, THF, −78−−−30 °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) H$_2$, 0.2 equiv of Ir(COD)(Py)(Cy)$_2$PF$_6$, CH$_2$Cl$_2$, 25 °C, 15 min, 80% of a 1:1 mixture of epimers; (e) 2.0 equiv of LiOH, MeOH:H$_2$O (4:1), 30 min, 100%; (f) 1.05 equiv of 2,4,6-trichlorobenzoyl chloride, 1.5 equiv of Et$_3$N, 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.
Scheme 6* Synthesis of DEFG Lactone Derivative 32

* Reagents and conditions: (a) H₂, 20 wt % of 10% Pd(OH)₂/C, EtOAc, 25 °C, 48 h, 93%; (b) 3.0 equiv of 4-bromobenzoyl chloride, 4.5 equiv of DMAP, CH₂Cl₂, 25 °C, 2 min, 72%.

migrated to the β,γ-position) by deconjugation with LiHMDS, followed by methanolic quenching (94% yield). Hydrogenation of ester 31 using Ir(COD)₃(pyr)₂(μ₂-C₆H₄)PF₆·H₂O (80% yield) followed by saponification furnished a 1:1 mixture (100% yield) of the corresponding hydroxyl acids. Finally, lactonization of the latter mixture under the Yamaguchi conditions gave a 1:1 mixture of lactones 6 and 6β (90% total yield) which was chromatographically separated into its pure components.

The structural assignment of lactone 6 was secured by X-ray crystallographic analysis of its bis(4-bromobenzoyl) derivative 32 (see ORTEP drawing, Figure 1), prepared as summarized in Scheme 6.

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 (Scheme 7). To this end, lactone 6 was converted to the thionolactone 33 (Scheme 7) by treatment with Lawesson's reagent at 180 °C (68% yield) and thence to the vinylstannane 34 via sequential treatment with LDA, n-Bu₃SnH, I(CH₂I), and 2,6-lutidine (50% overall yield). Conversion of 34 to the corresponding lithium reagent via tin–lithium exchange (n-BuLi, HMPA, THF, −78 °C) followed by addition of aldehyde 39 resulted in the formation of adduct 38 (40%, ca. 6:1 mixture of Cα epimers), together with oxepine 35 (20%) derived by protonation of the organo-metallic species. In an attempt to improve the coupling of the two partners (39 and 6), a second sequence was explored according to which lactone 6 was converted to its enol ether 36 (LiHMDS, HMPA, THF, −78 °C), then PhNTf₂, 93%) and thence to stannane enol ether 37 ([Me₃SnSnMe₃, Pd(PPh₃)₄ catalyst, LiCl, DMF, 95%] before metal exchange (n-BuLi, HMPA, THF, −78 °C) and addition of 39. Although the overall yield of converting 6 to the stanny 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.

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 (TBAB, 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.¹¹ The sequence leading to 47 involved initial deoxygenation of 38 via the Barton–McCombie two-step protocol [(a) KH–CS₂–MeI (70%); (b) n-BuSnH–AIBN, Δ (75%)] to afford compound 44 via xanthate 43 followed by hydroboration–oxidation of the resulting enol ether (44) leading, regio- and stereoselectively, to alcohol 45 (76% yield). Finally, oxidation of the latter

Figure 1. ORTEP drawing of 32.

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

* Reagents and conditions: (a) 6.0 equiv of Lawesson's reagent, xylene, 180 °C, 45 min, 68%; (b) 4.0 equiv of LDA, 5.0 equiv of n-BuSnH, −10 °C, THF, 30 min, then add 33, 30 min, 5.0 equiv of I(CH₂)₂, 10 equiv of 2,6-lutidine, 30 min, 50%; (c) 2.0 equiv of n-BuLi, 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; (d) 5.0 equiv of LiHMDS, 1.5 equiv of HMPA, THF, −78 °C, 2 h; then 2.0 equiv of PhNTf₂, −78 to −25 °C, 2 h, 93%; (e) 0.05 equiv of Pd(PPh₃)₄, 2.0 equiv of MesSnSnMe₃, 1.0 equiv of LiCl, DMF, 25 °C, 14 h, 95%; (f) 2.0 equiv of n-BuLi, 1.0 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.
Scheme 8 failed attempts to construct the C ring via conjugate addition.

Reagents and conditions: (a) 4.0 equiv of Dess-Martin periodinane, CH$_2$Cl$_2$, 3 h, 25 °C, 91%; (b) 2.0 equiv of TBAF, THF, 25 °C, 3 h, 93%.

Scheme 9 failed attempts to construct the C ring via reductive hydroxy ketone cyclization.

Reagents and conditions: (a) 10 equiv of KH, 5.0 equiv of CS$_2$, 25 °C, 2 h, then 20 equiv of MeI, 10 min, 70%; (b) 5.0 equiv of n-Bu$_3$SnH, benzene, 80 °C, 1 h, 75%; (c) 5.0 equiv of BH$_3$THF, THF, -30 °C, 12 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H$_2$O$_2$, 0 °C, 1 h, 90%; (d) 0.1 equiv of TPAP, 2.0 equiv of NMO, CH$_2$CN, 25 °C, 1 h, 90%; (e) 1.2 equiv of TBAF, THF, 25 °C, 7 h, 95%; (f) 10 equiv of Ph$_3$MeSiH, 1.2 equiv of TMSOTf, MeNO$_2$, 0 °C, 1 h.

The compound (45) with N-methylmorpholine N-oxide (NMO) in the presence of a catalytic amount (10%) of tetra-n-propyl-ammonium perruthenate (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).

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(CH$_2$)$_3$Cu(2-Th)CNLi]~(21) furnishing oxepene 49 (82%) which was subjected to hydroboron-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 (Ag$_2$CO$_3$/Celite, Δ) furnishing a mixture of lactones (52 and 52a, 96% total yield).~(22) Attempts to elaborate this pentacyclic system gave mixed results and discouraging results. For example, the corresponding triflate could only be obtained with difficulty and in low yield, whereas addition reactions to the corresponding thionoalactone 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.~(23) A number of second generation attempts to construct the ABCDEFG framework of brevetoxin B (I) from the DEFG system were then made. A new method of coupling

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(20) For a review on TPAP oxidations, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. Synthesis 1994, 639.


Scheme 11a Synthesis of Aldehydes 59 and 62

![Scheme 11a](image)

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 MeMgI (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 MeC(OMe), 0.1 equiv of CSA, DMF, 80 °C, 15 min, 60%; (f) 1.0 equiv of NaOAc, THF/H2O (1:1), 72 h, 90%; (g) 4.0 equiv of TBSOTf, 7.0 equiv of 2,6-lutidine, 0.1 equiv of DMAP, pyridine, 25 °C, 5 h, 99%; (h) H2, 0.1 equiv of 10% Pd/C, AcOH, 25 °C, 48 h, 91%; (i) 3.0 equiv of PivCl, 0.2 equiv of DMAP, pyridine, 25 °C, 24 h, 100%; (j) 1.1 equiv of Ph(OAc)2, CH2Cl2, 25 °C, 15 min, 91%.

Table 2. CrNi-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>PhCHO</td>
<td>39</td>
<td>59, 5:1</td>
</tr>
<tr>
<td>6.0 equiv of CrCl2</td>
<td>0.02 equiv of NiCl2</td>
<td>DMF, 25 °C, ultrasound</td>
</tr>
<tr>
<td>MeOH</td>
<td>63</td>
<td>68, 4:1</td>
</tr>
<tr>
<td>5.0 equiv of aldehyde</td>
<td>66, 6:1 ratio</td>
<td></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 deoxygenation9 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 acetonide 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 silyl 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 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 Dibal-H then furnished diol 76 (80% yield) which, however, resisted Perkin 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 Dibal-H-induced removal of the pivaloate group and Dess-Martin oxidation gave aldehyde 77 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 anomeric (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 IJK 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

Experimental Section

General Techniques. For a description of general techniques, see the preceding paper in this issue.1 NMR spectra were recorded on 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 (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, 165 mmol) in THF (200 mL) was treated dropwise with sodium bis(trimethylylamide (125 mL of a 1.0 M solution in THF, 126 mmol) at 0 °C. The resulting orange ylide solution was treated dropwise with a solution of the aldol (10.0 mL, 103 mmol) in THF (100 mL). The mixture was warmed to 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, 50–20% ether in petroleum ether) gave olefin 11 (61.3 g, 83.0 mmol, 99%).

**Diisyl Ether 12.** A mixture of the olefin 11 (61.3 g, 82.9 mmol), 10% Pd/C (6.1 g, 10% by weight), and sodium carbonate (900 mg, 8.30 mmol) in ethyl acetate (200 mL) was stirred under a H2 atmosphere for 12 h at 25 °C. The mixture was filtered and concentrated to give diisyl ether 12 (61.4 g, 82.9 mmol, 100%).

**Disilyl Ether 14.** A mixture of the olefin 11 (61.3 g, 82.9 mmol, 10% Pd/C (6.1 g, 10% by weight), and sodium carbonate (900 mg, 8.30 mmol) in ethyl acetate (200 mL) was stirred under a H2 atmosphere for 12 h at 25 °C. The mixture was filtered and concentrated to give diisyl ether 12 (61.4 g, 82.9 mmol, 100%).

**Lactone 7.** A mixture of carboxylic acid (5.02 g, 14.3 mmol) and triphenylphosphine (30 g, 40.4 mmol) in CH2Cl2/methanol (1:1, 80 mL) 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 lactone 7 (50.4 g, 84.4 mmol, 97%).

**Carboxylic Acid 14.** Oxalyl chloride (140 mL, 161 mmol) was added dropwise to a solution of DMSO (17.1 mL, 241 mmol) in CHCl3 (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 allowed to warm 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 aldehyde 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), NaNH2PO4·H2O (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 concentrated 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-n-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 (500 mL) and washed with 2 M hydrochloric acid (300 mL). The water layer was re-extracted with ethyl acetate and the combined organic layers were dried (MgSO4), concentrated, and chromatographed (silica, 0–20% methanol in ethyl acetate) to give hydroxy acid 15 (41.1 g, 71.0 mmol, 91%).

**Lactone 7.** A solution of hydroxy acid 15 (5.02 g, 14.3 mmol) and triphenylphosphine (20 mL, 14.3 mmol) in THF (100 mL) was treated with 2,4,6-trichlorobenzyl 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 Na/N-dimethyl-4-aminopyridine (5.8 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), 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.** A solution of hydroxy acid 15 (5.02 g, 14.3 mmol) and triphenylphosphine (20 mL, 14.3 mmol) in THF (100 mL) was treated with 2,4,6-trichlorobenzyl 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 Na/N-dimethyl-4-aminopyridine (5.8 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), 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 Derived Enol Triflate 16. A solution of lactone 7 (4.30 g, 8.50 mmol) and HMPA (2.2 mL, 12.8 mmol) in THF (30 mL) was treated with lithium bis(trimethylsilyl)amide (42.5 mL of a 1.0 M solution in THF, 42.5 mL) at −78 °C. After stirring at −78 °C for 2 h, the mixture was diluted with ether (1.5 L) and washed with aqueous triethylamine (10 mL) to give iodide 17 (19.2%, 830 mg, 0.66 mmol). IR (film) νmax 2962 (m), 2872 (m), 1710 (m), 1451 (m), 1379 (m), 1268 (m), 1178 (s), 982 (s), 833 (m) cm−1; 1H NMR (500 MHz, CDCl3) δ 3.94–3.84 (8.1 H, CH2); 2.77–2.15 (m, 2 H, CH2C); 2.23–1.91 (m, 2 H, CH2C); 1.58 (d, J = 6.5 Hz, 3 H, CH3C); 0.00 (s, 3 H, CH3). HRMS, calcd for C10H18O3Br (M + H+) 265.0439, found 265.0427.

Bromide 18. Thionyl bromide (104 g, 0.501 mol) was added to a mixture of γ-valerolactone (17, 100 g, 1.00 mol) and dry zinc bromide (11.3 g, 50.2 mmol) and the mixture was heated at 55 °C for 50 h. The reaction mixture was cooled to 25 °C, diluted with CH2Cl2 (300 mL), and concentrated to dryness and then added dropwise to a solution of N,N-dimethyl-4-aminopyridine (24.4 g, 0.200 mol), triethylamine (279 mL, 2.00 mol), and 3-methyl-3-oxotetranethanol (100 g, 1.00 mol) in CH2Cl2 at 0 °C. After stirring for 1 h at 25 °C, the mixture was filtered through Celite, diluted with 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 bromide 18 (55.7 g, 0.212 mol). 18: yellow oil; Rf = 0.32 (silica, 40% ether in petroleum ether); IR (film) νmax 2964 (s), 2930 (m), 2871 (m), 1739 (s), 1548 (m), 1380 (m), 1272 (m), 1163 (s), 982 (s), 833 (m) cm−1; 1H NMR (500 MHz, CDCl3) δ 4.52 (dd, J = 4.6, 1.4 Hz, 2 H, CH2O), 3.76–3.71 (m, 2 H, CH2C), 2.18–2.10 (m, 2 H, CH2C); 1.73 (d, J = 6.7 Hz, 3 H, CH3C); 1.32 (3 s, 3 H, CH3C); 1/12 NMR (125 MHz, CDCl3) δ 173.2, 79.9, 69.2, 50.7, 39.5, 36.2, 32.8, 26.9, 21.5; HRMS, calcd for C10H18O3Br (M + Na+) 299.2071, found 299.2083.

Orthoester 20. A stirred solution of orthoester 19 (4.24 g, 0.0201 mol) in CH2Cl2 (1 L) was treated dropwise with boron trifluoride etherate (6.26 mL, 0.0500 mmol) at −30 °C. After stirring for 1 h at −30 °C, the mixture was quenched with triethylamine (10 mL), diluted with ether (1 L), and washed with water (300 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 orthoester 20 (43.8 g, 0.14 mol, 70%). 20: white solid; Rf = 0.34 (silica, 30% ether in petroleum ether); IR (film) νmax 2928 (m), 2874 (m), 1450 (m), 1396 (m), 1348 (m), 1292 (m), 1059 (s), 922 (s), 887 (m) cm−1; 1H NMR (500 MHz, CDCl3) δ 3.94–3.84 (8.1 H, CH2); 2.77–2.15 (m, 2 H, CH2C); 2.23–1.91 (m, 2 H, CH2C); 1.58 (d, J = 6.5 Hz, 3 H, CH3C); 0.00 (s, 3 H, CH3C). 13C NMR (125 MHz, CDCl3) δ 120.9, 73.1, 72.6, 37.6, 37.5, 30.0, 29.0, 14.1; HRMS, calcd for C10H14O2 (M + H) 153.0301, found 153.0288.
Acid Hydroxide 29. A solution of trihydroxy ester 28 (2.41 mol of diastereoisomers, 1.52 g, 2.13 mmol) in 1,2-dimethoxyethane/H2O (25 mL, 4:1) was treated with lithium hydroxide hydrate (447 mg, 10.7 mmol) and stirred at 25 °C for 1 h. The mixture was acidified with 2 N hydrochloric acid to pH 1 and the water layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated to give acid hydroxide 29 (101 mg, 71.5%, 2.41 mol of diastereoisomers) that was used for the next step without further purification.

Lactone 6. A solution of acid hydroxide 29 (2.41 mol of diastereoisomers, 1.16 g, 1.90 mmol) and triethylamine (397 μL, 2.85 mmol) in THF (10 mL) was treated dropwise with 2,4,6-trichloro-trifluoromethanesulfonimide (3.50 g, 9.80 mmol) and the reaction was quenched with water (50 mL, containing 1% of triethylamine) and extracted with ether (200 mL). The organic layer was dried (MgSO4) concentrated, and subjected to flash chromatography (silica, 10% ether in petroleum ether containing 1% triethylamine) to give the lactone triflate 36 (4.40 g, 6.07 mmol, 93%).

Diketone 55. A solution of ketone 54 (15.0 g, 41.9 mmol) and Dess-Martin periodinane (40.4, 94.3 mmol) in CH2Cl2 (200 mL) was heated at 40 °C for 12 h. The mixture was diluted with ethyl acetate (300 mL) and washed with aqueous saturated sodium bicarbonate/sodium thiosulfate (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 azeotropically dried with toluene (500 mL) using a Soxhlet condenser containing 4 Å molecular sieves. After heating at 110 °C for 12 h, the solution was cooled to 0 °C and the crystalline diketone 55 was filtered off (14.0 g, 67.7 mol%, 90%).

Diol 56. A solution of metal magnesium iodide (68.0 mL of a 3.0 M solution in ethyl ether, 210 g, 0.65 mol) was added dropwise to a solution 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 (20~50% ethyl acetate in petroleum ether) to give diol 56 (12.0 g, 31.2 mmol, 92%).

6F: colorless needles, mp 126~127 °C (ether); Rf = 0.33 (silica, 70% ether in petroleum ether); IR (film) νmax 3413 (m), 2935 (m), 2911 (s), 2850 (m), 1726 (m), 1711 (m), 1600 (s), 1511 (m), 1378 (m), 1269 (m), 1211 (m), 1072 (s), 738 (m), 698 (m) cm⁻¹; 1H NMR (500 MHz, CDCl3) δ (major isomer) 7.35~7.25 (m, 10 H, ArH), 4.55 (d, J = 11.6 Hz, 1 H, CH2PhH), 4.46 (s, 2 H, CH2Ph), 2.81 (dt, J = 7.9, 2.3 Hz, 1 H, 3H-4), 2.25 (dd, J = 15.5, 13.0 Hz, 2 H, CH2O), 1.47 (dd, J = 11.5, 10.0 Hz, 1 H, CH2), 2.12~2.06 (m, 2 H, CH2), 0.20~0.91 (m, 3 H, CH3), 1.88~1.72 (m, 4 H, CH), 1.69~1.62 (m, 1 H, CH)=1.14 (m, 2 H, CH2), 1.31 (s, 3 H, CH3), 1.27 (s, 3 H, CH3), 1.07 (d, J = 6.5, 3 H, CH3); 13C NMR (125 MHz, CDCl3) δ 174.6, 138.0, 128.3, 128.7, 127.7, 127.5, 127.4, 127.3, 125.6, 123.1, 117.8, 117.2, 113.0, 112.5, 110.4, 110.2, 107.0, 105.6, 103.8, 103.1, 101.8, 101.5, 101.2, 100.5, 100.3, 73.8, 73.5, 71.3, 71.0, 66.0, 40.5, 39.8, 37.8, 33.0, 32.9, 28.5, 21.0, 20.1, 19.3, 17.3; HRMS calec for C21H2O3S (M + Cs⁺) 725.2454, found 725.2486.
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 (360 mg, 2.94 mmol), and nickel(II) chloride (2 mg, 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% ether in petroleum ether containing 1% triethylamine) gave the addition product 64 (425 mg, 0.844 mmol, 66%, 51% mixture of isomers). 

**Hydroxy Ketone 70.** A mixture of triol 68 (7 mg, 10 μmol) and Ag₂CO₃/Celite (50 mg in benzene (2 mL) was heated at 80 °C under azotropic removal of 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, 8.2 μmol, 82%).

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**Tertiary Alcohol 71.** A solution of alcohol 64 (20 mg, 23 μmol) in ether (200 μL) was treated with potassium hydroxide (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 pouted into aqueous saturated ammonium chloride (10 mL). The organic layer was dried (MgSO₄), filtered, concentrated, and subjected to preparative TLC (silica, 30% ether in petroleu ether) to give alcohol 71 (20 mg, 23 μmol, 100%).

**Aldehyde 62.** A solution of dipivalate 61 (6.7 g, 11.6 mmol) in CH₂Cl₂ (25 mL) was treated with lead tetraacetate (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 (200 mL), and dried (MgSO₄). Filtration, concentration, and flash chromatography (silica, 30–50% ether in petroleum ether) gave dipivalate 61 (6.7 g, 11.6 mmol, 100%).

**Dipivalate 61.** A solution of tetratol 60 (5.10 g, 11.6 mmol), N,N-dimethyl-4-aminopyridine (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 reaction 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 dipivalate 61 (6.7 g, 11.6 mmol, 100%).

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(s, 6 H, 2 × CH₃), 1.32 (s, 3 H, CH₃), 1.22 (s, 9 H, t-Bu), 1.21 (s, 3 H, CH₃), 0.98 (d, J = 6.9 Hz, 3 H, CH₃), 0.96 (s, 9 H, t-Bu), 0.14 (s, 3 H, SiCH₃), 0.11 (s, 3 H, SiCH₃); ¹³C NMR (125 MHz, CD₂Cl₂) δ 177.5, 156.7, 156.3, 139.2, 128.5, 128.3, 127.7, 127.6, 118.7, 86.4, 84.2, 78.6, 78.4, 77.9, 77.3, 74.7, 74.0, 73.5, 73.1, 71.2, 68.3, 66.4, 64.7, 43.0, 41.0, 38.8, 35.5, 29.6, 28.5, 27.4, 26.0, 22.1, 18.4, 17.8, 15.8, -4.3, -5.0; HRMS, calculated for C₃H₆O₂SiS₃ (M + Cs⁺⁺) 1011.4419, found 1011.4464.

Xanthate 72. A solution of alcohol 64 (650 mg, 0.717 mmol) and carbon disulfide (129 µL, 2.15 mmol) in ether (2 mL) was stirred at 25 °C with potassium hydride (1.43 g, 35.9 mmol, after washing with ether) for 6 h. The resulting orange suspension was diluted with ether (5 mL) and dried (MgSO₄), filtered, and concentrated to dryness. The xanthate was washed with ether, dried (MgSO₄), and subjected to flash chromatography (silica, 30% ether in petroleum ether) to give the alcohol 75 (82 mg, 0.093 mmol, 82%).

Disilyl Ether 74. A solution of xanthate 72 (620 mg, 0.640 mmol), 2-[azobis(isobutyronitrile)] (6 mg) and tri-n-butyltin hydride (690 µL, 2.92 mmol) in tetrahydrofuran (25 mL) was treated with 3 N sodium hydroxide (1.5 mL) at -30 °C and stirred at -30 °C for 1 h. The resulting mixture was treated with 3 N sodium hydroxide (1.5 mL) at 0 °C and stirred at 25 °C for 2 h. The mixture was dried (MgSO₄), filtered, and concentrated to dryness. The disilyl ether was washed with ether, dried (MgSO₄), and subjected to flash chromatography (silica, 10-30% ether in petroleum ether) to give the disilyl ether 76 (619 mg, 0.638 mmol, 89%, 5:1 major isomer): colorless foam, Rf = 0.49 (silica, 30% ether in petroleum ether), IR (film) νmax 2955 (m), 2857 (m), 1732 (m), 1672 (w), 1462 (m), 1147 (m), 1089 (s), 836 (m), 775 (m) cm⁻¹; [α]D = +1.6 (c 1.0, CHCl₃); UV (film) λmax 2876 (m), 1973 (s), 1925 (s), 1875 (s), 1773 (m), 71.1, 70.9, 69.0, 40.9, 40.8, 33.9, 30.1, 29.7, 28.6, 28.4, 27.5, 27.4, 26.1, 26.0, 21.6, 20.8, 17.9, 14.8, -1.9, -2.3; HRMS, calculated for C₁₀H₁₈O₃S₃ (M + Cs⁺⁺) 995.4469, found 995.4499.

Alcohol 75. A solution of alcohol ether 74 (100 mg, 0.115 mmol) in THF (0.5 mL) was treated with B₃H₆·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 (1.0 mL) at 0 °C and stirred for 1 h at 25 °C. The mixture was diluted with ether (100 mL) and the organic layer was washed with brine (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%).

Disilyl Ether 77. A solution of alcohol 75 (1.03 g, 1.16 mmol) and 2,6-lutidine (338 µL, 3.28 mmol) in CH₂Cl₂ (4.48 mL of a 1.0 M solution in CH₂Cl₂) was treated with 3 N sodium hydroxide (1.5 mL) at -30 °C and stirred at 25 °C for 18 h. The resulting mixture was treated with 3 N sodium hydroxide (1.5 mL) at 0 °C and stirred at 25 °C for 2 h. The mixture was dried (MgSO₄), filtered, and concentrated to dryness. The disilyl ether was washed with ether, dried (MgSO₄), and subjected to flash chromatography (silica, 10-30% ether in petroleum ether) to give the disilyl ether 78 (630 mg, 0.717 mmol) and 2,6-lutidine (338 µL, 3.28 mmol).
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) 3504 (w), 2953 (m), 2876 (m), 1458 (m), 1380 (m), 1254 (m), 1070 (s), 834 (m), 733 (m), 697 (m) cm⁻¹; [α]23D +19.3° (c 1.0, CHCl₃); 'H NMR (500 MHz, CDCl₃) δ 7.32–7.24 (m, 10 H, ArH), 4.54 (d, J = 11.6 Hz, 1 H, CH₂Ph), 4.45 (s, 2 H, CH₂Ph), 4.36 (d, J = 11.6 Hz, 1 H, CH₂Ph), 3.65–3.56 (m, 4 H, OCH), 3.55–3.45 (m, 5 H, OCH), 3.42 (bt, J = 8.9 Hz, 1 H, OCH), 3.33–3.22 (m, 4 H, OCH), 3.24 (bt, J = 12.0, 3.6 Hz, 1 H, OCH), 2.75–2.70 (m, 1 H, OCH), 2.27–2.17 (m, 1 H, OCH), 2.10 (dd, J = 11.6, 7.2 Hz, 1 H, OCH), 1.71–1.55 (m, 4 H, CH₂), 1.54 (dd, J = 14.8, 9.6 Hz, 1 H, CH), 1.43–1.37 (m, 2 H, CH), 1.26 (s, 6 H, 2 × CH₃), 1.24 (s, 3 H, CH₃), 1.18 (s, 3 H, CH₃), 1.06 (d, J = 6.3 Hz, 3 H, CH₃), 0.94 (t, J = 7.9 Hz, 9 H, Si(CH₂CH₃)₃), 0.85 (s, 9 H, t-Bu), 0.57 (q, J = 7.9 Hz, 6 H, Si(CH₂CH₃)₃), 0.08 (s, 3 H, SiCH₃), 0.07 (s, 3 H, SiCH₃); 13C NMR (125 MHz, CDCl₃) δ 138.5, 138.5, 128.3, 128.2, 127.7, 127.6, 127.5, 87.6, 86.7, 86.0, 83.0, 78.1, 77.9, 75.8, 75.1, 73.4, 73.3, 73.0, 71.0, 69.6, 66.0, 43.0, 40.3, 40.2, 38.1, 38.0, 31.1, 29.3, 29.1, 27.8, 25.8, 21.4, 20.2, 18.9, 18.1, 17.5, 7.4, 5.1, −1.9, −3.3; HRMS, calcd for C₅₇H₉₈O₇SiC₁₃ (M + Cs⁺) 1043.4865, found 1043.4814.

**Aldehyde 79.** A solution of alcohol 78 (955 mg, 1.05 mmol) in CH₂Cl₂ (20 mL) was treated with Dess-Martin periodinane (1.78 g, 4.20 mmol) at 25 °C for 3 h. The mixture was diluted with ether (25 mL) and washed with aqueous saturated sodium bicarbonate-hydroxide (1.06 mmol, 95%). 79: colorless foam; Rf = 0.58 (silica, 50% ether in petroleum ether); IR (film) 3504 (m), 1380 (m), 1254 (m), 1071 (s), 834 (m), 733 (m), 697 (m) cm⁻¹; [α]23D +19.3° (c 1.0, CHCl₃); 'H NMR (500 MHz, CDCl₃) δ 138.5, 138.5, 128.3, 128.2, 127.7, 127.6, 127.5, 87.6, 86.7, 86.0, 83.0, 78.1, 77.9, 75.8, 75.1, 73.4, 73.3, 73.0, 71.0, 69.6, 66.0, 43.0, 40.3, 40.2, 38.1, 38.0, 31.1, 29.3, 29.1, 27.8, 25.8, 21.4, 20.2, 18.9, 18.1, 17.5, 7.4, 5.1, −1.9, −3.3; HRMS, calcd for C₅₇H₉₈O₇SiC₁₃ (M + Cs⁺) 1043.4865, found 1043.4814.

**Lactol 80.** A mixture of silyl ether 79 (5 mg, 6 µmol) and camphorsulfonic acid (0.4 mg, 1 µmol) in MeOH/H₂O (100 µL, 4:1) 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). 80: colorless oil; Rf = 0.45 (silica, 50% ether in petroleum ether); 'H NMR (500 MHz, CDCl₃) δ 7.33–7.24 (m, 10 H, ArH), 4.73 (bs, 1 H, CHO), 4.55 (dd, J = 11.6 Hz, 1 H, CH₂Ph), 4.46 (s, 2 H, CH₂Ph), 4.37 (d, J = 11.6 Hz, 1 H, CH₂Ph), 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, OH), 2.10–1.92 (m, 2 H, CH), 1.82–1.64 (m, 10 H, CH), 1.47–1.37 (m, 3 H, CH), 1.32 (s, 3 H, CH₃), 1.30 (s, 3 H, CH₃), 1.25 (s, 3 H, CH₃), 1.19 (s, 3 H, CH₃), 1.03 (s, J = 7.0 Hz, 3 H, CH₃), 0.89 (s, 9 H, t-Bu), 0.08 (s, 3 H, SiCH₃), 0.07 (s, 3 H, SiCH₃); HRMS, calcd for C₅₇H₉₈O₇SiC₁₃ (M + Cs⁺) 928.0563, found 928.0520.

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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, 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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