Total Synthesis of Brevetoxin B. 3. Final Strategy and Completion

K. C. Nicolaou,* F. P. J. T. Rutjes, E. A. Theodorakis, J. Tiebes, M. Sato, and E. Untersteller

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 92093

Received March 2, 1995[⊗]

Abstract: The final strategy for the total synthesis of brevetoxin B (**1**) according to the retrosynthetic analysis shown in Scheme 1 is described. Starting with the tetracyclic ring system **8** [DEFG], the construction of the C ring was accomplished via an intramolecular conjugate addition (**7** → **13**). A hydroxy epoxide cyclization was then utilized for the formation of ring B (**6** → **21**). Ring A was introduced via an intramolecular phosphonate ester−ketone condensation (**5** → **27**) to produce, after side chain elaboration, the desired heptacyclic phosphonium iodide **4**. Formation of the tricyclic aldehyde **3** [IJK] starting from diol **34** is also described. Wittig coupling of **3** and **4** followed by selective deprotection, hydroxy dithioketal cyclization, and radical desulfurization produced the undecacyclic system **48** representing the complete brevetoxin B skeleton (**46** → **2** → **47** → **48**). Allylic oxidation of ring A (**48** → **49**) followed by side chain elaboration of the K ring side chain (**49** → **50** → **51** → **52**) led to the TBS protected brevetoxin B (**52**) which upon exposure to HF·pyridine treatment afforded natural brevetoxin B (**1**).

Introduction

In the preceding two papers[1,2] we discussed explorations of strategies directed toward the total synthesis of brevetoxin B (**1**). These studies led to the evolution of the final and successful approach to this target molecule. Below we present full details of the direct route via which the total synthesis of brevetoxin B (**1**) was succesfully accomplished.

Total Synthesis

The final approach to brevetoxin B (**1**) involved separate assembly of the ABCDEFG and IJK ring systems **4** and **3**, their coupling, and final elaboration to the end. We will first address the construction of the more complex ABCDEFG segment **4**.

Retrosynthetic Analysis and Strategy

The final synthetic strategy toward brevetoxin B (**1**) was designed on the basis of our experiences in the brevetoxin B project as described in the preceding papers[1,2] and the retrosynthetic analysis shown in Scheme 1. According to the strategy, the final stages of the synthesis would entail (a) coupling of intermediates **3** and **4** by a Wittig reaction to give the corresponding (*Z*)-olefin, (b) deprotection to afford the hydroxy dithioketal **2**, (c) ring closure to form the oxocene ring system, (d) desulfurization, and (e) functional group manipulation at the two ends of the molecule. The advanced ABCDEFG intermediate **4** was projected to be derived from DEFG lactone **9** (Scheme 1) by a sequence involving stepwise construction of the A, B, and C rings via ring closures as outlined in Scheme 1. The latter sequence was envisioned to involve (a) an intramolecular phosphonate ester−ketone condensation (**5** → **4**), (b) an intramolecular hydroxy epoxide cyclization (**6** → **5**), (c) an intramolecular conjugate addition (**7** → **6**), and (d) a Cr/Ni coupling reaction (**9** → **8**). The syntheses of both lactone **9**[2] and aldehyde **3**[3,4] starting with 2-deoxy-D-ribose (**10**) and D-mannose (**11**), respectively, have already been described. Unfolded below is the successful execution of this strategy and the completion of the total synthesis of brevetoxin B (**1**).

Construction of the ABCDEFG Ring System as Phosphonium Salt 4

The synthesis of the ABCDEFG segment **4** proceeded from the DEFG system **8** by constructing rings C, B, and A, one at a time and in that order. Thus, starting with aldehyde **8**,[2] the CDEFG ring system **13** was constructed as summarized in Scheme 2. Condensation of **8** with the potassium derivative of $(MeO)_2P(O)CH_2COOMe$ [KHMDS, 18-crown-6, THF] furnished the α,β-unsaturated ester **12** in 99% yield. Selective removal of the triethylsilyl (TES) group from **12** using methanolic camphorsulfonic acid (CSA) led, quantitatively, to the hydroxy ester **7**, which upon exposure to KH smoothly cyclized to afford the CDEFG ring system **13**, together with its epimer at C*. On prolonged reaction time, however, this initially formed mixture was converted to a single product **13** (90% yield) bearing the side chain at the equatorial position. The structure of this intermediate was unambiguously confirmed by X-ray crystallographic analysis at a later stage (*vide infra*).[5]

With the crucial fusion of the C ring onto the growing polycyclic framework accomplished, we then proceeded to

* Address correspondence to this author at either The Scripps Research Institute or the University of California, San Diego.

⊗ Abstract published in *Advance ACS Abstracts*, October 1, 1995.

(1) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Bal Reddy, K.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227−10238.

(2) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc.* **1995**, *117*, 10239−10251.

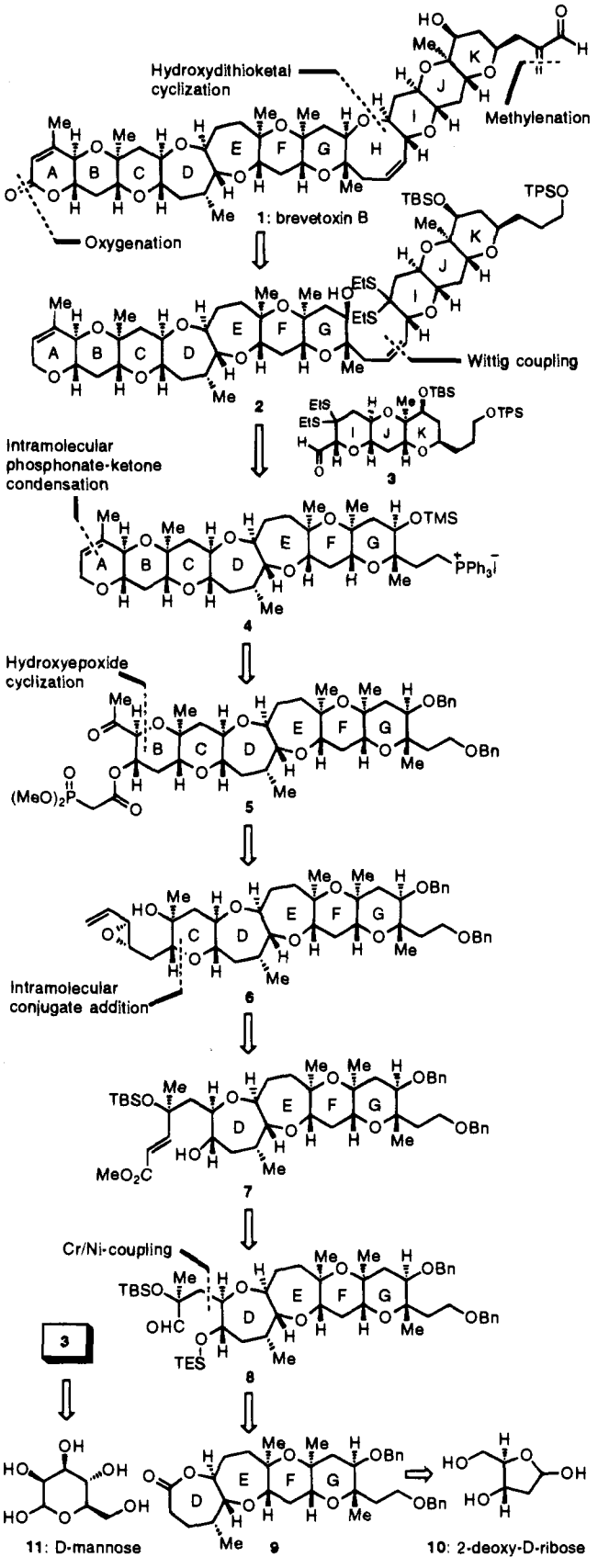
(3) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682.

(4) Nicolaou, K. C.; Tiebes, J.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Koide, K.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1994**, *116*, 9371.

(5) This result is in accordance with the stereochemical outcome of similar cyclizations by Martin *et al.* which were carried out under kinetic conditions (NaH, Et_2O, −30 °C) affording the cyclized product with the ester side chain in the axial position as a single isomer; see: Palázon, J. M.; Soler, M. A.; Ramirez, M. A.; Martin, V. S. *Tetrahedron Lett.* **1993**, *34*, 5467.

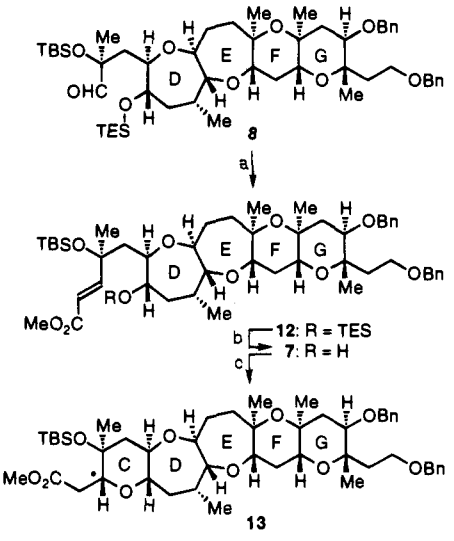
0002-7863/95/1517-10252$09.00/0

Scheme 1. Retrosynthetic Analysis and Strategic Bond Disconnections of Brevetoxin B (**1**): Third Generation Approach



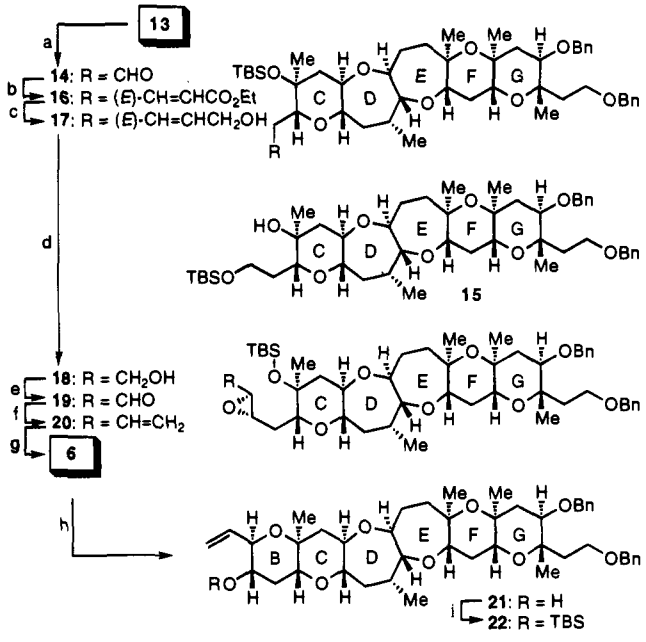
install the next heterocycle in line, namely ring B, as shown in Scheme 3. Thus, DIBALH reduction of ester **13** furnished aldehyde **14** in 80% yield, together with the over-reduced product **15** (18%) (Scheme 3) in which the silyl group had

Scheme 2. Construction of the CDEFG Ring System **13**[a]



[a] Reagents and conditions: (a) 3.0 equiv of KHMDS, 0.2 equiv of 18-crown-6, 6.0 equiv of $(MeO)_2P(O)CH_2CO_2Me$, THF, 25 °C, 30 min, then add **8**, 3 h, 25 °C, 99%; (b) 0.15 equiv of CSA, MeOH, 25 °C, 1 h, 100%; (c) 2.0 equiv of KH, THF, 25 °C, 20 min, 90%.

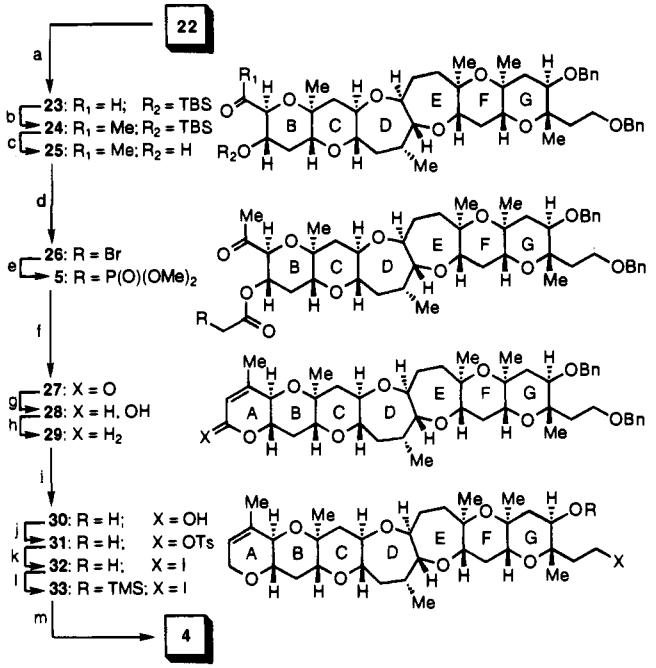
Scheme 3. Construction of the BCDEFG Ring System **22**[a]



[a] Reagents and conditions: (a) 2.5 equiv of DIBALH, CH_2Cl_2, −78 °C, 30 min; quench with MeOH, 80% of **14** and 18% of **15**; (b) 2.0 equiv of $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 25 °C, 12 h, 95%; (c) 3.0 equiv of DIBALH, CH_2Cl_2, −78 °C, 30 min, 96%; (d) 0.2 equiv of Ti(O-*i*-Pr)$_4$, 0.15 equiv of (+)-diethyl tartrate, 1.5 equiv of *t*-BuOOH (5−6 N in decane), CH_2Cl_2, −20 °C, 14 h, 99%; (e) 5.0 equiv of SO_3·pyridine, 10 equiv of Et_3N, CH_2Cl_2:DMSO (4:1), 0 °C, 5 h; (f) 4.0 equiv of NaHMDS, 5.0 equiv of $CH_3PPh_3^+Br^-$, THF, 0 °C, 30 min, 80% (over 2 steps); (g) 1.5 equiv of TBAF, THF, 25 °C, 10 h, 100%; (h) 0.5 equiv of PPTS, CH_2Cl_2, 0 °C, 14 h; (i) 2.0 equiv of TBSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 76% (2 steps).

migrated from the tertiary to the primary alcohol. After the following step, the latter compound could be recycled to **14** by silylation, selective desilylation at the primary oxygen, and Dess-Martin oxidation (80% overall yield). Condensation of aldehyde **14** with the stabilized phosphoranylidene $Ph_3P{=}CHCOOEt$ furnished selectively the *E* isomer **16** in 95% yield. DIBALH reduction of ester **16** furnished allylic alcohol **17** (96% yield).

Scheme 4. Synthesis of Phosphonium Iodide **4**[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C, 1 min, then 3.0 equiv of Ph_3P, 1 h, 100%; (b) 1.4 equiv of MeMgCl, THF, 0 °C, 30 min; 4.0 equiv of Dess-Martin periodinane, CH_2Cl_2, 25 °C, 2 h, 91%; (c) 1.1 equiv of TBAF, THF, 25 °C, 2 h, 90%; (d) 2.0 equiv of $BrCH_2COCl$, 10.0 equiv of pyridine, CH_2Cl_2, 0 °C, 15 min, 81%; (e) $(MeO)_3P$ (neat), 90 °C (sealed tube), 4 h; (f) 3.5 equiv of *i*-Pr_2EtN, 3.5 equiv of LiCl, CH_3CN, 25 °C, 3 h, 89% (over 2 steps); (g) 1.5 equiv of DIBALH, CH_2Cl_2, −78 °C, 0.5 h; (h) 1.0 equiv of $BF_3{\cdot}Et_2O$, 5.0 equiv of Et_3SiH, CH_2Cl_2, −10 °C, 30 min, 93% (over 2 steps); (i) 10.0 equiv of Li, liquid NH_3, −78 °C, 2 h, 92%; (j) 4.0 equiv of TsCl, CH_2Cl_2/pyridine (10:1), 25 °C, 12 h, 79%; (k) 5.0 equiv of NaI, acetone, 60 °C, 5 h; (l) 5.0 equiv of TMS−imidazole, CH_2Cl_2, 25 °C, 30 min, 96% (over 2 steps); (m) 10.0 equiv of PPh_3, CH_3CN, 80 °C, 42 h, 99%.

Sharpless asymmetric epoxidation[6] of the latter compound (**17**) using (+)-diethyl tartrate as the chiral auxiliary gave hydroxy epoxide **18** in 99% yield as a single isomer. Oxidation of **18** with $SO_3{\cdot}$pyr and olefination ($CH_3PPh_3^+Br^-$−NaHMDS) of the resulting aldehyde (**19**) afforded epoxy olefin **20** in 80% overall yield. Finally, desilylation of **20** using TBAF in THF gave hydroxy epoxide **6** (100%), which upon exposure to PPTS in CH_2Cl_2 underwent smooth and selective ring closure to the expected BCDEFG ring system **21**. Silylation of the latter compound with TBSOTf in the presence of 2,6-lutidine led to silyl ether **22** in 76% overall yield from **6**. The cyclization of **6** to **21** was rather slow compared to the similar cyclizations which formed the F and G rings.[7] Furthermore, activation of the epoxide with an ester substituted vinyl group (rather than the simple vinyl group shown in the scheme) was not sufficient to effect cyclization under acidic conditions.

The stage was now set for the introduction of the final ring (A) and the completion of the synthesis of the ABCDEFG ring system of brevetoxin B (**1**). Scheme 4 outlines the chemistry involved in achieving this goal. Ozonolysis of the terminal olefin in **22** followed by reductive workup with Ph_3P resulted in the quantitative formation of aldehyde **23**. The latter compound (**23**) was subjected to addition of methylmagnesium chloride, and the resulting secondary alcohol was oxidized with Dess-Martin periodinane leading to methyl ketone **24** in 91% overall yield for the two steps.[3,7] Removal of the silyl group from **24** with TBAF in THF liberated the secondary alcohol **25** (90%), which was esterified with bromoacetyl chloride in the presence of pyridine, to furnish bromide **26** (81% yield). Exchange of the bromide with a phosphonate group [$(MeO)_3P$, 90 °C] led to the formation of phosphonate **5** in high yield. After evaporation of the excess $(MeO_3)P$ and without further purification, crude **5** was subjected to intramolecular condensation in the presence of $^iPr_2EtN$ and LiCl[8] to furnish lactone **27** in 89% overall yield from **26**, thus completing the ABCDEFG ring framework of brevetoxin B (**1**). The following tactic of converting the ring A lactone to its cyclic allylic ether counterpart (**29**) was designed as a defensive measure against possible side reactions in the pending phosphorane generation with *n*-BuLi. This objective was easily accomplished by DIBALH reduction, followed by further $BF_3{\cdot}Et_2O$-catalyzed reduction with Et_3SiH of the resulting lactol (**28**, mixture of anomers), to afford compound **29** in 93% overall yield. In order to reach the targeted intermediate (**4**), the appendages of ring G needed to be modified, a task accomplished by the following sequence: (a) reduction with Li−liquid NH_3 to remove the benzyl ethers and produce diol **30** (92%); (b) selective monotosylation to afford primary tosylate **31** (79%); (c) exchange of the tosylate with iodide to give hydroxy iodide **32**; (d) silylation with TMS−imidazole to furnish TMS iodide **33** (93% overall yield for two steps); and (e) reaction with excess PPh_3 (CH_3CN, 80 °C) to afford the desired phosphonium salt **4** in 99% yield. Iodide **33**, mp 192−193 °C (from CH_3CN), was subjected to X-ray crystallographic analysis (see ORTEP drawing, Figure 1), confirming its structure and those of its predecessors.

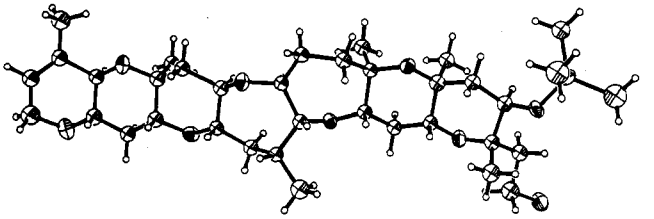


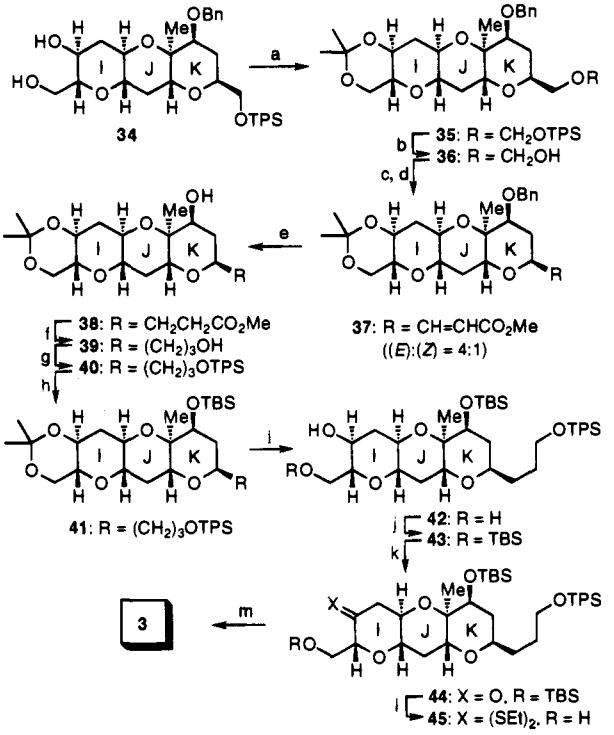
Figure 1. ORTEP drawing of **33**.

Coupling of the ABCDEFG Phosphonium Salt 4 with IJK Aldehyde 3 and Final Stages of the Synthesis

With the ABCDEFG phosphonium salt **4** at hand, we were now in a position to proceed with its coupling to the IJK aldehyde **3**. The latter compound was synthesized in a straightforward manner from the previously described intermediate **34**[3] as summarized in Scheme 5.[4] Thus, exposure of **34** to $CH_2{=}C(OMe)Me$ in the presence of CSA converted it to acetonide **35** (89%) which was desilylated by TBAF in THF affording primary alcohol **36** in 97% yield. Swern oxidation of the latter compound (**36**), followed by condensation of the resulting aldehyde with $Ph_3P{=}CHCOOMe$ furnished α,β-unsaturated ester **37** as a mixture of *E*:*Z* (*ca.* 4:1) isomers in 96% overall yield. This mixture was hydrogenated to its saturated counterpart with concomitant debenzylation leading to hydroxy ester **38** in quantitative yield. Reduction of the ester group in **38** with $LiAlH_4$ gave diol **39** (92% yield) which was subjected to sequential and selective silylation using *t*-$BuPh_2SiCl$ (TPSCl) and *t*-BuMeSiOTf (TBSOTf) to afford bis(silyl ether) **41** (93% overall yield) via monosilyl ether **40**. Removal of the acetonide group from **41** with CSA in CH_2Cl_2:MeOH (1:1) led to diol **42** (87%) which was selectively silylated with

(6) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.
(7) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517.
(8) Senfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

Scheme 5. Construction of the IJK Ring System Aldehyde **3**[a]



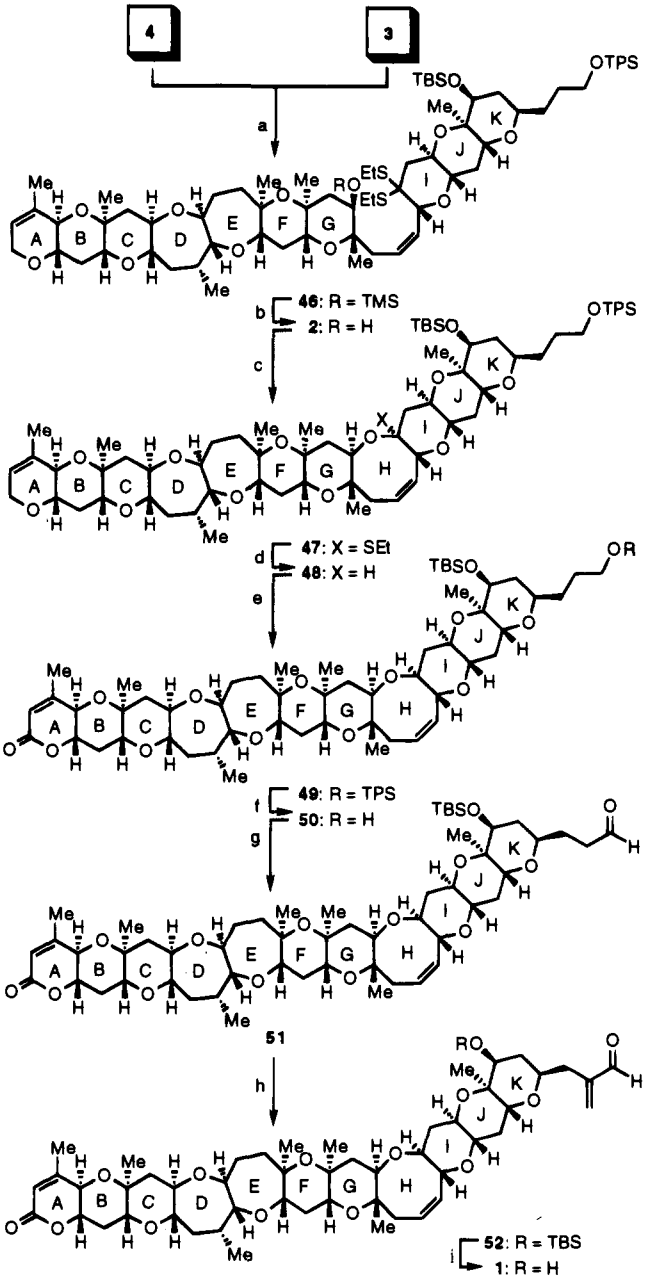
[a] Reagents and conditions: (a) 2.4 equiv of CH_2=C(OMe)Me, 0.2 equiv of CSA, CH_2Cl_2, 0 °C, 4 h, 89%; (b) 2.0 equiv of TBAF, THF, 25 °C, 2 h, 97%; (c) 1.7 equiv of $(COCl)_2$, 2.2 equiv of DMSO, CH_2Cl_2, −78 °C, 0.5 h, then 5.5 equiv of Et_3N, 100%; (d) 2.0 equiv of Ph_3P=$CHCO_2Me$, CH_2Cl_2, 25 °C, 5 h, 96% ((*E*):(*Z*) = 4:1); (e) H_2, $Pd(OH)_2$, EtOAc, 25 °C, 48 h, 100%; (f) 2.0 equiv of $LiAlH_4$, THF, 0 °C, 15 min, 92%; (g) 1.1 equiv of TPSCl, 2.0 equiv of Et_3N, 0.05 equiv of DMAP, CH_2Cl_2, 25 °C, 6 h, 93%; (h) 2.0 equiv of TBSOTf, 3.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 100%; (i) 0.2 equiv of CSA, CH_2Cl_2:MeOH (1:1), 0 °C, 2 h, 87%; (j) 1.0 equiv of TBSCl, 2.0 equiv of imidazole, DMF, 0 °C, 1 h, 94%; (k) 2.0 equiv of NMO, 0.05 equiv of TPAP, CH_3CN, 25 °C, 1 h, 96%; (l) 3.0 equiv of EtSH, 1.1 equiv of $Zn(OTf)_2$, CH_2Cl_2, 25 °C, 3 h, then 0.2 equiv of CSA, MeOH, 25 °C, 1 h, 74%; (m) 5.0 equiv of SO_3·pyridine, 10 equiv of Et_3N, CH_2Cl_2:DMSO (1:1), 0 °C, 1.5 h, 92%.

TBSCl, furnishing compound **43** (94% yield). The oxidation of **43** to ketone **44** was accomplished with *N*-methylmorpholine *N*-oxide (NMO) and tetra-*n*-propylammonium perruthenate (TPAP)[9] catalyst in 96% yield, while dithioketal formation from **44** proceeded smoothly in the presence of EtSH and $Zn(OTf)_2$ to afford, after mild acid treatment, compound **45** (74% yield). Finally, oxidation of the primary alcohol in the latter compound (**45**) with SO_3·pyr complex resulted in the formation of the desired dithioketal aldehyde **3** in 92% yield.

Generation of the ylide from phosphonium salt **4** using *n*-BuLi in the presence of HMPA in THF followed by addition of aldehyde **3** resulted in the formation of the (*Z*)-olefin **46** (J_{cis} = 10.7 Hz), which upon exposure to PPTS in CH_2Cl_2−MeOH lost its TMS group selectively, furnishing hydroxy dithioketal **2** (75% overall yield for the two steps) (Scheme 6). A byproduct in this Wittig reaction was the α,β-unsaturated aldehyde corresponding to **3** from which a molecule of EtSH had been eliminated, leading, in turn, to partial ylide quenching and regeneration of phosphonium salt **4**. The latter was recycled, thus increasing the yield of the product olefin **46**. Ring closure of hydroxy dithioketal **2** to the oxocene system **47** was effected, in 85% yield, by treatment with $AgClO_4$−$NaHCO_3$−SiO_2−4Å

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

Scheme 6. Total Synthesis of Brevetoxin B (**1**)[a]



[a] Reagents and conditions: (a) 1.05 equiv of *n*-BuLi, 3.0 equiv of HMPA, THF, −78 °C, then 1.5 equiv of **3**, 10 min; (b) 0.25 equiv of PPTS, CH_2Cl_2:MeOH (1:1), 25 °C, 30 min, 75% (over 2 steps); (c) 4.0 equiv of $AgClO_4$, 10.0 equiv of $NaHCO_3$, silica, 4 Å MS, CH_3NO_2, 25 °C, 40 h, 85%; (d) 10.0 equiv of Ph_3SnH, 0.1 equiv of AIBN, toluene, 110 °C, 3 h, 100%; (e) 5.0 equiv of PCC, benzene, 80 °C, 3 h, 85%; (f) 1.0 equiv of TBAF, THF, 25 °C, 13 h, 69%; (g) 3.0 equiv of Dess-Martin periodinane, CH_2Cl_2, 25 °C, 30 min, 100%; (h) 5.0 equiv of Me_2N=$CH_2^+I^-$, 20 equiv of Et_3N, CH_2Cl_2, 25 °C, 16 h, 83%; (i) HF·pyridine, CH_2Cl_2, 0 °C, 30 min, 91%.

MS in nitromethane at 25 °C.[10] The stereochemistry of the ethylthio (EtS) group in **47** was assumed to be α, in agreement with a model system whose structure was firmly established earlier by X-ray crystallographic analysis.[10] Reductive removal of the EtS group from **47** was achieved in quantitative yield and with complete stereocontrol [exclusive *trans* stereoselectivity, tentatively assigned by comparison with a truncated version of this compound][4] using Ph_3SnH−AIBN in toluene at

(10) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

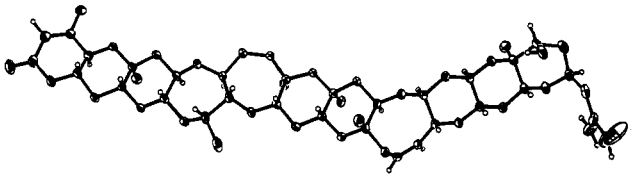


Figure 2. ORTEP drawing of synthetic brevetoxin B (**1**).

110 °C. The latter stereochemistry was eventually confirmed by the successful synthesis of brevetoxin B (**1**) and its X-ray crystallographic analysis.

With the entire polycyclic ring framework of brevetoxin B (**1**) in place, all that remained to be done was the final functionalization of the two ends of the molecule. To this end, ring A was first oxidized with PCC[11] in benzene at 80 °C to afford, in 85% yield, lactone **49**. Selective desilylation of the primary oxygen of the side chain using a stoichiometric amount of TBAF in THF afforded primary alcohol **50** (69% yield). Oxidation of the latter compound (**50**) with Dess-Martin periodinane furnished, quantitatively, aldehyde **51**, which upon exposure to Eschenmoser's reagent ($Me_2N{=}CH_2{}^+I^-$)[12] gave enal **52** (83% yield). Finally, HF·pyridine in CH_2Cl_2 removed the silicon group from **52**, furnishing brevetoxin B (**1**) in 91% yield. Synthetic brevetoxin B (**1**) crystallized from methanol in beautiful colorless crystals (mp 272 °C dec; lit. mp 270 °C dec)[13] and exhibited identical physical and spectroscopic data with those of an authentic sample (TLC, HPLC, $[\alpha]^{22}_D$, IR, ^1H and ^{13}C NMR, mass spec).[14] An X-ray crystallographic analysis of synthetic brevetoxin B (**1**) (see ORTEP drawing, Figure 2) completed the characterization of the synthetic material.

Conclusion

In this, and the preceding two articles[1,2] we presented the total synthesis of brevetoxin B (**1**) as it unfolded over the 12-year period from 1983 to 1994. The final strategy was not the one originally designed, but rather, one that evolved as new synthetic technology and tactics were discovered and developed in response to encountered problems. This process eventually led to a synthesis of the target molecule consisting of 123 steps in total, containing a set of 83 steps as the longest linear sequence (2-deoxy-D-ribose → brevetoxin B (**1**)) with an average yield per step of 91%.[15,16] Among the most significant discoveries and developments of this program are the following: (a) the regio- and stereospecific hydroxy epoxide openings to form functionalized tetrahydropyran systems;[17] (b) the powerful hydroxy dithioketal cyclization to construct oxocene ring systems;[10] (c) the bridging of macrodithionolactones to bicyclic and polycyclic systems;[18] (d) the photolytically-induced cyclization of dithionoesters to form oxepane systems;[1,19] (e) the reductive, silicon-induced cyclization of hydroxy ketones to form oxepane systems;[1,20] (f) the nucleophilic addition reactions of organometallic reagents to thionolactones;[21] (g) the new Cr/Ni promoted coupling reaction between aldehydes and lactone-derived enol triflates;[2] and (h) the synthesis of the first stable 1,2-dithietane system, dithiatopazine, and its novel chemistry.[22] Some of these methods were used in the final sequence, some were not. All of them, however, were worth inventing, encountering, and developing, since they provide new options and opportunities for explorations in other areas of chemistry. Finally, the sheer excitement of being able to devise, after a long and adventurous odyssey,[23] a suitable path to reach this complex target molecule was highly rewarding and worthwhile to all of us involved in this project. It is our hope that the reader will find the story equally worthwhile.[24]

Experimental Section

General Techniques. For a description of general techniques, see the preceding paper in this issue.[2]

α,β-Unsaturated Ester 12. A solution of trimethyl phosphonoacetate (878 μL, 5.42 mmol) in THF (5 mL) was treated dropwise with potassium bis(trimethylsilyl)amide (5.42 mL of a 0.5 M solution in toluene, 2.71 mmol) and 18-crown-6 (20 mg, 0.07 mmol) at 25 °C. After stirring for 30 min, a solution of aldehyde **8** (822 mg, 0.904 mmol) in THF (2 mL) was added dropwise and the resulting solution was stirred for 3 h at 25 °C. The reaction mixture was diluted with ether (25 mL), washed with brine (25 mL), dried ($MgSO_4$), and filtered. Concentration and flash chromatography (silica, 10→40% ether in petroleum ether) afforded α,β-unsaturated ester **12** (867 mg, 0.898 mmol, 99%). **12**: colorless foam; R_f = 0.50 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2953 (m), 2876 (m), 1726 (m), 1652 (w), 1462 (m), 1380 (m), 1256 (m), 1071 (s), 1014 (m), 836 (m), 733 (m) cm^{-1}; $[\alpha]^{22}_D$ +4.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 7.04 (d, *J* = 15.6 Hz, 1 H, =CH), 5.91 (d, *J* = 15.6 Hz, 1 H, =CH), 4.55 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.71 (s, 3 H, CO_2CH_3), 3.65−3.58 (m, 3 H, OCH), 3.50 (bq, *J* = 8.9 Hz, 1 H, OCH), 3.39 (bt, *J* = 9.3 Hz, 1 H, OCH), 3.33 (dd, *J* = 12.0, 3.5 Hz, 1 H, OCH), 3.27−3.23 (m, 2 H, OCH), 3.06 (dd, *J* = 11.6, 3.8 Hz, 1 H, OCH), 2.13−2.0 (m, 3 H, CH), 2.03−1.89 (m, 4 H, CH), 1.83−1.49 (m, 6 H, CH), 1.42−1.40 (m, 2 H, CH), 1.38 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.00 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.95 (t, *J* = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.92 (s, 9 H, *t*-Bu), 0.57 (q, *J* = 8.0 Hz, 6 H, $Si(CH_2CH_3)_3$), 0.11 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 156.6, 138.5, 138.5, 128.3, 128.2, 127.7, 127.6, 127.5, 116.7, 87.5, 86.9, 85.3, 82.8, 78.1, 78.0, 77.0, 76.0, 74.2, 73.5, 73.3, 73.0, 71.0, 66.0, 51.4, 47.7, 40.3,

(11) For a similar example, see: Bonadies, F.; DiFabio, R. *J. Org. Chem.* **1984**, *49*, 1647.

(12) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330. Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, Y.; Sugihara, K. Chem. *Lett.* **1989**, 1283.

(13) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.

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

(15) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171.

(16) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.

(17) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

(18) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, B. K.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800. Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.

(19) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1362.

(20) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.

(21) Nicolaou, K. C.; McGarry, D. G.; Veale, C. A.; Somers, P. K. *J. Am. Chem. Soc.* **1987**, *109*, 2504. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.

(22) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Carroll, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 3801. Nicolaou, K. C.; Hwang, C.-K.; DeFrees, S.; Stylianides, N. A. *J. Am. Chem. Soc.* **1988**, *110*, 4868. Nicolaou, K. C.; DeFrees, S. A.; Hwang, C.-K.; Stylianides, N.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3029.

(23) For a personal review, see: Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* Submitted for publication.

(24) For a pedagogical account of the brevetoxin synthesis, see: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH Publishers: Weinheim, in press.

40.2, 38.4, 38.1, 31.3, 29.3, 28.8, 26.0, 21.3, 20.2, 18.8, 18.3, 17.5, 6.9, 5.1, −1.9, −2.0; HRMS, calcd for $C_{55}H_{88}O_{10}Si_2Cs$ (M + Cs^+) 1097.4970, found 1097.4950.

Alcohol 7. A solution of ester **12** (867 mg, 0.898 mmol) and camphorsulfonic acid (30 mg, 0.129 mmol) in MeOH (10 mL) was stirred at 25 °C for 1 h. Triethylamine (1 mL) and ether (30 mL) were added and the mixture was washed with aqueous saturated ammonium chloride (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed to give alcohol **7** (765 mg, 0.898 mmol, 100%). **7**: colorless foam; R_f = 0.34 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 3478 (w), 2952 (s), 2857 (s), 1714 (s), 1633 (w), 1446 (s), 1360 (m), 1257 (s), 1068 (s), 836 (m) cm^{-1}; $[\alpha]^{22}_D$ +2.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 10 H, ArH), 7.02 (d, *J* = 15.5 Hz, 1 H, =CH), 5.93 (d, *J* = 15.5 Hz, 1 H, =CH), 4.53 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.71 (s, 3 H, CO_2CH_3), 3.64−3.56 (m, 3 H, OCH), 3.48−3.41 (m, 1 H, OCH), 3.33−3.20 (m, 4 H, OCH), 3.04 (dd, *J* = 11.6, 3.7 Hz, 1 H, OCH), 2.14−2.08 (m, 2 H, CH), 2.06−1.60 (m, 12 H, CH), 1.54−1.47 (m, 2 H, CH), 1.39 (s, 3 H, CH_3), 1.23 (s, 6 H, 2 × CH_3), 1.17 (s, 3 H, CH_3), 1.00 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.92 (s, 9 H, *t*-Bu), 0.12 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 156.2, 138.5, 138.4, 128.3, 128.2, 127.7, 127.5, 127.4, 116.8, 87.5, 86.7, 84.8, 82.7, 78.1, 78.0, 75.1, 74.4, 73.4, 73.3, 73.0, 71.0, 66.0, 51.4, 48.3, 40.3, 40.2, 38.3, 38.0, 31.4, 29.3, 28.8, 26.1, 21.4, 20.2, 18.6, 18.4, 17.5, −1.9, −2.0; HRMS, calcd for $C_{49}H_{74}O_{10}SiCs$ (M + Cs^+) 983.4106, found 983.4120.

Ester 13. A solution of alcohol **7** (765 mg, 0.898 mmol) in THF (10 mL) was treated with potassium hydride (72 mg, 1.80 mmol, after removal of the oil with THF) and stirred at 25 °C for 20 min. The mixture was diluted with ether (30 mL) and washed with aqueous saturated ammonium chloride (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica, 20→40% ether in petroleum ether) to afford ester **13** (680 mg, 0.799 mmol, 90%). **13**: colorless foam; R_f = 0.80 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2948 (s), 2866 (s), 1743 (s), 1459 (m), 1377 (m), 1257 (m), 1070 (s), 837 (m), 735 (s) cm^{-1}; $[\alpha]^{22}_D$ +3.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 4.53 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.44 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.69 (s, 3 H, CO_2CH_3), 3.64−3.58 (m, 4 H, OCH), 3.51−3.47 (m, 1 H, OCH), 3.33−3.29 (m, 2 H, OCH), 3.08−2.99 (m, 2 H, OCH), 2.62 (dd, *J* = 15.5, 1.7 Hz, 1 H, C*H*HCO$_2$CH$_3$), 2.24 (dd, *J* = 15.6, 10.4 Hz, 1 H, C*H*HCO$_2$CH$_3$), 2.11−2.06 (m, 3 H, CH), 2.00−1.88 (m, 3 H, CH), 1.82−1.65 (m, 8 H, CH), 1.52 (bd, *J* = 13.4 Hz, 1 H, CH), 1.39 (bt, *J* = 11.3 Hz, 1 H, CH), 1.27 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.00 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.82 (s, 9 H, *t*-Bu), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 138.5, 138.5, 128.3, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 87.8, 87.5, 83.7, 83.3, 83.1, 81.4, 78.1, 77.9, 73.4, 73.3, 73.0, 72.9, 71.0, 66.0, 51.7, 47.3, 40.3, 40.2, 38.0, 35.0, 34.2, 32.8, 29.7, 29.5, 28.9, 25.6, 22.3, 21.6, 20.2, 18.4, 17.9, 17.5, −2.1, −2.1; HRMS, calcd for $C_{49}H_{74}O_{10}SiCs$ (M + Cs^+) 983.4106, found 983.4122.

Aldehyde 14. A solution of ester **13** (665 mg, 0.781 mmol) in CH_2Cl_2 (10 mL) was treated at −78 °C with diisobutylaluminum hydride (1.97 mL of a 1.0 M solution in CH_2Cl_2, 1.97 mmol) and the mixture was stirred at −78 °C for 30 min. The reaction was quenched with MeOH (2 mL), diluted with EtOAc (20 mL), and stirred with aqueous saturated sodium potassium tartrate (20 mL) until the layers separated. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed to give a mixture of aldehyde **14** (0.62 mmol, 80%) and the tertiary alcohol **15** (0.14 mmol, 18%) which was used directly for the next step (0.765 mmol, 98%, ratio determined by ^1H NMR). **14** (purified by preparative TLC, silica, 30% ether in petroleum ether): colorless foam; R_f = 0.80 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2933 (m), 2861 (m), 1728 (m), 1460 (m), 1377 (m), 1255 (m), 1074 (s), 836 (m), 735 (m) cm^{-1}; $[\alpha]^{22}_D$ +0.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (dd, *J* = 2.4, 1.9 Hz, 1 H, CHO), 7.32−7.23 (m, 10 H, ArH), 4.53 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.44 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.64 (dd, *J* = 9.8, 2.9 Hz, 1 H, OCH), 3.61−3.52 (m, 4 H, OCH), 3.33 (dd, *J* = 8.9, 5.1 Hz, 1 H, OCH), 3.31 (dd, *J* = 11.7, 3.5 Hz, 1 H, OCH), 3.10−3.00 (m, 3 H, OCH), 2.58 (ddd, *J* = 16.3, 2.9, 1.9 Hz, 1 H, C*H*HCHO), 2.39 (ddd, *J* = 16.3, 9.8, 2.7 Hz, 1 H, C*H*HCHO), 2.15−2.08 (m, 3 H, CH), 2.00−1.88 (m, 3 H, CH), 1.83−1.77 (m, 2 H, CH), 1.74−1.64 (m, 6 H, CH), 1.52 (bd, *J* = 13.6 Hz, 1 H, CH), 1.39 (bt, *J* = 11.6 Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.01 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.82 (s, 9 H, *t*-Bu), 0.10 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 138.5, 138.5, 128.3, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 87.9, 87.5, 83.9, 83.4, 82.9, 79.8, 78.2, 77.9, 73.5, 73.3, 73.0, 71.0, 66.0, 47.4, 43.3, 40.3, 40.2, 38.0, 35.0, 32.8, 29.7, 29.5, 28.9, 25.7, 22.4, 21.6, 20.2, 18.5, 17.9, 17.5, −2.0, −2.1; HRMS, calcd for $C_{48}H_{72}O_9SiCs$ (M + Cs^+) 953.4000, found 953.4020. **15**: colorless foam; R_f = 0.32 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 3358 (m), 2933 (m), 2862 (m), 1462 (m), 1376 (m), 1256 (m), 1070 (s), 836 (m), 738 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 10 H, ArH), 4.53 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.44 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 3.82 (bs, 2 H, OCH), 3.65−3.51 (m, 4 H, OCH), 3.35−3.21 (m, 3 H, OCH), 3.09−2.98 (m 3 H, OCH), 2.68 (bs, 1 H, OH), 2.09 (dd, *J* = 9.8, 4.9 Hz, 1 H, C*H*$_2$-CHO), 1.97−1.87 (m, 4 H, CH), 1.84−1.55 (m, 10 H, CH), 1.50 (bd, *J* = 13.6 Hz, 1 H, CH), 1.39 (bt, *J* = 11.8 Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.02 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.79 (s, 9 H, *t*-Bu), 0.08 (s, 6 H, $SiCH_3$); HRMS, calcd for $C_{48}H_{74}O_9SiCs$ (M + Cs^+) 955.4153, found 955.4186.

Ester 16. A solution of the crude aldehyde **14** and alcohol **15** (total: 0.81 mmol) in CH_2Cl_2 (7 mL) was treated with (carbethoxyethylidene)triphenylphosphorane (558 mg, 1.62 mmol) and stirred at 25 °C for 12 h. The mixture was diluted with ether (25 mL) and washed with brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica, 10→30% ether in petroleum ether) to give ester **16** (586 mg, 0.658 mmol) and the unreacted tertiary alcohol **15** (130 mg, 0.15 mmol). The alcohol **15** was silylated (1.5 equiv of *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h), selectively deprotected (0.2 equiv of camphorsulfonic acid, MeOH, 25 °C, 1 h), and oxidized (2.0 equiv of Dess-Martin periodinane, CH_2Cl_2, 25 °C, 2 h) to give aldehyde **14** (110 mg, 0.134 mmol) which was again treated with (carbethoxyethylidene)triphenylphosphorane to give an additional amount of ester **16** (115 mg, 0.129 mmol). Total yield: 685 mg, 0.769 mmol, 95% (over 2 steps from **13**). **16**: colorless foam; R_f = 0.30 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 2936 (m), 2863 (m), 1720 (m), 1656 (w), 1460 (m), 1375 (m), 1258 (m), 1074 (s), 836 (m), 736 (m) cm^{-1}; $[\alpha]^{22}_D$ +18.7 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.24 (m, 10 H, ArH), 7.01 (dt, *J* = 15.6, 7.2 Hz, 1 H, =CH), 5.85 (d, *J* = 15.7 Hz, 1 H, =CH), 4.54 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.18 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 3.65−3.51 (m, 4 H, OCH), 3.34−3.30 (m, 2 H, OCH), 3.12−2.96 (m, 4 H, OCH), 3.12−2.96 (m, 4 H, OCH), 2.51 (dd, *J* = 14.9, 7.5 Hz, 1 H, CH), 2.15−2.07 (m, 4 H, CH), 2.00−1.89 (m, 3 H, CH), 1.82−1.77 (m, 2 H, CH), 1.75−1.62 (m, 6 H, CH), 1.58 (bt, *J* = 13.7 Hz, 1 H, CH), 1.39 (bt, *J* = 11.2 Hz, 1 H, CH), 1.29 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 1.28 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.01 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.83 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, 2 × $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 147.3, 138.5, 138.5, 128.3, 128.2, 127.7, 127.5, 127.4, 122.4, 87.8, 87.5, 83.9, 83.7, 83.2, 83.0, 78.1, 77.9, 73.4, 73.3, 73.0, 71.0, 66.0, 60.2, 47.5, 40.3, 40.2, 38.0, 35.0, 32.8, 31.6, 29.5, 28.9, 25.7, 22.1, 21.6, 20.2, 18.5, 17.5, 14.3, −2.0, −2.1; HRMS, calcd for $C_{52}H_{78}O_{10}SiCs$ (M + Cs^+) 1023.4419, found 1023.4440.

Allylic Alcohol 17. A solution of ester **16** (685 mg, 0.769 mmol) in CH_2Cl_2 (8 mL) was treated with diisobutylaluminum hydride (2.31 mL of a 1.0 M solution in CH_2Cl_2, 2.31 mmol) as described for aldehyde **14**. Flash chromatography (silica, 20→50% ether in petroleum ether) gave allylic alcohol **17** (630 mg, 0.742 mmol, 96%). **17**: colorless foam; R_f = 0.20 (silica, 30% ether in petroleum ether); IR (film) ν_{max} 3455 (w), 2932 (m), 2860 (m), 1459 (m), 1376 (m), 1254 (m), 1074 (s), 835 (m), 774 (m), 738 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ +11.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 10 H, ArH), 5.77 (dt, *J* = 15.4, 6.2 Hz, 1 H, =CH), 5.67 (dt, *J* = 15.4, 5.8 Hz, 1 H, =CH), 4.53 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.36 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.10 (d, *J* = 5.7 Hz, 2 H, CH_2-

OH), 3.64−3.55 (m, 3 H, OCH), 3.53 (bq, J = 8.1 Hz, 1 H, OCH), 3.34−3.29 (m, 2 H, OCH), 3.07 (dd, J = 11.6. 3.8 Hz, 1 H, OCH), 3.04−2.95 (m, 3 H, OCH), 2.38 (dd, J = 14.4, 7.5 Hz, 1 H, CH), 2.12−2.06 (m, 3 H, CH), 2.00−1.88 (m, 4 H, CH), 1.82−1.53 (m, 9 H, CH), 1.39 (bt, J = 11.4 Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.01 (d, J = 7.0 Hz, 3 H, CH_3), 0.83 (s, 9 H, *t*-Bu), 0.08 (2 × s, 3 H, 2 × $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 131.0, 130.2, 128.3, 128.2, 127.7, 127.6, 127.5, 87.8, 87.6, 85.1, 83.8, 83.2, 78.2, 77.9, 73.5, 73.5, 73.3, 73.0, 71.0, 66.0, 63.8, 47.7, 40.3, 40.2, 38.1, 35.1, 32.9, 31.4, 29.6, 28.9, 25.7, 22.2, 21.6, 20.2, 18.5, 18.0, 17.5, −2.0, −2.0; HRMS, calcd for $C_{50}H_{76}O_9SiCs$ (M + Cs^+) 981.4313, found 981.4333.

Epoxide 18. A solution of allylic alcohol **17** (630 mg, 0.742 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of (+)-diethyl-D-tartrate (26 μL, 0.15 mmol), 4 Å molecular sieves (420 mg), and titanium isopropoxide (34 μL, 0.11 mmol) in CH_2Cl_2 (3 mL) at −30 °C. After 30 min, *tert*-butyl hydroperoxide (224 μL, 1.12 mmol, 5−6 M in decane) was added and the reaction mixture was stored at −20 °C for 14 h. Cooling was stopped and the reaction mixture was filtered. The filtrate was diluted with EtOAc (25 mL), washed with aqueous saturated sodium sulfate (25 mL), dried ($MgSO_4$), and filtered through Celite. The filtrate was concentrated and chromatographed (silica, 30→50% ether in petroleum ether) to give epoxide **18** (636 mg, 0.735 mmol, 99%). **18**: colorless foam; R_f = 0.60 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 3476 (w), 2927 (m), 2863 (m), 1454 (m), 1375 (m), 1248 (m), 1073 (s), 834 (m), 699 (m) cm^{-1}; $[\alpha]^{22}_D$ +6.1 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 4.54 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2-Ph), 4.38 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.94 (bd, J = 12.7 Hz, 1 H, OCH), 3.66−3.60 (m, 4 H, OCH), 3.59 (bq, J = 7.5 Hz, 1 H, OCH), 3.36−3.31 (m, 2 H, OCH), 3.15−3.01 (m, 5 H, OCH), 2.93−2.92 (m, 1 H, OCH), 2.12−2.09 (m, 3 H, CH), 2.02−1.90 (m, 3 H, CH), 1.84−1.56 (m, 11 H, CH), 1.40 (bt, J = 11.5 Hz, 1 H, CH), 1.29 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.83 (s, 9 H, *t*-Bu), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 128.3, 128.3, 127.7, 127.5, 127.5, 87.8, 87.5, 83.6, 83.2, 83.0, 82.4, 78.1, 77.9, 73.5, 73.3, 73.2, 73.0, 71.0, 66.0, 61.7, 58.0, 54.4, 47.5, 40.3, 40.2, 38.0, 35.2, 32.8, 30.6, 29.5, 28.9, 25.7, 22.1, 21.6, 20.2, 18.5, 17.5, −2.0, −2.1; HRMS, calcd for $C_{50}H_{76}O_{10}SiCs$ (M + Cs^+) 997.4262, found 997.4250.

Olefin 20. To a solution of epoxide **18** (636 mg, 0.735 mmol), DMSO (800 μL), and triethylamine (1.01 mL, 7.3 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added sulfur trioxide·pyridine complex (574 mg, 3.6 mmol) in four portions. After 5 h, the reaction mixture was diluted with ether (30 mL), washed with aqueous saturated ammonium chloride (150 mL), dried ($MgSO_4$), and concentrated to give the crude epoxy aldehyde **19** (0.735 mmol) which was used directly for the next step. A mixture of triphenylphosphonium bromide (1.43 g, 4.01 mmol) in THF (8 mL) was treated with sodium bis(trimethylsilyl)amide (2.85 mL of a 1.0 M solution in THF, 2.85 mmol) at 0 °C. To the resulting yellow suspension was added dropwise a solution of the crude epoxy aldehyde **19** (0.735 mmol) in THF (10 mL) and the mixture was stirred at 0 °C for 30 min. Acetone (1 mL) was added, followed by ether (30 mL), and the mixture was washed with aqueous saturated ammonium chloride (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica, 20→50% ether in petroleum ether) to give olefin **20** (500 mg, 0.58 mmol, 80%). **20**: colorless foam; R_f = 0.70 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2933 (s), 2857 (s), 1455 (m), 1380 (m), 1252 (m), 1075 (s), 836 (m), 775 (m), 734 (m), 604 (m) cm^{-1}; $[\alpha]^{22}_D$ +15.3 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 5.60 (ddd, J = 17.4, 10.3, 7.6 Hz, 1 H, =CH), 5.46 (dd, J = 17.3, 1.3 Hz, 1 H, =C*H*H), 5.28 (dd, J = 10.2, 1.3 Hz, 1 H, =C*H*H), 4.55 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.66−3.59 (m, 3 H, OCH), 3.55 (bq, J = 7.5 Hz, 1 H, OCH), 3.36−3.31 (m, 2 H, OCH), 3.16 (dd, J = 9.6, 2.0 Hz, 1 H, OCH), 3.11−3.07 (m, 2 H, OCH), 3.04−3.02 (m, 3 H, OCH), 2.13−2.09 (m, 3 H, CH), 2.02−1.90 (m, 3 H, CH), 1.84−1.55 (m, 10 H, CH), 1.40 (bt, J = 11.8 Hz, 1 H, CH), 1.29 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.84 (s, 9 H, *t*-Bu), 0.10 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.4, 135.8, 128.2, 128.2, 127.6, 127.4, 127.4, 118.9, 87.7, 87.5, 83.5, 83.1, 82.9, 82.4, 78.0, 77.8, 73.4, 73.2, 73.1, 72.9, 70.9, 58.8, 58.4, 47.6, 40.2, 40.1, 38.0, 35.1, 32.7, 31.0, 29.4, 28.8, 25.6, 22.0, 21.5, 20.1, 18.4, 17.8, 17.4, −2.1, −2.2; HRMS, calcd for $C_{51}H_{76}O_9SiCs$ (M + Cs^+) 993.4313, found 993.4271.

Hydroxy Epoxide 6. A solution of epoxide **20** (500 mg, 0.581 mmol) in THF (6 mL) was treated with tetra-*n*-butylammonium fluoride (0.87 mL of a 1.0 M solution in THF, 0.87 mmol) and stirred at 25 °C for 10 h. The mixture was diluted with ether (25 mL), washed with aqueous saturated ammonium chloride (25 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 50→100% ether in petroleum ether) gave hydroxy epoxide **6** (435 mg, 0.581 mmol, 100%). **6**: colorless foam; R_f = 0.18 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 3441 (m), 2953 (m), 2871 (m), 1454 (m), 1380 (m), 1073 (s), 736 (m), 698 (m) cm^{-1}; $[\alpha]^{22}_D$ +14.6 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 5.57 (ddd, J = 17.3, 10.2, 7.6 Hz, 1 H, =CH), 5.47 (dd, J = 17.2, 1.4 Hz, 1 H, =C*H*H), 5.28 (dd, J = 10.3, 1.4 Hz, 1 H, =C*H*H), 4.54 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.66−3.53 (m, 4 H, OCH), 3.36−3.31 (m, 2 H, OCH), 3.20 (dd, J = 9.3, 2.8 Hz, 1 H, OCH), 3.17 (dd, J = 7.6, 2.2 Hz, 1 H, OCH), 3.10−2.99 (m, 4 H, OCH), 2.44 (bs, 1 H, OH), 2.15−2.01 (m, 3 H, CH), 1.98−1.66 (m, 10 H, CH), 1.59−1.55 (m, 2 H, CH), 1.44−1.38 (m, 2 H, CH), 1.29 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 6 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 135.7, 128.3, 128.2, 127.7, 127.5, 127.5, 119.3, 87.9, 87.4, 83.7, 83.3, 83.0, 81.6, 78.1, 77.9, 77.0, 73.4, 73.3, 73.0, 71.0, 70.9, 66.0, 58.5, 53.7, 47.6, 40.3, 40.2, 38.0, 35.1, 32.8, 31.0, 29.4, 28.9, 21.6, 21.5, 20.7, 20.2, 18.5, 17.5, 14.1; HRMS, calcd for $C_{45}H_{62}O_9Cs$ (M + Cs^+) 879.3448, found 879.3425.

Alcohol 21. A solution of hydroxy epoxide **6** (435 mg, 0.581 mmol) in CH_2Cl_2 (6 mL) was treated at 0 °C with pyridinium *p*-toluenesulfonate (70 mg, 0.28 mmol) and stirred at 0 °C for 14 h. The mixture was diluted with ether (30 mL) and washed with aqueous saturated ammonium chloride (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to yield alcohol **21** (435 mg) which was used without purification for the next step. **21**: colorless foam; R_f = 0.72 (silica, 90% ether in petroleum ether); IR (film) ν_{max} 3444 (w), 2946 (s), 2873 (s), 1457 (m), 1379 (m), 1073 (s), 920 (m), 734 (s), 699 (m) cm^{-1}; $[\alpha]^{22}_D$ +10.5 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 5.80 (ddd, J = 17.3, 10.3, 7.3 Hz, 1 H, =CH), 5.40 (dd, J = 17.4, 1.2 Hz, 1 H, =C*H*H), 5.33 (dd, J = 10.2, 1.4 Hz, 1 H, =C*H*H), 4.54 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.83 (dd, J = 9.1, 7.5 Hz, 1 H, C*H*CH=), 3.66−3.53 (m, 4 H, OCH), 3.42−3.34 (m, 2 H, OCH), 3.32 (dd, J = 12.0, 3.5 Hz, 1 H, OCH), 3.26−3.21 (m, 1 H, OCH), 3.13−3.06 (m, 3 H, OCH), 2.70−2.40 (bs, 1 H, OH), 2.21−2.09 (m, 4 H, CH), 2.02−1.90 (m, 3 H, CH), 1.85−1.59 (m, 8 H, CH), 1.53 (bt, J = 11.6 Hz, 1 H, CH), 1.40 (bt, J = 11.7 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 136.2, 128.3, 128.2, 127.7, 127.5, 127.4, 119.6, 88.0, 87.4, 85.1, 83.9, 83.8, 79.0, 78.1, 77.9, 76.3, 73.5, 73.3, 73.1, 73.0, 71.0, 69.8, 66.0, 45.0, 40.3, 40.2, 38.0, 35.3, 33.2, 32.5, 29.5, 28.9, 21.5, 20.2, 18.6, 17.5, 16.0; HRMS, calcd for $C_{45}H_{62}O_9Cs$ (M + Cs^+) 879.3448, found 879.3466.

Silyl Ether 22. A solution of the crude alcohol **21** (435 mg) in CH_2Cl_2 (6 mL) was treated at 0 °C with 2,6-lutidine (203 μL, 1.74 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (266 μL, 1.16 mmol) and stirred for 15 min at 0 °C. The mixture was diluted with ether (30 mL), washed with aqueous saturated ammonium chloride (25 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 10→30% ether in petroleum ether) gave silyl ether **22** (380 mg, 0.441 mmol, 76% (over 2 steps)). **22**: colorless foam; R_f = 0.60 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2952 (s), 2858 (s), 1462 (m), 1380 (m), 1255 (m), 1067 (s), 837 (m), 776 (m), 735 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ +20.6 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 5.81 (ddd, J = 17.0, 10.4, 6.3 Hz, 1 H, =CH), 5.32 (ddd, J = 17.0, 1.7, 1.2 Hz, 1 H, =C*H*H), 5.20 (ddd, J = 10.4, 1.7, 0.6 Hz, 1 H, =C*H*H), 4.55 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.84 (dd, J = 9.1, 6.5 Hz, 1 H, C*H*CH=), 3.66−3.53 (m,

4 H, OCH), 3.43−3.36 (m, 2 H, OCH), 3.33 (dd, J = 12.0, 3.5 Hz, 1 H, OCH), 3.25−3.20 (m, 1 H, OCH), 3.13−3.06 (m, 3 H, OCH), 2.13−2.06 (m, 3 H, CH), 2.02−1.91 (m, 3 H, CH), 1.83−1.79 (m, 3 H, CH), 1.76−1.53 (m, 6 H, CH), 1.53 (bt, J = 11.7 Hz, 1 H, CH), 1.40 (bt, J = 11.5 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.86 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 136.6, 128.3, 128.2, 127.7, 127.6, 127.5, 117.7, 88.0, 87.4, 85.0, 84.0, 83.8, 78.8, 78.1, 77.9, 76.7, 75.5, 73.3, 73.0, 72.7, 71.5, 71.0, 66.0, 45.2, 40.3, 40.2, 38.0, 35.4, 34.6, 33.2, 29.5, 28.8, 25.7, 21.5, 20.2, 18.6, 17.5, 16.0, −4.2, −4.5; HRMS, calcd for $C_{51}H_{76}O_9SiCs$ (M + Cs^+) 993.4313, found 993.4337.

Aldehyde 23. A solution of the silyl ether **22** (380 mg, 0.441 mmol) in CH_2Cl_2 (4 mL) was treated with ozone at −78 °C until a pale blue color appeared. Triphenylphosphine (370 mg, 1.41 mmol) was added and the mixture was stirred at 25 °C for 1 h. Concentration, flash chromatography (silica, 30→50% ether in petroleum ether), and azeotroping with benzene gave the aldehyde **23** (381 mg, 0.441 mmol, 100%). **23**: colorless foam; R_f = 0.20 (streak, silica, 70% ether in petroleum ether); IR (film) ν_{max} 2927 (s), 2851 (s), 1744 (m), 1462 (m), 1373 (m), 1256 (m), 1063 (s), 843 (m), 775 (m), 741(m), 699 (m) cm^{-1}; $[\alpha]^{22}_D$ +11.6 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (d, J = 1.1 Hz, 1 H, CHO), 7.33−7.24 (m, 10 H, ArH), 4.55 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.93 (dd, J = 9.8, 1.0 Hz, 1 H, C*H*CHO), 3.84−3.81 (m, 1 H, OCH), 3.65−3.55 (m, 4 H, OCH), 3.38−3.32 (m, 2 H, OCH), 3.26−3.15 (m, 1 H, OCH), 3.10−3.06 (m, 3 H, OCH), 2.18−2.08 (m, 4 H, CH), 2.04−1.93 (m, 3 H, CH), 1.90−1.82 (m, 3 H, CH), 1.76−1.59 (m, 6 H, CH), 1.40 (bt, J = 11.4 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.87 (s, 9 H, *t*-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 138.5, 138.5, 88.0, 87.3, 85.1, 84.1, 83.7, 78.1, 77.9, 77.8, 73.5, 73.3, 73.0, 71.0, 67.4, 66.0, 44.6, 40.3, 40.2, 38.0, 35.3, 34.5, 33.2, 29.4, 28.9, 25.7, 21.5, 20.2, 18.6, 17.5, 15.6, −4.2, −5.0; HRMS, calcd for $C_{50}H_{74}O_{10}SiCs$ (M + Cs^+) 995.4106, found 995.4073.

Ketone 24. A solution of the aldehyde **23** (418.7 mg, 0.485 mmol) in THF (4 mL) was treated dropwise with methylmagnesium chloride (208 μL of a 3.0 M solution in THF, 0.624 mmol) at 0 °C. After stirring at 0 °C for 30 min, the mixture was diluted with ether (25 mL), washed with aqueous saturated ammonium chloride (20 mL), and dried ($MgSO_4$). Filtration and concentration afforded the crude alcohol that was used immediately for the next step. The crude alcohol was dissolved in CH_2Cl_2 (5 mL) and treated with Dess-Martin periodinane (780 mg, 1.84 mmol). The resulting solution was stirred at 25 °C for 2 h, diluted with ether (25 mL), washed with aqueous sodium bicarbonate/sodium thiosulfate (1:1, 25 mL), and dried ($MgSO_4$). Filtration and concentration afforded the crude ketone **24** (387 mg, 0.441 mmol, 91%). **24**: colorless foam; R_f = 0.42 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2926 (s), 2854 (s), 1732 (m), 1462 (m), 1380 (m), 1256 (m), 1067 (s), 837 (m), 698 (m), 606 (s) cm^{-1}; $[\alpha]^{22}_D$ +10.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.24 (m, 10 H, ArH), 4.55 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.92 (d, J = 9.4 Hz, 1 H, C*H*C(O)), 3.78 (ddd, J = 10.5, 9.4, 5.2 Hz, 1 H, OCH), 3.66−3.53 (m, 4 H, OCH), 3.37 (dd, J = 8.4, 5.2 Hz, 1 H, OCH), 3.33 (dd, J = 12.0, 3.5 Hz, 1 H, OCH), 3.24−3.19 (m, 1 H, OCH), 3.13−3.06 (m, 3 H, OCH), 2.21 (s, 3 H, CH_3), 2.14−2.07 (m, 4 H, CH), 2.03−1.91 (m, 3 H, CH), 1.85−1.54 (m, 9 H, CH), 1.40 (bt, J = 11.5 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.84 (s, 9 H, *t*-Bu), 0.05 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 138.5, 138.5, 128.3, 127.7, 127.5, 127.5, 88.0, 87.3, 85.1, 84.0, 83.8, 78.6, 78.2, 78.1, 77.9, 73.5, 73.3, 73.0, 71.0, 68.5, 66.0, 44.8, 40.3, 40.2, 38.0, 35.3, 34.4, 33.1, 29.4, 28.9, 28.0, 21.5, 20.2, 18.6, 17.5, 15.8, −4.5, −5.0; HRMS, calcd for $C_{51}H_{76}O_{10}SiCs$ (M + Cs^+) 1009.4262, found 1009.4303.

Hydroxy Ketone 25. A solution of the crude ketone **24** (387 mg) in THF was treated with tetra-*n*-butylammonium fluoride (0.49 mL of a 1.0 M solution in THF, 0.49 mmol) and stirred at 25 °C for 2 h. The mixture was diluted with ether (25 mL), washed with aqueous saturated ammonium chloride (20 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 10→50% ether in petroleum ether) gave the hydroxy ketone **25** (270 mg, 0.354 mmol, 81% (2 steps)). **25**: colorless foam; R_f = 0.10 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 3505 (w), 2946 (m), 2873 (m), 1719 (m), 1457 (m), 1380 (m), 1073 (s), 912 (w), 734 (m) cm^{-1}; $[\alpha]^{22}_D$ −7.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10 H, ArH), 4.54 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.76−3.65 (m, 2 H, OCH), 3.64−3.53 (m, 5 H, OCH), 3.37 (dd, J = 8.3, 5.2 Hz, 1 H, OCH), 3.33 (dd, J = 11.9, 3.5 Hz, 1 H, OCH), 3.24−3.19 (m, 1 H, OCH), 3.13−3.09 (m, 2 H, OCH), 3.06 (dd, J = 12.8, 3.6 Hz, 1 H, OCH), 2.25 (s, 3 H, CH_3), 2.19−2.08 (m, 4 H, CH), 2.06−1.90 (m, 3 H, CH), 1.84−1.60 (m, 8 H, CH), 1.56 (bt, J = 11.7 Hz, 1 H, CH), 1.39 (bt, J = 11.6 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.03 (d, J = 7.1 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 138.5, 138.4, 128.3, 128.2, 127.6, 127.5, 127.3, 88.0, 87.4, 85.1, 83.8, 83.5, 78.2, 78.1, 77.9, 77.7, 73.8, 73.5, 73.3, 73.0, 71.0, 67.7, 66.0, 44.9, 40.3, 40.2, 37.9, 35.3, 33.2, 31.7, 29.4, 28.9, 26.8, 21.4, 20.2, 18.5, 17.5, 15.3; HRMS, calcd for $C_{45}H_{62}O_{10}Cs$ (M + Cs^+) 895.3397, found 895.3363.

α-Bromo Ester 26. To a solution of the hydroxy ketone **25** (270 mg, 0.354 mmol) in CH_2Cl_2 (4 mL) was added pyridine (272 μL, 3.37 mmol) and bromoacetyl chloride (58 μL, 0.70 mmol) at 0 °C. After stirring at 0 °C for 15 min, the mixture was diluted with ether (30 mL), washed with aqueous saturated ammonium chloride (20 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 20→40% ether in petroleum ether) afforded the α-bromo ester **26** (253 mg, 0.286 mmol, 81%). **26**: colorless foam; R_f = 0.71 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2924 (s), 2854 (s), 1731 (m), 1454 (m), 1380 (m), 1274 (m), 1071 (s), 1028 (m), 678 (m) cm^{-1}; $[\alpha]^{22}_D$ +1.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.24 (m, 10 H, ArH), 4.97 (ddd, J = 5.5, 10.1, 11.1 Hz, 1 H, CHOC(O)), 4.54 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.95 (d, J = 10.0 Hz, 1 H, CHC(O)), 3.80 (s, 2 H, CH_2Br), 3.66−3.54 (m, 4 H, OCH), 3.37 (dd, J = 8.2, 5.1 Hz, 1 H, OCH), 3.33 (dd, J = 12.0, 3.5 Hz, 1 H, OCH), 3.25−3.20 (m, 1 H, OCH), 3.16−3.10 (m, 2 H, OCH), 3.08 (dd, J = 11.7, 3.7 Hz, 1 H, OCH), 2.29−2.25 (m, 1 H, CH), 2.20 (s, 3 H, CH_3), 2.17−2.06 (m, 3 H, CH), 2.01−1.90 (m, 3 H, CH), 1.83−1.57 (m, 9 H, CH), 1.40 (bt, J = 11.7 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.03 (d, J = 7.1 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 166.0, 138.5, 138.4, 128.3, 128.2, 127.7, 127.5, 127.4, 88.1, 87.4, 85.1, 83.9, 83.4, 78.1, 77.8, 77.7, 75.6, 73.7, 73.7, 73.3, 73.0, 73.0, 68.9, 66.0, 44.7, 40.3, 40.2, 37.9, 35.3, 33.1, 29.7, 29.4, 28.9, 26.0, 25.5, 21.4, 20.3, 18.4, 17.5, 15.4; HRMS, calcd for $C_{47}H_{63}BrO_{11}Cs$ (M + Cs^+) 1015.2608, found 1015.2580.

Phosphonate 5. A solution of the α-bromo ester **26** (241 mg, 0.274 mmol) in $P(OMe)_3$ (7 mL) was heated in a sealed tube for 4 h at 90 °C and an additional 30 min at 120 °C. The mixture was concentrated and the resulting phosphonate **5** (250 mg, 0.274 mmol, 100%) was used without further purification for the next reaction. **5**: colorless foam; R_f = 0.05 (silica, 100% ether); IR (film) ν_{max} 2950 (m), 2871 (m), 1737 (s), 1651 (w), 1458 (m), 1379 (m), 1270 (s), 1068 (s), 1033 (s), 915 (m), 791 (m), 699 (m), 592 (m) cm^{-1}; $[\alpha]^{22}_D$ −0.7 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.23 (m, 10 H, ArH), 4.96 (dt, J = 5.5, 11.0 Hz, 1 H, CHOC(O)), 4.53 (d, J = 11.6 Hz, 1 H, C*H*HPh), 4.45 (s, 2 H, CH_2Ph), 4.36 (d, J = 11.6 Hz, 1 H, C*H*HPh), 3.95 (d, J = 10.1 Hz, 1 H, CHC(O)), 3.74 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.64−3.51 (m, 4 H, OCH), 3.36 (dd, J = 7.9, 5.2 Hz, 1 H, OCH), 3.31 (dd, J = 12.1, 3.5 Hz, 1 H, OCH), 3.24−3.19 (m, 1 H, OCH), 3.14−3.06 (m, 3 H, OCH), 2.95 (d, J = 11.5 Hz, 1 H, C*H*HP), 2.93 (d, J = 11.8 Hz, 1 H, C*H*HP), 2.29−2.25 (m, 1 H, CH), 2.19 (s, 3 H, CH_3), 2.13−2.08 (m, 3 H, CH), 2.04−1.88 (m, 3 H, CH), 1.82−1.55 (m, 9 H, CH), 1.39 (bt, J = 11.5 Hz, 1 H, CH), 1.29 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 164.4, 138.5, 138.4, 128.4, 128.3, 127.7, 127.5, 127.4, 88.0, 87.4, 85.1, 83.8, 83.4, 78.1, 77.8, 77.7, 75.6, 73.7, 73.4, 73.3, 73.0, 71.0, 68.4, 66.0, 44.6, 40.3, 40.2, 37.9, 35.3, 33.7, 33.1, 32.6, 29.7, 29.4, 28.8, 26.0, 21.4, 20.2, 18.4, 17.5, 15.4; HRMS, calcd for $C_{49}H_{69}O_{14}PCs$ (M + Cs^+) 1045.3479, found 1045.3520.

Lactone 27. A mixture of the crude phosphonate **5** (250 mg, 0.274 mmol), *N,N*-diisopropylethylamine (121 μL, 0.96 mmol), and lithium chloride (40 mg, 0.96 mmol) in CH_3CN (3 mL) was stirred at 25 °C for 3 h. The mixture was diluted with ether (50 mL), washed with brine (25 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 50→100% ether in petroleum ether) gave the lactone **27** (200 mg, 0.254 mmol, 89% (2 steps)). **27**: colorless foam; R_f = 0.35 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2942 (s), 2873 (s), 1731 (s), 1638 (w), 1457 (m), 1380 (m), 1270 (m), 1233 (m), 1066 (s), 956 (m), 880 (m), 737 (m), 703 (m) cm^{-1}; $[\alpha]^{22}_D$ +4.9 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 10 H, ArH), 5.73 (bs, 1 H, =CH), 4.54 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.37 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.26 (bd, *J* = 10.8 Hz, 1 H, CHC=), 4.00 (dt, *J* = 11.1, 4.6 Hz, 1 H, CHOC(O)), 3.70–3.56 (m, 4 H, OCH), 3.37 (dd, *J* = 8.3, 5.2 Hz, 1 H, OCH), 3.33 (dd, *J* = 11.9, 3.5 Hz, 1 H, OCH), 3.28–3.24 (m, 1 H, OCH), 3.13–3.07 (m, 4 H, OCH), 2.30–2.26 (m, 1 H, CH), 2.16–2.06 (m, 3 H, CH), 2.01–1.63 (m, 10 H, CH), 1.96 (s, 3 H, CH_3), 1.55 (bt, *J* = 11.7 Hz, 1 H, CH), 1.40 (bt, *J* = 11.7 Hz, 1 H, CH), 1.30 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.03 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 161.1, 138.5, 138.4, 128.2, 128.2, 127.6, 127.5, 127.4, 115.5, 88.0, 87.3, 85.4, 83.9, 83.5, 78.9, 78.1, 77.8, 76.5, 74.6, 73.4, 73.3, 73.0, 71.0, 68.3, 66.0, 44.6, 40.3, 40.2, 37.9, 35.3, 33.1, 30.0, 29.6, 29.4, 28.8, 21.4, 20.2, 18.4, 17.5, 17.3, 15.7; HRMS, calcd for $C_{47}H_{62}O_{10}Cs$ ($M + Cs^+$) 919.3394, found 919.3399.

Allylic Ether 29. A solution of the lactone **27** (200 mg, 0.254 mmol) in CH_2Cl_2 (2 mL) was treated with diisobutylaluminum hydride (0.38 mL of a 1.0 M solution in CH_2Cl_2, 0.38 mmol) at −78 °C. After stirring for 30 min at −78 °C, the reaction was quenched with MeOH (1 mL), diluted with EtOAc (25 mL), and washed with aqueous saturated sodium potassium tartrate (25 mL). The water layer was extracted with EtOAc (2 × 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the crude lactol **28**. The crude lactol **28** (0.254 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with triethylsilane (202 μL, 1.27 mmol) and boron trifluoride etherate (31 μL, 0.254 mmol) at −10 °C. After stirring at −10 °C for 30 min, the reaction was quenched with triethylamine (1 mL), diluted with ether (25 mL), and washed with brine (25 mL). Drying ($MgSO_4$), filtration, concentration, and flash chromatography (silica, 50→100% ether in petroleum ether) gave the allylic ether **29** (145 mg, 0.188 mmol) and monodebenzylated products (34 mg, 0.05 mmol). Combined yield: 0.24 mmol, 93%. **29**: colorless foam; R_f = 0.60 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2937 (m), 2866 (m), 1456 (m), 1377 (m), 1072 (s), 1023 (m), 737 (m), 697 (m) cm^{-1}; $[\alpha]^{22}_D$ +21.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 10 H, ArH), 5.35 (bs, 1 H, =CH), 4.55 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.46 (s, 2 H, CH_2Ph), 4.38 (d, *J* = 11.6 Hz, 1 H, C*H*HPh), 4.25 (bd, *J* = 14.3 Hz, 1 H, OC*H*HCH=), 4.14 (bd, *J* = 15.1 Hz, 1 H, OC*H*HCH=), 3.98 (bd, *J* = 7.9 Hz, 1 H, OCHC=), 3.66–3.54 (m, 4 H, OCH), 3.37 (dd, *J* = 8.3, 5.2 Hz, 1 H, OCH), 3.33 (dd, *J* = 12.0, 3.4 Hz, 1 H, OCH), 3.29–3.20 (m, 2 H, OCH), 3.14 (dd, *J* = 12.3, 3.7 Hz, 1 H, OCH), 3.11–3.07 (m, 2 H, OCH), 2.14–2.07 (m, 3 H, CH), 2.02–1.90 (m, 4 H, CH), 1.85–1.61 (m, 8 H, CH), 1.71 (s, 3 H, CH_3), 1.53 (bt, *J* = 11.7 Hz, 1 H, CH), 1.41 (bt, *J* = 11.5 Hz, 1 H, CH), 1.31 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.04 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.5, 134.5, 128.3, 128.3, 127.7, 127.6, 127.5, 121.0, 88.0, 87.4, 85.3, 83.9, 80.2, 78.1, 77.9, 74.7, 73.7, 73.5, 73.3, 73.0, 71.0, 69.5, 66.9, 66.0, 45.0, 40.3, 40.2, 38.0, 35.4, 33.2, 31.0, 29.7, 29.5, 28.9, 28.1, 21.5, 20.3, 18.5, 17.5, 17.2, 16.2; HRMS, calcd for $C_{47}H_{64}O_9Cs$ ($M + Cs^+$) 905.3605, found 905.3588.

Diol 30. A solution of dibenzyl ether **29** (145 mg, 0.188 mmol) and monobenzylated side products (34 mg, 0.05 mmol) obtained above in THF (1 mL) was added dropwise at −78 °C to a dark blue solution of lithium (100 mg) in liquid ammonia (ca. 45 mL). After stirring at −78 °C for 1 h, the reaction was quenched with ammonium chloride (100 mg) and the ammonia was allowed to evaporate. The residue was taken up in EtOAc (25 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography (silica, 100% ether → 100% ethyl acetate) to give diol **30** (128 mg, 0.216 mmol, 92%). **30**: colorless foam; R_f = 0.30 (silica, 100% ethyl acetate); IR (film) ν_{max} 3398 (m), 2935 (m), 2874 (m), 1458 (m), 1380 (m), 1270 (w), 1071 (s), 732 (m), 615 (m) cm^{-1}; $[\alpha]^{22}_D$ +44.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (d, *J* = 1.2 Hz, 1 H, =CH), 4.23 (dq, *J* = 16.0, 2.1 Hz, 1 H, OC*H*HCH=), 4.11 (dq, *J* = 16.2, 2.1 Hz, 1 H, OC*H*HCH=), 3.95 (bd, *J* = 8.1 Hz, 1 H, OCHC=), 3.85–3.77 (m, 3 H, OCH), 3.54 (bq, *J* = 8.3 Hz, 1H, OCH), 3.34 (dd, *J* = 8.3, 5.2 Hz, 1 H, OCH), 3.31 (dd, *J* = 12.0, 3.4 Hz, 1 H, OCH), 3.27–3.17 (m, 2 H, OCH), 3.12 (dd, *J* = 12.1, 3.4 Hz, 1 H, OCH), 3.10–3.05 (m, 2 H, OCH), 3.0–2.5 (bs, 2 H, 2 × OH), 2.12–2.04 (m, 3 H, CH), 2.02–1.96 (m, 2 H, CH), 1.92–1.86 (m, 1 H, CH), 1.83–1.70 (m, 5 H, CH), 1.68 (s, 3 H, CH_3), 1.66–1.58 (m, 4 H, CH), 1.51 (bt, *J* = 11.7 Hz, 1 H, CH), 1.44 (bt, *J* = 11.7 Hz, 1 H, CH), 1.29 (s, 3 H, CH_3), 1.26 (s, 6 H, 2 × CH_3), 1.24 (s, 3 H, CH_3), 1.01 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 121.0, 87.9, 87.6, 85.3, 83.9, 83.8, 80.2, 80.0, 78.0, 74.7, 73.9, 73.6, 73.3, 71.2, 69.5, 66.9, 59.2, 45.0, 43.7, 42.9, 37.9, 35.4, 33.2, 31.0, 29.4, 28.8, 21.5, 20.2, 18.5, 17.2, 16.2, 15.6; HRMS, calcd for $C_{33}H_{52}O_9Na$ ($M + Na^+$) 615.3509, found 615.3520.

Tosylate 31. A solution of diol **30** (128 mg, 0.216 mmol) and *p*-toluenesulfonyl chloride (162 mg, 0.864 mmol) in CH_2Cl_2/pyridine (10:1, 4 mL) was stirred at 25 °C for 12 h. The mixture was diluted with EtOAc (25 mL), washed with aqueous saturated ammonium chloride (20 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 50→100% ether in petroleum ether → 100% EtOAc) gave a mixture of tosylate **31** (80 mg) and diol **30** (50 mg). The latter compound was recycled twice to give an additional amount of tosylate **31** (total yield: 128 mg, 0.171 mmol, 79%). **31**: colorless foam; R_f = 0.40 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 3463 (w), 2945 (m), 2874 (m), 1458 (m), 1363 (m), 1177 (m), 1072 (s), 956 (m), 733 (m), 663 (m), 555 (m) cm^{-1}; $[\alpha]^{22}_D$ +39.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2 H, ArH), 7.33 (d, *J* = 8.0 Hz, 2 H, ArH), 5.33 (q, *J* = 1.4 Hz, 1 H, =CH), 4.26–4.11 (m, 4 H, OCH), 3.96 (bd, *J* = 7.8 Hz, 1 H, OCHC=), 3.71 (dd, *J* = 11.6, 5.4 Hz, 1 H, OCH), 3.53 (bq, *J* = 8.5 Hz, 1 H, OCH), 3.33 (dd, *J* = 8.4, 5.2 Hz, 1 H, OCH), 3.26–3.17 (m, 3 H, OCH), 3.12 (dd, *J* = 12.3, 3.7 Hz, 1 H, OCH), 3.07 (dd, *J* = 9.0, 2.4 Hz, 1 H, OCH), 3.03 (dd, *J* = 11.7, 3.8 Hz, 1 H, OCH), 2.44 (s, 3 H, CH_3), 2.12–2.07 (m, 3 H, CH), 2.00–1.96 (m, 2 H, CH), 1.94–1.87 (m, 2 H, CH), 1.82–1.72 (m, 3 H, CH), 1.69 (s, 3 H, CH_3), 1.67–1.58 (m, 5 H, CH), 1.51 (bt, *J* = 11.8 Hz, 1 H, CH), 1.40 (bt, *J* = 11.8 Hz, 1 H, CH), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.01 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 134.5, 133.0, 129.8, 127.9, 121.0, 87.9, 87.5, 85.3, 83.9, 83.8, 80.2, 78.0, 74.7, 73.9, 73.6, 73.2, 70.7, 69.5, 66.9, 66.8, 58.4, 45.0, 43.8, 39.3, 37.9, 35.4, 33.2, 31.0, 29.4, 28.6, 21.6, 21.5, 20.1, 18.5, 18.4, 17.1, 16.4, 16.2; HRMS, calcd for $C_{40}H_{58}O_{11}SCs$ ($M + Cs^+$) 879.2754, found 879.2717.

Iodide 33. A solution of tosylate **31** (42 mg, 0.055 mmol) in acetone (1 mL) was treated with sodium iodide (42 mg, 0.28 mmol) and heated at 60 °C for 5 h. The resulting solution was diluted with ether (25 mL), washed with aqueous saturated sodium thiosulfate (20 mL), and dried ($MgSO_4$). Filtration and concentration gave the crude iodo alcohol which was used directly for the next step. The iodo alcohol was dissolved in CH_2Cl_2 (2 mL), treated with (trimethylsilyl)imidazole (41 μL, 0.28 mmol), and stirred at 25 °C for 30 min. The mixture was diluted with ether (25 mL), washed with aqueous saturated ammonium chloride (20 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 20→40% ether in petroleum ether) afforded the iodide **33** (41 mg, 0.053 mmol, 96%). **33**: colorless plates, mp 192–193 °C (acetonitrile); R_f = 0.85 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2950 (s), 2874 (s), 1458 (m), 1379 (m), 1256 (m), 1073 (s), 883 (m), 842 (m), 734 (m), 648 (w) cm^{-1}; $[\alpha]^{22}_D$ +39.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (q, *J* = 1.5 Hz, 1 H, =CH), 4.23 (bd, *J* = 16.2 Hz, 1 H, OC*H*HCH=), 4.12 (bd, *J* = 16.2 Hz, 1 H, OC*H*HCH=), 3.95 (bd, *J* = 7.5 Hz, 1 H, CHC=), 3.65 (dd, *J* = 11.2, 5.4 Hz, 1 H, OCH), 3.54 (bq, *J* = 7.5 Hz, 1 H, OCH), 3.34 (dd, *J* = 8.3, 5.2 Hz, 1 H, OCH), 3.27–3.17 (m, 5 H, OCH), 3.12 (dd, *J* = 12.1, 3.5 Hz, 1 H, OCH), 3.10–3.06 (m, 1 H, OCH), 3.04 (dd, *J* = 11.6, 3.8 Hz, 1 H, OCH), 2.24–2.17 (m, 1 H, CH), 2.12–1.98 (m, 5 H, CH), 1.85–1.76 (m, 4 H, CH), 1.70–1.56 (m, 5 H, CH), 1.68 (s, 3 H, CH_3), 1.51 (bt, *J* = 11.7 Hz, 1 H, CH), 1.43 (bt, *J* = 11.6 Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.22 (s, 3 H,

CH_3), 1.12 (s, 3 H, CH_3), 1.01 (d, J = 7.1 Hz, 3 H, CH_3), 0.07 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 121.0, 88.0, 87.5, 85.3, 83.9, 83.8, 80.2, 79.8, 77.9, 74.7, 73.9, 73.4, 73.1, 71.3, 69.5, 66.9, 46.0, 45.0, 44.3, 38.0, 35.4, 33.2, 31.0, 29.4, 28.8, 21.5, 20.3, 18.5, 17.2, 16.2, 16.1, 0.3; HRMS, calcd for $C_{36}H_{59}IO_8SiNa$ ($M + Na^+$) 797.2922, found 797.2938.

Phosphonium Salt 4. A mixture of the iodide **33** (41 mg, 0.053 mmol) and triphenylphosphine (135 mg, 0.516 mmol) in CH_3CN (1 mL) was heated in a sealed tube at 80 °C for 42 h. The mixture was diluted with CH_3CN (25 mL) and washed with hexanes (6 × 10 mL). The acetonitrile layer was concentrated to give the phosphonium salt **4** (55 mg, 0.053 mmol, 100%). **4**: amorphous solid; R_f = 0.60 (silica, 30% acetone in CH_2Cl_2); IR (film) ν_{max} 2946 (m), 2872 (s), 1437 (m), 1380 (m), 1252 (m), 1072 (s), 882 (m), 843 (m), 742 (m), 693 (m), 592 (m), 508 (m) cm^{-1}; $[\alpha]^{22}_D$ +37.1 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.93–7.89 (m, 6 H, ArH), 7.31–7.27 (m, 9 H, ArH), 5.03 (bs, 1 H, =CH), 4.45–4.37 (m, 1 H, OCH), 4.08–3.99 (m, 3 H, OCH), 3.95 (dd, J = 11.0, 5.5 Hz, 1 H, OCH), 3.65 (bd, J = 7.5 Hz, 1 H, OCH), 3.48 (dd, J = 12.1, 3.1 Hz, 1 H, OCH), 3.36–3.31 (m, 2 H, OCH), 3.28–3.23 (m, 1 H, OCH), 3.17–3.10 (m, 2 H, OCH), 2.36 (dd, J = 11.3, 3.8 Hz, 1 H, CH), 2.31–2.29 (m, 1 H, CH), 2.25–2.12 (m, 4 H, CH), 2.05–2.00 (m, 3 H, CH), 1.97–1.75 (m, 9 H, CH), 1.78 (s, 3 H, CH_3), 1.67–1.62 (m, 1 H, CH), 1.59 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.12 (d, J = 6.8 Hz, 3 H, CH_3), 0.11 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6) δ 134.6, 134.5, 130.4, 130.3, 128.5, 128.3, 119.2, 118.6, 88.3, 88.0, 85.4, 84.3, 83.7, 80.7, 78.9, 78.8, 77.9, 75.2, 74.2, 74.1, 73.3, 72.9, 70.1, 66.7, 46.0, 38.1, 36.8, 34.3, 34.0, 33.6, 32.3, 32.2, 29.8, 29.5, 21.8, 21.3, 18.8, 17.5, 17.1, 16.3, 0.9; HRMS, calcd for $C_{54}H_{74}O_8PSi$ ($M - I^-$) 909.4891, found 909.4870.

Dithioketal 45. A solution of ketone **44** (1.46 g, 1.83 mmol) in CH_2Cl_2/EtSH (9 mL, 8:1) was treated with zinc triflate (690 mg, 1.90 mmol) and stirred at 25 °C for 3 h. After adding MeOH (4.5 mL) and camphorsulfonic acid (118 mg, 0.37 mmol), the mixture was stirred for 1 h at 25 °C, diluted with ether (50 mL), and washed with aqueous saturated sodium bicarbonate (50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography (silica, 40% ether in petroleum ether) to give dithioketal **45** (1.07 g, 1.36 mmol, 74%). **45**: colorless foam; R_f = 0.45 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 3465 (w), 2952 (s), 2929 (s), 2859 (s), 1463 (m), 1252 (m), 1112 (s), 1062 (s), 833 (s), 703 (s) cm^{-1}; $[\alpha]^{22}_D$ +52.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.62 (m, 4 H, ArH), 7.45–7.35 (m, 6 H, ArH), 4.00–3.65 (m, 10 H, OCH), 3.08–3.05 (m, 1 H, OCH), 2.71–2.56 (m, 4 H, 2 × SCH_2CH_3), 2.34–2.29 (m, 2 H, CH), 2.20–2.15 (m, 1 H, CH), 2.06–2.00 (m, 1 H, CH), 1.82 (dd, J = 13.2, 11.1 Hz, 1 H, CH), 1.73–1.52 (m, 5 H, CH), 1.26 (t, J = 7.4 Hz, 3 H, SCH_2CH_3), 1.25 (t, J = 7.4 Hz, 3 H, SCH_2CH_3), 1.23 (s, 3 H, CH_3), 1.04 (s, 9 H, *t*-Bu), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 134.0, 134.0, 133.9, 129.4, 127.5, 85.7, 79.3, 75.0, 72.9, 72.5, 67.5, 63.6, 63.2, 62.0, 60.0, 40.6, 34.5, 30.6, 29.9, 29.5, 26.8, 25.8, 23.7, 23.2, 19.0, 18.1, 14.5, 14.4, 13.9, −4.4, −5.0; HRMS, calcd for $C_{42}H_{68}O_6S_2Si_2Na$ ($M + Na^+$) 811.3894, found 811.3863.

Aldehyde 3. A mixture of dithioketal **45** (260 mg, 0.33 mmol) and triethylamine (0.46 mL, 3.30 mmol) in CH_2Cl_2/DMSO (3.5 mL, 1:1) was treated at 0 °C with sulfur trioxide·pyridine (260 mg, 1.65 mmol). After stirring at 0 °C for 1.5 h, the mixture was diluted with ether (25 mL), washed with aqueous saturated ammonium chloride (20 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 30% ether in petroleum ether) gave aldehyde **3** (238 mg, 0.302 mmol, 92%). **3**: colorless oil; R_f = 0.55 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2953 (s), 2929 (s), 2893 (s), 2855 (s), 1739 (s), 1472 (m), 1427 (m), 1253 (m), 1112 (s), 1063 (s), 835 (s), 702 (s) cm^{-1}; $[\alpha]^{22}_D$ +63.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (d, J = 1.0 Hz, 1 H, CHO), 7.66–7.64 (m, 4 H, ArH), 7.41–7.35 (m, 6 H, ArH), 4.09 (d, J = 1.0 Hz, 1 H, *CH*CHO), 3.94–3.88 (m, 2 H, OCH), 3.83–3.75 (m, 3 H, OCH), 3.66 (t, J = 6.1 Hz, 2 H, OCH), 3.06–3.02 (m, 1 H, OCH), 2.75–2.62 (m, 4 H, 2 × SCH_2CH_3), 2.35–2.28 (m, 2 H, CH), 2.18 (ddd, J = 14.6, 7.6, 3.2 Hz, 1 H, CH), 2.06 (dt, J = 11.3, 4.2 Hz, 1 H, CH), 1.89 (dd, J = 13.2, 11.0 Hz, 1 H, CH), 1.78 (q, J = 11.7 Hz, 1 H, CH), 1.64–1.49 (m, 4 H, CH), 1.28 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 1.25 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 1.24 (s, 3 H, CH_3), 1.04 (s, 9 H, *t*-Bu), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 6 H, 2 × $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 135.5, 134.0, 134.0, 129.5, 127.6, 87.5, 79.1, 75.3, 73.0, 72.6, 66.9, 63.7, 63.3, 59.4, 41.1, 34.5, 30.5, 30.0, 29.6, 26.9, 25.9, 23.4, 23.3, 19.2, 18.3, 14.6, 14.2, 14.0, −4.3, −5.0; HRMS, calcd for $C_{42}H_{66}O_6S_2Si_2Cs$ ($M + Cs^+$) 919.2894, found 919.2929.

Hydroxy Dithioketal 2. A solution of phosphonium salt **4** (117 mg, 0.113 mmol) and HMPA (59 μL, 0.338 mmol) in THF (2.0 mL) was treated dropwise with *n*-butyllithium (80 μL, 1.55 M solution in hexane, 0.12 mmol) at −78 °C. The mixture was stirred at −78 °C for 10 min and then a solution of aldehyde **3** (133 mg, 0.170 mmol) in THF (2 mL) was added dropwise at −78 °C and was kept at this temperature for 10 min. The mixture was then allowed to warm slowly to 25 °C and was directly subjected to flash chromatography (silica, 100% ether → 100% acetone) to give the corresponding silylated dithioketal and recovered phosphonium salt **4**. The phosphonium salt **4** was subjected to the same process (twice) to afford more product. The silylated dithioketal was dissolved in MeOH/CH_2Cl_2 (1:1) and treated with pyridinium *p*-toluenesulfonate (0.25 equiv). After stirring at 25 °C for 30 min, the mixture was diluted with ether (100 mL), washed with aqueous saturated ammonium chloride (25 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 20→50% ether in petroleum ether) gave the hydroxy dithioketal **2** (total yield: 115 mg, 0.085 mmol, 75% (2 steps)). **2**: amorphous solid; R_f = 0.22 (silica, 20% ethyl acetate in benzene); IR (film) ν_{max} 3474 (w), 2933 (s), 2861 (s), 1461 (m), 1380 (m), 1254 (m), 1105 (s), 1072 (s), 915 (m), 834 (m), 780 (m), 734 (m), 705 (m) cm^{-1}; $[\alpha]^{22}_D$ +50.4 (*c* 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.65 (m, 4 H, ArH), 7.41–7.37 (m, 6 H, ArH), 5.93–5.90 (m, 1 H, =CH), 5.79 (dd, J = 10.7, 9.2 Hz, 1 H, =CH), 5.34 (bs, 1 H, =CH), 4.33 (d, J = 8.6 Hz, 1 H, OC*H*CH=), 4.24 (bd, J = 15.7 Hz, 1 H, OC*H*HCH=), 4.13 (bd, J = 14.6 Hz, 1 H, OC*H*HCH=), 4.05–3.93 (m, 2 H, OCH), 3.90 (dd, J = 12.3, 3.8 Hz, 1 H, OCH), 3.82–3.74 (m, 3 H, OCH), 3.66 (d, J = 6.0 Hz, 1 H, OCH), 3.65 (d, J = 6.0 Hz, 1 H, OCH), 3.53 (bq, J = 7.7 Hz, 1 H, OCH), 3.38–3.19 (m, 4 H, OCH), 3.16–3.07 (m, 4 H, OCH), 2.72–2.63 (m, 4 H, 2 × SCH_2CH_3), 2.58 (dd, J = 14.6, 8.7 Hz, 1 H, =CHC*H*H), 2.43 (dd, J = 14.7, 6.3 Hz, 1 H, =CHC*H*H), 2.33–2.27 (m, 3 H, CH), 2.20–1.97 (m, 7 H, CH), 1.89 (dd, J = 11.8, 5.2 Hz, 1 H, CH), 1.84–1.43 (m, 14 H, CH), 1.70 (s, 3 H, CH_3), 1.28 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 1.27 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.25 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 1.24 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.04 (s, 9 H, *t*-Bu), 1.01 (d, J = 7.0 Hz, 3 H, CH_3), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 134.5, 134.0, 133.9, 131.7, 129.5, 127.6, 127.3, 121.0, 88.0, 87.5, 85.3, 83.9, 82.1, 80.2, 79.5, 78.5, 77.9, 75.1, 74.7, 73.9, 73.5, 73.4, 72.9, 72.6, 69.7, 69.5, 67.4, 66.9, 65.8, 63.6, 63.3, 62.9, 45.0, 43.8, 41.2, 39.1, 38.0, 35.4, 34.8, 33.2, 31.0, 30.9, 30.3, 29.9, 29.7, 29.6, 29.5, 28.8, 26.8, 25.9, 24.0, 22.8, 21.5, 20.1, 19.2, 18.5, 18.3, 17.2, 16.6, 16.2, 15.3, 14.6, 14.0, 13.8, −4.1, −5.0; HRMS, calcd for $C_{75}H_{116}O_{13}S_2Si_2Cs$ ($M + Cs^+$) 1477.6450, found 1477.6521.

Mixed Thioketal 47. A heterogeneous mixture of hydroxy dithioketal **2** (95 mg, 0.071 mmol), powdered 4 Å molecular sieves (160 mg), silica (160 mg), sodium bicarbonate (60 mg), silver perchlorate (60 mg), and dry nitromethane (855 μL) was stirred vigorously at 25 °C for 40 h. The mixture was diluted with EtOAc (30 mL), filtered through Celite, and subjected to flash chromatography (silica, 20→50% ether in petroleum ether) to give the mixed thioketal **47** (55 mg, 0.043 mmol, 85% based on 70% conversion)) and unreacted hydroxy dithioketal **2** (27 mg, 0.020 mmol). **47**: amorphous solid; R_f = 0.30 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2929 (m), 2856 (m), 1461 (m), 1378 (m), 1254 (m), 1069 (s), 834 (m), 778 (m), 704 (m) cm^{-1}; $[\alpha]^{22}_D$ +104.6 (*c* 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.64 (m, 4 H, ArH), 7.40–7.36 (m, 6 H, ArH), 5.88 (bq, J = 9.8 Hz, 1 H, =CH), 5.76 (dd, J = 10.6, 6.7 Hz, 1 H, =CH), 5.34 (bs, 1 H, =CH), 4.72 (dd, J = 12.1, 4.5 Hz, 1 H, OCH), 4.24 (bd, J = 16.3 Hz, 1 H, OC*H*HCH=), 4.13 (bd, J = 14.6 Hz, 1 H, OC*H*HCH=), 4.01–3.97 (m, 2 H, OCH), 3.89 (dd, J = 12.2, 3.9 Hz, 1 H, OCH), 3.80–3.76 (m, 3 H, OCH), 3.66 (d, J = 6.0 Hz, 1 H, OCH), 3.65 (d, J = 6.0 Hz, 1 H, OCH), 3.54 (bq, J = 7.7 Hz, 1 H, OCH), 3.36 (dd, J = 8.1, 5.4 Hz, 1 H, OCH), 3.31 (dd, J = 12.2, 3.4 Hz, 1 H, OCH), 3.29–3.19 (m, 2 H, OCH), 3.14 (dd, J = 12.0, 3.2 Hz, 1 H, OCH), 3.11–

3.07 (m, 2 H, OCH), 3.05−2.98 (m, 1 H, OCH), 2.55−2.25 (m, 6 H, SCH_2CH_3, CH), 2.19−2.09 (m, 4 H, CH), 2.01−1.95 (m, 2 H, CH), 1.84−1.51 (m, 16 H, CH), 1.70 (s, 3 H, CH_3), 1.45 (bt, J = 11.4 Hz, 1 H, CH), 1.35 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.26 (s, 6 H, 2 × CH_3), 1.25 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 1.20 (s, 3 H, CH_3), 1.04 (s, 9 H, t-Bu), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.88 (s, 9 H, t-Bu), 0.05 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 134.5, 134.0, 134.0, 132.5, 129.5, 128.9, 127.5, 121.0, 90.9, 88.2, 87.7, 85.3, 83.9, 83.7, 82.2, 81.5, 80.2, 79.0, 78.0, 74.9, 74.7, 74.3, 74.0, 73.9, 72.9, 72.6, 69.5, 68.6, 68.1, 66.9, 65.8, 63.7, 63.4, 45.0, 42.2, 40.9, 39.7, 38.1, 35.4, 34.5, 33.2, 31.0, 30.8, 30.3, 29.9, 29.6, 29.5, 28.8, 26.8, 25.9, 21.9, 21.1, 20.0, 19.2, 18.9, 18.3, 17.1, 16.2, 15.3, 14.6, 14.2, −4.1, −5.2; HRMS, calcd for $C_{73}H_{110}O_{13}SSi_2$-Cs (M + Cs^+) 1415.6260, found 1415.6316.

Oxocene 48. A mixture of the mixed thioketal **47** (55 mg, 0.043 mmol), 2,2′-azobis(isobutyronitrile) (1 mg) and triphenyltin hydride (150 mg, 0.428 mmol) in toluene (1.0 mL) was heated at 110 °C for 3 h. The mixture was concentrated and subjected to flash chromatography (silica, CH_2Cl_2 → 40% ether in petroleum ether) to give the oxocene **48** (52 mg, 0.043 mmol, 100%). **48**: amorphous solid; R_f = 0.30 (silica, 50% ether in petroleum ether); IR (film) ν_{max} 2931 (s), 2859 (s), 1462 (m), 1380 (m), 1252 (m), 1070 (s), 914 (m), 834 (m), 779 (m), 734 (m), 703 (m) cm^{-1}; $[\alpha]^{22}_D$ +89.4 (c 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4 H, ArH), 7.48−7.36 (m, 6 H, ArH), 5.83−5.77 (m, 2 H, CH=CH), 5.35 (bs, 1 H, =CH), 4.25 (bd, J = 15.5 Hz, 1 H, OC*H*HCH=), 4.14 (bd, J = 16.6 Hz, 1 H, OC*H*HCH=), 4.12−3.98 (m, 2 H, OCH), 3.90 (dd, J = 12.4, 4.0 Hz, 1 H, OCH), 3.86−3.79 (m, 2 H, OCH), 3.77 (bs, 1 H, OCH), 3.68 (d, J = 6.1 Hz, 1 H, OCH), 3.67 (d, J = 6.1 Hz, 1 H, OCH), 3.56 (bq, J = 7.7 Hz, 1 H, OCH), 3.37−3.20 (m, 6 H, OCH), 3.16 (dd, J = 12.3, 3.6 Hz, 1 H, OCH), 3.11−3.07 (m, 2 H, OCH), 2.95−2.88 (m, 1 H, OCH), 2.46 (dd, J = 12.3, 7.6 Hz, 1 H, CH), 2.37−2.20 (m, 3 H, CH), 2.21−1.98 (m, 7 H, CH), 1.85−1.44 (m, 16 H, CH), 1.71 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.05 (s, 9 H, t-Bu), 1.02 (d, J = 7.0 Hz, 3 H, CH_3), 0.89 (s, 9 H, t-Bu), 0.05 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.4, 134.5, 134.0, 134.0, 130.4, 129.5, 129.1, 127.5, 127.0, 121.0, 88.2, 87.7, 85.3, 83.9, 83.8, 80.2, 80.0, 79.8, 77.9, 76.4, 75.0, 74.8, 74.7, 74.0, 73.9, 73.9, 72.9, 72.5, 69.5, 69.0, 67.1, 63.7, 63.1, 45.0, 41.1, 39.3, 38.1, 37.6, 35.4, 34.4, 33.2, 31.0, 30.8, 30.0, 29.7, 29.6, 29.5, 28.9, 26.8, 25.9, 22.0, 19.9, 19.1, 18.5, 18.1, 17.1, 16.2, 14.3, −4.1, −5.2; HRMS, calcd for $C_{71}H_{106}O_{13}Si_2Na$ (M + Na^+) 1245.7070, found 1245.7011.

Lactone 49. A mixture of oxocene **48** (52 mg, 43 μmol), pyridinium chlorochromate (48 mg, 0.225 mmol), and benzene (5 mL) was heated at 80 °C for 3 h. The resulting dark brown solution was filtered through a short path of silica (ether), concentrated, and subjected to flash chromatography (silica, 20→50% ether in petroleum ether) to give lactone **49** (35 mg, 28 μmol, 85%, based on 75% conversion) and unreacted oxocene **48** (12 mg, 10 μmol). **49**: colorless needles; mp 256 °C (acetonitrile); R_f = 0.32 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2928 (s), 2855 (s), 1732 (s), 1463 (m), 1380 (m), 1266 (m), 1233 (m), 1060 (s), 834 (m), 778 (m), 703 (m) cm^{-1}; $[\alpha]^{22}_D$ +67.2 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4 H, ArH), 7.48−7.35 (m, 6 H, ArH), 5.82−5.76 (m, 2 H, CH=CH), 5.73 (bs, 1 H, =CH), 4.27 (bd, J = 10.6 Hz, 1 H, OCHC=), 4.03−3.97 (m, 2 H, OCH), 3.92−3.78 (m, 3 H, OCH), 3.76 (bs, 1 H, OCH), 3.67 (d, J = 6.1 Hz, 1 H, OCH), 3.66 (d, J = 6.1 Hz, 1 H, OCH), 3.55 (bq, J = 7.7 Hz, 1 H, OCH), 3.38−3.24 (m, 5 H, OCH), 3.13−3.07 (m, 3 H, OCH), 2.93−2.89 (m, 1 H, OCH), 2.46 (dd, J = 12.3, 7.6 Hz, 1 H, CH), 2.36−2.25 (m, 3 H, CH), 2.20−2.09 (m, 4 H, CH), 1.99−1.94 (m, 1 H, CH), 1.96 (s, 3 H, CH_3), 1.94−1.41 (m, 18 H, CH), 1.31 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.04 (s, 9 H, t-Bu), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.88 (s, 9 H, t-Bu), 0.04 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 161.1, 136.3, 135.5, 134.0, 134.0, 130.4, 129.5, 129.1, 127.5, 127.0, 115.6, 88.3, 87.6, 85.5, 83.9, 83.5, 80.0, 79.8, 78.9, 77.8, 76.5, 76.4, 75.0, 74.7, 74.0, 73.0, 72.6, 69.0, 68.4, 63.7, 63.2, 44.6, 41.1, 39.3, 38.0, 37.6, 35.3, 34.4, 33.2, 30.8, 30.0, 29.7, 29.6, 29.5, 28.8, 26.8, 25.9, 21.9, 19.9, 19.2, 18.5, 18.3, 18.1, 17.3, 15.7, 14.3, −4.1, −5.2; HRMS, calcd for $C_{71}H_{104}O_{14}Si_2Cs$ (M + Cs^+) 1369.6019, found 1369.6054.

Primary Alcohol 50. A solution of lactone **49** (23 mg, 19 μmol) in THF was treated with tetra-n-butylammonium fluoride (19 μL of a 1.0 M solution in THF, 19 μmol) and stirred at 25 °C for 13 h. The mixture was diluted with ether (20 mL), washed with aqueous saturated ammonium chloride (10 mL), and dried ($MgSO_4$). Filtration, concentration, and flash chromatography (silica, 70→100% ether in petroleum ether) gave primary alcohol **50** (13 mg, 13 μmol, 69%). **50**: amorphous solid; R_f = 0.60 (silica, 100% ether); IR (film) ν_{max} 3515 (w), 2936 (m), 2873 (m), 1734 (m), 1462 (m), 1380 (m), 1237 (m), 1061 (s), 838 (m), 777 (m) cm^{-1}; $[\alpha]^{22}_D$ +68.9 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 5.81−5.70 (m, 2 H, CH=CH), 5.73 (bs, 1 H, =CH), 4.27 (bd, J = 10.9 Hz, 1 H, OCHC=), 4.03−3.97 (m, 2 H, OCH), 3.94 (dd, J = 12.4, 4.0 Hz, 1 H, OCH), 3.88−3.84 (m, 2 H, OCH), 3.77 (t, J = 6.0 Hz, 1 H, OCH), 3.66−3.63 (m, 2 H, OCH), 3.55 (bq, J = 8.7 Hz, 1 H, OCH), 3.37−3.23 (m, 5 H, OCH), 3.13−3.06 (m, 3 H, OCH), 2.97−2.92 (m, 2 H, OCH), 2.45 (dd, J = 13.7, 7.9 Hz, 1 H, CH), 2.36−2.27 (m, 3 H, CH), 2.23−2.00 (m, 5 H, CH), 1.97 (s, 3 H, CH_3), 1.89−1.38 (m, 19 H, CH), 1.30 (s, 6 H, 2 × CH_3), 1.29 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.89 (s, 9 H, t-Bu), 0.05 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 161.1, 135.4, 127.6, 115.5, 88.3, 87.6, 85.5, 84.0, 83.5, 80.0, 79.8, 79.0, 77.9, 76.6, 76.5, 75.0, 74.7, 74.6, 74.0, 73.0, 72.5, 69.0, 68.3, 63.4, 62.8, 44.6, 41.1, 39.3, 38.0, 37.6, 35.3, 34.6, 33.2, 30.7, 30.4, 30.2, 29.7, 29.3, 28.9, 25.9, 22.0, 19.9, 18.5, 18.2, 17.5, 15.8, 14.3, −4.1, −5.2; HRMS, calcd for $C_{55}H_{86}O_{14}SiNa$ (M + Na^+) 1021.5685, found 1021.5733.

Silylated Brevetoxin B (52). A solution of primary alcohol **50** (13 mg, 13 μmol) in CH_2Cl_2 (0.5 mL) was treated with Dess-Martin periodinane (16 mg, 39 μmol) and stirred at 25 °C for 30 min. The resulting suspension was diluted with ether (25 mL) and washed with aqueous saturated sodium bicarbonate/sodium thiosulfate (1:1, 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the crude aldehyde **51** (13 mg). A solution of the crude aldehyde **51**, triethylamine (36 μL, 0.26 mmol), and $Me_2N{=}CH_2{}^+I^-$ (12 mg, 65 μmol) in CH_2Cl_2 (200 μL) was stirred at 25 °C for 16 h. The mixture was diluted with ether (10 mL), washed with aqueous saturated ammonium chloride (5 mL), and dried ($MgSO_4$). Filtration, concentration, and preparative TLC (silica, 70% ether in petroleum ether) afforded silylated brevetoxin B (**52**) (11 mg, 11 μmol, 83%). **52**: amorphous solid; R_f = 0.58 (silica, 50% ethyl acetate in benzene); IR (film) ν_{max} 2948 (m), 2865 (m), 1738 (m), 1694 (m), 1634 (w), 1456 (m), 1380 (m), 1233 (m), 1060 (s), 902 (m), 834 (m), 776 (m), 606 (m) cm^{-1}; $[\alpha]^{22}_D$ +101.6 (c 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1 H, CHO), 6.28 (s, 1 H, =C*H*H), 6.07 (s, 1 H, =C*H*H), 5.80−5.75 (m, 2 H, CH=CH), 5.73 (bs, 1 H, =CH), 4.27 (d, J = 10.8 Hz, 1 H, OCHC=), 4.04−3.95 (m, 4 H, OCH), 3.86 (dd, J = 8.8, 3.5 Hz, 1 H, OCH), 3.79 (bs, 1 H, OCH), 3.55 (bq, J = 7.8 Hz, 1 H, OCH), 3.39−3.23 (m, 6 H, OCH), 3.13−3.04 (m, 3 H, OCH), 3.00−2.95 (m, 1 H, OCH), 2.46−2.43 (m, 1 H, CH), 2.35−2.00 (m, 7 H, CH), 1.98−1.43 (m, 16 H, CH), 1.96 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 0.91 (s, 9 H, t-Bu), 0.08 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 163.7, 161.2, 148.0, 135.8, 135.4, 127.1, 115.6, 88.3, 87.6, 85.5, 84.0, 83.6, 80.0, 79.8, 79.0, 77.9, 76.6, 76.4, 75.0, 74.7, 74.6, 74.0, 72.4, 71.3, 69.1, 68.3, 63.3, 44.6, 41.2, 39.3, 38.0, 37.6, 35.3, 34.8, 33.2, 32.0, 30.6, 30.0, 29.5, 28.9, 25.9, 22.0, 19.9, 18.5, 18.2, 17.3, 15.8, 14.3, −4.1, −5.1; HRMS, calcd for $C_{56}H_{84}O_{14}SiNa$ (M + Na^+) 1331.5528, found 1331.5569.

Brevetoxin B (1). A solution of silylated brevetoxin B (**52**) (6 mg, 5.9 μmol) in CH_2Cl_2 (200 μL) was treated at 0 °C with HF·pyridine (10 μL) and stirred for 30 min at 0 °C. The mixture was quenched with aqueous saturated sodium bicarbonate (1 mL) and diluted with ether (10 mL) and the layers were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the residue was subjected to preparative TLC (silica, 100% ether) to give brevetoxin B (**1**) (4.8 mg, 5.4 μmol, 91%). **1**: colorless plates, mp 272 °C dec (methanol, lit.[13] mp 270 °C dec (acetonitrile)); R_f = 0.35 (silica, 100% ether); IR (film) ν_{max} 2926 (s), 2860 (s), 1730 (m), 1694 (m), 1455 (m), 1380 (m), 1234 (m), 1057 (s), 730 (m) cm^{-1}; $[\alpha]^{22}_D$ +154.0 (c 0.5, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1 H, CHO), 6.31 (s, 1 H, =C*H*H), 6.09 (s, 1 H, =C*H*H), 5.78−5.75 (m, 2 H, CH=CH), 5.73 (s,

1 H, =CH), 4.26 (d, J = 10.8 Hz, 1 H, OCHC=), 4.03−3.94 (m, 4 H, OCH), 3.88 (dd, J = 8.9, 3.2 Hz, 1 H, OCH), 3.81 (bs, 1 H, OCH), 3.55 (bq, J = 7.7 Hz, 1 H, OCH), 3.42−3.23 (m, 6 H, OCH), 3.13−3.02 (m, 4 H, OCH), 2.66 (bs, 1 H, OH), 2.45−2.26 (m, 4 H, CH), 2.21−2.08 (m, 4 H, CH), 2.05−1.43 (m, 16 H, CH), 1.96 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.29 (s, 6 H, 2 × CH_3), 1.22 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.02 (d, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 163.7, 161.2, 147.7, 136.1, 135.1, 127.2, 115.6, 88.3, 87.6, 85.5, 84.0, 83.6, 80.1, 79.8, 79.0, 77.8, 77.3, 76.6, 76.2, 75.1, 74.7, 74.7, 74.0, 73.9, 71.5, 71.4, 69.4, 68.3, 63.3, 44.6, 41.2, 39.4, 38.0, 37.5, 35.3, 33.2, 31.9, 31.7, 30.3, 30.1, 29.5, 28.8, 22.0, 19.9, 18.5, 18.2, 17.3, 15.8, 13.8; HRMS, calcd for $C_{50}H_{70}O_{14}Na$ ($M + Na^+$) 917.4663, found 917.4622.

Acknowledgment. We thank Drs. Dee H. Huang (TRSI), Gary Siuzdak (TSRI), Raj Chadha (TSRI), George Furst (University of Pennsylvania), John Dykins (University of Pennsylvania), and Pat Carroll (University of Pennsylvania) for their superb NMR (D.H.H.; G.F.), mass spectroscopic (G.S.; J.D.), and X-ray crystallographic (R.C.; P.C.) assistance. This work was carried out at the University of Pennsylvania where the project started, the University of California, San Diego, and The Scripps Research Institute where the project was completed. This program was financially supported by the National Institutes of Health, USA, by fellowships from The Netherlands Organization for Scientific Research (NWO) (F.P.J.T.R.), the Deutsche Forschungsgemeinschaft (J.T.), Unitika, Ltd. (MS), Rhone-Poulenc Rorer, S. A. (E.U.), the ALSAM Foundation (USA), Dainippon Pharm. Co., Ltd. (Japan), Glaxo, Inc. (USA), Hoffmann-La Roche (USA), Merck Sharp & Dohme (USA), Pfizer, Inc. (USA), Rhone-Poulenc Rorer (USA), Schering Plough (USA), and Smith Kline Beecham (USA).

Supporting Information Available: Experimental procedures and selected data for compounds **35**−**44**, as well as X-ray crystallographic data for compounds **33** and **1**, tables of anisotropic displacement coefficients and H atom coordinates, unit cell packing diagrams, stereo views, and torsion angles and mean plane equations (51 pages). Listing of structure factors (23 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.

JA9506925