Total Synthesis of Swinholide A, Preswinholide A, and Hemiswinholide A

K. C. Nicolaou,* A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, and M. J. Tomaszewski

Abstract: The total synthesis of swinholide A (**1**) has been accomplished via key intermediate aldehyde **12** (Fig. 3), whose construction started from L-rhamnose (**18**), epoxide **21**, and phenylsulfone orthoester **22**, and proceeded through an Enders asymmetric alkylation (**16** + **17** → **15**), a Ghosez cyclization (**21** + **22** → **20**), and a Corey–Sharpless coupling reaction (**13** + **14** → **12**). Elaboration of compound **12** along slightly different pathways culminated in the synthesis of carboxylic acid **10** and hydroxy compound **11**, whose union by an esterification reaction, followed by ring closure of the subsequently derived hydroxy acid under Yamaguchi conditions, led to swinholide A (**1**) upon deprotection. The chemistry developed also allowed the total synthesis of preswinholide A methyl ester (**7**), preswinholide A (**8**), and hemiswinholide A (**78**).

Keywords
natural products · swinholide A · total syntheses

Introduction

Swinholide A (**1**, Fig. 1), the most prominent member of the growing family of marine natural products, was originally isolated by Carmely and Kashman from a Red Sea sponge (*Theonella swinhoei*) as an antifungal agent but erroneously assigned a monomeric structure.[1a] The same compound was subsequently isolated by Kitagawa's group from an Okinawan sponge and correctly assigned as structure **1**, including absolute stereochemistry, based on NMR spectroscopy and X-ray crystallography.[2] Swinholides B (**2**) and C (**3**), isoswinholide A (**4**),[3] misakinolide A (bistheonellide A) (**5**),[4] and preswinholide A (**8**)[5] were also isolated from sponges of the *Theonella* genus. These compounds show a striking resemblance to scytophycin C (**6**),[6] a natural product isolated from the terrestrial blue-green algae *Scytonema pseudohofmanni* that exhibits both antifungal and cytotoxic properties. This resemblance, plus the presence of cyanobacteria in *T. swinhoei*,[2b] led to the reasonable hypothesis that all members of this family of compounds originate from cyanobacteria.[7] Recently, however, this proposal has been challenged by Faulkner and his group,[1b] who demonstrated the association of swinholide A with unicellular heterotrophic bacteria rather than cyanobacteria.

The strong cytotoxicity of swinholide A (in vitro IC_{50} value against KB and L1210 tumor cells 0.04 and 0.03 $\mu g\,mL^{-1}$, respectively)[2, 8] has been attributed to its ability to sequester actin dimers and cause disruption of the actin cytoskeleton.[9] The unusual "twisted saddle" conformation suggested by Kitagawa (see Fig. 2), in which the hydrocarbon backbone of the macrolide ring is directed towards the exterior of the "saddle" and the oxygen-containing functional groups are directed towards the interior, may play a role in this binding.

The structure of swinholide A (**1**) is characterized by *C*2 symmetry, two conjugated diene systems, two trisubstituted tetrahydropyran rings, two disubstituted dihydropyran systems and a 44-membered macrolide ring. A total of 30 stereogenic centers are present on the carbon backbone in compound **1**.[2] These novel structural features presented a formidable and attractive synthetic challenge which assumed further importance on considering the natural scarcity and important biological properties of swinholide A.[2, 9] Several groups have reported their work towards the synthesis of **1**,[10, 11] with Paterson and his group at Cambridge reporting the first total synthesis of swinholide A.[12] The total synthesis of this target molecule was undertaken in our laboratories[13] in the early 1990s and was completed in 1995. We now present a full account of this work, which led to the syntheses of both swinholide A (**1**) and pre-swinholide A (**8**), the presumed biosynthetic precursor of **1**.

Retrosynthetic Analysis and Strategy

The symmetrical nature of swinholide A's structure points to the rather daring idea of forming the 44-membered macrocyclic ring by dimerization of a suitably functionalized derivative of the corresponding hydroxy acid [e.g., an appropriate form of preswinholide A (**7**)]. Of course, the stepwise version of this approach would be safer and yet flexible enough to allow an attempt at the direct route of dimerization.[10] With these considerations in mind we proceeded to disassemble **1** retrosynthetically as outlined in Figure 3. Thus, appropriate protections followed by a retromacrolactonization disconnection allowed

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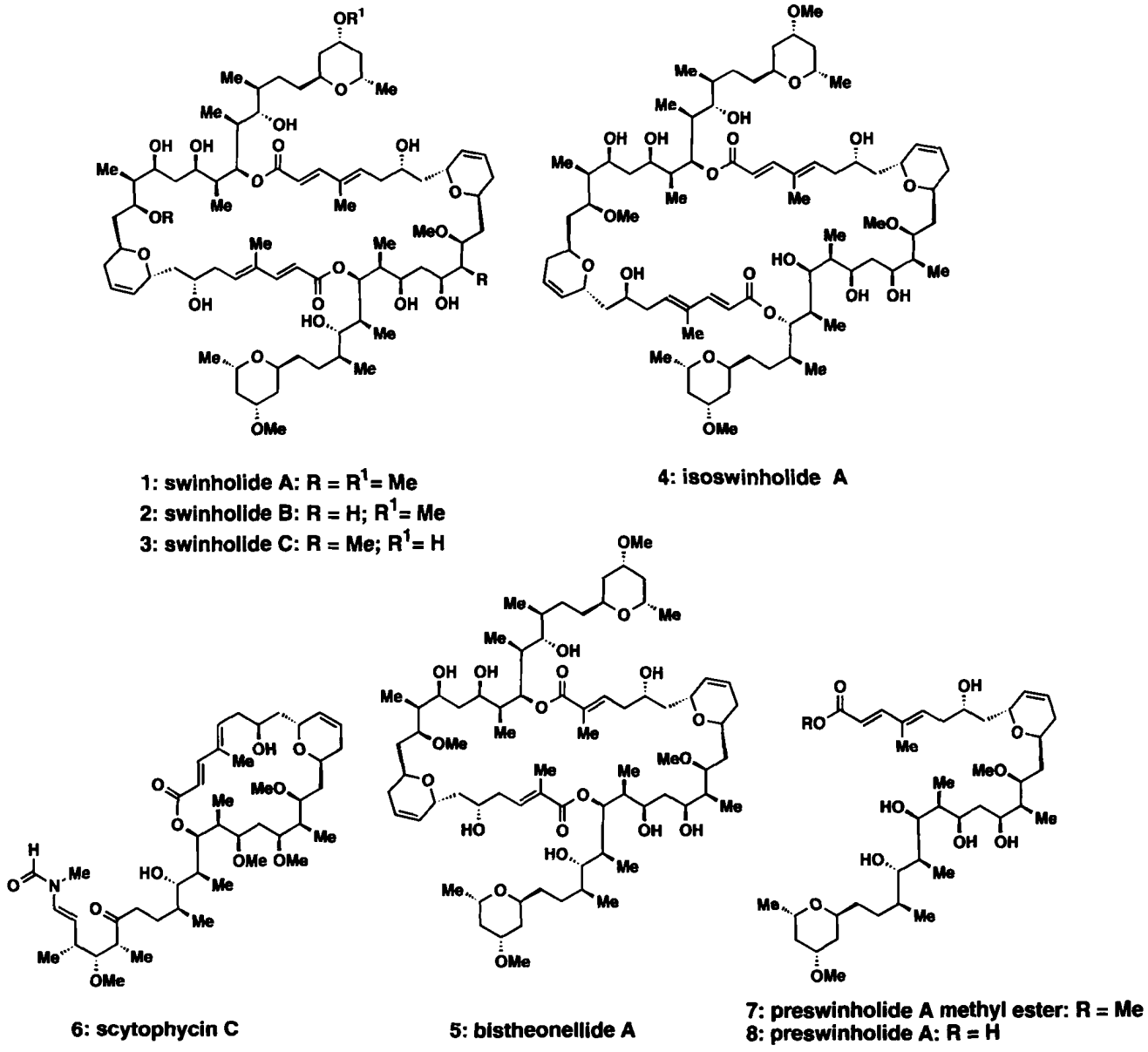

Fig. 1. Structures of swinholide A (1) and related compounds (2–8).

the generation of hydroxy acid **9** as a possible precursor.[14] Further disconnection at the ester linkage of **9**, as indicated, led to the two requisite units as slightly differentiated forms of protected preswinholide, carboxylic acid **10**, and hydroxy ester **11**. Both **10** and **11** can be traced to a common precursor, aldehyde **12**, by a retro Horner–Wadsworth–Emmons disconnection,[15] as shown in Figure 3. At this stage, the idea of using the Horner–Wadsworth–Emmons olefination reaction to construct the macroyclic ring was viewed as a strong option,[16] adding to the flexibility of the designed plan.

After appropriate functional group manipulations, the key intermediate **12** was then disconnected through the novel dithiane anion–cyclic sulfate[17] coupling reaction developed by van der Klein et al.[18] but rarely used for complex molecules.[18] Thus, the disconnection of the C17–C18 bond generated dithiane **14** and cyclic sulfate **13** as the requisite building blocks. The aldol reaction in its retro form[19, 20] was then used to simplify intermediates **14** and **13**, giving rise to compounds **19** and **15**, respectively. Using the Enders method[21] compound **15** can be traced sequentially to tetrahydropyran derivative **16** and hydrazone **17** (SAMP) and ultimately to L-rhamnose (**18**). Aldehyde **19**, on the other hand, was connected to the α,β-unsaturated enone **20** (by *C*-glycosidation chemistry),[22] whose origin could be traced to epoxide **21** and phenylsulfone orthoester **22** by Ghosez lactonization procedure,[23] another powerful yet rarely used synthetic reaction for complex molecule construction.

The retrosynthetic analysis discussed above led to a strategy that has the advantages of convergency and requires only readily available starting materials. It does, however, provide challenges to certain reactions and tactics that have to be tested experimentally. Below we discuss the execution of this plan.

Total Synthesis

a. Construction of C18–C32 fragment (13): The synthesis of cyclic sulfate **13**, the requisite C18–C32 fragment, began with

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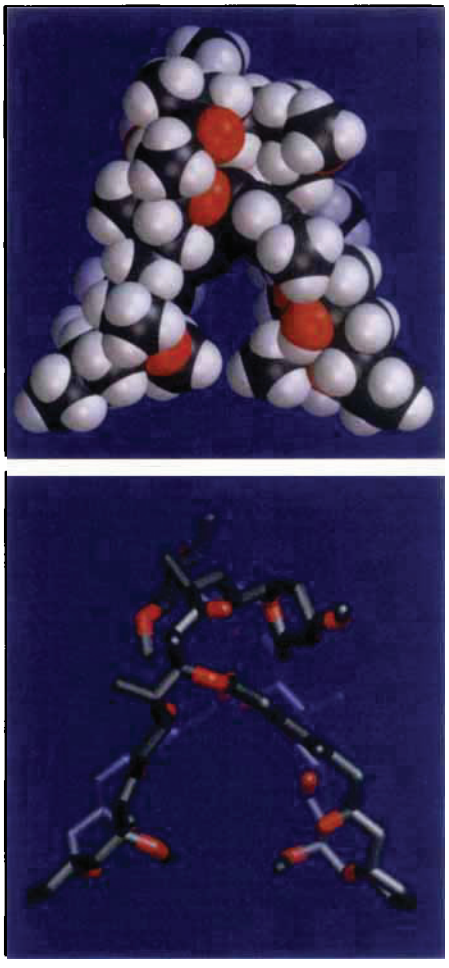

Fig. 2. Computer-generated molecular models of swinholide A showing the saddle-like conformation of the molecule.

L-rhamnose (**18**) and proceeded as summarized in Scheme 1. Peracetylation of **18** under standard conditions (Ac_2O, Et_3N, 4-DMAP) gave the tetraacetate **23** in 91% yield. Allylation of **23** with allyltrimethylsilane in the presence of a mixture of $BF_3 \cdot Et_2O$ and TMSOTf (10:1) in acetonitrile furnished compound **24** as the major isomer (81% yield),[22] whose transesterification with methanolic NaOMe led quantitatively to the triol **25**.[22c] Selective methylation of the C29 (swinholide numbering) hydroxyl group proceeded smoothly with the nBu$_2$SnO/CsF/MeI method[24] to afford compound **26** in 68% yield. The bisxanthate **27**, formed upon exposure of **26** to NaH/CS_2/MeI and imidazole (cat.), was subjected to a Barton–McCombie deoxygenation[25] [nBu$_3$SnH/AIBN (cat.)] to afford tetrahydropyran system **28**[10a] in 51% overall yield. The allylpyran **28** thus obtained was converted to the primary iodide **16**, employing a three-step two-pot procedure as follows: ozonolysis of **28** followed by $NaBH_4$ workup leading to alcohol **29** (87% yield) and subsequent conversion to iodide **16** by treatment with PPh_3/I_2/imidazole (83% yield). Coupling of the anion of SAMP hydrazone **17** (LDA, Et_2O, $-78\,^{\circ}C$) with iodide **16** ($-110 \rightarrow 25\,^{\circ}C$) gave compound **30** in 93% yield.[21] Ozonolytic removal of the hydrazone group afforded the ketone **15**, which was ready to undergo an aldol condensation with aldehyde **36**, a compound easily obtained in enantiomerically pure form and in large quantities from allyl alcohol (**31**) by the following sequence: a) benzylation under standard NaH/$PhCH_2Br$/nBu$_4$NI (cat.)/imidazole (cat.) conditions to afford **32** (90% yield); b) ozonolysis of **32** to generate aldehyde **33** (84% yield); c) addition of the chiral reagent derived from *cis*-2-butene, *t*BuOK, *n*BuLi, and (−)-*β*-methoxydiisopinocampheyl borane and $BF_3 \cdot OEt_2$ to aldehyde **33** at $-78\,^{\circ}C$, followed by basic H_2O_2 workup to afford enantiomerically enriched hydroxy olefin **34** (78% yield, only isomer detected by ^{1}H NMR spectroscopy at 500 MHz);[26] d) benzylation of **34** with KH/$PhCH_2Br$ afforded **35** (85% yield); and e) ozonolytic generation (Ph_3P) of aldehyde **36** (92% yield).

For the coupling of intermediates **15** and **36**, the titanium enolate of **15** was generated with $TiCl_4/Et_3N$ and reacted with **36** to afford aldol **37** as the major product (3:1) in 68% yield.[20] Next, the Evans–Hoveyda modification of the Tishchenko reduction[27] established the desired *anti* C21–C23 diol with concommitant differentiation of the two alcohols, affording **38** (89% yield), which upon silylation with TBSOTf-2,6-lutidine gave compound **39** in 86% yield. Finally, hydrogenolysis of the benzyl ethers in **39** (10% Pd/C, H_2) resulted in the formation of diol **40** (99% yield), which was cleanly converted to the desired cyclic sulfate **13** via sulfite **41** (two diastereoisomers by TLC) by reaction with $SOCl_2$ in the presence of Et_3N followed by oxidation with $NaIO_4$ and a catalytic amount of $RuCl_3 \cdot 3H_2O$.[17]

The relative stereochemistry of the C19, C21 and C23 stereocenters were next confirmed by the Rychnovsky[28a] and Evans[28b] correlation method of ^{13}C NMR chemical shifts (Fig. 4). The syntheses of the requisite C21–C19 (**62**) and C23–C21 (**57**) acetonides are summarized in Scheme 2. Exposure of benzoate **38** to Dibal-H reductively deprotected the C21 hydroxyl group, and treatment of the resulting diol with 2,2-dimethoxypropane in the presence of a catalytic amount of CSA provided the desired C23–C21 acetonide **57** in 90% yield for the two steps. The C21–C19 acetonide **62** was prepared by the following five-step sequence: a) protection of the C23 alcohol; b) reductive removal of the C21 benzoate with Dibal-H (**58** → **59**); c) treatment with H_2 and 10% Pd/C cat. (**59** → **60**, 78% yield from **58**); d) selective protection of the C18 primary alcohol as a TBDPS ether with TBDPSCl/imidazole (**60** → **61**, 60% yield); and e) exposure to 2,2-dimethoxypropane and a catalytic amount of CSA (**61** → **62**, 95% yield).

Figure 4 shows the observed ^{13}C NMR chemical shifts for the acetonides **57** and **62**. The tendency for acetonides prepared from *anti* 1,3-diols to adopt a twist-boat conformation as opposed to the chair conformation observed with 1,3-*syn* acetonides results in characteristic differences in ^{13}C NMR chemical shifts[28] (see A, Fig. 4). As expected, the chemical shifts of carbons C23–C21 (**57**) and C21–C19 (**62**) in the ^{13}C NMR spectrum were within the expected range for 1,3 related acetonides, confirming the proposed relative stereochemistry for stereocenters C19, C21 and C23.

b. Construction of the C3–C17 segment (14): The synthesis of the C3–C17 building block dithiane **14** proceeded from hydroxy methyl ester **42** as summarized in Scheme 3. Thus, **42** was protected as a *p*-methoxybenzyl ether (**43**, 95% yield) by treatment with *p*-methoxybenzyltrichloroacetimidate under acid catalysis, and reduced with Dibal-H to afford aldehyde **44** in 85% yield. Compound **45** was obtained as the major isomer (92% yield) upon addition of (+)-Ipc$_2$B(allyl) to aldehyde **44** in THF at $-100\,^{\circ}C$.[29] Compound **45** was converted regio- and stereoselectively to the iodocarbonate **46** by sequential exposure to *n*BuLi, CO_2, and I_2.[30] Upon treatment with methanolic K_2CO_3, compound **46** underwent carbonate cleavage and subsequent intramolecular iodide displacement to give exclusively hydroxy epoxide **47** (52% overall yield from **45**),[30] which was then methylated with NaH/MeI to afford compound **21** (91% yield). The expected 1,3-*syn* relationship of the epoxide oxygen

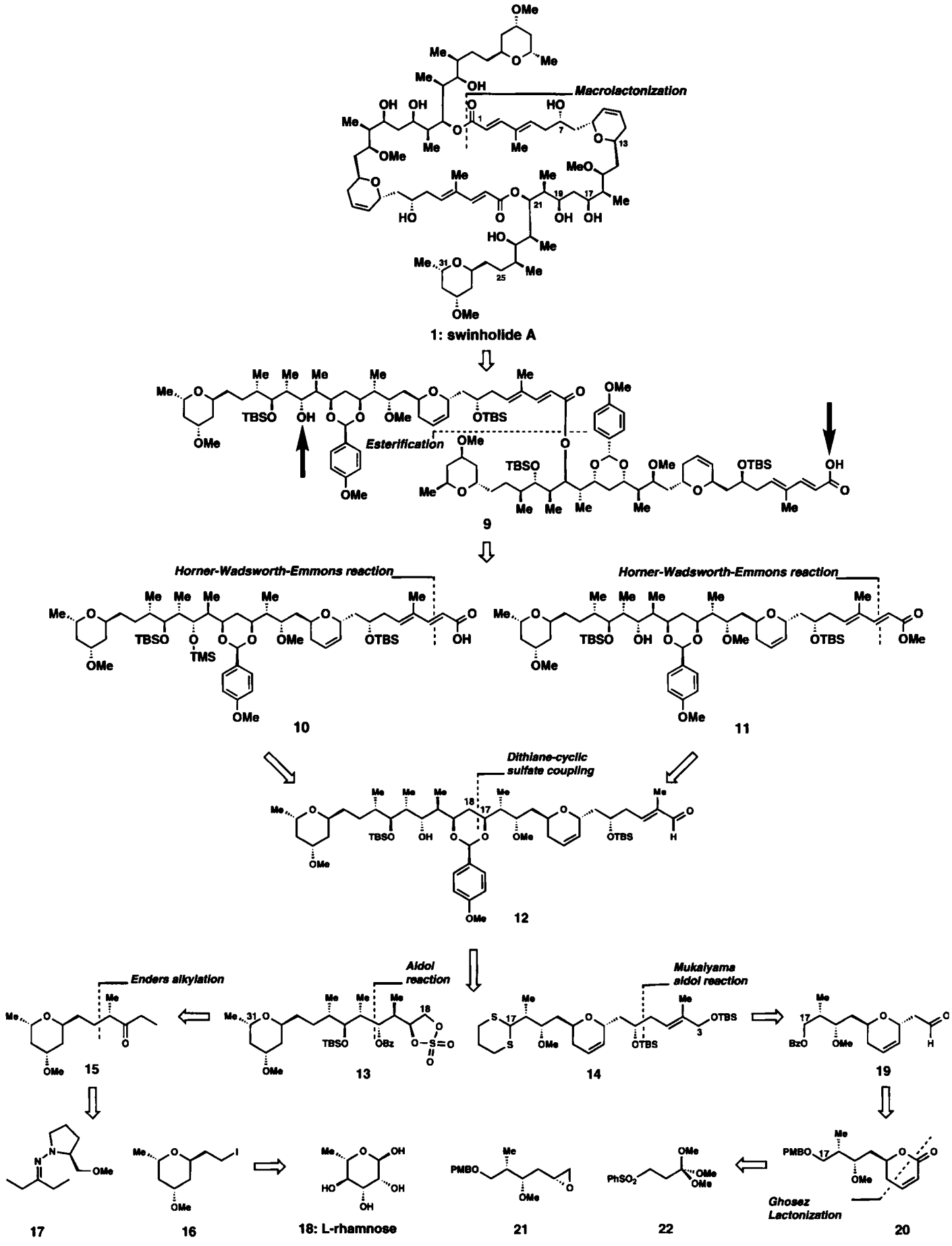

Fig. 3. Retrosynthetic analysis of swinholide A (1).

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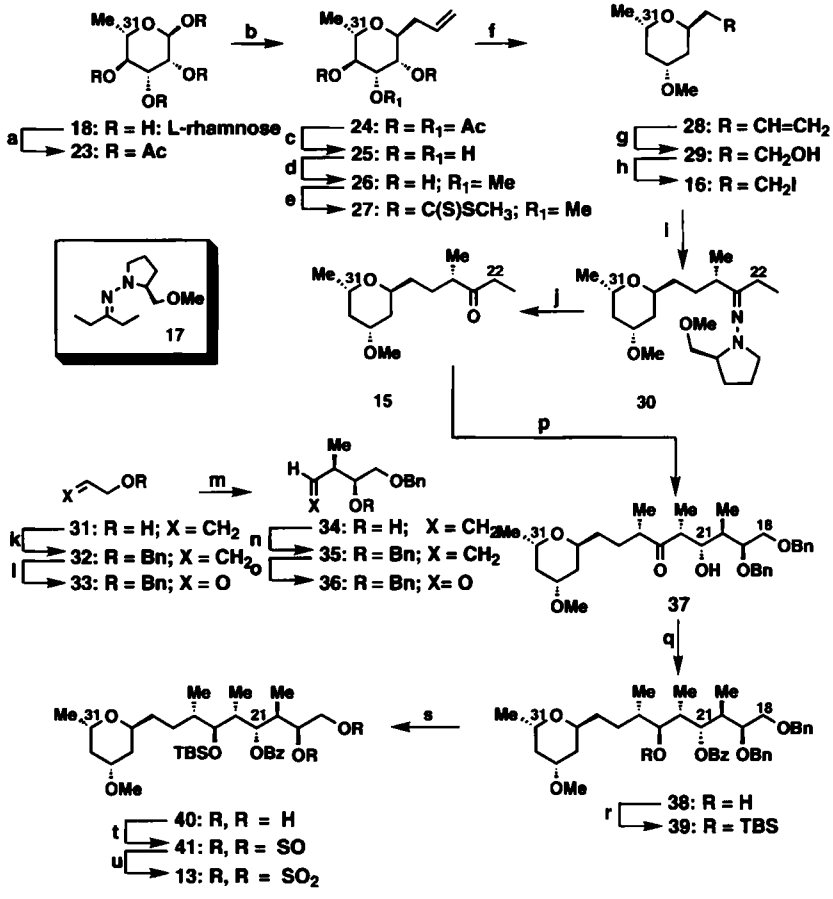


Scheme 1. Synthesis of C18–C32 fragment **13**. Reagents and conditions: a) 7 equiv Ac_2O, 8 equiv Et_3N, 0.2 equiv 4-DMAP, CH_2Cl_2 (0.4 M), 0 °C, 1 h, 91%; b) 2 equiv $CH_2{=}CHCH_2TMS$, 2 equiv $BF_3{\cdot}Et_2O$, 0.2 equiv TMSOTf, CH_3CN (0.55 M), 0 °C, 3 h, 81%; c) 0.1 equiv NaOMe, MeOH (0.5 M), 25 °C, 12 h, 100%; d) 1.2 equiv $n Bu_2SnO$, CH_3OH (0.25 M), reflux, 4 h, concentrate, then 1.2 equiv CsF, 1.5 equiv MeI, DMF (0.2 M), 40 °C, 12 h, 68%; e) 3 equiv NaH, 4 equiv CS_2, 3.4 equiv MeI, 0.02 equiv imidazole, THF (0.2 M), 25 °C, 2 h, 85%; f) 4 equiv $n Bu_3SnH$, 0.2 equiv AIBN, toluene (0.4 M), 110 °C, 1 h, 60%; g) O_3, CH_2Cl_2 (0.05 M), MeOH (0.05 M) until blue, then 2.5 equiv $NaBH_4$, −78 °C, 87%; h) 3 equiv I_2, 3 equiv Ph_3P, 3 equiv imidazole, CH_2Cl_2 (0.25 M), 40 °C, 2 h, 83%; i) 1.5 equiv SAMP hydrazone **17**, 1.5 equiv LDA, Et_2O (0.5 M), −78 °C, 3 h, then cool −110 °C, 1 equiv iodide **16**, −78 → 25 °C, 12 h, 93%; j) O_3, CH_2Cl_2 (0.1 M), till blue, −78 °C, 97%; k) 1.2 equiv NaH, 1 equiv $PhCH_2Br$, 0.02 equiv $n Bu_4NI$, 0.1 equiv imidazole, THF (1.0 M), 0 °C, 4 h, 90%; l) O_3, CH_2Cl_2 (0.1 M), until blue, −78 °C, then 3 equiv Me_2S, 84%; m) 1 equiv KO*t*Bu, 2 equiv cis-2-butene, 1 equiv *n*BuLi, THF (0.5 M), −78 → −55 °C, then 1.2 equiv (−)-*β*-methoxydiisopinocampheylborane, 1.34 equiv $BF_3{\cdot}Et_2O$, aldehyde **33**, −78 °C, 12 h, then 1.84 equiv NaOH, 1 equiv H_2O_2, −78 → 67 °C, 1 h reflux, 78%; n) 2 equiv $PhCH_2Br$, 2 equiv KH, DMF (0.5 M), 0 °C, 1 h, 85%; o) O_3, CH_2Cl_2 (0.05 M), until blue, −78 °C, then 2.2 equiv Ph_3P, 92%; p) 1.2 equiv $TiCl_4$, 1 equiv ketone **15**, CH_2Cl_2 (0.2 M), 1.2 equiv Et_3N, 1.1 equiv aldehyde **36**, −78 °C, 8 h, 68%; q) 5 equiv benzaldehyde, 0.3 equiv SmI_2, THF (0.22 M), −10 °C, 1 h, 89%; r) 1.5 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2 (0.5 M), 25 °C, 15 min, 86%; s) 0.05 equiv 10% Pd/C, EtOH (0.25 M), H_2, 25 °C, 2 days, 99%; t) 1.5 equiv $SOCl_2$ (6 M in CH_2Cl_2), 4 equiv Et_3N, CH_2Cl_2, 0 °C, 10 min; u) 0.03 equiv $RuCl_3$, 4 equiv $NaIO_4$, CCl_4:CH_3CN:H_2O (2:2:3), 0 °C, 1.5 h, 95% (2 steps). THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; Dibal-H = diisobutylaluminum hydride; SAMP = (*S*)-(−)-1-amino-2-methoxymethyl pyrrolidine; 4-DMAP = 4-dimethylaminopyridine; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; Tf = SO_2CF_3.

and the C15 methoxy substituent was confirmed by direct comparison with epoxide **21** prepared by our previously reported method.[13a] The crucial Ghosez lactonization[23] utilizing epoxide **21** and 3-phenylsulfonyl methyl orthopropionate (**22**) proceeded smoothly under sequential basic (*n*BuLi)–acidic (H_2SO_4, TsOH)–basic (Et_3N, DBU) conditions to afford *α*,*β*-unsaturated lactone **20** in 92% yield. In this reaction, the sulfone-stabilized anion generated from **22** added regioselectively to the terminus of epoxide **21** to form the C12–C13 bond, generating an oxygen nucleophile and thence a *δ*-lactone, which underwent elimination of $PhSO_2H$ to form the desired product **20**. Reduction of lactone **20** with 1.2 equiv of Dibal-H resulted in the formation of lactol **48** (94%, mixture of anomers) which reacted quantitatively and stereoselectively with allyltrimethyl silane[22] in the presence of $BF_3{\cdot}Et_2O$ to afford compound **49**, from which the *p*-methoxybenzyl group had been cleaved, apparently under the acidic conditions employed. Reprotection of **49** as a benzoate (PhCOCl, Et_3N, 97% yield), followed by selec-

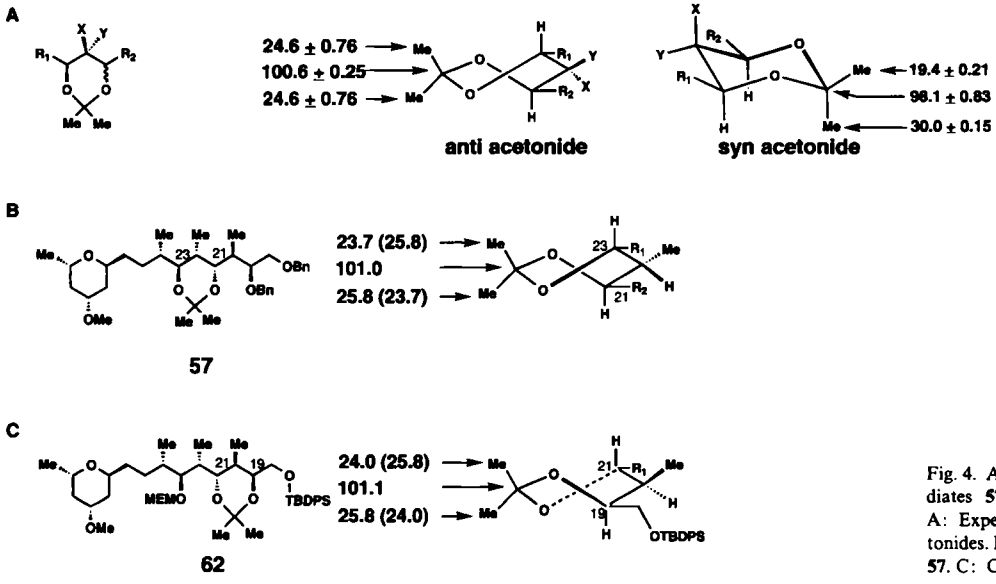
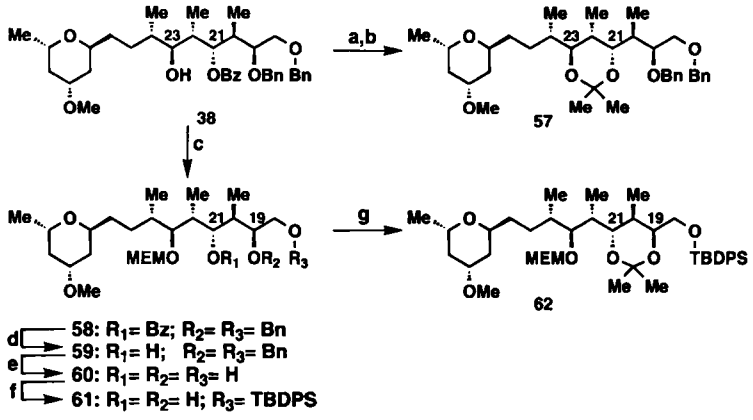
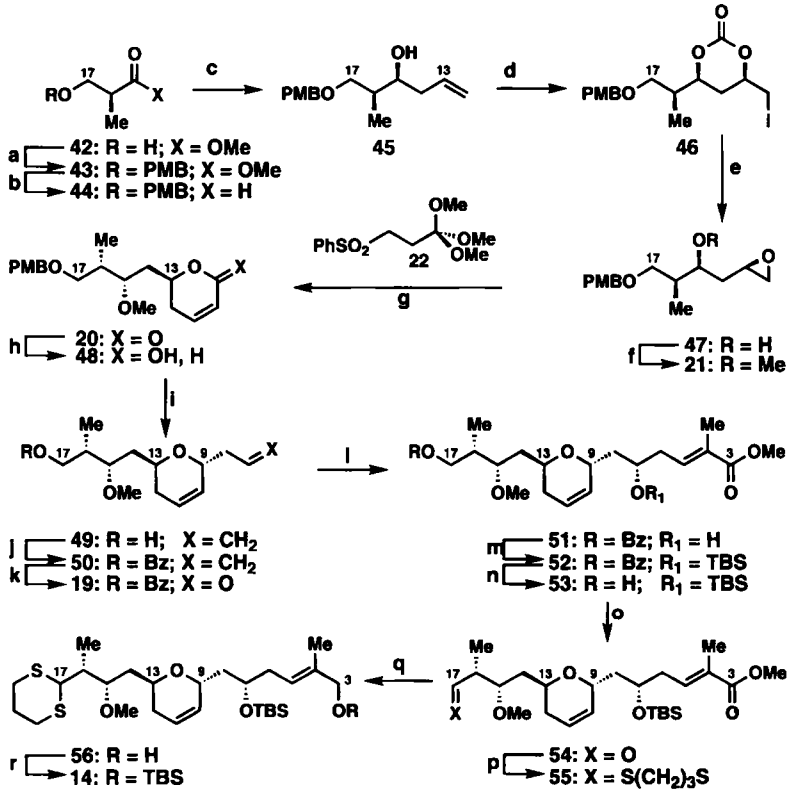


Fig. 4. Assignment of the stereochemistry of intermediates **57** and **62** based on ^{13}C chemical shifts. A: Expected chemical shifts for *anti* and *syn* acetonides. B: Chemical shifts observed for *anti* acetonide **57**. C: Chemical shifts observed for *anti* acetonide **62**.



Scheme 2. Synthesis of the acetonides **57** and **62**. Reagents and conditions: a) 2.1 equiv Dibal-H, THF (0.46 M), −78 °C, 2.5 h, 95%; b) 15 equiv 2,2-dimethoxypropane, 0.1 equiv CSA, acetone (0.37 M), 2.5 h, 95%; c) 0.25 equiv 4-DMAP, 10 equiv iPr_2NEt, 9 equiv MEMCl, CH_2Cl_2 (0.3 M), 25 °C, 48 h, 90%; d) 2.1 equiv Dibal-H, $PhCH_3$ (0.2 M), −78 °C, 2 h; e) 0.1 equiv 10% Pd/C, H_2, EtOH, 25 °C, 24 h, 78%, 2 steps; f) 2.4 equiv imidazole, 1.2 equiv TBDPSCl, DMF (0.32 M), 2.5 h, 60%; g) 15 equiv 2,2-dimethoxypropane, 0.1 equiv CSA, acetone (0.37 M), 2.5 h, 95%.



Scheme 3. Synthesis of C3–C17 fragment **14**. Reagents and conditions: a) 1.5 equiv *p*-MeO-$C_6H_4CH_2CO(NH)CCl_3$, 0.05 equiv CSA, CH_2Cl_2 (0.67 M), 25 °C, 18 h, 95%; b) 1.2 equiv Dibal-H (1 M in toluene), CH_2Cl_2 (0.15 M), −78 °C, 30 min, 85%; c) 1 equiv (−)-*β*-methoxydiisopinocampheylborane, Et_2O (1 M), 0.96 equiv allyl MgBr (1 M in Et_2O), 0 °C, 1 h, concentrate and remove salts, then 1 equiv aldehyde **44** (5 M in Et_2O), −110 °C, 3 h, then 1.84 equiv NaOH, 1 equiv H_2O_2, −78 → 67 °C, 1 h, reflux, 92%; d) i) 1.2 equiv *n*BuLi (1.6 M), THF (0.6 M), −20 °C, 1 h; ii) CO_2, −20 °C, 1.5 h, iii) 2.2 equiv I_2, −20 → 0 °C, 2 h; e) 3 equiv K_2CO_3, MeOH (0.15 M), 4 h, 0 °C, 4 steps, 52%; f) 1.5 equiv NaH, 5 equiv MeI, THF (0.15 M), 0 → 25 °C, 2 h, 91%; g) 4 equiv methyl-3-phenylsulfonyl orthopropionate (**22**), 16 equiv DMPU, THF (0.33 M), 4 equiv *n*BuLi, −78 °C, then epoxide **21**, −78 → −20 °C, 1 h, then 0 °C, 18 h, then H_2SO_4, 0 → 25 °C, 30 min then workup, resuspend in CH_2Cl_2 (0.33 M), 0.38 equiv TsOH, 48 h, then 1.5 equiv Et_3N, 4 equiv DBU, −10 °C, 2 h, 92%; h) 1.25 equiv Dibal-H, CH_2Cl_2 (0.05 M), −78 °C, 30 min, 94%; i) 4 equiv allyl TMS, 2 equiv $BF_3 \cdot Et_2O$, MeCN (0.5 M), −20 °C, 1 h, 100%; j) 2 equiv BzCl, 4 equiv Et_3N, CH_2Cl_2 (0.14 M), 25 °C, 3 h, 97%; k) 0.35 equiv OsO_4, acetone:H_2O (4:1, 0.04 M), 2.5 equiv NMO, then 1.27 equiv $Pb(OAc)_4$, PhH (0.03 M), 0 °C, 66%; l) 3 equiv 1 methoxy-1-trimethylsiloxy-2-methyl-1,3-butadiene, 1 equiv $TiCl_2(OiPr)_2$, $PhCH_3$, −78 °C, 5:1 (*α*:*β*), 75% (*α*); m) 3 equiv 2,6-lutidine, 1.25 equiv TBSOTf, CH_2Cl_2 (0.01 M), −78 → 25 °C, 1 h, 96%; n) 1.11 equiv K_2CO_3, MeOH (0.05 M), 25 °C, 4 h, 100%; o) 5 equiv $(COCl)_2$, 7 equiv DMSO, CH_2Cl_2 (0.1 M), −78 °C, 20 min, then 15 equiv Et_3N, −78 → 25 °C, 92%; p) 5 equiv 1,3-propanedithiol, 2 equiv $TiCl_4$, CH_2Cl_2 (0.03 M), −78 °C, 30 min, 85%; q) 3 equiv Dibal-H, THF (0.05 M), −78 °C, 2.5 h, 96%; r) 4 equiv 2,6-lutidine, 2 equiv TBSOTf, CH_2Cl_2 (0.033 M), −78 °C, 1 h, 92%. Ms = SO_2CH_3; CSA = camphorsulfonic acid; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene.

tive cleavage of the terminal double bond[31] by sequential treatment with *N*-methylmorpholine-*N*-oxide (NMMO) in the presence of a catalytic amount of OsO_4 followed by $Pb(OAc)_4$ furnished aldehyde **19** (66% overall yield). The latter compound (**19**) reacted with 1-methoxy-1-trimethylsiloxy-2-methyl-1,3-butadiene[32] and $TiCl_2(iPrO)_2$ in toluene at −78 °C to yield *α*,*β*-unsaturated ester **51** (75% yield)[19] together with a small amount of its C7 epimer. The assignment of the C7 stereochemistry for the two epimers was based on comparisons with the NMR data of bistheonellide A monomeric methyl ester (H-7: $\delta = 4.13$ m; C-7: $\delta = 66.0$ for bistheomellide A monomer; H-7: $\delta = 3.9$ m; C-7: $\delta = 65.8$ for major diastereoisomer **51**) and by comparison with the data of a similar intermediate reported by Paterson.[10b] The stereochemistry of the C7 alcohol was also confirmed by the successful completion of the total synthesis of both preswinholide A (**8**), and swinholide A (**1**) (vide infra). Protection of the hydroxyl group in **51** as a silyl ether with TBSOTf-2,6-lutidine (96% yield) followed by K_2CO_3/MeOH-induced removal of the benzoate (100% yield) led to the primary alcohol **53** via compound **52**. Swern oxidation[33] of **53** with oxalyl chloride gave aldehyde **54** in 92% yield; this was then converted to the corresponding dithiane **55** by treatment with 1,3-propanedithiol and $TiCl_4$[34] (85% yield). Finally, Dibal-H reduction of the ester group in **55** followed by protection of the resulting alcohol with TBSOTf-2,6-lutidine furnished the targeted C3–C17 fragment **14** in 88% overall yield via alcohol **56**.

c. Coupling of intermediates 13 and 14 and synthesis of preswinholide A: The coupling of cyclic sulfate **13** with dithiane **14** was accomplished by first generating the anion of **14** with *t*BuLi in THF in the presence of HMPA at −78 °C followed by reaction with **13** to produce, after acidic workup, coupling product **63** in 72% yield (Scheme 4). Interestingly, when the epoxide[13b] equivalent of **13** was used under similar conditions, only trace amounts of hydroxy dithiane **63** were obtained. Having successfully performed the coupling reaction, the task of converting the *β*-hydroxy dithiane to the corresponding *syn* 1,3-diol was then undertaken. While several of the standard protocols for unmasking of the dithiane to the corresponding ketone (for example, Hg salts, iodosobenzene, diacetate or bistrifluoroacetate, NBS) either failed or produced inconsistent yields of the desired ketone, the use of $NBS/AgClO_4$[35] consistently furnished ketone **64** in excellent yields (90–94%). We then envisioned the formation of *syn* 1,3-diol **65** by a chelation-controlled reduction. The use of $NaBH_4$ in the presence of nBu_2BOTf or BCl_3 in THF or THF/MeOH led to a retroaldol reaction, while the utilization of catecholborane or $Zn(BH_4)_2$ resulted in exclusive formation of the desired *syn* 1,3-diol (**65**)

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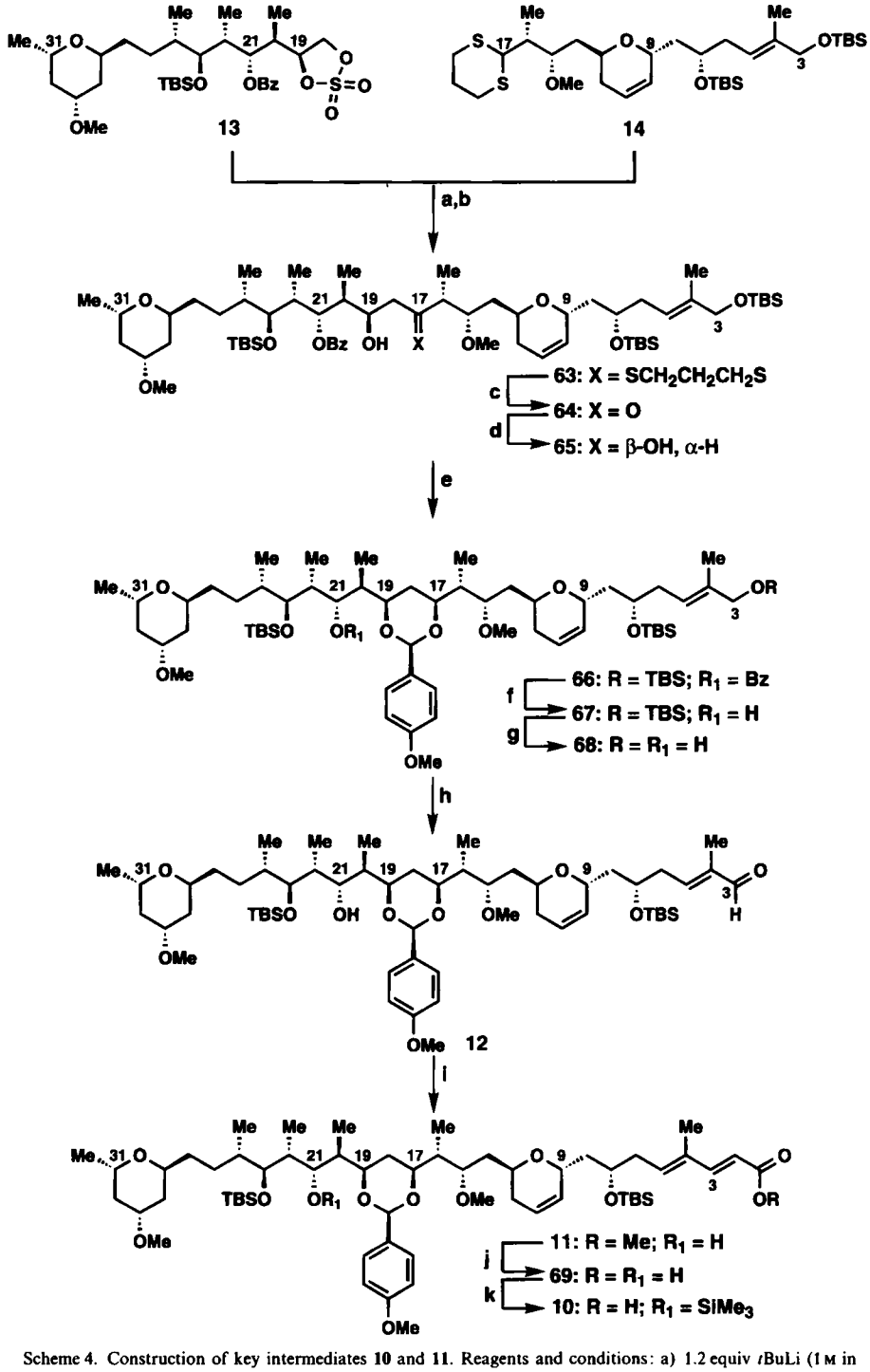
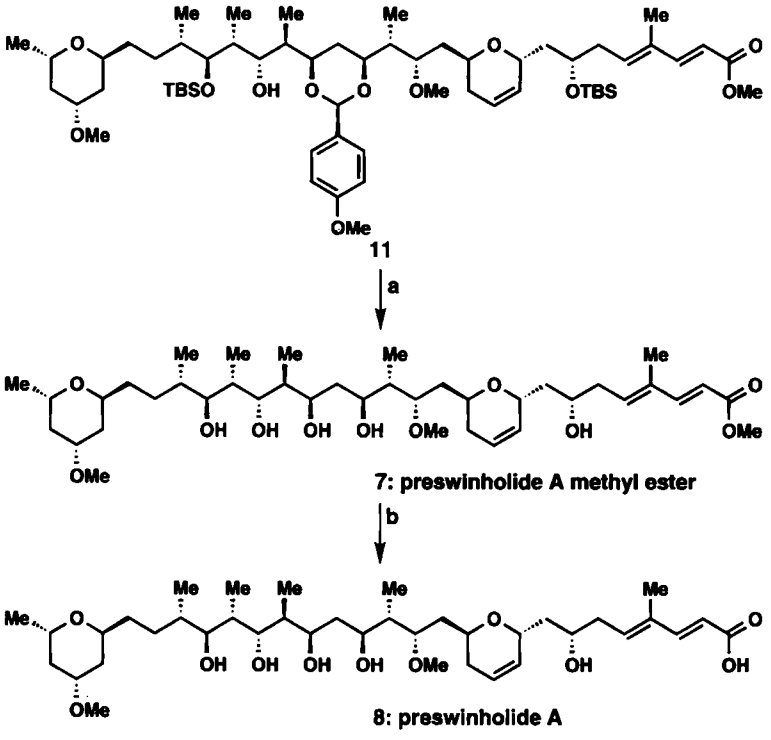


Scheme 4. Construction of key intermediates **10** and **11**. Reagents and conditions: a) 1.2 equiv *t*BuLi (1 M in hexanes), 4.0 equiv HMPA, THF (0.25 M), −78 °C, 10 min; then 1.1 equiv **13** (0.125 M in THF), −78 °C, 10 min; b) 2.0 equiv 10% aq. H_2SO_4, THF (0.2 M), 25 °C, 1 h, 72% (2 steps); c) 2.0 equiv NBS, 2.2 equiv $AgClO_4$, 10% aq. acetone (0.01 M), 0 °C, 30 s, 91%; d) 1.1 equiv nBu_3B (1 M in THF), THF (0.01 M), 25 °C, 2 h; then 2.2 equiv $NaBH_4$, −78 °C, 8 h; then 30% H_2O_2, 10% aq. NaOH, 0 °C, 3 h, 92%; e) 2.0 equiv *p*-MeO-$C_6H_4CH(OMe)_2$, 0.1 equiv CSA, CH_2Cl_2 (0.02 M), 0 °C, 3 h, 93%; f) 2.0 equiv Dibal-H, CH_2Cl_2 (0.03 M), −78 °C, 2.5 h, 97%; g) HF·pyr., pyr., CH_2Cl_2 (0.01 M), 0 °C, 2 h, 90%; h) 10.0 equiv MnO_2, CH_2Cl_2 (0.01 M), 25 °C, 4 h, 95%; i) 20.0 equiv $(MeO)_2P(O)CH_2CO_2Me$, 15.0 equiv *n*BuLi (1.6 M in hexanes), THF (0.005 M), 0 → 25 °C, 18 h, 97%; j) excess NaOH, MeOH:THF:H_2O (3:2:2, 0.004 M), 25 °C, 6 h, 92%, plus 6% recovered **11**; k) 12.5 equiv TMSOTf, 25 equiv iPr_2NEt, CH_2Cl_2 (0.017 M), 0 → 25 °C, 18 h, 89%. HMPA = hexamethylphosphoramide; NBS = *N*-bromosuccinimide.

but only in modest yields (50–60%). Finally we found that the use of nBu_3B/air/$NaBH_4$[36] consistently provided the desired compound **65** in excellent yield (92%). The 1,3-diol system in **65** was then protected with *p*-methoxybenzaldehyde dimethylacetal and camphorsulfonic acid as a catalyst leading to formation of the *p*-methoxybenzylidene derivative **66** in 93% yield. The *syn* relationship of the C–O bonds at C_{17} and C_{19} was established by ^1H and ^{13}C NMR studies on **66**. Specifically, only one isomer of **66** was observed[37] in both spectra (chair conformation of benzylidene ring). The benzoate and terminal TBS groups were then removed selectively from **66** by sequential treatment with Dibal-H (97%) and HF·pyr (90% yield) leading to compound **68** via **67**. A chemoselective oxidation of the allylic alcohol in **68** with MnO_2[38] furnished the key α,β-unsaturated aldehyde **12** in 95% yield. Reaction of this aldehyde (**12**) with the lithio derivative of $(MeO)_2P(O)CH_2CO_2Me$ generated by the action of *n*BuLi in THF[14, 15] at 0 → 25 °C, resulted in the formation of the conjugated dienoate **11** in 97% yield as a single geometrical isomer. The methyl ester group in the latter compound was hydrolyzed with aqueous NaOH in MeOH, leading to the hydroxy acid **69** (92% yield), which was then converted to the requisite TMS derivative **10** by reaction with TMSOTf and Hünig's base (89% yield).

Before discussing the coupling of the two half units of swinholide A (**1**) and the completion of its synthesis, it is appropriate to describe the synthesis of preswinholide A (**8**) and its methyl ester (**7**). As shown in Scheme 5, intermediate **11** was converted to **7** in 94% yield by a single operation employing aqueous HF in MeCN, conditions that smoothly removed both the TBS and the benzylidene protecting groups. Saponification of the methyl ester group in **7** with aqueous NaOH in MeOH followed by neutralization with saturated aqueous NH_4Cl solution led to preswinholide A (**8**) in 97% yield. The spectral data of the synthetic **8** were identical to those reported[2, 5] for natural **8**.

d. Coupling of preswinholide A units, cyclization reactions and completion of the synthesis: As mentioned in the retrosynthetic analysis section above, the Horner–Wadsworth–Emmons reaction for the construction of the macrocyclic ring[16] was an option to be explored. Thus, the diethylphosphonoacetate **70** was prepared by coupling alcohol **67** with diethylphosphonoacetic acid in the presence of DCC in $CHCl_3$ in 72% yield (Scheme 6). However, the coupling of this phosphonate with aldehyde **12** proved problematic. Thus all the conditions tried (e.g., $iPrNEt_2$, $iPrNEt_2$/LiCl, DBU, DBU/LiCl, LDA, *t*BuOK, K_2CO_3/18-C-6) failed to produce anything but a trace of the desired olefinic coupling product. The similarly



Scheme 5. Synthesis of preswinholide A methyl ester (7) and preswinholide A (8). Reagents and conditions: a) aq. HF, MeCN (0.0047 M), 0 °C, 5 h, 94%; b) excess NaOH (0.67 M), H_2O, MeOH (1:2, 0.0043 M), 25 °C, 4 h, 97%.

prepared aldehyde phosphonate **72** also failed to yield any monomeric or dimeric macrolide product upon treatment with a variety of basic conditions. We attribute these failures to severe steric congestion at the phosphonate site of compounds **70** and **72**. We then turned our attention to the esterification approach.

The direct approach involving the dimerization of hydroxy acid **69** was first attempted with the Yamaguchi protocol[14c] [2,4,6-$Cl_3(C_6H_2)$COCl, Et_3N, 4-DMAP, PhMe, 0.0057 M, 105 °C, 12 h] but provided only the monomeric, 22-membered macrolide (**77**) in 69% yield (Scheme 7). Deprotection of **77** with aqueous HF in MeCN furnished hemiswinholide A (**78**) in quantitative yield. Several other methods and conditions were tried but all resulted in similar outcomes with the desired dimeric lactone being formed only in trace amounts. We therefore focused our attention on a stepwise approach to form the swinholide A skeleton.

Coupling of carboxylic acid **10** (1 equiv) with alcohol **11** (1.25 equiv) assisted by the action of diisopropylcarbodiimide (DIC)[39] and 4-DMAP in concentrated chloroform solution proceeded to afford ester **74**, albeit in low yield (13%). A major by-product in this reaction was isolated and identified as the acyl urea **79** (Scheme 7, 50% yield). The sterically congested nature of the hydroxyl group in **11** apparently prevents it from competing favorably with the rearrangement of the initially formed adduct of the carboxylic acid with DIC (see Scheme 8). The Yamaguchi protocol[14c] was then employed for the coupling of carboxylic acid **10** with alcohol **11**. Thus, mixing **10** (1.0 equiv) and **11** (2.0 equiv) in toluene at 105 °C in the presence of 2,4,6-$Cl_3(C_6H_2)$COCl, Et_3N, 4-DMAP for 12 h resulted in the formation of coupling product **75** (46%), which had lost its TMS group. Selective hydrolysis of the methyl ester **75** with excess $Ba(OH)_2 \cdot 8H_2O$[12] in methanol afforded the desired hydroxy acid **9** in 83% yield. The latter compound was subjected to macrolactonization by Yamaguchi's protocol[14] [2,4,6-$Cl_3(C_6H_2)$COCl, Et_3N, 4-DMAP, PhMe, 0.0005 M, 110 °C, 24 h] to form protected swinholide A (**76**) in 38% yield based on 75% conversion. Finally, removal of all the protecting groups from **76** was achieved with aqueous HF in acetonitrile, furnishing swinholide A (**1**) in 60% yield.[1b,40] Synthetic **1** was identical with an authentic sample of swinholide A (**1**) by the usual criteria (TLC, HPLC, ^{1}H NMR, ^{13}C NMR, IR, and α_D).

Conclusion

The reported chemistry permits a convergent synthesis of swinholide A (**1**) and its relatives, preswinholide A methyl ester (**7**), preswinholide A (**8**), and hemiswinholide A (**78**).[40] The strategy demonstrates the power of two relatively new synthetic methods for C–C bond formation in total synthesis, namely the Ghosez cyclization[23] to form α,β-unsaturated δ-lactones from orthoester sulfones and epoxides, and the dithiane-stabilized anion opening of cyclic sulfates.[17,18] Both methods performed well in this instance and are expected to find further application in complex situations. The difficulties associated with esterification of the sterically hindered C_{21} swinholide hydroxyl, however, leaves room for improvement in this and other similar instances.

Experimental Procedure

General techniques: Melting points were determined on a Uni-Melt™ (Thomas Scientific) apparatus and are uncorrected. NMR spectra were recorded on Bruker AMX-500, AMX-400, AM-300, or AM-250 instruments with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standard: chemical shifts (δ) are reported in parts per million, and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), apt (apparent), br (broad), obs (obscured). IR spectra were recorded on Nicolet 205, Perkin Elmer 1600 or Galaxy 2020 series FT-IR spectrophotometers. Optical rotations were recorded with a Perkin Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) or electrospray conditions at the Scripps Research Institute.

All reactions were monitored by thin-layer chromatography (TLC), carried out on 250 μm Whatman silica gel plates (K6F-60 Å) under UV light, *p*-anisaldehyde, or 7% ethanolic phosphomolybdic acid and heat (200 °C) as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Dry THF and ethyl ether were distilled from sodium/benzophenone, methylene chloride was distilled from calcium hydride, and benzene and toluene were distilled from sodium immediately prior to use. All reagents were obtained from Aldrich Chemical Co. unless otherwise noted. Solvents used for workup, chromatography, and recrystallizations were reagent grade from Fisher Scientific and were used directly as received. All reactions were carried out under argon atmosphere with freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise stated.

Preparation of tetraacetate 23: To a solution of L-rhamnose (**18**) (100 g, 0.549 mol) in methylene chloride (1.35 L, 0.4 M) at 0 °C were added 4-DMAP (13.5 g, 0.109 mol), Et_3N (612 mL, 4.39 mol), and (dropwise) acetic anhydride (365 mL, 3.84 mol). The reaction mixture was stirred for 1 h at 0 °C and then quenched by dropwise addition of 5% aqueous HCl at 0 °C until reaching neutral pH. The reaction mixture was then diluted with ether (2.0 L) and washed with water (200 mL), saturated aq. $NaHCO_3$ (2 × 200 mL), and brine (200 mL). The combined aqueous layers were extracted with ether (500 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel, 50% ether in petroleum ether) yielded tetraacetate **23** (166 g, 91%) as a colorless amorphous solid. **23**: R_f = 0.25 and 0.33 (diastereoisomers) (silica gel, 50% ether in petroleum ether); $[\alpha]_D^{25} = -43.5$ (c = 0.95, $CDCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 2984.7, 2941.3, 1749.3, 1494.7, 1434.0, 1371.3, 1223.8, 1149.5, 1055.0, 975.0, 601.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer): δ = 6.01 (d, J = 2 Hz, 1H, H-1), 5.47–5.05 (m, 3H, H-2, H-3, H-4), 3.96–3.91 (m, 1H, H-5),

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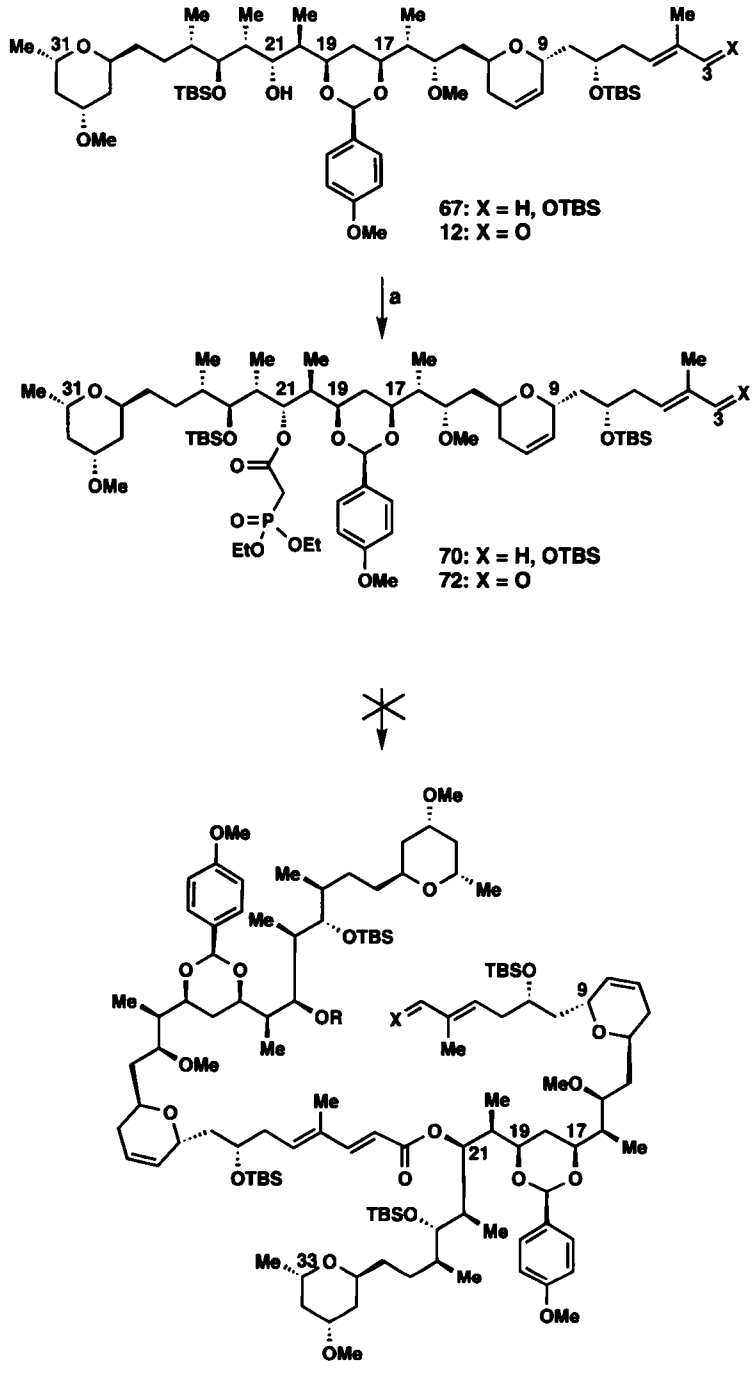


Scheme 6. Attempts to couple the preswinholide A units by the Horner–Wadsworth–Emmons reaction. Reagents and conditions: a) 5.0 equiv DCC, 1.0 equiv 4-DMAP, 5.0 equiv diethylphosphonoacetic acid, $CHCl_3$, 25 °C, 18 h, 65% →72%.

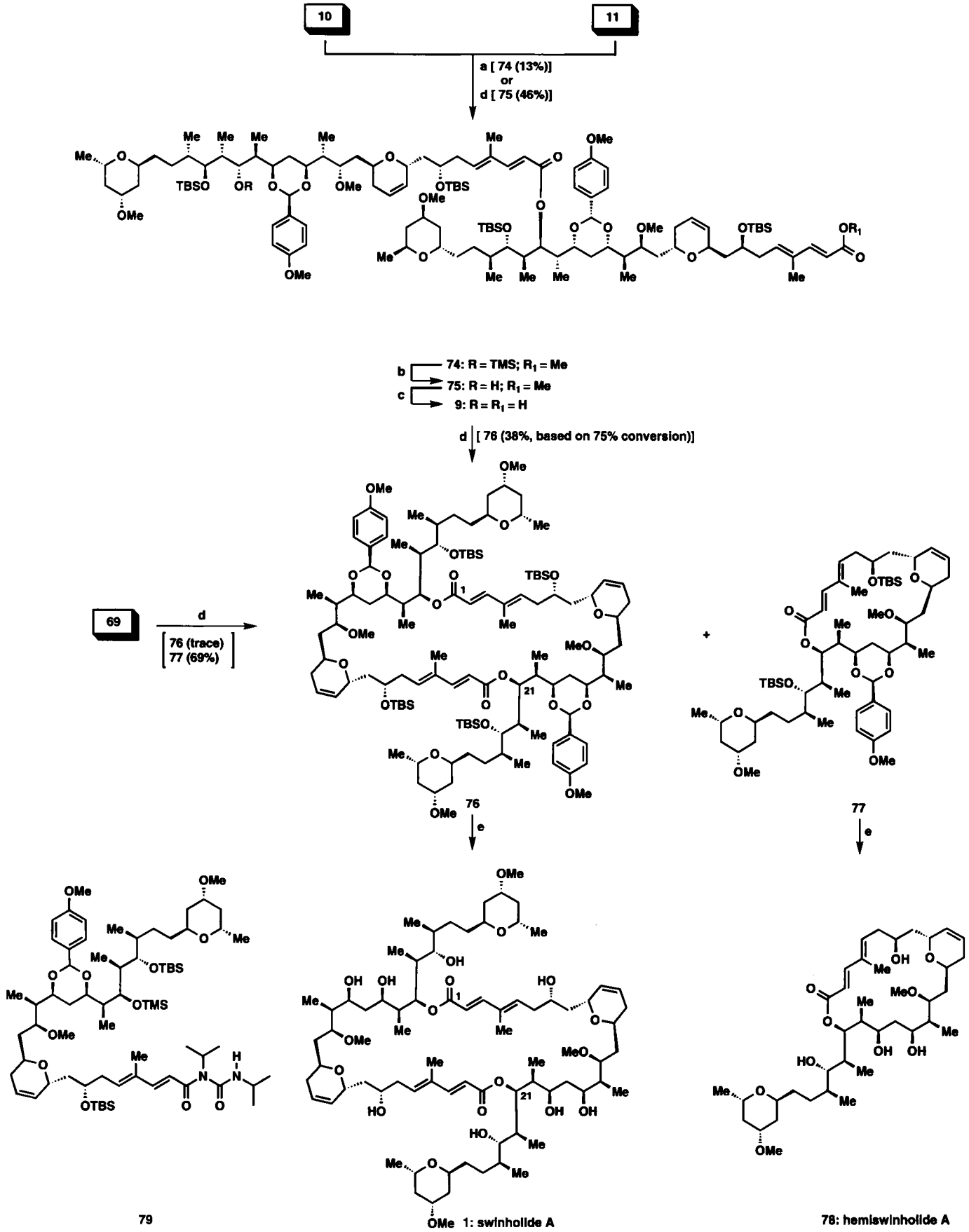
2.12 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.00(s, 3H, OAc), 1.23 (d, J = 6.5 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0–168.3 (4 carbons), 90.5, 70.3, 68.6, 68.5, 68.4, 20.6 (4 carbons), 17.3; HRMS (FAB): calcd for $C_{14}H_{20}O_9Na$ (M + Na^+) 355.1005, found 355.0990.

Preparation of allyl triacetate 24: Tetraacetate **23** was azeotroped with benzene (2 × 100 mL) and dried under vacuum (0.10 mmHg) overnight with P_2O_5. To a solution of dry tetraacetate **23** (166 g, 0.50 mol) and allyl trimethylsilane (159 mL, 1.0 mol) in CH_3CN (910 mL, 0.55 M) at 0 °C were added $BF_3 \cdot Et_2O$ (123 mL, 1.0 mol) and TMSOTf (19 mL, 0.10 mol) sequentially, and the reaction was monitored by TLC (3 h; the reaction took considerably longer if conditions were not completely anhydrous). The reaction mixture was diluted with ether (1 L) and slowly quenched by dropwise addition of saturated aqueous $NaHCO_3$ (500 mL) at 0 °C. The resulting mixture was then diluted with ethyl acetate (1 L) and washed with water (2 × 500 mL) and brine (250 mL). The aqueous layer was extracted with ethyl acetate (1 L), and the combined organic extracts were washed with brine (1 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (silica gel, 30% ether in petroleum ether) gave the C-glycosylated triacetate **24** (157 g, 81%) as a white foam. **24**: R_f = 0.21 (silica gel, 30% diethyl ether in petroleum ether); $[\alpha]_D^{25}$ = −7.4 (c = 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3637.5, 3078.2, 2982.7, 2940.3, 1745.5, 1643.3, 1435.0, 1372.3, 1227.6, 1116.7, 1052.1, 929.6, 762.8, 600.8, 491.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 9:1 α/β diastereoisomers): δ = 5.78–5.67 (m, 1H, H-2), 5.19–5.15 (m, 2H, H-1, *cis/trans*), 5.12–4.96 (m, 3H, H-5, H-6, H-7), 3.93–3.89 (m, 1H, H-8), 3.75–3.70 (m, 1H, H-4), 2.53–2.47 (m, 1H, H-3), 2.39–2.34 (m, 1H, H-3), 2.08 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.96 (s, 3H, OAc), 1.19 (d, 6.5 Hz, 3H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1–169.7 (3 carbons), 132.7, 118.0, 74.2, 71.3, 70.2, 68.8, 68.0, 33.4, 20.8–20.5 (3 carbons), 17.4; HRMS (FAB): calcd for $C_{15}H_{28}O_7$ (M + H^+) 315.1444, found 315.1456.

Preparation of triol 25: A solution of triacetate **24** (137 g, 0.436 mol) in methanol (850 mL, 0.5 M), was treated with NaOMe (2.4 g) and stirred at 25 °C for 24 h. The reaction mixture was then concentrated and purified by column chromatography (silica gel, 5% MeOH in ethyl acetate) to give pure triol **25** (82.0 g, 100%) as a white foam. **25**: R_f = 0.45 (silica gel, 10% methanol in ethyl acetate); $[\alpha]_D^{25}$ = −1.6 (c = 1.60, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3395.5, 2977.9, 2933.6, 2359.8, 1643.3, 1416.6, 1062.7, 981.7, 917.1, 825.5, 779.2, 668.3, 535.2 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (3:1 mixture of rotamers): δ = 5.78–5.70 (m, 1H, H-2), 5.13–5.05 (m, 2H, H-1), 4.85–4.35 (brs, 3H, OH), 3.95–3.72 (m, 2H, H-8, H-4), 3.52–3.22 (m, 3H, H-5, H-6, H-7), 2.51–2.23 (m, 2H, H-3), 1.26 (d, J = 5.0 Hz, 3H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.0, 117.5, 76.6, 76.1, 72.9, 71.4, 69.2, 33.3, 17.9; HRMS (FAB): calcd $C_9H_{16}O_4Na$ (M + Na^+) 211.0946, found 211.0938.

Preparation of diol 26: Triol **25** (82.0 g, 0.436 mol) was azeotroped with benzene (2 × 100 mL) and dried overnight under vacuum over P_2O_5. A mixture of dry **25**, nBu$_2$SnO (130 g, 0.523 mol), and dry methanol (1.75 L, 0.25 M) were heated under reflux until the solution became clear and homogeneous (4 h). The solvent was then removed in vacuo to give a foamy white tin complex which was azeotroped with benzene (2 × 100 mL) and dried overnight under vacuum over P_2O_5. Anhydrous DMF (2.18 L, 0.2 M) was added to redissolve the tin complex and then CsF (80 g, 0.523 mol) and methyl iodide (41 mL, 0.654 mol) were added and the mixture was heated at 40 °C for 16 h. The clear solution was partially distilled under vacuum (3.3 mmHg, 75–100 °C) to approximately one fifth of its original volume and diluted with ethyl acetate (2 L). The solution was then washed with water (2 × 100 mL) and the aqueous layer was extracted with ethyl acetate (3 × 500 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by column chromatography (silica gel, 25% ethyl acetate in petroleum ether) yielded the methylated diol **26** (59.0 g, 68%) as a yellow oil. **26**: R_f = 0.28 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ = −5.3 (c = 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3395.5, 3078.2, 2977.0, 2934.5, 2833.3, 2359.8, 1833.3, 1642.3, 1448.5, 1382.9, 1240.2, 1106.1, 1071.4, 984.6, 915.2, 825.5, 777.3, 656.7, 561.3, 487.0 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (dddd, J = 17.0, 10.0, 7.5, 7.0 Hz, 1H, H-2), 5.08 (ddd, J = 17.0, 3.0, 1.5 Hz, 1H, H-1 *cis*), 5.06 (dd, J = 10.0, 3.0 Hz, 1H, H-1 *trans*), 3.98 (dd, J = 7.0, 2.5 Hz, 1H, H-4), 3.94 (dq, J = 9.0, 5.5 Hz, 1H, H-8), 3.53 (dd, J = 9.0, 8.5 Hz, 1H, H-7), 3.52 (dd, J = 3.0, 2.5 Hz, 1H, H-5), 3.43 (s, 3H, C6-OCH_3), 3.30 (dd, J = 8.5, 3.0 Hz, 1H, H-6), 2.44 (ddd, J = 14.5, 7.0, 1.5 Hz, 1H, H-3a), 2.28 (ddd, J = 14.5, 7.5, 7.0 Hz, 1H, H-3b), 1.26 (d, J = 5.5 Hz, 3H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.9, 117.2, 81.4, 76.0, 71.4, 69.2, 67.0, 56.9, 33.6, 17.8; HRMS (FAB): calcd for $C_{10}H_{19}O_4$ (M + H^+) 203.1283, found 203.1274.

Preparation of bisxanthate 27: To a solution of diol **26** (59 g, 0.292 mol) in freshly distilled THF (1.46 L, 0.20 M) at 0 °C were added imidazole (0.40 g, 5.8 mmol) and sodium hydride (35 g, 0.876 mol, 60% dispersion in mineral oil). The mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. The reaction mixture was recooled to 0 °C, treated with carbon disulfide (70 mL, 1.168 mol), and stirred for 1 h. Methyl iodide (62 mL, 0.99 mol) was then added and the mixture was stirred for an additional 1 h. Saturated aqueous NH_4Cl (250 mL) was added dropwise to quench the reaction mixture at 0 °C and the mixture was then diluted with ethyl acetate (2 L), washed with water (2 × 250 mL) and brine (250 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (silica gel, 5 →10% ether in petroleum ether) yielded the bisxanthate **27** (95 g, 85%) as a yellowish crystalline solid (mp 96 °C; ether:petroleum ether) which was used directly in the next step without further purification. **27**: R_f = 0.44 (silica gel, 10% ether in petroleum ether); $[\alpha]_D^{25}$ = −38.3 (c = 2.5, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3075.3, 2979.8, 2933.6, 2834.2, 1642.3, 1423.4, 1376.1, 1296.1, 1212.2, 1161.1, 1069.5, 972.1, 920.0, 830.3, 694.3, 541.0, 455.2 cm^{-1};



Scheme 7. Final stages of the synthesis. Reagents and conditions: a) 3.0 equiv DIC, 1.0 equiv 4-DMAP, $CHCl_3$ (0.73 M), 37 °C, 24 h, 13%; b) 0.5 equiv PPTS, $CHCl_3$:MeOH (2:1, 0.0023 M), 25 °C, 80%; c) excess $Ba(OH)_2 \cdot 8H_2O$, MeOH (0.0021 M), 25 °C, 96 h, 83%; d) 15.0 equiv 2,4,6-$Cl_3(C_6H_2)COCl$, 18.0 equiv Et_3N, PhMe (0.0049 M), 25 °C, 2 h; then add 1.65 equiv DMAP, PhMe (0.001 M), 110 °C, 24 h, 38%, based on 75% conversion; e) aq. HF, MeCN (0.0018 M), 0 °C, 2 h, 60% for **1** (quantitative for **78**). DIC = diisopropyl carbodiimide; PPTS = pyridinium *p*-toluenesulfonate.

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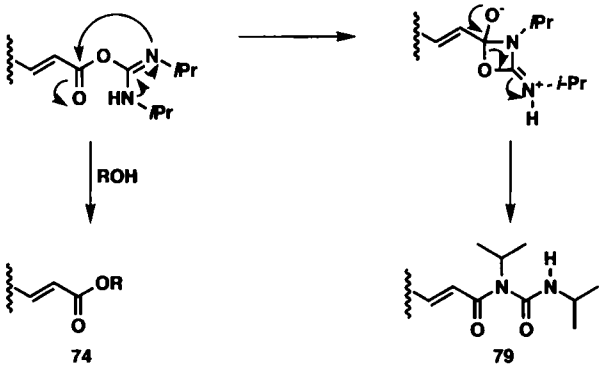

Scheme 8. Formation of dimer **74** and acyl urea **79**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.93 (dd, J = 6.5, 3.0 Hz, 1H, H-5), 5.90 (dd, J = 6.5, 5.5 Hz, 1H, H-7), 5.81 (dddd, J = 17.0, 10.0, 7.5, 7.0 Hz, 1H, H-2), 5.14 (ddd, J = 17.0, 3.0, 1.5 Hz, 1H, H-1 *cis*), 5.12 (dd, J = 10.0, 3.0 Hz, 1H, H-1 *trans*), 4.25 (brt, J = 6.5 Hz, 1H, H-4), 4.03 (qd, J = 7.0, 5.5 Hz, 1H, H-8), 3.94 (dd, J = 6.5, 3.0 Hz, 1H, H-6), 3.41 (s, 3H, C6-OCH_3), 2.60 (s, 3H, SCH_3), 2.59 (s, 3H, SCH_3), 2.42 (brd, J = 6.5 Hz, 2H, H-3), 1.36 (d, J = 7.0 Hz, 3H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.3 (2 carbons), 133.2, 117.7, 80.7, 78.8, 76.1, 70.0, 69.5, 58.7, 34.5, 19.1, 18.9, 16.8; HRMS (FAB): calcd for $C_{14}H_{23}O_4S_4$ (M + H^+) 383.0479, found 383.0492.

Preparation of allyl pyran 28: To a solution of bisxanthate **27** (47.5 g, 0.124 mol) in refluxing toluene (311 mL, 0.4 M), $n$$Bu_3$SnH (134 mL, 0.497 mol) was added slowly over 5 min. Then a solution of AIBN (2.0 g, 0.0124 mol, in 10 mL dry toluene) was added slowly over 5 min, and refluxing was continued for 30 min. A second portion of AIBN (2.0 g, 0.0124 mol, in 10 mL dry toluene) was added (if the reaction was incomplete) and the reaction mixture was allowed to reflux for an additional 0.5 h at 110 °C. The solvent was removed by distillation under reduced pressure (3.3 mmHg), and the reaction mixture was purified by column chromatography (silica gel, 2 → 5% ethyl acetate in petroleum ether). The product was obtained as a pale yellow oil (12.5 g, 60%). **28**: R_f = 0.24 (silica gel, 5% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = − 47.6 (c = 0.54, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3076.3, 2973.1, 2930.7, 2859.3, 2824.6, 1769.6, 1642.3, 1486.1, 1448.5, 1380.0, 1349.1, 1225.7, 1199.7, 1154.3, 1110.0, 1057.9, 1021.2, 913.2, 811.0, 671.2, 477.4 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.78 (dddd, J = 17.0, 10.0, 7.0, 7.0 Hz, 1H, H-2), 5.07 (ddt, J = 17.0, 3.0, 1.5 Hz, 1H, H-1 *cis*), 5.05 (dd, J = 10.0, 3.0 Hz, 1H, H-1 *trans*), 4.08 (dddd, J = 7.5, 7.5, 5.5, 2.5 Hz, 1H, H-4), 3.75 (qdd, J = 6.0, 3.0, 2.5, 1H, H-8), 3.52 (dddd, J = 10.0, 10.0, 4.5, 4.5, 1H, H-6), 3.32 (s, 3H, C6-OCH_3), 2.45 (dddd, J = 14.5, 7.5, 7.0, 1.5 Hz, 1H, H-3), 2.21 (ddd, J = 14.5, 7.5, 7.0 Hz, 1H, H-3), 1.97 (dddd, 12.5, 4.5, 2.5, 2.0 Hz, 1H, H-7eq), 1.86 (dddd, 12.5, 4.5, 2.5, 2.0 Hz, 1H, H-5eq), 1.54 (ddd, J = 12.5, 10.0, 3.0 Hz, 1H, H-7ax), 1.20 (d, J = 6.0 Hz, 3H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.0, 116.7, 72.9, 71.4, 65.0, 55.2, 38.4, 36.6, 33.6, 21.6; HRMS (FAB): calcd for $C_{10}H_{18}O_2Na$ (M + Na^+) 193.1205, found 193.1217.

Preparation of alcohol 29: Ozone was bubbled into a clear solution of olefin **28** (15.0 g, 0.0882 mol) in MeOH (882 mL, 0.1 M) and methylene chloride (882 mL, 0.1 M) at −78 °C. The solution turned light blue-green upon completion (10–20 min). At that point the ozonizer was turned off and oxygen was bubbled through the solution until the blue color dissipated. Sodium borohydride (8.3 g, 0.221 mol) was added at −78 °C in 2 portions, and the reaction mixture was gradually warmed to room temperature while stirred over a period of 7 h. The solvent was then evaporated and the product was purified by column chromatography (silica gel, 50 → 100% ethyl acetate in petroleum ether). Compound **29** was obtained as a yellow oil (13.3 g, 87%). **29**: R_f = 0.41 (silica gel, ethyl acetate); $[\alpha]_D^{25}$ = − 37.7 (c = 2.5, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3418.6, 2967.3, 2940.3, 2879.6, 2828.4, 2663.5, 1655.8, 1452.3, 1381.9, 1292.2, 1199.7, 1154.3, 1100.3, 1058.9, 1029.0, 975.9, 936.4, 907.6, 830.3, 664.4, 542.0, 457.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.22 (dddd, J = 8.0, 5.5, 5.0, 4.0 Hz, 1H, H-3), 3.80 (qdd, J = 6.5, 3.5, 3.0 Hz, 1H, H-7), 3.72 (dddd, J = 15.5, 11.0, 6.0, 5.0 Hz, 2H, H-1), 3.50 (dddd, J = 9.5, 9.25, 5.0, 4.5 Hz, 1H, H-5), 3.30 (s, 3H, C5-OCH_3), 2.79 (dd, J = 6.0, 5.0 Hz, 1H, OH), 2.02 (dddd, J = 17.5, 11.0, 7.0, 5.5 Hz, 1H, H-2), 1.94 (dddd, J = 12.5, 4.5, 3.0, 1.5 Hz, 1H, H-6eq), 1.77 (dddd, J = 13.0, 4.0, 4.0, 1.5 Hz, 1H, H-4eq), 1.60 (ddd, J = 9.5, 13.0, 5.5 Hz, 1H, H-4ax), 1.49 (dddd, J = 17.5, 6.5, 5.5, 4.0 Hz, 1H, H-2), 1.21 (ddd, J = 12.5, 10.0, 3.0 Hz, 1H, H-6ax), 1.20 (d, J = 6.5 Hz, 3H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 72.9, 70.48, 65.4, 61.1, 55.3, 37.6, 35.1, 33.9, 21.3; HRMS (FAB): calcd for $C_9H_{18}O_3Na$ (M + Na^+) 197.1154, found 197.1162.

Preparation of iodide 16: A solution of alcohol **29** (18.40 g, 0.105 mol) in methylene chloride (430 mL, 0.25 M) was cooled to 0 °C and treated with imidazole (21.6 g, 0.317 mol), triphenylphosphine (83.1 g, 0.317 mole), and iodine (80.85 g, 0.317 mol). The reaction mixture was then heated at 40 °C for 2 h, then cooled to 0 °C and quenched by adding a mixture of saturated aqueous $NaHSO_3$ (200 mL) and $Na_2S_2O_3$ (200 mL) (vigorously stirring for 1 h at room temperature). The mixture was then extracted with methylene chloride (3 × 200 mL), and the combined organic extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded pure iodide **16** (24.98 g, 83%) as a yellow oil. **16**: R_f = 0.48 (silica gel, 30% ether in petroleum ether); $[\alpha]_D^{25}$ = − 50.5 (c = 1.98, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 2969.2, 2931.6, 2859.3, 2822.7, 1450.4, 1380.0, 1354.0, 1244.0, 1199.7, 1153.4, 1099.4, 1082.0, 1021.3, 975.0, 856.3, 812.0, 750.3, 661.6, 488.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.06 (dddd, J = 8.0, 8.0, 5.0, 3.5 Hz, 1H, H-3), 3.63 (qdd, J = 6.0, 4.0, 3.5 Hz, 1H, H-7), 3.43 (dddd, J = 9.5, 9.5, 5.0, 4.0 Hz, 1H, H-5), 3.28, (s, 3H, C5-OCH_3), 3.21–3.16 (m, 1H, H-1a), 3.15–3.10 (m, 1H, H-1b), 2.23 (dddd, J = 18.0, 9.5, 8.0, 8.0 Hz, 1H, H-2a), 1.92 (dddd, J = 12.5, 4.0, 3.5, 1.5 Hz, 1H, H-6eq), 1.78 (dddd, J = 18.0, 8.0, 8.0, 5.0 Hz, 1H, H-2b), 1.72 (dddd, J = 13.0, 5.0, 3.5, 1.5 Hz, 1H, H-4eq), 1.57 (ddd, J = 13.0, 9.5, 5.0 Hz, 1H, H-4ax), 1.17 (ddd, J = 12.5, 9.5, 4.0 Hz, 1H, H-6ax), 1.18 (d, J = 6.0 Hz, 3H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 73.0, 71.3, 65.1, 55.3, 38.0, 35.9, 34.4, 21.5, 2.1; HRMS (FAB): calcd for $C_9H_{18}O_2I$ (M + H^+) 285.0352, found 285.0350.

Preparation of ketone 15: To a solution of freshly distilled diisopropylamine at 0 °C (4.7 mL, 0.034 mol) in ether (113.0 mL, 0.20 M) was added dropwise nBuLi (13.5 mL, 2.5 M solution in hexanes, 0.034 mol). Stirring was continued for 10 min and a solution of 3-pentanone-SAMP hydrazone (**17**) (6.7 g, 0.034 mol) in ether (10 mL) was added to the stirred mixture over a period of 5 min. Stirring was continued for 4 h at 0 °C, while the lithiated hydrazone precipitated. The reaction mixture was then cooled to −110 °C, and iodide **16** (6.4 g, 0.023 mol) was added dropwise in a minimal amount of ether (15 mL). The mixture was allowed to reach room temperature with stirring over a period of 12 h, and then poured into a 6:1 mixture of ether (350 mL) and water (55 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded hydrazone **30** (7.58 g, 93%) as a yellow oil. Hydrazone **30** was then subjected to ozonolysis in methylene chloride (1.2 L) at −78 °C (until the reaction color turned blue-green and TLC showed complete disappearance of the hydrazone). The mixture was allowed to warm to room temperature while a stream of argon was bubbled through the solution and then concentrated and purified by column chromatography (silica gel, 10% ether in petroleum ether) to give ketone **15** (5.30 g, 97%) as a yellow oil. **(Caution! The nitrosoamine formed after ozonolysis may be carcinogenic).** **15**: R_f = 0.74 (silica gel, 40% ether in petroleum ether); $[\alpha]_D^{25}$ = − 26.8 (c = 1.33, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3666.5, 3517.0, 3401.3, 2970.2, 2937.4, 2877.6, 2661.6, 2358.8, 1711.7, 1460.0, 1379.0, 1260.4, 1198.7, 1154.3, 1104.2, 1083.0, 1027.0, 954.7, 803.3, 667.3, 517.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92 (dddd, J = 9.0, 9.0, 5.5, 2.5 Hz, 1H, H-7), 3.63 (qdd, J = 6.5, 3.5, 2.5 Hz, 1H, H-11), 3.45 (dddd, J = 10.5, 10.0, 4.5, 4.0 Hz, 1H, H-9), 3.29 (s, 3H, C9-OCH_3), 2.52 (qdd, J = 6.5, 6.5, 7.0 Hz, 1H, H-4), 2.48–2.37 (m, 2H, H-2a, H-2b), 1.92 (dddd, J = 12.5, 4.5, 2.5, 2.0 Hz, 1H, H-10eq), 1.76 (dddd, J = 13.0, 4.0, 2.5, 2.0 Hz, 1H, H-8eq), 1.65–1.57 (m, 2H, H-5a, H-6a), 1.53 (ddd, J = 13.0, 10.5, 5.5 Hz, 1H, H-8ax), 1.45–1.39 (m, 1H, H-5b), 1.29–1.20 (m, 1H, H-6b), 1.15 (ddd, J = 12.5, 10.0, 3.5 Hz, 1H, H-10ax), 1.16 (d, J = 6.5 Hz, 3H, H-12), 1.05 (d, J = 7.0 Hz, 3H, C4-CH_3), 1.00 (t, J = 7.5 Hz, 3H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.0, 72.9, 71.7, 64.6, 55.2, 45.5, 38.4, 34.6, 34.0, 29.3, 29.1, 21.6, 16.3, 7.6; HRMS (FAB): calcd for $C_{14}H_{27}O_3$ (M + H^+) 243.1960, found 243.1960.

Preparation of 3-pentanone SAMP hydrazone (17): To a flask charged with (*S*)-(−)-1-amino-2-methoxymethylpyrrolidine (SAMP, 6.0 g, 46.1 mmol) was added freshly distilled 3-pentanone (5.9 mL, 55.8 mmol), and the mixture was warmed to 60 °C and stirred for 16 h. The crude product was diluted with ether (400 mL) and washed with water (50 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated. Purification by distillation (43–48 °C, 0.05 mmHg; 70–75 °C, 0.5 mmHg) yielded 7.49 g (82%) of 3-pentanone SAMP hydrazone (**17**) as a clear yellow oil. **17**: R_f = 0.50 (silica gel, 45% ether in petroleum ether); $[\alpha]_D^{25}$ = + 297.0 (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, 3H, J = 7.7 Hz, CH_3CH_2), 1.08 (t, 3H, J = 7.5 Hz, CH_3CH_2), 3.34 (s, 3H, OCH_3). For more data see ref. [21].

Preparation of allyl benzylether (32): To a solution of allyl alcohol (**31**) (100 mL, 1.47 mol) in THF (1.22 L, 1.0 M) at 0 °C were added imidazole (8.34 g, 0.122 mol) and sodium hydride (73.5 g, 1.84 mol) in small portions. After the mixture had been stirred at 0 °C for 1 h, benzyl bromide was introduced (146.0 mL, 1.22 mol), followed by $n$$Bu_4$NI (9.10 g, 0.025 mol). After 4 h the reaction mixture was quenched with water (200 mL) and diluted with ether (1.5 L), and the layers were separated. The organic phase was sequentially washed with saturated aqueous NH_4Cl (300 mL), water (300 mL), and brine (100 mL), and dried ($MgSO_4$). Purification by distillation (65–75 °C, 3.3 mmHg) yielded **32** (163.0 g, 90%) as a clear oil. **32**: R_f = 0.53 (silica gel, 5% ethyl acetate in petroleum ether); IR (KBr): $\tilde{\nu}_{max}$ = 3083.0, 3065.7, 3030.0, 2924.9, 2854.5, 1646.2, 1495.7, 1453.3, 1348.2, 1290.3, 1203.5, 1090.7, 1013.6, 923.8, 736.8, 697.2, 656.7, 595.0, 463.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.37 (m, 5H, ArH), 5.98 (dtd, J = 17.5, 10.5, 5.5 Hz, 1H, H-2), 5.34 (ddd, J = 17.5, 3.0, 1.5 Hz, 1H, H-1 *trans*), 5.23 (ddd, J = 10.5, 3.0, 1.5 Hz, 1H,

H-1 *cis*), 4.55 (s, 2H, CH_2-Ph), 4.06 (ddd, J = 5.5, 1.5, 1.5 Hz, 2H, H-3a, H-3b); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 134.6, 128.3 (2 carbons), 127.5 (3 carbons), 117.1, 72.0, 71.0; HRMS (FAB): calcd for $C_{10}H_{13}O$ ($M+H^+$) 149.0966, found 149.0970.

Preparation of benzyloxyacetaldehyde (33): Through a solution of olefin **32** (10.0 g, 0.067 mol) in methylene chloride (1.35 L, 0.05 M) at −78 °C was bubbled ozone until the color turned light blue (ca. 1–1.5 h). The ozonizer was then turned off and oxygen was purged through the solution until the blue color dissipated. Dimethyl sulfide (30.0 mL, 0.40 mol) was added at −78 °C and the solution was allowed to reach room temperature over a period of 22 h with stirring. The residual dimethyl sulfide and solvent were evaporated and the product was purified by distillation (75–76 °C, 1.2–1.5 mmHg) to give pure aldehyde **33** (8.50 g, 84%) as a yellow oil. **33**: R_f = 0.40 (silica gel, 20% ethyl acetate in petroleum ether); IR (KBr): $\tilde{\nu}_{max}$ = 3434.1, 3107.1, 3063.7, 3031.0, 2916.2, 2868.0, 2718.5, 1955.7, 1877.6, 1812.0, 1734.9, 1605.6, 1496.7, 1454.2, 1370.3, 1310.6, 1252.7, 1208.3, 1103.2, 1028.0, 910.3, 739.7, 698.2, 606.6, 465.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (s, 1H, CHO), 7.40–7.35 (m, 5H, ArH), 4.65 (s, 2H, H-2a, H-2b), 4.12 (s, 2H, CH_2Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.2, 128.4–127.6 (6 carbons), 75.1, 73.4 ; HRMS (FAB): calcd for $C_9H_{10}O_2Na$ ($M+Na^+$) 173.0578, found 173.0574.

Preparation of homoallyl alcohol 34: To a stirred suspension of KO*t*Bu (153.0 mL, 1.0 M solution in THF, 0.153 mol) in THF (307 mL, 0.5 M) at −78 °C was added *cis*-2-butene (28.0 mL, 0.307 mol) through a cannula. To the stirred mixture *n*BuLi (61.0 mL, 2.5 M solution in hexanes, 0.153 mol) was added dropwise such that the internal temperature did not exceed −65 °C. The mixture was stirred at −50 °C for 10 min, and then recooled to −78 °C. To the resulting orange solution, a solution of (−)-β-methoxydiisopinocampheylborane (58.20 g, 0.184 mol) was added dropwise in ether (50 mL). After stirring the reaction mixture at −78 °C for 30 min, $BF_3\cdot Et_2O$ (25.3 mL, 0.206 mol) was added dropwise and stirring was continued for an additional 30 min. A solution of aldehyde **14** (23.0 g, 0.153 mol) in THF (25 mL) was added dropwise, and the mixture was stirred at −78 °C for 3 h. The mixture was allowed to reach 0 °C, treated dropwise with 3 N NaOH (94.0 mL, 0.2821 mol) and 30% H_2O_2 (47.0 mL), and then refluxed for 1 h (until hydrolysis was complete). After cooling, the organic layer was diluted with ether (1.5 L), washed with water (150 mL) and then brine (150 mL), and dried over $MgSO_4$. The crude organic mixture was distilled at 85–90 °C (3.3 mmHg, bath 120 °C) to remove most of the by-product isopinocampheol, and the remaining oil was purified by column chromatography (silica gel, 10% ether in petroleum ether) to afford β-methylhomoallyl alcohol **34** (24.6 g, 78%) as a yellow oil. **34**: R_f = 0.61 (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = + 22.3 (c = 1.26, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3452.4, 3066.6, 3031.0, 2965.4, 2905.6, 2867.0, 1720.4, 1639.4, 1454.2, 1366.5, 1285.5, 1208.3, 1102.3, 1039.6, 998.1, 916.1, 818.7, 737.7, 698.2, 610.4, 475.4 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 5H, ArH), 5.75 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H, H-2), 5.07 (ddd, J = 17.5, 1.5, 1.5 Hz, 1H, H-1 *trans*), 5.03 (ddd, J = 10.0, 1.5, 0.5 Hz, 1H, H-1 *cis*), 4.55 (s, 2H, CH_2Ph), 3.66 (dddd, J = 7.5, 7.5, 3.0, 3.0 Hz, 1H, H-4), 3.57 (dd, J = 9.5, 3.0 Hz, 1H, H-5a), 3.41 (dd, J = 9.5, 7.5 Hz, 1H, H-5b), 2.51 (d, J = 3.0 Hz, 1H, OH), 2.34 (qdd, J = 7.5, 7.5, 6.5 Hz, 1H, H-3), 1.09 (d, J = 6.5 Hz, 3H, C3–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.2, 137.9, 128.4 (2 carbons), 127.6 (3 carbons), 115.0, 73.3, 73.3, 72.7, 41.0, 15.6; HRMS (FAB): calcd for $C_{13}H_{18}O_2Na$ ($M+Na^+$) 229.1205, found 229.1208.

Preparation of dibenzyl ether 35: A solution of alcohol **34** (22.0 g, 0.107 mmol) in DMF (214 mL, 0.5 M) was cooled to 0 °C and treated with KH (13.2 g, 30% dispersion in mineral oil, 0.214 mmol). The reaction mixture was allowed to warm to room temperature with continued stirring. After 1 h, the solution was recooled to 0 °C, treated with benzyl bromide (25.4 mL, 0.214 mmol), and stirred for a further 1.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and diluted with ethyl acetate (2 L). The two layers were separated and the organic phase was washed with water (2 × 100 mL), brine (100 mL), and dried ($MgSO_4$). Concentration followed by column chromatography (silica gel, 5% ether in petroleum ether) afforded the pure dibenzyl ether **35** (26.8 g, 85% yield) as a yellow oil. **35**: R_f = 0.45 (silica gel, 5% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = − 2.7 (c = 1.8, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3064.7, 3030.0, 2968.3, 2926.8, 2865.1, 2359.8, 1949.9, 1870.8, 1809.1, 1721.4, 1639.4, 1603.7, 1496.7, 1453.3, 1392.5, 1349.1, 1270.1, 1206.4, 1097.4, 1028.0, 998.1, 914.2, 817.8, 735.8, 697.2, 606.6, 462.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.37 (m, 10H, ArH), 5.93 (ddd, J = 17.0, 10.5, 7.5 Hz, 1H, H-2) 5.17 (dd, J = 17.0, 1.5 Hz, 1H, H-1 *trans*), 5.11 (dd, J = 10.5, 1.5 Hz, 1H, H-1 *cis*), 4.85 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.70 (d, J = 11.5 Hz, 1H, CH*H*Ph), 4.63 (s, 2H, CH_2Ph) 3.73 (brd, J = 10.5 Hz, 1H, H-5a), 3.67 (ddd, J = 10.0, 7.0, 3.0 Hz, 1H, H-5b), 3.60–3.51 (m, 1H, H-4), 2.63 (sextet, J = 6.5 Hz, 1H, H-3), 1.20 (d, J = 6.5 Hz, 3H, C3–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.9, 138.9, 138.4, 128.3–128.2 (4 carbons), 127.7–127.4 (6 carbons), 114.6, 81.8, 73.3, 72.7, 71.5, 40.0, 15.6; HRMS (FAB): calcd for $C_{20}H_{24}O_2Na$ ($M+Na^+$) 319.1674, found 319.1662.

Preparation of aldehyde 36: A solution of olefin **35** (35.0 g, 0.118 mol) in methylene chloride (2.4 L, 0.05 M) at −78 °C was treated with ozone for 4 h with stirring. The ozonizer was turned off and oxygen was bubbled through the solution until the blue color dissipated. Triphenylphosphine (68.2 g, 0.260 mol) was added at −78 °C and the reaction mixture was vigorously stirred, while it was allowed to warm to room temperature over 3 h. Concentration and purification by column chromatography (silica gel, 5 → 20% ether in petroleum ether) yielded aldehyde **36** (32.4 g, 92% yield) as a yellow oil. **36**: R_f = 0.73 (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = − 4.9 (c = 0.98, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3063.7, 3030.9, 2977.0, 2865.1, 2721.4, 1723.4, 1690.5, 1496.7, 1454.2, 1351.1, 1206.4, 1098.4, 1064.6, 1028.0, 912.3, 737.7, 698.2, 607.5, 475.4 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.73 (s, 1H, H-1), 7.38–7.29 (m, 10H, ArH), 4.67 (d, J = 11.5 Hz, 1H, C*H*H-Ph), 4.57 (d, J = 11.5 Hz, 1H, C*H*HPh), 4.54 (s, 2H, CH_2Ph), 4.08–4.05 (ddd, J = 7.5, 5.5, 5.0 Hz, 1H, H-3), 3.67–3.64 (dd, J = 10.0, 5.0 Hz, 1H, H-4a), 3.60–3.57 (dd, J = 10.0, 5.5 Hz, 1H, H-4b), 2.72–2.67 (qdd, J = 7.5, 7.0, 4.5 Hz, 1H, H-2), 1.13–1.12 (d, J = 7.0 Hz, 3H, C2–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.6, 137.2, 137.1, 128.3–127.6 (10 carbons), 78.5, 73.4, 72.2, 69.4, 48.5, 8.4; HRMS (FAB): calcd for $C_{19}H_{22}O_3Na$ ($M+Na^+$) 321.1467, found 321.1458.

Preparation of β-hydroxy ketone 37: A solution of ketone **15** (5.0 g, 20.7 mmol) in methylene chloride (105 mL, 0.20 M) was cooled to −78 °C and treated with $TiCl_4$ (2.5 mL, 22.7 mmol). After stirring for 5 min, Et_3N (3.5 mL, 24.8 mmol) was added slowly and the reaction mixture was stirred for another 2.5 h. Aldehyde **36** (7.4 g, 24.8 mmol) was added dropwise at −78 °C, and the solution was allowed to stir for an additional 2.5 h at that temperature. The reaction mixture was quenched with a 1:1 mixture of saturated aqueous NH_4Cl (10.0 mL) and water (10.0 mL) and allowed to warm to ambient temperature. The mixture was diluted with ethyl acetate (1.0 L), washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and then dried ($MgSO_4$). Concentration, then purification by column chromatography (silica gel, 10 → 25% ether in petroleum ether) yielded β-hydroxy ketone **37** (7.58 g, 68% yield) as a yellow oil. **37**: R_f = 0.54 (silica gel, 40% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −16.4 (c = 1.73, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3491.0, 3086.9, 3030.0, 2970.2, 2936.5, 2872.8, 1705.0, 1496.7, 1453.3, 1379.0, 1272.9, 1204.5, 1153.4, 1101.3, 1028.0, 975.0, 737.8, 698.2, 606.6, 541.0, 462.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 10H, ArH), 4.78 (d, J = 12.0 Hz, 1H, C*H*HPh), 4.65 (d, J = 12.0 Hz, 1H, C*H*HPh), 4.55 (d, J = 12.0 Hz, 1H, C*H*H-Ph), 4.51 (d, J = 12.0 Hz, 1H, CH*H*Ph), 4.17 (ddd, J = 7.0, 5.0, 2.5 Hz, 1H, H-2), 3.96 (dddd, J = 9.0, 9.0, 5.5, 2.5 Hz, 1H, H-10), 3.89 (ddd, J = 9.0, 3.0, 2.5 Hz, 1H, H-4), 3.70 (dd, J = 10.0, 7.0 Hz, 1H, H-1a), 3.63 (ddd, J = 6.5, 3.0, 2.5 Hz, 1H, H-14), 3.56 (dd, 10.0, 5.0 Hz, 1H, H-1b), 3.47 (dddd, J = 10.0, 9.5, 5.5, 4.5 Hz, 1H, H-12), 3.30 (s, 3H, C12–OCH_3), 2.78–2.72 (m, 2H, H-5, H-7), 1.92 (dddd, J = 12.5, 4.5, 2.5, 2.0 Hz, 1H, H-13eq), 1.82–1.77 (m, 2H, H-3, H-11eq), 1.69–1.63 (m, 2H, H-8a, H-9a), 1.56 (ddd, J = 13.0, 10.0, 5.5 Hz, 1H, H-11ax), 1.45–1.41 (m, 1H, H-8b), 1.33–1.28 (m, 1H, H-9b), 1.23–1.15 (m, 1H, H-13ax), 1.19 (d, J = 6.5 Hz, 3H, H-15), 1.10 (d, J = 7.0 Hz, 3H, C5–CH_3), 1.08 (d, J = 6.5 Hz, 3H, C7–CH_3), 0.86 (d, J = 7.0 Hz, 3H, C3–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 219.2, 138.8, 138.2, 128.3–128.2 (4 carbons), 127.7–127.4 (6 carbons), 76.7, 73.1, 73.0, 73.0, 71.8, 71.6, 71.3, 64.7, 55.2, 45.9, 44.1, 38.3, 37.3, 34.6, 29.2, 29.0, 21.6, 16.3, 10.4, 8.8; HRMS (FAB): calcd for $C_{33}H_{48}O_6Na$ ($M+Na^+$) 563.3349, found 563.3363.

Preparation of β-hydroxybenzoate 38: A solution of hydroxy ketone **37** (4.0 g, 7.4 mmol) and freshly distilled benzaldehyde (3.76 mL, 37.0 mmol) in THF was cooled to −10 °C, then treated with a stock solution of SmI_2 (22.2 mL of 0.1 M solution in THF, 2.22 mmol; stock solution was prepared by addition of diiodoethane (0.910 g, 3.22 mmol) in THF (30 mL, 0.1 M) to samarium metal (0.610 g, 4.06 mmol) followed by stirring at 25 °C for 3 h). The reaction mixture was stirred at −10 °C for 1 h, diluted with ether (30 mL), and then quenched with saturated aqueous $NaHCO_3$ (30 mL). The mixture was further diluted with ether (500 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL). The aqueous phase was extracted with ether (2 × 100 mL), and the combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, 30% ether in petroleum ether) afforded alcohol **38** (4.25 g, 89% yield) as a yellow oil. **38**: R_f = 0.76 (silica gel, 40% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = − 42.9 (c = 0.85, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3514.1, 3086.9, 3030.0, 2969.2, 2937.4, 2864.1, 1713.7, 1694.4, 1600.8, 1495.7, 1452.3, 1381.0, 1277.8, 1202.5, 1152.4, 1105.1, 1071.4, 1027.0, 972.0, 921.9, 804.3, 713.6, 607.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, J = 9.5, 1.0 Hz, 2H, ArH), 7.59 (m, 1H, ArH), 7.48–7.44 (m, 2H, ArH), 7.33–7.26 (m, 10H, ArH), 5.65 (d, J = 10.5 Hz, 1H, H-4), 4.55–4.32 (m, 4H, CH_2Ph, CH_2Ph), 4.05–3.99 (m, 1H, H-10), 3.73 (ddd, J = 6.0, 6.0, 1.5 Hz, 1H, H-2), 3.71–3.68 (m, 1H, H-14), 3.65 (dd, J = 9.5, 6.0 Hz, 1H, H-1a), 3.55 (dd, J = 9.5, 6.0 Hz, 1H, H-1b), 3.57–3.53 (m, 1H, H-12), 3.34 (s, 3H, C12–OCH_3), 3.05 (ddd, J = 12.5, 4.5, 2.5 Hz, 1H, H-6), 2.29–2.25 (m, 1H, H-5), 2.03–2.00 (m, 1H, H-3), 2.02–1.98 (m, 1H, H-13eq), 1.92 (qdd, J = 7.0, 4.0, 3.0 Hz, 1H, H-9a), 1.83 (dddd, J = 12.5, 4.0, 2.5, 2.0 Hz, 1H, H-11eq), 1.75–1.68 (m, 1H, H-8a), 1.61 (ddd, J = 12.5, 10.5, 5.5 Hz, 1H, H-11ax), 1.63–1.58 (m, 1H, H-7), 1.48–1.41 (m, 1H, H-8b), 1.36–1.28 (m, 1H, H-9b), 1.27–1.16 (m, 1H, H-13ax), 1.20 (d, J = 7.0 Hz, 3H, H-15), 1.00 (d, J = 6.5 Hz, 3H, C3–CH_3), 0.94 (d, J = 6.5 Hz, 3H, C5–CH_3), 0.91 (d, J = 6.0 Hz, 3H, C7–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 138.0, 137.5, 133.2, 129.8, 128.4–127.3 (15 carbons), 76.8, 75.8, 75.4, 73.3, 73.2, 71.6, 71.5, 64.4, 55.2, 38.7, 37.3, 36.8, 34.9, 32.8, 29.0, 24.0, 21.8, 17.8, 9.7, 9.0; HRMS (FAB): calcd for $C_{40}H_{54}O_7Na$ ($M+Na^+$) 669.3767, found 669.3751.

Preparation of dibenzyl ether 39: A solution of alcohol **38** (6.0 g, 9.3 mmol) in methylene chloride (250 mL, 0.4 M) was cooled to 0 °C and treated with 2,6-lutidine

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(1.6 mL, 13.9 mmol) and TBSOTf (3.2 mL, 13.9 mmol) sequentially. The solution was allowed to warm to room temperature with stirring. After 1 h the reaction mixture was quenched with saturated aqueous $CuSO_4$ (10 mL) and stirred vigorously for an additional 2 h. The layers were separated and the aqueous phase was extracted with methylene chloride (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Silica gel column chromatography (10% ether in petroleum ether) gave **39** (6.07 g, 86% yield) as a yellow oil. **39**: $R_f = 0.63$ (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -19.8$ ($c = 1.95$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3087.9, 3031.0, 2935.5, 2856.4, 1716.5, 1601.8, 1453.3, 1361.7, 1272.9, 1176.5, 1108.0, 1070.4, 1028.0, 948.0, 836.1, 775.3, 698.2, 608.5, 535.2, 461.9\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 8.0$ Hz, 2H, ArH), 7.55 (t, $J = 7.5$ Hz, 1H, ArH), 7.43 (t, $J = 7.5$ Hz, 2H, ArH), 7.32–7.23 (m, 10H, ArH), 5.57 (dd, $J = 9.5$, 2.0 Hz, 1H, H-4), 4.58–4.44 (m, 4H, CH_2Ph, CH_2Ph), 3.96–3.93 (m, 1H, H-10), 3.79 (t, $J = 6.0$ Hz, 1H, H-2), 3.64–3.58 (m, 3H, H-1a, H-6, H-14), 3.54 (dd, $J = 9.5$, 6.0 Hz, 1H, H-1b), 3.50 (dddd, $J = 9.5$, 9.0, 5.0, 4.5 Hz, 1H, H-12), 3.34 (s, 3H, C12–OCH_3), 2.18 (qdd, $J = 9.5$, 9.0, 0.5 Hz, 1H, H-3), 2.10 (qdd, $J = 7.0$, 7.0, 0.5 Hz, 1H, H-5), 1.98–1.95 (m, 1H, H-13eq), 1.82–1.77 (m, 2H, H-9a, H-11eq), 1.70–1.63 (m, 1H, H-8a), 1.56 (ddd, $J = 12.0$, 10.5, 5.5 Hz, 1H, H-11ax), 1.48–1.43 (m, 1H, H-8b), 1.33–1.24 (m, 1H, H-9b), 1.24–1.12 (m, 1H, H-7), 1.20 (d, $J = 6.0$ Hz, 3H, H-15), 1.18–1.11 (m, 1H, H-13ax), 1.03–1.02 (d, $J = 7.0$ Hz, 3H, C5–CH_3), 1.00 (d, $J = 7.0$ Hz, 3H, C7–CH_3), 0.94 (d, $J = 9.0$ Hz, 3H, C3–CH_3), 0.88 (s, 9H, *t*Bu), 0.18 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.8$, 139.1, 138.1, 132.6, 130.8, 129.6, 128.2–127.0 (15 carbons), 78.7, 75.8, 73.1, 72.6, 72.2, 71.6, 64.3, 55.1, 39.8, 38.8, 37.5, 36.3, 34.6, 29.7, 26.9, 26.3 (2 carbons), 25.6, 21.7, 18.6, 16.9, 10.6, 10.4, −3.2, −4.6; HRMS (FAB): calcd for $C_{46}H_{68}O_7SiNa$ ($M + Na^+$) 783.4632, found 783.4618.

Preparation of diol 40: A mixture of dibenzyl ether **39** (2.0 g, 2.6 mmol) and 10% palladium on carbon (0.56 g, 0.53 mmol) in anhydrous ethanol (26 mL, 0.1 M), under a hydrogen atmosphere, was stirred at room temperature for 48 h. The reaction mixture was filtered through Celite, and the filter cake was rinsed with ether (4 × 10 mL). Concentration and purification by column chromatography afforded pure diol **40** (1.51 g, 99% yield) as a white foam. **40**: $R_f = 0.41$ (silica gel, 40% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -15.9$ ($c = 1.30$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3455.3, 2936.5, 2857.4, 1715.6, 1697.3, 1601.8, 1584.4, 1452.3, 1382.9, 1314.4, 1277.8, 1257.5, 1199.7, 1153.4, 1109.0, 1070.4, 1028.0, 909.4, 836.1, 775.3, 712.7, 673.1, 521.7\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 7.0$ Hz, 2H, ArH), 7.57 (t, $J = 7.0$ Hz, 1H, ArH), 7.43 (t, $J = 7.5$ Hz, 2H, ArH), 5.30 (dd, $J = 9.5$, 2.0 Hz, 1H, H-4), 3.92–3.90 (m, 1H, H-10), 3.67 (dd, $J = 19.0$, 8.5 Hz, 1H, H-1a), 3.61 (dd, $J = 7.5$, 3.0 Hz, 1H, H-6), 3.62–3.60 (m, 1H, H-14), 3.47 (dddd, $J = 10.0$, 10.0, 5.5, 4.5 Hz, 1H, H-12), 3.43–3.38 (m, 1H, H-1b), 3.39 (td, $J = 8.5$, 2.0 Hz, 1H, H-2), 3.30 (s, 3H, C12–OCH_3), 2.87 (brs, 2H, C1–OH, C2–OH), 2.08 (qdd, $J = 7.5$, 7.0, 2.0 Hz, 1H, H-5), 1.95–1.93 (m, 1H, H-13eq), 1.86 (qdd, $J = 9.5$, 7.0, 2.0 Hz, 1H, H-3), 1.81–1.77 (m, 1H, H-9a), 1.76–1.72 (m, 1H, H-11eq), 1.63 (dddd, $J = 10.5$, 6.5, 6.5, 2.5 Hz, 1H, H-8a), 1.54 (ddd, $J = 12.5$, 10.0, 5.5 Hz, 1H, H-11ax), 1.39–1.34 (m, 1H, H-8b), 1.32–1.25 (m, 1H, H-9b), 1.16–1.14 (d, $J = 6.5$ Hz, 3H, H-15), 1.14–1.08 (m, 2H, H-7, H-13ax), 1.05 (d, $J = 7.0$ Hz, 3H, C3–CH_3), 0.91 (d, $J = 7.0$ Hz, 3H, C5–CH_3), 0.91 (d, $J = 7.0$ Hz, 3H, C7–CH_3), 0.86 (s, 9H, *t*Bu), 0.04 (s, 3H, $SiCH_3$), −0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.9$, 133.3, 129.8 (2 carbons), 128.4 (2 carbons), 78.5, 76.6, 73.1, 71.8, 70.4, 64.7, 64.3, 55.1, 38.6 (2 carbons), 37.2, 36.5, 34.7, 29.7, 27.0, 26.2 (4 carbons), 21.7, 18.5, 16.4, 10.5, 9.7, −4.0 (2 carbons); HRMS (FAB): calcd for $C_{32}H_{56}O_7SiCs$ ($M + Cs^+$) 713.2850, found 713.2871.

Preparation of cyclic sulfate 13: Diol **40** (212 mg, 0.37 mmol) was dissolved in methylene chloride (1.1 mL, 0.33 M) and cooled to 0 °C. Et_3N (200 μL, 1.5 mmol) and $SOCl_2$ (90 μL of 6 M solution in methylene chloride, 0.54 mmol) were added sequentially, and the reaction mixture was stirred at that temperature for 10 min. The solution was diluted with ethyl acetate (10 mL), washed with water (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The crude cyclic sulfite was concentrated and dried under vacuum for 1 h. The sulfite was resuspended in a mixture of CCl_4 (1.1 mL), CH_3CN (1.1 mL), and water (1.6 mL), and cooled to 0 °C. $RuCl_3$ (2 mg, 0.11 mmol) and $NaIO_4$ (310 mg, 1.5 mmol) were added and the suspension was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with ether (25 mL) and washed with water (2 × 5 mL) and brine (5 mL). The combined aqueous layers were extracted with ether (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, 20% ethyl acetate in petroleum ether) yielded the cyclic sulfate **13** (223 mg, 95% yield) as a white foam. **13**: $R_f = 0.55$ (silica gel, 40% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -26.92$ ($c = 1.3$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 2935.5, 2857.4, 1721.4, 1601.8, 1462.0, 1389.6, 1269.1, 1211.2, 1154.3, 1106.1, 1070.4, 1027.0, 973.0, 926.7, 836.1, 776.3, 712.7, 650.0, 531.4, 434.9\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 7.5$ Hz, 2H, ArH), 7.62 (t, $J = 7.5$ Hz, 1H, ArH), 7.49 (t, $J = 7.5$ Hz, 2H, ArH), 5.43 (dd, $J = 9.0$, 1.5 Hz, 1H, H-4), 5.09 (ddd, 8.5, 8.5, 6.0 Hz, 1H, H-2), 4.55 (dd, 8.5, 6.0 Hz, 1H, H-1 *cis*), 4.47 (t, $J = 8.5$ Hz, 1H, H-1 *trans*), 3.94 (dddd, $J = 10.0$, 5.5, 5.0, 2.5 Hz, 1H, H-10), 3.63 (qdd, $J = 7.0$, 3.5, 2.5 Hz, 1H, H-14), 3.50 (dddd, $J = 10.5$, 10.0, 5.5, 4.0 Hz, 1H, H-12), 3.45 (dd, $J = 7.5$, 2.5 Hz, 1H, H-6), 3.32 (s, 3H, C12–OCH_3), 2.34 (qdd, $J = 8.5$, 6.0, 1.5 Hz, 1H, H-3), 2.03 (qdd, $J = 9.0$, 7.5, 7.0 Hz, 1H, H-5), 1.98–1.95 (m, 1H, H-13eq), 1.84 (dddd, $J = 18.5$, 10.5, 10.5, 4.5 Hz, 1H, H-9a), 1.76 (dddd, $J = 12.5$, 4.0, 2.5, 2.0 Hz, 1H, H-11eq), 1.62 (qddd, $J = 7.0$, 4.0, 3.5, 2.5 Hz, 1H, H-7), 1.56 (ddd, $J = 12.5$, 10.5, 5.5 Hz, 1H, H-11ax), 1.40–1.34 (m, 1H, H-9b), 1.33–1.22 (m, 2H, H-8a, H-8b), 1.20 (d, $J = 7.0$ Hz, 3H, H-15), 1.18 (d, $J = 6.0$ Hz, 3H, C3–CH_3), 1.17–1.10 (m, 1H, 13ax), 1.02 (d, $J = 7.0$ Hz, 3H, C5–CH_3), 0.93 (d, $J = 7.0$ Hz, 3H, C7–CH_3), 0.89 (s, 9H, *t*Bu), 0.16 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.6$, 133.5, 129.6, 129.3, 128.7 (2 carbons), 83.0, 78.5, 75.4, 73.1, 72.1, 71.6, 64.4, 55.2, 39.6, 39.5, 38.5, 36.6, 34.8, 29.6, 26.8, 26.2 (4 carbons), 21.7, 18.5, 16.2, 12.4, 11.3, −3.5, −4.5; HRMS (FAB): calcd for $C_{32}H_{54}O_9SiSCs$ ($M + Cs^+$) 775.2312, found 775.2286.

Preparation of *p*-methoxybenzyl ether 43: A solution of (*S*)-(+)-3-hydroxy-2-methyl propionate (**42**) (25 g, 0.212 mmol) and *p*-methoxybenzyl trichloroacetimidate (66 mL, 0.317 mmol) in methylene chloride (300 mL, 0.67 M) at room temperature was treated with CSA (2.5 g, 0.016 mmol) and stirred for 18 h. The reaction mixture was diluted with ether (1.5 L) and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), water (2 × 100 mL), and brine (100 mL), and dried ($MgSO_4$). Concentration, and purification by column chromatography (silica gel, 10% ether in petroleum ether) afforded **43** (48 g, 95% yield) as a pale yellow oil. **43**: $R_f = 0.21$ (silica gel, 10% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = +11.2$ ($c = 1.1$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 1730$ (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.5$ Hz, 2H, ArH), 6.88 (d, $J = 9.0$ Hz, 2H, ArH), 4.46 (s, 2H, CH_2Ar), 3.80 (s, 3H, OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.63 (dd, $J = 9.0$, 7.0 Hz, 1H, H-3a), 3.46 (dd, $J = 9.0$, 6.0 Hz, 1H, H-3b), 2.77 (qdd, $J = 7.5$, 7.0, 6.0 Hz, 1H, H-2), 1.17 (d, $J = 7.5$ Hz, 3H, C2–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.3$, 138.1 (2 carbons), 128.4 (4 carbons), 127.6, 74.1 73.1, 71.9, 51.7, 40.2; HRMS (FAB): calcd for $C_{13}H_{18}O_4Na$ ($M + Na^+$) 261.1103, found 261.1106.

Preparation of aldehyde 44: To a cooled (−78 °C) solution of ester **43** (48.2 g, 0.203 mmol) in methylene chloride (1.35 L, 0.15 M) Dibal-H (232 mL of 1 M solution in methylene chloride, 232 mmol) was added dropwise over 20 min with stirring. The reaction mixture was allowed to stir at −78 °C for 1 h, then quenched with methanol (100 mL) and allowed to warm to room temperature. A saturated solution of sodium potassium tartrate (200 mL) was added and the mixture was stirred for 2 h to break down the initially formed emulsion. The layers were separated and the aqueous layer was extracted with methylene chloride (3 × 200 mL). The combined organic extracts were washed with brine (250 mL) and dried ($MgSO_4$). Concentration and purification by flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) yielded pure aldehyde **44** (35.8 g, 85% yield) as a pale yellow oil. **44**: $R_f = 0.66$ (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -4.4$ ($c = 1.04$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 1725$ (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.72$ (s, 1H, CHO), 7.30–7.24 (m, 2H, ArH), 6.90–6.87 (m, 2H, ArH), 4.47 (s, 2H, CH_2Ar), 3.81 (s, 3H, OCH_3), 3.70–3.60 (m, 2H, H-3a, H-3b), 2.74 (qdd, $J = 7.0$, 7.0, 5.5 Hz, 1H, H-2), 1.13 (d, $J = 7.0$ Hz, 3H, C2–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.1$, 138.0 (2 carbons), 128.4 (4 carbons), 127.5, 74.1, 71.8, 51.2, 40.2; HRMS (FAB): calcd for $C_{12}H_{16}O_3Na$ ($M + Na^+$) 231.0997, found 231.0974.

Preparation of alcohol 45: Aldehyde **44** (29.6 g, 0.143 mmol) in ether (25 mL) was added to a solution of (−)-diisopinocampheylallyl borane (300 mL of 0.5 M solution in ether, 150 mmol; prepared by the method of Brown and Racherla, *J. Org. Chem.* **1991**, 401) at −110 °C. The solution was warmed to −78 °C and stirred for 1 h, then warmed to 0 °C. The reaction mixture was treated with 3 N NaOH (87 mL, 0.261 mmol) and 30% H_2O_2 (43 mL) and heated under reflux for 1 h. The mixture was allowed to reach ambient temperature, then diluted with ether (300 mL), and the organic phase was sequentially washed with water (150 mL), brine (150 mL), and dried ($MgSO_4$). The crude mixture was distilled (85–90 °C, 3.3 mmHg) to remove most of the byproduct isopinocampheol, and the remaining oil was purified by column chromatography (silica gel, 30% ether in petroleum ether) to afford alcohol **45** (32.91 g, 92% yield) as a pale yellow oil. **45**: $R_f = 0.57$ (silica gel, 30% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -3.2$ ($c = 1.40$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3453.2, 3073.1, 2997.1, 2933.7, 2858.7, 2837.0, 2825.2, 1640.2, 1612.4, 1585.9, 1513.3, 1463.1, 1441.7, 1421.1, 1362.1, 1301.8, 1247.9, 1208.8, 1173.2, 1091.7, 1035.7, 986.6, 913.8, 870.0, 846.6, 820.2, 756.6, 709.6, 667.5, 637.6, 579.4, 515.8\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.26–7.24$ (m, 2H, ArH), 6.89 (d, $J = 8.5$ Hz, 2H, ArH), 5.85–5.81 (m, 1H, H-2), 5.13–5.07 (m, H-1 *cis*, H-1 *trans*), 4.44 (s, 2H, CH_2Ar), 3.84–3.79 (m, 1H, H-4), 3.80 (s, 3H, $ArOCH_3$), 3.50 (d, $J = 5.5$ Hz, 2H, H-6a, H-6b), 2.63 (brs, 1H, C4–OH), 2.25–2.17 (m, 2H, H-3a, H-3b), 1.91–1.87 (m, 1H, H-5), 0.95 (s, 3H, C5–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 158.0$, 135.5 (2 carbons), 130.0, 129.1 (4 carbons), 117.1, 113.7, 74.1, 72.9, 55.2, 38.7, 37.3; HRMS (FAB): calcd for $C_{15}H_{22}O_3Na$ ($M + Na^+$) 273.1467, found 273.1462.

Preparation of hydroxy epoxide 47: A solution of alcohol **45** (48 g, 192 mmol) in THF (320 mL, 0.6 M) was cooled to −20 °C and treated with *n*BuLi (144 mL of 1.6 M solution in hexanes, 230.4 mmol). CO_2 was bubbled through the solution for 1.5 h at −20 °C, then iodine (81.1 g, 422.4 mmol) was added and the solution was allowed to slowly warm to 0 °C with stirring over 2 h. The reaction mixture was diluted with ether (1.5 L) and washed with saturated aqueous $Na_2S_2O_3$ (2 × 150 mL), water (150 mL) and brine (150 mL), in that order. The organic phase was dried ($MgSO_4$), concentrated, and purified by column chromatography (silica gel, 30% ether in petroleum ether) to give the iodocarbonate **46** contaminated with a small amount

of alcohol **45**. The iodocarbonate (44.8 g, 106.71 mmol) was resuspended in methanol (712 mL, 0.15 M) and treated with K_2CO_3 (44.0 g, 320.14 mmol) at room temperature for 4 h with stirring. The reaction mixture was filtered through Celite, concentrated, and resuspended in ether (500 mL). The organic phase was washed sequentially with water (150 mL) and brine (150 mL), and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, 20% ether in petroleum ether) afforded pure (> 10:1 selectivity) hydroxy epoxide **47** (26.5 g, 52% yield, 2 steps) as a clear colorless oil. **47**: $R_f = 0.20$ (silica gel, 15% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -3.2$ ($c = 1.40$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3462.5, 3041.5, 2960.4, 2913.9, 2859.1, 1612.1, 1585.7, 1513.4, 1463.0, 1442.1, 1409.1, 1362.3, 1301.8, 1247.9, 1209.7, 1174.1, 1133.4, 1090.5, 1034.2, 985.1, 923.6, 828.6, 755.6, 710.0, 576.6, 517.0\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H, ArH), 6.88 (d, $J = 8.5$ Hz, 2H, ArH), 4.44 (s, 2H, CH_2Ar), 4.01–3.96 (m, 1H, H-4), 3.80 (s, 3H, $ArOCH_3$), 3.49 (d, $J = 4.5$ Hz, 2H, H-6a, H-6b), 3.12–3.08 (m, 1H, H-2), 2.93 (br s, 1H, C4–OH), 2.78 (dt, $J = 11.0$, 5.0 Hz, 1H, H-1 *cis*), 2.52 (dd, $J = 5.0$, 2.5 Hz, 1H, H-1 *trans*), 1.93–1.88 (m, 1H, H-5), 1.75 (ddd, $J = 14.5$, 9.5, 6.0 Hz, 1H, H-3a), 1.60 (ddd, $J = 14.5$, 5.0, 4.0 Hz, 1H, H-3b), 0.92 (d, $J = 7.0$ Hz, 3H, C5–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.5, 130.0, 129.2$ (2 carbons), 113.7 (4 carbons), 74.0, 73.0, 71.9, 55.0, 47.0, 37.5 12.5; HRMS (FAB): calcd for $C_{15}H_{22}O_4Na$ ($M + Na^+$) 289.1416, found 289.1419.

Preparation of epoxide 21: A solution of alcohol **47** (12.0 g, 45.06 mmol) in THF (300 mL, 0.15 M) was cooled to 0 °C and treated with NaH (2.7 g of 60% dispersion in mineral oil, 67.58 mmol) with stirring for 1 h. Methyl iodide (14.1 mL, 225.3 mmol) was added at 0 °C and the solution was stirred for 8 h. The reaction mixture was diluted with ether (1 L) and quenched with water (200 mL). The layers were separated and the organic phase was washed with brine (2 × 200 mL) and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, 15% ethyl acetate in petroleum ether) afforded pure epoxide **21** (11.5 g, 91% yield) as a colorless oil. **21**: $R_f = 0.40$ (silica gel, 15% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -43.5$ ($c = 0.91$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3041.0, 2963.2, 2934.3, 2977.5, 2856.0, 1612.2, 1585.7, 1513.2, 1463.4, 1442.6, 1420.9, 1408.2, 1363.6, 1301.5, 1247.5, 1207.7, 1172.7, 1135.8, 1089.8, 1035.2, 1011.9, 973.4, 927.9, 882.3, 821.1, 820.5, 780.3, 755.3, 709.0, 637.6, 579.3, 516.8\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.27–7.25$ (d, $J = 10.0$ Hz, 2H, ArH), 6.88 (d, $J = 10.0$ Hz, 2H, ArH), 4.43 (s, 2H, CH_2Ar), 3.81 (s, 3H, $ArOCH_3$), 3.45 (d, $J = 6.5$ Hz, 2H, H-14), 3.39–3.30 (obs m, 1H, H-15), 3.35 (s, 3H, C15–OCH_3), 3.00–2.96 (ddd, $J = 5.8$, 5.0, 3.4 Hz, 1H, H-13), 2.75 (dd, $J = 6.4$, 5.8 Hz, 1H, H-12 *cis*), 2.46 (dd, $J = 6.4$, 3.4 Hz, 1H, H-12 *trans*), 2.03–1.93 (m, 1H, H-16), 1.84–1.74 (m, 1H, H-14a), 1.63–1.56 (m, 1H, H-14b), 0.73 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.1, 130.6, 129.1, 113.6, 79.6, 72.8, 72.2, 58.0, 55.3, 50.1, 47.1, 37.1, 34.3, 11.9$; HRMS (FAB): calcd for $C_{16}H_{24}O_4Cs$ ($M + Cs^+$) 413.0729, found 413.0726.

Preparation of lactone 20: A solution of phenylsulfoneorthoester **22** (66.7 g, 243.4 mmol) in THF (491 mL, 0.5 M) was cooled to −78 °C with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (117.6 mL, 972.6 mmol), followed by dropwise addition of *n*BuLi (97.25ml of 2.5 M solution in hexanes, 243.4 mmol). The reaction mixture was stirred at −78 °C for 1 h, then warmed to −20 °C and allowed to stir at that temperature for 15 min. A solution of epoxide **21** (17.04 g, 60.79 mmol) in THF (245 mL, 0.25 M), was added dropwise at −20 °C and then stirred with gradual warming to 5 °C for 12 h. The reaction was quenched by addition of 3 M H_2SO_4 (634 mL) at 0 °C with vigorous stirring for 5 min. After stirring for an additional 20 min at ambient temperature, the layers were separated and the aqueous phase was extracted with ether (3 × 300 mL). The combined organic extracts were washed with water (100 mL), then brine (100 mL), and dried over $MgSO_4$. After filtration and concentration, the crude product was redissolved in methylene chloride (750 mL) with TsOH (3.97 g, 23.1 mmol, azeotroped with 75 mL benzene). The solution was stirred at room temperature for 48 h, then cooled to −10 °C. Et_3N (91.9 mmol, 12.2 mL) was added to the crude lactone, followed by dropwise addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (36.4 mL, 243.3 mmol). After 2 h stirring the dark brown solution was concentrated and purified by column chromatography (silica gel, 60 → 90% ether in petroleum ether) to afford pure lactone **20** (18.72 g, 92%) as a pale yellow oil. **20**: $R_f = 0.50$ (silica gel, ether); $[\alpha]_D^{25} = -50.6$ ($c = 0.09$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 2932.6, 1721.0, 1611.7, 1585.6, 1512.7, 1462.2, 1387.8, 1301.7, 1246.7, 1173.8, 1088.7, 1035.9, 960.4, 817.6, 755.6\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H, ArH), 6.87 (d, $J = 8.5$ Hz, 2H, ArH), 6.89–6.85 (obs m, 1H, H-11), 4.52 (tt, $J = 8.0$, 5.5 Hz, 1H, H-13), 4.42 (s, 2H, CH_2Ar), 3.80 (s, 3H, $ArOCH_3$), 3.50–3.47 (m, 1H, H-15), 3.45 (dd, $J = 14.5$, 6.5 Hz, 1H, H-17a), 3.34–3.30 (m, 1H, H-17b), 3.32 (s, 3H, C15–OCH_3), 2.38 (tdd, $J = 6.5$, 3.0, 1.5 Hz, 1H, H-12a), 2.37 (dt, $J = 6.5$, 2.5 Hz, 1H, H-12b), 2.03 (ddd, $J = 14.5$, 14.0, 7.0 Hz, 1H, H-14a), 2.00 (ddd, $J = 7.0$, 6.5, 5.5 Hz, 1H, H-16), 1.79 (ddd, $J = 14.5$, 6.2, 5.5 Hz, 1H, H-14b), 0.92 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 164.3, 159.0, 144.9, 130.4, 129.2, 121.2, 113.6, 78.8, 75.5, 72.7, 71.9, 57.5, 55.1, 36.3, 36.0, 29.3, 11.9$; HRMS (FAB): calcd for $C_{19}H_{26}O_5Na$ ($M + Na^+$) 357.1678, found 357.1663.

Preparation of lactol 48: A solution of lactone **20** (1.0 g, 2.994 mmol) in dry methylene chloride (60 mL, 0.05 M) was cooled to −78 °C, then treated with Dibal-H (3.3 mL of a 1 M solution in toluene, 3.3 mmol) with stirring. After 20 min the reaction mixture was quenched with isopropanol (0.58 mL, 8.98 mmol) at −78 °C and allowed to reach ambient temperature with stirring over 0.5 h. Saturated aqueous sodium potassium tartrate (70 mL) was added and the mixture was stirred for 2 h to break the initially formed emulsion. The layers were separated, and the aqueous phase was extracted with methylene chloride (3 × 25 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and dried ($MgSO_4$). Concentration followed by column chromatography (silica gel, 60% ether in petroleum ether) afforded pure lactol **48** (940 mg, 94% yield) as a colorless oil. **48**: $R_f = 0.68$ (silica gel, ether); IR (neat): $\tilde{\nu}_{max} = 3398.3, 3037.9, 2927.7, 1612.2, 1512.7, 1459.6, 1369.5, 1299.5, 1247.9, 1178.9, 1090.1, 1035.3, 938.4, 820.4, 732.3, 582.9, 512.7\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 8.5$ Hz, 2H, ArH), 6.88 (d, $J = 8.5$ Hz, 2H, ArH), 6.01 (ddd, $J = 12.6$, 5.4, 4.0 Hz, 1H, H-11), 5.77 (ddd, $J = 12.6$, 3.5, 2.7 Hz, 1H, H-10), 5.32 (br s, 1H, H-9), 4.43 (s, 2H, CH_2Ar), 4.10–4.00 (m, 1H, H-13), 3.80 (s, 3H, $ArOCH_3$), 3.58–3.54 (m, 1H, H-15), 3.49 (dd, $J = 8.0$, 7.5 Hz, 1H, H-17a), 3.31 (dd, $J = 7.5$, 6.5 Hz, 1H, H-17b), 3.32 (s, 3H, C15–OCH_3), 2.07–2.03 (m, 1H, H-12a), 2.01–1.94 (obs m, 2H, H-12b, H-14a), 1.88 (tdd, $J = 8.0$, 7.0, 6.5 Hz, 1H, H-16), 1.58 (ddd, $J = 14.0$, 7.5, 5.0 Hz, 1H, H-14b), 0.86 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.0, 159.0, 148.6, 130.4, 129.2, 128.6, 126.3, 113.6, 92.1, 78.8, 77.5, 72.6, 72.3, 57.7, 55.2, 36.1, 35.6, 30.7, 10.8$; HRMS (FAB): calcd for $C_{19}H_{28}O_5Na$ ($M + Na^+$) 359.1834, found 359.1846.

Preparation of dienic alcohol 49: Azeotropically dried (benzene, 3 × 50 mL) lactol **48** (17.96 g, 53.4 mmol) was dissolved in anhydrous acetonitrile (107.8 mL, 0.5 M) and the solution was cooled to −10 °C. Allyl trimethylsilane (33.9 mL, 213.6 mmol) and $BF_3 \cdot Et_2O$ (13.1 mL, 106.8 mmol) were added slowly and sequentially, and the solution was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (500 mL). After vigorous stirring the layers were separated. The aqueous layer was extracted with an ethyl acetate–ether mixture (1:1, 3 × 300 mL), and the combined organic extracts were washed with water (500 mL) and brine (500 mL). Drying (Na_2SO_4) followed by concentration and column chromatography (silica gel, 30 → 50% ethyl acetate in petroleum ether) gave pure alcohol **49** (12.82 g, quantitative) as a pale yellow oil. **49**: $R_f = 0.37$ (silica gel, 30% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -79.1$ ($c = 0.03$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3439.3, 3074.4, 3032.5, 2925.9, 1642.3, 1433.0, 1386.3, 1185.4, 1084.7, 916.0, 835.8, 792.4, 709.1, 628.1\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.88–5.81$ (m, 2H, H-11, H-7), 5.72 (br d, $J = 10.0$ Hz, 1H, H-10), 5.10 (br dd, $J = 10.0$, 1.5 Hz, 1H, H-6), 5.08 (br d, $J = 10.5$ Hz, 1H, H-6), 4.23 (m, 1H, H-9), 3.77 (m, 1H, H-13), 3.66 (dd, $J = 11.0$, 6.5 Hz, 1H, H-17), 3.61 (dd, $J = 11.0$, 5.0 Hz, 1H, H-17), 3.52 (dt, $J = 8.5$, 5.0 Hz, 1H, H-15), 3.35 (s, 3H, C15–OCH_3), 2.73 (br s, 1H, C17–OH), 2.39 (ddd, $J = 18.0$, 10.0, 2.0 Hz, 1H, H-8), 2.25 (ddd, $J = 18.0$, 9.0, 7.5 Hz, 1H, H-8), 2.03–1.86 (m, 3H, H-12, H-12, H-16), 1.89 (ddd, $J = 14.5$, 8.5, 6.5 Hz, 1H, H-14), 1.58 (ddd, $J = 14.5$, 6.5, 5.0 Hz, 1H, H-14), 0.88 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 135.0, 129.0, 124.0, 116.8, 81.3, 72.4, 66.6, 64.8, 56.9, 38.6, 36.2, 35.2, 30.7, 11.1$; HRMS (FAB): calcd for $C_{14}H_{24}O_3H$ ($M + H$)$^+$ 241.1804, found 241.1808.

Preparation of benzoate 50: A solution of alcohol **49** (12.82 g, 53.34 mmol) in methylene chloride (385 mL, 0.14 M) was cooled to 0 °C and treated with Et_3N (29.7 mL, 213.3 mmol), 4-DMAP (1.629 g, 13.33 mmol) and BzCl (12.4 mL, 106.7 mmol), sequentially. The solution was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (400 mL) and after vigorous mixing the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 100 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL). Drying (Na_2SO_4) followed by concentration and column chromatography (silica gel, 10% ethyl acetate in petroleum ether) gave pure benzoate **50** (17.81 g, 97%) as a colorless oil. **50**: $R_f = 0.49$ (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -63.0$ ($c = 0.04$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3070.3, 3033.1, 2972.1, 2928.0, 2824.6, 1914.9, 1719.8, 1642.8, 1602.6, 1452.9, 1387.2, 1273.9, 1180.6, 1094.5, 1028.2, 971.1, 916.2, 833.8, 802.3, 711.2\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.06$ (dd, $J = 8.0$, 1.5 Hz, 2H, ArH), 7.57 (tt, $J = 7.5$, 1.5 Hz, 1H, ArH), 7.45 (dd, $J = 8.0$, 7.5 Hz, 2H, ArH), 5.83 (m, 2H, H-11, H-7), 5.72 (br dd, $J = 10.5$, 1.5 Hz, 1H, H-6), 5.04 (br dd, $J = 17.5$, 2.0 Hz, 1H, H-10), 4.97 (br dd, $J = 10.5$, 1.5 Hz, H-6), 4.35 (dd, $J = 10.5$, 7.0 Hz, 1H, H-17), 4.28 (dd, $J = 11.0$, 7.0 Hz, 1H, H-17), 4.24–4.20 (m, 1H, H-9), 3.78–3.73 (m, 1H, H-13), 3.56 (ddd, $J = 8.0$, 5.5, 3.0 Hz, 1H, H-15), 3.37 (s, 3H, C15–OCH_3), 2.36 (ddd, $J = 14.0$, 8.0, 6.5 Hz, 1H, H-8), 2.22 (ddd, $J = 14.0$, 7.0, 3.5 Hz, 1H, H-8), 2.23–2.21 (m, 1H, H-16), 2.03–1.95 (m, 2H, H-12, H-12), 1.93 (ddd, $J = 14.5$, 9.0, 5.5 Hz, 1H, H-14), 1.63 (ddd, $J = 14.5$, 8.0, 5.0 Hz, 1H, H-14), 0.99 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.4, 134.8, 132.7, 130.3, 129.4, 129.0, 128.2, 124.0, 116.8, 79.4, 72.3, 67.1, 64.8, 57.5, 38.7, 36.1, 35.0, 30.8, 10.7$; HRMS (FAB): calcd for $C_{21}H_{28}O_4Na$ ($M + Na^+$) 367.1885, found 367.1875.

Preparation of aldehyde 19: The diene **50** (60 mg, 0.174 mmol) was dissolved in an acetone–water mixture (4:1, 4.4 mL, 0.04 M) at room temperature, and treated with 4-methylmorpholine *N*-oxide (NMO) (150 mg, 0.436 mmol) and OsO_4 (38 μL of 0.16 M aqueous solution, 0.006 mmol). After 2 h, the reaction mixture was acidified to pH 2 with 3 N H_2SO_4 and diluted with ethyl acetate (10 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (4 × 10 mL), and the combined organic extracts were washed with $NaHCO_3$ (5 mL) and brine (5 mL), and then dried ($MgSO_4$). Concentration and purification by column chromatogra-

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phy (silica gel, 50% ethyl acetate in petroleum ether) afforded the desired C6–C7 diol (47.2 mg, 79% yield based on recovered starting material) plus recovered diene **50** (12.6 mg). The diol was used in the next reaction without further characterization.

Diol to aldehyde 19: To a cold (0 °C) solution of azeotropically dried (benzene, 2 × 3 mL) diol (47.2 mg, 0.137 mmol) in benzene (4.5 mL, 0.03 M), $Pb(OAc)_4$ (77.0 mg, 0.174 mmol) was added in 4 portions over 10 min with continued stirring at 0 °C for 1 h. The reaction mixture was quenched with ethylene glycol (1 mL) and diluted with pH 7 buffer (8 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (4 mL) and dried over $MgSO_4$. Concentration and purification by column chromatography (silica gel, 30% ethyl acetate in petroleum ether) afforded the desired aldehyde **19** as a colorless oil (39.0 mg, 83% yield). **19**: $R_f = 0.58$ (silica gel, 40% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -29.4$ ($c = 3.94$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3513.7$, 3426.5, 3062.5, 3034.2, 2926.8, 2825.1, 2725.5, 1970.9, 1913.4, 1726.5, 1601.6, 1583.8, 1451.9, 1391.7, 1314.2, 1274.8, 1177.0, 1097.6, 1026.5, 973.1, 935.2, 806.7, 713.3, 688.2, 676.1, 567.7, 470.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.74$ (dd, $J = 2.5$, 1.5 Hz, 1H, H-7), 8.06 (md, $J = 7.5$ Hz, 2H, ArH), 7.56 (tt, $J = 7.5$, 2.0 Hz, 1H, ArH), 7.45 (brtt, $J = 7.5$, 1.5 Hz, 2H, ArH), 5.88 (ddd, $J = 10.0$, 5.0, 2.5 Hz, 1H, H-11), 5.70 (md, $J = 10.5$ Hz, 1H, H-10), 4.77 (brs, 1H, H-9), 4.36 (dd, $J = 11.0$, 6.5 Hz, 1H, H-17), 4.25 (dd, $J = 11.0$, 7.0 Hz, 1H, H-17), 3.73 (tt, $J = 8.0$, 4.0 Hz, 1H, H-13), 3.46 (dt, $J = 6.5$, 3.0 Hz, 1H, H-15), 3.56 (s, 3H, C15–OCH_3), 2.72 (ddd, $J = 16.0$, 7.5, 2.5 Hz, 1H, H-8), 2.53 (ddd, $J = 16.0$, 5.0, 1.5 Hz, 1H, H-8), 2.19 (ddd, $J = 14.0$, 7.0, 3.5 Hz, 1H, H-14), 2.06–1.97 (m, 2H, H-12, H-16), 1.92 (ddd, $J = 14.5$, 8.5, 6.5 Hz, 1H, H-12), 1.63 (ddd, $J = 14.0$, 7.0, 3.0 Hz, 1H, H-14), 0.99 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 200.6$, 166.5, 130.4, 129.5, 129.5, 128.3, 127.9, 125.1, 77.9, 68.0, 67.8, 67.0, 57.6, 47.9, 35.9, 35.2, 30.4, 11.1; HRMS (FAB): calcd for $C_{20}H_{26}O_5Na$ ($M + Na^+$) 369.1678, found 369.1670.

Preparation of hydroxy ester 51: A solution of $Ti(OiPr)_4$ (12.90 mL, 43.35 mmol) and $TiCl_4$ (43.35 mL, 1 M solution in toluene, 43.35 mmol) in toluene (200 mL, 0.2 M) was cooled to −78 °C and added to a solution of aldehyde **19** (10 g, 28.90 mmol) and 1-methoxy-1-trimethylsilyl-2-methyl-1,3-butadiene (10.59 g, 57.8 mmol) in toluene (100 mL, 0.29 M) at −78 °C through a cannula. The reaction mixture was stirred for 3 h at −78 °C, then quenched with saturated aqueous $NaHCO_3$ (200 mL). After vigorous mixing the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL) and then dried (Na_2SO_4). Concentration and column chromatography (silica gel, 10% ethyl acetate in petroleum ether) gave pure alcohol **51** (10 g, 75% yield), along with the unwanted C_2 epimer (2 g, 15%) and recovered aldehyde **19** (500 mg). **51**: pale yellow oil; $R_f = 0.35$ (silica gel, 30% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -27.8$ ($c = 2.85$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3499.3$, 3052.6, 2945.4, 2928.3, 1722.1, 1713.6, 1698.1, 1650.3, 1601.9, 1584.0, 1452.2, 1434.6, 1391.5, 1314.2, 1274.5, 1196.1, 1176.8, 1092.0, 1026.4, 972.2, 935.1, 851.9, 815.4, 746.2, 713.5, 474.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.03$ (dd, $J = 9.8$, 0.9 Hz, 2H, ArH), 7.55 (brt, $J = 9.8$ Hz, 1H, ArH) 7.43 (brt, $J = 9.8$ Hz, 2H, ArH), 6.73 (dt, $J = 9.3$, 1.6 Hz, 1H, H-5), 5.84–5.77 (m, 1H, H-11), 5.62 (md, $J = 12.8$ Hz, 1H, H-10), 4.48 (brdd, $J = 8.5$, 2.9 Hz, 1H, H-9), 4.36 (dd, $J = 13.4$, 8.5 Hz, 1H, H-17), 4.23 (dd, $J = 13.4$, 8.8 Hz, 1H, H-17), 4.02–3.97 (brm, 1H, H-7), 3.84 (tt, $J = 10.7$, 6.3 Hz, 1H, H-13), 3.69 (s, 3H, C3–OCH_3), 3.50 (brdt, $J = 8.2$, 4.0 Hz, 1H, H-15), 3.53 (s, 3H, C15–OCH_3), 2.58 (brd, $J = 5.4$ Hz, 1H, C7–OH), 2.30 (dd, $J = 13.5$, 8.8 Hz, 1H, H-6), 2.21 (obs dq, $J = 12.9$, 8.8 Hz, 1H, H-6), 2.15–2.12 (m, 1H, H-12), 2.02–1.88 (m, 2H, H-12, H-14), 1.83–1.71 (m, 2H, H-16, H-14), 1.79 (s, 3H, C4–CH_3), 1.62–1.52 (m, 2H, H-8), 0.99 (d, $J = 8.7$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.0$, 166.5, 138.0, 133.0, 130.3, 129.5, 129.3, 128.4, 128.4, 124.0, 78.3, 68.7, 67.6, 67.0, 65.8, 57.5, 51.7, 39.8, 36.8, 35.2, 35.1, 30.2, 12.8, 11.2; HRMS (FAB): calcd for $C_{26}H_{36}O_7Cs$ ($M + Cs^+$) 593.1515, found 593.1535.

Preparation of silylether 52: A solution of alcohol **51** (900 mg, 1.957 mmol) in methylene chloride (20 mL, 0.01 M) at 0 °C was treated sequentially with 2,6-lutidine (826 μL, 5.890 mmol) and TBSOTf (560 μL, 2.446 mmol). The solution was allowed to warm to room temperature while stirred. After 1 h the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and the layers were separated. The aqueous phase was extracted with methylene chloride (3 × 5 mL) and the combined organic extracts were washed once with brine (10 mL), then dried ($MgSO_4$) and concentrated. Column chromatography (silica gel, 10% ethyl acetate in petroleum ether) afforded **52** (1.06 g, 96% yield) as a colorless oil. **52**: $R_f = 0.62$ (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -40.3$ ($c = 0.99$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3037.4$, 2928.3, 2856.2, 1722.5, 1714.0, 1650.8, 1602.3, 1584.5, 1468.5, 1434.3, 1360.8, 1313.9, 1273.5, 1176.7, 1092.2, 1026.9, 972.0, 935.9, 836.4, 809.1, 776.0, 712.4, 688.0, 482.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.05$ (d, $J = 7.0$ Hz, 2H, ArH), 7.56 (brt, $J = 7.0$ Hz, 1H, ArH), 7.44 (brt, $J = 8.0$ Hz, 2H, ArH), 6.80 (dt, $J = 9.0$, 1.5 Hz, 1H, H-5), 5.83–5.79 (m, 1H, H-11), 5.70 (brd, $J = 9.0$ Hz, 1H, H-10), 4.48 (brd, $J = 9.0$ Hz, 1H, H-9), 4.37 (dd, $J = 10.5$, 6.5 Hz, 1H, H-17), 4.24 (dd, $J = 10.5$, 7.0 Hz, 1H, H-17), 3.93 (brt, $J = 4.0$ Hz, 1H, H-7), 3.78–3.74 (m, 1H, H-13), 3.72 (s, 3H, C3–OCH_3), 3.48–3.42 (m, 1H, H-15), 3.36 (s, 3H, C15–OCH_3), 2.41 (brd, $J = 10.0$ Hz, 1H, H-6), 2.37 (brd, $J = 10.0$ Hz, 1H, H-6), 2.28–2.22 (m, 1H, H-16), 2.01–1.84 (m, 4H, H-14, H-14, H-12, H-12), 1.81 (s, 3H, C4–CH_3), 1.63–1.59 (m, 2H, H-8, H-8), 1.01 (d, $J = 6.5$ Hz, 3H, C16–CH_3), 0.88 (s, 9H, *t*Bu), 0.09 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.0$, 166.4, 138.9, 132.7, 130.0, 129.4, 129.4, 128.2, 128.2, 123.7, 78.1, 69.2, 68.6, 66.8, 64.9, 57.5, 51.5, 41.4, 36.4, 36.0, 35.3, 30.5, 25.6, 17.5, 12.7, 11.4, −4.8, −4.8; HRMS (FAB): calcd for $C_{32}H_{50}O_7SiNa$ ($M + Na^+$) 597.3224, found 597.3224.

Preparation of alcohol 53: A solution of benzoate **52** (2.11 g, 3.659 mmol) in anhydrous methanol (73 mL, 0.05 M) was treated with K_2CO_3 (1.11 g, 8.049 mmol) at ambient temperature. After stirring for 3 h the reaction mixture was filtered through a short plug of silica gel. The filter cake was washed with ether (3 × 10 mL) and the combined filtrate was concentrated and redissolved in ether (200 mL). The solution was washed with water (50 mL), then dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel, 15% ether in petroleum ether) gave pure alcohol **53** (1.73 g, quantitative) as a colorless oil. **53**: $R_f = 0.18$ (silica gel, 10% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -49.8$ ($c = 2.2$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3479.0$, 3031.7, 2929.7, 2856.6, 1714.1, 1651.1, 1466.8, 1434.7, 1386.9, 1257.4, 1196.1, 1130.0, 1083.5, 1007.4, 980.2, 937.0, 895.2, 836.8, 778.4, 749.1, 701.0, 665.8, 478.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.76$, (dt, $J = 7.5$, 1.5 Hz, 1H, H-5), 5.79 (m, 1H, H-11), 5.65 (brd, $J = 10.0$ Hz, 1H, H-10), 4.36 (brd, $J = 10.5$ Hz, 1H, H-9), 4.03 (ddd, $J = 14.5$, 10.0, 3.5 Hz, 1H, H-7), 3.74 (s, 3H, C3–OCH_3), 3.62 (m, 3H, H-17a, H-17b, H-15), 3.54 (obs m, 1H, H-13), 3.35 (s, 3H, C15–OCH_3), 2.37 (t, $J = 7.0$ Hz, 2H, H-6), 2.01 (m, 1H, H-12a), 1.95 (brt, $J = 5.0$ Hz, 1H, H-12b), 1.95–1.83 (m, 2H, H-16, H-14), 1.84 (d, $J = 0.5$ Hz, 3H, C4–CH_3), 1.68 (ddd, $J = 14.5$, 10.5, 2.0 Hz, 1H, H-8a), 1.61 (ddd, $J = 14.0$, 8.0, 4.0 Hz, 1H, H-14), 1.36 (ddd, $J = 14.5$, 10.0, 2.5 Hz, 1H, H-8b), 0.90 (s, 9H, *t*Bu), 0.99 (obs d, $J = 6.5$ Hz, 3H, C16–CH_3), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.5$, 138.2, 130.2, 128.9, 123.6, 80.2, 68.9, 67.7, 66.4, 63.8, 56.9, 51.7, 40.4, 37.7, 36.8, 35.7, 31.0, 25.7, 17.9, 12.6, 10.5, −4.5, −4.8; HRMS (FAB): calcd for $C_{25}H_{51}O_6Si$ ($M + H^+$) 471.3142, found 471.3140.

Preparation of aldehyde 54: A solution of oxalyl chloride (371 μL, 4.249 mmol) in methylene chloride (20 mL) was treated with DMSO (422 μL, 5.948 mmol) at −78 °C and stirred for 20 min. Alcohol **53** (400 mg, 0.850 mmol) in methylene chloride (5 mL) was added to the reaction mixture at that temperature and stirring was continued for 20 min. Et_3N (1.7 mL, 12.746 mmol) was added dropwise and the solution was allowed to warm gradually to room temperature. The reaction mixture was diluted with water (10 mL) and the layers were separated. The aqueous layer was extracted with methylene chloride (2 × 25 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and brine (10 mL) and then dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, 12% ethyl acetate in petroleum ether) gave pure aldehyde **54** (366 mg, 92% yield) as a clear colorless oil. **54**: $R_f = 0.49$ (silica gel, 10% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -70.4$ ($c = 3.63$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3017.1$, 2930.4, 2871.8, 2856.6, 2825.0, 2708.8, 1715.8, 1653.7, 1471.9, 1462.1, 1436.0, 1389.4, 1287.3, 1255.9, 1196.0, 1129.9, 1086.9, 1005.0, 979.5, 935.9, 894.5, 836.7, 811.3, 776.7, 737.8, 701.2, 667.4, 550.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.76$ (d, $J = 0.5$ Hz, 1H, H-17), 6.72 (dt, $J = 7.5$, 1.5 Hz, 1H, H-5), 5.80 (dddd, $J = 10.5$, 5.5, 2.5, 2.0 Hz, 1H, H-11), 5.65 (dddd, $J = 10.5$, 2.0, 1.5, 1.0 Hz, 1H, H-10), 4.37 (brd, $J = 10.5$ Hz, 1H, H-9), 4.05–4.00 (m, 1H, H-7), 3.96 (ddd, $J = 8.5$, 5.0, 3.0 Hz, 1H, H-15), 3.72 (s, 3H, C3–OCH_3), 3.55 (tt, $J = 9.0$, 4.0 Hz, 1H, H-13), 3.30 (s, 3H, C15–OCH_3), 2.45 (brdq, $J = 7.0$, 3.0 Hz, 1H, H-16), 2.37 (t, $J = 7.0$ Hz, 2H, H-6a, H-6b), 2.03 (qd, $J = 12.5$, 2.5 Hz, 1H, H-14a), 1.96 (brt, $J = 4.5$ Hz, 1H, H-12a), 1.92 (ddd, $J = 14.5$, 9.0, 5.5 Hz, 1H, H-8a), 1.83 (d, $J = 1.0$ Hz, 3H, C4–CH_3), 1.68–1.60 (m, 2H, H-12b, H-14b), 1.39 (ddd, $J = 14.5$, 10.0, 2.5 Hz, 1H, H-8b), 1.12 (d, $J = 7.0$ Hz, 3H, C16–CH_3), 0.90 (s, 9H, *t*Bu), 0.13 (s, 3H, $SiCH_3$), 0.121 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.2$, 168.2, 137.8, 130.1, 129.1, 123.5, 77.1, 68.9, 67.7, 63.7, 57.1, 51.6, 48.7, 40.4, 37.6, 36.3, 30.8, 25.7, 17.9, 12.6, 7.2, −4.5, −4.8; HRMS (FAB): calcd for $C_{25}H_{44}O_6SiNa$ ($M + Na^+$) 491.2804, found 491.2800.

Preparation of dithiane 55: To a solution of aldehyde **54** (301 mg, 0.6422 mmol) and 1,3-propanedithiol (322 μL, 3.211 mmol) in methylene chloride (26 mL, 0.03 M) at −78 °C, $TiCl_4$ (139 μL, 1.2844 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, then quenched with saturated aqueous $NaHCO_3$ (20 mL) and allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated. Purification by column chromatography (silica gel, 8% ethyl acetate in petroleum ether) afforded pure dithiane **55** (305 mg, 85% yield) as a colorless oil. **55**: $R_f = 0.46$ (silica gel, 12% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -37.8$ ($c = 2.77$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3016.1$, 2930.3, 2897.1, 2855.6, 2826.9, 1713.8, 1650.4, 1471.2, 1462.1, 1434.0, 1380.7, 1360.1, 1257.5, 1201.2, 1087.6, 1005.6, 984.5, 938.0, 893.2, 837.4, 810.0, 776.3, 747.7, 702.4, 663.4, 565.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.93$ (dt, $J = 7.0$, 1.5 Hz, 1H, H-5), 5.80–5.77 (m, 1H, H-11), 5.64 (brd, $J = 10.5$ Hz, 1H, H-10), 4.35 (brd, $J = 10.0$, 5.0 Hz, 1H, H-9), 4.28–4.27 (m, 1H, H-7), 4.23 (d, $J = 7.5$ Hz, 1H, H-17), 3.77–3.73 (m, 1H, H-15), 3.74 (s, 3H, C3–OCH_3), 3.51 (tt, $J = 12.5$, 3.5 Hz, 1H, H-13), 3.36 (s, 3H, C15–OCH_3), 2.90 (dd, $J = 13.5$, 12.0 Hz, 2H, -CH_2S-), 2.82 (td, $J = 14.0$, 3.5 Hz, 2H, -CH_2S-), 2.41 (t, $J = 5.5$ Hz, 2H, H-6a, H-6b), 2.11 (brqd, $J = 14.0$, 2.0 Hz, 1H, H-14), 2.00–2.09 (brm, 1H, H-16), 1.94 (brt, $J = 4.5$ Hz, 1H, H-12), 1.90–1.84 (m, 3H, H-8, $SCH_2CH_2CH_2S$), 1.83 (s, 3H, C4–CH_3), 1.68–1.60 (m, 2H, H-12,

H-14), 1.43 (ddd, $J = 14.0$, 10.0, 2.0 Hz, 1H, H-8), 1.10 (d, $J = 6.5$ Hz, 3H, C16-Me), 0.89 (s, 9H, *t*Bu), 0.13 (s, 3H, $SiCH_3$), 0.090 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.4$, 138.9, 130.3, 128.6, 123.5, 77.0, 69.1, 67.4, 63.6, 56.8, 52.3, 51.5, 41.1, 40.6, 37.5, 36.8, 31.2, 30.9, 30.7, 26.1, 25.8, 17.9; HRMS (FAB): calcd for $C_{28}H_{51}O_5S_2Si$ ($M + H^+$) 599.2947, found 599.2950.

Preparation of allylic alcohol 56: A solution of ester **55** (800 mg, 1.431 mmol) in methylene chloride (29 mL, 0.05 M) was cooled to $-78\,^\circ C$ and treated with Dibal-H (4.3 mL, 1 M soln in methylene chloride, 4.294 mmol) while stirred. After 1 h the reaction mixture was quenched with methanol (600 μL), and allowed to warm to room temperature. Saturated aqueous sodium potassium tartrate (30 mL) was added, and the mixture was stirred for 2 h to break the initially formed emulsion. The layers were separated, and the aqueous phase was extracted with methylene chloride (3 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, 15% ethyl acetate in petroleum ether) afforded pure alcohol **56** (750 mg, 96% yield) as a colorless oil. **56**: $R_f = 0.60$ (silica gel, 15% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -37.9$ ($c = 2.49$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3442.5$, 3029.1, 2928.5, 2897.6, 2854.3, 1466.1, 1461.4, 1422.3, 1378.2, 1250.5, 1186.6, 1081.7, 1005.2, 901.0, 836.5, 817.2, 810.5, 775.3, 700.8, 666.8 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.79-5.75$ (m, 1H, H-11), 5.64 (br td, $J = 10.5$, 2.0 Hz, 1H, H-10), 5.50 (br t, $J = 7.0$ Hz, 1H, H-5), 4.34 (br d, $J = 10.5$ Hz, 1H, H-9), 4.30 (d, $J = 6.5$ Hz, 1H, H-17), 4.10-4.06 (m, 1H, H-7), 4.00 (d, $J = 6.5$ Hz, 2H, H-3a, H-3b), 3.63 (td, $J = 7.5$, 4.5 Hz, 1H, H-15), 3.57 (tt, $J = 9.0$, 3.0 Hz, 1H, H-13), 3.34 (s, 3H, C15-OCH_3), 2.93 (ddd, $J = 14.5$, 12.0, 2.5 Hz, 1H, CH_2S), 2.89 (dd, $J = 12.0$, 2.5 Hz, 1H, CH_2S), 2.85-2.80 (m, 2H, CH_2S), 2.28 (br t, $J = 4.5$ Hz, 1H, H-12), 2.22 (dd, $J = 8.5$, 8.0 Hz, 1H, H-6), 2.20-2.17 (obs m, 1H, H-6), 2.00-1.97 (br m, 1H, H-16), 1.95-1.83 (m, 4H, $SCH_2CH_2CH_2S$, H-8, H-12), 1.76 (ddd, $J = 14.5$, 10.5, 1.5 Hz, 1H, H-14), 1.65 (obs ddd, $J = 14.5$, 4.5, 3.0 Hz, 1H, H-14), 1.66 (s, 3H, C4-CH_3), 1.30 (ddd, $J = 14.0$, 10.0, 1.5 Hz, 1H, H-8), 1.11 (d, $J = 7.0$ Hz, 3H, C16-Me), 0.89 (s, 9H, *t*Bu), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 136.8$, 130.7, 123.3, 121.4, 78.1, 69.6, 68.6, 68.6, 63.0, 57.1, 52.2, 41.0, 40.0, 36.7, 36.4, 31.4, 31.0, 30.6, 26.1, 25.8, 17.9, 15.1, 11.6, -4.3, -4.7; HRMS (FAB): calcd for $C_{27}H_{50}O_4S_2SiCs$ ($M + Cs^+$) 663.1974, found 663.1950.

Preparation of dithiane 14: A stirred solution of alcohol **56** (750 mg, 1.415 mmol) and 2,6-lutidine (660 μL, 5.660 mmol) in methylene chloride (48 mL, 0.033 M) was cooled to $-78\,^\circ C$ and treated with TBSOTf (651 μL, 2.830 mmol). The reaction mixture was allowed to warm to room temperature over 30 min, and quenched with saturated aqueous copper sulfate (50 mL). The mixture was stirred for 1 h at room temperature and the layers were separated. The aqueous phase was extracted with methylene chloride (3 × 30 mL), and the combined organic extracts were washed with brine (25 mL) and dried (Na_2SO_4). Concentration and purification by column chromatography (silica gel, 5% ethyl acetate in petroleum ether) gave dithiane **14** (838 mg, 92% yield) as a colorless oil. **14**: $R_f = 0.21$ (silica gel, 6% ether in petroleum ether); $[\alpha]_D^{25} = -28.6$ ($c = 0.34$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 2927.1$, 2854.8, 1723.6, 1678.8, 1461.8, 1360.4, 1252.1, 1187.5, 1073.1, 1005.5, 938.6, 836.5, 775.2, 699.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.77-5.73$ (m, 1H, H-11), 5.59 (td, $J = 10.5$, 1.6 Hz, 1H, H-10), 5.54 (dt, $J = 8.0$, 1.2 Hz, 1H, H-5), 4.34 (br d, $J = 10.5$ Hz, 1H, H-9), 4.20 (d, $J = 7.3$ Hz, 1H, H-17), 4.13 (m, 1H, H-7), 4.03 (s, 2H, H-3a, H-3b), 3.75 (dt, $J = 7.7$, 5.2 Hz, 1H, H-15), 3.54 (m, 1H, H-13), 3.40 (s, 3H, C15-OCH_3), 2.92-2.79 (m, 4H, -CH_2S-), 2.27-2.22 (m, 2H, H-6a, H-6b), 2.11-2.06 (m, 1H, $SCH_2CH_2CH_2S$), 2.04-1.95 (m, 1H, H-12), 1.93-1.80 (m, 5H, H-16, H-14, H-12, $SCH_2CH_2CH_2S$), 1.68-1.58 (m, 1H, H-8), 1.60 (s, 3H, C4-CH_3), 1.38 (ddd, $J = 14.3$, 10.5, 2.4 Hz, 1H, H-8), 1.08 (d, $J = 6.8$ Hz, 3H, C16-CH_3), 0.89 (s, 9H, *t*Bu), 0.88 (s, 9H, *t*Bu), 0.15 (s, 6H, $SiCH_3$), 0.07 (s, 6H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 136.0$, 130.8, 123.3, 120.9, 77.3, 69.4, 68.9, 68.2, 63.6, 56.9, 52.3, 41.2, 40.3, 37.0, 36.4, 31.3, 31.0, 30.8, 26.3, 26.0, 18.4, 18.1, 13.8, 11.3, -4.2, -4.6, -5.2; HRMS (FAB): calcd for $C_{33}H_{64}O_4Si_2S_2Na$ ($M + Na^+$) 667.3682, found 677.3680.

Preparation of acetal 57: A solution of benzoate **38** (0.3 g, 0.464 mmol) in dry methylene chloride (1 mL, 0.46 M) was cooled to $-78\,^\circ C$ and treated with Dibal-H (0.98 mL, 1 M solution in toluene, 0.980 mmol) while stirred. After 20 min the reaction mixture was quenched with methanol (0.2 mL) at $-78\,^\circ C$ and allowed to reach ambient temperature over 0.5 h while stirred. Saturated aqueous sodium potassium tartrate (2 mL) was added and the mixture was stirred for 2 h to break the initially formed emulsion. The layers were separated and the aqueous phase was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$). Concentration, followed by flash column chromatography (silica gel, 15% ethyl acetate in petroleum ether) afforded the pure diol (239 mg, 95% yield) as a white foam.

Diol: $R_f = 0.82$ (silica gel, 50% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -13.4$ ($c = 1.15$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3418.3$, 3029.1, 2965.6, 2926.7, 2856.2, 2359.7, 2339.9, 1496.0, 1453.8, 1379.8, 1351.3, 1260.2, 1203.2, 1152.8, 1098.6, 1084.1, 1028.1, 971.4, 906.6, 802.7, 735.6, 697.7, 668.0, 602.7, 520.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.36-7.29$ (m, 10H, ArH), 4.77 (d, $J = 12.0$ Hz, 1H, CHPh), 4.67 (d, $J = 12.0$ Hz, 1H, CHPh), 4.58 (d, $J = 12.0$ Hz, 2H, CH_2Ph), 4.03-3.98 (m, 1H, H-10), 3.94 (dd, $J = 10.0$, 2.5 Hz, 1H, H-6), 3.90 (dd, $J = 6.5$, 3.5 Hz, 1H, H-4), 3.76 (dd, $J = 10.5$, 7.0 Hz, 1H, H-1a), 3.77-3.69 (m, 1H, H-14), 3.67 (dd, $J = 10.5$, 4.0 Hz, 1H, H-1b), 3.55 (br dd, $J = 10.0$, 4.5 Hz, 1H, H-12), 3.34 (s, 3H, C12-OCH_3), 3.23 ((obs) td, $J = 7.0$, 4.0 Hz, 1H, H-2), 2.00-1.96 (m, 2H, H-13eq, H-5), 1.87-1.81 (m, 2H, H-11eq, H-3), 1.77-1.74 (m, 1H, H-9a), 1.74-1.69 (m, 1H, H-7), 1.67-1.64 (m, 1H, H-11ax), 1.62-1.57 (m, 3H, H-8a, H-8b, H-9b), 1.35-1.28 (m, 1H, H-13ax), 1.21 (d, $J = 6.0$ Hz, 3H, C14-CH_3), 1.00 (d, $J = 7.0$ Hz, 3H, C3-CH_3), 0.84 (d, $J = 7.0$ Hz, 3H, C5-CH_3), 0.79 (d, $J = 7.0$ Hz, 3H, C7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 128.3-127.4$ (10 carbons), 80.5, 80.3, 73.3, 73.2, 72.7, 72.3, 71.0, 64.6, 64.0, 55.0, 38.5, 37.5, 35.9, 34.6, 34.3, 29.0, 28.9, 28.8, 21.7, 16.3, 11.9, 10.3, 0.1; HRMS (FAB): calcd for $C_{33}H_{50}O_6Cs$ ($M + Cs^+$) 675.2662, found 675.2644.

Acetal 57: A solution of the diol (0.20 g, 0.369 mmol) and 2,2 dimethoxypropane (1.0 mL) in acetone (1.0 mL, 0.37 M) was treated with CSA (4.0 mg, 0.036 mmol) at room temperature while stirred for 2.5 h. The reaction mixture was diluted with ether (5 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), brine (1 × 5 mL) and dried ($MgSO_4$). Purification by column chromatography (silica gel, 20% ether in petroleum ether) yielded the desired acetonide **57** (0.204 g, 95%) as a white foam. **57**: $R_f = 0.55$ (silica, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -14.3$ ($c = 1.02$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3029.3$, 2967.4, 2928.6, 2855.8, 1724.5, 1496.1, 1453.4, 1377.2, 1306.1, 1260.4, 1224.3, 1184.1, 1153.0, 1097.0, 1045.0, 1027.0, 998.3, 926.2, 882.2, 801.8, 734.4, 696.8, 608.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.35-7.26$ (m, 10H, ArH), 4.87 (d, $J = 12.0$ Hz, 1H, CHPh), 4.55 (d, $J = 12.0$ Hz, 2H, CH_2Ph), 4.49 (d, $J = 12.0$ Hz, 1H, CHPh), 4.11 (td, $J = 5.0$, 2.5 Hz, 1H, H-2), 4.03-3.96 (m, 1H, H-10), 3.81-3.78 (dd, $J = 10.5$, 3.5 Hz, 1H, H-4), 3.72-3.65 (m, 1H, H-14), 3.71 (dd, $J = 9.5$, 6.5 Hz, 1H, H-1a), 3.56-3.48 (m, 1H, H-12), 3.55 (dd, $J = 9.5$, 5.0 Hz, 1H, H-1b), 3.34 (s, 3H, C12-OCH_3), 3.11 (br t, $J = 6.0$ Hz, 1H, H-6), 1.98-1.96 (m, 1H, H-13eq), 1.87-1.79 (m, 3H, H-11eq, H-3, H-9a), 1.76-1.72 (m, $J = 6.5$, 3.5 Hz, 1H, H-5), 1.61-1.55 (m, 4H, H-7, H-8a, H-8b, H-11ax), 1.54-1.47 (m, 1H, H-9b), 1.31 (s, 3H, CH_3-acetonide), 1.30-1.28 (m, 1H, H-13ax), 1.26 (s, 3H, CH_3-acetonide), 1.20 (d, $J = 6.5$ Hz, 3H, C14-CH_3), 0.94 (d, $J = 7.0$ Hz, 3H, C3-CH_3), 0.87 (d, $J = 6.5$ Hz, 3H, C5-CH_3), 0.83 (d, $J = 7.0$ Hz, 3H, C7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 128.3-126.9$ (10 carbons), 100.6, 78.9, 76.7, 76.4, 73.4, 73.3, 72.6, 72.3, 69.4, 64.0, 55.0, 38.8, 37.0, 35.9, 34.8, 34.7, 29.3, 29.1, 28.2, 25.8, 23.7, 21.8, 15.7, 12.7, 8.9, 0.1; HRMS (FAB): calcd for $C_{36}H_{54}O_6Cs$ ($M + Cs^+$) 715.2975, found 715.2960.

Preparation of MEM ether 58: A solution of alcohol **38** (281 mg, 0.435 mmol) in methylene chloride (1.5 mL, 0.3 M) was treated with 4-DMAP (13 mg, 0.109 mmol), iPr_2NEt (777 μL, 4.35 mmol) and MEMCl (447 μL, 3.91 mmol) at room temperature. After stirring for 48 h, the reaction mixture was diluted with ether (50 mL) and washed with 10% aqueous HCl (2 × 20 mL), water (2 × 10 mL), and brine (10 mL). Concentration and purification by column chromatography (silica gel, 10% ethyl acetate in petroleum ether) afforded MEM ether **58** (280 mg, 90% yield) as a pale yellow oil. **58**: $R_f = 0.14$ (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -16.5$ ($c = 1.10$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3030.0$, 2965.4, 2926.7, 2874.6, 2360.6, 2340.0, 1714.2, 1601.4, 1583.8, 1495.9, 1452.1, 1380.6, 1364.1, 1312.4, 1273.1, 1199.3, 1176.0, 1152.9, 1108.8, 1070.4, 1027.2, 949.6, 849.0, 802.7, 736.3, 712.3, 698.4, 668.5, 611.8, 548.5, 464.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.06-8.04$ (m, 2H, ArH), 7.58-7.55 (m, 1H, ArH), 7.44 (t, $J = 7.5$ Hz, 2H, ArH), 7.32-7.23 (m, 10H, ArH), 5.66 (d, $J = 10.0$ Hz, 1H, H-4), 4.78 (d, $J = 6.5$ Hz, 1H, OCHHO), 4.72 (d, $J = 6.5$ Hz, 1H, OCHHO), 4.61 (d, $J = 11.5$ Hz, 1H, CHHPh), 4.52 (d, $J = 11.0$ Hz, 1H, CHHPh), 4.56 (dd, $J = 12.0$ Hz, 2H, CH_2Ph), 3.97-3.92 (m, 1H, H-10), 3.72-3.68 (m, 2H, H-2, H-14), 3.64 (dd, $J = 9.5$, 5.5 Hz, 1H, H-1a), 3.53 (dd, $J = 9.5$, 5.5 Hz, 1H, H-1b), 3.54-3.49 (m, 2H, H-12, OCHHCH$_2$O), 3.41-3.39 (m, 2H, OCH_2CH_2O), 3.33 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.29-3.27 (m, 1H, OCHHCH$_2$O), 3.12 (dd, $J = 8.0$, 3.5 Hz, 1H, H-6), 2.16-2.08 (m, 2H, H-3, H-5), 1.98-1.95 (m, 1H, H-13eq), 1.87-1.78 (m, 3H, H-7, H-9a, H-11eq), 1.56 (ddd, $J = 13.0$, 10.5, 6.0 Hz, 1H, H-11ax), 1.47-1.41 (m, 1H, H-9b), 1.26-1.22 (m, 2H, H-8a, H-8b), 1.19 (d, $J = 6.0$ Hz, 3H, C14-CH_3), 1.17-1.12 (m, 1H, H-13ax), 1.04 (d, $J = 7.0$ Hz, 3H, C3-CH_3), 0.97 (d, $J = 7.0$ Hz, 3H, C5-CH_3), 0.95 (d, $J = 7.0$ Hz, 3H, C7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.4$, 147.5, 144.0, 132.5, 129.0, 128.5-127.5 (15 carbons), 91.5, 86.7, 81.7, 79.0, 77.5, 73.2, 67.5, 64.2, 58.7, 55.8, 51.2, 49.0, 46.5, 41.0, 37.5, 34.9, 34.5, 34.4, 29.2, 27.5, 21.8, 21.7, 16.7, 15.5; HRMS (FAB): calcd for $C_{44}H_{62}O_9Cs$ ($M + Cs^+$) 867.3448, found 867.3421.

Preparation of triol 60: A solution of benzoate **58** (0.303 g, 0.413 mmol) in toluene (2 mL, 0.21 M) was cooled to $-78\,^\circ C$ and treated with Dibal-H (0.867 mL, 1 M solution in toluene, 0.867 mmol) while stirred. After 20 min the reaction mixture was quenched with methanol (0.2 mL) at $-78\,^\circ C$ and the solution was allowed to reach ambient temperature while stirred over 0.5 h. Saturated aqueous sodium potassium tartrate (2 mL) was added and the mixture was stirred for 2 h to break the initially formed emulsion. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), and dried ($MgSO_4$). The crude alcohol (**59**) was resuspended in anhydrous ethanol (10 mL, 0.04 M) with 10% palladium on carbon (30 mg, 0.041 mmol) and stirred at room temperature for 24 h. The reaction mixture was filtered through Celite and concentrated. Purification by column chromatography (silica gel, 2% methanol in ether) gave triol **60** (145 mg, 78% yield) as a pale yellow oil. **60**: $R_f = 0.72$ (silica gel, ethyl acetate); $[\alpha]_D^{25} = -11.1$ ($c = 1.01$, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max} = 3433.0$, 2966.0, 2935.2, 2359.6, 1454.1, 1380.9, 1260.5, 1198.9,

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1153.7, 1100.1, 1082.3, 1037.1, 975.8, 850.5, 799.9, 667.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.79 (dd, J = 7.0 Hz, 2H, OCH_2O), 4.04 (ddd, J = 10.5, 4.0, 2.0 Hz, 1H, H-4), 4.01–3.97 (m, 1H, H-10), 3.96–3.88 (m, 3H, H-1a, H-1b, H-2), 3.73–3.67 (m, 3H, OCH_2CH_2O, H-14), 3.63–3.50 (m, 3H, OCH_2CH_2O, H-12), 3.41 (s, 3H, OCH_3), 3.39 (dd, J = 8.0, 3.5 Hz, 1H, H-6), 3.34 (s, 3H, OCH_3), 2.01–1.95 (m, 1H, H-13eq), 1.91 (tdd, J = 7.0, 4.0, 3.0 Hz, 1H, H-3), 1.87–1.83 (m, 1H, H-5), 1.82–1.75 (m, 3H, H-11eq, H-9a, H-7), 1.61 (ddd, J = 12.5, 10.0, 5.5 Hz, 1H, H-11ax), 1.48–1.45 (m, 1H, H-9b), 1.27–1.21 (m, 2H, H-8a, H-8b), 1.21 (d, J = 6.0 Hz, 3H, C14–CH_3), 1.21–1.16 (m, 1H, H-13eq), 0.96 (d, J = 7.0 Hz, 3H, C3–CH_3), 0.87 (d, J = 7.0 Hz, 3H, C5–CH_3), 0.80 (d, J = 7.0 Hz, 3H, C7–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 98.3, 88.0, 74.7, 73.2, 71.8, 71.5, 68.2, 64.7, 64.2, 59.2, 55.3, 38.5, 37.7, 36.0, 34.9, 34.6, 29.5, 26.5, 21.7, 17.3, 12.1, 9.4; HRMS (FAB): calcd for $C_{23}H_{46}O_6Cs$ (M + Cs^+) 583.2247, found 583.2263.

Preparation of silyl ether 61: A solution of triol **60** (73 mg, 0.16 mmol) in DMF (500 µL, 0.32 M) at room temperature was treated sequentially with imidazole (26 mg, 0.38 mmol) and TBDPSCl (46 µL, 0.19 mmol). The reaction mixture was stirred at room temperature for 2.5 h, diluted with ether (10 mL) and washed sequentially with 5% aqueous HCl (2 × 10 mL), water (2 × 10 mL), and brine (10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by column chromatography (silica gel, 80% ether in petroleum ether) to give pure diol **61** (64 mg, 60% yield) as a yellow oil. **61**: R_f = 0.34 (silica gel, 50% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −12.8 (c = 1.21, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3482.6, 3069.7, 3047.6, 2931.1, 2856.6, 2360.2, 2339.8, 1458.2, 1427.6, 1381.0, 1362.0, 1260.3, 1197.9, 1186.6, 1153.7, 1111.5, 1039.0, 852.5, 823.1, 801.2, 741.5, 703.0, 613.4, 505.2, 491.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75–7.65 (m, 5H, ArH), 7.37–7.47 (m, 5H, ArH), 4.80 (d, J = 7.0 Hz, 1H, OC*H*HO), 4.78 (d, J = 7.5 Hz, 1H, OCH*H*O), 4.22–4.18 (m, 1H, H-10), 3.98 (d, J = 9.5 Hz, 1H, H-4), 3.92–3.82 (m, 1H, H-2), 3.75 (dd, J = 10.5, 7.5 Hz, 1H, H-1a), 3.67 (dd, J = 10.5, 4.5 Hz, 1H, H-1b), 3.69–3.61 (m, 1H, H-14), 3.59–3.49 (m, 5H, OCH_2CH_2O, H-12), 3.40 (dd, J = 7.5, 3.5 Hz, 1H, H-6), 3.38 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.21 (brs, 1H, OH), 2.00–1.96 (m, 1H, H-13eq), 1.83–1.76 (m, 4H, H-3, H-5, H-9a, H-11eq), 1.62–1.57 (m, 2H, H-11ax, H-7), 1.42–1.49 (m, 1H, H-9b), 1.26–1.22 (m, 2H, H-8a, H-8b), 1.20 (d, J = 6.5 Hz, 3H, C14–CH_3), 1.21–1.17 (m, 1H, H-13ax), 1.05 (s, 9H, *t*Bu), 0.96 (d, J = 7.0 Hz, 3H, C3–CH_3), 0.86 (d, J = 7.0 Hz, 3H, C5–CH_3), 0.72 (d, J = 7.0 Hz, 3H, C7–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.6 (5 carbons), 133.5, 129.6 (2 carbons), 127.7 (5 carbons), 98.2, 88.2, 73.2, 72.3, 71.8, 70.3, 68.3, 66.5, 64.7, 59.1, 55.3, 38.6, 37.6, 35.7, 34.8, 34.7, 29.5, 26.8 (4 carbons), 21.8, 19.2, 17.2, 10.5, 9.6; HRMS (FAB): calcd for $C_{39}H_{64}O_8SiCs$ (M + Cs^+) 821.3425, found 821.3406.

Preparation of acetonide 62: A solution of diol **61** (54 mg, 0.078 mmol), and 2,2-dimethoxypropane (1.5 mL) in acetone (1.5 mL, 0.05 M) was treated with CSA (2.0 mg, 0.018 mmol) at room temperature and stirred for 2.5 h. The reaction mixture was diluted with ether (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and brine (1 × 5 mL), and dried ($MgSO_4$). Purification by column chromatography (silica gel, 20% ether in petroleum ether) yielded the desired acetonide **62** (59 mg, 95%) as a white foam. **62**: R_f = 0.16 (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −13.7 (c = 1.35, $CHCl_3$); IR (KBr): $\tilde{\nu}_{max}$ = 3070.1, 2930.1, 2874.1, 2856.9, 2820.2, 1589.2, 1460.8, 1427.9, 1379.7, 1362.4, 1259.9, 1223.9, 1198.3, 1178.1, 1153.1, 1112.0, 1084.3, 1042.4, 1020.6, 998.0, 973.9, 935.3, 908.0, 886.8, 858.6, 823.0, 794.4, 740.0, 702.6, 689.5, 668.0, 613.6, 531.8, 505.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 4H, ArH), 7.39–7.36 (m, 6H, ArH), 4.76–4.76 (m, 2H, OCH_2O), 4.01–3.98 (m, 1H, H-10), 3.83–3.80 (m, 1H, H-2), 3.79 (dd, J = 11.0, 4.5 Hz, 1H, H-1a), 3.71–3.61 (m, 3H, H-1b, H-12, H-14), 3.56–3.54 (m, 4H, OCH_2CH_2O), 3.50 (d, J = 7.5 Hz, 1H, H-6), 3.38 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.29 (dd, J = 9.5, 1.5 Hz, 1H, H-4), 2.01–1.95 (m, 1H, H-13eq), 1.90–1.79 (m, 3H, H-3, H-9a, H-11eq), 1.73–1.67 (m, 1H, H-5), 1.63–1.57 (m, 2H, H-11ax, H-7), 1.45–1.39 (m, 1H, H-9b), 1.31–1.27 (m, 2H, H-8a, H-8b), 1.25 (s, 6H, CH_3-acetonide), 1.24–1.20 (m, 1H, H-13ax), 1.21 (d, J = 6.5 Hz, 3H, C14–CH_3), 1.05 (s, 9H, *t*Bu), 1.00 (d, J = 6.5 Hz, 3H, C3–CH_3), 0.85 (d, J = 7.0 Hz, 3H, C5–CH_3), 0.79 (d, J = 7.0 Hz, 3H, C7–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.6 (5 carbons), 133.8, 129.6 (2 carbons), 127.6 (5 carbons), 100.2, 98.2, 87.2, 73.3, 73.2, 71.7, 69.9, 67.3, 64.6, 63.5, 59.0, 55.2, 39.6, 38.5, 35.0, 34.8, 34.4, 29.7, 26.8 (3 carbons), 25.8, 25.3, 24.0, 21.7, 19.2, 17.5, 11.8, 10.5; HRMS (FAB): calcd for $C_{42}H_{68}O_8SiCs$ (M + Cs^+) 861.3738, found 861.3738.

Preparation of hydroxy dithiane 63: Azeotropically dried (benzene, 3 × 5 mL) dithiane **14** (250 mg, 0.387 mmol) was dissolved in THF (774 µl, 0.5 M), then freshly distilled HMPA (270 µL, 1.548 mmol) was added, and the mixture was cooled to −78 °C. The reaction mixture was treated dropwise with *t*BuLi (464.5 µL, 1 M solution in hexanes, 0.464 mmol) and stirred for 15 min at −78 °C. A solution of azeotropically dried (benzene, 3 × 5 mL) cyclic sulfate **13** (298 mg, 0.464 mmol) in THF (775 µL) was added to the reaction mixture and the mixture was stirred for an additional 30 min at −78 °C. The reaction was quenched with methanol (1 mL) and concentrated. Purification by preparative thin-layer chromatography (1000 µm silica gel plate, 6% MeOH in ethyl acetate) gave the desired sulfate dithiane, plus recovered dithiane **14** (63.7 mg). The sulfate salt isolated above was resuspended in dry THF (1.5 mL, 0.25 M) and treated with 30% aqueous H_2SO_4 (15 µL). The reaction mixture was stirred at 23 °C for 1 h, and quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with ethyl acetate (4 × 5 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Purification by preparative thin-layer chromatography (1000 µm silica gel plate, 15% ethyl acetate in petroleum ether) afforded hydroxy dithiane **63** (234 mg, 50% yield, 72% based on recovered starting material) as a white foam. **63**: R_f = 0.61 (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −2.4 (c = 1.35, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3510.6, 3062.2, 3030.9, 2930.1, 2896.6, 2855.3, 1715.6, 1690.8, 1601.6, 1583.9, 1471.5, 1462.0, 1382.7, 1360.8, 1313.8, 1275.1, 1254.8, 1177.0, 1153.5, 1084.5, 1027.0, 1005.1, 986.9, 927.8, 909.8, 836.0, 812.1, 775.0, 733.5, 711.5, 695.7, 668.5, 618.0, 519.6, 485.3, 485.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.0 Hz, 2H, ArH), 7.52 (t, J = 7.5 Hz, 1H, ArH), 7.41 (t, J = 7.5 Hz, 2H, ArH), 5.75 (ddd, J = 10.0, 5.5, 3.0 Hz, 1H, H-11), 5.62 (brd, J = 10.0 Hz, 1H, H-10), 5.50 (t, J = 6.5 Hz, 1H, H-5), 5.36 (brd, J = 10.0 Hz, 1H, H-21), 4.32 (brd, J = 9.5 Hz, 1H, H-9), 4.14–4.11 (m, 2H, H-7, H-19), 4.01 (s, 2H, H-3a, H-3b), 3.95–3.89 (m, 1H, H-27), 3.88 (brdd, J = 9.5, 2.5 Hz, 1H, H-15), 3.62 (qdd, J = 6.5, 4.0, 2.5 Hz, 1H, H-31), 3.51–3.45 (m, 1H, H-29), 3.48 (dd, J = 6.5, 1.5 Hz, 1H, H-23), 3.37–3.30 (m, 1H, H-13), 3.32 (s, 3H, C29–OCH_3), 3.26 (s, 3H, C15–OCH_3), 2.67–2.60 (m, 2H, SCH_2), 2.56 (brt, J = 5.5 Hz, 2H, SCH_2), 2.18–2.06 (m, 3H, H-6a, H-6b, H-22), 2.04–1.91 (m, 5H, $SCH_2CH_2CH_2S$, H-12eq, H-12ax, H-30eq), 1.85–1.71 (m, 5H, H-14a, H-14b, H-20, H-26a, H-28eq), 1.68–1.59 (m, 1H, H-24), 1.58–1.48 (m, 3H, H-8a, H-16, H-28ax), 1.54 (s, 3H, C4–CH_3), 1.45 (dd, J = 10.0, 2.5 Hz, 1H, H-18a), 1.42–1.39 (m, 1H, H-25a), 1.38 (dd, J = 10.0, 2.5 Hz, 1H, H-18b), 1.37–1.33 (m, 1H, H-8b), 1.32–1.28 (m, 1H, H-25b), 1.28–1.22 (m, 1H, H-26b), 1.18 (d, J = 6.5 Hz, 3H, C31–CH_3), 1.17–1.10 (m, 1H, H-30ax), 1.05 (d, J = 7.0 Hz, 3H, C23–CH_3), 1.05 (d, J = 6.5 Hz, 3H, C16–CH_3), 0.99 (d, J = 6.5 Hz, 3H, C24–CH_3), 0.91 (s, 9H, 2 × *t*Bu), 0.87 (s, 18H, 2 × *t*Bu), 0.12 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.2, 135.6, 132.7, 130.6, 130.4–128.2 (Ar, 6 carbons), 123.3, 120.3, 78.7, 77.2, 73.1, 72.1, 69.2, 68.6, 68.0, 66.6, 64.3, 64.0, 58.4, 55.6, 55.1, 43.9, 42.4, 41.1, 40.1, 39.6, 38.8, 38.7, 36.4, 35.7, 34.7, 31.0, 29.7, 26.9, 26.2, 25.8, 26.2, 24.8, 21.7, 17.9, 18.0, 17.9, 16.8, 13.7, 10.4, 9.5, 8.4, −3.7, −4.3, −4.4, −4.7, −5.4; HRMS (FAB): calcd for $C_{65}H_{118}O_{10}Si_3S_2Cs$ (M + Cs^+) 1339.6529, found 1339.6561.

Preparation of β-hydroxy ketone 64: NBS (35.4 mg, 0.199 mmol) and $AgClO_4$ (45.4 mg, 0.219 mmol) were dissolved in 10% aqueous acetone (9.9 mL, 0.01 M) and cooled to 0 °C. Dithiane **63** (120 mg, 0.0995 mmol) in acetone (1.0 mL) was added and the mixture was vigorously stirred at 0 °C for 30 s. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and warmed to room temperature. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solution was then filtered through a short plug of Celite and concentrated. The crude product was purified by column chromatography (silica gel, 15% ethyl acetate in petroleum ether) to afford pure β-hydroxy ketone **64** (100 mg, 91% yield) as a white foam. **64**: R_f = 0.52 (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −14.0 (c = 0.89, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3502.8, 3031.8, 2926.9, 2854.7, 2359.8, 1715.8, 1699.9, 1462.1, 1418.1, 1381.7, 1360.9, 1314.0, 1275.7, 1255.4, 1186.7, 1176.9, 1153.3, 1084.9, 1026.9, 1005.9, 937.6, 897.1, 835.9, 812.1, 775.1, 711.5, 668.0, 574.1, 502.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.0 Hz, 2H, ArH), 7.56 (t, J = 7.5 Hz, 1H, ArH), 7.44 (t, J = 7.5 Hz, 2H, ArH), 5.74 (ddd, J = 10.0, 5.0, 2.5 Hz, 1H, H-11), 5.62 (brd, J = 10.0 Hz, 1H, H-10), 5.42 (brt, J = 7.0 Hz, 1H, H-5), 5.34 (d, J = 10.0 Hz, 1H, H-21), 4.31 (brd, J = 9.5 Hz, 1H, H-9), 4.14–4.12 (m, 1H, H-19), 3.98 (s, 2H, H-3a, H-3b), 3.96–3.93 (m, 2H, H-7, H-27), 3.68–3.64 (m, 1H, H-15), 3.62 (qdd, J = 6.5, 3.5, 3.0 Hz, 1H, H-31), 3.59–3.54 (m, 1H, H-13), 3.48 (dddd, J = 10.0, 10.0, 6.0, 4.5 Hz, 1H, H-29), 3.43 (dd, J = 6.5, 2.0 Hz, 1H, H-23), 3.32 (s, 3H, C29–OCH_3), 3.24 (s, 3H, C15–OCH_3), 2.85 (dd, J = 17.0, 8.0 Hz, 1H, H-18), 2.67 (qd, J = 7.0, 4.5 Hz, 1H, H-16), 2.46 (dd, J = 17.0, 4.5 Hz, 1H, H-18), 2.19 (t, J = 6.5 Hz, 2H, H-6a, H-6b), 2.09–2.07 (m, 1H, H-22), 1.98–1.94 (m, 1H, H-30eq), 1.95–1.92 (m, 1H, H-12eq), 1.91–1.89 (m, 1H, H-12ax), 1.87–1.83 (m, 1H, H-20), 1.82–1.78 (m, 1H, H-26a), 1.77–1.70 (m, 3H, H-28eq, H-14a, H-14b), 1.65–1.60 (m, 2H, H-8a, H-24), 1.58–1.51 (m, 1H, H-28ax), 1.55 (s, 3H, C4–CH_3), 1.41–1.29 (m, 4H, H-8b, H-25a, H-25b, H-26b), 1.17 (d, J = 6.0 Hz, 3H, C31–CH_3), 1.15–1.11 (m, 1H, H-30ax), 1.06 (d, J = 7.5 Hz, 3H, C20–CH_3), 1.04 (d, J = 7.5 Hz, 3H, C16–CH_3), 0.95 (d, J = 6.5 Hz, 3H, C22–CH_3), 0.92 (d, J = 6.5 Hz, 3H, C24–CH_3), 0.89 (s, 9H, *t*Bu), 0.88 (s, 9H, *t*Bu), 0.870 (s, 9H, *t*Bu), 0.09 (3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.04 (s, 6H, 2 × $SiCH_3$), 0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.7, 167.0, 135.5, 133.1, 130.5, 130.0–128.3 (Ar, 6 carbons), 123.3, 120.2, 78.5, 78.3, 73.1, 72.0, 69.2, 68.6, 68.2, 65.4, 64.3, 63.9, 56.9, 55.1, 49.5, 46.2, 40.2, 39.4, 39.2, 38.7, 36.8, 36.4, 36.1, 34.7, 30.5, 29.7, 26.9, 26.2, 25.8, 21.7, 18.5, 18.3, 18.0, 16.6, 13.6, 10.8, 10.5, 9.6, −3.9, −4.2, −4.4, −4.8, −5.4; HRMS (FAB): calcd for $C_{62}H_{112}O_{11}Si_3Cs$ (M + Cs^+) 1249.6567, found 1249.6531.

Preparation of diol 65 and *p*-methoxybenzylidene acetal 66: A solution of β-hydroxy ketone **64** (75 mg, 0.067 mmol) in THF (0.7 mL, 0.01 M) was cooled to 0 °C and treated with nBu_3B (75 µL of 1 M solution in THF, 0.075 mmol). Air (3 mL) was slowly bubbled through the solution. After stirring at room temperature for 2 h the reaction mixture was cooled to −78 °C and treated with $NaBH_4$ (5.5 mg, 0.148 mmol) with continued stirring for 8 h. The reaction mixture was then gradu-

ally warmed to 0 °C and quenched by treatment with 30% H_2O_2 (0.2 mL, 1.7 mmol) and aqueous 2.5 M NaOH (0.1 mL, 0.25 mmol). After stirring at 0 °C for 3 h, the reaction mixture was diluted with brine (1 mL) and water (1 mL), and extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Purification by preparative thin-layer chromatography (1000 μm silica gel plate, 20% ethyl acetate in petroleum ether) afforded the pure diol **65** (69 mg, 92% yield) as a white foam.

Acetal 66: A solution of azeotropically dried (benzene, 3 × 5 mL) diol **65** (181 mg, 0.169 mmol) and *p*-methoxybenzaldehyde dimethyl acetal (55.1 μL, 0.324 mmol) in methylene chloride (6.5 mL, 0.025 M) at 0 °C was treated with CSA (3.8 mg, 0.016 mmol). The reaction mixture was stirred for 3 h at 0 °C, then quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by column chromatography (silica gel, 10% ethyl acetate in petroleum ether) yielding the *p*-methoxy benzylidene acetal **66** (185 mg, 93% yield) as a white foam. **66**: $R_f = 0.67$ (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -40.3$ ($c = 4.56$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3020.2, 2928.5, 2855.7, 1721.3, 1615.2, 1587.4, 1518.0, 1470.9, 1462.4, 1383.0, 1360.4, 1312.7, 1272.1, 1250.2, 1175.4, 1152.3, 1083.0, 1037.9, 938.2, 897.3, 836.1, 811.7, 775.8, 738.5, 710.8, 672.1, 600.8, 519.4\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 7.5$ Hz, 2H, ArH), 7.53 (t, $J = 7.5$ Hz, 1H, ArH), 7.40 (d, $J = 9.0$ Hz, 2H, ArH), 7.39 (t, $J = 7.0$ Hz, 2H, ArH), 6.83 (d, $J = 9.0$ Hz, 2H, ArH), 5.78–5.74 (brm, 1H, H-11), 5.63 (brd, $J = 10.5$ Hz 1H, H-10), 5.55 (d, $J = 8.5$ Hz, 1H, H-21), 5.41 (brt, $J = 7.5$ Hz, 1H, H-5), 5.27 (s, 1H, OC*H*ArO), 4.27 (brd, $J = 8.0$ Hz, 1H, H-9), 3.98 (s, 2H, H-3a, H-3b), 3.93–3.91 (m, 3H, H-7, H-15, H-27), 3.80 (s, 3H, ArOMe), 3.81 (obs t, 1H, H-19), 3.70 (brt, $J = 6.5$ Hz, 1H, H-17), 3.65–3.58 (m, 2H, H-13, H-31), 3.53 (dd, $J = 7.5$, 2.0 Hz, 1H, H-23), 3.51–3.45 (m, 1H, H-29), 3.32 (s, 3H, C29–OCH_3), 3.32 (s, 3H, C15–OCH_3), 2.12–2.10 (m, 2H, H-6), 1.98–1.90 (m, 6H, H-12, H-16, H-22, H-30), 1.81–1.70 (m, 5H, H-14, H-26a, H-28, H-20), 1.62–1.48 (m, 5H, H-8a, H-18a, H-18b, H-28, H-24), 1.54 (s, 3H, C4–CH_3), 1.47–1.40 (m, 3H, H-8b, H-25a, H-26b), 1.29–1.26 (m, 1H, H-25b), 1.17 (d, $J = 6.5$ Hz, 3H, C31–CH_3), 1.13 (d, $J = 12.5$ Hz, 1H, H-30), 1.06 (d, $J = 7.0$ Hz, 3H, C20–CH_3), 1.02 (d, $J = 7.0$ Hz, 3H, C16–CH_3), 0.93 (d, 6.5 Hz, 3H, C22–CH_3), 0.89 (s, 9H, *t*Bu), 0.88 (d, $J = 7.0$ Hz, 3H, C24–CH_3), 0.86 (s, 9H, *t*Bu), 0.84 (s, 9H, *t*Bu), 0.02 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.04 (s, 6H, 2 × $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), −0.05 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.6, 159.3, 135.8, 132.5, 131.6, 130.7, 130.6, 129.5, 128.2, 127.3, 122.2, 120.3, 113.1, 100.1, 78.9, 78.1, 75.9, 75.7, 75.6, 73.1, 72.1, 69.2, 68.6, 68.3, 64.4, 64.3, 58.1, 55.1, 42.0, 40.5, 40.4, 39.9, 38.8, 37.7, 36.3, 35.9, 34.7, 32.5, 30.7, 29.7, 26.9, 26.3, 25.8, 21.7, 18.5, 17.9, 16.9, 13.6, 11.0, 10.7, 8.2, −3.4, −4.5, −4.5, −4.9, −5.4$; HRMS (FAB): calcd for $C_{70}H_{120}O_{12}Si_3Cs$ ($M + Cs^+$) 1369.7142, found 1369.7195.

Preparation of alcohol 67: The benzoate **66** (308.8 mg, 0.250 mmol) was dissolved in methylene chloride (10 mL, 0.025 M) and cooled to −78 °C. Dibal-H (500 μL, 1 M solution in toluene, 0.500 mmol) was added to the solution at that temperature with continued stirring for 4 h. The reaction mixture was quenched with methanol (1.0 mL) at −78 °C and warmed to room temperature. Saturated aqueous sodium potassium tartrate (2 mL) was added, and the mixture was stirred for 2 h to break the initially formed emulsion. The layers were separated, and the aqueous phase was extracted with methylene chloride (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$). Concentration followed by column chromatography (silica gel, 20% ethyl acetate in petroleum ether) afforded pure alcohol **67** [250 mg, 97% yield based on recovered starting material (52 mg)] as a white foam. **67**: $R_f = 0.31$ (silica, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -38.0$ ($c = 4.17$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3506.5, 3030.7, 2929.1, 2856.1, 1726.1, 1658.0, 1614.9, 1589.0, 1517.9, 1462.4, 1380.7, 1302.1, 1250.5, 1169.9, 1153.1, 1082.5, 1038.1, 938.2, 899.7, 836.1, 775.5, 699.6\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 8.5$ Hz, 2H, ArH), 6.59 (d, $J = 8.5$ Hz, 2H, ArH), 5.74 (brm, 1H, H-11), 5.64 (brd, $J = 10.0$ Hz 1H, H-10), 5.54 (s, 1H, OC*H*ArO), 5.43 (t, $J = 6.5$ Hz, 1H, H-5), 4.29 (brd, $J = 11.0$ Hz, 1H, H-9), 4.30–4.27 (m, 1H, H-7), 4.11 (d, $J = 10.0$ Hz, 1H, H-21), 3.99 (s, 2H, H-3a, H-3b), 3.98–3.91 (m, 3H, H-15, H-19, H-27), 3.80 (s, 3H, $ArOCH_3$), 3.79 (brt, $J = 5.0$ Hz, 1H, H-17), 3.66–3.61 (m, 2H, H-13, H-31), 3.60 (dd, $J = 6.0$, 4.0 Hz, 1H, H-23), 3.52–3.50 (m, 1H, H-29), 3.38 (s, 3H, C29–OCH_3), 3.33 (s, 3H, C15–OCH_3), 2.14 (brs, 2H, H-6), 1.98–1.90 (m, 6H, H-12, H-16, H-22, H-30), 1.82–1.72 (m, 5H, H-14a, H-14b, H-20, H-26a, H-28a), 1.65–1.50 (m, 7H, H-8a, H-18a, H-18b, H-24, H-25a, H-26b, H-28b), 1.56 (s, 3H, C4–CH_3), 1.41 (m, 1H, H-8b), 1.29–1.25 (m, 1H, H-25b), 1.18 (d, $J = 6.0$ Hz, 3H, C31–CH_3), 1.13 (d, $J = 12.5$ Hz, 1H, H-30), 1.00 (d, $J = 7.0$ Hz, 3H, C20–CH_3), 0.95 (d, $J = 7.0$ Hz, 3H, C16–CH_3), 0.92 (d, 6.0 Hz, 3H, C22–CH_3), 0.92 (s, 9H, *t*Bu), 0.90 (s, 9H, *t*Bu), 0.88 (d, $J = 7.0$ Hz, 3H, C24–CH_3), 0.86 (s, 9H, *t*Bu), 0.13 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.05 (s, 6H, 2 × $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.4, 135.8, 132.0, 130.6, 127.2, 123.2, 120.4, 113.2, 100.2, 82.2, 78.5, 76.2, 75.8, 73.1, 71.9, 70.7, 69.1, 68.7, 68.3, 64.6, 64.4, 58.3, 55.1, 42.1, 40.8, 40.4, 38.5, 37.9, 37.4, 36.0, 35.2, 34.7, 31.8, 30.7, 30.0, 29.5, 28.9, 26.0, 25.8, 21.6, 18.2, 17.9, 16.1, 13.6, 11.2, 10.1, 8.2, −0.2, −3.9, −4.4, −4.9, −5.4$; HRMS (FAB): calcd for $C_{63}H_{116}O_{11}Si_3Cs$ ($M + Cs^+$) 1265.6880, found 1265.6937.

Preparation of diol 68: A solution of alcohol **67** (250 mg, 0.212 mmol) in methylene chloride (20 mL, 0.011 M) was cooled to 0 °C and treated with a stock solution of HF·pyr. (prepared by adding 5 mL of HF·pyr. to 20 mL of CH_2Cl_2 and 5 mL pyr. at 0 °C) and stirring for 1.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ until slightly basic (ca. 200 mL) and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with methylene chloride (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The crude reaction mixture was placed under vacuum for 2 h to remove excess pyridine and purified by column chromatography (silica gel, 25% ethyl acetate in petroleum ether) to afford diol **68** (191 mg, 85% yield) and recovered starting material (15 mg) as the only two products isolated (90% yield, based on recovered starting material). **68**: $R_f = 0.18$ (silica gel, 30% ethyl acetate in petroleum ether); $[\alpha]_D^{25} = -47.6$ ($c = 0.53$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3479.9, 2928.7, 2856.9, 1736.1, 1616.3, 1516.3, 1462.2, 1380.9, 1252.0, 1087.4, 1034.1, 834.6, 776.1, 737.5, 593.2\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 8.5$ Hz, 2H, ArH), 6.87 (d, $J = 8.5$ Hz, 2H, ArH), 5.76 (md, $J = 10.0$ Hz, 1H, H-11), 5.66 (brd, $J = 7.5$ Hz, 1H, H-10), 5.53 (s, 1H, OC*H*ArO), 5.31 (t, $J = 7.0$ Hz, 1H, H-5), 4.28 (brd, $J = 6.5$ Hz, 1H, H-9), 4.28 (m, 1H, H-7), 4.10 (d, $J = 9.5$ Hz, 1H, H-21), 3.96–3.82 (m, 3H, H-15, H-19, H-27), 3.80 (obs t, $J = 6.5$ Hz, 1H, H-17), 3.80 (s, 3H, $ArOCH_3$), 3.67–3.65 (m, 2H, H-13, H-31), 3.61–3.59 (m, 1H, H-31), 3.53–3.50 (m, 1H, H-29), 3.39 (s, 3H, C29–OCH_3), 3.33 (s, 3H, C15–OCH_3), 2.20–2.12 (m, 2H, H-6), 1.98–1.87 (m, 5H, H-12a, H-12b, H-16, H-22, H-30a), 1.85–1.72 (m, 6H, H-14a, H-14b, H-20, H-26a, H-28a, H-30b), 1.70–1.61 (m, 3H, H-24, H-26, H-28), 1.60–1.49 (m, 4H, H-8a, H-8b, H-18a, H-18b), 1.57 (s, 3H, C4–CH_3), 1.23–1.27 (m, 1H, H-25b), 1.18 (d, $J = 6.0$ Hz, 3H, C31–CH_3), 0.95 (d, $J = 6.5$ Hz, 3H, C20–CH_3), 0.94 (d, $J = 7.0$ Hz, 3H, C16–CH_3), 0.92 (s, 9H, *t*Bu), 0.90 (d, $J = 7.5$ Hz, 3H, C22–CH_3), 0.876 (s, 9H, *t*Bu), 0.863 (d, $J = 7.0$ Hz, 3H, C24–Me), 0.13 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.5, 136.6, 131.7, 130.5, 127.2, 123.4, 120.7, 113.3, 100.3, 82.1, 78.7, 76.7, 76.5, 76.1, 73.1, 72.0, 70.7, 69.5, 68.8, 68.2, 64.5, 63.8, 58.5, 55.2, 55.1, 42.0, 40.7, 40.1, 38.5, 38.3, 37.3, 36.2, 35.3, 34.7, 31.5, 31.0, 29.9, 29.6, 28.8, 26.1, 25.8, 21.6, 18.2, 18.0, 16.1, 13.9, 11.1, 10.2, −3.9 (2), −4.3, −4.8$; HRMS (FAB): calcd for $C_{57}H_{102}O_{11}Si_2Cs$ ($M + Cs^+$) 1151.6015, found 1151.6063.

Preparation of aldehyde 12: A solution of azeotropically dried (benzene, 2 × 2 mL) diol **68** (78 mg, 0.077 mmol) in methylene chloride (2 mL) was added to a suspension of MnO_2 (103 mg, 1.149 mmol) in methylene chloride (2 mL, final conc. 0.02 M) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 4 h, then filtered through Celite and concentrated. Purification by column chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave the desired α,β-unsaturated aldehyde **12** (74.1 mg, 95% yield) as a white foam. **12**: $R_f = 0.42$ (silica gel, 10% acetone in benzene); $[\alpha]_D^{25} = -50.2$ ($c = 0.81$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3478, 3016, 2932, 2858, 1681, 1603, 1518, 1463, 1382, 1258, 1094, 1014, 837\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.34$ (s, 1H, H-3), 7.38 (d, $J = 8.5$ Hz, 2H, ArH), 6.84 (d, $J = 8.5$ Hz, 2H, ArH), 6.48 (t, $J = 7.0$ Hz, 1H, H-5), 5.78 (md, $J = 10.0$ Hz, 1H, H-11), 5.60 (brd, $J = 10.0$ Hz, 1H, H-10), 5.55 (s, 1H, OC*H*ArO), 4.31 (brd, $J = 10.0$ Hz, 1H, H-9), 4.31–4.24 (m, 1H, H-7), 4.10 (d, $J = 9.5$ Hz, 1H, H-21), 4.06–4.01 (brm, 1H, H-27), 3.99–3.94 (m, 1H, H-13), 3.87 (td, $J = 8.5$, 4.0 Hz, 1H, H-19), 3.83 (td, $J = 7.5$, 1.5 Hz, 1H, H-17), 3.78 (s, 3H, $ArOCH_3$), 3.68–3.62 (m, 1H, H-15), 3.59 (dd, $J = 6.0$, 2.5 Hz, 1H, H-23), 3.54–3.49 (m, 2H, H-29, H-31), 3.39 (s, 3H, C29–OCH_3), 3.32 (s, 3H, C15–OCH_3), 2.40–2.28 (m, 2H, H-6a, H-6b), 1.97–1.90 (m, 5H, H-12a, H-12b, H-16a, H-22, H-30a), 1.85–1.69 (m, 6H, H-14a, H-14b, H-20, H-26a, H-28a, H-30b), 1.65 (s, 3H, C4–CH_3), 1.68–1.50 (m, 6H, H-8a, H-8b, H-18a, H-18b, H-25a, H-26b), 1.37 (ddd, $J = 14.0$, 9.5, 2.0 Hz, 1H, H-28), 1.28–1.20 (m, 1H, H-25b), 1.17 (d, $J = 6.0$ Hz, 3H, C32–CH_3), 1.16–1.10 (m, 1H, H-24), 0.95 (d, $J = 7.0$ Hz, 3H, C24–CH_3), 0.94 (d, $J = 6.5$ Hz, 3H, C20–CH_3), 0.91 (s, 9H, *t*Bu), 0.86 (obs d, $J = 7.0$ Hz, 3H, C22–CH_3), 0.85 (obs d, $J = 7.0$ Hz, 3H, C16–CH_3), 0.85 (s, 9H, *t*Bu), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 195.4, 159.4, 150.9, 140.2, 131.9, 130.0, 127.2, 123.8, 113.2, 100.2, 82.6, 78.4, 75.9, 75.5, 73.1, 71.9, 70.6, 69.0, 67.4, 64.6, 64.2, 58.2, 55.2, 55.1, 41.6, 40.8, 40.7, 38.5, 37.5, 37.4, 37.4, 34.9, 34.6, 32.2, 31.0, 30.0, 29.1, 26.1, 25.7, 21.6, 18.2, 17.9, 16.0, 11.3, 10.0, 9.3, 8.1, −3.9, −4.0, −4.4, −4.9$; HRMS (FAB): calcd for $C_{57}H_{100}O_{11}Si_2Cs$ ($M + Cs^+$) 1149.5859, found 1149.5793.

Preparation of ester 11: A solution of trimethyl phosphonoacetate (1.09 mL, 6.76 mmol) in dry THF (23 mL) was cooled to 0 °C and treated with *n*BuLi (3.16 mL of 1.6 M solution in hexanes, 5.08 mmol) while stirred for 15 min. A solution of aldehyde **12** (344 mg, 0.320 mmol) in THF (40 mL) was added to the reaction mixture and the solution was allowed to warm to room temperature with continued stirring for 18 h. The reaction mixture was poured into saturated aqueous NH_4Cl (600 mL), the aqueous phase was extracted with chloroform (600 mL × 1, 200 mL × 1, 100 mL × 1), and the combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (silica gel, 9% acetone in benzene) afforded the methyl ester **11** (351.3 mg, 96.8% yield) as a white foam. **11**: $R_f = 0.42$ (silica gel, 10% acetone in benzene); $[\alpha]_D^{25} = -62$ ($c = 0.65$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3500.1, 2932.3, 1718.3, 1620.5, 1516.3, 1462.3, 1380.9, 1307.4, 1250.8, 1167.8, 1090.9, 1034.7, 834.2, 774.3\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 8.5$ Hz, 2H, ArH), 7.31 (d, $J = 15.8$ Hz, 1H, H-3), 6.85 (d, $J = 8.5$ Hz, 2H, ArH), 5.92 (t, $J = 7.5$ Hz, 1H, H-5), 5.77 (d, $J = 15.8$ Hz, 1H, H-2), 5.75 (m, 1H, H-11), 5.61 (md, $J = 10.7$ Hz, 1H, H-10), 5.54 (s, 1H, OC*H*ArO), 4.30 (brd, $J = 10.0$ Hz, 1H, H-21), 4.27 (brd,

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J = 10.0 Hz, H-9), 4.11 (d, J = 8.5 Hz, 1H, H-7), 4.00–3.92 (m, 1H, H-15), 3.88–3.82 (m, 1H, H-17), 3.82–3.78 (m, 1H, H-19), 3.79 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, CO_2CH_3), 3.75–3.73 (m, 1H, H-27), 3.68–3.62 (m, 1H, H-31), 3.60 (dd, J = 6.0, 3.5 Hz, 1H, H-23), 3.62–3.59 (m, 1H, H-29), 3.51 (m, 1H, H-13), 3.39 (s, 3H, C29–OCH_3), 3.33 (s, 3H, C15–OCH_3), 2.28–2.24 (m, 2H, H-6a, H-6b), 2.00–1.87 (m, 4H, H-12, H-14a, H-22, H24), 1.86–1.78 (m, 3H, H-8a, H-16, H-26a), 1.71 (s, 3H, C4–CH_3), 1.68–1.60 (m, 5H, H-18a, H-18b, H-20, H-28a, H-30a), 1.60–1.53 (m, 5H, H-12b, H-14b, H-25a, H-25b, H-28b), 1.39 (ddd, J = 12.5, 8.0, 2.0 Hz, 1H, H-8b), 1.25 (brm, 2H, H-30b), 1.18 (d, J = 6.0 Hz, 3H, C31–CH_3), 1.16–1.09 (m, 1H, H-26b), 0.95 (d, J = 7.0 Hz, 3H, C22–CH_3), 0.95 (d, J = 7.0 Hz, 3H, C20–CH_3), 0.91 (s, 9H, *t*Bu), 0.87 (d, J = 6.5 Hz, 3H, C24–CH_3), 0.85 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.85 (s, 9H, *t*Bu), 0.13 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 159.4, 149.7, 138.2, 133.8, 131.9, 130.3, 127.2, 123.6, 115.0, 113.2, 100.2, 82.4, 78.4, 76.0, 75.6, 73.1, 72.0, 70.6, 69.1, 67.8, 64.6, 64.3, 58.3, 55.2, 55.1, 51.3, 41.8, 40.9, 40.6, 38.5, 37.7, 37.4, 37.2, 35.1, 34.6, 32.0, 30.9, 30.0, 29.6, 29.0, 26.1, 26.1, 25.8, 21.6, 21.6, 18.2, 17.9, 16.1, 12.3, 11.2, 10.0, 8.2, −3.9, −3.9, −4.5, −4.9; HRMS (FAB): calcd for $C_{60}H_{104}O_{12}Si_2Cs$ (M + Cs^+) 1205.6121, found 1205.6151.

Preparation of preswinholide A (**7**): A solution of ester **11** (5.0 mg, 4.66 × 10^{-3} mmol) in acetonitrile (0.79 mL, 0.0047 M) was cooled to 0 °C and treated with HF (210 μL of 48% aqueous solution). The reaction mixture was stirred at 0 °C for 3 h, then diluted with chloroform (20 mL) and quenched with saturated aqueous $NaHCO_3$ (20 mL). The layers were separated and the aqueous phase was extracted with chloroform (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by preparative thin-layer chromatography (500 μm silica gel plate, 10% methanol in methylene chloride) gave preswinholide A (**7**) (3.2 mg, 94% yield) as a colorless amorphous solid. **7**: R_f = 0.46 (silica, 10% methanol in methylene chloride); $[\alpha]_D^{25}$ = −39 (c = 0.28, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3395.2, 2918.8, 2851.2, 1713.5, 1622.5, 1460.7, 1380.3, 1213.5, 1081.1, 978.0, 850.7, 756.8, 666.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 15.5 Hz, 1H, H-3), 5.98 (dd, J = 7.5, 7.5 Hz, 1H, H-5), 5.82 (d, J = 15.5 Hz, H-2), 5.82 (m, 1H, H-11), 5.65 (brdd, J = 10.5, 2.0 Hz, 1H, H-10), 4.53 (brd, J = 8.0 Hz, 1H, H-9), 4.06 (m, 1H, H-21), 4.04 (m, 1H, H-19), 4.03 (m, 1H, H-7), 4.02 (m, 1H, H-27), 3.88 (m, 1H, H-17), 3.87 (m, 1H, H-13), 3.75 (s, 1H, C1–OMe), 3.73 (m, 1H, H-31), 3.65 (m, 1H, H-15), 3.55 (dddd, J = 10.0, 10.0, 4.5, 4.5 Hz, 1H, H-29), 3.41 (s, 3H, C15–OCH_3), 3.34 (s, 3H, C29–OCH_3), 3.33 (m, 1H, H-23), 2.47 (ddd, J = 15.0, 7.5, 7.4 Hz, 1H, H-6a), 2.40 (ddd, J = 15.0, 7.5, 6.5 Hz, 1H, H-6b), 2.19 (md, J = 17.5 Hz, 1H, H-12a), 2.05 (m, 1H, H-14), 1.99 (m, 1H, H-30), 1.97 (m, 1H, H-20), 1.93 (m, 1H, H-16), 1.92 (m, 1H, H-12b), 1.88 (m, 1H, H-28a), 1.84 (m, 1H, H-26a), 1.80 (s, 3H, C4–CH_3), 1.76 (m, 2H, H-8a, H-22), 1.75 (m, 1H, H-24), 1.70 (m, 1H, H-25a), 1.62 (m, 3H, H-18a, H-18b, H-28b), 1.60 (m, 1H, H-14b), 1.55 (m, 1H, H-8b), 1.31 (m, 2H, H-25b, H-26b), 1.21 (d, J = 6.0 Hz, 3H, C31–CH_3), 1.20 (m, 1H, H-30b), 1.03 (d, J = 7.0 Hz, 3H, C24–CH_3), 0.88 (d, 6.5 Hz, 3H, C22–CH_3), 0.86 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.76 (d, J = 7.0 Hz, 3H, C20–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 150.5, 139.6, 134.9, 130.9, 124.0, 116.1, 80.8, 78.4, 77.3, 76.5, 73.8, 73.5, 71.5, 68.6, 67.7, 65.7, 65.5, 57.2, 55.4, 51.5, 41.2, 41.1, 40.6, 38.9, 38.2, 36.6, 36.0, 36.0, 35.9, 35.3, 30.6, 29.7, 28.8, 22.2, 17.3, 13.0, 12.7, 11.3, 11.1; HRMS (FAB): calcd for $C_{40}H_{70}O_{11}Cs$ (M + Cs^+) 859.3972, found 859.3951.

Preparation of preswinholide A seco-acid (**8**): Preswinholide A methyl ester (**7**) (3.8 mg, 5.2 × 10^{-3} mmol) was dissolved in a mixture of methanol (610 μL) and water (300 μL), and cooled to 0 °C. The solution was treated with excess NaOH (300 μL of 0.67 M aqueous soln.) and stirred at room temperature for 3.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (18 mL) and extracted with chloroform (4 × 18 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by preparative thin-layer chromatography (500 μm silica gel plate, 10% methanol in methylene chloride) affording preswinholide A seco-acid (**8**) (3.6 mg, 97% yield) as a colorless amorphous solid. **8**: R_f = 0.40 (silica gel, 10% methanol in methylene chloride); $[\alpha]_D^{25}$ = −31 (c = 0.36, MeOH); IR (neat): $\tilde{\nu}_{max}$ = 3392.7, 2917.2, 2849.1, 1693.2, 1621.1, 1462.0, 1382.1, 1273.0, 1197.1, 1153.8, 1079.1, 981.0, 852.9, 755.1 cm^{-1}; ^1H NMR (500 MHz, C_5D_5N): δ = 7.83 (d, J = 15.5 Hz, 1H, H-3), 6.49 (t, J = 8.0 Hz, 1H, H-5), 6.22 (d, J = 15.5 Hz, H-2), 5.86 (brs, 2H, H-10, H-11), 5.00 (m, 2H, H-9, H-19), 4.68 (brd, J = 10.0 Hz, 1H, H-21), 4.67 (m, 1H, H-7), 4.28 (m, 1H, H-17), 4.21 (m, 1H, H-15), 4.06 (m, 1H, H-29), 3.88 (m, 1H, H-13), 3.72 (m, 1H, H-23), 3.69 (m, 1H, H-31), 3.54 (m, 1H, H-27), 3.40 (s, 3H, C15–OCH_3), 3.31 (s, 3H, C29–OCH_3), 2.70 (brt, J = 6.5 Hz, 2H, H-6a, H-6b), 2.13 (m, 1H, H-22), 2.12 (m, 1H, H-28a), 2.09 (m, 3H, H-25a, H-26a, H-30a), 2.02 (m, 1H, H-18a), 1.94 (m, 2H, H-14, H-20), 1.90 (m, 2H, H-12, H-24), 1.89 (m, 1H, H-16), 1.88 (s, 3H, C4–CH_3), 1.74 (m, 1H, H-18b), 1.67 (m, 1H, H-8), 1.66 (m, 1H, H-25b), 1.53 (m, 1H, H-28b), 1.30 (d, J = 7.0 Hz, 3H, C22–CH_3), 1.24 (m, 1H, H-30b), 1.22 (d, J = 6.0 Hz, 3H, C31–CH_3), 1.21 (m, 1H, H-26b), 1.09 (d, 6.7 Hz, 3H, C20–CH_3), 1.03 (d, J = 6.5 Hz, 3H, C16–CH_3), 1.01 (d, J = 6.5 Hz, 3H, C24–CH_3); ^{13}C NMR (125 MHz, C_5D_5N): δ = 170.3, 149.0, 139.9, 134.8, 131.9, 124.7, 118.1, 80.5, 77.5, 74.9, 73.2, 72.7, 72.4, 72.4, 70.4, 67.3, 65.3, 65.1, 57.6, 55.5, 43.7, 42.8, 42.0, 39.8, 39.3, 39.1, 37.7, 36.8, 36.2, 36.1, 32.2, 30.1, 29.4, 22.6, 17.4, 13.2, 11.6, 11.3, 10.4; HRMS (FAB): calcd for $C_{39}H_{68}O_{11}Cs$ (M + Cs^+) 845.3816, found 845.3811.

Preparation of hydroxy acid 69: A solution of methyl ester **11** (276.6 mg, 0.258 mmol) in a mixture of methanol (26.5 mL) and THF (17.7 mL) was cooled to 0 °C, and treated with excess NaOH (17.7 mL of 1.4 M aqueous soln., 24.8 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h, then poured into saturated aqueous NH_4Cl (1.6 L). The solution was extracted with chloroform (500 mL × 1, 200 mL × 1, 100 mL × 1) and the combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, 13% acetone in benzene, then 10% MeOH in methylene chloride) gave the hydroxy acid **69** (249.7 mg, 91.5% yield) and recovered methyl ester **11** (15.4 mg, 5.6%). **69**: R_f = 0.16 (silica gel, 10% acetone in benzene); $[\alpha]_D^{25}$ = −71 (c = 1.20, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3493.6, 2949.6, 2856.5, 1687.9, 1615.2, 1517.6, 1468.0, 1462.3, 1381.8, 1302.4, 1250.0, 1093.6, 1036.7, 835.7, 775.8, 756.8 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.5 Hz, 2H, ArH), 7.37 (d, J = 15.5 Hz, 1H, H-3), 6.85 (d, J = 8.5 Hz, 2H, ArH), 5.95 (t, J = 7.6 Hz, 1H, H-5), 5.76 (m, 1H, H-11), 5.75 (d, J = 15.5 Hz, 1H, H-2), 5.61 (md, J = 10.1 Hz, 1H, H-10), 5.55 (s, 1H, OC*H*ArO), 4.30 (brd, J = 11.0 Hz, 1H, H-21), 4.28 (brd, J = 9.9 Hz, 1H, H-9), 4.13 (d, J = 10.0 Hz, 1H, H-13), 3.98 (m, 1H, H-7), 3.84 (td, J = 10.0, 2.0 Hz, 1H, H-17), 3.83 (td, J = 6.0, 2.0 Hz, 1H, H-19), 3.78 (s, 3H, $ArOCH_3$), 3.68 (m, 1H, H-27), 3.61 (dd, J = 6.0, 3.5 Hz, 1H, H-23), 3.58 (m, 2H, H-31, H-29), 3.51 (m, 1H, H-15), 3.39 (s, 3H, C29–OCH_3), 3.33 (s, 3H, C15–OCH_3), 2.26 (m, 2H, H-6a, H-6b), 1.99–1.90 (m, 4H, H-12a, H-14a, H-22, H-24), 1.89–1.73 (m, 4H, H-8a, H-16, H-18a, H-26a), 1.71 (s, 3H, C4–CH_3), 1.66–1.57 (m, 4H, H-18b, H-20, H-28a, H-30a), 1.56–1.50 (m, 5H, H-12b, H-14b, H-25a, H-25b, H-28b), 1.39 (ddd, J = 12.0, 8.0, 2.0 Hz, 1H, H-8b), 1.25 (brm, 2H, H-30b), 1.19 (d, J = 6.5 Hz, 3H, C31–CH_3), 1.17 (m, 1H, H-26b), 0.96 (d, J = 6.5 Hz, 3H, C22–CH_3), 0.96 (d, J = 7.0 Hz, 3H, C20–CH_3), 0.92 (s, 9H, *t*Bu), 0.87 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.86 (d, J = 7.0 Hz, 3H, C24–CH_3), 0.83 (s, 9H, *t*Bu), 0.13 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), −0.12 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 159.3, 151.4, 139.3, 133.8, 131.9, 130.2, 128.2, 127.2, 123.6, 114.7, 113.2, 100.0, 82.5, 78.4, 76.0, 75.5, 73.1, 72.0, 70.8, 69.1, 67.8, 64.6, 64.2, 58.1, 55.1, 55.0, 41.5, 40.8, 40.8, 38.4, 37.6, 37.4, 34.9, 34.6, 32.1, 31.0, 30.0, 29.1, 26.0, 25.7, 21.6, 18.2, 17.9, 15.9, 12.3, 11.3, 10.0, 8.2, −4.0, −4.0, −4.4, −4.9; HRMS (FAB): calcd for $C_{59}H_{102}O_{12}Si_2Cs$ (M + Cs^+) 1191.5964, found 1191.6022.

Preparation of TMS acid 10: A solution of the hydroxy acid **69** (202.6 mg, 0.191 mmol) in methylene chloride (10 mL, 0.02 M) was cooled to 0 °C and treated with *i*Pr_2NEt (840 μL, 4.8 mmol) and TMSOTf (470 μL, 2.4 mmol) sequentially. The solution was warmed to room temperature and stirred for 18 h. The reaction was diluted with ethyl acetate (500 mL) and washed with $KHSO_4$ (500 mL, 5% soln. in water) and saturated aqueous $NaHCO_3$ (500 mL). The bicarbonate layer was extracted with ethyl acetate (200 mL × 2, 100 mL × 1), and the combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, 12% acetone in benzene, then 10% MeOH in methylene chloride) gave pure TMS acid **10** (192.6 mg, 89% yield). **10**: white foam; R_f = 0.28 (silica gel, 10% acetone in benzene); $[\alpha]_D^{25}$ = −67 (c = 0.71, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 2951.6, 2933.7, 2898.3, 2858.2, 1687.9, 1614.8, 1517.9, 1462.3, 1382.9, 1302.5, 1249.4, 1213.1, 1151.5, 1092.6, 1035.5, 835.5, 774.0, 756.7, 667.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.5 Hz, 2H, ArH), 7.36 (d, J = 15.5 Hz, 1H, H-3), 6.83 (d, J = 8.5 Hz, 2H, ArH), 5.95 (brt, J = 7.5 Hz, 1H, H-5), 5.76 (d, J = 15.5 Hz, 1H, H-2), 5.75 (m, 1H, H-11), 5.61 (md, J = 10.0 Hz, 1H, H-10), 5.46 (s, 1H, OC*H*ArO), 4.27 (brd, J = 10.0 Hz, 1H, H-9), 4.10 (brd, J = 11.0 Hz, 1H, H-21), 3.98 (m, 1H, H-7), 3.97 (d, J = 9.0 Hz, 1H, H-13), 3.85 (td, J = 9.0, 2.0 Hz, 1H, H-19), 3.81 (brt, J = 12.0 Hz, 1H, H-17), 3.78 (s, 3H, $ArOCH_3$), 3.67 (m, 1H, H-27), 3.55 (m, 2H, H-29, H-31), 3.54 (m, 2H, H-15, H-23), 3.41 (s, 3H, C29–OCH_3), 3.34 (s, 3H, C15–OCH_3), 2.25 (brdd, J = 7.0, 5.5 Hz, 2H, H-6a, H-6b), 2.01–1.90 (m, 4H, H-12a, H-14a, H-22, H-24), 1.87–1.81 (m, 3H, H-8a, H-16, H-26a), 1.72 (s, 3H, C4–CH_3), 1.70–1.59 (m, 5H, H-18a, H-18b, H-20, H-28a, H-30a), 1.58–1.48 (m, 5H, H-12b, H-14b, H-25a, H-25b, H-28b), 1.40–1.36 (m, 1H, H-8b), 1.210–1.182 (m, 2H, H-26b, H-30b), 1.20 (d, J = 6.5 Hz, 3H, C31–CH_3), 0.96 (d, J = 7.0 Hz, 3H, C22–CH_3), 0.94 (d, J = 7.0 Hz, 3H, C20–CH_3), 0.87 (d, J = 7.0 Hz, 3H, C24–CH_3), 0.86 (s, 9H, *t*Bu), 0.83 (s, 9H, *t*Bu), 0.76 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.090 (s, 9H, $Si(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), −0.11 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 159.3, 151.6, 139.4, 133.8, 131.7, 130.2, 128.2, 127.4, 123.6, 114.6, 113.1, 100.2, 79.1, 78.4, 75.8, 75.2, 74.6, 72.0, 69.2, 67.7, 64.4, 64.2, 58.1, 55.1, 55.0, 42.0, 41.5, 40.8, 40.6, 38.7, 37.3, 37.2, 36.3, 34.7, 33.0, 31.0, 29.8, 26.5, 26.2, 25.7, 21.7, 18.6, 17.9, 16.8, 12.3, 10.8, 10.2, 8.2, 1.45, −3.1, −3.6, −4.5, −5.0; HRMS (FAB): calcd for $C_{62}H_{110}O_{12}Si_3Cs$ (M + Cs^+) 1263.6359, found 1263.6301.

Preparation of phosphonates 70 and 72: In a typical procedure, a solution containing azeotropically dried (benzene) alcohol **67** (16.4 mg, 1.45 × 10^{-5} mol), phosphonoacetic acid (14.2 mg, 7.23 × 10^{-5} mol), and DCC (14.9 mg, 7.23 × 10^{-5} mol) in chloroform (1.0 mL) was treated with 4-DMAP (1.8 mg, 1.45 × 10^{-5} mol). The reaction mixture was stirred at room temperature for 24 h and loaded directly onto a PTLC plate (K 6 F 60 A silica gel plate, 500 μm, 10% acetone in benzene). Purification by PTLC gave the desired phosphonate **70** (13.6 mg, 72% yield) as a white foam. **70**: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.5 Hz, 2H, ArH), 6.83 (d, J = 8.5 Hz, 2H, ArH), 5.76 (brm, 1H, H-11), 5.65 (brd, J = 10.5 Hz 1H, H-10), 5.42 (s, 1H, OC*H*ArO), 5.42 (obs m, 1H, H-5), 5.31 (d, J = 9.5 Hz, 1H, H-21), 4.28 (brd, J = 8.0 Hz, 1H, H-9), 4.12 (q, J = 8.0 Hz, 4H, $P(OCH_2CH_3)_2$), 3.98 (s, 2H,

H-3a, H-3b), 3.98–3.91 (m, 3H, H-7, H-15, H-27), 3.86 (dt, J = 6.5, 1.5 Hz, 1H, H-19), 3.79 (obs t, J = 6.5 Hz, 1H, H-17), 3.79 (s, 3H, $ArOCH_3$), 3.65 (m, 2H, H-13, H-31), 3.57–3.44 (m, 2H, H-23, H-29), 3.38 (s, 3H, C29–OCH_3), 3.34 (s, 3H, C15–OCH_3), 2.92 (dd, J = 22.0, 2.5 Hz, 2H, PCH_2), 2.13 (brs, 2H, H-6a, H-6b), 2.01–1.79 (m, 10H, H-12a, H-12b, H-14a, H-14b, H-16, H-20, H-22, H-26a, H-28a, H-30a), 1.72–1.50 (m, 5H, H-8a, H-18a, H-18b, H-24, H-28b), 1.55 (s, 3H, C4–CH_3), 1.48–1.30 (m, 3H, H-8b, H-25b, H-26b), 1.30 (t, J = 8.0 Hz, 6H, $P(OCH_2CH_3)_2$), 1.28 (m, 1H, H-25), 1.18 (m, 1H, H-30b), 1.18 (brd, J = 6.0 Hz, 3H, C31–CH_3, C20–CH_3), 0.98 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.94 (d, 7.0 Hz, 3H, C22–CH_3), 0.89 (d, J = 7.0 Hz, 3H, C24–CH_3), 0.89 (s, 9H, tBu), 0.87 (s, 9H, tBu), 0.85 (s, 9H, tBu), 0.13 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.04 (s, 6H, 2 × $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), −0.03 (s, 3H, $SiCH_3$); FABMS (FAB): calcd for $C_{69}H_{127}O_{15}PSi_3Cs$ (M + Cs^+) 1443.7275, found 1443.

Properties of 72: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (s, 1H, H-3), 7.40 (d, J = 8.5 Hz, 2H, ArH), 6.82 (d, J = 8.5 Hz, 2H, ArH), 6.48 (t, J = 7.0 Hz, 1H, H-5), 5.79 (md, J = 10.0 Hz, 1H, H-11), 5.61 (brd, J = 10.0 Hz, 1H, H-10), 5.44 (s, 1H, OC*H*ArO), 5.38 (d, J = 9.5 Hz, 1H, H-21), 4.29 (brd, J = 10.0 Hz, 1H, H-9), 4.12 (dq, J = 8.5, 7.0 Hz, 4H, $P(OCH_2CH_3)_2$), 4.06–3.90 (m, 3H, H-7, H-13, H-27), 3.88 (dt, J = 8.5, 1.5 Hz, 1H, H-19), 3.83 (dt, J = 9.0, 2.5 Hz, 1H, H-17), 3.78 (s, 3H, $ArOCH_3$), 3.64 (m, 1H, H-15), 3.58–3.44 (m, 3H, H-23, H-29, H-31), 3.39 (s, 3H, C29–OCH_3), 3.34 (s, 3H, C15–OCH_3), 2.92 (dd, J = 22.0, 1.0 Hz, 2H, PCH_2), 2.40–2.30 (m, 2H, H-6a, H-6b), 2.05–1.78 (m, 10H, H-12a, H-12b, H-14a, H-14b, H-16a, H-20, H-22, H-26a, H-28a, H-30a), 1.71–1.50 (m, 5H, H-8a, H-18a, H-18b, H-24, H-28a), 1.67 (s, 3H, C4–CH_3), 1.42–1.30 (m, 3H, H-8b, H-25a, H-26b), 1.30 (dt, J = 7.0, 2.5 Hz, 6H, $P(OCH_2CH_3)_2$), 1.25 (m, 1H, H-25b), 1.18 (d, J = 6.0 Hz, 6H, C31–CH_3, C20–CH_3), 1.12 (m, 1H, H-30b), 0.98 (d, J = 6.5 Hz, 3H, C16–CH_3), 0.93 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.93 (d, J = 7.0 Hz, 3H, C22–CH_3), 0.89 (d, J = 7.0 Hz, 3H, C24–CH_3), 0.87 (s, 9H, tBu), 0.84 (s, 9H, tBu), 0.13 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), −0.07 (s, 3H, $SiCH_3$).

Preparation of dimer 74: Alcohol **11** (17.6 mg, 1.64×10^{-5} mol, 1.25 equiv) and TMS acid **10** (14.8 mg, 1.31×10^{-5} mol) were combined and azeotroped with benzene (2 × 5 mL). 4-DMAP (1.31×10^{-5} mol) and DIC (3.92×10^{-5} mol) [154 μL of a solution of 4-DMAP (16 mg) and DIC (61 μL) in 1.54 mL of $CHCl_3$] were added to the above mixture of **10** and **11** and sonicated for 10 min. The reaction mixture was heated at 37 °C for 24 h with the addition of 20 μL $CHCl_3$ at 4 h intervals. The reaction mixture was then diluted with $CHCl_3$ (0.5 mL) and loaded directly on a PTLC plate (K 6 F 60 A silica gel plate, 500 μm, 10% acetone in benzene). Purification by PTLC gave the desired coupled product **74** (3.7 mg, 13% yield), the DIC adduct **79** (8.2 mg, 50%), and recovered alcohol **11** (13.2 mg, 75%). **74**: R_f = 0.51 (silica gel, 10% acetone in benzene); $[\alpha]_D^{25}$ = −66 (c = 1.5, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 2930.6, 2855.7, 1714.4, 1652.0, 1645.5, 1619.7, 1589.1, 1571.9, 1562.2, 1517.8, 1470.7, 1462.3, 1381.1, 1361.1, 1349.9, 1303.5, 1249.3, 1214.9, 1169.2, 1090.7, 1035.9, 986.3, 925.9, 897.3, 835.5, 810.9 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.5 Hz, 2H, ArH), 7.39 (d, J = 8.5 Hz, 2H, ArH), 7.30 (d, J = 15.5 Hz, 1H, H-3 or H-3'), 7.28 (d, J = 15.5 Hz, 1H, H-3' or H-3), 6.83 (d, J = 8.5 Hz, 2H, ArH), 6.82 (d, J = 8.5 Hz, 2H, ArH), 5.95 (brt, J = 7.6 Hz, 1H, H-5 or H-5'), 5.92 (brt, J = 7.5 Hz, 1H, H-5' or H-5), 5.77 (d, J = 15.5 Hz, 1H, H-2 or H-2'), 5.76 (d, J = 15.5 Hz, 1H, H-2' or H-2), 5.76 (m, 2H, H-11, H-11'), 5.62 (m, 2H, H-10, H-10'), 5.46 (s, 1H, OC*H*ArO), 5.38 (d, J = 9.0 Hz, 1H, H-21'), 5.36 (s, 1H, OC*H*ArO), 4.28 (brm, 2H, H-9, H-9'), 4.10 (brd, J = 10.0 Hz, 1H, H-21), 3.97 (m, 2H, H-7, H-7'), 3.97 (brd, J = 9.5 Hz, 1H, H-13, H-13'), 3.86 (brt, J = 9.0 Hz, 2H, H-19, H-19'), 3.82 (m, 2H, H-17, H-17'), 3.78 (s, 3H, $ArOCH_3$), 3.77 (s, 3H, $ArOCH_3$), 3.74 (s, 3H, CO_2CH_3), 3.69–3.59 (brm, 6H, H-27, H-29, H-31, H-27', H-29', H-31'), 3.55–3.45 (brm, 4H, H-15, H-23, H-15', H-23'), 3.41 (s, 3H, C29–OCH_3 or C29'–OCH_3), 3.37 (s, 3H, C29'–OCH_3 or C29–OCH_3), 3.34 (s, 3H, C15–OCH_3 or C15'–OCH_3), 3.33 (s, 3H, C15'–OCH_3 or C15–OCH_3), 2.25 (brm, 4H, H-6a, H-6b, H-6a', H-6b'), 2.00–1.90 (brm, 8H, H-12a, H-14a, H-22, H-24, H-12a', H-14a', H-22', H-24'), 1.88–1.76 (brm, 6H, H-8a, H-16, H-26a, H-8a', H-16', H-26a'), 1.72 (s, 3H, C4–CH_3' or C4–CH_3), 1.70 (s, 3H, C4–CH_3 or C4'–CH_3), 1.70–1.58 (brm, 10H, H-18a, H-18b, H-20, H-28a, H-30a, H-18a', H-18b', H-20', H-28a', H-30a'), 1.58–1.46 (brm, 10H, H-12b, H-14b, H-25a, H-25b, H-28b, H-12b', H-14b', H-25a', H-25b', H-28b'), 1.45–1.36 (m, 2H, H-8b, H-8b'), 1.20–1.15 (brm, 4H, H-26b, H-30b, H-26b', H-30b'), 1.19 (d, J = 6.5 Hz, 3H, C31'–CH_3 or C31–CH_3), 1.18 (d, J = 6.5 Hz, 3H, C31–CH_3 or C31'–CH_3), 1.14 (d, J = 6.5 Hz, 3H, C22–CH_3), 0.98 (d, J = 6.5 Hz, 3H, C20–CH_3 or C20'–CH_3), 0.96 (d, J = 7.0 Hz, 3H, C22'–CH_3), 0.95 (d, J = 7.0 Hz, 3H, C20'–CH_3 or C20–CH_3), 0.86 (s, 36H, 4 × tBu), 0.85 (d, J = 7.0 Hz, 3H, C16–CH_3 or C16'–CH_3), 0.86 (d, J = 7.0 Hz, 3H, C24'–CH_3 or C24–CH_3), 0.84 (d, J = 7.0 Hz, 3H, C24–CH_3 or C24'–CH_3), 0.76 (d, J = 7.0 Hz, 3H, C16'–CH_3 or C16–CH_3), 0.13 (s, 3H, $SiCH_3$), 0.09 (s, 9H, $Si(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$), −0.09 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 166.7, 159.3, 159.2, 149.7, 149.2, 138.2, 137.6, 133.9, 133.8, 131.7, 131.6, 130.4, 127.4, 127.3, 127.2, 123.5, 115.8, 115.0, 113.1, 113.1, 100.2, 99.9, 79.1, 79.0, 78.5, 77.9, 77.2, 75.9, 75.6, 75.4, 75.2, 74.6, 74.5, 73.2, 73.1, 72.6, 72.1, 69.2, 69.1, 69.0, 67.8, 67.6, 64.4, 64.3, 64.2, 58.3, 55.1, 55.1, 51.3, 42.1, 42.0, 40.8, 40.7, 40.5, 40.3, 39.4, 38.8, 38.8, 37.6, 37.5, 37.2, 37.0, 36.4, 36.0, 34.7, 34.7, 32.9, 30.8, 30.7, 29.8, 29.6, 26.5, 26.3, 26.2, 26.1, 26.1, 26.0, 26.0, 25.8, 23.5, 23.4, 22.6, 21.7, 18.6, 18.2, 17.9, 16.9, 16.7, 13.8, 12.4, 12.3, 10.8, 10.7, 10.6, 10.1, 8.2, 8.2, 1.5, −3.2, −3.2, −3.6, −4.5, −4.5 (2), −4.9. Electrospray$^+$ MS: calcd for $C_{122}H_{212}O_{23}Si_3H$ (M + H^+ + 1 ^{13}C) 2187.4, found 2187.5.

Properties of 79: R_f = 0.42 (silica gel, 10% acetone in benzene); $[\alpha]_D^{25}$ = −57 (c = 1.3, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3269.1, 2952.2, 2932.7, 2856.1, 1703.7, 1644.5, 1614.1, 1518.2, 1462.1, 1366.1, 1302.2, 1249.3, 1092.7, 1035.7, 835.6, 810.8, 774.0, 755.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (brs, 1H, CON*H*R), 7.39 (d, J = 9.0 Hz, 2H, ArH), 7.32 (d, J = 15.0 Hz, 1H, H-3), 6.83 (d, J = 9.0 Hz, 2H, ArH), 6.10 (d, J = 15.0 Hz, 1H, H-2), 5.97 (t, J = 8.0 Hz, 1H, H-5), 5.75 (m, 1H, H-11), 5.60 (md, J = 10.0 Hz, 1H, H-10), 5.46 (s, 1H, OC*H*ArO), 4.49 (septet, J = 6.5 Hz, 1H, -NC*H*$(CH_3)_2$), 4.26 (brd, J = 10.0 Hz, 1H, H-9), 4.11 (brd, J = 11.8 Hz, H-21), 4.04–3.97 (m, 3H, H-7, H-13, -NC*H*$(CH_3)_2$), 3.84 (brt, J = 6.2 Hz, 1H, H-17), 3.81 (brt, J = 8.0 Hz, 1H, H-19), 3.78 (s, 3H, $ArOCH_3$), 3.67 (m, 1H, H-27), 3.62–3.50 (m, 4H, H-15, H-23, H-29, H-31), 3.41 (s, 3H, C29–OCH_3), 3.33 (s, 3H, C15–OCH_3), 2.23 (m, 2H, H-6a, H-6b), 2.00–1.88 (m, 4H, H-12, H-14a, H-22, H-24), 1.87–1.75 (m, 3H, H-8a, H-16, H-26a), 1.72 (s, 3H, C4–CH_3), 1.68–1.49 (m, 10H, H-12b, H-14b, H-18a, H-18b, H-20, H-25a, H-25b, H-28a, H-28b, H-30a), 1.43 (d, J = 7.0 Hz, 6H, -NCH$(CH_3)_2$, 1.38 (ddd, J = 12.5, 8.0, 2.0 Hz, 1H, H-8b), 1.25–1.10 (m, 2H, H-26b, H-30b), 1.20 (d, J = 6.5 Hz, 6H, -NHCH$(CH_3)_2$), 1.19 (d, J = 6.0 Hz, 3H, C31–CH_3), 0.96 (d, J = 7.0 Hz, 3H, C22–CH_3), 0.95 (d, J = 7.0 Hz, 3H, C20–CH_3), 0.88 (d, J = 7.0 Hz, 3H, C16–CH_3), 0.86 (s, 9H, tBu), 0.84 (s, 9H, tBu), 0.77 (d, J = 6.5 Hz, 3H, C24–CH_3), 0.09 (s, 9H, $Si(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$), −0.07 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 159.4, 149.7, 138.2, 133.8, 131.9, 130.3, 127.2, 123.6, 115.0, 113.2, 100.2, 82.4, 78.4, 76.0, 75.6, 73.1, 72.0, 70.6, 69.1, 67.8, 64.6, 64.3, 58.3, 55.2, 55.1, 51.3, 41.8, 40.9, 40.6, 38.5, 37.7, 37.4, 37.2, 35.1, 34.6, 32.0, 30.9, 30.0, 29.6, 29.0, 26.1, 26.1, 25.8, 21.6, 21.6, 18.2, 17.9, 16.1, 12.3, 11.2, 10.0, 8.2, −3.9, −3.9, −4.5, −4.9.

Preparation of dimer 75: Azeotropically dried (benzene, 2 × 1 mL) TMS acid **10** (6.0 mg, 5.3×10^{-6} mol) was treated with Et_3N (51 μL of 0.5 M solution in toluene, 2.4×10^{-5} mol) and 2,4,6-trichlorobenzoyl chloride (42 μL of a 0.5 M solution in toluene, 2.0×10^{-5} mol), and the reaction mixture was left standing at room temperature for 1.5 h. Alcohol **11** (11.4 mg, 1.06×10^{-5} mol) was azeotroped (benzene, 2 × 1 mL), dissolved in a solution of 4-DMAP (1.05 mg, 8.60×10^{-6} mol) in toluene (200 μL), and added to the solution of activated acid solution at room temperature with stirring. The reaction mixture was heated to 105 °C and stirred for 12 h. The mixture was then diluted with methylene chloride (800 μL) and loaded directly on a preparative thin-layer chromatography plate (silica gel, 250 μm). Purification by PTLC (10% acetone in benzene) afforded the dimeric hydroxy ester **75** (5.2 mg, 46.4% yield) and recovered alcohol **11** (8.0 mg). **75**: R_f = 0.37 (silica gel, 10% acetone in benzene); $[\alpha]_D^{25}$ = −75 (c = 1.0, $CHCl_3$); IR (neat): $\tilde{\nu}_{max}$ = 3503.7, 2929.2, 2855.5, 1711.7, 1619.6, 1517.6, 1462.0, 1381.6, 1303.6, 1249.5, 1169.5, 1090.6, 1036.8, 835.5, 775.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, J = 9.0 Hz, 2H, ArH), 7.37 (d, J = 9.0 Hz, 2H, ArH), 7.30 (d, J = 15.5 Hz, 1H, H-3 or H-3'), 7.29 (d, J = 15.5 Hz, 1H, H-3' or H-3), 6.85 (d, J = 9.0 Hz, 2H, ArH), 6.83 (d, J = 9.0 Hz, 2H, ArH), 5.95 (brt, J = 8.0 Hz, 1H, H-5 or H-5'), 5.91 (brt, J = 8.0 Hz, 1H, H-5' or H-5), 5.78 (d, J = 15.5 Hz, 1H, H-2 or H-2'), 5.77 (d, J = 15.5 Hz, 1H, H-2' or H-2), 5.76 (m, 2H, H-11, H-11'), 5.61 (md, J = 10.5 Hz, 2H, H-10, H-10'), 5.54 (s, 1H, OC*H*ArO), 5.38 (d, J = 9.5 Hz, 1H, H-21'), 5.36 (s, 1H, OC*H*ArO), 4.28 (brm, 2H, H-9, H-9'), 4.10 (brd, J = 9.8 Hz, 1H, H-21), 4.03–3.98 (m, 2H, H-7, H-7'), 3.98–3.93 (m, 2H, H-13, H-13'), 3.89–3.87 (m, 2H, H-19, H-19'), 3.83–3.77 (m, 2H, H-17, H-17'), 3.78 (s, 3H, $ArOCH_3$ or $ArOCH_3$'), 3.77 (s, 3H, $ArOCH_3$' or $ArOCH_3$), 3.74 (s, 3H, CO_2CH_3), 3.69–3.58 (brm, 6H, H-27, H-27', H-29, H-29', H-31, H-31'), 3.55–3.43 (brm, 4H, H-15, H-15', H-23, H-23'), 3.38 (s, 3H, C29–OCH_3 or C29'–OCH_3), 3.37 (s, 3H, C29'–OCH_3 or C29–OCH_3), 3.33 (s, 3H, C15–OCH_3 or C15'–OCH_3), 3.32 (s, 3H, C15'–OCH_3 or C15–OCH_3), 2.35–2.20 (brm, 4H, H-6a, H-6b, H-6a', H-6b'), 2.01–1.90 (brm, 8H, H-12a, H-14a, H-22, H-24, H-12a', H-14a', H-22', H-24'), 1.86–1.75 (brm, 6H, H-8a, H-16, H-26a, H-8a', H-16', H-26a'), 1.72 (s, 3H, C4–CH_3' or C4–CH_3), 1.70 (s, 3H, C4–CH_3 or C4–CH_3'), 1.66–1.46 (brm, 20H, H-12b, H-14b, H-18a, H-18b, H-20, H-25a, H-25b, H-28a, H-28b, H-30a, H-12b', H-14b', H-18a', H-18b', H-20', H-25a', H-25b', H-28a', H-28b', H-30a'), 1.45-1.36 (m, 2H, H-8b, H-8b'), 1.20–1.13 (brm, 4H, H-26b, H-30b, H-26b', H-30b'), 1.22 (d, J = 7.0 Hz, 3H, C22–CH_3), 1.18 (d, J = 6.0 Hz, 3H, C31'–CH_3 or C31–CH_3), 1.17 (d, J = 6.0 Hz, 3H, C31–CH_3 or C31'–CH_3), 0.98 (d, J = 6.5 Hz, 3H, C22'–CH_3), 0.95 (brd, J = 7.0 Hz, 6H, C20–CH_3, C20'–CH_3), 0.92 (s, 18H, 2 × tBu), 0.87 (d, J = 7.0 Hz, 3H, C16–CH_3 or C16'–CH_3), 0.86 (d, J = 7.0 Hz, 3H, C16'–CH_3 or C16–CH_3), 0.85 (d, J = 7.0 Hz, 3H, C24–CH_3 or C24'–CH_3), 0.84 (d, J = 7.0 Hz, 3H, C24'–CH_3 or C24–CH_3), 0.84 (s, 9H, tBu), 0.83 (s, 9H, tBu), 0.14 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), −0.04 (s, 3H, $SiCH_3$), −0.08 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 166.7, 159.4, 159.2, 149.7, 149.2, 138.2, 137.6, 133.9, 133.8, 131.9, 131.6, 130.3, 127.3, 127.2, 127.2, 123.5, 115.8, 115.0, 113.2, 113.1, 100.2, 99.9, 82.4, 79.0, 78.4, 77.9, 77.3, 76.1, 75.61, 75.6, 75.4, 74.5, 73.2, 73.1,72.1, 72.0, 70.6, 69.2, 68.9, 67.8, 67.6, 64.5, 64.4, 64.2, 58.44, 58.4, 58.3, 55.2, 55.1, 55.07, 51.3, 42.1, 41.9, 40.8, 40.7, 40.5, 40.3, 39.5, 38.8, 38.5, 37.8, 37.6, 37.4, 37.2, 37.0, 36.0, 35.0, 34.7, 34.6, 32.9, 31.9, 30.8, 30.6, 30.0, 29.6, 29.0, 26.5 (3 carbons), 26.3 (3 carbons), 26.1, 26.0, 25.8 (6 carbons), 21.7, 21.6, 18.6, 18.2, 17.9, 16.9, 16.1, 12.4, 12.3, 11.2, 11.1, 10.8, 10.5, 10.1, 8.2, 8.19, −3.2,

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−3.9, −4.5, −4.53 (2 carbons), −4.9; HRMS (FAB): calcd for $C_{119}H_{204}O_{23}Si_4Cs$ ($M+Cs^+$) 2246.2925, found 2246.3089

Preparation of hydroxy acid 9: To a solution of hydroxy ester **75** (7.4 mg, 3.5×10^{-6} mol) in methylene chloride (200 µL) and methanol (1.5 mL) was added excess $Ba(OH)_2\cdot8H_2O$ (1.07 g, pulverized). The resulting slurry was stirred uncapped at room temperature for 50 min (to remove the methylene chloride), diluted with methanol (0.5 mL), and recapped. The reaction mixture was stirred at room temperature for 4 d and then quenched by the addition of brine (9 mL) and 1 N HCl (6.75 mL). The solution was extracted with ethyl acetate (4 × 30 mL) while the pH of the aqueous phase was maintained at 3–4. The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Purification by preparative thin-layer chromatography (250 µm silica gel plate, 15% acetone in benzene) afforded the hydroxy acid **9** (6.1 mg, 83% yield) as a colorless solid. **9**: $R_f = 0.35$ (silica gel, 15% acetone in benzene): $[\alpha]_D^{25} = -73$ ($c = 0.44$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3492.5, 2928.1, 2855.6, 1711.1, 1619.8, 1517.8, 1462.3, 1381.4, 1302.6, 1249.8, 1170.1, 1093.0, 1036.6, 835.8, 775.6\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.42$ (d, $J = 9.0$ Hz, 2H, ArH), 7.38 (d, $J = 9.0$ Hz, 2H, ArH), 7.32 (d, $J = 15.5$ Hz, 1H, H-3 or H-3'), 7.29 (d, $J = 15.5$ Hz, 1H, H-3' or H-3), 6.85 (d, $J = 9.0$ Hz, 2H, ArH), 6.83 (d, $J = 9.0$ Hz, 2H, ArH), 5.93 (brt, $J = 8.0$ Hz, 1H, H-5 or H-5'), 5.89 (brt, $J = 8.0$ Hz, 1H, H-5' or H-5), 5.77 (d, $J = 15.5$ Hz, 1H, H-2 or H-2'), 5.74 (d, $J = 15.5$ Hz, 1H, H-2' or H-2'), 5.79–5.72 (m, 2H, H-11, H-11'), 5.63 (dm, $J = 10.0$ Hz, 2H, H-10, H-10'), 5.54 (s, 1H, OC*H*ArO), 5.39 (d, $J = 8.5$ Hz, 1H, H-21'), 5.37 (s, 1H, OC*H*ArO), 4.31–4.25 (brm, 2H, H-9, H-9'), 4.11 (brd, $J = 10.0$ Hz, 1H, H-21), 4.03–3.98 (m, 2H, H-7, H-7'), 3.98–3.92 (m, 2H, H-13, H-13'), 3.89–3.80 (m, 3H, H-19, H-19', H-17 or H-17'), 3.80–3.78 (obs m, 1H, H-17' or H-17), 3.78 (s, 3H, $ArOCH_3$ or $ArOCH_3'$), 3.77 (s, 3H, $ArOCH_3'$ or $ArOCH_3$), 3.68–3.57 (brm, 6H, H-27, H-29, H-31, H-27', H-29', H-31'), 3.53–3.44 (brm, 4H, H-15, H-23, H-15', H-23'), 3.39 (s, 3H, C29–OCH_3 or C29'–OCH_3), 3.37 (s, 3H, C29'–OCH_3 or C29–OCH_3), 3.33 (s, 3H, C15–OCH_3 or C15'–OCH_3), 3.326 (s, 3H, C15'–OCH_3 or C15–OCH_3), 2.37–2.23 (brm, 4H, H-6a, H-6b, H-6a', H-6b'), 2.01–1.90 (brm, 8H, H-12a, H-14a, H-22, H-24, H-12a', H-14a', H-22', H-24'), 1.87–1.77 (brm, 6H, H-8a, H-16, H-26a, H-8a', H-16', H-26a'), 1.72 (s, 3H, C4–CH_3' or C4–CH_3), 1.71 (s, 3H, C4–CH_3 or C4–CH_3'), 1.67–1.50 (brm, 20H, H-12b, H-14b, H-18a, H-18b, H-20, H-25a, H-25b, H-28a, H-28b, H-30a, H-12b', H-14b', H-18a', H-18b', H-20', H-25a', H-25b', H-28a', H-28b', H-30a'), 1.45–1.36 (m, 2H, H-8b, H-8b'), 1.21–1.15 (brm, 4H, H-26b, H-30b, H-26b', H-30b'), 1.18 (d, $J = 7.0$ Hz, 3H, C22–CH_3), 1.17 (brd, $J = 6.5$ Hz, 6H, C31'–CH_3, C31–CH_3), 0.99 (d, $J = 7.0$ Hz, 3H, C22'–CH_3), 0.95 (brd, $J = 7.0$ Hz, 6H, C20–CH_3, C20'–CH_3), 0.91 (s, 18H, *t*Bu), 0.87 (s, 9H, *t*Bu), 0.86 (d, $J = 6.5$ Hz, 3H, C16–CH_3 or C16'–CH_3), 0.85 (d, $J = 7.0$ Hz, 3H, C24–CH_3 or C24'–CH_3), 0.841 (s, 9H, *t*Bu), 0.84 (d, $J = 6.5$ Hz, 3H, C16'–CH_3 or C16–CH_3), 0.83 (d, $J = 7.0$ Hz, 3H, C24'–CH_3 or C24–CH_3), 0.12 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$) 0.01 (s, 3H, $SiCH_3$), −0.04 (s, 3H, $SiCH_3$), −0.10 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.7, 159.4, 159.3, 151.1, 149.3, 138.9, 137.7, 133.9, 133.9, 131.9, 131.6, 130.3, 127.3, 127.2, 123.6, 123.5, 115.9, 113.2, 113.1, 100.2, 100.0, 82.4, 79.1, 78.4, 77.9, 77.2, 76.5, 75.6, 75.6, 75.6, 73.2, 73.1, 72.1, 72.0, 70.7, 69.2, 69.0, 68.0, 67.6, 64.6, 64.5, 64.4, 64.3, 58.5, 58.2, 55.2, 55.1, 43.2, 42.1, 41.8, 41.5, 40.8, 40.6, 39.3, 38.7, 38.5, 37.9, 37.6, 37.5, 37.1, 36.1, 35.3, 35.0, 34.7, 34.6, 34.1, 32.9, 32.0, 31.8, 30.9, 30.8, 30.6, 30.2, 29.6, 29.0, 26.5$ (3 carbons), 26.3 (3 carbons), 26.1, 26.0, 25.8 (6 carbons), 21.7, 21.6, 18.6, 18.2, 17.9, 16.9, 15.4, 14.0, 12.4, 12.3, 11.3, 10.8, 10.77, 10.1, 9.0, −3.2, −3.88, −3.9, −4.4, −4.5, −4.9; FABMS: calcd for $C_{118}H_{202}O_{23}Si_4Cs^+$ ($M+Cs^+$) 2232, found 2232.

Preparation of the diolide 76: A solution of the azeotropically dried (benzene, 2 × 1 mL) seco-acid **9** (3.0 mg, 1.4×10^{-6} mol) in toluene (200 µL) was treated with Et_3N (17 µL, 0.5 M soln. in toluene, 8.6×10^{-6} mol) and 2,4,6-trichlorobenzoyl chloride (14 µL, 0.5 M soln. in toluene, 7.1×10^{-6} mol), and the mixture was stirred at room temperature for 1 h, then Et_3N (34 µL, 0.5 M soln. in toluene) and 2,4,6-trichlorobenzoyl chloride (28 µL, 0.5 M soln. in toluene) were added and the resulting mixture was stirred for another 1.5 h. The reaction mixture was then diluted with toluene (2 mL) and treated with a solution of 4-DMAP (0.29 mg, 2.4×10^{-6} mol) in toluene (1 mL). The reaction mixture was heated to 110 °C for 24 h, quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by preparative thin-layer chromatography (250 µm silica gel plate, 12% acetone in benzene) afforded the diolide **76** (0.90 mg, 30% yield) contaminated with a small amount of an unknown impurity and recovered seco-acid **9** (0.75 mg, 25%). **76**: $R_f = 0.46$ (silica gel, 10% acetone in benzene); $[\alpha]_D^{25} = -61$ ($c = 0.47$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 2928.0, 2855.4, 1711.4, 1617.9, 1588.2, 1517.7, 1462.1, 1381.5, 1302.3, 1249.0, 1214.7, 1170.3, 1153.6, 1085.4, 1036.2, 835.6, 775.7\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.40$ (d, $J = 8.5$ Hz, 4H, ArH), 7.36 (d, $J = 15.5$ Hz, 2H, H-3, H-3'), 6.83 (d, $J = 8.5$ Hz, 4H, ArH), 5.87 (brdd, $J = 8.0, 6.5$ Hz, 2H, H-5, H-5'), 5.78 (d, $J = 15.5$ Hz, 2H, H-2, H-2'), 5.80–5.75 (m, 2H, H-11, H-11'), 5.66 (brd, $J = 10.0$ Hz, 2H, H-10, H-10'), 5.36 (d, $J = 10.5$ Hz, 2H, H-21, H-21'), 5.34 (s, 2H, 2 × OC*H*ArO), 4.29 (brs, 2H, H-9, H-9'), 3.95 (m, 2H, H-7, H-7'), 3.89–3.80 (m, 2H, H-13, H-13'), 3.80–3.78 (obs m, 2H, H-17, H-17'), 3.77 (s, 6H, 2 × $ArOCH_3$), 3.70–3.57 (brm, 6H, H-23, H-27, H-31, H-23', H-27', H-31'), 3.55–3.41 (brm, 4H, H-15, H-29, H-15', H-29'), 3.36 (dd, $J = 5.5, 2.5$ Hz, 2H, H-19, H-19'), 3.33 (s, 12H, C15–OCH_3, C15'–OCH_3, C29–OCH_3, C29'–OCH_3), 2.35–2.22 (m, 4H, H-6a, H-6b, H-6a', H-6b'), 2.04–1.88 (brm, 8H, H-12a, H-14a, H-22, H-24, H-12a', H-14a', H-22', H-24'), 1.87–1.75 (brm, 6H, H-8a, H-16, H-26a, H-8a', H-16', H-26a'), 1.72 (s, 6H, C4–CH_3, C4'–CH_3), 1.65–1.50 (brm, 20H, H-12b, H-14b, H-18a, H-18b, H-20, H-25a, H-25b, H-28a, H-28b, H-30a, H-12b', H-14b', H-18a', H-18b', H-20', H-25a', H-25b', H-28a', H-28b', H-30a'), 1.39 (m, 2H, H-8b, H-8b'), 1.25–1.10 (brm, 4H, H-26b, H-30b, H-26b', H-30b'), 1.22 (d, $J = 7.0$ Hz, 6H, C31–CH_3, C31'–CH_3), 1.01 (d, $J = 6.5$ Hz, 6H, C22–CH_3, C22'–CH_3), 0.96 (d, $J = 6.0$ Hz, 6H, C20–CH_3, C20'–CH_3), 0.86 (d, $J = 6.5$ Hz, 6H, C16–CH_3, C16'–CH_3), 0.85 (s, 18H, 2 × *t*Bu), 0.84 (s, 18H, 2 × *t*Bu), 0.81 (d, $J = 7.0$ Hz, 6H, C24–CH_3, C24'–CH_3), 0.13 (s, 6H, 2 × $SiCH_3$), 0.05 (s, 6H, 2 × $SiCH_3$), 0.03 (s, 6H, 2 × $SiCH_3$), −0.03 (s, 6H, 2 × $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.1, 159.4, 149.5, 131.6, 130.3, 127.2, 123.6, 116.0, 113.1, 100.1, 78.9, 77.2, 76.9, 76.8, 73.2, 72.1, 69.6, 68.7, 64.3, 58.8, 55.1, 55.08, 42.6, 41.1, 40.4, 39.6, 38.8, 38.6, 36.2, 36.1, 34.8, 31.8, 29.61, 29.6, 29.2, 26.3, 26.1, 25.8, 22.6, 21.7, 18.6, 17.9, 16.9, 14.0, 12.4, 10.7, 8.3, 6.9, −3.3, −4.5, −4.7$; HRMS (FAB): calcd for $C_{118}H_{200}O_{22}Si_4Cs$ ($M+Cs^+$) 2214.2663, found 2214.2709.

Preparation of swinholide A: A solution of diolide **76** (4.7 mg, 2.3×10^{-6} mol) in acetonitrile (950 µL) was cooled to 0 °C and treated with 48% aqueous HF (250 µL). The resulting solution was stirred at 0 °C for 2 h and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Purification by preparative thin-layer chromatography (250 µm silica gel plate, 5% methanol in methylene chloride) yielded slightly impure swinholide A (**1**) (1.9 mg, 60% yield). The final product was purified by HPLC (reverse phase C-18 Vydac 210TP510 column, 95% MeOH: H_2O, 1 mL min^{-1}, retention time 18 min) to afford pure swinholide A (**1**) (1.6 mg, 50.5% yield). **1**: $R_f = 0.23$ (silica gel, 5% methanol in methylene chloride); $[\alpha]_D^{25} = -29$ ($c = 0.13$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3443.5, 2925.1, 1693.0, 1681.9, 1620.2, 1617.2, 1462.1, 1383.4, 1309.7, 1277.2, 1184.8, 1153.3, 1081.8, 987.6, 850.7, 754.9, 705.7, 665.9\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.57$ (d, $J = 15.8$ Hz, 2H, H-3, H-3'), 6.08 (dd, $J = 9.5, 5.0$ Hz, 2H, H-5, H-5'), 5.79 (d, $J = 15.8$ Hz, 2H, H-2, H-2'), 5.78 (brd, $J = 10.5$ Hz, 2H, H-11, H-11'), 5.70 (brdd, $J = 10.0, 2.0$ Hz, 2H, H-10, H-10'), 5.36 (d, $J = 10.7$ Hz, 2H, H-21, H-21'), 4.51 (brd, $J = 8.4$ Hz, 2H, H-9, H-9'), 4.15 (m, 2H, H-7, H-7'), 4.02 (m, 2H, H-27, H-27'), 4.01 (m, 2H, H-15, H-15'), 4.00 (m, 2H, H-19, H-19'), 3.86 (m, 2H, H-13, H-13'), 3.54 (dddd, $J = 10.0, 10.0, 5.5, 5.5$ Hz, 2H, H-29, H-29'), 3.35 (s, 6H, C15–OCH_3, C15'–OCH_3), 3.34 (s, 6H, C29–OCH_3, C29'–OCH_3), 3.12 (d, $J = 9.5$ Hz, 2H, H-23, H-23'), 2.45 (ddd, $J = 14.5, 9.5, 9.5$ Hz, 2H, H-6a, H-6a'), 2.29 (brd, $J = 16.0$ Hz, 2H, H-12a, H-12a'), 2.20–2.14 (m, 4H, H-6b, H-14, H-6b', H-14'), 1.97 (m, 2H, H-30, H-30'), 1.96 (m, 2H, H-22, H-22'), 1.91 (m, 2H, H-26a, H-26a'), 1.83 (m, 4H, H-12b, H-12b', H-28a, H-28a'), 1.81 (s, 6H, C4–CH_3, C4'–CH_3), 1.75 (dq, $J = 10.0$, 7.0 Hz, 2H, H-20, H-20'), 1.69 (m, 2H, H-18a, H-18a'), 1.68 (m, 2H, H-16, H-16'), 1.65 (m, 2H, H-24, H-24'), 1.63 (m, 2H, H-8a, H-8a'), 1.62 (m, 2H, H-18b, H-18b'), 1.60 (m, 2H, H-28b, H-28b'), 1.58 (m, 2H, H-8b, H-8b'), 1.46 (m, 2H, H-14b, H-14b'), 1.38 (m, 2H, H-25a, H-25a'), 1.30 (m, 2H, H-26b, H-26b'), 1.27 (m, 2H, H-25b, H-25b'), 1.20 (d, $J = 6.0$ Hz, 6H, C31–CH_3, C31'–CH_3), 1.17 (m, 2H, H-30b, H-30b'), 1.00 (d, $J = 7.0$ Hz, 6H, C24–CH_3, C24'–CH_3), 0.98 (d, $J = 7.4$ Hz, 6H, C20–CH_3, C20'–CH_3), 0.83 (d, $J = 7.0$ Hz, 6H, C22–CH_3, C22'–CH_3), 0.81 (d, $J = 7.0$ Hz, 6H, C16–CH_3, C16'–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.9, 153.1, 142.2, 134.8, 129.8, 123.1, 113.2, 75.9, 75.0, 74.6, 74.0, 73.2, 71.4, 71.4, 66.5, 65.8, 65.6, 64.5, 57.4, 55.2, 41.2, 41.1, 40.8, 38.6, 38.6, 37.4, 36.8, 34.8, 34.8, 33.2, 29.6, 29.3, 23.9, 21.7, 17.6, 12.2, 9.4, 9.2, 9.1$; FAB MS: calcd for $C_{78}H_{132}O_{20}Cs$ ($M+Cs^+$) 1521.8366, found 1521.8388.

Preparation of monomeric macrolide 77: A solution of the azeotropically dried (benzene, 2 × 1 mL) hydroxy acid **69** (4.0 mg, 3.8×10^{-6} mol) in toluene (200 µL) was treated with Et_3N (34 µL, 0.5 M soln. in toluene, 1.7×10^{-5} mol) and 2,4,6-trichlorobenzoyl chloride (28 µL, 0.5 M soln. in toluene, 1.4×10^{-5} mol) and left to stand at room temperature for 1.5 h. A solution of 4-DMAP (0.69 mg) in toluene (400 µL) was then added and the reaction mixture was heated at 105 °C for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by preparative thin-layer chromatography (250 µm silica gel plate, 10% acetone in benzene) afforded the monomeric macrolide **77** (2.7 mg, 69% yield) and a trace amount of the dimeric diolide **76**. **77**: $R_f = 0.55$ (silica gel, 10% acetone in benzene); $[\alpha]_D^{25} = -54$ ($c = 0.79$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 2932.6, 2855.9, 1698.9, 1615.1, 1517.6, 1462.6, 1380.6, 1250.9, 1085.5, 1032.3, 1005.9, 901.9, 835.7\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 15.7$ Hz, 1H, H-3), 7.47 (d, $J = 9.0$ Hz, 1H, ArH), 6.88 (d, $J = 9.0$ Hz, 2H, ArH), 5.72 (m, 1H, H-11), 5.70 (d, $J = 15.7$ Hz, 1H, H-2), 5.56 (brdt, $J = 10.0, 2.5$ Hz, 1H, H-10), 5.49 (s, 1H, OC*H*ArO), 5.12 (brdd, $J = 11.0, 7.0$ Hz, 1H, H-5), 4.96 (d, $J = 9.5$ Hz, 1H, H-21), 4.30 (brd, $J = 10.5$ Hz, 1H, H-9), 3.99 (m, 1H, H-7), 3.95 (brd, $J = 9.0$ Hz, 1H, H-13), 3.85 (m, 2H, H-19, H-17), 3.79 (s, 3H, $ArOCH_3$), 3.69–3.59 (m, 3H, H-27, H-29, H-31), 3.53 (m, 1H, H-15), 3.41 (s, 3H, C29–OCH_3), 3.34 (s, 3H, C15–OCH_3), 3.11 (brt, $J = 9.0$ Hz, 1H, H-23), 2.25 (brddd, $J = 9.0, 6.0, 2.0$ Hz, 1H, H-6a), 2.15 (q, $J = 12.0$ Hz, 1H, H-6b), 1.99–1.73 (m, 7H, H-8a, H-12a, H-14a, H-16, H-22, H-24, H-26), 1.68–1.52 (m, 10H, H-12b, H-14b, H-18a, H-18b, H-20, H-25a, H-25b, H-28a, H-28b, H-30a), 1.62 (s, 3H, C4–CH_3), 1.45–1.30 (m, 2H, H-8b, H-30b), 1.20–1.10 (obs m,

1H, H-26b), 1.19 (d, $J = 6.5$ Hz, 3H, C31–CH_3), 1.04 (d, $J = 7.5$ Hz, 3H, C20–CH_3), 0.96 (d, $J = 7.0$ Hz, 3H, C24–CH_3), 0.90 (s, 9H, *t*Bu), 0.88 (s, 9H, *t*Bu), 0.86 (d, $J = 7.0$ Hz, 3H, C16–CH_3), 0.79 (d, $J = 7.0$ Hz, 3H, C22–CH_3), 0.17 (s, 6H, 2 × $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.1$, 159.4, 149.6, 137.4, 133.5, 131.3, 130.5, 127.3, 123.7, 116.1, 113.3, 100.7, 81.2, 78.7, 78.3, 76.2, 76.1, 73.2, 72.2, 69.2, 68.6, 64.3, 63.2, 57.0, 55.2, 55.1, 42.1, 41.2, 40.5, 40.0, 38.8, 38.3, 36.4, 36.0, 34.8, 31.8, 29.7, 29.6, 28.7, 26.4, 25.9, 25.7, 21.7, 18.7, 18.0, 16.8, 15.6, 11.9, 10.6, 8.5, −2.6, −4.2, −4.9, −5.0; FABMS: calcd for $C_{59}H_{100}O_{11}Si_2Cs$ ($M + Cs^+$) 1174, found 1174.

Preparation of hemiswinholide A (78): The monomeric macrolide **77** (2.7 mg, 2.6×10^{-6} mol) was cooled to 0 °C and treated with a stock solution of aqueous HF in acetonitrile (675 μL; stock soln. prepared by adding 250 μL 48% aqueous HF to 950 μL acetonitrile). The reaction mixture was stirred at 0 °C for 2 h, diluted with chloroform (10 mL), and quenched with saturated aqueous $NaHCO_3$ (20 mL). The layers were separated and the aqueous phase was extracted with chloroform (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated and purified by preparative thin-layer chromatography (250 μm silica gel plate, 7% methanol in methylene chloride) yielding hemiswinholide A (**78**) (1.8 mg, quantitative) as a colorless solid. **78**: $R_f = 0.20$ (silica gel, 5% methanol in methylene chloride); $[\alpha]_D^{25} = -40$ ($c = 0.46$, $CHCl_3$); IR (neat): $\tilde{\nu}_{max} = 3441.5$, 2918.1, 1681.7, 1627.7, 1461.9, 1383.9, 1268.0, 1153.0, 1078.4, 984.5, 855.8, 755.4, 665.7 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.38$ (d, $J = 15.5$ Hz, 1H, H-3), 5.89 (dd, $J = 10.0$, 6.2 Hz, 1H, H-5), 5.82 (m, 1H, H-11), 5.81 (d, $J = 15.5$ Hz, 1H, H-2), 5.67 (br d, $J = 10.5$ Hz, 1H, H-10), 5.24 (dd, $J = 10.0$, 1.5 Hz, 1H, H-21), 4.47 (md, $J = 10.0$ Hz, 1H, H-9), 4.01 (m, 1H, H-7), 3.99 (m, 1H, H-27), 3.89 (m, 1H, H-19), 3.74–3.68 (m, 2H, H-17, H-31), 3.54 (ddt, $J = 12.0$, 10.0, 4.5 Hz, 1H, H-29), 3.50 (m, 1H, H-15), 3.41 (m, 1H, H-13), 3.37 (s, 3H, C15–OCH_3), 3.36 (obs dd, $J = 9.0$, 2.0 Hz, 1H, H-23), 3.35 (s, 3H, C29–OCH_3), 3.10 (br d, $J = 9.5$ Hz, 1H, OH), 2.50 (m, 2H, H-6a, H-6b), 2.05–1.98 (m, 4H, H-12a, H-20, H-26, H-30), 1.97–1.91 (m, 2H, H-12b, H-22), 1.84 (m, 2H, H-14, H-28), 1.81 (s, 3H, C4–CH_3), 1.75 (m, 1H, H-8), 1.72–1.68 (m, 3H, H-16, H-18, H-24), 1.65–1.55 (m, 3H, H-14, H-18, H-28b), 1.41 (m, 1H, H-25a), 1.35 (ddd, $J = 14.0$, 10.0, 2.5 Hz, 1H, H-8b), 1.31 (m, 1H, H-25b), 1.25 (m, 1H, H-26b), 1.20 (d, $J = 6.0$ Hz, 3H, C31–CH_3), 1.17 (m, 1H, H-30b), 1.02 (d, $J = 6.5$ Hz, 3H, C24–CH_3), 0.93 (d, $J = 7.0$ Hz, 3H, C20–CH_3), 0.87 (d, $J = 7.0$ Hz, 3H, C21–CH_3), 0.81 (d, $J = 7.0$ Hz, 3H, C16–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.8$, 149.8, 137.6, 134.8, 129.7, 124.5, 116.0, 80.0, 75.9, 73.8, 73.2, 71.5, 70.9, 70.5, 69.2, 65.4, 64.4, 56.7, 55.2, 41.5, 40.6, 39.9, 38.9, 38.7, 38.0, 37.3, 35.9, 34.9, 32.9, 31.1, 29.6, 29.0, 24.1, 21.7, 17.7, 12.3, 10.4, 9.8, 9.2; HRMS (FAB): calcd for $C_{39}H_{66}O_{10}Cs$ ($M + Cs^+$) 827.3710, found 827.3755.

Acknowledgments: We thank Drs. Dee H. Huang and Gary Siuzdak for their assistance with NMR and mass spectroscopy, respectively. We are grateful to Dr. John Faulkner for an authentic sample of swinholide A. This work was financially supported by the National Institutes of Health, USA, the ALSAM Foundation, Merck, Pfizer, Hoffmann La Roche, Schering-Plough, Amgen, and fellowships from Meiji Seika Kaisha (visiting scientist, KA), and NSERC (Canada) (MJT).

Received: February 8, 1996 [F298]

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