Total Synthesis of Rapamycin**

K. C. Nicolaou,* Anthony D. Piscopio, Peter Bertinato, Tushar K. Chakraborty, Nobuto Minowa, and Kazunori Koide

Abstract: Details of the total synthesis of rapamycin (**1**) are reported. The synthesis required the preparation of intermediates **4**–**9** in nonracemic form; key coupling reactions included a chromium-mediated addition of vinyl iodide **8** to aldehyde **7** and an Evans aldol reaction to couple fragments **62** and **9**. Intermediates **4** and **6** were joined through an amide bond formation to afford advanced intermediate **71**. Swern oxidation of the diol in **71** was followed by a selective removal of the TES groups and a second Swern oxidation. Finally, removal of the remaining silyl protecting groups provided fully deprotected, penultimate intermediate **2** in which all carbons were in their proper oxidation state. Macrocyclization was achieved through a tandem inter/intramolecular palladium-mediated Stille coupling reaction between distannylethene **3** and bis(vinyl iodide) **2**. This latter process accomplished in one step the installation of the remaining two carbons of the natural product and the completion of its total synthesis.

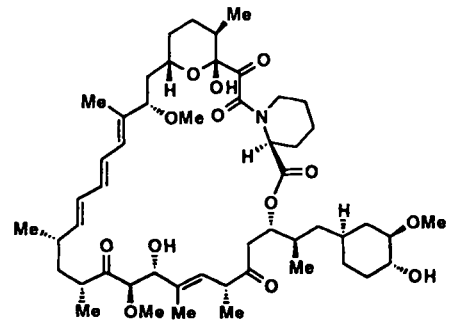
Keywords
rapamycin · stannylethenes · Stille coupling · vinyl iodides

Introduction

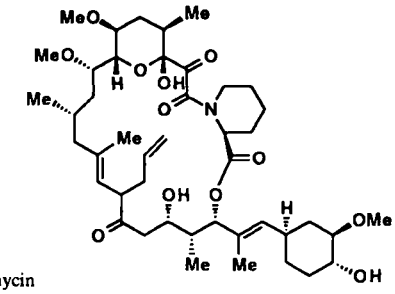
Rapamycin (**1**, Fig. 1), isolated in 1975 by Vézina and co-workers from the species *Streptomyces hygroscopicus* found in a soil sample collected on Easter Island,[1] is a powerful immunosuppressive agent. Fully characterized by standard spectroscopic and X-ray crystallographic methods,[2] the impressive molecular architecture of rapamycin gives rise to a wide range of biological activity, which includes cytotoxic, antifungal, and immunosuppressive properties.[3, 4]

In recent years immunosuppressive agents such as the clinically used cyclosporin[5] have made possible the transplantation of organs in humans. However, there is a need for improved agents owing to the side-effects of the existing drugs. Rapamycin binds to the same receptor, immunophilin FKBP12,[6, 7] as FK506, another structurally related natural product[8] with immunosuppressive properties.[9] The complex of rapamycin with FKBP12 binds to FRAP (FKBP12–rapamycin associated protein)[10] [RAFT1 = rapamycin–FKBP12 target 1),[11] TOR = target of rapamycin[12]], whereas the FK506–FKBP12 and the cyclosporin–cyclophilin complexes target calcineurin.[13, 14]

Rapamycin is currently under investigation by Wyeth-Ayerst as a potential clinical agent for use in organ transplantations and other immune-related conditions. Because of the biomedical relevance of this class of compounds and their novel molecular architecture, we initiated a program directed towards the total synthesis of rapamycin.[15, 16]



1 : Rapamycin



FK506

Fig. 1. Structures of rapamycin and FK506.

Results and Discussion

Retrosynthetic Analysis and Strategy: Rapamycin's imposing structure (**1**) contains 15 stereogenic centers, a 31-membered ring, a conjugated triene system, and a masked 1,2,3-tricarbonyl moiety. Its molecular complexity coupled with its chemical sensitivity presented us with a number of challenging problems among which was the formation of the macrocyclic ring. Solutions to this problem may be devised based on ring closure by

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[**] A list of abbreviations used in this article is given in ref. [49].

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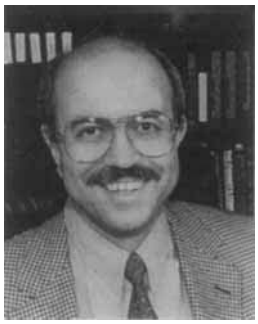
macrolactamization or macrolactonization strategies as demonstrated in the synthesis of the related natural product FK506 by the Merck[17] and the Harvard[18] groups. However, careful inspection of the structure of rapamycin suggested to us the possibility of constructing the macrocyclic ring by inserting a C19–C20 ethene unit between two terminal vinyl iodides to form simultaneously the triene and the 31-membered macrocyclic systems (Scheme 1). It was also anticipated that this "stitching cyclization" could be achieved after removal of all protecting groups and adjustment of oxidation states; this last step would then deliver rapamycin (**1**) directly.

Disconnection of the triene system in **1** (Scheme 1, Stille palladium-catalyzed coupling[19]) suggests bis(vinyl iodide) **2** and distannylethene **3**[20, 21] (C19–C20 fragment) as potential precursors. Further disconnection of the indicated amide and ester bonds in **2** and opening of the lactol ring reveals, upon appropriate functional group adjustments, compounds **4**–**6** as advanced key intermediates. The most complex of the latter three fragments, compound **6** was then dissected (Evans aldol reaction for the C34–C35 bond and a chromium–nickel coupling[22] for the C28–C29 bond) to afford, after functional group manipulations, compounds **7**–**9** as potential building blocks. Thus a strategy was devised entailing construction and coupling of intermediates **7**–**9** and final elaboration to rapamycin.

Total Synthesis of Rapamycin: The first task in the projected total synthesis of rapamycin was the construction of the key building blocks **4**, **7**, **8**, and **9**. These compounds were synthesized from readily available starting materials and by means of highly stereocontrolled sequences.



Editorial Board Member:[*] *K. C. Nicolaou was born in 1946 in Cyprus. In 1964 he went to England where he spent two years learning English and preparing to enter the University. He studied chemistry at the University of London and received his Ph.D. in 1972 from University College, London, under F. Sondheimer and P. J. Garratt. After postdoctoral work at Columbia University with T. J. Katz and at Harvard University with E. J. Corey, he joined the faculty at the University of Pennsylvania in 1976, where he was promoted to Rhodes-Thompson Professor of Chemistry. In 1989, he accepted joint appointments as Professor of Chemistry at the University of California, San Diego, and as Darlene Shiley Professor of Chemistry and Chairman of the Department of Chemistry at the Scripps Research Institute. His awards and honors include a Guggenheim Fellowship, a Humboldt Foundation Senior American Scientist Award, and the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry. Nicolaou's research interests focus on chemical synthesis, molecular design and molecular recognition, and the biological actions of molecules. He is the author or co-author of over 330 publications, 45 patents, and two books. Nicolaou's current research includes chemical synthesis, molecular design, and biological evaluation of compounds from the areas of taxoids, enediynes, carbohydrates, DNA interacting molecules, DNA replication, zaragozic acids, and brevetoxins.*

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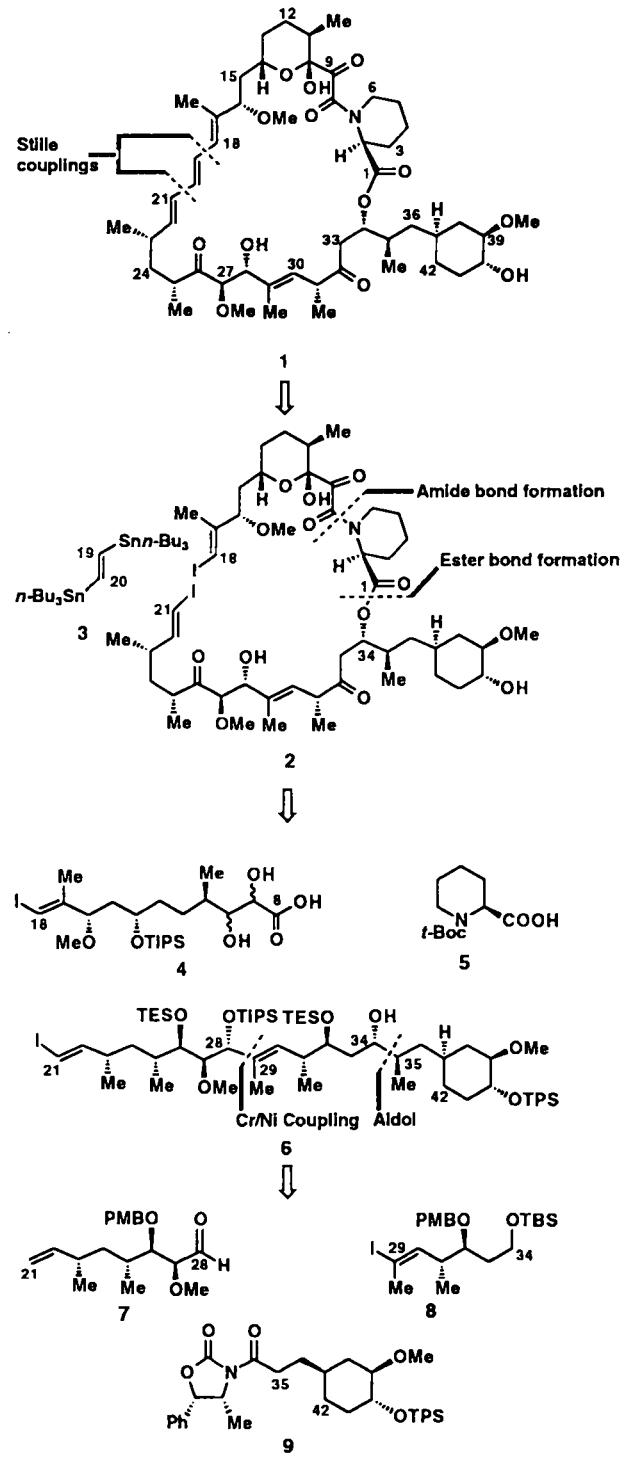
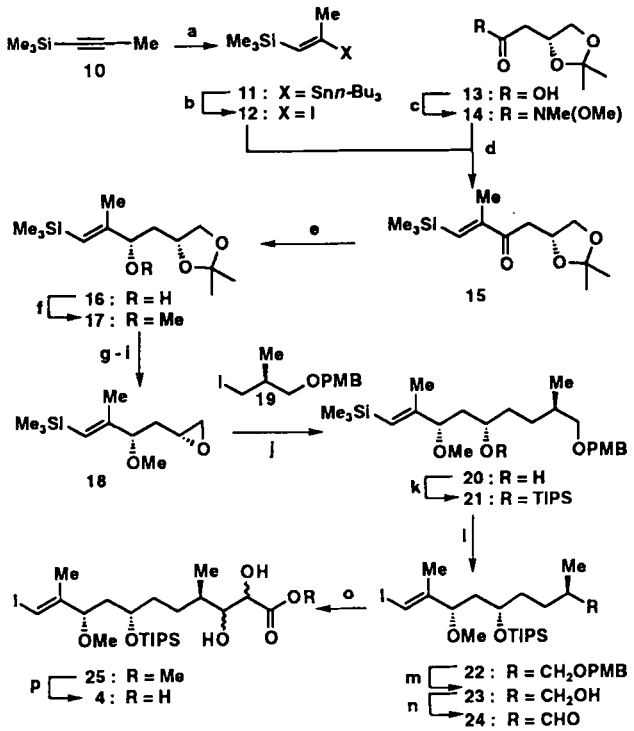


Scheme 1. Retrosynthetic analysis of rapamycin (**1**).

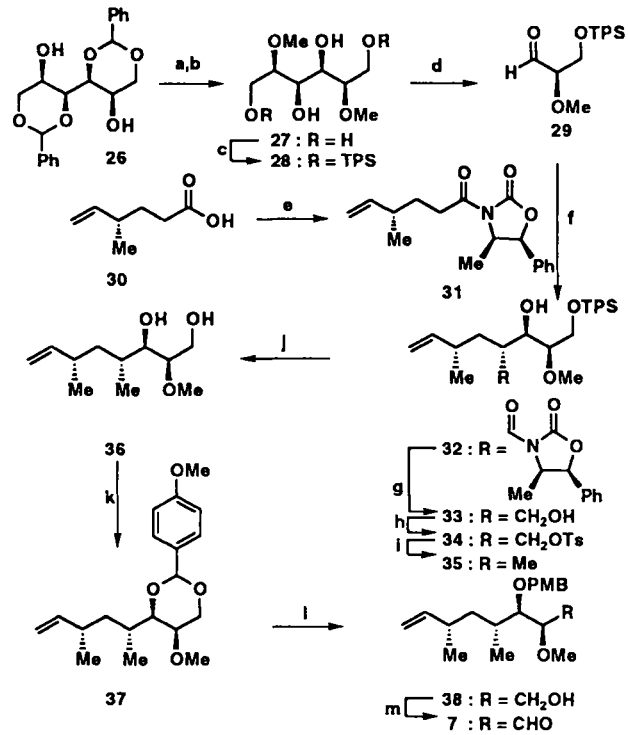
Construction of Building Block 4: Trimethylsilylpropyne **10** (Scheme 2) was converted[22] regio- and stereoselectively to stannane **11**, by addition of tri-*n*-butyltin hydride catalyzed by $[Mo(allyl)Br(CO)_2(CH_3CN)_2]$,[24] and then to its iodide counterpart **12** by exposure to iodine (81% overall yield).[26] The Weinreb amide **14** was prepared in 71% yield from carboxylic acid **13**[25] (Scheme 2) by reaction with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of DCC and triethylamine. Conversion of iodide **12** to its lithio derivative by halogen–metal exchange (*t*BuLi, Et_2O, −78 °C) followed by addition of **14** resulted in the formation of ketone **15** in 70% yield. Reduc-



Scheme 2. Construction of building block **4**. Reagents and conditions: a) nBu$_3$SnH (0.98 equiv), [Mo(allyl)Br(CO)$_2$(CH$_3$CN)$_2$] (0.1 equiv), THF, 25 °C, 30 min; b) I$_2$, CH$_2$Cl$_2$, 25 °C, 15 min, 81% from **10**; c) DCC (1.0 equiv), NHMe(OMe)·HCl (1.2 equiv), Et$_3$N (1.2 equiv), CH$_2$Cl$_2$, 25 °C, 2 h, 70%; d) **12** (1.2 equiv), tBuLi (4.0 equiv), Et$_2$O, −78 °C, 0.5 h, then **14** (1.0 equiv), −78 °C, 1 h, 70%; e) LiI (5.0 equiv), LiAlH$_4$ (5.0 equiv), Et$_2$O, −100 °C, 10 min, 86%; f) NaH (1.5 equiv), MeI (2.0 equiv), DMF, 25 °C, 1.5 h, 94%; g) CSA (0.02 equiv), MeOH, 25 °C, 5 h, 93%; h) CF$_3$SO$_2$Cl (1.0 equiv), Et$_3$N (2.0 equiv), CH$_2$Cl$_2$, 0 °C, 5 min; i) K$_2$CO$_3$ (1.0 equiv), MeOH, 25 °C, 10 min, 64% overall from **17**; j) **19** (5.0 equiv), tBuLi (10 equiv), Et$_2$O, −100 °C, 15 min, then 2-thienylCu(CN)Li (5.0 equiv), −100 → 0 °C, 15 min, then **18** (1.0 equiv), −30 → 0 °C, 0.5 h, 88%; k) TIPSOTf (1.2 equiv), 2,6-lutidine (1.5 equiv), CH$_2$Cl$_2$, 0 °C, 20 min, 98%; l) NIS (6.0 equiv), THF, 25 °C, 24 h, 97%; m) DDQ (1.2 equiv) CH$_2$Cl$_2$/H$_2$O (19:1), 25 °C, 1 h, 94%; n) (COCl)$_2$ (1.5 equiv), DMSO (3.2 equiv), Et$_3$N (6.0 equiv), CH$_2$Cl$_2$, −78 → 0 °C, 0.5 h, 98%; o) methyl glycolate (6.0 equiv), LDA (8.0 equiv), THF, −78 → 0 °C, 30 min, then **24** (1.0 equiv) in THF/HMPA (3:1), −78 °C; p) LiOH (4.0 equiv) THF/MeOH/H$_2$O (3:1:1), 0 °C, 1 h, 95%.

tion of **15** with LiAlH$_4$ in ether at −100 °C proceeded stereoselectively[27] to afford the allylic alcohol **16** as a single stereoisomer in 86% yield. Methylation of **16** under standard conditions (NaH/MeI) led to methoxy compound **17** (94% yield), which was transformed to epoxide **18** in 64% overall yield by the following sequence: a) CSA (cat.), MeOH; b) trifluoromethanesulfonyl chloride, Et$_3$N; and c) K$_2$CO$_3$, MeOH. Regioselective opening of the epoxide in **18** with the mixed cuprate[28] derived from the lithio derivative of **19**[29] (tBuLi) and 2-thienylCu(CN)Li at low temperature resulted in formation of compound **20** (88% yield). Exposure of alcohol **20** to triisopropylsilyl triflate and 2,6-lutidine furnished silyl ether **21** (98% yield), and stereospecific silicon–iodine exchange within the latter compound by means of N-iodosuccinimide[30] led to vinyl iodide **22** in 97% yield. Generation of the primary alcohol in **22** by DDQ-induced removal of the p-methoxybenzyl group gave compound **23** (94% yield), which was oxidized under Swern conditions to give aldehyde **24** (98% yield). The latter compound was combined with the dianion of methyl glycolate (LDA) in the presence of HMPA to provide aldol product **25** in 72% yield. Finally, the requisite dihydroxy carboxylic acid **4** was obtained by alkaline hydrolysis of the ester in 95% yield (Scheme 2).

Construction of Building Block 7: The commercially available carbohydrate derivative **26** (Scheme 3) was dimethylated with NaH/MeI (93% yield) and then subjected to hydrogenolysis (10% Pd/C, H$_2$, EtOH/EtOAc) to afford tetraol **27** (100% yield). Selective silylation of the primary hydroxyl groups in **27** with TPSCl and imidazole furnished bis(silyl ether) **28** (95% yield), and cleavage of the 1,2-diol with lead tetraacetate afforded aldehyde **29** (90% yield). The other requisite intermediate (**31**, Scheme 3) was prepared from carboxylic acid **30**[31] and (4R,5S)-4-methyl-5-phenyloxazolidone by combining the pivaloate mixed anhydride[32] of the former with the lithio derivative of the latter (−78 → 0 °C, ether) (90% yield). Reaction of the boron enolate of **31** (nBu$_2$BOTf/Et$_3$N) with aldehyde **29** in CH$_2$Cl$_2$ at low temperature furnished compound **32** stereoselectively (≥98% by ^{1}H NMR) in 73% yield. The next task, the generation of a methyl group from the side chain carrying the chiral auxiliary in **32**, was accomplished as follows:[31] a) reduction to the primary alcohol **33** with LiBH$_4$ (98% yield); b) tosylation with TsCl, Et$_3$N, and DMAP (cat.) to give **34** (78% yield); and c) reduction with superhydride (LiBEt$_3$H, 92% yield) leading to **35**. The silyl group was then removed from **35** with TBAF in THF (92% yield) and the 1,3-diol system in the resulting compound (**36**) was protected as a p-methoxybenzylidine system by exposure to p-methoxybenzaldehyde dimethyl acetal and CSA (97% yield). Finally, regioselective



Scheme 3. Construction of building block **7**. Reagents and conditions: a) NaH (2.3 equiv), DMF, 25 °C, 2 h, then CH$_3$I (3.0 equiv), 25 °C, 2 h, 93%; b) 10% Pd/C (0.05 wt%), H$_2$, EtOH/EtOAc (1:1), 24 h, 100%; c) TPSCl (2.2 equiv), imidazole (4.5 equiv), DMF, 25 °C, 4 h, 95%; d) Pb(OAc)$_4$ (1.05 equiv), Na$_2$CO$_3$ (1.05 equiv), CH$_2$Cl$_2$, 0 → 25 °C, 90%, 1.5 h; e) **32** (1.0 equiv), (CH$_3$)$_3$CCOCl (1.05 equiv), Et$_3$N (1.05 equiv), Et$_2$O, −78 → 0 °C, 1 h, then lithium (4R,5S)-4-methyl-5-phenyl-oxazolidone (1.0 equiv), −78 → 0 °C, 1 h, 90%; f) **33** (1.0 equiv), nBu$_2$BOTf (1.1 equiv), CH$_2$Cl$_2$, −78 °C, 5 min, then Et$_3$N (1.3 equiv), −78 → 0 °C, 1.5 h, **31** (1.3 equiv), −78 → −10 °C, 6 h, 73%; g) LiBH$_4$ (2.2 equiv), H$_2$O (2.2 equiv), Et$_2$O, 0 → 25 °C, 1 h, 98%; h) TsCl (1.2 equiv), Et$_3$N (3.0 equiv), DMAP (0.2 equiv), CH$_2$Cl$_2$, 0 °C, 12 h, 78%; i) LiEt$_3$BH (3.2 equiv), THF, 0 → 25 °C, 8 h, 92%; j) TBAF (1.5 equiv), THF, 25 °C, 1.5 h, 92%; k) p-anisaldehyde dimethyl acetal (1.5 equiv), CSA (0.2 equiv), CH$_2$Cl$_2$, 25 °C, 4 h, 97%; l) DIBAlH (1.75 equiv), CH$_2$Cl$_2$, −78 → 25 °C, 2 h, 96%; m) (COCl)$_2$, (1.5 equiv), DMSO (3.0 equiv), CH$_2$Cl$_2$, −78 °C, 1 h, then Et$_3$N, (5.0 equiv), −78 → 25 °C, 90 min, 97%.

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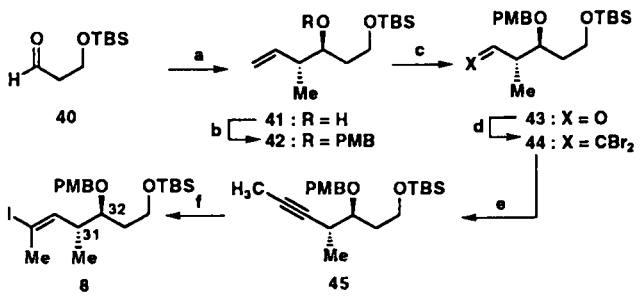
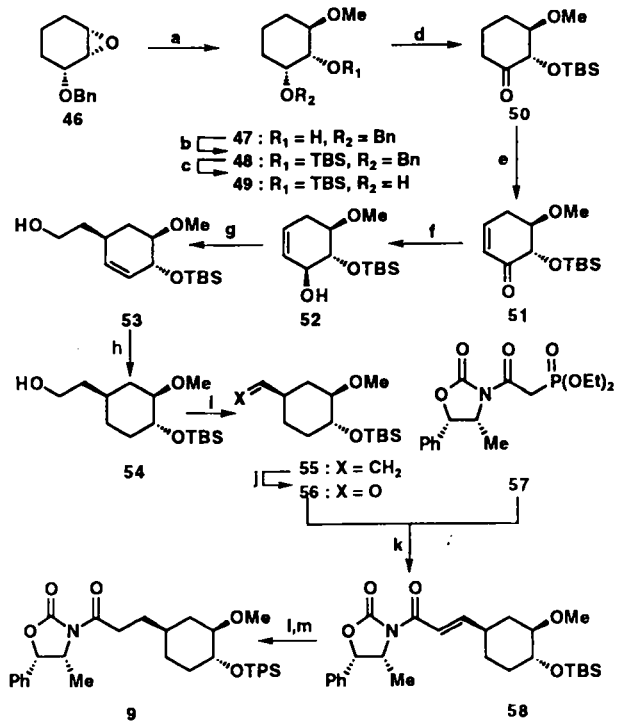
opening of the acetal in **37** by the action of DIBALH[17] followed by Swern oxidation led to the desired aldehyde **7** via primary alcohol **38** in 93% overall yield.

Construction of Building Block 8: For the stereoselective construction of vinyl iodide **8** we used the asymmetric crotylboration method developed by Brown.[33] Thus, aldehyde **40**[34] (Scheme 4) was reacted with the chiral boron reagent[33] derived from *trans*-2-butene, *n*BuLi, KO*t*Bu and (+)-Ipc$_2$BOMe in the presence of $BF_3 \cdot Et_2O$ to afford alcohol **41** in 75% yield. The hydroxyl group in **41** was protected as a PMB ether by the action of NaHMDS and *p*-methoxybenzyl bromide (90% yield). Ozonolysis of **42** furnished aldehyde **43** (80% yield), which was treated with $CBr_4/Ph_3P/Zn$ dust[35] to afford dibromoolefin **44** in 99% yield. Exposure of the dibromide **44** to *n*BuLi followed by quenching with MeI led to the methyl acetylene **45** in 98% yield. This compound was converted regioselectively and stereospecifically to vinyl iodide **8** by hydrozirconation (Cp_2ZrHCl)[36] and quenching with iodine (85% overall yield).



Scheme 4. Construction of building block **8**. Reagents and conditions: a) *trans*-2-butene (2.0 equiv), *n*BuLi (1.1 equiv), KO*t*Bu (1.0 equiv), (+)-Ipc$_2$BOMe (1.2 equiv), $BF_3 \cdot OEt_2$ (1.2 equiv), $-78 \rightarrow 25\,^{\circ}C$, 4 h, 75%; b) PMBBr (1.5 equiv), NaHMDS (1.2 equiv), THF/DMF (2:1), 2.5 h, 0 °C, 90%; c) O_3, CH_2Cl_2/MeOH/pyridine (5:5:1), $-78\,^{\circ}C$, then Me_2S, $-78 \rightarrow 25\,^{\circ}C$, 16 h, 80%; d) CBr_4 (2.7 equiv), Ph_3P (2.7 equiv), Zn dust (2.7 equiv), CH_2Cl_2, 25 °C, 2 h, 100%; e) *n*BuLi (2.1 equiv), THF, $-78 \rightarrow -20\,^{\circ}C$, 1 h, then CH_3I (5.0 equiv), $-20 \rightarrow 0\,^{\circ}C$, 2 h, 98%; f) Cp_2ZrHCl (2.5 equiv), 25 °C, 1.5 h, then I_2, 0 °C, 85%.

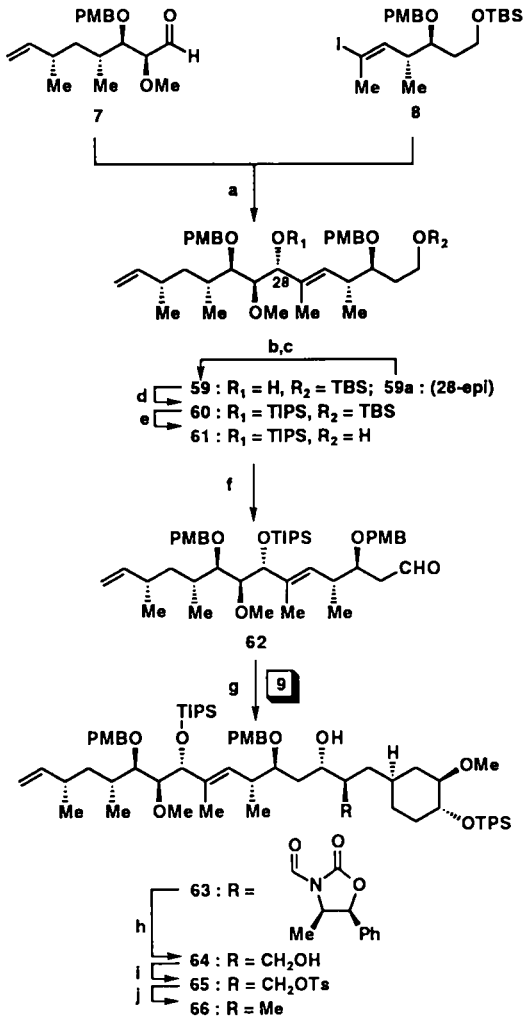
Construction of Building Block 9: Enantiomerically pure epoxide **46**[36] (Scheme 5) was treated with CSA in MeOH to afford regioselectively and stereospecifically hydroxy compound **47** (90% yield). Silylation of **47** with TBSOTf in the presence of 2,6-lutidine afforded silyl ether **48** in 91% yield. Hydrogenolysis of the benzyl ether in **48** (10% Pd/C, H_2, EtOH) led to alcohol **49** (98%), which was oxidized under Swern conditions to afford ketone **50** in 92% yield. Enone **51** was then formed from **50** via its TMS enol ether (LDA/TMSCl) by oxidation with $Pd(OAc)_2$[38] (83% overall yield). Stereoselective 1,2-reduction[39] of the enone functionality in **51** with $LiBH_4$ proceeded smoothly in the presence of $CeCl_3 \cdot 7H_2O$ at $-78\,^{\circ}C$ to afford allylic alcohol **52** in 95% yield. Exposure of **52** to *N*,*N*-dimethylacetamide dimethylacetal[40] followed by refluxing in xylenes and treatment with $LiEt_3BH$ resulted in the formation of primary alcohol **53**, in an Eschenmoser–Claisen rearrangement[40] followed by reduction (97% yield). Hydrogenation of the double bond in **53** (H_2, 10% Pd/C, EtOH) furnished **54** in quantitative yield. Conversion of the primary alcohol in **54** to the terminal olefin **55** (*o*-$NO_2C_6H_4SeCN$, nBu_3P then 30% H_2O_2, 86% yield)[41] followed by ozonolysis led to aldehyde **56** (88% yield). Condensation of amide phosphonate **57**[41] with aldehyde **56** in the presence of iPr_2NEt and LiCl[43] furnished



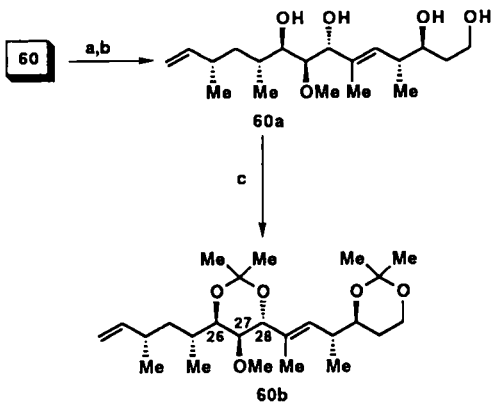
Scheme 5. Construction of building block **9**. Reagents and conditions: a) CSA (0.2 equiv), MeOH, 2 h, 25 °C, 90%; b) TBSOTf (1.2 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C, 1.5 h, 91%; c) H_2, 10% Pd/C (0.05 wt%), EtOH, 25 °C, 24 h, 98%; d) $(COCl)_2$ (1.5 equiv), DMSO (3.2 equiv), Et_3N (5.0 equiv), $-78 \rightarrow -10\,^{\circ}C$, 1 h, 92%; e) LDA (1.1 equiv), THF, $-78\,^{\circ}C$, 15 min, then TMSCl (1.5 equiv), $-78 \rightarrow 25\,^{\circ}C$, 4 h; followed by $Pd(OAc)_2$ (1.2 equiv), CH_3CN, 50 °C, 24 h, 83% overall; f) $LiBH_4$ (4.0 equiv), $CeCl_3 \cdot 7H_2O$ (2.0 equiv), THF/MeOH (1:1), $-78\,^{\circ}C$, 1 h, 95%; g) *N*,*N*-dimethylacetamide dimethyl acetal (5.0 equiv), xylenes, reflux, 48 h, then $LiEt_3BH$ (4.0 equiv), THF, 0 °C, 2 h, 97%; h) H_2, 10% Pd/C (0.05 wt%), EtOH, 16 h, 25 °C, 100%; i) *o*-$NO_2C_6H_4SeCN$ (1.2 equiv), nBu_3P (1.2 equiv), THF, 25 °C, 3 h, then H_2O_2 (30% aq.), THF, 25 °C, 6 h, 86%; j) O_3, MeOH/CH_2Cl_2 (1:1), $-78\,^{\circ}C$, then Me_2S (5.0 equiv), $-78 \rightarrow 25\,^{\circ}C$, 16 h, 88%; k) **57** (1.5 equiv), LiCl (2.0 equiv), *N*,*N*-diisopropylethylamine (2.0 equiv), then **56** (1.0 equiv), 25 °C, 6 h, 96%; l) $Rh(PPh_3)_3Cl$ (0.05 equiv), Et_3SiH, 50 °C, 2 h, then aq. HF in CH_3CN (10%), 25 °C, 3 h followed by TPSCl (1.5 equiv), imidazole (3.0 equiv), DMF, 25 °C, 16 h, 75% overall.

α,β-unsaturated amide **58** (96% yield), which was reduced[44] with Et_3SiH in the presence of Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] to the corresponding saturated counterpart of **58**. Treatment with aqueous HF in acetonitrile followed by exposure to TPSCl and imidazole in DMF furnished the requisite building block **9** in 75% overall yield from **58**.

Coupling of Building Blocks 7 and 8, and Synthesis of Advanced Key Intermediate 66: Coupling of intermediates **7** and **8** was carried out by means of the Nozaki-Hiyama-Kishi reaction ($CrCl_2/NiCl_2$)[122] in DMSO to give a mixture of the two diastereomeric alcohols **59** and **59a** in 83% total yield (**59**:**59a**, ca. 2:1) (Scheme 6). The stereochemistry of the major isomer (**59**) was confirmed by NMR spectroscopy performed on the bisacetonide **60b** (Scheme 7) prepared by a) DDQ-induced removal of the PMB ethers (82%); b) exposure to HF·pyridine to give the tetraol **60a** (97% yield); and c) treatment with 2,2-dimethoxypropane and CSA (77% yield plus 20% recovered starting material). In the ^{13}C NMR spectrum the chemical shifts of the acetonide methyl groups (δ = 24.84 and 24.26) supported[45] the *anti* stereochemical relationship of the oxygens at C26 and C28 in **60** and its progenitors. The undesired isomer **59a** was oxidized with Dess–Martin reagent to afford the corresponding ketone (91% yield), which was stereoselectively re-



Scheme 6. Synthesis of advanced key intermediate **66**. Reagents and conditions: a) $CrCl_2$ (containing 0.1% $NiCl_2$) (10 equiv), DMSO, 25 °C, 72 h, 83% (2:1 α:β); b) Dess–Martin periodinane (1.1 equiv), CH_2Cl_2, 25 °C, 1 h, 91%; c) DIBAlH (3.0 equiv), THF, −78 °C, 1 h, 85% (**59**/**59a** ca. 10:1); d) TIPSOTf (1.1 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C, 98%; e) HF·pyridine, THF, 25 °C, 2 h, 97%; f) $(COCl)_2$ (1.5 equiv), DMSO (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 → −10 °C, 3 h, 97%; g) **9** (1.5 equiv), $n$$Bu_2$BOTf (1.65 equiv), Et_3N (1.8 equiv), CH_2Cl_2, −78 → 0 °C, 1.5 h, then **62** (1.0 equiv), −78 → −5 °C, 12 h, 86%; h) $LiBH_4$ (2.2 equiv), H_2O (2.2 equiv), Et_2O, 0 → 25 °C, 1 h, 98%; i) TsCl (1.2 equiv), DMAP (0.2 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 91%; j) $LiEt_3BH$ (10 equiv), THF, 0 → 25 °C, 2.5 h, 91%.

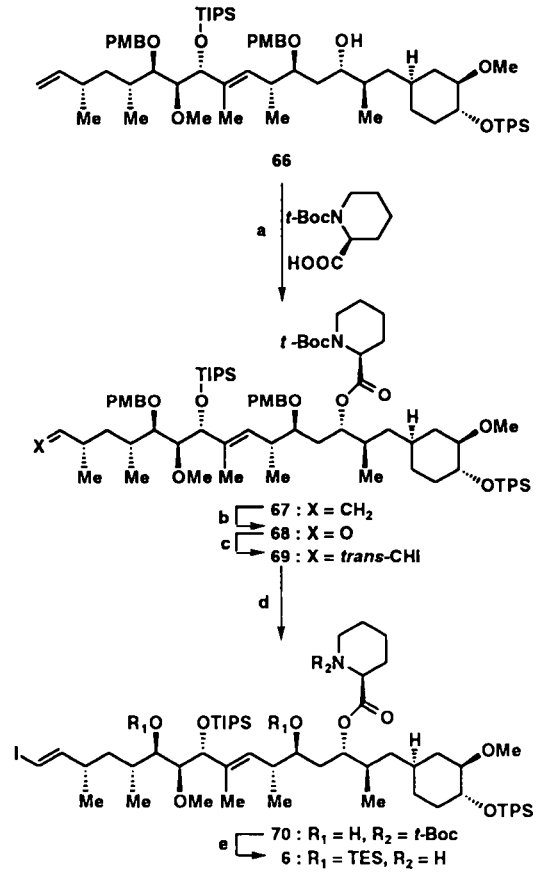


Scheme 7. Synthesis of bisacetonide **60b**. Reagents and conditions: a) DDQ (3.0 equiv), $CHCl_3/H_2O$ (20:1), 25 °C, 2 h; 82%; b) HF·pyridine, THF, 25 °C, 24 h, 97%; c) 2,2-dimethoxypropane (3.0 equiv), CSA (0.03 equiv), acetone, 25 °C, 2 h, 77% plus 20% recovered **60a**.

duced with DIBAL in THF at −78 °C; more hydroxy compound **59** was thus recovered (85% yield, ca. 10:1 ratio of **59**:**59a**) (Scheme 6).

Protection of the hydroxyl group in **59** as a silyl ether by treatment with TIPSOTf and 2,6-lutidine gave derivative **60** in 98% yield. This compound (**60**) was subjected to HF·pyridine in THF to furnish primary alcohol **61** through selective removal of the TBS group (97% yield). Swern oxidation of **61** led to aldehyde **62** (97%), which was condensed with the boron enolate ($n$$Bu_2$BOTf, Et_3N) of compound **9** at low temperature to afford, in 86% yield, aldol product **63** as the only isolated compound (≥98% diastereoselectivity). The chiral auxiliary in **63** was utilized to generate the requisite methyl group by the sequence **63** → **64** ($LiBH_4$, 98%), **64** → **65** (TsCl, Et_3N, DMAP, 91%), and **65** → **66** ($LiEt_3BH$, 91%) as described earlier.

Coupling of Advanced Intermediate ***66*** *and Building Block* ***5****, and Synthesis of Advanced Intermediate* ***6***: Intermediate **66** was esterified with *N*-Boc-L-pipecolic acid (**5**) in the presence of DIC, $i$$Pr_2$NEt, and 4-pyrrolidinopyridine to afford ester **67** in 85% yield (Scheme 8). The terminal olefin in **67** was then selectively oxidized by initial conversion to the corresponding diol (OsO_4 cat., *N*-methylmorpholine-*N*-oxide) followed by treatment of the latter with $Pb(OAc)_4$ in the presence of Na_2CO_3 to furnish



Scheme 8. Synthesis of advanced intermediate **6**. Reagents and conditions: a) *N*-Boc-L-pipecolic acid (5.0 equiv), DIC (5.0 equiv), *N*,*N*-diisopropylethylamine (5.0 equiv), 4-pyrrolidinopyridine (0.5 equiv), CH_2Cl_2, −20 °C, 24 h, 85%; b) OsO_4 (0.2 equiv), *N*-methylmorpholine-*N*-oxide (3.5 equiv), acetone/H_2O (2:1), 25 °C, 16 h, followed by $Pb(OAc)_4$, (1.5 equiv), Na_2CO_3 (3.0 equiv), C_6H_6, 0 → 25 °C, 1.5 h, 75% overall; c) CHI_3 (4.0 equiv), $CrCl_2$ (12 equiv), THF/dioxane (4:1), 25 °C, 1 h, 94%; d) DDQ (3.0 equiv), $CHCl_3/H_2O$ (19:1), 25 °C, 1 h, 98%; e) TESOTf (15 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, 0 °C, 1 h, then silica gel, CH_2Cl_2, 25 °C, 6 h, 94%.

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aldehyde **68** in 75% overall yield. Reaction of aldehyde **68** with iodoform (CHI_3) and $CrCl_2$[46] gave vinyl iodide **69** in 94% yield. The two PMB groups in **69** were removed by treatment with DDQ to give the diol **70** in 98% yield. Compound **70** was silylated with excess TESOTf in the presence of 2,6-lutidine to afford, after treatment with silica gel (which ensures the liberation of the free amine) and chromatography, the advanced intermediate **6** (94% yield).

Final Stages and Total Synthesis of Rapamycin: The final stages of the total synthesis of rapamycin (**1**) are shown in Scheme 9. Thus condensation of carboxylic acid **4** with amine **6** in the presence of 1-hydroxybenzotriazole and DIC resulted in the formation of amide **71** in 95% yield. Swern oxidation of diol **71** furnished diketone **72**, which was subjected to HF·pyridine in THF to remove selectively the TES groups. Oxidation of the latter group under Swern conditions furnished tetraketone **73**. Exposure of **73** to aqueous HF in CH_3CN removed the remaining three silyl groups leading to compound **2** in 70% overall yield from **71** (note that the lactol in **2** was formed as a mixture of diastereoisomers). Finally, exposure of the bis(vinyl iodide) **2** to distannylethene **3**[20] in the presence of catalytic amounts of $[Pd(CH_3CN)_2Cl_2]$[19, 21] and iPr_2NEt in DMF/THF at 25 °C resulted in the formation of rapamycin (**1**) in 27% yield. A "seco-vinyl iodide" in which only one vinyl iodide (presumably the less substituted one) had reacted with one end of the distannane **3** was also isolated in small amounts; under the same Stille reaction conditions used above, it furnished rapamycin (**1**) in 70% yield. Synthetic rapamycin (**1**) exhibited identical properties to those of an authentic sample (R_f, $[\alpha]_D^{22}$, IR, ^1H NMR, ^{13}C NMR, MS).[47]

Conclusion

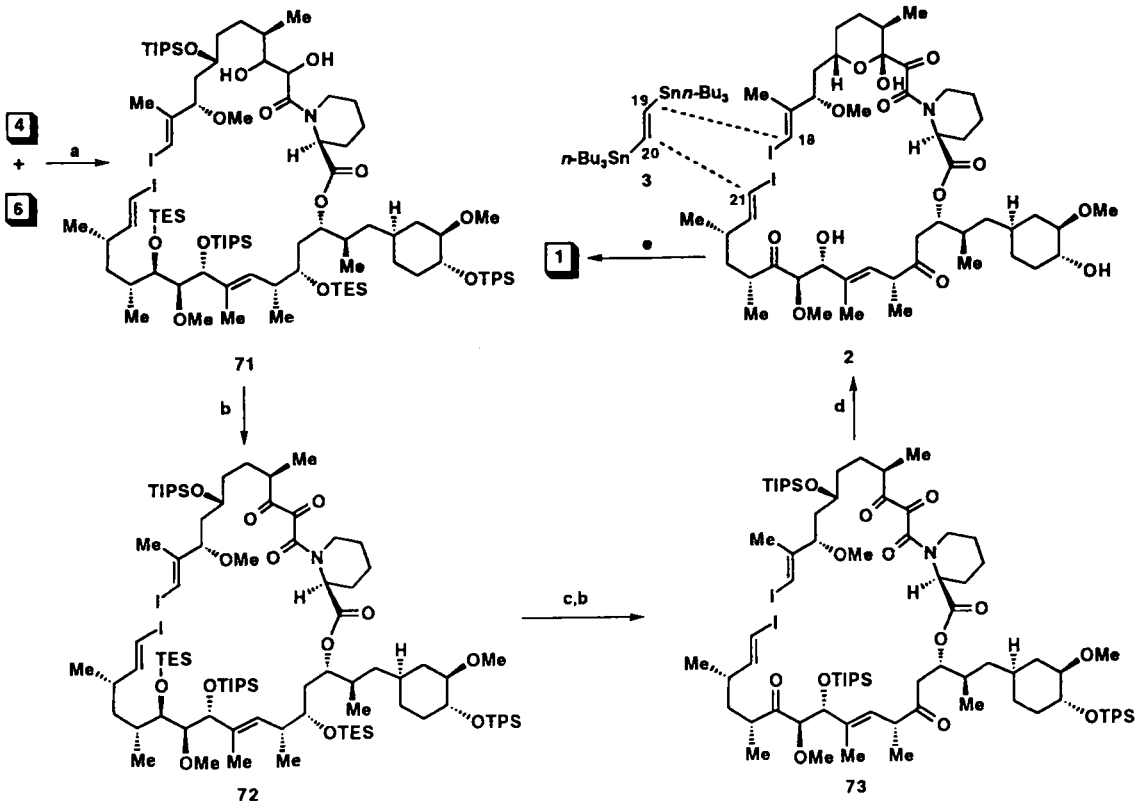
The described total synthesis of rapamycin (**1**) is characterized by high convergency and stereocontrol at several stages. It is also distinctly direct in its final stage in that the penultimate open-chain precursor, although highly functionalized, contains no protecting groups. The double Stille-type ring closure ("stitching cyclization"), first developed during this synthesis, is already finding other applications in macrocycle formation.[48] Finally the flexibility of the strategy makes it suitable for the synthesis of designed rapamycin analogues with potential applications in biology and medicine.

Experimental Section

General Techniques: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF and Et_2O were distilled from sodium–benzophenone; CH_2Cl_2, benzene, and toluene from calcium hydride. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless stated. All solutions used in workup were saturated unless otherwise noted. All reagents were purchased at highest commercial quality.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using light, 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on Brucker AMX-500 or AM-300 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. The carbon numbering of rapamycin was used to assign protons. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-



Scheme 9. Total synthesis of rapamycin (**1**). Reagents and conditions: a) **4** (3.0 equiv), 1-hydroxybenzotriazole (3.0 equiv), DIC (3.0 equiv), CH_2Cl_2, 0 °C, 3 h, then **6** (1.0 equiv), 0 °C, 16 h, 95%; b) $(COCl)_2$ (20 equiv), DMSO (40 equiv), Et_3N (100 equiv), CH_2Cl_2, −78 → 0 °C, 2 h; c) HF·pyridine (excess), THF, 0 → 25 °C, 2 h; d) aqueous HF in CH_3CN (10%), 25 °C, 48 h, 70% overall from **71**; e) **3** (1.25 equiv), $[Pd(CH_3CN)_2Cl_2]$ (20 mol%), *N*,*N*-diispropylethylamine (1.25 equiv), DMF/THF (2:1), (0.01 M), 25 °C, 48 h, 27%.

Elmer 1600 series FT-IR spectrometer or a Mattson Instruments 2020 Galaxy series FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mas spectrometer under fast atom bombardment conditions.

Vinylstannane 11: To a solution of **10** (18.00 g, 160.4 mmol) in THF (150 mL) was added $[Mo(allyl)Br(CO)_2(CH_3CN)_2]$ (2.64 g, 7.44 mmol) followed by tri-*n*-butyltin hydride (41.7 mL, 155 mmol), and the solution was stirred at ambient temperature for 30 min. The solvent was concentrated, and the residue was filtered through silica gel with petroleum ether as eluent. The solvent was evaporated to provide compound **11** (60.0 g, 93% yield), which was used in the next reaction without further purification: $R_f = 0.90$ (petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2955, 2924, 1985, 1714, 1558, 1458, 1369, 1247, 1073, 843\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.80$ (dq, $J = 100, 1.5$ Hz, 1H; Me_3SiCH), 2.03 (d, $J = 1.5$ Hz, 3H; vinyl-CH_3), 1.52–1.25 (m, 12H), 0.96–0.81 (m, 15H), 0.10 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 143.5, 29.2, 29.1, 27.5, 27.4, 13.7, 9.3, 0.4$; FAB HRMS calcd for $C_{18}H_{40}SnSi$ ($M-C_4H_9+2H$): 347.1217; found *m/e* 347.1216.

Vinyl iodide 12: To a solution of crude compound **11** (60.00 g, 149 mmol) in CH_2Cl_2 (400 mL) was added iodine (45.43 g, 179 mmol) in one portion, and the mixture was stirred at 0 °C for 15 min. The solution was concentrated, and the residue was purified by flash chromatography (silica gel, petroleum ether) to afford **12** (30.00 g, 81%) as a colorless oil: $R_f = 0.80$ (petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2955, 2916, 1715, 1593, 1427, 1371, 1251, 1050, 955, 845, 763, 692\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.26$ (d, $J = 0.96$ Hz, 1H; Me_3SiCH), 2.51 (d, $J = 0.96$ Hz, 3H; CH_3Cl), 0.11 (s, 9H; $(CH_3)_3Si$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.1, 110.0, 34.6, -0.2$; FAB HRMS (NBA) calcd for $C_6H_{13}SiI$: 239.9831; found *m/e* 239.9831.

Amide 14: To a stirred solution of carboxylic acid **13** (10.30 g, 64.40 mmol) in CH_2Cl_2 (150 mL) were added methoxymethylamine hydrochloride (6.28 g, 64.40 mmol), triethylamine (9.0 mL, 64.40 mmol), and DCC (13.30 g, 64.40 mmol) at ambient temperature, and the reaction was stirred overnight. The solution was concentrated and the residue was taken up in ethyl acetate (200 mL) and filtered. The solvent was evaporated, and the residue purified by flash chromatography (silica gel, 30% ethyl acetate in petroleum ether) to afford compound **14** (11.11 g, 85% yield) as a colorless oil: $[\alpha]_D^{23} = -28.1$ ($c = 2.40$, $CHCl_3$); $R_f = 0.26$ (silica gel, 33% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3580, 2984, 2936, 1713, 1660, 1424, 1375, 1220, 1158, 1060, 998, 861\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.48$ (m, 1H; 14-H), 4.19 (dd, $J = 8.4, 6.1$ Hz, 1H; 13-H), 3.66 (s, 3H; CH_3O), 3.61 (dd, $J = 8.4, 6.6$ Hz, 1H; 13-H'), 3.13 (s, 3H; CH_3N), 2.95 (dd, $J = 16.2, 5.4$ Hz, 1H; 15-H), 2.51 (dd, $J = 16.2, 7.8$ Hz, 1H; 15-H'), 1.38 (s, 3H; CH_3), 1.32 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 108.7, 72.2, 69.6, 61.2, 36.6, 31.8, 26.8, 25.3$; FAB HRMS (NBA) calcd for $C_9H_{18}NO_4$ ($M+H^+$): 204.1236; found *m/e* 204.1236.

Ketone 15: To a solution of vinyl iodide **12** (14.18 g, 59.08 mmol) in diethyl ether (140 mL) at −78 °C was added *tert*-butyllithium (69.5 mL, 1.7 M in pentane, 118.15 mmol) dropwise over 50 min. After 30 min, **14** (8.00 g, 39.36 mmol) in diethyl ether (5 mL) was added and the solution was stirred at −78 °C for 1.5 h. The reaction was quenched by careful addition of saturated aqueous NH_4Cl (50 mL). The layers were separated, and the aqueous phase extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 3% ethyl acetate in petroleum ether) to afford ketone **15** (6.23 g, 62% yield) as a colorless oil: $[\alpha]_D^{23} = -39.3$ ($c = 1.13$, $CHCl_3$); $R_f = 0.63$ (10% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2995, 2956, 1714, 1671, 1416, 1371, 1251, 1221, 1174, 1053, 851\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.68$ (s, 1H; 18-H), 4.47 (m, 1H; 14-H), 4.22 (dd, $J = 8.4, 6.1$ Hz, 1H; 13-H), 3.53 (dd, $J = 8.4, 6.7$ Hz, 1H; 13-H'), 3.30 (dd, $J = 17.2, 5.1$ Hz, 1H; 14-H), 2.80 (dd, $J = 17.2, 8.1$ Hz, 1H; 14-H'), 3.54 (t, $J = 7.7$ Hz, 1H; 16-H), 2.95 (s, 1H; OH), 1.79–1.68 (m, 2H; 15-H), 1.75 (s, 3H; C_{17}-CH_3), 1.41 (s, 3H; CH_3), 1.35 (s, 3H; CH_3), 0.09 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 154.8, 123.1, 109.3, 76.7, 75.5, 69.7, 39.1, 26.9, 25.7, 17.3, -0.12$; FAB HRMS (NBA/NaI) calcd for $C_{13}H_{24}O_3SiNa$ ($M+Na^+$): 281.1549; found *m/e* 281.1549.

Alcohol 16: To a suspension of of lithium iodide (13.07 g, 97.65 mmol) in ether (125 mL) at 0 °C was added enone **15** (5.00 g, 19.50 mmol) in ether (20 mL). After being stirred for 30 min at ambient temperature, the solution was cooled to −100 °C and treated with LAH (97.65 mL, 1.0 M in ether, 97.65 mmol) dropwise over 1 h. The resulting solution was stirred for 10 min before quenching with saturated aqueous Na_2SO_4 (40 mL). The mixture was filtered and concentrated. Purification of the residue by flash chromatography (silica gel, 15% ethyl acetate in petroleum ether) gave allylic alcohol **16** (4.32 g, 86% yield) as a colorless oil: $[\alpha]_D^{23} = -21.1$ ($c = 4.27$, $CHCl_3$); $R_f = 0.40$ (20% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3458$ (broad), 2984, 2952, 1711, 1621, 1413, 1374, 1249, 1221, 1157, 1063, 848 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.53$ (s, 1H; 18-H), 4.22 (m, 1H; 14-H), 4.15 (dd, $J = 8.4, 3.3$ Hz, 1H; 13-H), 4.07 (dd, $J = 8.4, 6.0$ Hz, 1H; 13-H'), 3.54 (t, $J = 7.7$ Hz, 1H; 16-H), 2.95 (s, 1H; OH), 1.79–1.68 (m, 2H; 15-H), 1.75 (s, 3H; 17-CH_3), 1.41 (s, 3H; CH_3), 1.35 (s, 3H; CH_3), 0.09 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 154.8, 123.1, 109.3, 76.7, 75.5, 69.7, 39.1, 26.9, 25.7, 17.3, -0.12$; FAB HRMS (NBA/NaI) calcd for $C_{13}H_{24}O_3SiNa$ ($M+Na^+$): 281.1549; found *m/e* 281.1549.

Methyl ether 17: Sodium hydride (60%, 2.16 g, 54.00 mmol) was washed with hexanes, taken up in DMF (20 mL), and cooled to 0 °C. A solution of alcohol **16** (6.98 g, 27.01 mmol) in DMF (60 mL) at 0 °C was added and the solution stirred for 30 min at ambient temperature. The solution was cooled to 0 °C and treated with methyl iodide (3.4 mL, 54.0 mmol). After being stirred for 40 min at ambient temperature, the solution was quenched with methanol (1 mL) and diluted with water (250 mL). The mixture was extracted with ether/petroleum ether (1:1, 3 × 150 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 3% ethyl acetate in petroleum ether) to afford pure **17** (7.14 g, 97% yield) as a colorless oil: $[\alpha]_D^{23} = -11.0$ ($c = 1.04$, $CHCl_3$); $R_f = 0.46$ (9% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2952, 1712, 1620, 1452, 1374, 1250, 1157, 1061, 851\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.46$ (s, 1H; 18-H), 4.04 (m, 1H; 14-H), 3.99 (dd, $J = 7.7, 5.8$ Hz, 1H; 13-H), 3.56–3.46 (m, 2H; 13-H' and 16-H), 3.15 (s, 3H; CH_3O), 1.95 (ddd, $J = 13.3, 6.2, 6.2$ Hz, 1H; 15-H), 1.66 (s, 3H; 17-CH_3), 1.64 (ddd, $J = 13.3, 6.6, 6.6$ Hz, 1H; 15-H'), 1.38 (s, 3H; CH_3), 1.31 (s, 3H; CH_3), 0.10 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.0, 127.9, 108.4, 86.1, 76.7, 69.3, 56.0, 37.1, 26.9, 25.7, 15.5, -0.14$; FAB HRMS (NBA/NaI) calcd for $C_{14}H_{28}O_3SiNa$ ($M+Na^+$): 295.1705; found *m/e* 295.1705.

Epoxide 18: To a solution of compound **17** (7.14 g, 26.21 mmol) in MeOH (350 mL) was added CSA (304 mg, 1.31 mmol) in one portion. After being stirred at ambient temperature for 3 h, the solution was cooled to 0 °C, quenched with triethylamine (2 mL), and concentrated. The residue was dissolved in ethyl acetate (100 mL) and washed with water (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude diol was used for the next reaction without further purification.

To a solution of the diol (from the procedure above) in CH_2Cl_2 (50 mL) at −78 °C was added triethylamine (6.86 mL, 49.0 mmol) followed by trifluoromethanesulfonyl chloride (1.56 mL, 24.57 mmol). After 25 min the solution was quenched with water (20 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude triflate was used in the next reaction without further purification.

To a solution of the triflate (from the procedure above) in MeOH (100 mL) at 0 °C was added potassium carbonate (3.40 g, 24.57 mmol) in one portion. After being stirred for 2 h at ambient temperature, the solution was concentrated. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 1:20 → 1:3, then 1:0) to afford epoxide **18** (3.76 g, 67% yield) as a colorless oil and recovered diol (1.05 g, 17%), which was resubmitted to the reaction conditions to provide a combined yield of 4.21 g (75% yield for 2 cycles) of epoxide **18**: $[\alpha]_D^{21} = -9.42$ ($c = 0.86$, $CHCl_3$); $R_f = 0.25$ (silica gel, 5% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2952, 1620, 1250, 1101, 849\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.50$ (d, $J = 0.7$ Hz, 1H; 18-H), 3.62 (t, $J = 6.9$ Hz, 1H; 16-H), 3.18 (s, 3H; OCH_3), 2.89 (m, 1H; 14-H), 2.72 (ddd, $J = 4.9, 4.9, 0.7$ Hz, 1H; 13-H), 2.46 (ddd, $J = 4.9, 2.7, 1.2$ Hz, 1H; 13-H'), 1.83 (ddd, $J = 13.4, 6.2, 6.2$ Hz, 1H; 15-H), 1.69 (d, $J = 0.7$ Hz, 3H; 17-CH_3), 1.65 (m, 1H; 15-H'), 0.10 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.1, 128.0, 86.4, 56.0, 49.7, 46.9, 36.7, 15.5, -0.18$; FAB HRMS (NBA) calcd for $C_{10}H_{19}O_2Si$ ($M-CH_3$): 199.1154; found *m/e* 199.1145.

Alcohol 20: To a cooled (−98 °C) solution of compound **19** (7.17 g, 22.39 mmol) in ether (75 mL) was added *tert*-butyllithium (21.4 mL, 1.7 M in pentane, 44.88 mmol) dropwise over 50 min. The mixture was stirred for 30 min at −98 °C. A solution of lithium 2-thienylcyanocuprate (89.6 mL, 0.25 M in THF, 22.4 mmol) was added, and the reaction mixture slowly allowed to warm to 0 °C. After 5 min the solution was cooled to −30 °C, and a solution of epoxide **18** (1.60 g, 7.48 mmol) in ether (10 mL) added. After being stirred for 1.5 h at 0 °C, the solution was quenched with aqueous ammonia buffered to pH = 8.0 with saturated NH_4Cl (50 mL). The resulting solution was extracted with ether (2 × 100 mL), and the combined organic layers washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in petroleum ether) to afford **20** (2.47 g, 81% yield) as a colorless oil: $[\alpha]_D^{23} = +19.0$ ($c = 1.00$, $CHCl_3$); $R_f = 0.18$ (silica gel, 16% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3506$ (broad), 2934, 1613, 1513, 1458, 1364, 1247, 1096, 1039, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.22$ (d, $J = 8.6$ Hz, 2H; Ar), 6.84 (d, $J = 8.6$ Hz, 2H; Ar), 5.43 (s, 1H; 18-H), 4.42 (s, 2H; OCH_2Ar), 3.78 (s, 3H; $ArOCH_3$), 3.73 (m, 1H; 14-H), 3.68 (dd, $J = 10.0, 3.2$ Hz, 1H; 16-H), 3.29 (d, $J = 15.0$ Hz, 1H; 10-H), 3.29 (d, $J = 2.7$ Hz, 1H; OH), 3.19 (d, $J = 15.0$ Hz, 1H; 10-H'), 3.19 (s, 3H; OCH_3), 1.75–1.40 (m, 6H; 12-H_2, 13-H_2, and 15-H_2), 1.12 (m, 1H; 11-H), 0.90 (d, $J = 6.7$ Hz, 1H; 11-CH_3), 0.10 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.0, 152.4, 130.8, 129.1, 127.0, 113.7, 90.4, 75.5, 72.6, 72.3, 55.9, 55.2, 40.7, 34.9, 33.5, 29.3, 17.2, 15.8, -0.15$; FAB HRMS (NBA/CsI) calcd for $C_{23}H_{40}O_4SiCs$ ($M+Cs^+$): 541.1750; found *m/e* 541.1777.

Silyl ether 21: A solution of alcohol **20** (3.60 g, 8.80 mmol) and 2,6-lutidine (2.05 mL, 17.60 mmol) in CH_2Cl_2 (36 mL) at 0 °C was treated with TIPSOTf (3.55 mL, 13.20 mmol). The reaction mixture was stirred 10 min and then quenched with MeOH (3 mL). The reaction mixture was concentrated and the residue purified by flash chromatography (silica gel, 2% ethyl acetate in petroleum ether) to afford

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compound **21** (4.65 g, 94% yield) as a colorless oil: $[\alpha]_D^{21} = -9.3$ ($c = 0.96$, $CHCl_3$); $R_f = 0.28$ (5% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2946, 2865, 1615, 1513, 1462, 1366, 1248, 1096, 848\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 8.6$ Hz, 2H; Ar), 6.83 (d, $J = 8.6$ Hz, 2H; Ar), 5.39 (s, 1H; 18-H), 4.42 (d, $J = 11.6$ Hz, 1H; OCH_2Ar), 4.38 (d, $J = 11.6$ Hz, 2H; OCH_2Ar), 3.81 (t, $J = 5.2$, Hz, 1H; 14-H), 3.76 (s, 3H; $ArOCH_3$), 3.55 (dd, $J = 7.6$, 5.3 Hz, 1H; 16-H), 3.26 (dd, $J = 9.1$, 6.0 Hz, 1H; 10-H), 3.17 (dd, $J = 9.1$, 6.8 Hz, 1H; 10-H'), 3.09 (s, 3H; 17-OCH_3), 1.72–1.53 (m, 4H; 13-H_2 and 15-H_2), 1.62 (s, 3H; 17-CH_3), 1.39 (m, 2H; 12-H_2), 1.14 (m, 1H; C_{11}-H), 1.03 (s, 18H; $Si(CH(CH_3)_2)_3$), 0.89 (d, $J = 6.7$ Hz, 3H; 11-CH_3), 0.09 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.0, 153.2, 130.9, 129.1, 127.0, 113.7, 86.2, 75.7, 72.6, 69.9, 55.9, 55.2, 40.6, 34.1, 33.8, 28.5, 18.3, 17.2, 15.6, 12.7, -0.11$; FAB HRMS (NBA/CsI) calcd for $C_{32}H_{60}O_4Si_2Cs$ ($M + Cs^+$): 697.3085; found *m/e* 697.3112.

Vinyl iodide 22: A solution of vinylsilane **21** (2.19 g, 3.88 mmol) in THF (40 mL) was treated with NIS (3.49 g, 15.51 mmol) in portions. The reaction mixture was stirred for an additional 30 min and then poured into petroleum ether (120 mL). The mixture was filtered through Celite and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, 2% EtOAc in petroleum ether) to provide vinyl iodide **22** (2.23 g, 93% yield) as a colorless oil: $[\alpha]_D^{23} = -7.1$ ($c = 1.49$, $CHCl_3$); $R_f = 0.27$ (silica gel, 5% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2938, 2864, 1715, 1512, 1460, 1364, 1247, 1097, 883\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.23$ (ddd, $J = 8.6$, 2.9, 2.0 Hz, 2H; Ar), 6.85 (ddd, $J = 8.6$, 2.9, 2.0 Hz, 2H; Ar), 6.14 (s, 1H; 18-H), 4.42 (d, $J = 11.9$ Hz, 2H; OCH_2Ar), 4.38 (d, $J = 11.9$ Hz, 2H; OCH_2Ar), 3.85 (m, 1H; 14-H), 3.79 (s, 3H; $ArOCH_3$), 3.76 (dd, $J = 8.3$, 4.6 Hz, 1H; 16-H), 3.26 (dd, $J = 9.1$, 6.1 Hz, 1H; 10-H), 3.21 (dd, $J = 9.1$, 6.5 Hz, 1H; 10-H'), 3.10 (s, 3H; 16-OCH_3), 1.77 (ddd, $J = 13.8$, 8.3, 5.1 Hz, 1H; 15-H), 1.70 (d, $J = 1.0$ Hz, 3H; 17-CH_3), 1.68 (m, 1H, 15-H'), 1.59–1.54 (m, 2H; 13-H_2), 1.19–1.10 (m, 3H; 11-H and 12-H_2), 1.02 (s, 18H; $Si(CH(CH_3)_2)_3$), 0.90 (d, $J = 6.7$ Hz, 3H; 11-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.0, 148.1, 130.8, 129.1, 113.7, 82.9, 82.1, 78.9, 75.6, 72.7, 69.6, 56.2, 56.1, 40.4, 33.9, 28.4, 18.7, 18.2, 17.2, 12.6$; FAB HRMS (NBA/CsI) calcd for $C_{26}H_{51}O_4SiICs$ ($M + Cs^+$): 751.1656; found *m/e* 751.1656.

Alcohol 23: Compound **22** (1.02 g, 1.65 mmol) in CH_2Cl_2 (20 mL) and water (1 mL) was treated with DDQ (449 mg, 1.98 mmol), and the mixture stirred at room temperature for 1 h. The reaction mixture was poured into aqueous $NaHCO_3$ (10 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (silica gel, 10% ethyl acetate in petroleum ether) of the residue provided alcohol **23** (730 mg, 89% yield) as a colorless oil: $[\alpha]_D^{21} = -5.4$ ($c = 2.45$, $CHCl_3$); $R_f = 0.10$ (9% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3374$ (broad), 2941, 2866, 1462, 1377, 1277, 1099, 1058, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.17$ (d, $J = 1.1$ Hz, 1H; 18-H), 3.87 (m, 1H; 14-H), 3.83 (dd, $J = 8.4$, 4.1 Hz, 1H; 16-H), 3.47 (dd, $J = 10.7$, 6.5 Hz, 1H; 10-H), 3.41 (dd, $J = 10.7$, 6.4 Hz, 1H; 10-H'), 3.13 (s, 3H; 16-OCH_3), 2.03 (s, 1H; O*H*), 1.82 (ddd, $J = 14.1$, 8.4, 4.5 Hz, 1H; 15-H'), 1.72 (d, $J = 1.1$ Hz, 3H; 17-CH_3), 1.64–1.55 (m, 2H; 13-H and 15-H), 1.46–1.19 (m, 3H; 12-H_2 and 13-H), 1.03 (s, 18H; $Si(CH(CH_3)_2)_3$), 0.89 (d, $J = 6.8$ Hz, 3H; 11-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 148.1, 82.8, 78.9, 69.7, 67.8, 56.2, 40.1, 35.7, 33.1, 27.6, 18.8, 18.2, 16.4, 12.6$; FAB HRMS (NBA/CsI) calcd for $C_{21}H_{43}O_3SiICs$ ($M + Cs^+$): 631.1081; found *m/e* 631.1091.

Aldehyde 24: A solution of oxalyl chloride (0.76 mL, 2.0 M in CH_2Cl_2, 1.52 mmol) in CH_2Cl_2 (1 mL) at −78 °C was treated with DMSO (0.13 mL, 1.90 mmol), and the mixture stirred for 15 min. Alcohol **23** (189 mg, 0.38 mmol) in CH_2Cl_2 (1 mL) was added, and the solution stirred for 1 h at −78 °C. The mixture was treated with triethylamine (0.53 mL, 3.80 mmol), slowly warmed to 0 °C, and stirred at this temperature for 15 min. The reaction mixture was poured into aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 5% EtOAc in petroleum ether) to afford aldehyde **24** (189 mg, 100%): $[\alpha]_D^{23} = -21.3$ ($c = 0.66$, $CHCl_3$); $R_f = 0.45$(9% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2940, 2866, 1709, 1462, 1377, 1277, 1251, 1099, 1059, 883\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.60$ (d, $J = 1.9$ Hz, 1H; 10-H), 6.19 (d, $J = 1.1$ Hz, 1H; 18-H), 3.93 (m, 1H; 14-H), 3.76 (dd, $J = 8.9$, 3.8 Hz, 1H; 16-H), 3.11 (s, 3H; 16-OCH_3), 2.31 (m, 1H; 10-H), 1.83 (ddd, $J = 13.8$, 8.9, 4.4 Hz, 1H; 15-H), 1.72 (d, $J = 1.1$ Hz, 3H; 17-CH_3), 1.71–1.45 (m, 5H; 12-H_2, 13-H_2 and 15-H'), 1.09 (d, $J = 7.1$ Hz, 3H; 11-CH_3), 1.03 (s, 18H; $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 205.1, 148.0, 82.7, 78.9, 69.2, 56.2, 46.5, 40.3, 33.4, 25.3, 18.8, 18.2, 13.5, 12.6$.

Ester 25: To a solution of methyl glycolate (66.5 mg, 0.738 mmol) in THF (3 mL) was added LDA (0.984 mL, 1.5 M, 1.476 mmol) at −78 °C, and the reaction mixture slowly warmed to 0 °C over 30 min. The solution was again cooled to −78 °C, and a solution of aldehyde **20** (61.0 mg, 0.123 mmol) in THF (1.5 mL) and HMPA (0.5 mL) added. After being stirred for 20 min at −78 °C, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate/petroleum ether) to afford compound **25** as a mixture of diols (52.0 mg, 72%). The crude mixture was used in the next reaction without further purification; however, for characterization purposes a sample of the mixture was subjected to PTLC to afford the (9*R*,10*S*) diol ester **25** [33]. Selected data for this diastereomer: $[\alpha]_D^{23} = +1.9$ ($c = 0.83$, $CHCl_3$); $R_f = 0.48$ (33% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3404$ (broad), 2933, 2865, 1744, 1642, 1453, 1375, 1334, 1273, 1089, 1047, 883, 673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.17$ (d, $J = 1.0$ Hz, 1H; 18-H), 4.27 (dd, $J = 6.1$, 1.1 Hz, 1H; 9-H), 3.93 (dd, $J = 8.6$, 3.2 Hz, 1H; 16-H), 3.88 (m, 1H; 14-H), 3.80 (s, 3H; CO_2CH_3), 3.60 (ddd, $J = 8.9$, 7.9, 1.1 Hz, 1H; 10-H), 3.12 (s, 3H; 16-OCH_3), 2.97 (d, $J = 6.1$ Hz, 1H; 9-O*H*), 2.64 (d, $J = 7.9$ Hz, 1H; C_{10}-O*H*), 1.89–1.82 (m, 2H), 1.72 (d, $J = 1.0$ Hz, 3H; 17-CH_3), 1.68–0.98 (m, 8H), 1.03 (s, 18H, $Si(CH(CH_3)_2)_3$), 0.93 (d, $J = 6.8$ Hz, 3H; 11-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.0, 148.0, 82.5, 78.9, 75.4, 70.0, 56.0, 52.7, 39.5, 35.0, 31.8, 27.0, 18.8, 18.2, 15.4, 12.5$; FAB HRMS (NBA/CsI) calcd for $C_{24}H_{47}O_6SiICs$ ($M + Cs^+$): 719.1241; found *m/e* 719.1235.

Dihydroxy acid 4: Ester **25** (106 mg, 0.181 mmol) in THF/MeOH/H_2O (3:1:1, 5 mL) at 0 °C was treated with LiOH (17.3 mg, 0.724 mmol), and the mixture stirred for 30 min. The solution was adjusted to pH 3.0 with 0.5 N aqueous $NaHSO_4$ and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The product was carried forward without any further purification. For characterization purposes the (9*R*,10*S*) diol ester was subjected to the same reaction conditions to provide (9*R*,10*S*) dihydroxy acid **4**: $R_f = 0.05$ (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20} = -4.1$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3410, 2941, 2867, 1729, 1624, 1462, 1379, 1256, 1271, 1095, 883, 759, cm^{-1}$; ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 6.35$ (d, $J = 1.0$ Hz, 1H; 18-H), 3.98 (d, $J = 3.0$ Hz, 1H; 9-H), 3.90–3.83 (m, 1H; 14-H); 3.80 (dd, $J = 8.4$, 4.1 Hz, 1H; 16-H), 3.38 (dd, $J = 7.3$, 3.0 Hz, 1H; 10-H); 3.33 (s, 3H; 16-OCH_3), 1.73 (ddd, $J = 13.6$, 8.6, 4.5 Hz, 1H), 1.65 (d, $J = 1.0$ Hz, 3H; 17-CH_3), 1.60–1.10 (m, 6H); 1.05–0.90 (m, 21H; $Si(CH(CH_3)_2)_3$), 0.88 (d, $J = 6.7$ Hz, 3H; 11-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 178.71, 147.75, 85.52, 79.32, 76.50, 71.78, 70.10, 56.09, 39.77, 34.86, 32.42, 27.60, 18.76, 18.24, 15.76, 12.62$; FAB HRMS (NBA/CsI) calcd for $C_{23}H_{44}O_6SiICs_2$ ($M - H^+ + 2Cs^+$): 837.0061; found *m/e* 837.0102.

Tetraol 27: To a suspension of NaH (4.82 g, 161 mmol) in DMF (400 mL) at ambient temperature was added in portions 1,3,4,6-di-*O*-benzylidene-D-mannitol (**26**) (25 g, 69.83 mmol). The mixture was stirred for 2 h and then treated with CH_3I (13.04 mL, 209.49 mmol) and stirred for an additional 2 h. The reaction mixture was quenched with water (1000 mL) and extracted with ethyl acetate (3 × 500 mL). The combined extracts were washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting white solid was taken up in ethyl acetate/ethanol (1:1, 500 mL), 10% Pd/C (1.35 g, 5 wt%) added, and the mixture stirred under an H_2 atmosphere for 48 h. The solution was filtered through Celite and concentrated to afford tetraol **27** (13.58 g, 93% yield) as a colorless solid, which was used in the next reaction without further purification: M.p. 39–42 °C; $R_f = 0.40$ (silica gel, 20% methanol in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.90$ (dd, $J = 11.9$, 3.4 Hz, 1H; 28-H), 3.78 (d, $J = 8.3$ Hz, 1H; 30-H), 3.68 (dd, $J = 11.9$, 4.5 Hz, 1H; 28-H'); 3.45 (s, 3H; OCH_3), 3.31 (ddd, $J = 8.3$, 4.5, 3.4 Hz, 1H; 29-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 82.7, 69.7, 61.5, 58.4$; FAB HRMS (NBA/NaI) calcd for $C_9H_{18}O_6Na$ ($M + Na^+$): 233.1001; found *m/e* 233.0995.

Bis(silyl ether) 28: Tetraol **27** (13.58 g, 64.69 mmol) and imidazole (19.82 g, 291.1 mmol) were dissolved in DMF (325 mL) and treated with *tert*-butyldiphenylsilyl chloride (37.25 mL, 145.55 mmol). The mixture was stirred for 4 h at ambient temperature, then diluted with ether (500 mL), and washed successively with 5% aqueous HCl (250 mL), water (2 × 100 mL), and brine (100 mL), then dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to provide bis(silyl ether) **28** (42.22 g, 95% yield) as a viscous oil: $R_f = 0.28$ (silica gel, 30% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3477, 3070, 2931, 2857, 1427, 1111, 707\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.72$–7.69 (m, 2H; Ar), 7.44–7.36 (m, 3H; Ar), 3.93 (d, $J = 6.4$ Hz, 1H; 30-H), 3.89 (dd, $J = 11.0$, 4.8 Hz, 1H; 28-H), 3.83 (dd, $J = 11.0$, 5.0 Hz, 1H, 28-H'), 3.44 (ddd, $J = 6.0$, 5.0, 4.8 Hz, 1H, 29-H), 3.39 (s, 3H; OCH_3), 3.26 (brs, 1H; O*H*), 1.05 (s, 9H; *t*Bu); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 136.1, 133.6, 130.2, 128.2, 83.0, 70.2, 63.8, 59.4, 27.2, 19.6$; FAB HRMS (NBA/NaI) calcd for $C_{40}H_{54}O_6Si_2Na$ ($M + Na^+$): 709.3357; found *m/e* 709.3335.

Aldehyde 29: Silyl ether **28** (48.23 g, 70.2 mmol) and Na_2CO_3 (6.12 g, 73.71 mmol) were taken up in CH_2Cl_2 (700 mL), cooled to 0 °C and treated with $Pb(OAc)_4$ (32.68 g, 73.71 mmol) added in portions. The mixture was allowed to slowly warm to room temperature and was stirred at this temperature for 90 min. The reaction mixture was quenched with ethylene glycol (1 mL) and stirred for an additional 5 min. The reaction mixture was filtered through Celite, and the filtrate washed with aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to provide aldehyde **29** (crude yield 43.09 g, 90%). The labile aldehyde **29** was used immediately without further purification.

Alcohol 32: Amide **31** (30.66 g, 107.13 mmol) in CH_2Cl_2 (150 mL) was cooled to −78 °C and treated with di-*n*-butylboryl triflate (117.8 mL, 1 M in CH_2Cl_2,

117.8 mmol). After 5 min Et_3N (19.42 mL, 139.27 mmol) was added, and the reaction mixture allowed to slowly warm to 0 °C and stirred at this temperature for 90 min. The mixture was again cooled to −78 °C, and aldehyde **29** (43.09 g, 0.126 mmol) in CH_2Cl_2 (75 mL) was added dropwise. The reaction mixture was stirred 15 min at −78 °C and then allowed to slowly warm to −10 °C, and held at this temperature for 6 h. Quenching of the reation mixture with phosphate buffer (pH = 7.0, 100 mL) and methanol (100 mL) was followed by cautious addition of 30% aqueous H_2O_2 (40 mL) and stirring for 2 h at ambient temperature. The mixture was then extracted with ether (3 × 250 mL). The combined ether layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel). Unreacted amide **31** (4.60 g, 15%) eluted first with 20% ether in petroleum ether, and then the desired aldol product **32** with 40% ether in petroleum ether. A colorless solid (49.21 g, 73% yield) was isolated: M.p. 41–44 °C; $[\alpha]_D^{23} = +8.2$ ($c = 0.81$, $CHCl_3$); $R_f = 0.2$ (silica gel, 40% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 3489, 2932, 2858, 1782, 1596, 1342, 1194, 1113\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.69–7.66$ (band, 4H; Ar), 7.44–7.26 (band, 11H; Ar), 5.60 (ddd, $J = 17.0, 10.3, 8.1$ Hz, 1H; 22-H), 5.55 (d, $J = 7.2$ Hz, 1H; PhC*H*), 4.99–4.87 (m, 2H; 21-H_2), 4.73 (dq, $J = 6.8, 6.7$ Hz, 1H; C*H*N), 4.18 (ddd, $J = 10.9, 5.2, 3.1$ Hz, 1H; 26-H), 3.93 (m, 1H; 25-H), 3.83 (dd, $J = 10.7, 6.1$ Hz, 1H; 28-H), 3.75 (dd, $J = 10.8, 5.4$ Hz, 1H; 28-H'), 3.32 (s, 3H; OCH_3), 3.26 (ddd, $J = 6.1, 5.4, 3.1$ Hz, 1H; 27-H), 2.72 (d, $J = 5.2$ Hz, 1H; O*H*), 2.11 (m, 1H; 23-H), 2.02 (m, 1H; 24-H), 1.60 (m, 1H; 24-H'), 1.05 (s, 9H; *t*Bu), 1.00 (d, $J = 6.6$ Hz, 3H; CH_3), 0.90 (s, 3H; $SiCH_3$), 0.88 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.1, 152.7, 143.5, 135.6, 133.2, 129.8, 128.7, 128.7, 127.7, 113.9, 81.2, 78.6, 72.9, 62.9, 58.6, 55.2, 44.6, 36.3, 35.0, 26.8, 21.1, 19.1, 14.4$; FAB HRMS (NBA/CsI) calcd for $C_{37}H_{48}O_6NSiCs$ ($M + Cs^+$): 762.2227; found *m/e* 762.2227.

Amide 31: To a mechanically stirred solution of carboxylic acid **30** (12.48 g, 97.37 mmol) in ether (1000 mL) at −78 °C was added Et_3N (14.26 mL, 102.33 mmol) followed by pivaloyl chloride (12.60 mL, 102.33 mmol). The resulting slurry was allowed to warm to 0 °C, stirred for 1 h and then again cooled to −78 °C. In a separate flask (4*R*,5*S*)-4-methyl-5-phenyl oxazolidone (16.08 g, 97.37 mmol) in THF (200 mL) at −78 °C was treated with *n*BuLi (64 mL, 1.6 M in hexanes). The mixture was stirred for 1 h and then added by cannula to the flask containing the mixed anhydride. The reaction mixture was allowed to warm to 0 °C and was stirred for 1 h at that temperature. It was then quenched with aqueous NH_4Cl (250 mL) and diluted with ether. The layers were separated, and the aqueous layer was extracted with ether (3 × 200 mL). The combined ether layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to provide amide **31** (25 g, 90% yield) as a colorless oil: $[\alpha]_D^{23} = +39.4$ ($c = 1.7$, $CHCl_3$); $R_f = 0.38$ (silica gel, 20% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3071, 2961, 2931, 2868, 1783, 1703, 1348, 1189\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43–7.27$ (band, 5H; Ar), 5.72–5.65 (m, 2H; OC*H*Ar, and 22-H), 5.01 (d, $J = 17.2$ Hz, 1H; 21-H_{trans}), 4.97 (d, $J = 10.2$ Hz, 1H; 21-H_{cis}), 4.76 (dq, $J = 6.8, 6.7$ Hz, 1H; C*H*N), 3.01–2.87 (m, 2H; 25-H), 2.22 (m, 1H; 23-H); 1.76–1.63 (m, 2H; 24-H_2); 1.05 (d, $J = 6.7$ Hz, 3H; $NCHCH_3$), 0.88 (d, $J = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (500 MHz, $CDCl_3$): $\delta = 173.6, 153.4, 144.0, 136.0, 133.8, 129.0, 126.0, 114.0, 79.3, 55.1, 37.9, 34.0, 31.2, 20.6, 15.0$; FAB HRMS calcd for $C_{17}H_{22}O_3N$ ($M + H^+$): 288.1600; found *m/e* 288.1610.

Diol 33: Compound **32** (49.27 g, 78.13 mmol) and water (3.1 mL, 171.88 mmol) in ether (780 mL) was cooled to 0 °C. The mixture was treated with $LiBH_4$ (86 mL, 2 M in THF, 171.88 mmol). The resulting white slurry was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with aqueous NH_4Cl (150 mL), and the layers were separated. The aqueous phase was extracted with ether (2 × 100 mL), and the combined ether phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 60:40:1 ether/petroleum ether/acetone) to afford diol **33** (40.19 g, 98% yield) as a colorless oil: $[\alpha]_D^{23} = -16.5$ ($c = 1.30$, $CHCl_3$); $R_f = 0.36$ (silica gel, 40% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3443, 3074, 2931, 2858, 1427, 1113\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.70–7.66$ (band, 4H; Ar), 7.46–7.39 (band, 6H, Ar), 5.42 (ddd, $J = 17.5, 10.5, 9.0$ Hz, 1H; 22-H), 4.95 (dd, $J = 17.5, 1.5$ Hz, 1H; 21-H_{trans}), 4.88 (dd, $J = 10.5, 1.5$ Hz, 1H; 21-H_{cis}), 3.99 (dd, $J = 6.0, 2.8$ Hz, 1H; 26-H), 3.82 (dd, $J = 11.4, 4.0$ Hz, 1H; 28-H), 3.78 (dd, $J = 11.3, 2.3$ Hz, 1H; CH_2OH), 3.73 (dd, $J = 11.3, 5.0$ Hz, 1H; CH_2OH), 3.65 (dd, $J = 11.4, 4.4$ Hz, 1H; 28-H'), 3.39 (s, 3H, OCH_3), 3.23 (ddd, $J = 6.0, 4.4, 4.0$ Hz, 1H; 27-H), 2.76 (brs, 2H; O*H*); 2.24 (m, 1H; 25-H), 1.70 (m, 2H; 24-H), 1.04 (s, 9H; *t*Bu), 1.01 (d, $J = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.4, 136.1, 136.0, 133.4, 130.3, 128.2, 114.4, 82.5, 75.5, 64.6, 62.5, 58.6, 39.6, 36.2, 31.9, 27.2, 22.3, 19.6$; FAB HRMS (NBA/CsI) calcd for $C_{27}H_{40}O_4SiCs$ ($M + Cs^+$): 589.1750; found *m/e* 589.1771.

Tosylate 34: A solution of diol **33** (32.90 g, 71.87 mmol) and Et_3N (30.06 mL, 215.6 mmol) in CH_2Cl_2 (350 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (16.44 g, 86.24 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 12 h, diluted with ether (700 mL), and washed with aqueous $NaHCO_3$ (150 mL). The aqueous layer was extracted with ether (2 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to afford the labile primary tosylate **34** (28.10 g, 64% yield) and starting diol **33** (7.24 g, 22%), which was resubmitted to the reaction conditions to provide an additional 6.18 g of the tosylate **34** (total yield 34.28 g, 78%).

Silyl ether 35: A solution of tosylate **34** (19.00 g, 31.10 mmol) in THF (126 mL) was cooled to 0 °C and treated with lithium triethylborohydride (100.84 mL, 1 M in THF, 100.84 mmol). The reaction mixture was stirred at room temperature for 8 h, cooled again to 0 °C, and quenched with MeOH (125 mL) and 1 N NaOH (125 mL), followed by cautious addition of 30% aqueous H_2O_2 (45 mL). The solution was warmed to room temperature and was stirred for 16 h. The reaction mixture was diluted with aqueous $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 15% ether in petroleum ether) to provide compound **35** (12.61 g, 92% yield) as a colorless oil: $[\alpha]_D^{23} = -8.6$ ($c = 2.5$, $CHCl_3$); $R_f = 0.63$ (silica gel, 25% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3467, 3071, 2959, 2930, 2858, 1427, 1113\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.72–7.67$ (band, 4H; Ar), 7.45–7.35 (band, 6H; Ar), 5.49 (ddd, $J = 17.4, 10.2, 8.6$ Hz, 1H; 22-H), 4.95 (ddd, $J = 17.4, 1.9, 0.6$ Hz, 1H; 21-H_{trans}), 4.87 (dd, $J = 10.2, 1.9$ Hz, 1H; 21-H_{cis}), 3.79 (dd, $J = 11.0, 4.6$ Hz, 1H; 28-H), 3.70 (dd, $J = 11.0, 4.9$ Hz, 1H; 28-H'), 3.46 (dd, $J = 5.3, 4.4$ Hz, 1H; 26-H), 3.37 (s, 3H; OCH_3), 3.23 (dt, $J = 4.6, 4.6$ Hz, 1H; 27-H), 2.42 (brs, 1H; O*H*), 2.22 (m, 1H, 23-H), 1.66 (m, 1H), 1.47 (ddd, $J = 14.5, 11.1, 2.8$ Hz, 1H; 24-H), 1.15 (ddd, $J = 14.5, 11.1, 3.8$ Hz, 1H; 24-H'), 1.05 (s, 9H; *t*Bu), 1.00 (d, $J = 6.7$ Hz, 3H; CH_3), 0.91 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.7, 136.1, 133.6, 130.2, 128.2, 113.7, 81.8, 76.1, 63.4, 59.0, 39.2, 36.3, 33.7, 27.3, 27.0, 22.5, 19.6$; FAB HRMS (NBA/CsI) calcd for $C_{27}H_{48}O_3SiCs$ ($M + Cs^+$): 573.1807; found *m/e* 573.1811.

Diol 36: A solution of compound **35** (11.80 g, 26.86 mmol) in THF (200 mL) at 0 °C was treated with TBAF (10.54 g, 40.30 mmol). The mixture was stirred at ambient temperature for 90 min, then diluted with aqueous NH_4Cl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 60% ethyl acetate in petroleum ether) to provide diol **36** (5.05 g, 93% yield) as a colorless oil: $[\alpha]_D^{23} = +16.1$ ($c = 2.8$, $CHCl_3$); $R_f = 0.2$ (silica gel, 25% petroleum ether in ether); IR (thin film): $\tilde{\nu}_{max} = 3419, 2960, 2930, 1460, 1108, 1070\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.57$ (ddd, $J = 17.6, 10.1, 8.6$ Hz, 1H; 22-H), 4.98 (ddd, $J = 17.6, 2.0, 0.9$ Hz, 1H; 21-H_{trans}), 4.94 (dd, $J = 10.1, 2.0$ Hz, 1H; 21-H_{cis}), 3.87 (dd, $J = 11.9, 4.1$ Hz, 1H; 28-H), 3.64 (dd, $J = 11.9, 4.0$ Hz; 1H, 28-H'), 3.49 (s, 3H; OCH_3), 3.41 (dd, $J = 6.0, 4.5$ Hz, 1H; 26-H), 3.29 (ddd, $J = 4.5, 4.1, 4.0$ Hz, 1H; 27-H), 2.24 (m, 1H; 23-H), 1.67 (m, 1H; 25-H), 1.50 (ddd, $J = 14.4, 11.3, 2.8$ Hz, 1H; 24-H), 1.15 (ddd, $J = 14.4, 11.3, 2.8$ Hz, 1H; 24-H'), 1.02 (d, $J = 6.7$ Hz, 3H; CH_3), 0.93 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 144.5, 113.9, 81.2, 77.2, 62.0, 58.7, 39.09, 36.3, 33.7, 22.5, 16.7$; FAB HRMS (NBA/CsI) calcd for $C_{11}H_{22}O_3Cs$ ($M + Cs^+$) 335.0623; found *m/e* 335.0632.

Acetal 37: Diol **36** (5.00 g, 24.22 mmol) and *p*-anisaldehyde dimethyl acetal (6.32 mL, 37.08 mmol) were dissolved in CH_2Cl_2 (40 mL), treated with CSA (1.15 g, 4.94 mmol), and stirred 4 h at ambient temperature. Triethylamine (1.38 mL, 9.89 mmol) was added, and the mixture concentrated. Flash chromatography (silica gel, 50% ether in petroleum ether) of the residue provided PMB acetal **37** (7.73 g, 97% yield) as a colorless solid: M.p. 62–64 °C; $[\alpha]_D^{23} = +5.08$ ($c = 0.59$, $CHCl_3$); $R_f = 0.38$ (50% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 2693, 2932, 1615, 1518, 1250, 1097, 1038\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 9.0$ Hz, 2H; Ar), 6.87 (d, $J = 9.0$ Hz, 2H; Ar), 5.63 (ddd, $J = 18.0, 10.1, 9.0$ Hz, 1H; 22-H), 5.38 (s, 1H; *H*CAr), 5.0–4.9 (m, 2H; 21-H_2), 4.49 (d, $J = 13.0$ Hz, 1H; 28-H), 3.84 (d, $J = 13.0$ Hz, 1H; 28-H'), 3.80 (s, 3H; $ArOCH_3$), 3.43 (overlapping m, 4H; OCH_3 and 26-H), 3.16 (s, 1H; 27-H), 2.32 (m, 1H), 2.09 (m, 1H), 1.83 (m, 1H), 1.00 (m, 1H), 1.00 (d, $J = 2.6$ Hz, 3H; CH_3), 0.87 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 161.0, 145.0, 127.8, 113.8, 113.4, 100.0, 84.9, 72.8, 67.5, 57.4, 55.8, 40.5, 36.1, 31.7, 22.5, 14.9$; FAB HRMS (NBA/CsI) $C_{19}H_{28}O_4$ ($M + Cs^+$): 453.1042; found *m/e* 453.1056.

Alcohol 38: A solution of compound **37** (6.20 g, 19.35 mmol) in CH_2Cl_2 (80 mL) was cooled to −78 °C and treated with DIBALH (33.86 mL, 1 M in CH_2Cl_2, 33.86 mmol). The reaction mixture was allowed to warm to room temperature, stirred at this temperature for 2 h, and then quenched with MeOH (4 mL). It was diluted with ether (150 mL) and aqueous sodium potassium tartrate (75 mL), and stirred vigorously for 90 min. The layers were separated, and the aqueous layer extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 50% ether in petroleum ether) to provide alcohol **38** (5.94 g, 96% yield) as a colorless oil: $[\alpha]_D^{23} = +3.8$ ($c = 1.17$, $CHCl_3$); $R_f = 0.24$ (silica gel, 50% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3449, 2959, 1612, 1514, 1462, 1246\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.29$ (d, $J = 8.6$ Hz, 2H; Ar), 6.88 (d, $J = 8.6$ Hz, 2H; Ar), 5.53 (ddd, $J = 17.2, 10.1, 8.7$ Hz, 1H; 22-H), 4.97 (ddd, $J = 17.2, 1.9, 1.0$ Hz, 1H; 21-H_{trans}), 4.93 (dd, $J = 10.1, 1.9$ Hz, 1H; 21-H_{cis}), 4.58 (ABq, $J_{AB} = 10.9$ Hz, $\Delta\nu_{AB} = 49.2$ Hz, 2H; OCH_2Ar), 3.81 (s, 3H; $ArOCH_3$), 3.73 (dd, $J = 11.6, 4.1$ Hz, 1H; 28-H), 3.53 (dd, $J = 11.6, 5.4$ Hz, 1H; 28-H'), 3.49 (s, 3H; OCH_3), 3.39 (ddd, $J = 6.2, 5.4, 4.1$ Hz, 1H; 27-H),

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3.32 (dd, J = 6.2, 4.1 Hz, 1H; 27-H), 2.21 (m, 1H; 23-H), 2.11 (br s, 1H; O*H*), 1.72 (m, 1H), 1.34–1.22 (overlapping m, 2H; 24-H$_2$), 0.99 (d, J = 6.7 Hz, 3H; C*H*$_3$); 0.97 (d, J = 6.7 Hz, 3H, CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 144.4, 131.4, 130.0, 114.2, 114.1, 84.5, 83.4, 74.6, 62.1, 59.4, 55.7, 38.7, 36.2, 32.5, 22.5, 17.1; FAB HRMS (NBA/CsI) calcd for $C_{19}H_{30}O_4Cs$ (M + Cs$^+$): 455.1198; found m/e 455.1198.

Aldehyde 7: Oxalyl chloride (2.41 mL, 27.59 mmol) in CH_2Cl_2 (40 mL) at −78 °C was treated with DMSO (3.91 mL, 55.17 mmol) in CH_2Cl_2 (70 mL) and the mixture stirred for 30 min. A solution of alcohol **38** (5.93 g, 18.39 mmol) in CH_2Cl_2 (95 mL) was added, and the reaction mixture stirred for 1 h at −78 °C. Triethylamine (12.81 mL, 91.95 mmol) was added, and the solution allowed to slowly warm to room temperature and stirred at that temperature for 90 min. It was then diluted with ether (250 mL), washed with aqueous NH_4Cl (100 mL), then brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to provide aldehyde **7** (5.78 g, 97% yield) as a pale yellow oil: $[\alpha]_D^{23}$ = − 55.9 (c = 0.53, $CHCl_3$); R_f = 0.65 (silica gel, 30% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2929, 1731, 1612, 1513, 1460, 1248, 1076 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.74 (d, J = 1.6 HZ, 1H; C*H*O), 7.19 (d, J = 8.7 Hz, 2H; Ar), 6.83 (d, J = 8.7 Hz, 2H; Ar), 5.52 (ddd, J = 17.1, 10.7, 8.6 Hz, 1H; 22-H), 4.94 (ddd, J = 17.1, 1.9, 0.7 Hz, 1H; 21-H$_{trans}$), 4.90 (dd, J = 10.2, 1.9 Hz, 1H; 21-H$_{cis}$), 4.43 (ABq, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 14.1 Hz, 2H; OC*H*$_2$Ar), 3.78 (s, 3H; ArOC*H*$_3$), 3.67 (dd, J = 3.6, 1.6 Hz, 1H; 27-H), 3.50 (dd, J = 6.4, 3.6 Hz, 1H; 26-H), 3.45 (s, 3H; OC*H*$_3$), 2.20 (m, 1H; 23-H), 1.90 (m, 1H; 25-H), 1.44, 1.10 (overlapping m, 2H; 24-H), 0.97 (d, J = 6.7 Hz, 3H; C*H*$_3$), 0.91 (d, J = 6.7 Hz, 3H; C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.4, 159.7, 144.2, 130.5, 130.1, 114.2, 114.0, 87.5, 83.4, 73.5, 59.5, 55.7, 39.7, 36.2, 32.6, 22.5, 16.1; FAB HRMS (NBA/CsI) calcd for $C_{19}H_{28}O_4Cs$ (M + Cs$^+$): 453.1042; found m/e 453.1033.

Alcohol 41: A three-liter three-neck flask equipped with a mechanical stirrer was charged with potassium *tert*-butoxide (32.18 g, 287 mmol) and THF (50 mL), and cooled to −78 °C. *trans*-2-Butene (52.4 mL, 574 mmol) was added followed by *n*BuLi (190 mL, 1.6 M in hexane, 303.57 mmol). The mixture was warmed to −45 °C and stirred at this temperature for 15 min, and then cooled again to −78 °C. A solution of (+)-Ipc$_2$BOMe (115.24 g, 364.28 mmol) in THF (360 mL) was added, and the mixture stirred for 30 min. $BF_3 \cdot OEt_2$ (37.33 mL, 303.57 mmol) was then added followed by aldehyde **40** (58.00 g, 307 mmol). The mixture was stirred for 4 h at −78 °C and then quenched with 3 N NaOH (220 mL), followed by cautious addition of 30% aqueous H_2O_2 (90 mL). The solution was stirred at room temperature for 16 h and then extracted with ether (3 × 250 mL). The combined ether layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford compound **41** (52.46 g, 75% yield) as a colorless oil: $[\alpha]_D^{23}$ = + 6.2 (c = 1.52, $CHCl_3$); R_f = 0.34 (10% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3455, 2957, 2931, 2858, 1472, 1256, 1089, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83 (m, 1H; 30-H), 5.09–5.04 (m, 2H; 29-H$_2$), 3.90–3.87 (m, 1H; 34-H), 3.83–3.78 (m, 1H; 34-H'), 3.26 (br s, 1H; O*H*), 2.24 (m, 1H; 31-H), 1.64 (m, 2H), 1.04 (d, J = 6.9 Hz, 3H; C*H*$_3$), 0.89 (s, 9H; *t*Bu), 0.42 (s, 3H; SiCH$_3$), 0.37 (s, 3H; SiCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.2, 115.6, 75.6, 63.3, 4.4, 35.9, 26.4, 17.4, 16.2, −4.8, −4.8; FAB HRMS calcd for $C_{13}H_{29}O_2Si$ (M + H$^+$): 245.1937; found m/e 245.1932.

PMB ether 42: Alcohol **41** (32.00 g, 131.48 mmol) and PMBBr (31.72 g, 157.78 mmol) were taken up in THF/DMF (2:1, 300 mL) and cooled to 0 °C. Sodium bis(trimethylsilyl)amide (157.78 mL, 1.0 M in THF, 157.78 mmol) was added. The mixture was allowed to warm to room temperature and stirred at that temperature 2.5 h. It was quenched with aqueous NH_4Cl (100 mL) and extracted with ether (3 × 100 mL). The combined ether layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to supply compound **42** (44.23 g, 90% yield) as a colorless oil: $[\alpha]_D^{23}$ = −14.8 (c = 0.68, $CHCl_3$); R_f = 0.30 (silica gel, 5% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2956, 2930, 2857, 1613, 1514, 1240, 1172 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.7 Hz, 2H; Ar), 6.87 (d, J = 8.7 Hz, 2H; Ar), 5.84–5.77 (m, 1H; 30-H), 5.05 (ddd, J = 6.0, 1.5, 1.5 Hz, 1H; 29-H$_{cis}$), 5.02 (dd, J = 11.0, 1.5 Hz, 1H; 29-H$_{trans}$), 4.47 (ABq, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 41.35 Hz, 2H; OC*H*$_2$Ar), 3.80 (s, 3H; ArOC*H*$_3$), 3.68 (t, J = 6.3 Hz, 2H; 24-H), 3.52–3.45 (m, 1H; 31-H), 2.53–2.50 (m, 1H), 1.64 (q, J = 6.9 Hz, 2H), 1.03 (d, J = 6.9 Hz, 3H; CH$_3$), 0.89 (s, 9H; *t*Bu), −0.042 (s, 3H; SiC*H*$_3$), −0.037 (s, 3H, SiC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5, 141.4, 131.36, 129.8, 115.0, 114.2, 79.5, 72.0, 60.5, 55.7, 40.9, 34.5, 26.4, 18.8, 15.0, −4.8, −4.8; FAB HRMS (NBA/CsI) calcd for $C_{21}H_{36}O_3SiCs$ (M + Cs$^+$): 497.1488; found m/e 497.1488.

Aldehyde 43: Compound **42** (59.58 g, 163.44 mmol) was dissolved in CH_2Cl_2/CH_3OH/pyridine (5:5:1, 1.5 L) and cooled to −78 °C. Ozone was bubbled through the solution until the starting material was consumed as noted by the blue coloration of the reaction mixture. Methyl sulfide (60 mL, 817 mmol) was added, and the mixture stirred at ambient temperature for 16 h. The solution was diluted with ether (1.5 L), washed with water (200 mL) and brine (200 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 15% ether in petroleum ether) to provide aldehyde **43** (48.06, 80% yield) as a colorless oil: $[\alpha]_D^{23}$ = + 6.3 (c = 2.45, $CHCl_3$); R_f = 0.4 (silica gel, 15% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2954, 2931, 2857, 1726, 1613, 1514, 1463, 1249, 1094, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.70 (d, J = 2.0 Hz, 1H; 30-H), 7.23 (d, J = 8.7 Hz, 2H; Ar), 6.86 (d, J = 8.7 Hz, 2H; Ar), 4.47 (ABq, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 25.2 Hz, 2H; OC*H*$_2$Ar), 3.91 (ddd, J = 7.5, 5.7, 4.3 Hz, 1H; 32-H), 3.78 (s, 3H; ArOC*H*$_3$), 3.77–3.69 (m, 2H; 34-H$_2$), 2.71–2.68 (dqd, J = 7.0, 5.7, 2.0 Hz, 1H; 31-H), 1.80–1.67 (band, 2H; 33-H$_2$), 1.09 (d, J = 7.0 Hz, 3H; C*H*$_3$), 0.89 (s, 9H; *t*Bu), 0.46 (s, 3H; SiC*H*$_3$), 0.40 (s, 3H; SiC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.3, 159.2, 130.2, 129.3, 113.7, 76.0, 71.6, 59.0, 55.2, 49.7, 34.6, 25.8, 18.2, 9.8, −5.4, −5.5; FAB HRMS (NBA/CsI) calcd for $C_{20}H_{34}O_4SiCs$ (M + Cs$^+$): 499.1281; found m/e 499.1277.

Dibromide 44: A mixture of carbon tetrabromide (48.64 g, 147 mmol), zinc dust (9.61 g, 147 mmol), and triphenylphosphine (38.56 g, 147 mmol) in CH_2Cl_2 (600 mL) was stirred at room temperature for 24 h, then aldehyde **43** (20 g, 54.41 mmol) was added. The mixture was stirred 2 h and then poured into hexanes (2.0 L). The solvent was decanted from the sticky precipitate, and the residue redissolved in CH_2Cl_2 (500 mL). The solution was again poured into hexanes (2.0 L), and the solvent decanted from the precipitate. This procedure was repeated twice more. The precipitate was then discarded, and the solvent fractions combined and concentrated. The resulting oil was dissolved in 10% ether in petroleum ether and filtered through a plug of silica gel. The solvent was evaporated to afford dibromide **44** (28.35 g, 100% yield) as a colorless oil: $[\alpha]_D^{23}$ = − 20.7 (c = 2.60, $CHCl_3$); R_f = 0.34 (silica gel, 10% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2954, 2929, 2856, 1616, 1524, 1249, 1093, 834, 778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.6 Hz, 2H; Ar), 6.87 (d, J = 8.6 Hz, 2H; Ar), 6.38 (d, J = 9.5 Hz, 1H; 30-H), 4.48 (ABq, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 14.0 Hz, 2H; OC*H*$_2$Ar), 3.80 (s, 3H; ArOC*H*$_3$), 3.67 (m, 2H; 34-H), 3.55 (ddd, J = 8.0, 4.5, 4.0 Hz, 1H; 32-H); 2.71 (dqd, J = 9.5, 6.9, 4.0 Hz, 1H; 31-H), 1.74, 1.57 (2 m, 2H; 33-H$_2$), 1.05 (d, J = 6.9 Hz, 3H; C*H*$_3$), 0.90 (s, 9H; *t*Bu), 0.05 (s, 6H; 2SiC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 141.1, 131.2, 129.2, 114.2, 89.0, 78.2, 72.6, 60.1, 55.7, 42.3, 35.7, 26.4, 18.7, 15.7, −4.82; FAB HRMS calcd for $C_{21}H_{34}O_2Br_2SiNa$ (M + Na$^+$): 543.0542/545/547; found m/e 543.0550/545/547.

Alkyne 45: Dibromide **44** (23.8 g, 47.00 mmol) in THF (300 mL) was cooled to −78 °C and treated with *n*BuLi (49 mL, 1.6 M in hexanes, 98.7 mmol). The mixture was slowly warmed to −20 °C and held at this temperature for 1 h. Methyl iodide (14.63 mL, 235 mmol) was added. The mixture was warmed to 0 °C, stirred at that temperature for 2 h, quenched with aqueous NH_4Cl (150 mL), and extracted with ether (3 × 150 mL). The combined ether layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (5% ether in petroleum ether) to provide compound **45** (17.35 g, 98% yield) as a colorless oil: $[\alpha]_D^{23}$ = − 8.7 (c = 0.9, $CHCl_3$); R_f = 0.41 (silica gel, 5% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2955, 2930, 2857, 1613, 1514, 1248, 1094, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, J = 9.0 Hz, 2H; Ar), 6.87 (d, J = 9.0 Hz, 2H; Ar), 4.50 (ABq, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 48.44, 2H; OC*H*$_2$Ar), 3.80 (s, 3H; ArOC*H*$_3$), 3.70 (dd, J = 7.3, 5.4 Hz, 2H; 34-H$_2$), 3.56 (dt, J = 8.0, 4.0 Hz, 1H; 32-H), 2.76 (m, 1H; 31-H), 1.87 (m, 1H; 33-H), 1.79 (d, J = 2.4 Hz, 3H; C*H*$_3$); 1.70 (m, 1H; 33-H'), 1.12 (d, J = 7.0 Hz, 3H; C*H*$_3$), 0.90 (s, 9H; *t*Bu), 0.045 (s, 6H, 2SiC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 131.4, 129.9, 114.2, 81.5, 79.4, 78.3, 72.1, 67.8, 60.5, 55.7, 34.6, 29.6, 26.3, 16.1, −4.8, −4.8; FAB HRMS (NBA/CsI) calcd for $C_{22}H_{36}O_3SiCs$ (M + Cs$^+$): 509.1488; found m/e 509.1499.

Vinyl iodide 8: To a solution of Cp_2ZrHCl (33.29 g, 129.11 mmol) in CH_2Cl_2 (120 mL) was added compound **45** (18.00 g, 51.65 mmol) in CH_2Cl_2 (30 mL). After 90 min, TLC analysis indicated complete consumption of starting material. The mixture was diluted with CH_2Cl_2 (250 mL), cooled to 0 °C, and titrated with a saturated solution of I_2 in CCl_4 until the iodine color persisted. The reaction mixture was washed with aqueous $Na_2S_2O_3$ (75 mL), water (75 mL), and brine (75 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified by flash chromatography (3% ether in petroleum ether) to provide vinyl iodide **8** (22.21 g, 85% yield) as a colorless oil: $[\alpha]_D^{23}$ = + 5.4 (c = 1.0, $CHCl_3$); R_f = 0.39 (silica gel, 5% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2952, 2858, 1612, 1512, 1463, 1378, 1300, 1249, 1174, 1093, 1042, 939 cm^{-1}; ^{1}H NMR (500 MHZ, $CDCl_3$): δ = 7.23 (d, J = 8.8 Hz, 2H; Ar), 6.86 (d, J = 8.8 Hz, 2H; Ar), 6.04 (dq, J = 9.8, 1.5 Hz, 1H; 30-H), 4.44 (s, 2H; OC*H*$_2$Ar), 3.78 (s, 3H; ArOC*H*$_3$), 3.62 (M, 2H; 34-H), 3.43 (dt, J = 7.7, 4.8 Hz, 1H; 32-H), 2.61 (m, 1H; 31-H), 2.29 (d, J = 1.5 Hz, 3H; 29-C*H*$_3$), 1.64 (m, 2H; 33-H$_2$), 0.92 (d, J = 6.8 Hz, 3H; 31-C*H*$_3$), 0.86 (s, 9H; *t*Bu), 0.026 (s, 3H; SiC*H*$_3$), 0.012 (s, 3H; SiC*H*$_3$); ^{13}C NMR (125 MHz): δ = 159.6, 144.1, 131.4, 129.9, 94.5, 79.1, 72.8, 60.1, 55.7, 39.7, 35.4, 28.4, 26.4, 16.5, −4.8, −4.8; HRMS FAB (NBA/CsI) calcd for $C_{22}H_{37}O_3ISiCs$ (M + Cs$^+$) 637.0611, found m/e 637.0611.

Alcohol 47: Epoxide **46** (30.25 g, 0.147 mmol) was dissolved in anhydrous methanol (600 mL), treated with CSA (6.62 g, 29.4 mmol), and stirred under argon for 2 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (150 mL) and concentrated. The aqueous phase was extracted with ether (3 × 100 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 40%

ether in petroleum ether) to yield alcohol **47** (31.22 g, 90% yield) as a pale yellow oil: $[\alpha]_D^{23} = -47.4$ ($c = 2.04$, $CHCl_3$); $R_f = 0.29$ (40% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3473$ (br), 2937, 2887, 1454, 1097; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.34-7.31$(band, 5H, Ar), 4.56 (ABq $J_{AB} = 11.8$ Hz, $\Delta\nu_{AB} = 40.6$ Hz, 2H; OCH_2AR), 3.80 (m, 1H; 41-H), 3.61 (dd, $J = 7.5$, 3.0 Hz, 1H; 40-H), 3.43 (ddd, $J = 8.0$, 7.5, 3.0 Hz, 1H; 39-H), 3.38 (s, 3H; OCH_3), 2.49 (brs, 1H; OH), 1.95 (m, 1H), 1.86 (m, 1H); 1.52 (m, 2H), 1.40 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 139.0$, 128.1, 128.0, 128.0, 80.4, 77.6, 73.8, 74.4, 57.5, 27.5, 27.3, 18.8; FAB HRMS (NBA/NaI) calcd for $C_{14}H_{20}O_3Na$ ($M + Na^+$): 259.1310; found *m/e* 259.1316.

Silyl ether 48: Alcohol **47** (31.22 g, 132 mmol) and 2,6-lutidine (46.35 mL, 398 mmol) were dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (33.48 mL, 0.146 mmol) was added dropwise and the mixture was stirred for 90 min at 0 °C. The reaction mixture was diluted with ether (300 mL), washed successively with 5% aqueous HCl (250 mL), brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to yield silyl ether **48** (42.14 g, 91% yield) as a colorless oil: $[\alpha]_D^{23} = -0.9$ ($c = 2.09$, $CHCl_3$); $R_f = 0.38$ (2% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2934$, 2857, 1460, 1101, 835, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.36-7.24$ (band, 5H; Ar), 4.60 (ABq, $J_{AB} = 12.0$ Hz, $\Delta\nu_{AB} = 30.74$ Hz, 2H; OCH_2Ar), 3.85 (brs, 1H; 41-H), 3.59 (m, 1H; 40-H), 3.39 (ddd, $J = 6.0$, 6.0, 3.5 Hz, 1H; 39-H), 3.33 (s, 3H; OCH_3), 1.85-1.73 (band, 2H), 1.59-1.40 (band, 4H), 0.91 (s, 9H: *t*Bu), 0.082 (s, 3H; $SiCH_3$), 0.077 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHZ, $CDCl_3$): $\delta = 139.9$, 128.6, 127.9, 127.6, 81.2, 77.9, 71.41, 57.3, 26.4, 26.4, 26.4, 26.3, 19.2, -4.0, -4.4; FAB HRMS calcd for $C_{20}H_{35}O_3Si$ (m + H^+): 351.2355; found *m/e* 351.2360.

Alcohol 49: Benzyl ether **48** (42.14 g, 120 mmol) and 10% Pd/C (2.1 g, 5 wt%) were taken up in ethanol (300 mL) and stirred under a hydrogen atmosphere for 24 h. The mixture was diluted with ether (200 mL) and filtered through Celite. The solvent was removed under reduced pressure to give alcohol **49** (30.63 g, 98% yield) as a colorless oil: $[\alpha]_D^{23} = -22.8$ ($c = 1.39$, $CHCl_3$); $R_f = 0.31$ (20% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3483$ (br), 2936, 2858, 1471, 1281, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.77$ (m, 1H; 41-H); 3.59 (dd, $J = 7.5$, 3.0 Hz, 1H; 40-H); 3.30 (s, 3H; OCH_3); 3.21 (m, 1H; 39-H) 2.32 (s, 1H; OH), 1.87 (m, 1H); 1.74 (m, 1H); 1.57-1.36 (band, 3H), 1.16 (m, 1H); 0.086 (s, 9H; *t*Bu); 0.055 (s, 3H; $SiCH_3$); 0.048 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 80.8$, 75.8, 70.8, 57.6, 30.1, 26.3, 26.3, 26.2, 18.6, -4.1, -4.5; FAB HRMS calcd for $C_{13}H_{29}O_3Si$ ($M + H^+$): 261.1866; found *m/e* 261.1873.

Ketone 50: A solution of oxalyl chloride (15.44 mL, 177 mmol) in CH_2Cl_2 (500 mL) was cooled to -78 °C, treated with a solution of DMSO (16.75 mL, 236 mmol) in CH_2Cl_2 (200 mL), and stirred for 30 min at -78 °C. Alcohol **49** (30.63 g, 118 mmol) in CH_2Cl_2 (100 mL) was then added dropwise. The solution was stirred at -78 °C for 1 h, and triethylamine (82.23 mL, 590 mmol) then added. The solution was allowed to slowly warm to room temperature. After being stirred at room temperature for 2 h, the mixture was diluted with ether (1000 mL), washed with 5% aqueous HCl (400 mL), then brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 15% ether in petroleum ether) to afford ketone **50** as a colorless solid (28.12 g, 92% yield): M.p. 59-60 °C; $[\alpha]_D^{23} = -13.7$ ($c = 0.87$, $CHCl_3$); $R_f = 0.37$ (20% ether in petroleum ether) IR (CH_2Cl_2): $\tilde{\nu}_{max} = 2847$, 2855, 1728, 1461, 1249, 1097, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.98$ (dd, $J = 8/0$, 1.5 Hz, 1H; 40-H); 3.38 (s, 3H; OCH_3); 3.27 (ddd, $J = 8.0$, 7.5, 4.0 HZ, 1H; 39-H); 2.49 (m, 2H; 42-H_2); 2.16 (m, 1H); 1.87 (m, 1H); 1.60 (m, 1H); 1.48 (m, 1H); 0.87 (s, 9H; *t*Bu); 0.05 (s, 3H; $SiCH_3$); 0.004 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 208.3$, 84.8, 81.0, 58.4, 39.4, 28.2, 26.2, 26.1, 21.0, -4.4, -4.9; FAB HRMS calcd for $C_{13}H_{2?}O_3Si$ ($M + H^+$): 259.1729; found *m/e* 259.1720.

Enone 51: A solution of diisopropylamine (7.98 mL, 56.93 mmol) in THF (100 mL) under argon at 0 °C was treated with *n*BuLi (32.62 mL, 1.6 M in hexanes, 52.16 mmol), and the mixture stirred at 0 °C for 1 h. The solution was cooled to -78 °C, and ketone **50** (12.24 g, 47.44 mmol) in THF (75 mL) added dropwise. The solution was stirred for 15 min, trimethylsilyl chloride (9.03 mL, 71.16 mmol) added in one portion, and the mixture allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C, quenched with phosphate buffer (pH = 7.0, 50 mL), and diluted with ether (200 mL). The layers were separated, and the organic phase was washed with aqueous $CuSO_4$ (100 mL) and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was taken up in 5% ether in petroleum ether and filtered quickly through a plug of silica gel. The solvent was evaporated, and the residue dissolved in anhydrous CH_3CN (150 mL). $Pd(OAc)_2$ (12.75 g, 56.93 mmol, 1.2 equiv) was added, and the mixture heated to 50 °C and stirred for 24 h. The solution was cooled to room temperature, diluted with ether, and filtered through Celite. The solvent was removed under reduced pressure, and the enone purified by flash chromatography (silica gel, 15% ether in petroleum ether). The enone **51** was obtained as a colorless oil (10.07 g, 83% yield): $[\alpha]_D^{23} = -32.3$ ($c = 1.16$, $CHCl_3$); $R_f = 0.30$ (15% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2930$, 2857, 1695, 1253, 1138 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.77$ (ddd, $J = 10.0$, 6.0, 3.0 Hz, 1H; 37-H), 5.97 (dd, $J = 10.0$, 3.0 Hz, 1H; 42-H), 4.07 (d, $J = 9.5$ Hz, 1H; 40-H), 3.50 (ddd, $J = 10.0$, 9.5, 4.5 Hz, 1H; 39-H), 3.43 (s, 3H; OCH_3), 2.83 (ddd, $J = 18.5$, 5.0, 4.5 Hz, 1H; 38-H), 2.33 (dddd, $J = 18.5$, 8.5, 3.0, 2.5 Hz, 1H; 38-H'), 0.89 (s, 9H; *t*Bu), 0.12 (s, 3H; $SiCH_3$), 0.05 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 198.4$, 146.1, 129.3, 81.5, 79.8, 59.1, 32.0, 26.2, 18.6, -4.2, -4.9 ; FAB HRMS calcd for $C_{13}H_{25}O_3Si$ ($M + H^+$): 257.1573; found *m/e* 257.1570.

Allylic alcohol 52: Enone **51** (10.98 g, 42.56 mmol) and $CeCl_3 \cdot 7H_2O$ (31.71 g, 85.12 mmol) were dissolved in THF/MeOH (1:1, 350 mL), and the solution cooled to -78 °C. $LiBH_4$ (85.12 mL, 2 M in THF, 170 mmol) was added dropwise, and the solution stirred at -78 °C for 1 h. The reaction mixture was quenched at -78 °C by the careful addition of 0.1 N HCl (150 mL), and the mixture stirred at room temperature for 2 h. The solution was diluted with ether (350 mL), and the layers were separated. The aqueous phase was extracted with ether (3 × 150 mL). The combined extracts were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residue provided alcohol **52** (10.51 g, inseparable ca. 7:1 mixture of epimers, 95% yield) as a colorless oil: $[\alpha]_D^{23} = +7.4$ ($c = 1.75$, $CHCl_3$); $R_f = 0.8$ (3% ether in CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3452$, 2930, 2856, 1252, 837, 778 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): $\delta = 5.62$ (m, 1H; 42-H), 5.57 (dddd, $J = 10.0$, 3.5, 3.5, 1.0 Hz, 1H; 37-H), 3.86 (m, 1H; 41-H), 3.73 (dd, $J = 7.5$, 5.0 Hz, 1H; 40-H), 3.33 (m, 1H; 39-H), 3.30 (s, 3H; OCH_3), 2.60 (brs, 1H; OH), 2.40 (m, 1H; 38-H), 2.03 (m, 1H; 38-H'), 0.83 (s, 9H; *t*Bu), 0.048 (s, 3H; $SiCH_3$), 0.043 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 128.2$, 125.1, 78.9, 74.2, 71.7, 57.5, 28.4, 26.2, 18.5, -4.2, -4.5; FAB HRMS calcd for $C_{13}H_{27}O_3Si$ ($M + H^+$): 259.1279; found *m/e* 259.1720.

Alcohol 53: Allylic alcohol **52** (11.6 g, 44.62 mmol) and *N,N*-dimethylacetamide dimethylacetal (32.60 mL, 223 mmol) were dissolved in xylenes (100 mL), and the mixture was heated to reflux for 48 h. The solution was concentrated under reduced pressure, and the residue taken up in THF (200 mL). The solution was cooled to 0 °C and treated with lithium triethylborohydride (178 mL, 1 M in THF, 178 mmol). The mixture was allowed to warm to room temperature and then stirred for 2 h. The solution was again cooled to 0 °C and quenched with MeOH (90 mL) and 1 N NaOH (90 mL). The heterogeneous mixture was cautiously treated with 30% aqueous H_2O_2 (90 mL) and stirred at ambient temperature overnight. The solution was extracted with ether (3 × 200 mL). The combined ether extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 40% ether in petroleum ether) to yield alcohol **53** (12.37 g, 97% yield) as a colorless oil: $[\alpha]_D^{23} = -4.9$ ($c = 2.56$, $CHCl_3$); $R_f = 0.35$ (40% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3406$, 2929, 2857, 1251, 1103, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.50$ (dd, $J = 10.0$, 1.5 Hz, 1H; 41-H), 5.40 (ddd, $J = 10.0$, 2.5, 1.5 HZ, 1H; 42-H), 4.10 (ddd, $J = 7.5$, 2.5, 1.5 Hz, 1H; 40-H), 3.65 (m, 2H; CH_2OH), 3.39 (s, 3H; OCH_3), 3.14 (ddd, $J = 8.5$, 7.5, 3.5 Hz, 1H; 39-H), 2.38 (m, 1H; 37-H), 2.22 (s, 1H; OH), 2.08 (m, 1H), 1.61 (m, 2H), 1.47 (m, 1H), 0.87 (s, 9H; *t*Bu), 0.06 (s, 3H; $SiCH_3$), 0.057 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 132.5$, 130.2, 83.3, 73.5, 60.3, 39.12, 33.2, 33.1, 26.3, -4.1, -4.3; FAB HRMS (NBA/NaI) calcd for $C_{15}H_{30}O_3SiNa$ ($M + Na^+$): 309.1862; found *m/e* 309.1867.

Alcohol 54: Compound **53** (12.37 g, 43.25 mmol) and 5% Pd/C (1.27 g, 10 wt%) were taken up in EtOH (100 mL) and stirred under an H_2 atmosphere for 16 h. The mixture was diluted with ether (200 mL) and filtered through Celite. The solvent was evaporated to provide compound **54** (12.35 g, 100%) as a colorless oil. The compound was taken forward without any further purification: $[\alpha]_D^{23} = -17.3$ ($c = 1.28$, $CHCl_3$); $R_f = 0.25$ (50% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3404$, 2930, 2857, 1336, 1112, 846, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.62$ (m, 2H; CH_2OH), 3.37 (s, 3H; OCH_3), 3.35 (m, 1H; 40-H); 2.88 (ddd, $J = 8.5$, 8.5, 4.5 Hz, 1H; 39-H), 2.14 (s, 1H; OH), 2.03 (m, 1H), 1.80 (m, 1H), 1.63 (m, 2H), 1.45 (m, 4H), 1.28 (m, 1H), 0.85 (s, 9H; *t*Bu), 0.040 (s, 3H; $SiCH_3$), 0.027 (s, 3H; $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 84.7$, 60.9, 58.4, 39.7, 37.1, 37.1, 34.4, 34.3, 32.9, 31.2, 26.3, -4.1, -4.3; FAB HRMS calcd for $C_{15}H_{33}O_3Si$ ($M + H^+$): 289.2199; found *m/e* 289.2210.

Olefin 55: Alcohol **54** (11.0 g, 38.19 mmol) and *o*-nitrophenylselenocyanate (10.4 g, 45.83 mmol) were dissolved in anhydrous THF (300 mL) and treated with tri-*n*-butylphosphine (11.42 mL, 45.83 mmol). After being stirred for 3 h, the reaction mixture was diluted with ether (300 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to provide the selenide (17.12 g, 93% yield). The selenide was taken up in THF (300 mL), and the mixture cooled to 0 °C and treated with 30% aqueous H_2O_2 (45 mL). The reaction mixture was stirred at room temperature for 6 h, then diluted with water (100 mL), and extracted (3 × 100 mL) with ethyl acetate. The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford olefin **55** (8.64 g, 86% yield) as a pale yellow oil: $[\alpha]_D^{23} = -27.7$ ($c = 1.35$, $CHCl_3$); $R_f = 0.42$ (5% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2930$, 2857, 1251, 1111, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.74$ (ddd, $J = 17.5$, 10.5, 6.5 Hz, 1H; 36-H), 4.98 (ddd, 1H; $J = 17.5$, 1.5, 1.5 Hz, 1H; 35-H_{trans}), 4.90 (ddd, $J = 10.5$, 1.5, 1.4 Hz, 1H; 35-H_{cis}), 3.41 (s, 3H; OCH_3), 3.38 (m, 1H; 40-H), 2.95 (ddd, $J = 11.3$, 8.5, 4.5 Hz, 1H; 39-H), 2.07 (m, 1H), 2.01 (m, 1H); 1.86 (m, 1H), 1.67 (m, 1H), 1.36 (m, 1H), 1.09 (m, 1H), 0.98 (m, 1H), 0.09 (s; 9H; *t*Bu),

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0.07 (s, 3H; SiCH_3), 0.04 (s, 3H; SiCH_3), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.2, 113.0, 84.8, 75.8, 58.4, 40.4, 36.2, 34.3, 30.4, 30.8, 26.4, 18.7, −4.0, −4.3; FAB HRMS (NBA/NaI) calcd for $C_{15}H_{30}O_2SiNa$ (M + Na^+) 293.1930; found 293.1920.

Aldehyde 56: Olefin **55** (6.2 g, 21.74 mmol) was dissolved in MeOH/CH_2Cl_2 (1:1, 120 mL) and cooled to −78 °C. Ozone was bubbled through the solution until the starting material was consumed. The solution was treated with methyl sulfide (10.86 mL, 108.68 mmol) and slowly warmed to room temperature and stirred overnight. The solvent was evaporated, and the aldehyde purified by flash chromatography (silica gel, 15% ether in petroleum ether). Aldehyde **56** was obtained as a mixture of epimers (resulting from the reduction of enone **52**) that were separable by chromatography (major 5.28 g, 88%, minor 0.58 g, 9.9%): $[\alpha]_D^{23}$ = − 31.1 (c = 0.67, $CHCl_3$); R_f = 0.26 major, R_f = 0.35 minor (15% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2951, 2857, 1729, 1252, 1109 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.64 (s, 1H; 36-H), 3.53 (ddd, J = 8.5, 7.0, 3.5 Hz, 1H; 40-H), 3.37 (s, 3H; OCH_3), 3.04 (ddd, J = 8.5, 7.0, 3.5 Hz, 1H; 39-H), 2.21–2.08 (m, 2H), 1.93–1.86 (m, 2H), 1.51–1.35 (m, 3H), 0.88 (s, 9H; tBu), 0.066 (s, 3H; SiCH_3), 0.061 (s, 3H; SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.9, 82.7, 72.9, 58.1, 47.7, 31.1, 28.5, 26.3, 22.6, 18.4, −4.2, −4.4; FAB HRMS (NBA/NaI) calcd for $C_{14}H_{28}O_3SiNa$ (M + Na^+): 295.1705; found m/e 295.1711.

Compound 58: To a flask containing a stir bar and anhydrous LiCl (1.85 g, 38.96 mmol) was added phosphonate **57** (10.05 g, 29.22 mmol) in anhydrous CH_3CN (250 mL). The mixture was treated with diisopropylethylamine (50.90 mL, 292.2 mmol). After 15 min, when most of the LiCl had dissolved, aldehyde **57** (5.28 g, 19.48 mmol) in CH_3CN (50 mL) was added. The mixture was stirred 6 h, then diluted with ether (500 mL), and washed with 5% aqueous HCl (200 mL). The aqueous phase was extracted ether (3 × 200 mL), and the combined ether layers were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The crude enone was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to provide pure **58** (8.91 g, 95% yield) as a colorless foam: $[\alpha]_D^{23}$ = − 9.7 (c = 2.35, $CHCl_3$); R_f = 0.29 (30% ether in petroleum ether); IR (CH_2Cl_2): 2931, 2856, 1783, 1685, 1636, 1349, 1196, 1111 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.31 (band, 5H; Ar), 7.26 (d, J = 15.0 Hz, 1H; 35-H), 7.07 (dd, J = 15.0, 7.0 Hz, 1H; 36-H), 5.68 (d, J = 8.0 Hz, 1H; ArCHO), 4.82 (dq, J = 8.0, 5.6 Hz, 1H; CH_3CHN), 3.45 (m, 1H; 40-H), 3.43 (s, 3H, OCH_3); 2.99 (ddd, J = 12.0, 9.0, 5.0, Hz, 1H; 39-H), 2.31 (m, 1H), 2.14 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.42 (m, 1H), 1.24 (m, 1H), 1.13 (m, 1H), 0.93 (d, J = 8.0 Hz, 3H; CH_3), 0.90 (s, 9H; tBu), 0.09 (s, 3H; SiCH_3), 0.08 (s, 3H; SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4, 154.5, 153.5, 133.8, 129.2, 126.1, 119.4, 84.4, 79.5, 75.3, 58.4, 55.4, 79.7, 35.5, 33.9, 29.3, 26.3, 18.6, 15.7, −4.1, −4.3; FAB HRMS (NBA/NaI) calcd for $C_{26}H_{39}NO_5SiNa$ (M + Na^+); 496.2495; found m/e 296.2499.

Fragment 9: Enone **58** (8.00 g, 16.78 mmol) and [$(PPh_3)_3$RhCl] (30 mg, 0.32 mmol) were dissolved in Et_3SiH (15 mL), and the solution heated to 50 °C for 2.5 h. The Et_3SiH was removed under reduced pressure, and the residue dissolved in CH_3CN (80 mL). The mixture was cooled to 0 °C and treated with 49% aqueous HF (8 mL). After being stirred for 3 h at room temperature, the solution was poured into aqueous $NaHCO_3$ (150 mL), and the pH of the solution made basic by the addition of solid $NaHCO_3$. The solution was extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated. The residue and imidazole (3.42 g, 50.34 mmol) were dissolved in DMF (40 mL) and treated with *tert*-butyldiphenylsilyl chloride (5.15 mL, 20.14 mmol) at ambient temperature. The mixture was stirred at that temperature for 16 h and then diluted with ether (150 mL), washed successively with 5% aqueous HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The product was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to yield compound **9** (7.60 g, 75% yield) as a colorless foam: $[\alpha]_D^{23}$ = + 3.6 (c = 0.87, $CHCl_3$); R_f = 0.35 (35% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 2930, 2858, 1763, 1701, 1455, 1350, 1197, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (band, 4H; Ar), 7.37 (band, 11H; Ar), 5.63 (d, J = 7.0 Hz, 1H; ArCHO), 4.71 (dq, J = 7.3, 6.6 Hz, 1H; CH_3CHN), 3.53 (ddd, J = 13.3, 8.6, 4.8 Hz, 1H; 40-H), 3.32 (s, 3H; OCH_3), 3.05 (ddd, J = 12.9, 8.6, 4.5 Hz, 1H; 39-H), 2.91 (ddd, J = 23.0, 8.0, 8.0 Hz, 1H; 35-H), 2.85 (ddd, J = 23.0, 8.0, 8.0 Hz, 1H; 35-H), 2.05 (m, 1H), 1.63 (m, 1H), 1.52 (band, 4H), 1.03 (s, 9H; tBu), 0.7 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4, 153.4, 136.4, 136.3, 135.5, 134.7, 133.7, 129.7, 129.7, 129.1, 129.1, 127.8, 127.7, 126.0, 84.7, 79.3, 76.4, 57.7, 55.1, 36.5, 35.7, 33.9, 33.8, 31.0, 30.4, 27.4, 19.7, 14.9; FAB HRMS (NBA/CsI) calcd for $C_{36}H_{45}NO_5SiCs$ (M + Cs^+): 732.2121; found m/e 732.2100.

Alcohol 59: Aldehyde **7** (2.49 g, 7.73 mmol) and vinyl iodide **8** (11.73 g, 23.19 mmol) were combined, azeotroped with benzene, and placed under high vacuum for 2 h. DMSO (200 mL) was added and the mixture degassed by freezing at −100 °C and pumping under high vacuum for 90 min. After warming to room temperature under argon, $CrCl_2$ (5.70 g, 46.38 mmol) containing 0.1% $NiCl_2$ was added. The resulting green suspension was stirred under argon for 48 h. An additional 4 equiv of $CrCl_2$ was then added, and the stirring continued for an additional 24 h. The mixture was diluted with aqueous NH_4Cl (500 mL) and extracted with ether (3 × 300 mL). The combined extracts were washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to afford the desired allylic alcohol **59** (3.1 g, 57% yield) as a colorless oil and its epimer **59a** (1.4 g, 26% yield). Selected data for **59**: $[\alpha]_D^{23}$ = − 10.6 (c = 1.06, $CHCl_3$); R_f = 0.1 (silica gel, 30% ether in petroeum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3476, 2056, 2930, 1612, 1514, 1249, 1090 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (band, 4H; Ar), 6.83 (band, 4H; Ar), 5.53 (overlapping m, 2H; 22-H, 30-H), 4.92 (m, 2H; 21-H_2), 4.48 (m, 4H; 2OCH_2Ar), 4.17 (dd, J = 5.3, 5.3 Hz, 1H; 28-H), 3.77 (s, 6H; 2 ArOCH_3), 3.65–3.62 (m, 2H; 34-H_2), 3.43 (m, 1H; 32-H), 3.38 (s, 3H; 27-OCH_3), 3.34 (dd, J = 5.3, 3.4 Hz, 1H; 26-H), 3.29 (dd, J = 5.3, 3.4 Hz, 1H; 27-H), 2.95 (d, J = 5.3 Hz, 1H; OH), 2.73 (m, 1H, 31-H), 2.19 (m, 1H; 23-H); 1.89 (m, 1H, 25-H); 1.68–1.58 (band, 5H; 33-H_2, 29-CH_3), 1.34, 1.11 (2m, 2H; 24-H_2), 0.98 (d, J = 6.9 Hz, 3H; CH_3), 0.97 (d, J = 6.6 Hz, 3H; CH_3),, 0.93 (d, J = 6.7 Hz, 3H; CH_3), 0.87 (s, 9H; tBu), 0.02 (s, 3H; SiCH_3), 0.01 (s, 3H; SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 158.9, 144.0, 134.4, 131.2, 130.4, 130.2, 130.1, 129.9, 129.2, 113.7, 113.6, 113.4, 82.0, 81.2, 78.8, 75.5, 72.7, 71.7, 67.1, 60.1, 58.8, 55.2, 39.4, 35.7, 35.2, 34.3, 31.6, 25.9, 21.9, 16.0, 15.8, 13.4, −4.4, −5.4; FAB HRMS (NBA/CsI) calcd for $C_{41}H_{66}O_7SiCs$ (M + Cs^+): 831.3632; found m/e 831.3635.

Synthesis of alcohol 59 from alcohol 59a: A solution of alcohol **59a** (4.05 g, 5.77 mmol) in CH_2Cl_2 (60 mL) was treated with Dess–Martin periodinane (2.70 g, 6.36 mmol). The solution was stirred at room temperature for 1 h and quenched with aqueous $Na_2S_2O_3$ (25 mL) and aqueous $NaHCO_3$ (25 mL). The layers were separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in 30% ether in petroleum ether (25 mL) and filtered through silica gel. The solvent was evaporated to provide the enone (3.67 g, 91% yield), which was used without further purification.
The enone (3.67 g, 5.26 mmol) from above was dissolved in THF (100 mL) and cooled to −78 °C. The solution was treated with DIBALH (15.78 mL, 1 M in CH_2Cl_2, 15.78 mmol) and stirred at −78 °C for 1 h. The reaction mixture was quenched with methanol (1.5 mL) and diluted with ether (100 mL). The mixture was poured into an Erlenmeyer flask and stirred vigorously for 2 h with aqueous sodium potassium tartrate (100 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 75 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to afford alcohol **59** (2.81 g, 76% yield) and its epimer **59a** (282 mg, 9% yield).

Silyl ether 60: Alcohol **59** (2.86 g, 4.09 mmol) and 2,6-lutidine (1.58 mL, 13.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C were treated with triisopropylsilyl trifluoromethanesulfonate (1.21 mL, 4.50 mmol). The mixture was stirred for 15 min, quenched with methanol (0.5 mL), and stirred for an additional 5 min. It was diluted with ether (60 mL), washed with aqueous $CuSO_4$ (40 mL), and brine (40 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford compound **60** (3.43 g, 98% yield) as a colorless oil: $[\alpha]_D^{23}$ = − 4.1 (c = 1.13, $CHCl_3$); R_f = 0.34 (silica gel, 10% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2956, 2866, 1613, 1514, 1463, 1251, 1089 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (band, 4H; Ar), 6.84 (band, 4H; Ar), 5.47 (ddd, J = 15.5, 10.2, 8.7 Hz, 1H; 22-H), 5.16 (d, J = 9.4 Hz, 1H; 30-H), 4.89 (dd, J = 15.5, 1.7 Hz, 1H; 21-H_{trans}), 4.87 (dd, J = 10.2, 1.7 Hz, 1H; 21-H_{cis}), 4.54 (ABq, J_{AB} = 10.6 Hz, $\Delta\nu_{AB}$ = 174.3 Hz, 2H; OCH_2Ar), 4.45 (ABq, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 36.9 Hz, 2H; OCH_2Ar), 4.10 (d, J = 3.3 Hz, 1H; 28-H), 3.77 (s, 6H; 2ArOCH_3), 3.64 (m, 1H; 27-H), 3.59 (m, 1H; 32-H), 3.55 (s, 3H; 27-OCH_3), 3.41 (m, 2H; 34-H), 3.07 (dd, J = 8.2, 2.0 Hz, 1H; 26-H), 2.74 (m, 1H; 31-H), 2.14 (m, 1H; 23-H), 1.76 (s, 3H; 29-CH_3), 1.66 (m, 1H; 25-H), 1.50 (m, 2H); 1.31, 1.22 (2m, 2H; 24-H_2), 1.04 (d, J = 5.7 Hz, 18H; Si(CH(CH_3)$_2$)$_3$), 0.96 (m, 6H; 2CH_3), 0.86 (band, 12H; CH_3 and tBu), 0.005 (s, 6H; SiCH(CH$_3$)$_2$ and SiCH_3), 0.002 (s, 3H: SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 158.8, 143.9, 136.1, 132.0, 131.4, 130.7, 130.5, 129.3, 129.1, 113.7, 113.6, 113.5, 87.6, 85.1, 75.2, 71.4, 71.4, 61.3, 60.4, 55.2, 37.0, 35.0, 34.8, 34.3, 32.1, 26.0, 22.0, 18.3, 18.1, 17.0, 15.6, 13.2, 12.4, −5.4; FAB HRMS (NBA/CSi) calcd for $C_{50}H_{86}O_7Si_2Cs$ (M + Cs^+): 987.4966; found m/e 987.4962.

Tetraol 60a: A solution of compound **60** (322 mg, 0.38 mmol) and DDQ (257 mg, 1.13 mmol) in $CHCl_3/H_2O$ (20:1, 10 mL) was stirred at room temperature for 1 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (10 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to give the diol (202 mg, 82% yield). The diol was dissolved in THF (15 mL) and treated with HF·pyridine (0.15 mL). The mixture was stirred at 25 °C for 24 h and then poured into aqueous $NaHCO_3$ (20 mL). The pH was adjusted to 8.0 with solid $NaHCO_3$, and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (silica gel, 10% MeOH in CH_2Cl_2) afforded tetraol **60a** (104 mg, 97% yield). Selected data for **60a**: $[\alpha]_D^{23}$ = +17.3 (c = 2.34, $CHCl_3$); R_f = 0.37 (silica gel, 10% methanol in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3382, 2960, 1452, 1378, 1101, 1063, 909 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.56 (ddd, J = 18.5, 10.1, 8.6 Hz, 1H; 22-H), 5.49 (br d, J = 9.7 Hz, 1H; 30-H), 4.94 (dd, J = 18.5, 1.8 Hz, 1H; 21-H_{trans}), 4.89 (dd, J = 10.1, 1.8 Hz, 1H; 21-H_{cis}), 4.32 (brs, 1H; 28-H), 3.81–3.60 (band, 4H; 34-H_2, 32-H,

27-H), 3.45 (s, 3H, 27-OCH_3), 3.26 (m, 1H; 26-H), 2.47 (m, 1H; 31-H), 2.21 (m, 1H; 23-H), 1.71 (m; 2H), 1.63 (s, 3H; 29-CH_3), 1.60 (m; 2H), 0.98 (d, J = 6.6 Hz, 3H; CH_3), 0.94 (d, J = 6.9 Hz, 3H; CH_3), 0.81 (d, J = 6.5 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.7, 135.6, 129.4, 128.7, 113.6, 79.9, 76.2, 76.0, 74.7, 61.8, 58.8, 40.1, 39.3, 36.2, 30.2, 22.5, 17.5, 16.1, 14.7; FAB HRMS (NBA/CsI) calcd for $C_{19}H_{36}O_5Cs$ (M + Cs^+): 477.1617; found m/e 477.1608.

Bisacetonide 60b: Tetraol **60a** (54 mg, 0.157 mmol) and CSA (1 mg, 4.3 μmol) were dissolved in CH_2Cl_2 (1 mL) and treated with 2,2-dimethoxypropane (40 μL, 0.316 mmol) at room temperature. After the mixture had been stirred for 1 h at the same temperature, additional 2,2-dimethoxypropane (20 μL, 0.157 mmol) was added. The mixture was stirred for an additional 1 h before it was concentrated. The residue was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to provide bisacetonide **60b** (47 mg, 70% yield, plus 11 mg, 20% recovered **60a**) as a viscous oil. Selected data for **60b**: $[\alpha]_D^{23}$ = − 34.7 (c = 0.80, $CHCl_3$); R_f = 0.33 (silica gel, 20% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 2986, 2872, 1458, 1377, 1223, 1179, 1102, 1080, 998 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ = 5.63 (ddd, J = 18.4, 10.2, 8.3 Hz, 1H; 22-H), 5.45 (dd, J = 9.4, 1.2 Hz, 1H; 30-H), 4.97 (ddd, J = 18.4, 2.0, 0.9 Hz, 1H; 21-H_{trans}), 4.89 (dd, J = 10.2, 2.0 Hz, 1H; 21-H_{cis}), 4.09 (d, J = 5.7 Hz, 1H; 28-H), 3.92 (ddd, J = 11.8, 11.8, 2.9 Hz, 1H; 34-H_{eq}), 3.82 (ddd, J = 11.8, 6.5, 2.5 Hz, 1H; 34-H_{ax}), 3.65 (ddd, J = 11.4, 6.5, 2.5 Hz, 1H; 32-H), 3.43 (dd, J = 5.7, 3.2 Hz, 1H; 27-H); 3.37 (s, 3H; 27-OCH_3); 3.30 (dd, J = 9.9, 3.2 Hz, 1H; 26-H), 2.45 (m, 1H; 31-H), 2.29 (m, 1H; 23-H), 1.87 (m, 1H), 1.75 (m, 1H), 1.72 (dd, J = 2.8, 2.8 Hz, 1H), 1.70 (s, 3H; 29-CH_3), 1.58 (m, 1H), 1.43 (m, 1H), 1.41 (s, 3H; CH_3); 1.36 (s, 3H; CH_3), 1.31 (s, 3H; CH_3), 1.27 (s, 3H; CH_3), 1.00 (d, J = 6.7 Hz, 3H; CH_3), 0.97 (d, J = 6.8 Hz, 3H; CH_3), 0.91 (ddd, J = 14.3, 10.3, 5.6 Hz, 1H), 0.83 (d, J = 6.6 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, C_6D_6): δ = 144.6, 135.6, 132.1, 113.1, 100.6, 98.0, 80.9, 80.3, 76.4, 73.2, 59.7, 58.9, 40.7, 38.0, 36.1, 30.3, 30.3, 29.3, 24.8, 24.3, 23.6, 19.1, 16.3, 15.5, 12.5; FAB HRMS (NBA/CsI) calcd for $C_{25}H_{44}O_5Cs$ (M + Cs^+): 557.2243, found m/e 557.2260.

Alcohol 61: A solution of compound **60** (3.43 g, 4.0 mmol) in THF (60 mL) at 0 °C was treated with HF·pyridine complex (0.6 mL). The mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was cautiously poured into aqueous $NaHCO_3$ (100 mL) and the solution was extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 1:1 ether/petroleum ether) to provide alcohol **61** (2.87 g, 97% yield) as a colorless oil: $[\alpha]_D^{23}$ = − 5.2 (c = 2.55, $CHCl_3$); R_f = 0.26 (silica gel, 20% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3454, 2958, 2866, 1612, 1513, 1462, 1248, 1059 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.26 (band, 4H; Ar), 6.89–6.84 (band, 4H; Ar), 5.49 (ddd, J = 17.0, 10.0, 9.0 Hz, 1H; 22-H), 5.08 (d, J = 9.0 Hz, 1H; 30-H), 4.94 (dd, J = 17.0, 2.0 Hz, 1H; 21-H_{trans}), 4.92 (dd, J = 10.0, 2.0 Hz, 1H; 21-H_{cis}), 4.56 (ABq, J_{AB} = 10.7 Hz, $\Delta\nu_{AB}$ = 162.6 Hz, 2H; OCH_2Ar), 4.53 (ABq, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 108.9 Hz, 2H; OCH_2Ar), 4.11 (d, J = 3.7 Hz, 1H; 28-H), 3.79 (s, 3H; ArOCH_3), 3.78 (s, 3H; ArOCH_3), 3.66 (t, J = 5.4 Hz, 2H; 34-H_2), 3.57 (s, 3H; OCH_3), 3.49 (dt, J = 10.0, 3.0 Hz, 1H; 32-H), 3.44 (dd, J = 8.0, 3.7 Hz, 1H; 27-H), 3.04 (dd, J = 8.0, 2.0 Hz, 1H; 26-H), 2.93 (m, 1H; 31-H), 2.16 (m, 1H; 23-H), 1.81 (d, J = 0.9 Hz, 3H; 29-CH_3), 1.76 (m, 1H), 1.62 (m, 1H), 1.49 (m, 1H), 1.34 (m, 1H), 1.22 (m, 1H), 1.06 (d, J = 5.9 Hz; 18H; Si(CH(CH_3)$_2$)$_3$), 0.99 (d, J = 6.9 Hz, 3H; CH_3), 0.98 (d, J = 6.6 Hz, 3H; CH_3), 0.83 (d, J = 6.6 Hz, 3H; CH_3), 0.005 (m, 3H; SiCH(CH$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.7, 159.4, 144.5, 137.3, 132.2, 131.1, 130.8, 129.9, 129.9, 129.6, 114.3, 114.1, 114.0, 87.8, 85.1, 82.1, 79.0, 75.5, 71.3, 62.2, 61.8, 55.7, 37.4, 36.2, 33.9, 32.7, 32.5, 22.4, 18.7, 18.6, 17.4, 14.5, 13.8, 12.9; FAB HRMS (NBA/CsI) calcd for $C_{44}H_{72}O_7SiCs$ (M + Cs^+) 873.4102; found m/e 873.4108.

Aldehyde 62: A solution of oxalyl chloride (389 μL, 4.46 mmol) in CH_2Cl_2 (7 mL) at −78 °C was treated with a solution of DMSO (674 μL, 9.50 mmol) in CH_2Cl_2 (12 mL), and the mixture stirred 30 min. Alcohol **61** (2.20 g, 2.97 mmol) in CH_2Cl_2 (15 mL) was added, and the resulting white slurry stirred for 1 h at −78 °C. Triethylamine (2.15 mL, 14.85 mmol) was added, and the mixture slowly warmed to 0 °C and stirred at this temperature for 3 h. The reaction mixture was quenched with aqueous NH_4Cl (20 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated. Flash chromatography of the residue (silica gel, 20% ether in petroleum ether) afforded aldehyde **62** (2.11 g, 96% yield) as a colorless oil: $[\alpha]_D^{23}$ = − 5.1 (c = 1.17, $CHCl_3$); R_f = 0.41 (silica gel, 20% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 2932, 2866, 1726, 1613, 1514, 1463, 1248, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.68 (t, J = 1.3 Hz, 1H; 34-H), 7.27 (d, J = 8.6 Hz, 2H; Ar), 7.23 (d, J = 8.6 Hz, 2H; Ar), 8.87 (d, J = 8.6 Hz, 2H; Ar), 6.85 (d, J = 8.6 Hz, 2H; Ar), 5.48 (ddd, J = 17.1, 10.1, 9.0 Hz, 1H; 22-H), 5.20 (d, J = 9.3 Hz, 1H; 30-H), 4.92 (dd, J = 17.1, 1.7 Hz, 1H; 21-H_{trans}), 4.90 (dd, J = 10.1, 1.7 Hz, 1H; 21-H_{cis}), 4.57 (ABq, J_{AB} = 10.7 Hz, $\Delta\nu_{AB}$ = 156.1 Hz, 2H; OCH_2Ar), 4.47 (ABq, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 44.0 Hz, 2H; OCH_2Ar), 4.10 (d, J = 3.7 Hz, 1H; 28-H), 3.85 (dt, J = 8.7, 3.6 Hz, 1H; 32-H), 3.78 (s, 3H; ArOCH_3), 3.77 (s, 3H; ArOCH_3), 3.56 (s, 3H; 27-OCH_3), 3.42 (dd, J = 7.9, 3.7 Hz, 1H; 27-H), 3.07 (dd, J = 7.9, 2.5 Hz, 1H; 26-H), 2.85 (m, 1H; 31-H), 2.60 (ddd, J = 16.6, 8.9, 1.3 Hz, 1H; 33-H), 2.28 (ddd, J = 16.6, 3.6, 1.3 Hz, 1H; 33-H'), 2.16 (m, 1H; 23-H), 1.79 (s, 3H; 29-CH_3), 1.63 (m, 1H, 23-H), 1.32, 1.24 (2m, 2H; 24-H_2) 1.06 (s, 21H; Si(CH(CH_3)$_2$)$_3$), 1.00 (d, J = 6.8 Hz, 3H; CH_3), 0.97 (d, J = 6.6 Hz, 3H; CH_3), 0.83 (d, J = 6.6 Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.4, 159.1, 158.9, 144.0, 137.5, 131.6, 130.3, 129.6, 129.4, 129.2, 113.7, 113.6, 113.5, 87.1, 84.5, 78.5, 76.7, 74.9, 71.3, 61.2, 55.1, 45.3, 36.9, 35.6, 34.4, 32.0, 21.9, 18.2, 18.1, 17.0, 14.9, 13.3, 12.4; FAB HRMS (NBA/CsI) calcd for $C_{44}H_{70}O_7SiCs$ (M + Cs^+): 871.3945; found m/e 871.3966.

Aldol product 63: A solution of amide **9** (2.48 g, 4.11 mmol) in CH_2Cl_2 (12 mL) at −78 °C was treated with di-n-butylboryl triflate (4.52 mL, 1.0 M in CH_2Cl_2, 4.52 mmol). The mixture was stirred for 5 min and then treated with triethylamine (687 μL, 4.93 mmol). The mixture was allowed to warm slowly to 0 °C and stirred at that temperature for 1.5 h before it was cooled to −78 °C. A solution of aldehyde **62** (2.00 g, 2.74 mmol) in CH_2Cl_2 (4 mL) was added. The mixture was stirred at −78 °C for 15 min, then allowed to warm to −5 °C, and stirred for a further 12 h. The reaction mixture was quenched with phosphate buffer (pH = 7.0, 35 mL) and methanol (35 mL), and then treated at 0 °C with 30% aqueous H_2O_2 (15 mL). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was taken up in 5% aqueous $NaHCO_3$ (25 mL), and the mixture extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to afford compound **63** (3.16 g, 86% yield) as a colorless foam: $[\alpha]_D^{23}$ = − 52.6 (c = 3.26, $CHCl_3$); R_f = 0.35 (silica gel, 40% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 3523, 2931, 2865, 1781, 1696, 1612, 1513, 1247, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.66 (band, 4H; Ar), 7.41–7.30 (band, 10H; Ar), 7.26–7.23 (band, 5H; Ar), 6.85–6.80 (band, 4H; Ar), 5.50 (overlapping m, 2H; 22-H, OCHAr), 5.13 (d, J = 9.0 Hz, 1H; 30-H), 4.94 (dd, J = 17.2, 1.4 Hz, 1H; 21-H_{trans}), 4.90 (dd, J = 10.2, 1.9 Hz, 1H; 21-H_{cis}), 4.72 (dq, J = 7.0, 6.8 Hz, 1H; CHN), 4.52 (ABq, J_{AB} = 10.5 Hz, $\Delta\nu_{AB}$ = 152.8 Hz, 2H; OCH_2Ar), 4.50 (ABq, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 75.4 Hz, 2H; OCH_2Ar), 4.14 (overlapping m, 2H; 30-H, 35-H), 3.95 (m, 1H; 32-H), 3.75 (s, 3H; ArOCH_3), 3.73 (s, 3H; ArOCH_3), 3.52 (s, 3H; 27-OCH_3), 3.46 (ddd, J = 11.1, 8.6, 4.7 Hz, 1H; 40-H), 3.39 (dd, J = 7.6, 3.9 Hz, 1H; 27-H), 3.26 (s, 3H; 29-OCH_3), 3.16 (dd, J = 7.6, 2.8 Hz, 1H; 26-H), 2.94 (m, 1H; 39-H), 2.82 (m, 1H; 31-H), 2.50 (brs, 1H; OH), 2.10–2.08 (band; 2H), 1.77 (s, 3H; 29-CH_3), 1.7–1.1 (band, 6H), 1.04 (d, J = 4.8 Hz, 18H; Si(CH(CH_3)$_2$)$_3$), 1.02 (s, 9H; tBu), 0.96 (d, J = 5.5 Hz, 3H; CH_3), 0.90 (d, J = 6.6 Hz, 3H; CH_3), 0.80 (d, J = 5.6 Hz, 3H; CH_3), 0.65 (m, 3H; Si)CH(CH$_3$)$_2$), ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4, 159.0, 158.8, 153.1, 144.0, 136.6, 136.0, 135.9, 135.1, 134.3, 133.2, 132.0, 131.0, 130.4, 129.3, 129.2, 129.1, 128.8, 128.7, 127.3, 127.2, 125.6, 113.7, 113.6, 113.5, 87.0, 84.6, 84.2, 79.3, 78.6, 78.7, 75.6, 74.8, 71.7, 70.2, 61.1, 56.9, 55.2, 55.0, 45.8, 37.3, 35.8, 35.5, 34.9, 34.4, 34.3, 34.0, 33.5, 32.2, 30.9, 27.0, 21.9, 19.3, 18.3, 18.1, 17.0, 15.3, 14.4, 13.4, 12.3; FAB HRMS (NBA/CsI) calcd for $C_{80}H_{115}O_{11}NSiCs$ (M + Cs^+): 1470.7012; found m/e 1470.6866.

Diol 64: A solution of amide **63** (1.08 g, 0.8 mmol) and water (32 μL, 1.77 mmol) in ether (10 mL) at 0 °C was treated with $LiBH_4$ (885 μL, 2 M in THF, 1.77 mmol). The resulting white slurry was slowly warmed to room temperature and stirred for 1 h. The reaction mixture was again cooled to 0 °C and quenched with aqueous NH_4Cl (20 mL). The layers were separated, and the aqueous phase extracted with ether (3 × 20 mL). The combined ether extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (silica gel, 30% ethyl acetate in petroleum ether) of the residue afforded diol **64** (1.01 g, 98% yield) as a viscous oil: $[\alpha]_D^{23}$ = + 0.11 (c = 0.32, $CHCl_3$); R_f = 0.35 (silica gel, 30% ethyl acetate in petroleum ether); IR (thin film): $\tilde{\nu}_{max}$ = 3416, 2932, 2865, 1514, 1110, 812, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.67 (band, 4H; Ar), 7.38–7.21 (band, 10H; Ar), 6.85–8.80 (band, 4H; Ar), 5.49 (ddd, J = 18.5, 9.7, 8.1 Hz, 1H; 22-H), 5.11 (d, J = 9.4 Hz, 1H; 30-H), 4.90 (dd, J = 18.5, 1.7 Hz, 1H; 21-H_{trans}); 4.88 (dd, J = 9.7, 1.7 Hz, 1H; 21-H_{cis}), 4.50 (ABq, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 80.1 Hz, 2H; OCH_2Ar), 4.47 (ABq, J_{AB} = 10.7 Hz, $\Delta\nu_{AB}$ = 149.5 Hz, 2H; OCH_2Ar), 4.13 (d, J = 3.8 Hz, 1H; 28-H), 3.96 (m, 1H; 32-H), 3.75 (s, 3H; ArOCH_3), 3.73 (s, 3H; ArOCH_3), 3.61-3.51 (overlapping m, 3H; CH_2 OH, 34-H), 3.51 (s, 3H; 27-OCH_3), 3.50 (m, 1H; 40-H), 3.36 (dd, J = 7.2, 3.8 Hz, 1H; 27-H), 3.29 (s, 3H; 39-OCH_3), 3.15 (dd, J = 7.2, 2.8 Hz, 1H; 26-H), 2.99 (ddd, J = 12.8, 8.4, 4.4 Hz, 1H; 39-H), 2.85 (m, 1H; 31-H), 2.20–2.00 (band, 5H), 1.78 (s, 3H; 29-CH_3), 1.69 (m, 1H), 1.60 (m, 1H), 1.49 (m, 1H), 1.40 (m, 1H), 1.25 (m, 2H), 1.04–1.03 (band, 27-H; tBu, Si(CH(CH_3)$_2$)$_3$), 0.95 (d, J = 6.6 Hz, 3H; CH_3), 0.93 (d, J = 6.9 Hz, 3H; CH_3), 0.86 (d, J = 6.4 Hz, 3H; CH_3), 0.63 (m, 3H; Si(CH(CH$_3$)$_2$)$_3$); ^{13}C NMR (125, MHz): δ = 159.2, 158.8, 144.1, 136.6, 136.0, 135.9, 135.1, 130.6, 130.5, 129.3, 129.1, 127.3, 127.2, 113.8, 113.5, 113.4, 86.8, 84.3, 84.2, 79.1, 78.6, 76.1, 74.5, 71.9, 71.6, 64.8, 61.0, 57.4, 55.2, 41.8, 37.3, 35.9, 35.6, 34.7, 33.6, 33.4, 33.3, 32.4, 32.2, 31.3, 27.0, 18.3, 18.1, 16.9, 15.4, 12.5 ; FAB HRMS (NBA/CsI) calcd for $C_{70}H_{108}O_{10}Si_2Cs$ (M + Cs^+): 1297.6535; found m/e 1297.6641.

Tosylate 65: Diol **64** (2.28 g, 1.77 mmol), triethylamine (740 μL, 5.31 mmol), and DMAP (43 mg, 0.35 mmol) were dissolved in CH_2Cl_2 (20 mL), cooled to 0 °C, and treated with p-tolunesulfonyl chloride (404 mg, 2.12 mmol). The mixture was stirred at room temperature for 24 h, then diluted with ether (60 mL), and washed with aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chro-

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matography (50% → 70% ether in petroleum ether) to provide 1.83 g of tosylate **65** plus 0.366 mg of recovered diol **64**, which was resubmitted to the reaction conditions, to provide, after workup and chromatography, a total of 2.13 g (91% yield, 2 cycles) of tosylate **67**: $[\alpha]_D^{23} = -7.73$ ($c = 3.00$, $CHCl_3$); $R_f = 0.29$ (50% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 3584, 2932, 2855, 1612, 1513, 1248, 1188, 1110, 820\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.75-7.69$ (band, 6H; Ar), 7.42–7.23 (band, 12H; Ar), 6.87–6.82 (band, 4H; Ar), 5.50 (ddd, $J = 17.5, 10.0, 9.0$ Hz, 1H; 22-H), 5.08 (br d, $J = 9.2$ Hz, 1H; 30-H), 4.91 (dd, $J = 17.5, 1.7$ Hz, 1H; 21-H_{trans}); 4.88 (dd, $J = 10.0, 1.7$ Hz, 1H; 21-H_{cis}); 4.60 (ABq, $J_{AB} = 11.4$ Hz, $\Delta\nu_{AB} = 103.0$ Hz, 2H; OCH_2Ar), 4.49 (ABq, $J_{AB} = 10.6$ Hz, $\Delta\nu_{AB} = 171.7$ Hz, 2H; OCH_2Ar), 4.12 (d, $J = 3.6$ Hz, 1H; 28-H), 3.99 (m, 1H; 32-H), 3.88 (m, 2H; CH_2OTs), 3.53 (s, 3H; 27-OCH_3), 3.50–3.38 (band, 3H; 27-H, 34-H, 40-H), 3.20 (s, 3H; 39-OCH_3), 3.11 (dd, $J = 7.7, 2.6$ Hz, 1H; 26-H), 2.93 (ddd, $J = 11.0, 8.5, 4.5$ Hz, 1H; 39-H), 2.84 (m, 1H; 31-H), 2.41 (s, 3H; $ArCH_3$), 2.14 (m; 1H), 1.92 (m, 1H), 1.80 (s, 3H; 29-CH_3), 1.66–1.56 (band, 3H), 1.35–1.21 (band, 6H), 1.55 (d, $J = 6.5$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.05 (s, 9H; *t*Bu), 0.98 (d, $J = 6.5$ Hz, 3H; CH_3), 0.93 (d, $J = 7.0$ Hz, 3H; CH_3), 0.85 (d, $J = 6.5$ Hz, 3H; CH_3), 0.55 (m; 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.7, 159.3, 145.3, 144.5, 137.3, 136.6, 136.4, 135.5, 134.7, 133.4, 132.4, 131.0, 130.8, 130.3, 129.9, 129.1, 128.8, 129.8, 129.8, 129.7, 128.4, 127.8, 127.8, 114.3, 114.0, 87.5, 85.0, 84.7, 79.1, 79.1, 76.3, 75.3, 71.9, 71.2, 67.8, 61.6, 57.8, 55.7, 41.5, 37.6, 36.0, 35.0, 35.0, 33.9, 33.8, 32.7, 32.4, 31.7, 27.5, 22.4, 22.1, 18.8, 18.7, 17.5, 15.7, 14.0, 13.0$; FAB HRMS (NBA/CsI) calcd for $C_{77}H_{114}O_{12}Si_2SCs$ ($M + Cs^+$) 1451.6624, found *m/e* 1451.6739.

Alcohol 66: A solution of tosylate **65** (2.13 g, 1.61 mmol) in THF (50 mL) at 0 °C was treated with lithium triethylborohydride (16.1 mL, 1 M in THF, 16.1 mmol). The mixture was allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was again cooled to 0 °C and quenched with methanol (13 mL) and 1 N NaOH (13 mL). The mixture was treated with 30% aqueous H_2O_2 (13 mL), stirred for 6 h at room temperature, and then concentrated under reduced pressure. The residue was taken up in aqueous $NaHCO_3$ (25 mL) and extracted with ether (3 × 25 mL). The combined ether extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (silica gel, 30% ether in petroleum ether) of the residue provided compound **66** (1.68 g, 91%) as a viscous oil: $[\alpha]_D^{23} = -10.4$ ($c = 1.78$, $CHCl_3$); $R_f = 0.34$ (silica gel, 30% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 3490, 2932, 2866, 1613, 1514, 1461, 1248, 1110, 818\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.74-7.70$ (band, 4H; Ar), 7.40–7.24 (band, 10H; Ar), 6.86–6.83 (band, 4H; Ar), 5.51 (ddd, $J = 17.0, 10.0, 9.0$ Hz, 1H; 22-H), 5.11 (d, $J = 9.0$ Hz, 1H; 30-H), 4.92 (dd, $J = 17.0, 2.0$ Hz, 1H; 21-H_{trans}); 4.90 (dd, $J = 10.0, 2.0$ Hz, 1H; 21-H_{cis}); 4.51 (ABq, $J_{AB} = 10.6$ Hz, $\Delta\nu_{AB} = 170$ Hz, 2H; OCH_2Ar), 4.50 (ABq, $J_{AB} = 11.3$ Hz, $\Delta\nu_{AB} = 88.4$ Hz, 2H; OCH_2Ar), 4.13 (d, $J = 3.5$ Hz, 1H; 28-H), 3.78 (s, 3H; $ArOCH_3$), 3.75 (s, 3H; $ArOCH_3$), 3.55 (s, 3H; 27-OCH_3), 3.54–3.50 (overlapping m, 3H; 32-H, 34-H, 40-H), 3.41 (dd, $J = 8.0, 3.5$ Hz, 1H; 27-H), 3.31 (s, 3H; OCH_3), 3.13 (dd, $J = 8.0, 3.0$ Hz, 1H; 26-H), 3.03 (ddd, $J = 11.0, 9.0, 4.0$ Hz, 1H; 39-H), 2.88 (m, 1H; 31-H), 2.17 (m; 1H), 2.02 (m; 1H), 1.80 (s, 3H; 29-CH_3), 1.63 (band, 2H), 1.53 (m, 1H), 1.42–1.18 (band, 5H), 1.16 (d, $J = 5.5$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.05 (s, 9H; *t*Bu), 0.98 (d, $J = 6.1$ Hz, 3H; CH_3), 0.97 (d, $J = 6.0$ Hz, 3H; CH_3), 0.89 (d, $J = 6.6$ Hz, 3H; CH_3), 0.80 (d, $J = 6.7$ Hz, 3H; CH_3), 0.60 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.0, 159.7, 159.3, 155.0, 144.5, 137.2, 136.5, 136.4, 135.5, 134.7, 133.4, 132.3, 131.0, 129.8, 129.7, 127.8, 127.7, 114.2, 114.0, 87.6, 85.0, 79.4, 79.1, 76.6, 75.4, 73.1, 71.9, 61.7, 57.7, 55.7, 39.4, 37.5, 36.7, 36.1, 36.0, 35.0, 34.2, 34.1, 33.7, 32.8, 32.2, 27.5, 22.4, 18.8, 18.6, 17.5, 16.1, 15.5, 13.9, 13.0$; FAB HRMS (NBA/CsI) calcd for $C_{70}H_{108}O_9Si_2Cs$ ($M + Cs^+$): 1281.2586; found *m/e* 1281.6503.

Ester 67: Alcohol **66** (542 mg, 0.47 mmol), *t*-Boc-L-pipecolinic acid (541 mg, 2.36 mmol), and 4-pyrrolidinopyridine (35 mg, 0.235 mmol) were dissolved in CH_2Cl_2 (18 mL), and the solution was cooled to −20 °C. *N,N*-diisopropylethylamine (411 μL, 2.36 mmol) and DIC (370 μL, 2.36 mmol) were added. The mixture was stirred at −20 °C for 24 h, diluted with ether (60 mL), and the solution was washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (silica gel, 20% ether in petroleum ether) of the residue provided compound **67** (544 mg, 85% yield) as a colorless foam: $[\alpha]_D^{23} = -3.9$ ($c = 0.67$, $CHCl_3$); $R_f = 0.28$ (20% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 2932, 2865, 1738, 1694, 1613, 1514, 1249, 1111, 810\ cm^{-1}$; ^1H NMR (500 MHz, 50 °C, $CDCl_3$): $\delta = 7.73-7.69$ (band, 4H; Ar), 7.38–7.22 (band, 10H; Ar), 6.86–6.82 (band, 4H; Ar), 5.54 (ddd, $J = 17.5, 10.0, 9.0$ Hz, 1H; 22-H), 5.20 (br s, 2H; 2-H, 30-H), 4.93 (dd, $J = 17.5, 1.5$ Hz, 1H; 21-H_{trans}), 4.88 (dd, $J = 10.0, 1.5$ Hz, 1H; 21-H_{cis}), 4.55 (ABq, $J_{AB} = 11.0$ Hz, $\Delta\nu_{AB} = 169.5$ Hz, 2H; OCH_2Ar), 4.54 (ABq, $J_{AB} = 11.2$ Hz, $\Delta\nu_{AB} = 180.7$ Hz, 2H; OCH_2Ar), 4.47 (br s, 1H; 6-H_{eq}), 4.19 (d, $J = 3.6$ Hz, 1H; 28-H), 3.77 (s, 3H; $ArOCH_3$), 3.75 (s, 3H; $ArOCH_3$), 3.52 (s, 3H; OCH_3), 3.51–3.48 (overlapping m, 3H; 32-H, 34-H, 40-H), 3.39 (m, 1H; 27-H), 3.25 (s, 3H; OCH_3), 3.20 (br s, 1H; 26-H), 2.96 (br s, 1H; 39-H), 2.78 (m, 1H; H_{31}), 2.13 (band; 2H), 1.93 (m; 1H), 1.77 (s, 3H; 29-CH_3), 1.69–1.43 (band; 9H), 1.40 (s, 9H; *t*-Boc), 1.31 (band; 2H), 1.07 (d, $J = 3.6$ Hz, 18H, $Si(CH(CH_3)_2)_3$), 1.06 (s, 9H; *t*Bu), 0.98 (overlapping dbls, $J = 6.6$ Hz, 6H; $2CH_3$), 0.93 (d, $J = 6.6$ Hz, 3H; CH_3), 0.81 (d, $J = 6.8$ Hz, 3H; CH_3), 0.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173, 159.7, 144.7, 137.3, 136.5, 136.5, 135.8, 135.2, 129.8, 129.7, 129.5, 128.8, 127.8, 127.7, 114.3, 114.2, 113.8, 84.9, 79.4, 76.7, 61.4, 57.5, 55.8, 39.8, 37.8, 36.5, 36.1, 34.9, 34.2, 33.6, 33.0, 32.8, 28.9, 27.6, 25.3, 22.4, 19.9, 18.8, 18.7, 17.8, 16.0, 13.9, 13.2$; FAB HRMS (NBA/CsI) calcd for $C_{81}H_{124}O_{12}Si_2NCs$ ($M + Cs^+$): 1492.7795; found *m/e* 1492.7800.

Vinyl iodide 69: Compound **67** (369 mg, 0.271 mmol), 4-methylmorpholine-*N*-oxide (163 μL, 60% in water, 0.948 mmol), and OsO_4 (330 μL, 4 wt% in water, 0.054 mmol) were dissolved in acetone/water (2:1, 9.5 mL). The mixture was stirred at room temperature for 16 h, and the pH adjusted to 2.0 with 0.1 N aqueous HCl. The reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude diol was used in the next reaction without further purification.

A solution of the crude diol obtained above and Na_2CO_3 (67 mg, 0.813 mmol) in benzene (15 mL) was cooled to 0 °C and treated with $Pb(OAc)_4$ (180 mg, 0.407 mmol). The mixture was allowed to warm to room temperature and stirred for 90 min. The reaction mixture was quenched with 2 drops of ethylene glycol, stirred for 5 min, diluted with ether (30 mL), and washed with aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting oil was taken up in 20% ether in petroleum ether and passed through a plug of silica gel. The solvent was evaporated to afford crude aldehyde **68** (276 mg, 75% yield from olefin **67**).

Aldehyde **68** (276 mg, 0.20 mmol) was immediately dissolved in THF:dioxane (4:1, 12 mL) and treated with iodoform (320 mg, 0.81 mmol) and $CrCl_2$ (300 mg, 2.49 mmol). The mixture was stirred for 90 min at room temperature, diluted with water (15 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, 20% ether in petroleum ether) to provide vinyl iodide **69** (283 mg, 94% yield) as a colorless foam: $[\alpha]_D^{23} = -4.0$ ($c = 0.58$, $CHCl_3$); $R_f = 0.31$ (silica gel, 20% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 2932, 2866, 1738, 1693, 1514, 1248, 1110, 822, 703\ cm^{-1}$; ^1H NMR (500 MHz, 70 °C, C_6D_6): $\delta = 7.92-7.87$ (m, 4H; Ar), 7.51 (m, 2H; Ar), 7.40 (d, $J = 8.5$ Hz, 2H; Ar), 7.25 (band, 6H; Ar), 6.91 (d, $J = 8.5$ Hz, 2H; Ar), 6.85 (d, $J = 8.5$ Hz, 2H; Ar), 6.38 (dd, $J = 14.3, 9.0$ Hz, 1H; 22-H), 5.87 (d, $J = 14.3$ Hz, 1H; 21-H), 5.55 (m, 1H; 2-H), 5.50 (d, $J = 9.2$ Hz, 1H; 30-H), 5.03 (d, $J = 10.9$ Hz, 2H; OCH_2Ar), 4.69 (m, 1H; 6-H_{eq}), 4.68 (ABq, $J_{AB} = 10.3$ Hz, $\Delta\nu_{AB} = 40.8$ Hz, 2H; OCH_2Ar), 4.40 (d, $J = 3.3$ Hz, 1H; 28-H), 3.71 (band, 2H), 3.67 (s, 3H; OCH_3), 3.61 (dd, $J = 8.0, 3.3$ Hz, 1H; 27-H), 3.49 (m, 1H), 3.43 (s, 3H; OCH_3), 3.41 (s, 3H; OCH_3), 3.20 (s, 3H; OCH_3), 3.03 (band, 2H; 31-H, 39-H), 2.15 (band, 2H), 2.06 (s, 3H; 29-CH_3); ^{13}C NMR (125 MHz, C_6H_6, 70 °C): $\delta = 173.0, 159.7, 152.0, 136.5, 136.4, 134.9, 130.3, 130.1, 129.8, 129.7, 129.6, 129.5, 127.8, 127.7, 114.3, 114.2, 114.1, 84.8, 84.8, 79.4, 79.1, 76.8, 76.6, 75.8, 75.2, 74.2, 61.0, 57.7, 55.7, 54.2, 42.6, 41.0, 39.6, 39.5, 39.0, 36.5, 36.2, 35.8, 34.8, 34.2, 33.4, 32.9, 32.3, 31.8, 31.4, 28.9, 28.8, 27.5, 27.3, 25.3, 21.7, 18.9, 18.8, 17.5, 16.1, 16.0, 13.0$; FAB HRMS (NBA/CsI) calcd for $C_{81}H_{124}O_{12}NISi_2Cs$ ($M + Cs^+$): 1618.6761, found *m/e* 1618.6856.

Diol 70: A solution of compound **69** (256 mg, 0.172 mmol) in $CHCl_3$ (4 mL) and water (0.2 mL) was treated with DDQ (117 mg, 0.517 mmol). The mixture was stirred for 1 h at room temperature and diluted with aqueous $NaHCO_3$ (10 mL). The layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to give diol **70** (202 mg, 94% yield) as a sticky white foam: $[\alpha]_D^{23} = -8.8$ ($c = 0.73$, $CHCl_3$); $R_f = 0.29$ (silica gel, 30% ether in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 3450, 2931, 2862, 1780, 1694, 1601, 1458, 1366, 1249, 1156, 1108, 882, 821, 702\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): (hindered rotation of the Boc group on N_7 produced broadening (br) or doubling (dbl) of various ^1H and ^{13}C signals): $\delta = 7.73-7.67$ (m, 4H; Ar), 7.39–7.32 (m, 6H; Ar), 6.27 (dd, $J = 14.4, 8.5$ Hz, 1H; 22-H), 5.94 (d, $J = 14.4$ Hz, 1H; 21-H), 5.22 and 5.17 (dbl d, $J = 9.6$ Hz, 1H; 30-H), 5.05 (m, 1H; 2-H), 4.78 and 4.70 (dbl d, $J = 3.5$ Hz, 1H; 28-H), 4.18 and 4.04 (dbl d, $J = 5.0$ Hz, 1H; 6-H_{eq}), 4.02 (m, 1H; C*H*O), 3.86 (m, 1H; C*H*O), 3.50 (m, 1H; C*H*O), 3.48 and 3.47 (dbl s, 3H; OCH_3), 3.32 (s, 3H; OCH_3), 3.30–3.21 (overlapping m, 2H; C*H*O), 3.01 (m, 1H; 39-H), 2.64 (br s, 2H; O*H*), 2.40 (m, 1H), 2.28 (m, 1H), 2.14 (d, $J = 12.5$ Hz; 1H), 1.98 (d, $J = 12.5$ Hz; 1H), 1.78 (m, 1H), 1.69 (s, 3H; C_{29}-CH_3), 1.63 (m, 1H), 1.42 and 1.40 (dbl s, 9H; *t*-Boc), 1.38–1.10 (band; 3H), 1.04 (d, $J = 4.1$ Hz, 18H; $Si(CH(CH_3)_2)_3$), 1.03 (s, 9H; *t*Bu), 0.99 (overlapping dbl, $J = 6.7$ Hz, 6H; $2CH_3$), 0.91 (t, $J = 7.6$ Hz, 1H), 0.81 (overlapping dbl, $J = 6.6$ Hz, 6H; $2CH_3$), 0.62 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 151.7, 137.0, 136.0, 135.9, 135.1, 132.0, 129.3, 129.2, 128.3, 127.3, 127.2, 84.4, 82.3, 82.2, 79.7, 76.1, 74.3, 73.4, 73.3, 71.4, 71.2, 60.4, 60.3, 57.4, 55.6, 54.8, 53.9, 42.1, 40.9, 38.9, 38.7, 38.6, 35.6, 35.3, 34.6, 34.4, 34.0, 33.6, 33.0, 32.9, 31.5, 28.3, 27.0, 26.9, 26.7, 24.8, 24.6, 21.3, 20.8, 19.3, 18.1, 16.8, 16.7, 15.8, 15.7, 15.5, 12.4$; FAB HRMS (NBA/CsI) calcd for $C_{65}H_{108}O_{10}NISi_2Cs$ ($M + Cs^+$) 1378.5611, found *m/e* 1378.5620.

Fragment 6: A solution of diol **70** (202 mg, 0.16 mmol) and 2,6-lutidine (140 μL, 1.2 mmol) in CH_2Cl_2 (4 mL) at 0 °C was treated with triethylsilyl trifluoromethanesulfonate (183 μL, 0.81 mmol). The mixture was stirred for 30 min, quenched with aqueous NH_4Cl (5 mL), and diluted with ether (15 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 5 mL). The combined ether extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (15 mL), and the mixture

stirred for 16 h in the presence of silica gel (1 g). The slurry was poured onto a flash chromatography column (silica gel) and eluted with 10% ether in CH_2Cl_2. The fractions containing product were combined and concentrated to afford amine **6** (207 mg, 94% yield) as a colorless foam: $[\alpha]_D^{23} = -4.3$ ($c = 0.3$, $CHCl_3$); $R_f = 0.3$ (silica gel, 70% ether in petroleum ether); IR (thin film): $\tilde{\nu}_{max} = 2926, 2863, 1733, 1459, 1377, 1236, 1187, 1108\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.7$ (m, 4H; Ar), 7.35 (m, 6H; Ar), 6.23 (dd, $J = 14.3$, 9.3 Hz, 1H; 22-H), 5.91 (d, $J = 14.3$ Hz, 1H; 21-H), 5.07 (d, $J = 10.6$ Hz, 1H; 30-H), 5.07 (m, 1H; 2-H), 4.08 (m, 1H), 3.56 (dt, $J = 9.2$, 6.2 Hz, 1H), 3.53–3.40 (m, 2H), 3.52 (s, 3H; 27-OCH_3), 3.38 (m, 1H; C*H*N), 3.32 (s, 3H; 39-OCH_3), 3.22 (m, 2H), 3.03 (ddd, $J = 12.5$, 8.3, 4.3 Hz, 1H; 39-H), 2.73 (m, 1H; C*H*N), 2.6 (m, 1H; 31-H), 2.21 (m, 1H; 23-H), 2.05–0.6 (m; 21-H), 1.74 (s, 3H; 29-CH_3), 1.07-1.03 (m, 18H; $SiCH(CH_3)_2$), 1.02 (s, 9H; *t*Bu), 1.0 (d, $J = 6.5$ Hz, 3H; CH_3), 0.95 (t, $J = 7.9$ Hz, 9H; $SiCH_2CH_3$), 0.92 (t, $J = 7.9$ Hz, 9H; $SiCH_2CH_3$), 0.77 (d, $J = 6.8$ Hz, 3H; CH_3), 0.59 (q, $J = 7.9$ Hz, 12H; $SiCH(CH_3)_2$), 0.55 (m, 3H; $SiCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 151.7, 136.5, 136.0, 135.9, 135.2, 134.4, 130.1, 129.3, 129.2, 127.3, 127.3, 86.5, 84.5, 79.4, 78.2, 76.16, 73.41, 71.5, 61.4, 57.3, 57.3, 39.8, 38.8, 38.5, 36.6, 35.7, 33.7, 33.2, 32.9, 30.5, 29.7, 27.0, 27.0, 21.3, 19.3, 18.4, 18.3, 17.6, 14.7, 13.2, 12.4, 12.4, 7.2, 7.1, 5.6, 5.6, 5.2$; FAB HRMS (NBA/CsI) calcd for $C_{72}H_{128}NO_8Si_4ICs$ ($M + Cs^+$): 1506.6818, found *m/e* 1506.6879.

Diol amide 71: Acid **4** (247 mg, 0.432 mmol) and 1-hydroxybenzotriazole (58 mg, 0.432 mmol) were dissolved in CH_2Cl_2 (7 mL), and the solution was cooled to 0 °C. DIC (67 µL, 0.432 mmol) was added, and the mixture stirred for 3 h. Amine **6** (198 mg, 0.144 mmol) in CH_2Cl_2 (3 mL) was added, and the mixture stirred at 0 °C for 16 h. The reaction mixture was quenched with aqueous NH_4Cl (10 mL) and diluted with ethyl acetate (20 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 30% ether in petroleum ether) to provide compound **71** (280 mg, 95% yield) as a sticky foam. For characterization purposes diasteriomerically pure **4** having the (9*R*,10*S*) configuration was subjected to the same reaction conditions to provide a sample of diastereomerically pure **71**: $R_f = 0.38$ (silica gel, 30% ether in petroleum ether); $[\alpha]_D^{20} = -6.7$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3463, 3012, 2949, 2926, 2861, 1731, 1647, 1456, 1377, 1214, 1106, 1054\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.70$ (m, 4H; Ar), 7.40–7.32 (m, 6H; Ar), 6.24 (dd, $J = 14.3$, 9.3 Hz, 1H; 22-H), 6.19 (s, 1H; 18-H), 5.91 (d, $J = 14.3$ Hz, 1H; 21-H), 5.15 (d, $J = 5.6$ Hz, 1H; 10-H), 5.10 (d, $J = 9.7$ Hz, 1H; 30-H), 5.02 (m, 1H; 2-H), 4.46 (s, 1H; 9-H), 4.09 (d, $J = 3.0$ Hz, 1H; 28-H), 3.89 (m, 1H; 14-H), 3.80 (dd, $J = 8.4$, 4.0 Hz, 1H; 16-H), 3.58 (dt, $J = 9.2$, 2.7 Hz, 1H; 34-H), 3.55–3.47 (m, 2H; 32-H, 40-H), 3.51 (s, 3H; 27-OCH_3), 3.44–3.37 (m, 2H; 6-H), 3.32 (s, 3H; 39-OCH_3), 3.03 (ddd, $J = 12.5$, 8.5, 4.3 Hz, 1H; 39-H), 2.59 (m, 1H; 31-H), 2.21 (m, 1H; 23-H), 2.18–0.60 (band, 28H), 1.75 (s, 3H; 29-CH_3), 1.72 (s, 3H; C_{17}-CH_3), 1.07–0.97 (m, 24H; $SiCH(CH_3)_2$, CH_3), 1.03 (s, 9H; *t*Bu), 0.94 (t, $J = 8.0$ Hz, 9H; $SiCH_2CH_3$), 0.94 (d, $J = 6.8$ Hz, 3H; CH_3), 0.91 (t, $J = 8.0$ Hz, 12H; $SiCH_2CH_3$), 0.55 (m, 6H; $SiCH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.1, 170.2, 151.7, 148.0, 136.5, 136.0, 135.9, 135.2, 134.4, 129.8, 129.3, 129.2, 127.2, 127.3, 86.2, 84.5, 82.8, 79.4, 79.0, 78.1, 76.1, 75.8, 75.5, 73.3, 71.6, 69.7, 68.2, 61.3, 57.4, 56.2, 53.0, 42.8, 40.4, 39.9, 39.0, 38.4, 37.5, 36.6, 35.9, 33.6, 33.3, 32.8, 32.5, 31.9, 30.6, 29.7, 29.4, 27.9, 27.0, 26.9, 24.7, 22.7, 21.3, 21.0, 19.3, 18.8, 18.4, 18.4, 18.3, 18.2, 17.7, 15.3, 15.1, 14.8, 14.1, 13.3, 12.7, 12.4, 7.2, 7.2, 5.6, 5.4, 5.2$; FAB HRMS (NBA/CsI): calcd for $C_{95}H_{171}NO_{13}Si_5I_2Cs$ ($M + Cs^+$): 2060.8741; found 2060.8933.

Bis(vinyl iodide) 2: A solution of oxalyl chloride (171 µL, 1.96 mmol) in CH_2Cl_2 (15 mL) at −78 °C was treated with DMSO (292 µL, 4.12 mmol, in 2 mL CH_2Cl_2), and the mixture stirred for 30 min. Diol **71** (200 mg, 0.098 mmol) in CH_2Cl_2 (3 mL) was added, and the mixture stirred for 45 min at −78 °C. Triethylamine (1.36 mL, 9.8 mmol) was added, and the solution allowed to slowly warm to 0 °C. The mixture was stirred at 0 °C for 2 h, then quenched with aqueous NH_4Cl (10 mL), and diluted with ether (20 mL). The layers were separated and the aqueous phase was extracted ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to provide crude **72**. Crude **72** was taken up in THF (4 mL), cooled to 0 °C, and treated with HF·pyridine complex (0.4 mL). The mixture was stirred at room temperature for 2 h and then cautiously poured into aqueous $NaHCO_3$ (15 mL). The product was extracted with ethyl acetate (4 × 15 mL), and the combined extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude material so obtained was resubmitted to the original Swern oxidation conditions and workup described above to afford compound **73**. Crude **73** was dissolved in CH_3CN (4 mL), cooled to 0 °C, and treated with 49% aqueous HF (0.4 mL). The mixture was stirred at room termperature for 48 h and then cautiously poured into aqueous $NaHCO_3$ (10 mL). The pH was made basic by the addition of solid $NaHCO_3$, and the mixture extracted with ethyl acetate (3 × 15 mL). The combined ethyl acetate extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 40% acetone in petroleum ether) to afford bis(vinyl iodide) **2** (78 mg, 70% yield from diol **71**). Selected data for **2**: Mixture of presumed C10 epimers (ca. 2:1); $R_f = 0.34$ (silica gel, 40% acetone in petroleum ether); $[\alpha]_D^{20} = -61.1$ ($c = 0.18$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3460, 3019, 2933, 1739, 1734, 1723, 1718, 1636, 1458, 1212\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.30$ (dd, $J = 14.4$, 8.9 Hz, 1H; 22-H), 6.22 (s, 1H, 18-H), 6.03 (d, $J = 14.4$ Hz, 1H, 21-H), 5.39 (d, $J = 9.8$ Hz, 1H; 30-H), 5.28–5.20 (m, 2H; 2-H; 34-H), 4.35–4.30 (m, 1H; 14-H), 4.24 (d, $J = 5.7$ Hz, 1H; 28-H), 3.85–3.68 (m, 3H; 27-H, 16-H; 6-H), 3.50–3.30 (m, 3H; 40-H, 6-H, 31-H), 3.38 (s, 3H; OCH_3), 3.36 (m, 3H; OCH_3), 2.92 (ddd, $J = 12.2$, 8.2, 4.0 Hz, 1H; 39-H), 2.80–2.65 (m, 3H; 25-H, 33-H_2), 2.56 (m, 1H, 23-H), 2.38–0.60 (m, 25H), 1.80 (s, 3H; CH_3), 1.79 (s, 3H; CH_3), 1.10 (d, $J = 6.9$ Hz, 3H; CH_3), 1.00–0.95 (3 overlapping doublets, 9H; CH_3), 0.84 (d, $J = 6.7$ Hz, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 213.7, 208.1, 193.3, 168.7, 166.9, 166.9, 150.8, 146.6, 136.5, 126.7, 98.1, 86.0, 84.3, 82.8, 80.2, 76.2, 76.0, 74.5, 73.8, 67.0, 58.8, 56.5, 56.0, 51.2, 46.4, 44.3, 40.6, 40.3, 39.0, 38.8, 38.6, 38.5, 34.7, 34.1, 33.5, 33.1, 31.1, 30.9, 29.6, 27.2, 26.2, 25.3, 24.3, 20.5, 17.9, 16.1, 15.9, 15.0, 14.9, 13.4$; FAB HRMS (NBA/CsI); calcd for $C_{49}H_{77}NO_{13}I_2Cs$ ($M + Cs^+$): 1274.2539; found 1274.2481.

Rapamycin (1): Bis(vinyl iodide) **2** (33 mg, 28.9 µmol) and $[Pd(CH_3CN)Cl_2]$ (1.5 mg, 5.78 µmol) were dissolved in DMF (3.0 mL). The solution was frozen at −95 °C and placed under high vacuum for 2 h. The flask was purged several times with argon and allowed to warm to room temperature under an argon atmosphere. Meanwhile a solution containing bisstannane **3** (22 mg, 36.15 µmol) and Hunig's base (6.3 µL, 36.15 µmol) in THF (1.0 mL) was degassed by bubbling argon through for 15 min. The THF solution was added to the DMF of solution of **2** by cannula, and the flask and cannula were rinsed with 0.5 mL of degassed THF. The reaction mixture was stirred in the dark for 48 h, diluted with water (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by PTLC (silica gel, 40% acetone in petroleum ether) to afford rapamycin (**1**) (7.97 mg, 27% yield). Synthetic rapamycin (**1**) exhibited physical and spectroscopic data (TLC, IR, ^1H and ^{13}C NMR, HRMS) identical with those of an authentic sample: $R_f = 0.31$ (70% ethyl acetate in C_6H_6); $R_f = 0.26$ (silica gel, 30% acetone in petroleum ether); IR (CH_2Cl_2): $\tilde{\nu}_{max} = 3434, 2933, 2870, 1721, 1642, 1451, 1378, 1192, 1091, 992, 737\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6) (ca. 4:1 mixture of isomers, ^1H and ^{13}C assignments listed are for the major isomer): $\delta = 6.62$ (dd, $J = 14.5$, 10.5, 1H; 20-H), 6.49 (dd, $J = 14.5$, 11.0 Hz, 1H; 19-H), 6.30 (d, $J = 11.0$ Hz, 1H; 18-H), 6.15 (dd, $J = 15.0$, 10.5 Hz, 1H; 21-H), 5.64 (dd, $J = 15.0$, 9.2 Hz, 1H; 22-H), 5.59 (d, $J = 7.6$ Hz, 1H, 21-H), 5.53 (ddd, $J = 6.0$, 5.9, 4.0 Hz, 1H; 34-H), 5.30 (brs, 1H, 2-H_{eq}), 4.35 (d, $J = 6.6$ Hz, 1H; 28-H), 4.20 (m, 1H; 14-H), 3.97 (dd, $J = 8.4$, 6.8 Hz, 1H; 16-H), 3.82 (s, 1H, OH), 3.69 (m, 1H; 6-H_{eq}), 3.58–3.55 (band, 3H; 6-H_{ax}, 40-H, 31-H), 3.30 (s, 3H; OCH_3), 3.24 (s, 3H; OCH_3), 3.23 (s, 3H; OCH_3), 2.97–2.84 (band, 4H), 2.73 (dd, $J = 17.0$, 5.9 Hz, 1H, 33-H), 2.30–2.11 (band, 10H), 1.81 (s, 3H; 29-CH_3), 1.72 (s, 3H, 17-CH_3), 1.68–1.61 (band, 6H), 1.15–1.45 (band, 5H), 1.28 (d, $J = 6.6$ Hz, 3H, 31-CH_3), 1.22 (d, $J = 6.7$ Hz, 3H, 23-CH_3), 1.14 (d, $J = 6.6$ Hz, 11-CH_3), 0.94 (d, $J = 6.8$ Hz, 3H, 35-CH_3), 0.76 (ddd, $J = 12.0$, 11.8, 11.8 Hz, 1H; 38-H_{ax}); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 215.2, 208.0, 170.0, 167.9, 141.7, 141.4, 137.5, 136.4, 134.8, 131.1, 130.7, 127.8, 127.2, 99.6, 85.9, 85.3, 78.7, 76.6, 74.8, 67.9, 60.7, 56.8, 56.3, 52.3, 47.2, 45.0, 41.8, 41.5, 40.9, 39.9, 39.2, 36.4, 35.2, 34.8, 34.2, 33.8, 32.5, 32.4, 32.2, 28.1, 27.4, 25.8, 22.4, 21.2, 17.2, 16.8, 16.1, 15.0, 13.2, 10.9$; FAB HRMS calcd for $C_{51}H_{79}NO_{13}Cs$ ($M + Cs^+$): 1046.4606; found *m/e* 1046.4655.

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