Aplyronine A, a Potent Antitumor Substance of Marine Origin, Aplyronines B and C, and Artificial Analogues: Total Synthesis and Structure−Cytotoxicity Relationships

Hideo Kigoshi, Kiyotake Suenaga, Tsuyoshi Mutou, Takeshi Ishigaki, Toshiyuki Atsumi, Hiroyuki Ishiwata, Akira Sakakura, Takeshi Ogawa, Makoto Ojika, and Kiyoyuki Yamada*

Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

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The enantioselective total synthesis of aplyronine A (**1**), a potent antitumor substance of marine origin, was achieved by a convergent approach. Three segments **4**, **5**, and **6**, corresponding to the C5−C11, C21−C27, and C28−C34 portions of aplyronine A (**1**), were prepared using the Evans aldol reaction and the Sharpless epoxidation as key steps. The coupling reaction of **4** with iodide **7** followed by Julia olefination with sulfone **8** gave the C5−C20 segment **9**, while the Julia coupling reaction between segments **5** and **6** provided the C21−C34 segment **10**. Julia olefination between segments **9** and **10** and the subsequent four-carbon homologation reaction led to seco acid **83**, which was converted into aplyronine A (**1**) by Yamaguchi lactonization followed by the introduction of two amino acids. The use of the [(3,4-dimethoxybenzyl)oxy]methyl group as a protecting group for the hydroxyl at C29 was crucial for this synthesis. The enantioselective synthesis of two natural congeners, aplyronines B (**2**) and C (**3**), was also carried out using the intermediates for the synthesis of **1**, which determined the absolute stereostructures of **2** and **3** unambiguously. To study the structure−cytotoxicity relationships of aplyronines, artificial analogues of **1** were synthesized and their cytotoxicities were evaluated: the trimethylserine moiety, two hydroxyl groups, and the side-chain portion in **1** turned out to be important in the potent cytotoxicity shown by **1**. Biological studies with aplyronine A (**1**) showed that **1** inhibited polymerization of G-actin to F-actin and depolymerized F-actin to G-actin.

The sea hare *Aplysia kurodai* is known to be a rich source of various unique metabolites.[1] In the course of our search for bioactive compounds from Japanese specimens of this animal, we isolated a strongly cytotoxic compound called aplyronine A (**1**) as a minute constituent and elucidated its gross structure.[2a] Further, the absolute stereochemistry of **1** was determined on the basis of NMR spectroscopy and organic synthetic methods.[2b−d] Aplyronines B (**2**) and C (**3**) were isolated from the sea hare *Aplysia kurodai* together with **1**, and their gross structures were deduced by comparison of their spectral data with those of **1**.[2a] In addition, their stereostructures were established by synthesis.[3c] The structural features of **1** are that **1** is a 24-membered macrolide which possesses a side chain with an *N*-formyl enamine group at its terminus and that the hydroxyl groups in **1** are esterified with two amino acids. Aplyronine A (**1**) is structurally related to a family of 22-membered macrolides called scytophycins,[4] which includes scytophycin C. While the *N,N,O*-trimethylserine group in **1** is known to play an important role in its cytotoxicity,[2a] more detailed studies on the structure−cytotoxicity relationships in **1** are needed. Although **1** exhibits strong cytotoxicity (IC_{50} = 0.48 ng/ mL against HeLa S_3 cells)[2a,5] and exceedingly potent antitumor activities in vivo (T/C: 545% against P388 murine leukemia, 556% against Lewis lung carcinoma, 398% against Ehrlich carcinoma, 255% against colon 26 carcinoma, and 201% against B16 melanoma),[2a] the scarcity of a natural supply has prevented the further evaluation of this compound as a potential therapeutic agent. These facts and the novel polyfunctional 24-membered lactone structures of **1**−**3** prompted us to attempt to synthesize these natural

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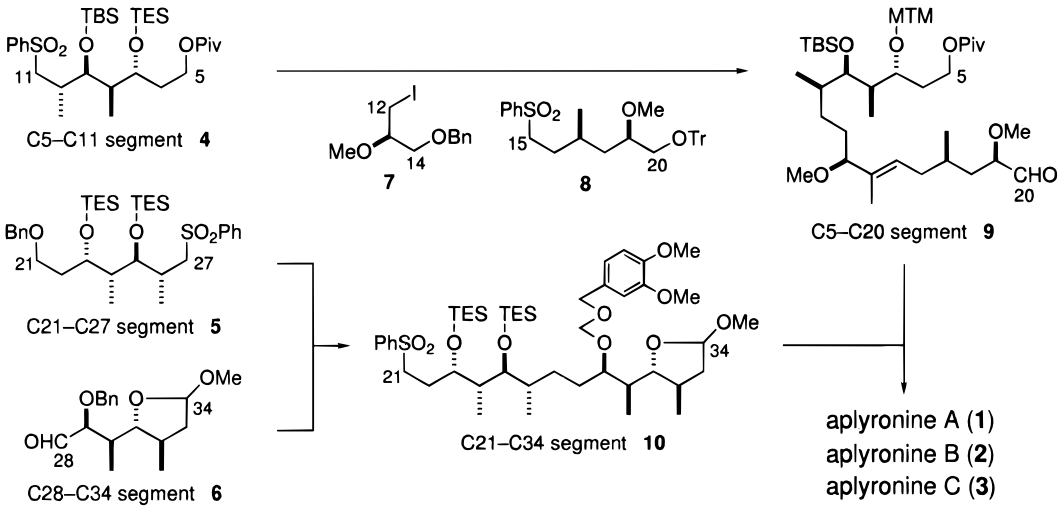
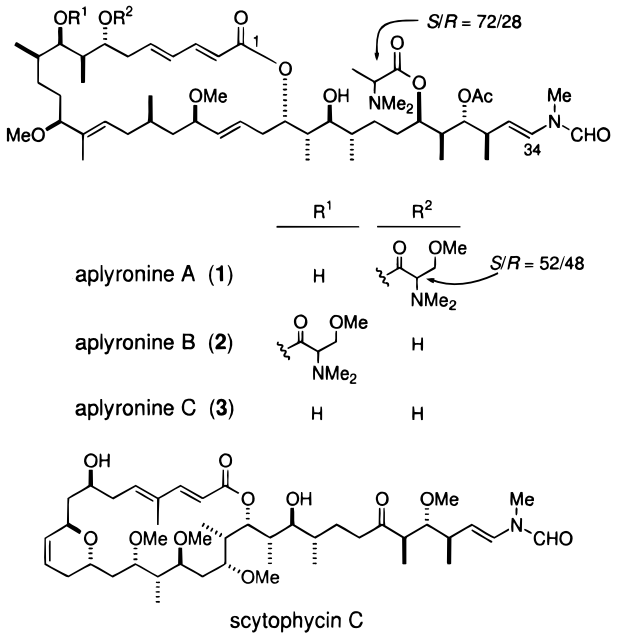
(5) The IC_{50} values for the cytotoxicities of aplyronines **1**−**3** are different from those[2a] previously reported. Since the IC_{50} values in the present study were shown to be reproducible, these values will be used hereafter.

S0022-3263(96)00611-1 CCC: $12.00

Scheme 1



compounds and their artificial analogues. We report here the detailed synthesis of aplyronines A (**1**),[3a,b] B (**2**),[3c] and C (**3**),[3c] and their artificial analogues, and describe the structure−cytotoxicity relationships in the aplyronines and artificial analogues, and further describe that the target biomolecule that interacts with **1** is actin, the protein in cytoskeleton.



Scheme 1 outlines the synthesis of the aplyronines, which includes the following key operations: (1) three of the four contiguous stereocenters, C7−C10[6] in the C5−C11 segment **4**, C23−C26 in the C21−C27 segment **5**, and C29−C32 in the C28−C34 segment **6**, were constructed by the Evans aldol reaction[7] and the Sharpless epoxidation;[8] (2) the C5−C20 segment **9** was synthesized by connecting segments **4**, **7**, and **8** in sequential order; (3) the C21−C34 segment **10** was prepared by connecting segments **5** and **6**; and (4) a Julia olefination reaction[9] between the C5−C20 segment **9** and the C21−C34 segment **10** and a macrolactonization by the Yamaguchi method.[10]

Results and Discussion

Synthesis of the C5−C20 Segment. Synthesis of the C5−C11 segment **4** began with the Evans aldol reaction between imide **11**[7] and (*R*)-3-(benzyloxy)-2-methylpropanal[11] to afford hydroxy imide **12** (88%) (Scheme 2). Removal of the chiral auxiliary in **12** with trimethylaluminum and *N*,*O*-dimethylhydroxylamine hydrochloride[12] gave amide **13** in 96% yield. Amide **13** was silylated with *tert*-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine,[13] to give silyl ether **14** quantitatively. Reduction of **14** with diisobutylaluminum hydride (DIBAL) gave aldehyde **15** (99%), the Horner−Emmons reaction of which with $(i\text{-PrO})_2P(O)CH_2COOEt$ gave conjugated ester **16** quantitatively. Ester **16** was reduced with DIBAL to allylic alcohol **17** quantitatively, which in turn was transformed into epoxide **18** under Sharpless asymmetric epoxidation conditions,[8] using (+)-diethyl tartrate, to give one diastereomer in 96% yield. Reductive cleavage of the oxirane ring in **18** with sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al)[14] afforded diol **19a** (74%), which possesses *anti-syn-anti* stereochemistry concerning the four contiguous stereocenters, along with triol **19b** (15%). The primary hydroxyl group in **19a** was protected by pivaloyl chloride and pyridine, giving ester **20** in 99% yield. Removal of the benzyl protecting group in **20** by hydrogenolysis afforded diol **21** in 99% yield. Diol **21** was converted with $Bu_3P-PhSSPh$[15] into sulfide **22** (91%), the secondary hydroxyl group of which was silylated with triethylsilyl chloride (TESCl) and imidazole to give silyl ether **23** quantitatively. Compound **23** was oxidized with

(6) The numbering used in this paper corresponds to that of aplyronine A (**1**).

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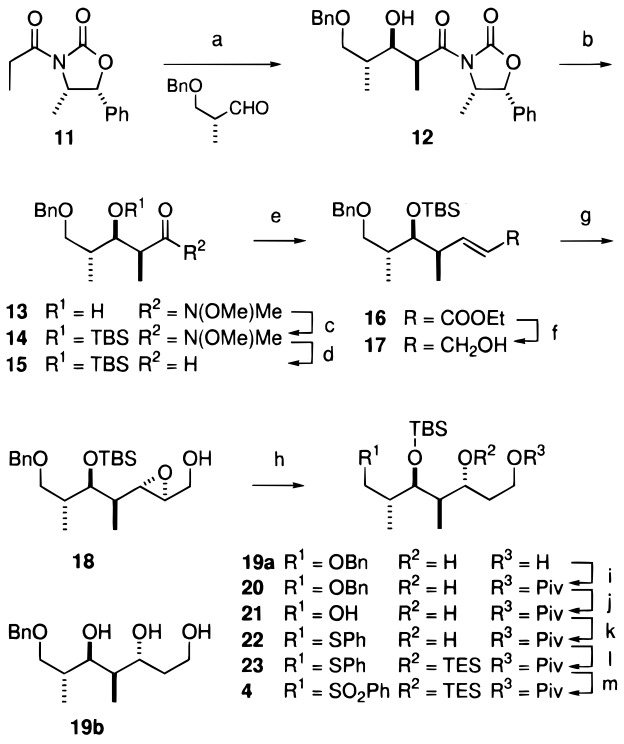
Scheme 2[a]



[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then (*R*)-3-(benzyloxy)-2-methylpropanal, −78 °C, 3 h → 0 °C, 20 min, 88%; (b) Me_3Al, MeONHMe·HCl, THF, toluene, CH_2Cl_2, −10 → 0 °C, 1.6 h, 96%; (c) *t*-$BuMe_2SiOTf$ (TBSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 100%; (d) DIBAL, THF, hexane, −78 °C, 2 h, 99%; (e) (*i*-$PrO)_2$-$P(O)CH_2COOEt$, *t*-BuOK, THF, −78 °C, 1 h → 0 °C, 1.5 h, 100%; (f) DIBAL, CH_2Cl_2, hexane, −78 °C, 1 h, 100%; (g) Ti(O-*i*-Pr)$_4$, (+)-diethyl tartrate, *t*-BuOOH, molecular sieves 4 Å, CH_2Cl_2, −23 °C, 1 h, 96%; (h) $NaAlH_2(OCH_2CH_2OMe)_2$, DME, 0 °C, 2 h, 74%; (i) pivaloyl chloride (PivCl), pyridine, 0 °C, 1.5 h, 99%; (j) H_2, 10% Pd−C, EtOH, 23 °C, 3.5 h, 99%; (k) $(PhS)_2$, Bu_3P, DMF, 23 °C, 12 h, 91%; (l) Et_3SiCl (TESCl), imidazole, DMF, 23 °C, 1.4 h, 100%; (m) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 23 °C, 1.5 h, 100%.

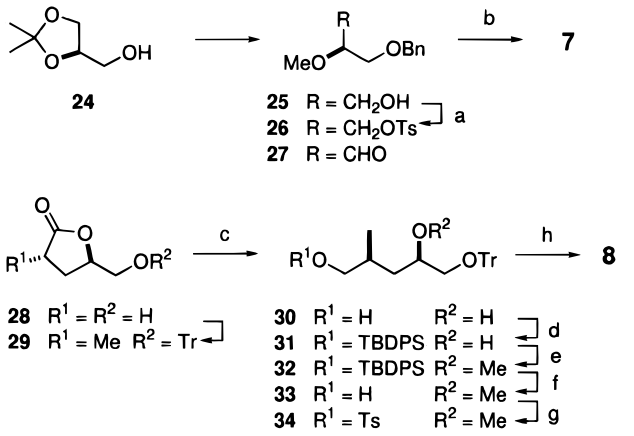
m-chloroperoxybenzoic acid to the C5−C11 segment **4** quantitatively.

Two small segments, iodide **7** and sulfone **8**, were prepared as follows (Scheme 3).

Iodide **7** was prepared from commercially available (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol (**24**), which was converted into alcohol **25**.[16] Reaction of alcohol **25** with *p*-toluenesulfonyl chloride gave tosylate **26**, which was converted into iodide **7** in 99% yield.

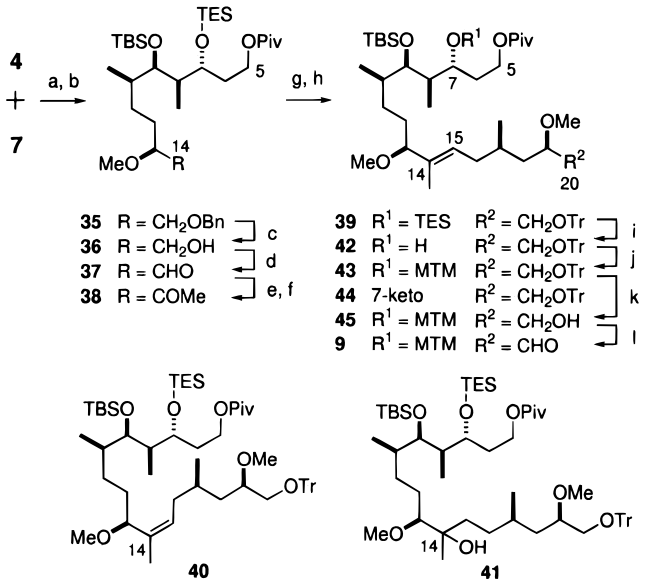
Sulfone **8** was synthesized from lactone **29**,[17] which was prepared from commercially available (*R*)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**28**). Reduction of **29** with $LiAlH_4$ gave diol **30** quantitatively. Protection of the primary hydroxyl group in **30** was effected selectively with *tert*-butyldiphenylsilyl chloride, and the secondary hydroxyl group of the resulting silyl ether **31** was methylated to afford methyl ether **32** (95% from **30**). The silyl group of **32** was removed with Bu_4NF to give alcohol **33** quantitatively. Alcohol **33** was converted into tosylate **34**, reaction of which with the carbanion of methyl phenyl sulfone gave sulfone **8** (77% from **33**).

Scheme 3[a]



[a] (a) *p*-Toluenesulfonyl chloride (TsCl), pyridine, 0 °C, 2 h; (b) NaI, $CaCO_3$, acetone, 50 °C, 13.5 h, 99% (2 steps); (c) $LiAlH_4$, THF, 23 °C, 1 h, 100%; (d) *t*-$BuPh_2SiCl$ (TBDPSCl), imidazole, DMF, 0 °C, 1.7 h; (e) MeI, NaH, THF, 0 °C, 1 h, 95% (2 steps); (f) Bu_4NF, THF, 23 °C, 12 h, 100%; (g) TsCl, pyridine, 0 °C, 2.5 h; (h) $PhSO_2Me$, BuLi, THF, 23 °C, 3.2 h, 77% (2 steps).

Scheme 4[a]



[a] (a) **4**, LDA, THF, −78 °C, 25 min, then **7**, HMPA, 23 °C, 1.5 h; (b) 5% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 2 h, 76% (2 steps); (c) H_2, 10% Pd−C, $NaHCO_3$, EtOH, 23 °C, 2.5 h, 98%; (d) Dess−Martin periodinane, pyridine, CH_2Cl_2, 23 °C, 0.7 h, 91%; (e) Me_2CuLi, Et_2O, −78 °C, 1 h; (f) Dess−Martin periodinane, pyridine, CH_2Cl_2, 23 °C, 0.7 h, 93% (2 steps); (g) **8**, BuLi, THF, −78 °C, 2 h; (h) 6% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 2.3 h, 44% (2 steps); (i) AcOH, H_2O, THF, 23 °C, 6.6 h, 97%; (j) DMSO, Ac_2O, AcOH, 23 °C, 2 h → 40 °C, 5.5 h, 86%; (k) HCO_2H, Et_2O, 23 °C, 15 min, 90%; (l) Dess−Martin periodinane, pyridine, CH_2Cl_2, 23 °C, 1 h, 80%.

Alkylation[18] of the carbanion generated from **4** with iodide **7** in THF−HMPA and subsequent reductive removal of the sulfonyl group with 5% sodium amalgam afforded benzyl ether **35** in 76% yield (Scheme 4). Addition of HMPA as a cosolvent in the alkylation reaction improved the yield of the alkylation product remarkably. Hydrogenolysis of **35** with 10% Pd−C as a catalyst gave alcohol **36** (98%). Although we examined the Julia olefination between **4** and aldehyde **27** and

(16) This compound was prepared by a route different from that employed in the present work: Takatani, M.; Yoshioka, Y.; Tasaka, A.; Terashita, Z.; Imura, Y.; Nishikawa, K.; Tsushima, S. *J. Med. Chem.* **1989**, *32*, 56−64.

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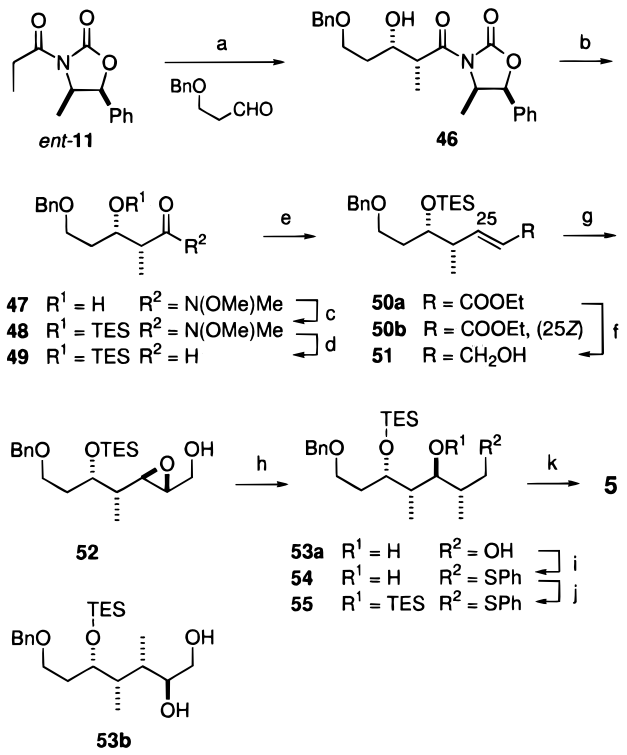
subsequent catalytic reduction that led to alcohol **36**, alcohol **36** was obtained in low yield (57% overall yield) and was contaminated with an epimer at C13. Dess−Martin oxidation[19] of alcohol **36** provided aldehyde **37** in 91% yield, whereas under Swern oxidation conditions[20] epimerization at C13 occurred to a considerable extent during the conversion of **36** into **37**. Addition of Me_2CuLi to aldehyde **37** gave a diastereomeric mixture of secondary alcohols, which was oxidized with the Dess−Martin periodinane to methyl ketone **38** in 93% yield.

Julia coupling between **38** and the carbanion generated from sulfone **8** provided a diastereomeric mixture of hydroxy sulfones, which was treated with 6% sodium amalgam to give (*E*)-olefin **39** (44%), (*Z*)-olefin **40** (19%), and a diastereomeric mixture of tertiary alcohol **41** (25%). (*Z*)-Olefin **40** could be isomerized to the desired (*E*)-olefin **39** under equilibrium conditions promoted by PhSH and AIBN[21] in 41% yield, and a diastereomeric mixture of tertiary alcohol **41** was dehydrated with $POCl_3$ and pyridine to give (*E*)-olefin **39** in 43% yield. At this stage, the TES protecting group at C7 in **39** was changed to a (methylthio)methyl (MTM) group, because the protecting group at C7 in **39** must be differentiated from the TES protecting groups at C23 and C25 in the C21−C34 segment **10** to be coupled with **9** later in the synthesis (cf. Scheme 8). Thus, the TES group in **39** was hydrolyzed selectively under acidic conditions using aqueous acetic acid in THF to give alcohol **42** in 97% yield. Protection of the hydroxyl group in **42** was effected by treatment with DMSO, Ac_2O, and AcOH to give MTM ether **43** (86%) along with ketone **44** (14%). Stereoselective reduction of ketone **44** to **42** could not be achieved with a variety of reagents ($NaBH_4$, $LiAlH(O\text{-}t\text{-}Bu)_3$, etc.). The trityl group in **43** was removed with formic acid in ether[22] to afford alcohol **45** (90%). Oxidation of the hydroxyl group in alcohol **45**, which possesses an MTM group that is liable to be oxidized, was effected with the Dess−Martin periodinane to give the C5−C20 segment **9** in 80% yield, while Swern oxidation of **45** gave the desired **9** in poor yield due to instability of the MTM group under the oxidation conditions.

Synthesis of the C21−C34 Segment. Synthesis of the C21−C34 segment was effected by connection of two segments, the C21−C27 and C28−C34 segments **5** and **6**, both of which have the *syn-anti-anti* relative stereochemistry with regard to the four contiguous stereocenters. Both segments were prepared by a synthetic strategy similar to that for the C5−C11 segment **4**. The synthesis of **5** started with the Evans aldol reaction between imide *ent*-**11** and 3-(benzyloxy)propanal to give hydroxy imide **46** in 85% yield as a single diastereomer (Scheme 5). Transamidation of **46** to amide **47** followed by protection of the hydroxy group in **47** afforded silyl ether **48** (99% from **46**). The amide group in **48** was reduced with DIBAL to give aldehyde **49** (98%). The Horner−Emmons reaction of **49** with $(i\text{-PrO})_2P(O)CH_2COOEt$ provided stereoselectively conjugated ester **50a** (96%) along with conjugated ester **50b** (3%). Conjugated ester **50a** was quantitatively converted into allylic alcohol **51** by DIBAL reduction. The Sharpless oxidation of **51** using (−)-diethyl tartrate gave epoxide **52** (99%), treatment of which with Me_2CuLi[23] provided diol **53a** (75%), which possesses the *syn-anti-anti* stereochemistry concerning the four contiguous stereocenters, along with diol **53b** (18%). Reaction of diol **53a** with $Bu_3P-PhSSPh$[15] gave sulfide **54** in 99% yield. Protection of the secondary hydroxy group in **54** afforded silyl ether **55**, the sulfide group of which was oxidized to give the C21−C27 segment **5** (quantitatively from **54**).

Synthesis of the C28−C34 segment **6** was effected using the same synthetic strategy as for **5**. The Evans aldol reaction of imide **11** with (benzyloxy)acetaldehyde gave hydroxy imide **56**[24] (79%), which was converted into amide **57**[25] in 99% yield (Scheme 6). The hydroxyl group of **57** was silylated with *tert*-butyldimethylsilyl chloride (TBSCl) to give silyl ether **58**[25] quantitatively. Silyl ether **58** was transformed into diol **63a** by the same sequence of reactions as described for the preparation of diol **53a** from silyl ether **48**. Thus, silyl ether **58** was reduced to aldehyde **59**[25] (99%), the Horner−Emmons reaction of which with $(i\text{-PrO})_2P(O)CH_2COOEt$ gave conjugated ester **60a** (90%) along with conjugated ester **60b** (7%). Reduc-

Scheme 5[a]



[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then 3-(benzyloxy)propanal, −78 °C, 2 h → 0 °C, 2 h, 85%; (b) Me_3Al, MeONHMe·HCl, THF, toluene, −10 → 0 °C, 1.5 h, 99%; (c) Et_3SiCl (TESCl), imidazole, DMF, 23 °C, 35 min, 100%; (d) DIBAL, THF, hexane, −78 °C, 1.5 h, 98%; (e) $(i\text{-PrO})_2P(O)CH_2COOEt$, *t*-BuOK, THF, −78 °C, 1.5 h → 0 °C, 1.5 h, 96%; (f) DIBAL, CH_2Cl_2, hexane, −78 °C, 1.5 h, 100%; (g) $Ti(O\text{-}i\text{-}Pr)_4$, (−)-diethyl tartrate, *t*-BuOOH, molecular sieves 4 Å, CH_2Cl_2, −23 °C, 2 h, 99%; (h) Me_2CuLi, Et_2O, −20 °C, 14 h → 0 °C, 2 h, 75%; (i) $(PhS)_2$, Bu_3P, DMF, 23 °C, 4 h, 99%; (j) Et_3SiCl (TESCl), imidazole, DMF, 23 °C, 2.5 h, 100%; (m) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 23 °C, 1 h, 100%.

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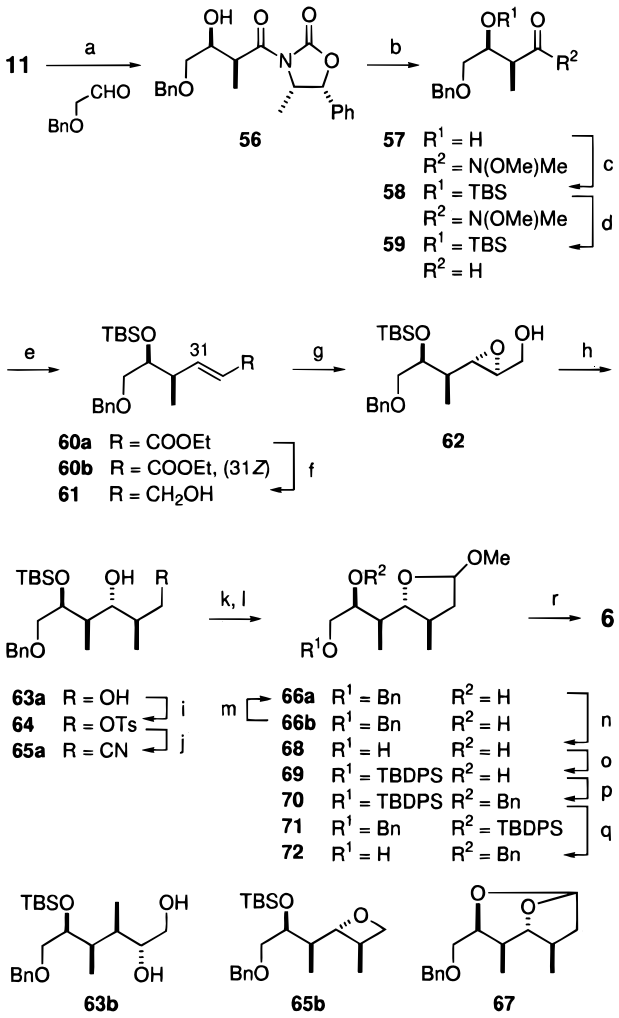
(22) Besodes, M.; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* **1986**, *27*, 579−580.
(23) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347−4350.
(24) For the preparation of *ent*-**56**, see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031.
(25) Preparation of this compound, which was described in our preliminary communication,[3a] was recently reported by Evans and co-workers: Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467.

Scheme 6[a]

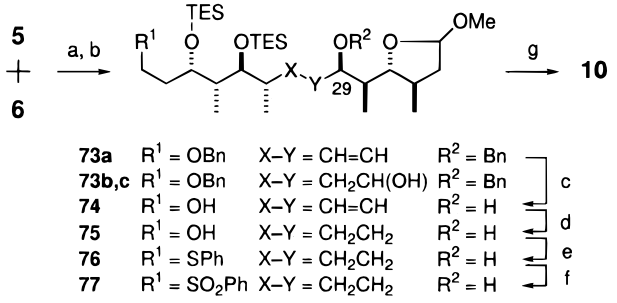


[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then (benzyloxy)acetaldehyde, −78 °C, 1 h → 0 °C, 3 h, 79%; (b) Me_3Al, MeONHMe·HCl, THF, toluene, CH_2Cl_2, 0 °C, 1.5 h, 99%; (c) *t*-$BuMe_2SiCl$ (TBSCl), imidazole, DMF, 23 °C, 5.5 h, 100%; (d) DIBAL, THF, hexane, −78 °C, 2 h, 99%; (e) $(i\text{-PrO})_2P(O)CH_2COOEt$, *t*-BuOK, THF, −78 °C, 1.5 h → 0 °C, 1.5 h, 90%; (f) DIBAL, CH_2Cl_2, hexane, −78 °C, 1 h, 97%; (g) Ti(O-*i*-Pr)$_4$, (+)-diethyl tartrate, *t*-BuOOH, molecular sieves 4 Å, CH_2Cl_2, −23 °C, 1.5 h, 96%; (h) Me_2CuLi, Et_2O, −23 °C, 6 h → 4 °C, 16 h, 93%; (i) *p*-toluenesulfonyl chloride (TsCl), pyridine, 0 °C, 5 h, 100%; (j) NaCN, DMSO, 50 °C, 2.5 h, 91%; (k) DIBAL, CH_2Cl_2, hexane, −78 °C, 1 h, then SiO_2, 23 °C, 14.5 h; (l) CSA, MeOH, reflux, 1.6 h; (m) CSA, MeOH, 23 °C, 14 h, 74% from **65a**; (n) Na, THF, liquid NH_3, −78 °C, 30 min, 100%; (o) *t*-$BuPh_2SiCl$ (TBDPSCl), imidazole, DMF, 0 °C, 1.3 h, 100%; (p) $PhCH_2Br$ (BnBr), NaH, DMF, 0 °C, 15 min → 23 °C, 1 h; (q) Bu_4NF, THF, 23 °C, 13 h, 74% (2 steps); (r) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 13 min, then Et_3N, 0 °C, 25 min, 100%.

tion of **60a** afforded allylic alcohol **61** (97%), which was transformed into epoxide **62** by Sharpless epoxidation using (+)-diethyl tartrate in 96% yield as a single diastereomer. Regioselective oxirane ring opening of **62** with Me_2CuLi gave diol **63a** in 93% yield, which possesses the *syn-anti-anti* stereochemistry with regard to the four contiguous stereocenters, along with diol **63b** (7%).

Diol **63a** was converted with *p*-toluenesulfonyl chloride and pyridine into tosylate **64** quantitatively, the reaction of which with NaCN gave nitrile **65a** (91%) and oxetane **65b** (7%). Reduction of **65a** with DIBAL and subsequent hydrolysis using silica gel afforded a hemiacetal, acid treatment of which in MeOH provided a separable mixture of diastereomeric acetals **66a** and **66b** and the

Scheme 7[a]



[a] (a) **5**, BuLi, THF, −78 °C, 30 min, then **6**, −78 °C, 3 h; (b) 5% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 2 h, 82% (2 steps); (c) Ca, liquid NH_3, THF, *i*-PrOH, −78 °C, 1 h, 98%; (d) H_2, 5% Rh-Al_2O_3, EtOH, 23 °C, 1.6 h, 91%; (e) $(PhS)_2$, Bu_3P, DMF, 23 °C, 14 h, 99%; (f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 23 °C, 1 h, 100%; (g) 3,4-$(MeO)_2$-$C_6H_3CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 23 °C, 16 h, 98%.

dioxabicyclo[3.2.1]octane compound **67**. After chromatographic separation, the two minor products **66b** and **67** were subjected to equilibration (camphorsulfonic acid, MeOH, 23 °C) to afford a mixture of **66a**, **66b**, and **67**, from which the major acetal **66a** was obtained. By repeating this procedure, **66b** and **67** could be transformed into **66a** (74% from **65a**). The benzyl protecting group in **66a** was removed with sodium in liquid ammonia to give diol **68**, the primary hydroxyl group of which was silylated with *tert*-butyldiphenylsilyl chloride to provide silyl ether **69** (quantitatively from **66a**). Protection of the secondary hydroxyl group in **69** as a benzyl ether group followed by desilylation with Bu_4NF afforded alcohol **72** (74% from **69**) along with silyl ether **71** (16%), which resulted from migration of the silyl group in **69**. Swern oxidation of **72** provided the C28−C34 segment **6** quantitatively.

Julia coupling of the carbanion generated from the C21−C27 segment **5** with the C28−C34 segment **6** afforded hydroxy sulfones, reduction of which gave olefin **73a** (82% from **6**) along with diastereomeric alcohols **73b** (7%) and **73c** (3%) (Scheme 7). Two benzyl protecting groups in **73a** were removed with calcium in liquid ammonia,[26] to furnish diol **74** (98%), hydrogenation of which provided diol **75** in 91% yield. Reaction of diol **75** with $Bu_3P-PhSSPh$[15] afforded sulfide **76** (99%), which was oxidized with *m*-chloroperoxybenzoic acid to sulfone **77** quantitatively.

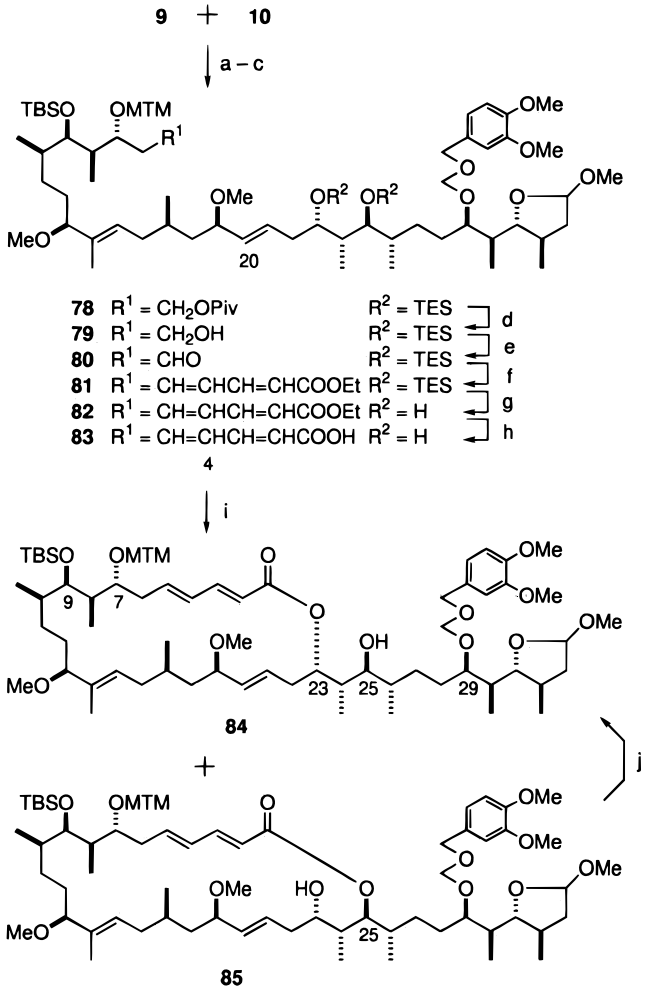
Selection of a protecting group for the C29 hydroxyl group in **77** was crucial to the synthesis of aplyronines. Initially, we chose a [(4-methoxybenzyl)oxy]methyl ether group[27] to protect the hydroxyl group in **77**, but it turned out that this protecting group could not be removed at the later stage of the synthesis without decomposition of the α,*β*,*γ*,*δ*-unsaturated lactone moiety in the synthetic intermediates. Thus, we chose a [(3,4-dimethoxybenzyl)-oxy]methyl ether group[28] because it can be removed under milder conditions using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) than those required for removal of a [(4-methoxybenzyl)oxy]methyl group. [(3,4-Dimethoxybenzyl)oxy]methyl chloride[28] was prepared from 3,4-dimethoxybenzyl alcohol by the procedure reported for

(26) Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E., Jr.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4731−4733.

(27) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762−763. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125−5128.

(28) Gündel, W.-H.; Kramer, W. *Chem. Ber.* **1978**, *111*, 2594−2604.

Scheme 8[a]



[a] (a) **10**, BuLi, THF, −78 °C, 30 min, then **9**, −78 °C, 2 h; (b) Ac_2O, DMAP, pyridine, 23 °C, 3 h; (c) 5% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 1.5 h, 88% (3 steps); (d) DIBAL, CH_2Cl_2, −78 °C, 2 h, 100%; (e) Dess−Martin periodinane, pyridine, CH_2Cl_2, 23 °C, 35 min, 85%; (f) LDA, $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, THF, −40 °C, 8 min → 0 °C, 15 min, 89%; (g) HF·pyridine, pyridine, THF, 23 °C, 3 h, 100%; (h) LiOH, MeOH, H_2O, 23 °C, 12 h, 100%; (i) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, $CHCl_3$, 23° C, 15 h, 40%; (j) Ti(O-*i*-Pr)$_4$, CH_2Cl_2, 23 °C, 19 h, 65%.

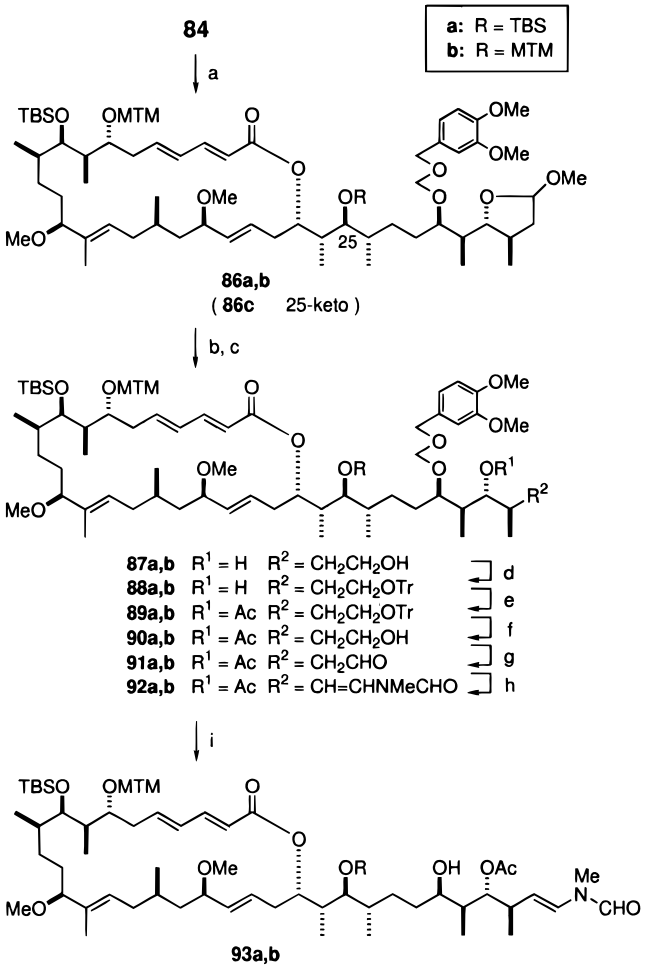
the preparation of [(4-methoxybenzyl)oxy]methyl chloride.[27] The C29 hydroxyl group of sulfone **77** was protected with [(3,4-dimethoxybenzyl)oxy]methyl chloride and *i*-Pr_2NEt to give the C21−C34 segment **10** in 98% yield.

Construction of the Macrolactone Ring and Synthesis of Aplyronine A. With the C5−C20 and C21−C34 segments **9** and **10** in hand, the stage was set for the task of connecting these two segments. The Julia coupling of **9** and the carbanion generated from **10** gave a diastereomeric mixture of hydroxy sulfones, acetylation of which and subsequent reduction gave olefin **78** (88% from **9**) (Scheme 8), which was obtained as an inseparable 9:1 mixture of (20*E*)- and (20*Z*)-isomers. The minor (20*Z*)-isomer could be separated by HPLC at a later stage in the synthesis, *i.e.*, after macrolactonization of seco acid **83**. The pivaloyl group of olefin **78** was removed by DIBAL reduction to give alcohol **79** quantitatively, and the resulting hydroxyl group in **79** was oxidized with the Dess−Martin periodinane to give aldehyde **80** in 85% yield. The Horner−Emmons reaction of aldehyde **80** with $(EtO)_2P(O)CH_2CH{=}CHCOOEt$[29] afforded α,β,γ,δ-unsaturated ester **81** in 89% yield, which was contaminated with a small amount (about 5%) of (4*Z*)-isomer. As described above, the minor geometrical isomers concerning the C4 and C20 double bonds were separated by HPLC after macrolactonization of seco acid **83**. Selective removal of the two TES groups in **81** gave diol **82**, the ester group of which was hydrolyzed with LiOH in aqueous methanol to afford seco acid **83** (quantitatively from **81**). The macrolactonization of **83** was accomplished by the modified Yamaguchi method,[10,30] to yield the 24-membered lactone **84** (40%) and the 26-membered lactone **85** (28%). The 26-membered lactone **85** could be isomerized to the 24-membered lactone **84** under equilibrium conditions (**84**/**85** = ca. 2.5/1) in the presence of Ti(O-*i*-Pr)$_4$[31] (**84**: 65% isolation yield).

Silylation of the hydroxyl group in **84** with TBSCl gave disilyl ether **86a** in 98% yield (Scheme 9). The cyclic acetal moiety of **86a** was hydrolyzed under acidic conditions to afford a hemiacetal, which was reduced with $NaBH(OMe)_3$ in MeOH to give diol **87a** in 72% yield. When the reduction described above was carried out with $NaBH_4$ in EtOH, reduction took place not only at the hemiacetal moiety but also at the α,β,γ,δ-unsaturated lactone system. The primary hydroxyl group of **87a** was protected as a trityl ether group to give trityl ether **88a** (98%), the secondary hydroxyl group of which was acetylated to afford acetate **89a** quantitatively. Removal of the trityl group of **89a** gave alcohol **90a** (84%), the Dess−Martin oxidation of which afforded aldehyde **91a** in 88% yield. The terminal *N*-formyl enamine structure was constructed by reaction[32] of **91a** with *N*-methylformamide in the presence of pyridinium *p*-toluenesulfonate (PPTS) to afford enamide **92a** in 48% yield. Removal of the protecting group at C29 in **92a** was effected with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone[33] (DDQ) in CH_2Cl_2−*t*-BuOH−phosphate buffer (pH 6) to give alcohol **93a** in 88% yield. The remaining task necessary for the synthesis of aplyronine A was the introduction of two amino acids into **93a** (Scheme 10). The hydroxyl group in **93a** was esterified with *N*,*N*-dimethylalanine under Keck conditions.[34] Esterification of alcohol **93a** with (*S*)-*N*,*N*-dimethylalanine gave a >9:1 mixture of the (*S*)- and (*R*)-dimethylalanine esters **94**, whereas esterification of **93a** with (*R*)-*N*,*N*-dimethylalanine afforded a 1:1 mixture of the (*S*)- and (*R*)-dimethylalanine esters **94**. These findings suggest that (*S*)-*N*,*N*-dimethylalanine differs from (*R*)-*N*,*N*-dimethylalanine with regard to the rate of the esterification reaction with alcohol **93a** and that the activated forms of (*S*)- and (*R*)-*N*,*N*-dimethylalanines are interconvertible with each other. On the basis of these findings, the hydroxyl group of **93a** was esterified with *N*,*N*-dimethylalanine (*S*/*R* = 3/2) under Keck conditions to give a diastereomeric mixture of dimethylalanine esters **94** (*S*/*R* = 4/1) in 94% yield. Further, hydrolysis

(29) Sato, K.; Mizuno, S.; Hirayama, M. *J. Org. Chem.* **1967**, *32*, 177−180.
(30) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367−6370.
(31) For titanium(IV) alkoxide-catalyzed transesterification, see: Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zügger, M. *Synthesis* **1982**, 138−141.
(32) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227−3230.
(33) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888; 889−892. Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162−3164.
(34) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395.

Scheme 9[a]



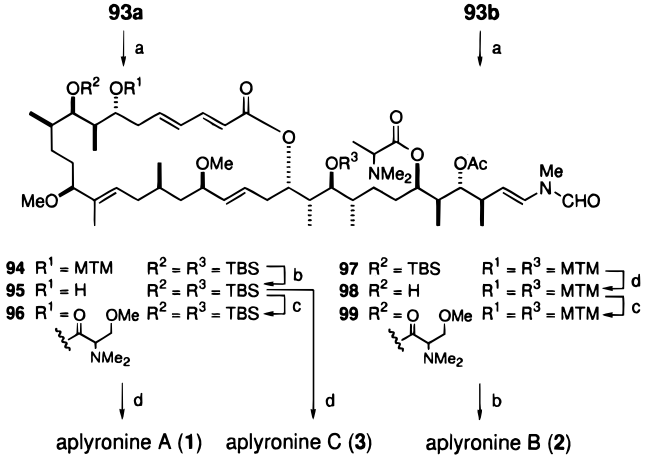
[a] (a) (**86a**) TBSCl, imidazole, DMF, 60 °C, 24 h, 98%; (**86b**) DMSO, Ac_2O, AcOH, 40 °C, 2 h, 43%; (b) HCl, H_2O, DME, 23 °C, 5.5 h; (c) $NaBH(OMe)_3$, MeOH, 23 °C, 4.5 h, (**87a**) 72% (2 steps), (**87b**) 71% (2 steps); (d) TrCl, pyridine, 50 °C, 11.5 h, (**88a**) 98%, (**88b**) 97%; (e) Ac_2O, DMAP, pyridine, 23 °C, 12.5 h, (**89a**) 100%, (**89b**) 99%; (f) HCO_2H, Et_2O, 23 °C, 15 min, (**90a**) 84%, (**90b**) 84%; (g) Dess−Martin periodinane, pyridine, CH_2Cl_2, 23 °C, 1.5 h, (**91a**) 88%, (**91b**) 73%; (h) MeNHCHO, PPTS, hydroquinone, molecular sieves 3 Å, benzene, reflux, 6.5 h, (**92a**) 48%, (**92b**) 42%; (i) DDQ, CH_2Cl_2, *t*-BuOH, phosphate buffer (pH 6), 23 °C, 110 min, (**93a**) 88%, (**93b**) 69%.

of the MTM group in **94** with $AgNO_3$[35] gave alcohol **95** in 97% yield. Esterification of alcohol **95** with (*S*)-*N*,*N*,*O*-trimethylserine gave a 3:2 mixture of (*S*)- and (*R*)-trimethylserine esters **96**, whereas esterification of alcohol **95** with (*R*)-*N*,*N*,*O*-trimethylserine afforded a 1:3 mixture of esters **96**. Thus, the hydroxyl group in **95** was esterified with *N*,*N*,*O*-trimethylserine (*S*/*R* = 5/2) to give a diastereomeric mixture of trimethylserine esters **96** (*S*/*R* = 4/3, 85%), the two silyl groups of which were removed to provide aplyronine A (**1**) in 84% yield. Synthetic aplyronine A (**1**) was found to correspond uniquely to natural aplyronine A (**1**) in all respects, including spectroscopic (UV, IR, ^1H and ^{13}C NMR, MS, α_D) and chromatographic properties and cytotoxicity, except for the signal intensities due to amino acid moieties in ^1H and ^{13}C NMR spectra.[36,37]

Synthesis of Aplyronines B and C. Assuming that the stereochemistry of the carbon backbone of aplyronines B (**2**) and C (**3**) is identical with that of aplyronine

(35) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269−3270.

Scheme 10[a,b]



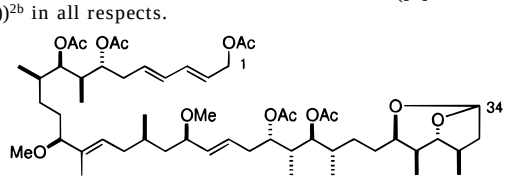
[a] Synthesis of aplyronines A (**1**) and B (**2**): (a) *N*,*N*-dimethylalanine (*S*/*R* = 3/2 for **94**; *S*/*R* = 8/5 for **97**), DCC, CSA, DMAP, CH_2Cl_2, 23 °C, 15 h, (**94**) 94%, (**97**) 79%; (b) $AgNO_3$, 2,6-lutidine, H_2O, THF, 30 °C, 16 h, (**95**) 97%, (**2**) 85%; (c) *N*,*N*,*O*-trimethylserine (*S*/*R* = 5/2 for **96**; *S*/*R* = 1/0 for **99**), DCC, CSA, DMAP, CH_2Cl_2, 35 °C, 1.5 h, (**96**) 85%; (**99**) 84%; (d) HF·pyridine, pyridine, 23 °C, 5 h, (**1**) 84%, (**98**) 88%. [b] Synthesis of aplyronine C (**3**): (a) *N*,*N*-dimethylalanine (*S*/*R* = 1/1), DCC, CSA, DMAP, CH_2Cl_2, 23 °C, 11.5 h, 78%; (b) $AgNO_3$, 2,6-lutidine, H_2O, THF, 30 °C, 18 h, 77%; (d) HF·pyridine, pyridine, 23 °C, 5 h, 45%.

A (**1**), we employed the synthetic intermediates of aplyronine A (**1**) for synthesis of aplyronines B (**2**) and C (**3**).

In the synthesis of aplyronine B (**2**), selection of the protecting group for the C25 hydroxyl in the 24-membered lactone **84** was important for the manipulation of hydroxyl groups at C7, C9, and C29 in the later stages of the synthesis. Initially, the 2,2,2-trichloroethoxycarbonyl group was chosen as a protecting group for the C25 hydroxyl, but was found to be labile under $NaBH_4$ or $NaBH(OMe)_3$ reduction. Next, the hydroxyl group at C25 in **84** was protected as a (methylthio)methyl (MTM) ether: *i.e.*, **84** was converted into MTM ether **86b** (43%) and ketone **86c** (50%) (Scheme 9). Ketone **86c** could be converted stereoselectively into **84** (75%) and the C25 epimer (9%). With the use of MTM ether **86b**, aplyronine B (**2**) was synthesized by a sequence of reactions similar to that for the synthesis of aplyronine A (**1**) from silyl ether **86a**. Thus, MTM ether **86b** was transformed into

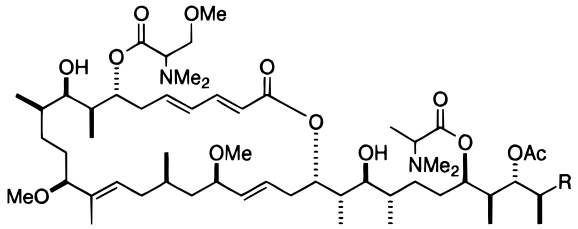
(36) The subtle differences in the signal intensities in the ^1H and ^{13}C NMR spectra which were observed between natural and synthetic aplyronine A (**1**) are due to the different diastereomeric ratios of two amino acid moieties. Natural aplyronine A (**1**) was obtained as a diastereomeric mixture with respect to two amino acids,[1a] and the ratio (*S*/*R*) of each amino acid in natural **1** varied with the animal samples employed, although compounds with the *S* configuration were always predominant (6−3/1 and 2−1.1/1 ratios for *N*,*N*-dimethylalanine and *N*,*N*,*O*-trimethylserine moieties, respectively). The diastereomeric ratios of the *N*,*N*-dimethylalanine part and the *N*,*N*,*O*-trimethylserine part in natural **1**, which were used for comparison purposes, were *S*/*R* = 72/28 and *S*/*R* = 52/48, respectively.

(37) To unambiguously identify the carbon backbone of synthetic and natural **1**, synthetic **1** was subjected to the same sequence of degradation reactions[2b] that was previously used with natural **1** to remove two amino acids to afford pentaacetate **i** ($[\alpha]^{21}_D$ −14 (*c* 0.06, $CHCl_3$)), which corresponds to the carbon backbone of **1**. The pentaacetate **i** thus obtained was identical to natural **i** ($[\alpha]^{24}_D$ −15 (*c* 0.16, $CHCl_3$))[2b] in all respects.



i

Scheme 11[a]



[a] (a) HCl, H_2O, dioxane, 50 °C, 1.5 h, 63% (b) $LiAlH(O\text{-}t\text{-}Bu)_3$, THF, 0 °C, 2 h, 60%.

diol **87b** (71%), which was subsequently converted into alcohol **90b** by three steps (81%). Oxidation of **90b** gave aldehyde **91b** (73%), which was transformed into enamide **92b** (42%). Deprotection of the [(3,4-dimethoxybenzyl)oxy]methyl group at C29 in **92b** and subsequent esterification with *N*,*N*-dimethylalanine (*S*/*R* = 8/5) afforded a diastereomeric mixture of *N*,*N*-dimethylalanine esters **97** (*S*/*R* = 4/1, 55%) (Scheme 10). Desilylation of **97** followed by esterification with (*S*)-*N*,*N*,*O*-trimethylserine gave a diastereomeric mixture of *N*,*N*,*O*-trimethylserine esters **99** (*S*/*R* = 5/6) in 74% yield. Finally, hydrolysis of the MTM groups in **99** furnished aplyronine B (**2**) in 85% yield. Synthetic aplyronine B (**2**) corresponded uniquely to natural aplyronine B (**2**) by comparison of their spectroscopic (UV, IR, ^1H NMR, FABMS, and CD) and chromatographic properties.[38]

Aplyronine C (**3**) was easily prepared from a synthetic intermediate **93a** of aplyronine A (**1**) by three steps (27%) (Scheme 10). The spectral data, including the CD spectrum, of synthetic aplyronine C (**3**) were identical with those of natural **3**.[39]

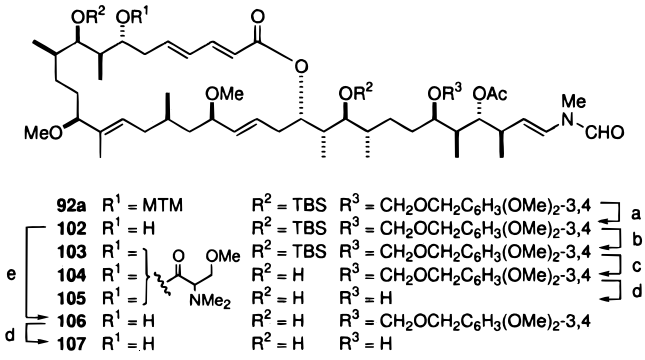
Thus, the absolute stereochemistry of aplyronine A (**1**) has been confirmed, and the absolute stereostructures of aplyronines B (**2**) and C (**3**) have been determined unambiguously by enantioselective total synthesis.

Synthesis of the Artificial Analogues of Aplyronine A. To investigate the structure−cytotoxicity relationships of aplyronines, their artificial analogues were synthesized.

First, two aplyronine derivatives that lack the *N*-formyl enamine moiety were prepared from aplyronine A (**1**). Acidic hydrolysis of the *N*-formyl enamine moiety of **1** gave aldehyde **100** (63%), which was reduced to give alcohol **101** (60%) (Scheme 11).

Next, the analogue which lacked the dimethylalanine moiety **105** was synthesized from a synthetic intermediate **92a** of aplyronine A (**1**) (Scheme 12). Deprotection of the MTM group of **92a** gave alcohol **102** (98%), which

Scheme 12[a]



[a] (a) $AgNO_3$, 2,6-lutidine, H_2O, THF, 30 °C, 16 h, 98%; (b) *N*,*N*,*O*-trimethylserine (*S*/*R* = 5/2), DCC, CSA, DMAP, CH_2Cl_2, 35 °C, 6 h, 84%; (c) HF·pyridine, pyridine, 23 °C, 4 h, 84%; (d) DDQ, CH_2Cl_2, *t*-BuOH, phosphate buffer (pH 6), 23 °C, 55 min, (**105**) 50%; (**107**) 70%; (e) HF·pyridine, pyridine, THF, 23 °C, 10 h, 89%.

was transformed into **105** by three steps (35%). An analogue without either of the amino acid moieties **107** was also prepared from alcohol **102** by sequential removal of the two protecting groups (62%).

Further, an analogue without the side chain of aplyronine A (**1**), **117**, was synthesized from a synthetic intermediate **9** of **1** (Scheme 13). Alcohol **118**[40] was transformed into sulfone **120** (97% from **118**) (Scheme 13). Olefin **108** (20*E*/20*Z* = 6/1) was prepared from the C5−C20 segment **9** and sulfone **120** by four steps (48% yield from **9**). Deprotection of the pivaloyl group in **108** followed by oxidation provided aldehyde **110** (43%), which was converted into α,β,γ,δ-unsaturated ester **111** in 72% yield (4*E*/4*Z* = 20/1). Deprotection of the TES group in **111** and subsequent hydrolysis gave seco acid **113** (83%). Macrocyclization of seco acid **113** afforded stereochemically pure lactone **114** in 51% yield after chromatographic purification. Further, lactone **114** was converted into analogue **117** by three steps (40%).

Structure−Cytotoxicity Relationships of Aplyronines and Artificial Analogues. The cytotocixities of aplyronines and artificial analogues against HeLa S_3 cells were evaluated in vitro. Aplyronines A (**1**), B (**2**), and C (**3**) showed cytotoxicities with IC_{50}s of 0.48, 3.11, and 21.2 ng/mL, respectively.[5] Three artificial analogues of aplyronines, **100**, **101**, and **105**, showed cytotoxicities with IC_{50}s of 2.02, 1.72, and 1.03 ng/mL, respectively. Three other analogues, **107**, aplyronine A diacetate, and **117**, showed cytotoxicities with IC_{50}s of 113, 216, and 2100 ng/mL, respectively. Comparison of the cytotoxicities of **1**−**3** revealed that the trimethylserine moiety plays an important role in the strong cytotoxicity of **1**. Two hydroxyl groups in aplyronine A (**1**) were shown to be responsible for its strong cytotoxicity through a comparison of the cytotoxicity of **1** and its diacetate. Aplyronine A (**1**) is ~4000-fold more cytotoxic than the analogue **117**, which indicates that the side chain of **1** is essential for the potent cytotoxicity of **1**. In contrast, the *N*-formyl enamine part and the dimethylalanine part of **1** were shown to be unimportant for the strong cytotoxicity of **1** by a comparison of **1** and the three analogues **100**, **101**, and **105**.

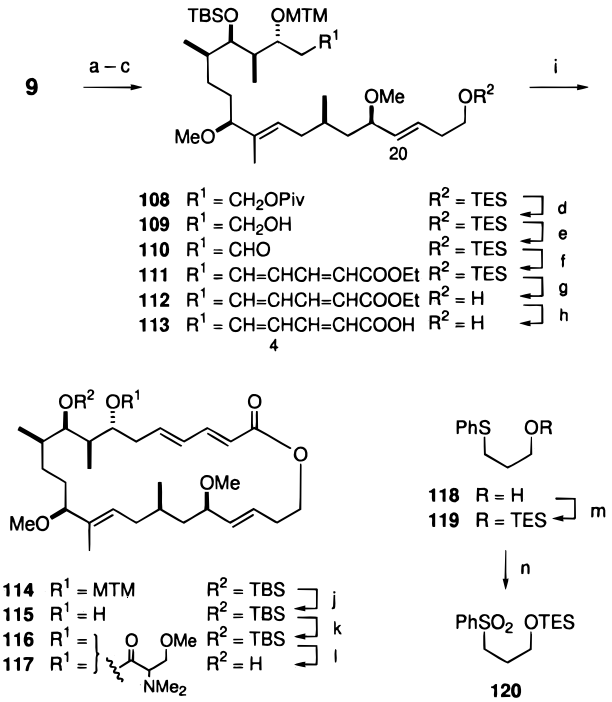
Further Biological Studies of Aplyronine A (1). Additional studies were performed to identify the target

(38) Natural aplyronine B (**2**) was obtained as a diastereomeric mixture with respect to two amino acids. The diastereomeric ratios of the *N*,*N*-dimethylalanine moiety and the *N*,*N*,*O*-trimethylserine moiety in natural **2**, which were used for comparison purposes, were *S*/*R* = 4/1 and *S*/*R* = 1/1, respectively. The small differences in the signal intensities in the NMR spectra and the differences in the specific rotation which were observed between natural and synthetic aplyronine B (**2**) are due to the different diastereomeric ratios of two amino acid parts. Natural and synthetic aplyronine B (**2**) were shown to have identical absolute stereochemistries with regard to the main chain by comparison of their CD spectra: both natural and synthetic aplyronine B (**2**) showed a negative Cotton effect at 265 nm.

(39) Natural aplyronine C (**3**) was obtained as a diastereomeric mixture with respect to *N*,*N*-dimethylalanine. The diastereomeric ratio of the *N*,*N*-dimethylalanine moiety in natural aplyronine C (**3**), which has been used for comparison purposes, was *S*/*R* = 2/1.

(40) Nambara, T.; Matsuhisa, N. *Yakugaku Zasshi* **1963**, *83*, 642−647.

Scheme 13[a]



[a] (a) **120**, BuLi, THF, −78 °C, 2.5 h; (b) Ac_2O, DMAP, pyridine, 23 °C, 2 h; (c) (i) 5% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 20 min; (ii) Et_3SiCl (TESCl), imidazole, DMF, 23 °C, 1 h, 48% (4 steps); (d) DIBAL, CH_2Cl_2, −78 °C, 25 min, 92%; (e) Dess−Martin periodinane, pyridine, CH_2Cl_2, 23 °C, 90 min, 47%; (f) LDA, $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, THF, −40 °C, 10 min → 0 °C, 20 min, 72%; (g) HF·pyridine, pyridine, THF, 23 °C, 20 min; (h) LiOH, MeOH, H_2O, 23 °C, 12.5 h, 83% (2 steps); (i) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, $CHCl_3$, 23° C, 2 h, 51%; (j) $AgNO_3$, 2,6-lutidine, H_2O, THF, 30 °C, 19.5 h, 94%; (k) *N*,*N*,*O*-trimethylserine (*S*/*R* = 5/2), DCC, CSA, DMAP, CH_2Cl_2, 35 °C, 45 min, 100%; (l) HF·pyridine, pyridine, 23 °C, 2 h, 63%; (m) Et_3SiCl (TESCl), pyridine, 23 °C, 30 min, 97%; (n) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 23 °C, 1 h, 100%.

biomolecules that interact with aplyronine A (**1**). No interaction was observed between aplyronine A (**1**) and DNA or microtubules. However, in an investigation performed by Professor H. Karaki, the University of Tokyo, aplyronine A (**1**) interacted with actin, the protein in cytoskeleton: **1** inhibited the polymerization of G-actin to F-actin and depolymerized F-actin to G-actin by severing.[41]

Conclusions

Enantioselective total synthesis of aplyronine A (**1**) was carried out by a convergent route (0.39% overall yield based on the longest linear sequence (47 steps), average yield for each step 89%), which confirmed the absolute stereochemistry of **1**. The absolute stereostructures of aplyronines B (**2**) and C (**3**), which were isolated only in very minute amounts from the natural source, were determined by enantioselective synthesis, which demonstrates the usefulness of organic synthesis in the structural elucidation of complex natural products. In addition, the structure−cytotoxicity relationships of aplyronines were determined to a considerable extent by organic synthesis.

(41) Saito, S.; Watabe, S.; Ozaki, H.; Kigoshi, H.; Yamada, K.; Karaki, H. Manuscript in preparation.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial supplies and used without further purification. All solvents were purified by a standard procedure before use. *tert*-Butyl hydroperoxide in toluene,[42] the Dess−Martin periodinane,[19,43] and copper(I) iodide[44] were prepared according to procedures in the literature. All reactions involving organometallic reagents were conducted under a nitrogen or argon atmosphere. Fuji silysia silica gel BW-820 MH and Merck aluminum oxide 90 (activity II−III) were used for column chromatography unless otherwise noted. Merck precoated silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC). Melting points are uncorrected. NMR spectra were measured at 270, 400, 500, or 600 MHz for ^1H and 67.8 MHz for ^{13}C. *J* values are given in Hz.

Experimental data for compounds **87b**−**93b**, **97**−**99**, **108**−**116**, **119**, and **120** are given in the the supporting information.

Hydroxy Imide 12. To a stirred solution of imide **11** (2.03 g, 8.71 mmol) in CH_2Cl_2 (17 mL) cooled at 0 °C were added a 1.0 M solution of dibutylboron triflate in CH_2Cl_2 (9.6 mL, 9.6 mmol) and triethylamine (1.7 mL, 12.0 mmol), successively. The reaction mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of (*R*)-3-(benzyloxy)-2-methylpropanal (1.55 g, 8.71 mmol) in CH_2Cl_2 (2.0 mL, 2.0 mL rinse) was added, and the reaction mixture was stirred at −78 °C for 3 h and at 0 °C for 20 min. The reaction was quenched by addition of 0.5 M phosphate buffer (pH 7, 20 mL) and MeOH (30 mL). After the reaction mixture was cooled to −10 °C, 30% aqueous hydrogen peroxide (15 mL) in MeOH (30 mL) was added over 10 min, and the resulting solution was stirred at 0 °C for 1 h. The organic solvents were evaporated, and Et_2O (30 mL) was added to the aqueous mixture. The mixture was cooled to 0 °C, and saturated aqueous $Na_2S_2O_3$ (30 mL) was added slowly. The resulting mixture was extracted with Et_2O (150 mL, 50 mL). The extracts were combined, washed with 5% aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−Et_2O 5:1 → 3:1 → 2:1 → 1:1 → Et_2O) to give **12** (3.16 g, 88%) as a colorless oil: $[\alpha]^{27}_D$ −30.9 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1775, 1705, 1455, 1370, 1345, 1235, 1195 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.41−7.25 (m, 10 H), 5.61 (d, *J* = 7.3 Hz, 1 H), 4.74 (dq, *J* = 7.3, 6.9 Hz, 1 H), 4.52 (s, 2 H), 3.96 (dq, *J* = 3.3, 6.6 Hz, 1 H), 3.90 (ddd, *J* = 2.6, 3.3, 8.3 Hz, 1 H), 3.73 (d, *J* = 2.6 Hz, 1 H), 3.62 (dd, *J* = 5.1, 9.2 Hz, 1 H), 3.58 (dd, *J* = 6.6, 9.2 Hz, 1 H), 1.99 (m, 1 H), 1.23 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H); MS (FAB) *m*/*z* 434 $(M + Na)^+$; HRMS (FAB) calcd for $C_{24}H_{29}NNaO_5$ $[(M + Na)^+]$ 434.1944, found 434.1925.

Amide 13. To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.8 g, 29 mmol) in THF (10 mL) cooled at −10 °C was added a 2.0 M solution of trimethylaluminum in toluene (14 mL, 28 mmol) dropwise. The resulting solution was stirred at 0 °C for 10 min and at room temperature for 30 min. The solution was recooled to −10 °C, and a solution of hydroxy imide **12** (5.50 g, 13 mmol) in 5:4 THF−CH_2Cl_2 (16 mL) was added. The reaction mixture was warmed to 0 °C, stirred for 1.6 h, and transferred into a rapidly stirred mixture of CH_2Cl_2 (40 mL) and 0.5 M aqueous HCl (40 mL) at 0 °C. The resulting two-phase mixture was stirred at 0 °C for 2 h and extracted with CH_2Cl_2 (300 mL then 2 × 50 mL). The extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (150 g, hexane−EtOAc 2:1 → 1:1 → EtOAc) to give **13** (3.8 g, 96%) as a colorless oil and 4-(*S*)-methyl-5-(*S*)-phenyl-2-oxazolidinone (2.3 g, 97%) as colorless crystals. **13**: $[\alpha]^{27}_D$ +14.1 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1635, 1480, 1455, 1420, 1390, 1360, 1090 cm^{-1}; ^1H

(42) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607−3608.
(43) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(44) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460−1469.

NMR (270 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5 H), 4.55 (d, J = 11.9 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 3.98 (br s, 1 H), 3.72 (dd, J = 3.1, 8.4 Hz, 1 H), 3.67 (s, 3 H), 3.66 (dd, J = 4.0, 8.9 Hz, 1 H), 3.57 (dd, J = 5.8, 8.9 Hz, 1 H), 3.18 (s, 3 H), 3.04 (m, 1 H), 1.89 (m, 1 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H); MS (FAB) m/z 318 $(M + Na)^+$; HRMS (FAB) calcd for $C_{16}H_{25}NNaO_4$ $[(M + Na)^+]$ 318.1681, found 318.1678.

Silyl Ether 14. To a stirred solution of amide **13** (1.66 g, 5.63 mmol) in CH_2Cl_2 (30 mL) cooled at 0 °C were added 2,6-lutidine (1.4 mL, 12.0 mmol) and *tert*-butyldimethylsilyl triflate (2.00 mL, 8.71 mmol). The mixture was stirred at 0 °C for 1 h and diluted with H_2O (30 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, CH_2Cl_2) to give **14** (2.30 g, 100%) as a colorless oil: $[\alpha]^{26}_D$ +9.18 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 1650, 1475, 1465, 1390, 1260, 1080, 1050, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5 H), 4.49 (d, J = 11.9 Hz, 1 H), 4.43 (d, J = 11.9 Hz, 1 H), 3.94 (dd, J = 2.6, 8.2 Hz, 1 H), 3.59 (dd, J = 5.3, 9.2 Hz, 1 H), 3.56 (s, 3 H), 3.19 (dd, J = 7.8, 9.2 Hz, 1 H), 3.14 (m, 1 H), 3.11 (s, 3 H), 1.93 (m, 1 H), 1.11 (d, J = 6.9 Hz, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); MS (FAB) m/z 432 $(M + Na)^+$; HRMS (FAB) calcd for $C_{22}H_{39}NNaO_4Si$ $[(M + Na)^+]$ 432.2546, found 432.2558.

Aldehyde 15. To a stirred solution of silyl ether **14** (2.06 g, 5.03 mmol) in THF (35 mL) cooled at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (10.0 mL, 10.0 mmol) dropwise. The solution was stirred at −78 °C for 2 h, and the reaction was quenched by addition of acetone (0.5 mL). The solution was stirred at −78 °C for 5 min and then transferred into a rapidly stirred mixture of hexane (80 mL) and 0.5 M aqueous tartaric acid (80 mL) at room temperature. The resulting two-phase mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with 1:3 CH_2Cl_2−hexane (4 × 80 mL). The organic layer and the extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (90 g, hexane−Et_2O 20:1 → 10: 1) to give **15** (1.75 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +35.0 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 2705, 1720, 1470, 1460, 1455, 1360, 1255, 1095, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.69 (d, J = 1.0 Hz, 1 H), 7.38−7.25 (m, 5 H) ,4.49 (d, J = 12.2 Hz, 1 H), 4.43 (d, J = 12.2 Hz, 1 H), 4.21 (dd, J = 3.9, 6.1 Hz, 1 H), 3.46 (dd, J = 5.6, 9.2 Hz, 1 H), 3.36 (dd, J = 5.9, 9.2 Hz, 1 H), 2.50 (ddq, J = 1.0, 3.9, 6.9 Hz, 1 H), 2.02 (dddq, J = 5.6, 5.9, 6.1, 6.9 Hz, 1 H), 1.10 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.86 (s, 9 H), 0.05 (s, 3 H), −0.01 (s, 3 H); MS (FAB) m/z 373 $(M + Na)^+$; HRMS (FAB) calcd for $C_{20}H_{34}NaO_3Si$ $[(M + Na)^+]$ 373.2175, found 373.2155.

Conjugated Ester 16. To a stirred solution of diisopropyl (ethoxycarbonyl)methylphosphonate (7.8 mL, 32.8 mmol) in THF (50 mL) cooled to 0 °C was added potassium *tert*-butoxide (3.34 g, 29.8 mmol), and the resulting solution was stirred at room temperature for 1 h. The solution was cooled to −78 °C, and a solution of aldehyde **15** (2.93 g, 8.36 mmol) in THF (25 mL) was added. After the reaction mixture was stirred at −78 °C for 1 h and at 0 °C for 1.5 h, Et_2O (75 mL) and saturated aqueous NH_4Cl (65 mL) were added. The resulting mixture was stirred at room temperature for 15 min and extracted with CH_2Cl_2 (3 × 70 mL). The extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (200 g, hexane−Et_2O 20:1 → 9: 1) to give **16** (3.52 g, 100%) as a colorless oil: $[\alpha]^{25}_D$ +26.5 (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 1710, 1655, 1475, 1465, 1455, 1370, 1260, 1095, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5 H), 6.97 (dd, J = 15.8, 7.9 Hz, 1 H), 5.77 (dd, J = 15.8, 1.3 Hz, 1 H), 4.46 (s, 2 H), 4.18 (q, J = 7.3 Hz, 2 H), 3.62 (dd, J = 5.3, 5.3 Hz, 1 H), 3.50 (dd, J = 5.1, 8.9 Hz, 1 H), 3.28 (dd, J = 7.3, 8.9 Hz, 1 H), 2.53 (m, 1 H), 1.97 (m, 1 H), 1.28 (t, J = 7.3 Hz, 3 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); MS (FAB) m/z 443 $(M + Na)^+$; HRMS (FAB) calcd for $C_{24}H_{40}NaO_4Si$ $[(M + Na)^+]$ 443.2594, found 443.2581.

Allylic Alcohol 17. To a stirred solution of conjugated ester **16** (2.44 g, 5.81 mmol) in CH_2Cl_2 (24 mL) and hexane (48 mL) cooled to −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (23.0 mL, 23.0 mmol) dropwise. The solution was stirred at −78 °C for 1 h, and the reaction was quenched by addition of MeOH (3.8 mL). After the mixture was warmed to room temperature, Et_2O (480 mL), saturated aqueous NaCl (7.7 mL), and anhydrous $MgSO_4$ (19 g) were added. The resulting mixture was stirred for 2 h and filtered through a pad of Celite, and the residue was washed with EtOAc (300 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (110 g, hexane−Et_2O 4:1 → 3: 2) to give **17** (2.29 g, 100%) as a colorless oil: $[\alpha]^{24}_D$ +19.7 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3610, 3440 (br), 1475, 1465, 1460, 1385, 1365, 1260, 1100, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5 H), 5.65 (dd, J = 6.6, 15.5 Hz, 1 H), 5.56 (td, J = 5.2, 15.5 Hz, 1 H), 4.50 (d, J = 12.1 Hz, 1 H), 4.44 (d, J = 12.1 Hz, 1 H), 4.04 (dd, J = 5.0, 5.2 Hz, 2 H), 3.56 (dd, J = 4.8, 9.1 Hz, 1 H), 3.50 (dd, J = 5.0, 5.0 Hz, 1 H), 3.25 (dd, J = 7.7, 9.1 Hz, 1 H), 2.38 (m, 1 H), 1.98 (m, 1 H), 1.18 (t, J = 5.0 Hz, 1 H), 0.98 (d, J = 6.9 Hz, 6 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); MS (FAB) m/z 401 $(M + Na)^+$; HRMS (FAB) calcd for $C_{22}H_{38}NaO_3Si$ $[(M + Na)^+]$ 401.2488, found 401.2469.

Epoxide 18. To a stirred mixture of powdered molecular sieves 4 Å (4.0 g) and titanium tetraisopropoxide (4.4 mL, 15 mmol) in CH_2Cl_2 (50 mL) cooled at −23 °C was added a 2.0 M solution of (+)-diethyl tartrate in CH_2Cl_2 (9.7 mL, 19.4 mmol). The mixture was stirred at −23 °C for 10 min, and a solution of allylic alcohol **17** (4.29 g, 11.3 mmol) in CH_2Cl_2 (12 mL) and a 3.4 M solution of *tert*-butyl hydroperoxide in toluene (8.0 mL, 27.2 mmol) were added, successively. The solution was stirred at −23 °C for 1 h and was diluted with 0.5 M aqueous tartaric acid (50 mL). The resulting mixture was stirred at −23 °C for 15 min and at room temperature for 2 h. The mixture was extracted with EtOAc (250 mL, 80 mL, then 2 × 50 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residual oil was dissolved in Et_2O (100 mL), and to this solution 1 M aqueous NaOH (40 mL) was added at 0 °C. After the mixture was stirred at 0 °C for 45 min, the organic layer was separated, and the aqueous layer was extracted with Et_2O (150 mL, 50 mL). The organic layer and the extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−EtOAc 10:1 → 5: 1 → 3: 1) to give **18** (4.27 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ −8.58 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3590, 3460 (br), 1475, 1465, 1455, 1380, 1360, 1255, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5 H), 4.52 (d, J = 12.1 Hz, 1 H), 4.46 (d, J = 12.1 Hz, 1 H), 3.88 (ddd, J = 2.0, 5.3, 12.2 Hz, 1 H), 3.81 (dd, J = 2.8, 6.9 Hz, 1 H), 3.63 (ddd, J = 4.0, 7.6, 12.2 Hz, 1 H), 3.56 (dd, J = 4.6, 8.9 Hz, 1 H), 3.28 (dd, J = 7.6, 8.9 Hz, 1 H), 2.95−2.89 (m, 2 H), 1.99 (m, 1 H), 1.66 (dd, J = 5.3, 7.6 Hz, 1 H), 1.47 (m, 1 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); MS (FAB) m/z 417 $(M + Na)^+$; HRMS (FAB) calcd for $C_{22}H_{38}NaO_4Si$ $[(M + Na)^+]$ 417.2438, found 417.2421.

Reduction of Epoxide 18. To a stirred solution of epoxide **18** (4.0 g, 10 mmol) in 1,2-dimethoxyethane (50 mL) cooled at −23 °C was added a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (6.0 mL, 22 mmol) dropwise. The mixture was warmed to 0 °C and stirred at 0 °C for 2 h. H_2O (3 mL) was added, and the mixture was warmed to room temperature. To the mixture were added Et_2O (70 mL) and 10% aqueous (+)-tartaric acid (50 mL). After being stirred at room temperature for 30 min, the mixture was extracted with EtOAc (150 mL and then 2 × 50 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−EtOAc 5:1 → 3:1 → 2:1 → 1:1 → EtOAc) to give diol **19a** (2.94 g, 74%) and triol **19b** (426 mg, 15%) as a colorless oil, repectively. **19a**: $[\alpha]^{20}_D$ +14.1 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 1475, 1465, 1455, 1255, 1070, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5 H), 4.49 (s, 2 H), 3.97 (br s, 1 H), 3.88 (dd, J = 2.5, 5.4 Hz, 1 H), 3.86−3.80 (m, 3 H),

3.61 (dd, J = 5.0, 9.2 Hz, 1 H), 3.34 (dd, J = 7.3, 9.2 Hz, 1 H), 2.99 (dd, J = 4.3, 5.9 Hz, 1 H), 2.09 (m, 1 H), 1.82−1.76 (m, 2 H), 1.59 (m, 1 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.10 (s, 3 H), 0.06 (s, 3 H); MS (FAB) m/z 419 (M + Na)$^+$; HRMS (FAB) calcd for $C_{22}H_{40}NaO_4Si$ [(M + Na)$^+$] 419.2594, found 419.2577. **19b**: $[\alpha]^{19}_D$ −36.8 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 1455, 1425, 1385, 1365, 1240, 1105, 1070, 975 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40−7.15 (m, 5 H), 4.54 (d, J = 12.2 Hz, 1 H), 4.50 (d, J = 12.2 Hz, 1 H), 4.30 (br s, 1 H), 4.05 (dd, J = 3.1, 6.4 Hz, 1 H), 3.98−3.78 (m, 4 H), 3.60 (dd, J = 4.4, 8.9 Hz, 1 H), 3.51 (dd, J = 8.9, 8.9 Hz, 1 H), 3.38 (br s, 1 H), 2.16−1.82 (m, 2 H), 1.71−1.53 (m, 2 H), 1.01 (d, J = 7.2 Hz, 3 H), 0.75 (d, J = 6.9 Hz, 3 H); MS (FAB) m/z 305 (M + Na)$^+$; HRMS (FAB) calcd for $C_{16}H_{26}NaO_4$ [(M + Na)$^+$] 305.1729, found 305.1729.

Ester 20. To a solution of diol **19a** (480 mg, 1.21 mmol) in pyridine (4.8 mL) cooled at 0 °C was added pivaloyl chloride (0.23 mL, 1.87 mmol) with stirring. The solution was stirred at 0 °C for 1.5 h and diluted with H_2O (10 mL). The resulting mixture was stirred at room temperature for 30 min and extracted with Et_2O (5 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (25 g, hexane−Et_2O 10:1 → 5:1 → 3:1) to give **20** (579 mg, 99%) as a colorless oil: $[\alpha]^{20}_D$ +24.4 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3460 (br), 1720, 1480, 1470, 1465, 1400, 1290, 1260, 1170, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5 H), 4.49 (s, 2 H), 4.31 (ddd, J = 5.3, 8.6, 11.2 Hz, 1 H), 4.21 (ddd, J = 4.9, 6.3, 11.2 Hz, 1 H), 3.95 (dd, J = 2.3, 5.9 Hz, 1 H), 3.61 (m, 1 H), 3.59 (dd, J = 4.9, 9.1 Hz, 1 H), 3.32 (dd, J = 7.6, 9.1 Hz, 1 H), 3.17 (d, J = 3.6 Hz, 1 H), 2.05 (m, 1 H), 1.92 (m, 1 H), 1.71−1.51 (m, 2 H), 1.19 (s, 9 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); MS (FAB) m/z 503 (M + Na)$^+$; HRMS (FAB) calcd for $C_{27}H_{48}NaO_5Si$ [(M + Na)$^+$] 503.3169, found 503.3181.

Diol 21. A mixture of ester **20** (1.31 g, 2.73 mmol) and 10% Pd on carbon (281 mg) in EtOH (40 mL) was stirred under a hydrogen atmosphere at room temperature for 3.5 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (200 mL). The filtrate and the washings were combined and concentrated. The residue was purified by column chromatography on silica gel (20 g, hexane−EtOAc 4:1 → 2:1 → 1:1) to give **21** (1.05 g, 99%) as colorless crystals: mp 104−105 °C (hexane); $[\alpha]^{24}_D$ +6.5 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1720, 1480, 1470, 1465, 1365, 1290, 1255, 1165, 1075, 840 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.44 (ddd, J = 4.3, 9.6, 11.2 Hz, 1 H), 4.12 (ddd, J = 5.6, 5.6, 11.2 Hz, 1 H), 4.08 (dd, J = 2.0, 5.6 Hz, 1 H), 3.65−3.47 (m, 3 H), 3.36 (d, J = 3.3 Hz, 1 H), 2.62 (dd, J = 5.0, 7.6 Hz, 1 H), 2.03−1.89 (m, 2 H), 1.66 (m, 1 H), 1.57 (m, 1 H), 1.20 (s, 9 H), 0.91 (s, 9 H), 0.90 (d, J = 7.2 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.11 (s, 3 H), 0.08 (s, 3 H); MS (CI) m/z (relative intensity) 391 [(M + H)$^+$, 5], 333 (17), 315 (13), 211 (41), 203 (51), 159 (50), 145 (100). Anal. Calcd for $C_{24}H_{42}O_5Si$: C, 61.49; H, 10.84. Found C, 61.64; H, 10.44.

Sulfide 22. To a stirred solution of diol **21** (434 mg, 1.11 mmol) and diphenyl disulfide (510 mg, 2.33 mmol) in DMF (11 mL) at room temperature was added tributylphosphine (0.56 mL, 2.25 mmol), and the resulting solution was stirred at room temperature for 12 h. H_2O (5 mL) was added, and the resulting mixture was concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane−Et_2O 40:1 → 20:1 → 10:1 → 3:1) to give **22** (490 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ +29.8 (*c* 0.888, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1720, 1585, 1480, 1475, 1460, 1285, 1255, 1165, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.13 (m, 5 H), 4.35 (ddd, J = 5.0, 8.9, 11.2 Hz, 1 H), 4.17 (ddd, J = 5.6, 5.6, 11.2 Hz, 1 H), 3.95 (dd, J = 2.0, 5.6 Hz, 1 H), 3.51 (dddd, J = 3.6, 3.6, 9.2, 9.2 Hz, 1 H), 3.27 (dd, J = 3.9, 12.5 Hz, 1 H), 3.09 (d, J = 3.6 Hz, 1 H), 2.63 (dd, J = 9.6, 12.5 Hz, 1 H), 2.00−1.86 (m, 2 H), 1.67 (m, 1 H), 1.55 (m, 1 H), 1.19 (s, 9 H), 1.07 (d, J = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.82 (d, J = 7.2 Hz, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); MS (FAB) m/z 505 (M + Na)$^+$; HRMS (FAB) calcd for $C_{26}H_{46}NaO_4SSi$ [(M + Na)$^+$] 505.2784, found 505.2782.

Silyl Ether 23. To a stirred solution of sulfide **22** (1.21 g, 2.51 mmol) and imidazole (600 mg, 8.80 mmol) in DMF (5 mL) at room temperarure was added triethylsilyl chloride (0.63 mL, 3.75 mmol). The resulting solution was stirred at room temperarure for 1.4 h, and a small amount of ice (*ca.* 1 g) and H_2O (1 mL) were added. The resulting mixture was stirred at room temperarure for 30 min and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (40 g, hexane−Et_2O 40:1) to give **23** (1.50 g, 100%) as a colorless oil: $[\alpha]^{21}_D$ +17.6 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1720, 1585, 1480, 1470, 1460, 1285, 1255, 1165, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.33−7.24 (m, 4 H), 7.16 (m, 1 H), 4.22 (ddd, J = 5.5, 5.5, 10.8 Hz, 1 H), 4.03 (ddd, J = 7.3, 7.3, 10.8 Hz, 1 H), 3.73 (ddd, J = 5.0, 5.0, 6.6 Hz, 1 H), 3.63 (dd, J = 3.6, 3.6 Hz, 1 H), 2.95 (dd, J = 5.8, 12.7 Hz, 1 H), 2.77 (dd, J = 8.6, 12.7 Hz, 1 H), 1.89 (m, 1 H), 1.78 (m, 1 H), 1.71−1.66 (m, 2 H), 1.21 (s, 9 H), 1.05 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 7.9 Hz, 9 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.57 (q, J = 7.9 Hz, 6 H), 0.02 (s, 3 H), −0.03 (s, 3 H); MS (FAB) m/z 619 (M + Na)$^+$; HRMS (FAB) calcd for $C_{32}H_{60}NaO_4SSi_2$ [(M + Na)$^+$] 619.3648, found 619.3649.

C5−C11 Segment 4. To a stirred solution of silyl ether **23** (2.66 g, 4.46 mmol) in CH_2Cl_2 (25 mL) cooled to 0 °C were added $NaHCO_3$ (2.4 g, 28 mmol) and *m*-chloroperoxybenzoic acid (2.3 g, 13 mmol). After 5 min, the mixture was warmed to room temperature and stirred at room temperature for 1.5 h. Saturated aqueous $Na_2S_2O_3$ (10 mL) and H_2O (20 mL) were added, and the resulting mixture was stirred at room temperature for 1 h and extracted with Et_2O (200 mL, 50 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−Et_2O 10:1 → 4:1) to give **4** (2.86 g, 100%) as a colorless oil: $[\alpha]^{20}_D$ +9.9 (*c* 0.989, $CHCl_3$); IR ($CHCl_3$) 1720, 1590, 1480, 1475, 1465, 1305, 1290, 1255, 1155, 1185, 935 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.92−7.89 (m, 2 H), 7.66−7.55 (m, 3 H), 4.18 (ddd, J = 6.2, 6.2, 10.9 Hz, 1 H), 4.01 (ddd, J = 7.1, 7.1, 10.9 Hz, 1 H), 3.73 (ddd, J = 3.5, 6.5, 6.5 Hz, 1 H), 3.52 (dd, J = 2.6, 5.0 Hz, 1 H), 3.12 (dd, J = 2.6, 14.2 Hz, 1 H), 2.87 (dd, J = 9.2, 14.2 Hz, 1 H), 2.28 (m, 1 H), 1.69−1.65 (m, 2 H), 1.57 (m, 1 H), 1.21 (s, 9 H), 1.12 (d, J = 6.9 Hz, 3 H), 0.95 (t, J = 7.6 Hz, 9 H), 0.86 (s, 9 H), 0.84 (d, J = 7.6 Hz, 3 H), 0.60 (q, J = 7.6 Hz, 6 H), 0.02 (s, 6 H); MS (FAB) m/z 651 (M + Na)$^+$. Anal. Calcd for $C_{32}H_{60}O_6SSi_2$: C, 61.10; H, 9.61. Found C, 61.10; H, 9.87.

Iodide 7. To a stirred solution of alcohol **25** (615 mg, 3.13 mmol) in pyridine (2.0 mL) cooled to 0 °C was added *p*-toluenesulfonyl chloride (1.82 g, 9.57 mmol). After 2 h, the reaction was quenched by addition of ice (0.5 g). The resulting mixture was stirred at room temperature for 1 h, diluted with H_2O (10 mL), and extracted with Et_2O (15 mL, 4 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give crude tosylate **26** (1.2 g) as a colorless oil, which was used in the next experiment without purification. To a stirred solution of **26** (1.2 g) in acetone (6.0 mL) were added $CaCO_3$ (634 mg, 6.33 mmol) and NaI (1.43 g, 9.54 mmol) at room temperature. The reaction mixture was warmed to 50 °C and stirred for 13.5 h. After cooling, H_2O (15 mL) was added, and the mixture was extracted with Et_2O (150 mL, 25 mL). The combined extracts were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 10:1 → 5:1) to give **7** (946 mg, 99%) as a colorless oil: $[\alpha]^{21}_D$ −6.7 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 1495, 1455, 1180, 1085, 1120, 1085, 1030, 905 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5 H), 4.56 (s, 2 H), 3.62 (dd, J = 4.6, 9.9 Hz, 1 H), 3.53 (dd, J = 5.3, 9.9 Hz, 1 H), 3.43 (s, 3 H), 3.42−3.26 (m, 3 H); MS (EI) m/z (relative intensity) 306 (M$^+$, 33), 185 (8), 147 (7), 117 (7), 91 (100); HRMS (EI) calcd for $C_{11}H_{15}IO_2$ (M$^+$) 306.0117, found 306.0118.

Diol 30. To a stirred solution of lactone **29** (5.97 g, 16.0 mmol) in THF (50 mL) cooled at 0 °C was added a 1.0 M solution of lithium aluminum hydride in THF (32.0 mL, 32.0

mmol) dropwise. The solution was stirred at room temperature for 1 h, and then NaF (4.09 g) and a solution of THF−H_2O (9:1, 100 mL) were added. After being stirred at room temperature for 20 min, the mixture was filtered through a pad of Celite. The residue was washed with THF (300 mL), and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (300 g, hexane−EtOAc 4:1 → 2: 1 → 1: 1 → 1: 4) to give **30** (6.03 g, 100%) as a colorless oil: $[\alpha]^{28}_D$ −6.2 (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 3580, 3400 (br), 1595, 1490, 1445, 1070 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.45−7.40 (m, 6 H), 7.36−7.21 (m, 9 H), 3.92 (m, 1 H), 3.37−3.54 (m, 2 H), 3.15 (dd, J = 3.6, 9.2 Hz, 1 H), 3.07 (dd, J = 7.9, 9.2 Hz, 1 H), 2.75 (br s, 1 H,), 2.35 (br s, 1 H), 1.80 (m, 1 H), 1.45 (ddd, J = 5.3, 7.9, 14.5 Hz, 1 H), 1.38 (ddd, J = 4.6, 6.8, 14.5 Hz, 1 H), 0.88 (d, J = 6.9 Hz, 3 H); MS (FAB) m/z 399 $(M + Na)^+$; HRMS (FAB) calcd for $C_{25}H_{28}NaO_3$ $[(M + Na)^+]$ 399.1936, found 399.1945.

Methyl Ether 32. To a stirred solution of diol **30** (1.34 g, 3.56 mmol) in DMF (13.5 mL) cooled at 0 °C were added imidazole (600 mg, 8.81 mmol) and *tert*-butyldiphenylsilyl chloride (0.96 mL, 3.69 mmol). After 1.7 h at 0 °C, the reaction was quenched by addition of H_2O (30 mL), and the resulting solution was stirred at room temperature for 30 min. The mixture was extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−ethyl acetate 20:1 → 10:1 → 5:1) to give a 13:1 mixture of silyl ether **31** and *tert*-butyldiphenylsilanol (2.16 g) as a colorless oil. To a stirred solution of the crude silyl ether (2.16 g) in THF (12 mL) cooled at 0 °C were added methyl iodide (0.85 mL, 13.6 mmol) and NaH (442 mg of 60% dispersion in mineral oil, 11.0 mmol), successively. After 1 h, the reaction was quenched by addition of ice (1 g) and saturated aqueous NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in Et_2O (40 mL), washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−Et_2O 40:1 → 20:1 → 10:1) to give **32** (2.13 g, 95%) as a colorless oil: $[\alpha]^{29}_D$ +5.5 (*c* 0.920, $CHCl_3$); IR ($CHCl_3$) 1590, 1490, 1445, 1425, 1110, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.66−7.61 (m, 4 H), 7.48−7.16 (m, 21 H), 3.50 (dd, J = 4.6, 9.9 Hz, 1 H), 3.43 (dd, J = 5.9, 9.9 Hz, 1 H), 3.32 (s, 3 H), 3.29 (m, 1 H), 3.09 (d, J = 4.6 Hz, 2 H), 1.76 (m, 1 H), 1.59 (ddd, J = 4.9, 6.9, 14.2 Hz, 1 H), 1.35 (ddd, J = 6.3, 7.9, 14.2 Hz, 1 H), 1.03 (s, 9 H), 0.93 (d, J = 6.6 Hz, 3 H); MS (FAB) m/z 651 $(M + Na)^+$; HRMS (FAB) calcd for $C_{42}H_{48}NaO_3Si$ $[(M + Na)^+]$ 651.3270, found 651.3274.

Alcohol 33. To a stirred solution of methyl ether **32** (1.35 g, 2.15 mmol) in THF (20 mL) was added a 1.0 M solution of Bu_4NF in THF (4.3 mL, 4.3 mmol) at room temperature. After 12 h, saturated aqueous NH_4Cl (25 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (8 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (75 g, hexane−Et_2O 2:1 → 1:1 → 1:2) to give **33** (854 mg, 100%) as a colorless oil: $[\alpha]^{19}_D$ +13.1 (*c* 0.861, $CHCl_3$); IR ($CHCl_3$) 3630, 3400 (br), 1600, 1490, 1450, 1090 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.49−7.42 (m, 6 H), 7.34−7.19 (m, 9 H), 3.48−3.31 (m, 3 H), 3.41 (s, 3 H), 3.21 (dd, J = 5.3, 9.9 Hz, 1 H), 3.12 (dd, J = 4.6, 9.9 Hz, 1 H), 2.48 (dd, J = 5.3, 7.3 Hz, 1 H), 1.76 (m, 1 H), 1.63−1.50 (m, 2 H), 0.88 (d, J = 6.9 Hz, 3 H); MS (FAB) m/z 413 $(M + Na)^+$; HRMS (FAB) calcd for $C_{26}H_{30}NaO_3$ $[(M + Na)^+]$ 413.2093, found 413.2098.

Sulfone 8. To a stirred solution of alcohol **33** (3.54 g, 9.08 mmol) in pyridine (8.0 mL) cooled at 0 °C was added *p*-toluenesulfonyl chloride (3.47 g, 18.2 mmol). After 2.5 h, the reaction was quenched by addition of ice (2 g) and H_2O (10 mL), and the resulting mixture was stirred at room temperature for 1 h. The mixture was extracted with Et_2O (150 mL, 25 mL). The combined extracts were washed with 5% aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated to give a crude tosylate **34** (5.9 g) as a colorless oil. Crude **34** was employed in the next experiment without purification. To a stirred solution of methyl phenyl sulfone (2.8 g, 18 mmol) in THF (160 mL) cooled at −23 °C was added a 1.52 M solution of BuLi in hexane (11.5 mL, 17.5 mmol). The mixture was warmed to room temperature and stirred for 40 min, and the solution of crude **34** (5.9 g) in THF (14 mL) was added. The mixture was stirred at room temperature for 3.2 h, and the reaction was quenched by addition of aqueous NH_4Cl (20 mL). The mixture was extracted with Et_2O (150 mL, 25 mL). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (150 g, hexane−Et_2O 5: 1 → 3:1 → 2:1 → 1:1) and by medium-pressure liquid chromatography (Fuji Silysia, Micro Bead Silica Gel B-(30−70)μ, 139 g, hexane−EtOAc 3.6:1 → 3.3:1 → 3.0:1, 8 mL/min) to give **8** (t_R = 110 min, 3.70 g, 77%) as a colorless oil: $[\alpha]^{27}_D$ +15.5 (*c* 0.866, $CHCl_3$); IR ($CHCl_3$) 1600, 1490, 1450, 1310, 1150, 1090 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.91−7.85 (m, 2 H), 7.68−7.51 (m, 3 H), 7.46−7.41 (m, 6 H), 7.32−7.19 (m, 9 H), 3.29 (s, 3 H), 3.20 (m, 1 H), 3.10−3.00 (m, 4 H), 1.73 (m, 1 H), 1.63−1.45 (m, 2 H), 1.38 (dd, J = 6.3, 6.3 Hz, 2 H), 0.83 (d, J = 6.3 Hz, 3 H); MS (FAB) m/z 551 $(M + Na)^+$; HRMS (FAB) calcd for $C_{33}H_{36}NaO_4S$ $[(M + Na)^+]$ 551.2232, found 551.2224.

Benzyl Ether 35. To a stirred solution of the C5−C11 segment **4** (401 mg, 0.64 mmol) in THF (1.5 mL) cooled at −78 °C under a stream of nitrogen was added a 0.6 M solution of lithium diisopropylamide (1.4 mL, 0.7 mmol) prepared from diisopropylamine (0.25 mL, 1.8 mmol), a 1.59 M solution of BuLi in hexane (0.95 mL, 1.5 mmol), and THF (1.8 mL) at −78 °C. After 25 min, the mixture was warmed to 0 °C. Hexamethylphosphoric triamide (0.49 mL, 2.8 mmol) was added, and the mixture was stirred at 0 °C for 5 min. A solution of iodide **7** (253 mg, 0.83 mmol) in THF (1.4 mL) was added at 0 °C, and the resulting mixture was warmed to room temperature and stirred at room temperature for 1.5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL) successively; dried (Na_2SO_4); and concentrated. The residual oil was purified by column chromatography on silica gel (40 g, hexane−Et_2O 40:1 → 20:1 → 10:1 → 5:1) to give a diastereomeric mixture of sulfones (462 mg) as a colorless oil, which was employed in the next experiment without separation of the diastereomers. To a vigorously stirred solution of the diastereomeric mixture of sulfones (462 mg) in MeOH (10 mL) cooled at 0 °C were added Na_2HPO_4 (1.21 g, 8.52 mmol) and 5% sodium amalgam (2.62 g, 5.70 mmol), and the mixture was stirred at 0 °C for 2 h. The mixture was diluted with saturated aqueous NH_4Cl (5 mL), stirred at room temperature for 1 h, and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (12 g, hexane−Et_2O 40:1 → 20:1 → 10:1) to give **35** (316 mg, 76%) as a colorless oil: $[\alpha]^{23}_D$ +18.0 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1720, 1465, 1290, 1255, 1165, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5 H), 4.56 (s, 2 H), 4.23 (ddd, J = 5.3, 5.3, 10.6 Hz, 1 H), 4.04 (ddd, J = 7.3, 7.3, 10.6 Hz, 1 H), 3.68 (ddd, J = 4.6, 4.6, 6.9 Hz, 1 H), 3.48 (d, J = 5.0 Hz, 2 H), 3.42 (dd, J = 4.0, 4.0 Hz, 1 H), 3.41 (s, 3 H), 3.30 (m, 1 H), 1.79 (m, 1 H), 1.70−1.01 (m, 7 H), 1.19 (s, 9 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.91−0.87 (m, 6 H), 0.89 (s, 9 H), 0.59 (q, J = 7.9 Hz, 6 H), 0.04 (s, 6 H); MS (FAB) m/z 689 $(M + Na)^+$; HRMS (FAB) calcd for $C_{37}H_{70}NaO_6Si_2$ $[(M + Na)^+]$ 689.4609, found 689.4614. Anal. Calcd for $C_{37}H_{70}O_6Si_2$: C, 66.61; H, 10.58. Found C, 67.05; H, 11.02.

Alcohol 36. A mixture of benzyl ether **35** (216 mg, 0.324 mmol), $NaHCO_3$ (33 mg, 0.39 mmol), and 10% Pd on carbon (106 mg) in EtOH (10 mL) was stirred under a hydrogen atmosphere at room temperature for 2.5 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (50 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by

column chromatography on silica gel (10 g, hexane−Et_2O 3:1 → 1:1) to give **36** (182 mg, 98%) as a colorless oil: $[\alpha]^{25}_D$ +32.9 (*c* 0.855, $CHCl_3$); IR ($CHCl_3$) 3580 (br), 1720, 1465, 1285, 1255, 1165, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.23 (ddd, J = 5.6, 5.6, 10.9 Hz, 1 H), 4.05 (ddd, J = 7.3, 7.3, 10.9 Hz, 1 H), 3.74−3.66 (m, 2 H), 3.49 (ddd, J = 5.6, 5.6, 5.6 Hz, 1 H), 3.42 (dd, J = 3.0, 4.6 Hz, 1 H), 3.40 (s, 3 H), 3.22 (dddd, J = 3.3, 6.3, 6.3, 6.3 Hz, 1 H), 1.92 (dd, J = 5.3, 6.9 Hz, 1 H), 1.79 (m, 1 H), 1.70−1.63 (m, 2 H), 1.58−1.41 (m, 4 H), 1.20 (s, 9 H), 1.15 (m, 1 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.92−0.88 (m, 6 H), 0.90 (s, 9 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.05 (s, 6 H); MS (FAB) m/z 599 $(M + Na)^+$; HRMS (FAB) calcd for $C_{30}H_{64}NaO_6Si_2$ [$(M + Na)^+$] 599.4140, found 599.4117.

Aldehyde 37. To a stirred solution of alcohol **36** (1.41 g, 2.45 mmol) in CH_2Cl_2 (20 mL) were added pyridine (3.0 mL, 37 mmol) and the Dess−Martin periodinane (1.71 g, 4.03 mmol) at room temperature. The mixture was stirred at room temperature for 0.7 h and was diluted with Et_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous $Na_2S_2O_3$ (10 mL). The resulting mixture was stirred at room temperature for 1 h, and extracted with Et_2O (100 mL, 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL) successively; dried (Na_2SO_4); and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 20:1 → 10: 1 → 3: 1) to give **37** (1.28 g, 91%) as a colorless oil: $[\alpha]^{27}_D$ −4.6 (*c* 0.968, $CHCl_3$); IR ($CHCl_3$) 2730, 1730 (sh), 1720, 1465, 1285, 1255, 1165, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.65 (d, J = 2.3 Hz, 1 H), 4.23 (ddd, J = 5.3, 5.3, 10.6 Hz, 1 H), 4.05 (ddd, J = 7.3, 7.3, 10.6 Hz, 1 H), 3.68 (ddd, J = 5.3, 5.3, 5.3 Hz, 1 H), 3.50 (ddd, J = 2.3, 5.0, 5.0 Hz, 1 H), 3.44 (s, 3 H), 3.42 (m, 1 H), 1.81−1.47 (m, 7 H), 1.19 (s, 9 H), 1.20 (m, 1 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.92−0.87 (m, 6 H), 0.90 (s, 9 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.04 (s, 6 H); MS (FAB) m/z 597 $(M + Na)^+$; HRMS (FAB) calcd for $C_{30}H_{62}NaO_6Si_2$ [$(M + Na)^+$] 597.3683, found 597.3654.

Methyl Ketone 38. To a suspension of copper(I) iodide (3.3 g, 17 mmol) in Et_2O (30 mL) cooled at −23 °C was added a 1.06 M solution of MeLi in Et_2O (28 mL, 30 mmol) dropwise. The mixture was stirred at −23 °C for 30 min and cooled to −78 °C, and then a solution of aldehyde **37** (1.60 g, 2.79 mmol) in Et_2O (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, and the reaction was quenched by addition of a 2:1 mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (45 mL). The resulting mixture was warmed to room temperature, stirred for 1 h, and extracted with Et_2O (100 mL, 20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 10:1 → 5: 1 → 3:1 → 1: 1) to give a diastereomeric mixture of secondary alcohols (1.60 g) as a colorless oil, which was employed in the next experiment without separation of the diastereomers. To a stirred solution of the diastereomeric mixture of secondary alcohols (1.60 g) in CH_2Cl_2 (25 mL) were added pyridine (3.0 mL, 37 mmol) and the Dess−Martin periodinane (1.89 g, 4.46 mmol) at room temperature. The mixture was stirred at room temperature for 0.7 h, and was diluted with Et_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous $Na_2S_2O_3$ (10 mL), and the stirring was continued for 1 h. The mixture was extracted with Et_2O (100 mL, 20 mL), and the combined extracts were washed with 5% aqueous $NaHCO_3$ (20 mL), H_2O (15 mL), and brine (15 mL) successively; dried (Na_2SO_4); and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 20:1 → 10: 1 → 5: 1) to give **38** (1.53 g, 93%) as a colorless oil: $[\alpha]^{27}_D$ −1.8 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1720, 1465, 1290, 1255, 1170, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.23 (ddd, J = 5.6, 5.6, 10.9 Hz, 1 H), 4.05 (ddd, J = 7.3, 7.3, 10.9 Hz, 1 H), 3.68 (ddd, J = 5.6, 5.6, 5.6 Hz, 1 H), 3.47 (dd, J = 4.6, 7.9 Hz, 1 H), 3.42 (dd, J = 3.0, 4.6 Hz, 1 H), 3.34 (s, 3 H), 2.15 (s, 3 H), 1.84−1.43 (m, 7 H), 1.19 (s, 9 H), 1.15 (m, 1 H), 0.97 (t, J = 7.9 Hz, 9 H), 0.91−0.87 (m, 6 H), 0.90 (s, 9 H), 0.61 (q, J = 7.9 Hz, 6 H), 0.05 (s, 6 H); MS (FAB) m/z 611 $(M + Na)^+$. Anal. Calcd for $C_{31}H_{64}O_6Si_2$: C, 63.21; H, 10.95. Found C, 63.11; H, 11.06.

Julia Coupling Reaction of Methyl Ketone 38 with Sulfone 8. To a stirred solution of sulfone **8** (125 mg, 0.237 mmol) in THF (2 mL) cooled at −78 °C was added a 1.56 M solution of BuLi in hexane (0.15 mL, 0.23 mmol) dropwise. The mixture was stirred at −78 °C for 30 min, and then a solution of methyl ketone **38** (70 mg, 0.12 mmol) in THF (1.5 mL) was added dropwise, and the resulting mixture was stirred at −78 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL), and the mixture was extracted with Et_2O (30 mL, 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−Et_2O 5:1 → 3: 1 → 2: 1 → 1: 1) to give a diastereomeric mixture of hydroxy sulfones (124 mg) as a colorless oil along with recovered **8** (48 mg, 38%). The hydroxy sulfones were employed in the next experiment without separation of the diastereomers. To a vigorously stirred solution of the diastereomeric mixture of hydroxy sulfones (124 mg) in MeOH (5 mL) cooled at 0 °C were added Na_2HPO_4 (357 mg, 2.51 mmol) and 6% sodium amalgam (510 mg, 1.33 mmol). The mixture was stirred at 0 °C for 2.3 h, diluted with saturated aqueous NH_4Cl (3 mL), then stirred at room temperature for 45 min, and extracted with Et_2O (30 mL, 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane−Et_2O 10:1 → 5: 1 → 3: 1 → 1: 1) to give a mixture of olefins (73 mg) and a diastereomeric mixture of tertiary alcohol **41** (27 mg, 25% from **38**) as a colorless oil, respectively. Further purification of olefins by medium-pressure liquid chromatography (Fuji Silysia, Micro Bead Silica Gel B-(30−70)μ, 8.2 g, hexane−EtOAc (45:1), 4 mL/min) afforded (*E*)-olefin **39** (t_R = 60 min, 50 mg, 44% from **38**) and (*Z*)-olefin **40** (t_R = 35 min, 22 mg, 19% from **38**) as a colorless oil, respectively. **39**: $[\alpha]^{26}_D$ +25.7 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) 1720, 1600, 1445, 1380, 1285, 1250, 1160, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.49−7.44 (m, 6 H), 7.33−7.19 (m, 9 H), 5.30 (dd, J = 7.3, 7.3 Hz, 1 H), 4.23 (ddd, J = 5.3, 5.3, 10.6 Hz, 1 H), 4.03 (ddd, J = 7.3, 7.3, 10.6 Hz, 1 H), 3.69 (ddd, J = 4.3, 4.3, 7.3 Hz, 1 H), 3.43 (s, 3 H), 3.43−3.30 (m, 3 H), 3.18−3.08 (m, 2 H), 3.11 (s, 3 H), 2.13 (ddd, J = 5.9, 7.3, 13.2 Hz, 1 H), 1.81−1.74 (m, 2 H), 1.67−1.17 (m, 9 H), 1.47 (s, 3 H), 1.19 (s, 9 H), 1.15 (m, 1 H), 0.95, (t, J = 7.9 Hz, 9 H), 0.89−0.85 (m, 9 H), 0.89 (s, 9 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.03 (s, 6 H); MS (FAB) m/z 981 $(M + Na)^+$; HRMS (FAB) calcd for $C_{58}H_{94}NaO_7Si_2$ [$(M + Na)^+$] 981.6437, found 981.6423. **40**: $[\alpha]^{20}_D$ +10.6 (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 1720, 1600, 1450, 1380, 1285, 1250, 1165, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.49−7.44 (m, 6 H), 7.33−7.19 (m, 9 H), 5.35 (dd, J = 6.6, 6.6 Hz, 1 H), 4.23 (ddd, J = 5.3, 5.3, 10.6 Hz, 1 H), 4.03 (ddd, J = 7.3, 7.3, 10.6 Hz, 1 H), 3.93 (dd, J = 7.6, 7.6 Hz, 1 H), 3.69 (ddd, J = 4.3, 4.3, 6.9 Hz, 1 H), 3.43 (s, 3 H), 3.43−3.31 (m, 2 H), 3.16−3.06 (m, 2 H), 3.13 (s, 3 H), 1.96 (dd, J = 6.6, 6.6 Hz, 2 H), 1.79 (m, 1 H), 1.68−1.33 (m, 10 H), 1.56 (s, 3 H), 1.19 (s, 9 H), 0.95, (t, J = 7.9 Hz, 9 H), 0.89−0.84 (m, 9 H), 0.88 (s, 9 H), 0.59 (q, J = 7.9 Hz, 6 H), 0.03 (s, 6 H); MS (FAB) m/z 981 $(M + Na)^+$; HRMS (FAB) calcd for $C_{58}H_{94}NaO_7Si_2$ [$(M + Na)^+$] 981.6437, found 981.6461. **41**: IR ($CHCl_3$) 3575(br), 1720, 1600, 1465, 1450, 1290, 1255, 1165 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.51−7.44 (m, 6 H), 7.34−7.18 (m, 9 H), 4.24 (ddd, J = 5.6, 5.6, 10.9 Hz, 1 H), 4.05 (ddd, J = 7.3, 7.3, 10.9 Hz, 1 H), 3.70 (m, 1 H), 3.47 (s, 3 H), 3.44 (m, 1 H), 3.42 (s, 3 H), 3.37 (m, 1 H), 3.11 (d, J = 4.5 Hz, 2 H), 2.88 (m, 1 H), 2.04 (br s, 1 H) [2.12], 1.88−1.00 (m, 15 H), 1.20 (s, 9 H), 1.13 (s, 3 H) [1.05], 0.96 (t, J = 7.6 Hz, 9 H), 0.93−0.85 (m, 9 H), 0.90 (s, 9 H), 0.60 (q, J = 7.6 Hz, 6 H), 0.05 (s, 6 H) (the minor counterparts of doubled signals in the ratio of 3:2 are in brackets); MS (FAB) m/z 999 $(M + Na)^+$; HRMS (FAB) calcd for $C_{58}H_{96}NaO_8Si_2$ [$(M + Na)^+$] 999.6542, found 999.6557.

Isomerization of (*Z*)-Olefin 40. A 0.02 M solution of benzenethiol in benzene (1.0 mL, 0.020 mmol) was added to (*Z*)-olefin **40** (21.2 mg, 0.0221 mmol) at room temperature. To the solution was added 2,2′-azobis(isobutyronitrile) (1.6 mg, 0.0097 mmol), and the resulting mixture was kept under reflux for 12.5 h. During the reaction, 2,2′-azobis(isobutyronitrile) (16.2 mg, 0.099 mmol) and a 0.078 M solution of benzenethiol

in benzene (1.25 mL, 0.098 mmol) were added in portions. The mixture was cooled to room temperature and concentrated. The residual oil was purified twice by column chromatography on silica gel [(2 g, hexane−EtOAc 47:1 → 23: 1 → 11: 1 → 7: 1) and (2 g, hexane−Et_2O 79:1 → 39:1 → 19:1 → 9: 1)] to give a mixture of olefins (**39**/**40** = 5/6) (18.9 mg, 90%) as a colorless oil.

Dehydration of Tertiary Alcohol 41. To a stirred solution of tertiary alcohol **41** (34.8 mg, 0.036 mmol) in pyridine (0.5 mL) cooled at 0 °C was added phosphoryl trichloride (0.1 mL, 1.07 mmol). The solution was stirred at 0 °C for 24 h and diluted with saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with Et_2O (3 × 5 mL). The combined extracts were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−Et_2O 12: 1 → 8:1) and medium-pressure liquid chromatography (Fuji Silysia, silica gel FL60D 6.4 g, hexane−EtOAc 40:1, 3 mL/min) to give (*E*)-olefin **39** (t_R = 50 min, 14.0 mg, 43%) and the mixture of isomeric olefins (10.6 mg, 32%).

Alcohol 42. To a stirred solution of (*E*)-olefin **39** (63 mg, 0.066 mmol) in THF (1.6 mL) was added a 4:1 mixture of acetic acid and H_2O (2 mL), and the mixture was stirred at room temperarture for 6.6 h. The mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) cooled at 0 °C, and the mixture was extracted with Et_2O (30 mL, 10 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−Et_2O 4:1 → 2: 1 → 1: 1) to give **42** (54 mg, 97%) as a colorless oil: $[\alpha]^{27}_D$ +19.9 (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 1720, 1600, 1450, 1380, 1285, 1255, 1165, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.48−7.44 (m, 6 H), 7.33−7.20 (m, 9 H), 5.30 (dd, *J* = 6.9, 6.9 Hz, 1 H), 4.33 (ddd, *J* = 5.0, 8.9, 10.9 Hz, 1 H), 4.20 (ddd, *J* = 5.0, 5.9, 10.9 Hz, 1 H), 3.80 (dd, *J* = 1.7, 5.0 Hz, 1 H), 3.54 (m, 1 H), 3.42 (s, 3 H), 3.40−3.30 (m, 2 H), 3.16−3.06 (m, 2 H), 3.11 (s, 3 H), 3.02 (br d, *J* = 3.6 Hz, 1 H), 2.14 (ddd, *J* = 5.6, 6.9, 12.9 Hz, 1 H), 1.92 (m, 1 H), 1.78 (m, 1 H), 1.67−1.17 (m, 10 H), 1.47 (s, 3 H), 1.20 (s, 9 H), 0.89 (s, 9 H), 0.88−0.86 (m, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m*/*z* 867 (M + Na)$^+$; HRMS (FAB) calcd for $C_{52}H_{80}NaO_7Si$ [(M + Na)$^+$] 867.5571, found 867.5597.

(Methylthio)methyl Ether 43 and Ketone 44. To a stirred solution of alcohol **42** (275 mg, 0.326 mmol) in DMSO (2 mL) was added a 1:5.6 mixture of acetic acid and acetic anhydride (1.65 mL) at room temperature. The mixture was stirred at room temperature for 2 h and at 40 °C for 5.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (35 mL) cooled at 0 °C, and the mixture was extracted with Et_2O (50 mL, 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−Et_2O 7:1 → 5: 1 → 3: 1) to give **43** (254 mg, 86%) and **44** (46 mg, 14%) as a colorless oil, respectively. **43**: $[\alpha]^{26}_D$ +40.7 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 1720, 1600, 1450, 1290, 1255, 1165, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.48−7.44 (m, 6 H), 7.34−7.20 (m, 9 H), 5.30 (dd, *J* = 6.9, 6.9 Hz, 1 H), 4.64 (d, *J* = 11.5 Hz, 1 H), 4.57 (d, *J* = 11.5 Hz, 1 H), 4.22−4.07 (m, 2 H), 3.63 (ddd, *J* = 3.0, 5.3, 8.3 Hz, 1 H), 3.49 (dd, *J* = 3.6, 3.6 Hz, 1 H), 3.42 (s, 3 H), 3.42−3.33 (m, 2 H), 3.16−3.06 (m, 2 H), 3.11 (s, 3 H), 2.15 (s, 3 H), 2.13 (ddd, *J* = 5.4, 6.9, 13.2 Hz, 1 H), 1.95 (m, 1 H), 1.86−1.67 (m, 3 H), 1.65−1.11 (m, 7 H), 1.48 (s, 3 H), 1.20 (s, 9 H), 1.04−0.85 (m, 10 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m*/*z* 927 (M + Na)$^+$; HRMS (FAB) calcd for $C_{54}H_{84}NaO_7SSi$ [(M + Na)$^+$] 927.5605, found 927.5610. **44**: $[\alpha]^{29}_D$ +19.3 (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) 1725, 1600, 1480, 1450, 1285, 1255, 1160, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.50−7.44 (m, 6 H), 7.34−7.19 (m, 9 H), 5.29 (dd, *J* = 6.9, 6.9 Hz, 1 H), 4.36−4.11 (m, 2 H), 3.85 (dd, *J* = 4.7, 4.7 Hz, 1 H), 3.42 (s, 3 H), 3.42−3.29 (m, 2 H), 3.16−3.08 (m, 2 H), 3.10 (s, 3 H), 2.81 (ddd, *J* = 6.3, 6.3, 17.0 Hz, 1 H), 2.73 (ddd, *J* = 6.3, 6.3, 17.0 Hz, 1 H), 2.67 (dq, *J* = 5.3, 6.9 Hz, 1 H), 2.12 (ddd, *J* = 5.9, 6.9, 13.2 Hz, 1 H), 1.76 (ddd, *J* = 6.9, 6.9, 13.2 Hz, 1 H), 1.64−1.31 (m, 8 H), 1.46 (s, 3 H), 1.16 (s, 9 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 0.87 (s, 9 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m*/*z* 865 (M + Na)$^+$; HRMS (FAB) calcd for $C_{52}H_{78}NaO_7Si$ [(M + Na)$^+$] 865.5414, found 865.5414.

Alcohol 45. To a stirred solution of (methylthio)methyl ether **43** (43.9 mg, 0.0486 mmol) in Et_2O (0.6 mL) was added formic acid (0.4 mL) at room temperature, and the mixture was stirred at room temperature for 15 min. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) cooled at 0 °C, and the resulting mixture was extracted with Et_2O (30 mL, 10 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−Et_2O 4:1 → 1: 1 → 1: 2) to give **45** (30.3 mg, 90%) as a colorless oil: $[\alpha]^{26}_D$ +34.5 (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3580, 3440 (br), 1720, 1465, 1285, 1255, 1165, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.33 (dd, *J* = 6.9, 6.9 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.20−4.08 (m, 2 H), 3.71 (ddd, *J* = 3.3, 6.6, 11.2 Hz, 1 H), 3.63 (ddd, *J* = 3.0, 5.3, 8.2 Hz, 1 H), 3.50 (dd, *J* = 3.6, 3.6 Hz, 1 H), 3.47−3.30 (m, 3 H), 3.41 (s, 3 H), 3.15 (s, 3 H), 2.17 (s, 3 H), 2.10 (m, 1 H), 1.99 (dd, *J* = 5.6, 5.6 Hz, 1 H), 1.96−1.32 (m, 11 H), 1.50 (s, 3 H), 1.21 (s, 9 H), 1.05−0.83 (m, 4 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m*/*z* 685 (M + Na)$^+$. Anal. Calcd for $C_{35}H_{70}O_7SSi$: C, 63.40; H, 10.64. Found C, 63.42; H, 10.69.

C5−C20 Segment 9. To a stirred solution of alcohol **45** (37.5 mg, 0.0565 mmol) in CH_2Cl_2 (0.8 mL) were added pyridine (0.04 mL, 0.5 mmol) and the Dess−Martin periodinane (31.5 mg, 0.0743 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was diluted with Et_2O (4 mL), saturated aqueous $NaHCO_3$ (3 mL), and saturated aqueous $Na_2S_2O_3$ (3 mL), stirred at room temperature for 30 min, and extracted with Et_2O (3 × 8 mL). The combined extracts were washed with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−Et_2O 5:1 → 3: 1 → 2: 1 → 1:1) to give **9** (30.0 mg, 80%) as a colorless oil: $[\alpha]^{19}_D$ +67.2 (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 2710, 1730 (sh), 1720, 1460, 1290, 1250, 1165, 830 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.3 Hz, 1 H), 5.33 (dd, *J* = 6.9, 6.9 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.22−4.07 (m, 2 H), 3.66−3.60 (m, 2 H), 3.50 (dd, *J* = 3.6, 3.6 Hz, 1 H), 3.43 (s, 3 H), 3.38 (dd, *J* = 6.9, 6.9 Hz, 1 H), 3.15 (s, 3 H), 2.17 (s, 3 H), 2.15 (m, 1 H), 1.98−1.32 (m, 11 H), 1.51 (s, 3 H), 1.20 (s, 9 H), 1.05−0.83 (m, 4 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m*/*z* 683 (M + Na)$^+$; HRMS (FAB) calcd for $C_{35}H_{68}NaO_7SSi$ (M + Na)$^+$ 683.4352, found 683.4351.

Hydroxy Imide 46. Experimental procedure was followed as described for compound **12.** **46**: $[\alpha]^{29}_D$ +8.56 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3690, 3500 (br), 1780, 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.44−7.27 (m, 10 H), 5.64 (d, *J* = 7.3 Hz, 1 H), 4.77 (dq, *J* = 6.6, 7.3 Hz, 1 H), 4.53 (s, 2 H), 4.19 (ddt, *J* = 2.3, 3.6, 9.2 Hz,1 H), 3.84 (dq, *J* = 3.6, 6.9 Hz, 1H), 3.70 (m, 2 H), 3.31 (d, *J* = 2.3 Hz, 1H), 1.96−1.71 (m, 2 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H); MS (FAB) *m*/*z* 420 (M + Na)$^+$, 398 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{28}NO_5$ [(M + H)$^+$] 398.1967, found 398.1979.

Amide 47. Experimental procedure was followed as described for compound **13**. **47**: $[\alpha]^{26}_D$ −11.1 (*c* 1.65, $CHCl_3$); IR ($CHCl_3$) 3660, 3470 (br), 1635, 1460, 1230, 1090, 995 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5 H), 4.52 (s, 2 H), 4.06 (m, 1 H), 3.91 (s, 1 H), 3.73−3.61 (m, 2 H), 3.66 (s, 3 H), 3.18 (s, 3 H), 2.92 (m, 1 H), 1.91−1.66 (m, 2 H), 1.20 (d, *J* = 6.9 Hz, 3 H); MS (FAB) *m*/*z* 304 (M + Na)$^+$, 282 (M + H)$^+$; HRMS (FAB) calcd for $C_{15}H_{23}NNaO_4$ [(M + Na)$^+$] 304.1525, found 304.1522.

Silyl Ether 48. Experimental procedure was followed as described for compound **23.** **48**: $[\alpha]^{26}_D$ −1.94 (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) 1650, 1460, 1240, 1110, 995, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5 H), 4.50 (d, *J* = 12.4 Hz, 1 H), 4.46 (d, *J* = 12.4 Hz, 1 H), 4.04 (dt, *J* = 7.9, 5.1 Hz, 1 H), 3.63−3.47 (m, 2 H), 3.59 (s, 3 H), 3.14 (s, 3 H), 2.97 (m, 1 H), 1.91−1.75 (m, 2 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 7.9

Hz, 9 H), 0.61 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 418 (M + Na)$^+$, 396 (M + H)$^+$; HRMS (FAB) calcd for $C_{21}H_{38}NO_4Si$ [(M + H)$^+$] 396.2570, found 396.2569.

Aldehyde 49. Experimental procedure was followed as described for compound **15**. **49**: $[\alpha]^{26}_D$ −53.8 (c 1.25, $CHCl_3$); IR ($CHCl_3$) 2720, 1725, 1455, 1105, 1010, 805 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.78 (d, J = 1.0 Hz, 1 H), 7.38−7.26 (m, 5 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.45 (d, J = 11.9 Hz, 1 H), 4.33 (ddd, J = 3.6, 5.6, 7.3 Hz, 1 H), 3.58−3.46 (m, 2 H), 2.47 (ddq, J = 1.0, 3.6, 6.9 Hz, 1 H), 1.91−1.70 (m, 2 H), 1.06 (d, J = 6.9 Hz, 3 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.58 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 359 (M + Na)$^+$; HRMS (FAB) calcd for $C_{19}H_{32}NaO_3Si$ [(M + Na)$^+$] 359.2018, found 359.2011.

Horner−Emmons Reaction of Aldehyde 49. Experimental procedure was followed as described for compound **16**. This reaction provided **50a** (96%) and **50b** (3%). **50a**: $[\alpha]^{26}_D$ −43.3 (c 1.03, $CHCl_3$); IR ($CHCl_3$) 1715, 1655, 1460, 1280, 1105, 1010, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5 H), 7.04 (dd, J = 6.9, 15.8 Hz, 1 H), 5.79 (dd, J = 1.3, 15.8 Hz, 1 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.45 (d, J = 11.9 Hz, 1 H), 4.18 (q, J = 7.3 Hz, 2 H), 3.85 (dt, J = 8.3, 4.3 Hz, 1 H), 3.52 (dd, J = 5.9, 6.9 Hz, 2 H), 2.45 (dddq, J = 1.3, 6.9, 8.3, 6.9 Hz, 1 H), 1.83−1.56 (m, 2 H), 1.28 (t, J = 7.3 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.59 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 407 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{39}O_4Si$ [(M + H)$^+$] 407.2617, found 407.2609. **50b**: $[\alpha]^{26}_D$ +44.8 (c 1.40, $CHCl_3$); IR ($CHCl_3$) 1710, 1640, 1190, 1095, 1015, 830 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5 H), 6.16 (dd, J = 10.2, 11.6 Hz, 1 H), 5.74 (dd, J = 1.0, 11.6 Hz, 1 H), 4.51 (d, J = 12.2 Hz, 1 H), 4.47 (d, J = 12.2 Hz, 1 H), 4.14 (q, J = 7.3 Hz, 2 H), 3.80 (dt, J = 6.9, 5.0 Hz, 1 H), 3.58 (dddq, J = 1.0, 6.9, 10.2, 6.9 Hz, 1 H), 3.55 (t, J = 6.6 Hz, 2 H), 1.92−1.69 (m, 2 H), 1.26 (t, J = 7.3 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 7.9 Hz, 9 H), 0.57 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 407 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{39}O_4Si$ [(M + H)$^+$] 407.2617, found 407.2641.

Allylic Alcohol 51. Experimental procedure was followed as described for compound **17.** **51**: $[\alpha]^{26}_D$ −38.4 (c 1.29, $CHCl_3$); IR ($CHCl_3$) 3610, 3440 (br), 1455, 1095, 1005, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5 H), 5.74 (dd, J = 6.6, 15.5 Hz, 1 H), 5.61 (dt, J = 15.5, 5.3 Hz, 1 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.45 (d, J = 11.9 Hz, 1 H), 4.09 (dd, J = 5.3, 5.9 Hz, 2 H), 3.75 (dt, J = 8.2, 4.0 Hz, 1 H), 3.53 (dd, J = 5.9, 7.3 Hz, 2 H), 2.31 (ddq, J = 6.6, 8.2, 6.9 Hz, 1 H), 1.82−1.59 (m, 2 H), 1.24 (t, J = 5.9 Hz, 1 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.59 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 365 (M + H$^+$); HRMS (FAB) calcd for $C_{21}H_{36}NaO_3Si$ [(M + Na)$^+$] 387.2331, found 387.2321.

Epoxide 52. Experimental procedure was followed as described for compound **18**. **52**: $[\alpha]^{23}_D$ −3.71 (c 0.921, $CHCl_3$); IR ($CHCl_3$) 3600, 3470 (br), 1455, 1090, 1005 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.46 (d, J = 11.9 Hz, 1 H), 4.02 (dt, J = 3.3, 6.3 Hz, 1 H), 3.91 (ddd, J = 2.3, 5.6, 12.5 Hz, 1 H), 3.61 (ddd, J = 4.3, 7.3, 12.5 Hz, 1 H), 3.49 (t, J = 6.6 Hz, 2 H), 2.98−2.92 (m, 2 H), 1.90−1.72 (m, 2 H), 1.74 (dd, J = 5.6, 7.3 Hz, 1 H), 1.48 (ddq, J = 3.3, 6.9, 6.9 Hz, 1 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.61 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 403 (M + Na)$^+$; HRMS (FAB) calcd for $C_{21}H_{36}NaO_4Si$ [(M + Na)$^+$] 403.2281, found 403.2282.

Oxirane Ring Opening of Epoxide 52. To a suspension of copper(I) iodide (2.56 g, 13.4 mmol) in Et_2O (15 mL) cooled at −23 °C was added a 1.09 M solution of MeLi in Et_2O (21 mL, 22.9 mmol) dropwise. After the solution was stirred at −23 °C for 30 min, a solution of epoxide **52** (461 mg, 1.23 mmol) in Et_2O (5.0 mL) was added. The reaction mixture was stirred at −23 °C for 2 h and kept at −20 °C for 12 h. After the mixture was warmed to 0 °C and stirred for 2 h, a 2:1 mixture of saturated aqueous NH_4Cl and 28% aqueous NH_3 (27 mL) was added. The resulting mixture was stirred at room temperature for 1.5 h, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer and the extracts were combined, washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 2:1 → 1:1 → 1:2) to give diol **53a** (360 mg, 75%) and diol **53b** (85 mg, 18%) as a colorless oil, respectively. **53a**: $[\alpha]^{25}_D$ −15.2 (c 1.13, $CHCl_3$); IR ($CHCl_3$) 3400 (br), 1450, 1090, 995 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5 H), 4.80 (d, J = 2.3 Hz, 1 H), 4.52 (d, J = 11.9 Hz, 1 H), 4.46 (d, J = 11.9 Hz, 1 H), 4.15 (ddd, J = 3.0, 5.0, 7.9 Hz, 1 H), 3.89 (ddd, J = 3.3, 3.3, 10.9 Hz, 1 H), 3.66 (ddd, J = 2.3, 4.3, 8.9 Hz, 1 H), 3.58 (ddd, J = 5.3, 6.6, 10.9 Hz, 1 H), 3.53 (t, J = 5.6, 2 H), 3.47 (dd, J = 3.3, 6.6 Hz, 1 H), 2.03 (m, 1 H), 1.91−1.70 (m, 3 H), 1.06 (d, J = 6.9 Hz, 3 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.84 (d, J = 7.3 Hz, 3 H), 0.64 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 419 (M + Na)$^+$, 397 (M + H)$^+$. Anal. Calcd for $C_{22}H_{40}O_4Si$: C, 66.62; H, 10.16. Found: C, 66.47; H, 10.41. **53b**: $[\alpha]^{25}_D$ +6.08 (c 1.35, $CHCl_3$); IR ($CHCl_3$) 3570, 3400 (br), 1450, 1075, 1000 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5 H), 4.49 (s, 2 H), 3.81 (dt, J = 5.9, 5.9 Hz, 1 H), 3.70−3.37 (m, 5 H), 3.29 (br s, 1 H), 2.19 (br s, 1 H), 1.97−1.62 (m, 4 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.75 (d, J = 6.9 Hz, 3 H), 0.61 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 419 (M + Na)$^+$, 397 (M + H)$^+$; HRMS (FAB) calcd for $C_{22}H_{41}O_4Si$ [(M + H)$^+$] 397.2774, found 397.2779.

Sulfide 54. Experimental procedure was followed as described for compound **22**. **54**: $[\alpha]^{23}_D$ −44.3 (c 1.24, $CHCl_3$); IR ($CHCl_3$) 3430 (br), 1585, 1455, 1110, 1090, 1000 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.37−7.12 (m, 10 H), 4.51 (d, J = 11.5 Hz, 1 H), 4.45 (d, J = 11.5 Hz, 1 H), 4.33 (d, J = 2.3 Hz, 1 H), 4.04 (m, 1 H), 3.53 (m, 1 H), 3.52 (t, J = 6.3 Hz, 2 H), 3.24 (dd, J = 3.3, 12.9 Hz, 1 H), 2.74 (dd, J = 9.6, 12.9 Hz, 1 H), 1.95 (m, 1 H), 1.80 (m, 1 H), 1.83 (td, J = 6.3, 6.3 Hz, 2 H), 1.13 (d, J = 6.9 Hz, 3 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.73 (d, J = 6.9 Hz, 3 H), 0.61 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 511 (M + Na)$^+$, 489 (M + H)$^+$; HRMS (FAB) calcd for $C_{28}H_{44}NaO_3SSi$ [(M + Na)$^+$] 511.2678, found 511.2690.

Silyl Ether 55. Experimental procedure was followed as described for compound **23**. **55**: $[\alpha]^{21}_D$ −11.7 (c 1.11, $CHCl_3$); IR ($CHCl_3$) 1580, 1455, 1080, 1005 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.12 (m, 10 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.45 (d, J = 11.9 Hz, 1 H), 3.94 (m, 1 H), 3.64 (dd, J = 2.6, 6.9 Hz, 1 H), 3.45 (t, J = 6.9 Hz, 2 H), 3.17 (dd, J = 3.0, 12.5 Hz, 1 H), 2.64 (dd, J = 10.2, 12.5 Hz, 1 H), 1.96−1.73 (m, 3 H), 1.61 (ddq, J = 4.0, 6.9, 6.9 Hz, 1 H), 1.09 (d, J = 6.9 Hz, 3 H), 0.94 (t, J = 7.6 Hz, 9 H), 0.93 (t, J = 7.6 Hz, 9 H), 0.77 (d, J = 6.9 Hz, 3 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.57 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 603 (M + H)$^+$; HRMS (FAB) calcd for $C_{34}H_{59}O_3SSi_2$ [(M + H)$^+$] 603.3723, found 603.3717.

C21−C27 Segment 5. Experimental procedure was followed as described for compound **4**. **5**: $[\alpha]^{21}_D$ +4.56 (c 1.10, $CHCl_3$); IR ($CHCl_3$) 1580, 1455, 1300, 1140, 1080, 1005 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.91−7.87 (m, 2 H), 7.66−7.50 (m, 3 H), 7.42−7.23 (m, 5 H), 4.50 (d, J = 11.9 Hz, 1 H), 4.43 (d, J = 11.9 Hz, 1 H), 3.91 (dt, J = 3.6, 6.6 Hz, 1 H), 3.56 (dd, J = 1.3, 6.9 Hz, 1 H), 3.40 (t, J = 6.6 Hz, 2 H), 3.27 (dd, J = 1.0, 14.5 Hz, 1 H), 2.85 (dd, J = 10.2, 14.5 Hz, 1 H), 2.23 (m, 1 H), 1.79 (dt, J = 6.6, 6.6 Hz, 2 H), 1.42 (ddq, J = 3.6, 6.9, 6.9 Hz, 1 H), 1.16 (d, J = 6.9 Hz, 3 H), 0.93 (t, J = 7.6 Hz, 9 H), 0.90 (t, J = 7.6 Hz, 9 H), 0.57 (d, J = 6.9 Hz, 3 H), 0.60 (q, J = 7.9 Hz, 6 H), 0.57 (q, J = 7.9 Hz, 6 H); MS (FAB) m/z 657 (M + Na)$^+$, 635 (M + H)$^+$. Anal. Calcd for $C_{34}H_{58}O_5SSi_2$: C, 64.30; H, 9.21. Found: C, 64.32; H, 9.25.

Horner−Emmons Reaction of Aldehyde 59. Experimental procedure was followed as described for compound **16**. This reaction provided **60a** (90%) and **60b** (7%). **60a**: $[\alpha]^{24}_D$ +14.1 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1705, 1650, 1365, 1255, 1090, 1030 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5 H), 6.98 (dd, J = 7.6, 15.8 Hz, 1 H), 5.81 (dd, J = 1.3, 15.8 Hz, 1 H), 4.52 (d, J = 11.9 Hz, 1 H), 4.47 (d, J = 11.9 Hz, 1 H), 4.18 (q, J = 7.3 Hz, 2 H), 3.82 (ddd, J = 4.6, 5.6, 5.6 Hz, 1 H), 3.42 (dd, J = 5.6, 9.6 Hz, 1 H), 3.36 (dd, J = 5.6, 9.6 Hz, 1 H), 2.60 (dddq, J = 1.3, 4.6, 7.6, 6.6 Hz, 1 H), 1.28 (t, J = 7.3 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H); MS (FAB) m/z 415 (M + Na)$^+$; HRMS (FAB) calcd for $C_{22}H_{36}NaO_4Si$ [(M + Na)$^+$] 415.2280, found 415.2296. **60b**: $[\alpha]^{24}_D$ −54.9 (c 1.02, $CHCl_3$); IR ($CHCl_3$) 1710, 1640, 1450, 1415, 1250, 1190, 1095, 1030 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5 H), 6.16 (dd, J = 10.2, 11.5 Hz, 1 H), 5.72 (dd, J = 0.8, 11.5 Hz, 1 H), 4.53 (d, J = 12.2 Hz, 1 H), 4.46 (d, J = 12.2 Hz, 1 H), 4.16

(q, J = 7.3 Hz, 2 H), 3.81 (ddd, J = 4.9, 4.9, 6.3 Hz, 1 H), 3.67 (dddq, J = 0.8, 4.9, 10.2, 6.6 Hz, 1 H), 3.45 (dd, J = 4.9, 9.9 Hz, 1 H), 3.39 (dd, J = 6.3, 9.9 Hz, 1 H), 1.27 (t, J = 7.3 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H); MS (FAB) m/z 415 $(M + Na)^+$; HRMS (FAB) calcd for $C_{22}H_{36}NaO_4Si$ [$(M + Na)^+$] 415.2280, found 415.2274.

Allylic Alcohol 61. Experimental procedure was followed as described for compound **17**. **61**: $[\alpha]^{24}_D$ +9.7 (c 1.10, $CHCl_3$); IR ($CHCl_3$) 3605, 3500 (br), 1450, 1360, 1250, 1090, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5 H), 5.70 (dd, J = 5.6, 15.8 Hz, 1 H), 5.61 (dt, J = 15.8, 4.9 Hz, 1 H), 4.50 (s, 2 H), 4.08 (dd, J = 4.9, 5.6 Hz, 2 H), 3.72 (ddd, J = 5.6, 5.6, 5.6 Hz, 1 H), 3.44 (dd, J = 5.6, 9.6 Hz, 1 H), 3.36 (dd, J = 5.6, 9.6 Hz, 1 H), 2.43 (ddq, J = 5.6, 5.6, 6.9 Hz, 1 H), 1.58 (t, J = 5.6 Hz, 1 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H); MS (FAB) m/z 373 $(M + Na)^+$; HRMS (FAB) calcd for $C_{20}H_{34}NaO_3Si$ [$(M + Na)^+$] 373.2175, found 373.2168.

Epoxide 62. Experimental procedure was followed as described for compound **18**. **62**: $[\alpha]^{23}_D$ −26.1 (c 1.09, $CHCl_3$); IR ($CHCl_3$) 3600, 3500 (br), 1475, 1450, 1250, 1360, 1090 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5 H), 4.54 (d, J = 12.2 Hz, 1 H), 4.46 (d, J = 12.2 Hz, 1 H), 4.05 (dt, J = 3.0, 5.9 Hz, 1 H), 3.90 (ddd, J = 2.3, 5.3, 12.5 Hz, 1 H), 3.61 (ddd, J = 4.3, 7.6, 12.5 Hz, 1 H), 3.42 (d, J = 5.9 Hz, 2 H), 2.98−2.92 (m, 2 H), 1.65 (dd, J = 5.3, 7.6 Hz, 1 H), 1.60 (ddq, J = 3.0, 6.9, 6.9 Hz, 1 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.06 (s, 3 H); MS (FAB) m/z 389 $(M + Na)^+$; HRMS (FAB) calcd for $C_{20}H_{34}NaO_4Si$ [$(M + Na)^+$] 389.2124, found 382.2132.

Oxirane Ring Opening of Epoxide 62. Experimental procedure was followed as described for compound **53a**. This reaction provided **63a** (93%) and **63b** (7%). **63a**: mp 32−34 °C (benzene); $[\alpha]^{24}_D$ −4.2 (c 1.30, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 1470, 1450, 1250, 1100, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5 H), 4.55 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.38 (d, J = 4.0 Hz, 1 H), 4.19 (dt, J = 2.6, 5.6 Hz, 1 H), 3.85 (ddd, J = 3.3, 5.6, 10.9 Hz, 1 H), 3.61 (ddd, J = 5.6, 5.6, 10.9 Hz, 1 H), 3.57 (m, 1 H), 3.51 (d, J = 5.6 Hz, 2 H), 3.37 (dd, J = 5.6, 5.6 Hz, 1 H), 2.05 (ddq, J = 2.6, 6.9, 6.9 Hz, 1 H), 1.79 (m, 1 H), 1.04 (d, J = 7.3 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); MS (EI) m/z (relative intensity) 382 (M^+, 13), 325 (100), 215 (55), 173 (70), 145 (82). Anal. Calcd for $C_{21}H_{38}O_4Si$: C, 65.92; H, 10.01. Found: C, 65.78; H, 9.73. **63b**: mp 72−73 °C (hexane); $[\alpha]^{24}_D$ −10.0 (c 0.974, $CHCl_3$); IR ($CHCl_3$) 3570, 3420 (br), 1475, 1450, 1390, 1360, 1250, 1075 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5 H), 4.51 (s, 2 H), 3.79 (dt, J = 5.0, 5.0 Hz, 1 H), 3.71 (m, 1 H), 3.49 (d, J = 5.0 Hz, 2 H), 3.57−3.40 (m, 2 H), 2.79 (d, J = 4.0 Hz, 1 H), 2.13 (dd, J = 4.6, 6.3 Hz, 1 H), 2.01 (m, 1 H), 1.68 (m, 1 H), 0.89 (s, 9 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); MS (FAB) m/z 383 $(M + H)^+$; HRMS (FAB) calcd for $C_{21}H_{39}O_4Si$ [$(M + H)^+$] 383.2618, found 383.2626.

Tosylate 64. To a stirred solution of diol **63a** (841 mg, 2.20 mmol) in pyridine (6.0 mL) cooled at 0 °C was added *p*-toluenesulfonyl chloride (1.34 g, 7.15 mmol). The mixture was stirred at 0 °C for 5 h, and the reaction was quenched by addition of H_2O (5 mL). The resulting mixture was stirred at room temperature for 1 h, diluted with H_2O (5 mL), and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane−Et_2O 10:1 → 5:1 → 2:1) to give **64** (1.18 g, 100%) as a colorless oil: $[\alpha]_D^{24}$ +24.2 (c 1.10, $CHCl_3$); IR ($CHCl_3$) 3420 (br), 1595, 1470, 1355, 1250, 1090, 955 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.81−7.75 (m, 2 H), 7.38−7.27 (m, 7 H), 4.53 (d, J = 12.0 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 4.27 (dd, J = 4.9, 9.7 Hz, 1 H), 4.06 (dt, J = 2.8, 6.3 Hz, 1 H), 3.89 (dd, J = 7.6, 9.7 Hz, 1 H), 3.84 (d, J = 3.9 Hz, 1 H), 3.49 (d, J = 6.3 Hz, 2 H), 3.40 (ddd, J = 3.9, 3.9, 8.2 Hz, 1 H), 2.44 (s, 3 H), 2.00 (m, 1 H), 1.92 (m, 1 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); MS (FAB) m/z 559 $(M + Na)^+$; HRMS (FAB) calcd for $C_{28}H_{44}NaO_4SSi$ [$(M + Na)^+$] 559.2525, found 559.2547.

Nitrile 65a. To a stirred solution of tosylate **64** (1.29 g, 2.40 mmol) in DMSO (15 mL) was added NaCN (0.53 g, 10.0 mmol) at room temperature. The reaction mixture was warmed to 50 °C and stirred for 2.5 h. After cooling, H_2O (20 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined extracts were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane−Et_2O 10:1 → 7:1 → 5:1 → 3:1 → 2:1) to give **65a** (1.05 g, 91%) and oxetane **65b** (76 mg, 7%) as a colorless oil, respectively. **65a**: $[\alpha]^{24}_D$ +12.2 (c 1.03, $CHCl_3$); IR ($CHCl_3$) 3420 (br), 2230, 1455, 1355, 1250, 1100, 1055 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1 H), 4.09 (dt, J = 3.0, 5.9 Hz, 1 H), 4.03 (d, J = 3.9 Hz, 1 H), 3.53 (d, J = 5.9 Hz, 2 H), 3.42 (ddd, J = 3.9, 3.9, 7.9 Hz, 1 H), 2.50 (dd, J = 4.6, 16.8 Hz, 1 H), 2.32 (dd, J = 8.9, 16.8 Hz, 1 H), 2.01 (m, 1 H), 1.90 (m, 1 H), 1.15 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); MS (FAB) m/z 414 $(M + Na)^+$; HRMS (FAB) calcd for $C_{22}H_{37}NNaO_3Si$ [$(M + Na)^+$] 414.2440, found 414.2431. **65b**: $[\alpha]^{24}_D$ −25.5 (c 2.23, $CHCl_3$); IR ($CHCl_3$) 1450, 1355, 1250, 1125, 1060, 1015, 955 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5 H), 4.56 (d, J = 12.0 Hz, 1 H), 4.54 (dd, J = 5.9, 7.9 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 4.18 (dd, J = 5.9, 6.6 Hz, 1 H), 4.14 (dd, J = 6.3, 9.9 Hz, 1 H), 4.05 (dt, J = 2.0, 6.6 Hz, 1 H), 3.38 (d, J = 6.6 Hz, 2 H), 2.65 (m, 1 H), 2.03 (m, 1 H), 1.20 (d, J = 6.6 Hz, 3 H), 0.87 (s, 9 H), 0.70 (d, J = 6.6 Hz, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H); MS (FAB) m/z 387 $(M + Na)^+$, 365 $(M + H)^+$; HRMS (FAB) calcd for $C_{21}H_{36}NaO_3Si$ [$(M + Na)^+$] 387.2331, found 387.2336.

Cyclic Acetals 66a,b and 67. To a stirred solution of nitrile **65a** (464 mg, 1.19 mmol) in CH_2Cl_2 (15 mL) cooled at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (5.5 mL, 5.5 mmol). The solution was stirred at −78 °C for 1 h, and the reaction was quenched by addition of MeOH (1.0 mL). After the mixture was warmed to room temperature, 0.5 M aqueous sodium potassium tartrate (12 mL) was added. The resulting mixture was stirred at room temperature for 2 h, and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The organic layer and the extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was dissolved in benzene (25 mL), and silica gel (12 g) was added. Benzene was completely evaporated from the mixture. The mixture of the crude products adsorbed on silica gel was kept at room temperature for 14.5 h and washed with MeOH. The eluate was concentrated to give a crude hemiacetal (493 mg) as a colorless oil. To a stirred solution of the crude hemiacetal (493 mg) in MeOH (12 mL) was added camphorsulfonic acid (138 mg, 0.59 mmol), and this mixture was kept under reflux for 1.6 h. After cooling, triethylamine (0.5 mL) was added, and the resulting mixture was concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 5:1 → 4:1 → 3:1 → 1:1) to give **66a** (134 mg, 38%) and a fraction containing **66b** and **67** (196 mg) as a colorless oil, respectively. To a stirred solution of the fraction containing **66b** and **67** (196 mg) in MeOH (5.0 mL) was added camphorsulfonic acid (81 mg, 0.34 mmol) at room temperature. After the mixture was stirred at room temperature for 14 h, triethylamine (0.3 mL) was added, and the resulting mixture was concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 5:1 → 4:1 → 3:1 → 1:1) to give **66a** (85 mg, 24%) and a fraction containing **66b** and **67** (106 mg) as colorless oil, respectively. Further, from the fraction containing **66b** and **67** (106 mg), **66a** (43 mg, 12%), **66b** (43 mg 12%), and **67** (7 mg, 2%) were obtained by repeating the procedure described above. **66a**: $[\alpha]^{22}_D$ +44.0 (c 1.11, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1455, 1385, 1230, 1100, 1030, 990 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5 H), 4.91 (d, J = 5.0 Hz, 1 H), 4.61 (d, J = 11.9 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H), 4.22 (m, 1 H), 3.59 (dd, J = 7.3, 7.3 Hz, 1 H), 3.54 (dd, J = 7.3, 9.6 Hz, 1 H), 3.49 (dd, J = 4.6, 9.6 Hz, 1 H), 3.31 (s, 3 H), 2.81 (d, J = 3.6 Hz, 1 H), 2.26 (dddq, J = 7.3, 7.3, 10.6, 6.6 Hz, 1 H), 2.08 (dd, J = 7.3, 12.9 Hz, 1 H), 1.74 (ddq, J = 2.0, 7.3, 7.3 Hz, 1 H), 1.63 (ddd, J = 5.0, 10.6, 12.9 Hz, 1 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 7.3 Hz, 3 H); MS (FAB) m/z 317 $(M + Na)^+$; HRMS (FAB) calcd for $C_{17}H_{26}NaO_4$ [$(M + Na)^+$]

317.1729, found 317.1737. **66b**: $[\alpha]^{22}_D$ −88.9 (*c* 0.713, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1455, 1385, 1360, 1235, 1100, 1025, 995 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5 H), 4.96 (dd, *J* = 2.3, 5.6 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.08 (m, 1 H), 3.61 (dd, *J* = 5.6, 7.9 Hz, 1 H), 3.54 (dd, *J* = 6.9, 9.6 Hz, 1 H), 3.49 (dd, *J* = 5.0, 9.6 Hz, 1 H), 3.30 (s, 3 H), 3.07 (d, *J* = 3.6 Hz, 1 H), 2.29 (ddd, *J* = 5.6, 9.9, 13.2 Hz, 1 H), 2.04 (m, 1 H), 1.80 (m, 1 H), 1.51 (ddd, *J* = 2.3, 5.9, 13.2 Hz, 1 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H); MS (FAB) *m*/*z* 317 $(M + Na)^+$; HRMS (FAB) calcd for $C_{17}H_{26}NaO_4$ [$(M + Na)^+$] 317.1729, found 317.1721. **67**: $[\alpha]^{23}_D$ −35.4 (*c* 0.819, $CHCl_3$); IR ($CHCl_3$) 1455, 1365, 1270, 1130, 1085, 1040, 960 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5 H), 5.46 (d, *J* = 4.6 Hz, 1 H), 4.62 (d, *J* = 12.2 Hz, 1 H), 4.48 (d, *J* = 12.2 Hz, 1 H), 4.11 (ddd, *J* = 3.6, 4.6, 6.9 Hz, 1 H), 3.78 (d, *J* = 1.7 Hz, 1 H), 3.47 (dd, *J* = 6.9, 9.6 Hz, 1 H), 3.36 (dd, *J* = 4.6, 9.6 Hz, 1 H), 2.37 (dd, *J* = 8.6, 13.5 Hz, 1 H), 2.22 (m, 1 H), 1.57−1.42 (m, 2 H), 1.09 (d, *J* = 6.3 Hz, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H); MS (FAB) *m*/*z* 285 $(M + Na)^+$; HRMS (FAB) calcd for $C_{16}H_{22}NaO_3$ [$(M + Na)^+$] 285.1466, found 285.1447.

Diol 68. Sodium (291 mg, 12.7 mmol) was added to a stirred solution of acetal **66a** (357 mg, 1.21 mmol) in THF (10 mL) and liquid NH_3 (10 mL) cooled at −78 °C. After the mixture was stirred at −78 °C for 30 min, saturated aqueous NH_4Cl (5 mL) was added. The mixture was allowed to warm to room temperature, stirred for 1.5 h, and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residual solid was purified by column chromatography on silica gel (6 g, hexane−EtOAc 1:1 → EtOAc) to give **68** (247 mg, 100%) as colorless crystals: mp 46−47 °C (hexane); $[\alpha]_D^{20}$ +83.0 (*c* 0.888, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1455, 1385, 1230, 1100, 1025, 990 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.93 (d, *J* = 4.9 Hz, 1 H), 3.94 (m, 1 H), 3.70 (ddd, *J* = 3.6, 7.9, 11.2 Hz, 1 H), 3.59 (ddd, *J* = 3.6, 8.2, 11.2 Hz, 1 H), 3.56 (dd, *J* = 7.6, 7.6 Hz, 1 H), 3.35 (s, 3 H), 3.26 (d, *J* = 5.3 Hz, 1 H), 2.27 (dd, *J* = 3.6, 8.2 Hz, 1 H), 2.28 (m, 1 H), 2.10 (dd, *J* = 6.9, 13.2 Hz, 1 H), 1.80 (ddq, *J* = 3.0, 7.6, 7.3 Hz, 1 H), 1.63 (ddd, *J* = 5.3, 10.6, 13.2 Hz, 1 H), 1.07 (d, *J* = 6.3 Hz, 3 H), 0.99 (d, *J* = 7.3 Hz, 3 H); MS (EI) *m*/*z* (relative intensity) 173 [$(M - OCH_3)^+$, 100], 155 (96), 137 (23), 115 (40). Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.93; H, 9.54.

Silyl Ether 69. To a stirred solution of diol **68** (152 mg, 0.744 mmol) in DMF (3.0 mL) cooled at 0 °C were added *tert*-butyldiphenylsilyl chloride (0.30 mL, 1.15 mmol) and imidazole (160 mg, 2.35 mmol). The mixture was stirred at 0 °C for 1.3 h, and the reaction was quenched by addition of ice (1 g) and H_2O (6 mL). The resulting mixture was warmed to room temperature, stirred for 40 min, and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual solid was purified by column chromatography on silica gel (20 g, hexane−Et_2O 7:1 → 4:1 → 2:1) to give **69** (329 mg 100%) as colorless crystals: mp 97−98 °C (pentane); $[\alpha]^{19}_D$ +28.4 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1590, 1465, 1430, 1365, 1230, 1115 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4 H), 7.47−7.33 (m, 6 H), 4.89 (d, *J* = 5.0 Hz, 1 H), 4.14 (dddd, *J* = 2.0, 3.3, 5.6, 7.3 Hz, 1 H), 3.71 (dd, *J* = 7.3, 10.1 Hz, 1 H), 3.62 (dd, *J* = 7.1, 7.1 Hz, 1 H), 3.61 (dd, *J* = 5.6, 10.1 Hz, 1 H), 3.25 (s, 3 H), 2.77 (d, *J* = 3.3 Hz, 1 H), 2.24 (dddq, *J* = 7.1, 7.1, 10.7, 6.8 Hz, 1 H), 2.07 (dd, *J* = 7.1, 12.7 Hz, 1 H), 1.75 (ddq, *J* = 2.0, 7.1, 7.1 Hz, 1 H), 1.63 (ddd, *J* = 5.0, 10.7, 12.7 Hz, 1 H), 1.09 (s, 9 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 7.1 Hz, 3 H); MS (EI) *m*/*z* (relative intensity) 410 [$(M - OCH_3)^+$, 5], 393 (5), 353 (55), 255 (55). Anal. Calcd for $C_{26}H_{38}O_4Si$: C, 70.55; H, 8.65. Found: C, 70.47; H, 8.65.

Alcohol 72. To a stirred solution of silyl ether **69** (1.92 g, 4.34 mmol) in DMF (10 mL) cooled at 0 °C were added benzyl bromide (1.65 mL, 13.9 mmol) and NaH (348 mg of 60% dispersion in mineral oil, 14.5 mmol), successively. The mixture was stirred at 0 °C for 15 min and at room temperature for 1 h. The reaction was quenched by addition of ice (3 g) and saturated aqueous NH_4Cl (50 mL). The resulting mixture was stirred at room temperature for 20 min and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−Et_2O 50:1 → 30:1 → 20:1 → 10:1 → 4:1) to give a 4:1 mixture of benzyl ether **70** and silyl ether **71** (2.18 g), which was dissolved in THF (15 mL). To this solution was added a 1.0 M solution of Bu_4NF in THF (7.0 mL, 7.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 13 h, and then saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−Et_2O 20:1 → 10:1 → 2:1 → 1:1 → 1:2) to give **72** (943 mg, 74% from **69**) and silyl ether **71** (368 mg 16% from **69**) as a colorless oil, respectively. **72**: $[\alpha]^{21}_D$ +45.1 (*c* 0.899, $CHCl_3$); IR ($CHCl_3$) 3560, 3450 (br), 1550, 1495, 1450, 1380, 1350, 1095, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.41−7.24 (m, 5 H), 4.93 (d, *J* = 4.6 Hz, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.67 (d, *J* = 11.5 Hz, 1 H), 3.91 (ddd, *J* = 3.3, 5.0, 6.6 Hz, 1 H), 3.72 (ddd, *J* = 5.0, 6.6, 10.2 Hz, 1 H), 3.61 (ddd, *J* = 5.0, 7.6, 10.2 Hz, 1 H), 3.56 (dd, *J* = 6.6, 9.6 Hz, 1 H), 3.32 (s, 3 H), 2.26 (m, 1 H), 2.11 (dd, *J* = 7.3, 12.5 Hz, 1 H), 2.05 (dd, *J* = 5.0, 7.6 Hz, 1 H), 1.73 (m, 1 H), 1.65 (ddd, *J* = 4.6, 9.9, 12.5 Hz, 1 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H); MS (EI) *m*/*z* (relative intensity) 263 [$(M - OCH_3)^+$, 12], 194 (34), 141 (53), 91 (100). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.28; H, 9.04. **71**: $[\alpha]^{21}_D$ −11.1 (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 1595, 1450, 1425, 1360, 1110, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.76−7.67 (m, 4 H), 7.44−7.28 (m, 6 H), 7.22−7.15 (m, 3 H), 6.99−6.93 (m, 2 H), 4.84 (d, *J* = 4.6 Hz, 1 H), 4.52 (ddd, *J* = 1.6, 5.9, 6.9 Hz, 1 H), 4.04 (d, *J* = 11.9 Hz, 1 H), 3.98 (d, *J* = 11.9 Hz, 1 H), 3.66 (dd, *J* = 6.6, 10.2 Hz, 1 H), 3.33 (dd, *J* = 6.9, 9.9 Hz, 1 H), 3.24 (dd, *J* = 5.9, 9.9 Hz, 1 H), 3.11 (s, 3 H), 2.22 (m, 1 H), 2.06 (dd, *J* = 7.6, 12.5 Hz, 1 H), 1.76 (m, 1 H), 1.60 (ddd, *J* = 4.6, 9.6, 12.5 Hz, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.02 (s, 9 H), 0.97 (d, *J* = 6.9 Hz, 3 H); MS (FAB) *m*/*z* 555 $(M + Na)^+$; HRMS (FAB) calcd for $C_{33}H_{44}NaO_4Si$ [$(M + Na)^+$] 555.2907, found 555.2925.

C28−C34 Segment 6. To a stirred solution of oxalyl chloride (0.03 mL, 0.34 mmol) in CH_2Cl_2 (3.0 mL) cooled at −78 °C was added a solution of DMSO (0.03 mL, 0.45 mmol) in CH_2Cl_2 (0.17 mL) dropwise. The resulting solution was stirred at −78 °C for 5 min, and a solution of alcohol **72** (66.7 mg, 0.227 mmol) in CH_2Cl_2 (0.5 mL, 2 × 0.5 mL rinse) was added dropwise. The mixture was stirred at −78 °C for 18 min and triethylamine (0.16 mL, 1.13 mmol) was added. The resulting mixture was warmed to 0 °C and stirred for 25 min. H_2O (3 mL) was added, and the solution was stirred at room temperature for 20 min. The mixture was extracted with a 4:1 mixture of benzene−Et_2O (3 × 10 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, hexane−Et_2O 5:1 → 3:1) to give **6** (66.6 mg, 100%) as a colorless oil: $[\alpha]^{19}_D$ +26.3 (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 2700, 1725, 1600, 1455, 1380, 1095, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.0 Hz, 1 H), 7.42−7.26 (m, 5 H), 4.92 (d, *J* = 4.9 Hz, 1 H), 4.73 (d, *J* = 11.2 Hz, 1 H), 4.61 (d, *J* = 11.2 Hz, 1 H), 4.23 (dd, *J* = 1.0, 2.9 Hz, 1 H), 3.60 (dd, *J* = 6.3, 9.8 Hz, 1 H), 3.31 (s, 3 H), 2.28 (m, 1 H), 2.12 (dd, *J* = 7.3, 12.7 Hz, 1 H), 2.10 (m, 1 H), 1.66 (ddd, *J* = 4.9, 9.8, 12.7 Hz, 1 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 0.92 (d, *J* = 7.3 Hz, 3 H); MS (FAB) *m*/*z* 315 $(M + Na)^+$; HRMS (FAB) calcd for $C_{17}H_{24}NaO_4$ [$(M + Na)^+$] 315.1572, found 315.1593.

Olefin 73a. To a stirred solution of the C21−C27 segment **5** (1.33 g, 2.09 mmol) in THF (9.0 mL) cooled at −78 °C was added a 1.52 M solution of BuLi in hexane (1.35 mL, 2.05 mmol) dropwise. The resulting yellow solution was stirred at −78 °C for 30 min, and a solution of the C28−C34 segment **6** (314 mg, 1.07 mmol) in THF (1.5 mL, 2 × 1.0 mL rinse) was added. The mixture was stirred at −78 °C for 3 h, and the reaction was quenched by addition of saturated aqueous NH_4Cl (12 mL). The mixture was stirred at room temperature for 10 min and extracted with Et_2O (3 × 25 mL). The combined extracts were washed with brine (7 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chro-

matography on silica gel (15 g, hexane−Et_2O 20:1 → 10:1 → 5:1 → 3:1 → 1:1) to give a diastereomeric mixture of hydroxy sulfones (958 mg) as a colorless oil along with recovered **5** (623 mg, 47%). These hydroxy sulfones were used in the next experiment without separation of the diastereomers. To a vigorously stirred solution of hydroxy sulfones (958 mg 1.03 mmol) in MeOH (35 mL) cooled at 0 °C were added Na_2HPO_4 (2.48 g, 17.5 mmol) and 5% sodium amalgam (5.28 g, 11.5 mmol). The mixture was stirred at 0 °C for 2 h, and then saturated aqueous NH_4Cl (50 mL) was added. The resulting mixture was warmed to room temperature, stirred for 70 min, and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (7 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (40 g, hexane−Et_2O 20:1 → 10:1 → 5:1 → 3:1) to give **73a** (673 mg, 82% from **6**) and two diastereomers of alcohols (more polar isomer **73b**, 53.3 mg, 7%; less polar isomer **73c**, 22.3 mg, 3% from **6**) as a colorless oil, respectively. **73a:** $[\alpha]^{19}_D$ +18.0 (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 1450, 1375, 1360, 1235, 1090, 950 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37−7.19 (m, 10 H), 5.83 (dd, *J* = 8.2, 15.8 Hz, 1 H), 5.47 (dd, *J* = 7.6, 15.8 Hz, 1 H), 4.90 (d, *J* = 4.9 Hz, 1 H), 4.54 (d, *J* = 11.9 Hz, 1 H), 4.46 (d, *J* = 12.2 Hz, 1 H), 4.41 (d, *J* = 12.2 Hz, 1 H), 4.33 (d, *J* = 11.9 Hz, 1 H), 4.21 (dd, *J* = 2.3, 7.6 Hz, 1 H), 3.99 (dt, *J* = 4.0, 6.9 Hz, 1 H), 3.67 (dd, *J* = 6.6, 8.9 Hz, 1 H), 3.64 (dd, *J* = 1.7, 8.9 Hz, 1 H), 3.42 (t, *J* = 6.9 Hz, 2 H), 3.29 (s, 3 H), 2.43 (m, 1 H), 2.23 (m, 1 H), 2.08 (dd, *J* = 7.6, 12.5 Hz, 1 H), 1.84 (dt, *J* = 6.9, 6.9 Hz, 2 H), 1.70−1.50 (m, 3 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.94−0.90 (m, 3 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.93 (t, *J* = 8.3 Hz, 9 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.61 (q, *J* = 7.9 Hz, 6 H), 0.58 (q, *J* = 8.3 Hz, 6 H); MS (FAB) *m*/*z* 791 $(M + Na)^+$; HRMS (FAB) calcd for $C_{45}H_{76}NaO_6Si_2$ [$(M+ Na)^+$] 791.5079, found 791.5073. **73b**: $[\alpha]^{18}_D$ +26 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3400 (br), 1455, 1360, 1240, 1095, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.40−7.22 (m, 10 H), 4.91 (d, *J* = 4.6 Hz, 1 H), 4.72 (d, *J* = 11.5 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.45 (s, 2 H), 4.05 (dt, *J* = 2.6, 6.9 Hz, 1 H), 3.79 (m, 1 H), 3.69 (dd, *J* = 1.7, 6.9 Hz, 1 H), 3.64 (dd, *J* = 2.3, 8.3 Hz, 1 H), 3.58 (br s, 1 H), 3.57 (dd, *J* = 6.9, 9.6 Hz, 1 H), 3.42 (t, *J* = 6.9 Hz, 2 H), 3.31 (s, 3 H), 2.26 (m, 1 H), 2.10 (dd, *J* = 7.3, 12.5 Hz, 1 H), 2.01 (m, 1 H), 1.87 (dt, *J* = 6.9, 6.9 Hz, 2 H), 1.82−1.45 (m, 5 H), 1.10 (d, *J* = 6.6Hz, 3 H), 1.05 (d, *J* = 7.3 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 8.2 Hz, 18 H), 0.80 (d, *J* = 6.9 Hz, 3 H), 0.65 (q, *J* = 8.2 Hz, 6 H), 0.59 (q, *J* = 8.2 Hz, 6 H); MS (FAB) *m*/*z* 809 $(M + Na)^+$, 787 $(M + H)^+$, 755 $(M - OCH_3)^+$; HRMS (FAB) calcd for $C_{45}H_{78}NaO_7Si_2$ [$(M + Na)^+$] 809.5185, found 809.5170. **73c:** $[\alpha]^{18}_D$ +11 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3550 (br), 1460, 1360, 1240, 1070, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.40−7.22 (m, 10 H), 4.92 (d, *J* = 5.0 Hz, 1 H), 4.83 (d, *J* = 11.5 Hz, 1 H), 4.71 (d, *J* = 11.5 Hz, 1 H), 4.47 (s, 2 H), 4.01 (dt, *J* = 3.3, 6.3 Hz, 1 H), 3.74 (dd, *J* = 1.7, 7.6 Hz, 1 H), 3.66 (m, 1 H), 3.61 (dd, *J* = 1.7, 7.6 Hz, 1 H), 3.57 (dd, *J* = 6.3, 9.9 Hz, 1 H), 3.44 (t, *J* = 6.9 Hz, 2 H), 3.30 (s, 3 H), 2.27 (br s, 1 H), 2.22 (m, 1 H), 2.11 (dd, *J* = 7.6, 12.2 Hz, 1 H), 2.02 (m, 1 H), 1.92−1.80 (m, 2 H), 1.73 (m, 1 H), 1.65 (ddd, *J* = 5.0, 9.6, 12.2 Hz, 1 H), 1.48 (m, 1 H), 1.42 (m, 1 H), 1.28 (m, 1 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 0.94 (t, *J* = 7.9 Hz, 18 H), 0.97−0.90 (m, 6 H), 0.83 (d, *J* = 7.3 Hz, 3 H), 0.61 (q, *J* = 7.9 Hz, 6 H), 0.58 (q, *J* = 7.9 Hz, 6 H); MS (FAB) *m*/*z* 809 $(M + Na)^+$, 787 $(M + H)^+$, 755 $(M - OCH_3)^+$; HRMS (FAB) calcd for $C_{45}H_{78}NaO_7Si_2$ [$(M + Na)^+$] 809.5185, found 809.5184.

Diol 74. Calcium (1.23 mg, 30.7 mmol) was added to a stirred solution of olefin **73a** (780 mg, 1.01 mmol) in THF (15 mL), isopropyl alcohol (4.5 mL), and liquid NH_3 (10 mL) cooled to −78 °C. After the mixture was stirred at −78 °C for 1 h, NH_4Cl (6.9 g) and $Fe(NO_3)_3{\cdot}9H_2O$ (1.1 g) were added. The mixture was stirred at −78 °C for 1 h and allowed to warm to room temperature. The residue was dissolved in H_2O (20 mL), and the mixture was stirred at room temperature for 1 h and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (30 g, hexane−Et_2O 3:1 → 1:1) to give **74** (586 mg, 98%) as a colorless oil: $[\alpha]^{19}_D$ +32.1 (*c* 0.878, $CHCl_3$); IR ($CHCl_3$) 3610, 3470 (br), 1455, 1410, 1380, 1235, 1020, 970 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 1.0, 7.6, 15.5 Hz, 1 H), 5.48 (ddd, *J* = 0.7, 6.3, 15.5 Hz, 1 H), 4.92 (d, *J* = 5.0 Hz, 1 H), 4.30 (m, 1 H), 3.99 (ddd, *J* = 5.0, 5.0, 6.3 Hz, 1 H), 3.82−3.60 (m, 3 H), 3.57 (dd, *J* = 7.9, 7.9 Hz, 1 H), 3.35 (s, 3 H), 3.14 (d, *J* = 6.3 Hz, 1 H), 2.39 (m, 1 H), 2.28 (m, 1 H), 2.18 (t, *J* = 5.3 Hz, 1 H), 2.08 (dd, *J* = 6.9, 12.5 Hz, 1 H), 1.93−1.66 (m, 4 H), 1.60 (ddd, *J* = 5.0, 10.6, 12.5 Hz, 1 H), 1.07 (d, *J* = 6.3 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 18 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.64 (q, *J* = 7.6 Hz, 6 H), 0.63 (q, *J* = 7.6 Hz, 6 H); MS (FAB) *m*/*z* 611 $(M + Na)^+$, 589 $(M + H)^+$; HRMS (FAB) calcd for $C_{31}H_{64}NaO_6Si_2$ [$(M+ Na)^+$] 611.4140, found 611.4158.

Diol 75. A mixture of diol **74** (218 mg, 0.356 mmol) and 5% Rh on alumina (60 mg) in EtOH (3.0 mL) was stirred under a hydrogen atmosphere at room temperature for 1.6 h. The reaction mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (40 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (40 g, hexane−Et_2O 3:1 → 1:1 → 1:2) to give **75** (200 mg, 91%) as a colorless oil: $[\alpha]^{19}_D$ +26.6 (*c* 0.693, $CHCl_3$); IR ($CHCl_3$) 3610, 3500 (br), 1460, 1415, 1360, 1240, 1100, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.91 (d, *J* = 5.0 Hz, 1 H), 4.00 (ddd, *J* = 4.7, 4.7, 6.4 Hz, 1 H), 3.88−3.62 (m, 3 H), 3.57 (dd, *J* = 6.6, 8.2 Hz, 1 H), 3.54 (dd, *J* = 3.0, 6.6 Hz, 1 H), 3.34 (s, 3 H), 2.76 (d, *J* = 5.0 Hz, 1 H), 2.28 (m, 1 H), 2.09 (dd, *J* = 6.9, 12.9 Hz, 1 H), 2.07 (t, *J* = 5.3 Hz, 1 H), 1.94−1.29 (m, 10 H), 1.06 (d, *J* = 6.6, 3 H), 0.97 (t, *J* = 7.6 Hz, 9 H), 0.96 (t, *J* = 7.6 Hz, 9 H), 0.98−0.93 (m, 6 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.63 (q, *J* = 7.6 Hz, 12 H); MS (FAB) *m*/*z* 613 $(M + Na)^+$, 591 $(M + H)^+$, 559 $(M - OCH_3)^+$; HRMS (FAB) calcd for $C_{31}H_{66}NaO_6Si_2$ [$(M+ Na)^+$] 613.4296, found 613.4292.

Sulfide 76. Experimental procedure was followed as described for compound **22**. **76**: $[\alpha]^{21}_D$ +20.7 (*c* 1.62, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1585, 1460, 1360, 1240, 1100, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30−7.14 (m, 5 H), 4.91 (d, *J* = 5.0 Hz, 1 H), 3.92 (ddd, *J* = 3.9, 5.6, 5.6 Hz, 1 H), 3.83 (m, 1 H), 3.57 (dd, *J* = 6.9, 8.2 Hz, 1 H), 3.52 (dd, *J* = 2.6, 6.9 Hz, 1 H), 3.34 (s, 3 H), 2.86 (dd, *J* = 7.3, 8.9 Hz, 2 H), 2.73 (d, *J* = 4.6 Hz, 1 H), 2.28 (m, 1 H), 2.09 (dd, *J* = 7.3, 12.9 Hz, 1 H), 1.88−1.78 (m, 2 H), 1.75−1.25 (m, 8 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 7.2 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.93 (t, *J* = 7.9 Hz, 18 H), 0.82 (d, *J* = 7.3 Hz, 3 H), 0.61 (q, *J* = 7.9 Hz, 6 H), 0.56 (q, *J* = 7.9 Hz, 6 H); MS (FAB) *m*/*z* 705 $(M + Na)^+$, 683 $(M + H)^+$, 651 $(M - OCH_3)^+$; HRMS (FAB) calcd for $C_{37}H_{70}NaO_5SSi_2$ [$(M + Na)^+$] 705.4380, found 705.4387.

Sulfone 77. Experimental procedure was followed as described for compound **4**. **77**: $[\alpha]^{24}_D$ +26.0 (*c* 0.730, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1460, 1360, 1310, 1230, 1150, 1085 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.94−7.88 (m, 2 H), 7.69−7.54 (m, 3 H), 4.91 (d, *J* = 5.0 Hz, 1 H), 3.80 (ddd, *J* = 5.3, 5.3, 5.3 Hz, 1 H), 3.82 (m, 1 H), 3.56 (dd, *J* = 6.6, 8.2 Hz, 1 H), 3.42 (dd, *J* = 3.0, 6.6 Hz, 1 H), 3.34 (s, 3 H), 3.20−2.98 (m, 2 H), 2.79 (br s, 1 H), 2.28 (m, 1 H), 2.09 (dd, *J* = 7.3, 12.9 Hz, 1 H), 1.93−1.82 (m, 2 H), 1.74−1.24 (m, 8 H), 1.06 (d, *J* = 6.6, 3 H), 0.96 (d, *J* = 7.3 Hz, 3 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 0.90 (t, *J* = 7.9 Hz, 9 H), 0.85 (d, *J* = 7.3 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H), 0.56 (q, *J* = 7.9 Hz, 6 H), 0.52 (q, *J* = 7.9 Hz, 6 H); MS (FAB) *m*/*z* 737 $(M + Na)^+$, 715 $(M + H)^+$, 683 $(M - OCH_3)^+$; HRMS (FAB) calcd for $C_{37}H_{70}NaO_7SSi_2$ [$(M + Na)^+$] 737.4278, found 737.4262.

C21−C34 Segment 10. Preparation of a Stock Solution of [(3,4-Dimethoxybenzyl)oxy]methyl Chloride. To a stirred solution of 3,4-dimethoxybenzyl alcohol (5.4 g, 32 mmol) in 1,2-dimethoxyethane (30 mL) cooled to 0 °C were added NaH (2.85 g of 60% dispersion in mineral oil, 71 mmol), NaI (5.5 g, 36 mmol), and (methylthio)methyl chloride (3.0 mL, 36 mmol), successively. The mixture was stirred at 0 °C for 15 min and at room temperature for 13 h. The reaction mixture was recooled to 0 °C, and the reaction was quenched by addition of H_2O (30 mL). The mixture was extracted with Et_2O (200 mL, 50 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane−EtOAc 5:1 → 3:1) to give 3,4-dimethoxybenzyl (methylthio)methyl ether (4.9 g, 67%) as a yellow oil.

To a stirred solution of 3,4-dimethoxybenzyl (methylthio)-methyl ether (721 mg, 3.16 mmol) in CH_2Cl_2 (8.0 mL) cooled at −78 °C was added a solution of sulfuryl chloride (0.26 mL, 3.23 mmol) in CH_2Cl_2 (6.2 mL). The mixture was stirred at −78 °C for 45 min and concentrated. The resulting yellow oil was dissolved in CH_2Cl_2 (3.0 mL) to give a solution of [(3,4-dimethoxybenzyl)oxy]methyl chloride (1.05 M solution in CH_2Cl_2).

To a stirred solution of sulfone **77** (157 mg, 0.220 mmol) in CH_2Cl_2 (2.0 mL) cooled at 0 °C were added diisopropylethylamine (2.0 mL, 11.5 mmol) and the 1.05 M solution of [(3,4-dimethoxybenzyl)oxy]methyl chloride in CH_2Cl_2 (2.7 mL, 2.84 mmol). The mixture was stirred at room temperature for 16 h, and the reaction was quenched by addition of MeOH (10 mL). The resulting mixture was stirred at room temperature for 2.5 h, and H_2O (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with hexane (4 × 15 mL). The oraganic layer and the extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on alumina (30 g, hexane−EtOAc 15:1 → 10:1 → 7:1 → 5:1 → 3:1) and subsequently on silica gel (8 g, hexane−EtOAc 6:1 → 4:1 → 3:1 → 2:1) to give **10** (194 mg, 98%) as a colorless oil: $[\alpha]^{27}_D$ +13.7 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 1595, 1515, 1460, 1305, 1260, 1150, 1095, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.92−7.87 (m, 2 H), 7.68−7.52 (m, 3 H), 6.92−6.88 (m, 2 H), 6.82 (d, J = 8.6 Hz, 1 H), 4.88 (d, J = 4.6 Hz, 1 H), 4.81 (s, 2 H), 4.60 (d, J = 11.6 Hz, 1 H), 4.55 (d, J = 11.6 Hz, 1 H), 4.02 (m, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.78 (ddd, J = 5.3, 5.3, 5.3 Hz, 1 H), 3.57 (dd, J = 6.6, 9.9 Hz, 1 H), 3.41 (dd, J = 2.6, 6.9 Hz, 1 H), 3.25 (s, 3 H), 3.15−2.94 (m, 2 H), 2.23 (m, 1 H), 2.09 (dd, J = 7.3, 12.2 Hz, 1 H), 1.91−1.78 (m, 2 H), 1.67−1.28 (m, 8 H), 1.10 (d, J = 6.6, 3 H), 0.95−0.85 (m, 6 H), 0.88 (t, J = 7.6 Hz, 18 H), 0.75 (d, J = 7.3 Hz, 3 H), 0.55 (q, J = 7.6 Hz, 6 H), 0.50 (q, J = 7.6 Hz, 6 H); MS (FAB) *m*/*z* 917 $(M + Na)^+$. Anal. Calcd for $C_{47}H_{82}O_{10}SSi_2$: C, 63.05; H, 9.23. Found: C, 62.92; H, 9.42.

Olefin 78. To a stirred solution of the C21−C34 segment **10** (248 mg, 0.277 mmol) in THF (2.0 mL) cooled at −78 °C was added a 1.59 M solution of BuLi in hexane (0.17 mL, 0.27 mmol) dropwise. The mixture was stirred at −78 °C for 30 min, and a solution of the C5−C20 segment **9** (101 mg, 0.153 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified twice by column chromatography on silica gel [(40 g, hexane−Et_2O 4:1 → 2: 1 → 1: 1 → 1: 2) and (30 g, benzene−Et_2O 20:1 → 15: 1 → 10: 1 → 5: 1)] to give a diastereomeric mixture of hydroxy sulfones (207 mg) as a colorless oil along with recovered **10** (121 mg, 49%). The hydroxy sulfones were employed in the next experiment without separation of the diastereomers. To a stirred solution of the diastereomeric mixture of hydroxy sulfones (207 mg) in pyridine (1.2 mL) were added acetic anhydride (0.6 mL) and 4-(dimethylamino)pyridine (5.4 mg, 0.044 mmol) at room temperature. The mixture was stirred at room temperature for 3 h and concentrated. The residue was purified by column chromatography on silica gel (20 g, hexane−Et_2O 2:1 → 1: 1 → 1: 2) to give a diastereomeric mixture of acetoxy sulfones (198 mg) as a colorless oil. The acetoxy sulfones were employed in the next experiment without separation of the diastereomers. To a vigorously stirred solution of the diastereomeric mixture of acetoxy sulfones (198 mg) in MeOH (4.0 mL) cooled at 0 °C were added Na_2HPO_4 (640 mg, 4.51 mmol) and 5% sodium amalgam (972 mg, 2.12 mmol), and the mixture was stirred at 0 °C for 1.5 h. The mixture was diluted with saturated aqueous NH_4Cl (5 mL), stirred at room temperature for 1 h, and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane−Et_2O 5: 1 → 3: 1 → 1: 1) to give **78** (20*E*/20*Z* = 9/1, by ^1H NMR) (187 mg, 88% from **9**) as a colorless oil: $[\alpha]^{25}_D$ +34.6 (*c* 0.904, $CHCl_3$); IR ($CHCl_3$) 1720, 1595, 1515, 1460, 1375, 1255, 1155, 1095, 1030, 970, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (20*E*-isomer) δ 6.92−6.89 (m, 2 H), 6.81 (d, J = 7.8 Hz, 1 H), 5.50 (ddd, J = 7.3, 7.3, 15.6 Hz, 1 H), 5.33 (dd, J = 6.8, 6.8 Hz, 1 H), 5.22 (dd, J = 8.3, 15.6 Hz, 1 H), 4.88 (d, J = 4.4 Hz, 1 H), 4.83 (d, J = 6.3 Hz, 1 H), 4.81 (d, J = 6.3 Hz, 1 H), 4.64 (d, J = 11.7 Hz, 1 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.58 (d, J = 11.2 Hz, 1 H), 4.56 (d, J = 11.7 Hz, 1 H), 4.20−4.09 (m, 2 H), 4.03 (m, 1 H), 3.96 (m, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.64 (m, 1 H), 3.59−3.48 (m, 4 H), 3.37 (dd, J = 6.8, 6.8 Hz, 1 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 3.15 (s, 3 H), 2.33−2.05 (m, 5 H), 2.16 (s, 3 H), 1.95 (m, 1 H), 1.86−1.74 (m, 2 H), 1.73−1.36 (m, 15 H), 1.50 (s, 3 H), 1.20 (s, 9 H), 1.10 (d, J = 6.4 Hz, 3 H), 1.01−0.93 (m, 17 H), 0.95 (t, J = 7.8 Hz, 9 H), 0.95 (t, J = 7.8 Hz, 9 H), 0.89 (s, 9 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.60 (q, J = 7.8 Hz, 6 H), 0.59 (q, J = 7.8 Hz, 6 H), 0.05 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m*/*z* 1419 $(M + Na)^+$; HRMS (FAB) calcd for $C_{76}H_{144}NaO_{14}SSi_3$ $[(M + Na)^+]$ 1419.9482, found 1419.9470.

Alcohol 79. To a stirred solution of olefin **78** (20*E*/20*Z* = 9/1) (80.7 mg, 0.0577 mmol) in CH_2Cl_2 (4.0 mL) cooled at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (0.23 mL, 0.23 mmol) dropwise. The mixture was stirred at −78 °C for 2 h and the reaction was quenched by addition of MeOH (0.5 mL), saturated aqueous sodium potassium tartrate (7.5 mL), and H_2O (7.5 mL). The resulting mixture was warmed to room temperature, stirred at room temperature for 30 min, and extracted with Et_2O (2 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−EtOAc 4:1 → 2: 1) to give **79** (20*E*/20*Z* = 9/1, by ^1H NMR) (76.6 mg, 100%) as a colorless oil: $[\alpha]^{25}_D$ +41.6 (*c* 0.915, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1595, 1515, 1465, 1380, 1255, 1095, 1030, 970, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (20*E*-isomer) δ 6.93−6.90 (m, 2 H), 6.82 (d, J = 8.3 Hz, 1 H), 5.50 (ddd, J = 7.3, 7.3, 15.1 Hz, 1 H), 5.34 (dd, J = 6.8, 6.8 Hz, 1 H), 5.22 (dd, J = 8.3, 15.1 Hz, 1 H), 4.88 (d, J = 4.4 Hz, 1 H), 4.83 (d, J = 6.8 Hz, 1 H), 4.81 (d, J = 6.8 Hz, 1 H), 4.69 (d, J = 11.7 Hz, 1 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.59 (d, J = 11.7 Hz, 1 H), 4.56 (d, J = 11.2 Hz, 1 H), 4.04 (dd, J = 6.8, 6.8 Hz, 1 H), 3.96 (m, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.81−3.68 (m, 3 H), 3.61−3.52 (m, 3 H), 3.49 (dd, J = 3.4, 4.4 Hz, 1 H), 3.38 (dd, J = 6.4, 6.4 Hz, 1 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 3.16 (s, 3 H), 2.56 (t, J = 5.4 Hz, 1 H), 2.40−2.05 (m, 5 H), 2.21 (s, 3 H), 1.97 (m, 1 H), 1.84 (m, 1 H), 1.71−1.30 (m, 16 H), 1.50 (s, 3 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.08−0.86 (m, 17 H), 0.96 (t, J = 7.8 Hz, 9 H), 0.95 (t, J = 7.8 Hz, 9 H), 0.89 (s, 9 H), 0.78 (d, J = 7.3 Hz, 3 H), 0.60 (q, J = 7.8 Hz, 6 H), 0.59 (q, J = 7.8 Hz, 6 H), 0.05 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m*/*z* 1335 $(M + Na)^+$; HRMS (FAB) calcd for $C_{71}H_{136}NaO_{13}SSi_3$ $[(M + Na)^+]$ 1335.8907, found 1335.8910.

Aldehyde 80. Experimental procedure was followed as described for compound **9**. **80** (20*E*/20*Z* = 9/1, by ^1H NMR): $[\alpha]^{25}_D$ +26.7 (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 2730, 1725, 1595, 1515, 1465, 1380, 1255, 1095, 1030, 970, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) (20*E*-isomer) δ 9.82 (t, J = 2.3 Hz, 1 H), 6.93−6.89 (m, 2 H), 6.82 (d, J = 8.3 Hz, 1 H), 5.51 (ddd, J = 7.9, 7.9, 15.2 Hz, 1 H), 5.34 (dd, J = 6.6, 6.6 Hz, 1 H), 5.22 (dd, J = 8.3, 15.2 Hz, 1 H), 4.88 (d, J = 5.0 Hz, 1 H), 4.82 (s, 2 H), 4.67 (d, J = 11.5 Hz, 1 H), 4.61 (d, J = 11.5 Hz, 1 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.55 (d, J = 11.5 Hz, 1 H), 4.10−3.92 (m, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.64−3.47 (m, 4 H), 3.38 (dd, J = 6.6, 6.6 Hz, 1 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 3.16 (s, 3 H), 2.65−2.48 (m, 2 H), 2.39−2.04 (m, 5 H), 2.14 (s, 3 H), 2.00 (m, 1 H), 1.84 (m, 1 H), 1.79−1.30 (m, 15 H), 1.50 (s, 3 H), 1.19−0.95 (m, 16 H), 1.09 (d, J = 6.6 Hz, 3 H), 0.96 (t, J = 7.6 Hz, 9 H), 0.95 (t, J = 7.6 Hz, 9 H), 0.89 (s, 9 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.60 (q, J = 7.6 Hz, 6 H), 0.59 (q, J = 7.6 Hz, 6 H), 0.05 (s, 6 H); MS (FAB) *m*/*z* 1333 $(M + Na)^+$; HRMS (FAB) calcd for $C_{71}H_{134}NaO_{13}SSi_3$ $[(M + Na)^+]$ 1333.8752, found 1333.8770.

***α,β,γ,δ*-Unsaturated Ester 81.** To a stirred solution of triethyl 4-phosphonocrotonate (101 mg, 0.404 mmol) in THF (3.0 mL) cooled at −40 °C was added a 0.5 M solution of lithium diisopropylamide (0.70 mL, 0.35 mmol) prepared from diisopropylamine (0.15 mL, 1.1 mmol), a 1.59 M solution of BuLi in hexane (0.65 mL, 1.0 mmol), and THF (1.2 mL) at

−78 °C. The mixture was stirred at −40 °C for 25 min, and a solution of aldehyde **80** (20*E*/20*Z* = 9/1) (150 mg, 0.115 mmol) in THF (0.6 mL) was added dropwise. The resulting mixture was stirred at −40 °C for 8 min and at 0 °C for 15 min. The mixture was diluted with saturated aqueous NH_4Cl (2 mL) and extracted with Et_2O (30 mL, 10 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−Et_2O 3: 1 → 1: 1) to give **81** (4*E*/4*Z* = 19/1, 20*E*/20*Z* = 9/1, by ^{1}H NMR) (144 mg, 89%) as a colorless oil: $[\alpha]^{25}_D$ +10.7 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 1705, 1645, 1615, 1595, 1515, 1465, 1365, 1260, 1095, 1025, 970, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) (4*E*,20*E*-isomer) δ 7.26 (dd, *J* = 9.6, 15.5 Hz, 1 H), 6.92−6.89 (m, 2 H), 6.82 (d, *J* = 7.9 Hz, 1 H), 6.25 (dd, *J* = 9.6, 15.2 Hz, 1 H), 6.15 (ddd, *J* = 6.3, 6.3, 15.2 Hz, 1 H), 5.80 (d, *J* = 15.5 Hz, 1 H), 5.50 (ddd, *J* = 7.3, 7.3, 15.2 Hz, 1 H), 5.34 (dd, *J* = 7.3, 7.3 Hz, 1 H), 5.22 (dd, *J* = 8.2, 15.2 Hz, 1 H), 4.88 (d, *J* = 4.6 Hz, 1 H), 4.82 (s, 2 H), 4.62 (d, *J* = 11.6 Hz, 1 H), 4.61 (d, *J* = 11.6 Hz, 1 H), 4.56 (d, *J* = 11.6 Hz, 1 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 4.20 (q, *J* = 7.3 Hz, 2 H), 4.03 (m, 1 H), 3.96 (m, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.65−3.46 (m, 5 H), 3.38 (dd, *J* = 6.6, 6.6 Hz, 1 H), 3.27 (s, 3 H), 3.22 (s, 3 H), 3.16 (s, 3 H), 2.45 (m, 1 H), 2.38−2.04 (m, 6 H), 2.14 (s, 3 H), 1.92−1.76 (m, 2 H), 1.68−1.26 (m, 15 H), 1.50 (s, 3 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 1.18−0.92 (m, 13 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 9 H), 0.95 (t, *J* = 7.6 Hz, 9 H), 0.89 (s, 9 H), 0.84 (d, *J*= 7.3 Hz, 3 H), 0.78 (d, *J* = 6.9 Hz, 3 H), 0.60 (q, *J* = 7.6 Hz, 6 H), 0.59 (q, *J* = 7.6 Hz, 6 H), 0.06 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m*/*z* 1429 (M + Na)$^+$; HRMS (FAB) calcd for $C_{77}H_{142}NaO_{14}SSi_3$ [(M + Na)$^+$] 1429.9326, found 1429.9310.

Diol 82. A solution of α,*β*,*γ*,*δ*-unsaturated ester **81** (4*E*/4*Z* = 19/1, 20*E*/20*Z* = 9/1) (91.9 mg, 0.0653 mmol) in a 5:3:1 mixture of THF, pyridine, and HF·pyridine (1 mL) was stirred at room temperature for 3 h. The mixture was diluted with EtOAc (5 mL) and cooled to 0 °C, and then saturated aqueous $NaHCO_3$ (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layer and the extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−EtOAc 2: 1 → 1: 1 → 1: 2 → EtOAc) to give **82** (4*E*/4*Z* = 19/1, 20*E*/20*Z* = 9/1, by ^{1}H NMR) (77.0 mg, 100%) as a colorless oil: $[\alpha]^{25}_D$ +5.1 (*c* 0.957, $CHCl_3$); IR ($CHCl_3$) 3470 (br), 1700, 1640, 1615, 1595, 1515, 1465, 1365, 1260, 1095, 1025, 970, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (4*E*,20*E*-isomer) δ 7.27 (dd, *J* = 10.2, 15.1 Hz, 1 H), 6.96−6.90 (m, 2 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 6.25 (dd, *J* = 10.2, 15.1 Hz, 1 H), 6.17 (ddd, *J* = 6.3, 6.3, 15.1 Hz, 1 H), 5.80 (d, *J* = 15.1 Hz, 1 H), 5.62 (ddd, *J* = 7.3, 7.3, 15.3 Hz, 1 H), 5.41−5.28 (m, 2 H), 4.90 (d, *J* = 4.9 Hz, 1 H), 4.86 (d, *J* = 6.8 Hz, 1 H), 4.83 (d, *J* = 6.8 Hz, 1 H), 4.63−4.56 (m, 4 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 4.06 (dd, *J* = 6.3, 6.3 Hz, 1 H), 3.97 (m, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.66−3.54 (m, 4 H), 3.38 (dd, *J* = 6.8, 6.8 Hz, 1 H), 3.31 (m, 1 H), 3.30 (s, 3 H), 3.23 (s, 3 H), 3.16 (s, 3 H), 2.85 (d, *J* = 2.4 Hz, 1 H), 2.81 (d, *J* = 5.4 Hz, 1 H), 2.54−2.37 (m, 2 H), 2.36−2.06 (m, 5 H), 2.14 (s, 3 H), 1.90−1.79 (m, 3 H), 1.72−1.30 (m, 14 H), 1.50 (s, 3 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 1.11−0.88 (m, 13 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 0.97 (d, *J* = 7.3 Hz, 3 H), 0.89 (s, 9 H), 0.84 (d, *J* = 7.3 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m*/*z* 1201 (M + Na)$^+$; HRMS (FAB) calcd for $C_{65}H_{114}NaO_{14}SSi$ [(M + Na)$^+$] 1201.7596, found 1201.7600.

Seco Acid 83. To a stirred solution of diol **82** (4*E*/4*Z* = 19/1, 20*E*/20*Z* = 9/1) (65.9 mg, 0.0589 mmol) in MeOH (4 mL) was added 5 M aqueous LiOH (0.5 mL) at room temperature, and the mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc (10 mL), cooled to 0 °C, and acidified (pH 1) with 1 M aqueous HCl (3 mL). Sodium chloride (2 g) was added to the mixture and the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layer and the extracts were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane−EtOAc 1: 1 → EtOAc) to give **83** (4*E*/4*Z* = 19/1, 20*E*/20*Z* = 9/1, by ^{1}H NMR) (65.1 mg, 100%) as a colorless oil: $[\alpha]^{26}_D$ −5.1 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3600−2200 (br), 1690, 1640, 1615, 1595, 1515, 1465, 1380, 1260, 1095, 1025, 970, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) (4*E*,20*E*-isomer) δ 7.28 (dd, *J* = 9.9, 15.5 Hz, 1 H), 6.95−6.90 (m, 2 H), 6.83 (d, *J* = 7.9 Hz, 1 H), 6.28 (dd, *J* = 9.9, 15.2 Hz, 1 H), 6.18 (ddd, *J* = 6.3, 6.3, 15.2 Hz, 1 H), 5.79 (d, *J* = 15.5 Hz, 1 H), 5.62 (ddd, *J* = 6.9, 6.9, 15.2 Hz, 1 H), 5.42−5.26 (m, 2 H), 4.91 (d, *J* = 5.0 Hz, 1 H), 4.86 (d, *J* = 6.9 Hz, 1 H), 4.83 (d, *J* = 6.9 Hz, 1 H), 4.65−4.55 (m, 4 H), 4.10−3.93 (m, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.68 (dd, *J* = 3.3, 3.3 Hz, 1 H), 3.64−3.57 (m, 3 H), 3.43−3.24 (m, 2 H), 3.31 (s, 3 H), 3.24 (s, 3 H), 3.16 (s, 3 H), 2.60−2.04 (m, 7 H), 2.14 (s, 3 H), 1.94−1.74 (m, 3 H), 1.72−1.26 (m, 14 H), 1.49 (s, 3 H), 1.21−0.82 (m, 13 H), 1.10 (d, *J* = 6.3 Hz, 3 H), 0.96 (d, *J* = 7.3 Hz, 3 H), 0.89 (s, 9 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H). Signals of three protons (COOH, 2 × OH) were not observed; MS (FAB) *m*/*z* 1173 (M + Na)$^+$; HRMS (FAB) calcd for $C_{63}H_{110}NaO_{14}SSi$ [(M + Na)$^+$] 1173.7282, found 1173.7270.

Macrolactonization of Seco Acid 83. To a stirred solution of seco acid **83** (4*E*/4*Z* = 19/1, 20*E*/20*Z* = 9/1) (39.8 mg, 0.0589 mmol) in $CHCl_3$ (150 mL) were added triethylamine (0.2 mL, 1.4 mmol), 4-(dimethylamino)pyridine (359 mg, 2.93 mmol), and 2,4,6-trichlorobenzoyl chloride (0.2 mL, 1.3 mmol), successively at room temperature. The mixture was stirred at room temperature for 15 h and washed with 1 M aqueous HCl (2 × 4 mL), saturated aqueous $NaHCO_3$ (2 × 4 mL), H_2O (7 mL), and brine (6 mL), successively; dried ($NaSO_4$); and concentrated. The residue was purified by column chromatography on silica gel (10 g, hexane−EtOAc 2: 1 → 1:1) and preparative HPLC (Develosil 30−10, 20 × 250 mm, hexane−EtOAc−MeOH 85:15:1, 5 mL/min) to give the 24-membered lactone **84** (t_R = 70 min, 15.5 mg, 40%) and the 26-membered lactone **85** (t_R = 84 min, 10.0 mg, 26%) as a colorless oil, respectively. **84**: $[\alpha]^{22}_D$ +56.9 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3490 (br), 1690, 1640, 1615, 1595, 1515, 1465, 1380, 1260, 1095, 1030, 970, 835 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 9.9, 15.5 Hz, 1 H), 6.90−6.94 (m, 2 H), 6.82 (d, *J* = 8.9 Hz, 1 H), 6.33−6.18 (m, 2 H), 5.84 (d, *J* = 15.5 Hz, 1 H), 5.54 (ddd, *J* = 4.4, 9.3, 15.4 Hz, 1 H), 5.37 (d, *J* = 11.0 Hz, 1 H), 5.09 (dd, *J* = 9.3, 15.4 Hz, 1 H), 5.05 (m, 1 H), 4.89 (d, *J* = 5.1 Hz, 1 H), 4.86 (d, *J* = 6.9 Hz, 1 H), 4.83 (d, *J* = 6.9 Hz, 1 H), 4.62 (d, *J* = 11.5 Hz, 1 H), 4.59 (d, *J* = 11.5 Hz, 1 H), 4.55 (d, *J* = 11.5 Hz, 1 H), 4.53 (d, *J* = 11.5 Hz, 1 H), 4.05 (ddd, *J* = 0.5, 6.6, 6.6 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.62 (m, 1 H), 3.56 (dd, *J* = 6.6, 9.9 Hz, 1 H), 3.54−3.44 (m, 2 H), 3.37 (dd, *J* = 4.5, 10.4 Hz, 1 H), 3.27 (s, 3 H), 3.20 (s, 3 H), 3.17 (s, 3 H), 3.14 (m, 1 H), 2.99 (ddd, *J* = 2.3, 4.6, 9.9 Hz, 1 H), 2.45 (ddd, *J* = 10.6, 10.6, 14.3 Hz, 1 H), 2.34 (ddd, *J* = 4.0, 8.2, 14.5 Hz, 1 H), 2.27−2.05 (m, 4 H), 2.15 (s, 3 H), 1.97 (m, 1 H), 1.89 (m, 1 H), 1.71 (m, 1 H), 1.68−1.39 (m, 10 H), 1.45 (s, 3 H), 1.35 (m, 1 H), 1.30−0.88 (m, 5 H), 1.10 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.89−0.87 (m, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 7.3 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H), 0.74 (d, *J* = 5.3 Hz, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m*/*z* 1155 (M + Na)$^+$. Anal. Calcd for $C_{63}H_{108}O_{13}SSi$: C, 66.75; H, 9.60. Found C, 66.71; H, 9.63. **85**: $[\alpha]^{22}_D$ +24.1 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1685, 1640, 1615, 1595, 1515, 1465, 1380, 1255, 1100, 1015, 970, 835 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 9.9, 15.5 Hz, 1 H), 6.93−6.90 (m, 2 H), 6.82 (d, *J* = 8.9 Hz, 1 H), 6.30 (dd, *J* = 9.9, 15.5 Hz, 1 H), 6.22 (ddd, *J* = 6.3, 6.3, 15.5 Hz, 1 H), 5.83 (d, *J* = 15.5 Hz, 1 H), 5.54 (ddd, *J* = 5.6, 8.9, 15.2 Hz, 1 H), 5.28 (dd, *J* = 8.2, 15.2 Hz, 1 H), 5.23 (dd, *J* = 6.0, 6.9 Hz, 1 H), 4.90 (d, *J* = 5.0 Hz, 1 H), 4.90 (m, 1 H), 4.86 (d, *J* = 6.9 Hz, 1 H), 4.83 (d, *J* = 6.9 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.60 (d, *J* = 11.5 Hz, 1 H), 4.60 (d, *J* = 11.5 Hz, 1 H), 4.59 (d, *J* = 11.5 Hz, 1 H), 4.07 (ddd, *J* = 0.5, 6.6, 6.6 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.78 (m, 1 H), 3.60−3,55 (m, 2 H), 3.53 (dd, *J* = 7.3, 15.5 Hz, 1 H), 3.46 (m, 1 H), 3.38 (dd, *J* = 6.9, 6.9 Hz, 1 H), 3.29 (s, 3 H), 3.21 (s, 3 H), 3.16 (s, 3 H), 2.73 (d, *J* = 3.6 Hz, 1 H), 2.51 (m, 1 H), 2.38−2.19 (m, 3 H), 2.19 (s, 3 H), 2.15−2.01 (m, 3 H), 1.94 (m, 1 H), 1.86 (m, 1 H), 1.78 (m, 1 H), 1.72 (m, 1 H), 1.68−1.10 (m, 13 H), 1.49 (s, 3 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 0.98 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.92−0.86 (m, 9 H), 0.89 (s, 9 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* =

6.6 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m/z* 1155 $(M + Na)^+$; HRMS (FAB) calcd for $C_{63}H_{108}NaO_{13}SSi$ [$(M + Na)^+$] 1155.7178, found 1155.7190.

Isomerization of 26-Membered Lactone 85 to 24-Membered Lactone 84. To a stirred solution of the 26-membered lactone **85** (9.6 mg, 0.0085 mmol) in CH_2Cl_2 (0.4 mL) was added titanium tetraisopropoxide (0.01 mL, 0.034 mmol) at room temperature. The solution was stirred at room temperature for 19 h and diluted with Et_2O (2 mL) and 10% aqueous (+)-tartaric acid (2 mL). The mixture was stirred at room temperature for 20 min and extracted with Et_2O (25 mL, 8 mL). The combined extracts were washed with brine (3 mL), dried ($NaSO_4$), and concentrated. The residual oil was purified by thin-layer chromatography on silica gel (200 × 200 × 0.25 mm, hexane−EtOAc 1:1) to give **84** (6.2 mg, 65%) along with recovered **85** (1.5 mg, 15%).

Disilyl Ether 86a. To a stirred solution of the 24-membered lactone **84** (15.5 mg, 0.0137 mmol) and imidazole (157 mg, 2.31 mmol) in DMF (0.2 mL) was added *tert*-butyldimethylsilyl chloride (149 mg, 0.989 mmol) at room temperature, and the resulting solution was stirred at 60 °C for 24 h. The mixture was cooled to room temperature, and ice (*ca.* 1 g) and H_2O (3 mL) were added. The mixture was stirred at room temperature for 20 min and extracted with Et_2O (3 × 6 mL). The combined extracts were washed with 1 M aqueous HCl (2 × 2 mL), saturated aqueous $NaHCO_3$ (4 mL), H_2O (3 mL), and brine (3 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane−EtOAc 5:1 → 2: 1) to give **86a** (16.8 mg, 98%) as a colorless oil: $[\alpha]^{22}_D$ +45.3 (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 1705, 1645, 1615, 1595, 1515, 1465, 1375, 1255, 1095, 1030, 970, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.21 (dd, J = 9.9, 15.2 Hz, 1 H), 6.94−6.88 (m, 2 H), 6.82 (d, J = 7.9 Hz, 1 H), 6.28−6.10 (m, 2 H), 5.81 (d, J = 15.2 Hz, 1 H), 5.55 (ddd, J = 4.0, 10.2, 15.2 Hz, 1 H), 5.26 (br dd, J = 4.3, 9.2 Hz, 1 H), 5.12−4.98 (m, 2 H), 4.89 (d, J = 4.6 Hz, 1 H), 4.83 (d, J = 6.9 Hz, 1 H), 4.81 (d, J = 6.9 Hz, 1 H), 4.59 (d, J = 11.6 Hz, 1 H), 4.58 (s, 2 H), 4.52 (d, J = 11.6 Hz, 1 H), 4.03 (br dd, J = 6.6, 6.6 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.65−3.43 (m, 5 H), 3.37 (dd, J = 4.3, 10.2 Hz, 1 H), 3.27 (s, 3 H), 3.19 (s, 3 H), 3.16 (s, 3 H), 2.43 (m, 1 H), 2.37−0.95 (m, 24 H), 2.16 (s, 3 H), 1.45 (s, 3 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.93−0.85 (m, 15 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.79 (d, J = 5.6 Hz, 3 H), 0.12 (s, 3 H), 0.05 (s, 9 H); MS (FAB) *m/z* 1269 $(M + Na)^+$; HRMS (FAB) calcd for $C_{69}H_{122}NaO_{13}SSi_2$ [$(M + Na)^+$] 1269.8042, found 1269.8060.

Diol 87a. To a stirred solution of disilyl ether **86a** (64.0 mg, 0.0513 mmol) in 1,2-dimethoxyethane (6.0 mL) was added 1 M aqueous HCl (1.5 mL) at room temperature. The solution was stirred at room temperature for 5.5 h, cooled to 0 °C, and diluted with Et_2O (5 mL) and saturated aqueous $NaHCO_3$ (2 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layer and the extracts were combined, washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane−EtOAc 5:1 → 3: 1 → 3: 2) to give a diastereomeric mixture of hemiacetals (48.0 mg) as a colorless oil along with recovered **86a** (9.6 mg, 15%). To a stirred solution of the hemiacetals (48.0 mg) in MeOH (2 mL) cooled at 0 °C was added sodium trimethoxyborohydride (66.6 mg, 0.521 mmol). The solution was stirred at room temperature for 4.5 h. The reaction was quenched by addition of acetone (0.2 mL), and the resulting mixture was stirred at room temperature for 10 min. Saturated aqueous NH_4Cl (2 mL) was added, and the mixture was extracted with Et_2O (3 × 5 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane−EtOAc 3: 1 → 1: 1 → 1: 2) to give **87a** (45.7 mg, 72%) as a colorless oil: $[\alpha]^{20}_D$ +31.5 (*c* 0.971, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 1705, 1645, 1615, 1595, 1515, 1465, 1375, 1260, 1030, 970, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 9.9, 15.2 Hz, 1 H), 6.90−6.86 (m, 2 H), 6.82 (d, J = 8.6 Hz, 1 H), 6.25−6.12 (m, 2 H), 5.83 (d, J = 15.2 Hz, 1 H), 5.54 (ddd, J = 4.3, 10.2, 14.9 Hz, 1 H), 5.25 (br dd, J = 5.0, 9.2 Hz, 1 H), 5.11−5.02 (m, 2 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.65 (d, J = 11.5 Hz, 1 H), 4.60 (d, J = 11.9 Hz, 1 H), 4.53 (d, J = 11.5 Hz, 1 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.04 (br s, 1 H), 3.89 (s, 3 H), 3.88 (m, 1 H), 3.87 (s, 3 H), 3.72 (ddd, J = 5.6, 5.6, 11.2 Hz, 1 H), 3.65−3.42 (m, 6 H), 3.38 (dd, J = 4.6, 10.2 Hz, 1 H), 3.20 (s, 3 H), 3.17 (s, 3 H), 3.12 (br s, 1 H), 2.44 (m, 1 H), 2.38−2.16 (m, 3 H), 2.16 (s, 3 H), 2.10−1.75 (m, 6 H), 1.75−0.95 (m, 15 H), 1.45 (s, 3 H), 1.01 (d, J = 7.3 Hz, 3 H), 0.95 (d, J = 7.3 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.91−0.88 (m, 6 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.87 (d, J = 7.3 Hz, 3 H), 0.78 (d, J = 5.9 Hz, 3 H), 0.11 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); MS (FAB) *m/z* 1257 $(M + Na)^+$; HRMS (FAB) calcd for $C_{68}H_{122}NaO_{13}SSi_2$ [$(M + Na)^+$] 1257.8042, found 1257.8020.

Trityl Ether 88a. To a stirred solution of diol **87a** (45.3 mg, 0.0367 mmol) in pyridine (0.4 mL) was added trityl chloride (40.2 mg, 0.144 mmol) at room temperature. The solution was stirred at 50 °C for 11.5 h and was cooled to room temperature. Ice (*ca.* 1 g) and H_2O (1 mL) were added, and the mixture was stirred at room temperature for 1 h and extracted with Et_2O (2 × 5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−Et_2O−triethylamine 80:20:1 → 1: 1: 0 → 1: 2: 0) to give **88a** (52.9 mg, 98%) as a colorless oil: $[\alpha]^{20}_D$ +37.7 (*c* 0.906, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1705, 1645, 1615, 1595, 1515, 1465, 1375, 1255, 1030, 970, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.48−7.39 (m, 6 H), 7.31−7.15 (m, 10 H), 6.89−6.86 (m, 2 H), 6.80 (d, J = 8.9 Hz, 1 H), 6.27−6.10 (m, 2 H), 5.82 (d, J = 15.2 Hz, 1 H), 5.55 (ddd, J = 4.3, 10.2, 14.9 Hz, 1 H), 5.27 (br dd, J = 4.0, 9.2 Hz, 1 H), 5.12−5.06 (m, 2 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.76 (d, J = 6.9 Hz, 1 H), 4.64 (d, J = 11.9 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.52 (d, J = 11.9 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.84 (m, 1 H), 3.59 (m, 1 H), 3.56−3.34 (m, 6 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 3.18 (m, 1 H), 3.01 (m, 1 H), 2.44 (m, 1 H), 2.37−0.95 (m, 24 H), 2.16 (s, 3 H), 1.45 (s, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.95−0.84 (m, 12 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.79 (d, J = 5.6 Hz, 3 H), 0.13 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m/z* 1499 $(M + Na)^+$.

Acetate 89a. To a stirred solution of trityl ether **88a** (18.0 mg, 0.0122 mmol) in pyridine (0.4 mL) were added acetic anhydride (0.2 mL) and 4-(dimethylamino)pyridine (1.0 mg, 0.0082 mmol) at room temperature. The mixture was stirred at room temperature for 12.5 h and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−Et_2O 2:1 → 1: 1 → 1: 2) to give **89a** (18.6 mg, 100%) as a colorless oil: $[\alpha]^{26}_D$ +43.2 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1725, 1710 (sh), 1645, 1615, 1595, 1515, 1465, 1380, 1255, 1030, 970, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.47−7.41 (m, 6 H), 7.33−7.18 (m, 10 H), 6.91−6.87 (m, 2 H), 6.82 (d, J = 8.6 Hz, 1 H), 6.27−6.12 (m, 2 H), 5.82 (d, J = 15.2 Hz, 1 H), 5.55 (ddd, J = 4.3, 10.6, 14.8 Hz, 1 H), 5.28 (br dd, J = 4.3, 9.2 Hz, 1 H), 5.12−4.95 (m, 3 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.67 (d, J = 6.9 Hz, 1 H), 4.62 (d, J = 11.5 Hz, 1 H), 4.59 (d, J = 11.5 Hz, 1 H), 4.52 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.59 (m, 1 H), 3.55−3.33 (m, 5 H), 3.19 (s, 3 H), 3.18 (m, 1 H), 3.17 (s, 3 H), 2.99 (m, 1 H), 2.44 (m, 1 H), 2.37−1.73 (m, 10 H), 2.16 (s, 3 H), 2.00 (s, 3 H), 1.72−0.90 (m, 14 H), 1.45 (s, 3 H), 1.12−0.86 (m, 12 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.79 (d, J = 5.6 Hz, 3 H), 0.71 (d, J = 6.9 Hz, 3 H), 0.14 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H); MS (FAB) *m/z* 1541 $(M + Na)^+$.

Alcohol 90a. Experimental procedure was followed as described for compound **45**. **90a**: $[\alpha]^{25}_D$ +46.9 (*c* 0.995, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 1725, 1710, 1645, 1615, 1595, 1515, 1465, 1380, 1255, 1030, 970, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.22 (dd, J = 9.9, 15.2 Hz, 1 H), 6.90−6.85 (m, 2 H), 6.82 (d, J = 8.6 Hz, 1 H), 6.30−6.10 (m, 2 H), 5.82 (d, J = 15.2 Hz, 1 H), 5.54 (ddd, J = 4.3, 10.6, 15.2 Hz, 1 H), 5.26 (br dd, J = 5.0, 9.9 Hz, 1 H), 5.14−5.00 (m, 2 H), 5.00 (dd, J = 2.3, 9.6 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 1 H), 4.61 (d, J = 11.9 Hz, 1 H), 4.60 (d, J = 11.9 Hz, 1 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.49 (d, J = 11.9 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.76 (m, 1 H), 3.69−3.41 (m, 6 H), 3.38 (dd, J = 4.6, 10.2 Hz, 1 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 2.51−2.16 (m, 4

H), 2.16 (s, 3 H), 2.04 (s, 3 H), 2.04−0.85 (m, 40 H), 1.45 (s, 3 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.79 (d, J = 5.6 Hz, 3 H), 0.13 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H); MS (FAB) m/z 1299 (M + Na)$^+$; HRMS (FAB) calcd for $C_{70}H_{124}NaO_{14}SSi_2$ [(M + Na)$^+$] 1299.8149, found 1299.8130.

Aldehyde 91a. Experimental procedure was followed as described for compound **9**. **91a**: $[\alpha]^{22}_D$ +49 (c 0.44, $CHCl_3$); IR ($CHCl_3$) 2725, 1730, 1710 (sh), 1645, 1615, 1595, 1515, 1465, 1375, 1250, 1045, 970, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (m, 1 H), 7.22 (dd, J = 9.9, 15.2 Hz, 1 H), 6.89−6.86 (m, 2 H), 6.82 (d, J = 8.9 Hz, 1 H), 6.25−6.14 (m, 2 H), 5.82 (d, J = 15.2 Hz, 1 H), 5.54 (ddd, J = 4.3, 10.2, 15.2 Hz, 1 H), 5.25 (dd, J = 4.9, 9.6 Hz, 1 H), 5.10−4.98 (m, 3 H), 4.76 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 1 H), 4.60 (d, J = 11.6 Hz, 1 H), 4.59 (d, J = 11.6 Hz, 1 H), 4.53 (d, J = 11.6 Hz, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.60 (m, 1 H), 3.53−3.35 (m, 5 H), 3.19 (s, 3 H), 3.16 (s, 3 H), 2.49−2.44 (m, 3 H), 2.37−2.16 (m, 4 H), 2.16 (s, 3 H), 2.04 (s, 3 H), 2.04−1.21 (m, 17 H), 1.45 (s, 3 H), 1.13−0.86 (m, 4 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.87 (d, J = 7.2 Hz, 3 H), 0.78 (d, J = 5.6 Hz, 3 H), 0.13 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H); MS (FAB) m/z 1297 (M + Na)$^+$; HRMS (FAB) calcd for $C_{70}H_{122}NaO_{14}SSi_2$ [(M + Na)$^+$] 1297.7992, found 1297.7980.

Enamide 92a. A solution of aldehyde **91a** (10.3 mg, 0.00808 mmol), *N*-methylformamide (0.1 mL, 1.7 mmol), hydroquinone (1.8 mg, 0.016 mmol), and pyridinium *p*-toluenesulfonate (3.8 mg, 0.015 mmol) in benzene (6 mL) was heated to reflux for 6.5 h under a stream of argon with continuous removal of water and use of molecular sieves 3 Å. During the reaction, benzene (7 mL) was added to the solution in portions. The mixture was cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ (1 mL), and extracted with EtOAc (10 mL, 5 mL, then 3 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified twice by column chromatography on silica gel [(2 g, hexane−EtOAc 5:1 → 3: 1 → 2: 1 → 1: 1) and (2 g, hexane−acetone 5:1 → 3:1 → 2:1)] to give **92a** (5.1 mg, 48%) as a colorless amorphous powder along with recovered **91a** (3.0 mg, 29%). **92a**: $[\alpha]^{25}_D$ +28 (c 0.42, $CHCl_3$); IR ($CHCl_3$) 1720 (sh), 1700, 1655, 1515, 1460, 1375, 1255, 1080, 1030, 970, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 [8.06] (s, 1 H), 7.22 (dd, J = 9.1, 15.1 Hz, 1 H), 6.89−6.86 (m, 2 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.48 [7.17] (d, J = 13.9 Hz, 1 H), 6.27−6.12 (m, 2 H), 5.82 (d, J = 15.1 Hz, 1 H), 5.53 (ddd, J = 4.0, 10.6, 14.8 Hz, 1 H), 5.25 (m, 1 H), 5.10−4.97 (m, 4 H), 4.76 [4.75] (d, J = 6.9 Hz, 1 H), 4.64 (d, J = 6.9 Hz, 1 H), 4.61 (d, J = 11.5 Hz, 1 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.53 (d, J = 11.5 Hz, 1 H), 4.49 (d, J = 11.5 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.60 (m, 1 H), 3.55−3.35 (m, 5 H), 3.19 (s, 3 H), 3.16 (s, 3 H), 2.99 [3.02] (s, 3 H), 2.56 (m, 1 H), 2.46 (br d, J = 10.7 Hz, 1 H), 2.37−2.16 (m, 3 H), 2.16 (s, 3 H), 2.07 [2.06] (s, 3 H), 2.01 (m, 1 H), 1.85−1.17 (m, 16 H), 1.45 (s, 3 H), 1.12−0.85 (m, 4 H), 1.03 [1.02] (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 7.3 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.89 (s, 18 H), 0.88 (d, J = 7.3 Hz, 3 H), 0.87 (d, J = 7.3 Hz, 3 H), 0.78 (d, J = 5.6 Hz, 3 H), 0.12 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H) (the minor counterparts of doubled signals in the ratio of 2:1 are in brackets); MS (FAB) m/z 1338 (M + Na)$^+$; HRMS (FAB) calcd for $C_{72}H_{125}NNaO_{14}SSi_2$ [(M + Na)$^+$] 1338.8258, found 1338.8280.

Alcohol 93a. To a stirred solution of enamide **92a** (2.3 mg, 0.0017 mmol) in CH_2Cl_2 (0.36 mL), *tert*-butyl alcohol (0.02 mL), and 1 M phosphate buffer (pH 6, 0.02 mL) cooled at 0 °C was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (0.5 mg, 0.0022 mmol). The mixture was warmed to room temperature and stirred at room temperature for 35 min. To the mixture cooled at 0 °C was added DDQ (0.7 mg, 0.0031 mmol), and the mixture was stirred at room temperature for 40 min. Further, the mixture was cooled to 0 °C and DDQ (0.5 mg, 0.0022 mmol) was added. After the mixture was stirred at room temperature for 35 min, 1 M phosphate buffer (pH 6, 2 mL) was added. The mixture was stirred at room temperature for 40 min and extracted with Et_2O (10 mL, 3 × 3 mL). The combined extracts were washed with 1 M phosphate buffer (pH 6, 2 mL), 5% aqueous $NaHCO_3$ (2 mL), H_2O (2 mL), and brine (2 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by thin-layer chromatography on silica gel (200 × 200 × 0.25 mm, $CHCl_3$−acetone 15:1) to give **93a** (1.7 mg, 88%) as a colorless amorphous powder: $[\alpha]^{23}_D$ +23 (c 0.075, $CHCl_3$); IR ($CHCl_3$) 3520 (br), 1730 (sh), 1710, 1655, 1465, 1375, 1255, 1080, 1050, 970, 835 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.29 [8.07] (s, 1 H), 7.21 (m, 1 H), 6.51 [7.18] (d, J = 14.2 Hz, 1 H), 6.27−6.12 (m, 2 H), 5.82 (d, J = 15.2 Hz, 1 H), 5.55 (ddd, J = 4.0, 10.2, 15.2 Hz, 1 H), 5.28 (m, 1 H), 5.09−4.96 (m, 3 H), 4.82 [4.81] (dd, J = 3.0, 9.9 Hz, 1 H), 4.60 (d, J = 11.6 Hz, 1 H), 4.53 (d, J = 11.6 Hz, 1 H), 3.60−3.35 (m, 7 H), 3.19 (s, 3 H), 3.16 (s, 3 H), 3.02 [3.05] (s, 3 H), 2.60−1.77 (m, 10 H), 2.16 (s, 3 H), 2.16 [2.15] (s, 3 H), 1.70−1.25 (m, 12 H), 1.45 (s, 3 H), 1.12−0.84 (m, 16 H), 1.06 [1.05] (d, J = 6.6 Hz, 3 H), 0.89 (s, 9 H), 0.89 (s, 9 H), 0.79 (d, J = 5.6 Hz, 3 H), 0.12 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H) (the minor counterparts of doubled signals in the ratio of 2:1 are in brackets); MS (FAB) m/z 1158 (M + Na)$^+$; HRMS (FAB) calcd for $C_{62}H_{113}NNaO_{11}SSi_2$ [(M + Na)$^+$] 1158.7470, found 1158.7480.

Dimethylalanine Esters 94. To a mixture of alcohol **93a** (5.6 mg, 0.0049 mmol), L-*N*,*N*-dimethylalanine (7.8 mg, 0.067 mmol), D-*N*,*N*-dimethylalanine (5.2 mg, 0.044 mmol), 4-(dimethylamino)pyridine (36.6 mg, 0.300 mmol), and (±)-camphorsulfonic acid (26.4 mg, 0.114 mmol) was added a 0.20 M solution of dicyclohexylcarbodiimide in CH_2Cl_2 (0.55 mL, 0.11 mmol) at room temperature. The mixture was stirred at room temperature for 15 h, and saturated aqueous $NaHCO_3$ (2.5 mL) was added. The mixture was stirred at room temperature for 1 h and extracted with EtOAc (5 × 3 mL). The combined extracts were washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in Et_2O (1 mL) and filtered through a small plug of cotton, and the residue was washed with Et_2O (4 mL). The filtrate and the washings were combined and concentrated. The residue was purified by column chromatography on silica gel (2 g, CH_2Cl_2−acetone 5: 1 → 3:1 → 1: 1) to give a diastereomeric mixture of dimethylalanine esters **94** (S/R = 4/1) (5.7 mg, 94%) as a colorless amorphous powder: $[\alpha]^{30}_D$ +11 (c 0.065, MeOH); IR ($CHCl_3$) 1725, 1700, 1655, 1465, 1375, 1250, 1080, 1035, 970, 835 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.37 [8.11][a] (s, 1 H), 7.25 (dd, J = 10.2, 15.2 Hz, 1 H), 6.85 [7.16][a] (d, J = 14.5 Hz, 1 H), 6.41 (dd, J = 10.2, 15.2 Hz, 1 H), 6.32 (m, 1 H), 5.93 (d, J = 15.2 Hz, 1 H), 5.57 (ddd, J = 4.3, 10.2, 14.8 Hz, 1 H), 5.31 (m, 1 H), 5.16 (dd, J = 3.4, 9.6 Hz, 1 H), 5.11−4.99 (m, 3 H), 4.82 (dd, J = 1.6, 9.9 Hz, 1 H), 4.68 (d, J = 11.9 Hz, 1 H), 4.63 (d, J = 11.9 Hz, 1 H), 3.72−3.66 (m, 2 H), 3.55 (m, 1 H), 3.50 (ddd, J = 6.0, 6.0, 9.6 Hz, 1 H), 3.44 (dd, J = 5.6, 10.0 Hz, 1 H), 3.21 (m, 1 H), 3.13 (s, 3 H), 3.13 (s, 3 H), 2.97 [3.09][a] (s, 3 H), 2.64 (m, 1 H), 2.49 (br d, J = 13.5 Hz, 1 H), 2.42−2.26 (m, 3 H), 2.35 [2.32][b] (s, 6 H), 2.19 (s, 3 H), 2.18−1.92 (m, 2 H), 1.86 (m, 1 H), 1.78−1.06 (m, 15 H), 1.46 (s, 3 H), 1.27 [1.22][b] (d, J = 7.1 Hz, 3 H), 1.03−0.95 (m, 18 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.81 (d, J = 6.4 Hz, 3 H), 0.17 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a) and 4:1 (superscript b) are in brackets); MS (FAB) m/z 1235 (M + H)$^+$; HRMS (FAB) calcd for $C_{67}H_{123}N_2O_{12}SSi_2$ [(M + H)$^+$] 1235.8336, found 1235.8300.

Alcohol 95. To a stirred solution of dimethylalanine esters **94** (S/R = 4/1) (3.8 mg, 0.0031 mmol) in THF (0.28 mL) and H_2O (0.07 mL) were added 2,6-lutidine (0.05 mL, 0.43 mmol) and silver nitrate (67.5 mg, 0.397 mmol) at room temperature. The mixture was stirred at 30 °C for 16 h in the dark and was filtered through a pad of Celite, and the residue was washed with EtOAc (10 mL). The filtrate and the washings were combined, washed with H_2O (2 mL) and brine (2 mL), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−EtOAc−MeOH 10:2:1 → 4:2:1) to give alcohol **95** (S/R = 4/1) (3.5 mg, 97%) as a colorless amorphous powder: $[\alpha]^{28}_D$ +10 (c 0.04, MeOH); IR ($CHCl_3$) 3450 (br), 1725 (sh), 1705, 1655, 1480, 1375, 1250, 1080, 1035, 970, 835 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.37 [8.12][a] (s, 1 H), 7.25 (dd, J = 11.0, 15.0 Hz, 1 H), 6.86

[7.16][a] (d, J = 15.0 Hz, 1 H), 6.43−6.33 (m, 2 H), 5.90 (d, J = 15.0 Hz, 1 H), 5.57 (ddd, J = 4.8, 10.2, 14.4 Hz, 1 H), 5.31 (m, 1 H), 5.19 (dd, J = 5.0, 9.3 Hz, 1 H), 5.12−4.99 (m, 3 H), 4.82 (dd, J = 2.1, 10.4 Hz, 1 H), 3.83 (dd, J = 2.4, 5.5 Hz, 1 H), 3.67 (br s, 1 H), 3.67 (m, 1 H), 3.55 (m, 1 H), 3.49 (m, 1 H), 3.43 (dd, J = 5.2, 10.2 Hz, 1 H), 3.23 (m, 1 H), 3.13 (s, 3 H), 3.12 (s, 3 H), 2.97 [3.09][a] (s, 3 H), 2.63 (m, 1 H), 2.50 (br d, J = 13.5 Hz, 1 H), 2.42−2.26 (m, 3 H), 2.35 [2.32][b] (s, 6 H), 2.18−1.83 (m, 3 H), 1.80−1.08 (m, 15 H), 1.45 (s, 3 H), 1.27 [1.24][b] (d, J = 7.1 Hz, 3 H), 1.02−0.85 (m, 18 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.81 (d, J = 6.6 Hz, 3 H), 0.16 (s, 3 H), 0.10 (s, 3 H), 0.10 (s, 6 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a) and 4:1 (superscript b) are in brackets); MS (FAB) m/z 1175 $(M + H)^+$; HRMS (FAB) calcd for $C_{65}H_{119}N_2O_{12}Si_2$ $[(M + H)^+]$ 1175.8302, found 1175.8290.

Trimethylserine Esters 96. To a mixture of alcohol **95** (S/R = 4/1) (3.5 mg, 0.0030 mmol), L-*N*,*N*,*O*-trimethylserine (4.9 mg, 0.033 mmol), D-*N*,*N*,*O*-trimethylserine (2.0 mg, 0.013 mmol), 4-(dimethylamino)pyridine (14.5 mg, 0.119 mmol), and (±)-camphorsulfonic acid (11.4 mg, 0.049 mmol) was added a 0.090 M solution of dicyclohexylcarbodiimide in CH_2Cl_2 (0.52 mL, 0.047 mmol) at room temperature. The mixture was stirred at 35 °C for 1.5 h, cooled to room temperature, and diluted with saturated aqueous $NaHCO_3$ (2 mL). The mixture was stirred at room temperature for 20 min and extracted with EtOAc (5 × 2 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in Et_2O (1 mL) and filtered through a small plug of cotton, and the residue was washed with Et_2O (4 mL). The filtrate and the washings were combined and concentrated. The residue was purified by column chromatography on silica gel (2 g, hexane−EtOAc−MeOH 10:10:1 → 4:4:1) to give a diastereomeric mixture of trimethylserine esters **96** (S/R = 4/3 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (3.3 mg, 85%) as a colorless amorphous powder: $[\alpha]^{28}_D$ −2.0 (c 0.020, MeOH); IR ($CHCl_3$) 1730, 1700 (sh), 1655, 1460, 1375, 1250, 1095, 970, 835 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.37 [8.11][a] (s, 1 H), 7.21 [7.22][c] (dd, J = 11.0, 15.3 Hz, 1 H), 6.86 [7.16][a] (d, J = 14.2 Hz, 1 H), 6.42 [6.43][c] (dd, J = 11.0, 15.3 Hz, 1 H), 6.25 (m, 1 H), 5.93 [5.94][c] (d, J = 15.3 Hz, 1 H), 5.56 (ddd, J = 4.0, 10.8, 14.4 Hz, 1 H), 5.31 (br d, J = 10.7 Hz, 1 H), 5.17 (m, 1 H), 5.12−4.98 (m, 3 H), 4.85 (m, 1 H), 4.81 (br d, J = 10.1 Hz, 1 H), 3.70 [3.69][c] (dd, J = 7.6, 9.2 Hz, 1 H), 3.62 (m, 1 H), 3.61 [3.59][c] (dd, J = 5.5, 9.2 Hz, 1 H), 3.54 (m, 1 H), 3.51−3.42 (m, 2 H), 3.38 (dd, J = 5.5, 7.6 Hz, 1 H), 3.34 [3.31][c] (s, 3 H), 3.20 (m, 1 H), 3.11 (s, 3 H), 3.11 (s, 3 H), 2.96 [3.08][a] (s, 3 H), 2.67 (m, 1 H), 2.56−2.43 (m, 3 H), 2.37 (s, 6 H), 2.33 [2.30][b] (s, 6 H), 2.18−1.87 (m, 3 H), 1.85 (m, 1 H), 1.73−1.47 (m, 9 H), 1.48 [1.51][c] (s, 3 H), 1.43−1.08 (m, 6 H), 1.25 [1.20][b] (d, J = 7.1 Hz, 3 H), 1.02−0.95 (m, 18 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.79 [0.79][c] (d, J = 6.4 Hz, 3 H), 0.15 (s, 3 H), 0.09 (s, 3 H), 0.09 (s, 6 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a), 4:1 (superscript b), and 4:3 (superscript c) are in brackets); MS (FAB) m/z 1304 $(M + H)^+$; HRMS (FAB) calcd for $C_{71}H_{130}N_3O_{14}Si_2$ $[(M + H)^+]$ 1304.9092, found 1304.9080.

Aplyronine A (1). A solution of trimethylserine esters **96** (S/R = 4/3 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (3.3 mg, 0.0025 mmol) in a 3:5 mixture of pyridine and HF·pyridine (0.3 mL) was stirred at room temperature for 5 h. The mixture was diluted with EtOAc (2 mL) and poured into saturated aqueous $NaHCO_3$ (8 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (4 × 8 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−EtOAc−MeOH 3: 3: 1 → 2: 2: 1 → 1: 1: 1) to give aplyronine A (**1**) (S/R = 4/3 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (2.3 mg, 84%) as a colorless amorphous powder: $[\alpha]^{28}_D$ +34 (c 0.038, MeOH) [natural $[\alpha]^{28}_D$ +33 (c 0.036, MeOH)]; UV (MeCN) λ_{max} 256 nm (ϵ 31 000) [natural UV (MeCN) λ_{max} 256 nm (ϵ 30 000)]; IR ($CHCl_3$) 3690, 3500 (br), 1730, 1690 (sh), 1655, 1455, 1370, 1240, 1095, 970 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.36 [8.10][a] (s, 1 H), 7.23 [7.24][c] (dd, J = 10.8, 15.3 Hz, 1 H), 6.84 [7.16][a] (d, J = 14.4 Hz, 1 H), 6.43 [6.46][c] (dd, J = 10.8, 15.2 Hz, 1 H), 6.29 (m, 1 H), 5.98 (d, J = 15.3 Hz, 1 H), 5.61 (ddd, J = 4.0, 10.5, 15.3 Hz, 1 H), 5.47 (br d, J = 10.7 Hz, 1 H), 5.18 (m, 1 H), 5.05 [5.11][a] (dd, J = 9.4, 14.4 Hz, 1 H), 5.03 (m, 1 H), 4.95 (dd, J = 9.3, 15.3 Hz, 1 H), 4.80 [4.81][a] (dd, J = 2.7, 10.0 Hz, 1 H), 4.75 [4.72][c] (br d, J = 10.0 Hz, 1 H), 3.69 [3.68][c] (dd, J = 7.6, 9.3 Hz, 1 H), 3.60 (dd, J = 5.5, 9.3 Hz, 1 H), 3.57 (d, J = 5.0 Hz, 1 H), 3.52 (m, 1 H), 3.50 (br s, 1 H), 3.47 (m, 1 H), 3.37 [3.38][c] (dd, J = 5.5, 7.6 Hz, 1 H), 3.34 [3.31][c] (s, 3 H), 3.30 (m, 1 H), 3.20 (m, 1 H), 3.13 (s, 3 H), 3.11 (s, 3 H), 3.06 (m, 1 H), 2.97 [3.09][a] (s, 3 H), 2.66 (m, 1 H), 2.51−2.38 (m, 2 H), 2.37 [2.38][c] (s, 6 H), 2.34 [2.32][b] (s, 6 H), 2.27 (m, 1 H), 2.18−1.85 (m, 4 H), 1.76−1.46 (m, 9 H), 1.51 [1.52][c] (s, 3 H), 1.43−1.08 (m, 6 H), 1.26 [1.21][b] (d, J = 7.1 Hz, 3 H), 1.03−0.96 (m, 15 H), 0.91−0.87 (m, 3 H), 0.76 [0.74][c] (d, J = 5.5 Hz, 3 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a), 4:1 (superscript b), and 4:3 (superscript c) are in brackets); ^{13}C NMR (67.8 MHz, acetone-d_6) δ 172.7, 170.7, 170.4 [170.6][c], 167.5, 162.9 [161.7][a], 145.1, 141.1, 135.4 [135.5][c], 133.4, 132.9, 131.7 [131.8][c], 131.1 [126.3][a], 130.7 [130.6][c], 121.7 [121.8][c], 110.0 [112.1][a], 86.8 [86.7][c], 82.4, 78.0, 77.4, 77.0, 76.6, 72.8, 72.8, 72.5, 68.0 [67.8][c], 63.5 [62.9][b], 59.0 [59.0][c], 55.5, 55.4, 42.6 [42.7][c], 41.9, 41.6, 41.0, 39.1 [39.3][c], 38.2, 38.1 [38.5][c], 38.1, 37.6 [37.8][a], 34.8, 33.3, 32.6 [32.6][c], 30.6, 27.3 [33.0][a], 25.3, 22.6, 21.0, 20.3, 19.9, 17.9, 16.4, 15.9 [15.2][b], 11.7 [11.5][c], 10.7, 10.3, 10.0 [10.0][a] (signals due to two carbons were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a), 4:1 (superscript b), and 4:3 (superscript c) are in brackets); MS (FAB) m/z 1076 $(M + H)^+$; HRMS (FAB) calcd for $C_{59}H_{102}N_3O_{14}$ $[(M + H)^+]$ 1076.7362, found 1076.7400.

(Methylthio)methyl Ether 86b and Ketone 86c. To a stirred solution of the 24-membered lactone **84** (17 mg, 0.015 mmol) in DMSO (0.24 mL) was added a 1:5.6 mixture of acetic acid and acetic anhydride (0.20 mL) at room temperature. The mixture was stirred at 40 °C for 2 h and poured into saturated aqueous $NaHCO_3$ (4 mL) cooled at 0 °C. The mixture was extracted with Et_2O (10 mL, 5 mL). The combined extracts were washed with H_2O (2 mL) and brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−EtOAc 2:1 → 1: 1) and preparative HPLC (Develosil 30−10, 20 × 250 mm, hexane−EtOAc−MeOH 80:20:1, 5 mL/min) to give **86b** (t_R = 35 min, 7.7 mg, 43%) and **86c** (t_R = 50 min, 8.4 mg, 50%) as a colorless oil, respectively. **86b**: $[\alpha]^{26}_D$ +61.2 (c 0.745, $CHCl_3$); IR ($CHCl_3$) 1705, 1645, 1515, 1465, 1260, 1140, 1095, 1030, 970, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 10.2, 15.6 Hz, 1 H), 6.93−6.89 (m, 2 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.26−6.15 (m, 2 H), 5.82 (d, J = 15.6 Hz, 1 H), 5.57 (ddd, J = 3.9, 10.2, 14.6 Hz, 1 H), 5.42 (br d, J = 11.2 Hz, 1 H), 5.06−4.98 (m, 2 H), 4.89 (d, J = 4.3 Hz, 1 H), 4.84 (d, J = 6.8 Hz, 1 H), 4.82 (d, J = 6.8 Hz, 1 H), 4.69 (d, J = 10.7 Hz, 1 H), 4.59 (d, J = 11.7 Hz, 1 H), 4.58 (s, 2 H), 4.53 (d, J = 10.7 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 4.03 (br dd, J = 6.3, 6.3 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.64−3.45 (m, 4 H), 3.37 (dd, J = 4.3, 10.7 Hz, 1 H), 3.27 (s, 3 H), 3.18 (s, 3 H), 3.16 (s, 3 H), 3.04 (dd, J = 2.9, 7.8 Hz, 1 H), 2.46−1.00 (m, 25 H), 2.22 (s, 3 H), 2.16 (s, 3 H), 1.44 (s, 3 H), 1.10 (d, J = 6.4 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.93−0.86 (m, 12 H), 0.88 (s, 9 H), 0.79 (d, J = 5.4 Hz, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H); MS (FAB) m/z 1215 $(M + Na)^+$; HRMS (FAB) calcd for $C_{65}H_{112}NaO_{13}S_2Si$ $[(M + Na)^+]$ 1215.7213, found 1215.7210. **86c**: $[\alpha]^{26}_D$ +67.3 (c 0.910, $CHCl_3$); IR ($CHCl_3$) 1715, 1705 (sh), 1645, 1515, 1465, 1260, 1135, 1095, 1030, 970, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 10.2, 15.1 Hz, 1 H), 6.93−6.89 (m, 2 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.25−6.15 (m, 2 H), 5.80 (d, J = 15.1 Hz, 1 H), 5.51 (ddd, J = 3.9, 10.2, 14.6 Hz, 1 H), 5.32 (m, 1 H), 5.06−4.98 (m, 2 H), 4.88 (d, J = 4.9 Hz, 1 H), 4.83 (d, J = 6.8 Hz, 1 H), 4.80 (d, J = 6.8 Hz, 1 H), 4.59 (d, J = 11.7 Hz, 1 H), 4.58 (d, J = 12.2 Hz, 1 H), 4.55 (d, J = 11.7 Hz, 1 H), 4.52 (d, J = 12.2 Hz, 1 H), 4.04 (br dd, J = 6.3, 6.3 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.60 (m, 1 H), 3.54 (dd, J = 6.4, 9.8

Hz, 1 H), 3.52−3.43 (m, 2 H), 3.37 (dd, J = 4.4, 10.3 Hz, 1 H), 3.26 (s, 3 H), 3.16 (s, 3 H), 3.15 (s, 3 H), 2.89 (dq, J = 6.8, 6.8 Hz, 1 H), 2.64 (ddq, J = 6.8, 6.8, 6.8 Hz, 1 H), 2.39−1.06 (m, 23 H), 2.15 (s, 3 H), 1.43 (s, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 1.09 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 5.9 Hz, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H); MS (FAB) m/z 1153 $(M + Na)^+$; HRMS (FAB) calcd for $C_{63}H_{106}NaO_{13}SSi$ $[(M + Na)^+]$ 1153.7021, found 1153.7020.

Reduction of Ketone 86c. To a stirred solution of ketone **86c** (11.5 mg, 0.0102 mmol) in MeOH cooled at −23 °C was added sodium borohydride (3.5 mg, 0.092 mmol). The solution was stirred at −23 °C for 3 h, and the reaction was quenched by addition of acetone (0.1 mL). The mixture was stirred at −23 °C for 30 min, diluted with saturated aqueous NH_4Cl (2 mL), and extracted with Et_2O (10 mL, 5 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by medium-pressure liquid chromatography (Fuji Silysia, silica gel FL60D, 6.4 g, hexane−EtOAc 3:2 → 1: 1, 2 mL/min) to give **84** (t_R = 25 min, 8.7 mg, 75%) along with the C25-epimer (t_R = 49 min, 1.1 mg, 9%) as a colorless oil, respectively. **C25-epimer**: $[\alpha]^{29}_D$ +48 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1705, 1640, 1515, 1465, 1260, 1095, 1030, 970, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.21 (dd, J = 10.3, 15.2 Hz, 1 H), 6.93−6.88 (m, 2 H), 6.83 (d, J = 7.9 Hz, 1 H), 6.25−6.14 (m, 2 H), 5.81 (d, J = 15.2 Hz, 1 H), 5.55 (ddd, J = 4.3, 10.2, 14.8 Hz, 1 H), 5.17 (m, 1 H), 5.12−5.00 (m, 2 H), 4.89 (d, J = 5.0 Hz, 1 H), 4.81 (s, 2 H), 4.59 (d, J = 11.5 Hz, 1 H), 4.57 (s, 2 H), 4.53 (d, J = 11.5 Hz, 1 H), 4.01 (m, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.64−3.43 (m, 4 H), 3.43−3.34 (m, 2 H), 3.28 (s, 3 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 2.45−0.96 (m, 26 H), 2.16 (s, 3 H), 1.44 (s, 3 H), 1.10 (d, J = 6.3 Hz, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.87 (d, J = 7.6 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.78 (d, J = 5.3 Hz, 3 H), 0.04 (s, 6 H); MS (FAB) m/z 1155 $(M + Na)^+$; HRMS (FAB) calcd for $C_{63}H_{108}NaO_{13}SSi$ $[(M + Na)^+]$ 1155.7178, found 1155.7210.

Aplyronine B (2). To a stirred solution of *N*,*N*,*O*-trimethylserine esters **99** (S/R = 5/6 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (1.3 mg, 0.0011 mmol) in THF (0.2 mL) and H_2O (0.05 mL) were added 2,6-lutidine (0.05 mL, 0.43 mmol) and silver nitrate (68 mg, 0.40 mmol) at room temperature, and the mixture was stirred at 30 °C for 16 h in the dark. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc (15 mL). The filtrate and the washings were combined, washed with saturated aqueous $NaHCO_3$ (2 mL), H_2O (2 mL), and brine (2 mL), and concentrated. The residual oil was purified by column chromatography on silica gel (0.5 g, hexane−EtOAc−MeOH 5:5:1 → 2:2:1) to give aplyronine B (**2**) (S/R = 5/6 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (1.0 mg, 85%) as a colorless amorphous powder: $[\alpha]^{24}_D$ −5.1 (*c* 0.051, MeOH) [natural $[\alpha]^{24}_D$ +3.7 (*c* 0.19, MeOH)]; CD (*c* 0.0041, MeOH) λ_{ext} 265 nm ($\Delta\epsilon$ −3.7) [natural CD (*c* 0.0039, MeOH) λ_{ext} 265 nm ($\Delta\epsilon$ −3.3)]; UV (MeCN) λ_{max} 258 nm (ϵ 29 000) [natural UV (MeCN) λ_{max} 258 nm (ϵ 30 200)]; IR ($CHCl_3$) 3470 (br), 1725, 1695, 1655, 1460, 1375, 1240, 1090, 975 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.37 [8.11][a] (s, 1 H), 7.27 (dd, J = 10.3, 15.4 Hz, 1 H), 6.85 [7.16][a] (d, J = 14.3 Hz, 1 H), 6.51−6.43 (m, 2 H), 5.94 (d, J = 15.4 Hz, 1 H), 5.62 (ddd, J = 4.0, 10.6, 15.0 Hz, 1 H), 5.49 (br d, J = 11.0 Hz, 1 H), 5.25 (m, 1 H), 5.05 [5.10][a] (dd, J = 9.5, 14.3 Hz, 1 H), 5.03 (m, 1 H), 4.98 (dd, J = 9.9, 15.0 Hz, 1 H), 4.93 (dd, J = 1.8, 9.2 Hz, 1 H), 4.80 [4.80][a] (dd, J = 2.6, 10.3 Hz, 1 H), 3.79 (dd, J = 4.8, 8.4 Hz, 1 H), 3.68 (dd, J = 7.3, 9.2 Hz, 1 H), 3.67 (br s, 1 H), 3.62−3.57 (m, 2 H), 3.53−3.46 (m, 2 H), 3.41 [3.40][c] (dd, J = 6.6, 6.6 Hz, 1 H), 3.29 [3.28][c] (s, 3 H), 3.18 [3.23][b] (m, 1 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 3.06 (m, 1 H), 2.97 [3.09][a] (s, 3 H), 2.65 (m, 1 H), 2.45 (m, 1 H), 2.36 [2.37][c] (s, 6 H), 2.35−2.23 (m, 2 H), 2.33 [2.31][b] (s, 6 H), 2.15 (m, 1 H), 2.09−1.91 (m, 3 H), 1.87−1.78 (m, 2 H), 1.73 (m, 1 H), 1.67−1.48 (m, 6 H), 1.45−1.08 (m, 6 H), 1.44 (s, 3 H), 1.26 [1.20][b] (d, J = 7.3 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 0.90 [0.91][c] (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.88 [0.94][c] (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a), 4:1 (superscript b), and 5:6 (superscript c) are in brackets); MS (FAB) m/z 1076 $(M + H)^+$; HRMS (FAB) calcd for $C_{59}H_{102}N_3O_{14}$ $[(M + H)^+]$ 1076.7362, found 1076.7370.

Aplyronine C (3). A solution of alcohol **95** (S/R = 2/1) (1.37 mg, 0.00116 mmol) in a 3:5 mixture of pyridine and HF•pyridine (0.5 mL) was stirred at room temperature for 5 h. The mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) cooled to 0 °C and extracted with EtOAc (5 × 5 mL). The combined extracts were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−EtOAc−MeOH 5: 5: 1 → 3: 3: 1 → 1: 1: 1) and preparative HPLC (Develosil ODS-HG-5, 10 × 250 mm, MeCN−0.02 M aqueous NH_4OAc, 3 mL/min, t_R = 12 min) and column chromatography on alumina (0.5 g, EtOAc → EtOAc−MeOH 95:5) to give aplyronine C (**3**) (S/R = 2/1) (0.50 mg, 45%) as a colorless amorphous powder: $[\alpha]^{27}_D$ +19 (*c* 0.042, MeOH) [natural $[\alpha]^{29}_D$ +21 (*c* 0.041, MeOH)]; CD (*c* 0.0033, MeOH) λ_{ext} 277 nm ($\Delta\epsilon$ −0.90) [natural CD (*c* 0.0033, MeOH) λ_{ext} 277 nm ($\Delta\epsilon$ −1.0)]; UV (MeCN) λ_{max} 259 nm (ϵ 33 000) [natural UV (MeCN) λ_{max} 260 nm (ϵ 30 000)]; IR ($CHCl_3$) 3620, 3480 (br), 1730, 1725 (sh), 1690, 1655, 1460, 1375, 1240, 1090, 1080, 970 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.37 [8.10] (s, 1 H), 7.26 (dd, J = 10.3, 15.4 Hz, 1 H), 6.85 [7.15] (d, J = 14.4 Hz, 1 H), 6.42 (ddd, J = 5.1, 9.2, 15.4 Hz, 1 H), 6.37 (dd, J = 10.3, 15.4 Hz, 1 H), 5.93 (d, J = 15.4 Hz, 1 H), 5.62 (ddd, J = 4.4, 10.6, 15.0 Hz, 1 H), 5.47 (br d, J = 11.4 Hz, 1 H), 5.22 (br dd, J = 4.8, 10.6 Hz, 1 H), 5.05 [5.11] (dd, J = 9.5, 14.3 Hz, 1 H), 5.03−4.99 (m, 2 H), 4.80 (br d, J = 9.9 Hz, 1 H), 3.80 (br d, J = 4.0 Hz, 1 H), 3.66 (m, 1 H), 3.60 (br d, J = 5.1 Hz, 1 H), 3.50−3.46 (m, 2 H), 3.40 (m, 1 H), 3.37 (br d, J = 5.1 Hz, 1 H), 3.18 (m, 1 H), 3.12 (s, 3 H), 3.11 (s, 3 H), 3.05 (m, 1 H), 2.97 [3.09] (s, 3 H), 2.66 (m, 1 H), 2.44 (m, 1 H), 2.34−2.22 (m, 2 H), 2.33 [2.31] (s, 6 H), 2.14 (m, 1 H), 2.08−1.91 (m, 2 H), 2.03 [2.02] (s, 3 H), 1.79 (m, 1 H), 1.73−1.70 (m, 2 H), 1.67−1.50 (m, 7 H), 1.45 (s, 3 H), 1.35 (m, 1 H), 1.31−1.13 (m, 5 H), 1.25 [1.20] (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.89 [0.90] (d, J = 7.0 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H) (the minor counterparts of doubled signals in the ratio of 2:1 are in brackets); MS (FAB) m/z 969 $(M + Na)^+$, 947 $(M + H)^+$; HRMS (FAB) calcd for $C_{53}H_{91}N_2O_{12}$ $[(M + H)^+]$ 947.6572, found 947.6600.

Aldehyde 100. To a stirred solution of aplyronine A (**1**) (S/R = 1.1/1 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (2.3 mg, 0.0021 mmol) in dioxane (0.6 mL) was added 2 M aqueous HCl (0.2 mL) at room temperature, and the resulting solution was stirred at 50 °C for 1.5 h. The mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (4 mL) cooled at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (4 × 4 mL). The combined extracts were washed with H_2O (2 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (2 g, hexane−EtOAc−MeOH 5:5:1 → 3: 3: 1 → 2: 2: 1) and preparative HPLC (Develosil 60−5, 10 × 250 mm, hexane−1,2-dichloroethane−MeOH−H_2O−triethylamine 50:45:4.5:0.25:0.25, 3.0 mL/min) to give **100** (S/R = 1.1/1 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (t_R = 41 min, 1.4 mg, 63%) as a colorless amorphous powder: $[\alpha]^{28}_D$ +54 (*c* 0.065, MeOH); UV (MeCN) λ_{max} 261 nm (ϵ 33 000); IR ($CHCl_3$) 3480 (br), 2720, 1730, 1700 (sh), 1645, 1620, 1460, 1375, 1240, 1095, 970 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 9.75 (dd, J = 1.4, 2.3 Hz, 1 H), 7.23 (dd, J = 10.5, 15.1 Hz, 1 H), 6.45 [6.46][a] (dd, J = 10.5, 15.0 Hz, 1 H), 6.29 [6.31][a] (ddd, J = 5.0, 9.6, 15.0 Hz, 1 H), 5.99 (d, J = 15.1 Hz, 1 H), 5.62 (ddd, J = 4.1, 11.0, 15.1 Hz, 1 H), 5.48 (br d, J = 11.0 Hz, 1 H), 5.18 (m, 1 H), 5.01 (ddd, J = 1.8, 6.9, 6.9 Hz, 1 H), 4.97 (dd, J = 9.6, 15.1 Hz, 1 H), 4.80 (dd, J = 2.8, 9.6 Hz, 1 H), 4.74 (br t, J = 12.0 Hz, 1 H), 3.69 [3.68][a] (dd, J = 7.8, 9.4 Hz, 1 H), 3.65−3.40 (m, 3 H), 3.60 (dd, J = 5.7, 9.4 Hz, 1 H), 3.48 (ddd, J = 4.1, 9.6, 10.9 Hz, 1 H), 3.38 [3.39][a] (dd, J = 5.7, 7.8 Hz, 1 H), 3.34 [3.31][a] (s, 3 H), 3.33 (m, 1 H), 3.20 [3.23][b] (q, J = 6.9 Hz, 1 H), 3.12 (s, 3 H),

3.10 (s, 3 H), 3.07 (m, 1 H), 2.61 (m, 1 H), 2.57 (m, 1 H), 2.52−2.40 (m, 2 H), 2.37 [2.38][a] (s, 6 H), 2.33 [2.31][b] (s, 6 H), 2.40−2.22 (m, 2 H), 2.16 (m, 1 H), 2.03 [2.01][b] (s, 3 H), 2.10−1.98 (m, 2 H), 1.92 (m, 1 H), 1.78 (m, 1 H), 1.72−1.46 (m, 8 H), 1.51 [1.52][a] (s, 3 H), 1.42 (m, 1 H), 1.36−1.08 (m, 5 H), 1.27 [1.21][b] (d, J = 6.9 Hz, 3 H), 1.04−0.98 (m, 12 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.76 [0.75][a] (d, J = 6.0 Hz, 3 H) (the minor counterparts of doubled signals in the ratios of 1.1:1 (superscript a) and 4:1 (superscript b) are in brackets); MS (FAB) m/z 1035 $(M + H)^+$; HRMS (FAB) calcd for $C_{57}H_{99}N_2O_{14}$ $[(M + H)^+]$ 1035.7097, found 1035.7080.

Alcohol 101. To a stirred solution of aldehyde **100** (S/R = 1.1/1 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (1.0 mg) in THF (0.05 mL) cooled at 0 °C was added a 0.5 M solution of lithium tri-*tert*-butoxyaluminum hydride [LiAlH(O-*t*-Bu)$_3$] (0.005 mL, 0.0025 mmol). After the mixture was stirred at 0 °C for 30 min, a 0.5 M solution of LiAlH(O-*t*-Bu)$_3$ (0.005 mL, 0.0025 mmol) was added, and the mixture was stirred at 0 °C for 50 min. Further, a 0.5 M solution of LiAlH(O-*t*-Bu)$_3$ (0.005 mL, 0.0025 mmol) was added, and the mixture was stirred at 0 °C for 40 min. After the reaction was quenched by addition of H_2O (0.03 mL), the mixture was filtered through a pad of Celite, and the residue was washed with THF (10 mL). The filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (1 g, hexane−EtOAc−MeOH 5:5:1 → 3: 3: 1 → 1: 1: 1) and preparative HPLC (Develosil 60−5, 10 × 250 mm, 1,2-dichloroethane−MeOH−H_2O−triethylamine 95:4.5:0.25:0.25, 3.0 mL/min) to give **101** (S/R = 1.1/1 as to the trimethylserine part, S/R = 4/1 as to the dimethylalanine part) (t_R = 29 min, 0.6 mg, 60%) as a colorless oil: $[\alpha]^{26}_D$ +42 (c 0.056, MeOH); UV (MeCN) λ_{max} 260 nm (ϵ 21 000); IR ($CHCl_3$) 3630, 3500 (br), 1730, 1700 (sh), 1645, 1605, 1460, 1375, 1245, 1100, 970 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.23 (dd, J = 11.0, 15.3 Hz, 1 H), 6.45 [6.46][a] (dd, J = 11.0, 15.0 Hz, 1 H), 6.29 [6.30][a] (ddd, J = 5.0, 10.0, 15.0 Hz, 1 H), 5.98 (d, J = 15.3 Hz, 1 H), 5.62 (ddd, J = 4.3, 10.7, 15.0 Hz, 1 H), 5.49 (br d, J = 10.7 Hz, 1 H), 5.18 (m, 1 H), 4.98 (dd, J = 6.1, 6.1 Hz, 1 H), 4.97 (dd, J = 8.2, 15.0 Hz, 1 H), 4.79 (dd, J = 2.8, 10.1 Hz, 1 H), 4.74 (br t, J = 11.5 Hz, 1 H), 3.70 [3.69][a] (dd, J = 7.6, 9.2 Hz, 1 H), 3.67 (m, 1 H), 3.60 (dd, J = 5.5, 9.2 Hz, 1 H), 3.56 (d, J = 5.2 Hz, 1 H), 3.56−3.41 (m, 5 H), 3.37 [3.38][a] (dd, J = 5.5, 7.6 Hz, 1 H), 3.34 [3.31][a] (s, 3 H), 3.19 [3.22][b] (q, J = 7.0 Hz, 1 H), 3.12 (s, 3 H), 3.10 (s, 3 H), 3.08 (m, 1 H), 2.46−2.20 (m, 4 H), 2.37 [2.38][a] (s, 6 H), 2.33 [2.31][b] (s, 6 H), 2.20−2.14 (m, 1 H), 2.09−1.90 (m, 3 H), 2.00 [1.98][b] (s, 3 H), 1.76−1.50 (m, 11 H), 1.51 [1.51][a] (s, 3 H), 1.41 (m, 1 H), 1.30−1.13 (m, 6 H), 1.25 [1.21][b] (d, J = 7.3 Hz, 3 H), 1.03−0.98 (m, 12 H), 0.92 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.76 [0.75][a] (d, J = 5.8 Hz, 3 H) (the minor counterparts of doubled signals in the ratios of 1.1:1 (superscript a) and 4:1 (superscript b) are in brackets); MS (FAB) m/z 1037 $(M + H)^+$; HRMS (FAB) calcd for $C_{57}H_{101}N_2O_{14}$ $[(M + H)^+]$ 1037.7253, found 1037.7230.

Alcohol 102. Experimental procedure was followed as described for compound **95**. **102** : $[\alpha]^{26}_D$ +21 (c 0.12, $CHCl_3$); IR ($CHCl_3$) 3480 (br), 1715, 1695, 1655, 1515, 1465, 1375, 1255, 1080, 970 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.27 [8.06] (s, 1 H), 7.22 (dd, J = 9.6, 15.5 Hz, 1 H), 6.89−6.85 (m, 2 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.48 [7.17] (d, J = 13.9 Hz, 1 H), 6.28−6.13 (m, 2 H), 5.79 (d, J = 15.5 Hz, 1 H), 5.50 (ddd, J = 4.3, 9.9, 14.5 Hz,1 H), 5.23 (m, 1 H), 5.18−4.97 (m, 4 H), 4.76 [4.76] (d, J = 7.3 Hz, 1 H), 4.64 (d, J = 7.3 Hz, 1 H), 4.56 (d, J = 11.5 Hz, 1 H), 4.49 (d, J = 11.5 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.79 (m, 1 H), 3.60 (m, 1 H), 3.53−3.38 (m, 5 H), 3.20 (s, 3 H), 3.16 (s, 3 H), 2.99 [3.02] (s, 3 H), 2.80−2.00 (m, 9 H), 2.07 [2.07] (s, 3 H), 1.83−1.10 (m, 14 H), 1.46 (s, 3 H), 1.03 [1.02] (d, J = 6.9 Hz, 3 H), 0.96−0.83 (m, 15 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.79 (d, J = 6.3 Hz, 3 H), 0.12 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 3 H) (the minor counterparts of doubled signals in the ratio of 2:1 are in brackets); MS (FAB) m/z 1278 $(M + Na)^+$; HRMS (FAB) calcd for $C_{70}H_{121}NNaO_{14}Si_2$ $[(M + Na)^+]$ 1278.8224, found 1278.8200.

Trimethylserine Esters 103. Experimental procedure was followed as described for compound **96**. **103** (S/R = 4/3): $[\alpha]^{26}_D$ +8 (c 0.11, $CHCl_3$); IR ($CHCl_3$) 1725, 1700, 1655, 1515, 1460, 1255, 1100, 1030, 970 cm^{-1}; ^{1}H NMR (270 MHz, acetone-d_6) δ 8.37 [8.11][a] (s, 1 H), 7.21 [7.21][b] (dd, J = 10.9, 15.5 Hz, 1 H), 6.97−6.84 (m, 3 H), 6.84 [7.17][a] (d, J = 14.2 Hz, 1 H), 6.48−6.15 (m, 2 H), 5.91 (d, J = 15.5 Hz, 1 H), 5.55 (m, 1 H), 5.30 (m, 1 H), 5.22−4.96 (m, 4 H), 4.85 (m, 1 H), 4.74 (d, J = 6.9 Hz, 1 H), 4.64 (d, J = 6.9 Hz, 1 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.76−3.27 (m, 8 H), 3.34 [3.31][b] (s, 3 H), 3.11 (s, 6 H), 2.95 [3.07][a] (s, 3 H), 2.75−1.10 (m, 23 H), 2.37 (s, 6 H), 1.48 (s, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.01−0.88 (m, 9 H), 0.97 (d, J = 6.3 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.79 (d, J = 6.3 Hz, 3 H), 0.15 (s, 3 H), 0.09 (s, 9 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a) and 4:3 (superscript b) are in brackets); MS (FAB) m/z 1407 $(M + Na)^+$; HRMS (FAB) calcd for $C_{76}H_{132}N_2NaO_{16}Si_2$ $[(M + Na)^+]$ 1407.9014, found 1407.8980.

Diol 104. Experimental procedure was followed as described for aplyronine A (**1**). **104** (S/R = 4/3): $[\alpha]^{26}_D$ +23 (c 0.075, $CHCl_3$); IR ($CHCl_3$) 3630, 3500 (br), 1730, 1690, 1655, 1515, 1460, 1375, 1240, 1025, 970 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.36 [8.09][a] (s, 1 H), 7.21 [7.22][b] (dd, J = 10.7, 15.1 Hz, 1 H), 6.96−6.85 (m, 3 H), 6.83 [7.16][a] (d, J = 14.2 Hz, 1 H), 6.44 (m, 1 H), 6.29 (m, 1 H), 5.97 (d, J = 15.1 Hz, 1 H), 5.57 (m, 1 H), 5.43 (br d, J = 11.2 Hz, 1 H), 5.17 (m, 1 H), 5.08 [5.13][a] (dd, J = 4.9, 14.2 Hz, 1 H), 5.01−4.89 (m, 2 H), 4.74 (d, J = 6.8 Hz, 1 H), 4.71 (m, 1 H), 4.65 (d, J = 6.8 Hz, 1 H), 4.61 (d, J = 11.5 Hz, 1 H), 4.44 (d, J = 11.5 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.68 [3.67][b] (dd, J = 7.9, 9.3 Hz, 1 H), 3.58 (dd, J = 5.4, 9.3 Hz, 1 H), 3.54−3.28 (m, 7 H), 3.33 [3.30][b] (s, 3 H), 3.11 (s, 3 H), 3.09 (s, 3 H), 3.05 (m, 1 H), 2.95 [3.07][a] (s, 3 H), 2.76−1.06 (m, 23 H), 2.35 [2.37][b] (s, 6 H), 1.49 (br s, 3 H), 1.02−0.95 (m, 12 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.75−0.71 (m, 3 H) (signals of three protons (CH_3COO) were overlapped with the solvent signals; the minor counterparts of doubled signals in the ratios of 2:1 (superscript a) and 4:3 (superscript b) are in brackets); MS (FAB) m/z 1179 $(M + Na)^+$; HRMS (FAB) calcd for $C_{64}H_{104}N_2NaO_{16}$ $[(M + Na)^+]$ 1179.7284, found 1179.7260.

Analogue 105. To a stirred solution of diol **104** (S/R = 4/3) (1.4 mg, 0.0012 mmol) in CH_2Cl_2 (0.36 mL), *tert*-butyl alcohol (0.02 mL), and 1 M phosphate buffer (pH 6, 0.02 mL) cooled at 0 °C was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (0.7 mg, 0.0031 mmol). The mixture was warmed to room temperature, and the stirring was continued for 20 min. To the mixture cooled at 0 °C was added DDQ (0.5 mg, 0.0022 mmol), and the resulting mixture was stirred at room temperature for 20 min. Again, the mixture was cooled to 0 °C and DDQ (0.6 mg, 0.0026 mmol) was added. After the mixture was stirred at room temperature for 15 min, 1 M phosphate buffer (pH 6, 1 mL) was added. The mixture was stirred at room temperature for 2 h and extracted with Et_2O (10 mL, 2 × 5 mL). The combined extracts were washed with 1 M phosphate buffer (pH 6, 2 mL), saturated aqueous $NaHCO_3$ (2 mL), H_2O (2 mL), and brine (2 mL), successively, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.5 g, CH_2Cl_2−acetone 5:1 → 3:1 → 2:1 → 1:1), preparative HPLC (Develosil ODS-HG-5, 10 × 250 mm, MeCN−0.02 M aqueous NH_4OAc 65:35, 2 mL/min), and column chromatography on alumina (0.1 g, EtOAc → EtOAc−MeOH 9: 1) to give **105** (S/R = 4/3) (0.6 mg, 50%) as a colorless amorphous powder along with recovered **104** (0.4 mg, 30%). **105**: $[\alpha]^{27}_D$ +29 (c 0.059, MeOH); UV (MeCN) λ_{max} 256 nm (ϵ 27 000); IR ($CHCl_3$) 3680, 3510 (br), 1715, 1695, 1660, 1480, 1250, 1075, 970 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.36 [8.09][a] (s, 1 H), 7.21 [7.21][b] (dd, J = 10.6, 15.4 Hz, 1 H), 6.84 [7.15][a] (d, J = 13.9 Hz, 1 H), 6.44 [6.45][b] (dd, J = 10.6, 16.1 Hz, 1 H), 6.29 (m, 1 H), 5.98 [5.98][b] (d, J = 15.4 Hz, 1 H), 5.61 (ddd, J = 4.0, 10.6, 15.0 Hz, 1 H), 5.47 (br d, J = 11.4 Hz, 1 H), 5.17 (m, 1 H), 5.07 [5.13][a] (dd, J = 9.5, 13.9 Hz, 1 H), 4.94 (dd, J = 9.2, 15.0 Hz, 1 H), 4.87 [4.88][a] (dd, J = 2.6, 10.1 Hz, 1 H), 4.71 (m, 1 H), 3.68 [3.67][b] (dd, J = 7.7, 9.5 Hz, 1 H), 3.58 (dd, J = 5.5, 9.5 Hz, 1 H), 3.53−3.44 (m, 5 H), 3.35 [3.37][b] (dd, J = 5.5, 7.7 Hz, 1 H), 3.33 [3.29][b] (s, 3 H), 3.30 (m, 1 H), 3.11 (s, 3 H), 3.09 (s, 3 H), 3.05−2.99 (m, 2 H), 2.96 [3.07][a] (s, 3 H), 2.63 (m, 1 H), 2.48−2.38 (m, 2

H), 2.35 [2.37][b] (s, 6 H), 2.29 (m, 1 H), 2.17−1.86 (m, 4 H), 2.09 [2.08][a] (s, 3 H), 1.75 (m, 1 H), 1.70−1.47 (m, 8 H), 1.50 [1.49][b] (s, 3 H), 1.44−1.04 (m, 6 H), 1.02 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.99 [0.97][b] (d, J = 7.0 Hz, 3 H), 0.94 [0.94][a] (d, J = 6.6 Hz, 3 H), 0.88 [0.88][a] (d, J = 7.0 Hz, 3 H), 0.85 [0.85][a] (d, J = 7.0 Hz, 3 H), 0.74 [0.73][b] (d, J = 6.2 Hz, 3 H) (the minor counterparts of doubled signals in the ratios of 2:1 (superscript a) and 4:3 (superscript b) are in brackets); MS (FAB) m/z 977 $(M + H)^+$; HRMS (FAB) calcd for $C_{54}H_{93}N_2O_{13}$ $[(M + H)^+]$ 977.6677, found 977.6696.

Triol 106. A solution of alcohol **102** (1.4 mg, 0.0011 mmol) in a 8:3:5 mixture of THF, pyridine, and HF·pyridine (0.4 mL) was stirred at room temperature for 10 h. The mixture was poured into saturated aqueous $NaHCO_3$ (6 mL) cooled at 0 °C, and the resulting mixture was extracted with EtOAc (20 mL, 2 × 15 mL). The combined extracts were washed with brine (4 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (0.2 g, CH_2Cl_2−acetone 5: 1 → 3: 1 → 2: 1 → 1: 1) to give **106** (1.0 mg, 89%) as a colorless oil: $[\alpha]^{27}_D$ +9 (c 0.091, $CHCl_3$); IR ($CHCl_3$) 3690, 3500 (br), 1730, 1695, 1655, 1520, 1465, 1375, 1245, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 [8.08] (s, 1 H), 7.28 (dd, J = 9.8, 15.1 Hz, 1 H), 6.90−6.86 (m, 2 H), 6.82 (d, J = 7.8 Hz, 1 H), 6.48 [7.17] (d, J = 14.2 Hz, 1 H), 6.24 (dd, J = 9.8, 14.6 Hz, 1 H), 6.17 (ddd, J = 5.4, 8.8, 14.6 Hz, 1 H), 5.84 (d, J = 15.1 Hz, 1 H), 5.52 (m, 1 H), 5.36 (br d, J = 10.7 Hz, 1 H), 5.18−4.98 (m, 4 H), 4.78 [4.77] (d, J = 6.8 Hz, 1 H), 4.66 [4.66] (d, J = 6.8 Hz, 1 H), 4.63 (d, J = 11.7 Hz, 1 H), 4.47 (d, J = 11.7 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.73 (m, 1 H), 3.63 (m, 1 H), 3.52−3.41 (m, 5 H), 3.33 (m, 1 H), 3.20 (s, 3 H), 3.18 (s, 3 H), 3.02 [3.05] (s, 3 H), 2.97 (m, 1 H), 2.63−2.32 (m, 5 H), 2.19−1.94 (m, 3 H), 2.08 [2.07] (s, 3 H), 1.78−1.05 (m, 15 H), 1.46 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 1.04−0.98 (m, 6 H), 0.91 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.73 (d, J = 5.9 Hz, 3 H) (the minor counterparts of doubled signals in the ratio of 2:1 are in brackets); MS (FAB) m/z 1050 $(M + Na)^+$; HRMS (FAB) calcd for $C_{58}H_{93}NNaO_{14}$ $[(M + Na)^+]$ 1050.6490, found 1050.6490.

Analogue 107. To a stirred solution of diol **106** (1.4 mg, 0.0014 mmol) in CH_2Cl_2 (0.36 mL), *tert*-butyl alcohol (0.02 mL), and 1 M phosphate buffer (pH 6, 0.02 mL) cooled at 0 °C was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (0.7 mg, 0.0031 mmol). The mixture was warmed to room temperature, and the stirring was continued for 20 min. To the mixture cooled at 0 °C was added DDQ (0.5 mg, 0.0022 mmol), and the resulting mixture was stirred at room temperature for 20 min. Again, the mixture was cooled to 0 °C, and DDQ (0.5 mg, 0.0022 mmol) was added. After the mixture was stirred at room temperature for 1 h, 1 M phosphate buffer (pH 6, 1 mL) was added. The mixture was stirred at room temperature for 1 h and extracted with Et_2O (20 mL, 2 × 10 mL). The combined extracts were washed with 1 M phosphate buffer (pH 6, 4 mL), saturated aqueous $NaHCO_3$ (4 mL), H_2O (4 mL), and brine (4 mL), successively; dried (Na_2SO_4); and concentrated. The residual oil was purified by column chromatography on silica gel (0.2 g, CH_2Cl_2−acetone 5:1 → 3:1 → 2:1 → 1:1) and preparative HPLC (Develosil ODS-HG-5, 10 × 250 mm, MeOH−H_2O 70:30, 2 mL/min) to give **107** (t_R = 44min, 0.8 mg, 70%) as a colorless amorphous powder: $[\alpha]^{27}_D$ +36 (*c* 0.11, MeOH); UV (MeCN) λ_{max} 260 nm (ϵ 29 000); IR ($CHCl_3$) 3500 (br), 1710 (sh), 1690, 1655, 1460, 1375, 1255, 970 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.36 [8.09] (s, 1 H), 7.25 (dd, J = 10.3, 15.0 Hz, 1 H), 6.84 [7.15] (d, J = 14.3 Hz, 1 H), 6.41 (ddd, J = 4.8, 8.7, 15.4 Hz, 1 H), 6.36 (dd, J = 10.3, 15.4 Hz, 1 H), 5.92 (d, J = 15.0 Hz, 1 H), 5.61 (ddd, J = 4.0, 10.6, 15.0 Hz, 1 H), 5.47 (br d, J = 11.0 Hz, 1 H), 5.20 (br dd, J = 3.7, 9.9 Hz, 1 H), 5.07 [5.13] (dd, J = 9.5, 14.3 Hz, 1 H), 4.98 (dd, J = 9.2, 15.0 Hz, 1 H), 4.87 [4.88] (dd, J = 2.9, 11.9 Hz, 1 H), 3.78 (br d, J = 4.4 Hz, 1 H), 3.66 (m, 1 H), 3.51−3.45 (m, 4 H), 3.38 (m, 1 H), 3.36 (br d, J = 5.5 Hz, 1 H), 3.11 (s, 3 H), 3.10 (s, 3 H), 3.04−2.97 (m, 2 H), 2.96 [3.08] (s, 3 H), 2.63 (m, 1 H), 2.44 (m, 1 H), 2.30 (m, 1 H), 2.23 (m, 1 H), 2.14−1.98 (m, 2 H), 2.09 [2.08] (s, 3 H), 1.93 (m, 1 H), 1.81−1.50 (m, 10 H), 1.44−1.00 (m, 6 H), 1.42 (s, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.88 [0.88] (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.77 (d, J = 6.6 Hz, 3 H) (the minor counterparts of doubled signals in the ratio of 2:1 are in brackets); MS (FAB) m/z 870 $(M + Na)^+$; HRMS (FAB) calcd for $C_{48}H_{81}NNaO_{11}$ $[(M + Na)^+]$ 870.5707, found 870.5696.

Analogue 117. A solution of ester **116** (S/R = 2/1) (1.5 mg, 0.0020 mmol) in a 7:10 mixture of pyridine and HF·pyridine (0.3 mL) was stirred at room temperature for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) cooled at 0 °C, and the mixture was extracted with EtOAc (5 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (1 g, hexane−EtOAc−MeOH 10: 10: 1 → 5: 5: 1 → 3: 3: 1) to give **117** (S/R = 2/1) (0.8 mg, 63%) as a colorless oil: $[\alpha]^{27}_D$ +61 (*c* 0.054, MeOH); UV (MeCN) λ_{max} 258 nm (ϵ 25 000); IR ($CHCl_3$) 3620, 3520 (br), 1740 (sh), 1715, 1650, 1620, 1465, 1270, 1095, 975 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.20 (dd, J = 11.0, 15.3 Hz, 1 H), 6.40 [6.41] (dd, J = 11.0, 14.7 Hz, 1 H), 6.22 (m, 1 H), 5.88 (d, J = 15.3 Hz, 1 H), 5.61 (ddd, J = 4.6, 9.8, 15.3 Hz, 1 H), 5.24 (m, 1 H), 5.07 (br dd, J = 8.9, 15.3 Hz, 1 H), 4.81 (m, 1 H), 4.47 (m, 1 H), 4.05 (m, 1 H), 3.71−3.29 (m, 5 H), 3.68 (m, 1 H), 3.59 (m, 1 H), 3.32 [3.30] (s, 3 H), 3.12 [3.12] (s, 3 H), 3.12 [3.12] (s, 3 H), 2.46−2.27 (m, 4 H), 2.37 [2.37] (s, 6 H), 2.09−0.80 (m, 20 H), 1.52 [1.52] (s, 3 H) (the minor counterparts of doubled signals in the ratio 2:1 are in brackets); MS (FAB) m/z 622 $(M + H)^+$; HRMS (FAB) calcd for $C_{35}H_{60}NO_8$ $[(M + H)^+]$ 622.4319, found 622.4312.

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Supporting Information Available: ^1H NMR spectra of natural and synthetic **1**−**3**; ^1H NMR spectra of **6**−**9**, **12**−**18**, **19a**,**b**, **20**, **22**, **23**, **30**, **32**, **33**, **35**−**44**, **46**−**49**, **50a**,**b**, **51**, **52**, **53a**,**b**, **54**, **55**, **60a**,**b**, **61**, **62**, **63b**, **64**, **65a**,**b**, **66a**,**b**, **67**, **71**, **73a**−**c**, **74**−**83**, **85**, **86a**−**93a**, **86b**−**93b**, **86c**, **94**−**111**, **113**−**117**, **119**, **120**, and, **C-25epimer**; and experimental data for **87b**−**93b**, **97**−**99**, **108**−**116**, **119** and **120** (124 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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