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Stereocontrolled Synthesis of C10-C22 Fragment of the Immunosuppressant FK 506. An Occurrence of Complementary Stereoselectivity in the C15 Ketone Reduction[1]

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Abstract: The stereoselective syntheses of the C10-C22 fragment **2a** and its C15-epimer **2b** of the immunosuppressant FK 506 **1** have been carried out through convergent coupling of the sulfone **3**, which could be constructed by highly stereocontrolled ester-enolate Claisen rearrangement of ene-ester **5**, and the aldehyde **4** which was prepared from D-mannitol via *anti* selective methallylsilane addition to aldehyde **6** followed by modest stereoselective hydroboration based on 1,3-asymmetric induction. In the course of this reaction sequence a complementary stereoselection dependent on the used hydride reagents has occurred in reduction of the coupling product **26**.

INTRODUCTION

Recent interest in the novel macrocyclic lactone FK 506 **1**, the potent immunosuppressive agent isolated from *Streptomyces tsukubaensis*,[2] has prompted extensive work[3] directed toward the synthesis of this substance. We have also explored a synthetic approach[4] toward FK 506 **1** and preliminarily reported the stereoselective synthesis of its C10-C22 fragment **2**, the synthetic plan of which is outlined in Fig. 1. That is, a disconnection of the C15-C16 bond can designate sulfone **3** and aldehyde **4** as a valid precursor. Trisubstituted double bond and C17 chiral center in the sulfone **3** can be concurrently constructed by ester-enolate Claisen rearrangement of the ester **5** readily available from L-malic acid. The counterpart **4** can be prepared through methallylsilane addition to the aldehyde **6** easily derived from D-mannitol, followed by hydroboration. In this article we would like to report in detail stereocontrolled syntheses of the C10-C22 fragment **2a** and C15-epimer **2b** of FK 506 **1**, especially featuring highly stereoselective ester-enolate Claisen rearrangement of the ene-ester **5**, *anti* selective methallylsilane addition to 2-*O*-benzyl-3-*O*-*tert*-butyldiphenylsilyl-D-glyceraldehyde **6**, and reagent-controlled complementary reduction of the C15 ketone **26**.

RESULTS AND DISCUSSION

The preparation of sulfone **3** is depicted in Scheme 1. A six-membered benzylidene acetal **9** was provided by reduction of the known diester **7**[5] which could be diastereoselectively prepared by *anti* selective allylation of L-diethyl malate according to the Seebach's protocol and subsequent regioselective acetalization[6] of the resulting triol **8**. The acetal **9** was subjected to the following usual procedures: 1) Swern oxidation,[7] 2) methylation, 3) Swern oxidation, and 4) Wittig methylenation, to give diene **12** whose *anti* stereochemistry was secured from

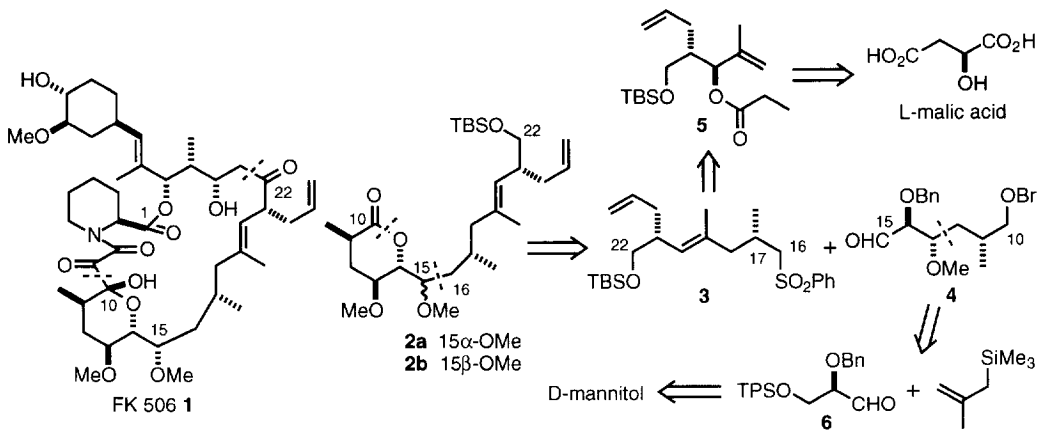
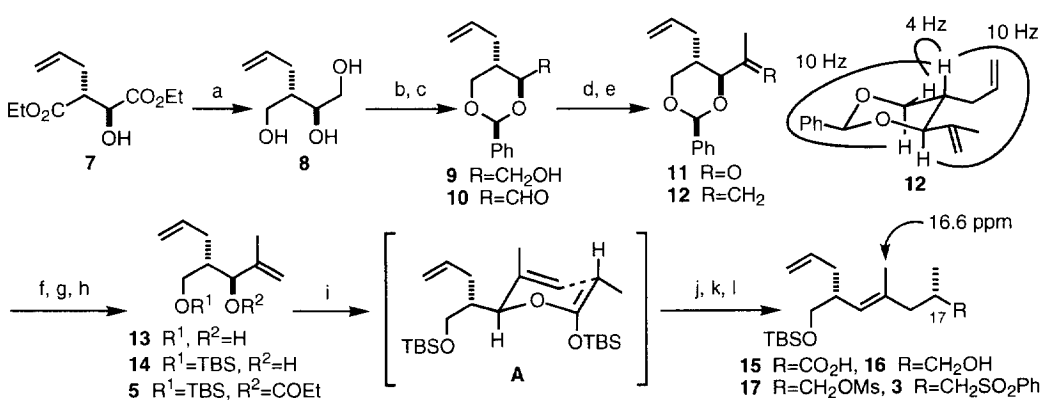
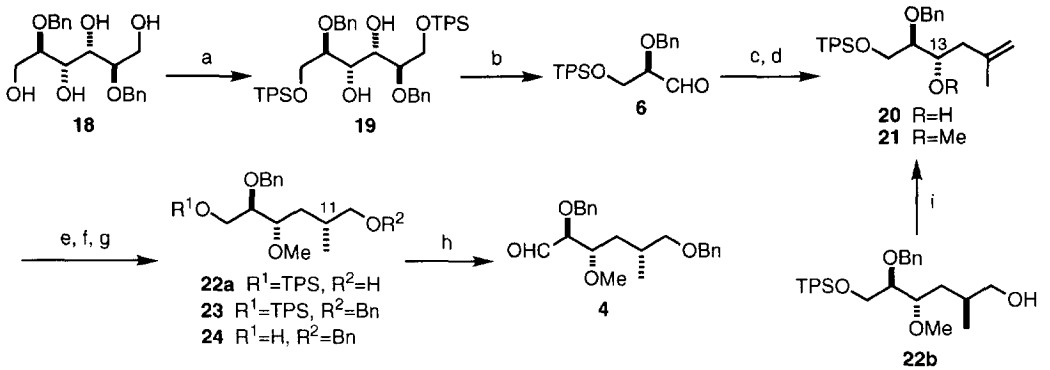


Fig. 1. Synthetic plan for the C10-C22 fragment **2** of FK 506 **1**.

coupling constants in its ^{1}H NMR spectrum as shown in **12**. The ene-ester **5**, substrate for the ester-enolate Claisen rearrangement, was synthesized by an acidic hydrolysis of **12**, protection of the primary alcohol as a *tert*-butyldimethylsilyl ether,[8] and esterfication of the secondary alcohol.[9] Treatment of **5** with lithium diisopropylamide and *tert*-butylchlorodimethylsilane in 23% HMPA-THF at -78 °C according to the Ireland's condition,[10] generating (*Z*)-silyl ketene acetal, followed by heating to reflux for 2 hours 30 minutes stereoselectively afforded caboxylic acid **15** after alkaline work-up with complete stereocontrol[11] of the (*E*)-olefin and high chirality transfer to C17 (α:β=>20:1), which could be rationalized by the reasonable six-membered chair transition state **A**. Finally, reduction of the carboxylic acid and sequential substitution reactions led **15** to the highly stereocontrolled sulfone **3**, C16-C22 fragment of **1**.

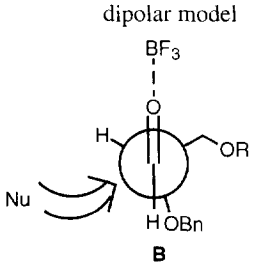


Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF, rt, 2 h, 83%; (b) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 4 h, 84%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 89%; (d) 1) MeLi, Et_2O, rt, 2 h; 2) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 81% (2 steps); (e) $Ph_3P{=}CH_2$, THF, rt, 6 h, 88%; (f) AcOH-THF-H_2O (4:1:1), 60 °C, 3 h, 91%; (g) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 88%; (h) $EtCO_2H$, DCC, DMAP, CH_2Cl_2, rt, 48 h, 99%; (i) LDA, TBSCl, HMPA-THF (23:77), -78 °C to reflux, 2.5 h, then NaOH, rt, 30 min, 77%; (j) $LiAlH_4$, THF, rt, 30 min, 86%; (k) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 98%; (l) 1) NaI, acetone, reflux, 48 h; 2) $PhSO_2Na$, DMF, 80 °C, 15 h, 83% (2 steps).



Scheme 2. Reagents and conditions: (a) TPSCl, imidazole, DMF, rt, 2 h, 100%; (b) $Pb(OAc)_4$, benzene, rt, 8 h, 100%; (c) $CH_2=C(CH_3)CH_2SiMe_3$, $BF_3{\bullet}OEt_2$, CH_2Cl_2, -78 °C, 30 min, 78%; (d) KH, MeI, THF, 90%; (e) thexyl-BH_2, THF, -15 °C, then H_2O_2, NaOH, 59%; (f) KH, BnBr, THF, rt, 2 h, 94%; (g) TBAF, THF, rt, 1 h, 92%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 95%; (i) *o*-nitrophenyl selenocyanate, *n*-Bu_3P, THF, rt, 30 min, and then H_2O_2, 80%.

Non-chelation-controlled addition of methallylsilane to 2-*O*-benzyl-3-*O*-*tert*-butyldiphenylsilyl-D-glyceraldehyde **6** prepared from tetraol **18**[13] according to the Reetz's method in the presence of boron trifluoride etherate stereoselectively gave *anti* adduct **20** (*anti*:*syn*=88:12) (Scheme 2). In case of monodentate BF_3-mediated allylsilane addition to α,β-dialkoxy carbonyl compounds non-chelation-control has been rationalized by a Cornforth-type dipolar transition state **B** (Fig. 2).[13,14] The enhancement of this *anti* selectivity compared with the original Reetz's stereoselectivity[13] might be attributed to steric bulkiness of CH_2OSiMe_2t-Bu versus CH_2OSiPh_2t-Bu.



	anti : *syn*
R=$SiMe_2t$-Bu (Reetz's substrate)[13]	77 : 23
R=$SiPh_2t$-Bu (our substrate)	88 : 12

Fig. 2.

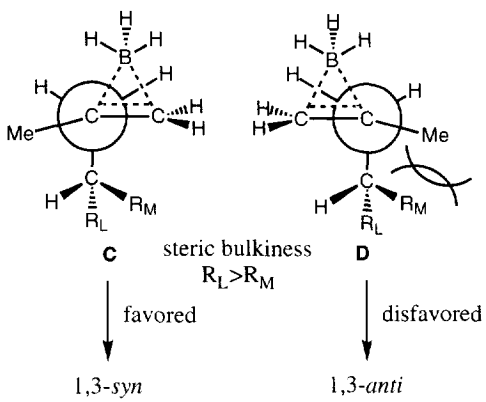
The next stage is 1,3-asymmetric induction in the hydroboration of methyl ether **21** with a variety of boranes. The results are summarized in Table 1. It has been found that although $BH_3{\bullet}SMe_2$ is non-selective reagent (entry 1), bulky mono and dialkylboranes indicate modest diastereoselectivities (entries 2-4). In order to further enhance diastereoselectivity of the hydroboration, chiral (+) and (-)-diisopinocampheylboranes derived from (-) and (+)-α-pinene,[15] respectively, were also examined not to be able to optimize the stereoselectivity obtained by achiral boranes (entries 5 and 6). A transition state model for 1,3-asymmetric induction in the hydroboration of terminal olefins such as **21** has been suggested by Evans *et al.*[16] (Fig. 3). In that model, they propose that the destabilizing feature which disfavors transition state **D** is the developing methyl↔R_M non-

Table 1. 1,3-Asymmetric Induction by Hydroboration of **21** with Various Boranes Followed by Oxidation with Alkaline Hydrogen Peroxide

entry	borane	solvent	temp (°C)	yield (%)[a]	**22a** : **22b**[b]
1	BH_3•SMe_2	THF	0	90	1 : 1
2	$(cyclohexyl)_2BH$	THF	0	89	1.5 : 1
3	thexyl-BH_2	THF	-15	98	1.5 : 1
4	$(sia)_2BH$	THF	-15	86	1.3 : 1
5	(+)-Ipc_2BH	THF	0	80	1.3 : 1
6	(-)-Ipc_2BH	THF	0	70	1.4 : 1

[a]Combined yields of **22a** and **22b**. [b]Ratios were based on isolated products.

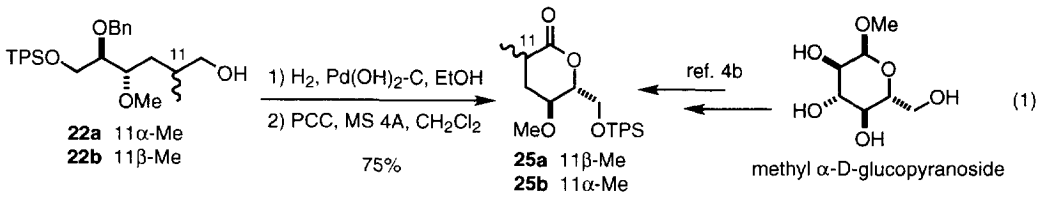
bonding interaction and actually report good π-facial selectivity when R_L>R_M and R_M=Me. As exemplified by an A-value of the homoallylic substituent R_M (Me=1.70 kcal/mol and OMe=0.60 kcal/mol),[17] a decrease of the π-facial selectivity in our substrate (R_M=OMe) may be attributed to deficiency in steric bulkiness of R_M requisite for good 1,3-asymmetric induction.



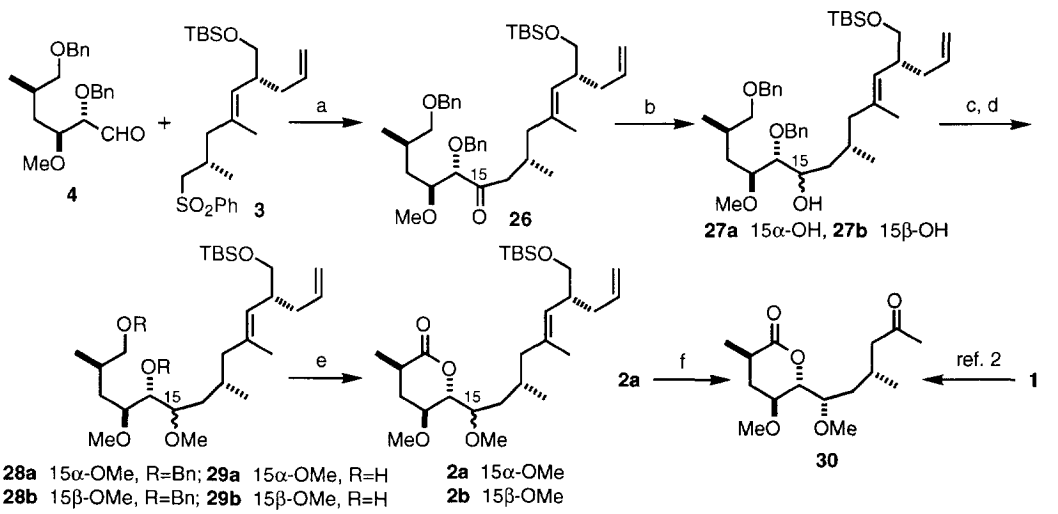
	A-value (kcal/mol)	π-facial selectivity (1,3-*syn* : 1,3-*anti*)
R_M=Me[16]	1.70	3.5~6.7 : 1
R_M=OMe	0.60	1~1.5 : 1

Fig. 3. Possible mechanism of 1,3-asymmetric induction in the hydroboration of terminal olefins such as **21** proposed by Evans.

After all the hydroboration products **22a** and **22b** were separated by column chromatography and the minor 11β-methyl isomer **22b** was recycled to the olefin **21** by an usual manner[18] (Scheme 2). The major 11α-methyl isomer **22a** was converted to the aldehyde **4**, C10-C15 fragment required for coupling with sulfone **3**, in high overall yields by benzylation, desilylation, and Swern oxidation.[7] The stereo-structure of the aldehyde **4** was secured by deriving hydroboration products **22a** and **22b** to the authentic six-membered lactones **25a**, $[\alpha]_D^{22}$ +22.5 (*c* 1.00, $CHCl_3$) {lit.[4b] $[\alpha]_D^{23}$ +23.7 (*c* 1.00, $CHCl_3$)}, and **25b**, mp 103-105 °C; $[\alpha]_D^{22}$ +57.9 (*c* 0.795, $CHCl_3$) {lit.[4b] mp 104-106 °C; $[\alpha]_D^{24}$ +59.0 (*c* 1.00, $CHCl_3$)}, respectively, independently synthesized from methyl α-D-glucopyranoside (equation 1).[4b]



Addition of an anion of the sulfone **3** to the aldehyde **4** in tetrahydrofuran at -78 °C provided four possible stereoisomeric adducts which were oxidized to α-sulfonyl ketone followed by reductive removal of the sulfonyl group with tri-*n*-butyltin hydride[3h] to give diastereomerically homogeneous ketone **26** (Scheme 3). Reductions of the ketone **26** to the desired 15α-hydroxy compound **27a** were then investigated with various hydride reagents and the results are shown in Table 2. The reductions with sodium and lithium borohydrides in polar protic solvents only afforded capricious and modest biases for the reduction products **27a** and **27b** (entries 1-4). Although lithium tri-*sec*-butylborohydride in tetrahydrofuran could not overcome the circumstance, the choice of diethyl ether as a solvent caused a dramatic enhancement of the stereoselectivity in the carbonyl reduction (entries 5 and 6).[19] The major product of the reduction was, however, an undesired 15β-hydroxy compound **27b** (**27a**:**27b**=1:20). Other reagents such as potassium tri-*sec*-butylborohydride, lithium aluminum hydride, and zinc borohydride in diethyl ether gave almost the same ratios as lithium tri-*sec*-butylborohydride in favor of the undesired **27b** (entries 7-9). After many unfavorable experimentations, fortunately, reversal of the stereoselectivity in the reduction occurred in receivable diastereoselectivities (**27a**:**27b**=8~11:1) utilizing diisobutylaluminum hydride reagent (entries 10-13). A reduction of the ketone **26** with diisobutylaluminum hydride in toluene at -78 °C for 20 minutes as an optimum condition afforded the desired 15α-hydroxy compound **27a** in 86% yield with high diastereoselectivity (15α:15β=11:1).



Scheme 3. Reagents and conditions: (a) 1) *n*-BuLi, THF, -78 °C, 10 min, then **4**, -78 °C, 2.5 h, 83%; 2) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 74%; 3) *n*-Bu_3SnH, AIBN, toluene, reflux, 77%; (b) DIBALH, toluene, -78 °C, 20 min, 86%; (c) KH, MeI, THF, rt, 94%; (d) Li, NH_3-THF, -78 °C, 95%; (e) PCC, MS 4A, CH_2Cl_2, rt, 2 h, 85%; (f) O_3, MeOH, -78 °C, then Me_2S, rt, 51%.

Table 2. Reductions of the Ketone **26** with a Wide Variety of Hydride Reagents

entry	reagent	solvent	temp (°C)	**27a** : **27b**[a]
1	$NaBH_4$	MeOH	-78→rt	2 : 1
2	$NaBH_4$	*i*-PrOH	0→rt	1 : 1.5
3	$NaBH_4$	THF-H_2O	0→rt	3 : 1
4	$LiBH_4$	MeOH	0	1.5 : 1
5	LiBH(*sec*-Bu)$_3$	THF	-78	1 : 3
6	LiBH(*sec*-Bu)$_3$	Et_2O	-78	1 : 20
7	KBH(*sec*-Bu)$_3$	Et_2O	-78	1 : 20
8	$LiAlH_4$	Et_2O	-78	1 : >20
9	$Zn(BH_4)_2$	Et_2O	-78→0	1 : 20
10	DIBALH	toluene	0	8 : 1
11	DIBALH	toluene	-78	11 : 1
12	DIBALH	CH_2Cl_2	-78	9 : 1
13	DIBALH	hexane	-78	9 : 1

[a]Ratios were determined by ^1H NMR integration of the products **27a** and **27b**.

These complementary stereoselectivities observed by switching hydride reagents used in the reduction may be rationalized as follows (Fig. 4).[20] The high 15β-selectivity with various metal hydride reagents in diethyl ether (entries 6-9) can be reasonably explained by considering rigid α-chelation model[21] **E** between benzyloxy group and carbonyl oxygen, though a behavior in tetrahydrofuran is unclear at present (entry 5). It seems that as in case of polar protic solvents such a rigid cyclic structure **E** could not be adopted, the decrease in stereoselectivity was observed (entries 1-4). On the other hand the reversal in the stereoselectivity with diisobutylaluminum hydride might be explainable by speculating a Cornforth-type dipolar model[14] **F** through coordination of the monodentate aluminum to the most basic carbonyl oxygen only of the substrate **26** (entries 10-13). We can not, however, rule out the possibility for transition states containing participation of other chiral centers than α-benzyloxy group in these complememtary stereoselectivities.

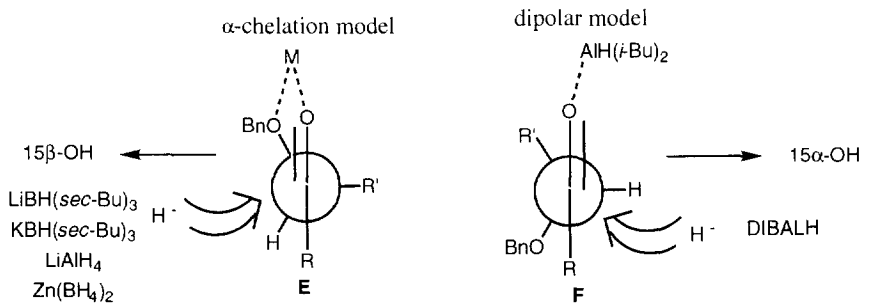


Fig. 4. Plausible models for complementary stereoselective reductions of the ketone **26**.

Methylation of an alcohol in the desirable **27a**, debenzylation, and lactonization with pyridinium chlorochromate[22] finally gave lactone **2a**, C10-C22 fragment of **1**, and the undesirable **27b** was also converted to the C15-epimer **2b** through the same reaction sequence as **27a** (Scheme 3). The structure of the synthetic **2a** including its stereochemistry was proven by the fact that a product **30** obtained by ozonolysis of **2a** was identical with the known degradation product[2] of FK 506 **1** in spectroscopic properties (^{1}H NMR and IR) including optical rotation, $[\alpha]_D^{21}$ +78.9 (*c* 0.130, $CHCl_3$) {lit.[3k] $[\alpha]_D^{23}$ +82.0 (*c* 0.3, $CHCl_3$)}.

In conclusion we have synthesized the C16-C22 fragment **3** possessing (*E*)-trisubstituted double bond by highly stereocontrolled ester-enolate Claisen rearrangement of **5** and the C10-C15 fragment **4** by *anti* selective methallylsilane addition to **6** followed by 1,3-asymmetric hydroboration in the synthetic studies on FK 506 **1**. Further, we have accomplished the stereoselective syntheses of the C10-C22 fragment **2a** and its C15-epimer **2b** by convergent coupling of **3** and **4** followed by reagent-controlled complementary diastereoselective reduction of the ketone **26**.

EXPERIMENTAL SECTION

General Procedures

Melting point is uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform on Hitachi R-90H (90 MHz), R-250H (250 MHz), and Bruker AM-400 (400 MHz) spectrometers. ^{13}C NMR spectrum was measured in deuteriochloroform on JEOL model JNM-GX 270 (67.5 MHz) spectrometer. Chemical shifts were reported in ppm down field from the peak of tetramethylsilane as an internal standard. The data are reported as follows: chemical shift, number of proton, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broadened), and coupling constants. Infrared (IR) spectra were recorded on a JASCO IR-S spectrophotometer. Optical rotations were determined on a JASCO DIP-360 digital polarimeter using the sodium D line (λ=589 nm) at the temperature indicated and are reported as follows: $[\alpha]_D^{temp}$, concentration (*c*=g/100 mL), and solvent. Low (EI, FD, and FI) and high (EI and FI) resolution mass spectra were determined on JEOL model JMS-DX 303, JMS-HX 110, and JMS-01SG-2 spectrometers.

Analytical and preparative thin layer chromatographies were carried out by precoated silica gel (Macherey-Nagel DC-Fertigplatten SIL G-25 UV_{254} and Merck DC-Fertigplatten Kieselgel 60 F_{254}). Silica gels used for column chromatographies were Merck kieselgel 60 Art 7734 and Amicon Matrex® silica Si chromatography medium. All reactions were performed in oven-dried glassware.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine, benzene, toluene, and isopropanol (*i*-PrOH) were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide. Ethanol (EtOH) was distilled from magnesium ethoxide. Acetone and propionic acid were distilled from potassium permanganate. Hexane was distilled from sodium metal. Dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride at reduced pressure. Activation of powdered 4A molecular sieves (MS 4A) involved heating in a vacuum oven at 160 °C and 0.05 mmHg pressure for at least 3 h.[23]

(2*S*,3*S*)-3-(2-Propenyl)-1,2,4-butanetriol 8

To a solution of lithium aluminum hydride (989 mg, 26.0 mmol) in 30 mL of THF at 0 ℃ under Ar was added dropwise 3.00 g (13.0 mmol) of diethyl (2*S*,3*R*)-3-(2-propenyl)malate **7**[5] dissolved in 15 mL of THF and the solution was stirred at room temperature for 2 h. The reaction was carefully quenched with 1 mL of water at 0 °C, followed by 1 mL of 15% aqueous NaOH, and then 3 mL of water. The resulting solution was vigorously stirred for 10 min, treated with anhydrous Na_2SO_4 for another 20 min, then filtered through a pad of Celite *in suction*, and evaporated *in vacuo*. The residue was subjected to column chromatography (8% MeOH/$CHCl_3$) on 90 g of silica gel to furnish triol **8** (1.58 g, 83% yield): $[\alpha]_D^{25}$ +10.0 (*c* 1.95, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J*=17, 10, 7 Hz), 5.06 (1H, d, *J*=17 Hz), 5.05 (1H, d, *J*=10 Hz), 4.00-3.30 (8H, m), 2.34-2.00 (2H, m), 2.00-1.54 (1H, m); IR (neat) 3340, 2915, 1640, 1446, 1068, 1030, 916 cm^{-1}; EI-MS *m/z* (relative intensity) 147 (M^++H, 0.43), 115 (26), 97 (26), 79 (20), 69 (39), 68 (35), 67 (53), 57 (29), 55 (20), 43 (47), 41 (100), 39 (27); EI-HRMS calcd for $C_7H_{15}O_3$ (M^++H) 147.1021, found 147.1025.

(2*S*,4*S*,5*S*)-4-Hydroxymethyl-2-phenyl-5-(2-propenyl)-1,3-dioxacyclohexane 9

To a solution of triol **8** (4.38 g, 30.0 mmol) and 4.95 mL (33.0 mmol) of benzaldehyde dimethyl acetal in 45 mL of CH_2Cl_2 at room temperature was added a portion of camphorsulfonic acid (348 mg, 1.50 mmol) and the mixture was stirred for 4 h under Ar. The reaction was quenched with 20 mL of saturated aqueous $NaHCO_3$ and the resulting mixtures were poured into 40 mL of water, followed by extracting with ether (40 mL × 3). The organic layer was washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/benzene) on 350 g of silica gel to provide benzylidene acetal **9** (5.90 g, 84% yield): $[\alpha]_D^{24}$ +6.45 (*c* 2.12, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.55-7.15 (5H, m), 6.00-5.41 (1H, m), 5.48 (1H, s), 5.20-4.88 (2H, m), 4.20 (1H, dd, *J*=12, 5 Hz), 4.00-3.37 (4H, m), 2.42-1.60 (4H, m); IR (neat) 3410, 2915, 2840, 1642, 1455, 1400, 1374, 1313, 1216, 1134, 1086, 1028, 991, 919, 765, 700 cm^{-1}; EI-MS *m/z* (relative intensity) 234 (M^+, 36), 233 (45), 203 (100), 107 (88), 105 (95), 91 (73), 79 (71), 77 (51), 67 (59), 41 (80); EI-HRMS calcd for $C_{14}H_{18}O_3$ (M^+) 234.1256, found 234.1228.

(2*S*,4*S*,5*S*)-4-Formyl-2-phenyl-5-(2-propenyl)-1,3-dioxacyclohexane 10

To a solution of oxalyl chloride (3.76 mL, 43.1 mmol) in 20 mL of CH_2Cl_2 was added dropwise 7.64 mL (0.108 mol) of dimethyl sulfoxide dissolved in 40 mL of CH_2Cl_2 at -78 ℃ and the solution was stirred for 10 min under Ar. To the solution was added dropwise benzylidene acetal **9** (5.05 g, 21.5 mmol) dissolved in 40 mL of CH_2Cl_2 and the mixture was stirred for 30 min at the same temperature. To the solution was added 30.0 mL (0.215 mol) of triethylamine at -78 °C and the mixture was vigorously stirred for additional 30 min at 0 °C. The reaction mixture was poured into 150 mL of water and extracted with CH_2Cl_2 (100 mL × 3). The extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography (4% EtOAc/hexane) on 152 g of silica gel afforded aldehyde **10** (4.44 g, 89% yield): $[\alpha]_D^{25}$ -18.6 (*c* 2.08, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 9.63 (1H, d, *J*=2 Hz), 7.65-7.10 (5H, m), 6.00-5.37 (1H, m), 5.50 (1H, s), 5.27-4.85 (2H, m), 4.29 (1H, dd, *J*=12, 5 Hz), 3.98 (1H, dd, *J*=10, 2 Hz), 3.60 (1H, dd, *J*=12, 10 Hz), 2.55-1.60 (3H, m); IR (neat) 2920, 2845, 1741, 1644, 1458, 1404, 1380, 1312, 1293, 1218, 1147, 1131, 1091, 1030, 995, 920, 764, 702 cm^{-1}; EI-MS *m/z* (relative intensity) 232 (M^+, 1.2), 203 (100), 107 (46), 105 (40), 91 (56), 79 (37), 77 (25), 69 (20), 67 (31), 41 (55); EI-HRMS calcd for $C_{14}H_{16}O_3$ (M^+) 232.1100, found 232.1093.

(2*S*,4*S*,5*S*)-4-Acetyl-2-phenyl-5-(2-propenyl)-1,3-dioxacyclohexane 11

To a solution of aldehyde **10** (3.86 g, 16.6 mmol) in 40 mL of Et_2O at 0 °C under Ar was added dropwise 29.9 mL (33.2 mmol) of methyllithium (1.11 M in Et_2O) and the solution was stirred for 2 h at room temperature. The reaction was carefully quenched with 20 mL of saturated aqueous NH_4Cl at 0 °C. The mixture was poured into 70 mL of water and extracted with ether (50 mL × 3). The ethereal layer was washed with 100

mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography (12% EtOAc/hexane) on 193 g of silica gel to yield secondary alcoholic mixture of 2.1:1 (3.60 g, 87% combined yield) which was directly used in the next reaction.

To a solution of oxalyl chloride (3.79 mL, 43.5 mmol) in 20 mL of CH_2Cl_2 was added dropwise 7.24 mL (0.102 mol) of dimethyl sulfoxide dissolved in 40 mL of CH_2Cl_2 at -78 °C and the solution was stirred for 10 min under Ar. To the solution was added dropwise the above mixture of secondary alcohol (3.60 g, 14.5 mmol) dissolved in 40 mL of CH_2Cl_2 and the mixture was stirred for 30 min at the same temperature. To the solution was added 25.2 mL (0.181 mol) of triethylamine at -78 °C and the mixture was vigorously stirred for additional 40 min at 0 °C. The reaction mixture was poured into 150 mL of water and extracted with CH_2Cl_2 (100 mL × 3). The extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography (4% EtOAc/hexane) on 108 g of silica gel afforded ketone **11** (3.31 g, 93% yield): $[\alpha]_D^{26}$ -61.4 (*c* 2.09, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.60-7.22 (5H, m), 6.02-5.45 (1H, m), 5.50 (1H, s), 5.24-4.88 (2H, m), 4.29 (1H, dd, *J*=12, 4 Hz), 4.00 (1H, d, *J*=10 Hz), 3.60 (1H, dd, *J*=12, 10 Hz), 2.50-1.75 (3H, m), 2.29 (3H, s); IR (neat) 3035, 2950, 2900, 2835, 1718, 1638, 1452, 1396, 1355, 1303, 1290, 1235, 1211, 1122, 1090, 1070, 1026, 990, 915, 751, 694 cm^{-1}; EI-MS *m/z* (relative intensity) 246 (M^+, 0.68), 203 (100), 107 (55), 105 (29), 91 (52), 79 (47), 77 (29), 69 (24), 67 (31), 43 (34), 41 (49); EI-HRMS calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1256.

(2*S*,4*S*,5*S*)-4-Isopropenyl-2-phenyl-5-(2-propenyl)-1,3-dioxacyclohexane 12

To a solution of methyltriphenylphosphonium bromide (18.2 g, 51.2 mmol) in 30 mL of THF at 0 °C under Ar was added 34.4 mL (51.2 mmol) of *n*-butyllithium (1.49 M in hexane) and then the mixture was stirred for 30 min at room temperature followed by cooling to -15 °C. To the solution was added dropwise ketone **11** (4.21 g, 17.1 mmol) dissolved in 45 mL of THF at -15 °C and the resulting mixture was stirred at room temperature for 6 h. After quenching with 20 mL of saturated aqueous NH_4Cl, the reaction mixture was poured into 80 mL of water and extracted with ether (80 mL × 3). The combined organic layers were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (100% benzene) on 42.1 g of silica gel to remove triphenylphosphine oxide by-product. The crude product was further purified by column chromatography (40% benzene/hexane) on 126 g of silica gel to give olefin **12** (3.68 g, 88% yield): $[\alpha]_D^{22}$ +19.8 (*c* 2.04, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.67-7.17 (5H, m), 6.03-5.48 (1H, m), 5.51 (1H, s), 5.17-4.86 (4H, m), 4.28 (1H, dd, *J*=12, 4 Hz), 3.99 (1H, d, *J*=10 Hz), 3.58 (1H, dd, *J*=12, 10 Hz), 2.35-1.55 (3H, m), 1.82 (3H, s); IR (neat) 3050, 2955, 2910, 2830, 1640, 1454, 1393, 1378, 1306, 1213, 1122, 1071, 1047, 1030, 989, 913, 759, 698 cm^{-1}; EI-MS *m/z* (relative intensity) 244 (M^+, 1.5), 107 (100), 105 (52), 79 (29), 77 (24), 68 (74), 67 (37), 41 (28); EI-HRMS calcd for $C_{16}H_{20}O_2$ (M^+) 244.1463, found 244.1442.

(2*S*,3*S*)-4-Methyl-2-(2-propenyl)-4-pentene-1,3-diol 13

To a solution of benzylidene acetal **12** (3.28 g, 13.4 mmol) in 20 mL of THF at room temperature were successively added 20 mL of water and 80 mL of acetic acid and then the mixture was stirred at 60 °C for 3 h. After cooling the reaction mixture to room temperature, it was treated with 187 mL of 30% aqueous NaOH and extracted with ether (150 mL × 3). The extracts were washed with 300 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (8% acetone/$CHCl_3$) on 98.4 g of silica gel to furnish diol **13** (1.89 g, 91% yield): $[\alpha]_D^{21}$ -5.93 (*c* 1.04, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.82 (1H, ddt, *J*=17, 10, 7 Hz), 5.23-4.80 (4H, m), 4.13 (1H, d, *J*=7 Hz), 3.88 (1H, dd, *J*=11, 4 Hz), 3.64 (1H, dd, *J*=11, 6 Hz), 2.55-1.60 (5H, m), 1.76 (3H, s); IR (neat) 3320, 3055, 2910, 1641, 1445, 1085, 1030, 998, 975, 909 cm^{-1}; EI-MS *m/z* (relative intensity) 156 (M^+, 0.09), 72 (22), 71 (74), 68 (100), 67 (88), 57 (22), 53 (27), 43 (35), 41 (64), 39 (33); EI-HRMS calcd for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1141.

(3*S*,4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-1,6-heptadien-3-ol 14

To a solution of diol **13** (2.82 g, 17.9 mmol) and 219 mg (1.79 mmol) of 4-dimethylaminopyridine in 10 mL of CH_2Cl_2 at 0 °C under Ar was added 3.00 mL (21.5 mmol) of triethylamine. To the solution at the same temperature was added dropwise 2.97 g (19.7 mmol) of *tert*-butylchlorodimethylsilane dissolved in 15 mL of CH_2Cl_2 and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was poured into 30 mL of water and extracted with CH_2Cl_2 (20 mL × 3). The organic layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/hexane) on 84.6 g of silica gel to give silyl ether **14** (4.27 g, 88% yield): $[\alpha]_D^{22}$ +0.659 (*c* 2.19, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.04-5.51 (1H, m), 5.20-4.87 (4H, m), 4.20-3.30 (1H, br s), 4.07 (1H, br d, *J*=7 Hz), 3.90 (1H, dd, *J*=11, 3 Hz), 3.61 (1H, dd, *J*=11, 5 Hz), 2.19 (2H, br t, *J*=7 Hz), 1.84-1.50 (1H, m), 1.71 (3H, br s), 0.91 (9H, s), 0.07 (6H, s); IR (neat) 3410, 3030, 2915, 2835, 1638, 1466, 1439, 1388, 1251, 1110, 1087, 1048, 1001, 904, 839, 813, 781 cm^{-1}; EI-MS *m/z* (relative intensity) 271 (M^++H, 0.03), 121 (19), 105 (67), 93 (18), 79 (12), 75 (100), 73 (24), 41 (10); EI-HRMS calcd for $C_{15}H_{31}O_2Si$ (M^++H) 271.2093, found 271.2065.

(1*S*,2*S*)-2-(*tert*-Butyldimethylsilyl)oxymethyl-1-isopropenyl-4-pentenyl propanoate 5

To a solution of alcohol **14** (4.27 g, 15.8 mmol), 4-dimethylaminopyridine (579 mg, 4.74 mmol), and *N*,*N*'-dicyclohexylcarbodiimide (9.77 g, 47.4 mmol) in 40 mL of CH_2Cl_2 at 0 °C under Ar was added 3.53 mL (47.4 mmol) of propionic acid and then the solution was stirred at room temperature for 48 h. The precipitates were filtered through a pad of Celite under reduced pressure and the filtrates were evaporated *in vacuo*. The residue was subjected to column chromatography (100% benzene) on 42.7 g of silica gel to remove residual precipitates. The crude product was further purified by column chromatography (4% ether/hexane) on 128 g of silica gel to provide ester **5** (5.11 g, 90% yield): $[\alpha]_D^{24}$ -2.77 (*c* 1.96, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.02-5.54 (1H, m), 5.32-4.89 (5H, m), 3.69-3.54 (2H, m), 2.34 (2H, q, *J*=7 Hz), 2.20-1.64 (3H, m), 1.72 (3H, s), 1.15 (3H, t, *J*=7 Hz), 0.91 (9H, s), 0.02 (6H, s); IR (neat) 2930, 1743, 1640, 1465, 1442, 1381, 1360, 1251, 1180, 1110, 1004, 938, 910, 840, 780 cm^{-1}; EI-MS *m/z* (relative intensity) 327 (M^++H, 0.02), 132 (13), 131 (100), 121 (19), 93 (17), 75 (44), 73 (21), 57 (25); EI-HRMS calcd for $C_{18}H_{35}O_3Si$ (M^++H) 327.2355, found 327.2359.

(2*S*,4*E*,6*R*)-6-(*tert*-Butyldimethylsilyl)oxymethyl-2,4-dimethyl-4,8-nonadienoic acid 15

To a solution of ester **5** (1.00 g, 3.06 mmol) in 10 mL of 23% HMPA/THF at -78 °C under Ar were successively added dropwise 3.37 mL (3.37 mmol) of lithium diisopropylamide (1.0 M in 23% HMPA/THF) and 3.37 mL (3.37 mmol) of *tert*-butylchlorodimethylsilane (1.0 M in 23% HMPA/THF) and the solution was stirred at the same temperature for 10 min. After the mixture was allowed to warm to room temperature, it was stirred at the same temperature for 30 min and further at reflux for additional 2 h 30 min. After cooling to room temperature, to the solution was added 6.12 mL (6.12 mmol) of 1N aqueous NaOH and the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into 40 mL of water and the aqueous layer was acidified to pH 3-4 with 1N aqueous HCl, followed by extracting with ether (30 mL × 3). The extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (8% EtOAc/benzene) on 50 g of silica gel to afford carboxylic acid **15** (772 mg, 77% yield): $[\alpha]_D^{26}$ -18.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz), 5.04-4.90 (3H, m), 3.45 (1H, dd, *J*=9.9, 5.8 Hz), 3.39 (1H, dd, *J*=9.9, 7.1 Hz), 2.61 (1H, ddq, *J*=8.5, 5.9, 6.8 Hz), 2.58-2.46 (1H, m), 2.43 (1H, dd, *J*=13.6, 5.9 Hz), 2.32 (1H, dt, *J*=13.9, 6.3 Hz), 2.05 (1H, dd, *J*=13.6, 8.5 Hz), 1.92 (1H, dt, *J*=13.9, 7.4 Hz), 1.62 (3H, s), 1.12 (3H, d, *J*=6.8 Hz), 0.88 (9H, s), 0.03 (6H, s); IR (neat) 3600-2200, 3045, 2910, 2835, 1705, 1638, 1460, 1437, 1412, 1383, 1359, 1289, 1247, 1200, 1094, 1056, 1000, 989, 933, 908, 833, 811, 774 cm^{-1}; EI-MS *m/z* (relative intensity) 326 (M^+, 0.13), 269 (M^+—*t*-Bu, 26), 177 (71), 149 (26), 121 (34), 107 (47), 93 (30), 89 (58), 75 (100), 73 (99), 41 (30); EI-HRMS calcd for $C_{14}H_{25}O_3Si$ (M^+—*t*-Bu) 269.1574, found 269.1577.

(2*S*,4*E*,6*R*)-6-(*tert*-Butyldimethylsilyl)oxymethyl-2,4-dimethyl-4,8-nonadien-1-ol 16

To a solution of lithium aluminum hydride (289 mg, 7.26 mmol) in 10 mL of THF at 0 °C under Ar was added dropwise 2.37 g (7.26 mmol) of carboxylic acid **15** dissolved in 25 mL of THF. After the addtion the solution was allowed to warm to room temperature and stirred for 30 min. The reaction was carefully quenched with 0.289 mL of water, followed by 0.289 mL of 15% aqueous NaOH, and then 0.867 mL of water. The resulting solution was vigorously stirred for 10 min, treated with anhydrous Na_2SO_4 for another 20 min, and then filtered through a pad of Celite *in suction*. The filtrates were evaporated *in vacuo* and the residue was subjected to column chromatography (8% EtOAc/hexane) on 71.1 g of silica gel to yield alcohol **16** (1.95 g, 86% yield): $[\alpha]_D^{23}$ -12.9 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J*=17.2, 10.0, 7.2 Hz), 5.07-4.87 (3H, m), 3.54-3.35 (4H, m), 2.61-2.42 (1H, m), 2.27 (1H, dt, *J*=13.2, 6.4 Hz), 2.15-1.76 (4H, m), 1.62 (3H, s), 0.88 (9H, s), 0.85 (3H, d, *J*=6.1 Hz), 0.03 (6H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.0, 135.3, 127.7, 115.5, 68.4, 66.3, 44.7, 40.8, 36.3, 33.6, 25.9, 18.3, 16.7, 16.5, -5.36, -5.39; IR (neat) 3320, 3045, 2930, 2900, 2835, 1638, 1464, 1439, 1385, 1359, 1250, 1095, 1036, 1002, 990, 937, 910, 838, 815, 779 cm^{-1}; EI-MS *m/z* (relative intensity) 312 (M^+, 0.33), 121 (43), 107 (52), 105 (41), 95 (42), 93 (42), 89 (63), 81 (50), 75 (99), 73 (100), 69 (42), 55 (41); EI-HRMS calcd for $C_{18}H_{36}O_2Si$ (M^+) 312.2484, found 312.2504.

(2*S*,4*E*,6*R*)-6-(*tert*-Butyldimethylsilyl)oxymethyl-2,4-dimethyl-4,8-nonadienyl methanesulfonate 17

To a solution of alcohol **16** (1.69 g, 5.41 mmol) in 17 mL of CH_2Cl_2 at 0 °C under Ar were sequentially added 1.66 mL (11.9 mmol) of triethylamine and 0.460 mL (5.95 mmol) of methanesulfonyl chloride, and then the mixture was stirred for 30 min. The reaction mixture was poured into 30 mL of water and extracted with CH_2Cl_2 (20 mL × 3). The extracted organic layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual oil was subjected to column chromatography (2% EtOAc/benzene) on 50.7 g of silica gel to provide mesylate **17** (2.07 g, 98% yield): $[\alpha]_D^{24}$ -8.93 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J*=17.0, 9.9, 7.0 Hz), 4.99 (1H, dd, *J*=17.0, 1.8 Hz), 5.07-4.85 (2H, m), 4.08 (1H, dd, *J*=9.4, 5.2 Hz), 4.00 (1H, dd, *J*=9.4, 6.1 Hz), 3.52-3.36 (2H, m), 2.99 (3H, s), 2.61-2.43 (1H, m), 2.37-2.23 (1H, m), 2.19-1.76 (4H, m), 1.60 (3H, s), 0.93 (3H, d, *J*=6.1 Hz), 0.88 (9H, s), 0.02 (6H, s); IR (neat) 2950, 2920, 2890, 2850, 1640, 1470, 1361, 1256, 1180, 1100, 964, 843, 783 cm^{-1}; FD-MS *m/z* (relative intensity) 390 (M^+, 8.0); EI-MS *m/z* (relative intensity) 349 (M^+—allyl, 1.6), 163 (55), 153 (100), 121 (67), 107 (74), 93 (60), 89 (68), 73 (96); EI-HRMS calcd for $C_{16}H_{33}O_4SSi$ (M^+—allyl) 349.1869, found 349.1882.

(4*R*,5*E*,8*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-6,8-dimethyl-9-(phenylsulfonyl)-1,5-nonadiene 3

A solution of mesylate **17** (2.05 g, 5.23 mmol) and sodium iodide (2.35 g, 15.7 mmol) in 30 mL of acetone under Ar was heated at reflux with stirring. After 2 d, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into 50 mL of 10% aqueous $Na_2S_2O_3$ and extracted with ether (50 mL × 3). The ethereal layer was washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to give iodide which was directly used in the next reaction.

To a solution of the above iodide (2.21 g, 5.23 mmol) in 30 mL of DMF was added a portion of sodium benzenesulfinate dihydrate (1.78 g, 8.89 mmol) and the solution was stirred at 80 °C for 15 h under Ar. An oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into 100 mL of water and extracted with ether (50 mL × 3). The ethereal layer was washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography (8% ether/hexane) on 66.3 g of silica gel to furnish sulfone **3** (1.91 g, 83% overall yield from mesylate **17**): $[\alpha]_D^{21}$ -16.6 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.93-7.84 (2H, m), 7.69-7.50 (3H, m), 5.69 (1H, ddt, *J*=17.1, 10.0, 7.1 Hz), 5.01-4.76 (3H, m), 3.42 (1H, dd, *J*=9.7, 5.2 Hz), 3.34 (1H, dd, *J*=9.7, 7.3 Hz), 3.07 (1H, dd, *J*=14.2, 4.3 Hz), 2.83 (1H, dd, *J*=14.2, 8.2 Hz), 2.54-2.37 (1H, m), 2.36-2.09 (2H, m), 2.02 (1H, dd, *J*=13.1, 7.0 Hz), 2.00-1.79 (2H, m), 1.44 (3H, d, *J*=1.2 Hz), 1.03 (3H, d, *J*=6.1 Hz), 0.87

(9H, s), 0.01 (6H, s); IR (neat) 3060, 2935, 2850, 1641, 1590, 1464, 1449, 1409, 1389, 1362, 1310, 1253, 1150, 1089, 1000, 940, 914, 842, 782, 755, 745 cm^{-1}; EI-MS *m/z* (relative intensity) 437 (M^++H, 0.27), 436 (M^+, 0.07), 380 (33), 379 (100), 199 (46), 135 (54), 121 (44), 93 (31), 89 (36), 75 (40), 73 (71); EI-HRMS calcd for $C_{24}H_{41}O_3SSi$ (M^++H) 437.2546, found 437.2557.

2,5-Di-*O*-benzyl-1,6-di-*O*-*tert*-butyldiphenylsilyl-D-mannitol 19

To a solution of tetraol **18**[13] (20.3 g, 50.3 mmol) and imidazole (16.0 g, 0.235 mol) in 200 mL of DMF at room temperature under Ar was added 30.6 mL (0.118 mol) of *tert*-butyldiphenylsilyl chloride and the solution was stirred at the same temperature for 2 h. The reaction mixture was poured into 800 mL of water and extracted with ether (300 mL × 3). The ethereal layer was washed with 500 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to column chromatography (2% EtOAc/benzene) on 609 g of silica gel to yield disilyl ether **19** (42.2 g, 100% yield): $[\alpha]_D^{23}$ -16.5 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.71-7.63 (8H, m), 7.46-7.24 (22H, m), 4.66 (2H, d, *J*=11.6 Hz), 4.52 (2H, d, *J*=11.6 Hz), 4.04 (2H, d, *J*=6.1 Hz), 3.92 (2H, dd, *J*=11.0, 4.9 Hz), 3.84 (2H, dd, *J*=11.0, 4.9 Hz), 3.69 (2H, dt, *J*=6.1, 4.9 Hz), 3.40-2.80 (2H, br s), 1.03 (18H, s); IR (neat) 3450, 3040, 2915, 2845, 1590, 1455, 1429, 1393, 1362, 1212, 1110, 1028, 939, 829, 803, 744, 700 cm^{-1}; FD-MS *m/z* (relative intensity) 838 (M^+, 4.0); EI-MS *m/z* (relative intensity) 593 (M^+—*t*-Bu—Phx2—OHx2, 0.10), 241 (10), 199 (10), 163 (12), 135 (12), 92 (10), 91 (100); EI-HRMS calcd for $C_{36}H_{41}O_4Si_2$ (M^+—*t*-Bu—Phx2—OHx2) 593.2544, found 593.2518.

2-*O*-Benzyl-3-*O*-*tert*-butyldiphenylsilyl-D-glyceraldehyde 6

To a solution of diol **19** (12.3 g, 14.6 mmol) in 120 mL of benzene at room temperature was added a portion of 7.12 g (16.1 mmol) of lead tetraacetate and the mixture was stirred at the same temperature under Ar for 8 h. The reaction mixture was filtered through a pad of Celite *in suction* and the filtrates were concentrated *in vacuo* to give unstable aldehyde **6** (12.2 g, 100% yield): ^1H NMR (90 MHz, $CDCl_3$) δ 9.69 (1H, br s), 7.75-7.45 (4H, m), 7.45-7.15 (11H, m), 4.63 (2H, s), 4.01-3.75 (3H, m), 1.05 (9H, s).

(2*R*,3*S*)-2-*O*-Benzyl-1-*O*-*tert*-butyldiphenylsilyl-5-methyl-5-hexene-1,2,3-triol 20

To a solution of aldehyde **6** (12.0 g, 28.7 mmol) in 120 mL of CH_2Cl_2 at -78 °C under Ar were successively added dropwise 3.88 mL (31.6 mmol) of freshly distilled boron trifluoride etherate and 9.19 mL (57.4 mmol) of methallyltrimethylsilane and the mixture was stirred at the same temperature for 30 min. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ and the resulting mixture was allowed to warm to room temperature. The mixture was poured into 100 mL of water and extracted with CH_2Cl_2 (50 mL × 3). The extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (2% EtOAc/benzene) on 360 g of silica gel to afford alcohol **20** (10.7 g, 78% yield): $[\alpha]_D^{23}$ -15.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (4H, d, *J*=6.8 Hz), 7.47-7.25 (11H, m), 4.85 (1H, br s), 4.77 (1H, br s), 4.67 (1H, d, *J*=11.7 Hz), 4.55 (1H, d, *J*=11.7 Hz), 4.00 (1H, ddd, *J*=9.8, 5.1, 3.2 Hz), 3.89 (1H, dd, *J*=11.2, 5.1 Hz), 3.85 (1H, dd, *J*=11.2, 5.1 Hz), 3.50 (1H, q, *J*=5.1 Hz), 2.33 (1H, dd, *J*=14.2, 3.2 Hz), 2.17 (1H, dd, *J*=14.2, 9.8 Hz), 1.75 (3H, s), 1.06 (9H, s); IR (neat) 3410, 3040, 2920, 2870, 2840, 1645, 1590, 1471, 1429, 1392, 1360, 1260, 1187, 1112, 1083, 1027, 1007, 938, 893, 826, 743, 700 cm^{-1}; FD-MS *m/z* (relative intensity) 474 (M^+, 15); EI-MS *m/z* (relative intensity) 400 (M^+—*t*-Bu—OH, 0.22), 93 (10), 92 (11), 91 (100); EI-HRMS calcd for $C_{26}H_{28}O_2Si$ (M^+—*t*-Bu—OH) 400.1859, found 400.1870.

(2*R*,3*S*)-2-*O*-Benzyl-1-*O*-*tert*-butyldiphenylsilyl-3-*O*,5-dimethyl-5-hexene-1,2,3-triol 21

Preparation from alcohol **20**.

To a suspension of potassium hydride (35% dispersion in mineral oil, 743 mg, 6.48 mmol) in 7 mL of THF at 0 °C under Ar was added 1.23 g (2.59 mmol) of alcohol **20** dissolved in 12 mL of THF and the solution was stirred at the same temperature for 30 min. To the solution was added dropwise 0.811 mL (13.0 mmol) of freshly distilled methyl iodide and the mixture was stirred at room temperature for additional 3 h. The reaction

was quenched with 5 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 30 mL of water, followed by extracting with ether (30 mL × 3). The combined ethereal layers were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (2% EtOAc/hexane) on 36.9 g of silica gel to provide methyl ether **21** (1.14 g, 90% yield): $[\alpha]_D^{22}$ -7.51 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.82-7.61 (4H, m), 7.52-7.22 (11H, m), 4.79 (1H, br s), 4.73 (1H, br s), 4.68 (1H, d, *J*=11.6 Hz), 4.60 (1H, d, *J*=11.6 Hz), 3.84 (1H, dd, *J*=11.0, 5.5 Hz), 3.76 (1H, dd, *J*=11.0, 4.3 Hz), 3.72-3.55 (2H, m), 3.35 (3H, s), 2.36-2.18 (2H, m), 1.74 (3H, s), 1.06 (9H, s); IR (neat) 3040, 2915, 2875, 2845, 1645, 1590, 1455, 1430, 1393, 1376, 1362, 1332, 1307, 1260, 1206, 1189, 1108, 1029, 1007, 971, 939, 892, 827, 810, 742, 700 cm^{-1}; FD-MS *m/z* (relative intensity) 488 (M^+, 11); EI-MS *m/z* (relative intensity) 431 (M^+—*t*-Bu, 0.27), 213 (15), 199 (11), 183 (12), 153 (16), 135 (11), 99 (12), 93 (16), 92 (10), 91 (100), 41 (11); EI-HRMS calcd for $C_{27}H_{31}O_3Si$ (M^+—*t*-Bu) 431.2042, found 431.2037.

Preparation from alcohol **22b**.

To a solution of alcohol **22b** (2.00 g, 3.95 mmol) and *o*-nitrophenyl selenocyanate (1.08 g, 4.74 mmol) in 30 mL of THF at room temperature under Ar was added dropwise 1.18 mL (4.74 mmol) of freshly distilled tributylphosphine and the mixture was stirred at the same temperature for 30 min. After 30 min, to the solution at 0 °C was added dropwise 10 mL of 30% aqueous hydrogen peroxide and then the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into 40 mL of water and extracted with ether (30 mL × 3). The ethereal layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (2% EtOAc/hexane) on 60 g of silica gel to yield olefin **21**, identical with the product prepared from **20**, (1.54 g, 80% yield).

(2*R*,4*S*,5*R*)-5-Benzyloxy-6-(*tert*-butyldiphenylsilyl)oxy-4-methoxy-2-methyl-1-hexanol 22a and its C2-epimer 22b

A procedure utilizing thexylborane is described as a representative.

To a solution of 30.8 mL (30.8 mmol) of borane (1.0 M in THF) at -15 °C under Ar was added 30.8 mL (30.8 mmol) of 2,3-dimethyl-2-butene (1.0 M in THF) and the solution was stirred at the same temperature for 2 h. To the solution of thexylborane at -15 °C was added dropwise olefin **21** (6.00 g, 12.3 mmol) dissolved in 60 mL of THF and the mixture was further stirred at the same temperature for additional 2 h. After the mixture was allowed to warm to room temperature, to the solution was sequentially added 10 mL of water, 5 mL of 15% aqueous NaOH, and 5 mL of 30% aqueous H_2O_2 and the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into 100 mL of water and extracted with ether (70 mL × 3). The ethereal layer was washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography on 300 g of silica gel eluting with 20% and 30% ether/hexane to afford the desired alcohol **22a** (3.68 g, 59% yield) and its C2-epimer **22b** (2.43 g, 39% yield), respectively.

Alcohol **22a**: $[\alpha]_D^{23}$ -11.4 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.71-7.63 (4H, m), 7.48-7.24 (11H, m), 4.66 (1H, d, *J*=11.9 Hz), 4.53 (1H, d, *J*=11.9 Hz), 3.84 (1H, dd, *J*=10.9, 4.9 Hz), 3.76 (1H, dd, *J*=10.9, 4.6 Hz), 3.66-3.51 (2H, m), 3.50-3.28 (2H, m), 3.35 (3H, s), 2.42 (1H, br s), 1.93-1.76 (1H, m), 1.67 (1H, ddd, *J*=15.2, 7.3, 4.5 Hz), 1.49 (1H, ddd, *J*=15.2, 7.9, 3.1 Hz), 1.06 (9H, s), 0.87 (3H, d, *J*=6.7 Hz); IR (neat) 3380, 3035, 2905, 2850, 1590, 1455, 1428, 1391, 1360, 1205, 1110, 1028, 828, 743, 700 cm^{-1}; FD-MS *m/z* (relative intensity) 506 (M^+, 7.7); EI-MS *m/z* (relative intensity) 418 (M^+—*t*-Bu—OMe, 0.37), 249 (23), 199 (22), 135 (10), 99 (12), 92 (10), 91 (100), 85 (32); EI-HRMS calcd for $C_{26}H_{30}O_3Si$ (M^+—*t*-Bu—OMe) 418.1967, found 418.1997.

C2-epimer **22b**: $[\alpha]_D^{22}$ -15.1 (*c* 1.20, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.65 (4H, br d, *J*=6.7 Hz), 7.50-7.18 (11H, m), 4.61 (2H, s), 3.90-3.25 (6H, m), 3.34 (3H, s), 1.87 (1H, br s), 1.90-1.65 (1H, m), 1.58 (1H, ddd, *J*=14.8, 9.8, 6.7 Hz), 1.29 (1H, ddd, *J*=14.8, 6.9, 1.8 Hz), 1.06 (9H, s), 0.91 (3H, d, *J*=6.7 Hz); IR (neat) 3400, 3040, 2920, 2850, 1590, 1455, 1428, 1390, 1360, 1189, 1106, 936, 825, 741, 696 cm^{-1}; EI-MS *m/z* (relative intensity) 507 (M^++H, 0.02), 249 (23), 199 (19), 99 (12), 92 (11), 91 (100), 85 (35); FI-MS

m/z (relative intensity) 507 (M^++H, 67), 506 (M^+, 14), 451 (16), 450 (40), 449 (100), 241 (12), 117 (11), 92 (11), 91 (75), 78 (11), 57 (30); FI-HRMS calcd for $C_{31}H_{43}O_4Si$ (M^++H) 507.2931, found 507.2948.

(2*R*,4*S*,5*R*)-5-(*tert*-Butyldiphenylsilyl)oxymethyl-4-methoxy-2-methyl-5-pentanolide 25a and its C2-epimer 25b

To a solution of benzyl ether **22a** (481 mg, 0.951 mmol) in 10 mL of EtOH was added a portion of 240 mg of 20% palladium hydroxide on carbon and the mixture was stirred at room temperature for 2 d under 1 atm of hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite *in suction* and concentrated under reduced pressure. The residual product was directly used in the next reaction.

To a solution of the above diol (396 mg, 0.951 mmol) and 792 mg of activated 4A molecular sieves in 20 mL of CH_2Cl_2 at room temperature was added a portion of pyridinium chlorochromate (2.05 g, 9.51 mmol) and the mixture was stirred at the same temperature under Ar for 16 h. The reaction mixture was filtered through a pad of Celite *in suction* and evaporated *in vacuo*. The residue was subjected to column chromatography (2% EtOAc/benzene) on 11.9 g of silica gel to provide lactone **25a**, identical with the authentic sample[4b] independently prepared from methyl α-D-glucopyranoside, (294 mg, 75% overall yield from **22a**): $[\alpha]_D^{22}$ +22.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78-7.59 (4H, m), 7.52-7.30 (6H, m), 4.17 (1H, dt, *J*=7.6, 2.5 Hz), 3.87 (2H, d, *J*=2.5 Hz), 3.84 (1H, ddd, *J*=10.8, 7.6, 5.0 Hz), 3.37 (3H, s), 2.52 (1H, ddq, *J*=12.5, 5.0, 6.9 Hz), 2.32 (1H, dt, *J*=12.5, 5.0 Hz), 1.58 (1H, dt, *J*=10.8, 12.5 Hz), 1.33 (3H, d, *J*=6.9 Hz), 1.05 (9H, s).

The C2-epimeric lactone **25b**, identical with the authentic sample[4b] independently prepared from methyl α-D-glucopyranoside, was also derived from benzyl ether **22b** through the same procedure as the above one.
C2-epimer **25b**: mp 103-105 °C; $[\alpha]_D^{22}$ +57.9 (*c* 0.795, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78-7.60 (4H, m), 7.53-7.30 (6H, m), 4.29 (1H, q, *J*=4.6 Hz), 3.86 (1H, dd, *J*=11.0, 4.6 Hz), 3.82 (1H, dd, *J*=11.0, 4.6 Hz), 3.74 (1H, dt, *J*=3.3, 4.6 Hz), 3.34 (3H, s), 2.73 (1H, dquintet, *J*=12.8, 6.4 Hz), 2.06 (1H, ddd, *J*=14.1, 6.4, 3.3 Hz), 1.77 (1H, ddd, *J*=14.1, 12.8, 4.6 Hz), 1.24 (3H, d, *J*=6.4 Hz), 1.06 (9H, s).

(2*R*,3*S*,5*R*)-2,6-Dibenzyloxy-1-(*tert*-butyldiphenylsilyl)oxy-3-methoxy-5-methylhexane 23

To a solution of potassium hydride (35% dispersion in mineral oil, 1.79 g, 15.6 mmol) in 20 mL of THF at -15 °C under Ar was added dropwise 3.94 g (7.79 mmol) of alcohol **22a** dissolved in 40 mL of THF and the solution was stirred at the same temperature for 15 min. To the solution was added dropwise 3.71 mL (31.2 mmol) of benzyl bromide and the mixture was stirred at room temperature for 2 h. The reaction was quenched with 10 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 60 mL of water, followed by extracting with ether (50 mL × 3). The combined ethereal layers were washed with 70 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (5% ether/hexane) on 118 g of silica gel to provide dibenzyl ether **23** (4.37 g, 94% yield): $[\alpha]_D^{24}$ -13.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72-7.59 (4H, m), 7.46-7.18 (16H, m), 4.65 (1H, d, *J*=12.2 Hz), 4.58 (1H, d, *J*=12.2 Hz), 4.45 (2H, s), 3.82 (1H, dd, *J*=11.0, 6.1 Hz), 3.72 (1H, dd, *J*=11.0, 4.6 Hz), 3.57 (1H, ddd, *J*=6.1, 4.6, 3.6 Hz), 3.48 (1H, dt, *J*=7.7, 3.6 Hz), 3.35 (1H, dd, *J*=9.2, 4.9 Hz), 3.31 (3H, s), 3.21 (1H, dd, *J*=9.2, 6.7 Hz), 2.04-1.84 (1H, m), 1.56-1.32 (2H, m), 1.05 (9H, s), 0.96 (3H, d, *J*=6.8 Hz); IR (neat) 3040, 2915, 2845, 1589, 1493, 1454, 1429, 1392, 1361, 1205, 1111, 1029, 828, 743, 699 cm^{-1}; FD-MS *m/z* (relative intensity) 596 (M^+, 31); EI-MS *m/z* (relative intensity) 431 (M^+—*t*-Bu—Ph—OMe, 0.17), 249 (14), 92 (10), 91 (100), 85 (53); EI-HRMS calcd for $C_{27}H_{31}O_3Si$ (M^+—*t*-Bu—Ph—OMe) 431.2043, found 431.2045.

(2*R*,3*S*,5*R*)-2,6-Dibenzyloxy-3-methoxy-5-methyl-1-hexanol 24

To a solution of silyl ether **23** (3.68 g, 6.17 mmol) in 37 mL of THF at room temperature under Ar was added tetrabutylammonium fluoride (1.0 M in THF, 12.3 mL, 12.3 mmol) and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with 10 mL of saturated aqueous NH_4Cl and the reaction mixtures were poured into 50 mL of water, followed by extracting with ether (50 mL × 3). The combined

ethereal layers were washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (12% EtOAc/benzene) on 110 g of silica gel to produce alcohol **24** (2.03 g, 92% yield): $[\alpha]_D^{25}$ -0.11 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.16 (10H, m), 4.65 (1H, d, *J*=11.6 Hz), 4.59 (1H, d, *J*=11.6 Hz), 4.48 (2H, br s), 3.76 (1H, dd, *J*=11.8, 5.0 Hz), 3.69 (1H, dd, *J*=11.8, 3.7 Hz), 3.54-3.42 (2H, m), 3.41 (3H, s), 3.33 (1H, dd, *J*=9.2, 6.1 Hz), 3.29 (1H, dd, *J*=9.2, 6.1 Hz), 2.19 (1H, br s), 2.02-1.81 (1H, m), 1.58 (1H, ddd, *J*=14.2, 7.3, 4.1 Hz), 1.43 (1H, ddd, *J*=14.2, 7.7, 6.1 Hz), 0.98 (3H, d, *J*=6.7 Hz); IR (neat) 3420, 3000, 2910, 2860, 1496, 1454, 1365, 1206, 1098, 1030, 910, 741, 699 cm^{-1}; FD-MS *m/z* (relative intensity) 358 (M^+, 23); EI-MS *m/z* (relative intensity) 359 (M^++H, 0.22), 92 (11), 91 (100), 85 (92); EI-HRMS calcd for $C_{22}H_{31}O_4$ (M^++H) 359.2222, found 359.2221.

(2*S*,3*S*,5*R*)-2,6-Dibenzyloxy-3-methoxy-5-methylhexanal 4

To a solution of oxalyl chloride (0.570 mL, 6.57 mmol) in 7 mL of CH_2Cl_2 at -78 °C under Ar was added dropwise 0.930 mL (13.1 mmol) of dimethyl sulfoxide dissolved in 4 mL of CH_2Cl_2 and the solution was stirred at the same temperature for 10 min. To the solution was added dropwise alcohol **24** (784 mg, 2.19 mmol) dissolved in 7 mL of CH_2Cl_2 at -78 °C and the mixture was stirred at the same temperature for 1 h. To the solution at -78 °C was added 2.44 mL (17.5 mmol) of triethylamine and the mixture was vigorously stirred at 0 °C for additional 30 min. The reaction mixture was poured into 40 mL of water and extracted with CH_2Cl_2 (30 mL × 3). The extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography (2% EtOAc/benzene) on 23.5 g of silica gel afforded unstable aldehyde **4** (742 mg, 95% yield): $[\alpha]_D^{23}$ -32.8 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.69 (1H, d, *J*=1.8 Hz), 7.42-7.17 (10H, m), 4.71 (1H, d, *J*=12.1 Hz), 4.62 (1H, d, *J*=12.1 Hz), 4.47 (2H, s), 3.88 (1H, dd, *J*=3.1, 1.8 Hz), 3.64 (1H, ddd, *J*=8.2, 5.0, 3.1 Hz), 3.34 (3H, s), 3.40-3.20 (2H, m), 2.20-1.83 (1H, m), 1.61 (1H, ddd, *J*=14.3, 8.2, 6.1 Hz), 1.52 (1H, ddd, *J*=14.3, 7.5, 5.0 Hz), 0.95 (3H, d, *J*=6.7 Hz); IR (neat) 3025, 2925, 2870, 1736, 1693, 1607, 1500, 1457, 1368, 1314, 1271, 1208, 1098, 1030, 911, 744, 700 cm^{-1}.

(2*R*,4*S*,5*S*,8*S*,10*E*,12*R*)-1,5-Dibenzyloxy-12-(*tert*-butyldimethylsilyl)oxymethyl-4-methoxy-2,8,10-trimethyl-10,14-pentadecadien-6-one 26

To a solution of sulfone **3** (660 mg, 1.51 mmol) in 6 mL of THF at -78 °C under Ar was added dropwise 1.40 mL (2.27 mmol) of *n*-butyllithium (1.62 M in hexane) and the solution was stirred at the same temperature for 10 min. To the solution at -78 °C was added dropwise aldehyde **4** (539 mg, 1.51 mmol) dissolved in 6 mL of THF and the mixture was stirred at the same temperature for 2 h 30 min. The reaction was quenched with 3 mL of saturated aqueous NH_4Cl and the temperature was allowed to warm to room temperature. The reaction mixture was poured into 25 mL of water and extracted with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography (10-30% ether/hexane) on 33.0 g of silica gel to give four diastereomeric mixtures of adduct (988 mg, 83% yield) which was directly used in the next reaction.

To a solution of oxalyl chloride (0.399 mL, 4.59 mmol) in 3 mL of CH_2Cl_2 at -78 °C under Ar was added dropwise 0.654 mL (9.21 mmol) of dimethyl sulfoxide dissolved in 2 mL of CH_2Cl_2 and the solution was stirred at the same temperature for 10 min. To the solution at -78 °C was added dropwise the above diastereomeric mixtures of adduct (510 mg, 0.644 mmol) dissolved in 4 mL of CH_2Cl_2 and the mixture was stirred at the same temperature for 1 h. To the solution at -78 °C was added 1.76 mL (12.6 mmol) of triethylamine and then the mixture was vigorously stirred at 0 °C for additional 2 h 30 min. The reaction mixture was poured into 25 mL of water and extracted with ether (30 mL × 3). The extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography (15% ether/hexane) on 51.0 g of silica gel to furnish two diastereomeric mixtures of α-sulfonyl ketone (376 mg, 74% yield) which was directly used in the next reaction.

To a solution of the above α-sulfonyl ketone (1.74 g, 2.20 mmol) and 2,2'-azobisisobutyronitrile (434 mg, 2.64 mmol) in 17 mL of toluene at room temperature under Ar was added 1.18 mL (4.40 mmol) of tributyltin hydride and then the mixture was stirred at reflux for 5 h. An oil bath was removed and the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (5% ether/hexane) on 52.2 g of silica gel to yield chirally homogeneous ketone **26** (1.10 g, 77% yield): $[\alpha]_D^{20}$ -26.9 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.50-7.19 (10H, m), 5.76 (1H, ddt, *J*=17.1, 10.1, 7.0 Hz), 5.08-4.78 (3H, m), 4.64 (1H, d, *J*=11.9 Hz), 4.57 (1H, d, *J*=11.9 Hz), 4.48 (2H, s), 3.93 (1H, d, *J*=3.6 Hz), 3.64 (1H, dt, *J*=8.9, 3.6 Hz), 3.46 (1H, dd, *J*=9.8, 5.8 Hz), 3.48-3.24 (2H, m), 3.33 (3H, s), 3.26 (1H, dd, *J*=9.2, 6.1 Hz), 2.61-2.12 (5H, m), 2.07-1.86 (3H, m), 1.83-1.37 (3H, m), 1.60 (3H, s), 0.97 (3H, d, *J*=6.7 Hz), 0.89 (9H, s), 0.80 (3H, d, *J*=6.7 Hz), 0.03 (6H, s); IR (neat) 2940, 2860, 1715, 1643, 1501, 1459, 1365, 1308, 1253, 1209, 1100, 1030, 1008, 942, 913, 842, 821, 782, 742, 700 cm^{-1}; FD-MS *m/z* (relative intensity) 650 (M^+, 45); EI-MS *m/z* (relative intensity) 485 (M^+—*t*-Bu—OBn, 0.28), 105 (12), 99 (15), 91 (74), 89 (11), 85 (100), 75 (16), 73 (24); EI-HRMS calcd for $C_{29}H_{45}O_4Si$ (M^+—*t*-Bu—OBn) 485.3087, found 485.3086.

(2*R*,4*S*,5*R*,6*S*,8*S*,10*E*,12*R*)-1,5-Dibenzyloxy-12-(*tert*-butyldimethylsilyl)oxymethyl-4-methoxy-2,8,10-trimethyl-10,14-pentadecadien-6-ol 27a

To a solution of ketone **26** (162 mg, 0.249 mmol) in 5 mL of toluene at -78 °C under Ar was slowly added diisobutylaluminum hydride (0.97 M in hexane, 0.513 mL, 0.498 mmol) and the mixture was stirred at the same temperature for 20 min. The reaction was carefully quenched with each appropriate amount of MeOH and water, and then the temperature was allowed to warm to room temperature. After vigorously stirring for 20 min, the resulting mixture was filtered through a pad of Celite *in suction* and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (6% EtOAc/hexane) on 16.2 g of silica gel to give desired alcohol **27a** (140 mg, 86% yield): $[\alpha]_D^{23}$ -13.1 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.20 (10H, m), 5.76 (1H, ddt, *J*=17.0, 10.0, 7.1 Hz), 5.10-4.91 (2H, m), 4.85 (1H, br d, *J*=9.2 Hz), 4.76 (1H, d, *J*=11.3 Hz), 4.54 (1H, d, *J*=11.3 Hz), 4.49 (2H, s), 3.91-3.77 (1H, m), 3.60-3.26 (6H, m), 3.42 (3H, s), 3.06 (1H, br d, *J*=4.0 Hz), 2.62-2.44 (1H, m), 2.42-2.27 (1H, m), 2.15 (1H, dd, *J*=13.0, 3.5 Hz), 2.07-1.72 (3H, m), 1.69-1.25 (5H, m), 1.56 (3H, s), 0.99 (3H, d, *J*=7.0 Hz), 0.89 (9H, s), 0.80 (3H, d, *J*=6.4 Hz), 0.02 (6H, s); IR (neat) 3480, 2920, 1639, 1497, 1452, 1379, 1360, 1249, 1092, 1025, 1002, 908, 838, 779, 735, 696 cm^{-1}; EI-MS *m/z* (relative intensity) 652 (M^+, 0.29), 99 (20), 92 (11), 91 (100), 85 (78), 75 (14), 73 (17); EI-HRMS calcd for $C_{40}H_{64}O_5Si$ (M^+) 652.4523, found 652.4493.

(2*R*,4*S*,5*R*,6*R*,8*S*,10*E*,12*R*)-1,5-Dibenzyloxy-12-(*tert*-butyldimethylsilyl)oxymethyl-4-methoxy-2,8,10-trimethyl-10,14-pentadecadien-6-ol 27b

To a solution of lithium aluminum hydride (11.7 mg, 0.308 mmol) in 2 mL of Et_2O at -78 °C under Ar was added dropwise ketone **26** (100 mg, 0.154 mmol) dissolved in 3 mL of Et_2O and the mixture was stirred at the same temperature for 30 min. The reaction was carefully quenched with 11.7 μL of water, followed by 11.7 μL of 15% aqueous NaOH, and then 35.1 μL of water. The resulting mixture was allowed to warm to room temperature and vigorously stirred at the same temperature for 10 min. To the mixture was further added anhydrous Na_2SO_4 and the mixtures were stirred for additional 20 min. The reaction mixture was filtered through a pad of Celite *in suction* and evaporated *in vacuo*. The residue was purified by column chromatography (7% EtOAc/hexane) on 10 g of silica gel to give undesired alcohol **27b** (92.5 mg, 92% yield): $[\alpha]_D^{24}$ -2.41 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.18 (10H, m), 5.76 (1H, ddt, *J*=17.2, 9.9, 6.9 Hz), 5.05-4.89 (2H, m), 4.86 (1H, br d, *J*=9.8 Hz), 4.73 (1H, d, *J*=11.5 Hz), 4.54 (1H, d, *J*=11.5 Hz), 4.49 (2H, s), 3.82-3.71 (1H, m), 3.58 (1H, dt, *J*=8.3, 3.2 Hz), 3.47 (1H, dd, *J*=9.8, 5.5 Hz), 3.45-3.30 (5H, m), 3.38 (3H, s), 2.60-2.43 (1H, m), 2.40-2.22 (2H, m), 2.08-1.34 (8H, m), 1.58 (3H, s), 0.99 (3H, d, *J*=6.7 Hz), 0.88 (9H, s), 0.79 (3H, d, *J*=6.1 Hz), 0.02 (6H, s); IR (neat) 3440, 2890, 2835, 1638, 1495, 1450, 1376, 1359, 1248, 1202, 1090, 1000, 907, 835, 779, 733, 694 cm^{-1}; EI-MS *m/z* (relative intensity) 652 (M^+, 0.16), 99 (24), 92 (11), 91 (99), 89 (12), 85 (100), 75 (12), 73 (16); EI-HRMS calcd for $C_{40}H_{64}O_5Si$ (M^+) 652.4523, found 652.4531.

(4*R*,5*E*,8*S*,10*S*,11*R*,12*S*,14*R*)-11,15-Dibenzyloxy-4-(*tert*-butyldimethylsilyl)oxymethyl-10,12-dimethoxy-6,8,14-trimethyl-1,5-pentadecadiene 28a and its C10-epimer 28b

To a suspension of potassium hydride (35% dispersion in mineral oil, 310 mg, 2.70 mmol) in 3 mL of THF at room temperature under Ar was added dropwise 587 mg (0.901 mmol) of alcohol **27a** dissolved in 6 mL of THF and the mixture was stirred at the same temperature for 10 min. To the solution was added dropwise 0.281 mL (4.51 mmol) of freshly distilled methyl iodide and the mixture was stirred for additional 1 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 25 mL of water, followed by extracting with ether (20 mL × 3). The combined ethereal layers were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/hexane) on 29.4 g of silica gel to afford methyl ether **28a** (565 mg, 94% yield): $[\alpha]_D^{19}$ -20.2 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.18 (10H, m), 5.76 (1H, ddt, *J*=17.2, 10.1, 7.1 Hz), 5.07-4.92 (2H, m), 4.85 (1H, br d, *J*=9.2 Hz), 4.76 (1H, d, *J*=11.6 Hz), 4.63 (1H, d, *J*=11.6 Hz), 4.49 (2H, s), 3.60-3.25 (7H, m), 3.42 (3H, s), 3.33 (3H, s), 2.62-2.44 (1H, m), 2.42-2.28 (1H, m), 2.20-1.86 (3H, m), 1.84-1.20 (6H, m), 1.55 (3H, s), 1.01 (3H, d, *J*=7.0 Hz), 0.89 (9H, s), 0.78 (3H, d, *J*=6.4 Hz), 0.03 (6H, s); IR (neat) 2920, 1640, 1498, 1452, 1377, 1360, 1248, 1203, 1085, 1025, 1001, 936, 907, 835, 777, 734, 694 cm^{-1}; EI-MS *m/z* (relative intensity) 666 (M^+, 0.12), 205 (10), 175 (11), 99 (27), 92 (11), 91 (100), 89 (19), 85 (89), 75 (14), 73 (23); EI-HRMS calcd for $C_{41}H_{66}O_5Si$ (M^+) 666.4680, found 666.4695.

The C10-epimeric methyl ether **28b** was also synthesized from alcohol **27b** by the same procedure as the above one.

C10-epimer **28b**: $[\alpha]_D^{22}$ -8.55 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.18 (10H, m), 5.77 (1H, ddt, *J*=17.1, 10.1, 7.0 Hz), 5.05-4.88 (2H, m), 4.87 (1H, br d, *J*=9.5 Hz), 4.68 (2H, s), 4.48 (2H, s), 3.55 (1H, br t, *J*=4.3 Hz), 3.47 (1H, dd, *J*=9.8, 5.8 Hz), 3.50-3.26 (4H, m), 3.34 (3H, s), 3.33 (3H, s), 3.28 (1H, dd, *J*=9.2, 6.7 Hz), 2.60-2.43 (1H, m), 2.41-2.26 (1H, m), 2.11-1.40 (8H, m), 1.58 (3H, d, *J*=0.9 Hz), 1.37-1.20 (1H, m), 1.00 (3H, d, *J*=6.7 Hz), 0.88 (9H, s), 0.80 (3H, d, *J*=6.4 Hz), 0.02 (6H, s); IR (neat) 2920, 1640, 1499, 1457, 1380, 1362, 1333, 1251, 1205, 1095, 1029, 1006, 940, 910, 840, 781, 739, 699 cm^{-1}; EI-MS *m/z* (relative intensity) 666 (M^+, 0.02), 175 (12), 105 (11), 99 (27), 91 (83), 89 (18), 85 (100), 75 (13), 73 (21); EI-HRMS calcd for $C_{41}H_{66}O_5Si$ (M^+) 666.4680, found 666.4702.

(2*R*,4*S*,5*R*,6*S*,8*S*,10*E*,12*R*)-12-(*tert*-Butyldimethylsilyl)oxymethyl-4,6-dimethoxy-2,8,10-trimethyl-10,14-pentadecadiene-1,5-diol 29a and its C6-epimer 29b

To a solution of lithium (300 mg, 43.2 mmol) in 8 mL of liquid ammonia at -78 °C under Ar was added dropwise dibenzyl ether **28a** (560 mg, 0.842 mmol) dissolved in 5 mL of THF and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with 10 g of NH_4Cl at -78 °C and the resulting mixture was allowed to warm to room temperature. The mixture was stirred for some time until ammonia has been removed. The reaction mixture was poured into 30 mL of saturated aqueous NH_4Cl and extracted with ether (30 mL × 3). The organic layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (30% EtOAc/benzene) on 16.8 g of silica gel to yield diol **29a** (389 mg, 95% yield): $[\alpha]_D^{25}$ +2.65 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J*=17.1, 10.1, 7.0 Hz), 5.07-4.82 (3H, m), 3.58-3.28 (7H, m), 3.42 (3H, s), 3.41 (3H, s), 2.61-2.26 (4H, m), 2.17-1.84 (3H, m), 1.84-1.32 (6H, m), 1.59 (3H, s), 0.95 (3H, d, *J*=7.0 Hz), 0.89 (9H, s), 0.83 (3H, d, *J*=6.1 Hz), 0.03 (6H, s); IR (neat) 3400, 2910, 1639, 1460, 1380, 1250, 1188, 1090, 1035, 990, 937, 910, 839, 816, 779 cm^{-1}; EI-MS *m/z* (relative intensity) 486 (M^+, 0.42), 107 (22), 99 (30), 95 (21), 89 (33), 85 (100), 81 (20), 75 (36), 73 (49), 67 (22), 55 (21), 41 (22); EI-HRMS calcd for $C_{27}H_{54}O_5Si$ (M^+) 486.3740, found 486.3730.

The C6-epimeric diol **29b** was also synthesized from dibenzyl ether **28b** by the same procedure as the above one.

C6-epimer **29b**: $[\alpha]_D^{23}$ +2.68 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.85-5.65 (1H, m), 5.06-4.80 (3H, m), 3.90 (1H, dd, *J*=6.1, 4.6 Hz), 3.53 (1H, dd, *J*=11.0, 4.6 Hz), 3.50-3.26 (5H, m), 3.36 (3H, s), 3.35 (3H, s), 2.55-2.26 (4H, m), 2.06-1.49 (9H, m), 1.58 (3H, s), 0.94 (3H, d, *J*=6.7 Hz), 0.87 (9H, s), 0.82 (3H, d, *J*=5.5 Hz), 0.02 (6H, s); IR (neat) 3420, 2940, 1641, 1464, 1384, 1361, 1251, 1188, 1090, 1005, 990, 939, 909, 840, 815, 780 cm^{-1}; EI-MS *m/z* (relative intensity) 486 (M^+, 0.52), 107 (20), 99 (27), 95 (21), 89 (30), 85 (100), 81 (21), 75 (31), 73 (43), 55 (22); EI-HRMS calcd for $C_{27}H_{54}O_5Si$ (M^+) 486.3740, found 486.3711.

(2*R*,4*S*,5*R*,6*S*,8*S*,10*E*,12*R*)-12-(*tert*-Butyldimethylsilyl)oxymethyl-4,6-dimethoxy-2,8,10-trimethyl-10,14-pentadecadien-5-olide 2a and its C6-epimer 2b

To a solution of diol **29a** (108 mg, 0.223 mmol) and 500 mg of activated 4A molecular sieves in 5 mL of CH_2Cl_2 at room temperature was added a portion of pyridinium chlorochromate (721 mg, 3.35 mmol) and the mixture was stirred at the same temperature under Ar for 2 h. The reaction mixture was filtered through a pad of Celite *in suction* and evaporated *in vacuo*. The residue was subjected to column chromatography (10% EtOAc/hexane) on 10.8 g of silica gel to provide lactone **2a** (91.5 mg, 85% yield): $[\alpha]_D^{17}$ +22.4 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.74 (1H, ddt, *J*=17.1, 10.1, 7.0 Hz), 4.97 (1H, dd, *J*=17.1, 2.0 Hz), 4.92 (1H, dd, *J*=10.1, 2.0 Hz), 4.87 (1H, dd, *J*=10.5, 0.8 Hz), 4.06 (1H, dd, *J*=7.9, 1.5 Hz), 3.68 (1H, ddd, *J*=11.0, 7.9, 4.6 Hz), 3.58-3.30 (3H, m), 3.40 (3H, s), 3.39 (3H, s), 2.60-2.41 (2H, m), 2.40-2.24 (2H, m), 2.14 (1H, m), 1.93 (1H, m), 1.81-1.43 (5H, m), 1.58 (3H, br s), 1.30 (3H, d, *J*=7.0 Hz), 0.89 (9H, s), 0.83 (3H, d, *J*=5.5 Hz), 0.03 (6H, s); IR (neat) 2940, 1747, 1641, 1465, 1383, 1252, 1175, 1090, 1022, 1006, 969, 938, 910, 840, 780 cm^{-1}; EI-MS *m/z* (relative intensity) 483 (M^++H, 0.18), 482 (M^+, 0.11), 425 (49), 175 (31), 107 (48), 99 (87), 95 (40), 93 (36), 89 (70), 85 (78), 81 (42), 75 (69), 73 (100), 71 (34), 69 (44), 67 (33), 57 (32), 55 (43), 45 (31), 41 (38); EI-HRMS calcd for $C_{27}H_{51}O_5Si$ (M^++H) 483.3506, found 483.3521.

The C6-epimeric lactone **2b** was also synthesized from diol **29b** by the same procedure as the above one. C6-epimer **2b**: $[\alpha]_D^{24}$ -2.52 (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J*=17.2, 10.0, 7.1 Hz), 5.07-4.82 (3H, m), 4.24 (1H, dd, *J*=6.7, 2.4 Hz), 3.74-3.26 (4H, m), 3.40 (3H, s), 3.36 (3H, s), 2.60-2.19 (4H, m), 2.15-1.10 (7H, m), 1.59 (3H, s), 1.30 (3H, d, *J*=7.0 Hz), 0.89 (9H, s), 0.84 (3H, d, *J*=6.1 Hz), 0.03 (6H, s); IR (neat) 2930, 1746, 1640, 1462, 1381, 1360, 1250, 1175, 1097, 1005, 937, 909, 838, 817, 780 cm^{-1}; EI-MS *m/z* (relative intensity) 483 (M^++H, 1.8), 482 (M^+, 0.15), 425 (22), 295 (17), 201 (30), 175 (38), 119 (31), 107 (41), 99 (66), 95 (38), 93 (33), 89 (72), 85 (91), 81 (32), 75 (66), 73 (100), 71 (31), 55 (37); EI-HRMS calcd for $C_{27}H_{51}O_5Si$ (M^++H) 483.3506, found 483.3488.

(2*R*,4*S*,5*R*,6*S*,8*R*)-4,6-Dimethoxy-2,8-dimethyl-10-undecanon-5-olide 30

To a solution of lactone **2a** (20.0 mg, 41.5 μmol) in 2 mL of MeOH at -78 °C was passed ozone gas until a color of the solution has become blue. After removing an excess of ozone gas by passing nitrogen gas, to the solution at -78 °C was added 61.0 μL (0.830 mmol) of dimethyl sulfide and then the mixture was allowed to warm to room temperature. The mixture was stirred at the same temperature for 5 h and concentrated *in vacuo*. Preparative thin layer chromatography (silica gel) of the residue with 50% EtOAc/benzene afforded lactone **30**, which was coincided with the authentic degradation product **30**[2] of FK 506 **1**, (6.0 mg, 51% yield): *Rf*=0.41 (50% EtOAc/benzene on silica gel); $[\alpha]_D^{21}$ +78.9 (*c* 0.130, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 4.11 (1H, dd, *J*=8.0, 1.5 Hz), 3.69 (1H, ddd, *J*=11.1, 8.0, 4.4 Hz), 3.47 (1H, ddd, *J*=7.8, 6.3, 1.5 Hz), 3.42 (3H, s), 3.40 (3H, s), 2.59-2.41 (1H, m), 2.51 (1H, dd, *J*=16.4, 4.9 Hz), 2.33 (1H, dt, *J*=12.5, 4.9 Hz), 2.30 (1H, dd, *J*=16.4, 9.0 Hz), 2.22-2.02 (1H, m), 2.15 (3H, s), 1.70-1.52 (2H, m), 1.53 (1H, dt, *J*=11.1, 12.5 Hz), 1.31 (3H, d, *J*=7.0 Hz), 0.95 (3H, d, *J*=6.4 Hz); IR (neat) 2950, 1742, 1720, 1463, 1377, 1254, 1195, 1175, 1106, 1088, 1025, 969, 935, 844, 780 cm^{-1}; EI-MS *m/z* (relative intensity) 286 (M^+, 0.08), 143 (46), 86 (10), 85 (100), 75 (19), 45 (13), 43 (23), 41 (12); EI-HRMS calcd for $C_{15}H_{26}O_5$ (M^+) 286.1780, found 286.1761.

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