An Efficient Asymmetric Synthesis of 1α,25-(OH)$_2$ Vitamin D$_3$ A-Ring Synthon

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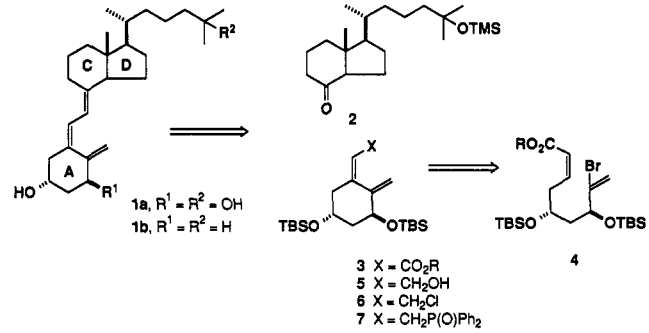
Chiral synthesis of the A-ring synthon **3** of 1α,25-dihydroxyvitamin D$_3$ (**1a**) based on palladium-catalyzed cyclization of 8-bromo-2,8-nonadienoates is described. Reaction of (*E*)-**4b** and (*Z*)-**4d** in the presence of Pd(OAc)$_2$, PPh$_3$, and K$_2$CO$_3$ gave (*E*)-**3b** and (*Z*)-**3d**, respectively. Optically active **4d** was prepared from **24** by asymmetric aldol reaction using **31**, which was cyclized to **3d**. With further reactions, 1α,25-dihydroxyvitamin D$_3$ (**1a**) was obtained.

Introduction

1α,25-Dihydroxyvitamin D$_3$ (**1a**) is known as a hormonally active form of vitamin D$_3$ (**1b**). Recently, this hormone was found to suppress proliferation and induce cell differentiation in human myeloid leukemia cells in addition to promoting intestinal calcium and phosphorous absorption and bone calcium mobilization.[1] Because of these potent biological activities, considerable synthetic efforts for 1α,25-dihydroxyvitamin D$_3$ (**1a**) have been made.[2] On the basis of Lythgoe's methodology,[3] Hoffman-La Roche's group achieved the synthesis of 1α,25-dihydroxyvitamin D$_3$ (**1a**) using **3** as a useful precursor of A-ring synthon.[4] So far several synthetic methods for **3** starting from chiral cyclohexanes have been reported.[2f,4,5] However, cyclization of acyclic compounds to give **3** has scarcely been reported[2h,6](Scheme I). The cyclization methodology has potent possibility to obtain various A-ring derivatives, because a variety of acyclic compounds are readily accessible. Recently we have reported a synthesis of A-ring synthon **3** by means of intramolecular Heck reaction.[7] Herein we wish to report a chiral synthesis of the A-ring synthon using the palladium-catalyzed cyclization of 8-bromo-2,8-nonadienoates **4** and its application toward the synthesis of 1α,25-dihydroxyvitamin D$_3$ (**1a**).

Scheme I



Palladium-Catalyzed Intramolecular Cyclization of 8-Bromo-2,8-nonadienoates. The A-ring synthon **3** has a characteristic exocyclic diene system, which posed synthetic problems. For an efficient synthesis of this exocyclic diene system, the Heck reaction was adopted.[8] The precursor of the intramolecular cyclization reaction **4a** was prepared in an enantiomerically pure form by reductive cleavage of the alkenyloxirane **12** (Scheme II). 2,3-Dibromopropene (**8**) was treated with *N*-*tert*-butylethanimine and LDA at 0 °C, followed by quenching with 3 N HCl to give the aldehyde, which was subsequently treated with (EtO)$_2$P(O)CH$_2$CO$_2$Et to afford the ester **9** in 30% yield from **8**. The ester was reduced with DIBAH at 0 °C to give the allylic alcohol **10**, which was then oxidized with *tert*-butyl hydroperoxide, (+)-DET, and Ti(O^{i}Pr)$_4$ to give the chiral epoxy alcohol **11** in 64% yield from **9**.[9] The enantiomeric excess of **11** was found to be more than 95% by the Mosher method. Oxidation of the epoxy alcohol **11** by the Swern method,[10] followed by treatment with (EtO)$_2$P(O)CH$_2$CO$_2$Et and NaH gave the (*E*)-α,β-unsaturated epoxy ester **12**. The epoxy functional group was reduced regioselectively by the palladium-catalyzed hydrogenolysis with formic acid[11] to give the optically active alcohol **13**, whose hydroxy group was protected as a silyl ether to give **4a** in 87% yield. The cyclization

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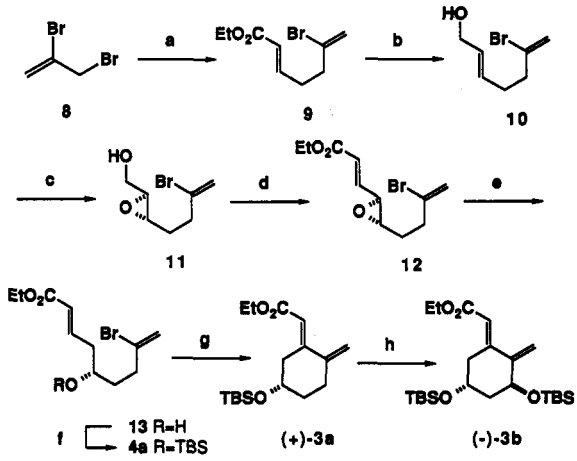
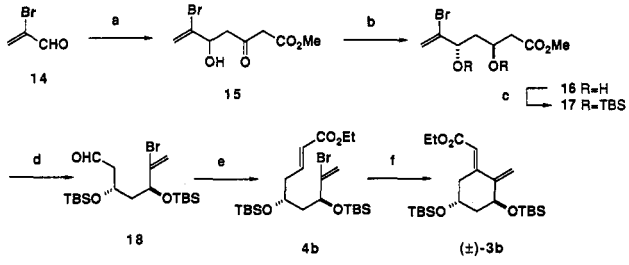
Scheme II



[a] (a) (1) *tert*-Bu-N=CHCH$_3$, LDA, THF, 0°C, (2) 3N HCl, (3) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, 0°C, 30% overall; (b) DIBAH, Et$_2$O, 0°C, 72%; (c) (+)-DET, Ti(O^{i}Pr)$_4$, TBHP, -23°C, 89%; (d) (1) (COCl)$_2$, DMSO, Et$_3$N, -78°C, (2) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, 0°C, 70% overall; (e) Pd$_2$(dba)$_3$CHCl$_3$, n-Bu$_3$P, HCO$_2$H, Et$_3$N, dioxane, 87%; (f) TBDMSCl, imidazole, DMF, 99%; (g) Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux, 72%; (h) (1) H$_2$SeO$_3$, NMO, MeOH-CH$_2$Cl$_2$, reflux, (2) TBDMSCl, imidazole, DMF, 29% overall.

Scheme III



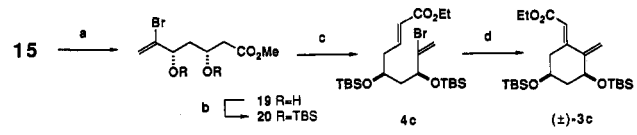
[a] (a) methyl acetoacetate, LDA (2.1 equiv), THF, 0°C, 75%; (b) Me$_4$NBH(OAc)$_3$, CH$_3$CN, 0°C, 75%; (c) TBDMSCl, imidazole, DMF, 95%; (d) DIBAH, toluene, 95%; (e) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, 0°C, 81%; (f) Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux, 86%.

reaction of **4a** to (+)-**3a** was achieved in 72% yield by treatment with 5 mol % of Pd(OAc)$_2$, 10 mol % of PPh$_3$, and 2 equiv of K$_2$CO$_3$ in CH$_3$CN at 80 °C for 12 h.[8b] Introduction of the 1α-hydroxy group was carried out with SeO$_2$ in methanol according to Hesse's procedure.[12] Silylation of the alcohol gave the known A-ring intermediate (-)-**3b** in 29% yield, which was identical with an authentic sample prepared by the literature procedure.[4]

Due to the unsatisfactory low yields of the **3a** to **3b** conversion, the hydroxy group at the C-1 position was introduced at an earlier stage. Thus, the disiloxy ester **4b** was prepared from α-bromoacrolein as shown in Scheme III.

The coupling reaction of α-bromoacrolein **14** and the dianion of methyl acetoacetate, prepared from 2 equiv of LDA and methyl acetoacetate, was carried out in 75% yield. Subsequent stereoselective reduction with Me$_4$NB(OAc)$_3$H gave the *anti*-diol **16** in 75% yield.[13] After protecting the alcohols as the silyl ethers, the ester group was reduced with DIBAH in dichloromethane to give the aldehyde, which was then treated with (EtO)$_2$P(O)CH$_2$CO$_2$Et and NaH to give the α,β-unsaturated ester **4b** in 73% yield from **16**. The ester **4b** was cyclized to **3b** as mentioned above in 86% yield. On the other hand, the *syn*-diol **19** was obtained by the reduction of **15** using Et$_3$B-NaBH$_4$[14] in 58% yield and was converted to the ester **4c**, which in turn was cyclized to **3c** in 72% yield (Scheme IV).

Scheme IV



[a] (a) Et$_3$B, NaBH$_4$, MeOH-THF, -78°C, 58%; (b) TBDMSCl, imidazole, DMF, 77%; (c) (1) DIBAH, toluene, -78°C, (2) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, 0°C, 80% over all; (d) Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, CH$_3$CN, reflux, 72%.

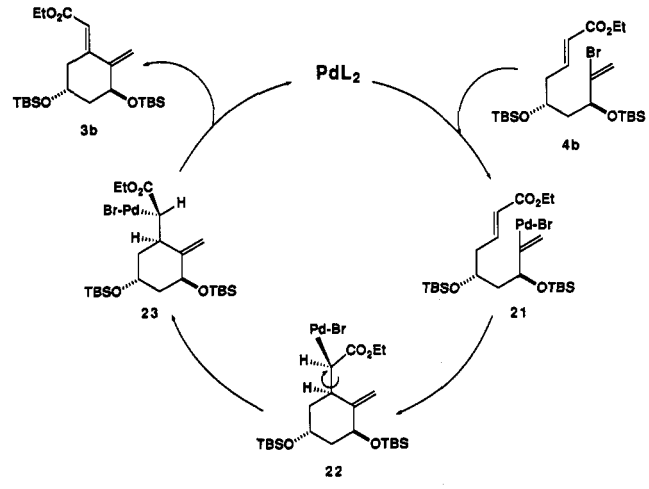


Figure 1.

The stereoselective conversion of acyclic **4a**, **4b**, and **4c** to the *exo*-dienes **3a**, **3b**, and **3c** respectively, containing an (*E*)-alkene moiety, is shown in Figure 1. The oxidative addition of palladium(0) complex to the vinyl bromide **4b** is presumed to give the product **21**. Intramolecular cis addition of palladium-carbon bond, followed by subsequent cis β-elimination of Pd-H is presumed to give the (*E*)-diene **3b**.[15] Similarly, the desired *Z* isomer **3d** can be obtained by the reaction of *Z*-isomer **4d**, which was prepared by Horner-Wittig type reaction using (CF$_3$CH$_2$O)$_2$P(O)CH$_2$CO$_2$Me and (TMS)$_2$NK in the presence of 18-crown-6.[16] The cyclization of **4d** gave the (*Z*)-diene **3d** in 90% yield without forming the *E* isomer (Scheme V).

Asymmetric Synthesis of the A-Ring Synthon and Its Application to the Synthesis of 1α,25-(OH)$_2$ Vitamin D$_3$. For the total synthesis of 1α,25-dihydroxyvitamin D$_3$ (**1a**) and its synthetic analogues, **3d** was prepared as an optically active pure form by the asymmetric aldol reaction with the chiral acetate **31**[17] (Scheme VI). Reaction of α-bromoacrolein (**14**) with lithium enolate of (-)-**31** in the presence of MgBr$_2$ at -100 °C gave **24**; subsequent protection of the hydroxy group as a silyl ether

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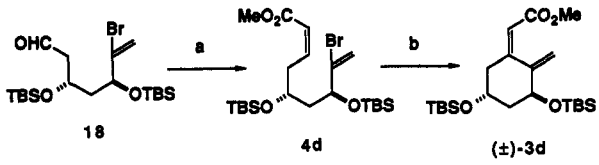
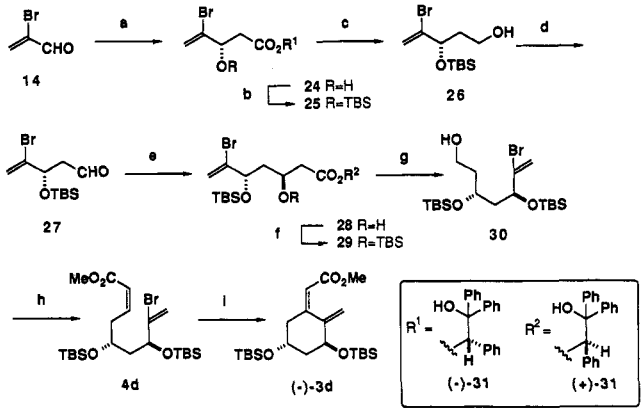
Scheme V



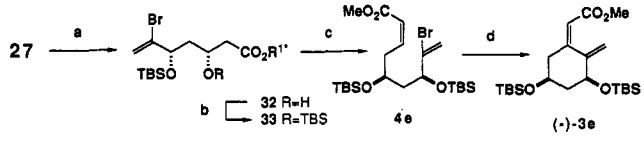
[a] (a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, -78°C, 80%; (b) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 90%.

Scheme VI



[a] (a) AcO(-)-R^1, LDA, $MgBr_2$; (b) (1) TBDMSCl, imidazole, DMF, (2) recrystallization from MeOH-CH_2Cl_2, 57% overall; (c) DIBAH, Et_2O, 0°C, 89%; (d) PCC, 3A-MS, 84%; (e) AcO(+)-R^2, LDA, $MgBr_2$, 85%; (f) TBDMSCl, imidazole, DMF, 98%; (g) DIBAH, Et_2O, 0°C, 83%; (h) (1) PCC, 3A-MS, (2) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, -78°C, 74% overall; (i) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 90%.

Scheme VII



[a] (a) AcO(-)-R^1, LDA, $MgBr_2$, 54%; (b) TBDMSCl, imidazole, DMF, 99%; (g) (1) DIBAH, Et_2O, 0°C, (2) PCC, 3A-MS, (3) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, -78°C, 84% overall; (d) $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 84%.

gave the ester **25**, whose diastereomeric excess was found to be ca. 6:1 as determined by high-field ^{1}H NMR (400 MHz). Fortunately, the optically pure form of **25** was obtained by recrystallization from methanol–dichloromethane in 57% yield from **14**. Removal of the chiral auxiliary with DIBAH followed by oxidation of the alcohol with PCC gave the aldehyde **27** in 75% yield. Reaction of the aldehyde **27** with the lithium enolate of (+)-**31** gave the alcohol **28**, whose hydroxy group was protected as the TBDMS ether to give **29** in 83% yield. The diastereoselectivity of the second aldol reaction was 6:1, which was similar as in the case of **24**. Without further purification, the diastereomeric mixture was reduced with DIBAH, oxidized with PCC, and treated with $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ and $(TMS)_2NK$ in the presence of 18-crown-6, to give the α,β-unsaturated ester (−)-**4d** in 61% yield from **29**. Cyclization reaction was carried out as described above to give the optically active A-ring synthon (−)-**3d** in 90% yield. Similarly, 3β-hydroxy A-ring synthon **3e** was synthesized selectively from **4e** in 84% yield (Scheme VII).

Finally, A-ring synthon (−)-**3d** was converted to the phosphinoxide **7** (60% yield from **3d**)[4] and coupled with Grundmann's ketone **2**[2b] to give the protected 1α,25-dihydroxyvitamin D$_3$. Subsequent deprotection with Bu_4NF gave 1α,25-dihydroxyvitamin D$_3$ (**1a**) in 59% yield from **7**.

Conclusion

Palladium-catalyzed cyclization of 8-bromo-2,8-nonadienoates proceeded stereoselectively to give 1α,25-dihydroxyvitamin D$_3$ A-ring synthons in good yields. Asymmetric synthesis of **3d** was performed from α-bromoacrolein **14** in 10 steps (19% overall) using an aldol reaction involving the chiral units **31** prepared from methyl mandelate.

Experimental Section

General Methods. Optical rotations were measured on a JASCO DIP-4 polarimeter using a sodium lamp (589 nm, D line). They are reported as follows: [α] ^{temperature}D (concentration (c, g/100 mL), solvent). ^{1}H NMR spectra were recorded on a JEOL (400 MHz) instrument. The spectra were referenced to $CDCl_3$ (7.26 ppm). Data are reported as follows: chemical shifts (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened), coupling constant (hertz), and integration). ^{13}C NMR spectra were recorded on a JEOL (100 MHz) or a HITACHI (22.5 MHz) instrument. Spectra were referenced to $CDCl_3$ (77.00 ppm). Infrared spectra (IR) were recorded on a Perkin-Elmer 1640 FT-IR spectrometer. Band frequencies are reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX300 mass spectrometer instrument. Elemental analyses were performed by Yanako MT-3. Ether and THF were distilled from benzophenone ketyl. CH_2Cl_2 was distilled on P_2O_5. DMSO and DMF were distilled on CaH_2. Thin-layer chromatography (TLC) was performed using Merck silica gel 60F glass plates (Art. 5715, 0.25 mm thick). Flash chromatography was performed using Wakogel C-300.

Ethyl (2*E*)-6-Bromo-2,6-heptadienoate (9). To a solution of diisopropylamine (6.6 mL, 50 mmol) in THF (100 mL) was added *n*-BuLi (1.6 M in hexane, 31.25 mL, 50 mmol) at 0 °C. To the resulting mixture was added a solution of *N*-*tert*-butylethanimine (4.95 g, 50 mmol) in THF (10 mL) and stirred for 20 min at 0 °C. A solution of 2,3-dibromopropene (**8**) (10.3 g, 50 mmol) in THF (10 mL) was added to the mixture, and the mixture was stirred for 30 min at 0 °C. To the reaction mixture was added 2 N HCl (80 mL), and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in THF (80 mL) and cooled at 0 °C under argon. A mixture of triethyl phosphonoacetate (12 mL, 60 mmol) and NaH (55% oil dispersion, 2.4 g, 60 mmol) in THF (20 mL) was added to the solution and stirred for 20 min. To the reaction mixture was added water (20 mL), and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated NH_4Cl and brine and dried over $MgSO_4$. The solvent was concentrated and the residue was purified by chromatography through silica gel with 10% ethyl acetate–hexane to give the ester **9** (3.48 g, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, J = 15.7, 6.6 Hz, 1 H), 5.85 (dt, J = 15.7, 1.1 Hz, 1 H), 5.58 (brs, 1 H), 5.42 (d, J = 1.5 Hz, 1 H), 4.17 (q, J = 7.6 Hz, 2 H), 2.6–2.4 (m, 4 H), 1.27 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.33, 146.28, 132.52, 122.45, 117.59, 60.24, 39.71, 30.44, 14.22; IR (neat) 2920, 1710 cm^{-1}; HRMS (CI) calcd for $C_9H_{14}O_2Br$ (MH^+) 233.0176, found 233.0198.

(2*E*)-6-Bromo-2,6-heptadien-1-ol (10). To a solution of the ester **9** (3.22 g, 13.8 mmol) in ether (30 mL) was added DIBAH (1 M in hexane, 33 mL, 33 mmol) at 0 °C, and it was stirred for 30 min. To the reaction mixture was added 3 N HCl (20 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography through silica gel with 30% ethyl acetate–hexane to give the alcohol **10** (1.91 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73–5.65 (m, 2 H), 5.56 (d, J = 1.9 Hz, 1 H), 5.40 (d, J = 1.4 Hz, 1 H), 4.08 (d, J = 4.7 Hz, 2 H), 2.50 (t, J = 7.4 Hz, 2 H), 2.32 (m, 2 H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 133.57, 130.57, 130.33, 116.94, 63.49, 40.89, 30.53; IR (neat) 3320, 2940, 2860, 1630 cm^{-1}; HRMS (CI) calcd for $C_7H_{12}OBr$ (MH^+) 191.0071, found 191.0029.

(2*S*,3*S*)-6-Bromo-2,3-epoxy-6-hepten-1-ol (11). To a solution of $Ti(O^iPr)_4$ (853 mg, 3.0 mmol), L-(+)-diethyl tartrate (620 mg, 3.0 mmol), and molecular sieves 4A in CH_2Cl_2 (100 mL) was added a solution of the alcohol **10** (1.13 g, 5.9 mmol) in CH_2Cl_2 (10 mL) with stirring at −23 °C. To the mixture was added a solution of *tert*-butyl hydroperoxide (5.1 M in dichloroethane, 2.4 mL, 12 mmol), and the mixture was stirred for 1 h at −23 °C. To the mixture were added Me_2S (4.4 mL, 60 mmol) and saturated NaF, and the resulting mixture was stirred at rt for 12 h. The mixture was filtered through a pad of Celite, the aqueous phase was extracted with CH_2Cl_2, and combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography through silica gel with 40% ethyl acetate–hexane to give the oxide **11** (1.10 g, 89%): $[\alpha]^{23}_D$ = −30° (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (q, *J* = 1.1 Hz, 1 H), 5.44 (d, *J* = 1.8 Hz, 1 H), 3.91 (ddd, *J* = 2.6, 6.2, 12.8 Hz, 1 H), 3.63 (ddd, *J* = 4.4, 8.8, 12.8 Hz, 1 H), 2.98 (m, 1 H), 2.58 (t, *J* = 9.1 Hz, 1 H), 2.35 (t, *J* = 5.5 Hz, 1 H), 1.93 (m, 1 H), 1.78 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.00, 117.49. 61.46, 58.49, 54.62, 37.89, 15.19; IR (neat) 3370, 2900, 1710, 1620 cm^{-1}; HRMS (CI) calcd for $C_7H_{12}O_2Br$ (MH^+) 207.0020, found 206.9968.

Ethyl (2*E*,4*S*,5*S*)-8-Bromo-4,5-epoxy-2,8-nonadienoate (12). To a solution of $(COCl)_2$ (1.11 mL, 12.5 mmol) in CH_2Cl_2 (10 mL) was added sequentially DMSO (2.23 mL, 31.3 mmol) and the alcohol **11** (1.30 g, 6.25 mmol) in CH_2Cl_2 (5 mL) at −78 °C and the mixture was stirred for 1 h. To the mixture was added triethylamine (8.71 mL, 62.5 mmol), and the resulting mixture was stirred for 1 h at rt. Saturated NH_4Cl was added to the mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in THF (20 mL) and cooled to 0 °C under argon. A mixture of triethyl phosohonoacetate (1.41 g, 6.3 mmol) and NaH (60% oil dispersion, 250 mg, 6.3 mmol) in THF (5 mL) was added to the solution and stirred for 30 min. To the reaction mixture was added water (10 mL), and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated NH_4Cl and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by chromatography through silica gel with 5% ethyl acetate–hexane to give the ester **12** (1.20 g, 70%): $[\alpha]^{22}_D$ = −14.8° (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 7.3, 15.8 Hz, 1 H), 6.12 (d, *J* = 15.8 Hz, 1 H), 5.64 (q, *J* = 0.8 Hz, 1 H), 5.44 (d, *J* = 1.9 Hz, 1 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 3.27 (dd, *J* = 1.4, 6.9 Hz, 1 H), 2.91 (t, *J* = 4.8 Hz, 1 H), 2.59 (t, *J* = 7.3 Hz, 2 H), 1.97 (m, 1 H), 1.82 (m, 1 H), 1.28 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.60, 144.17, 132.69, 123.91, 117.75, 60.62, 59.88, 56.34, 37.74, 30.32, 14.16; IR (neat) 2960, 1710, 1650, 1620 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{16}O_3Br$ (MH^+) 275.0283, found 275.0294.

Ethyl (2*E*,5*S*)-8-Bromo-5-hydroxy-2,8-nonadienoate (13). To a mixture of $Pd_2(dba)_3CHCl_3$ (62 mg, 0.06 mmol) and *n*-Bu_3P (30 μL, 0.12 mmol) in dioxane (5 mL) was added a mixture of HCOOH (0.6 mL, 12.5 mmol) and Et_3N (0.69 mL, 5.0 mmol) in dioxane (5 mL) at rt. The mixture was stirred for 5 min and the oxirane **12** (700 mg, 2.5 mmol) in dioxane (5 mL) was added to the solution. The mixture was stirred for 18 h and water was added to the reaction mixture. The organic layer was extracted with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography through silica gel with 30% ethyl acetate–hexane to give the alcohol **13** (600 mg, 87%): $[\alpha]^{23}_D$ = −0.78° (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.4, 7.7 Hz, 1 H), 5.92 (dt, *J* = 15.4, 1.1 Hz, 1 H), 5.61 (d, *J* = 1.1 Hz, 1 H), 5.42 (d, *J* = 1.8 Hz, 1 H), 4.19 (q, *J* = 6.9 Hz, 2 H), 3.81 (m, 1 H), 2.57 (m, 2 H), 2.39 (m, 2 H), 1.79 (m, 1 H), 1.68 (m, 1 H), 1.28 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.25, 144.51, 133.79, 124.28, 117.18, 69.11, 60.40, 40.32, 37.62, 35.17, 14.21; IR (neat) 3400, 2900, 1710, 1640, 1620 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{18}O_3Br$ (MH^+) 277.0439, found 277.0388. In order to determine the optical purity, the alcohol **13** was treated with (+)-MTPACl in pyridine to give the corresponding ester, whose ^{19}F NMR (84.6 MHz) spectrum appeared at δ 3.88 ppm as a singlet. Compared with the racemic MTPA ester of **13**, the enantiomeric excess of **13** was found to be more than 95%.

Ethyl (2*E*,5*S*)-8-Bromo-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,8-nonadienoate (4a). A mixture of the alcohol **13** (600 mg, 2.17 mmol), TBDMSCl (400 mg, 2.67 mmol), and imidazole (370 mg, 5.44 mmol) in DMF (1 mL) was stirred for 20 min at room temperature. To the mixture was added water (5 mL), and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography through silica gel with 5% ethyl acetate–hexane to give the silyl ether **4a** (845 mg, 99%): $[\alpha]^{24}_D$ = +2.5° (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 15.7, 7.3 Hz, 1 H), 5.84 (d, *J* = 15.7 Hz, 1 H), 5.56 (br s, 1 H), 5.39 (br s, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 3.82 (m, 1 H), 2.48 (m, 2 H), 2.35 (t, *J* = 5.8 Hz, 2 H), 1.71 (brq, 1 H), 1.59 (m, 1 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.058 (s, 3 H), 0.053 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.29, 145.21, 134.28, 123.60, 116.58, 70.03, 60.21, 39.97, 37.27, 35.49, 25.71, 18.02, 14.26, −4.46, −4.57; IR (neat) 2900, 2840, 1710 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{32}O_3BrSi$ (MH^+) 391.1303, found 391.1336.

General Procedure for Palladium-Catalyzed Cyclization of 8-Bromo-2,8-nonadienoate 4 to 3: Ethyl [5*S*-(1*E*,5β)]-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetate (3a). A mixture of the diene **4a** (51 mg, 0.13 mmol), $Pd(OAc)_2$ (6 mg, 0.013 mmol), PPh_3 (13 mg, 0.026 mmol), and K_2CO_3 (36 mg, 0.26 mmol) in CH_3CN (20 mL) was stirred for 18 h at reflux. The resulting mixture was filtered through a pad of Celite, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography through silica gel with 1% ethyl acetate–hexane to give **3a** (29 mg, 72%): $[\alpha]^{22}_D$ = +5.9° (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (s, 1 H), 5.02 (s, 1 H), 4.78 (s, 1 H), 4.16 (m, 2 H), 3.97 (m, 1 H), 3.16 (dd, *J* = 4.0, 14.7 Hz, 1 H), 2.92 (dd, *J* = 7.9, 15.8 Hz, 1 H), 2.55 (m, 1 H), 2.20 (m, 1 H), 1.84 (m, 1 H), 1.68 (m, 1 H), 1.28 (t, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 166.42, 157.34, 148.53, 114.93, 110.75, 68.95, 59.65, 38.24, 34.71, 30.59, 25.86, 18.18, 14.40, −4.71; IR (neat) 2920, 1710, 1620 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{31}O_3Si$ (MH^+) 311.2068, found 311.1945.

[3*S*-(1*E*,3α,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Ethyl Ester (3b). *N*-Methylmorpholine *N*-oxide (189 mg, 1.38 mmol) dissolved in CH_2Cl_2 (3 mL) was stirred with anhydrous $MgSO_4$ for 30 min. The liquid was filtrated into a solution of **3a** (86 mg, 0.28 mmol) dissolved in CH_2Cl_2 (3 mL), and the whole mixture was heated to reflux. A solution of H_2SeO_3 (36 mg, 0.28 mmol) and *N*-methylmorpholine (28 mg, 0.28 mmol) in CH_3CN (3 mL) was added to the resultant mixture and stirred for 4 h at reflux. The reaction mixture was diluted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 20% ethyl acetate–hexane to give the alcohol (25 mg): ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.17 (s, 1 H), 5.11 (s, 1 H), 4.57 (m, 1 H), 4.24 (m, 1 H), 3.23 (dd, *J* = 6.0, 15.0 Hz, 1 H), 2.87 (br d, *J* = 15.0 Hz, 1 H), 2.04 (m, 1 H), 1.83 (m, 1 H), 1.28 (t, *J* = 7.6 Hz, 3 H), 0.87 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.41, 156.07, 151.68, 117.00, 100.48, 69.97, 66.76, 59.87, 42.68, 37.58, 25.62, 18.04, 14.31, −4.46, −4.99; IR (neat) 3115-3605, 2945, 2925, 1720, 1710 cm^{-1}.

A mixture of the alcohol (25 mg, 0.077 mmol), TBDMSCl (14 mg, 0.19 mmol), and imidazole (13 mg, 0.19 mmol) in DMF (1 mL) was stirred for 30 min at room temperature. To the mixture was added water (5 mL) and aqueous layer was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography through silica gel with 3% ethyl acetate–hexane to give **3b** (33 mg, 29% overall): $[\alpha]^{23}_D$ = −4.9° (*c* 0.5, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 1 H), 5.08 (t, *J* = 1.8 Hz, 1 H), 5.06 (d, *J* = 1.8 Hz, 1 H), 4.57 (m, 1 H), 4.25 (m, 1 H), 4.17 (dd, *J* = 6.9, 11.1 Hz, 1 H), 4.11 (dd, *J* = 6.9, 11.1 Hz, 1 H), 3.38 (dd, *J* = 6.0, 15.0 Hz, 1 H), 2.65 (dt, *J* = 15.0, 2.1 Hz, 1 H), 1.96 (m, 1 H), 1.77 (ddd, *J* = 4.1, 7.3, 11.1 Hz, 1 H), 1.27 (t, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.85 (s, 9 H), 0.06 (s, 6 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.56, 157.05, 152.06, 116.46, 109.76, 70.06, 67.07, 59.75, 43.62, 37.42, 25.79, 25.67, 18.23,

18.02, 14.30, -4.89, -5.03, -5.05, -5.10; IR (neat) 2930, 2860, 1720, 1640, 1465, 1250 cm^{-1}; HRMS (CI) calcd for $C_{23}H_{25}O_4Si_2$ (MH$^+$) 441.2856, found 441.2929.

Methyl 6-Bromo-5-hydroxy-3-oxo-6-heptenoate (15). To a solution of diisopropylamine (2.9 mL, 21 mmol) in THF (80 mL) was added *n*-BuLi (1.58 M in hexane, 13 mL, 21 mmol) at -78 °C and the mixture was stirred for 10 min at 0 °C. To the resulting mixture was added methyl acetoacetate (1.13 mL, 10 mmol) in THF (10 mL) dropwise over 20 min and the mixture was stirred for 30 min. The resultant mixture was cooled to -78 °C and the aldehyde **14** (1.35 g, 10 mmol) in THF (10 mL) was added to the mixture and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 40% ethyl acetate–hexane to give the alcohol **15** (1.88 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, J = 1.0, 1.8 Hz, 1 H), 5.59 (d, J = 1.8 Hz, 1 H), 4.66 (dd, J = 3.6, 8.4 Hz, 1 H), 3.74 (s, 3 H), 3.55 (s, 2 H), 3.00 (dd, J = 3.6, 17.2 Hz, 1 H), 2.91 (dd, J = 8.4, 17.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.41, 167.20, 134.17, 117.37, 71.26, 52.32, 49.44, 47.80; IR (neat) 3479, 2945, 1731, 1715, 1628, 1439 cm^{-1}; HRMS calcd for $C_8H_{12}O_4Br$ (MH$^+$) 250.9919, found 250.9991.

Methyl (3*S,5*S**)-6-Bromo-3,5-dihydroxy-6-heptenoate (16).** To a solution of tetramethylammonium borohydride (212 mg, 2.4 mmol) was added anhydrous acetic acid (2 mL) at 0 °C and the mixture was stirred for 15 min at rt. The resulting mixture was cooled to 0 °C and diluted with CH_3CN (2 mL). To the mixture was added a solution of the keto ester **15** (300 mg, 1.2 mmol) in CH_3CN (3 mL), and the mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with water (5 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 25% ethyl acetate–hexane to give the diol **16** (225 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (t, J = 1.4 Hz, 1 H), 5.61 (t, J = 1.1 Hz, 1 H), 4.47 (t, J = 5.1 Hz, 1 H), 4.35 (quintet, J = 5.1 Hz, 1 H), 3.72 (s, 3 H), 2.53 (d, J = 2.2 Hz, 1 H), 2.52 (s, 1 H), 1.89 (d, J = 1.1 Hz, 1 H), 1.88 (dd, J = 1.8, 5.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.06, 135.72, 116.63, 73.21, 65.09, 51.86, 40.97, 39.61; IR (neat) 3416, 2953, 1737, 1631, 1440 cm^{-1}; HRMS (CI) calcd for $C_8H_{14}O_4Br$ (MH$^+$) 253.0075, found 253.0086.

Methyl (3*S,5*S**)-6-Bromo-3,5-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-6-heptenoate (17).** A mixture of the diol **16** (34 mg, 0.13 mmol), TBDMSCl (45 mg, 0.3 mmol), and imidazole (100 mg, 1.47 mmol) in DMF (0.5 mL) was stirred for 1 h at rt. To the mixture was added water (3 mL), and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 10% ethyl acetate–hexane to give **17** (65 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (t, J = 1.1 Hz, 1 H), 5.51 (t, J = 0.9 Hz, 1 H), 4.20 (m, 2 H), 3.65 (s, 3 H), 2.53 (dd, J = 4.8, 14.6 Hz, 1 H), 2.47 (dd, J = 7.3, 14.6 Hz, 1 H), 1.89 (dt, J = 5.5, 13.9 Hz, 1 H), 1.79 (dt, J = 6.8, 13.9 Hz, 1 H), 0.90 (s, 9 H), 0.85 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.68, 137.96, 116.77, 74.08, 66.91, 51.41, 44.78, 43.06, 25.72, 18.09, 17.91, -4.27, -4.49 (2 carbons), -4.96; IR (neat) 2954, 2886, 1743, 1624, 1471 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{42}O_4Si_2Br$ (MH$^+$) 481.1805, found 481.1761.

Ethyl (2*E*,5*R,7*S**)-8-Bromo-5,7-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-2,8-nonadienoate (4b).** To a solution of the ester **17** (120 mg, 0.23 mmol) in toluene (3 mL) was added DIBAH (1 M in toluene, 0.3 mL, 0.3 mmol) at -78 °C, and the mixture was stirred for 30 min. To the reaction mixture was added 2-propanol (0.5 mL), water (0.5 mL), and silica gel (200 mg), and the mixture was stirred for 1 h at rt. The mixture was filtered through a pad of Celite, and the solvent was concentrated in vacuo to give the aldehyde **18** (101 mg, 95%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.79 (t, J = 2.4 Hz, 1 H), 5.85 (br s, 1 H), 5.54 (br s, 1 H), 4.35–4.05 (m, 2 H), 2.59 (dd, J = 2.4, 5.1 Hz, 2 H), 1.89 (m, 2 H), 0.91 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 12 H); IR (neat) 2930, 1728, 01624, 1472 cm^{-1}.

To a suspension of NaH (55 wt% oil dispersion, 58 mg, 0.15 mmol) in THF (1 mL) was added triethyl phosphonoacetate (30 μL, 0.15 mmol) at 0 °C, and the mixture was stirred for 10 min. To the solution was added the aldehyde **18** (58 mg, 0.128 mmol) in THF (1 mL), and the mixture was stirred for 30 min at rt. The reaction mixture was quenched with water, and the aqueous layer was extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 10% ethyl acetate–hexane to give **4b** (54 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, J = 15.4, 6.4 Hz, 1 H), 5.85 (d, J = 15.4 Hz, 1 H), 5.82 (d, J = 1.1 Hz, 1 H), 5.51 (d, J = 1.1 Hz, 1 H), 4.19 (q, J = 6.9 Hz, 2 H), 4.17 (m, 1 H), 3.87 (m, 1 H), 2.42 (m, 1 H), 2.38 (m, 1 H), 1.78 (m, 2 H), 1.29 (t, J = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.083 (s, 3 H), 0.074 (s, 3 H), 0.065 (s, 6 H); IR (neat) 2955, 1724, 1656, 1472 cm^{-1}; HRMS (CI) calcd for $C_{23}H_{46}O_4Si_2Br$ (MH$^+$) 521.2118, found 521.2070.

Ethyl [3*S-(1*E*,3α,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetate (3b).** According to the general procedure, **4b** (24 mg, 0.046 mmol) was converted to **3b** (17 mg, 86%).

Methyl (3*R,5*S**)-6-Bromo-3,5-dihydroxy-6-heptenoate (19).** A solution of Et_3B (1 M in THF, 0.96 mL, 0.96 mmol) was added to a mixture of THF (8 mL) and methanol (2 mL) at rt. After stirring for 1 h, the mixture was cooled to -78 °C, followed by the addition of the hydroxy ketone **15** (200 mg, 0.8 mmol) and stirred for 30 min. $NaBH_4$ (36 mg, 0.96 mmol) was added and the mixture was stirred for 3 h at -78 °C. The reaction mixture was quenched with saturated NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Methanol was added to the mixture and evaporated in vacuo (three times). The residue was purified by flash chromatography through silica gel with 25% ethyl acetate–hexane to give the diol **19** (117 mg, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, J = 1.1 Hz, 1 H), 5.57 (d, J = 1.8 Hz, 1 H), 4.42 (br d, J = 7.0 Hz, 1 H), 4.26 (m, 1 H), 3.72 (s, 3 H), 2.54 (d, J = 1.4 Hz, 1 H), 2.52 (s, 1 H), 1.90 (ddd, J = 2.9, 3.7, 14.3 Hz, 1 H), 1.76 (ddd, J = 4.4, 9.1, 14.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.68, 135.66, 117.02, 75.15, 67.41, 51.82, 41.27, 40.79; IR 3443, 2953, 1737, 1626, 1440 cm^{-1}; HRMS calcd for $C_7H_{10}O_4Br$ (M$^+$ - CH_3) 236.9763, found 236.9817.

Methyl (3*R,5*S**)-6-Bromo-3,5-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-6-heptenoate (20).** As described for **17**, **19** (450 mg, 1.78 mmol) was converted to **20** (660 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (s, 1 H), 5.53 (d, J = 0.6 Hz, 1 H), 4.23 (m, 2 H), 3.64 (s, 3 H), 2.57 (dd, J = 4.1, 14.7 Hz, 1 H), 2.45 (dd, J = 8.1, 14.7 Hz, 1 H), 1.89 (ddd, J = 4.8, 7.0, 13.9 Hz, 1 H), 1.82 (ddd, J = 4.8, 7.2, 13.9 Hz, 1 H), 0.90 (s, 9 H), 0.85 (s, 9 H), 0.085 (s, 3 H), 0.068 (s, 3 H), 0.052 (s, 3 H), 0.026 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.95, 137.06, 116.61, 73.70, 66.52, 51.40, 43.71, 42.54, 25.72, 18.04, 17.88, -4.45, -4.66, -4.85, -5.07; IR (neat) 2953, 2886, 1740, 1624, 1471 cm^{-1}; HRMS calcd for $C_{16}H_{32}O_4Si_2Br$ (M$^+$ - ^{t}Bu) 423.1022, found 423.1014.

Ethyl (2*E*,5*S,7*S**)-8-Bromo-5,7-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-2,8-nonadienoate (4c).** As described for **4b**, the ester **20** (150 mg, 0.31 mmol) was converted to **4c** (130 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (dt, J = 15.5, 6.4 Hz, 1 H), 5.87 (s, 1 H), 5.84 (d, J = 15.5 Hz, 1 H), 5.52 (d, J = 1.8 Hz, 1 H), 4.22 (m, 1 H), 4.18 (q, J = 7.0 Hz, 2 H), 3.86 (m, 1 H), 2.48 (m, 1 H), 2.35 (m, 1 H), 1.82 (t, J = 5.8 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.070 (s, 3 H), 0.063 (s, 3 H), 0.051 (s, 3 H), 0.042 (s, 3 H); IR (neat) 2953, 1722, 1654, 1471 cm^{-1}; HRMS calcd for $C_{19}H_{36}O_4Si_2Br$ (M$^+$ - ^{t}Bu) 463.1335, found 463.1308.

[3*R-(1*E*,3β,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Ethyl Ester (3c).** According to the general procedure, **4c** (100 mg, 0.19 mmol) was converted to **3c** (62 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J = 2.2 Hz, 1 H), 5.16 (t, J = 2.2 Hz, 1 H), 5.12 (t, J = 2.2 Hz, 1 H), 4.17 (q, J = 6.9 Hz, 2 H), 4.05 (m, 1 H), 3.75 (m, 1 H), 2.21 (m, 1 H), 1.99 (ddd, J = 2.5, 11.0, 13.9 Hz, 1 H), 1.62 (q, J = 11.2 Hz, 2 H), 1.28 (t, J = 6.9 Hz, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.095 (s, 3 H), 0.090 (s, 3 H), 0.074 (s, 3 H), 0.069 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.36, 155.09, 151.39, 116.31, 109.40, 69.55, 67.29, 59.93, 45.55, 38.76, 25.80,

25.78, 18.29, 18.15, 14.29, −4.65, −4.81, −4.92, −5.06; IR (neat) 2953, 2886, 1718, 1639, 1472 cm^{-1}; HRMS calcd for $C_{19}H_{35}O_4Si_2$ ($M^+ - {}^tBu$) 383.2074, found 383.2049.

(5*R,7*S**,2*Z*)-8-Bromo-5,7-bis[(*tert*-butyldimethylsilyl)oxy]-2,8-nonadienoic Acid Methyl Ester (4d).** To a mixture of 18-crown-6 (304 mg, 1.15 mmol) and $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (0.063 mL, 0.3 mmol) in THF (2 mL) at −78 °C was added $(TMS)_2NK$ (0.5 M in toluene, 0.6 mL, 0.3 mmol). After stirring for 20 min, a solution of the aldehyde **18** (101 mg, 0.22 mmol) in THF (3 mL) was added to the mixture, and stirred for 30 min. The reaction mixture was quenched by addition of saturated NH_4Cl and water. The aqueous layer was extracted with ether, and the extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 5% ethyl acetate–hexane to give the ester **4d** (89 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (ddd, *J* = 8.4, 6.2, 11.6 Hz, 1 H), 5.90 (t, *J* = 1.8 Hz, 1 H), 5.87 (br s, 1 H), 5.51 (d, *J* = 1.4 Hz, 1 H), 4.20 (t, *J* = 6.2 Hz, 1 H), 3.86 (m, 1 H), 3.07 (dddd, *J* = 1.8, 4.7, 8.4, 15.7 Hz, 1 H), 2.71 (ddt, *J* = 1.8, 15.7, 5.5 Hz, 1 H), 1.82 (m, 1 H), 1.65 (m, 1 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.097 (s, 3 H), 0.071 (s, 3 H), 0.054 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.77, 146.41, 138.34, 120.75, 117.07, 73.70, 68.19, 51.02, 44.18, 36.09, 25.82, 25.75, 18.11, 18.03, −4.13, −4.36, −4.51, −4.94; IR (neat) 2929, 2857, 1723, 1647, 1472, 1438 cm^{-1}; HRMS (CI) calcd for $C_{22}H_{44}O_4BrSi_2$ (MH^+) 507.1962, found 507.1995.

[3*S-(1*Z*,3α,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Methyl Ester (3d).** According to the general procedure, **4d** (38 mg, 0.075 mmol) was converted to **3d** (29 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, 1 H), 5.17 (t, *J* = 1.8 Hz, 1 H), 4.98 (t, *J* = 1.8 Hz, 1 H), 4.53 (dd, *J* = 4.0, 8.8 Hz, 1 H), 4.23 (m, 1 H), 3.70 (s, 3 H), 2.42 (ddd, *J* = 1.1, 1.8, 13.2 Hz, 1 H), 2.26 (dd, *J* = 5.5, 13.2 Hz, 1 H), 1.97 (dt like, 1 H), 1.76 (dt like, 1 H), 0.90 (s, 9 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.57, 153.13, 147.73, 117.12, 110.27, 70.82, 67.39, 50.94, 46.05, 44.67, 25.76, 25.69, 18.28, 18.02, −4.85, −4.93, −4.95, −5.31; IR (neat) 2953, 2887, 1732, 1641, 1472 cm^{-1}; HRMS calcd for $C_{22}H_{42}O_4Si_2$ 426.2622, found 426.2590.

(*S*)-4-Bromo-3-hydroxy-4-pentenoic Acid (*S*)-1,2,2-Triphenyl-2-hydroxyethyl Ester (24). To a stirred suspension of (*S*)-(−)-2-acetoxy-1,1,2-triphenylethanol (1.0 g, 3.2 mmol) in THF (11 mL) at −78 °C was added LDA (7.9 mmol) in THF (11 mL) prepared from diisopropylamine (1.04 mL, 7.9 mmol) and *n*-BuLi (1.63 M in hexane, 4.73 mL, 7.7 mmol). The mixture was allowed to warm at 0 °C to give a clear solution. The resultant mixture was added to a suspension of $MgBr_2$ in ether prepared from magnesium (153 mg, 6.3 mmol) and 1,2-dibromoethane (0.55 mL, 6.4 mmol) at −78 °C, and the mixture was stirred for 1 h then cooled to −115 °C. To the resulting mixture was added α-bromoacrolein (**14**) (690 mg, 5.12 mmol) in THF (10 mL), and the mixture was stirred for 40 min. The reaction mixture was quenched with saturated NH_4Cl solution and warmed up to rt. The aqueous layer was extracted with chloroform, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2 100%) to give a solid of **24** (1.50 g, 99%) as a diastereomeric mixture (*ca.* 6:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.00 (m, 15 H), 6.70 (s, 1 H), 5.83 (dd, *J* = 1.0, 2.2 Hz, 1 H), 5.43 (d, *J* = 0.73, 1 H), 4.33 (dd, *J* = 4.0, 8.4 Hz, 1 H), 2.68 (dd, *J* = 4.0, 16.1 Hz, 1 H), 2.64 (dd, *J* = 8.4, 16.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.72, 133.53, 128.39, 127.56, 127.15, 126.24, 126.14, 80.19, 72.29, 40.30; IR (KBr) 3504, 1716, 1624, 1450, 1158, 1066 cm^{-1}.

(*S*)-4-Bromo-3-[(*tert*-butyldimethylsilyl)oxy]-4-pentenoic Acid (*S*)-1,2,2-Triphenyl-2-hydroxyethyl Ester (25). A mixture of the alcohol **24** (1.50 g, 3.2 mmol), *tert*-butyldimethylsilyl chloride (0.96 g, 6.4 mmol), and imidazole (1.09 g, 16.0 mmol) in DMF (6 mL) was stirred for 3 h at rt. The reaction mixture was quenched with water (5 mL), and the aqueous layer was extracted with ether. The extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with dichloromethane to give the silyl ether as a solid, which was recrystallized from $MeOH/CH_2Cl_2$ (1/1) to give **25** (1.07 g, 57%): $[\alpha]^{24}_D$ = −135.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.00 (m, 15 H), 6.69 (s, 1 H), 5.78 (br s, 1 H), 5.44 (d, *J* = 1.8 Hz, 1 H), 4.50 (t, *J* = 5.8 Hz, 1 H), 2.59 (m, 2 H), 0.697 (s, 9 H), −0.032 (s, 3 H), −0.189 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.33, 128.56, 128.36, 127.74, 127.40, 126.28, 126.18, 80.27, 78.81, 73.07, 41.97, 25.48, 17.87, −4.96, −5.55; IR (KBr) 3450, 2936, 2860, 1720, 1626, 1452, 1270 cm^{-1}; mp 178 °C. Anal. Calcd for $C_{31}H_{37}O_4BrSi$: C, 64.03; H, 6.37. Found: C, 63.91; H, 6.70.

(*S*)-4-Bromo-3-[(*tert*-butyldimethylsilyl)oxy]-4-penten-1-ol (26). To a solution of the ester **25** (158 mg, 0.273 mmol) in ether (4 mL) at 0 °C was added DIBAH (0.93 M in ether, 0.70 mL, 0.66 mmol) and stirred for 1 h. The reaction mixture was quenched with 2-propanol and a few drops of water. The resulting mixture was diluted with ether (5 mL), and silica gel and $MgSO_4$ were added and stirred for 1 h at rt. The mixture was filtered and the solvent was concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 10% ethyl acetate–hexane to give the alcohol **26** (71 mg, 89%): $[\alpha]^{24}_D$ = −25.8° (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (t, *J* = 1.4 Hz, 1 H), 5.58 (d, *J* = 1.7 Hz, 1 H), 4.42 (t, *J* = 5.3 Hz, 1 H), 3.80 (dt, *J* = 6.6, 5.3 Hz, 1 H), 3.70 (dt, *J* = 6.9, 5.3 Hz, 1 H), 1.96 (q, *J* = 5.3 Hz, 2 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.91, 116.60, 75.31, 59.35, 34.44, 25.71, 18.08, −4.82, −5.31; IR (neat) 3356, 2929, 2885, 1472 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{24}O_2BrSi$ (MH^+) 295.0728, found 295.0739.

(3*S*,5*S*)-6-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-6-heptenoic Acid (*R*)-1,2,2-Triphenyl-2-hydroxyethyl Ester (28). A mixture of the alcohol **26** (72 mg, 0.158 mmol), PCC (118 mg, 0.546 mmol), and Zeolite 3A (118 mg) in CH_2Cl_2 (2 mL) was stirred for 1 h at rt. The reaction mixture was filtered through a Florisil column, and the filtrate was concentrated in vacuo to give the aldehyde **27** (39 mg, 84%): $[\alpha]^{25}_D$ = −21.1° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1 H), 5.98 (d, *J* = 1.8 Hz, 1 H), 5.57 (d, *J* = 1.8 Hz, 1 H), 4.66 (dd, *J* = 4.0, 6.9 Hz, 1 H), 2.79 (ddd, *J* = 2.5, 7.3, 16.5 Hz, 1 H), 2.67 (ddd, *J* = 1.8, 4.0, 16.5 Hz, 1 H), 0.87 (s, 9 H), 0.80 (s, 6 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.22, 135.25, 117.11, 72.14, 49.54, 25.60, 18.05 −4.74, −5.24; IR (neat) 2956, 1728, 1427 cm^{-1}.

As described for **24**, **27** (210 mg, 0.71 mmol) was converted to **28** (380 mg, 85%) as a diastereomeric mixture (ca. 9:1): $[\alpha]^{28}_D$ = +114.3° (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 5.74 (br d, 1 H), 5.45 (d, *J* = 1.4 Hz, 1 H), 4.19 (t, *J* = 5.3 Hz, 1 H), 3.87 (m, 1 H), 2.34 (d, *J* = 7.3 Hz, 1 H), 2.33 (d, *J* = 5.1 Hz, 1 H), 1.61 (m, 2 H), 0.81 (s, 9 H), −0.014 (s, 3 H), −0.019 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.06, 143.32, 138.75, 135.42, 128.43, 128.05, 127.62, 127.47, 127.02, 126.28, 80.75, 80.21, 78.97, 78.01, 42.11, 42.07, 25.69, 18.45, −0.48; IR (KBr) 3528, 2932, 1702, 1626, 1494, 1450, 1358 cm^{-1}; mp 87–88 °C.

(3*S*,5*S*)-6-Bromo-3,5-bis[(*tert*-butyldimethylsilyl)oxy]-6-heptenoic Acid (*R*)-1,2,2-Triphenyl-2-hydroxyethyl Ester (29). As described for **25**, **28** (380 mg, 0.6 mmol) was converted to **29** (435 mg, 98%) as a white solid: $[\alpha]^{22}_D$ = +50° (ca 9:1 diastereomeric mixture, *c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.00 (m, 15 H), 6.71 (s, 1 H), 5.78 (br s, 1 H), 5.47 (d, *J* = 1.5 Hz, 1 H), 4.18 (dd, *J* = 4.7, 6.9 Hz, 1 H), 4.15 (t, *J* = 5.9 Hz, 1 H), 2.43 (d, *J* = 5.8 Hz, 2 H), 1.77–1.69 (m, 2 H), 0.86 (s, 9 H), 0.72 (s, 9 H), −0.01 (s, 6 H), −0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.90, 144.81, 142.62, 137.97, 135.70, 128.60, 126.15, 80.30, 78.44, 74.17, 66.48, 25.81, 25.68, 18.11, 17.81, −4.44, −4.48, −4.54, −4.84; IR (KBr) 3540, 2960, 2932, 1724, 1626 cm^{-1}; mp 117.3 °C.

(3*R*,5*S*)-6-Bromo-3,5-bis[(*tert*-butyldimethylsilyl)oxy]-6-penten-1-ol (30). As described for **26**, **29** (435 mg, 0.588 mmol) was converted to **30** (221 mg, 83%): $[\alpha]^{24}_D$ = −7.7° (ca 9:1 diastereomeric mixture, *c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 0.7, 1.8 Hz, 1 H), 5.52 (d, *J* = 1.8 Hz, 1 H), 4.15 (t, *J* = 6.4 Hz, 1 H), 3.94 (m, 1 H), 3.83 (br s, 1 H), 3.74 (br s, 1 H), 1.89 (m, 1 H), 1.70 (ddt, *J* = 4.4, 14.7, 5.8 Hz, 1 H), 0.899 (s, 9 H), 0.894 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.03, 116.94, 74.23, 68.96, 60.03, 43.79, 38.32, 25.83, 25.79, 25.77, 25.74, 18.13, 17.92, −4.23, −4.46, −4.50, −4.89; IR (neat) 3373, 2929, 2857, 1624, 1472, 1556, cm^{-1}; HRMS (CI) calcd for $C_{19}H_{42}O_3BrSi_2$ (MH^+) 453.1856, found 453.1868.

(5*R*,7*S*,2*Z*)-8-Bromo-5,7-bis[(*tert*-butyldimethylsilyl)oxy]-2,8-nonadienoic Acid Methyl Ester (4d). A mixture of the

alcohol **30** (555 mg, 1.22 mmol), PCC (791 mg, 3.67 mmol), and Zeolite 3A (791 mg) in CH_2Cl_2 (12 mL) was stirred for 1 h at rt. The reaction mixture was filtered through a Florisil column, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 4% ethyl acetate–hexane to give the aldehyde (451 mg, 82%) as a diastereomeric mixture: $[\alpha]^{24}_D = -13.0°$ (*c* 0.8, $CHCl_3$).

As described for (±)-**4d**, the aldehyde (347 mg, 0.77 mmol) was converted to the ester (−)-**4d** (357 mg, 91%) as a diastereomeric mixture: $[\alpha]^{24}_D = -28.5°$ (*c* 0.8, $CHCl_3$).

[3*S*-(1*Z*,3α,5β)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Methyl Ester (3d). According to the general procedure, **4d** (357 mg, 0.703 mmol) was converted to (−)-**3d** (270 mg, 90%) and (−)-**3e** (15 mg, 5%), which were purified by flash chromatography through silica gel with 2% ethyl acetate–hexane. **3d**: $[\alpha]^{24}_D = -57.2°$ (*c* 0.4, $CHCl_3$).

(3*R*,5*S*)-6-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxy-6-heptenoic Acid (*S*)-1,2,2-Triphenyl-2-hydroxyethyl Ester (32). As described for **28**, **27** (210 mg, 0.716 mmol) was converted to **32** (169 mg, 54%) and **28** (17 mg, 5%). **32**: $[\alpha]^{23}_D = +139.5°$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–6.90 (m, 15 H), 6.62 (s, 1 H), 5.78 (br s, 1 H), 5.43 (d, *J* = 1.8 Hz, 1 H), 4.30 (t, *J* = 5.3 Hz, 1 H), 3.99 (m, 1 H), 2.34 (dd, *J* = 4.0, 16.1 Hz, 1 H), 2.26 (dd, *J* = 8.4, 16.1 Hz, 1 H), 1.55 (m, 2 H), 0.79 (s, 9 H), −0.02 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.77, 128.36, 127.98, 127.79, 127.49, 127.08, 126.26, 126.19, 80.19, 78.89, 74.99, 65.68, 42.11, 41.86, 25.57, 18.00, −4.64, −5.09; IR (KBr) 3520, 2956, 2932, 1720, 1624, 1448 cm^{-1}.

(3*R*,5*S*)-6-Bromo-3,5-bis[(*tert*-butyldimethylsilyl)oxy]-6-heptenoic Acid (*S*)-1,2,2-Triphenyl-2-hydroxyethyl Ester (33). The alcohol **32** (169 mg, 0.27 mmol) was converted to **33** (200 mg, 99%) as a white solid: $[\alpha]^{23}_D = -107.3°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.00 (m, 15 H), 6.72 (s, 1 H), 5.79 (t, *J* = 0.7 Hz, 1 H), 5.51 (d, *J* = 1.8 Hz, 1 H), 4.17 (dd, *J* = 4.7, 6.9 Hz, 1 H), 4.15 (m, 1 H), 2.60 (d, *J* = 4.7 Hz, 1 H), 2.45 (d, *J* = 6.9 Hz, 1 H), 1.72 (dt, *J* = 5.1, 6.9 Hz, 1 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H), −0.02 (s, 3 H), −0.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.17, 144.81, 142.60, 137.25, 135.74, 128.60, 128.35, 127.72, 127.37, 126.92, 126.27, 126.24, 80.34, 78.42, 73.55, 65.84, 43.24, 42.07, 25.69, 25.65, 18.00, 17.78, −4.66, −5.03; IR (KBr) 3556, 2932, 1726, 1624 cm^{-1}; mp 83–84 °C.

(2*Z*,5*S*,7*S*)-8-Bromo-5,7-bis[(*tert*-butyldimethylsilyl)oxy]-2,8-nonadienoic Acid Methyl Ester (4e). **33** (220 mg, 0.297 mmol) was converted to **4e** (132 mg, 84%): $[\alpha]^{24}_D = +0.8°$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (ddd, *J* = 6.6, 8.0, 11.4 Hz, 1 H), 5.88 (dt, *J* = 1.8, 11.4 Hz, 1 H), 5.82 (br s, 1 H), 5.50 (d, *J* = 1.8 Hz, 1 H), 4.23 (t, *J* = 5.8 Hz, 1 H), 3.91 (dt, *J* = 10.9, 5.1 Hz, 1 H), 3.04 (dddd, *J* = 1.8, 8.3, 10.9, 15.7 Hz, 1 H), 2.79 (ddt, *J* = 1.8, 6.9, 15.7 Hz, 1 H), 1.76 (dt, *J* = 1.4, 6.6 Hz, 2 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.075 (s, 3 H), 0.065 (s, 3 H), 0.060 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.76, 146.33, 137.95, 120.78, 116.67, 73.78, 68.11, 51.03, 43.73, 35.66, 25.82, 25.74, 18.08, 18.02, −4.41, −4.55, −4.63, −5.04; IR (neat) 2954, 2929, 1724, 1647, 1463, 1472 cm^{-1}.

[3*S*-(1*Z*,3α,5α)]-[3,5-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]acetic Acid Methyl Ester (3e). According to the general procedure, **4e** (40 mg, 0.08 mmol) was converted to **3e** (28 mg, 84%): $[\alpha]^{23}_D = -87.8°$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (d, *J* = 1.8 Hz, 1 H), 5.25 (t, *J* = 1.8 Hz, 1 H), 4.96 (t, *J* = 1.8 Hz, 1 H), 4.11 (ddt, *J* = 4.7, 10.6, 5.1 Hz, 1 H), 3.75 (tt, *J* = 4.4, 11.0 Hz, 1 H), 3.63 (s, 3 H), 2.45 (ddd, *J* = 1.8, 4.4, 12.4 Hz, 1 H), 2.23 (m, 2 H), 1.57 (m, 1 H), 0.94 (s, 9 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.74, 151.63, 147.57, 117.32, 109.58, 69.40, 67.91, 51.13, 46.89, 46.25, 25.79, 25.75, 18.36, 18.10, −4.71, −4.70, −5.02, −5.25; IR (neat) 2929, 2857, 1736, 1641, 1472 cm^{-1}; HRMS (CI) calcd for $C_{22}H_{43}O_4Si_2$ (MH^+) 427.2700, found 427.2720.

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Supplementary Material Available: Copies of NMR spectra (32 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.