A Ring Closing Metathesis Approach to Dictyostatin

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Supporting Information

(Contains complete experimental information for all new compounds reported in this paper along with copies of ^1H and ^{13}C NMR spectra.)

General:

Dichloromethane, diethyl ether and tetrahydrofuran (THF), were purified by passing over activated alumina. Commercially available reagents were used as received from Aldrich Chemical Co. Reactions were monitored by thin layer chromatography (TLC) using Kieselgel 60 F₂₅₄ silica gel plates. Flash chromatography was performed over silica gel 60, 230-400 mesh, with the designated solvents. ¹H NMR and ¹³C NMR spectra were recorded on Burker DPX-300 or DPX-500 spectrometers using residual solvent peaks as an internal standard. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane and proton-proton coupling constants (*J*) in Hz. Infrared spectra (IR) were recorded with ATI Mattson Genesis Series FTIR spectrometer and are reported in reciprocal centimeter (cm⁻¹). Optical rotations were measured with Perkin-Elmer 241 digital polarimeter with sodium lamp at ambient temperature and are reported as follows: [α]_D (c = g/100 mL). Gas chromatography-mass spectrometry (GC-MS) was carried out on a Hewlett Packard 5890 Series II gas chromatograph and Hewlett Packard 5971 mass selective detector in the positive chemical ionization (PCI) mode using CH₄ as the reagent bath gas. Low and high-resolution spectra were obtained on a VG 70-G or Micromass Autospec double focusing instrument using EI or electro-spray ionization.

(2*R*,3*S*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2-methylhept-6-enoic acid (1*R*,2*S*)-1-[(1*S*)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-2-methylbut-3-enyl ester (8a). To a stirred solution of acid **18** (40.0 mg, 99.5 μmol) in benzene (1 mL) were added *i*-Pr₂NEt (52.0 μL, 299 μmol), Cl₃C₆H₂COCl (25.0 μL, 160 μmol), and DMAP (18.0 mg, 147 μmol). The alcohol^[1] (13.0 mg, 50.3 μmol) was then added in benzene (2 mL). The

¹ Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359.

resulting solution was stirred for 20 h. Benzene (30 mL) and saturated aqueous NaHCO₃ (30 mL) were added. The layers were separated, and the aqueous layer extracted with benzene (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 20:1) afforded **8a** (30.3 mg, 95% yield) as an oil. ¹H NMR (300 MHz, CDCl₃) δ 5.78 (m, 2H), 5.15-4.99 (m, 4H), 4.85 (dd, *J* = 6.1 Hz, *J* = 6.1 Hz, 1H), 4.12 (m, 2H), 3.69 (m, 1H), 3.33 (m, 1H), 2.64 (m, 1H), 2.54 (m, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.60-1.54 (m, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 1H), 0.89 (brs, 27H), 0.11-0.02 (m, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 174.1, 141.9, 140.8, 114.7, 114.5, 72.0, 70.8, 64.2, 45.4, 43.4, 39.1, 37.6, 25.9 (9C), 18.3, 18.1 (2C), 14.5, 14.3, 12.4, -3.5, -4.1, -4.2, -4.6, -5.3, -5.4; LRMS (EI) 585, 501, 171, 115, 109; HRMS (EI) calcd for C₃₀H₆₁O₅Si₃ 585.3827 (M – C₄H₉)⁺, found 585.3803.

(2*R*,3*S*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2-methylhept-6-enoic acid (1*S*,2*S*)-1-[(1*S*)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-2-methylbut-3-enyl ester (8b**).** To a stirred solution of acid **18** (100 mg, 248 μmol) in benzene (2.5 mL) were added *i*-Pr₂NEt (99.8 μL, 573 μmol), Cl₃C₆H₂COCl (85.6 μL, 548 μmol), and DMAP (151 mg, 1.24 mmol). The alcohol^[2] (32.1 mg, 124 μmol) was then added in benzene (1.5 mL). The resulting mixture was diluted with benzene (1.5 mL) and stirring continued for 20 h. Benzene (50 mL) and saturated aqueous NaHCO₃ (50 mL) were added. The layers were separated, and the aqueous layer extracted with benzene (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 30:1) afforded **8b** (68.0 mg, 85% yield) as an oil. ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.71 (m, 2H), 5.16-4.90 (m, 5H), 4.19-4.09

² Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348-6359.

(m, 2H), 3.51 (m, 1H), 3.38 (m, 1H), 2.62 (m, 1H), 2.48 (m, 1H), 1.93-1.79 (m, 2H), 1.60 (m, 1H), 1.14 (d, $J = 7.1$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H), 0.89 (brs, 27H), 0.09 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.0, 141.9, 140.3, 115.1, 114.4, 76.7, 72.0, 70.6, 65.6, 45.4, 43.6, 40.5, 37.5, 25.9 (9C), 18.2, 18.1, 17.3, 12.0, 11.9, -3.6, -4.1, -4.2, -4.6, -5.4, -5.5; LRMS (EI) 585, 501, 171, 115, 109; HRMS (EI) calcd for $\text{C}_{30}\text{H}_{61}\text{O}_5\text{Si}_3$ 585.3827 ($\text{M} - \text{C}_4\text{H}_9$) $^+$, found 585.3787.

(Z)-(3R,4S,6S,9S,10R)-4,6-Bis(*tert*-butyldimethylsilyloxy)-10-[(1S)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-3,9-dimethyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (9a). A solution of diene **8a** (20.0 mg, 31.1 μmol) and ruthenium complex **I** (13.2 mg, 15.6 μmol) in CH_2Cl_2 (18 mL) was refluxed for 24 h. The solution was cooled to room temperature, $\text{Pb}(\text{OAc})_4$ (10.7 mg, 24.1 μmol) was added and stirring continued overnight. The mixture was filtered through a pad of silica gel, washed with CH_2Cl_2 , and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 10:1) afforded lactone **9a** (13.6 mg, 71% yield) as an oil. ^1H NMR (300 MHz, CDCl_3) δ 5.41-5.27 (m, 2H), 4.67 (m, 1H), 4.24 (m, 1H), 3.76 (m, 2H), 3.29 (m, 1H), 3.10 (m, 1H), 2.40-2.32 (m, 1H), 2.08 (m, 1H), 1.90 (m, 1H), 1.22 (d, $J = 7.1$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.91 (brs, 18H), 0.85 (brs, 9H), 0.10-0.00 (m, 18 H); ^1H NMR (300 MHz, C_6D_6) δ 5.60 (dd, $J = 10.5$ Hz, $J = 10.5$ Hz, 1H), 5.30 (dd, $J = 10.6$ Hz, $J = 10.6$ Hz, 1H), 4.79 (m, 1H), 4.62 (m, 1H), 3.95-3.84 (m, 2H), 3.42 (m, 1H), 3.34 (m, 1H), 2.57 (m, 1H), 2.22 (m, 1H), 2.02 (m, 1H), 1.28 (d, $J = 7.0$ Hz, 3H), 0.99 (brs, 9H overlap 3H, CH_3), 0.96 (brs, 9H), 0.95 (brs, 9H overlap 3H, CH_3), 0.13-0.09 (brs, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.4, 134.9, 133.8, 78.6, 72.0, 64.7, 63.4, 50.1, 48.4, 37.9, 31.6, 25.9 (9C), 18.3, 18.1 (2C), 14.5, 14.3, 14.1, -4.2, -4.6, -5.3 (2C), -5.4 (2C); LRMS (EI) 615, 558,

355, 273, 115, 73; HRMS (EI) calcd for $C_{28}H_{58}O_5Si_3$ 558.3592 ($M - C_4H_9$)⁺, found 558.3565.

9b

(Z)-(3R,4S,6S,9S,10S)-4,6-Bis(*tert*-butyldimethylsilyloxy)-10-[(1S)-2-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-3,9-dimethyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (9b). A solution of diene **8b** (20.0 mg, 31.1 μ mol) and ruthenium complex **II** (13.2 mg, 15.5 μ mol) in CH_2Cl_2 (18 mL) was refluxed overnight. The solution was cooled to room temperature, $Pb(OAc)_4$ (10.3 mg, 23.3 μ mol) was added and stirring continued for another 10 h. The mixture was filtered through a pad of silica gel, washed with CH_2Cl_2 , and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 19:1) afforded lactone **9b** (16.0 mg, 84% yield) as an oil. 1H NMR (300 MHz, $CDCl_3$) δ 5.37 (dd, $J = 10.3$ Hz, $J = 10.3$ Hz, 1H), 5.15 (dd, $J = 9.8$ Hz, $J = 9.8$ Hz, 1H), 4.83 (d, $J = 11.9$ Hz, 1H), 4.70 (m, 1H), 3.66 (m, 1H), 3.39 (m, 2H), 2.69 (m, 1H), 2.46 (m, 1H), 2.06-1.96 (m, 3H), 1.09 (d, $J = 7.0$ Hz, 3H), 0.98 (dd, $J = 6.4$ Hz, $J = 6.4$ Hz, 6H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.10 (brs, 6H), 0.07 (s, 3H), 0.04 (s, 3H), -0.02 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 134.1, 133.2, 75.1, 71.3, 65.4, 64.4, 48.5, 46.5, 35.9, 34.2, 25.9 (9C), 18.2 (3C), 15.8, 15.2, 9.3, -4.3, -4.5 (2C), -4.8, -5.5 (2C); LRMS (EI) 615, 558, 355, 273, 180, 115; HRMS (EI) calcd for $C_{28}H_{58}O_5Si_3$ 558.3592 ($M - C_4H_9$)⁺, found 558.3569.

10a

(4R)-4-Benzyl-3-{(2R,3S,4R)-3-hydroxy-4-[(2S,4S,5S)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentanoyl}-oxazolidin-2-one (10a). The alcohol **10** (1.50 g, 5.64 mmol) in CH₂Cl₂ (56 mL) was treated with Dess-Martin periodinane (3.59 g, 8.46 mmol). After the reaction was completed, it was quenched with saturated aqueous NaHCO₃ (30 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 30 mL), and the combined organic layers were dried over anhydrous MgSO₄. Filtration and concentration *in vacuo*, followed by short flash chromatography filtration (hexane/EtOAc 9:1) provided 1.30 g (87%) of the corresponding crude aldehyde as an oil, which was used without further purification. (R)-4-Benzyl-3-propionyl-2-oxazolidinone (1.60 g, 6.88 mmol) was dissolved in CH₂Cl₂ (15 mL) and cooled to 0 °C. *n*-Bu₂BOTf (7.60 mL, 1.0 M in CH₂Cl₂, 7.60 mmol) was added over 15 min, followed by NEt₃ (1.17 mL, 8.37 mmol). After 15 min, the solution was cooled to –78 °C, and the crude aldehyde was added as a solution in CH₂Cl₂ (5 mL) *via* cannula, followed by a CH₂Cl₂ rinse (1 mL). After 90 min, the reaction mixture was placed in an ice bath and was allowed to warm to 0 °C. After 1 h stirring, the reaction was quenched with pH 7 phosphate buffer (15 mL) followed by MeOH (36 mL). MeOH/30% H₂O₂ (18 mL, 2:1) was added over 30 min, maintaining the temperature of the reaction mixture below 8 °C during addition, and then stirring was continued at 0 °C for 1h. The mixture was concentrated and the residue was extracted with ether (3 x 40 mL). The combined organic layers were washed successively with dilute aqueous NaHCO₃ (40 mL) and brine (40 mL), dried over MgSO₄ and concentrated. Purification by column chromatography (hexane/ EtOAc 4:1) yielded **10a** (2.03 g, 83%) as a white solid. Mp 98-101 °C: [α]_D²⁰ = +71.6 (c = 11.8, CHCl₃); IR (thin film on NaCl) 3514, 2965, 2877, 1780, 1211 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38 (m, 5H), 7.23 (d, *J* = 6.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.39 (s, 1H), 4.71-4.66 (m, 1H), 4.41 (d, *J* = 9.6 Hz, 1H), 4.22-4.15 (m, 3H), 4.00-3.95 (m, 1H), 3.80 (s, 3H), 3.72-3.70 (m, 1H), 3.55 (m,

1H), 3.24 (dd, J = 16.2, 3.6 Hz, 1H), 2.82 (m, J = 13.3, 9.5 Hz, 1H), 2.42-2.28 (m, 1H), 1.97-1.95 (m, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.26-1.20 (m, 2H), 1.09 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.7, 159.9, 152.6, 134.9, 130.6, 129.4 (2C), 128.9 (2C), 127.3, 127.1 (2C), 113.6 (2C), 101.9, 89.2, 73.0, 70.7, 65.8, 55.2, 54.9, 41.3, 37.6, 34.8, 30.9, 18.3, 15.5, 12.0, 11.3; LRMS (EI) 497, 321, 207, 137; HRMS (EI) calcd for $\text{C}_{28}\text{H}_{35}\text{NO}_7$ 497.2414 (M^+), found 497.2413.

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(2*S*,3*R*,4*R*)-4-[(2*S*,4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentane-1,3-diol (12). Lithium borohydride (2 M in THF, 4 mL, 8 mmol) was added dropwise to a stirred solution of the aldol adduct (1.98 g, 4.00 mmol) and MeOH (322 μL) in ether (16 mL) under argon at 0 °C. The mixture was stirred for 2 h at 0 °C and then warmed to ambient temperature. After 30 min, the reaction was quenched with aqueous NH_4Cl (16 mL) and extracted with ether (3×10 mL). The combined organic layers were dried over MgSO_4 , evaporated and subjected to flash chromatography (hexanes/EtOAc 7:3) to yield **12** (1.15 g, 89%) as a white solid. Mp = 101-104 °C; $[\alpha]_{\text{D}}^{25} +9.5$ (c = 5.20, CHCl_3); IR (thin film on NaCl) 3442, 2963, 2875, 1615, 1518, 1250, 1035 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.36 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.39 (s, 1H), 4.14 (dd, J = 11.2, 4.6 Hz, 1H), 3.99 (d, J = 7.7 Hz, 1H), 3.79 (s, 3H), 3.60-3.50 (m, 5H), 2.25 (m, 1H), 2.12 (m, 1H), 1.83 (m, 1H), 1.14 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.9, 130.6, 127.1 (2C), 113.6 (2C), 101.9, 89.6, 72.9, 72.4, 69.1, 65.9, 55.2, 38.6, 34.2, 30.8, 14.1, 13.8, 12.1, 11.7; LRMS (EI) 324, 265, 236, 207, 137; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{28}\text{O}_5$ 324.1937 (M^+), found 324.1933.

(4*R*,5*S*)-4-[(1*S*)-1-[(2*S*,4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]ethyl]-5-methyl[1,3]dioxane-2-thione (12a). A solution of diol **12** (1.00 g, 3.08 mmol) in THF (10 mL) was treated with thiocarbonyldiimidazole (660 mg, 3.69 mmol) and DMAP (20.0 mg, 150 μ mol). The resulting solution was stirred at room temperature for 30 min, and then warmed to 60 °C for 2 h. The reaction was quenched with H₂O. The phases were separated and the aqueous phase extracted with CH₂Cl₂ (3 x 10 mL). The organic extract was washed with brine, dried over MgSO₄ and concentrated. Purification by flash column chromatography (hexane/EtOAc/Et₃N 50:50:1) gave **12a** (900 mg, 79%) as a white solid. Mp = 201-204 °C; [α]_D +62.8 (c = 0.43, CHCl₃); IR (thin film on NaCl) 2965, 2838, 1752, 1615, 1518, 1253 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.41 (s, 1H), 4.58 (m, 1H), 4.52 (m, 1H), 4.23 (m, 1H), 4.12 (m, 1H), 3.81 (s, 3H), 3.47 (m, 1H), 2.62 (m, 1H), 2.21 (m, 1H), 1.96 (m, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 190.1, 160.0, 130.5, 127.0 (2C), 113.6 (2C), 101.4, 86.3, 85.0, 76.2, 73.0, 55.3, 35.4, 32.1, 28.7, 16.7, 12.5, 10.7; LRMS (EI) 324, 272, 207, 137.

(2*R*,4*R*)-4-[(2*S*,4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2-methylpentan-1-ol (13). A solution of **12a** (850 mg, 2.32 mmol) in toluene (100 mL) was heated to reflux. To this was added simultaneously a solution of Bu₃SnH (2.51 mL, 9.30 mmol) in toluene (5 mL) and a solution of AIBN (20.0 mg, 120 μ mol) in toluene (5

mL) *via* syringe over 1 h. The reaction mixture was stirred at reflux for 1 h and then left to cool to room temperature. The solution was concentrated *in vacuo* and 5 M NaOH (20 mL) was added. After stirring at 60 °C for 3 h, the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic extract was washed with brine, dried over MgSO₄ and concentrated. Purification by flash column chromatography (hexane/EtOAc 1:1) gave **13** (540 mg, 75%) as a white solid. Mp = 58-62 °C; [α]_D +62.8 (c = 0.43, CHCl₃); IR (thin film on NaCl) 3417, 2960, 2837, 1615, 1518, 1250, 1035 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 1H), 4.08 (m, 1H), 3.81 (s, 3H), 3.52-3.35 (m, 4H), 2.05 (m, 1H), 1.91(m, 1H), 1.70 (m, 1H), 1.44 (m, 1H), 1.21 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.60 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.7, 131.5, 127.2 (2C), 113.4 (2C), 101.1, 87.9, 73.1, 69.3, 55.2, 33.1, 32.7, 30.8, 30.4, 17.0, 15.7, 12.1; HRMS (EI) calcd for C₁₈H₂₈O₄ 308.1987 (M)⁺, found 308.1993.

(3R,4S,5S)-[4,6-Bis(*tert*-butyldimethylsilyloxy)-3,5-dimethyl-2-oxohexyl]phosphonic acid dimethyl ester (14**).** *n*-BuLi (1.6 M in hexanes, 1.21 mL, 1.94 mmol) was added slowly at -78 °C to a solution of dimethyl methanephosphonate (303 mg, 1.94 mmol) in THF (2 mL). After stirring for 15 min, a solution of the lactone (500 mg, 1.94 mmol) in THF (1 mL) was added drop-wise and stirring was continued for 30 min. LDA (1.8 M in heptane/ THF, 1.08 mL, 1.94 mmol) was added drop-wise to the solution. After another 30 min at -78 °C, TBSCl (585 mg, 3.88 mmol) in THF (1 mL) was added and the mixture was allowed to reach room temperature overnight. After hydrolysis with cold saturated aqueous NH₄Cl (2 mL), the phases were separated and the aqueous phase was extracted with Et₂O (3 x 5 mL). The organic extract was washed with brine, dried over MgSO₄ and concentrated. The crude material was purified by flash column chromatography (hexane/EtOAc 3:2) to give **14** (818 mg, 85%) as a slightly yellow oil.

$[\alpha]_D = -52.6$ ($c = 6.4$ CHCl_3); IR (thin film on NaCl) 2955, 2857, 1714, 1475, 1257, 1064 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.01 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.62 (m, 1H), 3.47-3.33 (m, 2H), 3.11-2.98 (m, 2H), 1.75 (m, 1H), 1.09 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H, overlap 3 H, CH_3), 0.87 (s, 9H), 0.09 (s, 3H), 0.04 (s, 6H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.4, 73.0, 64.8, 52.9, 52.8, 50.6, 41.3, 25.9 (3C), 25.6 (3C), 18.2, 13.8, 11.4, -4.2, -4.4, -5.4, -5.5; LRMS (EI) 439, 369, 323, 237, 185, 151, 73; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{40}\text{O}_6\text{Si}_2\text{P}$ 439.2101 ($\text{M} - \text{C}_4\text{H}_9$) $^+$, found 439.2098.

(2*S*,3*S*,4*R*,8*R*,10*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-10-[(2*S*,4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2,4,8-trimethylundec-6-en-5-one (15). A solution of alcohol **13** (52.0 mg, 168 μmol), NMO (25.0 mg, 210 μmol), and crushed 4 Å molecular sieves (20 mg) in 12 mL CH_2Cl_2 was stirred at room temperature for 20 min. To this was added TPAP (2 mg) and the resulting mixture stirred for 2 h. Water and ether were added. The aqueous layers was extracted with ether. The organic layers were combined, washed with brine, dried over MgSO_4 , passed through a short plug of silica gel, and concentrated. The crude material was then taken on to next step without further purification.

A mixture of ketophosphonate **14** (75.0 mg, 152 μmol) and $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (38.0 mg, 121 μmol ; activated by heating for 1.5 h before use) in THF (1 mL) was stirred at room temperature for 1 h. A solution of the aldehyde in 1.2 mL THF/ H_2O 40:1 was added and stirring continued at room temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NaHCO_3 (10 mL) and brine (10 mL). The organic solution was dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 5:1) gave **15** (83 mg, 81%) as a pale yellow oil. $[\alpha]_D = -24.3$ ($c = 3.4$, CHCl_3); IR (thin film on NaCl) 2957, 2856, 1697, 1620, 1462, 1251, 1094 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.40 (d, $J = 8.7$ Hz, 2H), 6.89 (d,

$J = 8.7$ Hz, 2H), 6.82 (m, 1H), 6.18 (m, 1H), 5.42 (s, 1H), 4.14-4.10 (m, 1H), 3.81 (s, 3H), 3.65 (m, 1H), 3.52-3.38 (m, 3H), 2.97 (m, 1H), 2.38 (m, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.80 (m, 1H), 1.47 (t, $J = 7.1, 6.9$ Hz, 1H), 1.10-1.04 (m, 9 H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.90 (brs, 18 H), 0.76 (d, $J = 6.6$ Hz, 3H), 0.05-0.01 (12H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.5, 159.7, 152.8, 131.4, 127.3 (2C), 126.7, 113.4 (2C), 101.2, 87.7, 74.0, 73.1, 65.0, 55.2, 47.8, 41.4, 35.8, 34.1, 31.2, 30.5, 26.0 (6C), 18.3, 18.1, 17.3, 14.2, 12.2, -3.9, -4.2, -5.3 (2C); LRMS (EI) 676, 619, 481, 185, 121; HRMS (EI) calcd for $\text{C}_{34}\text{H}_{59}\text{O}_6\text{Si}_2$ 619.3850 ($\text{M} - \text{C}_4\text{H}_9$) $^+$, found 619.3854.

15a

(2*S*,3*S*,4*R*,8*S*,10*R*)-1,3-Bis-(*tert*-butyldimethylsilanyloxy)-10-[(2*S*,4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2,4,8-trimethylundecan-5-one (15a). To a mixture of **15** (80.0 mg, 118 μmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (14.5 mg, 61.0 μmol) in MeOH (2.5 mL) was added NaBH_4 (9.20 mg, 244 μmol) in portions at 0 $^\circ\text{C}$. Within 5 min gas evolution started and the solution turned black. The reaction mixture was stirred for 45 min, filtered through a pad of Celite and concentrated *in vacuo*. The residue was dissolved in ether and H_2O 1:1 (20 mL). The mixture was extracted with ether (2×10 mL). The combined organic layers were dried over MgSO_4 , concentrated *in vacuo*, and subjected to flash column chromatography (hexane/EtOAc 5:1). The ketone (70.4 mg, 88%) was obtained as a pale yellow oil. $[\alpha]_{\text{D}} = +1.02$ ($c = 0.59$, CHCl_3); IR (thin film on NaCl) 2939, 2856, 1709, 1616, 1518, 1250, 835 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.41 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.42 (s, 1H), 4.11-4.00 (m, 2H), 3.81 (s, 3H), 3.65 (m, 1H), 3.48 (t, $J = 11.1$ Hz, 1H), 3.41-3.32 (m, 2H), 2.82 (m, 1H), 2.55-2.47 (m, 2H), 2.11-2.00 (m, 1H), 1.87 (m, 1H), 1.74 (m, 1H), 1.45 (m, 2H), 1.27-1.16 (m, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.89 (brs, 18 H, overlap 3H, CH_3), 0.86 (d, $J = 6.5$ Hz, 3H), 0.76 (d, $J = 6.6$ Hz, 3H), 0.07 (s, 3H), 0.05 (s, 9H), 0.01 (s, 3H); ^{13}C

NMR (75 MHz, CDCl₃) δ 213.6, 159.7, 131.6, 127.3 (2C), 113.4 (2C), 101.1, 88.0, 74.1, 73.1, 64.8, 55.2, 49.8, 41.1, 39.9, 36.6, 31.9, 31.1, 30.4, 29.9, 26.0 (6C), 18.7, 18.3, 17.0, 14.4, 12.7, 12.1, -4.0, -4.2, -5.30, -5.40; LRMS (EI) 621, 259, 185; HRMS (EI) calcd for C₃₄H₆₁O₆Si₂ 621.4007 (M – C₄H₉)⁺, found 621.3998.

15b

(2*S*,3*S*,4*S*,5*R*,8*S*,10*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-10-[(2*S*,4*R*,5*S*)-2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]-2,4,8-trimethylundecan-5-ol (15b). To a solution of **15a** (33.3 mg, 49.0 μ mol) in MeOH (2 mL) was added NaBH₄ (2.3 mg, 53 μ mol) at 0 °C, and the solution was stirred for 2 h. Brine was added to the solution, and the resulting mixture was extracted twice with EtOAc. The combined extracts were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient 7.5 to 20 % EtOAc/hexanes) to afford 22.1 mg (60%) of the major diastereomer **15b** along with 11.0 mg (33%) of the epimer. **15b**: [α]_D = +19.3 (c = 2.2 CHCl₃); IR (thin film on NaCl) 3483, 2956, 2856, 1615, 1518, 1250, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.42 (s, 1H), 4.08 (dd *J* = 11.1 Hz, 4.6 Hz, 1H), 3.91 (t, *J* = 4.0 Hz, 1H), 3.81 (s, 3H), 3.64-3.58 (m, 2H), 3.51-3.44 (m, 2H), 3.34 (d, *J* = 9.9 Hz, 1H), 2.08-1.99 (m, 2H), 1.87 (m, 2H), 1.73 (m, 2H), 1.45 (m, 6H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.91 (brs, 18 H overlap 9H, 3 CH₃), 0.75 (d, *J* = 6.7 Hz, 3H), 0.09 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.7, 131.7, 127.3 (2C), 113.4 (2C), 101.1, 88.1, 76.3, 75.2, 73.2, 65.5, 55.3, 40.7, 39.7, 36.9, 35.1, 32.4, 31.2, 30.4, 26.0 (3C), 25.9 (3C), 18.8, 18.3, 18.2, 17.1, 13.4, 12.2, 8.9, -3.7, -4.4, -5.4, -5.5; LRMS (EI) 623, 317, 273, 115, 73; HRMS (EI) calcd for C₃₄H₆₃O₆Si₂ 623.4163 (M – C₄H₉)⁺, found 623.4155. Epimer: [α]_D = +2.8 (c = 1.1 CHCl₃); IR (thin film on NaCl) 3483, 2955, 2856, 1615, 1518, 1250, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.43 (s, 1H),

4.14-4.08 (m, 1H), 3.92 (m, 1H), 3.81 (s, 3H), 3.73 (dd, $J = 10.0, 5.1$ Hz, 1H), 3.57 (m, 1H), 3.52-3.43 (m, 2H), 3.34 (dd, $J = 10.0, 1.8$, 1H), 2.07 (m, 1H), 1.91 (m, 2H), 1.69 (m, 1H), 1.59 (m, 1H), 1.46 (m, 1H), 1.41-1.35 (m, 2H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.91 (brs, 18H), 0.86 (d, $J = 6.2$ Hz, 3H), 0.85 (d, $J = 7.1$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.7, 131.7, 127.3 (2C), 113.4 (2C), 101.1, 88.1, 75.8, 73.5, 73.2, 65.7, 55.3, 42.0, 39.7, 37.1, 33.4, 32.6, 31.1, 30.4 (2C), 26.0 (6C), 18.5, 18.2 (2C), 17.1, 14.6, 12.6, 12.2, -4.3, -4.4, -5.3 (2C); LRMS (EI) 623, 531, 387, 317, 121; HRMS (EI) calcd for $\text{C}_{34}\text{H}_{63}\text{O}_6\text{Si}_2$ 623.4163 ($\text{M} - \text{C}_4\text{H}_9$) $^+$, found 623.4159.

15c

(2*S*,4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-4-[(1*R*,3*S*,6*R*,7*S*,8*S*,9*S*)-6,8,10-tris-(*tert*-butyldimethylsilyloxy)-1,3,7,9-tetramethyldecyl]-[1,3]dioxane (15c). To a solution of alcohol **15b** (27.3 mg, 40.0 μmol) in CH_2Cl_2 (1.5 mL) at 0 $^\circ\text{C}$ was added 2,6-lutidine (6 μL , 50 μmol) followed by TBSOTf (10 μL , 44 μmol). The mixture was stirred for 1 h at 0 $^\circ\text{C}$ before ether was added. The resulting mixture was washed with saturated aqueous NH_4Cl (5 mL), which was back extracted with ether (3 x 5 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 15:1) gave **15c** (28.9 mg, 90%) as a pale yellow oil. $[\alpha]_{\text{D}} = +2.1$ ($c = 1.9$, CHCl_3); IR (thin film on NaCl) 2956, 2856, 1616, 1518, 1471, 1250, 835 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.41 (d, $J = 6.6$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.42 (s, 1H), 4.08 (dd, $J = 11.1, 4.6$ Hz, 1H), 3.80 (s, 3H), 3.73-3.60 (m, 4H), 3.52-3.32 (m, 3H), 2.06 (m, 1H), 1.85 (m, 2H), 1.72 (m, 1H), 1.56-1.50 (m, 2H), 1.44-1.35 (m, 2H), 1.28-1.17 (m, 2H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.76 (d, $J = 6.7$ Hz, 3H), 0.06 (s, 6H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.7,

131.7, 127.3 (2C), 113.4 (2C), 101.2, 88.1, 74.7, 73.4, 73.2, 64.9, 55.2, 40.2, 39.8, 36.9, 32.9, 32.3, 31.6, 31.2, 30.7, 30.4, 26.2 (3C), 26.0 (6C), 22.6, 18.9, 18.6, 18.3, 17.1, 15.3, 14.1, 12.2, 10.4, -3.4, -3.6, -3.8, -4.3, -5.3; HRMS (EI) calcd for C₄₀H₇₇O₆Si₃ 737.5028 (M – C₄H₉)⁺, found 737.5044.

16

(2*S*,3*R*,4*R*,6*S*,9*R*,10*S*,11*S*,12*S*)-9,11,13-Tris(*tert*-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6,10,12-pentamethyltridecan-1-ol (16). A solution of acetal **15c** (27.8 mg, 35.0 μmol) in CH₂Cl₂ (1.5 mL) was cooled to -20 °C and treated with DIBAL-H (350 μl, 1 M in hexane, 350 μmol). The reaction mixture was allowed to warm to 0 °C over 2 h, and stirring continued for 7 h. Excess hydride was quenched by dropwise addition of aqueous saturated Na⁺/K⁺ tartrate (3.5 mL), and the mixture was allowed to warm to room temperature. After stirring for 1 h, the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 2:1) gave **16** (20.6 mg, 75 %). [α]_D = -6.3 (c = 0.97, CHCl₃); IR (thin film on NaCl) 3450, 2956, 2856, 1613, 1514, 1471, 1250, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.61 (d, *J* = 10.6 Hz, 1H), 4.49 (d, *J* = 10.6 Hz, 1H), 3.81 (s, 3H), 3.72-3.57 (m, 5H), 3.41 (m, 1H), 3.20 (m, 1H), 2.83 (br, 1H), 1.84 (m, 2H), 1.72 (m, 1H), 1.53 (m, 2H), 1.42 (m, 1H), 1.29-1.23 (m, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.90 (brs, 9H overlap 3H, CH₃), 0.89 (s, 9H), 0.85 (d, *J* = 6.2 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (2 s, 6H), 0.04 (2 s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 130.5, 129.3 (2C), 113.9 (2C), 90.1, 74.7, 73.4, 66.5, 64.9, 55.2, 40.2, 39.8, 39.2, 36.9, 33.4, 32.9, 32.2, 30.7, 26.2 (3C), 26.0 (6C), 19.0, 18.6, 18.3, 18.2, 16.8, 15.8, 15.3, 10.4, -3.4, -3.7, -3.8, -4.3, -5.3 (2C); LRMS (API-ES) 819.5 (M + Na)⁺.

16a

1-Methoxy-4-[(1*R*,2*S*)-2-methyl-1-[(1*R*,3*S*,6*R*,7*S*,8*S*,9*S*)-6,8,10-tris(*tert*-butyldimethylsilyloxy)-1,3,7,9-tetramethyldecyl]but-3-enyloxymethyl}benzene

(16a). To a solution of alcohol **16** (15.0 mg, 19.0 μmol) in CH_2Cl_2 (1 mL) at 0°C was added Dess-Martin periodinane (10.6 mg, 25.0 μmol). After stirring for 2.5 h, it was quenched with saturated aqueous NaHCO_3 (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2×1 mL), and the combined organic layers were dried over MgSO_4 . Filtration and concentration *in vacuo* gave the crude aldehyde as a pale yellow oil, which was used without further purification. To a suspension of methyltriphenylphosphonium bromide (19.7 mg, 42.0 μmol) in THF (3.5 mL) was added NaHMDS (1 M in THF, 38.0 μL) and the resulting solution was stirred for 30 min at 0°C . The mixture was cooled to -78°C and a solution of the crude aldehyde in THF (200 μL) was added. The mixture was gradually warmed to room temperature and stirred for 18 h. The mixture was diluted with EtOAc (5 mL) and filtered through a short column of silica gel. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 7:1) gave 11.8 mg (78 % 2 steps) of **16a** as a yellow oil. $[\alpha]_D = -1.2$ ($c = 0.50$, CHCl_3); IR (thin film on NaCl) 2956, 2925, 2853, 1550, 1250, 836 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.28 (d, $J = 7.0$ Hz, 2H), 6.87 (d, $J = 8.3$ Hz, 2H), 5.95 (m, 1H), 5.07-5.01 (m, 2H), 4.50 (s, 2H), 3.81 (s, 3H), 3.72-3.63 (m, 4H), 3.41 (m, 1H), 2.99 (m, 1H), 2.51 (m, 1H), 1.80 (m, 5H), 1.60-1.21 (5H), 1.15 (m, 3H), 0.90 (brs, 27H overlap 9H, 3 CH_3), 0.85 (m, 3H), 0.06 (brs, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.7, 141.3, 131.7, 127.3 (2C), 114.8, 113.4 (2C), 85.1, 74.9, 73.8, 73.2, 65.1, 55.3, 42.3, 40.9, 37.4, 31.6, 31.2, 30.5, 30.4, 29.9, 26.1 (3C), 26.0 (2C), 22.7, 18.6, 18.4, 18.1, 17.1, 14.1, 13.2, 12.2, -3.7 (2C), -4.07 (2C), -5.32 (2C); HRMS (EI) calcd for $\text{C}_{41}\text{H}_{79}\text{O}_5\text{Si}_3$ 735.5235 ($\text{M} - \text{C}_4\text{H}_9$) $^+$, found 735.5230.

(3*S*,4*R*,5*R*,7*S*,10*R*,11*S*,12*S*,13*S*)-10,12,14-Tris(*tert*-butyldimethylsilanyloxy)-3,5,7,11,13-pentamethyltetradec-1-en-4-ol (17). To a solution of **16a** (11.3 mg, 14.0 μmol) in a mixture of CH_2Cl_2 (100 μL) and phosphate buffer (pH 7, 100 μL) was added DDQ (4.8 mg, 21 μmol). After being stirred for 1 h at room temperature, the mixture was quenched with saturated aqueous Na_2SO_3 (100 μL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The organic phase was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification by flash column chromatography (hexane/EtOAc 7:1) gave **17** (8.5 mg, 90 %) as a yellow oil. $[\alpha]_{\text{D}} = -0.018$ ($c = 0.17$, CHCl_3); IR (thin film on NaCl) 3387, 2956, 2928, 1462, 1252 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.85-5.73 (m, 1H), 5.16-5.10 (m, 2H), 3.73-3.60 (m, 3H), 3.41 (m, 1H), 3.13 (m, 1H), 2.38 (m, 1H), 1.90-0.83 (br, 11H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.95-0.83 (m, 39H), 0.06 (s, 6H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 139.8, 113.4, 80.1, 75.0, 73.4, 73.2, 64.9, 40.2, 39.8, 36.9, 32.9, 32.3, 31.2, 30.7, 30.4, 26.3 (3C), 26.0 (6C), 18.9, 18.6, 18.2, 17.1, 15.3, 12.2, 10.4, -3.4, -3.6, -3.8, -4.3, -5.3 (2C); LRMS (EI) 615, 599, 483, 391; HRMS (EI) calcd for $\text{C}_{33}\text{H}_{71}\text{O}_4\text{Si}_3$ 615.4660 ($\text{M} - \text{C}_4\text{H}_9$) $^+$, found 615.4687.

(2*R*,3*S*,5*S*)-3,5-Bis(*tert*-butyldimethylsilanyloxy)-2-methylhept-6-enoic acid (18). To a solution of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (470 mg, 2.02 mmol) in CH_2Cl_2 (4 mL) at 0 $^\circ\text{C}$ was added *n*- Bu_2BOTf (2.1 mL, 1.0 M in CH_2Cl_2 , 2.1 mmol) over 15 min, followed by *i*- Pr_2NEt (459 μL , 2.63 mmol). After 15 min, the mixture was cooled to -78

°C and the aldehyde³ (749 mg, 3.05 mmol) was added as a solution in CH₂Cl₂ (1.5 mL) *via* cannula, followed by a CH₂Cl₂ rinse (200 µL). After 90 min, the reaction mixture was placed in an ice bath, allowed to warm to 0 °C, and quenched with phosphate buffer (pH 7, 5 mL). MeOH (8 mL) was added, followed by MeOH/30% H₂O₂ (12 mL, 2:1) over 30 min, maintaining the temperature below 8 °C. Stirring was continued at 0 °C for 1 h. The mixture was concentrated and the residue was extracted with ether (3 x 10 mL). The combined organic layers were washed successively with dilute aqueous NaHCO₃ (10 mL) and brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The resulting crude aldol adduct was of sufficient purity for use in the next step. For characterization, an analytically pure sample was obtained by flash chromatography (2:1 hexanes/EtOAc). [α]_D = -0.09 (c = 0.35, CHCl₃); IR (thin film on NaCl) 3451, 2953, 2855, 1781, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 5.88-5.84 (m, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 4.72 (m, 1H), 4.51 (m, 1H), 4.25-4.19 (m, 2H), 3.79 (m, 1H), 3.27 (m, 1H), 2.78 (m, 1H), 1.77 (m, 1H), 1.59 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); LRMS (EI) 390, 336, 252, 157, 121; HRMS (EI) calcd for C₂₀H₂₈NO₅Si 390.1737 (M – C₄H₉)⁺, found 390.1755. To a stirred mixture of crude aldol adduct and 2,6-lutidine (400 µL, 3.45 mmol) in CH₂Cl₂ (10 mL) at –20 °C under Ar was added drop-wise TBSOTf (696 µL, 3.03 mmol). The reaction mixture was allowed to warm to 0 °C over 1 h. Phosphate buffer (pH 7, 30 mL) and ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The resulting crude product was of sufficient purity for use in the next step. For characterization, an analytically pure sample was obtained by flash chromatography (hexane/ether 10:1). IR (thin film on NaCl) 2951, 2855, 1780, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 5.87 (m, 1H), 5.20 (d, *J* = 17.1 Hz, 1H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.59 (m, 1H), 4.22-4.07 (m, 4H), 3.95 (m, 1H), 3.28 (m, 1H), 2.77 (m, 1H), 1.92 (m, 1H), 1.69 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.08-0.00 (m, 12H). A solution of the crude material in THF/H₂O 4:1 (14 mL) was cooled to 0 °C. 30% H₂O₂ (668 µL, 6.51 mmol) and LiOH·H₂O (64.0 mg, 2.65 mmol) were added. After

³ Hatakeyama, S.; Okano, T.; Maeyama, J.; Esumi, T.; Hiyamizu, H.; Iwabuchi, Y.; Nakagawa, K.; Ozono, K.; Kawase, A.; Kubodera, N. *Bioorg. Med. Chem.* **2001**, *9*, 403-415.

stirring for 3 h, the reaction mixture was quenched with aqueous Na₂SO₃ (17 mL). THF was removed *in vacuo*, and the aqueous solution was extracted with CH₂Cl₂. The organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*, affording the chiral auxiliary (253 mg, 88% recovery). The aqueous phase was acidified to pH 3 with aqueous HCl (1.0 M) and extracted with EtOAc (4 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*, providing compound **18** (590 mg, 73% over 3 steps) as a yellow oil. [α]_D = +9.5 (c = 5.2, CHCl₃); IR (thin film on NaCl) 2955, 2858, 1710, 1472, 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.42 (brs, 1H), 5.79 (m, 1H), 5.14 (d, *J* = 24.1 Hz, 1H), 5.09 (d, *J* = 17.1 Hz, 1H), 4.16 (m, 2H), 2.66 (m, 1H), 1.77 (m, 1H), 1.62-1.53 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 9 H), 0.91 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.8, 141.4, 114.8, 71.9, 70.7, 44.6, 43.2, 25.9 (2C), 25.7 (4C), 18.1, 18.0, 9.8, -3.7, -4.3, -4.6, -4.7; LRMS (EI) 345, 291, 235, 213, 115; HRMS (EI) calcd for C₁₆H₃₃O₄Si₂ 345.1917 (M – C₄H₉)⁺, found 345.1899.

(1*R*,2*S*)-2-Methyl-1-[(1*R*,3*S*,6*R*,7*S*,8*S*,9*S*)-6,8,10-tris(*tert*-butyldimethylsilyloxy)-1,3,7,9-tetramethyldecyl]but-3-enyl-(2*R*,3*S*,5*S*)-3,5-bis(*tert*-butyldimethylsilyloxy)-2-methylhept-6-enoate (19). To a stirred solution of acid **18** (27.0 mg, 67.0 μ mol) in benzene (3 mL) were added *i*-Pr₂NEt (138 μ L, 792 μ mol), Cl₃C₆H₂COCl (118 μ L, 760 μ mol), and DMAP (210 mg, 1.72 mmol). Alcohol **17** (28.0 mg, 41.6 μ mol) was then added in benzene (4 mL). The resulting solution was stirred for 20 h. Benzene (30 mL) and saturated aqueous NaHCO₃ (30 mL) were added. The layers were separated, and the aqueous layer extracted with benzene (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 20:1) afforded **19** (38.5 mg, 88%) as a yellow oil. [α]_D =

-0.27 (c = 1.5, CHCl₃); IR (thin film on NaCl) 2955, 2929, 2885, 2857, 1732, 1471, 1254, 1083, 1030, 1005, 835, 809, 773; ¹H NMR (300 MHz, CDCl₃) δ 5.80 (m, 2H), 5.15-4.98 (m, 4H), 4.72 (m, 1H), 4.16 (m, 2H), 3.73-3.55 (m, 3H), 3.40 (m, 1H), 2.61 (m, 1H), 2.49 (m, 1H), 1.81 (m, 5H), 1.56 (m, 2H), 1.35 (m, 2H), 1.26-1.11 (m, 3H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.95-0.81 (m, 12H), 0.89 (brs, 45H), 0.07-0.02 (brs, 30H); ¹³C NMR (75 MHz, CDCl₃) δ 174.2, 141.9, 140.4, 114.9, 114.3, 80.5, 74.8, 73.8, 72.1, 70.5, 65.1, 45.3, 43.7, 42.3, 40.9, 39.9, 38.4, 33.4, 32.0, 30.6, 30.3, 29.9, 29.7, 25.9 (15C), 18.4, 18.1 (4C), 17.6, 16.2, 13.3, 11.9, 10.3, -3.6, -3.8, -4.1 (3C), -4.2, -4.6, -5.3 (3C); LRMS (API-ES) 1095.7 (M + K)⁺, 1079.6 (M + Na)⁺.

20

(*Z*)-(3*R*,4*S*,6*S*,9*S*,10*R*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-3,9-dimethyl-10-[(1*R*,3*S*,6*R*,7*S*,8*S*,9*S*)-6,8,10-tris(*tert*-butyldimethylsilyloxy)-1,3,7,9-tetramethyldecyl]-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (20). A solution of diene **19** (15 mg, 14.2 μmol) and the ruthenium complex **I** (6.1 mg, 7.2 μmol) in CH₂Cl₂ (15 mL) was refluxed for 24 h. The solution was cooled to room temperature, Pb(OAc)₄ (4.5 mg, 9.8 μmol) was added and stirring was continued overnight. The mixture was filtered through a pad of silica gel and washed with CH₂Cl₂, and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc 10:1) afforded lactone **20** (10 mg, 78%) as an oil. [α]_D = +16.7 (c = 0.24, CHCl₃); IR (thin film on NaCl) 2956, 2929, 2857, 1737, 1472, 1462, 1254, 1081, 1005, 835, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.37 (dd, *J* = 10.4 Hz, *J* = 10.4 Hz, 1H), 5.14 (dd, *J* = 9.8 Hz, *J* = 9.8 Hz, 1H), 4.71 (m, 1H), 4.60 (d, *J* = 10.4 Hz, 1H), 3.74-3.57 (m, 5H), 3.44 (m, 1H), 2.70 (m, 1H), 2.49 (m, 1H), 2.04-1.12 (m, 11H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.3 Hz, 3H), 0.91-0.85 (m, 57H), 0.11-0.04 (m, 30H); ¹³C NMR (75 MHz, CDCl₃) δ 175.9, 134.3, 133.1, 80.4, 75.0, 73.6, 71.1, 65.1,

64.5, 46.6, 42.3, 40.8, 40.3, 36.3, 34.1, 33.9, 29.9, 29.7, 29.5, 25.9 (15C), 18.5, 18.4, 18.2 (3C), 17.0, 15.6, 15.2, 13.0, 10.5, 10.1, -3.4 - -5.3 (10 C); LRMS (API-ES) 1067.6 (M + K)⁺, 1051.7 (M + Na)⁺.

(Z)-(2S,3S,5S,8S,9R,10R,12S,15R,16S,17S,18S)-3,5,15,17,19-Pentakis-(tert-butyltrimethylsilyloxy)-2,8,10,12,16,18-hexamethyl-nonadec-6-ene-1,9-diol (21).

To a stirred solution of lactone **20** (9.0 mg, 8.7 μ mol) in THF (1 mL) at -20°C was added LiAlH_4 (90 μ L of a 1M solution in THF, 90 μ mol). The reaction mixture was allowed to warm gradually to 0°C over 1 h. After 4 h at 0°C the reaction mixture was quenched by the addition of K^+/Na^+ tartrate (2 mL) and stirred vigorously at room temperature. After 1 h, the layers were separated and the aqueous layer was extracted with ether (3×10 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. Flash chromatography (gradient 20-40% EtOAc/hexane) afforded diol **21** (7.2 mg, 80%) as an oil. IR (thin film on NaCl) 3583, 3373, 2929, 2856, 1597, 1471, 1254, 1076, 835, cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.67 (dd, $J = 10.0$ Hz, $J = 10.0$ Hz, 1H), 5.34 (m, 1H), 4.08 (m, 1H), 3.73-3.60 (m, 7H), 3.48 (m, 1H), 3.17 (m, 1H), 2.49 (m, 2H), 1.83-1.11 (m 13H), 1.15 (d, $J = 7.1$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.89 (brs, 45H overlap 12H, 4 CH_3), 0.07 (brs, 30H); ^{13}C NMR (75 MHz, CDCl_3) δ 133.1, 127.6, 80.0, 75.0, 73.7, 71.2, 65.2 (2C), 46.7, 42.0, 40.8, 40.3, 40.0, 35.9, 33.9 (2C), 30.0, 29.7, 26.0 (15C), 18.2 (6C), 16.6, 15.8, 15.2, 13.0, 12.6, 10.1, -3.7 - -5.4 (10C); LRMS (API-ES) 1071.5 (M + K)⁺, 1055.6 (M + Na)⁺.

8b

9b

14

S38

15c

16

16a

16a

19

20

20

21

21