An Efficient Asymmetric Synthesis of (+)-SCH 351448

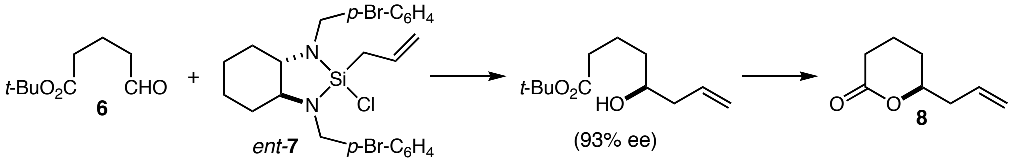
Sergei Bolshakov and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York, 10027

Supporting Information

General Information. Degassed solvents were purified by passage through an activated alumina column. Diisopopylamine and triethylamine were distilled from CaH_2 prior to use. All other commercially obtained reagents were used as received. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Low-resolution mass spectra were obtained on JEOL HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. ^{1}H NMR spectra were recorded on a Bruker DPX-500 (500 MHz), a Bruker DPX-400 (400 MHz) and a Bruker DPX-300 (300 MHz) spectrometers and are reported in ppm from $CDCl_3$ internal standard (7.26 ppm). Data are reported as follows: (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, tt = triplet of triplets, dq = doublet of quartets, ddt = doublet of doublet of triplets; coupling constant(s) in Hz; integration). Proton decoupled ^{13}C NMR spectra were recorded on Bruker DPX-500 (125 MHz), a Bruker DPX-400 (100 MHz) and a Bruker DPX-300 (75 MHz) spectrometers and are reported in ppm from $CDCl_3$ internal standard (77.0 ppm).

Experimental Procedures:



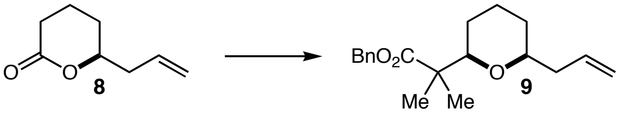
To a cooled (-20 °C) solution of aldehyde **6**[1] (16.40 g, 95 mmol) in 500 mL of CH_2Cl_2 was added solid allylation reagent *ent*-**7**[2] (58.1 g, 105 mmol). The solution was warmed to -10 °C and the reaction mixture was

---

(1) Bitan, G.; Muller, D.; Kasher, R.; Gluhov, E. V.; Gilon, C. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 1501

(2) Kubota, K.; Leighton, J.L. *Angew. Chem. Int. Ed.* **2003**, 42, 946.

kept for 20 h at this temperature. The reaction was quenched by the addition of 300 mL of saturated $NaHCO_3$ (aq). The layers were separated and the aqueous layer was extracted with 2 x 100 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in 350 mL of benzene, p-TsOH (1.268 g, 6.66 mmol) was added and the mixture was refluxed for 1 h. The solution was concentrated and the residue was purified by silica gel column chromatography with 4:1 Hex/EtOAc as eluent to provide lactone **8**[3] (9.61 g, 68.6 mmol, 93% ee[4], 72% yield).



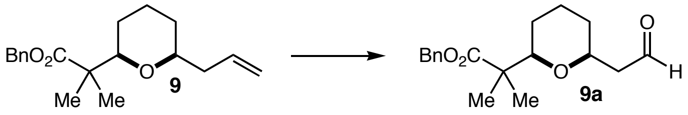
To a cooled (0 °C) solution of diisopropylamine (23.88 mL, 168 mmol) in 250 ml of THF was added *n*-butyllithium (67.0 mL, 168 mmol, 2.5 M in hexane). After 15 min, the solution was cooled to -78 °C and benzyl isobutyrate (30.2 mL, 168 mmol) was added. The mixture was stirred for 30 minutes at -78 °C and then warmed up to 0 °C and a solution of lactone **8** (8.1 g, 57.8 mmol) in 70 mL of THF was added by cannula. After stirring for 40 minutes at 0 °C the solution was quenched by the addition of 100 mL of 1N HCl. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in 200 mL of CH_2Cl_2 and the solution was cooled to -78 °C. To this solution was added triethylsilane (26.8 mL, 168 mmol) followed by boron trifluoride-diethyl etherate (8.53 mL, 69.3 mmol). The reaction mixture was stirred for 3 h at -78 °C, warmed up to 0 °C and then quenched by the addition of 50 mL of saturated aqueous ammonium chloride. The mixture was diluted with 50 mL of CH_2Cl_2 and the layers were separated. The aqueous layer was extracted with 2 x 30 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by flash chromatography on silica gel (5:1 hexane/EtOAc as eluent) afforded

---

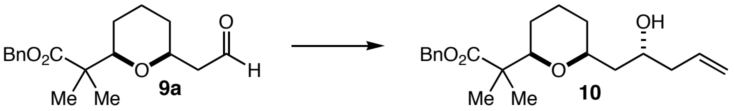
(3) Ramachandran, P. V.; Krzeminski, M. P.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron*: *Asymmetry* **1999**, *10*, 11.

(4) In order to determine the enantiomeric excess of allylation, an aliquot of the intermediate homoallylic alcohol was converted to its Mosher ester (Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543) which was analyzed by ^1H NMR spectroscopy.

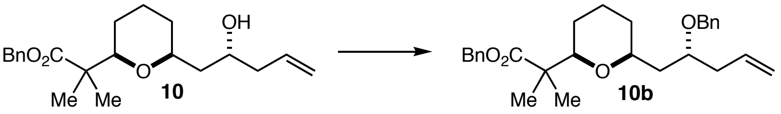
tetrahydropyran **9** (11.84 g, 39.2 mmol, 68% yield) as a colorless liquid: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37-7.29 (m, 5H), 5.84-5.76 (m, 1H), 5.17 (d, J = 12.6 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 5.07-4.95 (m, 2H), 3.56 (dd, J1 = 1.8 Hz, J2 = 10.8 Hz, 1H), 3.35-3.28 (m, 1H), 2.25-2.16 (m, 1H), 2.15-2.06 (m, 1H), 1.90-1.81 (m, 1H), 1.58-1.41 (m, 3H), 1.31-0.05 (m, 8H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 176.7, 136.5, 135.3, 128.3, 127.8, 127.7, 116.0, 82.1, 65.9, 46.7, 40.7, 31.0, 25.0, 23.5, 21.2, 20.1; IR (NaCl, thin film) ν_{max} : 3070, 3033, 2978, 2938, 2860, 1735, 1642, 1456, 1263, 1142, 1089, 1050, 913 cm^{-1}; $[\alpha]^{23}_D$ (*c* 3.50, CH$_2$Cl$_2$) -1.5°; LRMS (FAB+, M+H) *m/z* calculated for $C_{19}H_{26}O_3$: 303, found 303.



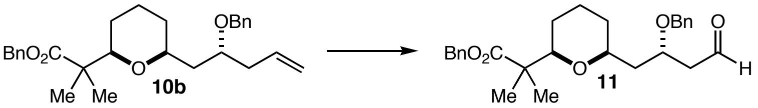
To a solution of tetrahydropyran **9** (10 g, 33.1 mmol) in 150 mL of 3:1 acetone/water was added *N*-methyl morpholine *N*-oxide (6.86 ml, 33.1 mmol) and osmium tetroxide (1wt % aqueous solution, 0.841 ml, 0.033 mmol). After 19 h, the reaction was quenched by adding 20 mL of saturated aqueous $Na_2S_2O_4$ followed by stirring for 20 minutes. The mixture was filtered through a pad of Celite with ethyl acetate washes. The aqueous phase was separated and extracted 3 x 50 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in 100 ml of THF/water (4:1) and sodium periodate (7.78 g, 36.4 mmol) was added and the resulting mixture was stirred for 2 h. The mixture was diluted with 20 mL of water and the layers were separated. The aqueous layer was extracted with 2 x 20 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by flash chromatography on silica gel (4:1 hexane/EtOAc as eluent) afforded aldehyde **9a** (8.76 g, 28.8 mmol, 87% yield) as a colorless liquid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.63 (dd, *J2* = 2.1 Hz, *J2* = 2.6, 1H), 7.37-7.28 (m, 5H), 5.12 (d, *J* = 12.5 Hz, 1H), 5.06 (d, *J* = 12.5 Hz, 1H), 3.83-3.76 (m, 1H), 3.56 (dd, *J1* = 1.8 Hz, *J2* = 10.8 Hz, 1H), 3.60 (dd, *J1* = 1.8 Hz, *J2* = 11.4 Hz, 1H), 2.43 (ddd, *J1* = 2.7 Hz, *J2* = 8.0 Hz, *J3* = 16.1 Hz, 1H), 2.34 (ddd, *J1* = 2.0 Hz, *J2* = 4.6 Hz, *J3* = 16.1 Hz, 1H), 1.89-1.78 (m, 1H), 1.58-1.44 (m, 3H), 1.30-1.19 (m, 2H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.3, 176.0, 136.1, 128.2, 127.7, 82.3, 73.5, 66.0, 49.7, 46.6, 31.3, 24.7, 23.4, 21.3, 20.1; IR (NaCl, thin film) ν_{max} : 3066, 3034, 2943, 2862, 2729, 1732, 1498, 1456, 1392, 1375, 1316, 1268, 1163, 1136, 1087, 1049, 910, 751, 698 cm^{-1}; $[\alpha]^{27}_D$ (*c* 3.00, CH$_2$Cl$_2$) -4.7°; LRMS *m/z* (FAB+, M+H) calculated for $C_{18}H_{24}O_4$: 305, found 305.



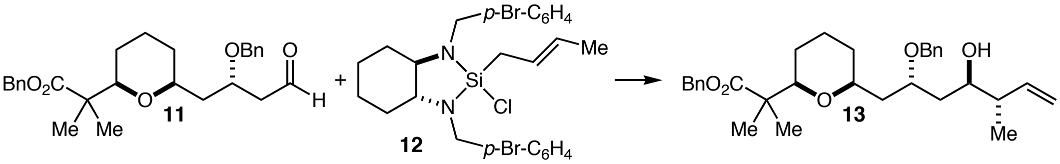
B-(+)-Methoxy isopinocampheylborane (8.96 g, 28.3 mmol) was dissolved in 35 mL of ethyl ether and the solution was cooled to 0 ºC. Allyl magnesium bromide (1.0 M solution in ethyl ether, 28.3 mL, 28.3 mmol) was added by syringe dropwise and the resulting solution was stirred for 1 h. The reaction mixture was then cooled to -100 ºC and a solution of aldehyde **9a** (7.50 g, 24.64 mmol) in 50 ml of diethyl ether was added dropwise by cannula. The mixture was stirred at -100 ºC for 1 h and then warmed to 0 ºC. The reaction was quenched by the ***DROPWISE*** addition of 15 mL of 30% H_2O_2 (aq) and 17 ml of 1N NaOH (**CAUTION!** Gas evolution!). The mixture was diluted with 20 mL of ethyl acetate and the layers were separated. The aqueous layer was extracted with 3 x 30 mL of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. ^{1}H NMR spectroscopic analysis confirmed the production of homoallylic alcohol with 10:1 *dr*. The crude reaction mixture was further purified by silica gel chromatography (9:1 Hex/EtOAc as eluent) to give alcohol **10** (7.85 g, 22.7 mmol, 92 % yield, 10:1 *dr*) as a clear liquid. ^{1}H NMR (400 MHz, C_6D_6) δ 7.29 (d, J = 7.6 Hz, 2H), 7.17-7.11 (m, 3H), 7.09-9.04 (m, 1H), 6.05-5.94 (m, 1H), 5.20 (d, *J* = 12.4, 1H), 5.12-5.05 (m, 3H), 3.82 (dd, *J1* = 6.5 Hz, *J2* = 14.2), 3.54-3.51 (m, 2H), 3.24 (t, *J* = 10.5, 1H), 2.39-2.31 (m, 1H), 2.24-2.17 (m, 1H), 1.65-1.46 (m, 2H), 1.28 (m, 1H), 1.21 (s, 3H), 1.16-1.06 (m, 4H), 1.05 (s, 3H), 0.99-0.89 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 175.9, 136.9, 136.0, 128.6, 128.5, 128.1, 116.6, 83.0, 79.5, 71.1, 66.5, 46.7, 42.8, 42.5, 32.0, 25.0, 23.5, 21.9, 20.0; IR (NaCl, thin film) ν_{max} : 3521, 3070, 3034, 2978, 2940, 2862, 2360, 1732, 1641, 1456, 1392, 1265, 1142, 1086, 1047, 913, 751, 698 cm-^{1}; $[\alpha]^{27}_D$ (*c* 2.50, CH_2Cl_2) +2.9°; LRMS (FAB+) *m/z* calculated for $C_{21}H_{31}O_4$ $[M+H]^+$ 347, found 347.



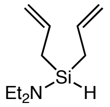
To a cooled (0 °C) solution of homoallylic alcohol **10** (7.54 g, 21.76 mmol) in 35 mL of dry DMF was added sodium hydride (60%) (2.61 g, 65.3 mmol) portionwise, and the resulting mixture was stirred for 20 min prior to the addition of benzyl bromide (4.66 mL, 39.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and quenched by the addition of 10 mL of water. The mixture was diluted with 20 mL of diethyl ether and the layers were separated. The aqueous layer was extracted with 2 x 20 mL of diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by chromatography (10:1 Hex/EtOAc as eluent) to furnish benzyl ether **10b** (8.86 g, 20.29 mmol, 93% yield) as a colorless liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (m, 10H), 5.57-5.81 (m, 1H), 5.13-5.02 (m, 4H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 3.61-3.56 (m, 1H), 3.52 (dd, *J1* = 1.3 Hz, *J2* = 11.7 Hz, 1H), 3.41 (m, 1H), 2.39-2.33 (m, 1H), 2.30-2.23 (m, 1H), 1.85 (m, 2H), 1.56-1.51 (m, 1H), 1.49-1.40 (m, 3H), 1.32-1.22 (m, 1H), 1.20 (s, 3H), 1.16-1.09 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.6, 138.9, 136.4, 135.1, 128.4, 128.2, 127.8, 127.6, 127.3, 116.8, 82.1, 75.3, 74.9, 70.6, 65.9, 46.7, 40.2, 37.9, 31.6, 25.1, 23.6, 21.2, 20.4; IR (NaCl, thin film) ν_{max} : 3066, 3032, 2977, 2941, 2861, 1950, 1808, 1733, 1640, 1497, 1455, 1391, 1315, 1265, 1196, 1137, 1089, 1048, 1002, 914, 735, 697 cm-^{1}; $[\alpha]^{27}_D$ (*c* 3.87, CH_2Cl_2) –8.8°; LRMS (FAB+) *m/z* calculated for $C_{28}H_{37}O_4$ [M+H]$^+$ 437, found 437.



To a solution of benzyl ether **10b** (8.46 g, 19.38 mmol) in 100 mL of 3:1 v/v acetone/water was added *N*-Methyl morpholine *N*-oxide (7.23 mL, 34.9 mmol) and osmium tetroxide (1 wt % aqueous solution, 0.493 mL, 0.019 mmol). After 19 h, the reaction was quenched by adding 20 mL of saturated aqueous $Na_2S_2O_4$. The mixture was filtered through a pad of Celite with ethyl acetate washes. The aqueous phase was extracted 3 x 50 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was dissolved in 100 ml of 4:1 THF/water, and sodium periodate (4.56 g, 21.32 mmol) was added and the resulting mixture was stirred for 2 h. The mixture was diluted with 20 mL of water and the layers were separated. The aqueous layer was extracted with 2 x 20 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by chromatography (5:1 Hex/EtOAc as eluent) to furnish aldehyde **11** (8.12 g, 18.52 mmol, 96% yield) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 2.1, 1H), 7.56-7.05 (m, 10H), 5.11 (d, *J* = 12.6 Hz, 1H), 5.05 (d, *J* = 12.6 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.10-4.02 (m, 1H), 3.53 (dd, *J1* = 1.5Hz, *J2* = 11.2 Hz, 1H), 3.44-3.37 (m, 1H), 2.62-2.57 (m, 2H), 1.94-1.82 (m, 2H), 1.64-1.55 (m, 1H), 1.50-1.45 (m, 3H), 1.31-1.09 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 176.5, 138.3, 136.3, 128.5, 128.4, 127.9, 127.7, 82.2, 74.3, 72.1, 71.6, 70.9, 66.0, 48.0, 46.7, 39.9, 31.8, 24.9, 23.5, 21.4, 20.1; IR (NaCl, thin film) ν_{max} : 3064, 3032, 2942, 2861, 2726, 1954, 1726, 1653, 1607, 1558, 1497, 1455, 1390, 1266, 1197, 1164, 1139, 1088, 1050, 913, 737, 698 cm^{-1}; $[\alpha]^{25}_{D}$ (*c* 3.25, CH_2Cl_2) +7.25°; LRMS (APCI+) *m/z* calculated for $C_{27}H_{35}O_5$ $[M+H]^+$ 439, found 439.



To a cooled (-20 °C) solution of aldehyde **11** (1.40 g, 3.19 mmol) in 80 mL of CH_2Cl_2 was added solid crotylation reagent **12**[5] (2.00 g, 3.51 mmol). The solution was warmed to 0 °C and the reaction mixture kept for 20 h at this temperature. The reaction was quenched by the addition of 80 mL of 1 M HCl (aq), and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted with 2 x 40 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by silica gel chromatography (6:1 Hex/EtOAc as eluent) afforded alcohol **13** (1.268 g, 2.56 mmol, 80% yield) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.24 (m, 10H), 5.88-5.75 (m, 1H), 5.15-5.00 (m, 4H), 4.51 (d, 1H), 4.43 (d, 1H), 3.87-3.82 (m, 1H), 3.77-3.67 (m, 1H), 3.51 (d, J = 9.9 Hz, 1H), 3.67-3.30 (m, 1H), 2.69 (d, J = 3.6 Hz, 1H), 2.22-2.12 (m, 1H), 1.97-1.82 (m, 2H), 1.73-1.41 (m, 6H), 1.31-1.13 (m, 8H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 140.7, 138.5, 136.4, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 115.1, 82.2, 74.9, 74.1, 71.4, 71.0, 66.0, 46.7, 44.0, 39.8, 37.1, 31.9, 25.1, 23.6, 21.3, 20.4, 16.0; IR (NaCl, thin film) ν_{max} : 3504, 3066, 3032, 2939, 2865, 1731, 1640, 1496, 1457, 1385, 1318, 1266, 1139, 1090, 1051, 913, 737, 697 cm^{-1}; $[\alpha]^{29}_{D}$ (*c* 1.05, CH_2Cl_2) +17.6°; LRMS (FAB+) *m/z* calculated for $C_{31}H_{43}O_5$ $[M+H]^+$ 495, found 495.

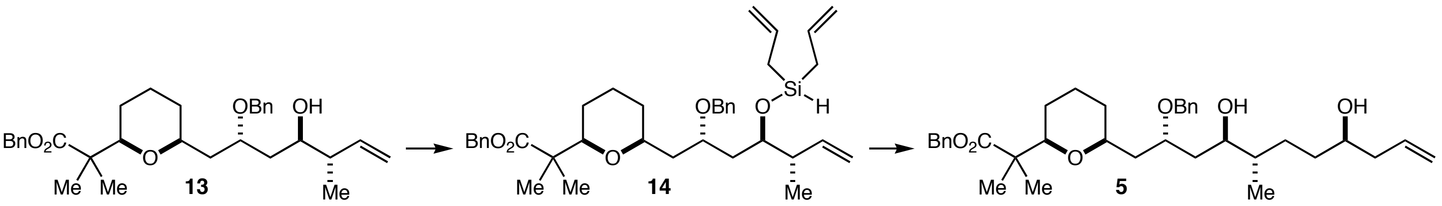


Diallyl-*N,N*-diethylsilanamine. To a cooled (-78 °C) solution of trichlorosilane (26.8 g, 198 mmol) in 250 mL of ether was added diethylamine (28.9 g, 396 mmol). The reaction mixture was warmed to ambient temperature, stirred for 30 min and filtered through dry Celite. The filtrate was cooled to -78 °C and

---

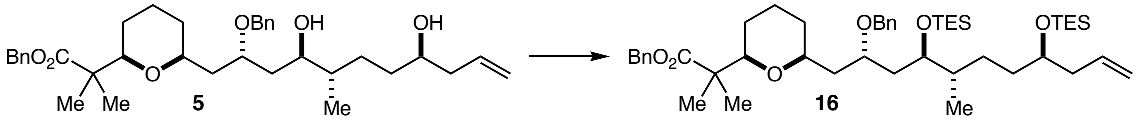
(5) Hackman, B. M.; Lombardi, P. J.; Leighton J.L. *Org. Lett.*, **2004**, *6*, 4375.

allylmagnesium bromide (57.5 g, 396 mmol) was added dropwise over 40 min. The solution was allowed to warm up to room temperature and stirred for 2 h, then the solution was transferred *via* cannula to a separate flask and concentrated. Purification by vacuum distillation (0.2 mm Hg, bp ≈ 60 °C) afforded diallyl-*N*,*N*-diethylsilanamine (22.7 g, 124 mmol, 63% yield) as a clear, colorless liquid: ^{1}H NMR (300 MHz, C_6D_6) δ 5.90-5.70 (m, 2H), 5.05-4.90 (m, 4H), 4.43-4.40 (m, 1H), 2.72 (q, *J* = 7.0 Hz, 4H), 1.70-1.50 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 134.7, 114.0, 41.4, 22.0, 15.5.

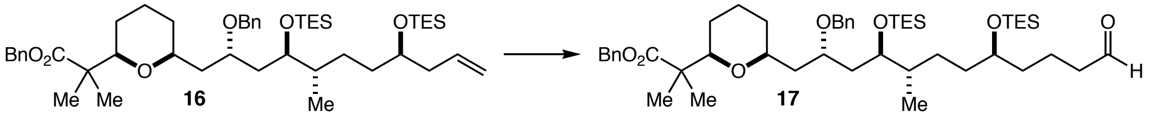


To a solution of alcohol **13** (1.60 g, 3.23 mmol) in 10 mL of dichloromethane was added 1.0 g of 4Å molecular sieves. After 1 h, diallyl-*N*,*N*-diethylsilanamine (0.771 g, 4.20 mmol) was added dropwise. The reaction mixture was stirred for 1h, and then the solution was concentrated *in vacuo*. A glass liner for a stainless steel 45 mL Parr high-pressure reactor equipped with a stir bar and septum was charged with a solution of **14** in 10 mL of benzene. The solution was cooled to -78 °C and Rh(acac)$(CO)_2$ (0.042 g, 0.162 mmol) was added. The liner was inserted into the Paar reactor, and the pressure gauge and gas inlet assembly were attached. The reactor was sealed, charged and vented 3 x 500 psi (3.4 MPa) of CO, then charged to 900 psi (6.9 MPa). The Parr apparatus was heated by immersion in an oil bath set at 60 °C. After 20 h, the reactor was cooled to 0 °C and vented. To a solution of the residue in 70 mL of THF was added 1.0 M solution of TBAF in THF (19.41 mL, 19.41 mmol) were added. The solution was heated at reflux for 2 h, and then cooled and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (4:1 Hex/EtOAc as eluent) delivered diol **5** (1.27 g, 2.23 mmol, 69% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.18 (m, 10H), 5.89-5.78 (m, 1H), 5.15-5.04 (m, 4H), 4.52 (d, *J* = 11.6 Hz, 2H), 4.42 (d, *J* = 11.6 Hz, 2H), 3.91-3.81 (m, 1H), 3.71-3.60 (m, 2H), 3.52 (dd, *J1* = 1.6 Hz, *J2* = 11.4 Hz, 1H), 3.36-3.31 (m, 1H), 2.34-2.27 (m, 1H), 2.18-2.10 (m, 1H), 1.97-1.90 (m, 1H), 1.87-1.83 (m, 1H), 1.73-1.33 (m, 10H), 1.30-1.13 (m, 9H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 138.2, 136.2, 134.8, 128.3, 128.2, 127.8, 127.5, 117.7, 82.2, 75.0, 74.3, 72.1, 71.2, 70.9, 66.1, 46.8, 41.9, 39.6, 39.1, 36.1, 34.5, 32.1, 28.3, 25.2, 23.8, 21.6, 20.4, 15.7; IR (NaCl, thin film) ν_{max} :

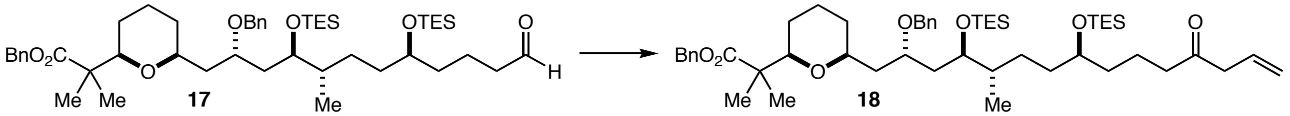
3445, 2937, 2866, 1729, 1457, 1384, 1267, 1139, 1089, 1050, 913, 739, 697 cm^{-1}; $[\alpha]^{23}_{D}$ (*c* 1.00, CH_2Cl_2) +16.6°; LRMS (FAB+) *m/z* calculated for $C_{35}H_{51}O_6$ $[M+H]^+$ 567, found 567.



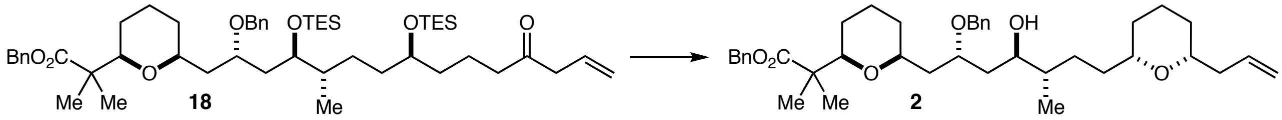
To a cooled (-78 °C) solution of diol **5** (0.4 g, 0.706 mmol) and triethylamine (0.214 g, 2.117 mmol) in CH_2Cl_2 (10 mL) was added TESOTf (0.399 mL, 1.764 mmol). The mixture was stirred for 15 min, warmed to ambient temperature and then washed with saturated NH_4Cl (aq). The aqueous layer was extracted with 2 x 20 mL EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (10:1 Hex/EtOAc as eluent) to afford bis-triethylsilyl ether **16** (0.558 g, 0.702 mmol, 99% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 10H), 5.86-5.75 (m, 1H), 5.15-5.11 (m, 2H), 5.04-4.99 (m, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.92-3.89 (m, 1H), 3.73-3.64 (m, 2H), 3.47 (dd, *J1* = 1.7 Hz, *J2* = 11.0 Hz, 1H), 3.41-3.35 (m, 1H), 2.22-2.17 (m, 2H), 1.90-1.77 (m, 2H), 1.64-1.41 (m, 8H), 1.39-1.33 (m, 4H), 1.25 (s, 3H), 1.17 (s, 3H), 0.97-0.90 (m, 18H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.77-0.52 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 139.1, 136.2, 135.1, 128.2, 128.0, 127.7, 127.6, 127.1, 126.9, 116.5, 81.9, 75.0, 73.6, 72.5, 72.1, 69.8, 66.0, 46.8, 42.0, 41.2, 39.7, 37.6, 35.2, 32.0, 28.8, 25.8, 23.8, 22.5, 20.2, 14.0, 7.3, 7.1, 5.6, 5.3; IR (NaCl, thin film) ν_{max} : 3067, 3033, 2952, 2913, 2875, 1737, 1641, 1454, 1414, 1378, 1264, 1238, 1137, 1090, 1006, 731, 696 cm^{-1}; $[\alpha]^{23}_{D}$ (*c* 1.00, CH_2Cl_2) +18.3°; LRMS (FAB+) *m/z* calculated for $C_{47}H_{79}O_6Si_2$ $[M+H]^+$ 796, found 796.



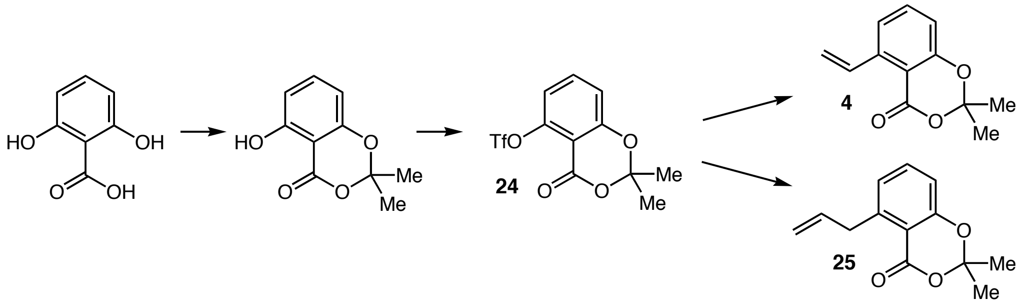
A glass liner for a stainless steel 45 mL Parr high-pressure reactor equipped with a stir bar was charged with a solution of bis-triethylsilyl ether **16** (0.55 g, 0.692 mmol) in THF (9 mL). Rh(acac)$(CO)_2$ (9.0 mg, 0.035 mmol) and Nixantphos (0.046 g, 0.083 mmol) were added. The liner was inserted into the Parr reactor and the pressure gauge and gas assembly were attached. The reactor was sealed, charged and vented with 2 x 400 psi with CO, recharged to 600 psi CO, and immersed (≈ 2.5 cm) in an oil bath set at 60 °C. After 15 h, the reactor was cooled to room temperature and vented. The solution was concentrated. Purification of the residue by flash chromatography on silica gel (4:1 hexane/EtOAc as eluent) afforded aldehyde **17** (0.453 g, 0.549 mmol, 79% yield) as a colorless liquid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.71 (t, *J* = 1.8 Hz, 1H), 7.34-7.21 (m, 10H), 5.11 (s, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 3.92-3.89 (m, 1H), 3.80-3.70 (m, 1H), 3.70-3.60 (m, 1H), 3.46 (dd, *J1* = 1.7 Hz, *J2* = 11.0Hz, 1H), 3.43-3.33 (m, 1H), 2.37 (td, *J1* = 1.7 Hz, *J2* = 7.3Hz, 2H), 1.91-1.78 (m, 2H), 1.72-1.00 (m, 23H), 0.97-0.90 (m, 18H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.61-0.53 (m, 12H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.1, 176.1, 139.1, 136.2, 128.2, 128.0, 127.7, 127.6, 127.2, 127.0, 82.0, 75.0, 73.6, 72.5, 72.1, 69.9, 66.0, 46.8, 44.1, 41.2, 39.8, 37.7, 36.4, 35.4, 32.0, 28.7, 25.8, 23.8, 22.6, 20.2, 18.2, 14.1, 7.3, 7.2, 5.6, 5.3; IR (NaCl, thin film) ν_{max} : 2952, 2914, 2876, 2714, 1729, 1454, 1413, 1379, 1264, 1238, 1136, 1088, 1067, 1050, 1009, 733, 696 cm^{-1}; $[\alpha]^{24}_D$ (*c* 0.70, CH$_2$Cl$_2$) +12.7°; LRMS (APCI+) *m/z* calculated for $C_{48}H_{81}O_7Si_2$ $[M+H]^+$ 825.5, found 825.5.



To a solution of aldehyde **17** (0.311 g, 0.390 mmol) in 5 mL of THF was added 0.3 mL of saturated aqueous NH$_4$Cl, allyl bromide (0.165 mL, 1.950 mmol) and Zn dust (0.128 g, 1.950 mmol). After 35 min, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. Excess allyl bromide was removed at room temperature *in vacuo*. The residue was dissolved in 4 mL of CH$_2$Cl$_2$ and a solution of Dess-Martin periodinane (0.248 g, 0.585 mmol) in 1.2 mL of CH$_2$Cl$_2$ was added dropwise. After 3 h, the solvent was removed and the reaction mixture was loaded directly onto a silica gel column and chromatographed (4:1 Hex/EtOAc as eluent) to deliver ketone **18** (0.290 g, 0.335 mmol, 86% yield) as a colorless oil: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.34-7.20 (m, 10H), 5.98-5.85 (m, 1H), 5.20-5.06 (m, 4H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.94-3.88 (m, 1H), 3.78-3.69 (m, 1H), 3.65-3.55 (m, 1H), 3.46 (m, *J* = 10.1 Hz, 1H), 3.43-3.35 (m, 1H), 3.14 (d, *J* = 6.8 Hz, 2H), 2.41 (t, *J* = 2.41 Hz, 2H), 1.93-1.75 (m, 2H), 1.68-1.00 (m, 25H), 0.99-0.90 (m, 18H), 0.86 (d, *J* = 6.7 Hz, 1H), 0.62-0.52 (m, 12H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 208.1, 176.2, 139.1, 136.2, 130.5, 128.3, 128.0, 127.7, 127.6, 127.3, 127.2, 127.0, 118.5, 82.0, 75.1, 73.6, 72.6, 72.3, 69.9, 66.0, 47.7, 46.9, 42.6, 41.3, 39.8, 37.6, 36.6, 35.5, 32.0, 28.8, 25.9, 23.8, 22.6, 20.2, 19.9, 14.0, 7.3, 7.2, 5.6, 5.3; IR (NaCl, thin film) ν_{max} : 2952, 2876, 1721, 1456, 1378, 1265, 1239, 1089, 1007, 916, 733, 697 cm-^{1}; $[\alpha]^{22}_D$ (*c* 1.00, CH$_2$Cl$_2$) +10.4°; LRMS (APCI+) *m/z* calculated for $C_{51}H_{85}O_7Si_2$ $[M+H]^+$ 866, found 866.



To a cooled (-78 °C) solution of ketone **18** (0.160 g, 0.185 mmol) in 5 mL of CH_2Cl_2 was added triethylsilane (0.118 mL, 0.740 mmol) and boron trifluoride-diethyl etherate (0.028 mL, 0.222 mmol). After 3 h, the reaction mixture was warmed to 0 °C and 3 ml of saturated aqueous NH_4Cl was added. The layers were separated. The aqueous layer was extracted with 2 x 20 mL of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification by flash chromatography on silica gel (4:1 hexane/EtOAc as eluent) afforded **2** (0.077 g, 0.124 mmol, 67 % yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.21 (m, 10H), 5.92-5.76 (m, 1H), 5.20-4.95 (m, 4H), 4.51 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 3.92-3.81 (m, 1H), 3.79-3.60 (m, 1H), 3.50 (d, J = 9.9 Hz, 1H), 3.41-3.15 (m, 3H), 2.84 (d, J = 3.6 Hz, 1H), 2.38-2.22 (m, 1H), 2.20-2.08 (m, 1H), 2.00-1.03 (m, 21H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 138.3, 136.2, 135.2, 128.3, 128.2, 127.7, 127.5, 127.4, 116.0, 82.2, 78.3, 77.4, 75.0, 74.3, 72.0, 70.9, 66.1, 46.8, 41.2, 39.8, 39.0, 35.9, 34.2, 32.1, 31.6, 31.4, 28.2, 25.3, 23.8, 21.5, 20.6, 15.4; IR (NaCl, thin film) ν_{max} : 3501, 2935, 2860, 1733, 1497, 1455, 1377, 1267, 1197, 1138, 1086, 1050, 913, 734, 697 cm^{-1}; $[\alpha]^{22}_D$ (c 1.00, CH_2Cl_2) +3.0°; LRMS (APCI+) m/z calculated for $C_{39}H_{57}O_6$ $[M+H]^+$ 621.4, found 621.8.

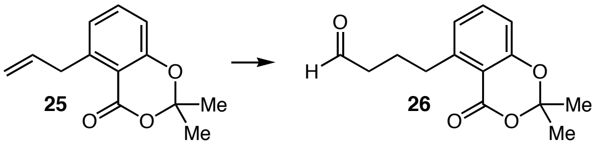


Compounds **4**[6] and **25**[7] are known compounds prepared by Stille couplings with triflate **24**, which may be prepared in two steps from 2,6-dihydroxybenzoic acid.[8] The procedures for the preparations of these compounds are given in the references provided.

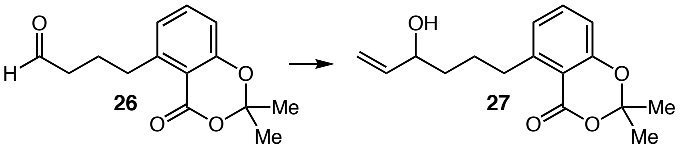
---

(6) Slusher, B. S.; Wozniak, K. U.S. Pat. Appl. 20030036534, *Chem. Abst.* 2001, *36*, 15255.

(7) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701.



A glass liner for a stainless steel 45 mL Parr high-pressure reactor equipped with a stir bar was charged with a solution of acetonide **25** (0.730 g, 3.34 mmol) in THF (9 mL). Rh(acac)(CO)$_2$ (0.043 g, 0.167 mmol) and NIXANTPHOS (0.221 g, 0.401 mmol) were added. The liner was inserted into the Parr reactor and the pressure gauge and gas assembly were attached. The reactor was sealed, charged and vented with 2 x 400 psi with CO, recharged to 600 psi CO, and immersed (≈ 2.5 cm) in an oil bath set at 70 °C. After 15 h, the reactor was cooled to room temperature and vented. The solution was concentrated. Purification by flash chromatography on silica gel (4:1 hexane/EtOAc as eluent) afforded aldehyde **26** (0.752 g, 3.03 mmol, 91% yield) as a colorless liquid: ^{1}H NMR (500 MHz, C_6D_6) δ 9.34 (s, 1H), 6.91 (t, *J* = 7.9 Hz 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 3.04 (t, *J* = 7.8 Hz, 2H), 1.98 (t, *J* = 7.1 Hz, 2H), 1.81 (quin, *J* = 7.5 Hz, 2H), 1.30 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.6, 159.6, 157.6, 147.3, 135.1, 125.3, 115.6, 112.7, 104.9, 43.5, 33.8, 25.3, 23.8; IR (NaCl, thin film) ν_{max} : 2999, 2943, 2869, 2825, 2725, 1732, 1606, 1583, 1478, 1448, 1390, 1380, 1314, 1270, 1209, 1168, 1145, 1070, 1042, 966, 925, 852, 810, 779, 697 cm^{-1}; LRMS (APCI+) *m/z* calculated for $C_{14}H_{17}O_4$ $[M+H]^+$ 249, found 249.

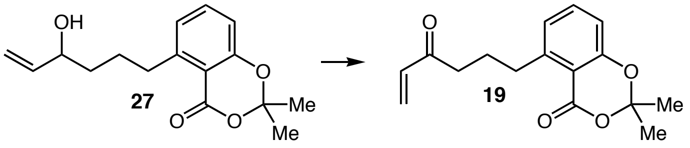


To a cooled (0 °C) solution of aldehyde **26** (0.730 g, 2.94 mmol) in 15 mL of THF was added vinylmagnesium bromide (3.23 ml, 3.23 mmol, 1.0 M in THF). After 10 min, the reaction was quenched by the addition of 15 mL of sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with 2 x 20 mL EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography on silica gel (5:1 hexane/EtOAc) afforded alcohol **27** (0.657 g, 2.378 mmol, 81% yield) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.9 Hz, 1H), 6.93 (d,

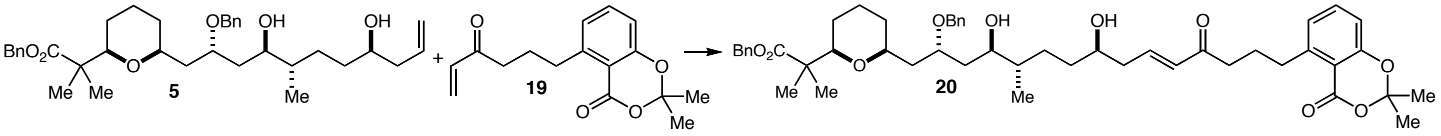
---

(8) (a) Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025 (b) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071.

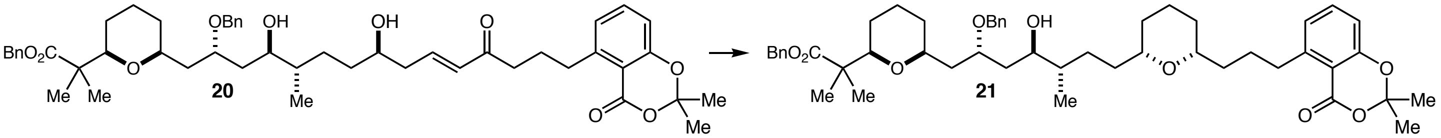
J = 7.6 Hz, 1H), 6.81 (dd, *J1* = 0.8 Hz, *J2* = 8.2 Hz, 1H), 5.92-5.83 (m, 1H), 5.23 (ddd, *J1* = 1.4 Hz, *J2* = 1.4 Hz, *J3* = 17.2 Hz, 1H), 5.09 (dd, *J1* = 1.3 Hz, *J2* = 10.4 Hz, 1H), 4.20-4.16 (m, 1H), 3.22-3.15 (m, 1H), 3.05-2.98 (m, 1H), 1.84 (br s, 1H), 1.74-1.59 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.9, 147.6, 140.9, 135.0, 125.0, 115.2, 114.3, 111.9, 105.0, 72.5, 36.9, 34.1, 27.1, 25.9, 25.7; IR (NaCl, thin film) ν_{max} : 3436, 3078, 2999, 2941, 2864, 1737, 1692, 1642, 1606, 1582, 1479, 1446, 1390, 1379, 1315, 1270, 1209, 1167, 1118, 1070, 1042, 991, 964, 923, 852, 811, 779, 733, 698 cm^{-1}; LRMS (FAB+) *m/z* calculated for $C_{16}H_{21}O_4$ $[M+H]^+$ 277, found 277.



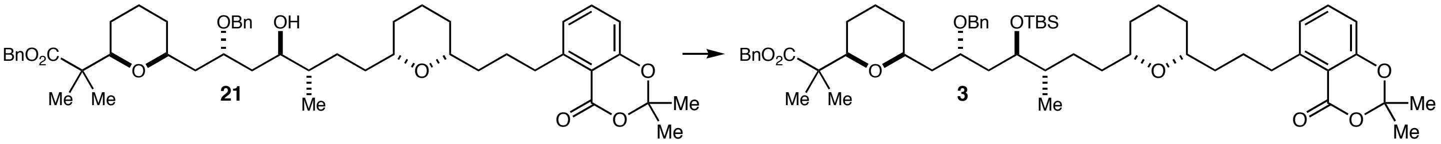
To a solution of alcohol **27** (0.644 g, 2.331 mmol) in 5 mL of CH_2Cl_2 was added diisopropylethylamine (3.96 mL, 23.31 mmol) followed by DMSO (0.414 mL, 5.83 mmol). To this solution was added sulfur trioxide-pyridine complex (1.113 g, 6.99 mmol) as a solid in one portion. The reaction mixture was stirred for 1 h and then quenched by the addition of 10 mL of saturated aqueous $NaHCO_3$. The mixture was diluted with 20 mL of diethyl ether and the layers were separated. The aqueous layer was extracted 2 x 15 mL EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 5:1 hexane/EtOAc to give ketone **19** (0.596 g, 2.173 mmol, 93% yield) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.35 (dd, *J1* = 7.8 Hz, *J2* = 13.3 Hz, 1H), 6.22 (dd, *J1* = 0.9 Hz, *J2* = 13.3 Hz, 1H), 5.82 (dd, *J1* = 0.9 Hz, *J2* = 7.8 Hz, 1H), 3.13-3.09 (m, 1H), 2.70 (t, *J* = 7.4 Hz, 2H), 1.97-1.89 (m, 2H), 1.70 (s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 160.0, 156.9, 146.9, 136.4, 135.1, 127.9, 125.0, 115.4, 111.9, 105.0, 39.5, 33.7, 25.8, 25.5; IR (NaCl, thin film) ν_{max}: 2997, 2942, 1777, 1737, 1680, 1606, 1582, 1479, 1447, 1402, 1390, 1379, 1312, 1270, 1209, 1168, 1142, 1101, 1048, 965, 924, 852, 811, 779, 697 cm^{-1}; LRMS (FAB+) *m/z* calculated for $C_{16}H_{19}O_4$ $[M+H]^+$ 275, found 275.



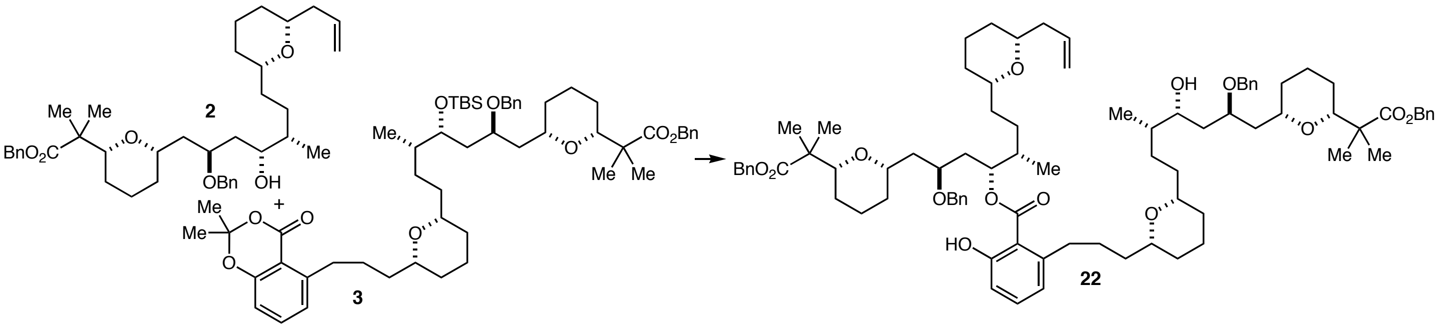
A solution of diol **5** (0.053 g, 0.094 mmol), enone **19** (0.064 g, 0.234 mmol) and second generation Grubbs catalyst (3.97 mg, 4.68 μmol) in CH_2Cl_2 (5 mL) was heated to reflux for 8 h. After cooling, the solution was concentrated and the residue was purified by flash column chromatography (5:1 hexane/acetone as eluent) to give enone **20** (0.0649 g, 0.080 mmol, 85 % yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.9, 1H), 7.32-7.22 (m, 10H), 6.94-6.78 (m, 3H), 6.14 (d, *J* = 15.9 Hz, 1H), 5.11 (d, *J* = 12.7 Hz, 1H), 5.06 (d, *J* = 12.7 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 3.89-3.79 (m, 1H), 3.77-3.61 (m, 2H), 3.51 (d, *J* = 9.8 Hz, 1H), 3.36-3.29 (m, 1H), 3.11-3.05 (m, 2H), 2.99 (br s, 1H), 2.66 (m, 2H), 2.45-2.22 (m, 2H), 1.97-1.82 (m, 3H), 1.78-1.33 (m, 17H), 1.23-1.10 (m, 9H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 176.8, 160.3, 157.2, 147.3, 143.7, 138.3, 136.3, 135.3, 132.4, 128.4, 127.9, 127.6, 125.2, 115.5, 112.0, 105.1, 82.3, 74.9, 74.3, 72.2, 71.1, 70.9, 66.1, 46.7, 40.4, 39.9, 39.4, 38.9, 36.1, 34.8, 33.7, 31.9, 28.1, 25.6, 25.0, 23.6, 21.5, 20.1, 15.6; IR (NaCl, thin film) ν_{max} : 3470, 2939, 2863, 1735, 1660, 1630, 1605, 1582, 1478, 1453, 1390, 1378, 1314, 1270, 1209, 1165, 1138, 1085, 1050, 924, 851, 810, 737, 698 cm^{-1}; $[\alpha]^{22}_D$ (*c* 1.00, CH_2Cl_2) +3.9°; LRMS (FAB+) *m/z* calculated for $C_{49}H_{65}O_{10}$ $[M+H]^+$ 813.5, found 813.9.



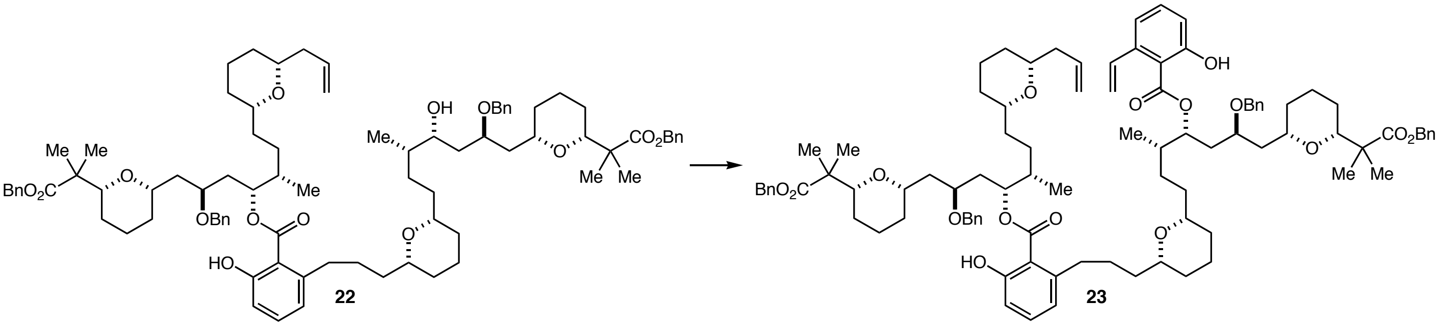
To a solution of enone **20** (0.065 g, 0.080 mmol) in 3:1 methanol/EtOAc (4 mL) was added Lindlar catalyst (8 mg) and the reaction mixture was stirred under 1 atm H_2 (balloon) for 40 min. The solution was filtered through a Celite pad and concentrated. The residue was dissolved in 4 mL of CH_2Cl_2 and the solution was cooled to -78 °C. To this solution was added triethylsilane (0.064 mL, 0.400 mmol) and boron trifluoride-diethyl etherate (0.012 mL, 0.096 mmol). After 3 h, the reaction mixture was warmed to 0 °C and quenched by the addition of 1 mL of sat. aq. NH_4Cl. The layers were separated. The aqueous layer was extracted with 2 x 2 mL of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (4:1 Hexane/EtOAc as eluent) afforded tetrahydropyran **21** (0.058 g, 0.073 mmol, 91% yield) as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37-7.20 (m, 11H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.13-5.02 (m, 2H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 3.89-3.79 (m, 1H), 3.70-3.60 (m, 1H), 3.49 (d, *J* = 9.8 Hz, 1H), 3.35-3.13 (m, 3H), 3.11-3.02 (m, 2H), 1.97-1.03 (m, 37H), 0.84 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.6, 160.2, 157.1, 148.2, 138.5, 136.4, 135.0, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 125.2, 115.1, 112.0, 104.9, 82.2, 78.2, 77.6, 75.0, 74.3, 72.0, 70.9, 66.0, 46.7, 39.7, 38.9, 36.4, 35.8, 34.2, 34.1, 31.9, 31.7, 31.5, 28.0, 27.1, 25.7, 25.6, 25.1, 23.7, 23.6, 21.3, 20.5, 15.2; IR (NaCl, thin film) ν_{max} : 3514, 2935, 2860, 1737, 1606, 1582, 1477, 1454, 1389, 1378, 1314, 1270, 1209, 1139, 1086, 1047, 923, 809, 735, 697 cm-^{1}; $[\alpha]^{22}_D$ (*c* 1.00, CH$_2$Cl$_2$) +1.1°; LRMS (FAB+) *m/z* calculated for $C_{49}H_{67}O_9$ $[M+H]^+$ 800, found 800.



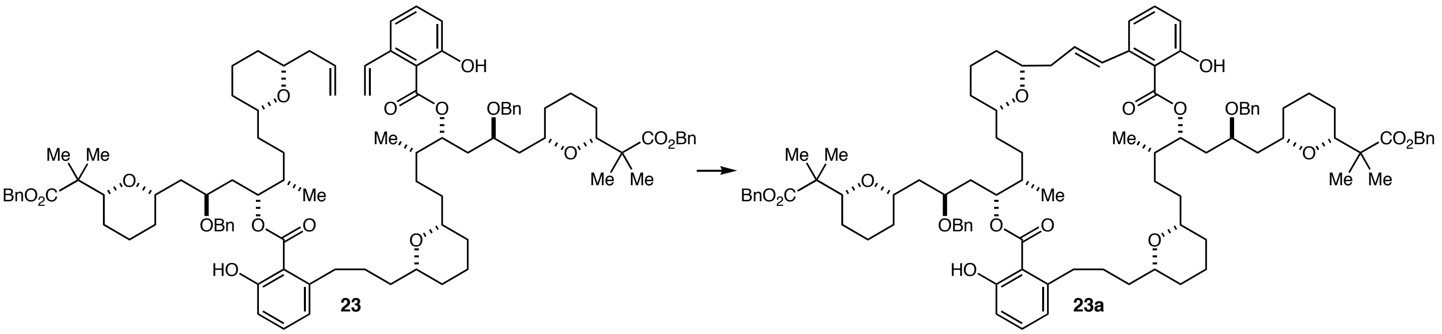
To a cooled (-78 °C) solution of tetrahydropyran **21** (0.055 g, 0.069 mmol) and triethylamine (0.020 ml, 0.145 mmol) in CH$_2$Cl$_2$ (1 mL) was added TBSOTf (0.024 mL, 0.103 mmol). The mixture was stirred for 40 min, warmed to ambient temperature and washed with 1 mL of saturated aqueous NH$_4$Cl. The aqueous layer was extracted with 2 x 2 mL EtOAc. The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated. The residue was purified by silica gel chromatography (10:1 Hex/EtOAc as eluent) to afford silyl ether **3** (0.062 g, 0.068 mmol, 99% yield) as a colorless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40-7.20 (m, 11H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.14 (d, *J* = 12.6 Hz, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 3.95-3.85 (m, 1H), 3.75-3.65 (m, 1H), 3.50-3.36 (m, 2H), 3.34-3.16 (m, 2H), 3.15-3.05 (m, 2H), 1.95-1.02 (m, 25H), 0.95-0.80 (m, 12H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.5, 160.1, 157.1, 148.2, 139.2, 136.4, 135.1, 135.0, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.1, 125.1, 115.0, 112.1, 112.0, 104.9, 104.8, 82.0, 78.0, 77.6, 75.1, 73.5, 72.4, 69.7, 65.9, 46.7, 41.2, 39.0, 37.4, 36.4, 34.7, 34.2, 31.7, 31.6, 28.8, 27.1, 26.0, 25.7, 25.6, 23.7, 23.6, 22.6, 22.4, 20.1, 18.1, 13.7, -4.2, -4.4; IR (NaCl, thin film) ν_{max} : 3032, 2934, 2857, 1739, 1606, 1583,1497, 1475, 1454, 1389, 1378, 1313, 1269, 1261, 1138, 1073, 1046, 966, 922, 835, 808, 774, 733, 697 cm-^{1}; $[\alpha]^{22}_D$ (*c* 1.15, CH$_2$Cl$_2$) +6.8°; LRMS (FAB+) *m/z* calculated for $C_{55}H_{81}O_9Si$ $[M+H]^+$ 914, found 914.



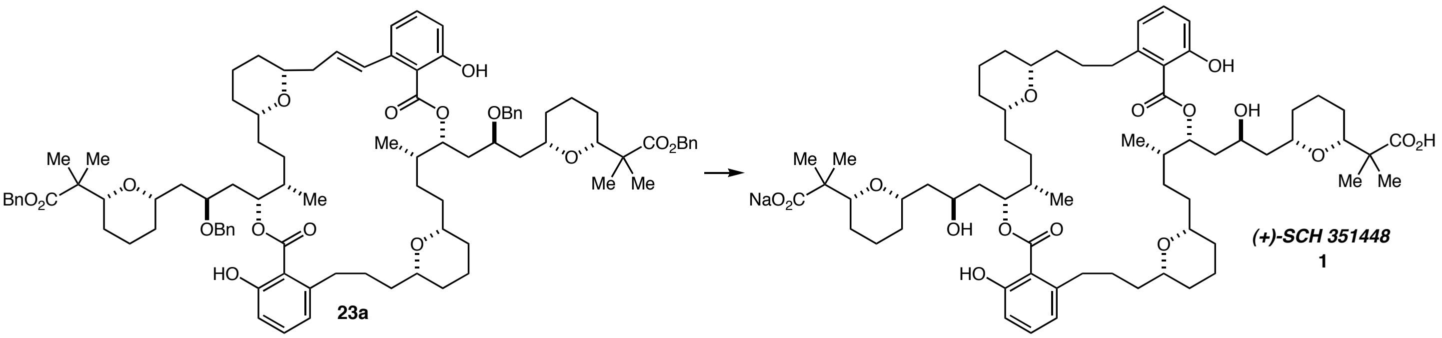
To a cooled (0 °C) solution of alcohol **2** (0.042 g, 0.068 mmol) in 0.35 ml of THF was added NaHMDS (0.046 ml, 0.092 mmol, 2.0 M in THF) and the reaction mixture stirred for 30 min. A solution of acetonide **3** (0.070 g, 0.077 mmol) in 0.45 mL of THF was then added and the reaction mixture was stirred for 30 min at 0 °C, and then 2 h at room temperature. The reaction was quenched by the addition of 1 mL of 1N HCl. The aqueous layer was extracted with 3 x 1 mL EtOAc. The combined organic layers were concentrated and the residue was dissolved in 1 mL of MeOH. 1 mL of 1N HCl solution in Et_2O was added and the mixture stirred for 2 h. The solvent was evaporated and the residue was loaded directly onto a silica gel column and chromatographed (3:1 Hex/EtOAc as eluent) to deliver alcohol **22** (0.0611 g, 0.045 mmol, 66% yield) as slightly yellow oil: ^{1}H NMR (300 MHz, C_6D_6) δ 11.78 (s, 1H), 7.45-7.40 (m, 1H), 7.36-6.95 (m, 21H), 6.66 (d, *J* = 7.1 Hz, 1H), 6.03-5.86 (m, 2H), 5.18 (d, *J* = 12.7 Hz, 1H), 5.14-4.98 (m, 5H), 4.53-4.37 (m, 4H), 4.06-3.76 (m, 2H), 3.83-3.73 (m, 1H), 3.63-3.51 (m, 2H), 3.48-3.03 (m, 8H), 2.69 (d, *J* = 4.1 Hz, 1H), 2.40-2.26 (m, 1H), 2.20-2.06 (m, 1H), 2.05-0.85 (m, 64H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 177.3, 172.0, 163.4, 146.4, 139.5, 139.4, 137.4, 136.3, 134.7, 129.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 123.1, 117.2, 116.6, 113.6, 83.2, 82.9, 79.3, 78.8, 78.7, 76.0, 75.6, 75.3, 73.9, 73.0, 72.2, 71.9, 67.1, 66.9, 47.7, 47.6, 42.0, 41.8, 40.7, 39.9, 37.8, 37.1, 37.0, 35.1, 35.0, 33.0, 32.9, 32.8, 32.5, 32.2, 30.7, 29.5, 29.0, 26.6, 26.1, 24.7, 24.6, 23.0, 22.3, 21.5, 21.0, 16.2; IR (NaCl, thin film) ν_{max} : 3468, 3032, 2933, 2859, 1731, 1650, 1605, 1497, 1453, 1374, 1312, 1265, 1213, 1164, 1087, 1049, 913, 816, 735, 697 cm-^{1}; $[\alpha]^{22}_D$ (*c* 0.28, CH_2Cl_2) +15.8°; LRMS (FAB+) *m/z* calculated for $C_{85}H_{117}O_{14}$ $[M+H]^+$ 1362, found 1362.



To a cooled (0 °C) solution of alcohol **22** (0.144 g, 0.106 mmol) in 0.60 mL was added NaHMDS (0.132 ml, 0.265 mmol, 2.0 M in THF). After 30 min, a solution of acetonide **4** (0.032 g, 0.159 mmol) in 0.25 mL of THF was added and the reaction mixture was stirred for 30 min at 0 °C, and then 1 h at room temperature. The reaction was quenched by the addition of 1 mL of 1N HCl. The layers were separated. The aqueous layer was extracted with 3 x 1 mL of ethyl acetate. The combined organic layers were concentrated, and the residue was loaded onto a silica gel column and eluted (4:1 Hex/EtOAc as eluent) to deliver bis-benzoyl ester **23** (0.101 g, 0.067 mmol, 63% yield) as slightly yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H), 11.21 (s, 1H), 7.39-7.11 (m, 23H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 5.88-5.72 (m, 1H), 5.61-5.48 (m, 2H), 5.38 (dd, *J1* = 1.5 Hz, *J2* = 17.3 Hz, 1H), 5.17 (dd, *J1* = 1.6 Hz, *J2* = 10.9 Hz, 1H), 5.07-4.90 (m, 6H), 4.50-4.41 (m, 2H), 4.49-4.25 (m, 2H), 3.62-3.12 (m, 10H), 2.98-2.81 (m, 2H), 2.30-2.21 (m, 1H), 2.19-2.03 (m, 1H), 1.92-1.01 (m, 68H), 0.98-0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 170.7, 170.4, 162.1, 145.1, 141.6, 138.6, 138.2, 136.1, 135.1, 134.0, 133.5, 128.2, 128.1, 127.9, 127.8, 127.6, 127.3, 121.9, 119.8, 117.1, 116.0, 115.5, 115.3, 112.5, 110.9, 81.9, 81.9, 77.8, 77.7, 76.8, 74.8, 74.6, 72.9, 72.7, 71.2, 71.0, 65.9, 46.7, 41.1, 40.9, 36.9, 36.8, 36.7, 36.2, 35.9, 34.2, 32.2, 32.0, 31.9, 31.6, 31.5, 31.4, 28.7, 28.4, 28.1, 25.7, 23.8, 22.2, 22.1, 20.2, 15.4, 15.2; IR (NaCl, thin film) ν_{max} : 3370, 3065, 3032, 2936, 2860, 1950, 1731, 1656, 1603, 1497, 1451, 1371, 1331, 1252, 1216, 1166, 1120, 1087, 1049, 914, 819, 735, 697 cm-^{1}; $[\alpha]^{24}_D$ (*c* 1.15, CH_2Cl_2) +28.5°; LRMS (FAB+) *m/z* calculated for $C_{94}H_{123}O_{16}$ $[M+H]^+$ 1508, found 1508.



A solution of bis-benzoyl ester **23** (0.022 g, 0.015 mmol) and second generation Grubbs catalyst (1.26 mg, 1.49 μmol) in 5 mL CH_2Cl_2 was heated to reflux for 8 h. After cooling, the solution was concentrated. The residue was purified by flash column chromatography (5:1 hexane/EtOAc as eluent) to give **23a** (0.018 g, 0.012 mmol, 83% yield) as oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 11.16 (s, 1H), 7.30-7.08 (m, 22H), 6.95 (d, *J* = 15.5 Hz, 1H), 6.80-6.65 (m, 3H), 6.51 (d, *J* = 7.3 Hz, 1H), 5.80-5.58 (m, 1H), 5.51-5.45 (m, 2H), 5.02-4.90 (m, 4H), 4.45-4.32 (m, 2H), 4.30-4.20 (m, 2H), 3.59-3.42 (m, 2H), 3.38-3.17 (m, 6H), 3.15-3.02 (m, 2H), 3.01-2.90 (m, 1H), 2.70-2.55 (m, 1H), 2.43-2.32 (m, 1H), 2.29-2.20 (m, 1H), 1.95-0.80 (m, 64H); 13C NMR (100 MHz, $CDCl_3$) δ 176.0, 171.0, 170.9, 162.1, 162.0, 145.2, 141.4, 138.4, 136.2, 136.1, 133.7, 133.4, 132.9, 128.8, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 122.0, 119.8, 116.3, 115.5, 112.4, 110.8, 81.9, 77.7, 77.6, 77.5, 77.2, 74.7, 73.1, 71.2, 71.1, 66.0, 65.9, 46.7, 41.0, 40.7, 38.0, 37.8, 37.5, 36.7, 34.3, 34.2, 32.1, 31.9, 31.5, 31.4, 31.3, 28.3, 27.8, 27.5, 25.7, 23.9, 23.8, 22.2, 20.0, 16.5, 16.4; IR (NaCl, thin film) ν_{max} : 3401, 3033, 2934, 2860, 1731, 1651, 1603, 1574, 1497, 1451, 1370, 1312, 1262, 1215, 1166, 1117, 1088, 1049, 1029, 916, 816, 735, 697 cm-^{1}; $[\alpha]^{24}_D$ (*c* 0.35, CH_2Cl_2) +58.9°; LRMS (FAB+) *m/z* calculated for $C_{92}H_{119}O_{16}$ $[M+H]^+$ 1480, found 1480.

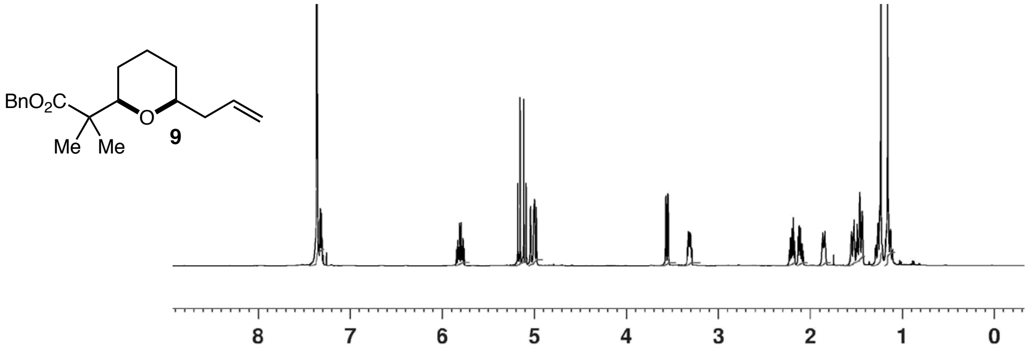


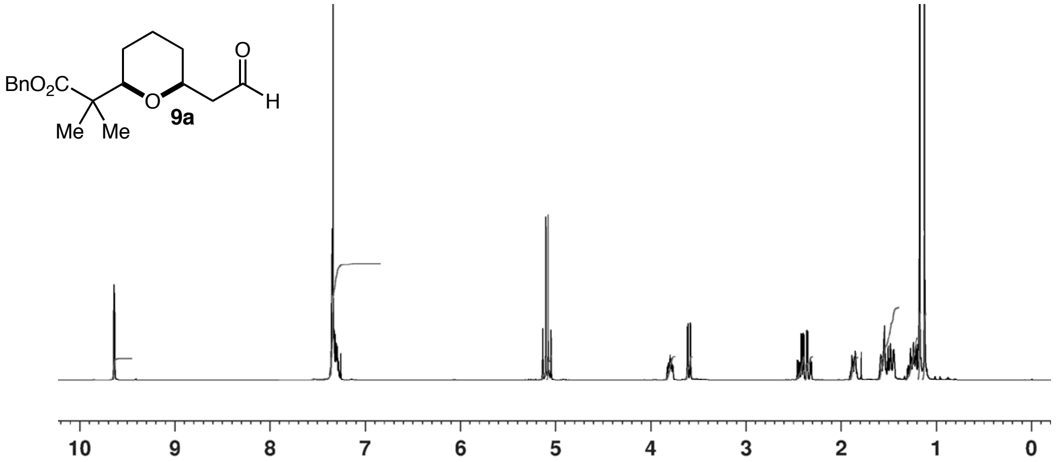
To a solution of **23a** (0.0097 g, 6.55 μmol) in a mixture of EtOAc (1 mL) and MeOH (3 mL), was added Pd/C (10% w/w, 1 mg) and the reaction mixture was stirred under 1 atm of H_2 (balloon) for 8 h. The solution was filtered and the filtrate was concentrated. The residue was diluted with 5 mL of hexane, and then washed with 2 mL of a 4 N HCl solution saturated with NaCl.[9] The aqueous layer was extracted with hexane (5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford (+)-SCH 351448 (**1**) (0.0052 g, 4.55 μmol, 69 % yield) as a white solid: ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.25 (t, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 7.4 Hz, 2H), 5.63-5.60 (m, 2H), 3.75-3.71 (m, 2H), 3.61-3.57 (m, 2H), 3.49 (d, *J* = 10.7 Hz, 2H), 3.18-3.08 (m, 6H), 2.56 (dt, *J1* = 12.5 Hz, *J2* = 3.9 Hz), 2.08-2.00 (m, 2H), 1.89-1.81 (m, 4H), 1.80-1.72 (m, 2H), 1.71-1.62 (m, 6H), 1.60-1.53 (m, 4H), 1.52-1.40 (m, 22H), 1.36-1.13 (m, 10H), 1.12 (s, 6H), 1.09 (s, 6H), 1.01 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 178.4, 171.1, 160.3, 145.1, 133.5, 122.3, 115.9, 115.4, 83.2, 79.1, 78.3, 78.1, 77.7, 67.4, 46.5, 43.7, 37.8, 37.4, 36.9, 36.6, 35.2, 32.9, 32.5, 31.9, 30.0, 29.5, 25.2, 24.3, 23.5, 23.2, 19.4, 15.1; IR (NaCl, thin film) ν_{max} : 3400, 2933, 2860, 1942, 1918, 1868, 1844, 1830, 1792, 1772, 1750, 1734, 1717, 1700, 1684, 1662, 1654, 1647, 1636, 1624, 1616, 1608, 1576, 1570, 1559, 1540, 1534, 1522, 1507, 1497, 1490, 1473, 1464, 1457, 1437, 1419, 1395, 1388, 1374, 1363, 1339, 1312, 1253, 1198, 1164, 1084, 1046 cm-^{1}; $[\alpha]^{25}_D$ (*c* 0.20, $CHCl_3$) +44.5°; LRMS (FAB+) *m/z* calculated for $C_{64}H_{96}O_{16}Na$ $[M+H]^+$ 1144, found 1144. HRMS (FAB+) *m/z* calculated for $C_{64}H_{96}O_{16}Na$ $[M+H]^+$ 1143.6596, found 1143.6593.

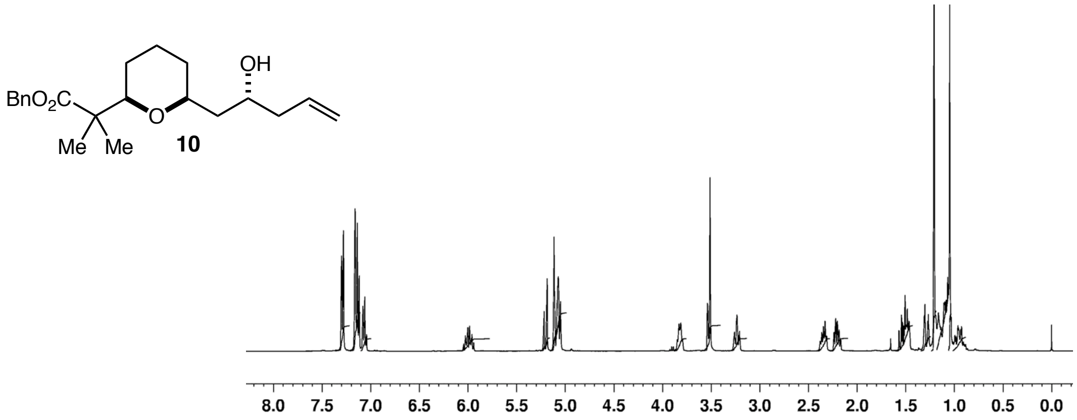
---

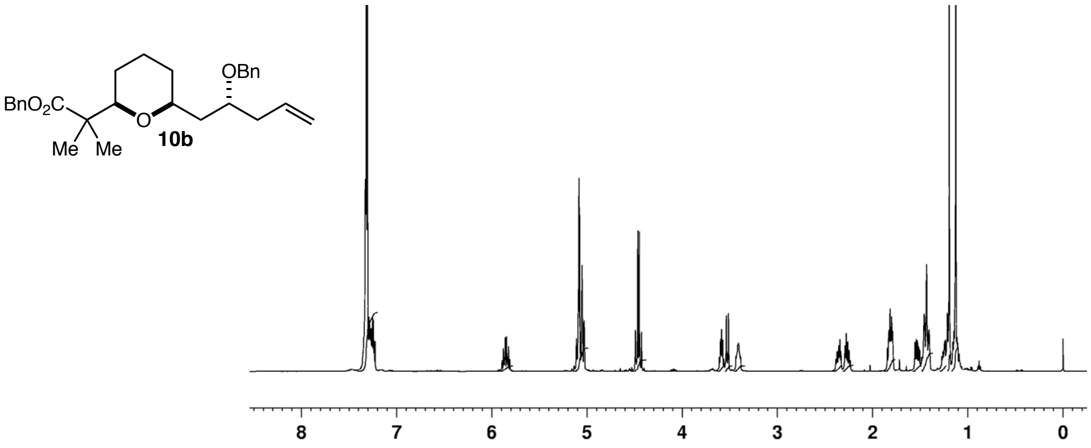
[9] Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680.

^{1}H NMR Spectra:

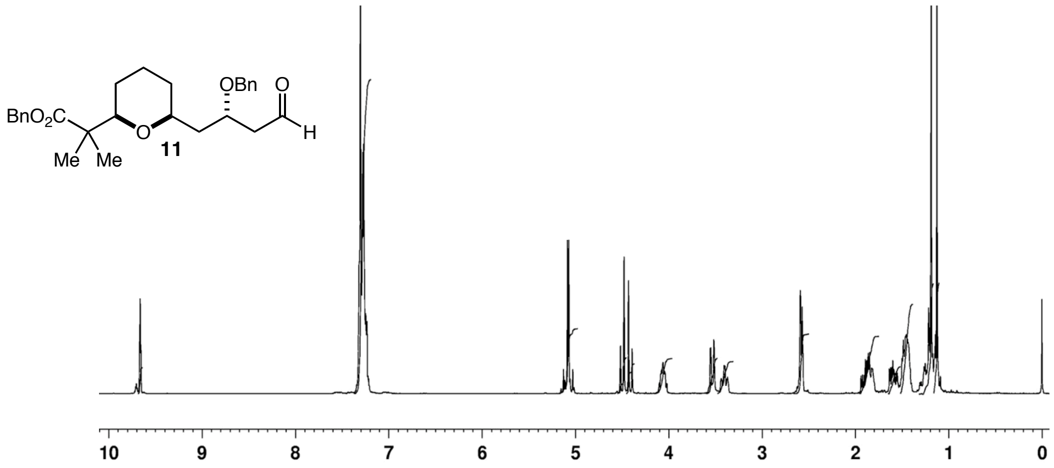




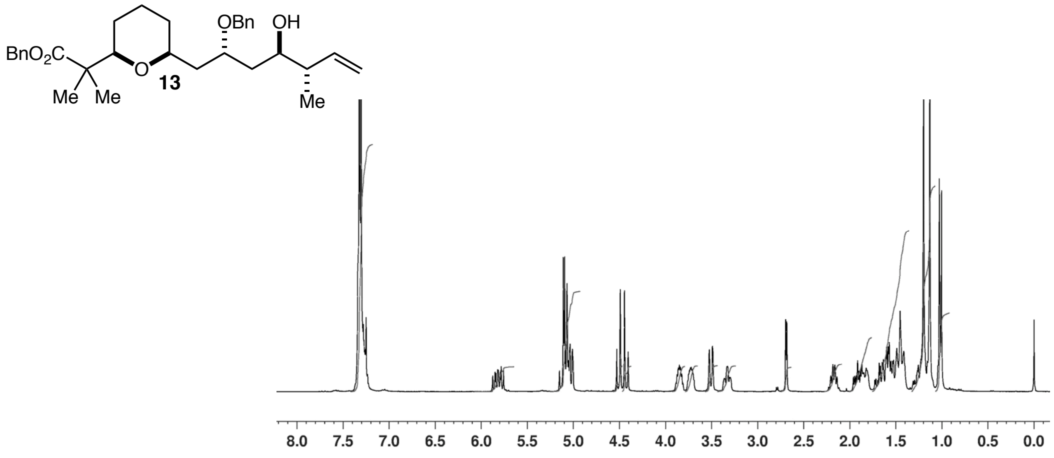



BnO$_2$C
OBn
O
Me
Me
8
7
6
5
4
3
2
1
0

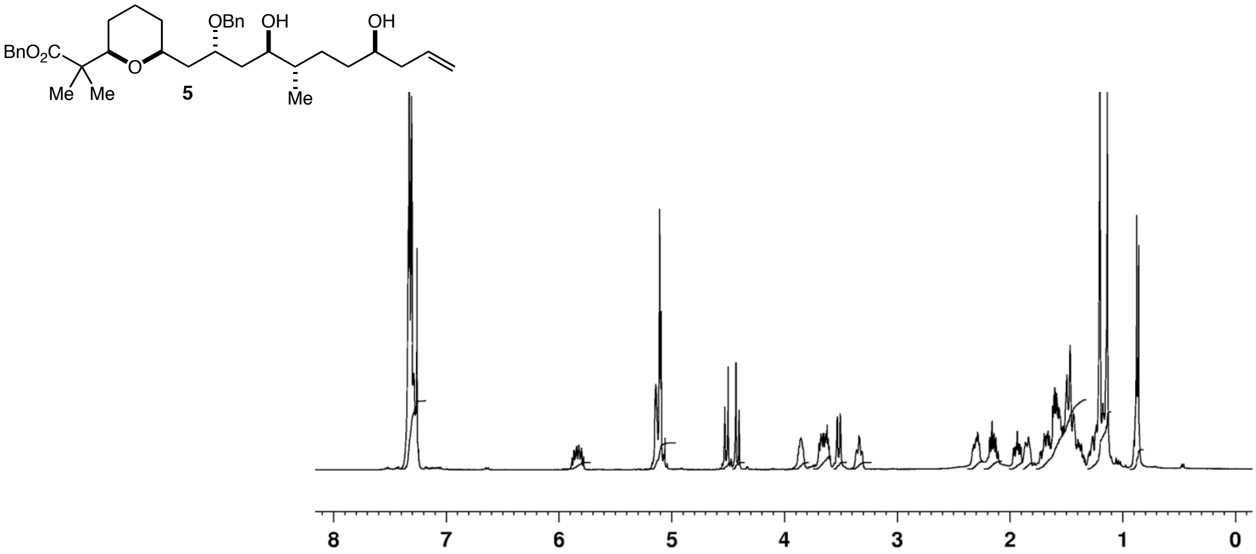
10b

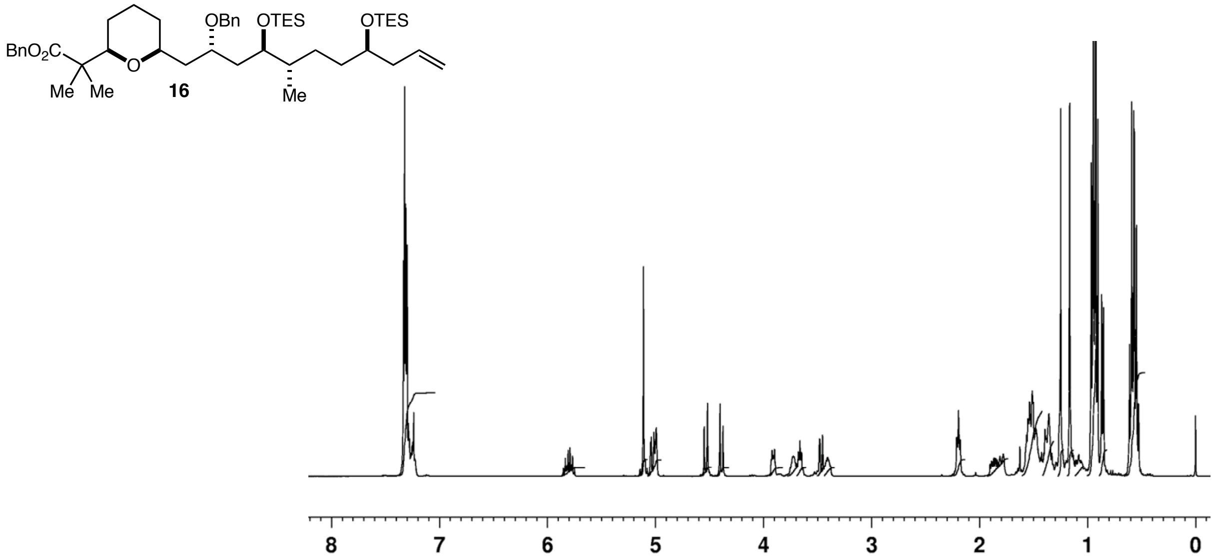

BnO$_2$C
OBn
O
O
H
Me
Me
10
9
8
7
6
5
4
3
2
1
0

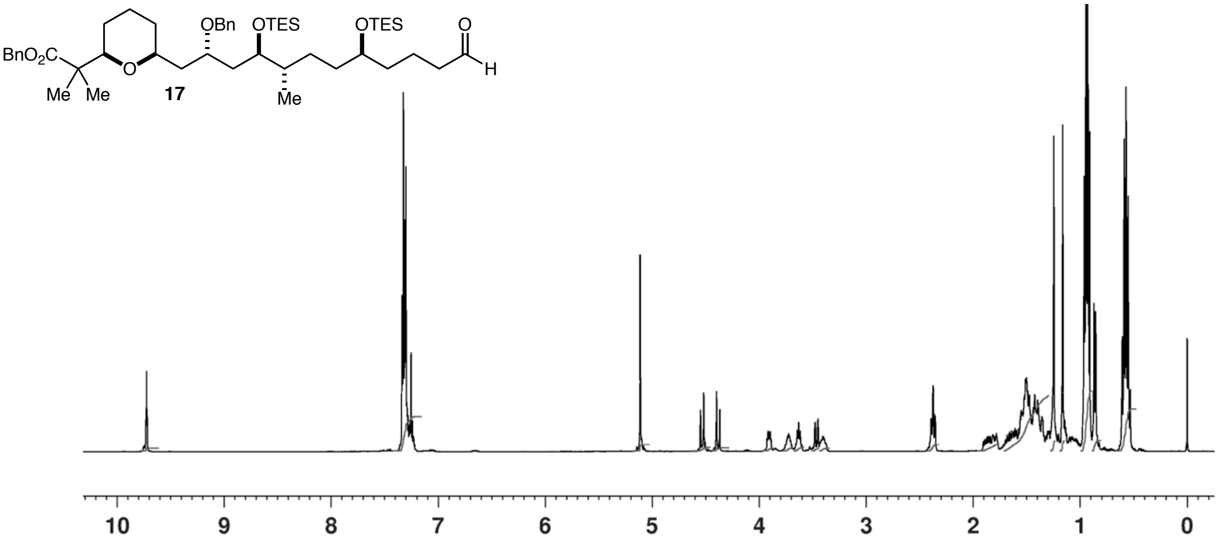
11

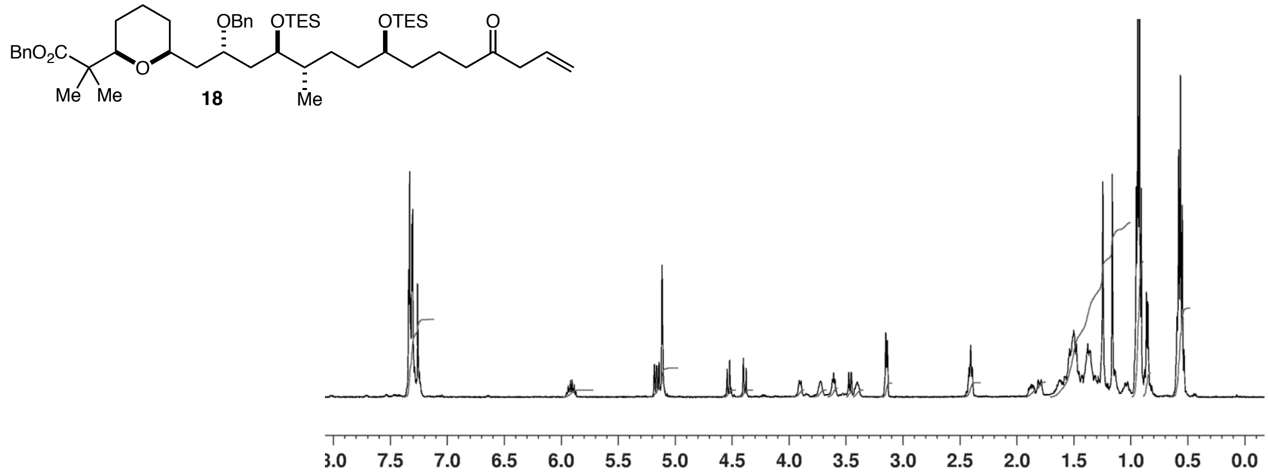

BnO$_2$C
OBn
OH
O
Me
Me
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

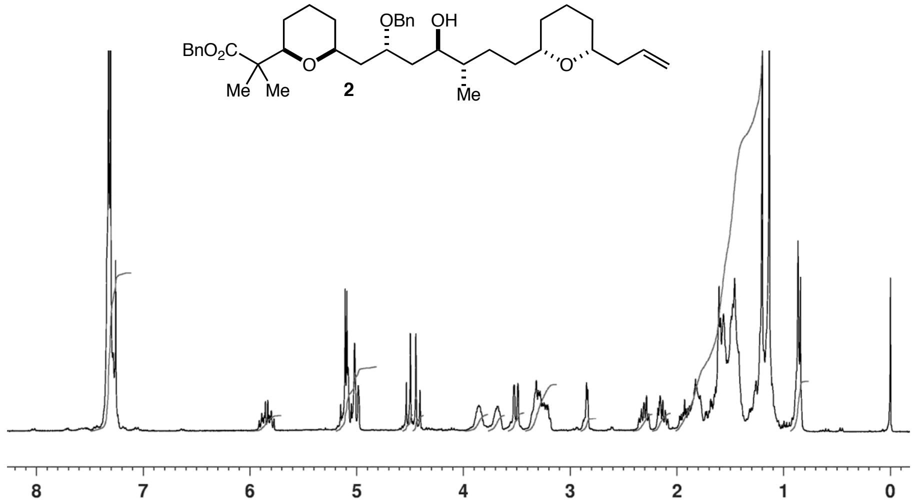
13

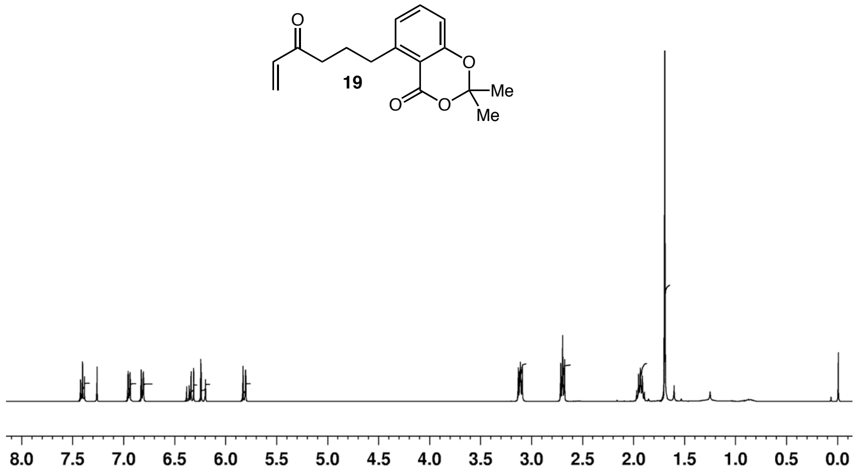

5
BnO2C
Me Me
OBn
OH
OH
Me
8
7
6
5
4
3
2
1
0

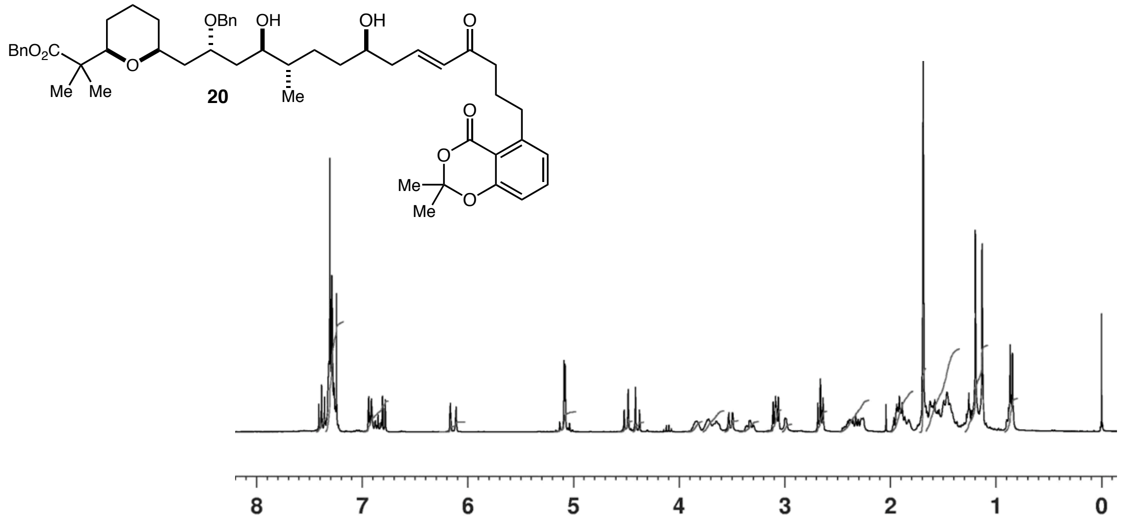

16
BnO2C
Me Me
OBn
OTES
OTES
Me
8
7
6
5
4
3
2
1
0


17
BnO2C
Me Me
OBn
OTES
OTES
O
H
Me
10
9
8
7
6
5
4
3
2
1
0


18
BnO$_2$C
Me Me
OBn
OTES
OTES
O
Me
3.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

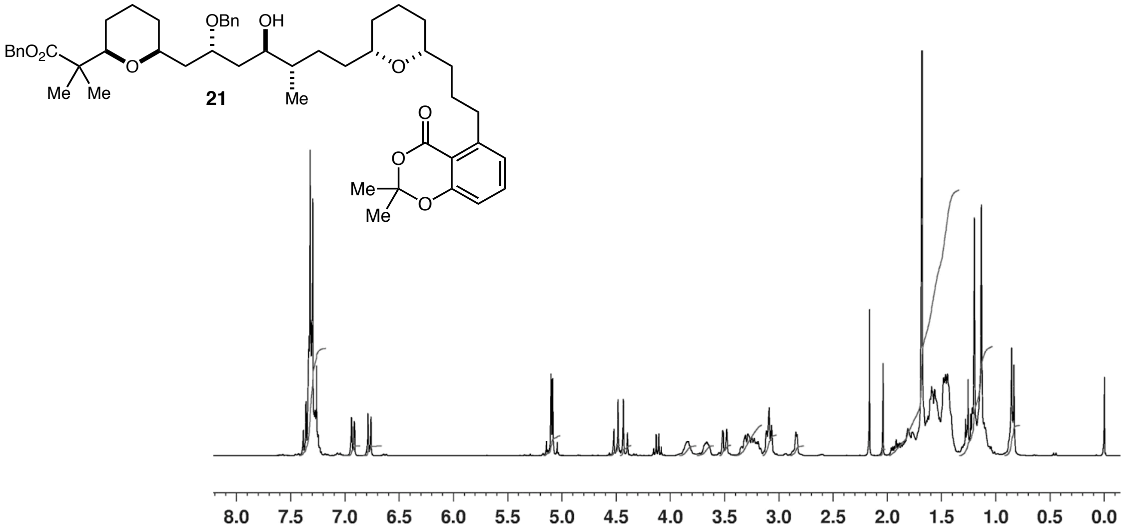

2
BnO$_2$C
Me Me
OBn
OH
O
O
Me
8 7 6 5 4 3 2 1 0


19
O
O
O
O
Me
Me
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0



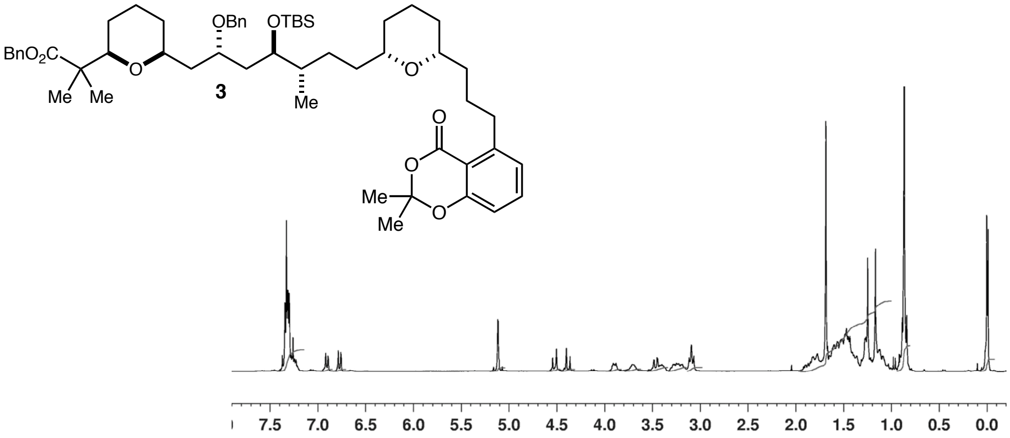
20

BnO2C
Me
Me
O
OBn
OH
OH
O
Me
O
O
O
Me
Me
8
7
6
5
4
3
2
1
0



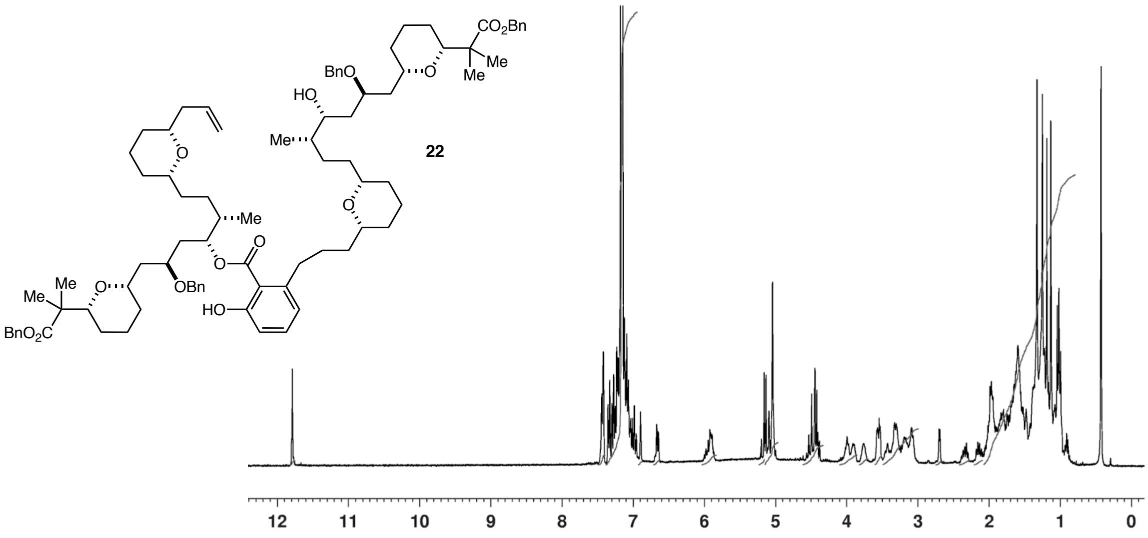
21

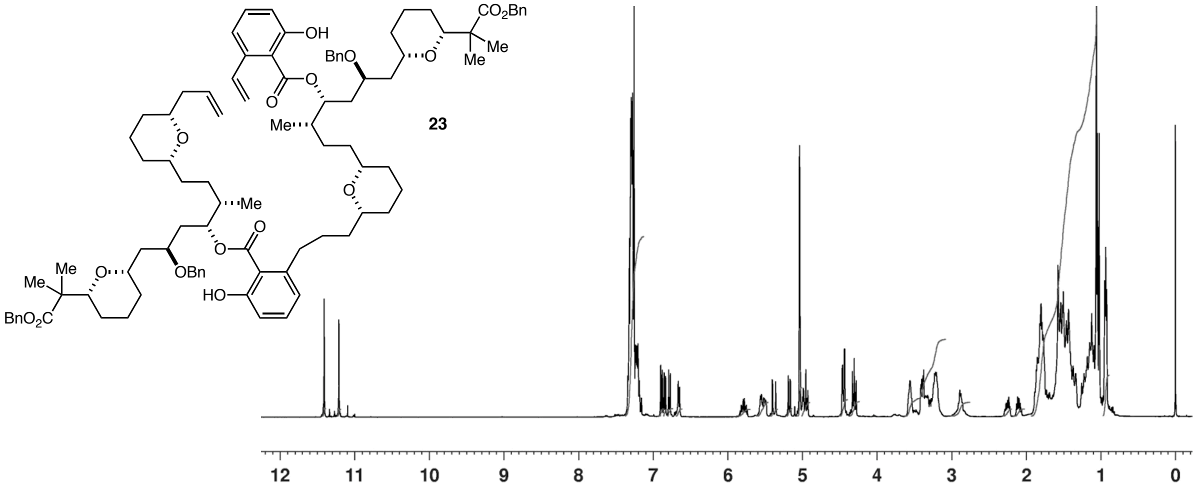
BnO2C
Me
Me
O
OBn
OH
Me
O
O
O
O
Me
Me
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

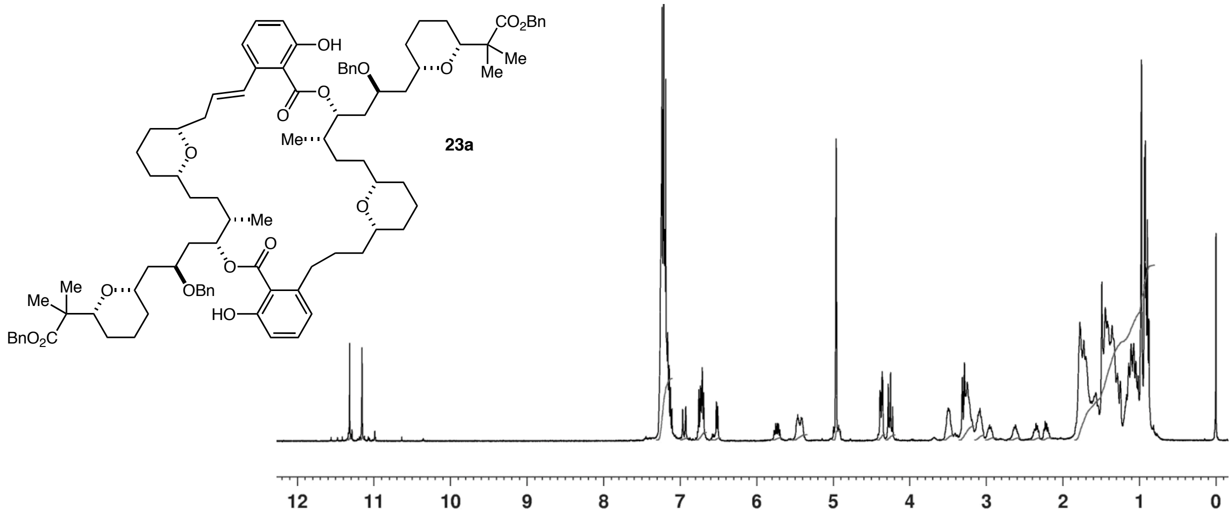


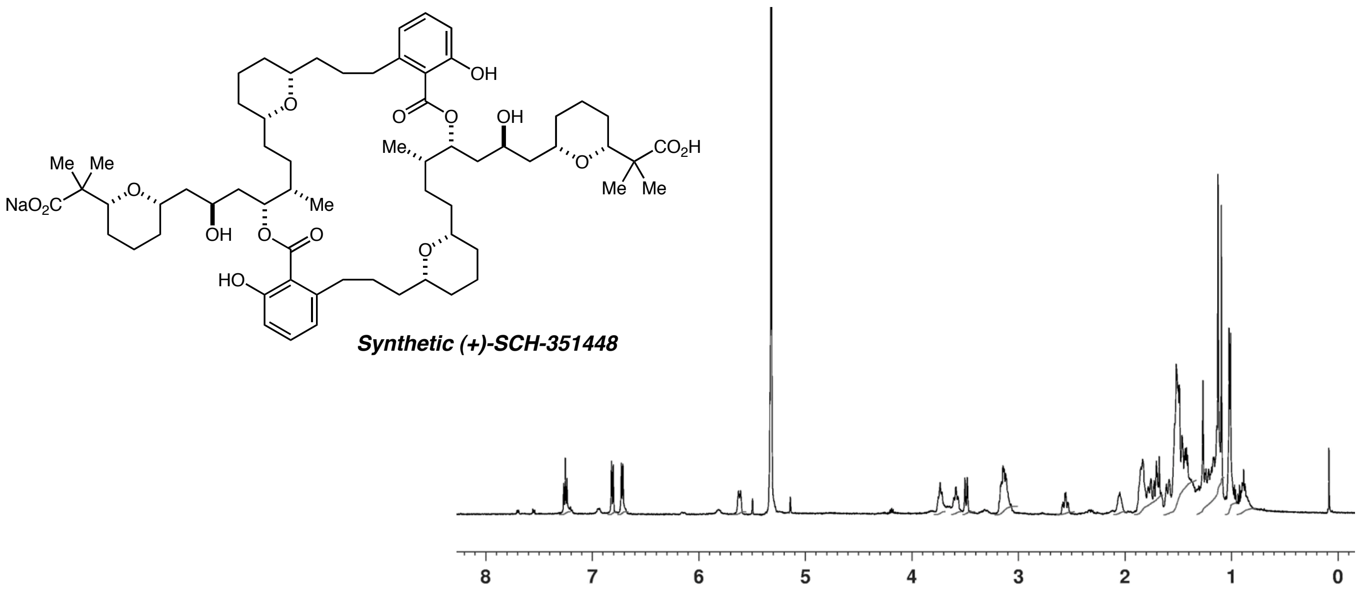
3

BnO2C
Me
Me
O
OBn
OTBS
Me
O
O
O
O
Me
Me
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


22
CO2Bn
Me
Me
BnO
HO
Me
O
O
Me
O
O
Me
Me
OBn
HO
BnO2C
12
11
10
9
8
7
6
5
4
3
2
1
0

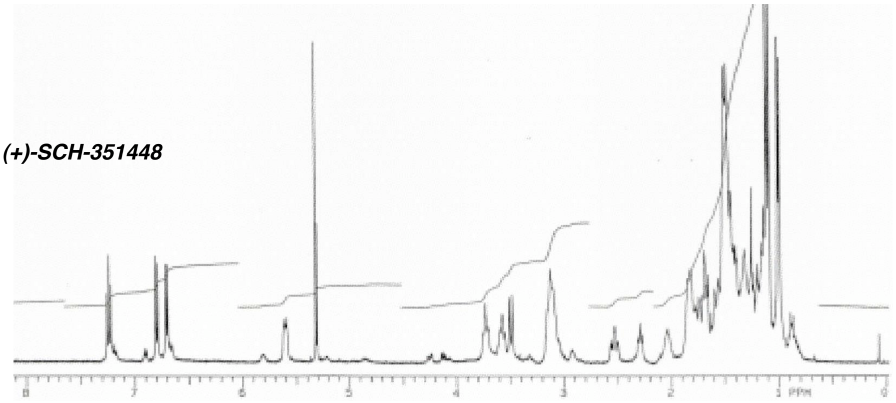

23
OH
CO2Bn
BnO
Me
Me
O
O
Me
O
O
Me
Me
Me
OBn
HO
BnO2C
12
11
10
9
8
7
6
5
4
3
2
1
0

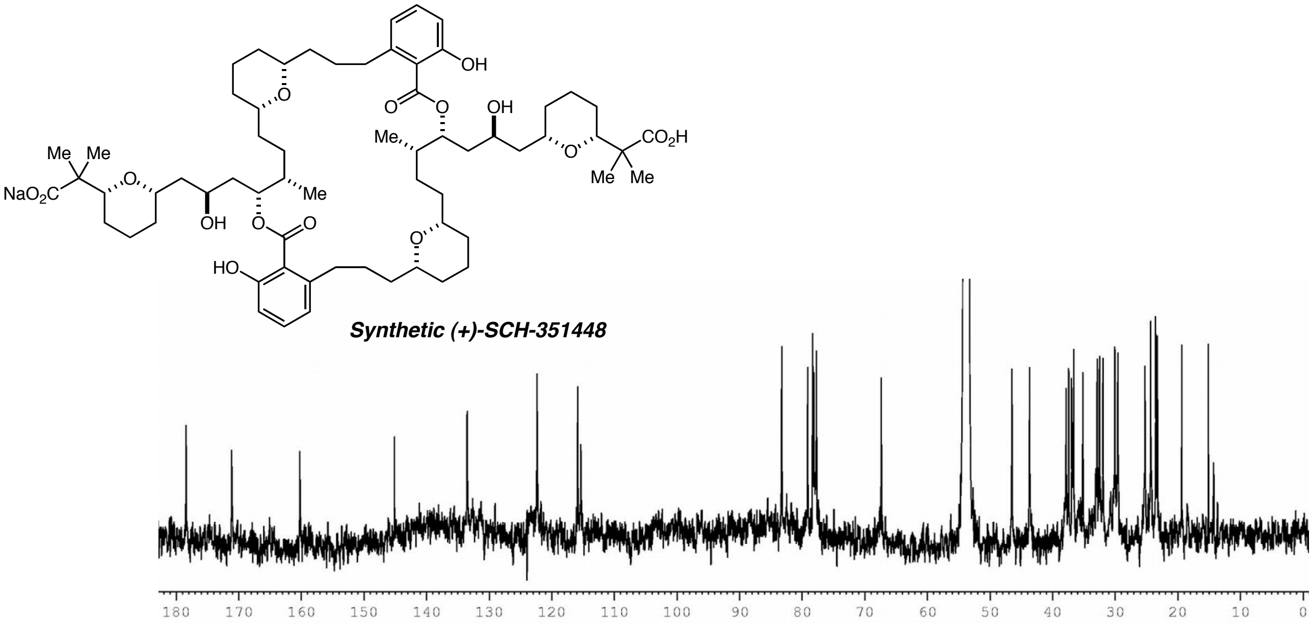

23a
OH
CO2Bn
BnO
Me
Me
O
O
Me
O
O
Me
Me
Me
OBn
HO
BnO2C
12
11
10
9
8
7
6
5
4
3
2
1
0



Synthetic (+)-SCH-351448

Natural (+)-SCH-351448





Synthetic (+)-SCH-351448

Natural (+)-SCH-351448