A Formal Synthesis of Psymberin

Supplemental Information

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General: Starting materials, reagents and solvents were purchased from commercial suppliers (Aldrich, Fischer, Advanced ChemTech) and used without further purification unless otherwise stated. All reactions were conducted in oven-dried (135 °C) glassware under an inert atmosphere of argon. The progress of reactions was monitored by silica gel thin layer chromatography (tlc) plates (mesh size 60Å with fluorescent indicator, Sigma-Aldrich), visualized under UV and charred using cerium or anisaldehyde stain. Products were purified by flash column chromatography (FCC) on 120-400 mesh silica gel (Fisher). Infrared (FTIR) spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on either a Varian-300 instrument (300 MHz) or a Varian-400 instrument (400 MHz) unless otherwise stated. Chemical shifts are reported in ppm relative to residual CHCl₃ signal. Data is reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), and coupling constants (Hz). Carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded on either a Varian-300 instrument (75 MHz) or a Varian-400 instrument (100 MHz) unless otherwise stated. Optical rotations were recorded at 25 °C using the sodium D line (589 nm), on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

To a solution of aldehyde **12** (1.65 g, 9.96 mmol) in DMF (12 ml) at 0 °C was added Hunig's base (5.2 ml, 29.9 mmol) and MOMCl (2.27 ml, 29.9 mmol). After stirring for 20 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl and then extracted with CH_2Cl_2 . The extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude was passed through a pad of silica gel and used for next step without further purification.

A solution of aldehyde (2.4 mg, 9.4 mmol) in 120 ml $\text{tBuOH-H}_2\text{O}$ (1:1) was cooled to 0 °C, to which was added $\text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O}$ (3.38 g, 28.2 mmol), 2-methyl-2-butene (12.1 ml from 2 M solution in THF, 28.2 mmol) and NaClO_2 (3.18 g, 28.2 mmol). After stirring for 4 h, the mixture was concentrated down, extracted with EtOAc and dried over Na_2SO_4 . The crude was passed through a pad of silica gel and used for next step without further purification.

A solution of acid (2.48 g, 9.2 mmol) in THF (25 ml) was treated with PPh_3 (4.82 g, 18.4 mmol) and MeOH (1.8 ml, 46 mmol) which was then cooled to 0 °C. DIAD (3.72 g, 18.4 mmol) was added to reaction mixture. After stirring for 12 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2 . The organic extracts were dried over Na_2SO_4 and concentrated down under reduced pressure. The crude was purified by FCC using hexane:ethyl acetate (10:1) as eluent to furnish ester **13** (2.43 g, 86% over 3 steps) as yellowish oil. IR ν_{max} (neat)/ cm^{-1} 2952, 2913, 2827, 1731, 1597, 1481, 1436, 1271, 1153, 923; ^1H NMR (400 MHz, CDCl_3) 6.77 (1H, s), 5.17 (2H, s), 5.13 (2H, s), 3.89 (3H, s), 3.46 (6H, s), 2.18 (3H, s), 2.11 (3H, s); ^{13}C NMR (100 MHz) 169.4, 156.5, 152.6, 135.6, 120.1, 119.5, 100.2, 95.3, 94.9, 56.4, 56.3, 52.3, 17.2, 11.6; m/z (ESIMS) calculated for $\text{C}_{14}\text{H}_{20}\text{O}_6\text{Na}$ $[\text{MNa}]^+$ 307.2, found: 307.2.

To a solution of K_2CO_3 (24.8 g, 180 mmol), TsN_3 (15.3 g, 78 mmol) in MeCN (400 mL) was syringed dimethyl-(2-oxapropyl) phosphonate (10.6 mL, 78 mmol) at rt. After stirring for 2 h, a solution of aldehyde **14** (13.3 g, 60 mmol) in 80 mL of MeOH was added. Stirring continued for 20 h, the mixture was concentrated under reduced pressure and then diluted with distilled water. The mixture was extracted with Et_2O and dried over Na_2SO_4 . Purification by FCC using ethyl acetate / hexane (1:20) afforded 11.4 g (85%) alkyne as a colorless oil. IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3290, 2970, 2934, 2100, 1612, 1586, 1513; ^1H NMR (400 MHz, CDCl_3) 7.28 (2H, d, $J = 8.4$ Hz), 6.88 (2H, d, $J = 8.4$ Hz), 4.54 (2H, s), 3.80 (3H, s), 3.29 (2H, s), 2.12 (1H, s), 1.23 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) 161.8, 159.1, 130.5, 129.1, 113.7, 90.3, 73.0, 68.1, 55.2, 32.2, 26.0. m/z (ESIMS) calculated for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Na}$ $[\text{MNa}]^+$ 241.12, found: 241.1.

To a solution of alkyne **14a** (6.3 g, 29.0 mmol) in THF (60 mL) was added $n\text{-BuLi}$ (21.0 mL, 33.0 mmol) at -78°C . After warming to 0°C and stirring for 30 min, the reaction mixture was cooled to -78°C and a solution of Weinreb amide (12.4 g, 34.7 mmol) in THF (40 mL) was added slowly. Stirring continued for 20 min at -78°C and for 1 h at 0°C and then the mixture was quenched with NH_4Cl solution. The mixture was extracted with CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:10) to give 11.1 g alkynone (72%) as a colorless oil. IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3068, 2950, 2925, 2200, 1696, 1673, 1612, 1513, 1427, 1110, 702; ^1H NMR (300 MHz, CDCl_3) 7.70-7.67 (4H, m), 7.44-7.35 (6H, m), 7.23 (2H, d, $J = 5.4$ Hz), 6.85 (2H, d, $J = 5.4$ Hz), 4.48 (2H, s), 4.29 (2H, s), 3.80 (3H, s), 3.3 (2H, s), 1.25 (6H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz) 186.3, 159.4, 135.7, 132.9, 130.4, 130.1, 129.3, 128.0, 113.9, 101.9, 78.9, 77.5, 73.2, 70.7, 55.4, 33.2, 26.9, 25.3, 19.5; m/z (ESIMS) calculated for $\text{C}_{32}\text{H}_{38}\text{O}_4\text{SiNa}$ $[\text{MNa}]^+$ 537.24, found: 537.3.

To a solution of Noyori catalyst in 60 ml iPrOH was added a solution of alkynone (15.0 g, 31.5 mmol) in 60 ml iPrOH. The mixture was stirred for 30 min, and then was concentrated in vacuo. Purification of the residue by FCC using hexane/ethyl acetate (1:10) furnished 15.0 g (98%) alcohol **15** as a colorless oil. $[\alpha]_D^{25} = -9.6$ ($c = 0.83$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3448, 3070, 2955, 2930, 2238, 1612, 1513, 1427, 1247, 1112, 702; ^1H NMR (300 MHz, CDCl_3) 7.71-7.65 (4H, m), 7.45-7.35 (6H, m), 7.24 (2H, d, $J = 5.4$ Hz), 6.84 (2H, d, $J = 5.4$ Hz), 4.49-4.45 (3H, m), 3.80-3.66 (4H, m), 1.20 (6H, s), 1.06 (9H, s); ^{13}C NMR (100 MHz) 159.2, 135.8, 135.7, 133.3, 133.1, 130.8, 130.7, 130.0, 129.3, 128.0, 113.9, 91.8, 78.3, 78.0, 73.1, 67.9, 63.9, 63.5, 55.5, 32.5, 26.9, 26.1, 19.5; m/z (ESIMS) calculated for $\text{C}_{32}\text{H}_{40}\text{O}_4\text{SiNa}$ $[\text{MNa}]^+$ 539.26, found: 539.4.

A solution of PPh_3 (6.9 g, 26.3 mmol) in 100 mL THF was cooled to -15°C and was added DIAD (5.17 ml, 26.3 mmol). The mixture was stirred for 10 min then a solution of alcohol **15** (9.05 g, 17.5 mmol) in 80 mL THF was added. After 10 min, NBSH (5.7 g, 26.3 mmol) in 100 mL THF was added at -15°C . Stirring continued after warming to rt for 12 h. The solvent was removed under vacuum and the crude was directly purified by FCC (silica gel, hexane/ethyl acetate 1:15) to afford allene (**15a**) (6.2 g, 70%) as a colorless oil. $[\alpha]_D^{25} = -35.7$ ($c = 1.82$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3070, 2958, 2930, 1962, 1612, 1513, 1112, 702; ^1H NMR (300 MHz, CDCl_3) 7.73-7.67 (4H, m), 7.42-7.26 (6H, m), 7.23 (2H, d, $J = 5.7$ Hz), 6.86 (2H, d, $J = 5.7$ Hz), 5.35-5.22 (2H, m), 4.43 (2H, s), 4.20 (2H, dd, $J = 2.7, 6.0$), 3.80 (3H, s), 3.15 (2H, s), 1.04 (9H, s), 1.02 (3H, s), 1.01 (3H, s); m/z (ESIMS) calculated for $\text{C}_{32}\text{H}_{40}\text{O}_3\text{SiNa}$ $[\text{MNa}]^+$ 523.26, found: 523.3.

To a solution of allene (6.25 g, 12.4) in CH_2Cl_2 (80 mL) was added buffer (8 mL, pH=7.40) and cooled to 0 °C. DDQ was added to the mixture and stirred for 30 min. The reaction mixture was quenched with NaHCO_3 , diluted with H_2O , extracted with CH_2Cl_2 and dried over Na_2SO_4 . Solvent was evaporated and the residue was purified by FCC using hexane/ethyl acetate (20:1) as eluent to furnish alcohol **16** (4.65 g, 98%) as a colorless oil. IR ν_{max} (neat)/ cm^{-1} 3419, 3071, 2959, 2930, 2858, 1962, 1471, 1427, 1112, 702; ^1H NMR (400 MHz, CDCl_3) 7.70-7.68 (4H, m), 7.45-7.36 (6H, m), 5.36-5.31 (1H, m), 5.17-5.14 (1H, m), 4.20-4.17 (2H, m), 3.42 (1H, d, $J=10.8$ Hz), 3.31 (1H, d, $J=10.8$ Hz), 1.05 (9H, s), 1.01 (6H, s); ^{13}C NMR (100 MHz) 201.9, 135.7, 133.6, 129.9, 127.9, 100.9, 93.7, 71.5, 62.0, 37.7, 26.9, 25.1, 24.9, 19.4; m/z (ESIMS) calculated for $\text{C}_{24}\text{H}_{32}\text{O}_3\text{2iNa}$ $[\text{MNa}]^+$ 403.2, found: 403.3.

A solution of alcohol (6.4 g, 16.8 mmol) in CH_2Cl_2 (100 mL) was treated with Dess-Martin Periodinone at room temperature. After stirring for 2 h, the mixture was quenched with a 2:1 (v/v) mixture of saturated NaHCO_3 and saturated $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 and solvent was removed in vacuo. The crude was passed through a pad of silica gel and used for next step without further purification.

To the solution of aldehyde (5.2 g, 13.7 mmol) in THF (80 mL) at -78 °C was added the ethynyl magnesium bromide solution slowly. After stirring for 5 min, the reaction mixture was placed in refrigerator for 12 h. The mixture was quenched with saturated NH_4Cl at cold temperature, extracted with CH_2Cl_2 and then dried over Na_2SO_4 . The crude was passed through a pad of silica gel and used for next step without further purification. Diastreomeric ratio was determined by ^1H NMR as 1:1. The crude alcohol was dissolved in CH_2Cl_2 (100 mL) and treated with Dess-Martin periodinone (8.2 g, 19.3 mmol) at room temperature. The mixture was stirred for 30 min and then

quenched with a 2:1 (v/v) mixture of saturated NaHCO_3 and saturated $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous phase was extracted with CH_2Cl_2 and dried over Na_2SO_4 . Evaporation of the solvent and then purification by FCC using hexane/ethyl acetate (20:1) as eluent afforded ketone (5.4 g, 80% over three steps) as a colorless oil. IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3269, 3071, 2961, 2931, 2091, 1964, 1680, 1464, 1427, 1112, 702; ^1H NMR (400 MHz, CDCl_3) 7.68-7.66 (4H, m), 7.42-7.35 (6H, m), 5.48-5.43 (1H, m), 5.35-5.32 (1H, m), 4.24-4.22 (2H, m), 3.13 (1H, s), 1.27 (6H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz) 203.3, 190.3, 135.7, 133.7, 129.9, 127.9, 97.6, 95.2, 80.8, 79.8, 61.9, 48.5, 27.0, 24.1, 23.8, 19.4; m/z (ESIMS) calculated for $\text{C}_{26}\text{H}_{30}\text{O}_2\text{SiNa}$ $[\text{MNa}]^+$ 425.19, found: 425.2.

A solution of S-(CBS) (2.6 g, 9.32 mmol) in THF (40 mL) at $-30\text{ }^\circ\text{C}$ was treated with $\text{BH}_3\cdot\text{SMe}_2$ (4.66 mL, 9.32 mmol, 2.0 M in THF). After stirring for 15 min, a solution of ketone (3.57 g, 8.80 mmol) in THF was added over the course of 10 min. The reaction mixture was stirred for 1 h and quenched with MeOH. The mixture was concentrated down and purified by FCC using hexane/ethyl acetate (1:30) as eluent to furnish alcohol (3.20 g, 90%, dr: 10:1) as a colorless oil. $[\alpha]_{\text{D}}^{25} = -83.5$ ($c = 1.70$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3303, 3071, 2961, 2930, 1953, 1472, 1427, 1112, 701; ^1H NMR (400 MHz, CDCl_3) 7.70-7.67 (m, 4H), 7.44-7.36 (m, 6H), 5.38 (dd, 1H, $J = 6.0, 12.0\text{ Hz}$), 5.27 (m, 1H), 4.21 (m, 2H), 4.06 (dd, 1H, $J = 2.4, 6.4\text{ Hz}$), 2.41 (d, 1H, $J = 2.0\text{ Hz}$), 2.16 (d, 1H, $J = 6.8\text{ Hz}$), 1.11 (s, 3H), 1.11 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz) 202.8, 135.6, 133.6, 133.5, 129.7, 127.7, 98.9, 93.9, 74.1, 70.2, 62.1, 40.3, 26.8, 24.1, 23.3, 19.2; m/z (ESIMS) calculated for $\text{C}_{26}\text{H}_{32}\text{O}_2\text{SiNa}$ $[\text{MNa}]^+$ 427.21, found: 427.2.

To a solution of allene (3.0 g, 7.42 mmol) in CHCl_3 (100 mL) was added DMDO in CHCl_3 (115 mL, 22 mmol) slowly at 0 °C. The mixture was stirred for 40 min at 0 °C, followed by addition of MeOH (100 ml). After stirring for 12 h at room temperature the mixture was concentrated down in vacuo. Purification by FCC using hexane/ethyl acetate (25:1) as eluent provided ketone **22** (2.33 g, 72 %) as a colorless oil. The ratio was 8:1, as determined by NMR. $[\alpha]_D^{25} = +6.76$ ($c = 1.05$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3500, 3285, 3071, 2962, 2931, 1732, 1471, 1428, 1113, 701; ^1H NMR (400 MHz, CDCl_3) 7.70-7.56 (4H, m), 7.48-7.36 (6H, m), 5.16 (1H, d, $J = 2.4$ Hz), 4.26 (2H, s), 4.0= 5 (1H, dd, $J = 11.6, 3.6$ Hz), 3.90 (1H, dd, $J = 11.6, 3.6$ Hz), 3.5 (1H, brs), 2.57 (1H, d, $J = 2.4$ Hz), 1.05 (9H, s), 1.04 (3H, s), 1.01 (3H, s); ^{13}C NMR (100 MHz) 208.6, 161.9, 135.75., 13c cd26, 135.0, 132.0, 130.1, 129.6, 128.0, 127.7, 81.5, 81.1, 79.1, 75.2, 73.1, 66.0, 44.4, 26.8: 6.6, 23.2, 19.1, 14.9; m/z (ESIMS) calculated for $\text{C}_{26}\text{H}_{34}\text{O}_4\text{SiNa}$ $[\text{MNa}]^+$ 459.20, found: 459.2.

To a solution of ketone **22** (2.03 g, 4.6 mmol) and $\text{Me}_4\text{NBH}(\text{OAc})_3$ (6.12 g, 23.3 mmol) , in CH_3CN (40 mL) at -40 °C was added acetic acid (10.0 mL). After 5 min, the reaction mixture was warmed to -20 °C and kept at -20 °C for 48 h. The mixture was quenched with saturated NaHCO_3 at cold temperature, extracted with CH_2Cl_2 and dried over Na_2SO_4 . Solvent was removed in vacuo and then the crude was purified by FCC using hexane/ethyl acetate (1:2) as eluent to give diol **22** (1.50 g, 74 %) as a white foam. $[\alpha]_D^{25} = +25.0$ ($c = 1.00$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3436, 3304, 3071, 2960, 2931, 1723, 1471, 1427, 1113, 702; ^1H NMR (400 MHz, CDCl_3) 7.72-7.69 (4H, m), 7.44-7.39 (6H, m), 4.30 (1H, d, $J = 2.4$ Hz), 4.2 (1H, q, $J = 5.2$ Hz), 4.07 (1H, dd, $J = 11.2, 4.8$ Hz) , 4.00-3.92 (2H, m), 3.55 (1H, d, $J = 8$ Hz), 2.48 (1H, d, $J = 2.4$ Hz), 1.10 (6H, s), 1.07 (9H, s); ^{13}C NMR (75 MHz) 135.8, 132.6, 130.1, 128.0, 80.5, 76.7, 75.2, 73.7, 71.4, 70.7, 63.2, 56.8, 39.9, 27.2, 24.3, 19.5; m/z (ESIMS) calculated for $\text{C}_{32}\text{H}_{40}\text{O}_3\text{SiNa}$ $[\text{MNa}]^+$ 461.21, found: 461.3.

To a solution of diol **23** (1.14 g, 2.6 mmol) in THF (20 mL, containing trace amount of water) at 0 °C was added NaH (832 mg, 10.4 mmol, 60% dispersion in mineral oil) and the mixture was stirred for 10 min. To this was added a solution of TsCl in 6mL THF and 200 μ l H₂O. After stirring for 30 min, the mixture was quenched with saturated NH₄Cl, extracted with CH₂Cl₂ and dried over Na₂SO₄. Solvent was removed and then the crude was purified by FCC using hexane/ethyl acetate (20:1) as eluent to furnish epoxide **24** (760 mg, 70%) as a colorless oil. $[\alpha]_D^{25} = -8.9$ ($c = 1.23$, CHCl₃); IR $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3285, 3071, 2960, 2930, 1471, 1427, 1113, 702; ¹H NMR (400 MHz, CDCl₃) 7.71-7.68 (4H, m), 7.50-7.40 (6H, m), 4.26 (1H, t, $J = 4.4$ Hz), 4.20 (1H, 2.4 Hz), 3.95-3.87 (1H, m), 3.38 (1H, d, $J = 4.0$ Hz), 3.00 (1H, d, $J = 4.0$ Hz), 2.51 (1H, d, $J = 2.4$ Hz), 1.24 (3H, s), 1.18 (3H, s), 1.09 (9H, s); ¹³C NMR (100 MHz) 135.6, 133.1, 129.9, 127.8, 80.1, 75.7, 70.7, 70.2, 64.9, 58.4, 53.1, 33.4, 26.8, 24.2, 21.6, 19.2; m/z (ESIMS) calculated for C₂₆H₃₂O₃Si Na [MNa]⁺ 443.20, found: 443.3.

To a solution of epoxide **24** (0.61 mg, 1.45 mmol) in Et₂O (10 mL) at 0 °C was added DIBAL (4.35 mL, 4.35 mmol, 1.0 M in hexane) at one portion. After 10 min, the reaction mixture was quenched with saturated Rochelle's salt and diluted with Et₂O. The resulting biphasic solution was stirred for 1 h. The layers were separated, and then the aqueous layer was extracted with Et₂O and dried over Na₂SO₄. Solvent was concentrated in vacuo and the crude was purified by FCC using hexane/ethyl acetate (10:1) as eluent to afford alcohol (489 mg, 80%) as a colorless oil. $[\alpha]_D^{25} = +2.44$ ($c = 0.41$, CHCl₃); IR $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3454, 3285, 3070, 2957, 2930, 1472, 1427, 1112, 702; ¹H NMR (400 MHz, CDCl₃) 7.69-7.67 (4H, m), 7.41-7.38 (6H, m), 4.40-4.20 (2H, m), 3.75 (2H, d, $J = 4.8$ Hz), 2.60-2.59 (1H, m), 2.38 (1H, d, $J = 8.4$ Hz), 2.04-1.97 (1H, m), 1.71-1.66 (1H, m); m/z (ESIMS) calculated for C₂₆H₃₄O₃SiNa [MNa]⁺

445.22, found: 445.3.

To a solution of alcohol (360 mg, 0.85 mmol) in DMF (10 mL) at 0 °C was added Hunig's base (1.5 mL, 8.53 mmol) followed by MOMCl (0.65 mL, 8.53 mmol). The reaction mixture was stirred for 24 h at room temperature, and then quenched with saturated NH_4Cl solution. The resulting mixture was extracted with CH_2Cl_2 . The organic layers were washed with H_2O , dried over Na_2SO_4 and concentrated under reduced pressure under reduced pressure in vacuo. The crude was purified by FCC using ethyl acetate/hexane (1:20) to give product **25** as colorless oil (390 mg, 97%). $[\alpha]_D^{25} = +0.91$ ($c = 1.10$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3288, 3071, 2949, 2930, 1472, 1428, 1042, 702; ^1H NMR (400 MHz, CDCl_3) 7.70-7.67 (4H, m), 7.41-7.39 (6H, m), 4.70 (1H, d, $J = 6.8$ Hz), 4.60 (1H, d, $J = 7.2$ Hz), 4.22-4.18 (2H, m), 3.74 (2H, J = 9.2 Hz), 3.55-3.52 (1H, m), 3.38 (3H, s), 1.94-1.89 (2H, m), 1.10 (3H, s), 1.07 (9H, s), 1.06 (3H, s); ^{13}C NMR (100 MHz) 135.7, 133.4, 129.7, 127.7, 95.9, 81.3, 77.8, 74.0, 71.7, 70.4, 65.9, 55.5, 37.9, 28.3, 26.8, 24.7, 19.2, 18.8; m/z (ESIMS) calculated for $\text{C}_{28}\text{H}_{38}\text{O}_4\text{SiNa}$ $[\text{MNa}]^+$ 489.24, found: 489.3.

To the 2-methyl-2-butene (2.30 mL of 2 M solution in THF, 4.60 mmol) cooled to 0 °C was added $\text{BH}_3\cdot\text{SMe}_2$ (1.15 mL of 1M solution in THF, 2.30 mmol) dropwise. The ice-bath was removed and the mixture was stirred for 1 h. The reaction mixture was cooled to 0 °C, to which was added a solution of alkyne **25** (356 mg, 0.76 mmol) in THF slowly. The mixture was stirred for 30 min at room temperature and cooled back to 0 °C. The reaction mixture was quenched with a precooled solution of 4 mL of 3N NaOH and 1.4 mL of 30% H_2O_2 dropwise. The resulting mixture was stirred for 30 min at room temperature, then and extracted with CH_2Cl_2 . The organic layers were

24.0, 19.3, 15.7, 11.5; IR ν max (neat) / cm^{-1} 3481, 2884, 2860, 1781, 1697, 1474, 1428, 1386, 1210, 1110, 1040, 914; m/z (ESIMS) calculated for $\text{C}_{41}\text{H}_{55}\text{O}_8\text{NSiNa}$ $[\text{MNa}]^+$ 740.36, found: 740.4.

To a suspension of $\text{CH}_3(\text{CH}_3\text{O})\text{NH}\cdot\text{HCl}$ (170 mg, 1.73 mmol) in 3.0 mL THF at 0°C was added AlMe_3 in toluene (0.80 mL, 1.0 M) slowly. The mixture was allowed to warm to room temperature and stirred for 30 min. The reaction was cooled again to 0°C and the aldol product (410 mg, 0.572 mmol) in 3 mL THF was added. The ice bath was removed and the reaction mixture was stirred for 2 h. Saturated Rochelle's salt solution was added to quench the reaction. After stirring for 30 min, the mixture was diluted with distilled water and extracted with CH_2Cl_2 . The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3) to give 331 mg product (96%) as white foam. $[\alpha]_D^{25} = +8.2$ (CHCl_3 , $c = 0.85$); ^1H NMR (400 MHz, CDCl_3) 7.69 (m, 4H), 7.42 (m, 6H), 4.65 (d, 1H, $J = 6.8$ Hz), 4.55 (d, 1H, $J = 6.8$ Hz), 4.31 (d, 1H, $J = 0.8$ Hz), 3.92 (m, 1H), 3.81 (dd, 1H, $J = 8.0, 10.8$ Hz), 3.64 (s, 3H), 3.57 (dd, 1H, $J = 5.2, 10.4$ Hz), 3.53 (dd, 1H, $J = 2.0, 10.8$ Hz), 3.39 (dd, 1H, $J = 4.8, 9.2$ Hz), 3.34 (s, 3H), 3.17 (s, 1H), 2.99 (br, 1H), 1.77 (m, 3H), 1.62 (m, 1H), 1.20 (d, 3H, $J = 6.8$ Hz), 1.06 (s, 9H), 0.92 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) 177.1, 135.9, 135.8, 133.4, 130.0, 128.0, 128.0, 96.1, 79.9, 78.3, 73.5, 71.5, 64.4, 61.6, 55.7, 40.7, 38.4, 32.6, 28.1, 26.9, 24.1, 19.3, 15.6, 13.6; IR ν max (neat)/ cm^{-1} 3484, 3072, 3048, 2880, 2852, 1659, 1471, 1428, 1389, 1112, 1040, 916; m/z (ESIMS) calculated for $\text{C}_{33}\text{H}_{51}\text{O}_7\text{NSiNa}$ $[\text{MNa}]^+$ 624.33, found: 624.4.

To a solution of the Weinreb amide (296 mg, 0.492 mmol) in 5.0 mL DMF at room

temperature was added imidazole (100 mg, 1.47 mmol) and TESCl (148 mg, 0.980 mmol). After stirring 1 h at room temperature, the reaction was quenched with water and extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was filtered through a pad of silica gel with ethyl acetate/hexane 1:5. The filtrate was concentrated and dissolved in 5 mL THF. The solution was cooled to -78 °C followed with the slow addition of DIBAL in hexane (1.35 mL, 1.0 M). After stirring at -78 °C for 30 min, the reaction was quenched with saturated Rochelle's salt solution. The mixture was stirred at room temperature for 30 min and extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:8) to give 292 mg compound **27** (90% over two steps) as colorless oil. $[\alpha]_D^{25} = -6.2$ (CHCl₃, c = 0.65); ¹H NMR (400 MHz, CDCl₃) 9.57 (s, 1H), 7.68 (m, 4H), 7.40 (m, 6H), 4.70 (d, 1H, J = 7.2 Hz), 4.60 (d, 1H, J = 6.8 Hz), 4.52 (m, 1H), 4.00 (m, 1H), 3.75 (dd, 1H, J = 5.6, 10.4 Hz), 3.66 (dd, 1H, J = 5.2, 10.4 Hz), 3.55 (dd, 1H, J = 4.0, 8.0 Hz), 3.38 (s, 3H), 3.36 (m, 1H), 2.50 (ddd, 1H, J = 2.8, 6.8, 14.0 Hz), 2.14 (m, 1H), 1.83 (m, 2H), 1.62 (ddd, 1H, J = 2.4, 10.0, 14.0 Hz), 1.07 (s, 9H), 1.01 (d, 3H, J = 6.8 Hz), 0.99 (s, 3H), 0.92 (m, 12H), 0.56 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) 204.9, 135.8, 135.8, 133.4, 130.0, 130.0, 128.0, 127.9, 96.3, 79.0, 76.4, 70.3, 68.5, 66.6, 55.7, 49.4, 37.9, 33.5, 28.9, 27.1, 24.8, 19.3, 17.1, 7.0, 6.2, 5.3; IR ν max (neat)/cm⁻¹, 3068, 3051, 2877, 1732, 1471, 1428, 1389, 1147, 1105, 1041, 919; *m/z* (ESIMS) calculated for C₃₇H₆₀O₆Si₂Na [MNa]⁺ 679.38, found: 679.4.

Na₂SO₄ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:3) to give recovered aldehyde **27** (43 mg, 35%) and 104 mg product **29** (63%, 94% based on starting material, 81 mg desired isomer **28**, 23 mg undesired isomer) as a colorless oil. $[\alpha]_D^{25} = +57.0$ (CHCl₃, c = 1.28); ¹H NMR (400 MHz, CDCl₃) 7.62 (m, 4H), 7.28 (m, 6H), 6.86 (s, 1H) 5.26 (m, 4H) 4.70 (d, 1H, J = 6.8 Hz) 4.60 (d, 1H, J = 6.8 Hz), 4.16 (ddd, 1H, J = 2.4, 8.0, 12.0 Hz), 4.06 (m, 1H), 3.94 (m, 1H), 3.73 (m, 2H), 3.63 (dd, 1H, J = 4.0, 10.0 Hz), 3.56 (m, 1H), 3.54 (s, 3H), 3.48 (s, 3H), 3.37 (s, 3H), 2.83 (dd, 1H, J = 2.0, 16.0 Hz), 2.16 (dd, 1H, J = 12.0, 16.0 Hz), 2.04 (m, 1H), 1.90 (s, 1H), 1.83 (m, 3H) 1.67 (m, 2H), 1.04 (m, 12H), 0.95 (s, 3H), 0.87 (m, 12H), 0.52 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) 163.4, 159.5, 158.8, 141.6, 135.9, 135.8, 133.5, 133.1, 129.9, 129.9, 127.9, 127.9, 117.4, 109.7, 102.1, 96.3, 96.1, 94.6, 79.2, 78.9, 77.4, 76.2, 70.7, 69.2, 68.2, 66.1, 56.8, 56.6, 55.7, 40.4, 38.1, 33.4, 30.0, 28.6, 27.1, 25.8, 24.4, 19.3, 15.5, 11.2, 9.0, 7.2, 5.6 ; IR ν_{max} (neat)/cm⁻¹, 3064, 3044, 1724, 1589, 1466, 1152, 1095, 1046, 1009; *m/z* (ESIMS) calculated for C₅₀H₇₆O₁₁Si₂Na [MNa]⁺ 931.48, found: 931.6.

To a solution of compound **29** (45 mg, 0.050 mmol) in 2 mL CH₂Cl₂ at 0 °C was added catechol borane bromide (200 mg, 1.00 mmol) in 2 mL CH₂Cl₂. The mixture was stirred at 0 °C for 1 h and quenched with THF/NaHCO₃ solution. After dilution with distilled water and extraction with CH₂Cl₂, the combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was filtrated through a pad of silica gel with ethyl acetate/hexane 1:2. The filtrate was concentrated and dissolved in 1 mL CH₂Cl₂. To the solution was added 1mL pyridine and 0.5 mL acetic anhydride. The reaction mixture was stirred at room temperature for 30 min and then diluted with CH₂Cl₂, washed with 1 M HCl. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:4) to give 31 mg product (75%) as a colorless oil. $[\alpha]_D^{25} = +46.2$ (CHCl₃, c = 0.52); ¹H NMR (400 MHz, CDCl₃) 7.65 (m, 4H), 7.30 (m, 6H), 7.22 (m, 1H), 5.00 (dd, 1H, J = 4.4, 8.8 Hz), 4.15 (m, 1H), 3.98 (m, 1H), 3.80 (dd,

1H, J= 5.2, 10.4 Hz), 3.68(dd, 1H, J = 4.4, 10.4 Hz), 3.53 (dd, 1H, J= 2.0, 10.8 Hz), 2.84 (dd, 1H, J= 2.4, 16.4 Hz), 2.36 (s, 3H), 2.34 (s, 3H), 2.14 (m, 2H), 2.09 (s, 3H), 2.02 (m, 2H), 1.95 (s, 3H), 1.83 (s, 3H), 1.78 (m, 2H), 1.11 (d, 3H, J= 6.8Hz), 1.06 (s, 9H), 0.97 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) 170.6, 170.6, 169.8, 168.4, 162.1, 153.1, 150.6, 141.7, 135.9, 135.8, 133.2, 133.0, 130.0, 129.9, 128.0, 127.9, 125.9, 117.0, 116.0, 78.6, 76.4, 74.7, 71.7, 66.2, 39.0, 37.2, 30.2, 29.3, 27.9, 27.1, 24.2, 22.4, 21.4, 21.4, 21.3, 21.0, 19.2, 16.3, 12.1, 9.4; IR ν max (neat)/ cm^{-1} 1774, 1731, 1369, 1240, 1191; m/z (ESIMS) calculated for $\text{C}_{46}\text{H}_{58}\text{O}_{12}\text{SiNa}$ $[\text{MNa}]^+$ 853.36, found: 853.4.

To a solution of TBDPS-protected alcohol (21 mg, 0.025 mmol) in 0.8 mL pyridine at 0 °C was added 0.2 mL HF. pyridine. The mixture was stirred at 0 °C for 30 min and then stirred at room temperature for 30 min. The reaction mixture was quenched with NaHCO_3 solution and extracted with CH_2Cl_2 . The combined organic extracts were washed with 1.0 M HCl, dried over Na_2SO_4 , and then concentrated under reduced pressure. The residue was filtrated through a pad of silica gel with ethyl acetate. The filtrate was concentrated under reduced pressure and dissolved in 1 mL CH_2Cl_2 . To the solution was added Dess-Martin reagent (42 mg, 0.100 mmol). The reaction mixture was stirred at room temperature for 30 min, quenched with water and extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (silica gel, ethyl acetate/hexane 1:1) to give 11 mg compound **29** (74%) as a white foam. $[\alpha]_D^{25} = +67.6$ (CHCl_3 , $c = 0.68$); ^1H NMR (400 MHz, CDCl_3); 9.57 (s, 1H), 6.82 (s, 1H), 5.41 (m, 1H), 4.48 (dd, 1H, J= 4.8, 11.7 Hz), 4.36 (m, 2H), 3.38 (t, 1H, J= 6.0Hz), 3.15 (dd, 1H, J= 3.0, 16.8 Hz), 2.92 (dd, 1H, J= 10.8, 16.8Hz), 2.40 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H), 2.28 (dd, 1H, J= 2.0, 4.8, 13.2 Hz); 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.93 (m, 1H), 1.83 (m, 2H), 1.17 (d, 3H, J= 6.9 Hz), 0.95 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) 201.9, 170.8, 170.4, 169.8 168.5, 162.0, 153.2, 150.7, 141.5, 126.0, 117.1, 116.2, 79.0, 78.0, 77.9, 73.8, 71.8, 38.8, 37.8, 31.1, 29.2, 25.5,