Rhenium Catalyzed Coupling of Propargyl Alcohols and Allyl Silanes

Michael R. Luzung, F. Dean Toste

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720

Supporting Information

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. ACS grade nitromethane was obtained from Aldrich Chemical Company. Tetrahydrofuran (THF) and toluene were dried according to a procedure by Bergman.¹ *mer*-[ReOCl₃(dppm)] was prepared according to literature procedures.² Extracts were dried over MgSO₄ and solvents were removed *in vacuo* via a rotary evaporator at aspirator pressure. TLC analysis of reaction mixtures was performed on Merck silica gel 60 F254 TLC plates. Chromatography was carried out on ICN SiliTech 32-63 D 60 Å silica gel. ¹H and ¹³C NMR spectra were recorded with Bruker AMX-300 and AMX-400 spectrometers and referenced to CDCl₃ unless otherwise noted. When ¹³C{H} NMR spectra were obtained with mixtures of diastereomers, some resonances overlapped. Therefore, the correct number of resonances may not be listed. Mass spectral and CHN data were obtained from the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

Representative procedure for generation of propargyl alcohol substrates

To 2.00 g (10.8 mmol) of 4-bromobenzaldehyde in a 100 mL flask was added 50 mL of dry THF. After cooling to 0 °C, 0.5 M 1-propynylmagnesium bromide (28.1 mL, 14.1 mmol) was added to the reaction mixture dropwise *via* syringe, then brought to room temperature and stirred for an additional two hours. The mixture was quenched with a saturated aqueous solution of ammonium chloride (NH₄Cl) and the aqueous layer was extracted with ether (Et₂O) (3 X 40 mL). The organic layers were then combined, washed with brine (3 X 40 mL), dried, and concentrated *in vacuo*. Flash chromatography eluting with 5:1 hexanes:ether affords 1-(4-bromophenyl)-2-butyne-1-ol, which solidified on standing (2.25 g, 92% yield).

Representative procedure for rhenium catalyzed substitutions

1-(4-Methoxyphenyl)-2-butyne-1-ol (100 mg, 0.57 mmol) was added to a 1 dram vial, with a threaded cap, containing three equivalents of allyltrimethylsilane (195 mg, 1.7 mmol). To the vial was then added (dppm)ReOCl₃ (16.7 mg, 0.023 mmol, 4 mol %) and NH₄PF₆ (3.7 mg, 0.023 mmol, 4 mol %) in a solution of 2.3 mL of nitromethane (0.25 M of the propargylic alcohol). The resulting green mixture was stirred at 65 °C for approximately 2 hrs, with the course of the reaction being monitored at intervals by thin layer chromatography. After completion, the reaction mixture was concentrated *in vacuo* and chromatographed directly. Flash chromatography eluting with hexanes affords the allyl adduct (109 mg, 96%) as a pale yellow oil.

Representative procedure for catalyst recovery

The substitution reaction was performed similarly to the above procedure, except that the reaction took place at room temperature. After completion and *in vacuo* concentration of the reaction mixture, the resulting green oil was dissolved in methylene chloride. The catalyst was precipitated by addition of hexanes or ethyl ether. The solid was collected by filtration, washed with H₂O and Et₂O to give the recovered catalyst (70-100% recovered).

Purified by chromatography on silica gel (hexanes); pale yellow oil (90%). ¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.30 (m, 3H), 7.26-7.20 (m, 2H), 5.94-5.80 (m, 1H), 5.09-5.03 (m, 2H), 3.68 (tt, 1H, *J* = 6.9, 2.4 Hz), 2.48, (t, 2H, *J* = 6.9 Hz), 2.25 (td, 2H, *J* = 6.9, 2.1 Hz), 1.58-1.28 (m, 4H), 0.94 (t, 3H, *J* = 7.2 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 142.2, 135.9, 128.3, 127.5, 126.6, 116.7, 83.8, 81.1, 43.1, 38.1, 31.2, 22.0, 18.5, 13.7 ppm; HRMS (EI) calc'd for C₁₆H₂₀: 212.1565, found: 212.1561.

Purified by chromatography on silica gel (hexanes); pale yellow oil (79 %). ¹H NMR (CDCl₃, 300 MHz) δ 7.37-7.25 (m, 10H), 6.02-5.89 (m, 1H), 5.17-5.10 (m, 2H), 3.95 (t, 1H, *J* = 6.9 Hz), 2.63 (t, 2H, *J* = 6.9 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 141.4, 135.5, 131.7, 128.5, 128.3, 127.9, 127.6, 126.9, 123.7, 117.1, 90.9, 83.9, 42.9, 38.6 ppm; HRMS (EI) calc'd for C₁₈H₁₆: 232.1252, found: 232.1252.

Purified by chromatography on silica gel (hexanes); colorless oil (82 %). ¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.22 (m, 5H), 5.92-5.79 (m, 1H), 5.08 (d, 1H, *J* = 3.9 Hz), 5.03 (s, 1H), 3.73 (t, 1H, *J* = 6.9 Hz), 2.50 (t, 2H, *J* = 7.2 Hz), 0.20 (s, 9H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 141.1, 135.3, 128.4, 127.6, 126.8, 117.0, 107.7, 87.8, 42.9, 38.9, 0.18 ppm; HRMS (EI) calc'd for C₁₅H₂₀Si: 228.1334, found: 228.1331.

Purified by chromatography on silica gel (hexanes); pale yellow oil (65 %). ¹H NMR (CDCl₃, 300 MHz) δ 7.42 (d, 2H, *J* = 8.4 Hz), 7.21 (d, 2H, *J* = 8.4 Hz), 5.85-5.75 (m, 1H),

5.04 (s, 1H), 5.01-4.99 (m, 1H), 3.61-3.57 (m, 1H), 2.42 (td, 2H, $J = 7.2, 0.8$ Hz), 1.85 (d, 3 H, $J = 2.4$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) $\square$ 147.1, 135.3, 131.4, 129.3, 120.4, 117.1, 79.7, 79.3, 42.6, 37.5, 3.6 ppm; HRMS (EI) calc'd for $\text{C}_{13}\text{H}_{13}\text{Br}$: 248.0200, found: 248.0182.

Purified by chromatography on silica gel (hexanes); pale yellow oil (96%). ^1H NMR (CDCl_3 , 300 MHz) $\square$ 7.29 (d, 2H, $J = 8.4$ Hz), 6.88 (d, 2H, $J = 8.1$ Hz), 5.94-5.81 (m, 1H), 5.10-5.04 (m, 2H), 3.80 (s, 3H), 3.62 (td, 1H, $J = 7.2, 2.4$ Hz), 2.45 (t, 2H, $J = 6.6$ Hz), 1.88 (dd, 3H, $J = 2.4, 0.9$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) $\square$ 158.3, 136.0, 134.3, 128.5, 116.7, 113.8, 80.7, 78.6, 55.2, 43.0, 37.2, 3.7 ppm; HRMS (EI) calc'd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.1201, found: 200.1201.

Purified by chromatography on silica gel (hexanes); pale yellow oil (82%). ^1H NMR (CDCl_3 , 400 MHz) $\square$ 7.56 (dd, 1H, $J = 7.6, 1.6$ Hz), 7.25-7.18 (m, 1H), 7.00-6.95 (m, 2H), 5.97-5.86 (m, 1H), 5.07-5.01 (m, 2H), 4.67 (q, 2H, $J = 2.4$ Hz), 4.18-4.14 (m, 1H), 2.53-2.47 (m, 1H), 2.40-2.33 (m, 1H), 1.87 (d, 3H, $J = 2.4$ Hz), 1.85 (t, 3H, $J = 2.4$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) $\square$ 154.5, 136.4, 131.1, 128.8, 127.6, 121.2, 116.3, 112.1, 83.5, 80.5, 78.1, 74.4, 71.5, 56.7, 41.0, 31.2, 3.7 ppm; Anal. calc'd for $\text{C}_{17}\text{H}_{18}\text{O}$: C, 85.67; H, 7.61. Found: C, 85.81; H, 7.84.

Purified by chromatography on silica gel (hexanes); light yellow oil (73%). ^1H NMR (CDCl_3 , 400 MHz) $\square$ 7.22 (d, 2H, $J = 8.4$ Hz), 6.85 (d, 2H, $J = 8.4$ Hz), 5.83-5.73 (m, 1H), 5.10-5.05 (m, 2H), 4.21 (q, 2H, $J = 7.2$ Hz), 3.78 (s, 3H), 3.73 (t, 1H, $J = 7.2$ Hz), 2.60-2.47 (m, 2H), 1.29 (t, 3H, $J = 6.8$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) $\square$ 158.8, 153.8, 134.4, 131.0, 128.6, 117.9, 114.1, 89.6, 75.6, 61.9, 55.3, 41.6, 37.0, 14.1 ppm; HRMS (EI) calc'd for $\text{C}_{16}\text{H}_{18}\text{O}_3$: 258.1256, found: 258.1257.

Purified by chromatography on silica gel (hexanes); light yellow oil (87%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.12-7.02 (m, 2H), 6.81 (dd, 1H, $J = 7.8, 1.2$ Hz), 5.96-5.82 (m, 1H), 5.08-5.00 (m, 2H), 4.11-4.05 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.45 (t, 2H, $J = 6.9$ Hz), 1.85 (dd, 3H, $J = 2.4, 0.3$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 152.5, 146.1, 136.1, 135.9, 123.9, 120.4, 116.5, 110.8, 80.8, 77.8, 60.8, 55.7, 41.6, 31.3, 29.7, 3.7 ppm; HRMS (EI) calc'd for $\text{C}_{15}\text{H}_{18}\text{O}_2$: 230.1307, found: 230.1303.

Purified by chromatography on silica gel (hexanes); light yellow oil (89%). ^1H NMR (CDCl_3 , 300 MHz) δ 6.88 (s, 2H), 5.97-5.83 (m, 1H), 5.17-5.06 (m, 2H), 4.13-4.07 (m, 1H), 2.75-2.65 (m, 2H), 2.48-2.38 (broad s, 6H), 2.30 (s, 3H), 1.85 (d, 3H, $J = 2.7$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 136.5, 135.9, 134.8, 130.0, 116.3, 80.3, 77.5, 38.8, 32.3, 29.8, 20.9, 20.8, 3.7 ppm; HRMS (EI) calc'd for $\text{C}_{16}\text{H}_{20}$: 212.1565, found: 212.1561.

Purified by chromatography on silica gel (hexanes); light yellow oil (99%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.29 (d, 2H, $J = 8.7$ Hz), 6.87 (d, 2H, $J = 8.7$ Hz), 5.21 (d, 1H, $J = 0.6$ Hz), 5.03 (d, 1H, $J = 0.9$ Hz), 4.09 (s, 2H), 3.80 (s, 3H), 3.78-3.73 (m, 1H), 2.64-2.50 (m, 2H), 1.85 (d, 3H, $J = 2.4$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 158.5, 142.6, 134.0, 128.4, 117.2, 113.9, 80.4, 79.1, 55.3, 48.4, 42.1, 36.1, 3.7 ppm; HRMS (EI) calc'd for $\text{C}_{15}\text{H}_{17}\text{ClO}$: 248.0968, found: 248.0976.

Purified by chromatography on silica gel (hexanes); pale yellow oil (89%). ^1H NMR (CDCl_3 , 300 MHz) δ 6.87 (s, 1H), 6.80-6.72 (m, 2H), 5.94 (s, 2H), 5.90-5.76 (m, 1H), 5.06 (d, 1H, $J = 5.4$ Hz), 5.01 (s, 1H), 3.58-3.53 (m, 1H), 2.43 (t, 2H, $J = 7.0$ Hz), 1.85 (d, 3H, $J = 2.4$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 147.6, 146.2, 136.1, 135.8, 120.5, 116.8, 108.0, 100.9, 80.4, 78.9, 43.0, 37.8, 3.6 ppm, 1 carbon unresolved; Anal. calc'd for $\text{C}_{14}\text{H}_{14}\text{O}_2$: C, 78.48; H, 6.59. Found: C, 77.39; H, 6.72. HRMS (EI) calc'd for $\text{C}_{14}\text{H}_{14}\text{O}_2$: 214.0994, found: 214.0998.

Purified by chromatography on silica gel (hexanes); clear oil (90%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.24 (app d, 1H, $J = 8.6$ Hz), 6.83 (app d, 1H, $J = 8.6$ Hz), 6.02-5.81 (m, 2H), 5.09-4.90 (m, 4H), 3.85 (s, 3H), 3.79 (s, 3H), 3.74 (m, 1H), 3.56 (dd, 1H, $J = 15.8$, 6.0 Hz), 3.40 (dd, 1H, $J = 15.8$, 6.0 Hz), 2.38 (t, 2H, $J = 7.4$ Hz), 1.85 (d, 3H, $J = 2.3$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 151.3, 147.0, 137.0, 136.2, 134.0, 130.8, 123.2, 116.5, 115.2, 110.6, 81.1, 77.7, 60.8, 55.6, 42.8, 33.4, 30.1, 3.7 ppm; Anal. calc'd for $\text{C}_{18}\text{H}_{22}\text{O}_2$: C, 79.96; H, 8.20. Found: C, 80.25; H, 8.40. HRMS (EI) calc'd for $\text{C}_{18}\text{H}_{22}\text{O}_2$: 270.1620, found: 270.1620.

Purified by chromatography on silica gel (hexanes); pale yellow oil (89%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.11 (s, 1H), 6.96 (s, 1H), 5.98 (s, 2H), 5.94-5.80 (m, 1H), 5.09-5.04 (m, 2H), 4.12 (dd, 1H, $J = 8.5$, 5.1 Hz), 2.51-2.27 (m, 2H), 0.18 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 147.4, 147.2, 134.8, 133.4, 117.4, 113.4, 112.5, 109.2, 107.0, 101.7, 88.3, 41.1, 38.2, 0.1 ppm; Anal. calc'd for $\text{C}_{16}\text{H}_{19}\text{BrO}_2\text{Si}$: C, 54.70; H, 5.45. Found: C, 54.92; H, 5.60. HRMS (EI) calc'd for $\text{C}_{16}\text{H}_{19}\text{BrO}_2\text{Si}$: 350.0338, found: 350.0337.

Mixture of diastereomers. Purified by chromatography on silica gel (hexanes); light yellow oil (78%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.25-7.18 (m, 2H), 6.85-6.80 (m, 2H), 5.48-5.23 (m, 2H), 3.79 (s, 3H), two distinct proton signals for the propargylic proton corresponding to two diastereomers 3.54-3.52 (m) and 3.47-3.45 (m) 1H, 2.41-2.33 (m, 1H), 1.89-1.87 (m, 3H), 1.64-1.62 (m, 3H), 1.04-0.96 (m, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 158.2, 135.1, 134.7, 133.5, 133.4, 133.3, 133.0, 129.3, 129.2, 129.1, 127.3, 125.1, 124.5, 124.2, 123.5, 113.4, 113.3, 113.2, 79.8, 79.4, 79.3, 79.2, 78.9, 78.8, 71.2, 55.2, 43.7, 43.5, 43.4, 43.3, 38.2, 38.1, 29.5, 19.4, 18.8, 18.0, 17.3, 16.5, 12.9, 3.7 ppm; HRMS (EI) calc'd for $\text{C}_{16}\text{H}_{20}\text{O}$: 228.1514, found: 228.1515. The *ee* was determined to be 94% by HPLC analysis: Chiralcel OD column, 99.9:0.1 hexanes:2-propanol, 1.0 mL/min; $\lambda = 250$ nm, retention times 10.94 min. and 12.02 for (*R,R*)- and (*S,S*)-**10** and 15.26 min and 15.46 for (*S,R*) and (*R,S*)-**10**.

Purified by chromatography on silica gel (hexanes); pale yellow oil (72%). ^1H NMR (CDCl_3 , 400 MHz) δ 6.86 (s, 2H), 5.61-5.43 (m, 2H), 3.76-3.74 (m, 1H), 2.73- 2.68 (m, 1H), 2.57 (broad s, 3H), 2.35 (broad s, 3H), 2.28 (s, 3H), 2.00- 1.97 (m, 1H), 1.80 (d, 3H, $J = 2.4$ Hz), 1.10 (s, 6H), 0.97 (q, 2H, $J = 3.2$ Hz), 0.81 (t, 3H, $J = 6.4$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 141.4, 137.0, 136.0, 135.8, 125.6, 135.5, 133.0, 130.9, 128.9, 128.8, 127.7, 80.4, 80.3, 77.6, 77.5, 42.1, 40.6, 40.5, 38.5, 38.3, 32.8, 29.8, 29.6, 22.4, 22.2, 21.6, 20.9, 20.7, 18.3, 3.7, 3.6, 0.9 ppm.

Purified by chromatography on silica gel (1:5 EA:Hex); pale yellow oil (77%). $[\alpha]_D^{23} = +24.1$ ($c = 1.3$, in CHCl_3), ^1H NMR (CDCl_3 , 300 MHz) δ 6.83 (2H), 3.91-3.82 (m, 3H), 2.49 (broad s, 3H), 2.35 (s, 1H), 2.32 (m, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.78 (d, 3H, $J = 2.4$ Hz), 0.70 (d, 3H, $J = 6.9$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 135.9, 134.0, 130.9, 129.1, 80.0, 78.3, 67.8, 39.0, 34.7, 21.5, 20.7, 14.9, 3.6 ppm.

Purified by chromatography on silica gel (hexanes); pale yellow oil (25%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.46-7.44 (m, 2H), 7.35- 7.28 (m, 3H), 6.06-5.93 (m, 1H), 5.20-5.13 (m, 2H), 2.82-2.73 (m, 1H), 2.41-2.26 (m, 2H), 1.30 (d, 3H, $J = 7.2$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 136.0, 131.6, 128.2, 127.6, 124.0, 116.7, 94.1, 81.1, 41.2, 26.5, 20.5 ppm; HRMS (EI) calc'd for $\text{C}_{13}\text{H}_{14}$: 170.11, found: submitted.

Purified by chromatography on silica gel (hexanes); pale yellow oil (58%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.50-7.48 (m, 2H), 7.38-7.31 (m, 3H), 6.17-6.06 (m, 1H), 5.24-5.19 (m, 2H), 2.35 (d, 2H, $J = 7.2$ Hz), 1.38 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 135.4, 131.7, 128.2, 127.6, 124.1, 117.5, 96.9, 80.8, 47.8, 31.5, 29.0 ppm; HRMS (EI) calc'd for $\text{C}_{14}\text{H}_{16}$: 184.13, found: submitted.

Di-*O*-Methyl-Calopin Synthesis

1-(2,3-dimethoxy-4-methylphenyl)-3-trimethylsilyl-2-propyn-1-ol. To a cooled solution (-78 °C) of trimethylsilylacetylene (8.34 g, 84.6 mmol) in 200 mL of THF was added *n*-BuLi (7.7 mL, 10.5 M, 77.5 mmol) dropwise over 5 minutes. The reaction mixture was warmed to 0 °C and was stirring for an additional 30 minutes to ensure deprotonation. The mixture was then cooled to -78 °C and a 20 mL solution of 2,3-dimethoxy-4-methylbenzaldehyde³ (12.7 g, 70.5 mmol) in THF was added dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours. After quenching the reaction mixture with saturated NH₄Cl (50 mL), the aqueous layer was washed with Et₂O (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL) and dried. After evaporation of the solvent, the crude yellow oil was purified by column chromatography (1:10 Et₂O:Hex) to afford 11.3 g (58%) of the propargyl alcohol. ¹H NMR (CDCl₃, 400 MHz) δ 7.10 (d, 1H, *J* = 8.0 Hz), 6.89 (dd, 1H, *J* = 8.0, 0.8 Hz), 5.50 (s, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 3.21 (s, 1H), 2.24 (s, 3H), 0.16 (s, 9H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 151.3, 150.7, 133.1, 132.6, 125.8, 122.4, 105.8, 90.2, 61.7, 60.8, 59.9, 15.88, -0.1 ppm; Anal. calc'd for C₁₅H₂₂O₃Si: C, 64.71; H, 7.96. Found: C, 64.54; H, 7.99.

6-(2,3-Dimethoxy-4-methylphenyl)-5-methyl-8-trimethylsilyl-oct-3-en-7-noic acid methyl ester. To a 0.25 M solution of propargyl alcohol (2.12 g, 7.62 mmol) in MeNO₂ (31 mL) was added (3-*S*,4-*E*)-methyl-3-(dimethylphenylsilyl)-4-hexenoate (3.00 g, 11.4 mmol) while stirring at room temperature. The catalyst, (dppm)ReOCl₃ (264 mg, 0.381 mmol), and NH₄PF₆ (62 mg, 0.381 mmol) were sequentially added to the reaction mixture. The reaction mixture was then heated to 60 °C for 1 hour. After evaporation of the solvent, the catalyst precipitated and was recovered by addition of Et₂O (50 mL) to the flask and filtration and washing of the catalyst (see general procedure). The solvent of the remaining filtrate was then evaporated. The resulting oil was purified by column chromatography (1:10 Et₂O:Hex) to afford the substituted adduct (2.40 g, 82 %, 1.2:1 *dr*). Major diastereomer: ¹H NMR (CDCl₃, 400 MHz) δ 6.99 (d, 1H, *J* = 7.6 Hz), 6.83 (d, 1H, *J* = 8 Hz), 5.60-5.54 (m, 1H), 5.37-5.29 (s, 1H), 3.94 (d, 2H, *J* = 6 Hz), 3.84 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H), 2.99 (d, 2H, *J* = 6.8 Hz), 2.48-2.43 (m, 1H), 2.22 (s, 3H), 1.08 (d, 3H, 6.8), 0.15 (s, 9H) ppm; Mixture of diastereomers: ¹³C NMR (CDCl₃, 100 MHz) δ 172.2, 151.0, 150.9, 150.2, 150.1, 138.0, 136.2, 131.7, 131.6, 130.8, 130.7, 125.1, 125.0, 124.1, 122.0, 121.4, 107.2, 107.1, 87.6, 87.5, 60.4, 60.3, 59.7, 59.6, 51.6, 51.5, 42.2, 42.0, 38.5, 38.4, 38.0, 37.9, 32.7, 32.4, 19.8, 18.9, 16.1, 15.7, 0.1 ppm; Anal. calc'd for C₂₂H₃₂O₄Si: C, 68.00; H, 8.30. Found: C, 68.22; H, 8.45.

1-{1-[2-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-3-trimethylsilanyl-prop-2-ynyl}-2,3-dimethoxy-4-methyl-benzene. To cooled solution (-78 °C) of allylated adduct (4.00 g, 10.3 mmol) in methanol (250 mL) was added Sudan III (3 mg). Ozone was bubbled through the pink reaction mixture until the solution became clear. Sodium borohydride, NaBH₄, (1.17 g, 30.8 mmol) was added to the reaction mixture in one portion. The reaction mixture was stirred for 1 hour at -78 °C and then warmed to room temperature for 2 hours. The solvent was evaporated to approximately 10 mL and quenched with saturated NH₄Cl (50 mL). Et₂O (100 mL) was added and the solution stirred for an additional 10 minutes. The biphasic layers were separated and the aqueous layer was washed with Et₂O (3 X 100 mL) and the combined organic layers were washed with brine (2 X 100 mL) and dried. Evaporation and purification of the corresponding red oil by column chromatography (1:3 Et₂O:Hex) gave two diastereomers of the free alcohol in 77% yield, 1.2:1 *dr*. The desired diastereomer (1.05 g, 3.27 mmol) was dissolved in 467 μ L of DMF. Imidazole (334 mg, 4.91 mmol) and *t*-butyldimethylsilylchloride (590 mg, 3.92 mmol) were sequentially added to the reaction mixture that was then stirred for 3 hours. Purification by column chromatography (1:20 Et₂O:Hex) afforded the corresponding protected alcohol (1.25 g, 68% over three steps). ¹H NMR (CDCl₃, 400 MHz) δ 7.10 (d, 1H, *J* = 8 Hz) and 6.91 (d, 1H, *J* = 8 Hz), 4.00 (d, 1H, *J* = 8 Hz), 3.91 (s, 3H), 3.83 (s, 3H), 3.82-3.77 (m, 2H), 2.29 (s, 1H), 2.05-2.03 (m, 1H), 0.98 (s, 9H), 0.96 (d, 3H, *J* = 6.8 Hz), 0.23 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 151.2, 150.7, 132.3, 130.7, 125.4, 123.9, 108.4, 86.3, 65.8, 60.3, 59.6, 41.4, 35.0, 26.0, 18.4, 15.7, 15.6, 0.2, -5.3, -5.4 ppm; Anal. calc'd for C₂₄H₄₂O₃Si₂: C, 66.30; H, 9.74. Found: C, 66.40; H, 9.92.

tert-Butyl-[3-(2,3-dimethoxy-4-methyl-phenyl)-2-methyl-pent-4-enyloxy]-dimethylsilane. To a solution of the protected alcohol (1.8 g, 4.2 mmol) in methanol (50 mL) was added potassium carbonate (3.00 g, 20.9 mmol). The reaction mixture was stirred stirring for 3 hours at room temperature. After filtration of the excess K₂CO₃, the solvent was evaporated giving the corresponding terminal alkyne. To a solution of alkyne (1.52 g, 4.18 mmol) in dry toluene (20 mL) was added 5% Pd on barium sulfate (200 mg, ca. 0.940 mmol) and quinoline (2.47 mL, 20.9 mmol). After evacuation of air from the reaction flask, the reaction mixture was placed under a hydrogen atmosphere with a balloon of hydrogen gas (1 atm). The reaction mixture was stirred for 12 hours at room temperature. After filtration of the reaction mixture through a plug of Celite, the solvent from the filtrate was evaporated and the resulting oil was purified by column

chromatography (1:20 Et₂O:Hex) to afford the terminal olefin (1.52 g, 100%). ¹H NMR (CDCl₃, 400 MHz) δ 6.89 (d, 1H, *J* = 8 Hz), 6.03-5.93 (m, 1H), 5.09-4.99 (m, 2H), 3.85 (s, 3H), 3.84 (m, 3H), 3.75 (dd, 1H, *J* = 3.2, 9.6 Hz), 3.63-3.51 (m, 2H), 2.26 (s, 3H), 1.99-1.95 (m, 1H), 0.90 (s, 9H), 0.81 (d, 3H, *J* = 6.8 Hz), 0.08 (s, 6H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 151.6, 151.0, 141.4, 135.6, 129.7, 125.7, 122.9, 115.0, 66.2, 60.4, 59.9, 46.0, 39.4, 26.0, 18.4, 15.8, 15.7, -5.3 ppm. Anal. calc'd for C₂₁H₃₆O₃Si: C, 69.18; H, 9.95. Found: C, 69.03; H, 9.96.

5-(tert-Butyl-dimethyl-silanyloxy)-3-(2,3-dimethoxy-4-methyl-phenyl)-4-methyl-pentane-1,2-diol. To a solution of OsO₄ (1.72 mL, 2.50 wt% in *t*-BuOH, 0.137 mmol) and 4-methylmorpholine *N*-oxide (390 mg, 3.29 mmol) in 1:1 H₂O: *t*-BuOH (20 mL) was added the terminal olefin (1.0 g, 2.7 mmol) in a 5 mL solution of *t*-BuOH. The reaction mixture was vigorously stirred at room temperature for 4 hours. The reaction mixture was quenched with Na₂SO₃ (4 g) and stirred for 1 hour. The organic layer was separated and the aqueous layer was washed with Et₂O (3 X 100 mL). The combined organic layers were washed with brine (2 X 100 mL), dried, and the solvent was evaporated. Purification by column chromatography (1:3 Et₂O:Hex) afforded the corresponding diol (diastereomer **A**: 342 mg, 31%, diastereomer **B**: 419 mg, 38%). ¹H NMR of the desired diastereomer **B** (CDCl₃, 400 MHz) δ 6.83 (d, 1H, *J* = 8 Hz), 6.70 (d, 1H, *J* = 8 Hz), 4.92 (s, 1H), 3.96 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.74 (m, 2H), 3.23-3.16 (m, 2H), 2.58 (s, 1H), 2.23 (s, 3H), 2.11 (s, 1H), 0.95 (s, 9H), 0.72 (d, 3H, *J* = 6.4 Hz), 0.14 (s, 3H), 0.13 (s, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 151.5, 151.1, 132.9, 130.4, 125.7, 123.4, 73.9, 68.3, 65.6, 60.3, 59.8, 44.7, 39.5, 25.8, 18.2, 16.8, 15.6, -5.3, -5.5 ppm. Anal. calc'd for C₂₁H₃₈O₅Si: C, 63.28; H, 9.61. Found: C, 63.26; H, 9.46.

5-(tert-Butyl-dimethyl-silanyloxy)-3-(2,3-dimethoxy-4-methyl-phenyl)-2-(4-methoxy-benzyloxy)-4-methyl-pentan-1-ol. To a solution of the diol (100 mg, 0.251 mmol) in CH₂Cl₂ (10 mL) was added anisaldehyde dimethyl acetal (64.0 μ L, 0.376 mmol) at room temperature. Pyridinium *p*-toluenesulfonate (4.0 mg, 0.016 mmol) was added in one portion and stirring was continued for 3 hours. The reaction mixture was quenched with triethylamine and filtered through a silica plug. The solvent was evaporated and the corresponding protected acetal (107 mg, 0.207 mmol) was dissolved in CH₂Cl₂ (10 mL). The solution was cooled to -78 °C. DIBAL-H (621 μ L, 1.0M solution in CH₂Cl₂, 0.621 mmol) was added dropwise *via* syringe. After 30 minutes, the reaction mixture was warmed to 0 °C. The reaction mixture was quenched with MeOH (1 mL) and a sat'd aq. solution of potassium sodium tartrate (5 mL). This mixture was

stirred for 3 hours. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 X 40 mL). The combined organic layers were washed with brine (2 X 40 mL), dried, and the solvent was evaporated. Purification by column chromatography (1:6 ethyl acetate:Hex) afforded the free primary alcohol (78 mg, 73% over two steps). ¹H NMR (CDCl₃, 400 MHz) δ 7.32 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 6.80 (d, 1H, *J* = 8 Hz), 6.71 (d, 1H, *J* = 7.6 Hz), 4.66 (d, 1H, *J* = 11.2 Hz), 4.58 (d, 1H, *J* = 11.2 Hz), 3.86 (broad s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70-3.67 (m, 2H), 3.60 (broad s, 1H), 3.32-3.28 (m, 2H), 2.36-2.29 (m, 1H), 2.22 (s, 3H), 2.16 (broad s, 1H), 0.90 (s, 9H), 0.81 (d, 3H, *J* = 6.8 Hz), 0.03 (s, 6H) ppm. ¹³C NMR (CDCl₃, 100 MHz) δ 159.2, 152.0, 151.4, 131.2, 130.6, 130.2, 129.6, 125.0, 124.0, 113.8, 80.4, 71.7, 67.1, 61.9, 60.3, 59.7, 55.2, 39.0, 36.2, 25.9, 18.3, 15.6, 14.5, -5.4 ppm. Anal. calc'd for C₂₉H₄₆O₆Si: C, 67.14; H, 8.94. Found: C, 67.24; H, 8.98.

5-(tert-Butyl-dimethyl-silanyloxy)-3-(2,3-dimethoxy-4-methyl-phenyl)-2-(4-methoxy-benzyloxy)-4-methyl-pentanal. To a cooled solution (0 °C) of the primary alcohol (763 mg, 1.47 mmol) in CH₂Cl₂ (15 mL) was added Dess-Martin periodinane (749 mg, 1.76 mmol) in portions over 5 minutes. After 2 hrs, the reaction mixture was quenched with *iso*-propanol (10 mL). After evaporation of the solvent, the slurry was purified by column chromatography (1:3 Et₂O:Hex) to afford the aldehyde (606 mg, 80%). ¹H NMR (CDCl₃, 400 MHz) δ 9.52 (d, 1H, *J* = 2.4 Hz), 7.24 (d, 2H, *J* = 8.8 Hz), 6.86-6.81 (m, 4H), 4.59 (d, 1H, *J* = 10.8 Hz), 4.44 (d, 1H, *J* = 11.2 Hz), 3.99 (d, 1H, *J* = 4.0 Hz), 3.82 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.69-3.62 (m, 2H), 3.56-3.52 (m, 1H), 2.29 (broad s, 1H), 2.23 (s, 3H), 0.92 (s, 9H), 0.76 (d, 3H, *J* = 6.8 Hz), 0.05 (s, 6H) ppm. ¹³C NMR (CDCl₃, 100 MHz) δ 202.1, 159.3, 151.4, 131.5, 130.7, 129.7, 129.5, 125.35, 123.9, 113.68, 85.1, 72.4, 66.2, 60.2, 59.7, 55.1, 40.2, 36.1, 25.9, 18.3, 15.7, 15.5, -5.4, -5.5 ppm. Anal. calc'd for C₂₉H₄₄O₆Si: C, 67.41; H, 8.58. Found: C, 67.15; H, 8.72.

4-(2,3-Dimethoxy-4-methyl-phenyl)-3-(4-methoxy-benzyloxy)-5-methyl-tetrahydro-pyran-2-one. To a solution of the aldehyde (210 mg, 0.406 mmol) in CH₂Cl₂ (10 mL) under nitrogen atmosphere was added tetrabutylammonium fluoride (1.22 mL, 1M, 1.22 mmol) dropwise over 5 min. The reaction mixture was stirred for 3 hours. The solvent was evaporated and the resulting oil was filtered through a silica plug and washed with ethyl acetate. After evaporation of the solvent, the lactol (139 mg, 0.346 mmol), 4-methylmorpholine *N*-oxide (53 mg, 0.45 mmol), and 4A MS (53 mg) was dissolved in CH₂Cl₂ (10 mL). Tetrapropylammonium perruthenate (6.07 mg, 0.0173 mmol) was added in portion to the reaction mixture. After 2 hrs, the solution was filtered

through a silica plug and washed with ethyl acetate. After solvent evaporation, the oil was purified by column chromatography (1:3 EA:Hex) to afford the protected lactone (106 mg, 66%) ^1H NMR (CDCl_3 , 400 MHz) δ 7.00 (d, 2H, $J = 8.4$ Hz), 6.90 (s, 2H), 6.75 (d, 2H, $J = 8.4$ Hz), 4.64 (d, 1H, $J = 11.6$ Hz), 4.41 (d, 1H, $J = 11.2$ Hz), 4.40 (d, 1H, $J = 11.6$ Hz), 4.02 (d, 1H, $J = 6.4$ Hz), 3.97 (d, 1H, $J = 10.8$ Hz), 3.78 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.39 (dd, 1H, $J = 6.0, 9.6$ Hz), 2.53-2.50 (m, 1H), 2.27 (s, 3H), 0.89 (d, 3H, $J = 6.4$ Hz) ppm. ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.8, 159.4, 151.6, 151.3, 131.4, 130.1, 129.9, 129.4, 125.4, 125.1, 113.8, 73.9, 73.2, 72.0, 60.7, 60.0, 55.4, 43.8, 31.7, 16.0, 15.9 ppm. Anal. calc'd for $\text{C}_{29}\text{H}_{46}\text{O}_6\text{Si}$: C, 68.98; H, 7.05. Found: C, 68.88; H, 7.24.

(-)-7, 8-di-O-methylcalopin. A solution of the protected lactone and 5% Pd/C (100 mg) in ethanol (5 mL) was placed under an atmosphere of H_2 and stirred overnight. After filtration through a Celite plug, the solvent was evaporated and the resulting oil was purified by column chromatography (1:10 EA:Hex) to afford (-)-7, 8-di-O-methylcalopin (36 mg, 48%). $[\alpha]_{\text{D}}^{23} = -46$ ($c = 0.9$, in CHCl_3), $[\alpha]_{\text{D}}^{23} = -33$ ($c = 0.9$, in MeOH). ^1H NMR (CDCl_3 , 300 MHz) δ 6.84 (d, 1H, $J = 7.8$ Hz), 6.68 (d, 1H, $J = 7.8$ Hz), 4.60 (dd, 1H, $J = 5.1, 9.9$ Hz), 4.30 (dd, 1H, $J = 5.1, 11.4$ Hz), 4.10 (t, 1H, $J = 11.7$ Hz), 3.85 (s, 3H), 3.78 (s, 3H), 3.57 (dd, 1H, $J = 7.8, 9.6$ Hz), 2.86 (d, 1H, $J = 5.1$ Hz), 2.34-2.26 (m, 1H), 2.22 (s, 3H), 1.04 (d, 3H, $J = 6.9$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 175.0, 151.5, 151.0, 131.9, 130.2, 125.5, 124.2, 70.9, 66.8, 60.2, 59.8, 45.4, 36.3, 16.4, 15.7 ppm. Anal. calc'd for $\text{C}_{15}\text{H}_{20}\text{O}_6\text{Si}$: C, 64.27; H, 7.19. Found: C, 62.70; H, 7.43.

References:

1. Alaimo, P.J.; Peters, D.W.; Arnold, J.; Bergman, R.G. *J. Chem. Ed.* **2001**, 78, 64.
2. Chat, J.; Rowe, G.A. *J. Chem. Soc.* **1962**, 4019. (b) Rossi, R.; Marchi, A.; Marvelli, L.; Magon, L.; Peruzzini, M.; Casellato, U.; Graziani, R. *Inorg. Chim. Acta.* **1993**, 204, 63.
3. Comins, D.L.; Brown, J.D. *J. Org. Chem.* **1984**, 49, 1078.