Titanium(IV) Promoted Mukaiyama aldol-Prins Cyclizations

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General experimental details: Moisture-sensitive reactions were carried out under an atmosphere of dry argon using flame dried glassware and standard syringe/septa techniques. Tetrahydrofuran and methylene chloride were dried according to the method described by Grubbs. All aldehydes were distilled immediately prior to use. Titanium isopropoxide, boron trifluoroetherate, and 2,6-di-*tert*-butylpyridine were distilled neat at the appropriate pressure. 2,6-Di-*tert*-butyl-4-methylpyridine was sublimed at 0.1 Torr (35 °C) and stored over P₂O₅. TiBr₄ solid was purchased from Aldrich and a stock solution in methylene chloride was made in a glove box (0.4-0.5 M) and stored in a Schlenk flask protected from light. All other commercial reagents were used as received unless otherwise noted.

Instrumentation and chromatography: Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV (0.25 mm) plates. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Sorbent Technologies 230-400 mesh silica gel. Enantiomeric excess was determined by HPLC analysis. Infrared spectra were recorded on a MIDAC Prospect FT-IR. NMR spectra were recorded on a Bruker DRX, Bruker GN500 and Bruker Omega500 MHz FT-NMR instruments. ¹H NMR spectra were reported in ppm relative to tetramethylsilane or residual solvent (CDCl₃: δ 7.26 ppm, C₆D₆: δ 7.16 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), coupling constant(s) in Hertz (Hz), and integration. Multiplets (m) are reported over the range (ppm) at which they appear. ¹³C NMR spectra were reported in ppm relative to the solvent signal (CDCl₃: 77.2, C₆D₆: 128.0 ppm). Capillary GC analysis was performed on

a Hewlett Packard Model 6890 instrument with a 30 m X 0.25 μ M Alltech EC-5 (SE-54) or Restek RTX-1701 capillary column equipped with a flame ionization detector. Optical rotations were determined on a JASCO DIP-370 digital polarimeter; concentration c is reported as g/100 mL. Mass spectral data was obtained on a MicroMass Autospec E spectrometer, or a MicroMass LCT Electrospray spectrometer. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

Synthesis of Cyclization Precursors

(S)-6-Phenyl-4-vinyloxyhex-1-ene (3). To a solution of (*S*)-4-hydroxy-6-phenylhex-1-ene (2.94 g, 16.7 mmol, 1.0 equiv) in ethyl vinyl ether (125 mL) was added mercuric trifluoroacetate (700 mg, 1.67 mmol, 0.1 equiv). The solution was allowed to stir at room temperature for two days after which the reaction was complete (TLC analysis). The solution was reduced *in vacuo* to one third the volume, after which saturated, aqueous sodium bicarbonate (70 mL) was added to remove the mercury salts. The aqueous layer was then extracted with diethyl ether (3 X 30 mL), and the organic layers combined and washed with deionized water (1 X 40 mL), dried with anhydrous magnesium sulfate and concentrated *in vacuo* afforded a pale yellow oil. The oil was purified by flash chromatography (5% diethyl ether/hexanes) on neutralized silica gel (Et_3N) to give a colorless oil (2.78 g, 13.7 mmol, 83%) in 94% ee (HPLC, Chiracel OD-H, 98:2 *n*-hexane:*i*-PrOH, 0.80 mL/min). R_f = 0.55 (5% diethyl ether/hexanes); $[\alpha]_D^{23} = -14.8$ (c 0.90, MeOH); IR (neat) 2936, 1633, 1194 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.24-7.30 (m, 2 H), 7.14-7.20 (m, 3 H), 6.32 (dd, 6.5, 14.1 Hz, 1 H), 5.79 (dddd, J = 7.1, 7.1, 10.3, 17.2 Hz, 1 H), 5.05-5.12 (m, 2 H), 4.30 (dd, J = 1.6, 14.1, Hz, 1 H), 4.01 (dd, 1.6, 6.6 Hz, 1 H), 3.76-3.83 (m, 1H), 2.76 (ddd, 5.8, 9.6, 13.9 Hz, 1 H), 2.64 (ddd, 6.9, 9.5, 13.8 Hz, 1 H), 2.29-2.42 (m, 2 H), 1.80-1.94 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.5, 142.0, 134.1, 128.7, 128.6, 126.1, 117.8, 88.6, 78.6, 38.7, 35.7, 31.7; HRMS (CI/NH_3), calcd for

C₁₄H₁₉O [M + H]⁺ 203.1436, found 203.1432; Anal. Calcd for C₁₄H₁₈O: C, 83.12; H, 8.97. Found: C, 83.36; H, 9.14.

6-(benzyloxy)-4-vinyloxyhex-1-ene (21). To solution of 6-(benzyloxy)-4-hydroxyhex-1-ene (2.00 g, 9.70 mmol, 1.0 equiv) in ethyl vinyl ether (200 mL) was added mercuric trifluoroacetate (414 mg, 0.970 mmol, 0.1 equiv). The solution was allowed to stir for 2 days after which the reaction was complete (TLC analysis). The solution was reduced *in vacuo* to one third the volume, after which saturated, aqueous sodium bicarbonate (70 mL) was added to remove the mercury salts. The aqueous layer was then extracted with diethyl ether (3 X 30 mL), and the organic layers combined and washed with deionized water (1 X 40 mL), dried with anhydrous magnesium sulfate and concentrated *in vacuo* give a pale yellow oil. The oil was purified by flash chromatography (5% diethyl ether/hexanes) to give a colorless oil (1.87 g, 8.05 mmol, 83%). *R*_f = 0.26 (5% diethyl ether/hexanes); IR (neat) 2861, 1633, 1184, 1100 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.26 (d, *J* = 8.2 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.28 (dd, *J* = 6.6, 14.1 Hz, 1 H), 5.79 (dddd, *J* = 7.1, 7.1, 14.1, 17.4 Hz, 1 H), 4.98-5.05 (m, 2 H), 4.43 (dd, *J* = 1.2, 14.2 Hz, 1H), 4.26 (s, 2H), 3.92-3.99 (m, 2 H), 3.44 (ddd, *J* = 6.6, 6.6, 9.3 Hz, 1 H), 3.34 (ddd, *J* = 5.4, 5.4, 11.0 Hz, 1 H), 2.14-2.27 (m, 2 H), 1.72-1.78 (m, 2 H); ¹³C NMR (125 MHz, C₆D₆) δ 152.3, 139.6, 134.7, 128.9, 128.1, 128.0, 117.8, 88.5, 76.8, 73.4, 66.9, 39.5, 35.0; HRMS (CI/NH₃), calcd for C₁₃H₁₆O₂ [M – C₂H₄]⁺ 204.1150, found 204.1153.

7-(benzyloxy)-4-vinyloxyhept-1-ene (24). To solution of 7-(benzyloxy)-4-hydroxyhept-1-ene (2.00 g, 9.08 mmol, 1.0 equiv) in ethyl vinyl ether (100 mL) was added mercuric trifluoroacetate (387 mg, 0.91 mmol, 0.1 equiv). The solution was allowed to stir for 2

days after which the reaction was complete (TLC analysis). The solution was reduced *in vacuo* to one third the volume, after which saturated, aqueous sodium bicarbonate (50 mL) was added to remove the mercury salts. The aqueous layer was then extracted with diethyl ether (3 X 20 mL), and the organic layers combined and washed with deionized water (1 X 20 mL), dried with anhydrous magnesium sulfate and concentrated *in vacuo* gave a pale yellow oil. The oil was purified by flash chromatography (5% diethyl ether/hexanes) to give a colorless oil (1.68 g, 6.81 mmol, 75%). R_f = 0.30 (5% diethyl ether/hexanes); IR (neat) 2857, 1633, 1183, 1102 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.29 (d, J = 7.6 Hz, 2 H), 7.18 (t, J = 7.3 Hz, 2 H), 7.10 (t, J = 7.3, 1 H), 6.19 (dd, J = 6.6, 14.1 Hz, 1 H), 5.75 (dddd, J = 7.1, 7.1, 14.1, 17.4 Hz, 1 H), 4.97-5.03 (m, 2 H), 4.39 (d, J = 14.1 Hz, 1 H), 4.30 (s, 2 H), 3.98 (d, J = 6.6 Hz, 1 H), 3.59 (dddd, J = 5.7, 5.7, 5.7, 5.7 Hz, 1 H), 3.21-3.29 (m, 2 H), 2.23 (dddd, J = 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 2.14 (dddd, J = 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 1.63-1.74 (m, 1 H), 1.52-1.63 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.8, 139.5, 134.6, 128.6, 127.8, 127.7, 117.4, 88.2, 79.3, 73.0, 70.3, 38.9, 31.0, 26.0; HRMS (CI/ NH_3), calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$ $[\text{M} - \text{C}_2\text{H}_4]^+$ 218.1307, found 218.1305.

General Procedure for Lewis acid blend experiments

Hydrocinnamaldehyde (56 μL , 0.423 mmol, 2.5 equiv), **3** (34 mg, 0.169 mmol, 1.0 equiv), and 2,6-di-*tert*-butylpyridine (345 μL , 0.254 mmol, 1.5 equiv) were dissolved in dichloromethane (5 mL). Upon cooling to -78°C a 2.0 M solution of the Lewis acid (210 μL , 0.423 mmol, 2.5 equiv) was added in one portion. The reaction was then stirred till completion by TLC at -78°C (5 min). The reaction was then quenched with saturated aqueous sodium bicarbonate (5 mL) at -78°C and allowed to warm to room temperature. The aqueous layer was then extracted with methylene chloride (3 X 5 mL) and the combined organic layers were dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The resulting oils were purified by flash chromatography.

Titanium dichloro-di(isopropoxide). To solution of TiCl_4 (1.0 mL, 1.0 M, 0.50 equiv) in methylene chloride was added $\text{Ti}(\text{O}^i\text{Pr})_4$ (297 μL , 1.00 mmol, 0.50 equiv) at 0 °C. The solution was then allowed to stir at room temperature for 30 min resulting in a 2.0 M $\text{TiCl}_2(\text{O}^i\text{Pr})_2$ solution in methylene chloride.

Titanium chloro-tri(isopropoxide). To solution of TiCl_4 (1.0 mL, 1.0 M, 0.25 equiv) in methylene chloride was added $\text{Ti}(\text{O}^i\text{Pr})_4$ (891 μL , 3.00 mmol, 0.75 equiv) at 0 °C. The solution was then allowed to stir at room temperature for 30 min resulting in a 2.0 M $\text{TiCl}(\text{O}^i\text{Pr})_3$ solution in methylene chloride.

1-[(2R*, 4R*, 6S*)-4-Chloro-6-(2-phenylethyl)tetrahydropyran-2-yl]-4-phenylbutan-2-ol (5). To a solution of hydrocinnamaldehyde (163 μL , 1.24 mmol, 2.0 equiv), 2,6-di-*tert*-butylpyridine (208 μL , 0.927 mmol, 1.5 equiv) and enol ether **3** (165 mg, 0.618 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at -78 °C was added a TiCl_4 solution (CH_2Cl_2) (1.2 mL, 1.0 M, 2.0 equiv) dropwise. TLC analysis showed immediate consumption of starting material. The reaction was then quenched with saturated, aqueous NaHCO_3 (8 mL) and allowed to come to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* that gave a colorless oil that was purified by flash column chromatography (5-20% diethyl ether/hexanes) to give a 1:1 diastereomeric ratio of **5** (143 mg, 0.383 mmol, 62%) as two colorless oils. Less polar isomer: R_f = 0.30 (10% ethyl acetate/hexanes); IR (neat) 3499, 2925, 1078, 750, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.16-7.30 (m, 10 H), 3.95 (dddd, J = 4.5, 4.5, 11.8, 11.8 Hz, 1 H), 3.86-3.91 (m, 1 H), 3.68 (s, 1 H), 3.53-3.58 (m, 1 H), 3.30-3.36 (m, 1 H), 2.61-2.83 (m, 4 H), 2.07-2.14 (m, 2 H), 1.54-1.94 (m, 8 H); ^{13}C NMR (125 MHz, CDCl_3)

δ 142.2, 141.2, 128.5, 128.5, 128.4, 128.3, 126.0, 125.7, 77.9, 75.9, 70.9, 54.8, 42.7, 42.3, 42.0, 39.1, 37.2, 31.6, 15.3; HRMS (CI/NH₃), calcd for C₂₃H₃₀ClO₂ [M]⁺ 373.1934, found 373.1917.

More polar isomer: R_f = 0.19 (10% ethyl acetate/hexanes); IR (neat) 3419, 2940, 1057, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.15-7.38 (m, 10 H), 3.90-4.01 (m, 2 H), 3.59-3.65 (m, 1 H), 3.25-3.31 (m, 1 H), 2.84 (ddd, *J* = 5.4, 9.9, 13.8 Hz, 1 H), 2.61-2.79 (m, 3 H), 2.08-2.13 (m, 1 H), 2.02-2.07 (m, 2 H), 1.52-1.92 (m, 8 H); ¹³C NMR (125 MHz, CDCl₃) δ 142.1, 141.4, 128.5, 128.4, 128.3, 125.9, 125.8, 125.7, 75.7, 74.2, 68.1, 55.3, 42.3, 42.2, 41.9, 39.2, 37.2, 32.2, 31.6; HRMS (CI/NH₃), calcd for C₂₃H₃₀ClO₂ [M + H]⁺ 373.1934, found 373.1927.

Acetal (4) To a solution of enol ether **3** (100 mg, 0.494 mmol, 1.0 equiv), hydrocinnamaldehyde (163 μ L, 0.124 mmol, 2.5 equiv), and 2,6-di-*tert*-butyl-4-methylpyridine (167 μ L, 0.742 mmol, 1.5 equiv) in CH₂Cl₂ (10 mL) at -78 °C was added BF₃·OEt₂ (157 mL, 1.24 mmol, 2.5 equiv). The solution was allowed to stir at -78 °C for 2 h at which point TLC analysis showed complete consumption of starting material. The reaction was quenched with saturated, aqueous NaHCO₃ (10 mL) and allowed to come to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 X 10 mL). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (0-20 % diethyl ether/hexanes) to give the product as a complex mixture of diastereomers (190 mg, 0.404 mmol, 82 %): R_f 0.65 (20 % diethyl ether/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.11-7.45 (m, 15 H), 5.79-6.00 (m, 1 H), 5.09-5.21 (m, 2 H), 4.85 (t, *J* = 5.3 Hz, 2 H), 4.61-4.71 (m, 0.4 H), 4.54 (q, *J* = 5.3 Hz, 0.4 H), 4.18-4.25 (m, 0.2 H), 4.15 (ddd, *J* = 5.6, 10.5, 10.5 Hz, 0.2 H), 3.81-3.90 (m, 0.6 H), 3.74-3.81 (m, 0.3 H), 3.51-3.66

(m, 0.6 H), 2.61-3.00 (m, 8.6 H), 2.18-2.60 (m, 2.6 H), 1.20-2.20 (m, 10.3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.6, 141.9, 141.4, 134.9, 134.6, 134.57, 134.2, 134.1, 128.6, 128.5, 126.1, 126.0, 125.95, 125.9, 125.7, 117.5, 117.34, 117.30, 117.1, 100.8, 100.7, 99.3, 98.13, 98.1, 96.3, 93.9, 92.4, 78.4, 76.6, 76.5, 75.8, 75.2, 74.0, 71.6, 71.4, 71.3, 40.7, 40.5, 39.0, 37.6, 37.4, 37.3, 36.7, 36.67, 36.4, 36.3, 36.1, 35.8, 33.9, 32.5, 32.2, 31.7, 31.3, 30.5, 30.4, 29.7; LRMS (EI), calcd for $\text{C}_{32}\text{H}_{38}\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$ 493.27, found 493.18.

General Procedure for the TiBr_4 catalyzed Mukaiyama Aldol-Prins Reaction

The aldehyde (1.6 mmol, 2.0 equiv), enol ether **3** (0.81 mmol, 1.0 equiv), and 2,6-di-*tert*-butylpyridine (1.2 mmol, 1.5 equiv) were dissolved in dichloromethane (8 mL). Upon cooling to -78°C , a solution of TiBr_4 (3.2 mL, 1.6 mmol, 2.0 equiv) was added quickly by syringe. The reaction was then stirred until completion at -78°C for 5 min. Saturated aqueous sodium bicarbonate (10 mL) was then added at -78°C and allowed to warm to room temperature. The aqueous layer was then extracted with dichloromethane (3 – 10 mL) and the combined organic layers were dried with anhydrous sodium sulfate and concentrated *in vacuo*. The resulting oils were purified by flash chromatography.

1-[(2*R, 4*R**, 6*S**)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-4-phenylbutan-2-ol (**5**)**. According to the general procedure described above, hydrocinnamaldehyde (215 μL , 1.63 mmol, 2.0 equiv) and enol ether **3** (165 mg, 0.816 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (0-15% diethyl ether/hexanes) to give a 1.1:1 diastereomeric ratio of **5** (214 mg, 0.513 mmol, 80%) as two colorless oils. Less polar isomer: R_f = 0.23 (10% ethyl acetate/hexanes); IR (neat) 3508, 2921, 1079, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44-7.61 (m, 10 H), 4.36

(dddd, $J = 4.4, 4.4, 12.0, 12.0$ Hz, 1 H), 4.14-4.20 (m, 1 H), 3.83 (t, $J = 10.8$ Hz, 1 H), 3.57-3.65 (m, 1 H), 3.89 (m, 4 H), 2.44-2.53 (m, 2 H), 1.96-2.23 (m, 8 H), 1.88 (d, $J = 14.7$ Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.3, 141.3, 128.7, 128.62, 128.55, 128.5, 126.2, 126.0, 78.8, 76.9, 70.9, 45.6, 43.6, 43.0, 42.5, 39.3, 37.3, 31.80, 31.76; HRMS (CI/NH_3), calcd for $\text{C}_{23}\text{H}_{30}\text{BrO}_2$ $[\text{M}]^+$ 416.1351, found 416.1353.

More polar isomer: $R_f = 0.14$ (10% ethyl acetate/hexanes); IR (neat) 3419, 2940, 1057, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.62 (m, 10 H), 4.39 (dddd, $J = 4.5, 4.5, 12.0, 12.0$ Hz, 1 H), 4.20-4.28 (m, 1 H), 3.92 (dddd, $J = 2.0, 3.2, 8.1, 11.2$ Hz, 1 H), 3.57 (dddd, $J = 2.0, 3.9, 8.6, 12.7$ Hz, 1 H), 3.14 (ddd, $J = 5.6, 10.0, 13.7$ Hz, 1 H), 2.90-3.10 (m, 4 H), 2.49 (dddd, $J = 2.2, 2.2, 4.4, 13.0$ Hz, 1 H), 2.44 (dddd, $J = 2.2, 2.2, 4.4, 12.7$ Hz, 1 H), 1.91-2.21 (m, 8 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.2, 141.6, 128.7, 128.59, 128.58, 128.53, 126.1, 126.0, 76.8, 75.3, 68.2, 46.3, 43.3, 43.2, 42.0, 39.4, 37.3, 32.3, 31.7; HRMS (CI/NH_3), calcd for $\text{C}_{23}\text{H}_{28}\text{BrO}$ $[\text{M} - \text{H}_2\text{O}]^+$ 398.1245, found 398.1243.

1-[(2R*, 4R*, 6S*)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-3-methylbutan-2-ol (6). According to the general procedure described above, isobutyraldehyde (145 μL , 1.60 mmol, 2.0 equiv) and enol ether **3** (162 mg, 0.801 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (5-20% ethyl acetate/hexanes) to give a 1.1:1 diastereomeric ratio of **6** (212 mg, 0.597 mmol, 78 %) as two colorless oils. Less polar isomer: $R_f = 0.17$ (10% ethyl acetate/hexanes); IR (neat) 3508, 2955, 1077, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.24-7.29 (m, 2 H), 7.14-7.20 (m, 3 H), 4.09 (dddd, $J = 4.4, 4.4, 12.0, 12.0$ Hz, 1 H), 3.59-3.65 (m, 1 H), 3.53-3.58 (m, 2 H), 3.32-3.38 (m, 1 H), 2.73 (ddd, $J = 5.5, 9.6, 14.2$ Hz, 1 H), 2.60-2.66 (m, 1 H), 2.21 (dd, $J = 4.4, 12.4$ Hz, 2 H), 1.84-1.92 (m, 1 H), 1.56-1.82 (m, 6 H), 0.93 (d, $J = 6.8, 3$ H), 0.92 (d, $J =$

6.8 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.4, 128.7, 128.6, 126.2, 79.2, 77.0, 76.7, 45.8, 43.8, 43.1, 39.0, 37.4, 33.9, 31.8, 18.5, 17.8; HRMS (CI/ NH_3), calcd for $\text{C}_{18}\text{H}_{28}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 355.1273, found 355.1273.

More polar isomer: R_f = 0.11 (10% ethyl acetate/hexanes); IR (neat) 3467, 2956, 1079, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.29 (m, 2 H), 7.15-7.20 (m, 3 H), 4.09 (dddd, J = 4.4, 4.4, 11.9, 11.9 Hz, 1 H), 3.59-3.67 (m, 2 H), 3.25-3.31 (m, 1 H), 2.73 (ddd, J = 5.4, 9.1, 14.1 Hz, 1 H), 2.62-2.69 (m, 1 H), 2.42 (br s, 1 H), 2.20 (ddd, J = 2.2, 4.4, 4.4 Hz, 1 H), 2.16 (ddd, J = 2.3, 4.4, 4.4 Hz, 1 H), 1.82-1.92 (m, 2 H), 1.60-1.77 (m, 5 H), 0.96 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.7, 128.6, 128.6, 126.1, 76.8, 75.4, 73.3, 46.6, 43.4, 43.2, 39.1, 37.4, 33.9, 31.8, 18.9, 18.0; HRMS (CI/ NH_3), calcd for $\text{C}_{18}\text{H}_{28}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 355.1273, found 355.1272; Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{BrO}_2$: C, 60.85; H, 7.66. Found: C, 60.97; H, 7.68.

1-[(2R*, 4R*, 6S*)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-2-cyclohexylethan-2-ol (7). According to the general procedure described above, cyclohexylcarboxaldehyde (215 μL , 1.65 mmol, 2.0 equiv) and enol ether **3** (167 mg, 0.826 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (5-30% diethyl ether/hexanes) to give a 1:1 diastereomeric ratio of **7** (268 mg, 0.678 mmol, 82 %) as two colorless oils. Less polar isomer: R_f = 0.39 (30% diethyl ether/hexanes); IR (neat) 3512, 2924, 1071, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.29 (m, 2 H), 7.15-7.20 (m, 3 H), 4.09 (dddd, J = 4.5, 4.5, 12.0, 12.0 Hz, 1 H), 3.60-3.63 (m, 1 H), 3.52-3.57 (m, 2 H), 3.32-3.37 (m, 1 H), 2.73 (ddd, J = 5.4, 9.6, 14.1 Hz, 1 H), 2.60-2.66 (m, 1 H), 2.21 (ddd, J = 1.2, 3.2, 12.6 Hz, 2 H), 1.84-1.92 (m, 1

H), 1.58-1.81 (m, 10 H), 1.31-1.38 (m, 1 H), 1.00-1.28 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.4, 128.7, 128.6, 126.2, 79.3, 77.1, 76.2, 45.8, 44.0, 43.8, 43.1, 39.3, 37.5, 31.9, 29.0, 28.3, 26.8, 26.6, 26.5; HRMS (CI/ NH_3), calcd for $\text{C}_{21}\text{H}_{32}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 395.1586, found 395.1588; Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{BrO}_2$: C, 63.79; H, 7.90. Found: C, 63.83; H, 8.01.

More polar isomer: R_f = 0.25 (30% diethyl ether/hexanes); IR (neat) 3466, 2924, 1069, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.27-7.30 (m, 2 H), 7.16-7.21 (m, 3 H), 4.13 (dddd, J = 4.5, 4.5, 12.0, 16.5 Hz, 1 H), 3.60-3.67 (m, 2 H), 3.29 (dddd, J = 1.9, 4.0, 8.6, 12.7 Hz, 1 H), 2.76 (ddd, J = 5.4, 9.1, 14.2 Hz, 1 H), 2.63-2.69 (m, 1 H), 2.19 (d, J = 4.7 Hz, 1H), 2.21 (dddd, J = 2.2, 2.2, 6.4, 12.8 Hz, 1H), 2.16 (dddd, J = 2.2, 2.2, 6.4, 12.8 Hz, 1 H), 1.62-1.92 (m, 11 H), 1.34 (dddd, J = 3.2, 3.2, 6.3, 8.5, 8.5 Hz, 1 H), 1.01-1.28 (m, 5 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.7, 128.7, 128.6, 126.2, 76.8, 75.5, 72.8, 46.6, 43.9, 43.4, 43.3, 39.2, 37.4, 31.8, 29.4, 28.5, 26.7, 26.5, 26.4; HRMS (CI/ NH_3), calcd for $\text{C}_{21}\text{H}_{32}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 395.1586, found 395.1575; Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{BrO}_2$: C, 63.79; H, 7.90. Found: C, 63.86; H, 8.05.

1-[(2R*, 4R*, 6S*)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-3,3-dimethylbutan-2-ol (8). According to the general procedure described above, pivalaldehyde (175 μL , 1.61 mmol, 2.0 equiv) and enol ether **3** (163 mg, 0.807 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (5-20% ethyl acetate/hexanes) to give a 1.2:1 diastereomeric ratio of **8** (220 mg, 0.597 mmol, 74 %) as a colorless oil and white solid. Less polar isomer: mp = 62-63 $^{\circ}\text{C}$; R_f = 0.28 (10% ethyl acetate/hexanes); IR (neat) 3515, 2954, 1078, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.26-7.30 (m, 2 H), 7.15-7.20 (m, 3 H), 4.10 (dddd, J = 4.5, 4.5, 12.0, 12.0 Hz,

1 H), 3.53-3.59 (m, 2 H), 3.44-3.48 (m, 1 H), 3.34-3.39 (m, 1 H), 2.73 (ddd, $J = 5.6, 9.7, 14.1$ Hz, 1 H), 2.61-2.67 (m, 1 H), 2.24 (dd, $J = 4.5, 12.5$ Hz, 2 H), 1.86-1.94 (m, 1 H), 1.68-1.83 (m, 3 H), 1.54 – 1.66 (m, 2 H), 0.91 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.4, 128.7, 128.6, 126.2, 79.9, 79.5, 77.4, 45.8, 43.8, 43.0, 37.4, 37.1, 34.8, 31.9, 25.9; HRMS (CI/ NH_3), calcd for $\text{C}_{19}\text{H}_{30}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 369.1429, found 369.1423.

More polar isomer: $R_f = 0.17$ (10% ethyl acetate/hexanes); IR (neat) 3488, 2955, 1082, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.26-7.29 (m, 2 H), 7.15-7.20 (m, 3 H), 4.13 (dddd, $J = 4.5, 4.5, 12.0, 12.0$ Hz, 1 H), 3.56-3.63 (m, 2 H), 3.28 (dddd, $J = 1.8, 4.2, 8.5, 12.8$ Hz, 1 H), 2.76 (ddd, $J = 5.5, 9.2, 14.1$ Hz, 1 H), 2.65-2.70 (m, 1 H), 2.29 (d, $J = 3.6, 1$ H), 2.21 (dddd, $J = 2.2, 2.2, 4.1, 12.7$ Hz, 1 H), 2.16 (dddd, $J = 2.2, 2.2, 4.1, 12.7$ Hz, 1 H), 1.84-1.92 (m, 2 H), 1.62-1.78 (m, 3 H), 1.54 (ddd, $J = 3.4, 10.5, 14.0$ Hz, 1 H), 0.91 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.8, 128.6, 128.6, 126.1, 77.4, 76.8, 75.6, 46.8, 43.4, 43.0, 37.4, 36.9, 34.7, 31.8, 25.8; HRMS (CI/ NH_3), calcd for $\text{C}_{19}\text{H}_{30}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 369.1429, found 369.1420; Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{BrO}_2$: C, 61.79; H, 7.91. Found: C, 62.00; H, 7.85.

1-[(2R*, 4R*, 6S*)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-4-(tert-butyl)diphenylsiloxy)butan-2-ol (9). According to the general procedure described above, 3-(*t*-butyldiphenylsiloxy)-propanal (425 mg, 1.36 mmol, 2.0 equiv) and enol ether **3** (138 mg, 0.682 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (10-20% diethyl ether/hexanes) to give a 1.2:1 diastereomeric ratio of **9** (284 mg, 0.477 mmol, 70 %) as colorless oils. Less polar isomer: $R_f = 0.34$ (30% diethyl ether/hexanes); IR (neat) 3513, 2931, 1111, 701 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.68 (ddd, 1.4, 1.4, 2.7 Hz, 2 H), 7.65 (dd, 1.5, 2.4 Hz, 2 H), 7.34-7.45 (m, 6 H), 7.26 (dd, $J =$

7.0, 7.0 Hz, 2 H), 7.13-7.19 (m, 3 H), 4.11 (dddd, $J = 4.6, 4.6, 12.0, 12.0$ Hz, 1 H), 4.05-4.09 (m, 1 H), 3.87 (ddd, $J = 5.1, 6.2, 11.2$ Hz, 1 H), 3.82 (ddd, $J = 5.1, 7.3, 12.2$ Hz, 1 H), 3.72 (d, $J = 1.5$ Hz, 1 H), 3.54 (dddd, $J = 1.7, 3.9, 9.0, 12.7$ Hz, 1 H), 3.31 (dddd, $J = 1.7, 4.2, 8.3, 12.5$ Hz, 1 H), 2.74 (ddd, $J = 5.4, 9.5, 14.2$ Hz, 1 H), 2.63 (ddd, $J = 7.3, 8.8, 16.3$, 1 H), 2.18-2.26 (m, 2 H), 1.87 (dddd, $J = 5.4, 8.8, 8.8, 17.4$ Hz, 1 H), 1.63-1.82 (m, 6 H), 1.59 (dd, $J = 3.2, 3.9$ Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.6, 135.8, 135.7, 133.7, 133.6, 129.9, 128.6 (2), 128.59 (2), 127.9, 126.1, 77.5, 76.8, 69.4, 62.1, 46.2, 43.5, 43.3, 42.8, 39.5, 37.5, 31.8, 27.1, 19.3; HRMS (EI), calcd for $\text{C}_{33}\text{H}_{43}\text{BrO}_3\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 617.2062, found 617.2084; Anal. Calcd for $\text{C}_{33}\text{H}_{43}\text{BrO}_3\text{Si}$: C, 66.54; H, 7.28. Found: C, 66.31; H, 7.19.

More polar isomer: $R_f = 0.25$ (30% diethyl ether/hexanes); IR (neat) 3514, 2950, 1111, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.65-7.70 (m, 4 H), 7.34-7.46 (m, 6 H), 7.24-7.30 (m, 2 H), 7.14-7.22 (m, 3 H), 4.19-4.28 (m, 1 H), 4.13 (dddd, $J = 4.4, 4.4, 11.7, 11.7$ Hz, 1 H), 3.85-3.90 (m, 2 H), 3.64 (dddd, $J = 2.0, 3.4, 8.8, 11.0$ Hz, 1 H), 3.54 (d, $J = 3.2$ Hz, 1 H), 3.30 (dddd, $J = 1.7, 3.9, 9.0, 12.7$ Hz, 1 H), 2.65-2.82 (m, 2 H), 2.19 (dddd, $J = 2.0, 4.6, 6.6, 11.2$ Hz, 2 H), 1.88 (dddd, $J = 5.4, 8.6, 8.6, 17.4$ Hz, 1 H), 1.52-1.82 (m, 7 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.8, 135.73, 135.70, 133.2, 133.1, 130.02, 129.99, 128.7, 128.6, 127.97, 127.96, 126.1, 76.3, 74.4, 68.0, 63.4, 46.8, 43.8, 43.5, 43.3, 39.0, 37.6, 31.8, 27.0, 19.2; HRMS (EI), calcd for $\text{C}_{33}\text{H}_{43}\text{BrO}_3\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 617.2062, found 617.2070; Anal. Calcd for $\text{C}_{33}\text{H}_{43}\text{BrO}_3\text{Si}$: C, 66.54; H, 7.28. Found: C, 66.50; H, 7.09.

1-[(2*R, 4*R**, 6*S**)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-2-phenylethan-2-ol (10).** According to the general procedure described above, benzaldehyde (162 μL , 1.59 mmol, 2.0 equiv) and enol ether **3** (161 mg, 0.796 mmol, 1.0 equiv) gave a colorless

oil that was purified by flash column chromatography (20% ethyl acetate/hexanes) to give an inseparable 1.3:1 diastereomeric ratio of **10** (164 mg, 0.421 mmol, 53 %) as a colorless oil. R_f = 0.15 (20% ethyl acetate/hexanes); IR (neat) 3515, 2954, 2865, 1496, 1454, 1078, 749, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.39 (m, 9 H), 7.24-7.31 (m, 5 H), 7.17-7.23 (m, 6 H), 4.99-5.05 (m, 1 H), 4.96 (dd, J = 3.4, 9.4 Hz, 1 H), 4.07 (ddd, J = 5.6, 9.7, 14.1 Hz, 2 H), 3.78 (s, 1 H), 3.50-3.62 (m, 2 H), 3.33-3.40 (m, 1 H), 3.25-3.32 (m, 1 H), 3.15 (d, J = 5.0 Hz, 1 H), 2.80 (ddd, J = 5.5, 9.3, 14.2 Hz, 2 H), 2.66-2.76 (m, 2 H), 2.10-2.26 (m, 4 H), 1.65-2.05 (m, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 144.6, 144.2, 141.6, 141.4, 128.8, 128.7, 128.7, 128.6, 127.7, 127.5, 127.5, 127.2, 127.2, 126.2, 126.0, 125.7, 78.2, 77.1, 76.9, 75.1, 74.1, 71.3, 46.1, 45.6, 45.1, 43.8, 43.5, 43.3, 43.2, 43.2, 37.4, 37.4, 31.9, 31.9; HRMS (CI/ NH_3), calcd for $\text{C}_{21}\text{H}_{26}\text{BrO}_2$ $[\text{M} + \text{H}]^+$ 389.1116, found 389.1119.

1-[(2R*, 4R*, 6S*)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-3-(benzyloxy)propan-2-ol (11). According to the general procedure described above, benzyloxyacetaldehyde (229 μL , 1.63 mmol, 2.0 equiv) and enol ether **3** (165 mg, 0.816 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (30% diethyl ether/hexanes) to give a complex diastereomeric ratio of **11** (251 mg, 0.579 mmol, 71 %) as a colorless oil. Due to overlap of four diastereomers, only relevant peaks for diastereoselectivity determination are reported. IR (neat) 3500, 2920, 1094, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.27-7.37 (m, 8.4 H), 7.13-7.21 (m, 3.0 H), 4.67-4.73 (m, 0.32 H, equatorial H, 4-THP), 4.54-4.59 (m, 2.9 H), 4.02-4.18 (m, 2 H), 3.87-3.98 (m, 0.34 H), 3.74-3.79 (m, 1 H), 3.59-3.63 (m, 1.3 H), 3.40-3.59 (m, 2.4 H), 3.24-3.40 (m, 1.4 H), 2.69-2.82 (m, 1.1 H), 2.58-2.70 (m, 1.3 H), 2.15-2.26 (m, 1.4 H), 1.93-2.00 (m, 1.1

H), 1.60-1.90 (m, 6.2H) ^{13}C NMR (125 MHz) δ 141.83, 141.79, 141.54, 138.4, 138.3, 138.2, 128.7, 128.66, 128.62, 128.58, 128.03, 128.01, 127.98, 127.96, 127.89, 126.2, 126.1, 126.0, 77.4, 76.9, 76.6, 74.6, 74.4, 74.2, 74.18, 73.7, 73.6, 73.5, 73.0, 72.1, 71.5, 70.6, 70.0, 69.7, 67.4, 62.2, 50.0, 46.6, 46.0, 43.8, 43.6, 43.5, 43.2, 39.3, 39.1, 37.6, 37.56, 37.5, 32.1, 32.09, 31.8, 31.8; HRMS (CI/NH₃), calcd for C₂₃H₃₀BrO₃ [M + H]⁺ 433.1378, found 433.1377.

1-[(2R*, 4R*, 6S*)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-4-(benzyloxy)butan-2-ol (12). According to the general procedure described above, 3-(benzyloxy)-propanal (212 mg, 1.29 mmol, 2.0 equiv) and enol ether **3** (131 mg, 0.646 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (30-50% diethyl ether/hexanes) to give a complex diastereomeric ratio of **12** (217 mg, 0.484 mmol, 75 %) as a colorless oil. Major isomer: R_f = 0.31 (50% diethyl ether/hexanes); IR (neat) 3501, 2920, 1096, 747, 699 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 7.25-7.36 (m, 7 H), 7.14-7.21 (m, 3 H), 4.53 (d, J = 3.9 Hz, 2 H), 4.10 (dddd, J = 4.5, 4.5, 8.9, 8.9 Hz, 1 H), 4.02-4.08 (m, 1 H), 3.60-3.72 (m, 3 H), 3.56 (dddd, J = 3.6, 3.6, 11.0, 12.7 Hz, 1 H), 3.29-3.36 (m, 1 H), 2.74 (ddd, 5.2, 9.4, 13.9 Hz, 1 H), 2.63 (ddd, J = 7.3, 9.2, 13.8 Hz, 1 H), 2.17-2.26 (m, 2 H), 1.69-1.92 (m, 7 H); ^{13}C NMR (125 MHz, CDCl₃) δ 141.8, 138.2, 128.7, 128.6, 128.6, 127.9, 127.9, 126.1, 76.6, 74.8, 73.5, 69.1, 67.8, 46.7, 43.7, 43.5, 43.0, 37.6, 37.1, 31.8; HRMS (CI/NH₃), calcd for C₂₄H₃₂BrO₃ [M + H]⁺ 447.1535, found 447.1526.

Minor isomer: R_f = 0.36 (50% diethyl ether/hexanes); ^1H NMR (400 MHz, CDCl₃) δ 7.32-7.36 (m, 4 H), 7.25-7.30 (m, 4 H), 7.15-7.21 (m, 3 H), 4.70 (dddd, J = 2.9, 2.9, 2.9,

2.9 Hz, 1 H), 4.53 (d, $J = 5.3$ Hz, 2 H), 4.08-4.20 (m, 2 H), 3.91-4.00 (m, 1 H), 3.86 (s, 1 H), 3.59-3.72 (m, 2 H), 2.76 (ddd, $J = 5.5, 10.4, 13.9$ Hz, 1 H), 2.65 (ddd, 6.4, 10.1, 13.9 Hz, 1 H), 1.91-2.03 (m, 2 H), 1.64-1.90 (m, 7 H).

1-[(2R, 4R, 6S)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-5-(benzyloxy)pentan-2-ol (13). According to the general procedure described above, 4-(benzyloxy)-butanal (265 mg, 1.48 mmol, 2.0 equiv) and enol ether **3** (150 mg, 0.742 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (10-30 % diethyl ether/hexanes) to give a 1.2:1 mixture of two diastereomers **13** (256 mg, 0.556 mmol, 75 %) as a colorless oil. $R_f = 0.23$ (30 % diethyl ether/hexanes); IR (neat) 3511, 2910, 1099, 749, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.24-7.28 (m, 8 H), 7.16-7.23 (m, 6 H), 7.07-7.13 (m, 6 H), 4.45 (s, 2 H), 4.44 (s, 2 H), 4.02 (dddd, $J = 4.6, 4.6, 12.0, 12.0$ Hz, 2 H), 3.82-3.88 (m, 1 H), 3.75-3.81 (m, 1 H), 3.60 (s, 1 H), 3.51-3.57 (m, 1 H), 3.41-3.48 (m, 5 H), 3.17-3.29 (m, 2 H), 2.96 (s, 1 H), 2.63-2.71 (m, 2 H), 2.52-2.62 (m, 2 H), 2.05-2.16 (m, 4 H), 1.42-1.85 (m, 22 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.7, 141.4, 138.6, 138.4, 128.6, 128.55, 128.54, 128.52, 128.50, 127.8, 127.79, 127.77, 127.70, 127.6, 126.1, 126.06, 78.5, 76.9, 76.6, 75.1, 73.2, 73.1, 71.2, 70.6, 70.4, 68.2, 46.5, 45.8, 43.6, 43.4, 43.38, 43.1, 42.5, 37.4, 37.39, 35.0, 34.5, 31.8, 31.76, 26.4, 25.9; HRMS (CI/ NH_3), calcd for $\text{C}_{25}\text{H}_{33}\text{BrO}_3$ $[\text{M}]^+$ 460.1613, found 460.1619.

1-[(2R, 4R, 6S)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-(3R, 2R)-3-(tert-butyldimethylsiloxy)butan-2-ol (14a). According to the general procedure described

above, (*S*)-(tert-butyltrimethylsiloxy) lactaldehyde (230 mg, 1.22 mmol, 2.0 equiv) and enol ether (–)-**3** (124 mg, 0.611 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (10 % diethyl ether/hexanes) to give a 1.6:1.0 diastereomeric ratio of **14a:14b** (combined material: 216 mg, 0.458 mmol, 75 %) as two colorless oils. Less polar isomer: R_f = 0.26 (10% diethyl ether/hexanes); IR (neat) 3525, 2954, 1093, 836, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.30 (m, 2 H), 7.14–7.21 (m, 3 H), 4.12 (dddd, J = 4.4, 4.4, 11.9, 11.9 Hz, 1 H), 3.78 (dddd, J = 6.2, 6.2, 6.2, 11.2, 1 H), 3.51–3.63 (m, 2 H), 3.32 (dddd, J = 2.0, 4.3, 8.4, 12.8 Hz, 1 H), 3.09 (d, J = 3.0 Hz, 1 H), 2.75 (ddd, J = 5.3, 9.3, 14.2 Hz, 1 H), 2.60–2.69 (m, 1 H), 2.30 (dddd, J = 2.2, 2.2, 4.5, 12.7 Hz, 1 H), 2.22 (dddd, J = 2.2, 2.2, 4.4, 12.7 Hz, 1 H), 1.87 (dddd, J = 5.4, 9.1, 9.1, 17.6 Hz, 1 H), 1.63–1.80 (m, 5 H), 1.14 (d, J = 6.2 Hz, 3 H), 0.89 (s, 9H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.7, 128.6, 128.6, 126.2, 77.1, 76.9, 74.3, 71.1, 46.4, 43.5, 43.4, 37.7, 37.5, 31.9, 26.1, 19.0, 18.3, –4.1, –4.6; HRMS (Cl/NH_3), calcd for $\text{C}_{23}\text{H}_{40}\text{BrO}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 471.1930, found 471.1928; Anal. Calcd for $\text{C}_{23}\text{H}_{39}\text{BrO}_3\text{Si}$: C, 58.58; H, 8.34. Found: C, 58.62; H, 8.12.

More polar isomer: 1-[(2*R*, 4*R*, 6*S*)-4-bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-(3*S*, 2*S*)-3-(tert-butyltrimethylsiloxy)butan-2-ol (**14b**). R_f = 0.15 (10 % diethyl ether/hexanes); IR (neat) 3520, 2954, 1085, 836, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25–7.30 (m, 2 H), 7.15–7.21 (m, 3 H), 4.13 (dddd, J = 4.4, 4.4, 11.9, 11.9 Hz, 1 H), 3.76–3.87 (m, 2 H), 3.61 (dddd, J = 2.8, 2.8, 8.2, 11.0 Hz, 1 H), 3.29 (dddd, J = 2.0, 3.9, 9.0, 10.9 Hz, 1 H), 2.76 (ddd, J = 5.2, 9.3, 13.8 Hz, 1 H), 2.63–2.70 (m, 1 H), 2.50 (d, J = 3.6 Hz, 1 H), 2.17–2.24 (m, 2 H), 1.86 (dddd, 5.1, 8.9, 8.9, 17.7 Hz, 1 H), 1.67–1.83 (m, 3 H), 1.11 (d, J = 6.2, 2 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz,

CDCl₃) δ 141.9, 128.7, 128.6, 126.1, 77.4, 76.5, 74.9, 72.0, 71.6, 46.7, 43.9, 43.6, 38.0, 37.7, 31.8, 26.0, 18.3, 17.8, -4.1, -4.6; HRMS (CI/NH₃), calcd for C₁₉H₃₀BrO₃Si [M - *t*-Bu]⁺ 413.1148, found 413.1152.

1-[(2R, 4R(S), 6S)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-(3S, 2S)-3-(benzyloxy)butan-2-ol (16). According to the general procedure described above, (*R*)-(benzyloxy)lactaldehyde (170 mg, 1.04 mmol, 2.0 equiv) and enol ether (–)-**3** (105 mg, 0.520 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (10-30% diethyl ether/hexanes) to give a 2.0:1.0 diastereomeric mixture of **3** (165 mg, 0.520 mmol, 72 %) as a colorless oil. R_f = 0.15 (30% diethyl ether/hexanes); IR (neat) 3482, 2864, 1071, 746 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25-7.37 (m, 14 H), 7.18 (t, J = 8.0 Hz, 6 H), 4.71 (dddd, J = 2.9, 2.9, 2.9, 2.9 Hz, 1 H), 4.68 (d, J = 11.6 Hz, 2 H), 4.46 (dd, J = 8.2, 11.6 Hz, 2 H), 4.21 (dddd, J = 1.7, 3.4, 8.8, 12.0 Hz, 1 H), 4.13 (dddd, J = 4.4, 4.4, 12.0, 12.0 Hz, 1 H), 3.90 (dddd, J = 1.5, 3.9, 9.0, 11.0 Hz, 1 H), 3.75-3.86 (m, 2 H), 3.63 (dddd, J = 2.2, 2.2, 8.8, 11.5 Hz, 1 H), 3.36-3.46 (m, 2 H), 3.29 (dddd, J = 1.7, 3.9, 8.8, 12.7 Hz, 1 H), 2.73-2.84 (m, 2 H), 2.72 (d, J = 4.4 Hz, 1 H), 2.62-2.70 (m, 3 H), 2.15-2.22 (m, 2 H), 1.93-2.01 (m, 2 H), 1.52-1.90 (m, 12 H), 2.230 (d, J = 6.1 Hz, 3 H), 2.225 (d, J = 6.1, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 142.3, 142.0, 138.7, 138.5, 128.8, 128.73, 128.68(2), 128.62, 128.60, 128.09, 128.06, 128.0, 127.9, 126.1, 126.0, 78.7, 78.6, 76.5, 74.3, 71.8, 71.4, 71.33, 71.31, 71.30, 69.6, 50.7, 47.0, 44.0, 43.6, 40.1, 40.0, 39.6, 39.2, 37.8, 37.7, 32.1, 31.9, 15.81, 15.80; HRMS (CI/NH₃), calcd for C₂₄H₃₁BrO₃ [M]⁺ 446.1457, found 446.1457.

1-[(2R , 4R (S), 6S)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-(3S)-benzyloxybutan-(2S)-ol (15). According to the general procedure described above, (S)-(benzyloxy)lactaldehyde (170 mg, 1.04 mmol, 2.0 equiv) and enol ether (–)-**3** (105 mg, 0.520 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (10-30% diethyl ether/hexanes) to give a 2.0:1.0 diastereomeric mixture of **15** (165 mg, 0.520 mmol, 74 %) as a colorless oil. R_f = 0.15 (30% diethyl ether/hexanes); IR (neat) 3482, 2864, 1071, 746 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.38 (m, 7 H), 7.13-7.21 (m, 3 H), 4.66 (dd, J = 11.7 Hz, 1 H), 4.46 (d, J = 11.7 Hz, 1 H), 4.07 (dddd, J = 4.6, 4.6, 12.0, 12.0 Hz, 1 H), 3.74-3.82 (m, 1 H), 3.52 (dddd, J = 6.1, 6.1, 6.1, 6.1 Hz, 1 H), 3.27 (d, J = 2.0 Hz, 1 H), 2.72 (ddd, J = 5.4, 9.8, 14.7 Hz, 1 H), 2.61 (ddd, J = 7.1, 9.3, 13.9 Hz, 1 H), 2.24 (dddd, J = 2.2, 2.2, 4.6, 13.0 Hz, 1 H), 2.15-2.20 (m, 1 H), 1.79-1.90 (m, 1 H), 1.51-1.79 (m, 5 H), 1.21 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.5, 138.6, 128.6, 128.55, 128.53, 128.52, 127.9, 126.1, 77.2, 76.9, 76.8, 76.4, 73.1, 71.1, 46.2, 43.4, 43.2, 37.6, 37.5, 31.8, 14.9; HRMS (CI/ NH_3), calcd for $\text{C}_{24}\text{H}_{31}\text{BrO}_3$ $[\text{M}]^+$ 446.1457, found 446.1451.

1-[(2R *, 4R *, 6S *)-4-Bromo-6-(2-benzyloxyethyl)tetrahydropyran-2-yl]-4-phenylbutan-2-ol (23). According to the general procedure described above, hydrocinnamaldehyde (170 μL , 1.29 mmol, 2.0 equiv) and enol ether **21** (150 mg, 0.646 mmol, 1.0 equiv) gave a colorless oil that was purified by flash column chromatography (15-30% diethyl ether/hexanes) to give **23** (226 mg, 0.490 mmol, 76 %) as two colorless oils in a 1.0:1.0 diastereomeric ratio. Less-Polar isomer: R_f = 0.30 (30% diethyl

ether/hexanes); IR (neat) 3420, 2922, 1094, 750, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.36 (m, 4 H), 7.25-7.30 (m, 3 H), 7.14-7.22 (m, 3 H), 4.49 (s, 2 H), 4.09 (dddd, J = 4.5, 4.5, 12.0, 12.0 Hz, 1 H), 3.77-3.84 (m, 2 H), 3.49-3.60 (m, 4 H), 2.76 (ddd, J = 5.5, 9.8, 13.9 Hz, 1 H), 2.62-2.70 (m, 1 H), 2.14-2.24 (m, 1 H), 1.63-1.86 (m, 7 H), 1.55 (ddd, J = 2.3, 2.3, 14.5 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.3, 138.4, 128.6, 128.55, 128.49, 127.9, 127.8, 125.9, 78.8, 75.3, 73.3, 71.0, 66.5, 45.7, 43.6, 43.1, 42.4, 39.3, 35.9, 31.8; HRMS (CI/ NH_3), calcd for $\text{C}_{24}\text{H}_{32}\text{BrO}_3$ $[\text{M} + \text{H}]^+$ 447.1535, found 447.1577; Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{BrO}_3$: C, 64.43; H, 6.98. Found: C, 64.43; H, 6.71.

More polar isomer: R_f = 0.25 (30 % diethyl ether/hexanes); IR (neat) 3498, 2910, 1096, 745, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.17-7.30 (m, 7 H), 7.11 (d, J = 7.4 Hz, 3 H), 4.42 (d, J = 11.9 Hz, 1 H), 4.38 (d, J = 11.9 Hz, 1 H), 4.06 (dddd, J = 4.4, 4.4, 12.0, 12.0 Hz, 1 H), 3.75-3.81 (m, 1 H), 3.56 (dddd, J = 2.0, 3.2, 8.1, 11.2 Hz, 1 H), 3.41-3.52 (m, 3 H), 2.72 (ddd, J = 5.6, 10.3, 13.9 Hz, 1 H), 2.57 (ddd, J = 6.6, 10.0, 13.9 Hz, 1 H), 2.38 (s, 1 H), 2.15 (dddd, J = 2.2, 2.2, 4.4, 12.7 Hz, 1 H), 2.07 (dddd, J = 2.2, 2.2, 4.4, 13.0 Hz, 1 H), 1.48-1.79 (m, 8 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.3, 138.5, 128.6, 128.57, 128.55, 127.9, 127.8, 126.0, 75.3, 75.0, 73.3, 68.2, 66.4, 46.2, 43.3, 43.1, 41.9, 39.2, 36.0, 32.3; HRMS (CI/ NH_3), calcd for $\text{C}_{24}\text{H}_{32}\text{BrO}_3$ $[\text{M} + \text{H}]^+$ 447.1535, found 447.1506; Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{BrO}_3$: C, 64.43; H, 6.98. Found: C, 64.58; H, 6.77.

1-[(2R *, 4R *, 6S *)-4-Bromo-6-(3-benzyloxypropyl)tetrahydropyran-2-yl]-4-phenylbutan-2-ol (25). According to the general procedure described above, hydrocinnamaldehyde (161 μL , 1.22 mmol, 2.0 equiv) and enol ether **24** (150 mg, 0.609 mmol, 1.0 equiv) gave a pale yellow oil that was purified by flash column chromatography (10-40% diethyl ether/hexanes) to give **25** (208 mg, 0.451 mmol, 74 %)

as two colorless oils in a 1.0:1.0 diastereomeric ratio. Less polar isomer: R_f = 0.23 (40 % diethyl ether/hexanes); IR (neat) 3410, 2932, 1094, 750, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.36 (m, 5 H), 7.25-7.30 (m, 2 H), 7.15-7.22 (m, 3 H), 4.48 (s, 2 H), 4.09 (dddd, J = 4.4, 4.4, 12.0, 12.0 Hz, 1 H), 3.78-3.84 (m, 1 H), 3.58 (s, 1 H), 3.50 (dddd, J = 2.2, 2.2, 10.8, 10.8 Hz, 1 H), 3.42-3.50 (m, 2 H), 3.34-3.40 (m, 1 H), 2.77 (ddd, J = 5.6, 9.8, 13.9 Hz, 1 H), 2.67 (ddd, J = 6.6, 9.8, 13.7 Hz, 1 H), 2.23 (dddd, J = 2.2, 2.2, 2.2, 12.7, 1 H), 2.17 (dddd, J = 2.2, 2.2, 2.2, 12.7 Hz, 1 H), 1.52-1.83 (m, 10 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.4, 138.7, 128.6, 128.5, 128.49, 127.9, 127.8, 125.9, 78.9, 77.8, 73.1, 71.1, 70.0, 45.8, 43.7, 43.1, 42.5, 39.4, 32.7, 31.9, 25.9; HRMS (CI/ NH_3), calcd for $\text{C}_{25}\text{H}_{33}\text{BrO}_3$ $[\text{M}]^+$ 460.1613, found 460.1603.

More polar isomer: R_f = 0.13 (40 % diethyl ether/hexanes); IR (neat) 3461, 2943, 1078, 739, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.43 (m, 4 H), 7.30-7.36 (m, 3 H), 7.21-7.28 (m, 3 H), 4.54 (s, 2 H), 4.17 (dddd, J = 4.4, 4.4, 12.0, 12.0 Hz, 1 H), 3.91-3.99 (m, 1 H), 3.66 (dddd, J = 2.0, 3.4, 8.3, 11.2 Hz, 1 H), 3.46-3.57 (m, 2 H), 3.32-3.40 (m, 1 H), 2.86 (ddd, J = 5.6, 10.3, 13.9 Hz, 1 H), 2.67-2.75 (m, 2 H), 2.27 (dddd, J = 2.2, 2.2, 4.4, 12.7 Hz, 1 H), 2.19 (dddd, J = 2.2, 2.2, 4.4, 12.7 Hz, 1 H), 1.58-1.91 (m, 10 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.3, 138.6, 128.54, 128.52, 128.50, 127.8, 127.7, 125.9, 77.6, 75.2, 73.0, 70.0, 68.1, 46.4, 43.3, 43.1, 41.9, 39.3, 32.7, 32.3, 25.8; HRMS (CI/ NH_3), calcd for $\text{C}_{25}\text{H}_{33}\text{BrO}_3$ $[\text{M}]^+$ 460.1613, found 460.1610.

1-[(2R , 6S)-6-(2-phenylethyl)tetrahydropyran-2-yl]-(3S)-benzyloxybutan-(2S)-ol (20). A mixture of THP **15** (220 mg, 0.492 mmol, 1.0 equiv), epimeric at C-4 was dissolved in tributyltin hydride (2 mL). Catalytic AIBN was then added in one portion and the solution was heated at 100 $^{\circ}\text{C}$ for 2 h. The solution was then immediately purified by flash chromatography (0-20 % MTBE/hexanes) to give a clear colorless oil (138 mg,

0.374 mmol, 76 %): R_f = 0.45 (30 % MTBE/hexanes); IR (neat) 3480, 2932, 1081, 739, 699 cm^{-1} ; $[\alpha]_D^{23}$ +12.8 (c 0.21, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.36 (m, 4 H), 7.24-7.30 (m, 3 H), 7.14-7.20 (m, 3 H), 4.65 (d, J = 12.0 Hz, 1 H), 4.51 (d, J = 11.7 Hz, 1 H), 3.86-3.91 (m, 1 H), 3.77 (d, J = 1.5 Hz, 1 H), 3.52-3.60 (m, 2 H), 3.33 (dddd, J = 1.7, 4.2, 8.1, 12.5 Hz, 1 H), 2.74 (ddd, J = 5.4, 10.0, 14.0 Hz, 1 H), 2.62 (ddd, J = 6.8, 9.5, 13.7 Hz, 1 H), 1.74-1.85 (m, 2 H), 1.60-1.74 (m, 4 H), 1.42-1.52 (m, 2 H), 1.25-1.35 (m, 2 H), 1.21 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.3, 139.0, 128.6, 128.53, 128.51, 127.9, 127.7, 125.9, 78.5, 77.4, 77.3, 73.9, 71.2, 38.3, 37.8, 32.12, 32.11, 31.6, 23.6, 14.8; HRMS (CI/ NH_3), calcd for $\text{C}_{24}\text{H}_{32}\text{O}_3$ $[\text{M}]^+$ 368.2351, found 368.2362.

1-[(2R, 4R, 6S)-4-Bromo-6-(2-phenylethyl)tetrahydropyran-2-yl]-3-(tert-butylidimethylsiloxy)butan-2-one (18). To a solution of an approximately 1:1 mixture alcohol epimers of THP **14** (103 mg, 0.218 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added solid NaHCO_3 (185 mg) and Dess Martin Periodinane (185 mg, 0.437 mmol, 2.0 equiv) sequentially. The heterogeneous mixture was allowed to stir for 30 min at room temperature at which point TLC analysis showed consumption of starting material. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with deionized water (2 X 10 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a crude oil that was purified by flash chromatography (0-10 % MTBE/hexanes) to give **18** (98 mg, 0.209 mmol, 94 %) as a clear colorless oil: R_f = 0.74 (30% MTBE/hexanes); IR (neat) 2954, 1721, 1121, 836 cm^{-1} ; $[\alpha]_D^{23}$ +4.0 (c 1.0, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.24-7.30 (m, 2 H), 7.13-7.20 (m, 3 H), 4.17 (dd, J = 6.8, 6.8 Hz, 1 H), 4.13 (dddd, J = 4.4, 4.4, 12.0, 12.0 Hz, 1 H), 3.84 (dddd, J = 2.0, 5.1, 7.1, 12.5 Hz, 1 H), 3.28 (dddd, J = 2.0, 4.2, 8.6, 14.9 Hz, 1 H), 2.94 (dd, J = 7.0, 17.2 Hz, 1 H), 2.66-2.74 (m, 1 H),

2.56-2.66 (m, 2 H), 2.23-2.30 (m, 1 H), 2.15-2.22 (m, 1 H), 1.77-1.86 (m, 1 H), 1.60-1.72 (m, 3 H), 1.29 (dd, $J = 6.3, 6.3$ Hz, 1 H), 0.93 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 211.2, 141.9, 128.7, 128.5, 126.0, 76.6, 75.2, 73.3, 46.3, 43.2, 43.1, 42.7, 37.5, 31.6, 25.9, 20.7, 18.2, -4.5, -4.8; HRMS (CI/NH_3), calcd for $\text{C}_{23}\text{H}_{38}\text{BrO}_3\text{Si}$ $[\text{M} + \text{H}]^+$ 469.1774, found 469.1762.