Axial-selective Prins Cyclizations by Solvolysis of β -Bromo Ethers

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General Experimental Details. ^1H NMR spectra were recorded at 400 or 500 MHz on Bruker NMR spectrometers and were referenced to residual solvent peaks. ^{13}C NMR spectra were recorded at 125 MHz on Bruker NMR spectrometers. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR. All reagents were obtained commercially and purified prior to use. Tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried by filtration through alumina according to the methods described by Grubbs.¹ Liquid chromatography was performed using forced flow of the indicated solvent system on reagent silica gel 60. Thin layer chromatography (TLC) was performed on Whatman 250 μm layer silica gel plates. Developed plates were visualized using α -anisaldehyde, potassium permanganate, I_2 stains and UV light. All glassware was flame-dried and cooled under an inert atmosphere of argon unless otherwise stated. Moisture sensitive reactions were carried out under an inert atmosphere of argon using standard syringe/septa techniques.

Procedures and Characterization:

Ester 28. To a cooled (0 °C) solution of oxazole carboxylic acid² (894 mg, 5.53 mmol, 1.1 equiv) and 1-phenyl-hex-5-en-3-ol (887 mg, 5.03 mmol, 1.0 equiv) in 20 mL of dichloromethane was added DCC (1.14 g, 5.53 mmol, 1.1 equiv) and DMAP (123 mg, 10.1 mmol, 0.2 equiv). The reaction mixture was warmed to 25 °C, stirred for 12 hours,

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, 15, 1518-1520.

² Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998**, 39, 3149-3152.

diluted with ether (20 mL) and filtered to remove the precipitated dicyclohexylurea. The resulting solution was concentrated *in vacuo* to provide a crude oil that was purified by flash chromatography on silica gel (10% ether/hexanes to 50% ether/hexanes) to afford **28** (1.35 g, 84%) as a colorless oil: IR (neat/NaCl) 2976, 1738, 1316, 1136, 1113 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1 H), 7.28–7.25 (m, 2 H), 7.19–7.15 (m, 3 H), 5.78 (dddd, $J = 17.2, 10.1, 7.1, 7.1$ Hz, 1 H), 5.28–5.21 (m, 1 H), 5.13–5.07 (m, 2 H), 4.65 (s, 2 H), 2.76–2.10 (m, 2 H), 2.47 (app t, $J = 6.7$ Hz, 2 H), 2.11–1.93 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.3, 159.8, 144.9, 141.2, 134.0, 133.1, 128.4, 128.3, 126.0, 118.3, 74.2, 38.7, 35.3, 35.2, 31.8; HRMS (CI/Ammonia) m/z calcd for $\text{C}_{17}\text{H}_{18}\text{ClNO}_3$ $[\text{M} + \text{H}]^+$ 320.1053, found 320.1051.

Acetoxy Ether 1. DIBAL-H reduction/*in situ* acetylation of ester **28** (710 mg, 2.22 mmol, 1.0 equiv) according to the general procedure for the preparation of α -acetoxy ethers³ provided crude acetoxy ether **1**, which was purified by flash chromatography on silica gel deactivated with 2% triethylamine (10% ether/hexanes to 50% ether/hexanes) to afford the title acetoxy-acetal (581 mg, 72%) as a colorless oil. The reported data represents a (1.1:1) mixture of diastereomers: IR (neat/NaCl) 3027, 2976, 2937, 1741, 1372, 1232, 1117 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, $J = 0.8$ Hz, 0.5 H), 7.72 (d, $J = 0.8$ Hz, 0.5 H), 7.30–7.25 (m, 2 H), 7.20–7.16 (m, 3 H), 6.87 (d, $J = 0.8$ Hz, 0.5 H), 6.84 (d, $J = 0.8$ Hz, 0.5 H), 5.89–5.75 (m, 1 H), 5.13–5.06 (m, 2 H), 4.61 (s, 1 H),

³ Reductive acetylation of ester substrates were carried out using the procedure described in the following citation: Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, 65, 191-198.

4.60 (s, 1 H), 3.95–3.86 (m, 1 H), 2.82 (ddd, $J = 15.5, 9.2, 6.9$ Hz, 0.5 H), 2.77–2.56 (m, 1.5 H), 2.14 (s, 1.5 H), 2.12 (s, 1.5 H), 1.93–1.79 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 170.4, 159.5(2), 141.9, 141.7, 139.3, 139.2, 138.0, 137.8, 134.1, 133.5, 128.4(2), 128.3, 125.9, 125.8, 118.2, 117.4, 91.2, 90.4, 80.0, 78.5, 77.2, 39.2, 38.9, 36.0, 35.9, 35.7(2), 31.6, 31.3, 21.3, 21.2; HRMS (CI/Ammonia) m/z calcd for $\text{C}_{19}\text{H}_{22}\text{ClNO}_4$ $[\text{M} + \text{H}]^+$ 364.1316, found 364.1312.

Tetrahydropyran 2. To a cooled (0 °C) solution of acetoxo ether **1** (200 mg, 0.550 mmol, 1.0 equiv) in 3.0 mL of dichloromethane was added TMSBr (160 μL , 1.21 mmol, 2.2 equiv) dropwise via syringe. The reaction mixture was stirred at 0 °C for 1.5 hours and was then diluted with saturated aqueous NaHCO_3 (10 mL) and ether (10 mL). After warming to 25 °C, the aqueous phase was extracted with ether (3 x 20 mL), and the combined organic extracts were washed with brine (60 mL), dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel (10% ether/hexanes to 50% ether/hexanes) to afford the title bromo-tetrahydropyran (184 mg, 85%) as a slightly yellow oil: IR (thin film) 3061, 2953, 2918, 2864, 1602, 1054 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 7.20–7.15 (m, 3 H), 7.12–7.06 (m, 3 H), 4.97 (d, $J = 10.9$ Hz, 1 H), 4.17 (quin, $J = 2.9$ Hz, 1 H), 3.98–3.96 (m, 1 H), 3.95 (s, 2 H), 2.73 (ddd, $J = 13.8, 10.2, 5.4$ Hz, 1 H), 2.53 (ddd, $J = 13.6, 10.0, 6.4$ Hz, 1 H), 2.21 (dq, $J = 14.6, 2.2$ Hz, 1 H), 1.80 (ddd, $J = 14.6, 11.2, 3.3$ Hz, 1 H), 1.72 (dddd, $J = 13.7, 10.0, 8.4, 5.4$ Hz, 1 H), 1.60 (dq, $J = 14.5, 2.2$ Hz, 1 H), 1.48 (dddd,

$J = 14.1, 10.4, 6.4, 4.1$ Hz, 1 H), 1.27 (ddd, $J = 14.3, 10.8, 3.3$ Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.4, 143.3, 142.7, 136.9, 129.1(2), 126.5, 72.4, 68.8, 50.4, 39.7, 39.1, 38.0, 36.1, 32.4; HRMS (CI/Ammonia) m/z calcd for $\text{C}_{17}\text{H}_{19}\text{BrClNO}_2$ $[\text{M}]^+$ 383.0287, found 383.0288.

General Procedure for Bromotrimethylsilane Initiated Cyclizations

Bromotetrahydropyran 5. To a cooled solution (0 °C) of acetoxy ether **4** (100 mg, 0.38 mmol, 1.0 equiv) in 2.0 mL dichloromethane was added 2,6-lutidine (8.8 μL , 0.076 mmol, 0.20 equiv) followed by addition of bromotrimethylsilane (130 μL , 0.95 mmol, 2.5 equiv). The reaction mixture was stirred for 1 h then warmed to room temperature and stirred for an additional 30 min. A saturated aqueous solution of sodium bicarbonate (5 mL) was then added to the reaction mixture and stirred for 5 min. The dichloromethane and aqueous layers were then separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organics were then dried over NaSO_4 and concentrated in vacuo. The resulting crude oil was purified by flash chromatography on silica gel (1% ether/hexanes) to afford bromotetrahydropyran **5** (105 mg, 98%) as a colorless oil: IR (neat) 2943, 2867, 1453, 1372, 1105, 913, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (m, 2 H), 7.22 (m, 3 H), 4.74 (quin, $J = 2.9$ Hz, 1 H), 4.03 (dq, $J = 11.3, 6.2$ Hz, 1 H), 3.91 (dddd, $J = 11.2, 9.2, 7.3, 1.8$ Hz, 1 H), 2.84 (ddd, $J = 14.1, 10.2, 5.5$ Hz, 1 H), 2.71 (ddd, $J = 13.7, 10.0, 6.5$ Hz, 1 H), 2.00 (m, 2 H), 1.89 (dtd, $J = 13.7, 9.8, 5.6$ Hz, 1 H), 1.74 (m, 3 H), 1.26 (t, $J = 6.3$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.1, 128.4, 128.3, 125.7, 71.4, 68.2, 50.8, 41.2, 39.3, 37.4, 31.7, 21.3;

LRMS (CI/NH₃) m/z calcd for C₁₄H₁₉BrO (M)⁺ 282, found 282. Anal. Calcd for C₁₄H₁₉BrO: C, 59.37; H, 6.76. Found: C, 59.50; H, 6.92.

Tetrahydropyran 7. IR (neat) 2955, 2866, 1455, 1072, 909, 735 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.29 (m, 2 H), 7.22 (m, 3 H), 4.81 (quin, J = 3.0 Hz, 1 H), 3.85 (dddd, J = 10.8, 8.9, 3.6, 2.0 Hz, 1 H), 3.50 (dd, J = 11.0, 1.7 Hz, 1 H), 2.87 (ddd, J = 14.2, 9.9, 5.1 Hz, 1 H), 2.70 (ddd, J = 13.8, 9.7, 6.9 Hz, 1 H), 1.97 (m, 2 H), 1.84 (dtd, J = 13.9, 9.4, 5.1 Hz, 1 H), 1.73 (m, 3 H), 0.96 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 142.4, 128.4, 128.3, 125.7, 79.3, 71.3, 52.1, 39.9, 37.6, 34.0, 33.9, 31.8, 26.0; LRMS (CI/NH₃) m/z calcd for C₁₇H₂₅BrO (M)⁺ 324, found 324. Anal. Calcd for C₁₇H₂₅BrO: C, 62.77; H, 7.75. Found: C, 62.58; H, 7.84.

Tetrahydropyran 14. IR (neat) 2936, 2865, 1453, 11102, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31 (m, 2 H), 7.23 (m, 3 H), 3.95 (ddd, J = 10.5, 6.2, 1.7 Hz, 1 H), 3.83 (dddd, J = 10.9, 8.4, 4.8, 2.3 Hz, 1 H), 2.85 (ddd, J = 13.9, 10.3, 5.5 Hz, 1 H), 2.72 (ddd, J = 13.8, 10.1, 6.3 Hz, 1 H), 2.07 (m, 1 H), 2.05 (m, 1 H), 1.89 (m, 4 H), 1.75 (m, 1 H), 1.33 (m, 2 H), 1.27 (d, J = 6.3 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 142.1, 128.4, 128.3, 125.7, 73.4, 70.1, 67.6, 49.1, 47.2, 37.3, 35.8, 31.8, 21.1; LRMS (CI/NH₃) m/z calcd for C₁₅H₂₅BrNO (M + NH₄)⁺ 314, found 314. Anal. Calcd for C₁₅H₂₁BrO: C, 60.41; H, 7.44. Found: C, 60.72; H, 7.07.

Tetrahydropyran 20. IR (neat) 2972, 2865, 1454, 1100, 701 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.30 (m, 2 H), 7.23 (m, 3 H), 4.51 (q, $J = 2.9$ Hz, 1 H), 4.17 (dtd, $J = 10.7, 6.6, 1.8$ Hz, 1 H), 3.62 (dq, $J = 9.3, 6.2$ Hz, 1 H), 2.97 (dd, $J = 13.8, 6.6$ Hz, 1 H), 2.68 (dd, $J = 13.8, 6.6$ Hz, 1 H), 2.08 (dt, $J = 14.3, 2.1$ Hz, 1 H), 1.90 (ddd, $J = 14.1, 10.7, 3.2$ Hz, 1 H), 1.42 (ddd, $J = 9.4, 6.6, 2.8$ Hz, 1 H), 1.20 (d, $J = 6.2$ Hz, 3 H), 0.95 (d, $J = 6.6$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.2, 129.4, 128.2, 126.2, 73.0, 72.5, 60.4, 41.9, 41.6, 40.5, 19.1, 17.1; LRMS (CI/ NH_3) m/z calcd for $\text{C}_{14}\text{H}_{23}\text{BrNO}$ ($\text{M} + \text{NH}_4$) $^+$ 300, found 300. Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{BrO}$: C, 59.37; H, 6.76. Found: C, 59.18; H, 6.70.

General Procedure for Iodotrimethylsilane Initiated Cyclizations

Iodotetrahydropyran 5. To a cooled solution (0 $^{\circ}\text{C}$) of acetoxymethyl ether **4** (100 mg, 0.38 mmol, 1.0 equiv) in 2.0 mL dichloromethane was added 2,6-lutidine (8.8 μL , 0.076 mmol, 0.20 equiv) followed by addition of iodotrimethylsilane (135 μL , 0.95 mmol, 2.5 equiv). The reaction mixture was stirred for 1 h then warmed to room temperature and stirred for an additional 30 min. An aqueous saturated solution of sodium bicarbonate (5 mL) was then added to the reaction mixture and stirred for 5 min. The biphasic mixture was then separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organics were then dried over NaSO_4 and concentrated in vacuo.

The resulting crude oil was purified by flash chromatography on silica gel (1% ether/hexanes) to afford iodotetrahydropyran **5** (115 mg, 92%) as a colorless oil: IR (neat) 2943, 2867, 1456, 1243, 1105, 913, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (m, 2 H), 7.22 (m, 3 H), 4.86 (quin, $J = 3.2$ Hz, 1 H), 3.97 (dq, $J = 10.8, 6.3$ Hz, 1 H), 3.86 (ddd, $J = 10.9, 8.5, 2.3$ Hz, 1 H), 2.84 (ddd, $J = 13.7, 10.2, 5.6$ Hz, 1 H), 2.71 (ddd, $J = 13.8, 10.1, 6.3$ Hz, 1 H), 2.03 (quin, $J = 1.9$ Hz, 1 H), 1.99 (quin, $J = 1.8$ Hz, 1 H), 1.92 (dddd, $J = 13.7, 10.1, 8.0, 5.7$ Hz, 1 H), 1.74 (dddd, $J = 13.6, 10.8, 5.6, 4.8$ Hz, 1 H), 1.51 (dddd, $J = 14.3, 10.2, 6.4, 3.6, 2$ H), 1.28 (d, $J = 6.3$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.0, 128.4, 128.3, 125.7, 72.8, 69.6, 42.3, 40.4, 37.2, 31.8, 31.0, 21.2; LRMS (CI/ NH_3) m/z calcd for $\text{C}_{14}\text{H}_{20}\text{IO}$ ($\text{M} + \text{H}$) $^+$ 331, found 331. Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{IO}$: C, 50.92; H, 5.80. Found: C, 51.18; H, 5.96.

Tetrahydropyran 11. IR (neat) 2964, 2871, 1457, 1098, 1016, 683 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.65 (q, $J = 1.8$ Hz, 1 H), 3.68 (m, 4 H), 3.48 (t, $J = 10.5$ Hz, 1 H), 1.31 (m, 2 H), 0.99 (d, $J = 6.5$ Hz, 3 H), 0.90 (d, $J = 6.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 76.8, 69.8, 57.5, 45.8, 37.5, 36.5, 19.2, 18.8; LRMS (CI/ NH_3) m/z calcd for $\text{C}_8\text{H}_{15}\text{ClIO}$ ($\text{M} + \text{H}$) $^+$ 289, found 289. Anal. Calcd for $\text{C}_8\text{H}_{14}\text{ClIO}$: C, 33.30; H, 4.89. Found: C, 33.46; H, 4.86.

Tetrahydropyran 16. IR (neat) 2955, 2869, 1467, 1226, 1068 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.88 (dddd, $J = 3.0$ Hz, 1 H), 4.06 (dt, $J = 9.2, 4.2$ Hz, 1 H), 3.93 (m, 1 H), 3.55 (m, 2 H), 2.10 (dd, $J = 14.5, 1.8$ Hz, 1 H), 1.97 (dd, $J = 14.7, 1.7$ Hz, 1 H), 1.81 (dt, $J = 13.5, 6.7$ Hz, 1 H), 1.59 (m, 2 H), 1.47 (ddd, $J = 14.3, 10.4, 3.5$ Hz, 1 H), 1.25 (ddd, $J = 13.0, 7.6, 5.0$ Hz, 1 H), 0.93 (m, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 73.3, 72.3, 46.6, 44.1, 40.6, 38.1, 29.6, 24.4, 22.9, 22.4; LRMS (CI/NH_3) m/z calcd for $\text{C}_{10}\text{H}_{19}\text{ClIO}$ ($\text{M} + \text{H}$) $^+$ 317, found 317. Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{ClIO}$: C, 37.94; H, 5.73. Found: C, 38.07; H, 5.57.

Tetrahydropyran 18. IR (neat) 2942, 2865, 1456, 1105, 1075 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.29 (m, 2 H), 7.21 (m, 3 H), 4.87 (dddd, $J = 2.0$ Hz, 1 H), 4.06 (m, 1 H), 3.85 (m, 3 H), 2.83 (ddd, $J = 13.9, 10.4, 5.4$ Hz, 1 H), 2.67 (ddd, $J = 13.8, 10.2, 6.3$ Hz, 1 H), 2.01 (m, 2 H), 1.77 (m, 4 H), 1.53 (m, 2 H), 1.10 (m, 21 H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.9, 128.4, 128.3, 125.7, 72.7, 70.3, 59.6, 40.9, 40.8, 38.9, 37.4, 31.9, 31.0, 18.1, 12.0; HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{42}\text{IO}_2\text{Si}$ ($\text{M} + \text{Na}$) $^+$ 539.1818, found 539.1818. Anal. Calcd for $\text{C}_{24}\text{H}_{41}\text{IO}_2\text{Si}$: C, 55.80; H, 8.00. Found: C, 55.66; H, 7.89.

Procedure for the Preparation of Bromoether 23 for NMR Characterization

Bromoether 23. To a cooled (-78°C) solution of acetoxo ether **4** (25 mg, 0.095 mmol, 1 equiv) in CD_2Cl_2 in an NMR tube was added bromotrimethylsilane (25 μL , 0.19 mmol, 2.0 equiv). The NMR tube was then briefly shaken and placed in the NMR probe which had previously been set to -50°C . After 15 minutes, complete consumption of **4** was observed. Characterization presented below is representative of a 2.1 to 1.0 ratio of bromoethers: ^1H NMR (500 MHz, CDCl_3) δ 7.25 (m, 2 H), 7.18 (m, 3 H), 6.24 (q, J = 5.3 Hz, 0.68 H), 6.21 (q, J = 5.3 Hz, 0.32 H), 5.78 (m, 1 H), 5.08 (m, 2 H), 3.82 (m, 1 H), 2.75 (m, 0.64 H), 2.58 (m, 1.36 H), 2.34 (m, 2 H), 1.98 (m, 3 H), 1.72 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.8, 142.2, 134.0, 133.3, 128.5, 128.4, 128.3, 128.2, 126.0, 125.8, 118.5, 117.5, 94.4, 94.3, 80.5, 79.2, 37.9, 37.6, 35.8, 34.5, 31.8, 30.7, 28.5, 28.3.