An Asymmetric Aminohydroxylation Approach to the Azepine Core of (-)-Balanol

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Experimental Section

General Experimental Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use and tetrahydrofuran (THF) was freshly distilled under argon from sodium / benzophenone ketyl. Benzyl carbamate was recrystallized from water prior to use. Isobutyraldehyde was distilled from calcium sulfate and stored over 4 Å sieves. Sodium hydride was purchased from Alfa Aesar (57-63% dispersion in oil) and used as received. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature. ^{13}C NMR were recorded on a 75.5 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0), deuterium oxide (^{1}H, δ 4.76), methanol (^{1}H, δ 3.31; ^{13}C, δ 49.15). All ^{13}C NMR were recorded with complete proton decoupling. Infrared spectra were recorded on a FT-spectrophotometer. Optical rotations were recorded on a digital polarimeter at 589 nm. High resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory. Analytical thin layer chromatography was performed on Whatman 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described.[1] When specified as "anhydrous," solvents were distilled and / or stored over 4 Å sieves prior to use. Unless otherwise noted, non-aqueous reactions were carried out in oven dried glassware under a dry argon atmosphere.

(para-Bromophenyl)diethylphosphonoacetate (5): To a solution of diethylphosphonoacetic acid (10.0 g, 0.050 mol, 1.1 equiv) in CH_2Cl_2 (100 mL, 0.5 **M**) at 0 °C,

was added *p*-bromophenol (8.0 g, 0.046 mol, 1.0 equiv), DCC (10.3g, 0.050 mole, 1.1 equiv), and catalytic DMAP (~ 10 mg). The reaction mixture was warmed to ambient temperature, with stirring, over a period of 10 hours. The reaction mixture was subsequently cooled to 0 °C, filtered, through Celite, washed with EtOAc (30 mL), and concentrated *in vacuo* to give crude **5** as a yellow-orange oil. The crude material was passed through a plug of silica gel (20 → 30% EtOAc/PE) to afford pure **5** as a yellow oil (16.8 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 8.8 Hz); 6.98 (d, 2H, J = 8.8 Hz); 4.12 (q, 4H, J = 6.8 Hz); 3.16 (d, 2H, J = 22 Hz); 1.34 (t, 6H, 6.8 Hz); ^{13}C (75.5 MHz, $CDCl_3$) δ 164.2, 149.8, 132.5, 123.4, 121.6, 118.8, 43.8, 30.7, 29.7, 29.5.

(para-Bromophenyl)-6-chloro-2-(*E*)-hexenoate (4): To a suspension of NaH (0.68 g, 17.02 mmol, 1.1 equiv) in THF (60 mL, 0.25 **M**) at 0 °C was added dropwise a solution of *p*-(bromophenyl)-diethylphosphonoacetate (**5**, 6.2 g, 17.02 mmol, 1.1 equiv) in dry THF (17 mL, 1**M**). The mixture was stirred for 10 minutes at 0 °C then warmed to ambient temperature for 10 minutes. To this yellow solution was added 4-chlorobutanal (1.64 g, 15.47 mmol, 1.0 equiv) and the solution stirred for 1 hour at ambient temperature. The reaction mixture was subsequently diluted with NH_4Cl (30 mL), extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification on SiO_2 (5 → 10% EtOAc/PE) afforded **4** as a light yellow oil (4.2 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 8.8 Hz); 7.16-7.01 (m, 1H); 6.99 (d, 2H, J = 9.6 Hz); 6.05 (d, 1H, J = 15.6 Hz); 3.57 (t, 2H); 2.49-2.43 (m, 2H); 2.03-1.95 (m, 2H); ^{13}C (75.5 MHz, $CDCl_3$) δ 164.2, 149.8, 132.5, 123.4, 121.6, 118.8, 43.8, 30.7, 29.7, 29.5.

(2*S*,3*R*)-(para-Bromophenyl)-2-benzylcarbamate-3-hydroxy-6-chlorohexanoate (6): A solution of 0.4 **N** sodium hydroxide (33 mL, 3.05 equiv) was stirred in an ambient temperature water bath in a dimly lit hood (due to the light sensitivity of the osmium source). A small amount of this solution (*ca.* 2.0 mL) was used to dissolve potassium osmate dihydrate

(0.065 g, 0.177 mmol, 0.04 equiv) in a separate vial. To the remaining sodium hydroxide solution was added n-propanol (20 mL) followed by benzyl carbamate (2.1 g, 13.7 mmol, 3.1 equiv). Freshly prepared t-butyl hypochlorite[2] (1.5 mL, 13.48 mmol, 3.05 equiv) was added to the reaction mixture and the mixture stirred for five minutes. To this homogeneous solution was added a solution of $(DHQD)_2$-AQN[3] ligand (0.19 g, 0.22 mmol, 0.05 equiv) in n-propanol (15 mL, 0.011 **M**) followed by olefin **4** (1.34 g, 4.42 mmol, 1.0 equiv) in n-propanol (2.0 mL, 0.75 **M**) and the potassium osmate dihydrate solution. The reaction mixture was stirred at ambient temperature for 4 hours at which time sodium bisulfite (2.0 g) was added and the reaction subsequently diluted with EtOAc (50 mL). The reaction mixture was extracted with EtOAc (3 x 25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification on SiO_2 (30% EtOAc/PE) afforded **6** as a yellow oil (1.1g, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 8.8 Hz); 7.35-7.30 (m, 5H); 6.93 (d, 2H, J = 8.8 Hz); 5.66 (br. t, 1H); 5.12-5.08 (m, 2H); 4.33 (d, 1H, J = 2.8 Hz); 4.16-4.11 (br. m, 1H); 3.56 (br. d, 1H); 2.77 (dq, 2H, J = 12.8Hz); 1.87-1.71 (m, 4H); ^{13}C (75.5 MHz, $CDCl_3$) δ 132.5, 129.8, 129.0, 123.1, 106.2, 67.9, 66.7, 66.5, 51.4, 47.8, 43.2, 39.3, 31.4, 29.0, 28.2, 7.2; FTIR (neat) ν_{max} 3450, 2400, 2350, 2080, 1663, 1540; CIHRMS $M+H^+$ (calculated for $C_{20}H_{22}BrClNO_5$): 470.0369, found 470.0402; $[\alpha]_{23}^D$ = +30.0 (c = 0.10, $CHCl_3$); 82% ee (The optical purity (*ee*) of this sample was determined by a Mosher analysis of the derived *R*-(O)-acetylmandelate ester. The mandelate ester was prepared in quantitative yield by the coupling of **6** (1.0 equiv) and *R*-(O)-acetyl-D-mandelic acid (1.2 equiv) with DCC (1.2 equiv.) and catalytic DMAP (0.05 equiv) in CH_2Cl_2 (0.1 **M**) at 0 °C. The diastereomeric resonances of the crude ester were used to determine the optical purity of the sample).

(2*S*, 3*R*)-Hydroxylysine (3) To a solution of **6** (0.080g, 0.17 mmol) in DMF (1.7 mL, 0.10 **M**) was added sodium azide (0.022g, 0.34 mmol, 2.0 equiv). The solution was stirred for 24 hours at ambient temperature and was subsequently diluted with excess H_2O (6 mL). The crude mixture was concentrated *in vacuo* to afford the crude azide. A dilute solution of the azide (0.17

mmol) in anhydrous MeOH (7.0 mL, 0.025 **M**) was treated with 10% Pd-C (0.010 g, 20 wt%). The suspension was stirred under 1 atmosphere of hydrogen for 12 hours. The resulting suspension was filtered through Celite, washed with MeOH, then washed with 1**N** HCl, and concentrated *in vacuo* to afford **3**. ^{1}H NMR (400 MHz, D_2O) δ 4.20 (m, 1H); 4.01 (d, 1H, J = 4.0 Hz); 3.02 (t, 2H, J = 7.2 Hz); 1.60-1.90 (m, 4H); ^{13}C (75.5 MHz, D_2O/CD_3OD) δ 170.0, 68.4, 66.4, 57.7, 66.5, 57.7, 39.9, 30.0, 23.0; CIHRMS M+H$^+$ (calculated for $C_6H_{15}N_2O_3$): 163.1082, found 163.0992; $[\alpha]_{23}^{D}$ = +17.0 (c = 1.05, MeOH). $[\alpha]_{23}^{D}$ (lit.[4]) = +16.9 (c = 1.83, MeOH).

(3*R*, 4*R*)-3-Amino-4-hydroxyazepine (2) Hydroxylysine dihydrochloride (**3**, 0.084 mmol) was added to hexamethyldisilazane (0.10 mL, 0.42 mmol, 5.0 equiv) in xylenes (1.0 mL, 0.085 **M**) and the mixture was heated to reflux. After heating for 2 hours, the homogeneous solution was treated with 2-propanol (0.10 mL, 0.34 mmol, 4.0 equiv). After 2 days at reflux, the mixture was cooled and treated with 1**N** HCl and stirred for 1 hour. The crude product was slurried in THF (1 mL, 0.085 **M**) and treated with borane (1**M** in THF, 0.50 mL, 0.50 mmol, 6.0 equiv) then heated to reflux for 18 hours. The reaction mixture was treated with methanol (10 mL) and concentrated to a glass. The glass was slurried in methanol, triturated with 2-propanol, and stirred overnight to give **2** as a white powder. ^{1}H NMR (400 MHz, D_2O) δ 3.75 (m, 1H); 3.6 (m, 2H); 3.21-3.40 (m, 3H); 2.2 (m, 1H); 2.05-2.10 (m, 1H); 1.70-1.80 (m, 2H); ^{13}C (75.5 MHz, D_2O/CD_3OD) δ 66.4, 52.5, 46.0, 42.0, 31.6, 18.2; FTIR (KBr) ν_{max} 3420, 2940, 1630; CIHRMS M+H$^+$ (calculated for $C_6H_{15}N_2O$): 131.1184, found 131.1180; $[\alpha]_{23}^{D}$ = -20.0 (c = 0.50, MeOH). $[\alpha]_{23}^{D}$ (lit.[9]) = -19.3 (c = 0.171, MeOH).

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1 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-2925.

2 M. J. Mintz, C. Walling, *Org. Synth.* **1973**, *Col. Vol 5*, 184-187.

3 Commercially available from Aldrich Chemical, Co.

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