

A Practical Synthesis of 1-Aryl-6-(hydroxymethyl)-2-ketopiperazines via a *6-exo* Amide-Epoxy Cyclization

Noel A. Powell*, Fred L. Ciske, Emma C. Clay, Wayne L. Cody, Dennis M. Downing,
Peter G. Blazicka, Daniel D. Holsworth, and Jeremy J. Edmunds.

Pfizer Global Research & Development, Michigan Laboratories

2800 Plymouth Road, Ann Arbor, MI 48105

noel.powell@pfizer.com

Supporting Information

I. General Information

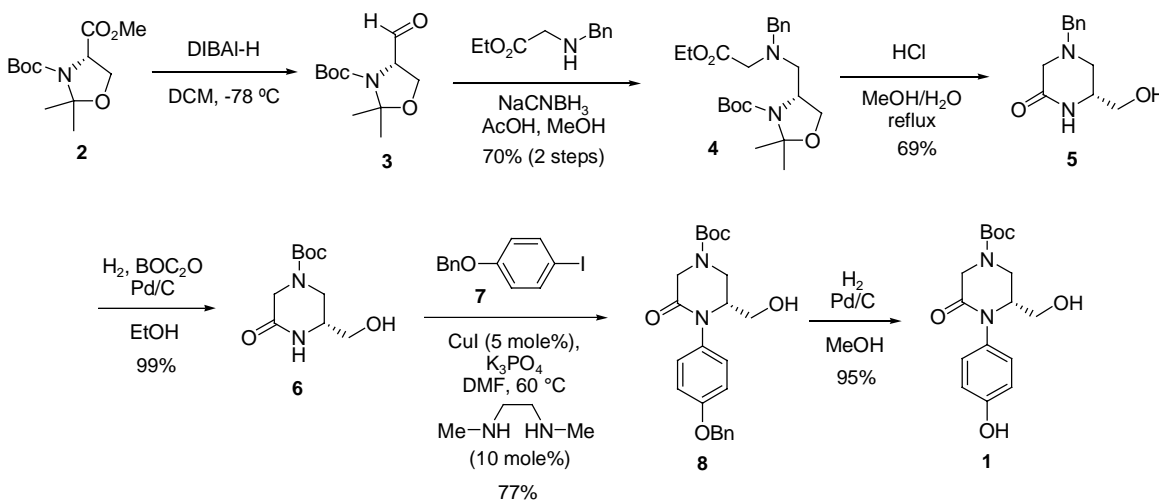
General Methods: All anhydrous reaction solvents were purchased from VWR as Baker-Dry solvents. Unless otherwise indicated, all commercial reagents were used as received without further purification. All reactions were conducted under a N₂ or Ar atmosphere.

Physical Properties and Spectroscopic Measurements: Melting points are reported uncorrected. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon-13 (¹³C) NMR spectra were recorded on a Varian VXR-400 spectrometer at 400 MHz and 100 MHz, respectively. The proton signal of residual, non-deuterated solvent (δ 7.25 ppm for CDCl₃; δ 2.49 ppm for DMSO-D₆) was used as an internal reference for ¹H spectra. For ¹³C spectra, chemical shifts are reported relative to the δ 77.0 ppm resonance for CDCl₃. Coupling constants are reported in Hz. Optical rotations were measured on an Autopol IV polarimeter using a quartz cell with 1 mL capacity and a 10 cm length.

Positive and negative ion atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Micromass Platform LC mass spectrometer operating in Open Access mode. Samples were introduced by loop injection using a Gilson 215 autosampler into a mobile phase of 80:20 acetonitrile:water flowing at 200 $\mu\text{L}/\text{min}$ delivered by a Hewlett-Packard HP1100 HPLC. The mass spectrometer source and probe temperatures were 150°C and 450°C, respectively. The cone voltage was 15V while the corona pin was held at 3.5 kV in positive ion and 3.0 kV in negative ion mode. IR spectra were obtained as KBr pellets, or with a diamond single-bounce horizontal attenuated total reflectance (ATR) accessory installed in a Avatar 370 FT-IR SensIR. Elemental analyses were performed by Quantitative Technologies, Inc.

II. Experimental Procedures

A. First Generation Synthesis of Compound 1



(S)-4-[(Benzyloxyethylamino)-methyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid *tert*-butyl ester (**4**).

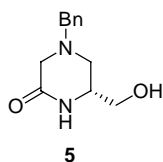
A 3-necked, 1000 mL round-bottom flask fitted with a N₂ inlet adapter, magnetic stir bar, drierite drying tube, internal temperature probe, and a septa was charged with methyl (S)-(-)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxazolidine-carboxylate **2** (15.42

g, 59.46 mmole) and anhydrous toluene (120 mL). The solution was cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath. In a separate flask, a 25 wt % solution of DIBAL-H in toluene (69.5 mL, 104.1 mmole,) was cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath, and added to the ester solution under N_2 pressure via a steel cannula over a period of 30 min. The rate of addition was adjusted to prevent the internal temperature of the reaction mixture from warming above $-70\text{ }^{\circ}\text{C}$. After the addition was complete, the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for an additional 30 minutes. Excess hydride was quenched by the dropwise addition of 20 mL of pre-chilled ($-78\text{ }^{\circ}\text{C}$) CH_3OH , again keeping the reaction temperature below $-70\text{ }^{\circ}\text{C}$. The resulting white slurry was poured into 500 mL of ice-cold 1 *N* HCl. The aqueous layer was extracted with EtOAc (3 \times 300 mL). The combined organic layers were washed with 300 mL 1 *N* HCl, and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to yield 14.65 g of (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylic acid *tert*-butyl ester **3** as a yellow oil, which was used immediately without further purification.¹

The residue was dissolved in 200 mL of anhydrous CH_3OH under a N_2 atmosphere. *N*-Benzylglycine ethyl ester (23.0 g, 118.9 mmole) and AcOH (6.8 mL, 118.9 mmole) were added, and the reaction mixture was cooled in an ice bath. A 1.0 M solution of NaBH_3CN in tetrahydrofuran (100 mL, 100 mmole) was added via a cannula under positive N_2 pressure. The reaction mixture was stirred at room temperature for 18h. A large excess of solid K_2CO_3 was added until gas evolution ceased. The slurry was concentrated almost to dryness under reduced pressure, and the residue was dissolved in 300 mL of CH_2Cl_2 . The organic layer was washed with 300 mL of 1:1:1 H_2O /saturated NaHCO_3 /brine. The aqueous layer was extracted with EtOAc (2 \times 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (SiO_2 , gradient: 15% ethyl acetate/hexane to 30% ethyl acetate/hexane) gave 16.83 g (70%) of (*S*)-4-[(benzylethoxycarbonyl-methylamino)-methyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid *tert*-butyl ester **4** as a clear viscous oil: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 1.24 (m, 3 H), 1.46 (m, 12 H), 1.55 (s, 3 H), 2.60 (m, 1 H), 2.98 (ddd, $J=12.6, 2.4, 2.4$ Hz, 1 H), 3.31 (m, 2 H), 3.73 (dd, $J=14.2, 8.8$ Hz, 1 H),

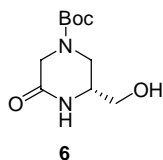
¹ Garner, P., Park, J. M. *Org. Synth., Coll. Vol. IX* **1998**, 300.

3.80 (m, 1 H), 3.90 (m, 1 H), 3.96 (m, 1 H), 4.04 (t, $J=8.4$ Hz, 1 H), 4.13 (m, 2 H), 7.30 (m, 5 H). MS calcd for $[C_{22}H_{34}N_2O_5+1]$: 407.2. Found (APCI): 407.3 (M+1).



(6R)-4-Benzyl-6-hydroxymethyl-piperazin-2-one (5).

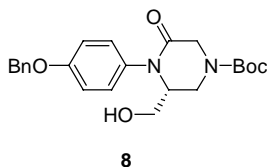
(S)-4-[(Benzyloxycarbonylmethylamino)-methyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid *tert*-butyl ester **4** (16.83 g, 41.41 mmole) was dissolved in 200 mL of CH_3OH . An aqueous 6 N HCl solution (20 mL) was added, and the reaction mixture was heated to reflux for 18 hr. After cooling to room temperature, the solution was made basic by the addition of saturated aqueous $NaHCO_3$ and concentrated to one quarter volume under reduced pressure. The resulting slurry was diluted with 300 mL of 1:1 H_2O /brine and extracted with CH_2Cl_2 (2 \times 300 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (SiO_2 , 93/7 CH_2Cl_2/CH_3OH then 90/10 CH_2Cl_2/CH_3OH) gave 6.27 g (69%) of (6R)-4-benzyl-6-hydroxymethyl-piperazin-2-one **5** as a pale yellow solid: $[\alpha]_D = -34.0^\circ$ ($c = 11.4$, $CDCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 2.58 (dd, $J = 11.8, 5.3$ Hz, 1 H), 2.71 (dd, $J = 11.7, 4.4$ Hz, 1 H), 3.08 (d, $J = 16.6$ Hz, 1 H), 3.19 (d, $J=16.6$ Hz, 1 H), 3.55 (s, 2 H), 3.53-3.57 (m, 1 H), 3.64 (d, $J = 4.4$ Hz, 2 H), 6.89 (bs, 1 H), 7.31 (m, 5 H); MS calcd for $[C_{12}H_{16}N_2O_2+1]$: 221.1. Found (APCI): m/z 221.0 (M+1).



(3R)-3-Hydroxymethyl-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester (6).

4-Benzyl-6-hydroxymethylpiperazin-2-one **5** (5.57 g, 25.3 mmole) was dissolved in 50 mL of absolute ethanol. Di-*tert*-butyl carbonate (6.7 g, 30.7 mmole) and 20% Pd/C (0.50 g) were added, and the resulting black slurry was shaken under a 50 psi hydrogen atmosphere for 6 hr. The slurry was filtered through a celite pad, which was rinsed with

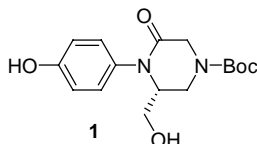
additional ethanol. The combined filtrates were concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, 100% CH₂Cl₂, then step gradient to 90/10 CH₂Cl₂/CH₃OH) to afford 5.76 g (99%) of (3*R*)-3-hydroxymethyl-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester **6** as a white solid: m.p.: 108-110 °C; [α]_D = -31.8° (*c* = 1.00, CHCl₃); IR (KBr) 3275, 2976, 1711, 1655, 1398, 1340, 1245, 1167, 1122 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (s, 9 H), 3.09 (t, *J* = 5.0 Hz, 1 H), 3.48 (m, 1 H), 3.55 (dd, *J* = 6.3, 3.4 Hz, 1 H), 3.60 (m, 2 H), 3.68 (dd, *J* = 12.6, 3.4 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 154.3, 81.2, 63.2, 53.0, 47.7, 41.0, 28.3 (3); Anal calcd for C₁₀H₁₈N₂O₄: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.29; H, 7.88; N, 12.07.



4-(4-Benzyloxy-phenyl)-3-hydroxymethyl-5-oxo-piperazine-1-carboxylic acid *tert*-butyl ester (8).

An oven-dried, 10 mL round bottom flask was charged with 1-benzyloxy-4-iodobenzene **7** (485 mg, 1.56 mmole), (3*R*)-3-hydroxymethyl-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester **6** (300 mg, 1.30 mmol), powered anhydrous potassium phosphate tribasic (553 mg, 2.61 mmol), and CuI (12 mg, 0.065 mmol). The flask was purged and back-filled with N₂. Anhydrous DMF (1.4 mL) was added, followed by 14 μL (0.13 mmole) of N,N'-dimethyl-1,2-ethylenediamine. The purple suspension was heated in a 60 °C oil bath for 12 hr. After cooling to room temperature, the white suspension was diluted with H₂O and EtOAc. The layers were separated, and the aqueous layer was washed with EtOAc (2×). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient: 50% EtOAc/hexanes to 70% EtOAc/hexanes) to provide 413 mg (77%) of (3*R*)-4-(4-benzyloxyphenyl)-3-hydroxymethyl-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester **8** as a white solid foam: [α]_D = -36.2° (*c* = 4.2, CH₂Cl₂); IR(ATR/diamond) 3436, 3317, 2934, 1683, 1640,

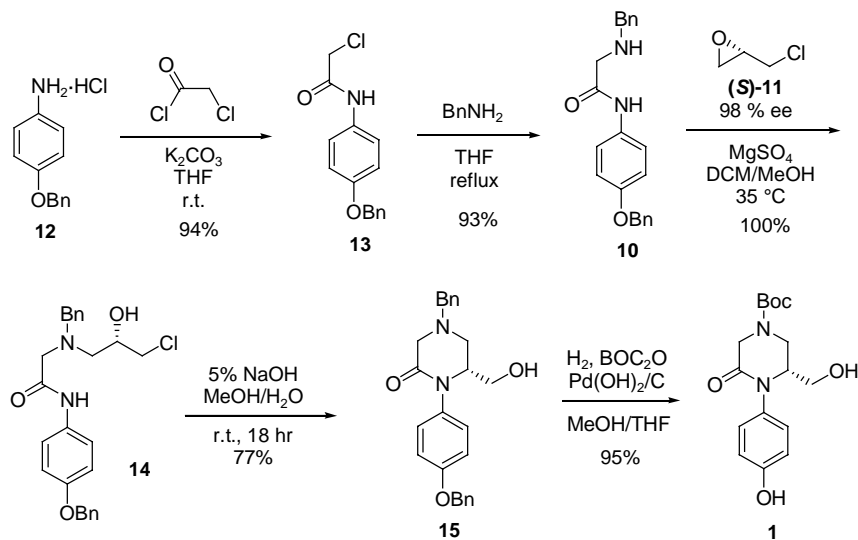
1508, 1416, 1249, 1238, 1149, 830 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.50 (s, 9 H), 2.96 (bs, 1 H), 3.42 (m, 2 H), 3.66 (m, 1 H), 3.75 (m, 1 H), 3.96 (d, $J = 18.3$ Hz, 1 H), 4.42 (m, 1 H), 4.56 (dd, $J = 18.6, 1.0$ Hz, 1 H), 5.05 (s, 2 H), 6.99 (d, $J = 9.0$ Hz, 2 H), 7.09 (d, $J = 9.0$ Hz, 2 H), 7.31-7.43 (m, 5 H); ^{13}C NMR (101 MHz, CDCl_3) δ 28.5 (3C), 41.5, 49.0, 60.6, 70.5, 81.8, 115.9, 127.7, 128.3, 128.6, 128.9, 133.5, 136.8, 158.3, 166.3. HRMS calcd for $[\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5+1]$: 413.2076. Found (ESI): 413.2080 (M+1).



(3R)-3-Hydroxymethyl-4-(4-hydroxy-phenyl)-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester (1).

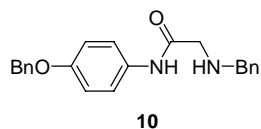
A solution of (3R)-4-(4-Benzyloxyphenyl)-3-hydroxymethyl-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester **8** (413 mg, 1.00 mmol) in EtOH (50 mL), was treated with 20% $\text{Pd}(\text{OH})_2/\text{C}$ (0.10 g). The reaction mixture was shaken under an atmosphere of H_2 gas at 48 psi for 26 hr. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , 50/48/2 EtOAc/hexanes/MeOH then gradient to 70/28/2 EtOAc/hexanes/MeOH) to yield 307 mg (95%) of (3R)-3-hydroxymethyl-4-(4-hydroxy-phenyl)-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester **1** as a white solid: $[\alpha]_{\text{D}} = -24.7^\circ$ ($c = 3.2$, CHCl_3); IR (ATR/diamond) 3240, 2983, 1676, 1629, 1515, 1420, 1251, 1149, 833 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.49 (s, 9 H), 3.41 (m, 2 H), 3.65 (dd, $J = 15.1, 3.7$ Hz, 1 H), 3.69 (m, 1 H), 3.96 (A of AB, $J_{\text{AB}} = 18.6$ Hz, 1 H), 4.39 (bd, $J = 12.7$ Hz, 1 H), 4.54 (B of AB, $J_{\text{AB}} = 18.8$ Hz, 1 H), 6.58 (d, $J = 8.6$ Hz, 2 H), 6.87 (d, $J = 8.6$ Hz, 2 H), 7.06 (bs, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 28.5 (3C), 41.5, 48.8, 60.5, 60.7, 82.0, 117.0 (2C), 128.4 (2C), 132.0, 156.3, 167.2; HRMS calcd for $[\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5+1]$: 323.1607. Found (ESI): 323.1592 (M+1). Anal. calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.40; H, 6.81; N, 8.55.

B. Intramolecular Epoxide Cyclization Route for the Synthesis of Compound 1



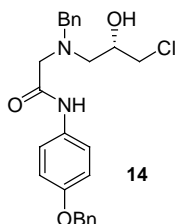
N-(4-Benzyloxyphenyl)-2-chloroacetamide (13)

4-Benzyloxyaniline hydrochloride (50 g, 0.21 mol) was dissolved in 750 mL of anhydrous THF. Solid K_2CO_3 (44 g, 0.32 mol) was added, and the mixture was stirred at room temperature for 15 min. Chloroacetyl chloride (26.35 g, 0.23 mol) was added via syringe at room temperature, and the reaction mixture was stirred at room temperature for 6 hr. Et_2O was added (300 mL), and the mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to a brown solid, which was washed with hexanes to afford 54.85 g (94 %) of N-(4-benzyloxyphenyl)-2-chloroacetamide **13** as a brown solid: m.p.: 132-134 °C; 1H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 2 H), 5.05 (s, 2 H), 6.96 (d, $J = 9.0$ Hz, 2 H), 7.32 (m, 1 H) 7.37 (m, 2 H), 7.40 (m, 2 H), 7.43 (d, $J = 9.0$ Hz, 2 H), 8.13 (bs, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 43.1, 70.5, 115.5, 122.2, 127.7, 128.3, 128.8, 130.1, 137.0, 156.4, 163.8. MS calcd for $[C_{15}H_{14}ClNO_2+1]$: 276.1. Found (APCI): 276.1 (M+1).



2-Benzylamino-N-(4-benzyloxyphenyl)-acetamide (10).

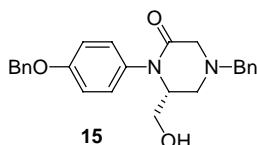
N-(4-Benzyloxyphenyl)-2-chloroacetamide **13** (54 g, 0.20 mol) was dissolved in THF (600 mL). Benzylamine (46.17 g, 0.43 mol) was added via syringe, and the reaction mixture was heated to reflux for 18 hr. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure to obtain a brown solid. The solid was washed with copious amounts of diethyl ether to obtain 63 g (93 %) of 2-benzylamino-N-(4-benzyloxyphenyl)-acetamide **10** as a beige solid: m.p.: 131-133 °C; IR (KBr) 3335, 3263, 3050, 2906, 2866, 1658, 1512, 1238, 1016, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.41 (s, 2 H), 3.83 (s, 2 H), 5.04 (s, 2 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 7.27-7.44 (m, 10 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 9.15 (bs, 1 H). Anal. calcd. for C₁₅H₁₄ClNO₂: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.20; H, 4.86; N, 5.03.



2-{Benzyl-[(2S)-3-chloro-2-hydroxypropyl]-amino}-N-(4-benzyloxyphenyl)-acetamide (14).

2-Benzylamino-N-(4-benzyloxyphenyl)-acetamide **10** (63 g, 0.18 mol) was dissolved in methanol (1L). Anhydrous MgSO₄ (26 g) was added, followed by 350 mL of CH₂Cl₂. *S*-(+)-Epichlorohydrin (42.07 g, 0.45 mol) was added via syringe. Once the addition was complete, the reaction mixture was heated in a 35 °C oil bath, and stirred for 72 hr. After cooling to room temperature, the reaction mixture was filtered through a pad of celite, which was washed with EtOAc. The filtrate was concentrated under reduced pressure to yield 79.8 g (100%) of 2-{benzyl-[(2S)-3-chloro-2-hydroxypropyl]-amino}-N-(4-benzyloxyphenyl)-acetamide **14** as a dark oil, which was used immediately without purification: ¹H NMR (400 MHz, CDCl₃) δ 2.71 (A of ABX, *J*_{AB} = 13.4 Hz, *J*_{AX} = 9.0 Hz, 1 H), 2.77 (B of ABX, *J*_{AB} = 13.7 Hz, *J*_{BX} = 3.2 Hz, 1 H), 3.25 (A of AB, *J*_{AB} = 17.1 Hz, 1

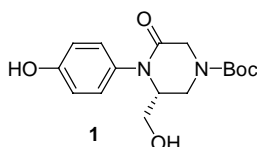
H), 3.35 (B of AB, $J_{AB} = 17.1$ Hz, 1 H), 3.46 (A of ABX, $J_{AB} = 11.0$ Hz, $J_{AX} = 6.3$ Hz, 1 H), 3.56 (B of ABX, $J_{AB} = 10.7$ Hz, $J_{BX} = 3.9$ Hz, 1 H), 3.68 (A of AB, $J_{AB} = 13.7$ Hz, 1 H), 3.88 (B of AB, $J_{AB} = 13.67$ Hz, 1 H), 4.03 (m, 1 H), 5.03 (s, 2 H), 6.91 (d, $J = 8.8$ Hz, 2 H), 7.36 (m, 10 H), 7.48 (d, $J = 8.8$ Hz, 2 H), 9.31 (bs, 1 H). MS calcd for $[C_{25}H_{27}ClN_2O_3+1]$: 439.2. Found (APCI): 439.1 (M+1).



(6R)-4-Benzyl-1-(4-benzyloxyphenyl)-6-hydroxymethylpiperazin-2-one (15).

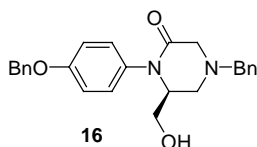
2-{Benzyl-[(2*S*)-3-chloro-2-hydroxypropyl]-amino}-N-(4-benzyloxyphenyl)-acetamide **14** (79.8 g, 0.18 mol) was dissolved in a 1:1 mixture of methanol and tetrahydrofuran (2L). A 5% solution of aqueous sodium hydroxide solution (1L) was added dropwise and the mixture stirred for 18 hr at room temperature. The reaction mixture was poured into brine (2L) and extracted with ethyl acetate (3×1L). The organic layer was washed with brine (2×500 mL) and dried over anhydrous $MgSO_4$. The mixture was filtered and the organic layer was concentrated under reduced pressure. The resulting beige solid (80 g) was recrystallized from hot EtOAc and ethanol to yield 31 g of (6*R*)-4-benzyl-1-(4-benzyloxyphenyl)-6-hydroxymethylpiperazin-2-one **15**. A second crop yielded 15 g. The remaining mixture was purified by flash column chromatography (silica gel, gradient: 50% EtOAc/hexanes to 75% EtOAc/hexanes) to yield 10 g of product. Total amount of (6*R*)-4-benzyl-1-(4-benzyloxyphenyl)-6-hydroxymethylpiperazin-2-one **15** isolated was 56 g (77%): m.p. = 152-154 °C; $[\alpha]_D = -16.4^\circ$ ($c = 2.8$, $CHCl_3$); Chiral HPLC $R_t = 20.88$ min, purity = 99% (Chiralpak AD, 4.6×250 mm, isocratic mobile phase 80% hexane/0.1% TFA//20% EtOH, flow = 0.4 mL/min); IR (KBr) 3227, 3030, 2949, 2833, , 1657, 1508, 1452, 1243, 1022 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 2.91 (d, $J = 10.5$ Hz, 1 H), 3.02 (d, $J = 16.6$ Hz, 1 H), 3.27 (d, $J = 12.0$ Hz, 1 H), 3.65 (m, 6 H), 5.04 (s, 2 H), 7.00 (d, $J = 9.0$ Hz, 2 H), 7.18 (d, $J = 8.8$ Hz, 2 H), 7.36 (m, 10 H); ^{13}C NMR (100 MZ, $CDCl_3$) 54.9, 57.62, 59.2, 62.3, 64.2, 70.4, 115.9 (2C), 127.7, 128.3, 128.9, 129.0, 129.1 (2C), 129.4, 135.8, 136.9, 158.3, 167.7.

MS calcd for [C₂₅H₂₆N₂O₃+1]: 403.2. Found (APCI): 403.1 (M+1). Anal. calcd. for C₂₅H₂₆N₂O₃: C, 74.60; H, 6.51; N, 6.96. Found: C, 71.74; H, 6.29; N, 6.70.



(3R)-3-Hydroxymethyl-4-(4-hydroxy-phenyl)-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester (1).

(6R)-4-Benzyl-1-(4-benzyloxyphenyl)-6-hydroxymethylpiperazin-2-one **15** (17 g, 42 mmol) was dissolved in mixture of CH₃OH and THF (1:1, 300 mL). Di-*tert*-butyl carbonate (11.1 g, 50 mmol) was added, followed by 2 g of 20% Pd(OH)₂/C. The reaction mixture was shaken under an atmosphere of H₂ gas at 55 psi for 17h. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient: 50% EtOAc/hexanes to 100% EtOAc) to yield 12.65 g (93%) of (3R)-3-hydroxymethyl-4-(4-hydroxy-phenyl)-5-oxopiperazine-1-carboxylic acid *tert*-butyl ester **1** as a white solid: [α]_D = -24.7° (*c* = 3.2, CHCl₃); IR (ATR/diamond) 3240, 2983, 1676, 1629, 1515, 1420, 1251, 1149, 833 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.49 (s, 9 H), 3.41 (m, 2 H), 3.65 (dd, *J* = 15.1, 3.7 Hz, 1 H), 3.69 (m, 1 H), 3.96 (A of AB, *J*_{AB} = 18.6 Hz, 1 H), 4.39 (bd, *J* = 12.7 Hz, 1 H), 4.54 (B of AB, *J*_{AB} = 18.8 Hz, 1 H), 6.58 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.06 (bs, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 28.5 (3C), 41.5, 48.8, 60.5, 60.7, 82.0, 117.0 (2C), 128.4 (2C), 132.0, 156.3, 167.2; HRMS calcd for [C₁₆H₂₂N₂O₅+1]: 323.1607. Found (ESI): 323.1592 (M+1). Anal. calcd. for C₁₆H₂₂N₂O₅: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.40; H, 6.81; N, 8.55.

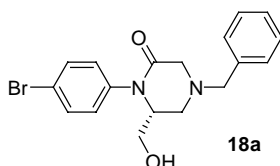


(3S)-4-Benzyl-1-(4-benzyloxyphenyl)-6-hydroxymethylpiperazin-2-one (16).

(3S)-4-Benzyl-1-(4-benzyloxyphenyl)-6-hydroxymethylpiperazin-2-one **16** was prepared in a similar fashion as described for (3R)-4-benzyl-1-(4-benzyloxyphenyl)-6-

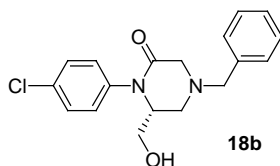
hydroxymethylpiperazin-2-one **15**, utilizing *R*-(-)-epichlorohydrin, to yield a white solid that possessed identical spectral data except for optical rotation and chiral HPLC retention times: $[\alpha]_D = +47.7^\circ$ ($c = 2.7$, CHCl_3); Chiral HPLC $R_t = 17.46$ min, 98.5% purity (Chiralpak AD, 4.6×250 mm, isocratic mobile phase 80% hexane/0.1% TFA//20% EtOH, flow = 0.4 mL/min).

C. Additional Cyclization Examples



(6R)-4-Benzyl-1-(4-bromophenyl)-6-hydroxymethyl-piperazin-2-one (18a).

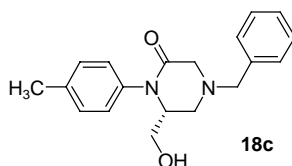
Compound **18a** was prepared as described for compound **15** in 83% to yield a white solid after recrystallization from EtOAc/hexanes: IR (KBr) 3396, 3028, 2808, 1640, 1487, 1452, 1421, 1067, 1010, 744, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.92 (d, $J = 12.0$ Hz, 1 H), 3.05 (d, $J = 16.6$ Hz, 1 H), 3.28 (d, $J = 11.7$ Hz, 1 H), 3.61 (s, 2 H), 3.65 (m, 4 H), 4.63 (bs, 1 H), 7.16 (d, $J = 8.8$ Hz, 2 H), 7.30-7.39 (m, 5 H), 7.53 (d, $J = 8.8$ Hz, 5 H); ^{13}C NMR (100 MHz, CDCl_3) δ 54.8, 57.5, 59.0, 62.2, 64.1, 121.8, 128.4, 129.1, 129.4, 149.8, 132.9, 135.6, 139.2, 167.4; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{BrN}_2\text{O}_2$: 375.0708. Found: 375.0704. Anal. calcd for $\text{C}_{18}\text{H}_{19}\text{BrN}_2\text{O}_2$: C, 57.61; H, 5.10; N, 7.47. Found: C: 57.68, H: 5.09, N: 7.47.



(6R)-4-Benzyl-1-(4-chlorophenyl)-6-hydroxymethyl-piperazin-2-one (18b).

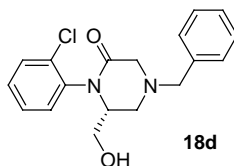
Compound **18b** was prepared as described for compound **15** in 85% yield as a white solid: $[\alpha]_D = -16.8^\circ$ ($c = 5.0$, EtOAc); IR (ATR/diamond) 3396, 2809, 1640, 1491, 1421, 1089 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.91 (dd, $J = 11.7, 2.9$ Hz, 1 H), 3.03 (d, $J = 16.9$ Hz, 1 H), 3.27 (ddd, $J = 12.0, 1.7$ Hz, 1 H), 3.59-3.3.67 (m, 6 H), 4.63 (bs, 1 H),

7.22 (d, $J = 8.8$ Hz, 4 H), 7.31 (m, 3 H), 7.34 (m, 2 H), 7.38 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 54.8, 57.5, 59.0, 62.2, 64.0, 128.4, 129.1 (2C), 129.4 (2C), 129.9 (2C), 130.0, 133.8, 138.6, 167.4; HRMS (ESI) calcd $\text{C}_{18}\text{H}_{20}\text{ClN}_2\text{O}_2$: 331.1213. Found: 331.1212. Anal. calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_2$: C, 65.35; H, 5.79; N, 8.47. Found: C: 65.17, H: 5.81, N: 8.35.



(6R)-4-Benzyl-1-(4-methylphenyl)-6-hydroxymethyl-piperazin-2-one (18c).

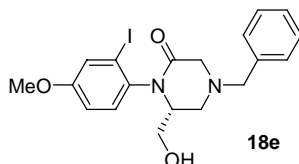
Compound **18c** was prepared as described for compound **15** in 69% to yield a white solid: $[\alpha]_{\text{D}} = -4.8^\circ$ ($c = 5.0$, EtOAc); IR (ATR/diamond) 3394, 3029, 2922, 2809, 1640, 1512, 1422, 1242, 1047 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.34 (s, 3 H), 2.91 (ddd, $J = 11.7, 2.9, 2.9$ Hz, 1 H), 3.02 (d, $J = 16.6$ Hz, 1 H), 3.26 (d, $J = 11.7$ Hz, 1 H), 3.58-3.68 (m, 4 H), 3.63 (s, 2 H), 4.71 (bs, 1 H), 7.14 (d, $J = 8.3$ Hz, 2 H), 7.21 (d, $J = 8.1$ Hz, 2 H), 7.31-7.37 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 54.8, 57.5, 59.0, 62.3, 64.2, 127.7 (2C), 128.3, 129.0 (2C), 129.4 (2C), 130.4 (2C), 135.6, 137.5, 137.9, 167.4; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2$: 311.1760. Found: 311.1766.



(6R)-4-Benzyl-1-(2-chlorophenyl)-6-hydroxymethyl-piperazin-2-one (18d).

Compound **18d** was prepared as described for compound **15** in 72% yield as a white solid: IR (ATR/diamond) 3433, 2822, 1640, 1481, 1062, 1039 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.96 (dd, $J = 11.7, 3.4$ Hz, 1 H), 3.08 (d, $J = 16.6$ Hz, 1 H), 3.27 (d, $J = 11.7$ Hz, 1 H), 3.56 (m, 1 H), 3.64 (m, 2 H), 3.68 (m, 3 H), 4.95 (bs, 1 H), 7.24-7.36 (m, 7 H), 7.40 (dd, $J = 7.6, 2.2$ Hz, 1 H), 7.47 (dd, $J = 7.3, 2.2$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 54.7, 57.2, 57.3, 62.3, 64.4, 128.0, 128.4, 129.1 (2C), 129.4 (2C), 129.8, 130.8, 131.9, 132.2, 135.6, 137.0, 167.2; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{ClN}_2\text{O}_2$: 331.1213.

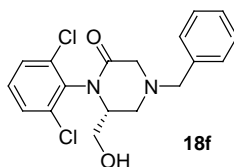
Found: 331.1227. Anal. calcd for C₁₈H₁₉ClN₂O₂: C, 65.35; H, 5.79; N, 8.47. Found: C, 65.05; H, 5.53; N, 8.28.



(6R)- 4-Benzyl-6-hydroxymethyl-1-(2-iodo-4-methoxyphenyl)-piperazin-2-one (18e).

Compound **18e** was prepared as described for compound **15** in 72% yield as a viscous oil that exists as a 2:1 mixture of hindered aryl rotational isomers. Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 2.73 (A of ABX, *J*_{AB} = 10.5 Hz, *J*_{AX} = 2.7 Hz, 1 H), 2.91 (d, *J* = 16.6 Hz, 1 H), 3.17 (m, 1 H), 3.22 (m, 1 H), 3.27 (m, 1 H), 3.39 (m, 1 H), 3.59 (A of AB, *J*_{AB} = 12.9 Hz, 1 H), 3.65 (B of AB, *J*_{AB} = 13.2 Hz, 1 H), 3.75 (s, 3 H), 4.74 (dd, *J* = 6.6, 4.2 Hz, 1 H), 6.97 (dd, *J* = 8.5, 2.7 Hz, 1 H), 7.08 (d, *J* = 8.5 Hz, 1 H), 7.27 (m, 2 H), 7.35 (m, 3 H), 7.44 (d, *J* = 2.9 Hz, 1 H); MS (APCI) calcd for C₁₉H₂₂IN₂O₃: 453.1. Found: 453.1.

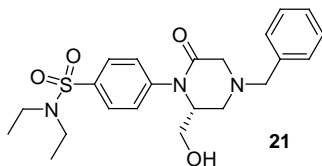
Diagnostic Peaks for minor rotational isomer: 2.76 (A of ABX, *J*_{AB} = 10.5 Hz, *J*_{AX} = 3.4 Hz, 1 H), 2.94 (d, *J* = 16.1 Hz, 1 H), 4.71 (dd, *J* = 5.6, 5.2 Hz, 1 H), 7.01 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.39 (d, *J* = 2.7 Hz, 1 H).



(6R)- 4-Benzyl-1-(2,6-dichlorophenyl)-6-hydroxymethyl-piperazin-2-one (18f).

Compound **18f** was prepared as described for compound **15** in 62% yield as a white powder: [α]_D = +15.2° (*c* = 5.0, EtOAc); IR (ATR/diamond) 3279, 2956, 2809, 1633, 1068, 786 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.95 (ddd, *J* = 12.0, 3.7, 1.0 Hz, 1 H), 3.10 (d, *J* = 17.1 Hz, 1 H), 3.27 (d, *J* = 12.0 Hz, 1 H), 3.66 (s, 2 H) 3.67-3.41 (m, 2 H), 3.73 (m, 1 H), 3.87 (ddd, *J* = 11.3, 4.5, 1.1 Hz, 1 H), 4.22 (bs, 1 H), 7.22 (t, *J* = 8.1 Hz, 1 H), 7.35 (m, 5 H) 7.40 (dd, *J* = 10.0, 1.4 Hz, 1 H) 7.42 (dd, *J* = 10.0, 1.9 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 53.0, 57.2, 58.7, 62.1,

64.1, 128.2, 129.0(2C), 129.3, 129.3, 129.4 (2C), 130.0, 134.0, 135.9, 136.0, 136.5, 166.6 ; HRMS (ESI) calcd for C₁₈H₁₉Cl₂N₂O₂: 364.0745. Found: 365.0815. Anal. calcd for C₁₈H₁₈Cl₂N₂O₂: C, 59.19; H, 4.97; N, 7.67. Found: C, 58.93; H, 4.74; N, 7.53.



4-([6R]-4-Benzyl-2-hydroxymethyl-6-oxo-piperazin-1-yl)-N,N-diethyl-benzenesulfonamide (21).

An oven-dried 25 mL round bottom flask was charged with 115 mg (2.88 mmole) of NaH and 6 mL of anhydrous DMF, and was cooled in an ice bath. 2-[Benzyl-([2S]-3-chloro-2-hydroxypropyl)-amino]-N-(4-diethylsulfamoylphenyl)-acetamide **19** (337 mg, 0.718 mmole) was dissolved in 2 mL of anhydrous DMF and added dropwise to the NaH suspension. The resulting gray suspension was stirred for 5 hr, while allowing the ice bath to gradually melt. Excess hydride was carefully quenched by the dropwise addition of H₂O, and the mixture was poured into 80 mL of H₂O and extracted with EtOAc (3×). The combined organics were washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated. Purification by flash column chromatography (SiO₂, gradient: 60/38/2 EtOAc/hexanes/MeOH to 90/8/2 EtOAc/hexanes/MeOH) gave 169 mg (54%) of 4-([6R]-4-benzyl-2-hydroxymethyl-6-oxo-piperazin-1-yl)-N,N-diethyl-benzenesulfonamide **21** as a white solid: [α]_D = -141.9° (c = 3.1, MeOH); IR (ATR/diamond) 3065, 2927, 1683, 1596, 1331, 1151 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 1.00 (t, J = 7.0 Hz, 6 H), 2.57 (A of ABX, J_{AB} = 11.7 Hz, J_{AX} = 3.7 Hz, 1 H), 2.64 (B of ABX, J_{AB} = 11.7 Hz, J_{AX} = 4.6 Hz, 1 H), 2.86 (A of AB, J_{AB} = 16.1 Hz, 1 H), 2.99 (B of AB, J_{AB} = 16.4 Hz, 1 H), 3.09 (q, J = 7.0 Hz, 4 H), 3.46 (A of AB, J_{AB} = 13.2 Hz, 1 H), 3.56 (B of AB, J_{AB} = 13.4 Hz, 1 H), 3.63 (bs, 1 H) 3.93 (dd, J = 9.2, 4.5 Hz, 1 H), 4.12 (dd, J = 8.3, 8.3 Hz, 1 H), 7.04 (d, J = 8.8 Hz, 2 H), 7.20 (m, 5 H) 7.67 (d, J = 8.8 Hz, 2 H), 7.97 (s, 1 H); ¹³C NMR (100 MHz, DMSO-d₆) δ 14.7 (2C), 42.4(2C), 50.3, 57.4, 61.0, 69.2, 115.6 (2C), 127.8, 128.8 (2C), 129.3 (2C), 129.5 (2C), 132.3, 138.0, 161.8, 168.6; HRMS (ESI) calcd for [C₂₂H₃₀N₃O₄S+1]: 432.1957. Found: 432.1945 [M+H]. Anal. calcd for C₂₂H₂₉N₃O₄S: C: 61.23, H: 6.77, N: 9.74. Found: C: 61.28, H: 6.70, N: 9.36.