Preparation of Substituted Piperazinones via Tandem Reductive Amination-(*N-N'*-Acyl Transfer)-Cyclization

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Supplementary Material

General Experimental Information: Proton NMR spectra were recorded on Varian Unity 400 or VRX-400 spectrometers (400 MHz), or Varian Unity or Varian Plus (500 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Low resolution electrospray mass spectra were recorded on a Micromass ZMD spectrometer using a Waters 2690 HPLC (2.1 x 100 mm C18 column, H₂O/MeCN w/0.05% TFA) for sample introduction. High resolution mass spectra were recorded on a Bruker 3T Fourier transform ion cyclotron resonance mass spectrometer equipped with electrospray ionization. The MH⁺ signal of the analyte of interest is mass measured against the internal calibrant, polypropylene glycol (average mass 425). Silica gel 60 (230-400) mesh from EM Science was used for flash column chromatography, and analytical thin layer chromatography was performed on EM Science Kieselgel 60 F254 plates. Solvents and reagents were obtained from commercial sources and used without further purification. The reported yields are the actual isolated yields of purified material and are not optimized. In the following paragraphs, the experimental procedures and spectroscopic data for the compounds included in the Letter are included. In those instances where a given compound structure does not appear in the graphics for the paper, it is not assigned a number, but is in order of synthetic sequence in which it was prepared and is correlated by name to the appropriate illustrated structure.

Preparation of *N*-Benzyl-*N*-(2-hydroxyethyl)acetamide. To a vigorously stirring 0 °C biphasic mixture of *N*-benzylethanolamine (16.8 g, 0.111 mol, 1.0 equiv.) in 150 mL EtOAc and 100 mL saturated aqueous NaHCO₃ was added acetyl chloride (9.48 mL, 0.133 mol, 1.2 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled alcohol as a colorless oil (8.18 g, 38%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 3.8:1) Rotamer A: δ 7.41-7.29 (m, 3H), 7.26-7.15 (m, 2H), 4.60 (s, 2H), 3.75 (t, *J* = 4.9 Hz, 2H), 3.57 (t, *J* = 5.0 Hz, 2H), 3.30 (br s, 1H), 2.18 (s, 3H); Rotamer B: δ 7.41-7.29 (m, 3H), 7.26-7.15 (m, 2H), 4.67 (s, 2H), 3.71 (t, *J* = 6.6 Hz), 3.43 (t, *J* = 5.6 Hz), 3.30 (br s, 1H), 2.25 (s, 3H); *m/z* (ES⁺) = 194.0 (MH⁺).

Preparation of *N*-Benzyl-*N*-(2-oxoethyl)acetamide (4a). A flame dried vessel was charged with 10 mL anhydrous dichloromethane, oxalyl chloride (4.43 mL, 50.8 mmol, 1.2 equiv.) was added and the vessel was cooled to -78 °C with vigorous stirring. Dimethylsulfoxide (7.21 mL, 0.102 mol, 2.4 equiv.) was added dropwise and after 15 minutes, a 20 mL dichloromethane solution of *N*-benzyl-*N*-(2-hydroxyethyl)acetamide (8.18 g, 42.3 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (17.7 mL, 0.127 mol, 3 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH₄Cl and chloroform. The organic layer was separated, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (40 to 70% ethyl acetate in hexanes) provided aldehyde **4a** (3.34 g, 41%). ¹H NMR (500 MHz, CDCl₃) δ 9.51 (s, 1H), 7.41-7.26 (m, 3H), 7.25-7.14 (m, 2H), 4.61 (s, 2H), 4.09 (s, 2H), 2.27 (s, 3H). *m/z* (ES⁺) = 192.0 (MH⁺).

Preparation of 3(R)-4-acetyl-1,3-dibenzylpiperazin-2-one (6a). To a 0 °C stirring suspension of D-phenylalanine methyl ester hydrochloride (100 mg, 0.464 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (83 µL, 1.4 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (147 mg, 0.693 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (106 mg, 0.557 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 7 hours, cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 50% ethyl acetate in dichloromethane) provided piperazinone **6a** as clear oil (103 mg, 69% yield). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 2.1:1) Rotamer A: δ 7.40-7.25 (m, 8H), 7.25-7.16 (m, 2H), 4.95 (d, *J* = 14.6 Hz, 1H), 4.66 (br dd, *J* = 13.8, 4.5 Hz, 1H), 4.50 (br dd, *J* = 9.5, 3.2 Hz, 1H), 4.29 (d, *J* = 14.6 Hz, 1H), 3.44-3.28 (m, 3H), 3.20 (dd, *J* = 13.5, 9.6 Hz, 1H), 3.07 (dd, *J* = 12.0, 4.1 Hz, 1H), 2.89 (ddd, *J* = 13.7, 13.4, 4.1 Hz, 1H) 1.46 (s, 3H); Rotamer B: δ 7.40-7.25 (m, 8H), 7.25-7.16 (m, 2H), 5.24 (br t, *J* = 4.8 Hz, 1H), 4.87 (d, *J* = 14.6 Hz, 1H), 4.34 (d, *J* = 14.6 Hz, 1H), 3.50 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.44-3.28 (m, 3H), 3.26-3.15 (m, 1H), 2.76 (dt, *J* = 12.0, 3.0 Hz, 1H), 2.59 (td, *J* = 11.1, 3.5 Hz, 1H), 2.07 (s, 3H). HRMS (ES) exact mass calculated for C₂₀H₂₃N₂O₂ (M+H⁺): 323.1754; found 323.1745. Chiral HPLC analysis (Chiralcel AD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:4/6 (A = 0.1% diethylamine in hexanes, B = ethanol); 20 minute run. Retention time for **6a** = 17.4 minutes (Area % = 97.57), enantiomer retention time = 6.5 minutes (Area % = 2.43); 95.1% enantiomeric excess.

Preparation of N-Benzyl-N-(2-hydroxyethyl)propanamide. To a vigorously stirring 0 °C biphasic mixture of N-benzylethanolamine (3.56 g, 23.5 mmol, 1.0 equiv.) in 40 mL EtOAc and 20 mL saturated aqueous NaHCO₃ was added propanoyl chloride (2.45 mL, 28.2 mmol, 1.2 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled product as a colorless oil (2.93 g, 60%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 4.7:1) Rotamer A: δ 7.40-7.28 (m, 3H), 7.25-7.14 (m, 2H), 4.60 (s, 2H), 3.75 (br t, *J* = 4.5 Hz, 2H), 3.58 (t, *J* = 4.9 Hz, 2H), 3.38 (br s, 1H), 2.42 (q, *J* = 7.4 Hz, 2H), 1.16 (t, *J* = 7.4 Hz, 3H); Rotamer B: δ 7.41-7.29 (m, 3H), 7.26-7.15 (m, 2H), 4.68 (s, 2H), 3.70 (br t, *J* = 5.4 Hz, 2H), 3.43 (t, *J* = 5.7 Hz, 2H), 3.38 (br s, 1H), 2.51 (q, *J* = 7.8 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H); *m/z* (ES⁺) = 208.1 (MH⁺).

Preparation of N-Benzyl-N-(2-oxoethyl)propanamide (4b). A flame dried vessel was charged with 50 mL anhydrous dichloromethane, oxalyl chloride (820 µL, 9.41 mmol, 1.3 equiv.) was added and the vessel was cooled to -78 °C with vigorous stirring. **4b** Dimethylsulfoxide (1.33 mL, 18.8 mmol, 2.6 equiv.) was added dropwise and after 15 minutes, a 20 mL dichloromethane solution of N-benzyl-N-(2-hydroxyethyl)propanamide (1.50 g, 7.24 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (5.04 mL, 36.2 mmol, 5 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH₄Cl and dichloromethane. The organic layer was separated, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided aldehyde **4b** (1.30 g, 88%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 5.3:1) Rotamer A: δ 9.51 (s, 1H), 7.40-7.28 (m, 3H), 7.24-7.14 (m, 2H), 4.61 (s, 2H), 4.08 (s, 2H), 2.53 (q, *J* = 7.3 Hz, 2H), 1.20 (t, *J* = 7.3 Hz, 3H); Rotamer B: δ 9.49 (s, 1H), 7.40-7.28 (m, 3H), 7.24-7.14 (m, 2H), 4.67 (s, 2H), 4.04 (s, 2H), 2.24 (q, *J* = 7.3 Hz, 2H), 1.13 (t, *J* = 7.3 Hz, 3H).

Preparation of 3(R)-1,3-dibenzyl-4-propionylpiperazin-2-one (6b). To a 0 °C stirring suspension of D-phenylalanine methyl ester hydrochloride (153 mg, 0.709 mmol, 1.0 equiv.), 4Å powdered molecular sieves (250 mg), acetic acid (120 µL, 2.13 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (225 mg, 1.06 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4b** (160 mg, 0.780 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 8 days, cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography (5% methanol in dichloromethane)

provided piperazinone **6b** as clear oil (181 mg, 76% yield). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 1.7:1) Rotamer A: δ 7.37-7.21 (m, 8H), 7.21-7.16 (m, 2H), 4.95 (d, *J* = 14.6 Hz, 1H), 4.67 (br d, *J* = 10.5 Hz, 1H), 4.28 (d, *J* = 14.6 Hz, 1H), 3.50 (dd, *J* = 12.9, 4.9 Hz, 1H), 3.40-3.27 (m, 1H), 3.24-3.10 (m, 1H), 3.06 (dd, *J* = 12.2, 4.1 Hz, 1H), 2.89 (td, *J* = 12.8, 4.0 Hz, 1H), 2.28 (q, *J* = 7.4 Hz, 2H), 1.40 (m, 1H), 0.82 (t, *J* = 7.5 Hz, 3H); Rotamer B: δ 7.37-7.21 (m, 8H), 7.21-7.16 (m, 2H), 4.89 (d, *J* = 14.6 Hz, 1H), 4.56 (br d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 14.6 Hz, 1H), 3.44 (br d, *J* = 13.7 Hz, 1H), 3.40-3.27 (m, 1H), 3.24-3.10 (m, 1H), 2.77 (br d, *J* = 12.0 Hz, 1H), 2.57 (td, *J* = 10.6, 3.3 Hz, 1H), 2.36 (q, *J* = 7.4 Hz, 2H), 1.92 (m, 1H), 1.13 (t, *J* = 7.5 Hz, 3H). HRMS (ES) exact mass calculated for C₂₁H₂₅N₂O₂ (M+H⁺): 337.1911; found 337.1910. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:85/15 (A=hexanes, B=ethanol); 30 minute run. Retention time for **6b** = 10.3 minutes (Area % = 68.96), enantiomer retention time = 16.9 minutes (Area % = 14.76); 64.8% enantiomeric excess.

Preparation of N-Benzyl-N-(2-hydroxyethyl)-2-methylpropanamide. To a vigorously stirring 0 °C biphasic mixture of *N*-benzylethanolamine (2.95 g, 19.5 mmol, 1.0 equiv.) in 40 mL EtOAc and 20 mL saturated aqueous NaHCO₃ was added 2-methylpropanoyl chloride (2.45 mL, 23.4 mmol, 1.2 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled product as a colorless oil (3.19 g, 74%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 3:1) Rotamer A: δ 7.40-7.28 (m, 3H), 7.26-7.13 (m, 2H), 4.64 (s, 2H), 3.75 (t, *J* = 5.0 Hz, 2H), 3.57 (t, *J* = 5.0 Hz, 2H), 2.81 (sept, *J* = 6.7 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H); Rotamer B: δ 7.40-7.28 (m, 3H), 7.26-7.13 (m, 2H), 4.66 (s, 2H), 3.71 (t, *J* = 5.7 Hz, 2H), 3.45 (t, *J* = 5.7 Hz, 2H), 2.59 (sept, *J* = 7.0 Hz, 1H), 1.21-1.10 (m, 6H); *m/z* (ES⁺) = 222.1 (MH⁺).

Preparation of N-Benzyl-2-methyl-N-(2-oxoethyl)propanamide (4c). A flame dried vessel was charged with 20 mL anhydrous dichloromethane, oxalyl chloride (384 μL, 4.41 mmol, 1.3 equiv.) was added and the vessel was cooled to -78 °C with vigorous stirring. Dimethylsulfoxide (625 μL, 8.81 mmol, 2.6 equiv.) was added dropwise and after 15 minutes, a 5 mL dichloromethane solution of *N*-benzyl-N-(2-hydroxyethyl)-2-methylpropanamide (750 mg, 3.40 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (2.36 mL, 16.9 mmol, 5 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH₄Cl and dichloromethane. The organic layer was separated, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided aldehyde **4c** (550 mg, 74%). ¹H NMR (500 MHz, CDCl₃) δ 9.51 (s, 1H), 7.40-7.28 (m, 3H), 7.22-7.14 (m, 2H), 4.65 (s, 2H), 4.05 (s, 2H), 2.94 (sept, *J* = 6.7 Hz, 1H), 1.21 (d, *J* = 6.6 Hz, 6H).

Preparation of 3(R)-1,3-dibenzyl-4-iso-butyrylpiperazin-2-one (6c). To a 0 °C stirring suspension of D-phenylalanine methyl ester hydrochloride (100 mg, 0.464 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (80 μL, 1.4 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (148 mg, 0.696 mmol, 1.5 equiv.) in 5 mL acetonitrile was added a 2.5 mL acetonitrile solution of aldehyde **4c** (112 mg, 0.510 mmol, 1.1 equiv.) dropwise. After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The pressure tube was sealed and heated to 120 °C for 4 days, cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 60% ethyl acetate in hexanes) provided piperazinone **6c** as clear oil (126 mg, 78% yield). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 3:2) Rotamer A: δ 7.36-7.27 (m, 4H), 7.25-7.06 (m, 6H), 4.92 (d, *J* = 14.6 Hz, 1H), 4.62 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.35 (d, *J* = 14.6 Hz, 1H), 3.37 (dd, *J* = 13.7, 3.4 Hz, 1H), 3.34-3.26 (m, 1H), 3.24-3.10 (m, 2H), 3.06 (dd, *J* = 12.1, 4.0 Hz, 1H), 2.90 (td, *J* = 13.4, 3.9 Hz, 1H), 2.63 (sept, *J* = 6.8 Hz, 1H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 3H); Rotamer B: δ 7.36-7.27 (m, 4H), 7.25-7.06 (m, 6H), 5.27 (t, *J* = 5.0 Hz, 1H), 4.93 (d, *J* = 14.9 Hz, 1H), 4.66 (dd, *J* = 13.7, 4.4 Hz, 1H), 4.30 (d, *J* = 14.6 Hz, 1H), 3.56-3.50 (m, 1H), 3.49 (dd, *J* = 13.5, 4.2 Hz, 1H), 3.34-3.26 (m, 1H), 2.82 (dt, *J* = 12.2, 2.9 Hz, 1H), 2.58 (qd, *J* = 11.5, 3.0 Hz, 1H), 2.05 (m, 1H), 1.09 (d, *J* = 7.8 Hz, 1H), 1.08 (d, *J* = 7.1 Hz, 1H). HRMS (ES) exact mass calculated for C₂₂H₂₇N₂O₂ (M+H⁺): 351.2067; found 351.2085. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:90/10 (A=0.1% diethylamine in hexanes, B=ethanol); 30 minute run.

Retention time for **6c** = 10.7 minutes (Area % = 47.98), enantiomer retention time = 18.9 minutes (Area % = 35.32); 15.2% enantiomeric excess.

Preparation of *N*-Benzyl-*N*-(2-hydroxyethyl)-2,2-dimethylpropanamide. To a vigorously stirring 0 °C biphasic mixture of *N*-benzylethanolamine (2.98 g, 19.7 mmol, 1.0 equiv.) in 40 mL EtOAc and 20 mL saturated aqueous NaHCO₃ was added 2,2-dimethylpropanoyl chloride (2.91 mL, 23.6 mmol, 1.2 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided the title alcohol as clear oil (2.92 g, 63% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.36 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 4.80 (s, 2H), 3.69 (br s, 2H), 3.49 (br t, *J* = 4.6 Hz, 2H), 1.34 (s, 9H); HRMS (ES) exact mass calculated for C₁₄H₂₂NO₂ (M+H⁺): 236.1645; found 236.1665.

Preparation of *N*-Benzyl-2,2-dimethyl-*N*-(2-oxoethyl)propanamide (4d**).** A flame dried vessel was charged with 20 mL anhydrous dichloromethane, oxalyl chloride (385 μL, 4.42 mmol, 1.3 equiv.) was added and the vessel was cooled to -78 °C with vigorous stirring. Dimethylsulfoxide (627 μL, 8.84 mmol, 2.6 equiv.) was added dropwise and after 15 minutes, a 5 mL dichloromethane solution of *N*-benzyl-*N*-(2-hydroxyethyl)-2,2-dimethylpropanamide (800 mg, 3.40 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (2.37 mL, 17.0 mmol, 5 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH₄Cl and dichloromethane. The organic layer was separated, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided aldehyde **4d** (641 mg, 81%). ¹H NMR (500 MHz, CDCl₃) δ 9.48 (s, 1H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 2H), 4.82 (s, 2H), 3.90 (s, 2H), 1.37 (s, 9H).

Preparation of 3(*R*)-1,3-dibenzyl-4-(2,2-dimethylpropanoyl)piperazin-2-one (6d**).** To a 0 °C stirring suspension of D-phenylalanine methyl ester hydrochloride (100 mg, 0.464 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (80 μL, 1.4 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (148 mg, 0.696 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4d** (119 mg, 0.510 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The pressure tube was sealed and heated to 120 °C for 48 hours. The mixture was cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 60% ethyl acetate in hexanes) provided piperazinone **6d** as clear oil (156 mg, 92% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.27 (m, 3H), 7.25-7.24 (m, 3H), 7.24-7.17 (m, 4H), 5.28 (t, *J* = 5.0 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.26 (d, *J* = 14.6 Hz, 1H), 3.89 (br d, *J* = 12.7 Hz, 1H), 3.51 (dd, *J* = 13.7, 5.1 Hz, 1H), 3.28 (dd, *J* = 13.5, 5.5 Hz, 1H), 3.23 (td, *J* = 11.8, 3.9 Hz, 1H), 2.87 (dt, *J* = 12.0, 2.5 Hz, 1H), 2.59 (br t, *J* = 11.3 Hz, 1H), 1.18 (s, 9H). HRMS (ES) exact mass calculated for C₂₃H₂₉N₂O₂ (M+H⁺): 365.2224; found 365.2202. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:80/20 (A=hexanes, B=2-propanol); 30 minute run. Retention time for **6d** = 11.0 minutes (Area % = 58.28), enantiomer retention time = 14.8 minutes (Area % = 33.64); 26.8% enantiomeric excess.

Preparation of *N*-Benzyl-*N*-(2-hydroxyethyl)benzamide. To a vigorously stirring 0 °C biphasic mixture of *N*-benzylethanolamine (3.67 g, 24.3 mmol, 1.0 equiv.) in 40 mL EtOAc and 20 mL saturated aqueous NaHCO₃ was added benzoyl chloride (3.94 mL, 34.0 mmol, 1.4 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the titled product as a colorless oil (2.93 g, 60%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 3.3:1) Rotamer A: δ 7.51-7.46 (m, 2H), 7.44-7.34 (m, 6H), 7.31 (m, 1H), 7.21 (m, 1H), 4.61 (br s, 2H), 3.82 (br s, 2H), 3.70 (br s, 2H); Rotamer B: δ 7.51-7.46 (m, 2H), 7.44-7.34 (m, 6H), 7.31 (m, 1H), 7.21 (m, 1H), 4.86 (br s, 2H), 3.63 (br s, 2H), 3.40 (br s, 2H); HRMS (ES) exact mass calcd for C₁₆H₁₈NO₂ (M+H⁺): 256.1333; found 256.1319.

Preparation of *N*-Benzyl-*N*-(2-oxoethyl)benzamide (4e**).** A flame dried vessel was charged with 10 mL anhydrous dichloromethane, oxalyl chloride (345 μ L, 3.96 mmol, 1.2 equiv.) was added and the vessel was cooled to -78°C with vigorous stirring. Dimethylsulfoxide (562 μ L, 7.92 mmol, 2.4 equiv.) was added dropwise and after 15 minutes, a 5 mL dichloromethane solution of *N*-benzyl-*N*-(2-hydroxyethyl)benzamide (842 mg, 3.30 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (1.38 mL, 9.89 mmol, 3 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH_4Cl and dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided aldehyde **4e** (740 mg, 88%). ^1H NMR (500 MHz, CDCl_3) (Rotamer A:B; 3.3:1) Rotamer A: δ 9.60 (s, 1H), 7.58-7.52 (m, 2H), 7.46-7.34 (m, 6H), 7.34-7.29 (m, 1H), 7.21-7.15 (m, 1H), 4.62 (br s, 2H), 4.21 (br s, 2H); Rotamer B: δ 9.40 (s, 1H), 7.58-7.52 (m, 2H), 7.46-7.34 (m, 6H), 7.34-7.29 (m, 1H), 7.21-7.15 (m, 1H), 4.82 (br s, 2H), 4.00 (br s, 2H).

Preparation of 3(*R*)-4-benzoyl-1,3-dibenzylpiperazin-2-one (6e**).** To a 0°C stirring suspension of D-phenylalanine methyl ester hydrochloride (100 mg, 0.464 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (80 μ L, 1.4 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (148 mg, 0.696 mmol, 1.5 equiv.) in 5 mL acetonitrile was added a 2.5 mL acetonitrile solution of aldehyde **4e** (129 mg, 0.510 mmol, 1.1 equiv.) dropwise. After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 4 hours, cooled and poured into aqueous saturated NaHCO_3 , which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 50% ethyl acetate in dichloromethane) provided piperazinone **6e** as clear oil (153 mg, 86% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.42-7.14 (m, 14H), 7.13-6.98 (m, 1H), 4.96 (d, $J = 14.2$ Hz, 1H), 4.76-4.58 (m, 1H), 4.31 (d, $J = 14.6$ Hz, 1H), 3.68-3.54 (m, 1H), 3.54-3.38 (m, 1H), 3.24-3.00 (m, 2H), 2.75 (br d, $J = 11.0$ Hz, 1H), 2.56 (br t, $J = 12.0$ Hz, 1H). HRMS (ES) exact mass calculated for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}^+$): 385.1910; found 385.1914. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:75/25 (A=hexanes, B=ethanol); 25 minute run. Retention time for **6e** = 12.1 minutes (Area % = 80.22), enantiomer retention time = 14.0 minutes (Area % = 0); >99.8% enantiomeric excess.

Preparation of *N*-Benzyl-2,2,2-trifluoro-*N*-(2-hydroxyethyl)acetamide. To a vigorously stirring 0°C biphasic mixture of *N*-benzylethanolamine (6.00 g, 39.68 mmol, 1.0 equiv.) in 100 mL EtOAc and 50 mL saturated aqueous NaHCO_3 was added trifluoroacetic anhydride (5.60 mL, 39.7 mmol, 1.0 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided the title alcohol as clear oil (1.41 g, 14% yield). ^1H NMR (500 MHz, CDCl_3) (Rotamer A:B; 1.7:1) Rotamer A: δ 7.42-7.30 (m, 3H), 7.28-7.24 (m, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 4.75 (s, 2H), 3.77 (t, $J = 5.2$ Hz, 2H), 3.52 (t, $J = 5.4$ Hz, 2H); Rotamer B: δ 7.42-7.30 (m, 3H), 7.28-7.24 (m, 1H), 7.22 (d, $J = 7.3$ Hz, 1H), 4.81 (s, 2H), 3.82 (t, $J = 5.6$ Hz, 2H), 3.54 (t, $J = 5.4$ Hz, 2H).

Preparation of *N*-Benzyl-2,2,2-trifluoro-*N*-(2-oxoethyl)acetamide (4f**).** A flame dried vessel was charged with 20 mL anhydrous dichloromethane, oxalyl chloride (646 μ L, 7.41 mmol, 1.3 equiv.) was added and the vessel was cooled to -78°C with vigorous stirring. Dimethylsulfoxide (1.05 mL, 14.82 mmol, 2.6 equiv.) was added dropwise and after 15 minutes, a 5 mL dichloromethane solution of *N*-benzyl-2,2,2-trifluoro-*N*-(2-hydroxyethyl)acetamide (1.41 g, 5.70 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (3.97 mL, 28.5 mmol, 5 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH_4Cl and dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 100% ethyl acetate in hexanes) provided aldehyde **4f** (1.20 g, 86%). ^1H NMR (500 MHz, CDCl_3) (Rotamer A:B; 2:1) Rotamer A: δ 9.44 (s, 1H), 7.42-7.32 (m, 3H), 7.24-7.20 (m, 2H), 4.70 (s, 2H), 4.10 (br s, 2H); Rotamer B: δ 9.46 (s, 1H), 7.42-7.32 (m, 3H), 7.24-7.20 (m, 2H), 4.71 (s, 2H), 4.18 (br s, 2H).

Preparation of 3(R)-1,3-dibenzyl-4-(trifluoroacetyl)piperazin-2-one (6f). To a 0 °C stirring suspension of D-phenylalanine methyl ester hydrochloride (100 mg, 0.464 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (80 µL, 1.39 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (148 mg, 0.696 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4f** (125 mg, 0.510 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The mixture was poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 30% ethyl acetate in hexanes) provided piperazinone **6f** as clear oil (151 mg, 87% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.25 (m, 5H), 7.23-7.16 (m, 5H), 5.14 (t, *J* = 4.9 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 2H), 4.27 (d, *J* = 14.6 Hz, 2H), 3.65 (br d, *J* = 15.6 Hz, 1H), 3.58 (dd, *J* = 13.9, 4.6 Hz, 1H), 3.32 (dd, *J* = 13.9, 5.2 Hz, 1H), 3.28 (td, *J* = 12.0, 3.9 Hz, 1H), 2.89 (dt, *J* = 12.5, 2.9 Hz, 1H), 2.61 (ddd, *J* = 14.9, 11.7, 3.5 Hz, 1H). HRMS (ES) exact mass calculated for C₂₀H₁₉F₃N₂O₂Na (M+Na⁺): 399.1291; found 388.1288. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:80/20 (A=hexanes, B=ethanol); 15 minute run. Retention time for **6f** = 6.7 minutes (Area % = 97.82), enantiomer retention time = 9.9 minutes (Area % = 0.03); >99.9% enantiomeric excess.

Preparation of Benzyl benzyl(2-hydroxyethyl)carbamate. To a vigorously stirring 0 °C biphasic mixture of *N*-benzylethanolamine (2.06 g, 13.7 mmol, 1.0 equiv.) in 30 mL EtOAc and 15 mL saturated aqueous NaHCO₃ was added benzyl chloroformate (2.53 mL, 17.7 mmol, 1.3 equiv.) dropwise. After stirring for 20 minutes, the reaction was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed once with 1N HCl, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 to 30% ethyl acetate in dichloromethane) provided the title alcohol as clear oil (2.09 g, 54% yield). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 2.2:1) Rotamer A: δ 7.41-7.25 (m, 9H), 7.26-7.15 (m, 1H), 5.20 (s, 2H), 4.56 (br s, 2H), 3.74 (br s, 2H), 3.47 (br s, 2H); Rotamer B: δ 7.41-7.25 (m, 9H), 7.26-7.15 (m, 1H), 5.20 (s, 2H), 4.59 (br s, 2H), 3.67 (br s, 2H), 3.41 (br s, 2H). HRMS (ES) exact mass calculated for C₁₇H₁₉NO₃Na (M+Na⁺): 308.1257; found 308.1252.

Preparation of Benzyl benzyl(2-oxoethyl)carbamate (4g). A flame dried vessel was charged with 20 mL anhydrous dichloromethane, oxalyl chloride (220 µL, 2.54 mmol, 1.5 equiv.) was added and the vessel was cooled to -78 °C with vigorous stirring. Dimethylsulfoxide (270 mL, 3.73 mmol, 2.2 equiv.) was added dropwise and after 15 minutes, a 5 mL dichloromethane solution of benzyl benzyl(2-hydroxyethyl)carbamate (484 mg, 1.70 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (1.18 mL, 8.48 mmol, 5 equiv.) was added and the reaction was warmed to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous saturated NH₄Cl and dichloromethane. The organic layer was separated, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide aldehyde **4g** (470 mg, 98%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 1.1:1) Rotamer A: δ 9.49 (s, 1H), 7.38-7.24 (m, 9H), 7.19-7.13 (m, 1H), 5.23 (s, 2H), 4.60 (s, 2H), 4.00 (s, 2H); Rotamer B: δ 9.40 (s, 1H), 7.38-7.24 (m, 9H), 7.19-7.13 (m, 1H), 5.18 (s, 2H), 4.57 (s, 2H), 3.91 (s, 2H).

Preparation of Benzyl 2(R)-2,4-dibenzyl-3-oxopiperazine-1-carboxylate (6f). To a 0 °C stirring suspension of D-phenylalanine methyl ester hydrochloride (100 mg, 0.464 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (80 µL, 1.39 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (148 mg, 0.696 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4g** (145 mg, 0.510 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The pressure tube was sealed and heated to 120 °C for 72 hours, cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 50% ethyl acetate in dichloromethane) provided piperazinone **6g** as clear oil (156 mg, 81% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.10 (m, 15H), 5.06 (br d, *J* = 12.2 Hz, 1H), 4.94 (br d, *J* = 13.9 Hz, 1H), 4.80-4.5 (m, 1H), 4.23

(br d, $J = 14.6$ Hz, 1H), 4.02 (br d, $J = 12.7$ Hz, 1H), 3.50-3.20 (m, 3H), 2.88 (br d, $J = 11.0$ Hz, 1H), 2.80-2.50 (m, 2H). HRMS (ES) exact mass calculated for $C_{26}H_{27}N_2O_3$ ($M+H^+$): 415.2016; found 415.2014. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:90/10 (A=hexanes, B=ethanol); 45 minute run. Retention time for **6g** = 33.9 minutes (Area % = 57.9), enantiomer retention time = 29.6 minutes (Area % = 22.53); 44.0% enantiomeric excess.

6h

Preparation of 4-acetyl-1-benzylpiperazin-2-one (6h). To a 0 °C stirring suspension of glycine methyl ester hydrochloride (75 mg, 0.60 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (100 μ L, 1.79 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (190 mg, 0.896 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (123 mg, 0.643 mmol, 1.2 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 1 hour, cooled and poured into aqueous saturated $NaHCO_3$, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 5% methanol in ethyl acetate) provided piperazinone **6h** as clear oil (73 mg, 53% yield). 1H NMR (500 MHz, $CDCl_3$) (Rotamer A:B; 2:1) Rotamer A: δ 7.38-7.28 (m, 3H), 7.26-7.13 (m, 2H), 4.62 (s, 2H), 4.20 (s, 2H), 3.76 (t, $J = 5.5$ Hz, 2H), 3.27 (t, $J = 5.4$ Hz, 2H), 2.10 (s, 3H); Rotamer B: δ 7.38-7.28 (m, 3H), 7.26-7.13 (m, 2H), 4.63 (s, 2H), 4.31 (s, 2H), 3.62 (t, $J = 5.3$ Hz, 2H), 3.38 (t, $J = 4.9$ Hz, 2H), 2.07 (s, 3H). HRMS (ES) exact mass calculated for $C_{13}H_{17}N_2O_2$ ($M+H^+$): 233.1285; found 233.1279.

6i

Preparation of Benzyl 3(S)-4-acetyl-1-benzyl-3-methylpiperazin-2-one (6i). To a 0 °C stirring suspension of L-alanine methyl ester hydrochloride (60 mg, 0.430 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (74 μ L, 1.29 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (136 mg, 0.645 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (99 mg, 0.52 mmol, 1.2 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 3 hours, cooled and poured into aqueous saturated $NaHCO_3$, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 50% ethyl acetate in dichloromethane) provided piperazinone **6i** as clear oil (85 mg, 80% yield). 1H NMR (500 MHz, $CDCl_3$) (Rotamer A:B; 2:1) Rotamer A: δ 7.37-7.28 (m, 3H), 7.26-7.21 (m, 2H), 4.82 (d, $J = 14.4$ Hz, 1H), 4.62-4.52 (m, 1H), 4.46 (q, $J = 7.1$ Hz, 1H), 4.38 (d, $J = 14.6$ Hz, 1H), 3.40-3.26 (m, 1H), 3.22-3.12 (m, 1H), 3.01 (td, $J = 12.0, 3.9$ Hz, 1H), 2.13 (s, 3H), 1.57 (d, $J = 7.1$ Hz, 3H); Rotamer B: δ 7.37-7.28 (m, 3H), 7.26-7.21 (m, 2H), 5.10 (q, $J = 7.0$ Hz, 1H), 4.68 (d, $J = 14.6$ Hz, 1H), 4.62-4.52 (m, 1H), 3.76-3.68 (m, 1H), 3.50 (td, $J = 11.0, 3.5$ Hz, 1H), 3.40-3.26 (m, 1H), 3.22-3.12 (m, 1H), 2.09 (s, 3H), 1.48 (d, $J = 7.1$ Hz, 3H). HRMS (ES) exact mass calculated for $C_{14}H_{19}N_2O_2$ ($M+H^+$): 247.1441; found 247.1449. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:90/10 (A=hexanes, B=ethanol); 25 minute run. Retention time for **6i** = 18.2 minutes (Area % = 87.9), enantiomer retention time = 14.6 minutes (Area % = 0.45); 99.0% enantiomeric excess.

6j

Preparation of Benzyl 3(S)-4-acetyl-1-benzyl-3-iso-butylpiperazin-2-one (6j). To a 0 °C stirring suspension of L-leucine methyl ester hydrochloride (153 mg, 0.842 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (140 μ L, 2.53 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (268 mg, 1.26 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (177 mg, 0.930 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 10 hours, cooled and poured into aqueous saturated $NaHCO_3$, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (5% methanol in dichloromethane) provided piperazinone **6j** as a white solid (186 mg, 77% yield). 1H NMR (500 MHz, $CDCl_3$) (Rotamer A:B; 1.2:1) Rotamer A: δ 7.37-7.33 (m, 2H), 7.32-7.28 (m, 1H), 7.25-7.21 (m, 2H), 4.84 (d, $J = 14.6$ Hz, 1H), 4.37 (dd, $J = 8.1, 6.1$ Hz, 1H), 4.31 (d, $J = 14.4$ Hz, 1H), 3.74-3.69 (m, 1H), 3.38-3.30 (m, 1H), 3.18-3.03 (m, 2H), 2.13 (s, 3H), 1.94-1.88 (m, 1H), 1.73-1.60 (m, 2H), 1.03 (d, $J = 8.3$ Hz, 3H), 1.02 (d, $J = 8.3$ Hz, 3H); Rotamer B: δ 7.37-7.33 (m, 2H), 7.32-7.28 (m, 1H), 7.25-7.21 (m, 2H), 5.24 (dd, $J = 9.5, 4.4$ Hz, 1H), 4.72 (d, $J = 14.6$ Hz, 1H), 4.58-4.51 (m, 1H), 4.47 (d, $J = 14.6$ Hz, 1H), 3.52 (ddd, $J = 15.1, 11.5, 4.0$ Hz, 1H), 3.38-

3.30 (m, 1H), 3.18-3.03 (m, 1H), 2.11 (s, 3H), 1.87-1.75 (m, 2H), 1.73-1.60 (m, 1H), 1.04 (d, $J = 4.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H). HRMS (ES) exact mass calculated for $C_{17}H_{25}N_2O_2$ ($M+H^+$): 289.1912; found 289.1915. Chiral HPLC analysis (Chiralcel AD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:85/15 (A=hexanes, B=2-propanol); 20 minute run. Retention time for **6j** = 8.5 minutes (Area % = 81.4), enantiomer retention time = 13.2 minutes (Area % = 3.5); 92% enantiomeric excess.

Preparation of Benzyl 3(S)-4-acetyl-1-benzyl-3-(hydroxymethyl)piperazin-2-one (6k).

To a 0 °C stirring suspension of L-serine methyl ester hydrochloride (75 mg, 0.482 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (83 μ L, 1.45 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (153 mg, 0.723 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (101 mg, 0.530 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 10 hours, cooled and poured into aqueous saturated $NaHCO_3$, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (0-10% methanol in dichloromethane) provided piperazinone **6k** as a clear oil (38 mg, 30% yield). 1H NMR (500 MHz, $CDCl_3$) (Rotamer A:B; 1.1:1) Rotamer A: δ 7.37-7.26 (m, 3H), 7.26-7.22 (m, 2H), 5.05 (t, $J = 4.1$ Hz, 1H), 4.73 (d, $J = 14.9$ Hz, 1H), 4.59 (d, $J = 14.6$ Hz, 1H), 4.18 (dd, $J = 11.0, 4.4$ Hz, 1H), 4.10-3.98 (m, 1H), 3.85-3.70 (m, 1H), 3.37 (ddd, $J = 16.8, 12.0, 4.6$ Hz, 1H), 3.23 (br d, $J = 12.2$ Hz, 1H), 3.18-3.04 (m, 1H), 2.13 (s, 3H), 1.95 (br s, 1H); Rotamer B: δ 7.37-7.26 (m, 3H), 7.26-7.22 (m, 2H), 4.84 (d, $J = 14.6$ Hz, 1H), 4.65 (dd, $J = 12.9, 3.9$ Hz, 1H), 4.49 (t, $J = 5.7$ Hz, 1H), 4.10-3.98 (m, 1H), 3.85-3.70 (m, 2H), 3.43-3.30 (m, 1H), 3.18-3.04 (m, 1H), 2.16 (s, 3H), 1.95 (br s, 1H). HRMS (ES) exact mass calculated for $C_{14}H_{19}N_2O_3$ ($M+H^+$): 263.1390; found 263.1397. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:65/35 (A=hexanes, B=2-propanol); 20 minute run. Retention time for **6k** = 8.5 minutes (Area % = 96.1), enantiomer retention time = 12.0 minutes (Area % = <0.1); >99% enantiomeric excess.

Preparation of Methyl [2(S)-1-acetyl-4-benzyl-3-oxopiperazin-2-yl]acetate (6l).

To a 0 °C stirring suspension of L-aspartate dimethyl ester hydrochloride (100 mg, 0.506 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (87 μ L, 1.52 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (161 mg, 0.759 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (106 mg, 0.557 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 10 hours, cooled and poured into aqueous saturated $NaHCO_3$, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (0-15% ethyl acetate in dichloromethane) provided piperazinone **6l** as a clear oil (83 mg, 54% yield). 1H NMR (500 MHz, $CDCl_3$) (Rotamer A:B; 1.5:1) Rotamer A: δ 7.38-7.33 (m, 2H), 7.33-7.27 (m, 2H), 7.26-7.13 (m, 1H), 5.07 (t, $J = 4.6$ Hz, 1H), 4.80 (d, $J = 14.9$ Hz, 1H), 4.53 (d, $J = 15.4$ Hz, 1H), 3.94 (td, $J = 11.1, 3.3$ Hz, 1H), 3.78-3.68 (m, 1H), 3.68 (s, 3H), 3.44-3.32 (m, 1H), 3.30-3.18 (m, 1H), 3.13-2.97 (m, 2H), 2.10 (s, 3H); Rotamer B: δ 7.38-7.33 (m, 2H), 7.33-7.27 (m, 2H), 7.26-7.13 (m, 1H), 4.89 (t, $J = 5.6$ Hz, 1H), 4.85 (d, $J = 14.6$ Hz, 1H), 4.66 (dd, $J = 10.8, 3.7$ Hz, 1H), 4.33 (d, $J = 14.6$ Hz, 1H), 3.78-3.68 (m, 1H), 3.73 (s, 3H), 3.44-3.32 (m, 1H), 3.30-3.18 (m, 1H), 3.13-2.97 (m, 1H), 2.22 (s, 3H). HRMS (ES) exact mass calculated for $C_{16}H_{21}N_2O_4$ ($M+H^+$): 305.1496; found 305.1481. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:80/20 (A=hexanes, B=ethanol); 20 minute run. Retention time for **6l** = 16.4 minutes (Area % = 73.6), enantiomer retention time = 14.2 minutes (Area % = 7.2); 82% enantiomeric excess.

Preparation of 3(S)-4-acetyl-1-benzyl-3-iso-propylpiperazin-2-one (6m).

To a 0 °C stirring suspension of L-valine methyl ester hydrochloride (151 mg, 0.901 mmol, 1.0 equiv.), 4Å powdered molecular sieves (250 mg), acetic acid (150 μ L, 2.70 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (286 mg, 1.35 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (189 mg, 0.99 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 24 hours, cooled and poured into aqueous saturated $NaHCO_3$, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in*

vacuo. Purification by flash chromatography (2% methanol in dichloromethane) provided piperazinone **6m** as a clear oil (143 mg, 58% yield). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 2:1) Rotamer A: δ 7.37-7.26 (m, 3H), 7.26-7.24 (m, 2H), 4.94 (d, *J* = 14.6 Hz, 1H), 4.23 (d, *J* = 14.4 Hz, 1H), 4.07 (d, *J* = 8.1 Hz, 1H), 3.77-3.69 (m, 1H), 3.36-3.29 (m, 1H), 3.17 (ddd, *J* = 12.2, 4.4, 2.9 Hz, 1H), 3.07 (ddd, *J* = 13.7, 10.7, 4.6 Hz, 1H), 2.34-2.26 (m, 1H), 2.13 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 7.1 Hz, 3H); Rotamer B: δ 7.37-7.26 (m, 3H), 7.26-7.24 (m, 2H), 5.00 (d, *J* = 6.6 Hz, 1H), 4.82 (d, *J* = 14.6 Hz, 1H), 4.42 (d, *J* = 14.6 Hz, 1H), 3.57 (ddd, *J* = 14.4, 10.5, 4.15 Hz, 1H), 3.36-3.29 (m, 1H), 3.21 (dt, *J* = 12.2, 3.6 Hz, 1H), 2.41-2.34 (m, 1H), 2.12 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). HRMS (ES) exact mass calculated for C₁₆H₂₃N₂O₂ (M+H⁺): 275.1754; found 275.1256. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:90/10 (A=hexanes, B=ethanol); 30 minute run. Retention time for **6m** = 17.4 minutes (Area % = 85.0), enantiomer retention time = 15.3 minutes (Area % = 6.7); 86% enantiomeric excess.

Preparation of 3(S)-4-acetyl-1-benzyl-3-phenylpiperazin-2-one (6n). To a 0 °C stirring suspension of L-phenylglycine methyl ester hydrochloride (154 mg, 0.764 mmol, 1.0 equiv.), 4Å powdered molecular sieves (250 mg), acetic acid (130 μL, 2.29 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (243 mg, 1.15 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (161 mg, 0.840 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 16 hours, cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (2% methanol in dichloromethane) provided piperazinone **6n** as a clear oil (198 mg, 84% yield). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 2:1) Rotamer A: δ 7.45 (br d, *J* = 7.6 Hz, 1H), 7.41 (br t, *J* = 7.2 Hz, 2H), 7.38-7.26 (m, 6H), 7.18 (br d, *J* = 6.6 Hz, 1H), 5.57 (s, 1H), 4.72 (d, *J* = 14.6 Hz, 1H), 4.54 (d, *J* = 14.6 Hz, 1H), 4.14 (br dt, *J* = 13.4, 6.0 Hz, 1H), 3.50-3.43 (m, 1H), 3.33-3.23 (m, 1H), 3.23-3.17 (m, 1H), 2.11 (s, 3H); Rotamer B: δ 7.45 (br d, *J* = 7.6 Hz, 1H), 7.41 (br t, *J* = 7.2 Hz, 1H), 7.38-7.26 (m, 7H), 7.18 (br d, *J* = 6.6 Hz, 1H), 6.38 (s, 1H), 4.83 (d, *J* = 14.6 Hz, 1H), 4.57 (d, *J* = 14.6 Hz, 1H), 3.72-3.65 (m, 1H), 3.56 (ddd, *J* = 13.4, 9.8, 4.0 Hz, 1H), 3.37 (ddd, *J* = 16.4, 12.7, 4.3 Hz, 1H), 3.33-3.23 (m, 1H), 2.16 (s, 3H). HRMS (ES) exact mass calculated for C₁₉H₂₁N₂O₂ (M+H⁺): 309.1599; found 309.1601. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:90/10 (A=hexanes, B=2-propanol); 20 minute run. Retention time for **6n** = 12.9 minutes (Area % = 74.0), enantiomer retention time = 16.4 minutes (Area % = 10.6); 84% enantiomeric excess.

Preparation of 2(S)-Methyl 1-[2-[acetyl(benzyl)amino]ethyl]-5-oxoprolinate (9). To a 0 °C stirring suspension of L-glutamic acid dimethyl ester hydrochloride (120 mg, 0.564 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (97 μL, 1.7 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (179 mg, 0.850 mmol, 1.5 equiv.) in 5 mL 1,2-dichloromethane was added dropwise over 5 minutes a 2.5 mL 1,2-dichloromethane solution of aldehyde **4a** (129 mg, 0.680 mmol, 1.2 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The mixture was poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (95/5–5/95:[water + 0.1% trifluoroacetic acid]/[acetonitrile + 0.1% trifluoroacetic acid]) provided pyroglutamate **9** as a clear oil (70 mg, 40% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.37 (t, *J* = 7.4 Hz, 2H), 7.34-7.25 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 4.65 (d, *J* = 17.1 Hz, 1H), 4.55 (d, *J* = 16.8 Hz, 1H), 4.66-4.52 (m, 1H), 4.14 (td, *J* = 10.5, 4.1 Hz, 1H), 4.05 (td, *J* = 10.7, 4.6 Hz, 1H), 3.77 (s, 3H), 2.99 (dt, *J* = 14.2, 4.3 Hz, 1H), 2.94 (dt, *J* = 12.9, 3.7 Hz, 1H), 2.50-2.43 (m, 1H), 2.39-2.28 (m, 2H), 2.10 (s, 3H), 2.10-2.04 (m, 1H). HRMS (ES) exact mass calculated for C₁₇H₂₃N₂O₄ (M+H⁺): 319.1652; found 319.1654.

Preparation of 1-Benzyl 5,5-dimethyl-2,3-dihydro-1H-pyrrolo[1,2a]imidazol-6(5H)-one (10). To a 0 °C stirring suspension of α-amino-*iso*-butyric acid methyl ester hydrochloride (125 mg, 0.814 mmol, 1.0 equiv.), 4Å powdered molecular sieves (250 mg), acetic acid (140 μL, 2.44 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (259 mg, 1.22 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4a** (171 mg, 0.90 mmol, 1.1 equiv.). After stirring for 90

minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The pressure tube was sealed and heated to 120 °C for 72 hours, cooled and poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (5% methanol in dichloromethane) provided bicycle **10** as clear oil (147 mg, 75% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.28 (m, 3H), 7.27-7.24 (m, 2H), 4.54 (s, 1H), 4.39 (s, 2H), 3.57 (t, *J* = 7.7 Hz, 2H), 3.40 (t, *J* = 7.7 Hz, 2H). HRMS (ES) exact mass calculated for C₁₅H₁₉N₂O (M+H⁺): 243.1493; found 243.1490.

Preparation of 3(R)-1-benzyl-3-iso-propyl-4-(trifluoroacetyl)piperazin-2-one (**6o**).

To a 0 °C stirring suspension of D-valine methyl ester hydrochloride (100 mg, 0.597 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (102 μL, 1.79 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (190 mg, 0.895 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4f** (161 mg, 0.657 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 40 hours. The mixture was poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 30% ethyl acetate in hexanes) provided piperazinone **6o** (155 mg, 79%). ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.28 (m, 4H), 7.27-7.20 (m, 1H), 4.95 (d, *J* = 14.6 Hz, 1H), 4.89 (d, *J* = 6.8 Hz, 1H), 4.31 (d, *J* = 14.6 Hz, 1H), 3.98 (br d, *J* = 14.4 Hz, 1H), 3.61 (ddd, *J* = 15.1, 11.6, 4.0 Hz, 1H), 3.38 (td, *J* = 12.1, 4.4 Hz, 1H), 3.23 (ddd, *J* = 12.3, 4.1, 2.1 Hz, 1H). HRMS (ES) exact mass calcd for C₁₆H₂₀F₃N₂O₂ (M+H⁺): 329.1471; found 329.1455. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:9/1 (A = 0.1% diethylamine in hexanes, B = ethanol); 20 minute run. Retention time for **6o** = 6.9 minutes (Area % = 87.02), enantiomer retention time = 8.9 minutes (Area % = 0); >99% enantiomeric excess.

Preparation of 3(R)-1-benzyl-3-phenyl-4-(trifluoroacetyl)piperazin-2-one (**6p**).

To a 0 °C stirring suspension of D-phenylglycine methyl ester hydrochloride (100 mg, 0.496 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (84 μL, 1.5 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (158 mg, 0.744 mmol, 1.5 equiv.) in 5 mL acetonitrile was added dropwise over 5 minutes a 2.5 mL acetonitrile solution of aldehyde **4f** (134 mg, 0.546 mmol, 1.1 equiv.). After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 40 hours. The mixture was poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 30% EtOAc in hexanes) provided piperazinone **6p** (145 mg, 81%). ¹H NMR (500 MHz, CDCl₃) (Rotamer A:B; 3.5:1) Rotamer A: δ 7.44-7.26 (m, 9H), 7.25-7.20 (m, 1H), 6.27 (s, 1H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.45 (d, *J* = 14.4 Hz, 1H), 3.91 (br d, *J* = 14.2 Hz, 1H), 3.61 (td, *J* = 12.6, 3.8 Hz, 1H), 3.46 (td, *J* = 11.7, 4.6 Hz, 1H), 3.30 (dt, *J* = 12.4, 3.0 Hz, 1H); Rotamer B: δ 7.44-7.26 (m, 9H), 7.25-7.20 (m, 1H), 5.82 (s, 1H), 4.84 (d, *J* = 14.6 Hz, 1H), 4.50 (d, *J* = 14.6 Hz, 1H), 4.26-4.17 (m, 1H), 3.44-3.34 (m, 2H), 3.21-3.14 (m, 1H). HRMS (ES) exact mass calcd for C₁₉H₁₈F₃N₂O₂ (M+H⁺): 363.1315; found 363.1310. Chiral HPLC analysis (Chiralcel OD column 250 X 4.6 mm; 220 nm; flow = 1.0 mL/minute of A/B:9/1 (A = 0.1% diethylamine in hexanes, B = ethanol); 20 minute run. Retention time for **6p** = 8.2 minutes (Area % = 91.85), enantiomer retention time = 10.7 minutes (Area % = 2.14); 95.4% enantiomeric excess.

Preparation of *tert*-Butyl(4-chloro-3-methylphenoxy)diphenylsilane.

4-Chloro-3-methylphenol (33.4 g, 0.234 mol, 1.0 equiv.), imidazole (48.3 g, 0.709 mol, 3 equiv.) and *tert*-butyldiphenylsilyl chloride (62.9 g, 0.229 mol, 1.0 equiv) were combined in 200 mL DMF and heated to 70 °C for 18 hours. The reaction was cooled, diluted with water and extracted twice with 1:1 EtOAc:Hex. The combined organic extracts were washed once with water and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the title compound as clear oil (88.7 g, 100% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.70 (dt, *J* = 8.3, 1.22 Hz, 4H), 7.43 (td, *J* = 7.1, 1.5 Hz, 2H), 7.37 (td, *J* = 7.8, 1.2 Hz, 4H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.68 (s, 1H), 6.45 (d, *J* = 8.8 Hz, 1H), 2.19 (s, 3H), 1.09 (s, 9H).

Preparation of [3-(bromomethyl)-4-chlorophenoxy](*tert*-butyl)diphenylsilane (15). *tert*-Butyl(4-chloro-3-methylphenoxy)diphenylsilane (88.7 g, 0.233 mol, 1.0 equiv.), *N*-bromosuccinimide (49.8 g, 0.279 mol, 1.2 equiv.) and 2,2'-azobis-*iso*-butyronitrile (3.82 g, 0.0233 mol, 0.1 equiv.) were combined in 500 mL CCl₄ and heated to reflux. After 7 hours, the reaction was concentrated *in vacuo*. The residue was taken up in a 10% ethyl acetate in hexanes solution. The precipitate was filtered and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (100% hexanes) provided bromide **15** (56.6 g, 53% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.68 (dt, *J* = 6.6, 1.5 Hz, 4H), 7.44 (td, *J* = 7.4, 1.5 Hz, 2H), 7.38 (td, *J* = 7.2, 1.5 Hz, 4H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 2.9 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.9 Hz, 1H), 4.38 (s, 2H), 1.10 (s, 9H).

Preparation of 2-[(5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-chlorobenzyl)amino] ethanol (16). A 100 mL acetonitrile solution of **15** (23.2 g, 50.7 mmol, 1.0 equiv.) was added dropwise over 15 minutes to a 400 mL acetonitrile solution of ethanolamine (31.0g, 0.507 mol, 10 equiv.) at ambient temperature. After 90 minutes, the reaction was concentrated *in vacuo*. The residue was partitioned between a 10% hexanes in EtOAc solution and water. The organic layer was separated, washed once with water and brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide aminoalcohol **16** (22.29 g, 100% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.69 (dd, *J* = 8.1, 1.5 Hz, 4H), 7.43 (tt, *J* = 7.4, 1.5 Hz, 2H), 7.37 (td, *J* = 7.2, 1.2 Hz, 4H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.9 Hz, 1H), 6.62 (dd, *J* = 8.8, 2.9 Hz, 1H), 3.66 (s, 2H), 3.50 (t, *J* = 5.1 Hz, 2H), 2.52 (t, *J* = 5.1 Hz, 2H), 1.094 (s, 9H); *m/z* (ES⁺) = 440.3 (MH⁺).

Preparation of sodium 1-(4-cyano-3-fluorobenzyl)-1*H*-imidazole-5-carboxylate (18). To a 25 mL solution of 2-fluoro-4-[(5-formyl-1*H*-imidazol-1-yl)methyl]benzonitrile (**17**) (480 mg, 2.09 mmol, 1.0 equiv.) was added 5 mL of 2-methyl-2-butene. A 5 mL aqueous solution of sodium chlorite (189 mg, 2.09 mmol, 1.0 equiv.) and sodium phosphate monohydrate (289 mg, 2.09 mmol, 1.0 equiv.) added and stirred for 18 hours at ambient temperature. The solid was filtered and dried to provide the sodium salt **18** (235 mg, 46% yield). ¹H NMR (400 MHz, CD₃OD): δ 8.06 (s, 1H), 7.71 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.68 (d, *J* = 0.9 Hz, 1H), 7.16 (d, *J* = 10.2 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 5.71 (s, 2H).

Preparation of *N*-(5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-chlorobenzyl)-1-(4-cyano-3-fluorobenzyl)-*N*-(2-hydroxyethyl)-1*H*-imidazole-5-carboxamide. Compound **18** (236 mg, 0.962 mmol, 1.0 equiv.), compound **16** (508 mg, 1.15 mmol, 1.2 equiv.), 1-hydroxybenzotriazole hydrate (155 mg, 1.01 mmol, 1.05 equiv.), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (194 mg, 1.01 mmol, 1.05 equiv.) and triethylamine (268 μL, 1.92 mmol, 2.0 equiv.) were combined in 5 mL DMF. After stirring at ambient temperature for 4 days, the mixture was poured into aqueous saturated NaHCO₃, which was extracted three times with dichloromethane. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 4% MeOH with 10% NH₄OH in dichloromethane) provided the title alcohol (476 mg, 74%). ¹H NMR (500 MHz, CDCl₃): δ 7.66 (d, *J* = 6.6 Hz, 4H), 7.58 (s, 1H), 7.40-7.28 (m, 7H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 9.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 6.43 (br s, 1H), 5.4 (br s, 2H), 4.5 (br s, 2H), 3.45 (br s, 2H), 2.5 (br s, 2H), 1.08 (s, 9H); *m/z* (ES⁺) = 667.1 (MH⁺).

Preparation of *N*-(5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-chlorobenzyl)-1-(4-cyano-3-fluorobenzyl)-*N*-(2-oxoethyl)-1*H*-imidazole-5-carboxamide (19). A flame dried vessel was charged with 20 mL anhydrous dichloromethane, oxalyl chloride (70 μL, 0.86 mmol, 1.2 equiv.) was added and the vessel was cooled to -78 °C with vigorous stirring. Dimethylsulfoxide (120 mL, 1.71 mmol, 2.4 equiv) was added dropwise and after 15 minutes, a 5 mL dichloromethane solution of *N*-(5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-chlorobenzyl)-1-(4-cyano-3-fluorobenzyl)-*N*-(2-hydroxyethyl)-1*H*-imidazole-5-carboxamide (476 mg, 0.713 mmol, 1.0 equiv.) was added slowly. After 15 minutes, triethylamine (300 μL, 2.14 mmol, 3 equiv.) was added and the reaction was allowed to warm to ambient temperature. After 45 minutes, the reaction was partitioned between aqueous

saturated NH_4Cl and dichloromethane. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide aldehyde **19** (470 mg, 100%). ^1H NMR (500 MHz, CDCl_3): δ 9.24 (s, 1H), 7.67 (br d, J = 6.3 Hz, 5H), 7.61 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.1 Hz, 4H), 7.19 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 9.5 Hz, 1H), 6.86 (br d, J = 8.1 Hz, 1H), 6.75 (br s, 1H), 6.46 (br s, 1H), 5.41 (br s, 2H), 4.50 (br s, 2H), 3.53 (br s, 2H), 1.08 (s, 9H); m/z (ES^+) = 665.1 (MH^+).

Preparation of 4-[(5-[(2R)-4-(5-[(tert-butyl(diphenyl)silyl]oxy)-2-chlorobenzyl)-2-methyl-3-oxopiperazin-1-yl]carbonyl]-1H-imidazol-1-yl)methyl]-2-fluorobenzonitrile (20**).**

To a 0 °C stirring suspension of D-alanine methyl ester hydrochloride (85 mg, 0.61 mmol, 1.0 equiv.), 4Å powdered molecular sieves (200 mg), acetic acid (104 μL , 1.83 mmol, 3.0 equiv.) and sodium triacetoxyborohydride (194 mg, 0.913 mmol, 1.5 equiv.) in 5 mL acetonitrile was added a 2.5 mL acetonitrile solution of aldehyde **19** (486 mg, 0.73 mmol, 1.2 equiv.) dropwise. After stirring for 90 minutes, the ice bath was removed and the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was heated to reflux for 3 hours, cooled and poured into aqueous saturated NaHCO_3 ,

which was extracted three times with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (0 to 4% methanol with 10% NH_4OH in dichloromethane) provided piperazinone **20** (317 mg, 72%). ^1H NMR (500 MHz, CDCl_3) δ 7.70 (d, J = 6.8 Hz, 2H), 7.66 (s, 1H), 7.64 (d, J = 6.8 Hz, 2H), 7.58 (dd, J = 7.8, 6.8 Hz, 1H), 7.46-7.40 (m, 1H), 7.39 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 5.4 Hz, 1H), 7.34 (t, J = 7.1 Hz, 2H), 7.25 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.98 (s, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.7, 2.8 Hz, 1H), 6.34 (br s, 1H), 5.45 (d, J = 15.6 Hz, 1H), 5.38 (d, J = 15.9 Hz, 1H), 5.30 (s, 2H), 4.87 (d, J = 15.6 Hz, 1H), 4.65 (br s, 1H), 4.00 (br t, J = 5.1 Hz, 2H), 2.58 (br s, 1H), 1.12 (d, J = 7.3 Hz, 3H), 1.06 (s, 9H). HRMS (ES) exact mass calcd for $\text{C}_{40}\text{H}_{40}\text{ClFN}_5\text{O}_3\text{Si}$ ($\text{M}+\text{H}^+$): 720.2568; found 720.2534.

Preparation of 20(R)-15-Chloro-19,20-dihydro-19,22-dioxo-20-methyl-5H,17H-18,21-ethano-6,10:12,16-dimetheno-22H-imidazo[3,4-h][1,8,11,14]oxatriaza-cycloeicosine-9-carbonitrile (14**).**

To a solution of **20** (317 mg, 0.440 mmol, 1.0 equiv.) in 44 mL of anhydrous acetonitrile was added 18-Crown-6 (12 mg, 0.044 mmol, 0.1 equiv.) and potassium fluoride on alumina (153 mg, 2.64 mmol, 6 equiv.). The reaction was warmed to 80 °C under argon for 2.5 hours, cooled and concentrated *in vacuo*. The residue was partitioned between aqueous saturated NaHCO_3 and dichloromethane, which was extracted twice with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered,

and concentrated *in vacuo*. Purification by silica gel chromatography (0 to 4% methanol with 10% NH_4OH in dichloromethane) provided macrocycle **14** (167 mg, 82%). ^1H NMR (500 MHz, CDCl_3) δ 7.87 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.14 (dd, J = 8.8, 2.7 Hz, 1H), 6.85 (s, 1H), 6.38 (d, J = 2.7 Hz, 1H), 5.80 (d, J = 14.9 Hz, 1H), 5.54 (d, J = 15.1 Hz, 1H), 5.08 (d, J = 14.9 Hz, 1H), 4.67 (qd, J = 7.3, 1.5 Hz, 1H), 4.39 (br d, J = 10.0 Hz, 1H), 4.02 (d, J = 15.4 Hz, 1H), 3.40 (s, 1H), 3.40 (ddd, J = 16.3, 12.0, 3.8 Hz, 1H), 3.12 (br d, J = 8.3 Hz, 1H), 1.71 (d, J = 7.3 Hz, 3H); HRMS (ES) exact mass calcd for $\text{C}_{24}\text{H}_{21}\text{ClN}_5\text{O}_3$ ($\text{M}+\text{H}^+$): 462.1328; found 462.1324.