Experimental

General Experimental Chemical Procedures. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) spectra were recorded on a Bruker DPX 400 or Bruker DPX 500 spectrometer. Melting points were taken using a TA Instruments DSCQ 100 apparatus. High-resolution mass spectra were taken on a Bruker microTOF apparatus. Infrared spectroscopy was performed on a Nicolet Avatar 360 FT-IR as a neat pellet. Flash column chromatography was performed using Merck silica gel 60. HPLC analysis was performed on a Hewlett Packard 1100 (Agilent ZORBAX® Eclipse XDB-C8, 5 μm, 4.6x150 mm, Flow rate 1 mL/min, Gradient (acetonitrile/water with 0.05% trifluoroacetic acid): 1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold at 99% acetonitrile/1% water). Combustion analyses were preformed by Numega Resonance labs, San Diego, California. All reagents were purchased from Aldrich and used as received with the exception of ethyl-4-aminobutyrate hydrochloride, which was purchased from Alfa Aesar. All solvents utilized were purchased in anhydrous form from E.M. Scientific and passed through two columns of neutral alumina (DCE, THF, MTBE, MeOH) or one column of neutral alumina and one column of Q5 oxygen scavenger (toluene) with the exception of 2-methyl THF and (trifluoromethyl)benzene which were purchased in anhydrous form from Aldrich in 'Sure Seal' glass bottles and used directly. "Brine" refers to a saturated aqueous solution of NaCl.

1-(1-Benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**). Method A: To a 5-liter, jacketed reactor equipped with an overhead mechanical stirrer, thermocouple probe, solid addition funnel, J-Kem dose controller and dynamic nitrogen inlet were added 1-benzyl-4-

piperidone (70.9 g, 0.375 mol), ethyl-4-aminobutyrate hydrochloride (75.6 g, 0.450 mol) and anhydrous 1,2-dichloroethane (1 L). To this stirring solution was added $NaBH(OAc)_3$ (103.3 g, 0.487 mol) in four portions over a one-hour period. During addition there was a noticeable gas evolution and the solution became very viscous. An exotherm of ~30 °C was also observed. The resultant heterogeneous solution was aged for 30 minutes. Triethylamine (189.7 g, 1.87 mol) was then added over a one-hour period. A slight temperature increase of ~5 °C was observed. The reaction was aged at 20 °C for 12 hours, then heated to 60 °C for an additional 8 hours. The reaction was cooled to 20 °C and quenched by the slow addition of water (1 L). The resultant layers were separated and the aqueous layer was extracted with 1,2-dichloroethane (2 x 300 mL). All organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The resultant oil was partitioned between 5% EtOAc / heptane (500 mL) and 1 N aqueous HCl (500 mL). The layers were separated and the organic layer was extracted with additional 1 N aqueous HCl (2 x 250 mL). The aqueous layers were combined, adjusted to a pH of ~11 with 6 N aqueous NaOH and extracted with *i*-PrOAc (3 x 200 mL). All organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The resultant brown oil was recrystallized from 5% EtOAc / heptane (10 ml / gram) to yield 1-(1-benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**) (91.6 g, 94.6 % yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.24 (m, 5H), 3.99 (tt, J = 11.9 Hz, J = 4.4 Hz, 1H), 3.50 (s, 2H), 3.35 (t, J = 7.0 Hz, 2H), 2.95-2.91 (m, 2H), 2.38 (t, J = 8.1 Hz, 2H), 2.09 (dt, J = 11.8 Hz, J = 2.6 Hz, 2H), 1.99 (pentet, J = 7.6 Hz, 2H), 1.72 (dq, J = 12.2 Hz, J = 8.3 Hz, 2H), 1.64-1.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.52, 138.31,

129.15, 128.22, 127.05, 63.08, 52.78, 48.88, 42.93, 31.57, 29.30, 18.14. IR (neat) 1667, 1492, 1421, 1365, 1342, 1310, 1265, 1220, 1145, 1124, 1023, 989, 792, 737, 698 cm^{-1}. Anal. Calcd (found): C, 74.38 (74.47); H, 8.58 (8.44); N, 10.84 (10.90). MS (electrospray): exact mass calcd for $C_{16}H_{22}N_2O$ 258.1732; m/z found, 259.1803 [M+H]+; mp 81.3 °C.

1-(1-Benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**). Method B: To a 5-liter, jacketed reactor equipped with an overhead mechanical stirrer, thermocouple probe, J-Kem dose controller and dynamic nitrogen inlet were added ethyl-4-aminobutyrate hydrochloride (150.9 g, 0.90 mol), $NaBH(OAc)_3$ (206.6 g, 0.97 mol), and anhydrous toluene (2.25 L). Stirring was commenced and triethylamine (379.5 g, 3.75 mol) was added over a 5-minute period. Once addition was complete, the reactor was aged at 20 °C for 10 minutes. A solution of 1-benzyl-4-piperidone (141.9 g, 0.75 mol) in anhydrous toluene (250 mL) was then added over a 1-hour period. A slight exotherm of ~6 °C was observed during addition. After completion of addition, the solution was aged at 20 °C for 1 hour, then heated to 75 °C for an additional 2 hours. The solution was then cooled to 20 °C and quenched by the slow addition of water (1 L). A mild exotherm of ~14 °C was observed during the addition. The layers were separated after 20 minutes of stirring and the organic layer was extracted again with water (1 L). The organic layer was then extracted with 1 N aqueous HCl (3 x 500 mL). The aqueous layers were combined, adjusted to a pH of ~12 with 6 N aqueous NaOH and extracted with *i*-PrOAc (2 x 1 L). All organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum until a thick, stirrable slurry was achieved. This slurry was diluted with heptane (1.5 L) with stirring. The resultant slurry was slowly

cooled to 10 °C and the product was collected by filtration. The cake was air dried for 20 minutes, then placed in a 55 °C vacuum oven for 24 hours to yield 1-(1-benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**) (178.0 g, 92% yield) as an off white solid.

1-(1-Benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**). Method C: To a 250-mL round-bottom flask were added 4-aminobutyric acid (5.45 g, 0.053 mol), $NaBH(OAc)_3$ (8.39 g, 0.039 mol), and anhydrous toluene (80 mL). A solution of 1-benzyl-4-piperidone (5.0 g, 0.026 mol) in anhydrous toluene (20 mL) was then added over a 5-minute period. The flask was aged at room temperature for 14 hours then heated to 65 °C for 4 additional hours. The solution was cooled to room temperature and extracted with 1 N aqueous HCl (2 x 50 mL). The aqueous layers were then combined, adjusted to a pH of ~12 with 6 N aqueous NaOH and extracted with *i*-PrOAc (3 x 50 mL). All organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to yield a yellow oil that solidified upon standing to a pale yellow solid. The crude product was recrystallized from hot 5% EtOAc / heptane (60 mL) yielding 1-(1-benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**) (5.72 g, 84% yield) as a white solid.

1-Piperidin-4-yl-pyrrolidin-2-one (**1**): To a 2.25-L Parr flask were added 1-(1-benzyl-piperidin-4-yl)-pyrrolidin-2-one (**10**) (91.6 g, 0.355 mol), ethanol (200 proof, 550 mL), and 10 wt.% Pd/C (9.0 g, wet catalyst). The Parr flask was then shaken under a hydrogen atmosphere (45 psi) until hydrogen consumption ceased, ~36 hours. The catalyst was removed through filtration (Zapcap®-CR, 0.45 micron Nylon) and washed with EtOAc. The combined filtrates were concentrated under vacuum to yield 1-piperidin-4-yl-pyrrolidin-2-one (**1**) (57.1 g, 95% yield) as a pale yellow oil that solidified

to an off white solid upon standing. On smaller scale (5.0 grams) the use of acidic media (3:1 EtOH / HOAc) reduced the reaction time to ~18 hours.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.06 (tt, *J* = 11.9 Hz, *J* =4.2 Hz, 1H), 3.37 (t, *J* = 7.0 Hz, 2H), 3.13-3.11(m, 2H), 2.71 (dt, *J* = 12.1 Hz, *J* = 2.5 Hz, 2H), 2.39 (t, *J* = 8.1 Hz, 2H), 1.99 (pentet, *J* = 7.6 Hz, 2H), 1.67-1.64 (m, 2H) 1.58 (dq, *J* = 12.1 Hz, *J* = 4.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.45, 49.05, 45.84, 42.95, 31.57, 30.42, 18.13. IR (neat) 2941, 1657, 1492, 1424, 1317, 1285, 1214, 1141, 1091, 1006, 932, 870, 810, 682, 633 cm^{-1}. Anal. Calcd (found): C, 64.25 (64.03); H, 9.59 (9.91); N, 16.65 (16.34). MS (electrospray): exact mass calcd for $C_9H_{16}N_2O$ 168.1263; m/z found, 169.1338 [M+H]+; mp 106.2 °C.

1'-Benzyl-[1,4']bipiperidinyl-2-one (**11**): To a 1-L, 3-necked, round-bottom flask equipped with an overhead mechanical stirrer, thermocouple probe, solid addition funnel, and a dynamic nitrogen inlet were added 5-aminovaleric acid hydrochloride (22.32 g, 0.145 mol), 1-benzyl-4-piperidone (11.0 g, 0.058 mol) and anhydrous 1,2-dichloroethane (220 mL). To this stirring solution was added $NaBH(OAc)_3$ (18.5 g, 0.087 mol) in four portions over a one-hour period. The flask was aged at room temperature for 30 minutes. The solid addition funnel was exchanged for a liquid addition funnel and triethylamine (14.7 g, 0.145 mol) was added over a 15-minute period. The flask was aged at room temperature for 14 hours then heated to 60 °C for 60 additional hours. The solution was cooled to room temperature and quenched by the slow addition of water (250 mL). The reaction was treated in an analogous fashion to Method A to yield 1'-benzyl-[1,4']bipiperidinyl-2-one (**11**) (14.2 g, 92% yield) as a pale yellow solid after recrystallization from heptane (~10 mL / gram). On small scale (1.0 gram), Method B

has also been shown to produce compound **11**. In this instance, the reaction was aged at room temperature for 24 hours then heated to reflux for 24 additional hours. This process yielded 1'-benzyl-[1,4']bipiperidinyl-2-one (**11**) (1.13 g, 52% yield) as a pale yellow solid after recrystallization.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.22 (m, 5H), 4.54 (tt, J = 12.2 Hz, J = 4.1 Hz, 1H), 3.49 (s, 2H), 3.19 (t, J = 5.7 Hz, 2H), 2.94-2.91 (m, 2H), 2.39 (t = 6.1 Hz, 2H), 2.11 (dt, J = 11.8 Hz, J = 2.3 Hz, 2H), 1.79-1.69 (m, 6H), 1.58-1.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.43, 138.37, 129.14, 128.19, 127.00, 63.03, 52.94, 50.43, 41.85, 32.60, 28.54, 23.35, 20.87. IR (neat) 1625, 1489, 1457, 1444, 1352, 1323, 1270, 1168, 1122, 788, 736, 696, 659, 613 cm^{-1}. Anal. Calcd (found): C, 74.96 (75.06); H, 8.88 (9.04); N, 10.28 (9.98). MS (electrospray): exact mass calcd for $C_{17}H_{24}N_2O$ 272.1889; m/z found, 273.1972 [M+H]+; mp 77.3 °C.

[1,4']Bipiperidinyl-2-one (**2**): Compound **2** was prepared from **11** in accordance with the synthesis of compound **1** from **10**. An input of 1'-benzyl-[1,4']bipiperidinyl-2-one (**11**) (14.2 g, 0.052 mol) yielded [1,4']bipiperidinyl-2-one (**2**) (9.1 g, 96 % yield) as a white solid. The reduction required ~36 hours under 50 psi of H_2 to reach completion.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (tt, *J* = 11.8 Hz, *J* = 4.4 Hz, 1H), 3.22-3.17 (m, 5H), 2.76 (dt, *J* = 12.0 Hz, *J* = 2.9 Hz, 2H), 2.40 (t, *J* = 6.2 Hz, 2H), 1.81-1.62 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.40, 50.25, 45.80, 41.94, 32.59, 29.20, 23.34, 20.85. IR (neat) 1617, 1482, 1463, 1446, 1415, 1350, 1324, 1299, 1280, 1261, 1195, 1180, 1170, 1142, 849, 808, 656 cm^{-1}. Anal. Calcd (found ($C_{10}H_{18}N_2O$•0.35H_2O)): C, 63.69 (63.7); H, 10.0 (9.9); N, 14.86 (14.8). MS (electrospray): exact mass calcd for $C_{10}H_{18}N_2O$ 182.1419; m/z found, 183.1501 [M+H]+; mp 58.3 °C.

4-Amino-3-hydroxy-butyric acid methyl ester (**16**): Compound **16** was prepared in accordance to the previously reported method: Brehm, L.; Jacobsen, P.; Johansen, J.; Krogsgaard-Larsen, P. J. *Chem. Soc., Perkin Trans. 1* **1983**, 1459.

1-(1-Benzyl-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one (**17**): Compound **17** was prepared in accordance with the synthesis of compound **10**, using Method A. An input of 1-benzyl-4-piperidone (10.0 g, 0.052 mol) yielded 1-(1-benzyl-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one (**17**) (11.6 g, 80% yield) as a tan solid after recrystallization from 50% EtOAc / heptane (~25 mL / g).

^{1}H NMR: (500 MHz, $CDCl_3$) δ = 7.34-7.26 (m, 5H), 4.49 (tt, *J* = 6.1 Hz, *J* = 2.4 Hz, 1H), 4.01 (tt, *J* = 11.9 Hz, *J* = 4.4 Hz, 1H), 3.57 (dd, *J* = 5.6 Hz, *J* = 5.1 Hz, 1H), 3.51 (s, 2H), 3.29 (dd, *J* = 8.6 Hz, *J* = 2.1 Hz, 1H), 2.97-2.92 (m, 2H), 2.69 (dd, *J* = 10.7 Hz, *J* = 6.5 Hz, 1H), 2.38 (dd, *J* = 14.7 Hz, *J* = 2.6 Hz, 1H), 2.13-2.06 (m, 2H), 1.79-1.60 (m, 4H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ = 172.94, 138.34, 129.67, 128.68, 127.60, 64.82, 63.44, 53.05, 52.59, 49.15, 42.09, 29.58, 29.46. IR (neat) 1643, 1479, 1448, 1437, 1302, 1274, 1105, 1080, 775, 737, 703, 686, 645, 613 cm^{-1}. Anal. Calcd (found): C, 70.04 (69.77); H, 8.08 (8.32); N, 10.21 (10.23). MS (electrospray): exact mass calcd for $C_{16}H_{22}N_2O_2$ 274.1681; m/z found, 275.1750 [M+H]+; mp 120.8 °C.

4-Hydroxy-1-piperidin-4-yl-pyrrolidin-2-one (**3**): To a 250-mL Parr flask were added 1-(1-benzyl-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one (**17**) (5.0 g, 0.018 mol), ethanol (200 proof, 50 mL), and 10 wt.% $Pd(OH)_2$ on carbon (1.0 gram). The Parr flask was then shaken under a hydrogen atmosphere (50 psi) until hydrogen consumption

ceased, ~36 hours. The catalyst was removed through filtration (Zapcap®-CR, 0.45 micron Nylon) and washed with EtOAc. The combined filtrates were concentrated under vacuum to yield 4-hydroxy-1-piperidin-4-yl-pyrrolidin-2-one (**3**) (3.3 g, 98% yield) as a tan, waxy solid.

^{1}H NMR (500 MHz, MeOD): δ 4.44-4.42 (m, 1H), 4.02 (tt, *J* = 11.4 Hz, *J* = 4.8 Hz, 1H), 3.66 (dd, *J* = 10.8 Hz, *J* = 5.4 Hz, 1H), 3.33-3.32 (m, 2H), 3.13-3.09 (m, 2H), 2.74-2.64 (m, 3H), 2.28 (dd, *J* = 15.3 Hz, *J* = 1.9 Hz, 1H), 1.69-1.57 (m, 4H). ^{13}C NMR (100 MHz, MeOD): δ 175.42, 65.54, 53.95, 50.89, 46.65, 46.60, 42.75, 31.16, 31.06. IR (neat) 3239, 2940, 1648, 1480, 1431, 1402, 1368, 1337, 1296, 1278, 1211, 1154, 1084, 1006, 998, 965, 829, 809, 734, 682 cm^{-1}. Anal. Calcd (found): C, 58.67 (58.31); H, 8.75 (8.65); N, 15.21 (14.85). MS (electrospray): exact mass calcd for $C_9H_{16}N_2O_2$ 184.1212; m/z found, 185.1285 [M+H]+. Mp 57.5 °C.