Two General Routes to 1,4-Disubstituted-2,3,4,5-tetrahydro-1*H*-3-benzazepines

Samuel W. Gerritz,* Jennifer S. Smith, Suganthini S. Nanthakumar, David E. Uehling, and Jeffery E. Cobb

Glaxo Wellcome, Inc.
Five Moore Drive
P.O. Box 13398,
Research Triangle Park, NC 27709

Email: swg25518@glaxowellcome.com

Supporting Information Available: Synthetic procedures for the preparation of **9a** from **4a** and **16a** from **10**.

Amino Alcohol 7a

To a 25º C solution of ketone **4a** (730 mg, 3.76 mmol) in anhydrous MeOH was added α–(aminomethyl)benzyl alcohol (**6**, 1.30 g, 9.49 mmol) and glacial acetic acid (290 μL, 4.9 mmol) and the resulting solution was stirred for 10 minutes. Sodium cyanoborohydride (235 mg, 3.8 mmol) was added and the solution was stirred for 15 hours at 25º C. The crude reaction mixture was concentrated *in vacuo* to a white solid which was treated with 1 M $HCl_{(aq)}$ (20 mL, 20 mmol) to quench any remaining borohydride. (Caution! Vigorous gas evolution). The resulting solution was stirred for 1 hour, and the mixture was neutralized with 1 M $NaOH_{(aq)}$. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were extracted with saturated $NaCl_{(aq)}$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. The oil was purified by flash chromatography (75%-100% EtOAc/Hexanes gradient) to afford **7a** (1.09 g, 92% yield) as a clear oil. Typically, the crude material obtained in this reaction was taken forward into the cyclization step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3H, *J*=6.4 Hz), 2.40 (diastereotopic s, 3H), 2.41 (diastereotopic s, 3H), 2.44-3.10 (m, 4H), 3.90 (s, 3H), 3.92 (s, 3H), 3.93 (m, 1H), 4.64 (m, 1H), 6.85-7.00 (m, 3H), 7.30-7.40 (m, 5H)

3-Benzazepine 8a

Amino alcohol **7a** (0.96 g, 3.04 mmol) was cooled to 0º C and methanesulfonic acid (3 mL) was added in one portion. The resulting solution was stirred for 1 hour at 0º C, then warmed to 25º C over 1 hour. The crude reaction mixture was poured over ice and neutralized with concentrated NH_4OH. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were extracted with saturated $NaCl_{(aq)}$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a pale yellow oil. The oil was purified by flash chromatography (75%-100% EtOAc/Hexanes) to afford **8a** (0.71 g, 79% yield) as an unassignable mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 3H, *J*=6.5 Hz), 2.60-2.80 (m, 2H), 3.11 (m, 1H), 3.22 (dd, 1H, *J*=13.8, 2.7 Hz), 3.69 (dd, 1H, *J*=13.8, 6.6 Hz), 3.90 (s, 3H), 3.92 (s, 3H), 4.16 (d, 1H, *J*=7.1 Hz), 6.64 (s, 1H), 6.70 (s, 1H), 7.10-7.40 (m, 5H)

3-Benzazepines *cis*-9a and *trans*-9a

To 3-Benzazepine **8a** (200 mg, 0.67 mmol) dissolved in methanol (4.0 mL) was added formaldehyde (1.0 mL of a 37% aqueous solution), glacial acetic acid (17 μL, 0.30 mmol) and sodium cyanoborohydride (63 mg, 1.00 mmol). The resulting solution was stirred for 15 hours at 25º C, and the crude reaction mixture was concentrated *in vacuo* to a white solid which was treated with 1 M $HCl_{(aq)}$ (4 mL, 4 mmol) to quench any remaining borohydride. (Caution! Vigorous gas evolution). The resulting solution was stirred for 1 hour, and the mixture was neutralized with 1 M $NaOH_{(aq)}$. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organics were extracted with saturated $NaCl_{(aq)}$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to a pale yellow oil. The oil was purified by flash chromatography (75%-100% EtOAc/Hexanes gradient) to afford *trans*-**9a** (42 mg, 20% yield) and *cis*-**9a** (127 mg, 61% yield) as a clear oils.

cis-**9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, 3H, *J*=6.8 Hz), 2.50 (s, 3H), 2.72 (dd, 1H, *J*=14.4, 6.8 Hz), 2.88 (dd, 1H, *J*=13.2, 2.0 Hz), 3.11 (m, 1H), 3.25 (dd, 1H, *J*=13.2, 10.0 Hz), 3.34 (d, 1H, *J*=14.8 Hz), 3.54 (s, 3H), 3.85 (s, 3H), 4.36 (d, 1H, *J*=7.6 Hz), 6.11 (s, 1H), 6.62 (s, 1H), 7.20 (d, 2H, *J*=7.2 Hz), 7.27 (t, 1H, *J*=7.2 Hz), 7.36 (t, 2H, *J*=7.2 Hz).

trans-**11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J*=6.0 Hz), 2.42 (s, 3H), 2.09-2.81 (m, 2H), 2.97 (dd, 1H, *J*=14.0, 2.0 Hz), 3.11 (dd, 1H, *J*=13.2, 8.8 Hz), 3.18 (dd, 1H, *J*=13.2, 4.0 Hz), 3.66 (s, 3H), 3.87 (s, 3H), 4.36 (m, 1H), 6.34 (s, 1H), 6.64 (s, 1H), 7.15 (d, 2H, *J*=7.6), 7.23 (t, 1H, *J*=7.6), 7.36 (t, 2H, *J*=7.6)

Oxazolidine 13

To a -78º C solution of Weinreb amide **10** (5.4 g, 25.8 mmoles) in dry THF (40 mL) was added diisobutylaluminum hydride (21.0 mL of a 1.5 M solution in toluene, 31.5 mmoles) over 30 minutes. The resulting solution was stirred at -78º C for 2 hours, then the reaction was quenched by inverse addition via cannula to 100 mL of a 1:1 mixture of Et_2O:saturated sodium potassium tartrate$_{(aq)}$ at 0º C. The resulting cloudy mixture was stirred vigorously for 1 hour at 0º C, then the organic layer was separated and the aqueous layer was extracted with 100 mL of EtOAc. The combined organics were dried over

$MgSO_4$, filtered, and then amino alcohol **11** (3.9 g, 26.0 mmoles) was added to the crude aldehyde solution. The solution was concentrated in vacuo to afford a tan oil which was azeotroped two times with 100 mL of toluene. The resulting crude oxazolidine was dissolved in 100 mL of EtOAc and extracted with saturated $NH_4Cl_{(aq)}$ (3 x 30 mL) and saturated $NaHCO_{3(aq)}$ (3 x 30 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford oxazolidine **13** (6.6 g, 90% crude yield)as a 1.2:1 mixture of diastereomers. In practice, we would dissolve **13** in sufficient toluene to obtain a 1.0 M solution which could be stored at 0º C for 2 months without observing any decomposition.

13: ^{1}H NMR (400 MHz): δ 2.35 (diastereotopic s, 3H), 2.40 (diastereotopic s, 3H), 2.47 (diastereotopic t, 1H, *J*=9.4 Hz), 2.8-3.0 (m, 2H + 1 diastereotopic H), 3.10 (diastereotopic dd, 1H, *J*=10.2, 5.0 Hz), 3.51 (diastereotopic dd, 1H, *J*=9.4, 58 Hz), 3.78 (s, 3H), 4.24 (diastereotopic t, 1H, *J*=5.2 Hz), 4.33 (diastereotopic t, 1H, *J*=4.8 Hz), 4.99 (diastereotopic dd, 1H, *J*=7.0, 5.4 Hz), 5.04 (diastereotopic dd, 1H, *J*=9.4, 5.8 Hz), 6.83 (d, 2H, *J*=8.4 Hz), 7.2-7.4 (m, 7H).

Amino alcohol 14a

To a 0° C solution of oxazolidine **13** (350 mg, 1.23 mmoles) in THF (4 mL) was added methylmagnesium bromide (1.2 mL of a 3.0 M solution in Et_2O, 3.60 mmoles) and the resulting solution was stirred at 0° C for 1 hour, then warmed to 25° C and stirred for 2 hours. The solution was recooled to 0° C and the excess Grignard reagent was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organics were extracted with saturated $NaHCO_{3(aq)}$ (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to an oil. The product was purified by flash chromatography (60% EtOAc:Hexanes) to afford amino alcohol **15a** (302 mg, 82%). Typically, the crude material obtained in this reaction was taken forward to the cyclization step without further purification.

15a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, 3H, *J*=6.4 Hz), 2.40 (diastereotopic s, 3H) 2.41 (diastereotopic s, 3H), 2.45-3.10 (m, 4H), 3.82 (s, 3H), 3.82 (m, 1H), 4.64 (m, 1H), 6.88 (d, 2H, *J*=8.5 Hz), 7.13 (d, 2H, *J*=8.5 Hz), 7.30-7.40 (m, 5H)

3-Benzazepine *cis*-16a and spiropiperidine dione *trans*-17a

Amino alcohol **15a** (210 mg, 0.70 mmol) was cooled to 0º C and methanesulfonic acid (1 mL) was added in one portion. The resulting solution was stirred for 1 hour at 0º C, then warmed to 25º C over 1 hour. The crude reaction mixture was poured over ice and neutralized with concentrated NH_4OH. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were extracted with saturated $NaCl_{(aq)}$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a pale yellow oil. The oil was purified by flash chromatography (75%-100% EtOAc/Hexanes) to afford *cis*-**16a** (112 mg, 57% yield) and *trans*-**17a** (49 mg, 26%) as colorless oils.

cis-**16a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3H, *J*=6.6 Hz), 2.53 (s, 3H), 2.73 (dd, 1H, *J*=14.6, 6.1 Hz), 2.94 (d, 1H, *J*=11.7 Hz), 3.19 (m, 1H), 3.29 (dd, 1H, *J*=13.2, 9.6 Hz), 3.46 (d, 1H, *J*=16.2 Hz), 3.65 (s, 3H), 4.43 (d, 1H, *J*=9.6 Hz), 6.16 (d, 1H, *J*=2.7 Hz), 6.65 (dd, 1H, *J*=8.3, 2.6 Hz), 7.04 (d, 1H, *J*=8.4 Hz), 7.20-7.25 (m, 5H).

trans-**17a**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (d, 3H, *J*=6.2 Hz), 1.46 (d, 1H, *J*=13.0 Hz), 1.83 (t, 1H, *J*=12.5 Hz), 2.27 (m, 1H), 2.42 (s, 3H), 2.95 (m, 2H), 3.20 (dd, 1H, *J*=9.0, 6.2 Hz), 6.05 (dd, 1H, *J*=10.1, 1.9 Hz), 6.24 (dd, 1H, *J*=10.4, 1.9 Hz), 6.76 (dd, 1H, *J*=10.1, 2.1 Hz), 7.53 (dd, 1H, *J*=10.6, 3.0 Hz)