Total Synthesis of Asperazine

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Supporting Information^{1,2}

Experimental procedures and characterization data for key transformations (preparation of **8**, **9**, **12**, **14**, and **1**) copies of ¹H and ¹³C NMR spectra of these compounds, tables comparing NMR spectra of synthetic and natural **1**, and the CD spectrum of synthetic **1** (24 pages).

Stille Coupling to Prepare 8 and Deprotection to Form Enolate 9. A suspension of Pd₂(dba)₃•CHCl₃ (145 mg, 0.280 mmol Pd⁰), (2-furyl)₃P (265 mg, 1.14 mmol), and dry NMP (8 mL) in a base-washed, flame-dried 100 mL Schlenk flask was stirred for 2 h to furnish a yellow-green homogenous solution. A solution of stannane **5** (1.70 g, 2.96 mmol), iodide **7** (1.04 g, 1.87 mmol), and NMP (12 mL) was added, and the reaction was degassed by the freeze-pump-thaw method at –78 °C three times. Copper(I) iodide (620 mg, 3.26 mmol) was added, the mixture was stirred for 19 h at rt, and the reaction was quenched by slow addition of saturated aqueous KF (10 mL). After stirring for 15 min, the mixture was diluted with MTBE (400 mL) and washed with water (300 mL) containing concentrated ammonia solution (15 mL). The aqueous layer was extracted with MTBE (200 mL). The combined organic extracts were dried (MgSO₄), filtered, concentrated, and the residue was purified by silica gel chromatography (13:1, 9:1, 6:1, 4:1 hexanes-ethyl acetate) to give 1.19 g of **8** as a colorless foam. Diagnostic data: MS (ESI) *m/z* 736.43 (736.38 calcd for C₃₈H₅₅N₃NaO₁₀, M+Na).

A solution of **8** (1.19 g) and DMSO (25 mL) was degassed [bubbling argon (30 min), evacuate (15 min, 5 mm), bubbling argon (30 min)] and then heated at 130 °C for 6.5 h. The reaction was poured into water (200 mL) and extracted with Et₂O (50 mL × 3). The combined organic extracts were dried (MgSO₄), filtered, concentrated, and the residue was purified by silica gel chromatography (8:1, 6:1, 5:1 hexanes-ethyl acetate) to give 939 mg (82%) of **9** as a colorless foam: [α]_D²⁴ = –41.7, [α]₅₇₇²⁴ = –43.9, [α]₅₄₆²⁴ = –52.6, [α]₄₃₅²⁴ = –126, [α]₄₀₅²⁴ = –166 (c 0.79, CHCl₃); ¹H NMR (500 MHz, DMSO, 80 °C) δ 10.23 (s, 1H, NH), 7.61 (br d, *J* = 7.7 Hz, 1H, ArH), 7.13 (d, *J* = 2.3 Hz, 1H, ArH), 7.01 (t, *J* = 7.6 Hz, 1H, ArH), 6.92 (dd, *J* = 7.2, 0.8 Hz, 1H, ArH), 6.28 (d, *J* = 8.0 Hz, 1H, C=CH), 5.16 (app td, *J* = 7.4, 4.3 Hz, 1H, CHN), 4.29 (dd, *J* = 9.0, 7.0 Hz, 1H, CH₂O), 4.14–4.10 (m, 1H, CHN), 3.98 (br, 1H, CH₂O), 3.80 (dd, *J* = 7.9, 5.8 Hz, 1H, CH₂O), 3.74 (dd, *J* = 8.8, 1.6 Hz, 1H, CH₂O), 3.68 (s, 3H, CO₂Me), 3.15 (dd, *J* = 13.8, 2.8 Hz, 1H, CH₂), 2.81 (dd, *J* = 13.8, 10.2 Hz, 1H, CH₂), 1.53 (s, 6H, Me₂C), 1.50 (s, 3H, MeCMe), 1.48 (s, 9H, *t*-Bu), 1.44 (s, 9H, *t*-Bu), 1.43 (s, 3H, MeCMe); ¹³C NMR (125 MHz, DMSO, 80 °C) δ 165.8, 151.2, 151.0, 146.7, 134.0, 130.2, 127.5, 123.4, 121.7, 121.3, 118.0,

¹ General experimental details have been described: Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, 62, 6379–6387.

² Abbreviations not defined in *J. Org. Chem.* **2001**, 66, 24A: dba = *trans,trans*-dibenzylideneacetone, NMP = 1-methyl-2-pyrrolidinone, SEMCl = 2-(trimethylsilyl)ethoxymethyl chloride, DMA = *N,N*-dimethylacetamide, HATU = *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (Carpino, L. A. *J. Am. Chem. Soc.* **1993**, 115, 4397–4398), MTBE = methyl *tert*-butyl ether.

117.9, 110.9, 93.3, 92.8, 79.2, 78.7, 67.6, 65.8, 56.9, 56.1, 51.2, 28.4, 27.8, 27.7, 26.7, 25.9, 24.1, 23.4; IR (neat) 3317, 2979, 1698, 1667, 1392, 1366 cm^{-1} ; MS (FAB) m/z 613.3363 (613.3363 calcd for $\text{C}_{33}\text{H}_{47}\text{N}_3\text{O}_8$, M). Anal. Calcd for $\text{C}_{33}\text{H}_{47}\text{N}_3\text{O}_8$: C, 64.58; H, 7.72; N, 6.85. Found: C, 64.44; H, 7.91; N, 6.75.

Heck Cyclization to Form Oxindole 12. A suspension of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (195 mg, 0.377 mmol Pd^0), $(2\text{-furyl})_3\text{P}$ (440 mg, 1.90 mmol), and dry DMA (15 mL) in a base-washed, flame-dried 100 mL Schlenk flask was stirred for 2 h to furnish a yellow-green homogenous solution. Anilide **11** (2.00 g, 1.88 mmol), 1,2,2,6,6-pentamethylpiperidine (2.00 mL, 11.1 mmol), and DMA (5 mL) were added, and the reaction was degassed by the freeze-pump-thaw method at -78°C three times. After 10 h at 90°C , the reaction was allowed to cool to rt, poured into saturated aqueous LiCl (100 mL), diluted with water (100 mL), and extracted with MTBE (100 mL $\times$ 3). The combined organic extracts were dried (MgSO_4), filtered, concentrated, and the residue was purified by silica gel chromatography (12:1, 9:1, 6:1, 4:1 hexanes-ethyl acetate) to give 1.16 g (66%) of **12** as a colorless foam: $[\alpha]_D^{27} = -120$, $[\alpha]_{577}^{27} = -127$, $[\alpha]_{546}^{27} = -147$, $[\alpha]_{435}^{27} = -305$, $[\alpha]_{405}^{27} = -409$ (c 0.75, CHCl_3); ^1H NMR (500 MHz, DMSO, 100°C) δ 7.62 (d, $J = 7.4$ Hz, 1H, ArH), 7.36 (td, $J = 7.7$, 1.2 Hz, 1H, ArH), 7.28 (s, 1H, ArH), 7.21 (d, $J = 7.0$ Hz, 1H, ArH), 7.19 (d, $J = 7.7$ Hz, 1H, ArH), 7.10 (td, $J = 7.3$, 0.9 Hz, 1H, ArH), 6.93 (t, $J = 7.7$ Hz, 1H, ArH), 6.76 (br d, $J = 7.1$ Hz, 1H, ArH), 6.41 (t, $J = 1.9$ Hz, 1H, C=CH), 5.71 (br, 2H, NCH_2O), 5.19 (d, $J = 10.9$ Hz, 1H, NCH_2O), 5.14 (d, $J = 10.9$ Hz, 1H, NCH_2O), 4.16–4.10 (m, 1H, CHN), 3.83 (dd, $J = 8.2$, 6.0 Hz, 1H, CH_2O), 3.77 (dd, $J = 12.9$, 1.8 Hz, 1H, CH_2O), 3.73 (dd, $J = 8.7$, 1.9 Hz, 1H, CH_2O), 3.72 (dd, $J = 13.5$, 1.8 Hz, 1H, CH_2O), 3.62–3.54 (m, 2H, CH_2O), 3.46–3.39 (br m, 1H, CH_2O), 3.34–3.27 (br m, 1H, CH_2O), 3.16 (dd, $J = 14.0$, 3.2 Hz, 1H, CH_2), 2.84 (dd, $J = 14.0$, 10.0 Hz, 1H, CH_2), 1.51 (s, 3H, MeCMe), 1.50 (s, 9H, *t*-Bu), 1.45 (s, 3H, MeCMe), 1.44 (s, 3H, MeCMe), 1.43 (s, 9H, *t*-Bu), 1.41 (s, 3H, MeCMe), 0.92–0.75 (m, 4H, CH_2Si), -0.04 (s, 9H Me_3Si), -0.07 (s, 9H Me_3Si); ^{13}C NMR (125 MHz, DMSO, 100°C) δ 177.1, 150.9, 149.6, 140.6, 136.8, 134.0, 133.6, 131.3, 127.9 (2), 124.5, 123.6, 122.83, 122.75, 118.6, 118.3, 112.3, 109.2, 105.5, 95.1, 92.7, 80.9, 78.7, 78.0, 69.0, 65.7, 65.1, 64.2, 63.6, 56.9, 56.7, 27.7 (2), 27.6, 26.9, 24.7, 24.4, 23.8, 17.1, 17.0, -2.06 , -2.12 ; IR (neat) 2953, 1703, 1384, 1366, 1074 cm^{-1} ; MS (ESI) m/z 955.5060 (955.5049 calcd for $\text{C}_{50}\text{H}_{76}\text{N}_4\text{NaO}_9\text{Si}_2$, M+Na). Anal. Calcd for $\text{C}_{50}\text{H}_{76}\text{N}_4\text{O}_9\text{Si}_2$: C, 64.34; H, 8.21; N, 6.00. Found: C, 64.64; H, 8.27; N, 5.93.

Hydrogenation of 13 to Form 14. A mixture of **13** (400 mg, 0.595 mmol), palladium on carbon (158 mg, 10 wt%, 0.148 mmol) and DMF (12 mL) was stirred in a pressure reactor under 1000 psi of hydrogen for 24 h at rt. This mixture was filtered through Celite, and the resulting filter cake was washed with MTBE (300 mL). The filtrate was washed with saturated aqueous LiCl (100 mL), and the resulting aqueous layer was extracted with MTBE (100 mL). The combined organic extracts were dried (MgSO_4), filtered, concentrated, and

the residue was purified by silica gel chromatography (4:1, 3:1 hexanes-ethyl acetate) to give 383 mg (95%) of **14**, a colorless foam, as an inseparable 4:1 mixture of epimers. All characterization data was obtained on this mixture: IR (neat) 3335, 2978, 1698, 1389, 1366 cm^{-1} ; MS (CI) m/z 674.3667 (674.3680 calcd for $\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_7$, M). Anal. Calcd for $\text{C}_{38}\text{H}_{50}\text{N}_4\text{O}_7$: C, 67.63; H, 7.47; N, 8.30. Found: C, 67.48; H, 7.51; N, 8.08.

NMR data for the major epimer (C11 α -H):³ ^1H NMR (500 MHz, DMSO, 100 $^\circ\text{C}$) δ 10.43 (s, 1H, NH), 9.87 (s, 1H, NH), 7.59-7.54 (m, 1H, ArH), 7.39 (d, J = 7.4 Hz, 1H, ArH), 7.32 (td, J = 7.7, 1.2 Hz, 1H, ArH), 7.17 (d, J = 2.4 Hz, 1H, ArH), 7.12 (td, J = 7.5, 1.0 Hz, 1H, ArH), 7.01 (d, J = 7.5 Hz, 1H, ArH), 6.97-6.91 (m, 2H, ArH), 4.15-4.08 (m, 1H, CHN), 3.83 (dd, J = 8.0, 5.9 Hz, 1H, CH_2O), 3.77 (dd, J = 8.7, 1.8 Hz, 1H, CH_2O), 3.73 (dd, J = 8.8, 1.9 Hz, 1H, CH_2O), 3.65-3.54 (m, 2H, CH_2O and CHN), 3.14 (dd, J = 14.0, 3.6 Hz, 1H, CH_2), 2.93 (dd, J = 13.6, 3.2 Hz, 1H, CH_2), 2.80 (dd, J = 14.1, 4.3 Hz, 1H, CH_2), 2.61 (d, J = 13.1 Hz, 1H, CH_2), 1.51 (s, 3H, MeCMe), 1.50 (s, 3H, MeCMe), 1.46 (s, 9H, *t*-Bu), 1.44 (s, 3H, MeCMe), 1.37 (s, 9H, *t*-Bu), 1.35 (s, 3H, MeCMe); ^{13}C NMR (125 MHz, DMSO, 100 $^\circ\text{C}$) δ 179.5, 150.9, 150.5, 140.9, 133.5, 129.3, 128.9, 127.9, 126.0, 123.3, 123.0, 121.0, 119.0, 118.0, 117.6, 110.9, 109.7, 92.6, 91.8, 78.8, 78.5, 65.9, 65.1, 56.9, 54.9, 54.0, 37.0, 28.1, 27.6, 27.5, 26.5, 26.4, 23.5, 23.4.

NMR data for the minor epimer (C11 β -H):^{3,4} ^1H NMR (500 MHz, DMSO, 100 $^\circ\text{C}$) δ 10.36 (s, 1H, NH), 10.08 (s, 1H, NH), 7.57 (1H, ArH), 7.41 (d, J = 7.6 Hz, 1H, ArH), 7.32 (1H, ArH), 7.17 (1H, ArH), 7.12 (1H, ArH), 7.02-6.91 (3H, ArH), 4.12 (1H), 4.04-3.98 (m, 1H, CHN), 3.83 (1H), 3.72 (dd, J = 8.8, 2.0 Hz, 1H, CH_2O), 3.29 (dd, J = 8.8, 5.8 Hz, 1H, CH_2O), 3.15 (1H, CH_2O), 2.99 (d, J = 14.0 Hz, 1H, CH_2), 2.86-2.77 (2H), 2.49 (1H, CH_2), 1.47 (s, 9H, *t*-Bu), 1.45 (s, 3H, MeCMe), 1.43 (s, 9H, *t*-Bu), 1.42 (s, 3H, MeCMe), 1.39 (s, 3H, MeCMe), 1.33 (s, 3H, MeCMe); ^{13}C NMR (125 MHz, DMSO, 100 $^\circ\text{C}$, diagnostic signals only) δ 178.5, 150.7, 141.1, 133.7, 130.3, 128.7, 127.9, 125.8, 123.0, 122.2, 121.0, 119.5, 117.7, 111.0, 109.8, 91.7, 78.9, 65.8, 65.0, 54.8, 54.2, 37.4, 28.0, 26.4, 26.2, 23.4.

Asperazine 1. A solution of **17** (21.7 mg, 0.0211 mmol) and formic acid (6 mL) was maintained at rt for 2 h. The formic acid was then removed as an azeotrope with heptane (15 mL $\times$ 3). Diagnostic data for the product: MS (ESI) m/z 729.42 (729.34 calcd for $\text{C}_{42}\text{H}_{45}\text{N}_6\text{O}_6$, M+H).

A solution of this deprotected tetrapeptide, acetic acid (400 μL , 7.0 mmol), and *n*-butanol (9.6 mL) was refluxed for 24 h. The acetic acid and *n*-butanol were then removed *in vacuo* (0.5 mm), and the resulting residue was purified by preparative TLC (9:1 chloroform-methanol) to give 8.2 mg (59%) of asperazine (**1**) as a colorless solid. This material showed ^1H NMR spectra in CDCl_3 , CH_2Cl_2 and CD_3CN , ^{13}C NMR spectra in CDCl_3 and CD_3CN , mass spectral data, and a CD spectrum in MeOH that compared favorably to those of the natural isolate.⁵ The optical rotation of synthetic asperazine, $[\alpha]_{\text{D}} +95.7$ (c 0.2, CH_3OH) was higher than that reported for the natural material, $[\alpha]_{\text{D}} +52$ (c 0.2, CH_3OH).⁵

³ The stereochemistry of the major and minor hydrogenation products was established by ^1H NOE analysis of **16**.

⁴ In cases where the multiplicity and/or peak assignment was not made, the peak was obstructed by the major isomer.

⁵ (a) Varoglu, M.; Corbett, T. H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **1997**, 62, 7078-7079. (b) Unpublished data for natural **1** kindly provided by Professor Phillip Crews.

Table 1: ¹H NMR Data (500 MHz, CD₃CN) for Natural and Synthetic Asperazine.⁶

Position	Natural	Synthetic
30	8.61 (br s)	8.82 (br s)
27	7.48 (dd, <i>J</i> = 7, 1 Hz)	7.49 (ddd, <i>J</i> = 7.6, 1.3, 0.7 Hz)
42, 44, 46	7.27 (m)	7.30–7.23 (m)
21	7.20 (m)	7.23–7.18 (m)
19, 20, 22, 23, 25, 26, 43, 45	7.12 (m)	7.14–7.06 (m)
31	6.918 (d, <i>J</i> = 2.5 Hz)	6.915 (d, <i>J</i> = 2.6 Hz)
5	6.82 (dd, <i>J</i> = 7, 1 Hz)	6.815 (ddd, <i>J</i> = 7.9, 1.0, 0.6 Hz)
8	6.815 (d, <i>J</i> = 7.5 Hz)	6.80 (ddd, <i>J</i> = 7.8, 0.6, 0.6 Hz)
6	6.66 (dd, <i>J</i> = 7, 1 Hz)	6.66 (ddd, <i>J</i> = 7.5, 7.5, 1.0 Hz)
38	6.49 (d, <i>J</i> = 4.5 Hz)	6.55 (br d, <i>J</i> = 3.9 Hz)
14	6.18 (br s)	6.26 (br d, <i>J</i> = 0.8 Hz)
35	6.16 (br s)	6.23 (br d, <i>J</i> = 0.5 Hz)
1	6.14 (br s)	6.16 (br d, <i>J</i> = 2.2 Hz)
2	5.71 (d, <i>J</i> = 1 Hz)	5.71 (d, <i>J</i> = 2.3 Hz)
37	4.12 (ddd, <i>J</i> = 6, 5, 4.5 Hz)	4.12 (dddd, <i>J</i> = 6.3, 4.4, 4.4, 0.5 Hz)
15	3.59 (ddd, <i>J</i> = 5.5, 5, 4.5 Hz)	3.59 (dddd, <i>J</i> = 5.6, 4.8, 2.0, 0.8 Hz)
34	3.51 (ddd, <i>J</i> = 6, 5.5, 3.5 Hz)	3.53 (dddd, <i>J</i> = 5.7, 4.7, 1.8, 0.8 Hz)
11	3.32 (dd, <i>J</i> = 9.5, 7.5 Hz)	3.34 (dd, <i>J</i> = 9.7, 7.5 Hz)
12	3.25 (dd, <i>J</i> = 14, 7.5 Hz)	3.23 (dd, <i>J</i> = 13.3, 7.5 Hz)
33	3.09 (dd, <i>J</i> = 14.5, 5.5 Hz)	3.11 (ddd, <i>J</i> = 14.9, 5.8, 0.7 Hz)
40	3.06 (dd, <i>J</i> = 14, 6 Hz)	3.075 (dd, <i>J</i> = 13.6, 6.3 Hz)
33	3.05 (dd, <i>J</i> = 14.5, 3.5 Hz)	3.070 (ddd, <i>J</i> = 14.9, 4.7, 0.7 Hz)
17	3.01 (dd, <i>J</i> = 13.5, 5.5 Hz)	3.00 (dd, <i>J</i> = 13.9, 5.6 Hz)
17	2.95 (dd, <i>J</i> = 13.5, 5 Hz)	2.92 (dd, <i>J</i> = 14.0, 4.7 Hz) ⁷
40	2.93 (dd, <i>J</i> = 14, 5 Hz)	2.96 (dd, <i>J</i> = 13.7, 4.9 Hz) ⁷
12	2.40 (dd, <i>J</i> = 14, 9.5 Hz)	2.44 (dd, <i>J</i> = 13.5, 9.7 Hz)

⁶ Our assignments were made in analogy to those made by Crews⁵ unless otherwise noted.⁷ A ¹H–¹H COSY experiment of synthetic **1** revealed this alternate assignment.

Table 2: ^{13}C NMR Data (125 MHz, CD_3CN) for Natural and Synthetic Asperazine.⁶

Position	Natural	Synthetic
13	169.98	169.84
36	169.64	169.43
16	168.89	168.78
39	168.84	168.67
9	148.57	148.48
18, 41 ⁸	137.72	137.69
29	135.45	135.42
4	134.16	134.41
42, 46	131.63	131.60
19, 23	131.46	131.44
7, 28 ⁹	130.45	130.47, 130.43
43, 45	130.15	130.17
20, 22	130.09	130.11
21	128.98	128.99
44	128.72	128.70
24 ¹⁰	126.31	126.57
5, 31 ¹¹	125.20	126.28, 125.21
6	120.93	121.50
26	120.61	120.97
25	120.24	120.63
27	119.02	120.29
8	112.41	112.41
32	111.15	111.20
2	84.20	84.46
37	60.46	60.71
3	59.28	59.38
11	57.79	58.16
15	57.14	57.40
34	56.36	56.31
40	40.72	41.18
17	40.40	40.73
12	39.55	40.01
33	30.20	30.68

⁸ Non-equivalent overlapping carbons.⁹ Spectra of natural **1** show a single peak with a small shoulder.⁵ Our spectra show this peak resolved into two distinct peaks.¹⁰ Unpublished ^{13}C NMR spectra of natural **1** show a peak at 126.56.⁵ This peak was not assigned, presumably because it is barely larger than the noise. Our ^{13}C NMR spectra show this peak to be real and we assign it to C24.¹¹ We assign the peak previously assigned to C24 (126.28), to either C5 or C31.

CD Spectrum of Asperazine (0.18 mg/mL methanol, 2 mm pathlength)

asp-cdc13 ~4mg/ml
1H spectrum

asp-cdc13 ~4mg/mL
1H spectrum

asp-cdc13-d11 expt3 .5mg/ml
1H spectrum

asp cd2c12 expt1 -- 2mg/ml
1H spectrum

asp-cd2c12_expt3 --.5mg/ml
1H spectrum

gn v-20-fc expt1 100degC
1H spectrum