Concise Synthesis of (±)-Cytisine *via* Lithiation of *N*-Boc Bispidine

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Supporting Information Available: Experimental procedures, full characterisation data and copies of all ^1H NMR and ^{13}C NMR spectra.

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General

Water is distilled water. Et₂O and THF were freshly distilled from benzophenone ketyl whereas CH₂Cl₂ was freshly distilled from CaH₂. ^sBuLi was titrated against *N*-benzylbenzamide before use. Petrol refers to the fraction of petroleum ether with a boiling point range of 40-60 °C. All reactions were carried out under oxygen free nitrogen or argon using oven-dried and/or flame dried glassware. Flash column chromatography was carried out using ICN Biomedics GmbH silica (60 Å). Thin layer chromatography was carried using Merck F₂₅₄ aluminium-backed silica plates. For Kügelrohr distillation, the temperatures quoted correspond to the oven temperatures.

Proton (270 MHz or 400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol EX 270 or a Joel ECX-400 instrument using an internal deuterium lock. All samples were recorded in CDCl₃. Chemical shifts are quoted in parts per million and referenced to CHCl₃ (7.27). Carbon NMR spectra were recorded with broadband proton decoupling and were assigned using DEPT and HSQC experiments. Infra-red spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer.

Preparation of CuCN•2LiCl solution

LiCl (341 mg, 8.04 mmol, 2.0 equiv) was heated at 150 °C for 4 h under high vacuum (0.5 mm Hg) in a 25 mL round bottomed flask equipped with a stirrer bar. After being allowed to cool to rt, the flask was purged with Ar and CuCN (360 mg, 4.04 mmol, 1.0 equiv) was added in one portion under a stream of Ar. Then, THF (6.73 mL) was added and the mixture was stirred for 10 min to give a pale green solution of CuCN•2LiCl in THF (0.6 M).

Allyl diphenyl phosphate

Et₃N (8.18 mL, 58.80 mmol) was added dropwise to a stirred solution of allyl alcohol (2.0 mL, 29.4 mmol) in dry THF (150 mL) at 0 °C under N₂. Diphenyl phosphorochloridate (9.14 cm³, 44.1 mmol) was then added dropwise and the resulting solution was stirred at rt for 16 h. Then, NH₄Cl_(aq) (75 mL) was added and the white precipitate was removed by filtration and the filter cake was washed with Et₂O (25 mL). The two layers were separated and the aqueous phase extracted with Et₂O (3 × 100 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude

product. Purification by flash column chromatography with petrol-Et₂O (3:2) as eluent gave allyl diphenyl phosphate (7.13 g, 91 %) as a colourless oil, R_F (3:2 petrol-Et₂O) 0.35; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.29 (m, 4H, Ph), 7.28-7.13 (m, 6H, Ph), 5.99-5.88 (m, 1H, CH=CH₂), 5.37 (d, J = 17.5 Hz, 1H, *trans*-CH=CH_AH_B), 5.26 (d, J = 10.5 Hz, 1H *cis*-CH=CH_AH_B), 4.76-4.71 (2 H, m, CH₂CH=CH₂). Spectroscopic data is consistent that reported in the literature.¹

Experimental procedures, full characterisation data and $^1\text{H}/^{13}\text{C}$ NMR spectra for all compounds

(1S*,5R*)-tert-Butyl 7-benzyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **8**

A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate **7** (1.0 g, 5.03 mmol), acetic acid (280 μL , 5.03 mmol) and benzylamine (564 μL , 5.15 mmol) in MeOH (6 mL) was added dropwise to a stirred suspension of paraformaldehyde (332 mg, 11.06 mmol) in MeOH (10 mL) at reflux under N_2 . The resulting mixture was then heated at reflux for 1 h and paraformaldehyde (332 mg, 11.06 mmol) was added. The mixture was heated at reflux for a further 4 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O (20 mL) and washed with 1 M $\text{KOH}_{(\text{aq})}$ (20 mL). The aqueous layer was extracted with Et_2O (5 x 20 mL). The combined organics were dried (MgSO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:1) as eluent gave bispidinone **8** (1.29 g, 78 %) as a colourless oil, R_F (3:1 petrol-EtOAc) 0.2; ^1H NMR (400 MHz, CDCl_3) rotamers present δ 7.32-7.24 (m, 5H, Ph), 4.58 (br d, $J = 13.5$ Hz, 1H, C(O)NCH), 4.42 (br d, $J = 13.5$ Hz, 1H, C(O)NCH), 3.54 (d, $J = 13.5$ Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 3.47 (d, $J = 13.5$ Hz, 1H, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 3.36 (d, $J = 13.5$ Hz, 1H, C(O)NCH), 3.28 (br d, $J = 13.5$ Hz, 1H, C(O)NCH), 3.20 (br d, $J = 11.5$ Hz, 1H, NCH), 3.16 (br d, $J = 11.5$ Hz, 1H, NCH), 2.72 (br dd, $J = 10.5, 3.5$ Hz, 1H, NCH), 2.66 (br dd, $J = 10.5, 3.5$ Hz, 1H, NCH), 2.44 (br s, 1H, CH), 2.40 (br s, 1H, CH) and 1.54 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, CDCl_3) δ 213.6 (bridge C=O), 154.7 (Boc C=O), 137.4 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 127.2 (Ph), 80.0 (CMe_3), 61.8 (CH_2Ph), 59.0 (NCH_2), 58.6 (NCH_2), 50.4 (C(O)NCH $_2$), 49.7 (C(O)NCH $_2$), 47.5 (2 x CH), 28.5 (CMe_3). Spectroscopic data is consistent with that reported in the literature.²

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(1S*,5R*)-tert-Butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **9**

p-Toluenesulfonyl hydrazide (339 mg, 1.82 mmol) was added in one portion to a stirred solution of bispidinone **8** (500 mg, 1.52 mmol) in EtOH (13 mL) at rt under N₂. The resulting solution was heated at reflux for 2 h (complete formation of the hydrazone was indicated by disappearance of **8** by TLC). After being allowed to cool to rt, the solvent was evaporated under reduced pressure. The residue was dissolved in THF-H₂O (4:1, 8 mL) and cooled to 0 °C. Then, NaBH₄ (575 mg, 15.2 mmol) was added portionwise over 20 min (CARE - vigorous effervescence). The resulting mixture was stirred at rt for 16 h. Then, the solution was heated at reflux for 3 h. After being allowed to cool to rt, water (15 mL) was added and the layers were separated. The aqueous layer was extracted with Et₂O (4 × 20 mL). Then, the combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave bispidine **8** (288 mg, 60 %) as a colourless oil which crystallised to a white solid on standing, mp 62-65 °C; *R*_F(4:1 petrol-EtOAc) 0.2; ¹H NMR (400 MHz, CDCl₃) rotamers present δ 7.38-7.19 (m, 5H, Ph), 4.17 (br d, *J* = 13.0 Hz, 1H, C(O)NCH), 4.00 (br d, *J* = 13.0 Hz, 1H, C(O)NCH), 3.40 (d, *J* = 13.5 Hz, 1H, CH_AH_BPh), 3.30 (d, *J* = 13.5 Hz, 1H, CH_AH_BPh), 3.13-3.02 (m, 2H, 2 × C(O)NCH), 3.01 (br d, *J* = 11.0 Hz, 1H, NCH), 2.89 (br d, *J* = 11.0 Hz, 1H, NCH), 2.22 (br d, *J* = 11.0 Hz, 1H, NCH), 2.16 (br d, *J* = 11.0 Hz, 1H, NCH), 1.88 (br s, 1H, CH), 1.79 (br s, 1H, CH), 1.69-1.42 (m, 2H, bridge CH₂), 1.53 (s, 9H CMe₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.0 (C=O), 139.0 (*ipso*-Ph), 128.5 (Ph), 128.0 (Ph), 126.6 (Ph), 78.7 (CMe₃), 63.5 (CH₂Ph), 59.0 (NCH₂), 58.7 (NCH₂), 48.4 (C(O)NCH₂), 47.5 (C(O)NCH₂), 31.1 (bridge CH₂), 28.9 (2 × CH), 28.7 (CMe₃). Spectroscopic data consistent with that reported in the literature.²

9

Title: m8694das

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tert*-Butyl 7-benzyl-2-methyl-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate **10*

^sBuLi (1.19 mL of a 1.20 M solution in cyclohexane, 1.44 mmol) was added dropwise over 1 min to a stirred solution of bispidine **9** (freshly distilled 230 °C/1.5 mm Hg, 284 mg, 0.90 mmol) and TMEDA (217 μ L, 1.44 mmol) in Et₂O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 7 h. Then, MeI (123 μ L, 1.98 mmol) was added dropwise and the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Water (5 mL) was then added (to dissolve any precipitate) followed by the addition of solid K₂CO₃ until pH $\geq$ 10. The two layers were separated and the aqueous layer extracted with Et₂O (5 x 5 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a brown oil. Purification by flash column chromatography on silica with petrol-EtOAc (85:15) as eluent gave methylated bispidine **10** (173 mg, 58 %) as a colourless oil, *R*_F(4:1 petrol-EtOAc) 0.4; IR (CDCl₃): 2927, 2800, 1682 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) rotamers present δ 7.32-7.23 (m, 5H, Ph), 4.28 (br s, 1H, C(O)NCHMe), 4.15-4.02 (br m, 1H, C(O)NCH), 3.54 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.33 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.15 (br d, *J* = 13.0 Hz, 1H, C(O)NCH), 2.92 (br d, *J* = 11.0 Hz, 1H, NCH), 2.56, (d, *J* = 10.0 Hz, 1H, NCH), 2.11-2.07 (br m, 1H, CH), 2.07-2.02, (m, 1H, NCH), 2.02-1.95 (br m, 1H, CH), 1.92 (dd, *J* = 11.0, 2.0 Hz, 1H, NCH), 1.65 (d, *J* = 12.5 Hz, 1H, bridge CH_AH_B), 1.47 (s, 9H, CMe₃), 1.31 (br d, *J* = 12.5 Hz, 1H, bridge CH_AH_B), 1.26 (d, *J* = 7.0 Hz, 3H, Me); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.8 (C=O), 138.7 (*ipso*-Ph), 129.0 (Ph), 128.9 (Ph), 126.9 (Ph), 78.8 (CMe₃), 63.0 (CH₂Ph), 58.5 (NCH), 55.4 (NCH), 50.7 (NCHMe), 43.2 (C(O)NCH), 31.0 (CH), 28.5 (CMe₃), 27.8 (bridge CH₂), 27.3 (CH), 15.3 (CHMe); MS (CI, NH₃) *m/z* 331 [(M + H)⁺, 100], 301 (10), 275 (50), 257 (15), 231 (63); HRMS (CI, NH₃) *m/z* [M + H]⁺ calcd for C₂₀H₃₀N₂O₂, 331.2386; found, 331.2385 and recovered bispidine **9** (68 mg, 24 %) as an off-white crystalline solid.

10

Title: m8943das

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Title: k8252das

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tert*-Butyl 2-allyl-7-benzyl-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate **11*

Procedure (i): Dieter protocol

^sBuLi (4.6 mL of a 1.03 M solution in cyclohexane, 4.74 mmol) was added dropwise over 1 min to a stirred solution of bispidine **9** (freshly distilled 230 °C/1.5 mmHg, 936 mg, 2.96 mmol) and TMEDA (713 μ L, 4.74 mmol) in Et₂O (8.4 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 7 h. Then, CuCN•2LiCl (4.9 mL of a 0.6 M solution in THF, 2.96 mmol) was added dropwise and the resulting solution was stirred at –78 °C for 40 min. Then, allyl diphenyl phosphate (1.49 mL, 6.5 mmol) was added dropwise and the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. NH₄OH_(aq) (1 mL), saturated NH₄Cl_(aq) (9 mL) and Et₂O (10 mL) were added and the mixture stirred at rt for 20 min. The solids were removed by filtration through a pad of Celite® and the filter cake was washed with Et₂O (10 mL). The two layers of the filtrate were separated and the blue aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (92:8) as eluent gave allylated bispidine **11** (631 mg, 60 %) as a colourless oil, *R*_F(85:15 petrol-EtOAc) 0.3; IR (CDCl₃) 2926, 2800, 1687 (C=O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.22 (m, 5H, Ph), 5.76-5.63 (m, 1H, CH=CH₂), 4.88 (d, *J* = 10.5 Hz, 1H, *cis*-CH=CH_AH_B), 4.71 (d, *J* = 17.5 Hz, 1H, *trans*-CH=CH_AH_B), 4.45-4.01 (br m, 2H, C(O)NCHallyl and C(O)NCH), 3.43 (s, 2H, CH₂Ph), 3.16 (br d, *J* = 12.5 Hz, 1H, C(O)NCH), 2.94 (br d, *J* = 11.5 Hz, 1H, NCH), 2.60 (br d, *J* = 10.5 Hz, 1H, NCH) 2.55-2.42 (m, 2H, CH₂CH=CH₂), 2.18-2.09 (br m, 1H, CH), 2.09-2.01 (br m, 1H, CH), 1.98 (dd, *J* = 10.5, 1.5 Hz, 1H, NCH), 1.95 (dd, *J* = 11.5, 2.5 Hz, 1H, NCH), 1.61 (br d, *J* = 13.0 Hz, 1H, bridge CH_AH_B), 1.47 (s, 9H, CMe₃), 1.37-1.21 (m, 1H, bridge CH_AH_B); ¹³C NMR (100.6 MHz, CDCl₃) δ 155.9 (C=O), 138.6 (*ipso*-Ph), 136.6 (CH=CH₂), 129.3 (Ph), 128.1 (Ph), 127.0 (Ph) 115.8 (CH=CH₂), 79.1 (CMe₃), 63.1 (CH₂Ph), 58.9 (NCH), 54.6 (NCH), 54.6 (NCHallyl), 43.6 (C(O)NCH₂), 34.7 (CH₂CH=CH₂), 29.4 (CH), 28.5 (CMe₃), 27.9 (bridge CH₂), 27.5 (CH); MS (CI, NH₃) *m/z* 357 [(M + H)⁺, 100], 301 (10), 275 (50),

257 (10); HRMS (CI, NH₃) *m/z*: [M + H]⁺ calcd for C₂₂H₃₂N₂O₂, 357.2542; found, 357.2541 and recovered bispidine **9** (297 mg, 32%) as an off-white crystalline solid.

Procedure (ii): Taylor protocol

^tBuLi (1.15 cm³ of a 1.10 M solution in cyclohexane, 1.26 mmol) was added dropwise over 1 min to a stirred solution of bispidine **2** (freshly distilled 230 °C/1.5 mmHg, 250 mg, 0.78 mmol) and TMEDA (191 μl, 1.26 mmol) in Et₂O (2.2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 5 h. Then, ZnCl₂ (2.03 mL of a 0.5 M solution in THF, 1.01 mmol) was added dropwise over 10 min and the resulting mixture was stirred at –78 °C for 20 min. The reaction mixture was allowed to warm to rt over 15 min and then re-cooled to –40 °C. Then, CuCN•2LiCl (1.30 cm³ of a 0.60 M solution in THF, 0.78 mmol) was added dropwise. The resulting solution was warmed to 0 °C over 15 min and then re-cooled to –40 °C. Then, allyl diphenyl phosphate (215 μL mmol, 1.2 eq) was added dropwise. The resulting solution was allowed to warm to rt over 16 h. NH₄OH_(aq) (0.5 mL), saturated NH₄Cl_(aq) (4.5 mL) and Et₂O (5 mL) were added and the mixture stirred at rt for 20 min. The solids were removed by filtration through a pad of Celite[®] and the filter cake was washed with Et₂O (5 mL). The two layers of the filtrate were separated and the blue aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (92:8) as eluent gave allylated bispidine **11** (118 mg, 42 %) as a colourless oil and recovered bispidine **9** (91 mg, 36 %) as an off-white crystalline solid.

11

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Title: m0463das

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1-(2-Allyl-7-benzyl-3,7-diaza-bicyclo[3.3.1]nonan-3-yl)prop-2-en-1-one **12**

TFA (2 mL) was added dropwise to a stirred solution of the bispidine **11** (378 mg, 1.06 mmol) in CH₂Cl₂ (2 mL) at 0 °C under N₂. The resulting solution was stirred at 0 °C for 2 h. Then, saturated NaHCO_{3(aq)} was added until pH 7-8 was obtained. The aqueous layer was extracted with CH₂Cl₂ (5 x 20 mL) and the combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude amine mono TFA salt (388 mg, 99%). To a stirred solution of the crude amine mono TFA salt (268 mg, 0.72 mmol) in CH₂Cl₂ (2.5 mL) was added 10% (w/v) NaOH_(aq) (2 mL), at rt under N₂. A solution of acryloyl chloride (70 μL, 0.86 mmol) in CH₂Cl₂ (0.5 mL) was then added dropwise and the resulting mixture was stirred at rt for 3 h. Then, a solution acryloyl chloride (23 μL, 0.30 mmol) in CH₂Cl₂ (0.25 mL) was added dropwise and the resulting mixture was stirred for 1 h. Then, CH₂Cl₂ (5 mL) and water (5 mL) were added and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were dried (MgSO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc-petrol (1:1) as eluent gave diene **12** (224 mg, 99 % over two steps) as a colourless oil, *R*_F(1:1 EtOAc-petrol) 0.3; IR (film) 2922, 2799, 2768, 1643 (C=O), 1607 (C=C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) rotamers present δ 7.40-7.23 (m, 5H, Ph), 6.60 (dd, *J* = 16.5, 10.5 Hz, 1H, COCH), 6.40-6.16 (br m, 1H, *trans*-COCH=CH_AH_B), 5.87-5.57 (br m, 1H, CH₂CH=CH₂), 5.64 (br d, *J* = 10.0 Hz, 1H, *cis*-COCH=CH_AH_B), 4.99-4.87 (br m, 1H, *cis*-CH₂CH=CH_AH_B), 4.87-4.75 (br m, 1H, C(O)NCH), 4.73 (br d, *J* = 17.5 Hz, 1H, *trans*-CH₂CH=CH_AH_B), 4.20 (br s, 0.5H, C(O)NCH), 3.95 (br s, 0.5H, C(O)NC), 3.63-3.42 (br s, 0.5H, C(O)NC), 3.46 (br s, 2H, CH₂Ph), 3.12 (br s, 0.5H, C(O)NCH), 3.10-2.89 (br m, 1H, NCH), 2.75-2.35 (br m, 3H, NCH and CH₂CH=CH₂), 2.24-2.09 (br m, 2H, 2 x CH), 2.08-1.95 (br, m, 2H, 2 x NCH), 1.56 (br d, *J* = 13.0 Hz, 1H, bridge CH_AH_B), 1.33 (br d, *J* = 13.0 Hz, 1H, bridge CH_AH_B); ¹³C NMR (100.6 MHz, CDCl₃) rotamers prevent full analysis of the spectrum δ 166.7 (C=O), 138.3, 129.2, 128.1, 127.1, 116.9, 115.6, 63.0, 58.4, 54.0, 27.8; MS (CI, NH₃) *m/z* 311 [(M + H)⁺, 100]; HRMS (CI, NH₃) *m/z* [M + H]⁺ calcd for C₂₀H₂₆N₂O, 311.2123; found, 311.2120.

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Title: m0940das

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Title: m0960das

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11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-4-en-6-one **13**

Grubbs 1st generation catalyst {Ru(PCy₃)₂Cl₂(=CHPh)} (28 mg, 0.034 mmol) was added in one portion to a stirred solution of diene **12** (86 mg, 0.28 mmol) in toluene (5.5 mL) at rt under N₂. The resulting solution was heated at reflux for 15 min. Then, the solution was allowed to cool to rt and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with MeOH-CH₂Cl₂-NH_{3(aq)} (3:96.5:0.5) as eluent gave dihydropyridone **13** (69 mg, 89 %) as a yellow oil which solidified on standing, mp 98-100 °C; *R*_F(MeOH-CH₂Cl₂-NH_{3(aq)} (3:96.5:0.5)) 0.4; IR (film) 1661 (C=O), 1601 (C=C) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.16 (m, 5H, Ph), 6.50 (ddd, *J* = 10.0, 6.0, 2.0 Hz, 1H, COCH=CH), 5.94 (dd, *J* = 10.0, 3.0 Hz, 1H, COCH), 4.21 (d, *J* = 14.0 Hz, 1H, C(O)NCH), 3.70 (dt, *J* = 14.0, 4.5 Hz, 1H, NCHCH₂), 3.52 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.19 (d, *J* = 13.0 Hz, 1H, CH_AH_BPh), 3.14 (ddd, *J* = 14.0, 5.0, 1.5 Hz, 1H, C(O)NCH), 2.99 (d, *J* = 10.5 Hz, 1H, NCH), 2.92 (d, *J* = 12.5 Hz, 1H, NCH), 2.40 (m, 2H, NCH and CH=CHCH_AH_B), 2.07-1.94 (m, 2H, CH and NCH), 1.92 (ddd, *J* = 17.5, 6.0, 4.5 Hz, 1H, CH=CHCH_AH_B), 1.83-1.66 (m, 3H, CH and bridge CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 164.95 (C=O), 138.9 (*ipso*-Ph), 138.4 (COCH=CH), 128.7 (Ph), 128.0 (Ph), 126.9 (Ph), 124.8 (COCH), 63.0 (CH₂Ph), 59.9 (NCH₂), 56.4 (C(O)NCH), 53.6 (NCH₂), 47.1 (C(O)NCH₂), 32.3 (CH), 31.4 (CH=CHCH₂), 28.4 (CH) and 28.2 (bridge CH₂); MS (CI, NH₃) *m/z* 283 [(M + H)⁺, 100]; HRMS (CI, NH₃) *m/z* [M + H]⁺ calcd for C₁₈H₂₂N₂O, 283.1810; found, 283.1809.

Crystal structure determination of dihydropyridone **13**

Crystal data. C₁₈H₂₂N₂O, *M* = 282.38, monoclinic, *a* = 13.8531(9), *b* = 8.9083(6), *c* = 12.8238(8) Å, β = 107.6950(10)°, *U* = 1507.68(17) Å³, *T* = 100 (2) K, space group P2₁/c, *Z* = 4, μ(Mo-Kα) = 0.078 mm⁻¹, 16383 reflections measured, 4328 unique (*R*_{int} = 0.0294) which were used in all calculations. The final *R*1 was 0.0457 (*I* > 2σ_{*I*}) and *wR*2 was 0.1260 (all data).

CCDC reference number 277535.

Title: m9792das

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Title: m1107das

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11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one **14** (*N*-benzylcytisine)

Procedure (i): Pd/C protocol

10% (w/w) Pd/C (20 mg, 0.018 mmol) was added in one portion to a stirred solution of dihydropyridone **13** (28 mg, 0.10 mmol) in 1,4 dioxane (3 mL) and cyclohexene (1 mL) under N₂. The resulting mixture was heated to 100 °C and stirred for 8 h. Then, the solution was allowed to cool to rt and CH₂Cl₂ (10 mL) was added. The solids were removed by filtration through a pad of Celite.[®] The filter-cake was washed with CH₂Cl₂ (30 mL) and the solvent was evaporated under reduced pressure to give the crude product as a brown oil. Purification by flash column chromatography on silica with MeOH-CH₂Cl₂-NH_{3(aq)} (3:96.5:0.5) as eluent gave *N*-benzyl-cytisine **14** (10.1 mg, 41 %) as a white solid, mp 129-132 °C (lit.³ 137.5-139 °C); *R*_F(MeOH-CH₂Cl₂-NH_{3(aq)} (3:96.5:0.5)) 0.35; ¹H NMR (400 MHz, CDCl₃) δ 7.27 (dd, *J* = 9.0, 7.0 Hz, 1H, C(O)CH=CH), 7.22-7.14 (m, 3H, Ph), 7.02-6.97 (m, 2H, Ph), 6.50 (dd, *J* = 9.0, 1.5 Hz, 1H, C(O)CH=CH), 5.92 (dd, *J* = 7.0, 1.5 Hz, 1H, C(O)CH=CHCH), 4.11 (d, *J* = 15.5 Hz, 1H, N(CO)CH_AH_B), 3.90 (dd, *J* = 15.5, 6.5 Hz, 1H, N(CO)CH_AH_B), 3.47 (d, *J* = 13.5 Hz, 1H, CH_AH_BPh), 3.40 (d, *J* = 13.5 Hz, 1H, CH_AH_BPh), 2.99-2.82 (m, 3H, 2 × NCH and CH), 2.48-2.40 (m, 1H, CH), 2.37 (d, *J* = 11.0 Hz, 1H, NCH), 2.27 (dd, *J* = 10.5, 2.0 Hz, 1H, NCH), 1.91-1.84 (m, 1H, bridge CH_AH_B), 1.75 (d, *J* = 13.0 Hz, 1H, bridge CH_AH_B); ¹³C NMR (100.6 MHz, CDCl₃) δ 163.6 (C=O), 151.4 (NC=CH), 138.6 (C(O)CH=CH), 138.0 (*ipso*-Ph), 128.1 (Ph), 126.9 (Ph), 116.5 (C(O)CH), 104.6 (NC=CH), 61.95 (CH₂Ph), 60.0 (NCH₂), 59.9 (NCH₂), 50.0 (N(CO)CH₂), 35.4 (CH), 28.1 (CH), 25.9 (bridge CH₂). Spectroscopic data is consistent with that reported in the literature.⁴

Procedure (ii): MnO₂ protocol

MnO₂ (116 mg, 1.33 mmol) was added in one portion to a stirred solution of dihydropyridone **13** (21 mg, 0.074 mmol) in benzene (1.5 mL) at rt under N₂. The resulting solution was heated at reflux for 3 h.

Then, the solution was allowed to cool to rt and the solids were removed by filtration through a pad of Celite[®]. The filter-cake was washed with EtOAc (100 mL) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with MeOH-CH₂Cl₂-NH_{3(aq)} (3:96.5:0.5) as eluent gave *N*-benzyl-cytisine **14** (1.2 mg, 6 %) as a white solid.

14

Title: m5384das

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(±)-Cytisine **1**

7,11-Diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-6-one **1 ((±)-Cytisine)**

10% (w/w) Pd/C (34 mg, 0.032 mmol) was added in one portion to a stirred solution of dihydropyridone **13** (42 mg, 0.15 mmol) in toluene (3 mL) and cyclohexene (1.5 mL) at rt under N₂. The resulting mixture was heated at 100 °C for 12 h. Then, the solution was allowed to cool to rt and CH₂Cl₂ (15 mL) was added. The solids were removed by filtration through a pad of Celite[®]. The filter-cake was washed with CH₂Cl₂ (50 mL) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with MeOH-CH₂Cl₂-NH_{3(aq)} (3:96.5:0.5) and MeOH-CH₂Cl₂-NH_{3(aq)} (10:89.5:0.5) as eluent gave (±)-cytisine **1** (21.4 mg, 76 %) as an off white solid, mp 143-147 °C (lit,³ 139-147 °C); *R*_F(MeOH-CH₂Cl₂-NH_{3(aq)} (7:92:1)) 0.5; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, *J* = 9.0, 7.0 Hz, 1H, C(O)CH=CH), 6.46 (dd, *J* = 9.0, 1.5 Hz, 1H, C(O)CH=CH), 6.00 (dd, *J* = 7.0, 1.5 Hz, 1H, C(O)CH=CHCH), 4.13 (d, *J* = 15.5 Hz, 1H, C(O)NCH_AH_B), 3.89 (ddd, *J* = 15.5, 6.5, 1.0 Hz, 1H, C(O)NCH_AH_B), 3.15-2.97 (m, 4H, 4 × NCH), 2.94-2.88 (m, 1H, CHC(N)=CH), 2.37-2.29 (m, 1H, CHCH₂N(CO)), 1.98-1.92 (m, 2H, bridge CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 163.6 (C=O), 151.0 (NC=CH), 138.7 (C(O)CH=CH), 116.6 (C(O)CH), 105.0 (NC=CH), 53.9 (NCH₂), 52.9 (N(CH₂)), 49.7 (N(CO)CH₂), 35.5 (CH), 27.7 (CH), 26.2 (bridge CH₂). Spectroscopic data is consistent with that reported in the literature.⁴

(±)-Cytisine 1

Title: m6536das

Converted from "C:\NMRDATA\ DARREN\M6536D-1.GXD"

References for supporting information:

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