Synthesis of (+)-Kuraramine.

Fabio Frigerio, Claire A. Haseler and Timothy Gallagher*

School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom

Fax: +44(0)1179251295

Email: t.gallagher@bristol.ac.uk

Experimental details and new compounds data.

The compound numbering system used in the supporting information is that used in the accompanying paper.

General Experimental Details

All reactions were performed under an atmosphere of dry nitrogen with either flame- or oven-dried glassware. Reactions were stirred using a Teflon® coated magnetic stirrer bar and a stirrer hot plate.

Reagents

Commercially available reagents were generally used as received and without further purification. MeOH was freshly distilled over CaH₂ prior to use. LDA and LiHMDS were synthesised using diisopropylamine and hexamethyldisilazane (1.0 equiv, both freshly distilled over CaH₂) respectively dissolved in THF (distilled over sodium & benzoquinone) then cooling to -78 °C and adding titrated n-BuLi in hexanes (0.9 equiv). n-BuLi was titrated using salicylaldehyde phenylhydrazone as indicator.¹ (-)-Cytisine 1 was extracted from local laburnum seeds following a pH-controlled extraction approach.² Bromide 6 was synthesised as we have previously described.³

NMR Spectra

Proton magnetic resonance spectra were recorded on Jeol Lambda 300 (300 MHz), Jeol JNM-ECP400, Varian 400-MR (400 MHz) and Varian VNMRS 500b (500 MHz) spectrometers at ambient temperatures. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (J) are reported to the nearest 0.5 Hz. Carbon magnetic resonance spectra were recorded on Varian 400-MR, Jeol JNM-ECP400 (101 MHz) and Jeol Lambda 300 (75.5 MHz) spectrometers at ambient...
temperatures. Chemical shifts ($\delta_C$) are reported in parts per million (ppm) and are referenced to the residual solvent peak.

**Mass Spectra**

Mass spectra were recorded using a VG Autospec (El/Cl mode) and a Brüker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS (ESI mode). Only molecular ions ($M^+$), fragments from the molecular ions and other major peaks are reported. High resolution mass spectra were recorded on a Brüker Daltonics Apex IV and are accurate to ±5 ppm.

**Infrared Spectra**

Infrared spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer as a thin film between NaCl plates. Absorption maxima ($\nu_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$).

**Polarimetry**

$[\alpha]_D$ values were recorded on a Bellingham & Stanley ADP220 polarimeter using a 1.0 dm sample tube.

**Chromatography**

Thin layer chromatography (TLC) was performed using aluminium-backed Merck plates (silica gel 60 F$_{254}$). The results were visualised by UV fluorescence and staining with alkaline KMnO$_4$ solution followed by heat. Flash column chromatography was carried out using 60 silica with an average particle size of 40-63 µm.
11-Methyl-7,11-diazatricyclo[7.3.1.0²₇] trideca-2,4-diene-6-one, (N-Methylcytisine and also known as caulophylline) (2)

![Chemical Structure of 2](image)

To a solution of (-)-cytisine 1 (100 mg, 0.53 mmol) in MeOH (3.0 mL) and THF (3.0 mL) was added formaldehyde (37% aq solution, 234 µL, 3.15 mmol) followed by NaCNBH₃ (119 mg, 1.89 mmol). The reaction mixture was stirred at r.t. for 1.5 h, then concentrated in vacuo and partitioned between CH₂Cl₂ (3 mL) and saturated aq NH₄Cl solution (3 mL) (CAUTION: Toxic gas liberated). The aqueous phase was extracted with CH₂Cl₂ (3 x 3 mL), then the combined organic washings were dried (Na₂SO₄), filtered and concentrated in vacuo to give 2 (107 mg, 99 %) as a colourless oil. Rᵣ 0.45 [CH₂Cl₂ : MeOH (10:1)]; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.69 - 1.76 (1H, m), 1.82 - 1.88 (1H, m), 2.12 (3H, s), 2.19 - 2.22 (1H, m), 2.24 (1H, dd, J = 10.5, 2.0 Hz), 2.39 - 2.45 (1H, m), 2.80 - 2.85 (1H, m), 2.85 - 2.91 (1H, m), 2.91 - 2.95 (1H, m), 3.90 (1H, ddd, J = 15.5, 7.0, 1.0 Hz), 4.04 (1H, m), 5.98 (1H, dd, J = 7.0, 1.5, Hz), 6.43 (1H, dd, J = 9.0, 1.5 Hz), 7.27 (1H, dd, J = 9.0, 7.0 Hz); ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 25.3, 27.8, 35.4, 46.1, 50.0, 62.1, 62.4, 104.9, 116.5, 138.7, 151.5, 163.7. Spectroscopic data were consistent with those reported in the literature.

11-Methyl-8-(dimethylphenylsilyl)-7,11-diazatricyclo[7.3.1.0²₇] trideca-2,4-diene-6-one (4)

![Chemical Structure of 4](image)

To a solution of (-)-N-methylcytisine 2 (106 mg, 0.52 mmol) in THF (5.0 mL) was added chlorodimethylphenylsilane (436 µL, 2.59 mmol). The reaction mixture was stirred at r.t. for 5 min then cooled to -78 °C. LDA (1.0 M in THF, 1.56 mL, 1.56 mmol) was added dropwise to the mixture then the reaction was stirred at -78 °C for 1 h followed by 16 h at r.t.. The reaction was quenched via addition of saturated aq NH₄Cl solution (1 mL) then concentrated in vacuo. The residue was partitioned between CH₂Cl₂ (10 mL) and saturated aq NH₄Cl solution, and the aqueous phase was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic washings were dried (Na₂SO₄), filtered and concentrated in vacuo to give 4 (165 mg, 90 %) as a colourless oil. Rᵣ 0.40 [CH₂Cl₂ : MeOH (10:1)]; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.68 (1H, t, J = 10.5 Hz), 2.04 (1H, ddd, J = 10.5, 7.0, 1.0 Hz), 2.23 (1H, ddd, J = 10.5, 7.0, 1.0 Hz), 2.68 (1H, dd, J = 10.5, 2.0 Hz), 2.12 (3H, s), 2.17 - 2.21 (1H, m), 2.22 - 2.25 (1H, m), 2.38 (1H, ddd, J = 15.5, 7.0, 1.0 Hz), 2.78 (1H, dd, J = 15.5, 7.0 Hz), 2.81 (1H, ddd, J = 15.5, 7.0, 1.0 Hz), 3.86 (1H, ddd, J = 15.5, 7.0, 1.0 Hz), 4.03 (1H, m), 5.97 (1H, dd, J = 7.0, 1.5, Hz), 6.43 (1H, dd, J = 9.0, 1.5 Hz), 7.28 (1H, dd, J = 9.0, 7.0 Hz); ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 25.3, 27.8, 35.4, 46.1, 50.0, 62.1, 62.4, 104.9, 116.5, 138.7, 151.5, 163.7.
solution (10 mL) then the aqueous phase was further extracted with CH₂Cl₂ (2 x 10 mL). The combined organic washings were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by column chromatography [CH₂Cl₂ : MeOH (99:1 – 96:4)] yielded 4 (84 mg, 48%) as a colourless oil. Rₚ 0.27 [CH₂Cl₂ : MeOH (95:5)]; νmax/cm⁻¹ (neat) 2937.4 (w), 2778.7 (w), 1653.2 (s), 1548.5 (s), 1426.5 (w), 1247.5 (w), 1144.0 (w), 1116.0 (w), 897.9 (w), 825.1 (m), 800.6 (m), 777.6 (m), 735.6 (w), 699.3 (w); ¹H NMR (500 MHz, CDCl₃) δ H ppm 0.32 (3H, s), 0.47 (3H, s), 1.45 (1H, dddd, J = 13.0, 4.0, 2.5, 1.5 Hz), 1.76 - 1.81 (1H, m), 2.03 (3H, s), 2.13 (1H, dd, J = 8.5, 2.0 Hz), 2.16 (1H, dd, J = 11.0, 2.5 Hz), 2.22 - 2.26 (1H, m), 2.42 - 2.45 (1H, m), 2.69 (1H, ddt, J = 10.5, 3.5, 1.5 Hz), 2.84 - 2.91 (2H, m), 4.34 (1H, d, J = 1.0 Hz), 5.94 (1H, dd, J = 7.0, 1.5 Hz), 6.30 (1H, dd, J = 9.0, 1.5 Hz), 7.16 (1H, dd, J = 9.0, 7.0 Hz), 7.28 - 7.32 (3H, m), 7.48 - 7.53 (2H, m); ¹³C NMR (126 MHz, CDCl₃) δ C ppm -3.2, -1.3, 24.8, 30.6, 35.4, 46.1, 54.2, 63.4, 104.9, 115.8, 127.5, 128.8, 134.3, 137.5, 138.4, 150.8; m/z (CI⁺) 339 ([M+H]⁺, 100%).

11-Methyl-8-(hydroxyl)-7,11-diazatricyclo[7.3.1.0²₇]trideca-2,4-diene-6-one (5)

To a solution of crude silane 4 (74 mg, 0.217 mmol) in acetic acid (3.0 mL) was added mercury (II) acetate (92 mg, 0.29 mmol) and peracetic acid (32 % solution in acetic acid, 1.51 mL, 7.16 mmol). The reaction mixture was stirred at r.t. for 1 h then cooled to 0°C and quenched with saturated aq Na₂S₂O₃ solution (5 mL). The aqueous phase was extracted with EtOAc (5 mL) then basified (pH = 9) with Na₂CO₃ and further extracted with CH₂Cl₂ (3 x 5 mL). The combined CH₂Cl₂ washings were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by column chromatography [EtOAc : MeOH (10:1)] yielded 5 (30 mg, 26% from 2) as a single diastereomer (based on ¹H NMR) and as a colourless oil. Rₚ 0.30 [CH₂Cl₂ : MeOH (10:1)]; ¹H NMR (400 MHz, CDCl₃) δ H ppm 1.77 - 1.80 (1H, m), 1.85 - 1.89 (1H, m), 2.08 (3H, s), 2.21 - 2.27 (1H, m), 2.28 - 2.33 (1H, m), 2.42 - 2.45 (1H, m), 2.82 - 2.88 (1H, m), 2.99 - 3.03 (1H, m), 3.03 - 3.08 (1H, m) 5.80 (1H, s), 6.11 (1H, dd, J = 7.0, 1.0 Hz), 6.54 (1H, dd, J = 9.0, 1.0 Hz), 7.39 (1H, dd, J = 9.0, 7.0 Hz); m/z (Cl⁺) 221 ([M+H]⁺, 100%).
6-((3R,5S)-5-(Hydroxymethyl)-1-methylpiperidin-3-yl)pyridin-2(1H)-one, (+)-Kuraramine (3)

To a solution of alcohol 5 (30 mg, 0.14 mmol) in MeOH (5.0 mL) at 0°C was added NaBH₄ (15 mg, 0.41 mmol). The reaction mixture was warmed to r.t. and stirred for 1.5 h then quenched by the addition of saturated aq NH₄Cl solution (0.5 mL) and concentrated in vacuo. Purification by column chromatography [CH₂Cl₂ : MeOH (85:15)] yielded 3 (22 mg, 70%) as an amorphous solid. Rf 0.15 [CH₂Cl₂ : MeOH (8:2)]; [α]D²⁰ = +9.5 (c = 2.1, EtOH), lit. value: [α]D²⁰ = +8.4 (c = 0.52, EtOH)⁴; νmax/cm⁻¹ (neat) 3370.1 (m), 2927.7 (m), 2854.6 (m), 2802.0 (m), 1652.8 (s), 1616.6 (s), 1549.8 (m), 1458.0 (m), 1168.6 (w), 1070.2 (m), 803.5 (m), 732.9 (m); ¹H NMR (400 MHz, CDCl₃) δH ppm 1.26 - 1.34 (3H, m), 1.87 (1H, t, J = 11.0 Hz), 2.01 - 2.12 (3H, m), 2.38 (3H, s), 2.92 - 2.99 (1H, m), 3.09 - 3.12 (2H, m), 3.53 (1H, dd, J = 11.0, 6.0 Hz), 3.57 (1H, dd, J = 11.0, 6.0 Hz), 6.08 (1H, dd, J = 7.0, 1.0 Hz), 6.44 (1H, dd, J = 9.0, 1.0 Hz), 7.37 (1H, dd, J = 9.0, 7.0 Hz); ¹³C NMR: (400 MHz, CDCl₃) δC 31.4, 38.4, 39.7, 45.9, 58.0, 59.8, 65.4, 103.9, 117.9, 141.8, 150.5, 165.3; m/z (EI⁺) 222 ([M]+, 65%); HRMS: (EI⁺) Found: [M]+ 222.1372, C₁₂H₁₈N₂O₂ calculated 222.1368. Spectroscopic data were mostly consistent with those reported in the literature.⁴ Minor discrepancies in the ¹H NMR data are most likely due to the different spectrometers used (100 MHz vs 400 MHz). Murakoshi et al. report the following signals - 1.27 (1H, m), 1.6-2.2 (4H, m), 3.49 (1H, s, OH), 3.56 (2H, d, J = 5.5 Hz), 13.03 (1H, br s, NH) - which differ from those observed in our work.

(±)-1-((1-Benzyl-6-oxopiperidin-3-yl)methoxy)pyridin-2(1H)-one (7)
To a solution of N-hydroxy-2-pyridone (100 mg, 0.90 mmol) in dry MeOH (4.0 mL) was added NaOMe (0.90 M in dry MeOH, 1.0 mL, 0.90 mmol) dropwise. The reaction mixture was stirred at r.t. for 2 h then a solution of bromide 6^3 (280 mg, 0.90 mmol) in dry MeOH (3.0 mL) was added dropwise. The reaction was stirred at r.t. for 2 h then warmed to 70 °C for 42 h. The reaction was cooled to r.t., quenched by addition of saturated aq NH₄Cl solution (0.5 mL) then concentrated in vacuo. The residue was partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL), then the aqueous phase was further extracted with CH₂Cl₂ (3 x 20 mL). The combined organic washings were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by column chromatography [CH₂Cl₂ : MeOH (99:1 – 96:4)] yielded 6 (135 mg, 48%) as a pale yellow oil. Rₖ 0.19 [CH₂Cl₂ : MeOH (95:5)]; ¹H NMR (400 MHz, CDCl₃) δppm 1.67 - 1.76 (1H, m), 1.98 - 2.06 (1H, m), 2.33 - 2.44 (1H, m), 2.50 (1H, ddd, J = 17.5, 10.0, 6.5 Hz), 2.59 (1H, ddd, J = 17.5, 6.5, 4.5 Hz), 3.24 (1H, dd, J = 12.5, 9.0 Hz), 3.47 (1H, ddd, J = 12.5, 5.0, 1.5 Hz), 4.08 (1H, t, J = 8.5 Hz), 4.24 (1H, dd, J = 8.5, 5.0 Hz), 4.60 (1H, d, J = 14.5 Hz), 4.66 (1H, d, J = 14.5 Hz), 6.08 (1H, ddd, J = 7.0, 6.5, 1.5 Hz), 6.65 (1H, ddd, J = 9.0, 1.5, 0.5 Hz), 7.21 (1H, ddd, J = 7.0, 2.0, 0.5 Hz), 7.27 - 7.38 (6H, m); ¹³C NMR (101 MHz, CDCl₃) δC ppm 23.8, 30.8, 32.9, 49.0, 50.2, 78.0, 105.2, 123.0, 127.5, 128.2, 128.7, 135.3, 137.1, 138.7, 158.5, 169.2; m/z (ESI⁺) 335 ([M+Na]⁺, 100%); HRMS: (ESI⁺) Found: [M+Na]⁺ 335.1373, C₁₈H₂₀N₂O₃Na calculated 335.1366. Purification by column chromatography also recovered bromide 6 (148 mg, 52%) [Rₖ 0.41, CH₂Cl₂ : MeOH (95:5)] as a colourless oil.

(±)-1-Benzyl-2-oxopiperidine-5-carbaldehyde (9)
To a solution of 7 (50 mg, 0.16 mmol) in THF (2.5 mL) at -78 °C was added LiHMDS (1.0 M in THF, 319 µL, 0.32 mmol) dropwise. The reaction was stirred at -78 °C for 2 h, then quenched via the addition of saturated aq NH₄Cl solution (5 mL) and warmed to r.t.. The reaction was partitioned between CH₂Cl₂ (30 mL) and saturated aq NH₄Cl solution (25 mL), then the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL), basified (pH = 10) with K₂CO₃ and further extracted with CH₂Cl₂ (4 x 30 mL). The combined organic washings were dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by column chromatography [EtOAc : n-hexane (8:2 – 1:0)] yielded 9 (31 mg, 89%) as a colourless oil. Rf 0.22 [EtOAc : MeOH (95:5)]; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.90 - 2.02 (1H, m), 2.14 – 2.24 (1H, m), 2.46 - 2.64 (2H, m), 2.67 - 2.76 (1H, m), 3.39 (1H, dd, J = 12.5, 5.5 Hz), 3.46 (1H, dd, J = 12.5, 5.5 Hz), 4.54 (1H, d, J = 14.5 Hz), 4.72 (1H, d, J = 14.5 Hz), 7.23 - 7.36 (5H, m), 9.63 (1H, s); ¹³C NMR (101 MHz, CDCl₃) δ ppm 21.1, 30.4, 45.4, 45.6, 50.2, 127.6, 128.1, 128.7, 136.6, 169.0, 200.3. Spectroscopic data were consistent with those reported in the literature.

References:

NMR spectra including n.O.e. are shown on the following pages:
11- Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}] trideca-2,4-diene-6-one, *Caulophylline* (2)

![Diagram of the molecule (2)](ff51789H-1.jdf)

FA-35(Me)
11- Methyl-7,11-diazatricyclo[7.3.1.0^2,7] trideca-2,4-diene-6-one, Caulophylline (2)
11-Methyl-8-(dimethylphenylsilyl)-7,11-diazatricyclo[7.3.1.0^2,7] trideca-2,4-diene-6-one (4)
11-Methyl-8-(dimethylphenylsilyl)-7,11-diazatricyclo[7.3.1.02,7] trideca-2,4-diene-6-one (4)
nOe Data for silane 4
nOe Data for silane 4

Synthesis of (+)-Kuraramine
Supporting Experimental Information
nOe Data for silane 4
nOe Data for silane 4

Synthesis of (+)-Kuraramine  
Supporting Experimental Information
nOe Data for silane 4
Synthesis of (+)-Kuraramine
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6-((3R,5S)-5-(Hydroxymethyl)-1-methylpiperidin-3-yl)pyridin-2(1H)-one, (+)-Kuraramine (3)
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Synthesis of (+)-Kuraramine  Supporting Experimental Information
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(±)-1-Benzyl-6-oxopiperidine-3-carbaldehyde (9)
(±)-1-Benzyl-6-oxopiperidine-3-carbaldehyde (9)