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Supporting Information

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A Flexible Strategy for Tri- and Tetracyclic Lupin Alkaloids. Synthesis of (+)-Cytisine, (±)-Anagyrine and (±)-Thermopsine.

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Full experimental and characterization details for new compounds.

Where compounds have been reported in the literature, the procedure has been omitted but an appropriate reference is provided, together with any additional and/or relevant data.

NMR assignments are based on 2D COSY analysis and where assignments are possible, these have been made. A numbered structure is also presented to indicate the numbering systems used.

Details of the crystal structure of lactam **19** are presented in Section 3.

Contents:

Section 1.

Synthesis of (+)-Cytisine 1

(±)-Methyl 1-benzyl-6-oxopiperidine-3-carboxylate (±)-5 [8,9]

R_f 0.37 (7:3 hexane – EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.95 - 2.02 (1H, m), 2.11 – 2.19 (1H, m), 2.45 (1H, ddd, *J* = 18.0, 10.0, 6.5), 2.61 (1H, ddd, *J* = 18.0, 6.5, 6.5), 2.76 – 2.83 (1H, m), 3.39 (1H, ddd, *J* = 13.0, 6.0, 1.5), 3.44 (1H, dd, J = 12.0, 8.5), 3.66 (3H, s, CO_2CH_3), 4.53 (1H, d, *J* = 14.5, $PhCH_AH_BN$), 4.69 (1H, d, *J* = 14.5, $PhCH_AH_BN$), 7.27 – 7.33 (5H, m, ArCH x 5); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 24.0 (CH_2), 30.7 (CH_2), 39.1 (CH), 48.1 (CH_2), 50.3 (CH_2), 52.2 (CO_2CH_3), 127.6, 128.2, 128.7 (ArCH x 5), 136.7 (*ipso* – Ph), 169.2 (C=O), 172.6 (C=O).

Methyl (3*R*) (+)-1-benzyl-6-oxopiperidine-3-carboxylate (5R)**-5 and (3*S*) 1-Benzyl-6-oxopiperidine-3-carboxylate** (5S)**-6**

Racemic ester (±)-**5** (800 mg, 3.6 mmol) was suspended in a mixture of 0.1 M phosphate buffer (pH 7.4) (80 mL) and acetone (8 mL), and a-chymotrypsin (220 mg) was added. The mixture was stirred at 30 °C and pH was constantly adjusted to 7.4 by autotitration of 0.1M NaOH. After 17 hours, when 0.1M NaOH (18.5 mL) had been consumed, the unreacted (*R*)-ester was recovered by extracting the reaction mixture into EtOAc (x3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford (*R*)-**5** (332 mg, 42 %) as a yellow oil; $[a]_D^{21}$ = +4.25 (*c* 4.0, $CHCl_3$). Spectroscopic data were consistent with those reported for the racemic material.[8]

Following extraction with ethyl acetate to separate (*R*)-**5**, the aqueous extract was acidified with 1M HCl then extracted into EtOAc (x3). These extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford enantioenriched acid (*S*)-**6** (366 mg, 48 %) as a colorless solid; m.p. 160 °C (ether); R_f 0.41 (9:1 EtOAc – methanol); ^{1}H NMR: (400 MHz, $CHCl_3$) δ_H 1.95 – 2.05 (1H, m), 2.12 – 2.19 (1H, m), 2.51 (1H, ddd, *J* = 18.0, 9.5, 6.5), 2.64 (1H, ddd, *J* = 18.0, 6.0, 5.5), 2.76 – 2.83 (1H, m), 3.37 – 3.47 (2H, m), 4.45 (1H, d, *J* = 14.5, $PhCH_AH_BN$), 4.75 (1H, d, *J* = 14.5, $PhCH_AH_BN$), 7.23 – 7.33 (5H, m, ArCH x 5), *A resonance attributable to OH was not observed*; ^{13}C NMR: (100 MHz, $CHCl_3$) δ_C 23.7 (CH_2), 30.5 (CH_2), 38.9 (CH), 48.2 (CH_2), 50.7 (CH_2), 127.7, 128.2, 128.7 (ArCH x 5), 136.4 (*ipso* – Ph), 170.2 (C=O), 175.3 (C=O). Spectroscopic data were consistent with those in the literature for racemic material.[9]

Acid **(*S*)-6** was dissolved in HCl (1.25 M solution in methanol, 3 mL) and stirred at room temperature

for 18 hours. The solution was concentrated *in vacuo* and the residue was dissolved in a minimum of isopropanol and filtered through a pad of silica to give ester **(*S*)-6** (331 mg, 96 % from acid). Spectroscopic data were consistent with those of the racemic material previously described.

The enantiomeric excess of ester **5** (i.e. (R)-**5** derived directly from the kinetic resolution step and (S)-**5** obtained by derivatisation of acid (S)-**6**) was determined by chiral HPLC (Chiracel OJ column) using (±)-**5** as a reference. Elution (gradient: hexane to 95:5 hexane – IPA over 70 minutes at 1 mL min^{-1}) of the racemic material gave R_t **(*R*)-5 =** 58.8 mins and R_t **(*S*)-5** = 62.5 mins. In this way, the enantiomeric excess of the unreacted ester **(*R*)-5** was assessed as > 98 % e.e. The enantiomeric excess of acid **(*S*)-6** was assessed (as its methyl ester) as 64 % e.e., but this assumes that no epimerisation occurs upon esterification.

(5*R*) (+)-1-Benzyl-5-(hydroxymethyl)piperidin-2-one

To a cold (-10 °C) solution of **(*R*)-5** (666 mg, 2.70 mmol) in THF (14 mL) was added lithium aluminium hydride (1M solution in THF, 1.35 mL, 1.35 mmol). The reaction mixture was stirred at -10 °C for 15 minutes then quenched by careful addition of 1M NaOH (0.1 mL). The suspension was filtered through celite® and concentrated *in vacuo*. Purification by flash column chromatography (9:1 EtOAc – methanol) gave the title alcohol (420 mg, 71 %) as a colorless oil; $[a]_D^{23}$ = +45.2 (*c* 1.26, $CHCl_3$); R_f 0.20 (9:1 EtOAc – methanol); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.51 – 1.61 (1H, m), 1.87 – 1.93 (1H, m), 2.00 – 2.09 (1H, m), 2.45 (1H, ddd, *J* = 18.0, 11.0, 6.5), 2.58 (1H, ddd, *J* = 18.0, 6.5, 3.5), 3.02 (1H, dd, J = 12.0, 9.5), 3.30 (1H, ddd, *J* = 12.0, 5.5, 1.5), 3.46 – 3.53 (2H, m), 4.60 (2H, s), 7.23 – 7.35 (5H, m, ArC<u>H</u> x 5), *A resonance attributable to O<u>H</u> was not observed*; ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 23.8 (<u>C</u>H_2), 31.2 (<u>C</u>H_2), 36.5 (<u>C</u>H), 49.7 (<u>C</u>H_2), 50.4 (<u>C</u>H_2), 64.5 (<u>C</u>H_2), 127.4, 128.3, 128.7 (Ar<u>C</u>H x 5), 137.1 (*ipso* –Ph), 170.0 (<u>C</u>=O). Spectroscopic data were consistent with those reported for the racemic material. [8]

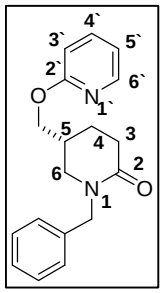
(5*R*) (+)-1-Benzyl-5-(bromomethyl)piperidin-2-one

To a 0 °C solution of alcohol (5*R*) (+)-1-benzyl-5-(hydroxymethyl)piperidin-2-one (325 mg, 1.5 mmol) in toluene (5 mL) was added phosphorus tribromide (169 µL, 1.8 mmol). The reaction mixture was heated at reflux for 3 hours then quenched by careful addition of water (1 mL) and then concentrated *in vacuo*. The residue was partitioned between water and EtOAc (x3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give bromide **(*R*)-7** (338 mg, 80 %) as a yellow oil; $[a]_D^{23}$ = +40.5 (*c* 1.16, $CHCl_3$); R_f 0.35 (EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.60 – 1.70 (1H,

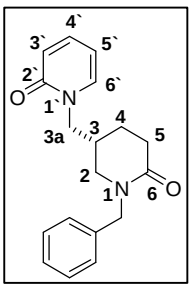
m), 1.98 – 2.01 (1H, m), 2.18 – 2.23 (1H, m), 2.50 (1H, ddd, *J* = 18.0, 11.0, 2.5), 2.63 (1H, ddd, *J* = 18.0, 5.5, 3.5), 3.05 (1H, dd, *J* = 12.0, 10.0), 3.26 (1H, dd, J = 10.5, 7.0, C$\underline{H}_A$H$_B$Br), 3.33 (1H, dd, J = 10.5, 5.0, CH$_A$$\underline{H}_B$Br), 3.38 (1H, ddd, *J* = 12.0, 5.0, 1.0), 4.56 (1H, d, *J* = 14.5, PhC$\underline{H}_A$H$_B$N), 4.64 (1H, d, *J* = 14.5, PhCH$_A$$\underline{H}_B$N), 7.24 – 7.37 (5H, m, ArC$\underline{H}$ x 5); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 26.2 ($\underline{C}H_2$), 31.0 ($\underline{C}H_2$), 34.7 (<u>C</u>-5), 36.0 ($\underline{C}H_2$), 50.3 ($\underline{C}H_2$Br), 51.1 ($\underline{C}H_2$), 127.6, 128.2, 128.7 (Ar$\underline{C}$H x 5), 138.8 (*ipso* - Ph), 169.3 (<u>C</u>=O). Spectroscopic data were consistent with those reported for the racemic material. [8]

(5*R*) 1-Benzyl-5-[(pyridin-2-yl)oxy]methylpiperidin-2-one *(O-alkylated adduct)* and **(3*R*) (+)-1-[(1-Benzyl-6-oxopiperidin-3-yl)methyl]-pyridin-2(1H)-one 8** *(N-alkylated adduct)*

A mixture of bromide **7** (200 mg, 0.71 mmol), 2-pyridone (67.4 mg, 0.71 mmol), potassium carbonate (196 mg, 1.42 mmol), tetrabutylammonium bromide (23 mg, 0.07 mmol) and water (0.03 mL) in toluene (6 mL) was heated at reflux for 18 hours. The reaction mixture was cooled, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) gave first the *O*-alkylated adduct (30 mg, 15 %) as a colorless oil; R_f 0.27 (EtOAc); IR: ν_{max} (neat) / cm^{-1} 1636 (s), 1270 (s), 1253 (s), 780 (s), 736 (s); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.54 – 1.77 (2H, m), 2.30 – 2.37 (1H, m), 2.48 (1H, ddd, *J* = 18.0, 11.5, 6.5), 2.61 (1H, ddd, *J* = 18.0, 6.0, 3.5), 3.10 (1H, dd, *J* = 12.0, 10.0), 3.38 (1H, ddd, *J* = 12.0, 5.0, 1.5), 4.13 (1H, dd, *J* = 10.5, 7.5), 4.25 (1H, dd, *J* = 10.5, 5.5), 4.60 (2H, s, NC$\underline{H}_2$Ph), 6.66 (1H, d, *J* = 8.5, C3`-<u>H</u>), 6.85 (1H, dd, *J* = 7.0, 5.0, C5`-<u>H</u>), 7.23 – 7.30 (5H, m, ArC<u>H</u> x 5), 7.54 (1H, ddd, *J* = 8.5, 7.0, 2.0, C4`-<u>H</u>), 8.10 (1H, dd, *J* = 5.0, 2.0, C6`-<u>H</u>); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 24.3 ($\underline{C}H_2$), 31.3 ($\underline{C}H_2$), 33.9 (<u>C</u>H), 50.0 ($\underline{C}H_2$), 50.4 ($\underline{C}H_2$), 67.2 ($\underline{C}H_2$), 111.1 (<u>C</u>H), 117.0 (<u>C</u>H), 127.4, 128.2, 128.6 (Ar<u>C</u>H x 5), 137.2 (*ipso* – Ph), 138.7 (<u>C</u>H), 146.9 (<u>C</u>H), 163.5 (<u>C</u>-2`), 169.7 (<u>C</u>-2); *m/z* (CI+) 297 ([M+H]$^+$, 100 %); HRMS: (EI$^+$) Found [M]$^+$ 296.1538, $C_{18}H_{20}N_2O_2$ requires 296.1525.



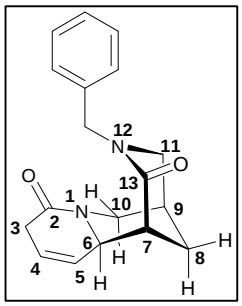
Increasing the polarity of the eluent to 95:5 EtOAc – methanol then gave *N*-alkylated adduct **8** (133 mg, 66 %) as a colorless solid; m.p. 105 – 107 °C (ether); (Found: C, 72.87; H, 6.92; N; 9.19; $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.80; N, 9.45); $[a]_D^{24}$ = +31.3 (*c* 0.8, $CHCl_3$); R_f 0.61 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 1655 (s), 1619 (s), 764 (s), 701 (s); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.52 – 1.60 (1H, m), 1.80 – 1.85 (1H, m), 2.32 – 2.40 (2H, m), 2.46 (1H, dt, *J* = 18.0, 5.0), 2.90 (1H, dd, *J* = 12.5, 9.0, C3a-$\underline{H}_A$H$_B$), 3.13 (1H, dd, *J* = 12.5, 3.5, C3a-H$_A$$\underline{H}_B$), 3.70 (2H, d, *J* = 7.0), 4.33 (1H,



d, *J* = 14.5, PhC$\underline{H}_A$H$_B$N), 4.60 (1H, d, *J* = 14.5, PhCH$_A$$\underline{H}_B$N), 5.96 (1H, m, C5`-$\underline{H}$), 6.43 (1H, d, *J* = 8.5, C3`-$\underline{H}$), 6.83 (1H, dd, *J* = 7.0, 1.5, C6`-$\underline{H}$), 7.13 – 7.23 (6H, m, ArC$\underline{H}$ x 5, C4`-$\underline{H}$); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 24.9 ($\underline{C}H_2$), 30.7 ($\underline{C}H_2$), 33.2 ($\underline{C}$-3), 49.7 ($\underline{C}H_2$), 50.2 ($\underline{C}H_2$), 52.2 ($\underline{C}H_2$), 106.0 ($\underline{C}$-5`), 121.2 ($\underline{C}$-3`), 127.6, 128.3, 128.7 (Ar$\underline{C}$H x 5), 137.0 (*ipso* – Ph), 137.8 ($\underline{C}$-6`), 139.8 ($\underline{C}$-4`), 162.6 ($\underline{C}$-2`), 169.3 ($\underline{C}$-6); *m/z* (EI+) 296 ([M]$^+$, 24 %); HRMS: (EI$^+$) Found [M]$^+$ 296.1525, $C_{18}H_{20}N_2O_2$ requires 296.1525.

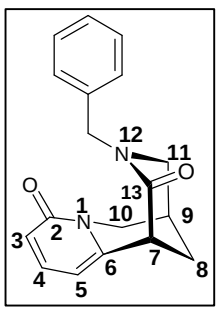
(+)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-3-ene-6,12-dione 9

To a solution of **8** (50 mg, 0.18 mmol) in THF (5 mL) at room temperature was added LiHMDS (1M solution in THF, 0.35 mL, 0.35 mmol) and the reaction mixture was heated at 70 °C in a sealed tube for 15 hours. Saturated aqueous NH_4Cl solution was added followed by EtOAc. The phases were separated and the aqueous phase was extracted into EtOAc and DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (95:5 EtOAc – methanol) gave cyclised adduct **9** (49 mg, 94 %) as a colorless solid; $[a]_D^{24}$ = +66.1 (*c* 2.3, $CHCl_3$); R_f 0.16 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 1623 (s), 728 (m), 699 (m), 676 (m); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 2.98 – 2.00 (1H, C8-$\underline{H}$ax), 2.15 (1H, ddd, *J* = 13.0, 5.5, 3.5, C8-$\underline{H}$eq), 2.20 – 2.23 (1H, m, C9-$\underline{H}$), 2.70 – 2.72 (1H, m, C10-$\underline{H}$ax), 2.75 – 2.77 (1H, m, C3-$\underline{H}$), 2.82 – 2.83 (1H, m, C3-$\underline{H}$), 2.87 - 2.89 (1H, m, C7-$\underline{H}$), 3.22 (1H, d, *J* = 12.5, C11-$\underline{H}$), 3.36 (1H, dd, *J* = 12.5, 6.0, C11-$\underline{H}$), 4.11 – 4.12 (1H, m, C6-$\underline{H}$), 4.45 (1H, d, *J* = 14.5, PhC$\underline{H}_A$H$_B$N), 4.52 (1H, d, *J* = 14.5, PhCH$_A$$\underline{H}_B$N), 4.87 (1H, dt, *J* = 13.5, 2.5, C10-$\underline{H}$eq), 5.72 – 5.81 (2H, m, C4-$\underline{H}$ and C5-$\underline{H}$), 7.11 – 7.25 (5H, m, ArC$\underline{H}$x5); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 27.7 ($\underline{C}$-9), 29.0 ($\underline{C}$-8), 31.4 ($\underline{C}$-3), 44.0 ($\underline{C}$-7), 47.3 ($\underline{C}$-10), 50.1 (Ph$\underline{C}H_2$N), 51.3 ($\underline{C}$-11), 60.3 ($\underline{C}$-6), 122.0, 123.8 ($\underline{C}$-4 and $\underline{C}$-5), 127.6, 128.3, 128.6 (Ar$\underline{C}$H x 5), 136.8 (*ipso* – Ph), 166.3 (C=O), 167.8 (C=O); HRMS: (ES$^+$) *m/z* found [M+Na]$^+$ 319.1428, $C_{18}H_{20}N_2O_2Na$ requires 319.1417.



(+)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-diene-6,12-dione 10

To a solution of **(+)-9** (48 mg, 0.16 mmol) in DCM (20 mL) was added manganese (IV) oxide (420 mg, 4.82 mmol). The reaction was stirred at room temperature for 18 hours then filtered through celite® and concentrated *in vacuo* to give **(+)-10** (37 mg, 79 %) as a colorless oil; $[a]_D^{19}$ = +180 (*c* 1.0, $CHCl_3$); R_f 0.14 (9:1 EtOAc – methanol); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 2.07 – 2.12 (1H, C8-$\underline{H}$), 2.21 (1H, ddd,



J = 13.0, 3.0, 1.0, C8-H), 2.76 (1H, s, C9-H), 3.17 (1H, d, *J* = 12.5, C11-H), 3.53 (1H, dd, *J* = 12.5, 8.0, C11-H), 3.74 (1H, dd, *J* = 5.0, 3.0, C7-H), 3.94 (1H, dd, *J* = 16.0, 6.5, C10-H), 4.04 (1H, d, *J* = 16.0, C10-H), 4.39 (1H, d, *J* = 14.5, PhCH$_A$H$_B$N), 4.50 (1H, d, *J* = 14.5, PhCH$_A$H$_B$N), 6.33 (1H, d, *J* = 7.0, C5-H), 6.49 (1H, d, *J* = 9.0, C3-H), 7.07 (2H, dd, *J* = 7.5, 2.0, ArCH x 2), 7.24 – 7.27 (3H, m, ArCH x 3), 7.31 (1H, dd, *J* = 9.0, 7.0, C4-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 23.2 (C-8), 25.8 (C-9), 43.3 (C-7), 49.7 (C-10), 50.1 (PhCH$_2$N), 53.0 (C-11), 106.5 (C-5), 118.4 (C-3), 127.8, 127.9, 128.9 (ArCH x 5), 136.2 (*ipso* - Ph), 139.2 (C-4), 144.0 (C-6), 163.4 (C-2), 167.4 (C-13); HRMS: (ES$^+$) *m/z* found $[M+Na]^+$ 317.1272, $C_{18}H_{18}N_2O_2Na$ requires 317.1260. Spectroscopic data were consistent with those reported for the racemic material,[8] and this material was judged pure (by TLC and ^{1}H NMR) and was used without further purification.

(+)-*N*-Benzylcytisine

To a cold (0 °C) solution of **10** (64 mg, 0.22 mmol) in THF (1 mL) was added borane-tetrahydrofuran complex (1M solution in THF, 0.22 mL, 0.22 mmol). The solution was warmed to room temperature and stirred for 1 hour then cooled to 0 °C and further borane-tetrahydrofuran complex (1M solution in THF, 0.22 mL, 0.22 mL) was added. The reaction mixture was then stirred for 2 hours at room temperature then cooled to 0 °C. Methanol (1 mL) and then water (1 mL) were added and the solution was extracted into EtOAc (x3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (94:5:1 EtOAc – methanol – NEt_3) gave **N-benzylcytisine** (60 mg, 97 %) as a colorless solid; $[a]_D^{23}$ = +218 (*c* 0.22, $CHCl_3$) (lit.[3j] $[a]_D^{25}$ = +216 (*c* 0.42, $CHCl_3$); R_f 0.36 (9:1 EtOAc – methanol); ^{1}H NMR: (270 MHz, $CDCl_3$) δ_H 1.74 (1H, d, *J* = 12.5, C8-H$_A$H$_B$),1.85 (1H, d, *J* = 12.5, C8-H$_A$H$_B$), 2.26 (1H, d, *J* = 11.0), 2.35 (1H, d, *J* = 11.0), 2.37 (1H, br, s), 2.79 (1H, d, *J* = 11.0), 2.88 (2H, br, s), 3.33 (1H, d, *J* = 13.5, PhCH$_A$H$_B$N), 3.40 (1H, d, *J* = 13.5, PhCH$_A$H$_B$N), 3.82 (1H, dd, *J* = 15.0, 6.5, C10-H$_A$H$_B$), 4.04 (1H, d, *J* = 15.0, C10-H$_A$H$_B$), 5.86 (1H, d, *J* = 6.5, C5-H), 6.43 (1H, d, *J* = 9.0, C3-H), 6.92 – 6.95 (2H, m), 7.11 – 7.25 (4H, m); HRMS: (ES$^+$) *m/z* found $[M+Na]^+$ 303.1478, $C_{18}H_{20}N_2ONa$ requires 303.1468. Spectroscopic data were consistent with those reported in the literature.[3e,8]

(+)-Cytisine 1 (free base)

To a solution of (+)-*N*-benzyl cytisine (31 mg, 0.11 mmol) in methanol (1.8 mL) was added HCl (1.25M solution in methanol, 88 µL). The reaction mixture was stirred for 10 minutes then 20 % palladium hydroxide on carbon (30 mg) was added and the reaction was stirred for 5 hours under 1

atmosphere of hydrogen. The mixture was then filtered through celite® and concentrated *in vacuo*. The residue was partitioned between 1M NaOH and EtOAc. The phases were separated and the aqueous phase was extracted into EtOAc and DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by preparative TLC (95:4:1 DCM – methanol – NH_4OH) gave **(+)-cytisine 1** (free base) (21 mg, 62 %): $[a]_D^{24}$ = +120 (*c* 0.1, EtOH); lit.[13a] $[a]_D$ -110 (*c* 0.5, EtOH); lit.[3j] $[a]_D$ +113.5 (*c* 0.3, EtOH); R_f 0.49 (92:7:1 DCM – methanol – NH_4OH); ^{1}H NMR: (400 MHz, **MeOD**) δ_H 1.86 – 2.03 (1H, m), 2.34 – 2.36 (1H, m), 2.94 – 2.07 (4H, m), 3.30 (2H, br, s), 3.91 (1H, dd, *J* = 15.5, 6.5), 4.06 (1H, d, *J* = 15.5), 6.28 (1H, dd, *J* = 7.0, 1.0), 6.43 (1H, dd, *J* = 9.0, 1.5), 7.30 (1H, dd, *J* = 9.0, 7.0), *A resonance attributable to NH was not observed*; ^{1}H NMR: (400 MHz, **$CDCl_3$**) δ_H 1.82 – 1.86 (1H, m), 1.95 – 1.97 (2H, m), 2.33 (1H, br, s), 2.90 (1H, br, s), 3.00 (2H, d, *J* = 12.5), 3.06 (1H, dd, *J* = 12.0, 2.5), 3.10 (1H, d, *J* = 12.5), 3.90 (1H, dd, *J* = 15.5, 6.5), 4.13 (1H, d, *J* = 15.5), 6.00 (1H, dd, *J* = 7.0, 1.0), 6.49 (1H, dd, *J* = 9.0, 1.0), 7.30 (1H, dd, *J* = 9.0, 7.0); HRMS: (ES^+) *m/z* found $[M+H]^+$ 191.1184, $C_{11}H_{15}N_2O$ requires 191.1179.

Spectroscopic data were consistent with those reported earlier[3,8] and matched those obtained from a commercially available (from Tocris-Cookson) sample of (-)-cytisine.

Section 2.

Synthesis of (±)-Anagyrine 3

Preparation of (±)-Ethyl 2-[N-benzylpiperidin-2-yl]acrylate 11

LiHMDS (1M solution in THF, 6.03 mL, 6.03 mmol) was added dropwise to a cold (-78 °C) solution of ethyl 2-[1-benzyl]piperidin-2-yl]propionate (1.05 g, 4.02 mmol) in THF (25 mL) The resulting solution was stirred at -78 °C for 1 hour then chloromethylethyl ether (560 µL, 6.03 mmol) was added. The resulting solution was stirred at -78 °C for 1.5 hours then warmed to room temperature and stirred for 4 hours. The solvent was removed *in vacuo* and the residue partitioned between water and EtOAc (x3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (90:9:1 petrol - EtOAc – NH_3) gave (±)-1-ethyl 3-ethoxy-2-[1-benzylpiperidin-2-yl]propionate (1.11g, 87 %) as a colorless oil; IR: ν_{max} (neat) / cm^{-1} 1734 (s), 1110 (s), 733 (s), 698 (s); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.13 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$), 1.21 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$), 1.25 – 1.63 (6H, m), 2.17 (1H, ddd, *J* = 13.0, 8.5, 3.5, $NC\underline{H}_AH_B$), 2.78 (1H, td, *J* = 7.5, 3.5, $NC\underline{H}$), 2.85 (1H, ddd, *J* = 13.0, 7.0, 3.0, $NCH_A\underline{H}_B$), 3.29 (1H, ddd, *J* = 9.0, 7.5, 3.5, $C\underline{H}CO_2$), 3.45 – 3.48 (2H, m, $CH_2OC\underline{H}_2CH_3$), 3.50 (1H, d, *J* = 13.5, $PhC\underline{H}_AH_BN$), 3.64 (1H, dd, *J* = 9.0, 3.5, $CHC\underline{H}_AH_BO$), 3.73 (1H, app. t, *J* = 9.0, $CHCH_AC\underline{H}_BO$), 3.92 (1H, d, *J* = 13.5, $PhCH_A\underline{H}_BN$), 4.11 – 4.23 (2H, m, $CO_2C\underline{H}_2CH_3$), 7.19 – 7.27 (5H, m, $ArC\underline{H}$x5); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 14.3 ($OCH_2\underline{C}H_3$), 15.1 ($OCH_2\underline{C}H_3$), 22.7 ($\underline{C}H_2$), 23.0 ($\underline{C}H_2$), 25.3 ($\underline{C}H_2$), 47.9 ($\underline{C}H$), 49.3 ($\underline{C}H_2$), 56.9 ($\underline{C}H_2$), 60.4 ($\underline{C}H_2$), 60.7 ($N\underline{C}H$), 66.6 ($O\underline{C}H_2$), 68.3 ($O\underline{C}H_2$), 126.8, 128.1, 128.7 ($Ar\underline{C}H$ x 5), 139.8 (*ipso* – Ph), 173.8 ($\underline{C}$=O); *m/z* (CI+) 320 ($[M+H]^+$, 68 %); HRMS: (CI^+) Found $[M+H]^+$ 320.2221, $C_{19}H_{30}NO_3$ requires 320.2226.

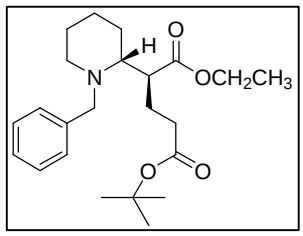
To a cold (-78 °C) solution of (±)-1-ethyl 3-ethoxy-2-[1-benzyl]piperidin-2-yl]propionate (prepared above) (691 mg, 2.17 mmol) in THF (2.8 mL) was added potassium *tert*-butoxide (1M solution in THF, 2.6 mL, 2.6 mmol) dropwise. The reaction mixture was stirred at -78 °C for 8.5 hours, then saturated aqueous NH_4Cl solution (1.1 mL) was added. The reaction mixture was warmed to room temperature and stirred for 18 hours then partitioned between water and EtOAc (x2). The aqueous phase was extracted into DCM (x2) and the organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (90:9:1 petrol - EtOAc – NH_3) gave **11** (499 mg, 84 %) as a colorless oil; R_f 0.56 (7:3 petrol – EtOAc); IR: ν_{max} (neat) / cm^{-1} 1723 (s), 734 (s), 697 (s); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.31 (3H, t *J* = 7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.36 – 1.57 (5H, m), 1.73 (1H, d, *J* = 10.5), 1.86 (1H, dd, *J* = 12.0, 3.0), 1.92 (1H, dd, *J* = 12.0, 3.0), 2.88 (1H, d, *J* =

13.5, PhC$\underline{H}_A$H$_B$N), 3.21 (1H, dd, *J* = 10.5, 3.0, NC$\underline{H}$), 4.01 (1H, d, *J* = 13.5, PhCH$_A$$\underline{H}_B$N), 4.23 (2H, q, *J* = 7.0, CO$_2$C$\underline{H}_2$CH$_3$), 6.11 (1H, d, *J* = 1.5, C=C$\underline{H}_A$H$_B$), 6.33 (1H, d, *J*= 1.5, C=CH$_A$$\underline{H}_B$), 7.19 – 7.34 (5H, m, ArC$\underline{H}$ x 5); ^{13}C NMR: (100 MHz, CDCl$_3$) δ_C 14.3 (CO$_2$CH$_2$$\underline{C}H_3$), 25.0 ($\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 35.4 ($\underline{C}H_2$), 53.5 ($\underline{C}H_2$), 59.3 ($\underline{C}H_2$), 60.7 (CO$_2$$\underline{C}H_2CH_3$), 62.8 (N$\underline{C}$H), 125.3 (C=$\underline{C}H_2$) 126.7, 128.2, 128.6 (Ar$\underline{C}$H x 5), 139.8 ($\underline{C}$=CH$_2$), 144.4 (*ipso* – Ph), 167.1 ($\underline{C}$=O); *m/z* (CI+) 274 ([M+H]$^+$, 100 %); HRMS: (EI$^+$) Found [M]$^+$ 273.1729, C$_{17}$H$_{23}$NO$_2$ requires 273.1729.

Preparation of Ethyl (1*S, 10*R**)-4-oxo-octahydro-quinolizine-1-carboxylate 12**

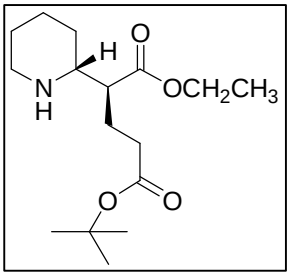
(a) (2*S) 2-((2*R**)-1-Benzylpiperidin-2-yl)pentandioic acid 1-ethyl ester 5-*tert*-butyl ester**

Diisopropylamine (132 µL, 0.94 mmol) in THF (0.2 mL) was cooled to 0 °C and *n*-BuLi (2.03M solution in hexane, 0.46 mL, 0.94 mmol) was added dropwise. The solution was stirred at 0 °C for 30 minutes, then cooled to -78 °C and a solution of *tert*-butyl acetate (121 µL, 0.90 mmol) in THF (1.7 mL) was added. The solution was stirred at -78 °C for 30 minutes then a solution of **11** (245 mg, 0.90 mmol) in THF (1 mL) was added. The reaction mixture was stirred at -78 °C for 2 hours then quenched by addition via double-ended needle to a rapidly stirred cold (0 °C) mixture of 1M HCl (1 mL)/ether (5 mL). Ether (20 mL) was added to the solution and the phases were separated. The aqueous phase was taken to pH 10 by addition of 1M NaOH and extracted into ether (x3). The organic extracts were combined, dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (90:9:1 petrol - EtOAc – NH$_3$) gave the title compound (239 mg, 68 %) as a pale yellow oil; R$_f$ 0.40 (90:9:1 petrol - EtOAc – NH$_3$); IR: ν_{max} (neat) / cm^{-1} 1727 (s), 734 (s), 698 (s); ^{1}H NMR: (400 MHz, CDCl$_3$) δ_H 1.22 (3H, t, *J* = 7.5 Hz, CO$_2$CH$_2$C$\underline{H}_3$), 1.37 – 1.48 (4H, m), 1.44 (9H, s, C(C$\underline{H}_3$)$_3$), 1.68 – 1.74 (2H, m), 1.84 – 1.93 (1H, m), 2.00 – 2.09 (1H, m), 2.14 – 2.20 (2H, m), 2.26 (1H, dd, *J* = 9.0, 5.5), 2.65 (1H, dt, *J* = 7.5, 3.0 Hz), 2.77 (1H, ddd, *J* = 13.0, 6.5, 3.5), 2.93 (1H, ddd, *J* = 10.5, 7.5, 3.5), 3.39 (1H, d, *J* = 13.0, PhC$\underline{H}_A$H$_B$N), 4.06 (1H, d, *J* = 13.0, PhCH$_A$$\underline{H}_B$N), 4.14 (2H, q, *J* = 7.5, CO$_2$C$\underline{H}_2$CH$_3$), 7.19 – 7.32 (5H, m, ArC$\underline{H}$ x 5); ^{13}C NMR: (100 MHz, CDCl$_3$) δ_C 14.2 (CO$_2$CH$_2$$\underline{C}H_3$), 22.0 ($\underline{C}H_2$), 23.1 ($\underline{C}H_2$), 24.8 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 28.0 (C($\underline{C}H_3$)$_3$), 33.5 ($\underline{C}H_2$), 46.3 ($\underline{C}$H), 49.5 ($\underline{C}H_2$), 56.3 ($\underline{C}H_2$), 60.3 ($\underline{C}H_2$), 61.8 (N$\underline{C}$H), 80.2 ($\underline{C}$(CH$_3$)$_3$), 126.6, 128.1, 128.6 (Ar$\underline{C}$H x 5), 140.0 (*ipso* – Ph), 172.4 ($\underline{C}$=O), 174.7 ($\underline{C}$=O); *m/z* (CI+) 390 ([M+H]$^+$, 30 %); HRMS: (CI$^+$) Found [M+H]$^+$ 390.2638, C$_{23}$H$_{36}$NO$_4$ requires 390.2644.



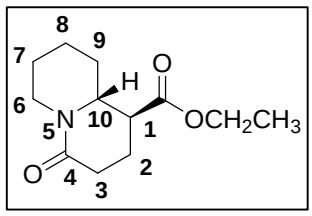
(b) (2*S) 2-((2*R**)-Piperidin-2-yl)pentandioic acid 1-ethyl ester 5-*tert*-butyl ester**

N-Benzyl piperidine (see (a) above) (150 mg, 0.35 mmol) was dissolved in ethanol (10 mL), 10 % palladium on carbon (135 mg) was added, and the reaction mixture was stirred under 1 atmosphere of hydrogen for 2 hours. The reaction mixture was filtered through celite® and concentrated *in vacuo* to afford the title compound (105 mg, 100 %) as a pale yellow oil; ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.20 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$), 1.34 – 1.43 (3H, m), 1.37 (9H, s, $C(C\underline{H}_3)_3$), 1.52 (2H, d, *J* = 12.5), 1.73 (1H, dd, *J* = 9.5, 2.5), 1.86 – 1.92 (2H, m), 2.09 – 2.17 (1H, m), 2.19 – 2.28 (1H, m), 2.37 (1H, dd, *J* = 14.0, 6.5), 2.56 (1H, td, *J* = 12.0, 3.0), 2.67 – 2.72 (1H, m), 3.06 (1H, d, *J* = 12.0), 4.09 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$), *A resonance attributable to N<u>H</u> was not observed*; ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 14.2 ($CO_2CH_2\underline{C}H_3$), 23.5 ($\underline{C}H_2$), 24.5 ($\underline{C}H_2$), 26.0 ($\underline{C}H_2$), 28.1 ($C(\underline{C}H_3)_3$), 29.9 ($\underline{C}H_2$), 33.3 ($\underline{C}H_2$), 49.9 ($\underline{C}H_2$), 50.3 ($\underline{C}H$), 58.1 ($\underline{C}H$), 60.4 ($\underline{C}H_2$), 80.3 ($\underline{C}(CH_3)_3$), 172.1 ($\underline{C}$=O), 174.1 ($\underline{C}$=O); *m/z* (CI+) 300 ($[M+H]^+$, 94 %); HRMS: (CI^+) Found $[M+H]^+$ 300.2171, $C_{16}H_{30}NO_4$ requires 300.2175.



(c) Ethyl (1*S,10*R**)-4-oxo-octahydro-quinolizine-1-carboxylate 12**

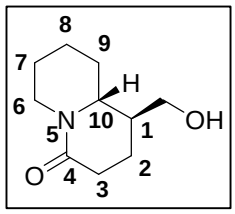
Acetic acid (1.7 mL) was added to a solution of piperidine (see (b) above) (336 mg, 1.12 mmol) in toluene (25 mL). The reaction mixture was heated at 80 °C for 18 hours then saturated aqueous $NaHCO_3$ solution was carefully added dropwise. The reaction mixture was extracted in to EtOAC (x2) then DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAc) gave lactam **12** (184 mg, 73 %) as a yellow oil; R_f 0.15 (EtOAc); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.21 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$), 1.29 – 1.45 (3H, m), 1.62 (1H, d, *J* = 14.0), 1.78 – 1.85 (2H, m, C3-$\underline{H}_2$), 1.88 – 2.03 (2H, m), 2.28 (1H, m), 2.39 – 2.49 (3H, m, C1-<u>H</u>, C6-<u>H</u>), 3.51 (1H, ddd, *J* = 11.5, 8.5, 2.5, C10-<u>H</u>), 4.12 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$), 4.73 (1H, m, C6-<u>H</u>); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 14.2 ($CO_2CH_2\underline{C}H_3$), 23.1 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 25.1 ($\underline{C}H_2$), 31.4 ($\underline{C}H_2$), 33.4 ($\underline{C}$-3), 42.7 ($\underline{C}$-6), 46.8 ($\underline{C}$-1), 58.0 ($\underline{C}$-10), 61.1 ($CO_2\underline{C}H_2CH_3$), 168.0 ($\underline{C}$=O), 173.0 ($\underline{C}$=O); *m/z* (EI+) 225 ($[M]^+$, 30 %); HRMS: (EI^+) Found $[M]^+$ 225.1355, $C_{12}H_{19}NO_3$ requires 225.1365. Spectroscopic data were consistent with those reported in the literature[17f]



(1*S,10*R**) 1-(Hydroxymethyl)octahydroquinolizin-4-one**

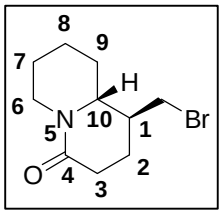
To a cold (-10 °C) solution of **12** (184 mg, 0.82 mmol) in THF (3.5 mL) was added lithium aluminium hydride (1M solution in THF, 0.41 mL, 0.41 mmol) dropwise. The reaction mixture was stirred at -10 °C for 15 minutes then quenched by careful addition of 1M NaOH (0.1 mL). The suspension was

filtered through celite® (washing with THF) and concentrated *in vacuo*. Purification by flash column chromatography (95:5 EtOAc - methanol) gave the title alcohol (110 mg, 73 %) as a pale yellow oil; R_f 0.24 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 3373 (br), 1607 (s), 2933 (m), 2857 (m), 1475 (m), 1421 (m), 1421 (m); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.20 – 1.70 (6H, m, C7-H$_2$, C9-H$_2$, C1-H), 1.83 – 1.90 (3H, m), 1.93 (1H, s, br, OH), 2.23 – 2.40 (2H, m), 2.40 – 2.48 (1H, m, C6-H), 3.08 (1H, ddd, *J* = 12.0, 7.5, 2.5, C10-H), 3.58 (1H, dd, *J* = 10.5, 4.5, CH$_A$H$_B$OH), 3.88 (1H, dd, *J* = 10.5, 5.5, CH$_A$H$_B$OH), 4.73 (1H, m, C6-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 22.1 (CH$_2$), 24.8 (CH$_2$), 25.4 (CH$_2$), 31.2 (CH$_2$), 33.5 (CH$_2$), 42.5 (C-1), 43.2 (C-6), 58.5 (C-10), 64.1 (CH$_2$OH), 169.0 (C-4); *m/z* (EI+) 183 ([M]$^+$, 80 %); HRMS: (EI$^+$) Found [M]$^+$ 183.1254, $C_{10}H_{17}NO_2$ requires 183.1259.



(1*S, 10*R**) 1-(Bromomethyl)octahydroquinolizin-4-one 13**

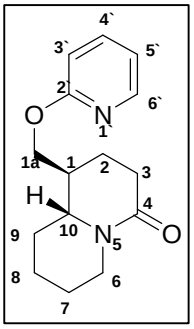
To a cold (0 °C) solution of (1*S**,10*R**) 1-(yydroxymethyl)octahydroquinolizin-4-one (38 mg, 0.21 mmol) in toluene (0.7 mL) was added phosphorus tribromide (24 µL, 0.25 mmol). The reaction mixture was heated at reflux for 2 hours then cooled and quenched by careful addition of a few drops of water then concentrated *in* vacuo. The mixture was partitioned between water and EtOAc. The phases were separated and the aqueous phase was further extracted into EtOAc and DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford bromide **13** (49 mg, 95 %) as a yellow oil; ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.23 – 1.53 (3H, m), 1.69 (1H, d, *J* = 12.5), 1.75 – 1.82 (1H, m), 1.88 – 1.95 (4H, m), 2.41 – 2.50 (2H, m), 2.61 (1H, dt, *J* = 17.5, 5.0, C6-H), 3.25 (1H, ddd, *J* = 11.5, 7.0, 2.5, C10-H), 3.45 (1H, dd, *J* = 10.5, 6.0, CH$_A$H$_B$Br), 3.54 (1H, dd, *J* = 10.5, 4.0, CH$_A$H$_B$Br), 4.78 (1H, m, C6-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 23.5 (CH$_2$), 24.4 (CH$_2$), 25.1 (CH$_2$), 30.2 (CH$_2$), 32.9 (CH$_2$), 35.6 (CH$_2$Br), 41.3 (C-1), 43.8 (C-6), 60.0 (C-10), 169.8 (C-4); HRMS: (ES$^+$) *m/z* found [M+H]$^+$ 246.0490, $C_{10}H_{17}{}^{79}BrNO$ requires 246.0488.



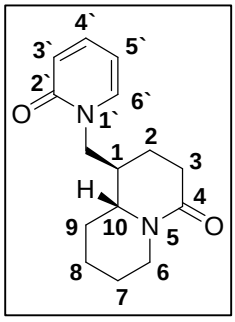
(1*S, 10*R**) 1-[(Pyridin-2-yloxy)methyl]octahydroquinolizin-4-one** (*O*-alkylated) and **1-[((1*S**,10*R**)-octahydroquinolizin-4-one-1-yl)methyl]pyridin-2(1H)-one** *(N-N*-alkylated*)* **14**

A mixture of bromide **13** (98 mg, 0.40 mmol), 2-pyridone (28 mg, 0.40 mmol), potassium carbonate (111 mg, 0.80 mmol), tetrabutylammonium bromide (13 mg, 0.04 mmol) and water (16 µL) in toluene (3.6 mL) was heated at reflux for 18 hours. The reaction mixture was cooled, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) gave first the *O*-alkylated adduct (14

mg, 14 %) as a colorless oil; R_f 0.20 (EtOAc); IR: ν_{max} (neat) / cm^{-1} 1610 (s), 1594 (s), 1570 (s), 1467 (s), 780 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.18 – 1.43 (3H, m), 1.59 – 1.98 (6H, m), 2.22 – 2.37 (2H, m), 2.43 (1H, dt, *J* = 17.0, 5.0), 3.14 (1H, ddd, *J* = 11.5, 7.5, 2.5, C10-H), 4.21 (1H, dd, *J* = 10.5, 6.0, C1a-H_AH_B), 4.32 (1H, dd, *J* = 10.5, 5.0, C1a-H_AH_B), 4.76 (1H, m, C6-H), 6.68 (1H, dt, *J* = 8.5, 1.0), 6.82 (1H, ddd, *J* = 7.0, 5.0, 1.0), 7.52 (1H, ddd, *J* = 8.5, 7.0, 2.0), 8.07 (1H, ddd, *J* = 5.0, 2.5, 1.0); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 22.6 (CH_2), 24.8 (CH_2), 25.4 (CH_2), 31.1 (CH_2), 35.5 (CH_2), 40.4 (C-1), 43.1 (C-6), 59.0 (C-10), 66.9 (C-1a), 111.2 (CH), 117.1 (CH), 138.8 (CH), 146.9 (CH), 163.6 (C-1), 168.9 (C-4); HRMS: (ES^+) *m/z* found $[M+Na]^+$ 283.1422, $C_{15}H_{20}N_2O_2Na$ requires 283.1417.

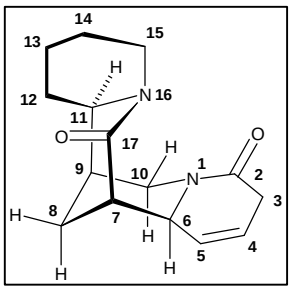


Increasing the polarity of the eluent to 9:1 EtOAc – methanol then gave *N*-alkylated adduct **14** (68 mg, 66 %) as a colorless solid; R_f 0.15 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 1655 (s), 1616 (s), 1580 (s), 1540 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.23 – 1.50 (4H, m), 1.59 – 1.62 (1H, m), 1.69 – 1.76 (1H, m), 1.81 – 1.84 (1H, m), 1.19 – 1.94 (1H, m), 2.04 – 2.11 (1H, m, C1-H), 2.18 (1H, ddd, *J* = 17.5, 10.0, 5.5), 2.32 (1H, td, *J* = 13.0, 2.5, C6-H_A), 2.39 (1H, dt, *J* = 17.5, 5.0), 2.97 (1H, ddd, *J* = 11.0, 7.5, 2.5, C10-H), 3.67 (1H, dd, *J* = 13.0, 9.0, C1a-H_AH_B), 4.10 (1H, dd, *J* = 13.0, 5.5, C1a-H_AH_B), 4.75 (1H, m, C6-H_B), 6.11 (1H, m, C5`-H), 6.51 (1H, dd, *J* = 9.0, 1.5, C3`-H), 7.14 (1H, dd, *J* = 6.5, 2.0, C6`-H), 7.29 (1H, ddd, *J* = 9.0, 6.5, 2.0, C4`-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 22.2 (CH_2), 24.6 (CH_2), 25.1 (CH_2), 30.6 (CH_2), 33.2 (CH_2), 38.7 (C-1), 43.2 (C-6), 52.7 (C-1a), 59.8 (C-10), 105.9 (C-1), 121.3 (C-3`), 137.9 (C-6`), 139.6 (C-4`), 162.6 (C-2`), 168.3 (C-4); HRMS: (ES^+) *m/z* found $[M+Na]^+$ 283.1422, $C_{15}H_{20}N_2O_2Na$ requires 283.1417.



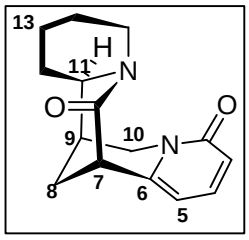
(±)-3,6-Dihydro-17-oxoanagyrine 15

n-BuLi (2.5M solution in hexane, 0.21 mL, 0.53 mmol) was added to a cold (0 °C) solution of diisopropylamine (73 µL, 0.52 mmol) in THF (3.3 mL). The solution was stirred at 0 °C for 30 minutes then a solution of **14** (68 mg, 0.26 mmol) in THF (3.3 mL) was added dropwise and the reaction was stirred at room temperature for 3 hours. Saturated aqueous NH_4Cl solution was added followed by EtOAc. The phases were separated and the aqueous phase was extracted into EtOAc and DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (60H SiO_2, 9:1 EtOAc – methanol) gave cyclised adduct **15** (30 mg, 44 %) as a colorless solid; R_f 0.30 (90:9:1 DCM – methanol – NH_4OH); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.32 – 1.62 (4H, m, C12-H$_2$, C14-H$_2$), 1.84 – 1.86 (3H, m, C8-Hax, C13-H$_2$), 1.90 (1H, t, *J* = 3.0, C9-H), 2.23 – 2.28 (1H, m, C8-Heq), 2.35 (1H, td, *J* = 13.0, 2.5, C15-Hax), 2.63 – 2.66 (1H, m, C7-H), 2.73 (1H, dd, *J* = 13.0, 2.0, C10-Hax), 2.87 (2H, d, *J* = 5.5, C3-H$_2$), 3.33 (1H, dd, *J* = 12.0, 2.0, C11-H), 4.09 – 4.13 (1H, m, C6-H), 4.65 (1H, m, C15-Heq), 4.99 (1H, dt, *J* = 13.0, 2.5, C10-Heq), 5.75 (2H, s, C4-H and C5-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 25.1 (C-13), 25.3 (C-14), 26.9 (C-8), 31.4 (C-3), 33.4 (C-12), 34.1 (C-9), 43.0 (C-15), 44.1 (C-7), 47.7 (C-10), 60.4 (C-6), 61.0 (C-11), 122.0 and 123.7 (C-4 and C-5), 166.4 (C=O), 167.2 (C=O); *m/z* (EI+) 260 ([M]$^+$, 21 %); HRMS: (EI$^+$) Found [M]$^+$ 260.1516, $C_{15}H_{20}N_2O_2$ requires 260.1525.



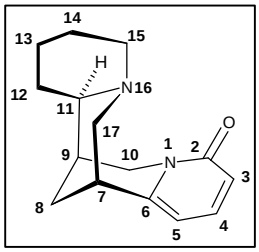
(±)-17-Oxoanagyrine 16

To a solution of **15** (30 mg, 0.12 mmol) in DCM (12 mL) was added manganese (IV) oxide (301 mg, 3.46 mmol). The reaction mixture was stirred for 23 hours at room temperature then filtered through celite® and concentrated *in vacuo* to give **16** (24 mg, 76 %) as a colorless solid; R_f 0.55 (90:9:1 DCM – methanol – NH_4OH); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.40 (1H, dt, *J* = 13.0, 3.5), 1.56 – 1.64 (2H, m), 1.67 (1H, s), 1.72 (1H, d, *J* = 8.5), 1.95 (1H, d, *J* = 7.5), 1.99 (1H, dt, *J* = 13.0, 3.0), 2.30 – 2.35 (1H, m), 2.40 (1H, dd, *J* = 13.0, 2.5), 2.44 (1H, d, *J* = 3.5), 3.33 (1H, d, *J* = 9.0), 3.61 (1H, d, *J* = 2.0), 3.90 (1H, dd, *J* = 16.0, 6.0), 4.21 (1H, d, *J* = 16.0), 4.56 (1H, dt, *J* = 13.0, 2.0), 6.28 (1H, d, *J* = 7.0, C5-H), 6.45 (1H, br. d, *J* = 9.0, C3-H), 7.26 (1H, dd, *J* = 9.0, 7.0, C4-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 20.6 (C-14), 25.0 (C-8), 25.1 (C-12), 32.2 (C-13), 33.2 (C-9), 43.2 (C-7), 43.9 (C-10), 50.8 (C-15), 63.6 (C-11), 106.7 (C-5), 118.3 (C-3), 139.4 (C-4), 144.1 (C-6), 163.6 (C-2), 166.1 (C-17); HRMS: (ES$^+$) *m/z* found [M+Na]$^+$ 281.1260, $C_{15}H_{18}N_2O_2Na$ requires 281.1260.



(±)-Anagyrine

To a cold (0 °C) solution of **16** (24 mg, 0.09 mmol) in THF (0.6 mL) was added borane-tetrahydrofuran complex (1M solution in THF, 0.17 mL, 0.17 mmol). The solution was stirred at 0 °C for 1 hour, warmed to room temperature and stirred for 1 hour then cooled to 0 °C and further borane-tetrahydrofuran complex (1M solution in THF, 0.17 mL, 0.17 mmol) was added. The solution was warmed to room temperature and stirred for 1 hour then cooled to 0 °C and further borane-tetrahydrofuran complex was added (1M solution in THF, 0.17 mL, 0.17 mmol). The reaction mixture was stirred for 1 hour at room temperature then cooled to 0 °C. Methanol (0.5 mL) then water was added and the solution was extracted into EtOAc (x2) and DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give anagyrine **3** (19 mg, 85 %) as a colorless solid, which was directly compared (using TLC, ^1H and ^{13}C NMR) to an authentic sample of anagyrine; R_f 0.36 (90:9:1 DCM – methanol – NH_4OH); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.16 (1H, d, *J* = 13.0, C14-$\underline{H}_A$), 1.50 (1H, m, C12-$\underline{H}_A$), 1.56 (1H, dt, *J* = 10.0, 3.5, C13-$\underline{H}_A$), 1.62 (1H, dt, *J* = 13.0, 3.5, C14$\underline{H}_B$), 1.67 (1H, br, s, C8-$\underline{H}_A$), 1.70 (1H, br, s, C13-$\underline{H}_B$), 1.89 (1H, d, *J* = 10.0, C12-$\underline{H}_B$), 2.01 (1H, d, *J* = 13.0, C8-$\underline{H}_B$), 2.16 (1H, br, s, C9-$\underline{H}$), 2.46 (1H, d, *J* = 11.5, C17-$\underline{H}_A$), 2.65 (1H, dt, *J* = 14.0, 2.0, C15-$\underline{H}_A$), 2.72 (1H, dd, *J* = 14.0, 3.0, C15-$\underline{H}_B$), 2.88 (1H, d, *J* = 12.0, C11-$\underline{H}$), 2.95 (1H, dd, *J* = 5.0, 3.0, C7-$\underline{H}$), 3.37 (1H, dd, *J* = 11.0, 3.0, C17-$\underline{H}_B$), 3.89 (1H, dd, *J* = 15.5, 6.5, C10$\underline{H}_A$), 4.06 (1H, d, *J* = 15.5, C10-$\underline{H}_B$), 5.96 (1H, dd, *J* = 7.0, 1.5, C5-$\underline{H}$), 6.43 (1H, dd, *J* = 9.0, 1.5, C3-$\underline{H}$), 7.27 (1H, dd, *J* = 9.0, 7.0, C4-$\underline{H}$); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 19.1 [18.9] (C-14), 20.8 [20.6] (C-8), 22.6 [22.3] (C-12), 25.6 [25.4] (C-13), 32.6 [32.4] (C-9), 35.6 [35.4] (C-7), 51.6 [51.4] (C-10), 52.9 [52.7] (C-17), 54.4 [54.2] (C-15), 63.1 [62.9] (C-11), 104.5 [104.5] (C-5), 116.6 [116.3] (C-3), 138.7 [138.6] (C-4), 152.0 [151.9] (C-6), 163.6 [163.4] (C-2); *m/z* (CI+) 245 ($[M+H]^+$, 50 %); HRMS: (CI^+) Found $[M+H]^+$ 245.1652, $C_{15}H_{21}N_2O$ requires 245.1654.



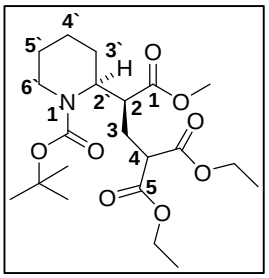
Spectroscopic data for synthetic anagyrine were consistent with those reported in the literature[15a,c,d] and the ^{13}C NMR literature values[15d] are present in []. An authentic sample of natural anagyrine was kindly supplied by Dr Ernest Boehm (Apin Chemicals Ltd) and was used for purposes of comparison (TLC and ^1H).

Section 3.

Synthesis of (±)-Thermopsine 4

(2S*)-2-((2S*)-1-*(tert*-Butoxycarbonyl)piperidin-2-yl)-4-ethoxycarbonylpentanedioic acid 5-ethyl ester 1-methyl ester 18

LiHMDS (1 M solution in THF, 25 mL, 25 mmol) was cooled to -78 °C and a solution of ester **17** (5.6 g, 21.7 mmol) in THF (70 mL) was added dropwise. The solution was stirred for 1 hour at - 78 °C then a solution of diethyl methylene malonate (3.8 g, 21.7 mmol) in THF (30 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction was quenched by addition of water and extracted into EtOAc (x3). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution; 4:1 to 3:2 hexane - EtOAc) gave alkylated adduct **18** (7.5 g, 79 %) as a pale yellow oil; R_f 0.68 (EtOAc); IR: ν_{max} (neat) / cm^{-1} 2980 (m), 2937 (m), 1732 (s), 1688 (s), 1157 (s); ^1H NMR: (500 MHz, $CDCl_3$, 50 °C) δ_H 1.26 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$), 1.28 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$), 1.36 – 1.62 (5H, m), 1.43 (9H, s, $C(C\underline{H}_3)_3$), 1.83 (1H, d, *J* = 10.5), 2.06 – 2.18 (2H, m, C3-$\underline{H}_2$), 2.88 (1H, app. t, *J* = 13.5, C2-H), 2.97 (1H, td, *J* = 11.0, 4.0, C6`-H), 3.29 (1H, dd, *J* = 10.5, 4.5, C4-H), 3.64 (3H, s, $CO_2C\underline{H}_3$), 3.98 (1H, br, d, *J* = 11.0, C6`-H), 4.15 – 4.23 (4H, m, 2 x $CO_2C\underline{H}_2CH_3$), 4.36 (1H, br, d, *J* = 8.5, C2`-H); $^{13}C$ NMR: (100 MHz, $CDCl_3$) $\delta_C$ 14.0 ($CO_2CH_2\underline{C}H_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 18.9 ($\underline{C}H_2$), 25.2 ($\underline{C}H_2$), 25.6 ($\underline{C}H_2$), 28.4 ($\underline{C}H_2$), 28.4 ($C(\underline{C}H_3)_3$), 39.2 (C-6`), 42.9 (C-2`), 50.1 (C-2), 51.8 ($CO_2\underline{C}H_3$), 61.5 ($CO_2\underline{C}H_2CH_3$), 61.6 ($CO_2\underline{C}H_2CH_3$), 79.5 ($\underline{C}(CH_3)_3$), 154.4 ($N\underline{C}O_2C(CH_3)_3$), 168.8 ($\underline{C}O_2CH_2CH_3$), 168.8 ($\underline{C}O_2CH_3CH_3$), 173.3 ($\underline{C}O_2CH_3$), *A resonance attributable to C-4 was not observed*; *m/z* (CI+) 430 ($[M+H]^+$, 2 %); HRMS: (CI^+) Found $[M+H]^+$ 430.2430, $C_{21}H_{36}NO_8$ requires 430.2441.

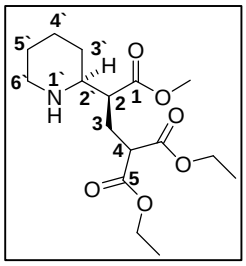


Preparation of Methyl (1*S,10*S**) 4-oxooctahydroquinolizine-1-carboxylate 19**

(a) (2*S)-2-((2*S**)-1-Piperidin-2-yl)-4-ethoxycarbonylpentanedioic acid 5-ethyl ester 1-methyl ester**

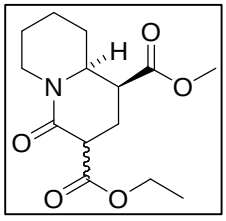
To a cold (0 °C) solution of **18** (10.5 g, 24.5 mmol) in DCM (500 mL) was added trifluoroacetic acid (17 mL). The solution was warmed to room temperature and stirred for 18 hours then concentrated *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ solution and DCM. The phases

were separated and the aqueous phase was re-extracted with DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the title amine (8.1 g, 100 %) as a pale yellow oil; R_f 0.30 (9:1 DCM – methanol); IR: ν_{max} (neat) / cm^{-1} 2855 (w), 1649 (w), 1728 (s), 1238 (s), 1149 (s), 1030 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.26 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$), 1.27 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$), 1.14 – 1.35 (3H, m), 1.55 – 1.58 (1H, m), 1.71 (1H, d, *J* = 11.0), 1.79 – 1.81 (1H, m), 2.19 (1H, ddd, *J* = 10.5, 10.0, 5.5, C3-$\underline{H}_A$), 2.26 (1H, ddd, *J* = 10.0, 10.0, 4.0, C3-$\underline{H}_B$), 2.42 (1H, ddd, *J* = 10.5, 6.5, 4.0, C2-$\underline{H}$), 2.61 (1H, dt, *J* = 12.0, 3.0, C6`-$\underline{H}$ax), 2.76 (1H, ddd, *J* = 11.0, 6.5, 2.5, C2`-$\underline{H}$), 3.06 (1H, d, *J* = 12.0, C6`-$\underline{H}$eq), 3.70 (3H, s, $CO_2C\underline{H}_3$), 3.32 (1H, dd, *J* = 10.0, 5.5, C4-$\underline{H}$), 4.17 (2H, q, *J* = 7.0, $CO_2C\underline{H}_2CH_3$), 4.20 (2H, qd, *J* = 7.0, 1.1, $CO_2C\underline{H}_2CH_3$), *A resonance attributable to the N$\underline{H}$ was not observed*; ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 14.0 ($CO_2CH_2\underline{C}H_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 24.6 ($\underline{C}H_2$), 26.4 ($\underline{C}H_2$), 27.7 ($\underline{C}$-3), 30.2 ($\underline{C}H_2$), 47.0 ($\underline{C}$-6`), 49.1 ($\underline{C}$H), 50.1 ($\underline{C}$H), 51.6 ($CO_2\underline{C}H_3$), 58.3 ($\underline{C}$H), 61.4 ($CO_2\underline{C}H_2CH_3$), 61.5 ($CO_2\underline{C}H_2CH_3$), 168.9 ($\underline{C}O_2CH_2CH_3$), 169.0 ($\underline{C}O_2CH_2CH_3$), 174.4 ($\underline{C}O_2CH_3$); *m/z* (CI+) 330 ($[M+H]^+$, 10 %); HRMS: (CI^+) Found $[M+H]^+$ 330.1919, $C_{16}H_{28}NO_6$ requires 330.1917.



(b) 1-Methyl 3-ethyl (1*S, 3*RS**, 10*S**) 4-oxooctahydroquinolizine-1,3-dicarboxylate**

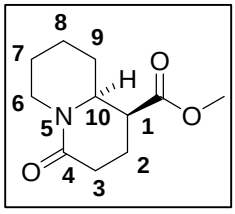
A mixture of amine (see (a) above) (1.4 g, 4.16 mmol), and acetic acid (6.5 mL) in toluene (45 mL) was heated at 80 °C for 18 hours. The reaction mixture was cooled and saturated aqueous $NaHCO_3$ solution was carefully added dropwise. EtOAc was added and the phases were separated. The aqueous phase was extracted into EtOAc (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (4:1 hexane – EtOAc) gave the title compound (1.1 g, 89 %) as a ca. 1:1 mixture of diastereomers and as a yellow oil; R_f 0.38 (EtOAc); IR: ν_{max} (neat) / cm^{-1} 2941 (m), 1731 (s), 1639 (s), 1246 (s), 1149 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.28 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$, *of A*), 1.30 (3H, t, *J* = 7.0, $CO_2CH_2C\underline{H}_3$, *of B*), 1.41 – 1.71 (11H, m, *of A and B*), 1.78 – 2.01 (1H, m, *of A or B*), 2.16 – 2.31 (2H, m, *of A*), 2.35 – 2.58 (2H, m, *of B*), 3.03 (1H, ddd, *J* = 13.0, 6.0, 3.0, *of A or B*), 3.25 – 3.49 (2H m, *of A and B*), 3.52 (1H, dd, *J* = 6.5, 2.5, *of A or B*), 3.73 (3H, s, $CO_2C\underline{H}_3$, *of A*), 3.74 (3H, s, $CO_2C\underline{H}_3$, *of B*), 4.16 – 4.30 (8H, m, $CO_2CH_2C\underline{H}_3$, *of A and B*), 4.68 – 4.81 (2H, m, *of A and B*); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 14.1 ($CO_2CH_2\underline{C}H_3$ *of A and B*), 23.1 ($\underline{C}H_2$ *of A and B*), 24.8 ($\underline{C}H_2$ *of A*), 24.9 ($\underline{C}H_2$ *of B*), 25.3 ($\underline{C}H_2$ *of A*), 25.4 ($\underline{C}H_2$ *of B*), 28.2 ($\underline{C}H_2$ *of A and B*), 39.9 ($\underline{C}$H *of A*), 41.9 ($\underline{C}$H *of B*), 45.0 ($\underline{C}H_2$ *of A*), 45.1 ($\underline{C}H_2$ *of B*), 47.3 ($\underline{C}$H *of A*), 49.0 ($\underline{C}$H *of B*), 52.3 ($CO_2\underline{C}H_3$ *of A*), 52.4 ($CO_2\underline{C}H_3$ *of B*), 58.0 ($\underline{C}$H *of A*), 58.3 ($\underline{C}$H *of B*), 61.4



($CO_2\underline{C}H_2CH_3$ *of A*), 61.5 ($CO_2\underline{C}H_2CH_3$ *of B*), 163.4 (N<u>C</u>=O *of A*), 164.2 (N<u>C</u>=O *of B*), 169.3 (<u>C</u>=O *of A*), 170.0 (<u>C</u>=O *of B*), 171.2 (<u>C</u>=O *of A*), 171.8 (<u>C</u>=O *of B*); *m/z* (CI+) 284 ($[M+H]^+$, 100 %); HRMS: (CI^+) Found $[M+H]^+$ 284.1495, $C_{14}H_{22}NO_5$ requires 284.1498.

(c) Methyl (1*S,10*S**) 4-oxooctahydroquinolizine-1-carboxylate 19**

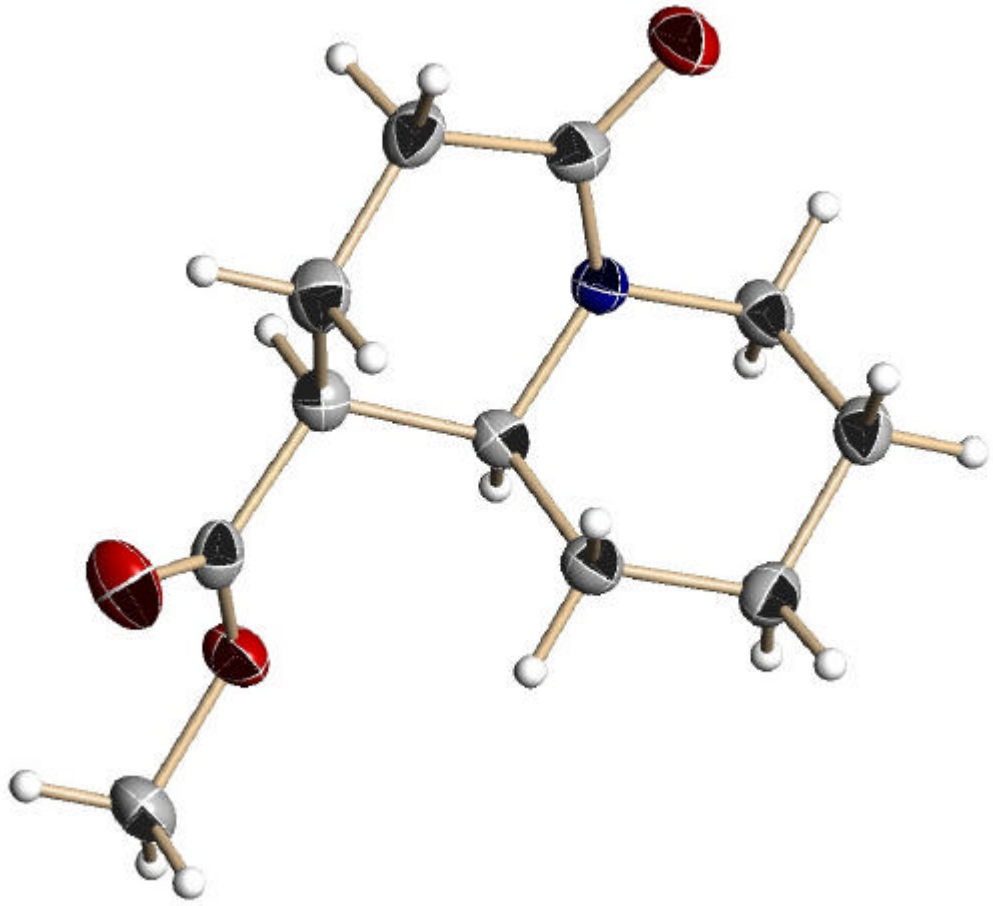
A mixture of amidoester (see (b) above) (4.2 g, 14.8 mmol), NaCl (17.8 mmol) and water (2.4 mL) in DMSO (52 mL) was heated at 130 °C for 72 hours. The solution was cooled, concentrated *in vacuo* and the residue was partitioned between 0.1M HCl and EtOAc. The phases were separated and the aqueous phase was extracted into EtOAc and DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution; 3:1 hexane – EtOAc to EtOAc) afforded ester **19** (2.3 g, 72 %) as a pale yellow solid; R_f 0.49 (9:1 DCM – methanol); IR: ν_{max} (neat) / cm^{-1} 2938 (m), 1741 (s), 1725 (s), 1623 (s), 1230 (s), 1167 (s); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.38 – 1.72 (6H, m), 1.90 – 2.08 (2H, m), 2.29 – 2.38 (1H, m), 2.44 – 2.56 (2H, m), 2.98 (1H, dt, *J* = 10.0, 6.0, C1-<u>H</u>), 3.68-3.72 (1H, m, C10-<u>H</u>), 3.74 (3H, s, $CO_2C\underline{H}_3$), 4.76 (1H, dt, *J* = 13.0, 2.0, C6-<u>H</u>); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 19.4 ($\underline{C}H_2$), 24.8 ($\underline{C}H_2$), 25.3 ($\underline{C}H_2$), 28.2 ($\underline{C}H_2$), 31.3 ($\underline{C}H_2$), 43.3 (<u>C</u>-1), 44.5 (<u>C</u>-6), 52.0 ($CO_2\underline{C}H_3$), 57.9 (<u>C</u>-10), 167.7 (<u>C</u>-4), 172.0 ($\underline{C}O_2CH_3$); *m/z* (CI+) 212 ($[M+H]^+$, 63 %); HRMS: (CI^+) Found $[M+H]^+$ 212.1285, $C_{11}H_{18}NO_3$ requires 212.1287.



A sample of **19** was crystallized from diethyl ether and the structure of **19** was established by crystallographic analysis.

Crystal data for lactam **19**: $C_{11}H_{17}NO_3$, *M* = 211.26, colorless plate (0.50 x 0.50 x 0.10 mm), Mo K_a radiation (l = 0.71073 Å) was used, intensity data were collected as *w* scans (frames, 0.3º width, $2q_{max}$ = 50º), a multi-scan (G. M. Sheldrick, *SADABS v2.03*, University of Göttingen, Germany, **2003**) absorption correction was applied (m = 0.094 mm^{-1}, T_{max} = 1.00, T_{min} = 0.94), the structure was solved and refined by standard techniques (G. M. Sheldrick, *SHELXS-97*, University of Göttingen, Germany, **1990**; G. M. Sheldrick, *SHELXL-97*, University of Göttingen, Germany, **1997**), triclinic crystal system, *a* = 9.3234(19), *b* = 10.175(2), *c* = 11.724(2) Å, a = 88.69(3), b = 75.71(3), g = 88.28(3)º, *V* = 1077.2(4) $Å^3$, r = 1.303, *T* = 173(2) K, space group $P\overline{1}$, *Z* = 4, R_{int} = 0.0456 (for 10271 measured reflections), 273 parameters were used in the refinement, hydrogen atoms were constrained to ideal geometries and refined with displacement parameters equal to 1.5 times (methyl H atoms) or 1.2 times (all other H atoms) U_{eq} of their parent atom, largest difference electron density map features were +0.192, -0.191 $eÅ^{-3}$, R_1 = 0.0423 [for 2532 unique reflections with $>2s(I)$], wR_2 = 0.0994 (for all 3787

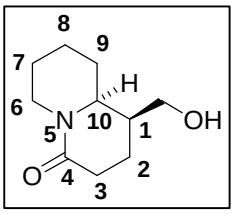
unique reflections). CCDC 289282 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.



View of Lactam 19. Note the ester moiety (at C(1)-quinolizidine numbering) sits in a pseudoequatorial conformation.

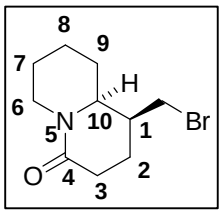
(*1S, 10*S**) 1-(Hydroxymethyl)octahydroquinolizin-4-one**

To a cold (-10 °C) solution of ester **19** (536 mg, 2.5 mmol) in THF (14 mL) was added lithium aluminium hydride (1M solution in THF, 1.27 mL, 1.27 mmol). The reaction mixture was stirred at -10 °C for 15 minutes then quenched by careful addition of a few drops of 1M NaOH then filtered through celite® and concentrated *in vacuo*. Purification by flash column chromatography (95:5 EtOAc – methanol) gave the title alcohol (343 mg, 75 %) as a pale yellow oil; R_f 0.32 (9:1 DCM – methanol); IR: ν_{max} (neat) / cm^{-1} 3374 (m), 2931 (m), 2860 (m), 1609 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.25 – 1.67 (7H, m), 2.01 (1H, d, *J* = 14.5), 2.14 – 2.22 (1H, m), 2.34 – 2.53 (3H, m), 3.52 (1H, dd, *J* = 13.0, 7.0, C10-H), 3.62 – 3.65 (2H, m, CH_2OH), 4.72 – 4.79 (1H, m, C6-H), *A resonance attributable to the OH was not observed*; ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 20.4 (CH_2), 25.1 (CH_2), 25.8 (CH_2), 26.7 (CH_2), 32.0 (CH_2), 39.5 (C-1), 44.7 (C-6), 58.8 (C-10), 63.3 (CH_2OH), 168.8 (C-4); *m/z* (EI+) 183 ($[M]^+$, 80 %); HRMS: (EI^+) Found $[M]^+$ 183.1259, $C_{10}H_{17}NO_2$ requires 183.1259.



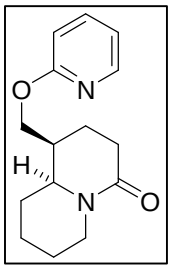
(1*S,10*S**) 1-(Bromomethyl)octahydroquinolizin-4-one 20**

To a cold (0 °C) solution of (*1**,10*S**) 1-(hydroxymethyl)octahydroquinolizin-4-one (230 mg, 1.3 mmol) in toluene (3 mL) was added phosphorus tribromide (0.15 mL, 1.6 mmol). The reaction mixture was heated at reflux for 2.5 hours then cooled and quenched by careful addition of a few drops of water then concentrated *in vacuo*. The residue was partitioned between water and EtOAc (x3). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford bromide **20** (296 mg, 96 %); m.p. 87 °C (ether); R_f 0.36 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 2941 (m), 2922 (m), 2856 (m), 1617 (s), 666 (m); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.22 – 1.83 (8H, m), 2.31 – 2.55 (4H, m), 3.24 (1H, app. t, *J* = 10.0, C10-H), 3.38 (1H, dd, *J* = 10.0, 6.5, CH_AH_BBr), 3.57 (1H, dd, *J* = 10.0, 6.5, CH_AH_BBr), 4.74 – 4.77 (1H, d, *J* = 10.0, C6-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 22.6 (CH_2), 24.9 (CH_2), 25.7 (CH_2), 26.0 (CH_2), 31.7 (CH_2), 33.2 (CH_2Br), 39.4 (C-1), 44.8 (C-6), 59.5 (C-10), 168.3 (C-4); *m/z* (CI+) 248/246 ($[M+H]^+$, 100 %); HRMS: (CI^+) Found $[M+H]^+$ 246.0483, $C_{10}H_{17}{}^{79}BrNO$ requires 246.0494.

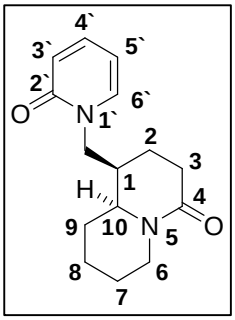


(1*S,10*S**) 1-[(Pyridin-2-yloxy)methyl]octahydroquinolizin-4-one** (*O*-alkylated) and **(±)-1-[((1*S*`,10*S*`) Octahydroquinolizin-4-one-1-yl)methyl]pyridin-2(1H)-one 21** (*N*-alkylated)

A mixture of bromide **20** (100 mg, 0.41 mmol), 2-pyridone (116 mg, 1.21 mmol), potassium carbonate (113 mg, 0.82 mmol), tetrabutylammonium bromide (13.2 mg, 0.04 mmol) and water (0.02 mL) in toluene (3.5 mL) was heated at reflux for 18 hours. The reaction mixture was cooled, filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) gave *O*-alkylated adduct (12 mg, 12 %) as a colorless oil; R_f 0.38 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 2935 (m), 1637 (s), 1625 (s), 1591 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.35 – 1.83 (7H, m), 1.93 – 1.97 (1H, m), 2.36 – 2.55 (4H, m), 3.58 (1H, ddd, *J* = 12.0, 5.5, 2.0), 4.25 – 4.28 (2H, m), 4.86-4.90 (1H, m), 6.75 (1H, dt, *J* = 8.5, 1.0), 6.89 (1H, ddd, *J* = 7.5, 5.0, 1.0), 7.59 (1H, ddd, *J* = 8.5, 7.5, 2.0), 8.15 (1H, ddd, *J* = 5.0, 2.0, 1.0); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 20.7($\underline{C}H_2$), 25.1 ($\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 26.8 ($\underline{C}H_2$), 32.0 ($\underline{C}H_2$), 36.6 ($\underline{C}H$), 44.5 ($\underline{C}H_2$), 58.8 ($\underline{C}H$), 65.8 ($\underline{C}H_2$), 111.2 ($\underline{C}H$), 117.1 ($\underline{C}H$), 138.8 ($\underline{C}H$), 146.9 ($\underline{C}H$), 163.5 ($\underline{C}$=O), 168.4 ($\underline{C}$=O); HRMS: (ES^+) *m/z* found $[M+Na]^+$ 283.1425, $C_{15}H_{20}N_2O_2Na$ requires 283.1417.



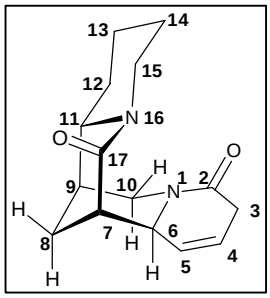
Increasing the polarity of the eluent to 9:1 EtOAc – methanol gave *N*-alkylated adduct **21** (76 mg, 71 %) as a colorless solid; R_f 0.20 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 1651 (s), 1544 (s), 729 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.43 – 1.76 (7H, m), 1.97 – 1.98 (1H, m), 2.27 (1H, ddd, *J* = 17.5, 12.0, 7.0), 2.43 – 2.55 (3H, m), 3.50 (1H, dd, *J* = 10.5, 5.0), 3.61 (1H, dd, *J* = 13.0, 9.5, C1a-$\underline{H_A}H_B$), 4.19 (1H, dd, *J* = 13.0, 5.0, C1a-$H_A\underline{H_B}$), 4.72 (1H, m, C6-$\underline{H}$), 6.20 (1H, m, C5`-$\underline{H}$), 6.59 (1H, d, *J* = 9.0, C3`-$\underline{H}$), 7.24 (1H, dd, *J* = 6.5, 2.0, C6`-$\underline{H}$), 7.36 (1H, ddd, *J* = 9.0, 6.5, 2.0, C4`-$\underline{H}$); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 20.9 ($\underline{C}H_2$), 25.0 ($\underline{C}H_2$), 25.6 ($\underline{C}H_2$), 27.1 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 36.6 ($\underline{C}$-1), 44.7 ($\underline{C}$-6), 51.1 ($\underline{C}$-1a), 59.3 ($\underline{C}$-10), 106.2 ($\underline{C}$-5`), 121.4 ($\underline{C}$-3`), 137.7 ($\underline{C}$-6`), 139.7 ($\underline{C}$-4`), 162.7 ($\underline{C}$-2`), 168.0 ($\underline{C}$-4); *m/z* (EI+) 260 ($[M]^+$, 25 %); HRMS: (EI^+) Found $[M]^+$ 260.1519, $C_{15}H_{20}N_2O_2$ requires 260.1525.



(±)-3, 6-Dihydro-17-oxothermopsine 22

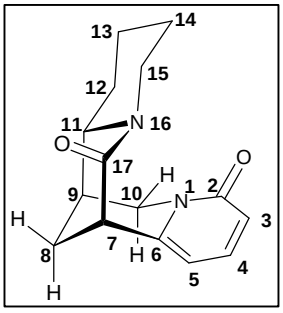
n-BuLi (2.5M solution in THF, 0.36 mL, 0.90 mmol) was added to a cold (0 °C) solution of diisopropylamine (125 µL, 0.89 mmol) in THF (5.6 mL). The solution was stirred at 0 °C for 30 minutes then a solution of **21** (116 mg, 0.45 mmol) in THF (5.6 mL) was added dropwise and the reaction was stirred at room temperature for 2.5 hours. Saturated aqueous NH_4Cl solution was added followed by EtOAc. The phases were separated and the aqueous phase was extracted into EtOAc and

DCM (x2). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (9:1 EtOAc – methanol) gave cyclised adduct **22** (30 mg, 26 %) as a colorless solid; R_f 0.22 (9:1 EtOAc – methanol); IR: ν_{max} (neat) / cm^{-1} 1612 (s), 729 (s); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.24 (1H, td, *J* = 13.0, 4.0, C12-H), 1.63 – 1.71 (3H, m, C12-H, C14-H_2), 1.84 (1H, s, C13-H), 1.87 – 1.92 (1H, m, C13-H), 2.04 (1H, dt, *J* = 12.5, 3.0, C8-Hax), 2.07 – 2.09 (1H, m, C9-H), 2.17 (1H, ddd, *J* = 12.5, 6.0, 2.5, C8-Heq), 2.35 (1H, dt, *J* = 13.0, 3.0, C15-H), 2.67 (1H, dd, *J* = 13.5, 2.5, C10-Hax), 2.73 – 2.75 (1H, m, C7-H), 2.90 – 2.91 (2H, m, C3-H_2), 2.31 (1H, ddd, *J* = 9.0, 5.5, 5.0, C11-H), 4.13 – 4.16 (1H, m, C6-H), 4.69 (1H, dq, *J* = 13.0, 2.0, C15-H), 5.10 (1H, dt, *J* = 13.5, 2.5, C10-Heq), 5.79 – 5.80 (2H, m, C4-H, C5-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 24.6 (C-13), 25.4 (C-14), 29.8 (C-8), 31.0 (C-12), 31.6 (C-3), 32.8 (C-9), 42.2 (C-10), 42.4 (C-15), 44.3 (C-7), 59.8 (C-11), 60.3 (C-6), 121.9, 123.8 (C-4 and C-5), 166.3 (C=O), 167.5 (C=O); *m/z* (CI+) 261 ($[M+H]^+$, 100 %); HRMS: (CI^+) Found $[M+H]^+$ 261.1605, $C_{15}H_{21}N_2O_2$ requires 261.1603.



(±)-17-Oxothermopsine 23

To a solution of **22** (15.2 mg, 0.06 mmol) in DCM (6 mL) was added manganese (IV) oxide (152 mg, 1.75 mmol). The reaction was stirred at room temperature for 72 hours then filtered through celite® and concentrated *in vacuo* to afford **23** (11 mg, 70 %) as a pale yellow solid; R_f 0.46 (90:9:1 DCM – methanol – NH_4OH); ^1H NMR: (400 MHz, $CDCl_3$) δ_H 1.23 – 1.45 (3H, m), 1.68 (1H, d, *J* = 14.0), 1.77 (1H, d, *J* = 13.0), 1.89 (1H, d, *J* = 14.0), 2.12 – 2.21 (2H, m, C8-H_2), 2.47 (1H, td, *J* = 13.0, 3.5, C15-H), 2.65 (1H, s, C9-H), 3.46 (1H, ddd, *J* = 11.5, 5.5, 2.5, C11-H), 3.58 (1H, dd, *J* = 16.0, 5.5, C10-H), 3.68 (1H, d, *J* = 2.0, C7-H), 4.57 (1H, dt, *J* = 13.0, 2.0, C15-H), 4.63 (1H, d, *J* = 16.0, C10-H), 6.30 (1H, d, *J* = 7.0, C3-H), 6.49 (1H, d, *J* = 9.5, C5-H), 7.29 (1H, dd, *J* = 9.5, 7.0, C4-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 23.5 (C-13), 24.3 (C-14), 24.8 (C-8), 30.6 (C-12), 31.9 (C-9), 43.0 (C-7), 43.3, 43.7 (C-10 and C-15), 59.4 (C-11), 106.4 (C-5), 118.1 (C-3), 139.3 (C-4), 143.8 (C-6), 163.5 (C-2), 167.4 (C-17); *m/z* (EI+) 258 ($[M]^+$, 100 %); HRMS: (EI^+) Found $[M]^+$ 258.1367, $C_{15}H_{18}N_2O_2$ requires 258.1368.



A small amount of unreacted **22** (5.3 mg, 18 %) was also reisolated.

(±)-Thermopsine 4

To a cold (0 °C) solution of **23** (11.6 mg, 0.044 mmol) in THF (0.3 mL) was added borane-tetrahydrofuran complex (1M solution in THF, 0.08 mL, 0.88 mmol). The solution was warmed to room temperature and stirred for 2 hours then cooled to 0 °C and further borane-tetrahydrofuran complex (1M solution in THF, 0.08 mL, 0.08 mmol) was added and the reaction mixture was stirred for 1 hour at room temperature. Methanol (1 mL), then water (1 mL) were added and the solution was extracted into EtOAc (x3). The organic extracts were combined, dried ($MgSO_4$), washed with saturated aqueous $NaHCO_3$ solution and concentrated *in vacuo* to afford racemic thermopsine **4** (6.1 mg, 57 %) as a colorless solid; R_f 0.49 (90:9:1 DCM – methanol – NH_4OH); ^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 1.25 (1H, m, C13-H$_A$), 1.41 – 1.43 (1H, m, C12-H$_A$), 1.52 – 1.68 (3H, m, C14-H$_2$, C12-H$_B$), 1.74 (1H, d, *J* = 13.0, C13-H$_B$), 1.86 (1H, dd, *J* = 11.5, 3.0, C15-H$_A$), 1.92 – 1.94 (2H, m, C8-H), 1.99 (1H, d, *J* = 12.0, C11-H), 2.07 (1H, br, s, C9-H), 2.32 (1H, dd, *J* = 11.0, 2.5, C17-H$_A$), 2.58 (1H, d, *J* = 11.5, C15-H$_B$), 2.77 (1H, d, *J* = 11.0, C17-H$_B$), 2.90 (1H, s, C7-H), 3.66 (1H, dd, *J* = 16.0, 6.5 C10-H$_A$), 4.25 (1H, d, *J* = 16.0, C10-H$_B$), 5.95 (1H, dd, *J* = 7.0, 1.0, C5-H), 6.43 (1H, d, *J* = 9.0, 1.0, C3-H), 7.27 (1H, dd, *J* = 9.0, 7.0, C4-H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ_C 24.4 [24.3] (C-13), 25.3 [25.2] (C-14), 27.7 [27.5] (C-8), 29.8 [29.7] (C-12), 33.0 [32.8] (C-9), 35.4 [35.2] (C-7), 45.0 [44.8] (C-10), 56.2 [56.0] (C-15), 63.5 [63.3] (C-17), 66.0 [65.9] (C-11), 104.6 [104.4] (C-5), 116.6 [116.4] (C-3), 138.7 [138.5] (C-4), 163.7 [163.6] (C-2), *A resonance attributable to C-6* [151.6] *was not observed*; *m/z* (EI+) 244 ([M]$^+$, 59 %); HRMS: (EI$^+$) Found [M]$^+$ 244.1575, $C_{15}H_{20}N_2O$ requires 244.1576. Spectroscopic data for synthetic thermopsine were consistent with those reported in the literature,[15a, d] and the ^{13}C NMR literature values[15d] are present in [].