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New Syntheses of (±)-Lamprolobine and (±)-Epilamprolobine

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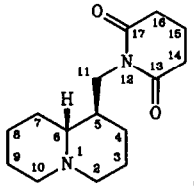
Abstract: (±)-Lamprolobine **1** and (±)-epilamprolobine **4** were prepared by a route featuring sulphide contraction of thiolactam **7** with bromoacetonitrile to give vinylogous cyanamide **8**, reduction and ring closure to the unsaturated quinolizidine **11**, and selective reduction of the latter to set up appropriate stereochemistry for the target alkaloids.

The alkaloid (+)-lamprolobine **1** (numbering shown) is an uncommon member of the populous family of quinolizidine alkaloids found in the Leguminosae (Fabaceae)[1]. Initially reported in 1968 as a metabolite of the Australian tree *Lamprolobium fruticosum*[2], it attracted attention as the first representative of a new variation in the biosynthetic pathway that leads to two major groups of tetracyclic alkaloids exemplified by lupanine **2** and matrine **3**, amongst many others. Lamprolobine was subsequently isolated from *Lupinus holosericeus*[3], *Sophora chrysophylla*[4] and *S. velutina*[5], and detected in seeds of *Thermopsis villosa*[6]. It has also been isolated from the root parasite *Castilleja hispida*[7], the parent genus of which is often hosted by plants that produce quinolizidine alkaloids[8]. Three syntheses of racemic lamprolobine were published in 1970[9-11], shortly after the first announcements of the alkaloid's isolation. One of these syntheses also yielded the epimer (±)-epilamprolobine[11], at that stage unknown as a natural product. (-)-Epilamprolobine **4** was later isolated from *Sophora tomentosa*[12] and *S. chrysophylla*[4], and the unnatural (+)-enantiomer has been prepared from naturally-occurring (-)-lupinine **5**[4]. Both lamprolobine and epilamprolobine have subsequently disappeared from the synthetic scene.



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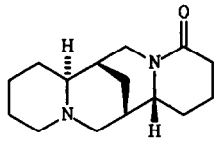

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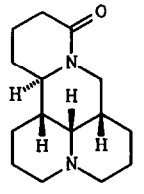

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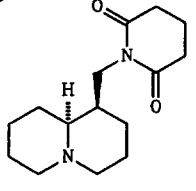

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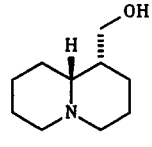
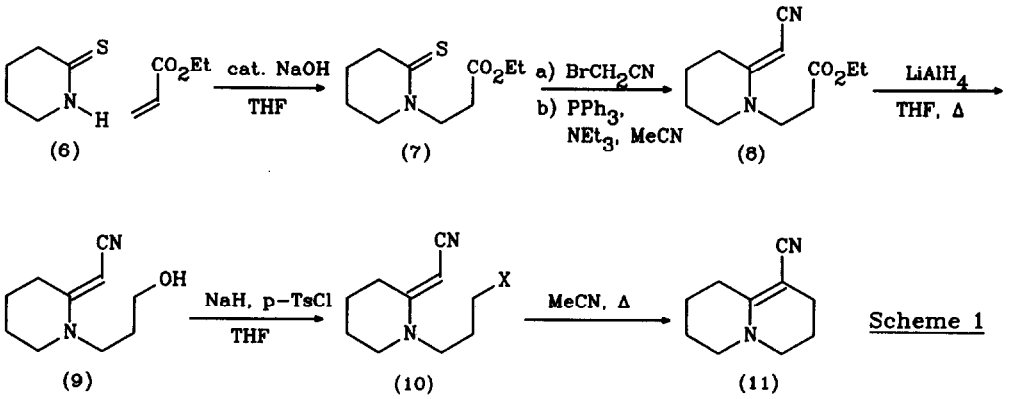


(5)

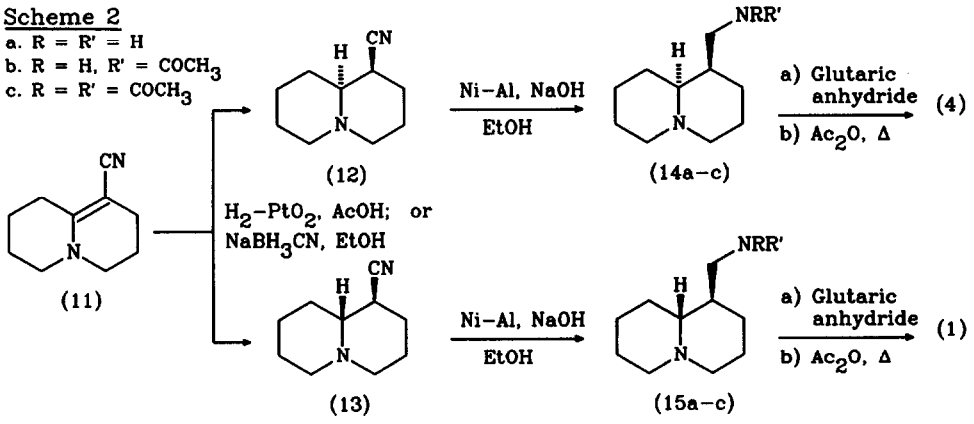
We now describe new syntheses of both alkaloids in racemic form. In line with the generalised approach to alkaloid synthesis that we have been developing[13], a focal feature is the use of the Eschenmoser sulphide contraction[14] (*e.g.* **7** to **8**) followed by controlled manipulation of the pivotal enamine intermediate formed thereby. The early stages in the synthesis are shown in Scheme 1 below. Thiolactam **7** was prepared as described previously[15] by conjugate addition of piperidine-2-thione **6**[16] to ethyl acrylate (99%). The salt formed from **7** and bromoacetonitrile, on exposure to triphenylphosphine and triethylamine in acetonitrile, yielded the vinylogous cyanamide **8** (85%) as a single geometrical isomer (presumably the *E* isomer, although we were not able to confirm the fact unambiguously). Selective reduction of the saturated ester group was achieved with lithium aluminium hydride in boiling tetrahydrofuran; the vinylogous cyanamide was remarkably robust under these conditions, and alcohol **9** was the only product isolated (74%). In order to create the quinolizidine ring system, it was necessary to activate the OH group towards intramolecular nucleophilic displacement. Tosylate **10** (X = OTs) was formed *in situ* under standard conditions (NaH, *p*-TsCℓ, THF); on replacing the solvent by refluxing acetonitrile, the bicyclic vinylogous cyanamide **11** was formed (70% from alcohol **9**) along with varying quantities of the chloride **10** (X = Cℓ, <10%).



Scheme 1

The important intermediate **11** serves as the precursor for both diastereomeric target alkaloids (Scheme 2). Catalytic hydrogenation of **11** over platinum oxide provided the expected *cis*-hydrogenated cyanoquinolizidine **12** (82%) as long as acetic acid was used as the solvent. A small quantity of the other diastereomer **13** (6%) was formed, but the isomers were very easily separated by chromatography on silica gel. By contrast, reduction of **11** with sodium cyanoborohydride in ethanol at pH *ca.* 4 gave a more nearly equal mixture of the isomers (**12**, 43%; **13**, 54%). The proportion of the latter compound could also be increased to 1.9:1 by equilibration of the isomer mixture with sodium hydride in boiling benzene. The preparation of **12** and **13** in fact completes formal syntheses of the target alkaloids[11]. We found, however, that the reported reduction of the nitrile group with lithium aluminium hydride gave variable results. We observed far cleaner reduction with sodium hydroxide and nickel-aluminium alloy[17] in ethanol, and isolated high yields of (±)-lupinamine **14a** (99%) and (±)-epilupinamine **15a** (84%), further characterised as the acetamide derivatives **14b** and **15b** after treatment with acetic anhydride. These derivatives gave NMR spectra that agree with recently reported data[18] (^{1}H and ^{13}C NMR for **14b**, ^{1}H NMR for **15b**; ^{13}C NMR of the latter has not been reported previously). Also isolated during these characterisations were the bis-acetyl imides

14c and **15c**, which are characterised in this study for the first time. On heating with glutaric anhydride followed by refluxing acetic anhydride, (±)-lupinamine **14a** was converted into (±)-epilamprolobine **4** (62%), and (±)-epilupinamine **15a** into (±)-lamprolobine **1** (54%). The acetamides **14b** and **15b** were identified as by-products (7%). Based on **7**, our overall yields of (±)-**1** and (±)-**4** are 1.2% and 21.9% respectively from the pathway proceeding through catalytic hydrogenation of **11**, and 10.7% and 11.5% respectively from the cyanoborohydride pathway.



All the saturated quinolizidines prepared in this study were inferred to have *trans* ring fusion on the basis of prominent Bohlmann bands[19] between 2750 cm^{-1} and 2835 cm^{-1} in their infra-red spectra. Other structural features discernible by infra-red and nuclear magnetic resonance spectroscopy were in line with precedents[20]. A previous observation[5] that certain differences in the ^{13}C NMR spectra of lamprolobine and epilamprolobine reflect the difference in relative stereochemistry between C-5 and C-6 appears to be general: the signals for C-3 and C-5 in compounds of the lamprolobine series (**13**, **15a-c**, **1**) are on average about 2 - 2.5 ppm downfield of those in the epilamprolobine series (**12**, **14a-c**, **4**), while the C-11 signals for compounds other than the nitriles **12** and **13** differ by about 3 ppm. Since assignment of the relative stereochemistry between C-5 and C-6 was nonetheless somewhat subjective, we also relied on generally straightforward comparisons of physical and spectroscopic properties with those reported in the literature[5,11,12,18]. In particular, **12** and (±)-epilamprolobine **4** are solids whose melting points agree with those reported[11], while **13** and (±)-lamprolobine **1** are liquids.

Experimental

Routine measurements were on Kofler micro hot-stage (m.p.), and Pye-Unicam SP3-300 or PU 9512 (IR), VG 7070E (MS), and Bruker AC200 (NMR) spectrometers. DEPT and CH-correlated spectra were routinely used for the complete assignment of NMR signals. Unless otherwise stated, ^{1}H spectra were recorded at 200.13 MHz, and ^{13}C spectra at 50.32 MHz. Thin-layer chromatography was on pre-coated silica gel plates (Merck F254), and column chromatography was on Merck silica gel (particle size 0.063 - 0.200 mm) or Merck silica gel (particle size 0.040 - 0.063 mm) for flash chromatography. Gas chromatograms were obtained on a Varian 3300 instrument with nitrogen as carrier gas and a bonded phase fused silica capillary

column (25 m × 0.22 mm internal diameter, BP10 phase, thickness 0.25 μm) supplied by Scientific Glass Engineering (Australia).

1-(2-Ethoxycarbonylethyl)piperidine-2-thione 7

Ethyl acrylate (23.15 ml, 21.4 g, 0.21 mol) was added dropwise to a solution of piperidine-2-thione **6**[16] (14.92 g, 0.13 mol) in dry THF (625 ml) containing sodium hydride (50% suspension in oil, 358 mg, 7.47 mmol), The resulting reaction mixture was stirred at 50-54°C for 44.5 h. After evaporation of the solvent, the yellow-orange residue was dissolved in dichloromethane (300 ml) and washed with water (3 x 100 ml) and saturated sodium chloride solution (3 x 15 ml). The combined washings were extracted with dichloromethane (50 ml). The organic extracts were dried ($MgSO_4$), then evaporated *in vacuo*. Vacuum distillation of half the material afforded 1-(2-ethoxycarbonylethyl)piperidine-2-thione **7** as a yellow liquid, b.p. 160-192°C/21mm Hg; column chromatography of the remaining material (SiO_2; 4:1 hexane - ethyl acetate as eluent) afforded product of comparable purity (27.74 g in total, 99% overall); R_F (2:1 hexane - acetone) 0.61; ν_{max} ($CHC\ell_3$) 2975 (m), 1730 (s, C=O), 1515 (m), 1350 (m), 1330 (m), 1185 (m), 1160 (m) cm^{-1}; δ_H ($CDC\ell_3$) 4.19 (2H, t, J 7.0 Hz, $NCH_2CH_2CO_2Et$), 4.15 (2H, q, J 7.1 Hz, OCH_2CH_3), 3.54 (2H, t, J 6.1 Hz, 6-H), 2.97 (2H, t, J 6.5 Hz, 3-H), 2.85 (2H, t, J 7.0 Hz, CH_2CO_2Et), 1.98 - 1.81 (2H, m, 5-H), 1.81 - 1.65 (2H, m, 4-H), 1.27 (3H, t, J 7.1 Hz, CH_3); δ_C ($CDC\ell_3$) 199.8 (C=S), 171.6 (C=O), 60.6 (OCH_2CH_3), 51.8 (C-6), 50.7 ($NCH_2CH_2CO_2Et$), 41.6 (C-3), 30.6 (CH_2CO_2Et), 22.8 (C-5), 20.2 (C-4), 14.0 (CH_3); *m/z* 215 (M^+, 57%), 186 (M^+ - Et, 95), 170 (M^+ - OEt, 19), 142 (M^+ - CO_2Et, 57), 128 (M^+ - CH_2CO_2Et, 15), 114 (M^+ - $(CH_2)_2CO_2Et$, 17), 91 (100), 82 (68), 55 (61), 44 (74), 41 (34) (Found: M^+, 215.0980. $C_{10}H_{17}NO_2S$ requires M^+, 215.0980).

1-(2-Ethoxycarbonylethyl)-2-cyanomethylenepiperidine 8

Bromoacetonitrile (0.39 ml, 670 mg, 5.6 mmol) was added dropwise to a chilled sample of 1-(2-ethoxycarbonylethyl)piperidine-2-thione **7** [83] (1.091 g, 5.07 mmol) at 0°C. The mixture was kept at room temperature for 4h, after which a white gum formed. Addition of a solution of triphenylphosphine (1.330 g, 5.07 mmol) in dry dichloromethane (10 ml) was followed by triethylamine (0.85 ml, 620 mg, 6.1 mmol). The resulting reaction mixture was stirred at room temperature for 165 min. Solvent and excess bromoacetonitrile were removed *in vacuo* after which diethyl ether was added to the residue. Triethylammonium bromide was removed by filtration and washed thoroughly with diethyl ether. The filtrate and washings were evaporated *in vacuo* and purified by column chromatography (SiO_2; hexane - ethyl acetate mixtures as eluent) to afford 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine **8** (959 mg, 85%) as a yellow liquid; R_F (1:1 hexane - ethyl acetate) 0.53; ν_{max} ($CHC\ell_3$) 2940 (w), 2860 (w), 2175 (m, CN), 1720 (s, C=O), 1570 (s, C=C), 1170 (m) cm^{-1}; δ_H ($CDC\ell_3$) 4.16 (2H, q, J 7.1 Hz, OCH_2CH_3), 3.76 (1H, s, =CH), 3.42 (2H, t, J 7.1 Hz, NCH_2CHCO_2Et), 3.23 (2H, t, J 6.1 Hz, 6-H), 2.67 (2H, t, J 6.4 Hz, 3-H), 2.57 (2H, t, J 7.1 Hz, CH_2CO_2Et), 1.87 - 1.75 (2H, m, 5-H), 1.75 - 1.59 (2H, m, 4-H), 1.28 (3H, t, J 7.1 Hz, CH_3); δ_C ($CDC\ell_3$) 171.4 (C=O), 161.1 (NC=CH), 122.0 (CN), 60.9 (OCH_2CH_3), 59.9 (=CH), 50.0 (C-6), 47.4 ($NCH_2CH_2CO_2Et$), 30.3 (CH_2CO_2Et), 28.2 (C-3), 23.5 (C-5), 19.6 (C-4), 14.1 (CH_3); *m/z* 222 (M^+, 40%), 177 (M^+ - OEt, 12), 149 (M^+ - CO_2Et, 94), 135 (M^+ - CH_2CO_2Et, 100), 122 (64), 121 (M^+ - $(CH_2)_2CO_2Et$, 20), 97 (84), 82 (37), 55 (78), 41 (36) (Found: M^+, 222.1374. $C_{12}H_{18}N_2O_2$ requires M^+, 222.1368).

On occasion, quantities of the hydrolysis product 1-(2-ethoxycarbonylethyl)-2-piperidinone **7** (O instead of S) were also obtained as a colourless liquid that was purified by distillation at 105-140°C/21mm Hg; R_F (11:9

hexane - acetone) 0.57; ν_{max} ($CHC\ell_3$) 2965 (m), 2935 (m), 1725 (s, ester C=O), 1625 (s, lactam C=O), 1495 (m), 1350 (m), 1170 (m) cm^{-1}; δ_H ($CDC\ell_3$) 4.14 (2H, q, J 7.1 Hz, $OC\underline{H}_2CH_3$), 3.61 (2H, t, J 7.2 Hz, $NC\underline{H}_2CH_2CO_2Et$), 3.35 (2H, br t, J 5.4 Hz, 6-H), 2.60 (2H, t, J 7.0 Hz, $C\underline{H}_2CO_2Et$), 2.36 (2H, br t, J 7.2 Hz, 3-H), 1.88 - 1.70 (4H, m, 4-H and 5-H), 1.26 (3H, t, J 7.1 Hz, $C\underline{H}_3$); δ_C ($CDC\ell_3$) 171.8 (lactam C=O), 169.7 (ester C=O), 60.3 ($O\underline{C}H_2CH_3$), 48.5 (C-6), 43.5 ($N\underline{C}H_2CH_2CO_2Et$), 32.2, 32.1 (C-3, $\underline{C}H_2CO_2Et$), 23.1 (C-5), 21.0 (C-4), 13.9 ($\underline{C}H_3$); *m/z* 199 (M^+, 38%), 154 (M^+ - OEt, 38), 143 (37), 126 (M^+ - CO_2Et, 36), 125 (41), 112 (M^+ - CH_2CO_2Et, 61), 98 (M^+ - $(CH_2)_2CO_2Et$, 37), 84 (100), 56 (47), 55 (61), 42 (60), 41 (25) (Found: M^+, 199.1228. $C_{10}H_{17}NO_3$ requires M^+, 199.1208).

1-(3-Hydroxypropyl)-2-cyanomethylenepiperidine ***9***

A stirred solution of 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine **8** (1.731 g, 7.79 mmol) in dry THF (125 ml) was cooled to 0°C. Lithium aluminum hydride (296 mg, 7.81 mmol) was added slowly. The reaction mixture was stirred at 0°C for 3 h and then at room temperature for a further 62 h. The reaction was quenched by the sequential addition of water (0.30 ml), aqueous sodium hydroxide solution (15% w/w, 0.30 ml) and water (0.89 ml). The THF solvent was removed *in vacuo*. The remaining yellow solid was partitioned between dichloromethane (250 ml) and saturated sodium chloride solution (3 x 50 ml). The organic phase was dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine **9** (1.038 g, 74%) as a light pink solid after column chromatography (SiO_2; hexane - ethyl acetate 2:3 as eluent); m.p. 58 - 60°C (from hexane - ethyl acetate 1:1) (Found: C, 66.42; H, 9.20; N, 15.48. $C_{10}H_{16}N_2O$ requires C, 66.64; H, 8.95; N, 15.54%); R_F (1:1 hexane - ethyl acetate) 0.11; ν_{max} ($CHC\ell_3$) 3610 (w, sharp, OH), 3425 (w, br, OH), 3000 (m), 2950 (m), 2875 (m), 2180 (s, CN), 1570 (s, C=C), 1345 (m), 1330 (m), 1170 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.82 (1H, s, =CH), 3.64 (2H, t, J 5.9 Hz, $C\underline{H}_2OH$), 3.42 -3.30 (1H, br s, OH), 3.30 - 3.16 (4H, m, both $C\underline{H}_2N$ units), 2.65 (2H, t, J 6.4 Hz, 3-H), 1.89 - 1.60 (6H, m, remaining H); δ_C ($CDC\ell_3$) 161.6 ($N\underline{C}$=CH), 123.0 (CN), 59.3 ($\underline{C}H_2OH$), 57.6 (=$\underline{C}$H), 49.4, 48.6 (C-6, $N\underline{C}H_2(CH_2)_2OH$), 28.0 (C-3), 27.8 ($CH_2\underline{C}H_2CH_2OH$), 23.2 (C-5), 19.4 (C-4); *m/z* 180 (M^+, 20%), 149 (M^+ - CH_2OH, 43), 140 (88), 136 (96), 135 (M^+ - $(CH_2)_2OH$, 100), 122 (67), 121 (M^+ - $(CH_2)_3OH$, 26), 94 (48), 82 (39), 55 (42), 54 (43), 41 (57) (Found: M^+, 180.1271. $C_{10}H_{16}N_2O$ requires M^+, 180.1263).

1-Azabicyclo[4.4.0]dec-5-ene-5-carbonitrile ***11***

A solution of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine **9** (1.793 g, 9.94 mmol) in dry THF (150 ml) was treated with sodium hydride (50% suspension in oil, 956 mg, 19.9 mmol). The resulting reaction mixture was stirred at room temperature for 72 min after which it was cooled to 0°C. *p*-Toluenesulphonyl chloride (3.797 g, 19.91 mmol) was added, after which the reaction mixture was alternately heated under reflux and stirred at room temperature for a total of 40 h and 11 d respectively. At this stage, TLC indicated complete consumption of **9**. THF was removed *in vacuo* and replaced by dry acetonitrile (150 ml). The mixture was heated under reflux for 14h and then stirred at room temperature overnight. After the solvent was removed *in vacuo*, the orange-brown residue was dissolved in dichloromethane (70 ml) and washed with water (40 ml). The aqueous layer was extracted with dichloromethane (4 x 40 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile **11** (1.135 g, 70%) as a yellow liquid after column chromatography (SiO_2; hexane - ethyl acetate mixtures as eluent); R_F (1:1 hexane - ethyl acetate) 0.67; ν_{max} ($CHC\ell_3$) 2930 (m), 2845 (m), 2155 (m, CN), 1580 (s, C=C), 1315 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.14 - 3.00 (4H, m, 2-H and 10-H), 2.52 (2H, t, J 6.3 Hz, 7-H), 2.20 (2H, t, J 6.2 Hz, 4-H), 1.89 - 1.71 (4H, m, 3-H and 9-H), 1.71 - 1.55 (2H, m, 8-H); δ_C ($CDC\ell_3$) 153.9 ($N\underline{C}$=C), 122.4

(CN), 69.8 (NC=C), 49.6 and 48.8 (C-2, C-10), 27.3 (C-7), 22.73 (C-3), 22.67 (C-4), 19.80 and 19.76 (C-8, C-9); *m/z* 162 (M^+, 63%), 161 (M^+ - H, 100), 133 (28), 122 (37), 79 (21), 55 (18), 44 (54), 41 (38) (Found: M^+, 162.1044. $C_{10}H_{14}N_2$ requires M^+, 162.1157).

In several repetitions of the above procedure, or on replacing *p*-toluenesulphonyl chloride by methanesulphonyl chloride, 1-(3-chloropropyl)-2-cyanomethylenepiperidine **10** (X = Cℓ) was formed as a by-product; R_F (1:1 hexane - ethyl acetate) 0.58; δ_H ($CDC\ell_3$) 3.79 (1H, s, =CH), 3.57 (2H, t, J 6.0 Hz, $CH_2C\ell$), 3.28 (2H, t, J 7.2 Hz, CH_2N), 3.22 (2H, t, J 6.0 Hz, CH_2N), 2.68 (2H, t, J 6.5 Hz, 3-H), 2.12 - 1.94 (2H, m, $CH_2CH_2C\ell$), 1.89 - 1.55 (4H, m, 4-H and 5-H); δ_C ($CDC\ell_3$) 161.4 (NC=CH), 122.3 (CN), 59.3 (=CH), 50.0, 48.9 (2 x NCH_2), 42.3 ($CH_2C\ell$), 28.1, 27.7 (C-3, $CH_2CH_2C\ell$), 23.4 (C-5), 19.5 (C-4); *m/z* 200 ([^{37}Cℓ]M^+, 3%), 198 (M^+, 11), 163 (M^+ - Cℓ, 100), 162 (48), 161 (72), 149 (M^+ - $CH_2C\ell$, 10), 136 (20), 135 (M^+ - $CH_2CH_2C\ell$, 28), 133 (17), 122 (28), 121 (M^+ - $(CH_2)_3C\ell$, 11), 55 (27), 54 (15), 41 (46) (Found: M^+, 198.0928. $C_{10}H_{15}N_2C\ell$ requires M^+, 198.0924).

Reduction of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile 11

a) A suspension of platinum dioxide (42 mg) in glacial acetic acid (15 ml) was prehydrogenated at 1 atm, after which a solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile **11** (393 mg, 2.42 mmol) in glacial acetic acid (15 ml) was added. The mixture was stirred at room temperature under a hydrogen atmosphere for 92 h. The reaction mixture was filtered with suction through celite, and the solids were washed with $CH_2C\ell_2$. The solvents were removed *in vacuo*. The residue was diluted with water (30 ml), made basic with NaOH solution (3M), and extracted with $CH_2C\ell_2$ (4 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Column chromatography (SiO_2; hexane - acetone 93:7 as eluent) afforded (±)-(5*R**,6*R**)-1-azabicyclo[4.4.0]decane-5-carbonitrile **12** (327 mg, 82%) and (±)-(5*R**,6*S**)-1-azabicyclo-[4.4.0]decane-5-carbonitrile **13** (25 mg, 6%).

(±)-(5*R**,6*R**)-1-Azabicyclo[4.4.0]decane-5-carbonitrile **12**: colourless solid (from hexane - ethyl acetate 1:1), m.p. 61°C (lit.[11], 62 - 63°C) (Found: C, 73.31; H, 10.07; N, 17.14. $C_{10}H_{16}N_2$ requires C, 73.13; H, 9.82; N, 17.06%); R_F (2:1 acetone - hexane) 0.89; ν_{max} ($CHC\ell_3$) 2945 (s), 2860 (m), 2810 and 2760 (Bohlmann bands, m), 2230 (m, CN), 1440 (m), 1345 (m), 1280 (m), 1120 (m), 1110 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.0 - 2.8 (2H, m, equatorial 2-H and 10-H), 2.73 (1H, td, J 4.2 Hz and 2.5 Hz, 5-H), 2.2 - 1.8 (5H, m, axial 2-H and 1-H, 6-H, one each of 3-H and 4-H), 2.2 - 1.5 (8H, m, remaining H); δ_C ($CDC\ell_3$) 120.5 (CN), 62.0 (C-6), 56.3 (C-10), 56.0 (C-2), 34.3 (C-5), 31.4 (C-7), 27.6 (C-4), 25.2 (C-9), 24.0 (C-8), 22.1 (C-3); *m/z* 164 (M^+, 17%), 111 (23), 110 (16), 97 (21), 83 (100), 55 (29), 54 (9), 41 (14) (Found: M^+, 164.1303. $C_{10}H_{16}N_2$ requires M^+, 164.1314).

(±)-(5*R**,6*S**)-1-Azabicyclo[4.4.0]decane-5-carbonitrile **13**: pale yellow liquid, R_F (2:1 acetone - hexane) 0.55; ν_{max} ($CHC\ell_3$) 2930 (s), 2850 (m), 2800 and 2755 (Bohlmann bands, m), 2225 (m, CN), 1430 (m), 1345 (m), 1290 (m), 1120 (m), (m) 1100 cm^{-1}; δ_H ($CDC\ell_3$) 3.0 - 2.8 (2H, m, equatorial 2-H and 10-H), 2.5 - 2.3 (1H, m, 5-H), 2.2 - 2.0 (4H, m, axial 2-H and 1-H, one each of 4-H and 7-H), 1.91 (1H, td, J 10.4 and 2.7 Hz, 6-H), 1.9 - 1.2 (8H, m, remaining H); δ_C ($CDC\ell_3$) 120.8 (CN), 63.4 (C-6), 56.2 (C-10), 55.5 (C-2), 34.9 (C-5), 31.3 (C-7), 28.8 (C-4), 25.4 (C-9), 24.2 (C-8), 24.0 (C-3); *m/z* 164 (M+, 72%), 163 (M^+ - H, 17), 111 (41), 110 (16), 97 (22), 83 (100), 55 (32), 41 (16) (Found: M^+, 164.1311. $C_{10}H_{16}N_2$ requires M^+, 164.1314).

b) 1-Azabicyclo[4.4.0]dec-5-ene-5-carbonitrile **11** (415 mg, 2.56 mmol) was dissolved in absolute ethanol (6.40 ml) to make up a 0.4M solution. Sodium cyanoborohydride (178 mg, 2.83 mmol) was added, followed by bromocresol green (0.5% solution in ethanol, 1 drop). Concentrated hydrochloric acid was dispensed when

necessary during the course of the reaction to ensure a permanent colour change to yellow (pH *ca.* 4). The reaction mixture was stirred at room temperature for 80 min. Water (36 ml) was added, and the solution was made basic with concentrated NH_3 (25%). The aqueous phase was extracted with diethyl ether (6 x 45 ml). The combined ethereal extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. A gc analysis of the mixture showed a ratio of 1.14:1 of **13**:**12**. Column chromatography as above afforded (±)-(5*R**,6*R**)-1-azabicyclo[4.4.0]decane-5-carbonitrile **12** (179 mg, 43%) and (±)-(5*R**,6*S**)-1-azabicyclo[4.4.0]decane-5-carbonitrile **13** (227 mg, 54%).

Conversion of 12 into 13

Partial epimerisation of **12** (86 mg, 0.53 mmol) to **13** was accomplished by heating under reflux with sodium hydride (50% suspension in oil, 17 mg, 0.35 mmol) in benzene (2 ml) for 6 days[11]. A second addition of sodium hydride (50% suspension in oil, 17 mg, 0.35 mmol) was made, after which heating under reflux was continued for a further 6 h. Water (10 ml) was added to the cooled reaction mixture and after separation of the two layers, the aqueous phase was extracted with $CH_2C\ell_2$ (3 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. A gc analysis of the mixture showed a ratio of 1.9:1 of **13**:**12**. Column chromatography afforded **13** (47 mg, 55%) and recovered **12** (25 mg, 29%).

*(±)-Lupinamine **14a***

A solution of (5*R**,6*R**)-1-azabicyclo[4.4.0]decane-5-carbonitrile **12** (327 mg, 1.99 mmol) in ethanol (96%, 8.2 ml) was treated with nickel-aluminum alloy (492 mg) followed by aqueous sodium hydroxide (3M, 8.2 ml). The heterogeneous mixture was stirred at room temperature for 94 h. The reaction mixture was filtered with suction through celite, and the solids were washed with $CH_2C\ell_2$. The solvents were removed *in vacuo*. The residue was diluted with water (20 ml), made basic with concentrated ammonia (25%), and extracted with $CH_2C\ell_2$ (4 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford (±)-lupinamine **14a** (333 mg, 99%) as a chromatographically and spectroscopically pure pale yellow liquid; R_F (9:1 CH_3OH - 25% NH_3 solution) 0.50; ν_{max} ($CHC\ell_3$) 3500 - 3200 (w, br, NH_2), 2930 (s), 2860 (m), 2800 and 2760 (Bohlmann bands, m), 1645 (m), 1455 (m), 1130 (m), 1110 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.0 - 2.7 (4H, m, equatorial 2-H and 10-H, C<u>H</u>$_2$NH$_2$), 2.15 - 1.0 (16H, m, remaining H); δ_C ($CDC\ell_3$) 64.8 (C-6), 57.2 (C-10), 56.4 (C-2), 41.5 (C-5), 39.4 (<u>C</u>H$_2$NH$_2$), 29.0 (C-7), 26.4 (C-4), 25.1 (C-9), 24.8 (C-8), 20.9 (C-3).

*(±)-Epilupinamine **15a***

A solution of (5*R**,6*S**)-1-azabicyclo[4.4.0]decane-5-carbonitrile **13** (228 mg, 1.39 mmol) in ethanol (96%, 5.7 ml) was treated as above with nickel-aluminum alloy (344 mg) followed by aqueous sodium hydroxide solution (3M, 5.7 ml). Work-up as described above yielded (±)-epilupinamine **15a** (196 mg, 84%) as a chromatographically and spectroscopically pure pale yellow liquid; R_F (9:1 CH_3OH - 25% aq. NH_3) 0.66; ν_{max} ($CHC\ell_3$) 3500 - 3200 (w, br, NH_2), 2930 (s), 2860 (m), 2805 and 2760 (Bohlmann bands, m), 1435 (m), 1120 (m), 1110 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.0 - 2.5 (6H, m, equatorial 2-H and 10-H, C<u>H</u>$_2$N<u>H</u>$_2$), 2.2 - 0.75 (14H, m, remaining H); δ_C ($CDC\ell_3$) 64.9 (C-6), 56.6 (C-2), 56.4 (C-10), 43.6 (<u>C</u>H$_2$NH$_2$), 43.4 (C-5), 29.3 (C-7), 28.2 (C-4), 25.2 (C-9), 24.7 (C-8), 24.3 (C-3).

Acetylation of lupinamine

Lupinamine **14a** (203 mg, 1.21 mmol) was heated under reflux in acetic anhydride (10 ml) for 5h. The solvent was removed *in vacuo*; the residue was dissolved in aqueous ammonia solution (1M, 30 ml) and extracted with $CH_2C\ell_2$ (4 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluent: 19:180:1 CH_3OH:$CH_2C\ell_2$:25% aq. NH_3) afforded N-acetyllupinamine **14b** (151 mg, 60%) and N,N-bis(acetyl)lupinamine **14c** (120 mg, 39%).

(±)-N-Acetyllupinamine **14b**: m.p. 122.5 - 125°C (from methanol) (lit.[11], 123 - 124°C); R_F (9:1 CH_3OH - 25% aq. NH_3) 0.57; ν_{max} ($CHC\ell_3$) 3450 (w, sharp), 3225 (w, br), 3000 (m), 2945 (s), 2865 (m), 2810 and 2770 (Bohlmann bands,m), 1660 (s, C=O), 1525 (S) cm^{-1}; δ_H ($CDC\ell_3$) 7.72 (1H, br s, NH), 3.55 - 3.35 (2H, m, $C\underline{H}_2NHAc$), 2.89 (2H, br d, J *ca.* 11.1 Hz, equatorial 2-H and 10-H), 2.3 - 2.0 (2H, m, axial 2-H and 10-H), 1.97 (3H, s, $C\underline{H}_3$), 2.0 - 1.05 (12H, m, remaining H); δ_C ($CDC\ell_3$) 169.8 (C=O), 64.1 (C-6), 56.7 (C-10), 55.8 (C-2), 39.7 ($\underline{C}H_2NHAc$), 36.3 (C-5), 29.3 (C-7), 28.1 (C-4), 24.7 (C-9), 24.3 (C-8), 22.9 ($\underline{C}H_3$), 21.2 (C-3); *m/z* 210 (M^+, 8%), 152 (M^+ - NHCOMe, 35), 138 (M^+ - $CH_2NHCOMe$, 100), 111 (37), 110 (39), 97 (27), 96 (26), 83 (95), 55 (32), 41 (27) (Found: M^+, 210.1733. $C_{12}H_{22}N_2O$ requires M^+, 210.1732).

(±)-N,N-Bis(acetyl)lupinamine **14c**: m.p. 39 - 41°C; R_F (9:1 CH_3OH - 25% aq. NH_3) 0.71; ν_{max} ($CHC\ell_3$) 2970 (m), 2885 (m), 2835 and 2790 (Bohlmann bands, w), 1700 (s, C=O), 1375 (m), 1265 (m) cm^{-1}; δ_H ($CDC\ell_3$) 4.14 (1H, dd, J 14.5 Hz and 10.8 Hz, $C\underline{H}_aH_bNAc_2$), 3.73 (1H, dd, J 14.5 Hz and 3.3 Hz, $CH_a\underline{H}_bNAc_2$), 2.88 (2H, br d, J *ca.* 9.6 Hz, equatorial 2-H and 10-H), 2.41 (6H, s, 2 x $C\underline{H}_3$), 2.2 - 1.7 and 1.7 - 1.2 (6H + 8H, m, remaining H); δ_C ($CDC\ell_3$) 173.5 (2 x C=O), 64.5 (C-6), 57.1 (C-10), 56.3 (C-2), 42.5 ($\underline{C}H_2NAc_2$), 38.2 (C-5), 28.7 (C-7), 26.2 (C-4), 25.8 (C-9), 24.9 (C-9), 24.6 (2 x $\underline{C}H_3$), 20.9 (C-3); *m/z* 252 (M^+, 8%), 209 (M^+ - $COCH_3$, 14), 152 (M^+ - NAc_2, 100), 150 (17), 138 (M^+ - CH_2NAc_2, 44), 111 (21), 110 (19), 83 (46), 55 (23), 43 (38), 41 (29) (Found: M^+, 252.1829. $C_{14}H_{24}N_2O_2$ requires M^+, 252.1838).

Acetylation of epilupinamine

This reaction was performed as described above with epilupinamine **15a** (196 mg, 1.17 mmol) and boiling acetic anhydride (10 ml). Workup and chromatography as described above yielded N-acetylepilupinamine **15b** (184 mg, 75%) and N,N-bis(acetyl)epilupinamine **15c** (74 mg, 25%).

(±)-N-Acetylepilupinamine **15b**: m.p. 128.5 - 131°C (from methanol) (lit.[11], 130 - 132°C); R_F (9:1 CH_3OH - 25% aq. NH_3) 0.66; ν_{max} ($CHC\ell_3$) 3460 (w, sharp), 3400 - 3200 (w, br, NH), 3000 (m), 2945 (s), 2870 (m), 2815 and 2775 (Bohlmann bands, m), 1660 (s, C=O), 1510 (m) cm^{-1}; δ_H ($CDC\ell_3$) 7.24 (1H, t, J 5.6 Hz, NH), 3.34 (1H, dt, J 13.6, 4.7 Hz, $C\underline{H}_aH_bNHAc$), 3.09 (1H, dt, J 13.6, 6.8 Hz, $CH_a\underline{H}_bNHAc$), 2.83 (2H, br t, J *ca.* 10.0 Hz, equatorial 2-H and 10-H), 1.99 (3H, s, CH_3), 2.2 - 1.0 (14H, m, remaining H); δ_C ($CDC\ell_3$) 170.3 (C=O), 64.9 (C-6), 56.1 (C-20), 55.8 (C-10), 40.9 (C-5), 40.7 ($\underline{C}H_2NHAc$), 28.8 (C-7), 28.3 (C-4), 24.6 (C-9), 24.0 (C-8), 23.8 (C-3), 22.4 ($\underline{C}H_3$); *m/z* 210 (M^+, 9%), 209 (M^+ - H, 5), 152 (M^+ - NHAc, 29), 138 (M^+ - CH_2NHAc, 100), 111 (36), 110 (40), 97 (28), 96 (23), 83 (91), 55 (27), 41 (21) (Found: M^+, 210.1728. $C_{12}H_{22}N_2O$ requires M^+, 210.1732).

(±)-N,N-Bis(acetyl)epilupinamine **15c**: yellow liquid, R_F (9:1 CH_3OH:25% NH_3 solution) 0.78; ν_{max} ($CHC\ell_3$) 2945 (m), 2865 (m), 2810 and 2770 (Bohlmann bands, w), 1700 (s, C=O) 1375 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.82 (1H, dd, J 14.3, 10.4 Hz, $C\underline{H}_aH_bNAc_2$), 3.63 (1H, dd, J 14.3, 4.4 Hz, $CH_a\underline{H}_bNAc_2$), 2.85 (2H, t with further fine coupling, J *ca.* 11 Hz, equatorial 2-H and 10-H), 2.41 (6H, s, 2 x CH_3) 2.15 - 1.95 (2H, m, axial 2-H and 10-H), 1.95 - 0.80 (12H, m, remaining H); δ_C ($CDC\ell_3$) 173.4 (2 x C=O), 65.9 (C-6), 56.4 (C-2), 56.1 (C-10), 45.9 ($\underline{C}H_2NAc_2$), 41.0 (C-5), 29.2 (C-7), 27.6 (C-4), 26.2 (2 x $\underline{C}H_3$), 25.0

(C-9), 24.4 (C-8), 24.1 (C-3); *m/z* 252 (M^+, 9%), 209 (M^+ - Ac, 15), 152 (M^+ - NAc_2, 100), 150 (18), 138 (M^+ - CH_2NAc_2, 48), 111 (21), 110 (19), 83 (42), 55 (19), 43 (27), 41 (19) (Found: M^+, 252.1841. $C_{14}H_{24}N_2O_2$ requires M^+, 252.1838).

(±)-Epilamprolobine **4**

A solution of lupinamine **14a** (165 mg, 0.982 mmol) in dry diethyl ether (*ca.* 12 ml) was added dropwise to a stirred solution of glutaric anhydride (117 mg, 1.02 mmol) in dry diethyl ether (*ca.* 15 ml). White crystals of the intermediate amide formed immediately. After 45 min the solvent was removed *in vacuo*; the residue was dissolved in acetic anhydride (4.1 ml, 4.4 g, 43 mmol) containing sodium acetate (410 mg, 5.00 mmol) and the resulting solution was stirred at 80-115°C for 70 min. Water (20 ml) was added to the cooled reaction and excess acetic anhydride was decomposed and neutralised with sodium carbonate solution. Extraction with chloroform (5 x 20 ml) followed. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash chromatography on silica gel (eluent: 40:59:1 CH_3OH:$CH_2C\ell_2$:25% aq. NH_3) afforded N-acetyllupinamine **14b** (14 mg, 7%; characterisation as above), and (±)-epilamprolobine **4** (141 mg, 54%) as a colourless solid, m.p. 66.5 - 67.5°C (lit.[11], 68 - 68.5°C) (from hexane - ethyl acetate 1:1) (Found: C, 68.54; H, 9.41; N, 10.71. $C_{15}H_{24}N_2O_2$ requires C, 68.15; H, 9.15; N, 10.60%); R_F (9:1 CH_3OH - 25% aq. NH_3) 0.82; ν_{max} ($CHC\ell_3$) 2925 (s), 2850 (m), 2800 and 2750 (Bohlmann bands, m), 1710 (m, C=O), 1660 (s, C=O), 1440 (m), 1345 (s), 1280 (m), 1125 (m), 1115 (m) cm^{-1}; δ_H ($CDC\ell_3$) 4.28 (1H, dd, J 13.0 Hz and 10.9 Hz, 11-H_a of AB system), 3.77 (1H, dd, J 13.0 Hz and 3.5 Hz, 11-H_b of AB system), 2.95 - 2.8 (2H, m, equatorial 2-H and 10-H), 2.65 (4H, t, J 6.5 Hz, 14-H, 16-H), 2.1 - 1.7 (8H, m, 5-H, 6-H, 7-H, 14-H, one each of 3-H and 8-H), 1.7 - 1.4 (4H, m, axial 2-H and 10-H, 9-H), 1.4 - 1.1 (4H, m, remaining H); δ_C ($CDC\ell_3$) 172.8 (2 x C=O), 65.2 (C-6), 57.6 (C-10), 57.1 (C-2), 37.7 (C-11), 37.0 (C-5), 33.1 (C-14, C-16), 29.4 (C-7), 26.5 (C-4), 25.5 (C-9), 25.0 (C-8), 21.0 (C-3), 17.2 (C-15).

(±)-Lamprolobine **1**

A solution of epilupinamine **15a** (270 mg, 1.61 mmol) in dry diethyl ether (*ca.* 13 ml) was added dropwise to a stirred solution of glutaric anhydride (194 mg, 1.70 mmol) in dry diethyl ether (*ca.* 20 ml). White crystals of the intermediate amide formed immediately. After a reaction time of 32 min, the solvent was removed *in vacuo*; the residue was dissolved in acetic anhydride (6.70 ml, 7.25 g, 71 mmol) containing sodium acetate (671 mg, 8.18 mmol) and the resulting solution was stirred at 120°C for 40 min. Workup and chromatography as described above afforded N-acetylepilupinamine **15b** (24 mg, 7%; characterisation as above), and (±)-lamprolobine **1** (261 mg, 61%) as a resin-like yellow oil, R_F (9:1 CH_3OH - 25% aq. NH_3) 0.79; ν_{max} ($CHC\ell_3$) 2945 (m), 2865 (m), 2810 and 2770 (Bohlmann bands, w), 1725 (m, C=O), 1675 (s, C=O), 1355 (m), 1170 (m), 1135 (m) cm^{-1}; δ_H ($CDC\ell_3$) 3.9 - 3.6 (2H, m, 11-H), 3.09 (2H, br t, J *ca.* 12.7 Hz, equatorial 2-H and 10-H), 2.70 (4H, t, J 6.5 Hz, 14-H, 16-H), 2.6 - 2.35 (2H, m, axial 2-H and 10-H), 2.35 - 1.0 (14H, m, remaining H); δ_C ($CDC\ell_3$) 172.2 (2 x C=O), 65.7 (C-6), 55.5 (C-2), 54.9 (C-10), 40.0 (C-11), 38.0 (C-5), 32.1 (C-14, C-16), 27.5 (C-7), 26.4 (C-4), 23.3 (C-9), 22.7 (C-8), 22.5 (C-3), 16.4 (C-15); *m/z* 264 (M^+, 21%), 222 (9), 152 (M^+ - $N(CO)_2(CH_3)_3$, 60), 150 (19), 138 (M^+ - $CH_2N(CO)_2(CH_2)_3$, 100), 136 (21), 124 (17), 111 (41), 110 (50), 98 (28), 97 (53), 96 (27), 84 (19), 83 (80), 82 (20), 56 (14), 55 (45), 41 (33) (Found: M^+, 264.1875. $C_{15}H_{24}N_2O_2$ requires M^+, 264.1838).

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