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An Efficient Route to the Pyrrolizidine Ring System *via* an *N*-Acyl Anion Cyclisation Process.

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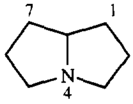
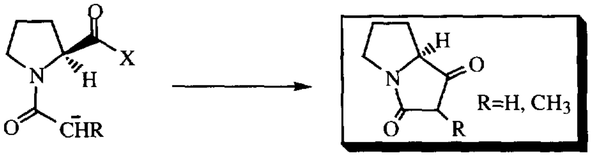
Abstract: An enantioselective route to the pyrrolizidine ring system has been developed which uses an *N*-acyl anion cyclisation reaction as the key step. This methodology has provided the natural pyrrolizidines (-)-(1R, 8S)-1-hydroxy-pyrrolizidine **7**, (-)-pyrrolizidin-1-ene-3-one **9** and (±)-trachelanthamidine **14**. Extension of the process to an N-propionyl substrate provides ready access to a series of 2-methyl pyrrolizidines.

Pyrrolizidine alkaloids, based on the bicyclic ring system **I** constitute a large class of naturally occurring compounds, and are found in a great variety of plant species spread throughout the world. Their diverse and potent biological properties have led to much interest in their pharmacology and preparation, and this ring system has been the target of a number of studies aimed at demonstrating the utility of new synthetic methodology[2].



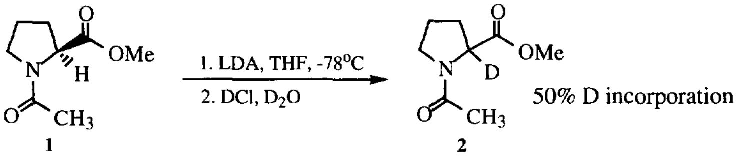
I

We have recently reported on the use of an *N*-acyl anion cyclisation reaction to construct the pyrrolizidine ring system[3], and this paper presents further details of these studies. The methodology relies on the construction of suitably activated proline derivatives (Equation 1), which undergo a base induced *5-exo-trig*[4] ring closure process. To our knowledge this cyclisation methodology has not yet been applied to the synthesis of enantiomerically pure products[5]. The resulting keto amides are versatile intermediates which are suitably functionalised for elaboration into a variety of naturally occurring pyrrolizidines.



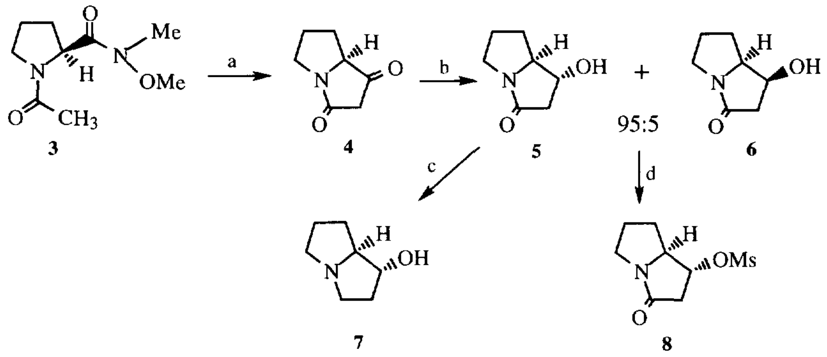
Equation 1

Initially it was considered that methyl *N*-acetyl prolinate **1** would be a suitable substrate for this process. However treatment of **1** with LDA in THF at -78°C caused competitive deprotonation at the stereogenic centre (verified by D_2O quench, 50% D incorporation), and resulted in the recovery of starting material which was essentially racemic (Scheme 1).



Scheme 1

To suppress this undesirable side reaction the corresponding *N*-methoxy-*N*-methyl amide **3**[6] was substituted for the ester, and was successfully cyclised to dione **4** (Scheme 2). The instability of **4** following removal of solvent necessitated its immediate conversion to a more suitable product for determination of enantiomeric purity and subsequently to optimise the reaction conditions. Unfortunately attempts to react **4** with various Grignard and organocerium reagents were unsuccessful, as was reaction with various methylenating reagents even under non basic conditions; presumably due to enolisation. Reduction of the ketone with sodium borohydride however proceeded with high diastereofacial selectivity to give the *exo* and *endo* alcohols **5** and **6** in a 95:5 ratio respectively[7]. The major isomer **5** was converted selectively to the mesylate **8** and utilised to determine the stereochemical outcome of the cyclisation step under different conditions.



Reagents: a. LDA or LHMDS, THF, -78°C; b. $NaBH_4$, EtOH, r.t., 24h (Table 1); c. $LiAlH_4$, THF, reflux, 4h (75 %); d. MsCl, Et_3N, CH_2Cl_2, 0°C 2h, r.t., 3h (85%).

Scheme 2

A number of variables were chosen for study and their effect on the yield and optical purity of **4** is shown below (Table 1). Product of high enantiomeric purity was obtained using 1.1 equivalents of LDA, however the overall yield for the transformation of **3** into **5** and **6** was low. An increase in the equivalents of base used improved the yield but a substantial loss of enantiomeric purity was observed. However, addition of lithium hexamethyldisilazide (2.0 equiv.) to **3** over 30min at -78°C, provided cyclised material in good overall yield (69% over 2 steps) which showed no detectable loss of enantiomeric purity[8] in the products (>99.5%

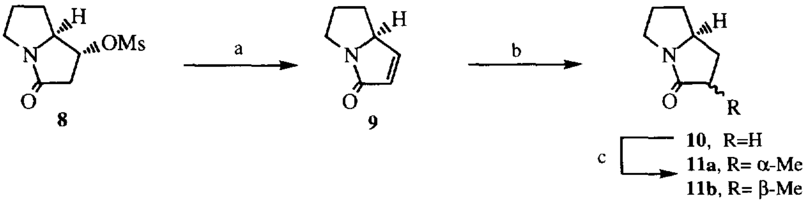
e.e.). Further reduction of **5** with lithium aluminium hydride afforded (1*R*, 8*S*)-1-hydroxy pyrrolizidine **7** (Scheme 2).

Table 1: Reaction Conditions for the Cyclisation of Amide 3.

Base Equivalents (Addition Rate)	Combined % yield (**5** and **6**)	Optical Purity of Mesylate **8** (% e.e.)
1.1[a]	39	93
2.2[a]	51	56
3.0[a]	64	13
2.0 (over 0.5h)[b,d]	67	73
2.0 (over 1.0h)[b,d]	75	75
2.0 (over 0.5h)[c,d]	69	>99.5

a) Substrate **3** added in one portion to solution of LDA, reaction time 2h; b) LDA added to solution of **3**; c) LHMDS added to solution of **3**; d) Reaction time 2h after complete addition of base.

Treatment of **8** with Et_3N in chloroform at reflux afforded (8*S*)-pyrrolizidin-1-en-3-one **9**, recently isolated by Grote *et al.*[9] from a microbial source. A slight loss of enantiomeric purity was observed in the product (93.5% e.e.), presumably due to spontaneous racemisation of **9** as reported previously[9]. Catalytic hydrogenation of **9** gave (8*S*)-pyrrolizidin-3-one **10** (93% yield, 90.7% e.e.), which was alkylated *via* the lactam enolate to provide an inseparable 2:3 mixture of the *exo* and *endo* diastereomers **11a** and **11b** respectively[10] (Scheme 3).

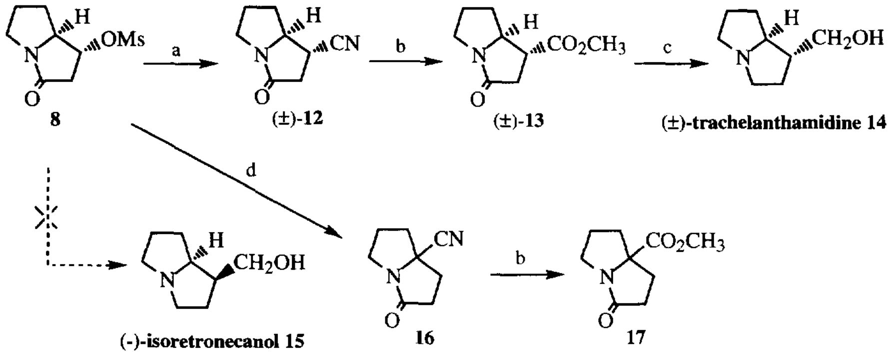


Reagents: a. Et_3N, $CHCl_3$, reflux, 5h (98%); b. H_2, Pd/C, $CHCl_3$, r.t., 24h (93%); c. LHMDS, THF, -78°C, 0.5h; MeI, 2h (43%).

Scheme 3

The possibility of preparing (-)-isoretronecanol **15** from the O-mesylate **8** was also investigated. Reaction of **8** with sodium cyanide in dimethyl sulphoxide at 90°C gave, surprisingly the *exo* nitrile **12**, in which essentially complete loss of enantiomeric purity had occurred. Methanolysis of **12** to the ester **13** followed by reduction with lithium aluminium hydride afforded (±)-trachelanthamidine **14**[14].

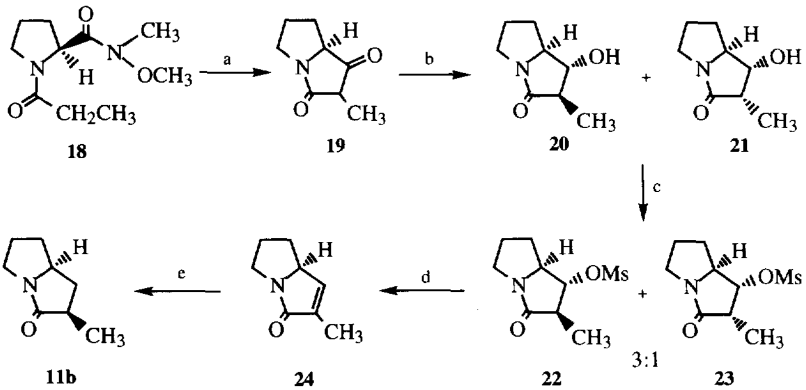
Reaction of mesylate **8** and sodium cyanide at a higher temperature (130°C) produced the regioisomeric nitrile **16** as the major product, as reported by Shono[11] who also proposed enone **9** as an intermediate. Methanolysis of **16** afforded the corresponding ester **17** (Scheme 4).



Reagents: a. NaCN, DMSO, 90°C, 3h (50 %); b. HCl(g), MeOH, 0°C, 24h (55%); c. $LiAlH_4$, THF, reflux, 18h (64%); d. NaCN, DMSO, 120°C, 3h (70 %).

Scheme 4

The cyclisation methodology has also been extended to the *N*-propionyl series. Amide **18** was cyclised under our favoured conditions and then reduced with sodium borohydride to provide a mixture of epimeric 2-methyl-pyrrolizidinones **20** and **21**[12] (Scheme 5). These were converted into the readily separable mesylates **22** and **23** (3:1 ratio, 98.9% e.e.) and treated with DBU to give the 2-methyl substituted enone **24** . Catalytic hydrogenation was highly diastereoselective (>100:1) and afforded (2*R*, 8*S*)-2-methyl-pyrrolizidine-3-one **11b**[10] (92% yield, 91.3% e.e.) which was identical to the major isomer prepared earlier (Scheme 3).



Reagents: a. LHMDS over 0.5h, THF, -78°C, 2.5h; b. $NaBH_4$, EtOH, 24h (51% from **18**); c. MsCl, Et_3N, CH_2Cl_2, 0°C 2h, r.t., 3h (99%); d. DBU, $CHCl_3$, r.t., 2.5h (86%); e. H_2, Pd/C, EtOH, r.t. (92%).

Scheme 5

In summary we have developed an *N*-acyl anionic cyclisation process which provides an efficient route to the pyrrolizidine ring system in high enantiomeric purity. Extension of the reaction to the *N*-propionyl series allows access to 2-methyl substituted pyrrolizidines. Work is currently ongoing to extend this methodology to the construction of other functionalised five and six ring heterocycles from appropriate α-amino acids and this work will be reported in due course.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were measured with a Unicam Mattson 1000. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker WM 250 or Bruker AMX 400 spectrometer using tetramethylsilane as internal standard. Optical rotations were measured with a Perkin Elmer 241 polarimeter. Elemental analysis was carried out on a Carlo Erba CA 1108 Analyser. Silica Gel (230-400 mesh) was used for flash chromatography. Enantiomeric purities were determined by GC against racemic samples as standards on a Kontron System utilising a Lipodex D column with hydrogen carrier gas. All experiments were performed under a nitrogen atmosphere unless stated otherwise.

N-Acetyl proline-*N'*-methoxy-*N'*-methyl amide (3).

To a solution of *N*-acetyl proline (2.98g, 19.0mmol) in CH_2Cl_2 (30ml) at -15°C was added *N*-methyl morpholine (3.84g, 38.0mmol) and then dropwise, *iso*-butylchloroformate (2.60g, 19.0mmol) and the resulting solution was stirred at this temperature for 15min. *N,O*-Dimethylhydroxylamine hydrochloride (2.00g, 21.0mmol) was added in one portion and the mixture stirred for 1h at -15°C, and for 3h at room temperature. Water was added to the reaction mixture, the aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (10 $CHCl_3$: 1 MeOH) to give **3** (3.16g, 83%) as a clear oil. $[\alpha]_D^{20}$ -48.5° (*c* 1, MeOH); IR υ_{max} ($CHCl_3$): 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.80-2.22 (7H, m, $COCH_3$, CH_2CH_2), 3.18 (3H, s, NCH_3), 3.32-3.71 (2H, m, NCH_2), 3.80 (3H, s, $NOCH_3$), 4.65-4.93 (1H, m, NCH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 22.3 ($COCH_3$), 24.8 (CH_2), 31.4 (CH_2), 48.2 (NCH_2), 56.2 (NCH_3), 58.4 (NCH), 61.3 (OCH_3), 169.3 (C=O), 173.0 (C=O). HRMS: Calcd. for $C_9H_{16}N_2O_3$: 200.1161. Found: 200.1161. Anal. Calcd. for $C_9H_{16}N_2O_3$: C, 54.0; H, 8.1; N, 14.0. Found: C, 53.8; H, 8.5; N, 14.1%.

(1*R*, 8*S*)-1-Hydroxy pyrrolizidin-3-one (5).

A solution of lithium hexamethyldisilazide (4.0ml of 1.0M solution in THF, 4.0mmol) in dry THF (20ml) at -78°C was added *via* cannula over 0.5h to a solution of amide **3**, (400mg, 2.0mmol) in THF (25ml) at -78°C. After 2h the reaction was allowed to warm to -30°C and acidified with 2M hydrochloric acid. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$) to provide a solution of crude pyrrolizidine-1,3-dione **4**. [Compound **4**: IR υ_{max} ($CHCl_3$): 1770, 1695cm^{-1}; ^{1}H NMR ($CDCl_3$, 250MHz) δ 1.70 (1H, dq, *J* = 9.2, 2.8 Hz, H-7), 1.93-2.20 (3H, m, 2H-6, H-7), 3.02 (1H, dd, *J* = 21.4, 1.4 Hz, H-2_{exo}), 3.11-3.24 (1H, m, H-5), 3.36 (1H, d, *J* = 19.8 Hz, H-2_{endo}), 3.86-3.99 (1H, m, H-5), 4.12-4.21 (1H, m, H-8)]. The solution was concentrated under reduced pressure to 50ml, diluted with ethanol (80ml) and sodium borohydride (84mg, 2.2mmol) was added. After 15h at room temperature the reaction mixture was quenched with 2M hydrochloric acid. Removal of solvent under reduced pressure and purification by flash chromatography (9 $CHCl_3$: 1 MeOH) afforded a 20:1 mixture (by ^{1}H NMR[7]) of diastereomeric alcohols **5** and **6** (195mg, 69%). Compound **5**: υ_{max} ($CHCl_3$): 1702 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.48 (1H, dq, *J* = 11.9, 9.1 Hz, H-7), 1.95-2.23 (3H, m, $2H_6$, H-7), 2.77 (2H, d, *J* =

8.3 Hz, 2H-2), 3.07 (1H, ddd, J = 12.0, 7.9, 4.2 Hz, H-5), 3.25 (1H, bs, OH, D_2O exch.), 3.57 (1H, dt, J = 11.5, 7.6 Hz, H-5), 3.76 (1H, dt, J = 9.0, 5.9 Hz, H-8), 4.25 (1H, dt, J =8.4, 5.9 Hz, H-1); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 26.7 (C-7), 29.9 (C-6), 41.7 (C-5), 44.6 (C-2), 69.5 (C-8), 73.3 (C-1), 172.9, (C-3). HRMS: Calcd. for $C_7H_{11}NO_2$: 141.0790. Found: 141.0791. Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.6; H, 7.85; N, 9.9. Found: C, 59.3; H, 7.9; N, 9.95%.

(1*R*, 8*S*)-1-Hydroxypyrrolizidine (7).

To a stirred solution of **5**, (200mg, 1.4mmol) in THF (30ml) was added lithium aluminium hydride, (300mg, 5.7mmol) and the reaction heated at reflux for 4h. After cooling to room temperature water (0.4ml) was added and the reaction stirred for 1h. The solid was removed by filtration, washed with $CHCl_3$ and the combined organic layers were evaporated under reduced pressure. The crude oily product was distilled (90°C/10mmHg) to give **7** (135mg, 75%) as a clear oil. $[\alpha]_D^{20}$ -31.6° (*c* 0.5, $CHCl_3$) {Lit.[11] $[\alpha]_D^{20}$ -26.0°, (c=2.3, $CHCl_3$)}; IR υ_{max} ($CHCl_3$): 3352, 3016, 2970, 1235, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.37 (1H, ddt, J = 12.4, 7.5, 7.5 Hz, H-7), 1.55-1.76 (3H, m, 2H-6 and H-7), 1.89-2.06 (2H, m, 2H-2), 2.46 (1H, dt, J = 10.7, 7.0 Hz, H-3 or H-5), 2.52 (1H, dt, J = 11.0, 6.5 Hz, H-3 or H-5), 2.95 (1H, dt, J = 11.0, 6.5 Hz, H-3 or H-5), 3.14 (1H, dt, J = 10.9, 6.7 Hz, H-3 or H-5), 3.21 (1H, dt, J = 7.3, 3.2 Hz, H-8), 3.90 (1H, dt, J = 5.0, 3.4 Hz, H-1), 4.6 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 25.8, 30.6, 34.0 (C-2, C-6 and C-7), 52.7, 55.4 (C-3 and C-5), 72.5, 77.4 (C-1 and C-8). HRMS: Calcd. for $C_7H_{13}NO$: 127.0997. Found: 127.0993.

(1*R*, 8*S*)-1-Mesyloxy-pyrrolizidin-3-one (8).

To a stirred solution of **5** and **6** (20:1 ratio), (2.0g, 14.0mmol) in CH_2Cl_2 (100ml) at 0°C was added methanesulphonyl chloride (2.27g, 19.8mmol) and then triethylamine (1.98g, 19.6mmol). After 2h at 0°C and then 3h at room temperature, removal of solvent under reduced pressure and purification by flash chromatography (12 $CHCl_3$: 1 MeOH) afforded **8** (2.65g, 85%) as a white solid, m.p. 82°C (Lit.[11] m.p. 85°C), >99.5% e.e. by chiral GC analysis. $[\alpha]_D^{20}$ -56.9° (*c* 1, $CHCl_3$); IR υ_{max} ($CHCl_3$): 1685, 1358, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (1H, dq, J = 12.4, 9.3 Hz, H-7), 1.98-2.09 (2H, m, H-6, H-7), 2.18-2.26 (1H, m, H-6), 2.89 (1H, ddt, J = 16.7, 7.5, 0.7 Hz, H-2_{exo}), 2.97 (1H, dd, J = 16.7, 8.4 Hz, H-2_{endo}), 3.05 (3H, s, CH_3), 3.05 (1H, m, H-5), 3.58 (1H, dt, J = 11.6, 7.9 Hz, H-5), 3.98 (1H, dt, J = 9.2, 5.7 Hz, H-8), 4.96 (1H, dt, J = 8.3, 5.2 Hz, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 26.3 (C-7), 29.9 (C-6), 38.6 (CH_3), 41.4, 41.9 (C-2 and C-5), 67.2 (C-8), 77.9 (C-1), 170.4 (C-3). HRMS: Calcd. for $C_8H_{13}NO_4S$: 219.0565. Found: 219.0587. Anal. Calcd. for $C_8H_{13}NO_4S$: C, 43.8; H, 6.0; N, 6.4; S, 19.8. Found: C, 43.85; H, 6.05; N, 6.4; S, 20.15%.

Pyrrolizidin-1-en-3-one (9).

A solution of **8**, (600mg, 2.7mmol) and triethylamine (830mg, 8.2mmol) in CH_2Cl_2 (50ml) was heated at reflux for 5h. Removal of solvent under reduced pressure and purification by flash chromatography (12 $CHCl_3$: 1 MeOH) afforded **9** (331mg, 98%), as a white solid, m.p. 60°C (Lit.[9] m.p. 62°C), 93.5% e.e. by chiral GC analysis. $[\alpha]_D^{20}$ +25.7° (*c* 1, $CHCl_3$) {Lit.[9] $[\alpha]_D^{20}$ +29.3° (*c* 1, $CHCl_3$)}; IR υ_{max} ($CHCl_3$): 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.06-1.22 (1H, dq, J = 11.3, 7.7 Hz, H-7), 2.02-2.17 (1H, m, H-7), 2.18-2.33 (2H, m, 2H-6), 3.28 (1H, ddd, J = 11.2, 8.4, 2.9 Hz, H-5), 3.40-3.53 (1H, m, H-5), 4.23-4.30, 1H, m, H-8), 6.00 (1H, dd, J = 5.7, 1.6 Hz, H-2), 7.15 (1H, dd, J = 5.7, 1.6 Hz, H-1). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 29.1, 30.0 (C-6 and C-7), 41.9 (C-5), 67.9 (C-8), 128.4 (C-2), 149.0 (C-1), 175.6 (C-3). HRMS: Calcd. for C_7H_9NO: 123.0684. Found: 123.0681. Anal. Calcd. for C_7H_9NO: C, 68.25; H, 7.35; N, 11.35. Found: C, 68.1; H, 7.6; N, 11.3%.

Pyrrolizidin-3-one (10).

A mixture of enone **9**, (193mg, 1.57mmol) and 10% palladium on charcoal (110mg) in CH_2Cl_2 (50ml) was hydrogenated at atmospheric pressure for 24h. The mixture was filtered through kieselgur and the filtrate evaporated under reduced pressure. Purification by flash chromatography (12 CH_2Cl_2: 1 MeOH) gave **10** (183mg, 93%) as a clear oil, 90.7% e.e. by chiral GC analysis. $[\alpha]_D^{20}$ -32.5° (*c* 1.1, $CHCl_3$) {Lit.[9] $[\alpha]_D^{20}$ -23.6° (*c* 1, $CHCl_3$)}; IR υ_{max} ($CHCl_3$): 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.20-1.43 (1H, m, H-7), 1.73 (1H, dddd, *J* = 12.6, 11.1, 9.4, 7.8 Hz, H-1), 1.94-2.38 (3H, m, H-7, 2H-6), 2.29 (1H, dddd, *J* = 12.1, 8.9, 6.8, 2.0 Hz, H-1), 2.44 (1H, ddd, *J* =16.6, 9.5, 2.0 Hz, H-2), 2.73 (1H, dddt, *J* = 16.6, 11.3, 9.0, 1.1 Hz, H-2), 3.05 (1H, dddd, *J* = 12.1, 9.2, 3.8, 1.5, H-5), 3.55 (1H, dt, *J* = 11.6, 7.7 Hz, H-5), 3.90 (1H, m, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.1, 27.2 (C-6 and C-7), 32.3, 35.4 (C-1 and C-2), 41.0 (C-5), 62.1 (C-8), 174.8 (C-3). HRMS: Calcd. for $C_7H_{11}NO$: 125.0841. Found: 125.0838.

(2*S*, 8*S*)-2-Methyl pyrrolizidin-3-one (11a) and (2*R*, 8*S*)-2-methyl pyrrolizidin-3-one (11b).

To a solution of **10**, (50mg, 0.4mmol) in THF (25ml) at -78°C was added lithium hexamethyldisilazide, (0.40ml of a 1.0M solution in THF, 0.4mmol). After 45 min. methyl iodide, (57mg, 0.4mmol) was added and the solution stirred for 2h. Addition of 2M hydrochloric acid and evaporation of the organic phase under reduced pressure gave a residue which was purified by flash chromatography (12 $CHCl_3$: 1 MeOH) to give an inseparable diastereomeric mixture[10] of **11a** and **11b** (24mg, 43%) as a clear oil (ratio 2 *exo* : 3 *endo* by NMR). ^1H NMR ($CDCl_3$, 250 MHz) Compound **11a**: δ: 1.22 (3H, d, *J* = 7.4 Hz, CH_3), 1.17-1.31 (2H, m, 2H-7), 1.85-2.11 (2H, m, 2H-6), 2.39-2.49 (2H, m, 2H-1), 2.50-2.62 (1H, dt, *J* = 7.1, 4.5 Hz, H-2), 2.94-3.02 (1H, m, H-5), 3.41-3.54 (1H, m, H-5), 3.79-3.90 (1H, m, H-8); Compound **11b**: δ: 1.07 (3H, dd, *J* = 5.9, 1.1 Hz, CH_3), 1.16-1.28 (2H, m, H-7, H-1), 1.86-2.04 (3H, m, H-7, 2H-6), 2.37-2.48 (1H, m, H-1), 2.69-2.79 (1H, m, H-2), 2.92-3.03 (1H, m, H-5), 3.43 (1H, dt, *J* = 11.6, 7.6 Hz, H-5), 3.63-3.75 (1H, m, H-8); ^{13}C NMR ($CDCl_3$, 62.5 MHz) Compound **11a**: δ: 17.6 (CH_3), 26.9 (C-7), 32.2 (C-6), 34.5 (C-2),41.3, 41.9 (C-1, C-5), 60.3 (C-8), 178.5 (C-3); Compound **11b**: δ: 15.8 (CH_3), 26.8 (C-7), 32.4 (C-6), 37.8 (C-1), 41.1, 41.3 (C-2 and C-5), 59.3 (C-8), 176.4 (C-3).

(±)-1-Cyanopyrrolizidine-3-one (12).

A solution of **8**, (3.0g, 13.7mmol) and sodium cyanide, (99mg, 18.4mmol) in DMSO (80ml) was heated at 90°C for 3h. Saturated ammonium chloride solution was added and the aqueous layer extracted with $CHCl_3$. The combined organic layers were washed with water and concentrated under reduced pressure. Purification of the residue by flash chromatography (12 $CHCl_3$: 1 MeOH) gave an 8:1 mixture of the exocyclic nitrile **12**, (1.0g, 50%) and the elimination product **9**. Compound **12**: IR υ_{max} ($CDCl_3$): 3023, 2254, 1696, 1422 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.51 (1H, dq, *J* = 12.0, 8.9 Hz, H-7), 2.05-2.32 (3H, m, 2H-6, H-7), 2.80-3.15 (4H, m, 2H-5, 2H-2), 3.49-3.60 (1H, m, H-8), 4.08-4.20 (1H, m, H-1).

(±)-8-Carbomethyloxypyrrolizidin-3-one (13).

Through a solution of nitrile **12**, (725mg, 1.84mmol) in methanol (50ml) at 0°C was bubbled hydrogen chloride for 1.5h and the reaction then sealed and left overnight at -20°C. The mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography (11 $CHCl_3$: 1 MeOH) to give **13**[13] (432mg, 55%) as a colourless oil. $[\alpha]_D^{20}$ -6.6° (*c* 0.5, $CHCl_3$); IR υ_{max} ($CHCl_3$): 1738, 1684 cm^{-1} ; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.39-1.54 (1H, m, H-7), 1.96-2.24 (3H, m, 2H-6, H-7), 2.67-2.81 (1H, m, H-2), 2.93-3.16 (3H, m, 2H-5, H-2), 3.56 (1H, dt, *J* = 11.6, 7.9 Hz, H-1), 3.75-3.77 (3H, s, CH_3), 4.01-4.13 (1H, m, H-8); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 26.8, 31.7 (C-6 and C-7), 38.6 (CH_3), 41.4 (C-5), 45.9 (C-

2), 52.5 (C-1), 64.0 (C-8), 172.3 (C=O), 172.6 (C=O). HRMS: Calcd. for $C_8H_{13}NO_3$: 183.0895. Found 183.0901. Anal. Calcd. for $C_8H_{13}NO_3$: C, 59.0; H, 7.15; N, 7.65. Found: C, 59.0; H, 7.1; N, 8.05%.

(±)-Trachelanthamidine (14).

To a suspension of lithium aluminium hydride (70mg of 95% w/w dispersion in mineral oil, 1.8mmol) in dry THF (40ml) was added a solution of the ester **13**, (281mg, 1.53mmol) in THF (5ml) and the reaction heated at reflux for 18h. Ether (5ml) was added followed by water (5ml) and the mixture stirred for a further 5h. The solid was removed by filtration, washed with $CHCl_3$ and the combined filtrates dried over Na_2SO_4. Evaporation under reduced pressure gave an oily residue which was purified by distillation (90°C, 0.1mm Hg) to afford (±)-trachelanthamidine **14** (137mg, 64%) as a clear oil. Picrate m.p. 168°C (Lit.[14] m.p. 165-168°C). $[\alpha]_D^{20}$ -0.9° (*c* 0.77, EtOH) {Lit.[14] $[\alpha]_D^{20}$ -13.8° (*c* 1.28, EtOH)}; IR υ_{max} ($CHCl_3$): 3332, 3204, 2973, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.48-2.06 (7H, m, 2H-2, 2H-6, 2H-7, H-1), 2.90 (1H, bs, OH), 2.52 (1H, dt, *J* =12.9, 9.6 Hz, H-3 or H-5), 2.59 (1H, dt, *J* = 10.5, 6.5 Hz, H-3 or H-5), 2.94 (1H, dt, *J* = 10.5, 6.2 Hz, H-3 or H-5), 3.08-3.22 (2H, m, H-3 or H-5, H-8), 3.61 (2H, d, *J* = 6.3 Hz, CH_2O).

(±)-8-Cyanopyrrolizidin-3-one (16).

A solution of **8**, (3.5g, 16.0mmol) and sodium cyanide, (1.06g, 21.6mmol) in DMSO (70ml) was stirred at 130°C for 3.5h. Work up and purification as for compound **12** afforded **16** (1.69g, 70%) as a colourless oil. IR υ_{max} ($CHCl_3$): 2244, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.76 (1H, ddd, *J* = 12.6, 10.7, 8.0 Hz, H-7), 2.15 (1H, ddd, *J* = 13.2, 11.4, 9.0 Hz, H-1), 2.20-2.26 (1H, m, H-6), 2.29-2.35 (1H, m, H-6), 2.43 (1H, ddd, *J* = 12.3, 7.1, 2.4 Hz, H-7), 2.49 (1H, ddd, *J* = 16.8, 9.1, 1.7 Hz, H-2), 2.66 (1H, ddd, *J* = 13.2, 8.8, 1.7 Hz, H-1), 2.90-2.97 (1H, m, H-2), 3.19-3.25 (1H, m, H-5), 3.61 (1H, dt, *J* = 11.6, 8.0 Hz, H-5); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 26.4 (C-6), 32.8 (C-1), 34.0 (C-2), 38.1 (C-7), 41.6 (C-5), 64.3 (C-8), 120.4 (CN), 173.9 (C-3). HRMS: Calcd. for $C_8H_{10}N_2O$: 150.0793. Found: 150.0784.

(±)-8-Carbomethyloxypyrrolizidine (17).

The nitrile **16** (209mg, 1.39mmol) was hydrolysed as for compound **12** to provide the ester **17** (143mg, 55%) as a white solid, m.p. 51-52°C (Lit.[11] m.p. 53-54°C). $[\alpha]_D^{20}$ -1.0° (*c* 4, $CHCl_3$); IR υ_{max} ($CHCl_3$): 3423, 3025, 1740, 1690, 1417, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.65 (1H, dt, *J* = 12.7, 9.4 Hz, H-7), 1.96-2.12 (3H, m, 2H-6, H-1), 2.36-2.44 (2H, m, H-7, H-2), 2.53 (1H, ddd, *J* = 13.1, 8.9, 1.6 Hz, H-1), 2.73-2.96 (1H, m, H-2), 3.12 (1H, dddd, *J* = 11.4, 8.5, 4.7, 1.2 Hz, H-5), 3.64 (1H, dt, *J* = 11.5, 7.5 Hz, H-5), 3.73 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 26.1 (C-6), 31.8 (C-1), 34.4 (C-2), 36.1 (C-7), 41.8 (C-5), 52.8 (CH_3), 73.6 (C-8), 174.4 (C=O ester), 173.9 (C-3). HRMS: Calcd. for $C_8H_{13}NO_3$:183.0895. Found: 183.0900. Anal. Calcd. for $C_8H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.2; H, 6.95; N, 7.7%.

(1*R*, 8*S*)-1-Hydroxy-(2*R*)-methyl pyrrolizidin-3-one (20) and (1*R*, 8*S*)-1-hydroxy-(2*S*)-methyl pyrrolizidin-3-one (21).

A solution of lithium hexamethyldisilazide (9.34ml of a 1.0M solution in THF, 9.34mmol) in THF (20ml) at -78°C was added *via* cannula over 0.5h to a solution of the amide **18** (1.0g, 4.67mmol) in THF (30ml) at -78°C. The reaction was stirred at this temperature for a further 2.5h, allowed to warm to -30°C and then acidified with 2M hydrochloric acid. The aqueous layer was extracted with $CHCl_3$, the combined organic layers dried (Na_2SO_4) and the solution was concentrated under reduced pressure to a volume of ca. 60ml. This was taken up into ethanol (120 ml) and sodium borohydride (190mg, 5mmol) was added in portions over 15 min. After 18h at room temperature the reaction mixture was worked up and the crude product purified as for compound **5** to afford an inseparable 3:1 mixture of diastereomeric alcohols **20** and **21**[12] (371mg, 51%). IR υ_{max} ($CHCl_3$): 3358, 3011, 1683 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) Compound **20**: δ: 1.18 (3H, d, *J* = 7.1 Hz, CH_3), 1.46 (1H, ddd, *J* = 12.4, 8.4, 8.4 Hz, H-7), 1.92-2.22 (3H, m, 2H-6 and H-7), 2.60-2.77 (1H, m, H-2), 2.96-3.10 (1H, m, H-5), 3.49 (1H, ddd, *J* = 11.5, 7.7, 7.7 Hz, H-5), 3.60-3.70 (2H, m, H-1, H-8), 4.34 (1H, d, *J* = 4.5 Hz, OH); Compound **21**: δ: 1.22 (3H, d, *J* = 7.5 Hz), 1.38-1.53 (1H, m, H-7), 1.92-2.22 (3H, m, 2H-6 and H-7), 2.60-2.77 (1H, m, H-2), 2.96-3.10 (1H, m, H-5), 3.40-3.60 (1H, m, H-5), 3.76 (1H, ddd, *J* = 8.5, 6.3, 6.3 Hz, H-8), 3.88 (1H, d, *J* = 4.9 Hz, OH), 4.11-4.19 (1H, m, H-1); ^{13}C NMR ($CDCl_3$, 62.5 MHz) Compound **20**: δ: 12.8 (CH_3), 26.8 (C-7), 30.0 (C-6), 41.8 (C-5), 49.1 (C-2), 66.7 (C-8), 82.0 (C-1), 174.4 (C-3); Compound **21**: δ: 10.5 (CH_3), 26.9 (C-7), 29.9 (C-6), 41.6 (C-5), 47.3 (C-2), 66.9 (C-8), 74.9 (C-1), 177.0 (C-3). Mixture of **20** and **21**. HRMS: Calcd. for $C_8H_{13}NO_2$: 155.0946. Found: 155.0948. Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.9; H, 8.45; N, 9.0. Found: C, 61.95; H, 8.5; N, 8.9%.

(1*R*, 8*S*)-1-Mesyloxy-(2*R*)-methyl pyrrolizidin-3-one (22) and (1*R*, 8*S*)-1-mesyloxy-(2*S*)-methyl pyrrolizidin-3-one (23).

To a stirred solution of **20** and **21** (3:1 ratio), (200mg, 1.29mmol) in CH_2Cl_2 (50ml) at 0°C was added methanesulphonyl chloride (206mg, 1.8mmol) and triethylamine (182mg, 1.8mmol). After 2h at 0°C and 3h at 20°C the solvent was removed under reduced pressure and the residue purified by flash chromatography (10 $CHCl_3$: 1MeOH) to give **22** (222mg, 73%) as a white solid, m.p. 98°C, together with **23** (77mg, 26%) as a white solid, m.p. 68°C, 98.9% e.e. by chiral GC. Compound **22**: $[\alpha]_D^{20}$ +30.4° (*c* 0.25, $CHCl_3$); IR υ_{max} ($CHCl_3$): 1702, 1348 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.23 (3H, d, *J* =7.1 Hz, CH_3), 1.55 (1H, dq, *J* = 8.9, 3.6 Hz, H-7), 1.89-2.09 (2H, m, H-7 and H-6), 2.24 (1H, dddd, *J* = 12.8, 6.6, 6.6, 3.6 Hz, H-6), 2.91-3.14 (2H, m, H-2, H-5), 3.05 (3H, s, SO_2CH_3), 3.53 (1H, dt, *J* = 11.4, 7.8 Hz, H-5), 3.92 (1H, ddd, *J* = 8.8, 6.2, 6.2 Hz, H-8), 4.44 (1H, dd, *J* = 8.3, 6.3 Hz, H-1); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 12.9 (CH_3), 26.3 (C-7), 30.3 (C-6), 38.5 (SO_2CH_3), 41.9, 46.6 (C-2 and C-5), 64.6 (C-8), 86.0 (C-1), 171.6 (C-3). HRMS: Calcd. for $C_9H_{15}NO_4S$: 233.0722. Found: 233.0711: Anal. Calcd. for $C_9H_{15}NO_4S$: C, 46.35; H, 6.5; N, 6.0; S, 13.75. Found: C, 46.55; H, 6.25; N, 5.8; S, 13.55%. Compound **23**: $[\alpha]_D^{20}$ -69.8° (*c* 0.92, $CHCl_3$); IR υ_{max} ($CHCl_3$): 1701, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.25 (3H, d, *J* = 7.5 Hz, CH_3), 1.49 (1H, dq, *J* = 9.0, 3.2 Hz, H-7), 1.84-2.08 (2H, m, H-7, H-6), 2.17 (1H, dddd, *J* = 12.4, 6.3, 6.3, 3.4 Hz, H-6), 2.86 (1H, dq, *J* = 7.6, 7.6 Hz, H-2), 2.94-3.10 (1H, m, H-5), 3.02 (3H, s, SO_2CH_3), 3.52 (1H, dt, *J* = 11.5, 7.8 Hz, H-5), 3.94 (1H, dt, *J* = 9.0, 6.1 Hz, H-8), 4.44 (1H, dd, *J* = 8.0, 6.1 Hz, H-1); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 11.3 (CH_3), 26.5 (C-7), 29.5 (C-6), 38.4 (SO_2CH_3), 41.9 , 45.5 (C-2 and C-5), 65.0 (C-8), 81.6 (C-1), 174.3 (C-3). HRMS: Calcd. for $C_9H_{15}NO_4S$: 233.0722. Found 233.0716: Anal. Calcd. for $C_9H_{15}NO_4S$: C, 46.35; H, 6.5; N, 6.0; S, 13.75. Found C, 46.35; H, 6.65; N, 6.0; S, 13.6%.

(2*R*, 8*S*)-2-Methyl-pyrrolizidin-1-ene-3-one (24).

A solution of **22**, (300mg, 1.3mmol) and DBU, (196mg, 1.3mmol) in CH_2Cl_2 (50ml) were stirred at 20°C for 2.5h. Removal of solvent under reduced pressure and purification of the residue by flash chromatography (12 $CHCl_3$: 1 MeOH) gave the enone **24**[10] (151mg, 86%) as a clear oil. $[\alpha]_D^{20}$ +12.2° (*c* 0.51, $CHCl_3$); IR υ_{max} ($CHCl_3$): 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.05 (1H, dq, *J* = 11.6, 7.7 Hz, H-7), 1.81 (3H, s, CH_3), 1.96-2.06 (1H, m, H-7), 2.16-2.34 (2H, m, H-6), 3.15-3.27 (1H, m, H-5), 3.33-3.55 (1H, m, H-5), 4.02-4.08 (1H, m, H-8), 6.76-6.78 (1H, m, H-1); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 11.4 (CH_3), 29.4, 29.8 (C-6 and C-7), 42.1 (C-5), 65.4 (C-8), 136.5 (C-2), 141.7 (C-1), 176.2 (C-3). HRMS: Calcd. for $C_8H_{11}NO$: 137.0841. Found: 137.0834.

(2*R*, 8*S*)-2-Methyl-pyrrolizidine-3-one (11b).

A mixture of the enone **24**, (60mg, 0.44mmol) and 10% palladium on charcoal (20mg) in $CHCl_3$ (15ml) was hydrogenated at atmospheric pressure for 18h. After filtration through kieselgur, the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (10 $CHCl_3$: 1 MeOH) to give **11b**[10] (56mg, 92%) as a clear oil, 91.3% e.e. by chiral GC. $[\alpha]_D^{20}$ +26.7° (*c* 0.27, $CHCl_3$); IR υ_{max} ($CHCl_3$): 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.07 (3H, dd, *J* = 5.9, 1.1 Hz, CH_3), 1.16-1.28 (2H, m, H-7, H-1), 1.86-2.04 (3H, m, H-7, 2H-6), 2.37-2.48 (1H, m, H-1), 2.69-2.79 (1H, m, H-2), 2.92-3.03 (1H, m, H-5), 3.43 (1H, dt, *J* = 11.6, 7.6 Hz, H-5), 3.63-3.75 (1H, m, H-8); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 15.8 (CH_3), 26.8 (C-7), 32.4 (C-6), 37.8 (C-1), 41.1, 41.3 (C-5 and C-2), 59.3 (C-8), 176.4 (C-3). HRMS: Calcd. for $C_8H_{13}NO$: 139.0997. Found: 139.0995.

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