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An Asymmetric Approach to the Pyrrolizidine Ring System *via N*-acetyl and *N*-propionyl Anion Cyclisation Processes.

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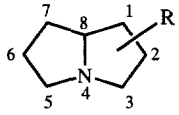
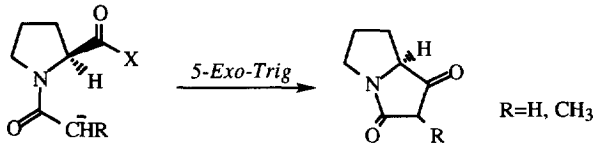
***Abstract**: An efficient route to the pyrrolizidine ring system has been developed. The method, which uses N-acetyl and N-propionyl anion cyclisation reactions as the key steps has provided the natural pyrrolizidines (-)-(1R, 8S)-1-hydroxy-pyrrolizidine (10), (-)-pyrrolizidin-1-ene-3-one (13), (±)-trachelanthamidine (18) together with a range of 2-methyl substituted pyrrolizidine-3-ones.*

Pyrrolizidine alkaloids, based on the bicyclic ring system below are found in a great variety of plant species spread throughout the world. Their diverse and potent biological properties has 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[1].

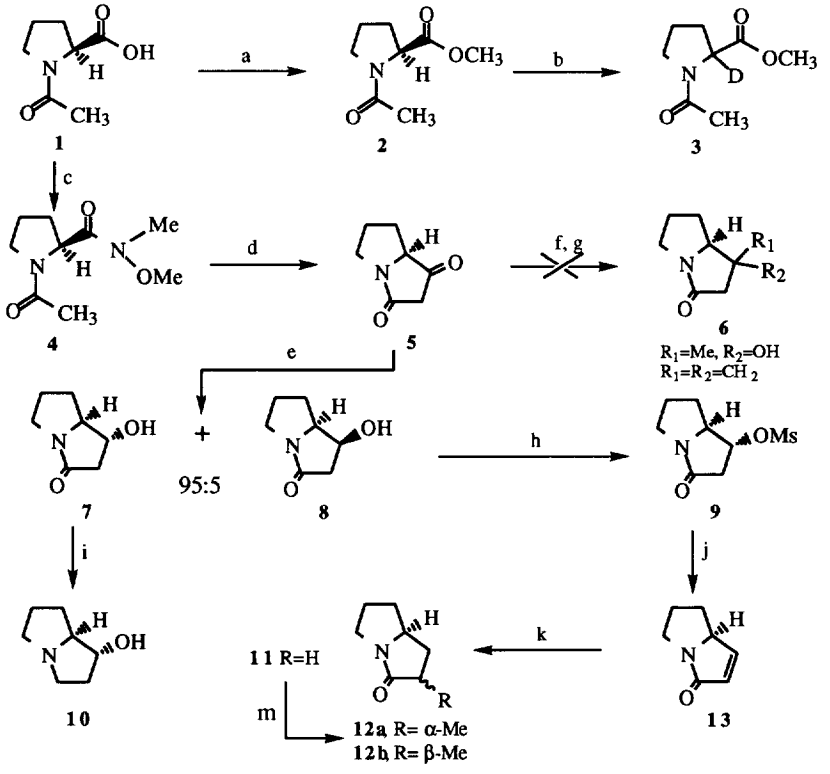


In this paper we report the use of an *N*-acyl anion-cyclisation reaction to construct the pyrrolizidine ring system *via* a suitably activated proline derivative (Equation 1). To our knowledge this cyclisation methodology has not yet been applied to the synthesis of enantiomerically pure products[2] although some stereochemical retention has recently been obtained by cyclising *N*-acyl oxazolidines[3]. The intermediate keto amide is suitably functionalised for elaboration into a variety of pyrrolizidines.



Equation 1

Initially it was considered that methyl-*N*-acetyl prolinate (2) would be a suitable precursor to the pyrrolizidine ring system. However it was found that upon treatment with lithium diisopropylamide at -78°C competitive deprotonation at the chiral centre was dominant (verified by D_2O quench, 50% D incorporation), resulting in 90% racemisation in the recovered starting material.



a. SO_2Cl_2, MeOH, r.t., 24h (96%); b. LDA , THF, -78C, 2h, DCl / D_2O; c. $(CH_2)_5NMe$, $ClCO_2{}^iBu$, CH_2Cl_2, -15°C, 0.5h; HCl.HNMe(OMe), 4h (83%); d. LHMDS (2eq over 0.5h), THF, -78 °C, 2h; e. $NaBH_4$, EtOH, 24h [69% from (4)]; f. MeMgBr, $CeCl_3$, THF, 0°C, 1.3h ; g. CH_2I_2, Zn, $TiCl_4$, CH_2Cl_2, r.t, 0.5h; h. MsCl, Et_3N, CH_2Cl_2, 0°C, 5h(85%) ; i. $LiAlH_4$, THF, reflux, 4h (75%); j. Et_3N, $CHCl_3$, reflux, 5h (98%); k. H_2, Pd/C, CH_2Cl_2, 24h (93%); m. LHMDS, -78°C, 0.5h; MeI , 2h (43%).

Scheme 1

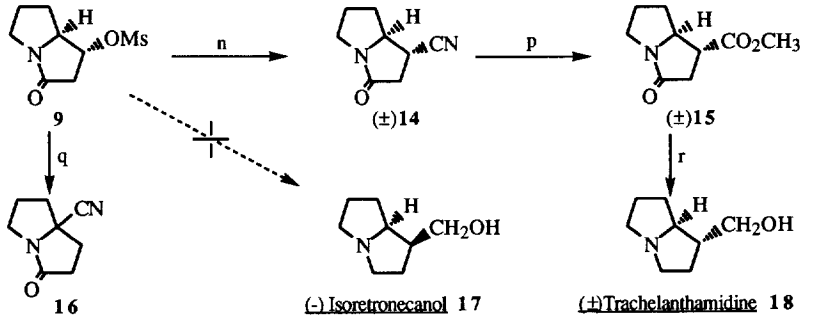
To suppress this unwanted side reaction the procedure was repeated on the corresponding *N*-methyl, *N*-methoxy amide (4)[4], prepared in 83% yield from *N*-acetyl proline (1) *via* a mixed anhydride. The use of lithium bis (trimethylsilyl) amide as the base led to the successful cyclisation of (4) and gave enantiomerically pure (8S) pyrrolizidin-1, 3-dione (5)[5], which was stable in solution but decomposed on removal of solvent (t.l.c and ^1H n.m.r.)

Unfortunately attempts to react (5) with various methylenating and Grignard reagents were unsuccessful even under non basic conditions, presumably due to enolisation. Reduction with sodium borohydride however, resulted in a 95:5 ratio of *exo* and *endo* alcohols (7) and (8)[6] respectively in 69% yield from amide (4). The

minor *endo* alcohol (8) could be removed by crystallisation and the major, *exo* isomer (7) reduced with lithium aluminium hydride to give (8S, 1R)-1-hydroxypyrrolizidine (10) in 75% yield. Alternatively, from the mixture (7) and (8) the *exo* alcohol could be converted selectively in 85% yield to give the (8S, 1R) mesylate (9) as the sole diastereomeric product (>99.9% e.e)[7]. Treatment with triethylamine in chloroform at reflux afforded (8S) pyrrolizidin-1-en-3-one (13), recently isolated by Grote *et al.*[8] We observed a slight loss of enantiomeric purity in the product (93.5% e.e.), presumably due to the spontaneous racemisation of (13) which has been reported previously[8]. Hydrogenation afforded (8S) pyrrolizidin-3-one (11) in 93% yield and 90.7% e.e., which was alkylated via the lactam enolate to provide the 2-methyl derivatives as an inseparable 2:3 mixture of *exo* and *endo* diastereomers (12a) and (12b) respectively[9] (Scheme 1).

An approach to (-)isoretronecanol (17) from (9) was also investigated. However reaction of (9) with sodium cyanide in dimethyl sulphoxide at 90°C gave, rather surprisingly the *exo* nitrile (14), in which loss of stereochemical integrity had occurred. Methanolysis of (14) to the ester (15) followed by reduction with lithium aluminium hydride afforded (±)trachelanthamidine (18).

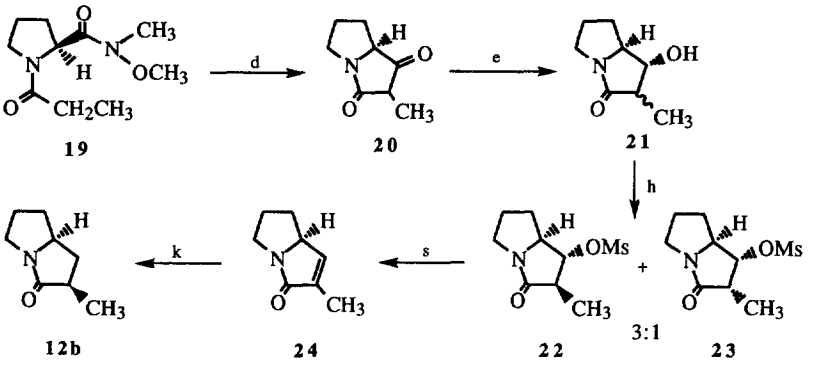
Reaction of mesylate (9) and sodium cyanide at a higher temperature (130°C) produced the regioisomeric nitrile (16) as the major product in good yield, together with a trace of the racemic nitrile (14) (Scheme 2). The formation of (16) has been reported by Shono *et al.*[10] who have proposed enone (13) as an intermediate.



n. NaCN, DMSO, 90° C, 3h (50%); p. $HCl_{(g)}$, MeOH, 0°C, 24h (55%); q. NaCN, DMSO,130 °C, 3h (70%)
r. $LiAlH_4$, THF, reflux, 18h (64%).

Scheme 2

The cyclisation methodology has also been extended to the *N*-propionyl series. Amide (19) was cyclised and reduced with sodium borohydride in an identical manner to give a mixture of diastereomeric 1-hydroxy-2-methyl-pyrrolizidine-3-ones (21)[11] in 51% yield (Scheme 3). Mesylation afforded the readily separable mesylates (22) and (23) in a 3:1 ratio and 98.9% e.e. Elimination using DBU provided the 2-methyl substituted enone (24)[9] in 86% yield. Diastereoselective hydrogenation afforded (8S, 2R)-2-methyl-pyrrolizidine-3-one (12b)[9] in 92% yield (91.3% e.e.) which was identical to the major isomer prepared earlier (Scheme 1).



d, e. [51% from (19)]; h(99%); s. DBU, $CHCl_3$, r.t., 2.5h (86%); k. (92%).

Scheme 3

In summary we have developed methodology for the synthesis of pyrrolizidines *via* a facile cyclisation process which should provide a versatile route to the construction of five and six membered ring heterocycles from appropriate α-amino acids. Further work in this area will be reported at a later date.

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References and Notes

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5. υmax ($CHCl_3$) 3025, 1770 (C=O ketone), 1695 (C=O amide), 1411 cm^{-1}; δH (250MHz): 1.70 (1H, dq, *J*=9.2, 2.8Hz, 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), 3.86 (1H, dd, *J*=19.8 Hz, H-2_{endo}), 3.86-3.99 (1H, m, H-5), 4.12-4.21 (1H, m, H-8).
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7. All enantiomeric purities quoted were determined by chiral gas chromatography, Lipodex D column. Relevant $[\alpha]_D^{20}$ values ($CHCl_3$): **9**, -56.9° (c=1); **10**, -31.6° (c=0.5); **11**, -32.5° (c=1.1); **13**, +25.7° (c=1); **22**, +30.4° (c=0.25); **23**, -69.8° (c=0.92); **24**, +12.2 (c=0.51); **12b**, +26.7° (c=0.27).
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