Homoproline homologation by enolate Claisen rearrangement or direct allylation: syntheses of (−)-trachelanthamidine, (−)-isoretronecanol and (±)-turneforcidine

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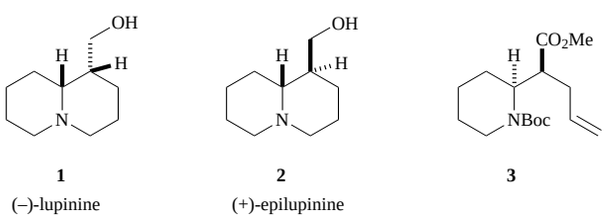
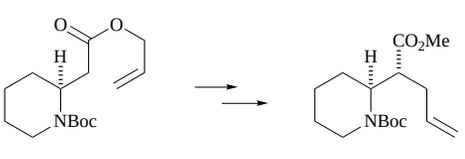
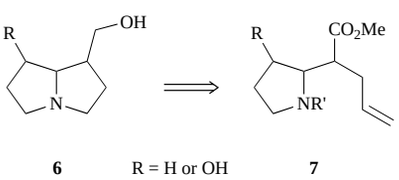
The pyrrolizidine precursors 13 and 14 are obtained both by enolate Claisen rearrangement of the homoproline allyl ester 12 and by direct allylation of *N*-protected homoproline ethyl ester 15. In both cases, the reactions show poor levels of stereoselectivity. Reduction gives the corresponding alcohols 20a and 21a which are separated and subsequently elaborated to (−)-trachelanthamidine 24 and (−)-isoretronecanol 25 respectively *via* reductive alkene cleavage, mesylation and spontaneous cyclisation following *N*-deprotection. The chiral integrity of the original proline-derived asymmetric centre is preserved throughout. A similar enolate allylation gives, with high stereoselectivity, the homologue 34 of the Geissman–Waiss lactone 32, which is similarly transformed into (±)-turneforcidine 31.

We have recently reported stereochemically complementary approaches to the lupinine quinolizidine alkaloids, exemplified by (−)-lupinine **1** and (+)-epilupinine **2**, from piperidine-2-acetic acid ester.[1] Whereas direct allylation of the lithium enolate of methyl (*S*)-*N*-Boc-piperidineacetate led largely to the α-allyl ester **3**, a precursor of the less thermodynamically stable lupinine stereochemistry **1**, Ireland enolate Claisen rearrangement of the related allyl ester **4** led, with an excellent level of stereocontrol, to the (−)-epilupinine precursor **5**. Completion of the sequence was achieved by hydroboration, methane sulfonate formation and deprotection followed by a facile cyclisation and ester reduction. Possible explanations, based on the likely transition state conformations, for the stereochemical paths followed by these two processes[1] led us to consider using similar tactics to prepare members of the more numerous pyrrolizidine-1-methanols **6**. This family of naturally occurring

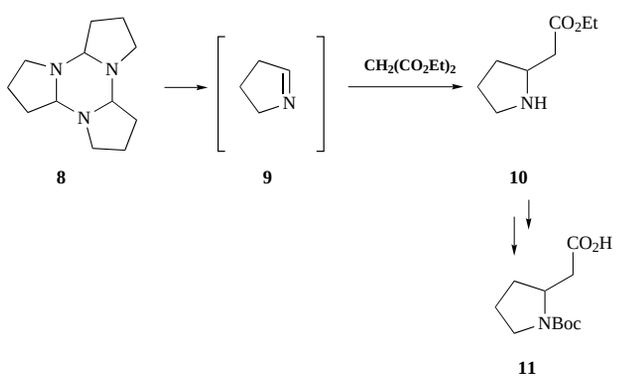






alkaloids[2] contains most of the possible enantiomers of structures **6** and their syntheses have provided a challenge for a plethora of diverse methodology. In view of the foregoing results, it appeared that these compounds could be readily accessible from the esters **7**, hopefully in a similarly stereochemically complementary fashion either by direct allylation or the Claisen pathway, from homoproline esters, following reductive cleavage of the alkene function and cyclisation.

Initially, we prepared the required homoproline **10** in racemic form using the method of Fukawa *et al.*[3] by silver-catalysed oxidation of pyrrolidine with sodium persulfate[4] to give the trimer **8** of 1-pyrroline **9**, and reaction with diethyl malonate (Scheme 1). We had hoped to obtain relatively large quantities



Scheme 1

of the corresponding acid by this method directly, as originally described,[3] but found it easier to first isolate the ester **10**; even so, we were unable to reproduce the yields originally reported but did secure sufficient material to proceed. This was first converted into the *N*-Boc derivative **15** required for the direct allylation studies. A sample was also saponified to give the acid **11** and thence coupled[5] with allyl alcohol to give the allyl ester **12** required for the enolate Claisen rearrangement (Scheme 2). Our previous work on enolate Claisen rearrangements of β-amino acid esters[6] had suggested that, in common with the corresponding rearrangements of α-amino acid allyl esters,[7] an optimum set of conditions was enolization using lithium diisopropylamine (LDA) in tetrahydrofuran (THF), *O*-silylation using chlorotrimethylsilane, all at −78 °C, and finally rearrangement at reflux. Under these conditions, a mixture of starting material **12** and the desired product, ominously as a gross mixture of isomers (**13a** and **14a**), was always isolated,

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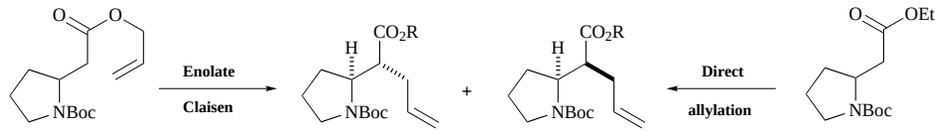


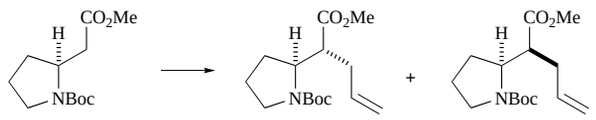
Scheme 2

even when excess base was used. The addition of varying amounts of hexamethylphosphoramide (HMPA) gave no improvement. However, when we turned to the use of lithium bis(trimethylsilyl)amide (LHMDS)[8] under otherwise the same conditions, only the desired product (**13a**/**14a**) was formed in good (> 80%) yield. Subsequently, even better yields were obtained by allowing the rearrangement to proceed at ambient temperature overnight. The initial acidic products were converted into the corresponding methyl esters (**13b**/**14b**) by treatment with diazomethane, prior to detailed characterisation. Unfortunately, the product was a 2:1 mixture of diastereoisomers. All attempts to improve upon this failed; these included the addition of HMPA, use of *tert*-butyldimethylsilyl chloride and changing the nitrogen protecting group to the less sterically demanding methoxycarbonyl function. Yields were much lower when the ester **12** was added to a premixed solution[9] of the base (LDA) and a silyl chloride at either −78 or −100 °C.

Analysis of the NMR data exhibited by esters **13b**/**14b** was difficult at ambient temperature due to extensive line broadening presumably caused by rotation of the *N*-Boc group and/or pseudorotation about the pyrrolidine ring. Fortunately, at 60 °C, the spectra became much better resolved and allowed reasonable analysis. At this stage, the relative stereochemistry of the two isomers **13b**/**14b** was unknown, especially as we were unable to separate them. Also unclear were likely reasons for the distinct lack of stereoselection, relative to the related piperidine examples (see above). In view of this, we turned to the direct synthesis of the same esters but by enolate allylation.

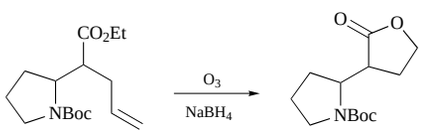
Reaction of the *N*-Boc ethyl ester **15** with one equivalent of LDA in THF at −78 °C followed by the addition of allyl bromide and warming to ambient temperature led directly to a good yield of the expected α-allyl ester but again, as a gross mixture (1.1:1) of the two possible diastereoisomers **13c** and **14c**. Much the same ratio was obtained using LHMDS as base while the addition of two equivalents of HMPA improved the ratio marginally to 1.6:1, with the same diastereoisomer as from the enolate Claisen route predominating. Increasing equivalents of HMPA gave an even poorer selection until ten equivalents were added when the yield was drastically reduced. Again, substitution of the *N*-Boc group by methoxycarbonyl failed to give any improvement. Counter ion exchange with either zinc ($ZnCl_2$ added) or magnesium ($MgCl_2 \cdot OEt_2$) resulted in extremely poor yields.

In order to try and identify the diastereoisomers **13**/**14** and to obtain some information on the possible origins of this lack of stereoselection, we turned to the optically pure (*S*)-homoproline derivative **16** which was prepared by a known Arndt–Eistert homologation of (*S*)-*N*-Boc-proline.[10] In view of the poor levels of stereoselection obtained with both the enolate Claisen and the direct allylation method, we chose the latter more direct approach and obtained a similar ratio (~1.4:1) of the expected products **17** and **18** which, again, we were unable to separate (Scheme 3). In order to access the pyrrolizidine-1-methanol system (**6**; R = H), we needed to reduce the ester function and reductively cleave the alkene, prior to cyclisation. During initial model studies, we chose the wrong option in the sense that ozonolysis of the mixture of ethyl esters **13c**/**14c**, followed



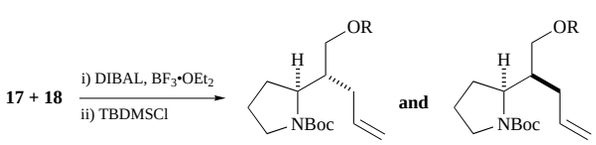
Scheme 3

by borohydride reduction of the resulting ozonides, gave largely the butyrolactone **19** (Scheme 4). We therefore elected to first



Scheme 4

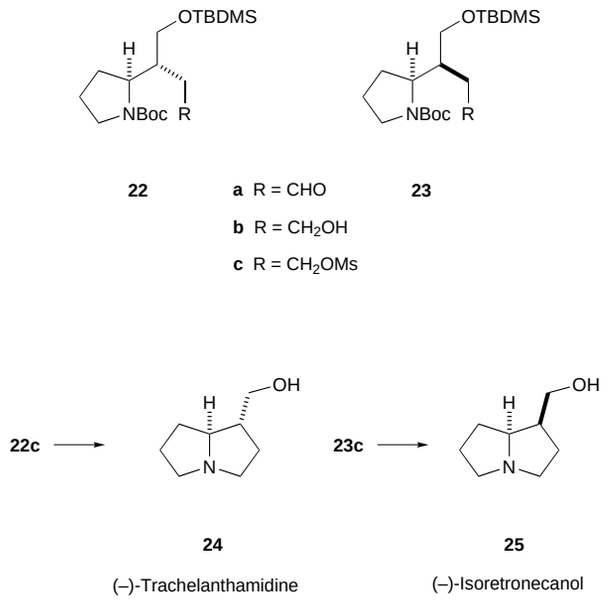
reduce the ester group; for this, a particularly suitable method is that reported by Moriwake and co-workers wherein boron trifluoride–diethyl ether is added, presumably to coordinate with the *N*-Boc group, prior to the addition of diisobutylaluminium hydride (DIBAL-H) to effect the desired reaction.[11,12] We were delighted to find that not only did this reduction work well but also that the two alcohols which resulted (**20a** and **21a**) (Scheme 5) were easily separated by column



Scheme 5

chromatography (R_F 0.25 and 0.53 respectively). In the absence of $BF_3 \cdot OEt_2$, yields were much lower.

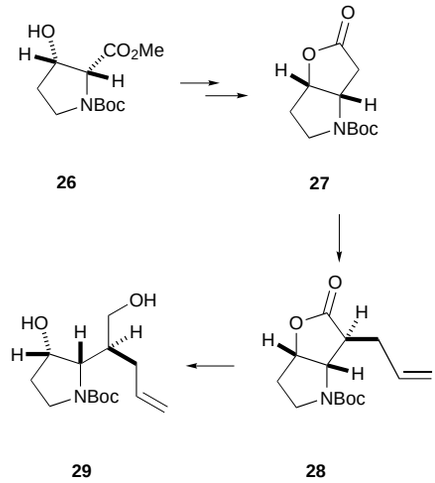
Encouragingly, both isomers showed optical activity; we therefore proceeded to a completion of the projected syntheses. Protection of the separated alcohols as the *tert*-butyldimethylsilyl (TBDMS) derivatives (**20b** and **21b**) proceeded smoothly. However, attempted cleavage of the alkene function by ozonolysis led to a complex mixture, no matter whether the reaction was worked up using sodium borohydride or triethylamine. Fortunately, the Johnson–Lemieux method[13] worked well to give the aldehydes (**22a** and **23a**) which were then smoothly reduced to the corresponding alcohols (**22b** and **23b**) using sodium borohydride and thence converted[14] into the methanesulfonates **22c** and **23c**. The nitrogen in methanesulfonate **22c** was then deprotected by treatment with 20% trifluoroacetic acid in dichloromethane[15] followed by basification using ice-cold 2 M aqueous sodium hydroxide. Fortunately, cyclisation of the pyrrolizidine occurred very rapidly, the TBDMS group having already been removed, presumably by the trifluoroacetic acid. The very polar product was identified



as (−)-trachelanthamidine **24** by comparison of its R_F value and spectral data with those quoted in the literature, as well as its optical rotation.[16–18] Application of the same sequence of the methanesulfonate **23c** delivered (−)-isoretronecanol **25** which again was identified by comparisons with literature spectral and rotational data.[17,18] Again, the complex proton NMR spectrum defied detailed analysis but was superimposable on an actual spectrum published by the Danishefsky group.[18,19]

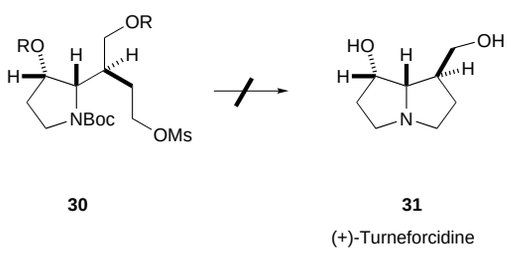
At the outset of these studies, we were somewhat concerned that enolization of ester **16** could result in elimination of the nitrogen group by a reverse Michael reaction leading to non-pyrrolidine products or to racemisation by a Michael reclosure. We have seen no evidence for the formation of such ring opened products and the fact that both pyrrolizidines **24** and **25** were obtained with excellent levels of optical purity mitigates against the occurrence of a ring opening–reclosing process. This then leaves open the reasons for the lack of stereoselection in both the Claisen rearrangements and the direct allylation method, in contrast to the highly selective formation of the homologous piperidine derivatives **3** and **5**.[1] We ascribe this simply to the less sterically biased nature of the pyrrolidine ring relative to the piperidines. In line with this, an alternative approach featuring an orthoester Claisen rearrangement of pyrrolidine-2-propenol have shown a similar lack of stereoselection, probably for the same reason.[12] However, and in complete contrast, an enolate Claisen rearrangement of the α-benzyloxyacetate of pyrrolidine-2-propenol proceeded with an excellent degree of stereoselection, a consequence of the presence of the additional benzyloxy group which is crucial in establishing a single, favoured transition state conformation.[20]

The efficiency of the direct allylation method led us to consider the use of more sterically biased substrates which could provide much better stereoselection in the preparation of intermediates suitable for the elaboration of additional pyrrolizidines **6** along the lines used in the foregoing syntheses. For this, a derivative of the Geissman–Waiss lactone [*e.g.* (−)-**27**] seemed an ideal candidate. This compound was a central intermediate in an original synthesis of the pyrrolizidine retronecine[21] and has subsequently become established as a generally useful intermediate in this area.[2,22] Optically pure material has been obtained by a number of routes of varying lengths which, in most cases, are designed to deliver the (+)-enantiomer which is a precursor to many of the common natural pyrrolizidines.[23] Routes to the (−)-enantiomer have also been reported;[24] our contribution to this area has been a preparation of the (−)-lactone **27** by one carbon homologation of the hydroxyproline derivative **26**, obtained with *ca.* 80% enantiomeric enrichment by yeast reduction of the corresponding keto proline.[25]



Scheme 6

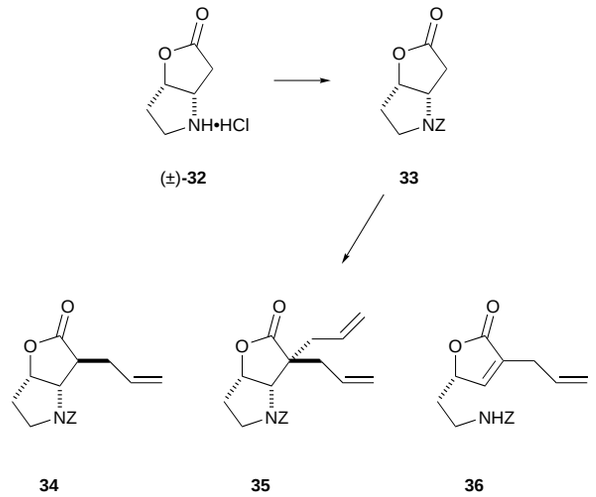
However, our initial attempts at the direct allylation of lactone **27** using LDA as the base were far from encouraging; yields of allylated material were in the order of 10–20% and were little improved by the addition of either HMPA or DMPU [1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one]. Again, we carried out these reactions at low temperatures, typically −78 °C, in the hope of minimising any ring opening reactions. Use of LHMDS as base gave even poorer yields; however, these were dramatically improved to 60–70% by addition of HMPA, two equivalents being optimum. We were gratified to find that the allylated product **28** was contaminated with < 5% of the 4-epimer, indicating that approach of the electrophile to the enolate of lactone **27** had occurred almost exclusively toward the convex face (Scheme 6). Subsequent reduction using DIBAL-H–BF_3·OEt_2[11,12] gave the corresponding diol **29** but which was always contaminated with varying amounts of the corresponding lactol, even when a large excess (8 equiv.) of the reducing agent was used. Fortunately, treatment of this mixture with sodium borohydride smoothly completed the reduction. The diol was then doubly protected with a variety of groups, including TBDMS, benzyl, acetate and methoxyethoxymethyl (MEM) and the alkene reductively cleaved as before (Scheme 7). The resulting alcohol was then smoothly converted into the



Scheme 7

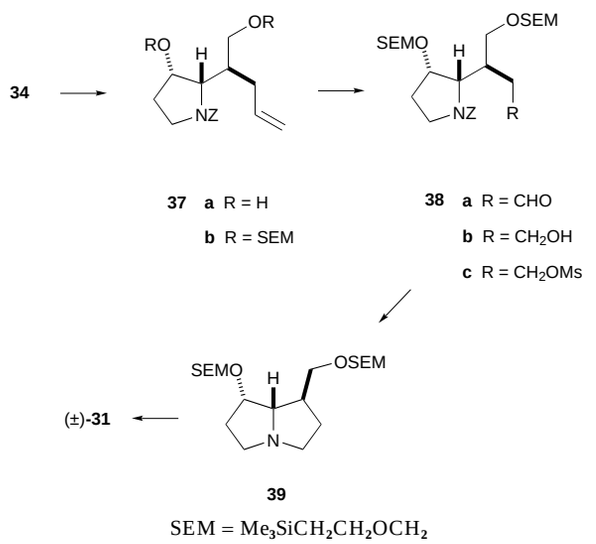
corresponding methanesulfonates **30** but, disappointingly, all attempts to convert these into turneforcidine **31** gave, at best, miniscule yields. We wondered if the acidic conditions used to remove the *N*-Boc function could be responsible, possibly because of protonation of the protected 3-hydroxy group and intramolecular displacement by nitrogen and subsequent decomposition. In any event, we then turned to the corresponding benzyloxycarbonyl group, as this should be removable under neutral, hydrogenolytic conditions.

Due to time constraints, we prepared the required *cis*-fused lactone **33** in racemic form from the hydrochloride **32**, which is available on a reasonably large scale starting from β-alanine and diethyl fumarate.[21,25,26] Allylation using the optimised conditions (LHMDS, THF, −78 °C, 2 equiv. HMPA) gave a slightly lower 52% isolated yield of the desired homologue **34**,



Scheme 8

accompanied by traces of the doubly allylated compound **35** and a ring opened product, the butenolide **36** (Scheme 8). This was then reduced to the corresponding diol **37a**, this time in a single step using sodium borohydride in ethanol, without the complication of obtaining some of the intermediate lactol (Scheme 9). Subsequent protection[27] as the bis(trimethylsilyl-



Scheme 9

ethyl) (SEM) ether **37b**, reductive cleavage of the alkene by sequential osmylation and cleavage[13] to the aldehyde **38a** and reduction provided the alcohol **38b** and thence the corresponding methanesulfonate **38c**. Gratifyingly, hydrogenolysis of this, in the presence of lithium carbonate, delivered the protected pyrrolizidine **39** in excellent yield. In our hands, the yield was much higher when the lithium carbonate had been freshly purified by crystallisation from water.[28] The reason for this was not clear, but is perhaps due to the different crystalline state of the carbonate samples. Finally, the SEM groups were removed by lengthy treatment with tetrabutylammonium fluoride (TBAF) in hot THF to give (±)-turneforcidine **31**, which exhibited chromatographic mobility,[29] and spectral and analytical data[30] identical to those previously reported. The availability of both enantiomers of lactone **33** suggests that this route could be used to prepare either enantiomer of turneforcidine **31**. In addition, the stability of the enolate derived from lactones **27** and **33**, as well as those from the homoproline ester **16**, with respect to ring opening at least at low temperatures, suggests that these could be utilised in other ways in the elaboration of numerous derivatives.

Experimental

General

Infrared spectra were obtained using a Pye-Unicam SP3-100 or a Perkin-Elmer 1600 series 1 FTIR spectrometer using liquid films on sodium chloride plates unless otherwise stated. ^{1}H NMR spectra were obtained using a Perkin-Elmer R32a instrument operating at 90 MHz (90) or a Bruker AM-400 instrument operating at 400 MHz (400). *J* Values are given in Hz. A JEOL FX90Q spectrometer operating at 22.6 MHz or the Bruker AM-400 instrument operating at 100.0 MHz were used to obtain ^{13}C NMR spectra [(90) or (400) respectively)]. All spectra were recorded using dilute solutions in deuteriochloroform, with tetramethylsilane as the internal standard. Mass spectra were obtained in the EI mode using either an AEI MS 902 or a VG 7070E instrument operating at 70 eV. Optical rotations were determined using an Optical Activity AA-10 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.

Solvents were purified and dried when necessary using standard procedures.[28] Unless stated otherwise, all reactions were performed under an atmosphere of dry nitrogen and all organic solutions from aqueous work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. CC refers to column chromatography using silica gel [SORBSIL® C60-H (40–60 μm)] and the eluents specified. Petrol refers to light petroleum with bp 40–60 °C and ether refers to diethyl ether.

Ethyl (±)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-acetate 15

To a stirred solution of (±)-homoproline ethyl ester **10** (3.32 g, 21 mmol)[3,4] in dry dichloromethane (25 ml) maintained at 0 °C was added triethylamine (2.95 ml, 21 mmol) followed by di-*tert*-butyl dicarbonate (4.62 g, 21 mmol). No more coolant was added and the mixture was stirred overnight then concentrated by rotary evaporation. The residue was dissolved in ether (25 ml) and the solution washed with saturated brine (3 × 10 ml) then dried and the solvent evaporated, finally at 1 mmHg, to give the *N*-Boc derivative **15** (4.70 g, 87%) as a colourless oil, R_F 0.45 [petrol–ether (2:1)]; ν_{max}/cm^{-1} 1731 and 1694; δ_H(90) 1.25 (3H, t, *J* 7.9, OCH_2CH_3), 1.50 (9H, s, CMe_3), 1.60–2.00 (4H, m, 2 × CH_2), 2.30 (1H, dd, *J* 14.8 and 9.8, CH_aH_bCO), 2.93 (1H, app, br d, *J ca.* 13.8, CH_aH_bCO), 3.35 (2H, m, CH_2N), 4.06–4.20 (1H, m, CHN) and 4.15 (2H, q, *J* 7.9, CH_2O).

(±)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-acetic acid 11

To a solution of potassium hydroxide (1.54 g, 27 mmol) in methanol (30 ml) and water (2 ml) at 0 °C was added the foregoing ester **15** (4.70 g, 18 mmol). The solution was stirred without further cooling overnight then the bulk of the solvents were removed by rotary evaporation. The residue was taken up in water (10 ml) and the resulting solution washed with ether (2 × 5 ml) then acidified to pH 4 using solid citric acid and extracted with ether (3 × 10 ml). The combined extracts were dried and evaporated to leave the acid **11** as a colourless crystalline solid, mp 124–125 °C; ν_{max}/cm^{-1} 3202, 1740 and 1665; δ_H(90) 1.50 (9H, s, CMe_3), 1.65–2.05 (4H, m, 2 × CH_2), 2.33 (1H, dd, *J* 15.9 and 8.9, CH_aH_bCO), 2.95 (1H, app. br d, *J ca.* 15.9, CH_aH_bCO), 3.36 (2H, app. t, *J* 5.9, CH_2N), 4.05–4.45 (1H, m, CHN) and 9.80–10.15 (1H, br s, OH).

(±)-Prop-2-en-1-yl 1-(*tert*-butoxycarbonyl)pyrrolidine-2-acetate 12

To a stirred solution of (±)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-acetic acid **11** (3.37 g, 12 mmol) in dry ether (30 ml) was added allyl alcohol (0.85 g, 15 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (~ 5 mg) followed by the dropwise addition of a solution of *N*,*N*′-dicyclohexylcarbodiimide (3.04 g, 15 mmol) in dry ether (10 ml) during 5 min. The resulting white suspension was stirred at ambient temperature for 16 h

then filtered. The solids were washed with ether and the combined filtrates concentrated by rotary evaporation. CC of the residue [petrol–ether (2:1)] gave the *allyl ester* **12** (2.40 g, 60%) as a colourless oil, R_F 0.4; ν_{max}/cm^{-1} 1737 and 1694; δ_H(90) 1.50 (9H, s, CMe_3), 1.25–2.05 (4H, m, 2 × CH_2), 2.35 (1H, dd, *J* 14.8 and 9.9, CH_aH$_b$C=O), 2.95 (1H, app. br d, *J ca.* 14.8, CH$_a$-H_bC=O), 3.39 (2H, app. t, *J* 5.9, CH_2N), 4.05–4.50 (1H, m, CHN), 4.65 (2H, dd, *J* 6.9 and *ca.* 1, CH_2O), 5.25 (1H, dd, *J* 10.0 and 2, CH=CH_{cis}H$_{trans}$), 5.35 (1H, dd, *J* 17.0 and 2.0, CH=CH$_{cis}H_{trans}$) and 5.90 (1H, ddd, *J* 17.0, 10.0 and 6.9, C*H*=CH$_2$); δ_C(90) 23.0 (CH_2), 28.3 (3 × Me), 30.8 (CH_2), 38.7 (*C*H$_2$CO), 46.2 (CH_2N), 53.9 (CHN), 64.7 (OCH$_2$), 79.0 (*C*Me$_3$), 117.8 (=CH$_2$), 132.1 (=CH), 153.9 (NCO) and 170.7 (OCO); *m/z* 213 (M − Bu^t, 7%), 196 (8), 170 (5), 168 (38), 128 (28), 114 (31), 70 (100) and 57 (72) (Found: C, 62.4; H, 8.7. $C_{14}H_{23}NO_4$ requires C, 62.4; H, 8.6%).

Methyl (2*SR*,α*RS*)- and (2*SR*,α*SR*)-1-(*tert*-butoxycarbonyl)-α-(prop-2-en-1-yl)pyrrolidine-2-acetate (13b and 14b)

Enolate Claisen method. To a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (0.42 ml, 2 mmol) in tetrahydrofuran (THF; 15 ml) maintained at −10 °C was slowly added butyllithium (1.25 ml of a 1.6 M solution in hexanes; 2 mmol). After 0.25 h, the solution was cooled to −78 °C and a solution of the foregoing racemic ester **12** (0.27 g, 1 mmol) in THF (1 ml) was added dropwise during 5 min. After a further 10 min, chlorotrimethylsilane (0.28 ml, 2 mmol) was added and, after 20 min, no further coolant was added and the solution was stirred overnight at ambient temperature. The solvents were then removed by rotary evaporation. The residue was dissolved in methanol and the resulting solution stirred at ambient temperature for 0.25 h then the methanol was removed by rotary evaporation. The residue was dissolved in saturated aqueous sodium hydrogen carbonate (10 ml) and the solution washed with ether (2 × 10 ml) then acidified to pH 4 using citric acid and extracted with ether (3 × 10 ml). The combined extracts were dried and evaporated to leave a crude mixture of the acids **13a** and **14a** (0.25 g) as a brown oil; ν_{max}/cm^{-1} ($CHCl_3$) 3000 and 1680; δ_H(90) 1.50 (9H, s, CMe_3), 1.60–2.05 (4H, m, 2 × CH_2), 2.05–2.60 (2H, m, CH_2CH=), 2.90–3.65 (3H, m, CH_2N and CHCO), 3.90–4.40 (1H, m, CHN), 5.05 (1H, dd, *J* 9.0 and *ca.* 2, CH=CH_{cis}H$_{trans}$), 5.15 (1H, dd, *J* 17.0 and *ca.* 2, CH=CH$_{cis}$-H_{trans}), 5.60–6.15 (1H, m, C*H*=CH$_2$) and 9.55–10.10 (1H, br s, OH); *m/z* 196 (M − Bu^t, 3%), 170 (10), 114 (86), 70 (100) and 57 (94).

To a stirred solution of the foregoing acids (0.25 g) was added ethereal diazomethane until TLC analysis indicated complete reaction. The solution was left overnight to allow excess reagent to evaporate and then was concentrated by rotary evaporation. CC of the residue [petrol–ether (2:1)] separated the *pyrrolidine esters* **13b** and **14b** (0.21 g, 78%) as a colourless oil, a 2:1 mixture of diastereoisomers; R_F 0.3; ν_{max}/cm^{-1} 1732 and 1694; δ_H(400, [^{2}H$_6$]DMSO at 333 K) 1.47 (6H, s, CMe_3), 1.49 (3H, s, CMe_3), 1.73–1.94 (4H, m, 2 × CH_2), 2.05–2.15 (0.33H, m, CH_aH$_b$CH=), 2.20 (0.67H, ddd, *J ca.* 14.3, 6.9 and 6.3, CH_aH$_b$CH=), 2.37–2.50 (1H, m, CH$_a$$H_b$-CH=), 2.94–3.17 (2H, m, CH_2N), 3.33–3.40 (1H, m, CHCO), 3.57 (2H, s, OMe), 3.59 (1H, s, OMe), 3.91 (0.67H, br s, CHN), 4.00 (0.33H, br s, CHN), 4.98 (1H, app. d, *J* 10.5, CH=CH_{cis}H$_{trans}$), 5.03 (1H, app. d, *J* 16.0, CH=CH$_{cis}H_{trans}$) and 5.65–5.85 (1H, m, C*H*= CH$_2$); δ_C(400, [^{2}H$_6$]DMSO at 333 K; * indicates the resonance for the major isomer in a related pair) 22.9*, 23.3, 27.1*, 27.5 (all pyrrolidine β-CH$_2$), 28.2 (3 × Me), 30.3, 33.3* (CH$_2$CH=), 46.3*, 46.7 (CH_2N), 47.2*, 47.6 (*C*HCHN), 51.3 (OMe), 58.1, 58.3* (CH*C*HN), 78.6 (*C*Me$_3$), 115.8, 116.3* (=CH$_2$), 135.8*, 136.4 (=CH), 153.6, 153.8 (NCO) and 173.0, 173.4* (OCO); *m/z* 251 (2%), 210 (2), 196 (4), 182 (6), 170 (8), 142 (6), 128 (12), 114 (51), 70 (100) and 57 (68) (Found: C, 63.8; H, 9.1; N, 5.0. $C_{15}H_{25}NO_4$ requires C, 63.6; H, 8.9; N, 4.9%).

Ethyl (2*SR*,α*RS*)- and (2*SR*,α*SR*)-1-(*tert*-butoxycarbonyl)-α-(prop-2-en-1-yl)pyrrolidine-2-acetate (13c and 14c)

Enolate allylation method. Butyllithium (2.68 ml of a 1.6 M solution in hexanes; 4.3 mmol) was added dropwise to a stirred solution of diisopropylamine (0.6 ml, 4.3 mmol) in THF (40 ml) at −5 °C. After 0.25 h, the solution was cooled to −78 °C and a solution of the racemic ethyl ester **15** (1.0 g, 3.89 mmol) in THF (1 ml) was added dropwise during 5 min. After 0.25 h, hexamethylphosphoramide (HMPA) (1.35 ml, 7.78 mmol) was added, followed, after a further 0.25 h, by allyl bromide (0.44 ml, 3.89 mmol). The solution was kept at −78 °C for 20 min then slowly warmed to ambient temperature and stirred for 1 h and quenched with water (2 drops). The bulk of the solvents was removed by rotary evaporation and the residue dissolved in ether and the resulting solution washed with saturated brine (3 × 10 ml), then dried and evaporated. CC of the residue [petrol–ether (2:1)] gave the *pyrrolidine esters* **13c** and **14c** (1.01 g, 87%) as a colourless oil, a 1.6:1 mixture of diastereoisomers, R_F 0.6; ν_{max}/cm^{-1} 1731 and 1694; δ_H(400, [^{2}H$_6$]DMSO at 333 K) 1.17 and 1.18 (3H, 2 × t, *J* 7.1 and 7.1, OCH$_2$CH_3), 1.42 (9H, s, CMe_3), 1.65–1.89 (4H, m, 2 × CH_2), 2.00–2.20 (0.39H, m, CH_aH$_b$CH=), 2.34 (0.61H, ddd, *J* 12.9, 7.1 and 5.8, CH_aH$_b$-CH=), 2.27–2.40 (1H, m, CH$_a$$H_b$CH=), 2.90–3.10 (2H, m, CH_2N), 3.30–3.45 (1H, m, CHCO), 3.90 (0.61H, app. q, *J* 6.4, CHN), 3.95–4.10 (2.39H, m, CHN and CH_2O), 4.98 (1H, app. d, *J* 10.0, CH=CH_{cis}H$_{trans}$), 5.04 (1H, dd, *J* 15.8 and 1.7, CH=CH$_{cis}H_{trans}$) and 5.65–5.80 (1H, m, C*H*=CH$_2$); δ_C(400, [^{2}H$_6$]DMSO at 333 K; * indicates the resonance for the major isomer in a related pair) 14.0 (CH_2*C*H$_3$), 22.9, 23.3*, 27.0, 27.4* (all pyrrolidine β-CH_2), 28.2 (3 × Me), 30.2, 33.3* (CH$_2$CH=), 46.4*, 46.8 (CH_2N), 47.0*, 47.6 (*C*HCHN), 58.1, 58.4* (CH*C*HN), 59.8 (OCH$_2$), 78.5, 78.6 (*C*Me$_3$), 115.8, 116.2*, (=CH$_2$), 135.9*, 136.5 (=CH), 153.6*, 153.7 (NCO) and 172.5, 173.0* (OCO); *m/z* 170 (11%), 156 (9), 142 (8), 128 (17), 114 (56), 70 (100) and 57 (56) (Found: C, 64.4; H, 9.5; N, 4.6. $C_{16}H_{27}NO_4$ requires C, 64.6; H, 9.2; N, 4.7%).

Methyl (2*S*,α*R*)- and (2*S*,α*S*)-1-(*tert*-butoxycarbonyl)-α-(prop-2-en-1-yl)pyrrolidine-2-acetate 17 and 18

Using the foregoing direct allylation method and 0.5 g (2.1 mmol) of the (2*S*)-methyl ester **16**, a 1.4:1 mixture of the expected products **17** and **18** (0.50 g, 84%) was isolated which showed identical spectroscopic data to that displayed by the product from the Claisen rearrangement in every respect, except for the slightly differing isomer ratios.

(2*S*,β*R*)- and (2*S*,β*S*)-1-(*tert*-Butoxycarbonyl)-β-(prop-2-en-1-yl)-pyrrolidine-2-ethanol 20a and 21a

To a stirred solution of the foregoing ester mixture (**17** and **18**) (0.63 g, 2.18 mmol) in dry dichloromethane (5 ml) maintained at −78 °C was added boron trifluoride–diethyl ether (0.30 ml, 2.44 mmol). After 0.5 h, diisobutylaluminium hydride (4.3 ml of a 1.5 M solution in toluene; 6.56 mmol) was added and the resulting solution stirred at −78 °C for 2.25 h.[11,12] The reaction was quenched by the addition of acetic acid (6.0 ml of a 5 M solution in dichloromethane) then warmed to ambient temperature and poured into aqueous tartaric acid (50 ml of a 10% solution). The organic phase was separated and the aqueous phase extracted with chloroform (3 × 30 ml). The combined organic solutions were washed with saturated brine (50 ml) then dried and evaporated. CC [CH_2Cl_2–EtOAc (9:1)] gave (i) a mixture of recovered starting esters **17** and **18** (0.08 g, 13%) as a colourless oil, R_F 0.79, (ii) the (2S,βS)-*pyrrolidineethanol* **21a** (0.175 g, 35%) as a colourless oil, R_F 0.53; $[\alpha]_D^{27}$ −24.8 (*c* 1.04 in CH_2Cl_2); ν_{max}/cm^{-1} 3380 and 1660; δ_H(400) 1.47 (9H, s, CMe_3), 1.53–1.63 (1H, m, β-CH), 1.82–1.95 (4H, m, 3- and 4-CH_2), 1.95–2.05 (1H, m, CH_aH$_b$CH=), 2.35–2.45 (1H, m, CH$_a$$H_b$CH=), 3.29 (1H, dd, *J* 11.0 and 7.0, CH_aH$_b$OH), 3.39–3.41 (1H, m, CH$_a$$H_b$OH), 3.49–3.65 (2H, m, CH_2N), 3.85 (1H, br dd, *J* 10.0 and 7.0, CHN), 4.15–4.40 (1H, br s, OH), 5.02

(1H, br d, *J* 10.2, CH=CH_{cis}H$_{trans}$), 5.10 (1H, dd, *J* 17.0 and 1.5, CH=CH$_{cis}$$H_{trans}$) and 5.83 (1H, ddd, *J* 17.0, 10.2 and 7.5, C*H*=CH$_2$); δ_C(400) 23.1 (pyrrolidine β-CH$_2$), 28.0 (3 × Me), 28.5 (pyrrolidine β-CH$_2$), 32.3 (*C*H$_2$CH=), 44.2 (*C*HCHN), 46.0 (CH$_2$N), 57.7 (CHN), 59.6 (CH$_2$OH), 79.7 (*C*Me$_3$), 115.7 (=CH$_2$), 136.7 (=CH) and 156.4 (NCO); *m/z* 236 (4%), 182 (5), 170 (9), 154 (11), 127 (15), 114 (36), 70 (47) and 57 (100) (Found: C, 65.7; H, 9.7; N, 5.6. $C_{14}H_{25}NO_3$ requires C, 65.9; H, 9.9; N, 5.5%) and (iii) the (2S,βR)-*pyrrolidineethanol* **20a** (0.223 g, 46%) as a colourless oil, R_F 0.25; $[\alpha]_D^{27}$ −24.9 (*c* 2.58 in CH_2Cl_2); ν_{max}/cm^{-1} 3380 and 1670; δ_H(400) 1.47 (9H, s, CMe$_3$), 1.52–1.63 (1H, m, β-CH), 1.75–2.09 (6H, m, 3- and 4-CH$_2$ and CH_2CH=), 3.19–3.25 (1H, m, CH_aH$_b$OH), 3.35–3.45 (1H, m, CH$_a$$H_b$OH), 3.45–3.72 (3H, m, CH$_2$N and CHN), 4.15–4.30 (1H, br s, OH), 5.01 (1H, app. d, *J* 10.1, CH=CH_{cis}H$_{trans}$), 5.06 (1H, app. d, *J* 17.0, CH=CH$_{cis}$$H_{trans}$) and 5.80 (1H, ddd, *J* 17.0, 10.1 and 7.0, C*H*=CH$_2$); δ_C(400) 24.0 (pyrrolidine β-CH$_2$), 28.1 (3 × Me), 28.5 (pyrrolidine β-CH$_2$), 31.1 (*C*H$_2$CH=), 45.1 (*C*HCHN), 47.5 (CH$_2$N), 56.6 (CHN), 62.6 (CH$_2$OH), 79.4 (*C*Me$_3$), 115.7 (=CH$_2$), 136.7 (=CH) and 156.0 (NCO); *m/z* 236 (4%), 182 (10), 170 (11), 154 (7), 127 (18), 114 (40), 70 (47) and 57 (100) (Found: C, 65.9; H, 9.6; N, 5.6%).

(2*S*,β*R*)-1-(*tert*-Butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-β-(prop-2-en-1-yl)pyrrolidine-2-ethanol 20b

A solution of the more polar (2*S*,β*R*)-pyrrolidineethanol **20a** (0.156 g, 0.6 mmol), imidazole (0.103 g, 1.52 mmol) and chloro-*tert*-butyldimethylsilane (0.106 g, 0.72 mmol) in *N*,*N*-dimethylformamide (0.5 ml) was stirred at 35 °C for 16 h, then diluted with water (5 ml) and extracted with ether (3 × 5 ml). The combined extracts were dried and evaporated and the residue purified by CC [petrol–ether (2:1)] to give the *silyl ether* **20b** (0.167 g, 76%) as a colourless oil, R_F 0.58; ν_{max}/cm^{-1} 1681; δ_H(90) 0.00 (6H, s, Me$_2$Si), 0.86 (9H, s, SiCMe$_3$), 1.43 (9H, s, CMe$_3$), 1.60–2.20 (7H, m, β-CH, 3- and 4-CH$_2$ and CH_2CH=), 3.06–3.26 (2H, m, CH$_2$OSi), 3.52 (2H, m, CH$_2$N), 3.88–3.96 (1H, m, CHN), 4.96 (1H, app. d, *J* 11.2, CH=CH_{cis}H$_{trans}$), 4.99 (1H, app. d, *J* 16.6, CH=CH$_{cis}$$H_{trans}$) and 5.64–5.94 (1H, m, C*H*=CH$_2$); *m/z* 296 (7%), 268 (23), 256 (87), 254 (5), 212 (16), 170 (11), 114 (65), 70 (100) and 57 (57) (Found: M$^+$ − OBu^t 296.2051. $C_{16}H_{30}NO_2Si$ requires *M*, 296.2046).

(2*S*,β*S*)-1-(*tert*-Butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-β-(prop-2-en-1-yl)pyrrolidine-2-ethanol 21b

By the foregoing method, the less polar (2*S*,β*S*)-pyrrolidineethanol **21a** (0.111 g, 0.41 mmol) was converted into the *silyl ether* **21b** (0.123 g, 77%), a colourless oil, R_F 0.58; ν_{max}/cm^{-1} 1681; δ_H(90) 0.00 (6H, s, Me$_2$Si), 0.86 (9H, s, SiCMe$_3$), 1.43 (9H, s, CMe$_3$), 1.60–2.18 (7H, m, β-CH, 3- and 4-CH$_2$ and CH_2CH=), 3.09–3.28 (2H, m, CH$_2$OSi), 3.50–3.57 (2H, m, CH$_2$N), 3.90–3.97 (1H, app. q, *J* 5.9, CHN), 4.88 (1H, app. d, *J* 10.7, CH=CH_{cis}H$_{trans}$), 4.96 (1H, app. d, *J* 16.2, CH=CH$_{cis}$$H_{trans}$) and 5.52–5.97 (1H, m, C*H*=CH$_2$); δ_C(90) −5.9 (2 × SiMe), 18.1 (SiC), 24.2 (pyrrolidine β-CH$_2$), 26.1 (SiC*Me*$_3$), 28.8 (3 × Me), 29.9 (pyrrolidine β-CH$_2$), 30.9 (*C*H$_2$CH=), 43.2 (*C*HCHN), 47.3 (CH$_2$N), 59.0 (CHN), 64.0 (CH$_2$OSi), 79.2 (*C*Me$_3$), 115.7 (=CH$_2$), 137.6 (=CH) and 155.0 (NCO); *m/z* 296 (2%), 268 (25), 256 (100), 254 (8), 212 (12), 170 (10), 114 (70), 70 (93) and 57 (53) (Found: M$^+$ − Bu^t 296.2043).

(2*S*,γ*R*)-1-(*tert*-Butoxycarbonyl)-γ-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine-2-propanol 22b

Sodium metaperiodate (0.150 g, 0.7 mmol) was added during 40 min to a vigorously stirred solution of the silyl ether **20b** (0.131 g, 0.35 mmol) and osmium tetroxide (0.03 g) in ether (1.5 ml) and water (1.0 ml). The resulting suspension was stirred for 16 h, then the layers were separated and the aqueous layer extracted with chloroform (3 × 3 ml). The combined organic solutions were passed through a pad of sodium sulfate and then evaporated to leave the pyrrolidine aldehyde **22a** (0.134 g, ~ 100%) as a dark oil, ν_{max}/cm^{-1} 1720 and 1685; δ_H(90) 0.00 (6H, s, 2 × Me$_2$Si), 0.87 (9H, s, SiCMe$_3$), 1.46 (9H, s, CMe$_3$) 1.60–2.00 (5H, m, β-CH, 3- and 4-CH$_2$), 2.50 (2H, br s, CH_2CHO), 3.00–4.00 (5H, m, CH$_2$OSi, CH$_2$N and CHN) and 9.70 (1H, s, CHO), which was reduced immediately without further purification.

To a vigorously stirred solution of the foregoing crude aldehyde **22a** (0.134 g, 0.35 mmol) in methanol (6 ml) maintained at 0 °C was added sodium borohydride (0.016 g). The resulting suspension was stirred for 0.5 h then quenched with water (2 drops) and the solvents evaporated. The residue was dissolved in chloroform (15 ml) and the solution washed with saturated aqueous ammonium chloride (3 × 3 ml) then dried and evaporated. Purification by CC [CH_2Cl_2–EtOAc (9:1)] afforded the *alcohol* **22b** (0.112 g, 83%), a colourless oil, R_F 0.1; ν_{max}/cm^{-1} 3361 and 1667; δ_H(90) 0.00 (6H, s, Me$_2$Si), 0.89 (9H, s, SiCMe$_3$), 1.46 (9H, s, CMe$_3$), 1.47–1.90 (5H, m, γ-CH and 3- and 4-CH$_2$), 2.00–2.40 (2H, m, β-CH$_2$) and 2.90–4.00 (7H, m, CH$_2$OSi, CH$_2$N, CHN and CH_2OH); δ_C(90) −5.5 (2 × SiMe), 18.3 (SiC), 24.1 (pyrrolidine β-CH$_2$), 25.9 (SiC*Me*$_3$), 28.6 (3 × Me), 29.7 (pyrrolidine β-CH$_2$), 33.8 (β-CH$_2$), 42.1 (γ-CH), 47.2 (CH$_2$N), 59.7 (CHN), 61.7 (CH$_2$OSi), 63.8 (CH$_2$OH), 79.4 (*C*Me$_3$) and 155.0 (NCO); *m/z* 170 (20%), 114 (64), 70 (89) and 57 (100) (Found: C, 61.4; H, 10.6; N, 3.6. $C_{19}H_{39}NO_4Si$ requires C, 61.1; H, 10.5; N, 3.8%).

(2*S*,γ*S*)-1-(*tert*-Butoxycarbonyl)-γ-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine-2-propanol 23b

In an identical fashion to the foregoing method, the silyl ether **21b** (0.110 g) was converted into the corresponding aldehyde **23a** (0.094 g, 90%) which showed ν_{max}/cm^{-1} 1721 and 1682; δ_H(90) 0.00 (6H, s, Me$_2$Si), 0.89 (9H, s, SiCMe$_3$), 1.49 (9H, s, CMe$_3$), 1.60–2.00 (5H, m, β-CH, 3- and 4-CH$_2$), 2.35 (2H, br d, *J* 8.0, CH_2CHO), 2.75–3.30 (2H, m, CH$_2$OSi), 3.60 (2H, app. t, *J* 6.0, CH$_2$N), 3.70–4.00 (1H, m, CHN) and 9.70 (1H, br t, *J ca.* 1, CHO) and then into the (2S,γS)-*alcohol* **23b** (0.057 g, 60%), a colourless oil, R_F 0.1; ν_{max}/cm^{-1} 3367 and 1668; δ_H(90) 0.00 (6H, s, Me$_2$Si), 0.83 (9H, s, SiCMe$_3$), 1.38 (9H, s, CMe$_3$), 1.47–1.97 (5H, m, γ-CH and 3- and 4-CH$_2$), 2.09–2.40 (2H, m, β-CH$_2$) and 3.06–3.70 (7H, m, CH$_2$OSi, CH$_2$N, CHN and CH_2OH); *m/z* 201 (7%), 170 (23), 114 (13), 70 (100) and 57 (21) (Found: C, 61.3; H, 10.8; N, 3.7%).

(1*R*,8*S*)-1-Hydroxymethylpyrrolizidine [(−)-trachelanthamidine] 24

Methanesulfonyl chloride (0.03 ml, 0.38 mmol) was added to an ice-cold, stirred solution of the (2*S*,γ*R*)-alcohol **22b** (0.102 g, 0.26 mmol) and dry triethylamine (0.06 ml, 0.4 mmol) in dry dichloromethane (15 ml). After 1 h, the mixture was warmed to ambient temperature and the solvents removed by rotary evaporation. The residue was partitioned between ether (15 ml) and water (6 ml) and the separated aqueous solution extracted with ether (2 × 5 ml). The combined organic solutions were washed with water (2 × 2 ml), then dried and the solvent evaporated to leave the crude methanesulfonate **22c** (0.119 g, 98%) as a brown oil, ν_{max}/cm^{-1} 1693; δ_H(90) 0.00 (6H, s, Me$_2$Si), 0.84 (9H, s, SiCMe$_3$), 1.40 (9H, s, CMe$_3$), 1.50–2.40 (7H, m, γ-CH and 3-, 4- and β-CH$_2$), 2.94 (3H, s, MeSO$_2$), 3.00–3.50 (2H, m, CH$_2$OSi), 3.50–3.78 (2H, m, CH$_2$N), 3.78–4.00 (1H, m, CHN) and 4.00–4.40 (2H, m, CH_2OMs), which was used directly in the final step.

To a stirred, ice-cooled solution of the foregoing, crude methanesulfonate **22c** (0.119 g, 0.26 mmol) in dichloromethane (6 ml) was added trifluoroacetic acid (0.75 ml). The resulting solution was stirred for 0.5 h and then the solvent and reagent were removed by rotary evaporation to leave the crude pyrrolidine salt which was dissolved in ice-cold water (3 ml). The resulting solution was basified using ice-cold 2 M aqueous sodium hydroxide and extracted with chloroform (5 × 3 ml). The combined extracts were dried and evaporated and the resi-

due purified by CC [$CHCl_3$–MeOH–aq. NH_4OH (5:4:1)][17] to give (1*R*,8*S*)-1-hydroxymethylpyrrolizidine [(−)-trachelanthamidine] **24** (0.017 g, 46%) as a colourless oil, R_F 0.21; $[\alpha]_D^{27}$ −14.0 (*c* 0.5 in EtOH) {lit.,[17] $[\alpha]_D$ −13.8 (*c* 1.28 in EtOH)}; ν_{max}/cm^{-1} 3397; δ_H(400)[18] 1.61–1.67 (1H, m), 1.81–2.09 (7H, m), 2.63–2.75 (2H, m), 3.00–3.31 (2H, m), 3.43 (1H, m) and 3.60–3.72 (2H, m); δ_C(400) 25.6, 29.3, 31.5 (all CH_2), 47.6 (CH), 54.6, 54.8 (both CH_2), 64.4 (CH) and 68.7 (CH_2OH); *m/z* 141 (M^+, 25%), 124 (18), 110 (12), 83 (100) and 82 (47) (Found: M^+, 141.1161. $C_8H_{15}NO$ requires *M*, 141.1154).

(1*S*,8*S*)-1-Hydroxymethylpyrrolizidine [(−)-isoretronecanol] 25

By the foregoing method, the (2*S*,γ*S*)-alcohol **23b** (0.055 g, 0.15 mmol) was converted into the methanesulfonate **23c** (0.067 g, ~100%), isolated as a crude brown oil, ν_{max}/cm^{-1} 1694; δ_H(90) 0.00 (6H, s, 2 × MeSi), 0.84 (9H, s, $SiCMe_3$), 1.40 (9H, s, CMe_3), 1.50–1.90 (5H, m, γ-CH and 3- and 4-CH_2), 1.90–2.40 (2H, m, β-CH_2) 2.90 (3H, s, $MeSO_2$), 3.00–3.30 (2H, m, CH_2OSi), 3.30–3.70 (2H, m, CH_2N), 3.70–4.00 (1H, m, CHN) and 4.00–4.50 (2H, m, C*H*$_2$OMs), which again was used directly in the final step.

Sequential treatment of the crude methanesulfonate **23c** (0.067 g) with trifluoroacetic acid and sodium hydroxide, as described above, then gave (1*S*,8*S*)-1-hydroxymethylpyrrolizidine [(−)-isoretronecanol] **25** (0.014 g, 68%) as a colourless oil, R_F 0.20; $[\alpha]_D^{27}$ −77.0 (*c* 0.3 in EtOH) {lit.,[17] $[\alpha]_D$ −78.2 (*c* 2.8 in EtOH)}; ν_{max}/cm^{-1} 3350; δ_H(400)[18] 1.41–1.55 (1H, m), 1.55–1.65 (1H, m), 1.65–1.80 (2H, m), 1.80–2.00 (2H, m), 2.43–2.56 (2H, m), 2.66–2.75 (1H, m), 2.81–3.27 (3H, m), 3.61–3.67 (1H, m) and 3.69 (1H, d, *J* 7.2); δ_C(400) 25.9, 26.6, 27.3 (all CH_2), 43.9 (CH), 54.0, 55.6 (both CH_2), 63.3 (CH) and 66.8 (CH_2OH); *m/z* 141 (M^+, 31%), 124 (21), 110 (13), 83 (100) and 82 (41) (Found: M^+, 141.1154).

(1*S*,4*S*,5*S*)-6-(*tert*-Butoxycarbonyl)-4-(prop-2-en-1-yl)-2-oxa-6-azabicyclo[3.3.0]octan-3-one 28

A solution of the lactone **27** (0.233 g, 1.03 mmol)[25] in THF (2 ml) was added dropwise during 10 min to a stirred solution of lithium bis(trimethylsilyl)amide (LHMDS) (1.13 ml of a 1 M solution in hexanes; 1.3 mmol) in THF (20 ml) maintained at −78 °C. After 0.25 h at this temperature, HMPA (0.35 ml, 2.0 mmol) was added followed, after a further 0.25 h, by allyl bromide (0.11 ml, 1.27 mmol). The resulting solution was stirred for 0.25 h then slowly warmed to ambient temperature and stirred for a further 1 h before being passed through a pad of silica gel. The pad was washed with fresh THF and the filtrate concentrated. CC of the residue [CH_2Cl_2–EtOAc (9:1)] afforded the *propenyl lactone* **28** (0.192 g, 70%) as a colourless oil, R_F 0.8; ν_{max}/cm^{-1} 1770 and 1700; δ_H(90) 1.40 (9H, s, CMe_3), 1.85–2.59 (4H, m, 8-CH_2 and C*H*$_2$CH=), 2.59–2.99 (1H, m, 4-CH), 3.24 (1H, ddd, *J* 11.2, 11.2 and 6.1, 7-H_a), 3.44–3.90 (1H, m, 7-H_b), 4.10 (1H, app. br d, *J* 4.8, 5-H), 4.90–4.95 (1H, m, 1-H), 5.16 (1H, app. d, *J* 10.9, CH=C*H*$_{cis}$$H_{trans}$), 5.20 (1H, app. d, *J* 17.0, CH=CH_{cis}*H*$_{trans}$) and 5.56–6.01 (1H, m, C*H*=CH_2); δ_C(90) 28.6 (3 × Me), 30.5 (8-CH_2), 35.6 (CH_2CH=), 44.2 (7-CH_2), 47.8 (4-CH), 62.8 (5-CH), 80.5 (CMe_3), 82.4 (1-CH), 118.9 (=CH_2), 133.4 (=CH), 153.5 (NCO) and 177.8 (OCO); *m/z* 225 (2%), 211 (50), 194 (14), 167 (19), 125 (10), 113 (10), 98 (6), 69 (20) and 57 (100) (Found: $M^+ - C_3H_6$, 225.1027. $C_{11}H_{15}NO_4$ requires *M*, 225.1001).

(2*S*,3*S*,β*S*)-1-(*tert*-Butoxycarbonyl)-3-hydroxy-β-(prop-2-en-1-yl)pyrrolidine-2-ethanol 29

To a stirred solution of the lactone **28** (0.192 g, 0.72 mmol) maintained at −78 °C in dry toluene (3 ml) was added boron trifluoride–diethyl ether (0.08 ml, 0.72 mmol).[11,12] After 0.5 h, diisobutylaluminium hydride (2.17 ml of a 1 M solution in toluene; 2.1 mmol) was added and the resulting solution stirred for 2 h. Acetic acid (2 ml of a 5 M solution in toluene) was then added and the mixture was allowed to warm to ambient temperature and then poured into aqueous tartaric acid (20 ml of a 10% solution). The organic phase was separated and the aqueous phase extracted with chloroform (5 × 10 ml). The combined organic solutions were washed with saturated brine (20 ml) then dried and evaporated to leave a mixture of a lactol and the diol **29**. This was dissolved in ethanol (10 ml) and the solution cooled in ice–water and, while vigorously stirred, treated with sodium borohydride (0.06 g, 1.6 mmol). After 16 h without further cooling, the solvent was evaporated and the residue dissolved in chloroform (10 ml). The resulting solution was washed with saturated aqueous ammonium chloride (3 × 5 ml) then dried and evaporated. CC of the residue [$CHCl_3$–MeOH (9:1)] separated the *diol* **29** (0.184 g, 94%) as a colourless oil, R_F 0.53; ν_{max}/cm^{-1} 3380 and 1670; δ_H(90) 1.38 (9H, s, CMe_3), 1.61–2.48 (5H, m, 4-CH_2, C*H*$_2$CH= and β-CH), 3.11–4.04 (5H, m, 5- and α-CH_2 and 3-H), 4.04–4.74 (1H, m, 2-H), 4.74–5.17 (2H, m, CH=C*H*$_2$) and 5.42–5.99 (1H, m, C*H*=CH_2); δ_C(90) 30.0 (3 × Me), 33.8 (4-CH_2), 34.2 (CH_2CH=), 41.8 (β-CH), 45.8 (5-CH_2), 63.2 (2-CH), 63.9 (α-CH_2), 73.6 (3-CH), 81.4 (CMe_3), 117.7, (=CH_2), 138.4 (=CH) and 156.9 (NCO); *m/z* 270 ($M^+ - H$, 2%), 251 (3), 196 (22), 170 (17), 168 (8), 152 (9), 151 (7), 150 (9), 130 (16), 86 (38), 68 (20) and 57 (100) (Found: $M^+ - H$, 270.1708. $C_{14}H_{24}NO_4$ requires *M*, 270.1705).

(1*S*,5*SR*)-6-(Benzyloxycarbonyl)-2-oxa-6-azabicyclo[3.3.0]-octan-3-one 33

To an ice-cold solution of the (±)-lactone hydrochloride **32** (2.50 g, 15.3 mmol)[21] in dry dichloromethane (30 ml) was added triethylamine (10.5 ml, 75.3 mmol) and benzyl chloroformate (5.5 ml, 38.5 mmol). The resulting mixture was warmed to ambient temperature and stirred for 1 h, diluted with dichloromethane (50 ml), then washed with saturated brine (3 × 10 ml), dried and evaporated. Crystallisation of the residue from toluene–hexanes gave the cis-*fused lactone* **33** (2.80 g, 71%) as a colourless solid, mp 100–101 °C; ν_{max}(KBr)/cm^{-1} 1774 and 1698; δ_H(90) 1.59–2.50 (2H, m, 8-CH_2), 2.80 (2H, app. br s, 4-CH_2), 3.43 (1H, ddd, *J* 10.9, 10.9 and 6.4, 7-H_a), 3.60–4.06 (1H, m, 7-H_b), 4.34–4.65 (1H, m, 5-H), 4.99–5.10 (1H, m, 1-H), 5.14 (2H, s, C*H*$_2$Ph) and 7.35 (5H, s, Ph); *m/z* 261 (M^+, 8%), 244 (2), 232 (3), 217 (3), 201 (8), 154 (4) and 91 (100) (Found: M^+, 261.0975. $C_{14}H_{15}NO_4$ requires *M*, 261.1001) (Found: C, 64.4; H, 6.0; N, 5.5. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%).

(1*SR*,4*SR*,5*SR*)-6-(Benzyloxycarbonyl)-4-(prop-2-en-1-yl)-2-oxa-6-azabicyclo[3.3.0]octan-3-one 34

Butyllithium (0.62 ml of a 1.6 M solution in hexanes; 0.99 mmol) was slowly added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.21 ml, 0.99 mmol) in THF (10 ml) at −5 °C. After 0.25 h, the solution was cooled to −78 °C and a solution of the *cis*-fused lactone **33** (0.235 g, 0.9 mmol) in THF (1 ml) was added dropwise during 10 min. After 0.25 h, HMPA (0.31 ml, 1.8 mmol) was added followed, after a further 0.25 h, by allyl bromide (0.09 ml, 1.1 mmol). The resulting solution was stirred at −78 °C for 20 min then slowly warmed to ambient temperature and stirred for a further 1 h, before being passed through a pad of silica gel which was washed with THF. The filtrate was concentrated by rotary evaporation and the residue separated by CC [CH_2Cl_2–EtOAc (9:1)] to give (i) the *cis*-fused *propenyl lactone* **34** (0.140 g, 52%) as a colourless oil, R_F 0.72; ν_{max}/cm^{-1} 1775 and 1698; δ_H(400; 297 K) 1.85–2.01 (1H, m, C$H_a$$H_b$CH=), 2.28 (1H, dd, *J* 13.9 and 5.8, CH$_a$$H_b$CH=), 2.39–2.58 (2H, m, 8-CH_2), 2.75–2.85 (0.5H, m, 4-H), 2.90–3.05 (0.5H, m, 4-H), 3.40 (1H, ddd, *J* 11.1, 11.1 and 6.2, 7-H_a), 3.78 (0.5H, app. dd, *J* 10.5 and 10.5, 7-H_b), 3.87 (0.5H, app. dd, *J* 10.5 and 10.5, 7-H_b), 4.20 (0.5H, app. d, *J* 4.8, 5-H), 4.27 (0.5H, app. d, *J* 4.8, 5-H), 4.90–5.30 (5H, m, CH_2Ph, CH_2=CH and 1-H), 5.53–5.60 (0.5H, m, C*H*=CH_2), 5.75–5.95 (0.5h, m, C*H*=CH_2) and 7.35 (5H, s, Ph); δ_H(400; 333 K) 1.85–2.65 (4H, m, 8-CH_2 and CH_2CH=), 2.70–2.95 (1H, m, 4-H), 3.30–3.50 (1H, m, 7-H_a), 3.70–3.90 (1H, m, 7-H_b), 4.15–4.30 (1H, m,

5-H), 4.90–5.30 (5H, m, CH_2Ph, CH_2=CH and 1-H), 5.50–6.00 (1H, m, CH=CH_2) and 7.35 (5H, s, Ph); δ_C(400; 297 K) 30.2 and 30.7 (8-CH_2), 34.2 (*C*H_2CH=), 44.1 and 44.4 (7-CH_2), 46.8 and 47.8 (4-CH), 62.3 and 63.2 (5-CH), 67.2 and 67.7 (*C*H_2Ph), 81.8 and 82.8 (1-CH), 118.8 and 119.0 (=CH_2), 128.0, 128.2, 128.6 (all CH), 133.2 (=CH), 135.9 and 136.2 (C), 153.8 and 154.2 (NCO) and 177.5 and 177.8 (OCO); δ_C(400; 333 K) 30.7 (8-CH_2), 34.3 (*C*H_2CH=), 44.4 (7-CH_2), 47.3 (4-CH), 63.1 (5-CH), 67.5 (*C*H_2Ph), 82.1 (1-CH), 118.7 (=CH_2), 128.3, 128.6 (CH), 133.4 (=CH), 136.4 (C), 153.9 (NCO) and 177.3 (OCO); *m/z* 301 (M^+, 1%), 210 (28), 194 (3), 166 (5), 130 (17), 91 (100) and 68 (9) (Found: M^+, 301.1320. $C_{17}H_{19}NO_4$ requires *M*, 301.1313) (Found: C, 67.6; H, 6.5; N, 4.4. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.6%); (ii) the *dipropenyl lactone* **35** (0.007 g, 2%) as a colourless oil, R_F 0.71; ν_{max}/cm^{-1} 1769 and 1696; δ_H(400; 297 K) 1.80–2.60 (6H, m, 2 × CH_2CH= and 8-CH_2), 3.10–3.25 (0.5H, m, 7-H_a), 3.30–3.50 (0.5H, m, 7-H_a), 3.87–4.05 (0.5H, m, 7-H_b), 4.05–4.20 (0.5H, m, 7-H_b), 4.54 (0.5H, app. d, *J* 5.9, 5-H), 4.64 (0.5H, app. d, *J* 5.9, 5-H), 4.80–5.30 (7H, m, CH_2Ph, 2 × CH_2=CH and 1-H), 5.50–5.70 (1H, m, CH=CH_2), 5.70–5.95 (1H, m, CH=CH_2) and 7.35 (5H, s, Ph) and (iii) the *butenolide* **36** (0.007 g, 3%) as a colourless oil, R_F 0.38; ν_{max}/cm^{-1} 1760 and 1703; δ_H(400; 297 K) 1.50–1.80 (2H, m, 6-H_a and NH), 1.95–2.15 (1H, m, 6-H_b), 3.03 (2H, d, *J* 6.6, CH_2CH=), 3.30–3.49 (2H, m, CH_2N), 4.90–5.05 (1H, app. br d, *J* 17.0 CHO), 5.05–5.20 (4H, m, CH_2Ph and CH_2=CH), 5.75–5.95 (1H, m, CH=CH_2), 7.07 (1H, br s, CH=C) and 7.35 (5H, s, Ph).

(2*SR*,3*SR*,β*SR*)-1-(Benzyloxycarbonyl)-3-hydroxy-β-(prop-2-en-1-yl)pyrrolidine-2-ethanol 37a

To a vigorously stirred solution of the *cis*-fused propenyl lactone **34** (0.292 g, 0.98 mmol) in ethanol (10 ml) maintained at 0 °C was added sodium borohydride (0.070 g, 1.9 mmol). No further coolant was added and the mixture was stirred overnight then quenched with water (2 drops) and the solvent removed by rotary evaporation. The residual solid was taken up into chloroform (10 ml) and the solution washed with saturated aqueous ammonium chloride (3 × 5 ml) then dried and evaporated. Purification by CC (ether) afforded the cis-*diol* **37a** (0.258 g, 87%) as a colourless oil, ν_{max}/cm^{-1} 3408 and 1694; δ_H(400) 1.50–2.50 (5H, m, 4-CH_2, CH_2CH= and β-CH), 3.35–3.60 (3H, m, α-CH_2 and 5-H_a), 3.73 (1H, app. dd, *J* 11.2 and 2.6, 5-H_b), 3.90–4.10 (1H, app. br s, 3-H), 4.35–4.50 (1H, m, 2-H), 4.90–5.20 (4H, m, CH_2Ph and CH=CH_2), 5.65–5.95 (1H, m, CH=CH_2) and 7.36 (5H, s, Ph); δ_C(90) 33.6 (4-CH_2), 33.8 (*C*H_2CH=), 41.4 (β-CH), 45.8 (5-CH_2), 63.1 (2-CH), 63.6 (α-CH_2), 68.5 (*C*H_2Ph), 72.7 (3-CH), 117.5 (=CH_2), 129.3, 129.4, 129.9 (all CH), 137.9 (C), 138.4 (=CH) and 157.4 (NCO); *m/z* 305 (M^+, 3%), 220 (38), 214 (2), 196 (3), 170 (15), 107 (5), 91 (100), 86 (11) and 68 (7) (Found: M^+, 305.1651. $C_{17}H_{23}NO_4$ requires *M*, 305.1627).

(2*SR*,3*SR*,1′*SR*)-1-(Benzyloxycarbonyl)-3-[2-(trimethylsilyl)-ethoxymethoxy]-2-{[2-(trimethylsilyl)ethoxymethoxymethyl]-but-3′-en-1′-yl}pyrrolidine 37b

A solution of the foregoing diol **37a** (0.258 g, 0.8 mmol), 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl; 1 ml, 5.6 mmol) and *N*,*N*-diisopropylethylamine (1.5 ml, 8.5 mmol) in dichloromethane (2 ml) was stirred at 40 °C for 16 h and the solvent evaporated. CC of the residue [ether–petrol (1:1)] afforded the *bis-SEM-ether* **37b** (0.373 g, 78%) as a colourless oil, ν_{max}/cm^{-1} 1704; δ_H(90) 0.00 (18H, s, 2 × $SiMe_3$), 0.90 (2H, t, *J* 9.0, CH_2Si), 1.01 (2H, t, *J* 9.0, CH_2Si), 1.60–2.56 (5H, m, 4-CH_2, CH_2CH= and 1′-CH), 3.16–3.85 (8H, m, 2 × OCH_2-CH_2Si, CH_2OSEM and 5-CH_2), 3.93–4.44 (2H, m, 2- and 3-H), 4.44–5.21 (6H, m, 2 × OCH_2O and CH=CH_2), 5.10 (2H, s, CH_2Ph), 5.50–6.07 (1H, m, CH=CH_2) and 7.32 (5H, s, Ph); δ_C(90) −1.3 (2 × $SiMe_3$), 18.2 (2 × CH_2Si), 29.9 (4-CH_2), 33.4 (*C*H_2CH=), 39.0 (1′-CH), 44.3 (5-CH_2), 59.0 (2-CH), 64.9, 65.5 (both *C*$H_2$$CH_2Si$), 66.9 (*C*$H_2$Ph), 69.4 (*C*$H_2$OSEM), 77.1 (3-CH), 94.2, 95.0 (both OCH_2O), 115.4 (=CH_2), 128.0, 128.5 (both CH), 136.9 (C), 137.7 (=CH) and 155.5 (NCO); *m/z* 430 (3%), 322 (7), 286 (5), 260 (11), 91 (100) and 73 (62) (Found: C, 61.6; H, 9.2; N, 2.3. $C_{29}H_{51}NO_6Si_2$ requires C, 61.6; H, 9.1; N, 2.5%).

(2*SR*,3*SR*,γ*SR*)-1-(Benzyloxycarbonyl)-3-[2-(trimethylsilyl)-ethoxymethoxy]-γ-[2-(trimethylsilyl)ethoxymethoxymethyl]-pyrrolidine-2-propanol 38b

Sodium metaperiodate (0.30 g, 1.4 mmol) was added during 40 min to a vigorously stirred solution of the foregoing pyrrolidine **37b** (0.339 g, 0.60 mmol) and osmium tetroxide (10 mg) in ether (1.5 ml) and water (1.5 ml). The resulting suspension was stirred at ambient temperature for 16 h then the aqueous layer was separated and extracted with chloroform (3 × 1 ml). The combined organic solutions were passed through a pad of sodium sulfate and the solid washed with chloroform. The filtrates were concentrated to give the crude aldehyde **38a** (0.29 g, 85%) as a dark oil, ν_{max}/cm^{1} 1694; δ_H(90) 0.00 (18H, s, 2 × $SiMe_3$), 0.89 (4H, t, *J* 8.6, 2 × CH_2Si), 1.76–2.23 (2H, m, 4-CH_2), 2.32–2.62 (2H, m, α-CH_2), 2.62–3.09 (1H, m, β-CH), 3.09–3.86 (8H, m, 2 × OC$H_2$$CH_2Si$, C$H_2$OSEM and 5-$CH_2$), 3.86–4.64 (2H, m, 2- and 3-H), 4.57 (2H, s, OCH_2O), 4.66 (2H, s, OCH_2O), 5.10 (2H, s, CH_2Ph), 7.32 (5H, s, Ph) and 9.61 (1H, br s, CHO); δ_C(90) −1.3 (2 × $SiMe_3$), 18.2 (2 × CH_2Si), 29.5 (4-CH_2), 35.4 (β-*C*HCH_2), 43.9 (α-CH_2), 44.1 (5-CH_2), 58.7 (2-CH), 65.2, 65.8 (both *C*$H_2$$CH_2Si$), 67.2 (*C*$H_2$Ph), 68.0 (*C*$H_2$OSEM), 76.9 (3-CH), 94.1, 94.7 (both OCH_2O), 127.9, 128.4 (both CH), 135.9 (C), 155.1 (NCO) and 201.5 (CHO), which was reduced immediately without further purification.

To a stirred solution of the foregoing crude aldehyde **38a** (0.29 g, 0.5 mmol) in ethanol (5 ml) maintained at 0 °C was added sodium borohydride (0.04 g, 1.0 mmol). The resulting suspension was stirred for 0.5 h then quenched with water (0.5 ml) and ethanol evaporated. The solid residue was dissolved in chloroform (5 ml) and the solution was washed with saturated aqueous ammonium chloride (3 × 1 ml) then dried and evaporated. CC [$CHCl_3$–MeOH (95:5)] gave the *alcohol* **38b** (0.194 g, 67%) as a colourless oil, ν_{max}/cm^{-1} 3437 and 1694; δ_H(90) 0.00 (18H, s, 2 × $SiMe_3$), 0.90 (4H, t, *J* 8.5, 2 × CH_2Si), 1.36–1.76 (2H, m, β-CH_2), 1.76–2.16 (2H, m, 4-CH_2), 2.16–2.67 (1H, m, γ-CH), 3.15–3.89 (10H, m, 2 × OC$H_2$$CH_2Si$, C$H_2$OSEM and α- and 5-$CH_2$), 3.89–4.09 (1H, m, 3-H), 4.09–4.43 (1H, app. q, *J* 6.6, 2-H), 4.59 (2H, s, OCH_2O), 4.66 (2H, s, OCH_2O), 5.11 (2H, s, CH_2Ph) and 7.32 (5H, s, Ph); δ_C(90) −1.3 (2 × $SiMe_3$), 18.2 (2 × CH_2Si), 30.1 (4-CH_2), 33.1 (β-CH_2), 37.3 (γ-CH), 44.5 (5-CH_2), 60.9 (2-CH), 61.7 (CH_2OH), 65.3, 65.8 (both *C*$H_2$$CH_2Si$), 67.1 (*C*$H_2$Ph), 70.5 (*C*$H_2$OSEM), 77.4 (3-CH), 94.3, 95.0 (both OCH_2O), 128.0, 128.5 (both CH), 136.9 (C) and 155.5 (NCO) (Found: C, 59.0; H, 9.2; N, 2.3. $C_{28}H_{51}NO_7Si_2$ requires C, 59.0; H, 9.0; N, 2.5%).

(1*SR*,7*SR*,8*SR*)-1-(Hydroxymethyl-7-hydroxypyrrolizidine [(1*SR*,7*SR*,8*SR*)-turneforcidine] 31

Methanesulfonyl chloride (0.05 ml, 0.6 mmol) was added to an ice-cold solution of the foregoing alcohol **38b** (0.194 g, 0.34 mmol) and triethylamine (0.08 ml, 0.6 mmol) in dry dichloromethane (7 ml). The solution was stirred at 0 °C for 1 h then warmed to ambient temperature and the solvent evaporated. The residue was dissolved in ether, the solution washed with water (3 × 1 ml) then dried and evaporated. CC (ether) gave the methanesulfonate **38c** (0.197 g, 90%) as a colourless oil, R_F 0.9; ν_{max}/cm^{-1} 1699; δ_H(90) 0.00 (18H, s, 2 × $SiMe_3$), 0.91 (4H, t, *J* 7.7, 2 × CH_2Si), 1.66–2.56 (5H, m, γ-CH, β- and 4-CH_2), 2.94 (3H, s, SO_2Me), 3.24–3.92 (8H, m, 2 × OC$H_2$$CH_2Si$, C$H_2$OSEM and 5-$CH_2$), 3.92–4.94 (4H, m, 2- and 3-H and CH_2OSO_2), 4.59 (2H, s, OCH_2O), 4.66 (2H, s, OCH_2O), 5.10 (2H, s, CH_2Ph) and 7.33 (5H, s, Ph); δ_C(90) −1.3 (2 × $SiMe_3$), 18.2 (2 × CH_2Si), 29.4 (SO_2Me), 30.0 (4-CH_2), 36.0 (β-CH_2), 37.3 (γ-CH), 44.4 (5-CH_2), 59.8 (2-CH), 65.1, 65.7 (both

CH_2CH_2Si), 67.0 (CH_2Ph), 69.5 (CH_2OMs), 69.8 (CH_2OSEM), 77.2 (3-CH), 94.3, 94.9 (both OCH_2O), 128.0, 128.4 (both CH), 136.8 (C) and 155.5 (NCO), which was used without further purification.

To a vigorously stirred solution of the foregoing methanesulfonate **38c** (0.197 g, 0.3 mmol) in ethyl acetate (20 ml) was added lithium carbonate (0.045 g, 0.6 mmol; freshly recrystallised from water[28]) followed by 10% palladium on carbon (0.019 g). The resulting suspension was stirred at ambient temperature for 24 h under an atmosphere of hydrogen. The reaction mixture was then washed with saturated aqueous sodium hydrogen carbonate, filtered through diatomite, dried and evaporated. CC of the residue [$CHCl_3$–NH_4OH (9:1)] gave the pyrrolizidine **39** (0.119 g, 94%) as a colourless oil which was deprotected without further purification; R_F 0.4; ν_{max}/cm^{-1} 1103; δ_H(90) 0.00 (18H, s, 2 × $SiMe_3$), 0.94 (4H, t, *J* 8.2, 2 × CH_2Si), 1.53–2.24 (4H, m, 2- and 6-CH_2), 2.24–2.88 (4H, m, 3- and 5-CH_2), 2.98–3.41 (3H, m, 1-, 8- and α-H_a), 3.41–3.78 (5H, m, 2 × OCH_2CH_2Si and α-H_b), 3.98–4.20 (1H, m, 7-H), 4.62 (2H, s, OCH_2O) and 4.68 (2H, s, OCH_2O); δ_C(400) −1.3 (2 × $SiMe_3$), 18.1, 18.2 (both CH_2Si), 31.7, 34.6 (2- and 6-CH_2), 37.0 (1-CH), 52.0, 55.0 (3- and 5-CH_2), 65.2, 65.5 (both CH_2CH_2Si), 70.0 (CH_2OSEM), 72.6 and 76.2 (7- and 8-CH), 94.0 and 95.0 (both OCH_2O).

A solution of the foregoing pyrrolizidine **39** (0.110 g, 0.26 mmol) and tetrabutylammonium fluoride (0.82 ml of a 1 M solution in THF; 0.82 mmol) in THF (1 ml) was refluxed for 24 h and the solvent removed by rotary evaporation. CC of the residue [$CHCl_3$–MeOH–NH_4OH (5:5:1)] separated (±)-turneforcidine **31**[29,30] (0.011 g, 41%) as a colourless oil, R_F 0.22; ν_{max}/cm^{-1} 3396; δ_H(400) 1.85–2.05 (1H, m), 2.05–2.40 (3H, m), 2.70–2.90 (1H, m), 3.00–3.15 (1H, m), 3.15–3.40 (3H, m), 3.50–3.85 (3H, m), 3.90–4.10 (1H, m) and 4.30–4.40 (1H, m); δ_C(400) 31.1, 37.0 (both CH_2), 40.4 (CH), 53.5, 56.3, 63.7 (all 5-CH_2), 70.7 and 75.7 (both CH); *m/z* 157 (19%), 139 (5), 113 (23), 83 (14), 82 (100) and 55 (9) (Found: M^+, 157.1105. $C_8H_{15}NO_2$ requires *M*, 157.1103.

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