Rearrangement of ammonium ylides produced by intramolecular reaction of catalytically generated metal carbenoids. Part 2. Stereoselective synthesis of bicyclic amines

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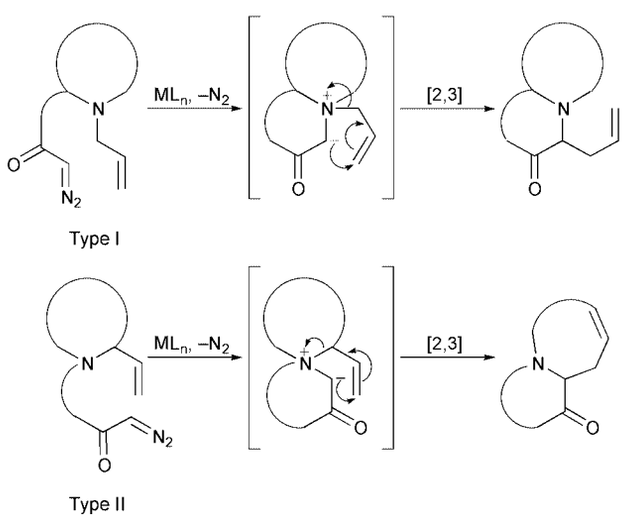
Ammonium ylides produced by intramolecular reaction of copper carbenoids tethered to cyclic allylic amines undergo [2,3]-rearrangement to deliver bicyclic amines. The reaction can be performed using a cyclic *N*-allylamine in which the diazo group is tethered adjacent to nitrogen, or a vinyl-substituted cyclic amine in which the diazo group is *N*-tethered to the ring. In the former type of reaction, stereoselective ylide formation and rearrangement usually delivers high levels of diastereocontrol. In the latter case, efficient 'chirality transfer' can be accomplished when the reaction is performed using an enantiomerically pure substrate. The reactions have been used to construct pyrrolizidine, indolizidine and quinolizidine systems, and the CE sub-unit found in the manzamine and ircinal alkaloids.

Introduction

In the preceding paper,[1] we demonstrated that simple five- to eight-membered cyclic amines can be prepared by [2,3]-sigmatropic rearrangement of cyclic allylic ammonium ylides produced upon *intramolecular* reaction of amines with catalytically generated copper carbenoids.[2,3] Although the yields of cyclic amine products were generally very good, low levels of diastereocontrol were obtained during the cyclisation of substrates possessing a stereogenic centre on the tether connecting the diazo ketone to the allylic amine.[1]

In order to identify applications of the reaction and address the issue of diastereocontrol, we investigated the intramolecular reaction of substrates in which the amine forms part of an existing ring (Scheme 1). Two classes of substrate were studied: one in which the diazo ketone group is tethered to the α-carbon of an *N*-allyl cyclic amine (Type I), and a second type in which the diazo carbonyl unit is attached to the nitrogen of an α-vinylic cyclic amine (Type II). For both types of substrate, [2,3]-sigmatropic rearrangement of the intermediate ammonium ylide should generate a bicyclic amine in which nitrogen is positioned at the ring junction. However, in the first case (Type I), the pre-existing ring and stereogenic centre would be preserved and an additional stereogenic centre would be created upon ylide rearrangement. In contrast, the ylide generated from the second class of substrate (Type II) should rearrange to give three-carbon ring-expansion of the original cyclic amine with concomitant loss of the original stereogenic centre and creation of a new stereogenic centre at the carbon that was formerly part of the ylide.



Scheme 1

Results and discussion

Pyrrolizidine,[4] indolizidine,[5] and quinolizidine†[5] alkaloids are widely distributed in nature, and frequently possess potent biological activity. In recent years, these natural products have become popular synthetic targets as a consequence of their bioactivity, moderate complexity and the diversity of possible synthetic strategies for their construction.[4,5]

It was apparent that treatment of Type I substrates with a suitable catalyst would result in tandem ammonium ylide formation and rearrangement to give a potentially stereoselective entry into pyrrolizidine, indolizidine and quinolizidine alkaloids, especially those bearing side chains of three-carbons or longer (Fig. 1). In order to establish the feasibility of the reaction and to determine the stereochemical outcome of these reactions, four diazo ketone Type I precursors were prepared.

The first cyclisation precursor, diazo ketone **5**, was prepared from (*S*)-proline by the route shown in Scheme 2. Treatment of (*S*)-proline with trifluoroacetic anhydride afforded the trifluoroacetamide **1**, and the α-diazo ketone **2** was then obtained in high yield by conversion of the *N*-protected amino acid **1** into the corresponding acid chloride and subsequent treatment with

† The IUPAC names for pyrrolizidine, indolizidine and quinolizidine are hexahydropyrrolizine, octahydroindolizine and octahydroquinolizine, respectively.

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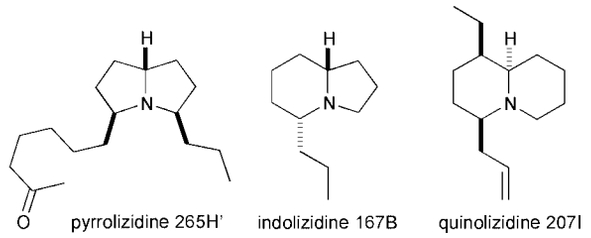
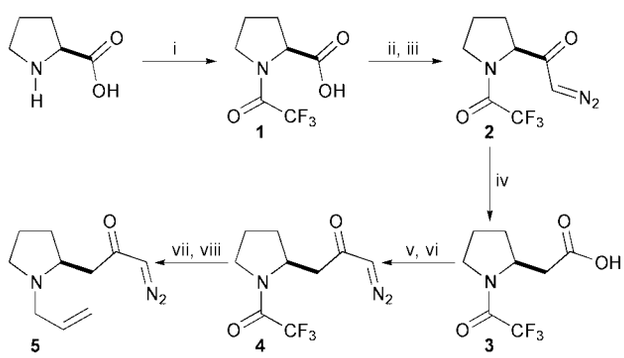


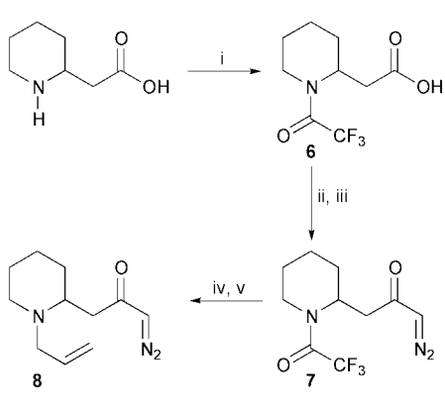
Fig. 1



Scheme 2 *Reagents and conditions*: (i), $(CF_3CO)_2O$, 0⟶80 °C (31%); (ii), $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (iii), CH_2N_2, Et_2O, 0 °C⟶rt (85%, 2 steps); (iv), $PhCO_2Ag$, dioxane–H_2O (2 : 1), 70 °C (84%); (v), $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (vi), CH_2N_2, Et_2O, 0 °C⟶rt (87%, 2 steps); (vii), $Ba(OH)_2$ aq., rt; (viii), CH_2CHCH_2Br, K_2CO_3, THF, rt (45%, 2 steps).

excess diazomethane. The homologated carboxylic acid **3** was obtained in 84% yield by treatment of the α-diazo ketone **2** with silver benzoate in aqueous dioxane to induce Wolff rearrangement.[6] The acid **3** was then converted into the α-diazo ketone **4** *via* the acid chloride in 87% yield over two steps. Subsequent removal of the trifluoroacetyl group was accomplished by hydrolysis of the amide **4** with a saturated aqueous solution of barium hydroxide,[1] and the resulting highly polar amine was immediately alkylated with allyl bromide to give the cyclisation precursor **5** in 45% yield over two steps.

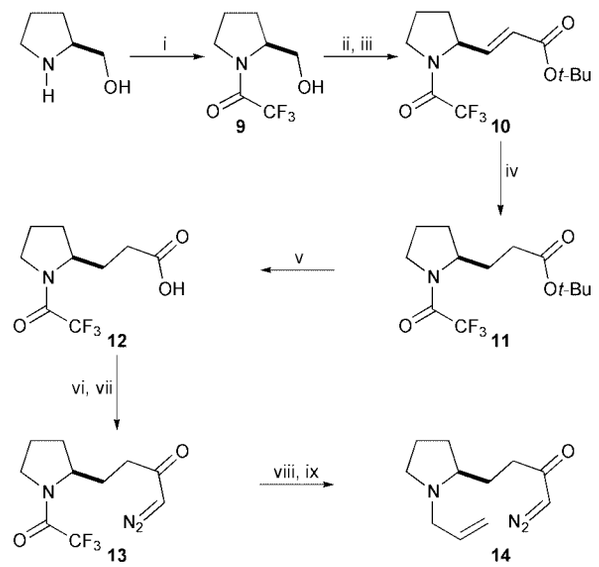
The synthesis of the cyclisation precursor **8** commenced from piperidinylacetic acid (Scheme 3), which was prepared by



Scheme 3 *Reagents and conditions*: (i), $(CF_3CO)_2O$, 0⟶80 °C (62%); (ii), $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (iii), CH_2N_2, Et_2O, 0 °C⟶rt (87%, 2 steps); (iv), K_2CO_3 aq., EtOH, rt; (v), CH_2CHCH_2Br, K_2CO_3, THF, rt (69%, 2 steps).

Jones oxidation of commercially available piperidinylethanol.[7] Treatment of the amino acid with trifluoroacetic anhydride afforded the *N*-protected amino acid **6** in reasonable yield. Conversion of the carboxylic acid **6** into the corresponding acid chloride and subsequent reaction with a large excess of diazomethane delivered the α-diazo ketone **7** in high yield. Removal of the trifluoroacetyl group was accomplished by hydrolysis with potassium carbonate in aqueous ethanol at room temperature, and the resulting polar amine was immediately treated with allyl bromide in the presence of potassium carbonate to give the allylic amine **8** in 69% yield over two steps. Although it was possible to purify the intermediate secondary amine prior to alkylation, the yield over two steps was significantly lower than that obtained when alkylation was performed directly on unpurified amine.

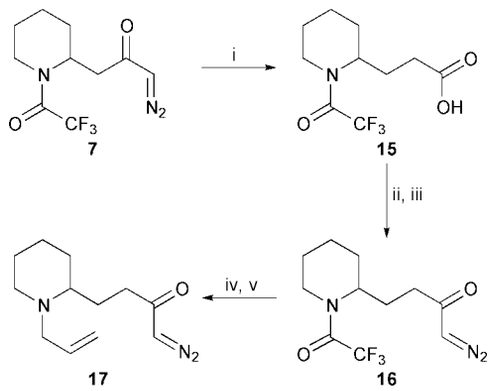
The cyclisation precursor **14** was prepared from (*S*)-prolinol, by the route shown in Scheme 4. (*S*)-Prolinol was first converted



Scheme 4 *Reagents and conditions*: (i), CF_3CO_2Et, Et_3N, MeOH, rt (84%); (ii), $(COCl)_2$, Me_2SO, CH_2Cl_2, Et_3N, −78 °C; (iii), $Bu^tO_2CCH_2P(O)(OEt)_2$, NaH, THF, 10 °C⟶rt (29%, 2 steps); (iv), Pd–C, H_2, MeOH–H_2O, rt (91%); (v), CF_3CO_2H, CH_2Cl_2, rt (91%); (vi), $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (vii), CH_2N_2, Et_2O, 0 °C⟶rt (93%, 2 steps); (viii), $Ba(OH)_2$ aq., rt; (ix), CH_2CHCH_2Br, K_2CO_3, THF, rt (32%, 2 steps).

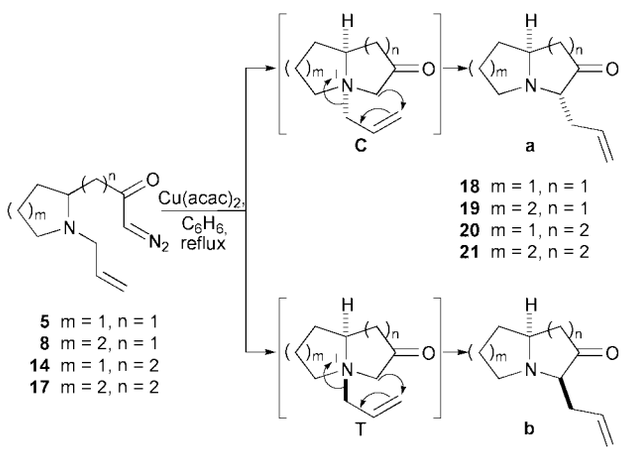
into the *N*-protected amino alcohol **9** in high yield by treatment with ethyl trifluoroacetate.[8] Swern oxidation and Horner–Emmons reaction of the resulting aldehyde with *tert*-butyl diethylphosphonoacetate delivered the α,β-unsaturated ester **10** in modest yield over two steps. Hydrogenation of the alkene using palladium on carbon at atmospheric pressure yielded the saturated ester **11** in high yield, and subsequent cleavage of the *tert*-butyl ester using trifluoroacetic acid gave the *N*-protected amino acid **12** in 91% yield. Conversion of the carboxylic acid **12** into the α-diazo ketone **13** *via* the acid chloride was achieved in an overall yield of 87%. The trifluoroacetyl group was then removed using a saturated aqueous solution of barium hydroxide, and the free amine was immediately alkylated with allyl bromide to give the required cyclisation precursor **14** in a 32% yield over two steps.

The final member of the Type I series of precursors was the α-diazo ketone **17** (Scheme 5). The synthesis of this compound commenced from the piperidine **7**, which had been used as an intermediate in the synthesis of the cyclisation precursor **8** (Scheme 3). Treatment of the α-diazo ketone **7** with silver(I) benzoate delivered an 83% yield of the homologated *N*-protected amino acid **15** resulting from Wolff rearrangement,[6] and the carboxylic acid was then converted into the α-diazo ketone **16** *via* the acid chloride in 91% yield (Scheme 5). *N*-Deprotection using a saturated aqueous solution of barium hydroxide proved to be unreliable and generally gave very low yields of the required amine. Removal of the trifluoroacetyl group with an aqueous solution of sodium hydroxide proved to be more satisfactory, but the overall yield for the deprotection and alkylation sequence was still modest. In spite of the rather low yield for the final step of the sequence, the route provided the cyclisation precursor **17** in sufficient quantities for study of the key cyclisation reaction.



Scheme 5 *Reagents and conditions*: (i), $PhCO_2Ag$, dioxane–H_2O (2 : 1), 70 °C (83%); (ii), $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C; (iii), CH_2N_2, Et_2O, 0 °C⟶rt (91%, 2 steps); (iv), 2 M NaOH, rt; (v), CH_2CHCH_2Br, K_2CO_3, THF, rt (18%, 2 steps).

Access to substantial quantities of the cyclisation precursors **5**, **8**, **14** and **17** by the routes outlined above allowed detailed exploration of the ammonium ylide formation and rearrangement reaction (Scheme 6). Treatment of the α-diazo ketone **5**



Substrate	Product ratio	Yield (%)
5	**18a** only	65
8	**19a** only	62
14	**20a**:**20b** 3.5:1	66
17	**21a**:**21b** 6:1/1:6	61

Scheme 6

with $Cu(acac)_2$ in benzene at reflux gave the pyrrolizidine **18a** in 65% yield with no evidence of formation of the diastereoisomeric product **18b**. When $Rh_2(OAc)_4$ was employed as the catalyst, the pyrrolizidine **18a** was isolated as the sole identifiable product, but in slightly lower yield (55%).

The exclusive formation of the isomer **18a** can be explained by preferential formation of the *cis*-fused bicyclic ammonium ylide **C** (n = 1, m = 1) rather than the *trans*-fused bicyclic ylide **T** (n = 1, m = 1). [2,3]-Sigmatropic rearrangement of the ammonium ylide **C** (n = 1, m = 1) is stereospecific and delivers the pyrrolizidine **18a** exclusively. Clearly, it is not possible for the intermediate ammonium ylide **C** (n = 1, m = 1) to adopt the transition state geometry necessary for concerted [2,3]-rearrangement to produce the isomer **18b**.

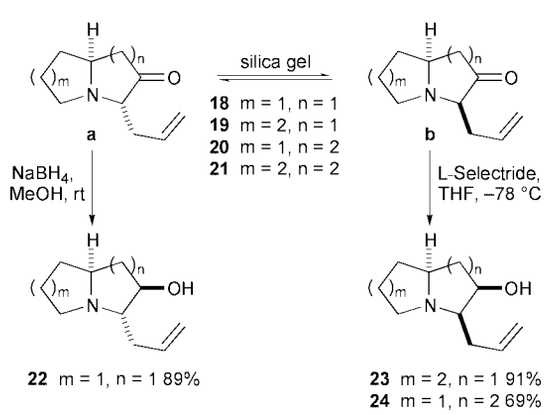
Treatment of the α-diazo ketone **8** with $Cu(acac)_2$ in benzene at reflux delivered a mixture (4 : 1) of the diastereoisomeric products **19a** and **19b** in a combined yield of 62% after purification by chromatography on silica gel. Analysis of the unpurified reaction mixture by ^{1}H NMR revealed that the isomer **19a**, derived from the ammonium ylide **C** (n = 2, m = 1), was produced exclusively during the reaction and suggested that the isomer **19b** was produced by partial epimerisation of isomer **19a** during purification. In order to confirm that epimerisation was occurring, a diethyl ether solution of a mixture (4 : 1) of isomers **19a** and **19b** was exposed to silica gel. Complete epimerisation of the indolizidinone **19a** was observed after 23 hours, and the isomeric compound **19b** was obtained as the sole product in 72% yield. This experiment confirmed that the kinetically favoured indolizidinone **19a** undergoes epimerisation when exposed to silica gel and demonstrated that the indolizidinone **19b** is the thermodynamically favoured epimer.

Cyclisation of the α-diazo ketone **14** was accomplished by treatment with $Cu(acac)_2$ in benzene at reflux (Scheme 6). Analysis of the unpurified reaction product by ^{1}H NMR revealed that a mixture (3.5 : 1) of the indolizidinone diastereoisomers **20a** and **20b** had been produced. In this case, cyclisation occurred to give mainly the ammonium ylide **C** (m = 1, n = 2), and this intermediate rearranged to deliver the indolizidinone **20a** as the major product. However, upon purification of the reaction mixture by chromatography on silica gel, the indolizidinone **20b** was obtained as the sole product in 66% yield. As in the previous case, the kinetically favoured diastereoisomer **20a** underwent complete epimerisation to give the thermodynamically favoured diastereoisomer **20b** upon exposure to silica gel.

Treatment of the final substrate in the series, diazo ketone **17**, with $Cu(acac)_2$ in benzene at reflux afforded a mixture (6 : 1 or 1 : 6) of two diastereoisomeric quinolizidinones **21a** and **21b** in a combined yield of 61%. Although the isomers were separable by column chromatography on neutral alumina, it was not possible to deduce the relative configuration of the major or minor isomer by ^{1}H NMR or X-ray crystallography.

Overlapping signals in the ^{1}H NMR spectra for compounds **18**–**21a**–**b** precluded unambiguous stereochemical assignment by analysis of coupling constant data or by NOE difference spectroscopy. Consequently, it was necessary to employ X-ray crystallography in order to establish the relative configurations of the stereogenic centres in the cyclisation products.

The ketones **18**–**21a**–**b** were liquids at room temperature and so crystalline derivatives suitable for X-ray analysis were prepared. Fortunately, stereoselective ketone reduction afforded a solid alcohol in each case (Scheme 7). For example, reduction of



Scheme 7

the pyrrolizidinone **18a** using sodium borohydride gave the crystalline amino alcohol **22** as a single isomer in 89% yield. Crystals of the alcohol **22** were suitable for X-ray analysis,‡ and the relative stereochemistry was determined unambiguously to be that shown in Scheme 6. The result confirmed that the pyrrolizidinone **18a** is the product arising from cyclisation of the α-diazo ketone **5**.

‡ CCDC reference numbers for alcohols **22**–**24** 172675–172677. See http://www.rsc.org/suppdata/p1/b1/b108182a/ for crystallographic data in .cif or other electronic format.

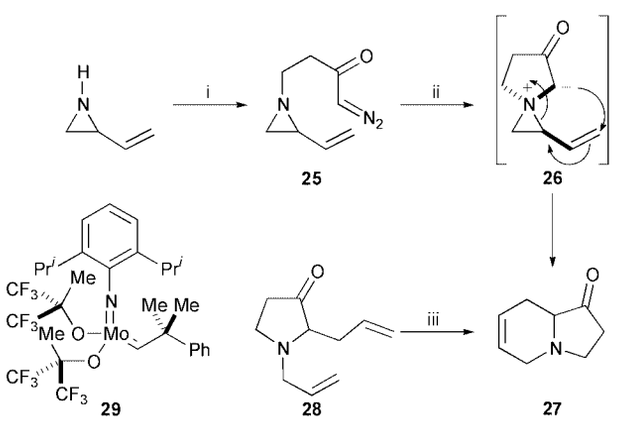
L-Selectride® reduction of the indolizidinone **19b** at low temperature provided the crystalline alcohol **23** as the sole product in 91% yield (Scheme 7). The relative stereochemistry of the alcohol **23** was established by X-ray analysis,‡ which confirmed that the indolizidinone **19b** is thermodynamically favoured and the isomer **19a** is produced upon cyclisation of the α-diazo ketone **8**.

Low temperature reduction of the indolizidinone **20b** with L-Selectride® provided the crystalline alcohol **24** as the sole product in 69% yield, and the relative configuration was established by X-ray crystallography.‡ In this case, cyclisation of the α-diazo ketone **14** affords the indolizidinone **20a** as the major product and the indolizidinone **20b** is the thermodynamically favoured diastereoisomer.

Attempts to determine the relative configuration of the quinolizidinone **21a**–**b** resulting from cyclisation of the α-diazo ketone **17** proved to be unsuccessful. Reduction of the major isomer with L-Selectride® afforded a single solid amino alcohol in 70% yield, but all attempts to recrystallise this compound failed to deliver crystals suitable for X-ray analysis. Consequently, the relative stereochemistry of the major isomer **21a**–**b** obtained upon cyclisation of the α-diazo ketone **17** was not determined unambiguously.

The successful diastereoselective synthesis of pyrrolizidine, indolizidine, and quinolizidine systems by copper-catalysed reaction of Type I substrates, encouraged us to investigate the complementary reactions of Type II substrates in which ring-expansion of the original cyclic amine was expected to occur. A vinylaziridine system was deemed to be a particularly attractive precursor because ring-expansion would be facilitated by the inherent ring strain. In fact, Coldham and Somfai had already shown that vinylaziridines undergo efficient conversion into substituted piperidines by a related base-promoted [2,3]-aza-Wittig rearrangement reaction.[9]

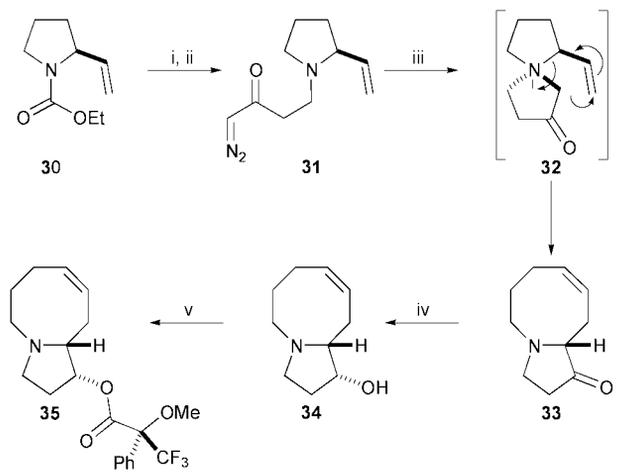
The cyclisation precursor **25** was prepared from 2-vinylaziridine by the route shown in Scheme 8. The starting material, 2-vinylaziridine, was obtained from butadiene monoxide using the procedure of Stogryn and Brois,[10] and reaction of this with 4-bromo-1-diazobutan-2-one[1,11] in the presence of triethylamine afforded the cyclisation precursor **25** in 53% yield. Treatment of the substrate with a sub-stoichiometric amount (2 mol%) of $Cu(acac)_2$ in benzene at reflux afforded a 24% yield of the indolizidine **27** resulting from [2,3]-rearrangement of the presumed spirocyclic ammonium ylide **26**. The modest yield of the indolizidine **27** can be attributed to its instability (substantial decomposition occurred within one day when it was stored under argon at −30 °C).



Scheme 8 *Reagents and conditions*: (i), $Br(CH_2)_2COCHN_2$, Et_3N, EtOAc, 60 °C (53%); (ii), $Cu(acac)_2$ (2 mol%), C_6H_6, reflux (24%); (iii), **29** (15 mol%), pentane, rt (55%).

To confirm the identity of the cyclisation product, the indolizidine **27** was prepared by ring-closing metathesis[12] of the diene **28**.[1] Treatment of the diene **28** with the molybdenum complex **29**[13] in pentane afforded the same product (55% yield) as obtained from copper-catalysed reaction of the diazo ketone **25**. The lower reaction temperature required for the ring-closing metathesis reaction probably accounts for the higher yield with respect to the ring-expansion reaction. Interestingly, attempted ring-closing metathesis of the diene **28** using the catalyst $Cl_2Ru(PCy_3)_2CHPh$ failed to deliver any of the indolizidine **27**, a finding which is in accord with the known incompatibility of the ruthenium metathesis catalyst with tertiary amines.[14]

The second Type II cyclisation reaction to be studied was that of the diazo ketone **31**. The precursor was prepared from the *N*-protected vinylpyrrolidine **30** (Scheme 9), which was obtained from (*S*)-prolinol by a literature route involving sequential carbamate formation, Parikh–Doering oxidation and methylenation.[15] Carbamate cleavage was accomplished by treatment of the vinylpyrrolidine **30** with a mixture of potassium hydroxide and hydrazine monohydrate in ethylene glycol at reflux (Scheme 9). The unpurified amine was then treated with 4-bromo-1-diazobutan-2-one in the presence of triethylamine to deliver the cyclisation precursor **31** in 55% yield over two steps. Exposure of the α-diazo ketone **31** to $Cu(acac)_2$ in benzene at reflux afforded the bicyclic amine **33** as the sole isolable product in 56% yield.



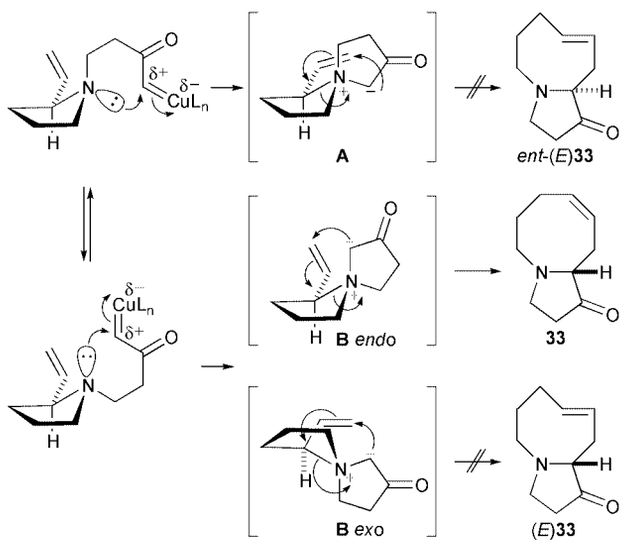
Scheme 9 *Reagents and conditions*: (i), KOH, $H_2NNH_2{\cdot}H_2O$, $HO(CH_2)_2OH$, reflux; (ii), $Br(CH_2)_2COCHN_2$, Et_3N, EtOAc, 60 °C (55%, 2 steps); (iii), $Cu(acac)_2$ (2 mol%), C_6H_6, reflux (56%); (iv), L-Selectride®, THF, 0 °C⟶rt (75%); (v), (*R*)-Ph(OMe)(CF_3)CCOCl, DMAP, Et_3N, CH_2Cl_2, 0 °C.

At this stage, it was unclear whether rearrangement had resulted in formation of an *E*- or *Z*-alkene. The alkene geometry was determined by NMR analysis of the alcohol **34** obtained by stereoselective reduction of the ketone **33** using L-Selectride®. The ^1H NMR spectrum of the alcohol **34** in D_6-benzene contained two distinct alkene multiplets corresponding to the vinylic hydrogens, and it was possible to extract the alkene *J* value of 10 Hz. ^1H NMR analysis of the crude product from cyclisation reaction of the α-diazo ketone **31** indicated that a very small amount of another alkene was produced (vinylic multiplet at 5.90 ppm, *J* 17 Hz), suggesting that some of the *E*-alkene product (*E*)-**33** may be produced upon ammonium ylide rearrangement. However, the minor product has insufficient stability to survive chromatography. The isolation of the *Z*-alkene as the sole product from our cyclisation reactions is consistent with results reported by Vedejs for the ring expansion of related ylides derived from ammonium salts of vinylpyrrolidines.[16]

The second stereochemical issue was whether efficient transfer of stereochemical information had occurred during rearrangement of the putative intermediate ammonium ylide **32**.[17] To eliminate the possibility of partial racemisation of the bicyclic amine **33** prior to determination of enantiomeric

purity, the ketone was reduced with L-Selectride® prior to purification. The enantiomeric excess of the resulting amino alcohol **34** was then determined by NMR analysis of the ester **35** produced upon reaction with excess (*R*)-Mosher's acid chloride (Scheme 9). Although ^{1}H NMR analysis of the crude Mosher ester was inconclusive, complete separation of the signals corresponding to the two diastereoisomers was observed in the ^{19}F NMR spectrum. The ^{19}F NMR analysis indicated the presence of less than 1% of the minor diastereoisomer, indicating an ee of >98%. A diastereoisomeric mixture of Mosher esters was also prepared from a racemic mixture of alcohol **34**. This confirmed that the observed peaks in the ^{19}F NMR spectrum corresponded to the two diastereoisomers and demonstrated that kinetic resolution during esterification of the alcohol **34** had not distorted the analysis.

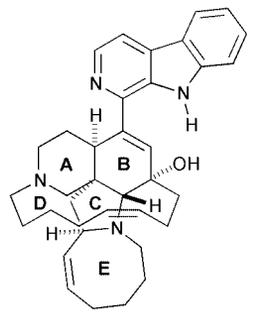
Remarkably, there is virtually complete transfer of stereochemical information during rearrangement of the spiro-fused ammonium ylide **32**, even though the original stereogenic centre is destroyed in the process. Although efficient transfer of stereochemical information during the [2,3]-rearrangement of ylides possessing an adjacent stereogenic centre or a stereogenic heteroatom is known,[17] the situation is complicated by the fact that two diastereoisomeric ylides (**A** and **B**) can be produced by reaction of the copper carbenoid with each nitrogen invertomer (Scheme 10). The ylide **B** can undergo rearrangement to give the



Scheme 10

bicyclic compound **33** *via* a transition state in which the vinyl group is positioned *endo* to the newly formed ring, or (*E*)-**33** *via* a transition state in which the vinyl group lies *exo* to the new ring. The ylide **A** can rearrange to give only *ent*-(*E*)-**33** because geometric constraints preclude attainment of the transition state required for formation of the *Z*-isomer (*ent*-**33**). The outcome of the reaction suggests the bicyclic product **33** results from *endo* rearrangement of the ylide (**B**) produced by reaction of the carbenoid with the amine from the face of the pyrrolidine which presents the vinyl group. An analogous result was obtained by Naidu and West during their synthesis of the alkaloid (−)-epilupinine by [1,2]-rearrangement of an ammonium ylide.[3b,3d] In that case, a spiro-fused bicyclic ylide was generated by attack of a carbenoid from the more hindered side of the pyrrolidine. McMills and co-workers have shown that a related enantiomerically pure α-diazo ester tethered 2-vinylpyrrolidine undergoes ammonium ylide formation and [2,3]-rearrangement with ring-expansion to produce an oxazabicyclo[6.4.0]dodecane in reasonable yield and with high ee.[18]

The six-step enantioselective synthesis of the azabicyclo[6.3.0]undecene **33** from (*S*)-prolinol constitutes a short, efficient and novel chiral-pool route to a model for the CE sub-unit



manzamine A

Fig. 2

found in many members of the manzamine and ircinal families of alkaloids (*e.g.*, manzamine A, Fig. 2).[19] The manzamines and ircinals are complex polycyclic natural products of marine origin, which possess significant cytotoxic, antileukemic and antibacterial activity.[19] The formidable synthetic challenges presented by the manzamines and ircinals coupled with their significant biological activity has stimulated the development of many approaches to these alkaloids.[20] However, only recently has this work culminated in total syntheses of some of these alkaloids,[21] and they remain important synthetic targets.

In summary, we have shown that ammonium ylides derived from copper carbenoids generated from Type I and Type II substrates undergo [2,3]-rearrangement to deliver bicyclic amines in a stereoselective manner (Scheme 1). Reactions of this type can be used to construct the core structures of pyrrolizidine, indolizidine and quinolizidine alkaloids, and a model for the CE sub-unit found in many manzamine and ircinal alkaloids.

Experimental

General

Air and/or moisture sensitive reactions were performed under an atmosphere of nitrogen in oven or flame dried apparatus. Organic solvents and reagents were dried and distilled using standard methods: tetrahydrofuran (potassium–benzophenone ketyl), diethyl ether (sodium metal–benzophenone ketyl), methanol (magnesium methoxide), ethyl trifluoroacetate (anhydrous calcium chloride), allyl bromide (anhydrous magnesium sulfate), benzene, dichloromethane and triethylamine (calcium hydride). All other solvents and reagents were used as received from commercial suppliers. All reactions were monitored by thin layer chromatography using plastic- or aluminium-backed silica gel 60 F_{254} plates. Thin layer chromatography plates were viewed under UV light or were visualised using either basic potassium permanganate solution or acidic ethanolic anisaldehyde solution. Flash column chromatography was performed using Merck 7734 grade silica gel or Fluka silica gel 60 (220–440 mesh). Melting points were determined using either Büchi 510 or Reichert hot-stage melting point apparatus. IR spectra were recorded as potassium bromide disks, as liquid films on sodium chloride plates, or as solutions in chloroform, using either a Perkin-Elmer 1720X or 1600 series FTIR spectrometer. ^{1}H NMR spectra were recorded using a Bruker DRX500 (500 MHz), AM400 (400 MHz) or WM250 (250 MHz) spectrometer. ^{1}H NMR data are expressed as chemical shifts in ppm from an internal standard of tetramethylsilane followed by the number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad), coupling constant(s) *J* (Hz), and assignment. ^{13}C NMR spectra were recorded using a JEOL EX270 (67.5 MHz), Bruker AM400 (100 MHz) or Bruker DRX500 (125 MHz) instrument and multiplicities were obtained using a DEPT sequence. ^{13}C NMR chemical shifts are

expressed in parts per million downfield from tetramethylsilane or the sodium salt of 3-(trimethylsilyl)propanesulfonic acid. High resolution mass spectra (HRMS) were obtained using an AEI MS902 or VG Micromass 70E mass spectrometer, using electron impact (EI), chemical ionisation (CI) or fast-atom bombardment (FAB). Microanalysis was performed by the microanalysis section of the School of Chemistry, University of Nottingham. Optical rotations were recorded using a JASCO DIP-370 digital polarimeter and are reported as $[\alpha]_D$ expressed in 10^{-1} deg cm^2 g^{-1} (concentration g cm^{-3}, solvent, temperature °C).

General procedure for the preparation of α-diazo ketones

Oxalyl chloride was added dropwise to a solution of the carboxylic acid in dry dichloromethane at room temperature or 0 °C. A few drops of dry dimethylformamide were added, and the resulting mixture was stirred at room temperature or 0 °C for the time indicated. The solvent was removed *in vacuo* and the residue dissolved in dry diethyl ether. The ethereal solution was added slowly to a solution of diazomethane in diethyl ether at 0 °C, and the resulting solution was stirred at 0 °C and then at room temperature. The remaining diazomethane was consumed by dropwise addition of glacial acetic acid and the solution was neutralised with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and aqueous phase extracted with diethyl ether. The combined organic extracts were dried and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the *α-diazo ketone*.

(*S*)-(−)-1-Trifluoroacetylpyrrolidine-2-carboxylic acid 1. Trifluoroacetic anhydride (19.0 g, 90.5 mmol) was added dropwise over 5 min to (*S*)-proline (8.0 g, 69 mmol) with vigorous stirring at 0 °C. The mixture was stirred at 0 °C for 10 min then heated at 80 °C for 2 h. The mixture was then diluted with 2 M hydrochloric acid (100 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The residue purified by flash column chromatography on silica gel (hexane–diethyl ether, 1 : 1) to give the *amide* **1** (4.6 g, 31%) as colourless needles; mp 47–49 °C [lit.,[22] 46–48 °C]; $[\alpha]_D^{24}$ −1.6 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3159, 2898, 1764, 1726, 1693; δ_H (400 MHz, $CDCl_3$) δ 4.60–4.56 (1H, m, NCHCO), 3.83–3.73 (2H, m, NCH_2), 2.33–1.95 (4H, m, NCH_2CH_2 and $NCHCH_2$); δ_C (67.8 MHz, $CDCl_3$) 176.3 (CO_2H), 156.2 (CON, q, $^2J_{FC}$ 38), 116.1 (CF_3, q, $^1J_{FC}$ 287), 60.0 (CH), 59.2 (CH), 48.2 (CH_2), 47.3 (CH_2), 31.6 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 21.1 (CH_2); *m/z* (EI) 211.0461 (M^+. $C_7H_8F_3NO_3$ requires 211.0456), 211 (M^+, 4%), 166 (100), 114 (3) (Found C, 39.8; H, 3.8; N, 6.5. $C_7H_8F_3NO_3$ requires C, 39.8; H, 3.8; N, 6.6%).

(*S*)-(−)-2-(2-Diazoacetyl)-1-trifluoroacetylpyrrolidine 2. Following the general procedure, the acid chloride was prepared by the reaction of the *N*-protected amino acid **1** (2.0 g, 9.5 mmol) with oxalyl chloride (4.8 g, 38 mmol) and dry dimethylformamide (two drops) in dry dichloromethane (50 cm^3) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The acid chloride was dissolved in dry dichloromethane (20 cm^3) and added to a solution of diazomethane (~40 mmol) in diethyl ether (100 cm^3) at 0 °C, and the mixture was allowed to warm to room temperature over 2 h. The remaining diazomethane was consumed with glacial acetic acid (2.80 cm^3, 49.0 mmol). Purification by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) afforded the *α-diazo ketone* **2** (1.9 g, 85%) as a yellow solid; mp 42–44 °C; $[\alpha]_D^{24}$ −4.6 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3116, 2956, 2898, 2113, 1693, 1651; δ_H (400 MHz, $CDCl_3$) 5.44 (1H, br s, CHN_2), 4.62–4.53 (1H, m, NCHCO), 3.82–3.75 (2H, m, NCH_2), 2.23–2.01 (4H, m, NCH_2CH_2 and $NCHCH_2$); δ_C (67.8 MHz, $CDCl_3$) 191.1 (CO), 155.7 (CON, q, $^2J_{FC}$ 38), 116.0 (CF_3, q, $^1J_{FC}$ 288), 64.1 (CH), 63.7 (CH), 53.9 (CH), 53.1 (CH), 48.2 (CH_2), 47.3 (CH_2), 31.7 (CH_2), 28.3 (CH_2), 24.7 (CH_2), 20.8 (CH_2); *m/z* (FAB) 236.0627 (M^+ + H. $C_8H_8F_3N_3O_2$ requires 236.0647), 236 (M^+ + H, 23%), 208 (100).

(*S*)-(+)-(1-Trifluoroacetylpyrrolidin-2-yl)ethanoic acid 3. Silver benzoate (0.19 g, 0.83 mmol) was added to a solution of the α-diazo ketone **2** (4.0 g, 17 mmol) in a mixture of 1,4-dioxane (165 cm^3) and water (85 cm^3). The mixture was heated at 70 °C for 3 h and then concentrated *in vacuo*. The residue was dissolved in a saturated aqueous solution of sodium bicarbonate (100 cm^3) and extracted with diethyl ether (2 × 100 cm^3). The aqueous layer was acidified with 2 M hydrochloric acid then extracted with diethyl ether (2 × 100 cm^3), and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane–diethyl ether, 1 : 1) to give the *carboxylic acid* **3** (3.2 g, 84%) as a white solid; mp 51–53 °C; $[\alpha]_D^{23}$ +2.3 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3196, 2897, 1714, 1603; δ_H (500 MHz, $CDCl_3$) 4.48–4.44 (1H, m, $NCHCH_2CO$), 3.70–3.66 (2H, m, NCH_2), 3.05 (1H, dd, *J* 16.2 and 3.6, 1 × CH_2CO), 2.51 (1H, dd, *J* 16.2 and 9.3, 1 × CH_2CO), 2.23–2.15 (1H, m, 1 × NCH_2CH_2 or $NCHCH_2$), 2.10–1.95 (2H, m, 1 × NCH_2CH_2 and 1 × $NCHCH_2$), 1.90–1.83 (1H, m, 1 × NCH_2CH_2 or $NCHCH_2$); δ_C (67.8 MHz, $CDCl_3$) 176.4 (CO_2H), 155.6 (CON, q, $^2J_{FC}$ 37), 116.0 (CF_3, q, $^1J_{FC}$ 287), 55.7 (CH), 47.0 (CH_2), 36.3 (CH_2), 29.4 (CH_2), 24.0 (CH_2); *m/z* (EI) 225.0610 (M^+. $C_8H_{10}F_3NO_3$ requires 225.0613), 225 (M^+, 9%), 179 (36), 166 (100), 69 (31).

(*S*)-(−)-1-Diazo-3-(1-trifluoroacetylpyrrolidin-2-yl)propan-2-one 4. Following the general procedure, the acid chloride was prepared by the reaction of the *N*-protected amino acid **3** (2.9 g, 13 mmol) with oxalyl chloride (4.5 cm^3, 52 mmol) and dry dimethylformamide (two drops) in dry dichloromethane (60 cm^3) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The acid chloride was dissolved in dry dichloromethane (25 cm^3) and added to a solution of diazomethane (~48 mmol) in diethyl ether (200 cm^3) at 0 °C, and the mixture was allowed to warm to room temperature over 2 h. The remaining diazomethane was consumed with glacial acetic acid (2.80 cm^3, 49.0 mmol). Purification by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) afforded the *α-diazo ketone* **4** (2.8 g, 87%) as a yellow solid; mp 37–39 °C; $[\alpha]_D^{24}$ −2.1 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3115, 2953, 2899, 2110, 1681, 1643; δ_H (250 MHz, $CDCl_3$) 5.33 (1H, br s, CHN_2), 4.37–4.30 (1H, m, $NCHCH_2CO$), 3.58–3.46 (2H, m, NCH_2), 2.90 (1H, m, 1 × CH_2CO), 2.34 (1H, dd, *J* 14.7 and 9.5, 1 × CH_2CO), 2.12–1.80 (4H, m, NCH_2CH_2 and $NCHCH_2$); δ_C (67.8 MHz, $CDCl_3$) 191.6 (CO), 190.6 (CO), 155.2 (CON, q, $^2J_{FC}$ 37), 115.9 (CON, q, $^1J_{FC}$ 288), 56.1 (CH), 55.0 (CH), 46.8 (CH_2), 46.7 (CH_2), 42.2 (CH_2), 30.9 (CH_2), 29.1 (CH_2), 24.0 (CH_2), 19.9 (CH_2); *m/z* (FAB) 250.0818 (M^+ + H. $C_9H_{11}F_3N_3O_2$ requires 250.0803), 250 (M^+ + H, 73%), 222 (100), 180 (5), 166 (41), 83 (10) (Found C, 43.4; H, 4.0; N, 16.6. $C_9H_{10}F_3N_3O_2$ requires C, 43.4; H, 4.0; N, 16.9%).

(*S*)-(−)-1-(1-Allylpyrrolidin-2-yl)-3-diazopropan-2-one 5. The α-diazo ketone **4** (1.0 g, 4.0 mmol) was dissolved in a saturated aqueous solution of barium hydroxide (30 cm^3) and stirred at room temperature for 1 h. The solution was then extracted with ethyl acetate (2 × 50 cm^3). The aqueous phase was concentrated to dryness *in vacuo* and the residue washed with ethyl acetate (2 × 30 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was dissolved in dry tetrahydrofuran (40 cm^3) and potassium carbonate (1.4 g, 10 mmol) was added followed by allyl bromide (0.7 g, 6 mmol). The mixture was stirred at room

temperature for 24 h. The solvent was then removed *in vacuo* and the residue diluted with a saturated aqueous solution of sodium bicarbonate (30 cm^3) and extracted with ethyl acetate (3 × 30 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1% triethylamine in diethyl ether) to give the *amine* **5** (0.35 g, 45%) as a yellow liquid; $[\alpha]_D^{24}$ −6.9 (*c* 1.05, $CHCl_3$); ν_{max}(film)/cm^{-1} 3079, 2967, 2875, 2805, 2104, 1634, 997, 921; δ_H (400 MHz, $CDCl_3$) 5.89 (1H, dddd, *J* 17.1, 10.2, 7.5 and 5.7, C*H*=CH_2), 5.36 (1H, br s, CHN_2), 5.20 (1H, dd, *J* 17.1 and 1.0, *trans* CH=CH_2), 5.11 (1H, d, *J* 10.2, *cis* CH=CH_2), 3.40 (1H, dd, *J* 10.4 and 5.6, 1 × CH_2CH=CH_2), 3.09–3.02 (1H, m, NC*H*-CH_2CO), 2.88–2.77 (2H, m, 1 × NCH_2CH_2 and 1 × CH_2CH=CH_2), 2.68–2.60 (1H, m, 1 × NCH_2CH_2), 2.34–2.17 (2H, m, CH_2CO), 2.08–1.98 (1H, m, 1 × $NCH_2CH_2CH_2$), 1.82–1.68 (2H, m, 1 × NCH_2CH_2 and 1 × $NCH_2CH_2CH_2$), 1.57, 1.43 (1H, m, 1 × NCH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 193.7 (CO), 135.9 (CH), 117.0 (CH_2), 60.6 (CH), 57.3 (CH_2), 55.1 (CH), 53.7 (CH_2), 45.9 (CH_2), 30.8 (CH_2), 22.2 (CH_2); *m*/*z* (CI, NH_3) 194.1287 (M^+ + H. $C_{10}H_{16}N_3O$ requires 194.1293), 194 (M^+ + H, 55%), 165 (20), 110 (100), 83 (16%).

2-(Piperidin-2-yl)ethanoic acid. 2-(Piperidin-2-yl)ethanol (5.00 g, 38.7 mmol) was suspended in water (10 cm^3) and the mixture cooled to 0 °C. A solution of chromium trioxide (10.0 g, 100 mmol) and concentrated sulfuric acid (20 g) in water (150 cm^3) was added dropwise over 1 h 15 min. The resulting solution was stirred at 0 °C for 2 h 15 min and at room temperature for 13 h. After this time, the solution was diluted with water and basified with solid barium hydroxide. Excess barium hydroxide was converted to the carbonate by passage of carbon dioxide and this was removed by filtration through Celite. The aqueous solution was concentrated *in vacuo*, and the residue recrystallised from methanol–diethyl ether to give (piperidin-2-yl)ethanoic acid (3.77 g, 68%) as a white solid; mp 217–219 °C [lit.,[7] 217–218 °C]; ν_{max}(KBr)/cm^{-1} 3424, 2954, 1644; δ_H (250 MHz, D_2O) 3.46–3.30 (2H, m, 1 × NCH_2 and NC*H*CH_2CO), 3.07–2.93 (1H, m, 1 × NCH_2), 2.49 (2H, d, *J* 6.7, CH_2CO), 2.00–1.75 (3H, m, $NCHCH_2CH_2$ and 1 × NCH_2CH_2), 1.75–1.41 (3H, m, 1 × NCH_2CH_2 and NCH_2-CH_2CH_2); δ_C (67.8 MHz, D_2O) 178.3 (CO_2H), 55.3 (CH), 45.4 (CH_2), 40.9 (CH_2), 29.0 (CH_2), 22.8 (CH_2), 22.4 (CH_2) (Found C, 58.6; H, 9.3; N, 9.6. $C_7H_{13}NO_2$ requires C, 58.7; H, 9.2; N, 9.8%).

2-(1-Trifluoroacetylpiperidin-2-yl)ethanoic acid 6. Trifluoroacetic anhydride (2.75 cm^3, 19.5 mmol) was added dropwise over 1 min to (piperidin-2-yl)ethanoic acid (2.53 g, 17.7 mmol) at 0 °C with vigorous stirring. The mixture was stirred at 0 °C for 5 min and a further portion of trifluoroacetic anhydride (0.50 cm^3, 3.5 mmol) was then added. The mixture was then warmed to 85 °C and maintained at this temperature for 1 h 30 min, then diluted with a 1 M hydrochloric acid (50 cm^3) and extracted with diethyl ether (6 × 50 cm^3). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (diethyl ether–hexane, 1 : 1) to give the *protected amino acid* **6** (2.62 g, 62%) as a white solid; mp 69–70 °C; ν_{max}($CHCl_3$)/cm^{-1} 3177, 2948, 2872, 1716, 1682; δ_H (400 MHz, $[CD_3]_2SO$, 393 K) 4.79–4.58 (1H, br m, NC*H*CH_2CO), 3.98–3.76 (1H, br m, 1 × NCH_2), 3.24–3.02 (1H, br m, 1 × NCH_2), 2.74–2.46 (2H, m, CH_2CO), 1.78–1.50 (5H, m, NCH_2CH_2, $NCHCH_2CH_2$ and 1 × $NCH_2CH_2CH_2$), 1.50–1.38 (1H, m, 1 × $NCH_2CH_2CH_2$); δ_C (100 MHz, $[CD_3]_2SO$, 393 K) 170.9 (CO), 154.8 (CON, q, $^2J_{FC}$ 35), 116.5 (CF_3, q, $^1J_{FC}$ 289), 48.7 (CH), 39.9 (CH_2), 34.8 (CH_2), 27.6 (CH_2), 24.7 (CH_2), 17.8 (CH_2); *m*/*z* (EI) 239 (M^+, 22%), 180 (100) (Found C, 45.4; H, 5.25; N, 6.0. $C_9H_{12}F_3NO_3$ requires C, 45.2; H, 5.1; N, 5.9%).

1-Diazo-3-(1-trifluoroacetylpiperidin-2-yl)propan-2-one 7. Following the general procedure, the acid chloride was prepared by the reaction of the *N*-protected amino acid **6** (1.59 g, 6.65 mmol) with oxalyl chloride (2.90 cm^3, 33.2 mmol) and dry dimethylformamide (two drops) in dry dichloromethane (10 cm^3) at 0 °C. The mixture was stirred at 0 °C for 50 min and at room temperature for 45 min. The acid chloride was dissolved in dry dichloromethane (10 cm^3) and added to a solution of diazomethane (~33 mmol) in diethyl ether (100 cm^3) at 0 °C, and the mixture was allowed to warm to room temperature over 16 h. The remaining diazomethane was consumed with glacial acetic acid (2.80 cm^3, 49.0 mmol). Purification by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) afforded the *α-diazo ketone* **7** (1.52 g, 87%) as a yellow solid (mixture of amide rotamers); mp 78–81 °C; ν_{max}($CHCl_3$)/cm^{-1} 2947, 2862, 2112, 1682, 1643; δ_H (400 MHz, $CDCl_3$) 5.42 (0.75H, br s, CHN_2), 5.29 (0.25H, br s, CHN_2 rotamer), 5.10–4.95 (1H, m, NC*H*CH_2CO), 4.70–4.40 (1H, m, 1 × NCH_2), 3.92–3.76 (1H, m, 1 × NCH_2), 3.27–3.15 (1H, m, 1 × CH_2CO), 3.00–2.45 (3H, m, 1 × CH_2CO, $NCHCH_2CH_2$), 1.90–1.40 (4H, m, NCH_2CH_2 and $NCH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 191.0 (CO), 190.4 (CO), 155.6 (CON, q, *J* 35), 155.1 (CON, q, $^2J_{FC}$ 35), 116.5 (CF_3, q, $^1J_{FC}$ 288), 116.3 (CF_3, q, *J* 288), 55.3 (CH), 55.0 (CH), 50.0 (CH), 47.6 (CH), 41.4 (CH_2), 41.3 (CH_2), 40.6 (CH_2), 40.3 (CH_2), 38.8 (CH_2), 28.1 (CH_2), 27.5 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 18.2 (CH_2); *m*/*z* (EI) 235.0801 ($M^+ - N_2$. $C_{10}H_{12}F_3NO_2$ requires 235.0820).

1-(Allylpiperidin-2-yl)-3-diazopropan-2-one 8. A 5% aqueous solution of potassium carbonate (50 cm^3) was added to a solution of the α-diazo ketone **7** (1.00 g, 3.80 mmol) in ethanol (30 cm^3). The resulting mixture was stirred at room temperature for 20 h and then extracted with diethyl ether (3 × 75 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The residue and potassium carbonate (1.36 g, 9.84 mmol) were suspended in dry tetrahydrofuran (20 cm^3) and allyl bromide (0.85 cm^3, 9.8 mmol) was added dropwise over 1 min. The mixture was stirred at room temperature for 22 h and the solvent then removed *in vacuo*. The residue was diluted with a saturated aqueous solution of sodium bicarbonate (50 cm^3) and extracted with diethyl ether (2 × 50 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (1% triethylamine in diethyl ether) to give the *allylic amine* **8** (0.54 g, 69%) as a green liquid; ν_{max}(film)/cm^{-1} 3078, 2934, 2857, 2795, 2104, 1636, 1000, 969, 920; δ_H (250 MHz, $CDCl_3$) 5.78 (1H, dddd, *J* 17.2, 10.0, 7.3 and 5.7, C*H*=CH_2), 5.38 (1H, br s, CHN_2), 5.18 (1H, dddd, *J* 17.2, 1.5, 1.0 and 0.7, *trans* CH=CH_2), 5.17–5.11 (1H, m, *cis* CH=CH_2), 3.25 (1H, ddt, *J* 13.9, 5.7 and 1.5, CH_2CH=CH_2), 2.96 (1H, ddt *J* 13.9, 7.3 and 1.0, NCH_2CH=CH_2), 2.96–2.87 (1H, m, NCH), 2.77–2.56 (2H, m, NCH_2CH_2), 2.39–2.23 (2H, m, CH_2CO), 1.77–1.31 (6H, m, $NCH_2CH_2CH_2$, $NCHCH_2$ and $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 193.7 (CO), 135.1 (CH), 117.4 (CH_2), 57.4 (CH_2), 56.7 (CH), 55.0 (CH), 50.7 (CH_2), 42.0 (CH_2), 30.8 (CH_2), 25.2 (CH_2), 22.3 (CH_2); *m*/*z* (EI) 179.1298 ($M^+ - N_2$. $C_{11}H_{17}NO$ requires 179.1310).

(*S*)-(−)-(1-Trifluoroacetylpyrrolidin-2-yl)methanol 9.[8] (*S*)-Pyrrolidinylmethanol (7.0 g, 69 mmol) and triethylamine (10.1 cm^3, 72.5 mmol) were dissolved in methanol (30 cm^3) and ethyl trifluoroacetate (12.4 cm^3, 104 mmol) was added dropwise to the mixture over a period of 30 min. The solution was stirred at room temperature for 18 h then diluted with 2 M hydrochloric acid (100 cm^3) and extracted with diethyl ether (3 × 120 cm^3). The aqueous phase was saturated with solid sodium chloride and extracted with diethyl ether (100 cm^3). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by

flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) to give the *amide* **9** (11.5 g, 84%) as a colourless oil; $[\alpha]_D^{28}$ −64.6 (*c* 1.10, $CHCl_3$); ν_{max}(film)/cm^{-1} 3425, 2979, 2889, 1791, 1686; δ_H (400 MHz, $CDCl_3$) 4.27–4.21 (1H, m, 1 × C*H*$_2$OH), 3.79–3.60 (4H, m, 1 × C*H*$_2$OH, NCH_2 and NC*H*-CH_2OH), 3.22 (1H, br s, OH), 2.13–1.86 (4H, m, NCH_2CH_2 and $NCHCH_2$); δ_C (67.8 MHz, $CDCl_3$) 156.6 (CON, q, $^2J_{FC}$ 37), 116.2 (CF_3, q, $^1J_{FC}$ 287), 63.3 (CH_2), 61.8 (CH), 59.3 (CH), 47.5 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 24.3 (CH_2), 20.4 (CH_2); *m*/*z* (FAB) 198.0741 (M^+ + H. $C_7H_{11}F_3NO_2$ requires 198.0742).

***tert*-Butyl (*S*)-(−)-3-(1-trifluoroacetylpyrrolidin-2-yl)propenoate 10.** Dimethyl sulfoxide (2.1 cm^3, 30 mmol) was added dropwise to a solution of oxalyl chloride (1.25 cm^3, 14.3 mmol) in dichloromethane (75 cm^3) at −78 °C over 15 min, and the mixture was stirred at this temperature for a further 15 min. A solution of the alcohol **9** (2.3 g, 12 mmol) in dichloromethane (25 cm^3) was then added over 30 min and the mixture was stirred at −78 °C for 1 h 30 min. Triethylamine (7.9 cm^3, 57 mmol) was added and the mixture was allowed to warm to room temperature. The solution was diluted with dichloromethane (25 cm^3) and washed with water (2 × 75 cm^3). The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting crude aldehyde was used without further purification.

Sodium hydride (0.30 g, 13 mmol) was suspended in dry tetrahydrofuran (10 cm^3) at room temperature, and *tert*-butyl diethylphosphonoacetate (3.0 g, 12 mmol) was added dropwise. The mixture was stirred for 30 min and then cooled to 5 °C. A solution of the aldehyde (2.0 g, 10 mmol) in dry tetrahydrofuran (40 cm^3) was added dropwise at such a rate as to keep the temperature below 10 °C. The mixture was stirred at room temperature for 4 h then concentrated *in vacuo*. The residue was dissolved in dichloromethane (100 cm^3) and washed successively with water (2 × 75 cm^3), a 20% w/v aqueous solution of sodium sulfite (75 cm^3) and brine (75 cm^3). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (hexane–diethyl ether, 5 : 1) to give the *alkene* **10** (1.0 g, 29%) as a white solid; mp 61–62 °C; $[\alpha]_D^{26}$ −1.00 (*c* 1.40, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2980, 2904, 1694, 1658, 978; δ_H (400 MHz, $CDCl_3$) 6.68 (1H, dd, *J* 15.6 and 5.8, CHC*H*=CH), 5.75 (1H, dd, *J* 15.6 and 1.4, CHCH=C*H*), 4.82–4.78, (1H, m, C*H*CH=CH), 3.79–3.64 (2H, m, NCH_2), 2.16–1.85 (4H, m, NCH-$_2$C*H*$_2$ and $NCHCH_2$), 1.47 (9H, s, $[CH_3]_3C$); δ_C (67.8 MHz, $CDCl_3$) 164.8 (CO_2), 155.1 (CON, q, $^2J_{FC}$ 37), 143.0 (CH), 123.1 (CH), 115.9 (CF_3, q, $^1J_{FC}$ 288), 80.2 (C), 58.7 (CH), 46.5 (CH_2), 29.3 (CH_2), 27.6 (CH_3), 23.7 (CH_2); *m*/*z* (FAB) 294.1313 (M^+ + H. $C_{13}H_{19}F_3NO_3$ requires 294.1317), 294 (M^+ + H, 12%), 236 (7), 220 (88).

***tert*-Butyl (*S*)-(−)-3-(1-trifluoroacetylpyrrolidin-2-yl)propanoate 11.** The alkene **10** (1.2 g, 4.1 mmol) and 10% palladium on activated charcoal (0.2 g) were added to a mixture of methanol (20 cm^3) and water (2 cm^3). The mixture was stirred at room temperature under 1 atmosphere of hydrogen for 12 h. The mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane–diethyl ether, 3 : 1) to give the *ester* **11** (1.1 g, 91%) as a colourless liquid; $[\alpha]_D^{26}$ −18.6 (*c* 1.30, $CHCl_3$). ν_{max}(film)/cm^{-1} 2979, 1729, 1691; δ_H (250 MHz, $CDCl_3$) 4.24–4.16 (1H, m, C*H*CH_2CH_2CO), 3.69–3.60 (2H, m, NCH_2), 2.28–2.21 (2H, m, CH_2CO), 2.20–1.91 (4H, m, C*H*$_2$-CH_2CO and $NCH_2CH_2CH_2$), 1.78–1.60 (2H, m, NCH_2CH_2), 1.45 (9H, s, $[CH_3]_3C$); δ_C (67.8 MHz, $CDCl_3$) 171.9 (CO_2), 155.4 (CON, q, $^2J_{FC}$ 36), 116.2 (CF_3, q, $^1J_{FC}$ 288), 80.2 (C), 58.5 (CH), 46.3 (CH_2), 46.3 (CH_2), 32.2 (CH_2), 28.6 (CH_2), 27.8 (CH_3), 24.0 (CH_2); *m*/*z* (CI, CH_4) 296.1473 (M^+ + H. $C_{13}H_{21}F_3NO_3$ requires 296.1474), 296 (M^+ + H, 100%), 239 (23), 222 (88), 166 (25).

(*S*)-(−)-3-(1-Trifluoroacetylpyrrolidin-2-yl)propanoic acid 12. Trifluoroacetic acid (1.3 cm^3, 17 mmol) was added to a solution of the ester **11** (1.0 g, 3.4 mmol) in dichloromethane (1 cm^3) and the mixture stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (hexane–diethyl ether, 2 : 1) to give the *carboxylic acid* **12** (0.74 g, 91%) as a white solid; mp 37–39 °C; $[\alpha]_D^{28}$ −2.27 (*c* 0.971, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2979, 1729, 1690; δ_H (400 MHz, $CDCl_3$) 4.27–4.20 (1H, m, C*H*CH_2-CH_2CO_2H), 3.72–3.60 (2H, m, NCH_2), 2.49–2.35 (2H, m, C*H*$_2CO_2H$), 2.18–1.90 (4H, m, C*H*$_2CH_2CO_2H$ and NCH_2-CH_2CH_2), 1.84–1.69 (2H, m, NCH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 178.0 (CO_2H), 155.4 (CON, q, $^2J_{FC}$ 37), 115.9 (CF_3, q, $^1J_{FC}$ 288), 58.2 (CH), 46.3 (CH_2), 30.3 (CH_2), 28.3 (CH_2), 27.2 (CH_2), 23.7 (CH_2); *m*/*z* (FAB) 240.0829 (M^+ + H. $C_9H_{12}F_3NO_3$ requires 240.0848), 240 (M^+ + H, 60%), 222 (89), 194 (5), 166 (19).

(*S*)-(−)-1-Diazo-4-(1-trifluoroacetylpyrrolidin-2-yl)butan-2-one 13. Following the general procedure, the acid chloride was prepared by the reaction of the *N*-protected amino acid **12** (0.50 g, 2.1 mmol) with oxalyl chloride (0.73 cm^3, 8.4 mmol) and dry dimethylformamide (one drop) in dry dichloromethane (15 cm^3) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The acid chloride was dissolved in dry dichloromethane (5 cm^3) and added to a solution of diazomethane (~10 mmol) in diethyl ether (50 cm^3) at 0 °C, and the mixture was allowed to warm to room temperature over 2 h. The remaining diazomethane was consumed with glacial acetic acid (0.6 cm^3, 10 mmol). Purification by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) afforded the *α-diazo ketone* **13** (0.51 g, 93%) as a yellow solid; mp 35–36 °C; $[\alpha]_D^{26}$ −6.98 (*c* 1.29, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3116, 2975, 2901, 2109, 1682, 1643; δ_H (400 MHz, $CDCl_3$) 5.39 (1H, br s, CHN_2), 4.25–4.12 (1H, m, C*H*CH_2CH_2CO), 3.68–3.60 (2H, m, NCH_2), 2.45–2.30 (2H, m, CH_2CO), 2.13–1.71 (6H, m, $NCH_2CH_2CH_2$, $CHCH_2CH_2CO$ and NCH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 194.0 (CO), 155.9 (CON, q, $^2J_{FC}$ 36), 116.4 (CF_3, q, $^1J_{FC}$ 288), 58.8 (CH), 54.6 (CH), 46.6 (CH_2), 37.6 (CH_2), 29.1 (CH_2), 28.2 (CH_2), 24.2 (CH_2); *m*/*z* (FAB) 235.0819 (M^+ − N_2. $C_{10}H_{12}$-F_3NO_2 requires 235.0820), 264 (M^+ + H, 100%), 236 (95), 166 (32), 97 (6).

(*S*)-(−)-1-(1-Allylpyrrolidin-2-yl)-4-diazobutan-3-one 14. The α-diazo ketone **13** (1.2 g, 4.6 mmol) was dissolved in a saturated aqueous solution of barium hydroxide (20 cm^3) and stirred at room temperature for 1 h. The solution was then extracted with ethyl acetate (2 × 30 cm^3). The aqueous phase was concentrated to dryness *in vacuo* and the residue washed with ethyl acetate (2 × 30 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was dissolved in dry tetrahydrofuran (30 cm^3), and potassium carbonate (1.2 g, 8.7 mmol) and allyl bromide (0.97 g, 8.0 mmol) were then added to the solution. The mixture was stirred at room temperature for 24 h and the solvent was then removed *in vacuo*. The residue was diluted with a saturated aqueous solution of sodium bicarbonate (30 cm^3) and extracted with ethyl acetate (3 × 30 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1% triethylamine in diethyl ether) to give the *allylic amine* **14** (0.30 g, 32%) as a yellow liquid; $[\alpha]_D^{24}$ −6.44 (*c* 1.01, $CHCl_3$); ν_{max}(film)/cm^{-1} 3077, 2960, 2873, 2794, 2101, 1641, 995, 918; δ_H (400 MHz, $CDCl_3$) 5.90 (1H, dddd, *J* 17.1, 10.3, 7.6 and 5.5, C*H*=CH_2), 5.25 (1H, br s, CHN_2), 5.18 (1H, dq, *J* 17.1 and 1.5, *trans* CH=C*H*$_2$), 5.11–5.07 (1H, m, *cis* CH=C*H*$_2$), 3.46 (1H, dddd, *J* 13.3, 5.5, 1.5 and 1.5, 1 × C*H*$_2$CH=CH_2), 3.08 (1H, ddd, *J* 9.6, 7.2 and 2.8, 1 × NCH_2), 2.75 (1H, dddd, *J* 13.3, 7.6, 0.9 and 0.9, 1 × C*H*$_2$CH=CH_2), 2.47–2.25 (3H, m, C*H*CH_2CH_2CO and CH_2CO), 2.15 (1H, td,

9.3 and 7.2, 1 × NCH_2), 2.04–1.94 (1H, m, 1 × CH_2CH_2CO), 1.93–1.86 (1H, m, 1 × $NCH_2CH_2CH_2$), 1.78–1.52 (3H, m, NCH_2CH_2 and 1 × CH_2CH_2CO), 1.45 (1H, dddd, *J* 12.5, 10.0, 7.5 and 5.2, 1 × $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 194.3 (CO), 135.4 (CH), 116.2 (CH_2), 62.4 (CH), 56.6 (CH_2), 53.6 (CH), 53.4 (CH_2), 36.8 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 21.5 (CH_2); *m*/*z* (CI, NH_3) 208.1449 (M^+ + H. $C_{11}H_{18}N_3O$ requires 208.1450), 208 (M^+ + H, 95%), 207 (M^+, 9), 179 (19), 110 (100).

3-(1-Trifluoroacetylpiperidin-2-yl)propionic acid 15. Silver benzoate (0.22 g, 0.96 mmol) was added to a solution of the α-diazo ketone **7** (5.0 g, 19 mmol) in a mixture of 1,4-dioxane (165 cm^3) and water (85 cm^3). The reaction mixture was heated at 70 °C for 3 h and then concentrated *in vacuo*. The residue was dissolved in a saturated aqueous solution of sodium bicarbonate (150 cm^3) and extracted with diethyl ether (2 × 100 cm^3). The aqueous layer was acidified with 2 M hydrochloric acid and then extracted with diethyl ether (2 × 150 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane–diethyl ether, 1 : 1) to give the *carboxylic acid* **15** (4.0 g, 83%) as a white solid (mixture of amide rotamers); mp 87–88 °C. ν_{max}($CHCl_3$)/cm^{-1} 3193, 2872, 2674, 1714; δ_H (400 MHz, $CDCl_3$) 4.70–4.60 (0.8H, m, $CHCH_2CH_2CO$), 4.36–4.32 (0.2H, m, 1 × NCH_2), 4.01 (0.2H, m, $CHCH_2CH_2CO$), 3.75–3.71 (0.8H, m, 1 × NCH_2), 3.16–3.10 (0.8H, m, 1 × NCH_2), 2.82–2.76 (0.2H, m, 1 × NCH_2), 2.34–2.10 (4H, m, CH_2CO and CH_2CH_2CO), 1.90–1.64 (5H, m, NCH_2CH_2, $NCH_2CH_2CH_2CH_2$, and 1 × $NCH_2CH_2CH_2$), 1.50–1.38 (1H, m, 1 × $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 178.9 (CO_2H), 178.6 (CO_2H), 156.4 (CON, q, $^2J_{FC}$ 34.3), 116.7 (CF_3, q, $^1J_{FC}$ 288), 116.7 (CF_3, q, $^1J_{FC}$ 288), 52.9 (CH), 50.0 (CH), 41.2 (CH_2), 38.4 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 26.0 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 24.4 (CH_2), 18.8 (CH_2), 18.6 (CH_2); *m*/*z* (EI) 253.0923 (M^+. $C_{10}H_{14}F_3NO_3$ requires 253.0926), 254 (M^+ + H, 100%), 253 (M^+, 5), 208 (10), 180 (26), 73 (24) (Found C, 47.8; H, 5.7; N, 5.8. $C_{10}H_{14}F_3NO_3$ requires C, 47.4; H, 5.6; N, 5.5%).

1-Diazo-4-(1-trifluoroacetylpiperidin-2-yl)butan-2-one 16. Following the general procedure, the acid chloride was prepared by the reaction of the *N*-protected amino acid **15** (3.9 g, 15 mmol) with oxalyl chloride (5.4 cm^3, 62 mmol) and dry dimethylformamide (two drops) in dry dichloromethane (75 cm^3) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The acid chloride was dissolved in dry dichloromethane (30 cm^3) and added to a solution of diazomethane (~60 mmol) in diethyl ether (250 cm^3) at 0 °C, and the mixture was allowed to warm to room temperature over 2 h. The remaining diazomethane was consumed with glacial acetic acid (3.9 g, 65 mmol). Purification by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) afforded the *α-diazo ketone* **16** (3.9 g, 91%) as a yellow liquid (mixture of amide rotamers); ν_{max}(film)/cm^{-1} 3090, 2944, 2868, 2104, 1682, 1642; δ_H (400 MHz, $CDCl_3$) 5.27 (1H, br s, CHN_2), 4.70 (0.8H, m, $CHCH_2CH_2CO$), 4.41–4.38 (0.2H, m, 1 × NCH_2), 4.04 (0.2H, m, $CHCH_2CH_2CO$), 3.77–3.73 (0.8H, m, 1 × NCH_2), 3.25–3.17 (0.8H, m, 1 × NCH_2), 2.88–2.82 (0.2H, m, 1 × NCH_2), 2.38–2.17 (4H, m, CH_2CO and CH_2CH_2CO), 2.01–1.67 (5H, m, NCH_2CH_2, $NCH_2CH_2CH_2CH_2$ and 1 × $NCH_2CH_2CH_2$), 1.53–1.43 (1H, m, 1 × $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 193.8 (CO), 193.3 (CO), 156.4 (CON, q, $^2J_{FC}$ 35), 155.8 (CON, q, $^2J_{FC}$ 35), 116.9 (CF_3, q, $^1J_{FC}$ 288), 116.8 (CF_3, q, $^1J_{FC}$ 288), 54.8 (CH), 53.3 (CH), 51.0 (CH), 50.6 (CH), 41.3 (CH_2), 38.4 (CH_2), 37.2 (CH_2), 36.8 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.3 (CH_2), 24.6 (CH_2), 18.9 (CH_2), 18.7 (CH_2); *m*/*z* (FAB) 278.1093 (M^+ + H. $C_{11}H_{15}F_3N_3O_2$ requires 278.1116), 278 (M^+ + H, 55%), 250 (100), 180 (29).

4-(1-Allylpiperidin-2-yl)-1-diazobutan-2-one 17. The α-diazo ketone **16** (1.0 g, 3.6 mmol) was dissolved in a 2 M aqueous solution of sodium hydroxide (30 cm^3) and the mixture was stirred at room temperature for 1 h. The solution was then extracted with ethyl acetate (2 × 30 cm^3). The aqueous phase was concentrated *in vacuo* and the dry residue washed with ethyl acetate (2 × 30 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was dissolved in dry tetrahydrofuran (30 cm^3), and potassium carbonate (1.1 g, 8.0 mmol) and allyl bromide (0.65 g, 5.4 mmol) were then added to the solution. The mixture was stirred at room temperature for 24 h, and the solvent was then removed *in vacuo*. The residue was diluted with a saturated aqueous solution of sodium bicarbonate (30 cm^3) and extracted with ethyl acetate (3 × 30 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1% triethylamine in diethyl ether) to give the *allylic amine* **17** (0.14 g, 18%) as a yellow liquid; ν_{max}(film)/cm^{-1} 3077, 2934, 2856, 2791, 2102, 1641, 994, 918; δ_H (500 MHz, $CDCl_3$) 5.91–5.82 (1H, m, CH=CH_2), 5.25 (1H, br s, CHN_2), 5.18 (1H, m, *trans* CH=CH_2), 5.06 (1H, m, *cis* CH=CH_2), 3.33 (1H, dd, *J* 14.0 and 5.7, 1 × CH_2CH=CH_2), 2.95 (1H, dd, *J* 14.0 and 7.4, 1 × CH_2CH=CH_2), 2.89 (1H, dt, *J* 11.7 and 4.1, 1 × NCH_2), 2.43–2.27 (3H, m, $CHCH_2CH_2CO$ and CH_2CO), 2.20–2.15 (1H, m, 1 × NCH_2), 1.92–1.78 (2H, m, CH_2CH_2CO), 1.72–1.24 (6H, m, NCH_2CH_2, $NCH_2CH_2CH_2$ and $NCH_2CH_2CH_2CH_2$); δ_C (125 MHz, $CDCl_3$) 195.2 (CO), 135.3 (CH), 117.5 (CH_2), 59.2 (CH), 56.6 (CH_2), 54.3 (CH), 51.9 (CH_2), 36.6 (CH_2), 30.1 (CH_2), 26.4 (CH_2), 25.3 (CH_2), 23.7 (CH_2); *m*/*z* (CI) 164 (3%), 124 (100).

General procedure for carbenoid generation, ylide formation and rearrangement

A solution of the α-diazo ketone in dry solvent was added dropwise from a pressure-equalising addition funnel through the condenser to a solution of the appropriate copper(II) or rhodium(II) complex in the same solvent at reflux. The resulting solution was stirred at reflux and the solvent was then removed *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the rearrangement product.

(3*S*,8*S*)-3-Allyltetrahydropyrrolizin-2(3*H*)-one 18a. According to the general procedure, a solution of the α-diazo ketone **5** (0.12 g, 0.62 mmol) in dry benzene (60 cm^3) was added to a solution of $Cu(acac)_2$ (3.2 mg, 0.012 mmol) in dry benzene (10 cm^3) at reflux, over a period of 30 min. The resulting solution was stirred at reflux for a further 15 min. Purification by flash column chromatography on silica gel (diethyl ether) gave the *pyrrolizidinone* **18a** (67 mg, 65%) as a colourless liquid.

According to the general procedure, a solution of the α-diazo ketone **5** (0.11 g, 0.57 mmol) in dry benzene (60 cm^3) was added to a solution of $Rh_2(OAc)_4$ (4.8 mg, 0.011 mmol) in dry benzene (10 cm^3) at reflux, over a period of 30 min. The resulting solution was stirred at reflux for a further 15 min. Purification by flash column chromatography on silica gel (diethyl ether) gave the *pyrrolizidinone* **18a** (52 mg, 55%) as a colourless liquid; $[\alpha]_D^{24}$ −8.0 (*c* 0.85, $CHCl_3$); ν_{max}(film)/cm^{-1} 2935, 2880, 1748, 1641, 997, 915; δ_H (500 MHz, $CDCl_3$) 5.85 (1H, dddd, *J* 17.0, 10.2, 7.4 and 6.9, CH=CH_2), 5.18–5.10 (1H, m, *trans* CH=H_2), 5.09–5.05 (1H, m, *cis* CH=CH_2), 3.67 (1H, dddd, *J* 8.0, 7.7, 7.7 and 4.0, $NCHCH_2CO$), 3.21–3.14 (1H, m, NCHCO), 2.90–2.81 (2H, m, NCH_2), 2.60 (1H, ddd, *J* 18.7, 8.0 and 0.6, 1 × CH_2CH=CH_2), 2.50–2.43 (1H, m, 1 × CH_2CH=CH_2), 2.36–2.24 (2H, m, CH_2CO), 2.12–2.05 (1H, m, 1 × NCH_2CH_2), 2.05–1.96 (1H, m, 1 × NCH_2CH_2), 1.90–1.81 (1H, m, 1 × $NCH_2CH_2CH_2$), 1.48–1.40 (1H, m, 1 × $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 217.6 (CO), 134.8 (CH), 117.4 (CH_2), 69.5 (CH), 60.0 (CH), 54.5 (CH_2), 42.2 (CH_2), 36.7 (CH_2), 31.6 (CH_2), 25.1 (CH_2); *m*/*z* (CI)

166.1231 (M^+ + H. $C_{10}H_{16}NO$ requires 166.1232), 165 (M^+, 50%), 124 (100).

(3*S,8a*S**)-3-Allylhexahydroindolizin-2(3*H*)-one 19a and (3*R**,8a*S**)-3-allylhexahydroindolizin-2(3*H*)-one 19b.** According to the general procedure, a solution of the α-diazo ketone **8** (198 mg, 0.955 mmol) in dry benzene (95 cm^3) was added to a solution of $Cu(acac)_2$ (5.1 mg, 0.019 mmol) in dry benzene (5 cm^3) at reflux, over a period of 2 h. The resulting solution was stirred at reflux for a further 10 min. Analysis of the crude reaction mixture by ^1H NMR indicated exclusive formation of indolizidinone **19a**. Purification by flash column chromatography on silica gel (hexane–diethyl ether, 2 : 1) gave the *indolizidinone* **19a** (83.7 mg, 49%) and the *indolizidinone* **19b** (21.8 mg, 13%), resulting from partial epimerisation during chromatography, as colourless liquids (combined yield of 62%). Data for **19a**; ν_{max}(film)/cm^{-1} 3077, 2932, 2854, 2801, 1755, 1640, 997, 914; δ_H (250 MHz, $CDCl_3$) 5.90–5.83 (1H, m, C*H*=CH_2), 5.14–5.04 (2H, m, CH=CH_2), 3.36 (1H, t, *J* 5.7, NCHCO), 3.25–3.14 (1H, m, NC*H*CH_2CO), 3.13–3.03 (1H, m, 1 × NCH_2), 2.77 (1H, ddd, *J* 12.6, 11.2 and 3.8, 1 × NCH_2), 2.56–2.21 (3H, m, 1 × CH_2CO and CH_2CH=CH_2), 2.09 (1H, dd, *J* 18.0 and 5.6, 1 × CH_2CO), 1.88–1.80 (1H, m, 1 × NCH_2-CH_2CH_2), 1.68–1.17 (5H, m, NCH_2CH_2, NCHC$H_2$$CH_2$ and 1 × NCH_2CH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 215.8 (CO), 134.7 (CH), 117.3 (CH_2), 64.8 (CH), 56.3 (CH), 46.6 (CH_2), 44.2 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 24.2 (CH_2), 21.7 (CH_2). Data for **19b**; ν_{max}($CHCl_3$)/cm^{-1} 2940, 2787, 1753, 994, 916; δ_H (250 MHz, $CDCl_3$) 5.81 (1H, m, dddd, *J* 17.1, 10.2, 7.2 and 6.2, C*H*=CH_2), 5.12–4.99 (2H, m, CH=CH_2), 3.19 (1H, dt, *J* 10.8 and 2.7, 1 × NCH_2), 2.51–2.27 (5H, m, NC*H*CH_2CO, NC*H*CO, CH_2CH=CH_2, and 1 × CH_2CO), 2.11–1.60 (6H, m, 1 × NCH_2, 1 × CH_2CO, NCH_2CH_2, 1 × NCHC$H_2$$CH_2$ and 1 × NCH_2-CH_2CH_2), 1.47–1.32 (2H, m, 1 × NCHC$H_2$$CH_2$ and 1 × NCH_2CH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 214.4 (CO), 134.9 (CH), 116.7 (CH_2), 70.9 (CH), 60.8 (CH), 51.4 (CH_2), 43.5 (CH_2), 32.7 (CH_2), 30.9 (CH_2), 25.4 (CH_2), 24.4 (CH_2); *m*/*z* (EI) 138.0912 ($M^+ - C_3H_5$. $C_8H_{12}NO$ requires 138.0919).

(3*R,8a*S**)-3-Allylhexahydroindolizin-2(3*H*)-one 19b.** Silica gel (1.0 g) was added to a solution of the indolizidinone **19a** (23.9 mg, 0.133 mmol) in diethyl ether (10 cm^3) and the mixture was stirred at room temperature for 15 h. Further silica gel (1.0 g) was added and the mixture was stirred at room temperature for an additional 8 h period. The mixture was filtered and the silica gel washed with further diethyl ether (3 × 15 cm^3). The combined solution and washings were concentrated *in vacuo*, and the crude product purified by flash column chromatography on silica gel (hexane–diethyl ether, 4 : 1) to give the *indolizidinone* **19b** (17.1 mg, 72%) as a colourless liquid.

(5*R*,9*S*)-5-Allylhexahydroindolizin-6(5*H*)-one 20b. According to the general procedure, a solution of the α-diazo ketone **14** (0.10 g, 0.48 mmol) in dry benzene (50 cm^3) was added to a solution of $Cu(acac)_2$ (2.5 mg, 0.0096 mmol) in dry benzene (10 cm^3) at reflux, over a period of 30 min. The resulting solution was stirred at reflux for a further 15 min. Purification by flash column chromatography on silica gel (hexane–diethyl ether, 2 : 1) gave the *indolizidinone* **20b** (57 mg, 66%) as a colourless liquid; $[\alpha]_D^{24}$ −1.2 (*c* 0.98, $CHCl_3$); ν_{max}(film)/cm^{-1} 2943, 2880, 2797, 2739, 1716, 1640, 995, 913; δ_H (500 MHz, $CDCl_3$) 5.93–5.84 (1H, m, C*H*=CH_2), 5.12 (1H, br d, *J* 17.2, *trans* CH=CH_2), 5.04 (1H, br d, *J* 10.1, *cis*, CH=CH_2), 3.29–3.23 (1H, m, NCHCO), 2.83–2.78 (1H, m, NC*H*CH_2CH_2), 2.65–2.59 (1H, m, 1 × NCH_2), 2.57–2.46 (3H, m, 1 × NCH_2 and CH_2CH=CH_2), 2.40–2.31 (1H, m, 1 × CH_2CO), 2.21–2.07 (2H, m, 1 × CH_2CO and 1 × NCH_2CH_2CH_2), 2.03–1.80 (3H, m, 1 × NCH_2CH_2CH_2 and C$H_2$$CH_2$CO), 1.75–1.66 (1H, m, 1 × NCH_2CH_2), 1.56–1.47 (1H, m, 1 × NCH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 207.5 (CO), 135.5 (CH), 116.5 (CH_2), 72.2 (CH), 62.9 (CH), 52.5 (CH_2), 38.8 (CH_2), 32.8 (CH_2), 30.1 (CH_2), 29.1 (CH_2), 22.2 (CH_2); *m*/*z* (EI) 179.1316 (M^+. $C_{11}H_{17}NO$ requires 179.1310), 180 (M^+ + H, 3%), 138 (53).

4-Allyloctahydroquinolizin-3-one 21a and 21b. According to the general procedure, a solution of the α-diazo ketone **17** (0.14 g, 0.63 mmol) in dry benzene (50 cm^3) was added to a solution of $Cu(acac)_2$ (3.3 mg, 0.013 mmol) in dry benzene (10 cm^3) at reflux, over a period of 30 min. The resulting solution was stirred at reflux for a further 15 min. Purification by flash column chromatography on neutral alumina (hexane–diethyl ether, 4 : 1) gave the *quinolizidinone* **21a**–**b** major (64 mg, 52%) and minor (11 mg, 9%) isomers as colourless liquids. Major isomer; ν_{max}(film)/cm^{-1} 2936, 2860, 2790, 2733, 1716, 1639, 995, 908; δ_H (400 MHz, $CDCl_3$) 5.67 (1H, dddd, *J* 16.7, 10.2, 8.0 and 6.6, C*H*=CH_2), 5.30–5.00 (2H, m, CH=CH_2), 3.25 (1H, dd, *J* 9.7 and 5.5, NCHCO), 2.86–2.79 (1H, m, NC*H*-CH_2CH_2), 2.68–2.59 (3H, m, NCH_2 and 1 × CH_2CH=CH_2), 2.48–2.32 (3H, m, CH_2CO and 1 × CH_2CH=CH_2), 1.97–1.91 (1H, m, 1 × NCHC$H_2$$CH_2$CO), 1.75–1.22 (7H, m, 1 × NCHC$H_2$$CH_2$CO, NCHC$H_2$$CH_2$, NCH_2C$H_2$$CH_2$ and NCH_2-CH_2CH_2); δ_C (125 MHz, $CDCl_3$) 209.2 (CO), 134.2 (CH), 117.1 (CH_2), 72.2 (CH), 51.9 (CH), 51.2 (CH_2), 36.5 (CH_2), 33.0 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 25.7 (CH_2), 23.7 (CH_2); *m*/*z* (EI) 152.1080 ($M^+ - C_3H_5$. $C_9H_{14}NO$ requires 152.1075). Minor isomer; ν_{max}(film)/cm^{-1} 3083, 2942, 2880, 2798, 2740, 2710, 1716, 1640, 995, 913; δ_H (400 MHz, $CDCl_3$) 5.85 (1H, dddd, *J* 17.2, 10.2, 6.9 and 6.9, C*H*=CH_2), 5.10 (1H, dd, *J* 17.2 and 1.6, *trans* CH=CH_2), 5.05 (1H, br d, *J* 10.2, *cis* CH=CH_2), 3.20–3.15 (1H, m, 1 × NCH_2), 2.76 (1H, dd, *J* 5.3 and 3.0, NCHCO), 2.68–2.61 (1H, m, 1 × CH_2CH=CH_2), 2.60–2.49 (2H, m, 1 × NCH_2 and 1 × CH_2CH=CH_2), 2.40–2.30 (2H, m, 1 × NC*H*-CH_2CH_2CO and 1 × CH_2CO), 1.97 (1H, dt, *J* 11.5 and 2.6, 1 × CH_2CO), 1.92–1.86 (1H, m, 1 × $COCH_2$CH_2), 1.80–1.27 (7H, m, 1 × $COCH_2$CH_2, NCH_2CH_2, NCH_2CH_2CH_2 and NCH_2-CH_2CH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 208.1 (CO), 135.5 (CH), 116.3 (CH_2), 71.9 (CH), 60.5 (CH), 52.5 (CH_2), 39.2 (CH_2), 33.2 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 25.6 (CH_2), 23.9 (CH_2).

(2*R*,3*S*,8*S*)-3-Allylhexahydropyrrolizidin-2-ol 22. Sodium borohydride (8 mg, 0.2 mmol) was added to a solution of the indolizidinone **18a** (50 mg, 0.30 mmol) in methanol (2 cm^3) and the mixture was stirred for 4 h at room temperature. The solvent was removed *in vacuo* and the residue washed with ethyl acetate. The organic washings were filtered, concentrated *in vacuo* and the residue washed with several portions of hexane to give the *alcohol* **22** (45 mg, 89%) as a white solid; mp 61–62 °C $[\alpha]_D^{28}$ −1.7 (*c* 0.49, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3619, 2962, 2871, 1639, 1000, 915; δ_H (500 MHz, $CDCl_3$) 6.02–5.94 (1H, dddd, *J* 17.1, 10.1, 7.3 and 7.3, C*H*=CH_2), 5.22 (1H, d, *J* 17.1, *trans* CH=CH_2), 5.12 (1H, d, *J* 10.1, *cis* CH=CH_2), 4.14–4.04 (1H, m, C*H*OH), 3.56–3.45 (1H, m, 1 × NCH_2), 3.02 (1H, ddd, *J* 12.0, 6.0 and 4.5, 1 × NCH_2), 2.73–2.68 (1H, m, 1 × CH_2CH=CH_2), 2.54 (m, 1H, 1 × CH_2CH=CH_2), 2.42–2.33 (3H, m, NC*H*CH_2, NC*H*CHOH and 1 × CH_2CHOH), 2.02–1.76 (4H, m, 1 × CH_2CHOH, NCH_2CH_2CH_2 and OH), 1.59–1.47 (2H, m, NCH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 136.3 (CH), 116.9 (CH_2), 77.8 (CH), 71.9 (CH), 61.1 (CH), 54.7 (CH_2), 40.3 (CH_2), 39.3 (CH_2), 33.1 (CH_2), 25.9 (CH_2); *m*/*z* (EI) 167.1312 (M^+. $C_{10}H_{17}NO$ requires 167.1310), 167 (M^+, 0.2%), 126 (100) (Found C, 71.7; H, 10.35; N, 8.4. $C_{10}H_{17}NO$ requires C, 71.8; H, 10.2; N, 8.4%).

Crystal structure determination of alcohol 22. ‡ *Crystal data.* $C_{10}H_{17}NO$, M = 167.25, monoclinic, a = 8.536(2), b = 11.150(3), c = 10.547(2) Å, β = 105.40(2)°, U = 967.8(4) $Å^3$, T = 150(2) K, space group $P2_1/c$ (No. 14), Z = 4, D_c = 1.148 g cm^{-3}, μ(Mo-Kα) = 0.073 mm^{-1}, 1702 unique reflections (R_{int} = 0.092) collected and used in all calculations. Final R_1 [1258 $F > 4\sigma(F)$] = 0.0570 and wR(all F^2) was 0.141.

General procedure for reduction of cyclisation products with L-Selectride®

L-Selectride® was added dropwise to a solution of the ketone in dry tetrahydrofuran at −78 °C over a period of 2 min. The resulting solution was stirred at −78 °C and the solvent was then removed *in vacuo*. The residue was stirred at room temperature with a saturated aqueous solution of sodium bicarbonate (5 cm^3) for 3 h and the mixture was then extracted with ethyl acetate (4 × 10 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (diethyl ether–methanol, 10 : 1) to give the *alcohol*.

(2*R,3*R**,8a*S**)-3-Allyloctahydroindolizin-2-ol 23.** Following the general procedure, the ketone **19b** (51.1 mg, 0.285 mmol) was reduced using L-Selectride® (0.85 cm^3 of a 1 M solution in dry tetrahydrofuran, 0.85 mmol) at −78 °C for 20 min. Purification gave the *alcohol* **23** (47.1 mg, 91%) as a colourless solid; mp 61–63 °C; $\nu_{max}(CHCl_3)/cm^{1}$ 3180, 2933, 2851, 2800, 1636, 1000, 918; δ_H (250 MHz, $CDCl_3$) 5.92 (1H, m, dddd, *J* 17.2, 10.2, 6.9 and 6.6, C*H*=CH_2), 5.17 (1H, dq, *J* 17.2 and 1.7, *trans* CH=CH_2), 5.11–5.04 (1H, m, *cis* CH=CH_2), 4.12 (1H, ddd, *J* 7.8, 4.8 and 3.3, C*H*OH), 3.17–3.07 (1H, m, 1 × NCH_2), 2.80 (1H, br s, OH), 2.40–2.29 (3H, m, 1 × NCHCH_2CHOH and CH_2CH=CH_2), 2.03 (1H, dt, *J* 5.1 and 7.2, NC*H*CHOH), 1.84–1.50 (6H, m, 1 × NC*H*CH_2, 1 × NCH_2, 1 × $NCH_2CH_2CH_2$, 1 × $NCH_2CH_2CH_2CH_2$ and NCH_2CH_2), 1.38–1.18 (3H, m, 1 × NCHCH_2CHOH 1 × NCHCH_2CH_2 and 1 × $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 136.5 (CH), 116.8 (CH_2), 70.9 (CH), 70.1 (CH), 64.4 (CH), 51.6 (CH_2), 41.2 (CH_2), 31.7 (CH_2), 31.6 (CH_2), 25.6 (CH_2), 25.0 (CH_2); *m*/*z* (EI) 181.1491 (M^+. $C_{11}H_{19}NO$ requires 181.1467).

Crystal structure determination of alcohol 23.‡ *Crystal data.* $C_{11}H_{19}NO$, *M* = 181.27, orthorhombic, *a* = 18.996(2), *b* = 8.413(3), *c* = 6.982(2) Å, *U* = 1115.8(5) $Å^3$, *T* = 293(2) K, space group $Pca2_1$(No. 29), *Z* = 4, D_c = 1.079 g cm^{-3}, μ(Cu-Kα) = 0.530 mm^{-1}, 637 unique reflections (R_{int} = 0.064) collected and used in all calculations. Final R_1 [543 $F > 4\sigma(F)$] = 0.0541 and *wR*(all F^2) was 0.141.

(5*R*,6*R*,9*S*)-5-Allyloctahydroindolizin-6-ol 24. Following the general procedure, the ketone **20b** (40 mg, 0.22 mmol) was reduced using L-Selectride® (0.67 cm^3 of a 1.0 M solution in tetrahydrofuran, 6.7 mmol) at −78 °C for 1 h. Purification gave the *alcohol* **24** (28 mg, 69%) as a colourless solid; mp 62–64 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3514, 2938, 2859, 2795, 1640, 996, 914; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, dddd, *J* 17.2, 10.0, 7.2 and 7.2, C*H*=CH_2), 5.16–5.10 (1H, m, *trans* CH=CH_2), 5.08–5.04 (1H, m, *cis* CH=CH_2), 3.73 (1H, br d, *J* 7.7, C*H*OH), 3.12 (1H, dt, *J* 8.6 and 2.2, NC*H*CHOH), 2.45 (1H, d, *J* 9.0, NC*H*CH_2CH_2), 2.36–2.33 (2H, m, NCH_2), 2.11–2.03 (2H, m, CH_2CH=CH_2), 1.96–1.60 (6H, m, NCH_2CH_2, $NCH_2CH_2CH_2$, CH_2CHOH), 1.54–1.34 (3H, m, CH_2CH_2CHOH and OH); δ_C (67.8 MHz, $CDCl_3$) 135.5 (CH), 117.1 (CH_2), 67.0 (CH), 65.6 (CH), 64.8 (CH), 51.1 (CH_2), 35.2 (CH_2), 31.8 (CH_2), 30.7 (CH_2), 25.7 (CH_2), 20.6 (CH_2); *m*/*z* (FAB) 182.1559 (M^+ + H. $C_{11}H_{20}NO$ requires 182.1545), 182 (M^+ + H, 15%), 164 (2), 140 (3).

Crystal structure determination of alcohol 24.‡ *Crystal data.* $C_{11}H_{19}NO$, *M* = 181.27, monoclinic, *a* = 7.554(4), *b* = 7.161(3), *c* = 19.49(2) Å, β = 100.12(8)°, *U* = 1037.9(13) $Å^3$, *T* = 150(2) K, space group $P2_1/n$ (No. 14), *Z* = 4, D_c = 1.160 g cm^{-3}, μ(Mo-Kα) = 0.073 mm^{-1}, 1355 reflections collected and used in all calculations. Final R_1 [850 $F > 4\sigma(F)$] = 0.0750 and *wR*(all F^2) was 0.199.

4-Allyloctahydroquinolizin-3-ol. Following the general procedure, the ketone **21** (major isomer) (45 mg, 0.23 mmol) was reduced using L-Selectride® (0.70 cm^3 of a 1.0 M solution in tetrahydrofuran, 0.70 mmol) at −78 °C for 1 h. Purification gave the *alcohol* (32 mg, 70%) as a colourless solid; mp 62–64 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3616, 2933, 2857, 1636, 997, 908; δ_H (400 MHz, $CDCl_3$) 5.92–5.81 (1H, dddd, *J* 17.1, 10.1, 7.1 and 7.1, C*H*=CH_2), 5.04–4.99 (1H, m, *trans* CH=CH_2), 4.93–4.90 (1H, m, *cis* CH=CH_2), 3.89–3.84 (1H, m, C*H*OH), 2.95–2.92 (1H, q, *J* 5.1, 1 × NCH_2), 2.63–2.60 (1H, m, 1 × NCH_2), 2.50 (1H, ddd, *J* 11.8, 11.8 and 3.0, 1 × CH_2CH=CH_2), 2.35–2.15 (3H, m, 1 × CH_2CH=CH_2, NC*H*CHOH, NC*H*CH_2CH_2), 1.80 (1H, s, OH), 1.80–1.39 (6H, m, CH_2CHOH, CH_2CH_2-CHOH, $NCH_2CH_2CH_2CH_2$), 1.29–1.05 (4H, m, NCH_2CH_2, $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 140.2 (CH), 115.7 (CH_2), 71.6 (CH), 65.4 (CH), 53.4 (CH), 52.9 (CH_2), 33.2 (CH_2), 32.1 (CH_2), 28.4 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 24.9 (CH_2); *m*/*z* (FAB) 196.1705 (M^+ + H. $C_{12}H_{22}NO$ requires 196.1701), 196 (M^+ + H, 18%), 154 (97).

1-Diazo-4-(2-vinylaziridin-1-yl)butan-2-one 25. A solution of 4-bromo-1-diazobutan-2-one[1,12] (0.51 g, 2.9 mmol), 2-vinylaziridine[11] (0.20 g, 2.9 mmol) and triethylamine (0.44 g, 3.2 mmol) in ethyl acetate (30 cm^3) was heated at 60 °C for 12 h. The mixture was cooled and washed with water (2 × 10 cm^3), and the aqueous phase was then extracted with ethyl acetate (2 × 15 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (dichloromethane–methanol 95 : 5) to give the *α-diazo ketone* **25** (0.25 g, 53%) as a yellow liquid; ν_{max}(film)/cm^{-1} 3084, 2981, 2845, 2104, 1740, 1637, 990, 915; δ_H (250 MHz, $CDCl_3$) 5.51 (1H, ddd, *J* 17.2, 10.1 and 7.6, C*H*=CH_2), 5.40 (1H, br s, CHN_2), 5.29 (1H, dd, *J* 17.2 and 1.6, *trans* CH=CH_2), 5.10 (1H, dd, *J* 10.1 and 1.6, *cis* CH=CH_2), 2.73–2.50 (4H, m, CH_2CO and CH_2CH_2CO), 1.90 (1H, ddd, *J* 7.6, 6.6 and 3.5, C*H*CH=CH_2), 1.76 (1H, d, *J* 3.5, 1 × CH_2CHCH=CH_2), 1.53 (1H, d, *J* 6.6, 1 × CH_2CHCH=CH_2); δ_C (67.8 MHz, $CDCl_3$) 193.5 (CO), 138.0 (CH), 116.1 (CH_2), 56.2 (CH_2), 55.3 (CH), 41.3, (CH), 40.9 (CH_2), 35.2 (CH_2); *m*/*z* (EI) 137 ($M^+ - N_2$, 5%), 69 (5), 41 (100).

2,3,8,8a-Tetrahydro-5*H*-indolizin-1-one 27. *Ammonium ylide formation and rearrangement.* According to the general procedure, a solution of the α-diazo ketone **25** (50 mg, 0.30 mmol) in dry benzene (25 cm^3) was added to a solution of $Cu(acac)_2$ (1.6 mg, 0.006 mmol) in dry benzene (5 cm^3) at reflux, over a period of 20 min. The resulting solution was stirred at reflux for a further 15 min. Purification by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) gave the unstable *indolizidinone* **27** (10 mg, 26%) as a colourless liquid.

Ring-closing metathesis. The molybdenum complex **29** (83 mg, 1.1 mmol) was added to a solution of the diene **28**[1] (0.10 g, 0.61 mmol) in degassed pentane (35 cm^3) under an atmosphere of argon and the mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (diethyl ether–hexane, 2 : 1) to give the unstable *indolizidinone* **27** (46 mg, 55%) as a colourless liquid; $\nu_{max}(CHCl_3)/cm^{-1}$ 2798, 1750, 1000; δ_H (400 MHz, $CDCl_3$) 5.82–5.72 (2H, m, C*H*=C*H*), 3.57–3.50 (1H, m, 1 × NCH_2CH=CH), 3.48–3.44 (1H, m, NCHCO), 3.05–2.98 (1H, m, 1 × NCH_2CH=CH), 2.58–2.33 (5H, m, NCH_2CH_2CO, CH=CHCH_2CH and 1 × CH_2CO), 2.20–2.09 (1H, m, 1 × CH_2CO); δ_C (67.8 MHz, $CDCl_3$) 214.4 (CO), 125.3 (CH), 124.4 (CH), 64.8 (CH), 53.0 (CH_2), 50.2 (CH_2), 36.1 (CH_2), 26.5 (CH_2).

(*S*)-(−)-1-Diazo-4-(2-vinylpyrrolidin-1-yl)butan-2-one 31. The *N*-protected vinylpyrrolidine **30**[16] (637 mg, 3.76 mmol) was added to a mixture of potassium hydroxide (6.46 g, 115 mmol) and hydrazine monohydrate (0.91 cm^3, 19 mmol) in ethylene glycol (9 cm^3). The mixture was heated at reflux for 3 h 10 min,

then cooled and extracted with ethyl acetate (4 × 15 cm^3). The ethyl acetate extracts were dried over anhydrous potassium carbonate, and the solution added to a solution of 4-bromo-1-diazobutan-2-one (803 mg, 4.54 mmol)[1,12] in dry ethyl acetate (5 cm^3). Triethylamine (0.783 cm^3, 5.62 mmol) was added to the reaction, and the mixture heated at 60 °C for 14 h. After this time, the reaction was washed with a saturated solution of sodium bicarbonate (50 cm^3), and the aqueous phase extracted with ethyl acetate (3 × 50 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (1% triethylamine in diethyl ether–hexane, 3 : 1) to give the *α-diazo ketone* **31** (399 mg, 55%) as a green liquid; $[\alpha]_D^{27} = -48.5$ (*c* 0.782, $CHCl_3$); ν_{max}(film)/cm^{-1} 3079, 2966, 2876, 2796, 2104, 1641, 995, 920; δ_H (250 MHz, $CDCl_3$) 5.67 (1H, ddd, *J* 17.1, 10.0 and 8.4, C*H*=CH_2), 5.39 (1H, br s, CHN_2), 5.20–5.06 (2H, m, CH=CH_2), 3.18–3.00 (2H, m, C*H*CH=CH_2 and 1 × NC$H_2$$CH_2$$CH_2$), 2.70 (1H, ddd, *J* 8.3, 8.0 and 7.9, 1 × NC$H_2$$CH_2$CO), 2.51–2.33 (3H, m, CH_2CO and 1 × NC$H_2$$CH_2$$CH_2$), 2.14 (1H, dt, *J* 8.7 and 8.6, 1 × NCH_2-CH_2CO), 2.01–1.52 (4H, m, $NCH_2CH_2CH_2$ and NCH_2-CH_2CH_2); δ_C (67.8 MHz, $CDCl_3$) 193.8 (CO), 140.4 (CH), 116.6 (CH_2), 68.8 (CH), 54.5 (CH), 53.3 (CH_2), 49.2 (CH_2), 40.1 (CH_2), 31.4 (CH_2), 22.0 (CH_2); *m*/*z* (EI) 165.1147 ($M^+ - N_2$. $C_{10}H_{15}NO$ requires 165.1154).

(8*R*)-(+)-9-Oxo-1-azabicyclo[6.3.0]undec-5-ene 33. According to the general procedure, a solution of the α-diazo ketone **31** (151 mg, 0.783 mmol) in dry benzene (40 cm^3) was added to a solution of $Cu(acac)_2$ (4.1 mg, 0.016 mmol) in dry benzene (8 cm^3) at reflux, over a period of 1 h. The resulting solution was stirred at reflux for a further 20 min. Purification by flash column chromatography on silica gel (hexane–diethyl ether, 3 : 1) gave the *bicyclic amine* **33** (72.4 mg, 56%) as a colourless liquid; $[\alpha]_D^{31} = +2.58$ (*c* 0.683, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2930, 2850, 2800, 1750, 1600; δ_H (250 MHz, $CDCl_3$) 5.78–5.64 (2H, m, $CHCH_2C$*H*=CH and $CHCH_2CH$=C*H*), 3.34–3.27 (1H, m, 1 × C$H_2$$CH_2$CO), 2.82 (1H, ddd, *J* 14.1, 5.5 and 2.2, 1 × NCH_2-CH_2CH_2), 2.75–2.64 (1H, m, 1 × C$H_2$$CH_2$CO), 2.62–2.32 (6H, m, NCHCO, CH_2CO, 1 × NCHCH_2, 1 × NC$H_2$$CH_2CH_2$ and 1 × $NCH_2CH_2C$$H_2$), 2.27–2.16 (1H, m, 1 × NCHCH_2), 2.08–1.97 (1H, m, 1 × $NCH_2CH_2C$$H_2$), 1.91–1.75 (1H, m, 1 × $NCH_2C$$H_2CH_2$), 1.47–1.32 (1H, m, 1 × $NCH_2C$$H_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 215.7 (CO), 131.8 (CH), 127.3 (CH), 72.6 (CH), 53.8 (CH_2), 52.1 (CH_2), 37.4 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 24.2 (CH_2); *m*/*z* (EI) 165.1154 (M^+. $C_{10}H_{15}NO$ requires 165.1154).

(8*R*,9*R*)-9-Hydroxy-1-azabicyclo[6.3.0]undec-5-ene 34. L-Selectride® (0.56 cm^3 of a 1 M solution in tetrahydrofuran, 0.56 mmol) was added dropwise to a solution of the ketone **33** (30.8 mg, 0.186 mmol) in dry tetrahydrofuran (5 cm^3) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and the solvent was then removed *in vacuo*. The residue was stirred at room temperature with a saturated aqueous solution of sodium bicarbonate (5 cm^3) for 20 h, and then extracted with ethyl acetate (4 × 6 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (diethyl ether–methanol, 4 : 1) to give the *alcohol* **34** (23.4 mg, 75%) as a colourless solid; mp 48–50 °C; $[\alpha]_D^{26} = -95.2$ (*c* 0.178, $CHC1_3$); ν_{max}($CHCl_3$)/cm^{-1} 3336, 2927, 2851, 1602, 1002, 908; δ_H (250 MHz, $CDCl_3$) 5.82–5.59 (2H, m, $CHCH_2C$*H*=CH and $CHCH_2CH$=C*H*), 4.09 (1H, m, ddd, *J* 7.2, 4.7 and 2.5, C*H*OH), 3.17 (1H, td, *J* 9.0 and 2.4, 1 × NCH_2-CH_2CHOH), 2.76–2.67 (2H, m, NC$H_2CH_2CH_2$), 2.54–1.96 (8H, m, NC*H*CHOH, 1 × NCH_2CH_2CHOH, $NCHCH_2$, $NCH_2CH_2CH_2$, 1 × NCH_2CH_2CHOH and OH), 1.87–1.62 (2H, m, 1 × $NCH_2CH_2CH_2$ and 1 × NCH_2CH_2CHOH), 1.45–1.30 (1H, m, 1 × $NCH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 130.1 (CH), 128.5 (CH), 75.7 (CH), 70.7 (CH), 55.9 (CH_2), 52.4 (CH_2), 33.5 (CH_2), 28.1 (CH_2), 27.6 (CH_2), 24.0 (CH_2); *m*/*z* (EI) 167.1306 (M^+. $C_{10}H_{17}NO$ requires 167.1310).

Preparation of the Mosher's ester 35. Triethylamine (0.45 μl, 0.32 mmol) was added dropwise to a solution of the amino alcohol **34** (17.8 mg, 0.106 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.8 mg, 0.007 mmol) in dry dichloromethane (3 cm^3) at 0 °C. The mixture was stirred at 0 °C for 5 min and then a solution of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride (67.4 mg, 0.267 mmol) in dry dichloromethane (2 cm^3) was added dropwise. The resulting solution was stirred at 0 °C for 1 h and at room temperature for 53 h. The reaction mixture was washed with saturated aqueous sodium bicarbonate (5 cm^3) and the aqueous phase extracted with dichloromethane (2 × 5 cm^3). The combined organic extracts were dried over anhydrous potassium carbonate and the solvent removed *in vacuo*. The residue was then analysed by ^{19}F NMR in $CDCl_3$ referenced to $CFCl_3$.

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