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FORMAL SYNTHESIS OF (5*R*,8*R*,8a*S*)-INDOLIZIDINE 209I *VIA* ENAMINONES INCORPORATING WEINREB AMIDES

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Abstract – A formal enantioselective synthesis of the amphibian alkaloid (5*R*,8*R*,8a*S*)-(–)-indolizidine **209I** (**6**) is reported. Control of the absolute stereochemistry at C-5 resulted from application of the Davies procedure, which entails stereoselective conjugate addition of (*R*)-(+)-*N*-benzyl-1-phenylethylamine to *tert*-butyl (*E*)-hex-2-enoate. The resulting chiral adduct **26** was converted in eight steps into a pivotal enaminone incorporating a Weinreb amide, the inherent nucleophilicity of which was exploited in a cyclisation that yielded the key bicyclic intermediate (5*R*)-*N*-methoxy- *N*-methyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxamide (**38**). Stereoselective catalytic hydrogenation of the alkene bond, reaction of the Weinreb amide with ethylmagnesium bromide, and epimerisation of the resulting ketone completed the formal synthesis of the target alkaloid.

INTRODUCTION

The indolizidine (1-azabicyclo[4.3.0]nonane) motif is well represented among the alkaloids isolated from the skins of amphibians.[1,2] This family of metabolites, most of which appear to be sequestered from insects upon which the animals feed, comprises several distinct classes, including 3,5- and 5,8-disubstituted indolizidines, for example, (–)-indolizidines **223AB** (**1**) and **209B** (**2**); 5,6,8-trisubstituted indolizidines such as (–)-indolizidine **223A** (**3**); and pumiliotoxins and allopumiliotoxins such as (+)-pumiliotoxin **251D** (**4**) and its hydroxy congener, allopumiliotoxin **267A** (**5**) (Figure 1). The 5,8-disubstituted indolizidines are particularly abundant, and about 80 members of this class have been partially or fully characterised to date.[2] These intriguing natural products, and especially those bearing a methyl substituent at C-8, have become popular targets for total synthesis.[3,4] More recently identified members of the series contain ethyl, propyl, butyl, vinyl or but-3-enyl substituents at C-8, while some also bear hydroxylated alkyl substituents at this site. The only examples of these longer-chain homologues to have been synthesised are indolizidines (–)-**209I** (**6**),[5,6]

(–)-**219F** (**7**),[7,8] (–)-**221I** (**8**),[7,9] (–)-**221K** (**9**),[10] (–)-**223J** (**10**),[5] (–)-**223V** (**11**)[11,12] and (–)-**251N** (**12**),[10] as well as racemic **209I** and **223J**.[13]

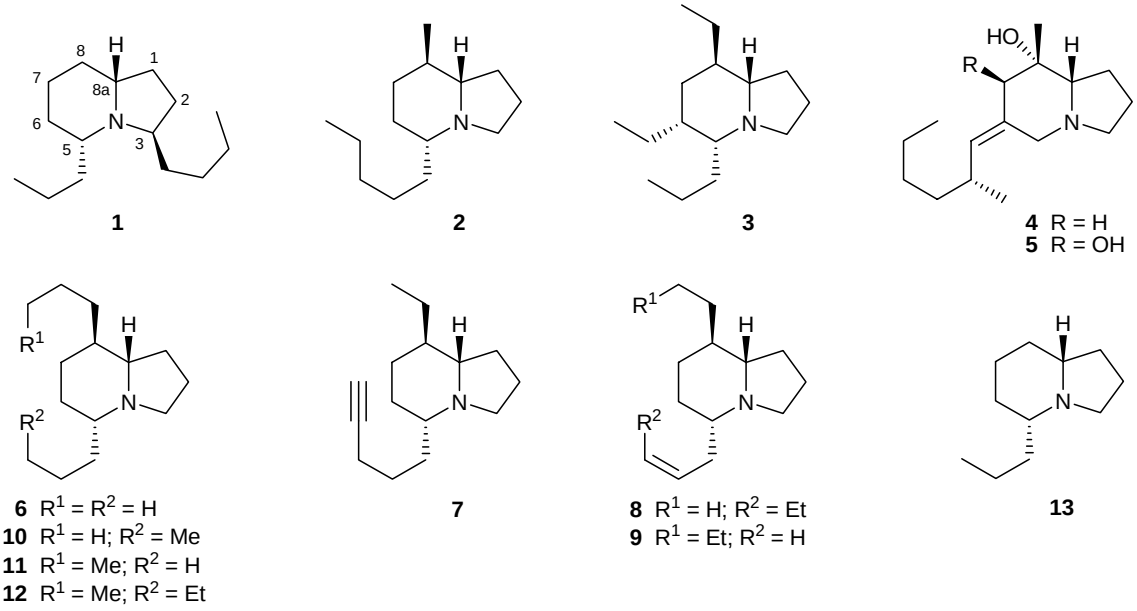
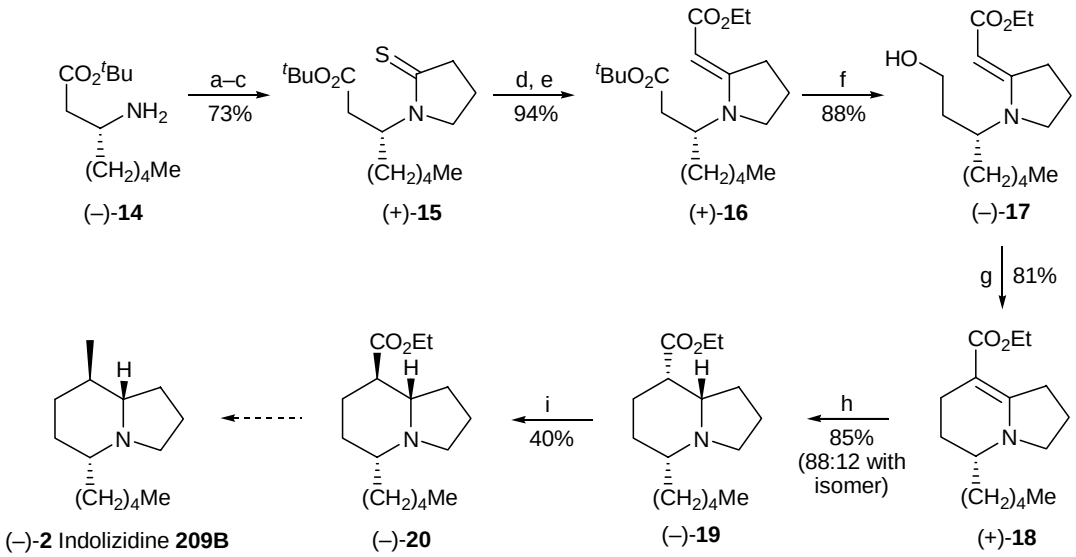


Figure 1. Representative indolizidine alkaloids. The conventional numbering scheme is shown in **1**.

In continuing investigations into the use of pyrrolidinylidene- and piperidinylidene-containing enaminones as key intermediates in the synthesis of alkaloids and other nitrogen heterocycles,[14] we previously reported enantioselective total syntheses of (–)-indolizidine **209B** (**2**)[15] and a monosubstituted analogue, (–)-indolizidine **167B** (**13**),[16,17] via chiral 3-amino esters prepared by the well-known Davies protocol.[18,19] In this article we present a formal synthesis of (–)-indolizidine **209I** (**6**) by a route that expands upon features introduced in our syntheses of **2** and **13**.

RESULTS AND DISCUSSION

Steps in our prior enantioselective synthesis of (–)-indolizidine **209B** (**2**)[15] that are relevant to the present report are shown in Scheme 1. The homochiral amine (–)-**14**, prepared by the Davies procedure from *tert*-butyl (*E*)-oct-2-enoate and (*R*)-*N*-benzyl-1-phenylethylamine followed by hydrogenolytic removal of the benzyl substituents, was converted in several steps into the thiolactam (+)-**15**. Eschenmoser sulfide contraction[20,21] with ethyl bromoacetate yielded the enaminone (vinylogous urethane) intermediate (+)-**16**, after which chemoselective reduction of the saturated ester produced the alcohol (–)-**17**. The bicyclic core of the alkaloid was then constructed by a cycloalkylation that took advantage of the nucleophilic reactivity of the enaminone. The synthesis was completed by chemoselective and reasonably diastereoselective reduction of the alkene bond of the bicyclic enaminone (+)-**18**, catalytic hydrogenation to (–)-**19**, and epimerisation of the ester group to give (–)-**20**. The ester finally served as the source of the methyl substituent at C-8.

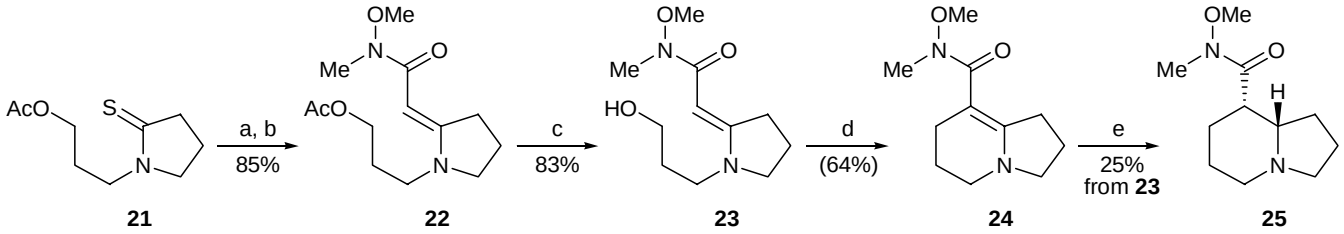


Scheme 1. *Reagents and conditions:* a, $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, reflux; b, KO^{t}Bu, ^{t}BuOH, rt; c, Lawesson's reagent, PhMe, reflux; d, $BrCH_2CO_2Et$, MeCN, rt; e, Ph_3P, Et_3N, MeCN, rt; f, $LiAlH_4$, THF, rt; g, I_2, imidazole, Ph_3P, PhMe, 110 °C; h, H_2 (1 atm), PtO_2, AcOH, rt; i, NaOEt (cat.), EtOH, reflux.

A similar route can be envisaged for the synthesis of indolizidine **209I** and other analogues, but in this case homologation of the C-8 substituent would be required in order to introduce the longer chains. In preliminary experiments, attempts to replace the ester group of the vinylogous urethane by appropriate ketones gave disappointing results. As an alternative, we turned to Weinreb amides, which have become standard intermediates for the production of ketones by virtue of their ready reaction with organometallic reagents.[22] However, we are aware of only three prior examples[23-25] of enaminones containing Weinreb amides (effectively, vinylogous ureas). Since the reactivity of such rare systems could not be predicted with confidence, we first investigated a simple model system to ascertain the feasibility of working with this type of compound.

The simple vinylogous urea **22** was readily prepared in 85% yield by alkylating 3-(2-thioxo-1-pyrrolidinyl)propyl acetate (**21**), a known compound,[26] with *N*-methoxy-*N*-methyl-2-bromoacetamide,[24] after which extrusion of sulfur was effected by treatment with triphenylphosphine and triethylamine in acetonitrile at ambient temperature (Scheme 2). The acetate was cleaved with potassium carbonate in methanol to give the alcohol **23** in 83% yield. The (*E*)-geometry of the double bond in these products was inferred from the chemical shift of the hydrogen atoms at C-3 in the ring (δ *ca*. 3.2), the downfield shift of about 0.6 ppm relative to (*Z*)-analogues[20] arising from the anisotropic deshielding effect of the carbonyl group. *In situ* conversion of the free alcohol into the corresponding iodide with iodine, triphenylphosphine and imidazole in a mixture of toluene and acetonitrile[27] and heating the reaction mixture under reflux produced the desired but hard-to-purify bicyclic product, **24**, in a moderate 64% yield. Unfortunately, this compound failed to undergo the typical alkylation reaction of Weinreb amides when

treated with a variety of organometallic reagents, including methyllithium, *n*-butyllithium, ethylmagnesium bromide and allylmagnesium bromide; in all cases, only unreacted **24** was recovered. This disappointing result was in line with the only previously reported attempt to alkylate Weinreb amides incorporated into an enaminone backbone with organometallics.[24] However, catalytic hydrogenation of **24** over Adams catalyst in glacial acetic acid produced the saturated compound **25** predominantly as one diastereomer (95 : 5, by NMR), although the overall yield based on alcohol **23** was only 25%. Nonetheless, these results served to establish proof of concept for the synthesis of indolizidine **209I**.

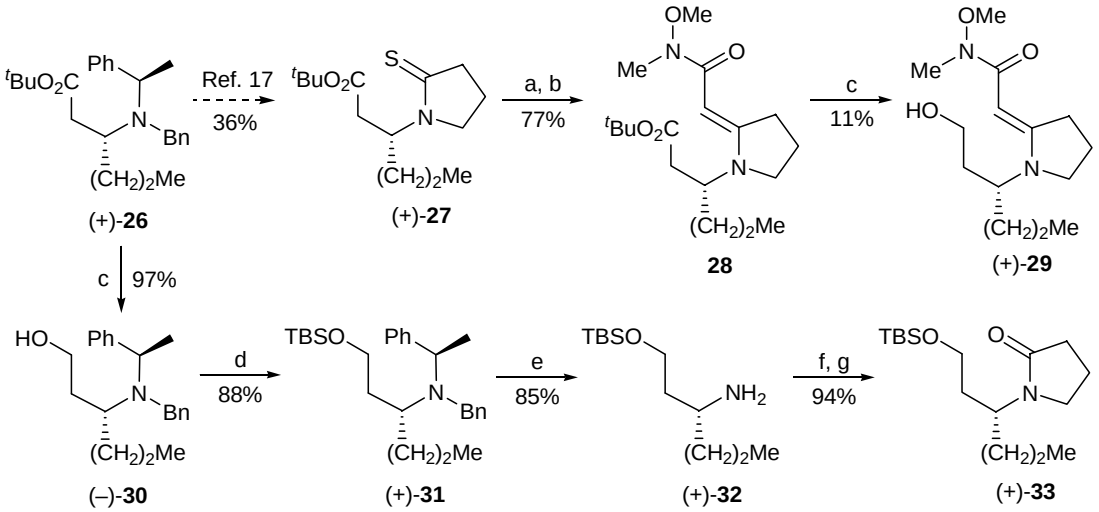


21 **22** **23** **24** **25**

Scheme 2. *Reagents and conditions:* a, $BrCH_2CONMe(OMe)$, CH_2Cl_2, rt; b, Ph_3P, Et_3N, MeCN, rt; c, K_2CO_3, MeOH, rt; d, I_2, PPh_3, imidazole, PhMe-MeCN (1 : 2), reflux; e, H_2 (1 atm), PtO_2 (cat.), AcOH.

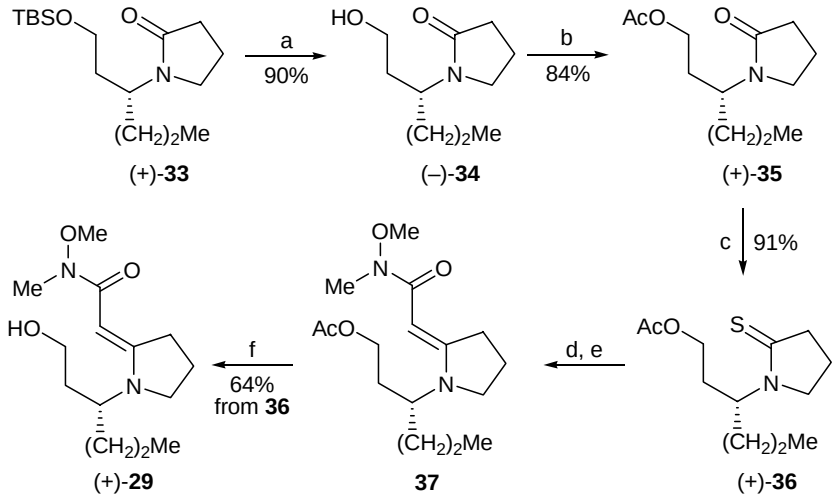
We next embarked on the synthesis of indolizidine **209I** by modifying the strategy shown in Scheme 1. The procedure commenced with (*R*)-(+)-**26**, the homochiral adduct from the Davies reaction of *tert*-butyl (*E*)-hex-2-enoate and (*R*)-*N*-benzyl-1-phenylethylamine.[17] The sequence shown in Scheme 3 (upper line) proceeded smoothly up to the formation of thiolactam (+)-**27**, an intermediate that featured in our prior synthesis of (–)-indolizidine **167B**.[17] Alkylation on sulfur with *N*-methoxy-*N*-methyl-2-bromoacetamide followed by Eschenmoser reaction afforded the unstable vinylogous urea **28** in 77% yield. However, all attempts to reduce the *tert*-butyl ester selectively with lithium aluminium hydride under various conditions were largely unsuccessful, the best yield of the desired alcohol (+)-**29** being 11%. Over-reduction of the vinylogous urea appears to be a serious competitor, in contrast to the relative robustness of analogous vinylogous urethanes. This setback, not entirely unexpected, necessitated a change of tactics.

Our prior experience with another very labile enaminone[28] suggested that the problem could be resolved by reduction of the saturated ester at a much earlier stage of the synthesis. In this case, the Davies adduct **26** was reduced with lithium aluminium hydride in 97% yield to give the alcohol (–)-**30**, which was protected as the *tert*-butyl(dimethylsilyl) ether (+)-**31** (Scheme 3, lower line). Hydrogenolytic removal of the benzyl groups was achieved by treatment with palladium on carbon under a moderate pressure of hydrogen (7 atmospheres) to give the primary amine (+)-**32**, which was immediately acylated with 4-chlorobutanoyl chloride. The resulting unstable amide underwent cyclisation to the lactam (+)-**33** on careful treatment with potassium *tert*-butoxide in dry *tert*-butyl alcohol. However, since the silyl ether subsequently did not survive attempted thionation of **33** under a variety of conditions – a problem that we had previously encountered in a related system[28] – yet another change of plans was required.



Scheme 3. *Reagents and conditions:* a, $BrCH_2CON(OMe)Me$, MeCN, rt; b, Ph_3P, Et_3N, MeCN, rt; c, $LiAlH_4$, Et_2O, 0 °C to rt; d, TBSCl, imidazole, DMF, rt; e, H_2 (7 atm), 10% Pd-C, EtOH, 3 d; f, $Cl(CH_2)_3COCl$, NEt_3, CH_2Cl_2, rt; g, KO^tBu, ^{t}BuOH, rt.

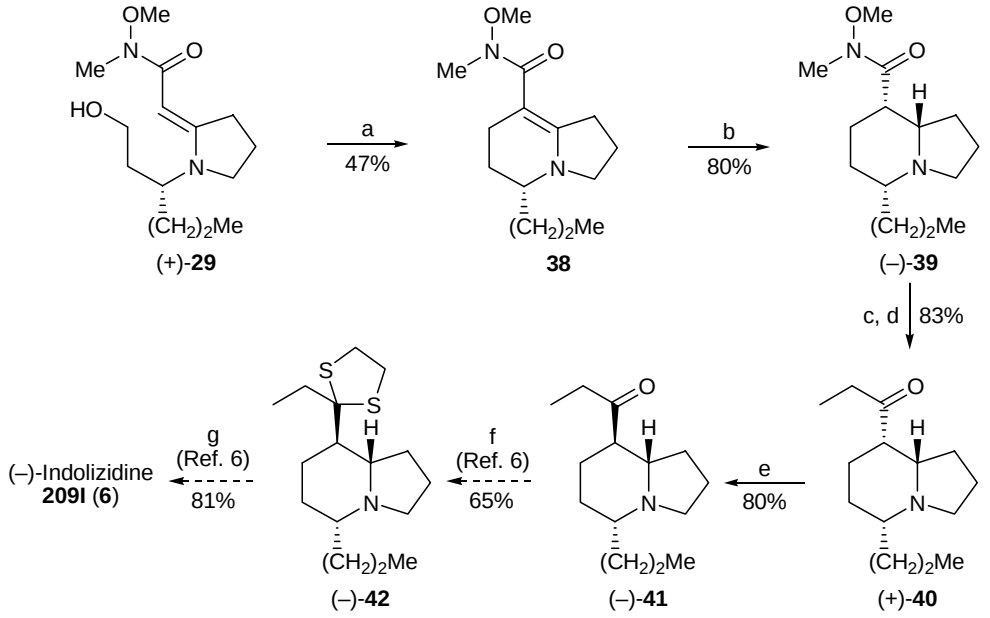
The solution, undoubtedly clumsy, required a change of protecting groups for the alcohol (Scheme 4). The silyl ether **33** was cleaved with aqueous hydrofluoric acid, after which the liberated alcohol (–)-**34** was acetylated to give (+)-**35** in an overall yield of 76% based on **33**. The lactam was then successfully thionated with phosphorus pentasulfide by the Brillon procedure,[29] giving (+)-**36** in 91% yield. Salt formation with *N*-methoxy-*N*-methyl-2-bromoacetamide followed by sulfide contraction afforded the vinylogous urea intermediate **37**, slightly contaminated with phosphorus-containing impurities that were difficult to remove. However, on hydrolysis of the acetate with potassium carbonate in methanol, the pure alcohol (+)-**29** could be isolated in an overall yield of 64% based on **36**. This product was identical in all respects with that prepared by the abortive route shown in Scheme 3.



Scheme 4. *Reagents and conditions:* a, aq. HF (40%), MeOH, rt; b, Ac_2O, py, rt; c, P_2S_5, Na_2CO_3. THF, rt; d, $BrCH_2CON(OMe)Me$, MeCN, rt; e, Ph_3P, Et_3N, MeCN, rt; f, K_2CO_3, MeOH, rt.

The stage was now set for the construction of the indolizidine nucleus. *In situ* conversion of the free alcohol **29** into the corresponding iodide and heating the reaction mixture under reflux produced the desired bicyclic product, (5*R*)-*N*-methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxamide **38**, in a somewhat disappointing yield of 47% (Scheme 5). However, hydrogenation over platinum dioxide was stereoselective, and gave the expected *cis*-hydrogenated product (–)-**39** as the only isolable isomer in 80% yield. The diastereofacial selectivity is in accord with what we have previously observed with related bicyclic vinylogous urethanes in both indolizidine[15] and quinolizidine[28] systems. In line with our expectations, there appears to be an equatorial preference for the propyl side chain in the developing chair conformation of the six-membered ring, and this in turn directs the reductant towards the less hindered distal face of the double bond. Support for the *cis*-relationship of the hydrogen atoms at C-5 and C-8a in the product was provided by a Bohlmann band[30] at *ca*. 2790 cm^{-1} in the FTIR spectrum, a feature that also implies a *trans*-disposition of the lone pair and 8a-H across the ring junction. At this point we took advantage of the characteristic reactivity of the Weinreb amide. Treating **39** with ethylmagnesium bromide in tetrahydrofuran followed by hydrolysis of the adduct with dilute hydrochloric acid furnished the 8-propanoylindolizidine (+)-**40** in 83% yield, without apparent epimerisation at C-8. Of course, the target alkaloid requires inversion of configuration at this site. This inversion was readily achieved by heating **40** with sodium methoxide in methanol at reflux. After workup and purification, an 80% recovery of the epimerised ketone (–)-**41** was obtained. This product has previously been reported by Ma and co-workers[6] as an intermediate in their synthesis of (–)-indolizidine **209I** (**6**). Our product gave nuclear magnetic resonance spectra that agreed with those reported by Ma to within 0.03 and 0.3 delta units for the ^{1}H and ^{13}C signals, respectively. Our synthesis thus constitutes a formal synthesis of (–)-indolizidine **209I**, since Ma converted **41** into the target alkaloid in 53% overall yield by treatment of the corresponding dithioacetal (–)-**42** with Raney nickel.

Our formal route to (–)-indolizidine **209I** (**6**) is, in principle, suitable for making most of the known members of the 5,8-disubstituted indolizidine family of alkaloids. The Davies procedure for preparing chiral 3-amino esters is versatile enough to permit introduction of many of the substituents found at C-5 simply by commencing with appropriate (*E*)-enoate esters at the outset. More importantly, we have shown that enaminones that incorporate a Weinreb amide unit provide a useful extension to our general approach to alkaloid synthesis; by treating late-stage intermediates such as **39** with organometallic reagents of different chain lengths, most of the substituents found at C-8 in the natural products should be accessible.



Scheme 5. *Reagents and conditions:* a, I_2, PPh_3, imidazole, PhMe-MeCN (1 : 2), reflux; b, H_2 (1 atm), PtO_2 (cat.), AcOH; c, EtMgBr, THF, 0 °C to rt; d, aq. HCl (6 M); e, NaOMe, MeOH, reflux; f, $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, 0 °C to rt; g, Raney Ni, ^{i}PrOH, 70 °C.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from Na/benzophenone; acetonitrile, *N*,*N*-dimethylformamide (DMF), dichloromethane and triethylamine from CaH_2; pyridine from potassium hydroxide; and toluene from Na metal. Commercially available chemicals were used as received. Melting points, recorded on a Reichert hot-stage microscope apparatus, are uncorrected. TLC was performed on aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Column chromatography was carried out on silica gel 60, particle size 0.063–0.200 mm (conventional columns) or Whatman Partisil Prep 40, particle size 0.040–0.063 mm (flash columns). FTIR spectra were recorded on a Bruker Vector 22 spectrometer. NMR spectra were recorded on a Bruker Avance 300 spectrometer (300.139 MHz for ^{1}H, 75.035 MHz for ^{13}C) in $CDCl_3$ as solvent and with TMS as internal standard. DEPT and CH-correlated spectra were routinely used for assignment of signals. *J* values are given in Hz. High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer at 70 eV and 200 μA with a MASPEC II data system. Optical rotations were measured on a Jasco DIP-370 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Precursors **26** and **27** were prepared as described previously.[17]

3-[(2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidin-1-yl]propyl acetate (22)

3-(2-Thioxo-1-pyrrolidinyl)propyl acetate[26] (**21**) (6.73 g, 33.5 mmol) and 2-bromo-*N*-methoxy-*N*-methylacetamide (6.39 g, 35.1 mmol) were stirred together in dry CH_2Cl_2 (67 cm^3) for 5 h. The solvent was removed under high vacuum and the resulting slurry was stirred at rt for a further 18 h. The salt was dissolved in MeCN (60 cm^3) and a homogeneous solution of PPh_3 (9.21 g, 35.1 mmol) and NEt_3 (3.55 g,

4.90 cm^3, 35.1 mmol) in MeCN (60 cm^3) was added in one portion. After 5 h the solution was filtered through a pad of celite and evaporated *in vacuo*. The residue was taken up in EtOAc (300 cm^3), triturated for 30 min and again filtered through a pad of celite. The filtrate was extracted with HCl (2 M, 3 × 300 cm^3), the aqueous extracts were basified to pH 11 with conc. aq. NH_3 solution (35%) and back-extracted with CH_2Cl_2 (3 × 100 cm^3). The organic extracts were combined, dried (anhydrous $MgSO_4$), filtered and evaporated *in vacuo*. Purification by column chromatography with CH_2Cl_2-MeOH (9 : 1) as eluent afforded 3-[(2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidin-1-yl]propyl acetate (**22**) as a light yellow oil (7.73 g, 85%); R_f (EtOAc–MeOH 4 : 1) 0.81; ν_{max} (film)/cm^{-1} 2939 (C-H, m), 1734 (ester C=O, s), 1646 (amide C=O, s), 1426 (m), 1367 (m) 1233 (s), 1042 (s), 998 (m); δ_H (300 MHz; $CDCl_3$) 5.10 (1H, s, C=C*H*), 4.11 (2H, t, *J* = 6.3 Hz, CH_2OAc), 3.67 (3H, s, O*Me*), 3.36 and 3.31 (4H, 2 × overlapping t, *J* = 7.1 Hz, *J* = 7.3 Hz, ring and chain CH_2N), 3.21 (2H, t, *J* = 7.7 Hz, CH_2C=), 3.15 (3H, s, N*Me*), 2.07 (3H, s, OCO*Me*), 1.94 (4H, coincident quintets, *J* = 6.8 Hz, remaining CH_2); δ_C (75 MHz; $CDCl_3$) 171.8, 170.8, 164.3, 76.7, 61.9, 60.8, 52.4, 43.1, 33.0, 32.6 , 25.4, 21.2, 20.8; *m/z* (EI) 270 (M^+, 1%), 211 (13), 210 (100), 168 (13), 148 (12), 74 (22). HRMS (EI) Found: M^+, 270.1562. $C_{13}H_{22}N_2O_4$ requires 270.1580.

(2*E*)-2-[1-(3-Hydroxypropyl)pyrrolidin-2-ylidene]-*N*-methoxy-*N*-methylethanamide (23)

3-[(2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl]propyl acetate (**22**) (7.73 g, 28.6 mmol) and K_2CO_3 (7.91 g, 57.2 mmol) were stirred in MeOH (100 cm^3) for 3 h. The mixture was filtered through celite. The filtrate was evaporate *in vacuo*, and then taken up in $CHCl_3$ (300 cm^3) and washed with a saturated sodium chloride solution (300 cm^3). The aqueous phases were back extracted with $CHCl_3$ (3 × 250 cm^3), dried (anhydrous $MgSO_4$), filtered and evaporated *in vacuo* to afford the crude product. Purification by column chromatography with CH_2Cl_2-MeOH (9 : 1) as eluent gave (2*E*)-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]-*N*-methoxy-*N*-methylethanamide (**23**) (5.45 g, 83%) as a yellow oil; R_f 0.85 (CH_2Cl_2-MeOH 7 : 3); ν_{max} (film)/cm^{-1} 3353 (O-H, v br, m), 2938 and 2874 (C-H, m) 1646 (s), 1613 (s), 1438 (m), 1423 (m), 1360 (m), 1170 (m), 1055 (m), 918 (m), 828 (m), 810 (m), 720 (m), 660 (m); δ_H (300 MHz; $CDCl_3$) 5.14 (1H, s, C=C*H*), 3.68 and 3.67 (5H, overlapping t and s, *J* = 6.0 Hz, CH_2OH and O*Me*), 3.38 and 3.36 (4H, 2 × overlapping t, *J* = 7.0 Hz, 6.9 Hz, ring and chain CH_2N), 3.22 (2H, t, *J* = 7.8 Hz, CH_2C=), 3.14 (3H, s, N*Me*), 2.04 (1H, s, O*H*), 1.93 (2H, quintet, *J* = 7.1 Hz, chain $CH_2CH_2CH_2$), 1.84 (2H, quintet, *J* = 6.6 Hz, ring 4-H); δ_C (75 MHz; $CDCl_3$) 172.1, 164.8, 76.3, 60.9, 59.9, 52.4, 42.9, 33.1, 32.7, 29.1, 21.2; *m/z* (EI) 228 (M^+, 2%), 169 (12), 168 (100), 150 (5), 120 (5) 110 (5), 108 (5). HRMS (EI) Found, M^+, 228.1467. $C_{11}H_{20}N_2O_3$ requires 228.1474.

***N*-Methoxy-*N*-methyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxamide (24)**

A solution of (2*E*)-2-[1-(3-hydroxypropyl)pyrrolidin-2-ylidene]-*N*-methoxy-*N*-methylethanamide (**23**) (0.776 g, 2.79 mmol) was dissolved in a mixture of MeCN (17 cm^3) and PhMe (8.5 cm^3). To this was added PPh_3 (1.46 g, 5.58 mmol) and imidazole (0.380 g, 5.58 mmol) followed by I_2 (1.42 g, 5.58 mmol). The solution was heated at reflux for 1 h. The reaction was quenched by the addition of a saturated solution of aq. $NaHCO_3$ (30 cm^3), and the aqueous residues were extracted with EtOAc (3 × 30 cm^3). The combined organic fractions were washed with saturated aq. $Na_2S_2O_3$ solution (30 cm^3). The organic washings were dried (anhydrous $MgSO_4$), filtered and evaporated *in vacuo* to yield the crude product. Purification by flash column chromatography with EtOAc-EtOH (19 : 1) as eluent yielded *N*-methoxy-*N*-methyl-1,2,3,5,6,7- hexahydroindolizine-8-carboxamide (**24**) (0.375 g, 64%); R_f (CH_2Cl_2-MeOH 19 : 1) 0.19; δ_H (300 MHz; $CDCl_3$) 3.62 (3H, s, O*Me*), 3.26 (2H, t, *J* = 7.0 Hz, 3-H or 5-H), 3.18 (2H, t, *J* = 5.8 Hz, 3-H or 5-H), 3.06 (3H, s, N*M*e), 3.01 (2H, t, *J* = 7.8 Hz, 1-H), 2.38 (2H, t, *J* = 6.0 Hz, 7-H), 1.90 and 1.83 (4H, 2 × overlapping quintet, *J* = 5.8 Hz, *J* = 5.8 Hz, 2-H and 6-H); δ_C (75 MHz; $CDCl_3$) 174.4, 157.7, 90.0, 59.7, 52.6, 45.0, 34.3, 31.7, 23.6, 21.9, 21.2. HRMS (EI) Found: M^+, 210.1352. $C_{11}H_{18}N_2O_2$ requires 210.1368.

***rel*-(8*R*,8a*S*)-*N*-Methoxy-*N*-methyloctahydroindolizine-8-carboxamide (25)**

A solution of bicyclic vinylogous urea **24** (0.173 g, 0.823 mmol) in glacial acetic acid (4.5 cm^3) containing a suspension of Adams' catalyst (41 mg) was hydrogenated for 24 h at 1 atmosphere. The mixture was filtered through celite and washed copiously with EtOH, after which the filtrates were evaporated *in vacuo*. Purification of the residue by column chromatography with CH_2Cl_2-MeOH (19 : 1) as eluent afforded *rel*-(8*R*,8a*S*)-*N*-methoxy-*N*-methyloctahydroindolizine-8-carboxamide (**25**) and an inseparable diastereomer (95 : 5) as a yellow oil (43 mg, 25%); ν_{max} (film)/cm^{-1} 2928 (C-H, s), 1663 (C=O, s), 1441 (m), 1378 (m), 1342 (m), 1160 (m), 1100 (m), 1039 (w), 998 (s), 963 (m); δ_H (300 MHz; $CDCl_3$; major isomer) 3.67 (3H, s, O*Me*), 3.26-3.20 (1H, M, 3-H-eq), 3.18 (3H, s, N*Me*), 3.08-2.94 (2H, m, 8-H and 8a-H), 2.38-2.31 (1H, m), 2.26-1.98 (3H, m), 1.95-1.43 (7H, m); δ_C (75 MHz; $CDCl_3$) 174.7 (*C*=O), 63.5 (C-8a), 61.2 (O*Me*), 54.4 (C-3), 51.8 (C-5), 37.0 (C-8), 29.6 (N*Me*), 26.1 (C-1), 25.2 (C-7), 22.8 (C-2), 20.4 (C-6). HRMS (EI) Found: M^+, 212.1518. $C_{11}H_{20}N_2O_2$ requires 212.1525.

***tert*-Butyl (3*R*)-3-[(2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidin-1-yl]hexanoate (28)**

tert-Butyl (3*R*)-3-(2-thioxopyrrolidin-1-yl)hexanoate[17] (**27**) (0.530 g, 1.95 mmol) and 2-bromo-*N*-methoxy-*N*-methylacetamide[24] (0.430 g, 2.34 mmol) were dissolved in dry MeCN (4.00 cm^3, 2.00 cm^3 $mmol^{-1}$). The mixture was stirred for 16 h at rt, after which time the solvent was removed *in vacuo* to afford a white salt. This was re-dissolved in dry MeCN (4.00 cm^3), and to this was added PPh_3 (0.614 g, 2.34 mmol) followed by NEt_3 (0.237 g, 0.330 cm^3, 2.34 mmol). The solution was stirred for 3 h,

during which time a white precipitate formed. The solution was filtered through a celite pad, the solvent was removed *in vacuo* and the resulting residue was triturated in EtOAc for 30 min. The solution was again filtered through celite, and the filtrate was then extracted with aq. HCl (2.0 M, 3 × 50 cm^3). The aqueous extracts were basified to ~ pH 10 with aq. NH_3, and then extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and evaporated *in vacuo* to yield a yellow oil. The crude oil was purified by column chromatography with MeOH-CH_2Cl_2 (1 : 19) as eluent to afford *tert*-butyl (3*R*)-3-[(2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}-pyrrolidin-1-yl]-hexanoate (**28**) as a light yellow oil (0.509 g, 77%). ν_{max} (film)/cm^{-1} 3084, 3062 and 3027 (=C-H, w), 2970, 2932 and 2872 (C-H, w), 1724 (C=O, s), 1493 (m), 1454 (m), 1367 (s), 1297 (m), 1230 (m), 1217 (m), 1143 (s), 1094 (m), 1026 (w), 749 (m), 698 (s); δ_H (300 MHz; $CDCl_3$) 5.26 (1H, s, C=C*H*), 4.17-4.07 (1H, m, NC*H*), 3.68 (3H, s, O*Me*), 3.32-3.19 (4H, m, ring NCH_2 and CH_2C=), 3.14 (3H, s, N*Me*), 2.44 (2H, dd, *J* = 6.0 and 7.1 Hz, NCHCH_2CO), 1.88 (2H, quintet, *J* = 7.3 Hz, ring $CH_2CH_2CH_2$), 1.67-1.45 (2H, m, NCHCH_2Et), 1.41 (9H, s, CMe_3), 1.36-1.20 (2H, m, CH_2Me), 0.93 (3H, t, *J* = 7.3 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 172.1, 170.1, 164.7, 80.8, 77.7, 60.8, 51.3, 45.6, 39.0, 34.3, 33.0, 32.6, 27.8, 21.1, 19.3, 13.7.

(2*E*)-2-{1-[(1*R*)-1-(2-Hydroxyethyl)butyl]pyrrolidin-2-ylidene}-*N*-methoxy-*N*-methylethanamide (29)

tert-Butyl (3*R*)-3-[(2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidin-1-yl]hexanoate (**28**) (0.167 g, 0.490 mmol) was added to a slurry of $LiAlH_4$ (0.022 g, 0.590 mmol) in Et_2O (1.00 cm^3) at 0 °C. The slurry was warmed to rt and stirred for 16 h. The reaction was quenched by the sequential addition of H_2O (0.1 cm^3), aq. NaOH solution (0.1 cm^3, 15% w/v) and finally H_2O (0.2 cm^3). The solids were filtered off by passing the mixture through a thin pad of celite and washing several times with CH_2Cl_2. The filtrate was dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield a brown-orange oil. Purification of the oil by column chromatography with EtOH-CH_2Cl_2 (1 : 19) as eluent afforded (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]pyrrolidin-2-ylidene}-*N*-methoxy-*N*-methylethanamide (**29**) as a clear oil (0.0150 g, 11%). R_f 0.59 (EtOH-CH_2Cl_2 1 : 9); $[\alpha]_D^{20}$ +3.85 (*c* 1.04 abs. EtOH); ν_{max} (film)/cm^{-1} 3358 (OH, v br, m), 2955, 2931 and 2870 (C-H, m), 1617 (C=O, m), 1553 (s), 1411 (m), 1279 (m), 1238 (m); δ_H (300 MHz; $CDCl_3$) 5.25 (1H, s, NC=C*H*), 3.91 (1H, br quintet, *J* = *ca* 7.2 Hz, NC*H*), 3.66 and 3.60-3.50 (4H, overlapping s and m, O*Me* and C$H_a$$H_b$OH), 3.50-3.35 (1H, m, $CH_a$$H_b$OH), 3.26 (2H, t, *J* = 7.9 Hz, ring NCH_2), 3.19 (2H, dt, *J* = 6.6 and 2.7 Hz, ring CH_2C=), 3.14 (3H, s, N*Me*), 1.90 (2H, quintet, *J* = 7.3 Hz, ring $CH_2CH_2CH_2$), 1,80-1.60 (3H, m, CH_2 and O*H*), 1.60-1.20 (4H, m), 0.92 (3H, t, *J* = 7.3 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 172.4, 165.9, 76.4, 60.9, 59.4, 50.6 , 45.3, 35.0, 34.8, 33.1, 32.9, 21.2, 19.5, 13.9.

(3*R*)-3-{Benzyl[(1*R*)-1-phenylethyl]amino}hexan-1-ol (30)

$LiAlH_4$ (1.36 g, 35.8 mmol) was added to a stirred solution of *tert*-butyl (3*R*)-3-((2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidinyl)hexanoate[17] (**26**) (12.4 g, 32.6 mmol) in Et_2O (65.0 cm^3) at 0 °C. The mixture was warmed to rt and stirred for 16 h. The reaction was quenched by the sequential addition of H_2O (7.2 cm^3), aq. NaOH solution (7.2 cm^3, 15% w/v) and finally H_2O (21.7 cm^3). The solids were removed by passing the mixture through a thin celite pad. The filtrate was dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield a light yellow oil. The solids and celite were recovered and dried in a desiccator, once dry they were ground to a fine powder. The powder was stirred in CH_2Cl_2 (100 cm^3), filtered and evaporated *in vacuo* to afford more of the light yellow oil. The crude oils were combined and purified by column chromatography with hexane-EtOAc (4 : 1) as eluent to give (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}hexan-1-ol (**30**) (9.84 g, 97%) as a clear oil. R_f 0.82 (hexane-EtOAc 1 : 1); $[\alpha]_D^{19}$ –32.1 (*c* 1.09, $CHCl_3$); ν_{max} (film)/cm^{-1} 3367 (OH, v br, w), 3084, 3062 and 3027 (ArC-H, w), 2956, 2931 and 2870 (C-H, m), 1602 (w), 1493 (m), 1452 (m), 1373 (m), 1204 (w), 1140 (w), 1052 (m), 1027 (m), 905 (w), 744 (s), 697 (s); δ_H (300 MHz; $CDCl_3$) 7.40-7.19 (10H, m, Ar-*H*), 3.95 (1H, q, *J* = 6.9 Hz, NC*H*Ph), 3.84 (1H, d, *J* = 13.7 Hz, NC$H_a$$H_b$Ph), 3.68 (1H, d, *J* = 13.7 Hz, NC$H_a$$H_b$Ph), 3.52-3.45 (1H, m, C$H_a$$H_b$OH), 3.24-3.17 (1H, m, C$H_a$$H_b$OH), 2.83-2.76 (1H, m, NC*H*CH_2Et), 2.64 (1H, br s, O*H*), 1.74-1.49 (2H, m, NC$H_2$$CH_2$OH), 1.45-1.23 and 1.39 (7H, overlapping m and d, *J* = 6.9 Hz, CH_2CH_2Me and PhCH*Me*), 0.93 (3H, t, *J* = 7.1 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 143.9, 140.8, 129.0, 128.3, 128.1, 128.0, 126.9 (2 signals), 61.8, 56.7, 54.8, 49.9, 34.9, 33.7, 20.8, 15.1, 14.4. HRMS (EI) Found, M^+, 311.2253. $C_{21}H_{29}NO$ requires 311.2249.

(3*R*)-*N*-Benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-[(1*R*)-1-phenylethyl]hexan-3-amine (31)

tert-Butyldimethylsilyl chloride (5.04 g, 33.1 mmol) in DMF (18.0 cm^3) was added dropwise to a stirred solution of (3*R*)-3-{benzyl[(1*R*)-1-phenylethyl]amino}hexan-1-ol (**30**) (9.37 g, 30.1 mmol) and imidazole (4.11 g, 60.1 mmol) in DMF (36.0 cm^3). The mixture was then stirred for 24 h. The reaction mixture was washed with ice/water (180 cm^3), and the aqueous residues were extracted with CH_2Cl_2 (5 × 180 cm^3). The combined organic residues were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (180 cm^3) and washed with H_2O (4 × 180 cm^3). The organic extract was dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield a crude yellow oil. Purification by column chromatography with hexane-EtOAc (9 : 1) as eluent afforded (3*R*)-*N*-benzyl-1-{[*tert*-butyl-(dimethyl)silyl]oxy}-*N*-[(1*R*)-1-phenylethyl]hexan-3-amine (**31**) (11.2 g, 88%), as a clear oil. R_f 0.72 (hexane-EtOAc 9 : 1); $[\alpha]_D^{20}$ +18.9 (*c* 1.27, $CHCl_3$); ν_{max} (film)/cm^{-1}; 3085, 3063 and 3028 (ArC-H, w), 2955, 2929 and 2857 (C-H, m), 1602 (w), 1493 (m), 1454 (m), 1373 (m), 1362 (m), 1253 (s), 1205 (w), 1144 (m), 1089 (s), 1027 (m), 1005 (m), 980 (m), 938 (m), 834 (s), 774 (s), 747 (s), 697 (s), 663 (m); δ_H

(300 MHz; $CDCl_3$) 7.40-7.16 (10H, m, Ar-*H*), 3.87 (1H, q, *J* = 6.9 Hz, NC*H*Ph), 3.78 (1H, d, *J* = 14.9 Hz, NC$H_a$$H_b$Ph), 3.64 (1H, d, *J* = 14.8 Hz, NC$H_a$$H_b$*P*h), 3.46 (1H, m, C$H_a$$H_b$OSi), 3.27 (1H, m, C$H_a$$H_b$OSi), 2.68 (1H, quintet, *J* = 6.1 Hz, NC*H*CH_2Et), 1.63-1.41 (2H, m, NC$H_2$$CH_2$OSi), 1.38-1.20 and 1.29 (7H, overlapping m and d, *J* = 6.9 Hz, CH_2CH_2Me and PhCH*Me*), 0.89-0.82 and 0.85 (12H, overlapping m and s, CH_2*Me* and SiCMe_3), –0.02 (6H, s, SiMe_2); δ_C (75 MHz; $CDCl_3$) 144.9, 142.7, 128.3, 128.1, 128.0, 127.9, 126.6, 126.3, 61.9, 58.1, 53.8, 50.2, 35.3, 34.5, 26.0, 20.5, 18.9, 18.3, 14.3, –5.3. HRMS (EI) Found, M^+, 425.3097. $C_{27}H_{43}NOSi$ requires 425.3114.

(3*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}hexan-3-amine (32)

10% Palladium on carbon (3.97 g), was added to a mixture of (3*R*)-*N*-benzyl-1-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-[(1*S*)-1-phenylethyl]hexan-3-amine (**31**) (11.1 g, 26.1 mmol) in absolute EtOH (104 cm^3). The stirred mixture was hydrogenated at 7 atm for 3 d at ambient temperature. The mixture was then filtered through celite and washed copiously with absolute EtOH, after which the combined organic phases were evaporated *in vacuo* to yield a grey oil. The oil was purified by column chromatography with EtOAc as the eluent to afford (3*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}hexan-3-amine (**32**) (5.11 g, 85%) as a clear oil. The unstable product was used immediately in the next reaction after cursory characterisation. R_f 0.38 (EtOAc); $[\alpha]_D^{21}$ +1.43 (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3377 (N-H, br, s), 2935 and 2871 (C-H, s), 1737 (w), 1615 (m), 1550 (s), 1460 (m), 1386 (m), 1310 (m), 1170 (s), 1099 (s), 1053 (s), 994 (s); δ_H (300 MHz; $CDCl_3$) 3.77-3.67 (2H, m, CH_2OSi), 2.90-2.84 (1H, m, NC*H*), 1.67-1.23 and 1.50 (8H, overlapping m and br s, 3 × CH_2 and NH_2), 0.89 and 0.87 (12H, overlapping t and s, *J* = 6.5 Hz, CH_2*Me* and SiCMe_3), 0.03 (6H, s, SiMe_2).

1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]pyrrolidin-2-one (33)

(a) 4-Chlorobutanoyl chloride (1.95 g, 1.10 cm^3, 13.8 mmol, 1.2 eq.) was added dropwise to a solution of (3*R*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}hexan-3-amine (**32**) (2.67 g, 11.5 mmol) and NEt_3 (2.91 g, 4.00 cm^3, 28.8 mmol) in dry CH_2Cl_2 (46.0 cm^3), causing a vigorous evolution of hydrogen chloride gas. The mixture was stirred for 30 min, after which time the reaction was quenched with H_2O (50 cm^3) and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 cm^3) and washed with H_2O (50 cm^3) and brine (50 cm^3). The aqueous extracts were back-extracted with CH_2Cl_2 (3 × 50 cm^3). The organic extracts were combined, dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield an orange oil. The crude oil was purified by column chromatography with hexane-EtOAc (1 : 1) as eluent to yield the unstable (1*R*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)butyl]-4-chlorobutanamide (3.89 g, 11.6 mmol, 100%) as a yellow oil that was used directly in the next reaction after cursory characterisation. $[\alpha]_D^{23}$

–1.75 (*c* 2.28, abs. EtOH); ν_{max} (film)/cm^{-1} 3281 (N-H, v br, m), 3075 (w), 2957 and 2932 (C-H, s), 2873 (C-H, m), 1727 (m), 1642 (C=O, s), 1546 (s), 1462 (m), 1442 (m), 1369 (m), 1306 (w), 1254 (m), 1155 (m), 1048 (m), 876 (m), 774 (m), 667 (m); δ_H (300 MHz; $CDCl_3$) 6.10 (1H, br d, *J* = *ca.* 7.3 Hz, N*H*), 4.11-3.97 (1H, m, NC*H*), 3.81-3.72 and 3.72-3.63 (2 × 1H, 2 × m, CH_aH_bOSi), 3.57 (2H, td, *J* = 6.2 and 1.9 Hz, CH_2Cl), 2.28 (2H, t, *J* = 7.1 Hz, CH_2C=O), 2.08 (2H, quintet, *J* = 6.2 Hz, CH_2CH$_2$Cl), 1.84-1.70 and 1.69-1.53 (2 × 1H, 2 × m, CH_aH_bCH$_2$OSi), 1.51-1.39 (2H, m, NCHCH_2Et), 1.37-1.19 (2H, m, CH_2Me), 0.92-0.85 and 0.89 (11H, overlapping m and s, CH$_2$*Me* and SiC*Me*$_3$), 0.05 (6H, s, Si*Me*$_2$).

(b) Potassium *tert*-butoxide (1.80 g, 16.1 mmol) was added in portions (~0.100 g per addition) to a solution of the preceding chlorobutanamide (3.60 g, 10.7 mmol) in dry *tert*-butyl alcohol (32.0 cm^3) over 5 h. The mixture was neutralized with glacial AcOH, and the solvent was removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (100 cm^3) and washed with H_2O (100 cm^3). The aqueous extracts were extracted with CH_2Cl_2 (3 × 100 cm^3), and the combined organic extracts were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to afford an orange oil. Purification of the crude oil by column chromatography with hexane-EtOAc (7 : 3) as eluent yielded 1-[(1*R*)-1-(2-{[*tert*-butyl(dimethyl)silyl]oxy} ethyl)butyl]pyrrolidin-2-one (**33**) (3.00 g, 94%) as a light yellow oil. R_f 0.58 (hexane-EtOAc 1 : 1); $[\alpha]_D^{19}$ –9.86 (*c* 0.71, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954, 2929 and 2857 (C-H, m), 1738 (w), 1668 (C=O, s), 1463 (m), 1423 (m), 1285 (m), 1253 (s), 1095 (s), 1007 (w), 942 (w), 834 (s), 774 (s), 663 (m); δ_H (300 MHz; $CDCl_3$) 4.21-4.05 (1H, m, NC*H*), 3.63-3.46 (2H, m, CH_2OSi), 3.32-3.18 (2H, m, NCH_2), 2.36 (2H, t, *J* = 8.1 Hz, ring CH_2C=), 1.96 (2H, quintet, *J* = 7.4 Hz, ring 4-H), 1.72-1.65 (2H, m, CH_2CH$_2$OSi), 1.50-1.39 (2H, m, NCHCH_2Et), 1.28-1.19 (2H, m, CH_2Me), 0.88 and 0.86 (12H, overlapping t and s, *J* = 7.3 Hz, CH$_2$*Me* and SiC*Me*$_3$), 0.02 and 0.01 (6H, 2 × s, diastereotopic Si*Me*$_2$); δ_C (75 MHz; $CDCl_3$) 174.9, 60.7, 48.5, 42.3, 35.6, 34.7, 31.5, 25.9, 19.4, 18.2 (2 overlapping signals), 13.8, –5.39 and – 5.44 (diastereotopic Si*Me*$_2$). HRMS (EI) Found, M$^+$, 299.2229. $C_{16}H_{33}NO_2Si$ requires 299.2281.

1-[(1*R*)-1-(2-Hydroxyethyl)butyl]pyrrolidin-2-one (34)

Aq. HF solution (40%, 10.1 cm^3) was added slowly to a solution of 1-[(1*R*)-1-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)butyl]pyrrolidin-2-one (**33**) (1.89 g, 6.32 mmol) in MeOH (240 cm^3). The reaction mixture was stirred at rt for 2 h before the careful addition of saturated aq. $NaHCO_3$ solution (380 cm^3), whereupon effervescence was observed. The reaction mixture was then extracted with EtOAc (3 × 200 cm^3) and the combined organic extracts were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield a light yellow oil. The crude oil was purified by column chromatography with EtOAc as eluent to give 1-[(1*R*)-1-(2-hydroxyethyl)butyl]pyrrolidin-2-one (**34**) (1.06 g, 5.69 mmol, 90%) as a clear oil; R_f 0.30 (EtOAc); $[\alpha]_D^{23}$ –0.61 (*c* 11.5, abs. EtOH); ν_{max}

(film)/cm^{-1} 3395 (O-H, v br, m), 2954 and 2872 (C-H, m), 1738 (m), 1655 (C=O, s), 1463 (m), 1424 (m), 1367 (m), 1289 (m), 1229 (m), 1217 (m), 1112 (w), 1048 (m), 1011 (w), 903 (w), 731 (w), 651 (w); δ_H (300 MHz; $CDCl_3$) 4.23-4.14 (1H, m, NC*H*), 3.52 (1H, ddd, *J* = 11.8, 5.3 and 3.2 Hz, CH_aH$_b$OH), 3.33 (1H, dd, *J* = 10.7 and 3.5 Hz, CH$_a$$H_b$OH), 3.28-3.11 and *ca* 3.11 (3H, overlapping m and br s, NCH_2 and O*H*), 2.41 (2H, td, *J* = 8.0 and 2.5 Hz, CH_2C=O), 1.99 (2H, quintet, *J* = 7.5 Hz, ring 4-H), 1.76-1.64 (1H, m, CH_aH$_b$CH$_2$OH), 1.56-1.35 (3H, m, CH$_a$$H_bCH_2$OH and NCHC$H_2$Et), 1.21 (2H, sextet, *J* = 7.3 Hz, CH_2Me), 0.87 (3H, t, *J* = 7.3 Hz, CH$_2$*Me*); δ_C (75 MHz; $CDCl_3$) 176.5, 58.4, 47.3, 41.9, 34.6, 34.4, 31.2, 19.5, 18.1, 13.7. HRMS (EI) Found: M^+, 185.1404. $C_{10}H_{19}NO_2$ requires 185.1416.

(3*R*)-3-(2-Oxopyrrolidin-1-yl)hexyl acetate (35)

A solution of acetic anhydride (1.37 g, 1.30 cm^3, 13.5 mmol) in dry pyridine (0.710 g, 0.800 cm^3, 8.97 mmol) was added dropwise to a stirred solution of 1-[(1*R*)-1-(2-hydroxyethyl)butyl]pyrrolidin-2-one (**34**) (1.66 g, 8.97 mmol) in pyridine (1.06 g, 1.10 cm^3, 13.5 mmol). The mixture was stirred at rt for 16 h, after which time the reaction mixture was diluted with EtOAc (45 cm^3) and washed with saturated aq. NH_4Cl solution (3 × 55 cm^3), which was then made basic to pH 10 with aq. NH_3 solution. The combined aqueous extracts were extracted further with CH_2Cl_2 (3 × 55 cm^3). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield a crude yellow oil. The crude oil was purified by column chromatography with hexane-EtOAc (3 : 2) as eluent to yield (3*R*)-3-(2-oxopyrrolidin-1-yl)hexyl acetate (**35**) (1.72 g, 84%) as a clear oil. R_f 0.33 (hexane-EtOAc 1 : 1); $[\alpha]_D^{23}$ +1.89 (*c* 11.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2957 and 2934 (C-H, s), 2873 (C-H, m), 1736 (ester C=O, s), 1678 (lactam C=O, s), 1462 (m), 1423 (m), 1367 (m), 1284 (m), 1232 (s), 1036 (m), 648 (m); δ_H (300 MHz; $CDCl_3$) 4.26-4.16 (1H, m, NC*H*), 4.01 (2H, t, *J* = 6.7 Hz, CH_2OAc), 3.33-3.20 (2H, m, NCH_2), 2.40 (2H, t, *J* = 8.0 Hz, CH_2C=O), 2.04 and 2.02 (5H, overlapping s and quintet, *J* = 7.4 Hz, OCO*Me* and ring 4-H), 1.88-1.76, 1.57-1.37 and 1.34-1.20 (3 × 2H, 3 × m, remaining CH_2), 0.91 (3H, t, *J* = 7.2 Hz, CH$_2$*Me*); δ_C (75 MHz; $CDCl_3$) 175.1, 171.0, 61.5, 47.9, 41.9, 34.5, 31.3, 31.2, 20.9, 19.3, 18.2, 13.8. HRMS (EI) Found: $(M–H)^+$, 226.1439. $C_{12}H_{20}NO_3$ requires 226.1438.

(3*R*)-3-(2-Thioxopyrrolidin-1-yl)hexyl acetate (36)

Phosphorus pentasulfide (4.87 g, 21.9 mmol) and Na_2CO_3 (1.17 g, 11.0 mmol) were dissolved in dry tetrahydrofuran (55.0 cm^3); the reaction was exothermic, and effervescence was observed. Once a homogeneous solution had formed, (3*R*)-3-(2-oxopyrrolidin-1-yl)hexyl acetate (**35**) (1.66 g, 7.31 mmol) was slowly added. The solution was stirred at rt for 3 h, after which the reaction was quenched by the addition of aq. Na_2CO_3 solution (10%, 55 cm^3). Vigorous effervescence was again observed. The solution was stirred for a further 10 min before adding EtOAc (40 cm^3) and hexane (13 cm^3). The organic phase

was separated and the aqueous phase was further extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic phases were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to yield a yellow oil. The crude oil was purified by column chromatography hexane-EtOAc (7 : 3) as eluent to give (3*R*)-3-(2-thioxopyrrolidin-1-yl)hexyl acetate (**36**) (1.61 g, 91%) as a yellow oil. R_f 0.25 (hexane-EtOAc 7 : 3); $[\alpha]_D^{17}$ +23.7 (*c* 1.69, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 5.19-5.10 (1H, br quintet, *J* = *ca* 7.5 Hz, NC*H*), 4.03 (2H, t, *J* = 6.7 Hz, NCH_2), 3.62-3.47 (2H, m, CH_2OAc), 3.03 (2H, t, *J* = 7.8 Hz, CH_2C=S), 2.06 and 2.05 (5H, overlapping quintet and s, *J* = 7.5 Hz, ring 4-H and OCO*Me*), 1.93-1.79, 1.62-1.50 and 1.39-1.15 (3 × 2H, 3 × m, remaining CH_2), 0.94 (3H, t, *J* = 7.2 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 202.3, 171.0, 61.2, 53.1, 48.6, 45.1, 34.7, 31.5, 21.0, 20.0, 19.2, 13.9. HRMS (EI) Found: M^+, 243.1285. $C_{12}H_{21}NO_2S$ requires 243.1293.

(3*R*)-3-[(2*E*)-2-{2-[Methoxy(methyl)amino]-2-oxoethylidene}pyrrolidin-1-yl]hexyl acetate (37)

(3*R*)-3-(2-Thioxopyrrolidin-1-yl)hexyl acetate (**36**) (1.58 g, 6.51 mmol) and 2-bromo-*N*-methoxy-*N*-methylacetamide (2.13 g, 11.7 mmol, 1.8 eq.) were dissolved in dry MeCN (26.0 cm^3) and stirred at rt for 16 h. The solvent and excess bromoacetamide were removed *in vacuo*, and the residue was re-dissolved in MeCN (26.0 cm^3). To this was added PPh_3 (2.57 g, 9.77 mmol), followed by NEt_3 (0.988 g, 1.36 cm^3, 9.77 mmol). The mixture was stirred at rt for 3 h, during which time a white precipitate formed. The reaction mixture was filtered through a thin pad of celite, and the solids were washed with EtOAc (100 cm^3) The solvent was removed *in vacuo*, and the residue was triturated with EtOAc (150 cm^3) for 30 min before being again filtered through a thin pad of celite. The filtrate was extracted with aq. HCl solution (2 M, 3 × 50 cm^3), and the aqueous extracts were basified to pH 10 with aq. NH_3 solution. The basic phase was then extracted with CH_2Cl_2 (3 × 100 cm^3), and the combined organic extracts were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to afford a crude orange oil. Spectroscopic analysis showed a mixture of (3*R*)-3-[(2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}-pyrrolidin-1-yl]hexyl acetate (**37**) and phosphorus-containing residues, which were inseparable by column chromatography, and as such the mixture was carried forward crude (~ 2g) after cursory characterisation; δ_H (300 MHz; $CDCl_3$) 5.19 (1H, s, C=C*H*), 4.11-4.01 and 4.00-3.90 (2 × 1H, 2 × m, CH_aH_bOAc), 3.85-3.75 (1H, m, NC*H*), 3.66 (3H, s, O*Me*), 3.28-3.19 and 3.24 (4H, m and t, *J* = 7.4 Hz, ring 5-H and 3-H), 3.14 (3H, s, N*Me*), 2.04 (3H, s, OCO*Me*), 1.95-1.83 (4H, m, ring 4-H and , C$H_2$$CH_2$Ac), 1.67-1.39 (2H, m, NHCH_2Et), 1.28 (2H, sextet, *J* = 7.4 Hz, CH_2Me), 0.92 (3H, t, *J* = 7.3 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 172.1, 170.8, 165.4, 76.9, 61.4, 60.7, 50.8, 45.3, 34.4, 32.8, 31.2 , 33.0, 21.1, 20.8, 19.4, 13.8.

(2*E*)-2-{1-[(1*R*)-1-(2-Hydroxyethyl)butyl]pyrrolidin-2-ylidene}-*N*-methoxy-*N*-methylethanamide (29)

K_2CO_3 (1.35 g, 9.77 mmol) was added to a stirred solution of crude (3*R*)-3-[(2*E*)-2-{2-[methoxy(methyl)amino]-2-oxoethylidene}pyrrolidin-1-yl]hexyl acetate (**37**) (~ 2g, ~6.5 mmol) in dry MeOH (10.4 cm^3). The mixture was stirred at rt for 3 h, after which time it was filtered through a thin pad of celite. The filtrate was evaporated *in vacuo* to afford an orange oil. The crude orange oil was purified by column chromatography with CH_2Cl_2-MeOH (19 : 1) as eluent to afford (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]pyrrolidin-2-ylidene}-*N*-methoxy-*N*-methylethanamide (**29**) (1.05 g, 64%, 3 steps from **36**) as a clear oil; characterisation as described previously.

(5*R*)-*N*-Methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxamide (38)

Imidazole (0.0790 g, 1.14 mmol, 3.0 eq.) and PPh_3 (0.301 g, 1.14 mmol, 3.0 eq.) were added to a stirred solution of (2*E*)-2-{1-[(1*R*)-1-(2-hydroxyethyl)butyl]pyrrolidin-2-ylidene}-*N*-methoxy-*N*-methylethanamide (**29**) (0.103 g, 0.379 mmol) in MeCN-PhMe (2.30 cm^3 : 1.10 cm^3). The solution was stirred for 30 min, after which time I_2 (0.192 g, 0.758 mmol) was added in one portion. The resulting homogenous solution was heated at reflux for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$ solution (4 cm^3), and extracted with EtOAc (3 × 20 cm^3). The combined organic fractions where washed with saturated aq. $Na_2S_2O_3$ solution (20 cm^3), separated, dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to give a yellow solid. The crude solid was purified by column chromatography, initially eluting the unreacted PPh_3 with CH_2Cl_2, then eluting the product with CH_2Cl_2-MeOH (19 : 1). (5*R*)-*N*-Methoxy-*N*-methyl-5-propyl- 1,2,3,5,6,7-hexahydroindolizine-8-carboxamide (**38**) was obtained as a light yellow oil (0.045 g, 47%); ν_{max} (film)/cm^{-1} 2928 and 2857 (C-H, m), 1630 (C=O, m), 1555 (C=C, s), 1438 (m), 1401 (m), 1361 (m), 1281 (s), 1194 (m), 1154 (m), 1118 (m), 1024 (m), 1003 (m), 725 (m), 696 (m); δ_H (300 MHz; $CDCl_3$) 3.63 (3H, s, O*Me*), 3.48 (1H, td, *J* = 8.5 and 5.2 Hz, 3_{eq}-H), 3.24-3.05 (2H, m, 3_{ax}-H and 5-H), 3.07 (3H, s, N*Me*), 2.34 (2H, br t, *J* = 6.2 Hz, 1-H or 7-H), 1.98-1.82 (2H, m, 1-H or 7-H), 1.80-1.52 (4H, m, 2-H and 6-H), 1.45-1.21 (4H, m, CH_2CH_2Me), 0.95 (3H, t, *J* = 6.9 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 174.4, 157.4, 90.1, 59.7, 53.8, 51.0, 35.1, 34.4, 32.1, 25.3, 21.5, 20.6, 19.0, 14.1. HRMS (EI) Found: M^+, 252.1828. $C_{14}H_{24}N_2O_2$ requires 252.1838.

(5*R*,8*S*,8a*S*)-*N*-Methoxy-*N*-methyl-5-propyloctahydroindolizine-8-carboxamide (39)

Adams catalyst (34 mg) was added to a solution of (5*R*)-*N*-methoxy-*N*-methyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxamide (**38**) (0.169 g, 0.670 mmol) in glacial AcOH (3.70 cm^3). This was stirred at rt under an atmosphere of H_2 for 24 h. The solution was filtered through a pad of celite, washed several times with EtOH, and evaporated *in vacuo* to afford a grey oil. The crude oil was taken up in H_2O (50 cm^3) and neutralized with saturated aq. $NaHCO_3$ solution. The neutralised aqueous fraction was extracted into CH_2Cl_2 (3 × 50 cm^3), the combined organic extracts were then dried

(anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to afford a grey oil. The crude oil was purified by column chromatography with CH_2Cl_2-MeOH (19 : 1) as eluent to yield (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl- 5-propyloctahydro-8-indolizinecarboxamide (**39**) as a clear oil (0.136 g, 80%); $[\alpha]_D^{21}$ –57.3 (3.07, abs. EtOH); ν_{max} (film)/cm^{-1} 2955, 2930 (C-H, m), 2880 (w), 2790 (w, Bohlmann band), 1668 (C=O, s), 1459 (m), 1372 (m), 1097 (m), 996 (s), 801 (m), 678 (s); δ_H (300 MHz; $CDCl_3$) 3.65 (3H, s, O*Me*), 3.33 (1H, td, *J* = 8.4 and 2.2 Hz, 3_{eq}-H), 3.17 (3H, s, N*Me*), 2.14-2.07 (1H, m), 2.04-1.91 (2H, m), 1.86-1.76 (4H, m), 1.74-1.50 (5H, m), 1.48-1.33 (4H, m), 0.90 (3H, t, *J* = 7.0 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 174.9, 65.7, 64.2, 61.0, 51.6, 43.9, 36.7, 35.8, 28.1, 27.3, 27.1, 19.9, 18.9, 14.5. HRMS (EI): no M^+ discernible.

1-[(5*R*,8*S*,8a*S*)-5-Propyloctahydroindolizin-8-yl]propan-1-one (40)

Ethylmagnesium bromide in THF (1.24 M, 1.20 cm^3, 1.49 mmol) was added slowly to a solution of (5*R*,8*S*,8a*S*)-*N*-methoxy-*N*-methyl-5-propyloctahydroindolizine-1-carboxamide (**39**) (0.0760 g, 0.300 mmol) in THF (3.00 cm^3) at 0 °C. The reaction mixture was allowed to warm to rt, then was stirred for a further 24 h. The reaction was then quenched with aq. HCl solution (6 M) and evaporated *in vacuo*. The residue was taken up in H_2O (50 cm^3), basified with conc. aq. NH_3 solution, and extracted with Et_2O (3 × 50 cm^3). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to afford a light yellow oil. The crude oil was purified by passing it through a short plug of silica, with CH_2Cl_2-MeOH (19 : 1) as eluent. 1-[(5*R*,8*S*,8a*S*)- 5-Propyloctahydroindolizin-8-yl]propan-1-one (**40**) was obtained as a clear oil (0.056 g, 83%). R_f 0.50 (CH_2Cl_2-MeOH 19 : 1); $[\alpha]_D^{19}$ +48.3 (*c* 0.95, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 3.28 (1H, br t, *J* = *ca* 8.3 Hz, 3_{eq}-H), 2.85-2.78 (1H, m, 8-H), 2.63 (1H, dq, *J* = 18.0 and 7.2 Hz, CH_aH$_b$C=O), 2.52-2.39 (1H, m, CH$_a$$H_b$C=O), 2.15-2.02 (1H, m, 3_{ax}-H, 5-H), 1.96-1.14 (15H, m), 1.01 (3H, t, *J* = 7.4 Hz, CH_2*Me*), 0.91 (3H, t, *J* = 7.0 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 213.6, 65.2, 63.9, 51.7, 48.4, 37.5, 36.8, 27.9, 27.3, 26.8, 20.4, 18.6, 14.5, 7.6. HRMS (EI) Found: M^+, 223.1936. $C_{14}H_{25}NO$ requires 223.1936.

1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydroindolizin-8-yl]propan-8-one (41)

A solution of NaOMe was prepared by adding metallic Na (0.010 g, 0.042 mmol) to dry MeOH (5.0 cm^3). To this solution was added 1-[(5*R*,8*S*,8a*S*)-5-propyloctahydroindolizin-8-yl]propan-1-one (**40**) (9.4 mg, 0.042 mmol) in one portion. The reaction mixture was heated at reflux for 3 h, then cooled to rt. The solvent was removed *in vacuo*, and the resulting residue was re-dissolved in H_2O (10 cm^3) and extracted with Et_2O (3 × 20 cm^3). The combined organic extracts were dried (anhydrous Na_2SO_4), filtered and evaporated *in vacuo* to give a yellow oil. The crude oil was purified by column chromatography CH_2Cl_2-MeOH (19 : 1) containing a few drops of propylamine as eluent.

1-[(5*R*,8*R*,8a*S*)-5-Propyloctahydroindolizin-8-yl]- propan-1-one (**41**) was obtained as a clear oil (7.5 mg, 80%). R_f 0.50 (CH_2Cl_2-MeOH 9 : 1); $[\alpha]_D^{17}$ –74.3 (*c* 0.35, $CHCl_3$), lit.,[6] $[\alpha]_D^{22}$ –84.4 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2958, 2930, 2873 (C-H, m), 2783 (Bohlmann band, m), 1715 (C=O, s), 1693 (s), 1458 (m), 1373 (m), 1262 (m), 1192 (m), 1120 (s), 1019 (m), 800 (m); δ_H (300 MHz; $CDCl_3$) 3.27 (1H, br t, *J* = *ca* 8.3 Hz, 3_{eq}-H), 2.59-2.35 (3H, m, C*H*$_2$C=O and 5-H), 2.15-1.70 (5H, m), 1.70-1.55 (3H, m), 1.45-1.20 (7H, m), 1.04 (3H, t, *J* = 7.3 Hz, CH_2*Me*), 0.91 (3H, t, *J* = 7.1 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 213.5, 65.5, 62.8, 54.6, 51.0, 36.7, 36.0, 28.7 (2 overlapping signals), 28.4, 20.5, 18.9, 14.5, 7.6. HRMS (EI) Found: M^+, 223.1925, $C_{14}H_{25}NO$ requires 223.1936.

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