Vinylogous urethanes in alkaloid synthesis. Applications to the synthesis of racemic indolizidine 209B and its (5*R**,8*S**,8a*S**)-(±) diastereomer, and to (−)-indolizidine 209B†

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Syntheses of racemic (5*R**,8*R**,8a*S**)-8-methyl-5-pentylindolizidine (indolizidine 209B) (±)-**1** and its hitherto unknown (5*R**,8*S**,8a*S**) diastereomer (±)-**20** were accomplished in eight steps from pyrrolidine-2-thione and ethyl oct-2-enoate. Key steps included cyclisations exploiting the nucleophilicity of vinylogous urethanes derived from ethyl (2*E*)-{1-[1-(2-hydroxyethyl)hexyl]pyrrolidin-2-ylidene}acetate **8**, and stereoselective reduction of the carbon–carbon double bond of a bicyclic vinylogous urethane **11**. An enantioselective modification of the route involving initial conjugate addition of the anion of (*R*)-(+)-*N*-benzyl-1-phenylethylamine to *tert*-butyl (2*E*)-oct-2-enoate resulted in a formal synthesis of (−)-indolizidine 209B.

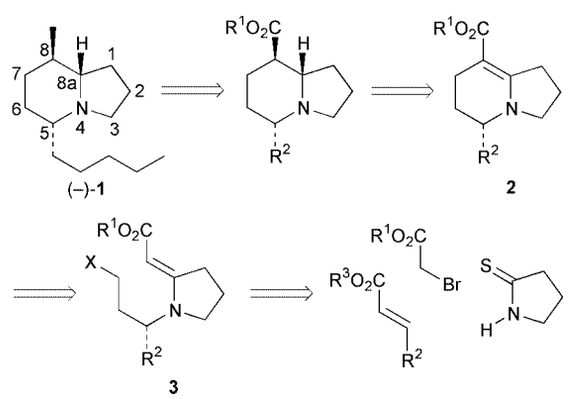
Introduction

Over 500 alkaloids have been isolated from the skins of amphibians.[1,2] There is a growing case for the hypothesis that most classes of amphibian alkaloids, the noxious effects of which undoubtedly serve to deter predators, are sequestered from dietary sources, especially from arthropods.[3] A number of 3,5-dialkylindolizidine alkaloids, for example, are common to myrmicine ants and to dendrobatid frogs from Central and South America, and a known amphibian 1,4-dialkylquinolizidine has also recently been isolated from a myrmicine ant.[4] However, among the alkaloids whose insect origins have not yet been identified are a growing family (perhaps as many as 60) of 5,8-disubstituted indolizidines.[2] Although discovered only relatively recently, these compounds have become popular synthetic targets, partly because they are simple enough to serve as models for illustrating emerging synthetic methodologies while at the same time offering worthwhile structural and stereochemical challenges.[5] Some have been shown to act as non-competitive blockers of sodium ion influx through nicotinic acetylcholine receptor channels in ganglia and muscle membranes.[6]

We have for some years been exploring the use of β-acylated enamines ("enaminones" in general) and related compounds as intermediates in alkaloid synthesis.[7] These readily accessible compounds can function both as nucleophiles and as electrophiles, their versatility in either case being extended by their ability to show ambident reactivity. They are easily incorporated into structures that contain the gross skeletal features found in many alkaloidal systems, and they offer ample opportunity for exploiting nuances associated with the control of diastereoselectivity and enantioselectivity. The amphibian indolizidines are convenient targets for exploring and applying all these aspects of enaminone reactivity. We have recently reported our results on the stereocontrolled synthesis of (±)- and (−)-indolizidine 167B, a simple 5-alkylindolizidine alkaloid.[8,9] In this paper we report in full the related synthesis of two diastereomeric 8-methyl-5-pentylindolizidines, one of which is generally accepted as being identical to the amphibian indolizidine alkaloid 209B **1**, a minor metabolite of Panamanian populations of the frog *Dendrobates pumilio* and a Colombian population of *D. histrionicus.*[10] We also report an enantioselective modification leading to (−)-indolizidine 209B. Preliminary aspects of these results have been published in a communication[11] and in a conference report.[12]

Results and discussion

Several total syntheses of racemic indolizidine 209B and its (−)- and (+)-enantiomers have been published to date.[13] Most of the published approaches involve creating bonds to the bridgehead nitrogen atom in order to form the heterocyclic rings. Our approach is unusual in that the key cyclisation creates the bond between C-7 and C-8 of the bicyclic target, as reflected in the disconnections shown in Scheme 1. The pivotal cyclisation depends on the enamine-like nucleophilicity of a cyclic vinylogous urethane **3**, intramolecular reaction of which with a strategically placed electrophilic partner serves to create the six-membered ring of the indolizidine nucleus. The scheme also suggests that stereoselective manipulation of the carbon–carbon double bond in the bicyclic product **2**, which is itself an enaminone, should permit access to the alternative diastereomers, the reasonable assumption being that steric effects at the



Scheme 1

† The IUPAC name for indolizidine is octahydroindolizine.

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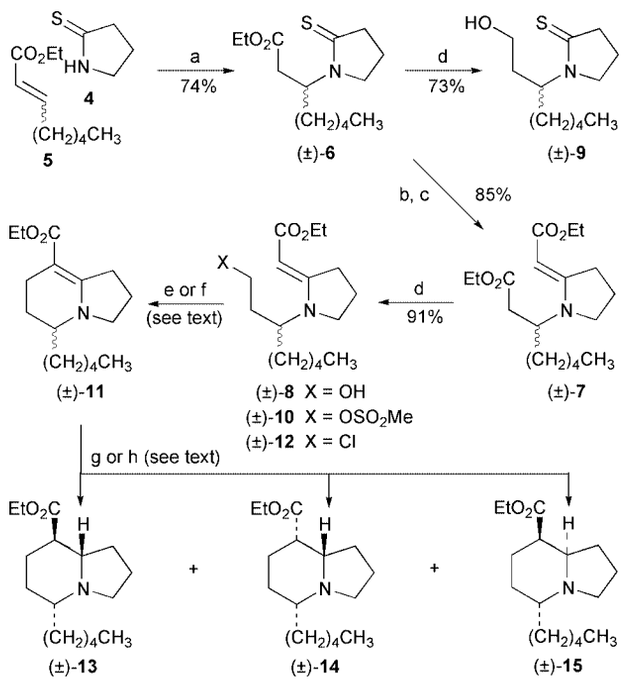
nearby stereogenic site destined to become C-5 in the indolizidine target will influence the diastereofacial selectivity in subsequent reactions of the enaminone. Moreover, if the C-5 site can be created enantioselectively at an early stage of the synthesis, then the alkaloid should be accessible in optically active form.

The approach was first tested with racemic intermediates (Scheme 2). Conjugate addition of pyrrolidine-2-thione **4**[14] to



Scheme 2 *Reagents and conditions*: a, NaOH (cat.), THF, rt; b, $BrCH_2CO_2Et$, MeCN, rt; c, PPh_3, NEt_3, MeCN, rt; d, $LiAlH_4$, THF, 0 °C to rt; e, (±)-**8** + CBr_4, PPh_3, NEt_3, MeCN, 0 °C to rt, then rt to reflux; f, (±)-**12** + NaI, MeCN, reflux; g, $NaBH_3CN$, HCl (pH 4), EtOH, rt; h, H_2 (1 atm), PtO_2, AcOH, rt.

ethyl oct-2-enoate **5**[15] in tetrahydrofuran (THF) was catalysed at room temperature by sodium hydroxide, and yielded the thiolactam (±)-**6** (74%). This reaction appears to be an equilibrium process, since exposure of **6** to a catalytic quantity of sodium hydroxide in THF induced some disproportionation to the precursors. Alkylation of **6** on sulfur with ethyl bromoacetate followed by Eschenmoser sulfide contraction[16,17] upon treatment with triphenylphosphine and triethylamine in acetonitrile afforded the vinylogous urethane (±)-**7** (85%). The (*E*)-geometry of the double bond was inferred from the chemical shift of the hydrogen atoms on C-3 of the pyrrolidine ring (δ 3.15), the downfield shift of about 0.6 ppm relative to (*Z*)-analogues[16] arising from the anisotropic deshielding effect of the carbonyl group.

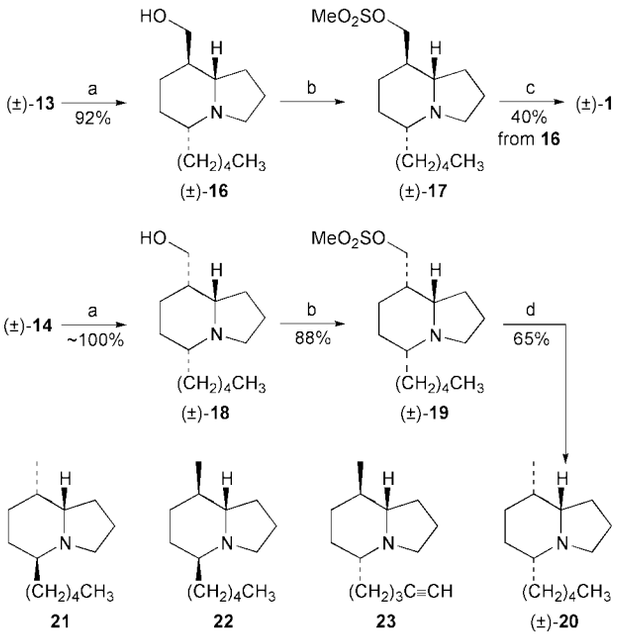
In order to construct the indolizidine nucleus by the cycloalkylation process implicit in Scheme 1, it was necessary to perform a chemoselective reduction of the saturated ester group of **7** while leaving the unsaturated ester of the vinylogous urethane untouched. Fortunately, vinylogous urethanes are remarkably robust; treatment of **7** with lithium aluminium hydride in THF at ambient temperature reduced only the saturated ester, and the racemic alcohol (±)-**8** was isolated in 91% yield. In an alternative approach to **8**, we found that the ester group of the thiolactam **6** could be reduced by treatment with lithium aluminium hydride in THF to yield alcohol (±)-**9** (73%). The thiocarbonyl group, to our surprise, was unaffected. However, **9** failed to give vinylogous urethane **8** on attempted salt formation and sulfide contraction with ethyl bromoacetate.

The critical cyclisation step that followed necessitated the replacement of the hydroxy substituent of (±)-**8** by a better leaving group. Although the methanesulfonate (±)-**10** could be prepared in modest yield (46%), this compound failed to cyclise under a variety of conditions. Cyclization was eventually accomplished *via* the corresponding bromide, prepared *in situ* by treating **8** with tetrabromomethane and triphenylphosphine in the presence of triethylamine. Simply heating the reaction mixture under reflux in acetonitrile brought about ring closure to the indolizidine (±)-**11** (85%) in a process that exploits the vinylogous urethane's enamine-like reactivity. When tetrachloromethane was used in place of the tetrabromo compound, the corresponding chloride **12** was isolated (93%), but it resisted cyclisation. However, treatment of **12** with sodium iodide in acetonitrile brought about cyclisation to (±)-**11**, though in a comparatively poor yield of 60%.

The greatest challenge in our approach is to reduce the carbon–carbon double bond of **11** in such a way that the two stereogenic centres introduced at C-8 and C-8a not only have the correct stereochemistry relative to each other, but also in relation to the more remote stereogenic centre already present at C-5. It seemed reasonable to expect conformational effects in the bicyclic system to dictate the transition state that develops during the reduction. The incipient chair conformation of the six-membered ring should result in an equatorial preference for the pentyl side chain, which in turn should bias the approach of the reductant towards the more remote face of the double bond. Furthermore, we reasoned that protonation of the vinylogous urethane would give an iminium ion intermediate whose reduction by a hydride reagent would proceed through a transition state that maintains maximum orbital overlap between the approaching nucleophile and the developing lone pair on nitrogen, as proposed by Stevens.[18] When (±)-**11** was reduced with sodium cyanoborohydride at pH 4, the major product was indeed the expected diastereomer (±)-**13** (33%), but it was accompanied by the isomer (±)-**14** (14%) and another diastereomer tentatively assigned as (±)-**15** (13%). Support for the *cis*-relationship of the hydrogen atoms at positions C-5 and C-8a in both **13** and **14** was provided by Bohlmann bands[19] in the FTIR spectra at *ca.* 2790 cm^{-1}, a feature that also implies a *trans*-fused indolizidine ring. The relative stereochemistries of (±)-**13** and (±)-**14** were further confirmed by the chemical transformations to be described below. For isomer **15**, the markedly downfield position of the 8a-H resonance at δ 4.70 (*cf.* δ < 2.35 for **13** and **14**) strongly suggests deshielding by the lone pair of electrons on nitrogen, implying *cis*-ring fusion of the indolizidine ring. This conformation would be favoured if the C-5 and C-8a substituents are both equatorial, as has been demonstrated for a related 5,8-disubstituted indolizidine system.[20]

The relative stereochemistry of racemic diastereomer **13** was substantiated by reduction with lithium aluminium hydride to the alcohol **16** (92%; Scheme 3), spectroscopic data for which have been reported by Holmes *et al.*,[21] and by Jefford *et al.*[22] Since the Holmes team has converted (−)-**16** into (−)-indolizidine 209B **1** by reducing the methanesulfonate derivative **17** with lithium triethylborohydride (Super-hydride), our synthesis of (±)-**16** completes a formal synthesis of racemic **1**. For the sake of completeness, we repeated Holmes's procedure to produce the methanesulfonate **17** (96%), following which treatment with lithium triethylborohydride effected partial hydrogenolysis to (±)-**1** (*ca.* 40%). The ^1H and ^{13}C NMR spectra of the product were identical to those published for synthetic indolizidine 209B.[13,21,22] The overall yield in this eight-step preparation of (±)-**1** from pyrrolidine-2-thione **4** was 5.9%.

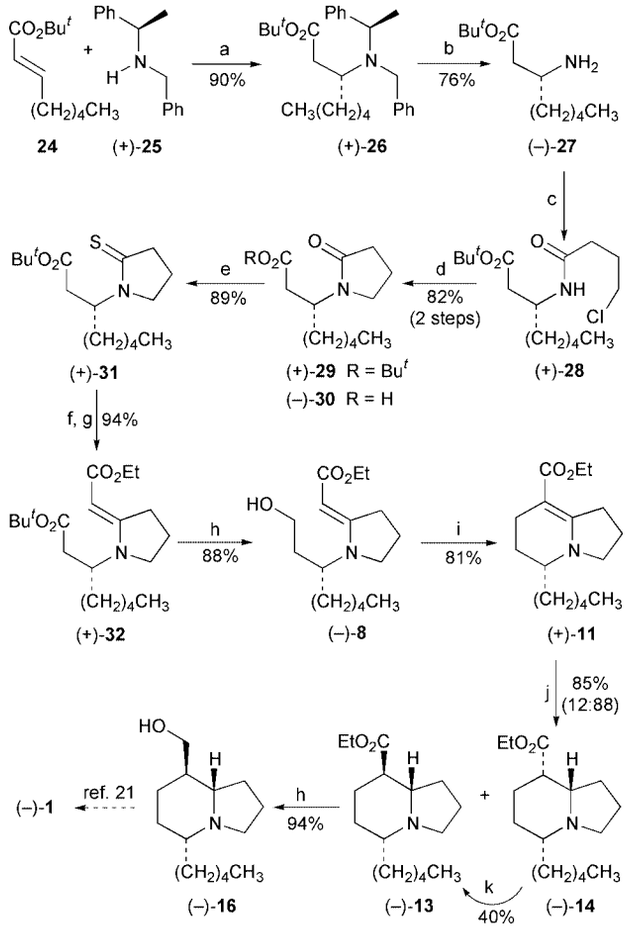
Much better diastereoselectivity was achieved when the bicyclic vinylogous urethane (±)-**11** was hydrogenated over platinum dioxide in acetic acid. Hydrogen was delivered in the expected *cis* fashion on to the less hindered face of the carbon–carbon double bond, giving mainly the ester (±)-**14** (71%) together with only a small quantity of compound **13** (6%). With isomer **14** available in quantity, we transformed it into the hitherto unknown (5*R**,8*S**,8a*S**)-diastereomer of indolizidine 209B as follows. Reduction with lithium aluminium



Scheme 3 *Reagents and conditions*: a, $LiAlH_4$, THF, 0 °C to rt; b, CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0 °C; c, $LiEt_3BH$ (1 M in THF), THF, 0 °C; d, Raney Ni W-2, EtOH, reflux.

hydride to alcohol (±)-**18** followed by methanesulfonylation yielded the derivative (±)-**19** (88%, two steps). Reductive demesylation with lithium triethylborohydride proved to be erratic, but we succeeded in hydrogenolysing **19** with freshly prepared Raney nickel[23] in boiling ethanol—an apparently unprecedented transformation with aliphatic methanesulfonates, although it is known with aromatic toluene-*p*-sulfonates[24] and, in one unique case, a naphthyl methanesulfonate.[25] The NMR spectra of the new diastereomer (±)-**20** (65% yield) are quite different from those of both indolizidine 209B **1** and the only other known diastereomer of the alkaloid, the structure of which was originally reported as **21**[26] but later revised to **22**.[27] Further support for the structure of **20** came from comparison of the NMR spectroscopic data with those published by Polniaszek and Belmont for all four synthetic diastereomers of indolizidine 205A **23**, a related frog alkaloid.[20] The ^{13}C NMR chemical shifts for the indolizidine nucleus of **20** were found to be in remarkable agreement (±0.3 ppm) with those of the analogous isomer of indolizidine 205A. In particular, the chemical shift of the methyl group at C-8 (δ_C 12.22 for **20**; *cf.* 18.84 for **1**) clearly supports the axial disposition of the substituent. The overall yield of (±)-(5*R**,8*S**,8a*S**)-**20** in this eight step synthesis was 19.8% based on pyrrolidine-2-thione **4**.

Modifying the successful synthesis of (±)-indolizidine 209B shown in Schemes 2 and 3 in order to produce a single enantiomer of the product requires that we devise a stereochemically unambiguous route to the thiolactam **6**, which contains the first of the target alkaloid's three stereogenic centres. The conjugate addition of pyrrolidine-2-thione **4** to an oct-2-enoyl system bearing a chiral auxiliary was extensively explored, but abandoned when all attempts showed that the addition could not be achieved under conditions of kinetic control; the diastereomeric ratios of the adducts were never far from 1:1.[12] We decided instead to generate the thiolactam from an optically pure β-amino acid derivative, numerous synthetic methods for which have been published.[28,29] The method of choice for our purpose, devised by Davies and Ichihara,[30] is a comparatively general route that involves the conjugate addition of lithium *N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amide or its enantiomer to *tert*-butyl (2*E*)-alk-2-enoates to give the desired adducts in excellent chemical yields, reproducibly high diastereoselectivities (>95% de), and with a predictable stereochemical



Scheme 4 *Reagents and conditions*: a, **25** + *n*-BuLi, THF, −78 °C, then **24**; b, H_2 (7 atm), 10% Pd/C, HOAc, rt; c, $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$, reflux; d, KOBu^t, Bu^{t}OH, rt; e, Lawesson's reagent, PhMe, reflux; f, $BrCH_2CO_2Et$, MeCN, rt; g, Ph_3P, Et_3N, MeCN, rt; h, $LiAlH_4$, THF, rt; i, I_2, imidazole, Ph_3P, PhMe, 110 °C; j, H_2 (1 atm), PtO_2, AcOH, rt; k, NaOEt (cat.), EtOH, reflux.

outcome.[31] Hydrogenolytic removal of the benzyl groups (7 atm H_2, 10% Pd/C, acetic acid) then yields enantiomerically pure β-amino esters.

For our projected synthesis of (−)-indolizidine 209B (Scheme 4), the requisite substrates are *tert*-butyl (2*E*)-oct-2-enoate **24** and (*R*)-(+)-*N*-benzyl-1-phenylethylamine **25**. As the success of the Davies method depends on **24** being free of its geometrical isomer, we prepared it by the Horner–Wadsworth–Emmons variation of the Wittig reaction between *tert*-butyl diethoxyphosphorylacetate[32] and hexanal in the presence of lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[33] The alkenoate **24** (96%) was obtained in better than 99:1 diastereoselectivity, as estimated from the ^{13}C NMR spectrum of the product. The anion of chiral amine **25**, prepared by treatment with *n*-butyllithium in THF solution at −78 °C, added smoothly to **24** to give the optically active amino ester (+)-**26** (90%). In line with expectations, the product was obtained as a single diastereomer, the ^{13}C NMR spectrum showing no doubling up of signals whatsoever. The (3*R*,1′*R*) absolute configuration was assigned in accordance with the model proposed by Davies and co-workers[31] as well as by analogy with lower[34] and higher[35] homologues prepared by the Davies group. The absolute stereostructure of **26** was later confirmed by means of X-ray crystallography on the hydrobromide salt of the corresponding carboxylic acid; not only was the (*R*) configuration at both stereogenic carbon atoms revealed, but the protonated nitrogen atom was also shown to have the (*S*) configuration.[36] Debenzylation of (+)-**26** under the Davies conditions gave the free amino ester (−)-**27** (76%).

Conversion of the amino ester (−)-**27** *via* chloroamide (+)-**28** into lactam (+)-**29** (82%) was achieved by a two-stage procedure[37] involving sequential treatment with 4-chlorobutyryl chloride and sodium carbonate in boiling chloroform, followed by cyclisation of the intermediate with potassium *tert*-butoxide in dry *tert*-butyl alcohol. If the solvent used in the second step was not scrupulously dried, a remarkably easy basic hydrolysis to carboxylic acid (−)-**30** took place. The thiolactam (+)-**31** was prepared from (+)-**29** by treatment with Lawesson's reagent in boiling toluene (89%), after which sulfide contraction with ethyl bromoacetate completed the synthesis of the (*R*)-(+)-vinylogous urethane **32** (94%). An alternative one-pot route to (+)-**32** involving treatment of amino ester (−)-**27** with ethyl 6-chloro-3-oxohexanoate[38] (a method we used previously for making *N*-aryl analogues of **32**[39]) was shorter but less efficient (*ca.* 49%; *cf.* 69% for the four-step process). Reduction of (+)-**32** with lithium aluminium hydride yielded the alcohol (−)-**8** (88%), at which point the synthesis converges with that shown in Scheme 3 for racemic indolizidine 209B. However, several minor changes were introduced to improve the overall process. When cycloalkylation of (−)-**8** *via* the bromide to give the bicyclic vinylogous urethane (+)-**11** proved erratic (*ca.* 47% yield at best), cyclisation of the corresponding iodide [prepared *in situ* by treating (−)-**8** with triphenylphosphine, iodine and imidazole in toluene at 110 °C[40]] was uniformly successful (81%). Secondly, since reduction of the carbon–carbon double bond of (+)-**11** with sodium cyanoborohydride at pH 4 afforded the indolizidine-8-carboxylic ester (−)-**13** in only 36% yield, we turned to the alternative catalytic hydrogenation with platinum oxide in acetic acid. This more diastereoselective reduction yielded an 88 : 12 mixture of **14** and **13** (85%). The axial ester group of **14** proved amenable to epimerization when the compound was heated with a catalytic quantity of sodium ethoxide in ethanol. Conversion into the desired equatorial isomer (−)-**13** was essentially complete (GLC analysis), although its recovery after column chromatography was not especially good (40%). Finally, reduction of (−)-**13** with lithium aluminium hydride yielded alcohol (−)-**16** (94%), thereby completing a formal synthesis of (−)-indolizidine 209B **1**. The spectroscopic data for (−)-**16** were in excellent agreement with those reported by other workers,[21,22] as was the optical rotation, $[a]_D$ −93.1 (*c* 0.58, MeOH) [*cf.* −93.3 (*c* 0.58, MeOH);[21] −93.6 (*c* 0.51, MeOH)[22]].

The methodology reported in this paper for the synthesis of (−)-indolizidine 209B is currently being extended to embrace the enantioselective synthesis of 1,4-disubstituted amphibian quinolizidine alkaloids[2] and 5,6,8-trisubstituted indolizidine alkaloids such as the recently described indolizidine 223A.[41]

Experimental

All solvents used for reactions and chromatography were distilled before use. Tetrahydrofuran (THF) and diethyl ether were distilled from Na–benzophenone, dichloromethane, acetonitrile, and triethylamine from CaH_2, and benzene and toluene from Na. 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). Gas chromatograms were recorded on a Hewlett Packard 5890A instrument equipped with an HP-1 methylsilicone gum column (5 m × 0.53 mm, film thickness 2.65 μm); nitrogen was used as carrier gas at an operating pressure of 100 kPa. Optical rotations were measured on a JASCO DIP-370 polarimeter; $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on JASCO IR Report-100 or Bruker IFS 25 spectrometers. NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 MHz for ^{1}H, 50.32 MHz for ^{13}C). $CDCl_3$ was used as solvent and TMS as internal standard. DEPT and CH-correlated spectra were routinely used for assignment of signals. *J* values are given in Hz, and ranges for multiplet signals in ^{1}H NMR spectra are recorded to the closest 0.05 ppm. Low-resolution mass spectra were recorded on a VG 70E mass spectrometer, and high-resolution spectra on a Kratos MS 9/50 instrument (70 eV).

(±)-Ethyl 3-(2-thioxopyrrolidin-1-yl)octanoate 6

Pyrrolidine-2-thione **4**[14] (906 mg, 8.96 mmol), ethyl oct-2-enoate **5**[15] (1.525 g, 8.96 mmol; 9 : 1 mixture of *E*- and *Z*-isomers from Wittig reaction between hexanal and ethoxycarbonyltriphenylphosphorane) and a catalytic quantity of finely crushed NaOH (*ca.* 50 mg) in dry THF (8 cm^3) were stirred together at rt for 20 h. The solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (50 cm^3) and washed with H_2O. The organic phase was dried ($MgSO_4$), filtered and evaporated to yield an oil (1.923 g) which, after purification by column chromatography (EtOAc–hexane 1 : 9–1 : 8) gave the *pyrrolidinethione* **6** as a chromatographically pure pale yellow oil (1.791 g, 74%). The product could be further purified by distillation (bp 90–100 °C, *ca.* 1 mmHg). R_f 0.75 (EtOAc–hexane 1 : 1); ν_{max}(film)/cm^{-1} 2925 (s), 2900 (s), 2830 (m), 1705 (s, C=O), 1470 (s), 1440 (s), 1423 (s), 1285 (s) and 1265 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.36 (1H, quintet, *J* 7.3, NC*H*), 4.11 (2H, q, *J* 7.1, OCH_2Me), 3.70 (1H, dt, *J* 10.6 and 7.2, NCH_aH$_b$), 3.57 (1H, dt, *J* 10.7 and 7.3, NCH$_a$$H_b$), 3.01 (2H, t, *J* 7.9, CH_2C=S), 2.61 and 2.53 (2H, 2 × dd, *J* 14.4 and 6.4, and *J* 14.4 and 8.3, CH_2CO$_2$Et), 2.04 (2H, quintet, *J* 7.4, ring CH$_2$CH_2CH$_2$), 1.7–1.6 (2H, m, CH_2Bu), 1.4–1.15 and 1.25 (9H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH$_2$*Me*) and 0.88 (3H, br t, *J ca.* 6.5, (CH$_2$)$_4$*Me*); δ_C (50 MHz; $CDCl_3$; Me_4Si) 202.09 (*C*=S), 170.36 (*C*=O), 60.81 (O*C*H$_2$Me), 53.21 (N*C*H), 49.21 (N*C*H$_2$), 45.06 (*C*H$_2$C=S), 37.14 (*C*H$_2$C=O), 32.03, 31.35, 25.51 and 22.31 [(*C*H$_2$)$_4$Me], 20.02 (ring CH$_2$*C*H$_2$CH$_2$), 14.03 (OCH$_2$*Me*) and 13.86 [(CH$_2$)$_4$*Me*]; *m*/*z* (EI) 271 (1%, M$^+$), 168 (24), 128 (48), 126 (20), 102 (100), 101 (22), 85 (43) and 55 (56) (Found: M$^+$, 271.1589. $C_{14}H_{25}NO_2S$ requires 271.1606).

(±)-Ethyl 3-[(2*E*)-2-(ethoxycarbonylmethylene)pyrrolidin-1-yl]-octanoate 7

The pyrrolidinethione **6** (5.01 g, 15.4 mmol) and ethyl bromoacetate (2.04 cm^3, 18.5 mmol) were stirred in dry acetonitrile (16 cm^3) at room temperature. When salt formation was complete (overnight), triphenylphosphine (4.44 g, 16.9 mmol) and dry NEt_3 (2.36 cm^3, 16.9 mmol) were added, after which stirring was continued at room temperature for 3 h. The resulting suspension was filtered, and the solids were washed with EtOAc–hexane (1 : 1). The combined filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 cm^3) and washed with H_2O (2 × 100 cm^3). The aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a viscous brown oil (9.375 g). Column chromatography (CH_2Cl_2 to remove phosphines, then EtOAc–hexane 1 : 1) gave the *vinylogous urethane* (±)-**7** as a viscous orange oil (4.257 g, 85%); R_f 0.36 (EtOAc–hexane 1 : 3); ν_{max}(film)/cm^{-1} 3070 (w, =C–H), 2975 (s), 2950 (s), 2925 (s), 2850 (m), 1720 (s, saturated C=O), 1660 (s, unsaturated C=O), 1570 (s, C=C), 1135 (s) and 900 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.67 (1H, s, =C*H*), 4.15–3.95, 4.09 and 4.07 (5H, m and 2 × q, *J* 7.1, NC*H* and 2 × OCH_2Me), 3.26 (2H, t with fine structure, *J* 6.6 and *ca.* 1, NCH_2), 3.15 (2H, t with fine structure, *J* 7.7 and <1, CH_2C=), 2.49 (2H, d, *J* 7.3, CH_2CO$_2$Et), 1.89 (2H, quintet, *J* 7.3, ring CH$_2$CH_2CH$_2$), 1.65–1.35 (2H, m, CH_2Bu), 1.35–1.15, 1.24 and 1.24 (12H, overlapping m and 2 × t, *J* 7.1, remaining CH_2 and 2 × OCH$_2$*Me*) and 0.88 [3H, br t, *J ca.* 6.5, (CH$_2$)$_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 170.74 (unconjugated *C*=O), 169.55 (conjugated *C*=O), 165.03

(N*C*=C), 78.63 (NC=*C*), 60.65 and 58.09 (2 × O*C*H_2Me), 51.53 (N*C*H), 45.88 (N*C*H_2), 37.31 (*C*H_2C=O), 32.59 (*C*H_2C=), 32.05, 31.35, 25.75 and 22.35 [(*C*H_2)$_4$Me], 20.95 (ring CH_2-*C*H_2CH_2), 14.61 and 13.97 (2 × OCH_2*Me*) and 13.84 [(CH_2)$_4$-*Me*]; *m/z* (EI) 325 (6%, M^+), 280 (29), 238 (100), 182 (78), 156 (53), 136 (30), 110 (71), 108 (46) and 55 (53) (Found: M^+, 325.2261. $C_{18}H_{31}NO_4$ requires 325.2253).

Ethyl (2*E*)-{1-[1-(2-hydroxyethyl)hexyl]pyrrolidin-2-ylidene}acetate 8

(a) Racemic compound. $LiAlH_4$ (697 mg, 18.4 mmol) was added slowly to a stirred solution of (±)-ethyl 3-[(2*E*)-2-(ethoxycarbonylmethylene)pyrrolidin-1-yl]octanoate **7** (5.97 g, 18.4 mmol) in dry THF (100 cm^3) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then allowed to warm to room temperature and stirred for an additional 3 h. The reaction was quenched by the sequential addition of H_2O (0.7 cm^3), NaOH solution (15% w/v, 0.7 cm^3) and H_2O (2.1 cm^3). The inorganic salts were filtered off and washed with CH_2Cl_2. The organic filtrate was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc–CH_2Cl_2 1:2), which gave the racemic *hydroxy ester* (±)-**8** as a very pale yellow oil (4.709 g, 91%); R_f 0.52 (EtOAc); ν_{max}(film)/cm^{-1} 3438 (m, br, OH), 2954 (s), 2932 (s), 2860 (s), 1682 (s, C=O), 1662 (s), 1582 (s, C=C), 1148 (s) and 1060 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.64 (1H, s, =C*H*), 4.06 (2H, q, *J* 7.1, OCH_2Me), 3.76 (1H, quintet, *J* 7.0, NC*H*), 3.65–3.45 (2H, m, CH_2OH), 3.23 (2H, t, *J* 7.0, NCH_2), 3.17 (2H, t with fine structure, *J* 7.3 and <1, CH_2C=), 2.62 (1H, br s, O*H*; exchanges with D_2O), 1.90 (2H, quintet, *J* 7.3, ring CH_2CH_2CH_2), 1.75 (2H, q, *J* 6.7, CH_2CH_2OH), 1.6–1.45 (2H, m, CH_2Bu), 1.35–1.2 and 1.24 (9H, m and t, *J* 7.1, remaining CH_2 and OCH_2*Me*) and 0.87 [3H, br t, *J ca.* 6.5, (CH_2)$_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 169.86 (*C*=O), 166.05 (N*C*=C), 77.33 (NC=*C*), 59.20 (*C*H_2OH), 58.13 (O*C*H_2Me), 51.27 (N*C*H), 45.61 (N*C*H_2), 34.77 (*C*H_2CH_2OH), 32.80 (*C*H_2C=), 32.32, 31.49, 25.82 and 22.35 [(*C*H_2)$_4$Me], 20.84 (ring CH_2*C*H_2CH_2), 14.56 (OCH_2*Me*) and 13.83 [(CH_2)$_4$*Me*]; *m/z* (EI) 283 (6%, M^+), 212 (17), 197 (15), 196 (73), 182 (51), 156 (64), 152 (39), 128 (15), 110 (78), 108 (30), 82 (21), 70 (22), 55 (46), 45 (21) and 44 (100) (Found: M^+, 283.2146. $C_{16}H_{29}NO_3$ requires 283.2147).

(b) (−)-Enantiomer. When the reaction was repeated with $LiAlH_4$ (34 mg, 0.90 mmol) and (+)-*tert*-butyl (3*R*)-3-[(2*E*)-2-(ethoxycarbonylmethylene)pyrrolidin-1-yl]octanoate **32** (see below; 159 mg, 0.45 mmol) in dry THF (10 cm^3) at room temperature, chromatographically pure *(−)-ethyl (2E)-{1-[(1R)-1-(2-hydroxyethyl)hexyl]pyrrolidin-2-ylidene}acetate* (−)-**8** was obtained after work-up as a pale yellow oil (113 mg, 88%); $[\alpha]_D^{26}$ −12.7 (*c* 1.10, absolute EtOH); δ_H within ±0.05 ppm of the values given above except for 2.27 (1H, br s, O*H*); δ_C within ±0.20 ppm of the values given above.

(±)-1-[1-(2-Hydroxyethyl)hexyl]pyrrolidine-2-thione 9

$LiAlH_4$ (66 mg, 1.8 mmol) was added to a solution of the pyrrolidinethione **6** (237 mg, 0.87 mmol) in dry THF (10 cm^3) at 0 °C. The solution was then allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the sequential addition of H_2O (0.1 cm^3), aqueous NaOH solution (15% w/v, 0.1 cm^3) and H_2O (0.3 cm^3). The insoluble salts were filtered off and washed with acetone. The organic filtrate was dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford the crude product (407 mg), which was purified by column chromatography (hexane–EtOAc 1:2). *(±)-1-[1-(2-Hydroxyethyl)hexyl]pyrrolidine-2-thione* **9** was obtained as a viscous, colourless oil (147 mg, 73%); R_f 0.34 (hexane–EtOAc 1:2); ν_{max}(film)/cm^{-1} 3396 (br s, OH), 2952 (s), 2928 (s), 2870 (s), 2860 (s), 1500 (s), 1464 (s), 1452 (s), 1426 (m), 1322 (s), 1312 (s), 1290 (s), 1108 (br s) and 736 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.09 (1H, 11-line m, NC*H*), 3.65–3.25 (5H, m, NCH_2 and CH_2O*H*), 3.09 (2H, t, *J* 7.6, CH_2C=S), 2.07 (2H, quintet, *J* 7.6, ring CH_2CH_2CH_2), 1.95–1.75, 1.7–1.5 and 1.4–1.1 (1H + 3H + 6H, clusters of m, remaining CH_2) and 0.88 [3H, br t, *J ca.* 6.5, (CH_2)$_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 202.26 (*C*=S), 57.75 (*C*H_2OH), 53.06 (N*C*H), 48.55 (N*C*H_2), 44.73 (*C*H_2C=S), 34.79 (*C*H_2CH_2OH), 32.67, 31.32, 25.67 and 22.31 [(*C*H_2)$_4$Me], 19.83 (ring CH_2*C*H_2CH_2) and 13.84 [(CH_2)$_4$*Me*].

(±)-Ethyl (2*E*)-(1-{1-[2-(methylsulfonyloxy)ethyl]hexyl}-pyrrolidin-2-ylidene)ethanoate 10

Freshly distilled methanesulfonyl chloride (0.08 cm^3, 1 mmol) was added dropwise to a solution of the hydroxy ester (±)-**8** (303 mg, 1.07 mmol) and dry NEt_3 (0.15 cm^3, 1.1 mmol) in dry CH_2Cl_2 (3 cm^3) at −20 °C. The mixture was stirred for 2 h, allowed to warm to room temperature and stirred for a further 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (50 cm^3) and extracted twice with CH_2Cl_2 (50 cm^3, 25 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford an orange oil (310 mg). Column chromatography (EtOAc–hexane 1:1) afforded the *methanesulfonate* **10** as a colourless oil that subsequently formed a low-melting (<25 °C) waxy white solid (177 mg, 46%); R_f 0.63 (EtOAc–hexane 1:1); ν_{max}(film)/cm^{-1} 2990 (s), 2960 (s), 2892 (m), 1678 (s, C=O), 1590 (s, C=C), 1362 (s), 1160 (s) and 1062 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.63 (1H, s, =C*H*), 4.22 (1H, dt, *J* 10.0 and 4.5, MsOCH_aH$_b$), 4.15–4.0 and 4.07 (3H, overlapping m and q, *J* 7.1, MsOCH$_a$$H_b$ and OCH_2Me), 3.74 (1H, br quintet, *J ca.* 7.2, NC*H*), 3.3–3.15 (4H, m, NCH_2 and CH_2C=), 3.01 (s, 3H, *Me*SO_2O), 2.05–1.85 (4H, m, CH_2CH$_2$-OMs and ring CH_2CH_2CH_2), 1.65–1.45 (2H, m, CH_2Bu), 1.4–1.15 and 1.23 (9H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH_2*Me*) and 0.88 [3H, br t, *J ca.* 6.5, (CH_2)$_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 169.38 (*C*=O), 165.78 (N*C*=C), 78.25 (NC=*C*), 66.70 (CH_2OMs), 58.12 (O*C*H_2Me), 50.89 (N*C*H), 45.49 (N*C*H_2), 37.18 (*Me*SO_2O), 32.64 (*C*H_2C=), 31.71 (*C*H$_2$-CH$_2$OMs), 32.23, 31.38, 25.72 and 22.31 [(*C*H_2)$_4$Me], 20.90 (ring CH_2*C*H_2CH_2), 14.59 (OCH_2*Me*) and 13.82 [(CH_2)$_4$*Me*]; *m/z* (EI) 361 (16%, M^+), 316 (46), 291 (22), 282 (43), 274 (94), 266 (42), 238 (24), 220 (21), 195 (28), 194 (60), 192 (20), 182 (82), 156 (100), 122 (45), 120 (36), 110 (74), 108 (24), 69 (22), 67 (22) and 55 (35) (Found: M^+, 361.1938. $C_{17}H_{31}NO_5S$ requires 361.1923).

Ethyl 5-pentyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 11

(a) Racemic compound. Dry NEt_3 (0.46 cm^3, 3.3 mmol) was added dropwise to a stirred mixture of hydroxy ester (±)-**8** (723 mg, 2.55 mmol), triphenylphosphine (870 mg, 3.32 mmol) and tetrabromomethane (1.088 g, 3.28 mmol) in dry acetonitrile (2.30 cm^3) at 0 °C. After 5 min the mixture was allowed to warm to room temperature and stirred for 13 h. Triethylammonium bromide was filtered off, more dry acetonitrile (10 cm^3) was added and the diluted mixture was heated under reflux for 2 h. The solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 cm^3) and washed with H_2O (50 cm^3). The aqueous layer was extracted with CH_2Cl_2 (4 × 30 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification of the crude material by column chromatography (EtOAc–hexane 1:3) afforded the racemic *indolizine ester* (±)-**11** as an orange oil (573 mg, 85%); R_f 0.52 (EtOAc–hexane 1:3); ν_{max}(film)/cm^{-1} 2932 (s), 2856 (m), 1676 (s, C=O), 1596 (vs, C=C), 1456 (m), 1368 (s), 1280 (s), 1196 (m), 1156 (m) and 1096 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.11 (2H, q, *J* 7.1, OCH_2Me), 3.51 (1H, dt, *J* 9.4 and 7.0, 3-H$_{eq}$), 3.25–3.15 and 3.18 (2H, overlapping m and dt, *J* 9.3 and 7.0, 5-H and 3-H$_{ax}$), 3.07 (2H, td, *J* 7.7 and 1.2, 1-H), 2.44 (1H, dt, *J* 15.9 and 4.6, 6-H$_a$), 2.3–2.1 (1H, m, 6-H$_b$), 1.90 (2H, quintet, *J ca.* 7.4, 2-H), 1.85–1.45 (4H, m, 7-H and CH_2Bu), 1.45–1.10 and 1.26 (9H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH_2*Me*) and 0.89 [3H, br t, *J ca.* 6.5, (CH_2)$_4$*Me*]; δ_C (50 MHz;

$CDCl_3$; Me_4Si) 168.66 (*C*=O), 158.43 (C-8a), 87.09 (C-8), 58.25 (OCH_2Me), 53.91 (C-5), 51.13 (C-3), 32.81 (C-1), 31.89, 31.79, 25.27 and 22.47 [$(CH_2)_4Me$], 24.39 (C-6), 21.02 (C-2), 18.49 (C-7), 14.71 (OCH_2Me) and 13.89 [$(CH_2)_4Me$]; *m*/*z* (EI) 265 (16%, M^+), 237 (20), 220 (24), 195 (51), 194 (100), 192 (51), 166 (40), 122 (83) and 120 (38) (Found: M^+, 265.2048. $C_{16}H_{27}NO_2$ requires 265.2042).

(b) (+)-Enantiomer. A mixture of (−)-ethyl (2*E*)-{1-[(1*R*)-1-(2-hydroxyethyl)hexyl]pyrrolidin-2-ylidene}acetate (−)-**8** (790 mg, 2.79 mmol), triphenylphosphine (2.19 g, 8.36 mmol), imidazole (0.57 g, 8.4 mmol) and iodine (1.42 g, 5.58 mmol) in dry toluene (30 cm^3) was stirred at 110 °C for 3.5 h and then allowed to cool to ambient temperature. The mixture was washed with saturated aqueous $NaHCO_3$ solution (50 cm^3). The aqueous layer was separated and extracted with EtOAc (2 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a dark red liquid which was purified by column chromatography (CH_2Cl_2 to remove phosphine, then EtOAc–hexane 3:7) to give *(+)-ethyl (5R)-5-pentyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate* (+)-**11** as a pale yellow oil (601 mg, 81%); $[\alpha]_D^{24}$ +3.4 (*c* 1.19, absolute EtOH); δ_H within ±0.05 ppm and δ_C within ±0.20 ppm of the values given for the racemic compound (Found: M^+, 265.2058. $C_{16}H_{27}NO_2$ requires 265.2042).

(±)-Ethyl (2*E*)-{1-[1-(2-chloroethyl)hexyl]pyrrolidin-2-ylidene}-ethanoate 12

Dry NEt_3 (0.11 cm^3, 0.79 mmol) was added dropwise to a stirred mixture of the hydroxy ester (±)-**8** (174 mg, 0.62 mmol), triphenylphosphine (210 mg, 0.80 mmol) and tetrachloromethane (0.08 cm^3, 0.80 mmol) in dry acetonitrile (0.55 cm^3) at 0 °C. After 5 min the mixture was allowed to warm to room temperature and stirred for 15 h. The solvent was evaporated *in vacuo*. Purification by column chromatography (EtOAc–hexane 1:3) afforded the *chloro ester* (±)-**12** as an orange oil (172 mg, 93%); R_f 0.53 (EtOAc–hexane 1:2); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.66 (1H, s, =C*H*), 4.08 (2H, q, *J* 7.1, OCH_2Me), 3.77 (1H, tt, *J* 8.8 and 5.6, NC*H*), 3.44 (2H, t, *J* 6.9, CH_2Cl), 3.25–3.15 (4H, m, NCH_2 and CH_2C=), 2.1–1.8 (4H, m, CH_2CH_2Cl and ring $CH_2CH_2CH_2$), 1.6–1.45 (2H, m, CH_2Bu), 1.4–1.1 and 1.25 (9H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH_2Me) and 0.88 [3H, br t, *J ca.* 6.5, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 169.68 (*C*=O), 165.67 (N*C*=C), 78.51 (NC=*C*), 58.26 (OCH_2Me), 52.14 (N*C*H), 45.94 (br, NCH_2), 41.42 (CH_2Cl), 35.22 (CH_2CH_2Cl), 32.79 (CH_2C=), 32.01, 31.53, 25.84 and 22.42 [$(CH_2)_4Me$], 21.04 (ring $CH_2CH_2CH_2$), 14.68 (OCH_2Me) and 13.91 [$(CH_2)_4Me$]; *m*/*z* (EI) 301 (5%, ^{35}Cl-M^+), 266 (44, $M^+ - Cl$), 216 (13), 214 (37), 194 (60), 182 (44), 156 (79), 122 (70), 120 (58), 110 (100), 108 (33) and 55 (46) (Found: M^+, 301.1788. $C_{16}H_{28}{}^{35}ClNO_2$ requires 301.1809).

Reduction of ethyl 5-pentyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 11 with sodium cyanoborohydride

(a) Racemic compounds. The racemic bicyclic vinylogous urethane (±)-**11** (787 mg, 2.97 mmol) was dissolved in absolute EtOH (7 cm^3) to make up a 0.4 M solution. Sodium cyanoborohydride (206 mg, 3.28 mmol) was added, followed by bromocresol green (0.5% solution in EtOH, 1 drop). Concentrated hydrochloric acid was dispensed when necessary during the course of the reaction to ensure a permanent colour change to yellow (pH *ca.* 4). The reaction mixture was stirred at room temperature for 2 h. H_2O (40 cm^3) was added, and the solution was made basic with concentrated ammonia (25%). The aqueous phase was extracted with diethyl ether (6 × 45 cm^3). The combined ethereal extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford an orange oil (744 mg), shown by GLC (see general conditions; operating temperature, 100 °C held for 2 min, then programmed increase to 250 °C at 20 °C min^{-1}) to consist of a mixture of three diastereomers. The mixture was purified by flash chromatography (EtOAc–hexane 1:1) to yield the following compounds, in order of elution:

(±)-Ethyl (5R,8R*,8aR*)-5-pentyloctahydroindolizine-8-carboxylate* **15** (tentative) orange oil (106 mg, 13%); GLC retention time: 6.55 min (purity 96.5%); R_f 0.90 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.70 (1H, ddd, *J* 7.6, 4.8 and 2.7, 8a-H), 4.16 (2H, 2 × virtually superimposed q, *J* 7.1, OCH_2Me), 3.39 (1H, td, *J* 8.8 and 2.8, 3-H_{eq}), 2.75–2.45 (2H, m, 5-H and 8-H), 2.31 (1H, dtd, *J* 14.7, 8.5 and 2.5, 6-H_a), 2.2–1.6 (7H, m, various CH_2), 1.45–1.1 and 1.27 (12H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH_2Me) and 0.89 [3H, br t, *J ca.* 6.6, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 173.93 (*C*=O), 68.84 (C-8a), 63.43 (C-5), 60.28 (OCH_2Me), 53.66 (C-8), 50.78 (C-3), 46.34 (C-1), 34.33 (C-6), 33.94, 32.16, 28.46 and 22.53 [$(CH_2)_4Me$], 29.87 (C-7), 25.05 (C-2), 14.15 (OCH_2Me) and 13.99 [$(CH_2)_4Me$]; *(±)-ethyl (5R*,8R*,8aS*)-5-pentyloctahydroindolizine-8-carboxylate* **13** orange oil (64.4 mg, 8%); GLC retention time, 5.45 min (purity 94%); R_f 0.48 (EtOAc–hexane 1:1); ν_{max}(film)/cm^{-1} 2934 (s), 2860 (m), 2782 (m, Bohlmann band), 1732 (s, C=O), 1458 (m), 1374 (m) and 1150 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.13 (2H, q, *J* 7.1, OCH_2Me), 3.26 (1H, td, *J* 8.4 and 2.6, 3-H_{eq}), 2.35–1.35 (12H, m, C*H* and CH_2), 1.35–1.15 and 1.25 (11H, overlapping m and t, *J* 7.1, remaining CH_2 and OCH_2Me) and 0.89 (3H, br t, *J ca.* 6.5, CH_2CH_2Me); δ_C (50 MHz; $CDCl_3$; Me_4Si) 174.42 (*C*=O), 65.57 (C-8a), 62.85 (C-5), 60.04 (OCH_2Me), 51.05 (C-3), 47.85 (C-8), 34.27, 32.14, 25.25 and 22.52 [$(CH_2)_4Me$], 29.99 (C-1), 28.98 (C-6), 28.22 (C-7), 20.22 (C-2), 14.15 (OCH_2Me) and 13.96 [$(CH_2)_4Me$]; *m*/*z* (EI) 267 (1%, M^+), 197 (14), 196 (100), 168 (11), 152 (5), 122 (15), 96 (16), 70 (18), 56 (5) and 55 (20) (Found: M^+, 267.2215. $C_{16}H_{29}NO_2$ requires 267.2198). Further fractions (312 mg, 39%) contained mixtures of **13** and *(±)-ethyl (5R*,8S*,8aS*)-5-pentyloctahydroindolizine-8-carboxylate* **14** (GLC retention time, 5.16 min; see below for further characterisation). The effective recoveries of the isomers **13** and **14** were calculated from the isolated masses and GLC analyses as 262 mg (33%) and 114 mg (14%) respectively.

(b) (−)-Enantiomer of **13**. When the reaction was repeated as described above with (+)-ethyl (5*R*)-5-pentyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (+)-**11** (103 mg, 0.39 mmol) and sodium cyanoborohydride (58 mg, 0.93 mmol) in absolute EtOH (5 cm^3) over 1 h, the only chromatographically pure isomer isolated after flash chromatography (EtOAc–hexane 2:3) was *(−)-ethyl (5R,8R,8aS)-5-pentyloctahydroindolizine-8-carboxylate* (−)-**13** as an orange oil (37 mg, 36%); $[\alpha]_D^{26}$ −89.8 (*c* 1.23, MeOH); δ_H within ±0.05 ppm and δ_C within ±0.05 ppm of the values given for the racemic compound.

Catalytic hydrogenation of ethyl 5-pentyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate 11

(a) Racemic compound. A suspension of platinum dioxide (20 mg) in glacial acetic acid (5 cm^3) was prehydrogenated at 1 atm, after which a solution of racemic bicyclic vinylogous urethane (±)-**11** (604 mg, 2.28 mmol) in glacial acetic acid (5 cm^3) was added. The mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 24 h. The reaction mixture was filtered through Celite and the solids washed with CH_2Cl_2. The filtrate was diluted with H_2O (30 cm^3), made basic with aqueous NaOH solution (3 M) and extracted with CH_2Cl_2 (50 cm^3, 3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil (533 mg). Gas chromatographic analysis provided evidence for two compounds in a 94:6 ratio. Repeated flash chromatography (EtOAc–hexane 1:1) yielded *(±)-ethyl (5R*,8R*,8aS*)-5-pentyloctahydroindolizine-8-carboxylate* (±)-**13** (46 mg, 6%; characterisation as described above) and *(±)-ethyl (5R*,8S*,8aS*)-5-pentyloctahydroindolizine-8-carboxylate* (±)-**14** as an orange oil (431 mg, 71%); R_f 0.20 (EtOAc); ν_{max}(film)/cm^{-1} 2980

(s), 2940 (s), 2880 (m) and 2790 (m, Bohlmann band); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.14 (2H, q, *J* 7.1, OCH_2Me), 3.30 (1H, br t with fine coupling, *J ca.* 7.9 and 2.6, 3-H_{eq}), 2.73–2.68 (1H, narrow m, 8-H), 2.2–2.0 (2H, m, 3-H_{ax} and 5-H), 1.95–1.55 (11H, m, ring C*H* and CH_2), 1.55–1.15 and 1.25 (9H, m and t, *J* 7.2, remaining CH_2 and OCH_2Me) and 0.89 [3H, br t, *J ca.* 6.5, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 173.13 (*C*=O), 65.46 (C-8a), 64.56 (C-5), 59.65 (OCH_2Me), 52.02 (C-3), 41.47 (C-8), 34.40, 32.22, 25.20 and 22.54 [$(CH_2)_4Me$], 27.57 (C-1), 27.13 (C-6), 27.03 (C-7), 20.16 (C-2), 14.24 (OCH_2Me) and 14.00 [$(CH_2)_4Me$]; *m*/*z* (EI) 267 (1%, M^+), 197 (14), 196 (100), 168 (11), 122 (19), 110 (7), 96 (18), 70 (29), 68 (11), 67 (11), 55 (27), 54 (13), 43 (23), 42 (16) and 41 (59) (Found: M^+, 267.2209. $C_{16}H_{29}NO_2$ requires 267.2198).

(b) (−)-Enantiomer of **14**. The above reaction was repeated with (+)-ethyl (5*R*)-5-pentyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (+)-**11** (217 mg, 0.82 mmol) and platinum dioxide (20 mg) in glacial acetic acid (5 cm^3) under an atmosphere of hydrogen gas for 36 h at room temperature. After work-up and column chromatography, a mixture of (−)-**13** and (−)-**14** was obtained (12 : 88 by GLC; 185 mg, 85%). This mixture was not separated, but was epimerised as described below.

Epimerisation of ethyl (5*R*,8*S*,8a*S*)-5-pentyloctahydroindolizine-8-carboxylate (−)-14

A solution containing a catalytic quantity of sodium ethoxide was generated *in situ* by adding a fragment of sodium metal (washed with dry diethyl ether) to dry EtOH (2 cm^3). Once all the sodium had reacted, the above mixture of isomers of ethyl 5-pentyloctahydroindolizine-8-carboxylate (172 mg, 0.64 mmol) was added, and the resulting solution was heated under reflux for 5 h. After cooling to ambient temperature, the mixture was treated with glacial acetic acid (5 drops). The solvent was evaporated *in vacuo* and the residue treated with CH_2Cl_2, filtered to remove the inorganic salts, and the filtrate evaporated *in vacuo* to yield an oil (147 mg) containing **13** and **14** in a ratio of 19 : 1 (GLC). Purification by flash chromatography (EtOAc) afforded *ethyl (5R,8R,8aS)-5-pentyloctahydroindolizine-8-carboxylate* (−)-**13** as a pale yellow oil (69 mg, 40% recovery); characterisation as described above.

[(5*R**,8*R**,8a*S**)-5-Pentyloctahydroindolizin-8-yl]methanol 16

(a) Racemic compound. $LiAlH_4$ (43 mg, 1.1 mmol) and racemic ethyl (5*R**,8*R**,8a*S**)-5-pentyloctahydroindolizine-8-carboxylate (±)-**13** (300 mg, 1.12 mmol) were stirred together in dry THF (11 cm^3) for 0.5 h at 0 °C and then allowed to warm to room temperature. The reaction was quenched by the sequential addition of H_2O (0.043 cm^3), aqueous NaOH solution (15% w/v, 0.043 cm^3) and finally H_2O (0.13 cm^3). The solids were filtered off, washed with CH_2Cl_2, EtOAc and MeOH, and the organic filtrate was dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a yellow oil (281 mg). Purification by column chromatography (1% concentrated ammonia in EtOAc) gave the racemic *octahydroindolizinylmethanol* (±)-**16** as a viscous colourless oil (233 mg, 92%); R_f 0.28 (MeOH–acetone 1 : 1); δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.63 (1H, dd, *J* 10.7 and 4.5, CH_aH_bOH), 3.42 (1H, dd, *J* 10.7 and 6.7, CH_aH_bOH), 3.26 (1H, td, *J* 8.3 and 2.0, 3-H_{eq}), 2.64 (1H, br s, O*H*), 2.05–1.8, 1.8–1.6, 1.6–1.4, 1.4–1.25 and 1.25–1.0 (20H, clusters of m, C*H* and CH_2) and 0.89 [3H, br t, *J ca.* 6.5, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 66.84 (C-8a), 65.31 (CH_2OH), 63.47 (C-5), 51.39 (C-3), 44.18 (C-8), 34.35, 32.16, 25.46 and 22.56 [$(CH_2)_4Me$], 30.50, 28.92 and 27.88 (C-1, C-6 and C-7), 20.49 (C-2) and 14.00 [$(CH_2)_4Me$]; *m*/*z* (EI) 225 (1%, M^+), 155 (10), 154 (100), 124 (2), 122 (4), 96 (13), 70 (11) and 55 (8) (Found: M^+, 225.2076. $C_{14}H_{27}NO$ requires 225.2093) [lit. for (−)-**16**,[21] δ_C 66.9, 65.3, 63.5, 51.4, 44.1, 34.3, 32.2, 30.5, 28.9, 27.9, 25.5, 22.6, 20.5 and 14.0].

(b) (−)-Enantiomer. The above experiment was repeated with $LiAlH_4$ (10 mg, 0.26 mmol), added in portions to a stirred solution of (−)-ethyl (5*R*,8*R*,8a*S*)-5-pentyloctahydroindolizine-8-carboxylate **13** (37 mg, 0.14 mmol) in dry THF (10 cm^3) at 0 °C. Stirring was maintained for 2 h at 0 °C. Work-up with H_2O (5 drops), filtration of the inorganic solids (copiously washed with CH_2Cl_2), drying of the filtrate ($MgSO_4$) and evaporation *in vacuo* yielded *(−)-[(5R,8R,8aS)-5-pentyloctahydroindolizin-8-yl]methanol* **16** as a chromatographically pure, viscous colourless oil (29 mg, 94%); $[\alpha]_D^{25}$ −93.1 (*c* 0.58, MeOH) [lit., −93.3 (*c* 0.58, MeOH),[20] −93.6 (*c* 0.51, MeOH)[21]]; δ_H within ±0.05 ppm and δ_C within ±0.2 ppm of the values given for the racemic compound.

(±)-[(5*R**,8*R**,8a*S**)-5-Pentyloctahydroindolizin-8-yl]methyl methanesulfonate 17

The racemic indolizinylmethanol **16** (161 mg, 0.71 mmol), methanesulfonyl chloride (0.11 cm^3, 1.4 mmol) and NEt_3 (0.40 cm^3, 2.9 mmol) were stirred in dry CH_2Cl_2 (12 cm^3) at 0 °C for 2 h. The solution was poured into saturated aqueous $NaHCO_3$ solution (25 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude mesylate as an orange oil (362 mg). Column chromatography with EtOAc–hexane (1 : 1) as eluent afforded the racemic *methanesulfonate* (±)-**17** as an orange oil (207 mg, 96%); R_f 0.72 (EtOAc–hexane 1 : 1); ν_{max}(film)/cm^{-1} 2935 (s), 2855 (m), 2780 (m, Bohlmann band), 1455 (m), 1350 (s, S=O), 1175 (s) and 820 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.18 and 4.10 (2H, 2 × dd, *J* 10.1 and 4.3, and *J* 10.1 and 5.3, CH_2OMs), 3.33 (1H, td, *J* 8.4 and 2.4, 3-H_{eq}), 3.01 (3H, s, OSO_2Me), 2.15–1.45 (11H, m, C*H* and CH_2), 1.45–1.05 (9H, m, remaining CH_2) and 0.89 [3H, br t, *J ca.* 6.5, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 71.84 (CH_2OMs), 66.19 (C-8a), 63.18 (C-5), 51.20 (C-3), 41.07 (C-8), 37.15 (OSO_2Me), 34.01, 32.05, 25.21 and 22.50 [$(CH_2)_4Me$], 29.94 (C-6), 28.63 (C-1), 27.42 (C-7), 20.29 (C-2) and 13.97 [$(CH_2)_4Me$]; *m*/*z* (EI) 303 (2%, M^+), 232 (100), 208 (26), 136 (20), 96 (9) and 70 (41) (Found: M^+, 303.1867. $C_{15}H_{29}NO_3S$ requires 303.1868).

(±)-(5*R**,8*R**,8a*S**)-8-Methyl-5-pentyloctahydroindolizine (Indolizidine 209B) 1

Lithium triethylborohydride (3.5 cm^3 of a 1 M solution in THF, 3.5 mmol) was added dropwise to a solution of the racemic methanesulfonate (±)-**17** (268 mg, 0.88 mmol) in dry THF (6 cm^3) at 0 °C. After 1 h, the mixture was poured into H_2O (50 cm^3) and extracted with CH_2Cl_2 (4 × 20 cm^3). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution (50 cm^3), dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford a brown oil (246 mg). Purification by column chromatography using acetone–hexane (1 : 2) as eluent yielded a mobile yellow oil (167 mg) consisting of an approximately 1 : 1 mixture (by ^1H NMR spectroscopy) of *(±)-octahydroindolizine* **1** (*ca.* 40% overall yield) and methanesulfonate **17**. Compound **1**: δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.27 (1H, dt, *J* 8.3 and 2.2, 3-H_{eq}), 2.3–2.05, 2.05–1.5 and 1.5–0.95 (22H, clusters of m, C*H* and CH_2) and 0.87 [6H, overlapping d and t, *J ca.* 6.4, CH*Me* and $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 71.32 (C-8a), 63.54 (C-5), 51.75 (C-3), 36.44 (C-8), 34.35, 32.21, 25.47 and 22.58 [$(CH_2)_4Me$], 33.62 (C-1), 31.11 (C-6), 28.91 (C-7), 20.27 (C-2), 18.84 (CH*Me*) and 14.02 [$(CH_2)_4Me$] (lit.,[21] δ_C 71.4, 63.6, 51.7, 36.3, 34.4, 33.6, 32.1, 31.0, 28.9, 25.5, 22.6, 20.3, 18.8 and 14.0).

(±)-[(5*R**,8*S**,8a*S**)-5-Pentyloctahydroindolizin-8-yl]-methanol 18

$LiAlH_4$ (31 mg, 0.82 mmol) and (±)-ethyl (5*R**,8*S**,8a*S**)-5-pentyloctahydroindolizine-8-carboxylate **14** (216 mg, 0.81 mmol) were stirred together in dry THF (10 cm^3) for 0.5 h at

0 °C and then allowed to warm to room temperature. The reaction was quenched by the sequential addition of H_2O (0.031 cm^3), aqueous NaOH solution (15% w/v, 0.031 cm^3) and finally H_2O (0.093 cm^3). The solids were filtered off, washed with CH_2Cl_2, EtOAc and MeOH and the organic filtrate was dried ($MgSO_4$), filtered and evaporated *in vacuo* to yield a yellow oil (277 mg). Purification by column chromatography with MeOH–acetone (17:83) as eluent gave the racemic *octahydroindolizinylmethanol* (±)-**18** as a viscous colourless oil (183 mg, 100%); R_f 0.25 (MeOH–acetone 1:4); ν_{max}(film)/cm^{-1} 3416 (br m, O–H), 2952 (s), 2932 (s), 2858 (s), 2788 (m, Bohlmann band), 2716 (w, Bohlmann band), 1460 (m), 1378 (m), 1096 (m) and 1052 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.9–5.3 (1H, br s, O*H*), 4.21 (1H, ddd, *J* 10.8, 4.0 and 1.3, CH_aH$_b$OH), 3.73 (1H, d with fine coupling, *J* 10.8, CH$_a$$H_b$OH), 3.25–3.15 [1H, m (= br t?), 3-H_{eq}], 2.4–2.3 (1H, m, 8a-H), 2.1–1.5 (13H, m, C*H* and CH_2), 1.5–1.2 (6H, m, remaining CH_2) and 0.88 [3H, br t, *J ca.* 6.5, $(CH_2)_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 67.19 (C-8a), 65.58 (*C*H$_2$OH), 63.86 (C-5), 51.68 (C-3), 34.70 (C-8), 34.45, 32.25, 26.16 and 22.55 [(*C*H$_2$)$_4$Me], 31.22, 28.15 and 24.19 (C-1, C-6 and C-7), 20.56 (C-2) and 14.03 [$(CH_2)_4$*Me*]; *m*/*z* (EI) 225 (1%, M^+), 194 (1), 155 (10), 154 (100), 124 (7), 122 (5), 96 (14), 70 (17) and 55 (10) (Found: M^+, 225.2078. $C_{14}H_{27}NO$ requires 225.2093) [lit. for (−)-**18**,[21] δ_C 67.2, 65.5, 63.9, 51.7, 34.8, 34.4, 32.2, 31.2, 28.1, 26.2, 24.2, 22.5, 20.6 and 14.0].

(±)-[(5*R**,8*S**,8a*S**)-5-Pentyloctahydroindolizin-8-yl]methyl methanesulfonate 19

(±)-[(5*R**,8*S**,8a*S**)-5-Pentyloctahydroindolizin-8-yl]-methanol **18** (159 mg, 0.71 mmol), methanesulfonyl chloride (0.20 cm^3, 2.6 mmol) and NEt_3 (0.82 cm^3, 5.9 mmol) were stirred in dry CH_2Cl_2 (12 cm^3) at 0 °C for 2 h. The solution was poured into saturated aqueous $NaHCO_3$ solution (25 cm^3) and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude mesylate as an orange oil (342 mg). Column chromatography with EtOAc–hexane (1:2) as eluent afforded the *methanesulfonate* (±)-**19** as a viscous yellow oil (188 mg, 88%); R_f 0.32 (EtOAc–hexane 1:2); ν_{max}(film)/cm^{-1} 2952 (s), 2934 (s), 2862 (m), 2786 (m, Bohlmann band), 1350 (m, S=O), 1314 (s), 1192 (s), 1174 (s) and 796 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.48 and 4.37 (2H, 2 × dd, *J* 9.7 and 4.9, and *J* 9.7 and 8.4, CH_2OMs), 3.22–3.12 (1H, m, 3-H_{eq}), 3.01 (3H, s, OSO_2*Me*), 2.3–2.1 (2H, m, 5-H and 8a-H), 2.05–1.8, 1.8–1.5 and 1.5–1.1 (18H, clusters of m, C*H* and CH_2) and 0.89 [3H, br t, *J ca.* 6.5, $(CH_2)_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 69.33 (*C*H$_2$OMs), 65.66 (C-8a), 64.36 (C-5), 51.91 (C-3), 37.05 (OSO_2*Me*), 35.20 (C-8), 34.41, 32.22, 24.81 and 22.57 [(*C*H$_2$)$_4$Me], 26.71 (C-1), 26.56 (C-6), 25.77 (C-7), 20.42 (C-2) and 14.03 [$(CH_2)_4$*Me*]; *m*/*z* (EI) 303 (2%, M^+), 232 (100), 208 (22), 136 (10), 96 (5) and 70 (26) (Found: M^+, 303.1859. $C_{15}H_{29}NO_3S$ requires 303.1868).

(±)-(5*R**,8*S**,8a*S**)-8-Methyl-5-pentyloctahydroindolizine 20

Raney nickel catalyst[23] (*ca.* 500 mg, suspension in absolute EtOH, W-2 activity) was added to the methanesulfonate (±)-**19** (152 mg, 0.50 mmol) in absolute EtOH (20 cm^3). The mixture was heated under reflux for 3 h under an atmosphere of nitrogen, cooled to room temperature and filtered through Celite. The solids were washed with CH_2Cl_2. The organic filtrate was evaporated *in vacuo* to afford a colourless oil (192 mg). Flash chromatography (2% concentrated ammonia in EtOAc) afforded *(±)-(5R*,8S*,8aS*)-8-methyl-5-pentyloctahydroindolizine* **20** as a mobile colourless oil (68 mg, 65%); R_f 0.19 (EtOAc); ν_{max}(film)/cm^{-1} 2954 (s), 2926 (s), 2856 (m), 1680 (m), 1658 (m), 1590 (m), 1572 (m), 1460 (m), 1294 (m) and 1248 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.3–3.2 (1H, m, 3-H_{eq}), 2.15–1.95, 1.95–1.75, 1.75–1.5 and 1.5–1.1 (20H, clusters of m, C*H* and CH_2), 0.97 (3H, d, *J* 7.0, CH*Me*) and 0.88 [3H, br t, *J ca.* 6.6, $(CH_2)_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 67.86 (C-8a), 65.21 (C-5), 52.27 (C-3), 34.39, 32.25, 25.37 and 22.61 [$(CH_2)_4$*Me*], 31.85 (C-8), 29.42 (C-1), 26.72 (C-6), 25.67 (C-7), 20.27 (C-2), 14.06 [$(CH_2)_4$*Me*] and 12.22 (CH*Me*); *m*/*z* (EI) 209 (4%, M^+), 208 (5), 168 (3), 154 (7), 152 (8), 139 (12), 138 (100), 136 (7), 96 (9), 70(8) and 55 (7) (Found: M^+, 209.2132. $C_{14}H_{27}N$ requires 209.2144).

tert-Butyl (2*E*)-oct-2-enoate 24

To a stirred suspension of lithium chloride (dried overnight at 140 °C, *ca.* 2 mmHg; 0.96 g, 23 mmol) in dry acetonitrile (150 cm^3) was added *tert*-butyl diethoxyphosphorylacetate[33] (5.22 g, 20.7 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.41 cm^3, 22.8 mmol) and hexanal (2.74 cm^3, 22.8 mmol). The mixture was stirred at room temperature for 16 h, after which the solvent was evaporated *in vacuo*. The residue was partitioned between H_2O and CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The yellow liquid thus obtained (4.74 g) was purified by bulb-to-bulb distillation (100–120 °C, *ca.* 1 mmHg) to give the *ester* **24** as a colourless liquid (3.933 g, 96%); ν_{max}(film)/cm^{-1} 2958 (s), 2928 (s), 2858 (s), 1718 (s, C=O), 1652 (s, C=C) and 1156 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.86 (1H, dt, *J* 15.6 and 6.9, C*H*=CHCO), 5.73 (1H, dt, *J* 15.6 and 1.6, CH=C*H*CO), 2.16 (2H, qd, *J* 6.9 and 1.6, CH_2CH=), 1.48 (9H, s, OCMe_3), 1.5–1.25 (6H, m, remaining CH_2) and 0.89 [3H, br t, *J ca.* 6.6, $(CH_2)_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 166.15 (*C*=O), 148.13 (*C*H=CHCO), 122.85 (CH=*C*HCO), 79.88 (O*C*Me$_3$), 31.97 (*C*H$_2$CH=), 31.30 (*C*H$_2$CH$_2$Me), 28.11 (OC*Me*$_3$), 27.72 (*C*H$_2$CH$_2$CH=), 22.39 (*C*H$_2$Me) and 13.90 (CH$_2$*Me*) (Found: M^+, 198.1635. $C_{12}H_{22}O_2$ requires 198.1620).

(+)-*tert*-Butyl (3*R*)-3-{*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amino}-octanoate 26

A solution of (+)-*N*-benzyl-*N*-[(1*R*)-1-phenylethyl]amine **25** (Aldrich; 5.03 g, 23.8 mmol) in dry THF (100 cm^3) was cooled to −78 °C. *n*-Butyllithium (1.37 M solution in hexane, 16.3 cm^3, 22.3 mmol) was added, and the resulting red solution was stirred for 30 min at −78 °C, after which a solution of *tert*-butyl (*E*)-oct-2-enoate **24** (3.93 g, 19.8 mmol) in dry THF (5 mmol) was added dropwise. Stirring was continued at −78 °C for 3 h before the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (8 cm^3). The solution was allowed to warm to room temperature, after which the solvent was evaporated *in vacuo*. The residue was diluted with H_2O (80 cm^3) and extracted with CH_2Cl_2 (80 cm^3, 2 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil (9.14 g) which was purified by column chromatography with EtOAc–hexane (1:19) as eluent. The *amino ester* (+)-**26** was obtained as a pale yellow oil (7.28 g, 90%); R_f 0.35 (EtOAc–hexane, 1:19); $[\alpha]_D^{25}$ +5.1 (*c* 1.07, absolute EtOH); ν_{max}(film)/cm^{-1} 2960 (s), 2930 (s), 2870 (m), 2858 (m), 1726 (s, C=O) and 1146 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.5–7.2 (10H, m, arom H), 3.84 (1H, q, *J* 7.0, NC*H*Me), 3.82 (1H, d, *J* 15.1, NCH_aH$_b$Ph), 3.50 (1H, d, *J* 15.1, NCH$_a$$H_b$Ph), 3.33 (1H, 7-line m, C*H*CH$_2$CO$_2$), 1.96 (1H, dd, *J* 14.6 and 3.6, CH_aH$_b$CO$_2$), 1.85 (1H, dd, *J* 14.6 and 7.8, CH$_a$$H_bCO_2$), 1.65–1.1, 1.42 and 1.35 [20H, overlapping m, s and d, *J* 7.0, (CH_2)$_4$Me, OCMe_3 and NCH*Me*] and 0.91 [3H, br t, *J ca.* 6.9, $(CH_2)_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 172.21 (*C*=O), 143.20 and 142.07 (2 × Ar C-1′), 128.16, 128.11, 128.04, 127.92 (Ar C-2′, C-3′, C-5′, C-6′), 126.82 and 126.47 (2 × Ar C-4′), 79.81 (O*C*Me$_3$), 58.39 (N*C*HMe), 53.98 (*C*HCH$_2$CO$_2$), 50.09 (NCH$_2$Ph), 37.84 (*C*H$_2$CO$_2$), 33.43, 31.79, 26.57 and 22.65 [(*C*H$_2$)$_4$Me], 28.03 (OC*Me*$_3$), 20.47 (NCH*Me*) and 14.06 [$(CH_2)_4$*Me*]; *m*/*z* (EI) 409 (1%, M^+), 338 (27), 318 (2), 304 (5), 294 (24), 190 (29),

105 (100) and 91 (77) (Found: M^+, 409.2973. $C_{27}H_{39}NO_2$ requires 409.2981).

(−)-*tert*-Butyl (3*R*)-3-aminooctanoate 27

The amino ester (+)-**26** (7.09 g, 17.3 mmol) and 10% palladium on activated carbon (2.58 g) were stirred in glacial acetic acid (74 cm^3) for 3 days under 7 atmospheres of hydrogen gas. The catalyst was removed by filtration through Celite, followed by several washings with H_2O. The filtrate was made basic with saturated aqueous sodium hydrogen carbonate solution, and the resulting mixture was extracted with CH_2Cl_2 (6 × 50 cm^3). The combined organic extracts were dried (K_2CO_3), filtered and evaporated *in vacuo* to afford a milky yellow oil (3.40 g), which was purified by column chromatography with MeOH–EtOAc mixtures (1 : 10 to 1 : 5) as eluent to give *(−)-tert-butyl (3R)-3-aminooctanoate* **27** as a pale yellow mobile oil (2.838 g, 76%); R_f 0.25 (MeOH–EtOAc, 1 : 9); $[\alpha]_D^{26}$ −17.7 (*c* 1.19, absolute EtOH); ν_{max}(film)/cm^{-1} 3382 (w, br, N–H), 2960 (s), 2930 (s), 2858 (s), 1726 (s, C=O), 1368 (m) and 1152 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 3.2–3.1 (1H, m, C*H*NH_2), 2.39 (1H, dd, *J* 15.6 and 4.2, C$H_aH_bCO_2$), 2.18 (1H, dd, *J* 15.6 and 8.7, C$H_aH_bCO_2$), 1.84 (2H, s, NH_2), 1.5–1.2 and 1.46 [17H, m and s, $(CH_2)_4$Me and OCMe_3] and 0.89 [3H, br t, *J ca.* 6.5, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 171.97 (*C*=O), 80.44 (O*C*Me_3), 48.40 (*C*HNH_2), 43.64 (*C*H_2CO_2), 37.29, 31.75, 25.65 and 22.53 [(*C*H_2)$_4$Me], 28.08 (OC*Me*$_3$) and 13.95 [$(CH_2)_4Me$]; *m/z* (EI) no discernible molecular ion (Found: $M^+ - Bu^t$, 158.1179. $C_8H_{16}NO_2$ requires 158.1180).

(+)-*tert*-Butyl (3*R*)-3-(2-oxopyrrolidin-1-yl)octanoate 29

(a) 4-Chlorobutanoyl chloride (0.62 cm^3, 5.6 mmol, 1.2 equiv.) was added to the amino ester (−)-**27** (1.00 g, 4.64 mmol) in dry $CHCl_3$ (20 cm^3) at room temperature. An exothermic process ensued. Sodium hydrogen carbonate (468 mg, 5.57 mmol) was added after 5 min, and the mixture was heated under reflux for 1 h. After cooling, the mixture was filtered through a thin pad of Celite, and the solids were washed copiously with CH_2Cl_2. The filtrate was evaporated *in vacuo* to afford the crude 4-chlorobutyramide **28** as a viscous yellow oil (1.744 g). To this was added a solution of potassium *tert*-butoxide (0.78 g, 7.0 mmol) in dry *tert*-butyl alcohol (30 cm^3). The mixture was stirred at room temperature overnight, and then neutralised by the addition of glacial acetic acid. The solvent was evaporated *in vacuo* and the white residue was dissolved in CH_2Cl_2 (50 cm^3), which was washed with H_2O (50 cm^3). The aqueous layer was extracted with additional CH_2Cl_2 (2 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford a yellow oil (1.61 g) which was purified by column chromatography with EtOAc–hexane (1 : 1) as eluent. This afforded *(+)-tert-butyl (3R)-3-[(4-chlorobutanoyl)amino]-octanoate* **28** as a pale yellow oil (139 mg, 9%); and *(+)-tert-butyl (3R)-3-(2-oxopyrrolidin-1-yl)octanoate* **29** as a very pale yellow oil (1.083 g, 82%). (+)-**28**: R_f 0.50 (EtOAc–hexane, 3 : 7); $[\alpha]_D^{25}$ +6.6 (*c* 1.14, absolute EtOH); ν_{max}(film)/cm^{-1} 3056 (w), 2960 (s), 2932 (s), 2860 (m), 1726 (s, ester C=O), 1648 (s, amide C=O), 1546 (m, N–H bend), 1454 (m), 1368 (s) and 1158 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 6.23 (1H, br d, *J ca.* 9.1, N*H*), 4.25–4.2 (1H, m, C*H*NH), 3.60 (2H, t, *J* 6.2, CH_2Cl), 2.45–2.4 (2H, m, NHCOCH_2), 2.34 (2H, d, *J* 7.2, CH_2CO_2), 2.11 (2H, quintet, *J* 6.4, CH_2CH_2Cl), 1.6–1.4 and 1.46 [17H, m and s, $(CH_2)_4$Me and OCMe_3] and 0.89 [3H, br t, *J ca.* 6.4, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 171.20 and 170.77 (2 × *C*=O), 81.02 (O*C*Me_3), 46.11 (*C*HNH), 44.37 (*C*H_2Cl), 39.59 (*C*H_2CO_2), 34.05 (NHCO*C*H_2), 33.36, 31.46, 25.72 and 22.40 [(*C*H_2)$_4$Me], 28.12 (*C*H_2CH_2Cl), 27.99 (OC*Me*$_3$) and 13.89 [$(CH_2)_4Me$]; *m/z* (EI) 319 (1%, M^+), 263 (15), 246 (15), 192 (42), 158 (46), 100 (40), 88 (100) and 57 (78) (Found: M^+, 319.1927. $C_{16}H_{30}NO_3Cl$ requires 319.1914). (+)-**29**: R_f 0.33 (EtOAc–hexane, 1 : 1); $[\alpha]_D^{24}$ +12.4 (c 1.29, absolute EtOH); ν_{max}(film)/cm^{-1} 2960 (s), 2930 (s), 2860 (m), 1728 (s, ester C=O), 1690 (s, amide C=O), 1286 (s) and 1156 (m); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.44 (1H, br quintet, *J ca.* 7.4, C*H*N), 3.36 (1H, dt, *J* 9.3 and 6.9, NCH_aH_b), 3.28 (1H, dt, *J* 9.4 and 6.9, NCH_aH_b), 2.55–2.25 (4H, m, 2 × CH_2CO), 1.99 (2H, quintet, *J* 7.5, ring $CH_2CH_2CH_2$), 1.55–1.1 and 1.42 [17H, m and s, $(CH_2)_4$Me and OCMe_3] and 0.87 [3H, br t, *J ca.* 6.5, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 174.58 (lactam *C*=O), 170.05 (ester *C*=O), 80.51 (O*C*Me_3), 48.58 (*C*HN), 42.26 (N*C*H_2), 39.18 (*C*H_2CO_2), 31.98 (superimposed *C*H_2CON and *C*H_2Bu), 31.23, 25.55 and 22.24 [(*C*H_2)$_3$Me], 27.68 (OC*Me*$_3$), 18.10 (ring $CH_2CH_2CH_2$) and 13.72 [$(CH_2)_4Me$]; *m/z* (EI) 283 (4%, M^+), 226 (58), 210 (40), 168 (76), 156 (48), 112 (46), 98 (31), 86 (57), 84 (49) and 57 (100) (Found: M^+, 283.2134. $C_{16}H_{29}NO_3$ requires 283.2147).

(b) When the cyclisation of crude chloroamide **28** was performed in undried *tert*-butyl alcohol, a quantity of *(3R)-(−)-3-(2-oxopyrrolidin-1-yl)octanoic acid* **30** was isolated as colourless spars, mp 125–126 °C (from hexane–EtOAc) (Found: C, 63.31; H, 9.43; N, 6.12. $C_{12}H_{21}NO_3$ requires C, 63.41; H, 9.31; N, 6.16%); $[\alpha]_D^{25}$ −8.8 (*c* 1.14, absolute EtOH); ν_{max}($CHCl_3$)/cm^{-1} *ca.* 3500–2500 (w, v br, CO_2H), 2932 (s), 2862 (m), 1718 (s, carboxylic acid C=O), 1674 (s, lactam C=O) and 1642 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 10.69 (1H, br s, CO_2H), 4.47 (1H, quintet, *J* 7.4, C*H*N), 3.5–3.25 (2H, m, NCH_2), 2.55–2.35 (4H, m, 2 × CH_2CO), 2.1–1.9 (2H, m, ring $CH_2CH_2CH_2$), 1.65–1.4 (2H, m, CH_2Bu), 1.4–1.1 [6H, m, $(CH_2)_3$Me] and 0.87 [3H, t, *J* 6.4, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 176.35 and 173.81 (2 × *C*=O), 49.11 (*C*HN), 42.97 (N*C*H_2), 37.59 (*C*H_2CO_2H), 32.06 (*C*H_2Bu), 31.27 (superimposed *C*H_2CON and another *C*H_2), 25.68 and 22.36 (2 × *C*H_2), 18.15 (ring $CH_2CH_2CH_2$) and 13.84 [$(CH_2)_4Me$].

(+)-*tert*-Butyl (3*R*)-3-(2-thioxopyrrolidin-1-yl)octanoate 31

The lactam (+)-**29** (1.034 g, 3.65 mmol) and Lawesson's reagent (Aldrich; 0.74 g, 1.8 mmol) were heated under reflux for 3 h in dry toluene (15 cm^3), after which the solvent was evaporated *in vacuo.* This afforded a red oil (1.90 g) which was purified by column chromatography with EtOAc–hexane (1 : 4) as eluent. The *pyrrolidinethione* (+)-**31** was obtained as an orange oil (977 mg, 89%); R_f 0.42 (EtOAc–hexane 1 : 4); $[\alpha]_D^{30}$ +17.2 (*c* 0.90, absolute EtOH); ν_{max}(film)/cm^{-1} 2958 (s), 2930 (s), 2860 (m), 1724 (s, C=O), 1596 (s), 1498 (s), 1462 (s), 1450 (s), 1308 (s), 1286 (s), 1264 (s), 1156 (s), 1122 (s) and 930 (br s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 5.36 (1H, quintet, *J* 7.5, CHN), 3.71 (1H, dt, *J* 10.7 and 7.2, NCH_aH_b), 3.56 (1H, dt, *J* 10.7 and 7.1, NCH_aH_b), 3.00 (2H, td, *J* 7.6 and 1.8, CH_2CS), 2.54 and 2.44 (2H, 2 × dd, *J* 14.3 and 6.1, and *J* 14.3 and 8.8 respectively, CH_2CO), 2.03 (2H, quintet, *J* 7.6, ring $CH_2CH_2CH_2$), 1.75–1.5 (2H, m, CH_2Bu), 1.45–1.1 [6H, m, $(CH_2)_3$Me], 1.43 (9H, s, OCMe_3) and 0.87 [3H, br t, *J ca.* 6.6, $(CH_2)_4Me$]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 201.72 (*C*=S), 169.53 (*C*=O), 81.02 (O*C*Me_3), 53.30 (*C*HN), 49.07 (N*C*H_2), 45.04 (*C*H_2COS), 38.81 (*C*H_2CO_2), 32.09, 31.38, 25.44 and 22.26 [(*C*H_2)$_4$Me], 27.79 (OC*Me*$_3$), 19.96 (ring $CH_2CH_2CH_2$) and 13.80 [$(CH_2)_4Me$]; *m/z* (EI) 299 (30%, M^+), 267 (12), 242 (95), 226 (22), 210 (100), 184 (9), 173 (32), 128 (20), 102 (67), 85 (19), 57 (36), 55 (20) and 41 (23) (Found: M^+, 299.1900. $C_{16}H_{29}NO_2S$ requires 299.1919).

(+)-*tert*-Butyl (3*R*)-3-[(2*E*)-(2-ethoxycarbonylmethylene)-pyrrolidin-1-yl]octanoate 32

(a) Ethyl bromoacetate (0.68 cm^3, 6.2 mmol) and the pyrrolidinethione (+)-**31** (921 mg, 3.08 mmol) were stirred for 20 h in dry acetonitrile (5 cm^3). Triphenylphosphine (1.61 g, 6.15 mmol) and dry NEt_3 (0.86 cm^3, 6.2 mmol) were added. The mixture was stirred at room temperature for 3 h and then filtered through a pad of Celite. The solids were washed copiously with EtOAc. The filtrate was evaporated *in vacuo* to afford an orange oil (3.436 g) which was purified by column chromato-

graphy. CH_2Cl_2 was used to elute triphenylphosphine sulfide and excess triphenylphosphine, after which hexane–EtOAc mixtures (4:1 to 7:3) eluted the *vinylogous urethane* (+)-**32** as an orange oil (1.020 g, 94%); R_f 0.42 (EtOAc–hexane, 1:4); $[a]_D^{25}$ +25.3 (*c* 1.26, absolute EtOH); ν_{max}(film)/cm^{-1} 2978 (m), 2932 (m), 1722 (s, br, unconjugated C=O), 1684 (s, conjugated C=O), 1590 (s, C=C), 1140 (s) and 1116 (s); δ_H (200 MHz; $CDCl_3$; Me_4Si) 4.68 (1H, s, =C*H*), 4.09 (2H, two sets of overlapping q, *J* 7.0, OCH_2Me), 4.01 (1H, quintet, *J* 7.1, C*H*N), 3.29 and 3.23 (2H, 2 × dt, *J* 9.3 and 7.1, and *J* 9.3 and 7.0, NCH_2), 3.16 and 3.14 (2H, 2 × dt, *J* 7.6 and 0.9, and *J* 7.7 and 3.7, =CCH_2), 2.42 (2H, d, *J* 7.4, CH_2CO), 1.89 (2H, quintet, *J* 6.9, ring CH_2-C$H_2$$CH_2$), 1.6–1.5 (2H, m, C$H_2$Bu), 1.41 (9H, s, OC$Me_3$), 1.35–1.2 and 1.24 (9H, m and t, *J* 7.1, remaining CH_2 and OCH_2*Me*) and 0.87 [3H, br t, *J ca.* 6.7, $(CH_2)_4$*Me*]; δ_C (50 MHz; $CDCl_3$; Me_4Si) 170.04 and 169.64 (2 × *C*=O), 165.10 (N*C*=C), 80.98 (O*C*Me_3), 78.83 (NC=*C*), 58.09 (O*C*H_2Me), 51.73 (*C*HN), 45.88 (N*C*H_2), 39.06 (*C*H_2CO_2), 32.67, 31.48, 25.80 and 22.40 [(*C*H_2)$_4$Me], 32.09 (*C*H_2C=), 27.85 (OCMe_3), 21.00 (ring CH_2*C*$H_2$$CH_2$), 14.69 (OC$H_2$*Me*) and 13.88 [$(CH_2)_4$*Me*]; *m*/*z* (EI) 353 (16%, M^+), 308 (31), 296 (13), 283 (16), 282 (5), 266 (77), 252 (53), 238 (56), 210 (59), 182 (100), 156 (94), 110 (53) and 57 (56) (Found: M^+, 353.2572. $C_{20}H_{35}NO_4$ requires 353.2566).

(b) A mixture of (−)-*tert*-butyl (3*R*)-3-aminooctanoate **27** (446 mg, 2.07 mmol), freshly distilled ethyl 6-chloro-3-oxohexanoate[38] (399 mg, 2.07 mmol), Na_2SO_4 (294 mg, 2.07 mmol), Na_2HPO_4 (294 mg, 2.07 mmol) and a small crystal of iodine was heated in an oil bath at 65–80 °C for 18 h. The mixture was diluted with CH_2Cl_2 (30 cm^3). The inorganic solids were removed by filtration and washed with CH_2Cl_2. The combined organic extracts were evaporated *in vacuo* to give a brown oil, which was purified by column chromatography (EtOAc–hexane 1:3) to give a mixture of recovered ethyl 6-chloro-3-oxohexanoate and *vinylogous urethane* (+)-**32** (660 mg; *ca.* 1:1.2 by ^{1}H NMR spectroscopy). The yield of **32** was approximately 49%.

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References

1 J. W. Daly, H. M. Garraffo and T. F. Spande, in *The Alkaloids* (*N. Y.*), ed. G. A. Cordell, Academic Press, San Diego, 1993, vol. 43, pp. 185–288.
2 J. W. Daly, H. M. Garraffo and T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon Press, Amsterdam, 1999, vol. 13, pp. 1–161.
3 J. W. Daly, in *The Alkaloids* (*N. Y.*), ed. G. A. Cordell, Academic Press, San Diego, 1998, vol. 50, pp. 141–169.
4 T. H. Jones, J. S. T. Gorman, R. R. Snelling, J. H. C. Delabie, M. S. Blum, H. M. Garraffo, P. Jain, J. W. Daly and T. F. Spande, *J. Chem. Ecol.*, 1999, **25**, 1179.
5 J. P. Michael, *Nat. Prod. Rep.*, 1999, **16**, 675.
6 J. W. Daly, Y. Nishizawa, W. L. Padgett, T. Tokuyama, A. L. Smith, A. B. Holmes, C. Kibayashi and R. S. Aronstam, *Neurochem. Res.*, 1991, **16**, 1213.
7 J. P. Michael, C. B. de Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly and T. V. Stanbury, *Pure Appl. Chem.*, 1999, **71**, 979.
8 J. P. Michael and D. Gravestock, *Eur. J. Org. Chem.*, 1998, 865.
9 J. P. Michael and D. Gravestock, *S. Afr. J. Chem.*, 1998, **51**, 146.
10 J. W. Daly, C. W. Myers and N. Whittaker, *Toxicon*, 1987, **25**, 1023.
11 J. P. Michael and D. Gravestock, *Synlett*, 1996, 981.
12 J. P. Michael and D. Gravestock, *Pure Appl. Chem.*, 1997, **69**, 583.
13 For syntheses of indolizine 209B published before 1996, see ref. 11. For subsequently published total or formal syntheses, see the following: (*a*) N. Toyooka, K. Tanaka, T. Momose, J. W. Daly and H. M. Garraffo, *Tetrahedron*, 1997, **53**, 9553; (*b*) A. Bardou, J.-P. Célérier and G. Lhommet, *Tetrahedron Lett.*, 1998, **39**, 5189.
14 D. Brillon, *Synth. Commun.*, 1990, **20**, 3085.
15 (*a*) R. S. Marmor, *J. Org. Chem.*, 1972, **37**, 2901; (*b*) I. Fleming and J. M. Mwaniki, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1237.
16 M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710.
17 K. Shiosaki, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 2, pp. 865–892.
18 R. V. Stevens, *Acc. Chem. Res.*, 1984, **17**, 289.
19 F. Bohlmann, *Chem. Ber.*, 1985, **91**, 2157.
20 R. P. Polniaszek and S. E. Belmont, *J. Org. Chem.*, 1991, **56**, 4868.
21 A. B. Holmes, A. L. Smith, S. F. Williams, L. R. Hughes, Z. Lidert and C. Swithenbank, *J. Org. Chem.*, 1991, **56**, 1393.
22 C. W. Jefford, K. Sienkiewicz and S. R. Thornton, *Helv. Chim. Acta*, 1995, **78**, 1511.
23 L. W. Covert and H. Adkins, *J. Am. Chem. Soc.*, 1932, **54**, 4116.
24 See, for example, (*a*) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 1949, S178; (*b*) J. Nieuwenhuis and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1958, **77**, 1153; (*c*) E. Caspi, E. Cullen and P. K. Grover, *J. Chem. Soc.*, 1963, 212.
25 R. G. F. Giles, I. R. Green, L. S. Knight, V. R. Lee Son and S. C. Yorke, *J. Chem. Soc., Perkin Trans. 1*, 1994, 859.
26 D. Gnecco, C. Marazano and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1991, 625.
27 Y.-S. Wong, D. Gnecco, C. Marazano, A. Chiaroni, C. Riche, A. Billion and B. C. Das, *Tetrahedron*, 1998, **54**, 9357.
28 D. C. Cole, *Tetrahedron*, 1994, **50**, 9517.
29 G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, 1996, **25**, 117.
30 S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183.
31 J. F. Costello, S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1994, **5**, 1999.
32 G. F. Griffiths, G. W. Kenner, S. W. McCombie, K. M. Smith and M. J. Sutton, *Tetrahedron*, 1976, **32**, 275.
33 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
34 S. G. Davies and D. R. Fenwick, *J. Chem. Soc., Chem. Commun.*, 1995, 1109.
35 M. E. Bunnage, A. J. Burke, S. G. Davies and C. J. Goodwin, *Tetrahedron: Asymmetry*, 1995, **6**, 165.
36 J. C. A. Boeyens and C. F. Broli, unpublished results.
37 M. S. Manhas and S. J. Jeng, *J. Org. Chem.*, 1967, **32**, 1246.
38 P. H. Lambert, M. Vaultier and R. Carrié, *J. Org. Chem.*, 1985, **50**, 5352.
39 J. P. Michael, G. D. Hosken and A. S. Howard, *Tetrahedron*, 1988, **44**, 3025.
40 P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2866.
41 H. M. Garraffo, P. Jain, T. F. Spande and J. W. Daly, *J. Nat. Prod.*, 1997, **60**, 2.