The Total Synthesis of (±)-indolizidines 235B and 235B'

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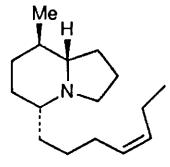
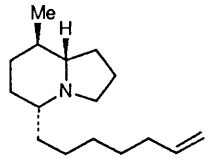
The total synthesis of racemic indolizidines 235B **1** and 235B' **2** is described, in which the key step is the intramolecular thermal cycloaddition of the (*Z*)-*N*-alkenylnitrones **10b** and **10a**, respectively. Cyclisation of the isoxazolidines **12**, followed by reductive N–O bond cleavage, epimerisation of the resulting axial hydroxymethyl side chain to the equatorial configuration, and further reduction to a methyl group gave the target molecules. Intramolecular cyclisation of the related nitrone **18**, a potential precursor to the solenopsins, was less regioselective, affording a 6:1 mixture of the adducts **19** and **20**, which indicates a dependence on the nature of the substituent α to nitrogen.

In recent years there has been incredible activity in the isolation, biological evaluation and total synthesis of naturally occurring alkaloids isolated from the skin extracts of the Dendrobatidae family of neotropical arrow poison frogs.[1] In particular, there exists a small sub-group of *trans*-substituted 8-methylindolizidines.[2] We have recently developed a rather general strategy for the synthesis of all-*cis* 2,3,6-trisubstituted piperidines,[3] which can be modified to embrace the members of the above described indolizidine family such as indolizidine 205A.[4] The related indolizidines 235B 1, isolated from *D. pumilio*,[5] and 235B' **2**[6] should also be amenable to synthesis by this strategy.



Indolizidine 235B 1



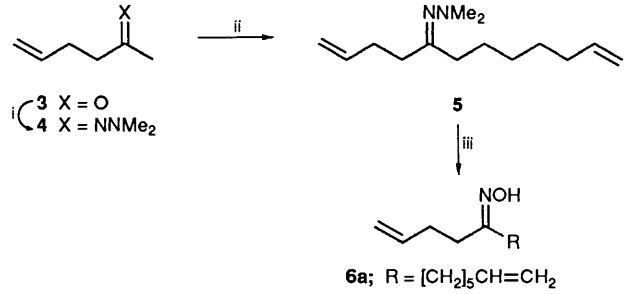
Indolizidine 235B' 2

In view of the interest in these compounds as partial agonists for the nicotinic acetyl choline receptor ion channel complex,[7] it was desirable to complete the synthesis of the remaining members of this family, as reported in the present paper. Contributions from other research groups to the synthesis of 5,8-disubstituted indolizidines have also been reported.[8]

Results and Discussion

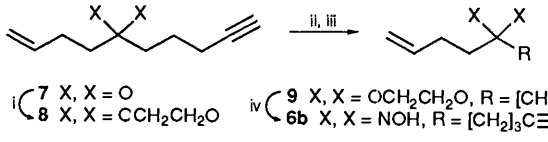
Our approach to the synthesis of indolizidines 1 and **2** employs the thermal intramolecular cycloaddition of a (*Z*)-*N*-alkenylnitrone to control the relative stereochemistry of the substituents in a potential 2,3,6-trisubstituted piperidine ring. The stereocontrol observed in the cycloaddition reaction arises from the preference for a chair-like folding in which the heptenyl substituent adjacent to nitrogen adopts a *pseudo*-equatorial orientation.[9] Similar methodology has led to a synthesis of related molecules such as pumiliotoxin C.[10]

The synthesis of the required oxime precursors **6a,b** is summarised in Schemes 1 (indolizidine 235B') and 2 (indolizidine 235B), respectively. For compound **6a**, commercially available hex-5-en-2-one **3** was converted into the corresponding dimethylhydrazone **4**. Regioselective alkylation of compound **4** with 6-bromohexene was achieved by the method of Corey and Enders.[11] Alkylation at −78 °C gave a mixture of mono- and dialkylated products in low yield. Better yield and selectivity were observed when the alkylation was carried out at −30 °C, giving a high proportion of monoalkylated product (7:1 by gas chromatographic analysis) with excellent regioselectivity (99:1 by gas chromatographic analysis). The crude alkylated dimethylhydrazone **5** could be converted directly into the oxime **6a** by treatment with buffered hydroxylamine hydrochloride solution (Scheme 1).



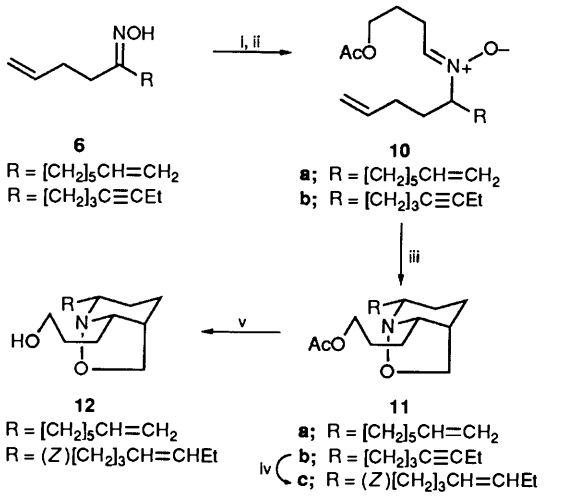
Scheme 1 *Reagents and conditions:* i, H_2NNMe_2, EtOH, reflux; ii, BuLi, −78 °C, THF then $Br[CH_2]_4CH{=}CH_2$, −78 °C→−30 °C; iii, $NH_2OH{\cdot}HCl$, NaOAc, aqueous EtOH, room temperature

For the oxime **6b**, the acetylenic ketone **7**[4] was protected as the dioxolane **8** and alkylated *via* the organolithium derivative with ethyl iodide in the presence of tetramethylethylene diamine (TMEDA). Transoximation of the resulting alkylation product **9** directly with hydroxylamine hydrochloride in acid gave the oxime **6b** in good yield (Scheme 2).



Scheme 2 *Reagents and conditions:* i, Ethylene glycol, pyridinium toluene-*p*-sulphonate (PPTS), benzene, reflux, 24 h; ii, BuLi, THF, 0 °C, TMEDA; iii, EtI, 0 °C (1 h) to 20 °C (16 h); iv, $NH_2OH{\cdot}HCl$, aqueous 2M-HCl, ethanol, 20 °C (7 h)

The oximes **6** were reduced with sodium cyanoborohydride at pH 3–4, and the resulting hydroxylamines were condensed immediately with 4-acetoxybutanal[12] to give the key (*Z*)-*N*-alkenylnitrones **10**. Intramolecular dipolar cycloaddition of **10** gave the isoxazolidines **11**, which were converted by methanolysis into the alcohols **12**. The acetylene **11b** was reduced with Lindlar catalyst exclusively to the *Z*-alkene **11c** (Scheme 3). It is noted in passing that the hydroxylamine

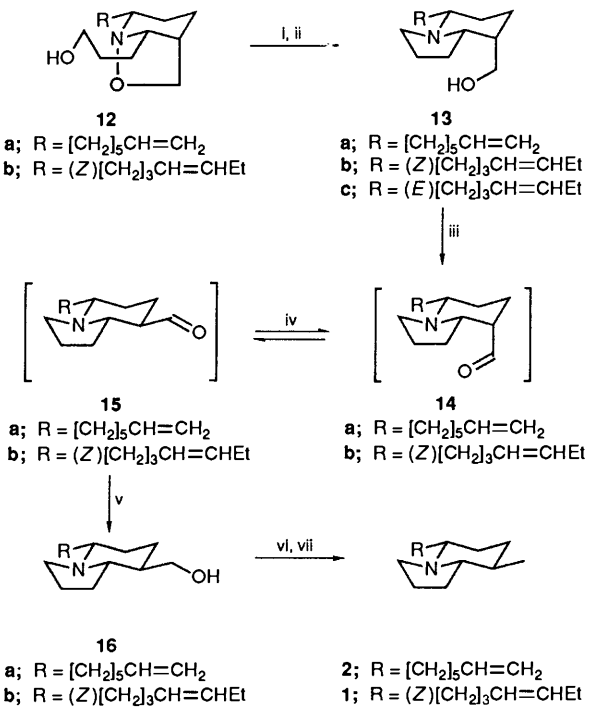


Scheme 3 *Reagents and conditions:* i, $NaCNBH_3$, aqueous MeOH, pH 3–4, 0 °C; ii, 4-acetoxybutanal, CH_2Cl_2, 0 °C; iii, toluene (for **10a**), benzene (for **10b**), reflux; iv, Lindlar catalyst, H_2, EtOAc; v, K_2CO_3 (catalytic), MeOH

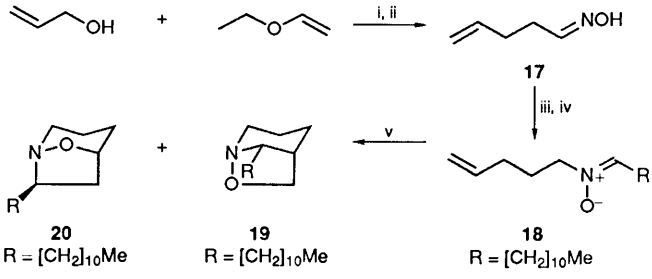
intermediates are very prone to oxidative radical cyclisation reactions,[9] and are best converted at low temperature into the nitrones **10** with minimum exposure to oxygen.

Mesylation of the alcohols **12** led to spontaneous cyclisation to the quaternary ammonium salt. Reductive cleavage of the N–O bond by zinc in aqueous acetic acid then give the axial indolizidine alcohols **13**. Some slight (about 10%) isomerisation of *Z*-**13b** to *E*-**13c** was observed during this reaction, which could be minimised by use of a more basic medium for the zinc reducing agent. Inversion of the stereochemistry at C-8 of compound **13** was achieved by Swern oxidation[13] to the aldehydes **14**, followed by epimerisation on basic alumina to give predominantly the equatorial aldehydes **15** (between 16:1 and 10:1 by NMR analysis). The epimerised aldehydes were reduced to the alcohols and separated by flash column chromatography to isolate the equatorial alcohols **16**. Mesylation of **16** and reduction with Super Hydride® gave the target molecules, indolizidine 235B **1** and 235B′ **2**, respectively, as summarised in Scheme 4. The ^1H NMR and mass spectra of synthetic **1**[5] and **2**[6] were in good agreement with those reported for the naturally occurring material, thus confirming the assigned structures.

It is appropriate to discuss the regiochemistry of the cyclisation of the nitrones **10**. In order to miminise the possibility of side reactions such as hydrolysis, the cycloadditions are carried out with complete exclusion of moisture by the use of a Dean–Stark trap. Under these conditions, only the regioisomer **11** shown, in which the oxygen of the nitrone has become attached to the CH_2 terminus of the dipolarophile double bond, is observed. This compound is easily distinguished from its regioisomeric adduct by the appearance of a characteristic 2 H multiplet at δ 3.8–3.73 in the ^1H NMR spectrum due to the CH_2 group adjacent to oxygen. On the other hand, the intramolecular dipolar cycloaddition of the nitrone **18**, which differs from compound **10** in not having a substituent adjacent to the nitrone nitrogen, and which was prepared as shown in Scheme 5, afforded a 6:1 mixture of the regioisomeric adducts **19** and **20**. The former adduct is a potential precursor of the solenopsins.[14] It has been suggested that the regiochemistry of such cyclisations is determined by the presence or absence of cation stabilising substituents at the internal position of the dipolarophile double bond in nitrones such as **10** and **18**.[9] However, we believe the regioselectivity of the cycloadditions is also affected by the size of the substituents α to nitrogen. Clearly, larger substituents on the nitrone double



Scheme 4 *Reagents and conditions:* i, MsCl, Et_3N, CH_2Cl_2, 0 °C; ii, Zn, aqueous AcOH, reflux, iii, Swern oxidation; iv, grade III basic alumina, room temperature; v, $NaBH_4$, EtOH, 0 °C then chromatography; vi, MsCl, Et_3N, CH_2Cl_2, 0 °C; vii, $LiBEt_3H$, THF, 0 °C→room temperature



Scheme 5 *Reagents and conditions:* i, $Hg(OAc)_2$, 150 °C; ii, NH_2OH·HCl; iii, $NaCNBH_3$; iv, $Me[CH_2]_{10}CHO$; v, refluxing toluene

bond, coupled with the absence of a substituent on the sp^3 carbon adjacent to nitrogen as in compound **18** above, can start to tilt the balance in the direction of the alternative regioisomer **20**, presumably for subtle stereochemical reasons concerned with the relative preference for equatorial positions around the bicyclic adduct skeleton.

In summary, the intramolecular nitrone cycloaddition strategy has proven an efficient route for the synthesis of *trans*-substituted 8-methylindolizidines derived from Panamanian neotropical arrow poison frogs.

Experimental

NMR spectra were recorded using Varian EM390A, Bruker WM250 and WM400 instruments. Low and high resolution electron impact mass spectra were determined on AEI MS902 and MS30 instruments, respectively. Chemical ionisation mass spectra were recorded by Dr. J. Ballantine and co-workers at the SERC Mass Spectrometry Service, Swansea. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer, calibrated relative to polystyrene. Microanalyses were performed by Mr. D. Flory and staff at the Department of Chemistry, Cambridge. M.p.s were determined on a Büchi 510 apparatus. Flash chromatography was carried out on Merck kieselgel 60 (230–400 mesh). Thin layer chromatography was carried out on

Merck Kieselgel 60 GF254 plates, coated to a thickness of 0.25 mm. Gas chromatography was performed on a Carlo Erba 4130 instrument, containing a BP5 205 m capillary column coated with 5% phenyl methyl siloxane, equivalent to SE54. An FID was used. THF refers to tetrahydrofuran distilled from potassium in a recycling still. Dimethyl sulphoxide (DMSO) was dried by distillation from calcium hydride, and stored over 4 Å molecular sieves. Ether refers to diethyl ether. Triethylamine and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) were dried by distillation from calcium hydride, and stored over calcium hydride or potassium hydroxide. Hydrochloride salts were obtained by passing dry HCl gas through a solution of the amine in dry diethyl ether for 5 min. Evaporation *in vacuo* and trituration with diethyl ether at −10 °C gave the salts as solids.

Hex-5-en-2-one N,N-*Dimethylhydrazone* **4**.—A solution of hex-5-en-2-one **3** (6 ml, 52 mmol) and 1,1-dimethylhydrazine (12 ml, 157 mmol, 3 equiv.) in dry ethanol (20 ml) was heated at reflux under nitrogen for 2.5 h. Solvent and excess of dimethylhydrazine were removed by evaporation, and the residues were distilled under reduced pressure to give the *dimethylhydrazone* **4** (4.88 g, 35 mmol, 67%) (b.p. 50–52 °C at 19 mmHg, as a mixture of geometrical isomers by ^{1}H NMR); ν_{max}(liquid film)/cm^{-1} 3070m (C=C–H), 1630s (C=C) and 900s (C=CH_2); δ_H(250 MHz; $CDCl_3$) 5.81–5.70 (1 H, m, C*H*=CH_2), 5.04–4.88 (2 H, m, CH=CH_2), 2.37 and 2.34 (6 H, 2 × s, $NNMe_2$), 2.23 and 2.22 (4 H, 2 × s, CH_2CH_2) and 1.89 and 1.86 (3 H, 2 × s, CH_3).

Dodeca-1,11-dien-5-one Oxime **6a**.—A 1.6M solution of butyllithium in hexane (22 ml, 35 mmol) was added dropwise to a stirred solution of the dimethylhydrazone **4** (4.86 g, 35 mmol) in dry THF (100 ml) at −78 °C under nitrogen. The resulting yellow solution was stirred for 45 min, forming a pale yellow precipitate. 1-Bromohex-5-ene (5.87 g, 36 mmol) was added dropwise (< −65 °C) and the resulting off-white suspension was stirred at −78 °C for 1.5 h. GC analysis showed only partial reaction. The temperature was allowed to rise to −30 °C, and GC analysis after 30 min showed almost complete depletion of starting materials. The reaction mixture was warmed to 0 °C during 1 h, and poured onto ice–water (250 ml). THF was removed by evaporation, and the aqueous solution was extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$), and solvent was removed to give the crude *alkylated dimethylhydrazone* **5**; ν_{max}(CCl_4)/cm^{-1} 3080w (C=C–H), 1630m (C=C) and 900s (C=CH_2); δ_H(250 MHz; $CDCl_3$) 5.85–5.70 (2 H, C*H*=CH_2), 5.07–4.88 (4 H, m, CH=CH_2), 2.53–2.29 [8 H, m, including 2.38 and 2.36, 6 H, 2 × s, $NNMe_2$ (2 isomers in 1:1 ratio)], 2.27–2.14 (4 H, m, CH_2), 2.06–1.97 (2 H, m, CH_2) and 1.56–1.26 (6 H, methylene envelope); δ_C(100 MHz; $CDCl_3$): 2 isomers, 1:1 ratio, 171.9 (s), 171.6 (s), 138.9 (d), 138.85 (d), 137.7 (d), 137.6 (d), 115.0 (t), 114.9 (t), 114.4 (t), 114.3 (t), 47.6 (q), 47.5 (q), 36.0 (t), 35.1 (t), 33.6 (t), 31.3 (t), 30.5 (t), 29.9 (t), 29.3 (t), 28.84 (t), 28.79 (t), 28.63 (t), 28.60 (t), 27.0 (t) and 26.3 (t); *m/z* (EI) 222 (M^+, 34%), 180 (41), 110 (14), 98 (27), 97 (75), 96 (15), 82 (27), 60 (62) and 55 (100) (Found: M^+, 222.2100. $C_{14}H_{26}N$ requires M, 222.2096).

The crude dimethylhydrazone **5** was redissolved in ethanol (60 ml), and added to a solution of hydroxylamine hydrochloride (7.3 g, 105 mmol) and sodium acetate (8.6 g, 105 mmol) in water (60 ml). The resulting emulsion was degassed (nitrogen, 10 min), and stirred under nitrogen at 20 °C for 3.5 h. Ethanol was removed by evaporation, and the aqueous residues extracted with dichloromethane (3 × 100 ml). The combined organic layers were dried ($MgSO_4$), and solvent was removed by evaporation to give the crude oximes. Flash column chromatography on silica, eluting with 2% ethyl acetate–hexane up to 100% ethyl acetate gave the *oxime* **6a** (4.70 g, 24 mmol, 69%); ν_{max}(CCl_4)/cm^{-1} 3590m (O-H free), 3250m (br, OH H-bonded), 3070m (C=CH), 1630m (C=C) and 900s (C=CH_2); δ_H(250 MHz; $CDCl_3$): 2 isomers 5.91–5.71 (2 H, m, C*H*=CH_2), 5.10–4.90 (4 H, m, CH=CH_2), 2.46–2.14 (6 H, m, CH_2), 2.08–2.00 (2 H, m, CH_2) and 1.57–1.26 (6 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 2 isomers , 1:1 ratio, 161.3 (s), 138.9 (d), 137.6 (d), 137.4 (d), 115.2 (t), 115.1 (t), 114.3 (t), 34.1 (t), 33.6 (t), 33.4 (t), 30.2 (t), 29.6 (t), 29.3 (t), 28.8 (t), 28.6 (t), 27.6 (t), 26.9 (t), 26.0 (t) and 25.4 (t); *m/z* (EI) 195 (M^+, 12%), 194 (19), 140 (15), 126 (30), 115 (100), 114 (22), 98 (37), 96 (15), 82 (15), 81 (40), 67 (20), 55 (80), 54 (20) and 53 (17) (Found: M^+, 195.1615. $C_{12}H_{21}NO$ requires M, 195.1623).

2-(*But-3-enyl*)-2-(*pent-4-ynyl*)-1,3-*dioxolane* **8**.—Ethane-1,2-diol (1.86 ml, 33.5 mmol) was dried by repeated removal of water as an azeotrope with toluene (2 × 10 ml). Dec-1-en-9-yn-5-one **7**[4] (1.0 g, 6.7 mmol), benzene (25 ml) and PPTS (0.01 g, cat.) were added. A Soxhlet extractor containing activated 4 Å molecular sieves was fitted, and the mixture was heated at reflux under nitrogen for 24 h. The reaction was followed by GC. The mixture was cooled to room temperature, and the benzene was evaporated under reduced pressure. The residue was dissolved in ether (50 ml) and washed with water (50 ml). The aqueous layer was extracted with ether (2 × 50 ml) and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by distillation (Kugelrohr) to give the *dioxolane* **8** as a colourless liquid (0.97 g, 75%), b.p. 73–75 °C at 0.2 mmHg; ν_{max}(CCl_4)/cm^{-1} 3300s, 3080m, 2120w and 1640 (m, C=C); δ_H(250 MHz; $CDCl_3$) 5.87–5.74 (1 H, m, C*H*=CH_2, 5.05–4.90 (2 H, m, CH=CH_2), 3.93 (4 H, s, CH_2–O), 2.23–2.07 (4 H, m), 1.94 (1 H, t, *J* 1.6 Hz, C≡C–H) and 1.76–1.56 (6 H, m); δ_C(100 MHz; $CDCl_3$) 138.45 (d), 114.26 (t), 111.12 (s), 84.21 (d), 68.47 (s), 64.97 (t), 36.35 (t), 36.15 (t), 28.04 (t), 22.63 (t) and 18.53 (t); *m/z* (EI) 194 (M^+, 9%), 166 (12), 155 (10), 139 (100), 127 (97) and 99 (22) (Found: C, 74.27; H, 9.33; M^+ (EI), 194.1293. $C_{12}H_{18}O_2$ requires C, 74.22; H, 9.28%; M, 194.1307).

2-(*But-3-enyl*)-2-(*hept-4-ynyl*)-1,3-*dioxolane* **9**.—A solution of alkynyl dioxolane **8** (2.83 g, 14.6 mmol) in dry THF (75 ml) was cooled to 0 °C under nitrogen. Butyllithium (9.12 ml of a 1.6 mol dm^3 solution in hexane, 14.6 mmol) was added dropwise to the stirred solution. After 10 min, TMEDA (2.20 ml, 146 mmol) was added dropwise. After a further 10 min, iodoethane (2.41 ml, 292 mmol), dried by passing through an alumina (U.G.1) column immediately before use, was added dropwise. The clear solution was stirred at 0 °C for 1 h, then warmed to 20 °C. On warming, a white precipitate began to form. The suspension was stirred at 20 °C for 16 h. Saturated aqueous ammonia solution (15 ml) was added, and the mixture stirred for 1 h, after which the phases were separated. The aqueous layer was extracted with ether (2 × 50 ml) and the combined organic layers were washed with brine (25 ml), then dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the crude compound was purified by flash chromatography on silica, eluting with hexane–ethyl acetate (95:5) to give the *ethylated alkynyl dioxolane* **9** as a colourless oil (2.17 g, 67%); ν_{max}(CCl_4)/cm^{-1} 3080m and 1640m; δ_H(250 MHz; $CDCl_3$) 5.87–5.81 (1 H, m, C*H*=CH_2), 5.05–4.90 (2 H, m, CH=CH_2), 3.93 (4 H, s, CH_2–O), 2.18–2.08 (6 H, m), 1.74–1.66 (4 H, m), 1.61–1.50 (2 H, m) and 1.10 (3 H, t, *J* 7.4 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) 138.54 (d), 114.21 (t), 111.27 (s), 82.01 (s), 79.04 (s), 64.95 (t), 36.31 (t), 28.05 (t), 20.05 (t), 23.50 (t), 18.90 (t), 14.33 (q) and 12.38 (t); *m/z* (EI) 167 (57%), 127 (100) and 99 (39); *m/z* (CI) 223 [$(M + H)^+$, 100%], 177 (54), 163 (46), 127 (42) and 99 (10). [Found: C, 75.69; H, 9.92; $(M + H)^+$ (CI), 223.1698. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.98%; (M + H), 222.1698].

Dodec-1-en-9-yn-5-one Oxime **6b**.—The dioxolane **9** (3.20 g, 14.41 mmol) was dissolved in ethanol (40 ml). Five drops of Methyl Orange indicator solution and hydroxylamine hydrochloride (3.00 g, 43 mmol) were added. Water was added dropwise to the stirred suspension at 20 °C until the hydroxylamine hydrochloride had dissolved. 2M Aqueous hydrochloric acid was added, until the pink colouration persisted (pH 3.3). The solution was stirred for 7 h at 20 °C, when it was poured into water (30 ml) and extracted with ether (3 × 40 ml). The combined organic layers were dried ($MgSO_4$). After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (5:1) to give the *oxime* **6b** as a pale yellow oil, as an approximately 1:1 mixture of *E*- and *Z*-isomers (2.63 g, 95%), and recovered starting material (156 mg, 4.9%); $\nu_{max}(CCl_4)/cm^{-1}$ 3610s, 3280br s, 3080m and 1640m; δ_H(250 MHz; $CDCl_3$) 5.91–5.81 (1 H, m, C*H*=CH_2), 5.10–4.95 (2 H, m, CH=CH_2), 2.53–2.39 (2 H, m), 2.35–2.26 (4 H, m), 2.23–2.09 (4 H, m), 1.76–1.63 (4 H, m), and 1.105 and 1.100 (3 H, 2 × t, *J* 7.4 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) 160.69 (s), 137.52 (d), 137.34 (d), 115.29 (t), 115.14 (t), 82.49 (s), 78.58 (s), 78.50 (s), 33.59 (t), 33.17 (t), 30.20 (t), 29.58 (t), 27.05 (t), 27.01 (t), 25.50 (t), 25.09 (t), 16.99 (t), 16.34 (t), 14.31 (q) and 12.38 (t); *m/z* (EI) 178 (27%), 167 (29), 148 (15), 134 (11), 127 (63), 120 (12), 113 (59), 98 (32) and 55 (100); *m/z* (CI) 194 [$(M + H)^+$, 100%], 178 (44) [Found: C, 74.30; H, 10.18; N, 7.02; $(M + H)^+$ (CI), 194.1544. $C_{12}H_{19}NO$ requires C, 74.57; H, 9.91; N, 7.24%; (M + H), 194.1545].

(*Z*)-4-[1-(*But-3-enyl*)*hept-6-enyl*]*iminobutyl Acetate* N-*Oxide* **10a**.—Sodium cyanoborohydride (0.44 g, 7 mmol) in dry methanol (7 ml) was added, at −5 °C, to a stirred, degassed (argon, 15 min) solution of the oxime **6a** (0.68 g, 3.5 mmol) and a few drops of Methyl Orange indicator, in dry methanol (15 ml). Hydrochloric acid in methanol (6 mol dm^{-3}) was added dropwise to keep the solution just pink (pH 3–4). The endpoint of the reaction was reached after 20 min, when the solution was made alkaline with aqueous sodium hydroxide (20%) and poured onto ice–brine (30 ml). The solution was extracted with dichloromethane (4 × 20 ml) and the combined organic layers were dried ($MgSO_4$). The combined extracts were added directly to a stirred solution of 4-acetoxybutanal[12] (0.6 g, 4.6 mmol) in dry dichloromethane (10 ml) with a little magnesium sulphate. The reaction mixture was stirred at 0 °C under nitrogen for 1.5 h, and then dried ($MgSO_4$), filtered and evaporated to give the crude nitrone. Flash column chromatography on silica, eluting with diethyl ether, gave the *nitrone* **10a** (0.65 g, 2.1 mmol, 60%) as a colourless liquid; $\nu_{max}(CCl_4)/cm^{-1}$ 3070w (C=CH), 1740s (C=O), 1635w (C=C), 1360m (O–CO–Me) and 910s (C=CH_2); δ_H(250 MHz; $CDCl_3$) 6.64 (1 H, t, *J* 5.8 Hz, HC=N), 5.80–5.67 (2 H, m, C*H*=CH_2), 5.01–4.86 (4 H, m, CH=CH_2), 4.07 (2 H, t, *J* 6.4 Hz, CH_2OAc), 3.55 (1 H, tt, *J* 9.6 and 5.5 Hz, HCN), 2.54 (2 H, dt, *J* 5.8 and 5.9 Hz, CH_2–CH=N) and 2.13–1.14 [19 H, methylene envelope, including 2.01 (3 H, s, CO–Me)]; δ_C(100 MHz; $CDCl_3$) 171.0 (s), 138.8 (d), 137.3 (d), 115.6 (t), 114.3 (t), 74.9 (d), 63.7 (t), 33.6 (t), 32.4 (t), 31.2 (t), 30.1 (t), 28.7 (t), 26.0 (t), 24.7 (t), 23.1 (t) and 20.9 (q); *m/z* (EI) 309 (M^+, 10%), 268 (10), 208 (15), 197 (15), 182 (17), 178 (24), 154 (10), 152 (21), 126 (22), 113 (43), 100 (100), 84 (10), 81 (10), 67 (10) and 55 (28) (Found: M^+, 309.2318. $C_{18}H_{31}NO_3$ requires 309.2304).

(*Z*)-4-[1-(*But-3-enyl*)*hex-5-ynyl*]*iminobutyl Acetate* N-*Oxide* **10b**.—A solution of the oxime **6b** (2.43 g, 12.6 mmol) in methanol (50 ml) was cooled to −10 °C. Sodium cyanoborohydride (1.317 g, 18.95 mmol) and 5 drops of Methyl Orange indicator solution were added. The solution was stirred at −10 °C under nitrogen and hydrochloric acid in methanol (6 mol dm^{-3}) was added dropwise so as to just keep the solution pink. After 45 min, the solution was made strongly basic with 20% aqueous sodium hydroxide and poured into saturated brine (50 ml) containing ice. The suspension was extracted with dichloromethane (6 × 50 ml), and the organic extracts were dried ($MgSO_4$) and immediately combined with a solution of 4-acetoxybutanal **8** (2.72 g, 20.91 mmol), in dichloromethane (20 ml) containing anhydrous $MgSO_4$. The suspension was stirred at 0 °C under nitrogen for 1 h and filtered. After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on a short silica column, eluting with ether–hexane (1:1) followed by dichloromethane–methanol (95:5) to give the *nitrone* **10b** as a pale yellow oil (3.48 g, 90%); $\nu_{max}(CCl_4)/cm^{-1}$ 3080m, 1730s and 1640m; δ_H(250 MHz; $CDCl_3$) 6.67 (1 H, t, *J* 5.8 Hz, N^+=CH), 5.80–5.66 (1 H, m, CH=CH_2), 5.03–4.95 (2 H, m, CH=CH_2), 4.09 (2 H, t, *J* 6.4 Hz, CH_2OAc), 3.67–3.59 (1 H, m, CHN^+), 2.60–2.51 (2 H, m, CH_2CH=N^+), 2.03 (3 H, s, CH_3CO), 2.18–1.31 (14 H, m) and 1.08 (3 H, t, *J* 7.4, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 171.01 (s), 137.73 (d), 137.27 (d), 115.62 (t), 82.31 (s), 78.44 (s), 74.44 (t), 63.73 (t), 31.60 (t), 31.19 (t), 30.09 (t), 25.46 (t), 24.71 (t), 23.16 (t), 20.70 (t), 18.37 (t), 14.27 (q) and 12.35 (t); *m/z* (EI) 307 (M^+, 20%), 292 (75), 290 (34), 252 (33), 248 (28), 234 (22), 206 (60) and 190 (55) [Found: M^+ (EI), 307.2141. $C_{18}H_{29}NO_3$ requires 307.2147].

(2R*,5S*,8S*)-8-(3-*Acetoxypropyl*)-2-(*hept-6-enyl*)-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* 11**a**.—A degassed (argon, 15 min) solution of the nitrone **10a** (0.64 g, 2.07 mmol) in dry toluene (150 ml) was heated under reflux, under Dean–Stark conditions, for 19 h. The clear solution was cooled, prior to removal of toluene by evaporation. Flash column chromatography on silica, eluting with hexane–ethyl acetate (2:1), gave the *isoxazolidine* 11**a** (0.55 g, 1.78 mmol, 86%) as a colourless liquid; $\nu_{max}(CCl_4)/cm^{-1}$ 3070w (C=CH), 1735s (C=O), 1630w (C=C), 1360s (OCOMe) and 900s (C=CH_2); δ_H(400 MHz; $CDCl_3$) 5.81 (1 H, ddt, *J* 16.9, 10.2 and 6.7 Hz, C*H*=CH_2), 4.99 (1 H, ddt, *J* 16.9, 1.8 and 1.8 Hz, CH=C*H*H′), 4.92 (1 H, ddt, *J* 10.2, 2.2 and 1.2 Hz, CH=CH*H*′), 4.09 (2 H, m, CH_2OAc), 3.83–3.77 (2 H, m, $NOCH_2$), 2.88 (1 H, dd, *J* 8.5 and 5.7 Hz, N–C*H*–CH), 2.59–2.54 (1 H, m, NC*H*CH_2), 2.44–2.43 (1 H, m, NCHC*H*) and 2.06–1.26 [21 H, methylene envelope, including 2.05 (3 H, s, O–CO–Me)]; δ_C(100 MHz; $CDCl_3$) 171.2 (s), 139.2 (d), 114.1 (t), 71.7 (t), 71.0 (t), 65.9 (d), 64.4 (t), 41.6 (d), 35.1 (t), 33.8 (t), 29.5 (t), 29.2 (t), 28.9 (t), 28.4 (t), 26.1 (t), 25.8 (t), 24.8 (t) and 21.0 (q); *m/z* (EI) 309 (M^+, 50%), 268 (82), 266 (34), 250 (57), 236 (40), 212 (32), 208 (65), 194 (29), 192 (38), 184 (28), 178 (46), 152 (58), 126 (44), 96 (47), 82 (38), 81 (81), 69 (32), 67 (67), 55 (100) and 54 (35) (Found: M^+, 309.2317. $C_{18}H_{31}NO_3$ requires 309.2304).

(2R*,5S*,8S*)-8-(3-*Acetoxypropyl*)-2-(*hept-4-ynyl*)-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* 11**b**.—A solution of the nitrone **10b** (3.48 g, 11.3 mmol) in benzene (500 ml) was refluxed under Dean–Stark conditions under nitrogen for 16 h. The solution was cooled to 20 °C and after evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography on silica, eluting with hexane–ether (70:30) to give the *isoxazolidine* **11b** as a pale yellow oil (2.79 g, 80%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740s; δ_H(250 MHz; $CDCl_3$) 4.11–4.01 (2 H, m, CH_2OAc), 3.81–3.73 (2 H, m, CH_2ON), 2.84 (1 H, dd, *J* 8.5 and 5.7 Hz, CHC*H*CN), 2.60–2.50 (1 H, m, CH_2C*H*CN), 2.40–2.38 (1 H, m, bridgehead CH), 2.20–2.08 (4 H, m), 2.02 (3 H, s, CH_3CO), 1.89–1.21 (12 H, m) and 1.078 (3 H, t, *J* 7.3 Hz, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 171.17 (s), 81.64 (s), 79.42 (s), 71.66 (t), 70.95 (d), 65.45 (d), 64.42 (t), 41.59 (d), 34.25 (t), 29.44 (t), 28.41 (t), 25.81 (t), 25.78 (t), 24.78 (t), 20.98 (q), 16.73 (t), 14.35 (q) and 12.40 (t); *m/z* (EI) 292 (100%), 124 (33), 96 (10), 79 (23) and 67 (17); *m/z* (CI) 308 [$(M + H)^+$, 100%] and 248 (3) [Found: C, 70.59; H, 9.43; N, 4.32; $(M + H)^+$ (CI) 308.2226. $C_{18}H_{29}NO_3$ requires C, 70.32; H, 9.51; N, 4.55%; (M + H), 308.2226].

(2R*,5S*,8S*)-(3-*Acetoxypropyl*)-2-[(Z)-*hept*-4-*enyl*]-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **11c**.—Lindlar catalyst (Hoffmann LaRoche Katalysator Typ A, 80 mg) was suspended in ethyl acetate (10 ml), and the suspension stirred under hydrogen at 20 °C for 1 h. A solution of the alkynylisoxazolidine **11b** (220 mg, 0.72 mmol) in ethyl acetate (1 ml) was added, and the reaction followed by GC. After 6 h, further catalyst (80 mg) was added, and the suspension stirred under hydrogen for a further 30 min. The suspension was filtered through a pad of Celite to remove the catalyst. After removal of the solvent under reduced pressure, the compound was purified by flash chromatography on silica, eluting with hexane–ether (30:70), to give the *Z-alkenylisoxazolidine* **11c** as a pale yellow oil (210 mg, 95%); $\nu_{max}(CCl_4)/cm^{-1}$ 1740s; δ_H(250 MHz; $CDCl_3$) 5.33–5.28 (2 H, m, C*H*=CH), 4.09–4.02 (2 H, m, CH_2OAc), 3.81–3.73 (2 H, m, CH_2ON), 2.84 (1 H, dd, *J* 8.5 and 5.6 Hz, CHC*H*N), 2.55–2.53 (1 H, m, CH_2CHCN), 2.40–2.37 (1 H, m, bridgehead CH), 2.02 (1 H, s, CH_3CO), 2.02–1.23 (16 H, m) and 0.92 (3 H, t, *J* 7.5 Hz, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 171.15 (s), 131.55 (d), 129.17 (d), 71.64 (t), 70.95 (d), 65.82 (d), 64.42 (t), 41.64 (d), 34.78 (t), 29.47 (t), 28.12 (t), 27.14 (t), 26.42 (t), 25.80 (t), 24.80 (t), 20.98 (q), 20.47 (t) and 14.37 (q); *m*/*z* (EI) 266 (12%), 208 (5), 124 (32), 96 (13), 81 (16), 67 (34), 55 (55) and 43 (100); *m*/*z* (CI) 310 [(M + H)$^+$, 100%] and 196 (3) [Found: C, 69.69; H, 10.05; N, 4.25; (M + H)$^+$ (CI), 310.2383. $C_{18}H_{31}NO_3$ requires C, 69.86; H, 10.09; N, 4.52%; (M + H), 310.2382].

(2R*,5S*,8S*)-8-(3-*Hydroxypropyl*)-2-(*hept*-6-*enyl*)-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **12a**.—A solution of the isoxazolidine **11a** (0.51 g, 1.65 mmol) and anhydrous potassium carbonate (0.03 g, 0.21 mmol, 13 mol%) in dry methanol (30 ml) was stirred at room temperature under nitrogen for 17 h. Methanol was removed by evaporation, and the residues were filtered through a short silica column, eluting with ether, to give the *isoxazolidine alcohol* **12a** (0.433 g, 1.62 mmol, 98%) as a pale yellow liquid; $\nu_{max}(CCl_4)/cm^{-1}$ 3620w (OH free), 3240m (br, OH H-bonded), 3070w (C=CH), 1630w (C=C) and 900s (C=CH_2); δ_H(250 MHz; $CDCl_3$) 5.77 (1 H, ddt, *J* 16.9, 10.2 and 6.7 Hz, C*H*=CH_2), 5.00–4.86 (2 H, m, CH=CH_2), 3.86–3.79 (2 H, m, N–O–CH_2), 3.70–3.51 (2 H, m, CH_2OH), 2.90–2.85 (1 H, m, N–C*H*CH), 2.70–2.58 (1 H, m, N–C*H*CH_2), 2.41–2.37 (1 H, m, NCHC*H*), 2.00 (2 H, dt, *J* 7.0 and 7.0 Hz, CH_2C=C) and 1.85–1.21 (16 H, methylene envelope); δ_C(100 MHz; $CDCl_3$) 139.2 (d), 114.1 (t), 72.2 (t), 71.9 (d), 65.7 (d), 62.7 (t), 42.5 (d), 35.0 (t), 33.8 (t), 31.0 (t), 30.6 (t), 29.3 (t), 29.2 (t), 28.7 (t), 25.9 (t) and 24.4 (t); *m*/*z* (NH_3, CI) 268 [(M + H)$^+$, 100], 267 (1.2), 242 (0.9), 238 (0.9) and 226 (0.9) [Found: (M + H)$^+$, 268.228 08. $C_{16}H_{30}NO_2$ requires 268.227 65].

(2R*,5S*,8S*)-(3-*Hydroxypropyl*)-2-[(Z)-*hept*-4-*enyl*]-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **12b**.—The isoxazolidine **11c** (210 mg, 0.68 mmol) was dissolved in methanol (10 ml) and anhydrous potassium carbonate (10 mg, cat.) was added. The solution was stirred for 7 h at 20 °C under nitrogen and then evaporated under reduced pressure. The residue was purified by filtering through a short column of silica, eluting with ether, to give the *alcohol* **12b** as a pale yellow oil (176 mg, 97%); $\nu_{max}(CCl_4)/cm^{-1}$ 3620w and 3560–3060br m; δ_H(250 MHz; $CDCl_3$) 5.37–5.22 (2 H, m, CH=CH), 3.82 and 3.81 (2 H, 2 × s, CH_2ON), 3.69–3.51 (2 H, m, CH_2OH), 2.86 (1 H, t, *J* 6.2 Hz, CHC*H*N), 2.67–2.57 (1 H, m, CH_2CHCN), 2.40–2.36 (1 H, m, bridgehead CH), 2.04–1.93 (4 H, m, CH_2CH=CHCH_2), 1.82–1.22 (12 H, m) and 0.91 (3 H, t, *J* 7.5 Hz, CH_3CH_2); δ_C(100 MHz; $CDCl_3$) 131.73 (d), 129.95 (d), 72.20 (t), 71.83 (d), 65.61 (d), 62.62 (t), 42.43 (d), 34.59 (t), 30.97 (t), 30.49 (t), 29.31 (t), 27.08 (t), 26.17 (t), 24.47 (t), 20.48 (t) and 14.35 (q); *m*/*z* (EI) 224 (13%), 124 (26), 96 (25), 82 (21), 67 (20), 55 (37) and 41 (100); *m*/*z* (CI) 268 [(M + H)$^+$, 100%] and 250 (8) [Found: C, 71.7; H, 11.7; N, 5.5; (M + H)$^+$ (CI), 268.2276. $C_{16}H_{29}NO_2$ requires C, 71.87; H, 11.69; N, 5.23%; (M + H) 268.2277].

(5R*,8S*,8aS*)-8-*Hydroxymethyl*-5-(*hept*-6-*enyl*)-*octahydroindolizine* **13a**.—Dry triethylamine (4.5 ml, 32 mmol) was added dropwise at 0 °C to a stirred solution of the isoxazolidine alcohol **12a** (0.85 g, 3.18 mmol) and methanesulphonyl chloride (1.24 ml, 16 mmol) in dry dichloromethane (30 ml). The resulting yellow suspension was stirred at 0 °C under nitrogen for 80 min. Solvent and excess of reagents were removed by evaporation to give the crude mesylate salt as an orange, crystalline solid. The salt was redissolved in 50% aqueous acetic acid (20 ml) to give a deep red solution, to which activated zinc dust (2.1 g, 32 mmol) was added. The resulting pale yellow suspension was stirred at 55 °C under nitrogen for 3 h. The cooled reaction mixture was filtered through Celite, and the filtrate was basified to pH 14 with aqueous sodium hydroxide (20%), before extraction with dichloromethane (2 × 150 ml, 2 × 100 ml). The combined organic layers were dried ($MgSO_4$), and evaporated to give the crude indolizidine alcohol as a brown oil. Flash column chromatography on silica, eluting with 5% ammonia–ether, gave the axial *indolizidine alcohol* **13a** (0.767 g, 3.05 mmol, 96%) as a yellow oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3640w (O–H free), 3260s (br, OH H-bonded), 3080m (C=CH), 2790s (NCH), 2720m (NCH), 1635m (C=C) and 900s (C=CH_2); δ_H(250 MHz; $CDCl_3$) 5.77 (1 H, ddt, *J* 16.9, 10.2 and 6.7 Hz, C*H*=CH_2), 4.99–4.88 (2 H, m, CH=CH_2), 4.18 (1 H, dd, *J* 10.8 and 4.0 Hz, C*H*HOH), 3.71 (1 H, d, *J* 10.8 Hz, CH*H'*OH), 3.21–3.14 (1 H, m, NCH), 2.37–2.30 (1 H, m, $HOCH_2CH$) and 2.05–1.23 (21 H, methylene envelope); δ_C(100 MHz; $CDCl_3$) 139.0 (d), 114.2 (t), 67.2 (d), 65.6 (t), 63.8 (d), 51.7 (t), 34.7 (d), 34.4 (t), 33.7 (t), 31.2 (t), 29.5 (t), 28.8 (t), 28.1 (t), 26.2 (t), 24.3 (t) and 20.6 (t); *m*/*z* (NH_3, CI) 253 [(M + 2 H)$^+$, 17.3%], 252 [(M + H)$^+$, 100], 251 (M$^+$, 0.7), 250 (1.9), 226 (1.0), 155 (1.8) and 154 (17.8) [Found: (M + H)$^+$, 252.233 37. $C_{16}H_{30}NO$ requires 252.232 74]. The oil **13a** was converted into the hydrochloride salt, m.p. 124–126 °C (Found: C, 66.57; H, 10.40; N, 4.73. $C_{16}H_{30}NOCl$ requires C, 66.76; H, 10.50; N, 4.87%).

(5R*,8S*,8aS*)-8-*Hydroxymethyl*-5-[(Z)-*hept*-4-*enyl*]-*octahydroindolizine* **13b**.—A solution of the alcohol **12b** (131 mg, 0.49 mmol) in dry dichloromethane (10 ml) was cooled to −10 °C under nitrogen. Methanesulphonyl chloride (0.16 ml, 2.45 mmol) was added dropwise, followed by dry triethylamine (0.68 ml, 4.9 mmol). The solution was stirred at −10 °C for 1 h to give a white precipitate. The suspension was evaporated under reduced pressure, at 20 °C to avoid sublimation of the mesylate salt after which the latter was dissolved in acetic acid–water (1:1) (10 ml). The solution was warmed to 55 °C. Activated zinc dust (320 mg, 4.9 mmol) was added, and the suspension stirred for 3 h at 55 °C. The suspension was filtered through Celite, and basified with 20% aqueous sodium hydroxide. The white suspension was extracted with dichloromethane (4 × 20 ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. ^{1}H NMR analysis showed the presence of an impurity, which could not be removed by washing the dichloromethane extracts with water, or by chromatography. The residue was dissolved in ether (20 ml) and washed with water (20 ml), which was extracted with ether (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$), and evaporated under reduced pressure and the compound was purified by flash chromatography on silica, eluting with dichloromethane–methanol–ammonia (97:2:1) to give the *indolizidine* **13b**, containing *ca.* 10% of the *E*-isomer **13c** as a pale yellow oil (118 mg, 90%); $\nu_{max}(CCl_4)/cm^{-1}$ 3280br m, 2780s and 2720w Bohlmann bands; δ_H(250 MHz; $CDCl_3$) 5.39–5.22 (2 H, m, C*H*=CH), 4.18 (1 H, ddd, *J* 10.9, 3.9 and 1.1 Hz, C*H*HOH) and 3.71 (1 H, d, *J* 10.9 Hz, CH*H*OH), 3.24–3.15 (1 H, m, CH ring junction), 2.37–2.31 (1 H,

m, CHN), 2.06–1.23 (18 H, m) and 0.93 (3 H, t, *J* 7.6 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) *Z*-isomer (90%) 131.89 (d), 128.82 (d), 67.26 (d), 65.54 (t), 63.79 (d), 51.71 (t), 34.69 (d), 33.98 (t), 31.14 (t), 28.12 (t), 27.30 (t), 26.16 (t), 24.69 (t), 20.56 (t), 20.52 (t) and 14.37 (q); *E*-isomer (10%) 32.97 (t), 32.81 (t), 25.57 (t), 24.25 (t) and 12.48 (q); *m/z* (EI) 154 (100%), 84 (17), 49 (33) and 41 (12); *m/z* (CI) 252 [$(M + H)^+$, 100%], 154 (10). [Found: C, 76.14; H, 11.59; N, 5.44; $(M + H)^+$ (CI), 252.2327. $C_{16}H_{29}NO$ requires C, 76.44; H, 11.63; N, 5.57%; (M + H), 252.2327].

(5R*,8R*,8aS*)-8-*Hydroxymethyl*-5-(*hept*-6-*enyl*)*octahydroindolizine* **16a**.—A solution of dry DMSO (1.41 mmol ml^{-1}, 4.43 ml, 6.24 mmol) in dry dichloromethane was added dropwise at −70 °C to a stirred solution of oxalyl chloride (0.27 ml, 3.12 mmol) in dry dichloromethane (10 ml). The clear solution was stirred at −70 °C under nitrogen for 20 min, followed by dropwise addition at −70 °C of axial indolizine alcohol **13a** (0.532 g, 2.08 mmol) in dry dichloromethane (5 ml). The clear solution was stirred for 30 min at −70 °C, followed by dropwise addition of dry triethylamine (2.17 ml, 15.6 mmol). The resulting white suspension was stirred at −70 °C for 75 min and then allowed to warm to 0 °C during 30 min. The reaction mixture was poured onto saturated aqueous sodium hydrogen carbonate (25 ml), and the aqueous layer was extracted with dichloromethane (3 × 40 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give the crude *axial aldehyde* **14a** as an orange oil; $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (C=C–H), 1720s (C=O), 1635m (C=C) and 900s (C=CH_2); δ_H(250 MHz; $CDCl_3$) O=CH_{axial} 10.00 (d, *J* 2.3 Hz).

The crude aldehyde was run onto a short column of freshly prepared grade III basic alumina (*ca.* 10 g). After 3 h, the aldehydes were eluted with 10% ammonia–ether. ^1H NMR indicated the equatorial epimer **15a** as the major product; δ_H(250 MHz; $CDCl_3$) 9.64 (d, *J* 2.3 Hz, O=CH_{eq}) and 10.00 (d, *J* 2.3 Hz, O=CH_{ax}), equatorial–axial (10:1).

The crude epimerised aldehydes were dissolved in dry ethanol (100 ml) at 0 °C under nitrogen. Sodium borohydride (0.20 g, 5.20 mmol) was added, and the solution stirred for 1 h. The reaction mixture was poured onto water (150 ml) and extracted with dichloromethane (4 × 50 ml). The combined organic layers were washed with water (50 ml), dried ($MgSO_4$) and evaporated to give the crude mixture of alcohols. Flash column chromatography on silica, eluting with 5% ammonia–ether, gave the *equatorial alcohol* **16a** (0.242 g, 0.963 mmol, 46%) as a pale yellow oil and compound **13a** (0.049 g, 0.195 mmol, 9%); $\nu_{max}(CCl_4)/cm^{-1}$ 3640m (OH free), 3200w (br, OH H-bonded), 3080m (C=CH), 2780s (NCH), 2700m (N–CH), 1635m (C=C) and 910s (C=CH_2); δ_H(400 MHz; $CDCl_3$) 5.79 (1 H, ddt, *J* 16.9, 10.2 and 6.7 Hz, C*H*=CH_2), 4.97 (1 H, ddt, *J* 16.9, 1.7 and 1.7 Hz, CH=C*H*H′), 4.91 (1 H, ddt, *J* 10.2, 2.1 and 1.1 Hz, CH=CH*H*′), 3.63 (1 H, dd, *J* 10.7 and 4.6 Hz, C*H*H′OH), 3.45 (1 H, dd, *J* 10.7 and 6.7 Hz, CH*H*′OH), 3.25 (1 H, ddd, *J* 1.9, 8.7 and 8.7 Hz, NC*H*CH) and 2.05–1.02 (22 H, methylene envelope); δ_C(100 MHz; $CDCl_3$) 139.1 (d), 114.2 (t), 66.8 (d), 65.7 (t), 63.4 (d), 51.4 (t), 44.3 (d), 34.4 (t), 33.7 (t), 30.6 (t), 29.5 (t), 29.0 (t), 28.8 (t), 27.8 (t), 25.6 (t) and 20.6 (t); *m/z* (NH_3, CI) 252 [$(M + H)^+$ (91%)], 226 (6), 200 (5), 154 (23), 119 (24), 96 (2), 77 (100) and 60 (100) [Found: $(M + H)^+$, 252.232 70. $C_{16}H_{30}NO$ requires 252.232 74]. The oil **16a** was converted into the hydrochloride salt, m.p. 100–104 °C (Found: C, 66.7; H, 10.4; N, 5.0. $C_{16}H_{30}ClNO$ requires C, 66.76; H, 10.50; N, 4.87%).

(5R*,8R*,8aS*)-8-*Hydroxymethyl*-5-[(Z)-*hept*-4-*enyl*]-*octahydroindolizine* **16b**.—A 10% solution of oxalyl chloride in dry dichloromethane (1.10 ml, 1.26 mmol) was added to dry dichloromethane (5 ml), and the solution cooled to −78 °C under nitrogen. A 10% solution of DMSO in dry dichloromethane (1.79 ml, 2.52 mmol) was added dropwise at −78 °C, and the solution stirred for 20 min at −78 °C. A solution of the alcohol **13b** (106 mg, 0.44 mmol) in dry dichloromethane (1.0 ml) was added dropwise at −78 °C. The solution was stirred at −78 °C for 30 min after which dry triethylamine (0.88 ml, 6.60 mmol) was added dropwise at the same temperature. The solution was stirred for 5 min at −78 °C, then warmed to 0 °C during 30 min. The white suspension was poured into saturated aqueous sodium hydrogen carbonate (20 ml), and extracted with dichloromethane (4 × 15 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude *aldehyde* **14b** as an orange oil; δ_H(250 MHz; $CDCl_3$) 9.93 (1 H, d, *J* 2.2 Hz, CHO).

The crude aldehyde **14b** containing a trace of epimer **15b** was dissolved in methanol (4 ml) and grade 3 alumina [alumina U.G.I.–water (94:6)] (250 mg, cat.) was added. The suspension was stirred for 12 h at 20 °C, after which the suspension was filtered, and the filtrate evaporated under reduced pressure, to give the epimerised aldehydes **14b** and **15b** in the ratio 2:3 (^1H NMR). This was dissolved in ether–ammonia (90:10) and applied to an alumina (grade 3) column which after 4 h was eluted with ether–ammonia (90:10). After evaporation of the solvent under reduced pressure, the ratio was 1:8 of axial **14b** and equatorial **15b** aldehydes (^1H NMR). The crude epimerised aldehyde **15b** was used without further purification; δ_H(250 MHz; $CDCl_3$) 9.59 (1 H, d, *J* 2.2 Hz, CHO).

The crude epimerised aldehydes **14b** and **15b** were dissolved in ethanol (4 ml), and the solution cooled to 0 °C. Addition of sodium borohydride (32 mg, 0.82 mmol) gave rise to effervescence. The solution was stirred for 15 min at 0 °C under nitrogen after which it was poured into distilled water (10 ml) and extracted with dichloromethane (4 × 15 ml). The organic extracts were combined, washed with saturated brine (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with ether–ammonia (95:5) to give the *equatorial alcohol* **16b**, containing *ca* 10% of the *E*-isomer **16c**, as a pale yellow oil (59 mg, 56% over three steps); $\nu_{max}(CCl_4)/cm^{-1}$ 3640m, 3200br w, 2780s and 2700w Bohlmann bands; δ_H(400 MHz; $CDCl_3$) 5.34–5.23 (2 H, m, CH=CH), 3.56 (1 H, dd, *J* 10.7 and 4.5 Hz, C*H*HOH) and 3.35 (1 H, dd, *J* 10.7 and 6.8 Hz, CH*H*OH), 3.20 (1 H, dd, *J* 8.7 and 7.4 Hz, ring junction CH), 2.01–1.17 (19 H, m), 1.04 (1 H, qd, *J* 12.6 and 3.5 Hz) and 0.89 (3 H, t, *J* 7.5 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) *Z*-isomer (90%) 131.76 (d), 128.74 (d), 66.87 (d), 65.14 (t), 63.33 (d), 51.34 (t), 44.05 (d), 33.88 (t), 30.43 (t), 28.85 (t), 27.81 (t), 27.22 (t), 25.87 (t), 20.43 (t), 20.43 (t) and 14.29 (q); *E*-isomer (10%) 132.15 (d), 33.75 (t), 32.68 (t), 25.72 (t), 25.47 (t) and 13.68 (q); *m/z* (EI) 251 (M^+, 3%), 180 (17), 167 (16), 154 (100), 96 (16), 70 (13) and 41 (19); *m/z* (CI) 252 [$(M + H)^+$, 100%] and 154 (43). [Found: $(M + H)^+$ (CI), 252.2327. $C_{16}H_{29}NO$ requires (M + H), 252.2327].

(5R*,8R*,8aS*)-8-*Methyl*-5-(*hept*-6-*enyl*)*octahydroindolizine* (*Indolizidine* 235B′ **2**).—Dry triethylamine (0.24 ml, 1.72 mmol) was added dropwise at 0 °C under nitrogen to a stirred solution of the equatorial alcohol **16a** (0.107 g, 0.424 mmol) and methanesulphonyl chloride (0.07 ml, 0.90 mmol) in dry dichloromethane (6 ml). The resulting orange solution was stirred for 1.5 h after which it was allowed to warm to room temperature. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 cm), and the aqueous layer was extracted with dichloromethane (4 × 10 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (10 ml), dried ($MgSO_4$) and evaporated to give the crude mesylate as an orange oil. This was dissolved in dry THF (5 ml), and a 1M THF solution of Super-Hydride (2.2 ml, 2.2 mmol) was added dropwise at 0 °C under nitrogen with stirring. The resulting yellow solution was stirred

for 30 min, followed by addition of further Super-Hydride solution (2.2 ml, 2.2 mmol, $LiEt_3BH$, Aldrich). The reaction mixture was stirred for 1 h and then quenched with water (10 ml) and poured onto brine (100 ml). The aqueous solution was saturated with sodium chloride and extracted with dichloromethane (1 × 40 ml, 5 × 30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give a yellow liquid. Flash column chromatography on silica, eluting with 40:60:1 hexane–ether–ammonia, gave indolizidine 235B′ **2** (0.058 g, 0.246 mmol, 58%) as a pale yellow, mobile liquid; $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (C=CH), 2780s (NCH), 2700m (NCH), 1635w (C=C) and 910s (C=CH_2); δ_H(400 MHz; $CDCl_3$) 5.77 (1 H, ddt, *J* 16.9, 10.2 and 6.7 Hz, C*H*=CH_2), 4.95 (1 H, dd, *J* 16.9 and 1.6 Hz with fine structure broadening, CH=C*H*H′), 4.89 (1 H, ddt, *J* 10.2, 1.9 and 1.1 Hz, CH=CH*H*′), 3.23 (1 H, ddd, *J* 2.0, 8.7 and 8.7 Hz, N–C*H*–CH), 2.00 (2 H, dt, *J* 7.0 and 7.0 Hz, CH_2), 1.95–0.86 (20 H, methylene enevelope) and 0.83 (3 H, d, *J* 6.5 Hz, CH_3); δ_C(100 MHz; $CDCl_3$) 139.1 (d), 114.1 (t), 71.3 (d), 63.5 (d), 51.8 (t), 36.5 (d), 34.5 (t), 33.71 (t), 33.65 (t), 31.2 (t), 29.5 (t), 29.0 (t), 28.8 (t), 25.6 (t), 20.3 (t) and 18.9 (q); *m/z* (NH_3, CI) 236 [$(M + H)^+$, 100], 138 (40), 110 (2), 96 (5), 70 (5) and 58 (3) [Found: $(M + H)^+$, 236.237 80. $C_{16}H_{30}N$ requires 236.237 82). The oil **2** was converted into the hydrochloride salt, m.p. 96–98 °C.

(5R*,8R*,8aS*)-8-*Methyl*-5-[(*Z*)-*hept*-4-*enyl*]*octahydroindolizine* (*Indolizidine* 235B 1).—A solution of the alcohol **16b** in dry dichloromethane (5 ml) was cooled to 0 °C under nitrogen. A 10% solution of methanesulphonyl chloride in dry dichloromethane (0.35 ml, 0.47 mmol) was added dropwise, followed by dry triethylamine (0.12 ml, 0.94 mmol). The solution was stirred at 0 °C for 1 h and then poured into saturated aqueous sodium hydrogen carbonate (15 ml) and extracted with dichloromethane (4 × 10 ml). The organic layers were washed with saturated aqueous sodium hydrogen carbonate (15 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude mesylate as a brown oil. This was dried by repeated removal of water as an azeotrope with carbon tetrachloride (3 × 1 ml).

The crude mesylate was dissolved in dry THF (1 ml) under nitrogen. Lithium triethylborohydride (1 mol dm^{-3} solution in THF; 0.94 ml, 0.94 mmol) was added at 20 °C under nitrogen. After 30 min, the solution was poured into water (10 ml) and extracted with dichloromethane (4 × 10 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonates (15 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with hexane–ether–ammonia (59:40:1) to give indolizidine 235B 1, containing 10% of the *E*-isomer, as a pale yellow oil (47 mg, 85%); $\nu_{max}(CCl_4)/cm^{-1}$ 2770s and 2700w Bohlmann bands; δ_H(250 MHz; $CDCl_3$) 5.39–5.24 (2 H, m, C*H*=CH), 3.28–3.20 (1 H, td, *J* 8.6 and 2.2 Hz, ring junction CH), 2.05–1.13 (20 H, m), 0.92 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 0.83 (3 H, d, *J* 6.4 Hz, $CHCH_3$); δ_C(100 MHz; $CDCl_3$) *Z*-isomer (90%) 131.77 (d), 128.90 (d), 71.33 (d), 63.42 (d), 51.80 (t), 36.49 (d), 34.14 (t), 33.62 (t), 31.16 (t), 29.00 (t), 27.36 (t), 25.94 (t), 20.51 (t), 20.29 (t), 18.86 (q) and 14.36 (q); *E*-isomer (10%) 132.17 (d), 33.99 (t), 32.80 (t), 25.81 (t), 25.56 (t) and 13.95 (q); *m/z* (EI) 164 (12%), 151 (12), 138 (100), 96 (17), 55 (13) and 41 (26); *m/z* (CI) 236 [$(M + H)^+$, 100%], 164 (6), 151 (6), 138 (44) and 96 (4) [Found: $(M + H)^+$, 236.2378 (CI). $C_{16}H_{29}N$ requires (M + H) 236.2378).

Pent-4-*enal Oxime* **17**.—Allyl alcohol (14.5 g, 250 mmol) and mercuric acetate (4.78 g, 15.00 mmol) in dry ethyl vinyl ether (120 ml) were heated in four sealed ampoules at 150 °C for 3 h and then cooled and stirred with 10% aqueous Na_2CO_3 (500 ml) for 1 h. The organic phase was separated, dried ($MgSO_4$) and evaporated under reduced pressure to one-third of the original volume. MeOH (300 ml) was added, followed by sodium acetate (41.0 g, 500 mmol) and hydroxylamine hydrochloride (34.75 g, 500 mmol) at room temperature. The solution was stirred for 12 h and then evaporated under reduced pressure. Saturated aqueous $NaHCO_3$ was added to the residue and the aqueous phase was extracted with ether (3 × 200 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was distilled to give the *oxime* **17** (12.36 g, 50%) as a colourless liquid and a mixture of isomers, b.p. 83–84 °C at 22 mmHg (lit.,[9] 70 °C at 13 mmHg); ν_{max}(liquid film)/cm^{-1} 3250br (OH), 3080s (sp^2 CH), 2980s and 2900s (sp^3 CH), 1650w, 1640m, 990m and 910s (CH=CH_2 sp^2 CH); δ_H(80 MHz; $CDCl_3$) 8.66 (1 H, br s, NOH), 7.43 (t, *J* 5.7 Hz) and 6.72 (t, *J* 5.1 Hz) (total 1 H, C*H*NOH of 2 isomers), 5.59–6.08 (1 H, m, C*H*=CH_2), 4.93–5.20 (2 H, m, CH=CH_2) and 2.08–2.64 (4 H, m, CH_2CH_2); *m/z* (EI) 99 (M^+, 7%), 98 (7), 84 (17), 82 (50), 81 (22), 80 (16), 70 (12), 67 (51), 59 (16), 57 (14), 56 (13), 55 (69) and 54 (100) (Found: C, 60.3; H, 9.2; N, 14.0; M^+, 99.0692. C_5H_9NO requires C, 60.6; H, 9.2; N, 14.1%; M, 99.0684).

(Z)-N-(*Dodecylidene*)*pent*-4-*eny*-1-*amine* N-*Oxide* **18**.—A solution of sodium cyanoborohydride (34.59 mg, 0.551 mmol) in MeOH (2 ml) was added dropwise together with concurrent dropwise addition of 6M HCl–MeOH (1:1) to a stirred solution of pent-4-enal oxime **17** (35.40 mg, 0.358 mmol) in MeOH (10 ml) [containing Methyl Orange (3 mg) so as to keep the mixture at pH 3] at 0 °C, under argon. After 30 min, the solution was basified with 6M KOH. The aqueous phase was extracted at 0 °C with dichloromethane (3 × 20 ml), and the combined organic phases were dried ($MgSO_4$). Dodecanal (98.98 mg, 0.537 mmol) in dry dichloromethane (2 ml) was added to a stirred mixture of the hydroxylamine (in dichloromethane) containing Na_2SO_4 (2.0 g) at 0 °C. After 12 h, the mixture was filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give the *nitrone* **18** (61 mg, 64%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2900s and 2840s (sp^3 CH), 1630w (C=C), 1590m (C=N^+), 1440m and 1140m (N^+–O^-), and 990m and 910m (C=CH_2 sp^2 C–H); δ_H(250 MHz; $CDCl_3$) 6.63 (1 H, t, *J* 5.8 Hz, CH=N^+), 5.72–5.79 (1 H, m, C*H*=CH_2) 4.99–5.08 (2 H, m, CH_2=CH), 3.74 (2 H, t, *J* 6.6 Hz, CH_2N^+), 2.44–2.52 (2 H, m, CH_2C=N^+), 1.98–2.11 (2 H, m, CH_2CH=CH), 1.24–1.53 (20 H, m, side chain CH_2s and $CH_2CH_2N^+$) and 0.86 (3 H, t, *J* 6.5 Hz, CH_3); *m/z* (EI) 267 (M^+ 3%), 250 (8), 196 (10), 140 (26), 124 (38), 114 (15), 112 (100), 110 (17), 99 (73), 97 (14), 96 (11), 83 (21), 72 (14), 70 (12), 69 (32), 68 (23), 67 (17), 57 (14), 56 (13) and 55 (22) (Found: C, 76.2; H, 12.1; N, 5.0; M^+, 267.2553. $C_{17}H_{33}NO$ requires C, 76.3; H, 12.4; N, 5.2%); M, 267.2562).

(5S*,8S*)-8-*Undecyl*-7-*oxa*-1-*azabicyclo*[3.2.1]*octane* **19** *and* (5R*,7R*)-7-*Undecyl*-8-*oxa*-1-*azabicyclo*[3.2.1]*octane* **20**.—Nitrone **18** (500 mg, 1.87 mmol) in dry toluene (150 ml) was heated under reflux for 8 h, cooled and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with ether–hexane (1:4) to give the less polar *isoxazolidine* **19** (310 mg, 62%) as a crystalline solid, m.p. 28–31 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2920s and 2840s (sp^3 CH) and 1440m; δ_H(250 MHz; $CDCl_3$) 3.96 (1 H, d, *J* 6.7 Hz, *endo*-OCH), 3.81 (1 H, t, *J* 5.8 Hz, *exo*-OCH), 3.31 (1 H, dd, *J* 14.0 and 6.2 Hz, NCH_{eq}), 2.82–2.88 (1 H, m, CHC*H*N), 2.77–2.82 (1 H, m, NCH_{ax}H), 2.43 (1 H, br s, bridgehead H), 1.18–2.02 (24 H, m, side chain CH_2s and ring CH_2CH_2) and 0.86 (3 H, t, *J* 6.6 Hz, CH_3); δ_C(63 MHz; $CDCl_3$) 72.0, 71.5, 57.0, 41.9, 32.3, 31.9, 29.7, 29.6, 29.3, 26.6, 22.6, 18.6 and 14.0; *m/z* (EI) 267 (M^+, 12%), 196 (10), 168 (10), 154 (15), 140 (27), 127 (15), 114 (10), 112 (100), 110 (23), 99 (48), 97 (43), 96 (14), 86 (10), 84 (13), 83 (12), 82 (12), 70 (11), 69 (16), 68 (11), 67 (11) and 55 (16) (Found: M^+, 267.2559. $C_{17}H_{33}NO$ requires M, 267.2562).

Further elution furnished the more polar *isoxazolidine* **20** (50 mg, 10%) as a crystalline solid, m.p. 33–35 °C; ν_{max}(liquid film/cm^{-1} 2930s and 2840s (sp^3 C–H), and 1460m; δ_H(250 MHz; $CDCl_3$) 4.43 (1 H, d, *J* 8.0 Hz, HCO), 3.34–3.47 (2 H, m, NC*H*CH_2 and NCHH_{ax}), 2.94 (1 H, dd, *J* 14.8 and 5.7 Hz, NCH_{eq}H), 2.39–2.51 (1 H, m, *exo*-C*H*HCHN), 2.00–2.09 (1 H, m, CH*H*CHO), 1.25–1.83 (24 H, m, side chain CH_2s, CH_2CH_2C*H*HCHO and *endo*-C*H*HCHN) and 0.87 (3 H, t, *J* 6.5 Hz, CH_3); *m/z* (EI) 267 (M^+, 3%), 238 (8), 196 (13), 182 (8), 154 (10), 140 (36), 127 (28), 113 (11), 112 (100), 99 (12), 97 (11), 86 (20), 85 (10), 84 (15), 71 (11), 70 (10), 69 (12), 68 (11), 67 (11), 56 (11) and 55 (13) (Found: C, 76.6; H, 12.2; N, 5.0; M^+, 267.2577. $C_{17}H_{33}NO$ requires C, 76.3; H, 12.4; N, 5.2%; M, 267.2562).

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Note added in proof. Indolizidine 235B has also been prepared by an intramolecular acyl nitroso cycloaddition. We thank Professor C. Kibayashi for informing us of his work.

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