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An Approach to the Manzamine Alkaloids Modelled on a Biogenetic Theory

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Abstract: Improved conditions for the preparation of **17** are reported together with the synthesis of an advanced intermediate **38** *en route* to keramaphidin B, a plausible biogenetic precursor to the manzamines.

The manzamines represent a fascinating group of structurally complex polycyclic β-carboline alkaloids which have been isolated from several different families of marine sponge. The first member of the group to be isolated, from an Okinawan sponge *Haliclona* sp., was manzamine A (**1**) which displayed potent antileukaemic properties against P388 leukaemia cells (IC_{50}: 0.07μg/ml).[1] Soon after the disclosure of the structure of **1**, an identical compound, keramamine A, was reported independently by Nakamura *et.al.* from a different Okinawan sponge *Pellina* sp.[2] Manzamine B (**2**) , and the structurally less complex manzamine C (**3**), were later isolated from the same sponge as manzamine A. These two less abundant alkaloids displayed reduced cytotoxicity compared with **1** (Figure 1).[3]

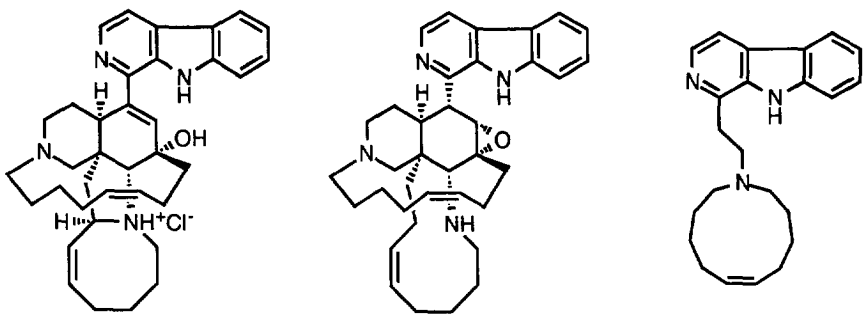

Figure 1

Since the isolation of manzamine A, a number of closely related β-carboline alkaloids have been isolated, many of which possess interesting biological properties.[4] The intriguing and complex structures of the manzamine alkaloids prompted us to consider a likely biogenetic pathway and in 1992 we put forward a

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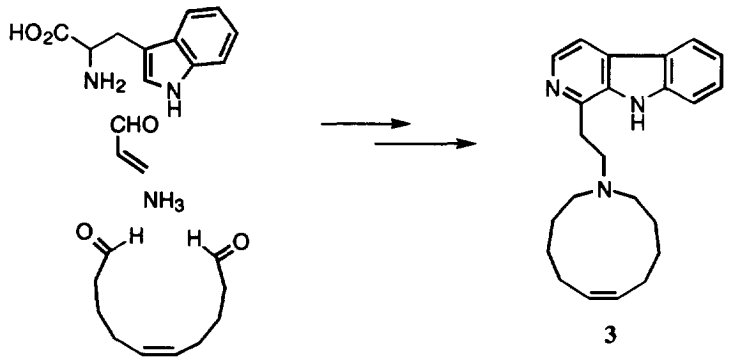
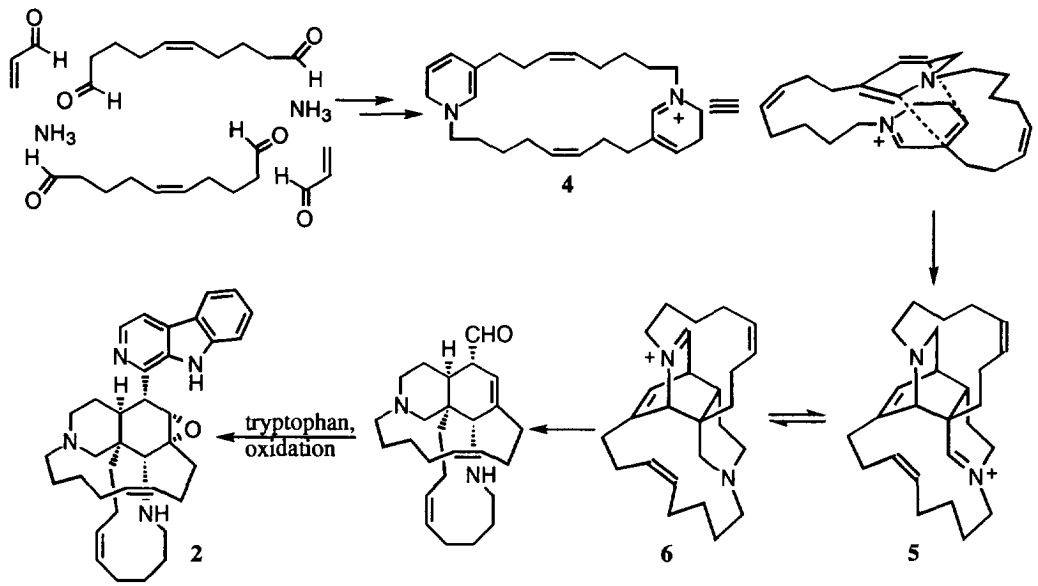
theoretical proposal which reduced the relatively simple structure of manzamine C (**3**) to four simple building blocks; ammonia, a C_{10} di-aldehyde, tryptophan and an acrolein equivalent (Scheme 1).[5]



Scheme 1

After close examination of the structures of the more complex manzamines, it became apparent that they too could be reduced to the same four building blocks (Scheme 2). In a forward sense, reductive condensation of two C_3 and two C_{10} units with two ammonias was envisaged to furnish the partially reduced bis-pyridinium species **4**. Intramolecular cycloaddition of **4** *via* an *endo* transition state gave the pentacyclic adduct **5** which was proposed to be in redox equilibrium with the isomeric pentacycle **6**. Hydrolytic ring-opening of **6** followed by condensation with tryptophan and oxidation was then proposed to yield manzamine B (**2**). Small modifications of this pathway provide access to other members of the manzamine group of alkaloids.



Scheme 2

At the time of publication there was little experimental evidence to support the proposal, however over the last few years a large number of sponge metabolites have been reported which bear a striking resemblance to

intermediates encompassed by it. Of particular note are the Ircinals A (**7**) and B (**8**),[4d] the aldehyde precursors of manzamines A (**1**) and J (**9**), and keramaphidin B (**10**),[6] the reduced form of the cycloadduct **5** (Figure 2).

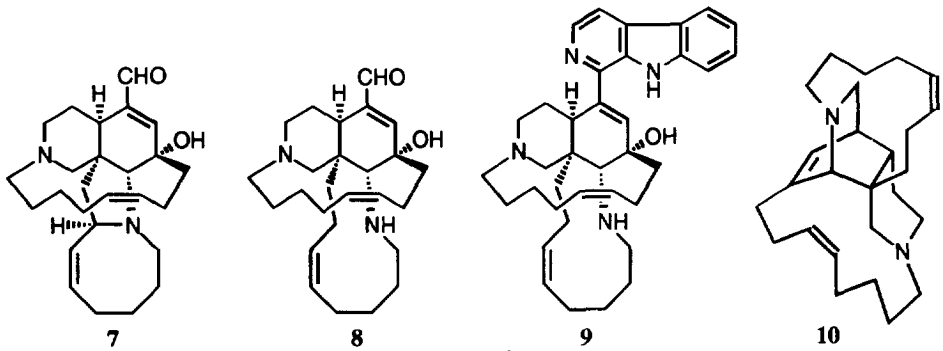
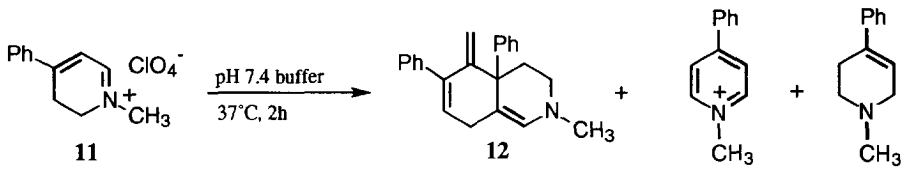


Figure 2

The proposal also provides an intriguing framework on which to base a synthetic approach to the manzamines and the purpose of this paper is to describe the current status of our work in this area.

Model Studies

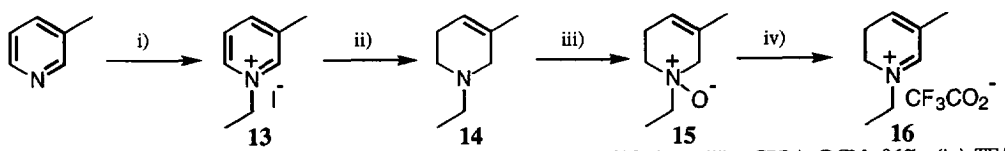
The cyclisation of partially reduced bis-pyridinium species **4** to adduct **5** was predicted to be the most challenging step of the sequence and initially we embarked on an investigation into the feasibility of this transformation using a simple model system. At the outset of this study, we were concerned by the fact that the reactive partners of the Diels-Alder reaction, a dihydropyridine and a dihydropyridinium ion would participate in an irreversible redox process, leading to a tetrahydropyridine and a pyridinium salt, rather than the desired cycloaddition. We were encouraged, however, by the observations of Leung *et al.*,[7] who proposed a related Diels-Alder reaction in their mechanistic explanation for the decomposition of *N*-methyl-4-phenyl-2,3-dihydropyridinium ion (**11**, MPDP+), to the hydroisoquinoline **12** in pH 7.4 buffer (Scheme 3).



11 **12** 8%

Scheme 3

Accordingly, we prepared the 5-methyl-2,3-dihydropyridinium ion **16** using a reported procedure,[8] with a view to examining its behaviour in a buffered medium (Scheme 4).

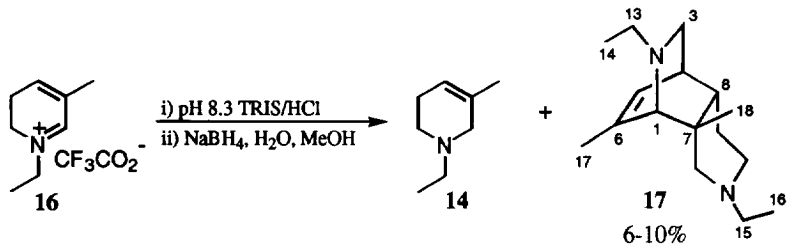


13 **14** **15** **16**

Reagents: i) Ethyl iodide, acetone, Δ, 97% ii) $NaBH_4$, MeOH, -78°C to 0°C, 95% iii) *m*CPBA, DCM, 96% (iv) TFAA, DCM, quant..

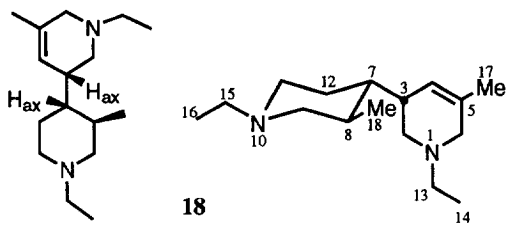
Scheme 4

It was found initially that dissolution of the crude iminium ion **16** in pH 8.3 TRIS/HCl buffer, stirring for 18 hours at room temperature followed by reduction with sodium borohydride at the same pH, furnished a crude product consisting predominantly of the volatile tetrahydropyridine **14** together with several other minor products. The formation of **14** was presumed to arise *via* reduction of either unreacted **16** or disproportionation products derived from **16**. Preparative gas chromatography of the crude mixture allowed isolation of a minor product component as a colourless liquid, which after extensive nmr analysis (^1H, ^{13}C, DQF COSY, DEPT, nOe), was assigned the reduced *endo* cycloadduct structure (**17**, Scheme 5).[9]



Scheme 5

When the reaction was carried out on a large scale, it proved possible to isolate a second minor component (<3% yield) which had a molecular weight two units greater than adduct **17**. Comprehensive nmr analysis of this material allowed assignment of the partially reduced bi-pyridyl structure **18** in which the two heterocyclic rings are approximately orthogonal and the dihedral angle between H3 and H7 is almost 90°. The connectivity between the rings and their relative stereochemistry were proved by homonuclear nOe difference experiments.[10,11]



Saturated Proton	selected nOe
H4	H3, 2.3%; H17, 4.3%
	$H12_{eq}$, 2.1%; H7, 4.5%
$H2_{ax}$	$H12_{ax}$, 5.0%
$H12_{ax}$	$H2_{ax}$, 5.0%
H18	H3 & $H2_{eq}$, 9.1%; H7, 1.8%

Figure 3

It is of interest to note the similarity between the structure of the reduced bi-pyridyl **18** and halicyclamine A (**19**) isolated in 1994 from an Indonesian sponge[12] and also the haliclonacyclamines A (**20**) and B (**21**) very recently isolated from an Australian sponge, *Haliclona* sp (Figure 4).[13]

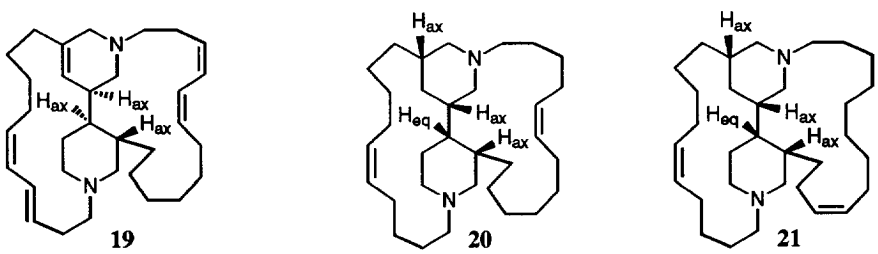
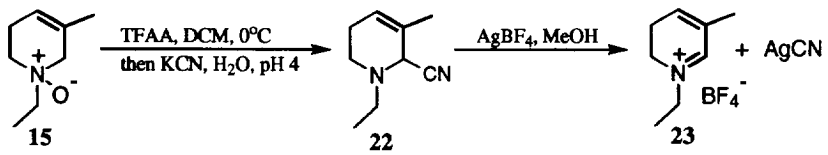


Figure 4

The low isolated yield (<10%) of tricycle **17** was disappointing and it was thought that this may be due, at least in part, to the presence of impurities in the crude iminium ion **16**. An alternative procedure for the formation of the dihydropyridinium salt was therefore investigated. The allylic α-aminonitrile **22** was prepared from *N*-oxide **15** using the method of Husson *et al.*[14] and was purified by rapid passage through neutral Al_2O_3. Subsequent treatment of a methanolic solution of **22** with $AgBF_4$ gave a clean sample of the tetrafluoroborate salt **23** after removal of precipitated AgCN.



Scheme 6

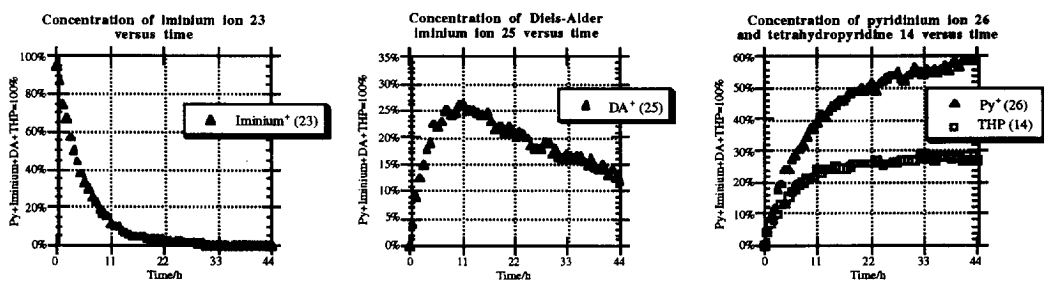
The iminium ion **23** prepared in this way was used in nmr studies which had been designed to monitor the progress of the cycloaddition reaction prior to reduction. A large number of experiments were carried out where small changes had been made to the reaction conditions; these give rise to four principle observations;

1) The relative concentration of cycloadduct quite rapidly reaches a maximum followed by a slow decrease. This is accompanied by increases in the concentrations of both tetrahydropyridine **14** and a pyridinium salt (Figure 5).

2) The rate of reaction is increased at higher pH.

3) At a given pH, the rate of reaction is increased at higher buffer concentrations. This is indicative of a *general base catalysed mechanism.*

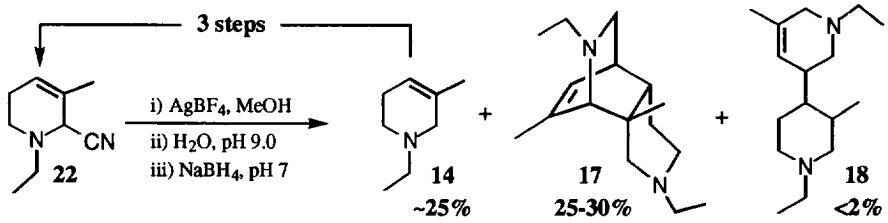
4) No signals corresponding to a bi-pyridyl type structure were observed during the experiments.



^1H nmr experiments performed at pH 8.3, 30°C and 1M D_5-TRIS/DCl buffer; see experimental section for typical procedure.

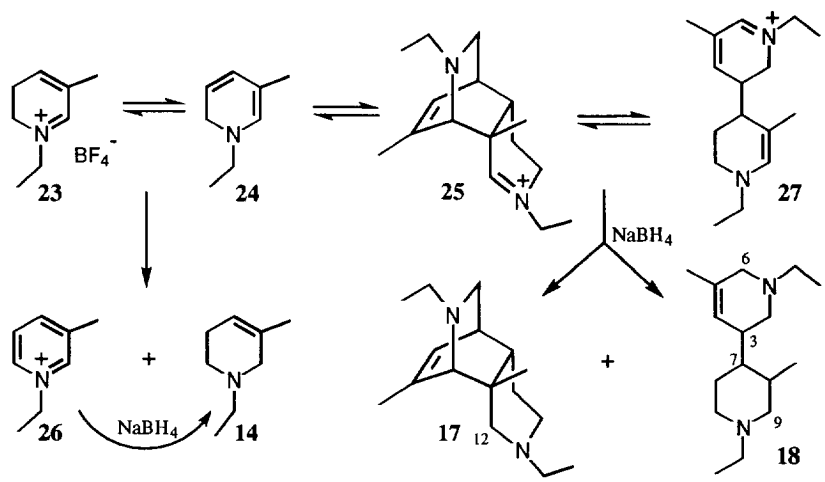
Figure 5

The last of these observations prompted an in-depth analysis of reduction conditions which were designed to maximise the ratio of reduced cycloadduct **17** to bi-pyridyl derivative **18**. A large number of experiments were undertaken in which the pH, solvent, reducing agent and temperature were varied. The main conclusion to be drawn from these experiments was that the yield of **18** could be minimised by carrying out the reduction either at lower pH (5-7), or at low temperature (between -78°C and 0°C). Using either technique, it is now possible to prepare the cycloadduct **17** routinely in 25-30% yield from the α-aminonitrile, accompanied by minimal formation of the bi-pyridyl **18**. The only other significant product is the volatile tetrahydropyridine **14** which can be isolated and channelled back through the reaction sequence (Scheme 7).



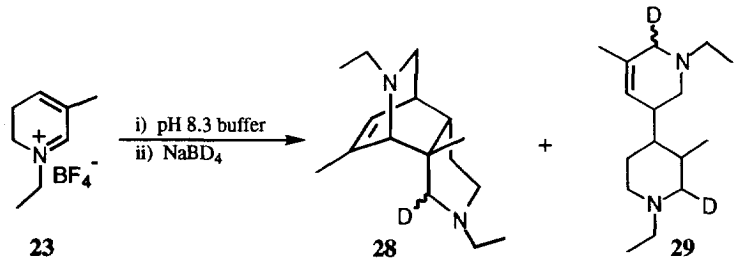
Scheme 7

A mechanistic rationale for our observations is outlined in Scheme 8. In an aqueous medium buffered to pH 9.0, general base mediated conversion of dihydropyridinium ion **23** to dihydropyridine **24** takes place. Thermodynamically favourable "hydride transfer" from **24** to **23** may then ensue, giving rise to the *irreversible* formation of pyridinium salt **26** and tetrahydropyridine **14**. Alternatively, cycloaddition of the electron-rich diene **24** to electron-deficient dienophile **23** can occur resulting in the *reversible* generation of cycloadduct **25**. We postulate that a further equilibrium also exists between **25** and the partially reduced bi-pyridyl **27** which, at the pH of the reaction medium, lies substantially on the side of **25**. Interconversion of **25** and **27** may arise *via* a stereoelectronically favourable retro aza-aldol fragmentation, using the nitrogen lone pair to eliminate enamine, which has precedent in the chemistry of the Iboga alkaloids.[15] The proposal that **27** is derived *via* a Diels-Alder/fragmentation process, rather than a simple alkylation of dihydropyridine **24** by the conjugated iminium ion **23**, is supported by the finding that the *relative stereochemistry* of H3 and H7 in **18** is consistent with such a mechanism. The pH dependence of the ratio of **17** to **18** is believed to be a consequence of protonation of the bridge nitrogen which disfavours fragmentation and "fixes" the equilibrium on the side of cycloadduct.



Scheme 8

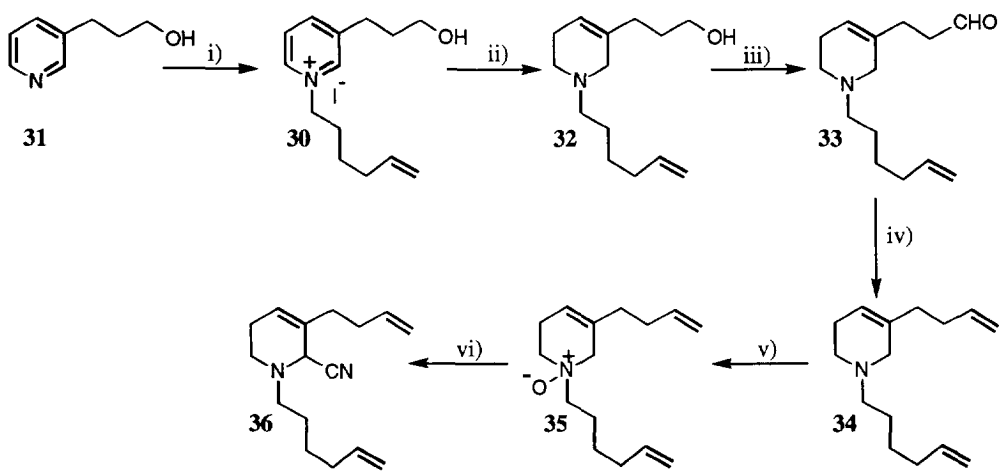
In accord with this mechanistic sequence, replacement of $NaBH_4$ by $NaBD_4$ yielded the reduced cycloadduct **28** with deuterium at C12 and the bi-pyridyl **29** in which deuterium was incorporated at C6 and C9 (Scheme 9).



Scheme 9

Preparation of a Synthetic Precursor to Keramaphidin B

Encouraged by the relative success of these initial studies we have attempted to utilise the chemistry developed on the model system to prepare a cycloadduct which may subsequently be processed to keramaphidin B. The pyridinium salt **30** was thus prepared by quaternisation of pyridine-3-propanol (**31**) with 6-iodohex-1-ene. Reduction with $NaBH_4$ in MeOH at low temperature furnished the tetrahydropyridine **32** as the major product which was oxidised using an activated dimethylsulphoxide procedure to give the aldehyde **33**.[16] Subsequent olefination with triphenylphosphonium methylide gave the triene **34** which was *N*-oxidised cleanly and quantitatively with *m*CPBA to give **35**. Application of the modified Polonovski reaction[17] followed by *in situ* trapping of the intermediate iminium ion gave the α-aminonitrile **36** in good yield (Scheme 10).

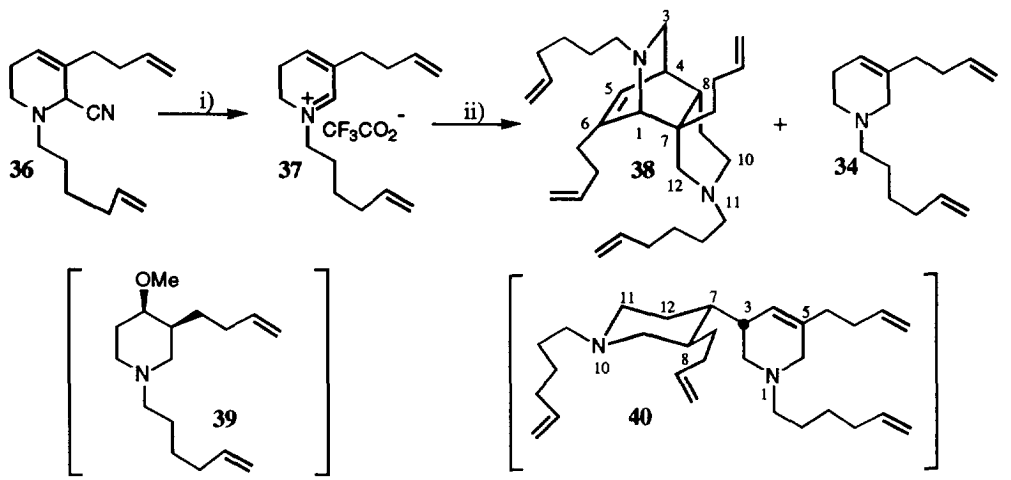


Reagents: i) 6-iodohex-1-ene, toluene, Δ, quant. ii) $NaBH_4$, MeOH, -78 to 0°C, 93% iii) DMSO, $(COCl)_2$, Et_3N, DCM, -78°C, 98% iv) methyltriphenylphosphonium bromide, ^nBuLi, THF, 90% v) *m*CPBA, DCM, 0°C, quant. vi) TFAA, DCM, 0°C then KCN, H_2O, pH 3-4, 87%.

Scheme 10

Treatment of the α-aminonitrile **36** with $AgOCOCF_3$ yielded the dihydropyridinium salt **37** which unfortunately, was only sparingly soluble in water, thus preventing the use of a purely aqueous medium. Methanol was investigated as an alternative solvent resulting in a 14% yield of **38**. Along with this was isolated a significant amount of the 4-methoxy-piperidine **39** (7%), presumably formed by addition of methoxide to **37** followed by reduction of the enamine. To avoid the formation of **39** an alternative solvent was sought. The cycloaddition was attempted in a 1:1 water: ethanol solvent mixture buffered with TRIS/HCl to approximately

pH 8.3. This prohibited the production of iminium ion addition products and provided a good balance between the solubilities of the buffer and reactant. After stirring at room temperature for one hour, the buffered reaction mixture was reduced with sodium borohydride between -78°C and 0°C. Kugelrohr distillation allowed recovery of tetrahydropyridine **34** (57%) and subsequent flash chromatography of the residue furnished the reduced cycloadduct **38** in a reproducible 22% yield. It was pleasing to find that the reduced bi-pyridyl **40** was not generated under these reaction conditions, however when the reduction step was carried out at room temperature, small quantities of **40** were produced. The structures of **38, 39** and **40** have been confirmed by extensive nmr analyses.



Reagents: i) $AgOCOCF_3$, EtOH ii) H_2O, EtOH, TRIS, pH 8.3, 1hr then $NaBH_4$, MeOH , -78°C to RT, 22% (**38**) overall.

Scheme 11

We are currently investigating the feasibility of applying the elegant ring-closure metathesis methodology developed by Grubbs[18] to the transformation of cycloadduct **38** into keramaphidin B (**10**).

In conclusion, using a biogenetic theory as a template, we have developed a useful synthetic approach to the core structure of the bridged hydroisoquinoline alkaloids, keramaphidin B, ingenamine[19] and the ingamines[20] and xestocyclamines.[21] The application of this methodology to the total synthesis of these alkaloids is currently being investigated, using both inter- and intra-molecular cycloaddition strategies.[10]

EXPERIMENTAL

Melting Points were obtained using a Cambridge Instruments Gallen™ III Köfler Block melting point apparatus or a Büchi 510 capillary melting point apparatus and are uncorrected. Microanalyses were performed by Mrs V. Lamburn and Mr Rodney Prior, Dyson Perrins Laboratory, University of Oxford and are quoted to the nearest 0.1% for all elements except for hydrogen which is quoted to the nearest 0.05%. Infrared spectra were recorded as thin films or KBr discs on a Perkin-Elmer 1750 Fourier Transform spectrometer with

absorption maxima reported in wavenumbers (cm^{-1}). The following abbreviations were used: w, weak; m, medium; s, strong; vs, very strong and br, broad.

^1H NMR spectra were recorded on Varian Gemini 200, Bruker WH300 and Bruker AM500 spectrometers. Chemical shifts (δ_H) are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. ^{13}C NMR spectra were recorded at 50.3MHz and 125.8MHz on a Varian Gemini 200 and Bruker AMX500 spectrometers respectively using DEPT editing. 125.8MHz spectra were performed by Mrs E. McGuinness. Chemical shifts (δ_C) are quoted in parts per million and to one or two decimal places for 50.3 and 125.8MHz spectra respectively, and are referenced to the solvent. ^2H NMR spectra were recorded at 38.4MHz and 76.8MHz on Bruker AM250 and Bruker AMX500 spectrometers respectively.

Low resolution mass spectra were recorded on a V.G. Micromass ZAB1F (FAB/CI/DCI), a V.G. Masslab 20-250 (CI/DCI/EI), a V.G. TRIO 1 (GCMS) or a V. G. BIO-Q (Electrospray) spectrometer with only molecular ions, fractions from molecular ions and other major peaks being reported.

Flash chromatography was carried out using Janssen silica 0.035-0.070mm or basic Laporte Actal U.G. alumina. Thin layer chromatography was performed on glass plates pre-coated with Merck silica gel 60 F_{254} or on aluminium sheets pre-coated with neutral aluminium oxide 60 F_{254} (type E). Visualisation was by the quenching of u.v. fluorescence (λ_{max} 254nm) and by staining with iodine. Retention factors (R_f) are quoted to 0.01. Kugelrohr distillations were performed using a Büchi GKR-50 distillation apparatus.

All reagents were purified in accordance with the instructions in D.D. Perrin and W.L.F. Armarego, "Purification of Laboratory Chemicals", Pergamon Press, Third edition, 1988 or used as obtained from commercial sources.

Synthesis of 1-ethyl-3-methyl-pyridinium iodide (13)

To a stirred solution of 3-methyl-pyridine (74.2g, 797mmol) in acetone (250ml) was added ethyl iodide (127.1g, 805mmol) and the reaction mixture was heated at reflux for 4 hours under nitrogen. Acetone was removed *in vacuo* to yield a white powder. Trituration with ether (3 x 50ml) followed by concentration *in vacuo* overnight afforded*1-ethyl-3-methyl-pyridinium iodide* (**13**) (193.4g, 97%) as a hygroscopic white powder. A small sample was recrystallised from ethyl acetate and ethanol for spectroscopic analysis; mp 103-104°C; (Found: C, 38.3; H, 4.60; N, 5.4. $C_8H_{12}IN$ requires C, 38.6; H, 4.85; N, 5.6%); ν_{max} (KBr disc)/cm^{-1} 3036m, 1633s, 1502s, 1157s, 810s; δ_H (200MHz; CD_3OD) 1.67 (3H, t, *J*7.5Hz, $CH_2C\underline{H}_3$), 2.61 (3H, s, $C\underline{H}_3$), 4.69 (2H, q, *J*7.5Hz, $C\underline{H}_2$), 8.02 (1H, pseudo t, *J*6.5Hz, C(5)$\underline{H}$), 8.46 (1H, d, *J*8Hz, C(4)$\underline{H}$), 8.89 (1H, d, *J*6Hz, C(6)$\underline{H}$), 8.99 (1H, s, C(2)$\underline{H}$); δ_C (50.3MHz; CD_3OD) 17.3 and 19.0 (2 x $\underline{C}H_3$), 58.4 ($\underline{C}H_2$), 129.0 ($\underline{C}H$), 141.2 (quaternary), 142.9, 145.6 and 147.5 (3 x $\underline{C}H$); *m/z* (positive electrospray) 122 ($C_8H_{12}N^+$, 100%).

Synthesis of 1-ethyl-5-methyl-1,2,3,6-tetrahydropyridine (14)

1-Ethyl-3-methyl-pyridinium iodide (**13**) (25.0g, 100mmol) was dissolved in methanol (500ml) under nitrogen and then cooled to -78°C. Sodium borohydride (7.59g, 201mmol) was added, and the mixture stirred for 20 minutes, after which it was allowed to warm to 0°C over 30 minutes. 2M HCl (50ml) was then added and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* to *ca.* 100ml, basified to pH 11 with 2M NaOH and then partitioned between a two phase solution of water (100ml) and dichloromethane

(100ml) and separated. The aqueous phase was extracted with dichloromethane (3 x 100ml), and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. Flash chromatography (SiO_2, dichloromethane: methanol; 9:1) afforded *1-ethyl-5-methyl-1,2,3,6-tetrahydropyridine* (**14**) (11.91g, 95%) (<2% of the double bond regioisomer) as a colourless oil; R_f 0.22 (dichloromethane: methanol; 9:1); ν_{max} (neat)/cm^{-1} 2970s, 2912s, 1654s, 1636m, 1457s, 1379s, 1179s, 1112s, 1061s; δ_H (200MHz; $CDCl_3$) 1.10 (3H, t, *J*7Hz, $CH_2C\underline{H}_3$), 1.61 (3H, s, $C\underline{H}_3$), 2.09-2.16 (2H, m, C(3)$\underline{H}_2$), 2.40-2.51 (4H, m, $C\underline{H}_2CH_3$ and C(2)$\underline{H}_2$), 2.80 (2H, s, C(6)$\underline{H}_2$), 5.37-5.43 (1H, m, C(4)$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 12.2 and 21.0 (2 x $\underline{C}H_3$), 26.0, 49.4, 52.1 and 56.5 (4 x $\underline{C}H_2$), 119.4 ($\underline{C}H$), 132.0 (quaternary); *m/z* (electron impact) 125 (M^+, 45%), 110 (100), 93 (40), 67 (41); HRMS found 126.1283; $C_8H_{16}N$ (MH^+) requires 126.1283.

Synthesis of (±)-1-ethyl-5-methyl-1,2,3,6-tetrahydropyridine-N-oxide (15)

To a stirred solution of 1-ethyl-5-methyl-1,2,3,6-tetrahydropyridine (**14**) (11.2g, 89.1mmol) in anhydrous dichloromethane (250ml) at 0°C under nitrogen was added *m*CPBA (87% active, 17.7g, 89.1mmol). The solution was stirred for 1 hour and then concentrated *in vacuo* at 15°C. Flash chromatography (Al_2O_3, dichloromethane: methanol; 199:1) followed by concentration *in vacuo* and storage under high vacuum for 96 hours afforded *(±)-1-ethyl-5-methyl-1,2,3,6-tetrahydropyridine-N-oxide* (**15**) (12.1g, 96%) as a hygroscopic white solid; R_f 0.35 (dichloromethane: methanol; 96:4); ν_{max} (KBr disc)/cm^{-1} 2915s, 2800s, 1451s, 1050s, 937m; δ_H (200MHz; $CDCl_3$) 1.43 (3H, t, *J*7Hz, $CH_2C\underline{H}_3$), 1.71 (3H, br s, $C\underline{H}_3$), 2.14-2.29 and 2.54-2.70 (each 1H, m, C(3)$\underline{H}_2$), 3.17-3.36 (4H, m, C(2)$\underline{H}_2$ and $C\underline{H}_2CH_3$), 3.68 (2H, br s, C(6)$\underline{H}_2$), 5.54-5.58 (1H, m, C(4)$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 7.7 and 20.3 (2 x $\underline{C}H_3$), 23.0, 60.2, 61.2 and 68.3 (4 x $\underline{C}H_2$), 118.4 ($\underline{C}H$), 128.0 (quaternary); *m/z* (chemical ionisation, NH_3) 142 (MH^+, 10%), 126 ($MH\text{-}O^+$, 100), 124 ($M\text{-}OH^+$, 73), 110 (12); HRMS found 142.1232; $C_8H_{16}NO$ (MH^+) requires 142.1232.

Synthesis of (±)-1-ethyl-3-methyl-1,2,5,6-tetrahydropyridine-2-carbonitrile (22)

To a stirred solution of (±)-1-ethyl-5-methyl-1,2,3,6-tetrahydropyridine-*N*-oxide (**15**) (3.30g, 23.4mmol) under nitrogen in anhydrous dichloromethane (100ml) at 0°C was added trifluoroacetic anhydride (6.60ml, 46.7mmol) dropwise over 10 minutes. After stirring for 1 hour at 0°C an aqueous solution of potassium cyanide (CAUTION: hydrogen cyanide) (3.04g in 50ml, 46.7mmol) was added and the aqueous phase adjusted to pH 3-4, by addition of sodium acetate, then the two phase system was stirred at room temperature for 1 hour. The aqueous phase was basified to pH 9 with a 2M sodium carbonate solution and the two layers were separated. The aqueous phase was then extracted with dichloromethane (3 x 50ml) and the combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The oil was then quickly filtered through a small pad of alumina with dichloromethane and concentrated *in vacuo* to afford *(±)-1-ethyl-3-methyl-1,2,5,6-tetrahydropyridine-2-carbonitrile* (**22**) (3.01g, 86%) as a colourless oil; ν_{max} (neat)/cm^{-1} 2974s, 2917s, 2824s, 2219w (CN), 1451m, 1178s, 1135m, 1058s, 888s; δ_H (500MHz; $CDCl_3$) 1.17 (3H, t, *J*7Hz, $CH_2C\underline{H}_3$), 1.84 (3H, dd, *J*2, 1Hz, $C\underline{H}_3$), 2.03-2.08 and 2.27-2.36 (each 1H, m, C(5)$\underline{H}_2$), 2.46 (1H, pseudo t d, *J*11.5, 4Hz, C(6)$\underline{H}$), 2.63 and 2.69 (each 1H, dq, *J*12.5, 7Hz, C(7)$\underline{H}_2$), 2.84 (1H, dd, *J*12, 6.5Hz, C(6)$\underline{H}$), 3.98 (1H, s, C(2)$\underline{H}$), 5.67-5.68 (1H, m, C(4)$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 12.3 and 20.2 (2 x $\underline{C}H_3$), 25.4, 45.1 and 49.3 (3 x $\underline{C}H_2$), 55.3 ($\underline{C}H$), 115.8 (quaternary), 124.4 ($\underline{C}H$), 127.5 (quaternary);

m/z (chemical ionisation, NH_3) 151 (MH^+, 100%), 140 (18), 124 ($M\text{-}CN^+$, 100); HRMS found 151.1235; $C_9H_{15}N_2$ (MH^+) requires 151.1235.

Synthesis of 1-ethyl-5-methyl-2,3-dihydropyridinium tetrafluoroborate (23)

(±)-1-Ethyl-3-methyl-1,2,5,6-tetrahydropyridine-2-carbonitrile (**22**) (195mg, 1.3mmol) was dissolved in methanol (20ml) and a methanolic solution (10ml) of silver tetrafluoroborate (254mg, 1.3mmol) was added. The mixture was stirred for 10 minutes and the precipitated silver cyanide was filtered through Celite®. The mixture was concentrated *in vacuo* and the remaining oil re-dissolved in methanol and filtered through cotton wool. The solution was again concentrated *in vacuo* to afford *1-ethyl-5-methyl-2,3-dihydropyridinium tetrafluoroborate* (**23**) (260mg, 95%) as a colourless oil; δ_H (500MHz; $CDCl_3$) 1.46 (3H, t, *J*7Hz, $CH_2C\underline{H}_3$), 2.03 (3H, pseudo q, *J*2Hz, $C\underline{H}_3$), 2.67-2.72 (2H, m, C(3)$\underline{H}_2$), 3.85 (2H, t, *J*9.5Hz, C(2)$\underline{H}_2$), 3.94 (2H, q, *J*7Hz, $C\underline{H}_2CH_3$), 6.80-6.82 (1H, m, C(4)$\underline{H}$), 8.38 (1H, d, *J*1Hz, C(6)$\underline{H}$); δ_C (125.8MHz; CD_3OD) 12.77 and 18.00 (2 x $\underline{C}H_3$), 23.66, 46.80 and 56.72 (3 x $\underline{C}H_2$), 129.51 (quaternary), 143.54 and 167.44 (2 x $\underline{C}H$).

Typical ^1H nmr experiment

The iminium ion **23** was derived from aminonitrile **22** (10mg) as described above and dissolved in D_2O (0.6ml). The solution was added to dry deuterated buffer (D_5-TRIS/DCl buffer (pH 8.3) was prepared from 0.6ml 1M buffer by repetitive evaporation and dissolution in D_2O) and transferred into a nmr tube and then the reaction progress was monitored by ^1H nmr at 30°C.

Synthesis of the Diels-Alder adduct 17

N-Ethyl-5-methyl-2,3-dihydropyridinium tetrafluoroborate (260mg, 1.23mmol) was dissolved in 6ml of a previously deuterated, aqueous buffer (2.7M TRIS/HCl, pH 9.0) and stirred at room temperature (22-24°C) until the amount of starting material had decreased to about 8-10% (4-5.5 hours). The mixture was diluted with methanol (40ml) and after adjusting the pH to 5-7 using methanolic 0.2M HCl, sodium borohydride (220mg, 5.8mmol) was added at -78°C and the mixture was allowed to warm up to -40°C. The mixture was stirred at -30 to -40°C for one hour and was then allowed to reach room temperature overnight. The solution was basified with sat. $NaHCO_3$ solution (60ml), diluted with water (120ml) and extracted with dichloromethane (3 x 80ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (Al_2O_3; gradient elution, dichloromethane to dichloromethane: methanol 100:1) of the crude oil (145mg) afforded *N-ethyl-5-methyl-1,2,3,6-tetrahydropyridine* (**14**) (35mg, 22%) further chromatography furnished cycloadduct **17** (47mg, 29%) as a colourless oil; R_f 0.26 (dichloromethane: methanol; 96:4); ν_{max} (KBr disc)/cm^{-1} 2965s, 2928s, 2872s, 1652w, 1445m, 1382m, 1343m, 1224m, 1131m, 1092m, 807m, 670m; δ_H (500MHz; CD_3OD; with resolution enhancement) 1.03 (3H, t, *J*7.3Hz, C(14)$\underline{H}_3$), 1.09 (3H, t, *J*7.2Hz, C(16)$\underline{H}_3$), 1.25-1.28 (1H, m, C(8)$\underline{H}$), 1.27-1.33 (1H, m, C(9)$\underline{H}$), 1.34 (3H, s, C(18)$\underline{H}_3$), 1.55-1.59 (1H, m, C(9)$\underline{H}$), 1.79 (1H, dd, *J*9.5, 2.8Hz, C(3)$\underline{H}$), 1.82 (3H, d, *J*1.8Hz, C(17)$\underline{H}_3$), 2.19-2.25 (2H, m, C(4)$\underline{H}$ and C(13)$\underline{H}$), 2.22 (1H, d, *J*11.8Hz, C(12)$\underline{H}$), 2.35 (1H, d, *J*11.8Hz, C(12)$\underline{H}$), 2.47 (1H, dq, *J*11.8, 7.3Hz, C(13)$\underline{H}$), 2.55-2.61 (3H, m, C(10)$\underline{H}$ and C(15)$\underline{H}_2$), 2.67 (1H, d, *J*1.8Hz, C(1)$\underline{H}$), 2.71-2.76 (1H, m, C(10)$\underline{H}$), 2.99 (1H, dd, *J*9.5, 2.1Hz, C(3)$\underline{H}$), 5.90 (1H, br d, *J*6.3Hz, C(5)$\underline{H}$); δ_C (125.8MHz; CD_3OD) 12.28 (C16), 14.00 (C14), 23.48 (C17), 27.73 (C9), 29.08 (C18), 39.44 (C4), 42.86 (C8), 42.93 (C7), 49.87 (C10), 52.77 (C13), 54.00 (C15), 56.14 (C3), 57.28

(C12), 67.54 (C1), 122.65 (C5), 141.05 (C6); *m/z* (chemical ionisation, NH_3) 249 (MH^+, 100%), 192 (10), 126 (35), 122 (65); HRMS found 249.2331; $C_{16}H_{29}N_2$ (MH^+) requires 249.2331.

The fragmentation product **18** was obtained from experiments carried out without lowering the pH prior to reduction at room temperature. Flash chromatography yielded the partially reduced bipyridyl **18** as a colourless oil; R_f 0.28 (dichloromethane: methanol; 96:4); ν_{max} (neat)/cm^{-1} 2967s, 2927s, 1668m, 1455m, 1379m, 1078m; δ_H (500MHz; $CDCl_3$) 0.89 (3H, d, *J*6Hz, C(18)$\underline{H}_3$), 1.01-1.07 (1H, m, C(7)$\underline{H}_{ax}$), 1.07 (3H, t, *J*7Hz, C(16)$\underline{H}_3$), 1.09 (3H, t, *J*7Hz, C(14)$\underline{H}_3$), 1.38 (1H, pseudo q d, *J*12.5, 4Hz, C(12)$\underline{H}_{ax}$), 1.51 (1H, d pseudo q, *J*13, 3Hz, C(12)$\underline{H}_{eq}$), 1.53 (1H, pseudo t, *J*10.5Hz, C(9)$\underline{H}_{ax}$), 1.55-1.62 (1H, m, C(8)$\underline{H}_{ax}$), 1.65 (3H, s, C(17)$\underline{H}_3$), 1.77 (1H, pseudo t d, *J*11.5, 2.5Hz, C(11)$\underline{H}_{ax}$), 1.97 (1H, pseudo t, *J*10Hz, C(2)$\underline{H}_{ax}$), 2.35 (2H, q, *J*7Hz, C(15)$\underline{H}_2$), 2.39-2.51 (2H, m, C(13)$\underline{H}_2$), 2.52 (1H, br d, *J*15Hz, C(6)$\underline{H}_{ax}$), 2.70-2.76 (2H, m, C(2)$\underline{H}_{eq}$ and C(3)$\underline{H}_{ax}$), 2.87 (1H, d pseudo t, *J*10, 2.5Hz, C(9)$\underline{H}_{eq}$), 2.95 (1H, dm, *J*11Hz, C(11)$\underline{H}_{eq}$), 3.01 (1H, d, *J*15.5Hz, C(6)$\underline{H}_{eq}$), 5.15 (1H, br s, C(4)$\underline{H}$); δ_C (125.8MHz; $CDCl_3$; quoted to 0.1ppm) 12.1 (C16), 12.1 (C14), 17.0 (C18), 21.0 (C17), 26.2 (C12), 32.7 (C8), 35.8 (C3), 46.3 (C7), 50.2 (C2), 52.2 (C13), 52.5 (C15), 54.2 (C11), 56.5 (C6), 62.2 (C9), 124.7 (C4), 132.4 (C5); *m/z* (chemical ionisation, NH_3) 251 (MH^+, 100%), 124 (15); HRMS found 250.2409; $C_{16}H_{30}N_2$ (M^+) requires 250.2409.

Synthesis of deuterio-Diels-Alder adduct 28

If the reduction is carried out with sodium borodeuteride, the deuterated cycloadduct **28** is obtained; ν_{max} (KBr disc)/cm^{-1} 2965s, 2928s, 2871s, 2178w, 1642w, 1445m, 1383m, 1345m, 1226m, 1135m; δ_H (500MHz; $CDCl_3$) 1.00 (3H, t, *J*7Hz, C(14)$\underline{H}_3$), 1.03 (3H, t, *J*7Hz, C(16)$\underline{H}_3$), 1.18-1.30 (2H, m, 8-H, 9-H), 1.31 (3H, s, C(18)$\underline{H}_3$), 1.47-1.52 (1H, m, C(9)$\underline{H}$), 1.73 (1H, dd, *J*9.5, 3Hz, C(3)$\underline{H}$), 1.78 (3H, d, *J*1.5Hz, C(17)$\underline{H}_3$), 2.15-2.22 (3H, m, C(4)$\underline{H}$, C(12)$\underline{H}$ and C(13)$\underline{H}$), 2.41 (1H, dq, *J*11.5, 7Hz, C(13)$\underline{H}$), 2.45-2.53 (3H, m, C(10)$\underline{H}$ and C(15)$\underline{H}_2$), 2.55 (1H, d, *J*1.5Hz, C(1)$\underline{H}$), 2.69 (1H, pseudo t d, *J*11, 4Hz, C(10)$\underline{H}$), 2.97 (1H, dd, *J*9.5, 2Hz, C(3)$\underline{H}$), 5.81 (1H, br d, *J*6.5Hz, C(5)$\underline{H}$); δ_D (38.4MHz; $CHCl_3$) 2.36 (1D, s, C(12)$\underline{D}$); δ_C (125.8MHz; CD_3OD) 12.8 (C16), 13.9 (C14), 23.2 (C17), 27.3 (C9), 28.6 (C18), 38.2 (C4), 41.4 (C8), 42.1 (C7), 49.1 (C10), 51.5 (C13), 52.9 (C15), 55.0 (C3), 55.7 (t, *J*20.5Hz, $\underline{C}$(12)HD), 66.2 (C1), 121.2 (C5), 139.7 (C6); *m/z* (chemical ionisation, NH_3) 250 (MH^+, 100%), 123 (50), 122 (45); HRMS found 250.2394; $C_{16}H_{28}D_2N_2$ (MH^+) requires 250.2394; accompanied by the 6,9-dideuterio-fragmentation product **29**; ν_{max} (neat)/cm^{-1} 2966s, 2928s, 1660m, 1448m, 1378m, 1077m; δ_H (500MHz; $CDCl_3$) 0.91 (3H, d, *J*6.5Hz, C(18)$\underline{H}_3$), 1.02-1.07 (1H, m, C(7)$\underline{H}_{ax}$), 1.08 (3H, t, *J*7Hz, C(16)$\underline{H}_3$), 1.10 (3H, t, *J*7Hz, C(14)$\underline{H}_3$), 1.39 (1H, pseudo q d, *J*12.5, 3.5Hz, C(12)$\underline{H}_{ax}$), 1.52 (1H, d pseudo q, *J*13, 3Hz, C(12)$\underline{H}_{eq}$), 1.57-1.61 (1H, m, C(8)$\underline{H}_{ax}$), 1.66 (3H, s, C(17)$\underline{H}_3$), 1.78 (1H, pseudo t d, *J*12, 2.5Hz, C(11)$\underline{H}_{ax}$), 1.94-1.99 (1H, m, C(2)$\underline{H}_{ax}$), 2.36 (2H, q, *J*7Hz, C(15)$\underline{H}_2$), 2.40-2.50 (2H, m, C(13)$\underline{H}_2$), 2.51 (0.5H, br s, C(6)$\underline{H}_{ax}$), 2.70-2.77 (2H, m, C(2)$\underline{H}_{eq}$ and C(3)$\underline{H}_{ax}$), 2.85 (1H, br s, C(9)$\underline{H}_{eq}$), 2.96 (1H, dm, *J*11Hz, C(11)$\underline{H}_{eq}$), 3.00 (0.5H, br s, C(6)$\underline{H}_{eq}$), 5.17 (1H, br s, C(4)$\underline{H}$); δ_D (76.8MHz; $CHCl_3$) 1.57 (1D, s, C(9)$\underline{D}$), 2.54 (0.5D, s, C(6)$\underline{D}$), 3.03 (0.5D, s, C(6)$\underline{D}$); δ_C (125.8MHz; $CDCl_3$; quoted to 0.1ppm) 12.0 (C16), 12.1 (C14), 16.9 (C18), 20.9 (C17), 26.1 (C12), 32.6 (C8), 35.7 (C3), 46.2 (C7), 50.1 (C2), 52.1 (C13), 52.4 (C15), 54.2 (C11), 56.0 (t, *J*19.5Hz, $\underline{C}$(6)HD), 61.5 (t, *J*19.5Hz, $\underline{C}$(9)HD), 124.7 (C4), 132.3 (C5) (assignment of **28** and **29** by comparison with **17** and **18**); *m/z* (chemical ionisation, NH_3) 253 (MH^+, 100%), 125 (40); HRMS found 253.2613; $C_{16}H_{29}D_2N_2$ (MH^+) requires 253.2613.

Synthesis of 6-iodohex-1-ene

Triphenylphosphine (3.66g, 14.0mmol) and imidazole (0.95g, 14.0mmol) were dried under vacuum then dissolved in anhydrous dichloromethane (30ml). Iodine (3.55g, 14.0mmol) was added over 5 minutes at 0°C and 5-hexen-1-ol (1.20ml, 9.98mmol) was added dropwise over 5 minutes. Monitoring by thin layer chromatography showed the completion of the reaction after 20 minutes. A solution of $Na_2S_2O_3$ (2.00g, 12.6mmol) in water (10ml) was added and stirred for 10 minutes. The aqueous layer was separated and extracted with dichloromethane (3 x 10ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in the minimum amount of dichloromethane, diluted with petroleum ether 40-60 and filtered through a short pad of silica with petroleum ether as an eluent. Evaporation of the solvent afforded clean *6-iodohex-1-ene* (2.05g, 98%) as a colourless liquid; bp 178°C (decomp.); (Found: C, 34.2; H, 5.30. $C_6H_{11}I$ requires C, 34.3; H, 5.30%); R_f 0.90 (SiO_2; petroleum ether 40-60); ν_{max} (neat)/ cm^{-1} 3076m, 2931s, 2855m, 1641m, 1428m, 1216s, 1174m, 993m, 913s; δ_H (500MHz; $CDCl_3$) 1.47-1.54 (2H, m, C(4)$\underline{H}_2$), 1.84 (2H, pseudo quintet, *J*7Hz, C(5)$\underline{H}_2$), 2.08 (2H, pseudo q, *J*7Hz, C(3)$\underline{H}_2$), 3.19 (2H, t, *J*7Hz, C(6)$\underline{H}_2$), 4.97 (1H, dd, *J*10, 1Hz, C(1)$\underline{H}$*trans*), 5.02 (1H, dm, *J*17Hz, C(1)$\underline{H}$*cis*), 5.79 (1H, ddt, *J*17, 10, 6.5Hz, C(2)$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 6.7, 29.6, 32.5, 32.8 and 115.2 (5 x $\underline{C}H_2$), 138.3 ($\underline{C}$H); *m/z* (electron impact) 210 (M^+, 7%), 169 (4), 155 (8), 127 (15), 95 (5) and 83 (100).

Synthesis of 1-(hex-5-enyl)-3-(3-hydroxy-propyl)-pyridinium iodide (30)

3-(3-Pyridyl)-1-propanol (**31**) (0.83g, 6.05mmol) and 6-iodohex-1-ene (1.27g, 6.05mmol) were heated under reflux in toluene (10ml) for 15 hours. After cooling, the toluene was removed *in vacuo* and the resulting brown oil was washed with diethyl ether (2 x 20ml) and dried under high vacuum to afford *1-(hex-5-enyl)-3-(3-hydroxy-propyl)-pyridinium iodide* (**30**) (2.10g, 100%) as a dark brown oil; (Found: C, 48.2; H, 6.35; N, 4.1. $C_{14}H_{22}INO$ requires C, 48.4; H, 6.40; N, 4.0%); ν_{max} (neat)/cm^{-1} 3031m, 2936s, 2865m, 1636m, 1505s, 1477m, 1458m, 1056m, 917m, 688s; δ_H (500MHz; CD_3OD) 1.47-1.53 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.92-1.98 (2H, m, $C\underline{H}_2CH_2OH$), 2.01-2.08 (2H, m, $NCH_2C\underline{H}_2$), 2.13-2.18 (2H, m, $C\underline{H}_2CH{=}CH_2$), 2.98 (2H, t, *J*7.5Hz, C(3)$C\underline{H}_2$), 3.63 (2H, t, *J*6Hz, $C\underline{H}_2OH$), 4.63 (2H, t, *J*7.5Hz, $NC\underline{H}_2$), 4.98 (1H, dm, *J*10Hz, CH=C$\underline{H}_2$*trans*), 5.04 (1H, dm, *J*17Hz, CH=C$\underline{H}_2$*cis*), 5.82 (1H, ddt, *J*17, 10, 6.5Hz, C$\underline{H}$=CH_2), 8.02 (1H, dd, *J*8, 6Hz, C(5)$\underline{H}$), 8.48 (1H, d, *J*8Hz, C(4)$\underline{H}$), 8.85 (1H, d, *J*6Hz, C(6)$\underline{H}$), 8.95 (1H, s, C(2)$\underline{H}$); δ_C (125.8MHz; CD_3OD) 25.83 ($NCH_2CH_2\underline{C}H_2$), 29.55 (C(3)$\underline{C}H_2$), 31.41 ($NCH_2\underline{C}H_2$), 33.50 ($\underline{C}H_2CH{=}CH_2$ and $\underline{C}H_2CH_2OH$), 61.08 ($\underline{C}H_2OH$), 62.23 ($N\underline{C}H_2$), 115.53 (CH=$\underline{C}H_2$), 128.73 (C5), 138.78 ($\underline{C}H{=}CH_2$), 143.15 (C6), 144.94 (C3), 145.20 (C2), 146.64 (C4); *m/z* (positive electrospray) 220 ($C_{14}H_{22}NO^+$, 100%).

Synthesis of 3-[1-(hex-5-enyl)-1,2,5,6-tetrahydro-3-pyridyl]-1-propanol (32)

1-(Hex-5-enyl)-3-(3-hydroxy-propyl)-pyridinium iodide (**30**) (584mg, 1.68mmol) was dissolved in anhydrous methanol (30ml) under nitrogen and then cooled to -78°C. Sodium borohydride (127mg, 3.36mmol) was added and stirred for 20 minutes, then the mixture was allowed to warm up to 0°C over 30 minutes. 2N HCl (5ml) was added and stirred for 10 minutes. The solution was then basified with 2M NaOH (10ml) and poured onto dichloromethane (20ml) and separated. The aqueous layer was extracted with dichloromethane (3 x 20ml) and the combined organic extracts were then washed with brine, dried over Na_2SO_4, filtered and

concentrated *in vacuo* to give a light yellow oil. Flash chromatography (SiO_2; dichloromethane: methanol; 9:1) yielded *3-[1-(hex-5-enyl)-1,2,5,6-tetrahydro-3-pyridyl]-1-propanol* (**32**) (348mg, 93%) (<5% of the double bond regioisomer) as colourless oil; bp 120°C (0.3mmHg); (Found: C, 75.1; H, 11.50; N, 6.3. $C_{14}H_{25}NO$ requires C, 75.3; H, 11.30; N, 6.3%); R_f 0.25 (dichloromethane: methanol; 9:1); ν_{max} (neat)/cm^{-1} 2937s, 1641m, 1441m, 1377m, 1114m, 1059m, 995m, 957m, 910m; δ_H (500MHz; $CDCl_3$) 1.40 (2H, quintet, *J*7.5Hz, $NCH_2CH_2C\underline{H}_2$), 1.49-1.57 (2H, m, $NCH_2C\underline{H}_2CH_2$), 1.64-1.69 (2H, m, $C\underline{H}_2CH_2OH$), 1.91 (1H, br s, O<u>H</u>), 2.01 (2H, t, *J*7.5Hz, C(3)$C\underline{H}_2$), 2.04-2.09 (2H, m, $C\underline{H}_2CH{=}CH_2$), 2.14 (2H, br s, C(5)$\underline{H}_2$), 2.38 (2H, t, *J*8Hz, $NC\underline{H}_2CH_2CH_2$), 2.47 (2H, t, *J*6Hz, C(6)$\underline{H}_2$), 2.84 (2H, br s, C(2)$\underline{H}_2$), 3.62 (2H, t, *J*6.5Hz, $C\underline{H}_2OH$), 4.93 (1H, dm, *J*10Hz, CH=C<u>H</u>$_2$*trans*), 4.99 (1H, dm, *J*17Hz, CH=C<u>H</u>$_2$*cis*), 5.46 (1H, br s, C(4)<u>H</u>), 5.79 (1H, ddt, *J*17, 10, 6.5Hz, $C\underline{H}{=}CH_2$); δ_C (125.8MHz; $CDCl_3$) 25.53 (C5), 26.12 ($NCH_2\underline{C}H_2CH_2$), 26.75 ($NCH_2CH_2\underline{C}H_2$), 30.48 ($\underline{C}H_2CH_2OH$), 31.32 (C(3)$\underline{C}H_2$), 33.43 ($\underline{C}H_2CH{=}CH_2$), 49.81 (C6), 55.55 (C2), 58.29 ($N\underline{C}H_2CH_2CH_2$), 61.70 ($\underline{C}H_2OH$), 114.29 ($CH{=}\underline{C}H_2$), 118.84 (C4), 135.33 (C3), 138.45 ($\underline{C}H{=}CH_2$); *m/z* (chemical ionisation, NH_3) 224 (MH^+, 100%), 164 (8) and 154 (45).

Synthesis of 3-[1-(hex-5-enyl)-1,2,5,6-tetrahydro-3-pyridyl]-propanal (33)

Dimethyl sulphoxide (1.15ml, 16.2mmol) was added dropwise to a solution of oxalyl chloride (1.30ml, 14.9mmol) in anhydrous dichloromethane (80ml) at -78°C under a stream of nitrogen. After 30 minutes, a solution of 3-[1-(hex-5-enyl)-1,2,5,6-tetrahydro-3-pyridyl]-1-propanol (**32**) (2.78g, 12.4mmol) in anhydrous dichloromethane (10ml) was added dropwise. After 90 minutes stirring at -78°C, triethylamine (7.87ml, 56.0mmol) was added. The temperature was then allowed to reach 15°C over 2 hours. The resulting white slurry was treated with 2M NaOH (20ml), and separated. The aqueous layer was extracted with dichloromethane (3 x 30ml) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting brown oil was distilled to give *3-[1-(hex-5-enyl)-1,2,5,6-tetrahydro-3-pyridyl]-propanal* (**33**) (2.67g, 98%) as a clear, colourless oil; bp 115°C (0.3mmHg); R_f 0.30 (SiO_2; dichloromethane: methanol; 9:1; 2,4-DNPH); δ_H (500MHz; $CDCl_3$) 1.37-1.44 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.51-1.57 (2H, m, $NCH_2C\underline{H}_2CH_2$), 2.04-2.09 (2H, m, $C\underline{H}_2CH{=}CH_2$), 2.14 (2H, br s, C(5)$\underline{H}_2$), 2.28 (2H, br t, *J*7.5Hz, C(3)$C\underline{H}_2$), 2.39 (2H, t, *J*8Hz, $NC\underline{H}_2CH_2CH_2$), 2.47 (2H, t, *J*6Hz, C(6)$\underline{H}_2$), 2.55 (2H, td, *J*7, 1.5Hz, $C\underline{H}_2CHO$), 2.84 (2H, br s, C(2)$\underline{H}_2$), 4.93 (1H, dm, *J*10Hz, CH=C<u>H</u>$_2$*trans*), 4.99 (1H, dm, *J*17Hz, CH=C<u>H</u>$_2$*cis*), 5.46 (1H, br s, C(4)<u>H</u>), 5.79 (1H, ddt, *J*17, 10, 6.5Hz, $C\underline{H}{=}CH_2$), 9.76 (1H, t, *J*1.5Hz, $CH_2C\underline{H}O$); δ_C (125.8MHz; $CDCl_3$) 25.83 (C5), 26.44 ($NCH_2\underline{C}H_2CH_2$), 26.77 ($NCH_2CH_2\underline{C}H_2$), 27.14 (C(3)$\underline{C}H_2$), 33.53 ($\underline{C}H_2CH{=}CH_2$), 41.59 ($\underline{C}H_2CHO$), 49.76 (C6), 55.79 (C2), 58.31 ($N\underline{C}H_2CH_2CH_2$), 114.35 ($CH{=}\underline{C}H_2$), 119.82 (C4), 134.20 (C3), 138.59 ($\underline{C}H{=}CH_2$), 201.87 ($CH_2\underline{C}HO$); *m/z* (chemical ionisation, NH_3) 222 (MH^+, 100%), 178 (9), 152 (42); HRMS found 222.1858; $C_{14}H_{24}NO$ (MH^+) requires 222.1858.

Synthesis of 5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine (34)

Methyltriphenylphosphonium bromide (17.58g, 49.2mmol) was dried *in vacuo* for 2 hours then suspended with stirring in anhydrous tetrahydrofuran (100ml) under nitrogen. The mixture was cooled to -78°C before ^{n}butyllithium (22.5ml, 51.7mmol) was added dropwise. After stirring for 2 hours being allowed to warm to 25°C, the bright orange solution was again cooled to -78°C and 3-[1-(hex-5-enyl)-1,2,5,6-tetrahydro-3-pyridyl]-propanal (**33**) (7.78g, 35.1mmol) in anhydrous tetrahydrofuran (30ml) was added by means of a

syringe. After 2.5 hours stirring at room temperature, the reaction was complete by thin layer chromatography. Water (20ml) was added and the resultant two phase mixture separated. The aqueous layer was extracted with ether and the combined organic layers concentrated to half of the volume and diluted with petroleum ether to precipitate the triphenylphosphine oxide. The precipitate was washed with petroleum ether until no product could be detected by thin layer chromatography of the filtrate. The combined organic layers were washed with brine, dried over K_2CO_3, filtered and concentrated *in vacuo*. The brown residue was purified by Kugelrohr distillation to give *5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine* (**34**) (6.91g, 90%) as a colourless oil; bp 105°C (0.6mmHg); R_f 0.47 (SiO_2; dichloromethane: methanol; 9:1); ν_{max} (neat)/cm^{-1} 3076m, 2931s, 2858m, 2802m, 2764m, 1641m, 1466m, 1436m, 1118m, 993m, 910s; δ_H (500MHz; $CDCl_3$) 1.38-1.44 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.53-1.57 (2H, m, $NCH_2C\underline{H}_2CH_2$), 2.01-2.13 (4H, m, C(5)$C\underline{H}_2$ and $NCH_2CH_2CH_2C\underline{H}_2$), 2.11-2.19 (4H, m, C(3)$\underline{H}_2$ and C(5)$CH_2C\underline{H}_2$), 2.39 (2H, t, *J*8Hz, $NC\underline{H}_2CH_2CH_2$), 2.48 (2H, t, *J*6Hz, C(2)$\underline{H}_2$), 2.84 (2H, br s, C(6)$\underline{H}_2$), 4.93-5.03 (4H, m, both CH=C$\underline{H}_2$), 5.46 (1H, br s, C(4)$\underline{H}$), 5.77-5.85 (2H, m, both C$\underline{H}$=CH_2); δ_C (125.8MHz; $CDCl_3$), 25.86 (C3), 26.51 ($NCH_2\underline{C}H_2CH_2$), 26.84 ($NCH_2CH_2\underline{C}H_2$), 31.83 (C(5)$CH_2\underline{C}H_2$), 33.57 ($NCH_2CH_2CH_2\underline{C}H_2$), 34.54 (C(5)$\underline{C}H_2$), 49.99 (C2), 55.87 (C6), 58.42 ($N\underline{C}H_2CH_2CH_2$), 114.32 and 114.34 (both CH=$\underline{C}H_2$), 119.05 (C4), 135.45 (C5), 138.29 and 138.61 (both $\underline{C}H$=CH_2); *m/z* (chemical ionisation, NH_3) 220 (MH^+, 100%), 178 (12), 150 (55); HRMS found 220.2065; $C_{15}H_{26}N$ (MH^+) requires 220.2065.

Synthesis of (±)-5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine-N-oxide (35)

To a stirred solution of 5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine (**34**) (490mg, 2.23mmol) in anhydrous dichloromethane (20ml) at 0°C was added 90% of a solution of 91% active *m*CPBA (385mg, 2.23mmol) in anhydrous dichloromethane (10ml). Thin layer chromatography analysis after 30 minutes showed the presence of starting material so the last 10% of the *m*CPBA solution was added. After a further 30 minutes the reaction mixture was concentrated *in vacuo* to yield a white foam. Flash chromatography (Al_2O_3; dichloromethane: methanol; 98:2) and storage under high vacuum for 24 hours afforded *(±)-5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine-N-oxide* (**35**) (525mg, 100%) as a hygroscopic, white solid; R_f 0.45 (dichloromethane: methanol; 98:2); ν_{max} (neat)/cm^{-1} 3200s (OH), 3076s, 2922s, 1641s, 1451m, 1051m, 996m, 911s, 823m; δ_H (500MHz; $CDCl_3$) 1.38-1.47 (2H, m, $NCH_2CH_2C\underline{H}_2$), 1.82-1.91 (1H, m, one of $NCH_2C\underline{H}_2CH_2$), 1.94-2.01 (1H, m, one of $NCH_2C\underline{H}_2CH_2$), 2.02-2.18 (6H, m, $NCH_2CH_2CH_2C\underline{H}_2$, C(5)$C\underline{H}_2$ and C(5)$CH_2C\underline{H}_2$), 2.20-2.25 and 2.51-2.57 (each 1H, m, C(3)$\underline{H}_2$), 3.07 (1H, td, *J*12, 5Hz, one of $NC\underline{H}_2CH_2CH_2$), 3.18 (1H, td, *J*12, 5Hz, one of $NC\underline{H}_2CH_2CH_2$), 3.22-3.27 and 3.31-3.36 (each 1H, m, C(2)$\underline{H}_2$), 3.65-3.75 (2H, ABq, J_{AB}16Hz, C(6)$\underline{H}_2$), 4.94-5.03 (4H, m, both CH=C$\underline{H}_2$), 5.55 (1H, s, C(4)$\underline{H}$), 5.69-5.80 (2H, m, both C$\underline{H}$=CH_2); δ_C (50.3MHz; $CDCl_3$) 21.7, 23.4, 25.9, 31.2, 33.2, 33.6, 61.4, 65.9, 68.6, 115.0 and 115.3 (11 x $\underline{C}H_2$), 118.2 ($\underline{C}H$), 131.9 (quaternary), 137.1 and 137.8 (2 x $\underline{C}H$); *m/z* (chemical ionisation, NH_3) 236 (MH^+, 32%), 220 ($MH\text{-}O^+$, 12), 138 (31), 128 (69), 126 (61), 112 (100), 110 (70), 100 (36); HRMS found 236.2014; $C_{15}H_{26}NO$ (MH^+) requires 236.2014.

Synthesis of (±)-3-(but-3-enyl)-1-(hex-5-enyl)-1,2,5,6-tetrahydropyridine-2-carbonitrile (36)

To a solution of the (±)-5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine-*N*-oxide (**35**) (300mg, 1.27mmol) in anhydrous dichloromethane (10ml) was added dropwise trifluoroacetic anhydride (0.54ml, 3.82mmol) at 0°C. After stirring for 1 hour at 0°C an aqueous solution of potassium cyanide (249mg,

3.82mmol) was added and the pH adjusted to 3-4 by the addition of solid sodium acetate. The two phase system was then stirred at room temperature for 1 hour. The aqueous phase was then basified with 2M sodium carbonate to pH 9 and the aqueous layer separated and extracted with dichloromethane (3 x 10ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield a light orange oil, which was dissolved in dichloromethane (2ml) and filtered through a short pad of alumina with dichloromethane (35ml). Solvent was removed *in vacuo* to afford *(±)-3-(but-3-enyl)-1-(hex-5-enyl)-1,2,5,6-tetrahydropyridine-2-carbonitrile* (**36**) (270mg, 87%) as a colourless oil; (Found: C, 78.6; H, 9.95; N, 11.6. $C_{16}H_{24}N_2$ requires C, 78.6; H, 9.90; N, 11.5%); ν_{max} (neat)/cm^{-1} 3077m, 2931s, 2836s, 2219w (CN), 1641m, 1441m, 1122m, 1046m, 996m, 912s; δ_H (500MHz; C_6D_6) 1.24-1.35 (4H, m, $NCH_2C\underline{H}_2CH_2$ and $NCH_2CH_2C\underline{H}_2$), 1.58 (1H, dm, *J*18Hz, C(5)$\underline{H}$), 1.89-2.04 (7H, m, C(5)$\underline{H}$, $NCH_2CH_2CH_2C\underline{H}_2$, C(3)$C\underline{H}_2$ and C(3)$CH_2C\underline{H}_2$), 2.31-2.43 (4H, m, C(6)$\underline{H}_2$ and $NC\underline{H}_2CH_2CH_2$), 3.69 (1H, s, C(2)$\underline{H}$), 4.93-5.03 (4H, m, both CH=C$\underline{H}_2$), 5.27 (1H, br d, *J*5Hz, C(4)$\underline{H}$), 5.60-5.76 (2H, m, both C$\underline{H}$=CH_2); δ_C (50.3MHz; $CDCl_3$) 25.4, 26.4, 31.4, 32.9, 33.5 and 45.6 (7 x $\underline{C}H_2$), 54.8 ($\underline{C}$H), 55.2, 114.7 and 115.3 (3 x $\underline{C}H_2$), 116.2 (quaternary), 124.0 ($\underline{C}$H), 131.0 (quaternary), 137.4 and 138.4 (2 x $\underline{C}$H); *m/z* (chemical ionisation, NH_3) 245 (MH^+, 100%), 218 (18), 203 (20), 134 (19).

Synthesis of 5-(but-3-enyl)-1-(hex-5-enyl)-2,3-dihydropyridinium tetrafluoroborate

To a stirred solution of (±)-3-(but-3-enyl)-1-(hex-5-enyl)-1,2,5,6-tetrahydropyridine-2-carbonitrile (**36**) (22.4mg, 92μmol) in D_4-methanol (0.4ml) was added silver tetrafluoroborate (17.9mg, 92μmol), stirring being maintained under nitrogen for 5 minutes. The precipitate was filtered through Celite® in a Pasteur pipette and washed through using D_4-methanol (0.4ml). The crude iminium ion was used without further purification for analysis; ν_{max} (neat)/cm^{-1} 3077m, 2928m, 2863m, 1641m, 1600m, 1445m, 1062s (BF), 918m; δ_H (500MHz; CD_3OD) 1.68 (2H, pseudo quintet, *J*7.5Hz, $NCH_2CH_2C\underline{H}_2$), 2.07 (2H, pseudo quintet, *J*7.5Hz, $NCH_2C\underline{H}_2CH_2$), 2.34-2.39 (2H, m, $NCH_2CH_2CH_2C\underline{H}_2$), 2.48-2.52 (2H, m, C(5)$CH_2C\underline{H}_2$), 2.65-2.68 (2H, m, C(5)$C\underline{H}_2$), 2.92 (2H, br s, C(3)$\underline{H}_2$), 4.05 (2H, t, *J*9.5Hz, C(2)$\underline{H}_2$), 4.12 (2H, t, *J*7.5Hz, $NC\underline{H}_2CH_2CH_2$), 5.20-5.30 (4H, m, both CH=C$\underline{H}_2$), 6.05-6.10 (2H, m, both C$\underline{H}$=CH_2), 7.06 (1H, br s, C(4)$\underline{H}$), 8.68 (1H, br s, C(6)$\underline{H}$); δ_C (125.8MHz; CD_3OD) 23.72 (C3), 26.89 ($NCH_2CH_2\underline{C}H_2$), 27.76 ($NCH_2\underline{C}H_2CH_2$), 32.48 (C(5)$\underline{C}H_2$), 33.65 (C(5)$CH_2\underline{C}H_2$), 34.16 ($NCH_2CH_2CH_2\underline{C}H_2$), 47.27 (C2), 61.69 ($N\underline{C}H_2CH_2CH_2$), 110.46 and 113.10 (both CH=$\underline{C}H_2$), 133.18 (C5), 136.84 and 137.64 (both $\underline{C}$H=CH_2), 144.82 (C4), 167.57 (C6).

Synthesis of cycloadduct 38 in methanol

To a stirred solution of (±)-3-(but-3-enyl)-1-(hex-5-enyl)-1,2,5,6-tetrahydropyridine-2-carbonitrile (**36**) (301mg, 1.23mmol) in anhydrous methanol (4ml) was added silver trifluoroacetate (272mg, 1.23mmol). After 15 minutes stirring under argon, AgCN was filtered off through Celite® and washed with methanol (4ml). To the stirred filtrate was added a methanolic solution of TRIS buffer (15ml, 0.5M, pH 8.3) and stirring was kept under nitrogen for 1 hour. The solution was cooled to -78°C and sodium borohydride (140mg, 3.69mmol) was added and stirred for 30 minutes. The reaction mixture was allowed to warm up to 0°C over 30 minutes. The solution was then poured into water (20ml) and dichloromethane (20ml) and separated. The aqueous layer was extracted with dichloromethane (3 x 20ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil (283mg). Volatile components were quickly

removed by Kugelrohr distillation (150°C, 0.2mmHg) and the residue was purified by flash chromatography (SiO_2; dichloromethane: methanol; 97:3) to give the cycloadduct **38** (37mg, 14%) as a colourless oil; R_f 0.24 (SiO_2; dichloromethane: methanol; 97:3); R_f 0.36 (Al_2O_3; dichloromethane: diethyl ether; 9:1); ν_{max} (neat)/cm^{-1} 3076m, 2976s, 2930s, 2857s, 1641m, 1443m, 993m, 908s; δ_H (500MHz; $CDCl_3$) 1.09 (1H, ddd, *J*11, 6.5, 2Hz, C(8)H), 1.29-1.48 (10H, m, C(9)H_2, 2 x NCH_2CH_2 and 2 x $NCH_2CH_2CH_2$), 1.72 (1H, dd, *J*9.5, 3Hz, C(3)H), 1.74-1.79 (2H, m, C(7)CH_2), 1.97 (1H, d, *J*12Hz, C(12)H), 2.02-2.12 (9H, m, C(7)CH_2, 2 x $NCH_2CH_2CH_2CH_2$, C(7)CH_2 and one of N(2)CH_2), 2.21-2.25 (3H, m, C(4)H and C(6)CH_2CH_2), 2.31 (1H, d, *J*12Hz, C(12)H), 2.37-2.40 (3H, m, one of N(2)CH_2 and C(7)CH_2), 2.45 (1H, ddd, *J*11.5, 11.5, 3.5Hz, C(10)H), 2.68 (1H, d, *J*2Hz, C(1)H), 2.70-2.72 (1H, m, C(10)H), 2.96 (1H, dd, *J*9.5, 2Hz, C(3)H), 4.91-5.07 (8H, m, 4 x CH=CH_2), 5.81-5.88 (5H, m, C(5)H and 4 x CH=CH_2); δ_C (125.8MHz; $CDCl_3$) 26.55 (two adjacent ^{13}C resonances can just be resolved, N(2)CH_2CH_2 and N(11)$CH_2CH_2CH_2$), 27.03 (two adjacent ^{13}C resonances can just be resolved, N(2)$CH_2CH_2CH_2$ and N(11)CH_2CH_2), 28.10 (C9), 28.87 (C(7)CH_2CH_2), 30.77 (C(6)CH_2CH_2), 33.61 and 33.71 (2 x $NCH_2CH_2CH_2CH_2$), 35.74 (C(6)CH_2), 37.77 (C4), 38.61 (C(7)CH_2), 42.96 (C8), 45.56 (C7), 49.60 (C10), 51.00 (C12), 54.83 (C3), 57.99 N(2)CH_2), 58.97 (N(11)CH_2), 62.58 (C1), 113.64 (C(7)$CH_2CH_2CHCH_2$), 114.30 (2 x $NCH_2CH_2CH_2CH_2CHCH_2$), 114.56 (C(6)$CH_2CH_2CHCH_2$), 121.27 (C5), 138.56 and 139.96 (2 x CCH_2CH_2CH), 138.90 (2 x $NCH_2CH_2CH_2CH_2CH$), 142.65 (C6); *m/z* (chemical ionisation, NH_3) 437 (MH^+, 14%), 220 (13), 217 (45), 176 (100), 160 (12); HRMS found 437.3896; $C_{30}H_{49}N_2$ (MH^+) requires 437.3896. Flash chromatography of the distillate (SiO_2; ethyl acetate: methanol: ammonia; 93:5:2) afforded *5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine* (**34**) (99mg, 37%) as a colourless oil; and *(±)-cis-3-(but-3-enyl)-1-(hex-5-enyl)-4-methoxy-piperidine* (**39**) (20mg, 7%) as a colourless oil; R_f 0.13 (ethyl acetate: methanol: ammonia; 93:5:2); ν_{max} (neat)/cm^{-1} 3077w, 2932s, 2857m, 2814m, 1641m, 1457m, 1098s, 994m, 909s; δ_H (500MHz; C_6D_6) 1.35-1.40 (2H, m, $NCH_2CH_2CH_2$), 1.42-1.46 (2H, m, $NCH_2CH_2CH_2$), 1.48-1.54 (2H, m, C(5)H and C(3)CH), 1.64-1.71 (1H, m, C(3)CH), 1.73-1.80 (2H, m, C(3)H and C(5)H), 1.99 (2H, pseudo q, *J*7.5Hz, $NCH_2CH_2CH_2CH_2$), 2.05 (2H, pseudo q, *J*7.5Hz, C(3)CH_2CH_2), 2.23 (2H, t, *J*7Hz, $NCH_2CH_2CH_2$), 2.33-2.35 (4H, m, C(2)H_2 and C(6)H_2), 3.07 (3H, s, OCH_3), 3.09-3.11 (1H, m, C(4)H), 4.98 (2H, d, *J*10Hz, both CH=CH_2*trans*), 5.04 (2H, pseudo t d, *J*17, 2Hz, both CH=CH_2*cis*), 5.73-5.85 (2H, m, both CH=CH_2); δ_C (125.8MHz; C_6D_6) 27.02 and 27.11 ($NCH_2CH_2CH_2$), 28.09 (C5 and C(3)CH_2), 31.84 (C(3)CH_2CH_2), 34.07 ($NCH_2CH_2CH_2CH_2$), 39.74 (C3), 49.61 (C6), 55.04 (C2), 55.75 (OCH_3), 58.75 ($NCH_2CH_2CH_2$), 76.85 (C4), 114.51 and 114.58 (both CH=CH_2), 139.12 and 139.38 (both CH=CH_2); *m/z* (chemical ionisation, NH_3) 252 (MH^+, 100%), 182 (23); HRMS found 252.2327; $C_{16}H_{30}NO$ (MH^+) requires 252.2327.

To hinder the fluxional nature of *(±)-cis-3-(but-3-enyl)-1-(hex-5-enyl)-4-methoxy-piperidine* (**39**) the tertiary amine was protonated with trifluoroacetic acid (6.1µl) in water (5ml) and freeze dried to give the trifluoroacetic acid salt as a colourless oil; δ_H (500MHz; $CDCl_3$) 1.29-1.36 (1H, m, C(3)CH), 1.41-1.47 (2H, m, $NCH_2CH_2CH_2$), 1.50-1.57 (1H, m, C(3)CH), 1.72-1.78 (2H, m, $NCH_2CH_2CH_2$), 1.97-2.16 (7H, m, C(3)H, C(5)H_2, both CH_2CH=CH_2), 2.70 (1H, pseudo q, *J*11.5Hz, C(2)H), 2.84-2.91 (1H, m, C(6)H), 2.94-2.98 (2H, m, $NCH_2CH_2CH_2$), 3.26 (1H, br d, *J*11.5Hz, C(2)H), 3.35 (3H, s, OCH_3), 3.41 (1H, br d, *J*12Hz, C(6)H), 3.46 (1H, s, C(4)H), 4.98-5.05 (4H, m, both CH=CH_2), 5.15 (1H, br s, NH), 5.70-5.81 (2H, m, both CH=CH_2).

Further chromatography of the residue from reactions where the reduction was carried out at room temperature afforded the reduced bi-pyridyl **40** as a colourless oil; R_f 0.14 (Al_2O_3; dichloromethane: diethyl ether; 9:1); ν_{max} (neat)/cm^{-1} 3076m, 2976m, 2932s, 2856m, 2803m, 2764m, 1641m, 1440m, 1416m, 993m, 909s; δ_H (500MHz; $CDCl_3$) 1.14-1.22 (2H, m, C(7)H and C(8)CH), 1.33-1.43 (5H, m, C(12)H and 2 x $NCH_2CH_2CH_2$), 1.48-1.61 (7H, m, 2 x NCH_2CH_2, C(12)H, C(8)H and C(9)H), 1.64-1.69 (1H, m, C(8)CH), 1.79 (1H, pseudo t d, *J*11, 2Hz, C(11)H), 1.95-2.00 (2H, m, one of C(8)CH_2CH_2 and C(2)H), 2.03-2.13 (7H, m, C(5)H_2, 2 x $NCH_2CH_2CH_2CH_2$ and one of C(8)CH_2CH_2), 2.15-2.20 (2H, m, C(5)CH_2CH_2), 2.26-2.32 (2H, m, N(10)CH_2), 2.37 (2H, t, *J*7.5Hz, N(1)CH_2), 2.57 (1H, br d, *J*15.5Hz, C(6)H), 2.68 (1H, dd, *J*11, 5.5Hz, C(2)H), 2.77 (1H, br s, C(3)H), 2.91 (1H, br d, *J*10.5Hz, C(11)H), 2.98 (1H, d, *J*9.5Hz, C(9)H), 3.02 (1H, d, *J*15.5Hz, C(6)H), 4.93-5.02 (8H, m, 4 x CH=CH_2), 5.17 (1H, s, C(4)H), 5.76-5.84 (4H, m, 4 x CH=CH_2); δ_C (125.8MHz; $CDCl_3$) 22.98 (2 x $NCH_2CH_2CH_2$), 26.19 (C12), 26.45 (2 x NCH_2CH_2), 29.92 (C8), 30.62 (C(8)CH_2CH_2), 32.00 (C(5)CH_2CH_2), 33.65 (2 x $NCH_2CH_2CH_2CH_2$), 34.58 (C(5)CH_2), 35.28 (C3), 36.71 (C8), 43.85 (C7), 50.82 (C2), 54.36 (C11), 55.95 (C6), 58.50 (N(10)CH_2), 58.99 (N(1)CH_2), 59.58 (C9), 114.45 (4 x CH=CH_2), 124.44 (C4), 135.82 (C5), 138.37 (C(8)CH_2CH_2CH), 138.74 (3 x CH=CH_2); *m/z* (chemical ionisation, NH_3) 439 (MH^+, 88%), 397 (25), 220 (54), 218 (100), 178 (79), 152 (35), 138 (44), 112 (47); HRMS found 439.4052; $C_{30}H_{51}N_2$ (MH^+) requires 439.4052.

*Synthesis of cycloadduct **38** in a 1:1 water: ethanol solvent mixture*

To a stirred solution of (±)-3-(but-3-enyl)-1-(hex-5-enyl)-1,2,5,6-tetrahydropyridine-2-carbonitrile (**36**) (107mg, 0.438mmol) in absolute ethanol (2ml) was added silver trifluoroacetate (96.8mg, 0.438mmol). After 5 minutes stirring under argon, AgCN was filtered off through Celite® and washed with ethanol (2ml). To the stirred filtrate was added to a 1:1 water: ethanol solution of TRIS buffer (0.5M, pH 8.3, 10ml) and stirring was kept under argon for 1 hour. The solution was cooled to -78°C and methanol was added (10ml) before sodium borohydride (49.7mg, 1.31mmol) was added and stirred for 10 minutes. The reaction mixture was allowed to warm up to room temperature over 30 minutes. The solution was then partitioned between water (20ml) and dichloromethane (20ml), separated, and the aqueous layer extracted with dichloromethane (3 x 20ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil (97.2mg). Kugelrohr distillation served to remove the more volatile *5-(but-3-enyl)-1-(hex-5-enyl)-1,2,3,6-tetrahydropyridine* (**34**) (55mg, 57%) cleanly as a colourless oil, and the residue was purified by flash chromatography (SiO_2; dichloromethane: methanol; 97:3) to afford the cycloadduct **38** (21.4mg, 22%) as a colourless oil.

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