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Total Synthesis of Micropine and Epimicropine

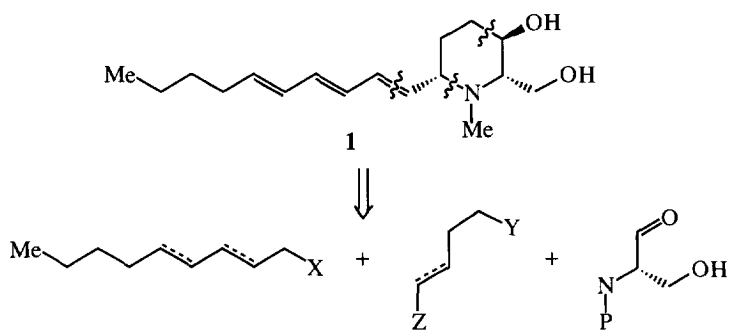
Aristea V. Bayquen and Roger W. Read*

School of Chemistry, The University of New South Wales, Sydney NSW 2052, Australia

Abstract: The enantioselective total synthesis of micropine, an unusual 2,6-disubstituted piperidine alkaloid, and epimicropine, through mercuric trifluoroacetate-catalysed intramolecular alkenylamide cyclisation is described. The synthesis proceeds from *L*-serine and affords material of the same positive sign of optical rotation as the natural product thereby confirming the absolute stereochemistry of micropine. Copyright © 1996 Published by Elsevier Science Ltd

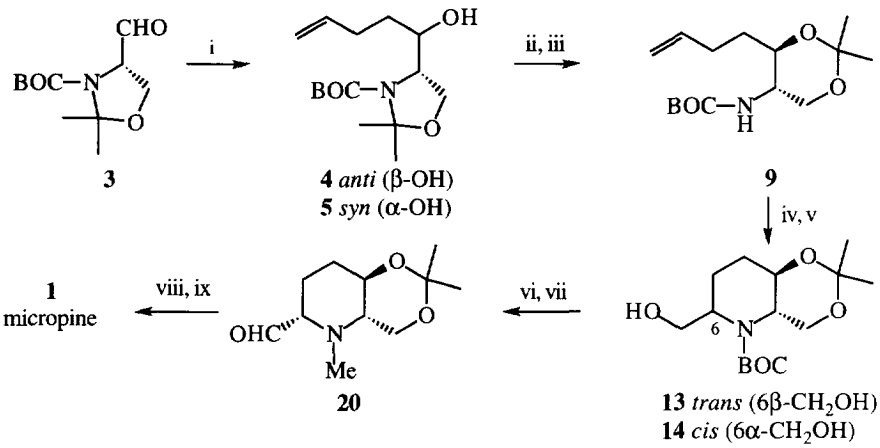
Micropine **1** is an unusual piperidine alkaloid, isolated from the leaves of *Microcos philippinensis* (Perk.) Burrett (Tiliaceae), a plant whose ethanol extracts show antimicrobial activity.[1,2] Its structure was elucidated by a combination of spectroscopic methods but, while micropine was optically active, its absolute configuration was not assigned.[2] The compound is most closely related to cryptophorine, but the two differ in the degree of unsaturation of the alkenyl chain, the oxidation level of the C2 substituent, the configuration at C3, and the sign of optical rotation.[3] The following synthesis was undertaken in order to confirm the structure of micropine and to determine its absolute stereochemistry.

A review of synthetic methods directed towards piperidines provided no one method that was suitable. Consideration of the retrosynthesis illustrated in Scheme 1, which utilises features of the strategies of Saitoh[4,5] and Takahata,[6] provided insight into the ultimately successful strategy that is shown in Scheme 2.



Scheme 1

The synthesis was designed to give enantiomerically pure material, and takes chirality from *L*-serine. It involves three key steps, namely, assembly of the piperidine carbons with 1,2-asymmetric induction, intramolecular amidocyclisation, and Wadsworth-Horner-Emmons attachment of the sidechain.



Reagents: i. CH_2=$CHCH_2CH_2MgBr$, THF; ii. Amberlyst 15, MeOH; iii. $Me_2C(OMe)_2$, PPTS, CH_2Cl_2; iv. (a) $Hg(OCOCF_3)_2$, THF; (b) $NaHCO_3$, KBr; v. O_2, $NaBH_4$, DMF; vi. $LiAlH_4$, ether; vii. $(COCl)_2$, DMSO, Et_3N; viii. $CH_3(CH_2)_3(CH)_4CH_2P(O)(OEt)_2$, KH, THF; ix. H_2SO_4, MeOH.

Scheme 2

The serine-derived Garner aldehyde **3**[7] provided an attractive starting point for the synthesis since it reacts with organometallic reagents with high diastereoselectivity and little racemization.[8,9] Most additions proceed with *anti*-stereoselectivity but *syn*-addition is possible through use of alkyl-Cu[9,10] and -Mn reagents[10] or addition of Lewis acids.[11]

In our hands, but-3-enyllithium in THF (best prepared from 4-bromobut-1-ene and *t*-BuLi) in the presence of HMPA gave low to moderate yields of diastereomeric alcohols **4** and **5** and up to 4:1 preference for the *anti* isomer (Table 1); notably, without the addition of HMPA, the reagent did not give the products at all. The Grignard reagent was much easier to prepare than the organolithium compound and gave excellent chemical yields of **4** and **5**, but the *anti*/*syn* isomer ratio was decreased (3:2); a cerium trichloride modified reagent gave marginally lower yields of the same products while the addition of copper (I) salts afforded equally high chemical yields as the Grignard reagent but an inverse diastereomer ratio.

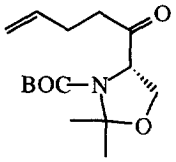
Table 1. Reaction of Aldehyde **3** with But-3-enylmetal Reagents.

Entry	Organometallic reagent		Additive (mol equiv)	Temperature (Time)	% Yield (**4** + **5**) (diastereomer ratio)
	RLi mol equiv	RMgBr mol equiv			
1	1.25	–	HMPA (1.25)	-78°C (2h) - r.t. (o/n)	14 (2:1)[a]
2	2.0	–	HMPA (1.25)	-78°C (3h) - r.t. (1h)	42 (4:1)[b]
3	2.0	–	HMPA (1.25)	-78°C (2h) - r.t. (o/n)	26
4	–	4.0	–	–78°C (2h)	98 (3:2)[b]
5	–	2.0	–	-78°C (2h)	98
6	–	1.5	$CeCl_3$ (1.6)	-40°C (4.5h) - r.t. (o/n)	85
7	–	2.0	CuI (3.0) / Me_2S	-40°C (1h) - r.t. (o/n)	96 (1:3)[b]

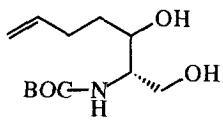
a Based on the percentage yields of isolated acetonide derivatives.

b Based on analysis of the ^{13}C NMR spectrum of the acetonide derivatives.

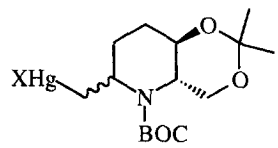
Failure to secure a direct, high yielding route to **4** prompted us to adopt the successful Grignard reaction in an indirect approach. Swern oxidation of the resulting mixture of **4** and **5** proceeded in 94% yield to give a single ketone **6**, which with $Zn(BH_4)_2$ in diethyl ether gave almost exclusively the desired *anti* isomer **4** in 96-99% yield. This pleasing outcome is consistent with currently accepted models of chelation, which portray the metal coordinated to the ketone and *N*-BOC groups in the transition state.



6



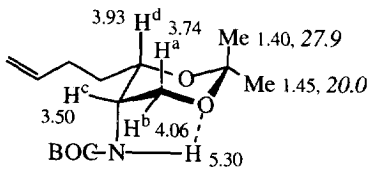
7 *anti* (β-OH)
8 *syn* (α-OH)



15 X = Cl
16 X = Br

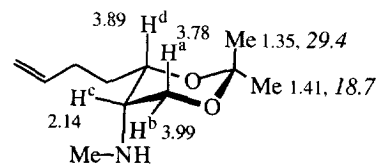
Diastereomers **4** and **5** could not be separated by chromatography, nor could their ratios be measured directly by ^1H or ^{13}C NMR analysis because of complexities caused by restricted rotation about their carbamate C–N bonds. Instead, the diastereomeric mixtures, or enriched samples of **4** from ketone **6**, were converted to the corresponding *anti* and *syn* 1,3-diols, **7** and **8**, and thence their acetonides **9** and **10**, respectively (Scheme 2). These substances could then be separated by repeated chromatography. The less polar *syn*-acetonide **10** was isolated as an oil while the more polar *anti*-acetonide **9** was secured as needles, m.p. 65-66°C.

Assignment of isomer configuration was possible through ^1H NMR spectroscopic analysis. In particular, the proton adjacent to nitrogen, at C5, in **10** was spin coupled to the well dispersed methylene protons at C6 and the methine proton at C4 with very small and near identical values (Figure 1), indicative of the equatorial arrangement of the proton. Similar behaviour was exhibited by the corresponding *N*-methyl derivative **11** which was derived by $LiAlH_4$ reduction of **10**. The configuration of acetonide **9** and the corresponding *N*-methyl derivative **12** could only be deduced because in the NMR spectrum of **9** the H4, H5 and H6 signals were inexplicably broad, and in **12**, the H5 and H6 signals were severely overlapped with each other, so that couplings could not be deciphered.



$J_{a,c} = J_{b,c} = J_{c,d} = 1.8$ Hz
$J_{c,NH} = 10.0$ Hz

10



$J_{a,c} = J_{b,c} = 1.8$ Hz; $J_{c,d} = 2.1$ Hz

11

Figure 1. Selected ^1H and ^{13}C (in italics) NMR spectroscopic data for acetonides **10** and **11**

The diastereomeric ratio of **9** and **10** was measured by integration of the N-H signals in the NMR spectrum. The *anti* isomer **9** consistently gave a broad singlet at δ 4.40, while the N-H signal from the *syn* isomer resonated at δ 5.30 as a doublet, perhaps a reflection of H–bonding to the neighbouring acetal oxygen. The ratios of ^{13}C NMR signals, especially those from the carbons bearing oxygen and nitrogen (δ 40-75), indicated similar proportions of products. Since the ratio of **9** to **10** was highly dependent on the method used

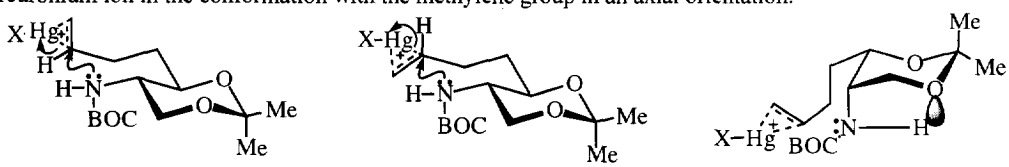
to prepare the alcohol precursors, and the stereochemical outcome was consistent with current understanding of asymmetric induction, it was assumed that the ratio of **9** and **10** reflected the ratio of **4** and **5**.

Nitrogen heterocycles have been prepared through intramolecular alkenylamino- and alkenylamido-cyclisation, many reactions yielding piperidine skeletons.[12] A mercury(II)-catalysed cyclisation, which would afford an hydroxymethyl piperidine derivative following reductive and then oxidative workup, was attractive in the synthesis of micropine **1** since it was proposed to attach the alkatrienyl sidechain through Wittig chemistry using the piperidine moiety as the electrophilic component.

Treatment of amidoalkene **9** with $Hg(OCOCF_3)_2$ according to Scheme 2 gave a 60:40 mixture of diastereomeric alcohols **13** and **14** in 40% yield. This result compared favourably with the outcome of the $Hg(OCOCH_3)_2$ catalysed reaction, which proceeded with noticeably lower conversion, 22% yield, and slightly decreased diastereomer ratio (56:44) of **13** and **14**. $Hg(OCOCF_3)_2$ was therefore the better of the two catalysts. Similar treatment of the unwanted amidoalkene **10** with either catalyst gave complex mixtures from which only trace amounts of the desired alcohols could be detected.

Interruption of the Hg^{2+} catalysed process before the second stage of reaction with oxygen and $NaBH_4$ gave a minor amount of an isolable organomercury intermediate, which was identified as the chloromercury derivative **15** rather than its bromo analogue **16**. The presence of chlorine in place of bromine was unexpected but was evident from elemental analysis. The source of the chlorine was traced to the use of brine washes during workup. Halide exchange is therefore facile and future applications of this method might be improved if chloride was excluded.

The modest diastereoselectivity towards the *trans* isomer in the cyclisation of *anti*-acetonide **9** probably reflects the stabilities of the transition states (Figure 2), favouring attack by the amido group on the bridged mercuronium ion in the conformation with the methylene group in an axial orientation.



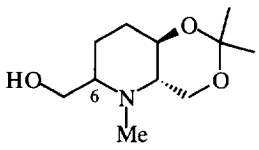
leading to *trans*-**15/16** leading to *cis*-**15/16** from *syn* isomer **10**

Figure 2

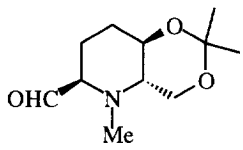
The low yield and complexity of the products from *syn* alkenylamide **10** are puzzling. The amido group, while present in an axial orientation in the ground state of the alkene (from NMR data), probably interacts with the axial non-bonded electrons on the neighbouring ring oxygen through H-bonding. This might limit the conformational freedom of the amido group, thereby preventing, in the transition state, the correct orientation of its nitrogen lone-pair for cyclisation, thereby opening the possibility for other reaction pathways.

Despite poor stereoselectivity during the ring closure reaction, it was anticipated that conversion of the hydroxymethyl group from either isomer into an aldehyde would result in an epimerisation that would provide the desired stereochemistry at the new centre.

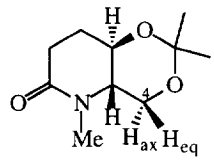
However, before the alcohols were oxidized it was decided to transform the *N*-BOC group into an *N*-Me group. This was achieved from a 75:25 mixture of **13** and **14** by reduction using $LiAlH_4$. The reaction in ether afforded a 70:30 mixture of *trans* and *cis* *N*-methyl derivatives **17** and **18**, respectively, in 52% yield. The mixture was then subjected to Swern oxidation to yield the corresponding aldehydes **19** and **20** in 69% yield as an equimolar mixture after chromatography on silica gel.



17 *trans* (6β-CH_2OH)
18 *cis* (6α-CH_2OH)



19

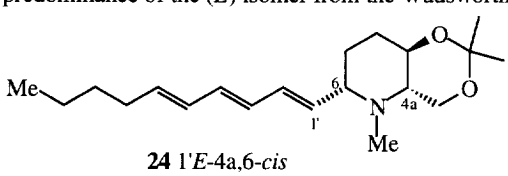


28

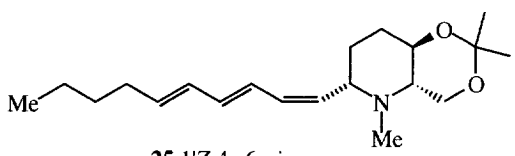
Some epimerisation had clearly taken place, but diminished sample quantity prevented the exploration of this phenomenon. Instead, the alkenyl side chain of micropine was introduced immediately with a view to generating 2,6-*cis* and 2,6-*trans* isomers for spectroscopic comparison.

Diethyl (2*E*,4*E*)-nonadienylphosphonate **21** was prepared in a short synthetic sequence from commercially available (2*E*,4*E*)-nonadienal through $NaBH_4$ reduction, conversion of alcohol **22** to the chloride **23** by treatment with $SOCl_2$, and subsequent reaction with triethyl phosphite. The (*E,E*) configuration of the dienylphosphonate **21** was readily confirmed from the ^1H NMR spectrum. The signals for H2 and H5 resonated at δ 5.45 and 5.59 as doublets of triplets with doublet couplings of 14.6 Hz and 14.9 Hz, respectively, entirely consistent with (*E*) geometry in each double bond.

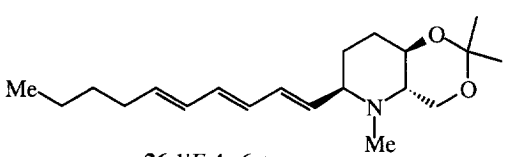
The alkenyl side chain was now ready to be added to the piperidine portion. An 80:20 enriched sample of *trans* and *cis* aldehydes **19** and **20**, upon treatment with a mixture of phosphonate **21** and KH, gave four products, presumed to be a mixture of the (*E*) and (*Z*) isomers of both *cis* and *trans* isomeric piperidine alkaloids **24-27**. Separation by chromatography gave pure samples of the major components, identified as the (1'*E*,*trans*) and (1'*E*,*cis*) isomers **26** and **24** (present in a ratio of 74:26 in the crude mixture), and one other substance that could not be purified, appeared to remain as two isomers and could not therefore be confirmed as isomer **27**. A similar reaction, performed on the pure *cis* aldehyde **20**, then yielded a 29:7:64 mixture of (1'*E*,*cis*) and (1'*Z*,*cis*) amines **24** and **25**, and lactam **28**. All these compounds were separable with some difficulty, and their spectra were consistent with retention of configuration about the piperidine ring and predominance of the (*E*) isomer from the Wadsworth-Horner-Emmons reactions.



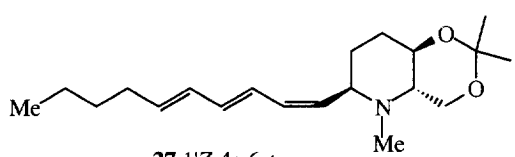
24 1'*E*-4a,6-*cis*



25 1'Z-4a,6-*cis*



26 1'*E*-4a,6-*trans*



27 1'Z-4a,6-*trans*

Formation of lactam **28** was unexpected. It might have arisen during the coupling process through oxidative decarbonylation of aldehyde **20** with concomitant reduction of the phosphonate reagent.

Provision of compounds **24-26** made it possible to identify the chemical shifts of H4a, H6 and H1' as important spectroscopic features that were sensitive to *cis*/*trans* stereochemistry of substituents next to the piperidine nitrogen; significant downfield shifts of the proton signals were observed in the *trans* isomer (Table 2). The chemical shift of H6 was also unexpectedly influenced by the C1'-C2' alkene geometry of the *cis*

isomers. However, the chemical shift of H1', and of course the magnitude of its spin coupling to H2', provided more reliable indicators of alkene configuration.

Deacetonation of **24** and **26** was achieved by treatment separately with conc. H_2SO_4 in methanol at r.t. overnight. The reactions yielded isomeric diols in 88 and 96% yield, respectively. The crystalline diol **1** (m.p. 143-145°C) from acetonide **24** was identical to natural micropine **1**, (m.p. 146-148°C) in its ^1H NMR, ^{13}C NMR and mass spectroscopic properties. The optical rotation of the chromatographically pure, but unrecrystallized synthetic micropine was measured as $[\alpha]_D^{21}$ -49° (EtOH, c. 0.08), which compared favourably with that of natural micropine, $[\alpha]_D^{20}$ -63° (EtOH, c. 0.15), and thereby established the absolute stereochemistry of the natural material.

Table 2. Selected ^1H NMR Spectroscopic Data for Acetonides **24 - 26**

	E-cis **24**		*Z-cis* **25**		*E-trans* **26**	
	δ	multiplicity (Hz)	δ	multiplicity (Hz)	δ	multiplicity (Hz)
N-Me	2.10	s	2.11	s	2.13	s
$H_{ax}4$	3.72	dd, 11.0, 10.5	3.73	dd, 11.0, 10.5	3.69	dd, 11.0, 10.5
$H_{eq}4$	4.03	dd, 11.0, 4.6	4.04	dd, 11.3, 4.6	3.91	dd, 11.0, 4.9
H4a	1.97	ddd, 10.2, 9.8, 4.6	2.01	ddd, 10.5, 9.5, 4.6	2.51	ddd, 10.3, 9.5, 4.9
H6	2.50	ddd, 9.9, 9.2, 3.2	2.99	m	3.28	m
H8a	3.67	ddd, 10.5, 9.5, 3.7	3.68	m	3.71	m
H1'	5.45	dd, 14.4, 9.0	5.22	dd, 10.3, 10.0	6.00	dd, 14.6, 9.0
H6'	5.71	dt, 14.9, 7.2	5.74	dt, 14.4, 6.9	5.71	dt, 14.9, 7.4

In contrast, the isomeric diol (named epimicropine) **29** from acetonide **26** was not crystalline. It was isolated as a gum which was more polar than **1** from TLC analysis. The ^1H NMR spectrum of the (*E*)-*trans* isomer **29** was quite different from that of the (*E*)-*cis* isomer **1**. It showed the H6 resonance at δ 3.40 compared to that of **1** at δ 2.60. The higher chemical shift in **29** indicated that H6 was equatorially disposed on the ring, as was the case in its precursor **26**. As a corollary, the unsaturated side chain of **29** was in an axial orientation, and because of this, other protons in the piperidine ring were of different chemical shift compared to those of **1**. In addition, the signals for H1" of **29** and **1** (δ 5.83 and 5.47, respectively) were sufficiently well separated from other signals to enable complete analysis of their spin coupling pattern. The *E* configuration of the two C1"-C2" bonds was readily confirmed from the large proton-proton coupling constants ($J_{H1"-H2"}$ 15.1 and 15.1 Hz, respectively).

The successful approach to micropine described in this paper is versatile and should enable analogues of micropine with varying side chains of differing oxidation levels to be prepared from the advanced intermediate **20**. Isomeric intermediates have also been synthesized and characterised. These might be useful in future in the synthesis of piperidine alkaloids that are stereochemically related to micropine.

Acknowledgement. AVB wishes to thank AIDAB, the Australian International Development Assistance Bureau, for the award of a postgraduate research scholarship and The University of Santo Tomas for leave of absence.

EXPERIMENTAL

General. All commercial materials were used as received except where indicated. Melting points were determined on a Mel-Temp or a Kofler hot-stage melting point apparatus and are uncorrected. Elemental microanalyses were performed by Dr P.H. Pham of the School of Chemistry Microanalytical Laboratory. Infrared spectra were recorded on an Hitachi 260-10 or a Perkin-Elmer 298 spectrophotometer. Routine ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC300F instrument and at 500 MHz on a Bruker AM500 or Avance DRX500 spectrometer. Unless otherwise stated, data refer to solutions in $CDCl_3$ with the residual solvent protons as internal reference. ^{13}C NMR spectra were measured at 75.47 MHz on the Bruker AC300F and at 125.76 MHz on the Bruker AM500 spectrometer. Chemical shifts were in parts per million (δ) relative to solvent nuclei as an internal reference. C-H correlations were carried out with inverse detection on the 500 MHz spectrometers at 300 K using the Bruker automation program XHCORR.AU. Proton-proton correlations were recorded using the program DQF-COSY. Routine mass spectra were recorded on a VG Quattro spectrometer at 70 eV ionizing potential and 8000 V accelerating voltage with an ion source temperature of 210°C, while high resolution mass spectra were recorded at the UNSW Biomedical Mass Spectrometry Unit on a VG Autospec Q instrument. Optical rotation was measured on a Jasco DIP-1000 digital polarimeter. Flash column chromatography was carried out using Merck silica gel 60 (Art. No. 9385) 230-400 mesh. Preparative thin layer chromatography was performed on 1 mm thick plates using Merck silica gel $60GF_{254}$ (Art. No. 7730). Anhydrous solvents were dried and distilled according to literature methods.

Reactions of (*S*)-3-(*t*-Butyloxycarbonyl)-2,2-dimethyloxazolidine-4-carboxaldehyde 3

a. With butenyllithium

t-BuLi (8.2 mL of 1.7M, 14.0 mmol) was added dropwise to a stirred solution of 4-bromo-1-butene (0.71 mL, 7.0 mmol) in THF (8 mL) at –78°C. After 5 min., HMPA (0.76 mL, 4.37 mmol) was added, followed by a solution of **3** (0.800 g, 3.50 mmol) in THF (4 mL). After 3 h at –78°C and 1 h without cooling, sat. NH_4Cl solution (10 mL) was added to the mixture, followed by water (20 mL). The product was extracted with ether, the extracts washed with brine, dried, and evaporated to afford a pale yellow, viscous oil (0.937 g). Flash column chromatography using 1:4 EtOAc-light petroleum afforded the major product *(4*S*,1*'R*)-3-(*t*-butyloxycarbonyl)-2,2-dimethyl-4-(1'-hydroxypent-4-enyl)-1,3-oxazolidine* **4** as a colourless gum (0.419 g, 42%) (Found: C, 63.40; H, 9.24; N, 4.96. $C_{15}H_{27}NO_4$ requires: C, 63.16; H, 9.47; N, 4.91%). ν_{max} (film) 3450, 3070, 2978, 2930, 2880, 1670, 1478, 1450, 1388, 1368, 1250, 1200, 1170, 1090, 1068, 995, 910, 845, 805, 768 cm^{-1}. ^{1}H NMR δ: 1.49, s, $CO_2C(CH_3)_3$; 1.44, s, 2-$(CH_3)_a$; 1.45, s, 2-$(CH_3)_b$; 1.58, m, $(H2')_2$; 2.15, m, H_a3'; 2.30, m, H_b3'; 3.82, br m, H4; 3.74, dd, *J* 12.0, 1.8 Hz, H_a5; 4.05, dd, *J* 12.0, 2.1 Hz, H_b5; 3.49, dt, *J* 10.0, 2.1 Hz, H1'; 4.97, m, $H_{trans}5'$; 5.09, m, $H_{cis}5'$; 5.82, m, H4'. ^{13}C NMR δ: 29.7, 2-$(CH_3)_a$; 30.9, 2-$(CH_3)_b$; 28.4, $CO_2C(\underline{C}H_3)_3$; 30.3, C2'; 33.5, C3'; 46.9 or 54.9, C4; 62.7 or 65.5, C5; 70.5 or 73.8, C1'; 79.8, $O\underline{C}(CH_3)_3$; 99.3, C2; 115.3, C5'; 138.1, C4'; 156.0, $N\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 286 (M^+, 2%), 230 (13), 200 (11), 170 (16), 144 (29), 100 (48), 83 (12), 59 (11), 57 (100), 55 (7).

b. With butenylmagnesium bromide

(i) 4-Bromo-1-butene (0.75 mL, 7.4 mmol) was added to Mg turnings (0.181 g, 7.4 mmol) in THF (5 mL). The mixture was refluxed for 40 min. then cooled to r.t. and placed in a bath at –78°C. Aldehyde **3** (1.710 g, 7.4 mmole) in THF (5mL) was added and the mixture stirred for 40 min. at –78°C. The mixture was then allowed to come to r.t., poured into water and extracted with ether. The extracts were washed with brine, dried, and evaporated to afford a yellow oil (1.66 g, 78%). Repeated preparative TLC (EtOAc-hexane, 1:5) afforded the major product *(4*S*,1*'R*)-3-(*t*-butyloxycarbonyl)-2,2-dimethyl-4-(1'-hydroxypent-4-enyl)-1,3-oxazolidine* **4** as a

yellow oil (0.097 g), (Found: C, 62.76; H, 9.22; N, 4.98. $C_{15}H_{27}NO_4$ requires: C, 63.16; H, 9.47; N, 4.91%). ν_{max} (film) 3445, 3080, 2980, 2935, 2880, 1735, 1678, 1480, 1452, 1362, 1250, 1202, 1165, 1080, 995, 908, 845, 810, 770, 735 cm^{-1}. ^1H NMR ($C_6D_5CD_3$, 100°C) Major component δ: 1.40, s, $CO_2C(CH_3)_3$; 1.46, s, 2-$(CH_3)_a$; 1.4-1.6, m, H_a2' and H_b2'; 1.59, s, 2-$(CH_3)_b$; 2.08-2.21, m, H_a3'; 2.5-2.33, m, H_b3'; 2.45, br s, H4 or OH; 3.66, d, *J* 3.8 Hz, OH or H4; 3.67, dd, *J* 8.9, 6.9 Hz, H_a5; 3.76, dd, *J* 9.0, 2.9 Hz, H_b5; 3.76-3.83, m, H1'; 4.95, dm, *J* 10.2 Hz, $H_{trans}5'$; 5.04, dm, *J* 17.1 Hz, $H_{cis}5'$; 5.83, ddt, *J* 17.1, 10.2 Hz, H4'. Minor component δ: 1.37, s, 2-$(CH_3)_a$; 1.41, s, $COC(CH_3)_3$; 1.4-1.6, m, H_a2' and H_b2'; 1.61, s, 2-$(CH_3)_b$; 2.08-2.21, m, H_a3'; 2.25-2.33, m, H_b3'; 2.80, br s, H4 or OH; 3.62, dd, *J* 9.4, 7.5 Hz, H_a5; 3.66, m (obscured), OH or H4; 3.71, d, *J* 9.1, 3.6 Hz, H_b5; 3.76-3.83, m, H1'; 4.95, dm, *J* 10.3 Hz, $H_{trans}5'$; 5.03, dm, *J* 17.2 Hz, $H_{cis}5'$; 5.82, ddt, *J* 17.2 Hz, *J* 10.3, 6.6 Hz, H4'. ^{13}C NMR δ: 26.4, 2-$(CH_3)_2$; 28.4, $OC(\underline{C}H_3)_3$; 30.2, C3' and/or C2'; 62.3, C4; 64.8, C5; 72.5, C1'; 81.1, $O\underline{C}(CH_3)_3$; 94.3, C2; 114.8, C5'; 138.5, C4'; 154.4, $N\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 285 (M^+, absent), 270 (trace), 258 (trace), 230 (1%), 200 (3), 170 (3), 144 (8), 100 (28), 57 (100).

(ii) In the presence of CuI. 4-Bromo-1-butene (1.67 mL 16.50 mmol) was added to a suspension of Mg turnings (0.401 g, 16.50 mmol) in THF (100 mL) and the mixture was heated at reflux for 5 h. The mixture was cooled to r.t., CuI which had been powdered and dried in the oven at 50°C (4.71 g, 24.8 mmol) was added, and the mixture cooled to –78°C. Me_2S (10 mL) was added and after 5 min., the mixture warmed to –40°C for 25 min. then returned to –78°C. A solution of the aldehyde **3** (1.280 g, 5.59 mmol) in THF (10 mL) was added dropwise to the mixture, which was warmed to –40°C for 2 h, allowed to come to r.t. overnight, and quenched with sat. NH_4Cl solution (100 mL) then H_2O (350 mL). The mixture was extracted with ether, the organic layer washed with 0.5 N HCl and brine, dried, and evaporated to afford a yellow oil (1.430 g). The residue was flash column chromatographed using 25-50% ether-hexane and the major component distilled to give *(4S,1'S)-3-(t-butyloxycarbonyl)-2,2-dimethyl-4-(1'-hydroxypent-4'-enyl)-1,3-oxazolidine* ***5*** as a yellow oil (0.297 g; 19%) b.p. 170°C / 0.75 mmHg, (Found: C, 62.90; H, 9.54; N, 4.96. $C_{15}H_{27}NO_4$ requires: C, 63.16; H, 9.47; N, 4.91%). ν_{max} (film) 3470, 3075, 2975, 2938, 2880, 1695, 1478, 1450, 1395, 1389, 1368, 1310, 1258, 1205, 1174, 1108, 1085, 1063, 995, 948, 915, 875, 855, 808, 770 cm^{-1}. ^1H NMR δ: 1.35-1.65, m, $(H2')_2$; 1.48, s, $OC(CH_3)_3$; 1.49, s, 2-$(CH_3)_a$; 1.58, s, 2-$(CH_3)_b$; 2.17, m, H_a3'; 2.29, m, H_b3'; 3.72, br m, H1'; 3.82, br m, H4; 3.90-3.97, m, $(H5)_2$; 4.97, dm, *J* 10.2 Hz, H_{trans} 5'; 5.04, ddt, *J* 16.9, 1.7, 1.8 Hz, $H_{cis}5'$; 5.83, ddt, *J* 16.9, 10.2, 6.7 Hz, H4'. ^{13}C NMR δ: 24.3, 2-$(CH_3)_a$; 27.1, 2-$(CH_3)_b$; 28.4, $OC(\underline{C}H_3)_3$; 29.6, C2'; 33.9, C3'; 62.3, C4; 64.9, C5; 73.6, C1'; 81.2, $O\underline{C}(CH_3)_3$; 94.1, C2; 114.8, C5'; 138.5, C4'; 155.2, $N\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 285 (M^+, absent), 258 (M-27, 1%), 230 (0.6), 212 (0.7), 200 (7), 174 (6), 144 (10), 100 (31), 57 (100).

(iii) In the presence of $CeCl_3$. The Grignard reagent prepared from 4-bromo-1-butene (0.17 mL, 1.65 mmol) and Mg turnings (0.040 g, 1.65 mmol) in THF (5 mL), was added to anhydrous $CeCl_3$ (0.615 g, 1.65 mmol) in THF (6 mL) under argon at r.t. The white suspension was stirred at –78°C for 30 min. before aldehyde **3** (0.252 g, 1.10 mmol) in THF (2 mL) was added. The mixture was stirred at –40°C for 4.5 h, allowed to warm to 0°C for 1.5 h, then left overnight at r.t. Sat. NH_4Cl solution (17 mL) and H_2O (17 mL) were added, and the mixture was extracted with ether. The extracts were washed with 0.5 M HCl and brine, dried, and evaporated to afford the major product, alcohol **5**, as a yellow oil (0.265 g, 85%). The ^1H NMR spectrum was similar to that of the product from part ii.

(4*S*,1'*S*)-3-(*t*-Butyloxycarbonyl)-2,2-dimethyl-4-(pent-4'-enoyl)oxazolidine 6

Distilled DMSO (0.5 mL, 7.1 mmol) was added to precooled oxalyl chloride (0.46 mL, 5.3 mmol) in CH_2Cl_2 (92 mL) at –78°C. A 60:40 mixture of alcohols **4** and **5** (1.00 g, 3.5 mmol) in CH_2Cl_2 (60 mL) was added dropwise and the solution stirred at –78°C for 2 h, then Et_3N (1.96 mL, 14.0 mmol) was added and the cooling bath was removed. After 10 min., water (160 mL) was added, the pH of the solution was adjusted to *ca.* 11 with aq. NH_3, and the solution was extracted with CH_2Cl_2. The extracts were washed successively with water and brine, dried over $MgSO_4$, and evaporated to afford a semi-solid (1.12 g). The product was extracted

into light petroleum to afford a yellow oil (0.93 g, 93%) which was flash column chromatographed using EtOAc-light petroleum (1:4) to afford *(4S,1'S)-3-(t-butyloxycarbonyl)-2,2-dimethyl-4-(pent-4'-enoyl)oxazolidine* **6** as a yellow oil (0.46 g, 46%) (Found: *m/z* 283.1785. $C_{15}H_{25}NO_4$ requires *m/z* 283.1784). ν_{max} (film) 3085 (m), 2985, 2940 (m), 1715, 1648 (m), 1482 (m), 1460 (m), 1395, 1385, 1370, 1270, 1250, 1210 (m), 1172, 1090, 1062, 915, 852, 770 cm^{-1}. ^1H NMR analysis revealed two amide rotomers in the ratio 58:42; δ (major isomer): 1.39, s, $OC(CH_3)_3$; 1.51, s, 2-$(CH_3)_a$; 1.70, s, 2-$(CH_3)_b$; 2.34, t, *J* 6.7 Hz, $(H2')_2$; 2.60, dt, *J* 7.4, 6.7 Hz, $(H3')_2$; 3.88, dd, *J* 9.5, 2.6 Hz, H_a5; 4.13, dd, *J* 9.5, 7.5 Hz, H4; 4.30, dd, *J* 7.5, 2.6 Hz, H_b5; 4.97, dd, *J* 10.3, 6.0 Hz, H_a5'; 5.03, dd, *J* 16.9, 6.0 Hz, H_b5'; 5.80, ddt, *J* 16.9, 10.3, 6.7 Hz, H4'. δ (minor isomer): 1.48, s, $OC(CH_3)_3$ and 2-$(CH_3)_a$; 1.64, s, 2-$(CH_3)_b$; 2.32, t, *J* 6.7 Hz, $(H2')_2$; 2.58, partially obscured dt, *J ca* 7, *ca* 7 Hz, $(H3')_2$; 3.92, dd, *J* 9.5, 2.3 Hz, H_a5; 4.11, dd, *J* 9.5, 7.2 Hz, H4; 4.43, dd, *J* 7.2, 2.3 Hz, H_b5; 4.97, dd, *J* 10.3, 6.0 Hz, H_a5'; 5.03, dd, *J* 16.9, 6.0 Hz, H_b5'; 5.80, ddt, *J* 16.9, 10.3, 6.7 Hz, H4'. ^{13}C NMR estimated rotomer ratio 60:40. δ (major isomer): 23.6, 2-$(CH_3)_a$; 25.4, 2-$(CH_3)_b$; 27.0, C3';[13] 28.3, $OC(\underline{C}H_3)_3$; 37.6, C2';[13] 65.3, C4; 65.6, C5; 80.6, $O\underline{C}(CH_3)_3$; 95.1, C2; 115.5, C5'; 136.8, C4'; 151.4, $N\underline{C}O_2Bu^t$; 207.8, C1'. δ (minor isomer): 24.7, 2-$(CH_3)_a$; 26.2, 2-$(CH_3)_b$; 27.0, C3';[13] 28.3, $OC(\underline{C}H_3)_3$; 38.1, C2';[13] 65.1, C4; 65.2, C5; 80.9, $O\underline{C}(CH_3)_3$; 94.4, C2; 115.2, C5'; 137.0, C4'; 152.4, $N\underline{C}O_2Bu^t$; 207.4, C1'. Mass spectrum: *m/z* 283.1785 ($C_{15}H_{25}NO_4$, 0.3%), 200.1284 ($C_{10}H_{18}NO_3$, 17), 168.1026 ($C_9H_{14}NO_2$, 2), 144.0663 ($C_6H_{10}NO_3$, 11), 100.0762 ($C_5H_{10}NO$, 39), 83.0508 (C_5H_7O, 13), 69.0215 (C_3H_3NO, 1), 57.0700 (C_4H_9, 100), 55.0547 (C_4H_7, 11).

Reduction of Ketone 6 with $Zn(BH_4)_2$

Zinc borohydride[14] (from $ZnCl_2$ (39.45 g, 0.289 mol) and $NaBH_4$ (26.44 g, 0.699 mol) in anhydrous ether (1.20 L)) was added *via* canula to a stirred solution of ketone **6** (32.77 g, 0.116 mol) in ether (350 mL) at –78°C. The solution was stirred for a further 30 min. at –78°C and then for 30 min. at –12°C before addition of H_2O (1.5 L). Ether extraction afforded alcohol **4** as a viscous oil (31.40 g, 95%) whose ^1H NMR spectrum was similar to that of a sample derived from the Grignard reaction, but with fewer extraneous signals.

(2*S*,3*R*)-2-(*t*-Butyloxycarbonylamino)hept-6-ene-1,3-diol 7

A 2:1 mixture of alcohols **4** and **5** (0.957 g, 3.36 mmol) was dissolved in MeOH (38 mL), Amberlyst 15 resin (1.782 g) was added, and the heterogeneous mixture was stirred vigorously at r.t. for 24 h. Filtration through filter aid and removal of solvent gave a thick brown oil (0.599 g), which was flash column chromatographed with an ether-hexane gradient. The fraction eluted with ether-hexane (1:1) was recrystallized from light petroleum to afford *(2S,3R)-2-(t-butyloxycarbonylamino)hept-6-ene-1,3-diol* **7** as fine white prisms (0.459 g, 56%) m.p. 43-45°C (Found: C, 58.35; H, 9.63; N, 6.00. $C_{12}H_{23}NO_4$ requires; C, 58.78; H, 9.39; N, 5.71%). ν_{max} (film) 3350, 3080, 2980, 2945, 1680, 1528, 1460, 1442, 1392, 1365, 1320, 1280, 1245, 1170, 1048, 902, 858, 780 cm^{-1}. ^1H NMR δ (major isomer): 1.42, s, $OC(CH_3)_3$; 1.45-1.71, m, $(H4)_2$; 2.5, m, H_a5; 2.27, m, H_b5; 2.61, br s, OH; 3.51, br m, H2; 3.74, dd, *J* 11.5, 3.3 Hz, H_a1; 3.78, dt, *J* 4.6, 7.4 Hz, H3; 3.96, dd, *J* 11.5, 3.6 Hz, H_b1; 4.98, ddm, *J* 10.3, 1.8 Hz, $H_{trans}7$; 5.03, ddm, *J* 17.2, 1.8 Hz, $H_{cis}7$; 5.41, d, *J* 8.2 Hz, $N\underline{H}CO_2Bu^t$; 5.82, ddt, *J* 17.2, 10.3, 6.7 Hz, H6. ^{13}C NMR δ (major isomer): 28.4, $OC(\underline{C}H_3)_3$; 30.2, C4; 33.5, C5; 55.1, C2; 62.6, C1; 73.6, C3; 79.8, $O\underline{C}(CH_3)_3$; 115.3, C7; 138.1, C6; 156.2, $HN\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 246 (M+1, 3%), 245 (M^+, absent), 190 (22), 160 (10), 146 (13), 143 (16), 114 (19), 104 (22), 87 (26), 60 (60), 57 (100).

(2*S*,3*S*)-2-(*t*-Butyloxycarbonylamino)-hept-6-ene-1,3-diol 8

A 25:75 mixture of alcohols **4** and **5** (0.521 g, 1.83 mmol) in MeOH (20 mL) was treated with Amberlyst 15 resin (0.970 g) at r.t. for 24 h as described for **7**. Filtration and evaporation gave a green oil (0.375 g), which was chromatographed, and the fraction eluted with ether-hexane (50%) was Kugelrohr distilled to afford

(2S,3S)-2-(t-butyloxycarbonylamino)hept-6-ene-1,3-diol ***8*** as a thick colourless oil (0.282 g, 63%) b.p. 220°C / 0.75 mmHg (Found: C, 58.53; H, 9.47; N, 5.86. $C_{12}H_{23}NO_4$ requires: C, 58.78; H, 9.39; N, 5.71%). ν_{max} (film) 3400, 3080, 2985, 2940, 1692, 1646, 1505, 1453, 1396, 1370, 1255, 1170, 1070, 1000, 915, 875, 855, 783 cm^{-1}. ^1H NMR δ: 1.41, s, $OC(CH_3)_3$; 1.45-1.70, m, $(H4)_2$; 2.02-2.25, m, $(H5)_2$; 2.71, br s, OH; 3.55, br m, H2; 3.69, d, *J* 4.9 Hz, $(H1)_2$; 3.89, br m, H3; 4.94, d, *J* 10.3 Hz, $H_{trans}7$; 5.01, dd, *J* 17.2, 1.7 Hz, $H_{cis}7$; 5.33, d, *J* 9.2 Hz, $N\underline{H}CO_2Bu^t$; 5.78, ddt, *J* 16.9, 10.3, 6.7 Hz, H6. ^{13}C NMR δ: 28.3, $OC(\underline{C}H_3)_3$; 29.9, C4; 33.1, C5; 54.6, C2; 64.1, C1; 71.1, C3; 79.7, $O\underline{C}(CH_3)_3$; 115.0, C7; 138.1, C6; 156.6, $HN\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 245 (M^+, absent), 214 (M^+-31, 0.3%), 172 (0.8), 160 (1.3), 158 (1.0), 156 (0.7), 114 (9), 60 (25), 57 (100).

(4*R*,5*S*)-4-But-3-enyl-2,2-dimethyl-5-(*t*-butyloxycarbonylamino)-1,3-dioxan 9

Pyridinium *p*-toluenesulfonate (7.83 g, 31.17 mmol) was added to a *ca.* 60:40 mixture of diols **7** and **8** (7.638 g, 31.17 mmol) and 2,2-dimethoxypropane (76.7 mL, 623.5 mmol) in CH_2Cl_2 (224 mL), and the solution kept at r.t. overnight. Volatiles were removed *in vacuo*, and the white residue extracted several times with 10:90 EtOAc-light petroleum. The extracts were filtered and evaporated to dryness to yield a thick oil (9.2 g), which was repeatedly chromatographed on silica gel (EtOAc-light petroleum, 1:9) to give, in turn, *(4S,5S)-4-but-3-enyl-2,2-dimethyl-5t-butylcarbonylamino-1,3-dioxan* ***10*** as a colourless gum (3.26 g, 37%), identical by spectroscopy to the compound isolated in the following experiment, and *(4R,5S)-4-but-3-enyl-2,2-dimethyl-5t-butylcarbonylamino-1,3-dioxan* ***9*** white fine needles (3.458 g, 39%) m.p. 65-66°C (light petroleum) (Found: C, 63.46; H, 9.62; N, 4.95. $C_{15}H_{27}NO_4$ requires: C, 63.16; H, 9.47; N, 4.91%). ν_{max} (Nujol) 3300, 2910, 2840, 1690, 1675, 1638 (w), 1532, 1455, 1374, 1362, 1302, 1238, 1170, 1010, 920 (m), 910 (m), 862 (m), 855 (m) cm^{-1}. ^1H NMR δ: 1.37, s, $2\text{-}(CH_3)_{ax}$; 1.39, s, $2\text{-}(CH_3)_{eq}$; 1.43, s, $OC(CH_3)_3$; 1.58, m, H_a1'; 1.72, m, H_b1'; 2.08, m, H_a2'; 2.22, m, H_b2'; 3.40-3.60, m, H5 and $(H6)_2$; 3.89, m, H4; 4.40, br s, NH; 4.96, d, *J* 10.8 Hz, $H_{trans}4'$; 5.00, dd, *J* 17.2, 1.5 Hz, $H_{cis}4'$; 5.78, m, H3'. ^{13}C NMR δ: 20.0, $2\text{-}(CH_3)_{eq}$; 27.9, $2\text{-}(CH_3)_{ax}$; 28.4, $OC(\underline{C}H_3)_3$; 29.2, C2'; 31.7, C1'; 49.6, C5; 63.5, C6; 71.8, C4; 79.7, $O\underline{C}(CH_3)_3$; 98.8, C2; 114.9, C4'; 138.2, C3'; 155.2, $N\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 286 (M+1, trace), 285 (M^+, absent), 260 (trace), 230 (1.5%), 214 (12), 172 (10), 143 (50), 115 (13), 87 (19), 59 (32), 57 (100), 43 (39); and the alcohols **4** and **5** as an oil (0.916 g, 10%).

(4*S*,5*S*)-4-But-3-enyl-2,2-dimethyl-5-(*t*-butyloxycarbonyl-amino)-1,3-dioxan 10

A 25:75 mixture of diols **7** and **8** (1.18 g, 4.8 mmol), pyridinium *p*-toluenesulfonate (1.21 g, 4.8 mmol) and 2,2-dimethoxypropane (11.8 mL, 96 mmol) in CH_2Cl_2 (30 mL) were reacted together as described above for **9** to yield the major component as a thick, pale yellow oil (1.26 g), which was further separated by repeated preparative TLC (EtOAc-hexane, 1:4) and finally distilled to afford *(4S,5S)-4-but-3-enyl-2,2-dimethyl-5-(t-butyloxycarbonylamino)-1,3-dioxan* ***10*** as a thick yellow oil (0.245 g, 18%) b.p. 159-161°C / 0.32 mmHg, (Found: C, 62.88; H, 9.70; N, 4.87. $C_{15}H_{27}NO_4$ requires: C, 63.16; H, 9.47; N, 4.91%). ν_{max} (film) 3450, 3330, 3070, 2970, 2934, 2860, 1708, 1638, 1490, 1380, 1363, 1270, 1242, 1165, 1080, 981, 945, 910, 845, 775 cm^{-1}. ^1H NMR[15] δ: 1.40, s, $2\text{-}(CH_3)_{ax}$; 1.42-1.62, m, $(H1')_2$; 1.446, s, $2\text{-}(CH_3)_{eq}$; 1.452, s, $OC(CH_3)_3$; 2.11, br dt, *J* 7.5, 7.0 Hz, $(H2')_2$; 3.50, ddd, *J ca* 7.5, *ca* 2.0, *ca* 2.0 Hz, H5; 3.74, dd, *J* 11.8, 1.8 Hz, H_a6; 3.93, ddd, *J* 7.4, 5.9, 1.8 Hz, H4; 4.06, dd, *J* 11.8, 1.8 Hz, H_b6; 4.97, d, *J* 11.0 Hz, $H_{trans}4'$; 5.02, dd, *J* 17.2, 1.8 Hz, $H_{cis}4'$; 5.30, d, *J* 10.2 Hz, NH; 5.76, ddt, *J* 17.2, 11.0, 6.7 Hz, H3'; ^{13}C NMR[15] δ: 18.5, $2\text{-}(CH_3)_{eq}$; 28.3, $OC(\underline{C}H_3)_3$; 28.8, C2'; 29.6, $2\text{-}(CH_3)_{ax}$; 30.7, C1'; 46.8, C5; 65.2, C6; 70.4, C4; 79.3, $O\underline{C}(CH_3)_3$; 99.0, C2; 115.0, C4'; 137.9, C3'; 155.7, $N\underline{C}O_2Bu^t$. Mass spectrum: *m/z* 286 (M+1, trace), 285 (M^+, absent), 230 (2%), 214 (9), 172 (9), 143 (39), 115 (11), 87 (21), 59 (45), 57 (100), 43 (77).

(4*R*,5*S*)-4-But-3-enyl-2,2-dimethyl-5-methylamino-1,3-dioxan 12

A suspension of $LiAlH_4$ (0.020 g, 0.526 mmol) in ether (4 mL) was refluxed for 35 min. then cooled to 0°C. Acetonide **9** (0.025 g, 0.088 mmol) in ether (3 mL) was added dropwise and the mixture refluxed for 24 h.

The mixture was again cooled to 0°C and 0.4 M aq. KOH (1.0 mL) was added. The mixture was then diluted with H_2O (1 mL), refluxed for 20 min., filtered while hot through a bed of filter aid, and washed well with a 9:1 CH_2Cl_2-MeOH mixture. The filtrates were combined, dried, and the volatiles removed to yield *(4R,5S)-4-but-3-enyl-2,2-dimethyl-5-methylamino-1,3-dioxan* ***12*** in essentially pure form as a colourless gum (0.014 g, 81%). ^{1}H NMR δ: 1.13, s, 2-$(CH_3)_a$; 1.15, s, 2-$(CH_3)_b$; 1.37-1.73, m, H_a1' and H_b1'; 2.00-2.14, m, $(H2')_2$; 2.45, s, N-Me; 2.40-2.55, m, H5; 2.58, br s, NH; 3.56, m, H4; 3.64, m, H_a6 and H_b6; 4.97, dd, J = 10.3, 2.0 Hz, H_{trans}4'; 5.02, *dd*, J 17.4, 2.0 Hz, H_{cis}4'; 5.80, ddt, J 17.4, 10.3, 6.2 Hz, H3'. ^{13}C NMR δ: 22.5, 2-$(CH_3)_a$; 23.1, C1'; 29.9, 2-$(CH_3)_b$; 30.6, C2'; 34.1, N-Me; 59.6, C5; 61.7, C6; 70.6, C4; 99.6, C2; 115.0, C4'; 138.1, C3'.

(4*S*,5*S*)-4-But-3-enyl-2,2-dimethyl-5-methylamino-1,3-dioxan 11

Acetonide **10** (1.142 g, 4.00 mmol) was treated with $LiAlH_4$ (0.535 g, 14.1 mmol) in ether as described for **9** to yield a residue (0.685 g, 82%), which was essentially pure by ^{1}H NMR spectroscopic analysis. Flash column chromatography using gradient elution with EtOAc-light petroleum mixtures then Kugelrohr distillation afforded *(4*S,5S)-4-but-3-enyl-2,2-dimethyl-5-methylamino-1,3-dioxan* ***11*** as a colourless oil (0.095 g) b.p. 78°C (oven)/0.4 mmHg (Found: C, 65.38; H, 10.72; N, 6.80. $C_{11}H_{21}NO_2$•0.17H_2O requires C, 65.31; H, 10.46; N, 6.92%). ν_{max} (film) 3350 (w), 3080 (w), 2995, 2935, 2860, 2800, 1643, 1477, 1450, 1382, 1272, 1200, 1137, 1072, 1025, 975, 913, 850, 718 cm^{-1}.^{1}H NMR δ: 1.35, s, 2$(CH_3)_{ax}$; 1.41, s, 2-$(CH_3)_{eq}$; 1.52-1.67, m, H_a1'; 1.69-1.79, m, H_b1'; 1.81, s, NH; 1.97-2.15, m, $(H2')_2$; 2.14, ddd, J 2.1, 1.8, 1.8 Hz, H5; 2.42, s, N-Me; 3.78, dd, J 12.1, 1.8 Hz, H_a6; 3.89, ddd, J 7.7, 5.4, 2.1 Hz, H4; 3.99, dd, J 12.1, 1.8 Hz, H_b6; 4.93, dd, J 10.0, 1.5 Hz, H_{trans}4'; 4.99, ddt, J 17.2, 1.8, 1.8 Hz, H_{cis}4'; 5.78, ddt, J 17.2,10.0, 6.7 Hz, H3'. ^{13}C NMR δ: 18.7, 2-$(CH_3)_{eq}$; 29.4, C1'; 29.7, 2-$(CH_3)_{ax}$; 30.9, C2'; 33.6, N-Me; 55.1, C5; 60.8, C6; 71.6, C4; 98.7, C2; 114.8, C4'; 138.4, C3'. Mass spectrum: *m/z* 199 (M+, 5%), 184 (10), 127 (7), 124 (9), 114 (6), 70 (83), 57 (100), 55 (12).

(4a*S*,6*R*,8a*R*)-5-*t*-Butyloxycarbonyl-6-hydroxymethyl-2,2-dimethyl-1,3-dioxa-5-azadecalin 13

Following the method of Hill,[12i] $Hg(OCOCF_3)_2$ (2.24 g, 5.26 mmol) was added to a solution of pure acetonide **9** (1.00 g, 3.51 mmol) in THF (40 mL). The mixture was stirred for 24 h at r.t. and then cooled in ice and treated with sat. $NaHCO_3$ solution (10 mL). After 30 min., sat. KBr solution (4.7 mL) was added and the cold mixture was warmed to r.t. The mixture was stirred for another 2 h and then extracted with EtOAc. The extracts were washed with brine, dried, and evaporated to afford a white foam (1.89 g, 95%) which was reacted further without purification. Oxygen was bubbled into a stirred suspension of $NaBH_4$ (0.179 g, 4.73 mmol) in DMF (40 mL) for 1 h, and to this was added dropwise a solution of the above foam (1.89 g, 3.34 mmol) in DMF (120 mL) over 3 h with continuous introduction of O_2. Passage of the O_2 into the mixture was continued for 1 h, and then ether (100 mL) was added. The reaction mixture was filtered through filter aid and the pad was washed thoroughly with ether. Light petroleum and water were added to the filtrate, and the aqueous layer was further extracted with ether. The combined organic extracts were washed with water and brine, dried, and evaporated. The resulting pale yellow oil (0.590 g) was flash column chromatographed on silica gel using EtOAc-light petroleum (2:3) to give a 69:31 mixture of (6*R*)- and (6*S*)-*(4a*S,*8a*R)-*5*-t-*butyloxycarbonyl-6-hydroxymethyl-2,2-dimethyl-1,3-dioxa-5-azadecalin* ***13*** and ***14*** as a pale yellow gum. Prolonged standing in high vacuum gave a white solid (0.251 g, 24%) m.p. 53-56°C (Found: C, 59.44; H, 8.84; N, 4.40. $C_{15}H_{27}NO_5$ requires: C, 59.78; H, 9.03; N, 4.65 %). ν_{max} (film) 3460, 2970, 2940, 2870, 1690, 1660, 1475 (w), 1450 (w), 1420 (m), 1380, 1365, 1308 (m), 1268, 1252, 1202 (m), 1168, 1135 (w), 1110 (w), 1092, 1080 (w), 1050, 980 (w), 952 (w), 912 (w), 868 (m), 764 (w) cm^{-1}. ^{1}H NMR[16] δ (major isomer **13**): 1.37, s, 2-$(CH_3)_{ax}$; 1.44, s, $OC(CH_3)_3$; 1.49, s, 2-$(CH_3)_{eq}$; 1.48-1.59, m, H_a8; 1.71-1.80, m, $(H7)_2$ and H_b8; 3.14, ddd, J 10.5, 10.0, 5.1 Hz, H4a; 3.64, dd, J 11.0, 6.6 Hz, 6-C$\underline{H}_a\underline{H}_b$OH; 3.64, m, H8a; 3.86, dd, J 11.0, 9.0 Hz, 6-C$\underline{H}_a\underline{H}_b$OH; 4.33, dd, J 11.8, 10.5 Hz, H_{ax}4; 4.39, m, H6; 4.42, dd, J 11.8, 5.1 Hz, H_{eq}4. ^{13}C NMR[15] δ (major isomer **13**): 19.2, 2-$(CH_3)_{eq}$; 23.2, C7; 26.6, C8; 28.4, OC($\underline{C}H_3)_3$; 29.4, 2-$(CH_3)_{ax}$; 53.7, C4a; 54.3, C6; 60.9, 6-CH_2OH; 63.1, C4;

70.8, C8a; 80.9, O<u>C</u>$(CH_3)_3$; 98.2, C2; 155.9, N<u>C</u>O_2Bu^t. Mass spectrum: *m/z* 302 (M+1, 31%), 301 (M^+, absent), 262 (12), 246 (32), 244 (9), 206 (19), 202 (19), 188 (47), 162 (15), 145 (9), 144 (100).

(4a*S*,6*S*,8a*R*)-5-*t*-Butyloxycarbonyl-6-hydroxymethyl-2,2-dimethyl-1,3-dioxa-5-azadecalin 14

Repetition of the reaction described above using pure *anti* acetonide **9** (5.066 g, 0.02 mol) afforded after careful chromatography more of the (6*R*) enriched alcohol **12** as a gum (1.35 g), and a minor fraction comprising a 40:60 mixture of (6*R*)- and (6*S*)-*(4a*S,*8a*R)-*5*-t-*butyloxycarbonyl-6-hydroxymethyl-2,2-dimethyl-1,3-dioxa-5-azadecalin **13*** and ***14*** as a colourless gum (0.674 g, 13%). ν_{max} (film) 3460 (br), 2980, 2940, 2880, 1690, 1480 (w), 1455 (m), 1370, 1255, 1170, 1098, 1080, 1050, 868, 845, 768 cm^{-1}. ^1H NMR δ (major isomer **14**): 1.39, s, 2-$(CH_3)_{ax}$; 1.47, s, 2-$(CH_3)_{eq}$ and OC$(CH_3)_3$; 1.65-1.80, m, H_b7 and H_a8; 1.84-1.96, m, H_a7 or H_b8; 1.98-2.10, m, H_a7 or H_b8; 3.26, ddd, *J* 10.3, 10.0, 4.6 Hz, H4a; 3.61-3.68, m, H8a; 3.81, dd, *J* 10.8, 10.3 Hz, 6-C<u>H_a</u>H_bOH; 3.99, dd, *J* 10.8, 5.6 Hz, 6-CH_a<u>H_b</u>OH; 4.32, dd, *J* 12.1, *ca* 10.5 Hz, $H_{ax}4$; 4.35, dd, *J* 11.0, 4.6 Hz, H6; 4.42, dd, *J* 12.1, 5.1 Hz, $H_{eq}4$. ^{13}C NMR δ (major isomer **14**): 19.6, 2-$(CH_3)_{eq}$; 22.4, C7; 25.5, C8; 28.4, OC(<u>C</u>$H_3)_3$; 29.1, 2-$(CH_3)_{ax}$; 55.5, C4a; 55.9, C6; 64.4, 6-CH_2OH; 67.4, C4; 68.0, C8a; 81.3, O<u>C</u>$(CH_3)_3$; 99.0, C2; 157.0, N<u>C</u>O_2Bu^t. Mass spectrum: *m/z* 302 (M+1, trace), 301 (M^+, absent), 286 (trace), 270 (1), 246 (2), 230 (2), 214 (2), 170 (9), 112 (17), 100 (35), 57 (100).

The ratio of 6*R*:6*S* isomers was determined by integration of the signals for H4a, δ 3.14 and 3.26, respectively.

(4a*S*,8a*S*)-(5-*t*-Butoxycarbonyl-2,2-dimethyl-1,3-dioxa-5-azadecalin-6-yl)methylmercury(II) Chloride 15

A 60:40 mixture of acetonides **9** and **10** (0.50 g, 1.75 mmol) was treated as above with $Hg(OCOCH_3)_2$ (0.839 g, 2.63 mmol) in THF (20 mL) for 18 h. The mixture was then cooled in ice, treated with sat. $NaHCO_3$ solution (5 mL) and sat. KBr solution (3.5 mL) and allowed to warm to r.t. for 2 h. Extraction gave a white foam (0.637 g), which was flash chromatographed on silica gel to yield in order of increasing polarity: a forerun (0.031 g), the starting materials, acetonide **10** (0.064 g) and acetonide **9** (0.079 g), and a fraction which was recrystallized from light petroleum to afford *(4a*S,*6*S,*8a*S)-*(5*-t-*butyloxycarbonyl-2,2-dimethyl-1,3-dioxa-5-azadecalin-6-yl)methyl-mercury II chloride **15*** as white prisms (0.077 g, 8%) m.p. 113-118°C (Found: C, 35.04; H, 5.15; N, 2.80. $C_{15}H_{26}O_4NHgCl$ requires: C, 34.62; H, 5.04; N, 2.69%). ^1H NMR δ: 1.39, s, 2-$(CH_3)_{ax}$; 1.47, s, OC$(CH_3)_3$; 1.50, s, 2-$(CH_3)_{eq}$; 1.58-1.82, m, H_a7, $(H8)_2$; 1.84-1.97, m, H_b7; 1.91, dd, *J* 12.6, 4.6 Hz, 6-C<u>H_a</u>H_bHgCl; 2.49, dd, *J* 12.1, 12.0 Hz, 6-CH_a<u>H_b</u>HgCl; 3.18, dt, *J* 9.7, 7.7 Hz, H4a; 3.66, ddd, *J* 12.0, 10.0, 4.6 Hz, H6; 4.33, d, *J* 7.7 Hz, $(H4)_2$; 4.57, dddd, *J ca*10, *ca*5, *ca*5, 1.5 Hz, H8a. ^{13}C NMR δ: 19.1, 2-$(CH_3)_{eq}$; 25.7, C7; 28.5, OC(<u>C</u>$H_3)_3$; 29.4, 2-$(CH_3)_{ax}$; 29.7, C8; 31.9, 6-<u>C</u>H_2HgCl; 52.1, C4a; 53.1, C6; 63.2, C4; 70.9, C8a; 81.9, O<u>C</u>$(CH_3)_3$; 98.2, C2; 154.4, N<u>C</u>O_2Bu^t. Mass spectrum: *m/z* 521 ($M^+(^{202}Hg)$, absent), 450 ($M(^{202}Hg)$-116, 3%), 448 ($M(^{200}Hg)$-116, 3), 407 (2), 405 (2), 363 (3), 361 (3), 306 (2), 304 (2), 228 (1), 212 (7), 170 (11), 126 (30), 57 (100).

(4a*S*,6*R*,8a*R*)-6-Hydroxymethyl-2,2,5-trimethyl-1,3-dioxa-5-azadecalin 17

A suspension of $LiAlH_4$ (0.45 g, 12.0 mmol) in ether (100 mL) was refluxed for 1 h then cooled in ice, and a solution of alcohol **13** (0.59 g, 1.96 mmol) in ether (50 mL) was added. The mixture was warmed to reflux for 24 h then again cooled to 0°C as 0.4 M aq. KOH solution (4 mL) was added dropwise. The mixture was diluted with H_2O (2 mL) and refluxed for a further 20 min. then filtered hot through a bed of filter aid and the bed washed well with hot CH_2Cl_2-MeOH (9:1). All filtrates were combined and dried, volatiles were evaporated, and the resulting gum (0.422 g) flash chromatographed using 1:9 $CHCl_3$-MeOH containing a few drops of Et_3N to yield a white solid (0.283 g). The solid was recrystallized from $CHCl_3$-light petroleum to afford *(4a*S,*6*R,*8a*R)-*6-hydroxymethyl-2,2,5-trimethyl-1,3-dioxa-5-azadecalin **17*** as white rods (0.192 g, 46%) m.p. 124-125°C (Found: C, 61.05; H, 10.00; N, 6.27. $C_{11}H_{21}NO_3$ requires; C, 61.37; H, 9.83, N, 6.51 %). ν_{max} (Nujol) 3140 (br), 2920 (br), 2860 (w), 1445, 1370, 1255 (m), 1198 (m), 1165 (m), 1145 (m), 1085 (m), 1056

(m), 1035 (m), 980 (w), 920 (m), 865, 730 cm^{-1}. ^1H NMR[16] δ: 1.37, s, 2-$(CH_3)_{ax}$; 1.46, s, 2-$(CH_3)_{eq}$; 1.49, obscured m, $H_{ax}8$; 1.74, obscured dm, *J ca* 12 Hz, H_b8; 1.77, dm, *J* 14.1 Hz, H_b7; 1.85, ddt, *J* 14.1, 13.8, 4.9 Hz, H_a7; 2.26, br s, OH; 2.39, s, *N*-Me; 2.53, ddd, *J* 10.2, 10.0, 4.9 Hz, H4a; 2.83, *dddd*, *J* 7.4, 6.9, 4.9, 1.8 Hz, H6; 3.58, dd, *J* 10.5, 7.4 Hz, 6-$C\underline{H_a}H_bOH$; 3.73, dt, *J* 11.0, 4.9 Hz, H8a; 3.75, dd, *J* 11.0, 10.5 Hz, $H_{ax}4$; 3.84, dd, *J* 11.0, 5.1 Hz, $H_{eq}4$; 3.89, dd, *J* 10.5, 6.9 Hz, 6-$CH_a\underline{H_b}OH$. ^{13}C NMR δ: 19.2, 2-$(CH_3)_{eq}$; 23.2, C7; 26.1, C8; 29.5, 2-$(CH_3)_{ax}$; 38.1, 5-CH_3; 55.7, C4a; 57.4, 6-CH_2OH; 61.6, C6; 63.2, C4; 69.5, C8a; 98.8, C2. Mass spectrum: *m/z* 216 (M+1, 5%), 215 (M^+, absent), 200 (14), 184 (100), 140 (31), 126 (60), 96 (58), 84 (49), 82 (89), 57 (35), 42 (52).

Swern Oxidation of Alcohols 17 and 18

Dried DMSO (0.42 mL, 5.8 mmol) was added dropwise to a precooled solution of oxalyl chloride (0.38 mL, 4.4 mmol) in dry CH_2Cl_2 (78 mL) at –78°C. A 70:30 mixture of alcohols **17** and **18** (0.628 g, 2.92 mmol) in CH_2Cl_2 (37 mL) was added dropwise, and the solution stirred at –78°C for 2 h, then Et_3N (1.63 mL, 11.6 mmol) was added and the cooling bath was removed. After 10 min., water (200 mL) was added, the mixture was basified to pH 10 with NH_4OH (1.5 mL), and extracted with CH_2Cl_2. The organic layer was washed successively with water and brine, then dried and evaporated to afford a yellow gum (0.564 g, 91%). The gum was flash chromatographed using MeOH-$CHCl_3$ (1:9) to yield the major component as a yellow gum (0.304 g, 49%). This polar substance consisted largely of the *trans* aldehyde **19** and was used immediately for the next step. A less polar fraction was resubjected to flash chromatography using gradient elution with light petroleum, CH_2Cl_2, and EtOAc mixtures to afford, in order, *(4aS,6S,8aR)-6-formyl-2,2,5-trimethyl-1,3-dioxa-5-azadecalin* ***20*** as a pale yellow solid (0.122 g, 20%) m.p. 61-63°C (Found: C, 61.97; H, 8.96; N, 6.48. $C_{11}H_{19}NO_3$ requires: C, 61.95; H, 8.98; N, 6.57%). ν_{max} (Nujol) 2960, 2920, 2860, 1738, 1720, 1460, 1375, 1268, 1248, 1200, 1180 (m), 1160 (m), 1125 (m), 1090, 1045, 1015 (m), 1000, 970 (m), 940 (m), 920, 865, 755 cm^{-1}. ^1H NMR δ: 1.36, s, 2-$(CH_3)_{ax}$; 1.41, obscured m, $H_{ax}7$; 1.45, s, 2-$(CH_3)_{eq}$; 1.58, dddd, *J* 13.5, 13.0, 12.5, 3.8 Hz, H_a8; 1.72, dm, *J* 12.8 Hz, H_b7; 1.92, dm, *J* 11.5 Hz, H_b8; 1.99, ddd, *J* 10.5, 9.2, 4.6 Hz, H4a; 2.12, s, *N*-Me; 2.61, ddd, *J* 11.8, 3.8, 3.5 Hz, H6; 3.63, ddd, *J* 11.0, 9.2, 3.8 Hz, H8a; 3.71, dd, *J* 11.0, 10.8 Hz, $H_{ax}4$; 4.00, dd, *J* 11.0, 4.6 Hz, $H_{eq}4$; 9.38, d, *J* 3.8 Hz, CHO. ^{13}C NMR δ: 19.0, 2-$(CH_3)_{eq}$; 24.1, C7; 28.7, C8; 29.4, 2-$(CH_3)_{ax}$; 39.9, *N*-Me; 62.5, C4a; 62.7, C4; 70.3, C6; 72.5, C8a; 98.5, C2; 202.2, CHO. Mass spectrum: *m/z* 213 (M^+, absent), 198 (7%), 184 (55), 138 (24), 126 (17), 110 (16), 96 (50), 82 (78), 55 (16), 43 (89), 42 (100); and *(4aS,6R,8aR)-6-formyl-2,2,5-trimethyl-1,3-dioxa-5-azadecalin* ***19*** (Found: *m/z* 184.1332. $C_{11}H_{19}NO_3$ requires *m/z* 213.1365). ^1H NMR δ: 1.31, m, H_a7; 1.38, s, 2-$(CH_3)_{ax}$; 1.47, s, 2-$(CH_3)_{eq}$; 1.79, m, H_b7; 1.89, ddd, *J* 14.1, 6.7, 4.1 Hz, H_a8; 2.17, dm, *J* 13.8 Hz, H_b8; 2.93, ddd, *J* 10.5, 9.5, 4.6 Hz, H4a; 2.52, s, *N*-Me; 3.31, dd, *J* 6.4, 1.9 Hz, H6; 3.63, ddd, *J* 11.3, 9.2, 4.1 Hz, H8a; 3.67, dd, *J* 10.8, 10.8 Hz, $H_{ax}4$; 4.03, dd, *J* 10.8, 4.6 Hz, $H_{eq}4$; 9.90, s, CHO. ^{13}C NMR δ: 19.2, 2-$(CH_3)_{eq}$; 22.6, C7; 26.9, C8; 29.5, 2-$(CH_3)_{ax}$; 38.0, *N*-Me; 57.7, C4a; 63.5, C4; 68.9, C6; 71.0, C8a; 98.9, C2; 204.0, CHO.

Preparation of Diethyl (2*E*,4*E*)-nonadienylphosphonate 21

(2E,4E)-Nonadien-1-ol ***22.*** $NaBH_4$ (0.30 g, 7.96 mmol) was added in portions to a solution of (2*E*,4*E*)-nonadienal (1.16 mL, 7.24 mmol) in EtOH (10 mL) in ice. The mixture was stirred at ambient temperature for 1 h then partitioned with ether to afford (2*E*,4*E*)-nonadien-1-ol **22** as a yellow oil (0.85 g, 84%). ^1H NMR δ: 0.90, t, *J* 7.0 Hz, $(H9)_3$; 1.24-1.42, m, $(H7)_2$, $(H8)_2$; 1.62, br s, OH; 2.08, dt, *J* 6.9, 6.4 Hz, $(H6)_2$; 4.14, d, *J* 6.2 Hz, $(H1)_2$; 5.695, dt, *J* 14.9, 6.9 Hz, H5; 5.705, dt, *J* 15.1, 6.2 Hz, H2; 6.03, ddt, *J* 14.9, 10.3, 1.5 Hz, H4; 6.20, ddt, *J* 15.1, 10.3, 1.5 Hz, H3.

(2E,4E)-1-Chloro-2,4-nonadiene ***23.*** A solution of (2*E*,4*E*)-nonadien-1-ol **22** (12.74 g, 90.9 mmol) in freshly distilled $CHCl_3$ (12 mL) was warmed to reflux. The solution was purged with argon and stirred while a solution of distilled $SOCl_2$ (7.96 mL, 109 mmol) in $CHCl_3$ (9 mL) was added dropwise. Heating and stirring were

continued for 5 h whereupon ether (250 mL) was added, the mixture was poured into ice-water, and the product extracted into ether. The combined ether extracts were washed successively with water, sat. $NaHCO_3$ solution and brine, dried, and the solvent evaporated to afford a 70:30 mixture of (2*E*,4*E*)-1-chloro-2,4-nonadiene **23** and (1*E*,3*E*)-nonadien-5-ol as a red oil (13.94 g). The mixture was unstable on silica gel and was used in the next step without purification.

*Diethyl (2*E*,4*E*)-nonadienylphosphonate **21**.* A solution of crude (2*E*,4*E*)-1-chloro-2,4-nonadiene **23** (12.89 g, 0.081 mol) and $P(OEt)_3$ (41.9 mL, 0.244 mol) was refluxed for 4.5 h. The solution was cooled, diluted with water and extracted with ether. The combined extracts were washed with water and brine, dried, and evaporated to afford a red oil, which was flash chromatographed using light petroleum-EtOAc mixtures to yield *diethyl (2*E*,4*E*)-nonadienylphosphonate **21*** as a very dark liquid (12.54 g, 59%) (Found: C, 59.65; H, 9.90. $C_{13}H_{25}O_3P$ requires: C, 59.98; H, 9.68 %). ν_{max} (film) 3475 (br) (H_2O), 1655 (m), 1460, 1446, 1400, 1250, 1170, 1100 (w), 1060, 1030, 990, 965, 872 (w), 845, 780 710 (m) cm^{-1}. ^1H NMR δ: 0.84, t, *J* 7.2 Hz, $(H9)_3$; 1.26, t, *J* 7.2 Hz, $OCH_2C\underline{H}_3$; 1.25-1.36, m, $(H7)_2$ and $(H8)_2$; 2.01, dt, *J* 7.2, 6.9 Hz, $(H6)_2$; 2.56, dd, *J* 22.3, 7.7 Hz, $(H1)_2$; 4.04, dq, *J* 7.7, 7.7 Hz, $OC\underline{H}_2CH_3$; 5.45, ddt, *J* 14.6, 7.4, 7.4 Hz, H2; 5.59, ddt, *J* 14.9, 2.6, 6.9 Hz, H5); 5.95, ddd, *J* 14.9, 10.3, 1.0 Hz, H4; 6.09, ddd, *J* 14.9, 10.3, 4.6 Hz, H3. ^{13}C NMR δ: 13.8, C9; 16.3, $OCH_2\underline{C}H_3$; 22.1, C8; 30.4, d, *J* 209.9 Hz, C1; 31.4, C7; 32.1, C6; 61.8, C1'; 119.1, C5; 129.3, C3; 134.7, C4; 135.3, C2. Mass spectrum: *m/z* 261 (M+1, 4%), 260 (M^+, 10), 231 (2), 217 (2), 152 (15), 122 (19), 109 (26), 81 (64), 79 (100), 67 (69).

Reaction of Aldehydes 19 and 20 with Phosphonate 21

(i) Following the method of Hensel,[17] KH (0.32 g of 35% oil dispersion) was suspended in THF (6 mL) and the suspension cooled in ice. Phosphonate **21** (0.440 g, 1.69 mmol) was added dropwise to the slurry, the mixture was stirred at ice temperature for 20 min. then cooled in a bath at –78°C. A *ca* 80:20 mixture of aldehydes **19** and **20** (0.300 g, 1.41 mmol) in THF (3.6 mL) was added and the mixture was stirred for 3 h at –78°C and then at ambient temperature overnight. Solvent was removed under vacuum at ambient temperature and the residue was extracted several times with ether. The extracts were filtered and evaporated *in vacuo* to afford a mixture of one major and two minor components as a red gum (0.419 g). Flash chromatography using light petroleum, followed by a solvent gradient mixture of EtOAc-CH_2Cl_2 yielded one of the minor, least polar components *(4a*S,*6*S,*8a*R)-6-[(1'*E*,3'*E*,5'*E*)-decatrienyl]-2,2,5-trimethyl-1,3-dioxa-5-azadecalin **24*** as canary yellow prisms (0.0145 g, 3%) R_f 0.59 using CH_2Cl_2-EtOAc (2:3) (Found: *m/z* 320.2581. $C_{20}H_{34}NO_2$ requires *m/z* 320.2589). ^1H NMR δ: 0.88, t, *J* 7.2 Hz, $(H10')_3$; 1.22-1.55, m, H_a7, H_a8, $(H8')_2$ and $(H9')_2$; 1.41, s, 2-$(CH_3)_{ax}$; 1.47, s, 2-$(CH_3)_{eq}$; 1.70, m, H_b7; 1.85, m, H_b8; 1.97, ddd, *J* 10.2, 9.8, 4.6 Hz, H4a; 2.05-2.17, partially obscured m, $(H7')_2$; 2.10, s, *N*-Me; 2.50, ddd, *J ca* 9.9, *ca* 9.2, 3.2 Hz, H6; 3.67, ddd, *J* 10.5, 9.5, 3.7 Hz, H8a; 3.72, dd, *J* 11.0, 10.5 Hz, $H_{ax}4$; 4.03, dd, *J* 11.0, 4.6 Hz, $H_{eq}4$; 5.45, dd, *J* 14.4, 9.0 Hz, H1'; 5.71, dt, *J* 14.9, 7.2 Hz, H6'; 5.99-6.20, m, H2', H3', H4', H5'. ^{13}C NMR δ: 13.9, C10'; 19.1, 2-$(CH_3)_{eq}$; 22.2, C9'; 29.5, 2-$(CH_3)_{ax}$; 30.0, C7; 31.2, C8; 31.4, C8'; 32.4, C7'; 38.8, *N*-Me; 63.1, C4; 63.7, C6; 67.8, C8a; 70.8, C4a; 98.2, C2; 129.7, 130.0, 132.3, 133.0, C2'-C5'; 135.1, C1'; 135.9, C6'. Mass spectrum: *m/z* 320.2581 ($C_{20}H_{34}NO_2$, 9), 319.2509 ($C_{20}H_{33}NO_2$, 17), 304.2301 ($C_{19}H_{30}NO_2$, 7), 276.2044 ($C_{18}H_{28}O_2$, 7), 261.2169 ($C_{18}H_{29}O$, 10), 230.1961 ($C_{16}H_{24}N$, 4), 204.1862 ($C_{15}H_{24}$, 4), 184.1379 ($C_{10}H_{18}NO_2$, 26), 148.1197 ($C_{11}H_{16}$, 9), 134.1037 ($C_{10}H_{14}$, 18), 120.0895 (C_9H_{12}, 13); *(4a*S,*6*R,*8a*R)-6-[(1'*E*,3'*E*,5'*E*)-decatrienyl]-2,2,5-trimethyl-1,3-dioxa-5-azadecalin **26*** (Found: *m/z* 319.2512. $C_{20}H_{33}NO_2$ requires *m/z* 319.2511). ^1H NMR δ: 0.89, t, *J* 7.0 Hz, $(H10')_3$; 1.23-1.65, m, H_a7, $(H8)_2$, $(H8')_2$ and $(H9')_2$; 1.40, s, 2-$(CH_3)_{ax}$; 1.48, s, 2-$(CH_3)_{eq}$; 1.72, m, H_b7; 1.97-2.20, m, $(H7')_2$; 2.13, s, N-Me; 2.51, ddd, *J* 10.3, 9.5, 4.9 Hz, H4a; 3.28, m, H6; 3.69, dd, *J* 11.0, 10.5 Hz, $H_{ax}4$; 3.71, m, H8a; 3.91, dd, *J* 11.0, 4.9 Hz, $H_{eq}4$; 5.71, dt, *J* 14.9, 7.4 Hz, H6'; 6.00, dd, *J* 14.6, 9.0 Hz, H1'; 6.00-6.23, m, H2', H3', H4', H5'. ^{13}C NMR δ: 14.0, C10'; 19.3, 2-$(CH_3)_{eq}$; 22.3, C9'; 25.7, C7;[13] 29.1, C8;[13] 29.6, 2-$(CH_3)_{ax}$; 31.5, C8'; 32.5, C7'; 38.2, *N*-Me; 57.0, C6; 63.4, C4; 69.0, C4a; 72.0, C8a; 98.8, C2; 123.5,

C1'; 129.6, 130.1, 133.4, 134.3, C2'-C5'; 136.2, C6'. Mass spectrum: *m/z* 319 (M^+, 67%), 304.2391 ($C_{20}H_{32}O_2$, 32), 276.1965 ($C_{17}H_{26}NO_2$, 25), 262.1798 ($C_{16}H_{24}NO_2$, 24), 222.1493 ($C_{13}H_{20}NO_2$, 23), 184.1339 ($C_{10}H_{18}NO_2$, 45), 147.0313 ($C_8H_5NO_2$, 30), 94.0655 (C_6H_8N, 32), 83.9517 (100); and impure azadecalin **27** (0.028 g) ^{1}H NMR δ: 0.89, t, *J* 7.0 Hz, $(H10')_3$; 1.23-1.53, m, 4H; 1.40, s, 2-$(CH_3)_{ax}$; 1.48, s, 2-$(CH_3)_{eq}$; 1.70, m, 1H; 1.95-2.15, m, 2H; 2.13, s, *N*-Me; 2.46-2.62, m, H4a; 3.69, dd, *J* 11.0, 10.5 Hz, $H_{ax}4$; 3.70, m, H8a; 3.92, ddd, *J* 11.0, 4.9, 4.6 Hz, $H_{eq}4$; 4.05-4.16, m, H6; 5.75, dt, *J* 14.6, 7.4 Hz, H6'; 5.80, dd, *J* 10.8, 10.3 Hz, H1'; 5.95-6.38, m, H2', H3', H4', and H5'. ^{13}C NMR δ: 13.9, C10'; 19.2, 2-$(CH_3)_{eq}$; 22.2, C9'; 25.7, C7';[13] 29.2, C8';[13] 29.6, 2-$(CH_3)_{ax}$; 31.4, C8'; 32.5, C7'; 38.2, *N*-Me; 56.5, C6; 63.1, C4a; 63.6, C4; 72.1, C8a; 98.7, C2; 124.7, C1'; 129.6, 130.2, 135.2, 136.1, C2'-C5'; 136.8, C6'.

(ii) Phosphonate **21** (0.082 g, 0.31 mmol) was added dropwise to an ice-cold slurry of KH (0.06 g of 35 % oil dispersion) in THF (1.1 mL), the mixture stirred at ice temperature for 20 min. then cooled in a bath at –78°C. Aldehyde **20** (0.056 g, 0.26 mmol) in dry THF (0.7 mL) was added to the phosphonate reagent and the mixture was stirred for 3 h at –78°C and then allowed to warm to r.t. overnight. The THF was removed under vacuum at room temperature and the residue was extracted several times with ether. The extracts were filtered and evaporated *in vacuo* to afford a 29:7:64 mixture of amines **24** and **25**, and lactam **28**, as an amber gum (0.061g). The three products were separated by preparative TLC using EtOAc-CH_2Cl_2 (3:7) to yield in order of increasing polarity: (1'*E*,6*S*) amine **24** as a pale yellow solid (0.014 g, 16%) R_f 0.43 using EtOAc-CH_2Cl_2 (2:3), *(4a*S,6S,*8a*R)-6-[(1'Z,3'E,5'E)-decatrienyl]-2,2,5-trimethyl-1,3-dioxa-5-azadecalin* ***25*** as a pale yellow solid (0.006 g, 7%) R_f 0.33 using EtOAc-CH_2Cl_2 (2:3). ^{1}H NMR δ: 0.90, t, *J* 7.2 Hz, $(H10')_3$; 1.23-1.58, m, H_a7, H_a8, $(H8')_2$ and $(H9')_2$; 1.41, s, 2-$(CH_3)_{ax}$; 1.48, s, 2-$(CH_3)_{eq}$; 1.70, m, H_b7; 1.88, m, H_b8; 2.01, ddd, *J* 10.5, 9.5, 4.6 Hz, H4a; 2.06-2.17, m, $(H7')_2$; 2.11, s, *N*-Me; 2.99, m, H6; 3.68, m, H8a; 3.73, dd, *J* 11.0, 10.5 Hz, $H_{ax}4$; 4.04, dd, *J* 11.3, 4.6 Hz, $H_{eq}4$; 5.22, dd, *J* 10.3, 10.0 Hz, H1'; 5.74, dt, *J* 14.4, 6.9 Hz, H6'; 6.07, dd, *J* 11.8, 11.0 Hz, H2'; 6.16, dd, *J ca* 14, *ca* 14 Hz, H3'; 6.20, dd, *J ca* 14, 10.3 Hz, H4'; 6.37, dd, *J* 13.6, 11.5 Hz, H5'. ^{13}C NMR δ: 13.9, C10'; 19.2, 2-$(CH_3)_{eq}$; 22.2, C9'; 29.5, 2-$(CH_3)_{ax}$; 30.0, C7';[13] 30.5, C8';[13] 31.4, C8'; 32.5, C7'; 38.7, *N*-Me; 62.1, C6; 63.2, C4; 63.9, C8a; 70.9, C4a; 98.2, C2; 125.2, 130.2, 130.4, 133.0, C2'-C5'; 134.7, C6'; 136.6, C1'; and *lactam* ***28*** as a yellow gum (0.0062 g, 12%) (Found: *m/z* 199.1209. $C_{10}H_{17}NO_3$ requires *m/z* 199.1208). ^{1}H NMR δ: 1.43, s, 2-$(CH_3)_{ax}$; 1.50, s, 2-$(CH_3)_{eq}$; 1.80, dddd, *J* 12.3, 12.0, 6.9, 5.4 Hz, H_a8; 1.97, dddd, *J ca* 11, *ca* 7, 3.7, 2.0 Hz, H_b8; 2.51, ddd, *J* 18.2, 12.0, 6.9 Hz, H_a7; 2.62, ddd, *J* 18.2, 6.7, 2.0 Hz, H_b7; 2.83, s, *N*-Me; 3.18, ddd, *J* 11.0, 9.0, 4.5 Hz, H4a; 3.74, dd, *J* 11.0, 10.8 Hz, $H_{ax}4$; 3.83, ddd, *J* 11.8, 9.0, 3.7 Hz, H8a; 4.12, dd, *J* 10.8, 4.5 Hz, $H_{eq}4$. ^{13}C NMR δ: 19.0, 2-$(CH_3)_{eq}$; 26.8, C8; 28.8, *N*-Me; 29.2, 2-$(CH_3)_{ax}$; 30.4, C7; 56.9, C4a; 63.3, C4; 69.4, C8a; 99.1, C2; 169.6, C6. Mass spectrum: *m/z* 199 (M^+, 3%), 184.0975 ($C_9H_{14}NO_3$, 15), 141.0789 ($C_7H_{11}NO_2$, 24), 124.0762 ($C_7H_{10}NO$, 34), 111.0684 (C_6H_9NO, 100), 98.0564 (C_5H_8NO, 12), 85.0273 ($C_4H_5O_2$, 20), 68.0500 (C_4H_6N, 17), 57.0582 (C_3H_7N, 72).

(2*S*,3*R*,6*S*)-1-Methyl-2-hydroxymethyl-3-hydroxy-6-(1"*E*,3"*E*,5"*E*-decatrienyl)piperidine (micropine) 1

Acetonide **24** (0.011 g, 0.035 mmol) was dissolved in MeOH (2.5 mL), 66% aq. H_2SO_4 (7 drops) was added, and the mixture stirred at r.t. overnight. The reaction mixture was diluted with water (10 mL), washed once with ether (5 mL), basified with NH_4OH (40 drops) to pH 11, and extracted with ether. The combined extracts were washed with brine, dried, and evaporated *in vacuo* to afford a pale yellow residue which was recrystallized from MeOH to yield *(2*S,*3*R,*6*S)-1-methyl-2-hydroxymethyl-3-hydroxy-6-(1"*E*,3"*E*,5"*E*-decatrienyl)piperidine 1* (0.008 g, 88%) m.p. 143-145°C, $[\alpha]_D^{21}$ -49° (EtOH, c. 0.08) (lit.[2] m.p. 146-148°C; $[\alpha]_D^{20}$ –63° (EtOH; c. 0.15)) R_f 0.26 using MeOH-$CHCl_3$ (1:9), with identical ^{1}H NMR, ^{13}C NMR and mass spectra to those reported for natural micropine **1**.

(2*S*,3*R*,6*R*)-1-Methyl-2-hydroxymethyl-3-hydroxy-6-(1"*E*,3"*E*,5"*E*-decatrienyl)piperidine (epimicropine) 29

Acetonide **26** (0.064 g, 0.200 mmol) was dissolved in MeOH (5 mL), 66% aq. H_2SO_4 (43 drops) was added, and the mixture was stirred at r.t. overnight. Water (20 mL) was then added to the mixture and the solution washed once with ether (20 mL), basified to pH 10 with NH_4OH (5 mL), and extracted with ether. The combined extracts were washed with brine, dried, and evaporated *in vacuo* to afford an amber gum. The gum was separated by preparative TLC using MeOH-$CHCl_3$ (1:9) to afford *(2*S*,3*R*,6*R*)-1-methyl-2-hydroxymethyl-3-hydroxy-6-(1"*E*,3"*E*,5"*E* decatrienyl)piperidine* ***29*** as a yellow gum (0.010 g, 18%), R_f 0.19 using MeOH-$CHCl_3$ (1:9). ^{1}H NMR[16] δ: 0.89, t, *J* 7.0 Hz, $(H10")_3$; 1.20-1.42, m, $(H8")_2$ and $(H9")_2$; 1.60-1.77, m, $H_{ax}5$ and $H_{ax}4$; 1.80-1.99, m, $H_{eq}4$ and $H_{eq}5$; 2.10, dt, *J* 6.9, 6.7 Hz, $(H7")_2$; 2.38, s, *N*-Me; 2.54-2.59, m, H2; 3.40, m, H6; 3.44, br s, $(OH)_2$; 3.73, dd, *J* 11.8, 4.6 Hz, H_a1'; 3.87, ddd, *J* 8.7, 8.5, 4.3 Hz, H3; 4.03, dd, *J* 11.8, 2.8 Hz, H_b1'; 5.73, dt, *J* 15.1, 6.9 Hz, H6"; 5.83, *dd*, *J* 15.1, 9.0 Hz, H1"; 6.06, dd, *J* 15.9, 10.3 Hz, H5"; 6.06-6.20, m, H3" and H4"; 6.20, dd, *J* 14.0, 10.0 Hz, H2". ^{13}C NMR[15] δ: 13.9, C10"; 22.2, C9"; 27.7, C5";[13] 27.8, C4";[13] 31.4, C8"; 32.5, C7"; 39.7, *N*-Me; 58.1, C1'; 62.5, C6; 64.9, C2; 66.7, C3; 128.0, C1"; 129.2, C3" or C4"; 130.0, C5"; 134.0, 134.6, C2" and C3" or C4"; 136.6, C6".

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