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TETRAHEDRON: *ASYMMETRY*

Studies into the asymmetric Meisenheimer rearrangement

Jonathan E. H. Buston,[a] Iain Coldham[a,*] and Keith R. Mulholland[b]

[a]*Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK*

[b]*SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK*

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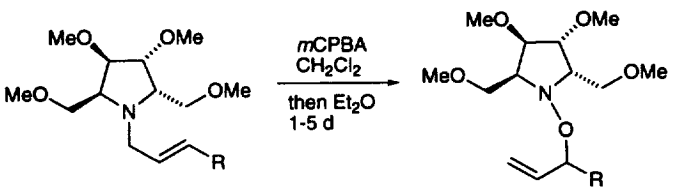
Abstract

Oxidation of a variety of *N*-allyl prolinol derivatives gave amine *N*-oxides with complete diastereoselectivity. On warming, these amine *N*-oxides undergo [2,3]-Meisenheimer rearrangement to give *O*-allyl hydroxylamines, albeit with low diastereoselectivity. Attempts to promote asymmetric *N*-oxidation of *N*-allyl tertiary amines with a variety of asymmetric oxidants produced only racemic *N*-oxides.

1. Introduction

The preparation of homochiral secondary and tertiary alcohols is an important area of contemporary organic synthesis.[1] One approach to the preparation of allylic alcohol products is the Meisenheimer rearrangement, first reported in 1919.[2] This involves the [2,3]-sigmatropic rearrangement of allylic tertiary amine-*N*-oxides to *O*-allyl hydroxylamines. Of a number of reports of this reaction in the literature,[3] only a few illustrate its potential for chirality transfer. Inouye,[4] Reetz[5] and more recently Davies[6] have shown 1,3-chirality transfer across the allyl system. A recent report by Enders[7] using C_2-symmetric amines gave *O*-allyl hydroxylamine products in 62–73% d.e. (Scheme 1).



Scheme 1.

An alternative and interesting approach to stereoselective alcohol formation is possible. A tertiary amine-*N*-oxide is configurationally stable and therefore there exists the possibility of transferring

* Corresponding author. Fax: 01392 263434; e-mail: I.Coldham@exeter.ac.uk

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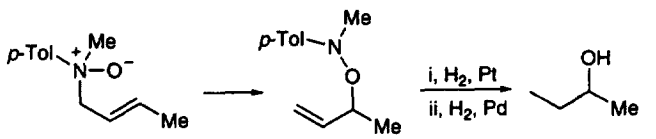
chirality from the nitrogen atom to the carbon centre. The use of non C_2-symmetric amines in the report by Enders[7] suggests that such asymmetric induction is very low. However, in these cases the diastereoselectivity on *N*-oxidation was unknown and it was therefore not possible to quantify the extent of any chirality transfer. Inouye[8] has shown (Scheme 2) that a chiral tertiary amine-*N*-oxide of 16% e.e. gave rise, after [2,3]-Meisenheimer rearrangement, N–O bond cleavage and olefin reduction, to a secondary alcohol with 13.6% e.e. This result suggests that transfer of chirality from the nitrogen atom to the carbon centre could be a useful procedure, although in this case selectivity in the oxidation to the amine-*N*-oxide was low. We report in this paper efforts directed towards the enantiospecific formation of tertiary amine-*N*-oxides and the transfer of chirality.

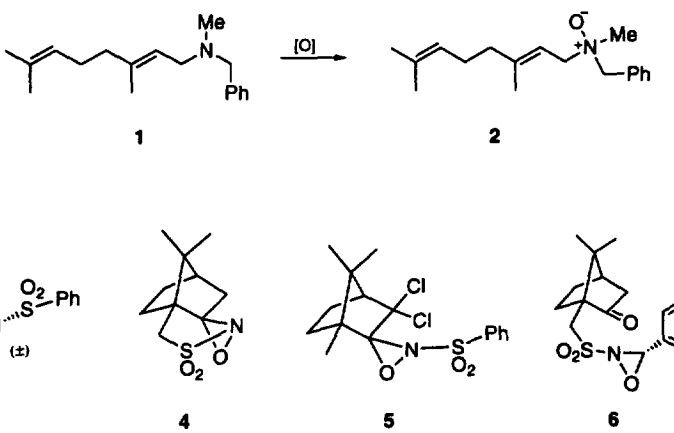


Scheme 2.

2. Results and discussion

The first aim of this work was to investigate the use of a chiral non-racemic oxidant to perform an asymmetric oxidation to an amine *N*-oxide. The extent of chirality transfer from the nitrogen atom to the carbon atom during the [2,3]-rearrangement could then be quantified. There has been remarkably little reported work on the asymmetric oxidation of amines, so our investigations of several approaches, analogous to the oxidation of sulfides to sulfoxides, are given below.

We first turned to the *N*-sulfonyl oxaziridines developed by Davis.[9] We found that, whilst the racemic sulfonyl oxaziridine **3**[10] would oxidise *N*-benzyl-*N*-methylgeranylamine **1**, neither of the two widely used chiral variants **4**[11] or **5**[12] gave any *N*-oxide **2** (Scheme 3). However, the oxaziridine **6**,[13] derived from camphor sulfonic acid, did oxidise the amine **1** in good yield, but the resultant amine *N*-oxide **2** was racemic, as determined by ^{1}H NMR spectroscopy in the presence of the Pirkle chiral solvating agent.[14] These results suggest that, for successful oxidation of a tertiary amine, an aromatic group is necessary on the *C*-terminus of the oxaziridine.

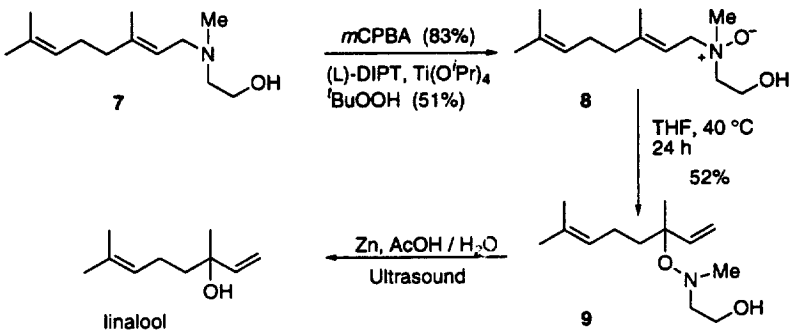


Scheme 3.

In a similar manner, the Jacobsen manganese salen complex,[15] popularised for asymmetric epoxidation, with hydrogen peroxide as the stoichiometric oxidant, gave only recovered unreacted amine **1**.

A range of conditions based on those developed by Kagan[16] and Uemura[17] for the asymmetric oxidation of sulfides were also investigated. Oxidation of amine **1** using ^{t}BuOOH with titanium(IV) isopropoxide, with or without tartrate co-ligand, or vanadium(IV) acetylacetonate failed to yield any amine *N*-oxide **2**, even after extended reaction times.

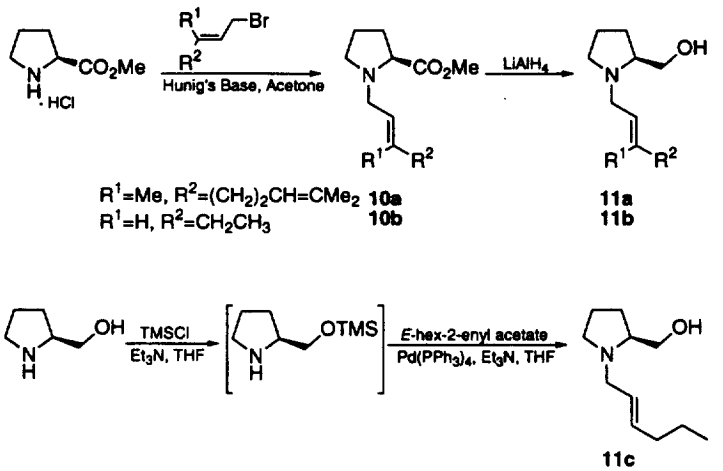
It has been reported that the kinetic resolution of a limited range of β-hydroxylamines is possible using a titanium(IV) isopropoxide/tartrate complex, but the enantioselectivity of oxidation at the nitrogen atom was not reported.[18] Therefore we synthesised the β-hydroxylamine **7** and subjected it to oxidation under the conditions developed by Sharpless. The resulting amine *N*-oxide **8** was racemic (as shown by ^{1}H NMR spectroscopy with the Pirkle chiral solvating agent) but was allowed to rearrange by refluxing in THF for 24 hours, to give the [2,3]-rearranged product **9** in reasonable yield (Scheme 4). The auxiliary was then cleaved by treatment with zinc in aqueous acetic acid (which required ultrasonic conditions[7]) to yield racemic linalool. Thus, while the presence of the β-hydroxyl functionality allowed oxidation of the amine, the oxidation gave racemic amine *N*-oxide.



Scheme 4.

Our attention then turned from the use of asymmetric oxidants to the use of chiral auxiliaries. It has been shown by O'Neil[19] that the oxidation of prolinamides and proline esters gives predominantly one amine *N*-oxide; we therefore investigated the used of prolinol as a chiral auxiliary. A range of *N*-allyl substituted prolinols was prepared by either *N*-alkylation of the appropriate proline ester followed by reduction (to the substrates **11a** and **11b**), or transient protection of prolinol with a trimethylsilyl group, palladium catalysed allylation and deprotection (to the substrate **11c**) (Scheme 5).

Oxidation of prolinols **11a–c** with *m*CPBA gave, in each case, only one diastereomer of the amine *N*-oxides **12a–c** in very good yields as stable crystalline products. The oxides were shown to be *syn* to the hydroxymethyl side-chain by ^{1}H NOE spectroscopy (d_6 acetone). This was later confirmed by an X-ray single crystal structure of the *N*-hexenyl compound **12c** (Fig. 1). The *N*-oxides **12a–c** were subjected to our optimised rearrangement conditions, by heating in THF at 40°C for 24 hours, to produce the trisubstituted hydroxylamines **13a–c** in good yield (Scheme 6). Examination (^{1}H NMR) of these resulting hydroxylamines showed that the diastereoselectivity in the rearrangement was very low. Separation of the diastereomeric linalyl hydroxylamines **13a** by careful column chromatography produced a sample of the hydroxylamine which had a *de* of 93% (determined by HPLC). Heating this purified hydroxylamine **13a** in THF for 24 hours caused a reduction of the *de* of this product to 25%. It therefore seems that, under the conditions needed to induce the Meisenheimer rearrangement in these compounds, the rearrangement is reversible, and little asymmetric induction occurs in the reaction. This may be attributed to the stability of the amine *N*-oxide provided by the hydrogen bonding between the oxide and hydroxymethyl side-chain.



Scheme 5.

Finally the C_2-symmetric bis(methoxymethyl)pyrrolidine **14** was prepared by the alkylation of the commercially available bis(methoxymethyl)pyrrolidine with geranyl bromide (Scheme 7). Applying the oxidation-rearrangement conditions developed by Enders,[7] led to a 60% yield of the desired product **15**, with a *de* at the newly formed centre being 29% (determined by ^{1}H NMR). The major product was found to have the (*S*)-configuration, as determined by the optical rotation of the linalool produced after cleaving the N–O bond with zinc/acetic acid/ultrasound.

3. Conclusion

We have found that the use of prolinol as a chiral auxiliary allows the formation of single diastereomeric amine *N*-oxides, although these oxides undergo the Meisenheimer rearrangement with low stereoselectivity. The direct asymmetric oxidation of tertiary amines with a chiral oxidant remains a challenge. The rearrangement of chiral allylic *N*-oxides which do not bear pendant hydroxyl groups may still allow the transfer of chirality from the nitrogen atom to the carbon centre.[20]

4. Experimental

Optical rotations were measured on an Optical Activity Ltd AA-1000 polarimeter, using a cell with a path length of 0.5 dm. IR spectra were recorded as liquid films on NaCl plates unless otherwise stated, using a Perkin–Elmer 881 spectrometer. Bands are recorded as broad (br), weak (w), medium (m) or strong (s) and are quoted to the nearest 5 cm^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on a Bruker AM 250 MHz, Jeol GX 270 MHz, Bruker AC 300 MHz, Bruker AMX 400 MHz or Bruker Avance DPX 400 MHz spectrometer using the solvent as an internal lock. Chemical shifts are recorded in parts per million. Coupling constants, *J*, are recorded to the nearest 0.1 Hz. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). ^{13}C NMR spectra are recorded on the above spectrometers operating at 63, 68, 75 or 100 MHz. Mass spectra were measured on either a Kratos Profile HV3 spectrometer using electron impact ionisation, or a VG Trio-2 single quadrapole spectrometer, with electron impact or ammonium ion ionisation. High resolution mass spectra are measured on the molecular ion.

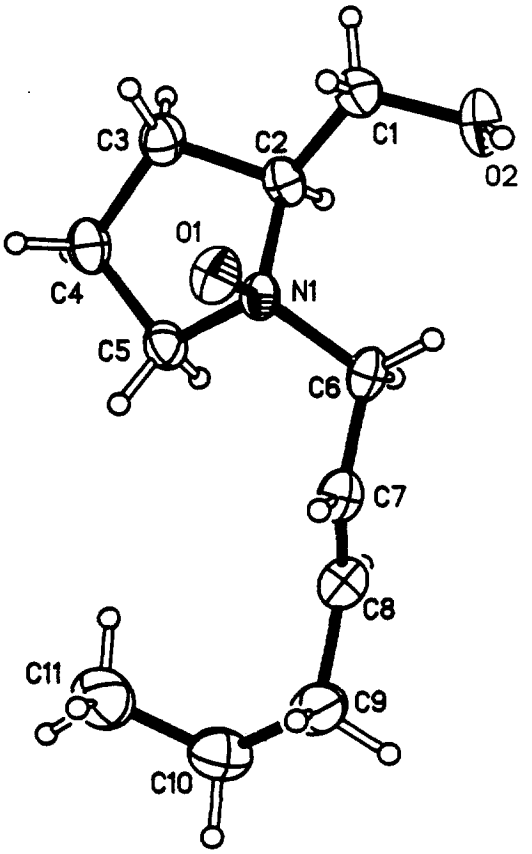
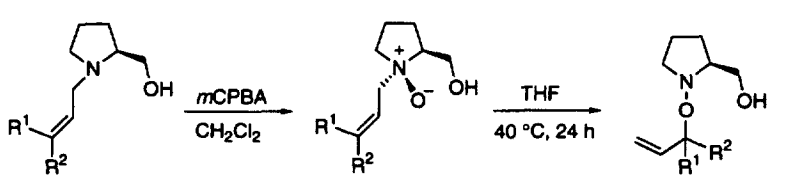


Fig. 1. X-Ray crystal structure of compound **12c**. Thermal ellipsoids are at the 50% probability level

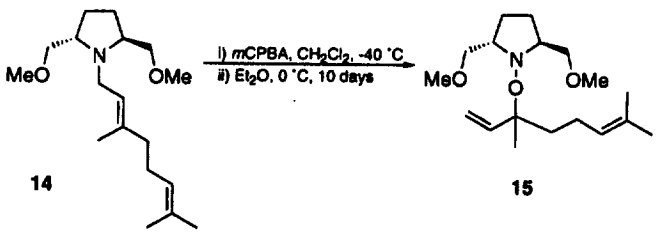


11 **12** **13**

Compound	R^1	R^2	**12** Yield (%), d.e. (%)	**13** Yield (%), d.e. (%)
a	Me	$(CH_2)_2CH{=}CMe_2$	80, 100	75, 5
b	H	CH_2CH_3	90, 100	78, 0
c	H	$CH_2CH_2CH_3$	92, 100	89, 0

Scheme 6.

THF was freshly distilled from sodium benzophenone ketal. Petrol, which refers to light petroleum (b.p. 40–60°C), CH_2Cl_2 and EtOAc were all distilled before use. Flash column chromatography was performed on silica gel 60H (230–400 mesh) (Merck 9385). T.L.C was performed on Kieselgel $60F_{254}$ 0.25 mm plates, and visualised by U.V. irradiation at 254 nm, ninhydrin or potassium permanganate dips. Ultrasonic irradiation was achieved by immersion in a Sonicor SC-120 cleaning bath.



Scheme 7.

*m*CPBA (35% supplied by Jannsen) was concentrated to ~85% before use by washing with a phosphate buffer solution at pH 7.5 and extraction into CH_2Cl_2. Zinc dust was activated by sequential washing in hydrochloric acid (2 M), water and ethanol, followed by drying *in vacuo*. All other chemicals were used as supplied.

4.1. N-*(2-Hydroxyethyl)*-N-*methylgeranylamine 7*

To a solution of sarcosine ethyl ester hydrochloride (3.07 g, 20 mmol) in acetone (50 cm^3) was added geranyl bromide (3.97 cm^3, 20 mmol) and ethyldiisopropylamine (10.4 cm^3, 60 mmol). This solution was stirred at room temperature for 24 hours before the solvent was removed *in vacuo*. The product was extracted with EtOAc (3×10 cm^3), washed with water (2×5 cm^3) and brine (5 cm^3), dried over Na_2SO_4 and purified by flash chromatography, eluting with petrol:EtOAc (4:1) to give *N*-geranyl sarcosine ethyl ester (3.32 g, 13 mmol, 65%) as an oil. R_f 0.23 (petrol:EtOAc=4:1); ν_{max}/cm^{-1} 1755 m, 1740 s (C=O); ^1H NMR (250 MHz) 1.23 (3H, t, *J* 7, CH_2CH_3), 1.56 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.97–2.07 (4H, m, CH_2CH_2), 2.32 (3H, s, NCH_3), 3.08 (2H, d, *J* 7, NCH_2CH), 3.18 (2H, s, NCH_2CO_2Et), 4.14 (2H, q, *J* 7, OCH_2CH_3), 5.04 (1H, t, *J* 4, $Me_2C=CH$), 5.21 (1H, t, *J* 7, NCH_2CH); ^{13}C NMR (63 MHz) 14.15 (CH_2CH_3), 16.17 (CH_3), 17.53 (CH_3), 25.53 (CH_3), 28.35 ($Me_2C=CHCH_2$), 39.70 ($Me_2C=CHCH_2CH_2$), 42.28 (NCH_3), 54.35 ($NCH_2CH=$), 57.57 (OCH_2CH_3), 60.22 (NCH_2CO_2Et), 121.02 ($NCH_2CH=$), 124.07 ($Me_2C=CH$), 131.38 ($Me_2C=CH$), 139.17 ($NCH_2CH=C$), 171.00 (C=O); *m/z* (EI^+) 253 (4%, M^+), 180 (33, M^+-CO_2Et), 166 (9), 137 (8), 81 (38), 69 (100, $Me_2C=CH_2^+$); found: M^+ 253.2042, $C_{15}H_{27}NO_2$ requires 253.2042.

To a solution of *N*-geranyl sarcosine ethyl ester (1.51 g, 6 mmol) in dry ether (30 cm^3) was added $LiAlH_4$ (1 M in ether, 15 cm^3, 15 mmol). The solution was stirred for 24 hours before the excess $LiAlH_4$ was quenched by the dropwise addition of NaOH (5 M). The product was extracted into Et_2O (2×10 cm^3), dried over Na_2SO_4 and purified by flash chromatography, eluting with CH_2Cl_2:EtOH:NH_3 (100:8:1) to give *N*-(2-hydroxyethyl)-*N*-methylgeranylamine **7** (1.11 g, 5.28 mmol, 88%) as an oil. ν_{max}/cm^{-1} 3400 bs (O–H), 1670 w (C=C); ^1H NMR (250 MHz) 1.54 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.95–2.05 (4H, m, CCH_2CH_2), 2.17 (3H, s, NCH_3), 2.46 (2H, t, *J* 5, NCH_2CH_2OH), 2.97 (2H, d, *J* 7, $NCH_2CH=$), 3.32 (1H, bs, OH), 3.55 (2H, t, *J* 5, CH_2OH), 5.00–5.05 (1H, m, $Me_2C=CH$), 5.18 (1H, td, *J* 7 and 1, $NCH_2CH=$); ^{13}C NMR (63 MHz) 16.22 (CH_3), 17.54 (CH_3), 25.33 (CH_3), 26.43 ($Me_2C=CHCH_2$), 39.71 (CH_2), 41.52 (NCH_3), 55.12 (NCH_2CH), 58.43 (CH_2), 58.65 (CH_2), 121.05 (NCH_2CH), 124.07 ($Me_2C=CH$), 131.34 ($Me_2C=CH$), 138.64 ($NCH_2CH=C$); *m/z* (EI^+) 211 (2.5%, M^+), 180 (46, M^+-CH_2OH), 137 (8), 81 (37), 69 (100, $Me_2C=CH_2^+$); found: M^+ 211.1931, $C_{13}H_{25}NO$ requires 211.1931.

4.2. N-(2-Hydroxyethyl)-N-methylgeranylamine N-oxide 8

Method 1: To *N*-(2-hydroxyethyl)-*N*-methylgeranylamine **7** (422 mg, 2 mmol) in CH_2Cl_2 was added *m*CPBA (70%, 491 mg, 2 mmol). After 2 hours, the solvent was evaporated and the residue was purified by flash chromatography, eluting with Et_2O:MeOH (1:1), to give *N*-(2-hydroxyethyl)-*N*-methylgeranylamine *N*-oxide **8** (377 mg, 1.66 mmol, 83%) as an oil. R_f 0.09 (Et_2O:MeOH, 7:3); ν_{max}/cm^{-1} 3200 bs (O–H), 925 m (N–O); ^1H NMR (300 MHz) 1.59 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.75 (3H, s, CH_3), 2.08–2.20 (4H, m, CCH_2CH_2), 3.09 (3H, s, NCH_3), 3.20–3.27 (1H, m, NCH^AH^BCH=), 3.34–3.47 (1H, m, NCH^AH^BCH=), 3.87–4.10 (4H, m, NCH_2CH_2OH), 5.00–5.09 (1H, m, Me_2C=C*H*), 5.37 (1H, t, *J* 7, NCH_2CH=); ^{13}C NMR (75 MHz) 16.79 (CH_3), 17.64 (CH_3), 25.62 (CH_3), 26.02 (Me_2C=CHCH_2), 39.80 (Me_2C=$CHCH_2CH_2$), 54.92 (NCH_3), 57.90 (NCH_2CH=), 65.69 (CH_2), 68.87 (CH_2), 113.87 (NCH_2CH=), 123.29 (Me_2C=CH), 132.18 (Me_2C=CH), 146.97 (NCH_2CH=*C*); *m/z* (EI^+) 227 (0.1%, M^+), 180 (13), 137 (10), 91 (51, M^+−geranyl), 81 (39), 69 (100, Me_2C=CH_2^+); found: M^+ 227.1885, $C_{13}H_{25}NO_2$ requires 227.1185.

Method 2: A solution of the aminoalcohol **7** (211 mg, 1 mmol), (L)-(+)-diisopropyltartrate (280 mg, 1.2 mmol) and titanium tetraisopropoxide (601 μl, 2.04 mmol) in dry CH_2Cl_2 (15 cm^3) was allowed to stir at room temperature for 30 minutes. The mixture was cooled to 0°C and ^{t}BuOOH (5 M in decane, 240 μl, 1.2 mmol) was added. This solution was then stirred at room temperature for 24 hours before being quenched by the dropwise addition of NaOH (5 M). After 5 hours a white suspension formed. The reaction mixture was then dried over Na_2SO_4, filtered through Kieselguhr and purified by flash chromatography as above to give *N*-(2-hydroxyethyl)-*N*-methylgeranylamine *N*-oxide **8** (115 mg, 0.51 mmol, 51%) as a colourless oil, spectroscopically identical to the product from the previous reaction. ^1H NMR studies with the Pirkle solvating agent showed that this compound was racemic.

4.3. Rearrangement to form N-(2-hydroxyethyl)-N-methyl-O-linalyl hydroxylamine 9

A solution of the amine *N*-oxide **8** (224 mg, 0.98 mmol) in THF (30 cm^3) was warmed (50°C) for 24 hours. The solvent was removed *in vacuo* and the residue purified by flash chromatography, eluting with petrol:EtOAc (4:1) to give *N*-(2-hydroxyethyl)-*N*-methyl-*O*-linalyl hydroxylamine **9** (116 mg, 0.50 mmol, 52%) as an oil. R_f 0.51 (petrol:EtOAc=4:1); ν_{max}/cm^{-1} 3390 bs (O–H), 1640 w (C=C), 920 s (N–O); ^1H NMR (300 MHz) 1.32 (3H, s, CH_3), 1.50–1.56 (2H, m, $OCCH_2CH_2$), 1.57 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.89–1.97 (2H, m, $OCCH_2CH_2$), 2.50 (1H, bs, OH), 2.58 (3H, s, NCH_3), 2.82–2.88 (2H, m, NCH_2), 3.63–3.70 (2H, m, CH_2OH), 5.06 (1H, t, *J* 6, Me_2C=C*H*), 5.11–5.19 (2H, m, CH=CH_2), 5.94 (1H, dd, *J* 18 and 11, CH=CH_2); ^{13}C NMR (75 MHz) 17.59 (CH_3), 21.07 (CH_3), 22.71 (Me_2C=$CHCH_2$), 25.60 ($OCCH_3$), 39.37 (Me_2C=$CHCH_2CH_2$), 47.38 (NCH_3), 59.53 (NCH_2CH_2OH), 63.41 (CH_2OH), 81.61 ($OCCH_3$), 114.57 (CH=CH_2), 124.30 (Me_2C=CH), 131.40 (Me_2C=CH), 143.01 (CH=CH_2); *m/z* (EI^+) 227 (0.4%, M^+), 180 (12), 137 (71, geranyl$^+$), 91 (100), 81 (91), 69 (96, Me_2C=CH_2^+), 60 (96, $NHCH_2CH_2OH^+$); found: M^+ 227.1885, $C_{13}H_{25}NO_2$ requires 227.1885.

4.4. N-Geranyl-(L)-proline methyl ester 10a

To a solution of (L)-proline methyl ester hydrochloride (0.99 g, 6.03 mmol) in acetone (30 cm^3) was added ethyldiisopropylamine (3.1 cm^3, 18.1 mmol) and geranyl bromide (1.31 cm^3, 6.63 mmol). The resulting solution was heated at reflux for 24 hours. Upon cooling a white precipitate formed. The acetone was removed *in vacuo*, and the resulting mixture extracted with EtOAc (2×20 cm^3), washed with water

(2×10 cm^3) and brine (1×5 cm^3), dried over Na_2SO_4, and purified by flash chromatography, eluting with petrol:EtOAc (4:1) to give *N*-geranyl-(L)-proline methyl ester **10a** (1.25 g, 4.7 mmol, 79%) as an oil. R_f 0.25 (petrol:EtOAc=4:1); $[\alpha]_D^{24}$ −63.53 (c 1.6 in $CHCl_3$); ν_{max}/cm^{-1} 1735 s (C=O); ^{1}H NMR (250 MHz) 1.49 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.66–2.04 (8H, m, $Me_2C{=}CCH_2CH_2$ and $NCH_2CH_2CH_2$), 2.21–2.32 (1H, m, $NCH^AH^BCH_2$), 2.96–3.11 (3H, m, $NCH^AH^BCH_2$ and $NCH_2CH{=}$), 3.22 (1H, dd, *J* 13 and 7, $NCHCO_2Me$), 3.65 (3H, s, OCH_3), 4.98 (1H, td, *J* 6 and 1, $CH{=}CMe_2$), 5.21 (1H, td, *J* 7 and 1, $NCH_2CH{=}$); ^{13}C NMR (62 MHz) 16.16 (CH_3), 17.50 (CH_3), 23.06 (CH_2, ring C_4), 25.51 (CH_3), 26.37 (CH_2), 29.43 (CH_2, ring C3), 39.69 (MeC–CH_2–), 51.53 (NCH_2CH), 53.27 (OCH_3), 53.36 (NCH_2CH_2), 65.19 ($NCHCO_2Me$), 120.85 ($NCH_2CH{=}$), 124.19 ($Me_2C{=}CH$), 131.32 ($Me_2C{=}CH$), 138.41 ($NCH_2CH{=}C$), 174.66 (C=O); *m/z* (EI$^+$) 266 (2%, MH^+), 207 (22, MH^+-CO_2Me), 136 (10), 122 (14), 70 (100), 69 (99, $Me_2C{=}CH_2^+$); found: M^+ 265.2042, $C_{16}H_{27}NO_2$ requires 265.2042.

4.5. N-*Geranyl-[2-(S)-hydroxymethyl]pyrrolidine* ***11a***

To a solution of $LiAlH_4$ (0.90 g, ~25 mmol) in dry THF (100 cm^3) was added dropwise a solution of *N*-geranyl-(L)-proline methyl ester (2.52 g, 9.53 mmol) in THF (15 cm^3). The resulting solution was stirred at room temperature for 3 hours before being quenched by the dropwise addition of NaOH (5 M). EtOAc (150 cm^3) was added and the solution was dried (Na_2SO_4). The resulting suspension was filtered through Kieselguhr and was purified by dry flash chromatography eluting with CH_2Cl_2:EtOH:NH_3 (100:8:1) to give *N*-geranyl prolinol **11a** (2.18 g, 9.2 mmol, 96%) as an oil. R_f 0.44 (CH_2Cl_2:EtOH=4:1); $[\alpha]_D^{20}$ −27.6 (c 1.7 in $CHCl_3$); ν_{max}/cm^{-1} 3415 bm (OH); ^{1}H NMR (300 MHz) 1.59 (3H, s, $MeCH_3C{=}CH$, *cis*), 1.62 (3H, s, $CH_2CH_3C{=}CH$), 1.66 (3H, s, $MeCH_3C{=}CH$, *trans*), 1.73–1.91 (4H, m, $NCH_2CH_2CH_2$), 1.95–2.11 (4H, m, $Me_2C{=}CCH_2CH_2$), 2.22–2.31 (1H, m, $NCH^AH^BCH_2$), 2.54–2.61 (1H, m, $NCHCH_2OH$), 2.94 (1H, dd, *J* 13 and 8, $NCH^AH^BCH{=}$), 3.04–3.11 (1H, m, $NCH^AH^BCH_2$), 3.30 (1H, dd, *J* 13 and 6, $NCH^AH^BCH{=}$), 3.38 (1H, dd, *J* 11 and 3, CH^AH^BOH), 3.61 (1H, dd, *J* 11 and 4, CH^AH^BOH), 5.06 (1H, t, *J* 8, $Me_2C{=}CH$), 5.26 (1H, t, *J* 8, $C{=}CHCH_2N$); ^{13}C NMR (75 MHz) 16.26 (CH_3), 17.63 (CH_3), 23.40 (NCH_2CH_2), 25.63 (CH_3), 26.43 ($MeCCH_2$), 27.85 ($NCHCH_2$), 39.72 ($Me_2C{=}CHCH_2$), 51.32 (NCH_2CH), 54.19 (NCH_2CH_2), 62.19 (CH_2OH), 64.05 ($NCHCH_2OH$), 121.60 ($NCH_2CH{=}$), 124.11 ($CH{=}CMe_2$), 131.44 ($NCH_2CH{=}C$), 137.81 ($CH{=}CMe_2$); *m/z* (CI$^+$, NH_3) 238 (100%, MH^+), 206 (95, M^+-CH_2OH), 70 (70); found: M^+ 237.2093, $C_{15}H_{27}NO$ requires 237.2093.

4.6. N-*Geranyl-[2-(S)-hydroxymethyl]pyrrolidine* N-*oxide* ***12a*** *(Fig. 2)*

To a solution of *N*-geranyl prolinol **11a** (750 mg, 3.16 mmol) in CH_2Cl_2 (25 cm^3) at room temperature was added *m*CPBA (80%, 680 mg, 3.16 mmol). The solution was stirred for 1 hour and the product was purified by flash chromatography, eluting with CH_2Cl_2:EtOH (4:1) to give an oil. This solidified after standing *in vacuo* for several hours and was recrystallised from CH_2Cl_2:Et_2O to give *N*-geranyl [2-(*S*)-hydroxymethyl]pyrrolidine *N*-oxide **12a** (636 mg, 2.51 mmol, 80%) as needles. M.p. 104–106°C; R_f: 0.24 (CH_2Cl_2:EtOH=4:1); $[\alpha]_D^{25}$ −1.96 (c 0.65 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3400 b (OH), 1670 w (C=C), 925 s (N–O); ^{1}H NMR (300 MHz) 1.53 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.67 (3H, s, $CH{=}CCH_3$), 1.74–1.96 (2H, m, NCH_2CH_2), 2.03–2.10 (4H, m, $Me_2C{=}CCH_2CH_2$), 2.23–2.39 (1H, m, $NCH_2CH_2CH^AH^B$), 2.51–2.65 (1H, m, $NCH_2CH_2CH^AH^B$), 3.15–3.31 (3H, m, H_a and NCH_2CH_2), 3.70 (1H, dd, *J* 13 and 4, OCH^AH^B), 3.92 (1H, dd, *J* 13 and 8, H_b), 4.02 (1H, dd, *J* 13 and 8, H_c), 4.16 (1H, dd, *J* 13 and 2, OCH^AH^B), 4.93–5.00 (1H, m, $Me_2C{=}CH$), 5.39 (1H, t, *J* 8,

NCH_2CH=); ^{13}C NMR (75 MHz) 16.72 (CH_3), 17.64 (CH_3CMe, *trans*), 20.36 (CH_2, ring C4), 23.33 (CH_2, ring C3), 25.60 (CH_3CMe, *cis*), 26.04 (Me_2C=$CHCH_2$), 39.78 ($MeCCH_2$), 59.37 (CH_2O), 63.42 (CH_bH_c), 66.42 (NCH_2), 70.50 (CH_a), 114.31 (NCH_2CH=), 123.39 (Me_2C=CH), 132.06 (Me_2C), 145.84 (NCH_2CH=C); *m/z* (CI^+, NH_3) 270 (12%, MNH_4^+), 254 (10, MH^+), 236 (20, M^+-OH), 206 (15); found: M^+ 253.2048, $C_{15}H_{27}NO_2$ requires 253.2042.

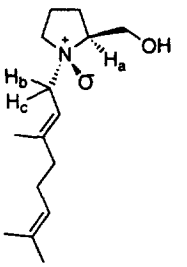


Fig. 2.

Further NMR experiments were carried out using d_6-acetone as a solvent to establish the stereochemistry of the product; ^1H NMR (400 MHz, d_6-acetone) 1.60 (3H, s, CH_3, *trans*), 1.66 (3H, s, CH_3, *cis*), 1.75 (3H, s, CH=CCH_3), 1.80–1.88 (1H, m, $NCH_2CH^AH^B$), 1.89–1.99 (1H, m, $NCH_2CH_2CH^AH^B$), 2.11–2.25 (5H, m, Me_2C=CCH_2CH_2 and $NCH_2CH^AH^B$), 2.47–2.57 (1H, m, $NCH_2CH_2CH^AH^B$), 3.09–3.15 (1H, m, $NCH^AH^BCH_2$), 3.34 (1H, dd, *J* 10 and 8, $NCH^AH^BCH_2$), 3.38–3.43 (1H, m, H_a), 3.59 (1H, dd, *J* 13 and 3, OCH^AH^B), 3.92 (1H, dd, *J* 13 and 8, H_c), 4.01 (1H, dd, *J* 13 and 7, H_c), 4.16 (1H, dd, *J* 13 and 2, OCH^AH^B), 5.08–5.13 (1H, m, Me_2C=CH), 5.64 (1H, t, *J* 8, NCH_2CH=); ^{13}C NMR (100 MHz, d_6-acetone) 15.89 (CH_3), 16.86 (CH_3CMe, *trans*), 20.14 (CH_2, ring C4), 23.27 (CH_2, ring C3), 24.95 (CH_3CMe, *cis*), 26.01 (Me_2C=$CHCH_2$), 39.60 ($MeCCH_2$), 59.09 (CH_2O), 63.52 (CH_bH_c), 66.45 (NCH_2), 70.65 (CH_a), 115.88 (NCH_2CH=), 123.90 (Me_2C=CH), 131.28 (Me_2C), 143.29 (NCH_2CH=C); NOE experiments: irradiation of H_a caused 4.1% enhancement of $H_{b,c}$; irradiation of $H_{b,c}$ caused 7.2% enhancement of H_a.

4.7. O-(R,S)-Linalyl-[2-(S)-hydroxymethyl]pyrrolidine hydroxylamine **13a**

A solution of *N*-oxide **12a** (504 mg, 1.99 mmol) in THF (20 cm^3) was heated at 50°C for 24 h. Evaporation gave the crude hydroxylamine **13a** (378 mg, 75%), which was a mixture of diastereomers (53:47, 6% d.e.). The diastereomeric excess was assessed by HPLC [Chiralpak AD column (250×4.6 mm), eluting with hexane:*i*-propanol (99:1) at a rate of 1.0 cm^3/min. Product detection was by UV at 215 nm]. Flash chromatography, eluting with petrol:EtOAc (4:1), partially separated these two diastereomers to give *O*-(*S*)-linalyl-[2-(*S*)-hydroxymethyl]pyrrolidine hydroxylamine **13a** (126 mg, 25%), 93% *de* as an oil. HPLC retention time 5.2 min; $[\alpha]_D^{20}$ −25.0 (c 1.5 in $CHCl_3$); ν_{max}/cm^{-1} 3455 bs (OH), 1640 w (C=C), 920 s (N–O); ^1H NMR (400 MHz) 1.34 (3H, s, $OCCH_3$), 1.42–1.53 (3H, m, CH_3), 1.58 (3H, s, CH_3), 1.62–1.71 (4H, m, CH_2CH_2), 1.76–2.00 (4H, m, CH_2CH_2), 2.45 (1H, bs, $NCHCH_2OH$), 2.88–2.96 (1H, m, NCH^AH^B), 3.07–3.18 (2H, m, NCH^AH^B and CH^AH^BOH), 3.30 (1H, bs, OH), 3.57–3.64 (1H, m, CH^AH^BOH), 5.03–5.10 (1H, m, Me_2C=CH), 5.14 (1H, dd, *J* 18 and 1, CH=CH^AH^B, *cis*), 5.19 (1H, dd, *J* 11 and 1, CH=CH^AH^B, *trans*), 5.95 (1H, dd, *J* 18 and 11, CH=CH_2); ^{13}C NMR (100 MHz) 17.62 (CH_3), 21.17 (CH_3), 21.58 (CH_2), 22.69 (CH_2), 24.11 (CH_2), 25.65 ($OCCH_3$), 39.97 ($OCCH_2$), 58.00 (NCH_2CH_2), 62.37 (CH_2OH), 69.32 ($NCHCH_2OH$), 81.37 (OC), 114.71 (CH=CH_2), 124.45 (CH=CMe_2), 131.33 (CH=CMe_2), 143.75 (CH=CH_2); *m/z* (EI^+) 254 (35%, MH^+), 137 (30, linalyl$^+$), 117 (75, $C_5H_{11}NO_2^+$), 86 (100, $C_4H_8NO^+$), 69 (78, $C_5H_9^+$); found: M^+ 253.2050, $C_{15}H_{27}NO_2$

requires 253.2042; and *O*-(*R*)-linalyl-[2-(*S*)-hydroxymethyl]pyrrolidine hydroxylamine **13a** (252 mg, 50%), 51% *de* as an oil. HPLC retention time of major diastereomer 6.1 min; $[\alpha]_D^{20}$ −14.4 (c 1.05 in $CHCl_3$); ν_{max}/cm^{-1} 3430 bm (OH), 1640 w (C=C), 920 s (N–O); ^1H NMR (400 MHz) 1.29 (3H, s, $OCCH_3$), 1.44–1.72 (10H, m, Me_2C and CH_2CH_2), 1.76–2.01 (4H, m, CH_2CH_2), 2.40 (1H, bs, $NCHCH_2OH$), 2.85–2.94 (1H, m, NCH^AH^B), 3.08–3.18 (2H, m, NCH^AH^B and CH^AH^BOH), 3.40 (1H, bs, OH), 3.61–3.65 (1H, m, CH^AH^BOH), 5.06–5.19 (3H, m, $Me_2C{=}CH$ and $CH{=}CH_2$), 5.97 (1H, dd, *J* 18 and 11, $CH{=}CH_2$); ^{13}C NMR (100 MHz) 17.66 (CH_3), 21.58 (CH_3), 21.84 (CH_2), 22.76 (CH_2), 23.87 (CH_2), 25.68 ($OCCH_3$), 38.80 ($OCCH_2$), 57.75 (NCH_2CH_2), 62.75 (CH_2OH), 68.96 ($NCHCH_2OH$), 81.09 (OC), 114.13 ($CH{=}CH_2$), 124.47 ($CH{=}CMe_2$), 131.36 ($CH{=}CMe_2$), 143.72 ($CH{=}CH_2$); *m/z* (EI^+) 254 (65%, MH^+), 206 (35), 137 (40, linalyl$^+$), 117 (80, $C_5H_{11}NO_2^+$), 86 (100, $C_4H_8NO^+$), 69 (75, $C_5H_9^+$).

4.8. *Epimerisation of* O-(S)-*linalyl-[2-(S)-hydroxymethyl]pyrrolidine hydroxylamine* **13a**

The (*S,S*)-hydroxylamine **13a** (106 mg, 0.42 mmol, *de*: 93%) in THF (20 cm^3) was heated at 50°C for 24 hours. The resulting mixture was analysed by HPLC (conditions as above) and found to consist of the (*S,S*)-hydroxylamine **13a** (R_t=5.2 minutes, 60% of the total area), the (*R,S*)-hydroxylamine **13a** (R_t=6.1 minutes, 35% of the total area) and an unidentifed impurity (R_t=6.5 minutes, 5% of the total area). Thus the *de* of the hydroxylamine **13a** had reduced to 25%.

4.9. *Cleavage of* O-(R)-*linalyl-[2-(S)-hydroxymethyl]pyrrolidine hydroxylamine* **13a**

A solution of (*R,S*)-hydroxylamine **13a** (213 mg, 0.84 mmol, 51% *de*) in AcOH:water (1:1) (20 cm^3) was subjected to ultrasonic irradiation in the presence of freshly activated zinc dust for 5 hours. The product was extracted with Et_2O (5×10 cm^3), dried (Na_2SO_4) and purified by flash chromatography, eluting with petrol:EtOAc (4:1) to yield (*R*)-linalool (110 mg, 0.71 mmol) as a fragrant oil, $[\alpha]_D^{25}$ −9.5 (c 0.64 in $CHCl_3$), with spectroscopic data in accordance with the literature.[21] The *ee* of the product was determined to be 45% by chiral GC; (Instrument HP5890 GC with a HP5970 MSD, detection by EI mass spectrometry. CP-cyclodextrin-β-236-M-19 column, 50 m×0.25 μm, 0.25 μm film; oven temperature 95°C, with helium (20 psi) as the carrier gas; retention times 37.54 and 38.15 min).

4.10. N-*Pent-2-enyl-(L)-proline methyl ester* **10b**

To a solution of (L)-proline methyl ester (5.55 g, 33.5 mmol) in MeCN (100 cm^3) was added 1-bromopent-2-ene (5.0 g, 33.5 mmol) and potassium carbonate (14 g, 100 mmol). The resulting suspension was heated at reflux for 24 h before the solvent was removed *in vacuo*, and the resulting mixture extracted with EtOAc (3×20 cm^3) washed with water (2×10 cm^3) and brine (5 cm^3) and dried (Na_2SO_4). The resultant oil was purified by flash chromatography, eluting with petrol:EtOAc (6:4) to give *N*-pent-2-enyl-(L)-proline methyl ester **10b** (2.95 g, 14.9 mmol, 45%) as an oil. R_f 0.21 (petrol:EtOAc=3:1); $[\alpha]_D^{20}$ −92.8 (c 1.8 in $CHCl_3$); ν_{max}/cm^{-1} 1735 s (C=O); ^1H NMR (400 MHz) 0.97 (3H, t, *J* 7, CH_2CH_3), 1.73–1.83 (1H, m, $NCHCH^AH^B$), 1.87–1.96 (2H, m, NCH_2CH_2), 1.99–2.06 (2H, m, CH_2CH_3), 2.08–2.17 (1H, m, $NCHCH^AH^B$), 2.32–2.41 (1H, m, $NCH^AH^BCH_2$), 3.06–3.23 (4H, m, $NCH_2CH{=}$, $NCHCO_2Me$ and $NCH^AH^BCH_2$), 3.71 (3H, s, OCH_3), 5.47–5.56 (1H, m, $NCH_2CH{=}CH$), 5.59–5.68 (1H, m, $NCH_2CH{=}CH$); ^{13}C NMR (100 MHz) 13.40 (CH_3), 23.14 (CH_2, ring C4), 25.28 (CH_2, ring C3), 29.56 ($=CHCH_2CH_3$), 51.75 (OCH_3), 53.60 (NCH_2CH_2), 57.01 ($NCH_2CH{=}$), 65.30 ($NCHCO_2Me$), 125.60 ($NCH_2CH{=}$), 134.74 ($NCH_2CH{=}CH$), 174.80 (C=O); *m/z* (EI^+) 198 (10%,

MH^+), 138 (100, M^+-CO_2Me), 70 (35, M^+-CO_2Me and pentenyl); found M^+ 197.1413, $C_{11}H_{19}NO_2$ requires 197.1416.

4.11. N-*Pent-2′-enyl-[2-(S)-hydroxymethyl]pyrrolidine* **11b**

To *N*-pent-2-enyl-(L)-proline methyl ester (1.5 g, 7.60 mmol) in dry ether (50 cm^3) was added a solution of $LiAlH_4$ (1.0 M in ether, 11.4 cm^3, 11.4 mmol). The resulting solution was stirred at room temperature for 3 days before being quenched by the dropwise addition of NaOH (5 M). EtOAc (150 cm^3) was added and the solution was dried (Na_2SO_4), filtered through Kieselguhr, evaporated and purified by flash chromatography, eluting with CH_2Cl_2:EtOH (9:1), to give *N*-pent-2′-enyl-[2-(*S*)-hydroxymethyl]pyrrolidine **11b** (0.82 g, 2.67 mmol, 64%) as an oil. $[\alpha]_D^{20}$ −35.5 (c 1.2 in $CHCl_3$); ν_{max}/cm^{-1} 3385 bm (OH), 1670 w (C=C); ^1H NMR (400 MHz) 0.99 (3H, t, *J* 7, CH_2CH_3), 1.67–1.81 (3H, m, $NCH_2CH_2CH^AH^B$), 1.84–1.94 (1H, m, $NCH_2CH_2CH^AH^B$), 1.99–2.11 (2H, m, $=CHCH_2CH_3$), 2.28–2.37 (1H, m, $NCH^AH^BCH_2$), 2.61–2.67 (1H, m, $NCHCH_2OH$), 2.86–2.94 (1H, m, $NCH^AH^BCH=$), 3.07–3.15 (1H, m, $NCH^AH^BCH_2$), 3.32–3.41 (2H, m, $NCH^AH^BCH=$ and OH), 3.43 (1H, dd, *J* 11 and 3, CH^AH^BOH), 3.64 (1H, dd, *J* 11 and 4, CH^AH^BOH), 5.46–5.55 (1H, m, $NCH_2CH=CH$), 5.62–5.69 (1H, m, $NCH_2CH=CH$); ^{13}C NMR (100 MHz) 13.58 (CH_2CH_3), 23.43 (CH_2, ring C4), 25.37 (CH_2, ring C3), 27.81 (CH_2CH_3), 54.19 ($NCH_2CH=$), 56.51 (NCH_2CH_2), 62.25 (CH_2OH), 64.24 ($NCHCH_2OH$), 125.83 ($NCH_2CH=CH$), 135.55 ($NCH_2CH=CH$); *m/z* (EI^+) 170 (MH^+, 100%), 168 (80), 152 (60, MH^+-CH_2OH), 138 (95), 70 (50); found: M^+ 169.1472, $C_{10}H_{19}NO$ requires 169.1467.

4.12. N-*Pent-2′-enyl-[2-(S)-hydroxymethyl]pyrrolidine* N-*oxide* **12b**

To prolinol **11b** (460 mg, 2.72 mmol) in CH_2Cl_2 (20 cm^3) at room temperature was added *m*CPBA (80%, 585 mg, 2.72 mmol). After stirring for 1 h, the solvent was evaporated and the product was purified by flash chromatography, eluting with CH_2Cl_2:EtOH (9:1) to give *N*-pent-2′-enyl-[2-(*S*)-hydroxymethyl]pyrrolidine *N*-oxide **12b** (455 mg, 2.05 mmol, 90%) as needles. M.p. 94–97°C; R_f 0.05 (Et_2O:MeOH=4:1); $[\alpha]_D^{20}$ 'no significant rotation' (c 1.1 in $CHCl_3$); ν_{max} (Nujol mull)/cm^{-1} 3340 bm (OH), 1665 w (C=C), 930 m (N–O); ^1H NMR (300 MHz) 0.90 (3H, t, *J* 8, CH_2CH_3), 1.72–1.91 (2H, m, NCH_2CH_2), 1.97–2.07 (2H, m, $=CHCH_2CH_3$), 2.16–2.30 (1H, m, $NCHCH^AH^B$), 2.37–2.49 (1H, m, $NCHCH^AH^B$), 3.16–3.28 (3H, m, $NCH_2CH=$ and $NCHCH_2OH$), 3.72 (1H, dd, *J* 13 and 4, CH^AH^BOH), 3.88 (1H, dd, *J* 13 and 8, $NCH^AH^BCH_2$), 3.99–4.08 (2H, m, CH^AH^BOH and $NCH^AH^BCH_2$), 5.54–5.61 (1H, m, $NCH_2CH=CH$), 5.63–5.77 (1H, m, $NCH_2CH=CH$); ^{13}C NMR (75 MHz) 13.65 (CH_2CH_3), 20.25 (CH_2, ring C4), 21.04 (CH_2, ring C3), 22.46 (CH_2CH_3), 59.36 (CH_2OH), 62.87 ($NCH_2CH=$), 66.80 (NCH_2CH_2), 71.63 ($NCHCH_2OH$), 118.27 ($NCH_2CH=CH$), 140.35 ($NCH_2CH=CH$); *m/z* (EI^+) 186 (100%, MH^+), 170 (90, M^+-OH), 138 (90), 117 (60), 86 (75), 70 (55); found: M^+ 185.1411, $C_{10}H_{19}NO_2$ requires 185.1416.

4.13. O-*(Pent-1′-en-3′-yl)-[2-(S)-hydroxymethyl]pyrrolidine hydroxylamine* **13b**

A solution of *N*-oxide **12b** (379 mg, 2.05 mmol) in THF (20 cm^3) was heated at 45°C. After 24 h the solvent was evaporated and the product was purified by flash chromatography, eluting with petrol:EtOAc (7:3), to give an inseparable mixture of the diastereomers of *O*-(pent-1′-en-3′-yl)-[2-(*S*)-hydroxymethyl]pyrrolidine hydroxylamine **13b** (297 mg, 1.60 mmol, 78%, 0% *de*) as an oil. $[\alpha]_D^{20}$ −29.6 (c 1.5 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3445 bs (OH), 1645 w (C=C); ^1H NMR (400 MHz) 0.89 (3H,

t, *J* 7, CH_2CH_3), 1.47–1.50 (1H, m, NCHCH^AH^B), 1.51–1.72 (3H, m, NCH_2CH_2 and NCHCH^AH^B), 1.77–1.91 (2H, m, $OCHCH_2CH_3$), 2.43 (1H, bs, OH), 2.82–2.91 (1H, m, NC$H^AH^BCH_2$), 3.04–3.24 (2H, m, NCHCH_2OH and NCH^AH^BCH_2), 3.28–3.36 (0.5H, m, OCH), 3.42–3.48 (0.5H, m, OCH), 3.63–3.73 (1H, m, CH^AH^BOH), 3.86–3.96 (1H, m, CH^AH^BOH), 5.15–5.26 (2H, m, CH=CH_2), 5.72–5.82 (1H, m, CH=CH_2); ^{13}C NMR (100 MHz) 9.76 and 9.86 (CH_2CH_3), 20.97 and 21.19 (CH_2, ring C4), 23.78 (CH_2, ring C3), 26.82 and 26.95 (CH_2CH_3), 55.35 and 56.44 (CH_2, ring C5), 61.91 and 62.40 (CH_2OH), 68.04 and 68.34 (NCHCH_2OH), 85.22 and 85.74 (OCH), 116.71 and 117.32 (OCH=CH_2), 139.81 and 139.91 (OCH=CH_2); *m/z* (EI$^+$) 186 (100%, MH$^+$), 117 (35, $C_5H_{11}NO_2^+$), 86 (65, $C_4H_8NO^+$); found: M$^+$ 185.1412, $C_{10}H_{19}NO_2$ requires 185.1415.

4.14. N-*Hex-2′-enyl-[2-(S)-hydroxymethyl]pyrrolidine* **11c**

To (*S*)-pyrrolidinemethanol (1.01 g, 10 mmol) in dry THF (25 cm^3) was added triethylamine (4.1 cm^3, 30 mmol) and trimethylsilyl chloride (0.95 cm^3, 11 mmol). As the solution was stirred a white precipitate formed. After two hours, tetrakis(triphenylphosphine) palladium(0) (4 mol%, ~500 mg, 0.4 mmol) and *trans*-hex-2-enyl acetate (1.3 cm^3, 13 mmol) was added. The resulting suspension was heated at reflux for 24 h, then cooled and extracted into EtOAc, washed with water (2×10 cm^3) and brine (5 cm^3), dried (Na_2SO_4) and purified by flash chromatography, eluting with CH_2Cl_2:EtOH:NH_3 (100:8:1) to give *N*-hex-2′-enyl-[2-(*S*)-hydroxymethyl]pyrrolidine **11c** (543 mg, 3.0 mmol, 30%) as an oil. R_f 0.35 (CH_2Cl_2:EtOH=9:1); $[\alpha]_D^{20}$ −33.0 (c 1.06 in $CHCl_3$); ν_{max}/cm^{-1} 3400 bm (OH); ^{1}H NMR (300 MHz) 0.88 (3H, t, *J* 7, CH_2CH_3), 1.32–1.44 (2H, m, CH_2CH$_3$), 1.65–1.78 (3H, m, $NCH_2CH_2CH^AH^B$), 1.80–1.91 (1H, m, $NCH_2CH_2CH^AH^B$), 1.95–2.02 (2H, m, =CHCH_2CH$_2$), 2.25–2.34 (1H, m, NC$H^AH^BCH_2$), 2.57–2.63 (1H, m, NCHCH_2OH), 2.84–2.90 (2H, m, NCH^AH^BCH= and OH), 3.04–3.11 (1H, m, NCH^{A}H^{B}CH$_2$), 3.29–3.34 (1H, m, NCH^{A}H^{B}CH=), 3.38 (1H, dd, *J* 11 and 4, CH^AH^BOH), 3.61 (1H, dd, *J* 11 and 4, CH^AH^BOH), 5.43–5.61 (2H, m, CH=CH); ^{13}C NMR (100 MHz) 13.67 (CH_2CH_3), 22.42 (CH_2CH_3), 23.45 (CH_2, ring C4), 27.88 (CH_2, ring C3), 34.42 (=CHCH_2CH_2), 54.23 (NCH_2CH=), 56.36 (NCH_2CH_2), 62.19 (CH_2OH), 63.85 (NCHCH_2OH), 127.51 (NCH$_2$CH=CH), 133.34 (NCH$_2$CH=CH); *m/z* (EI$^+$) 184 (7%, MH$^+$), 152 (100, MH$^+$−CH_2OH); found: M$^+$ 183.1622, $C_{11}H_{21}NO$ requires 183.1623.

4.15. N-*Hex-2′-enyl-[2-(S)-hydroxymethyl]pyrrolidine* N-*oxide* **12c**

To prolinol **11c** (225 mg, 1.4 mmol) in CH_2Cl_2 (20 cm^3) at room temperature was added *m*CPBA (80%, 300 mg, 1.4 mmol). The solution was stirred for 1 h and the product was purified by flash chromatography, eluting with CH_2Cl_2:EtOH (4:1) to give *N*-hex-2′-enyl-[2-(*S*)-hydroxymethyl]pyrrolidine *N*-oxide **12c** (256 mg, 1.28 mmol, 92%), which was recrystallised from CH_2Cl_2–Et_2O to give needles. M.p. 80–85°C; R_f 0.14 (CH_2Cl_2:EtOH=9:1); $[\alpha]_D^{25}$ 'no significant rotation' (c 0.67 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3075 b (OH), 1670 w (C=C), 925 m (N–O); ^{1}H NMR (400 MHz) 0.92 (3H, t, *J* 7, CH_2CH_3), 1.39–1.48 (2H, m, CH_2CH$_3$), 1.85–2.03 (2H, m, NCH_2CH_2), 2.07–2.15 (2H, m, =CHCH_2CH$_2$), 2.33–2.42 (1H, m, NCHCH^AH^B), 2.55–2.67 (1H, m, NCHCH^{A}H^B), 3.36–3.45 (3H, m, NCH_2CH= and NCH^AH^BCH$_2$), 3.78–3.85 (2H, m, NCH^{A}H^{B}CH$_2$ and NCHCH_2OH), 4.08 (1H, dd, *J* 13 and 6, CH^AH^BOH), 4.19 (1H, dd, *J* 13 and 1, CH^{A}H^{B}OH), 5.73–5.92 (2H, m, CH=CH); ^{13}C NMR (100 MHz) 13.65 (CH_2CH_3), 20.30 (CH_2, ring C4), 21.93 (CH_2CH_3), 23.50 (CH_2, ring C3), 34.55 (=CHCH_2CH_2), 59.52 (CH_2OH), 66.81 (NCH_2CH=), 68.81 (NCH_2CH_2), 71.27 (NCHCH_2OH), 120.18 (NCH$_2$CH=CH), 141.46 (NCH$_2$CH=CH); *m/z* (CI$^+$, NH_3) 200 (100%, MH$^+$), 184 (65, M$^+$−OH), 182 (75), 152 (55); found: M$^+$ 199.1569, $C_{11}H_{21}NO_2$ requires 199.1572.

4.16. O-(Hex-1′-en-3′-yl)-[2-(S)-hydroxymethyl]pyrrolidine hydroxylamine **13c**

A solution of *N*-oxide **12c** (800 mg, 4.02 mmol) in THF (20 cm^3) was heated at 45°C. After 48 h, the solvent was evaporated and the product was purified by flash chromatography to give an inseparable mixture of the diastereomers of *O*-(hex-1′-en-3′-yl)-[2-(*S*)-hydroxymethyl]pyrrolidine hydroxylamine **13c** (715 mg, 3.58 mmol, 89%, 0% *de*) as an oil. R_f 0.19 (petrol:EtOAc=4:1); $[\alpha]_D^{20}$ −6.0 (c 0.93 in $CHCl_3$); ν_{max}/cm^{-1} 3440 bs (OH), 1645 w (C=C), 920 s (N–O); ^1H NMR (400 MHz) 0.91 (3H, t, *J* 7, CH_2CH_3), 1.28–1.42 (3H, m, CH_2CH_3 and $NCHCH^AH^B$), 1.48–1.60 (2H, m, NCH_2CH_2), 1.62–1.73 (1H, m, $NCHCH^AH^B$), 1.77–1.91 (2H, m, $OCCH_2CH_2$), 2.47 (1H, bs, OH), 2.81–2.89 (1H, m, $NCH^AH^BCH_2$), 3.03–3.16 (1H, m, $NCHCH_2OH$), 3.16–3.23 (1H, m, $NCH^AH^BCH_2$), 3.29–3.37 (0.5H, m, OCH), 3.42–3.47 (0.5H, m, OCH), 3.62–3.71 (1H, m, CH^AH^BOH), 3.93–4.04 (1H, m, CH^AH^BOH), 5.12–5.23 (2H, m, $CH=CH_2$), 5.72–5.84 (1H, m, $CH=CH_2$); ^{13}C NMR (100 MHz) 14.03 (CH_2CH_3), 18.62 and 18.72 (CH_2CH_3), 21.10 (CH_2, ring C4), 23.82 (CH_2, ring C2), 36.11 and 36.30 ($CH_2CH_2CH_3$), 55.34 and 56.51 (CH_2, ring C5), 61.89 and 62.42 (CH_2OH), 68.07 and 68.40 ($NCHCH_2OH$), 83.58 and 84.23 (OCH), 116.45 and 117.07 ($OCH=CH_2$), 140.20 and 140.31 ($OCH=CH_2$); *m/z* (EI^+) 200 (15%, MH^+), 117 (35, $C_5H_{11}NO_2^+$), 86 (100, $C_4H_8NO^+$), 55 (75); found: M^+ 199.1573, $C_{11}H_{21}NO_2$ requires 199.1572.

4.17. N-Geranyl-(S,S)-2,5-bis(methoxymethyl)-pyrrolidine **14**

To (*S,S*)-2,5-bis(methoxymethyl)-pyrrolidine (870 mg, 5.47 mmol) in acetone (50 cm^3) was added di-*iso*-propylethylamine (3.5 cm^3, 20 mmol) and geranyl bromide (1.98 cm^3, 10 mmol). After heating at reflux for 24 h, the solvent was evaporated and the residue was extracted with EtOAc (2×20 cm^3) and washed with water (2×10 cm^3) and brine (1×5 cm^3). The organic layer was dried (Na_2SO_4) and purified by flash chromatography, eluting with Et_2O:MeOH (19:1) to give *N*-geranyl-(*S,S*)-2,5-bis(methoxymethyl)-pyrrolidine **14** (934 mg, 3.16 mmol, 58%) as an oil. $[\alpha]_D^{29}$ −62.4 (c 1.08 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2920 s (C–H), 1450 m, 1380 m, 1115 s (C–O); ^1H NMR (400 MHz) 1.58 (3H, s, CH_3), 1.62–1.70 (2H, m, 2×$NCHCH^AH^B$), 1.65 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.91–2.02 (4H, m, $CH_2CH_2CH=C$ and 2×$NCHCH^AH^B$), 2.05–2.10 (2H, m, $CH_2CH=CMe_2$), 3.13–3.18 (2H, m, 2×$NCHCH_2OMe$), 3.25–3.31 (3H, m, $NCH^AH^BCH=$ and 2×CH^AH^BOMe), 3.30 (6H, s, 2×OCH_3), 3.34–3.40 (3H, m, $NCH^AH^BCH=$ and 2×CH^AH^BOMe), 5.08 (1H, tt, *J* 7 and 1, $CH=CMe_2$), 5.32 (1H, t, *J* 7, NCH_2CH); ^{13}C NMR (100 MHz) 16.36 (CH_3), 17.61 (CH_3), 25.63 (CH_3), 26.44 ($CH_2CH=CMe_2$), 26.99 ($NCHCH_2CH_2$), 39.72 ($CH_2CH_2CH=CMe_2$), 46.68 (NCH_2), 58.96 (OCH_3), 60.79 ($NCHCH_2OMe$), 74.27 ($NCHCH_2OMe$), 122.99 ($NCH_2CH=$), 124.21 ($Me_2C=CH$), 131.36 ($Me_2C=CH$), 136.13 ($MeC=CH$); *m/z* (EI^+) 295 (0.2%, M^+), 250 (76, M^+-CH_2OMe), 114 (100), 69 (86, $Me_2C=CH_2^+$); found: M^+ 295.2511, $C_{18}H_{33}NO_2$ requires 295.2511.

4.18. O-Linalyl-(S,S)-2,5-bis(methoxymethyl)-pyrrolidine hydroxylamine **15**

To *N*-geranyl-(*S,S*)-2,5-bis(methoxymethyl)-pyrrolidine **14** (173 mg, 0.58 mmol) in CH_2Cl_2 (3 cm^3) at −40°C was added *m*CPBA (80%, 125 mg, 0.58 mmol). After 1 h, the solution was allowed to warm to 0°C and was extracted with K_2CO_3 solution (2 M, 2×5 cm^3), then washed with water (5 cm^3) and brine (2 cm^3) and was dried (Na_2SO_4). The solvent was evaporated and (after inspection by NMR) the *N*-oxide was redissolved in Et_2O (10 cm^3) and was allowed to stand at 4°C for 10 days. The solvent was evaporated and the residue was purified by flash chromatography, eluting with petrol:Et_2O (9:1), to give *O*-linalyl-(*S,S*)-2,5-bis(methoxymethyl)-pyrrolidine hydroxylamine **15** (108 mg, 0.35 mmol, 60%) as an

oil. The *de* of this product was determined (by ^{1}H NMR) to be 26%. R_f 0.32 (petrol:EtOAc=9:1), ν_{max} (neat)/cm^{-1} 2920 s (C–H), 1210 m, 1125 s (C–O), 925 m (N–O); ^{1}H NMR (400 MHz) 1.29 and 1.30 (3H, s, OCC*H*$_3$), 1.50–1.60 (3H, m, NCHC*H*^{A}H^{B}C*H*$_2$), 1.57 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.70–1.83 (2H, m, $OCCH_2$), 1.89–1.97 (3H, m, $OCCH_2CH_2$ and NCHCH^A*H*^{B}), 3.20–3.35 (3H, m, C*H*$_2$OMe and C*H*^{A}H^{B}OMe), 3.33 (6H, s, 2×OCH_3), 3.40–3.46 (2H, bm, NC*H*CH_2OMe and CH^A*H*^{B}OMe), 3.68–3.75 (1H, bs, NC*H*CH_2OMe), 5.05–5.13 (3H, m, CH=C*H*$_2$ and Me_2C=C*H*), 5.96–6.05 (1H, m, C*H*=CH_2); ^{13}C NMR (75 MHz) 17.52 (CH_3), 19.33 (CH_3), 22.96 (CH_2), 25.61 (CH_3), 39.48 and 39.66 (CH_2), 58.89 (OCH_3), 66.5 (CH), 72.3 (CH_2OMe), 74.3 (CH_2OMe), 80.98 and 81.08 (OCCH=CH_2), 113.58 and 113.63 (CH=*C*H_2), 124.67 (Me_2C=*C*H), 131.13 (Me_2*C*=CH), 143.37 (*C*H=CH_2); *m/z* (EI$^+$) 312 (66%, MH$^+$), 311 (0.7, M$^+$), 220 (22), 175 (60, M$^+$−linalyl), 130 (100, M$^+$−linalyl and CH_2OMe); found: M$^+$ 311.2449, $C_{18}H_{33}NO_3$ requires 311.2460.

4.19. Crystal structure analysis of **12c**

$C_{11}H_{21}NO_2$ (*M*=199.25); crystal dimensions 0.4×0.4×0.15 mm; orthorhombic; space group Pbca; *a*=11.886(3) *b*=9.582(2), *c*=19.999(4) Å, *V*=2277(9) Å^3; Z=8; calculated density 1.162 g/cm^3; absorption coefficient μ(Mo-K$_\alpha$) 0.079 mm^{-1}; F(000)=880; 2.04<θ<22.48.

Data was collected at 223(2) K on an Enraf Nonius CAD-4 diffractometer using graphite monochromated molybdenum radiation and an ω-2θ variable speed scan technique. 1471 independent reflections were recorded (R_{int}=0.000). The structure was solved by direct methods using the SHELXS program and refined by a full-matrix least-squares refinement on F^2 (using anisotropic thermal parameters for all non-hydrogen atoms and the hydroxyl hydrogen atom) with the SHELXL-93 program. Other hydrogen atoms were placed in idealised positions. The refinement converged to R_1=0.048 and wR_2=0.114 for I>2σ(I) and 132 refined parameters (goodness of fit on F^2=1.098. The largest peak and hole in the final difference map was 0.22 and −0.19 eÅ^{-3}.

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References

1. C. S. Han, A. N. Jarvis and J. B. Sweeney, *Contemp. Org. Synth.*, **1996**, *3*, 65–91.
2. J. Meisenheimer, *Chem. Ber.*, **1919**, *52*, 1667.
3. A. C. Cope and R. F. Kleinschmidt, *J. Am. Chem. Soc.*, **1944**, *66*, 1929; A. C. Cope and P. H. Towle, *J. Am. Chem. Soc.*, **1949**, *71*, 3423; V. Rautenstrauch, *Helv. Chim. Acta*, **1973**, *56*, 2492.
4. Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.*, **1976**, *41*, 303–306.
5. M. T. Reetz and E. H. Lauterbach, *Tetrahedron Lett.*, **1991**, *32*, 4481–4482.
6. S. G. Davies and G. D. Smyth, *Tetrahedron: Asymmetry*, **1996**, *7*, 1001–1004; 1005–1006.
7. D. Enders and H. Kempen, *Synlett*, **1994**, 969–971.
8. M. Moriwaki, Y. Yamamoto, J. Oda and Y. Inouye, *J. Org. Chem.*, **1976**, *41*, 300–303.
9. For reviews see F. A. Davis and A. C. Sheppard, *Tetrahedron*, **1989**, *45*, 5703–5742; F. A. Davis and B.-C. Chen, *Chem. Rev.*, **1992**, *92*, 919–934; F. A. Davis, R. T. Reddy, W. Han and R. E. Reddy, *Pure Appl. Chem.*, **1993**, *65*, 633–640.
10. L. C. Vishwakarma, O. D. Stringer, and F. A. Davis, *Org. Synth.*, **1988**, *66*, 203–210; W. W. Zajac, T. R. Walters and M. G. Darcy, *J. Org. Chem.*, **1988**, *53*, 5856–5860.
11. F. A. Davis, J. C. Towson, M. C. Weismiller, S. Lal and P. J. Carroll, *J. Am. Chem. Soc.*, **1988**, *110*, 8477–8482.

12. F. A. Davis, R. T. Reddy, W. Han and P. J. Carroll, *J. Am. Chem. Soc.*, **1992**, *114*, 1428–1437.
13. F. A. Davis, R. H. Jenkins, S. B. Awad, O. D. Stringer, W. H. Watson and J. Galloy, *J. Am. Chem. Soc.*, **1982**, *104*, 5412–5418.
14. W. H. Pirkle, R. L. Muntz and I. C. Paul, *J. Am. Chem. Soc.*, **1971**, *93*, 2817–2819.
15. M. Palucki, P. Hanson and E. N. Jacobson, *Tetrahedron Lett.*, **1992**, *33*, 7111–7114.
16. S. H. Zhao, O. Samuel and H. B. Kagan, *Tetrahedron*, **1987**, *43*, 5135–5144.
17. N. Komatsu, Y. Nishibayashi and S. Uemura, *Tetrahedron Lett.*, **1993**, *34*, 2339–4232.
18. S. Miyano, L. D.-L. Lu, S. M. Viti, and K. B. Sharpless, *J. Org. Chem.*, **1985**, *50*, 4350–4360.
19. I. A. O'Neil, N. D. Miller, J. Peake, J. V. Barkley, C. M. R. Low and S. B. Kalindjian, *Synlett*, **1993**, 515–518; I. A. O'Neil, N. D. Miller, J. V. Barklet, C. M. R. Low and S. B. Kalindjian, *Synlett*, **1995**, 617–618; I. A. O'Neil, N. D. Miller, J. V. Barklet, C. M. R. Low and S. B. Kalindjian, *Synlett*, **1995**, 619–621.
20. J. E. H. Buston, I. Coldham and K. R. Mulholland, *Synlett*, **1997**, 322–324.
21. G. Ohloff and E. Klein, *Tetrahedron*, **1962**, *18*, 37.