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ENANTIOSELECTIVE SYNTHESIS OF KAINOID ANALOGUES BY COBALT-MEDIATED CYCLISATIONS

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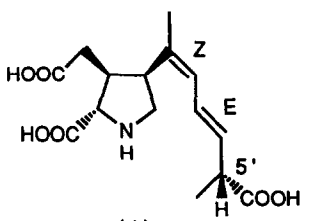
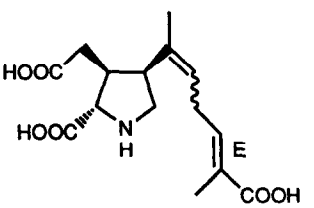
Key words : Kainoids, cobalt, radical, enantioselective, serine

Abstract : The synthesis of a C-8 side chain analogue of domoic acid, which uses a cobalt-mediated cyclisation in the key-step, is described.

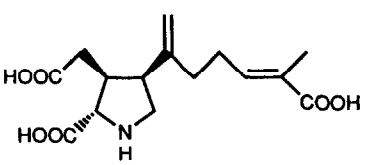
The kainoids are a class of naturally occurring non-proteinogenic amino acids which possess a common pyrrolidine dicarboxylic acid nucleus[1]. One of them, domoic acid (1), has recently been identified[2] as the toxin in Paralytic Shellfish Poisons, and was believed responsible for an outbreak of mussel poisoning in Canada . Domoic acid, like the other kainoids, exhibits powerful neuroexcitatory effects, and this has been ascribed to their acting as conformationally restricted analogues of glutamic acid[3].



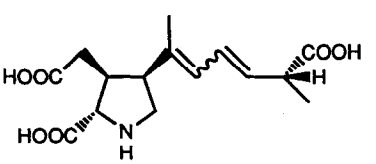
(1)



(2a) Isodomoic Acid A (Z, E)
(2b) Isodomoic Acid B (E, E)

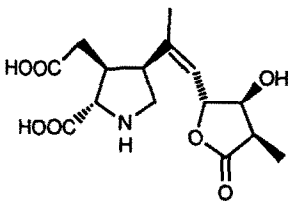


(3) Isodomoic Acid C



(4a) Isodomoic Acid D (Z, Z)
(4b) Isodomoic Acid E (E, E)
(4c) Isodomoic Acid F (E, Z)

Domoic acid has been isolated from the red algae *Chondria armata* and *Digenea simplex* [3], and a total synthesis has been described[4] which established the diene (Z, E) double bond stereochemistry as well as the absolute configuration at C-5'. The related isodomoic acids A-F (2-4), have also been isolated from *Chondria armata* [5,6], and they exhibit potent insecticidal activity, while domiolactones A(5) and B(6) (isolated from the same source) were much less active. In this paper, we report the synthesis of a C-8 side chain analogue (7) of domoic acid.



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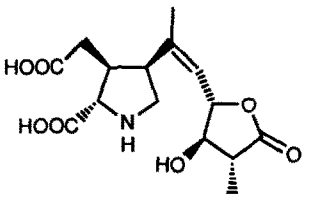

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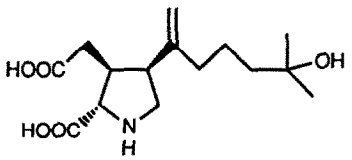
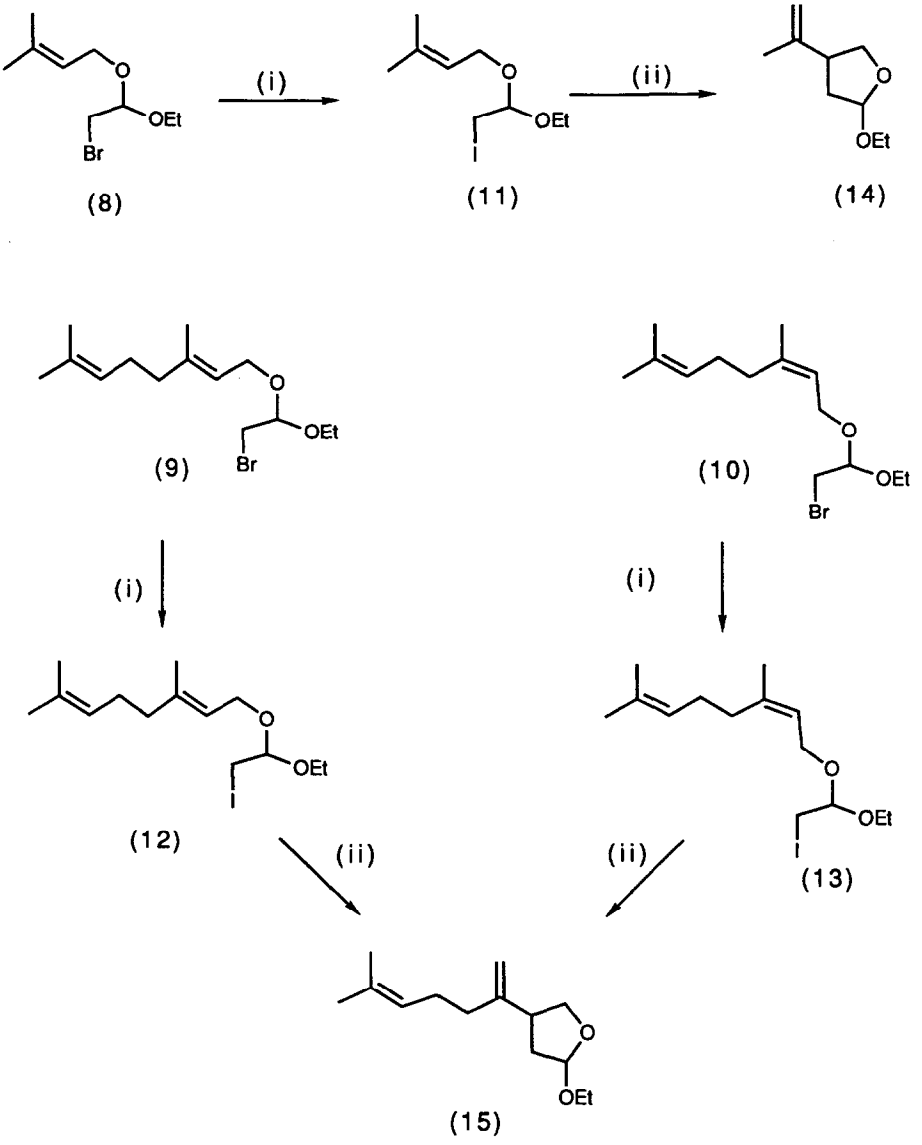


(7)

We recently described[7] the synthesis of kainic acid using a cobalt-mediated radical ring-closure on a prenylated serine derivative, and we were interested to explore the scope of this ring closure more fully. The possibility existed of its application to the synthesis of compounds possessing side chains other than those which would lead to kainic acid, and we reasoned that an analogue of domoic acid, starting from the corresponding geranyl amino acid derivative, should be available by this type of approach. Some model systems, which led to tetrahydrofuran products, were initially examined (Scheme 1).

The bromides (8)-(10) were prepared by treatment of 3-methyl-2-butenol, geraniol or nerol respectively with ethyl vinyl ether and N-bromosuccinimide. When the derivative (8) was treated with cobaloxime (I) under the previously described conditions[7], no reaction occurred, and only starting bromide (8) was recovered. Treatment of the bromides (8)-(10) with sodium iodide in acetone resulted in the formation of the iodides (11)-(13), and these crude iodides were then reacted with cobaloxime (I). Iodide (11) was converted to tetrahydrofuran (14), which was obtained as a diastereomeric mixture, together with inseparable reduced substrate, in 75% yield. Both the geranyl and neryl derivatives (12) and (13), upon treatment with Co (I), were converted to the same product (15), which was also obtained as an inseparable mixture of diastereomers, contaminated with reduced substrate. The geminal vinyl protons were clearly identified in the ^{1}H n.m.r. spectrum as singlets at δ 4.83 and 4.85. This result, confirming earlier work[8], clearly demonstrated that Co (I) mediated cyclisation using geranyl- or neryl-type side chains was feasible, and also that the double-bond stereochemistry of the starting iodide was not important, since identical products were obtained. Much work has already been reported concerning the formation of tetrahydrofuran rings by cobalt (I)-mediated ring closures.[9]

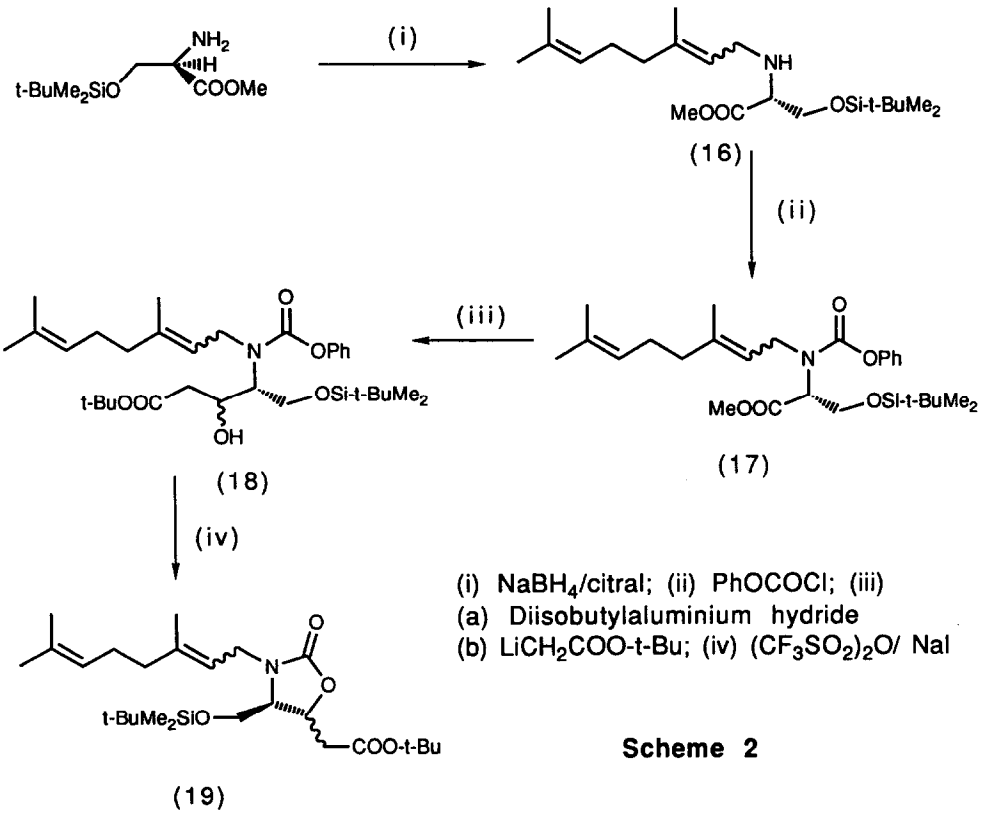


Scheme 1

This approach was then applied to the kainoid synthesis, using similar chemistry to that already described[7] (Scheme 2). Thus, reductive amination of O-silyl serine methyl ester with citral (a 95:5 mixture of geranial and neral, obtained from Aldrich) and sodium borohydride gave allylic amine (16), which was N-protected with

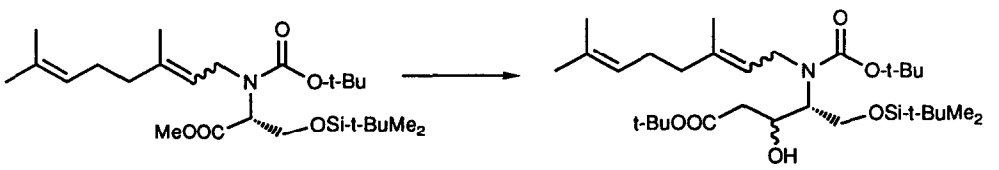
phenyl chloroformate to give (17) as a colourless liquid. Reduction (diisobutylaluminium hydride) to the aldehyde, followed by the addition of tert-butyllithioacetate[10], gave alcohol (18) in 52% yield [from methyl ester (16)].

Reaction of this alcohol with triflic anhydride followed by sodium iodide, however, did not lead to the expected iodide substitution product. Rather, a particularly facile cyclisation resulted in the formation of oxazolidinone (19); this cyclisation occurred both at -20°C and at 0°C, although at -78°C no reaction took place at all. Similarly, treatment of a mixture of the alcohol (17) and sodium iodide, with slow addition of triflic anhydride, in an attempt to intercept the intermediate triflate ester as it was formed, was not successful.



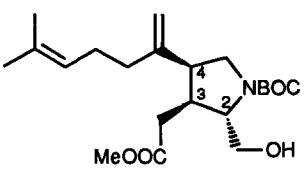
Scheme 2

An attempt to form the bromide using triflic anhydride/lithium bromide also met with failure. The alternatively protected N-tert-butyloxycarbonyl compound (21), derived from ester (20), underwent a similar cyclocarbamoylation to give (19) upon treatment with triflic anhydride/sodium iodide. Similar behaviour had been observed in the synthesis of kainic acid reported previously.[7]



(20) (21)

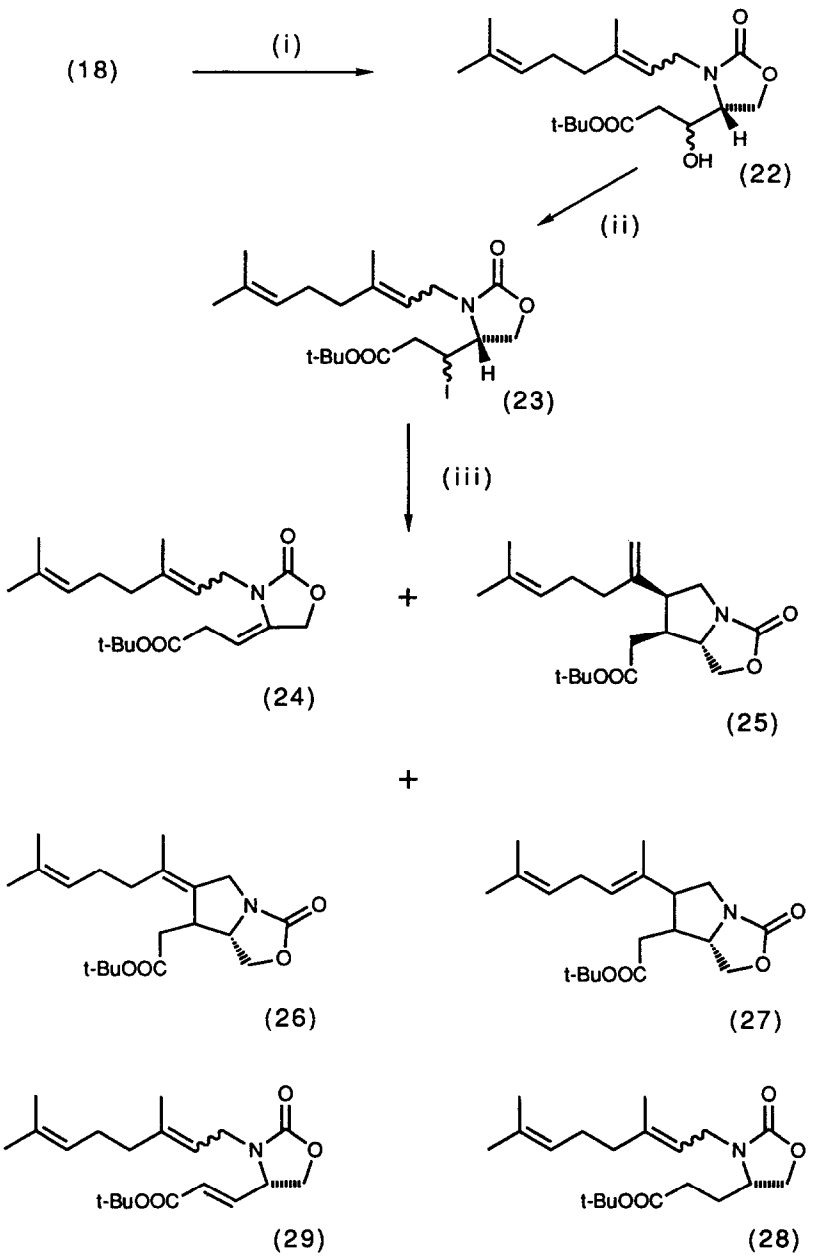
In an attempt to circumvent this difficulty of unwanted cyclisation, the alcohol (18) was treated with p-toluenesulphonic acid (Scheme 3) to remove the silyl ether, and the resulting diol was cyclised to give exclusively the alternative oxazolidinone (22), using potassium carbonate in aqueous methanol. This compound was obtained as a diastereomeric mixture, as indicated by multiple resonances in the ^{13}C n.m.r. spectrum. Treatment of this alcohol (22) with triflic anhydride and sodium iodide at 0°C gave the iodide (23) in 60% yield. Reaction of (23) with cobaloxime (I), generated under neutral[11] or basic[12] conditions, gave the products (24)-(29) in similar yields. Compounds (24) and (29) arose by elimination of the starting iodide, and compounds (25)-(27) by the desired ring closure. For example, under neutral conditions, the products (24) and (25) could be obtained pure by careful column chromatography in 25 and 29% yield respectively, although the other products (26)-(29) could not be separated, and were obtained in a combined yield of 13%[13].The predominance of alkene (25) was consistent with the work of Schrauzer[14], which demonstrated the preferential formation of products with the less substituted double bond in alkylcobalamin-mediated reactions.



	Irradiate	
Effect	H_3	H_4
H_2	0%	0%
H_3	-	6%
H_4	11.2%	-

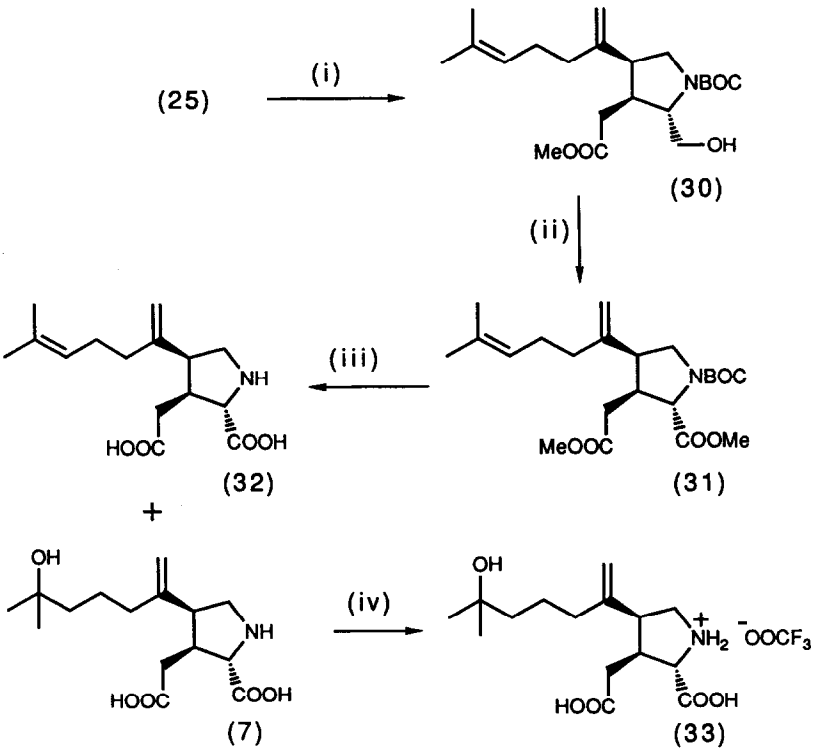
Figure 1

Reaction of oxazolidinone (25) with aqueous sodium hydroxide, followed by di-tert-butyl pyrocarbonate and then diazomethane (Scheme 4) gave pyrrolidine (30) in 50% yield. The cis-relationship of the C3/C4 ring protons was demonstrated by n.o.e. studies (Figure 1), implying that this compound possessed the desired kainic acid stereochemistry. This was further confirmed by the fact that two terminal olefinic protons appeared as two singlets in the ^1H n.m.r. spectrum (δ 4.94 and 4.71), as is typical of compounds with the kainic acid configuration[15].For allokainic acid, however, these two protons appear as one singlet[15].Oxidation of intermediate (30) (PDC), followed by esterification (CH_2N_2) gave dimethyl ester (31) as a colourless oil in 61% yield.Splitting of some of the ^{13}C n.m.r. signals due to hindered rotation of the tert-butyloxcarbonyl protecting group about the carbon-nitrogen bond, was also observed. This type of behaviour has also been reported in related proline derivatives[16].



(i) (a) p-TsOH/MeOH; (b) K_2CO_3/H_2O/MeOH; (ii) $(CF_3SO_2)_2O$/NaI; (iii) Co(I)

Scheme 3



(i) (a) aq NaOH; (b) BOC_2O; (c) CH_2N_2; (ii) (a) PDC; (b) CH_2N_2;
(iii) (a) aq KOH; (b) TFA; (iv) TFA

Scheme 4

Treatment of diester (31) with aqueous potassium hydroxide, followed by trifluoroacetic acid, gave a mixture of predominantly alcohol (7), with a trace of alkene (32). The major product (7) resulted from electrophilic addition of trifluoroacetic acid across the more electron-rich trisubstituted carbon-carbon double bond, followed by hydrolysis of the intermediate trifluoroacetate ester on work-up. After purification by ion-exchange chromatography the mixture was further treated with excess trifluoroacetic acid to give the tertiary alcohol product as the trifluoroacetate salt (33) in 72% yield.

The kainoid (33) has been tested for biological activity, and has been found to be moderately active at the kainate receptor site, but has no activity at the NMDA receptor[17].

Thus the application of a cobalt-mediated pyrrolidine ring closure reaction to the synthesis of a kainoid analogue has been demonstrated, and work is currently in progress to further develop this strategy to the synthesis of a range of kainoids and their analogues.

EXPERIMENTAL.

Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were on a Perkin-Elmer 241 Polarimeter with a path-length of 10 cm; concentrations are given in g/100 cm^3. Infrared spectra were recorded on either a Perkin-Elmer 781 spectrophotometer or a Perkin-Elmer 1750 IR FT spectrometer; only selected resonances are reported, and are reported as (s) strong, (m) medium, (w) weak or (br) broad. ^1H n.m.r. spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer, at 300 MHz on a Bruker WH 300 spectrometer and at 500 MHz on a Bruker AM 500 spectrometer. Chemical shifts are quoted on the scale using residual solvent as an internal. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. ^{13}C n.m.r. spectra were recorded at 50 MHz on a Varian Gemini 200 spectrometer or at 125 MHz on a Bruker AM 500 spectrometer; for samples in D_2O dioxan (δ 67.2) was added as a reference. Mass spectra were recorded on either a VG Micromass ZAB IF or a VG Mass lab 20-250 spectrometer using ammonia desorption chemical ionisation (DCI) or positive argon fast atom bombardment techniques. Gas chromatography mass spectra were recorded on a VG Trio-1 spectrometer. Microanalyses were performed by the microanalytical service of the Dyson Perrins Laboratory. T.l.c. was performed on aluminium plates coated with Merck silica gel $60F_{254}$. Compounds were visualised with iodine, or a solution of dodeca-Molybdophosphoric acid in ethanol or ninhydrin in methanol. Flash column chromatography was carried out using Sorbsil C60 40/60 flash silica gel. Ion exchange columns were packed with Aldrich 50 X, 2-100 resin in the H^+ form. All solvents were distilled before use using standard literature procedures[18].

General Procedure for the Preparation of the Bromoacetals (8, 9, 10).

To a mixture of the alcohol (3-methyl-2-butenol, geraniol or nerol) (19.49-34.83 mmol) and ethyl vinyl ether (3 mol equiv.) in dichloromethane (25-40 ml) at -23°C (carbon tetrachloride-dry ice) was added N-bromosuccinimide (1 mol equiv.) while stirring. After the mixture had been stirred for 2-3 h, it was allowed to warm slowly to r.t. The solution was then washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Purification by column chromatography (silica; hexane-ethyl acetate, 9:1) afforded the bromoacetal (8, 9, 10) (65-75%) as a colourless oil.

3-Methyl-1-(1-ethoxy-2-bromoethoxy)-but-2-ene (8).

Rf 0.62 (hexane-ethyl acetate, 9:1); υ_{max} (thin flim) 3000-2840 (s), 1740 (w), 1670 (w), 1470-1420 (m) 1395-1365 (m), 1355-1320 (w), 1210-1180 (w), 1150-1095 (s) and 1080-960 (s) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.36 (1H, t, J 7 Hz, C<u>H</u>=), 4.71 (1H, t, J 5.6 Hz, C<u>H</u>-CH_2Br), 4.14-4.09 (2H, m = C-C<u>H_2</u>-O), 3.80-3.50 (2H, m, O-C<u>H_2</u>CH_3), 3.39 (2H, d, J 5.6 Hz, C<u>H_2</u>Br), 1.76 (3H, s, C<u>H_3</u>-C=), 1.70 (3H, s, C<u>H_3</u>C=) and 1.25 (3H, t, J 7 Hz, O-CH_2C<u>H_3</u>); m/z (DCI, NH_3) 256 ($M^{81} + NH_4^+$, 18%), 254 ($M^{79} + NH_4^+$, 18%) and 86 (100).

3,7-Dimethyl-1-(1-ethoxy-2-bromoethoxy)-octa-2(E)-6-diene (9).

Rf 0.51 (hexane-ethyl acetate, 9:1); υ_{max} (thin film) 3000-2840 (s), 1670 (w), 1470-1420 (m), 1375 (m), 1340 (w), 1185 (m), 1140-1090 (s) and 1080-970 (s) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.35 (1H, t, J 8 Hz, C<u>H</u>=), 5.08 (1H, br s, C<u>H</u>=), 4.70 (1H, t, J 5.4 Hz, C<u>H</u>-CH_2Br), 4.15-4.11 (2H, m, = C-C<u>H_2</u>-O), 3.78-3.54 (2H, m, O-C<u>H_2</u>CH_3), 3.38 (2H, d, J, 5.4 Hz, C<u>H_2</u>Br), 2.12-2.07 (4H, br s, C<u>H_2</u>-C<u>H_2</u>), 1.68 (6H, s, C<u>H_3</u>-C=), 1.60

(3H, s, C<u>H</u>$_3$-C=) and 1.24 (3H, t, J 7 Hz, O-C<u>H</u>$_3$); δ_C (50 MHz; $CDCl_3$) 141.16, 131.85 (<u>C</u>=), 123.97, 120.09 (<u>C</u>H=), 100.7 (<u>C</u>H-CH_2Br), 63.1, 62.1 (=C-<u>C</u>H_2-O and <u>C</u>H_2Br), 39.4 (O-<u>C</u>H_2CH_3), 31.7 (<u>C</u>H_2-CH_2), 26.1 (CH_2-<u>C</u>H_2), 25.5 (<u>C</u>H_3-C=), 17.5 (<u>C</u>H_3-C=), 16.3 (<u>C</u>H_3-C=) and 15.0 (O-CH_2<u>C</u>H_3); m/z (DCI, NH_3) 324 (M^{81} + NH_4^+, 5%), 322 (M^{79} + NH_4^+, 5%), 154 (59), 137 (100) and 81 (70).

3,7-Dimethyl-1-(1-ethoxy-2-bromoethoxy)-octa-2(Z)-6-diene (10).

Rf 0.46 (hexane-ethyl acetate, 9:1); υ_{max} (thin film) 3000-2850 (s), 1665 (w), 1480-1415 (m), 1375 (m), 1355-1325 (w), 1185 (w), 1140-1110 (s) and 1075-960 (s) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.37 (1H, t, J 7.4 Hz, C<u>H</u>=), 5.10 (1H, br s, C<u>H</u>=), 4.71 (1H, t, J 5.4 Hz, C<u>H</u>-CH_2Br), 4.20-4.00 (2H, m, = C-<u>C</u>H_2-O), 3.74-3.55 (2H, m, O-<u>C</u>H_2CH_3), 3.39 (2H, d, J 5.6 Hz, <u>C</u>H_2Br), 2.09 (4H, br s, <u>C</u>H_2-<u>C</u>H_2), 1.76 (<u>C</u>H_3-C=), 1.70 (<u>C</u>H_3-C=), 1.61 (<u>C</u>H_3-C=) and 1.24 (3H, t, J 7 Hz, O-CH_2<u>C</u>H_3); m/z (GCMS) 324 (M^{81} + NH_4^+, 18%), 322 (M^{79} + NH_4^+, 18%), 273 (10), 154 (9) and 137 (100).

General Procedure for the Preparation of the Tetrahydrofurans (14, 15).

To a solution of the bromoacetal (8, 9, 10) (4.10-15.10 mmol) in acetone (30-100 ml) was added sodium iodide (10 mol equiv.) while stirring. The solution was then refluxed overnight, after which the acetone was removed *in vacuo*. Water and ethyl acetate was added to the residue, the organic layer was removed, washed with saturated aqueous sodium thiosulphate solution, water and dried ($MgSO_4$). Evaporation *in vacuo* afforded crude iodoacetal (80-87%) as a pale yellow liquid.

To a suspension of chlorocobaloxime (III) (0.2 mole equiv.) in methanol (20-25 ml) was added aqueous sodium hydroxide (10N, 0.34-0.43 ml) while stirring at 0°C. After 0.1 h, sodium borohydride (2 mole equiv.) was added portionwise. After a further 0.25 h, the crude iodoacetal (2.84-3.55 mmol) in methanol (2-3 ml) was added dropwise, the mixture was allowed to warm to r.t. and stirred overnight. The solvent was evaporated under reduced presssure, and ethyl acetate and water was added. The ethyl acetate layer was separated, washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Column chromatography (silica; hexane-ethyl acetate, 9:1) afforded the crude tetrahydrofurans (14, 15) (60-85%) as colourless liquids.

2-Ethoxy-4-(1-methylethenyl)-tetrahydrofuran (14).

The presence of this compound was indicated by the ^1H n.m.r. spectrum [δ (200 MHz; $CDCl_3$) 4.80 and 4.77 (s, <u>H</u>$_2$C=C), 1.77 and 1.74 (s, C<u>H</u>$_3$-C=)], ^{13}C n.m.r. spectrum [δ (50 MHz; $CDCl_3$) 145.0, 143.8 (<u>C</u>=), 111.2, 110.5 (H_2<u>C</u>=), 104.5, 104.1 (O-<u>C</u>H-O), 70.7, 69.6, 68.0, 63.1, 62.5, 45.7, 43.8, 37.6, 37.0 (O-<u>C</u>H_2-CH, CH-<u>C</u>H_2-CH and =C-<u>C</u>H), 21.3, 20.5, 20.2 (<u>C</u>H_3-C=) and 15.0 (O<u>C</u>H_2<u>C</u>H_3)], infra red spectrum [υ_{max} (thin film) 1645 (w, CH_2=), 1110 (s), 1050 (s), 1000 (s), 930 (m) and 890 (m) cm^{-1}] and mass spectrum [m/z (DCI, NH_3) 157 (M + H^+, 8%) and 111 (100)].

2-Ethoxy-4-[1-(4-methyl-pent-3-enyl)(ethenyl)]-tetrahydrofuran (15).

The presence of this compound was indicated by the ^1H n.m.r. spectrum [δ (200 MHz; $CDCl_3$) 4.85 and 4.83 (s, <u>H</u>$_2$C=C), 1.69 and 1.62 (s, C<u>H</u>$_3$-C=)], ^{13}C n.m.r. spectrum [δ (50 MHz; $CDCl_3$) 147.8 (<u>C</u>=), 131.9 (<u>C</u>=), 124.0, 123.9 (<u>C</u>H=), 109.6, 108.8 (H_2<u>C</u>=), 104.5, 104.0 (O-<u>C</u>H-O), 71.4, 70.1, 63.2, 62.6, 44.7, 42.8,

38.0, 37.2, 35.1, 26.5, 25.5 (O-$\underline{C}H_2$-CH, C-$\underline{C}H_2$-C, = C-$\underline{C}$H, $\underline{C}H_2$-CH_2 and CH_2-$\underline{C}H_2$), 17.5 and 15.1 ($\underline{C}H_3CH_2O$)], infra red spectrum [υ_{max} (thin film) 1640 (w, = CH_2), 1110 (s), 1050 (s), 1000 (s), 930 (m) and 890 (m) cm^{-1}] and mass spectrum [m/z (DCI, NH_3) 225 (M + H^+, 4%) 196 (25) and 179 (100)].

Methyl-(2*R*)-[3-(tert-butyldimethylsilyl)oxy]-2-[(3,7-dimethyl-2,6-octadienyl)amino] propionate (16).

To a solution of the D-serine silyl ether[7] (7.50 g, 30.31 mmol) in benzene (35 ml) was added 3,7-dimethyl-2,6-octadienal (5.77 g, 37.90 mmol) while stirring. After 0.5 h, ethyl acetate was added and the solution was dried ($MgSO_4$) and evaporated *in vacuo* to afford the crude imine as an orange liquid. Methanol (180 ml) was added to dissolve the imine followed by the portionwise addition of sodium borohydride (2.50 g, 66.1 mmol) at 0°C. After 0.25 h, the ice-bath was removed and stirring was continued for a further 0.3 h at r.t.. Water and ethyl acetate was then added. The ethyl acetate layer was then removed, washed with water (two times), brine, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (silica; hexane-ethyl acetate, 5.7:1) afforded amine (16) (8.90 g, 75%) as a colourless liquid; Rf 0.36 (hexane-ethyl acetate, 5.7:1); $[\alpha]_D^{24}$ + 7.3° (c 0.64, $CHCl_3$); (Found: C, 65.01; H, 10.81; N, 3.31. $C_{20}H_{39}NO_3Si$ requires C, 64.99; H, 10.63; N, 3.79%); υ_{max} (thin film) 2980-2820 (s), 1740 (s), 1480-1430 (m), 1380 (w), 1255 (s), 1200 (m), 1170 (w), 1150 (w), 1110 (m), 1045 (w), 1005 (w), 980 (w), 940 (w), 840 (s) and 775 (m) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.26 (1H, t, J 8 Hz, C$\underline{H}$=), 5.10 (1H, br s, C$\underline{H}$=), 3.92-3.73 (5H, m, $C\underline{H}_2OSi$ and $CO_2C\underline{H}_3$), 3.42-3.16 (3H, m, N-C$\underline{H}$ and $C\underline{H}_2$-C=), 2.05 (4H, br s, $C\underline{H}_2$-$C\underline{H}_2$), 1.77 (1H, br s, exch., N$\underline{H}$), 1.72-1.56 (9H, m, 3 x $C\underline{H}_3$-C=), 0.87 (9H, s, Si-C($C\underline{H}_3$)$_3$); δ_C (200 MHz; $CDCl_3$) 174.1 ($\underline{C}O_2CH_3$), 138.7, 131.8, 131.5, 124.2, 124.0, 123.2, 122.2 ($\underline{C}$H= and $\underline{C}$=), 64.4 ($\underline{C}H_2OSi$), 62.3, 62.1 (N-$\underline{C}$H), 51.5 ($CO_2\underline{C}H_3$), 45.1, 45.0 (N-$\underline{C}H_2$-C=), 31.8 ($\underline{C}H_2CH_2$), 26.4, 26.2 (CH_2-$\underline{C}H_2$), 25.5 (Si-$C(\underline{C}H_3)_3$), 23.2, 17.9, 17.4, 15.9 ($\underline{C}H_3$-C=), -5.8 and -5.9 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 370 (M + H^+, 100%).

Methyl-(2*R*)-[3-(tert-butyldimethylsilyl)oxy]-2-[(3,7-dimethyl-2,6-octadienyl) (phenyloxycarbonyl)amino] propionate (17).

To a solution of the amine (16) (9.19 g, 24.86 mmol) in ethyl acetate (155 ml) was added a saturated aqueous solution of sodium bicarbonate (22 ml) at 0°C while stirring. Phenyl chloroformate (3.1 ml, 24.9 mmol) was then added dropwise and the mixture was stirred at 0°C for 1 h. Water and ethyl acetate was added, the organic layer separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica (hexane-ethyl acetate, 5.7:1) afforded the carbamate (17) (10.96 g, 90%) as a colourless liquid; Rf 0.36 (hexane-ethyl acetate, 5.7:1); $[\alpha]_D^{24}$ + 42.7° (c 0.44, $CHCl_3$); (Found: C, 66.11; H, 9.18; N, 2.58. $C_{27}H_{43}NO_5Si$ requires C, 62.22; H, 8.85; N, 2.86%); υ_{max} (thin film) 3080-2820 (m), 1720 (s), 1665 (w), 1595 (w), 1490 (w), 1470-1400 (m), 1380 (w), 1340 (w), 1250 (m), 1200 (s), 1160 (m), 1115 (m), 1070 (m), 1005 (w), 940 (w), 910 (w), 835 (s), 775 (m), 750 (m), 690 (w) and 660 (w) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 7.40-7.05 (5H, m, aromatics), 5.41-5.35 (1H, m, C$\underline{H}$=), 5.11 (1H, br s, C$\underline{H}$=), 4.50-3.92 (5H, m, = C-$C\underline{H}_2$-N, N-C$\underline{H}$, C$\underline{H}$ and $C\underline{H}_2OSi$), 3.74 (3H, s, $CO_2C\underline{H}_3$), 2.10-2.00 (4H, br s, $C\underline{H}_2$-$C\underline{H}_2$), 1.77-1.62 (9H, m, 3 x $C\underline{H}_3$-C=), 0.93 (9H, s, Si-C ($C\underline{H}_3$)$_3$) and 0.10 (6H, s, Si-$C\underline{H}_3$); δ_C (50 MHz; $CDCl_3$) 169.9, 169.7

($\underline{C}O_2CH_3$), 154.6, 154.2 (N-$\underline{C}O_2$), 140.7, 138.2, 132.1, 131.8, 129.3, 125.4, 124.1, 124.0, 122.0, 121.8, 121.6, 121.1, 120.1 ($\underline{C}$= and $\underline{C}$H=), 61.9, 61.6, 61.4 (N-$\underline{C}$H and $\underline{C}H_2OSi$), 52.0, 51.9 ($CO_2\underline{C}H_3$), 46.3, 46.0 (= C-$\underline{C}H_2$-N), 31.8 ($\underline{C}H_2$-CH_2), 26.3, 25.7 (CH_2-$\underline{C}H_2$), 25.5 (Si-C($\underline{C}H_3$)$_3$), 23.3, 18.0, 17.5, 16.0 ($\underline{C}H_3$-C=) and -5.7 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 490 (M + H^+, 100%) and 432 (30).

tert-Butyl-(4*R*)-3-hydroxy-4-[(phenyloxycarbonyl)(3,7-dimethyl-2,6-octadienyl)amino]-5-[tert-butyldimethylsilyl)oxy] pentanoate (18).

To a solution of the methyl ester (17) (0.97 g, 1.99 mmol) in dry toluene (40 ml) was added diisobutylaluminium hydride (2.0 ml, 1.5 M, 2.98 mmol) dropwise while stirring at -78°C under a nitrogen atmosphere. After 4 h, methanol (1 ml) was added dropwise to quench the reaction, followed by saturated aqueous Rochelle salt solution[18]. The solution was then allowed to warm to room temperature, after which ethyl acetate and more aqueous Rochelle salt solution was added. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo*, to afford crude aldehyde (0.81 g, 89%) as a yellow liquid product.

To a solution of diisopropylamine (0.36 ml, 2.53 mmol) in dry tetrahydrofuran (15 ml) at -20°C was added n-butyllithium (1.58 ml, 1.6 M, 2.53 mmol) dropwise while stirring under nitrogen.After 1h, the bath temperature was lowered to -78°C and tert-butyl acetate (0.33 ml, 2.53 mmol) was added dropwise. After stirring for 0.25 h, the crude aldehyde (0.81 g, 1.7 mmol) in tetrahydrofuran (5 ml) was added dropwise and the reaction mixture was stirred for 0.25 h before saturated aqueous ammonium chloride: methanol (1:1, 10 ml) was added. The solution was then allowed to warm to room temperature and the solvent was removed *in vacuo*. Chromatography of the residue on silica (hexane-ethyl acetate, 5.7:1) afforded alcohol (18) (0.60 g, 52%) as a colourless viscous oil; Rf 0.34 (hexane-ethyl acetate, 5.7:1); $[\alpha]_D^{25}$ + 13.1° (c 0.51, $CHCl_3$); υ_{max} (thin film) 3600-3300 (m), 3000-2850 (m), 1720 (s), 1595 (w), 1495 (w), 1480-1360 (m), 1255 (m), 1210 (s), 1155 (m), 1110 (w), 910 (w) and 840 (m) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.41-7.09 (5H, m, aromatics), 5.36 (1H, m, $\underline{H}C$=), 5.11 (1H, br s, $\underline{H}C$=), 4.35-3.60 (7H, m, = C-$\underline{C}H_2$-N, $\underline{C}H_2OSi$, N-$\underline{C}H$, $\underline{C}H$-OH and CH-O$\underline{H}$), 2.77-2.36 (2H, m, $\underline{C}H_2CO_2$), 2.10 (4H, m, $\underline{C}H_2$-$\underline{C}H_2$), 1.77-1.59 (9H, m, 3 x $\underline{C}H_3$-C=), 1.47 (9H, s, $CO_2C(\underline{C}H_3)_3$), 0.93 (9H, s, Si-C($\underline{C}H_3$)$_3$) and 0.11 (6H, s, Si-$\underline{C}H_3$); δ_C (50 MHz; $CDCl_3$) 172.4, 172.0 ($CH_2\underline{C}O_2$), 155.4 (N-$\underline{C}O_2$), 151.4, 138.8, 138.7, 131.8 ($\underline{C}$=), 129.4, 125.4, 124.0, 123.8, 121.8, 120.0 ($\underline{C}$H=), 81.1 ($CO_2\underline{C}(CH_3)_3$), 68.8, 68.7 ($\underline{C}$HOH), 64.1, 64.0, 61.0, 60.8 (N-$\underline{C}$H and $\underline{C}H_2OSi$), 46.6 (=C-$\underline{C}H_2$-N), 40.1, 39.6 ($\underline{C}H_2CO_2$), 32.0 ($\underline{C}H_2$-CH_2), 28.0 ($CO_2C(\underline{C}H_3)_3$), 26.4, 25.7 ($CH_2$-$\underline{C}H_2$), 25.6 (Si-C($\underline{C}H_3$)$_3$), 23.3, 18.0, 17.6, 17.5, 16.1 ($\underline{C}H_3$-C=) and -5.7 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 576 (M + H^+, 18%), 520 (35), 482 (38), 426 (100) and 384 (75).

(4*R*)-3-(3,7-Dimethyl-2,6-octadienyl)-4-[(tert-butyldimethylsilyl)oxymethyl]-5-[(tert-butyloxycarbonyl)methyl]-2-oxazolidinone (19).

To a solution of alcohol (18) (0.32 g, 0.55 mmol) in dichloromethane (4 ml) was added pyridine (0.21 ml, 2.60 mmol) followed by triflic anhydride (0.14 ml, 0.84 mmol), dropwise while stirring at 0°C under an nitrogen atmosphere. After 1 h, sodium iodide in ethylene glycol dimethyl ether (1 M, 5 ml) was added, and the solution

was stirred at r.t. for a further 3 h. The solvent was then removed *in vacuo* and ethyl acetate and water was added to the residue. The organic phase was separated, washed with saturated aqueous sodium thiosulphate solution, aqueous sodium hydroxide solution (10%), water, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Chromatography on silica (hexane-ethyl acetate, 4:1) afforded the title compound (19) (0.32 g, 88%) as a pale yellow oil; Rf 0.43 (hexane-ethyl acetate, 4:1); (Found: C, 64.58; H, 10.17; N, 3.18. $C_{25}H_{47}NO_5Si$ requires C, 64.82; H, 9.83; N, 2.91%); υ_{max} (thin film) 3000-2840 (m), 1770-1720 (s), 1480-1360 (m), 1255 (m), 1225 (w), 1160 (m), 1140-1090 (m), 1040 (w), 830 (m), 780 (m) and 760 (w) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.17-5.03 (2H, m, C<u>H</u>=), 4.58 (1H, q, J 6.2 Hz, O-C<u>H</u>), 4.12-3.96 (1H, m, C<u>H</u>OSi), 3.73-3.61 (3H, m, C<u>H</u>OSi and N-C<u>H</u>$_2$), 3.43 (1H, m, N-C<u>H</u>), 2.74-2.47 (2H, m, C<u>H</u>$_2$CO$_2$), 2.06-2.03 (4H, m, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.71-1.52 (9H, m, 3 x C<u>H</u>$_3$C=), 1.43 (9H, s, $CO_2C(C\underline{H}_3)_3$), 0.86 (9H, s, Si-C (C<u>H</u>$_3$)$_3$) and 0.04 (6H, s, Si-C<u>H</u>$_3$); δ_C (50 MHz; $CDCl_3$) 168.90 ($CH_2\underline{C}O_2$), 157.6 (N-$\underline{C}O_2$), 140.6, 140.4, 131.9, 123.8, 123.6, 119.5, 118.5 (<u>C</u>= and <u>C</u>H=), 81.6 ($CO_2\underline{C}(CH_3)_3$), 72.6 (O-$\underline{C}H_2$), 62.0, 61.8 , 60.8, 60.7 ($\underline{C}H_2$OSi and N-<u>C</u>H), 40.6, 39.9, 39.8, 39.4 (=C-$\underline{C}H_2$-N and $\underline{C}H_2CO_2$), 31.9 ($\underline{C}H_2$-CH_2), 28.0 ($CO_2C(\underline{C}H_3)_3$), 26.3, 26.2 ($CH_2$-$\underline{C}H_2$), 25.5 (Si-C($\underline{C}H_3)_3$), 23.2, 17.9, 17.5, 16.1 ($\underline{C}H_3$-C=) and -5.8 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 482 ($M + H^+$, 100%), 426 (61) and 368 (15).

When alcohol (21) was treated with triflic anhydride under the same conditions the oxazolidinone (19) was isolated in 75% yield.

Methyl-(2*R*)-[3-(<u>tert</u>-butyldimethylsilyl)oxy]-2-[(3,7-dimethyl-2,6-octadienyl)(<u>tert</u>-butyloxycarbonyl)amino] propionate (20).

To a solution of di-<u>tert</u>-butyl dicarbonate (1.30 g, 5.95 mmol) in dichloromethane (5 ml) was added a solution of amine (16) (2 g, 5.41 mmol) and triethylamine (0.78 ml, 5.60 mmol) in dichloromethane (3 ml) over 0.2 h while stirring. After stirring at r.t. for 15 h, water and ethyl acetate was added. The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Column chromatography on silica (hexane-ethyl acetate, 9:1) afforded carbamate (20) (2.07 g, 81%) as a pale yellow liquid; Rf 0.33 (hexane-ethyl acetate, 9:1); υ_{max} (thin film) 3040-2840 (s), 1745 (s), 1700 (s), 1540-1400 (m), 1365 (m), 1250 (m), 1210 (w), 1165 (m), 1120 (m), 1075 (m), 1005 (w) and 910 (w) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.30 (1H, t, C<u>H</u>=), 5.10 (1H, s, C<u>H</u>=), 4.38-3.67 (8H, m, = C-C<u>H</u>$_2$-N, $CO_2C\underline{H}_3$, N-C<u>H</u> and C<u>H</u>$_2$OSi), 2.05 (4H, br s, C<u>H</u>$_2$-C<u>H</u>$_2$), 173-1.60 (9H, m, 3 x C<u>H</u>$_3$-C=), 1.43 (9H, s, $CO_2C(\underline{C}H_3)_3$), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.06 (6H, s, Si-C<u>H</u>$_3$); δ_C (50 MHz; $CDCl_3$) 171.0 ($\underline{C}O_2CH_3$), 154.2 (N-$\underline{C}O_2$), 139.0, 136.8, 131.9, 131.6, 124.1, 124.0 (<u>C</u>= and <u>C</u>H=), 80.2, 79.9 ($CO_2\underline{C}(CH_3)_3$), 62.3, 61.7, 61.3 (N-<u>C</u>H and $\underline{C}H_2$OSi), 51.7 ($CO_2\underline{C}H_3$), 45.8, 45.6 (=C-$\underline{C}H_2$-N), 31.8 ($\underline{C}H_2CH_2$), 28.2 ($CO_2C(\underline{C}H_3)_3$), 26.3 ($CH_2$-$\underline{C}H_2$), 25.6 (Si-C($\underline{C}H_3)_3$), 23.2, 18.0, 17.4, 15.9 ($\underline{C}H_3$-C=) and -5.8 (Si-$\underline{C}H_3$); m/z (DCI, NH_3) 470 ($M + H^+$, 26%), 414 (27) and 370 (100).

tert-Butyl(4*R*)-3-hydroxy-4-[(tert-butyloxycarbonyl)(3,7-dimethyl-2,6-octadienyl)amino]-5-[(tert-butyldimethylsilyl)oxy] pentanoate (21).

In a similar manner to that described for the preparation of compound (18) the methyl ester (20) (0.50 g, 1.06 mmol) was reacted with tert-butyllithioacetate (1.12 mmol) at -78°C under nitrogen. Purification by chromatography on silica (hexane-ethyl acetate, 9:1) afforded alcohol (21) (0.37 g, 62%) as a colourless oil; Rf 0.30 (hexane-ethyl acetate, 9:1); υ_{max} (thin film) 3620-3200 (m), 3000-2840 (s), 1740-1660 (s), 1490-1440 (m), 1390 (m), 1365 (s), 1250 (s), 1160 (s), 1110 (m), 1000 (w), 940 (w) and 840 (s) cm^{-1}, δ_H (200 MHz; $CDCl_3$) 5.20-5.10 (2H, br m, C<u>H</u>=), 4.42-3.37 (7H, m, = C-C<u>H</u>$_2$-N, C<u>H</u>$_2$OSi, N-C<u>H</u>, C<u>H</u>OH and CH-O<u>H</u>), 2.62-2.21 (2H, m, C<u>H</u>$_2$CO$_2$), 2.05 (4H, br s, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.72-1.60 (9H, m, 3 x C<u>H</u>$_3$-C=), 1.46 (9H, s, CO$_2$C(C<u>H</u>$_3$)$_3$), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$) and 0.06 (6H, s, Si-C<u>H</u>$_3$); δ_C (50 MHz; $CDCl_3$) 172.3, 172.0 (CH$_2$<u>C</u>O$_2$), 154.9 (N-<u>C</u>O$_2$), 137.2, 137.0, 131.9, 131.6, 124.1, 123.9, 122.8, 122.0 (<u>C</u>= and <u>C</u>H=), 80.8, 80.1 (CO$_2$<u>C</u>(CH$_3$)$_3$), 69.5, 69.3, 69.1 (<u>C</u>HOH), 63.4, 63.2, 63.0, 61.1, 61.0 (N-<u>C</u>H and <u>C</u>H$_2$OSi), 46.1, 46.0 (=C-<u>C</u>H$_2$-N), 40.2, 40.0, 39.5 (<u>C</u>H$_2$CO$_2$), 31.9 (<u>C</u>H$_2$-CH$_2$), 28.3, 27.9 (2 x CO$_2$C(<u>C</u>H$_3$)$_3$), 26.3, 26.1 (CH$_2$-<u>C</u>H$_2$), 25.7,(Si-C(<u>C</u>H$_3$)$_3$), 23.2, 18.0, 17.5, 16.0 (<u>C</u>H$_3$-C=) and -5.8 (Si-<u>C</u>H$_3$); m/z (DCI, NH_3) 556 (M + H^+, 49%), 500 (12) and 456 (100).

(4*R*)-3-(3,7-Dimethyl-2,6-octadienyl)-4-[2-(tert-butyloxycarbonyl)-1-(hydroxy)ethyl]-2-oxazolidinone (22).

To a solution of the alcohol (18) (0.39 g, 0.68 mmol) in methanol (10 ml) was added p-toluenesulphonic acid monohydrate (0.25 g, 1.31 mmol) while stirring. After 0.3 h, a saturated aqueous solution of sodium bicarbonate was added to quench the reaction, and the methanol was removed *in vacuo*. Ethyl acetate and water was added. The organic phase was separated, washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*, to afford crude tert-butyl-(4*R*)-3-hydroxy-4-[(phenyloxycarbonyl)(3,7-dimethyl-2,6-octadienyl)amine]-5-(hydroxy)-pentanoate (0.31 g) as a colourless liquid; Rf 0.54 and 0.52 (ethyl acetate-hexane, 2.3:1); δ_H (200 MHz; $CDCl_3$) 7.42-7.10 (5H, m, aromatics), 5.33 (1H, t, J 5.6 Hz, C<u>H</u>=), 5.09 (1H, br s, C<u>H</u>=), 4.57-3.55 (7H, m, = C-C<u>H</u>$_2$-N, C<u>H</u>$_2$OH, CH-O<u>H</u>, C<u>H</u>-OH and N-C<u>H</u>), 2.92 (1H, br s, CH$_2$O<u>H</u>), 2.75-2.40 (2H, m, <u>C</u>H$_2$CO$_2$), 2.08 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$), 1.77-1.62 (9H, m, 3 x C<u>H</u>$_3$-C=) and 1.48 (9H, s, CO$_2$C(C<u>H</u>$_3$)$_3$); m/z (DCI, NH_3) 462 (M + H^+, 7%), 368 (48) and 312 (100).

To a solution of this crude diol (0.31 g) in methanol : water (10:1, 11 ml) was added potassium carbonate (0.11 g) while stirring. After 12 h, the methanol was evaporated under reduced pressure and water and ethyl acetate was added to the residue. The ethyl acetate layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Chromatography on silica (hexane-ethyl acetate, 1:1) afforded the title compound (22) (0.14 g, 56%) as a colourless viscous oil; Rf 0.26 and 0.20 (hexane-ethyl acetate, 1.2:1); $[\alpha]_D^{21}$ -9.4° (c 0.91, $CHCl_3$), (Found: C, 65.10; H, 9.08; N, 4.11. $C_{20}H_{33}NO_5$ requires C, 65.37; H, 9.05; N, 3.81%); υ_{max} (thin film) 3600-3200 (m), 3000-2840 (m), 1765-1695 (s), 1600 (vw), 1475 (m), 1455 (m), 1370 (m), 1250 (m), 1165 (m), 1075 (m), 1030 (w), 985 (vw), 950 (vw), 840 (w) and 760 (w) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.17-5.02 (2H, m, C<u>H</u>=), 4.30-4.03 (4H, m, C<u>H</u>$_2$O, N-C<u>H</u> and C<u>H</u>-OH), 3.83-3.47 (3H, m, = C-C<u>H</u>$_2$-N and CH-O<u>H</u>), 2.43-2.18 (2H, m, C<u>H</u>$_2$CO$_2$), 2.09-2.04 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$), 1.69-1.58 (9H, m, 3 x C<u>H</u>$_3$-C=) and 1.44 (9H, s, CO$_2$C(C<u>H</u>$_3$)$_3$); δ_C (50 MHz; $CDCl_3$) 170.9 (CH$_2$<u>C</u>O$_2$), 158.8 (N-<u>C</u>O$_2$), 141.4,

132.3, 132.0, 123.8, 123.6, 118.9, 118.0 (C= and CH=), 81.7 ($CO_2C(CH_3)_3$), 65.5, 65.4 (CH_2O), 63.3, 62.2 (CH-OH), 57.9 (N-CH), 39.9, 39.4 (=C-CH_2-N), 37.8 (CH_2CO_2), 31.8 (CH_2-CH_2), 27.9 ($CO_2C(CH_3)_3$), 26.3, 26.1 (CH_2-CH_2), 25.5, 23.2, 17.5 and 16.1 (CH_3-C=); m/z (DCI, NH_3) 368 (M + H^+, 39%), 312 (100) and 298 (25).

(4*R*)-3-(3,7-Dimethyl-2,6-octadienyl)-4-[2-(tert-butyloxycarbonyl)-1-(iodo)ethyl]-2-oxazolidinone (23).

Triflic anhydride (90.1 ml, 0.60 mmol) was added dropwise to a solution of the alcohol (22) (0.14 g, 0.38 mmol) and pyridine (0.14 ml, 1.73 mmol) in dichloromethane (2.5 ml) while stirring at 0°C under an nitrogen atmosphere. After 1h, sodium iodide in ethylene glycol dimethyl ether (1M, 4 ml) was added and the solution was allowed to warm to r.t.. After stirring for a further 1.25 h, the solvent was removed under reduced pressure and ethyl acetate and water was added to the residue. The organic phase was separated, washed with saturated aqueous sodium thiosulphate solution, water, dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography on silica (hexane-ethyl acetate, 5.7 : 1) afforded iodide (23) (0.11 g, 60%) as a pale yellow oil; Rf 0.16 (hexane-ethyl acetate, 5.7 : 1); $[\alpha]_D^{21}$ + 42.8° (c 0.58, $CHCl_3$); ν_{max} (thin film) 3020-2840 (s), 1790-1710 (vs), 1440 (m), 1410 (m), 1370 (s), 1280 (m), 1235 (s), 1160 (s), 1060 (m), 1040 (w), 990 (vw), 930 (vw), 840 (w) and 760 (m) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.19-5.04 (2H, m, CH=), 4.52-3.94 and 3.74-3.60 (6H, m, = C-CH_2-N, O-CH_2, N-CH and CHI) 2.95-2.62 (2H, m, CH_2CO_2), 2.12-2.03 (4H, m, CH_2-CH_2), 1.73-1.61 (9H, m, 3 x CH_3-C=) and 1.47 (9H, s, $CO_2C(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 169.1, 169.0 (CH_2CO_2), 158.0 (N-CO_2), 142.4, 142.2, 132.4, 132.0, 123.6, 123.3, 118.1, 117.1 (C= and CH=), 82.1 ($CO_2C(CH_3)_3$), 65.7, 65.4 (O-CH_2), 59.7, 59.5 (N-CH), 40.2, 40.1 (=C-CH_2-N), 38.6, 38.5 (CH_2CO_2), 33.3, 32.2, 31.9 (CH_2-CH_2), 28.0 ($CO_2C(CH_3)_3$), 26.5, 26.2, 25.7 (CH_2-CH_2), 24.0, 23.8 (CHI), 23.4, 17.7, 17.6, 16.4 and 16.2 (CH_3-C=); m/z (DCI, NH_3) 495 (M + NH_4^+, 10%), 478 (M + H^+, 53), 422 (64) and 350 (100).

(2*S*,3*S*,4*S*)-1-(tert-Butyloxycarbonyl)-2-(hydroxymethyl)-3-[(methoxycarbonyl)methyl]-4-[1-(4-methyl-pent-3-enyl)(ethenyl)]pyrrolidine (30).

Cobalt oxidative cyclisation at neutral pH.

To a mixture of cobalt (II) acetate (0.11 g, 0.44 mmol) and dimethylglyoxime (0.10 g, 0.88 mmol) in methanol (3 ml) under nitrogen, was added iodide (23) (0.20 g, 0.42 mmol) dropwise while stirring followed by pyridine (0.04 ml, 0.44 mmol). The flask was then purged with hydrogen and stirred under a hydrogen atmosphere overnight. The solvent was then removed *in vacuo*, and ethyl acetate and water was added to the residue. The organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Column chromatography (silica; hexane-ethyl acetate, 2.3:1) yielded alkene (24) (36 mg, 25%) as a colourless oil [Rf 0.43 (hexane-ethyl acetate, 2.3:1)], oxazolidinone (25) (43 mg, 29%) [Rf 0.35 (hexane-ethyl acetate, 2.3:1)], and the minor products (26), (27),(28) and (29) (19 mg, 13%) [Rf 0.30 (hexane-ethyl acetate, 2.3:1)].

Alkene (24): υ_{max} (thin film) 3020-2820 (m), 1775 (s), 1730 (s), 1695 (s), 1435 (m), 1405 (m), 1365 (m), 1250 (w), 1210 (w), 1150 (s), 1110 (w), 1040 (m), 940 (w), 910 (w), 840 (w), 810 (w) and 765 (w) cm^{-1}; δ_H (500 MHz; $CDCl_3$) 5.17-5.01 (2H, m, C<u>H</u>=), 4.85 (2H, s, O-C<u>H</u>$_2$-C=), 4.68 (1H, t, J 8 Hz, C<u>H</u>=), 4.06 (2H, d, J 6.2 Hz, =C-C<u>H</u>$_2$-N), 2.80 (2H, d, J 7.6 Hz, = C-C<u>H</u>$_2$-CO_2), 2.18-1.96 (4H, m, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.75-1.57 (9H, m, 3 x C<u>H</u>$_3$-C=) and 1.44 (9H, s, CO_2C (C<u>H</u>$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 170.3 (CH$_2$<u>C</u>O$_2$), 157.0 (N-<u>C</u>O$_2$), 140.3, 136.4, 131.7, 123.7, 123.6, 118.2, 117.3, 89.8 (<u>C</u>= and <u>C</u>H=), 81.1 (CO$_2$<u>C</u>(CH$_3$)$_3$), 65.4 (<u>C</u>H$_2$OCO), 39.8, 39.4 (N-<u>C</u>H$_2$-C=), 33.3 (<u>C</u>H$_2$CO$_2$), 32.2 (<u>C</u>H$_2$-CH$_2$), 28.0 (CO$_2$C(<u>C</u>H$_3$)$_3$), 26.3, 25.6 (<u>C</u>H$_3$-C=), 23.2 (CH$_2$-<u>C</u>H$_2$), 17.6 and 16.4 (<u>C</u>H$_3$-C=); m/z (DCI, NH_3) 367 (M + NH_4^+, 8%), 350 (M + H^+, 100) and 294 (78).

Oxazolidinone (25): υ_{max} (thin film) 3020-2840 (m), 1780-1690 (s), 1645 (w), 1450 (w), 1390 (m), 1375 (m), 1270-1200 (m), 1150 (s), 1040 (w), 910 (w) and 840 (w) cm^{-1}; δ_H (300 MHz; $CDCl_3$) 5.10-5.00 (1H, m, C<u>H</u>=), 5.00 (1H, s, C<u>H</u>=), 4.80 (1H, s, C<u>H</u>=), 4.57 (1H, t, J 8.7 Hz, N-C<u>H</u>-CH$_2$), 4.25-4.19 (2H, m, C<u>H</u>2OCO), 3.84-3.77 (2H, m, N-C<u>H</u>$_2$), 3.19-3.13 (1H, m, = C-C<u>H</u>), 2.96-2.81 (C<u>H</u>CH$_2$CO$_2$), 2.63-1.88 (6H, m, C<u>H</u>$_2$-C<u>H</u>$_2$ and C<u>H</u>$_2$CO$_2$), 1.63 (C<u>H</u>$_3$-C=), 1.60 (C<u>H</u>$_3$-C=) and 1.44 (9H, s, CO$_2$C(C<u>H</u>$_3$)$_3$; δ_C (125MHz; $CDCl_3$) 171.5 (CH$_2$<u>C</u>O$_2$), 161.5 (N-<u>C</u>O$_2$), 146.6, 132.3 (<u>C</u>=), 123.3 (<u>C</u>H=), 112.3 (<u>C</u>H$_2$=), 81.2 (CO$_2$<u>C</u>(CH$_3$)$_3$), 69.1, 63.7 (N-<u>C</u>H-CO$_2$ and <u>C</u>H$_2$OCO), 50.3, 44.9, 43.4 (N-<u>C</u>H$_2$, =C-<u>C</u>H and CH-<u>C</u>H$_2$CO$_2$), 36.6, 34.9 (<u>C</u>HCO$_2$ and <u>C</u>H$_2$-CH$_2$), 28.0 (CO$_2$C(<u>C</u>H$_3$)$_3$), 26.3 (CH$_2$-<u>C</u>H$_2$), 25.6 and 17.7 (<u>C</u>H$_3$-C=); m/z (DCI, NH_3) 367 (M + NH_4^+, 7%), 350 (M + H^+, 100), 311 (23) and 294 (85).

<u>Cobalt oxidative cyclisation under basic conditions.</u>

Reaction of cobaloxime (I) with iodide (23) under the conditions described previously[7] gave identical products and yield to that described above.

To a solution of the oxazolidinone (25) (134 mg, 0.38 mmol) in dioxane (0.8 ml) was added aqueous sodium hydroxide solution (3N, 0.8 ml) while stirring. The solution was then heated to 70°C and then stirred overnight under an atmosphere of nitrogen. After cooling to r.t., di-<u>tert</u>-butyl pyrrocarbonate (0.21 g, 0.98 mmol) in dioxane (2 ml) was added dropwise and stirring was continued for 2 h. The solvent was removed *in vacuo*, water (5 ml) was added and the solution was neutralized with aqueous citric acid solution (10%) and extracted (three times) with ethyl acetate. The organic extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*.

To a solution of the crude hydroxy acid in methanol (2 ml) was added excess ethereal diazomethane at 0°C. The excess diazomethane was removed via a stream of nitrogen, after which solvent evaporation afforded crude product. Column chromatography on silica (hexane-ethyl acetate, 1.5:1) afforded the title compound (30) (73 mg, 50%) as a colourless oil; Rf 0.32 (hexane-ethyl acetate, 1.5:1); $[\alpha]_D^{25}$ -26.0° (c 0.2, $CHCl_3$); υ_{max} ($CHCl_3$) 3500-3100 (m), 3020-2820 (m), 1734 (s), 1670 (s), 1600 (w), 1439 (m), 1408 (s), 1370 (m), 1330 (w), 1223 (vs), 1168 (s), 1140 (s), 1020 (m) and 901 (m) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.08 (1H, t, J 6.8 Hz, C<u>H</u>=), 4.94 (1H, s, C<u>H</u>=), 4.71 (1H, s, C<u>H</u>=), 4.09 (1H, br s, N-C<u>H</u>-CH$_2$), 3.82-3.55 (5H, m, CO$_2$C<u>H</u>$_3$ and N-C<u>H</u>$_2$), 3.44 (2H, d, J 7.0 Hz, C<u>H</u>$_2$OH), 2.94 (1H, m, =C-C<u>H</u>), 2.47 (1H, m, CH$_2$-C<u>H</u>), 2.37-1.81 (6H, m, C<u>H</u>$_2$CO$_2$ and C<u>H</u>$_2$-C<u>H</u>$_2$), 1.67 (3H, s, C<u>H</u>$_3$-C=), 1.59 (3H, s, C<u>H</u>$_3$-C=) and 1.46 (9H, s, CO$_2$C(C<u>H</u>$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 172.5 (<u>C</u>O$_2$CH$_3$), 154.2 (N-<u>C</u>O$_2$), 145.3 (<u>C</u>=), 132.2 (<u>C</u>=), 123.5 (<u>C</u>H=), 111.4 (<u>C</u>H$_2$=) 80.6

($CO_2\underline{C}(CH_3)_3$), 66.6 ($\underline{C}H_2OH$), 65.2 ($CH_2$-$\underline{C}H$-N), 51.8 ($CO_2\underline{C}H_3$), 48.8 (N-$\underline{C}H_2$), 44.4 ($\underline{C}H$-C=), 39.2 ($\underline{C}HCH_2CO_2$), 35.8 ($\underline{C}H_2$-C=), 33.2 ($\underline{C}H_2CO_2$), 28.4 ($CO_2C(\underline{C}H_3)_3$), 26.2 ($\underline{C}H_2$-C=), 25.6 ($\underline{C}H_3$-C=) and 17.7 ($\underline{C}H_3$-C=); m/z (DCI, NH_3) 382 ($M + H^+$, 100%).

(2*S*,3*S*,4*S*)-1-(tert-Butyloxycarbonyl)-2-(methoxycarbonyl)-3-(methoxycarbonyl)methyl]-4-[1-(4-methyl-pent-3-enyl)(ethenyl)] pyrrolidine (31).

To a solution of the alcohol (30) (109 mg, 0.29 mmol) in dimethylformamide (10 ml) was added pyridinium dichromate (0.55 g, 1.45 mmol) while stirring. The dark coloured solution was then heated at 40°C and stirred overnight under an nitrogen atmosphere. After cooling to r.t., a solution of diazomethane in ether was added. The excess diazomethane was removed via a stream of nitrogen and the mixture was then poured into a saturated aqueous solution of sodium carbonate and extracted (three times) with ethyl acetate. The combined extracts were washed with water, brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue using column chromatography on silica (hexane-ethyl acetate, 2.3:1) afforded the title compound (31) (71 mg, 61%) as a colourless oil; Rf 0.44 (hexane-ethyl acetate, 2.3:1); $[\alpha]_D^{23}$ -6.3° (c 0.48, $CHCl_3$); υ_{max} ($CHCl_3$) 3050-2840 (m), 1737 (s), 1690 (s), 1603 (w), 1477 (w), 1456 (w), 1438 (m), 1407 (s), 1369 (m), 1330 (w), 1224 (s), 1209 (s), 1171 (s), 1135 (s), 1028 (w) and 900 (w) cm^{-1}; δ_H (200 MHz; $CDCl_3$) 5.07 (1H, t, J 6.6 Hz, C$\underline{H}$=), 4.96 (1H, s, C$\underline{H}$=), 4.75 (1H, s, C$\underline{H}$=), 4.14 (1H, dd, J 20 and 2.7 Hz, N-C$\underline{H}$-CO_2), 3.80-3.32 (8H, m, 2 x $CO_2\underline{C}H_3$ and N-$\underline{C}H_2$), 3.06 (1H, m, = C-C$\underline{H}$), 2.84 (1H, m, $\underline{C}HCH_2CO_2$), 2.45-1.85 (6H, m, $\underline{C}H_2$-$\underline{C}H_2$ and $\underline{C}H_2CO_2$), 1.67 (3H, s, $\underline{C}H_3$-C=), 1.59 (3H, s, $\underline{C}H_3$-C=), 1.47 and 1.40 (9H, s, $CO_2C(\underline{C}H_3)_3$); δ_C (125 MHz; $CDCl_3$) 172.6, 172.4 ($\underline{C}O_2CH_3$), 154.4, 153.8 ($N\underline{C}O_2$), 145.2, 145.0, 132.17, 123.4, 123.3 ($\underline{C}$= and $\underline{C}$H=), 111.8, 111.6 ($\underline{C}H_2$=), 80.2 ($CO_2\underline{C}(CH_3)_3$), 64.1, 63.8 (N-$\underline{C}$H-$CO_2$), 52.3, 51.8 ($CO_2\underline{C}H_3$), 47.8, 47.5 (N-$\underline{C}H_2$), 44.7, 44.0 (=C-$\underline{C}$H), 41.9, 40.9 ($\underline{C}HCH_2CO_2$), 35.8 ($\underline{C}H_2$-C=), 33.1 ($\underline{C}H_2CO_2$), 28.4, 28.3 ($CO_2C(\underline{C}H_3)_3$), 26.2 ($\underline{C}H_2$-C=), 25.6 and 17.6 ($\underline{C}H_3$-C=); m/z (DCI, NH_3) 410 ($M + H^+$, 15%) and 310 (100).

(2S,3S,4S)-2-Carboxy-4-[1-(4-hydroxy-4-methylpentyl)ethenyl]-3-pyrrolidineacetic acid, trifluoroacetate salt (33).

A mixture of diester (31) (57 mg, 0.14 mmol) and aqueous potassium hydroxide (9 ml, 2.5%) in methanol (1.5 ml) was refluxed for 4.5 h under nitrogen. The mixture was then cooled to r.t., the solvent was removed *in vacuo* and the solution was brought to pH 4-5 by the addition of aqueous citric acid (10%). The aqueous phase was then extracted (three times) with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford crude diacid (54 mg) as a colourless oil. A solution of the crude diacid (54 mg) in trifluoroacetic acid (5 ml) at r.t. was stirred for 0.5 h. The excess trifluoroacetic acid was then removed *in vacuo* and the resulting pale brown residue was partitioned between ethyl acetate and water. The aqueous layer was then removed and brought to pH 7 by the addition of aqueous sodium hydroxide (10%). This solution was then filtered through a column of ion exchange resin [Dowex (50 x 2)-100; elution with water followed by ammonium hydroxide (1N)] to give a mixture of amino acid (7) together with minor impurity (32). Water (5 ml) was added followed by trifluoroacetic acid (1 ml) and the solution was heated to 70°C for 0.1 h, after which the

solvent was evaporated *in vacuo* to afford the trifluoroacetate salt (33) (42 mg, 72%) as a white solid; υ_{max} (nujol mull) 3700-2350 (s), 1800-1550 (s), 1450 (m), 1370 (w), 1350 (w), 1250-1110 (s), 960 (w), 910 (w), 845 (m), 800 (m) and 775 (m) cm^{-1}; δ_H (300 MHz; D_2O and CF_3COOH, HOD suppressed) 5.09 (1H, s, C<u>H</u>=), 4.82 (1H, s, C<u>H</u>=), 4.23 (1H, d, J 3.7 Hz, N-C<u>H</u>-CO_2), 3.70-3.62 (1H, m, N-C<u>H</u>), 3.49-3.42 (1H, m, N-C<u>H</u>-CH), 3.20-3.06 (2H, m, = C-C<u>H</u> and C<u>H</u>CH_2CO_2), 2.57-2.38 (2H, m, $C\underline{H_2}CO_2$), 2.08-1.95 (2H, m, =C-$C\underline{H_2}$), 1.55-1.37 (4H, m, $C\underline{H_2}$-$C\underline{H_2}$) and 1.14 (6H, s, 2 x $C\underline{H_3}$-C-OH); δ_C (125 MHz; D_2O, HOD suppressed) 176.0, 171.5 (2 x $\underline{C}O_2H$), (163.1, 162.8, 162.5, 162.2 ($CF_3\underline{C}O_2H$)), 143.7 (<u>C</u>=), (120.1, 117.0, 115.4, 113.1 (CF_3CO_2H)), 113.7 ($\underline{C}H_2$=), 72.0 (CH_3-<u>C</u>-OH), 64.5 (N-<u>C</u>H-CO_2), 48.1 (N-$\underline{C}H_2$), 45.1, 42.9 (=C-<u>C</u>H and $\underline{C}HCH_2CO_2$), 40.8 ($\underline{C}H_2$-C-OH), 36.7 (=C-$\underline{C}H_2$), 33.5 ($\underline{C}H_2CO_2$), 28.30 (2 x $\underline{C}H_3$C-OH) and 22.4 (CH_2-$\underline{C}H_2$-CH_2); m/z (positive argon fast atom bombardment) 300 ($M + H^+$, 26%) and 282 (100).

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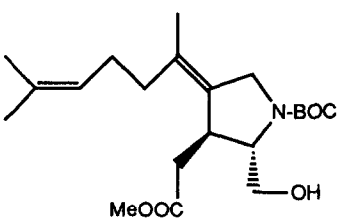
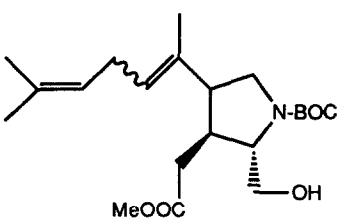
The structural assignment of the compounds (26) and (27) was confirmed further by sequential treatment of the mixture of (26)-(29) with aqueous sodium hydroxide, di-tert-butyl pyrocarbonate and diazomethane to give an inseparable mixture of the BOC-methyl esters (34) and (35) after column chromatography. The presence of these compounds was indicated by the ^{1}H n.m.r. spectrum at δ 5.15 - 5.0 (olefinic) and at δ 1.69, 1.62 and 1.59 (s, 3 x CH_3-C=), of signals in the ^{13}C n.m.r. spectrum at δ 132.2, 126.4, 122.4 (olefinic) and by mass spectral data [m/z (DCI, NH_3) 382(65%) and 326(100)].



(34)



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