

## ENANTIOSELECTIVE KAINOID SYNTHESIS BY COBALT-MEDIATED CYCLISATION OF AN AMINO ACID DERIVATIVE

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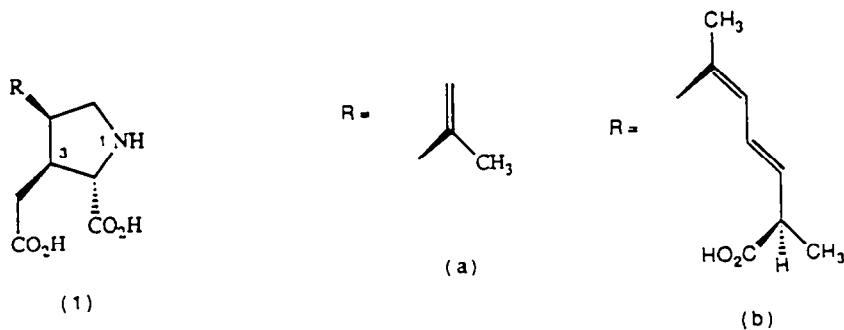
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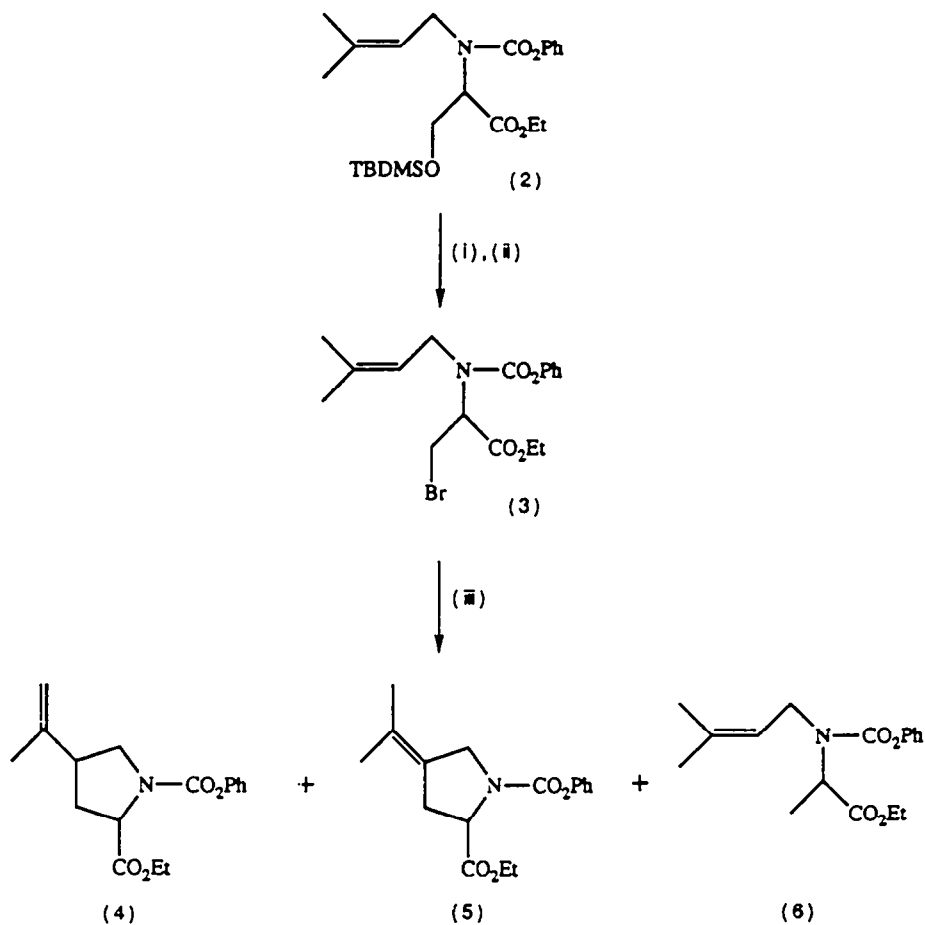
**Abstract:** A new synthesis of (-)-kainic acid is described based on a cobalt mediated cyclisation reaction of an appropriately modified serine precursor.

The kainoids, a class of naturally occurring non-proteinogenic amino acids, are of considerable interest since they have been found to exhibit powerful biological, principally neuroexcitatory activity<sup>1</sup>. The biological activity of these compounds, which possess a common pyrrolidine dicarboxylic acid nucleus (1) is known to vary with the nature of the isopropenyl side chain, and with the stereochemistry at the C-4 centre. The simplest member of this class of compounds, kainic acid (1a), possesses an unsubstituted isopropenyl side chain (Scheme 1). One of the most potent kainoids, domoic acid (1b), which has a dienoic side chain, has recently been responsible for fatal poisoning by the ingestion of contaminated shellfish<sup>2</sup>. The synthesis of these compounds presents a considerable challenge, and a short approach which allows the ready incorporation of a variety of different side chains, has not yet been developed.



SCHEME 1

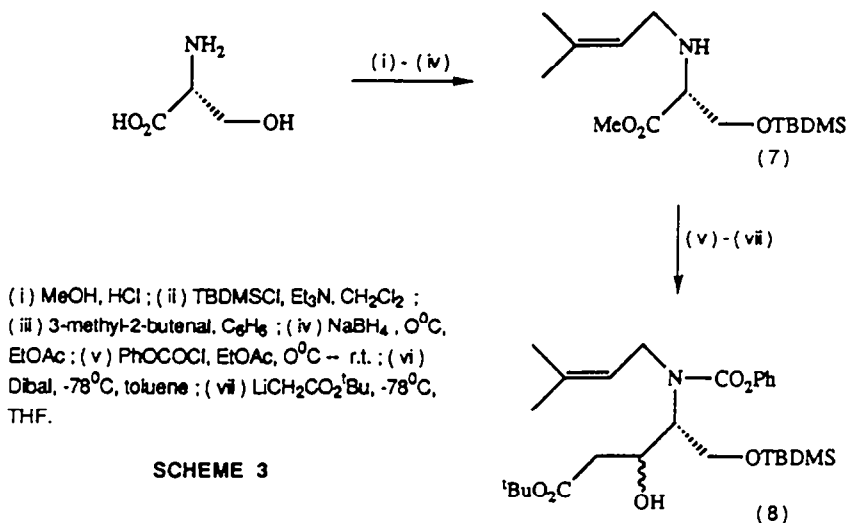
Amongst several different approaches to the synthesis of the kainoids<sup>3</sup>, we recently reported a synthesis which makes use of a cobalt-mediated radical cyclisation of an appropriate precursor<sup>4</sup>. The chemistry of the intermediate alkyl-cobalt (III) species has been thoroughly studied<sup>5</sup>, and has been used in the synthesis of a number of other natural products<sup>6</sup>. We now report in detail an efficient synthesis of (-)- $\alpha$ -kainic acid (1a) starting from D-serine, which makes use of a cobalt-mediated ring closure in the key step. This approach has potential application to the synthesis of a range of substituted kainoids.



(i) TsOH, EtOH; (ii) NBS, PPh<sub>3</sub>, THF; (iii) Co<sup>I</sup>, MeOH

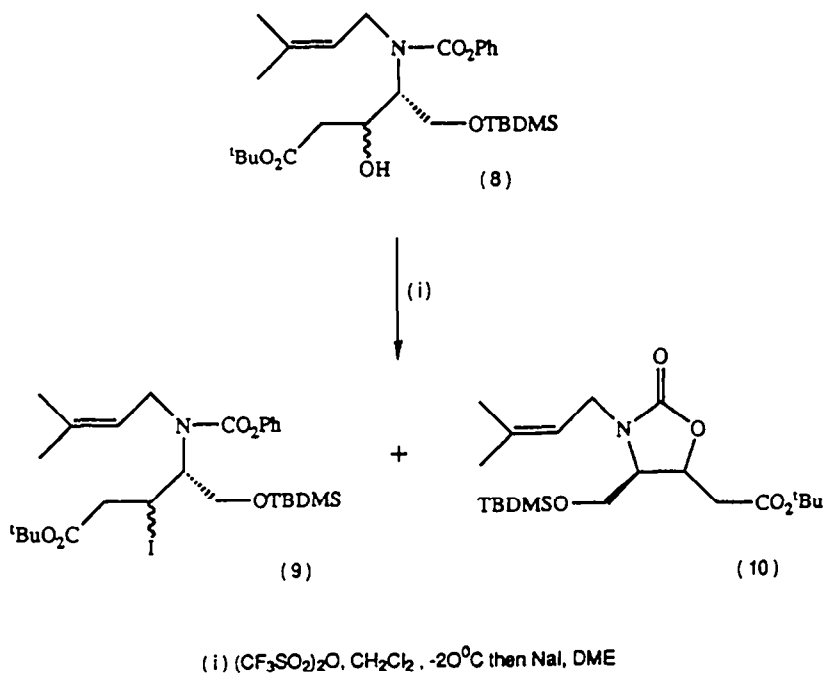
SCHEME 2

Initial studies to determine the feasibility of this approach involved the ring closure of an N-allylic DL-serine derivative, and confirmed the work of earlier studies<sup>4</sup>, which used differently protected substrates. Compound (2), prepared by reductive amination of suitably protected DL-serine as described later, was converted to the bromoester (3) in 79% yield, by treatment with N-bromosuccinimide/triphenylphosphine in tetrahydrofuran (Scheme 2). Reaction of bromoester (3) with cobaloxime (I) gave the products (4), (5) and (6) in the ratio 10:1:5 in 72% overall yield. Radical ring closure of the first formed alkylcobalt (III) species, followed by dehydrocobaltation, either away from the pyrrolidine ring, gave alkene (4), or towards the ring, gave exocyclic alkene (5). Reduction of the bromide (3), to give the alanine derivative (6) was also observed. The predominance of alkene (4) over exocyclic alkene (5) was expected from the work of Schrauzer<sup>7</sup>, which demonstrated that the dealkylation reaction of secondary alkylcobalamins strongly favoured the formation of the less substituted double bond. The pyrrolidine (4) was obtained as a mixture of epimers at C-4, corresponding to kainic and allo-kainic acid configurations<sup>3</sup>. This model study indicated that cyclisation of the intermediate radical to form the pyrrolidine ring was more facile than reduction, and that the required precursors could be readily generated from serine. Variation in the nature of the N-allylic substituent could ultimately be used to synthesise a range of kainoids.

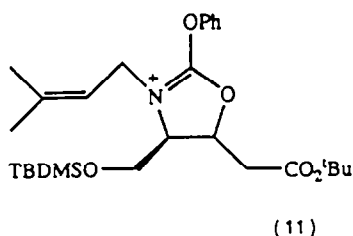


The application of this type of cyclisation approach to the synthesis of the kainoids required an additional two-carbon substituent on C-3, and this was incorporated using the following strategy. D-Serine methyl ester hydrochloride (prepared from D-serine with acidified methanol), after protection as the silyl ether, was treated

with 3-methyl-2-butenal followed by sodium borohydride at 0°C, to give the ester (7) as a colourless oil in 44% yield from D-serine (Scheme 3). This compound was N-protected by reaction with phenylchloroformate and the ester function was then reduced with diisobutylaluminium hydride (-78°C). The resultant N-protected  $\alpha$ -amino aldehyde, which was not isolated, was treated with tert-butyl-lithioacetate<sup>8</sup> at -78°C for 0.25 h to give alcohol (8) in 47% yield from amine (7). This was predominantly one epimer at the hydroxy-bearing carbon (as indicated by carbon -13 n.m.r. spectroscopy) and this could be the result of diastereoselective anion addition. The diastereoselective addition of carbanions to aldehydes, prepared by reduction of the corresponding optically pure  $\alpha$ -amino acids, has recently been shown to be a synthetically useful reaction<sup>9</sup>. However, longer reaction times for the reduction step gave lower isolated yields of the alcohol (8), along with the formation of phenol (as indicated by i.l.c. analysis). Attempted iodination of alcohol (8) by reaction with triflic anhydride followed by sodium iodide at -20°C<sup>10</sup>, gave a separable mixture of the desired iodide (9) along with oxazolidinone (10) as the major product (Scheme 4). The formation of oxazolidinone (10) was thought to arise via a cyclocarbamation<sup>11</sup> reaction in which the intermediate (11) is formed by triflate displacement.<sup>12</sup> The stereochemistry of oxazolidinone (10) could not be determined by n.O.e studies which gave inconclusive results.

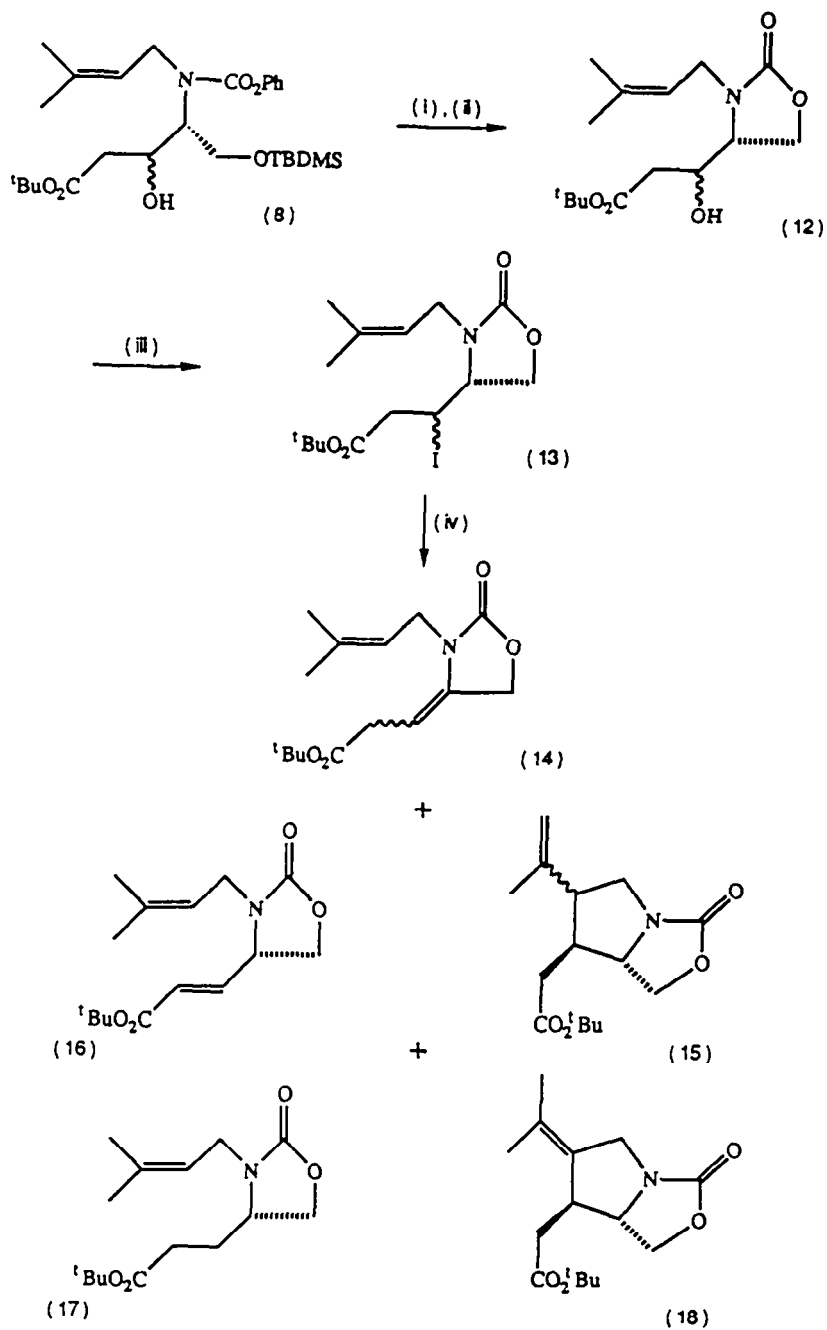


SCHEME 4



In an attempt to circumvent this difficulty of unwanted cyclisation, the alcohol (8) was treated with *p*-toluenesulphonic acid to remove the silyl ether, and the resulting alcohol was cyclised exclusively to the alternative oxazolidinone (12) using potassium carbonate in aqueous methanol (Scheme 5). The presence of the tert-butyl ester was thought to prevent the formation of any lactone arising by attack of the primary alcohol. The white crystalline oxazolidinone (12) appeared to be a single diastereomer, on the basis of a sharp melting point (94-96°C) and the carbon-13 n.m.r. spectrum. Reaction of alcohol (12) with triflic anhydride followed by the addition of sodium iodide, gave the corresponding iodide (13) as a colourless solid (m.p. 32-34°C). On treatment with cobaloxime (I) anion, generated under the normal basic conditions, the iodide (13) yielded a number of products. Column chromatography afforded three main fractions. The first fraction contained exocyclic alkene (14) in 15% yield. This could arise via base induced elimination of the starting iodide (13) or radical elimination of the intermediate cobalt (III) species. The second and major fraction contained the desired product (15) together with  $\alpha$ ,  $\beta$ -unsaturated ester (16) in a ratio of 3.5:1 in 51% yield. The formation of the  $\alpha$ ,  $\beta$ -unsaturated ester (16) appears to be dependent on the stoichiometry of the hydroxide base used to generate the cobalt anion, and could also occur by direct elimination of the iodide (13) or by elimination of the derived radical. The last fraction consisted of an inseparable mixture of compounds in 12% combined yield. <sup>1</sup>H n.m.r. analysis indicated the presence of reduced substrate (17) and exocyclic alkene (18). The exocyclic alkene (18) could arise by dehydrocobaltation towards the tertiary centre. As demonstrated by previous work<sup>4</sup>, the presence of the oxazolidinone ring in iodide (13) is expected to enhance the stereocontrol of the ring closure reaction, leading to a predominance of the desired kainic acid (rather than the alternative allo-kainic acid) configuration at C-4.

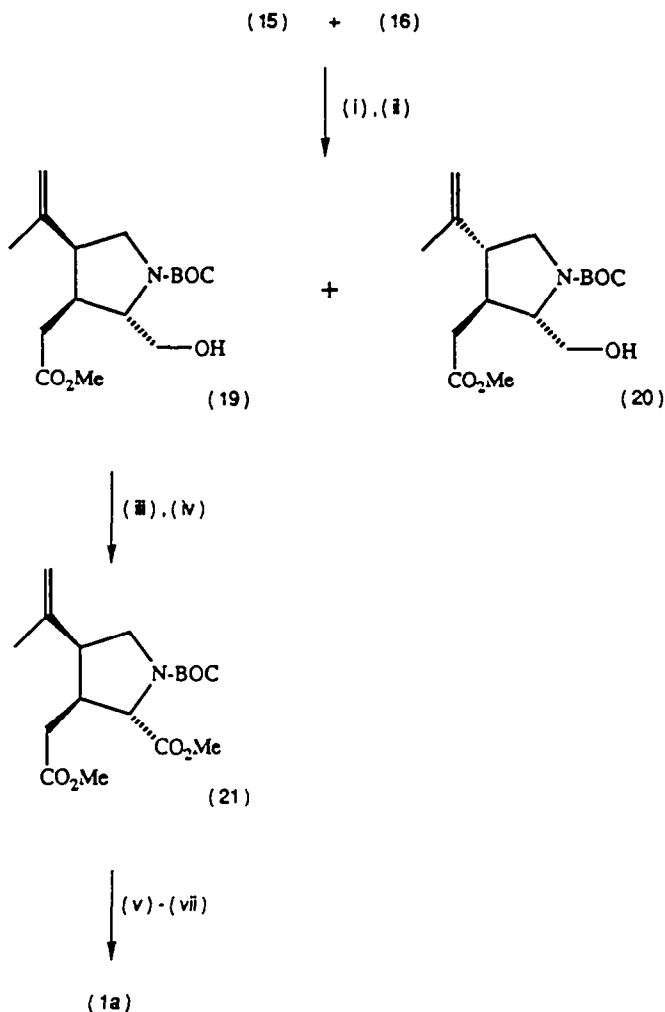
Treatment of the inseparable mixture of compounds (15) and (16) with aqueous base, to affect oxazolidinone ring opening, simultaneously removed the tert-butyl ester, re-protection of the nitrogen as the



(i) TsOH, MeOH; (ii)  $K_2CO_3$ , MeOH -  $H_2O$ ; (iii)  $(CF_3SO_2)_2O$ ,  $CH_2Cl_2$ ,  $0^\circ C$   
then NaI, DME; (iv)  $Co^I$ , MeOH

SCHEME 5

tert-butyloxycarbonyl derivative, followed by re-esterification (diazomethane) of the crude mixture afforded, after careful column chromatography, the pyrrolidines (19) and (20) in 45% and 11% yield respectively



(i) NaOH, dioxane, 70°C then (BOC)<sub>2</sub>O; (ii) CH<sub>2</sub>N<sub>2</sub>, MeOH; (iii) PDC, DMF, 60°C;  
 (iv) CH<sub>2</sub>N<sub>2</sub>, MeOH; (v) aq. KOH, MeOH, 70°C; (vi) TFA, CH<sub>2</sub>Cl<sub>2</sub>; (vii) Ion Exchange

SCHEME 6

(Scheme 6). This represented a better (4*S*:4*R*) stereocontrol of the radical ring closure from that reported earlier<sup>4</sup> (i.e. 4:1 compared to 1.7:1). The *cis*-relationship of the C-3 and C-4 protons of pyrrolidine (19) was confirmed by n.O.e experiments (Fig. 1 (a)) and by the fact that the two olefinic protons appeared as two

singlets ( $\delta$  4.89 and 4.65) in the  $^1\text{H}$  n.m.r. spectrum. Similarly the trans-relationship of the corresponding protons in the epimer (20) was indicated by the absence of any n.O.e (Fig. 1 (b)) and by the fact that the olefinic protons appeared as one singlet ( $\delta$  4.86).<sup>13</sup> Oxidation of pyrrolidine (19) with

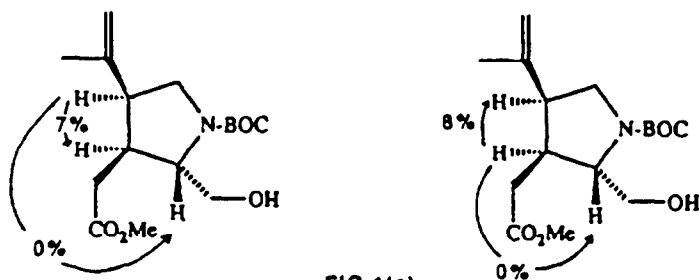


FIG. 1(a)

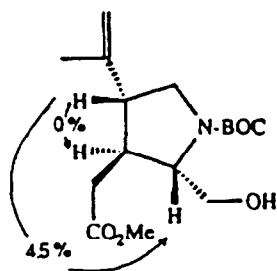


FIG. 1(b)

pyridinium dichromate in dimethylformamide, and subsequent esterification with diazomethane, gave the known protected kainate (21)<sup>14</sup> in 61% yield. This compound exhibited similar proton and carbon n.m.r. spectral data to related compounds reported in the literature<sup>3</sup>. Additional splitting of some carbon-13 n.m.r. signals, due to hindered rotation of the *tert*-butyloxycarbonyl protecting group about the carbon-nitrogen bond, was also observed. This kainate was deprotected in a two-step process by treatment with aqueous alkali, followed by excess trifluoroacetic acid. Purification by ion-exchange chromatography afforded (-)- $\alpha$ -kainic acid (1a) as colourless needles after recrystallisation from aqueous methanol. This product possessed identical spectral data and optical rotation value to that of authentic material.

This synthesis represents a short and convenient diastereoselective route to (-)- $\alpha$ -kainic acid (1a), and its application to the synthesis of other kainoids and their analogues, is currently in progress.



## EXPERIMENTAL

Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter with a path-length of 10 cm; concentrations are given in g/100 cm<sup>3</sup>. 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. <sup>1</sup>H 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 standard. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. <sup>13</sup>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<sub>2</sub>O, dioxan ( $\delta$  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<sub>254</sub>. 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<sup>+</sup> form. All solvents were distilled before use using standard literature procedures.<sup>17</sup>

### Ethyl-(2RS)-3-bromo-2-[(phenyloxycarbonyl) (3-methyl-2-butenyl) amino] propionate (3).

A mixture of the silyl ether (2) (2.9 g, 6.6 mmol) and *p*-toluenesulphonic acid monohydrate (catalytic) in ethanol (90 ml) was stirred overnight at r.t. The solvent was then removed in vacuo, and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic extract was removed, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure.

Chromatography on silica (hexane-ethyl acetate, 1.5:1) afforded Ethyl-(2RS)-3-hydroxy-2-[(phenyloxycarbonyl) (3-methyl-2-butenyl) amino] propionate (1.56 g, 73%) as a colourless liquid; R<sub>f</sub> 0.29 (hexane-ethyl acetate, 1.5:1); (Found: C, 63.64; H, 7.59; N, 4.41. C<sub>17</sub>H<sub>23</sub>NO<sub>5</sub> requires C, 63.54; H, 7.21; N, 4.36%);  $\nu_{\max}$  (thin film) 3600-3300 (br m), 3000-2840 (m), 1720 (s), 1590 (w), 1490 (w), 1450 (m),

1415 (m), 1370 (m), 1340 (m), 1250 (m), 1200 (s), 1160 (m), 1100 (w), 1070 (w), 1040 (w), 900 (w), 700 (m) and 690 (m)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 7.42-7.06 (5H, m, aromatics), 5.35 (1H, br s,  $\text{CH}=\text{}$ ), 4.28-3.81 (7H, m, = C- $\text{CH}_2\text{-N}$ ,  $\text{CH}_2\text{OH}$ ,  $\text{CH}_3\text{CH}_2$  and N- $\text{CH}$ ), 3.06 (1H, br s exch.,  $\text{CH}_2\text{OH}$ ), 1.79 (3H, s,  $\text{CH}_3\text{-C}=\text{}$ ), 1.72 (3H, s,  $\text{CH}_3\text{-C}=\text{}$ ) and 1.32 (3H, t, J 7.1 Hz,  $\text{CH}_3\text{CH}_2$ );  $\delta_{\text{C}}$  (125 MHz;  $\text{CDCl}_3$ ) 170.9, 170.1 ( $\text{C}=\text{O}$ ), 155.0, 154.0 ( $\text{C}=\text{O}$ ), 151.2, 150.9 ( $\text{C}=\text{}$ ), 137.2, 136.6 ( $\text{C}=\text{}$ ), 129.3, 125.4, 121.5, 121.3, 119.8, 119.4 ( $\text{CH}=\text{}$ ), 61.9, 61.7, 61.5, 61.0 (N- $\text{CH}$  and  $\text{CH}_2\text{-OH}$ ), 46.7, 46.3 (=C- $\text{CH}_2\text{-N}$ ), 25.7 ( $\text{CH}_2\text{CH}_3$ ), 17.8 ( $\text{CH}_3\text{-C}=\text{}$ ) and 14.1 ( $\text{CH}_3\text{-C}=\text{}$ );  $m/z$  (DCI,  $\text{NH}_3$ ) 322 ( $\text{M} + \text{H}^+$ , 1%) and 228 (100).

To a solution of the above alcohol (0.15 g, 1.6 mmol) in tetrahydrofuran (15 ml) was added triphenylphosphine (0.55 g, 2.1 mmol) followed by *N*-bromosuccinimide (0.38 g, 2.13 mmol) while stirring. After 0.75 h, the solvent was removed *in vacuo*. Chromatography of the residue on silica (hexane-ethyl acetate, 4:1) afforded the bromide (3) (0.49 g, 79%) as a pale yellow oil;  $R_f$  0.45 (hexane - ethyl acetate, 4:1);  $\nu_{\text{max}}$  (thin film) 3080-2850 (m), 1725 (s), 1595 (w), 1495 (w), 1450 (m), 1415 (m), 1370 (w), 1300 (m), 1255 (s), 1200 (s), 1160 (m), 1100 (w), 1070 (w), 1050 (w), 1025 (m), 960 (w), 920 (w) and 850 (w)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 7.42-7.09 (5H, m, aromatics), 5.44-5.37 (1H, m,  $\text{CH}=\text{}$ ), 4.48-3.89 (7H, m,  $\text{CH}_2\text{Br}$ , = C- $\text{CH}_2\text{-N}$ , N- $\text{CH}$  and  $\text{CH}_2\text{CH}_3$ ), 1.79 (3H, s,  $\text{CH}_3\text{-C}=\text{}$ ), 1.73 (3H, s,  $\text{CH}_3\text{-C}=\text{}$ ) and 1.31 (3H, t, J 7.2 Hz,  $\text{CH}_3\text{-CH}_2$ );  $m/z$  (GCMS) 403 ( $\text{M}^{81} + \text{NH}_4^+$ , 5%), 401 ( $\text{M}^{79} + \text{NH}_4^+$ , 5%), 385 ( $\text{M}^{81} + \text{H}^+$ , 20) and 386 ( $\text{M}^{79} + \text{H}^+$ , 21).

#### Reaction of bromide (3) with cobaloxime (I)

To a solution of cobalt (II) chloride hexahydrate (0.22 g, 0.9 mmol) and dimethylglyoxime (0.21 g, 1.8 mmol) in methanol (9 ml) was added aqueous sodium hydroxide (10 M, 0.18 ml) and pyridine (0.07 ml) while stirring. After 0.4 h, aqueous sodium hydroxide (10 M, 0.09 ml) and sodium borohydride (68 mg, 1.8 mmol) were added. After a further 0.1 hrs, the resulting cobaloxime (I) solution was treated with bromide (3) (0.35 g, 0.9 mmol) in methanol (1 ml) while stirring. After stirring overnight, the solvent was removed *in vacuo* and the resultant dark brown residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. Purification by column chromatography (hexane-ethyl acetate, 5.7:1) afforded pyrrolidine (4) (123 mg, 45%), alkene (6) (55 mg, 20%) and an inseparable mixture of alkene (6) and pyrrolidine (5) (1:1.4, 21 mg, 8%).

Pyrrrolidine (4): Rf 0.18 (hexane-ethyl acetate, 5.7:1);  $\nu_{\max}$  (thin film) 3070-2850 (w), 1730 (s), 1645 (w), 1595 (w), 1495 (w), 1450 (w), 1390 (s), 1205 (s), 1165 (m), 1070 (w), 1025 (w) and 900 (w)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) (2 pairs of enantiomers) 7.40-7.08 (10H, m, aromatics), 4.87 and 4.82 (4H, s,  $\text{C}=\text{CH}_2$ ), 4.65-3.88 (8H, m,  $\text{CH}-\text{CO}_2\text{Et}$ ,  $\text{CH}_2\text{CH}_3$  and  $\text{N}-\text{CH}_2$ ), 3.57-3.30 (2H, m,  $\text{N}-\text{CH}_2$ ), 3.18-2.74 (2H, m,  $\text{CH}-\text{C}=\text{C}$ ), 2.68-2.45 (1H, m,  $\text{CH}-\text{CH}-\text{N}$ ), 2.35-2.17 (2H, m,  $\text{CH}-\text{CH}-\text{N}$ ), 2.08-1.86 (1H, m,  $\text{CH}-\text{CH}-\text{N}$ ), 1.79 (6H, s,  $\text{CH}_3-\text{C}=\text{C}$ ) and 1.29 (6H, t,  $J$  7.1 Hz,  $\text{CH}_3\text{CH}_2$ );  $\delta_{\text{C}}$  (50 MHz;  $\text{CDCl}_3$ ) 172.7, 172.4 ( $\text{CO}$ ), 153.2, 152.8, 151.3 ( $\text{CO}$ ), 143.4, 142.9 ( $\text{C}=\text{C}$ ), 129.4, 125.5, 125.4, 121.7 ( $=\text{CH}$ ), 111.6, 111.2 ( $=\text{CH}_2$ ), 61.3 ( $\text{CO}_2\text{CH}_2\text{CH}_3$ ), 59.6, 59.3 ( $\text{CH}-\text{CO}_2$ ), 50.8, 50.6 ( $\text{N}-\text{CH}_2$ ), 44.9, 44.0, 43.5, 42.5 ( $=\text{C}-\text{CH}$ ), 35.3, 34.9, 34.4, 33.9 ( $\text{CH}_2-\text{C}-\text{N}$ ), 21.0 ( $\text{CH}_3-\text{C}=\text{C}$ ), 14.1 and 14.0 ( $\text{CO}_2\text{CH}_2\text{CH}_3$ );  $m/z$  (DCI,  $\text{NH}_3$ ) 321 ( $\text{M} + \text{NH}_4^+$ , 2%) and 304 (100).

Alkene (6): Rf 0.23 (hexane-ethyl acetate, 5.7:1);  $\nu_{\max}$  (thin film) 3070-2850 (m), 1730 (s), 1635 (w), 1595 (w), 1495 (w), 1450 (m), 1410 (m), 1380 (m), 1335 (w), 1300 (w), 1260 (m), 1205 (s), 1110 (w), 1070 (m), 1020 (m) and 855 (w)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 7.40-7.09 (5H, m, aromatics), 5.31 (1H, br s,  $\text{CH}=\text{C}$ ), 4.68-3.88 (5H, m,  $=\text{C}-\text{CH}_2-\text{N}$ ,  $\text{CH}_2-\text{CH}_3$  and  $\text{N}-\text{CH}$ ), 1.75-1.67 (6H, m,  $\text{CH}_3-\text{C}=\text{C}$ ), 1.60-1.54 (3H, m,  $\text{CH}_3-\text{CH}$ ) and 1.29 (3H, t,  $J$  7.1 Hz,  $\text{CH}_3\text{CH}_2$ );  $m/z$  (DCI,  $\text{NH}_3$ ) 306 ( $\text{M} + \text{H}^+$ , 100%).

Pyrrrolidine (5): The presence of this compound was indicated by the  $^1\text{H}$  n.m.r. spectrum ( $\delta$  1.68 and 1.60, ( $\text{CH}_3$ ) $_2-\text{C}=\text{C}$ ) and the mass spectrum [ $m/z$  (DCI,  $\text{NH}_3$ ) 304 ( $\text{M} + \text{H}^+$ )].

Methyl-(2R)-[3-(tert-butyl(dimethylsilyl)oxy)-2-[(3-methyl-2-butenyl)amino]propionate (7).

To a solution of D-serine (10 g, 95.2 mmol) in methanol (50 ml) was passed HCl gas until a saturated solution was obtained. The flask was then stored overnight at 0°C, after which the solvent was removed *in vacuo*, affording white crystals of D-serine methyl ester hydrochloride in quantitative yield.

A mixture of D-serine methyl ester hydrochloride (7.00 g, 45.0 mmol), triethylamine (22 ml) and tert-butyl(dimethylchlorosilane) (8.27 g, 54.8 mmol) in dichloromethane (150 ml), with catalytic 4-dimethylaminopyridine was stirred at r.t. for 4 h. A saturated solution of aqueous sodium bicarbonate (100 ml) was then added and the organic layer was separated, washed with water, brine, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to afford crude silyl ether (9.26 g).

To a solution of the crude silyl ether (9.26 g) in benzene (20 ml) was added 3-methyl-2-butenal (2.20 g, 26.1 mmol) dropwise while stirring at r.t. After 0.5 h, ethyl acetate was added and the solution was dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The crude imine was dissolved in methanol (100 ml) and sodium borohydride (1.5 g, 39.7 mmol) was added portionwise at 0°C. After 0.2 h, the ice-bath was removed and stirring was continued for a further 0.3 h. Water and ethyl acetate was then added. The organic layer was removed, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. Chromatography of the residue on silica (hexane - ethyl acetate, 4:1) afforded amine (7) (6.0 g, 44%) as a colourless liquid; R<sub>f</sub> 0.37 (hexane - ethyl acetate, 4:1); [α]<sub>D</sub><sup>21</sup> + 4.3° (c 0.6, CHCl<sub>3</sub>); (Found: C, 59.45; H, 10.27; N, 4.47. C<sub>15</sub>H<sub>31</sub>NO<sub>3</sub>Si requires C, 59.76; H, 10.36; N, 4.65%); ν<sub>max</sub> (thin film) 2980-2840 (s), 1740 (s), 1480-1430 (m), 1380 (w), 1360 (w), 1255 (m), 1200 (m), 1175 (m), 1150 (m), 1110 (m), 1040 (w), 980 (w), 940 (w) and 835 (s) cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 5.24 (1H, br t, J 7 Hz, CH=), 3.88-3.73 (5H, m, CH<sub>2</sub>OSi and CO<sub>2</sub>CH<sub>3</sub>), 3.40-3.15 (3H, m, N-CH and CH<sub>2</sub>-C=), 1.72 (3H, s, CH<sub>3</sub>-C=), 1.63 (3H, s, CH<sub>3</sub>-C=), 0.87 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>) and 0.03 (6H, s, Si-CH<sub>3</sub>); δ<sub>C</sub> (50 MHz; CDCl<sub>3</sub>) 174.1 (C=O), 135.1 (C=), 122.5 (CH=), 64.4 (CH<sub>2</sub>OSi), 62.2 (N-CH), 51.5 (CO<sub>2</sub>CH<sub>3</sub>), 45.2 (=C-CH<sub>2</sub>-N), 25.5 (Si-C(CH<sub>3</sub>)<sub>3</sub>), 17.9 (CH<sub>3</sub>-C=), 17.5 (CH<sub>3</sub>-C=), -5.8 and -5.9 (Si-CH<sub>3</sub>); m/z (GCMS) 302 (M + H<sup>+</sup>, 100%).

tert-Butyl-(4R)-3-hydroxy-4-[(phenyloxycarbonyl)(3-methyl-2-butenyl)aminol]-5-[tert-butyl dimethylsilyl]oxyl pentanoate (8).

To a solution of the amine (7) (3.3 g, 11.0 mmol) in ethyl acetate (70 ml) was added a saturated aqueous solution of sodium bicarbonate (10 ml) at 0°C while stirring, followed by phenyl chloroformate (1.4 ml, 1.73 g, 11.0 mmol). After 1 h, water was added and the solution was allowed to warm to r.t. The organic layer was then separated, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to afford crude product. Chromatography on silica (hexane - ethyl acetate, 4:1) afforded the title compound (4.27 g, 92%) as a colourless liquid; R<sub>f</sub> 0.44 (hexane-ethyl acetate, 4:1); [α]<sub>D</sub><sup>20</sup> + 17° (c 0.06, CHCl<sub>3</sub>); (Found: C, 62.75; H, 8.65; N, 3.57. C<sub>22</sub>H<sub>35</sub>NO<sub>5</sub>Si requires C, 62.68; H, 8.37; N, 3.32%); ν<sub>max</sub> (thin film) 3100-2820 (s), 1770-1690 (s), 1670 (w), 1590 (w), 1490 (m), 1470-1390 (m), 1380 (m), 1340 (m), 1250 (s), 1200 (s), 1160 (s), 1120 (s), 1070 (m), 1005 (m), 935 (w), 910 (w) and 835 (s) cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 7.40-7.05 (5H, m, aromatics), 5.45-5.28 (1H, m, CH=), 4.52-3.92 (5H, m, =C-CH<sub>2</sub>-N, CH<sub>2</sub>OSi and N-CH), 3.74 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 1.76 (3H, s, CH<sub>3</sub>-C=), 1.69 (3H, s, CH<sub>3</sub>-C=), 0.92 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), and 0.10 (6H, s, Si-CH<sub>3</sub>); δ<sub>C</sub> (50 MHz; CDCl<sub>3</sub>) 170.4, 170.2 (C=O), 154.8, 154.4 (C=O), 151.6, 151.3, 135.9,

134.9 (C=), 130.0, 129.3, 125.4, 121.8, 121.7, 121.2, 120.5, 120.3 (CH=), 62.0, 61.4, 61.1 (N-CH and CH<sub>2</sub>OSi), 52.1, 52.0 (CO<sub>2</sub>CH<sub>3</sub>), 46.3, 46.0 (= C-CH<sub>2</sub>-N), 25.7 (Si-C(CH<sub>3</sub>)<sub>3</sub>), 18.0, 17.7 (CH<sub>3</sub>-C=) and -5.74 (Si-CH<sub>3</sub>); m/z (DCI, NH<sub>3</sub>) 422 (M + H<sup>+</sup>, 60%), 364 (21) and 354 (100).

To a solution of the methyl ester (5 g, 11.9 mmol) in dry toluene (120 ml) was added diisobutylaluminium hydride (11.9 ml, 1.5 M, 17.8 mmol) dropwise while stirring at -78°C under a nitrogen atmosphere. After 1.85 h, methanol (2 ml) was added dropwise to quench the reaction, followed by saturated aqueous Rochelle salt solution<sup>15</sup> to solubilise the complex. The organic layer was separated, washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to afford crude amino aldehyde (4.36 g) as a colourless liquid.

To a solution of diisopropylamine (1.4 g, 14 mmol) in tetrahydrofuran (60 ml) at -20°C was added n-butyllithium (8.8 ml, 1.6 M, 14 mmol) while stirring under nitrogen. After 1 h, the bath temperature was lowered to -78°C and tert-butyl acetate (1.9 ml, 14 mmol) was added dropwise. After stirring for 0.25 h, the crude aldehyde (4.36 g, 11 mmol) in tetrahydrofuran (10 ml) was added dropwise and the reaction mixture was stirred for a further 0.25 h before saturated aqueous ammonium chloride: methanol (1:1, 5 ml) was added. After warming to r.t., ethyl acetate and water was added to the mixture. The organic extract was separated, washed with brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. Column chromatography on silica (hexane-ethyl acetate, 4:1) afforded the alcohol (8) (3.12 g, 52%) as a colourless viscous liquid as a mixture of diastereomers; R<sub>f</sub> 0.54 (hexane-ethyl acetate, 4:1); [α]<sub>D</sub><sup>20</sup> + 6.9° (c 0.6, CHCl<sub>3</sub>); ν<sub>max</sub> (thin film) 3620-3250 (m), 3080-2820 (s), 1720 (vs), 1590 (m), 1495 (m), 1460 (s), 1410 (s), 1390 (w), 1370 (s), 1340 (m), 1310-1290 (m), 1250 (vs), 1155 (vs), 1110 (s), 1030 (m), 1005 (w), 985 (w), 935 (vw), 905 (vw), 835 (vs) and 810 (w) cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 7.41-7.09 (5H, m, aromatics), 5.42-5.28 (1H, m, CH=), 4.48-3.87 (6H, m, = C-CH<sub>2</sub>-N, CH<sub>2</sub>OSi, CH-OH and CH-OH), 3.70-3.54 (1H, m, N-CH), 2.75-2.35 (2H, m, CH<sub>2</sub>CO<sub>2</sub>), 1.76 (3H, s, CH<sub>3</sub>-C=), 1.70 (3H, s, CH<sub>3</sub>-C=), 1.47 (9H, s, CH<sub>2</sub>CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 0.93 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>) and 0.10 (6H, s, Si-CH<sub>3</sub>); δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 171.7 (C=O), 155.1 (C=O), 151.3, 134.8 (C=), 129.2, 125.2, 121.7, 121.1 (CH=), 81.1 (C(CH<sub>3</sub>)<sub>3</sub>), 68.9, 68.2 (CHOH), 64.1, 62.5, 61.5, 61.0 (N-CH and CH<sub>2</sub>OSi), 46.7, 46.1 (= C-CH<sub>2</sub>-N), 40.3, 39.7 (CH<sub>2</sub>CO<sub>2</sub>), 28.1 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 25.8, 25.7 (Si-C(CH<sub>3</sub>)<sub>3</sub>), 18.2, 17.8 (CH<sub>3</sub>-C=) and -5.5 (Si-CH<sub>3</sub>); m/z (DCI, NH<sub>3</sub>) 508 (M + H<sup>+</sup>, 43%), 452 (43) and 422 (100).

tert-Butyl-(4R)-3-iodo-4-[(phenyloxycarbonyl)(3-methyl-2-butenyl)amino]-5-[(tert-butyldimethylsilyloxy)pentanoate (9) and (4R)-3-(3-methyl-2-butenyl)-4-[(tert-butyldimethylsilyloxy)methyl]-5-[(tert-butyloxycarbonyl)methyl]-2-oxazolidinone (10).

Triflic anhydride (0.25 ml, 1.5 mmol) was added dropwise to a solution of the alcohol (8) (0.50 g, 0.10 mmol) and pyridine (0.4 ml) in dichloromethane (10 ml) at -20°C under nitrogen. After 2.5 h, sodium iodide in ethylene glycol dimethyl ether (1 M, 10 ml) was added and the solution was allowed to warm to r.t. After stirring for a further 2 h, the solvent was evaporated *in vacuo* 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<sub>4</sub>) and evaporated *in vacuo* to afford crude product. Chromatography (hexane-ethyl acetate, 4:1) afforded iodide (9) (0.13 g, 22%) and oxazolidinone (10) (0.17 g, 42%) as pale yellow oils. Iodide (9); R<sub>f</sub> 0.62 (hexane - ethyl acetate, 5.7:1); [ $\alpha$ ]<sub>D</sub><sup>21</sup> = 11.7° (c 0.9, CHCl<sub>3</sub>);  $\nu_{\max}$  (thin film) 3000-2830 (m), 1720 (s), 1595 (w), 1495 (m), 1470-1450 (m), 1410 (m), 1390 (w), 1370 (m), 1340 (m), 1250 (s), 1205 (s), 1160 (s), 1120 (s), 1020 (w), 1010 (w), 970 (w), 940-900 (w), 840 (s) and 810 (w) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 7.42-7.09 (5H, m, aromatics), 5.39-5.32 (1H, m, CH=), 4.58-3.96 (6H, m, =C-CH<sub>2</sub>-N, CH<sub>2</sub>OSi, N-CH and CH-I), 3.28-3.15 (1H, m, CH-CO<sub>2</sub>), 2.91-2.77 (1H, m, CH-CO<sub>2</sub>), 1.73 (6H, br s, CH<sub>3</sub>-C=), 1.51 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 0.95 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>) and 0.14 (6H, s, Si-CH<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 169.9, 169.6 (C=O), 154.7, 154.4 (C=O), 151.3 (C=), 134.9 (C=), 129.2, 125.4, 125.2, 121.7, 121.6, 121.2, 120.4 (CH=), 81.5, 81.3 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 63.9, 63.7 (CH<sub>2</sub>OSi and N-CH), 44.1, 43.8 (CH<sub>2</sub>CO<sub>2</sub> and =C-CH<sub>2</sub>-N), 28.1 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 25.9 (Si-C(CH<sub>3</sub>)<sub>3</sub>), 23.5 (CH-I), 18.2, 17.9 (CH<sub>3</sub>-C=) and -5.5 (Si-CH<sub>3</sub>); m/z (DCI, NH<sub>3</sub>) 618 (M + H<sup>+</sup>, 5%) and 422 (100).

Oxazolidinone (10); R<sub>f</sub> 0.30 (hexane-ethyl acetate, 5.7:1); [ $\alpha$ ]<sub>D</sub><sup>21</sup> + 20.0° (c 0.53, CHCl<sub>3</sub>); (Found: C, 61.06; H, 9.30; N, 3.43. C<sub>21</sub>H<sub>39</sub>NO<sub>5</sub>Si requires C, 60.98; H, 9.50; N, 3.39%);  $\nu_{\max}$  (thin film) 3020-2800 (s), 1780-1690 (s), 1675 (w), 1470-1360 (s), 1330 (m), 1250 (s), 1220 (s), 1150 (s), 1130-1060 (s), 1040 (s), 980 (m), 940 (w), 880 (m), 835 (s) and 810 (m), cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 5.16 (1H, br t, J 6.4 Hz, CH=), 4.60 (1H, q, J 6.8 Hz, O-CH), 4.06 (1H, dd, J 5.6 Hz and 15 Hz, CHO), 3.74-3.63 (3H, m, CH-O and N-CH<sub>2</sub>-C=), 3.46 (1H, q, J 4.1 Hz, N-CH), 2.74-2.49 (2H, m, CH<sub>2</sub>CO<sub>2</sub>), 1.73 (3H, s, CH<sub>3</sub>-C=), 1.68 (3H, s, CH<sub>3</sub>-C=), 1.45 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 0.88 (9H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), and 0.06 (6H, s, Si-CH<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 168.6 (C=O), 157.3 (C=O), 136.8 (C=), 118.7 (CH=), 81.5 (C(CH<sub>3</sub>)<sub>3</sub>), 72.7 (O-CH), 62.2, 60.9 (CH<sub>2</sub>OSi and N-CH), 40.8, 40.2 (=C-CH<sub>2</sub>-N and CH<sub>2</sub>CO<sub>2</sub>), 28.0 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>),

25.7 (Si-C(CH<sub>3</sub>)<sub>3</sub>), 18.1, 17.9 (CH<sub>3</sub>-C=) and -5.6 (Si-CH<sub>3</sub>); m/z (DCI NH<sub>3</sub>) 431 (M + NH<sub>4</sub><sup>+</sup>, 1%), 414 (M + H<sup>+</sup>, 11) and 300 (100).

(4R)-3-(3-Methyl-2-butenyl)-4-[2-(tert-butyloxycarbonyl)-1-(hydroxy)ethyl]-2-oxazolidinone (12).

To a solution of the alcohol (8) (0.9 g, 1.8 mmol) in methanol (25 ml) was added *p*-toluenesulphonic acid monohydrate (0.66 g) while stirring. After 0.5 h, water and a saturated aqueous solution of sodium bicarbonate was added and the solvent was evaporated. Extraction with ethyl acetate, followed by washing with water, brine, drying (MgSO<sub>4</sub>) and solvent removal afforded the crude diol (0.71 g) as a colourless viscous oil.

Potassium carbonate (0.34 g) was added to the crude diol (0.71 g) in methanol: water (10:1, 33 ml) while stirring. After 2 h, the solvent was removed and ethyl acetate was added. The organic layer was separated, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The crude product was then purified by column chromatography (hexane - ethyl acetate, 1:1) giving the oxazolidinone (12) (0.38 g, 72%) as a white crystalline solid; R<sub>f</sub> 0.34 (hexane - ethyl acetate, 1:1); m.p. 94-96°C; [α]<sub>D</sub><sup>20</sup> -12° (c 0.1, CHCl<sub>3</sub>); (Found: C, 60.42; H, 8.80; N, 4.23. C<sub>15</sub>H<sub>25</sub>NO<sub>5</sub> requires C, 60.18; H, 8.42; N, 4.68%); ν<sub>max</sub> (nujol mull) 3600-3200 (s), 3020-2800 (vs), 1770-1680 (s), 1460 (s), 1370 (s), 1340 (m), 1280 (m), 1260 (m), 1230 (m), 1210 (w), 1180 (m), 1140 (s), 1095 (m), 1080 (s), 1020 (m), 990 (m), 955 (m), 940 (m), 890 (w) and 845 (m) cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 5.19 (1H, br t, J 8 Hz, CH=), 4.27-4.05 (4H, m, CH<sub>2</sub>O, N-CH and CH-OH), 3.84-3.73 (2H, m, =C-CH<sub>2</sub>-N), 3.46-3.38 (1H, m, CH-OH), 2.46-2.20 (2H, m, CH<sub>2</sub>-CO<sub>2</sub>), 1.75 (3H, s, CH<sub>3</sub>-C=), 1.72 (3H, s, CH<sub>3</sub>-C=), and 1.47 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>); δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 170.8 (C=O), 158.5 (C=O), 137.8 (C=), 118.2 (CH=), 81.9 (C(CH<sub>3</sub>)<sub>3</sub>), 65.9 (O-CH<sub>2</sub>), 62.3 (CH-OH), 58.0 (CH-N), 40.5 (=C-CH<sub>2</sub>-N), 37.7 (CH<sub>2</sub>CO<sub>2</sub>), 28.0 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 25.7 (CH<sub>3</sub>-C=) and 18.0 (CH<sub>3</sub>-C=); m/z (DCI, NH<sub>3</sub>) 317 (M + NH<sub>4</sub><sup>+</sup>, 3%), 300 (M + H<sup>+</sup>, 10), 261 (24) and 244 (100).

(4R)-3-(3-Methyl-2-butenyl)-4-[2-(tert-butyloxycarbonyl)-1-(iodo)ethyl]-2-oxazolidinone (13).

Triflic anhydride (0.25 ml, 1.43 mmol) was added dropwise to a solution of the alcohol (12) (0.29 g, 0.97 mmol) and pyridine (0.4 ml, 4.6 mmol) in dichloromethane (10 ml) at 0°C under a nitrogen atmosphere. After 1 h, sodium iodide in ethylene glycol dimethyl ether (1 M, 10 ml) was added and the solution was allowed to warm to r.t. After stirring for a further 1.2 h, the solvent was removed 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<sub>4</sub>) and evaporated *in vacuo*. Chromatography on silica (hexane - ethyl acetate, 1.5:1) afforded iodide (13) (0.27 g, 68%) as pale yellow crystals; R<sub>f</sub> 0.62 (hexane - ethyl acetate, 1.5:1); m.p. 32-34°C; [ $\alpha$ ]<sub>D</sub><sup>21</sup> + 63.8° (c 0.72, CHCl<sub>3</sub>);  $\nu_{\max}$  (nujol mull) 3020-2820 (s), 1780-1670 (s), 1515 (vw), 1470 (m), 1440 (m), 1420 (m), 1390 (m), 1356 (m), 1340 (w), 1325 (w), 1290-1240 (m), 1180-1140 (m), 1095 (m), 1060 (m), 1020 (m), 950 (m), 920 (m) and 850 (m) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 5.08 (1H, br t, J 8 Hz, CH=), 4.46-3.84 and 3.70-3.55 (6H, m, = C-CH<sub>2</sub>-N, O-CH<sub>2</sub>, N-CH and CH-I), 2.90-2.51 (2H, m, CH<sub>2</sub>-CO<sub>2</sub>), 1.66 (6H, s, CH<sub>3</sub>-C=) and 1.38 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 169.3 (C=O), 158.1 (C=O), 138.8 (C=), 117.6 (CH=), 81.9 (C(CH<sub>3</sub>)<sub>3</sub>), 65.6 (O-CH<sub>2</sub>), 59.6 (N-CH), 40.2 (=C-CH<sub>2</sub>-N), 38.3 (CH<sub>2</sub>CO<sub>2</sub>), 27.8 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 25.6 (CH<sub>3</sub>-C=), 24.00 (CH-I) and 17.7 (CH<sub>3</sub>-C=); m/z (DCI, NH<sub>3</sub>) 427 (M + NH<sub>4</sub><sup>+</sup>, 10%), 410 (M + H<sup>+</sup>, 7), 371 (22), 354 (54), 282 (86) and 226 (100).

(2S, 3S, 4S)-1-(tert-Butyloxycarbonyl)-2-(hydroxymethyl)-3-((methoxycarbonyl)methyl)-4-(1-methyl-ethenyl)pyrrolidine (19).

Aqueous sodium hydroxide (10N, 0.25 ml) was added dropwise while stirring at 0°C to a suspension of chlorocobaloxime (0.91 g) in methanol (25 ml). After stirring for 0.25 h, sodium borohydride (0.17 g) was added portionwise. The resulting dark solution was stirred for 0.25 h, after which a solution of iodide (13) (0.88 g, 2.15 mmol) in methanol (10 ml) was added dropwise. The solution was allowed to warm to r.t. and then stirred overnight. The solvent was evaporated and ethyl acetate and water was added to the residue. The organic layer was separated, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to afford crude dark brown liquid product. Column chromatography (hexane - ethyl acetate, 2.3:1) yielded alkene (14) (90 mg, 15%) as a colourless oil [R<sub>f</sub> 0.48 (hexane - ethyl acetate, 2.3:1)], an inseparable mixture of pyrrolidines (15) together with  $\alpha$ ,  $\beta$ -unsaturated ester (16) (0.31 g, 51%) [R<sub>f</sub> 0.36 (hexane - ethyl acetate, 2.3:1), and the minor products (17 and 18) (70 mg, 12%) [R<sub>f</sub> 0.42 (hexane-ethyl acetate, 2.3:1)] as an inseparable mixture.

Alkene (14):  $\nu_{\max}$  (thin film) 3020-2840 (m), 1770 (s), 1725 (s), 1695 (s), 1440 (m), 1410 (s), 1365 (s), 1280 (m), 1260 (m), 1150 (s), 1115 (m), 1085 (m), 1040 (m), 940 (w), 910 (m), 845 (m) and 810 (w), cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 5.11 (1H, br t, J 7.9 Hz, CH=), 4.85 (2H, s, O-CH<sub>2</sub>), 4.70-4.64 (1H, m, N-C=CH), 4.05 (2H, d, J 6.7 Hz, = C-CH-N), 2.81 (2H, d, J 7.6 Hz, CH<sub>2</sub>CO<sub>2</sub>), 1.74 (3H, s, CH<sub>3</sub>-C=), 1.71 (3H, s, CH<sub>3</sub>-C=) and 1.44 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 170.3 (C=O), 157.0 (C=O),



136.9 (C=), 136.3 (C=), 117.4 (CH=), 89.8 (C=), 81.1 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 65.4 (CH<sub>2</sub>O), 39.7 (N-CH<sub>2</sub>-C=), 33.2 (CH<sub>2</sub>CO<sub>2</sub>), 28.0 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 26.0 (CH<sub>3</sub>-C=) and 18.0 (CH<sub>3</sub>-C=); m/z (DCI, NH<sub>3</sub>) 299 (M + NH<sub>4</sub><sup>+</sup>, 5%), 282 (M + H<sup>+</sup>, 55) and 226 (100).

To the mixture of alkenes (15) and (16) (0.31 g) in dioxane (2 ml) was added aqueous sodium hydroxide (3N, 2 ml) while stirring. The solution was then heated to 60°C and then stirred for 15 h under an nitrogen atmosphere. After cooling to r.t., di-tert-butyl pyrocarbonate (0.48 g, 2.2 mmol) in dioxane was added portionwise and stirring was continued for 2 h. The dioxane was removed *in vacuo* and the aqueous phase was neutralized with aqueous citric acid solution (10%) and extracted (3 times) with ethyl acetate. The ethyl acetate extracts were washed with water, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*.

The residue was dissolved in methanol (10 ml) and excess ethereal diazomethane was added at 0°C. The excess diazomethane was removed via a stream of nitrogen, after which solvent evaporation afforded crude product. Column chromatography (hexane - ethyl acetate, 1:1) afforded pyrrolidine (20) (38 mg, 11%) and pyrrolidine (19) (155 mg, 45%) as colourless oils.

Pyrrolidine (20); Rf 0.40 (hexane - ethyl acetate, 1:1); [α]<sub>D</sub><sup>20</sup> -16.7° (c 0.58, CHCl<sub>3</sub>); δ<sub>H</sub> (200 MHz; CDCl<sub>3</sub>) 4.86 (2H, s, =CH<sub>2</sub>), 3.82-3.48 (8H, m, CO<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>OH, N-CH-CH<sub>2</sub> and N-CH<sub>2</sub>), 3.14 (1H, br t, J 12 Hz, CH-C=), 2.60-2.34 (3H, m, CH-CH<sub>2</sub>CO<sub>2</sub> and CH<sub>2</sub>CO<sub>2</sub>), 1.71 (3H, s, CH<sub>3</sub>-C=) and 1.48 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>); δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 172.1 (CO), 156.4 (CO), 141.6 (C=), 114.3 (H<sub>2</sub>C=), 80.6 (C(CH<sub>3</sub>)<sub>3</sub>), 66.3, 65.9 (CH<sub>2</sub>OH and CH<sub>2</sub>-CH-N), 52.0, 51.0, 50.6, 40.5, 36.1 (CO<sub>2</sub>CH<sub>3</sub>, CH-C=, CH-CH<sub>2</sub>CO<sub>2</sub>, CH<sub>2</sub>CO<sub>2</sub> and N-CH<sub>2</sub>), 28.4 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>) and 18.7 (CH<sub>3</sub>-C=); m/z (DCI, NH<sub>3</sub>) 328 (M + NH<sub>4</sub><sup>+</sup>, 2%), 314 (M + H<sup>+</sup>, 50) and 258 (100).

Pyrrolidine (19); Rf 0.36 (hexane - ethyl acetate, 1:1); [α]<sub>D</sub><sup>21</sup> -38.0° (c 0.20, CHCl<sub>3</sub>); ν<sub>max</sub> (CHCl<sub>3</sub>) 3500-3200 (br m), 3020-2840 (m), 1733 (s), 1669 (s), 1439 (s), 1409 (vs), 1369 (s), 1224 (s), 1168 (s), 1140 (s), 1027 (m) and 901 (m) cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz; CDCl<sub>3</sub>) 4.89 (1H, s, CH=), 4.65 (1H, s, CH=), 4.21 (1H, br s, N-CH-CH<sub>2</sub>), 3.76-3.64 (5H, m, CO<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>), 3.45 (2H, d, J 7.3 Hz, CH<sub>2</sub>OH), 2.91 (1H, m, =C-CH), 2.46 (1H, m, CH-CH<sub>2</sub>CO<sub>2</sub>), 2.32-2.18 (2H, m, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 1.69 (3H, s, CH<sub>3</sub>-C=) and 1.47 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>); δ<sub>C</sub> (125 MHz; CDCl<sub>3</sub>) 173.7 (CO), 156.8 (CO), 142.1 (C=), 113.1 (CH<sub>2</sub>=), 80.5 (C(CH<sub>3</sub>)<sub>3</sub>), 66.8, 65.1 (CH<sub>2</sub>OH and CH<sub>2</sub>-CH-N), 51.7 (CO<sub>2</sub>CH<sub>3</sub>), 49.0, 45.7, 39.5, 33.2 (CH-C=, CH-CH<sub>2</sub>CO<sub>2</sub>, CH<sub>2</sub>CO<sub>2</sub> and N-CH<sub>2</sub>), 28.5 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>) and 22.2 (CH<sub>3</sub>-C=); m/z (DCI, NH<sub>3</sub>) 328 (M + NH<sub>4</sub><sup>+</sup>, 0.4%), 314 (M + H<sup>+</sup>, 27) and 258 (100).

1-(tert-Butyloxycarbonyl) kainic Acid Dimethyl Ester (21).

A solution of the alcohol (19) (0.12 g, 0.38 mmol) and pyridinium dichromate (0.72 g, 1.91 mmol) in dimethylformamide (12 ml) was stirred at 40°C overnight under nitrogen. 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 brine, dried (MgSO<sub>4</sub>) and evaporated. The residue was purified with silica gel column chromatography (hexane - ethyl acetate, 2.3:1) to furnish diester (21) (80 mg, 61%) as a colourless oil; R<sub>f</sub> 0.34 (hexane - ethyl acetate, 2.3:1); [ $\alpha$ ]<sub>D</sub><sup>21</sup> -23.4° (c 0.68, CHCl<sub>3</sub>) [lit.,<sup>12</sup> [ $\alpha$ ]<sub>D</sub> -19.8 (c, 1.20, CHCl<sub>3</sub>)];  $\nu_{\max}$  (CHCl<sub>3</sub>) 3050-2840 (m), 1735 (s), 1690 (s), 1480 (w), 1450 (w), 1440 (s), 1405 (s), 1380 (s), 1370 (s), 1330 (w), 1260-1220 (m), 1170 (s), 1135 (s), 1005 (w), and 905 (s) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 4.93 (1H, s, CH=), 4.70 (1H, s, CH=), 4.13 (1H, dd, J 19 and 3.2 Hz, N-CH-CO<sub>2</sub>), 3.78-3.38 (8H, m, 2 x CO<sub>2</sub>CH<sub>3</sub> and N-CH<sub>2</sub>), 3.03 (1H, m, =C-CH), 2.86 (1H, m, CH-CH<sub>2</sub>CO<sub>2</sub>), 2.43-2.20 (2H, m, CH<sub>2</sub>CO<sub>2</sub>), 1.70 (3H, s, CH<sub>3</sub>-C=), 1.48 and 1.42 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (50 MHz; CDCl<sub>3</sub>) 172.6-172.5 (2 x CO<sub>2</sub>CH<sub>3</sub>), 154.0 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 141.6, 141.4 (C=), 113.5, 113.3 (CH<sub>2</sub>=), 80.2 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 63.9, 63.6 (N-CH-CO<sub>2</sub>), 52.1, 51.7 (CO<sub>2</sub>CH<sub>3</sub>), 47.5 (N-CH<sub>2</sub>), 45.9, 45.1, 41.7, 40.8 (=C-CH and CH-CH<sub>2</sub>CO<sub>2</sub>), 32.8 (CH<sub>2</sub>CO<sub>2</sub>), 28.2, 28.1 (CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 22.2 and 22.1 (=C-CH<sub>3</sub>); m/z (DCI, NH<sub>3</sub>) 359 (M + NH<sub>4</sub><sup>+</sup>, 0.8%), 342 (M + H<sup>+</sup>, 21) and 242 (100).

(-)- $\alpha$ -Kainic Acid (1a).

A mixture of diester (21) (93 mg, 0.27 mmol) and aqueous potassium hydroxide (17 ml, 2.5%) in methanol (3 ml) was brought to reflux for 3.5 h under nitrogen. After cooling 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 extracts were dried (MgSO<sub>4</sub>) and evaporated to afford crude tert-butyloxycarbonyl-kainic acid<sup>14</sup> (91 mg) as a viscous oil;  $\delta_{\text{H}}$  (200 MHz; CDCl<sub>3</sub>) 9.97 (2H, br s, 2 x CO<sub>2</sub>H), 4.96 (1H, s, CH=), 4.73 (1H, s, CH=), 4.20 (1H, d, J 32 Hz, N-CH-CO<sub>2</sub>), 3.77-3.30 (2H, m, N-CH<sub>2</sub>), 3.10-2.91 (2H, m, =C-CH and CH-CH<sub>2</sub>CO<sub>2</sub>), 2.43-2.28 (2H, m, CH<sub>2</sub>CO<sub>2</sub>), 1.73 (3H, s, CH<sub>3</sub>-C=), 1.49 and 1.43 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>); m/z (DCI, NH<sub>3</sub>) 331 (M + NH<sub>4</sub><sup>+</sup>, 5%), 314 (M + H<sup>+</sup>, 18), 275 (25), 258 (28), 214 (100) and 168 (72).

To the crude diacid (91 mg) in dichloromethane (4 ml) of 0°C was added trifluoroacetic acid (0.10 ml, 1.30 mmol) while stirring. After 0.5 h the solution was warmed to r.t and stirred for a further 0.25 h. The solvent was then removed *in vacuo* affording crude white crystalline product. This was then dissolved in

water and filtered through a column of ion exchange resin [Dowex (50 x 2)-100; elution with water followed by 1N NH<sub>4</sub>OH] to give a colourless solid. This material was recrystallised from aqueous methanol to give (-)- $\alpha$ -kainic acid (1a) (39 mg, 67%) as colourless needles; m.p. 248-249°C (dec.) [lit.,<sup>16</sup> m.p. 243-244°C (dec.)];  $[\alpha]_{\text{D}}^{21}$  -13.2 (c 0.55, H<sub>2</sub>O) [lit.,<sup>16</sup>  $[\alpha]_{\text{D}}^{27}$  -14.2 (c 0.23, H<sub>2</sub>O)];  $\nu_{\text{max}}$  (nujol mull) 3540 (m), 3150 (m), 3000-2820 (s), 2700-2500 (m), 1690 (m), 1620 (m), 1460 (s), 1380 (s), 1320 (m), 1280 (m), 920 (w) and 890 (w) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz; D<sub>2</sub>O, HOD suppressed) 4.94 (1H, s,  $\text{CH}=\text{}$ ), 4.63 (1H, s,  $\text{CH}=\text{}$ ), 3.99 (1H, d, J 3.4 Hz, N- $\text{CH}-\text{CO}_2$ ), 3.54-3.51 (1H, m, N- $\text{CH}-\text{CH}$ ), 3.35-3.30 (1H, m, N- $\text{CH}-\text{CH}$ ), 2.99-2.89 (2H, m, = C- $\text{CH}$  and  $\text{CH}-\text{CH}_2\text{CO}_2$ ), 2.37-2.23 (2H, m,  $\text{CH}-\text{CH}_2\text{CO}_2$ ) and 1.66 (3H, s,  $\text{CH}_3-\text{C}=\text{}$ );  $\delta_{\text{C}}$  (125 MHz; D<sub>2</sub>O, HOD suppressed) 177.5, 174.2 (2 x  $\text{C}=\text{O}$ ), 141.0 ( $\text{C}=\text{}$ ), 114.4 ( $\text{CH}_2=\text{}$ ), 66.7 (N- $\text{CH}-\text{CO}_2$ ), 47.5 (N- $\text{CH}_2$ ), 46.8, 41.8 (= C- $\text{CH}$  and  $\text{CH}-\text{CH}_2\text{CO}_2$ ), 34.6 ( $\text{CH}_2\text{CO}_2\text{H}$ ) and 23.1 ( $\text{CH}_3-\text{C}=\text{}$ ); m/z (positive argon fast atom bombardment) 214 (M + H<sup>+</sup>, 100%).

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