Total Synthesis of (−)-α-Kainic Acid

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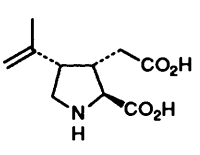
N-Alkylation of the β-amino acid derivative **16**, derived from (L)-aspartic acid, by the allylic chloride **12b** followed by deprotection and lactonization leads to the nine-membered azalactone **18**. Enolate Claisen rearrangement of this leads stereospecifically, *via* a boat-like transition state (*cf.* **6**), to the pyrrolidine acid **19**; subsequent one-carbon homologation, oxidation and deprotection affords (−)-(α)-kainic acid **1**.

(−)-α-Kainic acid **1** is the parent member of the kainoids, an unusual group of pyrrolidinedicarboxylic acids which display a variety of important biological activities, many of which are associated with the ability of these compounds to mimic glutamic acid.[1] (−)-α-Kainic acid itself occurs with its C-4 epimer, (+)-allokainic acid, in the marine alga *Digenea simplex* Ag.[2] and has also been found in the alga *Centrocerus clavulatum*,[3] and in a Corsican moss, *Alsidium helminthocorton*[4] and displays powerful neuroexcitatory and anthelmintic properties. Higher homologues of kainic acid all possess the same absolute configuration as the acid **1** and differ only in the nature of the C-4 side chain. (−)-Domoic acid **2**[5] occurs in the algae *D. simplex* and *Chondria armata* along with the closely related isodomoic acids,[6] further isomers of which have been identified in extracts of the toxic blue mussel, *Mytilus edulis*.[7] This mixture in which domoic acid predominates, has recently been shown to be the toxic factor responsible for outbreaks of food poisoning in Canada,[8] following the consumption of such species of shellfish. It also possesses powerful insecticidal activity against the American cockroach where it interferes with calcium transport and the release of glutamic acid.[9] The alga *C. armata* is also the source of the domiolactones A **3** and B which are presumably derived biosynthetically from domoic acid.[10] A rather different organism, the fungus *Clitocybe acromelalga* Ichimura, is the source of the acromelic acids A **4** and B, in which the pyrrolidine residue is joined to the 5 position of the pyridone ring.[11]



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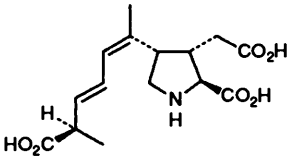

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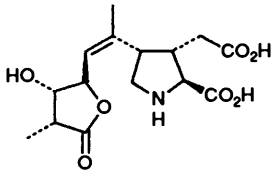

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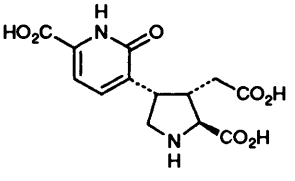

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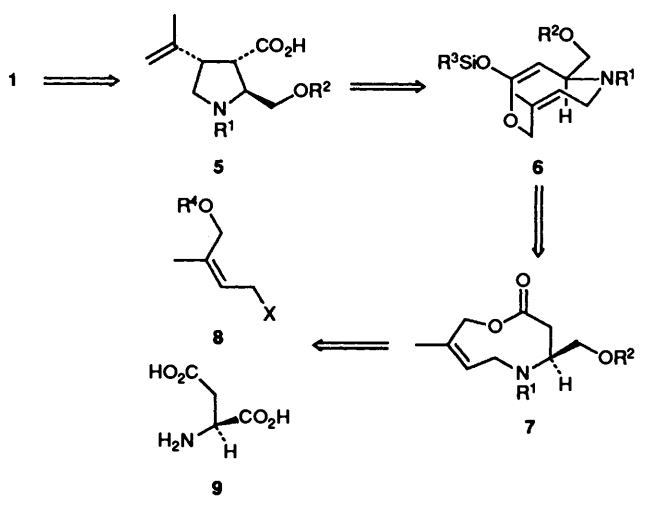
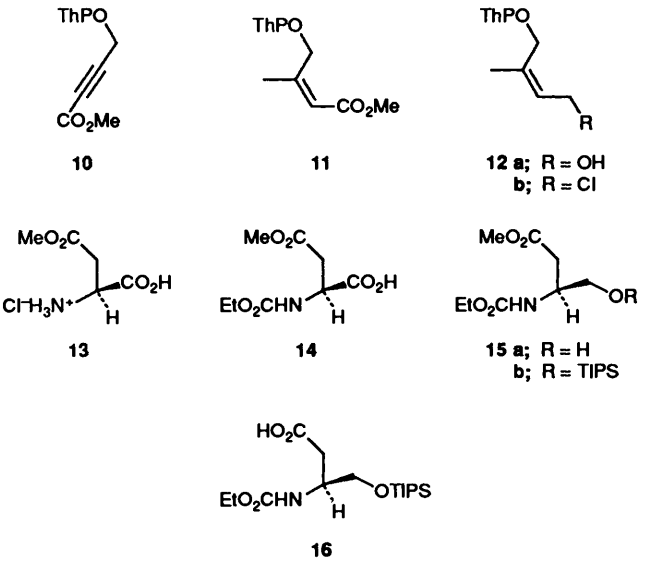
After some earlier and not especially efficient or stereoselective approaches to both kainic acid **1**[12] and allokainic acid,[13] the first syntheses of both (−)-kainic acid **1**[14] and allokainic acid[15] were developed by Oppolzer and his colleagues using highly diastereoselective intramolecular ene reactions. Intermolecular [1.3] dipolar cycloadditions of both thiazolium[16] and azomethine ylides[17] have also been used for the elaboration of the kainoids. These approaches led to racemic allokainic acid whereas a more recent intramolecular version of the latter type of cyclization has been successfully applied to a synthesis of (−)-(α)-kainic acid **1**,[18] in which (*S*)-2-(benzyloxymethyl)-oxirane was used as the source of chirality. An intramolecular Diels–Alder cyclization is a key step in another synthesis of (−)-(α)-kainic acid **1**,[19] while both racemic kainic and allokainic acids have been accessed by intramolecular, palladium-mediated olefin insertions.[20] Intramolecular Michael additions have also been used to prepare the pyrrolidine unit of these molecules.[21] An alternative and generally applicable approach to the kainoids features the use of cobalt-mediated intramolecular radical cyclizations; this methodology has been used to obtain both (−)-(α)-kainic acid and allokainic acid[22] as well as a domoic acid analogue[23] and acromelic acid A.[24] The original structural proof of (−)-domoic acid **2** was provided by a total synthesis, a key step in which was an intermolecular Diels–Alder cyclization with a chiral pyrrolidone as the dienophile.[25] Similarly, the structures of the acromelic acids A **4** and B were proven by synthesis, but starting from (−)-(α)-kainic acid itself.[26] Subsequently,[27] both have also been obtained using the intramolecular [1.3] dipolar cycloaddition method previously used in a synthesis of kainic acid.[18,28] Herein, we present full details of our total synthesis of (−)-(α)-kainic acid **1**,[29] which is based on the application of the alicyclic version of the enolate Claisen rearrangement[30] to azalactones.[31]

Previous studies[30] have shown that such enolate Claisen rearrangements of suitable (*Z*)-unsaturated lactones containing 12 atoms or less proceed exclusively *via* a boat-like transition state in which a substituent will be positioned pseudoequatorially; hence this approach provides carbocycles ranging from 2-vinylcyclopropane[32] to 2-vinylcyclooctanecarboxylic acids stereospecifically. By incorporating a suitably positioned nitrogen atom into the lactone ring, many of the corresponding nitrogen heterocyclic systems can, in principle, be obtained. Our model studies,[31] have shown that this is indeed the case with 4-vinylpyrrolidine-3-carboxylic acids. Our retrosynthetic approach to (−)-(α)-kainic acid **1** based on these findings is shown in Scheme 1. An initial pyrrolidine **5** should be available from enolate Claisen rerrangement of the chiral lactone **7**, which would be expected[31] to proceed *via* the boat-like transition state **6** wherein the hydroxymethyl residue is positioned exclusively equatorially as shown. Final conversion into (−)-(α)-kainic acid **1** would then entail a one-carbon homologation of the 3-carboxylic acid function, oxidation of the hydroxymethyl residue and deprotection. Preparation of the lactone **7** then requires *N*-alkylation of a suitably protected derivative of (L)-aspartic acid **9** by a (*Z*)-but-2-ene-1,4 diol derivative **8** followed by lactonization.



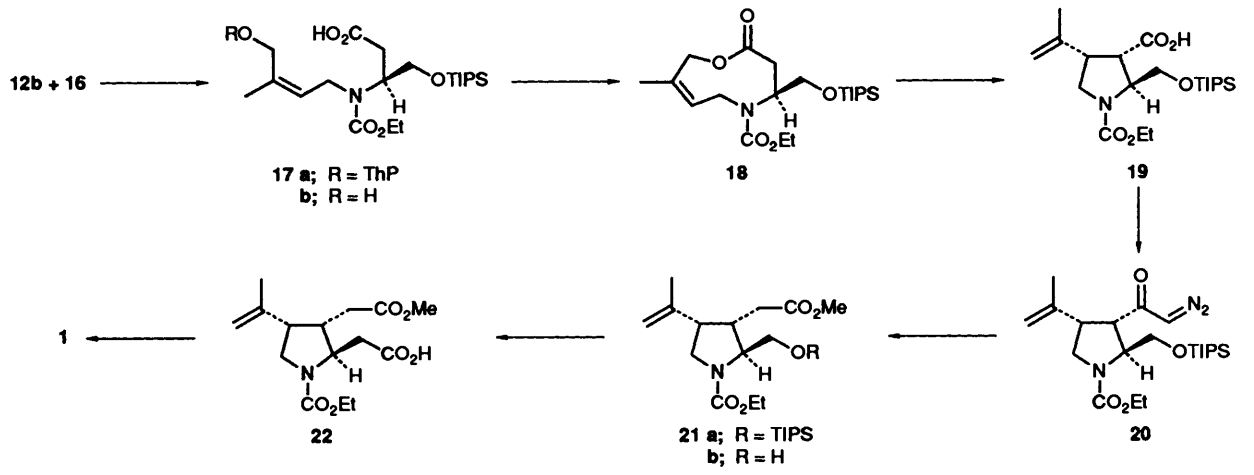
Scheme 1



A suitable (*Z*)-allylic chloride **12b** was prepared starting from the tetrahydropyranyl ether of prop-2-ynyl alcohol. Methoxycarbonylation leading to the butynoate **10** was found to proceed more efficiently using butyllithium as base at low temperature, rather than ethylmagnesium bromide as previously reported.[33] Subsequent Michael addition of lithium dimethylcuprate[34] then led stereospecifically to the (*Z*)-butenoate **11** which was smoothly reduced to the corresponding alcohol **12a**, using diisobutylaluminium hydride. Subsequent chlorination was then best achieved using the MsCl/LiCl method;[35] the pure and rather sensitive chloride **12b** was isolated in 61% yield with some loss upon chromatography. (Distillation resulted in greater loss of material.) Our choice of protecting groups for the aspartic acid unit was guided by our previous finding[31] that an *N*-*tert*-butoxycarbonyl (Boc) function did not survive the lactonization conditions which gave the highest yield of lactone (*vide infra*); we therefore used the robust ethoxycarbonyl group, in the expectation[31] that this could be successfully removed using trimethylsilyl iodide at a late stage without causing epimerization of the substrate. For the same reason and also to allow various selective deprotections to be carried out during the synthesis, we used the triisopropylsilyl (TIPS) function[37] to protect the pendant hydroxymethyl group. In addition, the bulk of this group should ensure that the key Claisen rearrangement proceeds only *via* the transition state **6**. Thus, the β-methyl ester hydrochloride of (L)-aspartic acid **13**[36] was efficiently converted into the corresponding *N*-ethoxycarbonyl derivative **14** which was then selectively reduced using borane•THF complex to the alcohol **15a**. Alternative methods gave inferior returns; for example, reduction using BH_3•SMe_2 was very slow whereas reductions of mixed anhydrides derivatives of the acid **14** using sodium borohydride resulted in simultaneous reduction of the β-methyl ester group. Subsequent conversion into the TIPS derivative **15b** proceeded smoothly as did the final saponification to the required acid **16**.

The key *N*-alkylation of the amino acid derivative **16** by the allylic chloride **12b** was effected using our procedure[31] involving formation of the dianion of acid **16** and subsequent addition of the chloride **12b**, crucially in the presence of dimethyl sulfoxide (DMSO) (Scheme 2). In this example, the yield of the *N*-alkylated product **17a** was improved by addition of the DMSO at −78 °C rather than at ambient temperature as was the case in the model studies.[31] The resulting homologue **17a** was then smoothly converted into the hydroxy acid **17b** by treatment with pyridinium toluene-*p*-sulfonate in hot methanol,[38] prior to lactonization. According to a number of trials,[39] this was best effected using Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide,[40] which delivered the required lactone **18** in 42% yield. This turned out to be rather sensitive and chromatographic purification was carried out using grade V neutral alumina; silica gel and even grade III neutral alumina caused significant decomposition. Efforts to recover the hydroxy acid **17b** by saponification of the reaction residues, which could contain polymeric ester and lactonic material, were not successful. An explanation for this has recently been provided by Funk and his colleagues[41] who demonstrated that the intermediate acyloxypyridinium species involved in this type of lactonization can undergo elimination to give the corresponding ketene. This can subsequently decompose or cyclize either by a [2 + 2] cycloaddition to the alkene function or possibly by attack of the hydroxy function, leading to the desired lactone **18**. In the event, we failed to isolate any other identifiable products from the lactonization of the hydroxy acid **17b**.

The crucial Claisen rearrangement step was effected using the 'pre-mix' method devised by Ireland and Norbeck.[42] This entailed addition of the lactone **18** to a mixture of lithium diisopropylamide and *tert*-butyldimethylsilyl chloride maintained at −100 °C in tetrahydrofuran. Presumably, immediate trapping of the intermediate lithio enolate occurred by *O*-silylation before the lactone ring opened by a retro-Michael reaction.[31] The rearrangement took place as the reaction mixture was warmed to ambient temperature and led to the desired pyrrolidine acid **19**, after hydrolysis of the initially formed silyl ester. According to ^{13}C NMR spectroscopy, the product was a single diastereoisomer, consistent with the exclusive intermediacy of the expected boat-like transition state **6**. The 3,4-*cis* relationship of the propenyl and carboxylic acid functions in pyrrolidine **19** was evident from the appearance, presumably due to restricted rotation, of two separate broad resonances for the two olefinic protons (δ 4.80 and 4.91); in the corresponding 3,4-*trans* epimers (*e.g.* allokainic acid), these appear as a single resonance.[43] One carbon homologation to the kainoid skeleton **21a** was achieved by the Arndt–Eistert method, *via* the acid chloride derived from acid **19**, and the diazoketone **20**. Mixed anhydrides derived from the acid **19** reacted very slowly with diazomethane and proved to be impractical intermediates for this step. Formation of the acid chloride was also extremely slow and inefficient using oxalyl chloride in ether until a trace of dimethylformamide was added.[44] Chromatographic purification of the diazoketone **20** was necessary in order to remove traces of the unhomologated methyl ester corresponding to the acid **19**. Subsequent Wolff



Scheme 2

rearrangement occurred smoothly upon treatment of the diazoketone **20** with a trace of silver benzoate in methanol to give the homologue **21a** in excellent yield. Removal of the triisopropylsilyl group was then effected using aqueous hydrogen fluoride in tetrahydrofuran to give the alcohol **21b**, again in excellent yield. Subsequent Jones oxidation then provided the corresponding acid **22**. We had hoped[31] that removal of the two remaining protecting groups would be possible in a single step using trimethylsilyl iodide[45] but even after treatment of the acid **22** with the latter reagent at 55 °C for 70 h in chloroform, some methyl ester remained and some decomposition was evident by ^{1}H NMR. Therefore, after removal of the *N*-ethoxycarbonyl group, which was complete in 5 h at 55 °C, the reaction mixture was treated with aqueous potassium hydroxide to effect complete hydrolysis of the methyl ester. After ion exchange chromatography and crystallization, (−)-(α)-kainic acid **1** was isolated which was identical with authentic material (Aldrich) according to its optical rotation, melting point, mixed melting point and spectroscopic data. No other isomers were found either in other chromatographic fractions or in the crystallization mother liquors, indicating that the key Claisen rearrangement had indeed been stereospecific and that no epimerization of the chiral centre derived from (L)-aspartic acid had occurred during the sequence.

Although the complete stereoselection of the Claisen step has plenty of precedence,[30–32] it was somewhat surprising that no epimerization was observed during the subsequent steps. A possible reason for this is that such a process would result in little or no lessening in steric interactions as the isomerized group, either a 2- or the 3-carboxylate, would still be *cis* to an adjacent functional group. The excellent level of stereoselection is a key feature of this relatively brief synthesis; however, the relative inefficiency of the lactonization step detracts somewhat from this. Efforts to find alternative and more efficient ways to prepare lactones **18** and relatives thereof are underway.

Experimental

For general details, see ref. 31.

Methyl 4-(*tetrahydropyran*-2-*yloxy*)*but*-2-*ynoate* **10**.—A solution of 3-(tetrahydropyran-2-yloxy)prop-1-yne (6.2 g, 44 mmol) in dry THF (200 cm^3) was stirred and cooled to −78 °C under nitrogen and treated dropwise with butyllithium (1.6 mol dm^{-3} solution in hexanes; 30 cm^3, 48 mmol) while the temperature was maintained < −70 °C. The solution was then slowly warmed to −20 °C during 1 h, and then recooled to −78 °C and treated dropwise with methyl chloroformate (4.5 g, 3.7 cm^3, 48 mmol), the temperature of the solution again being maintained < −70 °C. The resulting solution was slowly warmed to ambient temperature and then stirred overnight before it was evaporated under reduced pressure. The residue was taken up in ether (100 cm^3) and the resulting solution washed with water (2 × 30 cm^3), dried and evaporated. Distillation of the residue (Kugelrohr) then gave the ester **10** (6.9 g, 80%) as a colourless oil, b.p. (oven temp.) 130 °C at 0.2 mmHg; ν_{max}/cm^{-1} 2240 and 1712; δ_H 1.38–1.91 (6 H, m), 3.30–3.99 (2 H, m), 3.62 (3 H, s, OMe), 4.38 (2 H, s, C*H*$_2$OThP) and 4.66–4.85 (1 H, m, OCHO).[33]

(Z)-*Methyl* 3-*Methyl*-4-(*tetrahydropyran*-2-*yloxy*)*but*-2-*enoate* **11**.—To a stirred suspension of copper(I) iodide (14.3 g, 75 mmol) in dry THF (300 cm^3) maintained at 0 °C under nitrogen was added methyllithium (1.5 mol dm^{-3} solution in diethyl ether; 100 cm^3, 150 mmol). The resulting suspension was cooled in an acetone–solid CO_2 bath and methyl 4-(tetrahydropyran-2-yloxy)but-2-ynoate **10** (13.9 g, 70 mmol) was added dropwise; the mixture was stirred at this temperature for 3 h and then quenched by the addition of methanol (20 cm^3).[34] After warming to 0 °C, the mixture was poured into saturated aqueous ammonium chloride (300 cm^3) and ether (200 cm^3). After mixing, the resulting suspension was left for 0.25 h and then filtered and the residual solid washed with ether. The aqueous and organic layers were separated and the aqueous phase extracted with fresh ether (100 cm^3). The combined organic solutions were washed with saturated brine, dried and evaporated to leave the alkene **11** (14.3 g, 95%) as a straw-coloured oil, ν_{max}/cm^{-1} 1720; δ_H 1.36–1.92 (6 H, m), 1.97 (3 H, s, 3-Me), 3.34–3.97 (2 H, m), 3.64 (3 H, s, OMe), 4.54–4.64 (1 H, m, OCHO), 4.67 (2 H, s, CH_2CCH_3) and 5.66–5.78 (1 H, m, C=CH); *m/z* 115 (7%, $C_6H_{11}O_2$, M − ThP), 98 (24, $C_5H_6O_2$), 84 (100, C_5H_8O), 69 (71, C_4H_5O) and 55 (78, C_4H_7), which was isomerically and chemically pure according to the ^{1}H NMR data and TLC analysis. Distillation resulted in a considerable loss of material.

(Z)-3-*Methyl*-4-(*tetrahydropyran*-2-*yloxy*)*but*-2-*en*-1-*ol* **12a**.—To a solution of the foregoing ester **11** (9.64 g, 45 mmol) in dry ether (100 cm^3) maintained at < −70 °C under nitrogen was added slowly a solution of diisobutylaluminium hydride in toluene (1 mol dm^{-3} solution, 90 cm^3, 90 mmol). The resulting solution was stirred at this temperature for 2 h and then warmed slowly to ambient temperature and poured cautiously into a mixture of water (200 cm^3) and dichloromethane (200 cm^3). The precipitated salts were dissolved by the addition of 2 mol dm^{-3} aqueous sodium hydroxide (400 cm^3). The phases were

separated and the aqueous phase further extracted with dichloromethane (100 cm^3). The combined organic solutions were washed with saturated brine (200 cm^3) and then dried and evaporated to leave the *allylic alcohol* **12a** (7.9 g, 94%) as a straw-coloured oil, ν_{max}/cm^{-1} 3410; δ_H 1.38–2.02 (6 H, m), 1.80 (3 H, s, 3-Me), 2.66 (1 H, br s, OH), 3.40–4.35 (4 H, m), 4.14 (2 H, s, CH_2CCH_3), 4.58–4.74 (1 H, m, OCHO) and 5.67 (1 H, t, *J* 7, C=CH); *m/z* 185 (3%, $C_{10}H_{17}O_3$, M − H), 113 (6, $C_6H_9O_2$), 101 (35, $C_5H_9O_2$), 85 (100, C_5H_9O), 67 (48, C_5H_7) and 56 (94, C_4H_8) (Found: M^+ − H, 185.1169. $C_{10}H_{17}O_3$ requires *M*, 185.1178).

(Z)-4-*Chloro*-2-*methyl*-1-(*tetrahydropyran*-2-*yloxy*)*but*-2-*ene* **12b**.—To a stirred suspension of the foregoing allylic alcohol **12a** (10.0 g, 54 mmol), *s*-collidine (8 cm^3, 60 mmol) and anhydrous lithium chloride (2.4 g, 57 mmol) in dry DMF (25 cm^3) maintained at 0 °C under nitrogen was slowly added methanesulfonyl chloride (4.65 cm^3, 60 mmol). The reaction mixture was stirred at 0 °C for a further 2 h and then poured into iced water (250 cm^3) and extracted with ether–petroleum (1:1; 3 × 50 cm^3). The combined organic extracts were washed with saturated aqueous copper(II) nitrate (5 × 25 cm^3) and water (2 × 25 cm^3) and then dried and evaporated. Chromatography of the residue over silica gel eluted with 5% ether in light petroleum gave the *chloride* **12b** (6.7 g, 61%) as a colourless oil, ν_{max}/cm^{-1} 2948 and 1036; δ_H 1.38–2.02 (6 H, m), 1.87 (3 H, br s, 2-Me), 3.31–4.38 (2 H, m), 4.19 (2 H, d, *J* 8, CH_2Cl), 4.20 (2 H, s, CH_2CCH_3), 4.58–4.72 (1 H, m, OCHO) and 5.68 (1 H, t, *J* 8, C=CH); *m/z* 203 (3%, $C_{10}H_{16}ClO_2$, M − H), 103 (28, C_5H_8Cl, M − OThP), 102 (17, C_5H_7Cl), 101 (36, $C_5H_9O_2$), 85 (100, C_5H_9O), 75 (13, C_3H_4Cl) and 67 (52, C_5H_7) (Found: M^+ − H, 203.0825. $C_{10}H_{16}ClO_2$ requires *M*, 203.0839).

4-*Methyl Hydrogen* (S)-2-*Ethoxycarbonylaminobutanedioate* **14**.—To a stirred solution of (L)-aspartic acid β-methyl ester hydrochloride **13** (15.9 g, 87 mmol),[37] sodium hydroxide (3.5 g, 87 mmol) and sodium hydrogen carbonate (14.6 g, 174 mmol) [37] in water (180 cm^3) maintained at 0 °C was slowly added ethyl chloroformate (9.8 cm^3, 103 mmol). Stirring was continued for 1 h at this temperature and for a further 2 h at ambient temperature. The reaction mixture was then washed with ether (2 × 30 cm^3), acidified using concentrated hydrochloric acid, saturated with sodium chloride and extracted with chloroform (4 × 50 cm^3). The combined organic solutions were washed with water (2 × cm^3) and then dried and evaporated to give the *carbamate* **14** (18.1 g, 95%) as a colourless oil, $[\alpha]_D^{27}$ +7.7 (*c*, 1.77 in CH_2Cl_2); ν_{max}/cm^{-1} 318 and 1719; δ_H 1.26 (3 H, t, *J* 7, CH_2CH_3), 2.86–3.10 (2 H, m, $CHCH_2$), 3.76 (3 H, s, OMe), 4.19 (2 H, q, *J* 7, CH_2CH_3), 4.53–4.83 (1 H, m, $CHCH_2$), 5.77–6.13 (1 H, br d, *J* 9, NH) and 10.49 (1 H, s, CO_2H); *m/z* (99%, $C_7H_{12}NO_4$, M − CO_2H), 115 (100, $C_5H_9NO_2$), 102 (21, $C_4H_8NO_2$), 90 (26, $C_3H_8NO_2$), 86 (28, $C_3H_4NO_2$) and 74 (47, $C_3H_6O_2$) (Found: C, 43.5; H, 6.1; N, 6.3. $C_8H_{13}NO_6$ requires C, 43.8; H, 6.0; N, 6.4%).

(S)-*Methyl* 3-*Ethoxycarbonylamino*-4-*hydroxybutanoate* **15a**.—To a stirred solution of the foregoing acid **14** (10.0 g, 45.6 mmol) in dry THF (10 cm^3) maintained at −5 °C under nitrogen was slowly added borane–THF complex (1 mol dm^3 solution in THF; 100 cm^3). The resulting solution was stirred at −2 C for 27 h and then quenched with methanol and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (150 cm^3) and the solution washed with 1 mol dm^{-3} hydrochloric acid (40 cm^3), water (40 cm^3) and saturated aqueous sodium hydrogen carbonate (40 cm^3). The dried solution was evaporated under reduced pressure to leave the *alcohol* **15a** (3.9 g, 42%) as a clear oil, $[\alpha]_D^{27}$ −1.4 (*c*, 1.77 in CH_2Cl_2); ν_{max}/cm^{-1} 3354, 1724 and 1693; δ_H 1.22 (3 H, t, *J* 7, CH_2CH_3), 2.61 (2 H, d, *J* 7, CH_2CO_2), 2.81 (1 H, br s, OH), 3.70–3.92 (2 H, m, $CHCH_2O$), 3.87–4.14 (1 H, m, $CHCH_2$), 4.08 (2 H, q, *J* 7, CH_2CH_3) and 5.38–5.63 (1 H, br d, *J* 9, NH); *m/z* 174 (100%, $C_7H_{12}NO_4$), 115 (36, $C_5H_9NO_2$), 102 (26, $C_4H_8NO_2$), 90 (16, $C_3H_8NO_2$), 86 (26, $C_3H_4NO_2$) and 70 (15, C_3H_4NO) (Found: M^+, 174.0761. $C_7H_{12}NO_4$ requires *M*, 174.0767).

(S)-*Methyl* 3-*Ethoxycarbonylamino*-4-*triisopropylsilyloxybutanoate* **15b**.—To a stirred solution of the foregoing alcohol **15a** (3.9 g, 19 mmol) and imidazole (3.75 g, 55 mmol) in dry DMF (16 cm^3) at ambient temperature was added triisopropylsilyl chloride (5.1 g, 26.4 mmol).[37] The resulting solution was stirred for 24 h and then diluted with water (150 cm^3) and extracted with ether (3 × 50 cm^3). The combined organic solutions were washed with water (30 cm^3) and then dried and evaporated to leave the *silyl ether* **15b** (6.5 g, 95%) as a colourless oil, $[\alpha]_D^{27}$ −12.4 (*c*, 1.65 in CH_2Cl_2); ν_{max}/cm^{-1} 3325 and 1729; δ_H 1.04 (21 H, br s, 3 × Pr^i), 1.22 (3 H, t, *J* 7, CH_2CH_3), 2.62 (2 H, d, *J* 7, CH_2CO_2), 3.58–3.82 (2 H, m, $CHCH_2O$), 3.65 (3 H, s, OMe), 3.95–4.26 (1 H, m, NCH), 4.08 (2 H, q, *J* 7, CH_2CH_3) and 5.07–5.32 (1 H, br d, *J* 9, NH); *m/z* 318 (100%, $C_{14}H_{28}NO_5Si$, M − Pr^i), 272 (16, $C_{12}H_{22}NO_4Si$), 229 (39, $C_{11}H_{21}O_3Si$), 172 (61, $C_8H_{18}NOSi$), 159 (40, $C_8H_{19}OSi$), 145 (18, $C_6H_{15}NOSi$) and 89 (19, C_3H_9OSi) (Found: M^+ − Pr^i, 318.1734. $C_{14}H_{28}NO_5Si$ requires *M* − Pr^i, 318.1737).

(S)-3-*Ethoxycarbonylamino*-4-*triisopropylsilyloxybutanoic Acid* **16**.—The foregoing silyl ether **15b** (6.5 g, 18 mmol) was dissolved in methanol (50 cm^3) containing potassium hydroxide (1.85 g, 33 mmol) and the resulting solution was stirred at ambient temperature for 20 h and then evaporated to dryness. The residue was dissolved in water (150 cm^3) and the resulting solution washed with ether (3 × 30 cm^3) and then acidified using 2 mol dm^{-3} hydrochloric acid and finally extracted with ether (3 × 50 cm^3). The combined extracts were washed with water (30 cm^3) and then dried and evaporated, finally under high vacuum, to leave the *acid* **16** (4.7 g, 75%) as a colourless oil, $[\alpha]_D^{27}$ −16.7 (*c*, 1.47 in CH_2Cl_2); ν_{max}/cm^{-1} 3313 and 1710; δ_H 1.07 (21 H, br s, 3 × Pr^i), 1.26 (3 H, t, *J* 7, CH_2CH_3), 2.71 (2 H, d, *J* 7, CH_2CO_2), 3.72–3.90 (2 H, m, $CHCH_2O$), 3.99–4.33 (1 H, m, NCH), 4.19 (2 H, q, *J* 7, CH_2CH_3), 5.21–5.62 (1 H, br s, NH) and 8.29 (1 H, br s, CO_2H); *m/z* 304 (43%, $C_{13}H_{26}NO_5Si$, M − Pr^i), 258 (53, $C_{11}H_{20}NO_4Si$), 172 (29, $C_8H_{16}O_2Si$), 169 (100, $C_8H_{15}NOSi$), 131 (94, $C_5H_9NO_3$), 103 [55, C_3H_9NOSi (?)] and 75 (63, C_2H_7OSi) (Found: M^+ − Pr^i, 304.1567. $C_{13}H_{26}NO_5Si$ requires *M*, 304.1580]. The material was pure according to ^1H NMR data and TLC analysis.

(S)-(Z)-4-*Ethyl Hydrogen* 7-*Methyl*-8-(*tetrahydropyran*-2-*yloxy*)-3-*triisopropyloxymethyl*-4-*azaoct*-6-*ene*-1,4-*dioate* **17a**.—To a stirred solution of the protected β-amino-acid **16** (1.98 g, 5.7 mmol) in dry THF (11 cm^3), under nitrogen and maintained below −70 °C using a solid CO_2–acetone bath, butyllithium (1.6 mol dm^{-3} solution in hexanes; 7.8 cm^3, 12.5 mmol) was added dropwise. The resulting suspension was diluted with dry DMSO (1.5 cm^3), warmed to ambient temperature and then treated with the foregoing allylic chloride **12b** (1.40 g, 6.8 mmol). The resulting solution was stirred at this temperature for 16 h and then the THF was removed under reduced pressure. The residue was taken up in water (100 cm^3) and the resulting solution washed with ether (3 × 30 cm^3) and then acidified using 2 mol dm^{-3} hydrochloric acid and extracted with ether (3 × 50 cm^3). The combined organic solutions were washed with water (2 × 20 cm^3) and then dried and evaporated to leave the *acid* **17a** (2.1 g, 71%) as an oil, ν_{max}/cm^{-1} 3315 and 1708; δ_H 1.06 (21 H, br s, Pr^i), 1.26 (3 H, t, *J* 7, CH_2CH_3), 1.38–1.97 (6 H, m), 1.81 (3 H, s, CCH_3), 2.62–2.94 (2 H, m, CH_2CO_2), 3.42–4.43 (11 H, m), 4.63–4.76 (1 H, m, OCHO), 5.32–5.59 (1 H, m, C=CH) and 6.72 (1 H, br s, CO_2H); *m/z* 305 (46%, $C_{17}H_{27}NO_2Si$), 304

(100, $C_{13}H_{26}NO_5Si$), 215 (39, $C_{10}H_{19}O_3Si$), 172 (47, $C_8H_{18}NOSi$), 159 (20, $C_8H_{19}OSi$), 131 (45, $C_6H_{15}OSi$), 103 (39, C_3H_9NOSi) and 85 (30, C_5H_9O) (Found: M^+, 305.1807. $C_{17}H_{27}NO_2Si$ requires *M*, 305.1811).

(S)-(Z)-4-*Ethyl Hydrogen* 8-*Hydroxy*-7-*methyl*-3-*triisopropylsilyloxymethyl*-4-*azaoct*-6-*ene*-1,4-*dioate* **17b**.—A solution of the tetrahydropyranyl ether **17a** (1.95 g, 3.8 mmol) and pyridinium-toluene-*p*-sulfonate (PPTS)[38] (0.19 g, 0.75 mmol) in methanol (40 cm^3) was refluxed until TLC analysis indicated complete hydrolysis of the ether function (*ca.* 7 h). The solvent was evaporated and the residue taken up in ethyl acetate (100 cm^3). The resulting solution was washed with half-saturated brine (2 × 20 cm^3) and then dried and evaporated to leave the *hydroxy acid* **17b** (1.55 g, 95%) as a colourless oil, $[\alpha]_D^{27}$ −21.6 (*c*, 1.38 in CH_2Cl_2); ν_{max}/cm^{-1} 3330 and 1710; δ_H 1.06 (21 H, br s, 3 × Pr^i), 1.26 (3 H, t, *J* 7, CH_2CH_3), 1.83 (3 H, br s, CCH_3), 2.57–2.93 (2 H, m, CH_2CO_2), 3.70–4.74 (9 H, m), 5.26–5.62 (1 H, m, C=CH) and 7.46 (2 H, br s, 2 × OH); *m/z* 304 (100%, $C_{13}H_{26}NO_5Si$), 258 (20, $C_{11}H_{20}NO_4Si$), 215 (26, $C_{10}H_{19}O_3Si$), 172 (38, $C_8H_{18}NOSi$), 131 (58, $C_6H_{15}OSi$), 103 (41, C_3H_9NOSi) and 75 (78, C_2H_7Si) (Found: M^+, 304.1729. $C_{17}H_{26}NO_2Si$ requires M, 304.1733).

(3S,6Z)-4-*Ethoxycarbonyl*-3-*triisopropylsilyloxymethyl*-4-*azaoct*-6-*en*-8-*olide* **18**.—A solution of the hydroxy acid **17b** (1.50 g, 3.5 mmol) in dry acetonitrile (14 cm^3) and triethylamine (5.6 cm^3, 40 mmol) was added during 6 h, *via* a motor-driven syringe, to a stirred, refluxing solution of 2-chloro-1-methylpyridinium iodide (5.1 g, 20 mmol) in dry acetonitrile (1500 cm^3). The resulting solution was refluxed for a further 12 h, and then cooled and evaporated. The residue was partitioned between water (150 cm^3) and ether (50 cm^3) and the separated aqueous layer further extracted with ether (2 × 50 cm^3). The combined organic solutions were washed with saturated brine (25 cm^3) then dried and evaporated. Chromatography of the residue over neutral alumina (grade V), eluted with 5% ether in light petroleum gave the *azalactone* **18** (0.61 g, 42%) as a colourless oil $[\alpha]_D^{27}$ +15.2 (*c*, 1.41 in CH_2Cl_2); ν_{max}/cm^{-1} 1752 and 1698; δ_H 1.06 (21 H, br s, 3 × Pr^i), 1.24 (3 H, t, *J* 7, CH_2CH_3), 1.69 (3 H, br s, CCH_3), 2.64–2.92 (2 H, m, $CH_2C{=}O$), 3.43–3.74 (2 H, m, CH_2OSi), 3.81–4.26 (5 H, m, CH_2NCH and CH_2CH_3), 4.41–5.03 (2 H, m, $CH_2OC{=}O$) and 5.48–5.94 (1 H, m, C=CH); *m/z* 398 (15%, $C_{20}H_{36}NO_5Si$, M − Me), 370 (100, $C_{18}H_{32}NO_5Si$, M − Pr^i), 332 (65, $C_{15}H_{30}NO_5Si$), 318 (22, $C_{14}H_{28}NO_5Si$), 172 (52, $C_8H_{18}NOSi$), 159 (63, $C_8H_{19}OSi$) and 131 (26, $C_6H_{15}OSi$) (Found: M − Me, 398.2355. $C_{20}H_{36}NO_5Si$ requires *M*, 398.2363) (Found: C, 60.8; H, 10.2; N, 3.2. $C_{21}H_{39}NO_5Si$ requires C, 61.0; H, 9.5; N, 3.4%).

(2S,3S,4S)-1-*Ethoxycarbonyl*-4-*isopropenyl*-2-*triisopropylsilyloxymethylpyrrolidine*-3-*carboxylic Acid* **19**.—A solution of lithium diisopropylamide (LDA) [from diisopropylamine (0.27 cm^3, 1.93 mmol) and butyllithium (1.6 mol dm^{-3} solution in hexanes, 1.15 cm^3, 1.84 mmol)] in THF (3 cm^3) was cooled to −100 °C and treated sequentially, *via* a syringe, with solutions of *tert*-butyldimethylsilyl chloride (0.28 g, 1.84 mmol) in THF (1 cm^3) and the foregoing azalactone **18** (0.38 g, 0.92 mmol) in THF (2 cm^3), the latter during 5 min. After 0.5 h, the solution was slowly warmed to ambient temperature and then stirred for a further 0.5 h and evaporated. The residue was partitioned between water (10 cm^3) and ether (10 cm^3) and the separated aqueous layer was further extracted with ether (2 × 10 cm^3). The combined organic extracts were washed with brine (5 cm^3) and then dried and evaporated to leave the crude silyl ester as an oil. This was dissolved in methanol (11.5 cm^3) and THF (3.3 cm^3) and the resulting stirred solution was treated with a solution of potassium carbonate (0.38 g, 2.8 mmol) in water (3.3 cm^3). After 2 h at ambient temperature, the organic solvents were evaporated and the residue diluted with water (10 cm^3). The resulting mixture was washed with ether (3 × 5 cm^3) and the residual aqueous phase acidified to pH 3 using solid citric acid then extracted with ether (3 × 5 cm^3). The combined organic extracts were dried and evaporated to leave the *pyrrolidine acid* **19** (0.21 g, 55%) as a colourless oil, $[\alpha]_D^{27}$ −36.1 (*c*, 1.68 in CH_2Cl_2); ν_{max}/cm^{-1} 3170 and 1706; δ_H 1.08 (21 H, br s, 3 × Pr^i), 1.27 (3 H, t, *J* 7, CH_2CH_3), 1.82 (3 H, s, CCH_3), 3.12–4.38 (7 H, m), 4.20 (2 H, q, *J* 7, CH_2CH_3), 4.80 (1 H, br s, $C{=}CH_aH_b$), 4.91 (1 H, br s, $C{=}CH_aH_b$) and 9.17 (1 H, br s, CO_2H); δ_C 11.97 [$CH(CH_3)_2$], 14.81 (CH_2CH_3), 17.98 [$CH(CH_3)_2$], 22.54 ($C{=}CCH_3$), 45.34 and 46.14 (C-4), 48.82 (CH_2OSi), 49.20 and 49.63 (C-3), 61.20 and 62.01 (C-2), 61.38 (CH_2CH_3), 63.43 and 63.90 (C-5), 111.89 and 112.20 ($C{=}CH_2$), 141.51 and 141.67 ($C{=}CH_2$), 155.34 (NCO_2) and 177.64 (CO_2); *m/z* 370 (100%, $C_{18}H_{32}NO_5Si$, M − Pr^i), 226 (9, $C_{11}H_{16}NO_4$, M − CH_2OTIPS), 172 (9, $C_8H_{18}NOSi$), 159 (18, $C_8H_{19}OSi$), 131 (35, $C_6H_{15}OSi$) 103 (38, $C_4H_{11}OSi$) and 75 (70, C_2H_7OSi) (Found: C, 60.8; H, 9.2; N, 3.0. $C_{21}H_{39}NO_5Si$ requires C, 61.0; H,. 9.5; N, 3.4%).

(2S,3S,4S)-3-*Diazoacetyl*-1-*ethoxycarbonyl*-4-*isopropenyl*-2-*triisopropylsilyloxymethylpyrrolidine* **20**.—To an ice-cold, stirred solution of the pyrrolidinecarboxylic acid **19** (0.16 g, 0.39 mmol) in dry ether (3 cm^3) was added dry DMF (1 mm^3)[44] followed by freshly distilled oxalyl chloride (61 mm^3, 0.695 mmol). After 0.5 h at 0 °C and 1.5 h without cooling, the solvent was evaporated and to a solution of the residual acid chloride in dry ether (3 cm^3) was added an excess of an ice-cold, dried (KOH) solution of diazomethane in ether. The resulting solution was left at ambient temperature overnight and then evaporated. The residue was chromatographed over silica gel eluted with 10% ether–light petroleum to give the *diazoketone* **20** (0.12 g, 70%) as an oil, $[\alpha]_D^{27}$ −6.3 (*c*, 1.56 in CH_2Cl_2); ν_{max}/cm^{-1} 2112 and 1690; δ_H 1.08 (21 H, br s, 3 × Pr^i), 1.27 (3 H, t, *J* 7, CH_2CH_3), 1.79 (3 H, s, CCH_3), 3.03–4.37 (7 H, m), 4.19 (2 H, q, *J* 7, CH_2CH_3), 4.83 (1 H, br s, $C{=}CH_aH_b$), 4.95 (1 H, br s, $C{=}CH_aH_b$) and 5.26 (1 H, s, CHN_2); *m/z* 394 (18%, $C_{19}H_{32}N_3O_4Si$, M − Pr^i), 366 (100, $C_{19}H_{32}NO_4Si$, M − Pr^i and N_2), 222 (13, $C_{12}H_{16}NO_3$, M − CH_2OTIPS and N_2), 131 (15, $C_6H_{15}OSi$) and 103 (22, C_7H_5N) (Found: M − Pr^i 394.2154. $C_{19}H_{32}N_3O_4Si$ requires 394.2162). The sample was pure according to TLC evidence.

Methyl (2S,3S,4S)-1-*Ethoxycarbonyl*-4-*isopropenyl*-2-*triisopropylsilyloxymethylpyrrolidin*-3-*ylacetate* **21a**.—A solution of silver benzoate (0.005 g) in dry triethylamine (0.05 cm^3) was added to a solution of the diazoketone **20** (0.115 g, 0.26 mmol) in dry methanol (5 cm^3) and the resultant mixture stirred at ambient temperature for 16 h. It was then filtered through a Kieselguhr and evaporated. The residue was dissolved in ether (15 cm^3) and the resulting solution washed with saturated aqueous sodium hydrogen carbonate (3 cm^3) then dried and evaporated to leave the *pyrrolidinyl acetate* **21a** (0.110 g, 95%) as a colourless oil, $[\alpha]_D^{27}$ −35.9 (*c*, 1.38 in CH_2Cl_2); ν_{max}/cm^{-1} 1735 and 1694; δ_H 1.06 (21 H, br s, 3 × Pr^i), 1.28 (3 H, t, *J* 7, CH_2CH_3), 1.73 (3 H, s, CCH_3), 2.06–2.33 (2 H, m, CH_2CO_2), 2.73–4.36 (7 H, m), 3.65 (3 H, s, OMe), 4.14 (2 H, q, *J* CH_2CH_3), 4.69 (1 H, br s, $C{=}CH_aH_b$) and 4.91 (1 H, br s, $C{=}CH_aH_b$); *m/z* 398 (100%, $C_{20}H_{36}NO_5Si$, M − Pr^i), 254 (28, $C_{13}H_{20}NO_4$, M − CH_2OTIPS), 89 (5, C_2H_7NOSi), 75 (9, C_2H_7OSi) and 59 (7, C_2H_7Si) (Found: M − Pr^i 398.2371. $C_{20}H_{36}NO_5Si$ requires 398.2363). The sample was pure according to ^1H NMR data and TLC analysis.

Methyl (2S,3S,4S)-1-*Ethoxycarbonyl*-2-*hydroxymethyl*-4-*isopropenylpyrrolidin*-3-*ylacetate* **21b**.—To a stirred solution of the foregoing pyrrolidinylacetate **21a** (0.107 g, 0.24 mmol) in

THF (3 cm^3) at ambient temperature was added 40% hydrofluoric acid (0.5 cm^3, 10 mmol). The resulting mixture was stirred for 6 h and then diluted with saturated aqueous sodium hydrogen carbonate (10 cm^3) and extracted with ether (3 × 10 cm^3). The combined organic extracts were dried and concentrated to leave the *alcohol* **21b** (0.065 g, 94%) as a colourless oil, $[\alpha]_D^{27}$ −31.5 (*c*, 0.81 in CH_2Cl_2); ν_{max}/cm^{-1} 3395, 1726 and 1688; δ_H 1.28 (3 H, t, *J* 7, CH_2CH_3), 1.73 (3 H, s, CCH_3), 2.16–2.37 (2 H, m, CH_2CO_2), 2.45–3.26 (3 H, m, 3-H, 4-H and OH), 3.51 (2 H, d, *J* 8, CH_2OH), 3.61–3.98 (2 H, m, 5-H), 3.67 (3 H, s, OMe), 4.02–4.41 (1 H, m, 2-H), 4.14 (2 H, q, *J* 7, CH_2CH_3), 4.68 (1 H, br s, $C{=}CH_aH_b$) and 4.92 (1 H, br s, $C{=}CH_aCH_b$); *m/z* 267 (9%, $C_{14}H_{21}NO_4$, M − H_2O), 254 (100, $C_{13}H_{20}NO_4$, M − CH_2OH), 194 (18, $C_{10}H_{12}NO_3$), 152 (13, $C_8H_{10}NO_2$), 122 (22, $C_8H_{12}N$), 108 (15, $C_7H_{10}N$) and 80 (15, C_5H_6N) [Found: M − H_2O, 267.1480. $C_{14}H_{21}NO_4$ requires 267.1471]. The sample was pure according to ^1H NMR data and TLC analysis.

Methyl (2S,3S,4S)-2-*Carboxy*-1-*ethoxycarbonyl*-4-*isopropenylpyrrolidin*-3-*ylacetate* **22**.—A slight excess of Jones reagent was added to a stirred solution of the foregoing alcohol **21b** (0.060 g, 0.21 mmol) in ice-cold acetone (5 cm^3) during 20 min. After a further 10 min., the solution was diluted with saturated brine (10 cm^3) and extracted with chloroform (4 × 5 cm^3). The combined organic solutions were washed with water (2 × 3 cm^3) and then extracted with saturated aqueous sodium hydrogen carbonate (2 × 5 cm^3). The aqueous extracts were acidified to pH 3 using solid citric acid then extracted with chloroform (3 × 5 cm^3). The combined chloroform solutions were dried and evaporated to give the pyrrolidine acid **22** (0.039 g, 62%) as a colourless oil, $[\alpha]_D^{27}$ −60.9 (*c*, 0.35 in CH_2Cl_2); ν_{max}/cm^{-1} 3420, 1723 and 1686; δ_H 1.27 (3 H, t, *J* 7, CH_2CH_3), 1.75 (3 H, s, CCH_3), 2.21–2.43 (2 H, m, CH_2CO_2), 2.94–3.29 (2 H, m, 3- and 4-H), 3.46–3.94 (2 H, m, 5-H), 3.75 (3 H, s, OMe), 4.09–4.44 (1 H, m, 2-H), 4.22 (2 H, q, *J* 7, CH_2CH_3), 4.77 (1 H, br s, $C{=}CH_aH_b$), 5.02 (1 H, br s, $C{=}CH_aCH_b$) and 5.88 (1 H, br s, CO_2H); *m/z* 299 (27%, M^+, $C_{14}H_{21}NO_6$), 281 (100, $C_{14}H_{19}NO_5$, M − H_2O), 254 (98, $C_{13}H_{20}NO_4$, M − CO_2H), 182 (79, $C_{10}H_{16}NO_2$), 152 (65, $C_8H_{10}NO_2$), 122 (91, $C_8H_{12}N$) and 80 (79 C_5H_6N) (Found: M^+, 299.1361. $C_{14}H_{21}NO_6$ requires 299.1369]. The sample was pure according to ^1H NMR data and TLC analysis.

(−)-(α)-*Kainic Acid* **1**.—To a solution of the foregoing pyrrolidine acid **22** (0.028 g, 0.094 mmol) in dry deuteriochloroform (0.2 cm^3) and dry pyridine (7 mm^3, 0.085 mmol) was added trimethylsilyl iodide (60 mm^3, 0.42 mmol). The resulting solution was heated to 55 °C with regular ^1H NMR monitoring. Removal of the ethoxycarbonyl group was complete after 5 h at which point, the solution was poured into a 1.5 mol dm^{-3} solution of potassium hydroxide in water (3 cm^3). The resulting mixture was stirred at ambient temperature for 20 h then evaporated under reduced pressure. The residue, in water (1 cm^3), was passed through a short column of strongly acidic ion-exchange resin (Dowex 50 W/H), eluted first with water and then with 1 mol dm^{-3} aqueous ammonium hydroxide. The ammonium hydroxide fraction was concentrated under reduced pressure and the residue dissolved in water; the resulting solution was then passed through a short column of a weakly acidic ion-exchange resin (Amberlite CG50, 100–200 wet mesh) eluted with water. The aqueous elutant was concentrated under reduced pressure and the resulting off-white solid crystallized from water to give (−)-(α)-kainic acid monohydrate **1** (0.014 g, 70%) as colourless needles, m.p. 246–248 °C (lit.,[19] m.p. 243–244 °C), mixed m.p. 247–248 °C; $[\alpha]_D^{27}$ −13.3 (*c* 0.36 in H_2O) [lit.,[19] $[\alpha]_D^{27}$ −14.2 (*c*, 0.23 in H_2O)]; ν_{max}/cm^{-1} (KBr) 1687, 1620, 1436, 1382, 1321 and 1280; δ_H(250 MHz in D_2O; standard H_2O) 1.72 (3 H, s, CCH_3), 2.34 (1 H, dd, *J* 16.8 and 8.0, $CH_aH_bCO_2H$), 2.45 (1 H, dd, *J* 16.8 and 6.1, $CH_aCH_bCO_2H$), 2.93–3.07 (2 H, m, 3- and 4-H), 3.40 (1 H, dd, *J* 11.8 and 10.6, NCH_aCH_b), 3.60 (1 H, dd, *J* 11.8 and 7.1, NCH_aCH_b), 4.07 (1 H, d, *J* 2.9, 2-H), 4.73 (1 H, br s, $C{=}CH_aH_b$) and 5.01 (1 H, br s, $C{=}CH_aH_b$); *m/z* 213 (6%, M^+, $C_{10}H_{15}NO_4$), 168 (100, $C_9H_{14}NO_2$, M − CO_2H), 153 (23, $C_8H_{11}NO_2$, M − CH_2CO_2H), 122 (20, $C_8H_{12}N$, M − 2 × CO_2H), 108 (29, $C_7H_{10}N$, M − CO_2H and CH_2CO_2H), 87 (27, $C_3H_5NO_2$), 80 (36, C_5H_6N) and 69 (29, C_3H_3NO) (Found: C, 52.5; H, 7.3; N, 6.2. Calc. for $C_{10}H_{15}NO_4{\cdot}H_2O$: C, 51.9; H, 7.4; N, 6.1%]. the sample exhibited spectral data which were identical with those of the natural material. Examination of the remaining column fractions and the mother liquors from the final crystallization failed to reveal the presence of any other isomers.

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