Synthetic Studies in the α-Kainic Acid (2,3-*trans*,3,4-*cis*-2-Carboxy-4-isopropenylpyrrolidin-3-ylacetic Acid) Series

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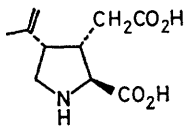
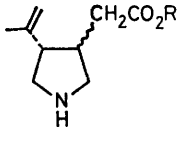
The synthesis of (±)-*cis*- and (±)-*trans*-4-isopropenylpyrrolidin-3-ylacetic acids and the attempted synthesis of (±)-2,3-*trans*,3,4-*cis*-2-carboxy-4-isopropenylpyrrolidin-3-ylacetic acid, α-kainic acid, by intramolecular ene reactions are described. The ene cyclisation reaction has been shown to be kinetically controlled with the relative stabilities of the transition states controlling the product distribution. No isomerisation of starting diene or product pyrrolidine occurs under the conditions of the reaction.

L-α-KAINIC ACID (1a) is a naturally occurring acidic amino-acid and a potent neuronal excitant [1] which was originally isolated from the marine algae *Digenea simplex*.[2] Neuronal lesions caused by intracranial injections of (1a) are widely used in investigations of neuronal networks in the central nervous system and as pharmacological models for human disease states including, *inter alia*, Huntington's chorea.[3] The 2-decarboxylated derivative of kainic acid, (2a), is of interest since it is a conformationally restricted analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). A recent report [4] claiming the synthesis of (2a) prompts us to report some of our investigations in the kainic acid and related fields.

Allan [4] oxidatively decarboxylated L-α-kainic acid to the pyrroline (3) by sodium metaperiodate. Reduction of (3) by sodium cyanoborohydride gave an optically active acid whose stereochemistry could not be defined because of the complexity of the proton n.m.r. spectrum. However elemental analysis and the i.r. spectrum were consistent with the product being either of the two diastereoisomers (2a),(2b) and it was assumed that the reaction had not affected the relative stereochemistry of the C(3)–C(4) substituent groups.

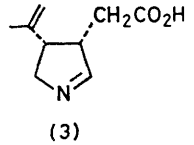


(1a)



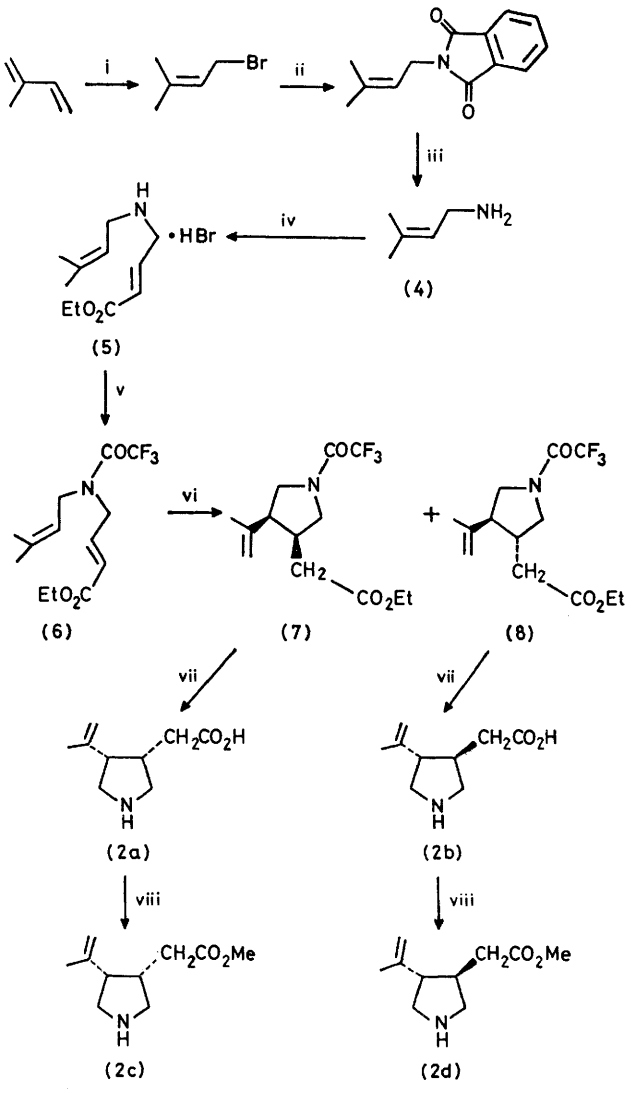
(2)

2(a) R = H, C(3)–C(4) *cis*
2(b) R = H, C(3)–C(4) *trans*
2(c) R = Me, C(3)–C(4) *cis*
2(d) R = Me, C(3)–C(4) *trans*



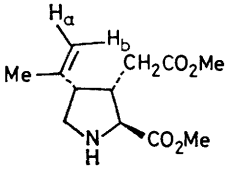
(3)

In view of this structural ambiguity we have investigated the synthesis of (2a) and (2b) by means of an intramolecular ene cyclisation [5,6] of a 1,6-diene to produce, in the key step, the pyrrolidine ring (Scheme 1). The ene reaction is a thermally induced intramolecular condensation reaction between an olefin carrying an allylic hydrogen atom (the ene) and an activated double bond (the enophile). The simplicity and applicability to a wide range of substituents has led to the reaction being

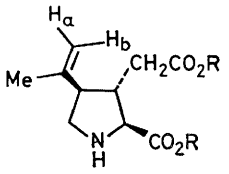


SCHEME 1 *Reagents:* i, HBr—AcOH; ii, potassium phthalimide–DMF; iii, $NH_2NH_2 \cdot H_2O$–EtOH; iv, $BrCH_2CH{=}CH\ CO_2Et$–aq Na_2CO_3; v, (a) aq Na_2CO_3, (b) TFAA–Et_2O; vi, heat; vii, NaOH–aq. EtOH; viii, HCl–MeOH

used for the synthesis of a number of complex structures.[7,8] The proposed mechanism of the reaction involves a supra-suprafacial *endo-* or *exo*-interaction strongly reminiscent of the Diels-Alder reaction and [1,5] sigmatropic shifts. The route chosen for the synthesis of racemic *cis-* and *trans*-pyrrolidine acids (2a) and (2b) is shown in Scheme 1. 1-Amino-3-methylbut-2-ene (4),[9] was alkylated with *trans*-ethyl 4-bromocrotonate to give the hydrobromide salt of *trans*-ethyl 4-[*N*-(3-methylbut-2-enyl)]aminobut-2-enoate (5) in 36% yield. This low yield was caused by the uncontrollable production of large amounts of di-alkylated material. Trifluoroacetylation of the free base of (5) gave (6) as a viscous oil. Whilst (6) could be purified by rapid distillation at low pressure (110—112 °C at 0.3 mmHg), thermolysis at 220 °C for 0.5 h gave a mixture of *cis-* and *trans*-pyrrolidine esters (7) and (8). High-performance liquid chromatography (h.l.p.c.) was used to separate the mixture into the individual isomers (7) and (8). The assignment of structures to (7) and (8) was based on the work of Kondo [10] on the proton n.m.r.



(1b)



(9a) R = H

(9b) R = Me

spectra of kainic acid and its isomers. The 2,3-*trans*-, 3,4-*cis*- arrangement of substituent groups in kainic acid (1a) and 2,3-*trans*-, 3,4-*trans*- arrangement in allokainic acid (9a) have been established by *X*-ray crystallography.[11] Kondo showed that signals due to the olefinic protons, H_a, H_b, of the dimethyl ester of kainic acid (1b) appear as two one-proton singlets at τ 5.08 and 5.15. However, in the allokainic diester (9b), the signal due to these protons was a two proton singlet at τ 5.24.

The difference in chemical shifts and signal appearance has been attributed to steric interactions between the C(3) side-chain and the olefinic protons in the 3,4-*cis*-isomer. This effect would be greatest for the H_b proton which is therefore shifted to lower field thus causing the signal to split into two separate resonances. The ^1H n.m.r. spectrum of the crude reaction mixture from the cyclisation showed the presence of both a singlet and a doublet in the region expected for the olefinic protons. After separation, the major product showed two broad singlets (τ 5.07 and 5.33) and was therefore assigned the *cis*-configuration (7). The minor product showed a two proton singlet at τ 5.07 and was correspondingly assigned the *trans*-configuration (8). Integration of the spectrum of the crude product showed that the ratio of isomers was 86 : 14 in favour of the *cis*-product.

Hydrolysis of the ester and trifluoroacetate groups of (7) and (8) gave the racemic *cis-* and *trans*-amino-acids (2a) and (2b) isolable by ion-exchange chromatography. Similar hydrolysis of the crude reaction mixture of course gave a mixture of isomeric acids but using a pure sample of (2a) as a seed it was possible to separate (2a) and (2b) by fractional crystallisation thus avoiding the difficult chromatographic separation. Esterification of (2a) and (2b) gave the respective esters (2c) and (2d). These compounds showed the expected olefinic proton n.m.r. signals, *i.e.* two broad singlets at τ 5.13 and 5.32 for (2c) and a two-proton singlet at τ 5.23 for (2d).

TABLE 1

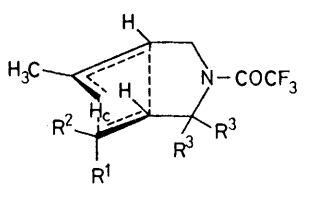
Cyclisation of the diene (6) in absence of solvent

Temp. (°C)	Time (h)	% *trans*-Isomer (8) *
100	48	Mainly starting material
120	48	Some product but mainly starting material
140	24	17
140	42	10
200	15	19
220	0.5	14

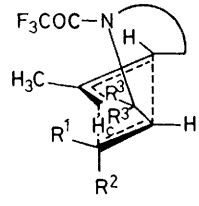
* As estimated by ^1H n.m.r. spectroscopy ($CDCl_3$).

The heavy preponderance of *cis*-isomer in the crude reaction product from the cyclisation seemed at first sight to be surprising. It was expected that the *cis*-isomer would be less thermodynamically stable than the *trans*-isomer and that the *trans*-isomer would, therefore, be the favoured product. Accordingly, this reaction was examined under a variety of conditions and the results reported in Table 1.

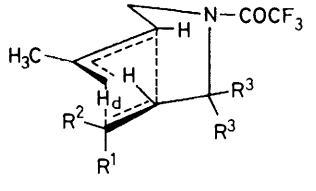
It can be seen that the ratio of products is, within experimental error, essentially independent of reaction



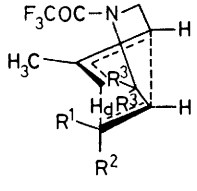
exo—(I)



endo—(II)



exo—(III)



endo—(IV)

a ; $R^1 = R^3 = H$; $R^2 = CO_2Et$

b ; $R^1 = R^3 = CO_2Et$; $R^2 = H$

c ; $R^1 = H$; $R^2 = R^3 = CO_2Et$

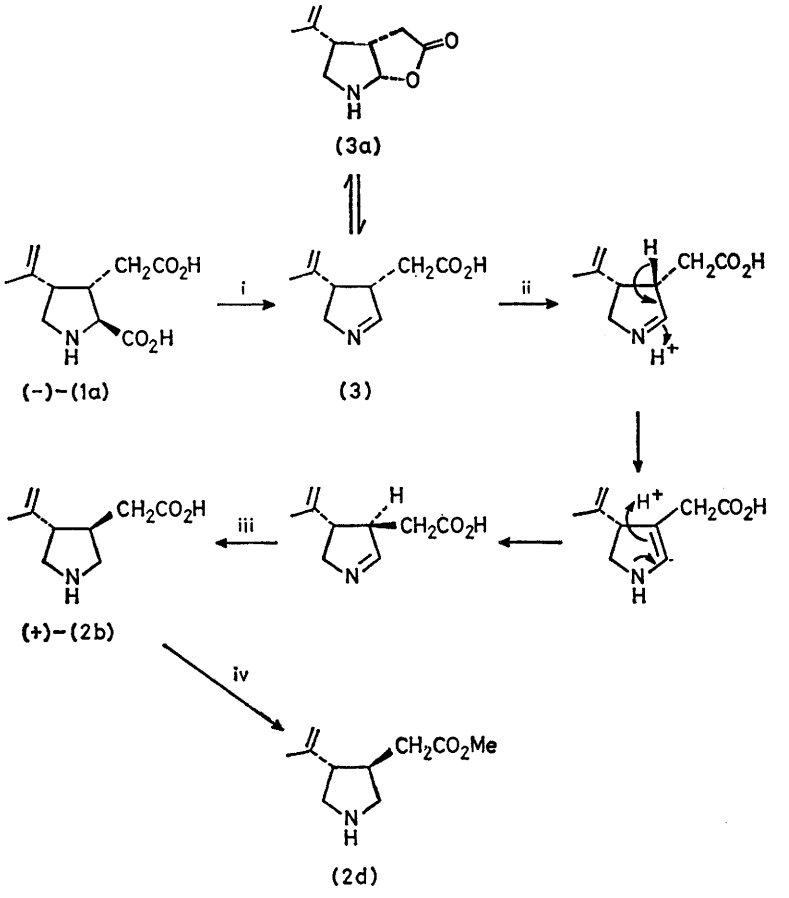
FIGURE

temperature or time. Therefore it is concluded that the reaction is kinetically controlled and that the isomer distribution is determined by the relative stabilities of the transition states leading to their production. The four

possible transition states giving maximum bond overlap are shown in the Figure. It should be noted that the allylic proton (H_c) undergoing migration in (I) and (II) is from a different methyl group than the proton (H_d) migrating in (III) and (IV). Transition states (Ia) and (IVa) which lead to the *cis*-product (7) must be favoured over the transition state (IIIa) leading to the *trans*-product (8). Models suggest that the fourth state (IIa) would be too strained to be a significant contributor to the reaction.

conditions of the reduction step to give the thermodynamically more stable product.

During the course of this study, Oppolzer and Andres [8] reported the synthesis of α-allokainic acid (9a); we now report some results which are at variance with their work. Scheme 3 shows the synthetic approach to the preparation of α-kainic and allokainic acids. Reaction of diethyl *N*-trifluoroacetylaminomalonate (10) with ethyl propiolate gave a mixture of *cis*- and *trans*-unsaturated triesters (11) and (12). These esters were again separ-

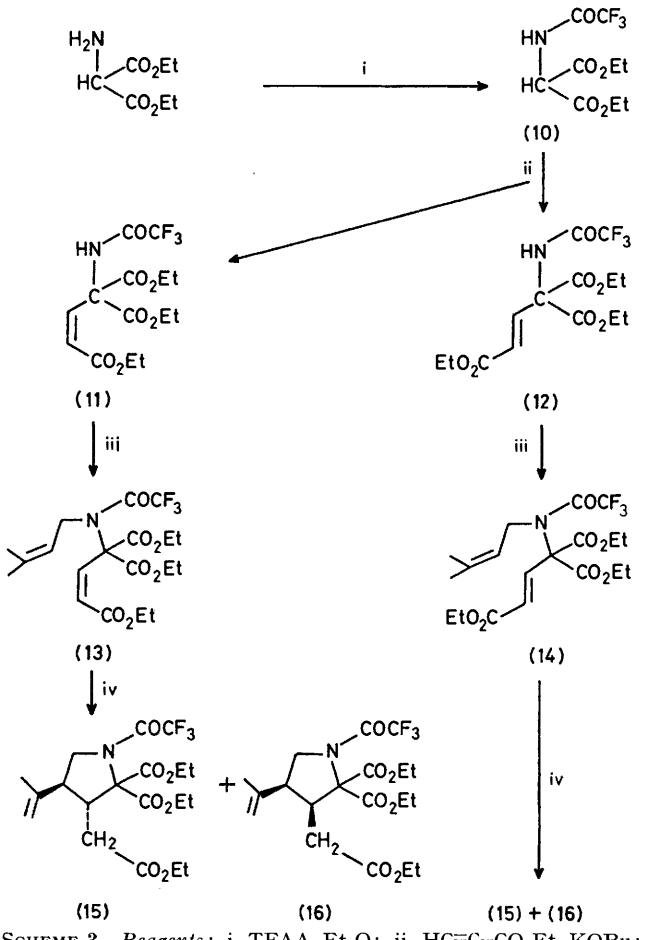


SCHEME 2 *Reagents:* i, $NaIO_4$–CH_2Cl_2–H_2O; ii, H^+; iii, $NaCNBH_3$–CH_3OH; iv, HCl–MeOH

In view of the fact that Allan was unable to identify positively the product from the decarboxylation of kainic acid, we repeated his work to compare his product with ours from the cyclisation reaction. Our product from the decarboxylation reaction (Scheme 2) was apparently identical with that of Allan but showed a broad two-proton singlet for the olefin protons at τ 5.01 indicating that it was in fact the *trans*-isomer (+)-(2b). Of course the product from the decarboxylation reaction was optically active whereas that from the cyclisation was racemic thus making their solid-state physical properties non-comparable. However the methyl ester of (+)-(2b), prepared as above gave an identical ^1H n.m.r. spectrum to (±)-(2d) with, in particular, a two-proton singlet at τ 5.23. We conclude that epimerisation of the intermediate pyrroline (3) must occur under the acidic

ated by h.p.l.c. Previous workers [8,12] had alkylated (10) with *cis*-ethyl 3-chloroacrylate to produce a single compound which on the basis of an olefinic coupling constant of 13 Hz in the ^1H n.m.r. spectrum was assigned the *trans*-configuration (12). However, by our route the more-abundant isomer, comprising 75% of the crude reaction product, showed an olefinic coupling constant of 16 Hz while the less-abundant product had a coupling constant of 12 Hz. We therefore conclude that the product actually isolated by previous workers had the *cis*-geometry (11). Alkylation of (11) and (12) with 1-bromo-3-methylbut-2-ene [13] proceeded smoothly to give (13), a low-melting crystalline solid and (14) a colourless viscous oil. Thermolysis of (13) and (14) in toluene at 80 °C or neat at 170 °C induced cyclisation to mixtures of *trans*- and *cis*-ethyl 2,2-diethoxycarbonyl-4-isopro-

penyl-1-trifluoroacetylpyrrolidin-3-ylacetates (15),(16). The ^1H n.m.r. spectrum of the crude product showed in the olefinic region three peaks at τ 4.98, 5.05, and 5.30. By analogy with the previous series the peaks at τ 4.98 and 5.30 were assigned to the *cis*-isomer (16) and that at τ 5.05 to the *trans*-isomer (15). The *cis*/*trans* ratios obtained separately from (13) and (14) under a variety of



SCHEME 3 *Reagents:* i, TFAA–Et_2O; ii, HC≡C–CO_2Et–KOBu; iii, $Me_2C{=}CHCH_2Br$–NaH–HMPA; iv, heat

conditions were estimated by integration of the olefinic signals and are shown in Table 2.

From Table 2 it can be seen that the reaction proceeds significantly more rapidly than in the decarboxy-series and that, whilst the amount of *cis*-pyrrolidine (16) produced from either (13) or (14) is different, it is essentially independent of the reaction temperature and time. Further investigations of the reactions in sealed n.m.r. tubes at 80 °C in [$^2H_8$]toluene solution established the following. (*a*) No initial *cis*/*trans* isomerisation [(13) ⇌ (14)] of the starting diene took place. (*b*) The cyclisation proceeded at about the same rate for both dienes and was virtually complete after 8 h. (*c*) An almost 1 : 1 mixture of *cis*- and *trans*-pyrrolidines (16),(15) was produced from (14) and this ratio did not vary throughout the reaction; *i.e.* there was no interconversion of (15) and (16). The *cis*-diene (13) gave a different mix of isomers but again no interconversion of (15) and (16) was seen.

TABLE 2

Cyclisation of the dienes (13) and (14) separately

Temperature (°C)	Solvent	Time (h)	% *cis*-Pyrrolidine (16) from (14)	% *cis*-Pyrrolidine (16) from (13)
80	Toluene	18	53	25
80	[$^2H_8$]Toluene *	24	50 *	27 *
170	Neat	0.5	52	32

* Reaction run in [$^2H_8$]toluene in sealed n.m.r. tube; in all other cases spectra were determined in $CDCl_3$.

It was therefore concluded that in this case also the reaction is kinetically and not thermodynamically controlled. The Figure shows that the *cis*-pyrrolidine (16) arises from the *trans*-diene (14) *via* transition states (Ic) and (IVc) whilst the *trans*-isomer arises from (IIc) and (IIIc). Molecular models indicate that (IIc) is highly strained and unfavourable thus rendering (IIIc) as the more probable transition state leading to (15). For the cyclisation of the *cis*-diene (13) the *endo*-transition state (IIb) is unlikely due to strain and dominance of the *exo*-transition state (IIIb) leading to the *trans*-pyrrolidine (15) is indicated by the product distribution.

The separation of the triesters (15) and (16) even by h.p.l.c. proved to be very difficult. The *trans*-compound (15) could be obtained free, by n.m.r. analysis, of the *cis*-pyrrolidine only after repeated chromatography whilst the *cis*-ester (16) was only isolated 90% pure. However, hydrolysis of the crude cyclisation product (15) + (16) by the method of Oppolzer,[8] gave a solid from which pure (±)-α-allokainic acid * could be obtained by recrystallisation. On the other hand, it proved to be impossible to isolate kainic acid itself by hydrolysis of either cyclisation reaction product and thus this sequence is not a viable route to this interesting amino-acid.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded with a Pye-Unicam SP 1 000 spectrophotometer. ^1H N.m.r. spectra were determined with a Perkin-Elmer R12A spectrophotometer at 60 MHz with tetramethylsilane as internal standard; (all NH peaks were removed by addition of D_2O). Mass spectra were obtained at 70 eV. Elemental analyses were carried out by C.H.N. Analysis Ltd., Leicester. Preparative h.p.l.c. was performed on a Jobin Yvon Chromatospac Prep 100. All thermolysis reactions were carried out in glassware that had been rinsed with 1,1,1,3,3,3-hexamethyldisilazane and dried. Light petroleum refers to the fraction of b.p. 40—60 °C unless otherwise specified. T.l.c. was carried out on Merck Kieselgel 60 F_{254} plates (0.25 mm) and silica gel for chromatography refers to Merck Kieselgel 60 (70—230 mesh) unless otherwise specified. All organic extracts were dried over anhydrous magnesium sulphate. Evaporations were carried out (<50 °C) under reduced pressure using a rotary evaporator.

trans-*Ethyl* 4-(3-*Methylbut-2-enylamino*)*but-2-enoate Hydrobromide* (5).—A mixture of 1-amino-3-methylbut-2-ene [9] (8.5 g, 0.1 mol) and *trans*-ethyl 4-bromocrotonate (19.3 g, 0.1 mol) in dichloromethane (600 ml) and 10% (w/v) sodium carbonate solution (150 ml) was stirred vigor-

* Shown by m.p. and i.r. spectrum to be identical to a sample kindly supplied by Professor W. Oppolzer for which we express our grateful thanks.

ously at room temperature for 1 h after which the organic layer was separated. The aqueous layer was extracted once with dichloromethane (100 ml) and the combined organic extract dried and evaporated to dryness. The residual oil was triturated with light petroleum, giving (5) (10.2 g, 36%) as a white crystalline solid, m.p. 151—153 °C (from ethyl acetate) (Found: C, 47.5; H, 7.1; Br, 28.8; N, 5.0. $C_{11}H_{20}BrNO_2$ requires C, 47.5; H, 7.25; Br, 28.7; N, 5.0%); $\nu_{max.}$ (KBr) 2 930, 2 780, 1 727, 1 665, 1 205, and 970 cm^{-1}; τ ($CDCl_3$) 1.80br (1 H, s, NH), 2.94 (1 H, dt, $J_{3,2}$ 16 Hz, $J_{3,4a} = J_{3,4b}$ 7 Hz, 3-CH), 3.81 (1 H, d, $J_{2,3}$ 16 Hz, 2-CH), 4.55br (1 H, t, $J_{2,1a} = J_{2,1b}$ 8 Hz, side-chain 2-CH), 5.83 (2 H, q, J 7 Hz, ethyl CH_2), 6.22 (2 H, d, $J_{4a,3} = J_{4b,3}$ 7 Hz, 4-CH_2), 6.35 (2 H, d, $J_{1a,2} = J_{1b,2}$ 8 Hz, side-chain 1-CH_2), 8.21 and 8.27 (2 × 3 H, 2 × s, 2 × side-chain CH_3), and 8.73 (3 H,t, J 7 Hz, ethyl CH_3); *m/e* 197 (M^+).

trans-*Ethyl* 4-[(3-*Methylbut*-2-*enyl*)*trifluoroacetylamino*]-*but*-2-*enoate* (6).—The hydrobromide salt (5) (12.5 g) was dissolved in water (75 ml) and the solution made basic by addition of solid sodium carbonate (5 g). The free base of the diene (5) was extracted with ether (2 × 150 ml) and the ethereal extract dried and evaporated to dryness. The residual oil was dissolved in dry ether (50 ml) and the solution cooled in an ice-bath. Trifluoroacetic anhydride (10 ml) was added dropwise to the stirred solution which was stirred at ice-bath temperature for 10 min before being evaporated to dryness. The residue was dissolved in ether (150 ml) and the solution washed with water (2 × 50 ml), 5% cold sodium hydrogen carbonate solution (2 × 50 ml), and water (50 ml), and then dried and evaporated. The residue was distilled under reduced pressure to give the diene (6) (7.5 g, 57%) as a colourless liquid, b.p. 110—112 °C at 0.3 mmHg (Found: C, 53.2; H, 6.25; F, 19.4; N, 4.7. $C_{13}H_{18}F_3NO_3$ requires C, 53.2; H, 6.2; F, 19.4; N, 4.8%); $\nu_{max.}$ (film) 2 980, 1 727, 1 700, 1 680, and 1 150 cm^{-1}; τ ($CDCl_3$) 3.15 (1 H, dt, $J_{3,2}$ 15 Hz, $J_{3,4a} = J_{3,4b}$ 5 Hz, 3-CH), 4.12br (1 H, d, $J_{2,3}$ 15 Hz, 2-CH), 4.87br (1 H, t, $J_{2,1a} = J_{2,1b}$ 8 Hz, side-chain 2-CH), 5.80 (2 H, q, J 7 Hz, ethyl CH_2), 5.90 (2 H, d, $J_{4,3a} = J_{4b,3}$ 5 Hz, 4-CH_2), 6.00 (2 H, d, $J_{1a,2} = J_{1b,2}$ 8 Hz, side-chain 1-CH_2), 8.24 and 8.33 (2 × 3 H, 2 × s, 2 × side-chain CH_3), and 8.72 (3 H, t, J 7 Hz, ethyl CH_3); *m/e* 293 (M^+).

Thermal Cyclisation of the trans-*Diene* (6) *to the* (±)-cis *and* trans-*Ethyl* 4-*Isopropenyl*-1-*trifluoroacetylpyrrolidin*-3-*ylacetates* (7) *and* (8) *at* 220 °C.—The diene (6) (2.1 g) was heated at 220 °C under an atmosphere of dry nitrogen for 30 min when t.l.c. indicated absence of starting material. The ^1H n.m.r. ($CDCl_3$) spectrum of the cooled crude mixture gave the (7)/(8) isomer ratio as 86 : 14. Distillation under reduced pressure gave the product as a colourless liquid (1.7 g, 81%), b.p. 122—124 °C at 0.6 mmHg with an unaltered isomer ratio.

The mixture of isomers (7) and (8) was separated by h.p.l.c. on Kieselgel 60 (230—400 mesh) (1.8 kg) using 10% ethyl acetate–light petroleum (b.p. 64—67 °C) as eluant. Evaporation of fractions containing the less-polar component gave (±)-*trans*-ethyl 4-isopropenyl-1-trifluoroacetylpyrrolidin-3-ylacetate (8) as a colourless oil (Found: C, 53.3; H, 6.3; F, 19.45; N, 4.7. $C_{13}H_{18}F_3NO_3$ requires C, 53.2; H, 6.2; F, 19.4; N, 4.8%); $\nu_{max.}$ (film) 2 980, 1 735, 1 690, 1 650, 1 460, 1 140, and 750 cm^{-1}; τ($CDCl_3$) 5.07br (2 H, s, =CH_2), 5.87 (2 H, q, J 7 Hz, ethyl −CH_2), 5.85—8.10 (8 H, m, CH_2CO_2Et and pyrrolidinyl), 8.27 (3 H, s, CH_3), and 8.76 (3 H, t, J 7 Hz, ethyl CH_3); *m/e* 293 (M^+).

Evaporation of the fractions containing the more-polar component gave (±)-*cis*-ethyl 4-isopropenyl-1-trifluoroacetylpyrrolidin-3-ylacetate (7) as a colourless oil (Found: C, 53.3; H, 6.3; F, 19.2; N, 4.7. $C_{13}H_{18}F_3NO_3$ requires C, 53.2; H, 6.2; F, 19.4; N, 4.8%); $\nu_{max.}$ (film) 2 960, 1 735, 1 695, 1 650, 1 460, 1 250, and 1 150 cm^{-1}; τ($CDCl_3$) 5.07 and 5.33br (2 × 1 H, 2 × s, =CH_2), 5.90 (2 H, q, J 7 Hz, ethyl −CH_2), 6.50—8.05 (8 H, m, CH_2CO_2Et and pyrrolidinyl), 8.25 (3 H, s, CH_3), and 8.77 (3 H, t, J 7 Hz, ethyl CH_3); *m/e* 293 (M^+).

(±)-cis-4-*Isopropenylpyrrolidin*-3-*ylacetic Acid* (2a).—The trifluoroacetylated ester (7) (0.115 g) was dissolved in ethanol (5 ml) and 1M-sodium hydroxide (1.25 ml) was added to the mixture; this was then heated on a water-bath for 1 h. The cooled mixture was evaporated to dryness and the residue, dissolved in water (1 ml), deposited on a 'Dowex' 50 W-X8 (H^+, 100—200 mesh, 10 g) ion-exchange column. Elution with water was followed by 1M-NH_4OH and evaporation of the appropriate fractions gave the amino-acid (2a) (0.039 g, 59%) as a white crystalline solid, m.p. 215—221 °C (decomp.) (from ethanol–water) (Found: C, 63.7; H, 8.9; N, 8.25. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%); $\nu_{max.}$ (KBr) 3 440, 3 200—2 000br, 1 650, 1 630, 1 380, and 890 cm^{-1}; τ (D_2O) 5.00br (1 H, s, =CH) (the second olefinic proton is masked by the H_2O peak), 6.30—8.10 (8 H, m, CH_2CO_2H and pyrrolidinyl), and 8.22 (3 H, s, CH_3); *m/e* 169.109 7 ± 0.000 3 (M^+) $C_9H_{15}NO_2$ requires 169.110 3.

(±)-cis-*Methyl* 4-*Isopropenylpyrrolidin*-3-*ylacetate* (2c).—The amino-acid (2a) (0.05 g) was dissolved in methanol saturated with dry hydrogen chloride gas (1 ml) at 0 °C and the solution stirred at first at that temperature for 1 h and then at room temperature for 16 h. The mixture was then evaporated to dryness, the residue taken up in water (1 ml), and the product extracted with ether (3 × 10 ml). The ethereal extract was dried and evaporated to dryness giving the ester (2c) (0.04 g, 74%) as a colourless oil, $\nu_{max.}$ (film) 2 940, 1 740, 1 645, 1 440, 1 065, and 890 cm^{-1}; τ ($CDCl_3$) 5.13 and 5.32br (2 × 1 H, 2 × s, =CH_2), 6.37 (3 H, s, CO_2CH_3), 6.40—8.00 (8 H, m, $-CH_2CO_2Me$ and pyrrolidinyl), 6.54br (1 H, s, NH), and 8.24 (3 H, s, CH_3).

(±)-trans-4-*Isopropenylpyrrolidin*-3-*ylacetic Acid* (2b).—The trifluoroacetylated ester (8) (0.12 g) was hydrolysed in a manner similar to that for the *cis*-isomer (7). Work-up on a 'Dowex' 50 W-X8 (H^+, 100—200 mesh, 10 g) ion-exchange column, using 1M NH_4OH as eluant gave the amino-acid (2b) (0.037 g, 53%) as a white crystalline solid, m.p. 206—211 °C (decomp.) (from ethanol) (Found: C, 63.6; H, 8.8; N, 8.2. $C_9H_{15}NO_2$ requires C, 63.9; H, 8.9; N, 8.3%); $\nu_{max.}$ (KBr) 3 420, 2 950, 3 150—2 000br, 1 655, 1 650, 1 530, 1 395, 885, and 740 cm^{-1}; τ(D_2O) 5.00 (2 H, s, =CH_2), 6.20—8.10 (8 H, m, $-CH_2CO_2H$ and pyrrolidinyl), and 8.25 (3 H, s, CH_3); *m/e* 169.109 7 ± 0.000 3 (M^+). $C_9H_{15}NO_2$ requires 169.110 3.

(±)-trans-*Methyl* 4-*Isopropenylpyrrolidin*-3-*ylacetate* (2d).—The amino-acid (2b) (0.03 g) was esterified in a manner similar to that for the *cis*-isomer (2a). The methyl ester (2d) (0.02 g, 62%) was obtained as a colourless oil, $\nu_{max.}$ (film) 3 400, 2 940, 1 737, 1 640, 1 440, and 890 cm^{-1}; τ($CDCl_3$) 5.23 (2 H, s, =CH_2), 6.38 (3 H, s, CO_2CH_3), 6.50—8.00 (8 H, m, CH_2CO_2Me and pyrrolidinyl), 7.60 (1 H, s, NH), and 8.29 (3 H, s, CH_3).

Oxidative Decarboxylation of L-α-*Kainic acid*.—L-α-Kainic acid (1.065 g, 5 mmol) was added to a solution of sodium metaperiodate (3.21 g 15 mmol) in water (32.5 ml) in a separatory funnel followed by dichloromethane (175 ml). After the mixture had been shaken for 10 min the organic

layer was separated and the aqueous layer extracted in a similar manner with further dichloromethane (2 × 175 ml). The combined dichloromethane extracts were dried and evaporated to dryness, giving the imino-acid (3) (0.66 g, 79%) as a white glassy solid. T.l.c. behaviour and i.r. spectra (KBr and $CHCl_3$ solution) indicate the presence of two interconvertible structures (3) and (3a); $\nu_{max.}$ (KBr) 3 400, 2 900, 3 250—2 350br, 1 770, 1 710, 1 640, and 890 cm^{-1}.

Reduction of the Pyrroline (3) *to Optically Active* (+)-trans-4-*Isopropenylpyrrolidin*-3-*ylacetic Acid* (2b).—To a stirred solution of the pyrroline (2) (0.6 g, 3.6 mmol) in methanol (50 ml) at room temperature was added, in small portions, sodium cyanoborohydride (0.226 g, 3.6 mmol). The pH of the reaction mixture was kept at 4.0 by dropwise addition of glacial acetic acid. The mixture was stirred for 30 min and then evaporated to dryness. The residual oil, dissolved in water (2 ml) was deposited on a ' Dowex ' 50W-X8 (H^+ form, 100—200 mesh, 40 g) ion-exchange column. Elution with water until neutral was followed by 1M-NH_4OH and evaporation of the appropriate fractions gave a colourless oil. Trituration with ethanol gave (+)-(2b) (0.34 g, 56%) as a white crystalline solid, m.p. 225—232 °C (decomp.) [lit.,[4] 227—234 °C (decomp.)] (from ethanol) (Found: C, 63.8; H, 8.7; N, 8.3. Calculated for $C_9H_{15}NO_2$, C, 63.9; H, 8.9; N, 8.3%); $[\alpha]_D^{20}$ +39.5° (*c* 0.5, H_2O) (lit.,[4] $[\alpha]_D^{19}$ +39° (*c* 1, H_2O); $\nu_{max.}$ (KBr) 3 440, 2 960, 3 200—2 000br, 1 655, 1 650, 1 550, 1 400, 905, and 655 cm^{-1}; τ(D_2O) 5.01 (2 H, s, $=CH_2$), 6.20—8.10 (8 H, m, CH_2CO_2H and pyrrolidinyl), and 8.26 (3 H, s, CH_3); *m/e* 169 (M^+).

Optically Active trans-*Methyl* 4-*Isopropenylpyrrolidin*-3-*ylacetate* (2d).—The methyl ester of the amino-acid (+)-(2b) (0.05 g) was prepared in a manner similar to that used for the (±)-*cis*-isomer (2c). The optically active ester (2d) (0.028 g, 50%) was obtained as a colourless oil. Its i.r. (film) and ^1H n.m.r. ($CDCl_3$) spectra were identical to those of racemic (2d).

Diethyl Trifluoroacetylaminomalonate (10).—Diethyl aminomalonate hydrochloride (15.87 g, 75 mmol) was dissolved in water (30 ml) and solid sodium hydrogen carbonate (6.72 g, 80 mmol) was added to it; the free base was then extracted with ether (3 × 100 ml). The ethereal extract was dried and evaporated to dryness. The residual oil was dissolved in dry ether (50 ml) and the solution stirred and cooled in an ice-bath whilst trifluoroacetic anhydride (15.7 g, 75 mmol) was added dropwise. After being stirred at ice-bath temperature for 10 min the solution was evaporated, the residue dissolved in ether (100 ml), and the ethereal solution washed successively with water (2 × 100 ml), cold 5% $NaHCO_3$ solution (2 × 100 ml), and water (100 ml); the solution was then dried and finally evaporated to give (10) (17.8 g, 87%) as colourless needles, m.p. 47—49 °C (from light petroleum–ether) (Found: C, 39.8; H, 4.4; F, 20.8; N, 5.25. $C_9H_{12}F_3NO_5$ requires C, 39.9; H, 4.5; F, 21.0; N, 5.1%); $\nu_{max.}$ (KBr) 3 300, 1 760, 1 735, 1 710, 1 545, 1 160, and 1 020 cm^{-1}; τ($CDCl_3$) 1.60br (1 H, s, NH), 4.85 (1 H, d, *J* 7 Hz, CH, collapses to a singlet τ 4.85 on D_2O shake), 5.70 (4 H, q, *J* 7 Hz, 2 × ethyl CH_2), and 8.70 (6 H, t, *J* 7 Hz, 2 × ethyl CH_3); *m/e* 271 (M^+).

cis- *and* trans-*Ethyl* 4,4-*Diethoxycarbonyl*-4-*trifluoroacetamidobut*-2-*enoates* (11) *and* (12).—Potassium (2.34 g, 0.06 g-atom) was dissolved in freshly distilled refluxing t-butyl alcohol (250 ml) by vigorous stirring under a stream of dry nitrogen and to the cooled mixture was added dropwise diethyl trifluoroacetylaminomalonate (10) (16.26 g, 60 mmol) in t-butyl alcohol (10 ml) followed by ethyl propiolate (5.88 g, 60 mmol). After being stirred at room temperature for 16 h the mixture was acidified with glacial acetic acid and evaporated. Water (100 ml) was added to the residue and the product extracted with ether (3 × 100 ml). Evaporation of the ethereal extract gave a mixture of *cis*- and *trans*-ethyl 4,4-diethoxycarbonyl-4-trifluoroacetamidobut-2-enoates (11) and (12), *cis*/*trans* isomer ratio 1 : 3 (from ^1H n.m.r. spectrum). The mixture was separated by h.p.l.c. on Kieselgel 60 (230—400 mesh) (1.5 kg) using light petroleum (b.p. 67—70 °C)–ethyl acetate (9 : 1) as eluant. The fractions containing the less-polar component on evaporation gave the *cis*-isomer (11) (4.7 g, 21%) as a colourless liquid, b.p. 109—110 °C at 0.2 mmHg (Found: C, 45.6; H, 4.9; F, 15.6; N, 3.7. $C_{14}H_{18}F_3NO_7$ requires C, 45.5; H, 4.9; F, 15.4; N, 3.8%); $\nu_{max.}$ (film) 3 390, 2 980, 1 760, 1 740, 1 715, 1 645, 1 525, and 1 220 cm^{-1}; τ($CDCl_3$) 1.77 (1 H, s, NH), 2.78 (1 H, d, $J_{3,2}$ 12 Hz, 3-CH), 3.98 (1 H, d, $J_{2,3}$ 12 Hz, 2-CH), 5.74 and 5.85 (6 H, 3 × q, *J* 7 Hz, 3 × CH_2), and 8.78 (9 H, t, *J* 7 Hz, 3 × CH_3); *m/e* 369 (M^+).

Evaporation of fractions containing the more-polar component gave the *trans*-isomer (12) (12.0 g, 54%) as a colourless liquid, b.p. 130—131 °C 0.2 mmHg (Found: C, 45.5; H, 4.95; F, 15.3; N, 3.7. $C_{14}H_{18}F_3NO_7$ requires C, 45.5; H, 4.9; F, 15.4; N, 3.8%); $\nu_{max.}$ (film) 3 380, 2 980, 1 755, 1 730, 1 715, 1 660, 1 520, and 1 270 cm^{-1}; τ($CDCl_3$) 2.12br (1 H, s, NH), 2.55 (1 H, d, $J_{3,2}$ 16 Hz, 3-CH), 4.08 (1 H, d, $J_{2,3}$ 16 Hz, 2-CH), 5.68 and 5.80 (6 H, 3 × q, *J* 7 Hz, 3 × CH_2), and 8.73 (9 H, t, *J* 7 Hz, 3 × CH_3); *m/e* 369 (M^+).

cis-*Ethyl* 4,4-*Diethoxycarbonyl*-4-[(3-*methylbut*-2-*enyl*)*trifluoroacetylamino*]*but*-2-*enoate* (13).—The triester (11) (3.7 g, 10 mmol) was dissolved in freshly distilled HMPA (20 ml) and sodium hydride (0.3 g, 80% dispersion in oil, 10 mmol NaH) was added in portions. The mixture was stirred at room temperature for 15 min and then 1-bromo-3-methylbut-2-ene [13] (1.94 g, 13 mmol) was added dropwise. After being stirred for 24 h the mixture was poured into water (200 ml) and the product extracted with ether. Evaporation of the ethereal extract gave a yellow oil which was purified on silica gel (250 g) using light petroleum (b.p. 60—80 °C)–ethyl acetate (9 : 1) as eluant. Evaporation of solvent gave an oil which crystallised with time in the cold. The white crystals of *cis*-diene (13) (1.1 g, 25%) were washed with light petroleum and dried, m.p. 48—49 °C (Found: C, 51.9; H, 5.8; F, 13.0; N, 3.2. $C_{19}H_{26}F_3NO_7$ requires C, 52.2; H, 6.0; F, 13.0; N, 3.2%); $\nu_{max.}$ (KBr) 2 990, 1 760, 1 710, 1 705, 1 700, 1 680, 1 300, 1 145, and 1 050 cm^{-1}; τ($CDCl_3$) 3.66 (1 H, d, $J_{3,2}$ 12 Hz, 3-CH), 3.94 (1 H, d, $J_{2,3}$ 12 Hz, 2-CH), 4.75br (1 H, t, side-chain 2-CH), 5.55—6.05 (8 H, m, 3 × ethyl CH_2 and side-chain 1-CH_2), 8.32 and 8.49 (2 × 3 H, 2 × s, 2 × side-chain CH_3), and 8.74 and 8.75 (9 H, t, *J* 7 Hz, 3 × ethyl CH_3); *m/e* 437 (M^+).

trans-*Ethyl* 4,4-*Diethoxycarbonyl*-4-[(3-*methylbut*-2-*enyl*)-*trifluoroacetylamino*]*but*-2-*enoate* (14).—This compound was prepared in a similar manner to the *cis*-diene (13) using *trans*-ethyl 4,4-diethoxycarbonyl-4-trifluoroacetamidobut-2-enoate (12) (5.54 g, 15 mmol), sodium hydride (0.45 g, 80% dispersion in oil, 15 mmol NaH), and 1-bromo-3-methylbut-2-ene [13] (2.91 g, 19.5 mmol) in HMPA (30 ml). Work-up gave a yellow oil which was purified on silica gel (300 g) using light petroleum (b.p. 60—80 °C)–ethyl acetate (4 : 1) as eluant giving the *trans*-diene (14) (4.8 g, 73%) as a colourless oil, attempted distillation of which under reduced pressure resulted in rapid cyclisation (Found: C,

52.3; H, 6.0; F, 12.8; N, 3.1. $C_{19}H_{26}F_3NO_7$ requires C, 52.2; H, 6.0; F, 13.0; N, 3.2%); $\nu_{max.}$ (film) 2 980, 1 760, 1 750, 1 730, 1 710, 1 680, 1 215, and 1 050 cm^{-1}; $\tau(CDCl_3)$ 2.85 (1 H, d, $J_{3,2}$ 16 Hz, 3-CH), 3.81 (1 H, d, $J_{2,3}$ 16 Hz, 2-CH), 4.82br (1 H, t, $J_{2,1a} = J_{2,1b}$ 7 Hz, side-chain 2-CH), 5.55—6.00 (8 H, m, 3 × ethyl CH_2 and side-chain 1-CH_2), 8.30 and 8.44 (2 × 3 H, 2 × s, 2 × side-chain CH_3), and 8.72 (9 H, t, J 7 Hz, 3 × ethyl CH_3); *m/e* 437 (M^+).

Thermal Cyclisation of the cis- *and* trans-*Dienes* (13) *and* (14) *to give* (±)-trans- *and* cis-*Ethyl* 2,2-*Diethoxycarbonyl*-4-*isopropenyl*-1-*trifluoroacetylpyrrolidin*-3-*ylacetates* (15) *and* (16).—(a) *Without solvent.* The *trans*-diene (14) (4 g) was heated neat at 170 °C under an atmosphere of dry nitrogen for 30 min; ^1H n.m.r. spectroscopy ($CDCl_3$) on the cooled crude mixture gave the ratio (15) : (16) as 48 : 52. Distillation under reduced pressure gave the product as a colourless viscous oil (2.8 g, 70%), b.p. 148—156 °C at 0.05 mmHg with unaltered isomer ratio (Found: C, 52.2; H, 6.0; F, 13.0; N, 3.2. $C_{19}H_{26}F_3NO_7$ requires C, 52.2; H, 6.0; F, 13.0; N, 3.2%); *m/e* 437 (M^+).

The mixture (0.03 g) was separated by repeated h.p.l.c. on Merck LiChrosorb Si 60 (10 g) using n-pentane–ethyl acetate (9 : 1) as eluant. Evaporation of fractions containing the less-polar component gave the *trans*-isomer (15) as a colourless oil, $\nu_{max.}$ (film) 2 980, 2 920, 1 750, 1 740, 1 730, 1 705, 1 640, 1 220, and 1 050 cm^{-1}; $\tau(CDCl_3)$ 5.05 (2 H, s, $=CH_2$), 5.50—6.30 (6 H, m, 3 × ethyl CH_2), 6.30—8.00 (6 H, m, pyrrolidinyl), 8.28 (3 H, s, CH_3), 8.50—8.90 (9 H, m, 3 × ethyl CH_3). Evaporation of fractions containing the more-polar component gave the *cis*-isomer (16) as a colourless oil, $\nu_{max.}$ (film) 2 980, 1 750, 1 740, 1 730, 1 710, 1 655, and 1 215 cm^{-1}; $\tau(CDCl_3)$ 4.98 and 5.30 (2 × 1 H, 2 × s, $=CH_2$), 5.45—6.15 (6 H, m, 3 × ethyl CH_2), 6.15—8.00 (6 H, m, pyrrolidinyl), 8.27 (3 H, s, CH_3), and 8.50—8.90 (9 H, m, 3 × ethyl CH_3). The *cis*-diene (13) (0.3 g) was cyclised by an identical method giving a mixture of (15) and (16) (68 : 32). Distillation under reduced pressure gave a colourless viscous oil (0.2 g, 66%), b.p. 150—156 °C at 0.05 mmHg with an unaltered isomer ratio.

(b) *In toluene.* The dienes (13) and (14) were cyclised separately by heating 5% solutions in dry toluene at 80 °C under an atmosphere of dry nitrogen for 18 h. The cooled solutions were evaporated giving colourless viscous oils as product.

(c) *In* [$^2H_8$]*toluene* (*sealed tube*). The dienes (13) and (14) (0.05 g) were dissolved separately in [$^2H_8$]toluene (1 ml) and the solutions heated at 80 °C in a sealed n.m.r. tube. The cyclisation was followed by the change in the ^1H n.m.r. spectrum after 1, 2, 4, 6, 8 and 24 h duration.

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