The Synthesis of a Cyclopropane Amino Acid, *trans*-α-(Carboxycyclopropyl)glycine, found in Ackee Seed

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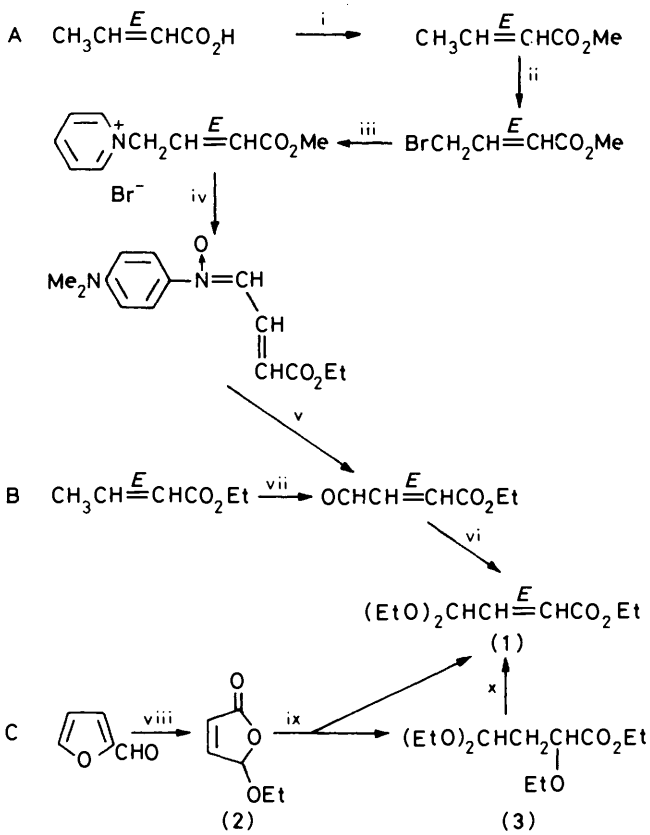
trans-α-(Carboxycyclopropyl)glycine, a constituent of ackee seed (*Blighia sapida*), has been synthesized *via* the key intermediate ethyl (*E*)-4,4-diethoxybut-2-enoate

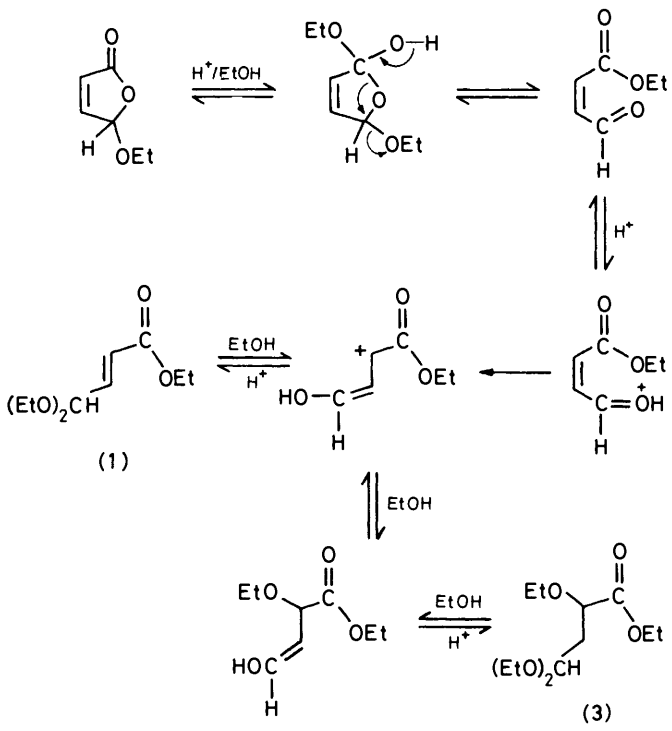
A number of naturally occurring amino acids, which are found in plants, contain the cyclopropyl moiety and two of these are found in ackee (akee) seed (*Blighia sapida*). The first to be investigated [1] was the strongly hypoglycemic 3-(methylenecyclopropyl)alanine (hypoglycin A) which was extracted from the seed (*ca.* 0.15%) and also from the unripe arillus. Hypoglycin A was synthesized in our laboratories and the absolute configuration determined.[2] A second amino acid, *trans*-α-(carboxycyclopropyl)glycine (11) (0.043%), was later isolated and characterised by Fowden [3] and the present work describes a convenient synthesis of this amino acid from ethyl (*E*)-4,4-diethoxybut-2-enoate (1). Three possible routes, A, B, and C, to this key intermediate are outlined in Scheme 1.

Initial attempts to synthesize ester (1) were concentrated on route A starting from (*E*)-but-2-enoic acid, and proceeding *via* formation of the methyl ester, allylic bromination, conversion into the pyridinium salt and then to ethyl (*E*)-3-formylpropenoate using modified literature methods [4,5] This route gave low and variable yields and a mixture of methyl and ethyl esters. An alternative synthesis of ethyl (*E*)-3-formylpropenoate (route B) utilised the allylic oxidation of ethyl (*E*)-but-2-enoate with selenium dioxide in dry dioxane [6] which proved tedious since the selenium formed during the oxidation tended to dissolve in the reaction mixture and had to be removed by prolonged shaking with mercury. The yield (24%) was somewhat improved over that reported [6] (15%). However, ethyl (*E*)-3-formylpropenoate synthesized by either route A or B could be converted into ethyl (*E*)-4,4-diethoxy-2-enoate (1) in excellent yield with 'super dry' ethanol and anhydrous calcium chloride.

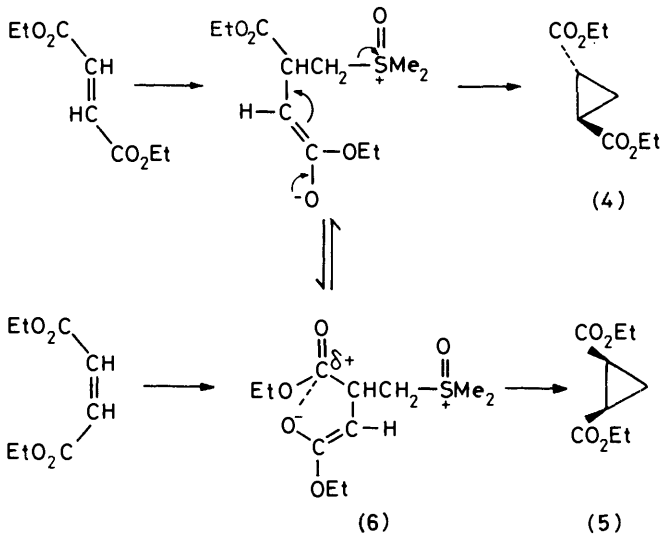
A more direct and higher yielding route C to the ester (1) is based on (*Z*)-3-formylacrylic acid pseudo-ester (2) [7] which was obtained by the photo-oxidation of 2-furaldehyde using oxygen and a high-pressure mercury vapour lamp for 24 h, in 68% yield. In our hands a medium-pressure lamp, under similar conditions, gave compound (2) (60%) after ten days. Using an ordinary fluorescent tube and monitoring the reaction by u.v. and i.r. spectroscopy, compound (2) (44%) was obtained in eight days, giving a convenient route to this compound. The conversion of the pseudo-ester (2) into ethyl (*E*)-4,4-diethoxybut-2-enoate (1) by sulphuric acid–ethanol as reported by



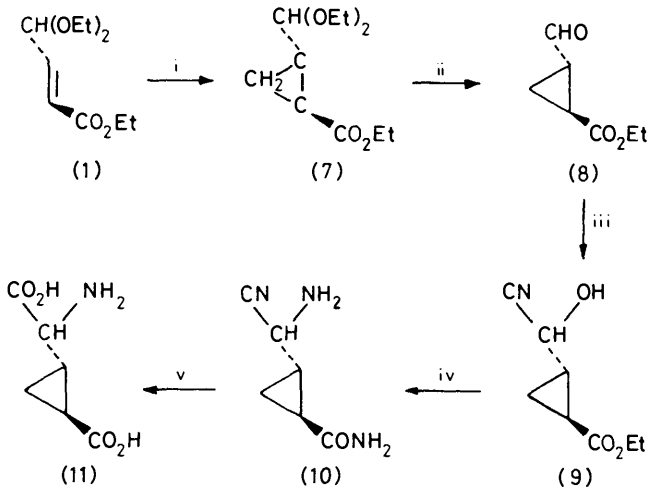
Scheme 1. *Reagents:* i, MeOH–H_2SO_4; ii, *N*-bromosuccinimide; iii, pyridine–benzene; iv, *N*,*N*-dimethyl-*p*-nitrosoaniline–EtOH; v, H_2SO_4; vi, $CaCl_2$–EtOH; vii, SeO_2–dioxane; viii, *hν*, eosin–EtOH, oxygen; ix, H_2SO_4–EtOH; x, sodium hydrogen sulphite



Scheme 2.



Scheme 3.



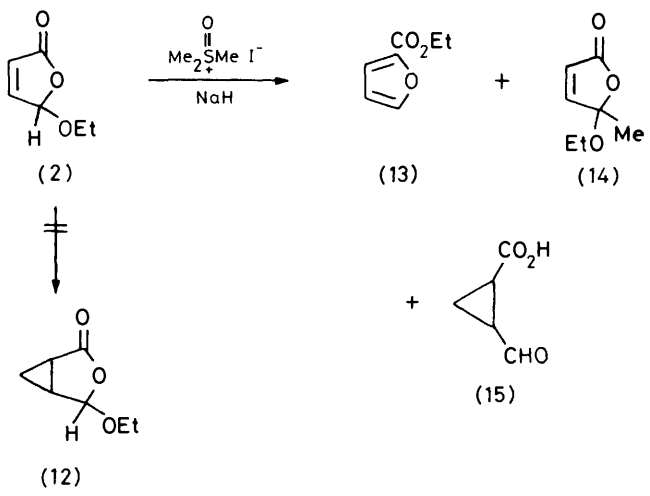
Scheme 4. *Reagents:* i, trimethylsulphoxonium iodide–NaH–DMSO; ii, H_2SO_4–H_2O; iii, HCl–KCN; iv, NH_4OH–NH_4Cl; v, HCl. Only one enantiomer is shown of (9), (10), and (11)

Farina and Victory [8] gave a mixture of the ester (1) and ethyl 2,4,4-triethoxybutyrate (3) in a 3 : 2 ratio. The mixture was converted into pure ester (1) by heating with sodium hydrogen sulphite for six hours, when g.l.c. showed one peak and the i.r. and n.m.r. spectra were identical with those of samples prepared by route A or B. A mechanistic route to esters (1) and (3) is outlined in Scheme 2.

The conversion of ethyl 4,4-diethoxybut-2-enoate (1) into the amino acid (11) is outlined in Scheme 4. The crucial first step in this synthesis determines the stereochemistry of the substituted cyclopropane. The addition of dimethylsulphoxonium methylide to αβ-unsaturated ketones and esters has been shown to give differing results, since either pure *trans* or *cis–trans* mixtures of substituted cyclopropanes have been obtained,[9] depending on the substituents. The reaction between diethyl fumarate and dimethylsulphoxonium methylide was chosen as a model to investigate the stereoselectivity of cyclopropane formation. Analysis of the product by g.l.c. on two different phases gave two peaks in the ratio 3 : 2 which, after separation by g.l.p.c. (gas–liquid preparative chromatography), were identified as the *trans*-dicarboxylate (4) and the *cis*-dicarboxylate (5) respectively by i.r. and n.m.r. spectroscopy and hydrolysis of the *trans* diester to the corresponding diacid. The same ratio of *trans* : *cis* esters was obtained starting with diethyl maleate, so it was reasoned that the two forms of the enolate (6) are involved, as outlined in Scheme 3. In the equilibrium of *s-trans* and *s-cis* forms of (6) the latter would be stabilised by electrostatic attraction between the enolate oxygen and the carbon of the ester carbonyl group, thus giving rise to some of the *cis*-dicarboxylate (5).

In the light of these previous results a careful investigation of the addition of dimethylsulphoxonium methylide to ester (1) was carried out (Scheme 4). When dimethylformamide (DMF) was used as solvent only a low yield (11%) of product was obtained but with dimethyl sulphoxide (DMSO) the yield increased to 65%. The distilled product gave a single peak on g.l.c. analysis on two different phases and was shown to be ethyl *trans*-(diethoxymethyl)cyclopropanecarboxylate (7) by i.r. and n.m.r. analysis. Here, the sterically more demanding acetal group directs the reaction to give the *trans* isomer only. Furthermore, the absence of a second ester carbonyl group precludes co-ordination of the enolate oxygen [as in (6), Scheme 3].

The ester (7) was converted in high yield at room temperature into the *trans*-aldehyde (8) and this also gave a single peak



Scheme 5.

on g.l.c. on two different stationary phases and was characterised by i.r. and n.m.r. spectra. An attempt was made to convert the aldehyde (8) into the amino acid (11) in one step [10] using NH_4Cl–KCN followed by hydrolysis, but this only yielded a few milligrams of the amino acid after preparative chromatography. However, the synthetic amino acid was compared with an authentic sample of the *trans* natural acid and found to have the same R_F value. Improved yields were obtained by first converting the aldehyde (8) into the cyanohydrin (9) and then into the amino nitrile (10) and hydrolysis to the *trans*-amino acid (11). An extensive purification (detailed in the Experimental section) was carried out and the synthetic (±)-*trans*-material was compared with the natural (+)-*cis* and (+)-*trans* amino acids (kindly supplied by Professor L. Fowden). The i.r. spectrum of the synthetic amino acid was in good agreement with that of the natural (+)-*trans* acid. The ^1H n.m.r. spectrum of the natural (+)-*trans* acid (in D_2O) showed two complex, almost symmetrical multiplets centred at τ 8.62 and 8.18 which integrated as four protons and was characteristic of the protons of the cyclopropyl ring. The α-proton appeared as a doublet at τ 6.70 (split by the proton of the ring, *J* 9 Hz). The synthetic (±)-*trans* isomer (in D_2O) showed

similar complex multiplets for the four ring protons but the α-proton appeared as a pair of doublets at τ 6.70 and 6.60 (τ 9 and 8.5 Hz), probably due to a mixture of diastereoisomeric forms which had not separated on chromatography. The *cis* and *trans* natural acids and the synthetic *trans* acid were subjected to descending paper chromatography under identical conditions and gave R_F 0.26 for synthetic and natural *trans*-α-(carboxycyclopropyl)glycine and R_F 0.36 for the natural *cis*-α-(carboxycyclopropyl)glycine. The evidence presented here thus confirms the structure of the natural amino acid.

An attempt was also made to synthesize *cis*-α-(carboxycyclopropyl)glycine [3] found in the seed of *Aesculus parviflora* through the key intermediate (12) (*cf.* Scheme 5) which could then be converted into the natural (±)-amino acid as in Scheme 4.

When *cis*-3-formylacrylic acid pseudo-ester (2) was treated with trimethylsulphoxonium iodide a low yield of a three-component mixture, (13), (14), and (15), was obtained in the proportions 2 : 2 : 1, separated by preparative g.l.c., and identified by microanalysis and spectra. The expected product (12) was not obtained and this synthesis has not yet been explored further.

Experimental

I.r. spectra were determined on liquid films or KBr discs using a Perkin-Elmer 337 spectrophotometer. ^{1}H N.m.r. spectra were determined with a Varian A60 instrument using tetramethylsilane as internal standard. G.l.c. was carried out using a Pye 104 flame-ionisation instrument fitted with 5 ft analytical columns and using N_2 carrier gas at a flow rate of 40 ml min^{-1}. Silicone oil refers to grade SE30 on Chromosorb W, and Carbowax to grade 20M on Chromosorb W. Paper chromatography was carried out on Whatman No. 1 paper. Amino acids were detected by spraying solvent-free chromatograms with 0.2% EtOH–ninhydrin solution followed by heating of the papers at 80 °C. Trimethylsulphoxonium iodide was prepared as indicated previously.[9b] Methyl 4-bromobut-2-enoate and *N*,*N*-dimethyl-*p*-nitrosoaniline were prepared by literature methods.[11] Ethereal solutions were dried over magnesium sulphate.

Ethyl (E)-3-*Formylpropenoate*.—*Method A*. Pyridine (9.4 g, 0.12 mol) was added to a solution of methyl (*E*)-4-bromobut-2-enoate (17 g, 0.1 mol) in dry benzene (20 ml) and the mixture was stirred for 2 h initially at 20 °C, and finally at 60—70 °C for 4 h. The liquid was decanted off and the brown crusty solid was treated with *N*,*N*-dimethyl-*p*-nitrosoaniline (15 g, 0.1 mol) in ethanol. Aqueous sodium hydroxide (100 ml; 1M) was added dropwise to the stirred and cooled mixture which was then stirred for 4 h. Some crystals of the crude imine oxide methyl ester were removed by filtration and dried under vacuum over P_2O_5; $\nu_{max.}$ 1 735 (C=O) and 1 600 (C=C) cm^{-1}; τ ($CDCl_3$) 6.98 (3 H, s, CO_2CH_3), 6.23 [6 H, s, $N(CH_3)_2$], 3.46 (3 H, m, =CH–CH=CH) and 2.32 (4 H, m, ArH). The aqueous ethanolic filtrate was evaporated (40 °C at 5 mmHg), and to a stirred solution of the oily residue in diethyl ether (200 ml) was added sulphuric acid (100 ml; 3M) and the mixture was then stirred for a further 2 h. The ether layer was separated and the water layer after being neutralised with saturated aqueous sodium hydrogen carbonate, was extracted with diethyl ether; evaporation and distillation of the combined organic phases gave (*E*)-3-formylpropenoate (5.5 g, 43%), b.p. 72—74 °C at 10 mmHg (lit.,[4] 74 °C at 16 mmHg), $\nu_{max.}$ 2 840, 2 760 (CHO), 1 730 (CO_2Et), 1 700 (CH=CHCHO), 1 660, and 975 cm^{-1} (*trans*-CH=CH); g.l.c. gave one peak, R_t 12 min (silicone oil; 80 °C) and R_t 15 min (Carbowax; 80 °C); τ ($CDCl_3$) 8.70 (3 H, t, CH_2CH_3), 5.72 (2 H, q, CH_2CH_3), 3.10 (2 H, dd, $J_{2,3}$ 12 Hz, C*H*=C*H*CHO), and 0.23 (1 H, dd, $J_{1,2}$ 6.5, $J_{1,3}$ 1.5 Hz, CH=CHC*H*O).

Method B.—Ethyl (*E*)-but-2-enoate (40 g, 0.33 mol), finely powdered selenium dioxide (26.6 g, 0.25 mol), and dry dioxane were heated under gentle reflux for 2 h. The bulk of the selenium produced was removed by pouring the mixture through glass wool and any selenium left in solution was removed by shaking with mercury until the solution became clear. After filtration and removal of dioxane (32 °C at 50 mmHg), diethyl ether was added to the residue and further treatment with mercury was carried out. The ethereal solution was dried, evaporated, and distilled to give ethyl (*E*)-3-formylpropenoate (9.1 g, 24%), b.p. 68—69 °C at 8 mmHg, with similar i.r. and n.m.r. spectra to the ester prepared by method A.

Ethyl (E)-4,4-*Diethoxybut*-2-*enoate* (1).—Ethyl (*E*)-3-formylpropenoate (5 g, 0.04 mol), absolute ethanol (7.5 ml), and calcium chloride (0.7 g) were shaken for 3 d at room temperature. The organic layer was evaporated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried over anhydrous potassium carbonate, evaporated, and distilled to give ethyl (*E*)-4,4-diethoxybut-2-enoate (1) (7.4 g, 94%), b.p. 92 °C at 5 mmHg; $\nu_{max.}$ 1 730 (C=O), 1 670, and 965 cm^{-1} (*trans*-CH=CH); g.l.c. gave one peak, R_t 11.4 min (Carbowax; 120 °C); τ ($CDCl_3$) 8.80 (6 H, t, OCH_2CH_3), 8.70 (3 H, t, $CO_2CH_2CH_3$), 6.38 (4 H, two overlapping quartets, OCH_2CH_3), and 5.78 (2 H, q, $CO_2CH_2CH_3$), 4.98 (1 H, dd, CHCH=CH), 3.88 (1 H, dd, $J_{1,2}$ 16 Hz, 3-H), and 3.15 (1 H, dd, $J_{1,2}$ 16 Hz, 2-H).

Method C. (Z)-3-*Formylpropenoic Acid Pseudo-ester* (5-*Ethoxy*-2,5-*dihydrofuran*-2-*one*) (2).—(a) A mixture of freshly distilled 2-furaldehyde (125 g), absolute ethanol (900 ml), and eosin (2 g), using the literature method [7] except that a medium-pressure lamp (Hanovia 100-W) was used, gave (*Z*)-3-formylpropenoic acid pseudo-ester (2) (99 g, 60%), b.p. 115—118 °C at 10 mmHg (lit.,[7] 96—99 °C at 12 mmHg; 68%); $\nu_{max.}$ 1 800, 1 700 (C=O), and 1 620 cm^{-1} (C=C); g.l.c. gave one peak, R_t 15 min (silicone oil; 120 °C); τ ($CDCl_3$) 8.78 (3 H, t, CH_2CH_3), 6.21 (2 H, q, CH_2CH_3), 3.95 (1 H, overlapping dd, $J_{1,2}$ 1.5, $J_{1,3}$ 1.5 Hz, CHOEt), 3.73 (1 H, dd, $J_{2,3}$ 6, $J_{2,1}$ 1.5 Hz, CH=CHCHOEt), and 2.62 (1 H, dd, $J_{3,2}$ 6, $J_{3,1}$ 1.5 Hz, CH=CHCHOEt).

(b) 2-Furaldehyde (100 g), absolute ethanol (750 ml), and eosin (2 g) were irradiated by light from a fluorescent tube (30-W) placed in the centre of two concentric tubes containing the reaction mixture and oxygen was bubbled through the mixture. The reaction was followed by the removal, at appropriate intervals, of aliquot portions and these were examined by u.v. and i.r. spectroscopy. The starting material had disappeared after 8 d and, after evaporation of ethanol, the residue was distilled and gave (*Z*)-3-formylpropenoic acid pseudo-ester (2) (55 g, 41%), b.p. 68 °C at 1 mmHg, with identical spectroscopic properties to the product obtained by method (a).

Ethyl (E)-4,4-*Diethoxybut*-2-*enoate* (1).—*cis*-3-Formylpropenoic acid pseudo-ester (2) (75 g), absolute ethanol (300 g), and concentrated sulphuric acid (3 ml) were heated under reflux for 1 d. After the solution had cooled, anhydrous sodium acetate (13.5 g) was added and the ethanol was evaporated off under reduced pressure. Inorganic solids were removed by filtration through Celite and g.l.c. showed two peaks in the ratio 3 : 2, R_t 11.4 and 16.2 min (Carbowax; 120 °C) which were ethyl 4,4-diethoxybut-2-enoate (1) and ethyl 2,4,4-triethoxybutyrate (3).[8] The mixture (74 g) was converted into the ester (1) by heating with sodium hydrogen sulphite (5.2 g) for

6 h at 90 °C and 15 mmHg, when g.l.c. gave one peak, R_t 11.4 min (Carbowax; 120 °C). Distillation gave ethyl (*E*)-4,4-diethoxybut-2-enoate (1) (57 g, 45%), b.p. 69 °C at 0.2 mmHg. The i.r. and n.m.r. spectra were identical with those of the ester prepared by method (a).

Diethyl cis- *and* trans-*Cyclopropane*-1,2-*dicarboxylate* (5) *and* (4).—(a) Solid trimethylsulphoxonium iodide (11.05 g, 52 mmol) was added in one portion to a stirred suspension of sodium hydride (1.2 g, 50 mmol) in dry DMSO (50 ml). An exothermic reaction took place with evolution of hydrogen and the mixture was stirred under N_2 for 20 min after the evolution of H_2 had ceased (*ca.* 5 min). Then a solution of diethyl fumarate (8.6 g, 50 mmol) in DMSO (10 ml) was added in one portion and the mixture was stirred for a further 1 h. The reaction mixture was then poured into ice–water (60 ml) and extracted with diethyl ether, the extract was washed with water and dried, and the ether was evaporated off. The residue was distilled to give a mixture of diethyl *trans*- (4) and *cis*- (5) cyclopropane-1,2-dicarboxylate (7.4 g, 80%), b.p. 108 °C at 12 mmHg; g.l.c. gave a ratio 3 : 2, R_t 14.4 and 19.2 min (Carbowax; 120 °C) and R_t 10.2 and 12.0 min (silicone oil; 120 °C). Separation was achieved by g.l.p.c. with a 7 ft Carbowax column at 120 °C and N_2 flow rate of 150 ml min^{-1}. The fraction with R_t 34 min was diethyl *trans*-cyclopropyl-1,2-dicarboxylate (4), $\nu_{max.}$ 1 740 (C=O) and 1 040 cm^{-1} (cyclopropyl); g.l.c. gave one peak, R_t 14.2 min (Carbowax; 120 °C) and R_t 10.2 min (silicone oil; 120 °C); τ (CCl_4) 8.75 (6 H, t, CH_2CH_3), 8.72 and 7.97 together (4 H, two complex multiplets, cyclopropyl), and 5.87 (4 H, q, CH_2CH_3). Hydrolysis of the *trans* ester with alcoholic potassium hydroxide gave *trans*-cyclopropanedicarboxylic acid, m.p. 174 °C (lit.,[12] 175 °C). A second fraction (from g.l.p.c.), with R_t 45 min, was diethyl *cis*-cyclopropane-1,2-dicarboxylate (5) (Found: C, 58.7; H, 8.0. Calc. for $C_9H_{14}O_4$: C, 58.1; H, 7.6%); $\nu_{max.}$ 1 730 (C=O) and 1 040 cm^{-1} (cyclopropyl); g.l.c. gave one peak, R_t 19.2 min (Carbowax; 120 °C) and R_t 12.0 min (silicone oil; 120 °C); τ ($CDCl_3$) 8.80 and 8.74 (together 6 H, overlapping triplets, CH_2CH_3), 9.28 and 8.77 (together 4 H, complex multiplets, cyclopropyl), 5.88 and 5.85 (4 H, overlapping quartets, CH_2CH_3).

(b) Diethyl maleate (8.6 g, 50 mmol) was treated with trimethylsulphoxonium iodide as in (a) and on work-up gave a mixture of diethyl *trans*- and *cis*-cyclopropane-1,2-dicarboxylate (7.2 g, 78%), b.p. 108 °C at 12 mmHg; g.l.c. gave a *trans* : *cis* ratio 3 : 2 and separation by g.l.p.c. gave diethyl *trans*- and *cis*-cyclopropane-1,2-dicarboxylate with identical spectroscopic properties to the compounds isolated in (a).

Ethyl trans-2-(*Diethoxymethyl*)*cyclopropane*-1-*carboxylate* (7).—(a) Solid trimethylsulphoxonium iodide (11.05 g, 52 mmol) and sodium hydride (1.2 g, 50 mmol) in dry DMF (100 ml) were allowed to react as for the preparation of the diesters (4) and (5), method (a), above. A solution of ethyl (*E*)-4,4-diethoxybut-2-enoate (10.1 g, 50 mmol) in DMF (15 ml) was added in one portion, the temperature was allowed to rise to 50 °C, and the mixture was stirred for a further 1 h. The mixture was then poured into a hydrochloric acid–ice–water mixture (100 ml; 3%) and extracted into diethyl ether. The extract was dried and evaporated and g.l.c. analysis of the crude product (1.2 g, 11.1%) showed substantially only one peak, R_t 16.8 min (Carbowax; 120 °C) with minor peaks (*ca.* 5%). A pure sample was obtained by g.l.p.c. with a 7 ft Carbowax column at 170 °C and N_2 flow rate of 80 ml min^{-1}. The fraction with R_t 35 min was *ethyl* trans-2-(*diethoxymethyl*)-*cyclopropane*-1-*carboxylate* (7) (Found: C, 61.1; H, 9.4. $C_{11}H_{20}O_4$ requires C, 60.8; H, 9.9%); $\nu_{max.}$ 1 740 (C=O) and 1 040 (cyclopropane) cm^{-1}; g.l.c. gave one peak, R_t 13.8 min (silicone oil; 120 °C) and R_t 16.8 min (Carbowax; 120 °C); τ ($CDCl_3$) 8.82 (6 H, t, CH_3CH_2), 8.8 and 8.35 (together 4 H, overlapping multiplets, cyclopropyl), 8.77 (3 H, t, CO_2CH_2-CH_3), 6.40 (4 H, dq, CH_3CH_2O), 5.87 (2 H, q, $CO_2CH_2CH_3$), and 5.55 [1 H, m, $CH(OEt)_2$].

(b) Using dry DMSO (50 ml) as solvent and ethyl (*E*)-4,4-diethoxybut-2-enoate (10.1 g, 50 mmol) in dry DMSO (10 ml), and stirring the mixture at the end of the reaction for 2 h, but otherwise under the conditions in (a), gave, after the reaction mixture had been poured into ice–water (60 ml) and worked up, ethyl *trans*-2-(diethoxymethyl)cyclopropane-1-carboxylate (7) (7 g, 65%), b.p. 74 °C at 6.4 mmHg, with g.l.c., i.r., and n.m.r. data identical with those of the sample obtained by method (a) using g.l.p.c.

Ethyl trans-2-*Formylcyclopropane*-1-*carboxylate* (8).—Ethyl *trans*-2-(diethoxymethyl)cyclopropane-1-carboxylate (7) (8.5 g, 40 mmol) was stirred at room temperature with dilute sulphuric acid (25 ml; 10%). The reaction was monitored by g.l.c. and was complete in about 3 h. The organic layer was separated, the aqueous layer was extracted with diethyl ether, and the combined organic phases were washed with water, dried, and evaporated to give ethyl *trans*-2-formylcyclopropane-1-carboxylate (8) (5 g, 93%), $\nu_{max.}$ 2 820, 2 780 (CH of CHO), 1 725 (C=O), and 1 030 cm^{-1} (cyclopropyl); g.l.c. gave one peak, R_t 4.2 min (silicone oil; 120 °C) and R_t 6.9 min (Carbowax; 120 °C); τ ($CDCl_3$) 8.75 (3 H, t, CO_2CH_2-CH_3), 8.65 and 7.68 (together 4 H, two complex multiplets, cyclopropyl), 5.88 (2 H, q, $CO_2CH_2CH_3$), and 0.08 (1 H, d, $J_{1,2}$ 4.5 Hz, CHO). No attempt was made to distil this unstable aldehyde and it was used directly in further reactions.

(±)-trans-α-(*Carboxycyclopropyl*)*glycine* (11).—(a) Ethyl *trans*-2-formylcyclopropane-1-carboxylate (8) (1.1 g) was added to a mixture of ammonium chloride (0.4 g), potassium cyanide (0.4 g), aqueous ammonium hydroxide (4 ml), and water (5 ml). The reaction mixture was shaken at room temperature for 12 h and then heated at 50 °C for 6 h. Hydrochloric acid (25 ml; 10M) was added and the mixture was gently refluxed for 1 h and then evaporated to dryness. Water (5 ml) was added and the mixture was again evaporated to dryness. The residue was dissolved in water, adjusted to pH 4 with dilute aqueous ammonium hydroxide, and again evaporated to small bulk. The solution was subjected to descending paper chromatography alongside an authentic sample of natural (+)-*trans*-α-(carboxycyclopropyl)glycine * and was found to have identical R_{Leu} values: 0.33 (butanol–acetic acid–water).

(b) (i) *Ethyl* trans-2-(*Cyanohydroxymethyl*)*cyclopropane*-1-*carboxylate* (9). Concentrated hydrochloric acid (20 ml) was added dropwise during 1 h at 0 °C to a stirred mixture of ethyl *trans*-2-formylcyclopropane-1-carboxylate (8) (10 g, 70 mmol) in diethyl ether (10 ml) containing potassium cyanide (8 g). The mixture was stirred at 0 °C for a further 6 h. The organic layer was separated, combined with three ethereal extracts of the aqueous layer, washed with water, dried, evaporated, and distilled to give *ethyl* trans-2-(*cyanohydroxymethyl*)*cyclopropane*-1-*carboxylate* (9) (6.1 g, 52%), b.p. 134 °C at 0.5 mmHg (Found: C, 56.5; H, 6.6; N, 7.5. $C_8H_{11}NO_3$ requires C, 56.8, H, 6.6; N, 8.3%); $\nu_{max.}$ 3 400 (OH), 2 100 (CN), 1 720 (CO), and 1 030 cm^{-1} (cyclopropyl); τ ($CDCl_3$) 8.72 (3 H, t, $CO_2CH_2CH_3$), 8.72 and 8.10 (together 4 H, two complex multiplets, cyclopropyl), 5.8 (2 H, q, CO_2-CH_2CH_3), 5.68 (1 H, s, disappears on deuteriation OH), and 5.67 and 5.77 (together 1 H, 2 d, CHCN).

(ii) (±)-trans-α-(*Carboxycyclopropyl*)*glycine* (11). Ethyl *trans*-2-(cyanohydroxymethyl)cyclopropane-1-carboxylate

* Kindly supplied by Professor L. Fowden.

(3.5 g, 20 mmol) was shaken with concentrated ammonia (0.88 w/w; 200 ml) and ammonium chloride (0.75 g) at room temperature for 10 d. The ammonia was evaporated off and the water was removed under reduced pressure (35 °C at 20 mmHg). The hygroscopic residue [amide (10)] was dried under vacuum over P_2O_5 and gave $\nu_{max.}$ (KBr) 3 300 and 3 400 (NH_2), 2 100 (CN), and 1 700 cm^{-1} ($CONH_2$).

The crude amide (3 g) was dissolved in concentrated hydrochloric acid (50 ml) and the solution was refluxed gently for 12 h. The mixture was reduced to small bulk by low-temperature evaporation (32 °C at 10 mmHg), and several times water was added to the residue and carefully removed by vacuum distillation. The resulting solution was decolourised with charcoal, adjusted to pH 4 with dilute ammonia, and the product was chromatographed on a Zeocarb 225 cation-exchange column in acid form. The column was washed free of chloride ion by elution with water until a negative test for chloride ion was observed. Elution with dilute aqueous ammonia (0.25M) and testing for ninhydrin-positive fractions gave, after evaporation under reduced pressure (32 °C at 10 mmHg) and drying *in vacuo* (P_2O_5), the ammonium salt of *trans*-α-(carboxycyclopropyl)glycine.

The free amino acid was obtained by chromatography of the ammonium salt on a De-acidite FF-IP anion-exchange resin (acetate form), prepared by washing the chloride form with 3M aqueous sodium acetate until it was free of chloride ion. The ammonium salt on the column was washed with water (*ca.* 250 ml) and eluted with acetic acid (0.3M); ninhydrin-sensitive fractions were collected and evaporated (32 °C at 10 mmHg), and the precipitated free amino acid was filtered off, recrystallised from water, and dried under vacuum over P_2O_5 to give (±)-trans-α-(*carboxycyclopropyl*)-*glycine* (11) as a white solid (540 mg, 17%) (Found: C, 44.9; H, 6.2. $C_6H_9NO_4$ requires C, 45.2; H, 5.8%); $\nu_{max.}$ 3 400—2 700 (NH, CH, and OH), 1 720 (C=O), and 1 640 and 1 570 cm^{-1} (CO_2^-) in agreement with the i.r. spectrum of an authentic sample; τ (D_2O) 8.63 and 8.17 (together 4 H, 2 complex multiplets, cyclopropyl) and 6.7 and 6.6 (together 1 H, 2 d, *J* 9 and 8.5 Hz, C*H*NH_2). A sample of the natural (+)-*trans*-amino acid gave τ (D_2O) 8.62 and 8.18 (together 4 H, 2 complex multiplets) and 6.70 (1 H, d, C*H*NH_2, *J* 8 Hz). The synthetic sample was subjected to descending paper chromatography alongside the natural *cis* and *trans* amino acids using the solvent system phenol–water 75% *w/w* in the presence of ammonia and gave R_F 0.26 for synthetic (±)-*trans*-α-(carboxycyclopropyl)glycine, R_F 0.27 for natural (+)-*trans*-α-(carboxycyclopropyl)glycine, and R_F 0.36 for natural (+)-*cis*-α-(carboxycyclopropyl)glycine.

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