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Syntheses of Some Cyclic Amino Acids Structurally Related to the GABA Analogue Homo-β-proline

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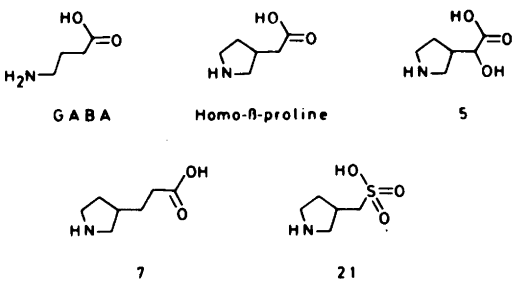
The synthesis of (±-α-hydroxy-3-pyrrolidineacetic acid (*5*), (*RS*)-3-pyrrolidinepropionic acid (*7*), (*RS*)-3-pyrrolidinemethanesulfonic acid (PMSA) (*21*) are described. Furthermore, an alternative route to (*RS*)-3-pyrrolidineacetic acid (homo-β-proline) (*13*) and attempts to prepare 3-pyrroline-3-ylacetic acid (*15*) and (±)-α-amino-3-pyrrolidinepropionic acid (*24*) are described.

A Doebner condensation of the protected 3-pyrrolecarbaldehyde *1* followed by catalytic hydrogenation gave *7*. A cyanohydrin synthesis with *1* performed under acylating conditions gave *2*, which was converted into *5 via 3* and *4*. A Wittig reaction on *8* gave a separable mixture of the enamide *11* and the *Z* and *E*-ethyl 1-methoxycarbonyl-$\Delta^{3,\alpha}$-pyrrolidineacetates (*9*, *10*). Catalytic hydrogenation of *11* and subsequent hydrolysis gave *13*. Alkaline hydrolysis and rearrangement of *9* or *10* gave *14*. Cleavage of *14* under a variety of conditions to give *15* were unsuccessful. KSCN treatment of *18* followed by oxidative chlorination and hydrolysis gave *21*.

The heterocyclic GABA analogue 3-pyrrolidineacetic acid (homo-β-proline) (*13*) is a very potent competitive inhibitor of the glial as well as of the presynaptic GABA uptake systems,[1,2] responsible for the termination of the GABA mediated synaptic transmission in the central nervous system.[3,4] Inhibitors of these uptake mechanisms have considerable pharmacological interest[4,5] and in an attempt to develop such compounds we have synthesized the following amino acids, (±)-α-hydroxy-3-pyrrolidineacetic acid (*5*), (*RS*)-3-pyrrolidinepropionic acid (*7*) and (*RS*)-3-pyrrolidinemethanesulfonic acid (PMSA) (*21*) structurally related to homo-β-proline. Attempts to prepare 3-pyrrolin-3-ylacetic acid (*15*) and α-amino-3-pyrrolidinepropionic acid (*24*) were unsuccessful.



A cyanohydrin synthesis performed under acylating conditions with the 3-pyrrolecarbaldehyde (*1*) gave compound *2*. Hydrolysis under Pinner conditions[6] followed by catalytic rhodium-Al_2O_3 hydrogenation afforded the hydroxyester *4*, which was converted into the amino acid *5*. 3-Pyrrolidinepropionic acid (*7*) was prepared from *1 via E*-3-pyrrolepropenoic acid (*6*).

Reaction of the pyrrolidone derivative *8* with triethylphosphonoacetate under Wittig conditions[7] gave a complex mixture from which the *Z*- and *E*-isomers *9* and *10* of ethyl 1-methoxycarbonyl-$\Delta^{3,\alpha}$-pyrrolidineacetate together with the enamine *11* were isolated by column chromatography. Low pressure hydrogenation of *11* and subsequent deprotection gave homo-β-proline (*13*). This synthetic sequence represents an alternative route to homo-β-proline (*13*). Alkaline treatment of *9*, *10* gave a

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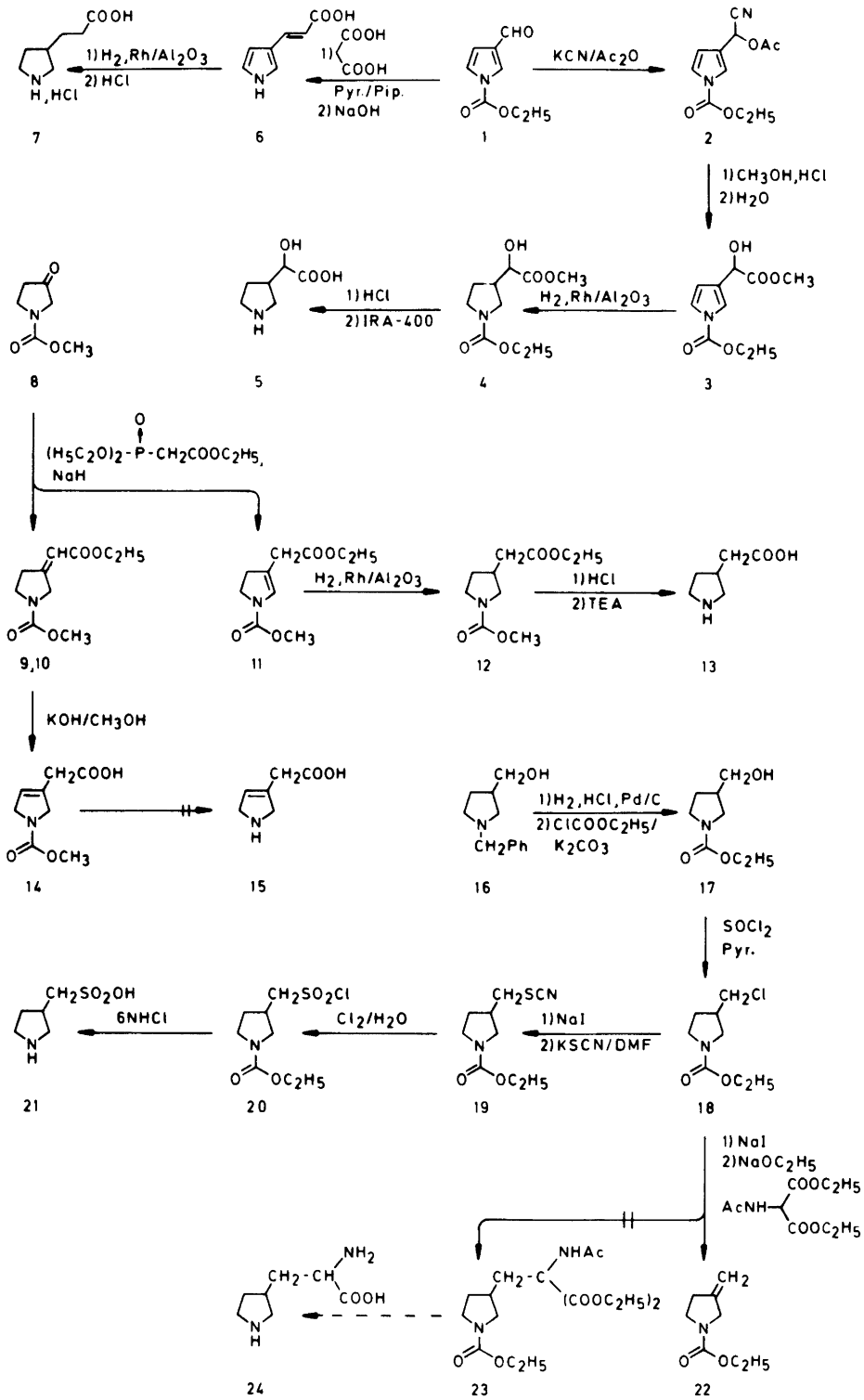

Scheme 1.

single compound, which was assigned the structure *14*. Attempts to deprotect *14* resulted in excessive decomposition.

Ethyl 3-chloromethylpyrrolidine-1-carboxylate (*18*) was prepared from *16* as outlined in Scheme 1. However, attempts to convert *18* into the acetaminomalonic ester *23* were unsuccessful, the dehydrohalogenated compound *22* being the only reaction product.

Compound *18* was converted into the thiocyanate *19*, which in turn was oxidized with chlorine to give the sulfonylchloride *20*. Hydrolysis and deprotection of *20* gave the sulfonic acid analogue of homo-β-proline, (*RS*)-3-pyrrolidinemethanesulfonic acid (PMSA) (*21*).

The structure determinations of the novel compounds were based on spectroscopic data supported by elemental analysis.

As generally accepted, the Doebner modification of the Knoevenagel reaction on compound *1* led to the formation of the unsaturated carboxylic acid *6*, of which the *trans* configuration corresponded with a strong UV absorption at 299 nm. Furthermore, the *trans* configuration was unequivocally shown by a coupling constant of 15.6 Hz in the ^{1}H NMR spectrum of *6*.

The enamine structure of compound *11* was supported by a UV absorption at 233 nm and a one proton singlet at δ 6.48 in the ^{1}H NMR spectrum.

The ^{1}H NMR spectra of *9* and *10* allow a tentative determination of the configuration at the double bonds. The signals originating in the C-2 and C-4 protons of compound *9* are found as a quartet centered at δ 4.24 and a multiplet centered at 3.1, respectively. The corresponding signals of compound *10* are found at δ 4.55 and δ 2.82. The anisotropy effect of the ester carbonyl group is assumed to cause shielding of the C-2 protons of the *Z*-form and the C-4 protons of the *E*-form, leading to upfield shifts of the C-2 proton signal of the *Z*-form and of the C-4 proton signal of the *E*-form. Consequently, *9* and *10* are assigned the *Z*- and *E*-configuration, respectively.

EXPERIMENTAL

Melting points determined in capillary tubes are corrected. Elemental analyses were made by Mr. G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, DK-2750 Ballerup, Denmark. A Perkin-Elmer grating infrared spectrophotometer model 402, and a JEOL JMN-C-60HL (60 MHz) ^{1}H NMR instrument were used. ^{1}H NMR spectra were recorded using TMS as an internal standard. Compounds dissolved in D_2O were referenced to TSP. Thin-layer chromatography (TLC) and column chromatography (CC) were accomplished using silica gel F_{254} plates (Merck) and silica gel (Woelm 0.063 – 1.00 mm), respectively. Columns were developed by stepwise gradient elution. The pK_A values were determined as described in a previous paper.[8]

(±)-α-Acetoxy-1-ethoxycarbonyl-3-pyrroleacetonitrile (2). To a solution of *1*[9] (3.1 g; 18.7 mmol) in glacial acetic acid (9 ml) was added potassium cyanide (1.82 g; 28 mmol). After stirring for 40 min acetic anhydride (2.04 g; 20 mmol) was added and the mixture was heated to 50 °C for 24 h. After cooling to room temperature, water (40 ml) was added and the mixture was extracted with ether (50 ml). The organic layer was washed with an aqueous solution of sodium carbonate (40 ml; 1 M), dried ($MgSO_4$) and evaporated *in vacuo* to give crude *2*, which submitted to CC [silica gel: 70 g; eluent: toluene containing ethyl acetate (5 – 15 %)] gave *2* (850 mg; 20 %) as an oil. An analytical sample was purified by ball-tube distillation at 5×10^{-3} Pa (oven temp. 200 °C). Found: C 55.80; H 5.25; N 11.80. Calc. for $C_{11}H_{12}N_2O_4$: C 55.93; H 5.12; N 11.86. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.59 (1 H, m), 7.38 (1 H, m), 6.6 – 6.3 (2 H, broad signal), 4.44 (2 H, q, *J* 7 Hz), 2.13 (3 H, s), 1.38 (3 H, t, *J* 7 Hz). IR (film): 3150 (m), 2980 (m), 2940 (m), 2320 (m), 1800 – 1660 (s), 1495 (s), 1420 (s), 1380 (s), 1345 (s), 1280 (s) cm^{-1}.

Methyl (±)-α-hydroxy-1-ethoxycarbonyl-3-pyrroleacetate (3). To an ice-cooled solution of methanol (6 ml) saturated with hydrogen chloride was added *2* (800 mg; 3.5 mmol) and the mixture was left at 4 °C for 16 h with stirring. The solution was evaporated *in vacuo* to give an oil, which was dissolved in water (4 ml) and extracted with ether (3 × 30 ml). The combined and dried ($MgSO_4$) organic phases were evaporated *in vacuo* to give crude *3* (0.71 g), which was submitted to CC [silica gel: 70 g; eluent: toluene containing ethyl acetate 15 – 20 %)] to give *3* (400 mg; 52 %). An analytical sample was purified by ball-tube distillation at 5×10^{-3} Pa (oven temp. 220 °C). Found: C 52.83; H 5.72; N 6.25. Calc. for $C_{10}H_{13}NO_5$: C 52.86; H 5.77; N 6.17. ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.40 (2 H, m), 6.40 (1 H, m), 5.23 (1 H, d, *J* 6 Hz), 4.46 (2 H, q, *J* 7 Hz), 3.83 (3 H, s), 3.28 (1 H, d, *J* 6 Hz), 1.40 (3 H, t, *J* 7 Hz). IR (film): 3480 (s), 3140 (m), 2980 (s), 2950 (s), 1800 – 1650 (s), 1580 (m), 1490 (s) cm^{-1}.

Methyl (±)-α-hydroxy-1-ethoxycarbonyl-3-pyrrolidineacetate (4). A solution of *3* (700 mg; 3.0 mmol) in ethanol (50 ml) was hydrogenated (*ca.* 300 kPa) for 20 h in a PARR low-pressure hydrogenation apparatus using 5 % Rh – Al_2O_3 (500 mg)

as a catalyst. Evaporation *in vacuo* gave a crude product which was submitted to CC [silica gel: 70 g; eluent: toluene containing ethyl acetate (15–25 %) and formic acid (1 %)] to give *4* (500 mg; 73 %) as an oil. Found: C 52.04; H 7.47; N 6.12. Calc. for $C_{10}H_{17}NO_5$: C 51.94; H 7.41; N 6.06. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.16 (2 H, q, *J* 7 Hz), 4.4–3.9 (1 H, m), 3.83 (3 H, s), 3.8–3.0 (4 H, m), 3.0–2.2 (2 H, m), 2.2–1.5 (2 H, m), 1.23 (3 H, t, *J* 7 Hz). IR (film): 3400 (s), 2950 (s), 2880 (s), 1735 (s), 1710–1600 (s, several bands), 1435 (s), 1380 (s) cm^{-1}.

(±)-α-Hydroxy-3-pyrrolidineacetic acid (5). A mixture of *4* (262 mg; 2 mmol) and hydrochloric acid (10 ml; 6 M) was refluxed for 2 h. After evaporation *in vacuo* the residue was dissolved in water (5 ml), passed through a column containing ion exchange resin [Amberlite IRA-400 (OH) (40 ml)] using acetic acid (6 %) as an eluent. The eluate was evaporated *in vacuo* to give *5* (120 mg; 39 %) as a glassy compound. Found: C 45.63; H 7.45; N 8.22. Calc. for $C_6H_{11}NO_3$,$\frac{1}{2}H_2O$: C 46.75; H 7.97; N 9.09. ^{1}H NMR (60 MHz, D_2O and acetonitrile as an internal standard): δ 4.2–3.6 (1 H, m), 3.6–2.7 (5 H, m), 2.3–1.3 (2 H, m). IR (KBr): 3700–2000 (s, several bands), 1740–1380 (s, several bands), 1360 (s), 1355–1140 (s) cm^{-1}.

E-*3-Pyrrolepropenoic acid (6).* To a solution of *1*[9] (3.0 g; 18 mmol) and malonic acid (3.8 g; 36 mmol) in pyridine (30 ml) was added piperidine (1.5 ml) with stirring while the solution was heated to 100 °C for 8 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was taken up in sodium hydroxide (25 ml; 1.5 M). After stirring for 1.5 h the reaction mixture was washed with ether (3 × 25 ml). The aqueous phase was acidified with hydrochloric acid (*ca.* 10 ml; 4 M) to pH 3 and was extracted with ether (5 × 30 ml). The pooled extracts were dried (Na_2SO_4) and concentrated to about 10 ml, after which *6* (1.2 g; 54 %) crystallized. An analytical sample was recrystallized (ethyl acetate) to give *6*, *m.p.* 180–184 °C. Anal. $C_7H_7NO_2$: C, H, N. ^{1}H NMR (DMSO-d_6): δ 11.18 (1 H, s), 7.58 (1 H, d, *J* 15.6 Hz), 7.22 (1 H, s), 6.82 (1 H, m), 6.43 (1 H, m), 5.97 (1 H, d, *J* 15.6 Hz), 5.69 (1 H, broad signal). IR (KBr): 3440 (m), 3150–2300 (m–w, several bands), 1690 (s), 1660 (s), 1600 (s), 1540 (w), 1500 (w), 1410 (m) cm^{-1}. UV [methanol (log ε)]: 211 (4.10), 299 (4.26) nm.

(RS)-3-Pyrrolidinepropionic acid hydrochloride (7). A mixture of *6* (2.0 g; 16 mmol), hydrochloric acid (4 ml; 16 mmol, 4 M), water (300 ml) and 5 % Rh–Al_2O_3 (1.5 g) was hydrogenated at *ca.* 300 kPa H_2-pressure in a PARR low-pressure hydrogenation apparatus for 18 h. The filtered mixture was evaporated to dryness *in vacuo* and the residue was crystallized (water–ethanol) to give *7* (1.2 g; 45 %), m.p. 104–105 °C. Anal. $C_7H_{14}ClNO_2$: C, H, Cl, N. ^{1}H NMR (60 MHz, D_2O): δ 3.7–2.7 (4 H, m), 2.7–2.2 (3 H, m), 2.2–1.5 (4 H, m). IR (KBr): 3420 (m), 3200–2300 (s–w, several bands), 1720 (s), 1460 (m), 1400 (m) cm^{-1}.

Z- *and* E-*Ethyl 1-methoxycarbonyl-*$\Delta^{3,\alpha}$*-pyrrolidineacetate (9,10) and ethyl 1-methoxycarbonyl-2-pyrroline-3-ylacetate (11).* To a suspension of sodium hydride (1.92 g; 80 mmol) in 1,2-dimethoxyethane (DME) (15 ml) was added dropwise a solution of triethylphosphonoacetate (17.92 g; 80 mmol) in DME (15 ml) with stirring, which was continued for 1 h. To the reaction mixture was added a solution of *8*[2] (11.44 g; 80 mmol) in DME (50 ml) and the resulting solution was stirred at room temperature for 12 h. The solvent was removed *in vacuo* to give a crude product, which was submitted to CC [silica gel: 1000 g; eluent: cyclohexane containing ethyl acetate (25–50 %)] to give *9* (710 mg; 3.9 %), *10* (800 mg; 4.5 %), and *11* (4.4 g; 24 %). Analytical samples of *9* and *10* were purified by recrystallization (cyclohexane–light petroleum) and *11* was purified by ball-tube distillation at 5×10^{-3} Pa (oven temperature 150 °C).

9: M.p. 80.0–81.5 °C. Found: C 55.77; H 7.04; N 6.57. Calc. for $C_{10}H_{15}NO_4$: C 56.32; H 7.09; N 6.57. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.04–5.79 (1 H, m), 4.42–4.05 (2 H, q. *J* 7 Hz), 4.24 (2 H, q, *J ca.* 2 Hz), 3.79 (3 H, s), 3.86–3.49 (2 H, m), 3.38–2.71 (2 H, m), 1.32 (3 H, t, *J* 7 Hz). IR (KBr): 3450 (m), 3000–2850 (n), 1720–1680 (s), 1660 (m), 1450 (s), 1400 (s), 1380 (s), 1340 (s), 1230 (s) cm^{-1}. UV [methanol (log ε)]: 215 (3.92) nm.

10: M.p. 62.5–65.5 °C. Found: C 56.20; H 7.09; N 6.46. Calc. for $C_{10}H_{15}NO_4$: C 56.32; H 7.09; N 6.57. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.00–5.79 (1 H, m), 4.55 (2 H, q, *J ca.* 2 Hz), 4.23 (2 H, q, *J* 7 Hz), 3.78 (3 H, s), 3.87–3.36 (2 H, m), 3.03–2.61 (2 H, m), 1.20 (3 H, t, *J* 7 Hz). IR (KBr): 4350 (m), 3000–2860 (m), 1730–1680 (s), 1640 (s), 1400 (s), 1380 (s), 1340 (m), 1300 (m), 1220 (s) cm^{-1}.

11: Found: C 55.38; H 6.98; N 6.64. Calc. for $C_{10}H_{15}NO_4$: C 56.32; H 7.09; N 6.57. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.48 (1 H, s), 4.16 (2 H, q, *J* 7 Hz), 3.92–3.36 (2 H, m), 3.10 (2 H, s), 2.92–2.36 (2 H, m), 1.26 (3 H, t, *J* 7 Hz). IR (film): 3450 (w), 3050–2800 (m), 1735–1680 (s), 1645 (s), 1460 (s), 1390 (s), 1280 (m) cm^{-1}. UV [methanol (log ε)]: 233 (4.20) nm.

(RS)-Ethyl 1-methoxycarbonyl-3-pyrrolidineacetate (12). A solution of *11* (225 mg; 1 mmol) in ethanol (50 ml) was hydrogenated (*ca.* 300 kPa) for 20 h in a PARR low-pressure hydrogenation apparatus using Rh–Al_2O_3 (200 mg) as a catalyst. After evaporation *in vacuo* the crude product was submitted to CC [silica gel: 20 g; eluent: toluene containing ethyl acetate (25–50 %)] to give *12* (120 mg; 53 %) as an oil. Found: C 55.50; H 7.99; N 6.29. Calc. for $C_{10}H_{17}NO_4$: C 55.80; H 7.96;

N 6.51. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.18 (2 H, q, *J* 7 Hz), 3.68 (3 H, s), 3.8–2.7 (7 H, m), 2.7–2.2 (2 H, m), 1.25 (3 H, t, *J* 7 Hz). IR (film): 3700–3200 (m), 3100–2800 (s), 1760–1600 (s), 1450 (s), 1395 (s) cm^{-1}.

(RS)-3-Pyrrolidineacetic acid (homo-β-proline) (13). A solution of *12* (880 mg; 4.1 mmol) in hydrochloric acid (40 ml; 5 M) was refluxed for 2 h. Evaporation *in vacuo* gave an oil, which was dissolved in ethanol (5 ml). To this solution was added a solution of triethylamine (412 mg; 4.1 mmol) in ethanol (3 ml). Filtration gave *13* (210 mg; 40 %) as crystals, m.p. 128–130 °C (decomp.). Found: C 55.26; H 8.84; N 10.51. Calc. for $C_6H_{11}NO_2$: C 55.79; H 8.58; N 10.85. ^{1}H NMR (60 MHz, D_2O): δ 3.8–3.0 (3 H, m), 3.0–2.5 (2 H, m), 2.6–1.4 (4 H, m). IR (KBr): 3700–3150 (s), 3150–2800 (s), 2800–2000 (m, several bands), 1405 (s), 1280 (s) cm^{-1}.

1-Methoxycarbonyl-3-pyrroline-3-ylacetic acid (14). To a solution of *9* or *10* (225 mg; 1 mmol) in methanol (5 ml) was added a solution of potassium hydroxide (60 mg; 1.2 mmol) in methanol (10 ml) with stirring, which was continued at room temperature for 4 days followed by evaporation *in vacuo*. The residue was dissolved in water (15 ml) and pH was adjusted to 4 using acetic acid. The reaction mixture was extracted with chloroform (5 × 10 ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to give an oil, which was submitted to CC [silica gel: 20 g; eluent: toluene containing ethyl acetate (50–80 %) and formic acid (1 %)] to give *14* (70 mg; 36 %) as an oil. Found: C 49.46; H 6.26; N 7.16. Calc. for $C_8H_{11}NO_4,\frac{1}{2}H_2O$: C 49.48; H 6.23; N 7.14. ^{1}H NMR (60 MHz, $CDCl_3$–D_2O:99–1): δ 6.3–5.8 (1 H, m), 4.26 (2 H, s), 3.83 (s) and 3.77 (s) (a total of 5 H), 3.23 (2 H, s). IR (film): 3600–2500 (s, several bands), 1770 (s), 1700 (s), 1400 (s), 1250 (m) cm^{-1}.

(RS)-1-Ethoxycarbonyl-3-hydroxymethylpyrrolidine (17). A solution of *16*[10] (8 g; 26 mmol) in a mixture of aqueous hydrochloric acid (260 ml; 0.1 M) and aqueous ethanol (120 ml; 50 %) was hydrogenated (*ca.* 300 kPa) for 20 h in a PARR low-pressure hydrogenation apparatus using 5 % Pd–C (2.5 g) as a catalyst. The reaction mixture was concentrated *in vacuo* to 100 ml and washed with methylene chloride (2 × 20 ml). The aqueous phase was evaporated *in vacuo* to give an oil (7 g). To an ice-cooled solution of the oil and potassium carbonate (9 g; 65 mmol) in water (90 ml) was added ethylchloroformate (7.8 g; 65 mmol) with stirring, which was continued for 1 h at 0 °C and then for 1 h at room temperature. The reaction mixture was extracted with ether (6 × 100 ml) and the combined and dried ($MgSO_4$) organic phases were evaporated *in vacuo* to give *17* (3.4 g; 80 %). An analytical sample was purified by ball-tube distillation at *ca.* 100 Pa (oven temperature 250 °C). Found: C 55.17; H 8.51; N 7.95. Calc. for $C_8H_{15}NO_3$: C 55.47; H 8.73; N 8.09. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.3–3.9 (3 H, m), 3.8–3.0 (6 H, m), 2.82–2.25 (1 H, m), 2.15–1.65 (2 H, m), 1.26 (3 H, t). IR (film): 3440 (m), 2955 (m), 2870 (w), 1740 (m), 1680 (s), 1460 (s), 1405 (s), 1270 (s) cm^{-1}.

(RS)-Ethyl 3-chloromethylpyrrolidine-1-carboxylate (18). To a stirred solution of *17* (2.0 g; 12.5 mmol) and pyridine (1.0 g; 12.5 mmol) in chloroform (50 ml) was added dropwise a solution of thionyl chloride (3.0 g; 25 mmol) in chloroform (10 ml). The reaction mixture was refluxed for 2.5 h and then evaporated *in vacuo* to dryness. Water (50 ml) was added followed by extraction with chloroform (3 × 75 ml). The combined and dried ($MgSO_4$) organic phases were evaporated *in vacuo* to give an oil, which was submitted to CC [silica gel: 200 g; eluent: toluene containing ethyl acetate (40–60 %)] to give *18* (1.12 g; 50 %). An analytical sample was purified by ball-tube distillation at *ca.* 100 Pa (oven temperature 100 °C). Found: 50.43; H 7.44; Cl 17.25; N 7.39. Calc. for $C_8H_{14}ClNO_2$: C 50.13; H 7.36; Cl 18.50; N 7.31. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.15 (2 H, q, *J* 7 Hz), 3.8–3.0 (6 H, m), 2.8–2.4 (1 H, m), 2.2–1.7 (2 H, m), 1.25 (3 H, t, *J* 7 Hz). IR (film): 2950 (s), 2870 (s), 1695 (s), 1450 (m), 1420 (s), 1380 (s), 1350 (s) cm^{-1}.

(RS)-Ethyl 3-thiocyanomethylpyrrolidine-1-carboxylate (19). A solution of *18* (6.0 g; 31.2 mmol) and sodium iodide (4.7 g; 31.2 mmol) in acetone (180 ml) was stirred at room temperature for 12 h, filtered and evaporated *in vacuo* to give an oil (5.5 g). To a solution of the oil in dimethylformamide (80 ml) was added potassium thiocyanate (16.6 g; 171 mmol) and the reaction mixture was heated to 85 °C for 5 days. The solvent was removed *in vacuo*, and the residue was submitted to CC [silica gel: 300 g; eluent: toluene containing ethyl acetate (50 %)] to give *19* (5.54 g; 83 %) as an oil. Found: C 50.61; H 6.68; N 12.71; S 14.18. Calc. for $C_{19}H_{14}N_2O_2S$: C 50.46; H 6.59; N 13.08; S 14.94. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.15 (2 H, q, *J* 7 Hz), 3.9–3.0 (6 H, m), 2.5 (1 H, m), 2.3–1.8 (2 H, m), 1.25 (3 H, t, *J* 7 Hz). IR (film): 3700–3300 (w), 2950 (s), 2910 (s), 2850 (s), 2150 (s), 1680 (s), 1500–1400 (s, several bands), 1380 (s) cm^{-1}.

(RS)-1-Ethoxycarbonyl-3-pyrrolidinemethanesulfonyl chloride (20). Chlorine gas was passed through an ice-cooled solution of *19* (2.0 g; 10.4 mmol) in water (40 ml) for 2.5 h, and then oxygen was bubbled through the reaction mixture for 10 min. The reaction mixture was extracted with ether (3 × 60 ml). The combined and dried ($MgSO_4$) organic phases were evaporated *in vacuo* to give *20* (2.3 g; 92 %) as an oil. Found: C 38.71; H 5.64; Cl 12.96; N 5.21; S 11.59. Calc. for $C_8H_{14}ClNO_4S$: C 37.58; H 5.52; Cl 13.87; N 5.48; S 12.51. ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.08 (2 H, q, *J* 7 Hz), 3.9–2.6 (7 H, m),

2.5–1.7 (2 H, m), 1.25 (3 H, t, *J* 7 Hz). IR (film): 3500–3100 (m), 2990 (s), 1800–1600 (s), 1450 (m), 1430 (s), 1380 (s) 1260 (s) cm^{-1}.

(RS)-3-Pyrrolidinemethanesulfonic acid (21). A solution of *20* (1.0 g; 4.14 mmol) in aqueous hydrochloric acid (10 ml); 6 M) was refluxed for 2 h. Evaporation *in vacuo* and recrystallization (methanol–ether) gave *21* (190 mg; 41.3 %), m.p. 268 °C (decomp.). Found: C 36.36; H 6.73; N 8.48; S 19.37. Calc. for $C_5H_{11}NO_3S$: C 36.36; H 6.71; N 8.48; S 19.38. ^1H NMR (60 MHz, D_2O): δ 3.7–2.8 (m), 2.5–2.0 (m) and 1.9–1.5 (m) (a total of 13 H). IR (KBr): 3700–3300 (m), 3230–2850 (s), 2850–2200 (m), 1610 (s), 1420 (s), 1300–1100 (s, several bands) cm^{-1}.

Ethyl 3-methylenepyrrolidine-1-carboxylate (22). To a stirred solution of sodium iodide (4.0 g; 27 mmol) and sodium thiosulfate (10 mg) in acetone (20 ml) was added a solution of *18* (4.0 g; 20 mmol) in acetone (20 ml). Stirring was continued at room temperature for 12 h. The reaction mixture was diluted with ether (100 ml), filtered and evaporated *in vacuo* to give an oil, which was dissolved in ethanol (10 ml). To a solution of sodium (460 mg; 20 mmol) and diethyl acetaminomalonate (4.34 g; 20 mmol) in ethanol (70 ml) was added the above solution and the reaction mixture was refluxed for 48 h, until it became neutral. The mixture was cooled, filtered and evaporated *in vacuo*, and the residue was dissolved in water (100 ml) followed by extraction with methylene chloride (5 × 30 ml). The combined and dried (Na_2SO_4) organic phases were evaporated *in vacuo* to give an oil, which was submitted to CC [silica gel: 200 g; eluent: toluene containing ethyl acetate (10–25 %)] gave *22* (3.0 g; 96.7 %). An analytical sample was purified by ball-tube distillation at 1.5×10^{-3} Pa (oven temperature 80 °C). Found: C 61.62; H 8.46; N 9.19. Calc. for $C_8H_{13}NO_2$: C 61.91; H 8.44; N 9.03. ^1H NMR (60 MHz, $CDCl_3$): δ 5.06 (2 H, s), 4.21 (4 H, m, *J* 7 Hz), 3.56 (2 H, t, *J* 7 Hz), 2.8–2.2 (2 H, m), 1.29 (3 H, t, *J* 7 Hz). IR (film): 3550–3150 (s), 3040–2750 (s, several bands), 1680 (s), 1580–1500 (m), 1420 (s), 1375 (s) cm^{-1}.

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