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SYNTHESIS OF CIS- AND TRANS-1-AMINO-3-HYDROXYMETHYL-CYCLOBUTANE-1-CARBOXYLIC ACIDS

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The stereospecific syntheses of cis- and trans-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acids from 3-oxabicyclo[3.1.1]heptan-2-one-1-carboxylic acid are described.

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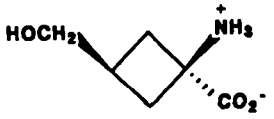
The three achiral cyclobutane amino acids, cis-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (1),[1] 2,4-methanoglutamic acid (3) and 2,4-methanoproline (4)[2] were first isolated from seeds of Atelia herbert-smithii Pittier (Leguminosae);[3] the three free cyclobutane amino acids have also been found in the seeds and leaves of four other Atelia species and of both species of the closely related genus Cyathostegia. No synthesis of 2,4-methanoglutamic acid (3) has been described; two syntheses of 2,4-methanoproline (4) involving [2+2] cycloadditions have appeared.[4,5] This paper reports short syntheses of the naturally occurring amino acid (1) and of trans-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (2) from 3-oxabicyclo[3.1.1]heptan-2-one-1-carboxylic acid (5)[6] as a common intermediate.



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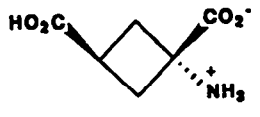

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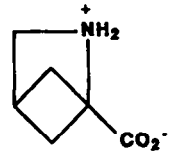

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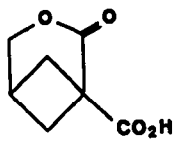

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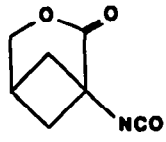

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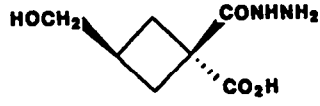

(7)

For the synthesis of the non-naturally occurring trans isomer (2), the bicyclic lactone acid (5) was treated with ethyl chloroformate in the presence of triethylamine, and subsequently with sodium azide to give the corresponding acyl

azide which on heating in toluene gave the crystalline isocyanate (6) in 62% yield. Reaction of (6) with aqueous hydrochloric acid resulted in hydration and decarboxylation of the isocyanate function and in hydrolysis of the lactone to afford, after purification by ion exchange chromatography, trans-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (2) in 66% yield [48% overall yield from (5)]; none of the cis epimer (1) was formed in this sequence.

For the synthesis of the naturally occurring cis-amino acid (1), the lactone (5) was reacted with hydrazine hydrate to form the monoacyl hydrazide (7) in 88% yield. Treatment of (7) with nitrous acid at 0°C gave the corresponding azide which was treated with excess trifluoroacetic anhydride to protect the free hydroxyl groups; the resulting protected acyl azide was heated in dry toluene and the product then treated with aqueous hydrochloric acid to give cis-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (1), with spectroscopic properties identical to those of an authentic sample [78% yield - 69% from (6)].[7] When the intermediate acyl azide is protected in this manner by trifluoroacetylation, only the cis isomer is formed uncontaminated with the trans compound (2); if the protection step is omitted, then a mixture of (1) and (2) is formed and separation of the two epimers subsequently is difficult.

The biological properties of (1) and (2) are currently being investigated and will reported elsewhere.[8]

Experimental.

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer; ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz). For NMR spectra in D_2O, 1,4-dioxan (δ 67.6) was used as the internal standard. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a solution of 5% dodecamolybdophosphoric acid in ethanol or a solution of 0.3% ninhydrin in ethanol. Toluene was dried with sodium and benzophenone.

3-Oxabicyclo[3.1.1]heptan-2-one-1-carboxylic acid (5) prepared as previously described,[6] m.p. 177°-178°C (lit.[6] 178°C), ^{1}H NMR (d_5-pyridine) δ 4.34 (2H, d, CH_2O, J 1.7 Hz), 2.67 (2H, m), 2.35 (1H, m) and 2.13 (2H, m). ^{13}C NMR (d_6-acetone) δ 29.48, 33.24 (t, CH_2), 52.74 (s), 74.06 (t, CH_2O), 170.67 (s, C=O) and 172.02 (s, C=O).

3-Oxabicyclo[3.1.1]heptan-2-onyl-1-isocyanate (6). Ethyl chloroformate (0.78 ml, 8.2 mmol) was added to a solution of 3-Oxabicyclo[3.1.1]heptan-2-one-1-carboxylic acid (5) (257 mg, 1.64 mmol) in acetone (10 ml) in the presence of triethylamine (0.84 ml, 4.1 mmol); the reaction mixture was stirred at 0°C for 3 h, treated with a solution of sodium azide (638 mg, 9.8 mmol) in water (5 ml), allowed to stand at 0°C for 1 h and then extracted with ether (2 x 20 ml). The ethereal extracts were then dried (sodium sulphate) and the solvent removed without heating to give an oil which was dissolved in dry toluene (15 ml); the resulting solution was heated at

110°C for 1 h. The solvent was then removed to give a residue which was crystallised from ether/petroleum ether (b.p. 60°-80°C) to give 3-oxabicyclo[3.1.1]heptan-2-onyl-1-isocyanate (6), (181 mg, 72%), m.p. 84°-86°C, ν_{max} (KBr): 3000, 2980, 2250 (NCO), 1735 (COO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.46 (2H, d, CH_2, J 1.8 Hz), 2.73 (1H, m), 2.52 (2H, m), 2.22 (2H, m). ^{13}C NMR ($CDCl_3$) δ 28.33 (d, C-3), 36.07 (t, CH_2), 58.20 (s, C-1), 72.67 (t, CH_2O), 126.03 (s, NCO), and 172.44 (s, C=O). m/z (CI,NH_3): 171 (100%, $M+NH_4^+$). (Found C, 55.11; H, 4.82; N, 9.15. $C_7H_7NO_3$ requires C, 54.90; H, 4.61; N, 9.15%).

trans-1-Amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (2). 3-Oxabicyclo[3.1.1]heptan-2-onyl-1-isocyanate (6) (175 mg, 1.12 mmol) was treated with aqueous hydrochloric acid (8 ml, 7M) and the reaction mixture was stirred at 100°C for 4 h; the solvent was removed, and the residue triturated with water. The crude product was purified by ion exchange chromatography (Dowex 50x 8-100, H^+ form, eluted with 1M aqueous pyridine) to give trans-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (2), (106 mg, 66%), m.p. 255°C (dec.), ν_{max} (KBr): 3500-2500, 1650, 1600 cm^{-1}. ^1H NMR (D_2O) δ 3.53 (2H, d, CH_2, J 7.0 Hz), 2.59 (1H, m), 2.23 (4H, m). ^{13}C NMR (D_2O) δ 28.65 (d, C-3), 31.85 (t, CH_2), 56.97 (s, C-1), 64.90 (t, CH_2O) and 176.16 (s, C=O). m/z (DCI,NH_3): 146 (100%, $M+H^+$), 145 (12%, M^+) and 128 (70%, $M-17^+$). (Found C, 49.14; H, 7.80; N, 9.28. $C_6H_{11}NO_3$ requires C, 49.65; H, 7.64; N, 9.65%).

3-Hydroxymethyl-cyclobutane-1,1-dicarboxylic acid monohydrazide (7). 3-Oxabicyclo[3.1.1]heptan-2-one-1-carboxylic acid (5) (403 mg, 2.58 mmol) was added to hydrazine hydrate (1.0 ml, 20.6 mmol) and ethanol (0.1 ml) and the resulting reaction mixture stirred for 18 h at room temperature. The solvent was removed and the residue triturated with toluene to remove traces of hydrazine. The crude product was purified by ion exchange chromatography (Dowex 50x 8-100, H^+ form, eluted with 1M aqueous pyridine) to give 3-hydroxymethyl-cyclobutane-1,1-dicarboxylic acid monohydrazide (7), (430 mg, 88%), m.p. 142°-143°C, ν_{max} (KBr): 3520, 3200-2900, 2680-2400, 1680, 1600-1500 cm^{-1}. ^1H NMR (D_2O) δ 3.36 (2H, d, J 5.8 Hz), 2.42 (3H, m), 2.08 (2H, m). ^{13}C NMR (D_2O) δ 31.10 (d, C-3), 32.19 (t, CH_2), 50.41 (s, C-1), 65.81 (t, CH_2O), 174.51 (s, C=O), and 177.43 (s, C=O). m/z (EI): 188 (1%, M^+), 169 (18%), 112 (100%) and 67 (75%).(Found C, 44.70; H, 6.60; N,14.71. $C_7H_{10}N_2O_4$ requires C, 44.68; H, 6.43; N, 14.89%).

cis-1-Amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (1). Ether (10 ml) was added to a solution of 3-hydroxymethyl-cyclobutane-1,1-dicarboxylic acid monohydrazide (7) (61 mg, 0.32 mmol) in aqueous hydrochloric acid (5 ml, 5 M) and the two-phase reaction mixture was treated with sodium nitrite (100 mg, 1.44 mmol) at 0°C. The reaction mixture was stirred for two hours and the layers separated. The aqueous layer was extracted with ether (3 x 30 ml) and the combined organic extracts were dried (sodium sulphate) and solvent removed at room temperature. The residue was treated with trifluoroacetic anhydride (1 ml); after two hours, the excess anhydride was removed at room temperature and the crude oil dissolved in dry toluene (20 ml) and the resulting solution was heated at 110°C for one hour. The solvent was removed and the residue was boiled in aqueous hydrochloric acid (4 ml, 7 M) for 3 h. The reaction mixture was then evaporated to dryness and the product purified by ion exchange chromatography (Dowex 50x 8-100, H^+ form, eluted with 1M aqueous pyridine) to give cis-1-amino-3-hydroxymethyl-cyclobutane-1-carboxylic acid (1), (41 mg, 78%), m.p. 210°C (dec.) [lit. m.p. 210°C (dec.)] with identical ^1H NMR and ^{13}C NMR spectra to those of an authentic sample.[7] (Found C, 43.90; H, 7.76; N, 8.22. $C_6H_{11}NO_3.H_2O$ requires C, 44.17; H, 7.60; N, 8.59%).

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