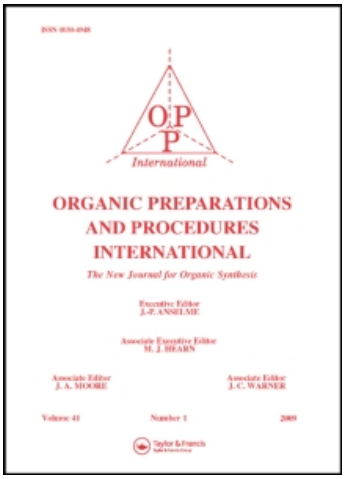

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A CONVENIENT SYNTHESIS OF (dl)-1-AMINO-4-CARBOXYCYCLOHEXANE-1-^{13}C-CARBOXYLIC ACID

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A CONVENIENT SYNTHESIS OF (dl)-1-AMINO-4-CARBOXYCYCLOHEXANE-1-^{13}C-CARBOXYLIC ACID

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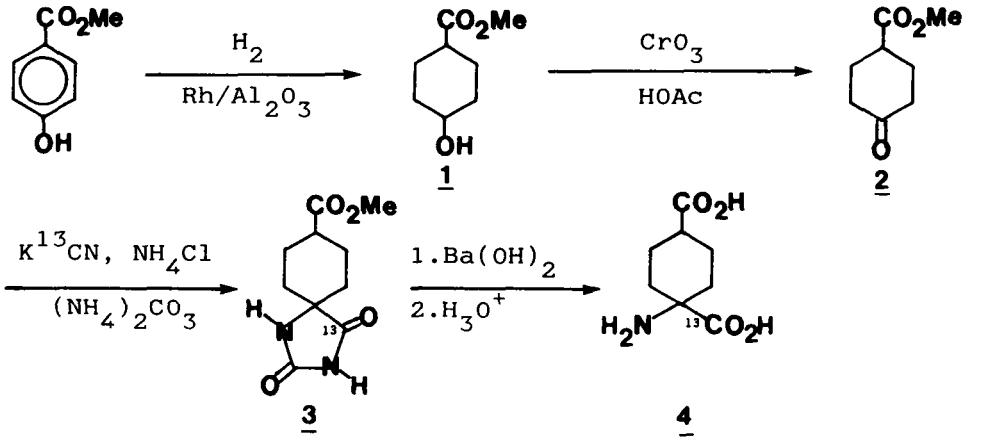
Nuclear spin-spin coupling provide an exceedingly important probe of peptide conformations in solution,[1] provided that the conformational dependencies can be established in suitable model compounds such as cyclic and bicylic lactams and amino acids.[2] For these purposes, we required a convenient synthesis of (d)-1-amino-4-carboxycyclohexane carboxylic acid (4) bearing a carbon-13 label in the amino acid carboxyl group which would permit us to obtain experimental spin-spin coupling.



constant data. The synthesis (4) shown here gave a 64% overall yield.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. and Mic-Anal Organic Microanalysis, Tucson, AZ. ^{1}H and ^{13}C nmr spectra were recorded on a JEOL FX-90Q FT NMR spectrometer. Chemical shifts are reported relative to TMS or DSS as internal standards. Mass spectra were determined on a Hewlett Packard 5995B GC/MS (electron impact) and a Finnigan-Mat 212B mass spectrometer (FAB). Infrared spectra were obtained on a Perkin-Elmer Model 1430 spectrophotometer.

Methyl 4-Hydroxycyclohexanecarboxylate (1).- Methyl p-hydroxybenzoate (30 g., 0.20 mol.) was hydrogenated over 5% rhodium on alumina (2 g.) in 150 ml glacial acetic acid at 50 psi (after thorough flushing the system with hydrogen). The adsorption of three equivalents of hydrogen required 24 hrs. The catalyst was removed by filtration through Celite and the solvent removed by evaporation in vacuo. The oily residue was taken up in ether, washed successively with water, saturated sodium bicarbonate solution and water. The ethereal solution was dried over magnesium sulfate and the ether removed in vacuo. The proton nmr indicated the absence of all aromatic protons and the IR (neat) revealed peaks at 3450 and 1750 cm^{-1} indicative of the desired hydroxy ether. The clear oily liquid (31.2 g., 100%) was used without further purification.

Methyl 4-Ketocyclohexanecarboxylate (2).- To a solution of methyl 4-hydroxycyclohexanecarboxylate (23.7 g., 0.15 mol) in 60 ml glacial acetic acid in a 250 ml round bottom reaction flask equipped with a thermometer, condenser, and pressure

equalizing addition funnel, was added chromium (VI) oxide (14.6 g., 0.146 mol) in 35 ml of glacial acetic acid and 9 ml water at such a rate as to maintain a temperature below 36°; the temperature was easily controlled by addition rate and an external tap water cooling bath. After the addition, the dark green mixture was allowed to stand overnight. The mixture was taken up in ether, extracted successively with water, saturated sodium bicarbonate solution and water. The ethereal solution was dried over anhydrous magnesium sulfate, filtered and the ether removed by evaporation in vacuo. Distillation of the clear light yellow liquid gave two fractions; the unreacted alcohol bp. 98-101°/2.0mm, lit.[3] bp. 150-161°/25mm and 20.1 g. (86%) of the desired ketone, bp. 94-96°/0.5mm, lit.[3] bp. 140°/2.0mm. IR (neat): 1725 cm^{-1}; ^{1}H nmr ($CDCl_3$ at 89.55 MHz): δ 2.19 (4H, m), 2.44 (4H, m), 2.80 (1H, m), 3.73 (3H, s); ^{13}C nmr ($CDCl_3$ at 22.49 MHz): δ 28.26 ($-CH_2-$) 39.45 ($-CH_2$ to CO), 40.29 (-CH-), 51.67 (methyl of ester), 174.32 (ester C=O), 209.63 (ketone C=O).

1.3-Diaza-8-carboxyspiro[4.5]decane-2.4-dione-4-^{13}C (3).- To a stirred solution of methyl-4-ketocyclohexanecarboxylate (1.60 g., 10.3 mmol) and ammonium chloride (0.83 g., 15.4 mmol) in 20 ml of ethanol-water (1:1) was added a solution potassium ^{13}C-cyanide (1.0 g., 15.4 mmol), 99 atom % C-13, in 5 ml of water. The solution was stirred at room temperature for 3 hrs. at which time ammonium carbonate (3.96 g., 41.2 mmol) in 15 ml of water was added over a 30 min. period. The solution was then heated at 60° for 18 hrs. The temperature was then raised to 90° and held for 1.5 hr. at that temperature to decompose

excess ammonium carbonate.[4] The reaction mixture was concentrated in vacuo to one half its volume and the aqueous solution allowed to stand in the cold room overnight. The white crystals were collected and washed with cold water until the filtrate was neutral to pH paper. Upon drying the crystalline hydantoin weighed 2.15 g. (92%), mp. 243-249°. IR (KBr): 1710, 1730, 3120, 3250 cm^{-1}; ^{1}H nmr (DMSO-d_6 at 89.55 MHz): δ 1.64 (8H, ml), 1.75 (1H, m), 3.61 (3H, s), 8.46 (2H, s); ^{13}C nmr (DMSO-d_6 at 22.49 MHz): δ 23.50 (-CH_2-), 32.40 (-CH_2-), 40.66 (-CH-), 51.51 (CH_3-of ester), 61.63 (-C-), 156.42 (-NH-CO-NH-), 174.71 (ester -CO-), 178.44 (-CO-NH-). ^{13}C nmr revealed also that the carbon label was located at the carbonyl adjacent to the cyclohexane ring, i.e., the amide carbonyl carbon. Additionally, the $^{3}J_{CC}$ of 3.10 Hz between the labeled carbonyl carbon and the cyclohexane ring methylene carbon indicated that the hydantoin is produced with the amide carbonyl preferentially in the equatorial position. MS: M^{+}: 227.1; calcd 227.1. Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.28; H, 6.21; N, 12.33

Found: C, 53.24; H, 6.33; N, 12.36

(dl)-1-Amino-4-carboxycyclohexane ^{13}C-carboxylic Acid (4).- 1,3-Diaza-8-carbomethoxyspiro[4.5]decane-2,4-dione-4-^{13}C (1.14 g., 5.0 mmol) was heated at reflux with barium hydroxide octahydrate (4.73 g., 15.0 mmol) in 50 ml of water for 24 hrs.[4] The reaction mixture was cooled to room temperature and acidified with concentrated H_2SO_4. The precipitated barium sulfate was removed by filtration and washed with hot water. The filtrate and hot water washes were combined and taken to dryness in vacuo. The white solid was taken up in water and carefully

acidified to pH 4.5 by the addition of 25% HCl at which time the solution became turbid. The solution was allowed to stand in the cold room overnight and the resulting white precipitate, after filtration and drying, weighed 0.76 g. (81%), mp. 274-275° and gave a positive ninhydrin test. IR (KBr): 2780-3300, 1690, 1605 cm^{-1}; MS: M^+ not seen (which is common for α-amino acids using electron impact mass spectroscopy) but parent ion m/e found to be 143.1 from loss (M-45) of the carboxyl adjacent to the amino group characteristic of α-amino acids. M-18 (loss of water) was also observed. To further substantiate the structure, a fast atom bombardment MS (which does provide a molecular ion peak as MH^+) was performed. Fast atom bombardment (FAB) mass spectrometry with thioglycerol as carrier provided MH^+ (m/e 188) as the parent ion and MH^+ plus thioglycerol at m/e 296. The total ion chromatogram from the FAB experiment indicated the compound to be pure. ^{1} nmr (D_2O/NaOD at 89.55 MHz): δ 1.67 (8H, m), 2.03 (1H, m); ^{13}C nmr (D_2O/NaOD at 22.49 MHz): δ 27.18 ($-CH_2-$), 37.00 ($-CH_2-$), 48.38 (-CH-), 59.89 (-C-), 187.87 (4-carboxyl -CO-), 188.40 (α-NH_2 -CO-).

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48

Found: C, 51.30; H, 7.19, N, 7.40

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