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Simple Synthesis of (R)-Carnitine from D-Galactono-1,4-lactone

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Abstract:

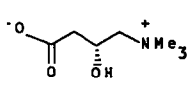
(R)–Carnitine was prepared by two simple, short and efficient syntheses starting from D-*galactono–1,4–lactone.*

INTRODUCTION

(R)-Carnitine, 1, the growth factor vitamin Bt of Tenebrio molitor,[1] has, since its isolation from meat in 1905[2], been subject to a large and increasing interest. (R)-Carnitine plays an important role in the metabolism of fatty acids, acting as a carrier of fatty acids over the mitochondrial membrane,[3] and it has been used in therapy as a stimulator of fatty acid degradation. The fact that (S)-carnitine is an inhibitor of carnitine acyltransferases[4] makes the availability of enantiomerically pure (R)-carnitine vital.

Therefore the enantioselective synthesis of 1 has recently received considerable attention. Several strategies have been used, for instance chirality has either been stereoselectively induced by means of yeast[5] or through chiral hydrogenation,[6] or it has been projected from chiral pool compounds like ascorbic acid,[7,8] L-arabinose[8] or (R)-malic acid.[9] As a continuation of our work on using aldonolactones as synthons, we now describe two syntheses of 1 from D-galactono-1,4-lactone.

Fig. 1



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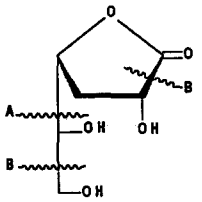

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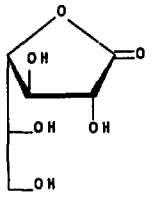

D-Galactonolactone

DISCUSSION

Some years ago we described the stereoselective hydrogenation of acetylated aldonolactones to give 3-deoxy-aldonolactones.[10] Cleavage of the C 4-5 bond of a 3-deoxy-hexonolactone, with 2-(R)-configuration, yields a four carbon fragment with the correct stereochemistry for the synthesis of 1 (Route A, Fig. 2). Alternatively, cleavage of both the C 1-2 and C 5-6 bonds of a 3-deoxy-hexonolactone, having 4-(R)-configuration, also yields a four carbon fragment which can be converted into 1. (Route B, Fig. 2). 3-Deoxy-D-*xylo*-hexono-1,4-lactone (2) has the correct configuration in both centers, and can thus be used as a common starting material in both approaches. Compound 2 can be made from D-galactono-1,4-lactone in two simple steps.[10]

Following Route A, 2 was treated with 40% aqueous Me_2NH for 1.5 h at 25°C to give the crystalline amide 3 in 76% yield. Shorter or longer reaction time gave a lower yield due to either incomplete reaction of 2 or to hydrolysis of 3. Reduction of 3 with $BH_3 \cdot SMe_2$ in boiling dioxane gave the dimethylamine 4 in 79% yield, and subsequent reaction of 4 with MeI in MeOH yielded the crystalline trimethylammonium iodide 5 in 89% yield. The critical step in the synthesis was the oxidative cleavage of the polyol chain in 5. It was found that oxidation with $KMnO_4$ in acidic media proceeded satisfactorily when only the stochiometric amount[11] of permanganate was used; excess reagent tended to give oxidative cleavage between C-2 and C-3 to give betain. Under the right conditions 5 was converted into 1 in 88% yield. Crystallisation gave optically pure 1 in 58% yield.[12]

In the alternative approach (Route B) the C 5-6 bond was cleaved as the first step. Thus 2, when treated with $NaIO_4$, gave a quantitative yield of the aldehyde 6, which was completely in the hydrate form. When dissolved in EtOH the compound formed hemiacetals that slowly gave the hydrate in H_2O. Since 6 was unstable it was not further characterised. Hydrogenation of 6 in the presence of $MeNH_2$ gave the 5-methylamino amide 7 in 90% yield. Hydrolysis of the latter in boiling aqueous KOH gave the corresponding amino acid 8 in 70% yield. A 2,4-dihydroxy-5-methylamino valeric acid with unknown stereochemistry has been described;[13] it had a different melting point. Quaternisation of 8 with $(MeO)_2SO_2/Na_2CO_3$ gave crystalline 9 (73 % yield). Finally, 9 was converted into 1 by oxidative cleavage in the same manner as for 5 to give crystalline 1 in 62% yield.

The procedures reported here have the advantages compared to previous syntheses, of having few steps, using inexpensive reagents and giving an enantiomerically pure product.

Fig. 2

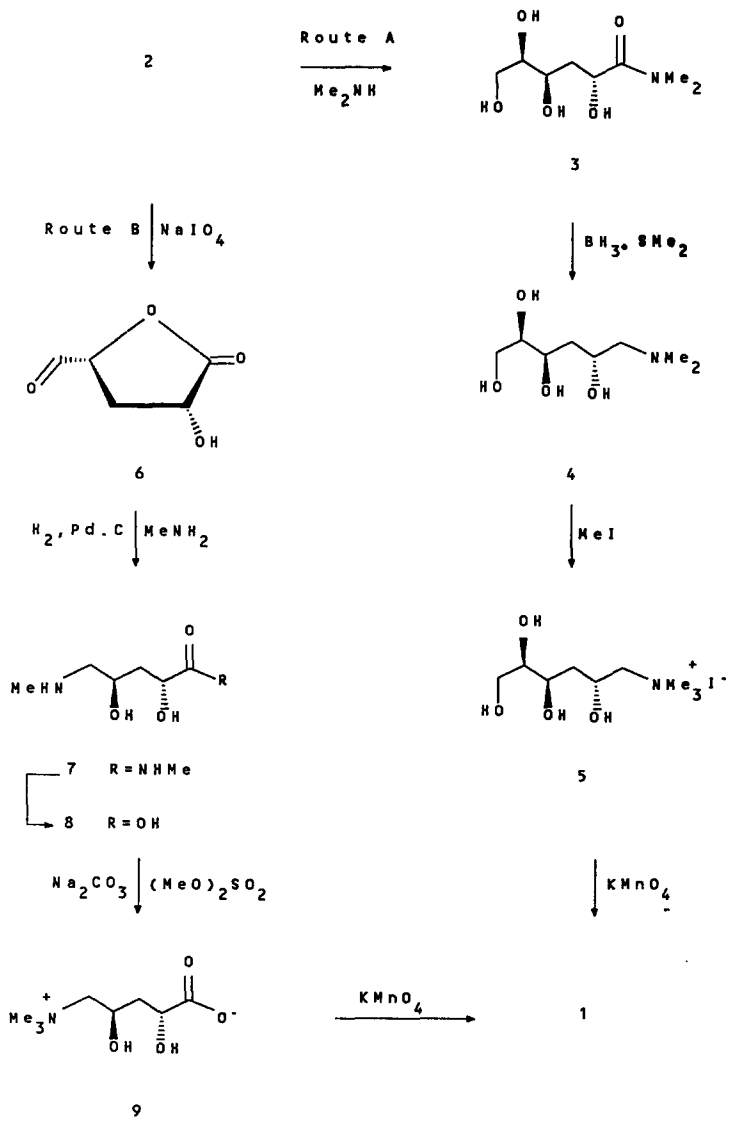

Fig 2. Synthetic routes from 3-deoxy-D-galactono-1,4-lactone (2) to (R)-Carnitine (1).

EXPERIMENTAL

^{13}C-NMR spectra were recorded on a Bruker AC-250 instrument with D_2O as solvent using 1,4-dioxane as internal reference (67.40 ppm). Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. Microanalyses were carried out by Leo Microanalytical Laboratory. Concentrations were performed on a rotary evaporator at a temperature below 40°C.

3-Deoxy-D-*xylo*-hexonic dimethylamide, 3

3-Deoxy-D-*xylo*-hexono-1,4-lactone,[10] 2 (6.5 g) and aqueous dimethylamine (26 ml, 40%) was stirred for 1.5 h at 25° C. Concentration left a colorless, sirupy residue, which crystallised on addition of EtOH (6.3 g, 76%, mp. 104-108° C). Recrystallisation from EtOH gave a product with mp: 109.5-112° C, $[\alpha]_D^{20}$ + 20.6° (*c* 0.7, EtOH), Anal: Calc. for $C_8H_{17}NO_5$ x 0.2 H_2O[14]: C, 45.58; H, 8.32; N, 6.64; Found: C, 45.57; H, 8.44; N, 6.58; ^{13}C-NMR: δ 36.6 and 37.4 (NMe_2). 37.7 (C-3), 63.5 (C-6), 65.8, 68.3 (C-2, C-4), 75.3 (C-5) and 176.0 ppm (C-1).

N,N-dimethyl-1-amino-1,3-dideoxy-D-*xylo*-hexitol, 4

To a solution of 3 (7.9 g) in dioxane (90 ml), was added a solution of $BH_3 \cdot SMe_2$ (25 ml, 10M) in dioxane (10 ml) at 0°C. The mixture was boiled, under N_2 atmosphere, for 4.5 h, and was then kept 18 h at 25°C. Hydrolysis was performed by adding HCl (60 ml, 0.7 M) and boiling for 2 h. Concentrating the mixture left a residue, from which MeOH was evaporated twice. The product was purified by absorbtion on a column of cation exchange resin (Amberlite IR-120, 100 ml, H^+), washing, and eluting with NH_4OH (150 ml, 12.5 %). Concentration of the eluate gave the desired product (5.8 g, 79%) as a colorless syrup $[\alpha]_D^{20}$ +21.9° (*c* 1.4, H_2O), Anal. Calc. for $C_8H_{19}NO_4$ x 0.2 H_2O[14]: C, 48.81; H, 9.93; N, 7.12; Found: C, 48.82; H, 10.05; N, 6.90; ^{13}C-NMR: δ 39.4 (C-3, t), 45.3 (NMe_2, q), 63.5 (C-6, t), 65.7 (C-1, t); 66.0 and 68.8 (C-2, C-4, d) and 75.6 (C-5, d).

N,N,N-trimethyl-1-amino-1,3-dideoxy-D-*xylo*-hexitol iodide, 5

N,N-dimethyl-1-amino-1,3-dideoxy-D-*xylo*-hexitol, 4 (2.0 g) was dissolved in MeOH (40 ml), and a solution of methyl iodide (1.0 ml) in MeOH (10 ml) was slowly added at 0° C. The solution was kept for 18 h at 25° C. Concentration gave a residue, which on addition of one drop of water and absolute EtOH gave crystalline 5. Yield: 3.1 g (89%, mp: 64-66° C). Recrystallisation from MeOH/Et_2O furnished a product with mp: 65-66.5° C, $[\alpha]_D^{20}$ -0.8° (*c* 1.0, H_2O). Anal. Calc for $C_9H_{22}NO_4I$ x H_2O[14]: C, 30.60; H, 6.85; N, 3.96; I, 35.95; Found: C, 30.63; H, 6.78; N, 3.82; I, 35.80; ^{13}C NMR: δ 38.9 (C-3), 55.0-55.1 (NMe_3), 63.4 (C-6), 63.8 (C-2), 67.8 (C-4), 71.6 (C-1) and 75.3 ppm (C-5).

(R)-Carnitine, 1, from 5

N,N,N-trimethyl-1-ammonium-1,3-dideoxy-D-*xylo*-hexitol, iodide 5 (1.0 g, 3 mmoles) was dissolved in

H_2SO_4 (4N, 10 ml), and an aqueous solution of $KMnO_4$ (0.25 M, 44 ml, 11 mmoles) was added dropwise keeping the temperature below 30° C. The mixture was stirred for 10 min and then filtered. I_2 was removed by extraction with CH_2Cl_2 (2 x 10 ml), and the aqueous phase was placed on an ion exchange column (IR-120, H^+, 80 ml). The column was washed with water and eluted with NH_4OH (10%, 250 ml). Concentration of the alkaline eluates left syrupy 1 (424 mg, 88%). By addition of acetone/EtOH colourless crystals were obtained (278 mg, 58%). mp. 184-188° C, $[\alpha]_D^{20}$ - 24.0° (*c* 0.77, H_2O), (Litt.[12] mp: 197-198 °C, $[\alpha]_D^{20}$ - 23.9° (c, 0.86, H_2O)). ^{13}C-NMR: δ 43.8 (C-2, t), 54.9 (NMe_3, q), 64.9 (C-3, d), 71.0 (C-4, t) and 178.9 (C-1, s).[15]

5-Amino-3,5-dideoxy-5-N-methyl-L-*threo*-pentonic acid, 8

To a solution of $NaIO_4$ (14.2 g) in water (150 ml) was added 3-deoxy-D-*xylo*-hexono-1,4-lactone, 2 (10.0 g) over 5 min at 5°C. The mixture was stirred at this temperature for 30 min, and $(CH_2OH)_2$ (0.30 ml) was added. $NaIO_3$ spontaneously crystallised and was removed by filtration. The filtrate was concentrated, and remaining $NaIO_3$ was precipitated by adding EtOH (50 ml). Filtration, concentration and coconcentration with water left the hydrate of 6 as a colorless syrup (9.36 g). This product was used directly in the next reaction. ^{13}C-NMR: δ 32.2 (C-3), 68.4 (C-4), 79.1 (C-2), 90.3 (C-1) and 179.8 (C-5).

To a solution of 6 (8.0 g) in EtOH (150 ml), $MeNH_2$ (40%, 10 ml) and Pd/C (5%, 400 mg) was added. The mixture was hydrogenated (5000 kPa) for 18 h, filtered and concentrated. The residue was absorbed on IR-120 (H^+, 80 ml) and eluted with 2% NH_4OH. The alkaline fraction was concentrated to give syrupy 7 (8.39 g, 90% from 2). ^{13}C-NMR: 26.4 (NMe-1), 35.2 (NMe-5), 39.6 (C-3), 56.8 (C-5), 66.6 and 69.2 (C-2 and C-4) and 178.1 (C-1).

A solution of 7 (7.0 g) in aqueous KOH (2M, 100 ml) was boiled for 80 min. The solution was cooled and poured on an ion exchange column (IR-120, H^+, 150 ml). The column was washed until neutral and eluted with 10% NH_4OH. Concentration of the alkaline fractions gave a crystalline residue of 8 (4.56 g, 70%). Recrystallization from EtOH gave a product (2.55 g, 39%) with the following data: mp. 158-160° C (litt.[13] (stereochemistry unknown) mp. 190-193°C). $[\alpha]_D^{20}$ + 11.2° (*c* 1.1, H_2O), Anal. Calc. for $C_6H_{13}NO_4$ x 0.5 H_2O[14]: C, 41.85; H, 8.20; N, 8.13 ; Found: C, 41.48; H, 8.24; N, 8.19. ^{13}C-NMR: δ 33.7 (NMe), 39.7 (C-3), 54.9 (C-5), 64.8 and 69.6 (C-2 and C-4), 182.0 (C-1).

5-Amino-3,5-dideoxy-N,N,N-trimethyl-L-*threo*-pentonic acid, 9

To a suspension of 8 (1.0 g) in MeOH (20 ml), Na_2CO_3 (2.0 g) and Me_2SO_4 (2.0 g, 1.5 ml) was added at 0-5°C. The mixture was stirred for 18 h at 25°C, concentrated and the residue was dissolved in water (50 ml). Absorbtion on IR-120 (H^+, 40 ml) eluting extensively with 10% NH_4OH (2 l), and concentration gave the desired product (1.12 g, 95%). A crystalline product was obtained from EtOH/acetone (0.86 g, 73%) mp. 215-216° C, $[\alpha]_D^{20}$ + 6.3° (*c* 1.7, H_2O). Anal. Calc. for $C_8H_{17}NO_4$ x H_2O[14]: C, 45.92; H, 9.15; N, 6.69: Found: C, 46.29; H, 9.08; N, 6.98 . ^{13}C-NMR: δ 40.5 (C-3, t), 55.0 (NMe_3, q), 64.1 and 69.3 (C-2 and C-4, d), 71.4 (C-5, t) and 181.8 (C-1, s).

(R)-Carnitine, 1, from 9

A solution of 9 (0.50 g, 2.6 mmoles) in H_2SO_4 (2N, 10 ml) was oxidised with $KMnO_4$ (0.25 M, 10.5 ml) as described above. A similar work-up procedure afforded crystalline (R)-carnitine (0.26 g, 62%) with the following data: mp: 190-192°C, $[\alpha]_D^{20}$ - 26.9° (*c* 0.7, H_2O).

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