Stereospecific Synthesis of (*R*)-Aminocarnitine (Emeriamine) Starting from (*R*)-Carnitine *via* Double Inversion of Configuration

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(*R*)-Aminocarnitine (**1**)[1] and its *N*-acyl derivatives have been reported to possess interesting pharmacological properties: in fact, they behave as inhibitors of fatty acid oxidation and act as hypoglycemic and antiketogenic compounds as well.[1a] In particular, they alter lipidic metabolism by inhibiting carnitine acetyltransferase (CAT)[1b] and carnitine palmitoyltransferase (CPT),[1b–d] which catalyze the transfer between the (*R*)-carnitine and CoASH of the acetyl group and the long-chain groups, respectively.

Despite its pharmacological interest, the currently available synthetic methods for (*R*)-aminocarnitine (corresponding to the *L*-isomer) are not satisfactory:[1b,e–k] complexity of the syntheses, low yields, and/or the necessity of separating diastereoisomeric mixtures are the limiting factors. Only one synthesis makes use of carnitine as the starting material, but it passes through dehydration with a concomitant loss of chirality, which is then recovered by formation of a diastereoisomeric amino derivative.[1l]

In this paper, we report the stereospecific conversion of (*R*)-(−)-carnitine (**2**) to (*R*)-(−)-aminocarnitine **1**.[1m] The reaction is performed in only five nominal steps, consecutively carried out with an overall chemical yield of 49%. The stereochemical control involves a double inversion of configuration of the stereogenic center. Actually, the reaction exploits the unique opportunity offered by easy access to the β−lactone derivative **5**, which we have already presented as the key intermediate in the totally enantioselective inversion of configuration of (*S*)-(+)-carnitine.[2]

It is also worth mentioning that (*R*)-(−)-carnitine (**2**), in the bulk market of pharmaceutical chemicals, is a relatively inexpensive material, especially when considering the recently discovered possibility of recovering tons of waste (*S*)-carnitine obtained during industrial production of the biologically active *R*-stereoisomer.[2]

Scheme 1 illustrates in detail the "β-lactone" strategy for stereochemical control as well as each individual reaction. Starting from (*R*)-(−)-carnitine **2**, its methanesulfonate derivative **4** was obtained by routine reactions;[2] it should be noted that the temporary protection of the carboxy function as the isobutyl ester **3** was necessary to avoid substrate decomposition during the mesylation step. Treatment of a dilute solution of **4** in DMSO with 1 equiv of $NaHCO_3$ for 6 h at rt afforded the noncrystallizable (*S*)-β-lactone derivative **5** with complete inversion of configuration.

As to the stereochemistry of this step,[2] hydrolysis to enantiomerically pure (*S*)-carnitine clearly proves its stereochemical characteristics.

Sodium azide was than added directly to the solution to afford, after 2 h, the newly inverted (*R*)-azidocarnitine **6** (see the following text for establishment of configuration). The crude product was taken up in MeOH, the insoluble matter was filtered, and the filtrate was subjected to catalytic reduction with 10% Pd/C for 1 night to give the (*R*)-(−)-aminocarnitine inner salt **1** after elution on Amberlite IRA-402 (OH^- form) and Amberlite IRC−50 (COOH form).

Yields after purification amount to 55% starting from mesylate **4**, and 49% starting from carnitine **2** itself. The enantiomeric purity (>99% ee)[3] is the measure of the optical efficiency of the process, which proceeds with overall retention of configuration.

The final stereochemical outcome of the entire process indicates that the two key steps (*i.e.*, closure to the β-lactone **5** and subsequent nucleophilic attack of the azide anion to the β carbon) must be totally stereoselective, giving, after double inversion of configuration of the stereogenic center, the (*R*)-(−)-aminocarnitine (**1**) with the same configuration as the starting carnitine **2**. Indeed, an important characteristic of the reaction is the site-selective attack of the azido nucleophile on the stereogenic center in the β-lactone ring (products arising from the possible oxygen−acyl bond fission in **5** do not appear to be formed in this reaction).[4] This peculiar behavior differs from the nucleophilic attack of the hydroxide anion, which is directed onto the carboxy carbon only,[2,5] and can be explained in terms of the hard and soft acids and bases (HSAB) theory.[6] It is probably unnecessary to emphasise that the reaction, as a whole, has been also successfully applied to the synthesis of (*S*)-aminocarnitine starting from (*S*)-carnitine. It should also be pointed out that direct treatment of the isobutyl ester of **4** with NaN_3 gave rise to racemic azidocarnitine isobutyl ester, formed through a β-elimination−addition reaction, as made evident by ^{1}H-NMR monitoring. A further observation is that both preparation of the lactone

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(3) We could not detect traces of the enantiomer of **1**. The enantiomeric purity (>99% ee) was determined by converting the final product to the derivative obtained with *o*-phthalaldehyde and acetyl-L-cysteine and examining this by HPLC; see: Buck, R. H.; Krummen, K. *J. Chromatogr.* **1987**, *387*, 255–265.

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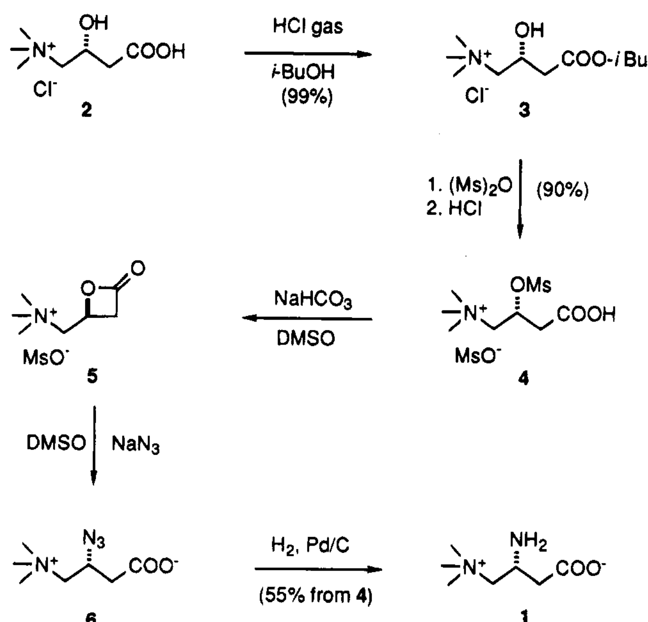
Scheme 1



via Mitsunobu reaction,[7] as well as direct inversion of configuration of the carnitine benzyl ester chiral center under the same conditions, also failed: probably, the trimethylammonium moiety inhibits formation of the intermediate triphenylphosphonium salt, due to the high degree of steric hindrance and charge concentration.

The transformations we have reported here represent an example of a straightforward, totally stereocontrolled synthesis of a β-amino acid derivative of significant biological importance and possible medical use, having the same chirality as the β-hydroxy acid employed as starting material.

Experimental Section

Melting points were determined by the capillary method on an electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were taken at 300 MHz; chemical shifts were expressed in δ values downfield from DSS. Sodium azide, sodium bicarbonate, and anhydrous DMSO were purchased from Aldrich. Hydrogen chloride gas was purchased from Fluka. Amberlite IRA-402 and Amberlite IRC-50 were purchased from Carlo Erba. (*R*)-Carnitine was obtained from Biosint (Sigma-Tau group).

The preparation of the methanesulfonic derivative **4** starting from isobutyl ester **3** was performed as described in ref 2.

(*R*)-Carnitine Isobutyl Ester (3). A suspension of **2** (9.9 g, 0.05 mol) in isobutyl alcohol (50 mL) was saturated with HCl gas and the resulting solution was refluxed for 3 h. The solution was then concentrated under vacuum, and the residue was taken up twice into isobutyl alcohol (2 × 50 mL) and concentrated to dryness. The residue was triturated with acetone to give after filtration **3** in quantitative yield (>99%). See ref 2 for analytical data.

(*R*)-Aminocarnitine Inner Salt (1). Sodium bicarbonate (0.5 g, 5.96 mmol) was added to **4** (2 g, 5.96 mmol) in DMSO (100 mL), and the resulting solution was stirred at room temperature for 6 h (until complete formation of **5**, monitored by HPLC and NMR). Sodium azide (0.387 g, 5.96 mmol) was added, and the resulting solution was kept under stirring at room temperature for 2 h. Following precipitation and repeated treatments with Et_2O, a raw material containing **6** was obtained: ^{1}H NMR (300 MHz, D_2O) $\delta = 4.48-4.38$ (m, 1H), 3.50–3.40 (m, 2H), 3.20 (s, 9H), 2.68–2.50 (m, 2H); IR (neat) 2121 (CN_3), 1595 (C=O) cm^{-1}. The crude product was taken up in MeOH, the insoluble matter was filtered, and the filtrate was subjected to catalytic hydrogenation on 10% Pd/C (0.098 g) at 45 psi. After 1 night, the reaction mixture was filtered on Celite, and the filtrate was concentrated, transferred into Amberlite IRA-402 (20 g, OH^- form), and eluted with deionized water to a pH of 7. The eluate was concentrated and transferred onto Amberlite IRC-50 (20 g, COOH form, previously washed with 2% NH_4OH, reactivated with 2 N HCl, and neutralized with H_2O) and eluted with deionized water until complete elution of neutral and acidic impurities. Following elution with 2% NH_4OH, eluate evaporation under vacuum, and trituration with CH_3CN, 0.53 g (55%) of **1** was obtained: mp 150 °C dec; $[\alpha]_D = -21.13$ (c = 0.4 in H_2O); ^{1}H NMR (300 MHz, D_2O) δ 3.72–3.62 (m, 1H), 3.48–3.38 (m, 2H), 3.22 (s, 9H) 2.50–2.36 (m, 2H); MS (FAB) *m/z* 161 $(M + H)^+$. Anal. Calcd for $C_7H_{16}N_2O_2$: C, 52.47; H, 10.06;, N, 17.48. Found: C, 52.15; H, 10.42; N, 17.22.

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