Efficient Enantioselective Synthesis of (*R*)-(−)-Carnitine from Glycerol

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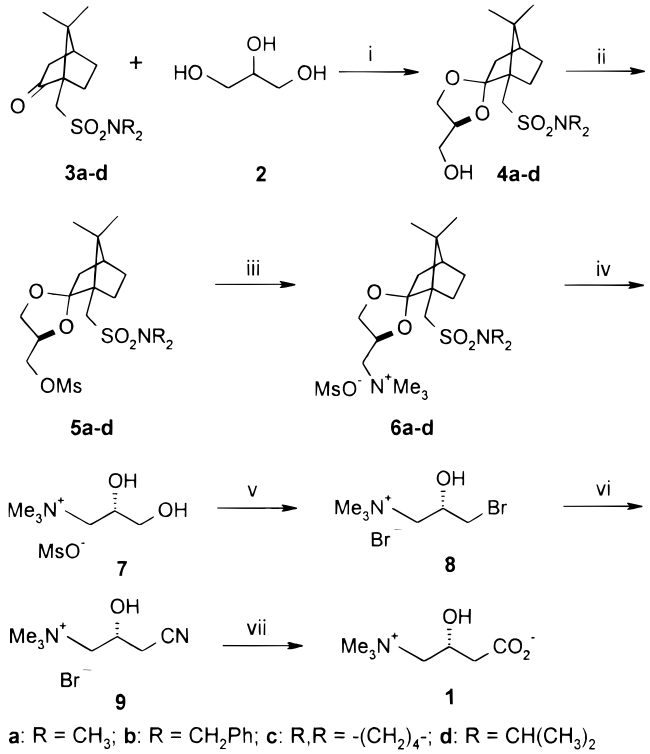
In biochemical pathways, (*R*)-(−)-carnitine **1** plays an important role in the β-oxidation of fatty acids and is also involved in other important metabolic roles, both as free carnitine and as acylcarnitines.[1,2] The increasing demand for this compound has led to the development of numerous procedures for (*R*)−(−)-carnitine synthesis, involving asymmetric synthesis,[3] resolution through diasteroisomeric derivatives,[4] microbiological or enzymatic tecniques,[5] and the use of chiral starting materials;[6] however, few of these procedures are of practical use.

In this paper, we report a convenient, high yielding and easy synthesis of the four carbon-atom molecule, (*R*)−(−)-carnitine **1**, starting from glycerol **2** (Scheme 1). Glycerol was first desymmetrized according to a procedure described by Uang,[7a] making use of a (1*R*)-(−)-10-camphorsulfonamide **3** derivative as the chiral auxiliary.[8] The stereochemistry of camphorsulfonamide was obviously chosen on the basis of the chirality of the carnitine isomer to be synthesized. The overall process is described in Scheme 1 while the yields of each step is given in Table 1.

The chiral information was introduced into glycerol by reaction with a selected (**3c**, vide infra) sulfonamide derivative.[7] Only one spiro-acetal, **4c**, of the four possible stereoisomers, formed in 60% yield based on **3c**. The correct (*S*)-configuration of the glycerol derivative **4c** was established on the basis of its final conversion to (*R*)-(−)-carnitine **1**. **4c** was then converted, in almost quantitative yield, into the corresponding mesylate **5c** by treatment with metanesulfonyl chloride and triethylamine, and the newly created leaving group was finally displaced by trimethylamine to form **6**, carrying the trimethylammonium moiety characteristic of carnitine. The chiral auxiliary was then cleaved off by HCl treatment, and thoroughly recovered from the organic layer after the reaction mixture workup, while the dihydroxypropyltrimethylammonium mesylate **7** was obtained by evaporation of the aqueous solution. **7** was then treated with HBr in acetic acid to form, exclusively, the primary bromide **8**.[9] **8** was in turn converted into the required four carbon atoms skeleton by nucleophilic substitution of bromine with potassium cyanide: **9** formed, which,

Scheme 1. Synthesis of Enantiopure (*R*)-(−)-Carnitine from Glycerol[a]



[a] Reagents and conditions: (i) TsOH (cat.), toluene, reflux; (ii) MsCl, Et_3N, CH_2Cl_2, rt; (iii) Me_3N, EtOH, 50 °C; (iv) HCl (1 N), rt; (v) CH_3COOH, HBr (48%), rt, then MeOH, reflux; (vi) NaCN, H_2O, 70 °C; (vii) HCl (37%), 90 °C.

Table 1. Synthesis of (*R*)-(−)-Carnitine from Glycerol: Product Yields

product	yield[a] (%)	product	yield[a] (%)
3a	72[b]	**5c**	90
3b	80[b]	**5d**[7b]	95
3c	82[b]	**6a**	98
3d	63[b]	**6b**	97
4a	50	**6c**	99
4b	43	**6d**	97
4c	60	**7**	99[c]
4d	33	**8**	92
5a	90	**9**	99
5b	95	**1**	80

[a] Isolated; refer to Scheme 1 for the starting compounds. Reactions were performed on 100 mmol scale. [b] Based on (1*R*)-(−)-10-camphorsulfonyl chloride. [c] Yields are always ≥99%, independently on the starting material (**6a**−**d**).

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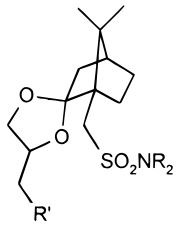

10 R' = Cl; **a**: R = CH_3; **b**: R = $CH(CH_3)_2$
11 R' = H; **a**: R = CH_3; **b**: R = $CH(CH_3)_2$

Figure 1.

without purification, was then hydrolyzed to (*R*)-(−)-carnitine **1** by concentrated HCl. The overall yield, starting from glycerol, was 40%, and the final product was synthesized with >98% ee.[10] The optical purity of **1** also serves as a criterion to evaluate the stereochemical progress of the entire synthetic route.

Each step of the reaction sequence is high yielding, with the exception of the first one, where the new stereocenter is created. The limiting factor of this passage appears to be the very low solubility of glycerol in toluene, which is the solvent necessary for azeotropic water removal; this also appears the reason for the very long reaction time (3 days). It is worth considering that the use of *N*,*N*-diisopropyl-10-camphorsulfonamide (**3d**) chiral auxiliary, as described in the literature,[7a] gave **4d**[7a,b] in only 33% yield (best result over 10 experiments), which is much less with respect to what reported (73%). Different solvents or modified reaction conditions targeted at water removal did not improve the reaction efficiency. On the other hand, when we used diols soluble in toluene, like 1,2-propanediol and 1,2-dihydroxy-3-chloropropane, under the same conditions employed in the reaction with glycerol (i.e., in large excess with respect to the sulfonamide), we obtained the spiro-acetals **10** and **11** (Figure 1) in quantitative yields, after only 16 h of reaction time.

As expected in these cases, no diastereoselectivity was observed and all the possible stereoisomers were formed in variable amounts. It is, indeed, the hydrogen bond between the free OH group in **4** and the sulfonamide moiety, rather than a possible steric factor, which drives the reaction stereochemistry.[7a] In the case of **10b**, the diastereoisomers mixture was in one step quantitatively converted into diastereoisomeric propyltrimethylammonium derivative **6d** which, after chromatographic separation, could be a suitable precursor of both (*R*)- and (*S*)-carnitine.

The possible effect of steric factor was also evaluated. We have, in fact, synthesized four (1*R*)-(−)-10-camphorsulfonamides (**3a**−**d**), each one differing from the other by the bulkiness of the amide moiety, the "Oppolzer" *N*,*N*-diisopropyl-10-camphorsulfonamide **3d**[8] being the reference reagent for the spiro-acetal formation reaction. Yields for the sulfonamides syntheses ranged from 63% (**3d**) to 82% (**3c**). **3a**−**d** were then reacted with glycerol to give the corresponding **4a**−**d** products, which were then sequentially, finally converted into (*R*)-(−)-carnitine **1**; in all cases, the ee of the final product was ≥98%, which means that always enantioselectivity in favor of the required stereoisomer was practically complete. The relatively low yields in the formation of dibenzyl and diisopropyl derivatives **4b** and **4d** respectively, indicate that the steric factor is partially involved in the spiro-ketal formation. This result, besides confirming hydrogen bonding as the only driving force for the observed diastereoselectivity, indicated that the bulkiness of the sulfonamide moiety played a secondary role. Since the yield of **4c** was the highest yields, with respect to **4a, 4b**, and **4d**, it is likely that a conformationally constrained amide like **3c** could favor the acetal formation. In any case yields were far from being quantitative: the starting sulfonamide always partially survives even after very long reaction times; on the other hand, no competing pathways have been revealed by examining the reaction mixtures.

In summary, new enantioselective synthesis of (*R*)-(−)-carnitine has been disclosed, which exploits the merits of the "Oppolzer" chiral auxiliary 10-camphorsulfonamide.[8] The synthesis fulfills also the requirements for a large scale process,[11] for the overall high yield of the process, for the low costs of the starting material and reagents, and also for the possibility of complete recovery of the chiral auxiliary.

Experimental Section

Analytical Methods. Melting points were determined by the capillary method and are uncorrected. ^{1}H NMR Spectra were taken at 300 MHz. ^{13}C NMR Spectra were taken at 75 or 50 MHz. Mass analyses were performed by using the fast atom bombardment technique, using glycerol as the matrix. Sulfur was determined by automatic titration. Optical rotation were measured at 27 °C.

Materials. Anhydrous solvents were purchased from Aldrich. Commercial reagents were purchased from Fluka or Aldrich and were used as received. Thin-layer chromatography was performed on 0.25 mm silica gel 60 F254 plates. Flash chromatography was performed using silica gel 60 (40−63 mesh). Non-aqueous reactions were carried out under nitrogen or argon atmosphere.

General Methods. Spectroscopic data of the compounds **3d**, **4d**, and **5d** correspond to those reported in the literature.[7a,b,8]

Synthesis of the Camphorsulfonamides 3a−d. General Procedures. To a solution of the amine (200 mmol) and DMAP (26 g, 222 mmol) in anhydrous CH_2Cl_2 (10% w/v solution) was added (−)-camphor-10-sulfonyl chloride (55.66 g, 222 mmol) under stirring at 0 °C. After 1 h of stirring, the reaction solution was diluted with ethyl acetate (1600 mL). The resulting solution was washed with water, then 1 N HCl, and then water again. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Camphorsulfonamides **3a**−**d** were obtained as pure products after flash chromatography.

(1*R*)-Camphor-10-sulfonyldimethylamine (3a). 3a was obtained as a colorless solid (72% yield): mp = 62−63 °C. TLC (*n*-hexane/ethyl acetate 7:3) R_f = 0.38; $[\alpha]_D$ = −35.4° (*c* = 1 in $CHCl_3$). Anal. Calcd for $C_{12}H_{21}NO_3S$: C, 55.60; H, 8.10; N, 5.40; S, 12.37. Found: C, 55.45; H, 8.20; N, 5.35; S 12.30.

(1*R*)-Camphor-10-sulfonyldibenzylamine (3b). 3b was obtained as a colorless solid (80% yield): mp = 73−75 °C; TLC (*n*-hexane/ethyl acetate 7:3) R_f = 0.58; $[\alpha]_D$ = −24.7° (*c* = 0.6 in CH_3OH). Anal. Calcd for $C_{24}H_{29}NO_3S$: C, 70.07; H, 7.05; N, 3.40; S, 7.79. Found: C, 69.90; H, 7.25; N, 3.28; S 7.70.

(1*R*)-Camphor-10-sulfonylpyrrolidine (3c). 3c was obtained as a colorless solid (82% yield): mp = 76−77 °C; TLC (*n*-hexane/ethyl acetate 7:3) R_f = 0.29; $[\alpha]_D$ = −34.8° (*c* = 1 in

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$CHCl_3$). Anal. Calcd for $C_{14}H_{23}NO_3S$: C, 62.01; H, 8.40; N, 5.16; S, 11.8. Found: C, 62.00; H, 8.42; N, 5.14; S 11.70.

Synthesis of the Spiro-Ketals 4a−d. General Procedure. Glycerol (6.6 g, 200 mmol) was suspended into a solution of (1*R*)-camphor-10-sulfonamide **3**(**a**−**d** according to cases) (100 mmol) with *p*-toluenesulfonic acid monohydrate (1 g) in 200 mL of anhydrous toluene. The mixture was heated under reflux for 3 h with azeotropic removal of produced water. Diluting with ethyl acetate (300 mL) quenched the reaction and the organic solution was washed with saturated $NaHCO_3$. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was then separated by flash chromatography.

(1*R*)-Camphor-2-glycerol-spiro-ketal-10-sulfonyldimethylamine (4a). 4a was obtained as an oil (50% yield): TLC (*n*-hexane/ethyl ether 6:4) $R_f = 0.18$; $[\alpha]_D = +13.1°$ ($c = 2$ in $CHCl_3$). Anal. for $C_{15}H_{27}NO_5S$: C, 54.06; H, 8.10; N, 4.20; S, 9.62. Found: C, 53.85; H, 8.20; N, 4.30; S 9.60.

(1*R*)-Camphor-2-glycerol-spiro-ketal-10-sulfonyldibenzylamine (4b). 4b was obtained as a colorless solid (43% yield): mp = 74−75 °C; TLC (*n*-hexane/ethyl acetate 7:3) $R_f = 0.46$; $[\alpha]_D = +1.2°$ ($c = 1$ in $CHCl_3$). Anal. Calcd for $C_{28}H_{37}NO_5S$: C, 67.34; H, 7.40; N, 2.80; S, 6.42. Found: C, 67.29; H, 7.50; N, 2.80; S 6.38.

(1*R*)-Camphor-2-glycerol-spiro-ketal-10-sulfonylpyrrolidine (4c). 4c was obtained as an oil (60% yield): TLC (*n*-hexane/ethyl acetate 7:3) $R_f = 0.15$; $[\alpha]_D = -11.8°$ ($c = 1$ in $CHCl_3$). Anal. Calcd for $C_{17}H_{29}NO_5S$: C, 56.84; H, 8.07; N, 3.89; S, 8.90. Found: C, 56.76; H, 8.10; N, 3.82; S 8.85.

Synthesis of the Spiro-Ketals 10a,b and 11a,b. General Procedure. Racemic 3-chloro-1,2-propanediol (1.1 g, 10 mmol) or racemic propanediol (1.55 gr, 10 mmol) was dissolved into a solution of (1*R*)-camphor-10-sulfonamide **3a** or **3d** (5 mmol) with *p*-toluenesulfonic acid monohydrate (200 mg) in 100 mL of anhydrous benzene. The mixture was heated under reflux for 16 h with azeotropic removal of produced water. Diluting with ethyl acetate (300 mL) quenched the reaction and the organic solution was washed with saturated $NaHCO_3$. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue oil was then separated by flash chromatography to give pure **10a**,**b** and **11a**,**b**.

(*R*,*S*)-Camphor-2-(1,2-dihydroxy-3-chloro)propane-spiroketal-10-sulfonyldimethylamine (10a). 10a, as a mixture of diastereoisomers, was obtained as an oil (98% yield): TLC (*n*-hexane/ethyl acetate 8:2) from $R_f = 0.31$ to $R_f = 0.22$. Anal. Calcd for $C_{15}H_{26}ClNO_4S$: C, 51.28; H, 7.40; Cl, 10.11; N, 3.98; S, 9.11. Found: C, 51.20; H, 7.45; Cl, 10.00; N, 3.70; S 9.10.

(*R*,*S*)-Camphor-2-(1,2-dihydroxy-3-chloro)propane-spiroketal-10-sulfonyldiisopropylamine (10b). 10b, as a mixture of diastereoisomers, was obtained as an oil (98% yield): TLC (*n*-hexane/ethyl acetate 8:2) from $R_f = 0.60$ to $R_f = 0.29$. Anal. Calcd for $C_{19}H_{34}ClNO_4S$: C, 56.01; H, 8.35; Cl, 8.72; N, 3.44; S, 7.86. Found: C, 55.70; H, 8.24; Cl, 8.70; N, 3.50; S, 7.54.

(*R*,*S*)-Camphor-2-(1,2-dihydroxy)propane-spiro-ketal-10-sulfonyldimethylamine (11a). 11a, as a mixture of diastereoisomers, was obtained as an oil (98% yield): TLC (*n*-hexane/ethyl acetate 8:2) from $R_f = 0.29$ to $R_f = 0.22$. Anal. Calcd for $C_{15}H_{27}NO_4S$: C, 56.90; H, 8.53; N, 4.42; S, 10.11. Found: C, 56.52; H, 8.42; N, 4.14; S, 10.00.

(*R*,*S*)-Camphor-2-(1,2-dihydroxy)propane-spiro-ketal-10-sulfonyldiisopropylamine (11b). 11b, as a mixture of diastereoisomers, was obtained as an oil (98% yield): TLC (*n*-hexane/ethyl acetate 8:2) from $R_f = 0.60$ to $R_f = 0.45$. Anal. Calcd for $C_{19}H_{35}NO_4S$: C, 61.12; H, 9.38; N, 3.75; S, 8.58. Found: C, 61.20; H, 9.30; N, 3.50; S, 8.56.

Synthesis of the Mesylates 5a−d. General Procedure. The spiro-acetals **4a**−**d** (100 mmol) and triethylamine (21.2 mL, 150 mmol) were dissolved in CH_2Cl_2 (500 mL) and cooled to 0 °C, neat MsCl (10 mL, 150 mmol) was added, and the solution was stirred at room temperature for 3 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with 1 N HCl. The organic layer was then washed with $NaHCO_3$ (5%) and dried over Na_2SO_4. The organic solution was concentrated under reduced pressure, and the residue oil was separated by flash chromatography to give pure **5a**−**d**.

(1*R*)-Camphor-2-(1-methansulfonyl)glycerol-spiro-ketal-10-sulfonyldimethylamine (5a). 5a was obtained as an oil (90% yield): TLC (*n*-hexane/ethyl acetate 7:3) $R_f = 0.25$; $[\alpha]_D = +13.5°$ ($c = 1$ in $CHCl_3$). Anal. Calcd for $C_{16}H_{29}NO_7S_2$: C, 46.72; H, 7.05; N, 3.40; S, 15.56. Found: C, 46.74; H, 7.00; N, 3.45; S, 15.60.

(1*R*)-Camphor-2-(1-methansulfonyl)glycerol-spiro-ketal-10-sulfonyldibenzylamine (5b). 5b was obtained as an oil (95% yield): TLC (*n*-hexane/ethyl acetate 8.5:1.5) $R_f = 0.15$; $[\alpha]_D = +2.7°$ ($c = 2$ in $CHCl_3$). Anal. Calcd for $C_{28}H_{37}NO_7S_2$: C, 59.70; H, 6.57; N, 2.48; S, 11.36. Found: C, 59.62; H, 6.60; N, 2.44; S 11.40.

(1*R*)-Camphor-2-(1-methansulfonyl)lycerol-spiro-ketal-10-sulfonylpyrrolidine (5c). 5c was obtained as oil (90% yield): TLC (*n*-hexane/ethyl acetate 7:3) $R_f = 0.19$; $[\alpha]_D = +12.5°$ ($c = 1$ in $CHCl_3$). Anal. Calcd for $C_{18}H_{31}NO_7S_2$: C, 49.45; H, 7.09; N, 3.20; S, 14.63. Found: C, 49.52; H, 7.20; N, 3.30; S, 14.64.

Synthesis of the Trimethylammonium Derivates 6a−d. General Procedure. 5a−**d** (or **10b**) (100 mmol) was added to 500 mL of a 33% ethanolic solution of trimethylamine and heated at 50 °C for 48 h. The solvent and excess base were then removed under reduced pressure. All crude products were separated by flash chromatography using ethyl acetate/methanol (1:1) as the solvent.

(1*R*)-Camphor-2-(1-trimethylammonium)glycerol-spiro-ketal-10-sulfonyldimethylamine Methanesulfonate (6a). 6a was obtained as hygroscopic solid (98% yield): TLC ($CHCl_3$/*i*-PrOH/MeOH/H_2O/CH_3COOH 4.2:0.7:2.8:1.05:1.05) $R_f = 0.60$; $[\alpha]_D = -8.85°$ ($c = 1$ in MeOH). Anal. Calcd for $C_{19}H_{38}N_2O_7S_2$: C, 48.53; H, 8.08; N, 5.95; S, 13.61. Found: C, 48.32; H, 8.30; N, 5.87; S, 13.58.

(1*R*)-Camphor-2-(1-trimethylammonium)glycerol-spiro-ketal-10-sulfonyldibenzylamine Methanesulfonate (6b). 6b was obtained as hygroscopic solid (97% yield): TLC ($CHCl_3$/*i*-PrOH/MeOH/H_2O/CH_3COOH 4.2:0.7:2.8:1.05:1.05) $R_f = 0.95$; $[\alpha]_D = -7.3°$ ($c = 1$ in MeOH). Anal. Calcd for $C_{31}H_{46}N_2O_7S_2$: C, 59.82; H, 7.39; N, 4.50; S, 10.28. Found: C, 59.62; H, 7.60; N, 4.44; S, 10.00.

(1*R*)-Camphor-2-(1-trimethylammonium)glycerol-spiro-ketal-10-sulfonylpyrrolidine Methanesulfonate (6c). Crude **6c** was obtained as hygroscopic solid (99% yield): TLC ($CHCl_3$/*i*-PrOH/MeOH/H_2O/CH_3COOH 4.2:0.7:2.8:1.05:1.05) $R_f = 0.66$; $[\alpha]_D = -13.5°$ ($c = 1$ in MeOH). Anal. Calcd for $C_{21}H_{40}N_2O_7S_2$: C, 50.83; H, 8.06; N, 5.64; S, 12.89. Found: C, 50.60; H, 8.25; N, 5.48; S, 12.70.

(1*R*)-Camphor-2-(1-trimethylammonium)glycerol-spiro-ketal-10-sulfonyldiisopropylamine Methanesulfonate (6d). Crude **6d** was obtained as a hygroscopic solid (97% yield): TLC ($CHCl_3$/*i*-PrOH/MeOH/H_2O/CH_3COOH 4.2:0.7:2.8:1.05:1.05) $R_f = 0.76$; $[\alpha]_D = -5.5°$ ($c = 1$ in $CHCl_3$). Anal. Calcd for $C_{23}H_{46}N_2O_7S_2$: C, 52.49; H, 8.74; N, 5.32; S, 12.16. Found: C, 52.39; H, 9.00; N, 5.48; S, 11.96.

(*S*)-3-Trimethylammonium-1,2-dihydroxypropane Methanesulfonate (7). A solution of **6a**−**d** (100 mmol) in methanolic HCl (75 mL of 3 N HCl in 500 mL of MeOH) was stirred at 70 °C for 18 h. The solvent was removed under reduced pressure. The crude product was redissolved in water and washed with ethyl acetate. Camphorsulfonamides **3a**−**d** were recovered from the organic layer, while the aqueous layer containing **7** was decolorized by activated charcoal and then concentrated under vacuum. Crude **7** was obtained as very hygroscopic colorless solid (yield = 99%): TLC ($CHCl_3$/*i*-PrOH/MeOH/H_2O/CH_3COOH 4.2:0.7:2.8:1.05:1.05) $R_f = 0.14$; $[\alpha]_D = -18°$ ($c = 1$ in H_2O). Anal. Calcd for $C_7H_{19}NO_5S$ (−2.5% H_2O): C, 35.75; H, 8.42; N, 5.95; S, 13.63. Found: C, 35.15; H, 8.84; N, 5.2; S, 13.03.

(*S*)-3-Trimethylammonium-1-bromo-2-hydroxypropane Bromide (8). 7 (23.1 g, 100 mmol) was dissolved in 410 mL of 30% HBr in acetic acid and 64 mL of acetic anhydride. The mixture was stirred at room temperature for 24 h. Then, MeOH (1800 mL) was added and the resulting solution was refluxed for 6 h. The solution was then concentrated under vacuum and the resulting oil was solidified by treating with ethyl ether. Crude **8** was crystallized from acetone giving hygroscopic solid (yield = 92%): TLC ($CHCl_3$/*i*-PrOH/MeOH/H_2O/CH_3COOH 4.2:0.7:2.8:1.05:1.05) $R_f = 0.20$; $[\alpha]_D = -18°$ ($c = 1$ in H_2O); FAB-MS (+ve) m/z = 196, 198. Anal. Calcd for $C_6H_{15}Br_2NO$ (−1% H_2O): C, 25.75; H, 5.51; N, 5.00. Found: C, 25.30; H, 5.80; N, 4.67.

(*R*)-3-Trimethylammonium-1-cyano-2-hydroxypropane Bromide (9). A solution of **8** (27.87 g, 100 mmol) and sodium cyanide (6.50 g, 100 mmol) in 280 mL of water, was stirred at 70 °C. When the reaction was complete (about 24 h, by HPLC), water was removed under vacuum to give a colorless solid (mixture of **9** and NaBr 1:1; yield = 99%).

(*R*)-(−)-carnitine Inner Salt (1). The mixture **9** (40 g, about 100 mmol) was added to 12 N HCl (50 mL), and the resulting solution was heated at 90 °C for 4 h. The black solution was then diluted with water (80 mL) and eluted through Amberlite IRA-402 (OH^- form) and successively through Amberlite IRC-50 (HCl form). The water solution was concentrated under vacuum to give a colorless syrup. By crystallization of the syrup with *i*-PrOH, pure (*R*)−(−)-carnitine **1** inner salt was obtained: mp 200 °C with dec (lit.[12] mp 197 °C with dec); $[\alpha]_D = -30.9°$ (*c* = 1 in H_2O) (lit.[13] $[\alpha]_D = -31.3°$ (*c* = 10 in H_2O)). Anal. Calcd for $C_7H_{15}NO_3$ (−0. 7% H_2O): C, 51.79; H, 9.39; N, 8.62. Found: C, 51.65; H, 9.50; N, 8.55.

Supporting Information Available: Spectral data of all the compounds synthesized; ^1H and ^{13}C NMR spectra of the compounds **1**, **3a**−**c**, **4a**−**c**, **5a**−**c**, **6a**−**d**, **7**−**9, 10a**,**b**, **11a**,**b**; mass spectra of the compounds **1**, **7**, and **8**; HPLC profiles of the compounds **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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