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Chemoenzymatic Synthesis of Phosphocarnitine Enantiomers

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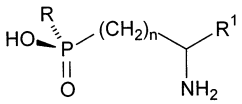
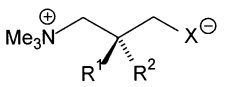
Abstract: Racemic phosphocarnitine **3** has been synthesized starting from diethyl 3-chloro-2-oxopropanephosphonate **4** in three steps involving reduction of **4** to the corresponding 2-hydroxyphosphonate **5**, conversion of the latter to phosphonic acid **6**, and final reaction with trimethylamine, affording the trimethylammonium salt of **3**. Baker's yeast reduction of **4** and enzymatic kinetic resolution of (±)-**5** afforded the enantiomerically pure precursors of phosphocarnitine, (*R*)-(+)-**5** and (*S*)-(−)-**5**, which were converted to (*S*)-(−)- and (*R*)-(+)-phosphocarnitine **3**, respectively.

The design and synthesis of extremely potent and specific inhibitors of enzyme-catalyzed reactions based on mechanistic enzymology has been actively investigated during the past decades.[1] Much of the progress in this field has been associated with aminophosphonic or aminophosphinic acids **1**,[2] which are phosphorus analogues of amino acids in which the planar carboxylic group is replaced by a phosphonic acid, $P(O)(OH)_2$, or phosphinic acid, P(O)(OH)R, moiety. Because of the tetrahedral configuration of phosphorus, these compounds serve as stable analogues of the unstable tetrahedral carbon intermediates formed in enzymatic processes and, therefore, act as enzyme inhibitors. For this reason, in addition to naturally occurring aminophosphonic acids, a large number of phosphonic acid analogues of protein or nonprotein amino acids have been synthesized and investigated. This resulted in a discovery of new drugs and other bioactive compounds with a great variety of commercial applications, ranging from agriculture to medicine.

(*R*)- and (*S*)-Carnitine **2** have attracted considerable attention in recent years, owing to their interesting biological properties and usefulness as pharmaceuticals.[3,4] (*R*)-Carnitine **2** plays an important role in the β-oxidation of fatty acids, acting as carrier of fatty acids over the mitochondrial membrane. It has been used in therapy as a stimulator of fatty acid degradation and also in the treatment of heart disease. The (*S*)-enantiomer of



1, R=OH, alkyl, aryl
R^1=alkyl, aryl
n=0, 1, 2, ...



Carnitine **2**, X=CO_2
(*R*)-(-)-**2**, R^1=OH, R^2=H
(*S*)-(+)-**2**, R^1=H, R^2=OH

Phosphocarnitine **3**, X=P(O)(OH)O
(*R*)-(+)-**3**, R^1=H, R^2=OH
(*S*)-(-)- **3**, R^1=OH, R^2=H

2 was found to be a competitive inhibitor of carnitine acyltransferase, causing depletion of (*R*)-carnitine level in heart tissue. However, despite these interesting biological properties of carnitine **2**, its phosphonic acid analogue, phosphocarnitine **3**, is practically unknown. The literature records only one short note on a stereoselective conversion of (*R*)-(−)-epichlorohydrin into the potassium salt of (*S*)-(−)-phosphocarnitine **3**.[5,6] As part of our program aimed at the elaboration of efficient and versatile total syntheses of biologically active compounds,[7] including also aminophosphonic acids,[8] we became interested in the preparation and investigation of bioactivity of phosphocarnitine **3**. In this paper we would like to disclose the details of our approach to racemic **3** and to describe the first preparation of both enantiopure forms of this target.

A total synthesis of (±)-**3** starting from readily available diethyl 3-chloro-2-oxopropanephosphonate **4**[9] is shown in Scheme 1. In the first step, β-ketophosphonate **4** was treated with sodium borohydride to give the corresponding β-hydroxyphosphonate **5** in 90% yield. Then, the phosphonic ester moiety was dealkylated using trimethylsilyl bromide in methylene chloride, and the free phosphonic acid **6** was treated with an aqueous solution of trimethylamine to afford the trimethylammonium salt **7**. For identification and comparison purposes, **7** was converted into the potassium salt **8** upon treatment with equimolar amounts of potassium carbonate in water. The last three steps were performed in almost quantitative yield.

Having efficiently prepared racemic phosphocarnitine **3**, we turned our attention to a prime goal of this work, i.e., the synthesis of enantiomers of **3**. According to the

(1) *Design of Enzymes Inhibitors as Drugs*; Sandler, M., Smith, H. J., Eds.; Oxford University Press: Oxford, 1989.
(2) *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley and Sons: Chichester, 2000.
(3) *L-Carnitine and Its Role in Medicine: From Function to Therapy*; Ferrari, R., Di Mauro, S., Sherwood, G., Eds.; Academic Press: San Diego, 1992.
(4) De Simone, C.; Famularo, G. *Carnitine Today*; Springer-Verlag: Heidelberg, 1997.
(5) Tadeusiak, E.; Krawiecka, B.; Michalski, J. *Tetrahedron Lett.* **1999**, *40*, 1791−1792.
(6) The authors of this work incorrectly used the designation (*R*) for the absolute configuration of the potassium salt of (−)-phosphocarnitine prepared.
(7) For a recent summary see: Mikołajczyk, M.; Mikina, M.; Żurawiński, R. *Pure Appl. Chem.* **1999**, *71*, 473−480.
(8) Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J.; Wieczorek, M. W.; Błaszczyk, J. *J. Chem. Soc., Chem. Commun.* **1996**, 1503−1504. Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991−3994.
(9) Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649−654.

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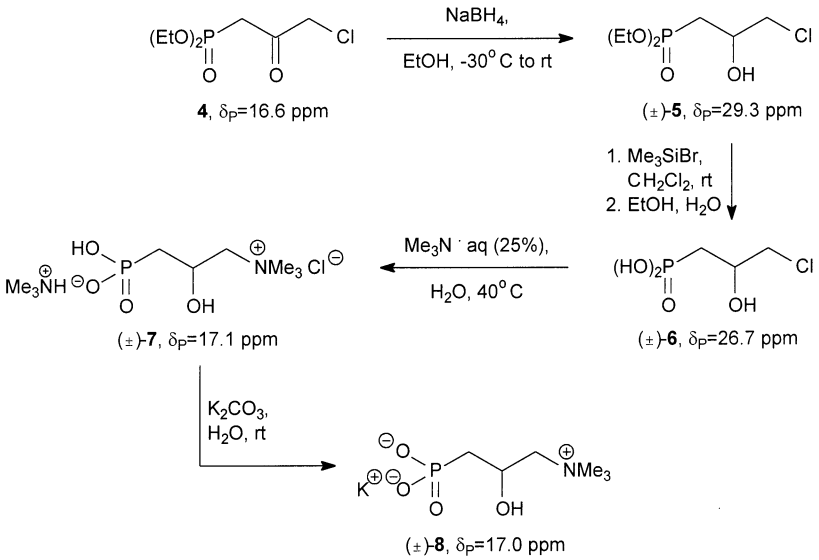
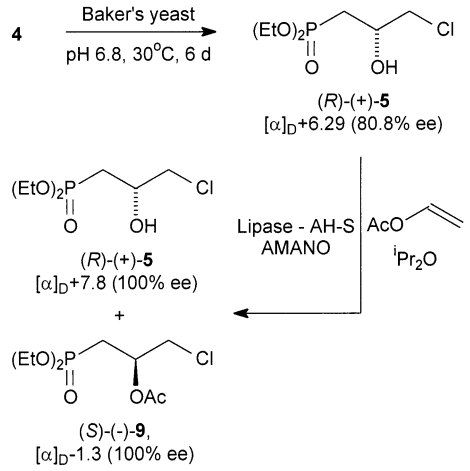
SCHEME 1



synthetic strategy shown in Scheme 1, the use of enantiomers of **5** as intermediates is required. In our first attempt to prepare optically active **5**, we reduced **4** with baker's yeast.[10] As expected, this bioreduction gave optically active β-hydroxypropanephosphonate (*R*)-(+)-**5** in ca. 90% yield.[11,12] Its optical rotation varied from $[\alpha]_D$ +5.33 to $[\alpha]_D$ +6.29 depending on a small variation in experimental conditions. The enantiomeric excess values of (+)-**5** obtained were determined by means of ^{31}P NMR spectra of their condensation products with dimenthyl chlorophosphite as a chiral derivatizing agent[13] (two well-separated signals at δ 26.21 and 26.42 ppm). Thus, the best reduction experiment afforded (+)-**5**, $[\alpha]_D$ +6.29, with 80.8% ee. A further increase of the enantiomeric purity to 100% was achieved, when the bioreduction products **5** were acetylated with vinyl acetate in the presence of lipase AH-S AMANO under controlled reaction conditions (^{31}P NMR assay). When the ratio of unconsumed (+)-**5** (δ_P 29.2 ppm) and the corresponding formed acetate **9** (δ_P = 25.7 ppm) reached the enantiomeric content of the substrate (+)-**5**, the enzymatic acetylation was stopped, and column chromatography furnished enantiomerically pure (+)-**5**, $[\alpha]_D$ +7.8, and acetate (−)-**9**, $[\alpha]_D$ −1.3 (Scheme 2).

Because the procedure discussed above led only to one enantiopure form of β-hydroxy-phosphonate **5**, we turned our attention to the kinetic resolution of racemic β-hydroxy-phosphonate **5**, which should, in principle, allow one to obtain both enantiomers of **5**. Thus, enzymatic acetylation of (±)-**5**, using lipase AH-S AMANO, afforded

SCHEME 2



after column chromatography unreacted (+)-**5** and acetate (−)-**9**, both in good yields and with the ee values 87% and 88%, respectively (Scheme 3).[14] To obtain enantiopure (+)-**5**, the same acetylation procedure was repeated starting from an enantiomerically enriched sample and afforded (+)-**5**, $[\alpha]_D$ +7.8 (Scheme 3). It should be stressed that both the yeast reduction of **4** and enzymatic kinetic resolution of racemic **5** furnished only the dextrorotatory enantiomer of **5**. To synthesize (−)-**5** it was necessary to remove the acetyl group from (−)-**9**. However, all attempts at the chemical hydrolysis or alcoholysis of **9** failed as a result of the formation of unidentified side products. Therefore, we decided to use a reverse reaction, i.e., the enzymatic hydrolysis of (−)-**9**. It was reasonable to apply the same enzyme as in the acetylation reaction, because an enzyme always recognizes and preferentially transforms the same enantiomer of a substrate. Hence, starting from racemic **9** the levorotatory enantiomer of **5** should be obtained. However, we found that the lipase-catalyzed hydrolysis of (±)-**9**, performed in diisopropyl ether saturated with a buffer

(10) For reduction of carbonyl compounds promoted by baker's yeast see: Santaniello, E.; Ferraboshi, P.; Manzocchi, A. In *Enzymes in Action, Green Solutions for Chemical Problems*; Zwanenburg, B.; Mikołajczyk, M., Kiełbasinski, P., Eds.; Kluwer Academic Publishers: Dordrecht, 2000; pp 95−115.

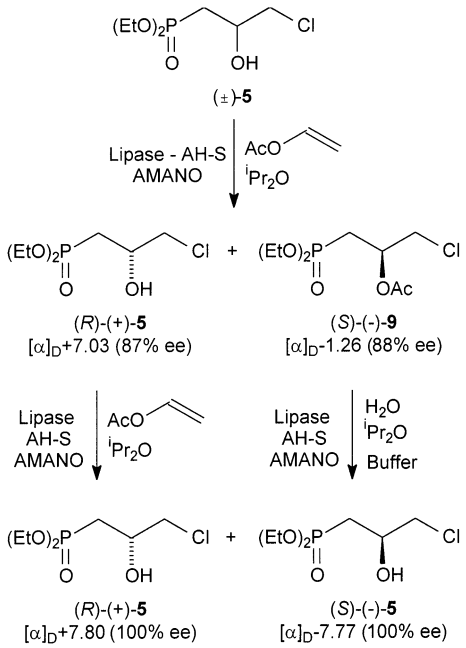
(11) During the course of this work Yuan at co-workers reported reduction of 3-halo-2-oxo-propanephosphonates by baker's yeast. Unfortunately, the authors did not give the optical rotation values for the reduction products. Yuan, Ch.; Wang, K.; Li, Z. *Heteroat. Chem.* **2001**, *12*, 551−556.

(12) The (*R*)-configuration of (+)-**5** was established on the basis of its final conversion to the phosphocarnitine potassium salt (*S*)-(−)-**8**.

(13) Kolodiazhnyi, O. I.; Demchuk, O. M.; Gerschkovich, A. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1729−1732.

(14) The ee value of (−)-**9** was estimated by ^{1}H NMR using (+)-*tert*-butylphenylphosphinothioic acid as a chiral solvating agent.[15]

SCHEME 3



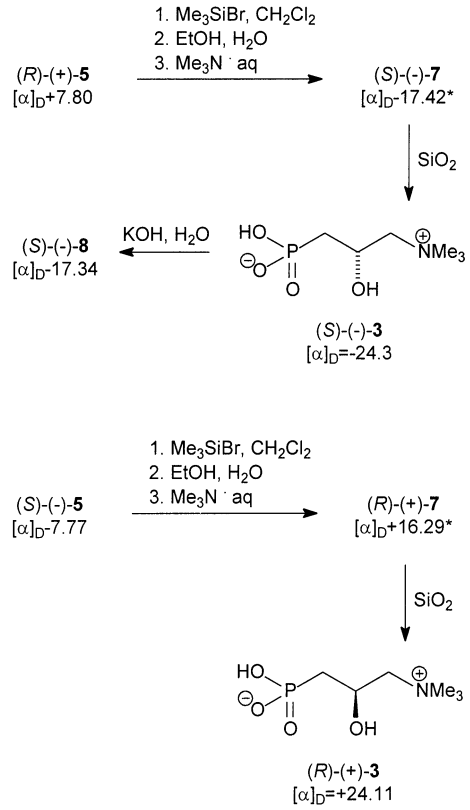
(pH = 7.2), was very slow. Therefore, to speed up the procedure, we used as a substrate an enantiomerically enriched sample of (−)-**9**, $[\alpha]_D$ −1.26, obtained from the kinetic resolution described above. Indeed, after quite a long reaction time enantiopure (−)-**5**, $[\alpha]_D$ −7.77, was isolated using the same purification methodology as described above. Unfortunately, the yield of (−)-**5** was (for unknown reasons) only low to moderate. Another experiment, in which *Pseudomonas fluorescens* lipase was applied as a biocatalyst for hydrolysis of (±)-**9**, gave almost identical results.

With the enantiomerically pure phosphocarnitine precursors (*R*)-(+)-**5** and (*S*)-(−)-**5** in hand, the synthesis of both enantiopure forms of phosphocarnitine **3** could be completed (Scheme 4). Thus, (*R*)-(+)-**5** was dealkylated according to the procedure described for racemic **5**, and the corresponding phosphonic acid **6** (δ_P = 26.9 ppm) formed was treated, without purification, with trimethylamine. The crude trimethylammonium salt, (*S*)-(−)-**7**, $[\alpha]_D$ −17.42, showing the correct ^{1}H, ^{13}C, and ^{31}P NMR spectra, was then subjected to column chromatography on silica gel. To our delight, we obtained in such a way phosphocarnitine (*S*)-(−)-**3**, $[\alpha]_D$ −24.3 in 81% yield. For correlation purposes, it was converted to the potassium salt (*S*)-(−)-**8**, $[\alpha]_D$ −17.34 i.e., the same as prepared by Tadeusiak et al. from (*R*)-epichlorohydrin.[5,16] Since in the transformation of (+)-**5** to (*S*)-(−)-**8** no bond formation or bond cleavage at the chiral β-carbon atom was occurring, we could assign the absolute configuration (*R*) to (+)-**5**.

In a similar way starting from (*S*)-(−)-**5** phosphocarnitine, (*R*)-(+)-**3**, $[\alpha]_D$ +24.11, was obtained in 84% yield.

In summary, we have developed a short and efficient synthesis of racemic and enantiopure forms of phosphocarnitine from easily available 3-chloro-2-oxopropanephosphonate. In the synthesis of enantiomers of phosphocarnitine we took advantage of biocatalytic reactions, i.e., enantioselective reduction of a substrate by baker's yeast to the corresponding alcohol and enzymatic kinetic resolution of the latter using lipase as a biocatalyst.

SCHEME 4



* - optical rotation refers to a crude reaction product

Experimental Section:

General Methods. NMR spectra were recorded at 200 MHz for ^{1}H, 50.32 MHz for ^{13}C, and 81 MHz for ^{31}P, with $CDCl_3$ or D_2O as solvents. Optical rotations were measured at 20 °C in $CHCl_3$, MeOH, or a 1:1 mixture of MeOH and H_2O as solvents. Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. Diethyl 3-chloro-2-oxopropanephosphonate **4** was prepared according to the literature procedure.[9]

(±)-Diethyl 3-Chloro-2-hydroxypropanephosphonate (5). To a stirred solution of **4** (2.28 g, 10 mmol) in EtOH (50 mL) was added sodium borohydride (125 mg, 3.3 mmol) at −30 °C. After 15 min the cooling bath was removed and stirring was continued at room temperature for 1 h. The solution was concentrated under reduced pressure and acidified with 5% H_2SO_4. The product was extracted with dichloromethane (6 × 15 mL). The organic layer was dried over $MgSO_4$, and the solvents were removed under vacuum. The crude product was purified by column chromatography using CH_2Cl_2−MeOH (98:2) as solvent. Yield: 2.08 g (90.4%). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 6H), 2.06 (m, 2H), 3.57 (m, 2H), 4.10 (m, 6H). ^{31}P NMR ($CDCl_3$): δ 29.27. ^{13}C NMR ($CDCl_3$): δ 16.21 (d, J = 6.09 Hz), 30.59 (d, J = 140.4 Hz), 49.02 (d, J = 16.43 Hz), 61.94 (d, J = 7.8 Hz), 62.09 (d, J = 7.4 Hz), 66.54 (d, J = 2.69 Hz). MS (EI): *m*/*z* 195, 181, 153, 125. For literature data see ref 17.

(15) For recent application of this chiral solvating agent, see: Mikołajczyk, M.; Mikina, M.; Jankowiak, A. *J. Org. Chem.* **2000**, *65*, 5127−5130.

(16) It should be noted that the optical rotation of our product is higher than that reported by Tadeusiak et al., $[\alpha]_D$ −11.7 (MeOH/H_2O, 1:1).

(17) Rabov, B. V.; Ionin, B. I.; Petrov, A. A. *Zh. Obsch. Khim.* **1988**, *58*, 969−983.

(±)-3-Chloro-2-hydroxypropanephosphonic Acid (6). To a solution of **5** (1.38 g, 6 mmol) in dichloromethane (15 mL) was added trimethylsilyl bromide (6.3 g, 40 mmol), and the mixture was left at room temperature for 24 h. The solvents were removed under reduced pressure, and a 1:1 mixture of ethanol and water (20 mL) was added to the residue. After 30 min the solvents were evaporated under reduced pressure. The latter operation was repeated three times to give 1.04 g (100%) of **6**. ^{1}H NMR (D_2O): δ 1.94−2.17 (m, 2H), 3.47−3.67 (m, 2H), 4.04−4.20 (m, 1H). ^{31}P NMR (D_2O): δ 26.69.

(±)-Phosphocarnitine Trimethylammonium Chloride (7). Phosphonic acid **6** obtained above was treated with trimethylamine (20 mL of a 25% solution in water) at 40° C for 48 h. Excess trimethylamine and water were removed under reduced pressure to give semisolid crystals (1.8 g), containing a certain amount of water. ^{1}H NMR (D_2O): δ 1.88 (m, 2H), 2.87 (s, 9H), 3.19 (s, 9H), 3.34−3.63 (m, 2H), 4.65 (m, 1H, partially shaded by water). ^{31}P NMR (D_2O): δ 17.11. ^{13}C NMR (D_2O): δ 37.53 (d, J = 129.4 Hz), 47.58, 57.05, 65.81, 73.44.

(±)-Phosphocarnitine Potassium Salt (8). To a solution of **7** (1.8 g, 6 mmol) in water (5 mL) was added a solution of potassium carbonate (0.828 g, 6 mmol) in water (5 mL). Water was then removed under vacuum. Methanol (10 mL) was added to the residue, and the precipitated KCl was filtered off and washed with methanol. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography (MeOH−H_2O, 8:2) to give pure **8** (1.78 g; theoret. 1.41 g) as white hygroscopic crystals. ^{1}H NMR (D_2O): δ 1.69 (d, J = 6.67 Hz, 1H), 1.77 (d, J = 6.67 Hz, 1H), 3.24 (s, 9H), 3.43−3.66 (m, 2H), 3.67−4.73 (m, 1H). ^{31}P NMR (D_2O): δ 17.0. MS (FAB): m/z 236.1 $(M + 1)^+$. HRMS: calcd for $C_6H_{16}NO_4PK$ $(M + 1)^+$ 236.0454, found 236.0457.

Reduction of Oxophosphonate 4 with Baker's Yeast. Baker's yeast (40 g) was suspended in water (200 mL), **4** (456 mg, 2 mmol) was added, and the mixture was stirred at 30° C for 120 h. The biomass was removed by centrifugation, and the supernatant was concentrated under reduced pressure to the volume of ca. 30 mL. The residue was extracted with chloroform (5 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give **5** as a pale yellow oil (428 mg, 93%). $[\alpha]_D$ +6.29 (c 1.45, MeOH); ee 80.8%. NMR spectra were identical with those of racemic **5**.

Kinetic Resolution of Enantiomerically Enriched Hydroxyphosphonate (5). To a stirred solution of (+)-**5** (ee 80.8%; 437 mg, 1.9 mmol) in diisopropyl ether (5 mL) was added vinyl acetate (5 mL), followed by lipase AH-S AMANO (100 mg). The cloudy solution was stirred at 25° C, and the conversion was controlled by ^{31}P NMR (for **5**, δ_P 29.2 ppm; for **9**, δ_P 25.7 ppm). When the ratio **5**:**9** reached 90:10, which approximately corresponded to the enantiomer ratio in the substrate (ca. 45 h), the reaction was stopped by filtering off the enzyme. After evaporation of the solvent the crude mixture was subjected to column chromatography using chloroform−methanol (in gradient 100:0 to 50:1) as eluent, which resulted in the separation of **5** (350 mg), $[\alpha]_D$ + 7.8 (c 2.24, MeOH), ee 100%, NMR spectra as for racemic **5**, and **9** (76 mg), $[\alpha]_D$ −1.3 (c 3.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.99 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H), 1.69 (s, 3H), 1.98 (d, J = 6.6 Hz, 1H), 2.07 (d, J = 6.6 Hz, 1H), 3.45−3.65 (m, 2H), 3.70−4.0 (m, 4H), 5.30−5.50 (m, 1H). ^{31}P NMR ($CDCl_3$): δ 25.4.

Kinetic Resolution of Racemic Hydroxyphosphonate (5). To a stirred solution of racemic **5** (2.3 g, 10 mmol) in diisopropyl ether (10 mL) were added vinyl acetate (10 mL) and lipase AH-S AMANO (50 mg). The cloudy solution was stirred at 25° C until the conversion of ca. 50% (^{31}P NMR control, as above) was reached (ca. 80 h). The unreacted (+)-**5** was separated from the acetylated product (−)-**9** by column chromatography (conditions as described above). **5**: yield 0.91 g (40%), $[\alpha]_D$ +7.0 (c 1.28, MeOH), ee 89%. **9**: yield 1.23 g (45%), $[\alpha]_D$ −1.26 (c 1.51, $CHCl_3$), ee 88%. To obtain enantiopure (*R*)-(+)-**5**, the enantiomerically enriched sample of **5** was once again subjected to the enzymatic acetylation, which led to the same result as in the case of the sample obtained from the baker's yeast reduction.

Synthesis of Enantiopure (*S*)-(−)-5 via Enzymatic Hydrolysis of (−)-9. The enantiomerically enriched acetate (−)-**9**, obtained from the kinetic resolution described above (ee 88%; 272 mg, 1 mmol), was dissolved in diisopropyl ether saturated with a pH 7.2 buffer (5 mL) and an enzyme was added (lipase AH-S AMANO, 20 mg, or lipase from *Pseudomonas fluorescens*, 10 mg). The solution was stirred at 30° C for ca. 25 days, during which time the conversion degree was controlled by ^{31}P NMR and small portions of the enzymes were added (lipase AH-S 3 × 10 mg, PFL 2 × 5 mg). When the ratio **5**:**9** reached the value of ca. 2.5:1, the reaction was stopped and the products were separated by column chromatography (as above) to give (*S*)-(−)-**5** in ca. 25% yield: $[\alpha]_D$ −7.77 (c 2.21, MeOH), ee 100%.

Conversion of (*R*)-(+)-5 into (*S*)-(−)-7. To a solution of (*R*)-(+)-**5**, $[\alpha]_D$ +7.8, 100% ee (300 mg, 1.3 mmol) in 5 mL of dichloromethane, was added trimethylsilyl bromide (1.4 mL), and the mixture was left for 24 h. The volatile materials were removed under reduced pressure, and a mixture of ethanol and water (2:1, 3 mL) was added. After 30 min the solvents were removed in vacuo. The latter operation was repeated three times to give crude **6** [^{31}P NMR (D_2O) δ 26.91], which without isolation was treated with trimethylamine (25% solution in water, 10 mL) and left at 40° C for 48 h. The solvents were removed under reduced pressure to give (*S*)-(−)-**7** (479 mg) as a semisolid material containing a certain amount of water. $[\alpha]_D$ −17.42 (c 1.83, MeOH−H_2O 1:1). ^{1}H NMR (D_2O): δ 1.84 (m, 2H), 2.82 (s, 9H), 3.15 (s, 9H), 3.30−3.57 (m, 2H), 4.39−4.60 (m, 1H). ^{31}P NMR (D_2O): δ 19.37. ^{13}C NMR (D_2O): δ 37.46 (d, J = 130.28 Hz), 47.61, 57.08, 65.77, 73.43.

Conversion of (*S*)-(−)-5 into (*R*)-(+)-7. The same procedure was applied. Starting from (*S*)-(−)-**5,** $[\alpha]_D$ −7.7, 100% ee (46 mg, 0.2 mmol), crude **6** was obtained [^{31}P NMR (D_2O) δ 26.63], which was transformed into (*R*)-(+)-**7** (60 mg), $[\alpha]_D$ +16.29 (c 5.1, MeOH−H_2O 1:1). NMR data as above.

Synthesis of (*S*)-(−)-Phosphocarnitine, (*S*)-(−)-3. A crude ammonium salt (*S*)-(−)-**7** (470 mg) was loaded on a column packed with silica gel (230−400 mesh) and eluted using methanol−water (in gradient 100:0 to 1:1). The fraction containing the desired product was collected, and the solvents were removed in vacuo to give (*S*)-(−)-**3** (207 mg, 81%) as a colorless oil; $[\alpha]_D$ −24.3 (c 2.3, MeOH−H_2O 1:1). ^{1}H NMR (D_2O): δ 1.73−1.99 (m, 2H), 3.19 (s, 9H), 3.33−3.66 (m, 2H), 4.41−4.74 (m, 1H). ^{31}P NMR (D_2O): δ 18.84. ^{13}C NMR (D_2O): δ 37.52 (d, J = 129.5 Hz), 56.98, 65.75, 73.45 (d, J = 9.02 Hz). MS (FAB): m/z 198.2 $(M + 1)^+$. HRMS: calcd for $C_6H_{17}NO_4P$ $(M + 1)^+$ 198.0895, found 198.0899.

Synthesis of (*R*)-(+)-Phosphocarnitine, (*R*)-(+)-3. Using the same procedure, from a crude ammonium salt (*R*)-(+)-**7** (60 mg) enantiopure (*R*)-(+)-**3** was obtained (33 mg, 84%) as a colorless oil; $[\alpha]_D$ +24.11 (c 2.09, MeOH−H_2O 1:1). ^{1}H NMR (D_2O): δ 1.84−1.97 (m, 2H), 3.22 (s, 9H), 3.28−3.65 (m, 2H). ^{31}P NMR (D_2O): δ 18.95. ^{13}C NMR (D_2O): δ 37.52 (d, J = 129.66 Hz), 57.0, 65.8, 73.5 (d, J = 9.37 Hz).

(*S*)-(−)-Phosphocarnitine Potassium Salt, (*S*)-(−)-8. To (*S*)-(−)-**3** (14.8 mg) was added a solution of KOH (4.2 mg) in 1:1 MeOH−H_2O. Then, the sample was filled with the same solvent mixture to the volume of 1 mL, and the optical rotation was measured: $[\alpha]_D$ −17.34 (c 1.84, MeOH−H_2O 1:1).

Acknowledgment. This research was supported by a grant from the State Committee of Scientific Research (008/T09/98).

Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P NMR and MS spectra of the compounds **4**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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