An Efficient Synthesis of Enantiomeric (*S*)-Phosphocarnitine

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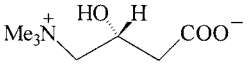
Keywords: Kinetic resolution / Regioselectivity / Amino acids / Chiral auxiliaries / Conformation analysis

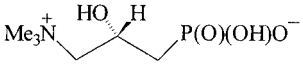
Diethyl (*S*)-2,3-epoxypropylphosphonate [(*S*)-**3**] was transformed into (*S*)-phosphocarnitine [(*S*)-**2**] in the following sequence of reactions: a C-3 regioselective opening of the oxirane ring with magnesium bromide, quantitative bromide displacement with trimethylamine, and ester hydrolysis. The epoxide ring opening of **3** with HCl/EtOAc gave a 92:8 mixture of 3- and 2-chloro-substituted phosphonates. Reaction of (*S*)-**3** with aqueous NMe_3 gave diethyl 3-hydroxy-1-propenylphosphonate as a major product.

Introduction

The importance of (*R*)-(−)-carnitine (**1**) in the oxidation of fatty acids and other metabolic pathways has been recognized in recent years.[1] Increasing use of this compound primarily as a dietary supplement has resulted in the elaboration of numerous synthetic procedures, including transformations of homochiral starting materials,[2−6] asymmetric synthesis,[7−14] applications of enzymes and related technologies[15−22] and also optical resolution of the racemic carnitine or its precursors.[23,24]



(*R*)-(−)-**1**



(*S*)-**2**

Various analogues of carnitine have been synthesised in order to study its mode of action and to reveal the structural features of binding sites.[25−34] Among them, phosphocarnitine (**2**), an analogue in which the carboxy group has been replaced with a phosphoryl residue, has recently been obtained.[35] Recent reports on the synthesis and biological activity of several structurally diversified carnitine analogues including phosphonates[36] and Bakers yeast reduction of 3-substituted 2-oxopropylphosphonates[37] has prompted us to disclose a new method for the preparation of (*S*)-**2** based on Jacobsen's hydrolytic kinetic resolution (HKR) of the racemic epoxyphosphonate **3**. In this paper we give a full account of our synthesis of optically active (*S*)-**3**[38] and describe its transformation into phosphocarnitine (*S*)-**2**.

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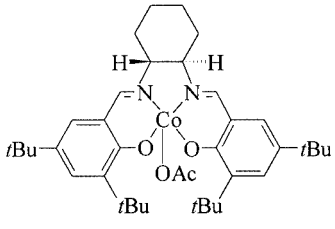
Results and Discussion

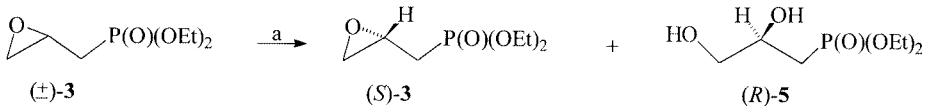
As already reported,[38] the racemic epoxyphosphonate **3** can be transformed in the presence of 0.2 mol % of (*R*,*R*)-salen-Co^{III}-OAc [(*R*,*R*)-**4**] after 72 h into a mixture of (*S*)-(−)-**3** and diethyl (*R*)-(−)-2,3-dihydroxypropylphosphonate (**5**) (Scheme 1). Optically active (*S*)-**3** was separated from the diol and the catalyst in 34% yield by distillation in vacuo. The absolute stereochemistries of the unchanged epoxide and the obtained diol were assigned by chemical correlation.[39] Furthermore, they are in agreement with the stereochemical outcome of the hydrolytic kinetic resolution of other terminal epoxides catalysed by (*R*,*R*)-**4**.[40]



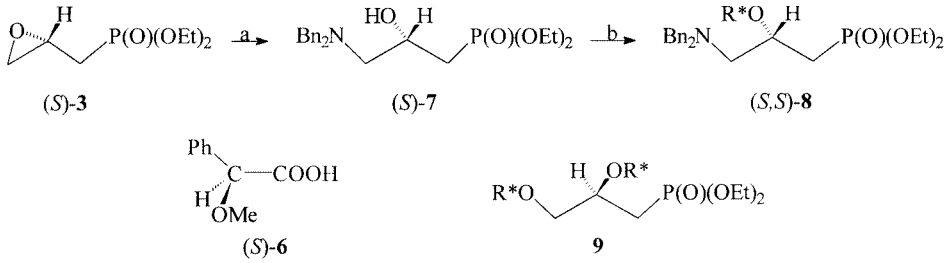
(*R*,*R*)-**4**

The 94% *ee* of the unchanged epoxide (*S*)-**3** was established by the ^{31}P NMR analysis of the derivative (*S*,*S*)-**8** obtained after the transformations depicted in Scheme 2. {NB The *ee* values reported have been corrected to take into account the 98.5% *ee* of the (*S*)-*O*-methylmandelic acid [(*S*)-**6**] starting material.[41]} The use of dibenzylamine led to the exclusive opening of the epoxide ring at the less hindered position to give (*S*)-**3**;[42] the reaction was complete in 24 h.

Separation of the diol (*R*)-**5** was achieved by further distillation of the residue left after recovery of (*S*)-**3**. The high boiling fraction contained minute quantities of the epoxide, which were removed by column chromatography to give pure diol (*ee* 86%) in 31% yield. This was the only way to



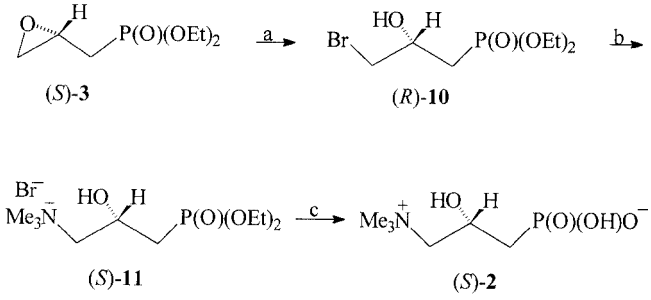
Scheme 1. Reagents and conditions: (a) (*R*,*R*)-salen-Co^{III}-OAc (0.2 mol %), H_2O (0.55 equiv.)



Scheme 2. Reagents and conditions: (a) Bn_2NH (1.1 equiv.), 60 °C, 20 h; (b) **6** (1.5 equiv.), 1,3-dicyclohexylcarbodiimide (DCC) (1.5 equiv.), 4-(dimethylamino)pyridine (DMAP) (0.1 equiv.), CH_2Cl_2

obtain (*R*)-**5** free from the catalyst. When the reaction mixtures formed in the hydrolytic kinetic resolution experiments were subjected to column chromatography, fractions containing (*S*)-**3** and (*R*)-**5** were contaminated with the catalyst. The enantiomeric purity of (*R*)-**5** was estimated by ^{31}P NMR spectroscopy after complete esterification with (*S*)-*O*-methylmandelic acid (**6**) to afford diester **9** (Scheme 2).

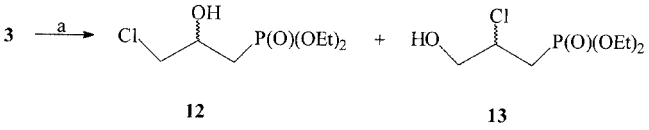
Our strategy for the synthesis of phosphocarnitine (*S*)-**2** is illustrated in Scheme 3.



Scheme 3. Reagents and conditions: (a) $MgBr_2$, diethyl ether; (b) 45% Me_3N in ethanol/water; (c) 12 M HCl, H_2O

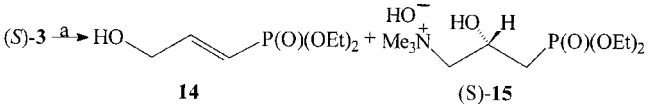
The epoxide (*S*)-**3** was reacted with $MgBr_2$ in diethyl ether[43] to afford the bromohydrin (*R*)-**10**. Complete C-3 regioselectivity of the epoxide opening was established by appearance of a ^{31}P NMR signal at $\delta = 29.06$ ppm and identification of the diol (*S*)-**5** ($\delta^{31}P = 30.7$ ppm) as a minor (< 0.5%) impurity of the crude product. The *ee* of (*R*)-**10** in the reaction mixture (94%) and in the purified sample (99.9%) was estimated by ^{31}P NMR spectroscopy after derivatisation with (*S*)-*O*-methylmandelic acid (**6**).

As an alternative approach to introduce a good leaving group at C-3 of the propylphosphonate framework, the epoxide ring opening in racemic **3** was studied with hydrogen chloride. Addition of 3.8 M HCl/EtOAc led to the formation of a 92:8 mixture of **12** and **13** (Scheme 4). Other research groups have reported full C-3 regioselectivity of the epoxide opening in **3** using hydrogen chloride in chloroform.[43−45]



Scheme 4. Reagents and conditions: (a) 3.8 M HCl/EtOAc, 20 °C, 0.5 h

Attempts to open the epoxide ring in **3** with aqueous trimethylamine gave diethyl 3-hydroxy-1-propenylphosphonate (**14**)[44,46,47] as a major component (60%) of the crude reaction mixture together with (*S*)-**15** (ca. 20%) and several unidentified products (Scheme 5).



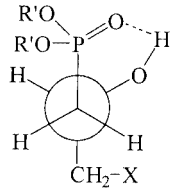
Scheme 5. Reagents and conditions: (a) Me_3N, 45% aqueous solution

In the presence of NMe_3 in water/ethanol solution the bromohydrin (*R*)-**10** was transformed quantitatively into the ammonium salt (*S*)-**11**. It is worth noting that the basicity of the reaction mixture is not high enough to reconvert (*R*)-**10** to (*S*)-**3**, since the ^{31}P NMR signal of **14** was not found in the spectrum of the crude product. The ammonium salt was isolated as an extremely hygroscopic solid. Attempts to purify it by crystallisation led to contamination with unidentified materials; however, column chromatography on silica gel afforded enantiomerically pure (*S*)-**11** in 82% yield.

Hydrolysis of (*S*)-**11** was accomplished with concentrated HCl under reflux to give (*S*)-**2**. After standard treatment with propylene oxide, the crude product was purified on

silanized silica gel to give an amorphous white solid in 78% yield, which was further crystallised from acetone/water.

The 2-hydroxypropylphosphonates **5**, **10**, **11** and **12** exist in [D]chloroform predominantly as their *anti* conformers **16** as can be judged from the large (15.5−16.9 Hz) values of their $^3J_{C,P}$ couplings together with the $^3J_{H1a\text{-}H2}$ and $^3J_{H1b\text{-}H2}$ couplings of 3.9−6.2 Hz and 6.9−8.7 Hz, respectively. However, the 3-hydroxypropylphosphonate **13** can rotate freely around the P−C1 and C1−C2 bonds ($^3J_{C,P}$ = 7.2, $^3J_{H1a\text{-}H2}$ = 7.5, $^3J_{H1b\text{-}H2}$ = 6.5 Hz). Based on these data we would like to emphasise the stabilising role of the intramolecular hydrogen bond in 2-hydroxypropylphosphonates.[48−50] The stability of the *anti* conformer **16** can be additionally increased if one assumes the formation of the hydrogen bond within a six-membered ring, which adopts a chair conformation **17** with the C-2 substituents in the equatorial positions.



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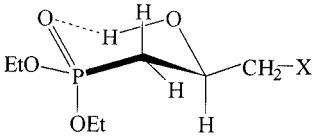

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Conformational studies on carnitine (**1**) revealed that it exists almost exclusively in a gauche conformation **18** about the C3−C4 bond, while, about the C2−C3 bond, a 53:42:5 mixture of conformers **19**, **20**, **21** is present.[51] These conclusions are based on the values of the vicinal couplings H3-H4a (1.9 Hz), H3-H4b (9.1 Hz), H2a-H3 (7.3 Hz) and H2b-H3 (6.0 Hz)[52] and were further supported by MM2 calculations;[51] the conformational preferences of the related phosphocarnitine (**2**) are similar. However, values of the H2-H3a and H2-H3b couplings (9.8 and 1.2 Hz, respectively) suggest the existence of the gauche conformer **22**. On the other hand, the conformational equilibrium of equally populated species **23** and **24** is proposed, as the H2-H1a and H2-H1b couplings are almost the same (6.6 and 6.8 Hz); the vicinal H2-P coupling (7.6 Hz) is in agreement with the gauche arrangement of these nuclei.[53]

Conclusions

An efficient synthesis of enantiomeric (*S*)-phosphocarnitine was elaborated, which relies on the hydrolytic kinetic resolution (HKR) of diethyl 2,3-epoxypropylphosphonate using Jacobsen's catalyst, followed by a fully C-3 regioselective opening of the highly enantiomerically enriched (*ee* 94%) epoxide with $MgBr_2$, bromide substitution with Me_3N and ester hydrolysis. Replacement of the carboxyl group by a phosphoryl residue reduces the conformational mobility of the carnitine skeleton.

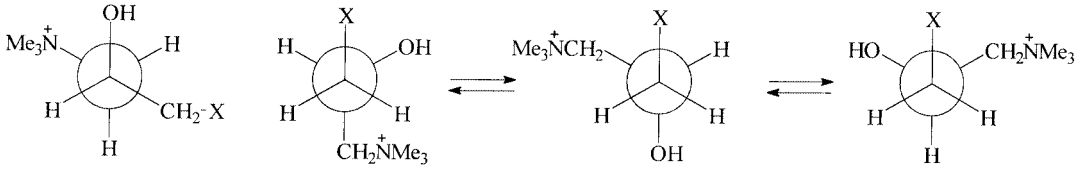
Experimental Section

General: ^{1}H NMR spectra were recorded with a Bruker DPX (250 MHz) spectrometer or with a Varian Mercury-300 spectrometer; chemical shifts are quoted in ppm with respect to TMS and coupling constants in Hz. ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DPX spectrometer at 62.9 and 101.25 MHz, or a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively. IR spectroscopic data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin−Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted on a Perkin−Elmer 241 MC apparatus.

The following absorbents were used: column chromatography, Merck silica gel 60 (70−230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in ethyl acetate/hexanes or $CHCl_3/CH_3OH$ solvent systems. Visualization of spots was effected with iodine vapours. All solvents were purified by methods described in the literature.[54]

Racemic **3** was prepared according to the literature procedure in 60% yield (δ^{31}_P = 26.71 ppm).[55,56] Before the estimation of *ee*'s, values and the separation of the ^{31}P NMR resonances of diastereoisomeric (*S*)-*O*-methylmandelic acid derivatives were assigned using racemic **3**, **5**, **10** and **11**.

Hydrolytic Kinetic Resolution of Racemic 3: A mixture of (*R*,*R*)-**4** (46.1 mg, 0.076 mmol), toluene (0.6 mL) and acetic acid (9.4 μL, 0.15 mmol) was stirred in air at room temperature for 1 h. After removal of the solvent, the brown residue was dried under vacuum. The racemic epoxide (7.415 g, 38.2 mmol) was added to the catalyst in one portion and the mixture was cooled in an ice-water bath. Water (0.378 mL, 21.0 mmol, 0.55 equiv.) was added over 0.5 h. After 1 h the bath was removed and the reaction mixture was stirred at room temperature for 72 h. Ethyl acetate (15 mL) was added followed by $MgSO_4$ (1 g). After removal of the drying agent and the solvent, the crude product was distilled to give (*S*)-(−)-**3** (2.557 g, 34%) as a colourless oil (b.p. 64−68 °C/0.05 Torr). $[\alpha]_D^{20}$ =



18 X = COO^-
22 X = $P(O)(OH)O^-$

19 **23** **20** **24** **21**

−3.3 (*c* = 1.38, ethanol), *ee* 94%. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 26.82 ppm.

Further distillation afforded a fraction (b.p. 100−130 °C/0.05 Torr) identified by ^{31}P NMR spectroscopy as a 9:91 mixture of (*S*)-**3** and (*R*)-**5** (2.674 g). After chromatography on a silica gel column (*R*)-**5** (2.500 g, 30%) was obtained as a very viscous colourless oil. $[\alpha]_D^{20}$ = −13.5 (*c* = 1.75, ethanol), *ee* 86% {ref.[39] $[\alpha]_D$ = −12.2 (*c* = 4.1, ethanol)}. IR (film): $\tilde{\nu}$ = 3375, 2985, 2932, 2913, 1224, 1031, 967 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.347 and 1.344 (2t, ^3J = 7.0, 6 H, CH_3), 1.95 (ddAB, ^2J = 19.2, $^2J_{AB}$ = 15.3, ^3J = 3.9, 1 H, 1b-H), 2.05 (ddAB, ^2J = 16.6, $^2J_{AB}$ = 15.3,^3J = 8.7, 1 H, 1a-H), 3.54 (dAB, $^2J_{AB}$ = 11.4, ^3J = 5.6, 1 H, 3b-H), 3.70 (ddAB, $^2J_{AB}$ = 11.4, ^3J = 3.6, ^4J = 1.4, 1 H, 3a-H), 4.0−4.2 (m, 5 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.51 (d, ^3J = 6.0, CH_3), 29.93 (d, ^1J = 140.0, C-1), 62.03 and 62.19 (2d, ^2J = 6.3, CH_2), 66.77 (d, ^3J = 15.5, C-3), 67.29 (d, ^2J = 3.4, C-2) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 30.78 ppm.

Alternatively, from the racemic epoxide **3** (2.60 g, 14.0 mmol) and water (0.138 mL, 7.70 mmol, 0.55 equiv.) in the presence of (*R*,*R*)-**4** (17 mg, 0.028 mmol), a 52:48 mixture of (*S*)-(−)-**3** and (*R*)-(−)-**5** was obtained after 19 h. Column chromatography on silica gel with chloroform/methanol mixtures (20:1 and 10:1, v/v) gave (*S*)-**3** (1.21 g, 44%) contaminated with traces of the catalyst (δ^{31}_P = 26.68 ppm) and (*R*)-**5** (0.90 g, 30%), as a very viscous almost colourless oil. $[\alpha]_D^{20}$ = −17.8 (*c* = 4.3, ethanol).

General Procedures for the Estimation of *ee*'s. a) Epoxides (*S*)-3: A mixture of the epoxide (40.0 mg, 0.21 mmol) and dibenzylamine (45.0 mg, 0.23 mmol, 1.1 equiv.) in an argon-filled flask was kept at 60 °C for 20 h. After cooling under argon to room temperature, CH_2Cl_2 (2 mL) was added followed by (*S*)-**6** (53.0 mg, 0.32 mmol, 1.5 equiv.), DCC (66.0 mg, 0.32 mmol, 1.5 equiv.) and DMAP (2.6 mg, 0.021 mmol, 0.1 equiv.). The reaction mixture was stirred for 72 h at room temperature. 1,3-Dicyclohexylurea (DCU) was filtered off, washed with a small amount of cold CH_2Cl_2, and the solution was concentrated. The residue was dissolved in $CDCl_3$ (0.6 mL) and the solution was analysed by ^{31}P NMR spectroscopy. No ^{31}P NMR signals of the unchanged epoxide or unchanged amino alcohol were found in the spectra. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.13 [(*S*,*S*)-**8**] and 27.59 ppm [(*R*,*S*)-**8**].

b) Diol (*R*)-5: (*S*)-**6** (70.0 mg, 0.42 mmol, 3.0 equiv.), DCC (87.0 mg, 0.42 mmol, 3.0 equiv.) and DMAP (3.7 mg, 0.03 mmol, 0.2 equiv.) were added to a solution of (*R*)-**5** (30.0 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at room temperature for 72 h. After removal of DCU, the solution was concentrated and the residue was analysed by ^{31}P NMR spectroscopy. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 25.02 [(*R*,*S*,*S*)-**9**] and 24.95 ppm [(*S*,*S*,*S*)-**9**].

c) Secondary Alcohols (*R*)-10 and (*S*)-11: The procedure described above for the diol was followed using (*R*)-**10** or (*S*)-**11** (0.15 mmol), (*S*)-**6** (1.5 equiv.), DCC (1.5 equiv.) and DMAP (0.1 equiv.) in CH_2Cl_2 (1.5 mL).
(*S*)-*O*-Methylmandelic acid esters of (*R*)-**10**: ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 24.80 (*R*,*S*) and 25.10 ppm (*S*,*S*).
(*S*)-*O*-Methylmandelic acid esters of (*S*)-**11**: ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 23.42 (*S*,*S*) and 23.75 ppm (*R*,*S*).

Diethyl (*R*)-3-bromo-2-hydroxypropylphosphonate (10): A solution of ethylene dibromide (2.07 g, 11.0 mmol) in dry diethyl ether (2 mL) was added dropwise to magnesium (0.29 g, 12.0 mmol) at a rate sufficient to maintain the diethyl ether at reflux. After 2 h of refluxing, more diethyl ether (20 mL) was added with a cannula, the ethereal solution of $MgBr_2$ was cooled to 0 °C under argon and a solution of (*S*)-**3** (1.05 g, 5.40 mmol) in dry diethyl ether (2 mL) was introduced slowly. The reaction mixture was stirred at 0−5 °C for 2 h and then quenched with cold saturated aqueous NH_4Cl (20 mL). The organic phase was separated, and the water phase was extracted with diethyl ether (3 × 5 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel with chloroform/methanol (100:1, v/v) to give (*R*)-**10** (1.18 g, 79%) as a colourless oil which solidified at low temperatures, but melted before reaching 20 °C. $[\alpha]_D^{20}$ = +12.4 (*c* = 4.12, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3333, 2915, 1221, 1027 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$: δ = 1.35 (t, ^3J = 7.0, 6 H, CH_3), 2.08 (ddAB, ^2J = 17.1, $^2J_{AB}$ = 15.3, ^3J = 8.3, 1 H, 1b-H), 2.16 (ddAB, ^2J = 18.6, $^2J_{AB}$ = 15.3, ^3J = 4.2, 1 H, 1a-H), 3.49 (ddAB, $^2J_{AB}$ = 10.3, ^3J = 5.4, ^4J = 1.3, 1 H, 3b-H), 3.52 (ddAB, $^2J_{AB}$ = 10.3, ^3J = 5.4, ^4J = 1.3, 1 H, 3a-H), 3.80 (d, ^3J = 4.0, 1 H, OH), 4.08−4.25 (m, 5 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.46 (d, ^3J = 6.3, CH_3), 31.69 (d, ^1J = 139.7, C-1), 38.74 (d, ^3J = 16.6, C-3), 61.99 and 62.20 (2d, ^2J = 6.4, CH_2), 66.15 (d, ^2J = 3.1, C-2) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.06 ppm. $C_7H_{16}BrO_4P$ (275.08): calcd. C 30.56, H 5.86; found C 30.58, H 5.60.

Reaction of Racemic 3 with 3.8 M HCl/EtOAc: Diethyl 2,3-epoxypropylphosphonate (**3**) (1.00 g, 5.15 mmol) was dissolved at room temperature in 2.7 mL of 3.8 M HCl/EtOAc. After disappearance of **3** (TLC) the solvent was evaporated in vacuo (0.1 Torr) and the residue (1.406 g) was analysed by ^{1}H, ^{13}C, ^{13}C(apt) and ^{31}P NMR spectroscopy. This material was chromatographed on a silica gel column with chloroform/methanol (50:1, v/v) to give **12** as a colourless oil (0.684 g, 58%) and various mixtures of **12** and **13**, including the most polar fraction of **12** and **13** (33:67) (47 mg).

Diethyl 3-Chloro-2-hydroxypropylphosphonate (12): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.0, 6 H), 2.07 (ddAB, ^2J = 17.1, $^2J_{AB}$ = 15.3, ^3J = 8.4, 1 H, 1b-H), 2.16 (ddAB, ^2J = 19.1, $^2J_{AB}$ = 15.3, ^3J = 3.9, 1 H, 1a-H), 3.61 (ddAB, $^2J_{AB}$ = 10.8, ^3J = 5.4, ^4J = 1.3, 1 H, 3b-H), 3.63 (ddAB, $^2J_{AB}$ = 10.8, ^3J = 5.4, ^4J = 1.3, 1 H, 3a-H), 4.06−4.29 (m, 5 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.51 (d, ^3J = 6.3, CH_3), 30.88 (d, ^1J = 140.6, C-1), 49.30 (d, ^3J = 16.9, C-3), 62.18 and 62.39 (2d, ^2J = 6.4, CH_2), 66.65 (d, ^2J = 3.7, C-2) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.29.

Diethyl 2-Chloro-3-hydroxypropylphosphonate (13): (NMR spectroscopic data taken from spectra of a 33:67 mixture of **12** and **13**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2, 6 H), 2.36 (ddAB, ^2J = 19.2, $^2J_{AB}$ = 15.5, ^3J = 6.5, 1 H, 1b-H), 2.41 (ddAB, ^2J = 18.5, $^2J_{AB}$ = 15.5, ^3J = 7.5, 1 H, 1a-H), 3.27 (brt, $^3J \approx$ 5.0, 1 H, OH), 3.87 (brt, $^3J \approx$ 4.6, 2 H, 3-H), 4.08−4.22 (m, 4 H), 4.24−4.35 (m, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.67 (d, ^3J = 6.0, CH_3), 32.60 (d, ^1J = 138.5, C-1), 56.78 (s, C-2), 62.52 and 62.56 (2d, ^2J = 6.5, CH_2), 67.09 (d, ^3J = 7.2, C-3) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 26.60 ppm.

(*S*)-3-(Diethoxyphosphoryl)-2-hydroxy-*N*,*N*,*N*-trimethylpropylammonium Bromide [(*S*)-11]: Ethanol (2 mL) was added to a mixture of (*R*)-**10** (0.942 g, 3.40 mmol) and 45% aqueous Me_3N (2.20 mL, 16.7 mmol, 5 equiv.) to get a homogenous solution, which was kept at 20 °C for 23 h. Volatiles were evaporated and the oily residue was subjected to column chromatography on silica gel (80 g) with chloroform/methanol (10:1, v/v) (800 mL) to give (*S*)-**11** (0.924 g, 82%) as a colourless oil. $[\alpha]_D^{20}$ = −16.4 (*c* = 2.27, ethanol). IR (film): $\tilde{\nu}$ = 3406, 2986, 2914, 1643, 1480, 1222, 1026 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.1, 6 H), 2.19 (ddAB, ^2J = 18.0, $^2J_{AB}$ = 15.5, ^3J = 6.9, 1 H, 1b-H), 2.25

(ddAB, ^2J = 18.0, $^2J_{AB}$ = 15.5, ^3J = 6.3, 1 H, 1a-H), 3.47 (s, 9 H), 3.70 (dd, ^2J = 13.3, ^3J = 10.1, 1 H, 3b-H), 4.03 (d, ^2J = 13.3, 3a-H), 4.14 (dq, ^3J = 7.7, ^3J = 7.1, 4 H), 4.70 (ddddd, ^3J = 10.5, ^3J = 10.1, ^3J = 6.9, ^3J = 6.3, ^3J = 6.1, 1 H, 2-H), 5.55 (d, ^3J = 6.1, 1 H, OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.65 (d, ^3J = 6.3, CH_3), 31.94 (d, ^1J = 138.0, C-1), 55.08, 62.13 (d, ^2J = 2.0, C-2), 62.70 and 62.78 (2d, ^2J = 6.6, CH_2), 70.64 (d, ^3J = 15.5, C-3) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 27.23 ppm. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.35 (t, ^3J = 7.1, 6 H), 2.14 (dd, ^2J = 18.4, ^3J = 6.3, 2 H, 1-H), 3.25 (s, 9 H), 3.50 and 3.52 (ddAB part of ABX system, $^2J_{AB}$ = 13.6, $^3J \approx$ 6.8, $^3J \approx$ 5.7, 2 H, 3ab-H), 4.1−4.2 (m, 4 H), 4.55 (ddtd, ^3J = 12.0, ^3J = 6.8, ^3J = 6.3, $^3J \approx$ 5.7, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, CD_3OD): δ = 16.94 (d, ^3J = 6.0, CH_3), 33.01 (d, ^1J = 139.7, C-1), 55.22 (three lines of equal intensity, ^1J = 3.5, CH_3), 63.28 (d, ^2J = 2.9, C-2), 63.74 and 63.82 (2d, ^2J = 6.1, CH_2), 71.62 (d, ^3J = 15.2, C-3) ppm. ^{31}P NMR (121.5 MHz, CD_3OD): δ = 28.57 ppm. $C_{10}H_{25}BrNO_4P\cdot 2H_2O$ (370.22): calcd. C 32.44, H 7.80, N 3.78; found C 32.51, H 7.90, N 3.56.

Phosphocarnitine [(*S*)-2]: A mixture of (*S*)-**11** (0.580 g, 1.74 mmol) and conc. HCl (9.3 mL) was refluxed for 5 h. Volatiles were evaporated, the residue was dried under vacuum and then dissolved in ethanol (5.4 mL). The precipitate formed after dropwise addition of propylene oxide (5.4 mL) was filtered off and chromatographed on a silanized silica gel [Kieselgel 60 silanisiert (70−230 mesh) Merck Art. 7719 was used] column with water to give (*S*)-**2** (0.270 g, 78%) as a white amorphous powder. Crystallisation from water/acetone gave a white solid. M.p. 270 °C (decomp.). $[\alpha]_D^{20}$ = −17.4 (*c* = 1.15, water). IR (KBr): $\tilde{\nu}$ = 3393, 2922, 2851, 1474, 1067, 985 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): δ = 1.76 (ddAB, ^2J = 16.6, $^2J_{AB}$ = 14.8, ^3J = 6.6, 1 H, 1a-H), 1.78 (ddAB, ^2J = 16.7, $^2J_{AB}$ = 14.8, ^3J = 6.8, 1 H, 1b-H), 3.25 (s, 9 H), 3.43 (dAB, $^2J_{AB}$ = 13.8, ^3J = 9.8, 1 H, 3a-H), 3.64 (dAB, $^2J_{AB}$ = 13.8, ^3J = 1.2, 1 H, 3b-H), 4.52 (brm, ^3J = 9.8, ^3J = 7.6, ^3J = 6.8, ^3J = 6.6, ^3J = 1.2, 1 H, 2-H) ppm. ^{13}C NMR (62.9 MHz, D_2O): δ = 32.93 (d, ^1J = 125.9, C-1), 52.35 (three lines of equal intensity, ^1J = 3.6), 61.67 (C-2), 69.36 (d, ^3J = 12.0, C-3) ppm. ^{31}P NMR (121.5 MHz, D_2O): δ = 17.8 ppm. HRMS (FAB+) $C_6H_{17}NO_4P$ (*m*/*z*): calcd. 198.0895; found 198.0898.

Acknowledgments

We thank Mrs Małgorzata Pluskota for her skilled experimental contributions. Financial support from the Medical University of Łódź (502-13-597 and 503-302-4) is gratefully acknowledged.

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Received March 26, 2002
[O02169]