Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1775–1779

TETRAHEDRON: *ASYMMETRY*

Preparation of (*R*)- and (*S*)-γ-amino-β-hydroxypropylphosphonic acid from glycine

Mario Ordóñez,* Angelina González-Morales, César Ruíz, Ricardo De la Cruz-Cordero and Mario Fernández-Zertuche

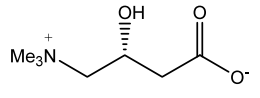
Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad No. 1001. 62210 Cuernavaca, Mor., Mexico

Received 10 October 2002; accepted 4 April 2003

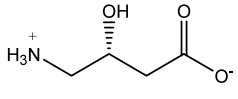
Abstract—An efficient synthesis of both enantiomers of γ-amino-β-hydroxypropylphosphonic acid, an analogue of GABOB, has been achieved for the first time starting from glycine, through the resolution of dimethyl (±)-3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate **7** with (*S*)-*O*-methylmandelic acid.

1. Introduction

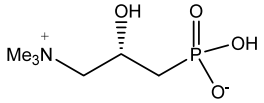
(*R*)-3-Hydroxy-4-trimethylaminobutyric acid (*L*-carnitine) **1** and (*R*)-γ-amino-β-hydroxybutyric acid (GABOB) **2** are two compounds with a very high level of medical significance due to their interesting biological properties and usefulness as pharmaceuticals. *L*-Carnitine **1** plays an important role in the oxidation of fatty acids and is involved in other important metabolic pathways, both as free carnitine and as acetylcarnitine; the latter are metabolic products of reactions that utilize acetyl CoA catalyzed by carnitine acetyltransferase.[1] The (*S*)-enantiomer of **1** acts as a competitive inhibitor of carnitine acetyltransferase[2] causing depletion of carnitine. (*R*)-γ-Amino-β-hydroxybutyric acid **2** is a well known drug that functions as an agonist of gamma-aminobutyric acid (GABA). It has been demonstrated to be effective in managing a variety of clinical conditions including schizophrenia, epilepsy and others illnesses that result in severe convulsions.[3]



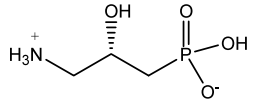
(*R*)-(-)-Carnitine **1**



(*R*)-(-)-GABOB **2**



(*S*)-(-)-Phosphocarnitine **3**



(*S*)-(-)-GABOB^{P} **4**

Because of the importance of *L*-carnitine and *L*-GABOB in medical science, many synthetic routes have been developed.[4]

Various analogues of carnitine have been synthesized, including phosphocarnitine **3**, an analogue in which the carboxylic group has been replaced with a phosphonic function. The stereoselective synthesis of phosphocarnitine **3** has been achieved from (*R*)-(−)-epichlorhidrin,[5] by hydrolysis of racemic diethyl 2,3-epoxipropylphosphonate in the presence of (*R*,*R*)-salen-Co(III)-OAc,[6] and by enzymatic kinetic resolution.[7] However, in the best of our knowledge the synthesis of the enantiomerically pure γ-amino-β-hydroxypropylphosphonic acid **4** has not been described.[8,9]

As part of our ongoing program directed towards the design of homochiral γ-amino-β-hydroxyphosphonates,[10] we report here a simple procedure for the synthesis of (*R*)- and (*S*)-γ-amino-β-hydroxypropylphosphonic acid **4**, which is based on reduction of the carbonyl group of the β-ketophosphonate **6**, derived from the readily available *N*,*N*-dibenzylglycinate **5**, and its resolution with (*S*)-*O*-methylmandelic acid.

2. Results and discussion

Initially, treatment of glycine with K_2CO_3 and excess of benzyl bromide under reflux, afford the mixture of the *N*,*N*-dibenzylglycinates **5**, which were cleanly separated on column chromatography affording the less polar *N*,*N*-dibenzylglycine benzyl ester[11] **5a** in 64% yield as a

* Corresponding authors. E-mail: palacios@buzon.uaem.mx

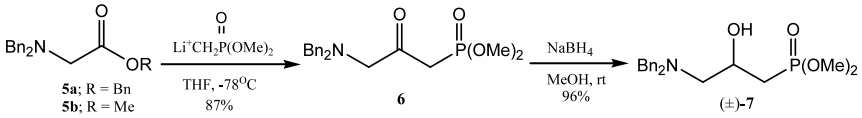
0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00371-9

solid and the more polar *N*,*N*-dibenzylglycine methyl ester[12] **5b** in 32% yield as a liquid. The reaction of the protected glycine **5a** or **5b** with two equivalents of the lithium salt of dimethyl methylphosphonate at −78°C in THF give the corresponding dimethyl 3-(*N*,*N*-dibenzylamino)-2-ketopropylphosphonate **6** in 87% yield. Reduction of 2-oxophosphonate **6** with $NaBH_4$ in methanol at room temperature afford the racemic mixture of the dimethyl 3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate **7** in 96% yield (Scheme 1).

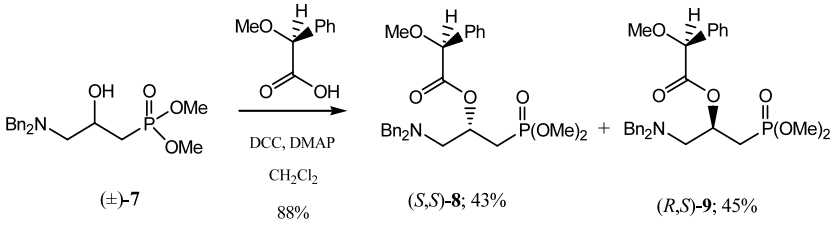
The resolution of (±)-**7** was achieved via *O*-methylmandelate derivatives.[13] Thus, the reaction of the racemic mixture (±)-**7** with (*S*)-*O*-methylmandelic acid in the presence of DCC and DMAP in dichloromethane at room temperature afford the respective mandelates in good yield. The mixture of diastereomers was cleanly separated on column chromatography affording the less polar diastereomer (*S*,*S*)-**8** in 43% yield as a liquid and the more polar diastereomer (*R*,*S*)-**9** in 45% yield as a liquid (Scheme 2). Their purity was ascertained from ^{1}H, ^{13}C, ^{31}P NMR spectra.

The absolute configuration of the C3-stereogenic centers of the diastereomers (*S*,*S*)-**8** and (*R*,*S*)-**9** were assigned, based on the analysis of ^{1}H and ^{31}P NMR spectral data of the mandelates. Thus, according to the Trost model,[13] both the methylene and methyl protons of the $CH_2P(O)(OMe)_2$ group in the diastereomer (*S*,*S*)-**8** are expected to be shielded, as well as the methylene protons on the CH_2NBn_2 group in the diastereomer (*R*,*S*)-**9**, since they are eclipsed with the phenyl ring of the mandelic functionality in the extended Newman projection (Fig. 1).

Both ^{1}H and ^{31}P NMR spectra revealed some significant differences between the (*S*,*S*)-**8** and *(R,S)*-**9** diastereomers (Table 1).



Scheme 1.



Scheme 2.

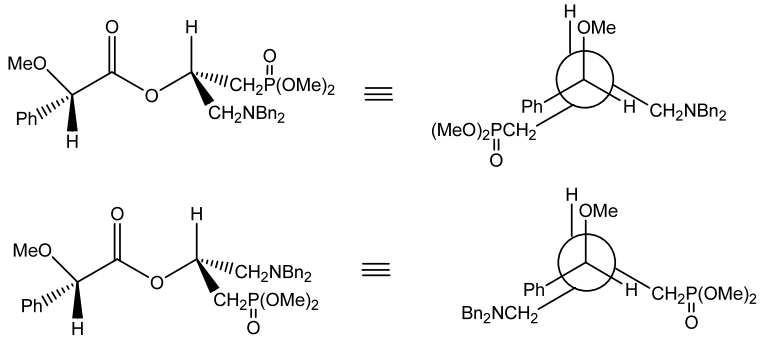


Figure 1. Extended Newman projections for the diastereomers (*S*,*S*)-**8** and (*R*,*S*)-**9**.

Table 1. ^{1}H and ^{31}P NMR chemical shifts of the mandelates (*S*,*S*)-**8** and (*R*,*S*)-**9**

Entry		Less polar mandelate	$\Delta\delta$ (ppm)	More polar mandelate	$\Delta\delta$ (ppm)
1	$CH_2P(O)$	1.79 and 2.11	0.32	1.97 and 2.14	0.17
2	CH_2NBn_2	2.60 and 2.66	0.06	2.45 and 2.55	0.10
3	CH_2Ph	3.59	0	3.38 and 3.43	0.05
4	$(CH_3O)_2P$	3.40 and 3.52	0.12	3.63 and 3.65	0.02
5	$(CH_3O)_2P$	30.47	–	30.78	–

The less polar diastereomer showed upfield shifts for the two methylene protons in $CH_2P(O)$ at 1.79 and 2.11 ppm, $\Delta\delta = 0.32$ ppm entry 1, and for the two methyl signals in $(CH_3O)_2P$ at 3.40 and 3.52 ppm, $\Delta\delta = 0.12$ ppm entry 4. On the other hand, the more polar diastereomer showed upfield shifts for two methylene protons in CH_2NBn_2 at 2.45 and 2.55 ppm, $\Delta\delta = 0.10$ ppm entry 2, and for the two methylenes in CH_2Ph at 3.38 and 3.43 ppm, $\Delta\delta = 0.05$ ppm entry 3. Additionally, the ^{31}P NMR chemical shifts for the less polar diastereomer appear at a higher field (30.47 ppm) than the more polar methylmandelate (30.78 ppm) entry 5. The same similarities in their ^{31}P NMR chemical shifts have been observed for the diethyl phosphonate analogs.[6a] These NMR data show that the less polar compound is the (*S*,*S*) diastereomer and the more polar compound is the (*R*,*S*) diastereomer.[14]

Treatment of (*S*,*S*)-**8** with LiOH in a mixture of MeOH:H_2O (8:2) at room temperature followed by separation of (*S*)-*O*-methylmandelic acid by column chromatography give (*S*)-**7** in 85% yield. In a similar manner, (*R*)-**7** was obtained from (*R*,*S*)-**9** in 83% yield (Scheme 3). Finally, hydrolysis of β-hydroxypropylphosphonates (*S*)-**7** and (*R*)-**7** with bromotrimethylsilane[15] at room temperature afforded the acid γ-(*N*,*N*-dibenzylamino)-β-hydroxy-propylphosphonic acid in quantitative yield, which without further purification were treated with palladium on carbon in methanol under hydrogen at room temperature to obtain (*S*)- and (*R*)-γ-amino-β-hydroxypropylphosphonic acid in 78% and 76% yield, respectively.

In conclusion, we have found a new methodology for the preparation of enantiomerically pure (*R*)- and (*S*)-γ-amino-β-hydroxypropylphosphonic acid from glycine, which are analogues of GABOB. Additionally, these compounds can be useful intermediates for the synthesis of (*S*)- and (*R*)-phosphocarnitine and other aminophosphonic acids derivatives.

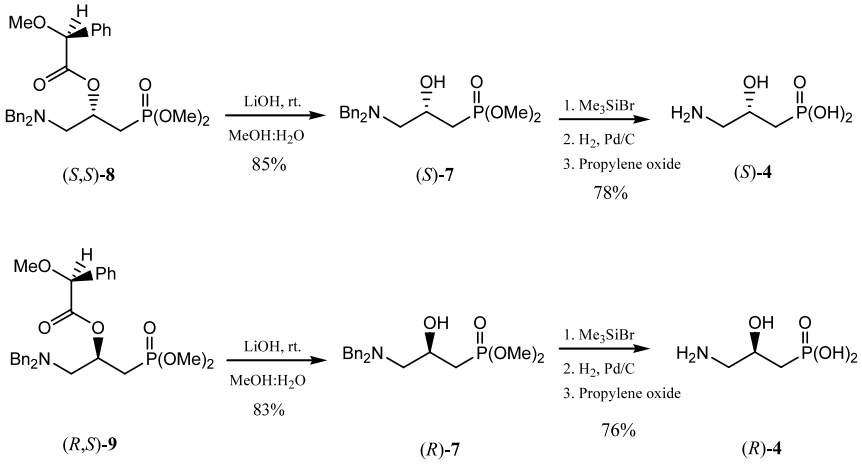
3. Experimental

Optical rotations were taken on a Perkin–Elmer 241 polarimeter in an 1 dm tube; concentrations are given in g/100 mL. For the flash chromatography, silica gel 60 (230–400 mesh ASTM, Merck) was used. ^1H NMR spectra were registered on a Varian (400 MHz) and ^{13}C NMR on AMX-500 (100 MHz). The spectras were recorded in D_2O or $CDCl_3$ solution, using TMS as internal reference. Microanalyses were registered on a Elemental VARIO EL III.

Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120°C and allowed to cool in a dessicator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl. The (*S*)-*O*-methylmandelic acid was prepared according to literature procedure.[16]

3.1. Dimethyl 3-(*N*,*N*-dibenzylamino)-2-oxopropylphosphonate 6

A solution of benzylbromide (45.6 g, 0.27 mol) in methanol (150 mL) was slowly added to a solution of the glycine (5 g, 0.07 mol) and K_2CO_3 (36.8 g, 0.27 mol) in a 5:1 mixture of methanol–water (350 mL). The reaction mixture was refluxed for 3 h, the solvent was removed under reduced pressure and water was added to the residue and extracted with ethyl acetate (3×150 ml). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude products were purified by flash chromatography (hexane-ethyl acetate 9:1) to afford *N*,*N*-dibenzylglycine benzyl ester[10] **5a** (14.7 g, 64%) as a solid, and the more polar *N*,*N*-dibenzylglycine methyl ester[11] **5b** (6.5 g, 32%) as a liquid. Dimethylmethylphosphonate (2.87 g, 23.15 mmol) was dissolved in dry THF (50 mL), cooled at −78°C, and treated with (23.2 mL, 25.5 mmol) of *n*-BuLi in hexanes (1.1 M) under nitrogen



Scheme 3.

atmosphere. The resulting solution was stirred at −50°C for 1 h, and after this period of time the solution was cooled at −78°C and was slowly added to a solution of the *N*,*N*-dibenzylglycine benzyl ester **5a** (4.0 g, 11.6 mmol) in THF (50 mL). The reaction mixture was stirred at −78°C for 3 h before the addition of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate–hexane 4:1) to afford **6** (3.65 g, 87%) as yellow oil. (Identical yield was obtained using the ester **5b**.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (d, J=22.4 Hz, 2H, $CH_2P(O)$), 3.35 (s, 2H, CH_2NBn_2), 3.66 (d, J=11.2 Hz, 6H, $(CH_3O)_2P$), 3.68 (s, 4H, CH_2Ph), 7.24–7.38 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1 (d, J= 129.1 Hz, $CH_2P(O)$), 53.0 (d, J=6.1 Hz, $(CH_3O)_2P$), 58.9 CH_2Ph, 63.8 CH_2NBn_2, 127.5, 128.6, 129.3, 138.6, 201.7 C=O. ^{31}P NMR (400 MHz, $CDCl_3$) δ 23.90.

3.2. Dimethyl (*RS*)-3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate (±)-7

A mixture of the dimethyl 3-(*N*,*N*-dibenzylamino)-2-oxopropylphosphonate **6** (3.7 g, 10 mmol), sodium borohydride (2.3 g, 60.7 mmol) and methanol (40 mL) was stirred at rt for 10 h under a nitrogen atmosphere. After the reaction mixture was carefully treated with a saturated solution of NH_4Cl. The solvent was removed in vacuo, and the residue was dissolved in water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate–hexane 4:1) to afford (±)-**7** (3.5 g, 96%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (ddd, J= 16.8, 15.2, 8.4 Hz, 1H, $CH_2P(O)$), 1.90 (ddd, J=18.8, 15.2, 4.0 Hz, 1H, $CH_2P(O)$), 2.49–2.58 (m, 2H, CH_2NBn_2), 3.49 (d, J=13.6 Hz, 2H, CH_2Ph), 3.70 (d, J=11.2 Hz, 3H, $(CH_3O)_2P$), 3.72 (d, J=11.2 Hz, 3H, $(CH_3O)_2P$), 3.76 (d, J=13.6 Hz, 2H, CH_2Ph), 4.03–4.12 (m, 1H, CH(OH)), 7.24–7.34 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8 (d, J=139.7 Hz, $CH_2P(O)$), 52.4 (d, J=6.1 Hz, $(CH_3O)_2P$), 52.6 (d, J=6.1 Hz, $(CH_3O)_2P$), 59.0 CH_2Ph, 60.2 (d, J=15.2 Hz, CH(OH)), 63.6 CH_2NBn_2, 127.4, 128.6, 129.3, 138.8. ^{31}P NMR (400 MHz, $CDCl_3$) δ 33.45.

3.3. Esterification of (±)-7 with (*S*)-*O*-methylmandelic acid

To a solution of (±)-**7** (3.5 g, 9.6 mmol) and (*S*)-*O*-methylmandelic acid (2.6 g, 15.4 mmol) in dichloromethane (60 mL) containing dimethylaminopyridine (176 mg, 1.45 mmol) and 1,3-dicyclohexylcarbodiimide (3.2 g, 15.4 mmol) was added. The reaction mixture was stirred at rt for 7 h. After 1,3-dicyclohexylurea was filtered off and the liquid layer was evaporated in vacuo. The crude product was purified by column chromatography (ethyl acetate–hexane 3:1) to afford (*S*,*S*)-**8** (2.1 g, 43%) as colorless oil (less polar) and (*R*,*S*)-**9** (2.2 g, 45%) as colorless oil (more polar).

3.4. Less polar diastereomer (*S*,*S*)-8

$[\alpha]_D^{20}$=+32 (*c* 2.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (ddd, J=17.6, 15.6, 7.2 Hz, 1H, $CH_2P(O)$), 2.11 (ddd, J=18.8, 15.6, 4.8 Hz, 1H, $CH_2P(O)$), 2.60 (dd, J=13.2, 6.0 Hz, 1H, CH_2NBn_2), 2.66 (ddd, J=13.2, 6.8, 2.4 Hz, 1H, CH_2NBn_2), 3.40 (d, J=11.0 Hz, 3H, $(CH_3O)_2P$), 3.42 (s, 3H, CH_3O), 3.52 (d, J=11.0 Hz, 3H, $(CH_3O)_2P$), 3.59 (s, 4H, CH_2Ph), 4.67 (s, 1H, $CH(OCH_3)$), 5.28–5.37 (m, 1H, $CHCH_2P(O)$), 7.30–7.39 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9 (d, J=141.9 Hz, $CH_2P(O)$), 52.3 (d, J=6.1 Hz, $(CH_3O)_2P$), 56.9 (d, J=6.1 Hz, $(CH_3O)_2P$), 57.5 (CH_3OCH), 58.9 CH_2NBn_2, 59.0 CH_2Ph, 68.4 ($CHCH_2P(O)$), 82.7 $CH(OCH_3)$, 127.2, 127.6, 128.4, 128.7, 128.8, 129.2, 136.1, 138.9, 169.9 C=O. ^{31}P NMR (400 MHz, $CDCl_3$) δ 30.47. Anal. calcd for $C_{28}H_{34}NO_6P$: C, 65.74; H, 6.70; N, 2.74. Found C, 65.57; H, 6.78; N, 2.69.

3.5. More polar diastereomer (*R*,*S*)-9

$[\alpha]_D^{20}$=+23.9 (*c* 1.09, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (ddd, J=16.8, 15.6, 8.0 Hz, 1H, $CH_2P(O)$), 2.14 (ddd, J=19.2, 16.0, 4.4 Hz, 1H, $CH_2P(O)$), 2.45 (dd, J=13.6, 6.0 Hz, 1H, CH_2NBn_2), 2.55 (ddd, J=13.6, 6.0, 2.0 Hz, 1H, CH_2NBn_2), 3.38 (d, J=13.8 Hz, 2H, CH_2Ph), 3.41 (s, 3H, CH_3O), 3.43 (d, J=13.8 Hz, 2H, CH_2Ph), 3.63 (d, J=10.8 Hz, 3H, $(CH_3O)_2P$), 3.65 (d, J=10.8 Hz, 3H, $(CH_3O)_2P$), 4.74 (s, 1H, $CH(OCH_3)$), 5.30–5.38 (m, 1H, $CHCH_2P(O)$), 7.17–7.45 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (d, J=141.9 Hz, $CH_2P(O)$), 52.5 (d, J=6.8 Hz, $(CH_3O)_2P$), 52.7 (d, J=6.8 Hz, $(CH_3O)_2P$), 57.1 CH_2NBn_2), 57.6 (CH_3OCH), 68.5 ($CHCH_2P(O)$), 59.0 CH_2Ph, 82.9 $CH(OCH_3)$, 127.3, 127.7, 128.5, 128.8, 129.0, 129.2, 136.4, 139.1, 170.1 C=O. ^{31}P NMR (400 MHz, $CDCl_3$) δ 30.78. Anal. calcd for $C_{28}H_{34}NO_6P$: C, 65.74; H, 6.70; N, 2.74. Found C, 65.71; H, 6.67; N, 2.65.

3.6. Dimethyl (*S*)-3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate 7

The diastereomer (*S*,*S*)-**8** (314 mg, 0.61 mmol) was dissolved in MeOH/H_2O 8:2 (20 mL) and stirred at rt with LiOH (29.4 mg, 1.22 mmol). After 8 h the volatiles were removed in vacuo. The residue was dissolved in ethyl acetate and washed with water. The layer organic was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate–hexane 4:1) to afford (*S*)-**7** (189 mg, 85%) as colorless oil. $[\alpha]_D^{20}$= −31.7 (*c* 1.42, $CHCl_3$). The NMR shifts are identical to (±)-**7**. Anal. calcd for $C_{19}H_{26}NO_4P$: C, 62.80; H, 7.21; N, 3.85. Found C, 62.65; H, 7.15; N, 3.79. In a

similar way, from (*R*,*S*)-**9** (477 mg, 0.93 mmol) afford (*R*)-**7** (281 mg, 83%) as colorless oil. $[\alpha]_D^{20} = +29.4$ (*c* 1.8, $CHCl_3$). Anal. calcd for $C_{19}H_{26}NO_4P$: C, 62.80; H, 7.21; N, 3.85. Found C, 62.73; H, 7.12; N, 3.82.

3.7. (*S*)-3-Amino-2-hydroxypropylphosphonic acid 4

Dimethyl (*S*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)propylphosphonate **7** (144 mg, 0.4 mmol) was treated with (135 mg, 0.12 mL, 0.88 mmol) of bromotrimethylsilane under nitrogen atmosphere. The reaction mixture was stirred at rt for 4 h, and after this period of time the volatiles materials were removed under reduced pressure, and water was added. After 30 min the solvents were removed in vacuo to give (*S*)-2-hydroxy-3-(*N*,*N*-dibenzylamino)propylphosphonic acid, which without isolation was treated with palladium on carbon 288 mg (5% wt) in methanol (20 mL) and stirred for 16 h under hydrogen gas at rt. The mixture was filtered through a pad of Celite, and the solvents were removed under reduced pressure. The residue was treated with propilen oxide (5 mL) to afford (48 mg, 78%) of (*S*)-γ-amino-β-hydroxypropylphosphonic acid **4**, as a white solid. p.f. = 175–178°C, $[\alpha]_D^{20} = -10.3$ (*c* 2.04, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.86 (ddd, J = 36.4, 14.8, 6.8 Hz, 1H, $CH_2P(O)$), 1.91 (ddd, J = 36.4, 14.8, 6.8 Hz, 1H, $CH_2P(O)$), 2.93 (dd, J = 13.2, 9.6 Hz, 1H, CH_2NH_2), 3.27 (dd, J = 13.2, 2.8 Hz, 1H, CH_2NH_2), 4.08–4.17 (m, 1H, CHOH). ^{13}C NMR (100 MHz, D_2O) δ 37.3 (d, J = 128.5 Hz), 48.3 (d, J = 9.9 Hz), 67.6. ^{31}P NMR (200 MHz, D_2O) δ 19.94.

The procedure described above for the (*S*)-enantiomer, was followed using (*R*)-3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate **7** (170 mg, 0.47 mmol) and bromotrimethylsilane (158 mg, 0.14 mL, 1.03 mmol), and the crude product was treated with palladium on carbon 316 mg (5% wt) in methanol (20 mL) and stirred for 16 h under hydrogen gas at rt, obtaining (56 mg, 76%) of (*R*)-γ-amino-β-hydroxypropyl-phosphonic acid **4**, as a white solid. p.f. = 176–178°C, $[\alpha]_D^{20} = +10.8$ (*c* 2.04, H_2O).

Acknowledgements

We wish to thank CONACyT (Project 28762-E and 41657-Q) and Victoria Labastida for financial and technical support. A.G.M. and R.C.C. would like to thank CONACyT for scholarship.

References

1. (a) De Simone, C.; Famularo, G. *Carnitine Today*; Springer-Verlag: Heilderberg, 1997; (b) Ferrari, R.; Di Mauro, S.; Sherwood, G. *L-Carnitine and its Role in Medicine*: *From Function to Therapy*; Academic Press: San Diego, 1992; (c) Fritz, I. B. In *Current Concepts in Carnitine Research*; Karter, A. L., Ed.; CRC, 1992; pp. 107–119.
2. (a) Vary, T. C.; Neely, J. R. *Am. J. Physiol.* **1982**, *242*, H585; (b) Bressler, R.; Brendel, K. *J. Biol. Chem.* **1966**, *241*, 4092.
3. (a) Tacaño, S.; Yanase, M.; Sekiguchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 1783; (b) Otsuka, M.; Obata, K.; Miyata, Y.; Yaneka, Y. *J. Neurochem.* **1971**, *18*, 287; (c) Buscaino, G. A.; Ferrari, E. *Acta Neurol.* **1961**, *16*, 748; (d) DeMaio, D.; Madeddu, A.; Faggioli, L. *Acta Neurol.* **1961**, *16*, 366.
4. (a) Jain, R. P.; Williams, R. M. *Tetrahedron* **2001**, *57*, 6505; (b) Marzi, M.; Minetti, P.; Moretti, G.; Tinti, M. O.; De Angelis, F. *J. Org. Chem.* **2000**, *65*, 6766; (c) Kanno, O.; Miyauchi, M.; Kawamoto, I. *Heterocycles* **2000**, *53*, 173; (d) Wang, G.; Hollingsworth, R. I. *Tetrahedron: Asymmetry* **1999**, *10*, 1895; (e) Puertas, S.; Rebolledo, F.; Gotor, V. *J. Org. Chem.* **1996**, *61*, 6024.
5. Tadeusiak, E.; Krawiecka, B.; Michalski, J. *Tetrahedron Lett.* **1999**, *40*, 1791.
6. (a) Wroblewsky, A. E.; Halajewska-Wosik, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2053; (b) Wroblewsky, A. E.; Halajewska-Wosik, A. *Eur. J. Org. Chem.* **2002**, 2758.
7. Mikolajczyk, M.; Luczak, J.; Kielbasinski, P. *J. Org. Chem.* **2002**, *67*, 7872.
8. For the synthesis of racemic γ-amino-β-hydroxypropylphosphonic acid, see: Dingwall, J. G. *Phosphorus and Sulfur* **1983**, *18*, 353.
9. For the synthesis of diethyl (*S*)-γ-amino-β-hydroxypropylphosphonate, see: Yuan, C.; Wang, K.; Li, Z. *Heteroatom Chem.* **2001**, *12*, 551.
10. Ordóñez, M.; De la Cruz, R.; Fernández-Zertuche, M.; Muñoz-Hernández, M.-A. *Tetrahedron: Asymmetry* **2002**, *13*, 559.
11. (a) Enders, D.; Schiffers, R. *Synthesis* **1994**, 53; (b) Hense, T.; Hoppe, D. *Synthesis* **1997**, 1394.
12. Guanti, G.; Banfi, L.; Narisano, E.; Scolastico, C. *Tetrahedron Lett.* **1984**, *41*, 4693.
13. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
14. For the assignment of absolute configuration of secondary alcohols by NMR, see: Seco, J. M.; Tseng, L.-H.; Godejohann, M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2149.
15. McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, 155.
16. Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.