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An efficient synthesis of an enantiomerically pure phosphonate analogue of L-GABOB

Andrzej E. Wróblewski* and Anetta Hałajewska-Wosik

Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, 90-151 Łódź, Muszyńskiego 1, Poland

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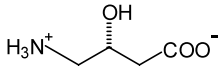
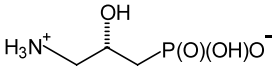
Abstract—Two reliable methods for the synthesis of the enantiomerically pure (*S*)-3-amino-2-hydroxypropylphosphonic acid (a phosphonate analogue of L-GABOB) from diethyl (*S*)-2,3-epoxypropylphosphonate are elaborated. The amplification of the enantiomeric purity of the intermediate diethyl (*S*)-3-(*tert*-butoxycarbonylamino)- and (*S*)-3-(diphenylmethylamino)-2-hydroxypropylphosphonates was observed on a silica gel column.

1. Introduction

(*R*)-4-Amino-3-hydroxybutyric acid (L-GABOB) **1** is an important aminoacid which acts as an agonist of γ-aminobutyric acid (GABA).[1,2] As a neuromodulator it has been tried in the treatment of several illnesses including epilepsy.[3,4] For these reasons, many methods for the synthesis of **1** have been reported. They are based on a chiral pool methodology,[5–14] asymmetric synthesis[15–22] and enzymatic or chemoenzymatic technologies.[23–28]



(*R*)-**1**



(*S*)-**2**

A number of phosphonate analogues of GABA have been synthesised in recent years and have been used for subtype receptor selectivity studies.[29,30] Although a phosphonate analogue of GABOB was described as early as 1969[31] with another method communicated in 1983,[32] the optically active **2** (e.e. 92%) has only recently been obtained chemoenzymatically by Bakers yeast reduction of diethyl 3-azido-2-oxopropylphosphonate followed by catalytic hydrogenation of the azido group.[33,34] However, this methodology is closely related to that described for **1**.[26,27] Very recently, an eight-step sequence to both enantiomers of **2** starting from glycine and including the resolution of the intermediate dimethyl 3-(*N*,*N*-dibenzylamino)-2-hydroxypropylphosphonate[35] with (*S*)-*O*-methylmandelic acid has been described.[36] Herein, we report a four-step approach to (*S*)-**2** which takes advantage of the hydrolytic kinetic resolution (HKR) of the racemic diethyl 2,3-epoxypropylphosphonate in the presence of the Jacobsen's catalyst.[35,37,38]

2. Results and discussion

Inspection of the ^{31}P NMR spectrum of the crude product obtained from the racemic **3** and 25% aqueous ammonia[31] led to the conclusion that diethyl 3-amino-2-hydroxypropylphosphonate was indeed the major constituent of the reaction mixture, but it was however contaminated with several organophosphorus compounds, most of which still remain unidentified.[39] Due to the enantiomeric purity of the optically active epoxide **3** produced by HKR being at best 94%, we looked for amines, which would selectively open the oxirane ring in **3** at C(3) and lead to crystalline aminoalcohols. Our first strategy to the phosphonate analogue of L-GABOB (*S*)-**2** is illustrated in Scheme 1.

When a 1.5:1 mixture of tritylamine and (*S*)-**3** was kept in toluene solution at 100°C for 7 days, the phosphonate (*S*)-**4** was obtained as a single product of the reaction. The excess of tritylamine was easily removed on a silica gel column. After crystallisation of the appropriate fractions, pure phosphonate was isolated. We noticed that at the same time the e.e. of (*S*)-**4** was

* Corresponding author. Fax: 48-42-678-83-98; e-mail: aewplld@ich.pharm.am.lodz.pl

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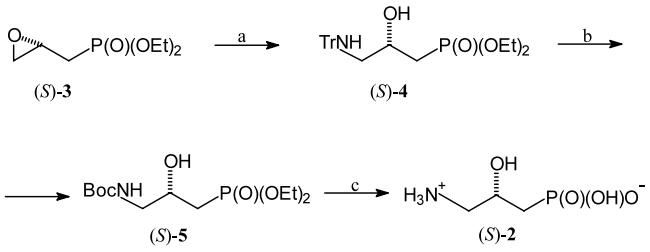


Scheme 1. *Reagents and conditions*: a. $TrNH_2$, 100°C, 7 days; b. H_2–Pd/C, Boc_2O; c. 12 M HCl; propylene oxide.

significantly increased. Thus, from (*S*)-**3** (e.e. 74%), the aminoalcohol (*S*)-**4** (e.e. 96%) was produced. Application of (*S*)-**3** (e.e. 85%) led again to (*S*)-**4** (e.e. 96%) after crystallisation. The same enantiomeric purity of (*S*)-**4** was found for the crystallised sample obtained from the epoxide (*S*)-**3** of the highest e.e. (94%). Unfortunately, further crystallisation did not improve the enantiomeric composition.

The trityl group was removed by hydrogenolysis in the presence of Boc_2O to afford the *N*-Boc derivative (*S*)-**5** as an oil, which after column chromatography was found to be enantiomerically pure. Finally, hydrolysis of the ester groups in (*S*)-**5** followed by standard treatment with propylene oxide led to (*S*)-**2**.

Another method for the synthesis of enantiomerically pure (*S*)-**2** was developed, when the reaction of the epoxide (*S*)-**3** with benzhydrylamine was studied (Scheme 2).

Initially the racemic epoxide **3** was used and we found that the opening of the oxirane ring in **3** with benzhydrylamine led to the formation of diethyl 2-hydroxy-3-(diphenylmethylamino)propylphosphonate **6** and bis-*N*,*N* - [2 - hydroxy - 3 - (diethoxyphosphoryl)propyl] - *N*-(diphenylmethyl)amine **7** in a 92:8 ratio. The bisphosphonate **7** was found to be a ca 1:1 meso/dl mixture. The major product **6** was separated from **7** on a silica gel column and the monophosphonate **6** was obtained in 78% yield after crystallisation. It is noteworthy that crystallisation of the crude product was not effective in removing *meso*/*dl*-**7** from **6**.

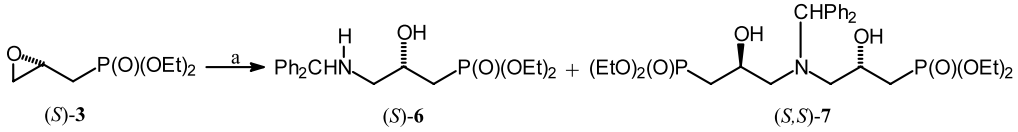
The reaction of enantiomerically enriched (*S*)-**3** (e.e. 80%) with one equivalent of benzhydrylamine allowed for the chromatographic separation of (*S*)-**6** in 77% yield as a yellowish oil, which did not crystallise. However, the product was shown to be enantiomerically pure by ^{31}P NMR analysis using quinine as an enantiodifferentiating compound.[40] In another experiment (*S*)-**3** (e.e. 85%) was used and the enantiomeric composition of the monophosphonate (*S*)-**6** in the crude product estimated as 90%. After column chromatography on silica gel again, enantiomerically pure (*S*)-**6** was obtained in 77% yield. Finally, (*S*)-**3** (e.e. 90%) was transformed into a crude (*S*)-**6** (e.e. 96%), which was refined on a silica gel to give an enantiomerically pure product.

The formation of the tertiary amine **7** as a *meso*/*dl* mixture was demonstrated by reacting 2.3 equiv. of racemic **3** with one equivalent of benzhydrylamine at 100°C for 115 h. The crude product, which still contained some unreacted epoxide **3** (2%) and the monophosphonate **6** (12%), was chromatographed to give *meso*/*dl*-**7** as a colourless oil in 50% yield.

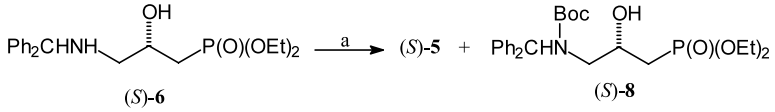
Transformation of the enantiomerically pure (*S*)-**6** into the *N*-Boc derivative (*S*)-**5** was accomplished by hydrogenation over Pd-C in the presence of Boc_2O (Scheme 3). We noticed that a crude (*S*)-**5** was contaminated with (*S*)-**8** (14%), when the reaction was carried out for 24 h, while after 120 h the amount of (*S*)-**8** dropped down to 5%. The by-product (*S*)-**8** was cleanly separated from the more polar (*S*)-**5** on a silica gel column, and the enantiomerically pure samples of (*S*)-**5** were obtained in 81 and 90% yield, respectively.

3. Conclusions

The epoxide ring in the phosphonate (*S*)-**3** was regioselectively opened at C(3) with trityl- and benzhydrylamines. While the *N*-tritylphosphonate (*S*)-**4** was too sterically crowded to react with another molecule of (*S*)-**3**, the *N*-benzhydrylphosphonate (*S*)-**6** used up some of the epoxide **3** to produce the bisphosphonate **7** (ca 8%). Although enantiomerically enriched samples of (*S*)-**3** (e.e. 74–94%) were used, enantiomerically pure phosphonate (*S*)-**5** (via *N*-trityl derivative) and (*S*)-**6**



Scheme 2. *Reagents and conditions*: (a) Ph_2CHNH_2, 100°C, 24 h.



Scheme 3. *Reagents and conditions*: (a) H_2, 10% Pd-C, Boc_2O.

(via *N*-benzhydryl derivative) were obtained after chromatography on silica gel. The phosphonate (*S*)-**5** (*N*-Boc) was transformed into the enantiomerically pure phosphonate analogue of L-GABOB (*S*)-**2** under standard conditions.

4. Experimental

^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm with respect to TMS; coupling constants *J* in Hz. ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury-300 machine at 75.5 and 121.5 MHz, respectively, except for the ^{13}C NMR spectrum of (*S*)-**2**, which was taken with a Bruker DPX (250 MHz) spectrometer at 62.9 MHz. IR spectral 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.

Racemic **3** was prepared according to the literature procedure in 60% yield (δ ^{31}P 26.71 ppm).[31,41] Before estimation of e.e.'s, values and the separation of the ^{31}P NMR resonances of diastereoisomeric (*S*)-*O*-methylmandelic acid derivatives were assigned using racemic **4** and **5**. The optimised (*S*)-**6** to quinine ratio was established taking ^{31}P NMR spectra for 1:1, 1:2, 1:3, 1:4 and 1:5 (w/w) mixtures of racemic **6** and quinine.

4.1. Diethyl (*S*)-2-hydroxy-3-(triphenylmethylamino)-propylphosphonate, (*S*)-4

A solution of the epoxide (*S*)-**3** (750 mg, 3.86 mmol) and tritylamine (1.50 g, 5.79 mmol) in toluene (5 mL) was maintained under argon at 100°C for 7 days. After evaporation of solvents, the residue was chromatographed on a silica gel column with methylene chloride–methanol mixtures (100:1, v/v). Appropriate fractions were collected and crystallised from diethyl ether–petroleum ether to give (*S*)-**4** (1.33 g, 76%) as a white solid. M.p. 80–81°C. $[\alpha]_D^{20}=-5.6$ ($c=3.3$ in $CHCl_3$), e.e. 96%; IR (KBr): $\nu=3437$, 3080, 2980, 2925, 2851, 1489, 1448, 1225, 1027, 754, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=1.30$ and 1.32 (2 t, $J=6.9$ Hz, 6H), 1.94 (ddd, $J_{1a\text{-}P}=19.0$ Hz, $J_{1a\text{-}1b}=15.3$ Hz, $J_{1a\text{-}2}=3.4$ Hz, 1H, H-1a), 2.05 (ddd, $J_{1b\text{-}1a}=15.3$ Hz, $J_{1b\text{-}P}=15.1$ Hz, $J_{1b\text{-}2}=9.1$ Hz, 1H, H-1b), 2.08–2.15 (brs, 1H, NH), 2.24 and 2.29 (AB part of ABX system, $J_{3a\text{-}3b}=11.5$ Hz, $J_{2\text{-}3a}=7.1$ Hz, $J_{2\text{-}3b}=3.9$ Hz, 2H, H-3a, 3b), 3.63 (d, $J=2.4$ Hz, 1H, OH), 4.03–4.20 (m, 5H, CH_2OP, H-2), 7.15–7.47 (m, 15H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=16.7$ (2d, $J=6.0$ Hz, CH_3), 31.9 (d, $J=139.0$ Hz, C-1), 50.2 (d, $J=17.8$ Hz, C-3), 62.0 and 62.1 (2d, $J=6.3$ Hz, CH_2O), 66.8 (d, $J=4.9$ Hz, C-2), 70.6, 126.4, 127.9, 128.7, 145.9; ^{31}P NMR ($CDCl_3$, 121.5 MHz): $\delta=30.78$. Anal. calcd for $C_{26}H_{32}NO_4P$: C, 68.86; H, 7.11; N, 3.09. Found: C, 68.68; H, 7.34; N, 3.14%.

4.2. Diethyl 2-hydroxy-3-(diphenylmethylamino)-propylphosphonate, 6

A mixture of the racemic epoxide **3** (1.00 g, 5.15 mmol) and benzhydrylamine (0.89 mL, 5.15 mmol) was maintained at 100°C for 24 h under argon atmosphere. The crude product was chromatographed on a silica gel column with methylene chloride–methanol (50:1, v/v). The appropriate fractions were collected and crystallised from diethyl ether–hexanes to give the phosphonate **6** (1.52 g, 78%) as white crystals. M.p. 67.5–69.0°C. IR (KBr): $\nu=3294$, 3061, 2984, 2924, 2799, 2730, 1603, 1493, 1466, 1449, 1223, 1117, 1059, 1028, 964, 742, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=1.31$ (t, $J=7.0$ Hz, 6H), 1.92 (ddd, $J_{1a\text{-}P}=18.9$ Hz, $J_{1a\text{-}1b}=15.3$ Hz, $J_{1a\text{-}2}=3.7$ Hz, 1H, H-1a), 2.04 (ddd, $J_{1b\text{-}P}=15.5$ Hz, $J_{1a\text{-}1b}=15.3$ Hz, $J_{1b\text{-}2}=8.9$ Hz, 1H, H-1b), 2.61 (dd, $J_{3a\text{-}3b}=12.0$ Hz, $J_{3a\text{-}2}=7.4$ Hz, 1H, H-3a), 2.76 (dd, $J_{3a\text{-}3b}=12.0$ Hz, $J_{3b\text{-}2}=3.7$ Hz, 1H, H-3b), 4.04–4.18 (m, 5H, OCH_2, H-2), 4.85 (s, 1H, $HCPh_2$), 7.18–7.40 (m, 10H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=16.6$ (2×d, $J=6.1$ Hz), 31.6 (d, $J=139.0$ Hz, C-1), 54.3 (d, $J=16.6$ Hz, C-3), 62.0 (d, $J=5.9$ Hz, CH_2O), 65.8 (d, $J=4.6$ Hz, C-2), 67.3 (s, $CHPh_2$), 127.1, 127.3, 127.3, 128.5, 128.5, 143.7, 143.9; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=31.28$. Anal. calcd for $C_{20}H_{28}NO_4P$: C, 63.65; H, 7.50; N, 3.71. Found: C, 63.87; H, 7.90; N, 4.05%.

4.2.1. Diethyl (*S*)-2-hydroxy-3-(diphenylmethylamino)-propylphosphonate, (*S*)-6. This compound was obtained from (*S*)-**3** (617 mg, 3.18 mmol) (e.e. 85%) and benzhydrylamine (0.550 mL, 3.18 mmol) as described above. Chromatographic purification gave (*S*)-**6** (0.924 g, 77%) as a yellowish oil. $[\alpha]_D^{20}=-4.05$ ($c=2.0$ in $CHCl_3$), e.e 100%; Anal. calcd for $C_{20}H_{28}NO_4Px1/2\ H_2O$: C, 62.17; H, 7.56; N, 3.60. Found: C, 61.94; H, 7.55; N, 3.32%. In a similar manner, (*S*)-**6** was obtained from (*S*)-**3** (e.e. 90%) in 74% yield after column chromatography. $[\alpha]_D^{20}=-3.95$ ($c=2.1$ in $CHCl_3$).

4.3. Bis-*N*,*N*-[2-hydroxy-3-(diethoxyphosphoryl)propyl]-*N*-(diphenylmethyl)amine, 7

A mixture of the racemic epoxide **3** (1.15 g, 5.87 mmol) and benzhydrylamine (0.444 mL, 2.58 mmol) was maintained at 100°C for 115 h. The crude product was chromatographed on a silica gel column with methylene chloride–methanol (100:1, v/v) to give **7** (736 mg, 50%) as a yellowish oil. IR (film): $\nu=3372$, 3060, 2982, 2931, 2908, 1493, 1448, 1392, 1223, 1164, 1029, 963, 833, 808, 765, 736, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.27$ and 1.28 (2t, $J=7.0$ Hz, 12H, CH_3 in *meso*-**7**), 1.30 (t, $J=7.0$ Hz, 12H, CH_3 in *dl*-**7**), 1.65–1.91 (m, 4H, H_2CP), 2.61–2.73 (m, 4H, CH_2N in *dl*-**7**), 2.73 (dd, $J=14.0$ Hz, $J=8.7$ Hz, 2H, *H*CHN in *meso*-**7**), 2.93 (dd, $J=14.0$ Hz, $J=3.2$ Hz, 2H, HC*H*N in *meso*-**7**), 3.90–4.10 (m, 10H, CH_2OP, *H*COH), 4.3 (brs, 2H, OH), 5.05 (s, $HCPh_2$ in *dl*-**7**), 5.17 (s, $HCPh_2$ in *meso*-**7**), 7.2–7.4 (m, 10H, H_{arom}); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=16.7$ (d, $J=6.0$ Hz), 31.5 and 31.6 (2d, $J=139.7$ Hz, CP), 58.5 (d, $J=17.6$ Hz, CN), 60.4 (d,

$J=18.0$ Hz, CN), 61.9 and 62.1 (2d, $J=6.0$ Hz, CH_2OP), 64.6 and 66.1 (2s, H*C*O), 71.3 (s, $NCHPh_2$), 127.1, 127.2, 127.4, 128.2, 128.4, 129.1, 129.3, 129.6, 140.2, 141.0, 141.6; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta=30.19$ (*dl*-**7**), 30.28 (*meso*-**7**). Anal. calcd for $C_{27}H_{43}NO_8P_2$: C, 56.74; H, 7.58; N, 2.45. Found: C, 56.53; H, 7.91; N, 2.80%.

4.4. Diethyl (*S*)-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropylphosphonate, (*S*)-5

4.4.1. From the *N*-tritylphosphonate (*S*)-4. A solution of (*S*)-**4** (391 mg, 0.862 mmol) in ethanol (3 mL) containing Boc_2O (207 mg, 0.948 mmol) was hydrogenated over 10% Pd–C (9 mg) under atmospheric pressure for 24 h. The catalyst was removed with filtration through Celite and the solution concentrated and chromatographed on a silica gel column with a methylene chloride–methanol mixture (50:1, v/v) to give (*S*)-**5** (219 mg, 82%) as a colourless hygroscopic oil. $[\alpha]_D^{20}=-2.6$ ($c=2.8$ in $CHCl_3$); IR (film): $\nu=3350$, 2977, 2920, 2851, 1716, 1686, 1522, 1456, 1367, 1252, 1161, 1057, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=1.34$ and 1.35 (2t, $J=7.0$ Hz, 6H), 1.45 (s, 9H), 1.85–2.02 (m, 2H, H_2CP), 3.15 (dt, $J_{3a\text{-}3b}=12.1$ Hz, $J_{3a\text{-}2}=6.0$ Hz, 1H, H-3a), 3.38 (very broad d, $J_{3a\text{-}3b}=12.1$ Hz, 1H, H-3b), 3.99 (s, 1H, OH), 4.03–4.20 (m, 5H, H_2CO, H-2), 5.05 (brt, $J\cong5.0$ Hz, NH); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=16.6$ (2d, $J=6.3$ Hz), 28.6, 31.0 (d, $J=139.4$ Hz, C-1), 46.9 (d, $J=17.7$ Hz, C-3), 62.1 and 62.2 (2d, $J=6.3$ Hz), 66.3 (d, $J=3.7$ Hz, C-2), 79.6, 156.6; ^{31}P NMR ($CDCl_3$, 121.5 MHz): $\delta=30.23$. Anal. calcd for $C_{12}H_{26}NO_6Px1/4\ H_2O$: C, 45.64; H, 8.46; N, 4.43. Found: C, 45.71; H, 8.63; N, 4.36%.

4.4.2. From the *N*-benzhydrylphosphonate (*S*)-6. A solution of (*S*)-**6** (268 mg, 0.710 mmol) and Boc_2O (168 mg, 0.770 mmol) in absolute ethanol (3 mL) was kept under hydrogen (balloon) in the presence of 10% Pd–C (15 mg) for 120 h. The suspension was filtered through Celite and the solution concentrated. The crude product was chromatographed as described above to give (*S*)-**5** (183 mg, 90%) as a colourless oil identical in all respects with the material obtained from (*S*)-**4**.

4.5. Diethyl (*S*)-3-[*tert*-butoxycarbonyl(diphenylmethyl)amino]-2-hydroxypropylphosphonate, (*S*)-8

A solution of (*S*)-**6** (234 mg, 0.620 mmol) and Boc_2O (149 mg, 0.680 mmol) in absolute ethanol (3 mL) was kept under hydrogen in the presence of 10% Pd-C (15 mg) for 24 h. The crude product obtained as described in 4.4.2. was chromatographed on a silica gel column with methylene chloride–methanol (50:1, v/v) to give (*S*)-**8** (35 mg, 11%) as a colourless oil. $[\alpha]_D^{20}=+6.6$ ($c=1.9$ in $CHCl_3$); IR (film): $\nu=3363$, 2980, 2931, 1690, 1453, 1394, 1251, 1030, 756, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=1.26$ and 1.27 (2d, $J=7.0$ Hz, 6H), 1.35 (brs, 9H), 1.56–1.72 (m, 2H, H-1a,b), 2.0–2.6 (brs, 1H, OH), 3.53 (dd, $J_{3a\text{-}3b}=14.3$ Hz, $J_{3a\text{-}2}=3.9$ Hz, 1H, H-3a), 3.50–3.70 (brm, 2H, H-2,3b), 3.94–4.07 (m, 4H), 6.34 (brs, 1H), 7.16–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=16.6$ (d, $J=6.0$ Hz), 28.4, 32.1 (d, $J=139.5$ Hz, C-1), 52.5 (brd, $J\cong18.0$ Hz, C-3), 61.8 and 61.9 (2d, $J=6.0$ Hz), 65.2 (brs), 67.0 (brs, C-2), 81.2, 127.4, 127.6, 128.5, 129.0, 140.0, 140.0, 156.8 (brs); ^{31}P NMR ($CDCl_3$, 121.5 MHz): $\delta=29.85$. Anal. calcd for $C_{25}H_{36}NO_6Px1/4\ H_2O$: C, 62.29; H, 7.63; N, 2.83. Found: C, 62.22; H, 7.84; N, 3.04.

Further elution afforded (*S*)-**5** as a colourless oil (156 mg, 81%), $[\alpha]_D^{20}=-2.1$ ($c=3.1$ in $CHCl_3$).

4.6. General procedures for the estimation of e.e.'s

4.6.1. *N*-Tritylphosphonates (*S*)-4. (*S*)-*O*-Methylmandelic acid (11 mg, 0.066 mmol), DCC (14 mg, 0.066 mmol) and one crystal of DMAP were added to a solution of (*S*)-**4** (20 mg, 0.044 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at room temperature for 24 h under argon atmosphere. 1,3-Dicyclohexylurea was filtered off and the solution was concentrated. The residue was dissolved in $CDCl_3$ (0.7 mL) and the solution analysed by ^{31}P NMR spectroscopy. (*S*)-*O*-Methylmandelic acid esters of (*S*)-**4**: ^{31}P NMR ($CDCl_3$, 121.5 MHz): $\delta=26.82$ (*S*,*S*-diastereoisomer), 27.01 (*R*,*S*-diastereoisomer).

4.6.2. *N*-Boc-phosphonates (*S*)-5. The procedure described above was followed using (*S*)-*O*-methylmandelic acid (8.8 mg, 0.053 mmol), DCC (11 mg, 0.053 mmol), one crystal of DMAP and (*S*)-**5** (11 mg, 0.035 mmol). (*S*)-*O*-Methylmandelic acid esters of (*S*)-**5**: ^{31}P NMR ($CDCl_3$, 121.5 MHz): $\delta=26.62$ (*S*,*S*-diastereoisomer), 26.79 (*R*,*S*-diastereoisomer).

4.6.3. *N*-Benzhydrylphosphonates (*S*)-6. A solution of (*S*)-**6** (15 mg, 0.040 mmol) in $CDCl_3$ (0.7 mL) containing quinine (75 mg, 0.23 mmol) was analysed by ^{31}P NMR spectroscopy. ^{31}P NMR ($CDCl_3$, 121.5 MHz): $\delta=30.55$ [(*S*)-**6**], 30.35 [(*R*)-**6**]. For analyses of crude products containing (*S*)-**6**, the amounts of the compounds were doubled.

4.7. (*S*)-3-Amino-2-hydroxypropylphosphonic acid, (*S*)-2

A mixture of the phosphonate (*S*)-**5** (143 mg, 0.460 mmol) and aqueous HCl (12 M, 1 mL) was refluxed for 3 days. Volatiles were evaporated, and the residue coevaporated with anhydrous ethanol (5x3 mL). A solution of the crude product in ethanol (1 mL) was treated dropwise with propylene oxide to pH 7. The precipitate was filtered off and chromatographed on a silanized silica gel column using water to give (*S*)-**2** (57 mg, 78%) as a white very hygroscopic powder, which decomposed before melting. $[\alpha]_D^{20}=-41.4$ ($c=0.9$ in H_2O); IR (KBr): $\nu=3423$, 2923, 2852, 1638, 1535, 1155, 1057, 994 cm^{-1}; ^1H NMR (D_2O, 300 MHz): $\delta=1.89$ (ddd, $J_{1a\text{-}1b}=15.2$ Hz, $J_{1a\text{-}P}=17.6$ Hz, $J_{1a\text{-}2}=7.1$ Hz, 1H, H-1a), 1.98 (ddd, $J_{1a\text{-}1b}=15.2$ Hz, $J_{1b\text{-}P}=18.5$ Hz, $J_{1b\text{-}2}=6.5$ Hz, 1H, H-1b), 2.99 (dd, $J_{3a\text{-}3b}=13.2$ Hz, $J_{3a\text{-}2}=9.6$ Hz, 1H, H-3a), 3.31 (dd, $J_{3a\text{-}3b}=13.2$ Hz, $J_{3b\text{-}2}=3.0$ Hz, 1H, H-3b), 4.17 (ddddd, $J_{2\text{-}3a}=9.6$ Hz, $J_{2\text{-}P}=8.9$ Hz, $J_{2\text{-}1a}=7.1$ Hz, $J_{2\text{-}1b}=6.5$ Hz, $J_{2\text{-}3b}=3.0$ Hz, 1H, H-2); ^{13}C NMR (D_2O/DSS, 62.9 MHz): $\delta=$

36.4 (d, $J=130.6$ Hz, C-1), 47.7 (d, $J=10.5$ Hz, C-3), 66.8 (s, C-2); ^{31}P NMR (D_2O, 121.5 MHz): $\delta=20.43$. HRMS (FAB+) $C_3H_{10}NO_4P$ (m/z): calcd 156.0438. Found 156.0423.

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