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Preparation of dimethyl (*R*)- and (*S*)-2-(2-aminophenyl)-2-hydroxyethylphosphonate from anthranilic acid

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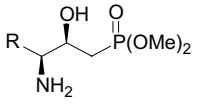
Abstract—An efficient synthesis of both enantiomers of dimethyl δ-amino-β-hydroxyethylphosphonate **6** has been achieved starting from anthranilic acid, through the resolution of dimethyl (±)-2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate **9** with (*S*)-*O*-methylmandelic acid. The absolute configuration of the enantiomers **9** was assigned by the Dale and Mosher approach using the extended Newman projections and molecular mechanics.

1. Introduction

Phosphonic acids and phosphonates containing amino and hydroxy groups have attracted considerable attention in recent years for their role in biologically relevant processes.[1] In particular γ-amino-β-hydroxyphosphonates (phosphostatine derivatives) **1** have resulted in excellent Leu[10]–Val[11] replacements (LVRs) in angiotensin II, providing a more potent inhibitory activity for rennin over porcine pepsin and bovine cathepsin D.[2,3] Phosphocarnitine[4] **2** and γ-amino-β-hydroxypropylphosphonic acid (GABOBP)[5] **3**, have been recognized in recent years as attractive analogues of 3-hydroxy-4-trimethylaminobutyric acid (carnitine) and γ-amino-β-hydroxybutyric acid (GABOB), respectively. On the other hand, racemic β-hydroxy- and γ-hydroxy phosphonic acids **4** and **5** containing either a C- or N-linked triazole via a three carbon chain to a phosphonic group, have shown inhibition of the enzyme *imidazole glycerol phosphate dehydratase*;[6] an enzyme involved in the biosynthesis of the essential plant amino acid's histidine.[7]



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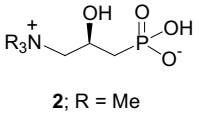
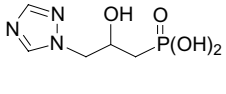


2; R = Me
3; R = H



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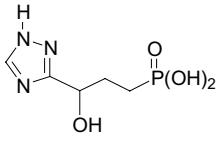

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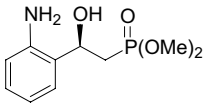
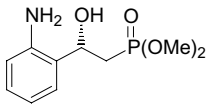
However, the literature records only one report on the preparation of (±)-**6**.[8] As a part of our program aimed at the elaboration of efficient and versatile syntheses of biologically active aminophosphonic acids and phosphonates containing amino and hydroxy groups,[3,5] we herein report the details of our approach for the



(*R*)-**6**



(*S*)-**6**

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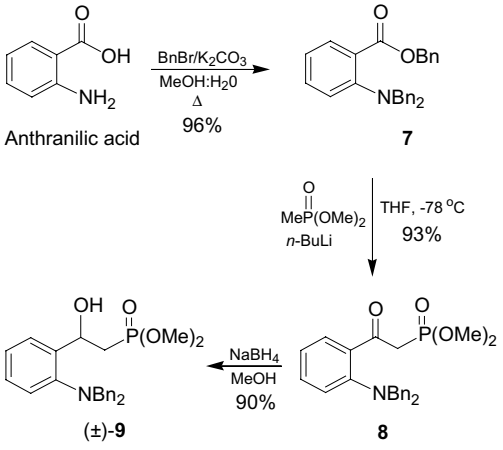
preparation of unnatural dimethyl (*R*)- and (*S*)-δ-amino-β-hydroxyethylphosphonate **6** from antranilic acid, which can be used for the preparation of short peptides.[8]

2. Results and discussion

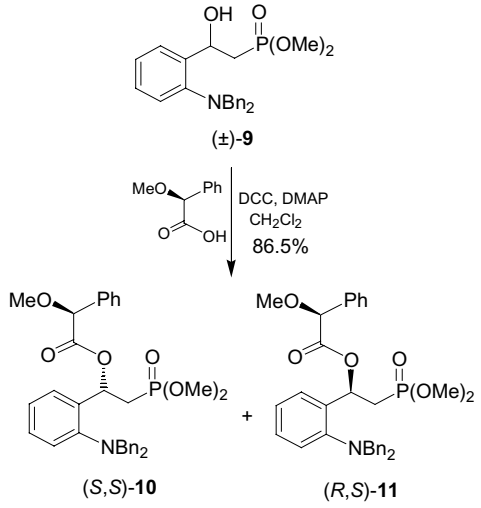
A total synthesis of (±)-**9** starting from the readily available anthranilic acid is shown in Scheme 1. In the first step, anthranilic acid was treated with K_2CO_3 and an excess amount of benzyl bromide under reflux in a mixture of MeOH:H_2O, to give the corresponding benzyl *N*,*N*-dibenzylanthranilate **7** in 96% yield. The benzyl-anthranilate **7** was then treated with 2 equiv of the lithium salt of dimethyl methylphosphonate at −78 °C in THF to afford the β-ketophosphonate **8** in 93% yield. Finally, the reduction of the β-ketophosphonate **8** was achieved with $NaBH_4$ in methanol at room temperature affording the racemic mixture of dimethyl 2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate (±)-**9** in 90% yield.

Having efficiently prepared racemic 2-hydroxyphosphonate (±)-**9**, we turned our attention to the prime goal of this work, that is, the preparation of enantiomers **9**. We first focused on the resolution of racemic 2-hydroxyphosphonate **9** via *O*-methylmandelate derivatives,[9] which should, in principle, allow us to obtain both enantiomers of **9**. Thus, the reaction of racemic mixture (±)-**9** with (*S*)-*O*-methylmandelic acid in presence of DCC and DMAP in dichloromethane at room temperature afforded the respective mandelates in good yield. The mixture of diastereomers was cleanly separated on column chromatography affording the less polar diastereomer (*S*,*S*)-**10** in 44.5% yield and the more polar diastereomer (*R*,*S*)-**11** in 42% yield (Scheme 2).

With diastereomerically pure (*S*,*S*)-**10** and (*R*,*S*)-**11** in hand, the next step was to assign the absolute configuration of the stereogenic center at C2 of the diastereomers (*S*,*S*)-**10** and (*R*,*S*)-**11**. To this purpose, we initially used the classical approach developed by Dale and Mosher,[10] based on the analysis of chemical shift changes in ^1H and ^{31}P NMR data of diastereomeric



Scheme 1.



Scheme 2.

derivatives. Thus, according to the Trost model,[9] the different orientation of the phenyl ring of mandelic functionality in the extended Newman projection (Fig. 1), leads to selective shielding or deshielding of $CH_2P(O)(OMe)_2$ and 2-(*N*,*N*-dibenzylaminophenyl) groups at the stereogenic center. Thus, the spatial relationship between the $CH_2P(O)(OMe)_2$/2-(*N*,*N*-dibenzylaminophenyl) groups and the phenyl ring were correlated with the observed chemical shift change, thus giving us the absolute configuration.[11]

The analysis of ^1H NMR spectroscopic data revealed some significant differences between the (*S*,*S*)-**10** and (*R*,*S*)-**11** diastereomers (Table 1).

From the spectral data of the diastereomeric derivatives summarized in the Table 1, we observed that the less polar diastereomer showed the two methyl signals for $(CH_3O)_2P$ at 3.45 and 3.51 ppm, entries 3 and 4, while the more polar diastereomer showed two signals at 3.69 and 3.76 ppm, giving differences of 0.24 and 0.25 ppm, respectively. These, differences can be explained as a result of the shielding of methyl signals by the phenyl ring of mandelic acid derivative in the less polar diastereomer. On the other hand, the less polar diastereo-

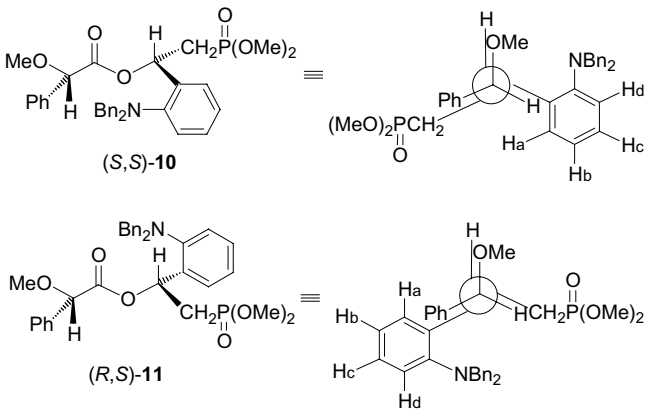


Figure 1. Extended Newman projections for (*S*,*S*)-**10** and (*R*,*S*)-**11**.

Table 1. ^{1}H and ^{31}P NMR chemical shifts of the mandelates (*S*,*S*)-**10** and (*R*,*S*)-**11**

Entry		Less polar mandelate	More polar mandelate	$\Delta\delta$ (ppm)
1	$CH_2P(O)$	1.71	1.67	0.04
2	$CH_2P(O)$	2.15	2.07	0.08
3	$(CH_3O)_2P$	3.45	3.69	0.24
4	$(CH_3O)_2P$	3.51	3.76	0.25
5	NCH_2Ph	3.98	3.92	0.06
6	NCH_2Ph	4.16	4.13	0.03
7	$CH(OH)$	6.85	6.87	0.02
8	H_a	7.45	7.08	0.37
9	H_b	7.04	6.79	0.25
10	H_c	7.15	7.11	0.04
11	H_d	7.45	6.62	0.83
12	$(CH_3O)_2P$	28.93	29.39	0.46

mer showed signals for H_a, H_b, H_c, and H_d of the phenyl ring of the anthranilic acid derivative at 7.43, 7.04, 7.15, and 7.45 ppm, respectively, while the more polar diastereomer showed these signals at 7.08, 6.79, 7.11, and 6.62, with differences of 0.37, 0.25, 0.04, and 0.83 ppm, respectively. These, differences were initially explained as a result of shielding to proton signals by the phenyl ring in the more polar diastereomer. However, after analysis of spectroscopic data, we found that the chemical shift for aromatic protons H_{a-d} in the more polar diastereomer were identical to compound **6**; therefore, the shielding of proton signals does not arise from the influence of the phenyl ring of the mandelic functionality.

Furthermore, the ^{31}P NMR chemical shift for the less polar diastereomer was 28.93 ppm while for the more polar diastereomer it was 29.39 ppm, giving a difference of 0.46 ppm. This difference could be explained as a result of the shielding by the phenyl ring of mandelic acid derivative in the less polar diastereomer.[12]

In order to have more evidence on the absolute configuration of the diastereomers (*S*,*S*)-**10** and (*R*,*S*)-**11**, we resorted to a conformational search by Molecular Mechanics (MM) using an MMX force field for geometry minimization and energy assessment on the mandelates.[13] Uniform synchronized scanning at 5° increments was carried out for dihedral angles D1 (C5–C6–O17–C18) and D2 (O17–C18–C20–O32), allowing for complete relaxation of the rest of the molecular coordinates.[14] (Fig. 2).

Examination of the only conformation showed that for (*S*,*S*)-**10** diastereomer (Fig. 2), the phenyl ring of mandelic acid derivative was close to the OMe groups on $P(OMe)_2$, which could produce the shielding effect in ^{1}H NMR. Additionally, analysis of the conformation for the (*S*,*S*)-**10** diastereomer (Fig. 2c), shows that proton H_x in C2 is *anti* to proton H_b and *gauche* to proton H_a in C1; furthermore, the proton H_a is close to aromatic ring, which could lead to selective shielding. Thus, the dihedral angles calculated for H_b/H_x and H_b/H_x are 175.2° and 67.3°, which correspond to J_{anti} and J_{gauche}, respectively. These values are also in line with the experimental data $J_{H_x/H_b} = 10$ and $J_{H_x/H_a} = 3.6$ Hz, respectively. Additionally, the chemical shifts for the proton H_a is 1.71 ppm, while for H_b is 2.15 ppm, which is consistent with the preferential conformation found by Molecular Mechanics for (*S*,*S*)-**10** diastereomer.

On the other hand, a similar conformational search on the (*R*,*S*)-**11** diastereomer showed three different conformations on the conformational population surface (Fig. 3).

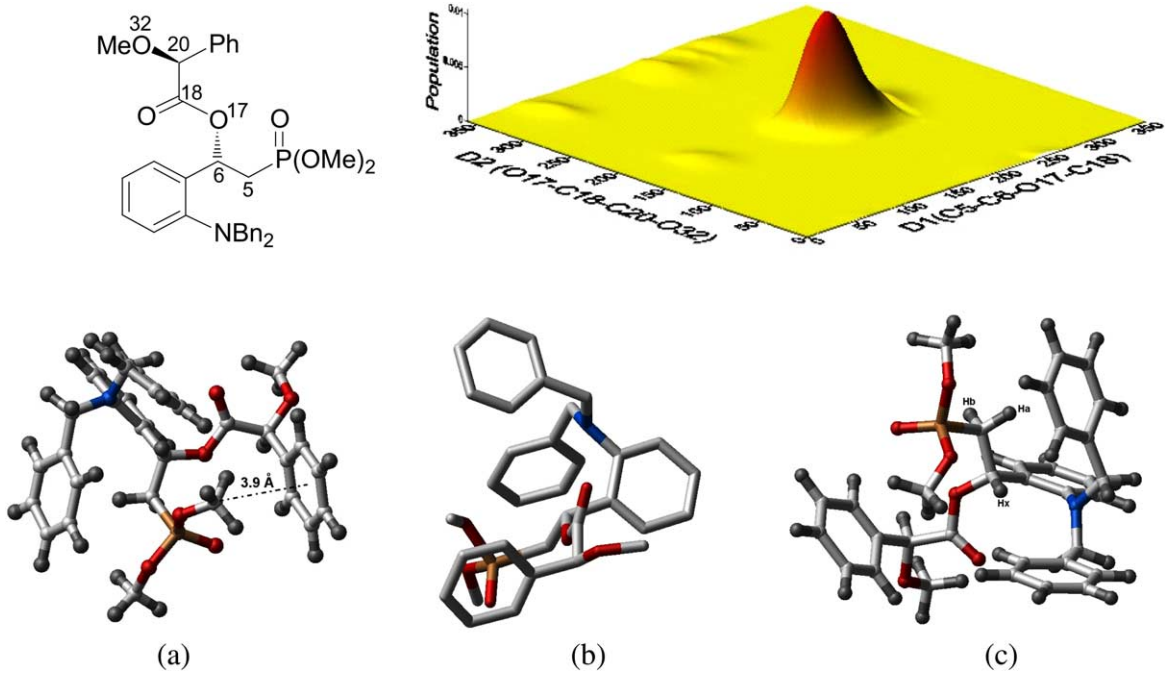


Figure 2. Conformational population surface for (*S*,*S*)-**10** diastereomer.

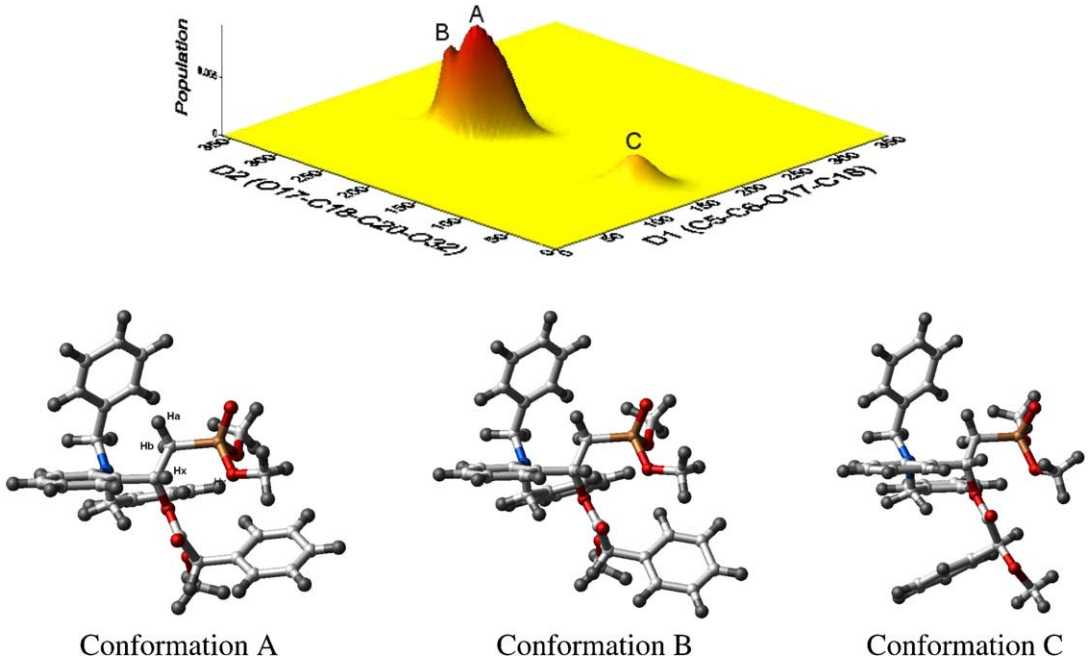


Figure 3. Conformational population surface and conformers for (*R*,*S*)-**11** diastereomer.

In conformation C (the least populated, Fig. 3), the effect of the phenyl ring of the mandelic functionality would be more important on the methylene of the benzyl group; however this effect is less significant on the ^{1}H NMR spectrum. On the other hand, conformations A and B (Fig. 3), show that the aromatic protons of the anthranilic acid derivative are far away from the phenyl rings of the mandelic functionality and benzyl groups: Therefore the shielding effect in ^{1}H NMR should not be observed. These results are consistent with the experimental ^{1}H NMR data obtained, where the chemical shifts for the aromatic protons of anthranilic fragment in (*R*,*S*)-**11** diastereomer were identical to those in compound **6**. Additional analysis of conformation A for (*R*,*S*)-**11** diastereomer (the more stable, Fig. 3), showed that proton H_x in C2 was *anti* to proton H_b and *gauche* to proton H_a in C1; furthermore, proton H_a was close to the aromatic ring, leading to selective shielding. Thus, the dihedral angles calculated for H_b/H_x and H_b/H_x were 171.3° and 71.1°, which corresponding to J_{anti} and J_{gauche}, respectively. These values correspond with the experimental data $J_{H_x/H_b} = 10$ and $J_{H_x/H_a} = 2.4$ Hz. Furthermore, the chemical shift for proton H_a is 1.67 ppm, while for H_b it is 2.07 ppm, which confirms the preferential conformation found by Molecular Mechanics for the (*R*,*S*)-**11** diastereomer (Fig. 3).

The combination of NMR and Molecular Mechanical data suggests strongly that the less polar compound is the (*S*,*S*)-diastereomer while the more polar compound is the (*R*,*S*)-diastereomer.[15]

With the absolute configuration assigned to the diastereomerically pure mandelates (*S*,*S*)-**10** and (*R*,*S*)-**11**, the preparation of both enantiopure forms of dimethyl γ-amino-β-hydroxyethylphosphonates **9** could be completed (Scheme 3). Thus, the treatment of (*S*,*S*)-**10** diastereomer with LiOH in a mixture of MeOH:H_2O (8:2) at room temperature followed by separation of the (*S*)-*O*-methylmandelic acid by column chromatography gave (*S*)-**9** in 93% yield. The X-ray crystal structure of (*S*)-**9** is shown in Figure 4. In a similar way starting from the (*R*,*S*)-**11** diastereomer, (*R*)-**9** was obtained in 89% yield. Finally, the β-hydroxyethylphosphonates (*S*)-**9** and (*R*)-**9** were treated with palladium on carbon in methanol under hydrogen gas at room temperature to obtain dimethyl (*S*)- and (*R*)-2-(2-aminophenyl)-2-hydroxyethylphosphonate **6** in 82% and 83.8% yield, respectively.

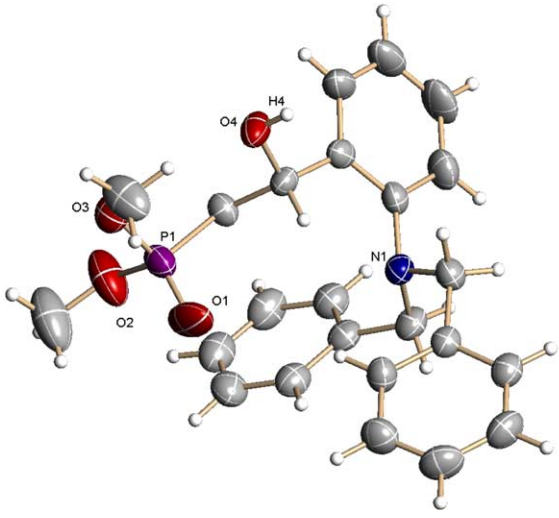
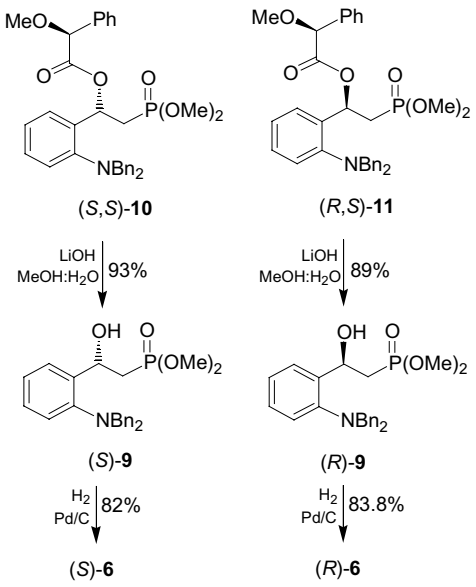


Figure 4. X-ray structure for (*S*)-**9**.[16]

In conclusion, we have found a new methodology for the preparation of enantiomerically pure dimethyl (*R*)- and (*S*)-δ-amino-β-hydroxyethylphosphonate **6** from anthranilic acid, which could be incorporated in short



Scheme 3.

peptides, as potential bioactive materials or used for the preparation of non-ionic selective X-ray contrast agents.[8]

3. Experimental

Optical rotations were taken on a Perkin–Elmer 241 polarimeter in a 1 dm tube; concentrations are given in g/100 mL. For flash chromatography, silica gel 60 (230–400 mesh ASTM, Merck) was used. ^{1}H NMR spectra were registered on a Varian INOVA 400 (400 MHz), ^{13}C NMR (100 MHz), and ^{31}P NMR on a Varian Mercury 200. The spectra were recorded in D_2O or $CDCl_3$ solution, using TMS as the internal reference. Microanalyses were registered on an Elemental VARIO EL III.

Flasks, stirrer 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.[17]

3.1. Synthesis of benzyl (*N*,*N*-dibenzyl)anthranilate 7

A solution of benzyl bromide (40 g, 0.23 mol) was slowly added to a solution of the anthranilic acid (8 g, 0.06 mol) and K_2CO_3 (32.3 g, 0.23 mol) in a 5:1 mixture of methanol–water (300 mL). The reaction mixture was refluxed for 2 h and the solvent removed under reduced pressure. Water was added to the residue and then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–ethyl acetate 9:1) to afford **7** (22.8 g, 96%) as a white solid, Mp 53–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 4H, NCH_2Ph), 5.35 (s, 2H, OCH_2Ph), 6.91 (d, $J = 8.0$ Hz, 1H, H_{arom}), 6.93 (ddd, $J = 7.6$, 7.6, 0.8 Hz, 1H, H_{arom}), 7.16–7.38 (m, 14H, H_{arom}), 7.45 (dd, $J = 7.6$, 1.6 Hz, 2H, H_{arom}), 7.72 (dd, $J = 7.6$, 1.8 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.1 (NCH_2Ph), 67.1 (OCH_2Ph), 121.0, 121.4, 124.9, 127.1, 128.3, 128.4, 128.5, 128.7, 128.7, 131.5, 132.0, 136.1, 138.0, 150.9, 168.3 C=O.

3.2. Synthesis of dimethyl 2-(2-*N*,*N*-dibenzylaminophenyl)-2-oxoethylphosphonate 8

A solution of dimethyl methylphosphonate (6.5 g, 52 mmol) and anhydrous THF (80 mL) was cooled at −78 °C before of the slow addition (16.4 mL, 25.5 mmol) of *n*-BuLi in hexane (2.4 M). The resulting solution was stirred at −50 °C for 1 h, after which the solution was cooled to −78 °C and then slowly added to a solution of the (*N*,*N*-dibenzyl)anthranilate **7** (5.34 g, 13.1 mmol) in THF (120 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 extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–hexane 4:1) to afford **8** (5.1 g, 93%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (d, $J = 11.2$ Hz, 6H, $(CH_3O)_2P$), 4.03 (d, $J = 22.0$ Hz, 2H, $CH_2P(O)$), 4.12 (s, 4H, NCH_2Ph), 6.96 (d, $J = 8.0$ Hz, 1H, H_{arom}), 7.05–7.11 (m, 5H, H_{arom}), 7.23–7.31 (m, 6H, H_{arom}), 7.35 (ddd, $J = 8.0$, 8.0, 1.6 Hz, 1H, H_{arom}), 7.53 (dd, $J = 7.6$, 1.6 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8 (d, $J = 129.1$ Hz, $CH_2P(O)$), 53.0 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 57.5 CH_2Ph, 121.6, 122.5, 127.6, 128.5, 129.1, 129.1, 130.5, 132.2, 133.9, 136.6, 149.9 C=O. ^{31}P NMR (200 MHz, $CDCl_3$) δ 24.56.

3.3. Synthesis of dimethyl (±)-2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate (±)-9

A mixture of dimethyl 2-(2-*N*,*N*-dibenzylaminophenyl)-2-oxoethylphosphonate **8** (5.34 g, 12.7 mmol), sodium borohydride (3.84 g, 0.1 mol) and methanol (100 mL) was stirred at room temperature 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 under reduced pressure, and the residue dissolved in water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was crystallized from ethyl acetate–hexane 4:1 to afford (±)-**9** (4.9 g, 90%) as a crystalline solid, Mp 115–118 °C. The NMR data is identical to (*R*)- and (*S*)-**9**.

3.4. Esterification of (±)-9 with (*S*)-*O*-methylmandelic acid

To a solution of (±)-**9** (9.0 g, 21.2 mmol) and (*S*)-*O*-methylmandelic acid (5.6 g, 33.9 mmol) in dichloromethane (250 mL), 4-dimethylaminopyridine DMAP

(400 mg, 3.2 mmol) and 1,3-dicyclohexylcarbodiimide DCC (7.0 g, 42 mmol) were added. The reaction mixture was stirred at room temperature for 20 h. After 1,3-dicyclohexylurea DCU was filtered off, the liquid layer was evaporated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate–hexane 6:4) to afford (*S*,*S*)-**10** (5.4 g, 44.5%) as a colorless oil (less polar) and (*R*,*S*)-**11** (5.1 g, 42%) as a colorless oil (more polar).

3.5. Less polar diastereomer (*S*,*S*)-10

$[\alpha]_D^{20} = +23.8$ ($c = 14$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (ddd, $J = 19.6$, 15.6, 3.6 Hz, 1H, $CH_2P(O)$), 2.15 (ddd, $J = 15.6$, 15.6, 10.0 Hz, 1H, $CH_2P(O)$), 3.33 (s, 3H, CH_3O), 3.45 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.51 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.98 (d, $J = 13.6$ Hz, 2H, NCH_2Ph), 4.16 (d, $J = 13.6$ Hz, 2H, NCH_2Ph), 4.75 (s, 1H, $CH(OCH_3)$), 6.85 (ddd, $J = 10.0$, 10.0, 3.6 Hz, 1H, CH(OH)), 7.04 (ddd, $J = 6.8$, 6.8, 0.8 Hz, 1H, H_{arom}), 7.13–7.37 (m, 16H, H_{arom}), 7.45 (dd, $J = 7.6$, 2.0 Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9 (d, $J = 138.2$ Hz, $CH_2P(O)$), 52.1 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.3 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 57.4 (CH_3OCH), 58.1 CH_2Ph, 67.9 (d, $J = 6.1$ Hz, $CHCH_2P(O)$), 82.8 $CH(OCH_3)$, 124.3, 125.3, 125.8, 127.0, 127.4, 128.1, 128.4, 128.5, 128.6, 129.4, 135.8, 137.1, 137.2, 148.3, 169.5 C=O. ^{31}P NMR (200 MHz, $CDCl_3$) δ 28.93. Anal. Calcd for $C_{33}H_{36}NO_6P$: C, 69.10; H, 6.33; N, 2.44. Found C, 68.97; H, 6.45; N, 2.69.

3.6. More polar diastereomer (*R*,*S*)-11

$[\alpha]_D^{20} = +35.1$ ($c = 5.3$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (ddd, $J = 18.4$, 15.6, 2.4 Hz, 1H, $CH_2P(O)$), 2.07 (ddd, $J = 15.6$, 15.6, 10.0 Hz, 1H, $CH_2P(O)$), 3.40 (s, 3H, CH_3O), 3.69 (d, $J = 11.0$ Hz, 3H, $(CH_3O)_2P$), 3.76 (d, $J = 11.0$ Hz, 3H, $(CH_3O)_2P$), 3.92 (d, $J = 13.6$ Hz, 2H, NCH_2Ph), 4.13 (d, $J = 13.6$ Hz, 2H, NCH_2Ph), 4.85 (s, 1H, $CH(OCH_3)$), 6.64 (dd, $J = 8.4$, 1.2 Hz, 1H, H_{arom}), 6.79 (ddd, $J = 8.0$, 8.0, 2.0 Hz, 1H, H_{arom}), 6.87 (ddd, $J = 10.0$, 10.0, 2.4 Hz, 1H, CH(OH)), 7.07–7.36 (m, 17H, H_{arom}). 13C NMR (100 MHz, $CDCl_3$) δ 32.3 (d, $J = 138.1$ Hz, $CH_2P(O)$), 52.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.8 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 57.5 (CH_3OCH), 58.3 CH_2Ph, 67.5 (d, $J = 6.1$ Hz, $CHCH_2P(O)$), 82.4 $CH(OCH_3)$, 124.1, 125.2, 125.6, 127.1, 127.6, 128.2, 128.3, 128.6, 128.7, 129.5, 135.9, 136.9, 137.1, 148.1, 169.3 C=O. ^{31}P NMR (200 MHz, $CDCl_3$) δ 29.39. Anal. Calcd for $C_{33}H_{36}NO_6P$: C, 69.10; H, 6.33; N, 2.44. Found C, 69.23; H, 6.38; N, 2.37.

3.7. Dimethyl (*S*)-2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate 9

The diastereomer (*S*,*S*)-**10** (2.03 g, 3.54 mmol) was dissolved in MeOH/H_2O 8:2 (100 mL) and stirred at room temperature with LiOH (206 mg, 8.46 mmol). After 15 h, the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by crystallization from ethyl acetate–dichloromethane to give (*S*)-**9** (1.4 g, 93%) as a white solid, Mp 115–118 °C. $[\alpha]_D^{20} = +5.9$ ($c = 1.4$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (ddd, $J = 18.4$, 15.2, 2.8 Hz, 1H, $CH_2P(O)$), 1.99 (ddd, $J = 15.2$, 15.2, 10.0 Hz, 1H, $CH_2P(O)$), 3.70 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.79 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.94 (d, $J = 2.8$ Hz, 1H, OH), 4.05 (s, 4H, CH_2Ph), 5.67 (tt, $J = 10.0$, 2.8 Hz, 1H, CH(OH)), 7.14–7.30 (m, 13H, H_{arom}), 7.40 (d, $J = 7.6$ Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4 (d, $J = 135.1$ Hz, $CH_2P(O)$), 52.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.6 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 59.4 CH_2Ph, 64.6 (d, $J = 3.8$ Hz, CH(OH)), 124.2, 125.9, 126.8, 127.4, 128.2, 128.4, 128.4, 129.5, 137.9, 148.1. ^{31}P NMR (200 MHz, $CDCl_3$) δ 33.03. Anal. Calcd for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found C, 67.73; H, 6.70; N, 3.33.

In a similar way, (*R*,*S*)-**11** (2.46 g, 4.3 mmol) afforded (*R*)-**9** (1.62 g, 89%) as a white solid, Mp 115–118 °C. $[\alpha]_D^{20} = -6.1$ ($c = 1.14$, $CHCl_3$). Anal. Calcd for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found C, 67.69; H, 6.78; N, 3.18.

3.8. Synthesis of dimethyl (*S*)-2-(2-aminophenyl)-2-hydroxyethylphosphonate 6[18]

Dimethyl (*S*)-2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate **9** (84 mg, 0.2 mmol) was treated with palladium on carbon (8.4 mg, 10% wt) in methanol (12 mL) and two drops of (20%) HCl/*i*PrOH and then stirred for 10 min under hydrogen gas at room temperature. The mixture was filtered through a pad of celite, and the solvents removed under reduced pressure. The residue was dissolved in dichloromethane (5 mL), washed with a saturated solution of $NaHCO_3$ (1 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane–hexane–methanol 4:4:1) to afford the enantiomer (*S*)-**6** (39.8 mg, 82%), as a yellow oil. $[\alpha]_D^{20} = +13.3$ ($c = 1.2$, $CHCl_3$). ^{1}H NMR (400 MHz, D_2O) δ 2.19 (ddd, $J = 18.8$, 15.2, 3.2 Hz, 1H, $CH_2P(O)$), 2.68 (ddd, $J = 15.2$, 10.4 Hz, 1H, $CH_2P(O)$), 3.71 ($d = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.75 ($d = 10.8$ Hz, 3H, $(CH_3O)_2P$), 5.13 (ddd, $J = 10.4$, 3.2 Hz, 1H, CHOH), 6.65 (d, $J = 8.0$ Hz, 1H, H_{arom}), 6.71 (ddd, $J = 8.0$, 1.2 Hz, 1H, H_{arom}), 7.06 (d, $J = 8.4$ Hz, 1H, H_{arom}), 7.08 (ddd, $J = 8.4$, 1.6 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, D_2O) δ 30.8 (d, $J = 135.8$ Hz, $CH_2P(O)$), 52.6 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.8 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 69.0 ($CHCH_2P(O)$), 117.1, 118.4, 126.6 (d, $J = 16$ Hz), 127.3, 129.0, 145.6. ^{31}P NMR (200 MHz, D_2O) δ 33.70.

The procedure described above for the (*S*)-enantiomer, was followed using the dimethyl (*R*)-2-(2-*N*,*N*-dibenzylaminophenyl)-2-hydroxyethylphosphonate **9** (77 mg, 0.18 mmol) and treated with palladium on carbon 8 mg (10% wt) in methanol (12 mL) and two drops of (20%)

HCl/*i*PrOH and stirred for 10 min under hydrogen gas at room temperature, obtaining (37 mg, 83.8%) dimethyl (*R*)-2-(2-aminophenyl)-2-hydroxyethylphosphonate **6**, as a viscous oil. $[\alpha]_D^{20} = -13.7$ ($c = 1.4$, $CHCl_3$). The NMR data are identical to (*S*)-**6**.

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$$Pi = \frac{e^{-Ei/RT}}{\sum_{i=1}^{n} e^{-Ei/RT}}$$

where *Ei* is the intramolecular conformational energy of the *i*th state.
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16. X-ray crystal data of (*S*)-**9** was collected at 298 K using a Bruker APEX instrument (MoK_α radiation, $\lambda = 0.71073$ Å). The SHELXTL v. 6.1 program package was used for structure solution and refinement. The structure was solved by direct methods and refined by full-matrix least squares procedures. All non-hydrogen atoms were refined anisotropically. (*S*)-**6**: $C_{24}H_{27}NO_4P$, $M = 424.44$, monoclinic space group $P2_1$, $a = 10.981(12)$, $b = 10.662(12)$, $c = 11.325(13)$ Å, $\beta = 117.001(2)°$, $V = 1181.3$ (2) Å^3, $Z = 2$, $D_c = 1.193$ g cm^{-1}, 11,418 reflections measured, 4166 unique ($R_{int} = 0.0223$), which were used in all calculations, final R values were 0.0602 [$F > 4\sigma(F)$] and 0.0619 (all data). Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 227064. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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