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Preparation of dimethyl (*R*)- and (*S*)-2-(2-hydroxyphenyl)-2-hydroxyethylphosphonate derived from salicylaldehyde via resolution using (*S*)-methoxyphenylacetic acid (MPA)

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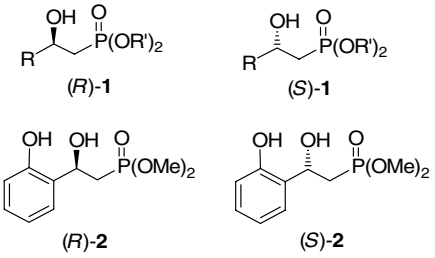
Abstract—The efficient preparation of both enantiomers of dimethyl δ,β-dihydroxyethylphosphonate **2** has been achieved from salicylaldehyde as a starting material, through the resolution of dimethyl (±)-2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate **4** using (*S*)-methoxyphenylacetic acid (MPA). The absolute configuration was assigned by the Dale and Mosher approach using extended Newman projections and ab initio calculations.

1. Introduction

Phosphonates and their derivatives have attracted considerable interest in recent years because of their application as enzymatic inhibitors, metabolic probes, mimetic peptides, antibiotics and pharmacological agents,[1] in addition to their traditional application as intermediates in organic synthesis.[2] In particular, enantiomerically pure β-hydroxyalkylphosphonates of type **1** have received significant attention due to their potential biological activity and versatility as substrates for the synthesis of organophosphorus derivatives.[3] For these reasons, several synthetic routes for the preparation of β-hydroxyalkylphosphonates **1** have been developed, which involve the stereoselective reduction of the corresponding β-ketophosphonates[4] and by biocatalytic synthesis.[5] Recently, we have described two alternative synthesis of γ-amino-β-hydroxyphosphonic acids via diastereoselective reduction of γ-amino-β-ketophosphonates[6] and by resolution of γ-amino-β-hydroxyphosphonates using (*S*)-methoxyphenylacetic acid (MPA).[7] Herein, we report the resolution of dimethyl 2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate **4** derived from salicylaldehyde via their diastereoisomeric esters formed with (*S*)-methoxyphenylacetic acid (MPA). A diastereoisomeric mixture of (*S*,*S*)-**5** and (*R*,*S*)-**6** was easily separated by column chromatography and efficiently converted into dimethyl β,δ-dihydroxyethylphosphonate **2**. The assignment of the absolute configuration of enantiomerically pure (*S*,*S*)-**5** and (*R*,*S*)-**6** was made by ^{1}H NMR based on the Dale and Mosher approach[8] using the extended Newman projections and ab initio calculations.



2. Results and discussion

As shown in Scheme 1, the racemic β-hydroxyphosphonate **4** was obtained in two steps from commercially available

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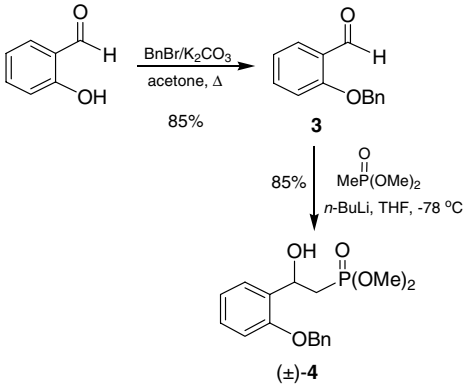
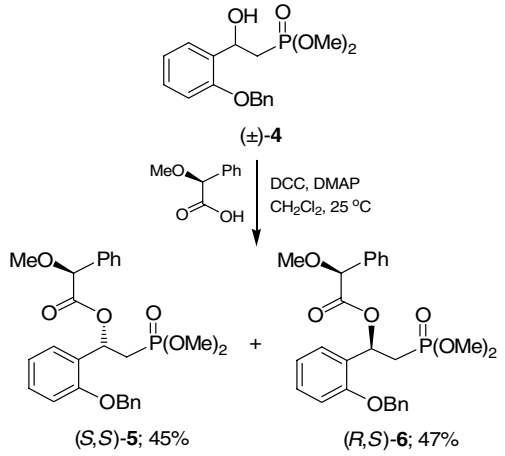
salicylaldehyde. In this context, the reaction of salicylaldehyde with excess of benzyl bromide in the presence of K_2CO_3 under reflux in acetone afforded the 2-benzyloxybenzaldehyde **3** in an 85% yield,[9] which by treatment with the lithium enolate obtained from dimethyl methylphosphonate and *n*-BuLi at −78 °C in THF gave (±)-β-hydroxyphosphonate **4** in an 85% yield (Scheme 1).



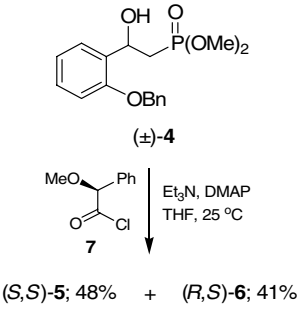
Scheme 1.

Having efficiently prepared the racemic β-hydroxyphosphonate (±)-**4**, we turned our attention to its resolution. Thus, the reaction of dimethyl 2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate (±)-**4** with (*S*)-methoxyphenylacetic acid (MPA) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane at room temperature, afforded the mixture of diastereoisomeric mandelates (*S*,*S*)-**5** and (*R*,*S*)-**6**, which were separated by column chromatography, obtaining (*S*,*S*)-**5** as the less polar diastereoisomer and (*R*,*S*)-**6** as the more polar diastereoisomer in 45% and 47% yields, respectively (Scheme 2).



Scheme 2.

However, under these conditions several filtration steps were necessary to completely eliminate the 1,3-dicyclohexylurea (DCU) from the desired mandelates. Therefore, we decided to use an alternative methodology for the preparation of diastereoisomerically pure (*S*,*S*)-**5** and (*R*,*S*)-**6**. In this context, the reaction of (*S*)-methoxyphenyl acyl chloride **7** readily obtained from (*S*)-methoxyphenylacetic acid and thionyl chloride, with the 2-hydroxyphosphonate (±)-**4** in the presence of triethylamine and catalytic amounts of DMAP in dry tetrahydrofuran at room temperature afforded mandelates (*S*,*S*)-**5** and (*R*,*S*)-**6** in 48% and 41% yields, respectively, after chromatographic separation (Scheme 3).



Scheme 3.

With the diastereoisomerically pure (*S*,*S*)-**5** and (*R*,*S*)-**6** in hand, the next step was the assignment of the absolute configuration of the stereogenic center at C2. For this purpose, we initially used the classical approach developed by Dale and Mosher,[8] which is based on the analysis of chemical shift changes in ^{1}H NMR spectral data in the diastereoisomerically pure mandelates. Thus, according to the Trost model,[10] the different orientation of the phenyl ring of the mandelic moiety on the extended Newman projections (Fig. 1), could leads to a selective shielding or deshielding of $CH_2P(O)(OMe)_2$ and 2-(*O*-benzylphenyl) groups around the asymmetric center, and the spatial relationship between $CH_2P(O)(OMe)_2$/2-(*O*-benzylphenyl) groups and the phenyl ring of the mandelic acid fragment could be correlated with the chemical shift changes.[11,12] Therefore, it is expected that the phosphonate group [$CH_2P(O)(OMe)_2$] in the less polar diastereoisomer will be shielded at a higher field than in the more polar diastereoisomer by the phenyl ring. The chemical shifts observed in ^{1}H and ^{31}P NMR for both less and more polar diastereoisomerically pure (*S*,*S*)-**5** and (*R*,*S*)-**6** are summarized in Table 1.

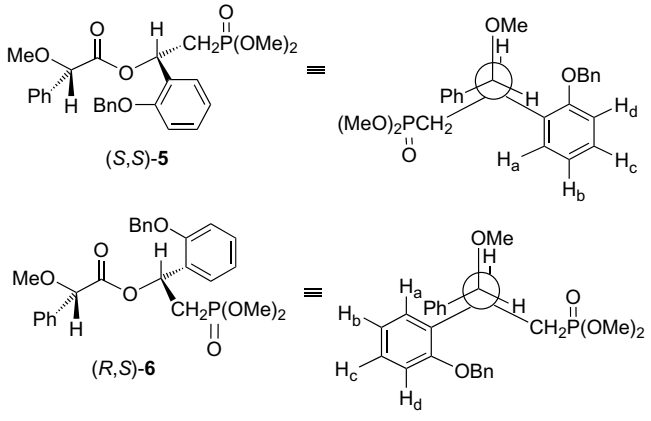


Figure 1. Extended Newman projections for the diastereoisomers (*S*,*S*)-**5** and (*R*,*S*)-**6**.

Table 1. ^{1}H and ^{31}P NMR chemical shifts for diastereoisomerically pure (*S*,*S*)-**5** and (*R*,*S*)-**6**

Entry	Group		More polar mandelate	Less polar mandelate	$\Delta\delta$ (ppm)
1		CH_2	2.32	2.36	0.04
2	$CH_2P(OMe)_2$	CH_2	2.41	2.36	0.05
3		$P(OCH_3)$	3.55	3.36	0.19
4		$P(OCH_3)$	3.58	3.39	0.19
5		$(CH_3O)_2P$	29.56	29.17	0.39
6	OCH_2Ph	CH_2Ph	5.03	5.09	0.06
7	H_a	H_a	6.85	6.90	0.05
8	H_b	H_b	7.14	7.22	0.08
9	H_c	H_c	6.66	6.90	0.24
10	H_d	H_d	6.66	7.22	0.56

From the NMR data of the diastereoisomerically pure mandelates summarized in Table 1, we observed that the ^{1}H NMR chemical shifts for the $(MeO)_2P$ group in the less polar diastereoisomer are at a higher field (3.36 and 3.39 ppm) than those for the same group in the more polar diastereoisomer (3.55 and 3.58 ppm), with $\Delta\delta = 0.19$ ppm (entries 3 and 4). The ^{31}P NMR chemical shift for the $(MeO)_2P$ group in the less polar diastereoisomer is also at a higher field (29.17 ppm) than that of the same group in the more polar diastereoisomer (29.56 ppm) with a $\Delta\delta = 0.39$ ppm, (entry 5). Additionally, in the more polar diastereoisomer, the H_c and H_d aromatic protons are at a higher field (6.66 ppm) than those of the same protons in the less polar diastereoisomer (6.90 and 7.22 ppm), with a $\Delta\delta = 0.24$ and 0.56 ppm, respectively. Therefore, these NMR data show that the less polar mandelate correlates with the diastereoisomer of configuration (*S*,*S*)-**5** and the more polar mandelate with the diastereoisomer (*R*,*S*)-**6**.

In a similar manner, analysis of the more and less polar mandelates by ^{13}C NMR (Table 2) shows that the chemical shifts for the $CH_2P(O)(OMe)_2$ group in the less polar diastereoisomer are at a higher field than those of the same group in the more polar diastereoisomer, and also the chemical shifts for the benzylic and aromatic carbons in the more polar diastereoisomer are at higher field than those of the same group in the less polar mandelate. These data again show that the less polar mandelate is the diastereoisomer (*S*,*S*)-**5**, and the more polar mandelate is the diastereoisomer (*R*,*S*)-**6**.

In addition to the NMR analysis mentioned above, a complexation experiment of the diastereoisomers (*S*,*S*)-**5** and (*R*,*S*)-**6** with barium(II) was accomplished. According to this protocol, the ^{1}H NMR spectra of each diastereoisomer were recorded in MeCN-d_3 after of the addition of $Ba(ClO_4)_2$.[13] The chemical shifts observed in ^{1}H and ^{31}P NMR for both diastereoisomers (*S*,*S*)-**5** and (*R*,*S*)-**6** are summarized in Table 3.

As a result of the complexation with Ba^{2+}, one conformer is preferentially stabilized as shown in Figure 2. In the fixed

Table 2. ^{13}C NMR chemical shifts for diastereoisomerically pure (*S*,*S*)-**5** and (*R*,*S*)-**6**

Entry	Group		More polar mandelate	Less polar mandelate	$\Delta\delta$ (ppm)
1		CH_2	31.0	30.6	0.40
2	$CH_2P(OMe)_2$	$P(OCH_3)$	52.46	52.16	0.30
3		$P(OCH_3)$	52.52	52.22	0.30
4		CH_2Ph	70.38	76.38	0.00
5	OCH_2Ph	C_a	111.85	112.23	0.38
6	a	C_b	128.10	128.11	0.01
7	d b	C_c	120.92	121.10	0.18
8	c	C_d	125.88	126.72	0.84

Table 3. ^{1}H NMR chemical shifts for (*S*,*S*)-**5**/Ba^{2+} and (*R*,*S*)-**6**/Ba^{2+} in MeCN-d_3

Entry	Group		More polar mandelate Ba^{2+}	Less polar mandelate Ba^{2+}	$\Delta\delta$ (ppm)
1		CH_2	2.48	2.46	0.02
2	$CH_2P(OMe)_2$	$P(OCH_3)$	3.60	3.40	0.02
3		$P(OCH_3)$	3.66	3.41	0.25
4		$(CH_3O)_2P$	28.85	28.52	0.33
5	OCH_2Ph	CH_2Ph	5.04	5.15	0.11
6	H_a	H_a	6.95	6.99	0.04
7		H_b	7.19	7.31	0.12
8	H_d H_b	H_c	6.66	6.99	0.33
9	H_c	H_d	6.66	7.31	0.65

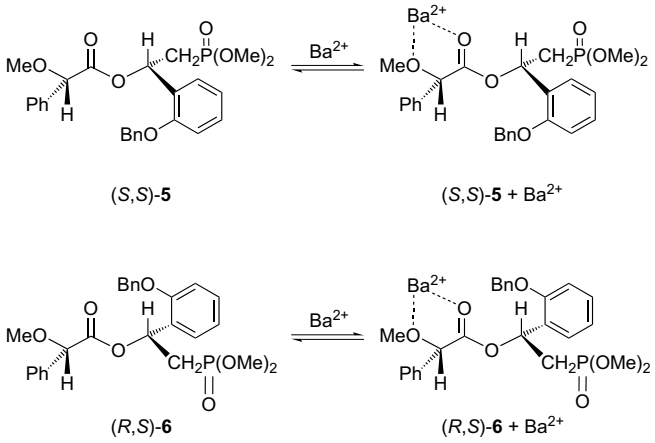


Figure 2. Complexation of mandelates (*S*,*S*)-**5** and (*R*,*S*)-**6** with Ba(II).

conformation, the protecting effect of the phenyl ring from the MPA fragment is more pronounced than that in the first set of experiments carried out in the absence of a barium salt. Hence, the values for $\Delta\delta$ have a significant increment, as shown in Table 3, while the same tendency in the selective shielding is maintained, as before $\Delta\delta^{Ba} = \delta[(R,S)\text{-}\mathbf{6}/Ba^{2+}] - [\delta(S,S)\text{-}\mathbf{5}/Ba^{2+}]$.

In addition to the NMR experiments, computational calculations were carried out in order to find the most stable conformer for each diastereoisomeric mandelate.[14] Conformational search and geometry optimization were made using ab initio calculations, and a global minimum was obtained. The employed method was Hartree–Fock with the basis set 6-311 + G**.

Results from this conformational analysis showed that the most stable conformer for the diastereoisomer (*S*,*S*)-**5** has the geometry predicted by Mosher's approximation, that is with the methoxy and carbonyl groups of MPA and the proton β to the phosphorus atom lying on the same plane (Fig. 3a). The phenyl ring is oriented to the same side of the $(MeO)_2P$ group. In addition to this protection effect, there is an extra shielding by the aromatic ring of the benzyl moiety (Fig. 3b).

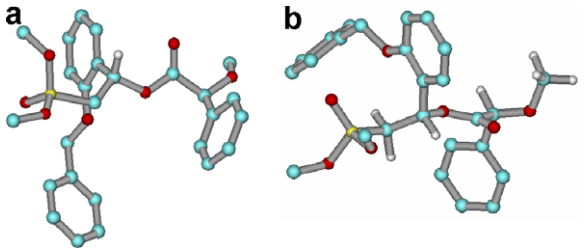


Figure 3. Minimum energy conformer for the mandelate (*S*,*S*)-**5**. Some ^1H atoms were omitted for clarity.

On the other hand, the conformational search for the diastereoisomer (*R*,*S*)-**6** exhibited a molecular geometry in which the methoxy and carbonyl groups of MPA and the proton β to the phosphorus atom are almost on the same plane (Fig. 4a). The protecting effect of the phenyl ring is now directed toward the aromatic protons of the salicylaldehyde fragment, which is in agreement with the ^1H NMR data. In a similar manner, it was possible to observe a correlation between the dipole moment in the most stable conformer for each diastereoisomer and their polarities. Thus, the more polar mandelate (*R*,*S*)-**6** shows a dipole moment of 5.10 Db, whereas the less polar mandelate (*S*,*S*)-**5** shows a dipole moment of 2.87 Db. These theoretical results reinforce the experimental observations.

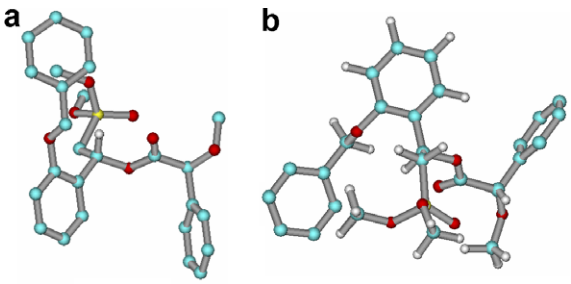
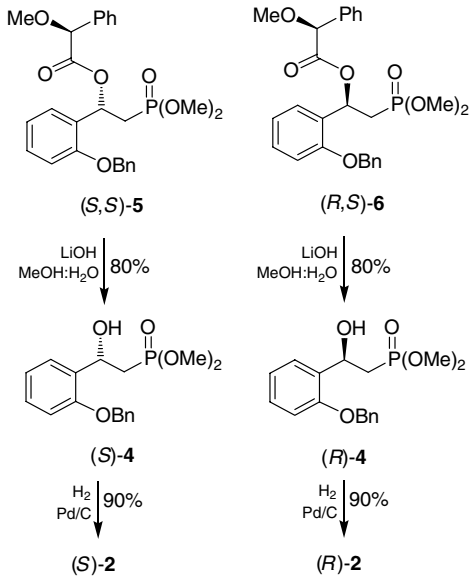


Figure 4. Minimum energy conformer for the mandelate (*R*,*S*)-**6**.

Once the absolute configuration was assigned, the preparation of both enantiomers of dimethyl 2-(2-hydroxyphenyl)-2-hydroxyethylphosphonate **2** was completed. In this context, hydrolysis of diastereoisomerically pure (*S*,*S*)-**6** with LiOH in a mixture of MeOH–H_2O (8:2) at room temperature afforded the enantiomerically pure β-hydroxyethylphosphonate (*S*)-**4** in a 80% yield. Cleavage of the benzyl group in (*S*)-**4** using Pd/C as a catalyst in methanol under a hydrogen atmosphere at room temperature gave the dimethyl (*S*)-2-(2-hydroxyphenyl)-2-hydroxyethylphosphonate (*S*)-**2** in a 90% yield. In a similar way, enantiomer (*R*)-**2** was obtained from (*R*,*S*)-**6** (Scheme 4).



Scheme 4.

3. Conclusion

In conclusion, we have found a methodology for the preparation of enantiomerically pure dimethyl (*R*)- and (*S*)-2-(2-hydroxyphenyl)-2-hydroxyethylphosphonates **2** from salicylaldehyde, which are versatile intermediates in organic chemistry. As a matter of fact, we are already using these hydroxyphosphonates as catalyst for the addition of cyanide to aldehydes.

4. 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) was used. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were registered on a Varian INOVA 400, and ^{31}P NMR (80.98 MHz) on a Varian Mercury 200. The spectra were recorded in $CDCl_3$ solution using TMS as internal reference. HRMS spectra were recorded on a JEOL JMS-700. Flasks, stirring 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 desiccator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl. The 2-(benzyloxy)-benzaldehyde **3** was prepared according to literature procedure.[9]

4.1. Dimethyl (±)-2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate (±)-4

A solution of dimethyl methylphosphonate (1.75 g, 14.1 mmol) and dry THF (70 mL) was cooled at −78 °C before the slow addition of *n*-BuLi (6.08 mL, 14.6 mmol) in hexanes (2.4 M). The resulting solution was stirred at −78 °C for 1 h, and after this period of time, the solution was slowly added to another solution of 2-(benzyloxy)benzaldehyde **3** (1.0 g, 4.7 mmol) in THF (60 mL). The reaction mixture was stirred at −78 °C for 4 h before the addition of a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography (ethyl acetate–hexane 3:1) obtaining (±)-**4** (1.4 g, 85%) as a yellow oil. The NMR data are identical to enantiomerically pure (*R*)- and (*S*)-**4**.

4.2. Mandelates (*S*,*S*)-5 and (*R*,*S*)-6

Procedure A: To a mixture of (±)-**4** (2.0 g, 5.95 mmol) and (*S*)-*O*-methylmandelic acid (1.58 g, 9.5 mmol) in dry dichloromethane (100 mL), were added 4-(*N*,*N*-dimethyl)-aminopyridine (110 mg, 0.9 mmol) and 1,3-dicyclohexylcarbodiimide (1.96 g, 9.5 mmol). The reaction mixture was stirred at room temperature for 12 h. After this time, the 1,3-dicyclohexylurea was filtered off and the filtrate was concentrated in vacuum. The crude product was purified by column chromatography (ethyl acetate–hexane 8:2) obtaining (*S*,*S*)-**5** (1.30 g, 45%) (less polar) and (*R*,*S*)-**6** (1.35 g, 47%) (more polar) both as yellow oils.

Procedure B: To a solution of (±)-**4** (1.15 g, 3.42 mmol) and 4-(*N*,*N*-dimethyl)aminopyridine (0.125 g, 1.026 mmol) in dry THF were added (*S*)-methoxyphenylacetic acid chloride (1.14 g, 6.154 mmol) and triethylamine (0.62 g, 0.86 mL, 6.15 mmol) at room temperature. After 10 h the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (ethyl acetate–hexane 8:2) obtaining (*S*,*S*)-**5** (0.80 g, 48%) (less polar) and (*R*,*S*)-**6** (0.68 g, 41%) (more polar) both as yellow oils.

4.2.1. Dimethyl (*S*)-2-(2-*O*-benzylphenyl)-2-[(*S*)-*O*-methylmandelate]ethylphosphonate (*S*,*S*)-5. $[\alpha]_D = +26.89$ (*c* 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (dd, $J = 17.6$, 6.4 Hz, 2H, CH_2P), 3.36 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.39 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.39 (s, 3H, CH_3OCH), 4.81 (s, 1H, $CHOCH_3$), 5.09 (s, 2H, CH_2Ph), 6.44 (dt, $J_{H/P} = 11.2$, $J = 6.4$ Hz, 1H, $CHCH_2P$), 6.90 (d, $J = 8.0$ Hz, 2H, H_a and H_c), 7.22 (d, $J = 8.0$ Hz, 2H, H_b and H_d), 7.29–7.48 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.6 (d, $J = 138.2$ Hz, CH_2P), 52.1 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.2 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 57.6 (CH_3OCH), 67.6 (d, $J = 3.1$ Hz, $CHCH_2P$), 70.4 (OCH_2Ph), 82.9 ($CHOCH_3$), 112.2, 121.1, 126.7, 127.4, 127.5, 127.6, 127.6, 128.1, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 129.5, 136.1, 136.8, 155.3, 169.6 (CO). ^{31}P NMR (80.98 MHz, $CDCl_3$): δ 29.17. HRMS, (CI^+, CH_4) calcd for $C_{26}H_{30}O_7P$ (MH^+) 485.1724, found 485.1704.

4.2.2. Dimethyl (*R*)-2-(2-*O*-benzylphenyl)-2-[(*S*)-*O*-methylmandelate]ethylphosphonate (*R*,*S*)-6. $[\alpha]_D = +27.18$ (*c* 1.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (ddd, $J = 15.6$, 15.6, 9.4 Hz, 1H, CH_2P), 2.41 (ddd, $J = 19.2$, 15.6, 3.6 Hz, 1H, CH_2P), 3.44 (s, 3H, CH_3OCH), 3.55 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.58 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 4.87 (s, 1H, $CH(OCH_3)$), 5.03 (s, 2H, CH_2Ph), 6.50 (ddd, $J_{H/P} = 11.1$, $J_{1/3} = 9.5$, $J_{1/3} = 3.7$ Hz, 1H, $CHCH_2P$), 6.66 (m, 2H, H_c and H_d), 6.85 (d, $J = 8.0$ Hz, 1H, H_a), 7.14 (ddd, $J = 8.4$, 6.0, 3.2 Hz, 1H, H_b), 7.31–7.45 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.0 (d, $J = 36.6$ Hz, CH_2P), 52.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.5 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 57.7 (CH_3OCH), 66.8 (d, $J = 4.6$ Hz, $CHCH_2P$), 70.4 (OCH_2Ph), 82.6 ($CHOCH_3$), 111.8, 120.9, 125.9, 127.5, 127.5, 127.7, 127.7, 128.1, 128.2, 128.3, 128.6, 128.7, 128.8, 128.8, 129.2, 136.2, 136.7, 154.9, 169.2 (CO). ^{31}P NMR (80.98 MHz, $CDCl_3$): δ 29.56. HRMS, (FAB^+) calcd for $C_{26}H_{30}O_7P$ (MH^+) 485.1724, found 485.1636.

4.3. Dimethyl (*S*)-2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate (*S*)-4

Diastereoisomer (*S*,*S*)-**5** (1.0 g, 2.06 mmol) was dissolved in a 8:2 mixture of MeOH/H_2O (50 mL) and stirred at room temperature with LiOH (433 mg, 10.3 mmol). After 6 h the volatiles were removed under reduced pressure. The residue was washed with a 5% solution of HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified

by column chromatography (ethyl acetate–hexane 8:2) to give (*S*)-**4** (560 mg, 80%) as a white solid, mp 63 °C. $[\alpha]_D = +46.8$ (*c* 1.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 2.14 (ddd, $J = 15.3$, 14.8, 9.7 Hz, 1H, CH_2P), 2.38 (ddd, $J = 18.1$, 15.3, 2.7 Hz, 1H, CH_2P), 3.58 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.59 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 5.02 (d, $J = 11.6$ Hz, 1H, CH_2Ph), 5.08 (d, $J = 12$ Hz, 1H, CH_2Ph), 5.40 (ddd, $J = 12.2$, 9.8, 2.6 Hz, 1H, CHAr), 6.92 (d, $J = 8.4$ Hz, 1H, H_{arom}), 7.00 (ddd, $J = 7.6$, 7.2, 0.8 Hz, 1H, H_{arom}), 7.23 (ddd, $J = 8.4$, 7.4, 1.4 Hz, 1H, H_{arom}), 7.29–7.42 (m, 5H, H_{arom}), 7.56 (dd, $J = 7.4$, 1.4 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.1 (d, $J = 133.6$ Hz, CH_2P), 52.4 (d, $J = 6.0$ Hz, $(CH_3O)_2P$), 52.5 (d, $J = 6.0$ Hz, $(CH_3O)_2P$), 64.4 (d, $J = 4.5$ Hz, CHOH), 70.0 (s, CH_2Ph), 111.3, 121.2, 126.2, 127.4, 127.5, 128.1, 128.5, 128.6, 131.8, 131.9, 136.7, 154.6. ^{31}P NMR (80.98 MHz, $CDCl_3$): δ 33.39. HRMS, (CI^+, CH_4) calcd for $C_{17}H_{22}O_5P$ (MH^+) 337.1205, found 337.1199.

4.4. Dimethyl (*R*)-2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate (*R*)-4

The procedure is the same as for (*S*)-**4**, using the diastereoisomer (*R*,*S*)-**6** as starting material. $[\alpha]_D = -47.2$ (*c* 1.18, $CHCl_3$). The NMR data are identical to (*S*)-**4**.

4.5. Dimethyl (*S*)-2-(2-hydroxyphenyl)-2-hydroxyethylphosphonate (*S*)-2

Dimethyl (*S*)-2-(2-*O*-benzylphenyl)-2-hydroxyethylphosphonate (*S*)-**4** (550 mg, 1.6 mmol) was treated with 110 mg (10 wt %) of palladium on carbon in methanol (20 mL) and stirred for 24 h under a hydrogen atmosphere at room temperature. The mixture was filtered through a bed of Celite, and the solvent was concentrated in vacuum. The crude product was purified by column chromatography (ethyl acetate–hexane 5:5) to obtain the enantiomer (*S*)-**2** (340 mg, 84%), as a colorless oil. $[\alpha]_D = -0.3$ (*c* 3.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.17 (ddd, $J = 17.4$, 8.0 Hz, 2H, CH_2P), 2.90 (ddd, $J = 12.0$, 8.0 Hz, 2H, CHAr), 2.9 (s, 1H, HOCH), 3.69 (d, $J = 10.8$ Hz, 6H, $(CH_3O)_2P$), 6.74–7.10 (4H, H_{arom}), 8.21 (s, 1H, HOAr). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0 (d, $J = 4.15$ Hz, CHOH), 24.9 (d, $J = 136.0$ Hz, CH_2P), 52.8 (d, $J = 6.45$ Hz, $(CH_3O)_2P$), 116.1, 119.9, 127.1, 127.4, 127.8, 129.8, 154.7. ^{31}P NMR (80.98 MHz, $CDCl_3$): δ 37.0. HRMS, (FAB^+) calcd for $C_{10}H_{16}O_5P$ (MH^+) 247.0735, found 247.0000.

4.6. Synthesis of dimethyl (*R*)-2-(2-hydroxyphenyl)-2-hydroxyethylphosphonate (*R*)-2

The procedure is the same as for (*S*)-**2**, using (*R*)-**4** as a starting material. $[\alpha]_D = +0.3$ (*c* 0.9, $CHCl_3$). The NMR data are identical to (*S*)-**2**.

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References

1. (a) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: New York, 2000, and references cited therein; (b) Koh, Y.; Shim, J. H.; Wu, J. Z.; Zhong, W.; Hong, Z.; Girardet, J. L. *J. Med. Chem.* **2005**, *48*, 2867–2875.
2. (a) Reichwein, J. F.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 1821–1824; (b) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579–594; (c) Maryanoff, B. E.; Reetz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
3. (a) Wróblesky, A. E.; Halajewska-Wosik, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2075–2077; (b) Kolodiazhna, A. O.; Kukhar, V. P.; Chernegu, A. N.; Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1961–1963; (c) Hirschmann, R.; Smith, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Spregenler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237.
4. (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931–2932; (b) Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry* **1995**, *6*, 1089–1092.
5. (a) Pàmies, O.; Bäckball, J. E. *J. Org. Chem.* **2003**, *68*, 4815–4818; (b) Zurawinski, R.; Nakamura, K.; Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3139–3145; (c) Zymanczyk-Duda, E.; Lejczak, B.; Kafarski, P.; Grimaud, J.; Fischer, P. *Tetrahedron* **1995**, *51*, 11809–11814.
6. (a) De la Cruz-Cordero, R.; Labastida-Galván, V.; Fernández-Zertuche, M.; Ordóñez, M. *J. Mex. Chem. Soc.* **2005**, *49*, 312–321; (b) De la Cruz-Cordero, R.; Hernández-Núñez, E.; Fernández-Zertuche, M.; Muñoz-Hernández, M. A.; Ordóñez, M. *Arkivoc* **2005**, 277–286; (c) Ordóñez, M.; De la Cruz-Cordero, R.; Fernández-Zertuche, M.; Muñoz-Hernández, M. A.; García-Barradas, O. *Tetrahedron: Asymmetry* **2004**, *15*, 3035–3043; (d) Ordóñez, M.; González-Morales, A.; Salazar-Fernández, H. *Tetrahedron: Asymmetry* **2004**, *15*, 2719–2725; (e) Ordóñez, M.; De la Cruz-Cordero, R.; Quiñónez, C.; González-Morales, A. *Chem. Commun.* **2004**, 672–673; (f) Ordóñez, M.; De la Cruz-Cordero, R.; Fernández-Zertuche, M.; Muñoz-Hernández, M. A. *Tetrahedron: Asymmetry* **2002**, *13*, 559–562.
7. (a) González-Morales, A.; Fernández-Zertuche, M.; Ordóñez, M. *Rev. Soc. Quím. Mex.* **2004**, *48*, 236–242; (b) González-Morales, A.; Díaz-Coutiño, D.; Fernández-Zertuche, M.; García-Barradas, O.; Ordóñez, M. *Tetrahedron: Asymmetry* **2004**, *15*, 457–463; (c) Ordóñez, M.; González-Morales, A.; Ruíz-Marcial, C. A.; De la Cruz-Cordero, R.; Fernández-Zertuche, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1775–1779.
8. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
9. (a) Kozuch, S.; Leyfels, T.; Meyer, D.; Sbaragli, L.; Shaik, S.; Woggon, W. *Synlett* **2005**, 675–684; (b) Boxhall, J. Y.; Bulman, P. C.; Chan, Y.; Hayman, C. M.; Heaney, H.; McGrath, M. J. *Synlett* **2003**, 997–1001.
10. 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*, 2370–2374.
11. For the assignment of absolute configuration of secondary alcohols by NMR, see: (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117, and references cited therein;

(b) Porto, S.; Duran, J.; Seco, J. M.; Quiñoa, E.; Riguera, R. *Org. Lett.* **2003**, *5*, 2979–2982; (c) Seco, J. M.; Tseng, L.-H.; Godejohann, M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2149–2153; (d) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925; (e) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

12. (a) For the assignment of the absolute configuration of β-hydroxyphosphonates by NMR, see: Refs. 4–6; (b) Maly, A.; Lejczak, B.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1019–1024; (c) Wroblewsky, A. E.; Piotrowska, D. G. *Tetrahedron: Asymmetry* **2000**, *11*, 2615–2624; (d) Kozlowski, J. M.; Rath, N. P.; Spilling, C. D. *Tetrahedron* **1995**, *51*, 6385–6396.
13. García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2002**, *67*, 4579–4589.
14. For the assignment of absolute configuration of secondary alcohols using molecular mechanics and NMR data, see: Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577.