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Efficient and Practical Synthesis of *syn*- and *anti*-β,γ-Dihydroxyphosphonates Derived from (*S*)-Mandelic Acid

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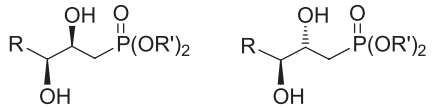
Abstract: A new efficient and practical synthesis of *syn*- and *anti*-β,γ-dihydroxyphosphonates **1** and **2** was developed in high diastereoselectivity via reduction of β-ketophosphonates readily obtained from (*S*)-mandelic acid. An example of "diastereoselective 1,2-induction" is showed and a mechanistic model to explain the stereochemical outcome is proposed. Assignment of the configuration at the new stereogenic centers was achieved by ^{1}H NMR spectral data of their corresponding acetonides.
Key words: Diastereoselective 1,2-induction, diastereoselective reduction, β,γ-dihydroxyphosphonates, β-ketophosphonates, (*S*)-mandelic acid.

Resumen: Se describe una nueva síntesis eficiente y práctica de *syn*- y *anti*-β,γ-dihidroxifosfonatos **1** y **2** mediante la reducción diastereoselectiva de β-cetofosfonatos fácilmente preparados a partir de ácido (*S*)-mandélico. Esta metodología representa un ejemplo de inducción "diastereoselectiva 1,2" y se propone un modelo mecanístico para explicar la alta diastereoselectividad. La configuración absoluta del nuevo centro estereogénico se llevó a cabo mediante el análisis de los espectros de RMN de ^{1}H de sus correspondientes acetales cíclicos.
Palabras clave: Inducción diastereoselectiva-1,2, reducción diastereoselectiva, β,γ-dihidroxifosfonatos, β-cetofosfonatos, ácido (*S*)-mandélico.

Introduction

Molecules with phosphonate functionalities are known to have significant importance in organic synthesis because of their anion stabilizing ability and their use in the construction of double bonds via the Horner-Wadsworth-Emmons reaction [1,2]. Additionally, the phosphonates display a broad spectrum of activities [3] including enzyme inhibitors [4] such as the synthase [5], HIV protease [6], rennin [7], phosphatasa [8], and PTPases [9]; they also are antibacterial [10], antiviral [11], antifungal agents [12], and antitumor agents [13], herbicides [14], plant regulators, potent antibiotics [15], and in the antibody generation [16]. Within this class of compounds the hydroxyphosphonates display interesting biological activities [17].

Synthesis of chiral hydroxyphosphonates includes opening reaction of epoxides with the anion of dialkylphosphites [18], nucleophilic addition of dialkylphosphites to aldehydes [19], enzymatic resolution of hydroxyphosphonates [20] and stereoselective reduction of ketophosphonates [21]. β,γ-Hydroxyphosphonates of type **1** and **2** have been mainly prepared by asymmetric dihydroxylation (AD) of the corresponding (*E*)- and (*Z*)-olefins [22], with the major disadvantage that AD reaction of (*Z*)-olefins proceeds with low enantioselectivities [23].

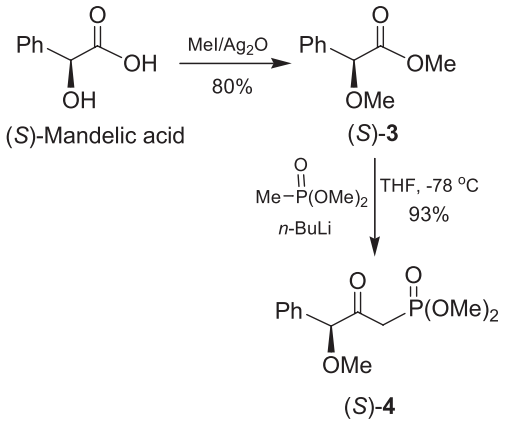


syn-**1** *anti*-**2**

Highly diastereoselective reduction of γ-amino-β-ketophosphonates has been recently applied in our laboratories for the synthesis of phosphogabob (GABOB^p)[24] and phosphostatine analogues [25]. Now, in this paper we report a new efficient and practical methodology for the synthesis of β,γ-dihydroxyphosphonates *syn*-**1** and *anti*-**2** via the diastereoselective reduction of (*S*)-β-ketophosphonates **4** and **9** readily obtained from (*S*)-mandelic acid.

Results and discussion

In our first attempt, the β-ketophosphonate (*S*)-**4** was prepared in two steps from (*S*)-mandelic acid as is showed in the Scheme 1. Thus, treatment of (*S*)-mandelic acid with iodomethane and silver oxide according to the literature procedure [26], afforded the methyl *O*-methylmandelate (*S*)-**3** in 80% yield [27], which by subsequent addition of the lithium salt of dimethyl methylphosphonate gave the β-ketophosphonate (*S*)-**4** in 93% yield (Scheme 1).



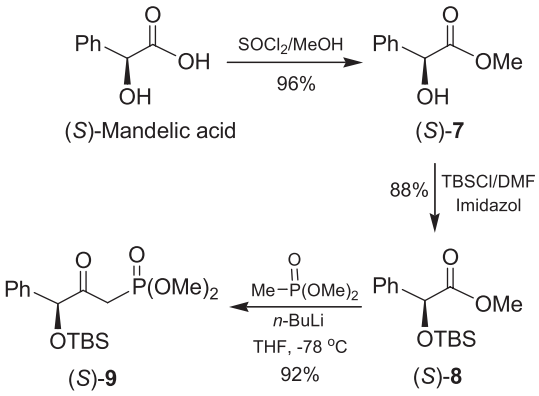
Scheme 1.

Having efficiently prepared the β-ketophosphonate (*S*)-**4**, initially we carried out its reduction using $NaBH_4$, $LiBH_4$, $Zn(BH_4)_2$, DIBAL-H and catecholborane (CB) as reducing agents, in order to obtain the *syn*-**5** and *anti*-b,g-hydroxyphosphonate **6** in high diastereoselectivity. Conditions, yields and diastereoisomeric ratio are summarized in the Table 1.

As shown in Table 1, reduction of b-ketophosphonate (*S*)-**4** with $NaBH_4$ in methanol at 0 °C afforded the corresponding β-hydroxyphosphonates *syn*-**5** and *anti*-**6** in excellent yield, but with only low diastereoselectivity (40:60) in favor of diastereoisomer *anti*-**6** (Table 1, entry 1). Identical results were obtained when the reduction of (*S*)-**4** was carried out with $NaBH_4$ and $NaBH_4/LiClO_4$ in methanol (Table 1, entries 2-3). A better diastereoselectivity in favor of *anti*-**6** was observed when the reduction of (*S*)-**4** was achieved using $LiBH_4$ as reducing agent (Table 1, entry 4); but the addition of $LiClO_4$ or $TiCl_4$ did not modify the diastereoselectivity (Table 1, entries 5-6). However, the reduction of (*S*)-**4** with $LiBH_4$ in the presence of $ZnCl_2$ afforded the β-hydroxyphosphonates *syn*-**5** and *anti*-**6** in quantitative yield and high diastereoselectivity (9:91) in favor of diastereoisomer *anti*-**6** (Table 1, entry 7). Contrary to what was expected, reduction of (*S*)-**4** with $Zn(BH_4)_2$ resulted in a low diastereoselectivity (Table 1, entry 8). On the other hand, a reversal diastereoselectivity was observed when the reduction of (*S*)-**4** was carried out with DIBAL-H and catecholborane, in both cases the diastereoisomeric ratio was 78:22 in favor of *syn*-**6** (Table 1, entries 9-10). The configuration of *syn*-**5** and *anti*-**6** was tentatively assigned by comparison of the ^{31}P NMR signals for the b-hydroxy-phosphonates *syn*-**10** and *anti*-**11** described below and some others reported in the literature [28].

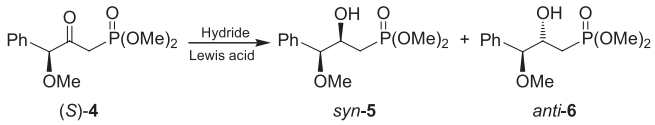
In order to have the β,γ-dihydroxyphosphonate **2**, the next step was the cleavage of methyl ether in *anti*-**6** with BCl_3 in dichlorometane. However, under these conditions only decomposition of the starting material was observed.

Due to the difficulties in the cleavage of methyl ether in *anti*-**6**, we considered other protecting group which could induce both a high diastereoselectivity and an easier cleavage. In this context, the *tert*-butyldimethylsilyl moiety was incorporated into the β-ketophosphonate (*S*)-**9**. Thus, (*S*)-mandelic acid was treated with thionyl chloride in methanol according to the literature procedure [29], obtaining the methyl ester (*S*)-**7** in 96% yield, which by reaction with *tert*-butyldimethylsilyl chloride and imidazol in DMF gave the silyl derivative (*S*)-**7** in 88% yield [30]. Finally, treatment of (*S*)-**7** with the lithiated anion of dimethyl methylphosphonate at -78 °C afforded the b-ketophosphonate (*S*)-**9** in 92% yield (Scheme 2).



Scheme 2.

Table 1. Diastereoselective reduction of (*S*)-**4** with several reducing agents.



Entry	Hydride	Lewis acid	Conditions	Yield (%)	*syn*-**5** : *anti*-**6**[a]
1	$NaBH_4$	—	MeOH, 0 °C	94	40 : 60
2	$NaBH_4$	—	MeOH, -78 °C	99	33 : 67
3	$NaBH_4$	$LiClO_4$	MeOH, 0 °C	99	36 : 64
4	$LiBH_4$	—	THF, -78 °C	80	18 : 82
5	$LiBH_4$	$LiClO_4$	THF, -78 °C	95	27 : 73
6	$LiBH_4$	$TiCl_4$	THF, -78 °C	99	17 : 83
7	$LiBH_4$	$ZnCl_2$	THF, -78 °C	98	09 : 91
8	$Zn(BH_4)_2$	—	THF, -78 °C	93	29 : 71
9	DIBAL-H	—	THF, -78 °C	92	78 : 22
10	CB[b]	—	THF, -78 °C	66	78 : 22

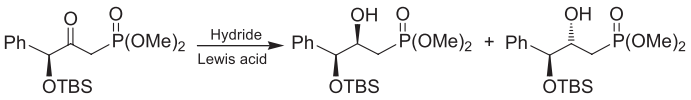
[a]Determined by ^{31}P NMR at 81 MHz. [b]Catecholborane.

Once again the reduction of (*S*)-**9** was performed with various reducing agents and reaction conditions, the results are summarized in the Table 2.

Reduction of (*S*)-**9** with $NaBH_4$ at 0 °C resulted in a preferential production of *anti*-**11** with a moderate diastereoselectivity (33:67), which was increased to (10:90) when the reduction was carried out at -78 °C (Table 2, entries 1-3). However, when the reduction of (*S*)-**9** was carried out using $NaBH_4$ at 0 °C in the presence of $LiClO_4$, a reversal diastereoselectivity was observed (82:18) now in favor of *syn*-**10** (Table 2, entry 3). With this result it was expected that reduction with $LiBH_4$ would afford the diastereoisomer *syn*-**10** as the major product. Effectively, reduction of (*S*)-**9** with $LiBH_4$, $LiBH_4/LiClO_4$ and $LiBH_4/ZnCl_2$ afforded the diastereoisomer *syn*-**10** as principal product (Table 2, entries 4-6), but a lost of the diastereoselectivity was observed when (*S*)-**9** was reduced with $LiBH_4$ in the presence of $TiCl_4$ (Table 2, entry 7). On the other hand, when the reduction of (*S*)-**9** was carried out with $Zn(BH_4)_2$, the diastereosiomer *syn*-**10** was obtained with excellent yield and good diastereoselectivity (90:10) in favor of *syn*-**10** (Table 2, entry 8). When DIBAL-H and DIBAL-H/$LiClO_4$ were used as reducing agent, the corresponding b-hydroxyphosphonates *syn*-**10** and *anti*-**11** were obtained in moderated yield and diasteroselectivity, in favor of *syn*-**10** (Table 2, entries 9 and 10), but a low diastereoselectivty was observed when DIBAL-H/$ZnCl_2$ and DIBAL-H/$TiCl_4$ were used (Table 2, entries 11-12). Reduction of (*S*)-**9** with CB, CB/$LiClO_4$ and CB/$TiCl_4$ gave the b-hydroxyphosphonates *syn*-**10** and *anti*-**11** in only moderated diastereoselectivity (Table 2, entries 13-15); however, reduction of (*S*)-**9** with CB in the presence of $ZnCl_2$ provided the b-hydroxy-phosphonates *syn*-**10** and *anti*-**11** in moderated yield and excellent diastereoselectivity (93:7) in favor of *syn*-**10** (Table 2, entry 16). At this point we had found the best conditions for the reduction of b-ketophosphonate (*S*)-**9**, obtaining *syn*-**10** or *anti*-**11** with excellent diastereoselectivity depending of reducing agent used.

The next step was the cleavage of the silyl protecting group in order to obtain the target molecules *syn*-**1** and *anti*-**2**. In this context, the standard literature procedures to remove the silyl group were attempted with unfavorable results, since the reaction of *syn*-**10** or *anti*-**11** with *n*-tetrabutylammonium fluoride or cesium fluoride led to decomposition of the starting β-hydroxyphosphonates, and under acid conditions (HCO_2H or AcOH) just did not proceed. An alternative methodology developed in our laboratory to cleavage the silyl ether in *syn*-**10** was their treatment with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid prior to the addition of cesium fluoride, obtaining the expected β-hydroxyphosphonate *syn*-**1**

Table 2. Diastereoselective reduction of (*S*)-**9** with several reducing agents.

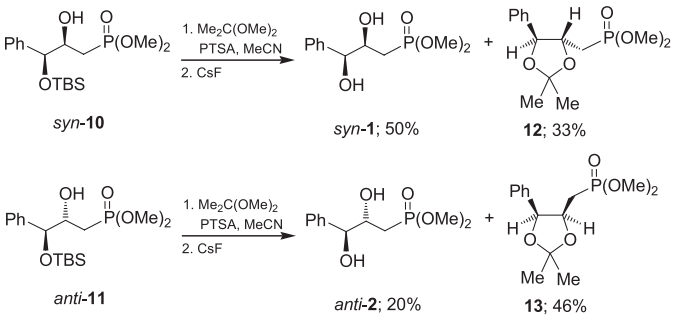


(*S*)-**9** *syn*-**10** *anti*-**11**

Entry	Hydride	Lewis acid	Conditions	Yield (%)	*syn*-**10** : *anti*-**11**[a]
1	$NaBH_4$	—	MeOH, 0 °C	94	33 : 67
2	$NaBH_4$	—	MeOH, -78 °C	96	10 : 90
3	$NaBH_4$	$LiClO_4$	MeOH, 0 °C	95	82 : 18
4	$LiBH_4$	—	THF, -78 °C	93	80 : 20
5	$LiBH_4$	$LiClO_4$	THF, -78 °C	97	86 : 14
6	$LiBH_4$	$ZnCl_2$	THF, -78 °C	93	81 : 19
7	$LiBH_4$	$TiCl_4$	THF, -78 °C	74	49 : 51
8	$Zn(BH_4)_2$	—	THF, -78 °C	98	90 : 10
9	DIBAL-H	—	THF, -78 °C	88	83 : 17
10	DIBAL-H	$LiClO_4$	THF, -78 °C	50	81 : 19
11	DIBAL-H	$ZnCl_2$	THF, -78 °C	33	42 : 58
12	DIBAL-H	$TiCl_4$	THF, -78 °C	53	61 : 39
13	CB[b]	—	THF, -78 °C	95	70 : 30
14	CB[b]	$LiClO_4$	THF, -78 °C	65	78 : 22
15	CB[b]	$TiCl_4$	THF, -78 °C	68	64 : 36
16	CB[b]	$ZnCl_2$	THF, -78 °C	65	93 : 07

[a]Determined by ^{31}P NMR at 81 MHz. [b]Catecholborane

in 50% yield and its corresponding cyclic acetonide **12** in 33% yield, whereas *anti*-**11** gave the β-hydroxyphosphonate *anti*-**2** in 20% yield and the cyclic acetonide **13** in 46% yield (Scheme 3).



Scheme 3.

^{1}H NMR analysis of acetonides **12** and **13** was used for the absolute configuration assignment in C_2. Thus, the coupling constant values for adjacent protons H_a and H_b at the stereogenic centers in acetonides **12** and **13** are J = 8.4 Hz and J = 6.1 Hz, respectively, which by comparison of these coupling constants values reported in the literature [31], particularly with those reported for phosphine oxide acetonides [32], where the coupling constant values are J = 8.0 Hz and J = 6.4 Hz, respectively. An additional coupling constant J = 1.8 Hz for H_b in acetonide **13** was observed (Figure 1). When the ^{1}H NMR spectrum decoupled to ^{31}P was carried out, the H_b signal changed from double of doublets J = 6.1, 1.8 Hz to doublet J = 6.1 Hz. From these values follows that H_b is coupled to phosphorus with a typical W coupling value (1.8 Hz). These data correlate with a structure depicted for diastereoisomer **13**, confirming the relative configuration.

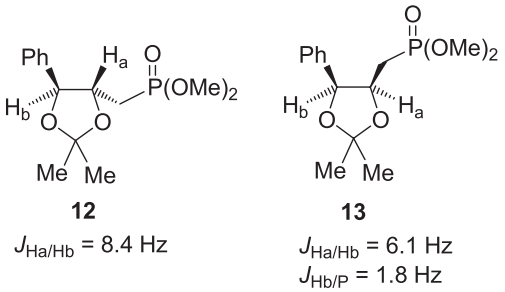


Figure 1. Vicinal coupling constant for acetonides **12** and **13**.

Therefore, we propose that the reduction of (*S*)-**9** with $NaBH_4$ took place under non-chelation control or the Felkin-Ahn model [33], where the conformer leading to the major product will be that one where the bulky OTBS group is perpendicular to the carbonyl plane and the smallest group (hydrogen) is almost eclipsed to it [34], in this model, the bulkyness of the OTBS group is sufficient to simultaneously limit the rotamer populations around the hinge bounds adjacent to the carbonyl group blocking the *si* face of the carbonyl group and, thereby allowing the addition of hydride take place from the *re* face leading to diastereoisomer *anti*-**11** (Figure 2a). On the other hand, when the reduction of (*S*)-**9** was carried out in the presence of Lewis acid or hydrides possessing metal ions with coordinating ability (such as lithium, zinc, aluminum and boron), a Cram's model is proposed[35], where the carbonyl, phosphoryl and OTBS groups are coordinated to the metal ion in a chair-like transition state **A** or **B** showed in Figure 2b. Because of the steric interactions between the phenyl group and the equatorial hydrogen in **A**, it is assumed that transition state **B** is favored, and the addition of hydride take place by the *si* face leading to *syn*-**10** as the principal product (Figure 2b).

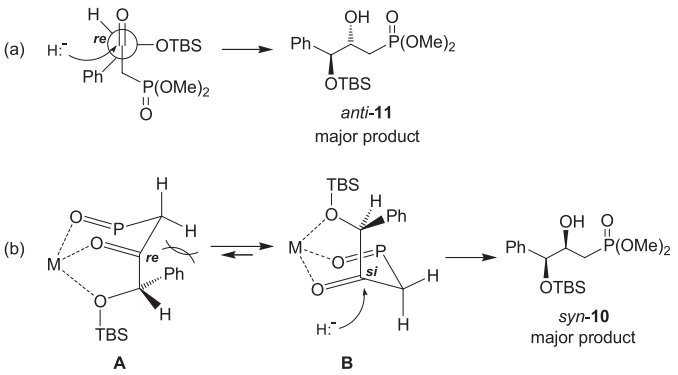


Figure 2. Reduction of (*S*)-**9**: (a) with $NaBH_4$, (b) in the presence of M^{n+}.

Conclusions

In summary, we have found an alternative and practical methodology for the synthesis of β,γ-dihydroxy-phosphonates *syn*-**1** and *anti*-**2** in high diastereoselectivity via the reduction of b-ketophosphonate (*S*)-**9** readily obtained from (*S*)-mandelic acid. Additionally, the conditions described in this paper show an example of highly diastereoselective 1,2-induction.

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) was used. ^{1}H NMR spectra were registered on a Varian Mercury 200 (200 MHz) and INOVA 400 (400 MHz); and ^{13}C NMR on a Varian Mercury 200 (50 MHz) and INOVA 400 (100 MHz), and ^{31}P NMR on a Varian Mercury 200 (81 MHz). The spectra were recorded in $CDCl_3$, DMSO-d_6 and CD_3OD solution, using TMS as internal reference. HRMS spectra were recorded on a JEOL JMS-700. Microanalyses were registered on an 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 desiccators over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.

Methyl (*S*)-*O*-methylmandelate (*S*)-3. Methyl ester (*S*)-**3** was obtained according to the literature procedure [26].

Methyl (*S*)-mandelic acid (*S*)-7. Methyl ester (*S*)-**7** was obtained according to the literature procedure [29].

Methyl 1-[(*tert*-butyldimethylsilyl)oxy]-1-phenylacetate (*S*)-8. Methyl ester (*S*)-**8** was obtained according to the literature procedure [30].

Dimethyl (*S*)-3-methoxy-3-phenyl 2-oxo-propylphosphonate (*S*)-4. A solution of dimethyl methyl-phosphonate 1.38 g (11.1 mmol) in anhydrous THF (80 mL) was cooled at -78 °C before the slow addition of 750 mg, 4.86 mL (11.7 mmol) of *n*-BuLi 2.4 M in hexanes. The resulting solution was stirred at -78 °C for 1.0 h, which was slowly added to a solution containing (*S*)-**3** 1.0 g (5.6 mmol) in THF (80 mL) at -78°C. The reaction mixture was stirred for 3.0 h, quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (3 × 60 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 1:1) to afford 1.41 g (93%) of (*S*)-**4** as a colorless oil. $[\alpha]_D$ = +25.5 (*c* = 3.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (dd, *J* = 22.0, 14.5 Hz, 1H, CH_2P), 3.21 (dd, *J* = 22.0, 14.5 Hz, 1H, CH_2P), 3.40 (s, 3H, CH_3O), 3.74 (d, *J* = 11.2, 3H, $((CH_3O)_2P)$, 3.75 (d, *J* = 11.2, 3H, $((CH_3O)_2P)$, 4.88 (s, 1H, CHPh), 7.34-7.39 (m, 5H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): d 36.3 (d, *J* = 132.1 Hz, CH_2P), 53.0 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 53.5 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 57.4 (CH_3O), 88.6 (CHPh), 127.4, 128.8, 128.8, 134.7, 199.4 (d, *J* = 6.0 Hz, CO). ^{31}P NMR (81 MHz, $CDCl_3$): d 23.42. HRMS (CI^+) calc. for $C_{12}H_{18}O_5P$ (MH^+) 273.0892; found 273.0973

Dimethyl (*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-3-phenyl-2-oxo-propylphosphonate (*S*)-9. A solution of dimethyl methylphosphonate 1.3 g (10.7 mmol) in anhydrous THF (70 mL) was cooled at -78 °C before the slow addition of 710 mg, 4.42 mL (11.0 mmol) of *n*-BuLi 2.5 M in hexanes. The resulting solution was stirred at -78 °C for 1.0 h, which was slowly added to a solution containing (*S*)-**8** 1.0 g, 3.6 mmol) in THF (80 mL) at -78 °C. The reaction mixture was stirred for 6.0 h, quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (3 × 60 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 1:1) to afford 1.22 g (92%) of (*S*)-**9** as a colorless oil. $[\alpha]_D$ = -5.15 (*c* = 4.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 3H, $(CH_3)_2Si$), 0.11 (s, 3H, $(CH_3)_2Si$), 0.9 (s, 9H, $(CH_3)_3CSi$), 3.16 (dd, *J* = 10.6, 7.8 Hz, 1H, CH_2P), 3.26 (dd, *J* = 10.6, 7.8 Hz, 1H, CH_2P), 3.66 (d, *J* = 12.0 Hz, 3H, $(CH_3O)_2P$), 3.69 (d, *J* = 12.0 Hz, 3H, $(CH_3O)_2P$), 5.19 (s, 1H, CHPh), 7.29-7.43 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): d -4.9 $(CH_3)_2Si$), 4.8 $(CH_3)_2Si$), 18.4 ($(CH_3)_3$**C**Si), 25.8 ($(\mathbf{C}H_3)_3CSi$), 34.2 (d, *J* = 136.3 Hz, CH_2P), 52.9 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 81.1 (d, *J* = 4.5 Hz, CHPh), 126.5, 128.6, 128.8, 137.7, 201.6 (d, *J* = 7.6 Hz, CO). ^{31}P NMR (81 MHz, $CDCl_3$): d 24.40. HRMS (FAB^+) calc. for $C_{17}H_{30}O_5PSi$ (MH^+) 373.1600; found 373.1597

General procedure for the reduction of (*S*)-4 and (*S*)-9 with $NaBH_4$. To a solution of β-ketophosphonate (*S*)-**4** or (*S*)-**9** (1.0 equiv.) in methanol (40 mL) was added $NaBH_4$ (4.0 equiv.) at room temperature, 0 and -78 °C. After 5.0 h, the solvent was evaporated and the residue was diluted with H_2O and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuum. The crude was analyzed by ^{1}H and ^{31}P NMR and purified by column chromatography.

General procedure for the reduction of (*S*)-4 and (*S*)-9 with $NaBH_4$/$LiClO_4$. To a solution of β-ketophosphonate (*S*)-**4** or (*S*)-**9** (1.0 equiv.) in methanol (40 mL), was added $LiClO_4$ (1.0 equiv.) at room temperature. After 1.0 h, $NaBH_4$ (4.0 equiv) was slowly added at 0 °C, and the reaction mixture was stirred for 5.0 h at 0 °C. The solvent was evaporated and the residue was diluted with H_2O and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuum. The crude was analyzed by ^{1}H and ^{31}P NMR and purified by column chromatography.

General procedure for the reduction of (*S*)-4 and (*S*)-9 with $LiBH_4$, $Zn(BH_4)_2$, DIBAL-H and Catecholborane (CB). To a solution of β-ketophosphonate (*S*)-**4** or (*S*)-**9** (1.0 equiv.) in anhydrous THF (50 mL) was added (2.0 equiv.) of the reducing agent at -78 °C. The reaction mixture was stirred for 5.0 h at -78 °C. The reaction was quenched with aqueous NH_4Cl solution, and extracted with ethyl acetate (3 × 40 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude was analyzed by ^{1}H and ^{31}P NMR and purified by column chromatography.

General procedure for the reduction of (*S*)-4 and (*S*)-9 with $LiBH_4$, DIBAL-H and CB in the presence of Lewis acid. To a solution of β-ketophosphonate (*S*)-**4** or (*S*)-**9** (1.0 equiv.) and Lewis acid (1.0 equiv.) in anhydrous THF (50 mL) was stirred for 1.0 h. After the reducing agent was added (2.0 equiv.) at -78 °C, and stirred for 5.0 h. The reaction was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 40 mL). The organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude was analyzed by ^{1}H and ^{31}P NMR and purified by column chromatography.

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxi]-2-hydroxy-3-phenylpropylphosphonate *syn*-10 (91% de). $[\alpha]_D$ = +37.4 (*c* = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ -0.18 (s, 3H, $(CH_3)_2Si$), 0.05 (s, 3H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3CSi$), 1.72 (ddd, *J* = 15.5, 15.5, 10.3 Hz, 1H, CH_2P), 1.84 (ddd, *J* = 19.7, 15.5, 2.5 Hz, 1H, CH_2P), 2.83 (b, 1H, OH), 3.70 (d, *J* = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.71 (d, *J* = 11.2 Hz, $(CH_3O)_2P$), 4.04 (dddd, *J* = 10.4, 10.4, 6.8, 2.8 Hz, 1H, C**H**OH), 4.55 (d, *J* = 6.8 Hz, 1H, CHPh), 7.28-7.37 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz,

$CDCl_3$): δ -4.8 $(CH_3)_2Si$), -4.3 $(CH_3)_2Si$), 18.4 (($(CH_3)_3$**C**Si), 26.0 (($\mathbf{C}H_3)_3$CSi), 28.2 (d, *J* = 141.1 Hz, CH_2P), 52.5 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 52.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 71.6 (d, *J* = 6.1 Hz, CHOH), 78.6 (d, *J* = 18.3 Hz, CHPh), 127.3, 128.1, 128.3, 140.2. ^{31}P NMR (81 MHz, $CDCl_3$): δ 33.82. HRMS (FAB^+) calc. for $C_{17}H_{32}O_5PSi$ (MH^+) 375.1757; found 375.1741

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxi]-2-hydroxy-3-phenylpropylphosphonate *anti*-11 (88% de). $[\alpha]_D$ = +48.0 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ -0.14 (s, 3H, $(CH_3)_2Si$), 0.07 (s, 3H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3$CSi), 1.93 (ddd, *J* = 15.5, 15.5, 10.3 Hz, 1H, CH_2P), 2.0 (ddd, *J* = 15.5, 15.5, 2.6 Hz, 1H, CH_2P), 2.80 (b, 1H, OH), 3.70 (d, *J* = 10.6 Hz, 3H, $(CH_3O)_2P$), 3.72 (d, *J* = 10.6 Hz, $(CH_3O)_2P$), 4.06 (dddd, *J* = 9.8, 9.8, 2.9, 1.8 Hz, 1H, C**H**OH), 4.66 (d, *J* = 4.8 Hz, 1H, CHPh), 7.28-7.36 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.6 $(CH_3)_2Si$), -4.4 $(CH_3)_2Si$), 18.4 (($(CH_3)_3$**C**Si), 26.0 (($\mathbf{C}H_3)_3$CSi), 27.3 (d, *J* = 141.1 Hz, CH_2P), 52.5 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 52.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 71.7 (d, *J* = 4.5 Hz, CHOH), 78.0 (d, *J* = 16.7 Hz, CHPh), 126.8, 127.8, 128.2, 140.9. ^{31}P NMR (81 MHz, $CDCl_3$): δ 34.89. HRMS (FAB^+) calc. for $C_{17}H_{32}O_5PSi$ (MH^+) 375.1757; found 375.1766

Cleavage of TBS ether in *syn*-10. To a solution of *syn*-**10** 800 mg (2.14 mmol) in acetonitrile (40 mL), 2,2-dimethoxypropane 334 mg, 0.39 mL (3.2 mmol) and *p*-toluenesulfonic acid 406 mg (2.14 mmol) were added at room temperature. After 2.0 h, cesium fluoride was added 487 mg (3.2 mmol) and the reaction mixture was stirred for 12 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate-hexane 4:1), obtaining 280 mg (50%) of *syn*-**1** and 210 mg (33%) of **12**, both as white solids.

(2*R*,3*S*)-2,3-Dihydroxy-3-phenylpropylphosphonate *syn*-1 (91% de). $[\alpha]_D$ = +17.6 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80-1.95 (m, 2H, CH_2P), 3.02 (b, 2H, OH), 3.70 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.73 (d, *J* = 10.8 Hz, $(CH_3O)_2P$), 4.11 (m, 1H, C**H**CH_2P), 4.55 (d, *J* = 6.2 Hz, 1H, CHPh), 7.31-7.37 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.0 (d, *J* = 139.7 Hz, CH_2P), 52.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 52.9 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 71.1 (d, *J* = 4.5 Hz, **C**HCH_2P), 78.0 (d, *J* = 18.3 Hz, CHPh), 127.1, 128.4, 128.7, 140.1. ^{31}P NMR (81 MHz, $CDCl_3$): d 33.76. HRMS (FAB^+) calc. for $C_{11}H_{18}O_5P$ (MH^+) 261.0892; found 261.0883

(4*S*,5*R*)-2,2-Dimethyl-4-phenyl-5-[(dimethylphosphono) methyl]-1,3-dioxolane 12. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.01-2.14 (m, 2H, CH_2P), 3.69 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.70 (d, *J* = 11.0 Hz, $(CH_3O)_2P$), 4.06 (m, 1H, C**H**CH_2P), 4.66 (d, *J* = 8.4 Hz, 1H, CHPh), 7.32-7.40 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3 (CH_3), 27.5 (CH_3), 27.8 (d, *J* = 143.0 Hz, CH_2P), 52.4 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 52.8 (d, *J* = 7.6 Hz, $(CH_3O)_2P$), 77.9 (d, *J* = 6.1 Hz, **C**HCH_2P), 84.0 (d, *J* = 16.7 Hz, CHPh), 109.6 (($CH_3)_2$**C**), 127.0, 128.2, 128.8, 140.3. ^{31}P NMR (81 MHz, $CDCl_3$): d 30.81. HRMS (FAB^+) calc. for $C_{14}H_{22}O_5P$ (MH^+) 301.1205; found 301.1190

Cleavage of TBS ether in *anti*-11. The procedure is similar as for *syn*-**10**, using *anti*-**11** as starting material. The reaction gave 115 mg (20%) of *anti*-**2** as a colorless oil and 295 mg (46%) of **13** as a white solid.

(2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropylphosphonate *anti*-2. $[\alpha]_D$ = +0.34 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (ddd, *J* = 19.2, 15.7, 2.8 Hz, 1H, CH_2P), 2.05 (ddd, *J* = 15.8, 15.8, 10.5 Hz, 1H, CH_2P), 3.63 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.65 (d, *J* = 11.0 Hz, $(CH_3O)_2P$), 4.17 (dddd, *J* = 10.5, 10.5, 2.8, 2.8 Hz, 1H, C**H**CH_2P), 4.28 (s, 2H, OH), 4.80 (dd, *J* = 3.5, 2.8 Hz, 1H, CHPh), 7.24-7.44 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (d, *J* = 141.3 Hz, CH_2P), 52.5 (d, *J* = 6.6 Hz, $(CH_3O)_2P$), 52.7 (d, *J* = 6.6 Hz, $(CH_3O)_2P$), 70.8 (d, *J* = 5.3 Hz, **C**HCH_2P), 76.3 (d, *J* = 15.9 Hz, CHPh), 126.2, 127.5, 128.3, 140.1. ^{31}P NMR (80.98 MHz, $CDCl_3$): δ 35.68. HRMS (CI^+) calc. for $C_{11}H_{18}O_5P$ (MH^+) 261.0892; found 261.0956

(4*S*,5*S*)-2,2-Dimethyl-4-phenyl-5-[(dimethylphosphono) methyl]-1,3-dioxolane 13. ^{1}H NMR (400 MHz, $CDCl_3$): d 1.31 (ddd, *J* = 20.0, 15.7, 2.6 Hz, 1H, CH_2P), 1.48 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.65 (ddd, *J* = 15.7, 15.7, 10.8 Hz, 1H, CH_2P), 3.70 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.73 (d, *J* = 11.0 Hz, $(CH_3O)_2P$), 4.75 (dddd, *J* = 10.8, 8.0, 6.6, 2.6 Hz, 1H, C**H**CH_2P), 5.30 (dd, *J* = 6.6, 1.8 Hz, 1H, CHPh), 7.27-7.38 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5 (CH_3), 27.8 (CH_3), 30.3 (d, *J* = 183.7 Hz, CH_2P), 52.2 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 53.0 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 74.1 (d, *J* = 4.5 Hz, **C**HCH_2P), 80.0 (d, *J* = 15.2 Hz, CHPh), 109.1 (($CH_3)_2$**C**), 126.6, 128.2, 128.6, 136.8. ^{31}P NMR (81 MHz, $CDCl_3$): δ 32.86. HRMS (FAB^+) calc. for $C_{14}H_{22}O_5P$ (MH^+) 301.1205; found 301.1190

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