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Highly diastereoselective reduction of β-ketophosphonates bearing homochiral bis(α-methylbenzyl)amine: preparation of both enantiomers of phosphogabob (GABOB^P)

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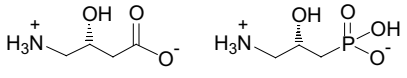
Abstract—The reduction of dimethyl 3-*N*,*N*-di(α-methylbenzyl)amino-2-ketophosphonates **9** with catecholborane at −78 °C in presence of $LiClO_4$, gave γ-amino-β-hydroxyphosphonates **10** and **11** in good yield and with excellent diastereoselectivity. This procedure represents an example of highly diastereoselective 1,4-induction. The hydrolysis and hydrogenation of **10** and **11** afforded the (*R*)- and (*S*)-γ-amino-β-hydroxypropylphosphonic acid (GABOB^P), respectively.

1. Introduction

(*R*)-γ-Amino-β-hydroxybutyric acid (L-GABOB) **1** is an important amino acid, which acts as an antipipetic and hypotensive drug,[1] and is an agonist of γ-aminobutyric acid (GABA).[2] As a neuromodulator it has been demonstrated to be effective in managing a variety of clinical conditions including schizophrenia, epilepsy, and other character-based disorders including severe convulsions.[3] Its use for the correction of some clinical conditions observed in children has also been reported. For these reasons, many synthetic routes of GABOB have been developed. They are based on either a chiral pool methodology,[4] asymmetric synthesis[5] and enzymatic or chemoenzymatic process.[6]



(*R*)-**1** (*S*)-**2**

On the other hand, it is known that phosphorus analogues of naturally occurring amino acids are produced by certain organisms and are of great interest in bioorganic and medicinal chemistry.[7] These molecules could act as enzyme inhibitors due to the mimetic behavior of the unstable tetrahedral carbon intermediates formed in the enzymatic processes. Thus, the synthesis of a phosphorus analogue of GABOB, namely phosphogabob (GABOB^P) **2**, is of great interest.

The first enantioselective synthesis of (*S*)-**2** was achieved using a Baker's yeast mediated bio-reduction of diethyl 3-azido-2-oxophosphonate, followed by catalytic hydrogenation of the azido group and dealkylation.[8,9] Wróblewski and Halajewska-Wosik reported the synthesis of (*S*)-**2** by means of the C3 regioselective opening of the oxirane ring of diethyl (*S*)-2,3-epoxypropylphosphonate with tritylamine, followed by hydrogenation of the trityl group and hydrolysis of the ester group.[10] Recently, we reported the preparation of the both enantiomers of GABOB^P **2** starting from glycine and including the resolution of the intermediate dimethyl-3-(*N*,*N*-dibenzyl)amino-2-hydroxypropylphosphonate with (*S*)-*O*-methylmandelic acid.[11] Herein, we report a more efficient approach to prepare enantiomerically pure (*R*)- and (*S*)-γ-amino-β-hydroxypropylphosphonic acid GABOB^P **2**, which takes advantage of the highly diastereoselective reduction of β-ketophosphonates derived from ethyl *N*,*N*-bis(α-methylbenzyl)glycinate.

2. Results and discussion

The importance of chiral amines such as α-methylbenzylamine (α-MBA) is well-recognized as a simple, yet powerful chiral auxiliaries.[12] Furthermore, both enantiomers of α-MBA are commercially accessible.

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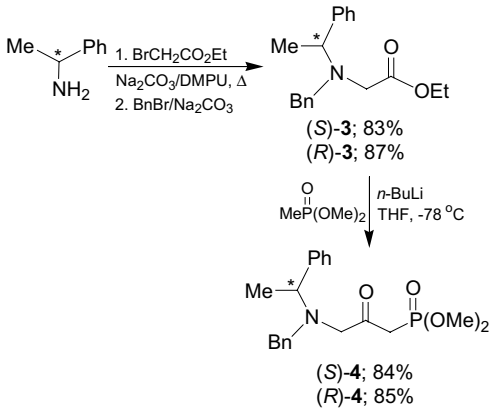
An additional advantage of α-MBA as a quiral auxiliary is its easy removal via reductive elimination. Therefore, α-MBA and its cognate bis-(α-methylbenzyl)amine have been used in several chemical processes with a good level of 1,4-stereoinduction.[13] In order to evaluate the 1,4-induction in the reduction of β-ketophosphonates bearing α-methylbenzylamine, the dimethyl (*S*)-3-(*N*-benzyl-*N*-α-methylbenzyl)amino-2-ketopropylphosphonate (*S*)-**4** was prepared as is shown in Scheme 1. In the first step, (*S*)-(−)-α-methylbenzylamine was initially treated with DMPU, Na_2CO_3 and an excess of ethyl bromoacetate under reflux,[14] to give the corresponding ethyl (*S*)-*N*-α-methylbenzylglycinate, that without further purification was treated with more Na_2CO_3 and excess of benzyl bromine under reflux, to obtain the ethyl (*S*)-(*N*-benzyl-*N*-α-methylbenzyl)glycinate **3** in 83% yield. Ethyl glycinate (*S*)-**3** was treated with 2 equiv of the lithium salt of dimethyl methylphosphonate at −78 °C in THF to afford (*S*)-**4** in 84% yield. Similar yields were obtained in the preparation of ester (*R*)-**3** and β-ketophosphonate (*R*)-**4** (Scheme 1).



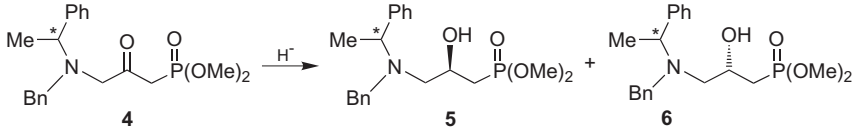
Scheme 1.

Having efficiently prepared β-ketophosphonates **4**, we turned our attention to its diastereoselective reduction to obtain β-hydroxyphosphonates **5** and **6**. Table 1 summarizes the conditions used for the reduction and results obtained.

Analysis of Table 1 reveals that excellent yield and moderate diastereoselectivity was obtained when the reduction of (*S*)-**4** was carried out with $NaBH_4$ (entry 1), and with a predominance of diastereomer (*R*,*S*)-**5**. However, only poor diastereoselectivities were obtained when the reduction of (*S*)-**4** was carried out with $LiBH_4$, $LiBH_4/LiClO_4$, $Zn(BH_4)_2$, and catecholborane (entries 3–6). On the other hand, the addition of $LiClO_4$ to $NaBH_4$ adversely affects the diastereoselectivity upon reduction of (*S*)-**4** (entry 2), but addition of $LiClO_4$ to catecholborane increases to some extent the diastereoselectivity (entry 7). Identical results were obtained in the reduction of β-ketophosphonate (*R*)-**4** when the reduction was carried out with $NaBH_4$, catecholborane, and catecholborane/$LiClO_4$ (entries 8–10), with a predominance of diastereomer (*S*,*R*)-**6**. Diastereomeric excesses were determined by means of ^1H and ^{31}P NMR while the absolute configuration at the stereogenic center at C3 of the diastereomers **5** and **6** were assigned in accordance with the classical approach developed by Dale and Mosher[15] using ^1H and ^{31}P NMR data of the diastereomeric *O*-methylmandelates derivatives.[16,17]

In order to induce a higher degree of diastereoselectivity in the reduction of β-ketophosphonates bearing α-methylbenzylamine, derivatives **9** were prepared (Scheme 2). Thus, (*S*,*S*)-(−)-bis(α-methylbenzyl)amine **7** was treated under reflux with an excess of ethyl bromoacetate, Na_2CO_3, and freshly distillate DMPU,[14] to obtain the corresponding ethyl (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)glycinate (*S*,*S*)-**8** in 82% yield.[13b] Treatment of ethyl ester **8** with 2 equiv of the lithium salt of dimethyl methylphosphonate at −78 °C in dry THF afforded β-ketophosphonate (*S*,*S*)-**9** in 87% yield. Ethyl glycinate (*R*,*R*)-**8** and β-ketopropylphosphonate (*R*,*R*)-**9**, were

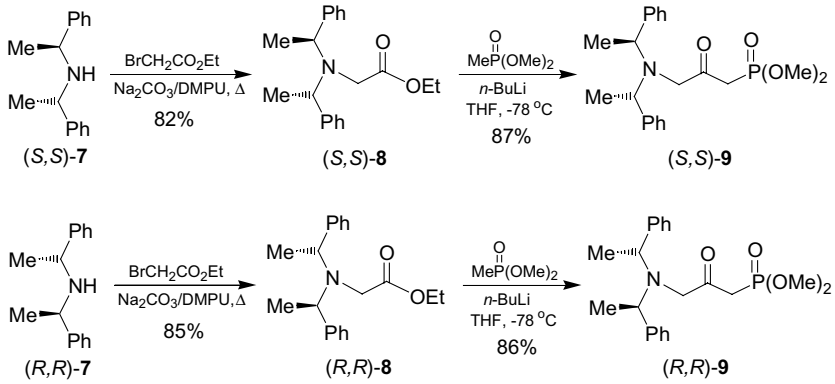
Table 1. The reduction of **4** with various reducing agents



4 **5** **6**

Entry	**4**	Hydride	Conditions	Yield[a] (%)	**5**:**6**[b]
1	(*S*)	$NaBH_4$	MeOH, 0 °C	97	72:28
2	(*S*)	$NaBH_4/LiClO_4$	MeOH, 0 °C	94	60:40
3	(*S*)	$LiBH_4$	THF, −78 °C	83	54:46
4	(*S*)	$LiBH_4/LiClO_4$	THF, −78 °C	93	48:52
5	(*S*)	$Zn(BH_4)_2$	THF, −78 °C	89	52:48
6	(*S*)	CB	THF, −78 °C	90	58:42
7	(*S*)	CB/$LiClO_4$	THF, −78 °C	91	63:37
8	(*R*)	$NaBH_4$	MeOH, 0 °C	96	26:74
9	(*R*)	CB	THF, −78 °C	95	42:58
10	(*R*)	CB/$LiClO_4$	THF, −78 °C	91	38:62

[a] Chemical yield after purification.
[b] Determined by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz.



Scheme 2.

obtained in similar fashion in 85% and 86% yield, respectively (Scheme 2).

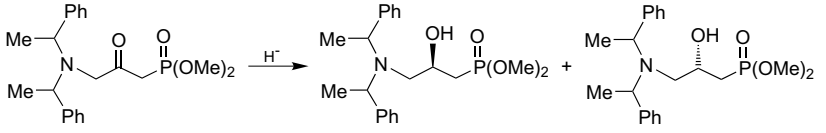
The efficient preparation of β-ketophosphonates (*S*,*S*)-**9** and (*R*,*R*)-**9**, encouraged us to perform their diastereoselective reduction to obtain β-hydroxyphosphonates **10** and **11**, Table 2.

The results collected in Table 2 show that the reduction of **9** with $NaBH_4$ at 0 °C in methanol or THF (entries 1–2) afforded β-hydroxyphosphonates (*R*,*S*,*S*)-**10** and (*S*,*S*,*S*)-**11** in good yield and with moderate diastereoselectivity with a predominance of diastereomer (*R*,*S*,*S*)-**10**. Similar diastereoselectivities and yields were obtained when the reduction of **9** was carried out with $LiBH_4$, and $Zn(BH_4)_2$ at −78 °C in THF (entries 3–4). However, a poor diastereoselectivity was obtained when the reduction of (*S*,*S*)-**9** was achieved with DIBAL-H at −78 °C in THF (entry 5). Remarkably, when the reduction of (*S*,*S*)-**9** was carried out with catecholborane at −78 °C in THF (entry 6), β-hydroxyphosphonates **10** and **11** were isolated in good yields and high diastereoselectivities in favor of diastereomer (*R*,*S*,*S*)-**10**. Outstanding diastereoselectivity and yield of the latter compound was obtained when the β-ketophosphonate (*S*,*S*)-**9** was reduced with catecholborane in the presence of 2.5 equiv of $LiClO_4$ at −78 °C in dry THF. Under these conditions only one diastereomer could be detected by both ^1H and ^{31}P NMR (entry 7). Identical results were obtained under the preceding conditions in the reduction of β-ketophosphonate (*R*,*R*)-**9** (entries 8 and 9), but now in favor of diastereomer (*S*,*R*,*R*)-**11**.

The absolute configuration of the stereogenic center at C3 of diastereomers (*R*,*S*,*S*)-**10**, (*S*,*S*,*S*)-**11**, (*R*,*R*,*R*)-**10**, and (*S*,*R*,*R*)-**11** were assigned according to the approach developed by Dale and Mosher[15] using ^1H and ^{31}P NMR data of diastereomeric *O*-methylmandelates derivatives.[16,17] Further confirmation was given by single crystal X-ray analysis of diastereomerically pure (*R*,*S*,*S*)-**10**, (Fig. 1).[18]

Finally, the hydrolysis of β-hydroxypropylphosphonates (*R*,*S*,*S*)-**10** and (*S*,*R*,*R*)-**11** with bromotrimethylsilane[19] at room temperature afforded γ-*N*,*N*-bis(α-methylbenzylamino)-β-hydroxypropylphosphonic acids, that without further purification were treated with palladium hydroxide on carbon in methanol under hydrogen gas at

Table 2. The reduction of **9** with various reducing agents



9 **10** **11**

Entry	**9**	Hydride	Conditions	Yield[a] (%)	**10**:**11**[b]
1	(*S*,*S*)	$NaBH_4$	MeOH, 0 °C	96	85:15
2	(*S*,*S*)	$NaBH_4$	THF, 0 °C	95	80:20
3	(*S*,*S*)	$LiBH_4$	THF, −78 °C	93	76:24
4	(*S*,*S*)	$Zn(BH_4)_2$	THF, −78 °C	95	77:23
5	(*S*,*S*)	DIBAL-H	THF, −78 °C	98	44:56
6	(*S*,*S*)	CB	THF, −78 °C	91	93:07
7	(*S*,*S*)	CB/$LiClO_4$	THF, −78 °C	89	>99:1
8	(*R*,*R*)	CB	THF, −78 °C	91	07:93
9	(*R*,*R*)	CB/$LiClO_4$	THF, −78 °C	87	1:>99

[a] Chemical yield after purification.
[b] Determined by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz.

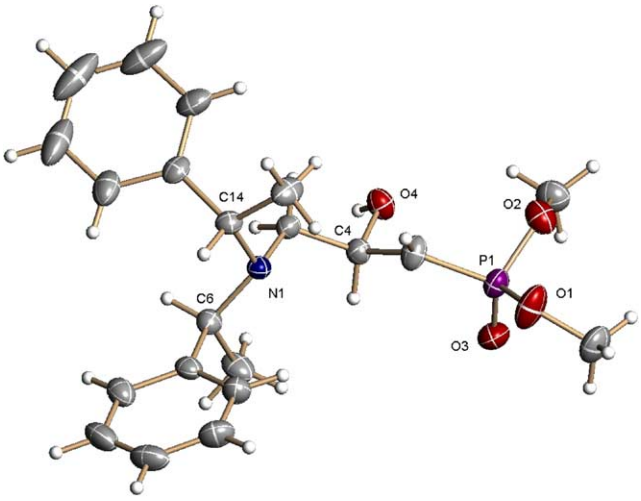
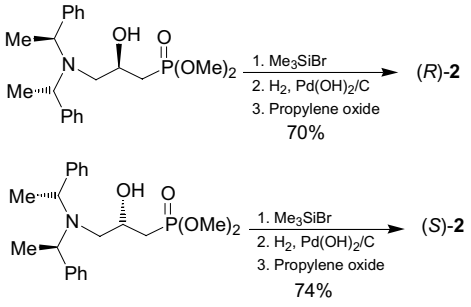


Figure 1. X-ray molecular structure of (*R*,*S*,*S*)-**10**.

60° and 60 psi to obtain the (*R*)- and (*S*)-γ-amino-β-hydroxypropylphosphonic acids **2** in 70% and 74% yield, respectively (Scheme 3).



Scheme 3.

3. Conclusion

In conclusion, we have found a new methodology for the preparation of both enantiomers of γ-amino-β-hydroxypropylphosphonic acid GABOB[P] enantiomerically pure. Additionally the reduction of dimethyl γ-*N*,*N*-bis(α-methylbenzyl)amino-β-ketopropylphosphonates (*S*,*S*)-**9** and (*R*,*R*)-**9** with catecholborane in presence of $LiClO_4$, represent an example of highly diastereoselective 1,4-induction.

4. Experimental

Optical rotations were taken at 20 °C on a Perkin–Elmer 241 polarimeter in an 1 dm tube; concentrations are given in g/100 mL. For the flash chromatography, silica gel 60 (230–400 mesh ASTM, Merck) was used. ^1H NMR spectra were registered on a Varian (400 MHz) and ^{13}C NMR on AMX-500 (100 MHz). The spectras were recorded in D_2O or $CDCl_3$ solution, using TMS as an internal reference. 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 dessicator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.

4.1. Ethyl (*S*)-(−)-(*N*-benzyl-*N*-α-methylbenzyl)glycinate (*S*)-3

A solution of (*S*)-(−)-α-methylbenzylamine 5 g (41.3 mmol), Na_2CO_3 8.74 g (82.5 mmol) and freshly distilled DMPU (100 mL), was treated under nitrogen atmosphere with ethyl bromoacetate 7.58 g, 5.03 mL (45.4 mmol). The reaction mixture was heated at 100 °C until no starting amine was observed by TLC (3 h). The reaction mixture was cooled to room temperature at which point was added Na_2CO_3 4.37 g (41.3 mmol) and benzyl bromide 7.06 g, 4.9 mL (41.3 mmol), and then heated at 100 °C for 3 h. The white suspension was then cooled at room temperature and treated with water until a solution was formed, which was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with water (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by column chromatography (hexane–AcOEt 90:10) to afford (*S*)-**3** (10.2 g, 83%) as white solid, mp 51–52 °C, $[\alpha]_D = -45.5$ (*c* 1.67, $CHCl_3$), lit.[13b] $[\alpha]_D = -37.0 \pm 1$ (*c* 0.785, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O), 1.39 (d, *J* = 7.0 Hz, 3H, CH_3CHPh), 3.21 (d, *J* = 17.0 Hz, 1H, CH_2N), 3.42 (d, *J* = 17.0 Hz, 1H, CH_2N), 3.71 (d, *J* = 14.0 Hz, 1H, CH_2Ph), 3.76 (d, *J* = 14 Hz, 1H, CH_2Ph), 4.11 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.13 (q, *J* = 7.0 Hz, 1H, $CH(CH_3)Ph$), 7.19–7.47 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3CH_2O), 19.1 (CH_3CHPh), 50.7 (CH_2Ph), 55.0 ($CH(CH_3)Ph$), 59.9 (CH_2O), 60.3 (CH_2N), 127.0, 127.1, 127.7, 128.3, 128.4, 128.5, 128.8, 139.8, 144.7, 172.1 C=O. Analysis for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71%. Found C, 76.81; H, 7.83; N, 4.74%.

4.2. Ethyl (*R*)-(+)-(*N*-benzyl-*N*-α-methylbenzyl)glycinate (*R*)-3

The procedure described above for the (*S*)-enantiomer was followed using (*R*)-(+)-α-methylbenzylamine 5 g (41.3 mmol), Na_2CO_3 8.74 g (82.5 mmol) and freshly distilled DMPU (100 mL) and ethyl bromoacetate 7.58 g, 5.03 mL (45.4 mmol), and thus with Na_2CO_3 4.37 g (41.3 mmol) and benzyl bromide 7.06 g, 4.9 mL (41.3 mmol), to give 10.7 g, 87% yield of (*R*)-**3** as a white solid, mp 51–52 °C, $[\alpha]_D = +44.9$ (*c* 2.04, $CHCl_3$), lit.[13b] $[\alpha]_D = +41 \pm 4$ (*c* 0.2345, MeOH). The spectroscopy data was identical to (*S*)-**3**. Analysis for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71%. Found C, 76.65; H, 7.91; N, 4.83%.

4.3. Dimethyl (*S*)-(−)-3-(*N*-benzyl-*N*-α-methylbenzyl)-amino-2-oxopropylphosphonate (*S*)-4

A solution of dimethyl methylphosphonate 2.51 g (20.2 mmol) in anhydrous THF (80 mL) was cooled at

−78 °C before the slow addition of 1.36 g, 18.93 mL (21.2 mmol) of *n*-BuLi 1.12 M in hexanes. The resulting solution was stirred at −50 °C for 1.5 h, then the solution cooled at −78 °C and slowly added to a solution of ethyl ester (*S*)-**3** 3.0 g (10.1 mmol) in anhydrous THF (80 mL). The reaction mixture was stirred at −78 °C for 4 h, quenched with aqueous NH_4Cl solution (15 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine solution (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by column chromatography (hexane–ethyl acetate 70:30) to afford 3.2 g, 84% yield, of (*S*)-**4** as a colorless oil. $[\alpha]_D = -28.42$ (*c* 8.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, $J = 6.8$ Hz, 3H, CH_3CHPh), 2.99 (dd, $J = 22.4$, 14.4 Hz, 1H, CH_2P), 3.08 (dd, $J = 22.4$, 14.4 Hz, 1H, CH_2P), 3.26 (d, $J = 17.0$ Hz, 1H, CH_2N), 3.46 (d, $J = 17.0$ Hz, 1H, CH_2N), 3.58 (d, $J = 13.4$ Hz, 1H, CH_2Ph), 3.56 (d, $J = 13.4$ Hz, 1H, CH_2Ph), 3.65 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.66 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 4.04 (q, $J = 6.8$ Hz, 2H, $CH(CH_3)Ph$), 7.24–7.42 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6 (CH_3CHPh), 37.5 (d, $J = 130.6$ Hz, CH_2P), 53.0 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 53.0 (d, $J = 4.5$ Hz, $(CH_3O)_2P$), 55.7 (CH_2Ph), 59.7 ($CH(CH_3)Ph$), 60.8 (CH_2N), 127.3, 127.4, 128.0 (2), 128.4, 128.5, 129.2 (2), 139.1, 143.0, 202.2 C=O. ^{31}P NMR (200 MHz, $CDCl_3$) δ 24.04.

4.4. Dimethyl (*R*)-(+)-3-(*N*-benzyl-*N*-α-methylbenzyl)-amino-2-oxopropylphosphonate (*R*)-4

The procedure described above for the (*S*)-enantiomer was followed using dimethyl methyl-phosphonate (2.51 g, 20.2 mmol), *n*-BuLi 1.12 M (1.36 g, 18.93 mL, 21.2 mmol), and ethyl glycinate (*R*)-**3** (3.0 g, 10.1 mmol), to give 3.21 g, 85% yield, of (*R*)-**4** as a colorless oil. $[\alpha]_D = +28.4$ (*c* 10.2, $CHCl_3$). The spectroscopy data were identical to (*S*)-**4**.

4.5. Ethyl (*S*,*S*)-(−)-*N*,*N*-bis(α-methylbenzyl)glycinate (*S*,*S*)-8

A solution of (*S*,*S*)-(−)-bis(α-methylbenzyl)amine[20] (*S*)-**7** (0.90 g, 3.99 mmol), Na_2CO_3 (1.27 g, 11.98 mmol), and freshly distilled DMPU (60 mL), was treated under a nitrogen atmosphere with ethyl bromoacetate 1.27 g, 1.77 mL (16.0 mmol). The reaction mixture was heated at 95 °C until no starting amine was observed by TLC (8 h). The white suspension was then cooled at room temperature and treated with water until a solution had formed, which was then extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with water (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by column chromatography (hexane–ethyl acetate 90:10) to afford (*S*,*S*)-**8** (0.98 g, 82%) as a colorless oil, $[\alpha]_D = -51.3$ (*c* 6.15, $CHCl_3$), lit.[13b] $[\alpha]_D^{20} = -9.0 \pm 2$ (*c* 0.748, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, $J = 6.8$ Hz, 3H, CH_3CH_2), 1.35 (d, $J = 6.8$ Hz, 6H, CH_3CHPh), 3.18 (d, $J = 17.6$ Hz, 1H, CH_2N), 3.44 (d, $J = 17.6$ Hz, 1H, CH_2N), 3.89–4.01 (m, 2H, CH_2CH_3), 4.10 (q, $J = 6.8$ Hz, 1H, $CH(CH_3)Ph$), 7.20–7.42 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3CH_2), 19.7 (CH_3CHPh), 48.2 ($CHCH_3$), 58.4 (CH_2O), 60.3 (CH_2N), 126.9, 127.8, 128.2, 144.3, 173.5 C=O.

4.6. Ethyl (*R*,*R*)-(+)-*N*,*N*-bis(α-methylbenzyl)glycinate (*R*,*R*)-8

The procedure described above for the (*S*,*S*)-enantiomer was followed using (*R*,*R*)-(+)-bis(α-methylbenzyl)amine (*R*,*R*)-**7** 1.13 g (5.01 mmol), Na_2CO_3 1.59 g (15.04 mmol), DMPU (80 mL), and ethyl bromoacetate 3.35 g, 2.22 mL (20.06 mmol), obtaining 1.26 g, 85% yield of (*R*,*R*)-**8** as colorless oil, $[\alpha]_D = +51.2$ (*c* 5.33, $CHCl_3$), lit.[13b] $[\alpha]_D = +67 \pm 8$ (*c* 0.165, MeOH). The spectroscopy data was identical to (*S*,*S*)-**8**.

4.7. Dimethyl (*S*,*S*)-(−)-3-*N*,*N*-bis(α-methylbenzyl)-amino-2-oxopropylphosphonate (*S*,*S*)-9

A solution of dimethyl methylphosphonate 1.43 g (11.56 mmol) in anhydrous THF (20 mL) was cooled at −78 °C before the slow addition of 0.56 g, 3.61 mL (8.67 mmol) of *n*-BuLi 2.4 M in hexanes. The resulting solution was stirred at −50 °C for 1.5 h, and then the solution cooled at −78 °C and slowly added to a solution of ethyl glycinate (*S*,*S*)-**8** 0.9 g (2.89 mmol) in anhydrous THF (20 mL). The reaction mixture was stirred at −78 °C for 4 h, quenched with aqueous NH_4Cl solution (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine solution (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by column chromatography (ethyl acetate–hexane 70:30) to afford 0.98 g, 87% yield of (*S*,*S*)-**9** as a colorless oil. $[\alpha]_D = -13.7$ (*c* 5.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, $J = 6.8$ Hz, 6H, CH_3CHPh), 2.86 (dd, $J = 22.0$, 14.0 Hz, 1H, CH_2P), 3.28 (dd, $J = 22.0$, 14.0 Hz, 1H, CH_2P), 3.13 (d, $J = 17.2$ Hz, 1H, CH_2N), 3.52 (d, $J = 17.2$ Hz, 1H, CH_2N), 3.67 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.68 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 4.02 (q, $J = 6.8$ Hz, 2H, $CH(CH_3)Ph$), 7.30–7.40 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1 (CH_3CH), 36.6 (d, $J = 129.0$ Hz, CH_2PO), 52.9 (d, $J = 6.0$ Hz, $(CH_3OP)_2$), 53.0 (d, $J = 6.0$ Hz, $(CH_3O)_2P$), 55.7 ($CH(CH_3)Ph$), 60.8 (CH_2N), 127.2, 128.0, 128.4, 143.4, 204.0 C=O. ^{31}P NMR (200 MHz, $CDCl_3$) δ 24.37.

4.8. Dimethyl (*R*,*R*)-(+)-3-*N*,*N*-bis(α-methylbenzyl)-amino-2-oxopropylphosphonate (*R*,*R*)-9

The procedure described above for the (*S*,*S*)-enantiomer was followed using dimethyl methylphosphonate (1.75 g, 14.13 mmol) in anhydrous THF (20 mL), *n*-BuLi 2.4 M in hexanes (0.68 g, 4.42 mL, 10.60 mmol), and ethyl glycinate (*R*,*R*)-**8** (1.1 g, 3.53 mmol) in anhydrous THF (30 mL), obtaining 1.18 g, 86% yield of (*R*,*R*)-**9** as a colorless oil. $[\alpha]_D = +13.7$ (*c* 4.72, $CHCl_3$). The spectroscopy data were identical to (*S*,*S*)-**9**.

4.9. General procedure for the reduction of β-ketophosphonates (*S*)-4, (*R*)-4, (*S*,*S*)-9, and (*R*,*R*)-9 with $NaBH_4$

To a solution of β-ketophosphonates **4** or **9** (1.0 equiv) in methanol or dry THF (20 mL) cooled at 0 °C was added $NaBH_4$ (4.0 equiv). The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated in vacuum, the residue dissolved in water (10 mL), and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude β-hydroxyphosphonates were analyzed by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and then purified by flash chromatography.

4.10. General procedure for the reduction of β-ketophosphonates (*S*)-4, (*R*)-4, (*S*,*S*)-9, and (*R*,*R*)-9 with $LiBH_4$, $Zn(BH_4)_2$, DIBAL-H, and catecholborane

To a solution of β-ketophosphonates **4** or **9** (1.0 equiv) in dry THF (50 mL) cooled at −78 °C was added the hydride (4.0 equiv). The reaction mixture was stirred at −78 °C for 4 h and then quenched with aqueous NH_4Cl solution. The solvent was evaporated in vacuum, the residue dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude β-hydroxyphosphonates were analyzed by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and then purified by flash chromatography.

Reduction of β-ketophosphonate (*S*,*S*)-9 with catecholborane/$LiClO_4$. To a solution of β-ketophosphonate (*S*,*S*)-**9** 140 mg (0.37 mmol), $LiClO_4$ 99 mg (0.93 mmol), and dry THF (20 mL) cooled at −78 °C were added 179 mg, 1.49 mL (1.49 mmol) of catecholborane 1 M in THF. The reaction mixture was stirred at −78 °C for 4 h, and at room temperature for 10 h. The reaction was quenched with aqueous NH_4Cl solution. The solvent was evaporated in vacuum, the residue was dissolved in water (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude β-hydroxyphosphonates were analyzed by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and then purified by flash chromatography (ethyl acetate–hexane 80:20) to afford 128 mg, 89% yield of dimethyl 3-[(*S*,*S*)-*N*,*N*-bis(α-methylbenzylamino)]-(2*R*)-hydroxypropylphosphonate (*R*,*S*,*S*)-**10** as a white solid, mp 115–118 °C, $[\alpha]_D$ = +23.1 (*c* 0.59, $CHCl_3$). NMR ^1H (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 7.0 Hz, 6H, CH_3CHPh), 1.72 (ddd, *J* = 23.2, 15.4, 8.0 Hz, 1H, CH_2P), 1.82 (ddd, *J* = 23.2, 15.4, 4.4 Hz, 1H, CH_2P), 2.46 (dd, *J* = 13.4, 9.2 Hz, 1H, CH_2N), 2.80 (dd, *J* = 13.4, 4.0 Hz, 1H, CH_2N), 3.08 (br, 1H, OH), 3.66 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.68 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.70–3.75 (m, 1H, CHOH), 4.05 (q, *J* = 7.0 Hz, 2H, $CH(CH_3)Ph$), 7.20–7.33 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (CH_3CHPh), 30.5 (d, *J* = 139.7 Hz, CH_2P), 52.3 (d, *J* = 14.4, CH(OH)), 52.4 (d, *J* = 6.0 Hz, $(CH_3O)_2P$), 52.5 (d, *J* = 6.0 Hz, $(CH_3O)_2P$), 57.1 ($CHCH_3$), 63.6 (CH_2N), 127.1 (2C), 127.9 (4C), 128.3 (4C), 144.0 (2C). ^{31}P NMR (400 MHz, $CDCl_3$) δ 33.43. Anal. Calcd for $C_{21}H_{30}NO_4P$: C, 64.43; H, 7.72; N, 3.58%. Found: C, 64.27; H, 7.85; N, 3.44%.

Reduction of β-ketophosphonate (*R*,*R*)-9 with catecholborane/$LiClO_4$. To a solution of β-ketophosphonate (*R*,*R*)-**9** 100 mg (0.26 mmol), $LiClO_4$ 69 mg (0.65 mmol), and dry THF (20 mL) cooled at −78 °C were added 124 mg, 1.1 mL (1.04 mmol) of catecholborane 1 M in THF. The reaction mixture was stirred at −78 °C for 4 h, and at room temperature for 10 h. The reaction was quenched with aqueous NH_4Cl solution. The solvent was evaporated in vacuum and the residue dissolved in water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude β-hydroxyphosphonates were analyzed by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and then purified by flash chromatography to afford 88 mg, 87% yield of dimethyl 3-[(*R*,*R*)-*N*,*N*-bis(α-methylbenzylamino)]-(2*S*)-hydroxypropylphosphonate (*S*,*R*,*R*)-**11** as a white solid, mp 115–117 °C, $[\alpha]_D$ = −22.6 (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}NO_4P$: C, 64.43; H, 7.72; N, 3.58%. Found: C, 64.11; H, 7.63; N, 3.47%. The spectroscopy data was identical to (*R*,*S*,*S*)-**8**.

(*R*)-3-Amino-2-hydroxypropylphosphonic acid 2. Dimethyl 3-[(*S*,*S*)-*N*,*N*-bis(α-methylbenzylamino)]-(2*R*)-hydroxypropylphosphonate (*R*,*S*,*S*)-**10** (228 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) was treated under a nitrogen atmosphere with 178 mg, 0.15 mL (1.16 mmol) of bromotrimethylsilane. The reaction mixture was stirred at room temperature for 6 h, and after this period of time the volatiles materials were removed under reduced pressure, and water was added. After 4 h under stirring, the solvents were removed in vacuum to give 3-[(*S*,*S*)-*N*,*N*-bis(α-methylbenzylamino)]-(2*R*)-hydroxypropylphosphonic acid, which without isolation was treated with palladium hydroxide on carbon 22 mg (20 wt%) in methanol (20 mL) and five drops of (20%) HCl/*i*PrOH and stirred for 48 h under hydrogen gas at 60 °C and 60 psi. The mixture was filtered through a pad of Celite, and the solvent were removed under reduced pressure. The residue was treated with propylene oxide (3 mL) to afford 63 mg, 70% yield of (*S*)-3-amino-2-hydroxypropylphosphonic acid **2**, as a white solid. Mp 175–178 °C, $[\alpha]_D$ = +11.1 (*c* 1.49, H_2O). The spectroscopy data were identical to those we reported.[11]

(*S*)-3-Amino-2-hydroxypropylphosphonic acid 2. The procedure described above for the (*R*)-enantiomer, was followed using dimethyl 3-[(*R*,*R*)-*N*,*N*-bis(α-methylbenzyl)]amino-(2*S*)-hydroxy-propylphosphonate (*S*,*R*,*R*)-**11** (222 mg, 0.57 mmol), CH_2Cl_2 (5 mL), and bromotrimethylsilane 174 mg, 0.15 mL (1.13 mmol). The crude product was treated with palladium hydroxide on carbon 22 mg (20 wt%) in methanol (20 mL) and five drops of (20%) HCl/*i*PrOH and stirred for 48 h under hydrogen gas at 60 °C and 60 psi obtaining 64 mg, 74% yield of (*S*)-3-amino-2-hydroxypropylphosphonic acid **2**, as a white solid. Mp 176–178 °C, $[\alpha]_D$ = −10.7 (*c* 1.87,

H_2O). The spectroscopy data was identical to that we reported.[11]

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17. For the assignment of absolute configuration of β-hydroxyphosphonates by NMR see Ref. 11.
18. X-ray crystal data of (*R*,*S*,*S*)-**10** were collected at 298 K using a Bruker APEX CCD instrument (Mo Kα 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 nonhydrogen atoms were refined anisotropically. Compound (*R*,*S*,*S*)-**10**: $C_{21}H_{30}NO_4P$, $M = 491.19$, monoclinic space group $P2_1/c$, $a = 12.145(3)$, $b = 19.419(5)$, $c = 9.464(2)$ Å, $\beta = 107.314(4)°$, $V = 2130.9(9)$ Å^3, $Z = 4$, $D_c = 1.217$ g cm^{-1}, 19,383 reflections measured, 3753 unique ($R_{int} = 0.0787$), which were used in all calculations, final R values were 0.0706 [$F > 4\sigma(F)$] and 0.0830 (all data). CCDC No. 235222.
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