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Preparation of Phosphostatine Analogues From L-amino acids

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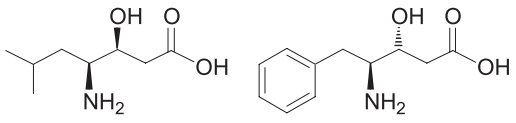
Abstract. Reduction of (3*S*)-*N,N*-dibenzylamino-2-ketophosphonates **9a-d** derived from L-amino acids was carried out with catecholborane at -20 ºC to afford the (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxy-phosphonates *syn*-**10a-d**, whereas the reduction of (3*S*)-*N*-benzylamino-2-ketophosphonates **13a-d** with $Zn(BH_4)_2$ at -78 ºC yield (3*S*)-*N*-benzylamino-(2*S*)-hydroxyphosphonates *anti*-**14a-d**. The reduction in both cases was in good chemical yields and with high diastereoselectivity. The hydrolysis and hydrogenolysis of **10a-d** and **14a-d** afford the (3*S*)-amino-(2*R*)-hydroxyphosphonic acids **6** and (3*S*)-amino-(2*S*)-hydroxyphosphonic acids **7**, respectively, which are analogues of phosphostatine.
Keywords: Phosphostatine, aminophosphonic acids, β-ketophosphonates, diastereoselective reduction.

Resumen. La reducción de (3*S*)-*N,N*-dibencilamino-2-cetofosfonatos **9a-d** preparados a partir de L-aminoácidos se llevó a cabo con catecolborano a -20 ºC, obteniendo los (3*S*)-*N,N*-dibencilamino-(2*R*)-hidroxifosfonatos *syn*-**10a-d**, mientras que la reducción de los (3*S*)-*N*-bencilamino-2-cetofosfonatos **13a-d** con $Zn(BH_4)_2$ a -78 ºC produce los (3*S*)-*N*-bencilamino-(2*S*)-hidroxifosfonatos *anti*-**14a-d**. La reducción en ambos casos procede con buen rendimiento químico y con una alta diastereoselectvidad. La hidrólisis e hidrógenolisis de los hidroxifosfonatos **10a-d** y **14a-d** proporciona a los ácidos (3*S*)-amino-(2*R*)-hidroxi-fosfónicos **6** y (3*S*)-amino-(2*S*)-hidroxifosfónicos **7**, respectivamente, los cuales son análogos de la fosfoestatina.
Palabras clave: Fosfoestatina, ácidos aminofosfónicos, β-cetofosfonatos, reducción diasteroselectiva.

Introduction

(4*S*)-Amino-(3*S*)-hydroxy-6-methylheptanoic acid (Statine) **1**, a nonproteinogenic amino acid, is a key component of pepstatin, a natural hexapeptide antibiotic isolated by Umezawa and coworkers from various species of actinomices [1]. Additionally, (-)-statine **1** has attracted a lot of interest because of its potential use in the treatment of hypertension, congestive heart failure, malaria and Alzheimer's disease. For these reasons, many synthetic routes toward statine **1** and their analogues **2-4** have been developed [2].


(-)-Statine **1**

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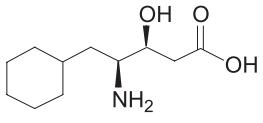
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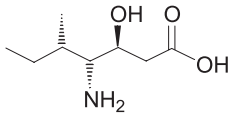
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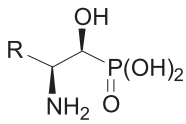
On the other hand, phosphonates and phosphinates functionalized with amino and hydroxy groups have attracted considerably attention in recent years for their role in biologically relevant processes such as inhibition of rennin and HIV protease, human calpain I and their use as haptens in the development of catalytic antibodies [3]. In particular, the esters of γ-amino-β-hydroxyphosphonic acids **5** and **6** have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis [4]. Additionally, the esters of the phosphonic acids **5**, **6** and their analogues have been used as inhibitors of D-alanine:D-alanine ligase [5], and as excellent Leu^{10}-Val^{11} replacements (LVRs) in the angiotensin II, providing a more potent inhibitory activity for rennin over porcine pepsin and bovine cathepsin D [6]. As result, numerous synthetic methods for chiral non-racemic β-amino-α-hydroxyphosphonic acid **5** have been developed [7]. However, to the best of our knowledge, only a few synthetic approaches to obtain optically active esters of 3-amino-2-hydroxyphosphonic acid **6** have been described in the literature, which involve the reaction of the anion of methylphosphonate with α-aminoaldehydes [5,6], and the catalytic asymmetric aminohydroxylation of β,γ-unsaturated phosphonates, [7f] but in both methodologies the yields and diastereoselectivities remain low. Recently, Yokomatsu *et al.* [8] described the synthesis of 3-amino-2-hydroxyphosphonates with an improved diastereoselectivity *via* the dihydroxylation of β,γ-unsaturated phosphonates and the subsequent regioselective amination of their cyclic sulfates.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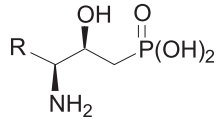
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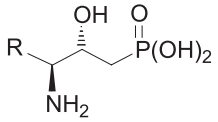
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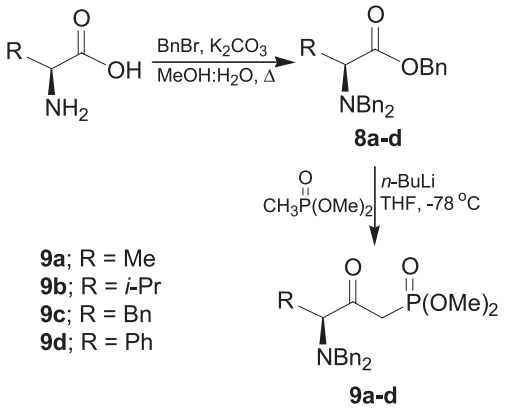
As part of our program directed to the synthesis of chiral 3-amino-2-hydroxyphosphonic acids [9], herein we describe a methodology that affords (3*S*)-amino-(2*R*)-hydroxyphosphonic acids **6a-d** and (3*S*)-amino-(2*S*)-hydroxyphosphonic acids **7a-d**, *via* a highly diastereoselective reduction of dimethyl (3*S*)-*N,N*-dibenzylamino- and (3*S*)-*N*-benzylamino-2-ketophosphonates derived from L-amino acids.

Results and Discussion

(3*S*)-*N,N*-Dibenzylamino-2-ketophosphonates **9a-d** were synthesized in two steps from L-amino acids (Scheme 1). Thus, the first step of the synthesis was the tribenzylation of L-amino acids with excess of benzyl bromide and K_2CO_3 under reflux in a mixture of MeOH:H_2O, to give the corresponding benzyl *N,N*-dibenzylamino esters **8a-d** [10]. Then, the resulting benzyl esters **8a-d** were treated with the lithium salt of dimethyl methylphosphonate at -78 °C in THF to obtain the (3*S*)-*N,N*-dibenzylamino-2-ketophosphonates **9a-d**. (Scheme 1) [11].

Having efficiently prepared the 2-ketophosphonates **9a-d**, initially we carried out their reduction with $BH_3.SMe_2$, $NaBH_4$, DIBAL-H and catecholborane, to obtain the 3-*N,N*-dibenzylamino-2-hydroxyphosphonates **10** and **11**.

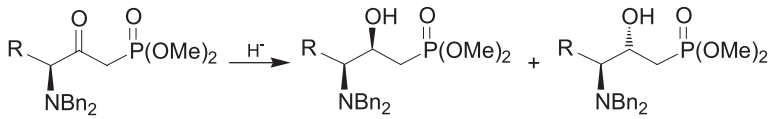


Scheme 1

Conditions, yields and diastereomeric excess are summarized in the Table 1 [12].

As shown in Table 1, the reduction of (3*S*)-*N,N*-dibenzylamino-2-ketophosphonates **9** with catecholborane in THF at -20 °C (entries 4-7) afforded the (3*S*)-*N,N*-dibenzylamino-2-hydroxyphosphonates *syn*-**10** and *anti*-**11** with good chemicals yields and excellent diastereoselectivity in favor of diastere-

Table 1. The Reduction of 2-Ketophosphonates 9a-d with Various Reducing Agents.



entry	R	Hidride	Conditions	Yield (%)[a]	*syn*-**10**:*anti*-**11**[b]
1	*i*-Pr	$NaBH_4$	MeOH, 0 °C	97	85:15
2	*i*-Pr	DIBAL-H	THF, -78 °C	50	82:18
3	*i*-Pr	$BH_3.SMe_2$	THF, -20 °C	[c]	[c]
4	Me	Catecholborane	THF, -20 °C	89	>98:2
5	*i*-Pr	Catecholborane	THF, -20 °C	85	>98:2
6	Bn	Catecholborane	THF, -20 °C	89	>98:2
7	Ph	Catecholborane	THF, -20 °C	82	90:10
8	*i*-Pr	DIBAL/$ZnCl_2$[d]	THF, -78 °C	66	78:22
9	*i*-Pr	$LiBH_4$	THF, -78 °C	92	78:22
10	*i*-Pr	$LiBH_4$/LiCl[d]	THF, -78 °C	94	78:22
11	*i*-Pr	L-selectride	THF, -78 °C	76	80:20
12	Me	$Zn(BH_4)_2$	THF, -78 °C	85	80:20
13	*i*-Pr	$Zn(BH_4)_2$	THF, -78 °C	87	90:10
14	Bn	$Zn(BH_4)_2$	THF, -78 °C	76	91:09
15	Ph	$Zn(BH_4)_2$	THF, -78 °C	77	75:25

[a]Chemical yield was determined after purification by column chromatography
[b]Determined by ^1H NMR at 400 MHz and ^{31}P NMR at 81 MHz
[c]The reaction does not proceed
[d] The reduction was carried out in presence of 2 and 6 equiv. of LiCl or $ZnCl_2$.

omer *syn*-**10**. Diastereomeric ratio of the reduction of **9** were determinated by means of ^{1}H and ^{31}P NMR. In fact, in ^{31}P NMR the signal for the diastereomers *syn*-**10** was more shielded that the diastereomers *anti*-**11**. The absolute configuration of the new stereogenic center in the 2-hydroxyphosphonates *syn*-**10** were assigned by analogy with other 2-hydroxyphosphonates reported in the literature [7f] and confirmed by X-ray crystal structure of the diastereomers *syn*-**10c** and *syn*-**10d** [12].

Therefore, we propose that the reduction of **9** with catecholborane took place under non-chelation control or a Felkin-Ahn model [13], and that the bulkiness of the *N,N*-dibenzylamino group is sufficient to simultaneously limit the rotamer populations around the hinge bounds adjacent to the carbonyl group blocking the *re* face of carbonyl group, thereby allowing the addition of hydride to take in a diastereoselective manner (Figure 1a). This diastereofacial preference is in agreement with that reported previously for the reduction of 1-aminoalkylchloromethyl ketones [14], for the reductive amination of α-amino ketones [15], and reduction of 1-aminoalkyl-chloromethyl ketimines [16].

In order to induce a chelation control in the reduction of 2-ketophosphonates **9a-d**, we decided used now additives as LiCl or $ZnCl_2$ and other reducing agents such as $LiBH_4$ and $Zn(BH_4)_2$ in such a way that the metal ions do bind sufficiently strongly to the *N,N*-dibenzylamino and keto groups to produce chelation control (Figure 1b) and thus obtain the 2-hydroxyphosphonates *anti*-11. However, the results shown that the metal ions of the reducing agents $LiBH_4$, DIBAL, L-selectride and $Zn(BH_4)_2$ (Table 1, entries 8-15) not bind sufficiently strongly to the *N,N*-dibenzylamino and keto groups to produce chelation control (Figure 1b).

In order to induce a chelation control in the reduction and obtain the *anti*-3-amino-2-hydroxyphosphonates, we decided to carried out the preparation and reduction of (3*S*)-*N*-benzylamino-2-ketophosphonates **13a-d**. Thus, the starting *N*-benzyl methyl esters **12a-d** were prepared by treatment of the corresponding amino methyl ester hydrochloride with benzyl bromide and K_2CO_3 in acetonitrile at room temperature. Then, the methyl esters **12a-e** were treated with the lithium salt of dimethyl methylphosphonate at -78 ºC in THF to afford the (3*S*)-*N*-benzylamino-2-ketophosphonates **13a-d** (Scheme 2), that without any further purification was used in the next step.

Having efficiently prepared the 2-ketophosphonates **13a-d**, we turned our attention to the diastereoselective reduction to obtain the 3-*N*-benzylamino-2-hydroxyphosphonates **14** and **15**. Again, the reduction was carried out with a variety of reducing agents and conditions. Yields and diastereomeric excess are summarized in the Table 2 [17].

From the results summarized in Table 2, it can be seen that the reduction of **13b** with $LiBH_4/ZnCl_2$ at -78 ºC (entry 8) the corresponding β-hydroxyphosphonates were obtained with high diastereoselectivity and with a predominance of the desired *anti* product. However, under these conditions the reaction was not completed, in spite of using excess of $LiBH_4$ and a long reaction time. On the other hand, best results were obtained when the reduction of **13a-d** was carried out using $Zn(BH_4)_2$ at -78 ºC in THF (entries 9-12), where the corresponding 3-*N*-benzylamino-2-hydroxyphosphonates *anti*-**14** and *syn*-**15** were obtained in high diastereoselectivity and good chemical yield, with a predominance of the desired *anti* product. The diastereomeric excess of the reduction of **13a-d** was determined by means of ^{1}H and ^{31}P NMR. In fact, the signals in ^{31}P NMR for the diastereomers *syn*-**15** were more shielded that for the diastereomers *anti*-**14**. The assignment of the absolute configuration of the new stereogenic center in the diastereomer *anti*-**14** was established by chemical correlation [18].

Therefore these results strongly suggest that the reduction of **13** took place predominantly under chelation control, where an acid-base reaction between the NH proton and $Zn(BH_4)_2$ takes place, with molecular hydrogen evolution, while the zinc ion coordinates with the oxygen of the carbonyl group (Figure

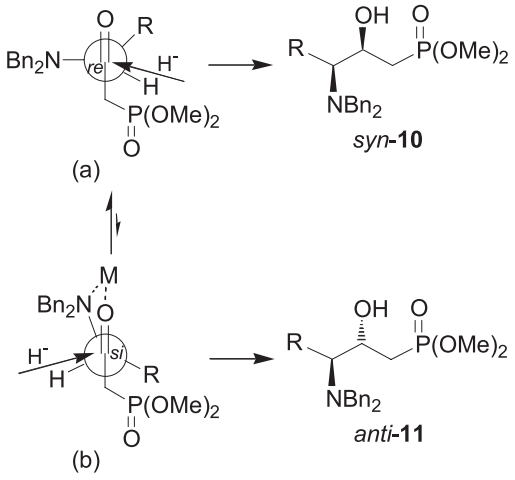
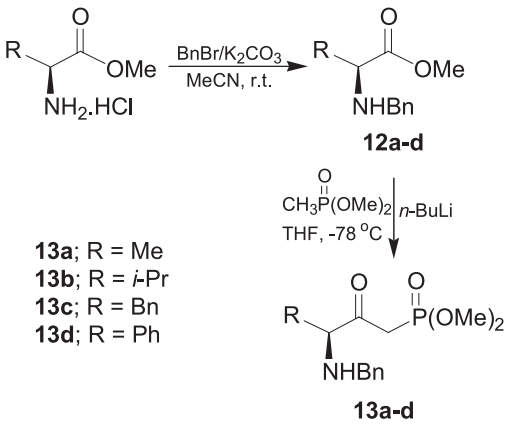
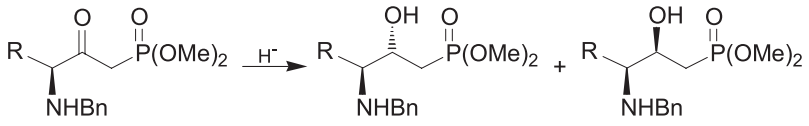


Fig. 1. Reduction of 2-ketophosphonates 9a-d: (a) non-chelation control, (b) chelation control.



Scheme 2

Table 2. The Reduction of 2-Ketophosphonates **13a-d** with Various Reducing Agents.



13a-d *anti*-**14a-d** *syn*-**15a-d**

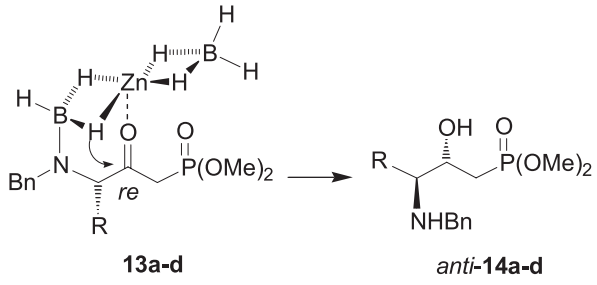
entry	R	Hydride	Conditions	Yield (%)[a]	*syn*-**14**:*anti*-**15**[b]
1	*i*-Pr	DIBAL-H	THF, -78 ºC	d	d
2	Me	$NaBH_4$	MeOH, 0 ºC	86	46:54
3	*i*-Pr	$NaBH_4$	MeOH, 0 ºC	70	85:15
4	Bn	$NaBH_4$	MeOH, 0 ºC	65	55:45
5	Ph	$NaBH_4$	MeOH, 0 ºC	75	63:37
6	*i*-Pr	Catecholborane	THF, -20 ºC	70	79:21
7	*i*-Pr	$LiBH_4$	THF, -78 ºC	78	79:21
8	*i*-Pr	$LiBH_4$/ $ZnCl_2$[a]	THF, -78 ºC	50	91:9
9	Me	$Zn(BH_4)_2$	THF, -78 ºC	88	67:33
10	*i*-Pr	$Zn(BH_4)_2$	THF, -78 ºC	85	96:04
11	Bn	$Zn(BH_4)_2$	THF, -78 ºC	70	96:04
12	Ph	$Zn(BH_4)_2$	THF, -78 ºC	80	88:12

[a] The reduction was carried out in presence of 1 equiv. of $ZnCl_2$.
[b] Chemical yield was determined after purification by column chromatography.
[c] Determined by ^1H NMR at 400 MHz and ^{31}P NMR at 81 MHz.
[d] The reaction does not proceed

2) [17]. The reducing agent is more tightly bound to the substrate, so hydrogen transfer takes place intramolecularly in a more rigid structure which is dependent of the steric demand placed upon the increasing size of the R group at C-3.

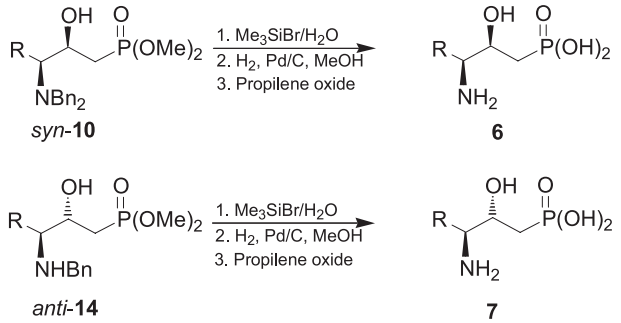
In order to illustrate the usefulness of this method, the compounds *syn*-**10a-d** and *anti*-**14a-d** were converted to the phosphostatine **6** and phosphoepistatine **7** analogues, respectively (Scheme 3). Thus, the hydrolysis of 2-hydroxypropylphosphonates *syn*-**10a-d** and *anti*-**14a-d** with bromotrimethylsilane at room temperature [9] afforded the 2-hydroxypropylphosphonic acid in quantitative yield, that without any further purification was treated with palladium on carbon in methanol under hydrogen gas atmosphere at room temperature, obtaining the phosphostatine **6** and phosphoepistatine **7**, respectively, in good chemical yield.

In summary, the conditions described in this paper make this experimental operation a good and simple method to obtain the (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxyphosphonates **10** and (3*S*)-*N*-benzylamino-(2*S*)-hydroxyphosphonates **14** in a high diastereoselective fashion, compounds which can been used in the preparation of phosphostatine **6** and phosphoepistatine **7** analogues.



13a-d *anti*-**14a-d**

Fig. 2. π-Facial selectivity in the reduction reaction of 2-ketophosphonates **13a-d** with $Zn(BH_4)_2$.



syn-**10** **6**

anti-**14** **7**

Esquema 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) was used. ^{1}H NMR spectra were recorded on a Varian INOVA 400 (400 MHz), ^{13}C NMR (100 MHz) and ^{31}P NMR on a Varian Mercury 200 instruments at 81 MHz. The spectra were recorded in D_2O or $CDCl_3$ solution, using TMS as internal reference. HRMS spectra were recorded on a JEOL JMS-700.

Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 ºC and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.

General procedure for the preparation of benzyl *N,N*-dibenzylaminoacids 8a-d. A solution of benzyl bromide (4 equiv) and methanol (40 mL) was slowly added to solution of the L-amino acid (1 equiv) and K_2CO_3 (3.5 equiv) in a 5:1 mixture of methanol-water (250 mL). The reaction mixture was refluxed for 14 h. Then, the solvent was evaporated under reduced pressure and water was added to the residue, and the resulting mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude products were purified by flash chromatography using hexane:AcOEt (20:1) as eluent. Physical properties are identical to those described in the literature [10].

General procedure for the preparation of (3*S*)-*N,N*-dibenzylamino-2-ketophosphonates 9a-d [11]. A solution of dimethyl methylphosphonate (3.5 equiv) in anhydrous THF (45 mL) was cooled at -78 ºC before the slow addition of *n*-BuLi 2.5 M in hexanes (3.5 equiv). The resulting solution was stirred at -50 ºC for 1.5 h and then cooled to -78 ºC. To this mixture was slowly added a solution of benzyl ester **8** (1 equiv) in dry THF (45 mL). The reaction mixture was stirred at -78 ºC for 4 h before the addition of a saturated solution of NH_4Cl. The solvent was evaporated under reduced pressure, the residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude 2-ketophosphonates were purified by flash chromatography using hexane:ethyl acetate (50:50) as eluent.

Dimethyl (3*S*)-*N,N*-dibenzylamino-2-oxobuthylphosphonate 9a. The reaction was carried out using dimethyl methylphosphonate (3.14 g, 25.3 mmol) in anhydrous THF (40 mL), *n*-BuLi 2.4 M in hexanes (10.8 mL, 26 mmol), benzyl *N,N*-dibenzylaminoacid ester **8a** (2.6 g, 7.2 mmol) in anhydrous THF (45 mL) following the general procedure. The crude product was purified by column chromatography using hexane:ethyl acetate (50:50) to give **9a** as a viscous liquid 2.6 g, 96% yield. $[\alpha]_D$ = -7.6 (c = 3.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.8 Hz, 3H, CH_3CH), 2.99 (dd, J = 21.8, 14.4 Hz, 1H, CH_2P), 3.42 (AB system, J = 13.6 Hz, 2H, CH_2Ph), 3.52 (q, J = 6.8 Hz, 1H, $CHNBn_2$), 3.54 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.67 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.67 (AB system, J = 13.6 Hz, 2H, CH_2Ph), 3.75 (dd, J = 21.8, 14.4 Hz, 1H, CH_2P), 7.25-7.35 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.5 (CH_3CH), 36.9 (d, J = 130.6 Hz, CH_2P), 52.9 (d, J = 6.0 Hz, $(CH_3O)_2P$), 53.0 (d, J = 6.0 Hz, $(CH_3O)_2P$), 54.9 (CH_2Ph), 62.9 (d, J=2.2 Hz, $CHNBn_2$), 127.6, 128.7, 129.2, 138.9, 203.5 (d, J = 6.6 Hz, C=O). ^{31}P NMR (81 MHz, $CDCl_3$) δ 24.87. HRMS (CI^+, CH_4) calcd. for $C_{20}H_{27}NO_4P$ (MH^+) 376.1678 found 376.1685.

Dimethyl (3*S*)-*N,N*-dibenzylamino-4-methyl-2-oxopenthylphosphonate 9b. The reaction was carried out using dimethyl methylphosphonate (2.91 g, 23.5 mmol) in anhydrous THF (40 mL), *n*-BuLi 2.4 M in hexanes (10.1 mL, 24.2 mmol), benzyl *N,N*-dibenzylaminoacid ester **8b** (2.6 g, 6.7 mmol) in anhydrous THF (45 mL) following the general procedure. The crude product was purified by column chromatography using hexane:ethyl acetate (50:50) to give **9b** as a viscous liquid 2.6 g, 96% yield. $[\alpha]_D$ = -224.4 (c = 1.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3H, $(CH_3)_2CH$), 1.15 (d, J = 6.6 Hz, 3H, $(CH_3)_2CH$), 2.29-2.39 (m, 1H, $CH(CH_3)_2$), 2.89 (dd, J = 21.6, 14.4 Hz, 1H, CH_2P), 3.10 (dd, J = 21.6, 14.4 Hz, 1H, CH_2P), 3.17 (d, J = 10.4 Hz, 1H, $CHNBn_2$), 3.62 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.69 (AB system, J = 13.6 Hz, 2H, CH_2Ph), 3.70 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.87 (AB system, J=13.6 Hz, 2H, CH_2Ph), 7.23-7.36 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 ($(CH_3)_2CH$), 20.8 ($(CH_3)_2CH$), 27.0 ($CH(CH_3)_2$), 41.1 (d, J = 129.8 Hz, CH_2P), 52.8 (d, J = 6.0 Hz, $(CH_3O)_2P$), 52.9 (d, J = 6.0 Hz, $(CH_3O)_2P$), 54.5 (CH_2Ph), 70.9 ($CHNBn_2$), 127.4, 128.6, 129.2, 139.4, 201.1 (d, J = 6.1 Hz, C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 24.18. HRMS (CI^+, CH_4) calcd. for $C_{22}H_{31}NO_4P$ (MH^+) 404.1991 found 404.1885.

Dimethyl (3*S*)-*N,N*-dibenzylamino-4-phenyl-2-oxobuthylphosphonate 9c. The reaction was carried out using dimethyl methylphosphonate (2.59 g, 20.9 mmol) in anhydrous THF (40 mL), *n*-BuLi 2.4 M in hexanes (9.0 mL, 21.5 mmol), benzyl *N,N*-dibenzylaminoacid ester **8c** (2.6 g, 5.97 mmol) in anhydrous THF (45 mL) following the general procedure. The crude product was purified by column chromatography using hexane:ethyl acetate (50:50) to give **9c** as a viscous liquid 2.5 g, 91% yield. $[\alpha]_D$ = -83.2 (c = 3.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (dd, J = 13.2, 3.6, Hz, 1H, CH_2CH), 2.95 (dd, J = 22.2, 14.0 Hz, 1H, CH_2P), 3.17 (dd, J = 13.2, 9.6 Hz, 1H, CH_2CH), 3.25 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.45 (d, J = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.47 (dd, J = 22.2, 14.0 Hz, 1H, CH_2P), 3.53 (AB system, J = 13.6 Hz, 2H, CH_2Ph), 3.72 (dd, J = 9.6, 3.6 Hz, 1H, $CHNBn_2$), 3.82 (AB system, J = 13.6 Hz, 2H, CH_2Ph), 7.14-7.36 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (CH_2CH), 38.5 (d, J = 129.1 Hz, CH_2P), 52.6 (d, J = 6.6 Hz, $(CH_3O)_2P$), 52.9 (d, J = 6.6 Hz, $(CH_3O)_2P$), 54.9 (CH_2Ph), 68.8 ($CHNBn_2$), 126.2, 127.7, 128.5, 128.8, 129.3, 129.8, 139.0, 139.3, 200.6 (d, J = 6.6 Hz, C=O). ^{31}P NMR (81 MHz, $CDCl_3$) δ 23.56. HRMS (CI^+, CH_4) calcd. for $C_{26}H_{31}NO_4P$ (MH^+) 452.1991 found 452.2074.

Dimethyl (3*S*)-*N,N*-dibenzylamino-3-phenyl-propylphosphonate 9d. The reaction was carried out using dimethyl methylphosphonate (2.68 g, 21.6 mmol) in anhydrous THF (40 mL), *n*-BuLi 2.4 M in hexanes (9.25 mL, 22.2 mmol), benzyl *N,N*-dibenzylaminoacid ester **8d** (2.6 g, 6.17 mmol) in anhydrous THF (45 mL) following the general procedure. The crude product was purified by column chromatography using hexane:ethyl acetate (50:50) to give **9d** as a viscous liquid 2.39 g, 89% yield. $[\alpha]_D$ = +0.22 (c = 3.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (dd, *J* = 22.0, 14.8 Hz, 1H, CH_2P), 3.19 (dd, *J* = 22.0, 14.8 Hz, 1H, CH_2P), 3.44 (AB system, *J* = 14.0 Hz, 2H, CH_2Ph), 3.60 (d, *J* = 11.4 Hz, 3H, $(CH_3O)_2P$), 3.67 (d, *J* = 11.4 Hz, 3H, $(CH_3O)_2P$), 3.89 (AB system, *J* = 14.0 Hz, 2H, CH_2Ph), 4.68 (s, 1H, $CHNBn_2$), 7.21-7.44 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.8 (d, *J* = 130.5 Hz, CH_2P), 52.9 (d, *J* = 6.2 Hz, $(CH_3O)_2P$), 53.0 (d, *J* = 6.2 Hz, $(CH_3O)_2P$), 54.5 (CH_2Ph), 73.2 ($CHNBn_2$), 127.3, 128.5, 128.6, 128.9, 129.1, 130.6, 133.8, 139.5, 201.8 (d, *J* = 6.6 Hz, C=O). ^{31}P NMR (81 MHz, $CDCl_3$) δ 23.97. HRMS (CI^+, CH_4) calcd. for $C_{25}H_{29}NO_4P$ (MH^+) 438.1804 found 418.1804.

General procedure for the reduction of dimethyl (3*S*)-*N,N*-dibenzylamino-2-ketophosphonates 9a-d. A solution of 2-ketophosphonate **9a-d** (1 equiv) in anhydrous THF (40 mL) was cooled at -78 °C before the slow addition of catecholborane 1 M in THF (4 equiv). The reaction mixture was stirred at -20 °C for 4 h and at room temperature for 3 h and quenched by the addition of a saturated aqueous solution of NH_4Cl (4 mL). The solvent was evaporated under reduced pressure, the residue was dissolved in water (40 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude 2-hydroxyphosphonates were analyzed by ^{1}H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and then purified by flash chromatography using hexane:AcOEt (1:2) as eluent.

Dimethyl (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxy-buthylphosphonate 10a. The reaction was carried out starting from 2-ketophosphonate **9a** (1.0 g, 2.7 mmol) in dry THF (40 mL) and chatecolborane 1M in THF (10.7 mL, 10.7 mmol) following the general procedure, to afford 850 mg, 85% yield of *syn*-**10a**. $[\alpha]_D$ = +12.6 (c = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.8 Hz, 3H, CH_3), 1.71 (ddd, *J* = 16.4, 15.2, 9.6 Hz, 1H, CH_2P), 1.91 (ddd, *J* = 20.8, 15.2, 2.4 Hz, 1H, CH_2P), 2.61 (dq, *J* = 9.2, 6.4 Hz, 1H, $CHNBn_2$), 3.31 (AB system, *J* = 13.2 Hz, 2H, CH_2Ph), 3.69 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.75 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.84 (AB system, *J* = 13.2 Hz, 2H, CH_2Ph), 3.87 (dd, *J* = 12.0, 9.6, 2.4 Hz, 1H, CHOH), 7.25-7.33 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3 (CH_3), 30.4 (d, *J* = 141.5 Hz, CH_2P), 52.4 (d, *J* = 5.9 Hz, $(CH_3O)_2P$), 52.8 (d, *J* = 5.9 Hz, $(CH_3O)_2P$), 53.7 (CH_2Ph), 59.1 (d, *J* = 18.3 Hz, CHOH), 67.1 (d, *J* = 6.6 Hz, $CHNBn_2$), 127.5, 128.7, 129.3, 138.9. ^{31}P NMR (81 MHz, $CDCl_3$) δ 33.74.

Dimethyl (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxy-4-methylpenthylphosphonate 10b. The reaction was carried out starting from 2-ketophosphonate **9b** (1.0 g, 2.48 mmol) in dry THF (40 mL) and chatecolborane 1 M in THF (9.9 mL, 9.91 mmol) following the general procedure, to afford 895 mg, 89% yield of *syn*-**10b**. $[\alpha]_D$ = -77.3 (c = 3.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 7.0 Hz, 3H, $(CH_3)_2CH$), 1.11 (d, *J* = 7.0 Hz, 3H, $(CH_3)_2CH$), 1.54 (ddd, *J* = 20.0, 15.2, 1.6 Hz, 1H, CH_2P), 1.93 (ddd, *J* = 15.2, 15.2, 10.4 Hz, 1H, CH_2P), 2.24 (dd, *J* = 6.4, 5.2 Hz, 1H, $CHNBn_2$), 2.28-2.36 (m, 1H, $CH(CH_3)_2$), 3.56 (AB system, *J* = 13.0 Hz, 2H, CH_2Ph), 3.70 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.73 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 4.01 (AB system, *J* = 13.0 Hz, 2H, CH_2Ph), 4.10-4.17 (m, 1H, CHOH), 7.21-7.32 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 ($(CH_3)_2CH$), 23.6 ($(CH_3)_2CH$), 26.9 ($CH(CH_3)_2$), 31.5 (d, *J* = 138.6 Hz, CH_2P), 52.4 (d, *J* = 6.6 Hz, $(CH_3O)_2P$), 52.6 (d, *J* = 6.6 Hz, $(CH_3O)_2P$), 55.4 (CH_2Ph), 65.3 (d, *J* = 5.8 Hz, $CHNBn_2$), 67.2 (d, *J* = 18.3 Hz, CHOH), 127.3, 128.5, 129.7, 139.9. ^{31}P NMR (81 MHz, $CDCl_3$) δ 34.91.

Dimethyl (3*S*)-*N,N*-dibenzylamino-4-phenyl-(2*R*)-hydroxy-buthylphosphonate 10c. The reaction was carried out starting from 2-ketophosphonate **9c** (1.0 g, 2.2 mmol) in dry THF (40 mL) and chatecolborane 1 M in THF (8.9 mL, 8.9 mmol) following the general procedure, to afford 890 mg, 88% yield of *syn*-**10c** as a white solid, mp 129-130 °C. $[\alpha]_D$ = +15.0 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (ddd, *J* = 20.0, 15.2, 1.6 Hz, 1H, CH_2P), 1.97 (ddd, *J* = 15.2, 15.2, 10.0 Hz, 1H, CH_2P), 2.74-2.79 (m, 1H, CHN), 2.86 (dd, *J* = 13.6, 8.4 Hz, 1H, CH_2CHNBn_2), 3.13 (dd, *J* = 13.6, 5.2 Hz, 1H, CH_2CHNBn_2), 3.42 (AB system, *J* = 13.2 Hz, 2H, CH_2Ph), 3.59 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.69 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.88-3.96 (m, 1H, CHOH), 4.06 (AB system, *J* = 13.2 Hz, 2H, CH_2Ph), 7.20-7.33 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7 (d, *J* = 138.2 Hz, CH_2P), 31.3 (CH_2CHNBn_2), 52.4 (d, *J* = 7.0 Hz, $(CH_3O)_2P$), 52.6 (d, *J* = 7.0 Hz, $(CH_3O)_2P$), 54.7 (NCH_2Ph), 64.2 (d, *J* = 18.2 Hz, CHOH), 66.5 (d, *J* = 6.1 Hz, $CHNBn_2$), 126.4, 127.3, 128.5, 128.8, 129.1, 129.4, 139.3, 140.1. ^{31}P NMR (81 MHz, $CDCl_3$) δ 34.88.

Dimethyl (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxy-3-phenyl-propylphosphonate 10d. The reaction was carried out starting from 2-ketophosphonate **9d** (1.0 g, 2.3 mmol) in dry THF (40 mL) and chatecolborane 1 M in THF (8.2 mL, 9.2 mmol) following the general procedure, to afford 820 mg, 82%, yield of *syn*-**10d** as a white solid, mp 115-117 °C. $[\alpha]_D$ = +3.5 (c = 2.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (ddd, *J* = 15.2, 15.2, 8.8 Hz, 1H, CH_2P), 1.64 (ddd, *J* = 20.0, 15.2, 2.4 Hz, 1H, CH_2P), 3.02 (AB system, *J* = 13.4 Hz, 2H, CH_2Ph), 3.51 (d, *J* = 10.4 Hz, 1H, $CHNBn_2$), 3.65 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.73 (d, *J* = 11.0 Hz, 3H, $(CH_3O)_2P$), 3.96 (AB system, *J* = 13.4 Hz, 2H, CH_2Ph), 4.57-4.65 (m, 1H, CHOH), 7.20-7.47 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (d, *J* = 142.7 Hz, CH_2P), 52.3 (d, *J* = 6.0 Hz, $(CH_3O)_2P$),

52.8 (d, J = 6.0 Hz, $(CH_3O)_2P$), 53.8 (CH_2Ph), 64.0 (d, J = 6.0 Hz, $CHNBn_2$), 68.5 (d, J = 21.3 Hz, CHOH), 127.6, 128.5, 128.8, 128.8, 129.3, 130.1, 133.2, 138.6. ^{31}P NMR (200 MHz, $CDCl_3$) δ 33.62.

General procedure for the preparation of *N*-benzylamino methyl esters 12a-d. Benzyl bromide (1.0 equiv) was slowly added to a solution of α-amino acid methyl ester hydrochloride (1 equiv) and K_2CO_3 (2.5 equiv) in acetonitrile (40 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 12 h. Then, water (30 mL) was added and the resulting mixture extracted with ethyl acetate (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude products were purified by flash chromatography using hexane:AcOEt (10:1) as eluent. Physical properties are identical to those described in the literature [19].

General procedure for the preparation of dimethyl (3*S*)-*N*-benzylamino-2-ketophosphonates 13a-d. A solution of dimethyl methylphosphonate (3.0 equiv) in anhydrous THF (30 mL) was cooled at -78 ºC before the slow addition of *n*-BuLi 2.4 M in hexanes (3.1 equiv). The resulting solution was stirred at -50 ºC for 1.5 h and then cooled at -78 ºC; to this mixture was slowly added a solution of benzyl ester **12** (1 equiv) in dry THF (25 mL). The reaction mixture was stirred at -78 ºC for 4 h before the addition of a saturated solution of NH_4Cl. The solvent was evaporated under reduced pressure, the residue was 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 evaporated under reduced pressure. The 2-ketophosphonates **13** are unstable and were used without any further purification in the next step. The crude product was analyzed by ^{31}P NMR to confirm its formation.

Dimethyl (3*S*)-*N*-benzylamino-2-oxobuthylphosphonate 13a. The reaction was carried out starting from dimethyl methylphosphonate 1.9 g (15.5 mmol) in anhydrous THF (25 mL), *n*-BuLi 2.4 M in hexanes (6.7 mL, 16 mmol), methyl *N*-benzylaminoacid ester **12a** (1.0 g, 5.2 mmol) in anhydrous THF (45 mL) following the general procedure. The crude product was used without any further purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ 24.13.

Dimethyl (3*S*)-*N*-benzylamino-2-oxopenthylphosphonate 13b. The reaction was carried out starting from dimethyl methylphosphonate 1.7 g (13.6 mmol) in anhydrous THF (25 mL), *n*-BuLi 2.4 M in hexanes (5.8 mL, 14 mmol), methyl *N*-benzylaminoacid ester **12b** (1.0 g, 4.5 mmol) in anhydrous THF (25 mL) following the general procedure. The crude product was used without any further purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ 24.23.

Dimethyl (3*S*)-*N*-benzylamino-4-phenyl-2-oxobuthylphosphonate 13c. The reaction was carried out starting from dimethyl methylphosphonate 1.4 g (11.0 mmol) in anhydrous THF (25 mL), *n*-BuLi 2.4 M in hexanes (4.8 mL, 11.5 mmol), methyl *N*-benzylaminoacid ester **12c** (1.0 g, 3.7 mmol) in anhydrous THF (25 mL) following the general procedure. The crude product was used without any further purification. ^{31}P NMR (200 MHz, $CDCl_3$) δ 24.13.

Dimethyl (3*S*)-*N*-benzylamino-3-phenyl-2-oxopropylphosphonate 13d. The reaction was carried out starting from dimethyl methylphosphonate 1.5 g (11.7 mmol) in anhydrous THF (25 mL), *n*-BuLi 2.4 M in hexanes (5.1 mL, 12.1 mmol), methyl *N*-benzylaminoacid ester **12d** (1.0 g, 3.9 mmol) in anhydrous THF (45 mL) following the general procedure. The crude product was used without any further purification. ^{31}P NMR (200 MHz, $CDCl_3$) δ 23.61.

General procedure for the reduction of (3*S*)-*N*-benzylamino-2-ketophosphonates 13a-d. A solution of 2-ketophosphonate **13** (1 equiv) in anhydrous THF (20 mL) was cooled at -78 ºC before the slow addition of freshly prepared $Zn(BH_4)_2$ 1 M in THF (4 equiv) [20]. The reaction mixture was stirred at -78 ºC for 4-6 h and quenched by the addition of a saturated aqueous solution of NH_4Cl (4 mL). The solvent was evaporated in *vacuo*, the residue was dissolved in water (40 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude 2-hydroxyphosphonates wer analyzed by ^1H NMR at 400 MHz and by ^{31}P NMR at 200 MHz, and then purified by flash chromatography using hexane:AcOEt (1:3) as eluent.

Dimethyl (3*S*)-(*N*-benzyl)amino-(2*S*)-hydroxybuthylphosphonate 14a. The reaction was carried out starting from 2-ketophosphonate **13a** (1.5 g, 5.1 mmol) in dry THF (20 mL) and $Zn(BH_4)_2$ 1 M in THF (94 mL, 21 mmol) following the general procedure, to afford 1.3 g, 88% yield of 2-hydroxyphosphonate *anti*-**14a** and *syn*-**15a**, in a 67:33 ratio respectively. The mixture was purified by flash chromatography obtaining the 2-hydroxyphosphonate *anti*-**14a** diastereomerically pure, as a viscous liquid; $[\alpha]_D$ = +0.2 (c = 2.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 6.8 Hz, 3H, CH_3), 1.71 (ddd, J = 16.4, 15.2, 9.6 Hz, 1H, CH_2P), 1.91 (ddd, J = 20.8, 15.2, 2.0 Hz, 1H, CH_2P), 2.61 (dq, J = 9.2, 6.4 Hz, 1H, CHNBn), 3.31 (AB system, J = 13.2 Hz, 1H, CH_2Ph), 3.69 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.75 (d, J = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.84 (AB system, J = 13.2 Hz, 1H, CH_2Ph), 3.86 (ddd, J = 12.0, 9.6, 2.4 Hz, 1H, CHOH), 7.25-7.33 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3 (CH_3), 30.4 (d, J = 141.5 Hz, CH_2P), 52.4 (d, J = 5.9 Hz, $(CH_3O)_2P$), 52.8 (d, J = 5.9 Hz, $(CH_3O)_2P$), 53.7 (CH_2Ph), 59.1 (d, J = 18.3 Hz, CHOH), 67.1 (d, J = 6.6 Hz, CHNBn), 127.5, 128.7, 129.3, 138.9. ^{31}P NMR (200 MHz, $CDCl_3$) δ 33.74.

Dimethyl (3*S*)-*N*-benzylamino-(2*S*)-hydroxy-4-methylpenthylphosphonate 14b. The reaction was carried out starting from 2-ketophosphonate **13b** (1.6 g, 4.5 mmol) in dry THF

(20 mL) and $Zn(BH_4)_2$ 1 M in THF (82 mL, 18 mmol) following the general procedure, to afford 1.2 g, 85% yield of 2-hydroxyphosphonate *anti*-**14b** and *syn*-**15b**, in a 96:4 ratio, respectively. The mixture was purified by flash chromatography obtaining the 2-hydroxyphosphonate *anti*-**14b** diastereomerically pure, as a viscous liquid, $[\alpha]_D$ = +17.5 (c = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.8 Hz, 3H, $(CH_3)_2CH$), 0.99 (d, *J* = 6.8 Hz, 3H, $(CH_3)_2CH$), 1.91 (ddd, *J* = 15.2, 15.2, 10.8 Hz, 1H, CH_2P), 1.88-1.95 (m, 1H, $CH(CH_3)_2$), 2.10 (ddd, *J* = 20.0, 15.2, 2.4 Hz, 1H, CH_2P), 2.43 (ddd, *J* = 5.6, 5.6, 0.8 Hz, 1H, CHNH), 3.77 (d, *J* = 10.8 Hz, 6H, $(CH_3O)_2P$), 3.83 (AB system, *J* = 12.4 Hz, 1H, CH_2Ph), 3.89 (AB system, *J* = 12.4 Hz, 1H, CH_2Ph), 4.03 (ddd, *J* = 10.8, 10.8, 5.6, 2.4 Hz, 1H, CHOH), 7.24-7.35 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4 ($(CH_3)_2CH$), 20.7 ($(CH_3)_2CH$), 28.7 (d, *J* = 139.7 Hz, CH_2P), 29.5 ($CH(CH_3)_2$), 52.5 (d, *J* = 6.0 Hz, $(CH_3O)_2P$), 52.7 (d, *J* = 6.0 Hz, $(CH_3O)_2P$), 54.7 (CH_2Ph), 67.0 (d, *J* = 15.2 Hz, CHOH), 67.3 (d, *J* = 4.6 Hz, CHNH), 127.3, 128.4, 128.7, 140.7. ^{31}P NMR (81 MHz, $CDCl_3$) δ 35.58.

Dimethyl (3*S*)-*N*-benzylamino-4-phenyl-(2*R*)-hydroxybuthylphosphonate 14c. The reaction was carried out starting from 2-ketophosphonate **13c** (1.5 g, 3.7 mmol) in dry THF (20 mL) and $Zn(BH_4)_2$ 1 M in THF (68 mL, 15 mmol) following the general procedure, to afford 950 mg, 70% yield of 2-hydroxyphosphonate *anti*-**14c** and *syn*-**15c**, in a 96:4 ratio, respectively. The mixture was purified by flash chromatography obtaining the 2-hydroxyphosphonate *anti*-**14c** diastereomerically pure, as a viscous liquid, $[\alpha]_D$ = +4.3 (c = 2.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (ddd, *J* = 17.2, 15.2, 8.4 Hz, 1H, CH_2P), 2.10 (ddd, *J* = 19.2, 15.2, 4.4 Hz, 1H, CH_2P), 2.67 (dd, *J* = 13.6, 9.2 Hz, 1H, CH_2CHN), 2.85 (dd, *J* = 13.6, 4.8 Hz, 1H, CH_2CHN), 2.90 (ddd, *J* = 9.2, 9.2, 4.4 Hz, 1H, CHNH), 3.64 (AB system, *J* = 13.2 Hz, 1H, CH_2Ph), 3.74 (d, *J* = 10.4 Hz, 3H, $(CH_3O)_2P$), 3.75 (AB system, *J* = 13.2 Hz, 2H, CH_2Ph), 3.77 (d, *J* = 10.4 Hz, 3H, $(CH_3O)_2P$), 4.03-4.10 (m, 1H, CHOH), 7.05-7.30 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (d, *J* = 139.7 Hz, CH_2P), 34.8 ($CH_2CHNHBn$), 51.7 (CH_2Ph), 52.5 (d, *J* = 7.5 Hz, $(CH_3O)_2P$), 52.8 (d, *J* = 7.5 Hz, $(CH_3O)_2P$), 62.1 (d, *J* = 13.7 Hz, CHOH), 66.1 (CHNHBn), 126.7, 127.2, 128.2, 128.6, 128.8, 129.4, 138.2, 139.9. ^{31}P NMR (200 MHz, $CDCl_3$) δ 34.81.

Dimethyl (3*S*)-*N*-benzylamino-(2*S*)-hydroxy-3-phenylpropylphosphonate 14d. The reaction was carried out starting from 2-ketophosphonate **13d** (1.5 g, 3.9 mmol) in dry THF (20 mL) and $Zn(BH_4)_2$ 1 M in THF (71 mL, 16 mmol) following the general procedure, to afford 1.0 g, 95% yield of 2-hydroxyphosphonate *anti*-**14d** and *syn*-**15d**, in a 88:12 ratio, respectively. The mixture was purified by flash chromatography obtaining the 2-hydroxyphosphonate *anti*-**14d** diastereomerically pure, as a viscous liquid, $[\alpha]_D$ = +5.61 (c = 5.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (ddd, *J* = 18.8, 15.2, 4.0 Hz, 1H, CH_2P), δ (ddd, *J* = 16.8, 15.2, 6.8 Hz, 1H, CH_2P), 3.59 (AB system, *J* = 13.4 Hz, 1H, CH_2Ph), 3.66 (d, *J* = 11.2 Hz, 3H, $(CH_3O)_2P$), 3.69 (d, *J* = 10.8 Hz, 3H, $(CH_3O)_2P$), 3.74 (AB system, *J* = 12.8 Hz, 1H, CH_2Ph), 3.85 (dd, *J* = 4.4, 0.8 Hz, 1H, CHNH), 4.19-4.26 (m, 1H, CHOH), 7.25-7.37 (m, 10H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7 (d, *J* = 142.7 Hz, CH_2P), 51.5 (CH_2Ph), 52.5 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 52.8 (d, *J* = 6.1 Hz, $(CH_3O)_2P$), 66.5 (d, *J* = 15.2 Hz, CHOH), 69.6 (d, *J* = 4.6 Hz, CHNH), 127.2, 127.9, 128.4, 128.4, 128.6, 128.8, 139.2, 140.3. ^{31}P NMR (81 MHz, $CDCl_3$) δ 35.20.

General procedure for the preparation of hydroxyphosphonic acids 6a-d and 7a-d analogues. 2-Hydroxyphosphonate *syn*-**10a-d** or *anti*-**14a-d** (1.0 equiv) was treated at 0 ºC under a nitrogen atmosphere with bromotrimethylsilane (2.2 equiv). The reaction mixture was stirred at room temperature for 6-8 h, and after this period of time the volatil materials were evaporated under reduced pressure, water was then added. After 30 min the solvents were evaporated in *vacuo* to give (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxyphosphonic acid or (3*S*)-*N*-benzylamino-(2*S*)-hydroxyphosphonic acid, which without isolation were treated with palladium on carbon (5 % wt) in methanol (20 mL) and stirred for 12 h under a hydrogen gas atmosphere at room temperature. The mixture was filtered through a pad of Celite, and the solvents were evaporated under reduced pressure. The residue was treated with propylene oxide (5 mL) to afford the 3-amino-2-hydroxyphosphonic acids **6a-d** or **7a-d**.

(3*S*)-Amino-(2*R*)-hydroxybutylphosphonic acid 6a. The reaction was carried out starting from 2-hydroxyphosphonate *syn*-**10a** (400 mg, 1.06 mmol), bromotrimethylsilane (357 mg, 0.30 mL, 2.33 mmol), and (200 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (153 mg, 85% yield) of **6a**, as a white solid, mp 223-225 °C. $[\alpha]_D$ = -4.4 (c = 2.4, H_2O). ^{1}H NMR (400 MHz, D_2O) δ d, *J* = 6.4 Hz, 3H, CH_3CH), 1.84 (ddd, *J* = 16.8, 15.2, 8.8 Hz, 1H, CH_2P), 1.97 (ddd, *J* = 19.2, 15.2, 4.0 Hz, 1H, CH_2P), 3.38 (q, *J* = 6.4 Hz, 1H, $CHNH_2$), 3.89-3.97 (m, 1H, CHOH). ^{13}C NMR (100 MHz, D_2O) δ 17.2 (CH_3CH), 34.3 (d, *J* = 132.1 Hz, CH_2P), 54.8 (d, *J* = 13.6 Hz, CHOH), 70.9 (d, *J* = 3.0 Hz, $CHNH_2$). ^{31}P NMR (200 MHz, D_2O) δ 21.56.

(3*S*)-Amino-(2*R*)-hydroxy-4-methylpentylphosphonic acid 6b. The reaction was carried out starting from 2-hydroxyphosphonate *syn*-**10b** (400 mg, 0.98 mmol), bromotrimethylsilane (332 mg, 0.28 mL, 2.17 mmol), and (177 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (177 mg, 91% yield) of **6b**, as a white solid, mp 213-214 °C. $[\alpha]_D$ = +0.80 (c = 2.5, H_2O). ^{1}H NMR (400 MHz, D_2O) δ d, *J* = 6.8 Hz, 3H, $(CH_3)_2CH$), δ d, *J* = 7.2 Hz, 3H, $(CH_3)_2CH$), 1.54 (ddd, *J* = 20.2, 15.2, 1.6 Hz, 1H, CH_2P), 1.93 (ddd, *J* = 15.2, 15.2, 10.4 Hz, 1H, CH_2P), 2.24 (dd, *J* = 6.4, 5.2 Hz, 1H, $CHNH_2$), 2.28-2.36 (m, 1H, $CH(CH_3)_2$), 4.10-4.17 (m, 1H, CHOH). ^{13}C NMR (100 MHz, D_2O) δ 20.6 ($(CH_3)_2CH$), 23.6

((CH_3)$_2$CH), 26.9 (CH(CH_3)$_2$), 31.5 (d, J = 138.6 Hz, CH_2P), 65.3 (d, J = 5.8 Hz, $CHNH_2$), 67.2 (d, J = 18.3 Hz, CHOH). ^{31}P NMR (200 MHz, D_2O) δ 22.87.

(3*S*)-Amino-(2*R*)-hydroxy-4-phenylbutylphosphonic acid 6c. The reaction was carried out starting from 2-hydroxyphosphonate *syn*-**10c** (400 mg, 0.88 mmol), bromotrimethylsilane (297 mg, 0.25 mL, 1.94 mmol), and (200 mg) of palladium on carbon (10 % wt) in methanol (10 mL). The product was not isolated in sufficiently pure form for spectra data analysis and to determine the specific rotation.

(3*S*)-Amino-(2*R*)-hydroxy-3-phenylpropylphosphonic acid 6d. The reaction was carried out starting from 2-hydroxyphosphonate *syn*-**10d** (530 mg, 0.80 mmol), bromotrimethylsilane (268 mg, 0.23 mL, 1.75 mmol), and (175 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (154 mg, 84% yield) of **6d**, as a white solid, mp 217-219 °C. $[\alpha]_D$ = +1.4 (c = 1.48, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.54 (ddd, J = 15.2, 15.2, 9.2 Hz, 1H, CH_2P), δ (ddd, J = 20.0, 15.2, 2.4 Hz, 1H, CH_2P), 3.51 (d, J = 10.4 Hz, 1H, $CHNH_2$), 4.61 (ddd, J = 10.4, 9.2, 2.4 Hz, 1H, CHOH), 7.20-7.47 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, D_2O) δ 30.4 (d, J = 142.7 Hz, CH_2P), 64.0 (d, J = 6.0 Hz, $CHNH_2$), 68.5 (d, J = 21.3 Hz, CHOH), 127.6 (C_{para}), 129.3 (C_{orto}), 130.1 (C_{meta}), 133.2 (C_{ipso}). ^{31}P NMR (81 MHz, D_2O) δ 33.62.

(3*S*)-Amino-(2*S*)-hydroxybutylphosphonic acid 7a. The reaction was carried out starting from 2-hydroxyphosphonate *anti*-**14a** (400 mg, 1.06 mmol), bromotrimethylsilane (357 mg, 0.30 mL, 2.33 mmol), and (200 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (153 mg, 85% yield) of **7a**, as a white solid, mp 218-220 °C. $[\alpha]_D$ = +2.10 (c = 0.21, H_2O). ^{1}H NMR (400 MHz, D_2O) δ d, J = 6.4 Hz, 3H, CH_3CH), 1.84 (ddd, J = 16.8, 15.2, 8.8 Hz, 1H, CH_2P), 1.97 (ddd, J = 19.2, 15.2, 4.0 Hz, 1H, CH_2P), 3.38 (c, J = 6.4 Hz, 1H, $CHNH_2$), 3.93 (dddd, J = 11.6, 8.8, 6.4, 4.0 Hz, 1H, CHOH). ^{13}C NMR (100 MHz, D_2O) δ 17.2 (CH_3CH), 34.3 (d, J = 132.1 Hz, CH_2P), 54.8 (d, J = 13.6 Hz, CHOH), 70.9 (d, J = 3.0 Hz, $CHNH_2$). ^{31}P NMR (81 MHz, D_2O) δ 19.57.

(3*S*)-Amino-(2*S*)-hydroxy-4-methylpentylphosphonic acid 7b. The reaction was carried out starting from 2-hydroxyphosphonate *anti*-**14b** (400 mg, 0.98 mmol), bromotrimethylsilane (332 mg, 0.28 mL, 2.17 mmol), and (200 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (177 mg, 91% yield) of **7b**. ^{1}H NMR (400 MHz, D_2O) δ d, J = 6.8 Hz, 3H, (CH_3)$_2$CH), δ d, J = 7.2 Hz, 3H, (CH_3)$_2$CH), 1.54 (ddd, J = 20.2, 15.2, 1.6 Hz, 1H, CH_2P), 1.93 (ddd, J = 15.2, 15.2, 10.4 Hz, 1H, CH_2P), 2.24 (dd, J = 6.4, 5.2 Hz, 1H, $CHNH_2$), 2.28-2.36 (m, 1H, CH(CH_3)$_2$), 4.10-4.17 (m, 1H, CHOH), ^{13}C NMR (100 MHz, D_2O) δ 20.6 ((CH_3)$_2$CH), 23.6 ((CH_3)$_2$CH), 26.9 (CH(CH_3)$_2$), 31.5 (d, J = 138.6 Hz, CH_2P), 65.3 (d, J = 5.8 Hz, $CHNH_2$), 67.2 (d, J = 18.3 Hz, CHOH). ^{31}P NMR (81 MHz, D_2O) δ 21.94.

(3*S*)-Amino-(2*S*)-hydroxy-4-phenylbutylphosphonic acid 7c. The reaction was carried out starting from 2-hydroxyphosphonate *anti*-**14c** (400 mg, 0.88 mmol), bromotrimethylsilane (297 mg, 0.25 mL, 1.94 mmol), and (200 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (187 mg, 87% yield) of **7c**, as a white solid, mp 227-229 °C. $[\alpha]_D$ = -25.5 (c = 2.6, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.94 (ddd, J = 18.0, 14.8, 8.0 Hz, 1H, CH_2P), 2.03 (ddd, J = 18.4, 14.8, 6.0 Hz, 1H, CH_2P), 2.79 (dd, J = 14.4, 11.2 Hz, 1H, CH_2Ph), 3.21 (dd, J = 14.4, 3.6 Hz, 1H, CH_2Ph), 3.75 (ddd, J = 11.2, 3.2, 3.2, 1H, $CHNH_2$), 4.24-4.32 (m, 1H, CHOH), 7.35-7.45 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, D_2O) δ 34.2 (d, J = 129.0 Hz, CH_2P), 34.7 (CH_2Ph), 60.0 (d, J = 9.1 Hz, CHOH), 69.74 ($CHNH_2$), 130.2 (C_{para}), 131.9 (C_{orto}), 132.0 (C_{meta}), 138.3 (C_{ipso}). ^{31}P NMR (81 MHz, D_2O) δ 20.33.

(3*S*)-Amino-(2*S*)-hydroxy-4-phenylpropylphosphonic acid 7d. The reaction was carried out starting from 2-hydroxyphosphonate *anti*-**14d** (350 mg, 0.80 mmol), bromotrimethylsilane (268 mg, 0.23 mL, 1.75 mmol) and (175 mg) of palladium on carbon (10 % wt) in methanol (10 mL), to afford (154 mg, 84% yield) of **7d**, as a white solid, mp 233-235 °C. $[\alpha]_D$ = -2.50 (c = 13.6, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.54 (ddd, J = 15.2, 15.2, 9.2 Hz, 1H, CH_2P), 1.64 (ddd, J = 20.0, 15.2, 2.4 Hz, 1H, CH_2P), 3.51 (d, J = 10.4 Hz, 1H, $CHNH_2$), 4.61 (ddd, J = 10.4, 9.2, 2.4 Hz, 1H, CHOH), 7.20-7.47 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, D_2O) δ 30.4 (d, J = 142.7 Hz, CH_2P), 64.0 (d, J = 6.0 Hz, $CHNH_2$), 68.5 (d, J = 21.3 Hz, CHOH), 127.6 (C_{para}), 129.3 (C_{orto}), 130.1 (C_{meta}), 133.2 (C_{ipso}). ^{31}P NMR (81 MHz, D_2O) δ 33.62.

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