

Article

## Synthesis of *syn*- $\gamma$ -Amino- $\beta$ -hydroxyphosphonates by Reduction of $\beta$ -Ketophosphonates Derived from L-Proline and L-Serine

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**Abstract:** The reduction of  $\gamma$ -*N*-benzylamino- $\beta$ -ketophosphonates **6** and **10**, readily available from L-proline and L-serine, respectively, can be carried out in high diastereoselectivity with catecholborane (CB) in THF at  $-78\text{ }^{\circ}\text{C}$  to produce the *syn*- $\gamma$ -*N*-benzylamino- $\beta$ -hydroxyphosphonates **11** and **13** as a single detectable diastereoisomer, under non-chelation or Felkin-Anh model control.

**Keywords:**  $\beta$ -ketophosphonates; diastereoselective reduction;  $\gamma$ -amino- $\beta$ -hydroxyphosphonates

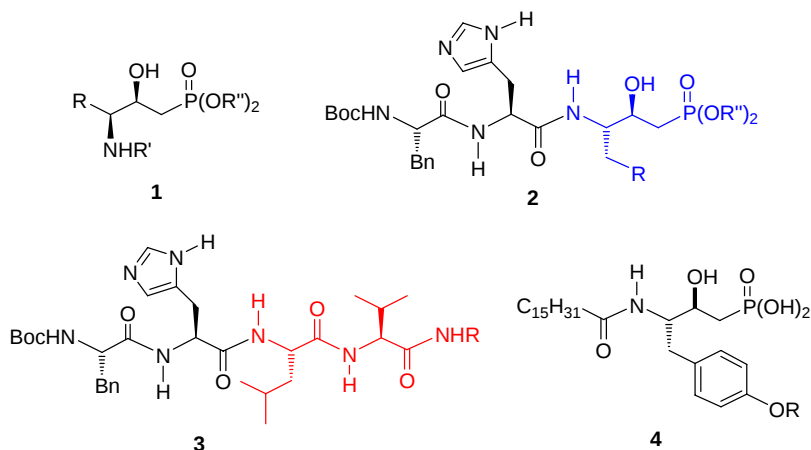
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### 1. Introduction

Aminoalkylphosphonic acids are structurally analogous to the amino acids, obtained by isosteric substitution of the planar and less bulky carboxylic acid ( $\text{CO}_2\text{H}$ ) group by a tetrahedral phosphonic acid ( $\text{PO}_3\text{H}_2$ ) functionality. Several aminophosphonic, aminophosphinic and aminophosphonous acids have been isolated from various natural sources, either as free amino acids or as constituents of more complex molecules [1–4]. In this context,  $\gamma$ -amino- $\beta$ -hydroxyphosphonates such as **1** (Figure 1) have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis [5,6]. The  $\gamma$ -amino- $\beta$ -hydroxyphosphonates **1** have been also used in the synthesis of complex molecules **2** (Figure 1) as Leu<sup>10</sup>-Val<sup>11</sup> replacement (LVRs) **3** (Figure 1), which act as rennin [7], and D-Ala-D-Ala ligase

inhibitors [8]. The  $\gamma$ -*N*-acylamino- $\beta$ -hydroxyphosphonic acids **4** (Figure 1) have been used as autotoxin (ATX) inhibitors [9]. Additionally, the  $\gamma$ -amino- $\beta$ -hydroxyphosphonic acids have been also used as potent sphingosine-1-phosphate (S1P) receptors [10], and as polysaccharide fragments [11,12].

**Figure 1.** Structures of compounds **1–4**.



In view of the different biological and chemical applications of the  $\gamma$ -amino- $\beta$ -hydroxyphosphonate phosphonic acid derivatives, in the last years the development of suitable synthetic methodologies for their preparation in diastereoisomerically pure form has been a topic of great interest in several research groups [13–29]. In this context, several protocols for efficient diastereoselective synthesis of  $\gamma$ -amino- $\beta$ -hydroxyphosphonic acids and derivatives have emerged, including ring opening of epoxides [30–33], type aldol reactions of  $\alpha$ -aminoaldehydes with dialkyl methylphosphonates [7,8,34–41], catalytic asymmetric aminohydroxylation of  $\beta,\gamma$ -unsaturated phosphonates [42–44], and diastereoselective reduction of  $\gamma$ -amino- $\beta$ -ketophosphonates [45–47].

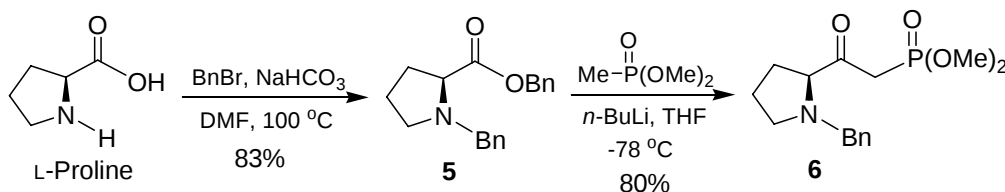
Recently, we reported the synthesis of phosphostatine and phosphoepistatine [48,49] *via* a high diastereoselective reduction of  $\gamma$ -amino- $\beta$ -ketophosphonates readily obtained from L-amino acids [50–52]. In order to establish a general methodology for the synthesis of *syn*- $\gamma$ -amino- $\beta$ -hydroxyphosphonates derived from L-amino acids, in this paper we would like to report the synthesis of  $\gamma$ -amino- $\beta$ -ketophosphonates **6** and **10** derived from L-proline and L-serine, respectively, and their highly diastereoselective reduction.

## 2. Results and Discussion

In our initial study, the synthesis of (*S*)-*N*-benzyl-*O*-benzylpyrrolidine-2-carboxylate (**5**) was carried out by treatment of L-proline with benzyl bromide and  $\text{K}_2\text{CO}_3$  in refluxing ethanol [50], however under this conditions a disappointing poor yield was obtained. For that reason, we decided to examine the methodology developed by Overman and co-workers [53] as a potentially more efficient and practical route to compound **5**. Thus, treatment of L-proline with benzyl bromide and  $\text{NaHCO}_3$  in *N,N*-dimethylformamide (DMF) at 100 °C provided the corresponding *N*-benzyl *O*-benzyl proline **5** in 83% yield. Nevertheless, with the *O*-benzyl ester **5** in our hands, we focused our attention on the transformation to  $\beta$ -ketophosphonate **6**. Thus, reaction of **5** with three equivalents of the lithium salt of

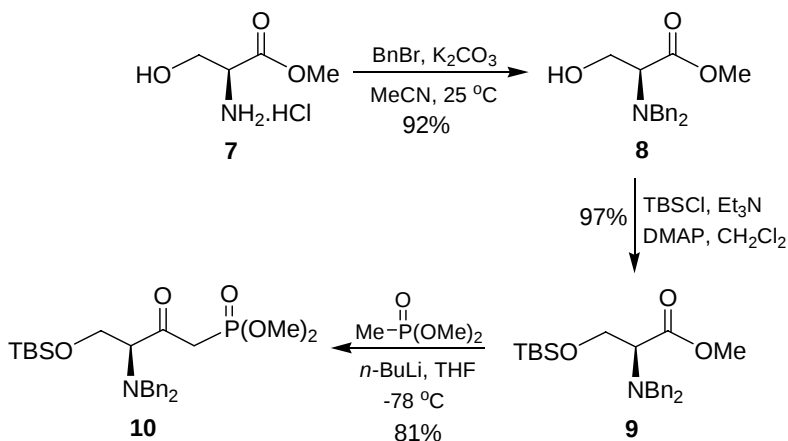
dimethyl methylphosphonate at  $-78\text{ }^{\circ}\text{C}$  in THF afforded the corresponding *N*-benzylamino- $\beta$ -ketophosphonate **6** in 80% yield (Scheme 1).

**Scheme 1.** Preparation of  $\beta$ -ketophosphonate **6**.

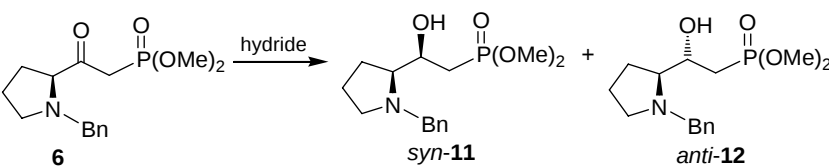


On the other hand, the reaction of hydrochloride salt of methyl ester of L-serine **7** readily obtained from commercial source or by treatment of L-serine with thionyl chloride in refluxing methanol, with benzyl bromide in the presence of  $\text{K}_2\text{CO}_3$  in acetonitrile at room temperature gave the *N,N*-dibenzyl ester **8** in 92% yield. Subsequent treatment with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of triethylamine and catalytic amounts of 4-*N,N*-dimethylaminopyridine (DMAP) in dichloromethane produced the full protected L-serine **9** in 97% yield [54]. *O*-protection in **8** with TBSCl and imidazole in DMF proceed in poor yield. Finally, reaction of **9** with the lithium salt of dimethyl methylphosphonate at  $-78\text{ }^{\circ}\text{C}$  in THF provided the corresponding  $\gamma$ -*N,N*-dibenzylamino- $\beta$ -ketophosphonate **10** in 81% yield (Scheme 2).

**Scheme 2.** Preparation of  $\beta$ -ketophosphonate **10**.



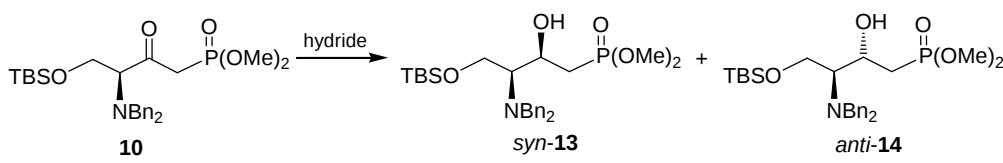
Having efficiently prepared the  $\beta$ -ketophosphonates **6** and **10**, we turned our attention to the diastereoselective reduction of the carbonyl groups to obtain the corresponding  $\gamma$ -*N*-dibenzylamino- and  $\gamma$ -*N,N*-dibenzylamino- $\beta$ -hydroxyphosphonates *syn*-**11** and *syn*-**13**, respectively. For this propose we choose  $\text{NaBH}_4$ ,  $\text{LiBH}_4$ , DIBAL-H and catecholborane (CB) as the reducing agents, according to our previous results. Diastereoisomeric excess of the reduction of the  $\beta$ -ketophosphonates **6** and **10** were determined by means of  $^{31}\text{P}$ -NMR. In fact, the signals for the diastereoisomers *syn* were more shielded than for the diastereoisomers *anti*. Conditions, yields and diastereoisomeric ratio are summarized in Tables 1 and 2.

**Table 1.** Diastereoselective reduction of  $\beta$ -ketophosphonate **6**.


| Entry | Hydride           | Conditions  | Yield (%) <sup>a</sup> | <i>syn</i> -11: <i>anti</i> -12 <sup>b</sup> |
|-------|-------------------|-------------|------------------------|----------------------------------------------|
| 1     | NaBH <sub>4</sub> | MeOH, 25 °C | 70                     | 69:31                                        |
| 2     | LiBH <sub>4</sub> | THF, -78 °C | 69                     | 75:25                                        |
| 3     | DIBAL-H           | THF, -78 °C | 69                     | 79:21                                        |
| 4     | CB                | THF, -78 °C | 78                     | ≥96:4                                        |

<sup>a</sup> Determined after purification; <sup>b</sup> *syn:anti* ratios have been determined on the crude products using <sup>31</sup>P-NMR.

As shown in the Table 1, when the reduction of  $\beta$ -ketophosphonate **6** was carried out with NaBH<sub>4</sub> in methanol (entry 1, Table 1), a mixture of the  $\gamma$ -amino- $\beta$ -hydroxyphosphonates *syn*-**11** and *anti*-**12** in a 69:31 ratio in favor of *syn*-**11** was obtained in good yield. The reduction of  $\beta$ -ketophosphonate **6** with LiBH<sub>4</sub> and DIBAL-H afforded the mixture of the diastereoisomers *syn*-**11** and *anti*-**12** in 69% yield and ratios of 75:25 and 79:21, respectively (entries 2 and 3, Table 1). Finally, the reduction of  $\beta$ -ketophosphonate **6** with catecholborane (CB) in THF at -78 °C (entry 4, Table 1), provided the corresponding  $\gamma$ -amino- $\beta$ -hydroxyphosphonates in 78% yield, with the *syn:anti* ratio ≥96:4 (the diastereoisomer *anti*-**12** was not observed by <sup>31</sup>P-NMR).

**Table 2.** Diastereoselective reduction of  $\beta$ -ketophosphonate **10**.


| Entry | Hydride           | Conditions  | Yield (%) <sup>a</sup> | <i>syn</i> -13: <i>anti</i> -14 <sup>b</sup> |
|-------|-------------------|-------------|------------------------|----------------------------------------------|
| 1     | NaBH <sub>4</sub> | MeOH, 25 °C | 70                     | 81:19                                        |
| 2     | LiBH <sub>4</sub> | THF, -78 °C | 75                     | 82:18                                        |
| 3     | DIBAL-H           | THF, -78 °C | 91                     | 88:12                                        |
| 4     | CB                | THF, -78 °C | 87                     | ≥96:4                                        |

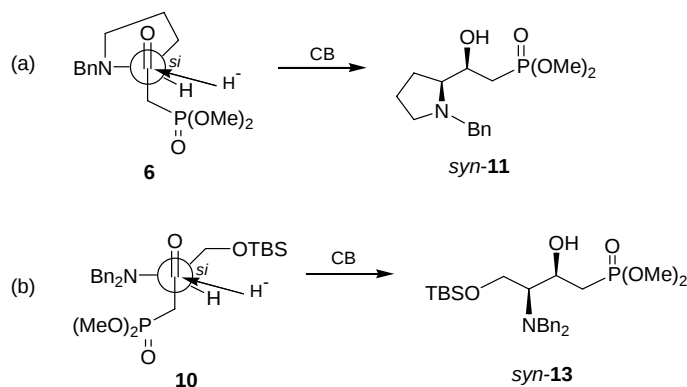
<sup>a</sup> Determined after purification; <sup>b</sup> *syn:anti* ratios have been determined on the crude products using <sup>31</sup>P-NMR.

Under similar conditions, the reduction of  $\gamma$ -*N,N*-benzylamino- $\beta$ -ketophosphonate **10** with NaBH<sub>4</sub> and LiBH<sub>4</sub> as reducing agents provided the mixture of the  $\gamma$ -*N,N*-benzylamino- $\beta$ -hydroxyphosphonates *syn*-**13** and *anti*-**14** in good yield and ratios of 81:19 and 82:18, respectively, (entries 1 and 2, Table 2). A better diastereoselectivity was observed when the  $\beta$ -ketophosphonate **10** was reduced with DIBAL-H in THF at -78 °C (entry 3, Table 2). Finally, reduction of **10** with catecholborane in THF at -78 °C (entry 4, Table 2), afforded the  $\gamma$ -*N,N*-dibenzylamino- $\beta$ -hydroxyphosphonates in 87% yield, with a *syn:anti* ratio ≥96:4 (the diastereoisomer *anti*-**14** was not observed by <sup>31</sup>P-NMR). The absolute configuration of the new stereogenic center in *syn*-**11**, *anti*-**12**, *syn*-**13** and *anti*-**14** was assigned by analogy with other  $\gamma$ -amino- $\beta$ -hydroxyphosphonates obtained in our laboratory.

The formation of the  $\gamma$ -amino- $\beta$ -hydroxyphosphonates *syn*-**11** and *syn*-**13** as major diastereoisomer in the reduction of the  $\beta$ -ketophosphonates **6** and **10**, respectively, with catecholborane, we propose that the reduction might took place under non-chelation or Felkin-Anh model control [55–58], and that

the bulkiness of the *N*-benzylamino- and *N,N*-dibenzylamino- groups in the  $\beta$ -ketophosphonates **6** and **10**, are sufficient to simultaneously limit the rotamer populations around the hinge bonds adjacent to the carbonyl group blocking the *re* face of carbonyl group and, thereby allowing the addition of hydride to take in a diastereoselective manner by the *si* face (Figure 1).

**Figure 2.** Reduction of the  $\beta$ -ketophosphonates **6** and **10** by non-chelation control.



### 3. Experimental

#### 3.1. General Procedures

Optical rotations were taken on a Perkin-Elmer 241 polarimeter in a 1 dm tube; concentrations are given in g/100 mL. For flash chromatography, silica gel 60 (230–400 mesh ASTM, Merck) are used.  $^1\text{H}$ -NMR spectra were recorded on a Varian INOVA 400 (at 400 MHz),  $^{13}\text{C}$ - (100 MHz) and  $^{31}\text{P}$ -NMR on a Varian Mercury 200 instrument. HRMS spectra were recorded on a JEOL JMS-700 instrument. Flasks, stirring bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl. The preparation and spectroscopic data for the compounds (*S*)-*N*-benzyl-*O*-benzylpyrrolidine-2-carboxylate (**5**) [53], (*S*)-methyl-2-(dibenzylamino)-3-hydroxypropanoate (**8**) [59] and (*S*)-methyl-3-(*tert*-butyldimethylsilyloxy)-2-(dibenzylamino) propanoate (**9**) [59], have all been described in the cited literature.

(*S*)-Dimethyl-2-(1-benzylpyrrolidin-2-yl)-2-oxoethylphosphonate (**6**). A solution of dimethyl methylphosphonate (830 mg, 6.8 mmol) in anhydrous THF (50 mL), was cooled at -78 °C before the slow addition of *n*-BuLi 2.35 M in hexanes (2.9 mL, 6.9 mmol). The resulting solution was stirred at -50 °C for 1.5 h and then cooled at -78 °C, followed by the addition of a solution of benzyl ester **5** (500 mg, 1.7 mmol) in anhydrous THF (50 mL). The reaction mixture was stirred at -78 °C for 4 h before the addition of a saturated solution of  $\text{NH}_4\text{Cl}$ . The solvent was evaporated under reduced pressure, the residue was dissolved in water (30 mL) and extracted with ethyl acetate ( $3 \times 30$  mL). The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane-ethyl acetate (50:50) as eluent to afford the desired product (420 mg, 80% yield) as a viscous oil.  $[\alpha]_{\text{D}} = -1.3$  ( $c = 1.37$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  1.77–2.15 (m, 4H), 2.36 (m, 1H), 2.98 (dd,  $J = 21.2, 15.0$  Hz, 1H,  $\text{CH}_2\text{P}$ ), 3.07 (m, 1H), 3.27 (dd,  $J = 9.2, 6.6$  Hz, 1H, CHN), 3.42 (dd,  $J = 21.2, 15.0$  Hz, 1H,

CH<sub>2</sub>P), 3.48 (system AB,  $J = 15.0$  Hz, 1H, CH<sub>2</sub>Ph), 3.75 (d,  $J = 11.2$  Hz, 3H, (CH<sub>3</sub>O)<sub>2</sub>P), 3.77 (d,  $J = 11.2$  Hz, 3H, (CH<sub>3</sub>O)<sub>2</sub>P), 3.82 (system AB,  $J = 15.0$  Hz, 1H, CH<sub>2</sub>Ph), 7.23–7.36 (m, 5 H, H<sub>arom</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) 23.9 (CH<sub>2</sub>CH<sub>2</sub>), 28.5 (CH<sub>2</sub>CH), 35.7 (d,  $J = 133.6$  Hz, CH<sub>2</sub>P), 53.1 [(CH<sub>3</sub>O)<sub>2</sub>P], 53.3 [(CH<sub>3</sub>O)<sub>2</sub>P], 54.2 (CH<sub>2</sub>N), 59.5 (CH<sub>2</sub>Ph), 73.7 (CHN), 127.4 (*C<sub>para</sub>*), 128.4 (*C<sub>meta</sub>*), 129.2 (*C<sub>ortho</sub>*), 138.4 (*C<sub>ipso</sub>*), 204.8 (C=O); <sup>31</sup>P-NMR (CDCl<sub>3</sub>)  $\delta$  25.94; HRMS (CI, CH<sub>4</sub>) calculated for C<sub>15</sub>H<sub>23</sub>O<sub>4</sub>NP (MH<sup>+</sup>) 312.1365, found 312.1287.

(*S*)-Dimethyl-4-(*tert*-butyldimethylsilyloxy)-3-*N,N*-(dibenzylamino)-2-oxobutylphosphonate (**10**). A solution of dimethyl methylphosphonate (3.30 g, 26.6 mmol) in anhydrous THF (125 mL), was cooled at -78 °C before the slowly addition of *n*-BuLi 2.15 M in hexanes (12.7 mL, 27.3 mmol). The resulting solution was stirred at -50 °C for 1.5 h and then cooled at -78 °C followed by the addition of a solution of benzyl ester **9** (2.75 g, 6.7 mmol) in anhydrous THF (125 mL). The reaction mixture was stirred at -78 °C for 4 h before the addition of a saturated solution of NH<sub>4</sub>Cl. 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<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane-ethyl acetate (50:50) as eluent to give the desired product (2.7 g, 81% yield) as a viscous oil.  $[\alpha]_D = -56.0$  ( $c = 1.17$ , CHCl<sub>3</sub>). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  0.09 (s, 3H, (CH<sub>3</sub>)<sub>2</sub>Si), 0.12 (s, 3H, (CH<sub>3</sub>)<sub>2</sub>Si), 0.93 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>C), 2.99 (dd,  $J = 21.9$  Hz,  $J = 14.5$  Hz, 1H, CH<sub>2</sub>P), 3.48 (dd,  $J = 21.9$  Hz,  $J = 14.5$  Hz, 1H, CH<sub>2</sub>P), 3.56 (d,  $J = 11.2$  Hz, 3H, (CH<sub>3</sub>O)<sub>2</sub>P), 3.63 (d,  $J = 11.2$  Hz, 3H, (CH<sub>3</sub>O)<sub>2</sub>P), 3.65 (t,  $J = 6.0$  Hz, 1H, CHN), 3.78 (system AB,  $J = 13.4$  Hz, 2H, CH<sub>2</sub>Ph), 3.84 (system AB,  $J = 13.4$  Hz, 2H, CH<sub>2</sub>Ph), 4.03 (dd,  $J = 11.0$  Hz,  $J = 6.1$  Hz, 1H, CH<sub>2</sub>OSi), 4.13 (dd,  $J = 11.0$  Hz,  $J = 6.1$  Hz, 1H, CH<sub>2</sub>OSi), 7.23–7.35 (m, 10 H, H<sub>arom</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$  -5.3 [(CH<sub>3</sub>)<sub>2</sub>Si], -5.2 [(CH<sub>3</sub>)<sub>2</sub>Si], 18.4 [C(CH<sub>3</sub>)<sub>3</sub>], 26.2 [CH<sub>3</sub>)<sub>3</sub>C], 38.6 (d,  $J = 130.6$  Hz, CH<sub>2</sub>P), 52.9 [d,  $J = 6.1$  Hz, (CH<sub>3</sub>O)<sub>2</sub>P], 52.9 [d,  $J = 6.0$  Hz, (CH<sub>3</sub>O)<sub>2</sub>P], 55.4 (CH<sub>2</sub>Ph), 60.1 (CH<sub>2</sub>OSi), 67.44 (CHN), 127.4 (*C<sub>para</sub>*), 128.5 (*C<sub>meta</sub>*), 129.2 (*C<sub>ortho</sub>*), 139.4 (*C<sub>ipso</sub>*), 201.8 (d,  $J = 6.1$  Hz, C=O); <sup>31</sup>P-NMR (CDCl<sub>3</sub>)  $\delta$  24.30; HRMS (CI, CH<sub>4</sub>) calculated for, C<sub>26</sub>H<sub>41</sub>O<sub>5</sub>NPSi (MH<sup>+</sup>) 506.2492, found 506.2575

*General procedure for the reduction of  $\beta$ -ketophosphonates (S)-6 and (S)-10 with NaBH<sub>4</sub>.* To a solution of  $\beta$ -ketophosphonate (S)-**6** or (S)-**10** (1.0 eq.) in methanol (40 mL) at 0 °C was added NaBH<sub>4</sub> (4.0 equiv.). After 5.0 h, the solvent was evaporated and the residue was diluted with H<sub>2</sub>O and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. The crude was analyzed by <sup>1</sup>H- and <sup>31</sup>P-NMR and purified by column chromatography.

*General procedure for the reduction of  $\beta$ -ketophosphonates (S)-6 and (S)-10 with LiBH<sub>4</sub>, DIBAL-H and catecholborane (CB).* To a solution of  $\beta$ -ketophosphonate (S)-**6** or (S)-**10** (1.0 eq.) in anhydrous THF (50 mL) was added (2.0 equiv.) of reducing agent at -78 °C. The reaction mixture was stirred for 5.0 h at -78 °C, and then was quenched with saturated solution of NH<sub>4</sub>Cl and extracted with ethyl acetate (3 × 40 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. The crude was analyzed by <sup>1</sup>H- and <sup>31</sup>P-NMR and purified by column chromatography.

(2*S*)-1-Benzylpyrrolidin-2-yl)-(2*R*)-hydroxyethylphosphonate (*syn*-**11**). Following the general procedure,  $\beta$ -ketophosphonate **6** (100 mg, 0.32 mmol) in anhydrous THF (20 mL), was treated with

catecholborane (CB), 1 M in THF, (1.5 mL, 1.5 mmol). After work up and chromatographic purification gave (78 mg, 78% yield) of  $\beta$ -hydroxyphosphonate *syn*-**11** as a viscous oil.  $[\alpha]_D = -2.0$  ( $c = 1.02$ ,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.24–1.90 (m, 7H), 2.48–2.58 (m, 1H,  $\text{CH}_2\text{P}$ ), 2.90–3.10 (m, 1H,  $\text{CH}_2\text{P}$ ), 3.421–3.614 (m, 1H), 3.48 (system AB,  $J = 13.0$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 3.68 (d,  $J = 11.0$  Hz, 3H,  $(\text{CH}_3\text{O})_2\text{P}$ ), 3.76 (d,  $J = 11.2$  Hz, 3H,  $(\text{CH}_3\text{O})_2\text{P}$ ), 4.02 (system AB,  $J = 13.0$  Hz, 1H,  $\text{CH}_2\text{Ph}$ ), 7.23–7.36 (m, 10 H,  $\text{H}_{\text{arom}}$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ) 21.6 ( $\text{CH}_2\text{CH}_2$ ), 29.5 ( $\text{CH}_2\text{CH}$ ), 330.1 (d,  $J = 133.6$  Hz,  $\text{CH}_2\text{P}$ ), 36.64 ( $\text{CH}_2\text{N}$ ), 46.8 ( $\text{NCH}_2\text{Ph}$ ), 51.7 [ $(\text{CH}_3\text{O})_2\text{P}$ ], 53.2 [ $(\text{CH}_3\text{O})_2\text{P}$ ], 68.20 ( $\text{CHN}$ ), 68.3 ( $\text{CHOH}$ ), 127.4 ( $C_{\text{para}}$ ), 128.4 ( $C_{\text{meta}}$ ), 129.2 ( $C_{\text{ortho}}$ ), 138.4 ( $C_{\text{ipso}}$ );  $^{31}\text{P-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  35.3; HRMS ( $\text{Cl}$ ,  $\text{CH}_4$ ) calculated for  $\text{C}_{15}\text{H}_{25}\text{O}_4\text{NP}$  ( $\text{MH}^+$ ) 314.1521, found 314.1506.

*Dimethyl-(2R,3S)-4-(tert-butyldimethylsilyloxy)-3-N,N-(dibenzylamino)-2-hydroxybutyl-phosphonate* (*syn*-**13**). Following the general procedure, (180 mg, 0.37 mmol) of  $\beta$ -ketophosphonate **10** in anhydrous THF (20 mL), was treated with catecholborane (CB) 1 M in THF (1.5 mL, 1.5 mmol) of. After work up and chromatographic purification, (150 mg, 87% yield) of  $\beta$ -hydroxyphosphonate *syn*-**13** was obtained as a viscosus oil.  $[\alpha]_D = +17.1$  ( $c = 1.01$ ,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.12 (s, 3H,  $(\text{CH}_3)_2\text{Si}$ ), 0.12 (s, 3H,  $(\text{CH}_3)_2\text{Si}$ ), 0.93 (s, 9H,  $(\text{CH}_3)_3\text{C}$ ), 1.79 (ddd,  $J = 20.0, 15.1, 5.8$  Hz, 1H,  $\text{CH}_2\text{P}$ ), 1.95 (ddd,  $J = 20.0$  Hz, 15.1, 5.8 Hz, 1H,  $\text{CH}_2\text{P}$ ), 2.64 (m 1H), 3.57 (system AB,  $J = 13.4$  Hz, 2H,  $\text{CH}_2\text{Ph}$ ), 3.67 (d,  $J = 11.0$  Hz, 3H,  $(\text{CH}_3\text{O})_2\text{P}$ ), 3.72 (d,  $J = 11.0$  Hz, 3H,  $(\text{CH}_3\text{O})_2\text{P}$ ), 3.90 (m, 2H,  $\text{CH}_2\text{OSi}$ ), 4.00 (system AB,  $J = 13.4$  Hz, 2H,  $\text{CH}_2\text{Ph}$ ), 4.03–4.13 (m, 1H), 7.22–7.33 (m, 10 H,  $\text{H}_{\text{arom}}$ );  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  -5.4 ( $(\text{CH}_3)_2\text{Si}$ ), -5.3 ( $(\text{CH}_3)_2\text{Si}$ ), 18.3 ( $\text{C}(\text{CH}_3)_3$ ), 26.1 ( $(\text{CH}_3)_3\text{C}$ ), 30.5 (d,  $J = 141.2$  Hz,  $\text{CH}_2\text{P}$ ), 52.5 (d,  $J = 13.6$  Hz, 2C,  $(\text{CH}_3\text{O})_2\text{P}$ ), 55.9 ( $\text{CH}_2\text{Ph}$ ), 59.6 ( $\text{CH}_2\text{OSi}$ ), 63.9 ( $\text{CHOH}$ ), 64.1 ( $\text{CHN}$ ), 127.4 ( $C_{\text{para}}$ ), 128.6 ( $C_{\text{meta}}$ ), 129.4 ( $C_{\text{ortho}}$ ); 139.4 ( $C_{\text{ipso}}$ );  $^{31}\text{P-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  33.92. HRMS ( $\text{Cl}$ ,  $\text{CH}_4$ ) calculated for  $\text{C}_{26}\text{H}_{43}\text{O}_5\text{NPSi}$  ( $\text{MH}^+$ ) 508.2648, found 508.2672.

#### 4. Conclusions

In conclusion, we have found that the reduction of *N,N*-disubstituted- $\gamma$ -amino- $\beta$ -ketophosphonates readily obtained from the appropriate L-amino acids, with catecholborane (CB) afforded the *syn*- $\gamma$ -amino- $\beta$ -hydroxyphosphonates as principal diastereoisomers, which could be used as template compounds for the synthesis of molecules with biological and chemical interest.

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Sample Availability: Samples of the compounds are available from authors.