Synthesis of syn-γ-Amino-β-hydroxyphosphonates by Reduction of β-Ketophosphonates Derived from L-Proline and L-Serine

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Abstract: The reduction of γ-N-benzylamino-β-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 ºC to produce the syn-γ-N-benzylamino-β-hydroxyphosphonates 11 and 13 as a single detectable diastereoisomer, under non-chelation or Felkin-Anh model control.

Keywords: β-ketophosphonates; diastereoselective reduction; γ-amino-β-hydroxyphosphonates

1. Introduction

Aminoalkylphosphonic acids are structurally analogous to the amino acids, obtained by isosteric substitution of the planar and less bulky carboxylic acid (CO2H) group by a tetrahedral phosphonic acid (PO3H2) 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, γ-amino-β-hydroxyphosphonates such as 1 (Figure 1) have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis [5,6]. The γ-amino-β-hydroxyphosphonates 1 have been also used in the synthesis of complex molecules 2 (Figure 1) as Leu10-Val11 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 ºC in THF afforded the corresponding N-benzylamino-β-ketophosphonate 6 in 80% yield (Scheme 1).

Scheme 1. Preparation of β-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 K₂CO₃ in acetonitrile at room temperature gave the N,N-dibenzyl ester 8 in 92% yield. Subsequent treatment with tert-butyldimethylsilyl chloride (TBSCI) 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 TBSCI and imidazole in DMF proceed in poor yield. Finally, reaction of 9 with the lithium salt of dimethyl methylphosphonate at -78 ºC in THF provided the corresponding γ-N,N-dibenzylamino-β-ketophosphonate 10 in 81% yield (Scheme 2).

Scheme 2. Preparation of β-ketophosphonate 10.

Having efficiently prepared the β-ketophosphonates 6 and 10, we turned our attention to the diastereoselective reduction of the carbonyl groups to obtain the corresponding γ-N-dibenzylamino- and γ-N,N-dibenzylamino-β-hydroxyphosphonates syn-11 and syn-13, respectively. For this propose we choose NaBH₄, LiBH₄, DIBAL-H and catecholborane (CB) as the reducing agents, according to our previous results. Diastereoisomeric excess of the reduction of the β-ketophosphonates 6 and 10 were determined by means of ³¹P-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 β-ketophosphonate 6.

![Chemical structure of 6 with hydride reduction](image)

| Entry | Hydride | Conditions     | Yield (%) | syn-11:anti-12<sup>b</sup> |
|-------|---------|----------------|-----------|----------------------------|
| 1     | NaBH₄   | MeOH, 25 ºC    | 70        | 69:31                      |
| 2     | LiBH₄   | THF, -78 ºC    | 69        | 75:25                      |
| 3     | DIBAL-H | THF, -78 ºC    | 69        | 79:21                      |
| 4     | CB      | THF, -78 ºC    | 78        | ≥96:4                      |

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

As shown in the Table 1, when the reduction of β-ketophosphonate 6 was carried out with NaBH₄ in methanol (entry 1, Table 1), a mixture of the γ-amino-β-hydroxyphosphonates syn-11 and anti-12 in a 69:31 ratio in favor of syn-11 was obtained in good yield. The reduction of β-ketophosphonate 6 with LiBH₄ 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 β-ketophosphonate 6 with catecholborane (CB) in THF at -78 ºC (entry 4, Table 1), provided the corresponding γ-amino-β-hydroxyphosphonates in 78% yield, with the syn:anti ratio ≥96:4 (the diastereoisomer anti-12 was not observed by ³¹P-NMR).

Table 2. Diastereoselective reduction of β-ketophosphonate 10.

![Chemical structure of 10 with hydride reduction](image)

| Entry | Hydride | Conditions     | Yield (%) | syn-13:anti-14<sup>b</sup> |
|-------|---------|----------------|-----------|----------------------------|
| 1     | NaBH₄   | MeOH, 25 ºC    | 70        | 81:19                      |
| 2     | LiBH₄   | THF, -78 ºC    | 75        | 82:18                      |
| 3     | DIBAL-H | THF, -78 ºC    | 91        | 88:12                      |
| 4     | CB      | THF, -78 ºC    | 87        | ≥96:4                      |

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

Under similar conditions, the reduction of γ-N,N-benzylamino-β-ketophosphonate 10 with NaBH₄ and LiBH₄ as reducing agents provided the mixture of the γ-N,N-benzylamino-β-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 β-ketophosphonate 10 was reduced with DIBAL-H in THF at -78 ºC (entry 3, Table 2). Finally, reduction of 10 with catecholborane in THF at -78 ºC (entry 4, Table 2), afforded the γ-N,N-dibenzylamino-β-hydroxyphosphonates in 87% yield, with a syn:anti ratio ≥96:4 (the diastereoisomer anti-14 was not observed by ³¹P-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 γ-amino-β-hydroxyphosphonates obtained in our laboratory.

The formation of the γ-amino-β-hydroxyphosphonates syn-11 and syn-13 as major diastereoisomer in the reduction of the β-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 bounds 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. $^1$H-NMR spectra were recorded on a Varian INOVA 400 (at 400 MHz), $^{13}$C- (100 MHz) and $^{31}$P-NMR on a Varian Mercuray 200 instrument. HRMS spectra were recorded on a JEOL JMS-700 instrument.

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 NH$_4$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 Na$_2$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. [$\alpha$]$_D$ = -1.3 (c = 1.37, CHCl$_3$). $^1$H-NMR (CDCl$_3$) $\delta$ 1.77–2.15 (m, 4H), 2.36 (m, 1H), 2.98 (dd, $J$ = 21.2, 15.0 Hz, 1H, CH$_2$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$_2$P), 3.48 (system AB, $J = 15.0$ Hz, 1H, CH$_2$Ph), 3.75 (d, $J = 11.2$ Hz, 3H, (CH$_3$O)$_2$P), 3.77 (d, $J = 11.2$ Hz, 3H, (CH$_3$O)$_2$P), 3.82 (system AB, $J = 15.0$ Hz, 1H, CH$_2$Ph), 7.23–7.36 (m, 5 H, H$_{aron}$); $^{13}$C-NMR (CDCl$_3$) 23.9 ([C(CH$_3$)$_3$]), 28.5 ([C(CH$_3$)$_3$]), 35.7 (d, $J = 133.6$ Hz, [C(CH$_3$)$_3$]), 53.1 ([CH$_3$O)$_2$P], 53.3 ([CH$_3$O)$_2$P], 54.2 ([CH$_3$N], 59.5 ([CH$_2$Ph]), 73.7 ([CHN]), 127.4 ([C$_{para}$]), 128.4 ([C$_{metal}$]), 129.2 ([C$_{ortho}$]), 138.4 ([C$_{ipso}$]), 204.8 ([C=O]); $^{31}$P-NMR (CDCl$_3$) $\delta$ 25.94; HRMS (CI, CH$_4$) calculated for C$_{15}$H$_{23}$O$_4$NP (MH$^+$) 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 ºC 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 ºC for 1.5 h and then cooled at -78 ºC 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 ºC for 4 h before the addition of a saturated solution of NH$_4$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$_2$SO$_4$ 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.

General procedure for the reduction of $\beta$-ketophosphonates (S)-6 and (S)-10 with NaBH$_4$. To a solution of $\beta$-ketophosphonate (S)-6 or (S)-10 (1.0 eq.) in methanol (40 mL) at 0 ºC was added NaBH$_4$ (4.0 equiv.). After 5.0 h, the solvent was evaporated and the residue was diluted with H$_2$O and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over Na$_2$SO$_4$ and evaporated in vacuum. The crude was analyzed by $^1$H- and $^{31}$P-NMR and purified by column chromatography.

General procedure for the reduction of $\beta$-ketophosphonates (S)-6 and (S)-10 with LiBH$_4$, 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 ºC. The reaction mixture was stirred for 5.0 h at -78 ºC, and then was quenched with saturated solution of NH$_4$Cl and extracted with ethyl acetate (3 × 40 mL). The organic layer was dried over Na$_2$SO$_4$ and evaporated in vacuum. The crude was analyzed by $^1$H- and $^{31}$P-NMR and purified by column chromatography.

*(2S)-1-Benzylpyrrolidin-2-yl)-(2R)-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 β-hydroxyphosphonate syn-11 as a viscous oil. [α]D = -2.0 (c = 1.02, CHCl3); 1H-NMR (CDCl3) δ 1.24-1.90 (m, 7H), 2.48-2.58 (m, 1H, CH2P), 2.90-3.10 (m, 1H, CH2P), 3.42-3.61 (m, 1H), 3.48 (system AB, J = 13.0 Hz, 1H, CH2Ph), 3.68 (d, J = 11.0 Hz, 3H, (CH3O)2P), 3.76 (d, J = 11.2 Hz, 3H, (CH3O)2P), 4.02 (system AB, J = 13.0 Hz, 1H, CH2Ph), 7.23–7.36 (m, 10 H, H arom); 13C-NMR (CDCl3) 21.6 (CH2CH2), 29.5 (CH2CH), 330.1 (d, J = 133.6 Hz, CH2P), 36.64 (CH2N), 46.8 (NCCH2Ph), 51.7 [(CH3O)2P], 53.2 [(CH3O)2P], 68.20 (CHN), 68.3 (CHOH), 127.4 (C para), 128.4 (C meta), 129.2 (C ortho), 138.4 (C ipso); 31P-NMR (CDCl3) δ 35.3; HRMS (CI, CH4) calculated for C15H25O4NP (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, 0.37mmol) of β-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 β-hydroxyphosphonate syn-13 was obtained as a viscosus oil. [α]D = +17.1 (c = 1.01, CHCl3); 1H-NMR (CDCl3) δ 0.12 (s, 3H, (CH3)2Si), 0.12 (s, 3H, (CH3)2Si), 0.93 (s, 9H, (CH3)3C), 1.79 (ddd, J = 20.0, 15.1, 5.8 Hz, 1H, CH2P), 1.95 (ddd, J = 20.0 Hz, 15.1, 5.8 Hz, 1H, CH2P), 2.64 (m 1H), 3.57 (system AB, J = 13.4 Hz, 2H, CH2Ph), 3.67 (d, J = 11.0 Hz, 3H, (CH3O)2P), 3.72 (d, J = 11.0 Hz, 3H, (CH3O)2P), 3.90 (m, 2H, CH2OSi), 4.00 (system AB, J = 13.4 Hz, 2H, CH2Ph), 4.03–4.13 (m, 1H), 7.22–7.33 (m, 10 H, H arom); 13C-NMR (CDCl3) δ -5.4 ((CH3)2Si), -5.3 ((CH3)2Si), 18.3 (C(CH3)3), 26.1 (CH3)C), 30.5 (d, J = 141.2 Hz, CH2P), 52.5 (d, J = 13.6 Hz, 2C, (CH3O)2P), 55.9 (CH2Ph), 59.6 (CH2OSi), 63.9 (CHOH), 64.1 (CHN), 127.4 (C para), 128.6 (C meta), 129.4 (C ortho), 139.4 (C ipso); 31P-NMR (CDCl3) δ 33.92. HRMS (Cl, CH4) calculated for C26H43O5NPSi (MH+) 508.2648, found 508.2672.

4. Conclusions

In conclusion, we have found that the reduction of N,N-disubstituted-γ-amino-β-ketophosphonates readily obtained from the appropriate L-amino acids, with catecholborane (CB) afforded the syn-γ-amino-β-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.

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