Preparation of phosphostatine and phosphoepistatine from L-leucine via high diastereoselective reduction of 3-amino-2-ketophosphonates

Ricardo De la Cruz-Cordero, Emanuel Hernández-Núñez, Mario Fernández-Zertuche, Miguel Angel Muñoz-Hernández, and Mario Ordóñez*

Centro de Investigaciones Químicas. Universidad Autónoma del Estado de Morelos
Av. Universidad No. 1001. 62210 Cuernavaca, Mor. México.
E-mail: palacios@ciq.uaem.mx

Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday
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Abstract
The reduction of (3S)-N,N-dibenzylamino-2-ketophosphonate 5 derived from L-leucine with catecholborane at -20 °C afford the (3S)-N,N-dibenzylamino-(2R)-hydroxyphosphonate syn-6, whereas the reduction of (3S)-N-benzylamino-2-ketophosphonate 9 with Zn(BH₄)₂ at -78 °C gave the (3S)-N-benzylamino-(2S)-hydroxyphosphonate anti-10. The reduction in both cases was in good chemical yields and high diastereoselectivity. The hydrolysis and hydrogenolysis of syn-6 and anti-10 gave phosphostatine 12 and phosphoepistatine 13, respectively.

Keywords: Phosphostatine, phosphoepistatine, aminophosphonic acids, β-ketophosphonates, diastereoselective reduction, statine analogues

Introduction

(4S)-Amino-(3S)-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 have been developed. 2

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, γ-amino-β-hydroxyphosphonic
acids 2 and 3 have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis. Additionally, the esters of the phosphonic acids 2, 3 and their analogues have been used as inhibitors of D-alanine-D-alanine ligase, and as excellent Leu10-Val11 replacements (LVRs) in the angiotensin II, providing a more potent inhibitory activity for rennin over porcine pepsin and bovine cathepsin D. As a result, numerous synthetic methods for chiral non-racemic \( \beta \)-amino-\( \alpha \)-hydroxyphosphonic acid 2 have been developed. However, to the best of our knowledge, only a few synthetic approaches to obtain optically active esters of 3-amino-2-hydroxyphosphonic acid 3 have been described in the literature, which involve the reaction of the anion of methylphosphonate with \( \alpha \)-aminoaldehydes, and the catalytic asymmetric aminohydroxylation of \( \beta,\gamma \)-unsaturated phosphonates, but in both methodologies the yields and diastereoselectivities remain low. Recently, Yokomatsu et al. described the synthesis of 3-amino-2-hydroxyphosphonates with an improved diastereoselectivity via the dihydroxylation of \( \beta,\gamma \)-unsaturated phosphonates and the subsequent regioselective amination of their cyclic sulfates.

As part of our program directed to the synthesis of chiral 3-amino-2-hydroxyphosphonic acids, herein we describe a new methodology that affords (3S)-amino-(2R)-hydroxy-5-methylhexyl-phosphonic acid (phosphostatine) and (3S)-amino-(2S)-hydroxy-5-methylhexylphosphonic acid (epiphosphostatine), via high diastereoselective reduction of dimethyl (3S)-[3-(\( N,N \)-dibenzyl-amino)] and (3S)-[3-(N-benzylamino)-5-methyl-2-oxohexylphosphonates, derived from L-leucine.

### Results and Discussion

\( (3S)\)-\( N,N \)-Dibenzylamino-2-ketophosphonate 5 was synthesized in two steps from L-leucine (Scheme 1). Thus, the first step of the synthesis was the tribenzylation of L-leucine with excess of benzyl bromide and \( K_2 CO_3 \) under reflux in a mixture of MeOH:H\( _2 O \), obtaining the corresponding (S)-\( N,N \)-dibenzyleucine benzyl ester 4 in 77% yield. Then, the resulting benzyl ester 4 was treated with the lithium salt of dimethyl methylphosphonate at -78 oC in THF, to obtain the (3S)-\( N,N \)-dibenzylamino-2-ketophosphonate 5 in 98% yield.

\[ \text{Scheme 1} \]
Having efficiently prepared the 2-ketophosphonate 5, we turned our attention to the diastereoselective reduction of the carbonyl group to obtain the (3S)-N,N-dibenzylamino-2-hydroxyphosphonates 6 and 7. The reduction was carried out using NaBH₄, Zn(BH₄)₂ and catecholborane as reducing agents. Conditions, yields and diastereomeric ratio are summarized in Table 1.

### Table 1. Reduction of 2-ketophosphonate 5 with various reducing agents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydride</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>syn-6:anti-7¹⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄</td>
<td>MeOH, 25 °C</td>
<td>94</td>
<td>86:14</td>
</tr>
<tr>
<td>2</td>
<td>Zn(BH₄)₂</td>
<td>THF, -78 °C</td>
<td>87</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>Catecholborane</td>
<td>THF, -20 °C</td>
<td>85</td>
<td>&gt;98:2</td>
</tr>
</tbody>
</table>

¹⁰ Chemical yield after purification by column chromatography.

⁰ Determined by ¹H NMR at 400 MHz and ³¹P NMR at 200 MHz.

As shown in Table 1, the reduction of 5 with NaBH₄ at 25 °C in methanol afford the 2-hydroxyphosphonates syn-6 and anti-7 with excellent chemical yield and moderate diastereoselectivity, in favor of diastereomer syn-6 (entry 1). Identical results were obtained in the reduction of 5 with Zn(BH₄)₂ (entry 2). Remarkably, when the reduction of 5 was carried out with catecholborane, only the diastereomer syn-6 could be detected by both ¹H and ³¹P NMR (entry 3). Diastereomeric ratio of the reduction of 5 was determined by means of ¹H and ³¹P NMR. In fact, in ³¹P NMR the signal for the diastereomer syn-6 was more shielded (34.72 ppm) than that the diastereomer anti-7 (35.37 ppm). The absolute configuration of the new stereogenic center in syn-6 and anti-7 was assigned by analogy with other (3S)-N,N-dibenzylamino-2-hydroxyphosphonates.

Therefore, we propose that the reduction of 5 with catecholborane took place under non-chelation control or Felkin-Ahn model, and that the bulkyness 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 and, thereby allowing the addition of hydride to take in a diastereoselective manner (Figure 1a). On the other hand, the reduction of 5 with Zn(BH₄)₂ seems to proceed in such way that the metal ions do not bind sufficiently strongly to the N,N-dibenzylamino and keto groups to induce chelation controlled reaction (Figure 1b). It was expected that the zinc ions would provide increased conformational control and hence higher diastereoselectivity toward the 2-hydroxyphosphonate anti-7; however,
this is not the case, thus, the counterion does not appear to be involved on the induction of diastereoselection. This diastereofacial preference is in agreement with that reported previously for the reduction of 1-aminoalkylchloromethyl ketones,\textsuperscript{14} for the reductive amination of $\alpha$-amino ketones,\textsuperscript{15} and reduction of 1-aminoalkylchloromethyl ketimines.\textsuperscript{16}

![Figure 1. Reduction of 2-ketophosphonates 5: (a) non-chelation control, (b) chelation control](image)

In order to induce the formation of $\textit{anti}$-$3$-amino-$2$-hydroxyphosphonate, now we turned to the preparation of (3$S$)-$N$-benzylamino-$2$-ketophosphonate 9 (Scheme 2).\textsuperscript{17} Thus, the starting (3$S$)-$N$-benzyleucine methyl ester 8 was prepared by treatment of the corresponding amino methyl ester hydrochloride with $K_2CO_3$ and benzyl bromide in acetonitrile at room temperature. Then, the methyl ester 8 was treated with the lithium salt of dimethyl methylphosphonate at -78 °C in THF, to afford the corresponding (3$S$)-$N$-benzylamino-$2$-ketophosphonate 9 (Scheme 2).

![Scheme 2](image)

Just as we have previously described,\textsuperscript{17} the reduction of 9 using Zn(BH$_4$)$_2$ at -78 °C in THF afforded the corresponding 3-$N$-benzylamino-$2$-hydroxyphosphonates $\textit{anti}$-10 and $\textit{syn}$-11 in good chemical yield and with high diastereoselectivity, with a predominance of the desired $\textit{anti}$ product (Scheme 3).

![Scheme 3](image)

Finally, the hydrolysis of 2-hydroxyphosphonates $\textit{syn}$-6 and $\textit{anti}$-10 with bromotrimethylsilane at room temperature\textsuperscript{9,18} afforded the corresponding 2-hydroxyphosphonic
acid, that without any further purification was treated with palladium on carbon in methanol under hydrogen gas atmosphere at room temperature, obtaining the phosphostatine 12 and phosphoepistatine 13, in 89% and 93% yield, respectively, (Scheme 4).

Scheme 4

In conclusion, we have found a new methodology for the preparation of phosphostatine and phosphoepistatine diastereomerically pure. Additionally, the conditions described in this paper, make this experimental operation a good and simple method to obtain the 3-amino-2-hydroxyphosphonates syn and anti in high diastereoselectivity changing the protective group on the nitrogen atom of L-amino acid.

Experimental Section

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) 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. The spectra were recorded in D$_2$O or CDCl$_3$ solution, using TMS as internal reference. Microanalyses were registered on an Elemental VARIO EL III. MS 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 °C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.

(S)-N,N-Dibenzyleucine benzyl ester 4. A solution of benzyl bromide (13.0 g, 9.1 mL, 76 mmol) and methanol (40 mL) was slowly added to a mixture of L-leucine (2.5 g, 19 mmol), K$_2$CO$_3$ (9.2 g, 67 mmol) in methanol-water (5:1, 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 x 150 mL). The combined
organic layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude product were purified by flash chromatography using hexane:AcOEt (20:1) as eluent, to give **4** as a viscous liquid 3.6 g, 77% yield. \([\alpha]_D = -102.1 (c = 3.6, \text{CHCl}_3)\).

**1H NMR** (400 MHz, CDCl₃) \(\delta\) 0.59 (d, J=6.8 Hz, 3H, \((\text{CH}_3)_2\text{CH})\), 0.81 (d, J=6.8 Hz, 3H, \((\text{CH}_3)_2\text{CH})\), 1.50 (ddd, J=14.0, 8.6, 5.6 Hz, 1H, CH₂CH(CH₃)₂), 1.70 (ddd, J=14.0, 8.6, 5.6 Hz, 1H, CH₂CH(CH₃)₂), 1.73-1.80 (m, 1H, CH(CH₃)₂), 3.42 (dd, J=8.6, 5.6 Hz, 1H, CHN), 3.49 (AB, J=13.6 Hz, 2H, NCH₂Ph), 3.89 (AB system, J=13.6 Hz, 2H, NCH₂Ph), 5.14 (AB system, J=12.4 Hz, 1H, OCH₂Ph), 5.26 (AB, J=12.4 Hz, 1H, OCH₂Ph), 7.18-7.44 (m, 15H, H_arom).

**13C NMR** (100 MHz, CDCl₃) \(\delta\) 21.7 ((CH₃)₂CH), 23.4 ((CH₃)₂CH), 24.6 (CH(CH₃)₂), 38.75 (CH₂CH(CH₃)₂), 54.6 (NCH₂Ph), 58.9 (CHN), 66.1 (OCH₂Ph), 127.1, 128.3, 128.4, 128.6, 128.8, 129.1, 136.3, 139.8, 173.4 (C=O).

**((S))-N-Benzyleucine methyl ester 8.** Benzyl bromide (2.8 g, 2.0 mL, 17 mmol) was slowly added to a solution of L-leucine methyl ester hydrochloride (3.0 g, 17 mmol) and K₂CO₃ (5.7 g, 41 mmol) in acetonitrile (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. Then, water (30 mL) was added and the resulting mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography using hexane:AcOEt (10:1) as eluent, to give **8** as a viscous liquid 2.9 g, 76% yield. \([\alpha]_D = -42.3 (c = 1.3, \text{CHCl}_3)\); Lit.\(^19\) \([\alpha]_D = -40.7 (c = 1.0, \text{CHCl}_3)\).

**Dimethyl (3S)-(3-N,N-dibenzylamino-5-methyl-2-oxohexylphosphonate 5.**\(^12\) A solution of dimethyl methylphosphonate (2.81 g, 22.7 mmol) in anhydrous THF (40 mL) was cooled at -78 °C before the slow addition of \(n\)-BuLi 2.5 M in hexanes (9.7 mL, 23.3 mmol). The resulting solution was stirred at -50 °C for 1.5 h and then cooled to -78 °C. To this mixture was slowly added a solution of benzyl ester **4** (2.6 g, 6.5 mmol) in dry THF (45 mL). The reaction mixture was stirred at -78 °C for 4 h before the addition of a saturated solution of NH₄Cl. The solvent was evaporated under reduced pressure, the residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane:ethyl acetate (50:50) to give **5** as a viscous liquid 2.7 g, 98% yield. \([\alpha]_D = -100 (c = 3.78, \text{CHCl}_3)\).

**1H NMR** (400 MHz, CDCl₃) \(\delta\) 0.80 (d, J=6.6 Hz, 3H, \((\text{CH}_3)_2\text{CH})\), 0.91 (d, J=6.6 Hz, 3H, \((\text{CH}_3)_2\text{CH})\), 1.34 (ddd, J=13.0, 9.2, 3.2 Hz, 1H, CH₂CH(CH₃)₂), 1.41-1.51 (m, 1H, CH(CH₃)₂), 1.84 (ddd, J=13.0, 9.2, 3.2 Hz, 1H, CH₂CH(CH₃)₂), 2.94 (dd, J=23.2, 14.0 Hz, 1H, CH₂P), 3.42 (AB system, J=13.0 Hz, 2H, NCH₂Ph), 3.45 (q, J=3.2 Hz, 1H, CHN), 3.48 (d, J=11.2 Hz, 3H, \((\text{CH}_3)_2\text{O})₂\text{P}\), 3.64 (dd, J=23.2, 14.0 Hz, 1H, CH₂P), 3.65 (d, J=11.2 Hz, 3H, \((\text{CH}_3)_2\text{O})₂\text{P}\), 3.68 (AB system, J=13.0 Hz, 2H, CH₂Ph), 7.24-7.36 (m, 10H, H_arom). **13C NMR** (100 MHz, CDCl₃) \(\delta\) 22.1 ((CH₃)₂CH), 23.8 ((CH₃)₂CH), 25.6 (CH₂CH(CH₃)₂), 30.5 (CH(CH₃)₂), 37.9 (d, J=128.3 Hz, CH₂P), 52.8 (d, J=6.1 Hz, \((\text{CH}_3)\text{O})₂\text{P}\), 52.9 (d, J=6.1 Hz, \((\text{CH}_3)\text{O})₂\text{P}\), 54.7 (CH₂Ph), 64.7 (CHNBn₂), 127.5, 128.6, 129.3, 139.3, 201.8 (d, J=6.8 Hz, C=O). **31P NMR** (200 MHz, CDCl₃) \(\delta\) 24.59. Anal. calcd. for C₂₃H₃₂NO₄P: C, 66.17; H, 7.61; N, 3.47%. Found C, 65.93; H, 7.61; N, 3.47%.
Dimethyl (3S)-N-benzylamino-5-methyl-2-oxobutylphosphonate 9. In an identical manner, the (S)-N-benzyleucine methyl ester 8 (1.0 g, 4.2 mmol) in dry THF (25 mL) at -78 °C, was treated with a solution of dimethyl methylphosphonate (1.6 g, 12.7 mmol) and n-BuLi 2.4 M in hexanes (5.5 mL, 13.2 mmol) in anhydrous THF (25 mL). The crude product (74%) was analyzed by $^{31}$P NMR (200 MHz, CDCl$_3$) $\delta$ 24.38, and without any further purification was used in the next step.

Reduction of $\beta$-ketophosphonate (S)-5 with NaBH$_4$. To a solution of $\beta$-ketophosphonates 5 (1.0 equiv) in methanol (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 was dissolved in water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuum. The crude $\beta$-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 (3S)-N,N-dibenzylamino-(2R)-hydroxy-4-methylhexylphosphonate (syn-6). To a solution of $\beta$-ketophosphonate 5 (1.0 g, 2.4 mmol) in dry THF (40 mL) cooled at -20 °C was added catecholborane (9.6 mL, 9.6 mmol) 1 M in THF. The reaction mixture was stirred at -78 °C for 4 h, and quenched with a saturated solution of NH$_4$Cl. The solvent was evaporated in vacuum, the residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuum. The crude $\beta$-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 to give as a viscous liquid (871 mg, 87% yield) of syn-6. $[^\alpha]D = -5.7$ (c = 2.9, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.92 (d, J=6.4 Hz, 3H, (CH$_3$)$_2$CH), 1.33 (ddd, J=13.6, 6.8, 6.8 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.58 (ddd, J=13.6, 8.0, 4.8 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.69-1.72 (m, 1H, CH(CH$_3$)$_2$), 1.77 (ddd, J=20.0, 15.2, 2.0 Hz, 1H, CH$_2$P), 1.95 (ddd, J=15.2, 15.2, 10.0 Hz, 1H, CH$_2$P), 2.48 (ddd, J=8.0, 8.0, 4.8 Hz, 1H, CHNBn$_2$), 3.43 (AB system, J=13.4 Hz, 2H, CH$_2$Ph), 3.71 (d, J=11.0 Hz, 3H, (CH$_3$O)$_2$P), 3.75 (d, J=11.0 Hz, 3H, (CH$_3$O)$_2$P), 3.86-3.92 (m, 1H, CHO), 3.92 (AB system, J=13.4 Hz, 2H, CH$_2$Ph), 7.21-7.32 (m, 10H, H$_{arom}$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.0 ((CH$_3$)$_2$CH), 23.6 ((CH$_3$)$_2$CH), 26.4 (CH$_2$CH(CH$_3$)$_2$), 30.8 (J=140.4 Hz, CH$_2$P), 34.9 (CH(CH$_3$)$_2$), 52.5 (d, J=6.6 Hz, (CH$_3$O)$_2$P), 52.8 (d, J=6.6 Hz, (CH$_3$O)$_2$P), 54.6 (CH$_2$Ph), 60.8 (d, J=18.2 Hz, CHO), 67.3 (d, J=6.1 Hz, CHNBn$_2$), 127.3, 128.6, 129.3, 139.7. $^{31}$P NMR (200 MHz, CDCl$_3$) $\delta$ 34.72. Anal. calcd. for C$_{23}$H$_{34}$NO$_4$P: C, 65.85; H, 8.17; N, 3.34%. Found C, 65.47; H, 8.04; N, 3.21%.

Dimethyl (3S)-N-benzylamino-(2S)-hydroxy-4-methylhexylphosphonate (anti-10). In an identical manner the 2-ketophosphonate 9 (1.4 g, 4.2 mmol) in dry THF (20 mL) was treated at -78 °C with a solution of Zn(BH$_4$)$_2$ (77 mL, 17 mmol) 1 M in THF, obtaining the mixture of 2-hydroxyphosphonates anti-10 and syn-11 in a 96:4 ratio, respectively. The mixture was purified by flash chromatography obtaining the 2-hydroxyphosphonate anti-10 diastereomerically pure as a viscous liquid (1.3 g, 95% yield). $[^\alpha]D = -9.9$ (c=2.2, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$)
δ 0.81 (d, J=6.8 Hz, 3H, (CH$_3$)$_2$CH), 0.91 (d, J=6.8 Hz, 3H, (CH$_3$)$_2$CH), 1.16 (ddd, J=14.0, 8.8, 4.8 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.33 (ddd, J=14.0, 8.8, 5.6 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.56-1.66 (m, 1H, CH(CH$_3$)$_2$), 1.87 (ddd, J=19.6, 15.2, 3.2 Hz, 1H, CH$_2$P), 2.00 (ddd, J=16.8, 15.2, 10.0 Hz, 1H, CH$_2$P), 2.70 (ddd, J=8.8, 8.8, 4.4 Hz, 1H, CHNH), 3.76 (d, J=10.8 Hz, 3H, (CH$_3$O)$_2$P), 3.77 (AB system, J=13.2 Hz, 1H, CH$_2$Ph), 3.78 (d, J=10.8 Hz, 3H, (CH$_3$O)$_2$P), 3.86 (AB system, J=13.2 Hz, 1H, CH$_2$Ph), 4.10-4.16 (m, 1H, CHOH), 7.23-7.35 (m, 5H, H$_{arom}$). 13C NMR (100 MHz, CDCl$_3$) δ 22.5 ((CH$_3$)$_2$CH), 23.6 ((CH$_3$)$_2$CH), 24.9 (CH$_2$CH(CH$_3$)$_2$), 28.1 (J=141.2 Hz, CH$_2$P), 38.6 (CH(CH$_3$)$_2$), 52.1 (CH$_2$Ph), 52.4 (d, J=7.6 Hz, (CH$_3$O)$_2$P), 52.8 (d, J=7.6 Hz, (CH$_3$O)$_2$P), 59.2 (d, J=15.2 Hz, CHOH), 66.5 (CHNH), 127.3, 128.4, 128.6, 140.4. 31P NMR (200 MHz, CDCl$_3$) δ 35.03. HRMS (CI$^+$, CH$_4$) calcd. for C$_{16}$H$_{29}$NO$_4$P (MH$^+$) 330.1756 found 330.1519.

(3S)-Amino-(2R)-hydroxy-5-methylhexylphosphonic acid (phosphostatine) (12). 2-Hydroxyphosphonate $\text{syn-6}$ (450 mg, 1.07 mmol) was treated at 0 °C under a nitrogen atmosphere with bromotrimethylsilane (361 mg, 0.31 mL, 2.36 mmol). The reaction mixture was stirred at room temperature for 6-8 h, and after this period of time the volatile materials were evaporated under reduced pressure, water was then added. After 30 min. the solvents were evaporated in vacuo to give (3S)-N,N-dibenzylamino-(2R)-hydroxyphosphonic acid, which without isolation were treated with palladium on carbon (5 % wt) 225 mg in methanol (10 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 solvent was evaporated under reduced pressure. The residue was treated with propylene oxide (5 mL) to give the title compound as a white solid (201 mg, 89% yield). m.p. 220-222 °C. [α]$_D$= -11.4 (c=2.76, H$_2$O). $^1$H NMR (400 MHz, D$_2$O) δ 0.93 (d, J=6.4 Hz, 3H, (CH$_3$)$_2$CH), 0.95 (d, J=6.4 Hz, 3H, (CH$_3$)$_2$CH), 1.51 (ddd, J=14.4, 6.4, 6.4 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.56 (ddd, J=14.4, 6.4, 6.4 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.71 (ninth, J=6.4 Hz, 1H, CH(CH$_3$)$_2$), 1.87 (ddd, J=17.6, 15.2, 8.0 Hz, 1H, CH$_2$P), 1.96 (ddd, J=19.6, 15.2, 4.8 Hz, 1H, CH$_2$P), 3.38 (dt, J=8.4, 5.2 Hz, 1H, CHNH$_2$), 4.00-4.07 (m, 1H, CHOH). 13C NMR (100 MHz, D$_2$O) δ 23.6 ((CH$_3$)$_2$CH), 24.7 ((CH$_3$)$_2$CH), 26.4 (CH$_2$CH(CH$_3$)$_2$), 34.8 (J=130.5 Hz, CH$_2$P), 40.9 (CH(CH$_3$)$_2$), 57.0 (d, J=12.1 Hz, CHOH), 69.4 (d, J=3.1 Hz, CHNH$_2$). 31P NMR (200 MHz, D$_2$O) δ 21.10. HRMS (CI$^+$, CH$_4$) calcd. for C$_{7}$H$_{19}$NO$_4$P (MH$^+$) 212.1959 found 212.1906.

(3S)-Amino-(2S)-hydroxy-5-methylhexylphosphonic acid (phosphoepistatine) (13). In an identical manner, the 2-hydroxyphosphonate $\text{anti-10}$ (350 mg, 1.06 mmol) was treated with bromotrimethylsilane (357 mg, 0.31 mL, 2.36 mmol) followed by palladium on carbon (5 % wt) 225 mg in methanol (10 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 solvent was evaporated under reduced pressure. The residue was treated with propylene oxide (5 mL) to give the title compound as a white solid (201 mg, 89% yield). m.p. 220-222 °C. [α]$_D$= -20.8, (c=1.81, H$_2$O). $^1$H NMR (400 MHz, D$_2$O) δ 0.92 (d, J=6.2 Hz, 3H, (CH$_3$)$_2$CH), 0.97 (d, J=6.2 Hz, 3H, (CH$_3$)$_2$CH), 1.46 (ddd, J=14.4, 10.0, 4.4 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.56 (ddd, J=14.4, 10.0, 4.4 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.62-1.72 (m, 1H, CH(CH$_3$)$_2$), 1.79 (ddd, J=18.0, 15.2, 8.4 Hz, 1H, CH$_2$P), 1.87 (ddd, J=18.8, 15.2, 5.6 Hz, 1H, CH$_2$P), 3.51 (ddd, J=9.6, 4.0, 4.0 Hz, 1H, CHNH$_2$), 4.17-4.24 (m, 1H, CHOH). 13C NMR (100 MHz, D$_2$O) δ 23.1 ((CH$_3$)$_2$CH), 25.2 ((CH$_3$)$_2$CH), 26.3 (CH$_2$CH(CH$_3$)$_2$), 33.4 (J=130.6 Hz, CH$_2$P), 37.7 (CH(CH$_3$)$_2$), 56.5 (d, J=10.6 Hz, CHOH), 70.1 (d, J=3.1 Hz, CHNH$_2$).
$^{31}$P NMR (200 MHz, D$_2$O) $\delta$ 21.14. HRMS (Cl$^+$, CH$_4$) calcd. for C$_7$H$_{19}$NO$_4$P (MH$^+$) 212.1959 found 212.1884.

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References and footnotes


10. Reduction of other 2-ketophosphonates have been described by us, see: Ordóñez, M.; De la Cruz-Cordero, R.; Fernández-Zertuche, M.; Muñoz-Hernández, M. A. Tetrahedron: Asymmetry 2002, 13, 559.
12. The preparation of 2-ketophosphonate 5 has been described, although to the best of our knowledge no data given: see ref. 11d.