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

Ricardo De la Cruz-Cordero, Emanuel Hernándes-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

Abstract

The reduction of (3*S*)-*N,N*-dibenzylamino-2-ketophosphonate **5** derived from L-leucine with catecholborane at -20 °C afford the (3*S*)-*N,N*-dibenzylamino-(2*R*)-hydroxyphosphonate *syn*-**6**, whereas the reduction of (3*S*)-*N*-benzylamino-2-ketophosphonate **9** with $Zn(BH_4)_2$ at -78 °C gave the (3*S*)-*N*-benzylamino-(2*S*)-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

(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 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.[4] Additionally, the esters of the phosphonic acids **2**, **3** 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 a result, numerous synthetic methods for chiral non-racemic β-amino-α-hydroxyphosphonic **2** 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 **3** 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.

Statine **1**   **2**   **3**
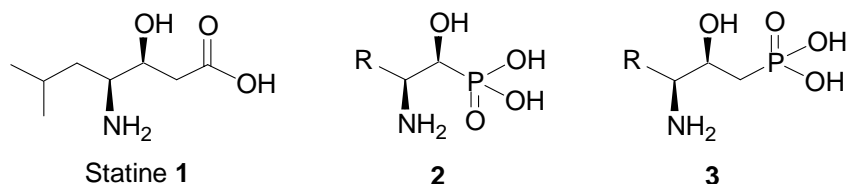
As part of our program directed to the synthesis of chiral 3-amino-2-hydroxyphosphonic acids,[9] herein we describe a new methodology that affords (3*S*)-amino-(2*R*)-hydroxy-5-methylhexyl-phosphonic acid (phosphostatine) and (3*S*)-amino-(2*S*)-hydroxy-5-methylhexylphosphonic acid (epiphosphostatine), *via* high diastereoselective reduction of dimethyl (3*S*)-[3-(*N,N*-dibenzyl-amino)- and (3*S*)-[3-(*N*-benzylamino)-5-methyl-2-oxohexylphosphonates, derived from L-leucine.[10]

Results and Discussion

(3*S*)-*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_2CO_3 under reflux in a mixture of $MeOH:H_2O$, obtaining the corresponding (*S*)-*N,N*-dibenzylleucine benzyl ester **4** in 77% yield.[11] Then, the resulting benzyl ester **4** was treated with the lithium salt of dimethyl methylphosphonate at -78 oC in THF, to obtain the (3*S*)-*N,N*-dibenzylamino-2-ketophosphonate **5** in 98% yield.[12]
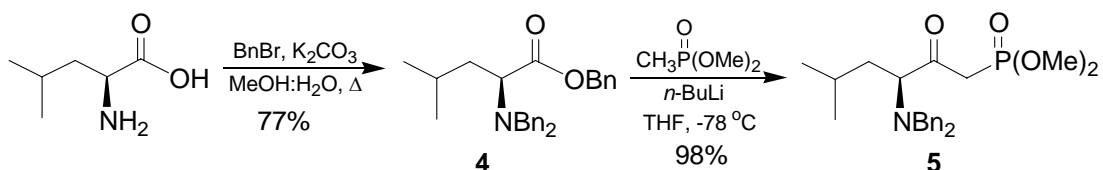
Scheme 1

Having efficiently prepared the 2-ketophosphonate **5**, we turned our attention to the diastereoselective reduction of the carbonyl group to obtain the (3*S*)-*N,N*-dibenzylamino-2-hydroxyphosphonates **6** and **7**. The reduction was carried out using $NaBH_4$, $Zn(BH_4)_2$ 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
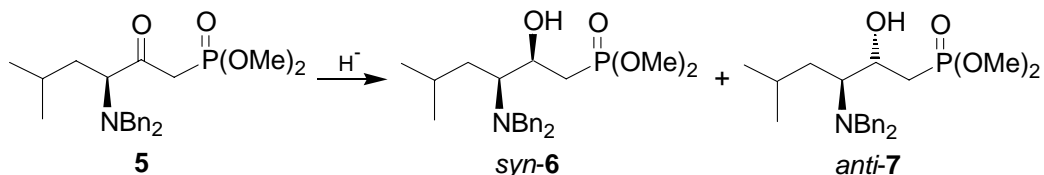
Entry	Hydride	Conditions	Yield (%)[a]	syn-**6**:anti-**7**[b]
1	$NaBH_4$	MeOH, 25 °C	94	86:14
2	$Zn(BH_4)_2$	THF, -78 °C	87	82:18
3	Catecholborane	THF, -20 °C	85	>98:2

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

As shown in Table 1, the reduction of **5** with $NaBH_4$ 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 $Zn(BH_4)_2$ (entry 2). Remarkably, when the reduction of **5** was carried out with catecholborane, only the diastereomer *syn*-**6** could be detected by both ^{1}H and ^{31}P NMR (entry 3). Diastereomeric ratio of the reduction of **5** was determinated by means of ^{1}H and ^{31}P NMR. In fact, in ^{31}P 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 (3*S*)-*N,N*-dibenzylamino-2-hydroxyphosphonates.[10]

Therefore, we propose that the reduction of **5** with catecholborane took place under non-chelation control or Felkin-Ahn model,[13] 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 $Zn(BH_4)_2$ 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,[14] for the reductive amination of α-amino ketones,[15] and reduction of 1-aminoalkylchloromethyl ketimines.[16]
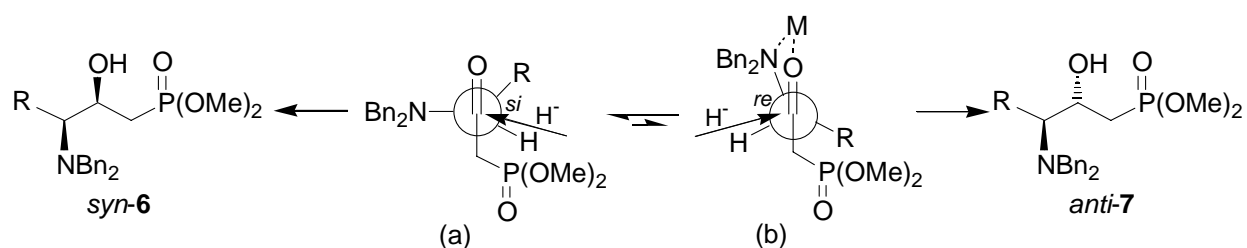

Figure 1. Reduction of 2-ketophosphonates **5**: (a) non-chelation control, (b) chelation control

In order to induce the formation of *anti*-3-amino-2-hydroxyphosphonate, now we turned to the preparation of (3S)-*N*-benzylamino-2-ketophosphonate **9** (Scheme 2).[17] Thus, the starting (S)-*N*-benzylleucine 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 (3S)-*N*-benzylamino-2-ketophosphonate **9** (Scheme 2).
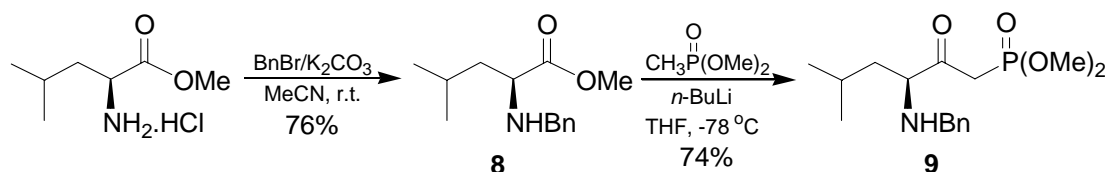
Scheme 2

Just as we have previously described,[17] the reduction of **9** using $Zn(BH_4)_2$ at -78 °C in THF afforded the corresponding 3-*N*-benzylamino-2-hydroxyphosphonates *anti*-**10** and *syn*-**11** in good chemical yield and with high diastereoselectivity, with a predominance of the desired *anti* product (Scheme 3).
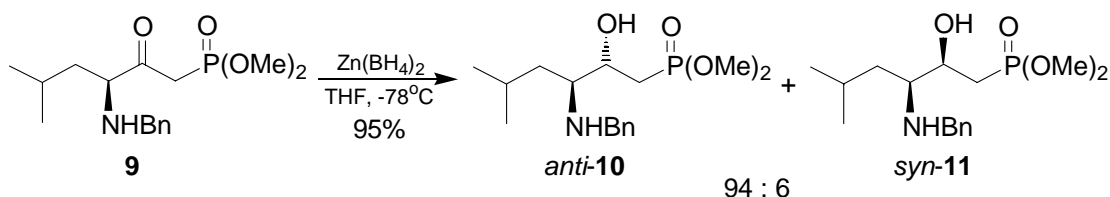
Scheme 3

Finally, the hydrolysis of 2-hydroxyphosphonates *syn*-**6** and *anti*-**10** with bromotrimethylsilane at room temperature[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).
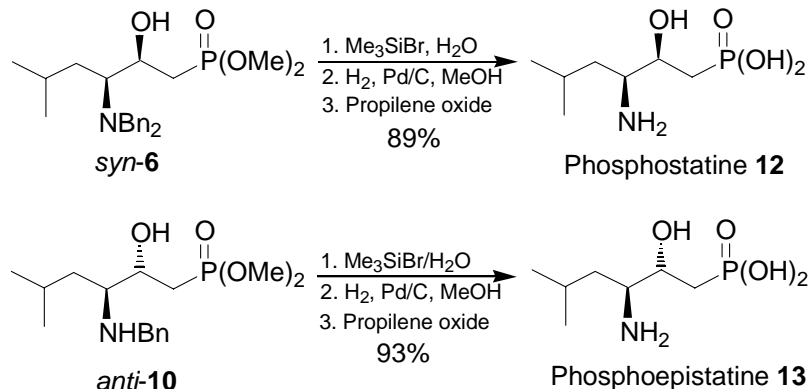
Scheme 4

In conclusion, we have found a new methodology for the preparation of phosphostatine and phosphoepistatine diastereomerically pures. 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_2O 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-Dibenzylleucine benzyl ester 4.[11] 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_2CO_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 Na$_2$SO$_4$, 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. [α]$_D$ = -102.1 (c = 3.6, CHCl$_3$). **^{1}H NMR** (400 MHz, CDCl$_3$) δ 0.59 (d, J=6.8 Hz, 3H, (CH$_3$)$_2$CH), 0.81 (d, J=6.8 Hz, 3H, (CH$_3$)$_2$CH), 1.50 (ddd, J=14.0, 8.6, 5.6 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.70 (ddd, J=14.0, 8.6, 5.6 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.73-1.80 (m, 1H, CH(CH$_3$)$_2$), 3.42 (dd, J=8.6, 5.6 Hz, 1H, CHN), 3.49 (AB, J=13.6 Hz, 2H, NCH$_2$Ph), 3.89 (AB system, J=13.6 Hz, 2H, NCH$_2$Ph), 5.14 (AB system, J=12.4 Hz, 1H, OCH$_2$Ph), 5.26 (AB, J=12.4 Hz, 1H, OCH$_2$Ph), 7.18-7.44 (m, 15H, H$_{arom}$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 21.7 ((CH$_3$)$_2$CH), 23.4 ((CH$_3$)$_2$CH), 24.6 (CH(CH$_3$)$_2$), 38.75 (CH$_2$CH(CH$_3$)$_2$, 54.6 (NCH$_2$Ph), 58.9 (CHN), 66.1 (OCH$_2$Ph), 127.1, 128.3, 128.4, 128.6, 128.8, 129.1, 136.3, 139.8, 173.4 (C=O).

(S)-N-Benzylleucine 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 K$_2$CO$_3$ (5.7 g, 41 mmol) in acetonitrile (40 mL) at 0 ^{o}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 Na$_2$SO$_4$, 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. [α]$_D$ = -42.3 (c = 1.3, CHCl$_3$); Lit.[19] [α]$_D$ = -40.7 (c = 1.0, 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 ^{o}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 ^{o}C for 1.5 h and then cooled to -78 ^{o}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 ^{o}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 x 40 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) to give **5** as a viscous liquid 2.7 g, 98% yield. [α]$_D$ = -100 (c = 3.78, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.80 (d, J=6.6 Hz, 3H, (CH$_3$)$_2$CH), 0.91 (d, J=6.6 Hz, 3H, (CH$_3$)$_2$CH), 1.34 (ddd, J=13.0, 9.2, 3.2 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 1.41-1.51 (m, 1H, CH(CH$_3$)$_2$), 1.84 (ddd, J=13.0, 9.2, 3.2 Hz, 1H, CH$_2$CH(CH$_3$)$_2$), 2.94 (dd, J=23.2, 14.0 Hz, 1H, CH$_2$P), 3.42 (AB system, J=13.0 Hz, 2H, CH$_2$Ph), 3.45 (q, J=3.2 Hz, 1H, CHN), 3.48 (d, J=11.2 Hz, 3H, (CH$_3$O)$_2$P), 3.64 (dd, J=23.2, 14.0 Hz, 1H, CH$_2$P), 3.65 (d, J=11.2 Hz, 3H, (CH$_3$O)$_2$P), 3.68 (AB system, J=13.0 Hz, 2H, CH$_2$Ph), 7.24-7.36 (m, 10H, H$_{arom}$). ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.1 ((CH$_3$)$_2$CH), 23.8 ((CH$_3$)$_2$CH), 25.6 (CH$_2$CH(CH$_3$)$_2$), 30.5 (CH(CH$_3$)$_2$), 37.9 (d, J=128.3 Hz, CH$_2$P), 52.8 (d, J=6.1 Hz, (CH$_3$O)$_2$P), 52.9 (d, J=6.1 Hz, (CH$_3$O)$_2$P), 54.7 (CH$_2$Ph), 64.7 (CHNBn$_2$), 127.5, 128.6, 129.3, 139.3, 201.8 (d, J=6.8 Hz, C=O). ^{31}P NMR (200 MHz, CDCl$_3$) δ 24.59. Anal. calcd. for C$_{23}$H$_{32}$NO$_4$P: 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-oxobuthylphosphonate 9. In an identical manner, the (S)-N-benzylleucine methyl ester **8** (1.0 g, 4.2 mmol) in dry THF (25 mL) at -78 ^{o}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$_3$) δ 24.38, and without any further purification was used in the next step.

Reduction of β-ketophosphonate (S)-5 with NaBH$_4$. To a solution of β-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 β-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 β-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 β-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**. [α]$_D$ = -5.7 (c = 2.9, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (d, J=6.4 Hz, 3H, (CH$_3$)$_2$CH), 0.93 (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, CHOH), 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$_3$) δ 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, CHOH), 67.3 (d, J=6.1 Hz, CHNBn$_2$), 127.3, 128.6, 129.3, 139.7. ^{31}P NMR (200 MHz, CDCl$_3$) δ 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 a -78°C with a solution of Zn(BH$_4$)$_2$ (77 mL, 17 mmol) 1 M in THF,[20] 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). [α]$_D$= -9.9 (c=2.2, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$)

δ 0.81 (d, J=6.8 Hz, 3H, $(CH_3)_2CH$), 0.91 (d, J=6.8 Hz, 3H, $(CH_3)_2CH$), 1.16 (ddd, J=14.0, 8.8, 4.8 Hz, 1H, $CH_2CH(CH_3)_2$), 1.33 (ddd, J=14.0, 8.8, 5.6 Hz, 1H, $CH_2CH(CH_3)_2$), 1.56-1.66 (m, 1H, $CH(CH_3)_2$), 1.87 (ddd, J=19.6, 15.2, 3.2 Hz, 1H, CH_2P), 2.00 (ddd, J=16.8, 15.2, 10.0 Hz, 1H, CH_2P), 2.70 (ddd, J=8.8, 8,8, 4.4 Hz, 1H, CHNH), 3.76 (d, J=10.8 Hz, 3H, $(CH_3O)_2P$), 3.77 (AB system, J=13.2 Hz, 1H, CH_2Ph), 3.78 (d, J=10.8 Hz, 3H, $(CH_3O)_2P$), 3.86 (AB system, J=13.2 Hz, 1H, CH_2Ph), 4.10-4.16 (m, 1H, CHOH), 7.23-7.35 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 ($(CH_3)_2CH$), 23.6 ($(CH_3)_2CH$), 24.9 ($CH_2CH(CH_3)_2$), 28.1 (J=141.2 Hz, CH_2P), 38.6 ($CH(CH_3)_2$), 52.1 (CH_2Ph), 52.4 (d, J=7.6 Hz, $(CH_3O)_2P$), 52.8 (d, J=7.6 Hz, $(CH_3O)_2P$), 59.2 (d, J=15.2 Hz, CHOH), 66.5 (CHNH), 127.3, 128.4, 128.6, 140.4. ^{31}P NMR (200 MHz, $CDCl_3$) δ 35.03. HRMS (CI^+, CH_4) calcd. for $C_{16}H_{29}NO_4P$ (MH^+) 330.1756 found 330.1519.

(3*S*)-Amino-(2*R*)-hydroxy-5-methylhexylphosphonic acid (phosphostatine) (12). 2-Hydroxy-phosphonate *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 (3*S*)-*N,N*-dibenzylamino-(2*R*)-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. $[\alpha]_D$= -11.4 (c=2.76, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 0.93 (d, J=6.4 Hz, 3H, $(CH_3)_2CH$), 0.95 (d, J=6.4 Hz, 3H, $(CH_3)_2CH$), 1.51 (ddd, J=14.4, 6.4, 6.4 Hz, 1H, $CH_2CH(CH_3)_2$), 1.56 (ddd, J=14.4, 6.4, 6.4 Hz, 1H, $CH_2CH(CH_3)_2$), 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_2P), 1.96 (ddd, J=19.6, 15.2, 4.8 Hz, 1H, CH_2P), 3.38 (dt, J=8.4, 5.2 Hz, 1H, $CHNH_2$), 4.00-4.07 (m, 1H, CHOH). ^{13}C NMR (100 MHz, D_2O) δ 23.6 ($(CH_3)_2CH$), 24.7 ($(CH_3)_2CH$), 26.4 ($CH_2CH(CH_3)_2$), 34.8 (J=130.5 Hz, CH_2P), 40.9 ($CH(CH_3)_2$), 57.0 (d, J=12.1 Hz, CHOH), 69.4 (d, J=3.1 Hz, $CHNH_2$). ^{31}P NMR (200 MHz, D_2O) δ 21.10. HRMS (CI^+, CH_4) calcd. for $C_7H_{19}NO_4P$ (MH^+) 212.1959 found 212.1906.

(3*S*)-Amino-(2*S*)-hydroxy-5-methylhexylphosphonic acid (phosphoepistatine) (13). In an identical manner, the 2-hydroxyphosphonate *anti*-**10** (350 mg, 1.06 mmol) was treated with bromotrimethylsilane (357 mg, 0.31 mL, 2.33 mmol) followed by palladium on carbon (10 % wt) (175 mg) in methanol (10 mL) and propylene oxide (5 mL) to give the title compound as a white solid (208 mg, 93% yield). m.p. 224-226 °C. $[\alpha]_D$= -20.8, (c=1.81, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 0.92 (d, J=6.2 Hz, 3H, $(CH_3)_2CH$), 0.97 (d, J=6.2 Hz, 3H, $(CH_3)_2CH$), 1.46 (ddd, J=14.4, 10.0, 4.4 Hz, 1H, $CH_2CH(CH_3)_2$), 1.56 (ddd, J=14.4, 10.0, 4.4 Hz, 1H, $CH_2CH(CH_3)_2$), 1.62-1.72 (m, 1H, $CH(CH_3)_2$), 1.79 (ddd, J=18.0, 15.2, 8.4 Hz, 1H, CH_2P), 1.87 (ddd, J=18.8, 15.2, 5.6 Hz, 1H, CH_2P), 3.51(ddd, J=9.6, 4.0, 4.0 Hz, 1H, $CHNH_2$), 4.17-4.24 (m, 1H, CHOH). ^{13}C NMR (100 MHz, D_2O) δ 23.1 ($(CH_3)_2CH$), 25.2 ($(CH_3)_2CH$), 26.3 ($CH_2CH(CH_3)_2$), 33.4 (J=130.6 Hz, CH_2P), 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_2O) δ 21.14. HRMS (CI[+], CH_4) calcd. for $C_7H_{19}NO_4P$ (MH[+]) 212.1959 found 212.1884.

Acknowledgements

References and footnotes

1. (a) Aoyagi, T.; Morishima, H.; Nishizawa, R.; Kunimoto, S.; Takeuchi, T.; Umezawa, H.; Ikezawa, H. *J. Antibiot.* **1972**, *25*, 689. (b) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.

2. For recent synthetic methodologies of statine and their analogues, see: (a) Yuste, F.; Diaz, A.; Ortiz, B.; Sánchez-Obregón, R.; Walls, F.; García-Ruano, J. L. *Tetrahedron: Asymmetry* **2003**, *14*, 549. (b) Yoo, D.; Oh, J. S.; Kim, Y. G. *Org. Lett*. **2002**, *4*, 1213. (c) Kwon, S. J.; Ko, S. Y. *Tetrahedron Lett.* **2002**, *43*, 639. (d) Ko, S. Y. *J. Org. Chem.* **2002**, *67*, 2689. (e) Pasenti, C.; Bravo, P.; Corradi, E.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 5637. (f) Travins, J. M.; Bursavich, M. G.; Veber, D. F.; Rich, D. H. *Org. Lett*. **2001**, *3*, 2725. (g) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292. (h) Sengupta, S.; Sarma, D. S. *Tetrahedron: Asymmetry* **1999**, *10*, 4633. (i) Lee, K.-Y.; Kim, H.-Y.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (j) Alemay, C.; Bach, J.; Farras, J.; García, J. *Org. Lett*. **1999**, *1*, 1831. (k) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 775. (l) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10419. (m) Veeresha, G.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 5223. (n) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5593. (o) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2365.

3. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*. Kukhar, V. P.; Hudson H. R., Eds; John Wiley: New York, 2000 and references therein.

4. (a) Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. A. K. *Tetrahedron* **1996**, *52*, 165. (b) Burke Jr. T. R.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. P. *J. Org. Chem.* **1993**, *58*, 1336.

5. (a) Dellaria, J. F., Jr.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perum, T. J. *J. Med. Chem.* **1990**, *33*, 534. (b) Dellaria, J. F.; Maki, R. G. *Tetrahedron Lett.* **1986**, *27*, 2337.

6. Chakravarty, P. K.; Greenlee, W. J.; Parsons, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Busch, R. D.; Melllin, T. N. *J. Med. Chem.* **1989**, *32*, 1886.

7. (a) Drag, M.; Latjka, R.; Gumienna-Kontecka, E.; Kozlowski, H.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1837.   (b) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron:*

Asymmetry **2002**, *13*, 2509 and references therein. (c) Hammerschmidt, F.; Wolfgang, W.; Wuggenig, F.; Zarbl, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2955. (d) Hammerschmidt, F.; Lindner, W.; Wuggenig, F.; Zarbl, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2955. (e) Barco, A.; Benetti, S.; Bergamini, P.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1999**, *40*, 7705. (f) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379. (g) Gravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745.

8. Yamagishi, T.; Fujii, K.; Shibuya, S.; Yokomatsu, T. *Synlett* **2004**, 2505.

9. (a) Ordóñez, M.; González-Morales, A.; Ruiz, C.; De la Cruz-Cordero, R.; Fernández-Zertuche, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1775. (b) Ordóñez, M.; González-Morales, A.; Salazar-Fernández, H. *Tetrahedron: Asymmetry* **2004**, *15*, 2719.

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.

11. The preparation of ester **4** has been described, although to the best of our knowledge no data given: (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed.* **1987**, *26*, 1141. (b) Cooke, J. W. B.; Davies, S. G.; Naylon, A. *Tetrahedron* **1993**, *49*, 7955. (c) Beaulieu, P. L.; Wernic, D. *J. Org. Chem.* **1996**, *61*, 3635. (d) Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 3027.

12. The preparation of 2-ketophosphonate **5** has been described, although to the best of our knowledge no data given: see ref. 11d.

13. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205. (c) Anh, N. T.; Eisenstein, O. *Nouv J. Chem.* **1977**, *1*, 61. (d) For an excellent summary, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 876.

14. Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696.

15. (a) Hoffmann, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045. (b) Reetz, M. T.; Schmitz, A. *Tetrahedron Lett.* **1999**, *40*, 2741.

16. Concellón, J. M.; Bernard, P. L.; Riego, E.; García-Granda, S.; Forcén-Acebal, A. *J. Org. Chem.* **2001**, *66*, 2764.

17. Preparation of 2-ketophosphonate **9** and dimethyl (3*S*)-*N*-benzylamino-(2*S*)-hydroxy-4-methylhexylphosphonate *anti*-**10** has been reported by us, but no data given: Ordóñez. M.; De la Cruz-Cordero, R.; Quiñónes, C.; González-Morales, A. *J. Chem. Soc., Chem. Commun.* **2004**, 672.

18. Chung McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, 155.

19. Laschat, S.; Frohlinch, R.; Wibbeling, B. *J. Org. Chem.* **1996**, *61*, 2829.

20. For the preparation of $Zn(BH_4)_2$ see: Pelter, A.; Smith, K.; Brown, H. *Borane Reagents*, Academic Press: London, 1988; p 414.