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Diastereoselective reduction of dimethyl γ-[(*N*-*p*-toluenesulfonyl)amino]-β-ketophosphonates derived from amino acids

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Abstract—The reduction of dimethyl γ-[(*N*-*p*-toluenesulfonyl)amino]-β-ketophosphonates **7a–e** with different hydrides gave dimethyl γ-[(*N*-*p*-toluenesulfonyl)amino]-β-hydroxyphosphonates **9a–e** and **10a–e** with good chemical yield and moderated diastereoselectivity. The configuration of all new stereogenic centers were assigned by X-ray analysis and chemical correlation.

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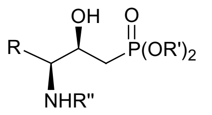
1. Introduction

Phosphonates and phosphinates functionalized with amino and hydroxy groups have attracted considerable attention in recent years for their role in biologically relevant processes such as the inhibition of rennin and HIV protease, human calpain I and their use as haptens in the development of catalytic antibodies.[1] In particular, γ-amino-β-hydroxyphosphonates **1** and **2** have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis.[2] Additionally, phosphonates **1** and **2** served as excellent Leu^{10}-Val^{11} replacements (LVRs) in angiotensin II, providing a more potent inhibitory activity for rennin over porcine pepsin, and bovine cathepsin D.[3] However, to the best of our knowledge, only a few synthetic approaches have been used to obtain optically active γ-amino-β-hydroxyphosphonates **1** and **2**, which involve the reaction of the anion of methylphosphonate with α-aminoaldehydes,[3,4] or the catalytic asymmetric aminohydroxylation of unsaturated phosphonates.[5] Although both synthetic strategies afford the γ-amino-β-hydroxyphosphonates **1** and **2**, both yields and diastereoselectivities remain low. Herein we report a new synthetic methodology that affords **2** with much better yields and moderate diastereoselectivities from readily available starting materials.



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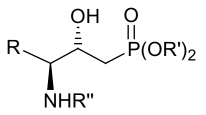

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2. Results and discussion

Recently we described the reduction of dimethyl γ-*N*,*N*-dibenzylamino-β-ketophosphonates **3** with catecholborane, obtaining dimethyl γ-*N*,*N*-dibenzylamino-β-hydrophosphonates *syn*-**4** with high diastereoselectivity and good chemical yield (Scheme 1).[6]

In order to induce the formation of *anti*-γ-amino-β-hydroxyphosphonates and inspired with the elegant work by Rapoport and co-workers,[7] who have demonstrated the highly stereoselective reduction of α-*N*-(phenylsulfonyl)amino ketones derived from serine, we decided to replace the benzyl groups of **3** with *p*-toluenesulfonyl. Thus, the total synthesis of

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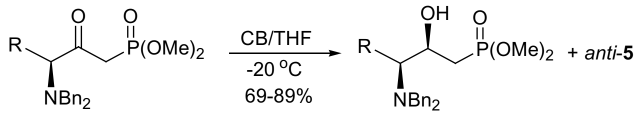
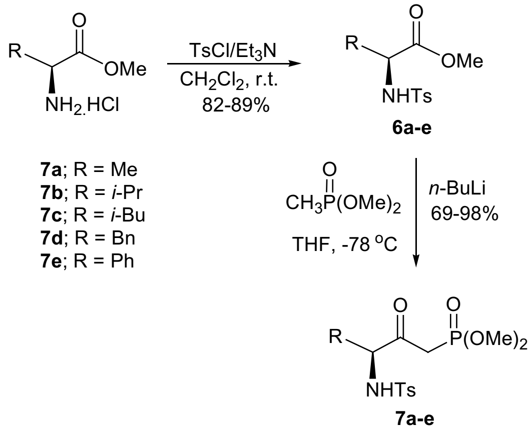


3; R = Me, *i*Pr, Bn, Ph

syn-**4**; 98% d.e.

Scheme 1.



6a-e

7a; R = Me
7b; R = *i*-Pr
7c; R = *i*-Bu
7d; R = Bn
7e; R = Ph

7a-e

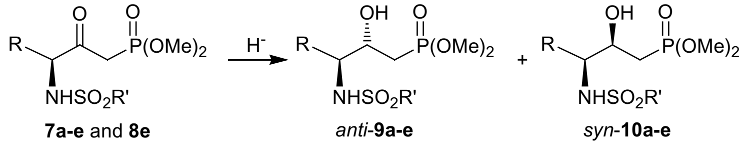
Scheme 2.

γ-[*N*-*p*-toluenesulfonyl)amino]-β-ketophosphonates **7a–e** starting from readily available α-amino acid methyl esters hydrochloride is depicted in Scheme 2. In the first step, α-amino amino methyl esters hydrochloride were treated with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane at room temperature, to give the corresponding *N*-*p*-toluenesulfonyl methyl esters **6a–e** in 82–89% yield. Then, methyl esters **6a–e** were treated with 3 equiv of the lithium salt of dimethyl methylphosphonate at −78 °C in dry THF to afford enantiomerically pure β-ketophosphonates **7a–e** in 69–98% yield. The γ-[*N*-*p*-methanesulfonyl)amino]-β-ketophosphonate **8e** (R = Ph and R′ = Me) was obtained in a similar fashion in 60% yield.

Having efficiently prepared β-ketophosphonates **7a–e** and **8e**, we turned out our attention to their diastereoselective reduction to obtain γ-[(*N*-*p*-toluenesulfonyl)-amino]-β-hydroxyphosphonates **9** and **10**. Table 1 summarizes the conditions used in the reduction and results obtained.

From the γ-[(*N*-*p*-toluenesulfonyl)amino]-β-ketophosphonates **7a–e** and **8e**, we initially selected the isopropyl analogue **7b** (R = *i*-Pr) to evaluate the diastereoselective reduction using a variety of reducing agents and conditions. Thus, the reduction of **7b** with NaBH$_4$ at 0 °C in methanol afforded γ-[(*N*-*p*-toluenesulfonyl)amino]-β-hydroxyphosphonates *anti*-**9b** and *syn*-**10b** in excellent yield and with good diastereoselectivity, in favor of diastereomer *anti*-**9** (entry 1). In a similar fashion excellent yields and good diastereoselectivities were obtained when the reduction of **7b** was carried out with Zn(BH$_4$)$_2$ and BH$_3$·SMe$_2$ (entries 2 and 3). Reduction of **7b** with

Table 1. Reduction of **7a–e** and **8e** with various reducing agents



7a-e and **8e**

anti-**9a-e**

syn-**10a-e**

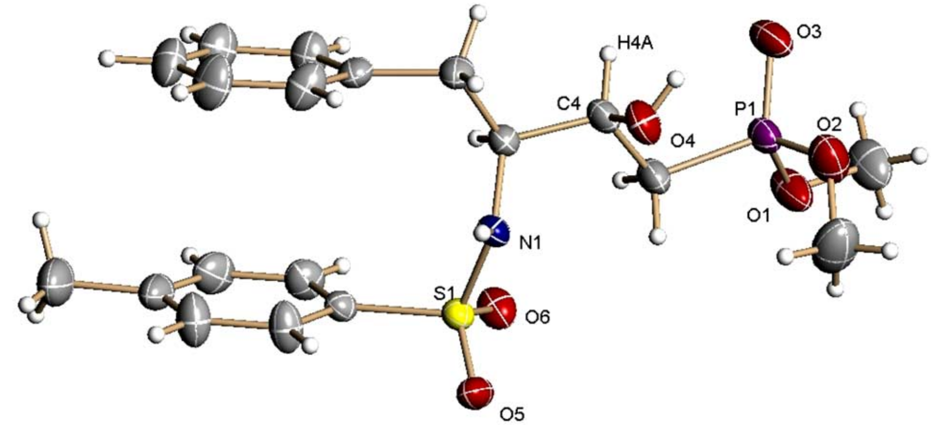
Entry	Compound	R	R′	Hydride	Conditions	Yield (%)[b]	*anti:syn*[c]
1	**7b**	*i*-Pr	*p*-Tol	NaBH$_4$	MeOH, 0 °C	99	81:19
2	**7b**	*i*-Pr	*p*-Tol	Zn(BH$_4$)$_2$	THF, −78 °C	91	77:23
3	**7b**	*i*-Pr	*p*-Tol	BH$_3$·SMe$_2$[a]	THF, −78 °C	95	76:24
4	**7b**	*i*-Pr	*p*-Tol	LiBH$_4$	THF, −78 °C	98	53:47
5	**7b**	*i*-Pr	*p*-Tol	LiBH$_4$/ZnCl$_2$	THF, −78 °C	80	72:28
6	**7b**	*i*-Pr	*p*-Tol	LiBH$_4$/BCl$_3$	THF, −78 °C	83	70:30
7	**7b**	*i*-Pr	*p*-Tol	LiBH$_4$/TiCl$_4$	THF, −78 °C	98	74:26
8	**7b**	*i*-Pr	*p*-Tol	LiBH$_4$/Et$_2$AlCl	THF, −78 °C	[d]	[d]
9	**7b**	*i*-Pr	*p*-Tol	DIBAL-H	THF, −78 °C	[d]	[d]
10	**7b**	*i*-Pr	*p*-Tol	L-selectride	THF, −78 °C	[d]	[d]
11	**7b**	*i*-Pr	*p*-Tol	CB	THF, −78 °C	[d]	[d]
12	**7a**	Me	*p*-Tol	NaBH$_4$	MeOH, 0 °C	96	29:71
13	**7c**	*i*-Bu	*p*-Tol	NaBH$_4$	MeOH, 0 °C	98	29:71
14	**7d**	Bn	*p*-Tol	NaBH$_4$	MeOH, 0 °C	97	64:36
15	**7e**	Ph	*p*-Tol	NaBH$_4$	MeOH, 0 °C	97	63:37
16	**7e**	Ph	*p*-Tol	NaBH$_4$	THF, 0 °C	97	62:38
17	**8e**	Ph	Me	NaBH$_4$	MeOH, 0 °C	98	61:39
18	**8e**	Ph	Me	NaBH$_4$	THF, 0 °C	98	62:38

[a] In presence of LiClO$_4$ (1 equiv).
[b] Chemical yield after purification.
[c] Determined by ^{1}H NMR at 400 MHz and ^{31}P NMR at 200 MHz in the crude.
[d] No reaction.

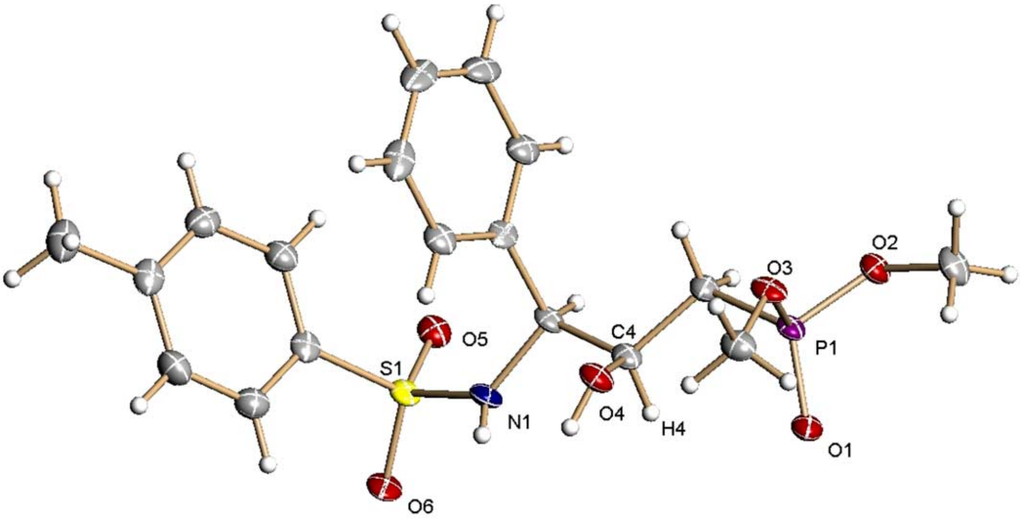
$LiBH_4$ at −78 °C in anhydrous THF (entry 4) afforded β-hydroxyphosphonates *anti*-**9b** and *syn*-**10b** in excellent yield but with low diastereoselectivity. On the other hand, when the reduction of **7b** was carried out with $LiBH_4$ at −78 °C in the presence of $ZnCl_2$, BCl_3, and $TiCl_4$ (entries 5–7), respectively, β-hydroxyphosphonates *anti*-**9b** and *syn*-**10b** were obtained in both good yield and diastereoselectivity. However, the reduction of **7b** with $LiBH_4$ at −78 °C in the presence of Et_2AlCl, or with other reducing agents such DIBAL-H, L-selectride, and catecholborane (entries 8–11) failed to provide β-hydroxyphosphonates *anti*-**9b** and *syn*-**10b**, despite the use of longer reaction time. In all these cases, β-ketophosphonate **7b** was recovered.

In the light of these results, we decided to carry out the reduction of the rest of β-ketophosphonates **7** with $NaBH_4$ at 0 °C in methanol (entries 12–15), where β-hydroxyphosphonates *anti*-**9** and *syn*-**10** were obtained in good chemical yields and moderate diastereoselectivity. The diastereofacial preference observed is in agreement with the results previously reported for the reduction of α-*N*-(phenylsulfonyl)amino ketones derived from serine.[7] Finally, the reduction of **7e** with $NaBH_4$ at 0 °C in methanol or anhydrous THF (entries 15 and 16), afforded γ-[(*N*-*p*-toluenesulfonyl)amino]-β-hydroxyphosphonates *anti*-**9e** and *syn*-**10e** with similar yields and diastereoselectivities. In addition, the substitution of a *p*-toluenesulfonyl group in the β-ketophosphonate **7e** by a methanesulfonyl group in **8e** did not improve the chemical yields and diastereoselectivities during the reduction reaction with $NaBH_4$ (entries 17 and 18). These last results suggest that the reduction of γ-[(*N*-*p*-toluenesulfonyl)amino]-β-ketophosphonates **7a–e** with $NaBH_4$ took place through an intermediate in which there is no hydrogen bonding between the NH proton and the carbonyl oxygen, and that the reaction is independent of the solvent polarity and of steric demands placed upon increasing the size of the R′ group at the sulfonyl group.

The diastereomeric excesses of the products obtained from the reduction of **7a–e** and **8e** were determined by ^1H and ^{31}P NMR data of the crude reaction mixtures, and the configuration of the new generated stereogenic center at C(3) was assigned by comparison with X-ray crystal structures of diastereomeric pure *syn*-**10d** and *anti*-**9e** (Fig. 1).[8,9] In addition, the absolute



syn-**10d**



anti-**9e**

Figure 1. X-ray molecular structure for *syn*-**10d** and *anti*-**9e**.

configurations of the new stereogenic center at C(3) in the β-hydroxyphosphonates *anti*-**9** and *syn*-**10** were also determined by chemical correlation. Thus, mixtures of dimethyl γ-*N*,*N*-dibenzylamino-β-hydroxyphosphonates *syn*-**4** and *anti*-**5** (R = Me, *i*-Pr, Bn), were treated with palladium on carbon in methanol under a hydrogen atmosphere at room temperature yielding the corresponding mixtures of dimethyl γ-amino-β-hydroxyphosphonates,[10] that without any further purification were treated with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane at room temperature, to give the corresponding γ-[(*N*-*p*-toluenesulfonyl)amino]-β-hydroxyphosphonates *anti*-**9** and *syn*-**10**.

In order to rationalize the observed stereoinduction in the reduction of **7a–e** and **8e**, the minimum energy conformers of the starting β-ketophosphonates were determined by applying the systematic search tool available in the PC Spartan Pro v.1.0.5[11] with a MMFF94 force field for geometry minimization and energy assessment[12] (Fig. 2).

Examination of the lowest energy conformations for β-ketophosphonates **7a–e**, show that for **7a** and **7c,** the nucleophilic attack of the hydride may take place via the less hindered *si* face, leading to the corresponding *syn*-β-hydroxyphosphonate **10** as the major product. On the other hand, the hydride addition to β-ketophosphonates **7b**, **7d–e**, and **8e**, may take place by the less hindered *re* face, leading to the *anti*-β-hydroxyphosphonate **9** as the major product. These theoretical calculations are in good agreement with the experimental data, and that the observed stereoselectivities depends on the size of the R group on the side chain, as has been shown with the reduction of α-amino ketones.[13] The stereoselectivity observed can be rationalized with the Felkin–Anh[14] model for the addition of hydride to the free carbonyl group.

3. Conclusion

In summary, easy access to γ-[(*N*-*p*-toluenesulfonyl)-amino]-β-ketophosphonates **7** in conjunction with the reduction of the carbonyl group using $NaBH_4$ with excellent yields and with good levels of diastereoselectivity has been obtained. We consider this experimental work an efficient and simple method to obtain diastereomerically enriched *anti*-γ-*N*-*p*-toluenesulfonylamino-β-hydroxyphosphonates.

4. Experimental

Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1 dm tube; concentrations are given in g/100 mL. Melting points were determined in a Büchi B-540 apparatus in open capillary tubes and are uncorrected. For flash chromatography, silica gel 60 (230–400 mesh ASTM, Merck) was used. The NMR spectra were recorded on a Varian INOVA 400, 400 MHz for ^1H and 100 MHz for ^{13}C, and on a Varian Mercury 200 for ^{31}P. The spectra were recorded in $CDCl_3$ solutions, using TMS as internal reference. Microanalyses were obtained from an Elemental VARIO EL III instrument.

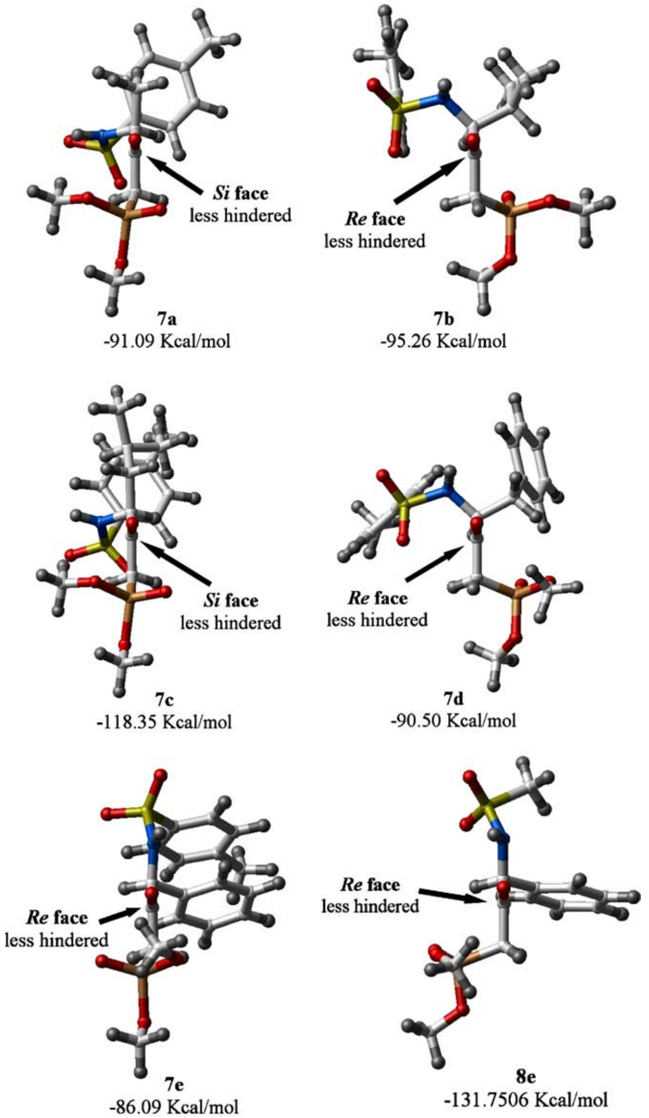


Figure 2. MMFF94 conformations of minimum energy for β-ketophosphonates **7a–e** and **8e**.

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.

4.1. General procedure for the preparation of (*S*)-*N*-*p*-toluenesulfonyl methyl esters 6a–e

To a stirred solution of 1.0 equiv of α-amino acid methyl ester hydrochloride and 2.2 equiv of triethylamine in dry dichloromethane (30 mL) at 0 °C, was added slowly 1.1 equiv of *p*-toluenesulfonyl chloride. The reaction was stirred at room temperature for 12 h. After this period of time, the solvent was removed in vacuo, the residue was dissolved in ethyl acetate (25 mL) and washed with water (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography.

4.1.1. (*S*)-*N*-*p*-Toluenesulfonyl-alanine methyl ester 6a. The reaction was carried out starting from (*S*)-alanine methyl ester hydrochloride (3.0 g, 21.5 mmol), triethylamine (4.78 g, 6.6 mL, 47.3 mmol), *p*-toluenesulfonyl chloride (4.5 g, 23.6 mmol), and dichloromethane (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (80:20) to give **6a** as a white solid, 4.86 g, 88% yield. Mp 94–95 °C. $[\alpha]_D = +0.4$ ($c = 1.2$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, $J = 7.6$ Hz, 3H, CH_3), 2.42 (s, 3H, CH_3Ar), 3.54 (s, 3H, OCH_3), 3.99 (m, 1H, CHN), 5.32 (d, $J = 7.2$ Hz, 1H, NH), 7.30 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.73 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9 (CH_3CH), 21.7 (CH_3Ar), 51.6 (CHN), 52.8 (OCH_3) 127.4, 129.8, 136.9, 143.9, 172.8 C=O. Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44%. Found C, 51.26; H, 5.89; N, 5.42%.

4.1.2. (*S*)-*N*-*p*-Toluenesulfonyl-valine methyl ester 6b. The reaction was carried out starting from (*S*)-valine methyl ester hydrochloride (3.0 g, 17.8 mmol), triethylamine (3.98 g, 5.5 mL, 39.4 mmol), *p*-toluenesulfonyl chloride (3.75 g, 19.7 mmol), and dichloromethane (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (80:20) to give **6b** as a white solid, 4.33 g, 85% yield. Mp 77–78 °C. $[\alpha]_D = +15.6$ ($c = 0.89$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, $J = 6.8$ Hz, 3H, CH_3), 0.95 (d, $J = 6.8$ Hz, 3H, CH_3), 1.97–2.08 (m, 1H, $CH(CH_3)_2$), 2.42 (s, 3H, CH_3Ar), 3.44 (s, 3H, OCH_3), 3.73 (dd, $J = 10.0$, 5.2 Hz, 1H, CHN), 5.12 (d, $J = 10.0$ Hz, 1H, NH), 7.29 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.71 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 ($(CH_3)_2CH$), 19.2 ($(CH_3)_2CH$), 21.8 (CH_3Ar), 31.9 ($CH(CH_3)_2$), 52.4 (OCH_3), 61.3 (CHN), 127.5, 129.7, 136.7, 143.8, 171.9 C=O. Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91%. Found C, 54.65; H, 6.84; N, 4.88%.

4.1.3. (*S*)-*N*-*p*-Toluenesulfonyl-leucine methyl ester 6c. The reaction was carried out starting from (*S*)-leucine methyl ester hydrochloride (3.0 g, 16.5 mmol), triethylamine (3.76 g, 5.1 mL, 36.3 mmol), *p*-toluenesulfonyl chloride (3.46 g, 18.2 mmol), and dichloromethane (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (80:20) to give **6c** as a colorless liquid, 4.83 g, 98% yield. $[\alpha]_D = +8.0$ ($c = 1.59$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J = 6.8$ Hz, 3H, CH_3), 0.90 (d, $J = 6.8$ Hz, 3H, CH_3), 1.46 (ddd, 16.8, 8.8, 6.0 Hz, 1H, CH_2), 1.49 (ddd, 16.8, 8.4, 5.6 Hz, 1H, CH_2), 1.74–184 (m, 1H, $CH(CH_3)_2$, 2.42 (s, 3H, CH_3Ar), 3.43 (s, 3H, OCH_3), 3.93 (ddd, $J = 10.0$, 8.4, 6.0 Hz, 1H, CHN), 5.06 (d, $J = 10.0$ Hz, 1H, NH), 7.25–7.29 (m, 2H, H_{arom}), 7.67–7.72 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 ($(CH_3)_2CH$), 21.7 (CH_3Ar), 22.9 ($(CH_3)_2CH$), 24.5 (CH_2), 42.5 ($CH(CH_3)_2$), 52.5 (OCH_3), 54.5 (CHNH), 127.5, 129.8, 136.9, 143.8, 172.9 (C=O). Anal. Calcd for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68%. Found C, 56.50; H, 7.26; N, 4.56%.

4.1.4. (*S*)-*N*-*p*-Toluenesulfonyl-phenylalanine methyl ester 6d. The reaction was carried out starting from (*S*)-phenylalanine methyl ester hydrochloride (3.0 g, 13.9 mmol), triethylamine (3.1 g, 4.3 mL, 20.6 mmol), *p*-toluenesulfonyl chloride (2.92 g, 15.3 mmol), and dichloromethane (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (80:20) to give **6d** as a white solid, 3.81 g, 82% yield. Mp 97–98 °C. $[\alpha]_D = +10.5$ ($c = 1.14$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3Ar), 3.03 (d, 6.0 Hz, 1H, CH_2Ph), 3.48 (s, 3H, OCH_3), 4.20 (dt, $J = 9.2$, 6.0 Hz, 1H, CHN), 5.10 (d, $J = 9.2$ Hz, 1H, NH), 7.05–7.08 (m, 2H, H_{arom}), 7.22–7.26 (m, 5H, H_{arom}), 7.63 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_3Ar) 39.5 (CH_2Ph), 52.6 (OCH_3), 56.8 (CHNH), 127.3, 127.4, 128.7, 129.6, 129.8, 135.1, 136.7, 143.8, 171.4 C=O. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20%. Found C, 61.29; H, 5.81; N, 4.23%.

4.1.5. (*S*)-*N*-*p*-Toluenesulfonyl-phenylglycine methyl ester 6e. The reaction was carried out starting from (*S*)-phenylglycine methyl ester hydrochloride (3.0 g, 14.9 mmol), triethylamine (3.31 g, 4.6 mL, 32.7 mmol), *p*-toluenesulfonyl chloride (3.12 g, 16.4 mmol), and dichloromethane (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (80:20) to give **6e** as a white solid, 4.21 g, 89% yield. Mp 131–133 °C. $[\alpha]_D = +102.0$ ($c = 1.12$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, CH_3Ar), 3.57 (s, 3H, OCH_3), 5.06 (d, $J = 7.6$ Hz, 1H, CHNH), 5.69 (d, $J = 7.6$ Hz, 1H, NH), 7.19–7.27 (m, 7H, H_{arom}), 7.62 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (CH_3Ar), 53.2 (OCH_3), 59.5 (CHNH), 127.3, 127.4, 128.8, 129.0, 129.7, 135.4, 137.1, 143.7, 170.8 C=O. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39%. Found C, 60.16; H, 5.48; N, 4.34%.

4.2. General procedure for the preparation of (*S*)-γ-*N*-*p*-toluenesulfonyl-β-ketophosphonates 7a–e and 8e

A solution of dimethyl methylphosphonate (3.0 equiv) in anhydrous THF (40 mL) was cooled at −78 °C before the slow addition of 3.1 equiv of *n*-BuLi in hexanes. The resulting solution was stirred at −50 °C for 1.5 h, and then the solution cooled at −78 °C and slowly added to a solution of methyl ester **6** (1.0 equiv) in anhydrous THF (30 mL). The reaction mixture was stirred at −78 °C for 4 h and quenched with aqueous NH_4Cl solution. The solvent was evaporated in vacuo, and the residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude β-ketophosphonates were purified by flash chromatography.

4.2.1. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-2-oxobutylphosphonate 7a. The reaction was carried out starting from dimethyl methylphosphonate (3.61 g, 29.1 mmol) in anhydrous THF (40 mL), *n*-BuLi in hexanes 2.5 M, (12.5 mL, 30.1 mmol), (*S*)-*N*-*p*-toluenesulfonyl-alanine methyl ester **6a** (2.5 g, 9.7 mmol) in anhydrous THF (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (1:2) to give **7a** as a white solid, 3.1 g, 90% yield. Mp 78–81 °C. $[\alpha]_D = +0.15$ ($c = 6.36$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, $J =$ 7.2 Hz, 3H, CH_3CH), 2.43 (s, 3H, CH_3Ar), 3.08 (dd, $J = 22.4$, 14.0, Hz, 1H, CH_2P), 3.54 (dd, $J = 22.4$, 14.0 Hz, 1H, CH_2P), 3.73 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.78 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 4.03 (q, $J = 7.6$ Hz, 1H, CHN), 6.19 (d, $J = 7.6$ Hz, 1H, NH), 7.31 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.75 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3CH), 21.7 (CH_3Ar), 37.9 (d, $J = 127.5$ Hz, CH_2P), 53.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 53.5 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 58.3 (CHN), 127.2, 129.9, 137.4, 143.8, 201.3 (d, $J = 4.5$ Hz, C=O). ^{31}P NMR (200 MHz, $CDCl_3$): δ 23.29. Anal. Calcd for $C_{13}H_{20}NO_6PS$: C, 44.70; H, 5.77; N, 4.01%. Found: C, 44.60; H, 5.77; N, 4.01%.

4.2.2. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-4-methyl-2-oxopentylphosphonate 7b. The reaction was carried out starting from dimethyl methylphosphonate (3.26 g, 26.3 mmol) in anhydrous THF (40 mL), *n*-BuLi in hexanes 2.5 M, (11.3 mL, 27.2 mmol), (*S*)-*N*-*p*-toluenesulfonyl-valine methyl ester **6b** (2.5 g, 8.8 mmol) in anhydrous THF (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (1:2) to give **7b** as a white solid, 3.25 g, 98% yield. Mp 108–110 °C. $[\alpha]_D = +66.1$ ($c = 5.92$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, $J =$ 6.8 Hz, 3H, $(CH_3)_2CH$), 0.94 (d, $J =$ 6.8 Hz, 3H, $(CH_3)_2CH$), 2.25 (m, 1H, $CH(CH_3)_2$), 2.41 (s, 3H, CH_3Ar), 2.98 (dd, $J = 22.4$, 14.4 Hz, 1H, CH_2P), 3.24 (dd, $J = 22.4$, 14.4, Hz, 1H, CH_2P), 3.69 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.73 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.99 (dd, $J = 9.0$, 3.6 Hz, 1H, CHN), 5.80 (d, $J = 9.0$ Hz, 1H, NH), 7.28 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.73 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 ($(CH_3)_2CH$), 20.1 ($(CH_3)_2CH$), 21.7 (CH_3Ar), 29.8 ($CH(CH_3)_2$), 38.5 (d, $J = 129.1$ Hz, CH_2P), 53.3 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 53.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 67.6 (d, $J = 2.3$ Hz, CHNH), 127.4, 129.8, 137.4, 143.7, 200.5 (d, $J = 6.0$ Hz, C=O). ^{31}P NMR (200 MHz, $CDCl_3$): δ 22.70. Anal. Calcd for $C_{15}H_{24}NO_6PS$: C, 47.74; H, 6.41; N, 3.71%. Found: C, 47.50; H, 6.38; N, 3.69%.

4.2.3. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-5-methyl-2-oxohexylphosphonate 7c. The reaction was carried out starting from dimethyl methylphosphonate (3.1 g, 25 mmol) in anhydrous THF (40 mL), *n*-BuLi in hexanes 2.5 M, (10.8 mL, 25.9 mmol), (*S*)-*N*-*p*-toluenesulfonyl-leucine methyl ester **6c** (2.5 g, 8.4 mmol) in anhydrous THF (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (1:2) to give **7c** as a colorless liquid, 2.82 g, 86% yield. $[\alpha]_D = +0.3$ ($c = 5.02$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (d, $J =$ 6.4 Hz, 3H, $(CH_3)_2CH$), 0.81 (d, $J =$ 6.4 Hz, 3H, $(CH_3)_2CH$), 1.37 (ddd, $J = 13.6$, 10.0, 4.4 Hz, 1H, CH_2CH), 1.51 (ddd, $J = 13.6$, 10.0, 4.4 Hz, 1H, CH_2CH), 1.53–1.64 (m, 1H, $CH(CH_3)_2$), 2.42 (s, 3H, CH_3Ar), 3.03 (dd, $J = 22.0$, 14.0 Hz, 1H, CH_2P), 3.47 (dd, $J = 22.0$, 14.0 Hz, 1H, CH_2P), 3.74 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.77 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.96 (ddd, $J = 9.6$, 8.8, 4.0 Hz, 1H, CHN), 5.97 (d, $J = 8.8$ Hz, 1H, NH), 7.30 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.75 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 ($((CH_3)_2CH$), 21.7 (CH_3Ar), 23.2 ($CH_3)_2CH$), 24.5 ($CH(CH_3)_2$), 38.1 (d, $J = 129.1$ Hz, CH_2P), 40.7 (CH_2CH), 53.3 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 53.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 61.1 (CHN), 127.4, 129.8, 137.4, 143.8, (201.9 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$): δ 23.45. Anal. Calcd for $C_{16}H_{26}NO_6PS$: C, 49.10; H, 6.70; N, 3.58%. Found: C, 48.88; H, 6.82; N, 3.54%.

4.2.4. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-2-oxo-4-phenylbutylphosphonate 7d. The reaction was carried out starting from dimethyl methylphosphonate (2.79 g, 22.5 mmol) in anhydrous THF (40 mL), *n*-BuLi in hexanes 2.5 M, (9.7 mL, 23.2 mmol), (*S*)-*N*-*p*-toluenesulfonyl-phenylalanine methyl ester **6d** (2.5 g, 7.5 mmol) in anhydrous THF (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (1:2) to give **7d** as a white solid, 2.99 g, 94% yield. Mp 110–112 °C. $[\alpha]_D = +0.2$ ($c = 4.73$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3Ar), 2.87 (dd, $J =$ 14.0, 8.4 Hz, 1H, CH_2Ph), 3.06 (dd, $J = 22.8$, 14.0 Hz, 1H, CH_2P), 3.08 (dd, $J = 14.0$, 5.2 Hz, 1H, CH_2Ph), 3.66 (dd, $J = 22.8$, 14.0 Hz, 1H, CH_2P), 3.71 (d, $J = 11.4$ Hz, 3H, $(CH_3O)_2P$), 3.77 (d, $J = 11.4$ Hz, 3H, $(CH_3O)_2P$), 4.17 (ddd, $J = 8.0$, 8.0, 5.2 Hz, 1H, CHN), 5.90 (d, $J = 8.0$ Hz, 1H, NH), 6.98 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.12–7.17 (m, 5H, H_{arom}), 7.44 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_3Ar), 37.8 (CH_2Ph), 38.7 (d, $J = 127.5$ Hz, CH_2P), 53.4 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 53.5 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 63.8 (CHN), 127.0, 127.1, 128.8, 129.5, 129.8, 135.8, 136.9, 143.6, 201.2 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$): δ 23.34. Anal. Calcd for $C_{19}H_{24}NO_6PS$: C, 53.64; H, 5.69; N, 3.29%. Found: C, 53.38; H, 5.52; N, 3.43%.

4.2.5. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-2-oxo-4-phenylpropylphosphonate 7e. The reaction was carried out starting from dimethyl methylphosphonate (2.91 g, 23.5 mmol) in anhydrous THF (40 mL), *n*-BuLi in hexanes 2.5 M, (10.1 mL, 24.3 mmol), (*S*)-*N*-*p*-toluenesulfonyl-phenylglycine methyl ester **6e** (2.5 g, 7.8 mmol) in anhydrous THF (30 mL) following the general procedure. The crude product was purified by column chromatography using hexane/ethyl acetate (1:2) to give **7e**

as a white solid, 2.23 g, 69% yield. Mp 129–130 °C. $[\alpha]_D = +0.5$ ($c = 5.71$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3Ar), 2.82 (dd, $J = 22.4$, 14.0 Hz, 1H, CH_2P), 3.18 (dd, $J = 22.4$, 14.0 Hz, 1H, CH_2P), 3.69 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.70 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 5.29 (d, $J = 6.0$ Hz, 1H, CHN), 6.23 (d, $J = 6.0$ Hz, 1H, NH), 7.11 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.12–7.14 (m, 2H, H_{arom}), 7.21–7.26 (m, 3H, H_{arom}), 7.51 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3Ar), 37.9 (d, $J = 129.1$ Hz, CH_2P), 53.4 (d, $J = 7.6$ Hz, $(CH_3O)_2P$), 53.4 (d, $J = 7.6$ Hz, $(CH_3O)_2P$), 66.5 (CHN), 127.2, 128.4, 129.1, 129.4, 129.5, 134.6, 137.4, 143.3, 196.5 (d, $J = 6.1$ Hz, C=O). ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.97. Anal. Calcd for $C_{18}H_{22}NO_6PS$: C, 52.55; H, 5.39; N, 3.40. Found: C, 52.36; H, 5.37; N, 3.40%.

4.2.6. Dimethyl (*S*)-3-[(methanesulfonyl)amino]-2-oxo-4-phenylpropylphosphonate 8e. The reaction was carried out starting from dimethyl methylphosphonate (1.53 g, 12.3 mmol) in anhydrous THF (30 mL), *n*-BuLi in hexanes 1.8 M, (7.1 mL, 12.7 mmol), (*S*)-*N*-*p*-methanesulfonyl-phenylglycine methyl ester (1.0 g, 4.1 mmol) in anhydrous THF (30 mL) following the general procedure. The crude product was purified by column chromatography using ethyl acetate/hexane (8:1) to give **8e** as a white solid, 1.1 g, 60% yield. Mp 107–108 °C. $[\alpha]_D = -0.2$ ($c = 2.11$, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.64 (s, 3H, CH_3SO_2), 2.89 (dd, $J = 22.4$, 14.0, Hz, 1H, CH_2P), 3.24 (dd, $J = 22.4$, 14.0 Hz, 1H, CH_2P), 3.77 (d, $J = 11.4$ Hz, 3H, $(CH_3O)_2P$), 3.79 (d, $J = 11.4$ Hz, 3H, $(CH_3O)_2P$), 5.44 (d, $J = 6.0$ Hz, 1H, CHN), 5.99 (d, $J = 6.0$ Hz, 1H, NH), 7.25–7.47 (m, 5H, H_{arom}). ^{13}C NMR (50 MHz, $CDCl_3$) 38.3 (d, $J = 128.5$ Hz, CH_2P), 42.1 CH_3SO_2, 53.6 (d, $J = 6.4$ Hz, $(CH_3O)_2P$), 53.7 (d, $J = 6.4$ Hz, $(CH_3O)_2P$), 66.6 (CHN), 128.3, 128.4, 129.7, 134.6, 196.3 (d, $J = 6.1$ Hz, C=O). ^{31}P NMR (200 MHz, $CDCl_3$): δ 21.76. Anal. Calcd for $C_{12}H_{18}NO_6PS$: C, 42.98; H, 5.41; N, 4.18. Found: C, 42.57; H, 5.32; N, 4.45%.

4.3. General procedure for the reduction of (*S*)-γ-*N*-*p*-toluenesulfonyl-β-ketophosphonates 7a–e and 8e with NaBH$_4$

A solution of (*S*)-γ-*N*-*p*-toluenesulfonyl-β-ketophosphonates **7** or **8** (1.0 equiv) in methanol or dry THF (50 mL) was cooled at 0 °C, and then $NaBH_4$ (4.0 equiv) added. The reaction mixture was stirred at room temperature for 4 h. The solvent was then evaporated in vacuo and the residue dissolved in water (30 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude β-hydroxyphosphonates were analyzed by ^{1}H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and purified by flash chromatography.

4.3.1. Reduction of 7a. The reaction was carried out starting from β-ketophosphonate **7a** (1.0 g, 2.9 mmol) in methanol (50 mL), $NaBH_4$ (433 g, 11.5 mmol) following the general procedure, to afford 962 mg, 96% yield of β-hydroxyphosphonates *anti*-**9a** and *syn*-**10a**, in the ratio 29:71, respectively. ^{31}P NMR (200 MHz, $CDCl_3$): δ 34.62 for *anti*-**9a** and 34.18 for *syn*-**10a**. The diastereomeric mixture was not isolated in a sufficiently pure form for elemental analysis and determining the specific rotation.

4.3.2. Reduction of 7b. The reaction was carried out starting from β-ketophosphonate **7b** (1.0 g, 2.65 mmol) in methanol (50 mL), $NaBH_4$ (401 mg, 10.6 mmol) following the general procedure, to afford 992 mg, 99% yield of β-hydroxyphosphonates *anti*-**9b** and *syn*-**10b**, in the ratio 81:19, respectively. ^{31}P NMR (200 MHz, $CDCl_3$): δ 34.69 for *anti*-**9b** and 34.46 for *syn*-**10b**. The diastereomeric mixture was not isolated in a sufficiently pure form for elemental analysis and determining the specific rotation.

4.3.3. Reduction of 7c. The reaction was carried out starting from β-ketophosphonate **7c** (1.0 g, 2.55 mmol) in methanol (50 mL), $NaBH_4$ (387 mg, 10.2 mmol) following the general procedure, to afford 981 mg, 98%, yield of β-hydroxyphosphonates *anti*-**9c** and *syn*-**10c**, in the ratio 29:71, respectively. ^{31}P NMR (200 MHz, $CDCl_3$): δ 34.75 for *anti*-**9c** and 33.80 for *syn*-**10c**. The diastereomeric mixture was not isolated in a sufficiently pure form for elemental analysis and determining the specific rotation.

4.3.4. Reduction of 7d. The reaction was carried out starting from β-ketophosphonate **7d** (1.0 g, 2.35 mmol) in methanol (50 mL), $NaBH_4$ (355 mg, 9.4 mmol) following the general procedure. The diastereomeric mixture was purified by flash chromatography hexane/AcOEt (1:3) to afford 978 mg, 97% yield.

4.3.5. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-(*S*)-2-hydroxy-4-phenylbutylphosphonate *anti*-9d. The diastereomer *anti*-**9d** was not isolated in a sufficiently pure form for elemental analysis and determining the specific rotation.

4.3.6. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-(*R*)-2-hydroxy-4-phenylbutylphosphonate *syn*-10d. White solid, mp 131–132 °C. $[\alpha]_D = -79.4$ ($c = 1.89$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (ddd, $J = 17.6$, 15.2, 2.0 Hz, 1H, CH_2P), 2.16–2.26 (m, 1H, CH_2P), 2.40 (s, 3H, CH_3Ar), 2.50 (dd, $J = 13.4$, 5.8 Hz, 1H, CH_2Ph), 2.87 (dd, $J = 13.4$, 9.4 Hz, 1H, CH_2Ph), 3.35–3.41 (m, 1H, CHOH), 3.68 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.73 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.91–3.98 (m, 1H, CHN), 5.56 (d, $J = 9.2$ Hz, 1H, NH), 7.03 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}), 7.14–7.25 (m, 5H, H_{arom}), 7.66 (AA′BB′ system, $J = 8.0$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_3Ar), 29.8 (d, $J = 139.6$ Hz, CH_2P), 38.4 (CH_2Ph), 52.8 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 52.9 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 60.3 (d, $J = 18.2$ Hz, CHOH), 65.4 (d, $J = 4.5$ Hz, CHNH), 126.7, 127.0, 128.7, 129.5, 129.9, 137.6, 138.5, 143.4. ^{31}P NMR (200 MHz, $CDCl_3$): δ 34.56. Anal. Calcd for $C_{19}H_{26}NO_6PS$: C, 53.39 H, 6.13; N, 3.22%. Found: C, 53.07; H, 6.06; N, 3.22%.

4.3.7. Reduction of 7e. The reaction was carried out starting from β-ketophosphonate **7e** (1.0 g, 2.43 mmol) in methanol (50 mL), $NaBH_4$ (368 mg, 9.7 mmol) following the general procedure. The diastereomeric mixture was purified by flash chromatography hexane/AcOEt (1:3) to afford 973 mg, 97% yield.

4.3.8. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-(*S*)-2-hydroxy-4-phenylpropylphosphonate *anti*-9e. White solid, mp 169–170 °C. $[\alpha]_D = +0.5$ ($c = 1.19$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (ddd, $J = 16.2$, 15.6, 10.0 Hz, 1H, CH_2P), 1.96 (ddd, $J = 19.6$, 15.6, 2.4 Hz, 1H, CH_2P), 2.31 (s, 3H, CH_3Ar), 3.69 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.73 (d, $J = 10.8$ Hz, 3H, $(CH_3O)_2P$), 3.97 (d, $J = 3.2$, 1H, OH), 4.29 (dd, $J = 7.6$, 4.4 Hz, 1H, CHNH), 4.31–4.38 (m, 1H, CHOH), 6.26 (d, $J = 7.6$ Hz, 1H, NH), 7.03–7.18 (m, 7H, H_{arom}), 7.46 (AA′BB′ system, $J = 8.4$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3Ar), 29.4 (d, $J = 139.7$ Hz, CH_2P), 52.8 (d, $J = 7.6$ Hz, $(CH_3O)_2P$), 53.0 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 62.5 (d, $J = 19.7$ Hz, CHOH), 69.1 (d, $J = 4.5$ Hz, CHNH), 127.2, 127.9, 128.3, 128.4, 129.4, 136.4, 137.7, 143.1. ^{31}P NMR (200 MHz, $CDCl_3$): δ 33.73. Anal. Calcd for $C_{18}H_{24}NO_6PS$: C, 52.29; H, 5.85; N, 3.39. Found: C, 52.11; H, 5.89; N, 3.42%.

4.3.9. Dimethyl (*S*)-3-[(*p*-toluenesulfonyl)amino]-(*R*)-2-hydroxy-4-phenylpropylphosphonate *syn*-10e. White solid, mp 150–153 °C. $[\alpha]_D = +0.6$ ($c = 1.23$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (ddd, $J = 19.6$, 15.6, 2.4 Hz, 1H, CH_2P), 2.08 (ddd, $J = 16.8$, 15.6, 10.8 Hz, 1H, CH_2P), 2.32 (s, 3H, CH_3Ar), 3.69 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 3.73 (d, $J = 11.2$ Hz, 3H, $(CH_3O)_2P$), 4.09–4.16 (m, 1H, CHOH), 4.20 (dd, $J = 7.2$, 5.6 Hz, 1H, CHNH), 4.28 (d, $J = 4.0$, 1H, OH), 6.19 (d, $J = 6.4$ Hz, 1H, NH), 7.04–7.16 (m, 7H, H_{arom}), 7.46 (AA′BB′ system, $J = 8.4$ Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3Ar), 29.8 (d, $J = 139.7$ Hz, CH_2P), 52.7 (d, $J = 6.1$ Hz, $(CH_3O)_2P$), 53.1 ($J = 6.1$ Hz, $(CH_3O)_2P$), 63.4 (d, $J = 19.8$ Hz, CHOH), 69.9 (d, $J = 4.6$ Hz, CHNH), 127.5, 127.2, 127.9, 128.5, 129.4, 137.7, 138.1, 143.1. ^{31}P NMR (200 MHz, $CDCl_3$): δ 33.66. Anal. Calcd for $C_{18}H_{24}NO_6PS$: C, 52.29; H, 5.85; N, 3.39. Found: C, 52.31; H, 5.93; N, 3.39%.

4.4. General procedure for the reduction of (*S*)-γ-*N*-*p*-toluenesulfonyl-β-ketophosphonates 7a–e with the rest of hydrides

A solution of (*S*)-γ-*N*-*p*-toluenesulfonyl-β-ketophosphonates **7** (1.0 equiv) dry THF (50 mL) was cooled at −78 °C, and then the corresponding hydride (4.0 equiv) added. The reaction mixture was stirred at −78 °C for 4 h, and then quenched with aqueous NH_4Cl solution. The solvent was evaporated in vacuo, the residue dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude β-hydroxyphosphonates were analyzed by ^1H NMR at 400 MHz and ^{31}P NMR at 200 MHz, and purified by flash chromatography.

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8. X-ray crystal data of *syn*-**10d** (CCDC 249670) were collected at 273(2) K using a Bruker APEX instrument (Mo Kα radiation, $\lambda = 0.71073$ Å). The SHELXTL v. 6.1 program package was used for structure solution and refinement. The structure was solved by direct methods and refined by full-matrix least squares procedures. All nonhydrogen atoms were refined anisotropically. *syn*-**10d**: $C_{19}H_{26}NO_6PS$, $M = 427.45$, monoclinic space group $P2_1$, $a = 9.2038(10)$, $b = 10.7658(12)$, $c = 10.9662(12)$ Å, $\alpha = 90°$, $\beta = 93.145(2)°$, $\gamma = 90°$, $V = 1085(2)$ Å^3, $Z = 2$, $D_c = 1.308$ g cm^{-1}, 11,608 reflections measured, 4662 unique ($R_{int} = 0.0182$), which were used in all calculations, final R values were 0.0379 [$I > 2\sigma(I)$] and 0.0390 (all data).
9. X-ray crystal data of *anti*-**9e** (CCDC 249669) were collected at 273(2) K using a Bruker APEX instrument (Mo Kα radiation, $\lambda = 0.71073$ Å). The SHELXTL v. 6.1 program package was used for structure solution and refinement. The structure was solved by direct methods and refined by full-matrix least squares procedures. All nonhydrogen atoms were refined anisotropically. *anti*-**9e**: $C_{18}H_{24}NO_6PS$, $M = 413.43$, triclinic space group P-1, $a = 6.9930(14)$, $b = 8.6008(18)$, $c = 17.012(4)$ Å, $\alpha = 92.665(3)°$, $\beta = 98.064(4)°$, $\gamma = 104.679(4)°$, $V = 976.4(3)$ Å^3, $Z = 2$, $D_c = 1.403$ g cm^{-1}, 4875 reflections measured, 3376 unique ($R_{int} = 0.0345$), which were used in all calculations, final R values were 0.0496 [$I > 2\sigma(I)$] and 0.0549 (all data).
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