

A New and Expedient Diastereoselective Synthesis of α -(Hydroxyamino)phosphonates and α -Aminophosphonates by Silyl Triflate Promoted Diethyl Phosphite Addition to Chiral *N*-Benzyl Nitrones

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An efficient methodology for the synthesis of α -aminophosphonates has been developed taking advantage of the *tert*-butyldimethylsilyl triflate activated addition of diethyl phosphite to *N*-benzyl nitrones derived from chiral α -alkoxy and α -(Boc-amino) aldehydes. The stereoselective carbon-phosphorus bond-forming reaction proceeded smoothly to

give α -(hydroxyamino)phosphonate intermediates as the primary adducts, which were subsequently converted into the corresponding polyhydroxylated α -amino- and α,β -diaminophosphonates by conventional reductive processes.
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Introduction

The biological importance of aminophosphonic acids was recognized over 40 years ago.^[1] Since then, a great number of papers dealing with their chemistry and biological activity have provided evidence for the growing and continuous interest in this promising and somewhat undiscovered class of potential drugs.^[2] Despite the well-known structural differences between the phosphonic and carboxylic functional groups (e.g., size, shape, acidity, and the pseudo-tetrahedral array about the P atom vs. trigonal array about the C atom), the phosphonic acid moiety has long been established as a bioisostere of a carboxyl unit. Consequently, α -aminophosphonic acids are considered important surrogates of α -aminocarboxylic acids and a variety of physiological responses can be obtained by using them in medicinal and pharmaceutical chemistry. Moreover, because of their ability to mimic transition states of hydrolysis, phosphonic acid derivatives having heteroatoms at the α - and/or β -positions have been shown recently to be inhibitors of various enzymes, including HIV-protease and hu-

man collagenase, and as haptens for the generation of catalytic antibodies. Aminophosphonic acids also have been proved to act as anti-thrombotic agents.^[3]

Therefore, in recent years the synthesis of phosphonic acid analogues of proteinogenic and non-proteinogenic α -amino acids has gained increasing importance, leading to the elaboration of numerous synthetic methods for aminophosphonates. In many cases, the absolute configuration at the α -position of the substituted phosphonic acids can affect their biological properties. As a result, the obvious need for enantiomerically homogeneous α -aminophosphonates with established absolute configuration at their stereogenic carbon atom has been realized by the development of several asymmetric syntheses of these compounds.

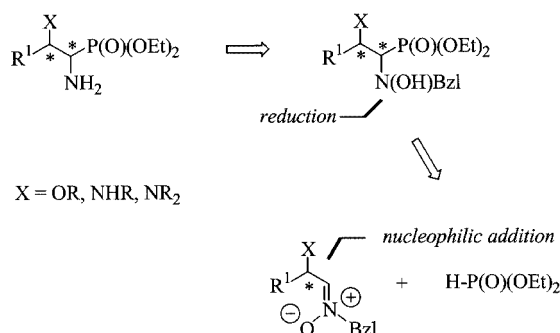
Results and Discussion

As a part of our ongoing interest in this field,^[4] we decided to develop a new synthetic approach to chiral polyhydroxylated α -amino- and α,β -diaminophosphonates. Our project was based on the synthesis of protected α -(hydroxyamino)phosphonates as the key intermediates, followed by the unmasking of the amino group. Interestingly, these primary adducts also belong to a class of biologically important compounds, since they are phosphorus isosters of α -(hydroxyamino)carboxylic acids.^[5] Thus, we envisioned a synthetic scheme that relied on the formation of the carbon-phosphorus bond through nucleophilic addition of a dialkyl phosphite to the iminium-like moiety of *N*-benzyl nitrones derived from chiral α -alkoxy and *N*-protected α -amino aldehydes (Scheme 1).^[6]

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Scheme 1

The addition reaction of nucleophiles to nitrones^[7] for the synthesis of nitrogen-containing compounds has several advantages over that employing more traditional C=N electrophiles, particularly imines. These include: a) the ease of the preparation, manipulation, and storage of nitrones because of their high stability and, quite often, crystallinity; b) the high reactivity determined by the superior electrophilic character of nitrones; c) the internal asymmetric induction by chiral substituents on the carbon or nitrogen atom; d) the control of the diastereofacial selectivity by pre-complexing agents. While various carbon nucleophiles have been employed by us and others,^[8] the use of heteronucleophiles appears to be quite rare.^[9] Vasella and co-workers^[10] reported the addition of phosphorus nucleophiles to *N*-glycosyl nitrones as the key step in synthetic routes to α -aminophosphonic acids.

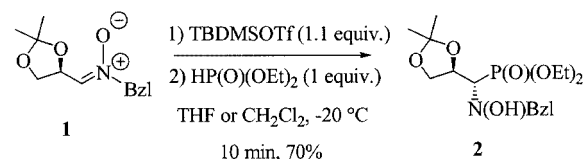
Addition Reactions

A set of experiments was carried out using the readily available D-glyceraldehyde-derived nitronium salt **1**^[8b] as the model compound. The results are collected in Table 1.

We observed that no reaction occurred when **1** was treated with diethyl phosphite in anhydrous CH_2Cl_2 or THF at room temperature, even in the presence of either a catalytic or stoichiometric amount of a base, such as 1,1,3,3-tetramethylguanidine (TMG), that has been used

successfully in earlier additions of diethyl phosphite to α,β -unsaturated carbonyl compounds, alkenenitriles, aldehydes, ketones, and imines.^[4a]

These observations suggested that the conjugate base of the phosphite is still too weak a nucleophile toward the nitronium, suggesting that activation of the latter is required for it to function as an acceptor in the carbon–phosphorus bond-forming reaction. Low yields (5–10%) of adduct were isolated by precomplexation of the nitronium with Lewis acids ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ or TMSCl) in THF or CH_2Cl_2 , but using 1.1 equiv. of *tert*-butyldimethylsilyl triflate (TBDMSOTf)^[11] at -20°C for 10 min remarkably facilitated the addition of the phosphorus reagent to give the α -(hydroxyamino)phosphonate **2** as a single product in 70% isolated yield (Scheme 2).



Scheme 2

The configuration at the newly formed stereocenter was established unequivocally by single-crystal X-ray analysis of **2** (Figure 1), which shows an *anti* relationship between the hydroxyamino group and the pre-existing alkoxy group.

Guided by this observation, next we examined the addition of diethyl phosphite to *N*-benzyl nitrones derived from other chiral alkoxy aldehydes (Scheme 3).

The reactions of nitrones **3a**^[8a] and **3b**^[8b] derived from protected L-threose and D-galactose respectively, proceeded smoothly under the same conditions as above (TBDMSOTf, THF or CH_2Cl_2 , -20°C , 10 min) to give the corresponding adducts **4a** and **4b** in very good yields. The structures of these compounds also were established by X-ray crystallography (Figures 2 and 3).

The observed diastereoselectivity is in agreement with the stereochemical outcomes of earlier Lewis acid promoted addition reactions of various nucleophiles to nitronium salt **1**.^[8b,12] Transition state models have been postulated that involve

Table 1. Addition of diethyl phosphite to nitronium salt **1**

Entry	Reactants (equiv.)	Conditions (solvent/temp.)	Yield (%) ^[a]
1	HP(O)(OEt)_2 (1)	THF or CH_2Cl_2 /room temp.	— ^[b]
2	HP(O)(OEt)_2 (2)	THF or CH_2Cl_2 /room temp.	— ^[b]
3	HP(O)(OEt)_2 (3)	THF or CH_2Cl_2 /room temp.	— ^[b]
4	HP(O)(OEt)_2 (1), TMG ^[c] (cat)	THF or CH_2Cl_2 /room temp.	— ^[b]
5	HP(O)(OEt)_2 (1), TMG (1)	THF or CH_2Cl_2 /room temp.	— ^[b]
6	HP(O)(OEt)_2 (1), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1)	THF or CH_2Cl_2 /0 $^\circ\text{C}$	— ^[b]
7	HP(O)(OEt)_2 (1), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.1)	THF or CH_2Cl_2 /room temp.	5
8	HP(O)(OEt)_2 (1), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.2)	THF or CH_2Cl_2 /room temp.	10
9	HP(O)(OEt)_2 (1), TMSCl (1.1)	THF or CH_2Cl_2 /−20 $^\circ\text{C}$	10
10	HP(O)(OEt)_2 (1), TMSCl (1.1)	THF or CH_2Cl_2 /0 $^\circ\text{C}$	5
11	HP(O)(OEt)_2 (1), TMSCl (1.1)	THF or CH_2Cl_2 /room temp.	— ^[b]
12	HP(O)(OEt)_2 (1), TBDMSOTf (1.1)	THF or CH_2Cl_2 /−20 $^\circ\text{C}$	70

^[a] Isolated yield. ^[b] Unchanged **1** was recovered totally. ^[c] 1,1,3,3-Tetramethylguanidine.

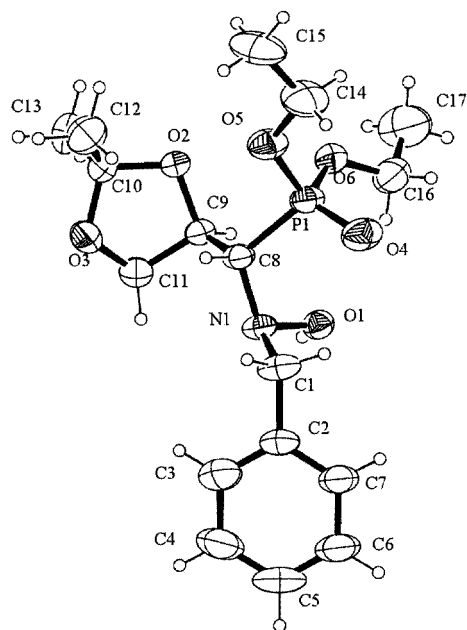
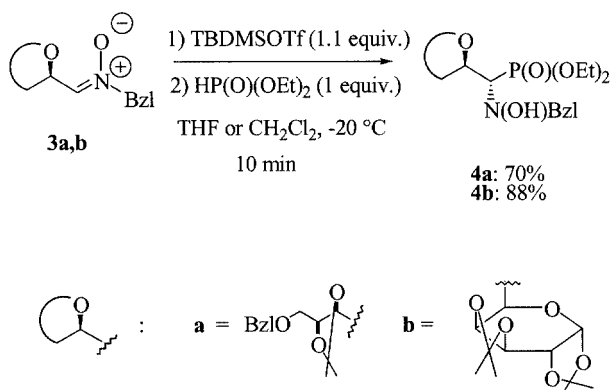


Figure 1. ORTEP view of compound **2** displaying the thermal ellipsoids at 30% probability



Scheme 3

the participation of the Lewis acid to give chelate structures through coordination to the nitron and alkoxy oxygen atoms.^[8b] Hence, it is likely that the silicon atom of the trialkylsilyl group coordinates to both the nitron oxygen atom and one of the oxygen atoms of the dioxolane ring. Hence, two transition state structures **A** and **B** are postulated, arising from coordination to the nitron oxygen atom and to the α -alkoxy (α -chelation) or β -alkoxy (β -chelation) groups, respectively (Figure 4). The formation of the *anti* isomer suggests that the addition of the nucleophile occurs preferentially to the *si* face of the nitron in the β -chelate model **B**.

As an extension of our method, next we focused attention on the addition of diethyl phosphite to α -amino nitrones **6a–d** derived from natural α -amino acids, namely serine, threonine, cysteine, and proline, respectively (Table 2). While the synthesis of L-serine-derived nitron **6a** has been described already,^[13] the hitherto unreported α -amino nitrones **6b–d** were readily prepared (Scheme 4) starting

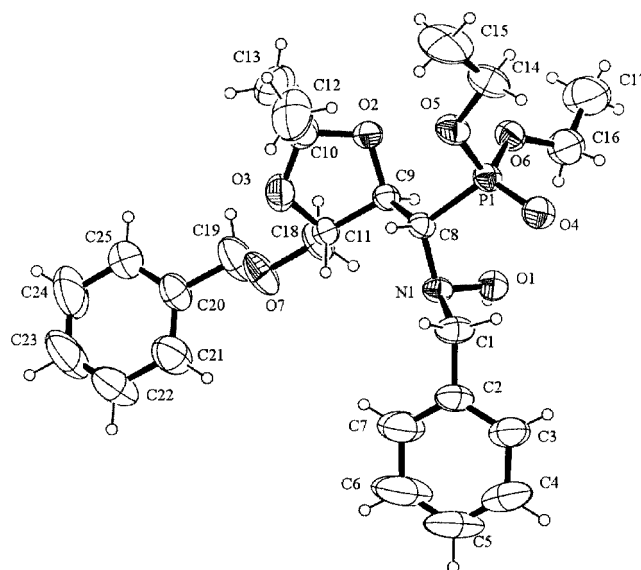


Figure 2. ORTEP view of compound **4a** displaying the thermal ellipsoids at 30% probability

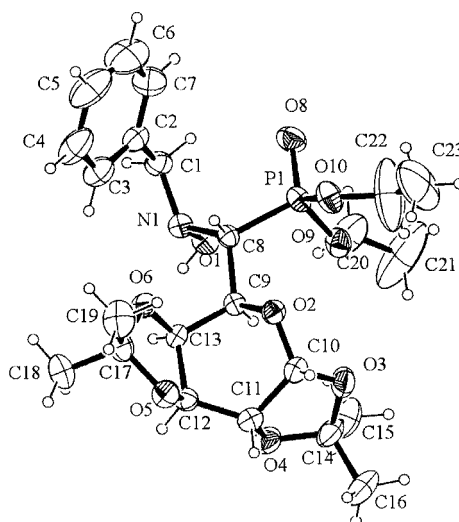


Figure 3. ORTEP view of compound **4b** displaying the thermal ellipsoids at 30% probability

from *N*-benzylhydroxylamine^[14] and the corresponding α -amino aldehydes **5b–d**, which in turn were easily prepared by literature procedures.^[15]

Nitrones **6b–d** are all solids that were purified by flash chromatography. Careful ¹H NMR analysis revealed that the (*Z*) isomer was obtained in all cases, since the nuclear Overhauser effect observed between the azomethine hydrogen atom (HC=N⁺) and the methylene group of the *N*-benzyl moiety (*N*-CH₂Ph) is diagnostic of the (*Z*) configuration.^[8b] The experiments using α -amino nitrones **6a–d** as substrates for the nucleophilic addition of diethyl phosphite gave results that were in marked contrast with those observed in the reactions of chiral α -alkoxy nitrones. Indeed, when these *N,N*-diprotected α -amino nitrones were treated with TBDMSOTf and then diethyl phosphite in THF or

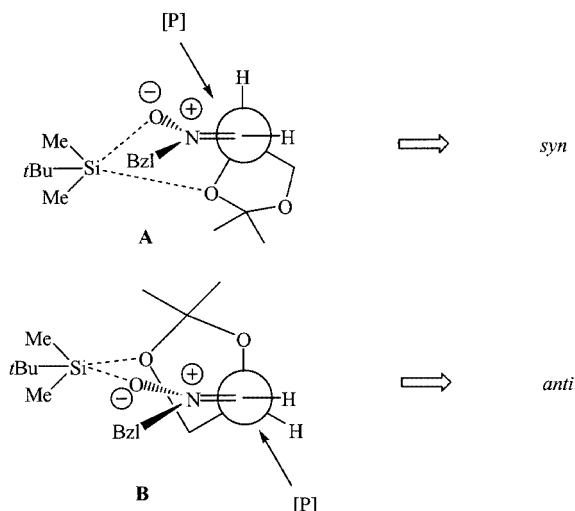
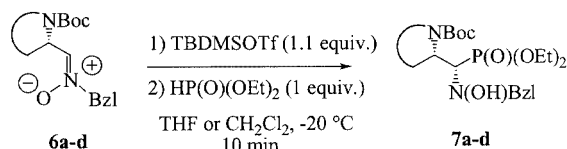
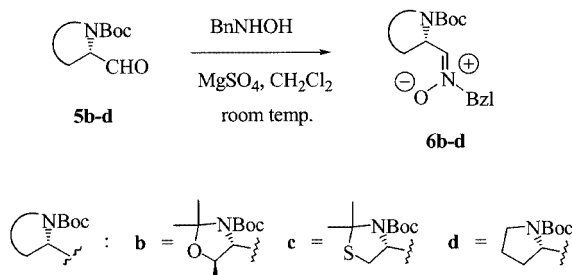


Figure 4. Proposed models for the addition of diethyl phosphite to the nitron 1

Table 2. Addition of diethyl phosphite to nitrones 6



Nitron	Product 7 (Yield [%])
6a	7a (80)
6b	7b (70)
6c	7c (74)
6d	7d (82)



Scheme 4

CH_2Cl_2 at -20°C , the *syn* adducts **7a–d** were obtained in good yields after flash chromatography (Table 2).

Being unable to obtain any compound **7a–d** as a single crystal suitable for X-ray analysis, their relative stereochemistries were attributed on the basis of spectroscopic data. The ^1H NMR spectra of the *syn* adducts **7a** and **7d** showed

similar features to those of the *syn*-hydroxylamines derived from the reaction of nitrones **6a** and **6d** with various nucleophiles.^[16] According to the model formulated by Merino et al.,^[16] these adducts exist in a rigid conformation because of hydrogen bonding between the hydroxyamino oxygen atom and the carbamate group (Figure 5).

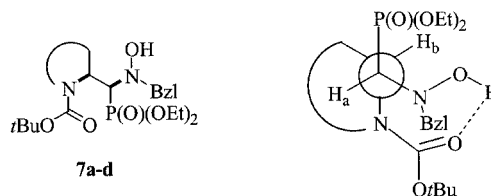
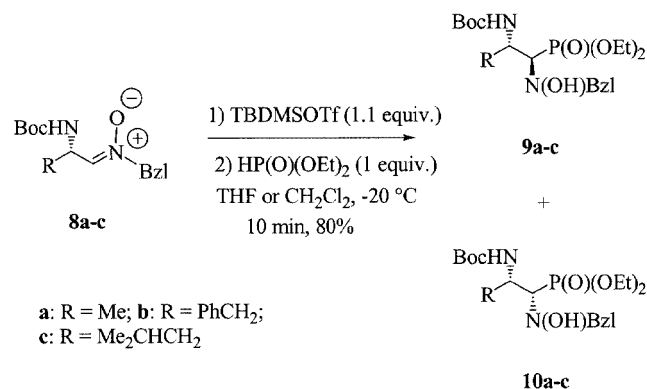


Figure 5. Conformations of hydroxylamines **7a–d**

Indeed, the ^1H NMR spectra of **7a** and **7d** did not show any changes in the range of temperatures between 25 and -55°C , and showed a low-field chemical shift for the hydroxyamino proton in the range between $\delta = 7.6$ and 7.9 ppm at various concentrations. Moreover, consistent with an antiperiplanar disposition of the hydrogen atoms linked to the two adjacent stereocenters, the ^1H NMR spectra at low temperature (from -40 to -55°C) showed values of $^3J_{\text{H,H}}$ coupling constants between these atoms of 10.37 Hz for **7a** and 10.20 Hz for **7d**. The relative stereochemistry of derivatives **7b** and **7c** was assigned by analogy to those of **7a** and **7d**.

We also examined the silyl triflate promoted diethyl phosphite addition to *N*-monoprotected α -amino nitrones **8a–c**, whose progenitors were alanine, phenylalanine, and leucine, respectively. Compounds **8a** and **8b** have been reported in the literature,^[13b,17] whereas the new compound **8c** was prepared from the corresponding aldehyde^[18] under the usual conditions (*N*-benzylhydroxylamine, MgSO_4 , CH_2Cl_2 , room temp.).

When TBDMSOTf-precomplexed nitrones **8a–c** were treated with diethyl phosphite in THF or CH_2Cl_2 at -20°C , 95:5 mixtures of diastereoisomeric hydroxylamines **9** and **10** were obtained in very good yields (80%) (Scheme 5). Only the major *anti* isomers **9a–c** were isolated by flash chromatography.



Scheme 5

X-ray crystallography of compound **9c** showed an *anti* relationship between the NHBoc and N(OH)Bzl groups (Figure 6).

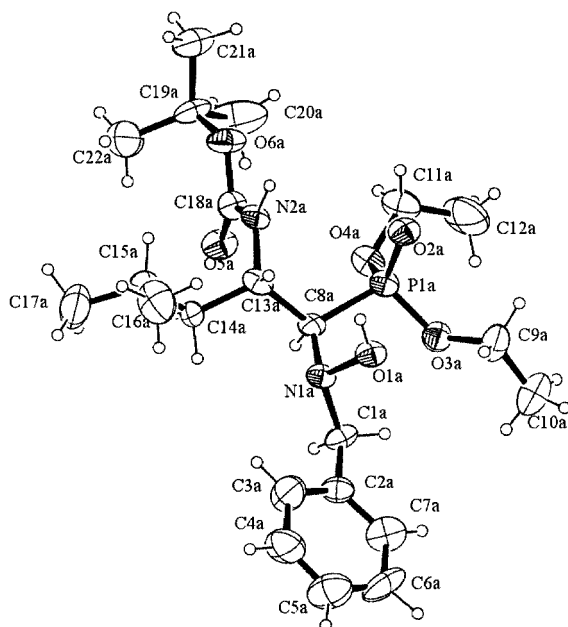


Figure 6. ORTEP view of compound **9c** displaying the thermal ellipsoids at 30% probability

These results are in agreement with the stereochemical outcome that we observed for the addition reaction of 2-lithiothiazole to the nitron derived from *N*-monoprotected serinal.^[13a] This result confirms the tunable *syn/anti* stereoselectivity of the nucleophilic addition reactions to α -amino nitrones of bis- and monoprotected amino groups.

Since compounds **9a–c** showed identical spectroscopic data, the same relative stereochemistry of **9c** was assigned to the products **9a** and **9b**. Indeed, the ^1H NMR spectra of compounds **9a–c** displayed a typical double doublet in the range between $\delta = 3.25$ and 3.34 ppm for the hydrogen atom linked to the carbon atom bearing the hydroxyamino moiety and the phosphonate group ($^2J_{\text{H-P}} = 17.0\text{--}17.5$ Hz and $^3J_{\text{H,H}} = 4.0\text{--}4.6$ Hz).

To explain the observed *syn/anti* stereoselectivity in the addition reaction to chiral α -amino nitrones, we postulate two reactive conformations **C** and **D** (Figure 7), in which the silicon atom of the trialkylsilyl group coordinates to both the nitron oxygen atom and the carbamate group. The difference between these conformations exists on the outside and inside positions of the medium-sized substituent.

The addition to *N,N*-disubstituted α -amino nitrones **6** should take place from the less-hindered side of the cyclic chelate **C** (*Re* attack) to give the *syn* adducts **7**, while the addition of diethyl phosphite to the *N*-monosubstituted derivatives **8** should occur from the less-hindered side of the cyclic chelate **D** leading to the *anti* products **9**, as assumed for the reaction of Grignard reagents with *N*-monopro-

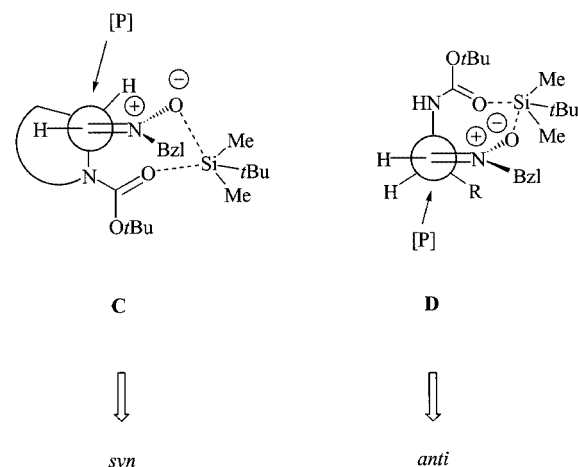


Figure 7. Proposed models for the addition of diethyl phosphite to *N,N*-disubstituted α -amino nitrones and *N*-monosubstituted α -amino nitrones

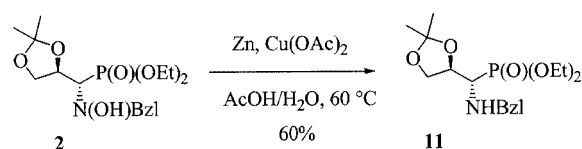
tected α -amino nitrones derived from natural α -amino acids, such as alanine and phenylalanine.^[17]

Synthesis of α -Amino- and α,β -Diaminophosphonates

We anticipated that the α -(hydroxyamino)phosphonates described in the previous section could serve as the precursors to chiral polyhydroxylated α -amino- and α,β -diaminophosphonates. This concept called for a reductive operation to transform the hydroxyamino group into the corresponding amine. Various methods for the reduction of *N,N*-dialkylhydroxylamines have been reported, including catalytic hydrogenation,^[19] reduction with SmI_2 ,^[19] Zn/HCl ,^[19] Raney Ni,^[19,20] aqueous TiCl_3 ,^[21,22] and $\text{Zn}/\text{Cu}(\text{OAc})_2$.^[8d,23]

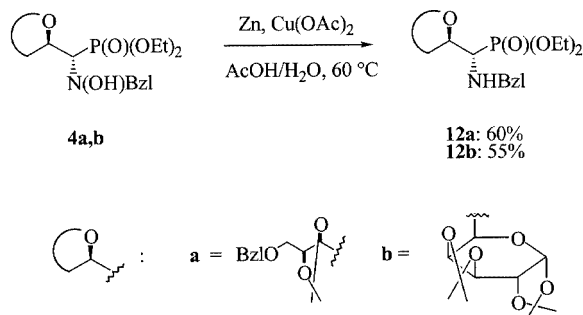
In our hands, the method of choice was strictly dependent on the nature of the hydroxylamine to be reduced. In particular, reduction of the hydroxyamino function of polyhydroxylated α -(hydroxyamino)phosphonates was easily achieved through both the zinc/copper(II) acetate system and catalytic hydrogenation, while the reduction of β -amino- α -(hydroxyamino)phosphonates took place conveniently only by catalytic hydrogenation. Other methods led to considerable decomposition of the starting materials.

Thus, when compound **2** was treated with a mixture of $\text{Zn}/\text{Cu}(\text{OAc})_2$ according to our earlier procedure,^[8d] the resulting α -(benzylamino)phosphonate **11** was isolated in 60% yield after flash chromatography (Scheme 6).



Scheme 6

The same protocol was applied to derivatives **4a** and **4b** to give α -(benzylamino)phosphonates **12a** and **12b** in satisfactory yields (Scheme 7).



Scheme 7

Alternatively, the α -(hydroxyamino)phosphonates **2** and **4a,b** were elaborated through concomitant deoxygenation and debenzylation. This process was achieved in one step by catalytic hydrogenation using palladium hydroxide [Pd(OH)₂] on charcoal as a catalyst, in the presence of di-*tert*-butyl dicarbonate (Boc₂O), to give the *N*-Boc-protected derivatives **13–15** in very good yields after purification by flash chromatography (Table 3). It is noteworthy that the reduction of **4a** proceeded with accompanying removal of the *O*-benzyl protecting group and protection of the so-formed primary hydroxy function to give the *N,O*-Boc-protected derivative **14** in 60% yield.

Table 3. Catalytic reduction of polyhydroxylated α -(hydroxyamino)phosphonates

2 and (4a,b)		13–15	
Hydroxyamine		Product	Yield (%)
2			70
4a			60
4b			80

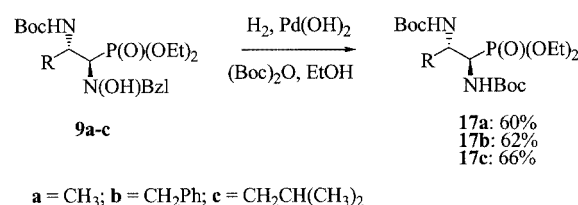
All attempts to convert phosphonates **7a–d** to their corresponding *N*-benzyl-protected amines by means of the Zn/Cu(OAc)₂ reducing system proved to be unsatisfactory, furnishing the expected products in very low yields. On the contrary, catalytic hydrogenation under the same conditions as above [H₂, Pd(OH)₂/C, Boc₂O] allowed us to remove both the benzyl and hydroxy groups from the hydroxy-

amino moiety with the concomitant protection of the free amino group to give derivatives **16a–d**, in satisfactory yields after purification by silica gel column chromatography (40–63%) (Table 4).

Table 4. Catalytic hydrogenation of β -amino- α -(hydroxyamino)-phosphonates

7a–d		16a–d	
Hydroxyamine		Product 16 (Yield [%])	
7a			16a (62)
7b			16b (63)
7c			16c (40)
7d			16d (61)

Finally, the reductive deprotection/reprotection sequence was applied to the pure *anti*- α -(hydroxyamino)phosphonates **9a–c** to furnish the derivatives **17a–c** in good yields (Scheme 8).



Scheme 8

Conclusion

In summary, chiral alkoxy and *N*-protected amino nitrones have been conveniently used in a Lewis acid stereocontrolled addition reaction with diethyl phosphite to obtain non-racemic α -(hydroxyamino)phosphonates in good yields and with high diastereoselectivity. These intermediate adducts represent the key intermediates in the synthesis of α -amino- and α,β -diaminophosphonates, a significant class of biologically active compounds to act as phosphorus isosteres of their parent carboxylic acids. The ready accessibility of the starting materials and the simplicity of all the synthetic steps make our method very practical for the synthesis of phosphonate-containing molecules, stressing once more the versatility of nitrone-based chemistry in the synthesis of biologically active compounds.

Experimental Section

General Remarks: Melting points were determined with a Büchi–Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded with an FT-IR Paragon 500 spectrometer. ^1H nuclear magnetic resonance (NMR) spectra were taken both with a Bruker AC-200 spectrometer at 200 MHz and a Varian 300 Unity spectrometer at 300 MHz, while ^{31}P NMR spectra were recorded with a Varian 300 Unity spectrometer at 121 MHz. Chemical shifts are given in ppm downfield from tetramethylsilane as the internal standard and coupling constants are given in Hz. Optical rotations were measured with a Perkin–Elmer 241 MC Polarimeter. Organic solutions were dried with anhydrous magnesium sulfate and the solvents evaporated with a rotary evaporator. Light petroleum refers to petroleum ether with boiling range 40–60 °C and ether to diethyl ether. Reactions were monitored by TLC on silica gel 60 F₂₅₄ with detection by charring with alcoholic solutions of ninhydrin or aqueous potassium permanganate solutions. Flash chromatography was carried out with Merck silica gel 60 (230–400 mesh). All moisture-sensitive reactions were performed under N_2 or Ar using oven-dried glassware. Elemental analyses were determined by the microanalytical laboratory of the Dipartimento di Chimica, University of Ferrara. α -Alkoxy nitrones **1**,^[8b] **3a**,^[8a] and **3b**,^[8b] and α -amino nitrones **6a**,^[13] **8a**, and **8b**,^[13b,17] were prepared according to the cited literature procedures.

General Procedure for the Synthesis of *N*-Benzyl Nitrones **6b–d and **8c**:** *N*-Benzylhydroxylamine (10 mmol) and anhydrous magnesium sulfate (10 mmol) were added successively to a well-stirred solution of the aldehyde (10 mmol) in dichloromethane (75 mL). Stirring was continued at room temperature for 5 h, the reaction mixture was filtered, and the filtrate concentrated. Nitrones **6b–d** were purified by flash chromatography or crystallization, while nitrone **8c** was used in the next step as obtained, since its purification by flash chromatography led to considerable decomposition.

(*Z*)-*N*-{[(2*S*)-2-(*N*-*tert*-Butoxycarbonyl)-4-methyl]pentylidene}-benzylamine *N*-Oxide (8c**):** This compound was obtained from the corresponding aldehyde,^[18] by using the aforementioned general procedure, as a yellow syrup, which was used in the addition reaction without further purification. Yield: 2.56 g (80%). IR (neat): $\tilde{\nu}$ = 1690, 1592 cm^{-1} . ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 0.94 [m, 6 H, $\text{HC}(\text{CH}_3)_2$], 1.42 (s, 9 H, *t*BuO), 1.54–1.70 (m, 3 H, $\text{HC}(\text{CH}_3)_2$ and H_2CCH), 4.50 (br., 1 H, HCNBoc), 4.87 (s, 2 H, NCH_2Ph), 5.92 (br., 1 H, NHBoc), 6.85 (br., 1 H, $\text{HC}=\text{N}$), 7.25–7.60 (m, 5 H, arom.) ppm. $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_3$ (320.2): calcd. C 67.47, H 8.81, N 8.74; found C 67.55, H 8.75, N 8.82.

(*Z*)-*N*-{[(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]methylidene}benzylamine *N*-Oxide (6b**):** This compound was obtained from **5b**,^[15a] by using the aforementioned general procedure, as a white solid after flash chromatography (eluent: diethyl ether/light petroleum, 9:1), yield: 2.78 g (80%), m.p. 65–67 °C, $[\alpha]_D^{20}$ = +15.6 (c = 1.0, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1690, 1592 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 1.33 (s, 3 H, OCCH_3), 1.45 (d, J = 7.0 Hz, 3 H, CH_3CHO), 1.47 (s, 9 H, *t*BuO), 1.61 (s, 3 H, OCCH_3), 4.13 (q, J = 6.1 Hz, 1 H, CH_3CHO), 4.60–4.80 (m, 1 H, HCNBoc), 4.89 (s, 2 H, NCH_2Ph), 6.67 (br., 1 H, $\text{HC}=\text{N}$), 7.25–7.60 (m, 5 H, arom.) ppm. $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4$ (348.2): calcd. C 65.49, H 8.10, N 8.04; found C 65.53, H 8.78, N 8.10.

(*Z*)-*N*-{[(4*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-1,3-thiazolidin-4-yl]methylidene}benzylamine *N*-Oxide (6c**):** This compound was obtained from **5c**,^[15b] by using the aforementioned general procedure, as a yellowish solid (light petroleum), yield: 2.63 g (75%),

m.p. 117–120 °C, $[\alpha]_D^{20}$ = –7.0 (c = 0.78, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1690, 1592 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 1.29 (s, 9 H, *t*BuO), 1.72 (s, 3 H, OCCH_3), 1.75 (s, 3 H, OCCH_3), 3.05–3.30 (m, 2 H, SCH_2), 4.83 (s, 2 H, NCH_2Ph), 5.26 (br., 1 H, HCNBoc), 6.82 (d, J = 5.30 Hz, 1 H, $\text{HC}=\text{N}$), 7.30–7.50 (m, 5 H, arom.) ppm. $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$ (350.2): calcd. C 61.69, H 7.48, N 7.99; found C 61.75, H 7.55, N 7.95.

(*Z*)-*N*-{[(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]methylidene}-benzylamine *N*-Oxide (6d**):** This compound was obtained from **5d**,^[15c] by using the aforementioned general procedure, as a white solid after flash chromatography (eluent: EtOAc/MeOH, 97:3), yield: 2.43 g (80%), m.p. 65–68 °C, $[\alpha]_D^{20}$ = –24.0 (c = 1.0, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1690, 1592 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 1.43 (s, 9 H, *t*BuO), 1.70–2.10 (m, 3 H), 2.20–2.50 (m, 1 H), 3.30–3.50 (m, 2 H), 4.77–4.85 (m, 1 H, HCNBoc), 4.86 (s, 2 H, NCH_2Ph), 6.70 (br., 1 H, $\text{HC}=\text{N}$), 7.30–7.50 (m, 5 H, arom.) ppm. $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3$ (304.2): calcd. C 67.08, H 7.95, N 9.20; found C 67.15, H 7.88, N 9.15.

General Procedure for the Synthesis of α -(Hydroxyamino)phosphonates: A cooled (–20 °C) solution of the appropriate nitron (1 mmol), in anhydrous THF or CH_2Cl_2 (3 mL) containing TBDMSOTf (1.1 mmol), was treated with diethyl phosphite (1 mmol). The reaction mixture was stirred at the same temperature for 10 min, and then saturated aqueous NaHCO_3 (2 mL) and EtOAc (5 mL) were added. The organic phase was separated, dried, and the solvent evaporated. The residue was purified by flash chromatography or crystallization to afford pure α -(hydroxyamino)-phosphonates.

Diethyl {[(1*S*,2*R*)-1-[Benzyl(hydroxy)amino]-2,3-(isopropylidenedioxy)propyl]phosphonate (2**):** This compound was obtained from **1**, by using the aforementioned general procedure, as a white solid, yield: 261 mg (70%), m.p. 113–114 °C (ether), $[\alpha]_D^{20}$ = +20.0 (c = 0.9, CHCl_3). IR (KBr): $\tilde{\nu}$ = 3207, 1220 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 1.30–1.50 [m, 12 H, $\text{P}(\text{OCH}_2\text{CH}_3)_2$ and $\text{OC}(\text{CH}_3)_2$], 3.27 (dd, 1 H, $^3J_{\text{H,H}} = 7.7$ Hz, $^2J_{\text{H,P}} = 15.3$ Hz, HCNOH), 4.00–4.30 (m, 7 H, OCH_2CH , $\text{P}(\text{OCH}_2\text{CH}_3)_2$ and NCHPh), 4.37 (d, 1 H, part of an AB system, J = 13.4 Hz, NCHPh), 4.42–4.55 (m, 1 H, OCH_2CH), 6.13 (br., 1 H, NOH), 7.20–7.40 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, CDCl_3 , 25 °C): δ = 24.85 ppm. $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_6\text{P}$ (373.2): calcd. C 54.68, H 7.56, N 3.75; found C 54.75, H 7.60, N 3.83.

Diethyl {[(1*S*,2*R*,3*S*)-1-[Benzyl(hydroxy)amino]-4-benzoyloxy-2,3-(isopropylidenedioxy)butyl]phosphonate (4a**):** This compound was obtained from **3a**, by using the aforementioned general procedure, as a white solid, yield: 345 mg (70%), m.p. 115–118 °C (EtOAc), $[\alpha]_D^{20}$ = –6.1 (c = 1.1, CHCl_3). IR (KBr): $\tilde{\nu}$ = 3262, 1229 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 1.32 (s, 3 H, OCCH_3), 1.36 [m, 6 H, $\text{P}(\text{OCH}_2\text{CH}_3)_2$], 1.42 (s, 3 H, OCCH_3), 3.27 (dd, 1 H, $^3J_{\text{H,H}} = 7.6$ Hz, $^2J_{\text{H,P}} = 15.1$ Hz, HCNOH), 3.73 (d, J = 4.8 Hz, 2 H, CH_2OBn), 4.10–4.50 [m, 8 H, $\text{P}(\text{OCH}_2\text{CH}_3)_2$, OCHCHO , and NCH_2Ph], 4.57 (s, 2 H, OCH_2Ph), 6.00 (br., 1 H, NOH), 7.20–7.40 (m, 10 H, arom.) ppm. ^{31}P NMR (121 MHz, CDCl_3): δ = 24.62 ppm. $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_7\text{P}$ (493.2): calcd. C 60.84, H 7.35, N 2.84; found C 60.90, H 7.40, N 2.90.

Diethyl {(*R*)-[Benzyl(hydroxy)amino](5-deoxy-1,2,3,4-di-*O*-isopropylidene- α -D-galactopyranos-5-yl)methyl]phosphonate (4b**):** This compound was obtained from **3b**, by using the aforementioned general procedure, as a white solid, yield: 441 mg (88%), m.p. 176–179 °C (EtOAc), $[\alpha]_D^{20}$ = –59.3 (c = 0.5, CHCl_3). IR (KBr): $\tilde{\nu}$ = 3236, 1218 cm^{-1} . ^1H NMR (200 MHz, CDCl_3 , 25 °C): δ = 1.30–1.45 [m, 15 H, $\text{P}(\text{OCH}_2\text{CH}_3)_2$, 3 OCCH_3], 1.54 (s, 3 H,

OCCH₃), 3.68 (dd, 1 H, $^3J_{\text{H,H}} = 10.0$ Hz, $^2J_{\text{H,P}} = 13.4$ Hz, HCNOH), 4.10–4.40 [m, 7 H, P(OCH₂CH₃)₂, NCHPh, 4'-H and 5'-H], 4.43 (d, 1 H, part of an AB system, $J = 13.6$ Hz, NCHPh), 4.62 (s, 2 H, 2'-H and 3'-H), 5.51 (d, $J = 4.9$ Hz, 1 H, 1'-H), 6.01 (br., 1 H, NOH), 7.20–7.48 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 26.31$ ppm. C₂₃H₃₆N₂O₉P (501.2): calcd. C 55.08, H 7.24, N 2.79; found C 55.15, H 7.32, N 2.75.

Diethyl {(S)-[Benzyl(hydroxy)amino][(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methyl}phosphonate (7a): This compound was obtained from **6a**, by using the aforementioned general procedure, as a yellowish syrup after flash chromatography (eluent: EtOAc/light petroleum, 2:1), yield: 378 mg (80%), $[\alpha]_{\text{D}}^{20} = +4.4$ ($c = 1.9$, CHCl₃). IR (neat): $\tilde{\nu} = 3341, 1667, 1220$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 1.30$ – 1.45 [m, 9 H, P(OCH₂CH₃)₂ and OCCH₃], 1.50 (s, 12 H, OCCH₃ and *t*BuO), 3.13 (dd, 1 H, $^3J_{\text{H,H}} = 10.4$ Hz, $^2J_{\text{H,P}} = 12.5$ Hz, HCNOH), 3.94 (dd, 2 H, $J = 5$ and 9.4 Hz, OCH₂CH), 4.05–4.32 [m, 5 H, P(OCH₂CH₃)₂ and NCHPh], 4.38–4.52 (m, 1 H, CHNBoc), 4.67 (d, 1 H, part of an AB system, $J = 13.8$ Hz, NCHPh), 7.20–7.40 (m, 5 H, arom.), 7.59 (s, 1 H, NOH) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 26.72$ ppm. C₂₂H₃₇N₂O₇P (472.2): calcd. C 55.92, H 7.89, N 5.93; found C 55.98, H 7.80, N 5.88.

Diethyl {(S)-[Benzyl(hydroxy)amino][(4S,5R)-3-(tert-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]methyl}phosphonate (7b): This compound was obtained from **6b**, by using the aforementioned general procedure, as a yellowish syrup after flash chromatography (eluent: diethyl ether/light petroleum, 6:1), yield: 340 mg (70%), $[\alpha]_{\text{D}}^{20} = +11.8$ ($c = 0.2$, CHCl₃). IR (neat): $\tilde{\nu} = 3341, 1667, 1218$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 1.22$ (s, 3 H, OCCH₃), 1.30–1.40 [m, 9 H, P(OCH₂CH₃)₂, CH₃CHO], 1.48 (s, 9 H, *t*BuO), 1.61 (s, 3 H, OCCH₃), 3.13 (dd, 1 H, $^3J_{\text{H,H}} = 10.4$ Hz, $^2J_{\text{H,P}} = 12.9$ Hz, HCNOH), 4.10 (d, 1 H, part of an AB system, $J = 13.6$ Hz, NCHPh), 4.15–4.40 [m, 5 H, P(OCH₂CH₃)₂ and OCHCH₃], 4.45 (m, 1 H, CHNBoc), 4.65 (d, 1 H, part of an AB system, $J = 13.6$ Hz, NCHPh), 7.20–7.40 (m, 5 H, arom.), 7.52 (s, 1 H, NOH) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 26.88$ ppm. C₂₃H₃₉N₂O₇P (486.2): calcd. C 56.78, H 8.08, N 5.76; found C 56.70, H 8.15, N 5.70.

Diethyl {(S)-[Benzyl(hydroxy)amino][(4R)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-thiazolidin-4-yl]methyl}phosphonate (7c): This compound was obtained from **6c**, by using the aforementioned general procedure, as a colourless syrup after flash chromatography (eluent: EtOAc/light petroleum, 1:2), yield: 342 mg (74%), $[\alpha]_{\text{D}}^{20} = -8.8$ ($c = 1.2$, CHCl₃). IR (neat): $\tilde{\nu} = 3341, 1667, 1228$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 1.35$ [dt, 6 H, $^3J_{\text{H,H}} = 6.9$ Hz, $^4J_{\text{H,P}} = 2.9$ Hz, P(OCH₂CH₃)₂], 1.45 (s, 9 H, *t*BuO), 1.55 (s, 3 H, OCCH₃), 1.79 (s, 3 H, OCCH₃), 3.10–3.30 (m, 2 H, SCH₂), 3.64 (dd, 1 H, $^3J_{\text{H,H}} = 10.2$ Hz, $^2J_{\text{H,P}} = 13.3$ Hz, HC-NOH), 4.04 (d, 1 H, part of an AB system, $J = 13.8$ Hz, NCHPh), 4.10–4.35 [m, 4 H, P(OCH₂CH₃)₂], 4.76 (d, 1 H, part of an AB system, $J = 13.8$ Hz, NCHPh), 4.87–5.00 (m, 1 H, CHNBoc), 7.10–7.40 (m, 6 H, arom. and NOH) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 26.88$ ppm. C₂₂H₃₇N₂O₆PS (488.2): calcd. C 54.08, H 7.63, N 5.73; found C 54.15, H 7.70, N 5.82.

Diethyl {(S)-[Benzyl(hydroxy)amino][(S)-1-(tert-butoxycarbonyl)-pyrrolidin-2-yl]methyl}phosphonate (7d): This compound was obtained from **6d**, by using the aforementioned general procedure, as a colourless syrup after flash chromatography (eluent: EtOAc/light petroleum, 1:1), yield: 363 mg (82%), $[\alpha]_{\text{D}}^{20} = +7.2$ ($c = 0.9$, CHCl₃). IR (neat): $\tilde{\nu} = 3320, 1668, 1220$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 1.34$ [dt, 6 H, $^3J_{\text{H,H}} = 7.1$ Hz,

$^4J_{\text{H,P}} = 3.7$ Hz, P(OCH₂CH₃)₂], 1.51 (s, 9 H, *t*BuO), 1.70–2.20 (m, 4 H), 2.77 (dd, 1 H, $^3J_{\text{H,H}} = 10.3$ Hz, $^2J_{\text{H,P}} = 13.4$ Hz, HCNOH), 3.10–3.50 (m, 2 H), 4.10–4.50 [m, 6 H, P(OCH₂CH₃)₂, NCHPh and CHNBoc], 4.64 (d, 1 H, part of an AB system, $J = 13.9$ Hz, NCHPh), 7.20–7.40 (m, 5 H, arom.), 7.88 (s, 1 H, NOH) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 27.51$ ppm. C₂₁H₃₅N₂O₆P (442.2): calcd. C 57.00, H 7.97, N 6.33; found C 57.15, H 8.10, N 6.40.

Diethyl {(1R,2S)- and (1S,2S)-1-[Benzyl(hydroxy)amino]-2-(tert-butoxycarbonylamino)propyl}phosphonates (9a and 10a): These compounds were obtained from **8a**, by using the aforementioned general procedure (333 mg, 80% overall yield). Flash chromatography (eluent: EtOAc/light petroleum, 1:1) of the crude reaction mixture furnished pure **9a** and a mixture of **9a** and **10a**. Data for **9a**: Yellowish syrup, $[\alpha]_{\text{D}}^{20} = -25.0$ ($c = 0.8$, CHCl₃). IR (neat): $\tilde{\nu} = 3341, 1667, 1215$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 1.20$ – 1.50 (m, 18 H, CH₃CH, P(OCH₂CH₃)₂ and *t*BuO), 3.25 (dd, 1 H, $^3J_{\text{H,H}} = 4.2$ Hz, $^2J_{\text{H,P}} = 17.5$ Hz, HCNOH), 4.00–4.30 [m, 6 H, P(OCH₂CH₃)₂, NCHPh and CHNH], 4.38 (d, 1 H, part of an AB system, $J = 13.3$ Hz, NCHPh), 5.25 (d, $J = 10$ Hz, 1 H, NHBoc), 6.48 (br., 1 H, NOH), 7.20–7.40 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 26.37$ ppm. C₁₉H₃₃N₂O₆P (416.2): calcd. C 54.80, H 7.99, N 6.73; found C 54.85, H 8.10, N 6.65. Selected spectroscopic data for **10a**: ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 2.78$ (dd, 1 H, $^3J_{\text{H,H}} = 8.2$ Hz, $^2J_{\text{H,P}} = 14.7$ Hz, HCNOH), 4.58 (d, 1 H, part of an AB system, $J = 10.5$ Hz, NCHPh), 4.81 (d, $J = 10.0$ Hz, 1 H, NHBoc), 7.00 (br., 1 H, NOH), 7.20–7.40 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 25.09$ ppm.

Diethyl {(1R,2S)- and (1S,2S)-1-[Benzyl(hydroxy)amino]-2-(tert-butoxycarbonylamino)-3-phenylpropyl}phosphonates (9b and 10b): These compounds were obtained from **8b** by using the aforementioned general procedure (394 mg, 80% overall yield). Flash chromatography (eluent: EtOAc/light petroleum, 1:1) of the crude reaction mixture furnished pure **9b** and a mixture of **9b** and **10b**. Data for **9b**: Yellowish syrup, $[\alpha]_{\text{D}}^{20} = -23.3$ ($c = 0.2$, CHCl₃). IR (neat): $\tilde{\nu} = 3336, 1691, 1220$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 1.20$ – 1.50 [m, 15 H, P(OCH₂CH₃)₂ and *t*BuO], 3.00–3.30 (m, 2 H, PhCH₂), 3.34 (dd, 1 H, $^3J_{\text{H,H}} = 4.6$ Hz, $^2J_{\text{H,P}} = 17.0$ Hz, HCNOH), 4.02 (d, 1 H, part of an AB system, $J = 13.2$ Hz, NCHPh), 4.10–4.30 [m, 6 H, P(OCH₂CH₃)₂, CHNH and NCHPh], 5.33 (d, $J = 9.4$ Hz, 1 H, NHBoc), 6.16 (br., 1 H, NOH), 7.10–7.50 (m, 10 H, arom.) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 25.55$ ppm. C₂₅H₃₇N₂O₆P (492.2): calcd. C 60.96, H 7.57, N 5.69; found C 61.10, H 7.60, N 5.60. Selected spectroscopic data for **10b**: ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 2.85$ (ddd, 1 H, $^4J_{\text{H,H}} = 1.7$, $^3J_{\text{H,H}} = 5.7$ Hz, $^2J_{\text{H,P}} = 13.0$ Hz, HCNOH), 4.50 (d, part of an AB system, $J = 13.0$ Hz, NCHPh), 5.50 (d, $J = 9.4$ Hz, 1 H, NHBoc) ppm. ^{31}P NMR (121 MHz, CDCl₃, 25 °C): $\delta = 25.94$ ppm.

Diethyl {(1R,2S)- and (1S,2S)-1-[Benzyl(hydroxy)amino]-2-(tert-butoxycarbonylamino)-4-methylpentyl}phosphonates (9c and 10c): These compounds were obtained from **8c** by using the aforementioned general procedure (367 mg, 80% overall yield). Flash chromatography (eluent: EtOAc/light petroleum, 1:1) of the crude reaction mixture furnished pure **9c** and a mixture of **9c** and **10c**. **9c**: White solid, m.p. 73–75 °C (EtOAc/cyclohexane), $[\alpha]_{\text{D}}^{20} = -50.0$ ($c = 0.5$, CHCl₃). IR (KBr): $\tilde{\nu} = 3336, 1691, 1220$ cm⁻¹. ^1H NMR (200 MHz, CDCl₃, 25 °C): $\delta = 0.90$ (d, $J = 5.9$ Hz, 3 H, HCCH₃), 0.91 (d, $J = 5.9$ Hz, 3 H, HCCH₃), 1.20–1.80 [m, 18 H, P(OCH₂CH₃)₂, *t*BuO, HC(CH₃)₂ and H₂CCH], 3.27 (dd, 1 H, $^3J_{\text{H,H}} = 4.0$ Hz, $^2J_{\text{H,P}} = 17.0$ Hz, HCNOH), 4.04 (d, 1 H, part of

an AB system, $J = 13.5$ Hz, $NCHPh$), 4.08–4.28 [m, 5 H, $P(OCH_2CH_3)_2$ and $CHNH$], 4.36 (d, 1 H, part of an AB system, $J = 13.5$ Hz, $NCHPh$), 5.26 (d, $J = 10.0$ Hz, 1 H, $NHBoc$), 6.31 (br., 1 H, NOH), 7.27–7.40 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): 25.31 ppm. $C_{22}H_{39}N_2O_6P$ (458.3): calcd. C 57.63, H 8.57, N 6.11; found C 57.70, H 8.65, N 6.00. Selected spectroscopic data for **10c**: 1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 2.82$ (dd, 1 H, $^3J_{H,H} = 7.7$ Hz, $^2J_{H,P} = 14.8$ Hz, $HCNOH$), 4.04 (d, 1 H, part of an AB system, $J = 10.5$ Hz, $NCHPh$), 4.61 (d, 1 H, part of an AB system, $J = 10.5$ Hz, $NCHPh$), 4.70 (d, $J = 10.0$ Hz, 1 H, $NHBoc$) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): 26.34 ppm.

General Procedure for the Synthesis of *N*-Benzyl-Protected α -Aminophosphonates: Zn dust (5 mmol) was added to a solution of $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol) in $AcOH$ (4 mL) and the resulting suspension was stirred at room temperature for 15 min. A solution of *N*-benzylhydroxylamine (1 mmol) in $AcOH/H_2O$ (3:1, 4 mL) was added. The reaction mixture was stirred at 70 °C overnight, then filtered through Celite. The filtrate was neutralized with an aqueous solution of 3 M $NaOH$, extracted with $EtOAc$ (3×5 mL), and washed with a saturated aqueous solution of $EDTA$. The organic phase was dried and concentrated, and the residue was purified by flash chromatography to furnish pure benzylamines.

Diethyl {(1*S*,2*R*)-1-(Benzylamino)-2,3-(isopropylidenedioxy)propyl}phosphonate (11**):** This compound was obtained from **2**, by using the aforementioned general procedure, as a yellowish oil after flash chromatography (eluent: $EtOAc$ /light petroleum, 2:1), yield: 214 mg (60%), $[\alpha]_D^{20} = +20.0$ ($c = 1.0$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3435$, 1242 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.20$ –1.40 [m, 9 H, $P(OCH_2CH_3)_2$ and $OCCH_3$], 1.43 (s, 3 H, $OCCH_3$), 2.10 (br., 1 H, NH), 3.23 (dd, 1 H, $^3J_{H,H} = 4.5$ Hz, $^2J_{H,P} = 14.4$ Hz, $HCNH$), 3.94 (d, 1 H, part of an AB system, $J = 13.0$ Hz, $NCHPh$), 4.00–4.30 [m, 7 H, $P(OCH_2CH_3)_2$, $NCHPh$, OCH_2CH], 4.40 (m, 1 H, OCH_2CH), 7.20–7.40 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): $\delta = 25.87$ ppm. $C_{17}H_{28}NO_5P$ (357.2): calcd. C 57.13, H 7.90, N 3.92; found C 57.20, H 7.80, N 4.05.

Diethyl {(1*S*,2*R*,3*S*)-1-(Benzylamino)-4-benzyloxy-2,3-(isopropylidenedioxy)butyl}phosphonate (12a**):** This compound was obtained from **4a**, by using the aforementioned general procedure, as a yellowish oil after flash chromatography (eluent: $EtOAc$), yield: 286 mg (60%), $[\alpha]_D^{20} = -5.0$ ($c = 1.3$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3436$, 1240 cm^{-1} . 1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.20$ –1.50 [m, 12 H, $P(OCH_2CH_3)_2$ and $OC(CH_3)_2$], 1.89 (br., 1 H, NH), 3.15 (dd, 1 H, $^3J_{H,H} = 6.4$ Hz, $^2J_{H,P} = 18.0$ Hz, $HCNH$), 3.50–4.30 [m, 10 H, $P(OCH_2CH_3)_2$, $PhCH_2$, $OCHCHO$ and NCH_2Ph], 4.60 (AB system, 2 H, $J = 12.1$ Hz, $PhCH_2O$), 7.20–7.40 (m, 10 H, arom.) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): $\delta = 26.78$ ppm. $C_{25}H_{36}NO_6P$ (477.2): calcd. C 62.88, H 7.60, N 2.93; found C 63.00, H 7.75, N 2.88.

Diethyl {(*R*)-(Benzylamino)(5-deoxy-1,2,3,4-di-*O*-isopropylidene- α -D-galactopyranos-5-yl)methyl}phosphonate (12b**):** This compound was obtained from **4b**, by using the aforementioned general procedure, as a colourless oil after flash chromatography (eluent: $EtOAc$ /light petroleum, 1:3), yield: 267 mg (55%), $[\alpha]_D^{20} = -24$ ($c = 1.0$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3430$, 1245 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.25$ –1.40 [m, 12 H, $P(OCH_2CH_3)_2$ and 2 $OCCH_3$], 1.45 (s, 3 H, $OCCH_3$), 1.58 (s, 3 H, $OCCH_3$), 3.35 (dd, 1 H, $^3J_{H,H} = 8.0$ Hz, $^2J_{H,P} = 12.0$ Hz, $HCNH$), 4.00 (s, 2 H, $PhCH_2$), 4.08–4.28 [m, 6 H, $P(OCH_2CH_3)_2$, NH and 4'-H], 4.31 (dd, $J = 1.0$, 5.0 Hz, 1 H, 5'-H), 4.60–4.72 (m, 2 H, 2'-H and 3'-H), 5.55

(d, $J = 5.0$ Hz, 1 H, 1'-H), 7.20–7.40 (m, 5 H, arom.) ppm. ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): $\delta = 27.77$ ppm. $C_{23}H_{36}NO_8P$ (485.22): calcd. C 56.90, H 7.47, N 2.88; found C 57.10, H 7.52, N 2.90.

General Procedure for the Synthesis of Compounds 13–15, 16a–d, and 17a–c: A solution of protected α -(hydroxyamino)phosphonate (1 mmol) and $(Boc)_2O$ (1.5 mmol) in $EtOH$ (10 mL) was hydrogenated at room temperature for the appropriate time under 5 atm in the presence of 20% palladium hydroxide on activated charcoal (Pearlman's catalyst). The reaction mixture was filtered through a plug of Celite, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography.

Diethyl [(1*S*,2*R*)-1-(*tert*-Butoxycarbonylamino)-2,3-(isopropylidenedioxy)propyl]phosphonate (13**):** This compound was obtained from **2** by using the aforementioned general procedure. Reaction time: 48 h. Yield: 257 mg (70%). White amorphous solid (eluent: $EtOAc$ /cyclohexane, 1:1, containing 0.1% Et_3N), m.p. 54–55 °C, $[\alpha]_D^{20} = +3.8$ ($c = 0.9$, $CHCl_3$). IR (KBr): $\tilde{\nu} = 3400$, 1691, 1225 cm^{-1} . 1H NMR (300 MHz, $DMSO$, 120 °C): $\delta = 1.28$ [dt, 6 H, $^4J_{H,P} = 2$ Hz, $^3J_{H,H} = 7.0$ Hz, $P(OCH_2CH_3)_2$], 1.30 (s, 3 H, $OCCH_3$), 1.36 (s, 3 H, $OCCH_3$), 1.43 (s, 9 H, $tBuO$), 3.87 and 3.98 (AB system, 1 H, $^4J_{H,P} = 1$ Hz, $^3J_{H,H} = 6.5$ Hz, $OCHCHO$), 3.90 and 3.95 (AB system, 1 H, $^4J_{H,P} = 1$ Hz, $^3J_{H,H} = 6.5$ Hz, $OCHCHO$), 4.00–4.17 [m, 5 H, $P(OCH_2CH_3)_2$ and NCH], 4.35 (m, 1 H, OCH_2CH), 6.40 (d, $J = 8$ Hz, 1 H, NH) ppm. ^{31}P NMR (121 MHz, $DMSO$, 120 °C): $\delta = 22.78$ ppm. $C_{15}H_{30}NO_7P$ (367.2): calcd. C 49.04, H 8.23, N 3.81; found C 49.10, H 8.16, N 3.90.

Diethyl [(1*S*,2*R*,3*S*)-1-(*tert*-Butoxycarbonylamino)-4-(*tert*-butoxycarbonyloxy)-2,3-(isopropylidenedioxy)butyl]phosphonate (14**):** This compound was obtained from **4a** by using the aforementioned general procedure. Reaction time: 48 h. Yield: 298 mg (60%). Yellow oil (eluent: $EtOAc$ /cyclohexane, 2:1, containing 0.1% Et_3N), $[\alpha]_D^{20} = -10.1$ ($c = 0.9$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3400$, 1691, 1220 cm^{-1} . 1H NMR (300 MHz, $DMSO$, 120 °C): $\delta = 1.29$ [dt, 6 H, $^4J_{H,P} = 4.5$ Hz, $^3J_{H,H} = 7.0$ Hz, $P(OCH_2CH_3)_2$], 1.41 (s, 9 H, $tBuO$), 1.48 (s, 3 H, $OCCH_3$), 1.50 (s, 12 H, $tBuO$ and $OCCH_3$), 3.96–4.24 [m, 9 H, $P(OCH_2CH_3)_2$, NCH , 2 $HCOC(CH_3)_2$ and CH_2OBoc], 5.40 (br., 1 H, NH) ppm. ^{31}P NMR (121 MHz, $DMSO$, 120 °C): $\delta = 22.79$ ppm. $C_{21}H_{40}NO_{10}P$ (497.2): calcd. C 50.70, H 8.10, N 2.82; found C 50.80, H 7.95, N 2.90.

Diethyl [(*R*)-(tert-Butoxycarbonylamino)(5-deoxy-1,2,3,4-di-*O*-isopropylidene- α -D-galactopyranos-5-yl)methyl]phosphonate (15**):** This compound was obtained from **4b** by using the aforementioned general procedure. Reaction time: 48 h. Yield: 396 mg (80%). Colorless syrup (eluent: $EtOAc$ /cyclohexane, 3:1, containing 0.1% Et_3N), $[\alpha]_D^{20} = -52.2$ ($c = 0.9$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3400$, 1691, 1218 cm^{-1} . 1H NMR (300 MHz, $DMSO$, 120 °C): $\delta = 1.27$ [t, $J = 5$ Hz, 6 H, $P(OCH_2CH_3)_2$], 1.32 (s, 6 H, 2 $\times$ $OCCH_3$), 1.42 (s, 12 H, $tBuO$ and $OCCH_3$), 1.47 (s, 3 H, $OCCH_3$), 4.00–4.20 [m, 6 H, $P(OCH_2CH_3)_2$, 5'-H and $HCNH$], 4.33 (dd, 1 H, $J = 2.5$ and 5 Hz, 2'-H), 4.40 (d, $J = 8$ Hz, 1 H, 4'-H), 4.62 (dd, 1 H, $J = 2.5$ and 8 Hz, 3'-H), 5.46 (d, $J = 5$ Hz, 1 H, 1'-H), 6.38 (d, $J = 8$ Hz, 1 H, NH) ppm. ^{31}P NMR (121 MHz, $DMSO$, 120 °C): $\delta = 23.37$ ppm. $C_{21}H_{38}NO_{10}P$ (495.2): calcd. C 50.90, H 7.73, N 2.83; found C 50.98, H 7.60, N 2.92.

Diethyl {(*S*)-(tert-Butoxycarbonylamino)[(4*S*)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]methyl}phosphonate (16a**):** This compound was obtained from **7a** by using the aforementioned general procedure. Reaction time: 72 h. Yield: 290 mg (62%). Yellowish syrup (eluent: $EtOAc$ /cyclohexane, 1:1, containing 0.1% Et_3N), $[\alpha]_D^{20} = -45.8$ ($c = 0.5$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3400$, 1690,

1225 cm⁻¹. ¹H NMR (300 MHz, DMSO, 120 °C): δ = 1.29 [dt, 6 H, ⁴J_{H,P} = 4.5 Hz, ³J_{H,H} = 7 Hz, P(OCH₂CH₃)₂], 1.41 (s, 9 H, *t*BuO), 1.48 (s, 3 H, OCCH₃), 1.49 (s, 12 H, OCCH₃ and *t*BuO), 3.86–4.26 [m, 8 H, P(OCH₂CH₃)₂, HNCH, HCNBoc and CH₂OC(CH₃)₂], 5.40 (br., 1 H, NH) ppm. ³¹P NMR (121, MHz, DMSO, 120 °C): δ = 22.81 ppm. C₂₀H₃₉N₂O₈P (466.2): calcd. C 51.49, H 8.43, N 6.00; found C 51.55, H 8.53, N 5.95.

Diethyl {(S)-(tert-Butoxycarbonylamino)[(4S,5R)-3-(tert-butoxycarbonyl)-2,2,5-trimethyl-1,3-oxazolidin-4-yl]methyl}phosphonate (16b): This compound was obtained from **7b** by using the aforementioned general procedure. Reaction time: 72 h. Yield: 303 mg (63%). Yellowish syrup (eluent: EtOAc/cyclohexane, 1:1, containing 0.1% Et₃N), [α]_D²⁰ = -26.8 (*c* = 0.4, CHCl₃). IR (neat): $\tilde{\nu}$ = 3400, 1690, 1220 cm⁻¹. ¹H NMR (300 MHz, DMSO, 120 °C): δ = 1.29 [m, 6 H, P(OCH₂CH₃)₂], 1.39 (d, *J* = 7 Hz, 3 H, CH₃CHO), 1.41 (s, 9 H, *t*BuO), 1.48 (s, 3 H, OCCH₃), 1.49 (s, 12 H, OCCH₃ and *t*BuO), 3.86–4.26 [m, 6 H, P(OCH₂CH₃)₂, HNCH, HCNBoc], 4.34–4.44 (m, 1 H, OCHCH₃), 5.40 (br., 1 H, NH) ppm. ³¹P NMR (121, MHz, DMSO, 120 °C): δ = 22.92 ppm. C₂₁H₄₁N₂O₈P (480.3): calcd. C 52.49, H 8.60, N 5.83; found C 52.60, H 8.48, N 6.00.

Diethyl {(S)-(tert-Butoxycarbonylamino)[(4R)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-thiazolidin-4-yl]methyl}phosphonate (16c): This compound was obtained from **7c** by using the aforementioned general procedure. Reaction time: 10 d. Yield: 193 mg (40%). Colorless syrup (eluent: EtOAc/cyclohexane, 1:1, containing 0.1% Et₃N), [α]_D²⁰ = -56.0 (*c* = 1.9, CHCl₃). IR (neat): $\tilde{\nu}$ = 3400, 1690, 1220 cm⁻¹. ¹H NMR (300 MHz, DMSO, 120 °C): δ = 1.29 [q, *J* = 5 Hz, 6 H, P(OCH₂CH₃)₂], 1.41 (s, 9 H, *t*BuO), 1.50 (s, 9 H, *t*BuO), 1.67 (s, 3 H, OCCH₃), 1.78 (s, 3 H, OCCH₃), 3.20 (d, *J* = 12.5 Hz, 1 H, SCH), 3.34 (ddd, 1 H, ⁴J_{H,P} = 1.0, ³J_{H,H} = 5.5, ²J_{H,H} = 12.5 Hz, SCH), 4.02–4.18 [m, 4 H, P(OCH₂CH₃)₂], 4.37 (dt, 1 H, ³J_{H,H} = 10.5 Hz, ²J_{H,P} = 14 Hz, HCNBoc), 4.66–4.76 (m, 1 H, CHNH), 5.33 (br. s, 1 H, NH) ppm. ³¹P NMR (121, MHz, DMSO, 120 °C): δ = 23.06 ppm. C₂₀H₃₉N₂O₇PS (482.2): calcd. C 49.78, H 8.15, N 5.81; found C 49.95, H 8.00, N 6.00.

Diethyl {(S)-(tert-Butoxycarbonylamino)[(S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl]methyl}phosphonate (16d): This compound was obtained from **7d** by using the aforementioned general procedure. Reaction time: 72 h. Yield: 266 mg (61%). Colorless syrup (eluent: EtOAc/cyclohexane, 1:1, containing 0.1% Et₃N), [α]_D²⁰ = -38.0 (*c* = 1.3, CHCl₃). IR (neat): $\tilde{\nu}$ = 3400, 1690, 1220 cm⁻¹. ¹H NMR (300 MHz, DMSO, 120 °C): δ = 1.29 [dt, 6 H, ⁴J_{H,P} = 2.6 Hz, ³J_{H,H} = 7.0 Hz, P(OCH₂CH₃)₂], 1.42 (s, 9 H, *t*BuO), 1.47 (s, 9 H, *t*BuO), 1.78–2.16 (m, 4 H, 3'-CH₂ and 4'-CH₂), 3.13–3.22 (m, 1 H, 5'-H), 3.28–3.40 (m, 1 H, 5'-H), 3.89–4.15 [m, 6 H, P(OCH₂CH₃)₂, HCNHBoc and HCNBoc], 5.51 (d, *J* = 8 Hz, 1 H, NH) ppm. ³¹P NMR (121, MHz, DMSO, 120 °C): δ = 23.80 ppm. C₁₉H₃₇N₂O₇P (436.2): calcd. C 52.28, H 8.54, N 6.42; found C 52.35, H 8.40, N 8.90.

Diethyl [(1R,2S)-1,2-Bis(tert-butoxycarbonylamino)propyl]phosphonate (17a): This compound was obtained from **9a** by using the aforementioned general procedure. Reaction time: 72 h. Yield: 246 mg (60%). Yellowish syrup (eluent: EtOAc/cyclohexane, 1:1, containing 0.1% Et₃N), [α]_D²⁰ = -21.6 (*c* = 0.4, CHCl₃). IR (neat): $\tilde{\nu}$ = 3400, 1690, 1220 cm⁻¹. ¹H NMR (300 MHz, DMSO, 120 °C): δ = 1.15 (d, *J* = 7 Hz, 3 H, CH₃CH), 1.28 [dt, 6 H, ⁴J_{H,P} = 5.0 Hz, ³J_{H,H} = 7.0 Hz, P(OCH₂CH₃)₂], 1.41 (s, 9 H, *t*BuO), 1.44 (s, 9 H, *t*BuO), 3.79–3.94 (m, 1 H, CH₃CHNH), 4.00–4.12 [m, 4 H, P(OCH₂CH₃)₂], 4.17 (ddd, 1 H, ³J_{H,H} = 5.0, ³J_{H,N} = 10.0, ²J_{H,P} = 18.0 Hz, HCP), 5.98 (d, *J* = 7.0 Hz, 1 H, HNCHCH₃), 6.15 (d,

J = 10 Hz, 1 H, HNCHP) ppm. ³¹P NMR (121 MHz, DMSO, 120 °C): δ = 23.87 ppm. C₁₇H₃₅N₂O₇P (410.2): calcd. C 49.75, H 8.60, N 6.83; found C 49.90, H 8.45, N 7.00.

Diethyl [(1R,2S)-1,2-Bis(tert-butoxycarbonylamino)-3-phenylpropyl]phosphonate (17b): This compound was obtained from **9b** by using the aforementioned general procedure. Reaction time: 72 h. Yield: 301 mg (62%). Yellowish syrup (eluent: EtOAc/cyclohexane, 3:1, containing 0.1% Et₃N), [α]_D²⁰ = -15.5 (*c* = 0.6, CHCl₃). IR (neat): $\tilde{\nu}$ = 3400, 1691, 1218 cm⁻¹. ¹H NMR (300 MHz, DMSO, 140 °C): δ = 1.27–1.36 [m, 15 H, P(OCH₂CH₃)₂ and *t*BuO], 1.45 (s, 9 H, *t*BuO), 2.74 (dd, *J* = 10 and 14 Hz, 1 H, CHPh), 3.07 (dd, *J* = 4, 14 Hz, 1 H, CHPh), 3.98–4.28 [m, 6 H, P(OCH₂CH₃)₂, HCNHBoc and HCP], 5.88 (d, *J* = 8.0 Hz, 1 H, HNCHCH₂), 6.20 (d, *J* = 8.0 Hz, 1 H, HNCHP), 7.10–7.50 (m, 5 H, arom.) ppm. ³¹P NMR (121 MHz, DMSO, 120 °C): δ = 23.91 ppm. C₂₃H₃₉N₂O₇P (486.2): calcd. C 56.78, H 8.08, N 5.76; found C 56.80, H 8.15, N 5.60.

Diethyl [(1R,2S)-1,2-Bis(tert-butoxycarbonylamino)-4-methylpentyl]phosphonate (17c): This compound was obtained from **9c** by using the aforementioned general procedure. Reaction time: 72 h. Yield: 300 mg (66%). Yellowish syrup (eluent: EtOAc/cyclohexane, 1:1, containing 0.1% Et₃N), [α]_D²⁰ = -23.2 (*c* = 1.3, CHCl₃). IR (neat): $\tilde{\nu}$ = 3400, 1691, 1215 cm⁻¹. ¹H NMR (300 MHz, DMSO, 120 °C): δ = 0.88 (d, *J* = 7.0 Hz, 3 H, HCCH₃), 0.91 (d, *J* = 7.0 Hz, 3 H, HCCH₃), 1.24–1.33 [dt, 6 H, ⁴J_{H,P} = 5.0 Hz, ³J_{H,H} = 7.0 Hz, P(OCH₂CH₃)₂], 1.41 (s, 9 H, *t*BuO), 1.43 (s, 9 H, *t*BuO), 1.59–1.73 [m, 3 H, HC(CH₃)₂ and H₂CCH(CH₃)₂], 3.78–3.92 (m, 1 H, CH₂CHNH), 4.00–4.12 [m, 4 H, P(OCH₂CH₃)₂], 4.15 (ddd, 1 H, ³J_{H,H} = 5.0, ³J_{H,N} = 10.0, ²J_{H,P} = 18.0 Hz, HCP), 4.30 (m, 1 H, HNCHCH₂), 5.91 (d, *J* = 7.0 Hz, 1 H, HNCH), 6.03 (d, *J* = 10 Hz, 1 H, HNCHP) ppm. ³¹P NMR (121 MHz, DMSO, 120 °C): δ = 23.86 ppm. C₂₀H₄₁N₂O₇P (452.3): calcd. C 53.08, H 9.13, N 6.19; found C 53.15, H 9.00, N 6.25.

X-ray Structure Determinations: X-ray diffraction data for compounds **2**, **4a**, **4b**, and **9c** were collected at 295 K with a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-K α radiation (λ = 0.7107 Å). The structures were solved by direct methods (SIR97)^[24] and refined (SHELXL-97)^[25] by a full-matrix least-squares method with anisotropic non-hydrogen and hydrogen atoms included in calculated positions riding on their carrier atoms, except for OH and NH hydrogen atoms in compounds **2**, **4a**, and **4b**, which were refined isotropically. ORTEP^[26] views are shown in Figures 1–3, and 6, respectively. Crystal Data: **2**: C₁₇H₂₈NO₆P; monoclinic, space group *P*2₁, *a* = 9.5358(6), *b* = 10.1850(3), *c* = 11.4938(7) Å, β = 110.621(2)°, *V* = 1044.8(1) Å³, *Z* = 2, *D*_c = 1.187 g·cm⁻³. Intensity data collected with $\theta \leq 27.5^\circ$; 2508 independent reflections measured; 1877 observed [*I* > 2 σ (*I*)]. Final *R* index = 0.041 (observed reflections). The molecules possess intermolecular hydrogen bonds between *N*-hydroxy and phosphonate groups, O1–H $\cdots$ O4 ($-x, 1/2 + y, 2 - z$) [O1 $\cdots$ O4 = 2.633(4) Å, O1–H $\cdots$ O4 = 177(4)°]. **4a**: C₂₅H₃₆NO₇P; monoclinic, space group *P*2₁, *a* = 11.750(1), *b* = 10.1491(7), *c* = 12.346(1) Å, β = 107.147(4)°, *V* = 1406.8(2) Å³, *Z* = 2, *D*_c = 1.165 g·cm⁻³. Intensity data collected with $\theta \leq 27.5^\circ$; 3341 independent reflections measured; 2466 observed [*I* > 2 σ (*I*)]. Final *R* index = 0.064 (observed reflections). The molecules possess intermolecular hydrogen bonds between *N*-hydroxy and phosphonate groups, O1–H $\cdots$ O4 [O1 $\cdots$ O4 = 2.685(5) Å, O1–H $\cdots$ O8 = 175(5)°]. **4b**: C₂₃H₃₆NO₉P; orthorhombic, space group *P*2₁2₁2₁, *a* = 9.9495(2), *b* = 14.1008(4), *c* = 19.3015(6) Å, *V* = 2707.9(1) Å³, *Z* = 4, *D*_c = 1.230 g·cm⁻³. Intensity data collected with $\theta \leq 27^\circ$; 3269 independent reflections measured; 2470 observed [*I* > 2 σ (*I*)]. Final *R* index = 0.069 (ob-

served reflections). The molecules possess intermolecular hydrogen bond between *N*-hydroxy and phosphonate groups, O1–H···O8 ($1/2 + x, 1/2 - y, 1 - z$) [O1···O8 = 2.648(6) Å, O1–H···O8 = 167(5)°]. **9c**: C₂₂H₃₉N₂O₆P; orthorhombic, space group *P*2₁2₁2₁, *a* = 9.8171(4), *b* = 11.0010(5), *c* = 49.372(2) Å, *V* = 5332.1(4) Å³, *Z* = 8, *D*_c = 1.142 g·cm^{−3}. Intensity data collected with $\theta \leq 25^\circ$; 3771 independent reflections measured; 2638 observed [*I* > 2σ(*I*)]. Final *R* index = 0.073 (observed reflections). The asymmetric unit comprises two independent molecules, which form a complex network of hydrogen bonds: O1A–H···O2B (*x, y, z*) [O1A···O2B = 2.783(6) Å, O1A–H···O2B = 146°]; N2A–H···O5B (*x, y, z*) [N2A···O5B = 2.916(6) Å, N2A–H···O5A = 134°]; O1B–H···O2A (*x, y, z*) [O1B···O2A = 2.669(6) Å, O1B–H···O2A = 128°]; N2B–H···O5A (*x + 1, y, z*) [N2B···O5A = 2.995(7) Å, N2B–H···O5A = 157°]. CCDC-165735 (**2**), -165736 (**4a**), -199534 (**4b**), and -199535 (**9c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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