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[4 + 2] Cycloadditions of 1-Phosphono-1,3-butadienes with Nitroso Heterodienophiles: A Versatile Synthetic Route for Polyfunctionalized Aminophosphonic Derivatives

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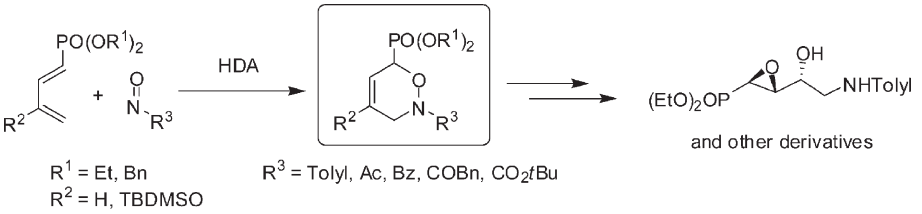

The hetero-Diels−Alder (HDA) reaction of 1-(diethoxyphosphonyl)-1,3-butadiene, 1-(dibenzyloxyphosphonyl)-1,3-butadiene, and 1-(diethoxyphosphonyl)-3-*tert*-butyldimethylsilyloxy-1,3-butadiene with various nitroso heterodienophiles has been investigated as a new synthetic route for aminophosphonic derivatives. The HDA cycloadditions regioselectively led to the proximal isomers, i.e., presenting the NR^3 group in the meta position regarding the phosphonate substituent. From the resulting 6-phosphono-3,6-dihydro-1,2-oxazine cycloadducts, a limited number of chemical steps were allowed to obtain a significant variety of aminophosphonic compounds of potential interest in medicinal chemistry. This has been illustrated through the synthesis of (*Z*)-4-(*o*-tolylamino)-1-hydroxybut-2-enylphosphonic acid, diethyl 3,4-dihydroxy-1-*o*-tolylpyrrolidin-2-yl-2-phosphonate, 4-(*o*-tolylamino)-1,2,3-trihydroxybutylphosphonic acid, diethyl 3-(2-(*o*-tolylamino)-1-hydroxyethyl)oxiran-2-yl-2-phosphonate, and diethyl 4,5-dihydroxymorpholin-6-yl-6-phosphonate.

Introduction

Recent discoveries of natural organophosphonate compounds with promising activities in both agricultural and medicinal fields have stimulated the development of synthetic analogues. In particular, aminophosphonic derivatives constitute an important class of pharmacologically active molecules.[1] Although displaying fundamental differences (in terms of pK_a, geometry, and shape), the phosphonate moiety is considered an analogue of the carboxylic group (i.e., bioisoster) in medicinal chemistry.[2] α-Aminophosphonic compounds and their diesters (phosphonates), as direct analogues of the natural α-amino acids, occupy a special place among diverse structures of aminophosphonic derivatives. Less attention is paid to β-, γ-, and δ-aminophosphonic compounds despite the increasing interest in Fosmidomycin and Rhizocticin families, for example (Figure 1).[3,4]

As part of a research program dedicated to the synthesis of aminophosphonic compounds based on the Diels−Alder (DA) reaction,[5] we became interested in the hetero-Diels−Alder (HDA) reaction of phosphonodienes (**1**) and nitroso dienophiles (**2**) as a versatile route toward 6-phosphono-3,6-dihydro-1,2-oxazine derivatives, precursors of δ-aminophosphonic compounds (Figure 2). Dienes possessing a dialkoxyphosphonyl substituent in the C(1) position are known to display a poor reactivity in [4 + 2] cycloadditions, as a consequence of their

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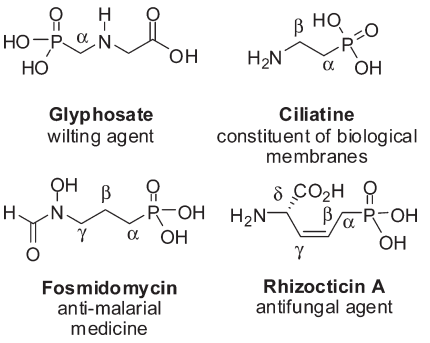
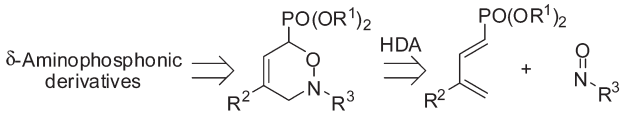


FIGURE 1. Some aminophosphonic compounds of interest.



R^1 = Et, R^2 = H (**1a**), R^1 = Bn, R^2 = H (**1b**), R^1 = Et, R^2 = OSi*t*BDM (**1c**) R^3 = 2-tolyl (**2a**), Me_2CCl (**2b**), *c*-$C_6H_{10}Cl$ (**2c**), CO_2tBu (**2d**), MeCO (**2e**), PhCO (**2f**), $PhCH_2CO$ (**2g**)

FIGURE 2. General strategy toward δ-aminophosphonic compounds.

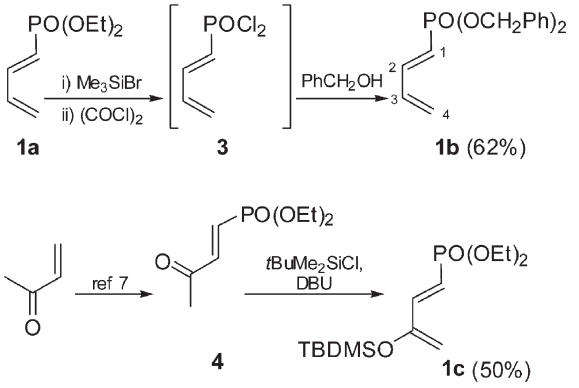
weak dienyl activation. Even with activated C=C dienophiles, the DA cycloaddition yields remain modest.[5b] We have recently reported that 2-nitrosotoluene (**2a**) is able to react quantitatively with 1-diethoxyphosphonyl-1,3-butadiene (**1a**) under microwave (MW) heating.[5e] This HDA reaction provides the first example of an efficient cycloaddition using a phosphonodiene.

Theoretical studies by Leach and Houk[6a] reported that the cycloadditions of inactivated or poorly activated dienes with nitroso dienophiles led to mixtures of proximal and distal regioisomers.[6b] Similarly, we investigated the HDA reaction of 1-diethoxyphosphonyl-1,3-butadiene (**1a**) with nitroso dienophiles (model compounds and reagents used in this work) by computational methods and concluded that the phosphonate moiety prevents the formation of the more constrained distal cycloadduct, leading to complete proximal regioselectivity (theoretical results not shown). This is experimentally shown below.

Three different phosphonodienes **1** were considered in our study. As phosphonic acids are particularly awkward to handle, due to their low solubility in common organic solvents, the release of free acids has to be performed in the last synthetic step, preferably avoiding purification. Accordingly, dienes **1a** and **1b** were used as simple C(1)-substituted 1,3-butadienes with two different P-protecting groups (**1a**, R^1 = Et and R^2 = H; **1b** R^1 = Bn and R^2 = H) which could be cleaved under selective conditions, nucleophilic substitution and catalytic hydrogenation, respectively. A third phosphonodiene **1c** (R^1 = Et, R^2 = OTBDMS) was synthesized in order to increase the butadienyl reactivity toward dienophiles. Various nitroso dienophiles were considered as partners, from a stable one (**2a**) to transient species (acylnitroso derivatives **2d**−**g**), covering some molecular diversity. Particular nitroso substituents (R^3) were used because of their convenient deprotection into free amines (e.g., **2b**−**d**).

The HDA cycloadditions of dienes **1a**−**c** with nitroso dienophiles **2a**−**g** (Figure 2) are fully discussed in this article, in continuation of our preliminary investigations already published.[5e] Some cycloadducts, i.e., 6-phosphono-3,6-dihydro-1,2-oxazines, have been further considered as synthons for the preparation of δ-aminophosphonic derivatives in the aliphatic series and in the pyrrolidine family.

SCHEME 1. Synthesis of Dienes (TBDMS = *tert*-Butyldimethylsilyl)



Results and Discussion

Synthesis of the Precursors. 1-(Diethoxyphosphonyl)-1,3-butadiene (**1a**), obtained in two steps from 1,4-*trans*-dichlorobutene according to a modified protocol of the literature,[5d] is the precursor of 1-(dibenzyloxyphosphonyl)-1,3-butadiene (**1b**) (Scheme 1). The recently described phosphonyl dichloride intermediate **3**[5c] reacted directly with 2 equiv of freshly distilled benzyl alcohol and pyridine. Dienes **1a** and **1b** are easily purified by column chromatography on silica gel; they are stable under storage at 4 °C during several months.

1-Diethoxyphosphonyl-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**1c**) was obtained from the known vinylphosphonate **4**.[7] Under the usual conditions for the synthesis of silyl enol ethers (TBDMSCl, NaI, Et_3N),[8] cleavage of the diethyl phosphonate moiety was observed due to the in situ formation of TBDMSI. In the absence of NaI, no reaction occurred. Optimal conditions were found using DBU in THF with 1 equiv of *tert*-butyldimethylsilyl chloride. Conversion of **4** was complete within 1 h (monitoring by ^{1}H NMR 500 MHz), but the purification induced loss of final pure product (50% isolated yield).

The C(1) typical ^{13}C NMR signals and J_{C-P} coupling constants are quite similar for dienes **1a**−**c** (δ = 115−118 ppm; ^1J = 189−191 Hz). However, the chemical shift belonging to C(4) appears significantly different for **1c** (δ = 102 ppm) compared to **1a**,**b** (δ = 124−125 ppm) because of an increase in electron density.

The most reactive nitroso dienophiles are those where the N=O group is directly linked to an electron-withdrawing substituent.[6,9] In contrast, arylnitroso dienophiles are stable

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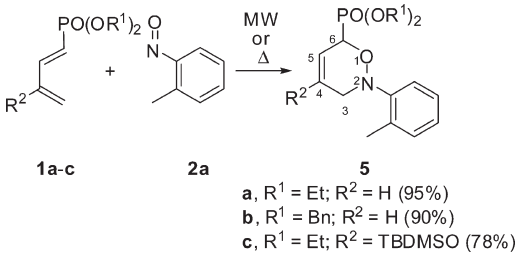
SCHEME 2. Cycloaddition of 1a−c to *o*-Nitrosotoluene



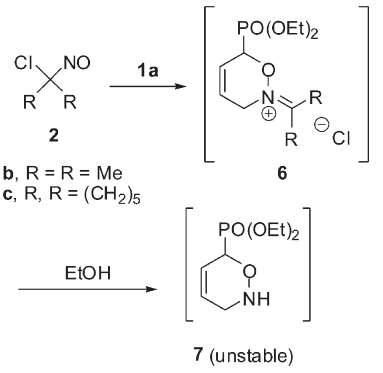
entities, and some of them are commercially available. Despite their stability, they are good dienophiles.[9] α-Chloro nitroso dienophiles react slowly with dienes, are poorly stable, and are light sensitive.[10] Nevertheless, their use in alcoholic solvent is of particular interest since the initial cycloadducts are solvolyzed in situ to give the corresponding N-deprotected oxazines.[11] Nitroso formate and acylnitroso dienophiles also offer the possibility of further deprotection of the cycloadducts, but these reagents are highly reactive and prone to rapid degradation. For this work, *o*-nitrosotoluene (**2a**) was purchased as its dimeric form, while the α-chloro (**2b**,**c**) and acylnitroso (**2d**−**g**) dienophiles were in situ prepared from their respective precursors (i.e., hydroxamic acids and 9,10-dimethylanthracenyl cycloadducts) according to established procedures.[12−15]

HDA Cycloadditions of Dienes 1a−c and Dienophiles 2a−g. The reactivity of dienes **1a**−**c** was first evaluated versus commercial *o*-nitrosotoluene (**2a**), used as a reference reagent, under classical thermal activation (reflux in dichloroethane (DCE)) and microwave (MW) heating. Although (chiral) catalysts have been shown to activate the HDA reactions of nitroso dienophiles,[9] we did not consider catalytic systems here because of the particular nature of the dienyl partners **1**. The phosphonate group behaves as a good Lewis base, trapping the Lewis acid catalysts and preventing from efficient complexation−decomplexation equilibria.[5a,b]

Similarly to diene **1a**,[5e] diene **1b** led to the cycloadduct **5b** within a short reaction time (1 h) and in high yield under MW heating (Scheme 2). As expected, the 3-silyloxy diene **1c** was more reactive than **1a**,**b** in DCE at reflux, yielding the corresponding cycloadduct **5c** within 4 h (100% conversion) instead of 12−17 h for dienes **1a**,**b**.

^{1}H, ^{13}C,and ^{31}P NMR spectroscopy allowed us to unambiguously confirm the proximal regioisomer of the cycloadducts **5** (see the Experimental Section). In particular, ^{13}C NMR chemical shifts and J_{C-P} coupling constants were very useful for the structural assignments.[16−18] The oxazines **5a**,**b** could be easily purified by column chromatography and stored for a long time without degradation. Unfortunately, cycloadduct **5c** was poorly stable and degraded quite rapidly under purification and storage, even at −20 °C. Attempts to directly deprotect or hydrolyze the silylenol ether function of crude **5c** led disappointingly to untractable mixtures. Consequently, **5c** could not be exploited as a useful synthon toward aminophosphonic derivatives, and its precursor, i.e., diene **1c**, was not further considered in the present study.

SCHEME 3. Cycloaddition of 1a to α-Chloronitroso Dienophiles



A freshly prepared solution of 2-chloro-2-nitrosopropane (**2b**) was engaged under mild HDA conditions with diene **1a** in chloroform at room temperature in the dark (Scheme 3). The reaction was monitored by NMR analysis. After 5 days, a mixture of several products was observed, containing mainly **1a** and the desired cycloadduct **6b** (≤20% of the crude material), easily identified by the typical $^{1}J_{C-P}$ value of 164.7 Hz observed in ^{13}C NMR for the C(6) peak at 74.3 ppm and an additional singlet at 207.1 ppm, characteristic of the imminium quaternary carbon.

A similar behavior has been observed in diethyl ether as solvent or when 1-chloro-1-nitrosocyclohexane (**2c**) is used as the dienophile. Complete degradation of the corresponding cycloadducts **6b**,**c** during solvolysis with ethanol, aqueous workup, or direct chromatography was observed. Hence, we were unable to isolate the N-deprotected oxazine **7**. Therefore, we considered the acylnitroso dienophiles.

Using standard conditions for the generation of acylnitroso species **2d**−**g** from the corresponding hydroxamic acids (i.e., oxidation with commercial butylammonium (meta)periodate), we never observed cycloadditions with diene **1a**. After complete consumption of the hydroxamic acids, phosphonodiene **1a** was recovered in more than 95% yield. Alternatively, the modified Moffatt−Swern protocol was used, but no cycloadducts were observed. This prompted us to consider another source of acylnitroso species, and we put our attention on anthracenyl acylnitroso cycloadducts **8**, well-known for their thermal instability. Modified protocols from the literature were applied to produce compounds **8d**−**g** (Scheme 4).[12] Treatment of a chloroform solution of 9,10-dimethylanthracene and butylammonium (meta)periodate with a dimethylformamide solution

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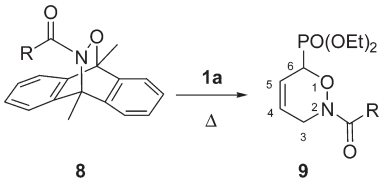
SCHEME 4. Cycloaddition of 1a to Acylnitroso Dienophiles Generated in Situ from Their 9,10-DMA Adducts



	R	8/1a	9 (%)
d	O*t*Bu	1.5	85
e	Me	1.0	77
f	Ph	1.5	56
g	CH_2Ph	2.0	71

TABLE 1. ^{13}C NMR (75 MHz, $CDCl_3$) Data of Cycloadducts 9 (δ Values (ppm) and J_{C-P} Values (Hz) in Parentheses)

	d		e		f		g	
C(3)	46.3	(0)	42.0	(0)	43.4	(0)	42.3	(0)
C(4)	125.1	(9.4)	124.7	(9.6)	124.8	(9.5)	124.6	(9.6)
C(5)	121.5	(5.5)	120.9	(3.6)	121.0	(5.7)	121.0	(3.8)
C(6)	73.9	(159.4)	75.8	(160.0)	75.5	(160.7)	76.0	(160.4)

of hydroxamic acids quantitatively led to the corresponding anthracenyl adducts **8**. After reductive workup (aqueous $Na_2S_2O_3$) to remove the excess of periodate, the precursors **8** were isolated with satisfying purity. They are stable under storage at −20 °C but degraded under chromatography conditions.

Several conditions for the reaction of **1a** and crude **8d−g** have been investigated. Complete transformation of diene **1a** (NMR analysis) occurred using a **8**/**1a** ratio between 1 and 2 in refluxing DCE overnight (Scheme 4). After purification, the cycloadducts **9d−g** were isolated in moderate to good yields. NMR analyses of the crude cycloadducts **9** were consistent with the formation of single regioisomers. The proximal regioselectivity was confirmed by comparison with the other series (see above, cycloadducts **5**) and further assessed by X-ray data from a functionalized derivative (see below, structure **23d**).

Typical ^{13}C NMR features are summarized in Table 1. For all of the cycloadducts, the experimental coupling constants are quite similar, in particular $^3J_{C-P}$ (9−10 Hz). This could be interpreted in terms of conformational behavior of heterocycles **5** and **9** and explained using the relevant Karplus curve.[19] Two stable conformers were computed for the 3,6-dihydro-1,2-oxazine **5a** at the B3LYP/6-31G** level of theory.[20] Conformer I presents the phosphonate substituent in a pseudoaxial position, while for conformer II, this group is in a pseudoequatorial position (Figure 3). Interestingly, both conformers show the 2-tolyl substituent in a pseudoaxial position, releasing the nitrogen lone pair in a pseudoequatorial position. In the most stable conformer II, the $\phi_{P-C(6)-C(5)-C(4)}$ dihedral angle is 137° and 73° for the other conformer I. These values correspond to $^3J_{P-C}$ coupling constants of 10 and 0 Hz from the Karplus curve, respectively.

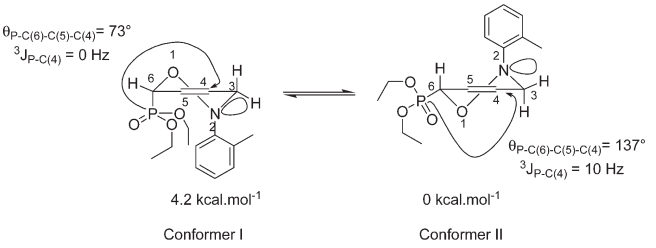
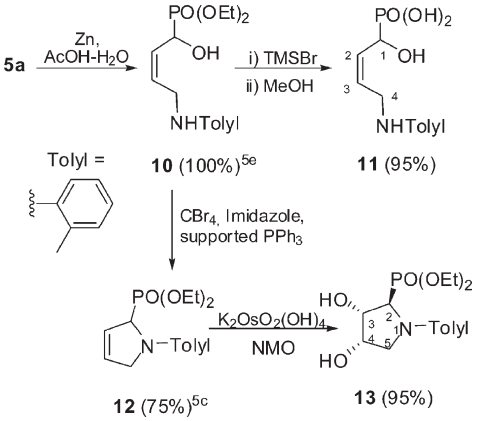


FIGURE 3. Conformers of cycloadduct **5a** and their relative energies (B3LYP/6-31G**).

SCHEME 5. Reductive Cleavage of 5a and Further Functionalizations



Our experimental data are in good agreement with the computed more stable conformer II (ΔE = 4.2 kcal·mol^{-1}).

Chemical Modification of the 3,6-Dihydro-1,2-oxazine Derivatives. Four diversification sites are identified on our cycloadducts, namely the N−O bond, the C=C double bond, the phosphonate, and the NR^3 groups. Accordingly, reductive cleavage, oxidation, functional group interconversion, or combinations of these reactions could provide a versatile synthetic route for aminophosphonic compounds in both aliphatic and heterocyclic series.

A first synthetic application of the 3,6-dihydro-1,2-oxazine framework is the selective reductive cleavage of the N−O bond to generate a 1,4-bifunctional 2-butene derivative with preserved (*Z*)-configuration (Scheme 5). In our case, reduction by zinc powder in acetic acid was the most efficient method for preparing (*Z*)-diethyl 4-(*o*-tolylamino)-1-hydroxy-2-butenyl-1-phosphonate (**10**) from **5a** in quantitative yield[5e] (structure confirmed by X-ray data; see Supporting Information).

Classically, the diethyl phosphonate group is deprotected with hot 6 N HCl, KOH_{aq}, or TMSX (X = Br or I),[21] trimethylsilylbromide being the most common method. The diester **10** was thus deprotected using TMSBr followed by the alcoholysis of the intermediate bis(trimethylsilyl) ester, leading to the desired (*Z*)4-(*o*-tolylamino)-1-hydroxy-2-butenyl-1-phosphonic acid (**11**) in high yield.

Compound **10** can be used as an intermediate for the synthesis of azaheterocyclic phosphonates. Indeed, ring closure into the pyrrolidine derivative **12** was realized

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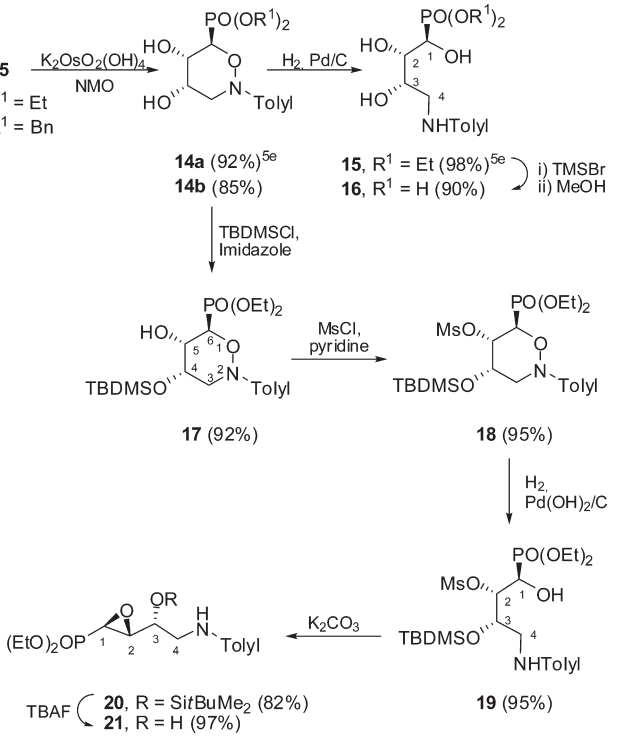
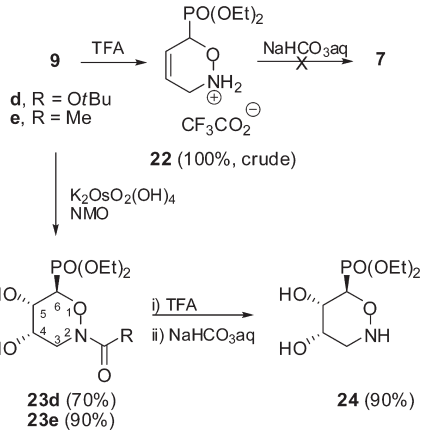
SCHEME 6. Dihydroxylation of 5a,b and Further Functionalizations



by first converting the hydroxyl group into a leaving group with CBr_4 and polymer-supported PPh_3. In the presence of imidazole, the intramolecular nucleophilic substitution by the aniline moiety led to diethyl 2,5-dihydro-1-*o*-tolyl-1-pyrrol-2-yl-2-phosphonate (**12**), recovered in good yield after filtration of the polymeric reagent (Scheme 5). Further treatment of **12** with osmium oxide and *N*-methylmorpholine oxide (NMO) gave the *syn*-diol **13** in high yield. The observation of a single peak in the ^{31}P NMR spectrum indicates that the dihydroxylation has proceeded with complete facial selectivity, leading to the formation of one stereoisomer, most probably with the *trans* relationship between P and O substituents for steric reasons. This suggests an efficient control of the relative stereochemistry by the bulky phosphonate group.

A second synthetic application of the 3,6-dihydro-1,2-oxazine starts with the selective oxidation of the C=C double bond. A *syn*-dihydroxylation, followed by N−O reductive cleavage and phosphonate deprotection provided a practical entry to polyhydroxylated δ-aminophosphonates (Scheme 6). Treatment of **5a** and **5b** under standard *syn*-dihydroxylation conditions (see above) gave the corresponding diols **14a**[5e] and **14b** as single stereoisomers from ^{31}P NMR spectra of the crude products (e.g., one signal observed). The trans relationship of the phosphonate group regarding the two hydroxyl groups was attributed on the basis of X-ray data recorded previously for a crystalline derivative of compound **14a**, namely the benzoyl bis-ester.[5e] Treatment of **14a**,**b** with Zn/AcOH led to complete degradation of the heterocycles. Fortunately, the reductive cleavage of **14a** was effective under catalytic hydrogenation conditions and gave the diethyl tris-(hydroxyamino)phosphonate **15** in 98% yield. Deprotection of the diethoxyphosphonyl ester was then accomplished with

SCHEME 7. N-Deprotection of Oxazine Derivatives



TMSBr/MeOH, yielding quantitatively to acid **16**. Hydrogenation of **14b** directly yielded the same aminophosphonic compound **16** with concomitant cleavage of the 1,2-oxazine pattern and benzyl ester moieties.

The *syn*-diol **14a** has also been considered as a valuable intermediate for the synthesis of α-epoxy δ-aminophosphonates **20** and **21** (Scheme 6). Addition of *tert*-butyldimethylsilyl chloride to a solution of **14a** and imidazole led to the C(4)-protected compound **17** with a total chemoselectivity due to the steric effect of the phosphonate group. Mesylation of the remaining C(5)-OH proceeded smoothly under standard conditions. The intermediate **18** crystallized from an ether/hexane mixture, allowing the unambiguous assignment of the relative stereochemistry by X-ray diffraction analysis (see the Supporting Information). Reductive cleavage of **18** under catalytic hydrogenation conditions gave 1-(diethoxyphosphonyl) 4-(*o*-tolylamino)-1-hydroxy-2-methanesulfonatobutan-3-yl-*tert*-butyldimethylsilane (**19**). This intermediate cyclized intramolecularly, upon K_2CO_3 treatment, to give the epoxide **20** in good yield. The oxirane structure was confirmed by NMR analysis: the signal of the C(1)-P carbon atom of **20** is strongly shielded (δ = 48.2 ppm) regarding the corresponding carbon of the precursor **19** (δ = 67.9 ppm, $^1J_{C-P}$ = 160.6 Hz) and the large $^1J_{C-P}$ value of 203.1 Hz are typical for 1,2-epoxyalkyl phosphonates.[16] Finally, deprotection of the silylated alcohol using tetrabutylammonium fluoride allowed the isolation of compound **21**, with an overall yield of 66% after column chromatography on silica gel (five steps from diol **14a**), as a single stereoisomer (one ^{31}P NMR signal).

Similar functionalizations have also been considered starting from the N-acylated cycloadducts **9** (see Scheme 4). Unfortunately, the N−O bond cleavage failed under standard conditions. Compounds **9** were unreactive with Zn in HCl or $Mo(CH_3CN)_3(CO)_3$, and complete degradation occurred in the presence of SmI_2.

Lastly, *N*-Boc deprotection of the oxazine **9d** was considered as the first step of a sequence of functionalization. Treatment of cycloadduct **9d** with trifluoroacetic acid (TFA) in dichloromethane at room temperature yielded the salt **22** (Scheme 7). Upon neutralization (aqueous $NaHCO_3$), complete degradation occurred, and the major product was the diene **1a** due to the retro-DA process.[5d] This result, consistent with the observed instability of cycloadducts **6** during workup, imposes

modification of the C=C double bond first (reduction or dihydroxylation) before cleavage of the N(2) substituent. Hence, we prepared the *syn*-diols **23d** and **23e** as previously described (Scheme 7). Here again, single stereoisomers were formed according to the ^{31}P NMR data.

X-ray diffraction analysis of a monocrystal **23d** confirmed both the trans relationship of the phosphonate group regarding the *syn*-hydroxyl groups and the proximal regioselectivity of the key HDA step (see the Supporting Information). Finally, **23d** was readily deprotected with TFA, yielding the stable oxazidine **24**.

Conclusion

A few HDA reactions with unsaturated phosphonates have been reported in the previous literature, such as the [4 + 2] cycloadditions of vinyl acyl phosphonates with enol ethers leading to dihydropyranphosphonates.[22] Here, we have further documented this domain of heterocyclic chemistry with the synthesis of dihydrooxazinephosphonates.

The 6-phosphono-3,6-dihydro-1,2-oxazine synthon resulting from the HDA reaction of 1-phosphonodienes and nitroso dienophiles offers a versatile synthetic route for the synthesis of polyfunctionalized aminophosphonic derivatives, with complete control of the regio- and stereoselectivities. Some compounds prepared from the precursors **5** and **9** are structurally related to natural products or analogues of potential interest in medicinal chemistry. For instance, compounds **10** and **11** possess the same skeleton as rhizocticin A,[23] and the pyrrolidine **13** can be considered as a bioisoster of dihydroxyproline (Scheme 5).[24] The triols **15** and **16** are related to xylose[25] and monomers for modified nylons[26] (Scheme 6). The 1,2-epoxyalkyl-1-phosphonate motif of **20** and **21** is similar to an antibiotic (Fosfomycin) isolated from *Streptomyces fradiae*, which has stimulated many synthetic efforts.[27] Hence, our HDA methodology can efficiently contribute to the current search of molecular diversity and offers new opportunities for the discovery of biologically active compounds.[28]

Experimental Section

All melting points are uncorrected. ^1H (300 or 500 MHz) and ^{13}C (75 or 125 MHz) NMR spectra were recorded on a 300 or a 500 MHz NMR spectrometer in $CDCl_3$ (with TMS for ^1H and $CDCl_3$ for ^{13}C as the internal reference) or D_2O. ^{31}P (121 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in $CDCl_3$ or D_2O (with H_3PO_4 as the internal reference).

The reagents were purchased from commercial sources and used without further purification. The solvents (anhydrous grade; $H_2O < 0.001\%$) were purchased from commercial sources and stored under argon atmosphere over molecular sieves. The vessel was flame dried under high vacuum and then cooled under argon atmosphere. TLC analyses were performed on aluminum plates coated with silica gel 60 F_{254} and visualized with UV (254 nm) or $KMnO_4$ solution.

Compounds **1a**, **5a**, **10**, **12**, **14a**, and **15** have been previously reported.[5d,e]

1-(Dibenzyloxyphosphonyl)-1,3-butadiene (1b). To a stirred solution of **1a** (2 g, 10.5 mmol) in dry dichloromethane (10 mL) at room temperature was added dropwise TMSBr (4 mL, 34.88 mmol) for 15 min. After complete consumption of **1a** (about 2 h, NMR control), the volatiles were removed under reduced pressure. The intermediate bis(trimethylsilyl) ester was dissolved in dry dichloromethane (10 mL) with a few drops of dry DMF. The resulting solution was treated dropwise with oxalyl chloride (3.55 mL, 42 mmol) under vigorous magnetic stirring at 20 °C. After 1 h, the crude material was concentrated under reduced pressure. The (*E*)-buta-1,3-diene 1-phosphonyl dichloride residue **3** was dissolved in anhydrous THF (20 mL) and treated with pyridine (2.21 mL, 27.4 mmol) and with freshly distilled benzyl alcohol (2.4 mL, 23.1 mmol) at 0 °C for 1 h. The mixture was allowed to slowly warm to room temperature and stirred overnight. Afterward, the crude material was concentrated under reduced pressure, diluted with ethyl acetate (20 mL), washed with aqueous saturated NH_4Cl (20 mL), dried over $MgSO_4$, filtered, and concentrated. The oily residue was purified by column chromatography on silica gel (toluene/ethyl acetate 5:2) to give **1b** as a pale yellow oil (4.6 g, 62%): R_f (toluene/ethyl acetate 5:2) = 0.6; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 10H), 7.06 (m, 1H), 6.36 (m, 1H), 5.72 (dd, $J_{H,H}$ = 19.4 Hz, $J_{H,P}$ = 17.2 Hz, 1H), 5.46 (m, 2H), 5.03 (d, $J_{H,P}$ = 8.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2 (d, $J_{C,P}$ = 5.9 Hz), 136.2, 136.1, 135.6 (d, $J_{C,P}$ = 27.4 Hz), 128.6, 128.4, 128.3, 128.0, 126.8, 125.3, 117.6 (d, $J_{C,P}$ = 191.8 Hz), 67.4 (d, $J_{C,P}$ = 5.4 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.47; IR (NaCl) ν 2972, 2908, 1613, 1525, 1220, 1072 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}O_3PNa$ [M + Na^+] 337.0970, found 337.0974.

1-(Diethoxyphosphonyl)-3-*tert*-butyldimethylsiloxy-1,3-butadiene (1c). A solution of 1-(diethoxyphosphonyl)but-1-en-3-one **4**[7] (2 g, 10 mmol) and TBDMSCl (1.6 g, 10 mmol) in anhydrous THF (50 mL) was treated dropwise by DBU (1.5 mL, 10 mmol) at 20 °C. After 1 h, the crude material was concentrated under reduced pressure, diluted with petroleum ether (30 mL), and filtered through a short silica gel pad to give pure diene **1c** as a yellow oil (1.6 g, 50%): R_f (EtOAc/cyclohexane 75:25) = 0.5; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, $J_{H,P}$ = 21.2 Hz, $J_{H,H}$ = 16.7 Hz, 1H), 5.98 (dd, $J_{H,P}$ = 20.0 Hz, $J_{H,H}$ = 16.7 Hz, 1H), 4.60 (2 s, 2H), 4.08 (dq, $J_{H,P}$ = 7.2 Hz, $J_{H,H}$ = 7.1 Hz, 4H), 1.32 (t, $J_{H,H}$ = 7.1 Hz, 6H), 0.96 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8 (d, $J_{C,P}$ = 23.8 Hz), 146.8 (d, $J_{C,P}$ = 7.5 Hz), 115.0 (d, $J_{C,P}$ = 190.1 Hz), 102.2, 62.1 (d, $J_{C,P}$ = 5.4 Hz), 26.0, 18.6, 16.7 (d, $J_{C,P}$ = 6.4 Hz), −4.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.51; IR (NaCl) ν 2957, 2931, 2902, 2858, 1252 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{29}O_4PSiNa$ [M + Na^+] calcd 343.1470, found 343.1482.

Dibenzyl 3,6-Dihydro-2-*o*-tolyl-1,2-oxazin-6-yl-6-phosphonate (5b). A solution of diene **1b** (2.1 g, 6.58 mmol) in dichloroethane (10 mL) and *o*-tolylnitroso **2a** (0.82 g, 6.58 mmol) was stirred in a microwave oven under 500 W irradiation at 100 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (toluene, then toluene/EtOAc 5:2) to give **5b** as a brown oil (2.57 g, 90%): R_f (toluene/EtOAc 5:2) = 0.4; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25−7.05 (m, 15H), 6.06 (broad s, 2H), 5.1−4.99 (m, 5H), 3.76 (m, 1H), 3.49 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 136.3 (d, $J_{C,P}$ = 6.2 Hz), 136.2 (d, $J_{C,P}$ = 5.9 Hz), 133.1, 130.9, 128.6, 128.6, 128.6, 128.4, 128.0, 126.7 (d, $J_{C,P}$ = 10.2 Hz),

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126.5, 125.9, 122.4 (d, $J_{C,P}$ = 5.0 Hz), 118.8, 75.9 (d, $J_{C,P}$ = 59.9 Hz), 68.7 (d, $J_{C,P}$ = 6.7 Hz), 68.1 (2 d, $J_{C,P}$ = 6.7 Hz), 52.4, 18.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 19.28; IR (NaCl) ν 2940, 1488, 1421, 1237, 1027, 972 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}NO_4PNa$ [M + Na$^+$] 458.1497, found 458.1491.

Diethyl 3,6-Dihydro-5-*tert*-butyldimethylsiloxy-2-*o*-tolyl-1,2-oxazin-6-yl-6-phosphonate (5c). A solution of diene **1c** (0.26 g, 0.7 mmol) and nitrosotoluene **2a** (0.1 g, 0.7 mmol) in refluxing dichloroethane (10 mL) was stirred 4 h. The reaction mixture was concentrated and purified by column chromatography on silica gel (toluene, then toluene/EtOAc 5:4) to give **5c** as a brown oil (0.28 g, 78%): R_f (toluene/EtOAc 5:4) = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 4H), 5.16 (d, $J_{H,H}$ = 5.3 Hz, 1H), 5.02 (ddd, $J_{H,P}$ = 13.4 Hz, $J_{H,H}$ = 5.3 Hz, $J_{H,H}$ = 2.1 Hz, 1H), 4.27−4.08 (m, 4H), 3.75 (ddd, $J_{H,H}$ = 15.3 Hz, $J_{H,P}$ = 4.6 Hz, $J_{H,H}$ = 2.1 Hz, 1H), 3.43 (d, $J_{H,H}$ = 15.3 Hz, 1H), 2.35 (s, 3H), 1.31 (t, $J_{H,H}$ = 7.1 Hz, 6H), 0.95 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (d, $J_{C,P}$ = 11.5 Hz), 147.3, 133.4, 131.2, 126.6, 126.1, 118.6, 97.9 (d, $J_{C,P}$ = 5.5 Hz), 73.6 (d, $J_{C,P}$ = 162.6 Hz), 63.4 (d, $J_{C,P}$ = 6.8 Hz), 63.0 (d, $J_{C,P}$ = 6.8 Hz), 55.5 (d, $J_{C,P}$ = 2.3 Hz), 25.9, 18.5, 18.3, 16.8 (d, $J_{C,P}$ = 5.3 Hz), −4.0, −4.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 19.02; HRMS (ESI) calcd for $C_{21}H_{37}NO_5PSi$ [M + H$^+$] 442.2179, found 442.2194.

General Cycloaddition Procedure toward N-Acylated 1,2-Oxazine Compounds 9d−g. A solution of 9,10-dimethylanthracene (1 g, 4.8 mmol) and *tert*-butylammonium metaperiodate (3.1 g, 7.2 mmol) in dry chloroform (30 mL) was treated dropwise by a DMF solution (10 mL) of hydroxamic acid (7.2 mmol) over 2 h at 0 °C. After complete addition, the ice bath was removed, and the mixture was allowed to slowly warm up to 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted in ethyl acetate (30 mL) and washed with saturated aqueous sodium thiosulfate (3 × 10 mL), brine (2 × 10 mL), and water (1 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and then concentrated. The yellow solid residue (**8d−g**) was dissolved in a mixture of dichloroethane (10 mL) and **1a** (in the molar ratios given in Scheme 4). After 15 h at reflux, the solvent was removed under reduced pressure. The residue was diluted in cold ethanol (30 mL), and the resulting suspension was filtered to remove 9,10-dimethylanthracene. Further purification was carried out by column chromatography on silica gel.

Diethyl 3,6-dihydro-2-(*tert*-butoxycarbonyl)-1,2-oxazin-6-yl-6-phosphonate (9d). Chromatography (toluene/EtOAc 5:4) gives **9d** as a yellow oil (1.85 g, 85%): R_f (toluene/EtOAc 5:4) = 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (broad s, 2H), 5.00 (broad d, $J_{H,P}$ = 17.1 Hz, 1H), 4.22 (m, 5H), 4.04 (m, 1H), 1.50 (s, 9H), 1.38 (t, $J_{H,H}$ = 6.9 Hz, 3H), 1.34 (t, $J_{H,H}$ = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 125.1 (d, $J_{C,P}$ = 9.4 Hz), 121.5 (d, $J_{C,P}$ = 5.5 Hz), 82.2, 73.9 (d, $J_{C,P}$ = 159.4 Hz), 63.9 (d, $J_{C,P}$ = 6.6 Hz), 63.2 (d, $J_{C,P}$ = 6.6 Hz), 45.2, 28.4, 16.6 (d, $J_{C,P}$ = 4.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.37; IR (NaCl) ν 2980, 1707, 1394, 1367, 1261, 1234, 1164, 1024, 972 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{24}NO_6PNa$ [M + Na$^+$] 344.1239, found 344.1243.

Diethyl 2-Acetyl-3,6-dihydro-1,2-oxazin-6-yl-6-phosphonate (9e). Chromatography (EtOAc) gives **9e** as a yellow oil (1.46 g, 77%): R_f (EtOAc) = 0.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (broad s, 2H), 4.86 (broad d, $J_{H,P}$ = 16.6 Hz, 1H), 4.17 (m, 6H), 2.21 (s, 3H), 1.34 (td, $J_{H,P}$ = 11.4 Hz, $J_{H,H}$ = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 124.7 (d, $J_{C,P}$ = 9.6 Hz), 120.9 (d, $J_{C,P}$ = 3.6 Hz), 75.8 (d, $J_{C,P}$ = 160.0 Hz), 64.0 (d, $J_{C,P}$ = 6.8 Hz), 63.2 (d, $J_{C,P}$ = 6.8 Hz), 41.2, 20.1, 16.7 (d, $J_{C,P}$ = 5.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.51; IR (NaCl) ν 2984, 1670, 1649, 1394, 1256, 1215, 1022, 970 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{18}NO_5PNa$ [M + Na$^+$] 286.0820, found 286.0815.

Diethyl 3,6-Dihydro-2-benzoyl-1,2-oxazin-6-yl-6-phosphonate (9f). Chromatography (EtOAc) gives **9f** as a yellow oil (1.31 g, 56%): R_f (EtOAc) = 0.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (m, 2H), 7.44−7.40 (m, 3H), 6.06 (broad s, 2H), 4.85 (broad d, $J_{H,P}$ = 19.9 Hz, 1H), 4.62 (m, 1H), 4.14−3.89 (m, 5H), 1.22 (td, $J_{H,P}$ = 17.2 Hz, $J_{H,H}$ = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 136.1, 133.5, 131.3, 128.8, 124.8 (d, $J_{C,P}$ = 9.5 Hz), 121.0 (d, $J_{C,P}$ = 5.7 Hz), 75.5 (d, $J_{C,P}$ = 160.7 Hz), 63.9 (d, $J_{C,P}$ = 6.7 Hz), 63.0 (d, $J_{C,P}$ = 6.4 Hz), 43.4, 16.5 (d, $J_{C,P}$ = 6.1 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 15.38; IR (NaCl) ν 1662, 1647, 1448, 1394, 1369, 1259, 1161, 1022, 976 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}NO_5PNa$ [M + Na$^+$] 348.0977, found 348.0986.

Diethyl 3,6-Dihydro-2-(2-phenylacetyl)-1,2-oxazin-6-yl-6-phosphonate (9g). Chromatography (EtOAc/cyclohexane 75:25) gives **9g** as a yellow oil (1.73 g, 71%): R_f (EtOAc/cyclohexane 75:25) = 0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.32 (m, 5H), 6.03 (m, 2H), 4.74 (broad d, $J_{H,P}$ = 16.2 Hz, 1H), 4.35 (dd, $J_{H,H}$ = 18.1 Hz, $J_{H,P}$ = 2.9 Hz, 1H), 4.24−4.12 (m, 5H), 3.96 (d, $J_{H,H}$ = 14.5 Hz, 1H), 3.83 (d, $J_{H,H}$ = 14.5 Hz, 1H), 1.39 (t, $J_{H,H}$ = 7.1 Hz, 3H), 1.35 (t, $J_{H,H}$ = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 134.8, 129.7, 128.8, 127.1, 124.6 (d, $J_{C,P}$ = 9.6 Hz), 120.9 (d, $J_{C,P}$ = 3.8 Hz), 76.0 (d, $J_{C,P}$ = 160.4 Hz), 64.0 (d, $J_{C,P}$ = 6.7 Hz), 63.3 (d, $J_{C,P}$ = 6.7 Hz), 39.9, 16.8 (d, $J_{C,P}$ = 5.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 16.48; IR (NaCl) ν 2982, 2384, 17118, 1437, 1394, 1022, 970 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}NO_5PNa$ [M + Na$^+$] 362.1133, found 362.1135.

(*Z*)-4-(*o*-Tolylamino)-1-hydroxybut-2-enylphosphonic Acid (11). To a solution of **10** (0.1 g, 0.32 mmol) in dry dichloromethane (2 mL) was added dropwise TMSBr (0.14 mL, 1 mmol) at 20 °C. After complete consumption of **10**, MeOH (5 mL) was added and the mixture stirred for 1 h. The volatiles were removed under reduced pressure. The oily residue was washed several times with ethyl acetate and then diethyl ether, yielding pure **11** as a yellow oil (0.08 g, >95%): ^{1}H NMR (500 MHz, D_2O) δ 7.43−7.39 (m, 4H), 5.99 (ddd, $J_{H,P}$ = 12.5 Hz, $J_{H,H}$ = 8.5 Hz, $J_{H,H}$ = 5.0 Hz, 1H), 5.87 (m, 1H), 4.71 (dd, $J_{H,P}$ = 13.4 Hz, $J_{H,H}$ = 8.5 Hz, 1H), 4.17 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 135.4 (d, $J_{C,P}$ = 3.4 Hz), 133.3, 133.0, 132.1, 130.6, 128.3, 123.7, 122.6 (d, $J_{C,P}$ = 11.8 Hz), 66.2 (d, $J_{C,P}$ = 158.4 Hz), 48.2, 17.0; ^{31}P NMR (121 MHz, D_2O) δ 20.92; IR (NaCl) ν 3334, 2928, 2771, 1576, 1170, 1084 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{17}NO_4P$ [M + H$^+$] 258.0895, found 258.0890.

Diethyl 3,4-Dihydroxy-1-*o*-tolylpyrrolidin-2-yl-2-phosphonate (13). A solution of **12** (2.78 g, 9.4 mmol) in acetone (30 mL) was treated successively with water (20 mL), NMO (2.42 g, 20.68 mmol), and $K_2OsO_2(OH)_4$ (0.17 g, 0.47 mmol) at 20 °C. After 24 h, toluene (30 mL) was added, and the mixutre was concentrated under vacuum. The resulting dark oil was purified by column chromatography on silica gel (ethyl acetate/*i*P-rOH 9:1) to give **13** as a yellow oil (2.9 g, >95%): R_f (ethyl acetate/*i*P-rOH 9:1) = 0.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.24 (m, 4H), 4.57 (ddd, $J_{H,P}$ = 10.9 Hz, $J_{H,H}$ = 4.6 Hz, $J_{H,H}$ = 4.6 Hz, 1H), 4.38 (dd, $J_{H,H}$ = 9.2 Hz, $J_{H,H}$ = 4.6 Hz, 1H), 4.13 (m, 1H), 3.87 (m, 4H + OH), 3.68 (dd, $J_{H,H}$ = 9.8 Hz, $J_{H,H}$ = 4.9 Hz, 1H), 2.88 (dd, $J_{H,H}$ = 9.8 Hz, $J_{H,H}$ = 4.5 Hz, 1H), 2.28 (s, 3H), 1.09 (dt, $J_{H,P}$ = 9.9 Hz, $J_{H,H}$ = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 134.1, 126.8, 124.0, 121.3, 73.7 (d, $J_{C,P}$ = 3.6 Hz), 71.9 (d, $J_{C,P}$ = 6.9 Hz), 63.0 (d, $J_{C,P}$ = 168.2 Hz), 62.9 (d, $J_{C,P}$ = 7.3 Hz), 62.5 (d, $J_{C,P}$ = 6.8 Hz), 59.4 (d, $J_{C,P}$ = 9.3 Hz), 18.9, 16.4 (d, $J_{C,P}$ = 5.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.75; IR (NaCl) ν 3325, 2929, 1492, 1225, 1049, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}NO_5PNa$ [M + Na$^+$] 352.1290, found 352.1280.

General Procedure for the *syn*-Hydroxylation of 5. A solution of **5a** or **5b** (9.4 mmol) in acetone (30 mL) was treated successively with water (20 mL), NMO (2.42 g, 20.68 mmol) and $K_2OsO_2(OH)_4$ (0.17 g, 0.47 mmol) at rt. After 24 h, toluene (30 mL) was added, and the mixture was concentrated under reduced pressure. The resulting dark oil was directly purified by column chromatography on silica gel to give the pure diols **14**.

Dibenzyl s*yn*-4,5-Dihydroxy-2-*o*-tolyl-3,4,5,6-tetrahydro-1,2-oxazin-6-yl-6-phosphonate (14b). The crude product was purified by column chromatography on silica gel (ethyl acetate/*i*-PrOH 95:5) to give **14b** as a yellow oil (85%): R_f (ethyl acetate/*i*-PrOH 94:5) = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.14 (m, 15H), 5.07 (m, 4H), 4.67 (dd, $J_{H,P}$ = 10.0 Hz, $J_{H,H}$ = 8.5 Hz, 1H), 4.32 (m, OH), 4.2 (broad s, 1H), 4.01 (m, 1H + OH), 3.48−3.36 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 136.1 (d, $J_{C,P}$ = 5.7 Hz), 135.9 (d, $J_{C,P}$ = 6.0 Hz), 133.6, 131.2, 131.1, 129.1, 128.9, 128.8, 128.4, 128.3, 126.6, 126.4, 118.8, 75.8 (d, $J_{C,P}$ = 156.9 Hz), 69.2 (d, $J_{C,P}$ = 6.9 Hz), 68.7 (d, $J_{C,P}$ = 6.4 Hz), 67.1, 66.4 (d, $J_{C,P}$ = 11.3 Hz), 58.0, 18.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.86; IR (NaCl) ν 3393, 2957, 2926, 1734, 1718, 1489, 1456, 1215, 1049, 1009, 997 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{28}NO_6PNa$ [M + Na$^+$] 492.1552, found 492.1541.

4-(*o*-Tolylamino)-1,2,3-trihydroxybutylphosphonic Acid (16). To a solution of compound **15** (0.5 g, 1.4 mmol) in dry dichloromethane (10 mL) was added dropwise TMSBr (1.17 mL, 8.6 mmol) at rt. After complete consumption of compound **15** (about 2 h, NMR control), MeOH (5 mL) was added and the mixture stirred for 1 h. The volatiles were removed under reduced pressure. The oily residue was washed with ethyl acetate (2 × 10 mL) and diethyl ether (2 × 10 mL) to give pure **16** as a yellow oil (0.39 g, 95%): ^{1}H NMR (500 MHz, D_2O) δ (major rotamer) 7.61−7.16 (m, 4H), 4.40−4.15 (m, 1H), 4.06−3.91 (m, 2H), 3.73 (dd, $J_{H,H}$ = 12.9 Hz, $J_{H,H}$ = 3.0 Hz, 1H), 3.55 (dd, $J_{H,H}$ = 12.9 Hz, $J_{H,H}$ = 9.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ (major rotamer) 133.6, 133.2, 132.1, 130.7, 128.4, 123.8, 73.7 (d, $J_{C,P}$ = 5.6 Hz), 69.6 (d, $J_{C,P}$ = 155.6 Hz), 67.2 (d, $J_{C,P}$ = 5.5 Hz), 53.4, 16.7; ^{31}P NMR (121 MHz, D_2O) δ 20.9; MS (ESI) calcd for $C_{11}H_{19}NO_6P$ [M + H$^+$] 292.24, found 292.17.

Alternative Synthesis of Compound 16. A solution of **14b** (0.5 g, 1.1 mmol) in ethanol (25 mL) with a drop of acetic acid was stirred for 15 h at rt under H_2 atmosphere in the presence of Pd−C as catalyst (5 mol %). Afterward, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel to give **16** as a yellow oil (>90%).

Diethyl *syn*-4-*tert*-Butyldimethylsilyloxy-5-hydroxy-2-*o*-tolyl-3,4,5,6-tetrahydro-1,2-oxazin-6-yl-6-phosphonate (17). To a solution of **14a** (4.27 g, 12.37 mmol) and imidazole (0.93 g, 13.61 mmol) in dry dichloromethane (20 mL) was added dropwise a solution of *tert*-butyl(chloro)dimethylsilane (1.97 g, 12.37 mmol) in dichloromethane (5 mL) over 30 min at 0 °C. After complete addition, the mixture was allowed to slowly warm to 20 °C and stirred overnight. The reaction mixture was washed with brine (1 × 10 mL) and water (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The oily residue was purified by column chromatography on silica gel (toluene/ethyl acetate 5:4) to give **17** as a colorless oil (5.2 g, 92%): R_f (toluene/EtOAc 5:4) = 0.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ (major rotamer) 7.48−6.64 (m, 4H), 4.60 (dd, $J_{H,P}$ = 11.8 Hz, $J_{H,H}$ = 6.3 Hz, 1H), 4.50 (m, 1H), 4.30−3.92 (m, 5H), 3.22 (broad d, $J_{H,H}$ = 4.4 Hz, 2H), 2.33 (s, 3H), 1.30 (t, $J_{H,H}$ = 7.0 Hz, 3H), 1.19 (t, $J_{H,H}$ = 7.0 Hz, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (major rotamer) 148.4, 131.7, 130.8, 126.6, 125.8, 119.0, 77.1 (d, $J_{C,P}$ = 158.3 Hz), 67.3 (d, $J_{C,P}$ = 6.7 Hz), 63.3 (d, $J_{C,P}$ = 6.6 Hz), 62.3 (d, $J_{C,P}$ = 6.5 Hz), 62.4, 58.9, 26.0, 18.8, 18.4, 17.8 (d, $J_{C,P}$ = 5.6 Hz), 17.8 (d, $J_{C,P}$ = 3.1 Hz), −4.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.82; IR (NaCl) ν 3366, 2927, 1489, 1252, 1103, 1047, 972 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{38}NO_6PSiNa$ [M + Na$^+$] 482.2104, found 482.2108.

Diethyl *syn*-4-*tert*-Butyldimethylsilyloxy-5-methanesulfonato-2-*o*-tolyl-3,4,5,6-tetrahydro-1,2-oxazin-6-yl-6-phosphonate (18). A solution of **17** (0.84 g, 1.92 mmol), DMAP (cat.), and pyridine (0.23 mL, 2.89 mmol) in anhydrous dichloromethane (5 mL) was treated dropwise by mesyl chloride (0.22 mL, 2.87 mmol) at 20 °C. After complete consumption of **17** (5 h, NMR control), water (5 mL) was added. The organic layer was washed with 10% aqueous NH_4Cl (1 × 5 mL), brine (1 × 5 mL), and water (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane/EtOAc 3:1) and could be recrystallized from an acetone/hexane 1:10 mixture to give **18** as colorless crystals (0.73 g, 70%): R_f (toluene/AcOEt 5:4) = 0.4; mp 98−99 °C; ^{1}H and ^{13}C NMR spectra were not exploitable due to low rotational equilibria; ^{31}P NMR (121 MHz, $CDCl_3$) δ 17.86; IR (NaCl) ν 2930, 1489, 1362, 1254, 1177, 1026, 970; HRMS (ESI) calcd for $C_{22}H_{40}NO_8PSiSNa$ [M + Na$^+$] 560.1879, found 560.1898.

1-(Diethoxyphosphonyl)-4-(*o*-tolylamino)-3-*tert*-butyldimethylsilyloxy-1-hydroxybutan-2-yl Methanesulfonate (19). A solution of **18** (0.53 g, 0.93 mmol) in ethyl acetate (5 mL) with a few drops of AcOH was stirred for 15 h at 20 °C under H_2 atmosphere in the presence of Pd−C as catalyst (5 mol %). The reaction mixture was concentrated under reduced pressure and further purified by column chromatography on silica gel (dichloromethane/EtOAc 3:1) to give **19** as a brown solid (0.48 g, 95%). Compound **19** could be recrystallized from an acetone/hexane/ether 10:5:5 mixture affording brown crystals (0.31 g, 61%): R_f (dichloromethane/EtOAc 3:1) = 0.4; mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.08 (m, 2H), 6.79−6.73 (m, 2H), 5.04 (m, 1H), 4.71 (m, 1H), 4.38 (dd, $J_{H,P}$ = 12.8 Hz, $J_{H,H}$ = 4.8 Hz, 1H), 4.18 (m, 4H), 3.49 (dd, $J_{H,H}$ = 12.2 Hz, $J_{H,H}$ = 6.9 Hz, 1H), 3.22 (dd, $J_{H,H}$ = 12.3 Hz, $J_{H,H}$ = 3.5 Hz, 1H), 3.12 (broad s, 3H), 2.22 (broad s, 3H), 1.36 (t, $J_{H,H}$ = 6.9 Hz, 3H), 1.25 (t, $J_{H,H}$ = 6.9 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H) and 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 130.6, 127.4, 124.8, 119.8, 112.6, 89.9 (d, $J_{C,P}$ = 10.9 Hz), 71.2 (d, $J_{C,P}$ = 3.3 Hz), 67.8 (d, $J_{C,P}$ = 160.6 Hz), 62.9 (d, $J_{C,P}$ = 7.5 Hz), 62.3 (d, $J_{C,P}$ = 6.8 Hz), 46.1, 38.9, 26.1, 18.3, 17.9, 16.7 (d, $J_{C,P}$ = 5.3 Hz), −4.6, −4.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 21.05; IR (NaCl) ν 3246, 2930, 1607, 1508, 1473, 1362, 1256, 1227, 1177, 1051, 974 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{42}NO_8PSiSNa$ [M + Na$^+$] 562.2036, found 562.2024.

Diethyl 3-*tert*-Butyldimethylsilyloxy-1,2-epoxy-4-*o*-tolylaminobutane-1-phosphonate (20). A solution of **19** (0.19 g, 0.35 mmol) in anhydrous dichloromethane (2 mL) with K_2CO_3 (0.24 g, 1.75 mmol) was stirred overnight at reflux. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted several times with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The oily residue was purified by column chromatography on silica gel (dichloromethane/EtOAc 3:1) to give **20** as a colorless oil (0.13 g, 82%): R_f (dichloromethane/EtOAc 3:1) = 0.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.07 (m, 2H), 6.68−6.55 (m, 2H), 4.17 (m, 4H), 3.93 (m, NH), 3.78 (td, $J_{H,H}$ = 5.6 Hz, $J_{H,H}$ = 5.5 Hz, 1H), 3.42 (ddd, $J_{H,H}$ = 5.5 Hz, $J_{H,P}$ = 5.4 Hz, $J_{H,H}$ = 2.5 Hz, 1H), 3.30 (m, 2H), 2.98 (dd, $J_{H,P}$ = 29.8 Hz, $J_{H,H}$ = 2.5 Hz, 1H), 2.15 (s, 3H), 1.33 (dt, $J_{H,H}$ = 7.1 Hz, $J_{H,P}$ = 5.2 Hz, 6H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 130.5, 127.4, 122.8, 117.7, 109.9, 71.5, 63.4, 63.2 (d, $J_{C,P}$ = 6.4 Hz), 59.0, 48.2 (d, $J_{C,P}$ = 203.1 Hz), 47.2, 26.1, 18.3, 17.8, 16.7 (d, $J_{C,P}$ = 5.7 Hz), −4.5, −4.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.59; IR (NaCl) ν 2930, 1607, 1508, 1473, 1257, 1101, 1053, 1024, 974 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{38}NO_5PSiNa$ [M + Na$^+$] 466.2155, found 466.2160.

Diethyl 1,2-Epoxy-3-hydroxy-4-*o*-tolylaminobutane-1-phosphonate (21). A solution of **20** (0.31 g, 0.7 mmol) in anhydrous THF (5 mL) was treated dropwise with tetrabutylammonium fluoride (1.05 mL, 1 M in THF, 1.05 mmol). After 2 h, the solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate (10 mL). The organic layer was then washed with brine (2 × 5 mL) and water (1 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (dichloromethane/EtOAc 3:1), affording pure **21** (0.22 g, 97%) as a yellow oil: R_f

(dichloromethane/EtOAc 3:1) = 0.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−7.05 (m, 2H), 6.6−6.65 (m, 2H), 4.17 (m, 4H), 4.00 (m, 2H), 3.48 (m, 2H), 3.32 (dd, $J_{H,H}$ = 12.9 Hz, $J_{H,H}$ = 7.0 Hz, 1H), 3.18 (dd, $J_{H,P}$ = 30.4 Hz, $J_{H,H}$ = 2.5 Hz, 1H), 3.00 (broad s, OH), 2.16 (s, 3H), 1.34 (t, $J_{H,H}$ = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 130.6, 127.4, 123.1, 118.1, 110.3, 67.8, 63.6 (d, $J_{C,P}$ = 6.4 Hz), 63.3 (d, $J_{C,P}$ = 6.3 Hz), 58.3, 47.5 (d, $J_{C,P}$ = 202.7 Hz), 47.7, 17.8, 16.7 (d, $J_{C,P}$ = 5.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.68; IR (NaCl) ν 3384, 2984, 2908, 1607, 1516, 1448, 1319, 1244, 1051, 1022, 978 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}NO_5PNa$ [M + Na$^+$] 352.1290, found 352.1296.

Trifluoroacetate Salt of Diethyl 3,6-Dihydro-1,2-oxazin-6-yl-6-phosphonate (22). A solution of **9d** (1 g, 3.11 mmol) in anhydrous dichloromethane (10 mL) at rt was treated dropwise with trifluoroacetic acid (0.46 mL, 6.23 mmol) over 10 min. After 15 h, the volatiles were removed under reduced pressure giving **22** (0.33 g, >90%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.28 (broad s, 2H), 6.21 (m, 2H), 5.14 (broad d, $J_{H,P}$ = 17.3 Hz, 1H), 4.17 (m, 6H), 1.38 (t, $J_{H,H}$ = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (q, $J_{C,F}$ = 40.8 Hz), 121.4 (d, $J_{C,P}$ = 10.3 Hz), 120.0 (d, $J_{C,P}$ = 4.3 Hz), 115.3 (q, $J_{C,F}$ = 286.3 Hz), 74.0 (d, $J_{C,P}$ = 160.0 Hz), 66.7 (d, $J_{C,P}$ = 7.3 Hz), 66.0 (d, $J_{C,P}$ = 7.8 Hz), 44.2 (d, $J_{C,P}$ = 2.6 Hz), 16.3 (d, $J_{C,P}$ = 4.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 14.3; IR (NaCl) ν 2991, 1780, 1636, 1209, 1164, 1030, 982 cm^{-1}; HRMS (ESI) calcd for $C_8H_{17}NO_4P$ [M + H$^+$] 222.0895, found 222.0889.

General Procedure for the Bishydroxylation of 9. A solution of **9d** or **9e** (2.4 mmol) in acetone (12 mL) was treated successively with water (6 mL), NMO (5.28 mmol), and $K_2OsO_2(OH)_4$ (0.12 mmol) at 20 °C. After 24 h, toluene (10 mL) was added, and the mixture was concentrated under reduced pressure. The resulting dark oil was directly purified by column chromatography on silica gel to give **23d** (0.6 g, >70%) and **23e** (0.64 g, >90%) as yellow oils.

***tert*-Butyl 6-(diethoxyphosphonyl)-4,5-dihydroxymorpholine-2-carboxylate (23d):** R_f (EtOAc/*i*-PrOH 9:1) = 0.3; mp 122−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (m, 1H + OH), 4.29 (m, 5H), 4.04 (m, 2H), 3.46 (broad d, $J_{H,H}$ = 14.5 Hz, 1H), 3.13 (broad s, OH), 1.50 (s, 9H), 1.40 (dt, $J_{H,P}$ = 7.6 Hz, $J_{H,H}$ = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 82.3, 72.1 (d, $J_{C,P}$ = 155.6 Hz), 66.8 (d, $J_{C,P}$ = 1.7 Hz), 64.9 (d, $J_{C,P}$ = 10.3 Hz), 64.2 (d, $J_{C,P}$ = 7.1 Hz), 64.0 (d, $J_{C,P}$ = 6.4 Hz), 51.2, 28.4, 16.6 (d, $J_{C,P}$ = 9.9 Hz), 16.6 (d, $J_{C,P}$ = 6.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 19.14; IR (NaCl) ν 3394, 2979, 1720, 1392, 1367, 1283, 1155, 1143, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{26}NO_8PNa$ [M + Na$^+$] 378.1294, found 378.1291.

Diethyl 2-acetyl-4,5-dihydroxymorpholin-6-yl-6-phosphonate (23e): R_f (EtOAc/*i*-PrOH 8:2) = 0.3; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (d, $J_{H,H}$ = 13.7 Hz, 1H), 4.48−3.92 (m, 7H), 3.32 (d, $J_{H,H}$ = 13.7 Hz, 1H), 2.16 (s, 3H), 1.38 (t, $J_{H,H}$ = 7.0, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 76.1 (d, $J_{C,P}$ = 160.4 Hz), 67.0, 64.8 (d, $J_{C,P}$ = 9.4 Hz), 63.8 (d, $J_{C,P}$ = 6.3 Hz), 63.5 (d, $J_{C,P}$ = 5.2 Hz), 47.0, 20.0, 16.5 (d, $J_{C,P}$ = 4.9 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.41; IR (NaCl) ν 3362, 1636, 1456, 1418, 1238, 1051, 1022, 980 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{20}NO_7PNa$ [M + Na$^+$] 320.0875, found 320.0886.

Diethyl 4,5-Dihydroxymorpholin-6-yl-6-phosphonate (24). A solution of **23d** (1.11 g, 3.11 mmol) in anhydrous dichloromethane (10 mL) at rt was treated dropwise with trifluoroacetic acid (0.46 mL, 6.23 mmol) over 10 min. After 15 h, the volatiles were removed under reduced pressure affording **24** (0.79 g, >90%) as a yellow oil: ^{1}H, ^{13}C, and ^{31}P NMR spectra were not exploitable; HRMS (ESI) calcd for $C_8H_{18}NO_6PNa$ [M + Na$^+$] 278.0769, found 278.0762.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds and X-ray data for compounds **10**, **18**, **19**, and **23d**. This material is available free of charge via the Internet at http://pubs.acs.org.