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Double Nucleophilic 1,2-Addition of Silylated Dialkyl Phosphites to 4-Phosphono-1-aza-1,3-dienes: Synthesis of γ-Phosphono-α-aminobisphosphonates

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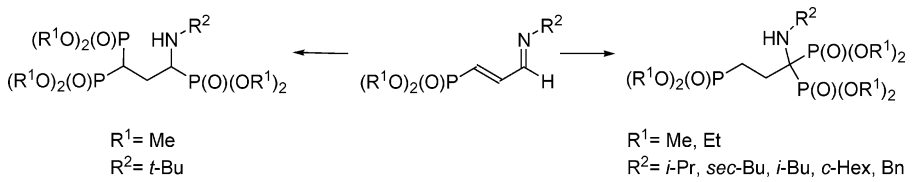
Received August 6, 2007



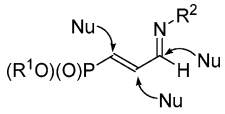
γ-Phosphono-α-aminobisphosphonates were synthesized from a new class of 4-phosphono-1-aza-1,3-dienes by the addition of dialkyl trimethylsilyl phosphites to these azadienes in the presence of acid. Depending on the steric demand of the group on nitrogen, double 1,2-addition or tandem 1,4−1,2-addition occurred.

Introduction

Azadienes in general are recognized as useful intermediates in synthetic chemistry for the construction of both heterocyclic systems as well as acyclic polyfunctionalized compounds.[1] The introduction of a phosphonate functionality on azadienes may be very interesting in view of inverse electron demand Diels−Alder reactions and for synthetic transformations leading to aminophosphonate derivatives and azaheterocyclic phosphonates.[2] Because of the lack of general methods for their synthesis, the reactivity of 4-phosphono-1-aza-1,3-dienes has not been described in the literature so far. Besides their potential usefulness in pericyclic reactions, these compounds could also serve as substrates for nucleophilic addition reactions.

In the case of 4-phosphono-1-aza-1,3-dienes **1**, nucleophiles can interact with several electrophilic centers. A 1,2- or 1,4-addition to the α,β-unsaturated imine functionality could occur, or a Michael addition to the vinylphosphonate could be envisaged. To investigate the regioselectivity of the addition to 4-phosphono-1-aza-1,3-dienes and to evaluate the synthesis of diphosphono derivatives, phosphorus nucleophiles were chosen.

The addition reactions of phosphorus nucleophiles have been extensively described in the literature, and several reviews have been published.[3] In general, the regioselectivity is strongly dependent on the type of phosphorus nucleophile, the substrate, and the reaction conditions. Recently, the tandem 1,4−1,2-addition of dialkyl trimethylsilyl phosphites and trialkyl phosphites to α,β-unsaturated imines derived from cinnamaldehyde was developed in our laboratory.[4]



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Depending on the regioselectivity of the addition of phosphorus nucleophiles to 4-phosphono-1-aza-1,3-dienes, the addition could lead to aminophosphonates or bisphosphonates. Aminophosphonates are known to efficiently mimic amino acids and to have a negligible mammalian toxicity. Although the biological importance of these compounds was recognized over

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(1) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.

(2) (a) Palacios, F.; Gil, M. J.; de Marigorta, E. M.; Rodriguez, M. *Tetrahedron* **2000**, *56*, 6319. (b) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Rodriguez, M.; Pagalday, J. *Tetrahedron* **2003**, *59*, 2617. (c) Vanderhoydonck, B.; Stevens, C. V. *Synthesis* **2004**, 722. (d) Vanderhoydonck, B.; Stevens, C. V. *J. Org. Chem.* **2005**, *70*, 191. (e) Palacios, F.; Vicario, J.; Maliszewska, A.; Aparicio, D. *J. Org. Chem.* **2007**, *72*, 2682. (f) For a review on azaheterocyclic phosphonates, see: Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177.

(3) (a) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81. (b) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 26.

(4) (a) Moonen, K.; Van Meenen, E.; Verwée, A.; Stevens, C. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 1. (b) Van Meenen, E.; Moonen, K.; Verwée, A.; Stevens, C. V. *J. Org. Chem.* **2006**, *71*, 7903.

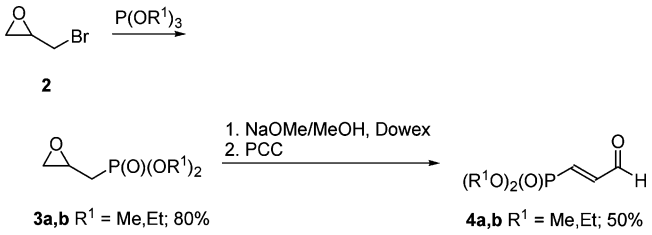
10.1021/jo701718t CCC: $37.00
Published on Web 10/31/2007

50 years ago, they still represent a promising class of potential drugs.[5] Bisphosphonates (BPs), on the other hand, are analogues of naturally occurring pyrophosphate (PPi) and are a major class of drugs for the treatment of bone diseases.[6] Besides their antiresorptive properties, several bisphosphonates are also potent growth inhibitors of some pathogenic trypanosomatids.[7]

Results and Discussion

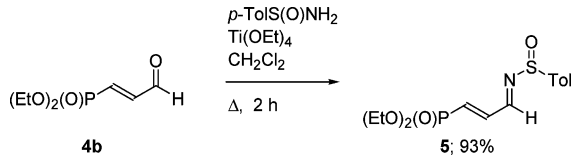
Synthesis of 4-Phosphono-1-aza-1,3-dienes. The precursor of 4-phosphono-1-aza-1,3-dienes, dialkyl (1*E*)-3-oxoprop-1-enylphosphonates **4**, were prepared starting from epibromohydrin **2**. An Arbuzov reaction between epibromohydrin **2** and trialkyl phosphites resulted in dialkyl 2,3-epoxypropylphosphonates **3** in reasonable yields.[8] After treatment of **3** with NaOMe in MeOH, followed by the addition of Dowex resin, and subsequent oxidation of the formed alcohol with PCC, dialkyl (1*E*)-3-oxoprop-1-enylphosphonates **4** were obtained in moderate yields (Scheme 1).[9]

SCHEME 1



Having the dialkyl (1*E*)-3-oxoprop-1-enylphosphonates **4** in hand, several 4-phosphono-1-aza-1,3-dienes were prepared. The synthesis of diethyl (1*E*,3*E*)-3-{[(4-methylphenyl)sulfinyl]-imino}prop-1-enylphosphonate **5** was initially evaluated. Recently, an attractive method for the synthesis of *N*-sulfonyl aldimines and *N*-sulfonyl ketimines via *N*-sulfinyl aldimines and *N*-sulfinyl ketimines has been published.[10] Imination of diethyl (1*E*)-3-oxoprop-1-enylphosphonate **4b** with *p*-toluenesulfinamide in the presence of $Ti(OEt)_4$ provided diethyl (1*E*,3*E*)-3-{[(4-methylphenyl)sulfinyl]imino}prop-1-enylphosphonate **5** in good yield (Scheme 2).

SCHEME 2



Several 4-phosphono-1-aza-1,3-dienes were prepared by reacting dialkyl (1*E*)-3-oxoprop-1-enylphosphonates **4** with amines in CH_2Cl_2 in the presence of $MgSO_4$ (Scheme 3 and Table 1).

Finally, hydrazones **6** were prepared to evaluate the reactivity of 4-phosphono-1-aza-1,3-dienes with an electron-donating group on the 1-position. Reaction of dialkyl (1*E*)-3-oxoprop-1-enylphosphonates **4** and dimethylhydrazine in the presence of acetic acid provided hydrazones **6** in reasonable to good yields (Scheme 4).

SCHEME 3

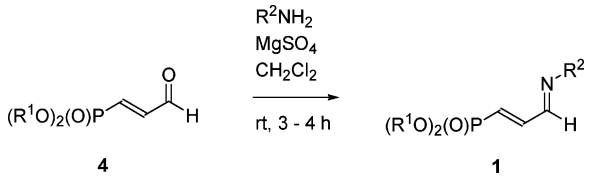
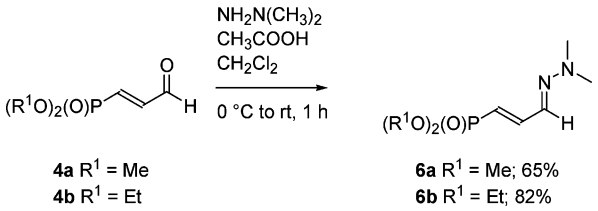


TABLE 1. Synthesis of 4-Phosphono-1-aza-1,3-dienes

R^1	R^2	product	yield (%)
Me	*t*-Bu	**1a**	91
Me	*i*-Pr	**1b**	91
Me	*sec*-Bu	**1c**	99
Me	*i*-Bu	**1d**	91
Me	*c*-Hex	**1e**	99
Me	Bn	**1f**	97[a]
Et	*t*-Bu	**1g**	93
Et	*i*-Pr	**1h**	99
Et	*sec*-Bu	**1i**	97
Et	*i*-Bu	**1j**	99
Et	*c*-Hex	**1k**	99

[a] Only stable for a few hours.

SCHEME 4



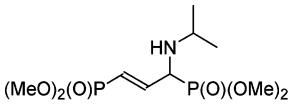
Addition of Dialkyl Trimethylsilyl Phosphite. To evaluate the addition of phosphorus nucleophiles to 4-phosphono-1-aza-1,3-dienes, dialkyl trimethylsilyl phosphites were chosen. Dialkyl trimethylsilyl phosphites were reported by Afarinkia et al. as excellent mild phosphonylation agents because the more nucleophilic $\sigma_3\lambda_3$ form of the dialkyl phosphite reagent could be obtained by O-silylation with trimethylsilyl chloride (TMSCl) in CH_2Cl_2 and triethylamine as a base.[11] Following the research of the one-pot tandem 1,4−1,2-addition of phosphites to α,β-unsaturated imines,[5a] reaction conditions, optimized during this research, were used. It was shown that, when mixing dialkyl trimethylsilyl phosphites (after filtration of triethylammonium hydrochloride salt) with an imine in dry dichloromethane, the reaction proceeded violently upon addition of 1 equiv of concentrated sulfuric acid and yielded the desired tandem product after 30 min at room temperature.[5a] Applying these reaction conditions to diethyl (1*E*,3*E*)-3-{[(4-methylphenyl)-sulfinyl]imino}prop-1-enylphosphonate **5** resulted in a mixture, which proved very difficult to transform into one end product. Increasing the reaction time and temperature did not give better results and had to be abandoned. Applying the same reaction conditions to another substrate (e.g., dimethyl (1*E*,3*E*)-3-(isopropylimino)prop-1-enylphosphonate **1b**) also resulted in a mixture, but a closer look at the ^1H NMR and ^{31}P NMR spectra

(5) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.* **2001**, *1*, 301.
(6) Graham, R.; Russell, G. *Ann. N.Y. Acad. Sci.* **2006**, *1068*, 367.
(7) Docampo, R.; Moreno, S. N. J. *Curr. Drug Targets* **2001**, *1*, 51.
(8) Griffin, C. E.; Kundu, S. K. *J. Org. Chem.* **1969**, *34*, 1532.
(9) Just, G.; Potvin, P.; Hakimelahi, G. H. *Can. J. Chem.* **1980**, *58*, 2780.
(10) Ruano, J. L.; Alemán, J.; Belén Cid, M.; Parra, A. *Org. Lett.* **2005**, *7*, 179.
(11) Afarinkia, K.; Rees, C. W.; Cadogan, J. I. G. *Tetrahedron* **1990**, *46*, 7175.

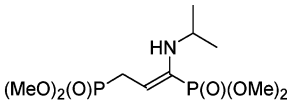
TABLE 2. Synthesis of γ-Phosphono-α-aminobisphosphonates

R^1	R^2	reagents	temperature	time (h)	product	yield (%)
Me	*i*-Pr	DMPTMS, H_2SO_4, CH_2Cl_2	rt	87	**9a**	71
Me	*sec*-Bu	DMPTMS, H_2SO_4, CH_2Cl_2	reflux	17	**9b**	77
Me	*i*-Bu	DMPTMS, H_2SO_4, CH_2Cl_2	rt	76	**9c**	72
			reflux	20		69
Me	*c*-Hex	DMPTMS, H_2SO_4, CH_2Cl_2	rt	126	**9d**	79
Me	Bn	DMPTMS, H_2SO_4, CH_2Cl_2	rt	103	**9e**	44
Et	*i*-Pr	DEPTMS in situ, CH_2Cl_2	rt	78	**9f**	76
			MW (80 °C)	3		73
Et	*sec*-Bu	DEPTMS, H_2SO_4, CH_2Cl_2	rt	110	**9g**	72
Et	*c*-Hex	DEPTMS, H_2SO_4, CH_2Cl_2	rt	90	**9h**	74
		DEPTMS in situ, CH_2Cl_2	MW (80 °C)	8		69

of this mixture revealed some interesting intermediates (e.g., 1,2-adduct **7** and enamine **8**).



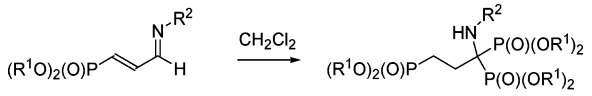
7



8

The formation of enamine **8** prompted us to increase the reaction time because tautomerism of this enamine would lead to an imine that is susceptible to a second addition of silylated phosphite. Analysis of the course of the reaction by ^{31}P NMR indicated the formation of a double 1,2-adduct that was in contrast with the spectra observed when studying the phosphite addition to α,*β*-unsaturated imines.[5] However, it took several days for the reaction to go to completion. Reducing the reaction time was possible by refluxing the reaction mixture; however, in most cases, side products were formed. Even under reflux, the reaction still required 24 h to complete. Therefore, microwave heating was evaluated. Under microwave conditions, double 1,2-addition was completed after several hours. Since in some cases side product formation was observed at higher temperatures when using DAPTMS and H_2SO_4, another method was evaluated. Substrates were added to freshly prepared DAPTMS (without filtration of the triethylammonium hydrochloride salt). In this case, the formation of the double 1,2-adduct was also observed. Unfortunately, in both cases (using DAPTMS in the presence of H_2SO_4 or using in situ DAPTMS in the presence of triethylammonium hydrochloride salts) purification was needed. Since chromatography on silica gel always resulted in a loss of product due to the high affinity of the end products to silica gel, we have optimized an acid−base extractive methodology from which the bisphosphonates could be isolated (Scheme 5 and Table 2).

SCHEME 5

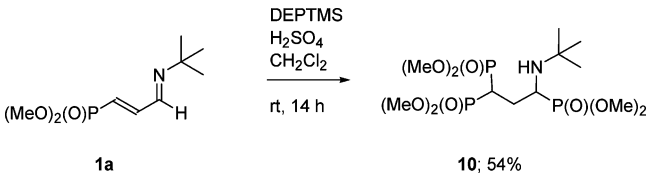


1 **9**

Applying these reaction conditions to dimethyl (1*E*,3*E*)-3-(*t*-butylimino)prop-1-enylphosphonate **1a**, another regioselectivity was observed (Scheme 6), leading to the formation of the 1,4−1,2-addition product **10**. Finally, when adding DAPTMS and H_2SO_4 to hydrazones **6**, no phosphonylation was observed.

Mechanism. Following the previously mentioned reactions with ^1H NMR and ^{31}P NMR, the appearance and disappearance

SCHEME 6



1a **10**; 54%

of α-amino-α,*β*-unsaturated phosphonates and α-amino-*β*,*γ*-unsaturated phosphonates could be followed (by P−P coupling) and allowed us to propose a possible mechanism for the double 1,2-addition. In this mechanism, the addition of acid to the reaction seems to be a crucial step to obtain full conversion. Besides the activation of the imine in the first step, the protons are also utilized during the imine tautomerization. Thus, at least 1 equiv of protons has to be present in the reaction mixture. On the other hand, an excess of protons will slow down the reaction, due to the protonation of the intermediate enamine and the subsequent blocking of the imine tautomerization (Scheme 7).

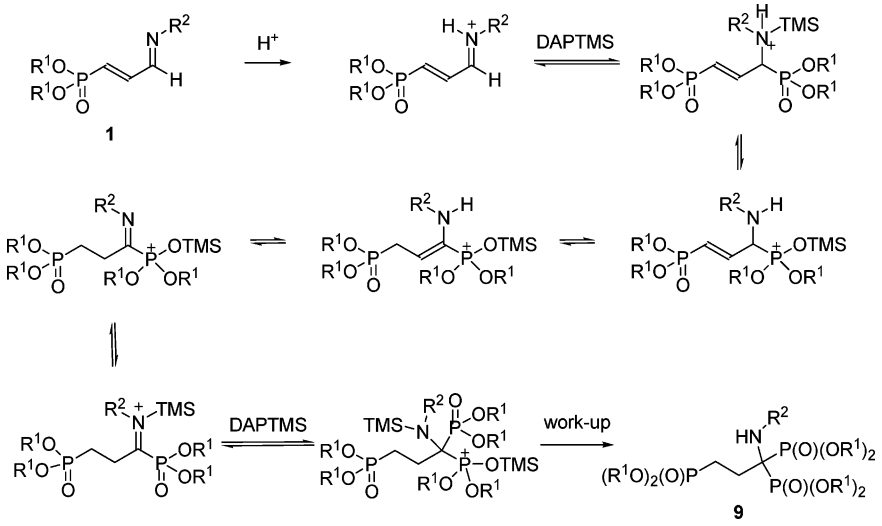
A possible reaction mechanism for the formation of **10** was already described for the tandem 1,4−1,2-addition of phosphites to α,*β*-unsaturated imines.[5a] The sterically demanding *t*-butyl group of **1a** is in favor of this tandem 1,4−1,2-addition, as the 1,2-addition should be slowed down by the steric bulk. Also, a parallel but reversible 1,2-addition was observed (Scheme 8).

In conclusion, a convenient methodology for the synthesis of *γ*-phosphono-α-aminobisphosphonates was developed in good yield from 4-phosphono-1-aza-1,3-dienes. In the case of the *N*-*t*-Bu derivative, a tandem 1,4−1,2-addition of silylated phosphite was observed.

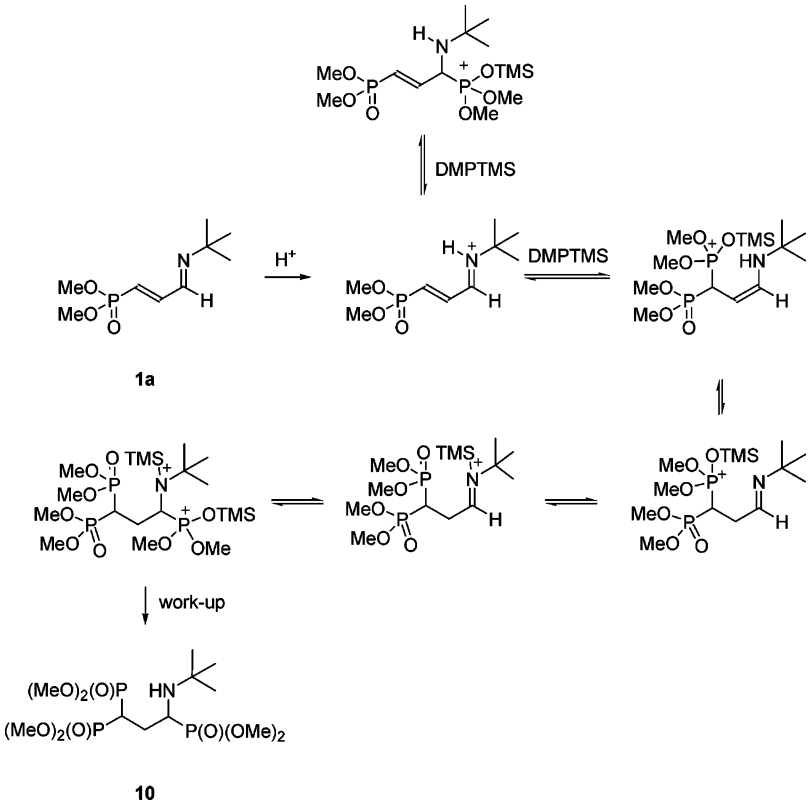
Experimental Section

Synthesis of 4-Phosphono-1-aza-1,3-dienes 1. Unless otherwise stated, all phosphonylated α,*β*-unsaturated aldimines were prepared by mixing di(m)ethyl (1*E*)-3-oxoprop-1-enylphosphonate **4a**,**b** with 1 equiv of amine (1.1 equiv in case of volatile amines) and 0.5 equiv of $MgSO_4$ in dry dichloromethane. The mixture was then stirred overnight and shielded from moisture using a $CaCl_2$ tube. The imines were obtained as yellowish/brownish oils (except for **1e** and **1f**: white crystals after recrystallization) in high purity and yield after filtration of the solids and evaporation of the solvent under reduced pressure. Dimethyl (1*E*,3*E*)-3-(*t*-butylimino)prop-1-enylphosphonate **1a**: yellowish oil. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 1.24 (9H, s, 3 × CH_3, *t*-Bu), 3.77 (6H, d, $^3J_{HP}$ = 11.0 Hz, 2 × P(O)OCH_3), 6.18 (1H, dd, $^2J_{HP}$ = 18.4 Hz, *J* = 17.3 Hz, CHP), 7.11 (1H, ddd, $^3J_{HP}$ = 20.6 Hz, *J* = 17.3 Hz, *J* = 8.5 Hz, *H*C=CHP), 7.95 (1H, d, *J* = 8.5 Hz, HC=N). ^{13}C NMR (75 MHz,

SCHEME 7



SCHEME 8



$CDCl_3$) δ: 29.4 (3 × CH_3, *t*-Bu), 52.7 (d, $^2J_{CP}$ = 5.8 Hz, 2 × P(O)OCH_3), 58.3 (C_{quat}, *t*-Bu), 125.2 (d, $^1J_{CP}$ = 189.2 Hz, CHP), 147.8 (d, $^2J_{CP}$ = 5.8 Hz, H*C*═CHP), 155.5 (d, $^3J_{CP}$ = 31.2 Hz, HC═N). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 19.77. IR (cm^{-1}) ν_{max}: 2969, 1252 (P═O), 1032 (br, P−O). MS *m*/*z* (%): (ES, Pos) 220 (M + H^+, 100). Elem. anal. calcd for $C_9H_{18}NO_3P$: C 49.31, H 8.28, N 6.39. Found: C 49.43, H 8.36, N 6.15. Yield: 91%.

Synthesis of Di(m)ethyl (1*E*)-3-Oxoprop-1-enylphosphonate 4a,b. Diethyl (1*E*)-3-oxoprop-1-enylphosphonate **4b** was prepared in several steps from epibromohydrin according to literature procedures. For the synthesis of dimethyl (1*E*)-3-oxoprop-1-enylphosphonate **4a**, the same procedures were followed.[9,10]

Synthesis of Diethyl (1*E*,3*E*)-3-{[(4-Methylphenyl)sulfinyl]-imino}prop-1-enylphosphonate 5. (See Ruano et al. for a general method for the preparation of *N*-sulfonyl aldimines and ketimines.)[10] To a solution of **4b** (0.62 g, 3.22 mmol) and *p*-toluenesulfinamide (0.50 g, 3.22 mmol) in dry CH_2Cl_2 (50 mL) was added $Ti(OEt)_4$ (2.94 g, 12.88 mmol). This mixture was refluxed under a N_2 atmosphere over a period of 16 h. After cooling down to room temperature, MeOH (15 mL) and a few drops of a $NaHCO_3$ solution (aq, saturated) (until precipitation of Ti salts) were added. The resulting suspension was filtrated over $MgSO_4$, and the solids were washed with EtOAc. The combined organic fractions were dried ($MgSO_4$), and after filtration, the solvent was removed under reduced pressure. As a result, **5** (0.99 g, 93%) was obtained as a brownish oil. Diethyl (1*E*,3*E*)-3-{[(4-methylphenyl)sulfinyl]imino}-prop-1-enyl-phosphonate **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (6H, t, J = 7.2 Hz, 2 × P(O)OCH_2CH_3), 2.41 (3H, s, CH_3), 4.07−4.19 (4H, m, 2 × P(O)OCH_2CH_3), 6.49 (1H, dd, $^2J_{HP}$ = 17.3 Hz, J = 17.1 Hz, CHP), 7.22 (1H, ddd, $^3J_{HP}$ = 19.8 Hz, J = 17.1 Hz,

J = 9.1 Hz, *H*C═CHP), 7.32 (2H, d, J = 8.0 Hz, 2 × CH_{arom}), 7.57 (2H, d, J = 8.0 Hz, 2 × CH_{arom}), 8.41 (1H, d, J = 9.1 Hz, HC═N). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5 (d, $^3J_{CP}$ = 6.9 Hz, 2 × P(O)OCH$_2$*C*H$_3$), 21.5 (CH_3), 62.6 (d, $^2J_{CP}$ = 5.8 Hz, 2 × P(O)-O*C*H$_2$CH$_3$), 124.7 (2 × CH_{arom}), 130.1 (2 × CH_{arom}), 132.5 (d, $^1J_{CP}$ = 186.9 Hz, CHP), 140.6 ($C_{quat,arom}$), 142.2 (d, $^2J_{CP}$ = 5.8 Hz, H*C*═CHP), 142.3 ($C_{quat,arom}$), 159.7 (d, $^3J_{CP}$ = 30 Hz, HC═N). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 15.04. IR (cm^{-1}) ν_{max}: 1575 (C═N), 1253 (P═O), 1096, 1051 (P−O), 1024 (P−O). MS *m*/*z* (%): (ES, Pos) 330 (M + H$^+$, 100). Elem. anal. calcd for $C_7H_{13}NO_4PS$: C 35.29, H 5.50, N 5.88. Found: C 34.99, H 5.21, N 6.06.

Synthesis of Di(m)ethyl (1*E*,3*E*)-3-(dimethylhydrazono)prop-1-enylphosphonate 6a,b. To a solution of 2.6 mmol of *N*,*N*-dimethylhydrazine in CH_2Cl_2 (2.5 mL) was added dropwise 2.6 mmol of AcOH (1.0 equiv) with continuous stirring. After cooling the mixture in an ice bath, 2.6 mmol of di(m)ethyl (1*E*)-3-oxoprop-1-enylphosphonate **4a**,**b** was added, and the whole mixture was stirred for 1 h without further cooling. After CH_2Cl_2 was added, the mixture was washed thoroughly with aqueous Na_2CO_3 and dried over $MgSO_4$. Removal of the solvent in vacuo afforded di(m)ethyl (1*E*,3*E*)-3-(dimethylhydrazono)prop-1-enylphosphonate **6a**,**b** as a yellowish oil. Dimethyl (1*E*,3*E*)-3-(dimethylhydrazono)prop-1-enylphosphonate **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.03 (6H, s, 2 × CH_3), 3.73 (d, $^3J_{HP}$ = 11.0 Hz, 2 × P(O)OCH_3), 5.58 (1H, dd, $^2J_{HP}$ = 18.4 Hz, J = 17.1 Hz, CHP), 6.86 (1H, d, J = 9.1 Hz, HC═N), 7.18 (1H, ddd, $^3J_{HP}$ = 20.9 Hz, J = 17.1 Hz, J = 9.1 Hz, *H*C═CHP). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.3 (2 × CH_3), 52.4 (d, $^2J_{CP}$ = 5.8 Hz, 2 × P(O)O*C*H$_3$), 110.6 (d, $^1J_{CP}$ = 196.1 Hz, CHP), 129.2 (d, $^2J_{CP}$ = 31.2 Hz, HC═N), 147.8 (d, J = 6.9 Hz, H*C*═CHP). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 23.87. IR (cm^{-1}) ν_{max}: 1598 (C═N), 1244 (P═O), 1031 (br, P−O). MS *m*/*z* (%): (ES, Pos) 207 (M + H$^+$, 74). Elem. anal. calcd for $C_7H_{15}N_2O_3P$: C 40.78, H 7.33, N 13.59. Found: C 40.65, H 7.57, N 13.67. Yield: 65%.

Synthesis of γ-Phosphono-α-aminobisphosphonates 9. Procedure with DAPTMS and H_2SO_4. A suitable 4-phosphono-1-aza-1,3-diene (5 mmol) dissolved in 15 mL of dry dichloromethane was allowed to stir at room temperature under a nitrogen atmosphere. Then, 10.5 mmol of DAPTMS (2.1 equiv) and 2.5 mmol of sulfuric acid (0.5 equiv; 1 equiv of H$^+$) were added consecutively. The mixture was allowed to react until completion as was determined by ^{31}P NMR (for reaction time and temperature, see Table 2). Then, the mixture was poured into 20 mL of a saturated $NaHCO_3$(aq) solution. The organic phase was recovered, and the remaining aqueous phase was washed 3 times with 5 mL of dichloromethane. The organics were dried ($MgSO_4$) and filtered. The solvent was removed in vacuo. Because of the excess of dialkyl trimethylsilyl phosphite used, the products had to be purified by an acid−base extraction. Therefore, the product was dissolved in 15 mL of ether. To this solution, 45 mL of 3 N HCl was added. The mixture was stirred for 30 min at room temperature, followed by three extractions with diethyl ether. The aqueous phase was basified with 3 N NaOH followed by extraction with CH_2Cl_2. The CH_2Cl_2 phase was dried with $MgSO_4$. After filtration and removal of the solvent in vacuo, the γ-phosphono-α-aminobisphosphonates were obtained in good yield and purity as yellowish oils.

Procedure with DAPTMS in Situ. Dialkyl phosphite (10.5 mmol) was mixed with 11.5 mmol of triethylamine (1.1 equiv) in 10 mL of dry dichloromethane in an oven dry flask under a nitrogen atmosphere. The mixture was then cooled to 0 °C, and 11.5 mmol of TMSCl (1.1 equiv) was added using a syringe. After 1 h at 0 °C, a suitable 4-phosphono-1-aza-1,3-diene (5 mmol) dissolved in 5 mL of dry dichloromethane was added to the in situ prepared DAPTMS. The mixture was allowed to react until completion as was determined by ^{31}P NMR (for reaction time and temperature, see Table 2). The workup and purification of the products were the same as for the procedure with DAPTMS and H_2SO_4. Dimethyl [1,3-bis(dimethoxyphosphoryl)-1-isopropylaminopropyl]-phosphonate **9a**: yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.10 (6H, d, J = 6.3 Hz, 2 × CH_3, *i*-Pr), 1.57 (1H, br s, NH), 2.07−2.30 (4H, m, C*H*$_2$C*H*$_2$P), 3.25 (1H, sept, J = 6.3 Hz, NCH, *i*-Pr), 3.75 (6H, d, $^3J_{HP}$ = 10.7 Hz, 2 × P(O)OMe), 3.85 (6H, d, $^3J_{HP}$ = 10.7 Hz, 2 × P(O)OMe), 3.86 (6H, d, $^3J_{HP}$ = 10.7 Hz, 2 × P(O)OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0 (dt, $^1J_{CP}$ = 140.8 Hz, $^3J_{CP}$ = 4.6 Hz, CH_2P), 24.3 (*C*H$_2$CH$_2$P), 25.9 (2 × CH_3, *i*-Pr), 44.3 (t, $^3J_{CP}$ = 6.9 Hz, NCH, *i*-Pr), 52.4 (d, $^2J_{CP}$ = 6.9 Hz, 2 × P(O)-OMe), 54.0 (dt, $^2J_{CP}$ = 45.0 Hz, $^4J_{CP}$ = 3.5 Hz, 4 × P(O)OMe), 62.9 (dt, $^1J_{CP}$ = 140.8 Hz, $^3J_{CP}$ = 19.6 Hz, $C_{quat}P_2$). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 24.47 (2 × P(O)(OMe)$_2$), 34.72 (P(O)(OMe)$_2$). IR (cm^{-1}) ν_{max}: 3480 (NH), 2958, 1248 (P═O), 1028 (br, P−O). MS *m*/*z* (%): (ES, Pos) 426 (M + H$^+$, 100), 316 (M$^+$ − P(O)-(OMe)$_2$, 69). Elem. anal. calcd for $C_{12}H_{30}NO_9P_3$: C 33.89, H 7.11, N 3.29. Found: C 33.62, H 7.11, N 3.03. Yield: 71%.

Synthesis of Dimethyl [1-*t*-Butylamino-3,3-bis(dimethoxyphosphoryl)propyl]phosphonate 10. Dimethyl (1*E*,3*E*)-3-(*t*-butylimino)prop-1-enylphosphonate **1a** (5 mmol) dissolved in 15 mL of dry dichloromethane was allowed to stir at room temperature under a nitrogen atmosphere. Then, 10.5 mmol of DAPTMS (2.1 equiv) and 2.5 mmol of sulfuric acid (0.5 equiv; 1 equiv of H$^+$) were added consecutively. The mixture was allowed to react until completion as was determined by ^{31}P NMR (see Scheme 7). The workup and purification of the products were the same as for the synthesis of γ-phosphono-α-aminobisphosphonates **9**. Dimethyl [1-*t*-butylamino-3,3-bis(dimethoxyphosphoryl)-propyl]phosphonate **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.14 (9H, s, 3 × CH_3, *t*-Bu), 1.89−2.41 (2H, m, CH_2), 3.27 (1H, ddt, J = 24.2 Hz, J = 7.7 Hz, J = 5.0 Hz, CHP_2), 3.60 (1H, dt, J = 7.8 Hz, J = 7.8 Hz, NCHP), 3.77 (3H, d, J = 10.5 Hz, P(O)OCH_3), 3.82 (3H, d, J = 11.0 Hz, P(O)OCH_3), 3.82 (3H, d, J = 10.5 Hz, P(O)OCH_3), 3.83 (3H, d, J = 11.0 Hz, P(O)OCH_3), 3.83 (3H, d, J = 11.0 Hz, P(O)-OCH_3), 3.84 (3H, d, J = 10.5 Hz, P(O)OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.3 (br, CH_2), 29.9 (*t*-Bu), 31.4 (dt, $^1J_{CP}$ = 133.8 Hz, $^3J_{CP}$ = 4.6 Hz, CHP_2), 47.3 (ddd, $^1J_{CP}$ = 152.3 Hz, $^3J_{CP}$ = 9.2 Hz, $^3J_{CP}$ = 4.6 Hz, NCHP), 51.6 (d, $^3J_{CP}$ = 6.9 Hz, C_{quat}, *t*-Bu), 52.7 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$), 53.2 (d, $^2J_{CP}$ = 6.9 Hz, 2 × P(O)-OCH$_3$), 53.3 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$), 53.5 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$), 53.6 (d, $^2J_{CP}$ = 6.9 Hz, P(O)OCH$_3$). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 26.60, 27.15 (d, J = 2.2 Hz), 31.12. IR (cm^{-1}) ν_{max}: 3476, 3418, 1248 (P═O), 1228 (P═O), 1017 (br, P−O). MS *m*/*z* (%): (ES, Pos) 440 (M + H$^+$, 100). Elem. anal. calcd for $C_{13}H_{32}NO_9P_3$: C 35.54, H 7.34, N 3.19. Found: C 35.53, H 7.40, N 3.26. Yield: 54%.

Supporting Information Available: General information and spectroscopic data of all compounds synthesized with complete peak assignments. Copies of ^{1}H NMR spectra and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701718T