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Efficient synthesis of racemic β-aminophosphonates via aza-Michael reaction in water

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ABSTRACT

Water as a solvent significantly accelerates the addition of various amines to diethyl vinylphosphonate to yield β-aminophosphonates without any catalyst compared to known procedures for such aza-Michael reactions. The products are obtained in quantitative yields and high purity over short reaction times. Using a reactant ratio (vinylphosphonate/amine) of 2:1 resulted in double phosphorylation of primary amines.

The key role of naturally occurring amino acids in the chemistry of life has led to the synthesis and investigation of the biological activity of synthetic analogues. Among these, the so-called 'phosphorus analogues' have attracted particular attention due to their diverse biological activity.[1] In this area, derivatives of β-aminophosphonic acid, first isolated from *Celiate protozoa* by Horiguchi and Kandatsu[2] in 1959, are important. These compounds demonstrate diverse biochemical properties such as antibacterial, anti-HIV and protease-inhibiting activities.[3] They also show complexing properties which are advantageous for selective ionophores or membrane carrier design.[3b] Hence, the development of procedures for the efficient preparation of amino acid analogues including asymmetric synthesis is currently of high importance.

Different methods such as carbon–phosphorus, carbon–carbon or carbon–nitrogen bond formation reactions have been utilised for the synthesis of β-aminophosphonic and phosphinic acid derivatives. The aza-Michael addition is an important method for C–N bond formation and involves the conjugate addition of N-nucleophiles to vinylphosphoryl compounds. In 1951, Pudovik[4] reported the addition of amines to vinylphosphonates to afford β-aminophosphonates, and work in this area has been further developed.[1,3,5,6] Thus, secondary amines such as dimethylamine and piperidine, being active nucleophiles, react exothermically with diethyl vinylphosphonate in the absence of a solvent; however, an additional 24 h are required for completion of the reaction along with the use of 10–15% excess of the amine. Less active primary amines and ammonia react only in the presence of basic catalysts such as sodium or sodium alkoxides and require elevated temperatures and prolonged reaction times; arylamines do not add to vinylphosphinates even under severe conditions. A wide range of β-aminophosphonates have been prepared in good yields including quaternary β-aminophosphonates, which are useful as synthetic nonviral vector-mediated gene transfer agents,[7] those bearing perfluoroalkyl groups,[8] and phosphorylated analogues of putrescine and spermidine,[9] etc. However, despite satisfactory results, the reported procedures used hazardous organic solvents, excess amine and catalysts which are not desirable from a green chemistry point of view. Here, we report a very simple and high yielding procedure for β-aminophosphonate synthesis in water without any catalyst or organic co-solvent.

Organic reactions in water have received increased attention due to environmental safety, low cost and the possibility to accelerate a variety of important reactions such as Diels–Alder, aldol, alkylation reactions, Claisen rearrangements and so on.[10] Recently, the use of water as reaction medium for Michael reactions of ketones and aldehydes with nitroolefins using diamine/TFA, (*S*)-pyrrolidinesulfonamide or pyrrolidine–thiourea organocatalysts[11] as well as amine additions to activated non-phosphorylated alkenes without any catalyst[12] was reported. Possibly due to the fact that water has an adverse effect on organophosphorus reactants due to side reactions, for example, hydrolysis, it has not found wide application as a medium in organophosphorus chemistry with examples being restricted to Wittig reactions.[13]

We have found that various primary and secondary alkylamines add smoothly and rapidly to diethyl vinylphosphonate in water

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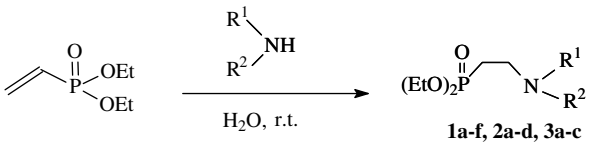


Scheme 1.

(Scheme 1). The difference in chemical shifts of the phosphorus substrate and the product allows easy monitoring of the reaction by ^{31}P NMR spectroscopy. Both the nucleophilic and steric properties of the amine influence the reaction rate which decreased in the series: $Alk_2NH > AlkNH_2 > ArCH_2NH_2$ and with an increase in the bulkiness of the substituents on the nitrogen atom of the amine. Among secondary amines, cyclic examples such as piperidine and morpholine were more active than their acyclic analogues (Table 1).

At room temperature, the reaction of $(EtO)_2P(O)CH{=}CH_2$ with piperidine was complete (quantitative) in 7 min (Table 1, entry 10, compound **2b**), while the yields of the corresponding β-aminophosphonates over the same period of time were 73%, 25% and 5% for reaction with diethylamine, *n*-butylamine and *tert*-butylamine, respectively (Table 1, entries 1, 2 and 8). After 45 min, the reaction was complete for Et_2NH and *n*-$BuNH_2$, but for sterically hindered *tert*-butylamine the yield of the final product **1b** was 78% after 70 h at rt. It should be noted that without water, active amines such as diethylamine did not add to the vinylphosphonate at room temperature even over long reaction times. Elongation of the alkyl chain in the alkylamine resulted in a decrease in reactivity, and at room temperature, long-chain aliphatic dialkylamines ($>C_8$) did not react with vinylphosphonate in water. Aromatic amines and amino acids and their esters did not react, possibly due to a decrease in their nucleophilic properties.

If more than one amine functionality was present in the starting reactant, addition to the vinylphosphonate in water proceeded readily with participation of all the amine functionalities. Thus, reaction with ethylenediamine, *meta*-xylylenediamine and tris(2-aminoethylamine) resulted in bis(aminophosphonates) **3a**,**c** and tris(aminophosphonate) **3b** in almost quantitative yields (Table 1, entries 13–15).

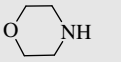
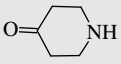
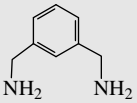
To reduce the reaction time, elevated temperatures can be used and no side reactions were observed even at reflux. At 100 °C the reactions with benzylamine and $N(CH_2CH_2NH_2)_3$ were complete in 45 min; however, with ^{t}BuNH$_2$ and $PhCH(CH_3)NH_2$, 3 h were required to afford the products in high yields (Table 2).

When the starting reactants were used in the ratio 1:1, only mono adducts were formed in the case of primary amines and no traces of the corresponding bis-addition products were observed. However, use of the reactants in the ratio $(EtO)_2P(O)CH{=}CH_2$/amine=1:2 allowed double phosphorylation of primary amines (Table 3). To the best of our knowledge, no examples of such reactions have been observed previously under common reaction conditions. According to ^{31}P NMR monitoring, the reaction proceeded via a stepwise process giving firstly the mono adducts followed by addition to a second molecule of vinylphosphonate. In the case of aza-Michael reactions of non-phosphorylated activated alkenes in water,[12] double addition to primary amines was not observed.

The amount of water used did not influence the reaction rate significantly. The use of 2 ml of water per 1 mmol of amine was appropriate. All the reactions were very clean and often did not require further purification. Moreover, as the final β-aminophosphonates are very soluble in water, extraction of the product into DCM or $CHCl_3$ led to partial loss of the compound (ca. 15–25%). Lyophilisation of the crude reaction mixture followed by additional purification (if necessary) using flash chromatography gave the best results. It should be mentioned that the compounds form stable solvates with $CHCl_3$ or hydrates (compounds **3c**, **4a**,**b**,**d** and **1b**,**d**, respectively), which lost the solvent molecule only under prolonged drying in vacuo (1 Hg) at ca. 100 °C. The formation of strong solvates with $CHCl_3$ serving as a proton donor for aminophosphonates has been reported in the literature.[14]

Despite the reaction rate for the aza-Michael addition in water at room temperature with vinylphosphonate being a little bit lower compared with other activated alkenes bearing more acidic

Table 1
Aza-Michael reaction of diethyl vinylphosphonate and various amines in water according to Scheme 1

Entry	Amine	Product	Time	Yield[a] (%)
1	^{n}BuNH$_2$	**1a**	7 min	25
			45 min	70
			1.5 h	93 (65)[b]
2	^{t}BuNH$_2$	**1b**	45 min	5
			3 h	18
			70 h	78 (68)[b]
3	^{n}HexNH$_2$	**1c**	45 min	77
			3 h	Quant (95)
4	^{n}OctNH$_2$	**1d**	45 min	75
			3 h	Quant (94)
5	$PhCH_2NH_2$	**1e**	45 min	35
			3 h	75
			24 h	96 (92)
6	$PhCH(CH_3)NH_2$	**1f**	45 min	9
			24 h	79
			48 h	Quant (92)
7	$PhNH_2$	—	No reaction	
8	Et_2NH	**2a**	7 min	73
			45 min	96 (92)
9	Oct_2NH	—	No reaction	
10		**2b**	7 min	Quant (95)
11		**2c**	7 min	50
			45 min	Quant (95)
12		**2d**	45 min	42
			5 h	88 (75)[b]
13	$H_2NCH_2CH_2NH_2$	**3a**	45 min	25
			48 h	Quant (97)
14	$N(CH_2CH_2NH_2)_3$	**3b**	3 h	72
			20 h	Quant (92)
15		**3c**	45 min	52
			3 h	86
			20 h	Quant (96)

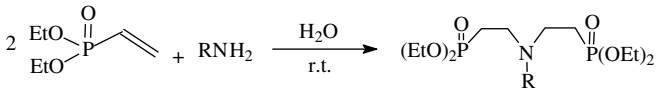
[a] Yield according to ^{31}P NMR spectroscopy. Isolated yield after lyophilization shown in brackets.
[b] Work-up comprised extraction with DCM followed by chromatographic purification.

Table 2
Influence of reaction temperature on the rate of the aza-Michael addition in water

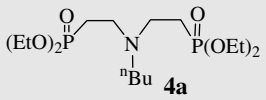
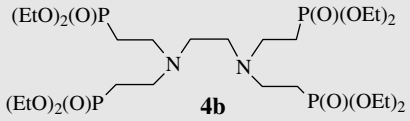
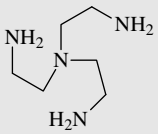
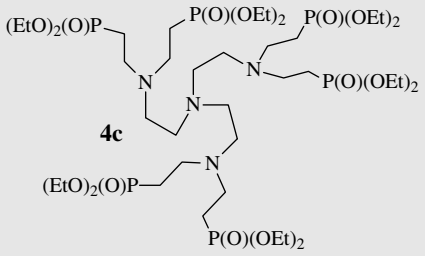
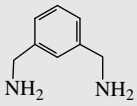
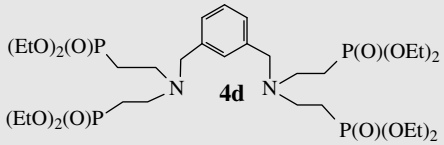
Entry	Amine	Product	Temperature (°C)	Time	Yield[a] (%)
1	^{t}BuNH$_2$	**1b**	20	3 h	18
			100	45 min	65
			100	3 h	100
2	$PhCH_2NH_2$	**1e**	20	45 min	35
			100	45 min	100
3	$PhCH(CH_3)NH_2$	**1f**	20	45 min	9
			100	45 min	75
			100	3 h	100
4	$N(CH_2CH_2NH_2)_3$	**3b**	20	45 min	20
			100	45 min	100

[a] Yield according to ^{31}P NMR spectroscopy.

Table 3
Synthesis of bis(diethylphosphorylethyl) substituted amines **4a-d**



4a-d

Entry	Amine	Product	Time	Yield[a] (%)
1	$^{n}BuNH_2$	 **4a**	45 min 24 h 48 h	2 70 96 (87)
2	$H_2NCH_2CH_2NH_2$	 **4b**	72 h	90 (71)
3		 **4c**	96 h	90 (85)
4		 **4d**	120 h	90 (83)

[a] Yield according to ^{31}P NMR spectroscopy. Isolated yield after extraction with CH_2Cl_2 and further chromatographic purification shown in brackets.

substituents, that is, α,β-unsaturated carboxylic esters, ketones, nitriles and amides,[12] it proceeds much faster in comparison with known procedures for β-aminophosphonate synthesis (Table 4).

It seems reasonable that acceleration of the aza-Michael addition in water is promoted by both hydrogen bond formation between the H-atom of water and the oxygen atom of the phosphoryl moiety increasing the electrophilic character of the β-carbon atom and between the H-atom of the amine and the oxygen atom of water resulting in increased amine nucleophilic properties.

In conclusion, we have demonstrated that water activates the aza-Michael addition between amines and diethyl vinylphosphonate. The reported procedure being extremely simple opens wide possibilities for the design of molecular sensors and oligodentate ligands bearing β-aminophosphonate moieties.

General procedure for the synthesis of diethyl 2-aminoethylphosphonates: To a solution of the amine (1 mmol) in water (2 ml) at room temperature was added the appropriate stoichiometric amount of diethyl vinylphosphonate. The mixture was stirred over the time mentioned in the Tables 1–3 either at room temperature or at reflux if desired. In the case of quantitative reaction, lyophilisation of the crude reaction mixture afforded the pure product. Otherwise, the reaction solution was extracted with

Table 4
Synthesis of β-aminophosphonates under various conditions

Amine	Solvent	Catalyst	Reaction conditions	Isolated yield (%)
$^{n}BuNH_2$	Excess amine	MeONa	Reflux, 4 h	75[15]
	Water	—	rt, 1.5 h	88
$^{t}BuNH_2$	Excess amine	EtONa	Reflux, 20 h	—[15]
	Water	—	r.t., 70 h	68
$PhCH_2NH_2$	Excess amine	EtONa	Reflux, 5 h	75[15]
	Water	—	rt, 24 h	92
$H_2NCH_2CH_2NH_2$	Excess diethyl vinylphosphonate	EtONa	rt, 96 h, then 100 °C, 30 min	64[16]
	Water	—	rt, 48 h	89
Et_2NH	Excess amine	Na	90 °C, 5 h	66[17]
	Water	—	rt, 45 min	92
	Excess amine	—	rt, 24 h	56[18]
	Water		rt, 7 min	95
	Excess amine	—	70 °C[a]	80[6]
	Water	—	rt, 45 min	95

[a] Reaction time not quoted.

CH_2Cl_2 (3 × 5 ml), the combined extracts were dried over Na_2SO_4 and evaporation of the solvent under reduced pressure to dryness afforded the crude final product with purity >95% according to NMR data. Further purification by column chromatography (SiO_2, $CHCl_3$/ethanol, 100:6) gave pure β-aminophosphonates as oils after evaporation of the appropriate fractions (according to TLC and ^{31}P NMR data) in vacuum (20 Hg, 60 °C, 3 h).

In some cases (compounds **1c** and **4c**), elemental analysis data were obtained for free phosphonous acids (prepared via reaction with trimethylsilyl bromide in chloroform followed by the treatment with aq MeOH) as hydrobromides or as hydrobromide-hydrates.

Physicochemical constants and spectral data of known compounds (**1a**,[6] **1e**,[15] **2a**,[6] **2b**,[18] **2c**,[6] **3a**[16]) correlate well the literature data.

Diethyl 2-(tert-butylamino)ethylphosphonate (**1b**): Yield 68% (purified by column chromatography), pale yellow oil. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.4. ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H, CH_3 in ^{t}Bu), 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3 in Et), 1.90 (dt, $^2J_{PH}$ = 18 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2–P), 2.38 (br s, 1H, NH), 2.81 (dt, $^3J_{PH}$ = 14.9 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2–NH), 4.02–4.11 (m, 4H, OCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.87 (d, $^3J_{PC}$ = 5.6 Hz, CH_3 in Et), 26.46 (d, $^1J_{PC}$ = 139.4 Hz, CH_2–P), 28.12 (s, CH_3 in ^{t}Bu), 35.79 (s, CH_2–NH), 50.34 (s, C in ^{t}Bu), 61.04 (s, OCH_2), 61.08 (s, OCH_2). IR (thin layer) ν/cm^{-1}: 1029 (P–O–C), 1235 br (P=O), 3298, 3468 (N–H). Anal. Calcd for $C_{10}H_{24}NO_3P{\cdot}0.17H_2O$: C, 49.99; H, 10.21; P, 12.89. Found: C, 50.14; H, 10.15; P, 12.44.

Diethyl 2-(hexylamino)ethylphosphonate (**1c**): Yield 95% (after freeze-drying), pale-yellow oil. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.8. ^1H NMR (400 MHz, $CDCl_3$): δ 0.80–0.83 (m, 3H, CH_3 in Hex), 1.22–1.29 (m, 12H, CH_3 in Et, CH_2 in Hex), 1.38–1.43 (m, 2H, CH_2 in Hex), 1.92 (dt, $^2J_{PH}$ = 18.3 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2–P), 2.53 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_2N in Hex), 2.84 (dt, $^3J_{PH}$ = 14.8 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2–NH), 3.99–4.19 (m, 4H, OCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.32 (s, CH_3), 15.74 (d, $^3J_{PC}$ = 6.3 Hz, CH_3 in Et), 21.88 (s, CH_2), 25.78 (d, $^1J_{PC}$ = 139.3 Hz, CH_2–P), 26.31 (s, CH_2), 29.29 (s, CH_2), 31.06 (s, CH_2), 42.69 (d, $^2J_{PC}$ = 3.7 Hz, CH_2–NH), 48.95 (s, CH_2), 60.73 (s, OCH_2), 60.79 (s, OCH_2). IR (KBr) ν/cm^{-1}: 1214 (P=O). Elemental analysis data were obtained for the corresponding phosphonous acid hydrobromide, mp 195 °C. Anal. Calcd for $C_8H_{20}NO_3P{\cdot}1HBr{\cdot}0.6H_2O$: C, 31.94; H, 7.44; N, 4.65; P, 10.29. Found: C, 31.66; H, 6.96; N, 4.55; P, 10.62.

Diethyl 2-(octylamino)ethylphosphonate (**1d**): Yield 94% (after freeze-drying), pale yellow oil. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.7. ^1H NMR (400 MHz, $CDCl_3$): δ 0.78–0.82 (m, 3H, CH_3 in Oct), 1.19–1.22 (m, 10 H, CH_2 in Hex), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3 in Et), 1.39–1.42 (m, 2H, CH_2 in Oct), 1.92 (dt, $^2J_{PH}$ = 18.3 Hz, $^3J_{HH}$ = 7.4 Hz, 2H, CH_2–P), 2.52 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_2N in Oct), 2.83 (dt, $^3J_{PH}$ = 14.8 Hz, $^3J_{HH}$ = 7.4 Hz, 2H, CH_2–NH), 3.99–4.15 (m, 4H, OCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.52 (s, CH_3 in Oct), 15.89 (d, $^3J_{PC}$ = 6.3 Hz, CH_3 in Et), 22.09 (s, CH_2 in Oct), 25.93 (d, $^1J_{PC}$ = 138.9 Hz, CH_2–P), 26.78 (s, CH_2 in Oct), 28.69 (s, CH_2 in Oct), 28.95 (s, CH_2 in Oct), 29.46 (s, CH_2 in Oct), 31.26 (s, CH_2 in Oct), 42.82 (d, $^2J_{PC}$ = 3.7 Hz, CH_2–NH), 49.09 (s, NH–CH_2 in Oct), 60.90 (s, OCH_2), 60.97 (s, OCH_2). IR (thin layer) ν/cm^{-1}: 1031 (P–O–C), 1242 (P=O), 3306, 3464 (N–H). Anal. Calcd for $C_{14}H_{32}NO_3P{\cdot}0.7H_2O$: C, 55.01; H, 11.00; N, 4.59. Found: C, 55.06; H, 10.69; N, 4.14.

Diethyl 2-[(1-phenylethyl)amino]ethylphosphonate (**1f**): Yield 92% (after freeze-drying), pale yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.7. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (td, $^3J_{HH}$ = 7.0 Hz, $^4J_{PH}$ = 3.1 Hz, 6H, CH_3 in Et), 1.34 (d, $^3J_{HH}$ = 6.6 Hz, 3H, CH_3), 1.92 (dt, $^2J_{PH}$ = 18 Hz, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2–P), 2.37 (br s, 1H, NH), 2.65-2.73 (m, 2H, CH_2–NH), 3.76 (q, $^3J_{HH}$ = 6.6 Hz, 1H, CH), 3.99–4.07 (m, 4H, OCH_2), 7.22 (br t, $^3J_{HH}$ = 4.4 Hz, 1H, *para*-H in C_6H_5), 7.28–7.29 (m, 4H, C_6H_5). ^{13}C NMR (101 MHz, $CDCl_3$): δ 16.08 (d, $^3J_{PC}$ = 5.9 Hz, CH_3 in Et), 23.88 (s, CH_3), 26.96 (d, $^1J_{PC}$ = 139.4 Hz, CH_2–P), 40.78 (s, CH_2–NH), 57.71 (s, CH), 61.21 (s, OCH_2), 61.29 (s, OCH_2), 126.28 (s, *meta*-C in C_6H_5), 126.73 (s, *para*-C in C_6H_5), 128.16 (s, *ortho*-C in C_6H_5), 144.56 (s, *ipso*-C in C_6H_5). IR (KBr) ν/cm^{-1}: 1021 (P–O–C), 1270 (P=O). Elemental analysis data were obtained for the corresponding solid hydrochloride obtained by treatment with HCl/Et_2O; mp 142 °C (hydroscopic). Anal. Calcd for $C_{14}H_{25}ClNO_3P{\cdot}0.3H_2O$: C, 51.30; H, 7.89; N, 4.27; P, 9.45. Found: C, 51.28; H, 7.42; N, 4.23; P, 9.27.

Diethyl 2-(4-oxo-1-piperidinyl)ethylphosphonate (**2d**): Synthesized from 4-piperidone hydrochloride monohydrate in the presence of potassium carbonate. Yield 75% (after column chromatography), pale yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.8. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, $^3J_{HH}$ = 6.3 Hz, 3H, CH_3), 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.87–1.98 (m, 2H, CH_2–P), 2.38–2.39 (m, 4H, CH_2 in piperidone), 2.69–2.75 (m, 6H, CH_2–N, CH_2 in piperidone), 3.99–4.05 (m, 4H, OCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.99 (d, $^3J_{PC}$ = 5.9 Hz, CH_3), 23.84 (d, $^1J_{PC}$ = 139.7 Hz, CH_2–P), 40.60 (s, CH_2 in piperidone), 50.18 (s, CH_2–N), 52.04 (s, CH_2 in piperidone), 61.07 (s, OCH_2), 61.14 (s, OCH_2), 207.91 (s, C=O). IR (thin layer) ν/cm^{-1}: 1022 (P–O–C), 1234 (P=O), 1729 (C=O). Anal. Calcd for $C_{11}H_{22}NO_4P$: C, 50.18; H, 8.42; N, 5.32; P, 11.76. Found: C, 49.93; H, 8.58; N, 5.18; P, 11.44.

Diethyl [6-{2-[2-(diethoxyphosphinyl)ethyl]aminoethyl}-12-ethoxy-12-oxido-13-oxa-3,6,9-triaza-12-phosphapentadec-1-yl]phosphonate (**3b**): Yield 92% (after freeze-drying), pale-yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.5. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 18H, CH_3 in Et), 2.07 (dt, $^2J_{PH}$ = 18.4 Hz, $^3J_{HH}$ = 7.8 Hz, 6H, CH_2–P), 2.57–2.68 (m, 12H, N–CH_2CH_2–N), 2.77–2.82 (m, 6H, CH_2–N), 4.06–4.14 (m, 12H, OCH_2). ^{13}C NMR (75 MHz, C_6D_6): δ 16.38 (d, $^3J_{PC}$ = 5.7 Hz, CH_3 in Et), 26.86 (d, $^1J_{PC}$ = 137.9 Hz, CH_2–P), 43.77 (s, CH_2–N), 47.44 (s, N–CH_2*CH_2*–N), 54.82 (s, N–*CH_2*CH_2–N), 60.93 (s, OCH_2), 61.01 (s, OCH_2). IR (thin layer) ν/cm^{-1}: 1036 (P–O–C), 1244br (P=O), 3400 (N–H). Anal. Calcd for $C_{24}H_{57}N_4O_9P_3$: C, 45.14; H, 9.00; P, 14.55. Found: C, 44.81; H, 8.73; P, 14.32.

1,3-Bis{[(diethoxyphosphoryl)ethyl]aminomethyl}benzene (**3c**): Yield 96% (after freeze-drying), pale yellow oil. ^{31}P NMR (121 MHz, $CDCl_3$): δ 31.5. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 12H, CH_3), 2.01 (dt, $^2J_{PH}$ = 18.4 Hz, $^3J_{HH}$ = 7.4 Hz, 2H, CH_2–P), 2.90 (dt, $^3J_{PH}$ = 14.6 Hz, $^3J_{HH}$ = 7.4 Hz, 4H, CH_2–NH), 3.77 (s, 4H, CH_2–Ar), 4.00–4.09 (m, 8H, OCH_2), 7.20–7.31 (m, 4H, C_6H_4). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.20 (d, $^3J_{PC}$ = 6.2 Hz, CH_3), 25.15 (d, $^1J_{PC}$ = 139.0 Hz, CH_2–P), 41.49 (s, CH_2–N), 52.16 (s, CH_2–Ar), 60.15 (s, OCH_2), 60.22 (s, OCH_2), 124.56 (s, C[5]), 125.51 (s, C[4], C[6]), 127.18 (s, C[2]), 139.01 (s, C[1], C[3]). IR (thin layer) ν/cm^{-1}: 1029 (P–O–C), 1238 br (P=O), 3304, 3465 (N–H). This product was significantly retained on silica gel if purified by column chromatography, such purification decreased the yield up to 20% and gave the chloroform solvate. Anal. Calcd for $C_{20}H_{38}N_2O_6P_2{\cdot}0.8CHCl_3$: C, 44.61; H, 6.98. Found: C, 44.48; H, 7.08.

Diethyl 2-[butyl{2-(diethoxyphosphinyl)ethyl}amino]ethylphosphonate (**4a**): Yield 87% (after column chromatography), pale yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.7. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3 in Bu), 1.16–1.23 (m, 2H, CH_2–CH_3), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 12H, CH_3 in Et), 1.32–1.39 (m, 2H, CH_2–CH_2CH_3), 1.84 (dt, $^2J_{PH}$ = 19.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2–P), 1.86 (dt, $^2J_{PH}$ = 19.2 Hz, $^3J_{HH}$ = 8.2 Hz, 2H, CH_2–P), 2.33-2.36 (m, 2H, N–CH_2 in Bu), 2.68-2.74 (m, 4H, CH_2–N), 4.00–4.07 (m, 8H, OCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.70 (s, CH_3 in Bu), 16.20 (d, $^3J_{PC}$ = 6.2 Hz, CH_3 in Et), 20.27 (s, CH_2CH_3), 22.87 (d, $^1J_{PC}$ = 137.5 Hz, CH_2–P), 28.80 (s, CH_2–CH_2CH_3), 46.18 (s, CH_2–N), 52.28 (s, N–CH_2 in Bu), 61.32 (s, OCH_2), 61.39 (s, OCH_2). IR (thin layer) ν/cm^{-1}: 1032 (P–O–C), 1247 br (P=O). Anal. Calcd for $C_{16}H_{37}NO_6P_2{\cdot}0.4CHCl_3$: C, 43.85; H, 8.39; N, 3.12. Found: C, 43.90; H, 8.60; N, 2.90.

Diethyl [3,6-bis{2-(diethoxyphosphinyl)ethyl}-9-ethoxy-9-oxido-10-oxa-3,6-diaza-9-phosphadodec-1-yl]phosphonate (**4b**): Yield 71% (after column chromatography), pale yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 24H, CH_3 in Et), 1.85 (dt, $^2J_{PH}$ = 19.2 Hz, $^3J_{HH}$ = 8.1 Hz, 8H, CH_2–P), 2.46 (s, 4H, NCH_2CH_2N), 2.70–2.75 (m, 8H, CH_2–N), 4.01–4.10 (m, 16H, OCH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 16.38 (d, $^3J_{PC}$ = 6.2 Hz, CH_3 in Et), 26.42 (d, $^1J_{PC}$ = 139.4 Hz, CH_2–P), 48.77 (s, CH_2–N), 51.65 (s, N–CH_2CH_2–N), 61.57 (s, OCH_2), 61.63 (s, OCH_2). IR (thin layer) ν/cm^{-1}: 1031 (P–O–C), 1247 br (P═O). Anal. Calcd for $C_{26}H_{60}N_2O_{12}P_4{\cdot}1.5CHCl_3$: C, 36.87; H, 6.92; P, 13.83. Found: C, 36.85; H, 6.84; P, 13.77.

Diethyl [6-{2-[bis[2-(diethoxyphosphinyl)ethyl]aminoethyl}-3,9-bis-[2-(diethoxyphosphinyl)ethyl]-12-ethoxy-12-oxido-13-oxa-3,6,9-triaza-12-phosphapentadec-1-yl]phosphonate (**4c**): Yield 85% (after column chromatography), pale yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 36H, CH_3 in Et), 1.84 (dt, $^2J_{PH}$ = 19.2 Hz, $^3J_{HH}$ = 8.0 Hz, 12H, CH_2–P), 2.25–2.53 (m, 12H, N–CH_2CH_2–N), 2.67–2.73 (m, 12H, CH_2–N), 3.98–4.08 (m, 24H, OCH_2). ^{13}C NMR (101 MHz, D_2O): δ 15.91 (d, $^3J_{PC}$ = 5.6 Hz, CH_3 in Et), 24.45 (d, $^1J_{PC}$ = 136.6 Hz, CH_2–P), 42.05 (s, CH_2–N), 45.64 (s, N–CH_2CH_2–N), 53.28 (s, N–CH_2CH_2–N), 63.33 (s, OCH_2), 63.39 (s, OCH_2). IR (thin layer, ν/cm^{-1}): 1031 (P–O–C), 1246br (P═O). Anal. for the corresponding *tris*(phosphonous acid) trihydrobromide, mp 163 °C. Anal. Calcd for $C_{18}H_{48}N_4O_{18}P_6{\cdot}3HBr$: C, 20.84; H, 4.96; N, 5.40. Found: C, 20.78; H, 5.04; N, 5.05.

1,3-Bis{(N,N-bis[(diethoxyphosphoryl)ethyl])aminomethyl}benzene (**4d**): Yield 83% (after column chromatography), pale-yellow oil. ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.4. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 24H, CH_3), 1.92 (dt, $^2J_{PH}$ = 19.3 Hz, $^3J_{HH}$ = 8.1 Hz, 8H, CH_2–P), 2.77 (dt, $^3J_{PH}$ = 8.0 Hz, $^3J_{HH}$ = 7.9 Hz, 8H, CH_2–N), 3.53 (s, 4H, CH_2–Ar), 3.99–4.07 (m, 16H, OCH_2), 7.17–7.21 (m, 4H, C_6H_4). ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.74 (d, $^3J_{PC}$ = 5.9 Hz, CH_3), 22.54 (d, $^1J_{PC}$ = 137.5 Hz, CH_2–P), 45.66 (s, CH_2–N), 56.75 (s, CH_2–Ar), 60.79 (s, OCH_2), 60.85 (s, OCH_2), 126.93 (s, C^5), 127.60 (s, C^4, C^6), 128.35 (s, C^2), 137.98 (s, C^1, C^3). IR (thin layer, ν/cm^{-1}): 1031 (P–O–C), 1248 br (P═O). Anal. Calcd for $C_{32}H_{64}N_2O_2P_4{\cdot}0.6CHCl_3$: C, 45.30; H, 7.50; P, 14.33. Found: C, 45.39; H, 7.53; P, 14.02.

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