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Synthesis of bis(hydroxymethyl)phosphorylated compounds, analogs of α-aminophosphonic acids or alkylidenebisphosphonic acids

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Abstract—The synthesis of two new series of functional phosphines oxides is described: analogs of glyphosate [α-aminomethylbis-(hydroxymethyl)phosphine oxide] and bisphosphonic acids [bis(hydroxymethyl)phosphoryl methylphosphonic acid] substituting the phosphonic group [$-P(O)(OH)_2$] by the bis(hydroxymethyl)phosphoryl group [$-P(O)(CH_2OH)_2$], have been synthesized in good yields, using the bis(benzyloxymethyl)chloromethyl phosphine oxide as a common precursor. The further purpose of this work is to evaluate the biological interest of the bis(hydroxymethyl)phosphoryl group in comparison to the phosphonic group present in a wide range of biological molecules.

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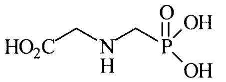
1. Introduction

The replacement of the phosphonic group [$-P(O)(OH)_2$], present in a wide range of biological molecules, by the bis(hydroxymethyl)phosphoryl group [$-P(O)(CH_2OH)_2$] should modify the physical and chemical properties of the substrates. These modifications could improve, by the change of lipophilicity, the bio-availability and the transmembranar transport of these compounds. The replacement of the alkyl groups in phosphine oxide compounds by two hydroxymethyl groups should also increase the complexation properties. Therefore, the purpose was to synthesize new analogs of α-aminophosphonic acids or alkylidenebisphosphonic acids to evaluate the biological interest of the bis(hydroxymethyl)phosphoryl group in comparison to the phosphonic group.

α-Aminophosphonic acids are of great interest as inhibitors of biological processes;[1] they are used in medicinal or agricultural fields, as antibacterial agents, neuroactive compounds, anticancer drugs or pesticides.

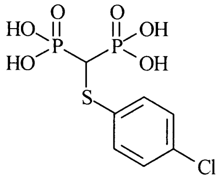
Among these, the glyphosate has achieved a prodigious importance and is the world's largest sold herbicide.[2]



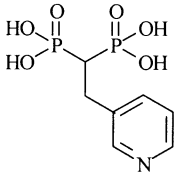
glyphosate®

Bisphosphonates are analogs of endogenous pyrophosphates and exhibit profound effects on bone metabolism.[3] They can exert physico-chemical effects, binding to the surface of calcium phosphate crystals and increasing their formation and aggregation as well as their dissolution. Many of them are very powerful inhibitors of bone resorption. They are used in human therapy, among others in Paget's disease, tumor bone disease, and osteoporosis.[4] A drawback of the bisphosphonates, as a class of drugs, is their poor bio-availability which is mostly attributed to their highly ionic and polar structure.[5] So they are not well absorbed through the intestine, which means many of them cannot be given orally.[6]

We have chosen to work on two monofunctionnalized bisphosphonates: on one hand the tiludronate®, an arylthiomethylenebisphosphonate which was discovered by Sanofi[7] and developed as anti-inflammatory and anti-rheumatismal agent, and, on the other hand, the [2-(3′-pyridyl)-ethylidene]bisphosphonic acid 2-(3′-PEBP) which has shown very promising bone anti-resorptive properties.[8]



tiludronate®



2-(3'PEBP)

Keywords: Michaelis–Arbuzov reaction; Williamson reaction; α-aminophosphonic acid; bis(hydroxymethyl) phosphoryl group; bisphosphonic acid.

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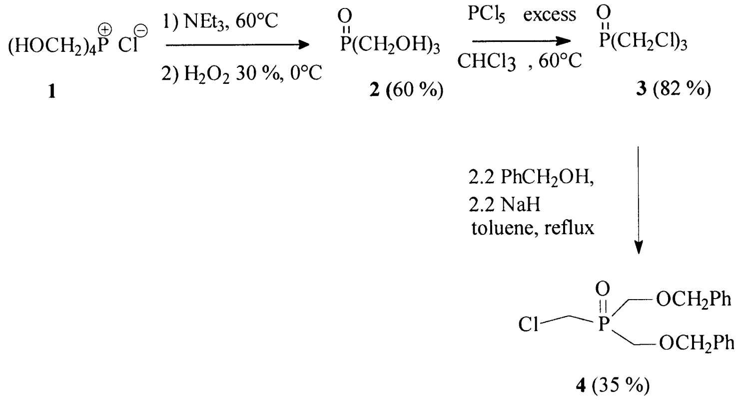


Scheme 1.

2. Results and discussion

The synthesis of glyphosate analogs, in which the phosphonic group [$-P(O)(OH)_2$] is substituted by the bis(hydroxymethyl)phosphoryl [$-P(O)(CH_2OH)_2$] group, has been performed using the tris(hydroxymethyl)phosphine oxide **2** as precursor.

Tris(hydroxymethyl)phosphine oxide **2** is synthesized in two steps[9] (60% overall yield) by reaction of tetrakis(hydroxymethyl)phosphonium chloride **1** with triethylamine, to give the corresponding tris(hydroxymethyl)phosphine, followed by oxidation with hydrogen peroxide (Scheme 1).

Tris(chloromethyl)phosphine oxide **3** is then synthesized by action of phosphorus pentachloride on compound **2**,[10] and two chlorine atoms are substituted by benzyloxy groups using a Williamson reaction between tris(chloromethyl)phosphine oxide **3** and two equivalents of benzyl alcoholate.

Bis(benzyloxymethyl) chloromethylphosphine oxide **4** is formed in 63% yield, but is obtained only in 23% yield after purification.

This low yield can be explained by the formation of a mixture (20:63:17) of mono-, di- and trisubstituted derivatives (Table 1), which are hardly separated by column chromatography or by distillation.

Therefore, to improve the separation by column chromatography, by decreasing the number of compounds in the crude mixture, an excess of benzyl alcohol (2.2 equiv.) was used, to limit the formation of the monosubstituted derivative **5** (Table 1).

The ratio 2.2:1 of reagents affords less than 3% of the monosubstituted compound **5** together, of course, with an increased yield (37%) of the trisubstituted product **6**. Using this excess of benzyl alcohol (2.2 equiv.) bis(benzyloxymethyl) chloromethylphosphine oxide **4** is obtained in 60% yield in the crude mixture and in 35% yield after purification.

2.1. Synthesis of an analog of glyphosate

Starting from bis(benzyloxymethyl) chloromethylphosphine oxide **4**, two different pathways were used in order to build the (O)P–C–N linkage (Scheme 2).

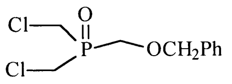
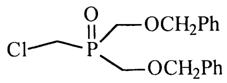
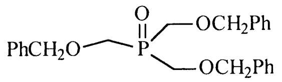
> In the first way (i), compound **7** is synthesized by alkylation of benzyl *N*-benzylglycinate with bis(benzyloxymethyl) chloromethylphosphine oxide **4** (Scheme 2).

The benzyl groups are then cleaved by catalytic hydrogenolysis (ii) using 10% Pd/C and ammonium formate[11] as the hydrogen donor to give finally compound **8** in 64% yield.

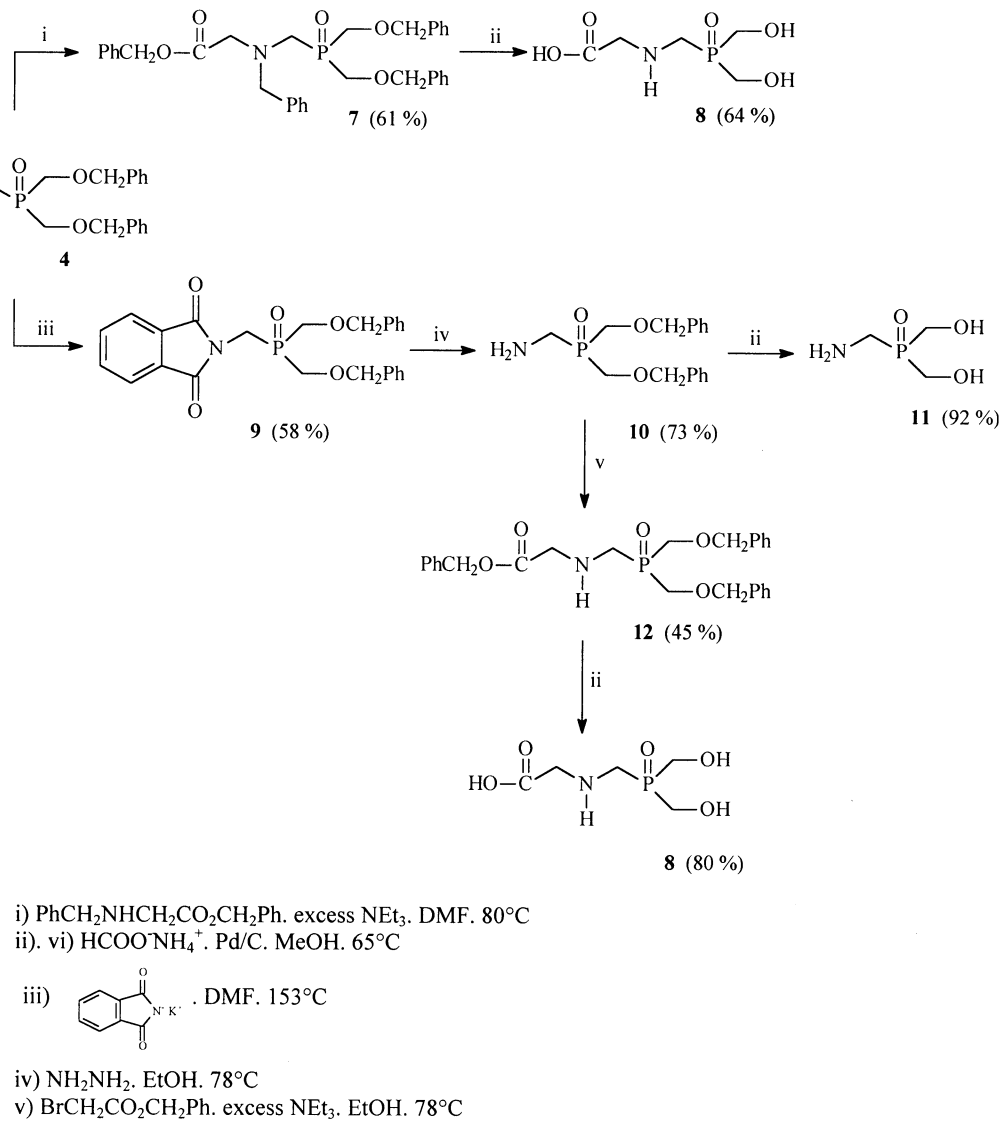
> In the second way (iii), compound **10** is obtained from bis(benzyloxymethyl) chloromethylphosphine oxide **4** by a Gabriel reaction using potassium phthalimide and subsequent hydrazinolysis of **9**.[12]

The alkylation of compound **10** by benzyl bromoacetate using an excess of triethylamine in dimethylformamide

Table 1.

	Formation yields (%)		
$PhCH_2OH/O{=}P(CH_2Cl)_3$	 **5** (δ $^{31}P^*$ = 36.57 ppm)	 **4** (δ $^{31}P^*$ = 36.77 ppm)	 **6** (δ $^{31}P^*$ = 37.05 ppm)
2:1	20	63	17
2.2:1	3	60	37

* represents shifts in toluene.



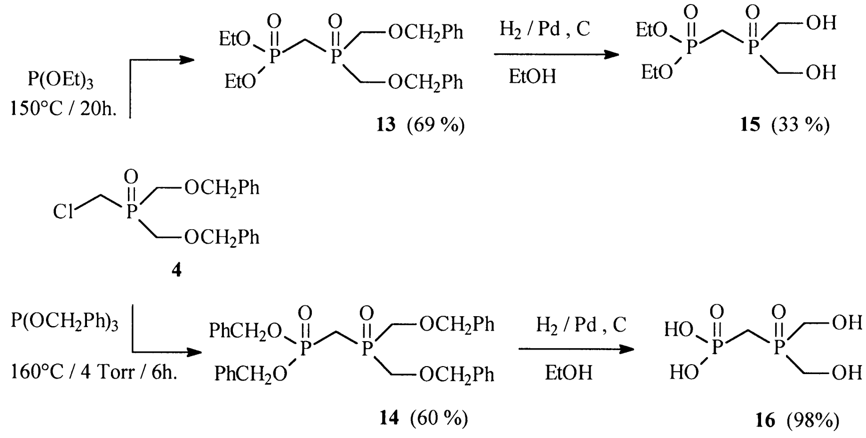
i) $PhCH_2NHCH_2CO_2CH_2Ph$. excess NEt_3. DMF. 80°C
ii). vi) $HCOO^-NH_4^+$. Pd/C. MeOH. 65°C
iii) . DMF. 153°C
iv) NH_2NH_2. EtOH. 78°C
v) $BrCH_2CO_2CH_2Ph$. excess NEt_3. EtOH. 78°C

Scheme 2.

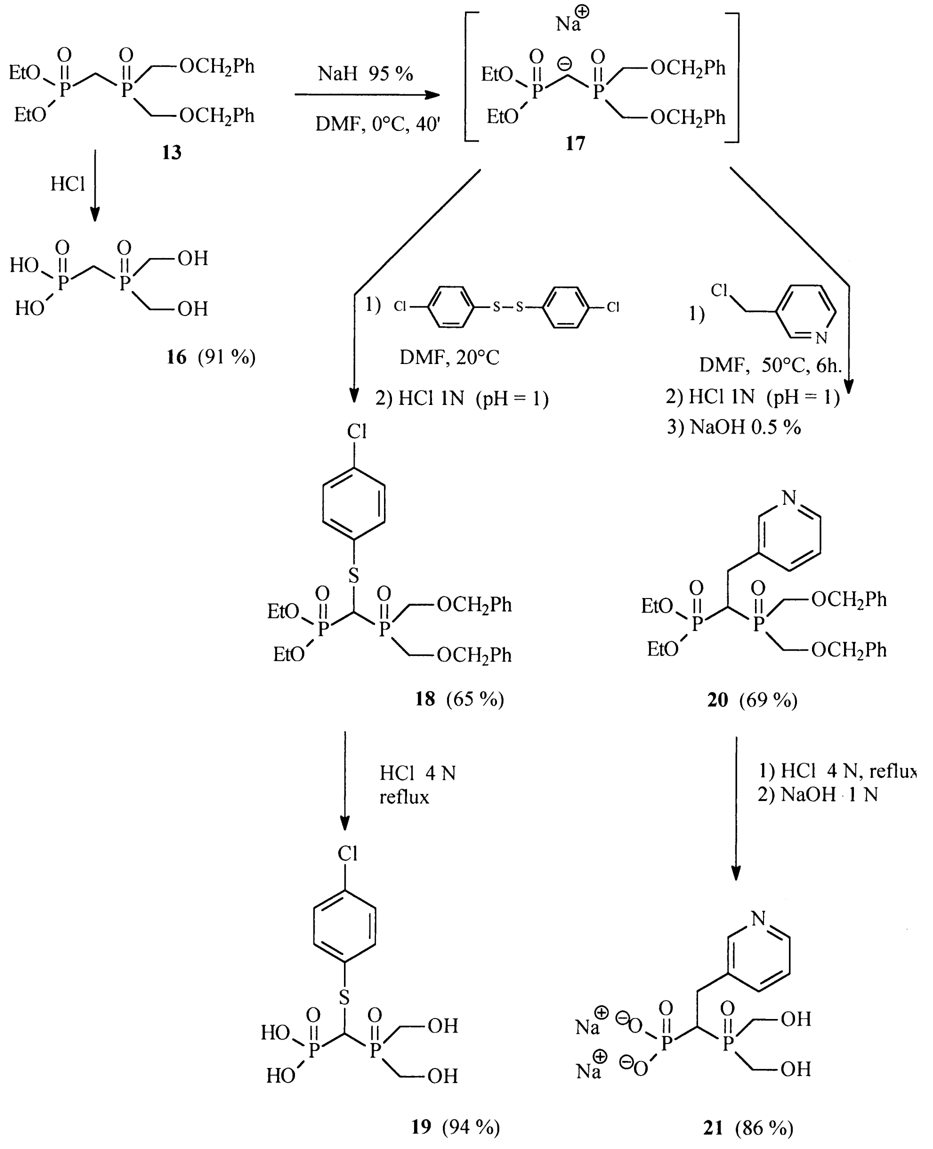
affords the compound **12**, and deprotection of the benzyl groups is carried out by catalytic hydrogenation (ii), in the same way as for compound **7**, to give the desired compound **8** in 80% yield.

The various compounds obtained have been characterized by IR, ^{31}P, ^{1}H, ^{13}C NMR spectra and mass spectroscopy.

The second way is interesting because we obtained, after



Scheme 3.



Scheme 4.

deprotection of the benzyl groups by catalytic hydrogenolysis of compound **10**, the α-aminomethyl bis(hydroxymethyl)phosphine oxide **11**, an analog of the α-aminomethylphosphonic acid which can act as plant growth regulator.[13] But, the first way is more satisfactory for two reasons, first the limited number of steps, and secondly the better overall yield obtained in this case.

2.2. Bisphosphonates

The purpose was to synthesize analogs of tiludronate and 2-(3′-PEBP) in which only one phosphonic acid group is replaced by a bis(hydroxymethyl)phosphine oxide group. In a first step, we chose to build the PCP link by Michaelis–Arbuzov reaction, between a phosphite and a chloromethylphosphine oxide.[14]

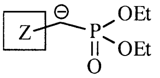
The synthesis is carried out without solvent by heating, at 150°C for 6–20 h, chloromethyl bis(benzyloxymethyl)phosphine oxide **4** with a small excess of triethyl phosphite or tribenzyl phosphite to obtain, respectively, compounds **13** and **14** in good yields (Scheme 3).

The use of tribenzyl phosphite in the Michaelis–Arbuzov reaction requires an efficient removal of the benzyl chloride generated during the reaction. This is achieved at high temperature (160°C) and reduced pressure (4 Torr).[15]

In the next step various electrophiles react with the carbanion **17** obtained from compound **13**, to give, after acidic hydrolysis of the protecting groups the analogs **19** or **21** of tiludronate or 2-(3′-PEBP) (Scheme 4)

Till now, all the compounds tested, exhibit poor herbicide or insecticide properties. Further, the potential therapeutic properties are, at the present time, under investigations. But, concerning their physico-chemical properties, a preliminary work was done with the goal to evaluate the electronic effects of the $-P(O)(CH_2OCH_2Ph)_2$ group in comparison to the $-P(O)(OEt)_2$ group: a correlation between the variation Δδ of the ^{13}C chemical shifts for

Table 2.

		H–CH^2–Z
Z	σ^-	p*K*a
–P(O)(OEt)$_2$	0.64	31
–P(O)(CH$_2$OCH$_2$Ph)$_2$	0.66	30
–C(O)OMe	0.74	25
–C(O)Me	0.82	20

the –CH$_2$Z methylenic carbon and the corresponding anion $-{}^{-}$CHZ [$\Delta\delta = \delta_{\text{anion}} - \delta_{\text{neutral}}$], substituted by various *Z* withdrawing groups (Table 2), and the values of known $\sigma_Z{}^-$ Hammett constants,[16] allowed to determine, for the first time, the σ^- Hammett constant for the –P(O)(OEt)$_2$ and –P(O)(CH$_2$OCH$_2$Ph)$_2$ groups.

We also evaluated the acidity of diethylmethylphosphonate and methyl bis(benzyloxymethyl) phosphine oxide. The p*K*a values higher than 30, are consistent with the literature who recommend strong bases as R$_2$NLi or RLi for the metallation of these compounds.[17] From Table 2, we can establish a classification of the substituents to stabilize the carbanion:

$$\text{–C(O)Me} > \text{–C(O)OMe} > \text{–P(O)(CH}_2\text{OCH}_2\text{Ph)}_2 \sim \text{–P(O)(OEt)}_2$$

3. Conclusion

In order to evaluate the biological interest of the bis(hydroxymethyl)phosphoryl group in comparison to the phosphonic group present in a wide range of biological molecules, two kinds of derivatives have been synthesized as analogs to glyphosate® and tiludronate® or 2-(3′PEBP).

First, we elaborated a new chloromethylphosphorylated building block **4** allowing the access to the various target molecules. Then we have developed from this building block, some synthetic ways leading to the analogs **8** and **11** of α-aminoalkylphosphonic acids, and analogs **19**, **21** and **22** of the bisphosphonic acids in good yields.

4. Experimental

4.1. General

All solvents were distilled prior to use, and commercially available reagents used without further purification. All reactions were monitored by TLC (Merck, SIL G/UV$_{254}$) or ^{31}P NMR. Merck silica gel (20–40 μm) was used for flash column chromatography and Merck silica gel (63–200 μm) for column chromatography. Melting points were determined using a Wild Leitz 350 and are given uncorrected. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a BRUKER AC-200 spectrometer. Chemical shifts are expressed in ppm and coupling constants in Hz. IR spectra were obtained with a Perkin–Elmer 377. Mass spectra were measured with a Jeol JMS DX-300 spectrometer.

4.1.1. Tris(hydroxymethyl)phosphine oxide 2[9] and tris(chloromethyl)phosphine oxide 3.[10] The titled compounds were prepared according to the literature.

4.1.2. Bis(benzyloxymethyl) chloromethylphosphine oxide 4 and tris(benzyloxymethyl) phosphine oxide 6. To a suspension of tris(chloromethyl)phosphine **3** (3 g, 15.4 mmol), sodium hydride 95% (0.87 g, 33.9 mmol) in toluene (60 ml), benzyl alcohol (3.66 g, 33.9 mmol) was added dropwise. The mixture was heated to 110°C for 3 h. After cooling to room temperature, the residue was diluted with water (20 ml) and then treated with 1N HCl until neutral pH.

The aqueous layer was extracted with CH$_2$Cl$_2$. After extraction, the organic layer was dried (MgSO$_4$) and concentrated. The residue was purified by two successive flash chromatography (CH$_2$Cl$_2$/MeOH, 100:0–95:5) to give 35% yield of compound **4** (1.82 g, 5.38 mmol) as a colorless oil and 20% yield of compound **6** (1.25 g, 3.0 mmol) as a white solid.

Compound **4**: ^{31}P NMR (81 MHz, CDCl$_3$): δ 40.66 (s); ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.76 (2H, d, $^2J_{\text{PH}}$=6.2 Hz), 4.00 (4H, d, $^2J_{\text{PH}}$=5.6 Hz), 4.63 (4H, s), 7.30–7.34 (10H, m); ^{13}C NMR (50 MHz, CDCl$_3$): δ 33.45 (d, $^1J_{\text{PC}}$=64.4 Hz, CH$_2$), 63.11 (d, $^1J_{\text{PC}}$=83.7 Hz, CH$_2$), 75.65 (d, $^3J_{\text{PC}}$=11.3 Hz, CH$_2$), 127.98 (s, CH), 128.21 (s, CH), 128.49 (s, CH), 136.36 (s, C); MS FAB$^+$ (NBA): $[\text{M+H}]^{+:}$ 339; IR (NaCl): ν 2890, 1500, 1455, 1435, 1210, 1190, 1095 cm^{-1}.

Compound **6**: Mp 60°C; ^{31}P NMR (81 MHz, CDCl$_3$): δ 41.22 (s); ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.97 (6H, d, $^2J_{\text{PH}}$= 5.4 Hz), 4.62 (6H, s), 7.24–7.37 (15H, m); ^{13}C NMR (50 MHz, CDCl$_3$): δ 62.95 (d, $^1J_{\text{PC}}$=79.9 Hz, CH$_2$), 75.52 (d, $^3J_{\text{PC}}$=10.4 Hz, CH$_2$), 128 (s, CH), 128.10 (s, CH), 128.51 (s, CH), 136.88 (s, C); MS FAB$^+$ (NBA): $[\text{M+H}]^+$: 411; IR (CCl$_4$): ν 2865, 1500, 1455, 1430, 1390, 1240, 1205, 1185, 1095, 1030 cm^{-1}.

4.1.3. Bis(benzyloxymethyl) phtalimidomethylphosphine oxide 9. A suspension of bis(benzyloxymethyl) chloromethylphosphine oxide **4** (2.61 g, 7.7 mmol) and potassium phtalimide (1.71 g, 9.25 mmol) in DMF (30 ml) was refluxed for 3 h. Water (50 ml) was added to the cooled reaction mixture. The aqueous layer was extracted with CH$_2$Cl$_2$. The organic layer was dried (MgSO$_4$), concentrated, and the residue purified by column chromatography with CH$_2$Cl$_2$/MeOH (100:0–95:5) to give 58% yield of compound **9** (2 g, 4.45 mmol) as a colorless oil.

^{31}P NMR (81 MHz, CDCl$_3$): δ 38.65 (s); ^{1}H NMR (200 MHz, CDCl$_3$): δ 4.06 (4H, d, $^2J_{\text{PH}}$=5.9 Hz), 4.26 (2H, d, $^2J_{\text{PH}}$=6.9 Hz), 4.60 (4H, s), 7.22–7.32 (10H, m), 7.59–7.75 (4H, 2m); ^{13}C NMR (50 MHz, CDCl$_3$): δ 33.03 (d, $^1J_{\text{PC}}$= 66.2 Hz, CH$_2$), 65.15 (d, $^1J_{\text{PC}}$=79.9 Hz, CH$_2$), 75.77 (d, $^3J_{\text{PC}}$=11.2 Hz, CH$_2$), 123.42 (s, CH), 127.89 (s, CH), 127.97 (s, CH), 128.43 (s, CH), 131.82 (s, C), 134.15 (s, CH), 136.69 (s, C), 167.49 (s, C); MS FAB$^+$ (NBA): $[\text{M+H}]^+$: 450; IR (CCl$_4$): ν 1740, 1470, 1455, 1260, 1195, 1180, 1095 cm^{-1}.

4.1.4. Bis(benzyloxymethyl) aminomethyl phosphine oxide hydrochloride 10, HCl. Hydrazine hydrate (0.27 g, 5.35 mmol) was added with stirring to a solution of compound **9** (2 g, 4.45 mmol) in absolute ethanol (13 ml) and the mixture refluxed for 1 h and 30 min. The reaction mixture was filtered after cooling, and the filtrate concentrated before addition of 30 ml of water. The reaction mixture was then extracted, dried ($MgSO_4$) and concentrated. The light-yellow oily residue was dissolved in 100 ml of dry ether to which a solution of ether hydrochloric acid 5N was added. The white crystalline hydrochloride formed was filtered off, washed with ether and dried to give 73% yield of compound **10** (1.18 g, 3.32 mmol).

Mp: 155.5°C; ^{31}P NMR (81 MHz, $CDCl_3$): δ 36.37 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.54 (2H, d, $^{2}J_{PH}=6.6$ Hz), 4.14 (4H, d, $^{2}J_{PH}=6.3$ Hz), 4.50 (4H, s), 7.16–7.26 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.37 (d, $^{1}J_{PC}=64.5$ Hz, CH_2), 63.70 (d, $^{1}J_{PC}=84.7$ Hz, CH_2), 75.43 (d, $^{3}J_{PC}=12.7$ Hz, CH_2), 127.91 (s, CH), 127.97 (s, CH), 128.33 (s, CH), 138.68 (s, C).

4.1.5. Bis(benzyloxymethyl) aminomethyl phosphine oxide 10. To a suspension of compound **10**, HCl (1.5 g, 4.22 mmol) in dry ether (20 ml) was added triethylamine (0.51 g, 5.06 mmol). After stirring the triethylammonium chloride formed was filtered off, and the filtrate was concentrated. An oil was obtained (1.32 g, 4.13 mmol) corresponding to compound **10** (98% yield).

^{31}P NMR (81 MHz, $CDCl_3$): δ 42.78 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (2H, bs, NH_2), 3.22 (2H, d, $^{2}J_{PH}=5.2$ Hz), 3.93 (4H, d, $^{2}J_{PH}=5.9$ Hz), 4.59 (4H, s), 7.26–7.36 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.71 (d, $^{1}J_{PC}=68.4$ Hz, CH_2), 63.73 (d, $^{1}J_{PC}=78.6$ Hz, CH_2), 75.53 (d, $^{3}J_{PC}=11.1$ Hz, CH_2), 127.95 (s, CH), 128.11 (s, CH), 128.46 (s, CH), 136.60 (s, C); MS FAB^{+} (NBA): $[M+H]^{+}$: 320; IR (CCl_4): ν 3500, 1495, 1455, 1435, 1210, 1195, 1095 cm^{-1}.

4.1.6. Benzyl *N*-bis(benzyloxymethyl)phosphorylmethylglycinate 12. To a stirred mixture of compound **10** (1.3 g, 4 mmol) and triethylamine (2 g, 20 mmol) in absolute ethanol (2 ml), was added benzyl bromoacetate (0.93 g, 4 mmol) and refluxed for 18 h.[18] After concentration of the excess of triethylamine, the residue mixture was dissolved in ether and the triethylammonium chloride formed was filtered off. After filtration, the organic layer was washed with aq. NH_4OH (10%) and dried ($MgSO_4$). Removal of solvent in vacuum yielded an oil, which was purified by column chromatography (AcOEt/MeOH, 100:0–95:5).

Compound **12** (0.83 g, 1.78 mmol) was obtained in 45% yield as a yellow oil. ^{31}P NMR (81 MHz, $CDCl_3$): δ 43.21 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.01 (1H, bs, NH), 3.19 (2H, d, $^{2}J_{PH}=7.7$ Hz), 3.51 (2H, s), 3.93 (4H, d, $^{2}J_{PH}=5.9$ Hz), 4.60 (4H, s), 5.15 (2H, s), 7.26–7.35 (15H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 43.66 (d, $^{1}J_{PC}=75.8$ Hz, CH_2), 51.80 (d, $^{3}J_{PC}=12.3$ Hz, CH_2), 63.60 (d, $^{1}J_{PC}=80.2$ Hz, CH_2), 66.50 (s, CH_2), 75.43 (d, $^{3}J_{PC}=10.9$ Hz, CH_2), 127.93 (s, CH), 128.04 (s, CH), 128.28 (s, CH), 128.34 (s, CH), 128.43 (s, CH), 128.53 (s, CH), 135.43 (s, C), 136.73 (s, C), 171.52 (d, $^{4}J_{PC}=0.55$ Hz, C); MS FAB^{+} (NBA): $[M+H]^{+}$: 468; IR (NaCl): ν 3450, 1740, 1500, 1455, 1435, 1215, 1175, 1145, 1095 cm^{-1}.

4.1.7. Benzyl *N*-bis(benzyloxymethyl)phosphorylmethyl-*N*-benzylglycinate 7. To a solution of compound **4** (1.78 g, 5.3 mmol) in DMF (10 ml), was added triethylamine (5.6 g, 37 mmol) and benzyl *N*-benzylglycinate[18] (2.56 g, 10.6 mmol). The reaction mixture was heated for 7 days at 80°C. After concentration of solvent and excess of triethylamine, the residue was dissolved in ether and the triethylammonium chloride formed was filtered off. After removal of solvent in vacuum, the residue was redissolved in CH_2Cl_2, washed with 10% HCl and water to eliminate benzyl *N*-benzylglycinate. The organic layer was washed with NH_4OH (10%) and dried ($MgSO_4$). Removal of solvent in vacuum yielded an oil, which was purified by column chromatography (AcOEt/hexane, 50:50–70:30). Compound **7** (1.18 g, 3.23 mmol) was obtained in 61% yield as a colorless oil.

^{31}P NMR (81 MHz, $CDCl_3$): δ 44.73 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.33 (2H, d, $^{2}J_{PH}=5.5$ Hz), 3.64 (2H, s), 3.90–3.92 (4H, m, ABX system, $^{2}J_{HAHB}=-12.6$ Hz, $^{2}J_{PHA}=4.9$ Hz, $^{2}J_{PHB}=6.4$ Hz), 3.92 (2H, s), 4.52–4.54 (4H, m, AB system, $^{2}J_{HAHB}=-12.1$ Hz), 5.13 (2H, s), 7.25–7.37 (20H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 47.35 (d, $^{1}J_{PC}=80.1$ Hz, CH_2), 55.19 (d, $^{3}J_{PC}=4.3$ Hz, CH_2), 60.37 (d, $^{3}J_{PC}=7.5$ Hz, CH_2), 62.35 (d, $^{1}J_{PC}=80.4$ Hz, CH_2), 66.19 (s, CH_2), 75.40 (d, $^{3}J_{PC}=11.0$ Hz, CH_2), 127.57 (s, CH), 127.97 (s, CH), 128.07 (s, CH), 128.34 (s, CH), 128.36 (s, CH), 128.45 (s, CH), 128.50 (s, CH), 128.63 (s, CH), 129.25 (s, CH), 135.75 (s, C), 136.95 (s, C), 137.98 (s, C), 190.17 (d, $^{4}J_{PC}=1.3$ Hz, C); MS FAB^{+} (GT): $[M+H]^{+}$: 558; IR (NaCl): ν 1739, 1497, 1454, 1430, 1207, 1179, 1098 cm^{-1}.

4.1.8. Diethyl bis(benzyloxymethyl)phosphorylmethylphosphonate 13. A stirred mixture of bis(benzyloxymethyl)chloromethylphosphine oxide **4** (2.3 g, 6.7 mmol) and triethyl phosphite (1.34 g, 8 mmol), under nitrogen was heated at 150°C for 20 h. Excess triethyl phosphite was removed by vacuum distillation. The residue was purified by flash chromatography (AcOEt/MeOH, 100:0–93:7) to give 69% of compound **13** (2.04 g, 4.63 mmol) as a colorless oil.

^{31}P NMR (81 MHz, $CDCl_3$): δ 21.21 (d, $^{2}J_{PP}=12.8$ Hz), 39.06 (d, $^{2}J_{PP}=12.7$ Hz); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (6H, t, $^{3}J_{HH}=7.1$ Hz), 2.41 (2H, dd, $^{2}J_{P1H}=20.4$ Hz, $^{2}J_{P2H}=13.9$ Hz), 4.00–4.03 (4H, m, system ABX, $^{2}J_{HAHB}=-12.9$ Hz, $^{2}J_{P2HA}=5.2$ Hz, $^{2}J_{P2HB}=6.6$ Hz), 4.15 (4H, m, A_2M_3X system, $^{3}J_{MHA}=7.1$ Hz, $^{3}J_{P1HA}=8.2$ Hz), 4.62–4.63 (4H, m, AB system. $^{2}J_{HAHB}=-12.1$ Hz), 7.26–7.32 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.20 (d, $^{3}J_{P1C}=6.4$ Hz, CH_3), 21.30 (dd, $^{1}J_{P1C}=135.5$ Hz, $^{1}J_{P2C}=53.39$ Hz, CH_2), 62.61 (d, $^{2}J_{P1C}=6.4$ Hz, CH_2), 64.13 (dd, $^{1}J_{P2C}=85.5$ Hz, $^{3}J_{P1C}=3.5$ Hz, CH_2), 75.45 (d, $^{3}J_{P2C}=11.7$ Hz, CH_2), 128.02 (s, CH), 128.10 (s, CH), 128.47 (s, CH), 136.80 (s, C); MS FAB^{+} (matrice NBA): $[M+H]^{+}$: 441; IR (NaCl) ν 1720, 1495, 1455, 1250, 1190, 1095, 1050, 1025 cm^{-1}.

4.1.9. Dibenzyl bis(benzyloxymethyl)phosphorylmethylphosphonate 14. A stirred mixture of bis(benzyloxymethyl)chloromethylphosphine oxide **4** (0.78 g, 2.3 mmol) and tribenzyl phosphite[19] (2.08 g, 5.9 mmol) was heated for 6 h at 160°C/4 mmHg. The crude mixture was purified by flash chromatography (CH_2Cl_2/MeOH, 100:0–98:2) to give 60% of compound **14** (0.78 g, 1.38 mmol) as a colorless oil.

^{31}P NMR (81 MHz, $CDCl_3$): δ 22.56 (d, $^2J_{PP}$=12.8 Hz); 38.24 (d, $^2J_{PP}$=12.7 Hz); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (2H, dd, $^2J_{P1H}$=20.7 Hz, $^2J_{P2H}$=13.8 Hz), 3.96–3.98 (4H, m, ABX system, $^2J_{HAHB}$=−12.9 Hz, $^2J_{P2HA}$=5.4 Hz, $^2J_{P2HB}$=6.6 Hz), 4.55–4.56 (4H, m, AB system, $^2J_{HAHB}$=−11.9 Hz), 5.07 (4H, m, ABX system, $^2J_{HAHB}$=−12.0 Hz, $^3J_{P1HA}$=7.9 Hz, $^3J_{P1HB}$=8.3 Hz), 7.22–7.33 (20H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.58 (dd, $^1J_{P1C}$=133.9 Hz, $^1J_{P2C}$=53.5 Hz, CH_2), 65.04 (dd, $^1J_{P2C}$=85.0 Hz, $^3J_{P1C}$=4.1 Hz, CH_2), 67.85 (d, $^2J_{P1C}$=6.1 Hz, CH_2), 75.28 (d, $^3J_{P2C}$=11.5 Hz, CH_2), 127.86–128.50 (CH), 135.85 (dd, $^3J_{P1C}$=6.4 Hz, $^5J_{P2C}$=0.5 Hz, C), 136.77 (s, C); MS FAB$^+$ (NBA): $[M+H]^+$: 565; IR (NaCl): ν 1495, 1457, 1259, 1183, 1085, 1000, 876, 825 cm^{-1}.

4.1.10. Diethyl bis(benzyloxymethyl)phosphoryl-4-chlorophenylthiomethylphosphonate 18. To a solution of compound **13** (0.3 g, 0.68 mmol) in DMF (6 ml) was added under nitrogen, at 0°C, sodium hydride (0.03 g, 1.36 mmol) in small portions. After 40 min, bis(4-chlorophenyl)-disulfide[20] (0.22 g, 0.75 mmol) was added in one portion. The mixture was stirred for 3 h at room temperature.

After acidification with HCl (1N) and filtration, the reaction mixture was concentrated and then purified by flash chromatography (AcOEt/hexane, 50:50–90:10). Compound **18** (0.26 g, 0.45 mmol) was obtained in 65% yield as a colorless oil.

^{31}P NMR (81 MHz, $CDCl_3$): δ 18.77 (d, $^2J_{PP}$=6.6 Hz), 43.44 (d, $^2J_{PP}$=6.6 Hz); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 and 1.26 (6H, 2t, $^3J_{HH}$=7.2 and 7.2 Hz), 3.59 (1H, dd, $^2J_{P1H}$=19.7 Hz, $^2J_{P2H}$=12.3 Hz), 4.10–4.37 (8H, m), 4.36. 4.47 (2H, m, AB system, $^2J_{HAHB}$=−11.4 Hz), 4.59–4.71 (2H, m, AB system, $^2J_{HAHB}$=−11.7 Hz), 7.06–7.46 (m, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.67 (d, $^3J_{P1C}$=5.7 Hz, CH_3), 39.39 (dd, $^1J_{P1C}$=138.9 Hz, $^1J_{P2C}$=42.3 Hz, CH), 62.55 and 65.35 (dd, $^1J_{P2C}$=89.8 Hz, $^3J_{P1C}$=5.0 Hz, d, $^1J_{P2C}$=82.2 Hz, CH_2), 64.26 and 64.44 (2d, $^2J_{P1C}$=6.3 and 6.8 Hz, CH_2), 75.88 and 76.03 (2d, $^3J_{P2C}$=12.6 and 10.9 Hz, CH_2), 128.04 (s, CH), 128.13 (s, CH), 128.44 (s, CH), 129.32 (s, CH), 132.68 (s, CH), 132.94 (dd, $^3J_{PC}$=2.01, 3.02 Hz, C), 134.23 (s, C), 136.57 and 137.03 (2s, C); MS FAB$^+$ (NBA): $[M+H]^+$: 584; IR (NaCl): ν 1495f, 1480, 1455, 1250, 1190, 1095, 1050, 1020, 970 cm^{-1}.

4.1.11. Diethyl bis(benzyloxymethyl)phosphoryl-2-(3-pyridyl)ethylphosphonate 20. To a solution of compound **13** (0.6 g, 1.36 mmol) in dimethylformamide (6 ml) was added under nitrogen, at 0°C, sodium hydride (0.07 g, 2.70 mmol) in small portions. After 40 min, 3-picolylchloride (0.2 g, 1.49 mmol) was added in one portion. The mixture was heated at 50°C for 6 h. After cooling to room temperature, the mixture was treated with HCl (1N). After filtration, the residue was washed successively with NaOH 5% and water, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on alumina (AcOEt/MeOH, 100:0–97:3). Compound **20** (0.5 g, 0.94 mmol) was obtained in 69% yield as a yellow oil.

^{31}P NMR (81 MHz, $CDCl_3$): δ 24.45 (d, $^2J_{PP}$=1.9 Hz); 44.07 (d, $^2J_{PP}$=1.9 Hz); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 and 1.30 (6H, 2d, $^3J_{HH}$=7.1 and 7.1 Hz), 2.77 (1H, m, AMNXY system, $^2J_{P1H}$=22.2 Hz, $^2J_{P2H}$=13.5, $^3J_{HH}$=8.3, 5.2 Hz), 3.20–3.69 (2H, m), 3.76–4.35 (4H, m), 4.17–4.27 (2H, m, ABXY system, $^2J_{HAHB}$=−13.2 Hz, $^2J_{P2HA}$=7.6 Hz, $^2J_{P2HB}$=6.3 Hz, $^4J_{P1HA}$=2.6 Hz), 3.65–4.08 (2H, m, ABXY system, $^2J_{HAHB}$=−12.7 Hz, $^2J_{P2HA}$=6.6 Hz, $^2J_{P2HB}$=6.4 Hz, $^4J_{P1HA}$=2.0 Hz), 4.42–4.45 (2H, m, AB system, $^2J_{HAHB}$=−11.5 Hz), 4.61–4.74 (2H, m, AB system, $^2J_{HAHB}$=−11.7 Hz), 7.13–7.54 (12H, m), 8.45 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.97 and 16.27 (2d, $^3J_{P1C}$=6.5, 6.2 Hz, CH_3), 26.94 (dd, $^2J_{P1C}$=5.2 Hz, $^2J_{P2C}$=2.7 Hz, CH_2), 36.97 (dd, $^1J_{P1C}$=131.5 Hz, $^1J_{P2C}$=49.5 Hz, CH), 62.15 and 63.03 (2d, $^2J_{P1C}$=6.6, 6.4 Hz, CH_2), 63.27 and 66.13 (dd, $^1J_{P2C}$=83.8 Hz, $^3J_{P1C}$=5.9 Hz, d, $^1J_{P2C}$=82.2 Hz, CH_2), 75.57 and 75.64 (2d, $^3J_{P2C}$=12.3, 10.67 Hz, CH_2), 123.17 (s, CH), 127.99 (s, CH), 128.05 and 128.14 (2s, CH), 128.22 (s, CH), 128.42 and 128.50 (2s, CH), 134.65 (dd, $^3J_{PC}$=5.58, 7.07 Hz, C), 136.52 (s, CH), 137.09 (s, C), 148. 05 and 150.40 (2s, CH); FAB$^+$ (NBA): $[M+H]^+$: 532; IR (NaCl): ν 1496, 1450, 1248, 1185, 1092, 1040, 1020, 970, 825, 740, 710 cm^{-1}.

4.2. General procedure for deprotection

4.2.1. Hydrogenolysis

4.2.1.1. Hydrogenolysis of benzyl *N*-bis(benzyloxymethyl)phosphorylmethyl-*N*-benzyl glycinate 7. To a solution of compound **7** (0.2 g, 0.36 mmol) in dry methanol (10 ml) was added under nitrogen, Pd/C 10% (0.04 mg) and ammonium formate (0.11 g, 1.81 mmol). The mixture is refluxed during 4 h. After cooling, the reaction mixture was filtered on celite, and the filtrate concentrated to give an oil. After precipitation in a mixture of water/acetone, compound **8** (0.05 g, 0.23 mmol) was obtained as a white powder (yield 64%).

Mp: 133–135°C: ^{31}P NMR (81 MHz, D_2O): δ 44.47 (s); ^{1}H NMR (200 MHz, D_2O): δ 3.76 (2H, d, $^2J_{PH}$=7.6 Hz), 3.80 (2H, s), 4.31 (4H, d, $^2J_{PH}$=2.7 Hz); ^{13}C NMR (50 MHz, D_2O): δ 41.92 (d, $^1J_{PC}$=59.6 Hz, CH_2), 53.77 (d, $^3J_{PC}$=5.5 Hz, CH_2), 58.38 (d, $^1J_{PC}$=78.5 Hz, CH_2), 173.45 (s, C); FAB$^+$ (NBA): $[M+H]^+$: 198.

4.2.1.2. Hydrogenolysis of benzyl *N*-bis(benzyloxymethyl)phosphorylmethylglycinate 12. To a solution of compound **12** (0.2 g, 0.43 mmol) in dry methanol (10 ml) was added, under nitrogen, Pd/C 10% (0.04 mg) and ammonium formate (0.135 g, 2.14 mmol). The mixture was refluxed during 4 h, then, after cooling, filtered on celite and the filtrate concentrated to give compound **8** as a yellow oil. After precipitation in a mixture of water/acetone, compound **8** was obtained as a white powder (68 mg, 0.35 mmol) (yield 80%).

4.2.1.3. Hydrogenolysis of diethyl bis(benzyloxymethyl)phosphorylmethylphosphonate 13. To a solution of compound **13** (0.28 g, 0.64 mmol) in absolute ethanol (1 ml) was added Pd/C 10% (0.03 mg), After consumption of the required volume of hydrogen in 2 h, the mixture was filtered on celite and the filtrate concentrated to give compound **15** (54.6 mg, 0.21 mmol) as a yellow oil (yield 33%).

^{31}P NMR (81 MHz, D_2O): δ 22.43 (d, $^{2}J_{\mathrm{PP}}$=13.3 Hz), 44.17 (d, $^{2}J_{\mathrm{PP}}$=13.3 Hz); ^{1}H NMR (200 MHz, CD_3OD): δ 1.32 (6H, t, $^{3}J_{\mathrm{HH}}$=7.0 Hz), 2.67 (2H, dd, $^{2}J_{\mathrm{P1H}}$=20.7 Hz, $^{2}J_{\mathrm{P2H}}$=13.4 Hz), 4.06–4.09 (4H, m, ABX system, $^{2}J_{\mathrm{HAHB}}$=−14.1 Hz, $^{2}J_{\mathrm{P2HA}}$=3.1 Hz, $^{2}J_{\mathrm{P2HB}}$=4.2 Hz), 4.18 (4H, m, A_2M_3X system, $^{3}J_{\mathrm{MHA}}$=7.2 Hz, $^{3}J_{\mathrm{P1HA}}$=7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.24 (d, $^{3}J_{\mathrm{P1C}}$=6.4 Hz, CH_3), 22.18 (dd, $^{1}J_{\mathrm{P1C}}$=134.4 Hz, $^{1}J_{\mathrm{P2C}}$=48.3 Hz), 57.85 (dd, $^{1}J_{\mathrm{P2C}}$=78.6 Hz, $^{3}J_{\mathrm{P1C}}$=3.5 Hz, CH_2), 63.07 (d, $^{2}J_{\mathrm{P1C}}$=6.5 Hz, CH_2); MS FAB^{+} (NBA): $[M+H]^{+}$: 261; IR (NaCl): ν 3200–3500, 1240, 1165, 1095, 1050, 1025, 975F cm^{-1}.

4.2.1.4. Hydrogenolysis of dibenzyl bis(benzyloxymethyl)phosphorylmethylphosphonate 14. To a solution of compound **14** (0.2 g, 0.45 mmol) in absolute ethanol (1 ml) was added Pd/C 10% (0.02 mg). After consumption of the required volume of hydrogen, the mixture was filtered on celite and the filtrate concentrated to give compound **16** (90 mg, 0.44 mmol) as a yellow oil (yield 98%).

^{31}P NMR (81 MHz, D_2O): δ 17.01 (d, $^{2}J_{\mathrm{PP}}$=12.9 Hz), 47.18 (d, $^{2}J_{\mathrm{PP}}$=12.6 Hz); ^{1}H NMR (200 MHz, D_2O): δ 2.57 (2H, dd, $^{2}J_{\mathrm{P1H}}$=19.8 Hz, $^{2}J_{\mathrm{P2H}}$=14.6 Hz), 4.18 (4H, d, $^{2}J_{\mathrm{P2H}}$=2.7 Hz); ^{13}C NMR (50 MHz, D_2O): δ 25.70 (dd, $^{1}J_{\mathrm{P1C}}$=129.20 Hz, $^{1}J_{\mathrm{P2C}}$=53.0 Hz, CH_2), 59.25 (dd, $^{1}J_{\mathrm{P2C}}$=81.0 Hz, $^{3}J_{\mathrm{P1C}}$=3.4 Hz, CH_2); MS FAB^{+} (NBA): $[M+ H]^{+}$: 205.

4.2.2. Hydrolysis.

4.2.2.1. Hydrolysis of diethyl bis(benzyloxymethyl)phosphorylmethylphosphonate 13. A stirred mixture of compound **13** (0.2 g, 0.45 mmol) in HCl 4N (1.5 ml, 18 mmol) is refluxed at 100°C for 12 h. The excess HCl and water were removed by vacuum distillation. After addition of the same quantity of ethanol, the mixture is concentrated by vacuum in order to remove the traces of HCl. This last step is repeated five times. We obtained compound **16** (84 mg, 0.41 mmol) as a yellow oil (yield 91%).

4.2.2.2. Hydrolysis of diethyl bis(benzyloxymethyl)phosphoryl-4-chlorophenylthiomethyl phosphonate 18. A stirred mixture of compound **18** (0.3 g, 0.51 mmol) in HCl 4N (2 ml, 24 mmol) is refluxed at 100°C for 18 h. Excess HCl and water are removed by vacuum distillation, After addition of 5 ml of ethanol, the mixture is concentrated by vacuum in order to remove HCl. This last step is repeated five times. Compound **19** (0.168 g, 0.48 mmol) is obtained as a colorless oil (yield 94%).

^{31}P NMR (81 MHz, D_2O): δ 11.72 (d, $^{2}J_{\mathrm{PP}}$=10.6 Hz); 53.71 (d, $^{2}J_{\mathrm{PP}}$=10.6 Hz); ^{1}H NMR (200 MHz, D_2O): δ 3.12 (1H, dd, $^{2}J_{\mathrm{P1H}}$=17.5 Hz, $^{2}J_{\mathrm{P2H}}$=10.7 Hz), 3.98–4.12 (4H, m), 7.26–7.32 (4H, m; ^{13}C NMR (50 MHz, D_2O): δ 45.12 (dd, $^{1}J_{\mathrm{P1C}}$=112.3 Hz, $^{1}J_{\mathrm{P2C}}$=40.7 Hz, CH), 59.78 and 60.89 (d, $^{1}J_{\mathrm{P2C}}$=78.4 Hz, dd, $^{1}J_{\mathrm{P2C}}$=73.1 Hz, $^{3}J_{\mathrm{P1C}}$=2.9 Hz), 130.29 (s, CH), 132.88 (s, CH), 133.04 (dd, $^{3}J_{\mathrm{PC}}$=1.6, 2.6 Hz, C), 136.01 (s, C); MS FAB^{+} (NBA): $[M+H]^{+}$: 347.

4.2.2.3. Hydrolysis of diethyl bis(benzyloxymethyl)phosphoryl-2-(3-pyridyl)ethylphosphonate 20. A stirred mixture of compound **20** (0.15 g, 0.28 mmol) in HCl 4N (1 ml, 12 mmol) is refluxed at 100°C for 18 h. The excess HCl and water is removed by vacuum distillation. After addition of 5 ml of ethanol, the mixture is concentrated by vacuum in order to remove HCl. After a chromatographic separation on reverse phase (H_2O/MeOH, 50:50–60:40 we obtained, after basification with NaOH (1N) (pH=11–12), 86% yield of compound **21** (0.082 g, 0.24 mmol) as a yellow oil.

^{31}P NMR (81 MHz, D_2O): δ 12.73 (bs); 52.62 (d, $^{2}J_{\mathrm{PP}}$=5.1 Hz); ^{1}H NMR (200 MHz, D_2O): δ 2.65 (1H, m), 3.23 (2H, m), 3.87 and 4.23 (4H, 2m), 7.44 (1H, m), 7.91 (1H, m), 8.45 (1H, m); ^{13}C NMR (50 MHz, D_2O): δ 31.16 (m, CH_2); 42.01 (dd, $^{1}J_{\mathrm{P1C}}$=109.1 Hz, $^{1}J_{\mathrm{P2C}}$=45.5 Hz, CH), 58.76 and 60.78 (d, $^{1}J_{\mathrm{P2C}}$=71.6 Hz, dd, $^{1}J_{\mathrm{P2C}}$=72.1 Hz, $^{3}J_{\mathrm{P1C}}$=2.5 Hz, CH_2), 135.70 (m, C), 140.69 (s, CH), 149.29 and 151.83 (2s, CH).

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