Synthesis and Characterization of New $C_{\alpha,\alpha}$-Disubstituted (Diarylaminomethyl)-phosphonates

Henri-Jean Cristau,* Jean-Marc Lambert, Jean-Luc Pirat*

Laboratoire de Chimie Organique, E.S.A. 5076 du C.N.R.S., Ecole Nationale Supérieure de Chimie de Montpellier 8, Rue de l'Ecole Normale, F-34296 Montpellier Cedex 5, France

Fax +33(4)67144319; E-mail: pirat@cit.enscm.fr

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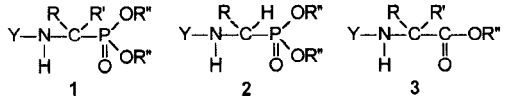
Abstract: A convenient and efficient three-step procedure for the preparation of *N*-protected or unprotected $C_{\alpha,\alpha}$-disubstituted (diarylaminomethyl)phosphonates **1** is reported. This method allows diversification of the substituents on the carbon in the α-position to the phosphorus, as well as the protective group on the amine and the phosphonate ester group.

Key words: $C_{\alpha,\alpha}$-disubstituted (diarylaminomethyl)phosphonates, Arbuzov reaction, Kabachnik–Fields reaction, imine acylation

Over the past three decades, several research projects have been directed toward the synthesis of α-aminophosphonic acids **2** and their esters, analogs of amino acids, to find new biologically active molecules. These compounds did indeed show enzyme inhibition, antibacterial, antitumoral, herbicidal and fungicidal activities.[1–15]

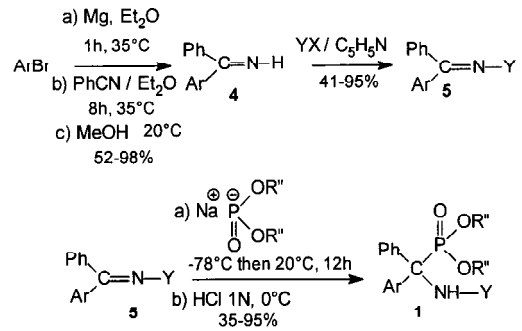
Recently, C. Toniolo[16] reported "the explosive interest in the study of $C_{\alpha,\alpha}$-disubstituted amino acids" **3**. These compounds '*peptaibols*' are used as proteolytic enzyme inhibitors and exhibit several attractive biological activities, for example, against epilepsy.

For these reasons, we decided to develop a convenient and efficient method for the preparation of $C_{\alpha,\alpha}$-disubstituted (aminomethyl)phosphonates **1**, another class of new less well-known compounds.



1 **2** **3**

The procedure used for the synthesis of **1** is a generalization of the Kabachnik–Fields method described in the literature.[17] This method, in three steps, leads to **1** with good yields (Scheme).



Scheme

The first step is the preparation of the imines **4**, by reacting arylmagnesium bromide with benzonitrile. The yields obtained are between 60 and 98%. When the substituents (Ph- and Ar-) are different, two isomers *E* and *Z* can be characterized by NMR and GC/MS; for example, with compound **4b** (R' = 2-tolyl) the ratio *Z*/*E* is 40:60. The *E* isomer is the major product, likely for steric reasons.

The second step is the protection of the amine function with different groups leading to compounds **5**. These protective groups can be released from $C_{\alpha,\alpha}$-disubstituted (aminomethyl)phosphonates by basic and/or acidic conditions. This could be crucial for the biological activity of the $C_{\alpha,\alpha}$-disubstituted (aminomethyl)phosphonates and in particular for the stability of these compounds in biological media. Further, the benzyloxycarbonyl protective group can be specifically cleaved by hydrogenolysis, for synthetic purpose. The yields obtained for this protection step are between 41 and 95%.

The last step of the synthesis is an extension of the reactivity of phosphonate anions on imino electrophiles. This step gives **1** with good yields, between 35 and 96%. The *N*-protected $C_{\alpha,\alpha}$-disubstituted (aminomethyl)phosphonates have been characterized unambiguously by IR, ^{31}P, ^{1}H, ^{13}C NMR spectra, elemental analyses and mass spectrometry.

The results are presented in Table 1. One of the compounds **1g**, characteristic of this (aminomethyl)phosphonate family, has been analyzed by X-ray diffraction (Figure). A dimer, i.e. structure, induced by intermolecular

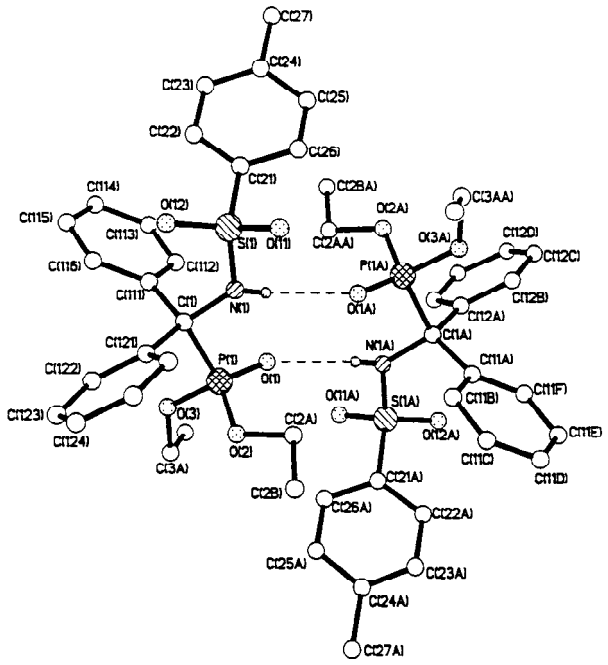
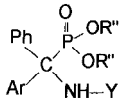


Figure. Dimer structure of compound **1g**

Table 1. Characteristics of the New $C_{\alpha,\alpha}$-Disubstituted (Aminomethyl)phosphonates **1**



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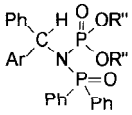

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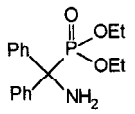
Entry	Ar	Y	R″	Yield (%) (3 steps)	mp (°C) (Solvent)	Molecular Formula[a] and MS (matrix)
1a	Ph	PhC(O)	Et	60, 85, 85	111–113 (heptane)	$C_{24}H_{26}NO_4P$, EI: M + H = 424
1b	*o*-tolyl	PhC(O)	Et	52, 41, 75	95 (heptane)	$C_{25}H_{28}NO_4P$, EI: M + H = 438
1c	1-naphthyl	PhC(O)	Et	98, 95, 90	172–173 (heptane)	$C_{28}H_{28}NO_4P$, FAB+ : (NBA) M + H = 474
1d	Ph	*o*-tolylC(O)	Et	77, 85, 60	103–104 (heptane)	$C_{25}H_{28}NO_4P$, FAB+ : (NBA) M + H = 438
1e	Ph	MeC(O)	Et	60, 54, 35	149–150 (heptane)	$C_{19}H_{24}NO_4P$, FAB+: (NBA) M + H = 362
1f	Ph	$PhCH_2OC(O)$	Et	60, 41, 52	112–114 (heptane)	$C_{25}H_{28}NO_5P$, FAB+: (NBA) M + H = 454
1g	Ph	Ts	Et	60, 81, 96	185–187 (MeOH/heptane)	$C_{24}H_{28}NO_5PS$, FAB+: (NBA) M + H = 474
6[b]	Ph	$Ph_2P(O)$[b]	Et	60, 86, 81	125–127 (heptane)	$C_{29}H_{31}NO_4P_2$, FAB+: (GT) M + H = 520
1h	Ph	PhC(O)	CH_2Ph	60, 81, 85	129–130 (heptane)	$C_{34}H_{30}NO_4P$, FAB+: (NBA) M + H = 548

[a] For all compounds, the elemental microanalytical data are satisfactory: C ± 0.35; H ± 0.27; N ± 0.38; O ± 0.37.

[b] This compound (the starting compound **5i** is obtained from the protection of compound **4** by chlorodiphenylphosphine oxide) is an isomer of the expected compound: surprisingly the phosphonate anion reacts on the nitrogen and not on the carbon atom (the structure has been proved by ^{13}C NMR and by hydrogenolysis affording diphenylmethane and diphosphorylated amine).

hydrogen bonding, can be observed: no significant intramolecular hydrogen bonds can be seen.

Deprotection studies were performed on three compounds **1a**, **1f** and **1h**, as examples, to obtain either free aminophosphonate, *N*-protected monoester or *N*-protected phosphonic acid.



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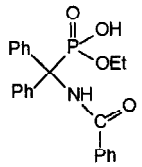

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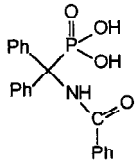

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In conclusion, we have developed a convenient and efficient three-step procedure for the preparation of *N*-protected or unprotected $C_{\alpha,\alpha}$-disubstituted (diarylaminomethyl)phosphonates which allows modulation of the substituents on the carbon in the α-position to the phosphorus, as well as the protective group on the amine and the phosphonate ester group.

All the experiments were carried out under N_2 with anhydrous solvents. Mps were determined with a Metler FP5 and a Wild Leitz 350 apparatus. The compounds are characterized by ^1H NMR (200.132 MHz), ^{13}C NMR (50.323 MHz) and ^{31}P NMR (50.323 MHz). Elemental analyses were performed by the "Service Central de Microanalyse du CNRS", in Montpellier. IR spectra were obtained using a Perkin–Elmer Spectrum 1000 spectrophotometer. MS were performed using FAB or EI (70 eV).

Imines 4; General Procedure:
To an arylmagnesium bromide solution prepared from magnesium (1.25 g, 55.4 mmol), a catalytic amount of iodine and aryl bromide (50 mmol) in Et_2O (50 mL), at 25 °C, was added benzonitrile(4.64 g, 45 mmol) in Et_2O (40 mL). The mixture was stirred for 3 h. Then anhyd MeOH (12 mL) was added dropwise, the precipitate was filtered and the filtrate concentrated. The crude oil was distilled under vacuum [bp: **4a** 111 °C; **4b** 127 °C/0.4 Torr]. A white colorless oil (yield: 50–98%) was isolated in a Schlenk tube and characterized by GC/MS.

Protection of Aryl Phenyl Imines; General Procedure:
To a solution of acyl chloride or sulfonyl chloride (30 mmol) in anhyd pyridine (150 mmol), the imine **4** (26.5 mmol) was added dropwise at 5–10 °C, and the mixture was heated to 65 °C for 2 h. A white solid precipitated, then the mixture was cooled to –5 °C and poured quickly into 1 N aq HCl (250 mL). The solid was filtered, dried under vacuum and then recrystallized (heptane). White crystals (yield: 41–95%) were isolated and characterized by elemental analysis (Table 2).

Table 2. Characteristics of Compounds **5**

Entry	Y	Ar	mp (°C) (Solvent)
5a, h	PhC(O)	Ph	117 (heptane)
5b	PhC(O)	*o*-tolyl	109–112 (heptane)
5c	PhC(O)	1-naphthyl	142–143 (heptane)
5d	*o*-tolylC(O)	Ph	70 (heptane)
5e	MeC(O)	Ph	81 (heptane)
5f	$PhCH_2OC(O)$	Ph	58–60 (heptane)
5g	Ts	Ph	106–108 (heptane)
5i	$Ph_2P(O)$	Ph	124–126 (heptane)

[a] All compounds gave satisfactory elemental microanalytical data: C ± 0.41; H ± 0.37; N ± 0.46.

***N*-Protected $C_{a,a}$-Disubstituted (Aminomethyl)phosphonates 1; General Procedure:**
Diethyl phosphite (0.82 mL, 6.37 mmol) in anhyd THF (15mL) was added, at –78 °C, to a suspension of NaH (6.37 mmol) in anhyd THF (15 mL). The mixture was held at –40 °C for 30 min, then, at –78 °C, electrophile **5** (7 mmol) was slowly added. The mixture was stirred for a further 12 h at 20 °C, then treated with 1 N aq HCl (4 mL) at 0 °C. The aqueous layer was extracted with Et_2O. After extraction, the or-

ganic layer was washed successively with aq Na_2HCO_3 and water until the pH was neutral, dried (Na_2SO_4) and concentrated. An oil was obtained, crystallizing after 12 h at 0°C. The white solid was recrystallized with an appropriate solvent to give white crystals. (yield: 35–96%).

1a:
IR (KBr): ν = 1678 vs (C=O), 1277–1246 s (P=O), 1056–1018 cm^{-1} vs (P–O).
^{31}P NMR ($CDCl_3$): δ = 22.96.
^1H NMR ($CDCl_3$): δ = 1.13 dt (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz; $^4J_{H-P}$ = 0.7 Hz) 3.9 m (4H, OCH_2).
^{13}C NMR ($CDCl_3$): δ = 16.21 d (2C, CH_3, $^3J_{C-P}$ = 5.7 Hz); 64.00 d (2C, OCH_2, $^2J_{C-P}$ = 7.6 Hz); 67.26 d (1C, C_α, $^1J_{C-P}$ = 145.5 Hz); 134.76 s (1C, C_i); 137.30 d (2C, C_i, $^2J_{C-P}$ = 4.5 Hz); 166.10 d (1C, C=O, $^3J_{C-P}$ = 11.3 Hz).

1b:
IR (KBr): ν = 1683 vs (C=O), 1265–1236 s (P=O), 1054–1022 cm^{-1} vs (P–O).
^{31}P NMR ($CDCl_3$): δ = 22.76.
^1H NMR ($CDCl_3$): δ = 1.14 and 1.20 dt (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz) 1.92 s (3H, CH_3 *ortho*); 3.83 and 4.01 dm (4H, OCH_2).
^{13}C NMR ($CDCl_3$): δ = 16.29 and 16.48 dd {2C, CH_3 (OEt), $^3J_{C-P}$ = 5.7 and 5.2 Hz}; 21.88 d (1C, CH_3, $^4J_{C-P}$ = 0.7 Hz); 63.67 and 63.78 dd (2C, OCH_2, $^2J_{C-P}$ = 7.4 and 7.9 Hz); 67.66 d (1C, C_α, $^1J_{C-P}$ = 151.0 Hz); 135.32 s (1C, C_i); 136.21 s (1C, C_i); 137.07 d (1C, C_i (Me), $^3J_{C-P}$ = 11.5 Hz); 138.54 d (1C, C_i, $^2J_{C-P}$ = 3.9 Hz); 165.15 d (1C, C=O, $^3J_{C-P}$ = 3.47 Hz).

1c:
IR (KBr): ν = 1681 vs (C=O), 1243–1232 s (P=O), 1053–1031 vs (P–O).
^{31}P NMR ($CDCl_3$): δ = 23.08.
^1H NMR ($CDCl_3$): δ = 1.11 and 1.15 dt (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz); 3.83 and 4.02 dm (4H, OCH_2).
^{13}C NMR ($CDCl_3$): δ = 16.29 and 16.33 dd (2C, CH_3, $^3J_{C-P}$ = 5.7 and 5.1 Hz); 63.73 and 64.02 dd (2C, OCH_2, $^2J_{C-P}$ = 7.4 and 7.9 Hz); 68.30 d (1C, C_α, $^1J_{C-P}$ = 149.8 Hz); 134.54 s (1C, C_i); 135.44 s (1C, C_i); 138.65 d (1C, C_i, $^2J_{C-P}$ = 3.5 Hz); 165.40 d (1C, C=O, $^3J_{C-P}$ = 4.5 Hz).

1d:
IR (KBr): ν = 1675 vs (C=O), 1231 vs (P=O), 1060–1031 vs (P–O).
^{31}P NMR ($CDCl_3$): δ = 22.84.
^1H NMR ($CDCl_3$): δ = 1.12 dt (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz; $^4J_{H-P}$ = 0.5 Hz); 2.43 s (3H, CH_3 *ortho*); 3.79 and 3.97 m (4H, OCH_2); 7.04 d (NH, $^3J_{H-P}$ = 10.55 Hz).
^{13}C NMR ($CDCl_3$): δ = 16.20 d (2C, CH_3, $^3J_{C-P}$ = 5.8 Hz); 19.87 s (1C, CH_3); 63.84 d (2C, OCH_2, $^2J_{C-P}$ = 7.7 Hz); 67.44 d (1C, C_α, $^1J_{C-P}$ = 147.0 Hz); 136.25 s (1C, C_i); 136.73 s (1C, C_i); 137.49 d (2C, C_i, $^2J_{C-P}$ = 4.3 Hz); 168.62 d (1C, C=O, $^3J_{C-P}$ = 10.3 Hz).

1e:
IR (KBr): ν = 1694 s (C=O), 1220 s (P=O), 1059–1031 cm^{-1} vs (P–O).
^{31}P NMR ($CDCl_3$): δ = 22.79.
^1H NMR ($CDCl_3$): δ = 1.08 dt (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz; $^4J_{H-P}$ = 0.5 Hz); 2.04 s (3H, CH_3); 3.67 to 3.96 m (4H, OCH_2); 6.78 d (NH, $^3J_{H-P}$ = 11.1 Hz).
^{13}C NMR ($CDCl_3$): δ = 16.13 d (2C, CH_3, $^3J_{C-P}$ = 5.8 Hz); 24.23 s (1C, CH_3); 63.85 d (2C, OCH_2, $^2J_{C-P}$ = 7.7 Hz); 67.13 d (1C, C_α, $^1J_{C-P}$ = 146.7 Hz); 137.48 d (2C, C_i, $^2J_{C-P}$ = 4.5 Hz); 169.00 d (1C, C=O, $^3J_{C-P}$ = 10.8 Hz).

1f:
IR (KBr): ν = 1721 vs (C=O), 1243–1214 s (P=O), 1049–1017 cm^{-1} vs (P–O).
^{31}P NMR (CD_3OD): δ = 22.26.
^1H NMR (CD_3OD): δ = 1.11 t (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz); 2.33 s (3H, CH_3); 3.73 to 3.94 m (4H, OCH_2); 4.99 s (2H, CH_2); 6.23 d (1H, NH, $^3J_{H-P}$ = 10.3 Hz); 7.26 to 7.39 m (11H, aromatics) 7.60 to 7.66 (4H, aromatics).
^{13}C NMR (CD_3OD): δ = 16.17 d (2C, CH_3, $^3J_{C-P}$ = 5.7 Hz); 63.87 d (2C, OCH_2, $^2J_{C-P}$ = 7.6 Hz); 66.42 d (1C, C_α, $^1J_{C-P}$ = 147.4 Hz); 66.83 s (1C, CH_2); 136.30 s (1C, C_i,); 137.59 d (2C, C_i, $^2J_{C-P}$ = 4.9 Hz).

1g:
IR (KBr): ν = 1369 m (S=O), 1227 vs (P=O), 1049–1025 cm^{-1} vs (P–O).
^{31}P NMR ($CDCl_3$): δ = 19.01.
^1H NMR ($CDCl_3$): δ = 1.14 t (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz); 2.33 s (3H, CH_3); 4.00 to 3.6 m (4H, OCH_2); 7.01 to 7.25 m (10H, aromatics); 7.49 to 7.54 (4H, aromatics).
^{13}C NMR ($CDCl_3$): δ = 16.54 d (2C, CH_3, $^3J_{C-P}$ = 5.8 Hz); 21.39 s (1C, CH_3); 65.52 d (2C, OCH_2, $^2J_{C-P}$ = 8.2 Hz); 70.19 d (1C, C_α, $^1J_{C-P}$ = 152.2 Hz); 137.75 d (2C, C_i, $^2J_{C-P}$ = 4.2 Hz); 141.33 d (1C, C_i, $^4J_{C-P}$ = 0.6 Hz); 143.72 s (1C, C_i).

1h:
IR (KBr): ν = 1679 s (C=O), 1249 vs (P=O), 1024–1005 cm^{-1} s (P–O).
^{31}P NMR ($CDCl_3$): δ = 23.66.
^1H NMR ($CDCl_3$): δ = 4.68 dd (2H, H_B, $^2J_{H-H}$ = 11.7 Hz; $^3J_{H-P}$ = 8.4 Hz); 4.90 dd (2H, H_A, $^2J_{H-H}$ = 11.7 Hz; $^3J_{H-P}$ = 7.4 Hz); 7.51 d (NH, $^3J_{H-P}$ = 7.3 Hz).
^{13}C NMR ($CDCl_3$): δ = 67.60 d (1C, C_α, $^1J_{C-P}$ = 147.1 Hz); 69.05 d (2C, OCH_2, $^2J_{C-P}$ = 7.6 Hz); 134.50 s (1C, C_i); 136.02 d (2C, C_i, $^3J_{C-P}$ = 6.1 Hz); 137.37 d (2C, C_i, $^2J_{C-P}$ = 4.2 Hz).

6:
IR (KBr): ν = 1255 s (P=O), 1199 s (P=O), 1016 s (P–O), 953 cm^{-1} s (P–N).
^{31}P NMR ($CDCl_3$): δ = 31.41 d [1P, $Ph_2P(O)$, $^2J_{P-P}$ = 13.6 Hz]; 3.86 d [1P, $(EtO)_2P(O)$, $^2J_{P-P}$ = 13.6 Hz].
^1H NMR ($CDCl_3$): δ = 6.33 dd (1H, CH, $^3J_{H-P}$ = 13.6 Hz; $^3J_{H-P}$ = 21.9 Hz); 7.19 to 7.41 m (12H, aromatics); 7.44 to 7.50 m (4H, aromatics).
^{13}C NMR ($CDCl_3$): δ = 64.75 s (1C); 132.14 d (1C, C_α, $^1J_{C-P}$ = 127.4 Hz).

Deprotection Studies; General Procedure:
Hydrogenolysis of Compound **1f**:
To a solution of **1f** (0.27 g, 0.6 mmol) in anhyd MeOH (25mL) was added Pd/C (0.02g). After consumption of the necessary hydrogen volume, the mixture was filtered on Celite and the filtrate concentrated to give **7** as an oil (yield: 95%).
IR (KBr): ν = 3391 m (NH_2), 1241 s (P=O), 1024 cm^{-1} s (P–O).
FAB+: (GT) M + H = 320.
^{31}P NMR ($CDCl_3$): δ = 25.38.
^1H ($CDCl_3$): δ = 1.16 t (6H, CH_3, $^3J_{H-H}$ = 7.1 Hz); 2.23 s (2H, NH_2); 3.92 m (4H, OCH_2, $^3J_{H-H}$ = 7.1 Hz); 7.27 m (6H, aromatics); 7.66 m (4H, aromatics).
^{13}C NMR ($CDCl_3$): δ = 16.32 d (2C, CH_3, $^3J_{C-P}$ = 5.4 Hz); 62.97 d (1C, C_α, $^1J_{C-P}$ = 147.8 Hz); 63.14 d (2C, OCH_2, $^2J_{C-P}$ = 7.4 Hz); 127.25 d (4C, C_m, $^4J_{C-P}$ = 1.2 Hz); 127.75 d (4C, C_o, $^3J_{C-P}$ = 6 Hz); 128.07 s (2C, C_p); 142.37 s (2C, C_i).

Hydrogenolysis of Compound **1h**:
Using the same procedure, **9** was obtained as a white solid [mp 283–285°C ($MeOH/H_2O$); yield: 100%].
IR (KBr) : ν = 3430 w (NH), 1655 s (C=O), 1260 s (P=O), 1060 cm^{-1} s (P–O).
FAB+: (GT) M + H = 368.
^{31}P NMR (CD_3OD): δ = 20.45.

^{1}H NMR (DMSO-d_6): δ = 7.33 m (6H, aromatics), 7.53 m (7H, aromatics), 7.89 d (2H, aromatics, $^3J_{H-H}$ = 7.2 Hz), 8.96 d (1H, N_2, $^3J_{H-P}$ = 11.7 Hz).
^{13}C NMR ($CDCl_3$): δ = 67.08 d (1C, C_α, $^1J_{C-P}$ = 135.9 Hz); 126.96 s (2C, C_p); 127.5 s (4C, C_m); 127.67 s (2C, C_m); 128.37 s (2C, C_o); 128.52 d (4C, C_o, $^3J_{C-P}$ = 4.68 Hz); 131.95 s (1C, C_p); 133.77 s (1C, C_i); 139.43 d (2C, C_i, $^2J_{C-P}$ = 2 Hz); 168.19 d (1C, C=O, $^3J_{C-P}$ = 5.9 Hz).

Hydrolysis of Compound **1a**:
Under weakly acidic conditions (pH 2.07, 40 °C, 334 h), hydrolysis of compound **1a** (0.1g, 0.24 mmol) in a solution of H_2O/EtOH/HCl (1mL), gave, after evaporation, **9** as a white solid (yield: 100%).
Under basic conditions (pH 14, 40 °C, 120 h), and after treatment with 1 N HCl, the hydrolysis of compound **1a** (0.1 g, 0.24 mmol) in H_2O/EtOH/NaOH (1 mL), gave, on evaporation, the monoester compound **8** [mp 167 °C (cyclohexane), yield: 60%].
IR (KBr): ν = 3430 w (NH), 1655 s (C=O), 1260 s (P=O), 1060 cm^{-1} s (P–O).
^{31}P NMR ($CDCl_3$): δ = 21.20.
^{1}H NMR ($CDCl_3$): δ = 1.02 t (3H, CH_3, $^3J_{H-H}$ = 7.1 Hz); 3.7 dq (2H, OCH_2, $^3J_{H-H}$ = 7.3 Hz, $^3J_{H-P}$ = 7.6 Hz); 7.45 m (13H, aromatics); 7.83 m (2H, aromatics).
^{13}C NMR ($CDCl_3$): δ = 16.31 d (1C, CH_3, $^3J_{C-P}$ = 5.9 Hz); 63.40 d (1C, CH_2, $^2J_{C-P}$ = 7.1 Hz); 67.83 d (1C, C_α, $^1J_{C-P}$ = 140.7 Hz); 127.36 s (2C, C_p); 128.21 s (4C, C_m); 128.31 s (2C, C_m); 128.51 s (4C, C_o); 128.89 s (2C, C_o), 132.57 s (1C, C_p); 133.24 s (1C, C_i); 138.90 s (2C, C_i); 168.85 d (1C, C=O, $^3J_{C-P}$ = 3.1 Hz).

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