A GENERAL SYNTHETIC APPROACH TO α-HYDROXY PHOSPHORYL COMPOUNDS

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A general synthetic way for the preparation of a large variety of α-hydroxy phosphoryl compounds is here reported. In our approach, trialkyl phosphite is added in equimolar amount, at room temperature and under strong acidic conditions (HCl gas), to the corresponding carbonyl compound dissolved in anhydrous dioxane. The reaction is quite exothermic and cooling is often needed; 10–15 min reaction time is sufficient in order to assure almost quantitative yields in the desired product, which can be easily isolated as a white pure solid by concentration of the reaction mixture. The reaction works in an excellent way with all kind of aliphatic, aromatic and heteroaromatic aldehydes. The α-hydroxy phosphonates obtained were fully characterized by ^{1}H- and ^{31}P-NMR, by FAB-MS and IR spectroscopy. When *o*-carboxybenzaldehyde was used as a reagent, cyclic dialkyl phthalide-3-phosphonates were obtained in very good yields (≥90%).

INTRODUCTION

α-Hydroxy phosphoryl compounds (phosphonates and phosphonic acids) are compounds of significant biological activity[1,2] and have been shown to inhibit enzymes such as renin[3], EPSP synthase[4] and HIV protease[5]. In addition, α-hydroxyphosphonates are useful intermediates in the synthesis of other α- and γ-substituted phosphonates and phosphonic acids[6,7].

So far, as can be inferred from a literature survey, these compounds have been prepared by thermal non catalyzed addition[8–11] or base catalyzed addition[12–20]

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of dialkyl phosphite to aldehydes or even by the reaction of dialkyl phosphite with aldehydes or ketones in the presence of potassium or cesium fluorides, without solvent[21].

Furthermore, Burkhouse and Zimmer[22] have found that arylaldehyde diethyl acetals react with triethyl phosphite in the presence of $BF_3 \cdot Et_2O$ cleanly to yield the desired diethyl 1-alkoxy-1-arylmethane phosphonates, indicating that an acetalic carbon atom can undergo nucleophilic attack from trialkylphosphite in the presence of a Lewis acid.
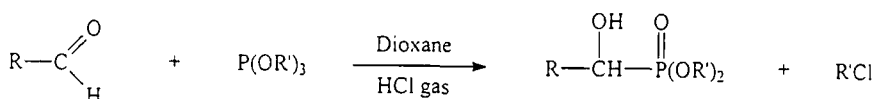
By means of the Pudovik reaction[17] using chiral bases such as quinine, α-hydroxy phosphonate esters with excellent enantiomeric enrichment (85%) were obtained by Wymber et al.[23]; alternatively, other authors[24,25], recently performed the addition of dialkyl phosphites to aldehydes catalyzed by a lanthanum or titanium (R)-binaphthoxide complex in order to prepare (S)-hydroxy phosphonates with modest enantio selectivity, whereas the oxaborolidine catalyzed reduction of α-keto phosphonates yielded α-hydroxyarylmethyl phosphonates with moderate enantioselectivity[26].

However, depending on the starting carbonyl derivatives, all these synthetic methods suffer of some disadvantages: the yields are not always so good as expected and mixtures of products are sometime obtained[27–29]. Alkaline solutions often are reported to cleave the α-hydroxyphosphonates to the starting carbonyl compounds[8] or rearrange them to the corresponding phosphates[27,29], specially when the carbonyl group is activated by electron withdrawing groups in α-position; furthermore, when α-haloketones are employed as starting materials epoxyalkane phosphonates and unsaturated derivatives are usually obtained[12,14,15,27]. Therefore, on the basis of the foregoing considerations, we wanted to find a more convenient and general synthetic approach for preparing variously substituted α-hydroxy phosphonic acid esters in good yield.

This paper is devoted to this task.

RESULT AND DISCUSSIONS

In our synthesis, following previous literature[30,31] reports in which 1,2-dihydroxy-1,2-bisphosphonylethanes and 1,4-bis(dialkoxyphosphinyl)benzene were obtained by reacting glyoxal[30] or 1,4-benzenedicarboxaldehyde[31] respectively with phosphorus acid triesters, trialkyl phosphite was added, at room temperature, under strong acidic conditions to the corresponding carbonyl compound (R = alkyl, aryl, heteroaryl) dissolved in anhydrous dioxane:

$$R-C\overset{\displaystyle O}{\underset{\displaystyle H}{\Big\langle}} \quad + \quad P(OR')_3 \quad \xrightarrow[\text{HCl gas}]{\text{Dioxane}} \quad R-\overset{OH}{\underset{}{C}}H-\overset{O}{\underset{}{P}}(OR')_2 \quad + \quad R'Cl$$

The reaction is quite exothermic and cooling is often needed; 10–15 min. reaction time is sufficient in order to assure almost quantitative yields of the desired product, which can be easily isolated as a white pure solid by concentration of the reaction mixture. Physical properties of the synthesized α-hydroxy phosphonates are reported in Tables I–III. The solvent's choice is very crucial: in fact, it is imperative that it must be inert towards the starting aldehyde and should dissolve easily the reactants and the final products, including large quantities of gaseous HCl. Chemical considerations, coupled with the necessity of using strictly anhydrous conditions, led us to select dioxane as the solvent for our reaction. In order to improve yields HCl gas must be used in great excess with respect to stoichiometry, indicating that it is participating as a reagent in our syntheses; in fact, reactions performed in presence of small quantities of HCl gave very low yields and unreacted reagents were recovered. In order to avoid hydrolysis of the phosphonic esters, strictly anhydrous conditions must be employed.

The addition reaction is quite general and it works well with all kinds of aliphatic, aromatic and heteroaromatic aldehydes. The α-hydroxy phosphonates so obtained are white, crystalline compounds and their complete spectroscopic characteristics (^{1}H-NMR, ^{31}P-NMR, FAB-MS, IR) are reported in the experimental part.

The most important features are as follow:

i) The methyne proton of our hydroxy-phosphonates resonates in CDCl$_3$ as solvent as a doublet with a negative geminal coupling constant $^2J_{PH}$ in the range (9–12) Hz, which is much smaller when compared with the same coupling observed in several 1-amino-phosphonates ($^2J_{PH}$ = minus 18–24 Hz)[32]. In DMSO-d$_6$ as solvent, additional coupling of the methyne hydrogen with the oxydrilic proton generates an ABX system as shown in Figure 1 ($^2J_{PH}$ = −(12–15) Hz and $^3J_{HH}$ = 4–6 Hz). The oxydrilic proton resonates as a doublet of doublet with a coupling constant $^3J_{PH}$ in the range of 10–16 Hz.

ii) The alkyl protons of the alkoxy groups are also very diagnostic: due to the proximity of the chiral center, the two P(OR')$_2$ groups reside in diastereotopic environment and therefore two distint doublets are observed for the methoxy groups and two distinct triplets for the ethoxy groups. The difference in chemical shifts of these signals is a function of the diamagnetic anisotropy of the residue attached to the -CH-P(OR')$_2$ moiety[32].
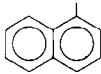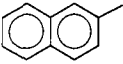
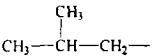TABLE I   Preparation of α-Hydroxy Phosphonates of General Formula

$$X_n \overset{OH}{\underset{}{\bigcirc}} - \underset{CH}{\overset{}{}} - \underset{}{\overset{O}{P}} \overset{OR}{\underset{OR}{}}$$

N.	X_n	R	Yield %	m.p. (°C)	$\delta_{PCH}{}^a$ $(^2J_{PH}$, Hz)	$\delta_{P(OR)_2}{}^b$
					¹H-NMR δ (CDCl₃, TMS)	
1	H	C₂H₅	91	78–80ᶜ	5.02 (10.54)	1.21, 1.26
2	2-Cl	C₂H₅	78	76–78	5.58 (11.50)	1.21, 1.30
3	3-Cl	C₂H₅	96	53–54	5.01 (11.29)	1.24, 1.28
4	4-Cl	C₂H₅	76	70–72	5.00 (10.93)	1.23, 1.37
5	4-Cl	CH₃	74	87–89	5.04 (11.02)	3.70, 3.71
6	2-OCH₃	CH₃	85	86–88	5.48 (11.80)	3.64, 3.76
7	3-OCH₃	C₂H₅	84	oil	5.00 (11.20)	1.22, 1.27
8	3-OCH₃	CH₃	84	73–75	5.01 (10.93)	3.68, 3.70
9	4-OCH₃	C₂H₅	88	118–120	4.95 (10.09)	1.22, 1.27
10	2-OH	CH₃	86	oil	5.19 (12.36)	3.67, 3.74
11	2-OH	C₂H₅	85	oil	5.15 (12.49)	1.23, 1.27
12	3-OH	C₂H₅	93	101–102	4.93 (12.06)	1.14, 1.24
13	4-OH	C₂H₅	92	180–182	4.78 (12.26)ᵈ	1.11, 1.17
14	3-CH₃	C₂H₅	88	oil	4.97 (10.77)	1.21, 1.25
15	4-CH₃	C₂H₅	74	98–100	4.97 (10.43)	1.22, 1.27
16	4-F	C₂H₅	77	57–59	5.01 (10.40)	1.23, 1.27
17	4-NO₂ᵉ	C₂H₅	40	82–84	5.19 (12.39)	1.27, 1.30
18	3-NO₂	C₂H₅	83	88–90	5.18 (11.40)	1.27, 1.31
19	2-OCOPh	C₂H₅	87	115–117	5.37 (11.87)	1.16, 1.18
20	4-N(CH₃)₂	C₂H₅	70	81–83	4.89 (9.76)ᶠ	1.22, 1.29
21	4-COOH	C₂H₅	81	163–164	5.07 (14.57)ᵈ,ᶠ	1.16, 1.17
22	4-CHO	CH₃	73	90–92	5.08 (12.40)	3.64, 3.65
23	2,4-Cl₂	C₂H₅	93	66–68	5.51 (11.24)	1.24, 1.30
24	2,3-Cl₂	C₂H₅	73	68–70	5.61 (11.67)	1.22, 1.30
25	2,6-Cl₂	C₂H₅	70	95–96	5.84 (19.60)	1.17, 1.38
26	2,4-(OCH₃)₂	C₂H₅	63	83–84	5.34 (11.30)	1.21, 1.31
27	2,3-(OCH₃)₂	C₂H₅	92	77–78	5.38 (12.17)	1.19, 1.33
28	3-OCH₃, 4-OH	C₂H₅	90	88–90	4.92 (10.38)	1.21, 1.28
29	2,3,4-(OCH₃)₃	C₂H₅	93	85–86	5.28 (11.63)	1.20, 1.33
30	3,4,5-(OCH₃)₃	C₂H₅	98	90–92	4.96 (10.82)	1.25, 1.30
31	3,5-(OCH₃)₂, 4-OCOCH₃	C₂H₅	84	143–144	4.96 (11.02)	1.25, 1.28

ᵃDoublet, unless otherwise noticed; the $^2J_{PH}$ values are all negative.
ᵇTwo methyl doublets ($^3J_{PH}$ = 10 Hz) for R = CH₃; two methyl triplets ($^2J_{HH}$ = 7 Hz) for R = C₂H₅.
ᶜReference 8 reports m.p. 83°C.
ᵈMeasured in DMSO-d₆. ᵉObtained through Pudovik's reaction[17].
ᶠDoublet of doublet.

iii) The $^{31}P\{^1H\}$-NMR spectra of our mono-α-hydroxy-phosphonates show singlets in the region of δ = 20–25 ppm, a value consistent with the presence of phosphonic acid diester moiety[32] and very much far apart from the value expected for the corresponding phosphates (δ ≅ 0 ppm).

TABLE II Preparation of α-Hydroxy Phosphonates of General Formula

$$R^1\text{—}\underset{\underset{OH}{|}}{CH}\text{—}\underset{\underset{OR}{}}{\overset{\overset{O}{\|}}{P}}\overset{OR}{}$$

N.	R^1	R	Yield %	m.p. (°C)	^{1}H-NMR δ (CDCl$_3$, TMS)	
					$\delta_{PCH}{}^a$ ($^2J_{PH}$, Hz)	$\delta_{PCH}{}^a$
1		C$_2$H$_5$	81	117–118	5.87 (11.52)	1.04, 1.19
2		C$_2$H$_5$	85	89–90	5.20 (11.19)	1.19, 125
3		C$_2$H$_5$	77	30–32	5.24 (10.49)	1.26, 1.30
4		C$_2$H$_5$	85	oil	5.22 (12.08)	1.21, 1.35
5		C$_2$H$_5$	88	oil	3.67 (6.39)^c	1.34
6	CH$_3$—CH—CH$_2$— (CH$_3$)	CH$_3$	90	50–52^d	4.00^e	3.81, 3.82
7^f		CH$_3$	53	197–198	3.22 (8.89)^c	3.41

^{a}Doublet, unless otherwise noticed; the $^2J_{PH}$ values are all negative.
^{b}Two methyl doublets ($^3J_{PH}$ = 10 Hz) for R = CH$_3$; two methyl triplets ($^2J_{HH}$ = 7 Hz) for R = C$_2$H$_5$.
^{c}Doublet of doublet.
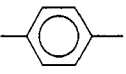^{d}Reference 20 reports m.p. 52–54°C.
^{e}Multiplet.
^{f}Phosphonic acid mono-methyl ester.

The ^{31}P-NMR spectra were also extremely useful in determining the diastereomeric purity of bis-α-hydroxyphosphonates, which, by virtue of possessing two identical chiral centers, can exist as two diastereomeric pairs (meso and racemic).

In fact, although the ^{1}H-NMR spectra of compound **1** of Table **III** shows only one signal for the methyne protons, which could indicate the presence of only one diastereomer formed in the addition reaction, on the contrary the ^{31}P{^{1}H}-NMR spectrum reveals indeed the presence of two singlets at δ = 22.866 and δ = 23.611 ppm, in the ratio 3:2 indicating that our reaction was not at all stereoselective (Figure **2**).

TABLE III   Preparation of bis-α-Hydroxy Phosphonates of General Formula:

$$RO \underset{RO}{\overset{O}{\underset{}{}}} P \overset{OH}{\underset{}{CH}} \text{—} \bigcirc \text{—} \overset{OH}{\underset{}{CH}} \text{—} P \underset{OR}{\overset{O}{\overset{OR}{}}}$$

N.		R	Yield%	m.p. (°C)	^{1}H-NMR δ (DMSO-d_6, TMS)	
					$\delta_{PCH}{}^a$ ($^2J_{PH}$, Hz)	$\delta_{P(OR)_2}{}^b$
1	—◯—	CH_3	89	204–206	5.00 (12.20)^c	3.57, 3.62
2	—◯—	C_2H_5	85	202–204^d	4.92 (12.22)^c	1.13, 1.17
3	◯	CH_3	87	185–186	5.00 (12.75)	3.57, 3.62

^{a}Doublet. unless otherwise noticed; the $^2J_{PH}$ values are all negative.
^{b}Two methyl doublets ($^3J_{PH}$ = 10 Hz) for R = CH_3; two methyl triplets ($^2J_{HH}$ = 7 Hz) for R = C_2H_5.
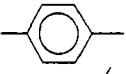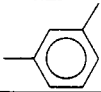^{c}Doublet of doublet.
^{d}Reference 32 reports m.p. 216–218°C after recrystallization from DMSO.

Plotting the methyne proton chemical shifts of our para-substituted α-hydroxy-phosphonates against Hammett's σ_p values[33] a linear correlation was observed (Figure 3); in particular, electronwithdrawing substituents play a deshielding effect and thus the methyne protons are moved to lower fields with respect to the unsubstituted cognate. For the same compounds, opposite trend was noticed looking at the ^{31}P chemical shifts, although a linear correlation still exist when δ values are plotted against the Hammett's σ_p (Figure 4). The interpretation of such an effect is connected with a change in the bond order dπ–pπ[34].
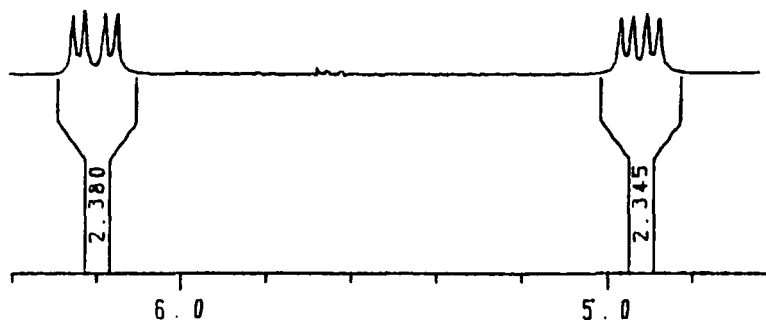
FIGURE 1   Typical ABX system for α-hydroxy phosphonates in DMSO-d_6. Ranges of vicinal P-CH-OH coupling in Hz: $^2J_{PH}$ = −(9–15); $^3J_{HH}$ = (4–6); $^3J_{PH}$ = (10–15).
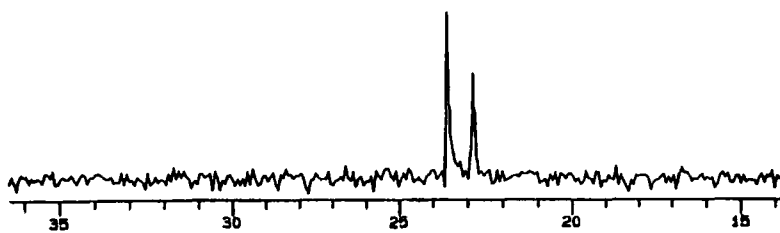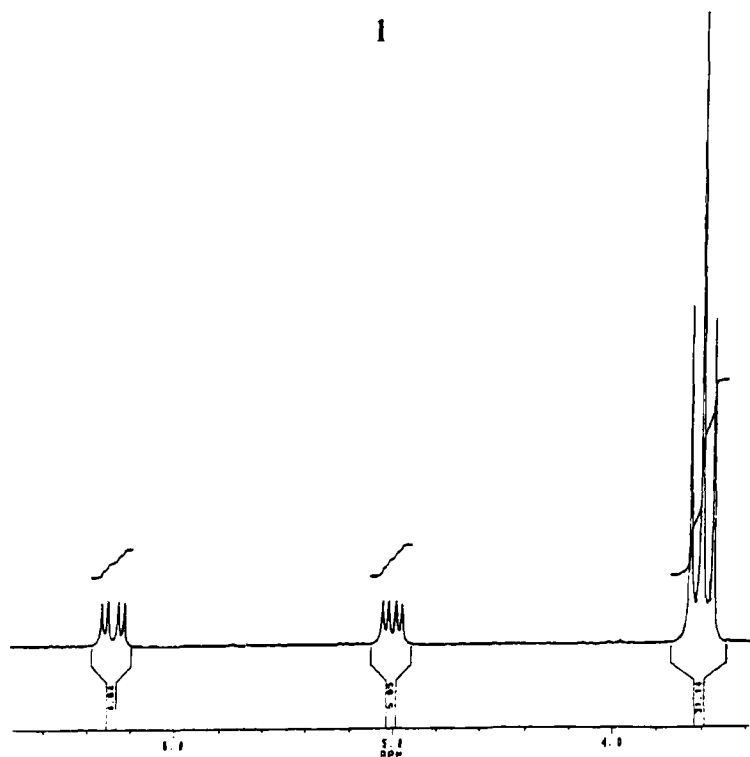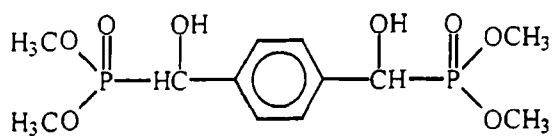
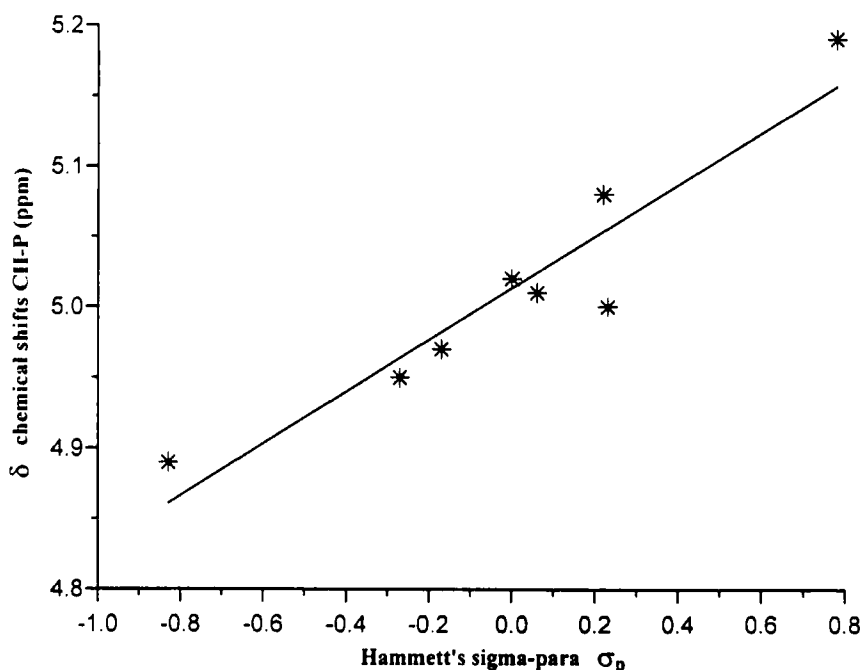FIGURE 2 Top: ^{1}H-NMR in DMSO-d_6 of compound **1** (Table **III**); bottom: ^{31}P{^{1}H}-NMR in CDCl$_3$ of the some compound.

FIGURE 3   Plot of ^{1}H-NMR (in CDCl$_3$ solution) chemical shifts of the CHP proton of compounds 1, 4, 9, 15–17, 20, 22 of Table I versus Hammett's σ_p values (n = 7; δ^1H = 5.02 + 0.19σ_p; R-square 0.95).

The characterization of our synthesized compounds was also performed by FAB-MS techniques. The main and general conclusions are as follows:

The quasi-molecular peak at m/z = [M + H]$^+$ was always observed, and generally it represents the base peak of our spectrum. Other intense signals always present were the peak at m/z = [M + H − 18]$^+$ generated by a loss of water molecule; and peaks due to the loss of one molecule of HP(O)(OC$_2$H$_5$)$_2$ for the diethyl esters or one molecule of HP(O)(OCH$_3$)$_2$ for the dimethyl esters, *i.e.* fragments at m/z = [M + H − 138]$^+$ and m/z = [M + H − 110]$^+$, respectively. In all MS spectra peaks due to the ion at m/z [M + 23]$^+$ were also observed indicating that our phosphonates possess a great tendency to interact with the Na$^+$ cation. More interesting, cluster peaks due to the ions at m/z [xM + H]$^+$, where x varies between 2 and 5 were always observed and their intensities are quite remarkable, indicating how easily such molecules yield cluster structures also in the gas phase, as already observed for other similar compounds[32] (Figure 5).
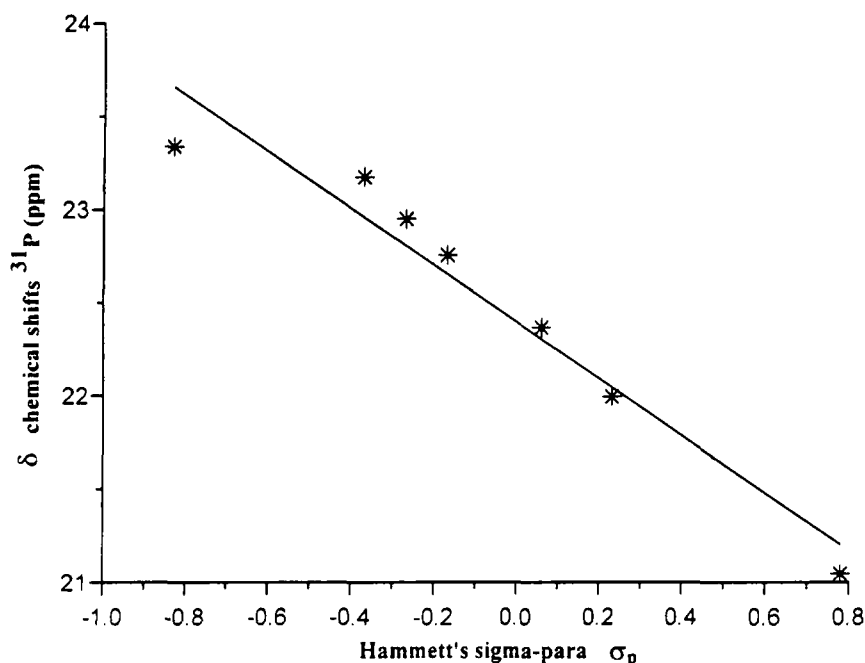
FIGURE 4 Plot of ^{31}P{^{1}H}-NMR (in DMF solution) chemical shifts of the compounds **4, 9, 13, 15–17, 20** of Table I versus Hammett's σ_p (n = 7, δ^{31}P = 22.40 − 1.52 σ_p; R-square 0.96).

The IR spectroscopy showed, as expected, a strong band in the region at 3500-3100 cm^{-1} due to the OH stretching, a band relative to the P=O stretching was evident as doublet in the region around 1250 cm^{-1}, whereas the stretching band of the POR group was noticed as a doublet in the region centered at 1050 cm^{-1}.

Interesting enough, when o-carboxybenzaldehyde was used as a reagent, cyclic dialkyl phthalide-3-phosphonates (**I**) were obtained in excellent yields (90%).
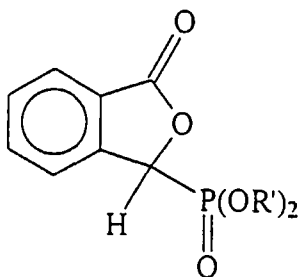
Ia R' = Me

Ib R' = Et

Ic R' = *i*-Pr
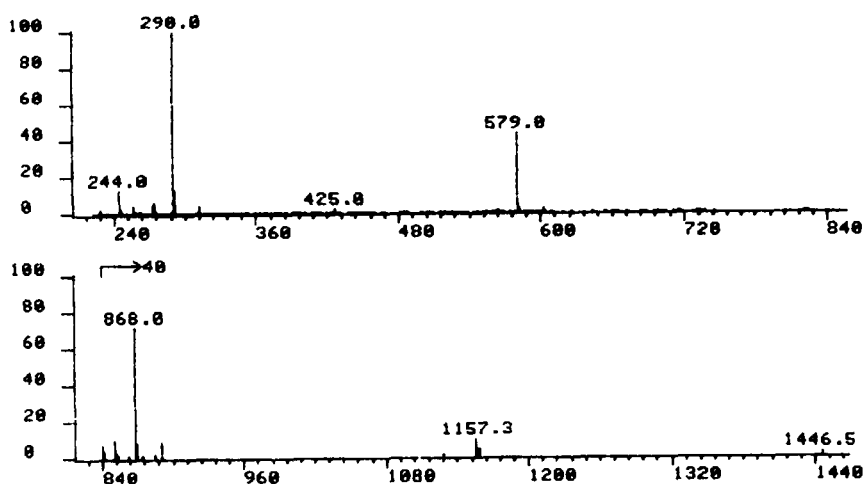
FIGURE 5   FAB-MS spectrum of compound **18** Table **I** as recorded and normalized with respect to the peak at 290 D $[M + H]^+$. 2-Nitrobenzylalcohol was used as matrix.

Compounds **Ia–Ic**, although already described in the literature[35,1] were further characterized by ^{1}H-NMR, MS-FAB and IR spectroscopy (see experimental section).

In any case the major diagnostic physical characteristic are as follow:

i) The ^{1}H-NMR spectra of **Ia–Ic** do not show any evidence of the presence of the -OH group, contrary to what observed for the *para*-carboxy isomers.

ii) The MS-FAB technique reveals molecular peaks which differ by 18 units (one H_2O molecule) from the corresponding *para*-carboxy derivatives.

iii) By IR spectroscopy the main differences between **Ia–Ic** and the isomeric *para* derivatives are the absence of the OH stretching band at $\sqrt{} = 3300$ cm^{-1} whereas stretching frequencies of the carbonyl group $\sqrt{}_{C=O}$ are quite different from those of the *para*-isomers and diagnostic for a lactone structure and consistent with literature data[35].

Thus, with our reaction, which probably proceeds according to the pathway described in Scheme **I**, we were able to synthesize in excellent yields lactones bearing the phosphoryl group, which in turn could be of interest for the synthesis of novel phosphonates molecules and of phosphorus containing polycondensates.
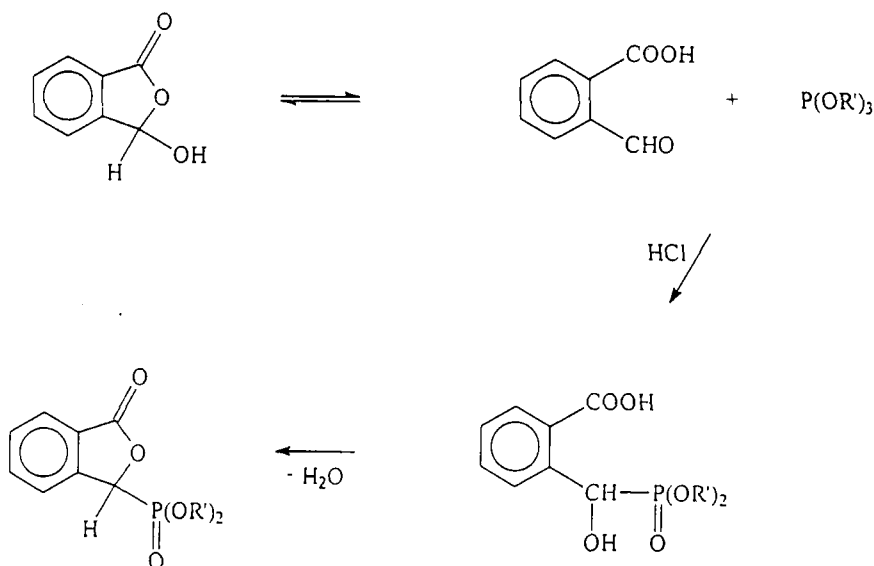
SCHEME I.

EXPERIMENTAL

Aldehydes, trialkyl phosphites as well as solvents used were high purity commercial products from Aldrich. All syntheses were performed under a dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6, with TMS as an internal standard using a Bruker AC-200 instrument operating at 200 MHz. ^{31}P-NMR were recorded in DMF at the Institute of Organic Chemistry of Ukrainian Academy of Sciences at Kiev with a Varian VXR spectrometer operating at 121 MHz using 85% H_3PO_4 as external reference, unless otherwise noticed.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system. 3-Nitrobenzylalcohol was used as matrix. IR spectra were recorded on a Perkin-Elmer 1725X FT-IR spectrometer on KBr pellets. Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

General Procedure for Preparation of α-Hydroxy Phosphoryl Compounds

In a four-necked flask, equipped with a magnetic stirred, gas inlet, thermometer, a condenser with a nitrogen inlet and a gas trap, 10 mmol of the aldehyde precursor were dissolved in 15–25 ml of dry 1,4-dioxane and then was slowly added under nitrogen atmosphere at room temperature an equimolar amount of

trialkyl phosphite. To this stirred solution hydrogen chloride was bubbled for 10–15 min. and the temperature of the reaction was maintained below 25–30°C by external cooling. The hydrogen chloride was stopped when it did not raise anymore the bath temperature and when no more unreacted aldehyde was observed by TLC on silica gel. The reaction mixture was then stirred at room temperature for an additional hour, the solvent was removed under reduced pressure (except for compounds where a large amount of white solid separated during the reaction period) and the tick oil obtained was diluted with 20 ml of diethyl ether containing few drops of ethyl acetate, in order to allow it to crystallize in a white mass.

Spectroscopic Characteristics of Compounds Listed in Table I

1 ^{1}H-NMR (CDCl$_3$, TMS): 7.49 (m, 2H, ArH), 7.34 (m, 3H, ArH), 5.02 (d, 1H, CHP, $^2J_{PH}$ = −10.54 Hz), 4.10-3.90 (m, 4H, OCH$_2$), 1.26 (t, 3H, CH$_2$CH$_3$), 1.21 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (CDCl$_3$, 85% H$_3$PO$_4$): 24.15.

2 ^{1}H-NMR (CDCl$_3$, TMS): 7.77 (m, 1H, ArH), 7.28 (m, 3H, ArH), 5.58 (d, 1H, CHP, $^2J_{PH}$ = −11.50 Hz), 4.20-3.80 (m, 4H, OCH$_2$), 1.30 (t, 3H, CH$_2$CH$_3$), 1.21 (t, 3H, CH$_2$CH$_3$).

3 ^{1}H-NMR (CDCl$_3$, TMS): 7.51 (s, 1H, ArH), 7.35 (m, 1H, ArH), 7.27 (m, 2H, ArH), 5.01 (d, 1H, CHP, $^2J_{PH}$ = −11.29 Hz), 4.20–4.00 (m, 4H, OCH$_2$), 1.28 (t, 3H, CH$_2$CH$_3$), 1.24 (t, 3H, CH$_2$CH$_3$).

4 ^{1}H-NMR (CDCl$_3$, TMS): 7.43 (m, 2H, ArH), 7.32 (m, 2H, ArH), 5.00 (d, 1H, CHP, $^2J_{PH}$ = −10.93 Hz), 4.20–4.00 (m, 4H, OCH$_2$), 1.27 (t, 3H, CH$_2$CH$_3$), 1.23 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (DMF, 85% H$_3$PO$_4$): 21.99.

5 ^{1}H-NMR (CDCl$_3$, TMS): 7.42 (m, 2H, ArH), 7.33 (m, 2H, ArH), 5.04 (d, 1H, CHP, $^2J_{PH}$ = −11.02 Hz), 4.44 (brd s, 1H, OH, exchange with D$_2$O), 3.71 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.55 Hz), 3.70 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.37 Hz).

6 ^{1}H-NMR (CDCl$_3$, TMS): 7.56 (m, 1H, ArH), 7.30 (m, 1H, ArH), 7.00 (t, 1H, ArH), 6.90 (d, 1H, ArH), 5.48 (d, 1H, CHP, $^2J_{PH}$ = −11.80 Hz), 3.86 (s, 3H, ArOCH$_3$), 3.76 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.57 Hz), 3.64 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.38 Hz); ^{31}P{^{1}H}-NMR (CDCl$_3$, 85% H$_3$PO$_4$): 24.91.

7 ^{1}H-NMR (CDCl$_3$, TMS): 7.25 (m, 1H, ArH), 7.05 (m, 2H, ArH), 6.84 (m, 1H, ArH), 5.00 (d, 1H, CHP, $^2J_{PH}$ = −11.20 Hz), 4.51 (brd s, 1H, OH, exchange with D$_2$O), 4.1-3.9 (m, 4H, OCH$_2$), 3.80 (s, 3H, ArOCH$_3$), 1.27 (t, 3H, CH$_2$CH$_3$), 1.22 (t, 3H, CH$_2$CH$_3$).

8 ^{1}H-NMR (CDCl$_3$, TMS): 7.26 (m, 1H, ArH), 7.04 (m, 2H, ArH), 6.85 (m, 1H, ArH), 5.01 (d, 1H, CHP, $^2J_{PH}$ = −10.93 Hz), 3.81 (s, 3H, ArOCH$_3$), 3.70 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.50 Hz), 3.68 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.20 Hz).

9 ^{1}H-NMR (CDCl$_3$, TMS): 7.41 (d, 2H, ArH), 6.89 (d, 2H, ArH), 4.95 (d, 1H, CHP, $^2J_{PH}$ = −10.09 Hz), 4.10–3.90 (m, 4H, OCH$_2$), 3.80 (s, 3H, ArOCH$_3$), 1.27 (t, 3H, CH$_2$CH$_3$), 1.22 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (DMF, 85% H$_3$PO$_4$): 22.95; FAB-MS: [M + H − H$_2$O]$^+$ m/z = 257 (base peak), [M + H]$^+$ m/z = 275, [2M + H]$^+$ m/z = 549, [M + Na]$^+$ m/z = 297, [3M + H]$^+$ m/z = 823.

10 ^{1}H-NMR (CDCl$_3$, TMS): 7.17 (m, 2H, ArH), 6.90 (m, 2H, ArH), 5.19 (d, 1H, CHP, $^2J_{PH}$ = −12.36 Hz), 3.74 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.33 Hz), 3.67 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.39 Hz).

11 ^{1}H-NMR (CDCl$_3$, TMS): 7.16 (m, 2H, ArH), 6.89 (m, 2H, ArH), 5.15 (d, 1H, CHP, $^2J_{PH}$ = −12.49 Hz), 4.10–3.90 (m, 4H, OCH$_2$), 1.27 (t, 3H, CH$_2$CH$_3$), 1.23 (t, 3H, CH$_2$CH$_3$).

12 ^{1}H-NMR (CDCl$_3$, TMS): 7.26 (s, 1H, ArH), 7.16 (m, 1H, ArH), 6.83 (m, 2H, ArH), 4.93 (d, 1H, CHP, $^2J_{PH}$ = −12.06 Hz), 4.10–3.70 (m, 4H, OCH$_2$), 1.24 (t, 3H, CH$_2$CH$_3$), 1.14 (t, 3H, CH$_2$CH$_3$).

13 ^{1}H-NMR (DMSO-d$_6$, TMS): 9.40 (s, 1H, ArOH), 7.22 (d, 2H, ArH), 6.71 (d, 2H, ArH), 6.00 (brd s, 1H, OH, exchange with D$_2$O), 4.78 (d, 1H, CHP, $^2J_{PH}$ = −12.26 Hz), 4.1–3.8 (m, 4H, OCH$_2$), 1.17 (t, 3H, CH$_2$CH$_3$), 1.11 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (DMF, 85% H$_3$PO$_4$): 23.17; FAB-MS: [M + H − H$_2$O]$^+$ m/z = 243 (base peak), [M + H]$^+$ m/z = 261, [2M + H]$^+$ m/z = 521.

14 ^{1}H-NMR (CDCl$_3$, TMS): 7.25 (m, 3H, ArH), 7.11 (m, 1H, ArH), 4.97 (d, 1H, CHP, $^2J_{PH}$ = −10.77 Hz), 4.10–3.90 (m, 4H, OCH$_2$), 2.35 (s, 3H, ArCH$_3$), 1.25 (t, 3H, CH$_2$CH$_3$), 1.21 (t, 3H, CH$_2$CH$_3$).

15 ^{1}H-NMR (CDCl$_3$, TMS): 7.37 (d, 2H, ArH), 7.16 (d, 2H, ArH), 4.97 (d, 1H, CHP, $^2J_{PH}$ = −10.43 Hz), 4.20–3.90 (m, 4H, OCH$_2$), 2.34 (s, 3H, ArCH$_3$), 1.27 (t, 3H, CH$_2$CH$_3$), 1.22 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (DMF, 85% H$_3$PO$_4$): 22.75.

16 ^{1}H-NMR (CDCl$_3$, TMS): 7.47 (m, 2H, ArH), 7.05 (m, 2H, ArH), 5.01 (d, 1H, CHP, $^2J_{PH}$ = −10.40 Hz), 4.20–3.90 (m, 4H, OCH$_2$), 1.27 (t, 3H, CH$_2$CH$_3$), 1.23 (t, 3H, CH$_2$CH$_3$).

17 ^{1}H-NMR (CDCl$_3$, TMS): 8.23 (d, 2H, ArH), 7.68 (d, 2H, ArH), 5.19 (d, 1H, CHP, $^2J_{PH}$ = −12.39 Hz), 4.20–4.00 (m, 4H, OCH$_2$), 1.30 (t, 3H, CH$_2$CH$_3$), 1.27 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (DMF, 85% H$_3$PO$_4$): 21.1; ^{13}C{^{1}H}-NMR (CDCl$_3$): 147.49, 144.34, 127.69, 123.22, 70.03 (d, $^1J_{PC}$ = 158.30 Hz), 63.94 (d, $^2J_{PC}$ = 7.29 Hz), 63.25 (d, $^2J_{PC}$ = 7.69 Hz), 16.36.

18 ^{1}H-NMR (CDCl$_3$, TMS): 8.42 (s, 1H, ArH), 8.16 (d, 1H, ArH), 7.82 (d, 1H, ArH), 7.53 (t, 1H, ArH), 5.18 (d, 1H, CHP, $^2J_{PH}$ = −11.40 Hz), 4.2–4.0 (m, 4H, OCH$_2$), 1.31 (t, 3H, CH$_2$CH$_3$), 1.27 (t, 3H, CH$_2$CH$_3$); FAB-MS: [M + H]$^+$ m/z = 290 (base peak), [2M + H]$^+$ m/z = 579, [M + H − NO$_2$]$^+$ m/z = 244, [3M + H]$^+$ m/z = 868, [4M + H]$^+$ m/z = 1175, [5M + H]$^+$ m/z = 1446.

19 ^{1}H-NMR (CDCl$_3$, TMS): 8.22 (m, 2H, ArH), 7.80 (m, 1H, ArH), 7.66 (m, 1H, ArH), 7.50 (m, 2H, ArH), 7.4–7.2 (m, 3H, ArH), 5.37 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.87 Hz), 4.1–3.9 (m, 4H, OCH$_2$), 1.18 (t, 3H, CH$_2$CH$_3$), 1.16 (t, 3H, CH$_2$CH$_3$).

20 ^{1}H-NMR (CDCl$_3$, TMS): 7.35 (d, 2H, ArH), 6.71 (m, 2H, ArH), 4.89 (dd, 1H, CHP, ^{2}J$_{PH}$ = −9.76 Hz, ^{3}J$_{HH}$ = 4.88 Hz), 4.20–3.90 (m, 4H, OCH$_2$), 3.30 (dd, 1H, OH, exchange with D$_2$O, ^{3}J$_{HH}$ = 4.88 Hz, ^{3}J$_{PH}$ = 10.38 Hz), 2,95 (s, 6H, N(CH$_3$)$_2$), 1.29 (t, 3H, CH$_2$CH$_3$), 1.22 (t, 3H, CH$_2$CH$_3$); ^{31}P{^{1}H}-NMR (DMF, 85% H$_3$PO$_4$): 23.4

21 ^{1}H-NMR (DMSO-d$_6$, TMS): 7.93 (d, 2H, ArH), 7.55 (d, 2H, ArH), 6.38 (dd, 1H, OH, exchange with D$_2$O, ^{3}J$_{PH}$ = 15.20 Hz, ^{3}J$_{HH}$ = 5.67 Hz), 5.07 (dd, 1H, CHP, ^{2}J$_{PH}$ = −14.57 Hz, ^{3}J$_{HH}$ = 5.45 Hz), 4.10–3.90 (m, 4H, OCH$_2$), 1.17 (t, 3H, CH$_2$CH$_3$), 1.16 (t, 3H, CH$_2$CH$_3$), IR (KBr pellet): 3390 cm^{-1} (ν_{O-H}), 1687 cm^{-1} ($\nu_{C=O}$), 1187 cm^{-1} ($\nu_{P=O}$), 1171 cm^{-1} ($\nu_{P=O}$), 1062 cm^{-1} (ν_{P-OR}), 1047 cm^{-1} (ν_{P-OR}).

22 ^{1}H-NMR (CDCl$_3$, TMS): 9.92 (s, 1H, CHO), 7.80 (d, 2H, ArH), 7.58 (d, 2H, ArH), 5.08 (d, 1H, CHP, ^{2}J$_{PH}$ = −12.40 Hz), 3.65 (d, 3H, OCH$_3$, ^{3}J$_{PH}$ = 10.45 Hz), 3.64 (d, 3H, OCH$_3$, ^{3}J$_{PH}$ = 10.50 Hz); FAB-MS: [M + H]$^+$ m/z = 245 (base peak), [M + H − HPO(OCH$_3$)$_2$]$^+$ m/z = 135, [2M + H]$^+$ m/z = 489, [M + H − H$_2$O]$^+$ m/z = 227, [M + Na]$^+$ m/z = 267.

23 ^{1}H-NMR (CDCl$_3$, TMS): 7.70 (m, 1H, ArH), 7.37 (m, 1H, ArH), 7.30 (m, 1H, ArH), 5.51 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.24 Hz), 4.20–4.00 (m, 4H, OCH$_2$), 1.30 (t, 3H, CH$_2$CH$_3$), 1.24 (t, 3H, CH$_2$CH$_3$).

24 ^{1}H-NMR (CDCl$_3$, TMS): 7.67 (m, 1H, ArH), 7.42 (m, 1H, ArH), 7.26 (t, 1H, ArH), 5.61 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.67 Hz), 4.20–3.90 (m, 4H, OCH$_2$), 1.30 (t, 3H, CH$_2$CH$_3$), 1.22 (t, 3H, CH$_2$CH$_3$).

25 ^{1}H-NMR (CDCl$_3$, TMS): 7.34 (m, 2H, ArH), 7.19 (m, 1H, ArH), 5.84 (d, 1H, CHP, ^{2}J$_{PH}$ = −19.60 Hz), 4.30–3.90 (m, 4H, OCH$_2$), 1.38 (t, 3H, CH$_2$CH$_3$), 1.17 (t, 3H, CH$_2$CH$_3$).

26 ^{1}H-NMR (CDCl$_3$, TMS): 7.46 (d, 1H, ArH), 6.52 (d, 1H, ArH), 6.45 (s, 1H, ArH), 5.34 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.30 Hz), 4.20–3.80 (m, 4H, OCH$_2$), 3.83 (s, 3H, ArOCH$_3$), 3.81 (s, 3H, ArOCH$_3$), 3.30 (brd s, 1H, OH, exchange with D$_2$O), 1.31 (t, 3H, CH$_2$CH$_3$), 1.21 (t, 3H, CH$_2$CH$_3$).

27 ^{1}H-NMR (CDCl$_3$, TMS): 7.18 (m, 1H, ArH), 7.08 (t, 1H, ArH), 6.85 (m, 1H, ArH), 5.38 (d, 1H, CHP, ^{2}J$_{PH}$ = −12.17 Hz), 4.20–3.80 (m, 4H, OCH$_2$), 3.92 (s, 3H, ArOCH$_3$), 3.87 (s, 3H, ArOCH$_3$), 1.33 (t, 3H, CH$_2$CH$_3$), 1.19 (t, 3H, CH$_2$CH$_3$).

28 ^{1}H-NMR (CDCl$_3$, TMS): 7.08 (s, 1H, ArH), 6.88 (m, 1H, ArH), 4.92 (d, 1H, CHP, ^{2}J$_{PH}$ = −10.38 Hz), 4.10–3.90 (m, 4H, OCH$_2$), 3.85 (s, 3H, ArOCH$_3$), 1.28 (t, 3H, CH$_2$CH$_3$), 1.21 (t, 3H, CH$_2$CH$_3$).

29 ^{1}H-NMR (CDCl$_3$, TMS): 7.26 (d, 1H, ArH), 6.71 (d, 1H, ArH), 5.28 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.63 Hz), 4.30–3.90 (m, 4H, OCH$_2$), 3.96 (s, 3H, ArOCH$_3$), 3.87 (s, 3H, ArOCH$_3$), 3.85 (s, 3H, ArOCH$_3$), 1.33 (t, 3H, CH$_2$CH$_3$), 1.20 (t, 3H, CH$_2$CH$_3$).

30 ^{1}H-NMR (CDCl$_3$, TMS): 6.75 (s, 2H, ArH), 4.96 (d, 1H, CHP, ^{2}J$_{PH}$ = −10.82 Hz), 4.20–4.00 (m, 4H, OCH$_2$), 3.86 (s, 6H, ArOCH$_3$), 3.84 (s, 3H, ArOCH$_3$), 1.30 (t, 3H, CH$_2$CH$_3$), 1.25 (t, 3H, CH$_2$CH$_3$).

31 ^{1}H-NMR (CDCl$_3$, TMS): 6.79 (s, 2H, ArH), 4.96 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.02 Hz), 4.10–4.00 (m, 4H, OCH$_2$), 3.82 (s, 6H, ArOCH$_3$), 2.33 (s, 3H, CH$_3$CO), 1.28 (t, 3H, CH$_2$CH$_3$), 1.25 (t, 3H, CH$_2$CH$_3$).

Spectroscopic Characteristics of Compounds Listed in Table II

1 ^{1}H-NMR (CDCl$_3$, TMS): 8.07 (m, 1H, ArH), 7.86 (m, 3H, ArH), 7.50 (m, 3H, ArH), 5.87 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.52 Hz), 4.10–3.70 (m, 4H, OCH$_2$), 3.65 (brd s, 1H, OH, exchange with D$_2$O), 1.19 (t, 3H, CH$_2$CH$_3$), 1.04 (t, 3H, CH$_2$CH$_3$).

2 ^{1}H-NMR (CDCl$_3$, TMS): 7.59 (s, 1H, ArH), 7.82 (m, 3H, ArH), 7.58 (m, 1H, ArH), 7.47 (m, 2H, ArH), 5.20 (d, 1H, CHP, ^{2}J$_{PH}$ = −11.19 Hz), 4.10–3.90 (m, 4H, OCH$_2$), 1.25 (t, 3H, CH$_2$CH$_3$), 1.19 (t, 3H, CH$_2$CH$_3$).

3 ^{1}H-NMR (CDCl$_3$, TMS): 7.29 (m, 1H, ArH), 7.18 (m, 1H, ArH), 7.00 (m, 1H, ArH), 5.24 (d, 1H, CHP, ^{2}J$_{PH}$ = −10.49 Hz), 4.20–4.00 (m, 4H, OCH$_2$), 1.30 (t, 3H, CH$_2$CH$_3$), 1.26 (t, 3H, CH$_2$CH$_3$).

4 ^{1}H-NMR (CDCl$_3$, TMS): 8.65 (d, 1H, ArH), 7.81 (m, 1H, ArH), 7.60 (m, 1H, ArH), 7.35 (m, 1H, ArH), 5.22 (d, 1H, CHP, ^{2}J$_{PH}$ = −12.08 Hz), 4.30–3.90 (m, 4H, OCH$_2$), 1.35 (t, 3H, CH$_2$CH$_3$), 1.21 (t, 3H, CH$_2$CH$_3$).

5 ^{1}H-NMR (CDCl$_3$, TMS): 4.30–4.10 (m, 4H, OCH$_2$), 3.67 (dd, 1H, CHP, ^{2}J$_{PH}$ = −6.39 Hz, ^{3}J$_{HH}$ = 6.38 Hz), 3.44 (brd s, 1H, OH, exchange with D$_2$O), 2.00 (m, 1H, cycloexylH), 1.9–1.6 (m, 5H, cycloexylH), 1.4–1.1 (m, 5H, cycloexylH), 1.34 (t, 6H, CH$_2$CH$_3$).

6 ^{1}H-NMR (CDCl$_3$, TMS): 4.00 (m, 1H, CHP), 3.82 (d, 3H, OCH$_3$, ^{3}J$_{PH}$ = 10.31 Hz), 3.81 (d, 3H, OCH$_3$, ^{3}J$_{PH}$ = 10.37 Hz), 1.93 (m, 1H, CH$_2$), 1.71 (m, 1H, CH$_2$), 1.45 (m, 1H, CH), 0.97 (d, 3H, CH$_3$, ^{3}J$_{HH}$ = 6.66 Hz), 0.92 (d, 3H, CH$_3$, ^{3}J$_{HH}$ = 6.35 Hz).

7 ^{1}H-NMR (CDCl$_3$, TMS): 3.41 (d, 3H, OCH$_3$, ^{3}J$_{PH}$ = 9.58 Hz), 3.22 (dd, 1H, CHP, ^{2}J$_{PH}$ = −8.89 Hz, ^{3}J$_{HH}$ = 5.40 Hz), 1.97 (m, 1H, cycloexylH), 1.8–1.5 (m, 5H, cycloexylH), 1.3–0.9 (m, 5H, cycloexylH).

Spectroscopic Characteristics of Compounds Listed in Table III

1 ^{1}H-NMR (DMSO-d$_6$, TMS): 7.39 (s, 4H, ArH), 6.28 (dd, 2H, OH, exchange with D$_2$O, ^{3}J$_{PH}$ = 15.30 Hz, ^{3}J$_{HH}$ = 5.70 Hz), 5.00 (dd, 2H, CHP, ^{2}J$_{PH}$ = −12.20

Hz, $^3J_{HH}$ = 5.62 Hz), 3.62 (d, 6H, OCH$_3$, $^3J_{PH}$ = 10.34 Hz), 3.57 (d, 6H, OCH$_3$, $^3J_{PH}$ = 10.32 Hz); ^{31}P{^{1}H}-NMR (CDCl$_3$, 85% H$_3$PO$_4$): 23.61, 22.89; FAB-MS: [M + H]$^+$ m/z = 355 (base peak), [M + H − HPO(OCH$_3$)$_2$]$^+$ m/z = 245, [2M + H]$^+$ m/z = 709, [M + H − H$_2$O]$^+$ m/z = 337, [M + Na]$^+$ m/z = 377.

2 ^{1}H-NMR (DMSO-d$_6$, TMS): 7.38 (s, 4H, ArH), 6.20 (dd, 2H, OH, exchange with D$_2$O, $^3J_{PH}$ = 15.28 Hz, $^3J_{HH}$ = 5.77 Hz), 4.92 (dd, 2H, CHP, $^2J_{PH}$ = −12.22 Hz, $^3J_{HH}$ = 5.76 Hz), 4.00–3.80 (m, 8H, OCH$_2$); 1.17 (t, 6H, CH$_2$CH$_3$), 1.13 (t, 6H, CH$_2$CH$_3$).

3 ^{1}H-NMR (DMSO-d$_6$, TMS): 7.49 (s, 1H, ArH), 7.34 (m, 3H, ArH), 5.00 (d, 2H, CHP, $^2J_{PH}$ = −12.75 Hz), 3.62 (d, 6H, OCH$_3$, $^3J_{PH}$ = 9.15 Hz), 3.57 (d, 6H, OCH$_3$, $^3J_{PH}$ = 9.16 Hz); ^{31}P{^{1}H}-NMR (CDCl$_3$, 85% H$_3$PO$_4$): 24.65.

Spectroscopic Characteristics of Cyclic Dialkyl Phthalyde-3-phosphonates

Compound Ia

^{1}H-NMR (CDCl$_3$, TMS): 7.97 (m, 1H, ArH), 7.76 (m, 2H, ArH), 7.63 (m, 1H, ArH), 5.75 (d, 1H, CHP, $^2J_{PH}$ = −10.88 Hz), 3.94 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.95 Hz), 3.61 (d, 3H, OCH$_3$, $^3J_{PH}$ = 10.66 Hz); FAB-MS: [M + H]$^+$ m/z = 243 (base peak), [2M + H]$^+$ m/z = 485, [M + Na]$^+$ m/z = 265; IR (KBr pellet): 1770 cm^{-1} ($\nu_{C=O}$), 1284 cm^{-1} ($\nu_{P=O}$), 1260 cm^{-1} ($\nu_{P=O}$), 1061 cm^{-1} ($\nu_{P\text{-}OR}$), 1045 cm^{-1} ($\nu_{P\text{-}OR}$).

Compound Ib

^{1}H-NMR (CDCl$_3$, TMS): 7.96 (m, 1H, ArH), 7.77 (m, 2H, ArH), 7.61 (m, 1H, ArH), 5.72 (d, 1H, CHP, $^2J_{PH}$ = −10.91 Hz), 4.40–4.20 (m, 2H, OCH$_2$), 4.1–3.8 (m, 2H, OCH$_2$), 1.41 (t, 3H, CH$_2$CH$_3$), 1.09 (t, 3H, CH$_2$CH$_3$); FAB-MS: [M + H]$^+$ m/z = 271 (base peak), [2M + H]$^+$ m/z = 541, [M + Na]$^+$ m/z = 293; IR (KBr pellet): 1776 cm^{-1} ($\nu_{C=O}$), 1286 cm^{-1} ($\nu_{P=O}$), 1258 cm^{-1} ($\nu_{P=O}$), 1042 cm^{-1} ($\nu_{P\text{-}OR}$), 1024 cm^{-1} ($\nu_{P\text{-}OR}$).

Compound Ic

^{1}H-NMR (CDCl$_3$, TMS): 7.94 (m, 1H, ArH), 7.73 (m, 2H, ArH), 7.59 (m, 1H, ArH), 5.66 (d, 1H, CHP, $^2J_{PH}$ = −11.12 Hz), 4.86 (m, 1H, OCH), 4.50 (m, 1H, OCH), 1.41 (d, 3H, CH$_3$, $^3J_{HH}$ = 6.16 Hz), 1.40 (d, 3H, CH$_3$, $^3J_{HH}$ = 6.18 Hz); 1.24 (d, 3H, CH$_3$, $^3J_{HH}$ = 6.17 Hz), 0.90 (d, 3H, CH$_3$, $^3J_{HH}$ = 6.19 Hz); FAB-MS: [M + H]$^+$ m/z = 299 (base peak), [M + H − C$_3$H$_6$]$^+$ m/z = 257, [2M + H]$^+$ m/z = 597, [M + Na]$^+$ m/z = 321, [2M + H − C$_3$H$_6$]$^+$ m/z =

555, $[2M + H - 2C_3H_6]^+$ m/z = 513, $[2M + Na]^+$ m/z = 619; IR (KBr pellet): 1774 cm^{-1} ($\nu_{C=O}$), 1287 cm^{-1} ($\nu_{P=O}$), 1259 cm^{-1} ($\nu_{P=O}$), 1052 cm^{-1} (ν_{P-OR}), 1029 cm^{-1} (ν_{P-OR}).

Acknowledgements

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Endnotes

1. In the literature report[35] these compounds were obtained by cumbersome procedures and/or as by-products of the reaction used in the conversion of phthalic anhydride into biphthalyl by trialkyphosphites.