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α -AMINOPHOSPHONATES BEARING FREE HYDROXYL GROUPS IN THE AROMATIC RINGS. SYNTHESIS AND NMR CHARACTERIZATION

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α -AMINOPHOSPHONATES BEARING FREE HYDROXYL GROUPS IN THE AROMATIC RINGS. SYNTHESIS AND NMR CHARACTERIZATION

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In this paper we describe a useful synthetic procedure leading in very good yields to mono- and bis- α -aminophosphonic acid dialkylesters containing the free phenolic hydroxyl group in a strategic position of the aromatic ring in order to enhance complexation with metal ions. This synthetic procedure is based on the addition of a solution of sodium dialkyl phosphite in phosphite to imine precursors. The addition reaction is highly stereospecific: only one diastereomer for each of the bis- α -aminophosphonic acid dialkylesters is formed. All compounds were characterized by NMR (¹H and ³¹P) and by FAB-MS spectroscopy.

Keywords: Metal chelating phosphonates; NMR and FAB-MS characterization; Monomers for polycondensates

INTRODUCTION

α -Aminophosphonic acids are bioisosters of natural aminoacids serving as important surrogates in order to modify biological processes inhibiting enzyme activity^[1] and bacterial growth.^[2] Furthermore these compounds, as well as their di- and mono-alkyl esters, are widely used in agrochemistry as antifungal

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agents,^[3] herbicides^[4] and as plant regulators. Self condensation of α -aminophosphonic acids produces phosphonodi- and tri-peptides clinically studied as antibiotics^[5] and condensation of racemic phosphonate esters with vinblastine gave epimers showing antitumor activity.^[6]

In addition, α -aminophosphonic acids and their mono-alkyl esters are of interest also in hydrometallurgy in order to extract metals^[7] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinides.^[8,9]

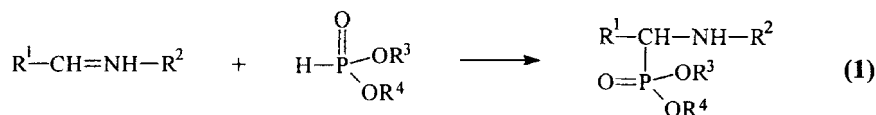
The recent growing interest in lanthanide and transition metal chelates of phosphonate derivatives containing imino^[10,11] and amino functional groups,^[12,13] has led us to investigate efficient methods to prepare novel α -aminophosphonate derivatives containing ancillary complexing groups. Suitable candidates in order to enhance both hydrophilic and complexing properties are molecules containing, in addition to the phosphonate moiety, free carboxylic groups, heteronuclei or free hydroxylic functions.

We already reported on the synthesis and characterization of α -aminophosphonates containing the first two ancillary functionalities;^[12–14] we wish now to report on a new synthetic procedure which enabled us to obtain in very good yields both mono- and bis- α -aminophosphonic acid dialkylesters containing the free hydroxyl group in a strategic position of the aromatic ring for enhancing complexation properties towards metals.

RESULTS AND DISCUSSION



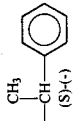
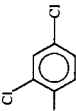
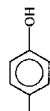
The new compounds synthesized can be depicted by the general formulas I and II, and are fully described in Tables I and II.

We already reported^[15] that, among the possible different synthetic routes which can yield α -amino-phosphonic acid dialkyl esters, the addition of dialkyl phosphites neat or in solvents (polar or apolar) to the Schiff base precursors (readily available from the condensation of primary amines with aldehydes) is one of the best procedure (Equation 1):




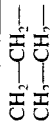
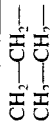


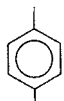
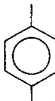
In order to facilitate the addition reaction a catalytic amount of NaH was used. According to this procedure we prepared in good yields α -aminophosphonic dialkyl esters **IIIa-IIIg**, where the X and Y substituents range from hy-

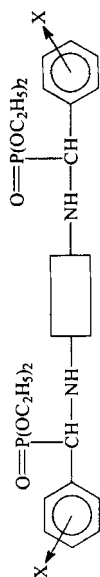
TABLE I Preparation of Mono α -Amino Phosphonate Diethyl Esters of General Formula I:



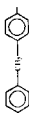
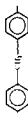
| N. | X | R ² | Yield % | m.p. (°C) | ¹ H-NMR ^a δ (CDCl ₃ , TMS) | | | ³¹ P ^b |
|-----------|------|---|------------|--------------|---|--|--|------------------------------|
| | | | | | δ_{CH} ^c (² J _{PH}) | $\delta\text{P}(\text{OCH}_2\text{CH}_3)_2$ ^d | $\delta\text{P}(\text{OCH}_2\text{CH}_3)_2$ ^e | |
| 1a | 2-OH |  | 56 | 69–72 | 4.39 (–20) | 4.09–3.88 | 1.25, 1.23 | 23.32 |
| 1b | 2-OH |  | 60 | 60–63 | 4.89 (–22.8) | 4.11–4.00 | 1.26, 1.22 | – |
| 1c | 4-OH |  | 67 | 106–108 | 4.03 (–20) | 4.21–3.83 | 1.31, 1.14 | – |
| 1d | 2-OH |  | 95 | 113–114 | 5.14 ^f (–24) | 4.16–4.08 | 1.27 | 24.40 |
| 1e | 2-OH |  | 43 | 146–148 | 4.75 (–22.2) | 4.10–3.97 | 1.26, 1.22 | 24.87 |

^aOnly diagnostic signals are here reported; chemical shifts [ppm], coupling constants [Hz]; for full NMR characterization see experimental part. ^bIn CHCl₃ using 85% H₃PO₄ as external reference. ^cDoublet unless otherwise noticed. ^dComplex multiplet. ^eTwo methyl triplets (³J_{HH} = 7 Hz). ^fQuartet of an ABX system.

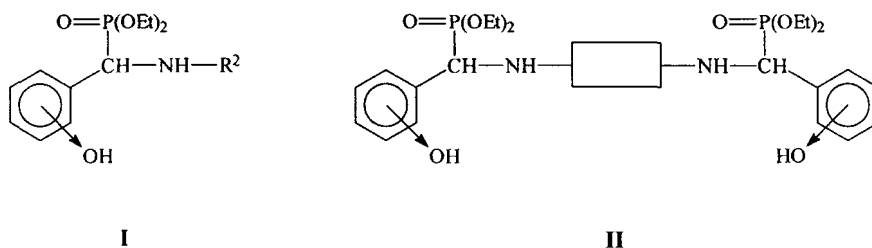
TABLE II Preparation of Bis- α -Amino Phosphonate Diethyl Esters of General Formula II:

| N. | X |  | Yield % | m.p. (°C) | ¹ H-NMR ^a δ (CDCl ₃ , TMS) | | | ³¹ P ^b |
|------|----------------------------|---|------------|--------------|---|---|------------|------------------------------|
| | | | | | δPCH ^c (² J _{PH}) | δP(OCH ₂ CH ₃) ₂ ^d | | |
| | | | | | | δP(OCH ₂ CH ₃) ₂ ^e | | |
| IIa | 2-OH |  | 30 | 94-96 | 4.06 ^f | 4.16-3.95 | 1.29, 1.22 | — |
| IIb | 3-OCH ₃ 4-OH |  | 45 | 125-126 | 4.05 ^f | 4.11-3.85 | 1.28, 1.15 | 22.20 |
| IIc | 2-OH |  | 75 | 159-161 | 4.29 (-20.5) | 4.05-3.90 | 1.22 | 20.90 (70%) 20.92 (30%) |
| IIId | 3-OCH ₃ 4-OH |  | 50 | 133-134 | 4.03 ^f | 4.12-3.72 | 1.26, 1.11 | 22.8 |
| IIe | 2-OH |  | 38 | 175-177 | 5.05 ^g (-24.2) | 4.09-3.56 | 1.17, 0.96 | 25.16 |
| IIIf | 4-OH |  | 68 | 208-210 | 4.66 ^g (-24.2) | 4.05-3.60 | 1.15, 1.00 | 25.07 (96%) 24.90 (4%) |



| N. | X |  | Yield % | m.p. (°C) | ¹ H-NMR ^a δ (CDCl ₃ , TMS) | ³¹ P ^b |
|-----|----------------------------|---|------------|--------------|--|------------------------------|
| IIg | 3-OCH ₃ 4-OH |  | 70 | 166-167 | δ PCH ^c (³ J _{PH}) 4.68 ^g (-24.0) δ P(OCH ₂ CH ₃) ₂ ^d 4.04-3.62 δ P(OCH ₂ CH ₃) ₂ ^e 1.16, 1.02 | 24.97 |
| IIh | 4-OH |  | 48 | 128-131 | 4.65 (-24.0) 4.12-3.90 1.24, 1.10 | 21.67 (85%) 21.59 (15%) |
| IIi | 2-OH |  | 20 | 98-100 | 4.75 (-22.8) 4.02-3.89 1.16, 1.11 | 22.7 |

^aOnly diagnostic signals are here reported; chemical shifts [ppm], coupling constants [Hz]; for full NMR characterization see experimental part. ^bIn CHCl₃ except **Ile**, **IIf**, **Ilg** measured in DMSO using H₃PO₄ as external reference; first signal refers to the major diastereomer. ^cDoublet unless otherwise noticed. ^dComplex multiplet. ^eTwo methyl triplets (³J_{HH} = 7 Hz). ^fMasked by OCH₂ resonance. ^gQuartet of an ABX system (DMSO-d₆ as solvent).



drogen, halogens, trifluoromethyl groups, methoxy, carbomethoxy and phenylazo moieties, to free carboxylic groups.

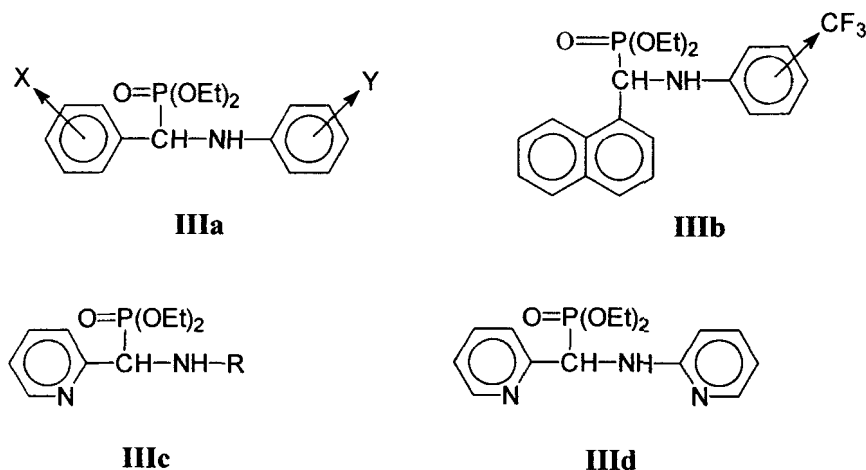
However, when X and Y in **IIIa**, **IIIe** and **IIIf** are free -OH groups this procedure does not work and complex mixture of oily products are generally obtained.

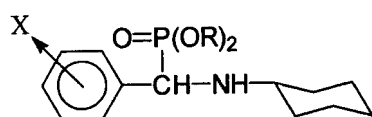
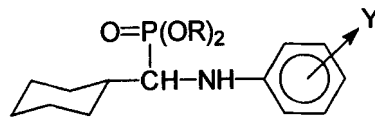
In particular, by using halogenated solvents in the addition of dialkyl phosphites to both mono- or bis-imine derivatives from salicylaldehyde, oily phosphates are obtained according to the reaction Scheme 1 outlined below:

The characterization of **IV** was performed by $^1\text{H-NMR}$ spectroscopy and by reaction with primary amines in order to produce imino-phosphates.

It follows that the presence of the free -OH group(s) in imines derived from aromatic hydroxy-aldehydes precludes our very simple and useful addition reaction.

Thus, in order to avoid the undesired acidic reactivity of such hydroxyl groups we thought that salification with alkaline metals could help in obtaining the desired α -aminophosphonates starting from the imine precursors.

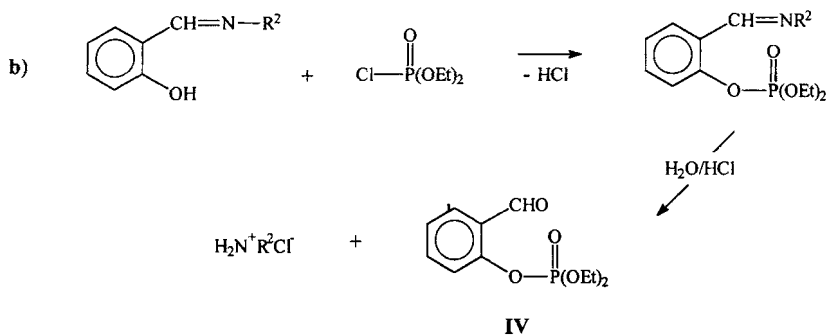
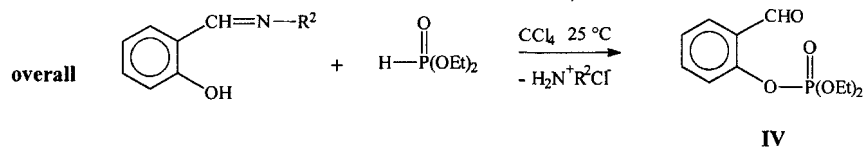


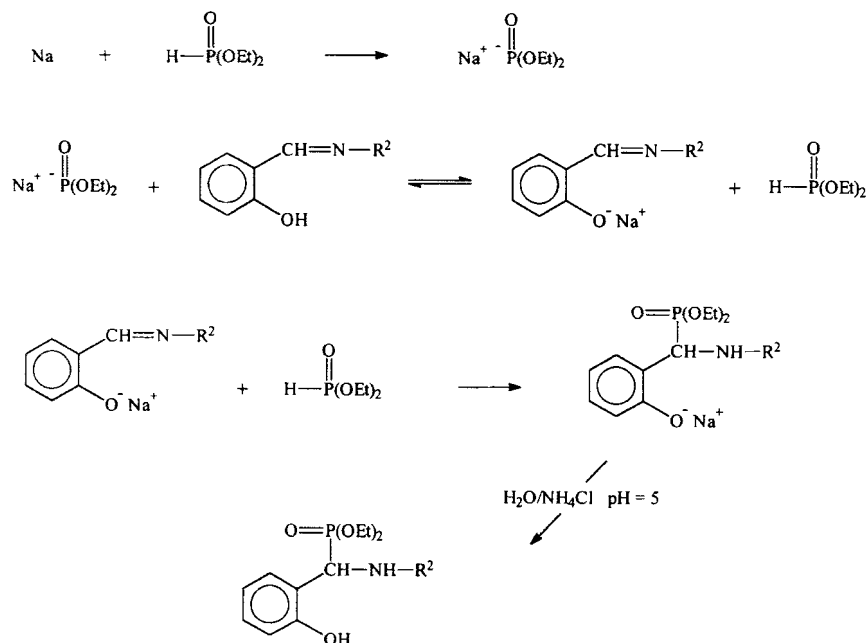
**IIIe****IIIf**

Therefore our phosphite addition reaction was performed using equimolar amount of Na metal, which was easily dissolved at room temperature in a large excess of diethyl phosphite (Scheme 2 and experimental part).

Inspection of Tables I and II clearly shows that such reaction works very well with all imines and bis-imines bearing free -OH groups and the yields are certainly satisfactory.

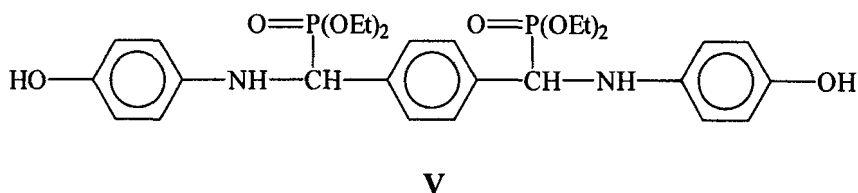
Moreover, the procedure (see experimental part) is very simple and the reaction is very fast at room temperature (few minutes). Considering that the imines, as well the bis-imines, derived from aromatic hydroxy aldehydes or aromatic hydroxy amines are deeply coloured whereas the α -aminophosphonates are not (white solids) the advancement of the reaction can be easily monitored.





Inspection of Tables I and II reveal that the ^1H -NMR patterns are consistent with the assigned structures and the most diagnostic peaks (reported in Tables) are the two triplets for the methyl groups of the ethoxy moiety, a complex multiplet for the ethoxy methylene protons and a doublet or a quartet for the methine protons, as one should expect for such class of compounds.^[13–18] The chemical shifts of the methine protons are very sensitive to the electronic effects of the groups linked to the NH moiety; in particular, they are moved from *ca.* 4.0 ppm to 5.14 ppm going from alkyl groups to aryl rings containing electron withdrawing substituents. Much more intriguing are the NMR spectra of compounds of Table II, which by virtue of the presence of two identical chiral centers can exist as two different diastereomers: the *meso* (R,S) and the *racemic* (RR/SS) ones.

However, the ^1H -NMR spectra of almost all bis-phosphonates of Table II do not show the complexity expected for a mixture of diastereomers and they seem to indicate the presence of only one isomer (one CHP signal, one set of triplets for the ethoxy methyl groups, etc.). Such interpretation is also nicely confirmed by the ^{31}P -NMR spectra which show only one sharp signal for all the samples synthesized, except for **IIc** (see Table II). Thus, we conclude that once again, the synthesis of bis-phosphonates is occurring with high stereospecificity yielding



as major product only one of the two diastereomers, as previously observed in similar reactions.^[15,16,19]

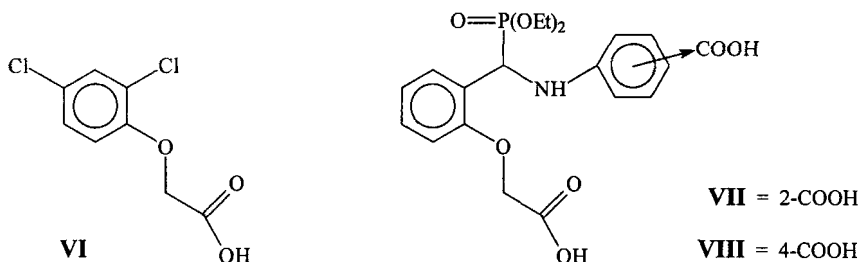
According to previous calculations^[19] and X-ray structural information^[20] the major isomer should possess a *meso* structure.

Inspection of Tables I and 2 reveals that the molecular skeleton of most of the synthesized amino-phosphonates are suitable starting compounds for obtaining linear polymers and/or macrocycles once such bis-hydroxyl monomers are condensed with bis-isocyanates (polyurethanes), bis-dialkyl halides (polyethers), bis-carbonylchlorides (polyesters), etc.

Thus, for this particular purpose, we synthesized, inter alia, molecule **V** which possess a rigid aromatic skeleton with two aminophosphonic groups and reactive free hydroxyl groups in a strategic position in order to yield linear and thermal resistant polymers.

Also in case of **V**, the synthesis is highly stereospecific yielding only one of the two diastereomers, as judging by its ³¹P-NMR spectrum where only one sharp signal at δ 24.54 ppm is present.

Considering that 2,4-dichlorophenoxyacetic acid (**VI**) is a powerful large-spectrum herbicide, we wanted to prepare phosphonates **VII** and **VIII** in order to test their agrochemical properties and moreover for disposing of suitable monomers for polycondensates bearing the α -amino phosphonate function and free carboxylic groups useful in complexation studies. These phosphonates were obtained by addition of a large excess of diethyl phosphite to the corresponding imine precursors, in presence of LiH or metallic sodium.



In fact, the phosphonates **VII** and **VIII** are so insoluble in the reaction medium $[\text{H-P(O)(OEt)}_2]$ that a large excess of it will favour the addition reaction without precluding an easy work-up. Furthermore, this procedure avoids the use of solvents; in order to get the pure compounds recrystallization from water of the crude phosphonates was found to be the most suitable purification procedure.

In conclusion, our synthetic approach and our molecules, besides the possible use as complexing agents towards lanthanides, can serve as interesting monomers for polycondensates bearing the amino-phosphonates moiety.

By use of mono-functional reagents, a great variety of interesting molecules (ureas, esters, ether, etc.) containing a potentially active group in agrochemistry ($-\text{NH-CH-PO}_3\text{R}_2$) can also be easily prepared.

EXPERIMENTAL

Aldehydes, amines, diethyl phosphite, metallic sodium, ammonium chloride as well as solvents used were high purity commercial products from Aldrich. All syntheses were performed under a dry N_2 atmosphere.

$^1\text{H-NMR}$ spectra were recorded in CDCl_3 or DMSO-d_6 , with Me_4Si as an internal standard using a Bruker AC-200 instrument operating at 200 MHz. Phosphorus NMR-spectra were recorded in CHCl_3 or DMSO at Düsseldorf University with a Bruker AM 200 MHz spectrometer with a resolution > 0.003 ppm using 85% H_3PO_4 as external reference.

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.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

General Procedure for Preparation of α -Aminophosphonates (**I** and **II**) Bearing Free Hydroxyl Groups

In a four-necked flask, equipped with a magnetic stirrer, gas inlet, thermometer, a condenser with a nitrogen inlet and a gas trap, was placed a certain amount (generally 20–30 ml) of freshly distilled $\text{H-P(O)(OC}_2\text{H}_5)_2$ to which was added in small portions and by controlling the bath temperature, metallic sodium in small pellets (CAUTION). Once all the weighted Na (1.1 molar ratio to the imine) was dissolved at room temperature, the solid imine was added under vigorous stirring. The Schiff base dissolved immediately into the reaction me-

dium and its colour disappeared, almost instantaneously. Towards the end of the reaction the solution became very viscous but still homogeneous. Once all the imine was added and after disappearance of the colour (10 \div 20 min) a saturated solution of NH_4Cl in H_2O was added. The two layers separated, and generally, after standing at $\text{pH} \leq 5.5$ for half-a-day the solid α -amino phosphonate separated as a white solid from the water reaction mixture. If no solid was obtained, the desired product was extracted with CHCl_3 or CH_2Cl_2 and the solvent removed at reduced pressure. The crude product was then recrystallized from the appropriate solvent (generally ethyl acetate).

Spectroscopic Characterization of Compounds Listed in Tables I, II and in the Text

Ia m.p. 69–72 °C; ^1H -NMR (CDCl_3 , TMS): 7.18 (m, 1H, ArH), 7.03 (m, 1H, ArH), 6.78 (m, 2H, ArH), 4.39 (d, 1H, CHP, $^2J_{\text{PH}} = -20$ Hz), 4.09–3.88 (m, 4H, OCH_2), 2.49 (m, 1H, NH), 2.08–2.16 (m, 6H, cyclohexyl), 1.22 (m, 11H, cyclohexyl and CH_3); ^{31}P -NMR (CHCl_3 , 85% H_3PO_4): 23.32 ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 342$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 204$ (base peak).

Ib m.p. 60–63 °C; ^1H -NMR (CDCl_3 , TMS): 7.20 (m, 2H, ArH), 6.92 (m, 4H, ArH), 6.60 (d, 2H, ArH, $J = 8.4$ Hz), 4.89 (d, 1H, CHP, $^2J_{\text{PH}} = -22.8$ Hz), 4.11–4.00 (m, 4H, OCH_2), 2.20 (s, 3H, CH_3), 1.26 (t, 3H, CH_3 , $J = 7$ Hz), 1.22 (t, 3H, CH_3 , $J = 7$ Hz); FAB-MS: $[\text{M} + \text{H}]^+ m/z = 350$ (base peak).

Ic m.p. 106–108 °C; ^1H -NMR (CDCl_3 , TMS): 7.25 (m, 5H, ArH), 7.07 (m, 2H, ArH), 6.66 (d, 2H, ArH, $J = 8.2$ Hz), 4.03 (d, 1H, CHP, $^2J_{\text{PH}} = -20$ Hz), 4.21–3.83 (m, 5H, OCH_2 and CHCH_3), 1.35 (t, 3H, CH_3 , $J = 7$ Hz), 1.33 (d, 3H, CH_3 , $J = 8$ Hz), 1.14 (t, 3H, CH_3 , $J = 7$ Hz).

Id m.p. 113–114 °C; ^1H -NMR (CDCl_3 , TMS): 7.18 (m, 3H, ArH), 6.90 (m, 3H, ArH), 6.47 (d, 1H, ArH, $J = 8.8$ Hz), 5.36 (m, 1H, NH), 5.14 (dd, 1H, CHP, $^2J_{\text{PH}} = -24$ Hz, $^3J_{\text{HH}} = 8$ Hz), 4.16–4.08 (m, 4H, OCH_2), 1.27 (t, 6H, CH_3 , $J = 7$ Hz); ^{31}P -NMR (CHCl_3 , 85% H_3PO_4): 24.40 ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 404$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 266$ (base peak).

Ie m.p. 146–148 °C; ^1H -NMR (CDCl_3 , TMS): 7.16 (m, 2H, ArH), 6.89 (m, 2H, ArH), 6.59 (m, 4H, ArH), 4.75 (d, 1H, CHP, $^2J_{\text{PH}} = -22.2$ Hz), 4.10–3.97 (m, 4H, OCH_2), 1.26 (t, 3H, CH_3 , $J = 7$ Hz), 1.22 (t, 3H, CH_3 , $J = 7$ Hz); ^{31}P -NMR (CHCl_3 , 85% H_3PO_4): 24.87 ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 352$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 214$ (base peak).

IIa m.p. 94–96 °C; ^1H -NMR (CDCl_3 , TMS): 7.18 (m, 2H, ArH), 6.98 (m, 2H, ArH), 6.84 (m, 4H, ArH), 4.16–3.95 (m, 10H, OCH_2 and CHP), 2.79 (m, 4H, NCH_2), 1.29 (t, 6H, CH_3 , $J = 7$ Hz), 1.22 (t, 6H, CH_3 , $J = 7$ Hz); FAB-MS:

$[M + H]^+ m/z = 545$, $[(M + H)\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 407$, $[(M + H)\text{-}2\text{HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 269$ (base peak).

IIb m.p. 125–126 °C; $^1\text{H-NMR}$ (CDCl_3 , TMS): 6.98 (s, 2H, ArH), 6.83 (m, 4H, ArH), 4.11–3.85 (m, 12H, OCH_2 , NH and CHP), 3.86 (s, 6H, ArOCH_3), 2.66 (m, 4H, NCH_2), 1.28 (t, 6H, CH_3 , $J = 7$ Hz), 1.15 (t, 6H, CH_3 , $J = 7$ Hz); $^{31}\text{P-NMR}$ (CHCl_3 , 85% H_3PO_4): 22.20 ppm; FAB-MS: $[M + H]^+ m/z = 605$, $[(M + H)\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 467$, $[(M + H)\text{-}2\text{HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 329$ (base peak).

IIc m.p. 159–161 °C; $^1\text{H-NMR}$ (CDCl_3 , TMS): 11 (brd s, 2H, OH), 7.18 (m, 2H, ArH), 6.99 (m, 2H, ArH), 6.79 (m, 4H, ArH), 4.29 (d, 2H, CHP, $^2J_{\text{PH}} = -20.5$ Hz), 4.05–3.90 (m, 8H, OCH_2), 2.48 (brd s, 2H, NH), 2.16–1.95 (m, 8H, cyclohexyl), 1.22 (t, 12H, CH_3 , $J = 7$ Hz), 1.05 (m, 2H, cyclohexyl); $^{31}\text{P-NMR}$ (CHCl_3 , 85% H_3PO_4): 20.92 (30%), 20.90 (70%) ppm; FAB-MS: $[M + H]^+ m/z = 599$, $[(M + H)\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 461$, $[(M + H)\text{-}2\text{HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 323$ (base peak).

IId m.p. 133–134 °C; $^1\text{H-NMR}$ (CDCl_3 , TMS): 6.95 (s, 2H, ArH), 6.85 (m, 4H, ArH), 4.12–3.72 (m, 10H, OCH_2 and CHP), 3.87 (s, 6H, ArOCH_3), 2.31 (m, 2H, NH), 2.05–1.65 (m, 6H, cyclohexyl), 1.26 (t, 6H, CH_3 , $J = 7$ Hz), 1.11 (t, 6H, CH_3 , $J = 7$ Hz), 0.97 (m, 4H, cyclohexyl); $^{31}\text{P-NMR}$ (CHCl_3 , 85% H_3PO_4): 22.8 ppm; FAB-MS: $[M + H]^+ m/z = 659$, $[(M + H)\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 521$, $[(M + H)\text{-}2\text{HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 383$ (base peak).

IIe m.p. 175–177 °C; $^1\text{H-NMR}$ (DMSO-d_6 , TMS): 9.7 (s, 2H, ArOH), 7.35 (m, 2H, ArH), 7.00 (m, 2H, ArH), 6.73 (m, 4H, ArH), 6.44 (s, 4H, ArH), 5.41 (t, 2H, NH, $J = 8$ Hz),), 5.05 (dd, 2H, CHP, $^2J_{\text{PH}} = -24.2$ Hz, $^3J_{\text{HH}} = 8$ Hz), 4.09–3.56 (m, 8H, OCH_2), 1.17 (t, 6H, CH_3 , $J = 7$ Hz), 0.96 (t, 6H, CH_3 , $J = 7$ Hz); $^{31}\text{P-NMR}$ (DMSO , 85% H_3PO_4): 25.16 ppm; FAB-MS: $[M + H]^+ m/z = 593$, $[(M + H)\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 455$ (base peak), $[(M + H)\text{-}2\text{HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 317$.

IIf m.p. 208–210 °C; $^1\text{H-NMR}$ (DMSO-d_6 , TMS): 9.31 (s, 2H, ArOH, exchange with D_2O), 7.22 (d, 4H, ArH, $J = 8$ Hz), 6.64 (d, 2H, ArH, $J = 8$ Hz), 6.47 (s, 4H, ArH), 5.34 (t, 2H, NH $J = 7$ Hz, exchange with D_2O), 4.66 (dd, 2H, CHP, $^2J_{\text{PH}} = -24.2$ Hz, $^3J_{\text{HH}} = 10$ Hz), 4.05–3.60 (m, 8H, OCH_2), 1.15 (t, 6H, CH_3 , $J = 7$ Hz), 1.00 (t, 6H, CH_3 , $J = 7$ Hz); $^{31}\text{P-NMR}$ (DMSO , 85% H_3PO_4): 25.07 (96%), 24.90 (4%) ppm; FAB-MS: $[M + H]^+ m/z = 593$ (base peak), $[(M + H)\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 455$, $[(M + H)\text{-}2\text{HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 317$.

IIg m.p. 166–167 °C; $^1\text{H-NMR}$ (DMSO-d_6 , TMS): 8.85 (s, 2H, ArOH, exchange with D_2O), 7.05 (s, 2H, ArH), 6.82 (d, 2H, ArH, $J = 8$ Hz), 6.64 (d, 2H, ArH, $J = 8$ Hz), 6.52 (s, 4H, ArH), 5.38 (m, 2H, NH, exchange with D_2O),

4.68 (dd, 2H, CHP, $^2J_{\text{PH}} = -24.0$ Hz, $^3J_{\text{HH}} = 10.2$ Hz), 4.04–3.62 (m, 8H, OCH₂), 3.71 (s, 6H, ArOCH₃), 1.16 (t, 6H, CH₃, $J = 7$ Hz), 1.02 (t, 6H, CH₃, $J = 7$ Hz); ^{31}P -NMR (DMSO, 85% H₃PO₄): 24.97 ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 653$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 515$ (base peak), $[(\text{M} + \text{H})\text{-2HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 377$.

Ih m.p. 128–131 °C; ^1H -NMR (CDCl₃, TMS): 7.18 (m, 4H, ArH), 6.84 (d, 4H, ArH, $J = 8$ Hz), 6.69 (d, 4H, ArH, $J = 8$ Hz), 6.46 (d, 4H, ArH, $J = 8$ Hz), 4.65 (d, 2H, CHP, $^2J_{\text{PH}} = -24.0$ Hz), 4.12–3.90 (m, 8H, OCH₂), 3.63 (s, 2H, ArCH₂), 1.24 (t, 6H, CH₃, $J = 7$ Hz), 1.10 (t, 6H, CH₃, $J = 7$ Hz); ^{31}P -NMR (CHCl₃, 85% H₃PO₄): 21.67 (85%), 21.59 (15%) ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 683$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 545$, $[(\text{M} + \text{H})\text{-2HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 407$ (base peak).

Ii m.p. 98–100 °C; ^1H -NMR (CDCl₃, TMS): 7.10 (m, 4H, ArH), 6.80 (m, 8H, ArH), 6.48 (d, 4H, ArH, $J = 8.4$ Hz), 4.75 (d, 2H, CHP, $^2J_{\text{PH}} = -22.8$ Hz), 4.02–3.89 (m, 8H, OCH₂), 3.59 (s, 2H, ArCH₂), 1.16 (t, 6H, CH₃, $J = 7$ Hz), 1.11 (t, 6H, CH₃, $J = 7$ Hz); ^{31}P -NMR (CHCl₃, 85% H₃PO₄): 22.7 ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 683$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 545$, $[(\text{M} + \text{H})\text{-2HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 407$ (base peak).

IV ^1H -NMR (CDCl₃, TMS): 9.92 (s, 1H, CHO), 7.58 (m, 2H, ArH), 6.99 (m, 2H, ArH), 4.07 (q, 4H, OCH₂, $J_{\text{HH}} = 7.0$ Hz), 1.33 (t, 6H, CH₃, $J_{\text{HH}} = 7.0$ Hz); ^{31}P -NMR (CDCl₃, 85% H₃PO₄): -6.02 ppm. An authentic sample of **IV** was also obtained by reacting salicylaldehyde in CCl₄ at room temperature with an equimolar amount of H-P(O)(OC₂H₅)₂ and Et₃N. The reaction is very fast and exothermic.

V m.p. 202 °C (dec); ^1H -NMR (DMSO-*d*₆, TMS): 8.41 (s, 2H, ArOH), 7.39 (s, 4H, ArH), 6.57 (d, 4H, ArH, $J = 8.8$ Hz), 6.41 (d, 4H, ArH, $J = 8.8$ Hz), 5.59 (brd t, 2H, NH), 4.79 (dd, 2H, CHP, $^2J_{\text{PH}} = -23.8$ Hz, $^3J_{\text{HH}} = 10.2$ Hz), 4.02–3.48 (m, 8H, OCH₂), 1.14 (t, 6H, CH₃, $J = 7$ Hz), 0.90 (t, 6H, CH₃, $J = 7$ Hz); ^{31}P -NMR (DMSO, 85% H₃PO₄): 24.54 ppm; FAB-MS: $[\text{M} + \text{H}]^+ m/z = 593$, $[(\text{M} + \text{H})\text{-HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 455$ (base peak), $[(\text{M} + \text{H})\text{-2HPO}(\text{OCH}_2\text{CH}_3)_2]^+ m/z = 317$.

VII m.p. 178–181 °C; ^1H -NMR (DMSO-*d*₆, TMS): 7.79 (m, 1H, ArH), 7.33 (m, 1H, ArH), 7.04 (m, 2.5H, ArH), 6.81 (m, 2.5H, ArH), 6.63 (d, 1H, NH), 6.44 (m, 1H, ArH), 5.47 (d, 1H, CHP, $^2J_{\text{PH}} = -24.0$ Hz), 4.35 (s, 2H, CH₂), 4.12–3.87 (m, 4H, OCH₂), 1.16 (t, 3H, CH₃, $J = 7$ Hz), 1.07 (t, 3H, CH₃, $J = 7$ Hz); ^{31}P -NMR (DMSO, 85% H₃PO₄): 23.95 ppm.

VIII m.p. 217–218 °C; ^1H -NMR (DMSO-*d*₆, TMS): 7.57 (m, 3H, ArH), 7.19 (m, 2H, ArH), 6.98–6.82 (m, 4H, ArH and NH), 5.42 (dd, 1H, CHP, $^2J_{\text{PH}} = -24.2$ Hz, $^3J_{\text{HH}} = 9.6$ Hz), 4.82 (s, 2H, CH₂), 4.10–3.68 (m, 4H, OCH₂), 1.18 (t, 3H, CH₃, $J = 7$ Hz), 0.94 (t, 6H, CH₃, $J = 7$ Hz); ^{31}P -NMR (DMSO, 85%

H₃PO₄): 23.82 ppm; FAB-MS: [M + Na]⁺ m/z = 450, [(M + Na)-HPO(OCH₂CH₃)₂]⁺ m/z = 312 (base peak).

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