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RESEARCH ARTICLE

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Synthesis of new functionalized aryl-substituted methylphosphonic and methylenediphosphonic acids and their derivatives

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Abstract

The convenient syntheses of new aryl-substituted hydroxymethylphosphonic and methylenediphosphonic acids from the aromatic aldehydes, their derivatives, and phosphorous acid esters in the presence of the effective catalysts (trimethylsilyl trifluoromethanesulfonate, zinc chloride, and cadmium iodide) were developed.

1 | INTRODUCTION

Functionalized hydroxymethylphosphonates and methylenediphosphonates and their derivatives are not only widely used in organic synthesis, but many of them attract attention as efficient ligands and may be considered as very promising biologically active compounds.[1,2] Interaction of phosphorous acid trimethylsilyl esters with a variety of carbonyl compounds is a convenient method for the synthesis of a number of hydroxymethyl-functionalized organophosphorus compounds—structural biomimetics of important hydroxyl or amino acids.[3–7] We studied in detail the reaction of diethyl trimethylsilyl and tris(trimethylsilyl) phosphites with various aromatic aldehydes and their derivatives, containing functional groups, in the presence of following catalysts—trimethylsilyl triflate, zinc chloride, and cadmium iodide. Such approach is of a considerable interest as perspective direct route to new aryl-substituted methylenediphosphonate—significant structural analogs of the natural pyrophosphates.

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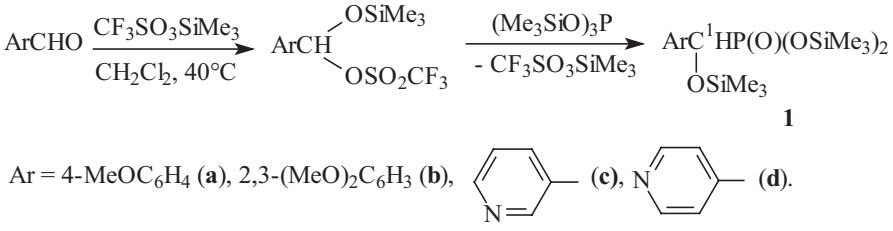
2 | RESULTS AND DISCUSSION

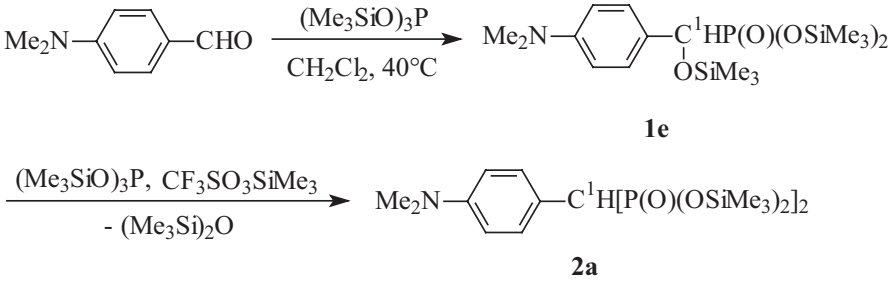
It was found that the addition of tris(trimethylsilyl) phosphite at carbonyl group of aromatic aldehydes is significantly accelerated in the presence of trimethylsilyl triflate as a catalyst and proceeds exothermically, leading to various trimethylsiloxymethylphosphonates **1** in high yield (Scheme 1). It is obvious that the formation of highly reactive intermediate adducts—electrophilic sulfon-containing acetals—is the key stage of this process (cf [8]).

It should be noted that the phosphonate **1e** is obtained in a high yield in the absence of any catalysts, but in the presence of trimethylsilyl triflate, diphosphonate **2a** is unexpectedly formed in high yield (Scheme 2).

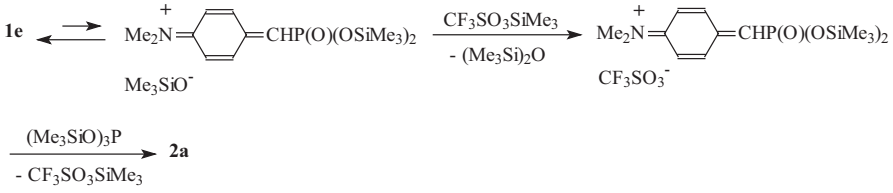
We believe that easy substitution of trimethylsiloxy group at C^1 in phosphonate **1e** is connected with the activating influence of the *para*-dimethylamino group, which promotes the formation of highly reactive intermediate—methylenequinone (Scheme 3).



SCHEME 1 Synthesis of phosphonates **1**



SCHEME 2 Synthesis of phosphonate **1e** and diphosphonate **2a**



SCHEME 3 A possible route of the formation of diphosphonate **2a**

Easily available aromatic aldehydes diethyl acetals[9] react with trimethylsilyl phosphites similarly but only under heating at 100-150°C to give ethoxymethylphosphonates **3** in high yields. The synthesis of the phosphonate **3b** proceeds only in the presence of a mixture of zinc chloride and cadmium iodide as catalysts. In contrast, the mixture of compounds was obtained as the result of ethoxy group to trimethylsilyl group exchange at the phosphorus atom when trimethylsilyl triflate was used as catalyst. It is important that 4-dimethylaminobenzaldehyde diethyl acetal as well as the corresponding aldehyde reacts exothermically with tris(trimethylsilyl) phosphite in the presence of trimethylsilyl triflate to form diphosphonate **2a** in high yield (Scheme 4). The greater reactivity of this acetal in comparison with corresponding aldehyde in this reaction may be related to the intermediate formation of more electrophilic disulfon-containing acetal.

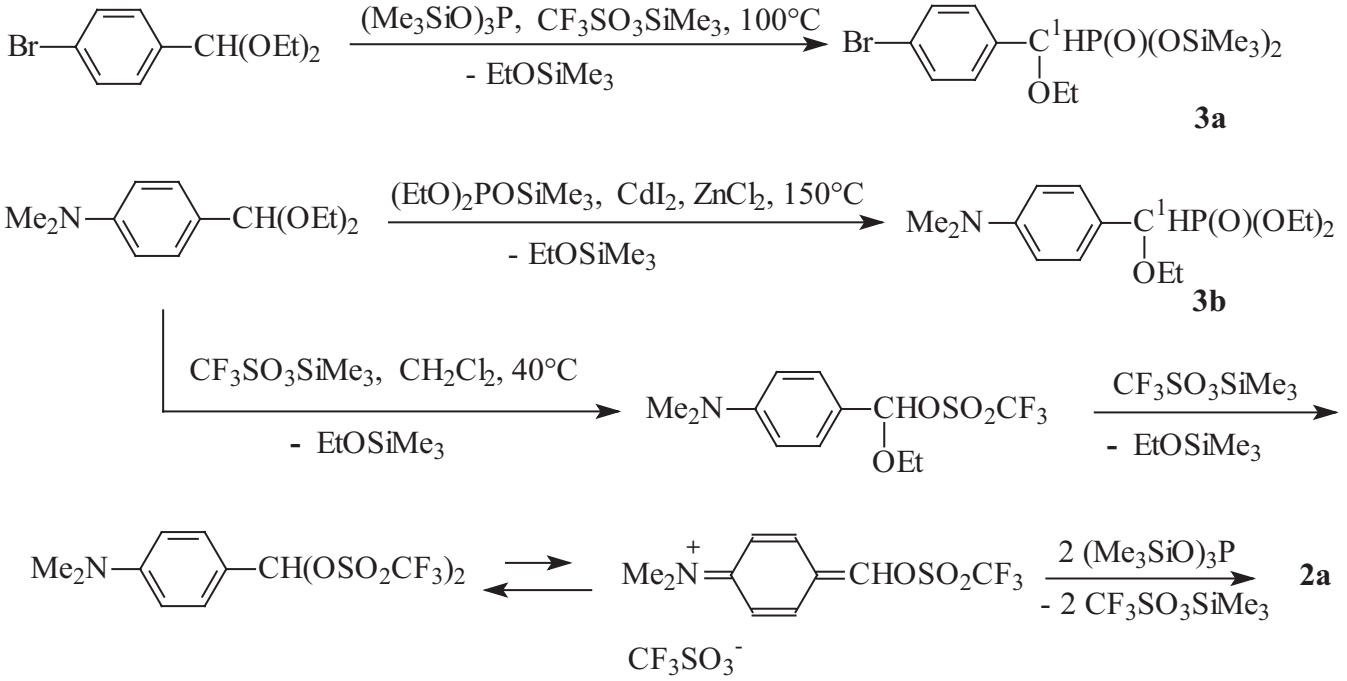
Readily available functionalized benzalchlorides[10] interact with an excess of triethyl- and tris(trimethylsilyl) phosphites under heating at 150-160°C. This reaction proceeds according to the Arbuzov rearrangement scheme in the presence of zinc chloride as a catalyst and lead to aryl-substituted chloromethylphosphonates **4** or methylenediphosphonate **2b, c** depending on the structure of the starting compounds (Scheme 5) (cf [11]).

Thus, the direction of this reaction is determined by the electronic effects of the substituents on the benzene ring of starting benzalchlorides and the volume of the substituents in the molecules of phosphites. The electronic influence of substituents in the *o* and *p* positions of the aromatic moiety also facilitates the generation of highly reactive intermediates—*o*- and *p*-methylenequinones during this process (Scheme 6).

Under similar conditions, the interaction of diethyl (trimethylsilyl) phosphite with anizalchloride proceeds nonselectively and leads to a mixture of diphosphonates **2b** and **2d** in the ratio of 1:1. The further treatment of the mixture of diphosphonates **2b** and **2d** with concentrated hydrochloric acid and bis(trimethylsilyl)amine provides a high yield of diphosphonate **2e** (Scheme 7).

In contrast, the reaction of triethyl phosphite excess with unsubstituted benzalchloride proceeds via complicated red-ox process forming the mixture of benzylphosphonate, pyrophosphate, and yellow polymer (Scheme 8).

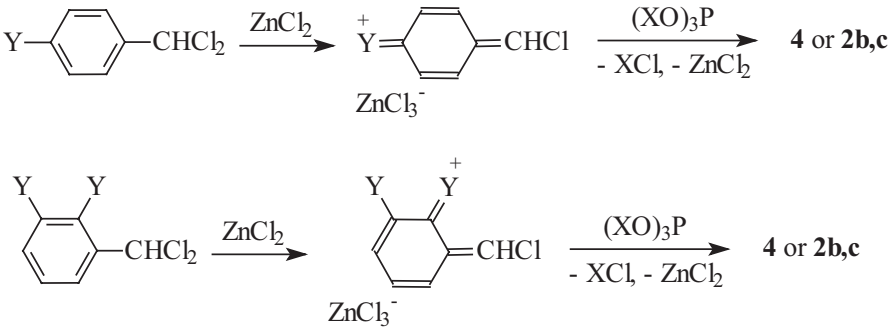
The resulting compounds are the convenient synthons for the preparation of the corresponding aryl-substituted methylphosphonic and methylenediphosphonic acids which are promising polydentate ligands and biologically active substances with various properties. Thus, the trimethylsilyl ethers **1** and **2** readily react with methanol excess under mild



SCHEME 4 Synthesis of phosphonates **3a,b** and diphosphonate **2a**

X = Et (**4a,b**), Me_3Si (**4c**); Ar = 4-FC_6H_4 (**4a**), 2,3-$(MeO)_2C_6H_3$ (**4b**), 4-$MeOC_6H_4$ (**4c, 2b**), 2,5-$(MeO)_2C_6H_3$ (**2c**).

SCHEME 5 Synthesis of phosphonates **4a-c** and diphosphonates **2b,c**



SCHEME 6 Possible routes of formation of phosphonates **4** and diphosphonates **2b,c**

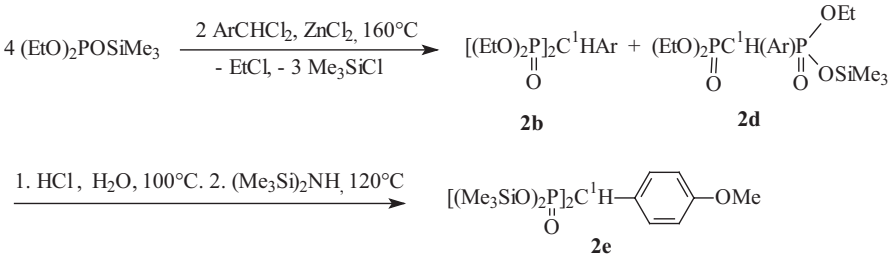
Y = F, MeO; X = Et, Me_3Si.

conditions to give functionalized mono- and diphosphonic acids **5** and **6**, respectively (Scheme 9).

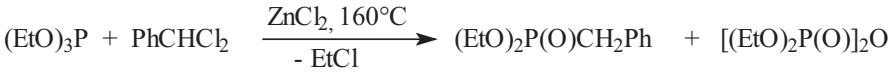
Chloromethylphosphonates **4a** and **4c** and diphosphonate **2b** are easily hydrolyzed by boiling with concentrated hydrochloric acid to form the aryl-substituted hydroxymethylphosphonic and diphosphonic acids **5a**, **5g**, and **6b** (Scheme 10). Also, cleavage of chlorine-carbon bond occurs under these conditions of hydrolysis.

3 | CONCLUSIONS

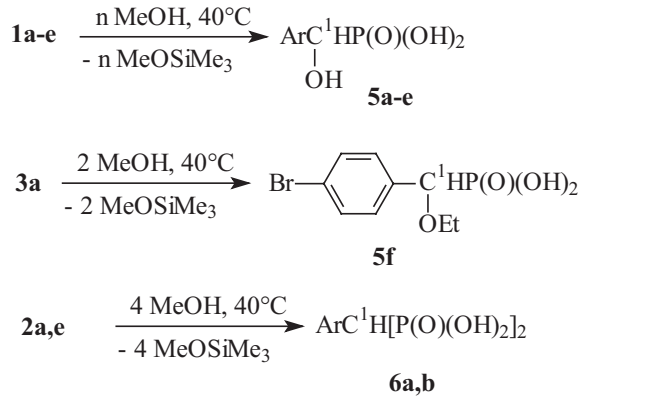
Thus, we have proposed the convenient methods for the synthesis of new aryl-substituted hydroxymethylphosphonic and methylenediphosphonic acids as well as their derivatives. The resulting compounds **1-6** can be of interest as promising polydentate ligands and biologically active substances with the various properties.



SCHEME 7 Synthesis of diphosphonate **2e**

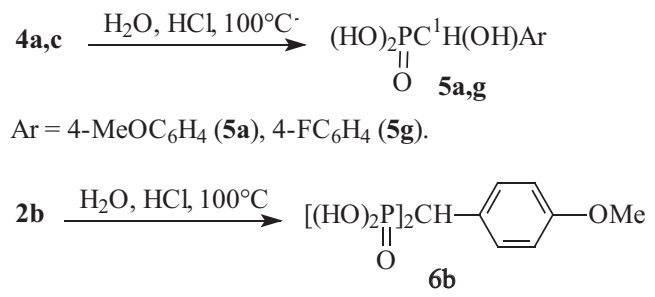


SCHEME 8 The reaction of triethyl phosphite with benzalchloride



Ar = 4-$MeOC_6H_4$ (**5a,6a**), 2,3-$(MeO)_2C_6H_3$ (**5b**), 3-Py (**5c**), 4-Py (**5d**), 4-$Me_2NC_6H_4$ (**5e,6b**).

SCHEME 9 Synthesis of acids **5** and **6**



Ar = 4-$MeOC_6H_4$ (**5a**), 4-FC_6H_4 (**5g**).

SCHEME 10 Synthesis of acids **5a,g** and **6b**

4 | EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) against TMS (^1H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were carried out under dry argon in anhydrous solvents. The starting trimethylsilyl esters of trivalent phosphorus acids,[3,4] aldehyde acetales,[9] and substituted benzalchlorides[10] were prepared as described below.

4.1 | Bis(trimethylsilyl) 4-methoxyphenyl (trimethylsiloxy)methylphosphonate (1a)

Trimethylsilyl trifluoromethanesulfonate (0.5 mL) was added with the stirring to a mixture of tris(trimethylsilyl) phosphite (30 g, 0.10 mol), *p*-anisaldehyde (5.5 g, 0.04 mol), and methylene chloride (40 mL). At once the exothermic reaction proceeded, then the mixture was refluxed for 1 hour, the solvent was removed, and the residue was distilled to obtain 15.1 g of phosphonate **1a**. Yield 86%, bp 144°C (1 mm Hg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: −0.17 (s, 9H, Me_3Si), −0.06 (s, 18H, 2 Me_3Si), 3.56 (s, 3H, MeO), 4.62 (d, 1H, $^2J_{PH}$ = 12.0 Hz, C^1H), 6.62 (d, 2H, $^3J_{PH}$ = 8 Hz, $2CH_{Ph}$), 7.08 (d, 2H, $^3J_{PH}$ = 8.0 Hz, 2 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: −0.3 (s, Me_3Si), 0.5 (s, 2 Me_3Si), 54.9 (s, MeO), 71.8 (d, $^1J_{PC}$ = 180.0 Hz), 113.1 (s), 128.3 (d, $^3J_{PC}$ = 7.0 Hz), 129.9 (s), 159.2 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: −4.0 (s) (cf [5]).

Phosphonates **1b-1e** were obtained similarly, phosphonate **1e** was obtained without a catalyst.

4.2 | Bis(trimethylsilyl) 2,3-dimethoxypheny l(trimethylsiloxy)methylphosphonate (1b)

Yield 84%, bp 143°C (0.5 mm Hg), mp 29°C. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: −0.21 (s, 9H, Me_3Si), −0.02 (s, 18H, 2 Me_3Si), 3.56 (s, 3H, MeO), 3.63 (s, 3H, MeO), 5.17 (d, 1H, $^2J_{PH}$ =14.4 Hz, C^1H), 6.55-6.90 (m, 3H, C_6H_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: −0.3 (s, Me_3Si), 0.5 (s, 2 Me_3Si), 55.4 (s, MeO), 60.3 (s, MeO), 65.2 (d, $^1J_{PC}$ = 182.8 Hz), 111.9 (s), 120.4 (d, $^3J_{PC}$ = 3.2 Hz), 123.3 (s), 131.0 (s), 146.0 (d, $^3J_{PC}$ = 8.0 Hz), 151.9 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 3.7 (s). Anal. Calcd for $C_{18}H_{37}O_6PSi_3$ C 46.52; H 8.02. Found: C 46.26; H 7.94.

4.3 | Bis(trimethylsilyl) pyrid-3-yl(trimethylsiloxy)methylphosphonate (1c)

Yield 89%, bp 152°C (1 mm Hg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: −0.11 (s, 9H, Me_3Si), −0.10 (s, 9H, Me_3Si), 0.02 (s,

9H, Me_3Si), 4.72 (d, 1H, $^2J_{PH}$ = 15.2 Hz, C^1H), 7.09-7.13 (m, 2H, CH_{Py}), 7.65 (d, 1H, $^3J_{HH}$ = 8.0 Hz, CH_{Py}), 8.32-8.34 (m, 1H, CH_{Py}), 8.43 (s, 1H, CH_{Py}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: −0.3 (s, Me_3Si), 0.6 (s, Me_3Si), 0.7 (s, Me_3Si), 69.9 (d, $^1J_{PC}$ = 179.3 Hz, C^1), 123.05 (s), 134.3 (s), 135.4 (d, $^3J_{PC}$ = 4.6 Hz), 147.9 (d, $^3J_{PC}$ = 6.5 Hz), 148.4 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 2.4 (s). Anal. Calcd for $C_{15}H_{32}NO_4PSi_3$ C 44.41; H 7.95. Found: C 44.26; H 7.89.

4.4 | Bis(trimethylsilyl) pyrid-4-yl(trimethylsiloxy)methylphosphonate (1d)

Yield 86%, bp 149°C (1 mm Hg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: −0.09 (s, 9H, Me_3Si), −0.07 (s, 9H, Me_3Si), 0.06 (s, 9H, Me_3Si), 4.68 (d, 1H, $^2J_{PH}$ = 17.2 Hz, C^1H), 7.18 (d, 2H, $^3J_{HH}$ = 5.6 Hz, 2 CH_{Py}), 8.35 (d, 2H, $^3J_{HH}$ = 5.6 Hz, 2 CH_{Py}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: −0.7 (s, Me_3Si), 0.2 (s, Me_3Si), 0.4 (s, Me_3Si), 70.6 (d, $^1J_{PC}$ = 174.7 Hz, C^1), 121.5 (s), 147.2 (br. s), 148.5 (d, $^3J_{PC}$ = 2.0 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 1.9 (s). Anal. Calcd for $C_{15}H_{32}NO_4PSi_3$ C 44.41; H 7.95. Found: C 44.28; H 7.86.

4.5 | Bis(trimethylsilyl) 4-dimethylaminophenyl(trimethylsiloxy)methylphosphonate (1e)

Yield 89%, bp 164°C (1 mm Hg), mp 55°C. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: −0.29 (s, 9H, Me_3Si), −0.19 (s, 9H, Me_3Si), −0.16 (s, 9H, Me_3Si), 2.59 (s, 6H, Me_2N), 4.64 (d, 1H, $^2J_{PH}$ = 16.0 Hz, C^1H), 6.43 (d, 2H, $^3J_{HH}$ = 7.2 Hz, 2 CH_{Ph}), 6.93 (d, 2H, $^3J_{HH}$ = 7.2 Hz, 2 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: −0.7 (s, Me_3Si), 0.1 (s, Me_3Si), 40.5 (s, Me_2N), 71.4 (d, $^1J_{PC}$ = 181.4 Hz, C^1), 112.2 (s), 127.8 (d, $^3J_{PC}$ = 6.0 Hz), 130.5 (s), 148.8 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 4.4 (s) (cf [5]).

4.6 | Tetra(trimethylsilyl) (4-dimethylaminophenyl) methylenediphosphonate (2a)

Trimethylsilyl trifluoromethanesulfonate (0.9 g, 0.004 mol) in 5 mL of methylene chloride was added with the stirring to a mixture of tris(trimethylsilyl) phosphite (18.0 g, 0.060 mol), 4-dimethylaminobenzaldehyde diethylacetal (3.4 g, 0.015 mol), and methylene chloride (15 mL). At once the exothermic reaction proceeded, then the mixture was kept for 24 hour at 20°C, the solvent was removed, the residue was washed with cooled hexane to give 8.6 g of diphosphonate **2a** as white crystals, yield 96%, mp 144°C. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.07 (s, 36H, 4 Me_3Si), 3.22 (s, 6H, Me_2N), 3.48 (t, 1H, $^2J_{PH}$ = 25.2 Hz, C^1H), 7.53 (d, 2H, $^3J_{HH}$ = 8.4 Hz, 2 $C_{Ph}H$), 7.65 (d, 2H, $^3J_{HH}$ = 8.4 Hz, 2 $C_{Ph}H$). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 0.3 (s, 2 Me_3Si), 46.8 (s, Me_2N), 48.3 (t, $^1J_{PC}$ = 135.9 Hz, C^1), 120.3 (s), 132.1 (t, $^3J_{PC}$ = 5.9 Hz), 135.4 (t, $^3J_{PC}$ = 8.5 Hz), 141.6 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: −1.5 (s). Anal. Calcd for $C_{21}H_{47}NO_6P_2Si_4$ C 43.20 H, 8.11. Found: C 43.06; H 8.06.

4.7 | Bis(trimethylsilyl) (4-bromophenyl) ethoxymethylphosphonat (3a)

Trimethylsilyl trifluoromethanesulfonate (1.0 g, 0.0045 mol) in 5 mL of methylene chloride was added with the stirring to a mixture of tris(trimethylsilyl) phosphite (19.0 g, 0.08 mol), 4-bromobenzaldehyde diethylacetal (3.9 g, 0.015 мol), and methylene chloride (15 mL). The mixture was heated under a boiling water bath to complete the stripping of low-boiling compounds and then distilled to give 5.0 g of phosphonate **3a**, yield 74%, bp 104°C (2 mm Hg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.07 (s, 18H, 2 Me_3Si), 1.05 (t, 3H, $^3J_{HH}$ 7.2 Hz, CH_3), 3.30-3.40 (m, 2H, CH_2O), 4.43 (d, 1H, $^2J_{PH}$ = 7.2 Hz, C^1H), 7.15 (d, 2H, $^2J_{HH}$ = 8.0 Hz, 2 CH_{Ph}), 7.30 (d, 2H, $^2J_{HH}$ = 8.0 Hz, 2 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 0.7 (s, 2 Me_3Si), 15.0 (s, Me), 66.4 (d, $^3J_{PC}$ = 13.8 Hz, CH_2O), 78.1 (d, $^1J_{PC}$ = 175.6 Hz, C^1), 121.9 (d, $^2J_{PC}$ = 4.6 Hz), 129.5 (d, $^2J_{PC}$ = 5.6 Hz), 131.2 (s), 134.7 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 0.7 (s). Anal. Calcd for $C_{15}H_{28}BrO_4PSi_2$ C 41.00; H 6.42. Found: C, 40.86; H, 6.33.

4.8 | Diethyl (4-dimethylaminophenyl) ethoxymethylphosphonate (3b)

A mixture of 4-dimethylaminobenzaldehyde diethylacetal (3.4 g, 0.015 mol), diethyl trimethylsilyl phosphite (12.6 g, 0.060 mol), zinc chloride (0.1 g, 0.0004 mol), and cadmium iodide (0.1 g, 0.0003 mol) was heated at 140°C to complete distillation of ethoxytrimethylsilane (bp 74°C). The residue was distilled to give 4.2 g of phosphonate **3b**, yield 86%, bp 195°C (2 mm Hg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.97 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 0.98 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.05 (t, 3H, $^3J_{HH}$ = 6.8 Hz, CH_3), 2.72 (s, 6H, Me_2N), 3.20-3.35 (m, 2H, CH_2O), 3.60-3.90 (m, 4H, 2 CH_2O), 4.29 (d, 1H, $^2J_{PH}$ = 15.2 Hz, C^1H), 6.47 (d, 2H, $^3J_{HH}$ = 8.8 Hz, 2 CH_{Ph}), 7.08 (d, 2H, $^2J_{HH}$ = 8.8 Hz, 2 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 14.9 (s, Me), 16.2 (d, $^3J_{PC}$ = 5.5 Hz, Me), 40.2 (s, Me_2N), 62.4 (d, $^3J_{PC}$ = 6.5 Hz, CH_2O), 62.6 (d, $^2J_{PC}$ = 6.4 Hz, CH_2O), 65.4 (d, CH_2O, $^3J_{PC}$ = 14.7 Hz), 78.0 (t, $^1J_{PC}$ 171.0 Hz, C^1), 111.8 (s), 121.9 (s), 128.9 (d, $^3J_{PC}$ = 5.5 Hz), 150.3 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 20.0 (s). Anal. Calcd for $C_{15}H_{26}NO_4P$: C 57.13; H 8.31. Found: C 56.94; H 8.26.

4.9 | Diethyl chloro(4-fluorophenyl) methylphosphonate (4a)

A mixture of 4-fluorobenzal chloride (3 g, 0.017 mol), triethyl phosphite (7 g, 0.042 mol), and zinc chloride (0.1 g,

0.0007 mol) was heated at 150-160°C for 2 hour and then was distilled to obtain 3 g of phosphonate **4a**, yield 64%, bp 152°C (2 mm Hg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 4.75 (d, 1H, $^{2}J_{PH}$ = 12 Hz, C^{1}H), 6.82 (d, 2H, $^{3}J_{HH}$ = 8 Hz, 2 CH_{Ph}), 7.32 (d, 2H, $^{3}J_{HH}$ = 8 Hz, 2 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 52.5 (d, $^{1}J_{PC}$ = 160 Hz, C^{1}), 130.2 (t, $^{2}J_{PC}$ = $^{4}J_{FC}$ = 3.5 Hz, C^{2}), 130.7 (dd, $^{3}J_{PC}$ = 6 Hz, $^{3}J_{FC}$ = 8 Hz, C^{3}), 115.3 (d, $^{2}J_{FC}$ = 22.0 Hz), 130.2 (t, $^{2}J_{PC}$ = $^{4}J_{FC}$ = 3.5 Hz), 130.7 (dd, $^{3}J_{PC}$ = 6.0 Hz, $^{3}J_{FC}$ = 8.0 Hz), 162.7 (d, $^{1}J_{FC}$ = 248.0 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 16.9 (s). Anal. Calcd for $C_{11}H_{15}ClFO_3P$: C 47.07; H 5.39. Found: C 46.89; H 5.26.

Compounds **4b,c** and **2b,c** were obtained by similar procedure.

4.10 | Diethyl chloro(2,3-dimethoxyphenyl) methylphosphonate (4b)

Yield 68%, bp 184°C (2 mm Hg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 5.35 (d, 1H, $^{2}J_{PH}$ 16.0 Hz, C^{1}H), 3.60 (s, 3H, MeO), 3.65 (s, 3H, MeO), 6.64-7.17 (m, 3H, 3 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 45.6 (d, $^{1}J_{PC}$ = 163.0 Hz, C^{1}), 55.5 (s, MeO), 55.7 (s, MeO), 112.8 (d, $^{3}J_{PC}$ = 3.0 Hz), 118.0 (s), 121.6 (d, $^{2}J_{PC}$ = 4.0 Hz), 124.0 (s), 146.6 (d, $^{3}J_{PC}$ = 9.0 Hz), 152.0 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 18.0 (s). Anal. Calcd for $C_{13}H_{20}ClO_5P$: C 48.38; H 6.25. Found: C 48.23; H 6.16.

4.11 | Bis(trimethylsilyl) chloro(2,3-dimethoxyphenyl) methylphosphonate (4c)

Yield 81%, bp 166°C (1 mm Hg), mp 65°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.09 (s, 9H, Me_3Si), 0.19 (s, 9H, Me_3Si), 4.71 (d, 1H, $^{2}J_{PH}$ = 12.0 Hz, C^{1}H), 3.60 (s, 3H, MeO), 3.72 (s, 3H, MeO), 6.80 (d, 2H, $^{3}J_{HH}$ = 8.0 Hz), 7.36 (d, 2H, $^{3}J_{HH}$ = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 0.6 (s, Me_3Si), 0.8 (s, Me_3Si), 54.6 (d, $^{1}J_{PC}$ = 168.2 Hz, C^{1}), 55.2 (s, 2 MeO), 113.8 (s), 126.9 (t, $^{2}J_{PC}$ = 3.0 Hz), 130.2 (d, $^{3}J_{PC}$ = 6.0 Hz), 160.0 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: −0.8 (s). Anal. Calcd for $C_{16}H_{26}ClO_4P$: C 55.10; H 7.51. Found: C 54.59; H 7.43.

4.12 | Tetraethyl (4-methoxyphenyl) methylenediphosphonate (2b)

Yield 78%, bp 202°C (2 mm Hg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 3.47 (t, 1H, $^{2}J_{PH}$ = 24.0 Hz, C^{1}H), 3.54 (s, 3H, MeO), 6.63 (d, 2H, $^{3}J_{HH}$ = 8.0 Hz), 7.17 (d, 2H, $^{3}J_{HH}$ = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 44.4 (t, $^{1}J_{PC}$ = 132.5 Hz, C^{1}), 54.9 (s, MeO), 113.7 (s), 121.7 (t, $^{2}J_{PC}$ 8.0 = Hz), 131.3 (t, $^{3}J_{PC}$ = 6.5 Hz), 158.9 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 18.7 (s). Anal. Calcd for $C_{16}H_{28}O_7P_2$: C 48.73; H 7.16. Found: C, 48.59; H, 7.05.

4.13 | Tetraethyl (2,5-dimethoxyphenyl) methylenediphosphonate (2c)

Yield 76%, bp 212°C (2 mm Hg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 3.52 (s, 3H, MeO), 3.55 (s, 3H, MeO), 4.35 (t, 1H, $^{2}J_{PH}$ = 26.0 Hz, C^{1}H), 6.45-6.60 (m, 2H), 7.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 35.5 (t, $^{1}J_{PC}$ = 133.0 Hz, C^{1}), 55.3 (s, OMe), 56.3 (s, OMe), 111.8 (s), 113.9 (s), 116.2 (t, $^{3}J_{PC}$ = 4.5 Hz), 119.3 (t, $^{2}J_{PC}$ = 8.0 Hz), 150.8 (t, $^{3}J_{PC}$ = 7.0 Hz), 153.1 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 19.1 (s). Anal. Calcd for $C_{17}H_{30}O_8P_2$: C 48.11; H 7.13. Found: C, 48.02; H, 7.06.

4.15 | Tetra(trimethylsilyl) (4-methoxyphenyl) methylenediphosphonate (2e)

A mixture of anisylidene dichloride (4.4 g, 0.023 mol), diethyl trimethylsilyl phosphite (14 g, 0.067 mol), and zinc chloride (0.2 g, 0.0015 mol) was heated under 160°C for 2 hour and was then distilled. The fraction at 120-180°C (1 mm Hg) contained diphosphonate **2b** (δ_P 18.8, s) and diphosphonate **2d** (δ_P 19.2 [d, $^{2}J_{PP}$ = 45.4 Hz], 9.2 [d, $^{2}J_{PP}$ = 45.4 Hz]). The mixture of diphosphonates **2b** and **2d** and concentrated hydrochloric acid (40 mL) was heated on a boiling water bath for 4 hour and then evaporated to dryness at 7 mm Hg, then water (30 mL) was added to the residue and distilled off in a vacuum 7 mm Hg. The residue was refluxed with bis(trimethylsilyl)amine (30 mL) and chlorotrimethylsilane (5 g) to complete ammonium chloride sublimation. The excess of bis(trimethylsilyl) amine was removed, and the residue was distilled to obtain 10.5 g of diphosphonate **2e**. Yield 80%, bp 168°C (1 mm Hg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: −0.17 (s, 18H, 2 Me_3Si), −0.15 (s, 18H, 2 Me_3Si), 3.07 (t, 1H, $^{2}J_{PH}$ = 26.0 Hz, C^{1}H), 3.43 (s, 3H, MeO), 6.51 (d, 2H, $^{3}J_{HH}$ = 8.0 Hz, 2 CH_{Ph}), 6.99 (d, 2H, $^{3}J_{HH}$ = 8.0 Hz, 2 CH_{Ph}). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 0.5 (s, Me_3Si), 47.9 (t, $^{1}J_{PC}$ = 140.0 Hz, C^{1}), 54.9 (s, MeO), 124.2 (t, $^{2}J_{PC}$ = 8.0 Hz), 131.3 (t, $^{2}J_{PC}$ = 6.5 Hz), 113.37 (s), 158.77 (s). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: −0.5 (s). Anal. Calcd for $C_{20}H_{44}O_7P_2Si_4$: C 42.08; H 7.77. Found: C 41.74; H 7.64.

4.16 | Reaction of triethyl phosphite and benzylidene dichloride

A mixture of triethyl phosphite (10.0 g, 0.06 mol), benzylidene dichloride (4.0 g, 0.025 mol), and zinc chloride (0.2 g, 0.0015 mol) was heated at 160°C and then distilled. The fraction boiling at 120-125°C (2 mm Hg) contained diethyl benzylphosphonate. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 2.96 (d, 2H, $^{2}J_{PH}$ = 24 Hz, CH_2P). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 33.5 (d, $^{1}J_{PC}$ = 137 Hz, CH_2P). ^{31}P NMR

($CDCl_3$, 162 MHz), δ, ppm: 26.3 (s) and tetraethyl pyrophosphonate (δ_P −13.2 ppm, s).

4.17 | Hydroxy(4-methoxyphenyl) methylphosphonic acid (5a)

A solution of 10.6 g (0.025 mol) of phosphonate **1a** in ether (15 mL) was added to methanol (40 mL) under stirring and cooling to 10°C, a mixture was refluxed, then the solvent was removed. White crystals were kept in vacuum 1 mm Hg for 1 hour to give 4.7 g of acid **5a**, yield 96%, mp 78°C. ^{1}H NMR (D_2O, 400 MHz), δ, ppm: 3.44 (s, 3H, MeO), 4.71 (d, 1H, $^2J_{PH}$ = 12.0 Hz, C^{1}H), 6.67 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 7.12 (d, 2H, $^3J_{HH}$ = 8.0 Hz). ^{13}C NMR (D_2O, 100 MHz), δ, ppm: 55.2 (s, MeO), 69.8 (d, $^1J_{PC}$ = 160.0 Hz, C^1), 113.9 (s), 128.5 (d, $^3J_{PC}$ = 6.0 Hz), 129.0 (s), 158.3 (s). ^{31}P NMR (D_2O, 162 MHz), δ, ppm: 20.8 (s) (cf [5]).

The acids **5b-f** and **6a,b** were prepared similarly.

4.18 | Hydroxy(2,3-dimethoxyphenyl) methylphosphonic acid (5b)

Yield 95%, viscous oil. ^{1}H NMR (CD_3OD, 400 MHz), δ, ppm: 3.84 (s, 3H, MeO), 3.88 (s, 3H, MeO), 5.47 (d, 1H, $^2J_{PH}$ = 12.8 Hz, C^{1}H), 6.98 (d, 1H, $^3J_{HH}$ = 8.0 Hz), 7.12 (t, 1H, $^3J_{HH}$ = 8 Hz), 7.28 (d, 1H, $^3J_{HH}$ = 8.0 Hz). ^{13}C NMR (CD_3OD, 100 MHz), δ, ppm: 55.1 (s, MeO), 60.2 (s, MeO), 63.9 (d, $^1J_{PC}$ = 164.5 Hz, C^1), 112.1 (s), 120.8 (d, $^3J_{PC}$ = 2.7 Hz), 123.8 (s), 131.6 (s), 146.5 (d, $^3J_{PC}$ = 7.4 Hz), 152.3 (s). ^{31}P NMR (CD_3OD, 162 MHz), δ, ppm: 21.3 (s). Anal. Calcd for $C_9H_{13}O_6P$: C 43.56; H 5.18. Found: C 43.46; H 5.30.

4.19 | Hydroxy(3-pyridyl)methylphosphonic acid (5c)

Yield 94%, mp 219°C (decomposition). ^{1}H NMR (D_2O-C_5D_5N, 400 MHz), δ, ppm: 4.40 (d, 1H, $^2J_{PH}$ = 13.6 Hz, C^{1}H), 6.53 (br. s, 1H), 7.38 (br. s, 1H), 7.42 (br. s, 1H), 7.96 (br. s, 1H). ^{13}C NMR (D_2O-C_5D_5N, 100 MHz), δ, ppm: 69.1 (d, $^1J_{PC}$ = 148.3 Hz, C^1), 122.91 (s), 136.5 (s), 136.1 (s), 144.2 (s), 144.5 (d, $^3J_{PC}$ = 3.0 Hz). ^{31}P NMR (D_2O-C_5D_5N, 162 MHz), δ, ppm: 14.7 (s). Anal. Calcd for $C_6H_8NO_4P$: C 38.11; H 4.26. Found: C 37.89; H 4.15.

4.20 | Hydroxy(4-pyridyl)methylphosphonic acid (5d)

Yield 96%, mp 239°C (decomposition). ^{1}H NMR (D_2O-C_5D_5N, 400 MHz), δ, ppm: 6.69 (br. s, 1H, C^{1}H), 7.20 (d, 2H, $^3J_{HH}$ = 5.2 Hz), 7.87 (d, 2H, $^3J_{HH}$ = 5.2 Hz). ^{13}C NMR (D_2O-C_5D_5N, 100 MHz), δ, ppm: 71.3 (d, $^2J_{PC}$ = 141.4 Hz, C^1), 122.0 (d, $^3J_{PC}$ = 3.5 Hz), 145.5 (s), 153.0 (s). ^{31}P NMR (D_2O-C_5D_5N, 162 MHz), δ, ppm: 13.8 (s). Anal. Calcd for $C_6H_8NO_4P$: C 38.11; H 4.26. Found: C 37.99; H 4.12.

4.21 | (4-Dimethylaminophenyl) hydroxymethylphosphonic acid (5e)

Yield 96%, mp 152°C. ^{1}H NMR (D_2O-C_5D_5N, 400 MHz), δ, ppm: 1.85 (s, 6H, 2 CH_3), 4.30 (d, 1H, $^2J_{PH}$ = 11.6 Hz, C^{1}H), 5.85 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 6.73 (d, 2H, $^3J_{HH}$ = 8.0 Hz). ^{13}C NMR (D_2O-C_5D_5N, 100 MHz), δ, ppm: 40.1 (s, 2 Me), 71.1 (d, $^1J_{PC}$ = 152.4 Hz, C^1), 113.1 (s), 127.4 (d, $^3J_{PC}$ = 4.9 Hz), 129.7 (s), 147.8 (s). ^{31}P NMR (D_2O-C_5D_5N, 162 MHz), δ, ppm: 17.2 (s). Anal. Calcd for $C_9H_{14}NO_4P$: C 46.46; H 6.10. Found: C 46.64; H 6.16.

4.22 | (4-Bromophenyl) ethoxymethylphosphonic acid (5f)

Yield 96%, viscous oil. ^{1}H NMR (CD_3OD, 400 MHz), δ, ppm: 1.21 (t, 3H, CH_3, $^3J_{HH}$ = 7.2 Hz), 3.53 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2O), 4.62 (d, 2H, $^2J_{PH}$ = 16.4 Hz, C^{1}H), 7.40 (d, 2H, $^3J_{HH}$ = 7.2 Hz), 7.50 (d, 2H, $^3J_{HH}$ = 7.2 Hz). ^{13}C NMR (CD_3OD, 100 MHz), δ, ppm: 14.6 (s, Me), 66.5 (d, $^2J_{PC}$ = 12.8 Hz, CH_2O), 78.0 (d, $^1J_{PC}$ = 164.5 Hz, C^1). ^{31}P NMR (CD_3OD, 162 MHz), δ, ppm: 17.8 (s). Anal. Calcd for $C_9H_{12}BrO_4P$: C, 36.64; H, 4.10. Found: C 36.52; H 4.03.

4.23 | (4-Dimethylaminophenyl) methylenediphosphonic acid (6a)

Yield 98%, mp 147°C. ^{1}H NMR (D_2O, 400 MHz), δ, ppm: 2.45 (s, 6H, Me_2N), 3.75 (t, 1H, $^2J_{PH}$ = 23.2 Hz, C^{1}H), 6.26 (d, 2H, $^2J_{PH}$ = 6.8 Hz), 7.40 (d, 2H, $^3J_{HH}$ = 6.8 Hz). ^{13}C NMR (D_2O, 100 MHz), δ, ppm: 40.7 (s, Me_2N), 48.2 (t, $^1J_{PC}$ = 117.2 Hz), 113.1 (s), 125.6 (t, $^2J_{PC}$ = 6.5 Hz), 131.3 (s), 147.6 (s). ^{31}P NMR (D_2O, 162 MHz), δ, ppm: 17.0 (s). Anal. Calcd for $C_9H_{15}NO_6P_2$: C, 36.62; H, 5.12. Found: C, 36.52; H, 5.06.

4.24 | (4-Fluorophenyl) hydroxymethylphosphonic acid (5g)

A mixture of phosphonate **4a** (3 g, 0.011 mol) and concentrated hydrochloric (20 mL) was heated on a boiling water bath for 4 hour and then evaporated to dryness at 7 mm Hg. Water (30 mL) was added to the residue and then was distilled off in a vacuum to give 2 g of acid **5g**, yield 92%, mp 69°C. ^{1}H NMR (D_2O, 400 MHz), δ, ppm: 4.72 (d, 1H, $^2J_{PH}$ = 12.0 Hz, C^{1}H), 7.10-7.15 (m, 2H), 7.41-7.44 (m, 2H). ^{13}C NMR (D_2O, 100 MHz), δ, ppm: 70.1 (d, $^1J_{PC}$ 160.0 Hz, C^1), 136.7 (s), 129.7 (s), 114.7 (d, $^2J_{FC}$ = 21.0 Hz), 161.8 (d, $^1J_{FC}$ = 244.0 Hz). ^{31}P NMR (D_2O, 162 MHz), δ, ppm: −18.5 (s) (cf [12]).

The acids **5a**, **6b** were prepared similarly.

4.25 | (4-Methoxyphenyl) methylenediphosphonic acid (6b)

Yield 96%, mp 92°C. ^{1}H NMR (D_2O, 400 MHz), δ, ppm: 3.59 (t, 1H, $^{2}J_{PH}$ = 26.2 Hz, C^{1}H), 3.57 (s, 3H, MeO), 6.65 (d, 2H, $^{3}J_{PH}$ = 8.0 Hz), 7.20 (d, 2H, $^{3}J_{PH}$ = 8.0 Hz). ^{13}C NMR (D_2O, 100 MHz), δ, ppm: 45.1 (t, $^{1}J_{PC}$ = 126.5 Hz, C^{1}), 54.7 (s, MeO), 114.72 (s), 125.0 (t, $^{2}J_{PC}$ = 7.5 Hz), 131.1 (t, $^{3}J_{PC}$ = 6 Hz), 157.8 (s). ^{31}P NMR (D_2O, 162 MHz), δ, ppm: 17.9 (s). Anal. Calcd for $C_8H_{12}O_7P_2$: C 34.06; H 4.29. Found: C 33.94; H 4.38.

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