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Bisphosphonate prodrugs: synthesis of new aromatic and aliphatic 1-hydroxy-1,1-bisphosphonate partial esters

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Abstract—Methods for the preparation of various 1-hydroxy-1,1-bisphosphonate partial esters were developed. They were obtained from (alkyl or phenyl) bis(trimethylsilyl) phosphite and aromatic or aliphatic acid chlorides, followed by methanolysis.

1. Introduction

1-Hydroxymethylene-1,1-bisphosphonic acids (HMBP) are an important class of drugs used clinically in the treatment of bone diseases involving excessive bone destruction or resorption such as Paget's disease, osteoporosis and bone metastases.[1,2] They are also routinely used as ^{99}Tc complexes in skeletal scintigraphy. They are structural analogues of natural pyrophosphates containing a P–C–P backbone and so are stable to enzymatic hydrolysis. More recently, bisphosphonates have been used for treatment of metastatic cancer. It has been shown that these compounds were able to inhibit bone metastases proliferation in prostate or breast cancer.[3–5] They also inhibit experimental angiogenesis in vitro and in vivo.[2,6–8] In addition, HMBP have also activity against several trypanosomatid and apicomplexan parasites.[9,10]

Unfortunately, the bio-availability of HBMP's is very poor because of their strong hydrophilicity and their negative charges due to their high ionization at physiological pH values. These properties characterize poor cell membrane permeability. Moreover, they also have powerful complexation properties towards calcium and other divalent metal cations decreasing their gastro-intestinal absorption. As such, only 3–7% of the drug is metabolized.[11] As the side chain of HMBP is responsible for most of the activity, the modification of some of the phosphonic acid functions should be a satisfying way to increase lipophilicity. Masking groups for the negative charge, introduced as phosphonoester, could be an interesting approach for a prodrug strategy. Few studies about the design of bisphosphonate prodrugs have been reported in the literature.[12–14] Only a few reports with phosphonoesters prodrugs[15,16] but such a modification is widely used in phosphate chemistry.[17,18]

Synthesis of 1-hydroxymethylene-1,1-bisphosphonate is usually achieved from condensation of a trialkylphosphite on an acid chloride leading to an α-ketophosphonate which then reacts with a dialkyl phosphite.[19–21] Different improvements of this method were proposed. Burgada et al.[22–24] described a one pot reaction between acid halides and a mixture of trialkyl and dialkyl phosphites and Ruel et al.[25] used anions of dialkyl phosphites to obtain directly the bisphosphonate tetraesters, at low temperature. The main drawback of these techniques are the thermal and basic instability of bisphosphonate tetraesters that promote their phosphonate–phosphate isomerisation.[26] Moreover the regioselective dealkylation to obtain partial esters is difficult and does not occur in good yield. Our group recently proposed a very mild and one-pot synthesis to obtain bisphosphonate methyl esters from bis(trimethylsilyl)-methyl phosphite and acyl chloride.[27]

Herein, we will present the extension of this synthesis to various 1-hydroxymethylene-1,1-bisphosphonate diesters using several alkyl or aryl substituents.

2. Results and discussion

Alkyl or arylbis(trimethylsilyl) phosphites **2** were obtained

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from corresponding dialkyl phosphite first by dealkylation with ammonia and then by silylation of the ammonium monoalkyl or aryl phosphite **1**. The silylphosphites were then reacted with acid chlorides to yield after hydrolysis, the corresponding HMBP symmetrical diesters **3** (Scheme 1).

Mono alkyl or aryl phosphites were synthesized as described by Hammond[28] from the dialkyl (or diphenyl) phosphites by reaction with a 30% ammonia solution. Reactions were exothermic and addition of the ammonia solution was carefully done at 0 °C. The course of the reactions were followed by $^{31}P\{^{1}H\}$ NMR and depending on the nature of the alkyl or aryl substituent the reaction time varied from one hour starting from dimethyl phosphite to one day for the less reactive ditetradecyl phosphite (Table 1). For all compounds **1a-e**, co-evaporation with dry pyridine and benzene was necessary to get rid of water at the end of the reaction. In the case of ammonium phenyl **1d**, or tetradecyl phosphites **1e**, products were further precipitated in dry ether and washed several times to remove phenol or tetradecanol formed. All the obtained compounds gave in $^{31}P\{^{1}H\}$ NMR a large doublet centred around 4–10 ppm with a characteristic coupling constant $^{1}J_{P-H} \approx 640$ Hz (Table 1).

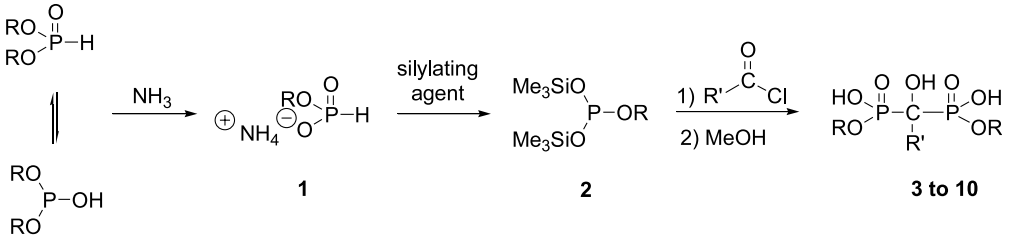
Numerous silylating reagents were described to silylate mono(alkyl or aryl) phosphites. Voronkov and Orlov[29,30] initially used trimethylsilyl chloride in pyridine and Sekine described use of HMDS, BSA, BSTFA.[31,32] In our case with alkyl phosphites, the use of hexamethyldisilazane gave good results. Reactions were conducted by heating the ammonium mono(alkyl or phenyl) phosphite in freshly distilled HMDS, under nitrogen and using dry vessels. Reaction evolution was followed by $^{31}P\{^{1}H\}$ NMR. We first observed the formation of the monosilylated phosphite giving a signal at approximately 13 ppm and then the formation of the alkyl or arylbis(trimethylsilyl) phosphite giving a characteristic signal between 115–125 ppm (Table 1). Once again we observed a difference in reactivity depending on the ammonium mono(alkyl or aryl) phosphite. Reaction time needed to achieve completion increased from methyl bis(trimethylsilyl) phosphite **2a** to tetradecyl (trimethylsilyl) phosphite **2e**. Moreover, in the case of the reaction of ammonium phenyl phosphite **1d** with HMDS, yield was lower than with ammonium alkyl phosphite. If heated to more than 90 °C a new signal was observed in $^{31}P\{^{1}H\}$ NMR at 114 ppm corresponding to the formation of tris(trimethylsilyl) phosphite. The same phenomenon was observed with tetradecyl phosphite but in a less extent. All (alkyl or phenyl) bis(trimethylsilyl) phosphite were distilled prior use except for the tetradecyl bis(trimethylsilyl) phosphite **2e** which was used, after HMDS evaporation, without further purification. To avoid the formation of tris(trimethylsilyl) phosphite when synthesizing phenyl bis(trimethylsilyl) phosphite, BSA could be used as silylating agent. In this case, the reaction was performed at −10 °C, in 1 h, using 5 equiv of BSA.

Table 1. Preparation of alkyl bis(trimethylsilyl) phosphites or aryl bis(trimethylsilyl) phosphites

Compound	R	Reaction conditions	$^{31}P\{^{1}H\}$ NMR (D_2O) ppm	Yield %
1a	CH_3	6 h, rt	9.2	95
1b	CH_3CH_2	6 h, rt	6.9	87
1c	$(CH_3)_2CH$	12 h, rt	4.9	50
1d	C_6H_5	2 h, rt	4.5	95
1e	$C_{14}H_{29}$	24 h, rt	6.2	85
2a	CH_3	6 h, reflux, HMDS	115.8	58
2b	CH_3CH_2	8 h, reflux, HMDS	116.1	55
2c	$(CH_3)_2CH$	24 h, reflux, HMDS	118.2	60
2d	C_6H_5	2 h, 90 °C, HMDS	121.5	45
2e	$C_{14}H_{29}$	24 h, reflux, HMDS	115.0	80

As previously described for reaction between tris(trimethylsilyl) phosphite with acid chlorides the procedure for (alkyl or phenyl) bis(trimethylsilyl) phosphites was still efficient in aromatic or aliphatic series. Various aliphatic acid chlorides, differently substituted aromatics acid chlorides and heterocyclic acid chlorides have been used, all giving good yields of HMBP (Table 2). The key features of this synthetic pathway were the use of silylated phosphites **2** which reacted readily with acid chlorides. A first equivalent reacted following an Arbuzov mechanism yielding a silylated α-ketophosphonate intermediate (Scheme 2). A second addition of the (alkyl or aryl) bis(trimethylsilyl) phosphite led to the fully silylated symmetrical bisphosphonate diester. This product was then hydrolyzed with methanol to the corresponding symmetrical bisphosphonate diester.

For each addition of the aryl or alkyl bis(trimethylsilyl) phosphite **2** the reaction always evolved towards the leaving of a silyl group rather than the alkyl or the aryl group. In fact, alkyl or aryl esters of phosphite were less reactive than silyl esters towards nucleophiles. Typically alkyl and aryl bis(trimethylsilyl) phosphites **2** and acid chloride were reacted for 2 h at room temperature under nitrogen without solvent or in a minimum of dry THF for solid acid chlorides. The reaction was strongly exothermic and the addition must be done in an ice bath. Reactions were followed by $^{31}P\{^{1}H\}$



Scheme 1.

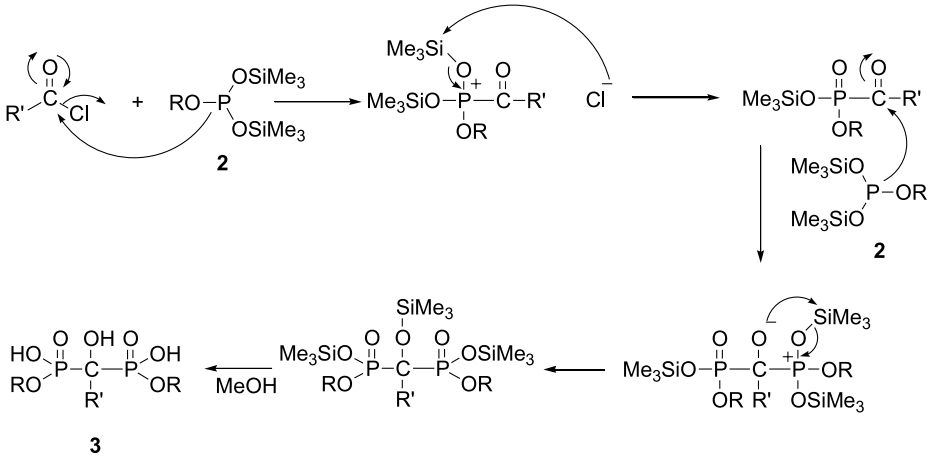
Table 2. Synthesis of HMBP partial esters **3** to **10** produced via Scheme 1

HMBP partial esters	R	R′	$^{31}P\{^{1}H\}$ NMR (D_2O) ppm	Yield %
3a	CH_3	CH_3	23.9	90
3b	CH_3CH_2	CH_3	19.9	95
3c	$(CH_3)_2CH$	CH_3	18.8	90
3d	C_6H_5	CH_3	17.4	65
3e	$C_{14}H_{29}$	CH_3	19.4	88
4a	CH_3	$(CH_3)_2CH$	24.2	85
4b	CH_3CH_2	$(CH_3)_2CH$	20.8	86
4c	$(CH_3)_2CH$	$(CH_3)_2CH$	20.4	92
4d	C_6H_5	$(CH_3)_2CH$	17.4	49
4e	$C_{14}H_{29}$	$(CH_3)_2CH$	20.9	81
5a	CH_3	$C_{15}H_{31}$	24.1	85
5b	CH_3CH_2	$C_{15}H_{31}$	20.2	95
5c	$(CH_3)_2CH$	$C_{15}H_{31}$	18.5	93
5d	C_6H_5	$C_{15}H_{31}$–	16.2	37
5e	$C_{14}H_{29}$	$C_{15}H_{31}$–	20.6	69
6a	CH_3	C_6H_5–CH_2	20.8	90
6b	CH_3CH_2	C_6H_5–CH_2	19.7	95
6c	$(CH_3)_2CH$	C_6H_5–CH_2	18.0	55
6d	C_6H_5	C_6H_5–CH_2	15.9	90
6e	$C_{14}H_{29}$	C_6H_5–CH_2	15.4	63
7a	CH_3	C_6H_5	18.2	90
7b	CH_3CH_2	C_6H_5	16.9	85
7c	$(CH_3)_2CH$	C_6H_5	16.4	95
7d	C_6H_5	C_6H_5	11.6	78
7e	$C_{14}H_{29}$	C_6H_5	15.3	77
8a	CH_3	C_6H_4–Br	17.3	90
8b	CH_3CH_2	C_6H_4–Br	16.4	72
8c	$(CH_3)_2CH$	C_6H_4–Br	15.6	80
8d	C_6H_5	C_6H_4–Br	12.8	70
8e	$C_{14}H_{29}$	C_6H_4–Br	14.6	80
9a	CH_3	C_6H_4–OCH_3	16.3	92
9b	CH_3CH_2	C_6H_4–OCH_3	17.3	60
9c	$(CH_3)_2CH$	C_6H_4–OCH_3	16.6	77
9d	C_6H_5	C_6H_4–OCH_3	13.5	81
9e	$C_{14}H_{29}$	C_6H_4–OCH_3	15.4	69
10a	CH_3	C_5H_4N	14.8	75
10b	CH_3CH_2	C_5H_4N	14.8	90
10c	$(CH_3)_2CH$	C_5H_4N	13.0	90
10d	C_6H_5	C_5H_4N	18.3	73
10e	$C_{14}H_{29}$	C_5H_4N	12.5	50

NMR. After evaporation of the volatile fractions and methanolysis, crude products were purified by precipitation. Products presented a unique signal in $^{31}P\{^{1}H\}$ NMR as expected for symmetric bisphosphonates. Observed chemical shifts were slightly lower than what was described for corresponding 1-hydroxymethylene-1,1-bisphosphonic acids. This decrease in the $^{31}P\{^{1}H\}$ NMR chemical shift value was more pronounced in the alkyl family from methyl to isopropyl and even more pronounced for phenyl esters. All compounds also presented in $^{13}C\{^{1}H\}$ NMR a triplet for the carbon bearing the two phosphonate groups with a coupling constant of approximately 145–155 Hz. Yields were usually good whether substrates were aliphatic, aromatic or heteroaromatic. They were slightly higher varying from 60 to 95% for alkyl esters compared to phenyl esters. This fact could be explained by the relative thermal instability of such diphenyl bisphosphonates. When reacting phenyl bis(trimethylsilyl) phosphite **2d** with acid chlorides, addition must be carried out carefully to avoid thermal dealkylation of the diphenyl bisphosphonate formed. For example, when reacting phenyl bis(trimethylsilyl) phosphite with palmitoyl chloride, if the addition was not done in an ice bath, new signals appeared in $^{31}P\{^{1}H\}$ NMR. After methanolysis, together with the signal at 15.7 ppm for the symmetrical bisphosphonate diphenyl ester **5d**, we observed two doublets centred on 16.2 and 20.1 ppm corresponding to the bisphosphonate monophenyl ester. This compound which was not symmetric possessed two different phosphorus atoms which coupled together with a 42 Hz coupling constant.

3. Conclusion

We have described a convenient route to a new class of bisphosphonate partial ester derivatives. This procedure offers many possibilities for combining together different aromatic and aliphatic phosphonic ester groups and aromatic and aliphatic substituents on 1-hydroxymethylene-1,1-bisphosphonic side chain group. It allows access to an extremely varied library of bisphosphonate partial esters with potent biological applications. Recently, we have shown that these compounds have anti-angiogenic and anti-tumor effects in breast carcinoma models.[33]



Scheme 2.

4. Experimental

4.1. General methods

Unless otherwise noted, all solvents and reagents were high-purity-grade materials and used without further purification. THF was distilled from benzophenone sodium. Diethylether, benzene and hexane were distilled from sodium. Pyridine was distilled from potassium hydroxide. Hexamethyldisilazane was distilled prior use. Solid acyl chlorides were used directly and liquid acid chlorides were distilled under reduced pressure. Ditetradecyl phosphite was obtained from transesterification of diphenyl phosphite as described by G Le Bolc'h.[34]

Boiling points are given in Torr (Bp_{value}). NMR spectra were recorded with a VARIAN Unity Inova 500 MHz (^{13}C: 125.9 MHz, ^{1}H: 500.6 MHz, ^{31}P: 200.7 MHz) or a VARIAN Gemini 200 MHz (^{13}C: 50.3 MHz, ^{1}H: 200 MHz, ^{31}P: 80.9 MHz) spectrometer in D_2O, $CDCl_3$, or DMSO-d^6. Chemical shifts (δ) are given in ppm. ^{31}P and ^{13}C NMR spectra were recorded with phosphoric acid and methanol as external references, respectively. ^{1}H NMR spectra were recorded using HOD or trimethylsilane as internal standard in D_2O or $CDCl_3$. Attribution of aromatic carbons and protons is given in the text by adding *o* for ortho, *m* for meta and *p* for para.

Mass spectra were recorded in positive reflectron mode with DHB as a matrix on a MALDI-TOF-MS (Bruker). Microanalyses were performed by the Service Central d'Analyse, CNRS, F-69390, Vernaison, France.

4.2. General procedure for synthesis of ammonium alkyl phosphites 1a to 1e

In a 250 mL round bottom three neck flask, equipped with a thermometer and a condenser, 20 mL of concentrated ammonia solution (33%) were added carefully over 30 min, to dialkylplhosphite (**1**, 75 mmol). An exothermic reaction took place for **1d** and **1e** and the solution was therefore kept at room temperature using an ice bath. When the addition was completed, the mixture was set aside at room temperature for 2 h for **1d**, 6 h for **1a** and **1b**, 12 h for **1c** and 24 h for **1e**. Except for **1d**, which gave an emulsion the other compounds gave clear solutions. Then solutions were concentrated in vacuo. The resulting solid was dried by repeated co-evaporation with dry benzene (3×20 mL), and then dry pyridine (3×20 mL) and finally, precipitated in diethylether for **1d** and **1e**.

4.2.1. Ammonium methyl *H*-phosphonate (1a). Yield: 95%. Mp 108 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, D_2O) δ 9.2. ^{1}H NMR (200 MHz, D_2O) δ 3.39 (d, 3H, $^{3}J_{P-H}=12.4$ Hz, OCH_3). ^{13}C NMR $\{^{1}H\}$ (125.9 MHz, D_2O) δ 53.9 (OCH_3).

4.2.2. Ammonium ethyl *H*-phosphonate (1b). Yield: 87%. Mp 93 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, D_2O) δ 6.9. ^{1}H NMR (200 MHz, D_2O) δ 1.09 (t, 3H, $^{3}J_{H-H}=7$ Hz, OCH_2CH_3) 3.75 (dt, 2H, $^{3}J_{H-H}=7$ Hz; $^{3}J_{P-H}=7$ Hz, OCH_2CH_3). ^{13}C NMR $\{^{1}H\}$ (125.9 MHz, D_2O) δ 18.4 (OCH_2CH_3), 63.1 (OCH_2CH_3).

4.2.3. Ammonium isopropyl *H*-phosphonate (1c). Yield: 50%. Mp 132 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, D_2O) δ 4.9. ^{1}H NMR (200 MHz, D_2O) δ 1.08 (d, 3H, $^{3}J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 1.18 (d, 3H, $^{3}J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 4.15–4.43 (m, 1H, $OCH(CH_3)_2$). ^{13}C NMR $\{^{1}H\}$ (125.9 MHz, D_2O) δ 26.6 ($OCH(CH_3)_2$), 72.3 ($OCH(CH_3)_2$).

4.2.4. Ammonium phenyl *H*-phosphonate (1d). Yield: 95%. Mp 133 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, D_2O) δ 4.5. ^{1}H NMR (200 MHz, D_2O) δ 6.94–7.07 (m, 3H, C_6H_5), 7.20–7.23 (m, 2H, C_6H_5). ^{13}C NMR $\{^{1}H\}$ (125.9 MHz, D_2O) δ 124.1 (*o*-C_6H_5), 127.9 (*p*-C_6H_5), 133.2 (*m*-C_6H_5), 153.9 (OC_6H_5).

4.2.5. Ammonium tetradecyl *H*-phosphonate (1e). Yield: 85%. Mp 52 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, D_2O) δ 6.2. ^{1}H NMR (200 MHz, D_2O) δ 0.85 (t, 3H, $^{3}J_{H-H}=6.5$ Hz, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.23–1.27 (m, 22H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.30–1.33 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$), 4.10–4.11 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$). ^{13}C NMR $\{^{1}H\}$ (125.9 MHz, D_2O) δ 17.1 ($OCH_2CH_2(CH_2)_{11}CH_3$), 26.0 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 29.2, 33.2, 33.7 ($OCH_2CH_2(CH_2)_{10}$–$CH_2CH_3$), 35.5 ($OCH_2CH_2(CH_2)_{11}CH_3$), 67.5 ($OCH_2CH_2(CH_2)_{10}$–$CH_2CH_3$).

4.3. General procedure for synthesis of alkyl or aryl bis(trimethylsilyl) phosphite 2

In a 100 mL round-bottom three-neck flask equipped with a condenser and a thermometer, ammonium alkyl (or phenyl) phosphite **1** (20 mmol) was mixed, under nitrogen, with freshly distilled hexamethyldisilazane (95 mmol, 20 mL). Except in the case of synthesis of **2d** which was heated at 90 °C for 2 h, all the other products were obtained by refluxing the ammonium salts in hexamethyldisilazane, respectively, 6 h for **2a**, 8 h for **2b** and 24 h for **2c** and **2e**. For each compound, reaction evolution was monitored by ^{31}P $\{^{1}H\}$ NMR. Hexamethyldisilazane was then evaporated in vacuo (0.1 Torr). Tetradecylbis(trimethylsilyl) phosphite **2e** was used without further purification. All the other silyl phosphites **2a** to **2d** were distilled under vacuum.

4.3.1. Methyl bis(trimethylsilyl) phosphite (2a). Yield: 58%. $Bp_{0.1}$ 42 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, $CDCl_3$) δ 115.8. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.28 (s, 18H, $Si(CH_3)_3$), 3.4 (d, 3H, $^{3}J_{P-H}=12.1$ Hz, OCH_3).

4.3.2. Ethyl bis(trimethylsilyl) phosphite (2b). Yield: 55%. $Bp_{0.1}$ 50 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, $CDCl_3$) δ 116.1. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.21 (s, 18H, $Si(CH_3)_3$), 1.23 (t, 3H, $^{3}J_{H-H}=7$ Hz, OCH_2CH_3), 3.75–3.89 (m, 2H, OCH_2CH_3).

4.3.3. Isopropyl bis(trimethylsilyl) phosphite (2c). Yield: 60%. $Bp_{0.1}$ 54 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, $CDCl_3$) δ 118.2. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.20 (s, 18H, $Si(CH_3)_3$), 1.20 (d, 3H, $^{3}J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 1.34 (d, 3H, $^{3}J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 4.40–450 (m, 1H, $OCH(CH_3)_2$).

4.3.4. Phenyl bis(trimethylsilyl) phosphite (2d). Yield: 45%. $Bp_{0.1}$ 83 °C. ^{31}P NMR $\{^{1}H\}$ (80.9 MHz, $CDCl_3$) δ

121.5. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.22 (s, 18H, Si(CH_3)$_3$), 7.00–7.08 (m, 2H, C_6H_5), 7.24–7.31 (m, 3H, C_6H_5).

4.3.5. Tetradecyl bis(trimethylsilyl) phosphite (2e). Yield: 80%. ^{31}P NMR {^{1}H} (80.9 MHz, $CDCl_3$) δ 115.0. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.33 (s, 18H, Si(CH_3)$_3$), 0.88 (t, 3H, $^{3}J_{H-H}$=7 Hz, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.16–1.41 (m, 22H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.60–1.80 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.96–4.07 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$).

4.4. General procedure for synthesis of bisphosphonate dialkyl or diaryl esters 3-10

In a 50 mL round-bottom three-neck flask equipped with a thermometer, acid chloride (2.5 mmol) was added dropwise, under argon, at −5 °C, to dialkyl or diaryl phosphite (5 mmol). When addition was completed, reaction mixture was allowed to stand at room temperature for 2 h. The evolution of the reaction was monitored by ^{31}P {^{1}H} NMR. Then, volatile fractions were evaporated under reduced pressure (0.1 Torr) before being hydrolyzed with methanol. After evaporation, crude products were precipitated in an appropriate mixture of solvent.

4.4.1. [1-Hydroxy-1-(hydroxy-methoxy-phosphoryl)-ethyl]-phosphonic acid monomethyl ester (3a). Precipitation in diethylether. Yield: 90%. Mp 76 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 23.9. ^{1}H NMR (500 MHz, D_2O) δ 1.04 (t, 3H, $^{3}J_{P-H}$=16 Hz, CH_3–C(OH)), 3.14–3.22 (m, 6H, OCH_3). ^{13}C NMR {^{1}H} (50.3 MHz, D_2O) δ 17.7 (CH_3–C(OH)), 51.6 (OCH_3), 69.1 (t, $^{1}J_{P-C}$=152.6 Hz, P–C(OH)–P). Anal. Calcd for $C_4H_{12}O_7P_2$: C, 20.52; H, 5.17; P, 26.46; Found: C, 20.57; H, 5.19; P, 26.51.

4.4.2. [1-Hydroxy-1-(hydroxy-ethoxy-phosphoryl)-ethyl]-phosphonic acid monoethyl ester (3b). Precipitation in diethylether. Yield: 95%. Mp>260 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 19.9. ^{1}H NMR (500 MHz, D_2O) δ 1.26 (t, 6H, $^{3}J_{H-H}$=7 Hz, OCH_2CH_3), 1.52 (t, 3H, $^{3}J_{P-H}$=15 Hz, C(OH)CH_3), 3.98–4.10 (m, 4H, OCH_2CH_3). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 19.7 (OCH_2CH_3), 23.7 (CH_3C(OH)), 65.2 (s, OCH_2CH_3), 75.5 (t, $^{1}J_{P-C}$=146.0 Hz, P–C(OH)–P). Anal. Calcd for $C_6H_{16}O_7P_2$: C, 27.49; H, 6.15; P, 23.63; Found: C, 27.43; H, 6.13; P, 23.58.

4.4.3. [1-Hydroxy-1-(hydroxy-isoproxy-phosphoryl)-ethyl]-phosphonic acid monoisopropyl ester (3c). Precipitation in diethylether/hexane: 80/20. Yield: 90%. Mp 128 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 18.8. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, 6H, $^{3}J_{H-H}$=6.0 Hz, $OCH(CH_3)_2$), 1.33 (d, 6H, $^{3}J_{H-H}$=6.0 Hz, $OCH(CH_3)_2$), 1.62 (t, 3H, $^{3}J_{P-H}$=16.0 Hz, CH_3C(OH)), 4.77–4.86 (m, 2H, $OCH(CH_3)_2$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 18.4 (CH_3C(OH)), 23.9 ($OCH(CH_3)_2$), 24.3 ($OCH(CH_3)_2$), 71.4 (t, $^{1}J_{P-C}$=154.4 Hz, P–C(OH)–P), 73.1 ($OCH(CH_3)_2$). Anal. Calcd for $C_8H_{20}O_7P_2$: C, 33.11; H, 6.95; P, 21.35; Found: C, 33.15; H, 6.96; P, 21.44.

4.4.4. Disodium salt of [1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)-ethyl]-phosphonic acid monophenyl ester (3d). Precipitation in diethylether/hexane: 95/5. Yield: 65%. Mp>260 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 17.4. ^{1}H NMR (500 MHz, D_2O) δ 1.78 (t, 3H, $^{3}J_{P-H}$=16.0 Hz, CH_3C(OH)), 7.19 (t, 1H, $^{3}J_{H-H}$=7 Hz, p-C_6H_5), 7.26–7.29 (m, 2H, o-C_6H_5), 7.28–7.41 (m, 2H, m-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 23.7 (CH_3C(OH)), 75.5 (t, $^{1}J_{P-C}$=149.2 Hz, P–C(OH)–P), 124.2 (o-C_6H_5), 127.1 (p-C_6H_5), 132.7 (m-C_6H_5), 155.2 (OC_6H_5). Anal. Calcd for $C_{14}H_{14}Na_2O_7P_2$: C, 41.81; H, 3.51; P, 15.40; Found: C, 41.88; H, 3.53; P, 15.47.

4.4.5. [1-Hydroxy-1-(hydroxy-tetradecyloxy-phosphoryl)-ethyl]-phosphonic acid monotetra decyl ester (3e). Precipitation in diethylether. Yield: 88%. Mp<50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 19.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 6H, $^{3}J_{H-H}$=6.5 Hz, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.19–1.33 (m, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.30–1.37 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.63 (t, 3H, $^{3}J_{P-H}$=16 Hz, CH_3–COH), 4.08–4.14 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 ($OCH_2CH_2(CH_2)_{11}CH_3$), 22.9 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 25.9 (s, CH_3–COH), 29.9–30.7 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 32.2 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 67.8 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 71.6 (t, $^{1}J_{P-C}$=152.7 Hz, P–C(OH)–P). MS ($C_{30}H_{64}O_7P_2$): m/z 621.3 [M+Na+H]$^{+}$, 599.3 [M+H]$^{+}$. Anal. Calcd for $C_{30}H_{64}O_7P_2$: C, 60.18; H, 10.77; P, 10.35; Found: C, 60.13; H, 10.75; P, 10.31.

4.4.6. [1-Hydroxy-1-(hydroxy-methoxy-phosphoryl)-2-methyl-propyl]-phosphonic acid mono methyl ester (4a). Precipitation in diethylether. Yield: 85%. Mp 125 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 24.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (d, 3H, $^{3}J_{H-H}$=7 Hz, $(CH_3)_2CH$), 1.10 (d, 3H, $^{3}J_{H-H}$=7 Hz, $(CH_3)_2CH$), 2.16–2.28 (m, 1H, $(CH_3)_2CH$), 3.64–3.66 (m, 6H, OCH_3). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 17.1 ($(CH_3)_2CH$), 39.4 ($(CH_3)_2CH$), 57.4 (OCH_3), 78.1 (t, $^{1}J_{P-C}$=152.2 Hz, P–C(OH)–P). Anal. Calcd for $C_6H_{16}O_7P_2$: C, 27.49; H, 6.15; P, 23.63; Found: C, 27.43; H, 6.13; P, 23.60.

4.4.7. [1-Hydroxy-1-(hydroxy-ethoxy-phosphoryl)-2-methyl-propyl]-phosphonic acid mono ethyl ester (4b). Precipitation in diethylether. Yield: 86%. Mp 216 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 20.8. ^{1}H NMR (500 MHz, D_2O) δ 1.07 (d, 6H, $^{3}J_{H-H}$=7 Hz, $(CH_3)_2CH$), 1.19 (t, 6H, $^{3}J_{H-H}$=7 Hz, OCH_2CH_3), 2.14–2.26 (m, 1H, $(CH_3)_2CH$), 4.02–4.08 (m, 4H, OCH_2CH_3). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 19.1 (OCH_2CH_3), 20.8 ($(CH_3)_2CH$), 37.0 ($(CH_3)_2CH$), 66.6 (OCH_2CH_3), 80.6 (t, $^{1}J_{P-C}$=146.5 Hz, P–C(OH)–P). Anal. Calcd for $C_8H_{20}O_7P_2$: C, 33.11; H, 6.95; P, 21.35; Found: C, 33.07; H, 6.86; P, 21.28.

4.4.8. [1-Hydroxy-1-(hydroxy-isopropoxy-phosphoryl)-2-methyl-propyl]-phosphonic acid mono isopropyl ester (4c). Precipitation in diethylether.Yield: 92%. Mp 200 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 20.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, 6H, $^{3}J_{H-H}$=6.8 Hz, $(CH_3)_2CHCOH$), 1.32 (d, 6H, $^{3}J_{H-H}$=6 Hz, $OCH(CH_3)_2$), 1.34 (d, 6H, $^{3}J_{H-H}$=6 Hz, $OCH(CH_3)_2$), 2.30–2.42 (m, 1H, $(CH_3)_2CHCOH$), 4.76–4.86 (m, 2H, $OCH(CH_3)_2$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 18.3 ($(CH_3)_2CHCOH$), 24.0 ($OCH(CH_3)_2$), 24.4 ($OCH(CH_3)_2$), 32.9 ($(CH_3)_2CHCOH$), 72.5 ($OCH(CH_3)_2$), 77.4 (t, $^{1}J_{P-C}$=147.1 Hz, P–C(OH)–P). Anal. Calcd for $C_{10}H_{24}O_7P_2$: C, 37.74; H, 7.60; P, 19.47; Found: C, 37.82; H, 7.61; P, 19.51.

4.4.9. Disodium salt of [1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)-2-methyl-propyl]-phosphonic acid monophenyl ester (4d). Precipitation in water as diacid form. Yield: 49%. Mp 122 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 17.4. ^{1}H NMR (500 MHz, D_2O) δ 1.34 (d, 6H, $^{3}J_{H-H}$= 6.8 Hz, (CH_3)$_2$CH), 2.50–2.59 (m, 1H, (CH_3)$_2$C*H*), 7.20–7.26 (m, 6H, C_6H_5), 7.39 (t, 4H, $^{3}J_{H-H}$=7.5 Hz, *m*–C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 21.2 ((CH_3)$_2$CH), 37.5 ((CH_3)$_2$*C*H), 82.1 (t, $^{1}J_{P-C}$=143.9 Hz, P–*C*(OH)–P), 124.2 (*o*-C_6H_5), 127.8 (*p*-C_6H_5), 132.9 (*o*-C_6H_5), 153.9 (OC_6H_5). Anal. Calcd for $C_{16}H_{18}Na_2O_7P_2$: C 44.67; H, 4.22; P, 14.40; Found: C, 44.72; H, 4.23; P, 14.48.

4.4.10. [1-Hydroxy-1-(hydroxy-tetradecyloxy-phosphoryl)-ethyl]-phosphonic acid mono tetradecyl ester (4e). Yellow oil. Yield: 81%. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 20.9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 6H, $^{3}J_{H-H}$=6.5 Hz, OCH$_2$CH$_2$(CH$_2$)$_{11}$C*H*$_3$), 1.13–1.27 (m, 50H, OCH$_2$CH$_2$(C*H*$_2$)$_{11}$CH$_3$; (CH_3)$_2$CH), 1.32–1.33 (m, 4H, OCH$_2$C*H*$_2$(CH$_2$)$_{11}$CH$_3$), 2.46–2.53 (m, 1H, (CH_3)$_2$C*H*), 3.96–4.10 (m, 4H, OC*H*$_2$CH$_2$(CH$_2$)$_{11}$CH$_3$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 (OCH$_2$CH$_2$(CH$_2$)$_{11}$*C*H$_3$), 18.3 ((CH_3)$_2$CH), 22.9 (OCH$_2$CH$_2$(CH$_2$)$_{10}$*C*H$_2$CH$_3$), 25.7–30.7 (OCH$_2$CH$_2$(*C*H$_2$)$_{10}$CH$_2$CH$_3$), 32.1 (OCH$_2$*C*H$_2$(CH$_2$)$_{10}$CH$_2$CH$_3$), 32.8 ((CH_3)$_2$*C*H), 67.6 (O*C*H$_2$CH$_2$(CH$_2$)$_{10}$CH$_2$CH$_3$), 71.8 (t, $^{1}J_{P-C}$=152.7 Hz, P–*C*(OH)–P). MS ($C_{32}H_{66}O_7P_2Na_2$): *m/z* 670.8 [M+H]$^{+}$. Anal. Calcd for $C_{32}H_{68}O_7P_2$: C, 61.32; H, 10.93; P, 9.88; Found: C, 61.39; H, 10.95; P, 9.96.

4.4.11. [1-Hydroxy-1-(hydroxy-methoxy-phosphoryl)-hexadecyl]-phosphonic acid mono methyl ester (5a). Precipitation in diethylether. Yield: 85%. Mp 64 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 24.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 3H, $^{3}J_{H-H}$=7 Hz, C*H*$_3$(CH$_2$)$_{14}$COH), 1.23–1.26 (m, 24H, CH$_3$(C*H*$_2$)$_{12}$CH$_2$CH$_2$COH), 1.52–1.64 (m, 2H, CH$_3$(CH$_2$)$_{12}$C*H*$_2$CH$_2$COH), 1.96–1.99 (m, 2H, CH$_3$(CH$_2$)$_{12}$CH$_2$C*H*$_2$COH), 3.82–3.84 (m, 6H, OC*H*$_3$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$(CH$_2$)$_{15}$COH), 22.9 (CH$_3$*C*H$_2$(CH$_2$)$_{13}$COH), 23.4–30.5 (CH$_3$CH$_2$(*C*H$_2$)$_{11}$CH$_2$CH$_2$COH), 32.1 (CH$_3$CH$_2$(CH$_2$)$_{11}$*C*H$_2$CH$_2$COH), 33.4 (CH$_3$CH$_2$(CH$_2$)$_{11}$CH$_2$*C*H$_2$COH), 54.1 (*C*H$_3$O), 75.0 (t, $^{1}J_{P-C}$=151.0 Hz, P–*C*(OH)–P). Anal. Calcd for $C_{17}H_{37}O_7P_2$: C 49.15; H, 8.98; P, 14.91; Found: C, 49.07; H, 8.96; P, 14.82.

4.4.12. [1-Hydroxy-1-(hydroxy-ethoxy-phosphoryl)-hexadecyl]-phosphonic acid monoethyl ester (5b). Precipitation in diethylether. Yield: 95%. Mp 66 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 20.2. ^{1}H NMR (500 MHz, D_2O) δ 0.74 (t, 3H, $^{3}J_{H-H}$=7 Hz, C*H*$_3$(CH$_2$)$_{14}$COH), 1.15 (m, 30H, CH$_3$(C*H*$_2$)$_{12}$CH$_2$CH$_2$COH; OCH$_2$C*H*$_3$), 1.55–1.63 (m, 2H, CH$_3$(CH$_2$)$_{12}$C*H*$_2$CH$_2$COH), 1.93–2.07 (m, 2H, CH$_3$(CH$_2$)$_{12}$CH$_2$C*H*$_2$COH), 4.18–4.28 (m, 4H, OC*H*$_2$CH$_3$). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 17.1 (*C*H$_3$(CH$_2$)$_{14}$COH), 19.5 (OCH$_2$*C*H$_3$), 22.9 (CH$_3$*C*H$_2$(CH$_2$)$_{13}$COH), 25.9–33.4 (CH$_3$CH$_2$(*C*H$_2$)$_{11}$CH$_2$CH$_2$COH), 35.3 (CH$_3$CH$_2$(CH$_2$)$_{11}$*C*H$_2$CH$_2$COH), 37.6 (CH$_3$CH$_2$(CH$_2$)$_{11}$CH$_2$*C*H$_2$COH), 65.9 (O*C*H$_2$CH$_3$), 75.1 (t, $^{1}J_{P-C}$=149.2 Hz, P–*C*(OH)–P). Anal. Calcd for $C_{20}H_{24}O_7P_2$: C, 52.39; H, 9.67; P, 13.51; Found: C, 52.30; H, 9.65; P, 13.43.

4.4.13. [1-Hydroxy-1-(hydroxy-isopropoxy-phosphoryl)-hexadecyl]-phosphonic acid mono isopropyl ester (5c). Precipitation in diethylether. Yield: 93%. Mp<50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 18.5. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 3H, $^{3}J_{H-H}$=7 Hz, C*H*$_3$(CH$_2$)$_{14}$COH), 1.23–1.34 (m, 36H, CH$_3$(C*H*$_2$)$_{12}$CH$_2$CH$_2$COH; OCH(C*H*$_3$)$_2$), 1.53–1.62 (m, 2H, CH$_3$(CH$_2$)$_{12}$C*H*$_2$CH$_2$COH), 1.99–2.12 (m, 2H, CH$_3$(CH$_2$)$_{12}$CH$_2$C*H*$_2$COH), 4.79–4.83 (m, 2H, OC*H*(CH$_3$)$_2$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$(CH$_2$)$_{14}$COH), 22.9 (CH$_3$*C*H$_2$(CH$_2$)$_{13}$COH), 24.0 ((CH_3)$_2$CH), 24.3 ((CH_3)$_2$CH), 29.8 ((CH_3)$_2$*C*H), 32.1 (CH$_3$CH$_2$(CH$_2$)$_{11}$*C*H$_2$CH$_2$COH), 33.4 (CH$_3$CH$_2$(CH$_2$)$_{11}$CH$_2$*C*H$_2$COH), 72.7 (O*C*H(CH$_3$)$_2$), 74.3 (t, $^{1}J_{P-C}$=151.2 Hz, P–*C*(OH)–P). Anal. Calcd for $C_{21}H_{45}O_7P_2$: C, 53.49; H, 9.62; P, 13.14; Found: C, 53.54; H, 9.64; P, 13.20.

4.4.14. [1-Hydroxy-1-(hydroxy-phenoxy-phosphoryl)-hexadecyl]-phosphonic acid mono phenylester (5d). Yellow oil. Yield: 37%. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 16.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, $^{3}J_{H-H}$=7 Hz, C*H*$_3$(CH$_2$)$_{14}$COH), 1.15–1.29 (m, 24H, CH$_3$(C*H*$_2$)$_{12}$CH$_2$CH$_2$COH), 1.54–1.65 (m, 2H, CH$_3$ (CH$_2$)$_{12}$C*H*$_2$CH$_2$COH), 2.30 (t, 2H, $^{3}J_{H-H}$=8 Hz, CH$_3$ (CH$_2$)$_{12}$CH$_2$C*H*$_2$COH), 6.99–7.24 (m, 10H, C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$(CH$_2$)$_{14}$COH), 22.9 (CH$_3$*C*H$_2$(CH$_2$)$_{13}$COH), 24.9–30.1 (CH$_3$CH$_2$(*C*H$_2$)$_{11}$ CH$_2$CH$_2$COH), 32.2 (CH$_3$CH$_2$(CH$_2$)$_{11}$*C*H$_2$CH$_2$COH), 34.2 (CH$_3$CH$_2$(CH$_2$)$_{11}$CH$_2$*C*H$_2$COH), 75.0 (t, $^{1}J_{P-C}$=152.9 Hz, P–*C*(OH)–P), 121.0 (*o*-C_6H_5), 124.9 (*p*-C_6H_5), 129.7 (*m*-C_6H_5), 150.7 (OC_6H_5). Anal. Calcd for $C_{28}H_{44}O_7P_2$: C 60.64; H, 8.00; P, 11.17; Found: C, 60.59; H, 7.99; P, 11.12.

4.4.15. [1-Hydroxy-1-(hydroxy-tetradecyloxy-phosphoryl)-hexadecyl]-phosphonic acid mono tetradecyleste r (5e). Precipitation in hexane. Yield: 69%. Mp<50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 20.6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 9H, $^{3}J_{H-H}$=7 Hz, O(CH$_2$)$_{13}$C*H*$_3$; C*H*$_3$(CH$_2$)$_{14}$COH), 1.23–1.30 (m, 70H, OCH$_2$CH$_2$(C*H*$_2$)$_{11}$CH$_3$; CH$_3$(C*H*$_2$)$_{13}$CH$_2$COH), 1.56–1.61 (m, 4H, OCH$_2$C*H*$_2$(C*H*$_2$)$_{11}$CH$_3$), 1.86–2.00 (m, 2H, CH$_3$ (CH$_2$)$_{13}$C*H*$_2$COH), 4.01–4.09 (m, 4H, OC*H*$_2$CH$_2$(CH$_2$)$_{11}$CH$_3$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 (*C*H$_3$ (CH$_2$)$_{14}$COH; OCH$_2$CH$_2$(CH$_2$)$_{11}$*C*H$_3$), 22.9 (OCH$_2$(CH$_2$)$_{11}$*C*H$_2$CH$_3$; CH$_3$*C*H$_2$(CH$_2$)$_{13}$COH), 26.0–30.9 (OCH$_2$CH$_2$ (*C*H$_2$)$_{10}$CH$_2$CH$_3$; CH$_3$CH$_2$(*C*H$_2$)$_{11}$CH$_2$CH$_2$COH), 32.2 (CH$_3$CH$_2$(CH$_2$)$_{11}$*C*H$_2$CH$_2$COH; OCH$_2$*C*H$_2$(CH$_2$)$_{10}$CH$_2$CH$_3$), 34.2 (CH$_3$CH$_2$(CH$_2$)$_{11}$CH$_2$*C*H$_2$COH), 67.1 (O*C*H$_2$CH$_2$(CH$_2$)$_{10}$CH$_2$CH$_3$), 74.7 (t, $^{1}J_{P-C}$=148.3 Hz, P–*C*(OH)–P). MS ($C_{44}H_{90}O_7P_2Na_2$, pH=7.5): *m/z* 817.6 [M+Na+H]$^{+}$, 795.6 [M+H]$^{+}$. Anal. Calcd for $C_{44}H_{92}O_7P_2$: C, 66.46; H, 11.66; P, 7.79; Found: C, 66.53; H, 11.68; P, 7.84.

4.4.16. [1-Hydroxy-1-(hydroxy-methoxy-phosphoryl)-2-phenyl-ethyl]-phosphonic acid mono-methyl ester (6a). Precipitation in diethylether. Yield: 90%. Mp 130 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 20.8. ^{1}H NMR (500 MHz, D_2O) δ 3.16 (t, 2H, $^{3}J_{P-H}$=13.5 Hz, C_6H_5C*H*$_2$-COH), 3.44–3.49 (m, 6H, OC*H*$_3$), 7.14–7.20 (m, 3H, C_6H_5), 7.26 (d, 2H, $^{3}J_{H-H}$=6.5 Hz, C_6H_5). ^{13}C NMR {^{1}H} (50.3 MHz, DMSO-d_6) δ 37.2 (C_6H_5–*C*H$_2$–COH), 51.1 (O*C*H$_3$), 73.4 (t, $^{1}J_{P-C}$=145.4 Hz, P–*C*(OH)–P), 125.1 (*p*-C_6H_5–CH$_2$), 126.1 (*m*-C_6H_5–CH$_2$), 129.5 (*o*-C_6H_5–CH$_2$), 134.1 (C_6H_5–CH$_2$). Anal. Calcd for $C_{10}H_{16}O_7P_2$: C, 38.72; H, 5.20; P, 19.97; Found: C, 38.65; H, 5.19; P, 19.88.

4.4.17. [1-Hydroxy-1-(hydroxy-ethoxy-phosphoryl)-2-phenyl-ethyl]-phosphonic acid monoethyl ester (6b). Precipitation in diethylether. Yield: 95%. Mp 134 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 19.7. ^{1}H NMR (500 MHz, D_2O) δ 1.04 (t, 6H, $^{3}J_{H-H}=7$ Hz, OCH_2CH_3), 3.17 (t, 2H, $^{3}J_{P-H}=13.3$ Hz, $C_6H_5CH_2COH$), 3.84–3.91 (m, 4H, OCH_2CH_3), 7.16–7.21 (m, 3H, C_6H_5), 7.26 (d, 2H, $^{3}J_{H-H}=6.5$ Hz, *o*-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 19.2 (OCH_2CH_3), 42.0 (C_6H_5–CH_2–COH), 66.4 (OCH_2CH_3), 74.4 (t, $^{1}J_{P-C}=143.8$ Hz, P–*C*(OH)–P), 130.2 (*p*-C_6H_5–CH_2), 131.2 (*m*-C_6H_5–CH_2), 134.5 (*o*-C_6H_5–CH_2), 138.8 (C_6H_5–CH_2). Anal. Calcd for $C_{12}H_{20}O_7P_2$: C, 42.61; H, 5.96; P, 18.32; Found: C, 42.70; H, 5.97; P, 18.39.

4.4.18. [1-Hydroxy-1-(hydroxy-isopropoxy-phosphoryl)-2-phenyl-ethyl]-phosphonic acid mono isopropyl ester (6c). Precipitation in diethylether. Yield: 55%. Mp 130 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 18.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, $^{3}J_{H-H}=6.5$ Hz, 6H, ($OCH(CH_3)_2$), 1.22 (d, 6H, $^{3}J_{H-H}=6.5$ Hz, ($OCH(CH_3)_2$), 3.46 (t, 2H, $^{3}J_{P-H}=13.5$ Hz, $C_6H_5CH_2COH$), 4.72–4.81 (m, 2H, $OCH(CH_3)_2$), 7.26–7.29 (m, 3H, C_6H_5), 7.36 (d, 2H, $^{3}J_{H-H}=6.5$ Hz, *o*-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 26.9 ($OCH(CH_3)_2$), 27.2 ($OCH(CH_3)_2$), 42.4 (C_6H_5–CH_2–COH), 72.7 ($OCH(CH_3)_2$), 78.9 (t, $^{1}J_{P-C}=$ 140.8 Hz, P–*C*(OH)–P), 129.6 (*p*-C_6H_5–CH_2), 130.9 (*m*-C_6H_5–CH_2), 134.9 (*o*-C_6H_5–CH_2), 140.7 (C_6H_5–CH_2). Anal. Calcd for $C_{14}H_{24}O_7P_2$: C, 45.91; H, 6.60; P, 16.91; Found: C, 45.82; H, 6.58; P, 16.83.

4.4.19. Disodium salt of [1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)-2-phenyl-ethyl]-phosphonic acid monophenyl ester (6d). Yellow oil in the acidic form. Yield: 90%. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 15.9. ^{1}H NMR (500 MHz, D_2O) δ 3.56 (t, 2H, $^{3}J_{P-H}=13.0$ Hz, $C_6H_5CH_2COH$), 6.99–7.55 (m, 15H, C_6H_5). ^{13}C NMR {^{1}H} (50.3 MHz, D_2O) δ 38.2 (C_6H_5–CH_2–COH), 74.6 (t, $^{1}J_{P-C}=146.1$ Hz, P–*C*(OH)–P), 119.8 (*o*–C_6H_5), 125.2 (*p*–C_6H_5), 126.5 (*m*-C_6H_5), 128.2 (*p*-C_6H_5–CH_2), 130.4 (*m*-C_6H_5–CH_2), 135.7 (*o*-C_6H_5–CH_2), 137.6 (C_6H_5–CH_2), 150.7 (C_6H_5O). Anal. Calcd for $C_{20}H_{18}Na_2O_7P_2$: C, 50.27; H, 3.79; P, 12.95; Found: C, 50.35; H, 3.80; P, 12.99.

4.4.20. [1-Hydroxy-1-(hydroxy-tetradecyloxy-phosphoryl)-2-phenyl-ethyl]-phosphonic acid mono tetradecyl ester (6e). Precipitation in diethylether. Yield: 63%. Mp <50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 15.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 6H, $^{3}J_{H-H}=6.5$ Hz, $O(CH_2)_{13}CH_3$), 1.15–1.32 (m, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.39–1.47 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.39 (t, 2H, $^{3}J_{P-H}=13.5$ Hz, $C_6H_5CH_2COH$), 3.84–4.01 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 7.20–7.25 (m, 3H, C_6H_5), 7.37 (d, 2H, $^{3}J_{H-H}=6.5$ Hz, *o*-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 ($OCH_2CH_2(CH_2)_{11}CH_3$), 22.9 ($OCH_2(CH_2)_{11}CH_2CH_3$), 29.9–30.4 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$) 30.4 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 41.0 ($C_6H_5$–$CH_2$–COH), 67.8 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 76.8 (t, $^{1}J_{P-C}=$ 145.6 Hz, P–*C*(OH)–P), 123.5 (*p*-C_6H_5–CH_2), 133.9 (*m*-C_6H_5–CH_2), 136.2 (*o*-C_6H_5–CH_2), 137.7 (C_6H_5–CH_2). MS ($C_{36}H_{66}O_7P_2Na_2$, pH=7.5): *m/z* 697.5 $[M+Na+H]^+$, 675.4 $[M+H]^+$. Anal. Calcd for $C_{36}H_{68}O_7P_2$: C, 64.07; H, 10.16; P, 9.18; Found: C, 64.08; H, 10.15; P, 9.10.

4.4.21. [1-Hydroxy-(1-hydroxy-methoxy-phosphoryl)-2-phenyl-methyl]-phosphonic acid monomethyl ester (7a). Precipitation in diethylether. Yield: 90%. Mp 195 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 18.2. ^{1}H NMR (500 MHz, D_2O) δ 3.49–3.52 (m, 6H, OCH_3), 7.24–7.29 (m, 1H, *p*-C_6H_5), 7.33 (t, 2H, $^{3}J_{H-H}=7$ Hz, *m*-C_6H_5), 7.63 (d, 2H, $^{3}J_{H-H}=7$ Hz, *o*-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 56.9 (OCH_3), 79.6 (t, $^{1}J_{P-C}=148.4$ Hz, P–*C*(OH)–P), 129.1 (*o*-C_6H_5), 131.1 (*p*-C_6H_5), 131.4 (*m*-C_6H_5), 138.5 ($C_6H_5C(OH)$). Anal. Calcd for $C_9H_{14}O_7P_2$: C, 36.50; H, 4.76; P, 20.92; Found: C, 36.43; H, 4.74; P, 20.90.

4.4.22. [1-Hydroxy-1-(hydroxy-ethoxy-phosphoryl)-2-phenyl-methyl]-phosphonic acid monoethyl ester (7b). Precipitation in diethylether. Yield: 85%. Mp 168 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 16.9. ^{1}H NMR (500 MHz, D_2O) δ 1.14 (t, 6H, $^{3}J_{H-H}=6.5$ Hz, OCH_2CH_3) 3.89–3.98 (m, 4H, OCH_2CH_3), 7.33–7.38 (m, 1H, *p*-C_6H_5), 7.41 (t, 2H, $^{3}J_{H-H}=7.0$ Hz, *m*-C_6H_5), 7.73 (d, 2H, $^{3}J_{H-H}=7.0$ Hz, *o*-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 19.1 (OCH_2CH_3), 67.2 (OCH_2CH_3), 79.5 (t, $^{1}J_{P-C}=148.9$ Hz, P–*C*(OH)–P), 129.2 (*o*-C_6H_5), 131.1 (*p*-C_6H_5), 131.4 (*m*-C_6H_5), 138.6 ($C_6H_5C(OH)$). Anal. Calcd for $C_{11}H_{18}O_7P_2$: C, 40.75; H, 5.60; P, 19.11; Found: C, 40.84; H, 5.62; P, 19.20.

4.4.23. [1-Hydroxy-(1-hydroxy-isopropoxy-phosphoryl)-2-phenyl-methyl]-phosphonic acid mono isopropyl ester (7c). Precipitation in diethylether. Yield: 95%. Mp 174 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 16.4. ^{1}H NMR (500 MHz, D_2O) δ 1.09 (d, 6H, $^{3}J_{H-H}=6.5$ Hz, ($OCH(CH_3)_2$), 1.20 (d, 6H, $^{3}J_{H-H}=6.5$ Hz, $OCH(CH_3)_2$), 4.45–4.53 (m, 2H, ($OCH(CH_3)_2$), 7.35–7.40 (m, 1H, *p*-C_6H_5), 7.43 (t, 2H, $^{3}J_{H-H}=7.0$ Hz, *m*-C_6H_5), 7.76 (d, 2H, $^{3}J_{H-H}=7.0$ Hz, *o*-C_6H_5). ^{13}C NMR{^{1}H} (125.9 MHz, D_2O) δ 26.2 ($OCH(CH_3)_2$), 26.6 ($OCH(CH_3)_2$), 76.3 ($OCH(CH_3)_2$), 79.3 (t, $^{1}J_{P-C}=143.1$ Hz, P–*C*(OH)–P), 129.4 (*o*-C_6H_5), 131.0 (*p*-C_6H_5), 131.3 (*m*-C_6H_5), 138.6 ($C_6H_5C(OH)$). Anal. Calcd for $C_{13}H_{22}O_7P_2$: C, 44.33; H, 6.30; P, 17.59; Found: C, 44.25; H, 6.29; P, 17.48.

4.4.24. Disodium salt of [1-hydroxy-(1-hydroxy-phenoxy-phosphoryl)-2-phenyl-methyl]-phosphonic acid monophenyl ester (7d). Precipitation in diethylether. Yield: 78%. Mp <50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 11.6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75–7.89 (m, 15H, C_6H_5). ^{13}C NMR {^{1}H} (50.3 MHz, D_2O) δ 76.9 (t, $^{1}J_{P-C}=143.1$ Hz, P–*C*(OH)–P), 119.9–128.6 (C_6H_5; $C_6H_5C(OH)$), 136.8 ($C_6H_5C(OH)$), 150.7 (C_6H_5O). Anal. Calcd for $C_{19}H_{16}Na_2O_7P_2$: C, 49.15; H, 3.47; P, 13.34; Found: C, 49.22; H, 3.48; P, 13.39.

4.4.25. [1-Hydroxy-(1-hydroxy-tetradecyloxy-phosphoryl)-2-phenyl-methyl]-phosphonic acid mono tetradecyl ester (7e). Precipitation in diethylether. Yield: 77%. Mp <50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 15.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 6H, $^{3}J_{H-H}=6.5$ Hz, $O(CH_2)_{13}CH_3$), 1.04–1.29 (m, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.30–1.36 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.59–3.69 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.80–3.88 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$), 7.23–7.29 (m, 1H, *p*-C_6H_5), 7.33 (t, 2H, $^{3}J_{H-H}=8$ Hz, *m*-C_6H_5), 7.82 (d, 2H, $^{3}J_{H-H}=8$ Hz, *o*-C_6H_5). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.2

($OCH_2CH_2(CH_2)_{11}CH_3$), 22.8 ($OCH_2(CH_2)_{11}CH_2CH_3$), 29.2–30.3 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 30.3 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 32.1 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 76.5 (t, $^1J_{P-C}=153.7$ Hz, P–*C*(OH)–P), 126.2 (*o*-C_6H_5), 127.8 (*p*-C_6H_5), 128.0 (*m*-C_6H_5), 133.6 ($C_6H_5C(OH)$). MS ($C_{35}H_{64}O_7P_2Na_2$, pH =7.5): *m/z* 684.4 $[M+Na+H]^+$, 661.4 $[M+H]^+$. Anal. Calcd for $C_{35}H_{66}O_7P_2$: C, 63.61; H, 10.07; P, 9.37; Found: C, 63.70; H, 10.09; P, 9.45.

4.4.26. (4-Bromo-phenyl)-hydroxy-(hydroxy-methoxy-phosphoryl)-methyl]-phosphonic acid monomethyl ester (8a). Precipitation in diethylether. Yield: 90%. Mp 165 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 17.3. ^{1}H NMR (500 MHz, D_2O) δ 3.79 (d, 3H, $^3J_{P-H}=3.0$ Hz, OCH_3), 3.81 (d, 3H, $^3J_{P-H}=3.0$ Hz, OCH_3), 7.59 (d, 2H, $^3J_{H-H}=8.0$ Hz, *m*-C_6H_4), 7.66 (d, 2H, $^3J_{H-H}=8.0$ Hz, *o*-C_6H_4). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 56.8 (OCH_3), 74.6 (t, $^1J_{P-C}=$ 146.2 Hz, P–*C*(OH)–P), 124.4 (*p*-C_6H_4), 131.1 (*m*-C_6H_4), 134.3 (*o*-C_6H_4), 138.9 ($C_6H_4C(OH)$). Anal. Calcd for $C_9H_{13}BrO_7P_2$: C, 28.82; H, 3.49; P, 16.52; Found: C, 28.92; H, 3.50; P, 16.57.

4.4.27. (4-Bromo-phenyl)-hydroxy-(hydroxy-ethoxy-phosphoryl)-methyl]-phosphonic acid monoethyl ester (8b). Precipitation in diethylether.Yield: 72%. Mp 199 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 16.4. ^{1}H NMR (500 MHz, D_2O) δ 1.16 (t, 6H, $^3J_{H-H}=6.5$ Hz, OCH_2CH_3), 3.89–3.98 (m, 4H, OCH_2CH_3), 7.60 (d, 2H, $^3J_{H-H}=8.5$ Hz, *m*-C_6H_4), 7.68 (d, 2H, $^3J_{H-H}=8.5$ Hz, *o*-C_6H_4). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 19.2 (OCH_2CH_3), 66.9 (OCH_2CH_3), 79.1 (t, $^1J_{P-C}=138.2$ Hz, P–*C*(OH)–P), 119.5 (*p*-C_6H_4), 131.2 (*m*-C_6H_4), 134.2 (*o*-C_6H_4), 138.9 ($C_6H_4C(OH)$). Anal. Calcd for $C_{11}H_{17}BrO_7P_2$: C, 32.78; H, 4.25; P, 15.37; Found: C, 32.71; H, 4.24; P, 15.30.

4.4.28. (4-Bromo-phenyl)-hydroxy-(hydroxy-isopropoxy-phosphoryl)-methyl]-phosphonic acid monoisopropyl ester (8c). Precipitation in diethylether. Yield: 80%. Mp 198 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 15.6. ^{1}H NMR (500 MHz, D_2O) δ 1.09 (d, 3H, $^3J_{H-H}=6$ Hz, $OCH(CH_3)_2$), 1.20 (d, 6H, $^3J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 4.41–4.50 (m, 2H, $OCH(CH_3)_2$), 7.61 (d, 2H, $^3J_{H-H}=8.5$ Hz, *m*-C_6H_4), 7.69 (d, 2H, $^3J_{H-H}=8.5$ Hz, *o*-C_6H_4). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 26.5 ($OCH(CH_3)_2$), 27.0 ($OCH(CH_3)_2$), 74.0 ($OCH(CH_3)_2$), 76.8 (t, $^1J_{P-C}=$ 143.5 Hz, P–*C*(OH)–P), 123.1 (*p*-C_6H_4), 131.4 (*m*-C_6H_4), 133.6 (*o*-C_6H_4), 140.9 ($C_6H_4C(OH)$). Anal. Calcd for $C_{13}H_{21}BrO_7P_2$: C, 36.21; H, 4.91; P, 14.37; Found: C, 36.28; H, 4.93; P, 14.42.

4.4.29. (4-Bromo-phenyl)-hydroxy-(hydroxy-phenoxy-phosphoryl)-methyl]-phosphonic acid monophenyl ester (8d). Precipitation in diethylether.Yield: 70%. Mp 92 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 12.8. ^{1}H NMR (500 MHz, D_2O) δ 6.93–7.80 (m, 14H, C_6H_4; C_6H_5). ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 77.1 (t, $^1J_{P-C}=145.4$ Hz, P–*C*(OH)–P), 116.1 (C_6H_5), 121.5 (C_6H_5), 124.6 (*p*-C_6H_4), 129.9 (C_6H_5), 130.7 (*m*-C_6H_4), 130.8 (*o*-C_6H_4), 137.5 ($C_6H_4C(OH)$), 152.3 (O–C_6H_5). Anal. Calcd for $C_{19}H_{17}BrO_7P_2$: C, 45.72; H, 3.43; P, 12.41; Found: C, 45.62; H, 3.42; P, 12.36.

4.4.30. (4-Bromo-phenyl)-hydroxy-(hydroxy-tetradecyloxy-phosphoryl)-methyl]-phosphonic acid monotetradecyl ester (8e). Precipitation in diethylether/hexane: 50/50. Yield: 80%. Mp 54 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 14.6. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 6H, $^3J_{H-H}=7.0$ Hz, $O(CH_2)_{13}CH_3$), 1.15–1.31 (m, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.33–1.39 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.72–3.80 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.86–3.94 (m, 2H, $OCH_2CH_2(CH_2)_{11}CH_3$), 7.47 (d, 2H, $^3J_{H-H}=$ 8.0 Hz, *m*-C_6H_4), 7.70 (d, 2H, $^3J_{H-H}=8.0$ Hz, *o*-C_6H_4). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 ($O(CH_2)_{13}CH_3$), 22.9 ($O(CH_2)_{12}CH_2CH_3$), 25.3–30.4 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 32.1 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 69.0 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 76.2 (t, $^1J_{P-C}=148.6$ Hz, P–*C*(OH)–P), 122.4 (*p*-C_6H_4), 127.9 (*m*-C_6H_4), 131.4 (*o*-C_6H_4), 132.6 ($C_6H_4C(OH)$). MS ($C_{35}H_{63}O_7P_2Na_2$, pH=7.5): *m/z* 763.3 $[M+Na+2H]^+$739.3 $[M+H]^+$. Anal. Calcd for $C_{35}H_{65}BrO_7P_2$: C, 56.83; H, 8.86; P, 8.37; Found: C, 56.89; H, 8.88; P, 8.43.

4.4.31. [Hydroxy-(hydroxy-methoxy-phosphoryl)-(4-methoxy-phenyl)-methyl]-phosphonic acid monomethyl ester (9a). Precipitation in diethylether. Yield: 92%. Mp 225 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 16.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38–3.60 (m, 6H, OCH_3), 3.80 (s, 3H, $C_6H_4OCH_3$), 6.86 (d, 2H, $^3J_{H-H}=8.0$ Hz, *m*-$C_6H_4OCH_3$), 7.5 (d, 2H, $^3J_{H-H}=8.0$ Hz, *o*-$C_6H_4OCH_3$). ^{13}C NMR {^{1}H} (50.3 MHz, DMSO-d_6) δ 53.5 (OCH_3), 55.0 ($C_6H_4OCH_3$), 75.8 (t, $^1J_{P-C}=145.8$ Hz, P–*C*(OH)–P), 112.5 (*m*-C_6H_4), 127.8 (*o*-C_6H_4), 128.9 ($C_6H_4C(OH)$), 158.1 (*p*-C_6H_4). Anal.Calcd for $C_{10}H_{16}O_8P_2$: C, 36.82; H, 4.94; P, 18.99; Found: C, 36.76; H, 4.93; P, 18.92.

4.4.32. [Hydroxy-(hydroxy-ethoxy-phosphoryl)-(4-methoxy-phenyl)-methyl]-phosphonic acid monoethyl ester (9b). Precipitation in diethylether. Yield: 60%. Mp 172 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 17.3. ^{1}H NMR (500 MHz, D_2O) δ 1.11 (t, 6H, $^3J_{H-H}=6.5$ Hz, OCH_2CH_3), 3.78 (s, 3H, $C_6H_4OCH_3$), 3.86–3.95 (m, 4H, OCH_2CH_3), 6.98 (d, 2H, $^3J_{H-H}=9.0$ Hz, *m*-$C_6H_4OCH_3$), 7.64 (d, 2H, $^3J_{H-H}=$ 9.0 Hz, *o*-$C_6H_4OCH_3$). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 19.1 (OCH_2CH_3), 58.6 ($C_6H_4OCH_3$), 67.3 (OCH_2CH_3), 79.0 (t, $^1J_{P-C}=145.9$ Hz, P–*C*(OH)–P), 116.8 (*m*-C_6H_4), 130.7 (*o*-C_6H_4), 130.8 ($C_6H_4C(OH)$), 161.7 (*p*-C_6H_4). Anal. Calcd for $C_{12}H_{20}O_8P_2$: C, 40.69; H, 5.69; P, 17.49; Found: C, 40.75; H, 5.71; P, 17.58.

4.4.33. [Hydroxy-(hydroxy-isopropoxy-phosphoryl)-(4-methoxy-phenyl)-methyl]-phosphonic acid monoisopropyl ester (9c). Precipitation in diethylether. Yield: 77%. Mp 187 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 16.6. ^{1}H NMR (500 MHz, D_2O) δ 1.09 (d, 6H, $^3J_{H-H}=6$ Hz, ($OCH(CH_3)_2$), 1.21 (d, 6H, $^3J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 3.85 (s, 3H, $C_6H_4OCH_3$), 4.45–4.49 (m, 2H, $OCH(CH_3)_2$), 7.04 (d, 2H, $^3J_{H-H}=9.0$ Hz, *m*-$C_6H_4OCH_3$), 7.69 (d, 2H, $^3J_{H-H}=9.0$ Hz, *o*-$C_6H_4OCH_3$). ^{13}C NMR {^{1}H} (125.9 MHz, DMSO-d_6) δ 26.2 ($OCH(CH_3)_2$), 26.6 ($OCH(CH_3)_2$), 58.6 ($C_6H_4OCH_3$), 76.2 ($OCH(CH_3)_2$), 76.6 (t, $^1J_{P-C}=144.6$ Hz, P–*C*(OH)–P), 116.7 (*m*-C_6H_4), 130.9 (*o*-C_6H_4), 131.0 ($C_6H_4C(OH)$), 161.7 (*p*-C_6H_4). Anal. Calcd for $C_{14}H_{24}O_8P_2$: C, 43.99; H, 6.33; P, 16.20; Found: C, 44.08; H, 6.34; P, 16.25.

4.4.34. Disodium salt of [hydroxy-(hydroxy-phenoxy-phosphoryl)-(4-methoxy-phenyl)-methyl]-phosphonic acid monophenyl ester (9d). Precipitation in diethylether/hexane: 80/20 in the acid form. Yield: 81%. Mp 198 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 13.5. ^{1}H NMR (500 MHz, D_2O) δ 3.87 (s, 3H, $C_6H_4OCH_3$), 6.92–7.82 (m, 14H, $C_6H_4OCH_3$; C_6H_5). ^{13}C NMR {^{1}H} (50.3 MHz, D_2O) δ 55.7 ($C_6H_4OCH_3$), 77.9 (t, $^{1}J_{P-C}=144.5$ Hz, P–*C*(OH)–P), 113.4, 119.0, 121.2, 123.8, 127.8, 129.4, 132.1 (C_6H_5; C_6H_4), 152.2 (OC_6H_5), 157.8 (*p*-C_6H_4). Anal. Calcd for $C_{20}H_{18}Na_2O_8P_2$: C, 48.60; H, 3.67; P, 12.53; Found: C 48,.51; H, 3.65; P, 12.49.

4.4.35. [Hydroxy-(hydroxy-tetradecyloxy-phosphoryl)-(4-methoxy-phenyl)-methyl]-phosphonic acid monotetradecyl ester (9e). Precipitation in diethylether/hexane: 80/20. Yield: 69%. Mp <50 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 15.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 6H, $^{3}J_{H-H}=6.5$ Hz, $O(CH_2)_{13}CH_3$), 1.02–1.29 (m, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.32–1.35 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.78 (s, 3H, $C_6H_4OCH_3$), 3.82–3.86 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 6.87 (d, 2H, $^{3}J_{H-H}=9.0$ Hz, *m*-$C_6H_4OCH_3$), 7.73 (d, 2H, $^{3}J_{H-H}=9.0$ Hz, *p*-$C_6H_4OCH_3$). ^{13}C NMR {^{1}H} (125.9 MHz, $CDCl_3$) δ 14.3 ($O(CH_2)_{13}CH_3$), 22.9 ($O(CH_2)_{12}CH_2CH_3$), 29.5–30.3 ($OCH_2CH_2(CH_2)_{10}CH_2CH_3$), 32.8 ($OCH_2CH_2(CH_2)_{11}CH_3$), 55.4 ($C_6H_4OCH_3$), 69.0 ($OCH_2CH_2(CH_2)_{11}CH_3$), 76.2 (t, $^{1}J_{P-C}=145.9$ Hz, P–*C*(OH)–P), 113.6 (*m*-C_6H_4), 127.5 (*p*-C_6H_4), 132.8 ($C_6H_4C(OH)$), 159.5 (*p*-C_6H_4). MS ($C_{35}H_{63}O_7P_2Na_2$, pH=7.5) *m/z* 713.4 $[M+Na+H]^+$, 691.3 $[M+H]^+$. Anal. Calcd for $C_{36}H_{68}O_8P_2$: C, 64.07; H, 10.16; P, 9.18; Found: C, 65.10; H, 10.18; P, 9.24.

4.4.36. Sodium salt of [hydroxy-(hydroxy-methoxy-phosphoryl)-pyridin-3-yl-methyl]-phosphonic acid monomethyl ester (10a). Precipitation in diethylether in the acidic form. Yield: 75%. Mp 220 °C. ^{13}P NMR {^{1}H} (200.7 MHz, D_2O) δ 14.8. ^{1}H NMR (500 MHz, D_2O) δ 3.48 (d, 6H, $^{3}J_{P-H}=9.0$ Hz, OCH_3), 7.82–7.94 (m, 1H, *H5*–C_5H_4N), 8.47–8.55 (m, 1H, *H4*–C_5H_4N), 8.70–8.79 (m, 1H, *H6*–C_5H_4N), 8.86 (s, 1H, *H2*–C_5H_4N). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 54.9 (OCH_3), 78.9 (t, $^{1}J_{P-C}=142.1$ Hz, P–*C*(OH)–P), 129.6 (*C5*–C_5H_4N), 141.9 (*C3*–C_5H_4N), 142.5 (*C4*–C_5H_4N), 143.4 (*C6*–C_5H_4N), 147.4 (*C2*–C_5H_4N). Anal. Calcd for $C_8H_{12}NNaO_7P_2$: C, 30.11; H, 3.79; N, 4.39; P, 19.41; Found: C, 30.08; H, 3.78; N, 4.38; P, 19.35.

4.4.37. Sodium salt of [hydroxy-(hydroxy-ethoxy-phosphoryl)-pyridin-3-yl-methyl]-phosphonic acid monoethyl ester (10b). Precipitation in diethylether in the acid form. Yield: 90%. Mp >260 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 14.8. ^{1}H NMR (200 MHz, D_2O) δ 0.96 (t, 6H, $^{3}J_{H-H}=7.2$ Hz, OCH_2CH_3), 3.68–3.75 (m, 4H, OCH_2CH_3), 7.31–7.42 (m, 1H, *H5*–C_5H_4N), 8.06–8.20 (m, 1H, *H4*–C_5H_4N), 8.26–8.35 (m, 1H, *H6*–C_5H_4N), 8.72 (s, 1H, *H2*–C_5H_4N). ^{13}C NMR {^{1}H} (50.3MHz, D_2O) δ 14.3 (OCH_2CH_3), 60.8 (OCH_2CH_3), 74.8 (t, $^{1}J_{P-C}=140.1$ Hz, P–*C*(OH)–P), 121.8 (*C5*–C_5H_4N), 134.7 (*C3*–C_5H_4N), 143.3 (*C4*–C_5H_4N), 143.5 (*C6*–C_5H_4N), 147.2 (*C2*–C_5H_4N). Anal. Calcd for $C_{10}H_{16}NNaO_7P_2$: C, 34.60; H, 4.65; N, 4.05; P, 17.84; Found: C, 34.54; H, 4.64, N, 4.04; P, 17.80.

4.4.38. Sodium salt of [hydroxy-(hydroxy-isopropoxy-phosphoryl)-pyridin-3-yl-methyl]-phosphonic acid monoisopropyl ester (10c). Precipitation in diethylether in the acidic form. Yield: 90%. Mp 197 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 13.0. ^{1}H NMR (500 MHz, D_2O) δ 1.15 (d, 6H, $^{3}J_{H-H}=6$ Hz, $OCH(CH_3)_2$), 1.20 (d, 6H, $^{3}J_{H-H}=7$ Hz, $OCH(CH_3)_2$), 4.16–4.56 (m, 2H, $OCH(CH_3)_2$), 8.07 (dd, 1H, $^{3}J_{H-H}=5.0$, 8.0 Hz, *H5*–C_5H_4N), 8.72 (d, 1H, $^{3}J_{H-H}=5.0$ Hz, *H4*–C_5H_4N), 8.94 (d, 1H, $^{3}J_{H-H}=8.0$ Hz, *H6*–C_5H_4N), 9.05 (s, 1H, *H2*–C_5H_4N). ^{13} C NMR {^{1}H} (125.9 MHz, D_2O) δ 26.6 ($OCH(CH_3)_2$), 75.3 ($OCH(CH_3)_2$), 78.6 (t, $^{1}J_{P-C}=139.9$ Hz, P–*C*(OH)–P), 129.5 (*C5*–C_5H_4N), 141.9 (*C3*–C_5H_4N), 142.4 (*C4*–C_5H_4N), 143.5 (*C6*–C_5H_4N), 147.6 (*C2*–C_5H_4N). Anal. Calcd for $C_{12}H_{20}NNaO_7P_2$: C, 38.41; H, 5.37; N, 3.73; P, 16.51; Found: C, 38.55; H, 5.38; N, 3.74; P, 16.57.

4.4.39. Sodium salt of [hydroxy-(hydroxy-phenoxy-phosphoryl)-pyridin-3-yl-methyl]-phosphonic acid monophenyl ester (10d). Precipitation in methanol in the acid form. Yield: 73%. Mp 134 °C. ^{31}P NMR {^{1}H} (200.7 MHz, D_2O) δ 18.3. ^{1}H NMR (500 MHz, D_2O) δ 6.96–7.34 (m, 10H, C_6H_5), 7.74–7.95 (m, 1H, *H5*–C_5H_4N), 8.55–8.82 (m, 2H, *H4*–C_5H_4N; *H6*–C_5H_4N), 9.04 (s, 1H, *H2*–C_5H_4N). ^{13}C NMR {^{1}H} (125.9 MHz, D_2O) δ 77.6 (t, $^{1}J_{P-C}=140.4$ Hz, P–*C*(OH)–P), 117.7 (C_6H_5), 122.9 (C_6H_5), 129.8 (*C5*–C_5H_4N), 132.2 (C_6H_5), 141.6 (C_6H_5), 141.9 (*C3*–C_5H_4N), 144.6 (*C4*–C_5H_4N), 146.8 (*C6*–C_5H_4N), 149.2 (*C2*–C_5H_4N). Anal. Calcd for $C_{18}H_{16}NNaO_7P_2$: C, 48.77; H, 3.64; N, 3.16; P, 13.98; Found: C, 48.85; H, 3.65; N, 3.17; P, 14.04.

4.4.40. Sodium salt of [hydroxy-(hydroxy-tetradecyloxy-phosphoryl)-pyridin-3-yl-methyl]-phosphonic acid monotetradecyl ester (10e). Precipitation in methanol in the acidic form. Yield: 50%. Mp 146 °C. ^{31}P NMR {^{1}H} (200.7 MHz, $CDCl_3$) δ 12.5. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 6H, $^{3}J_{H-H}=7.0$ Hz, $O(CH_2)_{13}CH_3$), 0.98–1.48 (m, 44H, $OCH_2CH_2(CH_2)_{11}CH_3$), 1.51–1.87 (m, 4H, $OCH_2CH_2(CH_2)_{11}CH_3$), 3.60–4.16 (m, 4H $OCH_2CH_2(CH_2)_{11}CH_3$), 7.50–7.85 (m, 1H, *H5*–C_5H_4N), 8.25–8.58 (m, 1H, *H4*–C_5H_4N), 8.65–8.94 (m, 1H, *H6*–C_5H_4N), 9.4 (s, 1H, *H2*–C_5H_4N). MS ($C_{34}H_{64}NNaO_7P_2$, pH=7.5) *m/z* 684.4 $[M+H]^+$. Anal. Calcd for $C_{34}H_{64}NNaO_7P_2$: C, 59.72; H, 9.43; N, 2.05; P, 9.06; Found: C, 59.81; H, 9.45; N, 2.08; P, 9.12.

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