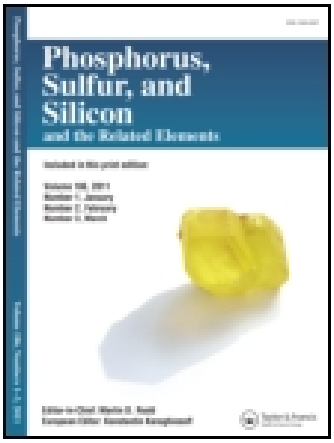

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Synthesis of New Benzylic Di-, Tri-, and Tetraphosphonic Acids as Potential Chelating Agents

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SYNTHESIS OF NEW BENZYLIC DI-, TRI-, AND TETRAPHOSPHONIC ACIDS AS POTENTIAL CHELATING AGENTS

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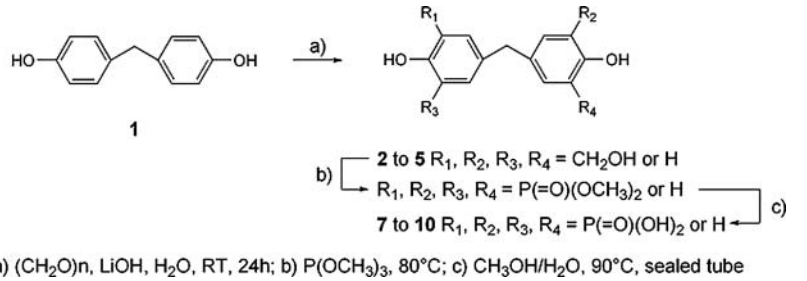
GRAPHICAL ABSTRACT



Abstract *New di-, tri-, and tetraphosphonic acids were synthesized starting from four o-hydroxymethyl phenol derivatives and obtained in three steps in good overall yield. The phosphonic acids were isolated and purified using semi-preparative C_{18} HPLC column. The new compounds were characterized using different spectroscopic methods (^1H, ^{13}C, and ^{31}P NMR; ESI MS; and MS^n, IR).*

Keywords Characterization; polyphosphonic acids; synthesis

INTRODUCTION

Phosphonates belong to a class of molecules containing one or more R-PO(OR′)$_2$ groups. Phosphonate additives are used worldwide in a broad spectrum of applications, including household and industrial detergents,[1–3] industrial water treatment,[4,5] industrial

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cleaners, and enhanced oil recovery operations, as well as in corrosion control.[6–8] Recently the effect of phosphonates used in Russian heat-power engineering on the corrosion of carbon steel in deaerated delivery water at 90°C has been studied. It was shown that introduction of phosphonates reduced the susceptibility of steel to local corrosion.[9] This class of products also finds applications in medicinal chemistry as antiviral agents, in such a way that they can be considered as analogues of natural pyrophosphates.[10–12] The search for new, more efficient, more specific polyphosphonate chelating agents represents a considerable challenge and is of great interest in the field of environmental remediation. In the design of inorganic hybrid metal complexes, the phosphonic acids are of potential interest because of their high number of hydrogen bond acceptors and their remarkable acidity (higher than those of the corresponding carboxylic acids). Therefore these ligands have been successfully used as extractants,[13] and their complexing properties have been examined.[14]. Böhmer et al. have synthesized a series of mono- and bisphosphonic acids stemming from phenols.[15] Organo-phosphonic acids have been used as complexing agents due to their strong binding ability and the stability of the complexed species.[15–22] Recently calix[4]resorcinolarenes with phosphinoylalkyl substituents with acidic phosphonate fragments were shown to be efficient extracting agents of the metal ions of the lanthanum group from acidic solutions.[23,24] Structurally related derivatives, calix[4]arene methylenebisphosphonic acids, also displayed strong inhibition of calf intestine alkaline phosphatase.[25] Another recent report showed that derivatives of calix[4]arenes bearing phosphonic acids or lithium methyl phosphonate groups behave as host molecules, as they form complexes with ephedrine, norephedrine, and noradrenaline hydrochlorides in phosphate buffer at deuterated phosphate buffer pD 7.3.[26] In order to enhance the number of complexing sites, we have used as starting material the methylene-4,4′-bis(phenol) backbone **1**. At the same time, this allowed us to keep some kind of flexibility, as the two aromatic rings were linked via a methylene group. In this article, we describe the synthesis of new compounds bearing two, three, and four phosphonic acid functions.

RESULTS AND DISCUSSION

Synthesis of the Phosphonic Acids 7–10

To access the intermediate phosphonic esters, various approaches are possible starting from the phenol derivatives. Baimukhametov et al. reported the preparation of diethyl 5-allyl-2-hydroxybenzyl phosphonate in 33% yield via the intermediate 2-diethylaminomethyl-4-allyl phenol, derived from the corresponding substituted phenol derivative.[27] We could also either use *o*-hydroxybenzyl alcohols or convert them first into the corresponding halogen derivatives prior to the reaction with a trialkyl phosphite. This latter option may require either stirring with 48% HBr in acetic acid[28,29] or two additional steps, which could limit the final overall yield: activation of the hydroxyl group, followed by its displacement (with a sodium halide, for example). On the other hand, halomethylation of substituted phenols has also been reported recently, but the yields decrease with increasing the steric demand of the substituents.[30]

o-Hydroxybenzyl alcohols have already been reported to react with trialkyl phosphites. Ivanov and Ageeva initiated those reactions leading, after rearrangement, according to the authors, to cyclic phosphites.[31] The proposed mechanism was first called into question by Miles et al.[32] and was later confirmed by means of NMR analysis by Chasar.[33] The

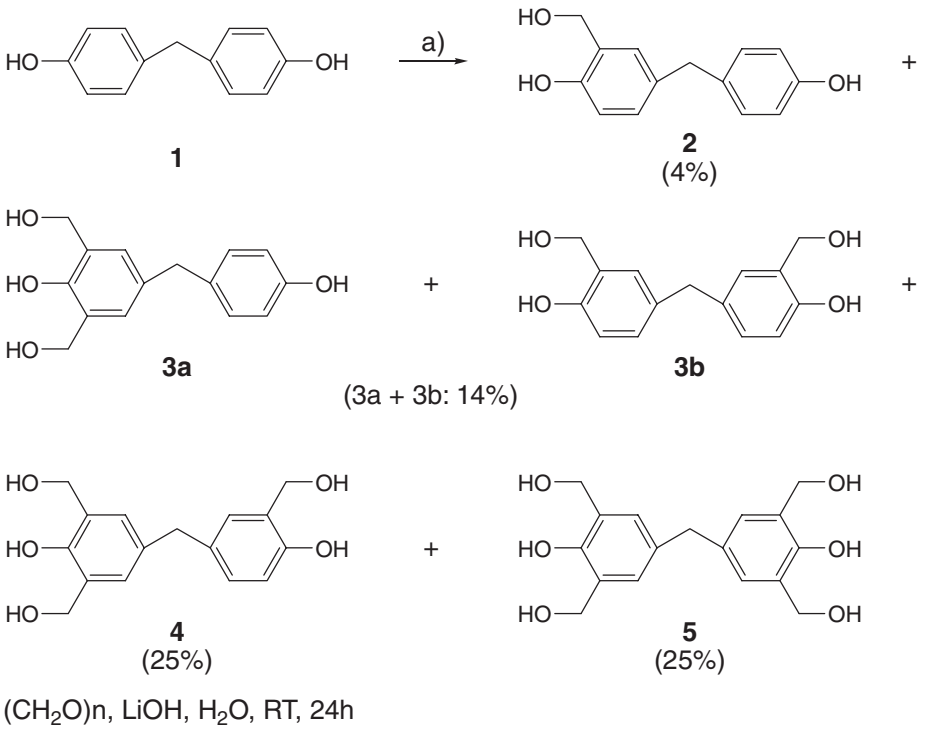
latter author could show that phosphonates were formed when *o*-hydroxybenzyl phenols reacted with trialkyl phosphites in DMF.

Considering all these previous studies and results, we decided to develop what we considered to be the most straightforward pathway to synthesize our target phosphonic acids: (i) phenol-formaldehyde reaction with alkaline catalyst; (ii) Michaelis–Arbuzov reaction involving the corresponding alcohols and trialkyl phosphite for several hours following the modifications reported by Vogt and colleagues[15,34]; and (iii) hydrolysis of the ester products.

It has to be mentioned that 4,4′-methylene bis[2,6-bis(hydroxymethyl)phenol] **5** was already obtained from phenol in the presence of an excess of formaldehyde under various basic conditions, albeit with a very low yield.[35–38] The influence of the basic catalyst on the phenol-formaldehyde reaction mechanism and kinetics has been previously investigated by Grenier-Loustalot et al.[39] When bis(4-hydroxyphenyl)methane **1** was used as starting material, substitution occurred in the ortho and ortho′ positions leading to **5** with 20% yield.[40] Keeping in mind the results reported by Perrin et al.,[37] we slightly modified the experimental conditions, using LiOH as a base rather than NaOH in the presence of **1** as starting material.

A mixture of the diphenol **1**, an aqueous solution of lithium hydroxide, and formaldehyde (ratio, 1:1:4) was stirred for 24 h at room temperature to afford a mixture of tetrahydroxymethyl derivative **5**, trihydroxymethyl derivative **4**, dihydroxymethyl derivatives (**3a** + **3b**), and monohydroxymethyl derivative **2** (Scheme 1). These compounds were purified and isolated by silica gel flash column chromatography with yields of 25%, 25%, 14%, and 4%, respectively. Using a controlled excess amount of formaldehyde of 2 and 10 molar equivalents led to the mixture (**3a** + **3b**) with 75% yield and to compound **5** with 70% yield, respectively. The mixture (**3a** + **3b**) was used as such for the following steps. It must be noted that the monohydroxymethyl compound **2** was not considered for further investigations.

The direct reaction of the *o*-hydroxybenzyl alcohol with trialkylphosphite has been previously developed to prepare phenolic benzylphosphonate esters, with the phenolic group in *o*-position relative to the phosphonomethyl group.[34] As already reported and demonstrated by Vogt, the *ortho*-phenol function is essential to make this modification of the Arbusov procedure efficient. Thus the tetrahydroxymethyl derivative **5** was mixed with a slight excess of trimethyl phosphite, and the resulting mixture was heated progressively up to 80°C and left for 4 h at this temperature. A ^{1}H NMR analysis of the crude mixture confirmed the formation of the expected phosphonate ester **6**. Unfortunately, purification by silica gel chromatography led to the pure product with only 3% yield. To overcome this problem encountered during the purification process, we decided to perform directly the hydrolysis step on the crude ester **6**. Among the different procedures known to make such a transformation, we used the very mild conditions previously developed by Böhmer et al.[15] Applying this strategy with pure ester **6** showed to be successful leading to a quantitative yield. As has already been reported for the reaction of *ortho*-hydroxybenzyl alcohols with trialkyl phosphites, the phenolic function appeared also in this case to be essential for a successful hydrolysis of the methyl phosphonate groups to the corresponding acid.[15] Assistance by neighboring functional groups has been previously invoked for the hydrolysis mechanism of salicyl phosphates.[41,42] As a hypothesis, a similar participation of the *ortho*-phenol function could be involved in the synthesis of phosphonic acids from the corresponding esters.

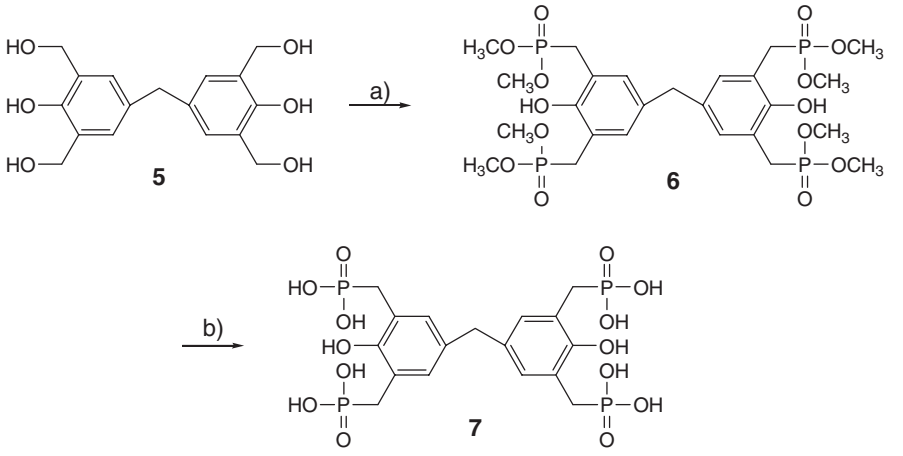


Scheme 1

The unpurified ester **6** was then heated in a water/methanol solution at 90°C in a sealed tube for 30 h (Scheme 2). The classical procedure, consisting of heating with HCl, led to slightly lower yields, although reaction times were sometimes shorter. HPLC purification, using a semi-preparative C_{18} column with an acidic elution system (0.1% aqueous solution of formic acid/acetonitrile, 90:10), allowed the isolation of the pure tetraphosphonic acid **7** with 76% yield over two steps. This result confirmed that the previous yield of 3% for **6** was really linked to a problem occurring during the purification step. We can imagine that an unexpected hydrolysis occurred, and the corresponding acids could not be eluted from the silica gel column. Therefore, intermediate esters had to be used unpurified as the starting material of the hydrolysis reaction in order to optimize the yield of the final phosphonic acids.

This two-step procedure was then applied to compound **4** leading to the triphosphonic acid **8** with 64% yield (Scheme 3). The diacids **9** and **10**, prepared using the same experimental conditions starting from the mixture of alcohols **3a** and **3b**, were separated using the HPLC purification procedure described above and obtained with 65% and 25% yield, respectively.

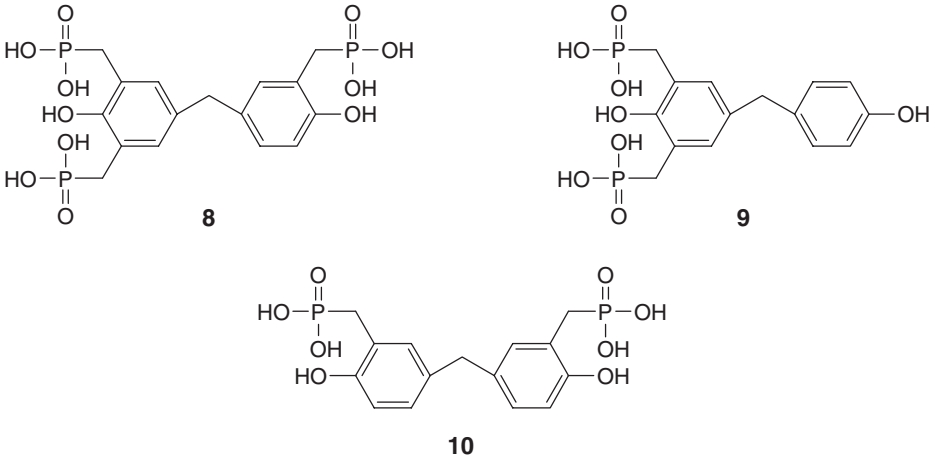
Negative ion electrospray ionization (ESI), with double octopoles and ion trap instruments, was chosen to record the mass spectroscopy data for the acids **7–10**.[43,44] Mass spectra of these derivatives showed peaks corresponding to double and/or triple charged ions, losses of water from these ions, and formation of sodium adducts from double charged ions. The $[M\text{-}H]^-$ ions for the different compounds were observed at m/z = 574.9 and 480.8 for **7** and **8**, respectively, and at m/z = 386.8 for both isomers **9** and **10**.



Scheme 2

$[M\text{-}2H]^{2-}$ ions were observed for compounds **7**, **8**, and **10** at m/z = 286.9, 239.7, and 192.7, respectively. It must be noted that the peak corresponding to a double deprotonation was not observed for isomer **9**. This may point out that for the other acids, double deprotonation occurred for two functions located on separated aromatic rings; for compound **9** both acid functions are on the same ring and the second deprotonation is not favored.

In the case of compound **7**, the fragmentation pattern of the ion at m/z = 286.9 provided by ion trap MS^n experiments could be explained by the loss of one, two, three, and four water molecules producing ions at m/z = 277.92, 268.9, 259.89, and 250.85, respectively. The first two losses of H_2O could be the result of a dehydration of a phosphonic acid moiety to yield a $-PO_2$ group, as proposed by Huikko et al.[44] The third and fourth loss of H_2O can follow two distinct pathways: dehydration between an OH group of a phosphonic



Scheme 3

moiety and the spatially close acidic phenol proton giving rise to an oxaphosphole structure, or delocalization of the negative charge of a singly deprotonated phosphonic acid and capture of the phenolic proton, leading to a phenolate appendage and a new $-PO_2$ group.

Nevertheless, formation of a five-membered ring has already been invoked during the degradation of alkyl polyphosphonates, though via the dehydration of two phosphonic acid moieties. In both cases, there was just one phosphonic acid function left on each benzene ring, while the third and fourth losses occurred. Participation of another type of acidic proton—the phenolic ones—could be involved in the rearrangement of these ions. Eventually this hypothetical process could give rise to oxaphosphole rings, which were proved to be stable when synthesized by flash vacuum pyrolysis of arylphosphites.[45–48]

Moreover, in the case of compound **7**, $[M\text{-}2H+Na]^-$ and $[M\text{-}3H+2Na]^-$ ions were observed at m/z = 596.9 and 618.9, respectively. $[M\text{-}3H]^{3-}$ ion at m/z = 190.8 was observed only for compound **7**, proving that, for particular cases, deprotonation could occur on two phosphonic acid moieties located on the same benzene ring. The fragmentation of this ion with the successive loss of one, two, and three water molecules leads to the ions at m/z = 184.9, 178.9, and 172.8, respectively.

These different dehydration pathways were confirmed by MS^n experiments with the intensity of the parent ions decreasing and/or vanishing and at the same time the intensity of peaks corresponding to losses of water increasing. The dehydration pathways proposed for compound **7** are shown in Scheme 4.

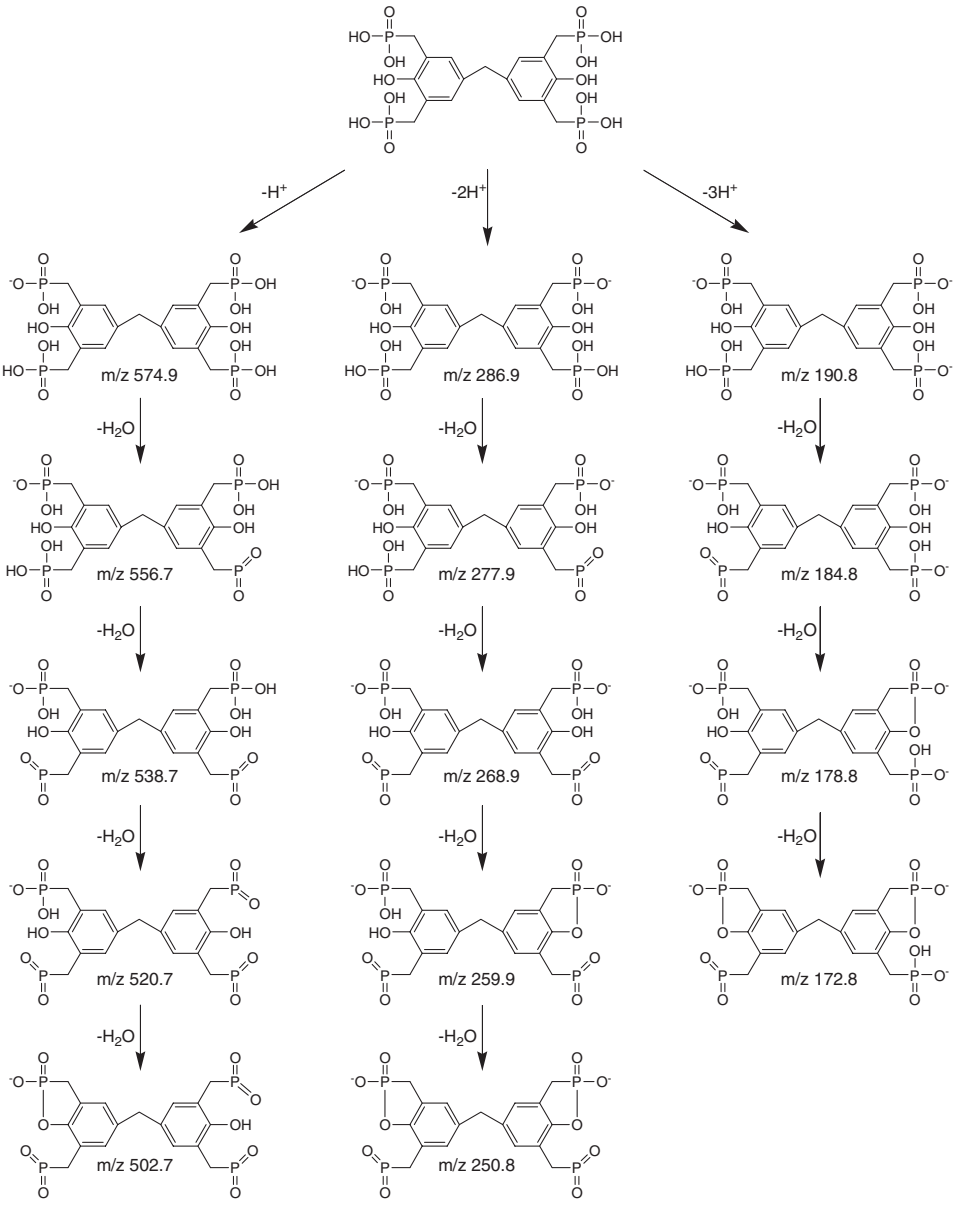
CONCLUSION

We have describe here a straightforward and efficient three-step synthesis leading to novel bisphenyl structures bearing methylene phosphonic acid groups and two phenolic functions with satisfactory overall yields. Using the optimized conditions (i) working with 10 equivalents of formaldehyde, (ii) reaction with triethylphosphite, (iii) hydrolysis of the crude ester, and (iv) HPLC purification, allowed the synthesis of the highly substituted phosphonic acid **7** with 53% yield. Characterization and MS^n degradation studies of the different ions have been performed for the new phosphonic acids. The study of the chelating properties of these new polyfunctionalized structures, especially with divalent and trivalent cations, is currently ongoing and will be reported and discussed soon.

EXPERIMENTAL

Melting points were determined with a Büchi 510 apparatus. IR spectra were recorded as potassium bromide pellets with a Bruker FT IR Vector 22 spectrophotometer. TLC was performed on a DC Alufolien Kieselgel 60 F254 (VWR). Column chromatography was performed using silica-gel 60 (0.040–0.063 mm, SDS). NMR spectra were recorded with a Jeol GX instrument operating at 270 MHz (^1H), 67.5 MHz (^{13}C), and 109.38 MHz (^{31}P). Chemical shifts (δ-scale) are given in parts per million values downfield from tetramethylsilane (Me_4Si) (^1H, ^{13}C) or phosphoric acid (85% H_3PO_4) (^{31}P). Low resolution mass spectra were recorded with a Jeol JMS 700 B/E instrument in the ESI negative mode (ESI^-, ion source temperature: 200°C, electron energy: 80 eV, accelerating voltage: 8 keV) or with a Bruker Daltonics Esquire 3000 Plus (ESI^-) instrument equipped with double octopoles and an ion trap. Samples were dissolved in a 50/50 mixture of CH_3CN/H_2O.

The alcohol derivatives were isolated and purified by silica gel column chromatography using a gradient ethyl acetate/dichloromethane as eluting solvent. Purification of



Scheme 4

the phosphonate derivatives was performed with a Hewlett-Packard 1100 HPLC system using semi-preparative C_{18} column (250 × 25 mm) with a mixture of aqueous formic acid solution pH = 3/acetonitrile (90/10) at a flow rate of 4 mL/min. Peaks were detected by ultraviolet absorption with a diode array detector.

Synthesis of the Alcohols 2, 3a, 3b, 4, and 5: General Procedure

In a modification of the already described procedure,[24] 1 mol of bis(4-hydroxyphenyl)methane **1** (2 g), 1 mol of LiOH (0.24 g) dissolved in water (2.3 mL) and 4 mol of 37% aqueous formaldehyde solution (3 mL) were mixed at room temperature and stirred for 24 h. The mixture was then neutralized with H_2SO_4 (1N), extracted with ethyl acetate (10 mL), and dried over sodium sulfate. The crude product was separated by column chromatography (elution with a gradient of ethyl acetate/dichloromethane from 40% to 100% of ethyl acetate).

4,4′-Methylenebis[2,6-bis(hydroxymethyl)phenol] (5). Yield = 25% (20% [20]); mp = 155°C; IR (KBr), ν(cm^{-1}): 3482*s* (OH), 3030*w* (arom. C-H), 1612*m* (arom. C=C), 1253*s* (arom. C-OH), 1070*s* (CH_2-OH), 762*m* (CH_2). ^{1}H NMR (270 MHz, CD_3OD): δ = 3.78 (s, 2H, Ph-CH_2-Ph), 4.65 (s, 8H, CH_2-OH), 6.98 (s, 4H, arom-H). ^{13}C NMR (67.5 MHz, CD_3OD): δ = 41.5 (Ph-*C*H_2-Ph), 62.1 (*C*H_2-OH), 128.1 (*C*-CH_2-OH), 128.5 (*C*H), 134.1 (*C*-CH_2-*C*), 152.8 (*C*-OH). MS (ESI): $[M-H]^-$ m/z obs. 319.1197 (m/z exp. 319.1181).

4-[4-Hydroxy-3-(hydroxymethyl)benzyl]-2,6-bis(hydroxymethyl)phenol (4). Yield = 25%; mp = 136°C; IR (KBr), ν(cm^{-1}): 3416*s* (OH), 3030*w* (arom. C-H), 1613*m* (arom. C=C), 1265*s* (arom. C-OH), 1072*s* (CH_2-OH), 760*m* (CH_2). ^{1}H NMR (270 MHz, CD_3OD): δ = 3.77 (s, 2H, Ph-CH_2-Ph), 4.58 (s, 2H, CH_2OH), 4.65 (s, 4H, CH_2OH), 6.65 (d, J = 8.0 Hz, 1H, arom-H); 6.89 (dd, J = 8.0 Hz, 2.0 Hz, 1H, arom-H), 6.96 (s, 2H, arom-H), 7.06 (d, J = 2.0 Hz, 1H, arom-H). ^{13}C NMR (67.5 MHz, CD_3OD): δ = 41.5 (Ph-*C*H_2-Ph), 61.2 (*C*H_2-OH), 62.2 (*C*H_2-OH), 115.8 (*C*H), 128.1 (*C*-CH_2-OH), 128.3 (*C*-CH_2-OH), 128.5 (*C*H), 129.5 (*C*H), 129.6 (*C*H), 134.0 (*C*-CH_2-C), 134.3 (C-CH_2-*C*), 152.8 (*C*-OH), 154.3 (*C*-OH). MS (ESI-): $[M-H]^-$ m/z obs. 289.0434 (m/z exp. 289.1076).

4-(4-Hydroxybenzyl)-2,6-bis(hydroxymethyl)phenol (3a) and 4,4′-methylenebis[2-(hydroxy-methyl)phenol] (3b). A mixture of **3a** and **3b** (yield = 14%) was obtained from the chromatographic separation. The mass spectrum indicated only one value for this isomeric mixture (MS-ESI $[M-H]^-$ m/z obs. 259.0028, m/z exp. 259.0970). The ^{1}H NMR analysis showed a 1:3 ratio in favor of the asymmetric isomer **3a**, whose ^{1}H NMR spectrum exhibits two singlets corresponding to non coupled protons, versus **3b**, which displays an ABX spin system located in the aromatic region. The mixture was used without further purification. ^{13}C NMR (67.5 MHz, CD_3OD): δ = 41.3 (Ph-*C*H_2-Ph), 41.4 (Ph-*C*H_2-Ph), 61.2 (*C*H_2-OH), 62.1 (*C*H_2-OH), 115.8 (*C*H), 116.0 (*C*H), 128.1 (*C*-CH_2-OH), 128.3 (*C*-CH_2-OH), 128.5 (*C*H), 129.6 (*C*H), 129.7 (*C*H), 130.7 (*C*H), 134.1 (*C*-CH_2-C), 134.3 (C-CH_2-*C*), 152.8 (*C*-OH), 154.3 (*C*-OH), 156.4 (*C*-OH). MS (ESI-): $[M-H]^-$ m/z obs. 259.0028 (m/z exp. 259.0970).

Synthesis of the Phosphonic Acids: General Procedure

According to the conditions for the Michaelis–Arbuzov reaction, each fraction (0.1 mol) was introduced into a two-necked, 100 mL, round-bottom flask equipped with a reflux condenser. 0.105 mol of $P(OMe)_3$ was added for every CH_2OH group in one portion, and the mixture was heated to 80°C for 4 h. The excess of trimethylphosphite was co-evaporated under reduced pressure with diethyl ether. The alkyl ester was then hydrolyzed by heating in a mixture of MeOH/H_2O. Following this procedure, compounds **7–10** were obtained.

Octomethyl {methylenebist(2-hydroxy-5,1,3-phenylene)bismethylene]} tetraphosphonate (6). After evaporation of the excess of trimethyl phosphite, the

residue was purified by silica gel column chromatography with MeOH/ethyl acetate (20/80): yield = 3%. ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 3.16$ (d, $J = 21.4$ Hz, 8H, CH_2-P), 3.62 (d, $J = 10.7$ Hz, 24 H, PO-CH_3), 3.72 (s, 2H, Ph-CH_2-Ph), 6.87 (s, 4H, arom-H). ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 27.7$ (d, $J_{PC} = 137.0$ Hz, CH$_2$-P), 39.9 (s, Ph-CH$_2$-Ph), 53.1 (t, $J_{PC} = 3.0$ Hz, OCH$_3$), 120.2 (t, $J_{PC} = 6.5$ Hz, C-CH$_2$-P), 130.7 (t, $J_{PC} = 5.0$ Hz, CH), 133.8 (t, $J_{PC} = 2.5$ Hz, C-CH$_2$-C), 151.6 (t, $J_{PC} = 5.5$ Hz, C-OH). MS-ESI: [M-H]$^-$ m/z obs. 687.0150 (m/z exp. 687.1295).

{Methylenebis[(2-hydroxy-5,1,3-phenylene)bismethylene]}tetraphosphonic acid (7). Keeping in mind the poor yield obtained after purification for the ester **6**, this latter was directly hydrolyzed. For the hydrolysis, the ester **6** (0.2 mmol) was dissolved in MeOH (5 mL) and water (20 mL). The solution was heated in a sealed tube at 90°C for 30 h. The solvent was then removed in vacuo. The residue was eventually purified by HPLC (C_{18} column) with a 90/10 aqueous formic acid solution at pH = 3/acetonitrile mixture as eluent at a flow rate of 4 mL/min. The product peak detected at 280 nm appeared at retention times of 50–70 min. The pure fractions were collected and concentrated under reduced pressure to give compound **7** as a brown solid with 76% yield. IR (KBr), ν(cm^{-1}): 1652*w*, *broad* (POH), 1218*s* (P=O), 1106*s*, 930*s*, 994*s* (P-OH). ^{1}H NMR (270 MHz, D_2O): $\delta = 3.04$ (d, $J_{PH} = 20.7$ Hz, 8H, CH_2-P), 3.68 (s, 2H, Ph-CH_2-Ph), 6.93 (s, 4H, arom-H). ^{13}C NMR (67.5 MHz, D_2O): $\delta = 30.3$ (d, $J_{PC} = 132.0$ Hz, CH$_2$-P), 40.0 (s, Ph-CH$_2$-Ph), 122.6 (m, C-CH$_2$-P), 131.2 (s, CH), 135.4 (t, $J_{PC} = 2.5$ Hz, C-CH$_2$), 151.0 (t, $J_{PC} = 6.0$ Hz, C-OH). ^{31}P{^{1}H} NMR (109.38 MHz, D_2O): $\delta = 25.9$. MS-ESI: [M-H]$^-$ m/z obs. 575.0065 (m/z exp. 575.0043).

{5-[4-Hydroxy-3,5-bis(phosphonomethyl)benzyl]-2-hydroxybenzyl}phosphonic acid (8). The synthesis procedure used for **7** was applied also for the synthesis of **8**. Compound **4** (0.1 mol) was dissolved in trimethylphosphite (0.3 mol). The crude ester was directly hydrolyzed. The residue was purified by HPLC (C_{18} column) with a 90/10 aqueous formic acid solution at pH = 3/acetonitrile mixture as eluent at a flow rate of 3 mL/min. The product peak appeared at retention times of 68–98 min with ultraviolet detection at 280 nm. The pure fractions were collected and concentrated under reduced pressure to give compound **8** as a brown oil (yield 64%). IR (KBr), ν(cm^{-1}): 1650*w*, *broad* (POH), 1199*s* (P=O), 1094*s*, 993 s, 955*s* (P-OH). ^{1}H NMR (270 MHz, D_2O): $\delta = 2.98$ (d, $J_{PH} = 20.9$ Hz, 6H, CH_2-P), 3.56 (s, 2H, Ph-CH_2-Ph), 6.51 (d, $J = 8.1$ Hz, 1H, arom-H), 6.62 (s, 3H, arom-H), 6.75 (s, 1H, arom-H). ^{13}C NMR (67.5 MHz, D_2O): $\delta = 29.0$ (d, $J_{PC} = 132.0$ Hz, CH$_2$-P), 30.2 (d, $J_{PC} = 133.0$ Hz, CH$_2$-P), 40.0 (s, Ph-CH$_2$-Ph), 116.7 (s, CH); 119.9 (d, $J_{PC} = 10.5$ Hz, C-CH$_2$-P), 122.2 (dd, $J_{PC} = 9.5$ Hz, 2.0 Hz, C-CH$_2$-P), 129.2 (d, $J_{PC} = 2.0$ Hz, CH), 131.2 (s, CH), 132.4 (d, $J_{PC} = 6.0$ Hz, CH), 134.5 (d, $J_{PC} = 2.0$ Hz, C-CH$_2$-Ph), 135.5 (s, C-CH$_2$-Ph), 150.8 (t, $J_{PC} = 5.0$ Hz, C-OH), 152.7 (d, $J_{PC} = 6.0$ Hz, C-OH). ^{31}P{^{1}H} NMR (109.38 MHz, D_2O): $\delta = 26.0$, 26.5. MS-ESI: [M-H]$^-$ m/z obs. 480.8 (m/z exp. 481.03).

{[2-Hydroxy-5-(4-hydroxybenzyl)-1,3-phenylene]bis(methylene)}bisphosphonic acid (9) and {methylenebis[(2-hydroxy-5,1-phenylene)methylene]} bisphosphonic acid (10). The procedure used for the synthesis of compounds **7** and **8** was applied to the mixture of **3a** and **3b**. The residue was purified by HPLC (C_{18} column) with a 90/10 aqueous formic acid solution at pH = 3/acetonitrile mixture as eluent at a flow rate of 2 mL/min. Two product peaks appeared at retention times from 98–126 min and 127–140 min with ultraviolet detection at 280 nm. The pure fractions were collected and concentrated under reduced pressure to give compounds **9** and **10** as brown solids with 65% and 25% yield, respectively.

Compound 9: IR (KBr), $\nu(cm^{-1})$: 1611*w*, *broad* (POH), 1150*s* (P=O), 1019*s*, 951*s* (P-OH). ^1H NMR (270 MHz, D_2O): $\delta = 2.99$ (d, $J_{PH} = 20.5$ Hz, 4H, CH_2-P), 3.67 (s, 2H, Ph-CH_2-Ph), 6.66 (d, $J = 8.1$ Hz, 2H, arom-H); 6.99 (d, $J = 7.8$ Hz, 2H, arom-H); 6.82 (s, 2H, arom-H). ^{13}C NMR (67.5 MHz, D_2O): $\delta = 30.5$ (d, $J_{PC} = 132.0$ Hz, CH$_2$-P), 39.9 (s, Ph-CH$_2$-Ph), 115.7 (s, *C*H), 122.5 (d, $J_{PC} = 9.0$ Hz, *C*-CH$_2$-P), 130.4 (s, *C*H), 130.7 (s, *C*H), 134,3 (s, *C*-CH$_2$-Ph), 135.3 (s, *C*-CH$_2$-Ph), 150.6 (s, *C*-OH), 154.1 (s, *C*-OH). $^{31}P\{^1H\}$ NMR (109.38 MHz, D_2O): $\delta = 25.3$. MS-ESI: $[M\text{-}H]^-$ m/z obs. 386.8 (m/z exp. 387.05).

Compound 10: IR (KBr), $\nu(cm^{-1})$: 1634*w*, *broad* (POH), 1166*s* (P=O), 1100*s*, 999*s* (P-OH). ^1H NMR (270 MHz, D_2O): $\delta = 2.99$ (d, $J = 20.5$ Hz, 4H, CH_2-P), 3.60 (s, 2H, Ph-CH_2-Ph), 6.69 (d, $J = 8.1$ Hz, 2H, arom-H), 6.86 (d, $J = 8.1$ Hz, 2H, arom-H), 6.94 (s, 2H, arom-H). ^{13}C NMR (67.5 MHz, D_2O): $\delta = 30.2$ (d, $J_{PC} = 132.0$ Hz, CH$_2$-P), 40.0 (s, Ph-CH$_2$-Ph), 117.2 (s, *C*H), 121.2 (s, *C*-CH$_2$-P), 129.0 (s, *C*H), 132.4 (s, *C*H), 135,1 (s, *C*-CH$_2$-Ph), 152.7 (s, *C*-OH). $^{31}P\{^1H\}$ NMR (109.38 MHz, D_2O): $\delta = 26.0$. MS-ESI: $[M\text{-}H]^-$ m/z obs. 386.8 (m/z exp. 387.05).

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