

Catechol–Bisphosphonate Conjugates: New Types of Chelators for Metal Intoxication Therapy

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ABSTRACT: *Three new types of bisphosphonates conjugated with catechol were synthesized to explore their possibilities for the treatment of metal intoxication.* © 2004 Wiley Periodicals, Inc. *Heteroatom Chem* 15:549–555, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20056

INTRODUCTION

Human metal intoxication has caused more and more concerns in modern society. Chelating agents are the only choice for the treatment of such cases. Bisphosphonates have received considerable attention because of their high efficiency in binding with various metal ions such as Ca(II), Mg(II), Fe(II), Fe(III), Cu(II), and Al(III) [1]. On the other hand, catecholate ligands bearing a variety of electron withdrawing substituents have been extensively studied for their extraordinary high affinity with high oxidation state metals such as Fe(III) and actinides such as uranium(IV) and thorium(IV) [2].

The purpose of this investigation is to synthesize new chelators that have mixed functional groups such as bisphosphonate and catechol in order to enhance their binding affinity with concerned metal ions. In the previous paper [3], we described the

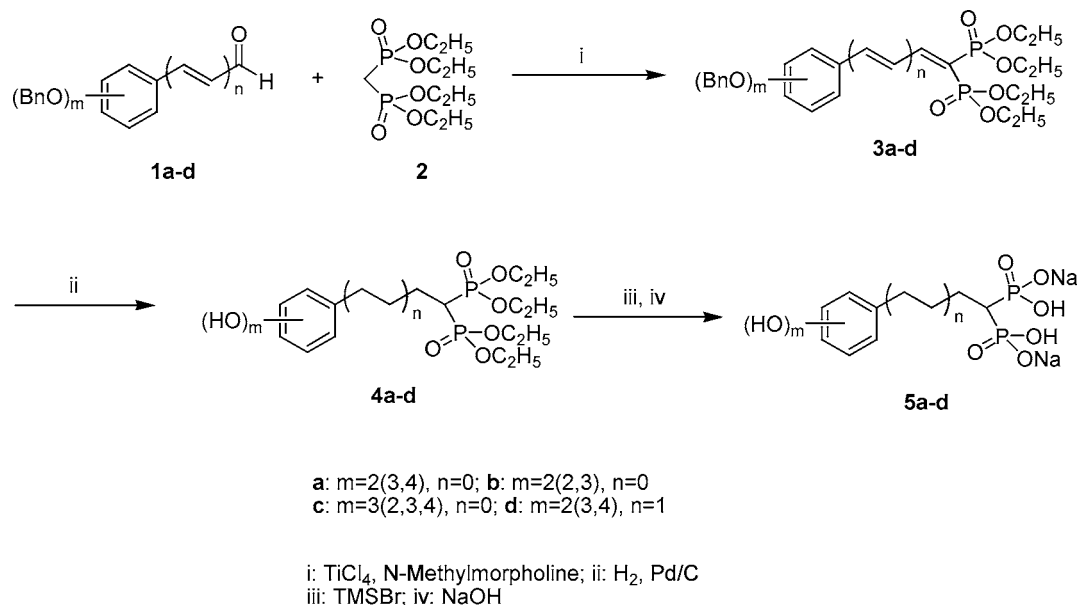
synthesis of conjugates in which bisphosphonate was linked with catechol by an amide bond or a nitrogen–carbon single bond. The preliminary assessment on the chelating potency of those catechol–bisphosphonates conjugates was encouraging, thus it prompted us to further our efforts in studies on this type of chelators. Here, we would like to report the synthesis of new chelating agents (compounds **5**, **9**, **11**) in which bisphosphonate and catechol were linked by carbon–carbon single or double bond directly.

RESULTS AND DISCUSSION

Compounds **5** were prepared as shown in scheme 1. The polybenzyloxy phenylalkenylaldehydes **1** [4] were condensed with tetraethyl bisphosphonates catalyzed by titanium tetrachloride and *N*-methylmorpholine at room temperature [5]. The obtained alkenylidene bisphosphonates **3** were then hydrogenated with Pd/C to give polybenzyloxy phenylalkyl bisphosphonates **4**. Considering the sensitivity of catechol moiety, bromotrimethylsilane (Me₃SiBr) was used to convert the alkyl bisphosphonates **4** into the corresponding trimethylsilyl bisphosphonates, which were readily transformed into the disodium salt of catechol bisphosphonic acids **5** by hydrolysis with aq. NaOH.

Similarly, we synthesized compounds **9** in which the central carbon atom was substituted by alkyl group (Scheme 2). The reduction of the alkenylidene

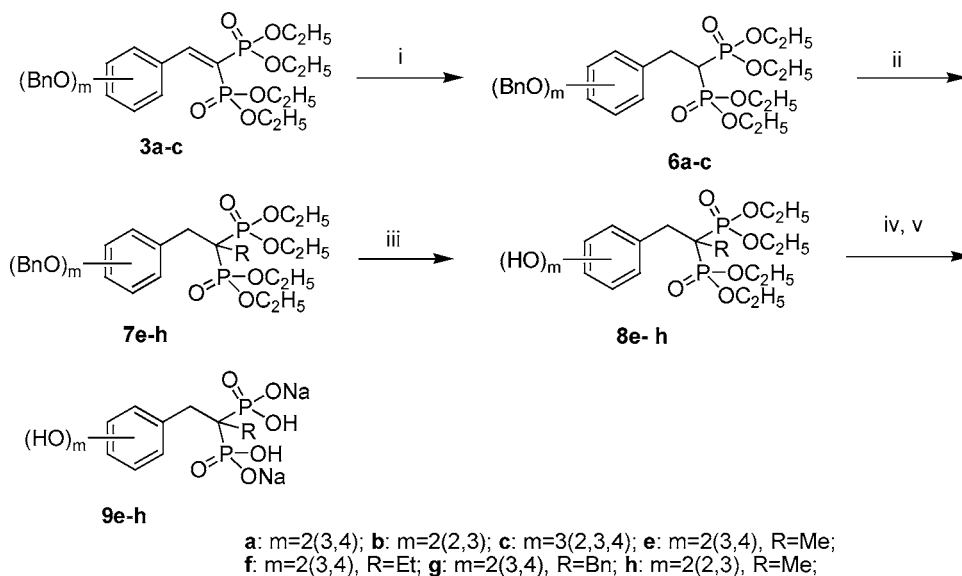
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SCHEME 1

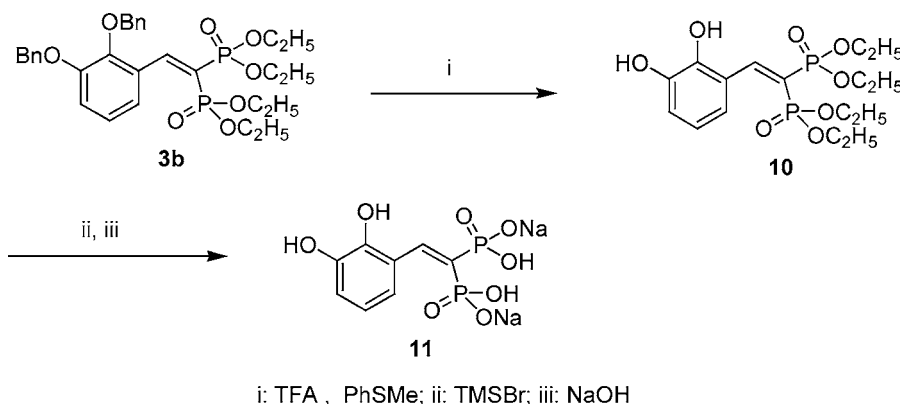
bisphosphonates **3** was accomplished by using NaBH_4 at r.t. Compounds **6** thus formed were then alkylated with sodium hydride and alkyl halide to give compounds **7**. Deprotection of **7** with Pd/C in ethanol provided compounds **8**, which was subsequently converted to compounds **9** by similar method as described for preparing of compounds **5**.

A disodium salt of alkenylidene bisphosphonic acid **11** was also prepared (Scheme 3). To obtain the intermediate **10**, several attempts had been made to remove the benzyl group while having the carbon-carbon double bond retained. At last, a thioanisole-trifluoroacetic acid reagent system [6] was found to be most suitable for this purpose, by which



i: NaBH_4 ; ii: NaH , RX; iii: H_2 , Pd/C
iv: TMSBr; v: NaOH

SCHEME 2



SCHEME 3

compound **10** was obtained in good purity. Compound **11** was finally prepared by using TMSBr followed by hydrolysis with aq. NaOH.

In summary, three new types of disodium salts of bisphosphonic acid bearing catechol moiety were efficiently prepared, their chelating properties will be reported elsewhere.

EXPERIMENTAL

Melting points were determined using a Büchi 510 melting point apparatus and are uncorrected. NMR, ^1H (400.13 MHz), ^{13}C (100.61 MHz), and ^{31}P (161.99 MHz), spectra were recorded on a Bruker-400 NMR spectrometer with TMS as internal standard (^1H and ^{13}C) and 85% H_3PO_4 as an external standard (^{31}P). Microanalyses were carried out on a Leco CHN-2000 elemental analyzer.

Tetraethyl 3,4-dibenzyloxyphenylethenylidenebisphosphonate (3a)

Under nitrogen, 10 mL of dry THF was placed in a 25 mL flask and was cooled to 0°C . Titanium tetrachloride (380 mg, 2.00 mmol), 3,4-dibenzyloxybenzaldehyde (245 mg, 0.77 mmol), tetraethyl methylenebisphosphonate (288 mg, 0.77 mmol), and *N*-methylmorpholine (404 mg, 4.00 mmol) were added successively. The mixture was stirred for 2 h at room temperature and concentrated under vacuum. The residue was partitioned between Et_2O and H_2O . The ether phase was washed with aqueous NaHCO_3 to neutral, dried over anhydrous Na_2SO_4 , and evaporated to dryness. The residue was purified by column chromatography (SiO_2 , 1/30 $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 320 mg (70.1%) of pale yellow oil **3a**. ^1H NMR (CDCl_3): δ 8.17 (dd, $J = 29.5, 47.8$ Hz, 1H, CH), 7.77–6.90 (m, 13H, ArH), 5.21 (s, 2H, ArCH_2O), 5.19 (s,

2H, ArCH_2O), 4.22–4.00 (m, 8H, CH_2CH_3), 1.40–1.14 (m, 12H, CH_2CH_3). Compounds **3b–d** were prepared using the method described for the preparation of **3a**.

Tetraethyl 2,3-dibenzyloxyphenylethenylidenebisphosphonate (3b)

70.0%, pale yellow oil, ^1H NMR (CDCl_3): δ 8.45 (dd, $J = 28.7, 47.9$ Hz, 1H, CH), 7.44–7.00 (m, 13H, ArH), 5.13 (s, 2H, ArCH_2O), 5.05 (s, 2H, ArCH_2O), 4.16–3.89 (m, 8H, CH_2CH_3), 1.33–1.10 (m, 12H, CH_2CH_3).

Tetraethyl 2,3,4-tribenzyloxyphenylethenylidenebisphosphonate (3c)

61.1%, pale yellow oil, ^1H NMR (CDCl_3): δ 8.47 (dd, $J = 28.9, 48.3$ Hz, 1H, CH), 7.80–6.77 (m, 17H, ArH), 5.15 (s, 2H, ArCH_2O), 5.09 (s, 2H, ArCH_2O), 5.04 (s, 2H, ArCH_2O), 4.20–3.90 (m, 8H, CH_2CH_3), 1.35–1.10 (m, 12H, CH_3).

Tetraethyl 3,4-dibenzyloxyphenylbutadienylidenebisphosphonate (3d)

75.0%, pale yellow oil, ^1H NMR (CDCl_3): δ 8.40–7.69 (m, 3H, $\text{Ar}-\text{CH}=\text{CH}-\text{CH}$), 7.48–6.85 (m, 13H, ArH), 5.23 (s, 2H, ArCH_2O), 5.20 (s, 2H, ArCH_2O), 4.22–4.06 (m, 8H, CH_2CH_3), 1.37–1.32 (t, 12H, CH_2CH_3).

Tetraethyl 3,4-dihydroxyphenylethenylidenebisphosphonate (4a)

Compound **3a** (2.00 g, 3.40 mmol) was dissolved in ethanol (25 mL), and the solution was hydrogenated over 0.5 g of 10% palladium on carbon at room temperature for 8 h. The catalyst was filtered, the solvent was removed, and the residue

was purified by column chromatography on silica gel (1/30 MeOH/CH₂Cl₂) to give 1.30 g (93.2%) of a white solid. mp 71–73°C, ¹H NMR (CDCl₃): δ 6.85 (s, 1H, Ar-2H), 6.75 (d, *J* = 8.1 Hz, 1H, Ar-5H), 6.62 (d, *J* = 8.1 Hz, 1H, Ar-6H), 4.10–4.00 (m, 8H, O–CH₂), 3.13 (dt, *J* = 6.2, 16.7 Hz, 2H, Ar–CH₂), 2.80–2.60 (m, 1H, CH), 1.30–1.20 (m, 12H, CH₃); ¹³C NMR (CDCl₃): δ 144.31, 143.40, 130.68, 120.41, 116.02, 115.18 (6s, Ph–C), 62.97 (t, OCH₂), 38.87 (t, CH), 30.48 (s, Ph–CH₂), 16.23 (s, CH₃); ³¹P NMR (CDCl₃): δ 24.98; Anal. Calcd for C₁₆H₂₈O₈P₂: C, 46.83; H, 6.82. Found: C, 47.02; H, 6.88. Compounds **4b–d** were prepared using the method described for the preparation of **4a**.

Tetraethyl 2,3-dihydroxyphenylethylidenebisphosphonate (4b)

90.1%, white solid, mp 134–136°C, ¹H NMR (CDCl₃): δ 9.20 (s, 1H, OH), 6.83–6.67 (m, 3H, ArH), 6.10 (s, 1H, OH), 4.30–4.00 (m, 8H, O–CH₂), 3.23 (dt, *J* = 5.8, 17.0 Hz, 2H, Ar–CH₂), 2.55 (tt, *J* = 5.8, 23.9 Hz, 1H, CH), 1.40–1.20 (m, 12H, CH₃); ³¹P NMR (CDCl₃): δ 26.48; Anal. Calcd for C₁₆H₂₈O₈P₂: C, 46.83; H, 6.82. Found: C, 47.09; H, 6.66.

Tetraethyl 2,3,4-trihydroxyphenylethylidenebisphosphonate (4c)

87.1%, white solid, mp 127–129°C, ¹H NMR (CDCl₃): δ 6.58 (dd, *J* = 1.4, 8.4 Hz, 1H, Ar-6H), 6.45 (dd, *J* = 3.6, 8.4 Hz, 1H, Ar-5H), 4.20–4.00 (m, 8H, O–CH₂), 3.16 (dt, *J* = 5.9, 16.6 Hz, 2H, Ar–CH₂), 2.69 (tt, *J* = 5.9, 24.0 Hz, 1H, CH), 1.40–1.20 (m, 12H, CH₃); ³¹P NMR (CDCl₃): δ 26.36; Anal. Calcd for C₁₆H₂₈O₉P₂: C, 45.07; H, 6.57. Found: C, 45.05; H, 6.63.

Tetraethyl 3,4-dihydroxyphenylbutylidenebisphosphonate (4d)

91.2%, pale yellow oil, ¹H NMR (CDCl₃): δ 6.76 (d, *J* = 8.2 Hz, 1H, Ar-5H), 6.70 (d, *J* = 2.2 Hz, 1H, Ar-2H), 6.50 (dd, *J* = 2.2, 8.2 Hz, 1H, Ar-6H), 4.20–4.08 (m, 8H, OCH₂), 2.48 (t, *J* = 7.0 Hz, 2H, Ar–CH₂), 2.31 (tt, *J* = 6.0, 24.4 Hz, 1H, CH₂CH), 2.00–1.80 (m, 4H, Ar–CH₂CH₂CH₂), 1.34–1.27 (m, 12H, CH₃).

3,4-Dihydroxyphenylethylidenebisphosphonic Acid Disodium (5a)

Under N₂, 312 mg (2.05 mmol) of Me₃SiBr was added dropwise to a solution of compound **4a** (154 mg, 0.38 mmol) in 20 mL of dry dichloromethane. The mixture was stirred at r.t. for 30 h. Then the reaction solution was evaporated in vacuum, and the red residue

was treated with 3 mL of aqueous NaOH (30 mg, 0.76 mmol). Seventy four milligram of product **9e** (54.5%) was obtained after removing the excess water under reduced pressure and recrystallized from water and methanol as a white solid. mp >300°C, ¹H NMR (D₂O): δ 6.71 (d, *J* = 1.5 Hz, 1H, Ar-2H), 6.64 (d, *J* = 8.1 Hz, 1H, Ar-5H), 6.61 (dd, *J* = 1.5, 8.1 Hz, 1H, Ar-6H), 2.82 (dt, *J* = 6.2, 16.1 Hz, 2H, CH₂), 2.06 (tt, *J* = 6.2, 22.0 Hz, 1H, CH); ¹³C NMR (D₂O): δ 143.92, 142.33, 134.88, 121.58, 117.14, 116.42 (6s, Ph–C), 41.24 (s, CH₂), 30.85 (s, CH); ³¹P NMR (D₂O): δ 20.32; Anal. Calcd for C₈H₁₀O₈P₂Na₂·H₂O: C, 26.67; H, 3.33. Found: C, 26.78; H, 3.62. Compounds **5b–d** were prepared using the method described for the preparation of **5a**.

2,3-Dihydroxyphenylethylidenebisphosphonic Acid Disodium (5b)

54.4%, white solid, mp > 300°C, ¹H NMR (D₂O): δ 7.15–7.00 (m, 3H, ArH), 3.36 (dt, *J* = 5.9, 16.1 Hz, 2H, CH₂), 2.48 (tt, *J* = 5.9, 22.0 Hz, 1H, CH); ³¹P NMR (D₂O): δ 20.81; Anal. Calcd for C₈H₁₀O₈P₂Na₂·CH₃OH·H₂O: C, 27.55; H, 4.08. Found: C, 27.50; H, 4.04.

2,3,4-Trihydroxyphenylethylidenebisphosphonic Acid Disodium (5c)

49.3%, white solid, mp > 300°C, ¹H NMR (D₂O): δ 6.78 (d, *J* = 8.4 Hz, 1H, Ar-6H), 6.55 (d, *J* = 8.4 Hz, 1H, Ar-5H), 3.12 (dt, *J* = 5.6, 16.0 Hz, 2H, CH₂), 2.35 (tt, *J* = 5.6, 22.5 Hz, 1H, CH); ³¹P NMR (D₂O): δ 21.73; Anal. Calcd for C₈H₁₀O₉P₂Na₂·CH₃OH: C, 27.69; H, 3.59. Found: C, 27.37; H, 3.59.

3,4-Dihydroxyphenylbutylidenebisphosphonic Acid Disodium (5d)

47.3%, white solid, mp > 300°C, ¹H NMR (D₂O): δ 6.90 (d, *J* = 8.1 Hz, 1H, Ar-5H), 6.88 (s, 1H, Ar-2H), 6.78 (dd, *J* = 1.4, 8.1 Hz, 1H, Ar-6H), 2.58 (t, *J* = 6.8 Hz, 2H, Ar–CH₂), 2.13 (tt, *J* = 5.5, 22.8 Hz, 1H, CH(P₂)), 1.98–1.83 (m, 4H, CH₂CH₂CH); ³¹P NMR (D₂O): δ 21.97; Anal. Calcd for C₁₀H₁₄O₈P₂Na₂·CH₃OH: C, 32.83; H, 4.46. Found: C, 32.60; H, 4.28.

Tetraethyl 3,4-dibenzyloxyphenylethylidenebisphosphonate (6a)

Compound **3a** (1.99 g, 3.38 mmol) was added to a solution of 0.19 g NaBH₄ (5 mmol) in EtOH (25 mL), and the mixture was stirred at r.t. for 3 h. The ethanol solution was evaporated, and the residue

was partitioned between 2.5 N HCl and EtOAc. Evaporation of the dried organic phase gave an oil that was purified by silica gel chromatography (1/30 MeOH/CH₂Cl₂), to give 1.80 g (90.0%) of colorless oil. ¹H NMR (CDCl₃): δ 7.46–7.27 (m, 10H, ArH–CH₂O), 6.90 (d, *J* = 2.1 Hz, 1H, O–Ar–2H), 6.83 (d, *J* = 8.2 Hz, 1H, O–Ar–5H), 6.77 (dd, *J* = 2.1, 8.2 Hz, 1H, O–Ar–6H), 5.14 (s, 2H, ArCH₂O), 5.13 (s, 2H, ArCH₂O), 4.14–3.98 (m, 8H, CH₂CH₃), 3.14 (dt, *J* = 6.2, 16.6 Hz, 2H, CH₂CH), 2.54 (tt, *J* = 6.2, 23.8 Hz, 1H, CH₂CH), 1.28–1.22 (m, 12H, CH₂CH₃). Compounds **6b** and **6c** were prepared using the method described for the preparation of **6a**.

Tetraethyl 2,3-dibenzyloxyphenylethylidenebisphosphonate (6b)

90.1%, colorless oil, ¹H NMR (CDCl₃): δ 7.46–7.27 (m, 10H, ArH–CH₂O), 6.97–6.88 (m, 3H, ArH–CH₂CH), 5.12 (s, 2H, ArCH₂O), 5.08 (s, 2H, ArCH₂O), 4.10–3.90 (m, 8H, CH₂CH₃), 3.26 (dt, *J* = 7.2, 16.6 Hz, 2H, CH₂CH), 3.09 (tt, *J* = 7.2, 22.7 Hz, 1H, CH₂CH), 1.21–1.16 (m, 12H, CH₂CH₃).

Tetraethyl 2,3,4-tribenzyloxyphenylethylidenebisphosphonate (6c)

67.0%, pale yellow oil, ¹H NMR (CDCl₃): δ 7.47–7.27 (m, 15H, ArH–CH₂O), 6.95 (d, *J* = 8.5 Hz, 1H, O–Ar–6H), 6.68 (d, *J* = 8.5 Hz, 1H, O–Ar–5H), 5.13 (s, 2H, ArCH₂O), 5.11 (s, 2H, ArCH₂O), 5.02 (s, 2H, ArCH₂O), 4.1–3.9 (m, 8H, CH₂CH₃), 3.20 (dt, *J* = 7.0, 15.9 Hz, 2H, CH₂CH), 3.05 (tt, *J* = 7.0, 22.7 Hz, 1H, CH₂CH), 1.20–1.13 (m, 12H, CH₂CH₃).

Tetraethyl 1-(3,4-dibenzyloxybenzyl)-1-methylene-bisphosphonate (7e)

Compound **6a** (0.78 mg, 1.32 mmol) was added slowly to a suspension of 60% NaH (0.11 g, 2.75 mmol) in 5 mL of dry THF at r.t., and the mixture was stirred for 30 min. Methyl iodide (0.75 g, 5.28 mmol) was then added, and the reaction mixture was stirred at 40°C for 20 h. After CH₂Cl₂/H₂O partition, the organic phase was dried and evaporated. Column chromatography (SiO₂, 1/50 MeOH/CH₂Cl₂) gave 0.39 g (37.6%) of colorless oil **7e**. ¹H NMR (CDCl₃): δ 7.46–7.28 (m, 10H, ArH–CH₂O), 6.92 (s, 1H, O–Ar–2H), 6.80 (s, 2H, O–Ar–5, 6H), 5.15 (s, 2H, ArCH₂O), 5.14 (s, 2H, ArCH₂O), 4.14–4.04 (m, 8H, CH₂CH₃), 3.18–3.08 (dd, *J* = 13.4, 15.8 Hz, 2H, C(P₂)–CH₂), 1.33 (t, *J* = 16.7 Hz, 3H, C(P₂)–CH₃), 1.27–1.20 (m, 12H, CH₂CH₃). Compounds **7f–h** were prepared using the method described for the preparation of **7e**.

Tetraethyl 1-(3,4-dibenzyloxybenzyl)-1-ethyl-methylene-bisphosphonate (7f)

37.2%, colorless oil, ¹H NMR (CDCl₃): δ 7.45–7.26 (m, 10H, ArH–CH₂O), 6.95 (d, *J* = 1.7 Hz, 1H, O–Ar–2H), 6.84 (dd, *J* = 1.7, 8.4 Hz, 1H, O–Ar–6H), 6.81 (d, *J* = 8.4 Hz, 1H, O–Ar–5H), 5.16 (s, 2H, ArCH₂O), 5.14 (s, 2H, ArCH₂O), 4.14–4.00 (m, 8H, OCH₂CH₃), 3.15 (dd, *J* = 12.2, 16.7 Hz, 2H, ArCH₂C(P₂)), 1.88–1.76 (m, 2H, C(P₂)CH₂CH₃), 1.28–1.16 (m, 12H, OCH₂CH₃), 1.12 (t, 3H, *J* = 7.4 Hz, C(P₂)CH₂CH₃).

Tetraethyl 1-(3,4-dibenzyloxybenzyl)-1-phenyl-methylene-bisphosphonate (7g)

48.7%, colorless oil, ¹H NMR (CDCl₃): δ 7.45–7.19 (m, 15H, Ar–CH₂O), 7.10 (d, *J* = 2.0 Hz, 1H, O–Ar–2H), 6.98 (dd, *J* = 2.0, 8.2 Hz, 1H, O–Ar–6H), 6.82 (d, *J* = 8.2 Hz, 1H, O–Ar–5H), 5.15 (s, 4H, ArCH₂O), 4.04–3.87 (m, 8H, CH₂CH₃), 3.24 (t, *J* = 16.1 Hz, 4H, C(P₂)–CH₂), 1.14–1.09 (m, 12H, CH₂CH₃).

Tetraethyl 1-(2,3-dibenzyloxybenzyl)-1-methyl-methylene-bisphosphonate (7h)

43.1%, colorless oil, ¹H NMR (CDCl₃): δ 7.45–7.27 (m, 10H, ArH–CH₂O), 7.14 (dd, *J* = 1.9, 7.3 Hz, 1H, O–Ar–6H), 6.93 (t, *J* = 7.3, 8.1 Hz, 1H, Ar–5H), 6.90 (dd, *J* = 1.9, 8.1 Hz, 1H, O–Ar–4H), 5.12 (s, 2H, ArCH₂O), 4.95 (s, 2H, ArCH₂O), 4.20–4.00 (m, 8H, CH₂CH₃), 3.35 (dd, *J* = 13.5, 16.1 Hz, 2H, CH₂C), 1.40 (t, *J* = 17.0 Hz, 3H, C(P₂)CH₃), 1.24–1.18 (m, 12H, CH₂CH₃).

Tetraethyl 1-(3,4-dihydroxybenzyl)-1-methyl-methylene-bisphosphonate (8e)

Compound **7e** (0.51 g, 0.84 mmol) in 10 mL EtOH was hydrogenated over 0.2 g of 10% palladium on carbon at r.t. for 6 h. Then the solution was filtered through Celite, concentrated, and the residue was chromatographed on silica gel (1/20, MeOH/CH₂Cl₂) to yield 0.32 g (89.4%) of white solid **8e**. mp 159–161°C, ¹H NMR (CDCl₃): δ 8.02 (s, 1H, OH), 7.97 (s, 1H, OH), 6.74–6.60 (m, 3H, ArH), 4.22–4.02 (m, 8H, CH₂CH₃), 3.14 (dd, *J* = 13.6, 15.8 Hz, 2H, Ar–CH₂), 1.44 (t, *J* = 16.7 Hz, 3H, C(P₂)CH₃), 1.34–1.21 (m, 12H, CH₂CH₃); ³¹P NMR (CDCl₃): δ 27.05; Anal. Calcd for C₁₇H₃₀O₈P₂: C, 48.11; H, 7.08. Found: C, 48.33; H, 6.83. Compounds **8f–h** were prepared using the method described for the preparation of **8e**.

Tetraethyl 1-(3,4-dihydroxybenzyl)-1-ethyl-methylene-bisphosphonate (8f)

85.1%, white solid, mp 133–135°C, ^1H NMR (CDCl_3): δ 7.02 (d, $J = 2.0$ Hz, 1H, Ar-2H), 6.73 (d, $J = 8.2$ Hz, 1H, Ar-5H), 6.63 (dd, $J = 2.0, 8.2$ Hz, 1H, Ar-6H), 4.19–3.98 (m, 8H, OCH_2CH_3), 3.17 (dd, $J = 12.7, 16.7$ Hz, 2H, Ar- CH_2), 2.01–1.91 (m, 2H, $\text{C}(\text{P}_2)\text{CH}_2\text{CH}_3$), 1.32–1.18 (m, 15H, OCH_2CH_3 , $\text{C}(\text{P}_2)\text{CH}_2\text{CH}_3$); ^{31}P NMR (CDCl_3): δ 27.05; Anal. Calcd for $\text{C}_{18}\text{H}_{32}\text{O}_8\text{P}_2$: C, 49.32; H, 7.31. Found: C, 49.30; H, 7.27.

Tetraethyl 1-(3,4-dihydroxybenzyl)-1-phenyl-methylene-bisphosphonate (8g)

83.7%, white solid, mp 145–147°C, ^1H NMR (CDCl_3): δ 7.44–7.18 (m, 7H, OH, CCH_2ArH), 7.05 (d, $J = 2.0$ Hz, 1H, Ar-2H), 6.78 (dd, $J = 2.0, 8.1$ Hz, 1H, Ar-6H), 6.72 (d, $J = 8.1$ Hz, 1H, Ar-5H), 4.10–3.85 (m, 8H, CH_2CH_3), 3.38–3.18 (m, 4H, CH_2), 1.21–1.11 (m, 12H, CH_3); ^{31}P NMR (CDCl_3): δ 26.70; Anal. Calcd for $\text{C}_{23}\text{H}_{34}\text{O}_8\text{P}_2$: C, 55.20; H, 6.80. Found: C, 55.21; H, 6.82.

Tetraethyl 1-(2,3-dihydroxybenzyl)-1-methyl-methylene-bisphosphonate (8h)

75.8%, white solid, mp 124–126°C, ^1H NMR (CDCl_3): δ 9.55 (s, 1H, OH), 6.82 (dd, $J = 1.7, 7.9$ Hz, 1H, Ar-6H), 6.74 (t, $J = 7.6, 7.9$ Hz, 1H, Ar-5H), 6.60 (dd, $J = 1.7, 7.6$ Hz, 1H, Ar-4H), 6.15 (s, 1H, OH), 4.30–3.90 (m, 8H, CH_2CH_3), 3.23 (t, 2H, Ar- CH_2), 1.45 (t, $J = 16.7$ Hz, 3H, $\text{C}(\text{P}_2)\text{CH}_3$), 1.40–1.15 (m, 12H, CH_2CH_3); ^{31}P NMR (CDCl_3): δ 29.00; Anal. Calcd for $\text{C}_{17}\text{H}_{30}\text{O}_8\text{P}_2$: C, 48.11; H, 7.08. Found: C, 48.31; H, 7.08.

1-(3,4-Dihydroxybenzyl)-1-methyl-methylene-bisphosphonic Acid Disodium (9e)

Under N_2 , Me_3SiBr (325 g, 2.12 mmol) was added to a stirred solution of compound **8e** (150 mg, 0.35 mmol) in 20 mL of dry CH_2Cl_2 at r.t. After stirring for 30 h, the alkyl bromide byproducts and excess bromotrimethylsilane were removed in vacuo and the residue was treated with 5 mL of aq. NaOH (28 mg, 0.70 mmol). Sixty milligram of product **9e** (47.6%) was obtained after removing the excess water under reduced pressure and recrystallized from water and methanol as a white solid. mp > 300°C, ^1H NMR (D_2O): δ 6.76 (s, 1H, ArH), 6.65 (s, 2H, ArH), 2.87 (t, $J = 14.5$ Hz, 2H, CH_2), 1.10 (t, $J = 16.1$ Hz, 3H, CH_3); ^{31}P NMR (D_2O): δ 25.60; Anal. Calcd for $\text{C}_9\text{H}_{12}\text{O}_8\text{P}_2\text{Na}_2 \cdot \text{CH}_3\text{OH} \cdot \text{H}_2\text{O}$: C, 29.55; H, 4.43. Found: C, 29.62; H, 4.51. Compounds **9f–h**

were prepared using the method described for the preparation of **9e**.

1-(3,4-Dihydroxybenzyl)-1-ethyl-methylene-bisphosphonic Acid Disodium (9f)

43.2%, white solid, mp > 300°C, ^1H NMR (D_2O): δ 7.25 (d, $J = 1.7$ Hz, 1H, Ar-2H), 7.09 (dd, $J = 1.7, 8.1$ Hz, 1H, Ar-6H), 7.04 (dd, $J = 1.3, 8.1$ Hz, 1H, Ar-5H), 3.30 (t, $J = 14.6$ Hz, 2H, Ar- CH_2), 2.00 (m, 2H, CH_2CH_3), 1.36 (t, $J = 7.5$ Hz, 3H, CH_2CH_3); ^{31}P NMR (D_2O): δ 24.33; Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_8\text{P}_2\text{Na}_2 \cdot \text{CH}_3\text{OH} \cdot \text{H}_2\text{O}$: C, 31.43; H, 4.76. Found: C, 31.51; H, 4.75.

1-(3,4-Dihydroxybenzyl)-1-phenyl-methylene-bisphosphonic Acid Disodium (9g)

63.7%, white solid, mp > 300°C, ^1H NMR (D_2O): δ 7.80–7.47 (m, 5H, 3-ArH), 7.28 (d, $J = 2.0$ Hz, 1H, 1-Ar-2H), 7.15 (dd, $J = 2.0, 8.1$ Hz, 1H, 1-Ar-6H), 7.04 (d, $J = 8.1$ Hz, 1H, 1-Ar-5H), 3.41 (t, $J = 16.8$ Hz, 2H, CH_2), 3.32 (t, $J = 16.8$ Hz, 2H, CH_2); ^{31}P NMR (D_2O): δ 23.49; Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_8\text{P}_2\text{Na}_2 \cdot \text{CH}_3\text{OH} \cdot 1.5\text{H}_2\text{O}$: C, 39.10; H, 4.68. Found: C, 38.94; H, 4.74.

1-(2,3-Dihydroxybenzyl)-1-methyl-methylene-bisphosphonic Acid Disodium (9h)

42.9%, white solid, mp > 300°C, ^1H NMR (D_2O): δ 7.09–7.05 (m, 3H, ArH), 3.42 (t, $J = 15.1$ Hz, 2H, CH_2), 1.55 (t, $J = 16.1$ Hz, 3H, CH_3); ^{31}P NMR (D_2O): δ 26.68; Anal. Calcd for $\text{C}_9\text{H}_{12}\text{O}_8\text{P}_2\text{Na}_2 \cdot 1.5\text{CH}_3\text{OH}$: C, 31.19; H, 4.46. Found: C, 31.06; H, 4.59.

Tetraethyl 2,3-dihydroxyphenylethenyl-idenebisphosphonate (10)

A mixture of compound (**3b**) (0.52 g, 0.88 mmol) and thioanisole (5.48 g, 44 mmol) in TFA (2 mL) was kept at room temperature overnight. Then the solution was concentrated in vacuum, and the residue was dissolved in CH_2Cl_2 . The solution was washed with saturated NaHCO_3 solution and water, dried (MgSO_4), filtered, concentrated. The residue was purified by chromatography over silica gel (1/30, $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to yield **10** as a colorless oil (0.16 g, 44.4%). ^1H NMR (CDCl_3): δ 8.12 (dd, $J = 24.1, 40.6$ Hz, 1H, CH), 7.14 (dt, $J = 1.7, 8.1$ Hz, 1H, Ar-6H), 7.09 (t, $J = 7.4, 8.1$ Hz, 1H, Ar-5H), 6.99 (dd, $J = 1.7, 7.4$ Hz, 1H, Ar-4H), 4.34–4.18 (m, 8H, CH_2), 1.43–1.33 (m, 12H, CH_3); ^{31}P NMR (CDCl_3): δ 20.83 (d, $J = 52.5$ Hz), 15.71 (d, $J = 51.0$ Hz).

2,3-Dihydroxyphenylethenylidenebisphosphonic Acid Disodium (11)

TMSBr (225 mg, 1.47 mmol) was added dropwise to a solution of bisphosphonate **10** (100 mg, 0.24 mmol) in dry CH₂Cl₂ (10 mL) under N₂. After stirred for 30 h, the reaction solution was concentrated, and the residue was treated with 5 mL of aq. NaOH (20 mg, 0.48 mmol). Then the excess water was removed to give a white precipitate, which was purified by recrystallization from water and methanol to provide product **11** (41 mg, 49.4%) as a white solid. mp >300°C, ¹H NMR (D₂O): δ 7.49–7.33 (m, 1H, CH), 6.90–6.87 (m, 3H, ArH); ³¹P NMR (D₂O): δ 9.01 (d, *J* = 44.1 Hz), 5.59 (d, *J* = 45.2 Hz); Anal. Calcd for C₈H₈O₈P₂Na₂·1.5CH₃OH: C, 29.38; H, 3.60. Found: C, 29.68; H, 3.25.

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