Heteroatom Chemistry
Volume 15, Number 7, 2004

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

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Received 15 July 2004; revised 6 September 2004

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 bisphoshonate and catechol were linked by carbon–carbon single or double bond directly.

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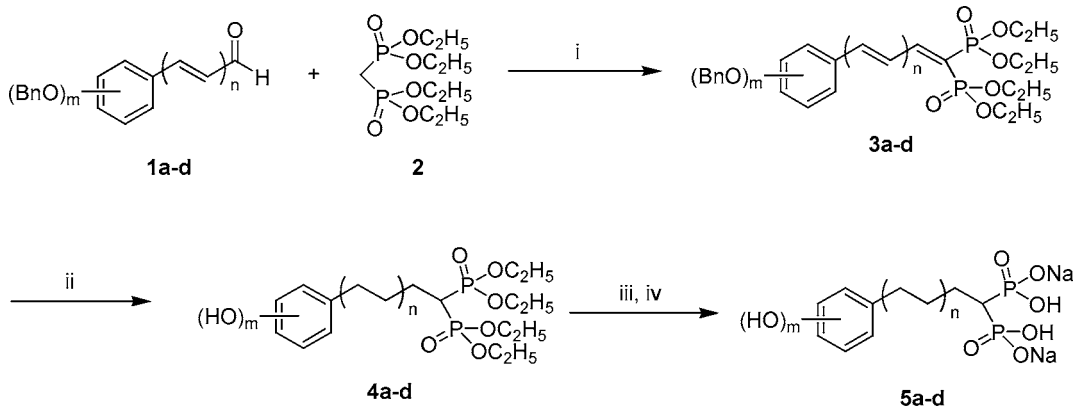
RESULTS AND DISCUSSION

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*-methylmorpoline 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 (Me_3SiBr) 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



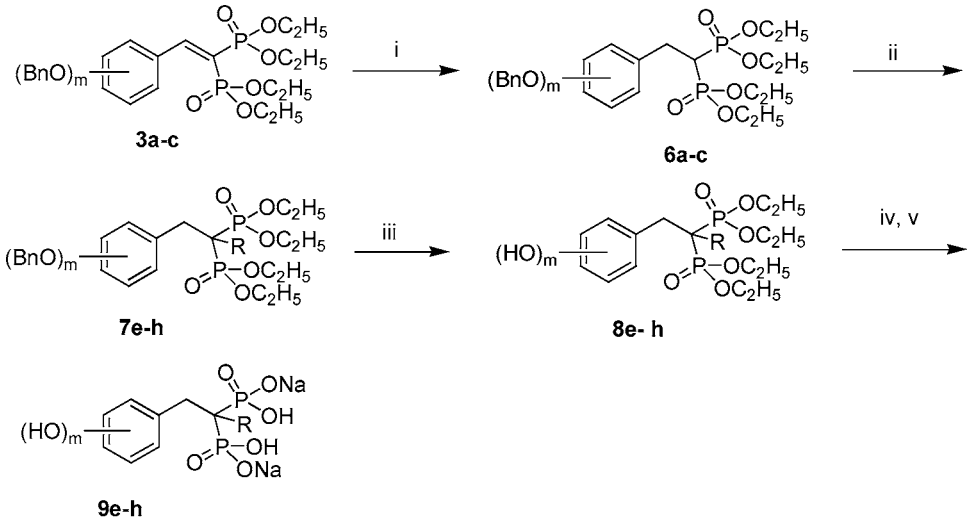
a: m=2(3,4), n=0; **b**: m=2(2,3), n=0
c: m=3(2,3,4), n=0; **d**: m=2(3,4), n=1

i: $TiCl_4$, N-Methylmorpholine; ii: H_2, Pd/C
iii: TMSBr; iv: NaOH

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**.

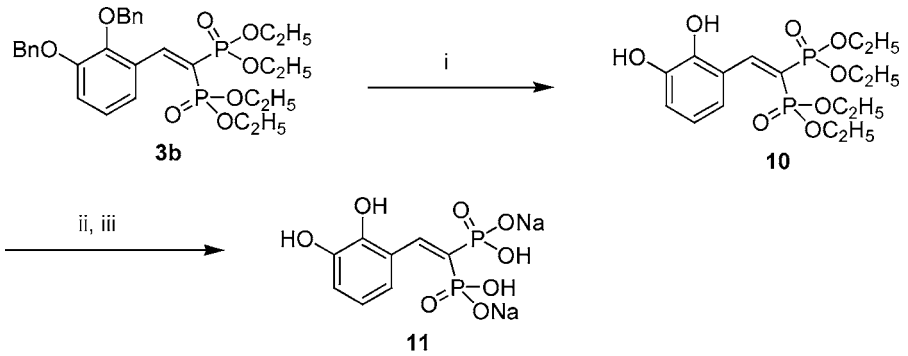
A disodium salt of alkenylidene bisphosphonic acid **11** was also prepared (Scheme 3). To obtain the intermediate **10**, several attempts had been made to remove the benzyl group while having the carbon–carbon double bond retained. At last, a thioanisole–trifluoroacetic acid reagent system [6] was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



a: m=2(3,4); **b**: m=2(2,3); **c**: m=3(2,3,4); **e**: m=2(3,4), R=Me;
f: m=2(3,4), R=Et; **g**: m=2(3,4), R=Bn; **h**: m=2(2,3), R=Me;

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

SCHEME 2



i: TFA , PhSMe; ii: TMSBr; iii: NaOH

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, ^{1}H (400.13 MHz), ^{13}C (100.61 MHz), and ^{31}P (161.99 MHz), spectra were recorded on a Brucker-400 NMR spectrometer with TMS as internal standard (^{1}H 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 MeOH/CH_2Cl_2) to give 320 mg (70.1%) of pale yellow oil **3a**. ^{1}H 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, ArC$\underline{H}_2$O), 5.19 (s, 2H, ArC$\underline{H}_2$O), 4.22–4.00 (m, 8H, C$\underline{H}_2$CH$_3$), 1.40–1.14 (m, 12H, CH$_2$C$\underline{H}_3$). Compounds **3b–d** were prepared using the method described for the preparation of **3a**.

*Tetraethyl 2,3-dibenzyloxyphenylethenylidenebisphosphonate (**3b**)*

70.0%, pale yellow oil, ^{1}H 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, ArC$\underline{H}_2$O), 5.05 (s, 2H, ArC$\underline{H}_2$O), 4.16–3.89 (m, 8H, C$\underline{H}_2$CH$_3$), 1.33–1.10 (m, 12H, CH$_2$C$\underline{H}_3$).

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

61.1%, pale yellow oil, ^{1}H 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, ArC$\underline{H}_2$O), 5.09 (s, 2H, ArC$\underline{H}_2$O), 5.04 (s, 2H, ArC$\underline{H}_2$O), 4.20–3.90 (m, 8H, C$\underline{H}_2$CH$_3$), 1.35–1.10 (m, 12H, CH$_3$).

*Tetraethyl 3,4-dibenzyloxyphenylbutadienylidenebisphosphonate (**3d**)*

75.0%, pale yellow oil, ^{1}H NMR ($CDCl_3$): δ 8.40–7.69 (m, 3H, Ar–C$\underline{H}$=C$\underline{H}$–C$\underline{H}$), 7.48–6.85 (m, 13H, ArH), 5.23 (s, 2H, ArC$\underline{H}_2$O), 5.20 (s, 2H, ArC$\underline{H}_2$O), 4.22–4.06 (m, 8H, C$\underline{H}_2$CH$_3$), 1.37–1.32 (t, 12H, CH$_2$C$\underline{H}_3$).

*Tetraethyl 3,4-dihydroxyphenylethylidenebisphosphonate (**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/CH_2Cl_2) to give 1.30 g (93.2%) of a white solid. mp 71–73°C, ^{1}H NMR ($CDCl_3$): δ 6.85 (s, 1H, Ar-2H), 6.75 (d, J = 8.1 Hz, 1H, A-5H), 6.62 (d, J = 8.1 Hz, 1H, Ar-6H), 4.10–4.00 (m, 8H, O—CH_2), 3.13 (dt, J = 6.2, 16.7 Hz, 2H, Ar—C$\underline{H}_2$), 2.80–2.60 (m, 1H, CH), 1.30–1.20 (m, 12H, CH_3); ^{13}C NMR ($CDCl_3$): δ 144.31, 143.40, 130.68, 120.41, 116.02, 115.18 (6s, Ph—C), 62.97 (t, OCH_2), 38.87 (t, CH), 30.48 (s, Ph—$\underline{CH}_2$), 16.23 (s, CH_3); ^{31}P NMR ($CDCl_3$): δ 24.98; Anal. Calcd for $C_{16}H_{28}O_8P_2$: 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, ^{1}H NMR ($CDCl_3$): 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—CH_2), 3.23 (dt, J = 5.8, 17.0 Hz, 2H, Ar—C$\underline{H}_2$), 2.55 (tt, J = 5.8, 23.9 Hz, 1H, CH), 1.40–1.20 (m, 12H, CH_3); ^{31}P NMR ($CDCl_3$): δ 26.48; Anal. Calcd for $C_{16}H_{28}O_8P_2$: 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, ^{1}H NMR ($CDCl_3$): 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—CH_2), 3.16 (dt, J = 5.9, 16.6 Hz, 2H, Ar—C$\underline{H}_2$), 2.69 (tt, J = 5.9, 24.0 Hz, 1H, CH), 1.40–1.20 (m, 12H, CH_3); ^{31}P NMR ($CDCl_3$): δ 26.36; Anal. Calcd for $C_{16}H_{28}O_9P_2$: C, 45.07; H, 6.57. Found: C, 45.05; H, 6.63.

*Tetraethyl 3,4-dihydroxyphenylbutylidenebisphosphonate (**4d**)*

91.2%, pale yellow oil, ^{1}H NMR ($CDCl_3$): 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, OCH_2), 2.48 (t, J = 7.0 Hz, 2H, Ar—C$\underline{H}_2$), 2.31 (tt, J = 6.0, 24.4 Hz, 1H, $CH_2C\underline{H}$), 2.00–1.80 (m, 4H, Ar—C$\underline{H}_2$C$\underline{H}_2$CH$_2$), 1.34–1.27 (m, 12H, CH_3).

*3,4-Dihydroxyphenylethylidenebisphosphonic Acid Disodium (**5a**)*

Under N_2, 312 mg (2.05 mmol) of Me_3SiBr 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 recrystalized from water and methanol as a white solid. mp >300°C, ^{1}H NMR (D_2O): 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, CH_2), 2.06 (tt, J = 6.2, 22.0 Hz, 1H, CH); ^{13}CNMR (D_2O): δ 143.92, 142.33, 134.88, 121.58, 117.14, 116.42 (6s, Ph—C), 41.24 (s, CH_2), 30.85 (s, CH); ^{31}P NMR (D_2O): δ 20.32; Anal. Calcd for $C_8H_{10}O_8P_2Na_2.H_2O$: 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, ^{1}H NMR (D_2O): δ 7.15–7.00 (m, 3H, ArH), 3.36 (dt, J = 5.9, 16.1 Hz, 2H, CH_2), 2.48 (tt, J = 5.9, 22.0 Hz, 1H, CH); ^{31}P NMR (D_2O): δ 20.81; Anal. Calcd for $C_8H_{10}O_8P_2Na_2\cdot CH_3OH\cdot H_2O$: 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, ^{1}H NMR (D_2O): 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, CH_2), 2.35 (tt, J = 5.6, 22.5 Hz, 1H, CH); ^{31}P NMR (D_2O): δ 21.73; Anal. Calcd for $C_8H_{10}O_9P_2Na_2\cdot CH_3OH$: 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, ^{1}H NMR (D_2O): 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—C$\underline{H}_2$), 2.13 (tt, J = 5.5, 22.8 Hz, 1H, CH(P_2)), 1.98–1.83 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$CH); ^{31}P NMR (D_2O): δ 21.97; Anal. Calcd for $C_{10}H_{14}O_8P_2Na_2\cdot CH_3OH$: 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 $NaBH_4$ (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/CH_2Cl_2), to give 1.80 g (90.0%) of colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.46–7.27 (m, 10H, ArH—CH_2O), 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, ArCH_2O), 5.13 (s, 2H, ArCH_2O), 4.14–3.98 (m, 8H, CH_2CH_3), 3.14 (dt, J = 6.2, 16.6 Hz, 2H, CH_2CH), 2.54 (tt, J = 6.2, 23.8 Hz, 1H, CH_2CH), 1.28–1.22 (m, 12H, CH_2CH_3). Compounds **6b** and **6c** were prepared using the method described for the preparation of **6a**.

*Tetraethyl 2,3-dibenzyloxyphenylethylidenebisphosphonate (**6b**)*

90.1%, colorless oil, ^{1}H NMR ($CDCl_3$): δ 7.46–7.27 (m, 10H, ArH—CH_2O), 6.97–6.88 (m, 3H, ArH—CH_2CH), 5.12 (s, 2H, ArCH_2O), 5.08 (s, 2H, ArCH_2O), 4.10–3.90 (m, 8H, CH_2CH_3), 3.26 (dt, J = 7.2, 16.6 Hz, 2H, CH_2CH), 3.09 (tt, J = 7.2, 22.7 Hz, 1H, CH_2CH), 1.21–1.16 (m, 12H, CH_2CH_3).

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

67.0%, pale yellow oil, ^{1}H NMR ($CDCl_3$): δ 7.47–7.27 (m, 15H, ArH—CH_2O), 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, ArCH_2O), 5.11 (s, 2H, ArCH_2O), 5.02 (s, 2H, ArCH_2O), 4.1–3.9 (m, 8H, CH_2CH_3), 3.20 (dt, J = 7.0, 15.9 Hz, 2H, CH_2CH), 3.05 (tt, J = 7.0, 22.7 Hz, 1H, CH_2CH), 1.20–1.13 (m, 12H, CH_2CH_3).

*Tetraethyl 1-(3,4-dibenzyloxybenzyl)-1-methylmethylene-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 CH_2Cl_2/H_2O partition, the organic phase was dried and evaporated. Column chromatography (SiO_2, 1/50 MeOH/CH_2Cl_2) gave 0.39 g (37.6%) of colorless oil **7e**. ^{1}H NMR ($CDCl_3$): δ 7.46–7.28 (m, 10H, ArH—CH_2O), 6.92 (s, 1H, O—Ar—2H), 6.80 (s, 2H, O—Ar—5, 6H), 5.15 (s, 2H, ArCH_2O), 5.14 (s, 2H, ArCH_2O), 4.14–4.04 (m, 8H, CH_2CH_3), 3.18–3.08 (dd, J = 13.4, 15.8 Hz, 2H, $C(P_2)$-CH_2), 1.33 (t, J = 16.7 Hz, 3H, $C(P_2)$—CH_3), 1.27–120 (m, 12H, CH_2CH_3). Compounds **7f–h** were prepared using the method described for the preparation of **7e**.

*Tetraethyl 1-(3,4-dibenzyloxybenzyl)-1-ethylmethylene-bisphosphonate (**7f**)*

37.2%, colorless oil, ^{1}H NMR ($CDCl_3$): δ 7.45–7.26 (m, 10H, ArH—CH_2O), 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, ArCH_2O), 5.14 (s, 2H, ArCH_2O), 4.14–4.00 (m, 8H, OCH_2CH_3), 3.15 (dd, J = 12.2, 16.7 Hz, 2H, Ar$CH_2C(P_2)$), 1.88–1.76 (m, 2H, $C(P_2)CH_2CH_3$), 1.28–1.16 (m, 12H, OCH_2CH_3), 1.12 (t, 3H, J = 7.4 Hz, $C(P_2)CH_2CH_3$).

*Tetraethyl 1-(3,4-dibenzyloxybenzyl)-1-phenylmethylene-bisphosphonate (**7g**)*

48.7%, colorless oil, ^{1}H NMR ($CDCl_3$): δ 7.45–7.19 (m, 15H, Ar—CH_2O), 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, ArCH_2O), 4.04–3.87 (m, 8H, CH_2CH_3), 3.24 (t, J = 16.1 Hz, 4H, $C(P_2)$-CH_2), 1.14–1.09 (m, 12H, CH_2CH_3).

*Tetraethyl 1-(2,3-dibenzyloxybenzyl)-1-methylmethylene-bisphosphonate (**7h**)*

43.1%, colorless oil, ^{1}H NMR ($CDCl_3$): δ 7.45–7.27 (m, 10H, ArH—CH_2O), 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, ArCH_2O), 4.95 (s, 2H, ArCH_2O), 4.20–4.00 (m, 8H, CH_2CH_3), 3.35 (dd, J = 13.5, 16.1 Hz, 2H, CH_2C), 1.40 (t, J = 17.0 Hz, 3H, $C(P_2)CH_3$), 1.24–1.18 (m, 12H, CH_2CH_3).

*Tetraethyl 1-(3,4-dihydroxybenzyl)-1-methylmethylene-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/CH_2Cl_2) to yield 0.32 g (89.4%) of white solid **8e**. mp 159–161°C, ^{1}H NMR ($CDCl_3$): δ 8.02 (s, 1H, OH), 7.97 (s, 1H, OH), 6.74–6.60 (m, 3H, ArH), 4.22–4.02 (m, 8H, CH_2CH_3), 3.14 (dd, J = 13.6, 15.8 Hz, 2H, Ar—CH_2), 1.44 (t, J = 16.7 Hz, 3H, $C(P_2)CH_3$), 1.34–1.21 (m, 12H, CH_2CH_3); ^{31}P NMR ($CDCl_3$): δ 27.05; Anal. Calcd for $C_{17}H_{30}O_8P_2$: 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, ^{1}H 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-6Hz), 4.19–3.98 (m, 8H, $OC\underline{H}_2CH_3$), 3.17 (dd, J = 12.7, 16.7 Hz, 2H, Ar—$C\underline{H}_2$), 2.01–1.91 (m, 2H, $C(P_2)C\underline{H}_2CH_3$), 1.32–1.18 (m, 15H, $OCH_2C\underline{H}_3$, $C(P_2)CH_2C\underline{H}_3$); ^{31}P NMR ($CDCl_3$): δ 27.05; Anal. Calcd for $C_{18}H_{32}O_8P_2$: 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, ^{1}H NMR ($CDCl_3$): δ 7.44–7.18 (m, 7H, OH, $CCH_2\underline{ArH}$), 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, $C\underline{H}_2CH_3$), 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 $C_{23}H_{34}O_8P_2$: 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, ^{1}H 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, $C\underline{H}_2CH_3$), 3.23 (t, 2H, Ar—$C\underline{H}_2$), 1.45 (t, J = 16.7 Hz, 3H, $C(P_2)CH_3$), 1.40–1.15 (m, 12H, $CH_2C\underline{H}_3$); ^{31}P NMR ($CDCl_3$): δ 29.00; Anal. Calcd for $C_{17}H_{30}O_8P_2$: 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 recrystalized from water and methanol as a white solid. mp > 300°C, ^{1}H 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 $C_9H_{12}O_8P_2Na_2{\cdot}CH_3OH{\cdot}H_2O$: 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, ^{1}H 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, $ArC\underline{H}_2$), 2.00 (m, 2H, $C\underline{H}_2CH_3$), 1.36 (t, J = 7.5 Hz, 3H, $CH_2C\underline{H}_3$); ^{31}P NMR (D_2O): δ 24.33; Anal. Calcd for $C_{10}H_{14}O_8P_2Na_2{\cdot}CH_3OH{\cdot}H_2O$: 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, ^{1}H NMR (D_2O): δ 7.80–7.47 (m, 5H, 3-$\underline{ArH}$), 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 $C_{15}H_{16}O_8P_2Na_2{\cdot}CH_3OH{\cdot}1.5H_2O$: 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, ^{1}H 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 $C_9H_{12}O_8P_2Na_2{\cdot}1.5CH_3OH$: 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, $MeOH/CH_2Cl_2$) to yield **10** as a colorless oil (0.16 g, 44.4%). ^{1}H 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 CH_2Cl_2 (10 mL) under N_2. 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 recrystalization from water and methanol to provide product **11** (41 mg, 49.4%) as a white solid. mp $>300^{\circ}$C, ^{1}H NMR (D_2O): δ 7.49–7.33 (m, 1H, CH), 6.90–6.87 (m, 3H, ArH); ^{31}P NMR (D_2O): δ 9.01 (d, $J = 44.1$ Hz), 5.59 (d, $J = 45.2$ Hz); Anal. Calcd for $C_8H_8O_8P_2Na_2 \cdot 1.5CH_3OH$: C, 29.38; H, 3.60. Found: C, 29.68; H, 3.25.

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