# Synthesis of 1-Hydroxymethylene-1,1-bis(phosphonic acids) from Acid Anhydrides: Preparation of a New Cyclic 1-Acyloxymethylene-1,1-bis(phosphonic acid)

**Erwann Guenin,*[a] Estelle Degache,[a] Jean Liquier,[a] and Marc Lecouvey[a]**

**Keywords:** Bis(phosphonates) / Anhydrides / Tris(trimethylsilyl) phosphite / Arbuzov reaction / NMR spectroscopy

In continuing with our work to find new pathways to bis(phosphonate) structures we report on their synthesis from tris(trimethylsilyl) phosphite and acid anhydride. This new synthesis allows a direct access to a 1-hydroxymethylene-1,1-bis(phosphonic acid) functionalised by a carboxylic function on the side chain. Moreover, we describe the formation of an original cyclic bis(phosphonate) obtained from phthalic anhydride.
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2004)

## Introduction

1-Hydroxymethylene-1,1-bis(phosphonic acids) (HMBP) (Figure 1) are known to have a large spectrum of therapeutic interest.[1] They are routinely used as $^{99}$Tc complexes in skeletal scintigraphy due to their ability to chelate metal ions and metalloid ions.[2−6] They are also used for the treatment of intoxication by metals. Moreover, they are powerful inhibitors of bone resorption,[7,8] and so are widely used for the treatment of diseases characterised by abnormal calcium metabolism[9] such as Paget's disease, osteoporosis and bone tumoral metastasis.[10,11] They are also known to induce inhibition of breast and prostate cancer cell proliferation[12−14] and, more recently, to inhibit angiogenesis in vitro and in vivo.[11,15−17]

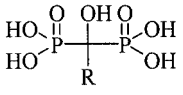


Figure 1. 1-Hydroxymethylene-1,1-bis(phosphonic acids) (HMBP)

Several chemical classes of bis(phosphonates) have been synthesised and studied for all these applications. They usually differ from each other by the side chain (R) which can be an aliphatic or aromatic group that can contain a heteroatom. All these compounds are generally obtained from two different synthetic methods. The first method involves the reaction of carboxylic acid and phosphorus trichloride.[18] Although efficient for aliphatic substrates, this synthesis requires harsh acidic conditions and high temperatures that are not always suitable for all substrates. The second method involves the synthesis of bis(phosphonate) tetraester from α-ketophosphonate and dialkyl phosphite.[19,20] Bis(phosphonate) tetraesters can be then hydrolysed to their acidic forms by chlorhydric acid hydrolysis,[21] or by a dealkylation reaction with trimethylsilyl bromide followed by methanolysis.[22] The main drawback of this technique is the instability of bis(phosphonate) tetraesters which isomerise to form phosphonate-phosphates under basic or thermal conditions.[23−25]

As an alternative to these two pathways our group recently proposed a very mild and one-pot synthesis of 1-hydroxymethylene-1,1-bis(phosphonic acids) from tris(trimethylsilyl) phosphite and acyl chloride.[26] The interest in this procedure lies in the fact that it could be used with both aliphatic and aromatic substrates.

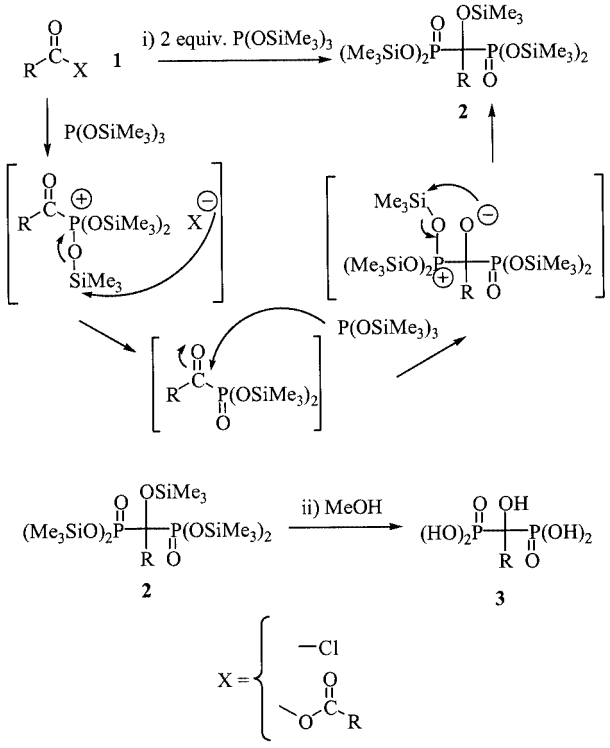
## Results and Discussion

In continuing with this work, we would like to report on the preliminary results of the adaptation of this reaction for the use of acid anhydride. The reaction conditions with acid anhydride are quite similar to those with the acyl chloride. Two equivalents of tris(trimethylsilyl) phosphite reacted in a single step with the acid anhydride **1** to yield the fully trimethylsilylated bis(phosphonate) **2** (Scheme 1). The reaction was carried out at room temperature for one hour and monitored by $^{31}$P NMR spectroscopy. After evaporation of the volatile fractions, the fully trimethylsilylated bis(phosphonate) **2** then underwent methanolysis at 25 °C for

[a] LPBC-CSSB (UMR CNRS 7033) UFR S.M.B.H., Université Paris 13,
74 rue Marcel Cachin,
93017 Bobigny Cedex, France
Fax: (internat.) +33-148387625
E-mail: guenin@smbh.univ-paris13.fr
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

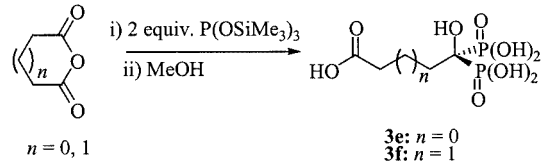
 **DOI: 10.1002/ejoc.200400053** © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

one hour to afford the bis(phosphonic) tetraacid **3**. The reaction followed the same mechanism as described previously[26] based on an Arbuzov reaction and a second addition of tris(trimethylsilyl) phosphite. The first equivalent of tris(trimethylsilyl) phosphite reacted with the acid anhydride to give a bis(trimethylsilyl) α-ketophosphonate and a trimethylsilyl carboxylate (Scheme 1). The use of silyl phosphite was of crucial importance for this first Arbuzov reaction; the ease with which transfer of a silyl group occurred from the initially formed phosphonium intermediates and the higher nucleophilicity of silyl phosphite relative to the analogous trialkyl phosphites were the key features for this step. Addition of the second equivalent of tris(trimethylsilyl) phosphite on the highly reactive α-ketophosphonate led to the fully trimethylsilylated bis(phosphonate) **2**.

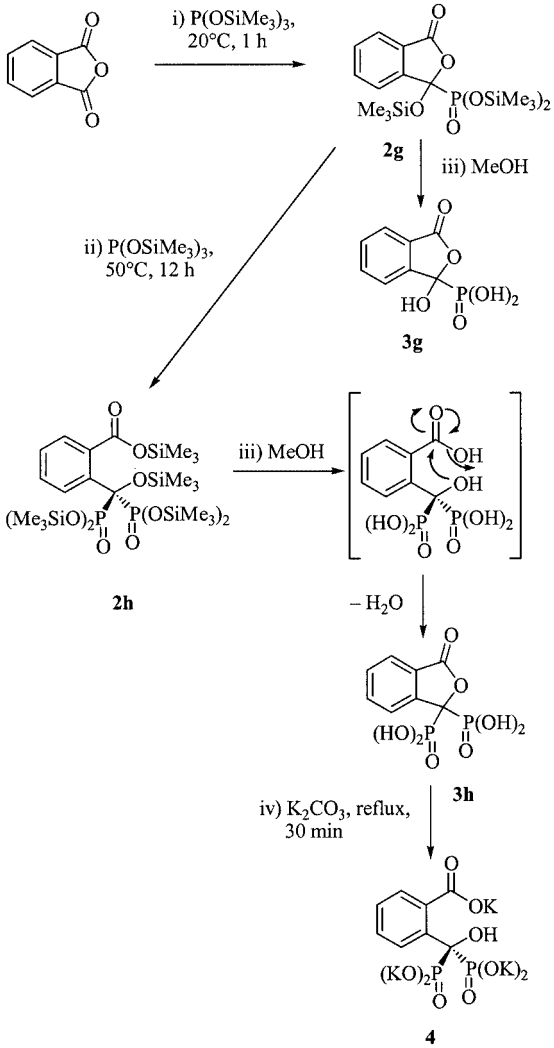


Scheme 1

The reactions with linear acid anhydrides with aliphatic or aromatic substrates were similar and gave comparable yields of the bis(phosphonate) **3** with those obtained from acyl chlorides (Table 1 Entries a, b, c and d). However, with cyclic acid anhydrides, the results were different depending on whether the substrate was subject to conformational restriction. On one hand, reactions with succinic or butyric anhydride (Table 1, Entries e and f) under standard conditions gave an easy access to the bis(phosphonic) tetraacid functionalised by a carboxylic acid on the side chain (**3e**, **3f**, Scheme 2). On the other hand, when phthalic anhydride reacted with tris(trimethylsilyl) phosphite at room temperature in tetrahydrofuran, the unique product isolated after methanolysis was the cyclic hydroxymonophosphonate **3g** (Scheme 3). To obtain the bis(phosphonate) **3h**, the reaction needed to be heated for 12 hours at 50 °C. By monitoring this reaction by $^{31}P$ NMR spectroscopy, we clearly identified the fully trimethylsilylated monophosphonate **2g** ($\delta$ = −6.06 ppm) after one hour at room temperature; this product did not form if a second equivalent of tris(trimethylsilyl) phosphite was added at room temperature. This silylated monophosphonate **2g** was isolated and the $^{13}C$ NMR spectrum shows a doublet at 102.9 ppm ($J_{C,P}$ = 228.9 Hz) that is consistent with a quaternary carbon (disappearing in DEPT 135 $^{13}C$ NMR mode) coupling with one phosphonate. In the $^{13}C$ NMR spectrum no signal corresponding to



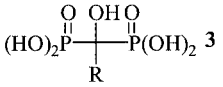
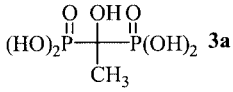
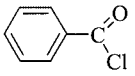
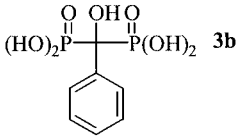
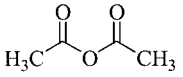
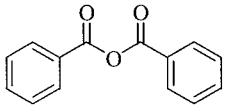
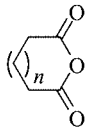
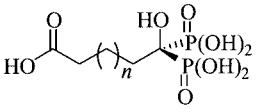
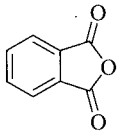
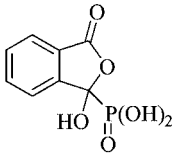
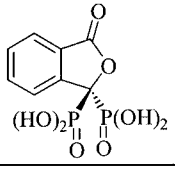
Scheme 2



Scheme 3

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

Table 1. Reactions with acyl chlorides and acid anhydrides; the experimental conditions, products formed, yields and characterisation by $^{31}P$ NMR spectroscopy are shown

|  **1** | **Operating conditions** |  **3** | Yield | $^{31}P$ **NMR** |
|---|---|---|---|---|
|  **1a** | 25°C, no solvent, 1 h |  **3a** | 98% | 19.4 |
|  **1b** | 25°C, no solvent, 1 h |  **3b** | 90% | 15.9 |
|  **1c** | 25°C, no solvent, 1 h | **3a** | 90% | 19.4 |
|  **1d** | 25°C, no solvent, 1 h | **3b** | 90% | 15.9 |
|  **1e:** $n = 0$ **1f:** $n = 1$ | 25°C, no solvent, 1 h |  **3e:** $n = 0$ **3f:** $n = 1$ | **3e**: 90% **3f**: 80% | 14.8 19.2 |
|  **1g** | 25°C, THF, 1 h |  **3g** | 71% | 9.1 |
| | 50°C, THF, 12 h |  **3h** | 97% | 9.0 |

a carbonyl carbon atom from an α-ketophosphonate structure was found. Thus, we proposed a cyclic structure for this intermediate **2g** obtained directly from the rearrangement of the silylated α-ketophosphonate. This structure has already been described by Griffiths[27] and could explain the lack of reactivity towards a second equivalent of tris(trimethylsilyl) phosphite at room temperature. The signal in the $^{31}P$ NMR spectrum corresponding to **2g** started to disappear only after **2g** was heated, with the appearance of the signal for the fully trimethylsilylated bis(phosphonate) **2h** ($\delta = -8.60$ ppm) (Scheme 3). After 12 hours, the reaction was then complete and bis(phosphonate) **3h** was isolated after treatment with methanol. Both products **3g** and **3h** present very similar $^{31}P$ and $^{1}H$ NMR spectra ($^{31}P$ NMR: $\delta = 9.02$ ppm and $\delta = 9.08$ ppm for **3g** and **3h**, respectively). The $^{13}C$ NMR spectrum undoubtedly proves the mono- or diphosphonate structure. The signal for the carbon bearing phosphonate(s) appear as a doublet ($\delta = 107.6$ ppm, $J_{P,C} = 198.5$ Hz) or a triplet ($\delta = 89.5$ ppm, $J_{P,C} = 141$ Hz). Both the monophosphonate and bis(phosphonate) have also been characterised by ESI-TOF mass spectrometry. Cyclic structures for these two compounds were proved by FT-IR spectroscopy; the spectra show a vibration around 1752 $cm^{-1}$ characteristic of the carbonyl bound in lactone structure.[28] The very low $^{31}P$ NMR chemical shift observed for the bis(phosphonate) **3h** can be explained by the formation of the cyclic species. The formation of this cyclic compound has been explained by an es-

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

terification reaction during methanolysis. This esterification is possible with phthalic acid anhydride due to conformational restriction in the molecule. With succinic acid anhydride which is not subject to conformational restriction cyclisation is not observed. With the conformationally restricted maleic acid anhydride, the reaction was also carried out; however, if a signal at δ = 9.00 ppm in the $^{31}P$ NMR spectrum, which could be assigned to the cyclic monophosphonate, was observed, it was not possible to isolate the product or to further obtain the bis(phosphonate). Side reactions always occurred, corresponding to, possibly, 1,4 addition of tris(trimethylsilyl) phosphite on such α,β-unsaturated carbonyls.[29] For **3h** the cyclic structure was also proved by a further saponification that led to the formation of the acyclic 1-hydroxymethylene-1,1-bis(phosphonate) **4**, together with side products. The $^{31}P$ NMR spectrum of compound **4** shows an expected chemical shift at δ = 16.13 ppm.

## Conclusion

Formation of hydroxymonophosphonate from phthalic anhydride and silylated phosphites has already been described by Griffiths,[27] but to the best of our knowledge, such a cyclic bis(phosphonate) has never been described in the literature. This compound presents a real biological interest as it could act as a prodrug. The hydroxy function which is essential to the HMBP biological properties is in this particular case totally hidden, but could be reformed in the cell by esterase activity. Such acyloxymethyl bis(phosphonate) prodrugs have already been described and the protection shown to be reversible.[30]

In conclusion, we have shown that our previous syntheses of HMBP structures from acyl chlorides and tris(trimethylsilyl) phosphite can be extended to acid anhydride substrates. The use of cyclic acid anhydrides led to interesting results. Starting with succinic or butyric anhydride we found a direct access to 1-hydroxymethylene-1,1-bis(phosphonates) functionalised by an acid carboxylic function on the side chain. Lastly, with phthalic anhydride we described the formation of an original cyclic bis(phosphonate) structure which could have interesting biological properties that are currently being investigated.

## Experimental Section

**General Remarks:** Unless otherwise noted, materials were obtained from commercial suppliers. Cyclic acid anhydrides were recrystallised from diethyl ether and acyl chlorides, and linear acid anhydrides were distilled prior to use. THF was distilled from benzophenone sodium. 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 $D_2O$ or $CDCl_3$. 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 $CDCl_3$. IR spectra were recorded with a Perkin−Elmer FT-IR model 2000 spectrophotometer in the 4000−500 $cm^{-1}$ spectral domain. Spectral resolution was 2 $cm^{-1}$ and usually 5 scans were accumulated. Multiple point baseline correction was performed using the PE Spectrum software. Samples were studied in $H_2O$ and $D_2O$ solutions placed in cells closed by ZnSe windows. Mass spectra were determined by electrospray ionization time-of-flight mass spectrometry (ESI-TOF MS) performed on a Mariner Biospectrometry Workstation mass spectrometer. Microanalyses were performed by the Service Central d'Analyse, CNRS, F-69390, Vernaison.

**General Procedure for Reaction of Acyl Chloride or Anhydride with Tris(trimethylsilyl) Phosphite:** To tris(trimethylsilyl) phosphite (8 mmol) under $N_2$ in a 25 mL round bottom flask was added acyl chloride or acid anhydride (4 mmol) at room temperature. The resulting mixture was stirred for 1 h. The volatile fractions were then evaporated under vacuum (0.1 Torr) at 50 °C. Methanol was added to the residue and the solution was stirred for 1 hour. After solvent removal in vacuo, the residue was washed with 3 × 50 mL of diethyl ether to remove traces of $H_3PO_3$. Lyophilisation then yielded 80 to 90% of white powder.

**(1-Hydroxy-1-phosphonoethyl)phosphonic Acid (3a):** Yield: 90%. M.p. 195 °C. IR ($H_2O$): $\tilde{\nu}$ = 1451, 1183, 1128, 1018, 930, 817 $cm^{-1}$. $^{1}H$ NMR ($D_2O$, 500.6 MHz, 298 K): δ = 1.47 (t, $^{3}J_{P,H}$ = 16.2 Hz, 3 H, C$H_3$) ppm. $^{13}C$ NMR{$^{1}H$} ($D_2O$, 125.9 MHz, 298 K): δ = 75.5 (t, $J_{P,C}$ = 145 Hz, *C*OH), 19.0 (s, *C*$H_3$) ppm. $^{31}P$ NMR{$^{1}H$} ($D_2O$, 200.7 MHz, 298 K): δ = 19.4 (s) ppm.

**[Hydroxy(phenyl)phosphonomethyl]phosphonic Acid (3b):** Yield: 90%. M.p. 186 °C. IR ($D_2O$): $\tilde{\nu}$ = 1645, 1598, 1495, 1450 (C=C), 1185, 1031, 1015, 970, 923, 775, 704, 667 $cm^{-1}$. $^{1}H$ NMR ($D_2O$, 500.6 MHz, 298 K): δ = 7.71 (d, $^{3}J_{H,H}$ = 7.3 Hz, 2 H, *o*-$C_6H_5$), 7.38 (dd, $^{3}J_{H,H}$ = 7.3 Hz, 2 H, *m*-$C_6H_5$), 7.33 (d, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, *p*-$C_6H_5$) ppm. $^{13}C$ NMR{$^{1}H$} ($D_2O$, 50.3 MHz, 298 K): δ = 140.0 (HO*C*$_6H_5$), 131.4 (*m*-$C_6H_5$), 131.0 (*o*-$C_6H_5$), 129.2 (*p*-$C_6H_5$), 78.8 (t, $J_{C,P}$ = 145.7 Hz, *C*OH) ppm. $^{31}P$ NMR{$^{1}H$} ($D_2O$, 200.7 MHz, 298 K): δ = 15.9 (s) ppm. $C_7H_{10}O_7P_2$ (268.1): calcd. C 31.36, H 3.76, P 23.11; found C 31.32, H 4.01, P 22.65.

**4-Hydroxy-4,4-bis(phosphono)butyric Acid (3e):** Yield: 90%. M.p. > 260 °C. IR ($H_2O$): $\tilde{\nu}$ = 1762 (C=O), 1465, 1417, 1320, 1202, 1064, 1043, 939 $cm^{-1}$. $^{1}H$ NMR ($D_2O$, 500.6 MHz, 298 K): δ = 2.76 (t, $^{3}J_{H,H}$ = 8.0 Hz, 2 H, −C$H_2$COOH), 2.65 (tt, $^{3}J_{H,H}$ = 8.0, $^{3}J_{P,H}$ = 16.2 Hz, 2 H, HOC−C$H_2$−) ppm. $^{13}C$ NMR{$^{1}H$} ($D_2O$, 125.9 MHz, 298 K): δ = 182.5 (*C*OOH), 83.9 (t, $J_{C,P}$ = 151.5 Hz, *C*OH), 29.8 (−*C*H$_2$COOH), 27.3 (−*C*H$_2$−COH) ppm. $^{31}P$ NMR{$^{1}H$} ($D_2O$, 200.7 MHz, 298 K): δ = 14.8 (s) ppm. $C_4H_{10}O_9P_2$ (264.1): calcd. C 18.19, H 3.82, P 23.46; found C 17.89, H 4.17, P 23.22.

**5-Hydroxy-5,5-bis(phosphono)pentanoic Acid (3f):** Yield: 80%. M.p. > 260 °C. IR ($H_2O$): $\tilde{\nu}$ = 1694 (C=O), 1464, 1308, 1213, 1174, 1149, 1059, 983, 938, 923 $cm^{-1}$. $^{1}H$ NMR ($D_2O$, 500.6 MHz, 298 K): δ = 2.40 (m, 2 H, −C$H_2$COOH), 1.85−2.00 (m, 4 H, HOC−C$H_2$−C$H_2$−) ppm. $^{13}C$ NMR{$^{1}H$} ($D_2O$, 125.9 MHz, 298 K): δ = 185.2 (*C*OOH), 76.3 (t, $J_{C,P}$ = 132.0 Hz, *C*OH), 37.5 (−*C*H$_2$COOH), 36.0 (−*C*H$_2$−COH), 22.4 (−CH$_2$−*C*H$_2$−CH$_2$−) ppm. $^{31}P$ NMR{$^{1}H$} ($D_2O$, 200.7 MHz, 298 K): δ = 19.2 (s) ppm.

**Synthesis of (1-Hydroxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonic Acid (3g):** To a solution of tris(trimethylsilyl) phosphite (1.2 g, 4 mmol) in 5 mL of THF was added, in a 25 mL round bottom flask under $N_2$, phthalic anhydride (0.59 g, 4 mmol) at room temperature. The resulting mixture was stirred for 1 h. The volatile fractions were evaporated under vacuum (0.1 Torr) at 50

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

°C. At this stage, $^{31}P$, $^{1}H$ and $^{13}C$ NMR spectra of the crude silylated intermediate were performed in $CDCl_3$. Twenty mL of methanol was then added to the residue and the solution was stirred for 1 h. After solvent removal in vacuo, the residue was washed with 3 × 50 mL of diethyl ether to remove traces of $H_3PO_3$. Lyophilisation then yielded 0.64 g (71%) of a white powder. M.p. 202 °C. IR ($D_2O$): $\tilde{\nu}$ = 3397 (O−H), 1752 (C=O), 1602, 1465 (C=C), 1266, 1109, 911, 766, 695, 557 $cm^{-1}$. $^{1}H$ NMR ($D_2O$, 500.6 MHz, 298 K): δ = 7.94 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, $C_6H_4$, H4), 7.89 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, $C_6H_4$, H7), 7.84 (dd, $^{3}J_{H,H}$ = 7.5 Hz, $C_6H_4$, 1 H, H6), 7.67 (dd, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, $C_6H_4$, H5) ppm. $^{13}C$ NMR{$^{1}H$} ($D_2O$, 50.3 MHz, 298 K): δ = 173.5 (O=*C*,*C*3), 148.9 ($C_6H_4$, C7a), 138.3 ($C_6H_4$, C7a), 134.0 ($C_6H_4$, C6), 128.5 ($C_6H_4$, *C*4), 128.3 ($C_6H_4$, C4a), 128.2 ($C_6H_4$, C5), 126.7 ($C_6H_4$, C7), 107.6 (d, $J_{C,P}$ = 196.8 Hz, P−*C*−OH, C1) ppm. $^{31}P$ NMR{$^{1}H$} ($D_2O$, 200.7 MHz, 298 K): δ = 9.08 (s) ppm. [M − H]: 228.5. $C_8H_7O_6P$ (230.1): calcd. C 41.76, H 3.07, P 13.46; found C 41.31, H 3.46, P 13.23.

**Silylated Intermediate 2g:** $^{1}H$ NMR ($CDCl_3$, 500.6 MHz, 298 K): δ = 7.69 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, $C_6H_4$, H4), 7.62 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1 H, $C_6H_4$, H7), 7.57 (dd, $^{3}J_{H,H}$ = 7.5 Hz, $C_6H_4$, 1 H, H6), 7.47 (dd, $^{3}J_{H,H}$ = 7.5 Hz, $C_6H_4$, 1 H, H5), 0.15 (s,3 H, SiC$H_3$), −0.13 (s,3 H, SiC$H_3$), −0.18 (s, 3 H, SiC$H_3$) ppm. $^{13}C$ NMR{$^{1}H$} ($CDCl_3$, 125.9 MHz, 298 K): δ = 167.9 (O=*C*, C3), 146.9 ($C_6H_4$, C7a), 134.7 ($C_6H_4$, C6), 131.3 ($C_6H_4$, C4), 127.3 ($C_6H_4$, C4a), 125.4 ($C_6H_4$, C5), 125.3 ($C_6H_4$, C7), 102.9 (d, $J_{C,P}$ = 228.9 Hz, P−*C*−OH, C1), 1.5, 1.2, 0.9 (Si*C*$H_3$) ppm. $^{13}C$ NMR DEPT 135 Mode: δ = 134.7 ($C_6H_4$, C6), 131.3 ($C_6H_4$, C4), 125.4 ($C_6H_4$, C5), 125.3 ($C_6H_4$, C7), 1.5, 1.2, 0.9 (Si*C*$H_3$) ppm. $^{31}P$ NMR{$^{1}H$} (CDCl3, 200.7 MHz, 298 K): δ = −6.06 (s) ppm.

**Synthesis of (3-Oxo-1-phosphono-1,3-dihydroisobenzofuran-1-yl)-phosphonic Acid (3h):** To a solution of tris(trimethylsilyl) phosphite (2.4 g, 8 mmol) in 5 mL THF was added, in a 25 mL round bottom flask under $N_2$, phthalic anhydride (0.59 g, 4 mmol) at room temperature. The resulting mixture was stirred for 12 h at 50 °C, and the reaction was monitored by $^{31}P$ NMR spectroscopy. The volatile fractions were evaporated under vacuum (0.1 Torr) at 50 °C. Twenty mL of methanol was then added to the residue and the solution was stirred for 1 h. After solvent removal in vacuo, the residue was washed with 3 × 50 mL of diethyl ether to remove traces of $H_3PO_3$. Lyophilisation then yielded 1.2 g (97%) of a white powder. M.p. > 260 °C. IR ($D_2O$): $\tilde{\nu}$ = 3418 (O−H), 1752 (C=O), 1609, 1596, 1470 (C=C), 1295, 1106, 948, 755, 695 $cm^{-1}$. $^{1}H$ NMR ($D_2O$, 500.6 MHz, 298 K): δ = 7.76 (d, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, $C_6H_4$, H4), 7.70 (dd, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, $C_6H_4$, H6), 7.63 (d, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, $C_6H_4$, H7), 7.56 (dd, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, $C_6H_4$, H5) ppm. $^{13}C$ NMR{$^{1}H$} ($D_2O$, 125.9 MHz, 298 K): δ = 176.5 (O=*C*, C3), 148.6 ($C_6H_4$, C7a), 138.4 ($C_6H_4$, C6), 133.0 ($C_6H_4$, C4), 129.0 ($C_6H_4$, C4a), 127.2 ($C_6H_4$, C5), 127.1 ($C_6H_4$, C7), 89.5 (t, $J_{C,P}$ = 141.0 Hz, P−*C*−P, C1) ppm. $^{31}P$ NMR{$^{1}H$} ($D_2O$, 200.7 MHz, 298 K): δ = 9.02 (s) ppm. [M − H]: 292.4. $C_8H_8O_8P_2$ (294.1): calcd. C 32.67, H 2.74, P 21.06; found C 33.01, H 3.12, P 21.41.

## Acknowledgments

We express our thanks to Dr. F. Taran from Service de Marquage Moléculaire et de Chimie Bio-organique, CEA, Saclay, France, for the mass spectrum analysis.

[1] L. Widler, K. A. Jaeggi, M. Glatt, K. Muller, R. Bachmann, M. Bisping, A. R. Born, R. Cortesi, G. Guiglia, H. Jeker, R. Klein, U. Ramseier, J. Schmid, G. Schreiber, Y. Seltenmeyer, J. R. Green, *J. Med. Chem.* **2002**, *45*, 3721.
[2] E. Gumienna-Kontecka, J. Jezierska, M. Lecouvey, Y. Leroux, H. Kozlowski, *J. Inorg. Biochem.* **2002**, *89*, 13.
[3] E. Gumienna-Kontecka, R. Silvagni, R. Lipinski, M. Lecouvey, F. Cesare Marincola, G. Crisponi, V. M. Nurchi, Y. Leroux, H. Kozlowski, *Inorg. Chim. Acta* **2002**, *339*, 111.
[4] H. Khadrahoui, H. Gillier, D. El Manouni, Y. Leroux, A. Neuman, T. Prangé, J. P. Silvestre, N. Q. Dao, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *127*, 67.
[5] M. Dyba, M. Jezowska-Bojczuk, E. Kiss, T. Kiss, H. Kozlowski, *J. Chem. Soc., Dalton Trans.* **1996**, *6*, 1119.
[6] M. Dyba, H. Kozlowski, A. Tlalka, Y. Leroux, D. El Manouni, *Pol. J. Chem.* **1998**, *72*, 1148.
[7] R. G. Russell, P. I. Croucher, M. J. Rogers, *Osteoporos. Int.* **1999**, *9*, 66.
[8] R. G. Russell, M. J. Rogers, J. C. Frith, S. P. Luckman, F. P. Coxon, H. L. Benford, P. I. Croucher, C. Shipman, H. A. Fleisch, *J. Bone Miner. Res.* **1999**, *14*, 53.
[9] H. Fleisch, *Prog. Mol. Subcell. Biol.* **1999**, *23*, 197.
[10] J. R. Green, *Semin. Oncol.* **2002**, *29*, 3.
[11] P. Clezardin, P. Fournier, S. Boissier, O. Peyruchaud, *Curr. Med. Chem.* **2003**, *10*, 173.
[12] T. Yoneda, A. Sasaki, C. Dunstan, P. J. Williams, F. Bauss, Y. A. De Clerck, G. R. Mundy, *J. Clin. Invest.* **1997**, *99*, 2509.
[13] S. Boissier, M. Ferreras, O. Peyruchaud, S. Magnetto, F. H. Ebetino, M. Colombel, P. Delmas, J. M. Delaisse, P. Clezardin, *Cancer Res.* **2000**, *60*, 2949.
[14] J. E. Brown, R. E. Coleman, *Breast Cancer Res.* **2002**, *4*, 24.
[15] P. Fournier, S. Boissier, S. Filleur, J. Guglielmi, F. Cabon, M. Colombel, P. Clezardin, *Cancer Res.* **2002**, *62*, 6538.
[16] Y. Hamma-Kourbali, M. Di Benedetto, D. Ledoux, O. Oudar, Y. Leroux, M. Lecouvey, M. Kraemer, *Biochem. Biophys. Res. Commun.* **2003**, *310*, 816.
[17] J. Wood, K. Bonjean, S. Ruetz, A. Bellahcene, L. Devy, J. M. Foidart, V. Castronovo, J. R. Green, *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1055.
[18] M. Lecouvey, Y. Leroux, *Heteroat. Chem.* **2000**, *11*, 556.
[19] J. M. Benech, D. El Manouni, Y. Leroux, *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *113*, 295.
[20] I. Mallard, J. M. Benech, M. Lecouvey, Y. Leroux, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *162*, 15.
[21] K. Kanaan, R. Burgada, *Phosphorus Sulfur* **1988**, *37*, 217.
[22] C. E. McKenna, M. T. Higa, N. H. Cheung, M. C. McKenna, *Tetrahedron Lett.* **1977**, *2*, 155.
[23] S. J. Fitch, K. Moedritzer, *J. Am. Chem. Soc.* **1962**, *84*, 1876.
[24] D. A. Nicholson, H. Vaughn, *J. Org. Chem.* **1971**, *36*, 3843.
[25] R. Ruel, J. P. Bouvier, R. N. Young, *J. Org. Chem.* **1995**, *60*, 5209.
[26] M. Lecouvey, I. Mallard, T. Bailly, R. Brugada, Y. Leroux, *Tetrahedron Lett.* **2001**, *42*, 8475.
[27] D. V. Griffiths, P. Duncanson, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2213.
[28] R. N. Jones, C. L. Angell, T. Ito, R. J. D. Smith, *Can. J. Chem.* **1959**, *37*, 2007.
[29] B. B. V. Soma Sekhar, W. G. Bentrude, *Tetrahedron Lett.* **1999**, *40*, 1087.
[30] R. Niemi, P. Turhanen, J. Vepsalainen, H. Taipale, T. Jarvinen, *Eur. J. Pharm. Sci.* **2000**, *11*, 173.

Received January 27, 2004

 © 2004 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 