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Michael addition of Grignard reagents to tetraethyl ethenylidenebisphosphonate

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Abstract

Tetraethyl ethenylidenebisphosphonate can undergo facile Michael type addition reaction with simple Grignard reagents to give alkyl, arylalkyl, aryl C-substituted methylene bisphosphonates. This addition easily occurs even if funtionalised Grignard reagents are used. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Tetraethyl ethenylidenebisphosphonate; Grignard reagents; Michael addition; Bisphosphonates

1. Introduction

gem-Bisphosphonic acids are taken up by the skeleton and inhibit osteoclast mediated bone resorption [1]. They are currently used in the management of bone diseases including postmenopausal osteoporosis, Paget's disease, tumour- and nontumour-induced hypercalcemia. In addition they can be useful in controlling bone resorption and soft time inflammation associated with rheumatoid arthritis and osteoarthritis [1]. Recently, antiprotozoal activity was reported for these compounds [2].

One of the synthetic routes to these compounds goes through the corresponding alkyl esters which can be easily hydrolysed to the related acids [3]. Interestingly, some of them show *anti*-inflammatory and -arthritic activities unrelated to direct effect on calcium metabolism [4a]. Access to tetraalkyl *gem*-bisphosphonic esters utilizing the electrophilic character of tetraalkyl ethenylidenebisphosphonates was proposed. These ethenylidene derivatives are able to react under mild conditions with nitrogen, phosphorous or sulphur nucleophiles to give the corresponding 1,4-addition products in high yields [5]. Also the addition of simple and polyfunctional carbanions with tetraethyl ethenylidenebisphosphonate (**1**) was explored [4b,6]. By contrast, to our knowledge, only scattered examples of addition of a Grignard reagent are described [4]. In this note we show that Grignard reagents can be used to prepare, by reaction with **1**, a wide range of simple and functionalised tetraethyl *gem*-bisphosphonates.

2. Results and discussion

In a first series of experiments we studied the reaction between **1** and straight and branched alkyl, phenyl and alkylphenylmagnesium halogenides (Scheme 1). The reaction was run by slow addition of a THF solution of the appropriate Grignard reagent to a dry and stirred THF solution of **1** kept under argon at −15 °C. The expected 1,4 addition occurred and products **2**–**6** were isolated in good yield (64–72%). No compound derived from 1,2-addition was produced in a significant manner.

Under the same reaction conditions, in a second series of experiments (see Scheme 1), we studied the reaction between functionalised Grignard reagents and **1**. In order to introduce into the final bisphosphonate a hydroxy function, the possibility of the addition to **1** of the '*Normant*' reagents [7] was explored. As an example of this type of reagent the compound **7a** was selected.

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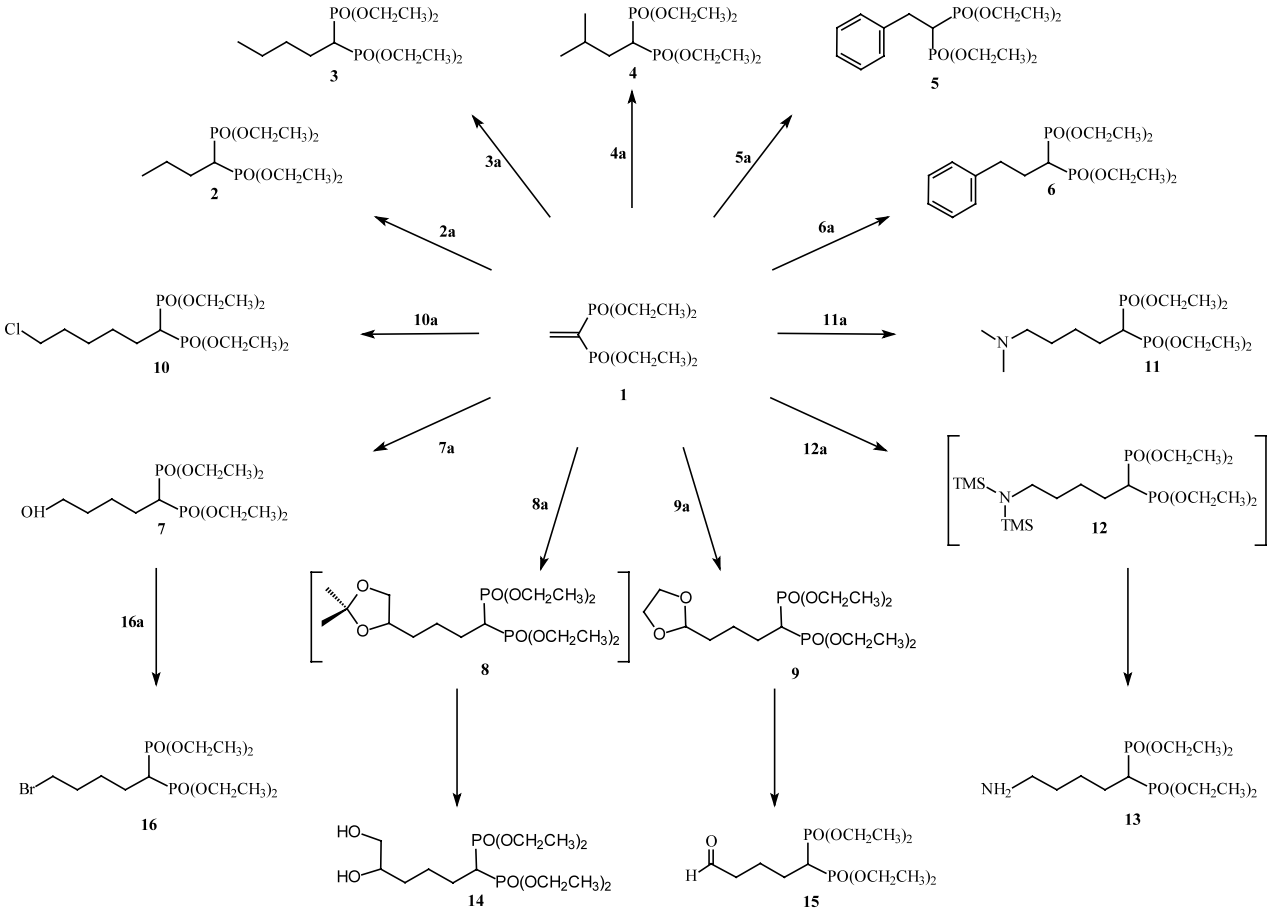
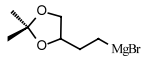
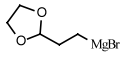
Slow addition of a THF solution of this reagent to a mechanically stirred dry THF solution of **1** resulted in the formation of a precipitate, presumably the insoluble magnesium 1,4 Michael adduct. The reaction mixture was treated by standard procedure to give in high yield (92%) the expected bisphosphonate **7**, bearing a hydroxy group in the lateral chain. The dihydroxybisphosphonate **14** was similarly realized by using 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylmagnesium bromide (**8a**). In this case, the instable dioxolane intermediate **8** was immediately hydrolysed by dilute acetic acid in THF to the final dihydroxy derivative **14** (overall yield 42%). If 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (**9a**) is used in the reaction, the obtained dioxolane bisphosphonate **9** is stable and can be isolated and characterized (yield 75%). Hydrolysis of **9** in 80% acetic acid at 65 °C provides the corresponding aldehyde **15**. Also bisphosphonates bearing a chlorine atom in the lateral chain can be easily obtained by using chloroalkylmagnesium bromides as demonstrated by the reaction of 4-chlorobutylmagnesium bromide (**10a**) with **1**. The yield in the final product **10** was 70%. Bromoalkylbisphosphonate **16** cannot be easily prepared from the corresponding 4-bromobutylmagnesium bromide since this reagent is not known and is very difficult to prepare [8]. By contrast, the bromoalkylbisphosphonate **16** can be easily obtained from the alcohol **7** by treatment with triphenylphosphine and *N*-bromosuccinimide (NBS).

Finally, the amino bisphosphonates **11** and **13** were obtained by using the appropriate Grignard reagents. 3-Dimethylaminopropylmagnesium chloride (**11a**) [15] lead to the addition product **11** in 79% yield. The Grignard derivative **12a**, bearing an amino group protected as bis(trimethylsilyl)amide, was successfully obtained by direct addition of 3-(bistrimethylsilylamino)-1-bromopropane [16] to a stirred suspension of an excess of highly active magnesium (Mg*, Rieke magnesium [9]) kept below −12 °C. Immediate reaction of **12a** with **1** gave the expected product **12** which



a) All the reactions were run (except for the entries **13**, **14**, **15**, and **16**) in dry THF under argon at -15 °C. **2a**, CH_3CH_2MgCl; **3a**, $CH_3CH_2CH_2MgCl$; **4a**, $(CH_3)_2CHMgCl$; **5a**, C_6H_5MgBr; **6a**, $C_6H_5CH_2MgBr$; **7a**, $ClMg(CH_2)_3OMgCl$; **8a**,  ; **9a**,  ; **10a**, $Cl(CH_2)_4MgBr$; **11a**, $(CH_3)_2N(CH_2)_3MgCl$; **12a**, $[(CH_3)_3Si]_2N(CH_2)_3MgBr$; **16a**, Triphenylphosphine, NBS.

Scheme 1.

was, without any further purification, directly transformed by treatment with acetic acid in THF in the final derivative **13** (overall yield 42%).

All the final bisphosphonates were characterized by ^{1}H-, ^{13}C-, ^{31}P-NMR spectra, data of which are listed in Section 3. Spectral assignments were given on the basis of chemical shifts, signal multiplicity and coupling constant values [10a,10b]. ^{1}H-NMR and proton decoupled ^{13}C-NMR spectra show rather complex patterns due to coupling with the two phosphorous nuclei, often resulting in second order multiplets, and/or to diastereotopic effects. The protonic pattern of the –CH group bearing the two phosphonic groups is peculiar in all the spectra. It occurs in the region 2.5–2.8 ppm and appears as a triplet of triplets due to coupling with the two chemically equivalent phosphorous atoms ($^{2}J_{HP}$ about 24 Hz) and with vicinal CH_2 protons ($^{3}J_{HH}$ about 6 Hz). By contrast, the chemical shift and the multiplicity of the latter, vary according to the chemical environment. ^{1}H- and ^{13}C-NMR signals of the tetraethyl moiety also appear as complex patterns due to coupling interactions with the two nonmagnetically equivalent phosphorous nuclei. Nevertheless, the appearance of such multiplets was characteristic and diagnostic to our purposes. For this reason, the values of the virtual coupling constants are also reported in spectral characterization [10b]. Proton decoupled ^{31}P-NMR spectra display only one signal indicating that the two nuclei are isochronous. They appear in the range 24.1–24.6 ppm with respect to external phosphoric acid. Only in the case of compound **14** are observed two peaks (24.6 and 24.5 ppm, respectively), due to diastereotopicity.

3. Experimental

The compounds were routinely checked by IR spectroscopy (Shimadzu, FTIR 8101 M) and mass spectrometry (Finnigan-MatTSQ-700 spectrometer, 70 eV, direct inlet). ^{1}H-, proton decoupled ^{13}C- and proton decoupled ^{31}P-NMR spectra, were recorded on a Bruker AC-200 spectrometer. The following abbreviations are used to indicate peak multiplicity: s = singlet; d = doublet; t = triplet; qt = quartet; qn = quintet; m = multiplet. ^{31}P-NMR chemical shifts are referred to 85% H_3PO_4. Flash column chromatography was performed on silica gel (Merck Kiesekgel 60, 230–400 mesh ASTM) using the indicated eluents. Thin layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm. When necessary they were developed with iodine and $KMnO_4$. Anhydrous $MgSO_4$ was used as the drying agent of the organic extracts. Elemental analysis of the new compounds is within ± 0.4% of the theoretical values. Alkyl, phenyl and alkylmagnesium alogenides **2a**–**6a** are commercial products. Tetraethyl ethenylidenebisphosphonate (**1** [11]) and functionalised Grignard reagents (**7a** [7], **8a** [12], **9a** [13], **10a** [14], **11a** [15]) were synthesized in accord with literature methods. 3-(Bistrimethylsilylamino)-1-bromopropane was prepared in according with the Gomes method [16]. It was purified by double distillation under reduced pressure and stored under Ar atmosphere at low temperature. All the Grignard reagents were titrated immediately before use [17]. Tetrahydrofuran (THF) was distilled immediately before use from Na and benzophenone under a positive atmosphere of N_2. All reaction were performed in flame- or over-dried glassware under a positive pressure of dry N_2 or Ar. All the reactions were carried three times without any attempts to optimize the yields.

3.1. Michael reactions: general procedure

A titrated solution containing 1.66 mmol of the Grignard reactant (0.062–2.44 M) in Et_2O (compounds **2**, **3**) or THF (compounds **4**–**12**) was slowly added to a magnetically stirred solution of tetraethyl ethenylidenebisphosphonate (500 mg; 1.66 mmol) in dry THF (10 ml) kept at − 15 °C under Ar. The reaction progress was followed by TLC. Usually, at the end of the addition the reaction was completed. The mixture was allowed to reach room temperature (r.t.) and then it was slowly poured into a saturated solution of NH_4Cl (20 ml). The mixture was extracted with Et_2O (2 × 20 ml) and the combined dried organic layers were concentrated under reduced pressure. The crude residue so obtained was purified by flash chromatography using the appropriate eluent system to give the pure product as an oil.

3.1.1. Tetraethyl butylidenebisphosphonate (2)

Colorless oil; yield 64%; Rf 0.61 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography eluent: CH_2Cl_2–MeOH, 98:2 v/v; ^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, $^{3}J_{HH}$ 7.0 Hz, $CH_3CH_2CH_2CH$–), 1.31 (t, 12H, $^{3}J_{HH}$ 7.0 Hz, –PO(OCH_2CH_3)$_2$), 1.5–1.7 (m, 2H, $CH_3CH_2CH_2CH$–), 1.7–2.0 (m, 2H, $CH_3CH_2CH_2$-CH–), 2.25 (tt, 1H, $^{3}J_{HH}$ 6.0 Hz, $^{2}J_{PH}$ 24.0 Hz, –CH-(PO(OCH_2CH_3)$_2$)$_2$), 4.07–4.22 (m, 8H, –PO(OCH_2-CH_3)$_2$); ^{13}C-NMR ($CDCl_3$) δ 13.6 (s, $CH_3CH_2CH_2$-CH–), 16.2 (d, $^{3}J_{PC}$ 5.5 Hz, –PO(OCH_2CH_3)$_2$), 22.2 (t, $^{3}J_{PC}$ 7.0 Hz, $CH_3CH_2CH_2CH$–), 27.4 (t, $^{2}J_{PC}$ = 5.0 Hz, $CH_3CH_2CH_2CH$–), 36.4 (t, $^{1}J_{PC}$ 132.0 Hz, –CH(PO-(OCH_2CH_3)$_2$)$_2$), 62.2 (t, virtual J = 7.0 Hz, –PO(OCH_2-CH_3)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.6; MS (CI) 331 [M + 1]$^{+}$; Anal. (drying conditions: 40 °C, 8 h, pressure < 1 mmHg) Found: C, 40.69; H, 8.33. Calc. for $C_{12}H_{28}O_6P_2 \cdot 1.2H_2O$: C, 40.96; H, 8.71%.

3.1.2. Tetraethyl pentylidenebisphosphonate (3)

Colorless oil; yield 67%; Rf 0.50 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography elu-

ent: CH_2Cl_2–MeOH, 98:2 v/v; ^{1}H-NMR ($CDCl_3$) δ 0.91 (t, 3H, $^3J_{HH}$ 7.0 Hz, CH_3CH$_2$–), 1.34 [(t, 12H, $^3J_{HH}$ 7.0 Hz, –PO(OCH$_2$CH_3)$_2$), (m, 2H, CH$_3$CH_2–)], 1.5–1.6 (m, 2H, –CH_2CH$_2$CH–), 1.8–2.1 (m, 2H, –CH$_2$CH_2-CH–), 2.27 (tt, 1H, $^3J_{HH}$ 6.0 Hz, $^2J_{HP}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 4.1–4.3 (m, 8H, –PO(OCH_2-CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 13.6 (s, CH$_3$CH$_2$–), 16.3 (d, $^3J_{PC}$ 6.5 Hz, –PO(OCH$_2C$H$_3$)$_2$), 22.3 (s, CH$_3C$H$_2$–), 25.1 (t, $^3J_{PC}$ 5.0 Hz, –CH$_2$CH$_2$CH–), 31.2 (t, $^2J_{PC}$ 6.0 Hz, –CH$_2C$H$_2$CH–), 36.6 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 62.3 (t, virtual $J = 7.0$ Hz, –PO(OCH$_2$CH$_3$)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.7; MS (CI) 345 $[M+1]^+$; Anal. (drying conditions: 40 °C, 48 h, pressure <1 mmHg) Found: C, 43.62; H, 8.88. Calc. for $C_{13}H_{30}O_6P_2 \cdot 0.9H_2O$: C, 43.09; H, 8.90%.

3.1.3. Tetraethyl (3-methylbutylidene)bisphosphonate (4)

Colorless oil; yield 67%; Rf 0.66 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography eluent: CH_2Cl_2–MeOH, 98:2 v/v; ^{1}H-NMR ($CDCl_3$) δ 0.87 (d, 6H, $^3J_{HH}$ 6.4 Hz, (CH_3)$_2$CHCH$_2$–), 1.30 (t, 12H, $^3J_{HH}$ 7.0 Hz, –PO(OCH$_2$CH_3)$_2$), 1.6–1.9 (m, 3H, (CH$_3$)$_2$CHCH$_2$–), 2.32 (tt, 1H, $^3J_{HH}$ 6.0 Hz, $^2J_{PH}$ 24 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 4.1–4.2 (m, 8H, –PO(OCH_2-CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ 6.0 Hz, –PO(OCH$_2C$H$_3$)$_2$), 21.8 (s, (CH$_3$)$_2$CHCH$_2$–), 26.7 (t, $^3J_{PC}$ 6.0 Hz, (CH$_3$)$_2C$HCH$_2$–), 34.0 (t, $^2J_{PC}$ 5.5 Hz, (CH$_3$)$_2$CHCH$_2$–), 34.6 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO-(OCH$_2$CH$_3$)$_2$)$_2$), 62.2 (t, virtual $J = 8.0$ Hz, –PO(OCH$_2$CH$_3$)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.7; MS (CI) 345 $[M+1]^+$; Anal. (drying conditions: 40 °C, 20 h, pressure <1 mmHg) Found: C, 45.40; H, 8.88. Calc. for $C_{13}H_{30}O_6P_2$: C, 45.35; H, 8.78%.

3.1.4. Tetraethyl (2-phenylethylidene)bisphosphonate (5)

Pale yellow oil; yield 72%; Rf 0.65 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography eluent: CH_2Cl_2–MeOH, 98:2 v/v; ^{1}H-NMR ($CDCl_3$) δ 1.23 (dt, 12H, $^3J_{HH}$ 7.0 Hz, virtual $^4J_{PH}$ 3.8 Hz, –PO(OCH$_2$CH_3)$_2$), 2.63 (tt, 1H, $^3J_{HH}$ 6.4 Hz, $^2J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 3.22 (td, 2H, $^3J_{HH}$ 6.2 Hz, $^3J_{PH}$ 16.4 Hz, PhCH_2CH–), 4.0–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$), 7.2–7.3 (m, 5H, C$_6H_5$–); ^{13}C-NMR ($CDCl_3$) δ 16.0 (d, $^3J_{PC}$ 5.7 Hz, –PO(OCH$_2C$H$_3$)$_2$), 31.0 (t, $^2J_{PC}$ 5.0 Hz, PhCH$_2$CH–), 38.8 (t, $^1J_{PC}$ 131.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 62.2–62.5 (m, –PO(OCH$_2$-CH$_3$)$_2$), 126.2 (s, Ph($C$4)), 128.0/128.7 (s/s, Ph($C$2)/Ph($C$3)), 139.4 (t, $^3J_{PC}$ 7.0 Hz, Ph($C$1)); ^{31}P-NMR ($CDCl_3$) δ 23.5; MS (EI) 378 $[M^+]$; Anal. (drying conditions: 40 °C, 16 h, pressure <1 mmHg) Found: C, 49.10; H, 7.40. Calc. for $C_{16}H_{28}O_6P_2 \cdot 0.6H_2O$: C, 49.38; H, 7.56%.

3.1.5. Tetraethyl (3-phenylpropylidene)bisphosphonate (6)

Colorless oil; yield 66%; Rf 0.39 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography eluent: CH_2Cl_2–IsopropylOH, 95:5 v/v; ^{1}H-NMR ($CDCl_3$) δ 1.33 (dt, 12H, $^3J_{HH}$ 7.0 Hz, $^4J_{PH}$ 3.8 Hz, –PO(OCH$_2$-CH_3)$_2$), 2.09–2.47 (m, 3H, PhCH$_2$CH_2CH(PO(OCH$_2$-CH$_3$)$_2$)$_2$), 2.90 (t, 2H, $^3J_{HH}$ 7.4 Hz, PhCH_2CH$_2$CH–), 4.04–4.27 (m, 8H, –PO(OCH_2CH$_3$)$_2$), 7.19–7.32 (m, 5H, C$_6H_5$–); ^{13}C-NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ 6.7 Hz, –PO(OCH$_2C$H$_3$)$_2$), 27.1 (t, $^2J_{PC}$ 4.5 Hz, PhCH$_2$CH_2-CH–), 34.5 (t, $^3J_{PC}$ 6.0 Hz, PhCH$_2$CH$_2$CH–), 35.6 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 62.3 (t, virtual $J = 7.0$ Hz, –PO(OCH$_2$CH$_3$)$_2$), 126.0 (s, Ph($C$4)), 128.3/128.5 (s/s, Ph($C$2/$C$3)), 140.8 (s, Ph($C$1)); ^{31}P-NMR ($CDCl_3$) δ 24.3; MS (EI) 392 $[M^+]$; Anal. (drying conditions: 42 °C, 8 h, pressure <1 mmHg) Found: C, 52.04; H, 7.84. Calc. for $C_{17}H_{30}O_6P_2$: C, 52.04; H, 7.71%.

3.1.6. Tetraethyl (5-hydroxypentylidene)bisphosphonate (7)

Due to the precipitation of a white crystalline solid (Mg 1,4 Michael adduct), the solution of tetraethyl ethenylidene bisphosphonate was mechanically stirred during the addition of the *Normant* reagent. Colorless oil; yield 92%; Rf 0.59 (TLC eluent: CH_2Cl_2–MeOH, 9:1 v/v); ^{1}H-NMR ($CDCl_3$) δ 1.34 (t, 12H, $^3J_{HH}$ 6.0 Hz, –PO(OCH$_2$CH_3)$_2$), 1.5–2.2 (m, 6H, –CH_2CH_2CH_2-CH–), 2.25 (tt, 1H, $^3J_{HH}$ 6.0 Hz, $^2J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 3.64 (t, 2H, $^3J_{HH}$ 6.0 Hz, OHCH_2CH$_2$–), 4.1–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ 5.8 Hz, –PO(OCH$_2$-CH_3)$_2$), 24.7/24.9 (*overlapping triplets*, –CH_2CH$_2$CH–), 31.9 (s, –CH$_2$CH$_2$OH), 36.5 (t, $^1J_{PC}$ 133.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 61.7 (s, –CH$_2C$H$_2$OH), 62.2–62.5 (m, –PO(OCH$_2$CH$_3$)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.5; MS (CI) 361 $[M+1]^+$; Anal. (drying conditions: 40 °C, 24 h, pressure <1 mmHg) Found: C, 42.97; H, 8.50. Calc. for $C_{13}H_{30}O_7P_2$: C, 43.33; H, 8.39%.

3.1.7. Tetraethyl (6-chlorohexylidene)bisphosphonate (10)

Colorless oil; yield 69%; Rf 0.48 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography eluent: CH_2Cl_2–MeOH, 98:2 v/v; ^{1}H-NMR ($CDCl_3$) δ 1.34 (t, 12H, $^3J_{HH}$ 7.0 Hz, –PO(OCH$_2$CH_3)$_2$), 1.4–2.1 (m, 8H, ClCH$_2$CH_2CH_2CH_2CH_2CH–), 2.27 (tt, 1H, $^3J_{HH}$ 6.0 Hz, $^2J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 3.53 (t, 2H, $^3J_{HH}$ 6.6 Hz, ClCH_2CH$_2$–), 4.1–4.3 (m, 8H, –PO(OCH_2CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.3 (d, $^3J_{PC}$ 6.0 Hz, –PO(OCH$_2C$H$_3$)$_2$), 25.3 (t, $^3J_{PC}$ 5.0 Hz, –CH$_2C$H$_2$CH$_2$CH–), 26.4 (s, ClCH$_2$CH$_2C$H$_2$–), 28.2 (t, $^2J_{PC}$ 6.0 Hz, –CH$_2$CH$_2C$H$_2$CH–), 32.0 (s, ClCH$_2$-CH_2CH$_2$–), 36.6 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$-CH$_3$)$_2$)$_2$), 44.8 (s, ClCH_2CH$_2$–), 62.4 (t, virtual $J = 7.0$ Hz, –PO(OCH$_2$CH$_3$)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.5; MS (CI) 393/395 $[M+1]^+$; Anal. (drying conditions:

40 °C, 72 h, pressure < 1 mmHg) Found: C, 42.10; H, 8.06. Calc. for $C_{14}H_{31}ClO_6P_2$: C, 42.81; H, 7.95%.

3.1.8. Tetraethyl (5-bromopentylidene)bisphosphonate (16)

NBS (2.96 g; 16.64 mmol) was added over 1 h to a magnetically stirred at −15 °C under Ar solution of tetraethyl (5-hydroxypentylidene)bisphosphonate (5.00 g; 13.87 mmol) and triphenylphosphine (4.36 g; 16.64 mmol) in dry CH_2Cl_2 (50 ml). At the end of the addition the mixture was allowed to reach r.t. and then was washed with a saturated solution of NaCl (3 × 15 ml). The aq. layers were extracted with CH_2Cl_2 (15 ml). The combined organic layers were dried and then concentrated under reduced pressure. The solid crude material so obtained was extracted with hexane (5 × 20 ml). The organic extracts were concentrated under reduced pressure and the residue was purified by flash chromatography (eluent CH_2Cl_2–MeOH, 98:2 v/v) to give the title compound as a colorless oil. Yield 44%; Rf 0.67 (TLC eluent: CH_2Cl_2–MeOH, 9:1 v/v); ^{1}H-NMR ($CDCl_3$) δ 1.34 (t, 12H, $^3J_{HH}$ 7.0 Hz, –PO(OCH$_2$CH_3)$_2$), 1.6–2.2 (m, 6H, –CH_2CH_2CH_2CH–), 2.26 (tt, 1H, $^3J_{HH}$ 6.0 Hz, $^3J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 3.41 (t, 2H, $^3J_{HH}$ 6.0 Hz, BrCH_2CH$_2$–), 4.1–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ 6.5 Hz, –PO(OCH$_2$CH_3)$_2$), 24.7 (t, $^3J_{PC}$ 5.2 Hz, –CH$_2$CH_2CH$_2$CH–), 27.5 (t, $^2J_{PC}$ 6.0 Hz, –CH$_2$CH$_2$CH_2CH–), 32.25/33.05 (s/s, BrCH_2CH_2–), 36.5 (t, $^1J_{PC}$ 133.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 62.4 (t, virtual J = 7.0 Hz, –PO(OCH_2CH$_3$)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.6; MS (CI) 423/425 $[M+1]^+$; Anal. (drying conditions: 40 °C, 8 h, pressure < 1 mmHg) Found: C, 37.09; H, 7.01. Calc. for $C_{13}H_{29}BrO_6P_2$: C, 36.89; H, 6.91%.

3.1.9. Tetraethyl (5-dimethylaminopentylidene)-bisphosphonate (11)

Pale yellow oil; yield 79%; Rf 0.37 (TLC eluent: CH_2Cl_2–MeOH, 9:1 v/v); flash chromatography eluent: CH_2Cl_2–MeOH, 9:1 v/v then pure MeOH; ^{1}H-NMR ($CDCl_3$) δ 1.31 (t, 12H, $^3J_{HH}$ 7.0 Hz, –PO(OCH$_2$CH_3)$_2$), 1.4–2.4 (m, 9H, (CH$_3$)$_2$NCH_2CH_2CH_2CH_2CH–), 2.56 (s, 6H, (CH_3)$_2$NCH$_2$–), 4.1–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.3 (d, $^3J_{PC}$ 6.1 Hz, –PO(OCH$_2$CH_3)$_2$), 25.4 (t, $^2J_{PC}$ 6.0 Hz, –CH$_2$CH$_2$CH_2CH–), 26.6 (t, $^3J_{PC}$ 5.3 Hz, –CH$_2$CH_2CH$_2$CH–), 26.9 (s, –CH_2CH$_2$N(CH$_3$)$_2$), 36.6 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 45.0 (s, (CH_3)$_2$NCH$_2$–), 59.1 (s, (CH$_3$)$_2$NCH_2–), 62.36 (t, virtual J = 7.2 Hz, –PO(OCH_2CH$_3$)$_2$); ^{31}P-NMR ($CDCl_3$) δ 24.6; MS (EI) 387 $[M]^+$; Anal. (drying conditions: r.t., 3 weeks, pressure < 1 mmHg) Found: C, 44.13; H, 8.96; N, 3.42. Calc. for $C_{15}H_{35}NO_6P_2 \cdot H_2O$: C, 44.44; H, 9.20; N, 3.46%.

3.1.10. Tetraethyl (4-(1,3-dioxolan-2-yl)butylidene)-bisphosphonate (9)

Colorless oil; yield 75%; Rf 0.38 (TLC eluent: CH_2Cl_2–MeOH, 95:5 v/v); flash chromatography eluent: CH_2Cl_2–MeOH, 95:5 v/v; ^{1}H-NMR ($CDCl_3$) δ 1.33 (t, 12H, $^3J_{HH}$ 7.4 Hz, –PO(OCH$_2$CH_3)$_2$), 1.6–2.1 (m, 6H, –CH_2CH_2CH_2CH–), 2.27 (tt, 1H, $^3J_{HH}$ 5.8 Hz, $^2J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 3.8–4.0 (m, 4H, –OCH_2CH_2O–), 4.1–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$), 4.84 (t, 1H, $^3J_{HH}$ 4.0, (O)CH(O)); ^{13}C-NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ 5.8 Hz, –PO(OCH$_2$CH_3)$_2$), 23.5 (t, $^3J_{PC}$ 7.0 Hz, –CH$_2$CH_2CH$_2$CH–), 25.3 (t, $^2J_{PC}$ 4.2 Hz, –CH$_2$CH$_2$CH_2CH–), 34.0 (s, (O)CH(O)CH_2–), 36.6 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 62.3 (t, virtual J = 7.0 Hz, –PO(OCH_2CH$_3$)$_2$), 64.70 (s, –OCH_2-CH_2O–), 104.0 (s, (O)CH(O)); ^{31}P-NMR ($CDCl_3$) δ 24.4; MS (CI) 403 $[M+1]^+$; Anal. (drying conditions: 40 °C, 8 h, pressure < 1 mmHg) Found: C, 44.72; H, 8.07. Calc. for $C_{15}H_{32}O_8P_2$: C, 44.78; H, 8.02%.

3.1.11. Tetraethyl (5-oxopentylidene)bisphosphonate (15)

A solution of tetraethyl (4-(1,3-dioxolan-2-yl)butylidene)bisphosphonate (**9**) (487 mg; 1.21 mmol) in 80% AcOH (10 ml) was heated at 65 °C for 1.5 h. The progress of the reaction was followed by TLC (CH_2Cl_2–MeOH, 95:5 v/v). The mixture was allowed to reach r.t. and then was concentrated under reduced pressure. The residue so obtained was dissolved in CH_2Cl_2 (15 ml) and the resulting solution was washed with a saturated solution of $NaHCO_3$ (4 × 5 ml), dried and then concentrated under reduced pressure. The crude material so obtained was purified by flash chromatography (eluent CH_2Cl_2–MeOH from 98:2 to 95:5 v/v) to give the pure compound as a colorless oil. Yield 60%; Rf 0.54 (TLC eluent: CH_2Cl_2–MeOH, 9:1 v/v); ^{1}H-NMR ($CDCl_3$) δ 1.35 (t, 12H, $^3J_{HH}$ 7.1 Hz, –PO(OCH$_2$CH_3)$_2$), 1.8–2.5 (m, 7H, –CH_2CH_2CH_2-CH–), 4.1–4.3 (m, 8H, –PO(OCH_2CH$_3$)$_2$), 9.8 (m, 1H, $^3J_{HH}$ 1.5 Hz, CH(O)CH$_2$–); ^{13}C-NMR ($CDCl_3$) δ 16.3 (d, $^3J_{PC}$ 5.5 Hz, –PO(OCH$_2$CH_3)$_2$), 21.5 (t, $^3J_{PC}$ 7.2 Hz, –CH$_2$CH_2CH$_2$CH–), 25.0 (t, $^2J_{PC}$ 5.2 Hz, –CH$_2$CH$_2$-CH_2CH–), 36.5 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$-CH$_3$)$_2$)$_2$), 43.3 (s, HC(O)CH_2–), 62.5 (t, virtual J = 7.2 Hz, –PO(OCH_2CH$_3$)$_2$), 201.8 (s, HC(O)CH$_2$–); ^{31}P-NMR ($CDCl_3$) δ 24.1; MS (CI) 359 $[M+1]^+$; Anal. (drying conditions: 40 °C, 8 h, pressure < 1 mmHg) Found: C, 42.00; H, 7.99. Calc. for $C_{13}H_{28}O_7P_2 \cdot 0.6H_2O$: C, 42.30; H, 7.97%.

3.1.12. Tetraethyl (5,6-dihydroxyhexylidene)bisphosphonate (14)

A solution of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylmagnesium bromide (0.062 M; 3.97 mmol; 64 ml) was added over 2 h to a stirred at −15 °C solution of **1**

(1.19 g; 3.97 mmol) in dry THF (40 ml) under inert atmosphere (Ar). The progress of the reaction was followed by TLC (eluent: CH_2Cl_2–MeOH, 9:1 v/v). The mixture was allowed to reach r.t. and then poured-into a saturated solution of NH_4Cl (60 ml). The mixture was extracted with Et_2O (60 ml); the dried organic layer was concentrated under reduced pressure to give the crude tetraethyl (4-(2,2-dimethyl-1,3-dioxolan-4-yl)butylidene)bisphosphonate (**8**). Due to its instability the dioxolane intermediate **8** was immediately transformed into the corresponding diol without any further purification. A solution of crude **8** (119 mg; 0.28 mmol) in 30% aq. AcOH (3 ml) was stirred at r.t. for 2 h. The progress of the reaction was followed by TLC (eluent: CH_2Cl_2–MeOH, 9:1 v/v). The mixture was concentrated under reduced pressure and the residue was dissolved into CH_2Cl_2 (10 ml). The resulting solution was washed with a saturated solution of $NaHCO_3$ (2×5 ml). The aq. layers were extracted with CH_2Cl_2 (4×10 ml) and then the combined organic layers were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: CH_2Cl_2–MeOH, 98:2 v/v) to give the desidered compound as a colorless oil. Yield 42%; Rf 0.36 (TLC eluent: CH_2Cl_2–MeOH, 9:1 v/v); ^{1}H-NMR ($CDCl_3$) δ 1.34 (t, 12H, $^3J_{HH}$ 7.0 Hz, –PO(OCH$_2$CH_3)$_2$), 1.44 (q, 2H, $^3J_{HH}$ 6.8 Hz, HOCHCH_2CH$_2$–), 1.6–1.8 (m, 2H, –CH$_2$CH_2CH$_2$CH–), 1.8–2.1 (m, 2H, –CH$_2$CH$_2$CH_2-CH–), 2.31 (tt, 1H, $^3J_{HH}$ 5.6 Hz, $^2J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 3.4–3.7 (m, 3H, OHCH_2-(OHCH)CH$_2$–), 4.1–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.2 (d, $^3J_{PC}$ 6.1 Hz, –PO(OCH$_2$CH_3)$_2$), 24.6/24.9 (overlapping triplets, –CH$_2$CH_2CH_2CH–), 32.2 (s, –CH_2CH$_2$CH$_2$CH–), 36.3 (t, $^1J_{PC}$ 133.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 62.3–62.7 (m, –PO(OCH_2CH$_3$)$_2$), 66.6 (s, OHCH_2–), 71.2 (s, OHCH–); ^{31}P-NMR ($CDCl_3$) δ 24.5/24.6; MS (CI) 391 $[M+1]^+$; Anal. (drying conditions: 40 °C, 8 h, pressure <1 mmHg) Found: C, 42.49; H, 8.43. Calc. for $C_{14}H_{32}O_8P_2$: C, 43.08; H, 8.26%.

*3.1.13. 3-(Bistrimethylsilylamino)propylmagnesium bromide (**12a**)*

3-(Bistrimethylsilylamino)-1-bromopropane (1.5 g; 5.32 mmol) was slowly added to a stirred suspension of Rieke magnesium (Mg*; 10.64 mmol) in dry THF (40 ml) under Ar, keeping the temperature of the mixture below -12 °C. At the end of the addition the stirred mixture was allowed to reach 0 °C and then, after 5 min, it was again cooled at -15 °C. The mixture was stirred at this temperature for 5 min then the stirring was stopped. After sedimentation, the clear solution was titrated [17]. Yield 56%. This reagent was immediately used in the preparation of **12** according to the general procedure above reported.

*3.1.14. Tetraethyl (5-aminopentylidene)bisphosphonate (**13**)*

A solution of **12** (823 mg; 1.63 mmol) in dry THF (20 ml) and AcOH (2 ml) was stirred at r.t. for 4 h. The mixture was concentrated under reduced pressure and the residue was dissolved in water (5 ml). The resulting solution, maintained at pH 10 by addition of 2 M NaOH, was extracted with CH_2Cl_2 (7×10 ml). The combined organic layers were concentrated obtaining the pure product as a colorless oil. Yield 42%; Rf 0.5 (TLC eluent: CH_2Cl_2–MeOH–NH_4OH (30% v/v), 9:1:0.1 v/v/v); ^{1}H-NMR ($CDCl_3$) δ 1.33 (t, 12H, $^3J_{HH}$ 7.2 Hz, –PO(OCH$_2$CH_3)$_2$), 1.4–2.0 (m, 8H, H_2NCH$_2$-CH_2CH_2CH_2–), 2.27 (t, 1H, $^3J_{HH}$ 6.0 Hz, $^2J_{PH}$ 24.0 Hz, –CH(PO(OCH$_2$CH$_3$)$_2$)$_2$), 2.69 (t, 2H, $^3J_{HH}$ 6.8 Hz, H$_2$NCH_2–), 4.1–4.2 (m, 8H, –PO(OCH_2CH$_3$)$_2$); ^{13}C-NMR ($CDCl_3$) δ 16.3 (d, $^3J_{PC}$ 6.5 Hz, –PO(OCH$_2$-CH_3)$_2$), 25.2 (t, $^3J_{PC}$ 5.2 Hz, –CH$_2$CH_2CH$_2$CH–), 26.2 (t, $^2J_{PC}$ 7.0 Hz, –CH$_2$CH$_2$CH_2CH–), 33.1 (s, –CH_2CH$_2$-CH$_2$CH–), 36.54 (t, $^1J_{PC}$ 132.0 Hz, –CH(PO(OCH$_2$-CH$_3$)$_2$)$_2$), 41.5 (s, H$_2$NCH_2–); 62.3 (t, virtual $J = 7.8$ Hz, –PO(OCH_2CH$_3$)$_2$), ^{31}P-NMR ($CDCl_3$) δ 24.6; MS (CI) 360 $[M+1]^+$; Anal. (drying conditions: 40 °C, 8 h, pressure <1 mmHg) Found: C, 40.70; H, 8.56; N, 3.59. Calc. for $C_{13}H_{31}NO_6P_2 \cdot 1.25H_2O$: C, 40.89; H, 8.84; N, 3.67%.

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