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# Synthesis of functionalized alkoxyalkylidene *gem*-bisphosphonates

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ABSTRACT

We report the synthesis of a series of new functionalized bisphosphonates and bisphosphonic acids with an alkoxy group fixed at the geminal carbon, which is proposed to increase their lipophilicity and so their bioavailability. Subsequently, the alkylation of these alkoxy bisphosphonates with allyl bromide is reported. The reactivity of the allyl group has been studied to give access to alkoxy bisphosphonates functionalized by diverse groups including alcohol, aldehyde, carboxylic acid, epoxide and amine.



## 1. Introduction

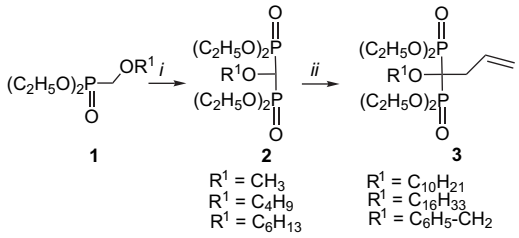
Bisphosphonates represent an important class of pharmacologically active molecules, which are widely used in the treatment of various bone diseases, such as osteoporosis,[1] Paget's disease,[2] hypercalcaemia[3] and bone metastases secondary to breast cancer[4] and prostate cancer.[5] Recent studies have shown that anti-tumour properties of bisphosphonates included inhibition of tumour cell proliferation and invasion,[6] inhibition of tumour cell adhesion to bone,[7] inhibition of angiogenesis[8] or induction of apoptosis.[9] Some bisphosphonates also activate the γδ T cell population, which shows potential cytotoxic activity towards a broad spectrum of tumours.[10] Some others possess anti-inflammatory properties and may be effective in the treatment of rheumatoid arthritis[11] or exhibit anti-parasitic activity.[12]

Due to their exceptional bone affinity, bisphosphonates can serve also as drug carriers or prodrugs for bone diseases. For several years, our laboratory has been studying this concept by developing the chemistry of 1,1-*gem*-bisphosphonates functionalized derivatives and their conjugation with different drugs.[13]

However, bisphosphonic acids and their conjugates are suffering from their very low oral bioavailability[14] due to their high hydrophilicity. Consequently, to improve the lipophilic character of these compounds, some authors[15] have converted hydroxy or/and amino group or phosphonic acid groups into an enzyme- or acid-triggerable group like esters or amides. In this paper, we describe the synthesis of new alkoxy bisphosphonates and we report their alkylation with allylbromide. Based on the reactivity of the allyl group, the introduction of several functionalities, including alcohol, aldehyde, carboxylic acid, epoxide and amine, is reported.

## 2. Results and discussion

In our laboratory, Sturtz and Ollivier[16] synthesized alkoxy bisphosphonate derivatives **2**, and interestingly showed that the increasing lipophilicity of the substituent $R^1$ ($R^1$=Me, Bu) does not reduce the osteotropism of these compounds. Following this reported methodology, we have prepared (Scheme 1) a series of compounds **2**, including four new compounds (**2c**–**2f**), with different $R^1$ substituents and have submitted them to deprotonation/alkylation sequences.




**Scheme 1.** (i) LDA, THF, $(C_2H_5O)_2P(O)Cl$, −78 °C to 0 °C and (ii) NaH, allyl bromide, DMF, rt.

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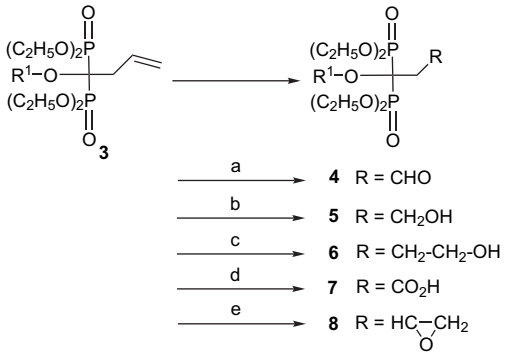
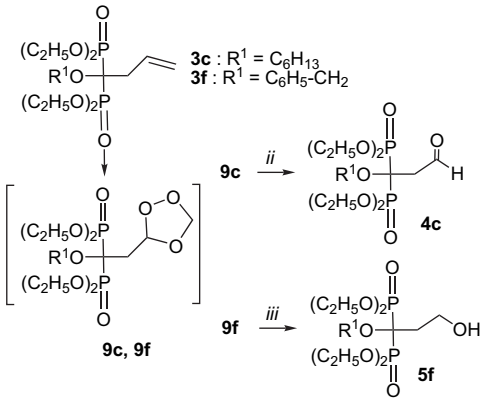
Alkylation of compounds **2** with allyl bromide (NaH, DMF) gives the expected bisphosphonates **3** in good yields (60–80%). But attempts to alkylate compounds **2** with other alkyl bromides including benzyl bromide, ethyl bromoacetate or bromoacetonitrile failed whatever the conditions employed (solvent, temperature). These observations could be explained by a nucleophilic substitution that could take place in the case of allyl bromide, probably at the allylic carbon and with an allylic rearrangement, following an $S_N2'$ reaction. The alkylation with a Michael acceptor as electrophile (e.g., ethyl acrylate, acrylonitrile) did not produce better results, indicating that the steric hindrance could inhibit this alkylation reaction. However, the introduced allyl group offers a great potential for the incorporation of different functionalities to produce a wide range of products as reported in Scheme 2.



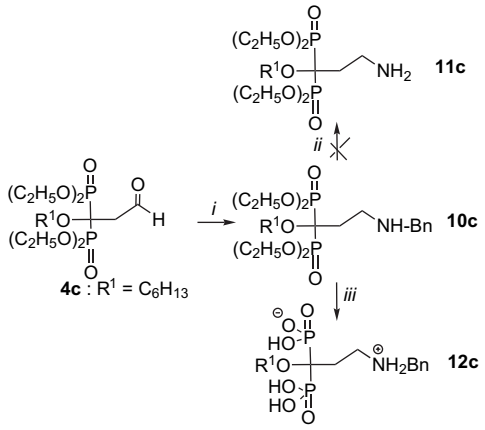

**Scheme 2.** (a) $O_3$, $CH_2Cl_2$, −78 °C then $(CH_3)_2S$, rt; (b) $O_3$, $CH_2Cl_2$, −78 °C then $BH_3$–$(CH_3)_2S$, rt; (c) $BH_3$–THF, THF, 0 °C, 1.5 h, then MeOH, 3 M NaOH, 30% $H_2O_2$, 50 °C, 1 h; (d) $NaIO_4$, $RuCl_3$, $CCl_4$, $CH_3CN$, $H_2O$, rt; and (e) *m*-CPBA, $CH_2Cl_2$, rt.

Compounds **3c** and **3f** have been treated with ozone in dichloromethane at −78 °C to afford the ozonides **9c** and **9f**, which have not been isolated. The ozonide **9c** was slowly decomposed with dimethylsulfide[17] at room temperature to give, after 4 days, as monitored by $^{31}P$ NMR, the aldehyde **4c** in a quantitative yield. In a different way, the ozonide **9f** was reduced with $BH_3$–DMS[18] giving rise to the alcohol **5f** in 76% yield (Scheme 3).

The aldehyde **4c** was then treated with benzylamine and methanolic pyridine–borane in the presence of 4 Å molecular sieves to effect reductive amination[19] to afford **10c** (Scheme 4). This compound was isolated in moderate yield (32%) and all attempts to get the debenzylated compound **11c** ($H_2$/P–C, $Pd(OH)_2$[20]) failed. Then, the corresponding phosphonic acid **12c** was obtained almost quantitatively by treatment with an excess of bromotrimethylsilane[21] followed by the methanolysis of the resulting trimethylsilyl ester.

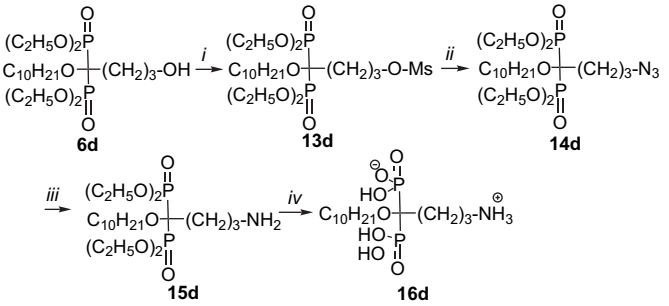



**Scheme 3.** (i) $O_3$, $CH_2Cl_2$, −78 °C; (ii) $(CH_3)_2S$, rt, 96 h; and (iii) $BH_3$–$(CH_3)_2S$, rt, 48 h.




**Scheme 4.** (i) $BnNH_2$, 4 Å sieves, Pyr–$BH_3$, MeOH, rt, 7 h; (ii) 20% $Pd(OH)_2$, $H_2$, MeOH, 15 h; and (iii) $(CH_3)_3SiBr$, $CH_2Cl_2$, rt, 15 h then MeOH.

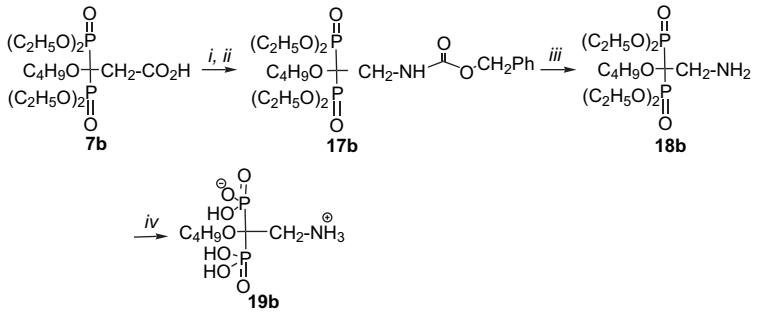
Another strategy has been investigated to produce the alkoxy methylene bisphosphonate functionalized by an amino group as depicted in Scheme 5. The alcohol **6d**, which is synthesized following a hydroboration–oxidation procedure[22] starting from **3d** (Scheme 2), reacts with mesylchloride to give compound **13d**. In a second step, **13d** reacts with sodium azide to produce compound **14d**, which is subsequently reduced in **15d** with triphenylphosphine, according to a modified Staudinger procedure.[23] The corresponding phosphonic acid **16d** was then obtained in an overall yield of 25% by treatment with an excess of bromotrimethylsilane as previously described.




**Scheme 5.** (i) $CH_3SO_2Cl$, $Et_3N$, $CH_2Cl_2$, rt, 2 h; (ii) $NaN_3$, DMF, rt, 6 h; (iii) $Ph_3P$, THF, $H_2O$, rt; and (iv) $(CH_3)_3SiBr$, $CH_2Cl_2$, rt, 15 h then MeOH.

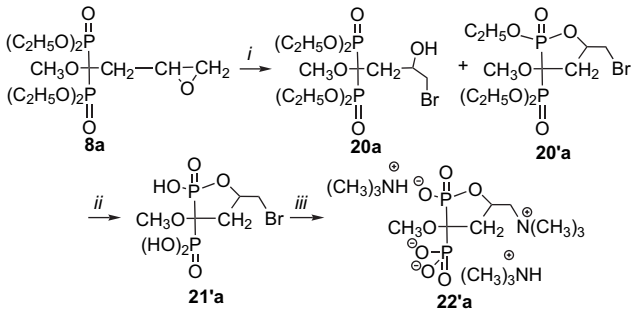
The oxidative cleavage of the double bond of **3b** is accomplished with $RuCl_3$–$NaIO_4$ under Sharpless conditions[24] producing the carboxylic acid **7b** in a quantitative yield. This acid was then converted into the amine **18b** (Scheme 6) by a Curtius reaction using the Yamada reagent[25] (diphenylphosphonic azide—DDPA). First, the azide group is transferred by the reaction of the carboxylic acid **7b** with DDPA. Benzyl alcohol is then added to the isocyanate intermediate, to afford the carbamate **17b** in 76% yield. The removal of the benzyl group by catalytic hydrogenolysis with 10% Pd–C under $H_2$ atmosphere gives quantitatively the amino compound **18b**. The phosphonic acid **19b** was isolated after the classical silylation ($Me_3SiBr$)/alcoholysis procedure.

Epoxidation of **3a** with *m*-chloroperoxybenzoic acid in $CH_2Cl_2$ affords quantitatively the epoxide **8a**. Treatment of **8a** with triphenylphosphine and bromine[26] in dichloromethane at room temperature affords, before the purification by chromatography on silica gel, a mixture of triphenylphosphine oxide and bromohydrin **20a** (Scheme 7). After chromatography, a mixture of compounds **20a** and **20′a** in the ratio of 1/9 is isolated. The formation of **20′a** results from an intramolecular cyclization of **20a**. Of note, this kind



**Scheme 6.** (i) $N_3$–P(O)(OPh)$_2$, $Et_3N$, benzene, reflux; (ii) $PhCH_2OH$; (iii) $H_2$, Pd–C, MeOH; and (iv) $(CH_3)_3SiBr$, $CH_2Cl_2$, rt, 15 h then MeOH.

of cyclization has been previously reported in the literature.[27] Compound **20′a** exists in a mixture of two diastereoisomers in a ratio 70/30. Treatment of the mixture of **20a** and **20′a** with bromotrimethylsilane has completed the cyclization and gives only the acid **21′a** as two diastereoisomers in a 70/30 ratio. The addition of an aqueous solution of trimethylamine on **21′a** gives rise to the product of substitution **22′a** in a quantitative yield.



**Scheme 7.** (i) $Ph_3PBr_2$, $SiO_2$, 99/1: ethyl acetate/ethanol; (ii) $(CH_3)_3SiBr$, $CH_2Cl_2$, rt, 15 h then MeOH; and (iii) $N(CH_3)_3$ 40 wt% in $H_2O$.

## 3. Conclusion

In this paper, the alkylation of alkoxy methylene bisphosphonate **2** with allyl bromide is reported. The introduced allyl group has been chemically transformed in order to incorporate new functionalities including alcohol, aldehyde, carboxylic acid, epoxide and amine. The resulting bisphosphonate have been hydrolyzed to give access to a wide family of new functionalized alkoxy bisphosphonic acids. We expect, for these new bisphosphonic acids, a decrease of their hydrophilic character and therefore a better bioavailability by oral administration. The evaluations of their biological activities are currently in progress. Furthermore, the functionalities introduced could be useful for the synthesis of conjugate of alkoxy methylene bisphosphonates.

## 4. Experimental section

### 4.1. General

$^1$H (300 MHz), $^{13}$C (75 MHz) and $^{31}$P NMR (120 MHz) spectra were recorded on a Bruker AC 300 spectrometer using chloroform as an internal reference in $CDCl_3$ solutions (7.24 ppm) for $^1$H NMR spectra and (77.0 ppm) for $^{13}$C NMR spectra, and phosphoric acid (85%) for $^{31}$P NMR spectra. Chemical shifts ($\delta$) are given in parts per million; multiplicities are indicated by s (singlet), br s (broad singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet), qt (quintuplet), m (multiplet) or st (sextuplet). Coupling constants ($J$) are reported in hertz. Analytical TLCs were performed on silica gel plates (Merck, 60$F_{254}$) and bisphosphonates were visualized with a solution of Mo/$MoO_3$ staining reagent.[28] Liquid chromatographies were carried out on silica gel (Merck 60, 70–230 mesh).

### 4.2. General procedure for the synthesis of alkoxy methylene bisphosphonates 2

The following compounds have been prepared as described by Ollivier et al.[16]

To a solution of diisopropylamine (10.5 g, 104 mmol) in dry THF, under nitrogen, cooled to −78 °C, was added a 2.5 M solution of BuLi in hexane (40 mL, 100 mmol). Then, phosphonate **1** (50 mmol) was introduced in the mixture and diethyl chlorophosphate (10.35 g, 60 mmol) was added dropwise. The reaction mixture was allowed to warm up to 0 °C, hydrolyzed with water and extracted with $CH_2Cl_2$ (3×100 mL). The extract was dried over $MgSO_4$, filtered and concentrated to give the crude bisphosphonate **2**, which is purified by fractional distillation under vacuo or by chromatography on silica gel.

#### *4.2.1. Tetraethyl 1-methoxymethylene-1,1-bisphosphonate **2a***

Yield: 87%. $^1$H NMR ($CDCl_3$) $\delta$ 4.32–4.18 (m, 8H), 3.79 (t, 1H, $^2J_{HP}$=17), 3.62 (s, 3H), 1.34 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 15.1; $^{13}$C NMR ($CDCl_3$) $\delta$ 74.7 (t, $^1J_{CP}$=157), 63.2, 62.3, 16.2; Anal. Calcd for $C_{10}H_{24}O_7P_2$ (318.2): C 37.7, H 7.6, P 19.5. Found: C 37.4, H 7.7, P 19.3.

#### *4.2.2. Tetraethyl 1-butoxymethylene-1,1-bisphosphonate **2b***

Yield: 87%; $^1$H NMR ($CDCl_3$) $\delta$ 4.32–4.12 (m, 8H), 3.9 (t, 1H, $^2J_{HP}$=18), 3.74 (t, 2H, $^3J_{HH}$=7), 1.56 (qt, 2H, $^3J_{HH}$=7), 1.44–1.20 (m, 14H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 17.0; $^{13}$C NMR ($CDCl_3$) $\delta$ 74.7, 73.1 (t, $^1$JCP=158), 63.2, 63.0, 31.5, 18.7, 16.2, 13.5; Anal. Calcd for $C_{13}H_{30}O_7P_2$ (360.3): C 43.3, H 8.4, P 17.2. Found: C 43.1, H 8.5, P 17.0.

#### *4.2.3. Tetraethyl 1-hexoxymethylene-1,1-bisphosphonate **2c***

Yield: 82%; $^1$H NMR ($CDCl_3$) $\delta$ 4.29–4.16 (m, 8H), 3.9 (t, 1H, $^2J_{HP}$=18), 3.74 (t, 2H, $^3J_{HH}$=7), 1.6 (qt, 2H, $^3J_{HH}$=7), 1.38–1.18 (m, 6H), 1.34 (t, 12H, $^3J_{HH}$=7), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 16.5; $^{13}$C NMR ($CDCl_3$) $\delta$ 75.0, 73.1 (t, $^1J_{CP}$=157), 63.1, 62.0, 31.2, 29.3, 25.2, 22.2, 16.1, 13.6; Anal. Calcd for $C_{15}H_{34}O_7P_2$ (388.4): C 46.4, H 8.8, P 15.9. Found: C 46.2, H 8.9, P 15.8.

#### *4.2.4. Tetraethyl 1-decoxymethylene-1,1-bisphosphonate **2d***

Yield: 80%; $^1$H NMR ($CDCl_3$) $\delta$ 4.29–4.14 (m, 8H), 3.90 (t, 1H, $^2J_{HP}$=18), 3.74 (t, 2H, $^3J_{HH}$=7), 1.6 (qt, 2H, $^3J_{HH}$=7), 1.39–1.16 (m, 14H), 1.38 (t, 12H, $^3J_{HH}$=7), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 16.5; $^{13}$C NMR ($CDCl_3$) $\delta$ 75.0, 73.1 (t, $^1J_{CP}$=157), 63.0, 62.8, 31.5, 29.4, 29.2, 28.9, 25.5, 22.3, 16.1, 13.7; Anal. Calcd for $C_{19}H_{24}O_7P_2$ (444.5): C 51.3, H 9.5, P 13.9. Found: C 51.0, H 9.6, P 13.7.

#### *4.2.5. Tetraethyl 1-hexadecoxymethylene-1,1-bisphosphonate **2e***

Yield: 75%; $^1$H NMR ($CDCl_3$) $\delta$ 4.30–4.10 (m, 8H), 3.90 (t, 1H, $^2J_{HP}$=18), 3.75 (t, 2H, $^3J_{HH}$=7), 1.57 (qt, 2H, $^3J_{HH}$=7), 1.40–1.15 (m,

26H), 1.34 (t, 12H, $^3J_{HH}$=7), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 16.5; $^{13}$C NMR ($CDCl_3$) $\delta$ 75.5, 73.5 (t, $^1J_{CP}$=157), 63.3, 63.2, 31.9, 29.6, 29.3, 25.8, 22.7, 16.4, 14.1; Anal. Calcd for $C_{25}H_{54}O_7P_2$ (528.6): C 56.8, H 10.3, P 11.7. Found: C 56.4, H 10.5, P 11.9.

*4.2.6. Tetraethyl 1-benzyloxymethylene-1,1-bisphosphonate **2f***

Yield: 78%; $^1$H NMR ($CDCl_3$) $\delta$ 7.41–7.26 (m, 5H), 4.83 (s, 2H), 4.30–4.08 (m, 8H), 4.06 (t, 1H, $^2J_{HP}$=17), 1.34 (t, 6H, $^3J_{HH}$=7), 1.33 (t, 6H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 16.4; $^{13}$C NMR ($CDCl_3$) $\delta$ 135.6, 127.9, 127.5, 74.9, 70.8 (t, $^1J_{CP}$=157), 62.6, 62.5, 15.6; Anal. Calcd for $C_{16}H_{28}O_7P_2$ (394.3): C 48.7, H 7.2, P 15.7. Found: C 48.4, H 7.3, P 15.5.

### 4.3. General procedure for the synthesis of tetraethyl 1-alkoxybut-3-enylidene-1,1-bisphosphonate 3

To a solution of NaH (8 mmol) in dry DMF (30 mL) was added bisphosphonate (6 mmol) at room temperature, under $N_2$. After 45 min, allyl bromide (10 mmol) was added and the mixture was stirred at room temperature for 12 h. Then, the mixture was concentrated in vacuo, diluted with $CH_2Cl_2$ (30 mL) and washed with brine (20 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by chromatography to yield compounds **3**.

*4.3.1. Tetraethyl 1-methoxybut-3-enylidene-1,1-bisphosphonate **3a***

Yield: 75%; $^1$H NMR ($CDCl_3$) $\delta$ 6.0 (m, 1H), 5.1–5.2 (m, 2H), 4.1–4.3 (m, 8H), 3.6 (s, 3H), 2.9 (m, 2H), 1.3 (m, 12H); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.2; $^{13}$C NMR ($CDCl_3$) $\delta$ 131.6, 116.0, 77.3 (t, $^1J_{CP}$=151), 62.3, 53.5, 34.7, 15.6; Anal. Calcd for $C_{13}H_{28}O_7P_2$ (358.1): C 43.6, H 7.9, P 17.3. Found: C 43.4, H 8.0, P 17.1.

*4.3.2. Tetraethyl 1-butoxybut-3-enylidene-1,1-bisphosphonate **3b***

Yield: 70%; $^1$H NMR ($CDCl_3$) $\delta$ 6.0 (m, 1H), 5.1 (m, 2H), 4.2 (m, 8H), 3.8 (t, 2H, $^3J_{HH}$=7), 2.9 (m, 2H), 1.5 (m, 16H), 0.9 (t, 2H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.0; $^{13}$C NMR ($CDCl_3$) $\delta$ 132.3, 117.4, 80.2 (t, $^1J_{CP}$=151), 65.7, 63.0, 62.7, 35.5, 32.0, 18.8, 16.1, 13.6; Anal. Calcd for $C_{16}H_{34}O_7P_2$ (400.4): C 48.6, H 8.6, P 15.5. Found: C 48.3, H 8.7, P 15.3.

*4.3.3. Tetraethyl 1-hexoxybut-3-enylidene-1,1-bisphosphonate **3c***

Yield: 80%; $^1$H NMR ($CDCl_3$) $\delta$ 6.0 (m, 1H), 5.1 (m, 2H), 4.2 (m, 8H), 3.8 (t, 2H, $^3J_{HH}$=7), 2.9 (td, 2H, $^3J_{HP}$=14.2, $^3J_{HH}$=7), 1.5 (m, 2H), 1.3 (m, 18H), 0.9 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.1; $^{13}$C NMR ($CDCl_3$) $\delta$ 132.4, 117.3, 80.2 (t, $^1J_{CP}$=151), 66.0, 63.0, 62.6, 35.5, 31.3, 29.8, 25.2, 22.2, 16.1, 13.6; Anal. Calcd for $C_{18}H_{38}O_7P_2$ (428.4): C 50.5, H 8.9, P 14.5. Found: C 50.3, H 9.0, P 14.3.

*4.3.4. Tetraethyl 1-decoxybut-3-enylidene-1,1-bisphosphonate **3d***

Yield: 77%; $^1$H NMR ($CDCl_3$) $\delta$ 6.0 (m, 1H), 5.1 (m, 2H), 4.2 (m, 8H), 3.8 (t, 2H, $^3J_{HH}$=7), 2.9 (m, 2H), 1.5 (m, 2H), 1.3 (m, 12H), 1.2 (m, 14H), 0.9 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.1; $^{13}$C NMR ($CDCl_3$) $\delta$ 132.4, 117.3, 80.3 (t, $^1J_{CP}$=151), 66.0, 63.0, 62.6, 35.5, 31.6, 29.9, 29.2, 29.0, 25.6, 22.3, 16.2, 13.7; Anal. Calcd for $C_{22}H_{46}O_7P_2$ (484.5): C 54.5, H 9.6, P 12.8. Found: C 54.2, H 9.8, P 12.6.

*4.3.5. Tetraethyl 1-hexadecoxybut-3-enylidene-1,1-bisphosphonate **3e***

Yield: 72%; $^1$H NMR ($CDCl_3$) $\delta$ 6.08 (m, 1H), 5.11 (m, 2H), 4.2 (m, 8H), 3.8 (t, 2H, $^3J_{HH}$=7), 2.9 (td, 2H, $^3J_{HP}$=14.2, $^3J_{HH}$=7), 1.5 (m, 2H), 1.3 (m, 12H), 1.2 (m, 26H), 0.8 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.1; $^{13}$C NMR ($CDCl_3$) $\delta$ 132.8, 117.6, 80.6 (t, $^1J_{CP}$=151), 66.3, 63.3, 62.9, 35.8, 31.9, 30.2, 29.7, 29.5, 29.3, 25.9, 22.7, 16.5, 14.1; Anal. Calcd for $C_{28}H_{58}O_7P_2$ (568.7): C 59.1, H 10.3, P 10.9. Found: C 59.2, H 10.3, P 10.9.

*4.3.6. Tetraethyl 1-benzyloxybut-3-enylidene-1,1-bisphosphonate **3f***

Yield: 60%; $^1$H NMR ($CDCl_3$) $\delta$ 7.2–7.4 (m, 5H), 6.1 (m, 1H), 5.1–5.2 (2dd, 2H, $^1J_{HH}$=1.6, $^3J_{HHcis}$=10.0, $^3J_{HHtrans}$=17.1), 4.9 (s, 2H), 4.8 (td, 2H, $^2J_{HP}$=14.1, $^3J_{HH}$=7.0), 4.1–4.3 (m, 8H), 1.3 (m, 12H); $^{31}$P NMR ($CDCl_3$) $\delta$ 16.6; $^{13}$C NMR ($CDCl_3$) $\delta$ 132.2, 127.7, 117.5, 80.3 (t, $J_{CP}$=150), 69.7, 62.2, 35.9, 16.0; Anal. Calcd for $C_{19}H_{32}O_7P_2$ (434.4): C 52.5, H 7.4, P 14.3. Found: C 52.2, H 7.5, P 14.1.

### 4.4. Tetraethyl 1-hexoxy-3-oxopropylidene-1,1-bisphosphonate 4c

A solution of alkene **3d** (0.48 g, 1 mmol) in $CH_2Cl_2$ (20 mL) was cooled to −78 °C. The effluent stream of an ozone generator was bubbled into the methylene chloride solution until the blue colour of unreacted ozone was noticeable. Then, dry nitrogen was bubbled through the reaction mixture for 10 min and 5 mL of methylsulfide was added. The reaction mixture was allowed to warm up to room temperature and was stirred until the entire disappearance of the ozonide **9c** followed by $^{31}$P NMR (**9c**: $\delta$ $^{31}$P 18.25, 17.9 (dd, AB, $J_{PP}$=40 Hz) (4 days)). The solution was evaporated in vacuo to give quantitatively the aldehyde **4c**. $^1$H NMR ($CDCl_3$) $\delta$ 9.87 (t, 1H, $^3J_{HH}$=3), 4.31–4.16 (m, 8H), 3.91 (t, 2H, $^3J_{HH}$=7), 2.96 (dt, 2H, $^3J_{HH}$=3, $^3J_{HP}$=14), 1.57 (qt, 2H, $^3J_{HH}$=7), 1.42–1.18 (m, 6H), 1.33 (t, 12H, $^3J_{HH}$=7), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 17.7; $^{13}$C NMR ($CDCl_3$) $\delta$ 198.7 (d, $^3J_{CP}$=29), 77.1 (t, $^1J_{CP}$=151), 66.8, 62.9, 62.6, 44.2, 30.7, 29.2, 24.6, 21.6, 15.5, 13.1; Anal. Calcd for $C_{17}H_{36}O_8P_2$ (430.4): C 47.4, H 8.4, P 14.4. Found: C 47.1, H 8.5, P 14.3.

### 4.5. Tetraethyl 3-benzylamino-1-hexoxypropylene-1,1-bisphosphonate 10c

To MeOH (15 mL) containing 71 mg of 4 Å molecular sieves was added sequentially the aldehyde **4c** (0.43 g, 1 mmol), benzylamine (0.107 g, 1 mmol) and pyridine–borane (0.08 mL, 0.8 mmol). After 7 h, the resulting mixture was treated with 2 mL of 1 N HCl for 5 min and then pH adjusted to 14 using 2 N NaOH. Three extractions were performed with $CH_2Cl_2$, and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by chromatography (silica, ethyl acetate/ethanol: 5/1) to give the pure compound **10c** as an uncoloured oil. Yield: 32%; $^1$H NMR ($CDCl_3$) $\delta$ 7–7.4 (m, 5H), 4.25–4.04 (m, 8H), 3.80 (s, 2H), 3.75 (t, 2H, $^3J_{HH}$=7), 2.93 (t, 2H, $^3J_{HH}$=7), 2.33 (tt, 2H, $^3J_{HH}$=7, $^3J_{HP}$=14), 1.68 (qt, 2H, $^3J_{HH}$=7), 1.14 (m, 18H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.3; $^{13}$C NMR ($CDCl_3$) $\delta$ 139.6, 128.3, 127.2, 80.1 (t, $^1J_{CP}$=150), 66.3, 63.3, 63.0, 53.3, 43.9, 40.9, 31.4, 25.6, 22.4, 16.4, 13.8; Anal. Calcd for $C_{24}H_{45}NO_7P_2$ (521.6): C 55.3, H 8.7, N 2.7, P 11.9. Found: C 55.0, H 8.8, N 2.6, P 11.7.

### 4.6. 3-Benzylamino-1-hexoxypropylene-1,1-bisphosphonic acid 12c

A solution of **10c** (0.15 g, 0.29 mmol) and bromotrimethylsilane (0.26 mL, 2 mmol) in $CH_2Cl_2$ (5 mL) was stirred under $N_2$ at room temperature for 15 h and then evaporated. The residue was dissolved in 5 mL of MeOH and evaporated to give quantitatively the acid **12c** as a viscous oil. $^1$H NMR ($CD_3OD$) $\delta$ 7.6–7.4 (m, 5H), 4.20 (s, 2H), 3.95 (t, 2H, $^3J_{HH}$=7), 3.43 (t, 2H, $^3J_{HH}$=7), 2.51 (tt, 2H, $^3J_{HH}$=7, $^3J_{HP}$=14), 1.68 (qt, 2H, $^3J_{HH}$=7), 1.15 (m, 6H), 0.85 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CD_3OD$) $\delta$ 19.6; $^{13}$C NMR ($CD_3OD$) $\delta$ 130.5, 128.7, 128.1, 76.7 (t, $^1J_{CP}$=145), 66.4, 50.3, 43.2 (t, $^3J_{CP}$=8), 31.5, 29.65, 28.0, 25.6, 22.5, 13.8; Anal. Calcd for $C_{16}H_{29}NO_7P_2$ (409.35): C 46.95, H 7.14, N 3.42, O 27.36, P 15.13. Found: C 47.0, H 7.2, N 3.5, P 14.9.

### 4.7. Tetraethyl 1-benzyloxy-3-hydroxypropylene-1,1-bisphosphonate 5f

A solution of alkene **3f** (0.43 g, 1 mmol) in $CH_2Cl_2$ (20 mL) was cooled to −78 °C. The effluent stream of an ozone generator was bubbled into the methylene chloride solution until the blue colour of unreacted ozone was noticeable. The reaction mixture was allowed to warm up to room temperature, and dry nitrogen was bubbled through it for 10 min. Borane–dimethyl sulfide complex (3.5 mmol) was added by syringe over several minutes, and the reaction mixture was allowed to stand at room temperature for 48 h. Aqueous 5% HCl (0.3 mL) was added, and the resulting mixture was vigorously stirred for 1 h. Solid $NaHCO_3$ was added until the aqueous layer was basic, and anhydrous $MgSO_4$ was added as drying agent. The reaction mixture was filtered and concentrated with a rotary evaporator to give the desired alcohol **5f** as a colourless oil. Yield: 76%; $^1$H NMR ($CDCl_3$) $\delta$ 7.14–7.39 (m, 5H), 4.92 (s, 2H), 4.11–4.34 (m, 8H), 3.94 (t, 2H, $^3J_{HH}$=7), 2.47 (tt, 2H, $^3J_{PH}$=15, $^3J_{HH}$=7), 1.34 (t, 6H, $^3J_{HH}$=7), 1.33 (t, 6H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.5; $^{13}$C NMR ($CDCl_3$) $\delta$ 137.0, 127.4, 126.9, 79.3, (t, $^1J_{CP}$=150 Hz), 67.9, 62.7, 51.1, 33.8, 15.6; Anal. Calcd for $C_{18}H_{32}O_8P_2$ (438.4): C 49.3, H 7.4, P 14.1. Found: C 49.1, H 7.5, P 14.0.

### 4.8. Tetraethyl 1-decoxy-4-hydroxybutylene-1,1-bisphosphonate 6d

To a solution of **3d** (2.2 g, 4.5 mmol) in dry THF (12 mL) cooled with an ice-water bath was added a 1 M solution of $BH_3$THF in THF (7.4 mL) under nitrogen. After stirring for 1.5 h, the reaction mixture was quenched with methanol followed by the addition of aqueous 3 M NaOH (2.5 mL) and 30% $H_2O_2$ (2.4 mL). The solution was heated at 50 °C for 1.5 h, then it was stirred at room temperature for 15 h. Aqueous saturated sodium chloride solution was added, and the product was extracted with diethyl ether and then chloroform. The extracts were combined, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure, leaving the desired alcohol **6d** as a colourless oil, which was used in the next step without further purification. $^1$H NMR ($CDCl_3$) $\delta$ 4.08–4.24 (m, 8H), 3.77 (t, 2H, $^3J_{HH}$=7), 3.65 (t, 2H, $^3J_{HH}$=7), 2.07–2.27 (m, 3H), 1.77–1.93 (m, 2H), 1.56 (qt, 2H, $^3J_{HH}$=7), 1.1–1.30 (m, 26H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.7; $^{13}$C NMR ($CDCl_3$) $\delta$ 80.7 (t, $^1J_{CP}$=151), 66.2, 63.2, 62.8, 62.6, 31.8, 30.1, 29.4, 29.2, 27.7, 26.7, 25.9, 22.5, 16.4, 14.0.

### 4.9. Tetraethyl 1-decoxy-4-[(methylsulfonyl)oxy]butylene-1,1-bisphosphonate 13d

To a solution of **6d** and $Et_3N$ (0.5 g, 5 mmol) in dry $CH_2Cl_2$ (20 mL) cooled with an ice-water bath was added dropwise a solution of $CH_3SO_2Cl$ (0.51 g, 4.5 mmol) in $CH_2Cl_2$ (10 mL). After stirring at room temperature for 2 h, the mixture was poured into $H_2O$ and extracted with $CH_2Cl_2$. The extract was dried over $MgSO_4$, filtered and evaporated to give **13d**, which is used in the next step without further purification. $^1$H NMR ($CDCl_3$) $\delta$ 4.09–4.34 (m, 10H), 3.77 (t, 2H, $^3J_{HH}$=7), 3.0 (s, 3H), 1.95–2.32 (m, 4H), 1.57 (qt, 2H, $^3J_{HH}$=7), 1.11–1.31 (m, 26H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.3.

### 4.10. Tetraethyl 4-azido-1-decoxybutylene-1,1-bisphosphonate 14d

To a solution of **13d** in anhydrous DMF (20 mL) was added $NaN_3$ (0.31 g, 4.5 mmol), and the mixture was stirred at room temperature for 6 h. After evaporation of the DMF under reduced pressure, the residue was dissolved in $CH_2Cl_2$, washed with $H_2O$, dried over $MgSO_4$, concentrated and purified by chromatography (silica, 2/1: ethyl acetate/hexane) to give 950 mg (40% overall yield) of **14d** as a colourless oil. $^1$H NMR ($CDCl_3$) $\delta$ 4.11–4.34 (m, 8H), 3.76 (t, 2H, $^3J_{HH}$=7), 3.3 (t, 2H, $^3J_{HH}$=7), 2.0–2.23 (m, 2H), 2.79–2.94 (m, 2H), 1.56 (qt, 2H, $^3J_{HH}$=7), 1.18–1.46 (m, 26H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.4; $^{13}$C NMR ($CDCl_3$) $\delta$ 80.5 (t, $^1J_{CP}$=150), 66.2, 63.2, 62.9, 45.9, 32.8, 30.7, 30.2, 29.3, 26.4, 23.5, 23.0, 16.4, 13.6; Anal. Calcd for $C_{22}H_{47}N_3O_7P_2$ (527.6): C 50.1, H 9.0, N 8.0, P 11.7. Found: C 49.8, H 9.1, N 8.1, P 11.6.

### 4.11. Tetraethyl 4-amino-1-decoxybutylene-1,1-bisphosphonate 15d

To a solution of **14d** (0.9 g, 1.7 mmol) in THF cooled to 0 °C was added $Ph_3P$ (0.44 g, 1.7 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Then, $H_2O$ (0.045 g, 2.5 mmol) was added and stirring was maintained for 16 h. THF was removed under reduced pressure and the crude product was diluted with a mixture 1/1 of diethyl ether and petroleum ether to precipitate $Ph_3P(O)$. After filtration, the solvents were removed in vacuo. The residue was partitioned between diethyl ether (60 mL) and 3 M HCl (20 mL). The organic layer was discarded and the aqueous layer was basified with 4 M NaOH (20 mL) at 0 °C. Then, the solution was extracted with $CH_2Cl_2$, dried over MgSO4, filtered and evaporated to give **15d** as a viscous oil. Yield: 78%; $^1$H NMR ($CDCl_3$) $\delta$ 4.1–4.3 (m, 8H), 3.75 (t, 1H, $^3J_{HH}$=7), 3.65 (t, 1H, $^3J_{HH}$=7), 2.9–3.15 (m, 2H), 2.38 (br s, 2H), 2.05–2.25 (m, 2H), 1.85–2.05 (m, 2H), 1.53 (qt, 1H, $^3J_{HH}$=7), 1.45 (qt, 1H, $^3J_{HH}$=7), 1.18–1.36 (m, 26H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 19.4, 19.0.

### 4.12. 4-Amino-1-decoxybutylene-1,1-bisphosphonic acid 16d

A solution of **15d** (1.7 mmol) and bromotrimethylsilane (1.6 mL, 12.2 mmol) in $CH_2Cl_2$ (20 mL) was stirred under $N_2$ at room temperature for 15 h and then evaporated. The residue was dissolved in 10 mL of MeOH and evaporated to give the crude acid **19b** as a viscous oil. Addition of $CH_2Cl_2$ gave a precipitate, which is filtered and dried in a desiccator. Product was re-crystallized from methanol to give a white powder. Yield: 80%;$^1$H NMR ($CD_3OD$) $\delta$ 3.90 (t, 2H, $^3J_{HH}$=7), 2.99 (t, 2H, $^3J_{HH}$=7), 2.23–2.1 (m, 2H), 2.04 (qt, 2H, $^3J_{HH}$=7), 1.62 (t, 2H, $^3J_{HH}$=7), 1.45–1.22 (m, 14H), 0.90 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CD_3OD$) $\delta$ 21.1; $^{13}$C NMR ($CD_3OD$) $\delta$ 79.8 (t, $^1J_{CP}$=145), 67.9, 41.1, 33.0, 31.5, 30.7, 30.4, 29.8, 27.0, 23.7, 23.4, 14.4; Anal. Calcd for $C_{14}H_{33}NO_7P_2$ (389.4): C 43.2, H 8.5, N 3.6, P 15.9. Found: C 43.1, H 8.6, N 3.5, P 15.8.

### 4.13. 3-Butoxy-3,3-bis(diethoxyphosphoryl)propanoic acid 7b

To a mixture of alkene **3b** (1 g, 2.5 mmol) and sodium periodate (2.19 g, 4.1 equiv) in 5 mL of carbon tetrachloride, 5 mL of acetonitrile and 7.5 mL of water was added 14 mg (5.5 mol %) of ruthenium trichloride hydrate. The mixture was then stirred vigorously for 24 h at room temperature. Then, 25 mL of $CH_2Cl_2$ was added and the mixture was filtered through a Celite pad, and the aqueous phase was extracted three times with $CH_2Cl_2$. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 0.95 g (90% yield) of the crude acid **7b** as a dark oil. $^1$H NMR ($CDCl_3$) $\delta$ 4.14–4.34 (m, 8H), 3.98 (t, 2H, $^3J_{HH}$=7), 3.17 (t, 2H, $^3J_{HP}$=15), 1.57 (qt, 2H, $^3J_{HH}$=7), 1.25–1.4 (m, 14H), 0.9 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 18.0; $^{13}$C NMR ($CDCl_3$) $\delta$ 168.7, 76.9 (t, $^1J_{CP}$=154), 66.7, 63.2, 36.3, 31.3, 18.0, 15.5, 12.9; Anal. Calcd for $C_{15}H_{32}O_9P_2$ (418.4): C 43.1, H 7.7, P 14.8. Found: C 42.9, H 7.8, P 14.6.

### 4.14. Tetraethyl 2-[(benzyloxycarbonyl)amino]-1-butoxyethylene-1,1-bisphosphonate 17b

Acid **7b** (0.95 g, 2.25 mmol) was refluxed in benzene (20 mL) with an equimolar mixture of diphenylphosphonic azide and

triethylamine for 1 h. Then, a slight excess of benzyl alcohol (2 mL) was added and the mixture was refluxed for 17 h. The mixture was concentrated in vacuo, diluted with $CH_2Cl_2$ (30 mL), washed five times with 20 mL of saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated. Then, the residue was purified by chromatography (silica, ethyl acetate) to give 0.9 g (76% yield) of **17b** as a colourless oil. $^1$H NMR ($CDCl_3$) $\delta$ 7.27–7.41 (m, 5H), 5.88 (t, 1H, $^3J_{HH}$=5), 5.1 (s, 2H), 4.11–4.32 (m, 8H), 3.89 (dt, 2H, $^3J_{HH}$=5, $^3J_{HP}$=13), 3.79 (t, 2H, $^3J_{HH}$=7), 1.50 (qt, 2H, $^3J_{HH}$=7), 1.20–1.41 (m, 14H), 0.87 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 17.9; $^{13}$C NMR ($CDCl_3$) $\delta$ 156.1, 136.7, 128.4, 128.0, 79.3 (t, $^1J_{CP}$=151), 66.5, 63.6, 41.2, 32.2, 19.0, 16.4, 13.8; Anal. Calcd for $C_{22}H_{39}NO_9P_2$ (523.5): C 50.5, H 7.5, N 2.7, P 11.8. Found: C 50.2, H 7.6, N 2.6, P 11.6.

### 4.15. Tetraethyl 2-amino-1-butoxyethylene-1,1-bisphosphonate 18b

A mixture of tetraethyl 2-[(benzyloxycarbonyl)amino]-1-butoxyethylene-1,1-bisphosphonate **17b** (360 mg, 0.65 mmol) and 10% Pd–C (30 mg) in absolute EtOH (15 mL) was stirred under a hydrogen atmosphere (1 atm) at room temperature for 15 h. After removal of the catalyst by filtration, the filtrate was evaporated to dryness in vacuo, to give quantitatively the amino compound. $^1$H NMR ($CDCl_3$) $\delta$ 5.07 (br s, 2H), 4.09–4.32 (m, 8H), 3.92 (t, 2H, $^3J_{HH}$=7), 3.43 (t, 2H, $^3J_{HP}$=13), 1.56 (qt, 2H, $^3J_{HH}$=7), 1.20–1.41 (m, 14H), 0.88 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CDCl_3$) $\delta$ 17.8; $^{13}$C NMR ($CDCl_3$) $\delta$ 77.8 (t, $^1J_{PC}$=148), 66.6, 62.7, 41.4, 31.2, 18.0, 15.4, 12.9; Anal. Calcd for $C_{14}H_{33}NO_7P_2$ (389.4): C 43.2, H 8.5, N 3.6, P 15.9. Found: C 43.0, H 8.7, N 3.5, P 15.8.

### 4.16. 2-Amino-1-butoxyethylene-1,1-bisphosphonic acid 19b

A solution of tetraethyl 2-amino-1-butoxyethylene-1,1-bisphosphonate **18b** (0.65 mmol) and bromotrimethylsilane (0.61 mL, 4.7 mmol) in $CH_2Cl_2$ (20 mL) was stirred under $N_2$ at room temperature for 15 h and then evaporated. The residue was dissolved in 10 mL of MeOH and evaporated to give the crude acid **19b** as a viscous oil. $^1$H NMR ($CD_3OD$) $\delta$ 4.1 (t, 2H, $^3J_{HH}$=7), 3.5 (m, 2H), 1.6 (qt, 2H, $^3J_{HH}$=7), 1.41 (st, 2H, $^3J_{HH}$=7), 0.9 (t, 3H, $^3J_{HH}$=7); $^{31}$P NMR ($CD_3OD$) $\delta$ 15.2; $^{13}$C NMR ($CD_3OD$) $\delta$ 76.1 (t, $^1J_{CP}$=142), 69.3, 43.2, 33.3, 19.8, 14.2; Anal. Calcd for $C_6H_{17}NO_7P_2$ (277.1): C 26.0, H 6.2, N 5.0, P 22.3. Found: C 25.8, H 6.3, N 4.8, P 22.1.

### 4.17. Tetraethyl 3,4-epoxy-1-methoxybutylene-1,1-bisphosphonate 8a

A mixture of alkene **3a** (3.58 g, 10 mmol) and 70% 3-chloroperoxybenzoic acid (3.15 g, 14 mmol) in $CH_2Cl_2$ (50 mL) was stirred for 2 days at room temperature. Aqueous 10% $Na_2SO_3$ was added and the organic phase was extracted, washed with satd aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated to give 3.7 g (100% yield) of **8a** as a colourless oil. $^1$H NMR ($CDCl_3$) $\delta$ 4.29–4.20 (m, 8H), 3.64 (s, 3H), 3.32 (m, 1H), 2.80 (t, 1H, $^3J_{HH}$=5), 2.63–2.45 (m, 1H), 2.58 (dd, 1H, $^3J_{HH}$=5, $^2J_{HH}$=3), 2.14–2.01 (m, 1H), 1.38–1.28 (m, 12H); $^{31}$P NMR ($CDCl_3$) $\delta$ 18.9, 18.6 (dd AB, $^2J_{PP}$=35); $^{13}$C NMR ($CDCl_3$) $\delta$ 78.6 (t, $^1J_{CP}$=151), 62.6, 62.3, 54.0, 47.3, 33.6, 15.6; Anal. Calcd for $C_{13}H_{28}O_8P_2$ (374.3): C 41.7, H 7.5, P 16.5. Found: C 41.5, H 7.6, P 16.4.

### 4.18. Tetraethyl 4-bromo-3-hydroxy-1-methoxybutylene-1,1-bisphosphonate 20a and diethyl 5-(bromomethyl)-2-ethoxy-3-methoxy-2-oxido-1,2-oxaphospholan-3-ylphosphonate 20′a

To a magnetically stirred solution of bromine (0.074 mL, 1.45 mmol) in anhydrous $CH_2Cl_2$ (25 mL), triphenylphosphine (0.38 g, 1.45 mmol) was added in one portion. The brown solution turned immediately to a pale yellow colour and then, tetraethyl 3,4-epoxy-1-methoxybutylene-1,1-bisphosphonate **8a** (0.5 g, 1.32 mmol) in a solution of $CH_2Cl_2$ (2 mL) was added also in one portion. After stirring for 15 min, the reaction mixture was poured into cold 1 N aq $NaHCO_3$ (100 mL) and extracted three times with $CH_2Cl_2$ (30 mL). The extracts were combined, dried and evaporated to give quantitatively a mixture of compound **20a** and $Ph_3PO$. The chromatography of this mixture on silica gel with ethyl acetate as eluent to eliminate $Ph_3PO$ gave 300 mg of a mixture of compounds **20a** and **20′a** in the ratio 10/90. Product **20′a** appeared as two diastereoisomers in the ratio 70/30. $^1$H NMR ($CDCl_3$) **20a** $\delta$ 4.35–4.29 (m, 1H), 4.29–4.20 (m, 8H), 3.66 (s, 3H), 3.46 (dd, 2H, $^2J_{HH}$=2, $^3J_{HH}$=5), 2.49–2.28 (m, 2H), 1.39 (t, 12H); $^{31}$P NMR ($CDCl_3$) **20a** $\delta$ 19.2, 19.6 (dd AB, $^2J_{PP}$=34); $^1$H NMR ($CDCl_3$) **20′a** $\delta$ 4.77–4.46 (m, 1H), 4.46–4.16 (m, 6H), 3.62 (s, 3H), 3.62–3.39 (m, 2H), 3.0–2.29 (m, 2H), 1.51–1.28 (m, 9H); $^{31}$P NMR ($CDCl_3$) **20′a** $\delta$ 34.3 (d, $^2J_{PP}$=51, diast 1), 32.7 (d, $^2J_{PP}$=48, diast 2), 18.0 (d, $^2J_{PP}$=48, diast 2), 17.4 (d, $^2J_{PP}$=51, diast 1).

### 4.19. 5-(Bromomethyl)-2-hydroxy-3-methoxy-2-oxido-1,2-oxaphospholan-3-ylphosphonic acid 21′a

To a mixture of **20a** and **20′a** (0.3 g) in anhydrous $CH_2Cl_2$ (15 mL) was added bromotrimethylsilane (1 mL). After stirring for 20 h, the solution was evaporated in vacuo and MeOH (1 mL) was added. After stirring for 15 min, the solution was evaporated again to give compound **21′a** in a quantitative yield as a viscous oil. $^1$H NMR ($CD_3OD$) $\delta$ 5.99 (s, 3H, OH), 4.64–4.46 (m, 1H), 3.68, 3.67 (2s, 3H), 3.67–3.37 (m, 2H), 3.03–2.39 (m, 2H); $^{31}$P NMR ($CD_3OD$) $\delta$ 34.9 (d, $^2J_{PP}$=46, diast 1), 33.9 (d, $^2J_{PP}$=45, diast 2), 15.9 (d, $^2J_{PP}$=45, diast 2), 15.1 (d, $^2J_{PP}$=46, diast 1); $^{13}$C NMR ($CD_3OD$) $\delta$ 77.5 (dd, $^1J_{CP}$=163.6, $J_{CP}$=127, diast 1), 77.0 (dd, $J_{CP}$=158, $J_{CP}$=127, diast 2), 75.8 (diast 2), 75.6 (diast 1), 56.6 (diast 2), 56.1 (diast 1), 38.9, 35.2 (diast 1), 34.5 (diast 2); Anal. Calcd for $C_5H_{11}BrO_7P_2$ (324.0): C 18.5, H 3.4, Br 24.6, P 19.1. Found: C 18.3, H 3.6, Br 24.4, P 19.2.

### 4.20. Hydrogen 2-hydroxy-3-methoxy-2-oxido-5-[(trimethylammonio)methyl]-1,2oxaphospholan-3-ylphosphonate 22′a

A mixture of **21′a** (0.2 g) and trimethylamine solution 40% in water (4 mL) was stirred for 5 h. Then, the solution was evaporated to give quantitatively compound **22′a** as a viscous oil. $^1$H NMR ($CD_3OD$) $\delta$ 2.32 (m, 1H), 2.66 (m, 1H), 2.91 (s, 27H), 3.61 (m, 5H), 4.46 (m, 1H), 4.80 (br s, OH); $^{31}$P NMR ($CD_3OD$) $\delta$ 37.2 ($\delta$, $J_{PP}$=30, diast 1), 35.2 (d, $J_{PP}$=23, diast 2), 12.3 (d, $J_{PP}$=23, diast 2), 10.6 (d, $J_{PP}$=30, diast 1); $^{13}$C NMR ($CD_3OD$) $\delta$ 76.5 (t, $J_{CP}$=148), 73.4, 71.7, 64.3, 45.2, 45.0, 37.9; Anal. Calcd for $C_{14}H_{37}N_3O_7P_2$ (421.4): C 39.9, H 8.9, N 10.0, P 14.7. Found: C 39.1, H 8.8, N 9.9, P 14.9.

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