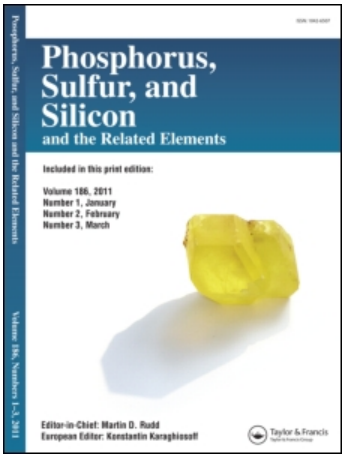

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PREPARATION OF TETRAETHYL BUT-3-ENYLIDENE-1,1-BISPHOSPHONATE AND STUDY OF ITS REACTIVITY AS A SYNTHON OF TETRAETHYL 3,4-DIAMINOBUTYLIDENE-1,1-BISPHOSPHONATE

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PREPARATION OF TETRAETHYL BUT-3-ENYLIDENE-1,1-BISPHOSPHONATE AND STUDY OF ITS REACTIVITY AS A SYNTHON OF TETRAETHYL 3,4-DIAMINOBUTYLIDENE-1,1-BISPHOSPHONATE

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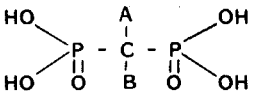
Key words: *Gem*-bisphosphonates; vic-diamine; 3,4-diaminobutylidene-1,1-bisphosphonates; synthesis of

We describe a new preparation of tetraethyl but-3-enylidene-1,1-bisphosphonate **7**. This preparation requires the phosphonylation of diethyl but-3-enyl-1-phosphonate which is obtained by the Michaelis-Becker reaction.

Various methods of vic-diamination are studied to obtain tetraethyl 3,4-diaminobutylidene-1,1-bisphosphonate **11**. The best approach consists in preparing the diazide by action of sodium azide, in the presence of manganese (III) acetate, and by reducing it in solution in tetrahydrofurane by triphenylphosphine in the presence of water. Hydrolysis by concentrated hydrochloric acid produces 3,4-diaminobutylidene1,1-bisphosphonic acid **3**.

INTRODUCTION

The recent interest in the synthesis of *gem*-bisphosphonic acids **1** is particularly due to the biological properties of some of them. Those properties result partly from their structural analogy to pyrophosphoric acid **2** and they are potentialized by a much larger hydrolytic stability. This stability is due to the presence of a P—C—P bond which resists the hydrolysis whereas the acid anhydride function existing at the stage of the pyrophosphoric bridge P—O—P does not.[1]



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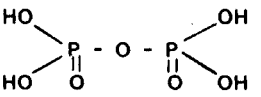


2

A = H, alkyl with a possible functional group, OR, SR, SO_2R, Cl...
B = H, OH, Cl, NH_2, NHR, NR_2...

†Correspondence and reprints.

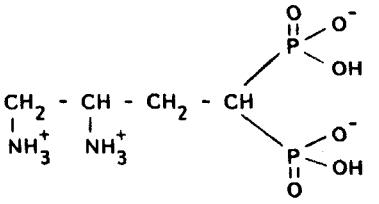
Thanks to this structural analogy and to this increased stability *gem*-bisphosphonic acids absorb to bone tissue and have an effect on the bone metabolism.[2]

Thus, they can be used in bone scintigraphy,[3] for the treatment of PAGET's disease,[4] of rheumatoid arthritis and for the preventive treatment of osteoporosis.[5] More recently, the properties of 3-amino-1-hydroxypropylidene-1,1-bisphosphonate in hypercalcemia of malignant tumors have been reported.[6]

Moreover, the significance of primary vic-diamine function for synthesis chemistry as well as for therapeutics is well known.[7] Thus, vic-diamine analogues of cisplatine have recently undergone clinical trials for the treatment of some cancers.[8]

The chemical and also pharmacological potential of these two functions encouraged us to combine them into a single molecule.

Therefore, we present in this report our various attempts to prepare the 3,4-diaminobutylidene-1,1-bisphosphonic acid **3**.

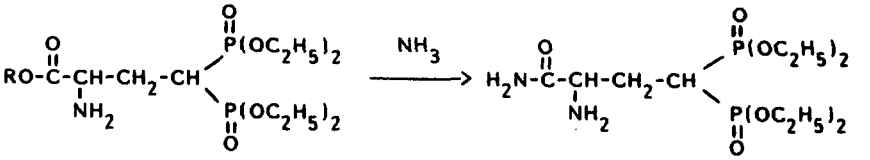


3

RESULTS AND DISCUSSION

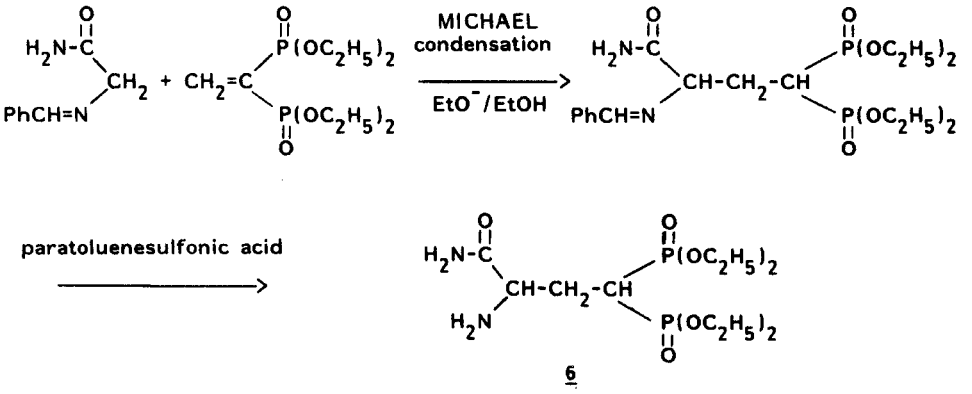
The initially tested synthetical approach led us to study the nucleophilic addition to tetraethyl vinylidenebisphosphonate of entities which are liable to lead later to the vic-diamine system.[9a]

Thus, having described the synthesis of the tetraethyl 3-amino-3-ethoxycarbonylpropylidene-1,1-bisphosphonate **4** and the tetraethyl 3-amino-3-methoxycarbonylpropylidene-1,1-bisphosphonate **5**[9a,b,c] we were able to prepare the tetraethyl 3-amino-3-carbamoylpropylidene-1,1-bisphosphonate **6** by ammonolysis according to:



5 R=CH_3 4 R=C_2H_5 6

We were also able to obtain it more directly according to a process derived from the Michaël addition of N-benzylideneglycinamide carbanion to tetraethyl vinylidenebisphosphonate[9a]:



6

Unfortunately all our attempts to reduce the amide function by borane-dimethyl sulfide failed in getting a selective reaction.[9a] We recorded ^{31}P NMR spectra on samples taken from the reaction medium after hydrolysis of the boron-nitrogen intermediates. Apart from some peaks of low intensity, the zone between 19 and 22 ppm presents a great number of various peaks. It seems that those peaks cannot be assigned to multiplets due to couplings. They may correspond to several compounds. Besides, the thin layer chromatography (ethyl acetate/ethanol 50/50) indicates various phosphorus products (Dittmer reagent) which we did not try to isolate.

This mixture was hydrolysed with HCl in order to obtain the phosphonic acids. The ^{31}P NMR spectra indicates the presence of a phosphonic derivative (0–2 ppm) which would come from the break down of the *gem*-bisphosphonic structure. One singlet of average intensity at 20 ppm could correspond to a bisphosphonic by-product. A peak of higher intensity at 21 ppm was then identified as 3,4-diaminobutylidene-1,1-bisphosphonic acid as the dihydrochloride salt **12** obtained selectively by a reaction which will be described in this paper. Finally, a triplet at 30 ppm is seen in the zone where the aliphatic monophosphonates are usually located. Moreover, the ^{13}C NMR spectra indicates also the presence of a product containing a carboxylic acid function coming from the hydrolysis of the non-reduced amid function.

Considering this lack of selectivity we tried other methods of reduction by sodium borohydride but we did not get better results.[9a] These observations led us to think of another method of synthesis requiring the reactivity of tetraethyl but-3-enylidene-1,1-bisphosphonate **7**.

A certain number of general methods of vic-diamination are based on the nucleophilic power of the ethylenic double bond. We shall describe below our attempts in this direction.

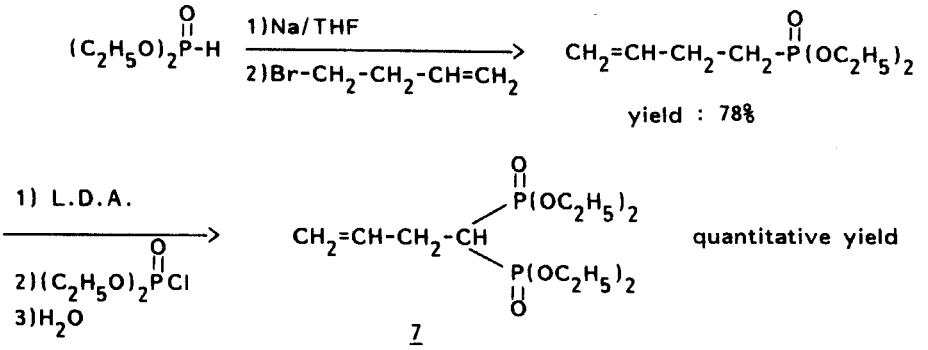
Synthesis of Tetraethyl But-3-enylidene-1,1-bisphosphonate **7**

The preparation of this molecule, which was initially described by C. R. Degenhardt[10] by direct alkylation of the tetraethyl methylenebisphosphonate carbanion with

allylbromide gives a modest 28% yield which might be explained by the competition between monoalkylation and dialkylation.

It is the reason why we investigated a further selective method hopefully leading to a better yield.

This aim was achieved by using the reaction route shown in Scheme I:

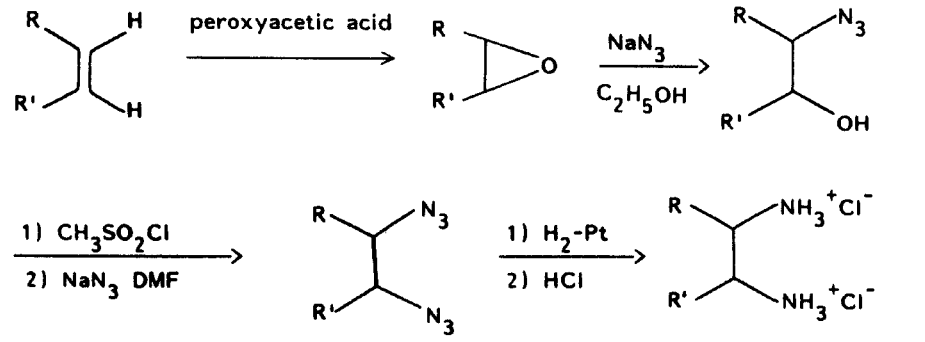


SCHEME I

Using this molecule we investigated several methods of syntheses of vicinal diamines, described in the literature, in order to define the best way.

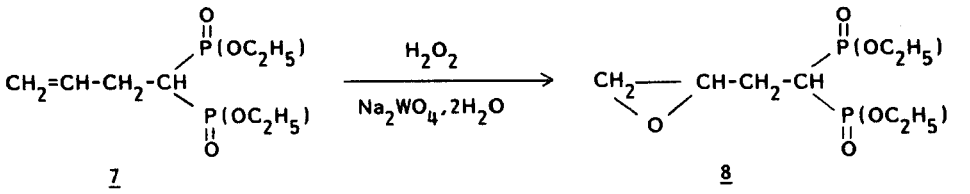
Study of G. Swift and D. Swern Reaction[11]*: Epoxidation and Ring Opening of Tetraethyl 3,4-Epoxybutylidene-1,1-bisphosphonate* **8** *by Sodium Azide*

This synthetical approach is summarized in Scheme II:



SCHEME II

We prepared initially the tetraethyl 3,4-epoxybutylidene-1,1-bisphosphonate **8** by action of hydrogen peroxide on compound **7** in the presence of sodium tungstate according to a protocol described by G. B. Payne and Colleagues[12] and adapted to the phosphonate series in our laboratory.[13]

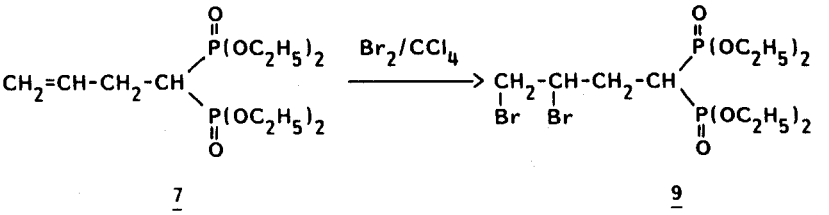


7 8

The ring opening of the epoxide **8** by sodium azide was attempted in refluxing 80% ethanol in the presence of ammonium chloride, according to the G. Swift and D. Swern process.[11] However, this did not lead to a uniform product.

Study of the M. S. Okamoto and E. Kent Barefield Reaction[14]*: Action of Sodium Azide on Tetraethyl 3,4-Dibromobutylidene-1,1-bisphosphonate* **9**

The tetraethyl 3,4-dibromobutylidene-1,1-bisphosphonate **9** was prepared by the electrophilic addition of bromine to the bisphosphonic alkene **7** in solution in carbon tetrachloride:



7 9

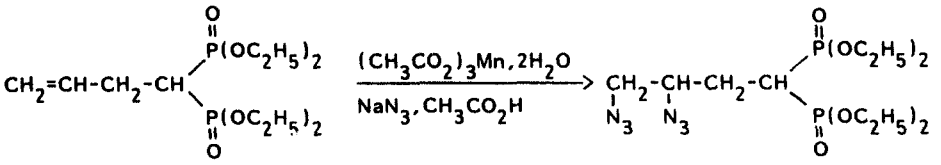
This compound in solution in DMSO was heated in the presence of sodium azide (two equivalents) at 70°C. The spectra indicated that in addition to the desired product many other compounds were produced also. Therefore this reaction was not pursued further.

It seemed necessary to study another way to vicinal diamines liable to lead to tetraethyl 3,4-diaminobutylidene-1,1-bisphosphonate **11**, without side reactions.

Study of the W. E. Fristad and Colleagues Reaction[15]*; Action of Sodium Azide on But-3-enylidene-1,1-bisphosphonate* **7** *in the Presence of Manganese* (**III**) *acetate*

According to this method, the γ,δ-ethylenic bisphosphonate **7** was treated in glacial acetic acid solution (0.4 mol/l) with sodium azide (15 equivalents) and manganese (III) acetate (3 equivalents); heating of this mixture to 98°C led to a change of colour, which is typical to manganese (III) reduction, and to the diazide **10** formation observed in thin layer chromatography (ethyl acetate/ethanol 95/15).

Under these conditions no degradation reaction was observed and the tetraethyl 3,4-diazidobutylidene-1,1-bisphosphonate **10** could be isolated with a good yield (69%) after extraction and chromatography on silica gel column.



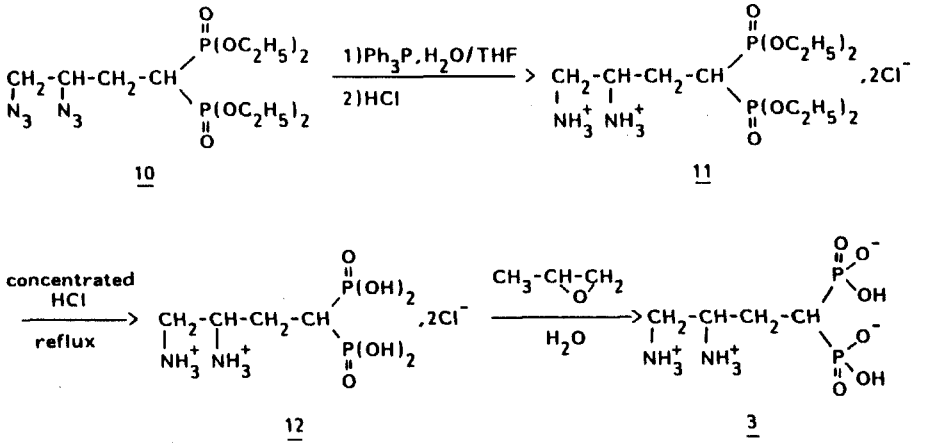
7 10

Reduction of Azide Functions and Hydrolysis of Phosphonic Esters

To reduce the diazide **10** into diamine **11**, we chose the simple, efficient and selective Staudinger process as modified by R. Carrié.[16]

In tetrahydrofuran, treatment of compound **10** by triphenylphosphine (2 equivalents) and water (3 equivalents) led to tetraethyl 3,4-diaminobutylidene-1,1-bisphosphonate **11**, isolated as the dihydrochloride salt (Scheme III).

The hydrolysis of phosphonic ester functions was performed in concentrated hydrochloric acid under reflux for one night. The action of an excess propylene oxide on an aqueous solution of the dihydrochloride salt **12** leads to the formation of bizwitterion **3**, insoluble in water (Scheme III).



10 11

12 3

SCHEME III

CONCLUSION

In this work, we show that tetraethyl but-3-enylidene-1,1-bisphosphonate **7**, obtained by a phosphonylation reaction of diethyl but-3-enyl-1-phosphonate can be easily transformed into a vicinal diazide **10** by the direct reaction of sodium azide on **7** in the presence of manganese (III) acetate.

The reduction of **10** by triphenylphosphine in the presence of water, followed by hydrolysis with concentrated hydrochloric acid produces the 3,4-diaminobutylidene-1,1-bisphosphonic acid **3** with an overall 48% yield starting from the γ,δ-ethylenic monophosphonate.

EXPERIMENTAL

Diethylphosphite was distilled and all other reactives are standard commercial materials (purchased from Aldrich Chemical Co., Janssen-Chimica, Merck, Prolabo). The solvents were distilled for reactions and for chromatography. Tetrahydrofuran was dried on a molecular sieve 4 Å. The purity of products and the reaction progress were monitored on CCM plates ($60F_{254}$ Merck) and liquid chromatography was carried out on a silica gel column (Merck 60, 70–230 mesh).

^{31}P NMR spectra were recorded on a JEOL JNM-FX 100 FT spectrometer; The chemical shifts are reported in ppm with reference to phosphoric acid (85% H_3PO_4 in heavy water). ^1H and ^{13}C NMR spectra were recorded on JEOL C60 HL (*), JEOL PMX 60_{SI} (*), JEOL JNM-FX 100 FT (■) and BRUCKER AC 300 (♦) spectrometers; the chemical shifts are reported in ppm with reference to TMS (tetramethylsilane) in organic solvent ($CDCl_3$) or with reference to TMPS (3-trimethylsilylperdeuteropropanoic acid, sodium salt). Coupling constants J are reported in Hertz.

IR spectra were achieved on a PERKIN-ELMER 297 and PYE UNICAM SP2000 spectrometers between KBr and NaCl slides or in KBr tabloids; The waves numbers are reported in cm^{-1}.

Mass spectra were obtained on a HEWLETT-PACKARD 5995 apparatus (direct introduction, electron impact).

Microanalysis were carried out at the "Service Central d'Analyse du C.N.R.S."

Diethyl but-3-enyl-1-phosphonate. Under a dry nitrogen atmosphere 52.56 g (0.38 mole) of diethylphosphite dissolved in THF (75 ml) is added dropwise to 8.75 g (0.38 mole) of sodium in THF (200 ml) and the mixture is warmed to 40–60°C. Then 44.36 g (0.33 mole) of 4-bromo-but-1-ene is added at room temperature and the mixture refluxed for two hours. After evaporation of THF, the product is dissolved in water (70 ml) and extracted twice with CH_2Cl_2 (250 and 100 ml); the two organic layers are combined and washed with a saturated aqueous NaCl solution (70 ml) then dried (Na_2SO_4). The solvent is evaporated under vacuum and the crude product is purified by vacuum distillation to yield 48 g (78%) of diethyl but-3-enyl-1-phosphonate, $C_8H_{17}O_3P$, (MW = 192.02) b.p. 68°C/0.05 mmHg

NMR ($CDCl_3$) ^{31}P: 31.0
^1H(*): 1.32 (t, 6H, CH_3); 1.6–2.7 (m, 4H, CH_2—CH_2); 4.1 (m, 4H, CH_2—O, $^3J_{H-H}$ = $^3J_{H-P}$ = 7.5); 4.85–5.25 (m, 2H, CH=C$\underline{H}_2$); 5.5–6.3 (m, 1H, C$\underline{H}$ = CH_2).
IR: 1650 ($\nu_{C=C}$); 1250 ($\nu_{P=O}$); 1030 (ν_{P-O-C}); 970 and 920 (γ_{C-H}).

Tetraethyl but-3-enylidene-1,1-bisphosphonate **7**. Under a dry nitrogen atmosphere 195 ml (0.48 mole) of n-butyllithium (2.5 M in hexane) is added to 52.43 g (0.52 mole) of diisopropylamine in solution in 300 ml of THF and previously cooled to −70°C. 47.0 g (0.244 mole) of diethyl but-3-enyl-1-phosphonate is introduced into the mixture and then 55.59 g (0.31 mole) of diethyl chlorophosphate is added at −70°C. After 40 min the solution is allowed to warm to room temperature and poured into 250 ml of cooled distilled water. After extraction with CH_2Cl_2 (3 × 400 ml), the combined organic layers are washed with a saturated aqueous NaCl solution (180 ml) and dried over Na_2SO_4. After evaporation of the solvent under vacuum, there is obtained 80 g of **7** (≈100%) as a yellow oil pure enough to be used in the following manipulations.

$C_{12}H_{26}O_6P_2$, MW = 328.00

	C	H	P
calc.:	43.94	7.92	18.88%
found:	43.71	8.05	18.49%

NMR ($CDCl_3$) ^{31}P: 22.7
^1H(♦): 1.34 (t, 12H, CH_3); 2.38 (tt, 1H, CH—P, $^2J_{H-P}$ = 23.8); 2.6–2.77 (m, 2H, CH_2); 4.10 (m, 8H, CH_2—O, $^3J_{H-H}$ = $^3J_{H-P}$ = 7.5); 5.04–5.13 (2dd, 2H, —CH=C$\underline{H}_2$, $^2J_{H-Hgem}$ = 1.6, $^3J_{H-Hcis}$ = 10, $^3J_{H-Htrans}$ = 16.9); 5.96 (ddt, 1H, C$\underline{H}$=CH_2).
^{13}C(■): 15.6 (d, CH_3, $^3J_{C-P}$ = 6.1); 29.1 (t, CH_2, $^2J_{C-P}$ = 4.5); 36.3 (t, C$\underline{H}$—P, $^1J_{C-P}$ = 133); 61.5 and 61.8 (2d, CH_2—O, $^2J_{C-P}$ = 3); 115.6 (s, CH=C$\underline{H}_2$); 135 (t, C$\underline{H}$=CH_2), $^3J_{C-P}$ = 7.6).
IR: 1660 ($\nu_{C=C}$); 1260 ($\nu_{P=O}$); 1040 (ν_{P-O-C}); 970 and 910 (γ_{C-H}).

MS m/e (relative intensities ≥ 25): 328 (M^+, 5); 191 (100); 163 (25); 135 (46).

Tetraethyl 3,4-epoxybutylidene-1,1-bisphosphonate **8**. 4.4 g (0.013 mole) of $Na_2WO_4,2H_2O$ is dissolved in 30% hydrogen peroxide (150 ml). The solution is warmed to 50°C and 24.0 g (0.073 mole) of compound **7** is added dropwise. The reaction mixture is kept at this temperature. The progress of the reaction can be monitored by ^{31}P NMR or by TLC until it is complete (12 h – 24 h). If the solution becomes colourless and if the reaction is incomplete, hydrogen peroxide and catalyst are added. After cooling the product is extracted with CH_2Cl_2 (4 × 180 ml). The combined organic layers are washed with a 10% sodium

sulfite solution (3 × 80 ml) in order to destroy the peroxides, then with saturated NaCl solution (80 ml). These are dried over Na_2SO_4 and the solvent is evaporated under vacuum to yield 18 g (70%) product **8** as a pale-yellow oil.

$C_{12}H_{26}O_7P_2$, MW = 343.99, Rf = 0,4 (ethyl acetate/ethanol 80/20)

	C	H	P
calc.:	41.89	7.56	18.01%
found:	42.04	7.72	17.41%

NMR ($CDCl_3$) ^{31}P: 22.31; 22.4

^1H(♦): 1.34 (t, 12H, CH_3); 2.0–2.2 (m, 2H, $C\underline{H}_2$—CH—P); 2.45–2.8 (m, 3H, CH—P and CH—$C\underline{H}_2$); 3.2–3.3 (m, 1H, $C\underline{H}$—CH_2); 4.2 (m, 8H, CH_2—O, $^3J_{H-H}$ = $^3J_{H-P}$ = 7).

^{13}C(■): 15.83 (d, CH_3, $^3J_{C-P}$ = 6.1); 28.7 (t, $\underline{C}H_2$—CH—P, $^2J_{C-P}$ = 4.5); 33.56 (t, CH—P, $^1J_{C-P}$ = 134.2); 47.7 (s, CH—$\underline{C}H_2$); 50.16 (dd, $C\underline{H}$—CH_2, $^3J_{C-P}$ = 6.1 and 10.6); 62.04 and 62.25 (2d, CH_2O, $^2J_{C-P}$ = 4.5).

IR: 1260 ($\nu_{P=O}$); 1040 (ν_{P-O-C}); 830 (ν_{C-C}).

MS m/e (relative intensities ≥ 44): 344 (M^+, 3); 301 (44); 215 (52); 207 (87); 201 (52); 165 (92); 155 (61); 137 (53); 135 (41); 127 (45); 121 (52); 109 (100).

Tetraethyl 3,4-dibromobutylidene-1,1-bisphosphonate **9**. 12.0 g (0.036 mole) of γ,δ-ethylenic bisphosphonate **7** is dissolved in 12 ml of dry CCl_4. 1.95 ml (0.039 mole) of bromine dissolved in 7 ml of CCl_4 is added dropwise keeping the temperature at 0–5°C. A few minutes after the end of the addition (5–10 min) the solvent is evaporated under vacuum and the residue is dissolved again in 150 ml of CCl_4; the organic layer is washed with water (3 × 75 ml) to remove the by-products then dried over Na_2SO_4 and the solvent is evaporated to yield 12.6 g (72%) of product **9**.

$C_{12}H_{26}Br_2O_6P_2$, MW = 487.8

	C	H	Br	P
calc.:	29.54	5.33	32.76	12.69%
found:	29.78	5.21	32.39	12.35%

NMR ($CDCl_3$) ^{31}P: 21.8; 21.7

^1H(♦): 1.36 and 1.37 (2t, 12H, CH_3); 2.1–2.33 (m, 1H, CH—P); 2.68–2.85 (m, 2H, CH_2); 3.64 and 3.91 (2dd, 2H, CH_2—Br, $^2J_{H-H}$ = 10.4, $^3J_{H-H}$ = 4.1 and 9.6); 4.13–4.28 (m, 8H, CH_2—O); 4.62–4.69 (m, 1H, CHBr).

^{13}C(■): 16.0 (d, CH_3, $^3J_{C-P}$ = 6.1); 33.0 (t, CH_2, $^2J_{C-P}$ = 4.5); 35.0 (t, CH—P, $^1J_{C-P}$ = 133.5); 35.9 (s, CH_2Br); 51.3 (t, CHBr, $^3J_{C-P}$ = 7.6); 62.37 and 62.62 (2d, CH_2—O, $^2J_{C-P}$ = 6.1);

IR: 1260 ($\nu_{P=O}$); 1040 (ν_{P-O-C}); 580 (ν_{C-Br}).

MS m/e (relative intensities ≥ 34): 407 (96); 409 (95); 301 (34); 299 (70); 271 (48); 243 (55); 215 (100); 197 (43); 191 (65); 163 (38); 165 (37); 135 (91); 133 (39); 117 (36); 110 (54); 109 (41); 108 (55).

Tetraethyl 3,4-diazidobutylidene-1,1-bisphosphonate **10**. Under nitrogen, 3.14 g (9.6 mmole) of ethylenic bisphosphonate **7**, 8.92 g (0.137 mole) of sodium azide and 7.72 g (0.029 mole) of manganese (III) acetate are introduced into 25 ml of glacial acetic acid and the mixture is heated to 98°C. After 20–40 min, the colour of the reaction mixture lightens from dark brown to light brown and the end of the reaction is observed by TLC. Once cooled to room temperature, 400 ml of water is added and the product is extracted with CH_2Cl_2 (4 × 50 ml). The combined extracts are washed with saturated bicarbonate solution (50 ml) then dried over Na_2SO_4 and the solvent is evaporated under vacuum. The crude product is chromatographed on a silica gel column (ethyl acetate then ethyl acetate/ethanol 95/5); 2.7 g (69%) of pure compound **10** are isolated as a yellow oil.

$C_{12}H_{26}N_6O_6P_2$, MW = 412, Rf = 0.25 (ethyl acetate/ethanol 95/5)

	C	H	N
calc.:	34.98	6.31	20.39%
found:	35.15	6.50	19.98%

NMR ($CDCl_3$) ^{31}P: 22.2; 22.46

^1H(♦): 1.37 and 1.35 (2t, 12H, CH_3); 1.91–2.09 (m, 2H, CH_2); 2.5–2.7 (m, 1H, CH—P); 3.37 and 3.49 (2dd ABX, 2H, CH_2N_3, $^2J_{H-H}$ = 12.7, $^3J_{H-H}$ = 3.2 and 7.9); 3.9–4.0 (m, 1H, CH—N_3); 4.2 (m, 8H, $^3J_{H-H}$ = $^3J_{H-P}$ = 7).

$^{13}C(\blacklozenge)$: 15.6 and 15.54 (2d, CH_3, $^3J_{C-P}$ = 5.9); 27.5 (t, CH_2, $^2J_{C-P}$ = 4.5); 32.7 (t, CH—P, $^1J_{C-P}$ = 133.5); 54.2 (s, CH_2—N_3); 59.6 (dd, CH—N_3, $^3J_{C-P}$ = 8.6 and 11.5); 61.89 and 61.92 (2d, CH_2O, $^2J_{C-P}$ = 7).

IR: 2100 (νN_3); 1260 ($\nu_{P=O}$); 1040 (ν_{P-O-C}).

MS m/e (relative intensities ≥ 23): 413 (M + 1,1); 370 (M—N_3,5); 328 (44); 300 (23); 272 (33); 244 (49); 216 (84); 189 (70); 165 (83); 137 (40); 134 (75); 109 (100).

Tetraethyl 3,4-diaminobutylidene-1,1-bisphosphonate **11**. 3.43 g (12.8 mmole) of triethylphosphine is added to a solution of 2.64 g (6.4 mmole) of diazidobisphosphonate **10** by cooling with a cold water bath; N_2 evolution is observed. Then 0.39 ml (21.6 mmole) of distilled water is added and the mixture is stirred during about 15 hours at room temperature. The THF is eliminated under vacuum and 10 ml of water, then 16 ml of 1 N hydrochloric acid is added; the aqueous layer is washed with benzene then evaporated under vacuum. Compound **11** is obtained as a dihydrochloride salt with a quantitative yield as a hygroscopic pale-yellow solid. If the product is not pure enough it can be dissolved in $CHCl_3$ and extracted with water.

$C_{12}H_{30}N_2O_6P_2$, 2HCl; M = 432.9

	C	H	N
calc.:	33.29	7.39	6.47%
found:	33.05	7.28	6.13%

NMR(D_2O) ^{31}P: 25.1

$^1H(\blacklozenge)$: 1.37 (t, 12H, CH_3); 2.35 (m, 2H, CH_2, $^3J_{H-P}$ = 16); 3.14 (tt, 1H, CH—P, $^1J_{H-P}$ = 24.5); 3.43 and 3.36 (2dd ABX, 2H, $^2J_{H-H}$ = 14.2, $^3J_{H-H}$ = 5 and 7.1); 3.94 (m, 1H, CH—NH_2); 4.27 (m, 8H, CH_2O, $^3J_{H-H}$ = $^3J_{H-P}$ = 7.2).

$^{13}C(\blacklozenge)$: 18.8 (d, CH_3, $^3J_{C-P}$ = 5.5); 29.1 (t, CH_2, $^2J_{C-P}$ = 4.5); 34.4 (t, CH—P, $^1J_{C-P}$ = 135); 43.6 (s, CH_2NH_2); 51.6 (t, $CHNH_2$, $^3J_{C-P}$ = 7.5); 67.66 and 67.76 (2d, CH_2O, $^2J_{C-P}$ = 7.1).

IR: 3600–2400 (ν_{N-H}); 1540 and 1650 (δ_{N-H}); 1240 ($\nu_{P=O}$); 1040 (ν_{P-O-C}).

3,4-Diaminobutylidene-1,1-bisphosphonic acid **3**. 2.66 g (6.14 mmole) of diaminobisphosphonate **11** is dissolved in 20 ml of concentrated hydrochloric acid and the mixture is heated under reflux for 20 h. Then the solution is decolorized with activated charcoal, then filtrated and concentrated.

A large excess propylene oxide (13 ml, 0.18 mole) is slowly added to this solution which is initially cooled down to 10°C. A white precipitate is formed and stirring is continued during 12 hours. After addition of ethanol (25 ml), the solid is filtrated, washed with ethanol and ether then dried under vacuum at 40°C to yield 1.37 g (90%) of compound **3**.

$C_4H_{14}N_2O_6P_2$, MW = 247.92

	C	H	N
calc.:	19.37	5.64	11.29%
found:	19.33	6.08	10.51%

NMR (D_2O, after addition of NaOH, pH = 10.9).

^{31}P: 22.0

$^1H(\blacklozenge)$: 1.76–2.15 (m, 3H, CH—CH_2); 2.83 and 2.71 (2dd, ABX, 2H, CH_2NH_2, $^2J_{H-H}$ = 13.41, $^3J_{H-H}$ = 5 and 7); 3.21–3.35 (m, 1H, CH—NH_2)

$^{13}C(\blacklozenge)$: 33.35 (CH_2); 41.4 (t, CH—P, $^1J_{C-P}$ = 119); 47.4 (CH_2—NH_2); 55.2 (CH—NH_2).

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