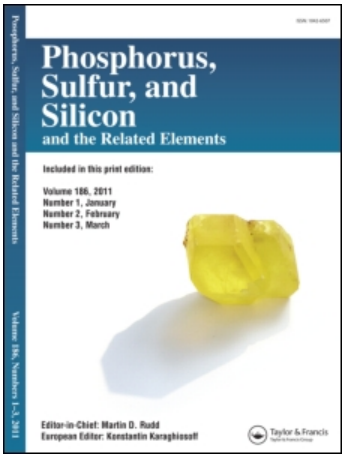


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# SYNTHESIS OF SUBSTRATE ANALOGUES AND INHIBITORS FOR THE PHOSPHOGLYCERATE MUTASE ENZYME

P. De Macedo Puyau[a]; J. J. Perie[a]
[a] Groupe de Chimie Organique Biologique, UMR CNRS 5623-Bt. IIRI-Université, TOULOUSE, Cedex

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# SYNTHESIS OF SUBSTRATE ANALOGUES AND INHIBITORS FOR THE PHOSPHOGLYCERATE MUTASE ENZYME

P. DE MACEDO PUYAU and J. J. PERIE

*Groupe de Chimie Organique Biologique, UMR CNRS 5623-Bât. IIR1-Université Paul Sabatier-118 Route de Narbonne-31062 TOULOUSE Cedex*

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Several substrate analogues of the title enzyme were synthesized as well as with possible irreversible inhibitors, analogues of phosphoglycolate, the cofactor for this enzyme. The main routes involved an Arbuzov type reaction on functionalized halides, a reaction significantly improved by a sonication procedure and reaction of the diethylphosphite anion on tosylates. Phosphorylated epoxides were obtained by quantitative oxidation of conjugate double bonds using DMDO. Preliminary assays indicated a promising activity in some of these compounds.

*Keywords:* phosphonates; inhibitors; phosphoglycerate Mutase; Arbuzov; DMDO

*Symbols:* PGM: phosphoglycerate mutase, 1,3-diPGA: 1,3-diphosphoglycerate, 2-PGA: 2-phosphoglycerate, 3-PGA: 3-phosphoglycerate, 2,3-diPGA: 2,3-diphosphoglycerate, PG: phosphoglycolate, DMDO: dimethyldioxirane, m-CPBA: meta-chloroperbenzoic acid

## INTRODUCTION

In the search for inhibitors of glycolytic enzymes, both for mechanistic purposes and as well as for the design of biologically active compounds,[1–3] our interested was focused on the enzyme phosphoglycerate mutase for several reasons:

- this enzyme, which involves four different substrates and cofactors has a rather complicated mechanism which corresponds to three different activities: synthase for the conversion of 1,3-diPGA to 2,3-diPGA, phosphatase for the conversion of 2,3-diPGA to 3-PGA and mutase for the interconversion of 3-PGA to 2-PGA.[4] Although some features are clearly established, based on the characterization of a phosphoenzyme intermediate[5] and also

on site-directed mutagenesis experiments,[6] many aspects remain to be more clearly understood. Significant progress in this understanding should come from the x-ray analysis of a complex formed between a substrate analogue and the enzyme. So far, only the x-ray structure of the yeast enzyme has been obtained[7] and low resolution of it does not allow the rational design of possibly active compounds. Substrate analogues are therefore needed for such cocrystallization experiments;

- one of the products and substrates of the reactions catalyzed by PGM, 2,3-diPGA is an effector of oxyhemoglobin which controls the availability of oxygen in the muscles.[8] Defect of this effector is responsible for a disease known as ischemia.[9] A possible route for therapy in this disease may come from the specific blocking of the phosphatase activity. This might be made possible by the fact that this phosphatase activity is mediated by a specific cofactor, phosphoglycolate[10] which binds in the erythrocyte PGM in the vicinity of a residue cystein (cystein 22).[11] Phosphoglycolate analogues, bearing a reactive group towards this cystein (an epoxide or an $\alpha$-enone, as successfully developed for another active-thiol enzyme, glyceraldehyde-phosphate-dehydrogenase[12]) were therefore considered as being of interest.

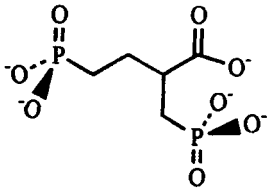
Only a few inhibitors have been designed for PGM: this includes non specific polyanionic compounds such as tartrate, citrate, polycarboxyl or polyphosphate groups bearing compounds, such as benzene hexa-carboxylate or inositol-hex-aphosphate, these compounds interacting with arginin residues close to the active site or lysil residues of the C terminal part.[4,13] Other phosphonate inhibitors analogues of 3-PGA and 2,3-diPGA[14,15] have also been described with vanadates,[16] in the latter as a mimic of the pentacovalent structure of the forming or collapsing phospho-enzyme intermediate.

Based on different reactions described for the synthesis of phosphonates such as the Arbuzov reaction, improved in some cases by a sonication technique and those developed by Pfeiffer,[17] analogues of the substrates 1,3-diPGA and 2,3-diPGA bearing different functional groups and whose global negative charge was varied were synthesized; functionalized analogues of 2-phosphoglycolate were also prepared.

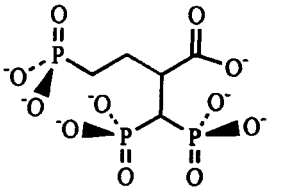
## RESULTS AND DISCUSSION

### 2,3-diphosphoglycerate Analogues

Compounds **1** and **2**



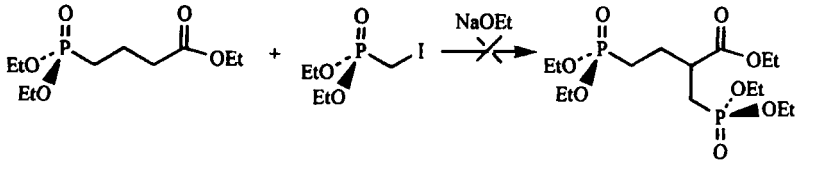
**1**



**2**

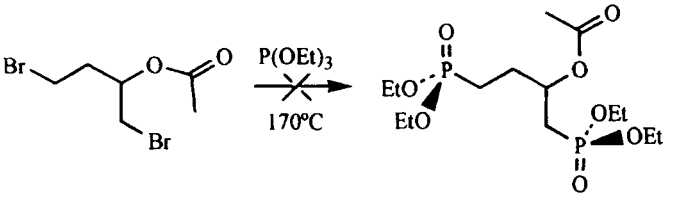
Several phosphonate analogues, with open chains or conformationally restricted were synthesized.

The phosphonate analogue of 2,3-diPGA, although previously described[15] could not be reproduced through this route. Therefore other possibilities were looked for. The first attempts included reactions 1 to 3.

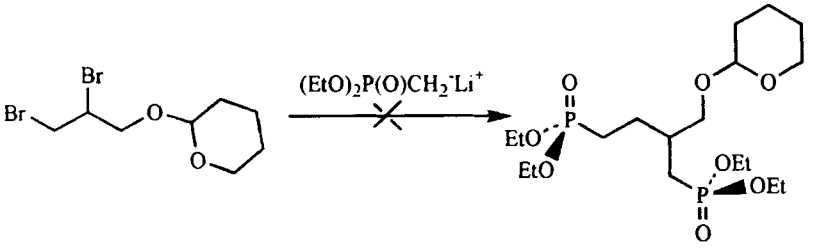
(1) 

Whatever the base used ($EtO^-$, LDA or Buli) or reaction conditions, no condensation was observed, likely owing to proton abstraction of the phosphonate by the carbanion to the carbonyl of the ester group.

Reaction 2 was based on the reaction with triethylphosphite in Arbuzov conditions or with the carbanion methyl-diethyl phosphonate of a properly protected dihalogeno-compound.

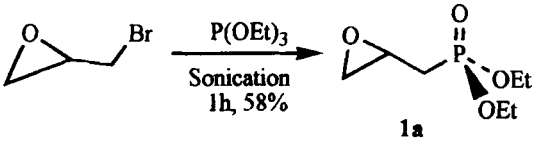



(2)

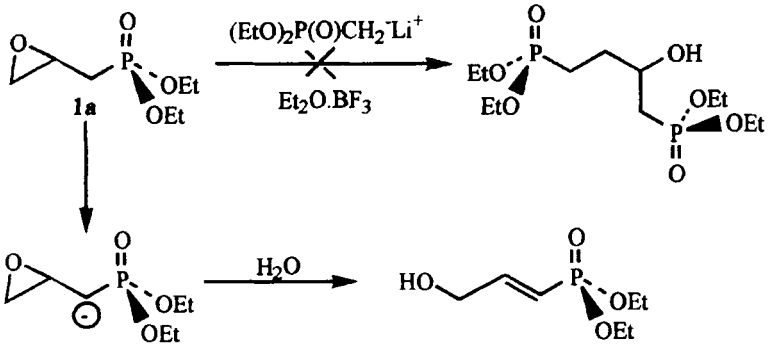



In the first case many side products were obtained, in the second only an elimination product.

Reaction 3 was an attempt at an epoxide ring opening reaction on **1a** by the same anion as that used in reaction 2; the epoxyde was obtained by an Arbuzov reaction using the sonication technique which allows to lower the temperature and also the extend of the side self-Arbuzov reaction.



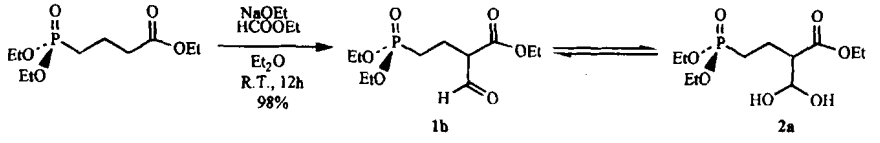

(3)



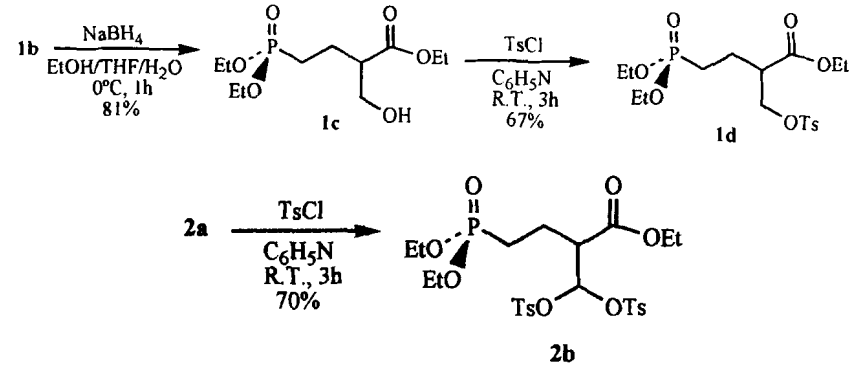

The second step did not proceed as expected, despite attempts carried out in different conditions; the only product obtained was an ethylenic alcohol resulting

from the ring opening reaction following the carbanion formation $\alpha$ to phosphorus. This compound will be used later on in this work.

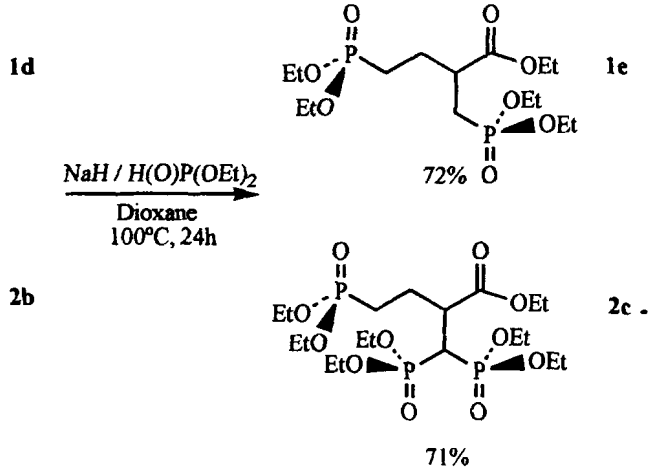
Based on these results, another route was considered: formylation of the carbanion used in reaction 1, the corresponding product leading to two parallel syntheses, owing to a favourable equilibrium between the aldehyde **1b** and the corresponding hydrate **2a**.




Reduction of **1b** by sodium borohydride followed by tosylation, led to the corresponding intermediate **1d**; similarly, the ditosylation of **2a** gave **2b**.

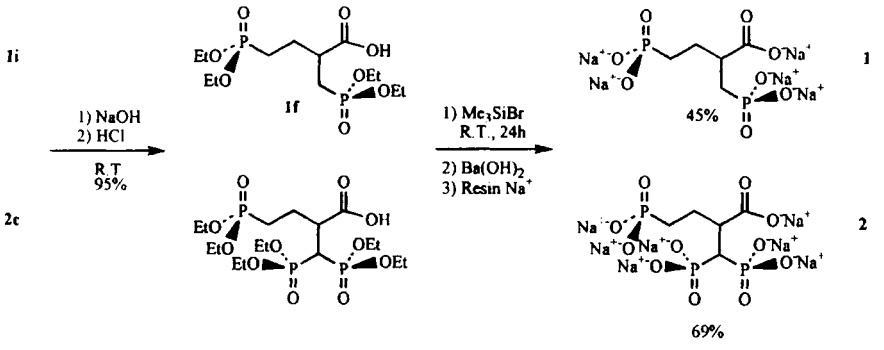



The two tosylates **1d** and **2b** (purified by column chromatography) were then caused to react with the diethylphosphite anion leading to the expected products:

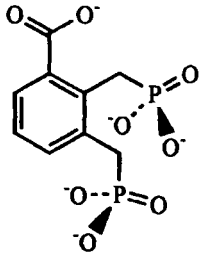


One step deprotection of the carboxylate and phosphonate groups was attempted by reaction with bromotrimethylsilane but failed. The carboxylate was therefore first deprotected by sodium hydroxide (pH = 12 at room temperature); the product was extracted by ether after acidification, subsequently the phosphonates were deprotected by trimethylbromosilane.

The corresponding acids were then purified by precipitation as barium salts; further treatment by a sodium exchange resin led to sodium salts **1** and **2**, used for the assays with the enzyme.



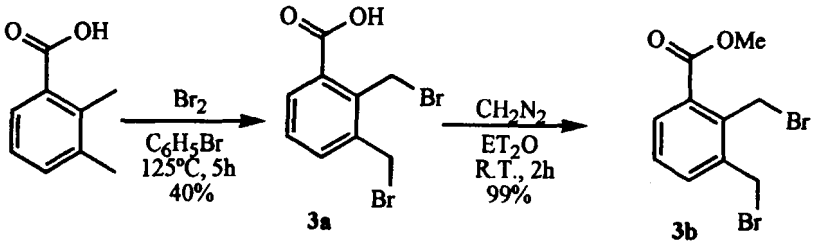

Both compounds **1** and **2** are racemic mixtures and were assayed in this form.



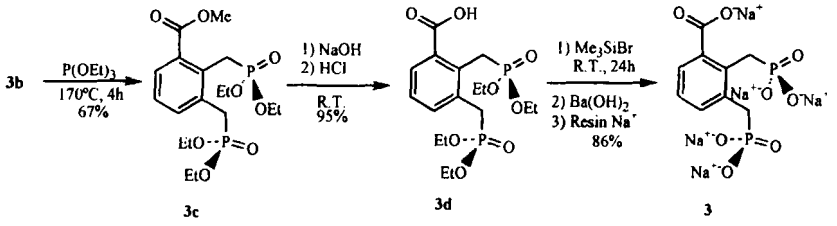
**3**

**3** is a rigid analogue of 2,3-diPGA where the three functional groups are branched on an aromatic ring.

This compound was prepared from 2,3-dimethylbenzoic acid, first transformed to the corresponding dibromo compound then esterefied, as follows.



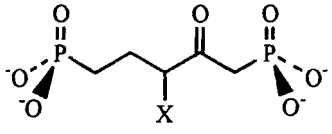

The next step was a standard Arbuzov reaction followed by deprotection first of the ester then of the two phosphonate groups:



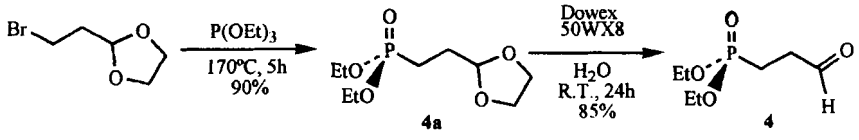

## 1,3-diphosphoglycerate Analogues

Several syntheses were undertaken to obtain phosphonate derivatives, analogues in structure, particularly chain length, to the title substrate, bearing different functionnal groups.

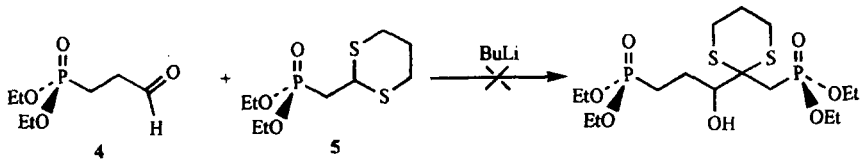
The basic structure corresponds to the frame with X equals OH for the substrate analogue, H, or an halogen atom.



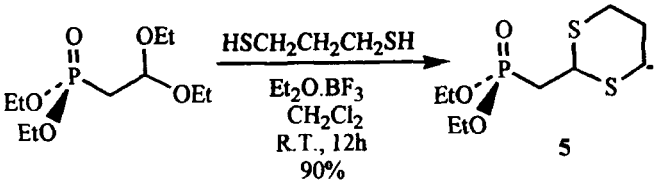

One of the common synthons to the different syntheses was the aldehyde **4**.



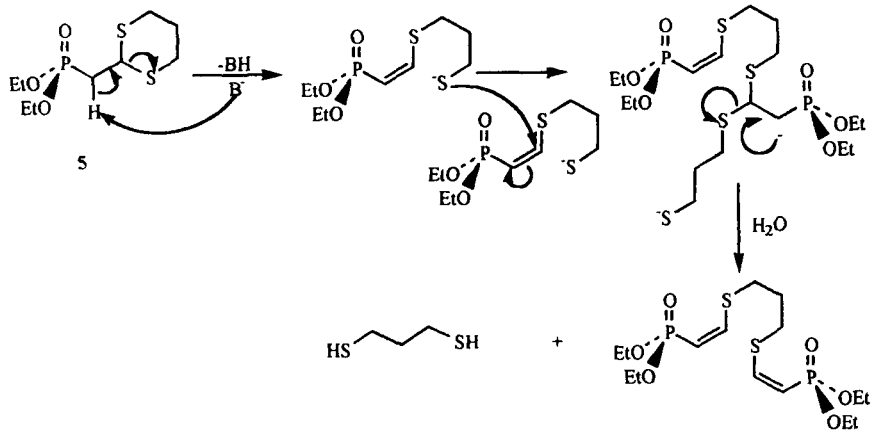

The following reaction was then considered:



Synthon **5** was obtained through a transacetalisation reaction.

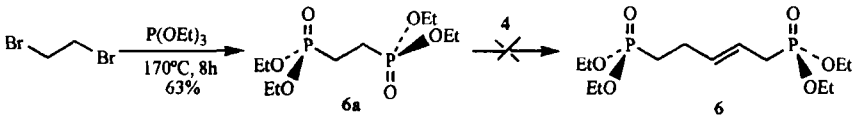


But the expected reaction between **4** and **5** failed, the carbanion $\alpha$ to phosphorus in **5** being prefered to that $\alpha$ to the two sulfur atoms. Therefore the following sequence was observed:

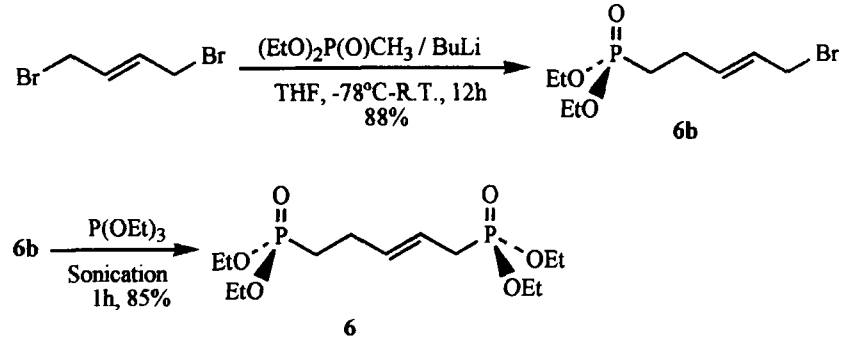


It is noteworthy that not only the reactivity in synthon **5**, but also the driving force for the dimerisation reaction is under the control of the preferred carbanion $\alpha$ to phosphorus.

As ketophosphonates and diphosphonates lead in basic conditions to a Horner-Wadsworth-Emmons type reaction,[18] synthon **4** was considered for the synthesis of compound **6**, the subsequent functionalization of which then opened a route to different analogues.



**6** could not be obtained by this route, the reaction leading to the aldolisation product of the aldehyde **4** after proton transfer from the carbanion formed with the phosphonate: in this case, there is no other possible reaction for the latter carbanion. However, this strategy was pursued, synthon **6** being an interesting precursor. It was prepared by the following sequence:

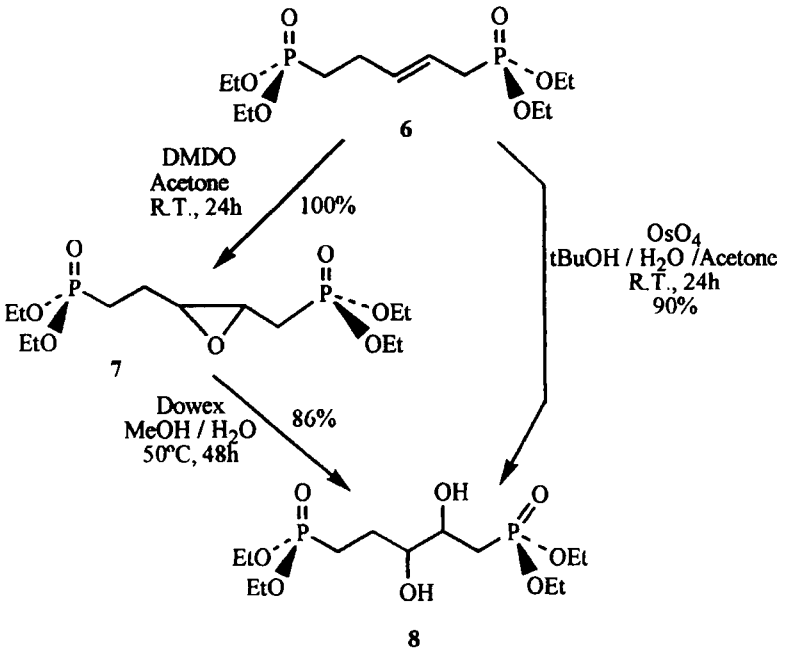


Functionalization of compound **6**

First attempts to synthesize the corresponding diol by potassium permanganate oxidation led to cleavage reaction products. But the corresponding epoxide **7** could be easily obtained by meta-chloroperbenzoic acid oxidation (80%) or even better with DMDO,[19] since in this case the oxidation is quantitative and the purification is simplified.

The direct transformation into the corresponding $\alpha$-ketol, phosphonate analogue of 1,3-diPGA or its regio-isomer, from the epoxide **7** was first considered. This reaction, which involves a ring opening reaction catalyzed by boron trifluoride and the oxidation of the second carbon by DMSO,[20] did not lead to the product, whatever the acid catalyst ($Et_2O \cdot BF_3$, diluted perchloric acid, dowex acid resin).

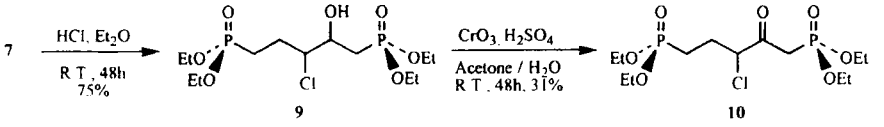
However, the two diastereoisomeric diols could be obtained either directly from **6** by osmium tetroxide oxidation (to give **8** threo), or through the epoxide **7** (**8** erythro) according to the following scheme:




The followings attempts were then made to further functionalize the diol **8**, but they all failed:

- oxidation of the diol **8** to an $\alpha$ keto-alcohol by silver carbonate in accordance with Fetizon;[21]
- oxidation of the diol or the protected diol with an isopropylidene bridge by DMDO[22] or on trityltetrafluoroborate according to Barton;[23]
- oxidation by bromine of the stannyl derivative formed by ring closure of the diol with $Bu_2SnO$;[24]
- partial hydrolysis of the corresponding diacetate by an esterase.[25]

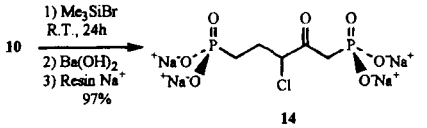
Finally, other analogues of 1,3-diPGA, apart from **7** and **8**, were first obtained by a ring opening reaction of the epoxide **7** by hydrochloric-acid, and then further oxidation of the corresponding chlorhydrin.

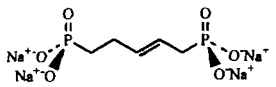


The structure of the regio-isomer for **9** and **10** was laid down from the NMR spectra analysis ($^{1}H$ and $^{13}C$) of the complete set of diphosphonates: carbon at position 3 in the chain is ascribed on the basis of the $^{13}C$ multiplicity signal since this carbon couples with the two phosphorus atoms, whereas carbon 2 signal only splits with the nearest phosphorus atom. Changes on the two atoms initially bearing OH groups carbon of the diol **8**, are therefore easily identified in compounds **6**, **7**, **9**, **11** and **12**.

Different attempts were made to transform **10** into the corresponding $\alpha$ ketoalcohol: in basic conditions (potassium hydroxide in water), the reaction led to degradation products; in milder conditions (triethylamine in water), an enolisation (double bond to phosphorus: seen with $^{31}P$ NMR) and elimination were obtained. An addition of 5 % sodium iodide introduced no improvement. Finally, the different analogues obtained, **6**, **8**, **9** and **10**, were then deprotected at the phosphonate part to lead to the corresponding products **11** to **14**. The conditions were in all cases identical, with yields ranging from 80 % for **6** to **9** to 97 % for **10** to **14**.

For example:

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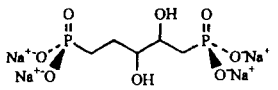
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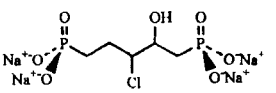
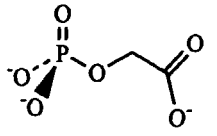

13



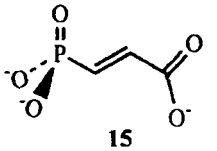
## Synthesis of Functionalized Phosphonates Analogues of Phosphoglycolate

Compound analogues of phosphoglycolate, the activator for the phosphatase activity of PGM, were also synthesized.

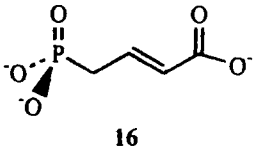


**2-phosphoglycolate**

Compounds **15** and **16**



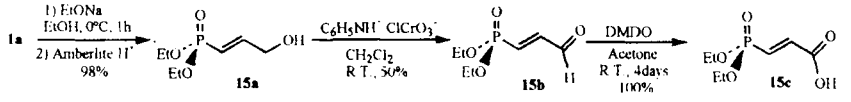
**15**



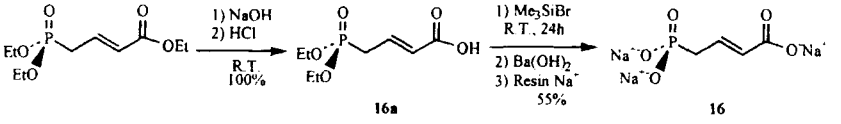
**16**

These compounds were synthesized first to make a rigid analogue of 2-PG, and also a possible irreversible Michael type inactivation, if the electrostatic interaction of the carboxylate group with a positively charged part of the enzyme were strong enough.

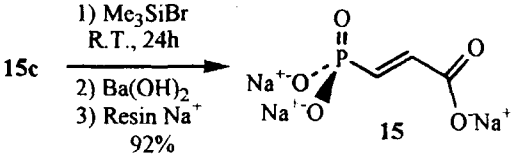
Compound **15** results from the epoxyde **1a** (described in part 1) to give the alcohol **15a** and after an oxidation, the parent aldehyde. They were prepared according to the procedure described by Lauth and al. on the dimethyl phosphonate.[26] A second oxidation with DMDO gave the corresponding carboxylic acid **15c**.



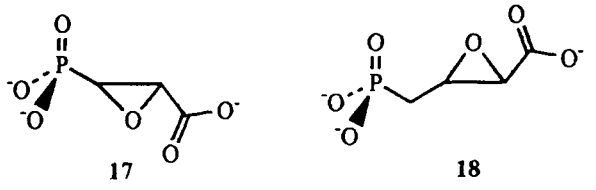

A similar analogue **16** with one more carbon atom in the chain was in addition prepared, in this case from the commercially available corresponding ester, deprotected as above.




An identical reaction performed with compound **15c** gave **15** in a 92 % yield.



Compounds **17** and **18**

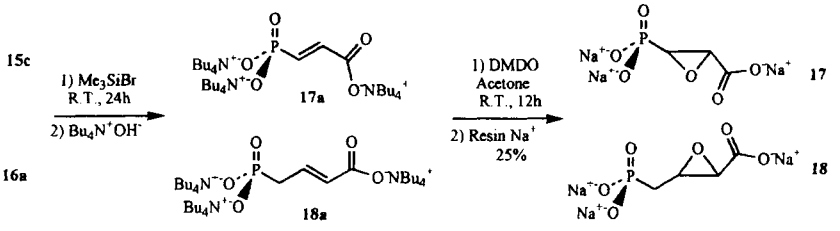


**17** **18**

Subsequently, the formation of the epoxides resulting from the oxidation of the corresponding alkenes **15** and **16** turned out to be a rather problematical reaction. Whatever substrate, deprotected **15** or **16**, or partially protected at the carboxylate group, or fully protected, no oxidation could be obtained using the standard reagents m-CPBA, magnesium peroxyphtalate, hydrogen peroxide even at high concentration, with or without tungsten tetroxide as generally used for unreactive substrates.[27] Such a limitation was previously documented by Arbuzov[28] and other groups[29] for conjugated alkenes.

A completely satisfactory solution was found by using DMDO. After the transformation of sodium salts **15** and **16** into the corresponding N-tetrabutylammonium salts for solubility reasons in organic medium, quantitative oxidations to the corresponding epoxides were obtained. Further treatment with a sodium ion exchange resin, produced epoxides **17** and **18** as sodium salts.

For example:




Both double bonds in precursors **17a** and **18a** being only E, the corresponding epoxides **17** and **18** come out as a single diastereoisomer.

## CONCLUSION

The different conclusions which can be drawn from this work are the following:

- firstly it can be observed that proton abstraction by an $\alpha$ keto-carbanion on a halogeno-phosphonate is preferred over the alternative SN2 displacement

reaction (reaction 1); also that such an $\alpha$ keto-carbanion is more reactive than the carbanion $\alpha$ to a phosphorus atom of a phosphonate, as indicated by the formylation reaction leading to **1a** (pKa is 24 for $CH_2$ $\alpha$ of an ester group[30] and it is over 35 for the phosphonate carbanion[31]);

- secondly, such a carbanion $\alpha$ to a phosphorus atom reacts rather as a base than as a nucleophile when the two reactions are possible as indicated from reactions 2 and 3. Moreover, the formation of such an $\alpha$ carbanion in a phosphonate is preferred over the umpoled carbanion formation in compound **5**-and also accounts for the self-condensation of this anion.

Part of the target compounds were obtained by reaction of diethylphosphite anion on a functionalized tosylate and by an Arbuzov type reaction, significantly improved by the sonication technique: i.e. using it, lowers the temperature from 170°C to 100°C, which is an interesting feature for sensitive halides, and also improves the yield since the side self-Arbuzov reaction is suppressed owing to the elimination of the halide formed.

For compounds analogue to 1,3-diPGA, the best strategy was above all the synthesis of the diphosphono-alkene **6**, with further functionalization of the double bond. This reaction was only possible with reagents that were not too bulky.*

Finally functionalized epoxides, analogue to the PG cofactor, were synthesized owing to the significant and specific activity of DMDO; this reaction was found particularly useful after many unsuccessful attempts with other general efficient reagents such as hydrogen peroxide-tungsten tetroxide.

Preliminary PGM tests indicated efficient competitive inhibitions with compounds **1** to **3**, which therefore may to serve for cocrystallization experiments; also enzyme inactivation was observed with **22**. Moreover, 1,3-diphosphoanalogues in the series **11** to **15** also revealed a high inhibition activity on glyceraldehyde-phosphate dehydrogenase, an enzyme which equally has 1,3-diPGA as substrate in the gluconeogenesis direction.

## GENERAL METHODS

All reagents were purified before use and stored under argon. Reactions progress was followed by TLC on silica gel (Merck 60F254); products were characterized with iodine, or spray (sulfuric acid 10%, with 5% in amonium cerium nitrate, or sulfuric acid 10% in methanol with 1% vanilin, or ortho-dianisidin in acetic acid). Products purification was made by flash chromatography on silica gel 60, 230–450 mesh (Merck).

*Numbering of the phosphorus atom corresponds to its position in the chain.

NMR spectra were recorded on Brucker AC-80, AC-200 and ARX-400. References were TMS for $^{1}H$ and $^{13}C$ nuclei, phosphoric acid 85% for $^{31}P$ nucleus; IR spectra were recorded on 1610-IR Perkin Elmer equipped with Fourier transform. Mass spectra were run on a Nermag R10-10 machine.

## GENERAL CHEMICAL PROCEDURES

*a-Deprotection of carboxylic esters* was made with sodium hydroxide at pH = 12, 1 hour stirring at room temperature; the solutions were then brought to pH2 with hydrochloric acid and the product extracted with ethyl acetate. Solutions were dried over magnesium sulfate, then the solvent evaporated after filtration.

*b-Deprotection of phosphonates* were made by addition of 2.5 equivalents of bromo-trimethylsilane (no solvent), the mixture stirred 24 h at room temperature. Diethyl ether was added, then water. The aqueous layer was brought to pH 7.5 with barium hydroxide then the solution lyophilized. The resulting powder was resolubilized in the minimum amount of water and filtered, then the water solution poured in a large volume of acetone. The *precipitate* was collected by *centrifugation*, washed with acetone. Ion exchange to the sodium salt (Sodium resin Biorex 70) was performed on the baryum salt dissolved in water. After filtration, the resulting solution was then lyophilized leading to the product as a white powder.

*c-Arbuzov reactions* were performed by mixing the bromide compound with 3 equivalents of triethyl-phosphite, and sonication with a machine operating at 20 kHz with an oxygen stream (12 ml/mn) during 1 hour. The excess of triethyl-phosphite was eliminated by distillation under vacuum, the phosphonate then purified by flash chromatography or by distillation.

*d-Dimethyl dioxirane oxidations* were made with solution of DMDO 2M in acetone (prepared according to Adam[32] with improvement of the yield obtained by a more efficient trapping of DMDO using a double wall cell filled with dry ice, the collecting flask being immerged in liquid nitrogen). After stirring overnight at room temperature, acetone was evaporated leading in all cases to a pure product.

### *Diethyl (2,3-epoxypropano)-phosphonate (1a)*

The mixture of 38.5ml triethyl phosphite (0.22mole) and 23.6ml epibromhydrin (0.28mole) were sonicated 1h. The reaction temperature was 102°C. The product was purified by distillation under reduced pressure (0.5mmHg) $Eb_i$ 80°C. 25.26g of a colourless oil were obtained (58%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1256 (P=O); 1163 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.95 (qd, $^3J_{HP}$ = 7Hz, 4H) $CH_2OP$; 3.00 (m,1H) CH; 2.40–2.64 (dd,2H) $CH_2O$ epoxide; 1.70–2.00 (dd,$^2J_{HP}$ = 14Hz,2H) $PCH_2$; 1.15 (td,$^3J_{HH}$ = 7Hz,6H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 61.60 (d,$^2J_{CP}$ = 6.4Hz, $CH_2OP$); 47.60 (d,$^3J_{CP}$ = 7.3Hz, $C_2$ epoxide); 46.64 (d,$^2J_{CP}$ = 1.6Hz, CHO); 30.01 (d,$^1J_{CP}$ = 139Hz, $PCH_2$); 16.30 (d,$^3J_{CP}$ = 4Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 26.10.

**SM**(DCI/$NH_3$) m/z: 195 ($MH^+$); 212 ($MNH_4^+$).

### *Triethyl 4-phosphono 2-methanal butanoate (1b)*

To 460mg of sodium in 30ml of diethyl ether was added 1.2ml of ethanol. A mixture of 5g of triethyl 3-phosphonobutyrate (19.8 mmoles) and 1.84g of ethyl formate was slowly added to the solution at O°C. The reaction mixture was stirred overnight at room temperature. The orange solution obtained was diluted with 45ml ice then separated. The aqueous layers were joined and acidified with diluted hydrochloride acid to a pH 2.5 then extracted with methylene chloride (4 × 100 ml). The organic layers joined were washed with brine and dried over $MgSO_4$. 5.44g of colourless oil were obtained after concentration under reduced pressure (98%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1744 (C=O ester); 1693 (CHO); 1194 (P=O); 968 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 9.60 (s,1H) CHO; 4.12 (q,2H) $CH_2O$ carboxylic ester, 3.97 (qd,$^3J_{HP}$ = 1.3Hz, $^3J_{HH}$ = 5.9Hz,4H) $CH_2O$ phosphonic ester, 3.70–3.37 (m,1H) CHOH; 2.50 (m,1H) $C_1H$ and $C_2H$; 1.80 (m,9H) $CH_3$, 1.75 (m,2H) $PCH_2$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 196.11 (CHO); 61.84 (d,$^2J_{CP}$ = 12.7Hz, $CH_2O$ phosphonic ester); 59.46 ($CH_2O$ carboxylic ester); 57.89 (d,$^3J_{CP}$ = 14.4Hz,CH); 25.76 (d,$^1J_{CP}$ = 138.8Hz, $PCH_2$); 21.12 (d,$^2J_{CP}$ = 12.6Hz, $CH_2$); 16.42 (d,$^3J_{CP}$ = 11.9Hz,$CH_3$ phosphonic ester); 14.21 ($CH_3$ carboxylic ester).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 31.37.

### *Triethyl 4-phosphono 2-(hydroxymethyl)-butanoate (1c)*

5.44g of compound **1b** (19.4mmoles) were dissolved in 8ml of ethanol, water and THF mixture (1:1:1). This solution was slowly added to 735mg of $NaBH_4$ in 25ml of the same solvent mixture at O°C. After one hour stirring, the mixture was neutralised by acetic acid. THF and ethanol were evaporated. The aqueous

solution was diluted with brine and extracted by methylene chloride (5 × 100ml). The organic layer was washed with a satured aqueous solution of $NaHCO_3$ then dried over $MgSO_4$ and concentrated. 4.44g of a colourless oil were obtained after chromatography (methylene chloride/methanol: 99/1) (81%).

**IR**(film) $\nu_{max}(cm^{-1})$: 3374 (OH); 1731 (C=O); 1226 (P=O); 962 (P-O).

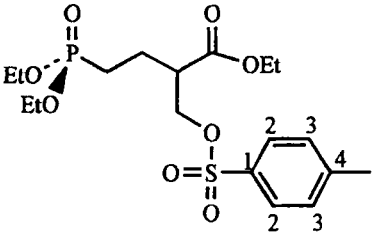
**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.96–4.09 (m,6H) $CH_2O$ ester; 3.66 (d,2H) $CH_2O$ alcohol, 3.38 (s,1H) OH; 2.28–2.58 (t,1H) CH; 1.65–1.85 (m,4H) $CH_2$; 1.18–1.23 (t,6H) $CH_3$ phosphonic ester, 1.14–1.20 (t,3H) $CH_3$ carboxylic ester.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 174.00 (C=O); 62.47 (d,$^2J_{CP}$ = 9.0Hz, $CH_2O$ phosphonic ester); 61.60 ($CH_2O$ carboxylic ester); 48.07 (d,$^3J_{CP}$ = 15.0Hz,CH); 26.24 (d,$^1J_{CP}$ = 141.0Hz, $PCH_2$); 24.57 ($CH_2O$ alcohol); 21.75 (d,$^2J_{CP}$ = 25.0Hz,$CH_2$); 16.44 (d,$^3J_{CP}$ = 55.0Hz,$CH_3$ phosphonic ester); 14.19 ($CH_3$ carboxylic ester).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 31.43.



***Triethyl 4-phosphono 2-(toluene sulfonyl methyl)-butanoate (1d)***




1.70g of **1c** (6mmoles) were dissolved in 10ml of pyridin, the solution then cooled at O°C. 2.3g of tosyl chloride were added. The mixture was stirred two hours at O°C then three hours at room temperature. Then 150 ml of diethyl ether and 45ml of chlorhydric acid 3N were added. After separation, the aqueous layer was extracted twice with 50ml of diethyl ether. The joined organic layers were washed with diluted chlorohydric acid, water, satured aqueous solution of $NaHCO_3$ then with water and dried over $MgSO_4$ and then concentrated. 1.76g of a yellow oil were obtained after purification by chromatography (methylene chloride methanol: 99/1) (67%).

**IR**(film) $\nu_{max}(cm^{-1})$: 2982 (CH=); 1734 (C=O); 1595 and 1447 (C=C); 1370 (S=O); 1292 (P=O); 965 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 7.67 (d,2H) $H_2$; 7.30 (d,2H) $H_3$, 3.96–4.08 (m,8H) $CH_2O$; 2.70 (m, 1H) CH; 2.37 (s,3H) $CH_3$ tosyl; 1.50–1.90 (m,4H) $CH_2$, 1.10–1.27 (m,9H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 171.21 (C=O); 145.08 ($C_1$); 132.46 ($C_4$); 129.91 ($C_2$); 127.90 ($C_3$); 69.03 ($CH_2O$ tosyl); 61.71 (q,$^2J_{CP}$ = 6.5Hz,$CH_2O$ phosphonic ester); 61.16 ($CH_2O$ carboxylic ester); 44.87 (d,$^3J_{CP}$ = 16.1Hz,CH); 22.89 (d,$^1J_{CP}$ = 142.4Hz,$PCH_2$); 21.51 ($CH_3$ tosyl); 21.29 ($CH_2$); 16.44 (d,$^3J_{CP}$ = 16.1Hz,$CH_3$ phosphonic ester); 14.15 ($CH_3$ carboxylic ester).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 30.18.

### *Triethyl 4-phosphono 2-(diethyl phosphono methyl)-butanoate (1e)*

To a suspension of 0.66g of NaH in 60ml of dioxane cooled at O°C, were added 4.87ml of diethylphosphite. After stirring of the mixture for 15mn a solution of 2.33g of **1d** (5.34mmoles) in 10ml of dioxane was added. The solution was refluxed 24 hours. The solvent was eliminated and the product separated from diethyl phosphite by distillation. Then the residue was purified by chromatography with a gradient elution (methylene chloride then methylene chloride methanol: 98/2). 1.55g of a yellow oil were obtained (72%).

**IR**(film) $\nu_{max}$($cm^{-1}$): 1732 (C=O); 1164 (P=O); 963 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.85–3.97 (m,10H) $CH_2O$; 2.65–2.75 (m,1H) CH, 1.50–2.10 (m,6H) $CH_2$; 1.08–1.20 (m,15H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 173.57 (d,$^3J_{CP}$ = 8.0Hz,C=O); 61.63 (d,$^2J_{CP}$ = 42.8Hz, $CH_2O$ phosphonic ester); 61.52 ($CH_2O$ carboxylic ester); 40.35 (d,$^2J_{CP}$ = 18.1Hz,CH); 27.47 (d,$^1J_{CP}$ = 136.9Hz, ③$PCH_2$*); 25.98 ($CH_2$); 23.02 (d,$^1J_{CP}$ = 142.4Hz, ④$PCH_2$); 16.33 (d,$^3J_{CP}$ = 5.0Hz, $CH_3$ phosphonic ester); 14.03 ($CH_3$ carboxylic ester).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 30.42 ④P; 23.40 ②P.

### *4-(diethyl phosphono) 2-(diethyl phosphono methyl)-butanoic acid (1f)*

1g of **1e** (2.5mmoles), according to the general procedure **a**, gave 936mg of a yellow oil (95%).

**IR**(film) $\nu_{max}$($cm^{-1}$): 3396 (OH); 1700 (C=O); 1230 (P=O); 964 (P-O).

**NMR$^1$H**($CDCl_3$, 200 MHz) $\delta$(ppm): 4.08–4.21 (m,8H) $CH_2O$; 2.60 (m,1H) CH, 1.65–2.30 (m,6H) $CH_2$; 1.23–1.37 (m,12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 183.40 (C=O); 66.10 (d,$^2J_{CP}$ = 6.5Hz,$CH_2O$); 45.97 (d,$^3J_{CP}$ = 19.1Hz,CH); 31.06 (d,$^1J_{CP}$ = 123.8Hz, $^2PCH_2$); 28.30 ($CH_2$); 25.84 (d,$^1J_{CP}$ = 137.9Hz, $^4PCH_2$); 18.33 (d,$^3J_{CP}$ = 6.0Hz,$CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 35.64 ④P; 34.14 ②P.

*4-phosphono 2-(phosphomethyl)-butanoic acid Pentasodium Salt (1)*

900mg of **1f** (2.4mmoles), according to the general procedure **b**, gave 380mg of a white powder (45%).

**IR**(KBr) $\nu_{max}$($cm^{-1}$): 1700 (C=O); 1054 (P=O); 964 (P-O).

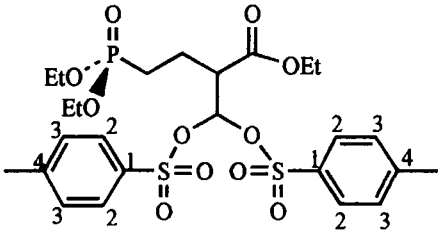
**NMR$^{1}$H**($D_2O$, 200MHz) $\delta$(ppm): 3.52–3.54 (m,1H) CH; 1.28–2.30 (m,6H) $CH_2$.

**NMR$^{13}$C**($D_2O$,50MHz) $\delta$(ppm): 188.27 (d,$^3J_{CP}$ = 13.1Hz, C=O); 48.61 (dd,$^3J_{CP}$ = 18.1Hz, $^2J_{CP}$ = 2.5Hz,CH); 34.51 (d,$^1J_{CP}$ = 130.3Hz, ②$PCH_2$); 31.12 ($CH_2$); 29.62 (d,$^1J_{CP}$ = 109.7Hz,④$PCH_2$).

**NMR$^{31}$P**($D_2O$, 81MHz)$\delta$(ppm): 23.79 ④P; 22.55 ②P.



*Triethyl 4-phosphono 2-bis-(toluene sulfonyl methyl)-butanoate (2b)*




1.19g of compound **2a** (4mmoles) with 1.6g of tosyl chloride, according to the same procedure as **1d**, gave 1.70g of a yellow oil (70%).

**IR**(film) $\nu_{max}$($cm^{-1}$): 2985 (CH=); 1718 (C=O); 1595 and 1450 (C=C); 1371 (S=O); 1220 (P=O); 970 (P-O).

**NMR$^{1}$H**($CDCl_3$, 200MHz) $\delta$(ppm): 7.70 (d,4H) $H_2$; 7.30 (d,4H) $H_3$, 3.89–4.17 (m,7H) $CH_2O$ and OCHO; 2.39 (s,6H) $CH_3$ tosyl; 2.31 (m,1H) CH; 1.30–1.70 (m,4H) $CH_2$, 1.12–1.32 (m,9H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 172.73 (C=O); 146.25 ($C_1$); 132.12 ($C_4$); 130.30 ($C_2$); 127.97 ($C_3$); 61.61 (q,$^2J_{CP}$=7.3Hz, $CH_2O$ phosphonic ester); 61.08 ($CH_2O$ tosyl); 60.43 ($CH_2O$ carboxylic ester); 44.89 (d,$^3J_{CP}$ = 16.0Hz, CH); 24.28 (d,$^1J_{CP}$ = 139.4Hz, $PCH_2$); 21.76 ($CH_3$ tosyl); 18.01 (d,$^3J_{CP}$ = 7.7Hz,$H_2$); 16.41 (d,$^3J_{CP}$ = 7.6Hz, $CH_3$ phosphonic ester); 14.20 ($CH_3$ carboxylic ester).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 29.77.

*Triethyl 4-phosphono 2-bis-(diethyl phosphono methyl)-butanoate (2c)*

1.27g of **2b** (2.1mmoles), 375mg of NaH and 2.68ml of diethyl phosphite, according to the same procedure as **1e**, gave 801mg of a yellow oil after chromatography (71%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1727 (C=O); 1163 (P=O); 960 (P-O).

**NMR$^{1}$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.98–4.09 (m,14H) $CH_2O$; 3.10 (td, 1H) CH, 1.30–2.10 (m,5H) $CH_2$ and PCHP; 1.16–1.24 (m,21H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 172.26 (C=O); 63.01 (dd,$^{2}J_{CP}$ = 7.0Hz, $CH_2O$②P); 61.46 (d,$^{2}J_{CP}$ = 6.5Hz, $CH_2O^{4}P$); 61.17 ($CH_2O$); 43.30 (dd,$^{2}J_{CP}$ = 19.6Hz, CH); 39.10 (t,$^{1}J_{CP}$ = 133.9Hz,PCHP); 25.08 (d,$^{1}J_{CP}$ = 140.4Hz, $^{4}PCH_2$); 21.85 ($CH_2$); 16.43 (d,$^{3}J_{CP}$ = 4.5Hz, $CH_3$ de ②P); 16.24 (d,$^{3}J_{CP}$ = 5.5Hz, $CH_3$ de ④P); 14.05 ($CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 31.27 $^{4}$P; 21.82 and 20.75 $^{2}$P.

*4-(Diethyl Phosphono) 2-bis-(Diethyl Phosphono Methyl)-butanoic Acid (2d)*

700mg of **2c** (1.3mmoles), according to the general procedure **a**, gave 630mg of a yellow oil (95%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1715 (C=O); 1158 (P=O); 958 (P-O).

**NMR$^{1}$H**($CDCl_3$, 200MHz) $\delta$(ppm): 4.00–4.10 (m,12H) $CH_2O$; 3.10 (td, 1H) CH, 1.27–2.25 (m,5H) $CH_2$ and PCHP; 1.08–1.20 (m,18H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 182.30 (C=O); 63.10 (dd,$^{2}J_{CP}$ = 7.0Hz, $CH_2O$②P); 61.56 (d,$^{2}J_{CP}$ = 6.7Hz, $CH_2O^{4}P$); 43.50 (dd,$^{2}J_{CP}$ = 20.1Hz, CH); 39.18 (t,$^{1}J_{CP}$ = 135.0Hz,PCHP); 25.00 (d,$^{1}J_{CP}$ = 140.0Hz, ④$PCH_2$); 21.55 ($CH_2$); 16.50 (d,$^{3}J_{CP}$ = 5.0Hz, $CH_3$ de ②P); 16.12 (d,$^{3}J_{CP}$ = 5.0Hz, $CH_3$ de ④P).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 31.07 ④P; 21.80 and 20.55 ②P.

*4-phosphono 2-bis-(Phosphono Methyl)-butanoic Acid Heptasodium Salt (2)*

510mg of **2d** (1mmoles), according to the general procedure b, gave 327mg of a white powder (69%).

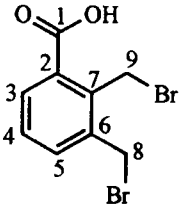
**IR**(KBr) $\nu_{max}(cm^{-1})$: 1700 (C=O); 1061 (P=O); 967 (P-O).

**NMR$^{1}$H**($D_2O$, 200MHz) $\delta$(ppm): 2.58–2.63 (m,1H) CH; 1.23–2.35 (m,5H) $CH_2$ and PCHP.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 186.30 (d,$^{3}J_{CP}$ = 12.0Hz,C=O); 47.48 (dd,$^{3}J_{CP}$ = 16.0Hz, $^{2}J_{CP}$ = 5.0Hz,CH); 39.10 (t,$^{1}J_{CP}$ = 138.4Hz,PCHP); 30.08($CH_2$); 29.03 (d,$^{1}J_{CP}$ = 138.8Hz, ④$PCH_2$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 23.69 ④P; 19.50 and 18.75 ②P.

***2,3-bis-(Bromo Methyl) Benzoic Acid (3a)***



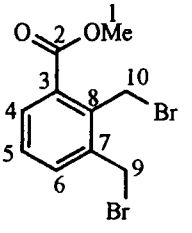

1g of 2,3-dimethylbenzoic acid (6.7mmoles) were refluxed in 10ml of bromobenzene (125, 130°C); 2.8ml of $Br_2$ were slowly added. After 5 hours stirring, the solution was cooled to −20°C. The precipitate was filtered and washed with bromobenzene. The product was recrystallised in ethanol to give 820mg of white crystals (40%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 3647 (OH); 2866 (CH=); 1694 (C=O); 1584 and 1463 (C=C); 1186 ($CH_2Br$).

**NMR$^1$H**($CD_3COCD_3$, 200MHz) δ(ppm): 8.01 (dd,1H) $H_5$; 7.76 (dd,1H) $H_3$, 7.49 (t,1H) $H_4$; 5.28 (s,2H) $H_9$; 4.87 (s,2H) $H_8$.

**NMR$^{13}$C**($CD_3COCD_3$, 50MHz) δ(ppm): 139.56 ($C_2$); 138.63 ($C_7$); 135.85 ($C_5$); 132.58 ($C_3$); 132.21 ($C_4$); 129;94 ($C_5$); 30.52 ($C_9$); 26.32 ($C_8$).

***Methyl 2,3-bis-(Bromo Methyl) Benzoate (3b)***



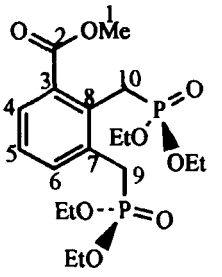

To diazomethane (≈22mmoles) in diethyl ether at −70°C were added 1.54g of **3a** (5mmoles) in 100ml of THF. After 2h stirring at room temperature the diazomethane excess and solvents were evaporated to give 1.60g of a white powder (99%).

**IR**(film) $\nu_{max}(cm^{-1})$: 2950 (CH=); 1721 (C=O); 1584 and 1457 (C=C); 1188 ($CH_2Br$).

**NMR$^1$H**($CDCl_3$, 200MHz) δ(ppm): 7.86 (dd,1H) $H_6$; 7.52 (dd,1H) $H_4$, 7.32 (t,1H) $H_5$; 5.11 (s,2H) $H_9$; 4.65 (s,2H) $H_{10}$; 3.91 (s,3H) $H_1$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 166.15 ($C_2$); 138.37 ($C_8$); 137.80 ($C_7$); 134.91 ($C_6$); 131.72 ($C_4$); 130.91 ($C_3$); 128.98 ($C_5$); 52.65 ($C_1$); 29.78 ($C_9$); 25.72 ($C_{10}$).

***Methyl 2,3-bis-(Diethyl Phosphono Methyl) Benzoate (3c)***




1g of **3b** (3.1mmoles) gave by an Arbuzov reaction (general procedure **c**), after chromatography (ethyl acetate/toluene: 1/1, ethylacetate and ethylacetate/methanol: 95/5) 908mg of a yellow oil (67%).

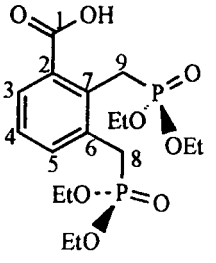
**IR**(film) $\nu_{max}$($cm^{-1}$): 2985 (CH=); 1721 (C=O); 1636 and 1473 (C=C); 1200(P=O); 960 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 7.80 (dd,1H) $H_4$; 7.50 (dd,1H) $H_6$, 7.30 (t,1H) $H_5$; 4.00 (m,8H) $CH_2O$; 3.87 (s,3H) $H_1$; 1.26–1.30 (m,4H) $H_9$ and $H_{10}$; 1.14–1.26 (m,12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 169.18 ($C_2$); 135.95 ($C_4$); 134.87 ($C_8$); 133.46 ($C_7$); 129.91 ($C_5$); 127.22 ($C_6$); 62.49 (d,$^2J_{CP}$ = 9.0Hz, $CH_2O^{⑨}P$); 62.35 (d,$^2J_{CP}$ = 8.1Hz, $CH_2O^{⑩}P$); 52.48 ($C_1$); 33.46 (d,$^1J_{CP}$ = 119.8Hz, $C_9$); 28.54 (d,$^1J_{CP}$ = 133.3Hz, $C_{10}$); 16.71 ($CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 27.06 $^{⑧}$P; 26.91 $^{⑨}$P.

*2,3-bis-(Diethyl Phosphono Methyl) Benzoic Acid (3d)*



654mg of **3c** (2.1mmoles), according to the general procedure a, gave 605mg of a yellow oil (95%).

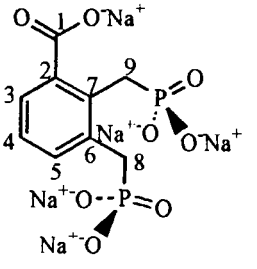
**IR**(film) $\nu_{max}(cm^{-1})$: 2981 (CH=); 1720 (C=O); 1654 and 1438 (C=C); 1251 (P=O); 959 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 7.70 (d,1H) $H_3$; 7.31 (d,1H) $H_5$, 7.19 (t,1H) $H_4$; 3.88–4.08 (m,8H) $CH_2O$; 1.12–1.31 (m,12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 168.46 ($C_1$); 135.17 ($C_3$); 132.93 ($C_7$); 132.21 ($C_6$); 129.69 ($C_4$); 126.58 ($C_5$); 62.13 (d,$^2J_{CP}$ = 11.0Hz, $CH_2O$); 31.41 (d,$^1J_{CP}$ = 135.8Hz, $C_9$); 26.49 (d,$^1J_{CP}$ = 134.1Hz,$C_8$); 16.30 (d,$^3J_{CP}$ = 5.0Hz,$CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 26.62 ⑧P; 26.35 ⑨P.

*2,3-bis-(Phosphono Methyl) Benzoic Acid Pentasodium Salt (3)*



422mg of **3d** (1mmole), according to the general procedure b, gave 361mg of a white powder (86%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 2930 (CH=); 1757 (C=O); 1654 and 1466 (C=C); 1175 (P=O); 1070 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 7.25–7.61 (m,3H) CH=, 1.12–1.19 (m,4H) $CH_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) δ(ppm): 174.43 (C=O); 138.83 (d,$^3J_{CP}$ = 13.1Hz,$C_2$); 137.90 ($C_3$); 137.35 (dd,$^2J_{CP}$ = 4.5Hz, $^3J_{CP}$ = 21.0Hz, $C_7$); 136.36 (dd,$^2J_{CP}$ = 3.0Hz, $^3J_{CP}$ = 11.6Hz, $C_6$); 131.02 ($C_4$); 128.48 (d,$^3J_{CP}$ = 9.0Hz, $C_5$); 32.03 (d,$^1J_{CP}$ = 124.7Hz, $C_8$); 36.48 (d,$^1J_{CP}$ = 125.2Hz, $C_9$).

**NMR$^{31}$P**($D_2O$, 81MHz) δ(ppm): 22.61 ⑧P; 20.35 ⑨P.

### *3-(Diethyl Phosphono) Oxo-propane Ethylene Acetal (4a)*

3g of 2-(2-bromoethyl) 1.3-dioxolane (16.6mmoles), according to the general procedure c for Arbuzov reaction, gave after chromatography (methylene chloride and methylene chloride/methanol: 93/7) 3.54g of a yellow oil (90%).

**IR**(film) $\nu_{max}$($cm^{-1}$): 1280 (P=O); 964 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) δ(ppm): 4.80 (t,1H) CH; 3.91–3.99 (qd,$^3J_{HH}$ = 1.7Hz,4H) $CH_2O$ ester; 3.75–3.79 (m,4H) $CH_2O$ acetal; 1.58–1.81 (m,4H) $CH_2$; 1.18 (t,6H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) δ(ppm): 103.21 (d,$^3J_{CP}$ = 19.1Hz,CH); 65.01 ($CH_2O$ acetal); 61.43 (d,$^2J_{CP}$ = 6.5Hz,$CH_2O$ ester); 26.82 (d,$^2J_{CP}$ = 4.4Hz,$CH_2$); 19.47 (d,$^1J_{CP}$ = 144.3Hz,$PCH_2$); 16.34 (d,$^3J_{CP}$ = 6.0Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) δ(ppm): 31.93.

### *3-(Diethyl Phosphono) Propanal (4)*

To 1.5g of **4a** (63mmoles) in 20ml of water were added 10ml of dowex 50WX8. After 24 hours stirring at room temperature, the solution was filtered. The filtrat was satured with NaCl and the product was extrated with ethyl acetate (3 × 50ml). The organic layer was dried over $MgSO_4$ and solvent evaporated to give 1.04g of a colourless oil (85%).

**IR**(film) $\nu_{max}$($cm^{-1}$): 1723 (C=O); 1241 (P=O); 965 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) δ(ppm): 9.64 (s,1H) CHO; 3.96 (qd,4H) $CH_2O$; 2.71 (m,2H) $CH_2$; 1.90 (td,2H) $PCH_2$; 1.18 (q,6H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) δ(ppm): 199.20 (d,$^3J_{CP}$ = 15.0Hz,CHO); 61.75 (d,$^2J_{CP}$ = 6.5Hz, $CH_2O$); 36.79 (d,$^2J_{CP}$ = 3.9Hz,$CH_2$); 17.83 (d,$^1J_{CP}$ = 147.4Hz,$PCH_2$); 16.26 ($CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) δ(ppm): 30.69.

### *Diethyl Phosphono Ethyl 1,3-dithiane (5)*

To 2g of diethylphosphono acetaldehyde diethyl acetal (7.87mmoles) in 20ml of methylene chloride were added propane dithiol and trifluoroboride etherate. After 12h stirring at room temperature, the solution was washed with water,

KOH 2N and water. The organic layer were dried over $MgSO_4$ and the solvent evaporated. 395mg of a colourless oil was obtained after chromatography (methylene chloride/methanol: 99/1) (59%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1252 (P=O); 965 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 4.23 (m, 1H) CHS; 3.95–4.07 (qd,$^3J_{HP}$ = 1.2Hz, $^3J_{HH}$ = 7.2Hz,4H) $CH_2O$; 2.74–2.85 (m,4H) $SCH_2$; 2.10 (dd, $^2J_{HP}$ = 18.4Hz, $^3J_{HH}$ = 7.2Hz,2H) $PCH_2$; 1.80 (m, 2H) $CH_2$; 1.24 (t,3H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 62.10 (d, $^2J_{CP}$ = 6.4Hz, $CH_2O$); 40.60 (d, $^2J_{CP}$ = 2.7Hz,CH); 32.61 (d, $^1J_{CP}$ = 141.4Hz,$PCH_2$); 30.48 ($CH_2S$); 24.98 ($CH_2$); 16.38 (d, $^3J_{CP}$ = 6.1Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 25.89.

### *1,2-bis-(Diethyl Phosphono) Ethane (6a)*

9g of 1,2-dibromoethane (47.9mmoles) gave by Arbuzov procedure (**c**), after chromatography (methylene chloride/methanol: 98/2) 6.4g of a colourless oil (63%)

**IR**(film) $\nu_{max}(cm^{-1})$: 1240 (P=O); 954 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.85–4.04 (m, 8H) $CH_2O$; 1.82 (d, $^2J_{HP}$ = 10.5Hz, 4H) $PCH_2$; 1.17 (t, 12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 61.91 (d, $^2J_{CP}$ = 3.1Hz, $CH_2O$); 19.06 (d, $^1J_{CP}$ = 139.0Hz, $PCH_2$); 16.36 (d, $^3J_{CP}$ = 3.0Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 29.69.

### *5-(Diethyl Phosphono) 1-bromo 2-pentene (6b)*

To 16.763g of diethyl methyl phosphonate (0.11 mole) in 50ml of THF at 78°C were added 68.9ml of butyl lithium (1.6M in hexane). After 30mn the solution was transfered on 23.6g of 1,4-dibromo 2-butene (0, 12mole) in 50ml of THF at −78°C. The solution was warmed up to room temperature and stirred over 12h. $NH_4Cl$ saturating in water was added to a pH of 7.4. THF was evaporated under reduce pressure. The product was solubilized in ethyl acetate and washed with brine. The organic layer was dried with $MgSO_4$ and the solvent evaporated. 27.64g of a yellow oil were obtained after chromatography (methylene chloride/methanol: 98/2) (88%).

**IR**(film) $\nu_{max}(cm^{-1})$: 2954 (CH=); 1661 (C=C); 1208 (P=O); 1179 ($CH_2Br$); 988 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 5.67–5.76 (m, 2H) CH=; 3.98–4.08 (qd, $^3J_{HH}$ = 7.1Hz, $^3J_{PH}$ = 1.6Hz, 4H) $CH_2O$; 3.90 (d, 2H) $CH_2Br$; 2.33 (m, 2H) $PCH_2$; 1.68–1.85 (m, 2H) $CH_2$; 1.27 (t, 3H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 134.50 (d, $^3J_{CP}$ = 16.9Hz, $C_3$); 127.17 ($C_2$); 61.60 (d, $^2J_{CP}$ = 6.5Hz, $CH_2O$); 32.77 ($CH_2Br$); 25.95 (d, $^2J_{CP}$ = 4.5Hz, $CH_2$); 24.99 (d, $^1J_{CP}$ = 141.0Hz, $PCH_2$); 16.51 (d, $^3J_{CP}$ = 6.0Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 30.85.

**SM**($DCI/NH_3$) m/z: 285 ($MH^+$).

### *1,5-bis-(Diethyl Phosphono) 2-pentene (6)*

22.8g of **6b** (80mmoles) gave by an Arbuzov reaction (**c**), 22.4g of a yellow oil (85%).

**IR**(film) $\nu_{max}$($cm^{-1}$): 2360 (CH=); 1680 (C=C); 1264 and 1211 (P=O); 852 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 5.36–5.48 (m, 2H) CH=; 3.87–4.02 (qdd, 8H) $CH_2O$; 2.32–2.47 (dd, $^3J_{HH}$ = 21.4Hz, $^2J_{HP}$ = 7.5Hz, 2H) $H_2$; 2.19 (m, 2H) $H_5$; 1.60–1.73 (m, 2H) $H_4$; 1.19 (m, 12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 134.21 (dd, $^3J_{CP}$ = 17.6Hz, $C_3$); 119.67 (d, $^2J_{CP}$ = 11.2Hz, $C_2$); 61.51 (2d, $^2J_{CP}$ = 6.7Hz, $CH_2O$); 30.39 (d, $^1J_{CP}$ = 155.9Hz, $C_1$); 25.27 (d, $^1J_{CP}$ = 143.9Hz, $C_5$); 25.48 ($CH_2$); 16.39 (d, $^3J_{CP}$ = 5.9Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 31.20 ⑤P; 27.55 ①P.

**SM**($DCI/NH_3$) m/z: 344 ($MH^+$).

### *1,5-bis-(Diethyl Phosphono) 2,3-pentane Diol (8)*

*Method 1 (erythro)*

200mg of 7 (0.56mmoles) in 5ml of methanol, 10ml of water and 2g of dowex 50WX8 were stirred 48h at 50°C. The resin was filtred and washed with methanol. This solvent was evaporated and water lyophilized to lead to 180mg of a yellow oil (86%).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 5.00 (s,2H) OH; 4.02–4.09 (m, 10H) $CH_2O$ and CHO; 1.75–2.10 (m, 6H) $CH_2$; 1.28 (td, 12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 74.29 (dd, $^3J_{CP}$ = 14.1Hz, $C_3$); 69.47 (d, $^2J_{CP}$ = 5.2Hz, $C_2$); 62.06 (2d, $^2J_{CP}$ = 14.3Hz, $CH_2O$); 28.70 (d, $^1J_{CP}$ = 140.5Hz, $C_1$); 25.20 ($C_4$); 21.83 (d, $^1J_{CP}$ = 141.5Hz, $C_5$); 16.42 (d, $^3J_{CP}$ = 5.5Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 33.66 ⑤P; 31.68 ①P.

*Method 2 (threo)*

To 10g of **6** (29.2mmoles) at 0°C were added 3.9g of N-methyl morpholine, 100ml of water, 20ml of acetone, 10ml of ter-butanol and 200mg of osmium

tetroxide. The solution was stirred 24h at room temperature. 12.5g of sodium hydrosulfite and 15g of magnesium silicate were added. The mixture was filtred and washed with water. The filtrat was neutralised with $H_2SO_42N$. Acetone was evaporated and water lyophilized, then the residue was solubilized with ethyl acetate. The solvent was evaporated after filtration leading to 10.3g of black oil (90%).

**IR**(film) $\nu_{max}(cm^{-1})$: 3360–3314 (OH); 1224 and 1198 (P=O); 960 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.98–4.10 (m, 10H) $CH_2O$ and CHO; 3.45 (s, 2H) OH; 1.75–2.08 (m, 6H) $CH_2$; 1.25 (td, 12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 74.10 (dd, $^3J_{CP}$ = 14.8Hz, $C_3$); 68.94 (d, $^2J_{CP}$ = 4.6Hz, $C_2$); 61.88 (2d, $^2J_{CP}$ = 10.6Hz, $CH_2O$); 30.15 (d, $^1J_{CP}$ = 139.5Hz, $C_1$); 26.21 (d, $^2J_{CP}$ = 4.2Hz, $C_4$); 22.05 (d, $^1J_{CP}$ = 141.8Hz, $C_5$); 16.37 (d, $^3J_{CP}$ = 4.3Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 33.15 ⑤P; 30.68 ①P.

**SM**(DCI/$NH_3$) m/z: 377 ($MH^+$).

### *1,5-bis-(Diethyl Phosphono) 3-chloro 2-pentanol (9)*

Chorhydric acid was bubbled into a solution of 2g of 7 (5.6mmoles) in 50ml of diethyl ether during 48h at room temperature. The solution was cooled at 0°C and neutralized with an aqueous solution of $NaHCO_3$. The solvent was evaporated and water lyophilized. The product was extracted with ethyl acetate, then the solution filtered. The solvent was then evaporated and the product was purified by chromatography (methylene chloride and methylene chloride/methanol: 99/1) to give 1.65g of a yellow oil (75%).

**IR**(film) $\nu_{max}(cm^{-1})$: 3313 (OH); 1218 and 1162 (P=O); 970 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 4.45 (s,1H) OH; 3.98–4.09 (m, 10H) $CH_2O$, CHO and CHCl; 1.78–2.30 (m, 6H) $CH_2$; 1.25 (m, 12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 69.56 (d, $^2J_{CP}$ = 4.6Hz, $C_2$); 66.18 (dd, $^3J_{CP}$ = 17.6Hz, $C_3$); 61.95 (2d, $^2J_{CP}$ = 10.2Hz, $CH_2O$); 30.07 (d, $^1J_{CP}$ = 140.5Hz, $C_1$); 26.88 (d, $^2J_{CP}$ = 2.9Hz, $C_4$); 22.31 (d, $^1J_{CP}$ = 142.5Hz, $C_5$); 16.44 (2d, $^3J_{CP}$ = 2.2Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 31.24 ⑤P; 29.68 ①P.

**SM**(DCI/$NH_3$) m/z: 395 ($MH^+$).

### *1,5-bis-(Diethyl Phosphono) 3-chloro 2-pentanone (10)*

To 1.22g of **9** (31mmoles) in 5ml of acetone at 0°C were added 935mg of $CrO_3$, 2.7ml of water and 0.79ml of $H_2SO_4$. After 48h at room temperature the solution was neutralised with an aqueous solution of $NaHCO_3$. Acetone was evaporated

and water lyophilized. The product was extracted with ethyl acetate and filtred. The solvent was evaporated and the product purified by chromatography (methylene chloride/methanol: 98/2) to give 380mg of a green oil (31%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1720 (C=O); 1251 (P=O); 1025 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 3.97–4.16 (m,9H) $CH_2O$ and CHCl; 1.65–2.30 (m, 6H) $CH_2$; 1.28 (m, 12H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 195.34 (d, $^2J_{CP}$ = 6.1Hz, $C_2$); 62.88 (2d, $^2J_{CP}$ = 5.7Hz, $CH_2O^1P$); 62.19 (d, $^3J_{CP}$ = 18.0Hz, $C_3$); 61.82 (d, $^2J_{CP}$ = 6.2Hz, $CH_2O^5P$); 38.98 (d, $^1J_{CP}$ = 129.0Hz, $C_1$); 26.03 (d, $^2J_{CP}$ = 3.5Hz, $C_4$); 22.21 (d, $^1J_{CP}$ = 143.0Hz, $C_5$); 16.37 (d, $^3J_{CP}$ = 5.9Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 29.95 ⑤P; 18.71 ①P.

**SM**(DCI/$NH_3$) m/z: 393 ($MH^+$).

### *2-pentene 1,5-bisphosphonic Acid Tetrasodium Salt (11)*

1.506g of **6** (4.4mmoles), according to general procedure **b**, gave 1.1g of a white powder (79%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 3121 (CH=); 1684 (C=C); 1139 (P=O); 869 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 5.30–5.52 (m, 2H) CH=; 2.05–2.24 (m, 2H) $H_4$; 1.22–1.43 (m, 4H) $H_1$ and $H_5$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 135.69 (dd, $^3J_{CP}$ = 12.8Hz, $C_3$); 126.35 (d, $^2J_{CP}$ = 9.9Hz, $C_2$); 36.67 (d, $^1J_{CP}$ = 127.6Hz, $C_1$); 31.36 (d, $^1J_{CP}$ = 129.9Hz, $C_5$); 29.67 (d, $^2J_{CP}$ = 15.8Hz, $C_4$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 23.54 ⑤P; 20.40 ①P.

### *2,3-pentane Diol 1,5-bisphosphonic Acid Tetrasodium Salt (12)*

1g of **8** (2,66mmoles), according to general procedure **b**, gave 770mg of a white powder (82%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 3178 (OH); 1114 (P=O); 985 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 4.05 (s, 2H) OH; 3.81 (m, 1H) $H_2$; 3.40 (m, 1H) $H_3$; 1.36–1.64 (m, 6H) $CH_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 78.25 (dd, $^3J_{CP}$ = 15.2Hz, $C_3$); 73.17 (d, $^2J_{CP}$ = 3.4Hz, $C_2$); 34.63 (d, $^1J_{CP}$ = 126.4Hz, $C_1$); 29.97 ($C_4$); 28.10 (d, $^1J_{CP}$ = 131.5Hz, $C_5$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 23.95 ⑤P; 20.40 ①P.

### *3-chloro 2-pentanol 1,5-bisphosphonic Acid Tetrasodium Salt (13)*

900mg of **9** (2.3mmoles), according to general procedure **b**, gave 430mg of a white powder (51%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 3132 (OH); 1138 (P=O); 865 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 4.00–4.15 (m, 2H) $H_2$ and $H_3$; 1.50–2.25 (m, 6H) $CH_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 76.30 (d, $^2J_{CP}$ = 17.7Hz, $C_2$); 73.84 ($C_3$); 33.42 (d, $^1J_{CP}$ = 126.0Hz, $C_1$); 30.74 ($C_4$); 29.13 (d, $^1J_{CP}$ = 131.0Hz, $C_5$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 22.73 ⑤P; 20.03 ①P.

### *3-chloro 2-pentanone 1,5-bisphosphonic Acid Tetrasodium Salt (14)*

130mg of **10** (0.33mmoles), according to general procedure **d**, gave 118mg of a white powder (97%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 1698 (C=O); 1192 (P=O); 962 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 3.64–3.94 (m, 1H) CHCl; 1.25–2.37 (m, 6H) $CH_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 210.49 (C=O); 81.02 (d, $^3J_{CP}$ = 9.3Hz, CHCl); 45.50 (d, $^1J_{CP}$ = 102.2Hz, $C_1$); 29.32 ($C_4$); 22.30 (d, $^1J_{CP}$ = 118.5Hz, $C_5$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 46.16 ⑤P; 10.28 ①P.

### *3-(diethyl phosphono) 2-propenoic Acid (15c) Z*

1g of **15b** (5,2mmoles) with four equivalents of freshly prepared DMDO (general procedure **d**) gave after 4 days (followed by NMR$^{31}$P) 1.08g of colourless crystals after solvant excess evaporation (100%).

**IR**(film) $\nu_{max}(cm^{-1})$: 3031 (OH); 1713 (C=O); 1205 (P=O); 983 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 10.00 (s,1H) OH; 6.65 (2d, $^3J_{HH}$ = 20.0Hz,2H) $H_2$ and $H_3$; 4.04 (2q, $^3J_{HH}$ = 7.0Hz,4H) $CH_2O$, 1.21 (t, $^3J_{HH}$ = 7.0Hz,6H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 168.01 (d, $^3J_{CP}$ = 27.0Hz,C=O); 140.46 (d, $^2J_{CP}$ = 8.7Hz, $C_2$); 129.69 (d, $^1J_{CP}$ = 184.0Hz, $C_3$); 62.68 (d, $^2J_{CP}$ = 6.0Hz, $CH_2O$), 16.27 (d, $^3J_{CP}$ = 6.0Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 15.93.

**SM**(DCI;$NH_3$) m/z: 226 ($MH^+$).

### *3-phosphono 2-propenoic Acid Trisodium Salt (15)*

500mg of **15c** (2,4mmoles), according to general procedure **b**, gave 485mg of a white powder (92%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 3583 (CH=); 1692 (C=O); 1574 (C=C); 1204 (P=O); 1130 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 7.22–7.08 (dd, $^2J_{HP}$ = 12.4Hz; $^3J_{HH}$ = 17.1Hz,1H) $H_3$; 5.70–5.82 (dd, $^3J_{HH}$ = 9.0Hz; $^3J_{HP}$ = 7.6Hz, 1H) $H_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 182.88 (d, $^3J_{CP}$ = 15.9Hz, C=O); 138.38 (d, $^1J_{CP}$ = 160.3Hz, $C_3$); 136.52 (d, $^2J_{CP}$ = 12.8Hz, $C_2$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 13.88.

### *Diethyl Phosphono Crotonic Acid (16a)*

10g of triethylphosphono crotonate (40mmoles), according to general procedure **a**, gave 8.85g of white crystals (100%).

**IR**(film) $\nu_{max}(cm^{-1})$: 3029 (CH=); 1708 (C=O); 1212 (P=O); 988 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 10.19 (s, 1H) OH; 6.81 (tdd, $^3J_{HH}$ = 8.0Hz, 1H) $H_3$; 5.90 (dd, $^3J_{HH}$ = 5.0Hz, $^4J_{HP}$ = 15.5Hz,1H) $H_2$; 4.00–4.14 (qd, $^3J_{HP}$ = 7.0Hz, $^3J_{HH}$ = 7.0Hz,4H) $CH_2O$; 2.66–2.81 (dd, $^2J_{HP}$ = 23.8Hz, $^3J_{HH}$ = 8.4Hz, 2H) $PCH_2$; 1.26 (t,6H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 168.17 (d, $^4J_{CP}$ = 2.0Hz, C=O); 137.84 (d,$^3J_{CP}$ = 11.3Hz, $C_2$); 126.15 (d, $^2J_{CP}$ = 13.9Hz, $C_3$); 62.68 (d, $^2J_{CP}$ = 6.5Hz, $CH_2O$); 30.20 (d, $^1J_{CP}$ = 138.7Hz, $PCH_2$); 16.22 (d, $^3J_{CP}$ = 5.7Hz, $CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 25.13.

### *Phosphono Crotonic Acid Trisodium Salt (16)*

4.42g of **16a** (20mmoles), according to general procedure **b**, gave 2.55g of a white powder (55%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 3191 (CH=); 1654 (C=O); 1117 (P=O); 880 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 6.48–6.67 (td, $^3J_{HH}$ = 7.9Hz; $^3J_{HP}$ = 5.7Hz, 1H) $H_3$; 5.69–5.79 (dd,$^3J_{HH}$ = 15.4Hz; $^4J_{HP}$ = 4.3Hz, 1H) $H_2$; 2.25–2.40 (dd, $^2J_{HP}$ = 20.5Hz, $^3J_{HH}$ = 8.1Hz, 2H) $PCH_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 178.82 (C=O); 143.58 (d, $^3J_{CP}$ = 9.5Hz, $C_2$); 129.91 (d, $^2J_{CP}$ = 11.7Hz, $C_3$); 37.03 (d, $^1J_{CP}$ = 121.4Hz, $PCH_2$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 17.53.

### *Phosphono Crotonic Acid Tri-(tetrabutyl ammonium) Salt (18a)*

500mg of **16** (2.25mmoles) and 1.5ml of trimethylbromosilane were stirred for 24h at room temperature. Diethyl ether was added then water. The aqueous layer was then brought to pH 7.5 with tetrabutyl amonium hydroxide. After lyophilisation, a colourless oil was obtained.

**IR**(film) $\nu_{max}(cm^{-1})$: 1651 (C=O); 1164 (P=O); 1068 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 6.48 (td, $^3J_{HH}$ = 5.0Hz, 1H) $C_3$; 5.80 (dd, $^3J_{HH}$ = 5.0Hz, 1H) $C_2$; 3.05–3.13 (m, 24H) $NCH_2$; 2.39 (dd, $^2J_{HH}$ = 2.5Hz, $^2J_{HP}$ = 5.0Hz, 2H) $PCH_2$; 1.54 (m, 24H) $CH_2$; 1.20–1.30 (m, 24H) $CH_2$; 0.80–0.87 (t, 36H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 173.29 (C=O); 135.87 (d, $^2J_{CP}$ = 9.7Hz, $C_3$); 131.14 (d, $^3J_{CP}$ = 12.6Hz, $C_2$); 58.59 ($C_5$); 34.44 (d, $^1J_{CP}$ = 127.6Hz, $PCH_2$); 23.95 ($C_6$); 19.63 ($C_7$); 13.71 ($CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 17.63.

### *4-phosphono 2,3-epoxy Butanoic Acid Trisodium Salt (18)*

500mg of **18a** (1.1mmoles), according to the general procedure **d**, gave the epoxide. Cations were exchanged with sodium resin to give 35 mg of a white powder (25%).

**IR**(KBr) $\nu_{max}(cm^{-1})$: 1716 (C=O); 1090 (P=O); 974 (P-O).

**NMR$^1$H**($D_2O$, 200MHz) $\delta$(ppm): 3.17 (m, 2H) CH epoxide; 1.50–1.89 (m, 2H) $PCH_2$.

**NMR$^{13}$C**($D_2O$, 50MHz) $\delta$(ppm): 179.38 (C=O); 59.02 (d, $^3J_{CP}$ = 6.0Hz, $C_3$); 58.39 ($C_2$); 35.19 (d, $^1J_{CP}$ = 124.0Hz, $C_4$).

**NMR$^{31}$P**($D_2O$, 81MHz) $\delta$(ppm): 16.20.

### *3-phosphono 2-propenoic Acid Tri-(tetrabutyl amonium) Salt (17a)*

500mg of **15c** (2,4mmoles), according to the same procedure as **18a**, gave a colourless oil.

**IR**(film) $\nu_{max}(cm^{-1})$: 1690 (C=O); 1160 (P=O); 980 (P-O).

**NMR$^1$H**($CDCl_3$, 200MHz) $\delta$(ppm): 6.37 (td, $^3J_{HH}$ = 6.0Hz, 1H) $C_3$; 5.78 (dd, $^3J_{HH}$ = 6.0Hz, 1H) $C_2$; 3.15–3.18 (m,24H) $NCH_2$; 1.49 (m,24H) $CH_2$; 1.18–1.30 (m,24H) $CH_2$; 0.80–0.90 (t,36H) $CH_3$.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 178.03 (C=O); 140.65 (d, $^2J_{CP}$ = 10.0Hz, $C_3$); 131.47 (d, $^3J_{CP}$ = 12.1Hz, $C_2$); 60.72 ($CH_2N$); 36.00 (d, $^1J_{CP}$ = 151.0Hz, PCH); 25.76 ($CH_2$); 21.78 ($CH_2$); 15.51 ($CH_3$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 17.63.

### *3-phosphono 2,3-epoxy Propanoic Acid Trisodium Salt (17)*

845mg of **17a** (1.9mmoles), according to the same procedure as **18**, gave 104mg of a white powder (25%).

**IR**(film) $\nu_{max}(cm^{-1})$: 1709 (C=O); 1165 (P=O); 921 (P-O).

**NMR$^{1}$H**($CDCl_3$, 200MHz) $\delta$(ppm): 4.70 (m, 2H)CHO.

**NMR$^{13}$C**($CDCl_3$, 50MHz) $\delta$(ppm): 160.00 (C=O); 68.57 ($C_3$); 65.49 ($C_2$).

**NMR$^{31}$P**($CDCl_3$, 81MHz) $\delta$(ppm): 8.82.

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