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The Syntheses and Properties of 1,2-Epoxyalkylphosphonates

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Abstract. The present review article deals with the methods of preparation of dialkyl 1,2-epoxyalkylphosphonates as well as synthetically useful reactions of this class of compounds. Four main routes to 1,2-epoxyalkylphosphonates are described, in which new developments adapted to each processes are given, including the choice of the leaving group, new cyclisation methods and stereocontrol induction. Thermal and acid catalyzed rearrangements are also covered, and the use of the oxirane ring by nucleophilic opening is highlighted. Particular emphasis is placed on the synthetic approaches to antibiotic fosfomycin.

Key words: Darzens reaction, halohydrins, haloketones, fosfomycin, opening and rearrangement reactions.

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1. Introduction

The discovery of antibiotic fosfomycin¹ [(-) (1*R*,2*S*)-(Z)-1,2-epoxypropylphosphonic acid] in 1969 has generated a regular interest in the chemistry of 1,2-epoxyalkylphosphonates and gave rise to a large number of synthetic preparations. It has also given to 1,2-epoxyalkylphosphonates and derivatives a biochemical significance. As a consequence of this discovery, a lot of research has resulted in the extensive development of methodologies in order to prepare analogs of fosfomycin and to diversify the syntheses. These techniques have largely contributed to extend the synthetic utility of the epoxyphosphonate function and have greatly diversified the reactions available for the construction of the epoxide ring. As synthetic intermediates, these compounds owe their interest to the presence of the epoxide ring, which participates as an electrophilic site and governs their chemical reactivity. The purpose of this review is to provide a general overview of the synthetic reactions, which have been realized in the epoxyphosphonate field and to help focus attention on these valuable derivatives. In this paper, the various methods of preparation of 1,2-epoxyalkylphosphonates, with an emphasis on the syntheses of fosfomycin, and the types of reactions they undergo are summarized.

2. Preparations

Several methods of synthesis of dialkyl 1,2-epoxyalkylphosphonates are known, they may be classified into four main categories of reactions including (a) the Darzens reaction of dialkyl chloromethylphosphonates with carbonyl compounds, (b) the reaction of sodium dialkylphosphites with α -haloketones, (c) the reaction of dialkyl halohydrinphosphonates with bases, and (d) the oxidation of 1,2-unsaturated phosphonates with a peroxide. These procedures, which usually involve a one-step operation, allow the coverage of a large variety of dialkyl 1,2-epoxyalkylphosphonates.

2.1. The Darzens reaction

The Darzens synthesis of glycidic esters by the condensation of carbonyl compounds with α -haloesters² is an important and useful method, which has been extended in phosphorus chemistry. Unquestionably, the most general and perhaps most widely employed method for the synthesis of dialkyl 1,2-epoxyalkylphosphonates involves the reaction of dialkyl chloromethylphosphonates **1** with carbonyl compounds. The synthetically useful dialkyl chloromethylphosphonates **1** were readily obtained by standard alcoholysis under anhydrous

conditions of the chloromethylphosphonyl dichloride.³ The latter was obtained in up to 67% yield from phosphorus trichloride and paraformaldehyde at 250°C.⁴ Several variations on the preparation of dialkyl 1,2-epoxyalkylphosphonates **3** from dialkyl chloromethylphosphonates **1** and different carbonyl partners have been reported. The conditions of generating the α -metallated dialkyl chloromethylphosphonates were found to be critical due to their notorious instability. With alkoxide bases, the addition of sodium ethoxide or potassium *t*-butoxide to an equimolecular amount of dialkyl chloromethylphosphonate and carbonyl compound (aromatic aldehydes or ketones) in diethyl ether or *t*-butyl alcohol at temperatures varying between -10°C and +10°C leads to dialkyl 1,2-epoxyalkylphosphonates in low to good yields (10-68%).⁵ Best yields were obtained when the dialkyl chloromethylphosphonates **1** were metallated by treatment with *n*-BuLi in THF at low temperature.⁶ The resulting carbanions **2** undergo facile addition with carbonyl compounds to give the almost immediate formation of chlorohydrins, which on warming conduce quantitatively to dialkyl 1,2-epoxyalkylphosphonates **3** without trace of side products (Scheme 1). These conditions were found to be preferable for preparing dialkyl 1,2-epoxyalkylphosphonates **3** in pure form and in good to excellent yield (50-90%). This method appears to be applicable to a wide range of carbonyl compounds so that aliphatic and aromatic aldehydes as well as aliphatic, cyclic and aromatic ketones may be introduced in the reaction (Table 1). The Darzens process was without side reactions, but was not stereoselective, and mixtures of *E* and *Z* isomers were frequently obtained with the *E* form being preferred. Metallated diethyl chloromethylthiophosphonates have also served as precursors to diethyl 1,2-epoxyalkylthiophosphonates.⁶

Scheme 1

Diethyl 1,2-epoxyalkanephosphonates⁶: A 1.45 molar solution of *n*-butyllithium in hexane (0.054 mol + 5%) is placed in a three necked flask equipped with a stirrer, an addition funnel, a low temperature thermometer and a nitrogen inlet tube. An equal volume of tetrahydrofuran (~40 ml) is added to the cooled (-20°) solution. Subsequently diethyl chloromethanephosphonate (10 g, 0.054 mol) in tetrahydrofuran (15 ml) is added dropwise at -70°C. After ~10 min the clear reaction mixture becomes turbid and the carbonyl compound (0.054 mol) in tetrahydrofuran (10 ml) is added at -75° to -70°. The mixture becomes clear, stirring is continued for 1 h at -70°, and then the mixture is allowed to warm to room temperature within a few min. Stirring is continued at room temperature for 17 h, water (40 ml) is added, and the product is extracted into 1:1 ether / dichloromethane (3 x

50 ml). The combined organic layers are dried with magnesium sulfate, the solvent is removed under reduced pressure and the product is purified by vacuum distillation.

Table 1. Synthesis of dialkyl 1,2-epoxyalkylphosphonates by the Darzens reaction.

3	R¹	R²	R³	Base/Solvent	Yield (%)	Ref.
a	Et	Me	Me	<i>n</i> -BuLi/THF	80	6
				NaH/DMSO	61	16
b	Et	Et	Et	<i>n</i> -BuLi/THF	89	6
c	Et	<i>i</i> -Pr	<i>i</i> -Pr	<i>n</i> -BuLi/THF	88	6
d	Et	Me	Et	<i>n</i> -BuLi/THF	85	6
e	Et	Me	<i>i</i> -Pr	<i>n</i> -BuLi/THF	86	6
f	Et	Me	<i>t</i> -Bu	<i>n</i> -BuLi/THF	75	6
g	Et	Me	<i>i</i> -Bu	<i>n</i> -BuLi/THF	81	6
h	Et	Me	$-\text{CH}=\text{CH}_2$	<i>n</i> -BuLi/THF	36	6
i	Et	Me	$-\text{C}=\text{CH}_2$ Me	<i>n</i> -BuLi/THF	75	6
			$-\text{CH}(\text{OMe})_2$	<i>n</i> -BuLi/THF	76	6
k	Et	Me		<i>n</i> -BuLi/THF	90	6
l	Et	Me		<i>n</i> -BuLi/THF	51	6
				NaH/DMSO	-	13
m	Et	H	Me	<i>n</i> -BuLi/THF	65	6
n	Et	H	<i>i</i> -Pr	<i>n</i> -BuLi/THF	66	6
o	Et	H	<i>i</i> -Bu	<i>n</i> -BuLi/THF	57	6
p	Et		$-(\text{CH}_2)_4-$	<i>n</i> -BuLi/THF	76	6
q	Me	Me	$-(\text{CH}_2)_2\text{CH}(\text{Me})_2$	EtONa/ether	37	5
r	Et	H		EtONa/ether	31	5
				<i>t</i> -BuOK/ <i>t</i> -BuOH	43	5
s	Me	Me		EtONa/ether	21	5
				<i>t</i> -BuOK/ <i>t</i> -BuOH	36	5
t	Me	H		<i>t</i> -BuOK/ <i>t</i> -BuOH	65	5
				EtONa/ether	14	5
u	Et	H		<i>t</i> -BuOK/ <i>t</i> -BuOH	61	5
				NaH/DMSO	-	13
v	Me	Me	Me	NaH/DMSO	-	13

w	Me	Ph	Ph	NaH/DMSO	-	13
x	Et	Ph	Ph	NaH/DMSO	-	13
y	Et		$-(\text{CH}_2)_5-$	NaH/DMSO	-	13
				$\text{NaNH}_2/\text{C}_6\text{H}_6$	-	14
z	Me	H		<i>t</i> -BuOK/ <i>t</i> -BuOH	68	5
aa	Me	H		<i>t</i> -BuOK/ <i>t</i> -BuOH	10	5
ab	Et	H		NaH/ C_6H_6	-	15

Several recent innovations have significantly extended the scope and synthetic utility of the classical Darzens reaction. For example, a useful supplement applicable to the formation of 1-substituted-1,2-epoxyalkylphosphonates has been described to convert diethyl alkylphosphonates **4** into diethyl 1-substituted-1,2-epoxyalkylphosphonates **6** by a one-step process.⁷ Metallation of diethyl alkylphosphonates **4** with 2 eq. of *n*-BuLi in THF at low temperature followed by electrophilic chlorination using benzenesulfonyl chloride yields the diethyl 1-lithiochloroalkylphosphonates **5**, which were converted into diethyl 1-substituted-1,2-epoxyalkylphosphonates **6** by reaction with carbonyl compounds in moderate to good overall yields (30 to 80%) (Scheme 2).

Scheme 2

Diethyl 1,2-epoxyalkanephosphonates⁷: To a stirred solution of diethyl alkanephosphonate (1 mmol) in dry THF (3 ml) is added *n*-butyllithium (2.2 mmol, 1.6 M in hexane) at -78°C under nitrogen atmosphere. After being stirred for 30 min at same temperature, benzenesulfonyl chloride (1 mmol) and carbonyl compound (1 mmol) are added successively and the mixture is allowed to warm with stirring to room temperature. Stirring is continued at room temperature for 15 h, sat. NH₄Cl solution (10 ml) is added, and the mixture is extracted with ether (3 x 20 ml). The combined organic layer is dried with MgSO₄, the solvent is removed under reduced pressure and the product is purified by column chromatography on silica gel (ethyl acetate / hexane = 1 / 1).

The halogen-metal exchange reaction of diethyl 1,1-dichloroalkylphosphonates **7** with *n*-BuLi provides another convenient preparation of diethyl 1-lithio-1-chloroalkylphosphonates **5**.⁸

This gives a somewhat higher yield of carbanion than is obtained by the chlorination procedure. For example, trapping of diethyl 1-lithio-1-chloroethylphosphonate **5** ($R^4=Me$) with aliphatic or aromatic aldehydes and aliphatic ketones provides a suitable route to diethyl 1-methyl-1,2-epoxyalkylphosphonates **6** ($R^4=Me$) in good yields (61-81%) (Scheme 3) as a mixture of *Z* and *E* isomers in approximately equal amounts.⁹

Scheme 3

Diethyl 1,2-dimethyl-1,2-epoxypropanephosphonate⁹: A solution of diethyl 1,1-dichloroethane-phosphonate (5.9 g, 25 mmol) in ether (25 ml) and THF (20 ml) is placed in a three necked flask equipped with a stirrer, addition funnel, low temperature thermometer, and nitrogen inlet tube, *n*-BuLi (21.2 ml of a 1.25 M solution in ether, 5% excess), is added dropwise to the cooled solution ($-100^\circ C$) under nitrogen (5 min). When the addition is finished the temperature is allowed to reach $-85^\circ C$ for 30 min. Then, at $-90^\circ C$, a solution of acetone (1.5 g, ~26 mmol) in ether (10 ml) is added and the cooling is removed. When the temperature has reached $-50^\circ C$, a 1+1 mixture (10 ml) of HMPT-THF is added and stirring is continued for 30 min at $0^\circ C$. Then, 2 normal sulfuric acid (20 ml) is rapidly added and the mixture is extracted with ether (3 x 50 ml). The organic phase is washed with 1 normal sulfuric acid (50 ml) and with saturated sodium chloride solution (2 x 100 ml), it is dried with magnesium sulfate, the solvents are removed at reduced pressure, and the oily residue is distilled in vacuo; yield: 4.5 g (80%); b.p. $70^\circ C / 0.25$ torr.

A new technique for the formation of 1,2-epoxyalkylphosphonates **3** is based upon the reactivity towards aromatic aldehydes of electrochemically generated carbanion of diethyl chloromethylphosphonate **1** ($R^1=Et$) in DMF.¹⁰ The yield of 72% obtained with *p*-methoxybenzaldehyde was promising. However, the major disadvantage, which attends the use of the electrochemical route is the difficulty that may be encountered in the electrogeneration of species sufficiently basic to deprotonate the chloromethylphosphonates.

An interesting and useful variant of the Darzens reaction has been reported for the preparation of fosfomycin from diethyl chloromethylphosphonate **1** ($R^1=Et$).¹¹ Nucleophilic substitution of the chlorine in diethyl chloromethylphosphonate with dimethyl sulfide gives the sulfonium salt **8**, which may be further converted into its stable ylide by the use of $MeS(O)CH_2Na$. The use of the ylide in addition to acetaldehyde produces the diethyl 1,2-epoxypropylphosphonate **9**, thus avoiding the problems associated with stability of chloromethylphosphonate carbanions (Scheme 4).

Scheme 4

The use of diazomethane derivatives represents another modification of the Darzens reaction (Scheme 5). However, the reaction was not effective enough and remains undeveloped.¹² Diphenyldiazomethane on reaction with dimethyl α -ketophosphonates **10** undergoes reactions typical of carbonyl compounds to give the corresponding dimethyl 1-substituted-2,2-diphenyl-1,2-epoxyethylphosphonates **11**.

Dimethyl 1-(4-methoxyphenyl)-2,2-diphenyl-1,2-epoxyethylphosphonate¹⁷: It was prepared by adding diphenyldiazomethane (2.7 g, 14 mmole) with stirring over a 3 day period to 16 g (66 mmole) of dimethyl *p*-methoxybenzoylphosphonate. The reaction temperature was maintained at 62°C, and the rate of addition determined by the disappearance of the red color of the diazomethane. Colorless crystals of epoxide precipitated. This material was recrystallized from benzene-hexane to afford 2.8 g (49%) of epoxide, mp 142.0-144.0°C.

Scheme 5

2.2. The reaction of sodium dialkylphosphite with α -haloketones

In connection with the reaction of α -haloketones with nucleophiles, which is a standard epoxide synthesis,¹⁸ it is well recognized that reaction of α -haloketones **13** with the appropriate phosphorus nucleophiles can constitute an interesting but somewhat limited method of synthesis of dialkyl 1,2-epoxyalkylphosphonates **6**. Effectively, the conditions required for this procedure may not be compatible with the sensitive functionalities of α -haloketones, and the reaction sometimes proceeds with a lack of regiospecificity to produce a mixture of phosphorus compounds. Thus, this reaction has been reported to give the epoxide alone,^{24,28} the vinyl phosphate alone,^{25,36} a mixture of the epoxide and vinyl phosphate,^{20,21,23} or a mixture of the epoxide and β -ketophosphonate.^{22,26,27,29} A large number of investigations have led to propose four types of mechanisms involving an initial attack of the phosphorus on: the halogen,³¹ the carbonyl oxygen,³² the α -carbon bound to the halogen³³ or on the carbonyl carbon.^{34,35} Formation of the vinyl phosphate, epoxyphosphonate and phosphate halohydrin is believed to result from attack by the

phosphorus at the carbonyl carbon. Formation of the β -ketophosphonate results from attack at the α -halo carbon. Alkali metal derivatives of dialkylphosphites **12** (M=Na, K) attack α -haloketones **13** (X=Cl, Br) primarily at the carbonyl carbon atom forming an alkoxide anion **14**, which displaces the β -halogen to give the dialkyl 1,2-epoxyalkylphosphonates **6** (Scheme 6) with reasonable yields in the range 55 to 71% (Table 2). In some cases, however, formation of vinyl phosphate **15** can be a competing reaction.^{20,21,23,30} This procedure appears to be limited to the synthesis of epoxides having only one non-hydrogen β -substituent since the α -halo carbon cannot be tertiary, the vinyl phosphate being the main product.^{20-22,36,37}

Scheme 6

1-Méthyl-1,2-époxyéthylphosphonate de diéthyle²⁴: Dans un tricol de 500 ml muni d'une ampoule isobare, d'un agitateur, d'un thermomètre, et isolé de l'extérieur par un tube à CaCl₂, on place 0,3 M de phosphite sodé en solution étherée. On refroidit à -70°C à l'aide d'un mélange carboglace-acétone. On ajoute alors goutte à goutte une solution 0,3 M de chloracétone diluée dans son volume d'éther anhydre. On maintient le Dewar toute la nuit. Le lendemain matin, la température est de 30°C. On supprime le refroidissement, on laisse le mélange revenir progressivement à température ordinaire. On chauffe ensuite 2 h à reflux. La minéralisation qui devait se produire n'apparaît pas. La solution laiteuse est très difficile à centrifuger. On ajoute 150 ml de DMF et ayant placé une petite colonne, l'éther est distillé jusqu'à ce que la température atteigne 110°C. On adapte alors un réfrigérant ascendant, et cette température est maintenue pendant 1 h. Il se forme une importante minéralisation. Après refroidissement, on centrifuge, on chasse le DMF à la trompe et distille. Une rectification soignée donne E.b.=75°C / 0,6 mm Hg; Pds=35 g.

Table 2. Synthesis of dialkyl 1,2-epoxyalkylphosphonates from sodium dialkylphosphites and α -haloketones.

6	R ¹	R ²	R ³	R ⁴	X	Yield (%)	Ref.
a	Me	H	H	Me	Cl	74.4	45
b	Me	C ₆ H ₅	H	C ₆ H ₅	Cl	-	14
c	Me	C ₆ H ₅	H	4-MeO-C ₆ H ₄	Cl	-	14
d	Et	H	H	C ₆ H ₅	Cl	56	23

e	Et	H	H	Me	Cl	76.6	45
					Cl	27	22
					Cl	65	24
f	Et	H	H	Et	Cl	71.5	24
g	Et	H	H	C ₆ H ₅	Br	-	20b
h	Et	H	-(CH ₂) ₃ -		Cl	-	21
i	Et	H	-(CH ₂) ₄ -		Cl	-	21
					Br		20a
j	Et	Me	H	Me	Cl	52.6	45
					Br	-	22
k	Et	Me	H	C ₆ H ₅	Br	-	20b
l	Et	C ₆ H ₅	H	Me	Cl	-	14
m	Et	C ₆ H ₅	H	<i>t</i> -Bu	Cl	-	14
n	<i>i</i> -Pr	H	H	Me	Cl	68.7	45
					Cl	-	22
o	<i>n</i> -Bu	H	H	Me	Cl	69.1	45
					Cl	69	24

An alternative procedure for the preparation of dialkyl 1,2-epoxyalkylphosphonates **6** from α -haloketones is the action of sodium methoxide (1 eq.) on a mixture of α -chloroketones **13** (X=Cl) and dimethyl- or diethylphosphite (1 eq.) in methanol at room temperature.³⁷ The reproducible yields of 53 to 84% obtained by this technique represent a significant improvement over the yields of 30 and 63% reported for the one-step reaction of α -chloroketones with sodium diethylphosphite. This procedure appears to give only the epoxides with aliphatic α -chloroketones and attempts to form the epoxide by reaction of α -chloroacetophenone with dimethylphosphite resulted in the formation of dimethyl 1-phenylvinylphosphate. However, in spite of the difficulties frequently encountered in the choice of the α -chloroketones, this facile and convenient procedure is a useful variant of the classical approach as illustrated by the results gathered in the Table 3.

Table 3. Synthesis of dialkyl 1,2-epoxyphosphonates from dialkylphosphites, α -chloroketones and sodium methoxide.

6	R ¹	R ²	R ³	R ⁴	Yield (%)	Ref.
a	Me	H	H	Me	84	37
e	Et	H	H	Me	83	37
p	C ₆ H ₅ CH ₂	H	H	Me	48	37

q	Me	H	H	<i>t</i> -Bu	87	37
r	Me	H	Me	<i>t</i> -Bu	70	37
s	Me	H	Me	Me	53	37
t	Me	H	-(CH ₂) ₄ -		33	37

Dimethyl 1,2-epoxy-2-propylphosphonate³⁷: A solution of sodium methoxide was prepared by dissolving 0.06 mol (1.37 g) of sodium in 25 ml of methanol. The sodium methoxide was then added dropwise over a period of 15 min to a mixture of 0.06 mol (5.55 g) of chloroacetone and 0.06 mol (6.60 g) of dimethyl phosphite in 5 ml of methanol at room temperature. After stirring for 1h the solution was filtered, distilled to remove methanol, and refiltered. Ether was then added to precipitate any remaining sodium chloride. The solution was filtered again and ether evaporated off. A short-pass distillation gave the title compound: b.p. 75-76°C (0.7 mm Hg).

The reaction between diethylphosphite and α -chloroketones **13** (X=Cl) can also be accomplished by fluoride ion-deprotonation reaction in DMF (dry KF or KF·2H₂O are fluoride ion source), which proves a non-basic route to diethyl 1,2-epoxyalkylphosphonates. However, the application of this technique provides a mixture of 1,2-epoxyphosphonate (about 50%) and vinyl phosphate (about 30%) whatever the α -chloroketones.³⁸

The reaction conditions required for the preparation of halogenoketones frequently may not be compatible with the sensitive functionalities that are present in complex polyfunctional molecules. Recent innovations in the standard synthetic procedure using α -haloketones have featured the use of a new class of leaving groups, α -tosyloxyketones.³⁹⁻⁴³ For example, a relatively general procedure for the quantitative generation of dialkyl 1,2-epoxyphosphonates **17** possessing a sugar or a steroid appendage using α -tosyloxyketones **16** has been employed. Generation of the epoxides may be conveniently executed under a variety of reaction conditions. They include sodium diethylphosphite in EtOH at reflux (69%),³⁹ diethylphosphite in the two-phase system CH₂Cl₂/NaOH 50%/TBAC at room temperature⁴¹ or diethylphosphite in MeOH in the presence of DBU at 0°C (62-90%)^{42a,42b,43} (Scheme 7). This attractive procedure appears as a useful modification having a great synthetic utility since the leaving group is introduced in mild conditions by merely treating the sensitive substrat containing a primary alcohol with TsCl in the presence of pyridine.⁴³

Scheme 7

(5R or 5S)-5,6-anhydro-3-O-benzyl-5-C-(dimethoxyphosphinyl)-1,2-O-isopropylidene- α -D-xylo-hexofuranose⁴²: To a mixture of 3-O-benzyl-1,2-O-isopropylidene-6-O-*p*-tolylsulfonyl- α -D-xylo-hexofuranose (5.6 g) and dimethyl phosphite (1.5 g) in methanol (10 ml) was added DBU (2.1 g) during 1 h at 0°C, and the solution was kept in a refrigerator for 48 h. The methanol and unreacted dimethyl phosphite were removed in vacuo, and then a solution of the residue in chloroform was successively washed with aqueous sodium hydrogencarbonate and water, dried (sodium sulfate), and evaporated, to afford a syrup, which was chromatographed in a column of silica gel, using 1:2 (v/v) ethyl acetate-petroleum ether as the eluant. The fractions were suitably pooled, and evaporated in vacuo to give a syrup (3.4 g, 70%), which crystallized after 2 days; m.p. 107-108°C (ethyl acetate-hexane).

Another variation reports a one-pot synthesis of diethyl 1-(perfluoroalkyl)-1,2-epoxyalkylphosphonates **19** using the nucleophilic attack of lithium diethylphosphite on the carbonyl carbon atom of the perfluorinated β -oxophosphonium salts **18** (Scheme 8).⁴⁴ The resulting intermediate can eliminate in two directions. When the oxygen anion with the least sterically hindered position attacks the neighbouring carbon atom it gives, after elimination of triphenylphosphine (*anti* fashion), the diethyl 1-(perfluoroalkyl)-1,2-epoxyalkylphosphonates **19** in moderate yields (42-51%). The formation of the α -(perfluoroalkyl)vinylphosphonates **20** by attack at phosphorus (*syn* fashion) can be a competing reaction. The results indicate that the selectivity could be controlled to produce exclusively either epoxyphosphonates or vinylphosphonates depending on steric factors (R^2, R^3) and the base used.

Scheme 8

Diethyl (3,3-dimethyl-2-pentafluoroethyloxiran-2-yl)phosphonate⁴⁴: *n*-Butyllithium (3.0 mmol) or methyllithium (3.0 mmol) in dry tetrahydrofuran (THF) was added dropwise to a stirred suspension of the phosphonium salt **18** (3.0 mmol) in absolute THF (30 ml) at -20°C under nitrogen. The mixture was stirred for 30 min at 0°C and cooled to -78°C ; the perfluoroalkanoic anhydride (2.5 mmol) was slowly added until the characteristic ylidic colour had disappeared. The mixture was stirred at -78°C for 5 min and a solution of diethyl lithium phosphite [prepared by the reaction of ethyl hydrogen phosphite (0.41 g, 3.0 mmol) and methyllithium (3.0 mmol) in THF (10 ml) for 30 min at -78°C] was slowly added. The mixture was allowed to warm to room temperature, stirred for a further 2 h, and diluted with light petroleum (b.p. $60-90^\circ\text{C}$). Filtration and evaporation of filtrate gave a residue, which was purified by column chromatography on silica gel with light petroleum (b.p. $60-90^\circ\text{C}$)-ethyl acetate (10:1) as eluant to give the title product: yield 42%; b.p. $84^\circ\text{C} / 2 \text{ mm Hg}$.

The most recent development in the field has featured the use of phase transfer catalyst conditions in the preparation of dialkyl 1,2-epoxyalkylphosphonates from dialkylphosphites and α -haloketones **13** ($\text{X}=\text{Cl}$).⁴⁵ A first procedure uses potassium carbonate in excess as base, and a second a mixture of potassium carbonate and sodium hydrogen carbonate, TBAB being introduced as phase transfer catalyst. Each reaction was carried out in the absence of solvent, the liquid phase being formed by the starting reagents. This method does not improve the yields of dialkyl 1,2-epoxyalkylphosphonates, which are roughly comparable to those previously reported. However, the absence of undesired side products, which usually accompany this reaction renders this methodology a viable alternative to the methods, which require the use of a solvent.

2.3. The reaction of dialkyl halohydrinphosphonates and related structure with bases

In addition to the two previous methodologies, there is a technique, which employs the conversion of halohydrinphosphonates into epoxyphosphonates by formation of an alkoxide anion. This two-step procedure appears to be limited to the synthesis of dialkyl 1,2-epoxyethylphosphonates having hydrogens or only one non-hydrogen substituent. Formation of halohydrinphosphonates can be accomplished by two procedures, which exploit either the condensation of a dialkylphosphite with an α -chlorocarbonyl compound or the halohydroxylation of a vinylphosphonate. The reaction of dialkylphosphites proceeds upon heating for a long time with α -chloroketones at $100-165^\circ\text{C}$ with a catalyst (MeONa/MeOH)¹⁹

or at 100-120°C without catalyst,⁴⁷ and with chloroacetaldehyde⁴⁶ at 100°C without any catalyst to give, in 50 to 100% yields, the chlorohydrinphosphonates having the hydroxyl group in the α position. The reaction between diethylphosphite and chloroacetaldehyde can proceed also at room temperature in the presence of catalytic amount of triethylamine.⁴⁸

Diethyl 2-chloro-1-hydroxyethylphosphonate⁴⁸: A mixture of diethyl phosphite (27.6 g) and chloroacetaldehyde (15.6 g) was stirred at room temperature for 3 h in the presence of a few drops of triethylamine. Distillation in vacuo of the resultant reaction mixture gave 23.7 g (63%) of the title compound; b.p.=116-118°C / 0.06 mm Hg.

The halohydroxylation method has been developed for exploiting the reactivity of the double bond present in the dialkyl vinyl- and propenylphosphonates. The preparation of the halohydrins of diethyl vinylphosphonate **21**, which failed to be accomplished using N-bromosuccinimide or N-bromoacetamide, was achieved on large scale by treatment of diethyl vinylphosphonate **21** with sodium hypochlorite or hypobromite in aqueous medium at pH<3 to give the halohydrins **22** with the hydroxyl group in the β position (anti Markovnikoff addition) having a 95% purity for the chlorohydrin and a 65-85% purity for the bromohydrin (Scheme 9).⁴⁹ As a consequence of the acid conditions, the preparation of halohydrins **22** was generally accompanied by the formation of undesired diethyl 1,2-dihalogenophosphonates **23**.⁴⁹

Scheme 9

1-Chloro-2-hydroxyéthylphosphonate de diéthyle⁴⁹: Dans un erlenmeyer muni d'une vive agitation magnétique, on place 0,1 mole de diéthyl vinylphosphonate dissous dans 700 ml d'eau. La solution est portée à un pH <3 par addition d'HCl concentré (d=1,19). On ajoute alors par petites portions (~15 ml) la solution d'hypochlorite de sodium, tout en maintenant le pH de la solution ≤ 3 par addition simultanée d'HCl concentré. La réaction est considérée comme terminée lorsque le test à l'IK est positif après 15 mn d'attente après la dernière addition de NaOCl. (test à l'iodure de potassium dans un tube à essai, verser 1 ml du milieu réactionnel et 1 ml d'une solution à 10% d'IK. L'apparition d'une coloration jaune-brun atteste la présence d'acide hypohalogéneux). La quantité habituelle d'hypochlorite de sodium additionnée est de l'ordre de 50 à 55 ml et celle de HCl environ 10 ml. Une fois l'addition de NaOCl terminée, le milieu est extrait par 6 x 50 ml de CH₂Cl₂ et 100 ml de CHCl₃. Les phases organiques sont rassemblées et séchées sur Na₂SO₄ anhydre. Après évaporation des solvants, le résidu est distillé sous vide de la pompe. Le distillat est identifié comme un mélange des composés **22** et **23**. **22**: Eb.=105-108°C / 0,05 mmHg; Rdt=86%. **23**: Eb.=92°C / 0,05 mmHg.

Synthetic reactions, which result in the bromohydroxylation of the monoester of propenylphosphonate⁵⁰ with N-bromoacetamide in water at 15°C and in the chloro- or bromohydroxylation of the diacid with N-chloro- or bromosuccinimide, were particularly useful to provide in good conditions the two isomeric *threo*-halohydrins, which can be separated prior to epoxidation. For example, crystallization from acetone of the mixture of diastereomeric bromohydrins prepared by bromohydroxylation of the monoester of propenylphosphonate provided the preferred *threo*-bromohydrin in diastereomerically pure form.⁵⁰

A variety of procedures have been developed to effect the conversion of α - or β -hydroxy halohydrins into 1,2-epoxyalkylphosphonates (NaH / THF;⁴⁹ KOH / THF;⁴⁹ EtO⁻ / EtOH;⁴⁹ KOH / EtOH;^{19,46,47,49} K₂CO₃ / MeOH or EtOH;⁴⁹ NaOH / CH₂Cl₂ / TBAS⁴⁹). Generally, bromohydrinphosphonates give better results than corresponding chlorohydrinphosphonates. The phase transfert catalysis using the chlorohydrin **22** (X=Cl) of diethyl vinylphosphonate and concentrated (50%) sodium hydroxyde at room temperature has been found to be the method of choice for preparing the diethyl 1,2-epoxyethylphosphonate **24** (74%) on large scale (Scheme 9).⁴⁹ The methods using alkoxide anion or KOH in alcohol tend to be accompanied by important monodealkylation at carbon ester. The preferred *threo*-bromohydrin obtained from propenylphosphonic acid was converted to epoxide by reaction with MeONa in MeOH at 40°C.⁵⁰

Diethyl 1,2-epoxyethylphosphonate⁴⁸.

Method A : An ethanolic solution of 32 g of potassium hydroxide was added dropwise with stirring to a solution of the chlorohydrin (124 g) in ethanol (300 ml) at 4-6°C. Stirring was continued at room temperature for 10 h. The mixture was then filtered, concentrated, and distilled in vacuo; yield: 57.6 g (54%).

Method B : An ethanolic solution of 19.2 g of sodium ethoxide was added dropwise with stirring to a solution of the chlorohydrin (60 g) in ethanol (300 ml) at 10-18°C. Stirring was continued at room temperature for 7 h. The mixture was then filtered, concentrated, and distilled in vacuo; yield: 28.6 g (56%).

Method C : An aqueous solution of 10 g of potassium hydroxide was added dropwise with stirring to the chlorohydrin (30.5 g) at room temperature. Stirring was continued for 5 h. The mixture was then concentrated, extracted with ether, the ether distilled, and the residue distilled in vacuo; yield: 5.7 g (23%), b.p.=86-89°C / 2 mm Hg.

Oxidation of the tetraethyl ethenylidene-1,1-diphosphonate **25** with aqueous NaOCl gives directly the tetraethyl oxiranylidene-1,1-diphosphonate **26** via nucleophilic Michael β -addition of the hypochlorite anion followed by ring closure (Scheme 10).⁵¹ Preparation of the tetrasodium salt **28** of the corresponding epoxide was accomplished in a two step process through the bromohydrin **27**. The latter was prepared from **25** by treatment of the double bond with Br₂ / H₂O, followed by ring closure by addition to a concentrated solution of NaOH.

Scheme 10

Oxidation of the methyldene double bond in triethyl α -phosphonoacrylate **29** has been investigated in details using O₂, catalytic RuO₄ (made in situ from RuO₂ / NaOCl or RuO₂ / NaIO₄) or stoichiometric RuO₄ (Scheme 11).⁵² Treatment of triethyl α -phosphonoacrylate **29** on large scale in a two-phase (CCl₄ / H₂O) reaction mixture with catalytic RuO₄ using NaOCl as co-oxidant or with NaOCl alone at room temperature produces triethyl α -phosphonoacrylate oxide **30** in up to 79% isolated yield. As above, epoxidation of the double bond would begin with nucleophilic addition of the ClO⁻ followed by ring closure. When NaOCl was replaced with NaIO₄ as the RuO₂ reoxidant in a two-phase (CHCl₃ / H₂O) reaction mixture, the major product in the aqueous phase was the triethyl dihydroxyphosphonoacetate **31**, the hydrate of triethyl oxophosphonoacetate.

Scheme 11

***dl*-Triethyl α -phosphonoacrylate oxide⁵²:** A 1 l flask was charged with CCl₄ (alternatively, CHCl₃) (250 ml) and 5.25% sodium hypochlorite solution (400 ml; 282 mmol). RuO₂ (11 mg; 0.08 mmol) was added, and observed to immediately oxidize to RuO₄ (yellow organic phase). A small portion of triethyl α -phosphonoacrylate was added with vigorous shaking, causing the color of the reaction mixture to change

briefly to black; when the mixture again became yellow, more alkene was added in the same manner. After 10 min, addition of alkene was complete (10 g; 42 mmol) and the two phases were separated. The organic layer was treated with isopropanol (1 ml), then filtered through Celite, dried (MgSO₄), re-filtered, and evaporated under reduced pressure. The pale brown, oily residue was distilled under reduced pressure to give 7.49 g (71%) of the product as a colorless oil, b.p. 92-94°C (0.002 mm).

In the steroid field,⁵³ bromohydroxylation of the vinylphosphonate derived from cholestanone was carried out with bromine in aqueous acetic acid to afford a mixture of products containing the desired bromohydrin, which was converted to the epoxide by further treatment with MeONa in MeOH.

One ingenious procedure for the construction of a nucleoside epoxyphosphonate from a 1,2-dihydroxyalkylphosphonate exploits the properties of triflates, which serve as a good leaving groups (Scheme 12).⁵⁴ Treatment of 1,2-diol **32** with trifluoromethanesulfonyl chloride (TfCl) and 4-dimethylaminopyridine (DMAP) directly affords the epoxide **33** in 31% yield via displacement of an intermediate 2'-triflate unfortunately accompanied by formation of a significant by-product identified as a methylated uracil derivative **34**. When the hydroxyphosphonate was treated with trifluoromethanesulfonyl chloride and 4-pyrrolidinopyridine (4-PDP) in CH₂Cl₂ at 0°C, the nucleoside epoxyphosphonate **33** was obtained in 74% yield, and no alkylated by-products were detected. The trityl group was removed by treatment of **33** with acetic acid in water, providing the final target 1-(2,3-anhydro-3-(diethoxyphosphinyl)-β-D-lyxofuranosyl)uracil **35** in 88% yield. The same strategy could also be used to prepare the isomeric 2',3'-epoxy-2'-phosphono derivative.

Scheme 12

1-[2,3-Anhydro-3-(diethoxyphosphinyl)-5-O-trityl-β-D-lyxofuranosyl]uracil⁵⁴: To an ice cold solution of compound **32** (146 mg, 0.23 mmol) and 4-pyrrolidinopyridine (4-PDP, 210 mg, 1.42 mmol) in CH₂Cl₂ (4 ml) was added dropwise triflyl chloride (30 μl, 0.28 mmol) under N₂. The reaction mixture was allowed to warm to r.t. over 1 h with stirring, and then poured into water (20 ml). After separation of the layers, the water phase was extracted with CH₂Cl₂ (15 ml x 3), and the combined organic phase was washed with brine (20 ml x 2), and water (20 ml x 2) and then dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by radial chromatography (CHCl₃ : MeOH, 95 : 5) to give the title compound (105 mg, 74%).

2.4. The direct epoxidation of α,β -unsaturated phosphonates

The most attractive and potentially most general route for the synthesis of dialkyl 1,2-epoxyalkylphosphonates and its various α - and β -substituted analogs **6** appears to be the direct epoxidation of the corresponding dialkyl vinylphosphonates **36** (Scheme 13). The syntheses of dialkyl vinylphosphonates with essentially any desired combination of α and β substituents can be achieved readily by a number of procedures.⁵⁵ The use of vinylphosphonates offers appreciable advantages. Not only are the two isomeric unsaturated phosphonates formed when R^2 or $R^3 \neq H$ readily separable prior to *cis*- or *trans*-epoxidation of the appropriate isomer, but the use of these unsaturated intermediates permits an acid-catalyzed hydrolysis of the ester functions prior to epoxidation.

Scheme 13

In view of the relative weak electrophilicity of the double bond of vinylphosphonates and the tendencies of these compounds to undergo nucleophilic addition (Michael addition), epoxidations with either strongly electrophilic peracids or nucleophilic oxidants (alkaline hydrogen peroxide and *t*-butylhydroperoxide) were experimented. Full utilization of peracids is often handicapped by the apparition of competing side reaction resulting in addition on the double bond or opening of epoxide ring.⁵⁶ For example, when a buffered trifluoroperacetic acid solution in CH₂Cl₂ was used as oxidant, ring opening of the so formed epoxide could be observed. The use of *t*-butylhydroperoxide in benzene with Triton B as catalyst has been shown to result in the Michael addition product of the butoxide to the olefin.⁵⁶ In a further example of a Mo(CO)₆ catalyzed reaction, *t*-butylhydroperoxide in 1,2-dichloroethane at reflux fails to react with diethyl 2-methyl- and 1-methylvinylphosphonate.⁵⁷ These disadvantages were overcome when these reagents were replaced by an alkaline hydrogen peroxide solution (30% solution) in alcohol. Alkaline hydrogen peroxide is recognized as the most common and perhaps most generally useful reagent for epoxidation of double bonds conjugated with electron-withdrawing groups. Although hydrogen peroxide has proved to be ineffective at pH 4.7 in the oxidation of diethyl 2-methyl- and 1-methylvinylphosphonate in the presence of Na₂WO₄ at 55-60°C without solvent, the hydrogen peroxide in alcoholic solution at more basic pH appears to have a great synthetic utility in the epoxidation of phosphonate diesters or diacids having electron-withdrawing groups. Several oxidizing systems have been developed with success including H₂O₂ / Na₂WO₄ / NEt₃ / *n*-PrOH / pH 5.8-5.9 / 40-55°C, 1h;⁵⁸ H₂O₂ / Na₂CO₃ / MeOH / 15°C, 3-12h;⁵⁹ H₂O₂ / NaOH / MeOH / rt, 1h;⁶⁰ H₂O₂ /

NaHCO₃ / EtOH / rt, 2h.⁶¹ The epoxidation of **25** (Scheme 10) was achieved very efficiently in 95% EtOH with the use of 30% aqueous H₂O₂ and sodium bicarbonate for 2h at room temperature, instead of NaOCl, to give **26** as a pure product in excellent yield (93%).⁶¹

Tetraethyl oxiranylidenebis(phosphonate)⁶¹: A solution of tetraethyl ethenylidene-1,1-bis(phosphonate) (1.510 g, 0.0050 mol), 30% aqueous H₂O₂ (1 ml), and NaHCO₃ (0.424 g) in 95% EtOH (5 ml) was stirred at rt for 2 h, diluted with brine, and extracted twice with CH₂Cl₂. The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give the title compound as a clear, colorless oil (1.472 g, 0.00465 mol, 93%). A sample of the oil was distilled, b.p.=121-123°C (0.07 mm Hg).

Similarly, the dimethyl 3-oxo-1-cycloalkenylphosphonates **37** (n=1,2) were converted to the corresponding epoxy derivatives **38** by treatment in MeOH with H₂O₂ in the presence of Na₂CO₃ for 3h with 63% (n=1) and 81% (n=2) yields, respectively (Scheme 14).⁵⁹

Scheme 14

Dimethyl (1,2-epoxy-3-oxocyclohex-1-yl)phosphonate⁵⁹: To a solution of dimethyl (3-oxo-1-cyclohexen-1-yl)phosphonate (10 mmol) in MeOH (25 ml) are added subsequently at 10-15°C, 30% aq H₂O₂ (2 ml) in one portion and then dropwise a solution of Na₂CO₃ (500 mg, 4.7 mmol) in H₂O (10 ml). Stirring is continued at 15-20°C until the complete consumption is confirmed by TLC. TLC probes are diluted with CH₂Cl₂ and shaken with a few drops of H₂O prior placing them on the TLC plate. R_f values of the products differ only slightly from the slower moving starting materials, but the epoxides are easily detected by their dark brown spots with iodine vapour. The mixture is evaporated at reduced pressure to 1/3 of the volume and then partitioned between H₂O (25 ml) and CH₂Cl₂ (50 ml). The product is extracted with CH₂Cl₂ (3 x 40 ml) and the combined organic phases are dried (Na₂SO₄) and evaporated under reduced pressure. The crude epoxide is purified by flash chromatography on silica gel and/or Kugelrohr distillation at 0.01 Torr (0.0135 mbar): yield 81%.

Very recently, a variety of diethyl vinylphosphonates **36** (R¹=Et) were oxidized in moderate to good yields (19-84%) using dioxirane generated in situ from buffered monopersulfate (oxone) and a ketone in a two-phase (CH₂Cl₂ / H₂O) reaction mixture.⁶² On account of the pH dependence of the dioxirane stability, the process needs an accurate control of the pH at 7.4. However, the reaction is often very sluggish, requiring regular addition of fresh portions of oxone and lengthy reaction times.

3. Preparations of fosfomycin

Fosfomycin **39**, formerly called phosphonomycin, is a low molecular weight antibiotic of unusual structure, which was originally isolated in 1969 from used culture medium of *Streptomyces fradiae*.^{1,63} The structure was established by NMR and IR, by MS of its dimethylester, and by direct comparison of the monobenzylammonium salt of the natural and synthetic products.⁶⁴ The absolute configuration was determined chemically as (-)(1*R*,2*S*)-(Z)-1,2-epoxypropylphosphonic acid. Fosfomycin is also produced by various species of *Pseudomonas* such as *Pseudomonas syringae*⁶⁵ or *Pseudomonas viridiflava*.⁶⁶ Fosfomycin is a broad spectrum antibiotic effective against both Gram-positive and Gram-negative infections in mammals, and its effectiveness is comparable with that of tetracycline or chloramphenicol.⁶⁷ The antibiotic irreversibly inactivates the uridine-5'-diphospho-N-acetylglucosamine-3-*O*-enolpyruvyltransferase (MurA), the enzyme which catalyzes the first committed step in cell wall biosynthesis.⁶⁸ The inactivation occurs through alkylation of a cysteine residue (Cys 115 of the enzyme from *Escherichia coli*) in the active site of MurA.^{68,69} The antibiotic, whose action has been investigated in depth⁷⁰, can be administered orally or by intravenous way and shows little toxicity to humans. Early reported works using isotope labelling techniques have shown that labelling of carbons C1 and C2 was provided by [1,6-¹⁴C]glucose, which primarily labels C1, [2-¹⁴C]glucose, which labels C2 and [2-¹⁴C]acetate, which labels both C1 and C2 in equal amounts.⁷¹ From these data, phosphoenolpyruvate was suggested as the most likely precursor of carbons C1 and C2 of fosfomycin.⁷¹ More recently reported works have shown that when 1,1-dideuterio-2-hydroxyethylphosphonic acid is fed to *Streptomyces fradiae* the deuterium is incorporated into the fosfomycin derived therefrom, via phosphonoacetaldehyde.⁷² Fosfomycin is thought to be produced from phosphoenolpyruvate via phosphonopyruvate and phosphonoacetaldehyde through the addition of a one carbon species to the pro-(*S*) face of the carbonyl group.⁷³ Only the (*S*) form of 2-hydroxy-[2-²H₁]ethylphosphonic acid was incorporated into the fosfomycin of *Streptomyces fradiae*.⁷⁴ Fosfomycin is present on the pharmaceutical market as the disodium,⁷⁵ calcium,⁷⁶ and tris(hydroxymethyl)ammonium salts.⁷⁷ The structure of the diester, monoester, disodium, calcium and phenethylammonium salts of fosfomycin have been studied by ¹H, ¹³C, ³¹P NMR, IR and Raman spectroscopy, and X-ray crystallography. ⁷⁸Presently a number of methods are available for its synthesis and we selected the more attractive ones.

Figure 1

The first racemic synthesis of fosfomycin **39** described in 1969 was based on the oxidation of the ($\pm$) (*Z*)-1-propenylphosphonic acid **42** (Scheme 15).⁶⁴ The reaction was effectively achieved using an excess of H₂O₂ (30% solution) at 60°C in the presence of Na₂WO₄ as catalyst (2%) at pH 5.5. The (*Z*)-1-propenylphosphonic acid **42** was obtained by stereospecific reduction, with Lindlar catalyst, of the dibutyl 1-propynylphosphonate **40** into dibutyl (*Z*)-1-propenylphosphonate **41** followed by hydrolysis with concentrated hydrochloric acid of the ester functions. Optical resolution of the racemic ($\pm$) (*Z*)-1,2-epoxypropylphosphonic acid to fosfomycin was accomplished by way of the quinine salt.

Scheme 15

Latter, the synthesis has been improved using the acid sensitive *t*-butyl alcohol as blocking group instead of *n*-butyl alcohol and propargyl alcohol instead of propyne. A sequence of reactions for the conversion of propargyl alcohol into ($\pm$) (*Z*)-1-propenylphosphonic acid, which proceeds in 81% overall yield via the alkadienylphosphonate has been developed (Scheme 16).^{58,79} After rearrangement of the alkynylphosphite into alkadienylphosphonate **43** (Boisselle and Meinhardt rearrangement),⁸⁰ this one was selectively and stereospecifically hydrogenated in benzene with Pd/C, with hydrogen attacking only the terminal double bond of the allene moiety, to give the di-*t*-butyl (*Z*)-1-propenylphosphonate **44**. The rapid removal of the two *t*-butyl groups was accomplished by refluxing the benzene solution with a strong acid catalyst. An elegant procedure was to use (*Z*)-1-propenylphosphonic acid as catalyst to avoid contaminating the product with a foreign acid. Removal of the solvent leaves (*Z*)-1-propenylphosphonic acid **42** in 81% overall yield after five reactions in the same pot. Conversion of ($\pm$) (*Z*)-1-propenylphosphonic acid **42** to fosfomycin **39** was accomplished by using (+)- α -phenethylamine as resolving base in propanol, followed by treatment at pH of

5.8-5.9 with H₂O₂ in the presence of Na₂WO₄ at 50-55°C. A single recrystallization from aqueous propanol afforded fosfomycin salt of 100% optical purity.

Scheme 16

(+)- α -Phenethylammonium (-)-*cis*-1,2-epoxypropylphosphonate⁵⁸: *cis*-Propenylphosphonic acid having C=C purity of 83% (148 g, 1.00 mol "pure") was dissolved in propanol (800 ml). To the stirred solution was added (+)- α -phenethylamine (80.5 g, 0.665 mol), followed by enough triethylamine (56 g, 0.553 mol) to reach a pH of 5.8-5.9. The resulting warm solution was treated in one portion with sodium tungstate dihydrate (5.0 g, 0.015 mol) and disodium ethylenediaminetetraacetic acid (1.0 g) dissolved together in 15 ml of warm (65-70°C) water. Hydrogen peroxide (1.53 mol, 157 ml of a 30% solution) was then added dropwise with stirring over a 15 min period while maintaining the temperature between 40 and 55°C. After the addition was complete, the reaction was kept at 50-55°C for 1 h to complete the epoxidation. The solution was then cooled to -5°C over a 30 min period to initiate crystallization. After stirring for 2 h at -5°C, the product was filtered and the cake washed with cold propanol (four 50 ml portions). This salt when dried weighed 106 g, and was about 92% optically pure. To complete the resolution, the salt was dissolved in 770 ml of hot (75-80°C) propanol. The slightly turbid solution was charcoal treated (2.5 g) and filtered while hot through a preheated funnel. To the hot filtrate was added 80 ml of warm (60-70°C) water. Crystallization of the monohydrate began within a few minutes. After stirring the mixture at 0°C for 2 h the product was filtered, washed with cold propanol (three 25 ml portions), and dried in vacuo at 45°C. The yield of phosphonomycin salt was 90.1 g (32.5%); m.p. 132-134°C (dec.).

An alternative synthesis of fosfomycin **39** has also been realized by the halohydrin route.⁸¹ Treatment of ($\pm$) (*Z*)-1-propenylphosphonic acid **42** in aqueous solution with *t*-butyl- or sodium hypochlorite afforded *threo*-1-chloro-2-hydroxypropylphosphonic acid (85%). Resolution was accomplished with (-) α -phenylethylamine to yield (+)-chlorohydrin (80%), which was converted to (-) fosfomycin **39** (85-90%) in 10 M aqueous sodium hydroxide.

With the aim in view to cover the access to fosfomycin, several important and attractive synthetic methods were reported in patents. They include, for example, precursors such as dimethyl hydroxymethylphosphonate,⁸² dimethyl, dibenzyl, and diallyl formylphosphonate,⁸³ trimethylphosphite and 2-cyano-1-hydroxypropene,⁸⁴ trialkylphosphite and 2-chloropropionaldehyde or 2-acetoxypromionaldehyde,⁸⁵ diethyl chloromethylphosphonate,¹¹ dibenzylphosphite and 1-chloro-1,2-propylene oxide,⁸⁶ propynylphosphonic acid,⁸⁷ propenylphosphonic acid,⁸⁸ 2-chloro-(*cis*-1,2-epoxypropyl)phosphonic acid,⁸⁹ and extrusion reactions upon thermolysis.⁹⁰ The resolution of racemic acids has also been reported.⁹¹

The first nonmicrobial asymmetric synthesis of fosfomycin **39** was based on the use of tartaric acid as a chiral auxiliary in directing an appropriate bifunctionalization of prochiral

(*Z*)-1-propenylphosphonic acid (Scheme 17).⁵⁰ Thus, the reaction of (2*S*,3*S*)-tartaric acid derivatives with (*Z*)-1-propenylphosphonic dichloride¹¹³ in CH₂Cl₂ at -10°C gave rise to the cyclic phosphonates that after ring opening and crystallization afforded the monoesters (70%). The bromohydroxylation, carried out in water at 15°C under neutral or acidic conditions with N-bromoacetamide (NBA) is highly chemoselective, regiospecific and stereospecific providing *threo*-bromohydrins (1*R*,2*S*) and (1*S*,2*R*) in a 70:30 ratio with yields higher than 90%. Crystallization of the mixture of diastereomeric bromohydrins provided the preferred (1*R*,2*S*) in diastereomerically pure form. After elimination of tartaric acid, the *threo*-bromohydrin was easily converted to fosfomycin as the sodium salt **50** by reaction with MeONa in MeOH at 40°C for 3 h.

Scheme 17

(1*R*,2*S*)-(1,2-Epoxypropyl)phosphonic acid, disodium salt⁵⁰: A solution of 46% aqueous HBr (26.5 ml) was added to a solution of **48** (5.69 g, 13.12 mmol) in water (26.5 ml). The solution was kept at 100°C for 16 h. The solvent was removed by distillation under reduced pressure. Ethyl acetate (285 ml) was added and the mixture was kept at reflux for 2 h, cooled to ambient temperature, and filtered. Evaporation of the solvent under reduced pressure gave a residue that was added to acetone. The precipitate was filtered off. Evaporation of the solvent under reduced pressure gave crude containing (1-bromo-2-hydroxypropyl)phosphonic acid **49** and tartaric acid. The crude **49**, thus obtained, was dissolved in methanol (50 ml) and the solution was added dropwise at 40°C under nitrogen to a solution of sodium methoxide in methanol (5.55 M, ca. 15 ml), in such a way as to maintain the pH at 12.5-13. At complete conversion of **49**, the reaction mixture was cooled to ambient temperature and filtered. The pH of the solution was brought to pH 9-10 with methanesulfonic acid. The mixture was concentrated under reduced pressure to half volume and filtered. Evaporation of the solvent under reduced pressure gave a residue (3.38 g) containing 63% w/w of the title compound (2.13 g, 11.7 mmol) as determined by HPLC. The residue was dissolved in methanol (18 ml) and added, under stirring at ambient temperature, to 2-propanol (90 ml). Methanesulfonic acid (2.5 g, 26 mmol) was added to the suspension at 15°C. The mixture was kept at 15°C for 15 min and filtered. The solution was added at 15°C to a solution of sodium methoxide in methanol (5.55 M, 4.32 ml) and kept at 15°C for 2 h. The precipitate was filtered and dried at 50°C under reduced pressure to yield (1*R*,2*S*)-(1,2-epoxypropyl)phosphonic acid, disodium salt **50** (1.91 g, 10.5 mmol).

Recently the conditions for a large scale synthesis of fosfomycin **39** based on the enantioselective formation of the (1*R*, 2*S*) *threo*-bromohydrin by enantioselective hydrogenation of prochiral β -ketophosphonates have been described (Scheme 18).⁹² The starting racemic dimethyl α -bromo- β -ketophosphonate **51** was prepared by the reaction of dimethyl 2-oxopropylphosphonate with hydrogen bromide (8.8 M) and H₂O₂ (30%) in THF at 25°C. Hydrogenation of a racemic α -substituted- β -ketophosphonate usually gives four possible stereoisomers. The lability of the α -stereogenic center allows for the stereoselective synthesis of a single isomer via dynamic kinetic resolution utilizing *in situ* stereoinversion. The stereoinversion to hydrogenation of racemic α -bromo- β -ketophosphonate **51** depends on the determination of suitable stereochemical and kinetic parameters by computer-aided analysis of experimental conditions. In this way, the (*S*)-BINAP-Ru(II) complex formed *in situ* by simple heating of a mixture of [RuCl₂(benzene)]₂ and (*S*)-BINAP in DMF acts as an excellent catalyst for the enantioselective hydrogenation of prochiral **51**, leading to the dimethyl (1*R*,2*S*)-1-bromo-2-hydroxypropyl-phosphonate **52** in 98% ee and 84% yield. The reaction takes place smoothly in MeOH under 4 atm at 25°C during 100 h. With these conditions, a partial (15%) hydrogenolytic debromination was observed, which can be completely achieved using Pd/CaCO₃-90% MeOH. The fosfomycin, as the sodium salt **50**, can be obtained by acid-catalyzed hydrolysis of the hydrogenation product, followed by treatment with sodium hydroxide.

Scheme 18

Another recent asymmetric synthesis of fosfomycin was based on the formation of a protected 1,2-dihydroxyphosphonate by stereoselective addition of trimethylsilyl-dibenzylphosphite **54** to the (*S*)-triisopropylsilyloxylactaldehyde **53** at low temperature (Scheme 19).⁹³ The crude reaction mixture afforded the protected α -hydroxyphosphonates **55**, which on reaction with methanesulfonyl chloride followed by flash chromatography gave the methanesulfonate **56**. The latter was treated with TBAF in THF with the aim to simultaneously deprotect the hydroxy group and to achieve the ring closure to give **57** as a single diastereoisomer (77%). After deprotection at phosphorus, fosfomycin was isolated as the sodium salt **50** in 76% yield.

Scheme 19

The oxidation of (*Z*)-propenylphosphonic acid **42** to fosfomycin **39** by a fermentation process has also been investigated.⁹⁴ Thus, it has been demonstrated that *Penicillium spinulosum* may be effectively employed to transform the biologically inactive (*Z*)-propenylphosphonic acid **42** into biologically active fosfomycin **39**. At optimum levels of glucose, used as the carbon source, an epoxidation efficiency in olefin approaching 90% was obtained after 10 days of incubation at 28°C and at pH 5.6. It is not known if this reaction is involved in the biosynthesis of the antibiotic by *Streptomyces*. Moreover, the epoxidizing systems show substrate specificity since (*E*)-propenylphosphonic acid was not epoxidized.

4. Rearrangements of 1,2-epoxyalkylphosphonates

A variety of skeletal rearrangements of organophosphorus compounds involving migration of a phosphorus substituent are well established reactions. The ability of a phosphorus substituent to migrate from carbon to oxygen,⁹⁵ oxygen to carbon,^{80,96} carbon to nitrogen,⁹⁷ nitrogen to carbon⁹⁸ and nitrogen to oxygen⁹⁹ has been reported by several workers. The first example of thermal and acid-catalyzed shifts from carbon to carbon was reported in 1966.¹³ It has been reported that diethyl 2,2-disubstituted-1,2-epoxyethylphosphonates **58** readily undergo specific rearrangement to yield, as a result of the phosphoryl group migration, diethyl 1,1-disubstituted-1-formylmethylphosphonate **59** (Scheme 20). The thermal specificity and hence applicability was limited to those substrates, which can rearrange at a temperature not exceeding 170°C (0.7 mm) and evidence for an efficient reaction was obtained in only one instance.¹³ In other cases, the rearranged products were frequently unstable at the temperature (270-300°C, 0.6-0.7 mm) required for rearrangement and only the dephosphorylated aldehydes were isolated accompanied by polymeric material.

Scheme 20

The thermal technique has largely been supplanted in recent years by the use of Lewis acids, which are much more generally useful in this reaction.^{13,14,17,56a,100-103} The preferred catalyst for this reaction was found to be boron trifluoride etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$). Its use increases reaction rates and yields. Rearrangement of readily available diethyl 2,2-disubstituted-1,2-epoxyethylphosphonates **58** to diethyl 1,1-disubstituted-1-formylmethylphosphonates **59** can be effected on large scale in benzene or CH_2Cl_2 at room temperature in few minutes. In every instance, only the carbonyl compound was isolated. It necessarily involved formation of a carbonium ion **60** and migration of the phosphoryl group rather than the hydrogen atom to the carbonium ion. The boron trifluoride-catalyzed rearrangement of β -disubstituted epoxyphosphonates constitutes an expeditious route for the synthesis of diethyl 1-formylalkylphosphonates (Scheme 21),¹⁰² and a large variety of 1,1-disubstituted phosphonoacetaldehydes have been synthesized on preparative scale and in excellent yields from symmetrical or unsymmetrical ketones as outlined in Table 4. The preferred catalyst for this rearrangement was found to be $\text{BF}_3 \cdot \text{Et}_2\text{O}$ since diethyl 2,2-disubstituted-1,2-epoxymethylphosphonates **58** on treatment with other Lewis acids such as SnCl_4 , SnBr_2 , ZnCl_2 , ZnBr_2 , or TaF_5 in C_6H_6 or CH_2Cl_2 gave mixture of products in which **59** was the major compound.

Scheme 21

O,O-Diethyl 1-formyl-1-methyl-1-cyclopropylmethylphosphonate¹⁰²: To the O,O-diethyl-2-cyclopropyl-1,2-epoxyethylphosphonate (11.7 g; 0.05 mol) in CH_2Cl_2 (200 ml) cooled at 0°C under an atmosphere of nitrogen is added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3.6 g; 0.025 mol) in CH_2Cl_2 (50 ml). After 30 min at 0°C the reaction mixture is kept for two hours at room temperature then transferred in a separatory funnel and washed with an aqueous NaHCO_3 solution (3 x 20 ml) and water (20 ml). The organic layer is dried over sodium sulfate. After removal of the solvent under reduced pressure we obtained a colourless liquid purified by vacuum distillation: yield 72%, b.p. $112-114^\circ\text{C} / 2$ torr.

Table 4. Synthesis of diethyl 1,1-dialkyl-1-formylmethylphosphonates

59	R ²	R ³	Yields (%)
a	Me	Me	76
b	Me	Et	78
c	Me	<i>i</i> -Pr	75
d	Me	<i>n</i> -Pr	75
e	Me		72
f	Me	<i>t</i> -Bu	62
g	Me	<i>n</i> -Pent	68
h	Me	C ₆ H ₅	68
i	Et	Et	78
j	<i>n</i> -Pr	<i>n</i> -Pr	75
k	<i>i</i> -Pr	<i>i</i> -Pr	76
l	<i>i</i> -Bu	<i>i</i> -Bu	76
m	-(CH ₂) ₄ -		25
n	-(CH ₂) ₅ -		61
o	-(CH ₂) ₄ -CMe ₂ -		71
p	-(CH ₂) ₆ -		60

However, it has been found that there were limitations in this rearrangement. For example, the 1,2-epoxyphosphonates prepared from cyclic ketones **61** (cyclopentanone, cyclohexanone, cycloheptanone, etc...) upon treatment with BF₃·Et₂O undergo a competing proton migration (Scheme 22)¹⁰² and consequently give a mixture of diethyl 1,1-disubstituted-1-formylphosphonates **62** (70%) and diethyl 1-hydroxyallylphosphonates **63** (30%).

Scheme 22

The occurrence of rearrangement being dependent upon the stability of the incipient carbonium ion at the β position, the unsubstituted dialkyl 1,2-epoxyphosphonates upon treatment with BF₃·Et₂O undergo ring opening without rearrangement. From the results of the

hydroxy-2-ethoxyethylphosphonates in 55-62% yields.^{56a} However, it has been reported, and proofs were given by means of mass spectrometry, that diethyl 1-methyl-1,2-epoxyethylphosphonate **6c** under conditions of acid-catalysis ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ or H_2SO_4) was attacked at the α position by alcohols to give the diethyl 1-alkoxy-1-methyl-2-hydroxyethylphosphonate.¹⁰⁴

An attractive procedure for the preparation of phosphorylated amino alcohols from 1,2-epoxyphosphonates involves the oxirane ring opening by amines. The reaction follows the general pattern of nucleophilic attack at C2 established with electronegative substituents at C1. The structures of reaction products demonstrate that ring opening in 1,2-epoxyphosphonates **6c** and **24** was directionally specific and results of attack at C2 by ammonia or amines. Analysis of the isolated products failed to produce any information for production of isomers resulting from attack at C1. Thus, the 1-hydroxy-2-aminoethylphosphonic acids **66** were obtained by reaction of diethyl 1,2-epoxyethylphosphonate **24** or diethyl 1-methyl-1,2-epoxyethylphosphonate **6c** with aqueous ammonia at 0°C for 24 h or amines at room temperature for 48 h, followed by acid hydrolysis (Scheme 24).¹⁰⁵ By contrast, ring opening of **24** with aniline was realized in 90% yield by heating at 120°C for 24h.^{56a}

Scheme 24

1-Hydroxy-1-methyl-2-N-benzylaminoethanephosphonic acid¹⁰⁵: Equimolar mixture of diethyl 1,2-epoxy-1-methylphosphonate and benzylamine (0.05 mol scale) was kept for 48 h at room temperature and the resulting mixture was hydrolyzed by refluxing in concentrated HCl for 7 h. The solution after hydrolysis was decolorized with carbon (when necessary), evaporated to dryness and the residue was dissolved in ethanol. Treatment with propylene oxide precipitated crude product, which was purified by crystallization from water-ethanol mixtures: yield 64.8%, m.p. $237-240^\circ\text{C}$.

The reaction of tetraethyl oxiranylidene-1,1-diphosphonate **26** with several primary amines, including *n*-propylamine, cyclohexylamine, benzylamine and allylamine has been examined. From the reaction of **26** and primary amines, the phosphinyl phosphates **67** were isolated as the major products in 40-63% yields (Scheme 25).⁶¹ It seems very likely that the formation of **67** was the result of a rearrangement either in concert with (path a) or subsequent to opening of the epoxide with amine and generation of an intermediate alkoxide (path b). When di-*n*-

propylamine was used, a second product, ethylidene-1-phosphinyl-1-phosphate, corresponding to the loss of the amine by elimination, was formed (32%) in addition to the phosphinyl phosphate (20%). Exposed to hydrolytic conditions at different pH (2, 6, 10), **26** reacts with water very slowly.⁶¹

Scheme 25

Phosphoric acid, 1-(diethoxyphosphinyl)-2-(2-propen-1-ylamino)ethyl diethyl ester⁶¹: A solution of allylamine (2.855 g, 0.05 mol) and tetraethyl oxiranylidenebis(phosphonate) (3.00 g, 0.0095 mol) in methanol (20 ml) was cooled to 0-5°C by means of an ice-water bath. The mixture was stirred while the low temperature bath came to r.t. and then stirring was continued overnight at r.t. TLC (10% of a 10% NH₃/CH₃OH solution in CH₂Cl₂) indicated that starting material was consumed. The solvent and excess of allylamine were removed *in vacuo* to give 3.621 g of crude material from which 1.025 g was chromatographed (flash, 160 g, 0.0403-0.063 mm silica gel, 4 cm wide, 20-30% acetone in CH₂Cl₂) to give the title compound (0.635 g, 63% overall yield) as a clear oil.

Fosfomycin **39** on treatment with saturated aqueous ammonia for 3 days at 55-60°C gives as major component the (-) (1*R*,2*R*)-(2-amino-1-hydroxypropyl)phosphonic acid **68** resulting from preferential attack of nucleophile at the C2 carbon (Scheme 26).^{72,106} Similarly, treatment of **39** on an acid Dowex 50 column with 0.1N H₂SO₄ delivers the corresponding diol.⁷²

Scheme 26

Under normal physiologic conditions, it is established that opening of fosfomycin can occur either at C2 or at C1. Thus, the inactivation of enzyme MurA by fosfomycin **39** occurs through alkylation by the thiol of a cysteine residue at C2 of the antibiotic in the active site of MurA. By contrast, the plasmid-mediated resistance to the antibiotic involves the reaction catalyzed by FosA¹⁰⁷ (fosfomycin-specific metalloglutathione transferase) of fosfomycin **39** with glutathione by attack of the thiol of glutathione at C1 of the antibiotic. The latter addition is somewhat surprising in that nucleophilic substitutions α to phosphoryl are difficult. Very recently it has been shown that L-cysteine can act as an alternative thiol substrate for FosA (Scheme 27).¹⁰⁸ The regiochemistry of the reaction was the same as that exhibited with normal substrate, glutathione, with addition of the nucleophile at the most hindered carbon, C1. The stereochemical course of the reaction was shown to occur with inversion of configuration at C1 of **39**, suggesting that the enzyme catalyzes the reaction via an S_N2 or borderline S_N2 mechanism.

Scheme 27

Treatment of diethyl 1,2-epoxyethylphosphonate **24** with an alkylmagnesiumbromide failed to result in the formation of the expected hydroxyalkylphosphonate. The oxirane ring was opened by reaction with magnesium bromide to yield the halohydrin, which was hydrolyzed to the glycol during product isolation.^{56a}

The readily available diethyl 1,2-epoxyalkylphosphonates **69** have proved to be valuable synthetic intermediates. On treatment with sodium dialkylphosphites in ethanolic solution they undergo a rearrangement via an oxirane opening reaction. The sodium dialkylphosphite attacks on the β carbon atom of the epoxide ring to give unstable sodium α -hydroxyphosphonates **70**, which eliminate sodium diethylphosphite to produce the dialkyl 1-formylethyl- ($R^4 = H$) or 2-oxoalkyl- ($R^4 = Me$) phosphonates **71** in 50-85% yield (Scheme 28).¹⁰⁹

Scheme 28

Diethyl 2-oxopropylphosphonate¹⁰⁹: To diethyl 1,2-epoxypropanephosphonate (19.4 g, 0.1 mol) an ethanol solution of sodium diethyl phosphite [0.1 mol, prepared from sodium (2.3 g) in ethanol (80 ml)] is added with stirring at 20°C. After the addition is completed, the reaction mixture is heated under reflux for 2-5 h. It is then hydrolysed by addition of water (50 ml). The aqueous solution is extracted with chloroform, the organic phases are combined, and dried with sodium sulfate. The organic solvent is removed under reduced pressure to give an oil, which is distilled in vacuo: yield 85%, b.p. 90°C / 0.1 torr.

The diisopropyl (*E*)-1,2-epoxy-3-oxoalkylphosphonates **72**, which were easily prepared by epoxidation of the corresponding alkenyl compounds, underwent heterocyclisation with various 1,3-bidentate nucleophiles, such as ethyl 2-pyridylacetate, 2-aminopyridine, 2-aminopyrimidine, thiourea, and thiocarboxamides (Scheme 29)^{59,110} to produce **73** and **74**, arising from regioselective oxirane opening and subsequent dehydration.

Scheme 29

α -Metallated 1,2-epoxyethylphosphonate¹¹¹ **75** can serve as precursor to higher homologues (Scheme 30). Reaction of diethyl 1,2-epoxyethylphosphonate **24** with LDA in THF at very low temperature resulted in deprotonation at the α position giving high yield of diethyl α -lithioepoxy-ethylphosphonate **75**, which can be captured under internal quench conditions by electrophiles R^4X ($R^4=Me_3Si$, 91% and $R^4=Me$, 57%), as illustrated by the obtention of **76**.

Scheme 30

Diethyl 1-trimethylsilyl-1,2-epoxyethylphosphonate¹¹¹: A solution of 1.08 g (6 mmol) of diethyl 1,2-epoxyethylphosphonate and 1.14 ml (9 mmol) of chlorotrimethylsilane dissolved in 18 ml of THF, 4 ml of ether and 4 ml of hexane was cooled to -115°C and then treated with 8.3 mmol of lithium diisopropylamide in 6 ml of THF and 5 ml of hexane (generated from diisopropylamine (8.3 mmol) and 8.3 mmol of *n*-butyllithium in hexane) over 40 min. After an additional 15 min the solution was allowed to warm to 0°C and then quenched with 3 ml of water. The usual workup and the removal of volatiles under reduced pressure gave the crude trimethylsilyl derivative in 91% yield (1.85 g). Distillation yielded 1.72 g (84%) of title compound: b.p. $115-120^\circ\text{C}$ (0.1 mm Hg).

When diethyl 1-methyl-1,2-epoxyethylphosphonate **19** ($R^2=R^3=H$, $R^4=Me$) was subjected to the action of *n*-BuLi in excess in THF at low temperature for two hours, the 1-hydroxy-2-methyl-2-hexene was obtained in 45% yield (Scheme 31).¹¹² This reaction has been extended to a variety of 1- or 2-substituted 1,2-epoxyphosphonates to give in each case the allylic alcohols **77** in low yields (15-32%) as a mixture of *E* and *Z* isomers.

Scheme 31

The reverse oxidation reaction of vinylphosphonates was also described. When dialkyl 1-alkyl-1,2-epoxyethylphosphonates **6** were treated with an excess of thiourea in MeOH at reflux, dialkyl 1-alkylvinylphosphonates **79** were produced in generally good yields (Scheme 32).^{42c}

Scheme 32

6. Conclusion

The 1,2-epoxyalkylphosphonates constitute a valuable class of phosphorus compounds. The popularity of these molecules emanates from their simplicity, access and efficiency. The fosfomycin phenomenon has largely contributed to their popularity. Fosfomycin is still present on the pharmaceutical market owing to several drugs,¹¹⁴ such as Fosfocine[®], Monuril[®] and Uridoz[®], employed in the treatment of acute cystitis. It has induced a systematic study of epoxidation reactions, resulting in various attempts to arrive at satisfying syntheses and to extend the family. Among the four classes of reaction, which resume almost all the ways of access to 1,2-epoxyphosphonates, the halohydrins and α,β unsaturated intermediates are the most efficient precursors in terms of stereoselectivity. Undoubtedly, significant progress have been achieved. However, the efforts being largely confined to fosfomycin or analogs, most of these investigations have captured the energy of chemists to the detriment of the search of new phosphonic structures containing the epoxide moiety. The prochiral vinylphosphonates of controlled geometry being easily available, it would be interesting to develop the asymmetric functionalization of these attractive intermediates by employing both the halohydrin and peroxide approaches with chiral ester substituents at phosphorus or chiral epoxidation reagents. The exploration of new mild epoxidation processes with the aim to introduce biologically active groups would be a useful improvement. Careful investigations of α -metallated epoxyalkyl-phosphonates may also afford some unusual compounds.

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(from the left to the right)

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Philippe Savignac graduated as Ingénieur of the ENSCT in 1963 has received his Ph. D from the Sorbonne (Paris) in 1968. He became an Attaché de Recherche (CNRS) in 1970 in the laboratory of Professor Henri Normant in the Sorbonne and Directeur de Recherche (CNRS) in 1976. In 1977 he joined the research group gathered in Thiais around F. Mathey. Since 1987 he has been working at the Ecole Polytechnique (France). His research interests include organic and organometallic chemistry of phosphorus, synthesis of new phosphorylated reagents, phosphoramidates, phosphonates and α -halogenated phosphonates.