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**Dave, Paritosh Ramesh**

ORGANOPHOSPHORUS SYNTHESIS

*City University of New York* PH.D. 1986

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# ORGANOPHOSPHORUS SYNTHESIS

BY

PARITOSH R. DAVE

Dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

The City University of New York
1986

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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# ABSTRACT

## ORGANOPHOSPHORUS SYNTHESIS

BY

PARITOSH R. DAVE

Adviser: Dr. Robert Engel

The following analogs of glycerol-3-phosphate have been synthesized for the purpose of affinity label experiments: 1. Monotriethyl ammonium 3,4-dihydroxy 1,2-epoxybutylphosphonate. 2. Dimethyl 3,4-O-isopropylidene-3,4-dihydroxy-2-ketobutylphosphonate.

The first of these has been prepared by sodium tungstate catalyzed epoxidation of the corresponding trans alkene phosphonate with hydrogenperoxide.

The second of these has been prepared by alkylation of lithio dimethyl methylphosphonate with methyl glycerate 2,3-acetonide.

The Darzen's condensation has been applied to the synthesis of diethyl 3,4-O-isopropylidene-3,4-dihydroxy-1,2-epoxybutylphosphonate, although all attempts to hydrolyze the product resulted in attack at the oxirane ring.

Attempts to synthesize 3,4-dihydroxy-1-ketobutylphosphonic acid via 1,3-dithiane-2-ylphosphonate and other methods were unsuccessful.

A method for one pot conversion of bromides to aldehydes using DMSO, NaI and base has been developed.

## ACKNOWLEDGEMENTS

I would like to thank Dr. Robert Engel for his able guidance and support that has made this thesis a reality. I thank the members of the thesis committee for their guidance. I thank Dr. G. Axelrad for his support.

My thanks to my cousins Mrs. and Mr. Joshi for their support and encouragement throughout this period of my life.

My special thanks to my parents and family for their everlasting support.

Dedicated

To my parents

Mrs. and Mr. R. P. Dave

INDEX

# INTRODUCTION

Organic esters of phosphoric acid play an integral role in the biochemical processes of all living systems[1]. The study of the chemistry of phosphonates has accelerated in recent years owing to a recognition of their structural relationship to the phosphates, coupled with the role of natural phosphonates in living systems.

Glycerol may serve as a precursor to glycerol 3-phosphate (G3P)[2], a metabolite of significance both in lipid metabolism and as a by-product of glycolysis. The metabolism of glycerol and glycerol 3-phosphate in mammals is governed mainly by three enzymes: glycerol kinase, the cytosolic $NAD^+$-dependent glycerol 3-phosphate dehydrogenase, and the mitochondrial FAD-linked glycerol 3-phosphate dehydrogenase [fig 1, ][3].

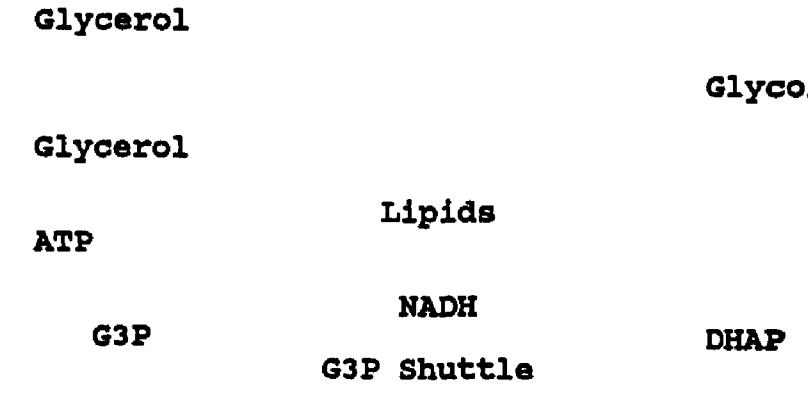
Bucher and Klingenberg[4] and Estabrook and Sactor[5] proposed a G3P SHUTTLE on the basis of:

(a) the inability of intact rat liver mitochondria to oxidize external or cytosolic NADH[6],

(b) the ability of mitochondria to oxidize G3P but not dihydroxy-acetone phosphate (DHAP), and

(c) the existence of a cytosolic $NAD^+$-linked enzyme that thermodynamically favours the formation of G3P and $NAD^+$.

Reducing equivalents in glycolysis are deposited temporarily in DHAP converting it to G3P, which then




(Figure 1)

ATP= adenosine triphosphate
G3P= glycerol 3-phosphate
DHAP= dihydroxy-acetone phosphate
FAD= flavin adenosine dinucleotide

enters the outer mitochondrial membrane and is reoxidized to DHAP. The DHAP can then return to cytosol to be recycled. In this cycle, reducing equivalents are disposed in the cytosol in exchange for oxidative phosphorylation in mitochondria. Although the importance of this process for the generation of metabolic energy in muscles of insects is well established[7,8], there is no evidence that the shuttle plays a major role in this respect in vertebrates.

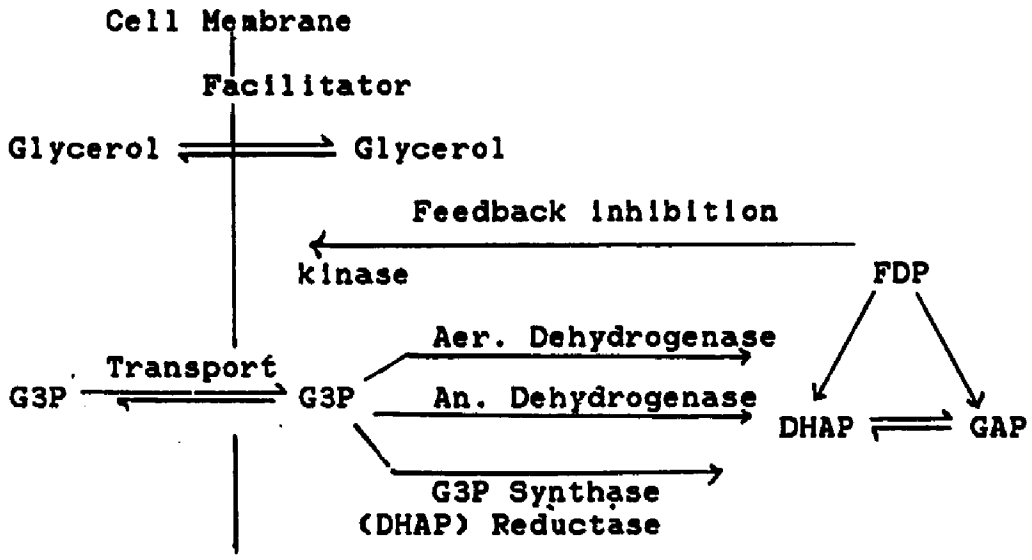
In bacteria, glycerol is dissimilated in two ways[8].

One begins with dehydrogenation followed by phosphorylation, and the other begins with phosphorylation followed by dehydrogenation. In both cases the terminal product is DHAP. The complexity of enzymology that brings forth these transformations is not obvious from the above simplistic representation of the chemical reactions of glycerol. Certain organisms are able to utilize not only external glycerol, but also G3P and/or dihydroxy acetone DHA, the intermediates of the two pathways. A special permeation protein would be required for metabolic access to all three. Also, although having a single pathway in principle should suffice for utilization, some bacteria are equipped with both pathways, in some cases requiring at least seven different catalytic proteins, each subset being adapted to serve under a particular circumstance. In addition to these, there are considerable variations in the mechanisms of dehydrogenation.

The kinds of proteins employed by one bacterial species, Escherichia coli, for the utilization of glycerol, G3P, and DHAP are summarized in fig 2., and discussed briefly below.

(1) Glycerol facilitator (or facilitator protein):

This protein catalyzes the equilibration of the substrate across the cell membrane rather than transport against a concentration gradient[9a].




(figure 2)

FDP= fructose 1,6-diphosphate
GAP= glycerol acetone phosphate
AER= aerobic
AN= anaerobic

(2) G3P transport (or permease):

This protein catalyzes the active transport of sn G3P[9b].

(3)Glycerol Kinase (ATP: glycerol 3-phosphotransferase):

Its function is to catalyze phosphorylation of glycerol and is feedback inhibited by fructose 1,6-diphosphate[9c].

(4) Anaerobic G3P dehydrogenase:

This enzyme catalyzes the oxidation of G3P to DHAP and is coupled to a fumarate or nitrate reductase chain[9d].

(5) Aerobic G3P dehydrogenase:

This enzyme also catalyzes the oxidation of G3P to DHAP. In this case either oxygen or nitrate can serve as the ultimate electron acceptor[9e].

(6) G3P synthase (or DHAP reductase) (G3P:$NADP^+$ 2-oxidoreductase)

This enzyme catalyzes the conversion of DHAP to G3P. As such it serves as the link between glycolysis and phosphoglyceride synthesis. It is inhibited by high concentrations of the product G3P.

(7) G3P acyltransferase (acyl-Co-A:G3P O-acyl transferase):

This enzyme catalyzes the first step in phosphoglyceride synthesis, the formation of monoacyl G3P. It is an important step in metabolic control.

Consideration of some of the important roles played by glycerol 3-phosphate makes it a prime target for antimetabolic activity by structurally related phosphonic acids. One of the most common modes by which phosphonic acids and phosphonates may act as an antimetabolite involves introduction of a phosphonic acid linkage in place of the normal phosphate ester portion of a metabolite while the remaining functionalities remain the same. Since the carbon-phosphorous bond is incapable of hydrolysis by phosphoesterases, there exists the potential to perturb one or more biochemical processes. For

optimization of activity, other structural variations might be desirable.

Several aspects of change must be considered in addition to bestowing resistance to hydrolysis. One of the prime considerations would be the steric factor, i.e. the distances between the phosphorus acid site and the other functionalities. For example, 2,3-dihydroxypropyl-1-phosphonic acid, generated in both racemic[10] and chiral forms[11] as a potential antimetabolite for sn-glycerol-3-phosphate utilizing, processes was found to be totally without inhibitory action toward L-glycerophosphate:NAD oxidoreductase[12].

However 3,4-dihydroxybutyl-1-phosphonic acid[13-18], an isosteric analog of G3P, was found to be oxidized by the L-glycerol-3-phosphate:NAD oxidoreductase at approximately the same rate as the natural substrate and to have nearly the same value of Km.

For some other systems the isosteric requirement is not valid. For example, the "shortened" nonisosteric analogue of UDP-glucose[19] (phosphorus bound directly to 5' carbon of the nucleoside sugar) has been found to substitute for the natural material as substrate for UDP-glucose dehydrogenase. Moreover, while both isosteric and nonisosteric phosphonic acid analogues of 3-deoxy-D-arabinoheptulosonate-7-phosphate and D-gluco-7-phosphate are competitive inhibitors of the 3-dehydroquinate

synthetase of E. coli, the nonisosteric systems are far better inhibitors than the isosteric systems[20].

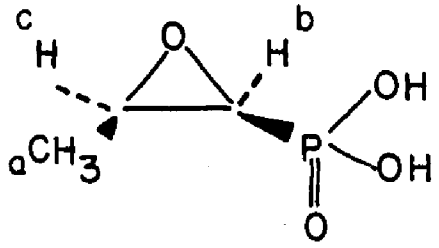
Another factor of difference between the natural phosphate and the structurally related designed phosphonate is the loss of binding capability resulting from elimination of esteratic oxygen of the natural phosphate linkage. This might be of no consequence for a given phosphonic acid antimetabolite whereas it might preclude other potential antimetabolite from activity in a different metabolic system. For example, in vitro enzymatic studies with 3,4-dihydroxybutyl-1-phosphonic acid have shown it to serve as a substrate for CDP-diglyceride:sn-glycerol-3-phosphate phosphatidyl transferase and is an inhibitor of the anaerobic sn-glycerol-3-phosphate:NAD(P)oxidoreductase of E. coli[14,21]. But, it does not appear to interact with the catabolic membrane bound glycerol-3-phosphate dehydrogenase, CDP-diglyceride:L-serine phosphatidyltransferase, or acyl coenzyme A:sn-glycerol-3-phosphate acyl transferase[21]. The lack of interaction of these latter systems has been attributed to the loss of binding capability.

In an effort to test this hypothesis further, species have been synthesized without the esteratic oxygen but still bearing a potential binding functionality. Tang et al.[15] synthesized 1,3,4-trihydroxybutyl-1-phosphonic acid. When this material was investigated with acyl coenzyme

A:sn-glycerol-3-phosphate acyl transferase it was found to serve as a substrate[22,23].

It may be concluded that both the steric factors and the binding capabilities are of consequence.

It is also of interest to consider a naturally occurring phosphonic acid which is bactericidal. The novel structure of the antibiotic phosphonomycin [1], has generated much interest in epoxyphosphonates[24,25]. Phosphonomycin was first isolated from fermentation broth in which Streptomyces fradiae was grown and has been shown to have the following structure, based on its synthesis from (-)-cis-propenyl phosphonic acid as its (+)-phenethylammonium salt[25] and its ammonium salt[42] by epoxidation with hydrogen peroxide in the presence of sodium tungstate.

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NMR ($D_2O$)[25] a: 1.48 d J= 5.4 Hz., b: 2.84 (J= 18.5 and 5.1 Hz.), c: 3.27 m.

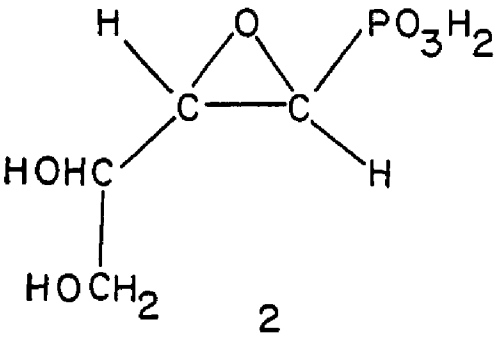
A number of bacterial strains exposed to

phosphonomycin in growth medium of high osmolarity, are converted to spheroplasts, strongly implicating the interaction of phosphonomycin in cell wall formation. Moreover, biochemical investigations[26] have shown that phosphonomycin attaches covalently to, and thus inhibits irreversibly, phosphoenolpyruvate:uridine diphospho-N-acylglucosamine transferase in extracts from several gram positive and gram negative microorganisms[27]. This enzyme catalyzes the first step in the biosynthetic pathway of the nucleotide muramyl peptides that serve as cell wall precursors in all bacteria.

Phosphonomycin, administered orally, is effective in protecting mice against a number of infections caused by gram positive and gram negative organisms. It is an effective chemotherapeutic agent and compares favourably with tetracycline and chloramphenicol.

Thus it is clear that preparation of phosphonic acids structurally related to natural phosphates would be of considerable importance. A reasonable structure for biological studies would be 1,2-epoxy 3,4-dihydroxybutylphosphonic acid [2].

The stereochemistry of the epoxide was not considered critical as the epoxide functionality was chosen to provide a reactive site only.



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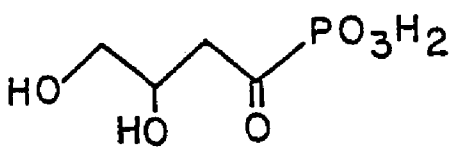
It embodies the following features that make it an attractive synthetic target:

(1) Structural relationship to phosphonomycin,

(2) Binding and reactive capability of the epoxide oxygen,

(3) Isosteric to glycerophosphate.

Other species that lack the esteratic oxygen of glycerophosphate but still posses binding capability are the alpha- and beta-keto phosphonates shown below [3 and 4].



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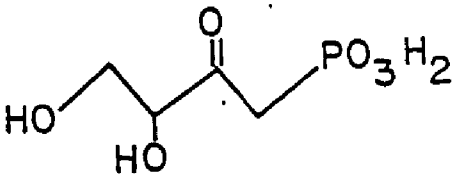

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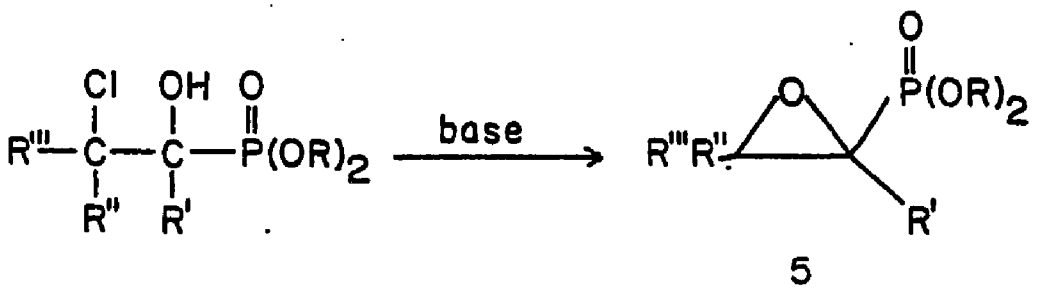
The methods leading to 1,2-epoxyphosphonates have been reviewed [28,29]. These include :

(a) The reaction of a dialkylphosphonate halohydrin with base ;

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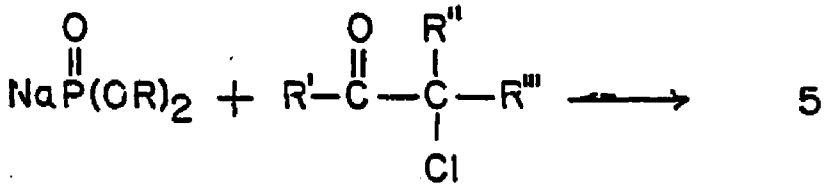
Scheme I

(b) The reaction of a dialkyl sodioalkane phosphonate with an alpha-haloketone ;

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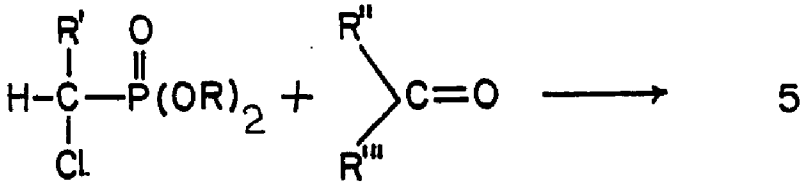
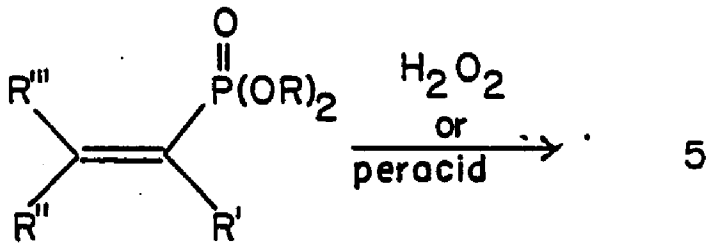
Scheme II

(c) Darzens reaction of a dialkyl chloromethylphosphonate with a carbonyl compound , and ,



Scheme III

(d) Direct epoxidation of an alkenephosphonate :



Scheme IV

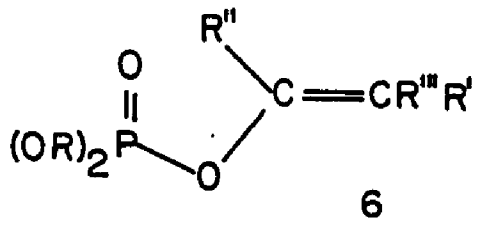
Phosphonomycin has been synthesized by method (d) [25,42], and its dialkyl esters have been synthesized by methods (a) [83] and (c) [36].

Wendler et. al [83]. synthesized phosphonomycin from the corresponding halohydrin using 10 N NaOH. The product thus prepared was isolated as its monobenzylammonium salt and found to be identical in all respects with material derived from natural sources. Our target epoxide would not survive the above conditions and so it was not considered a viable approach.

LIMITATIONS:

The yields of these reactions are low and there are certain limitations as indicated below .

The formation of alpha substituted 1,2-epoxyphosphonates in the reaction of sodium-dialkylphosphonates with halomethyl ketones[30,31], but the yields are low and a complex mixture of products that includes enolphosphate [6] via Perkov reaction and beta ketoalkylphosphonate [7] via Arbuzov reaction is formed.



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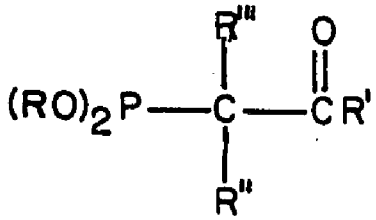

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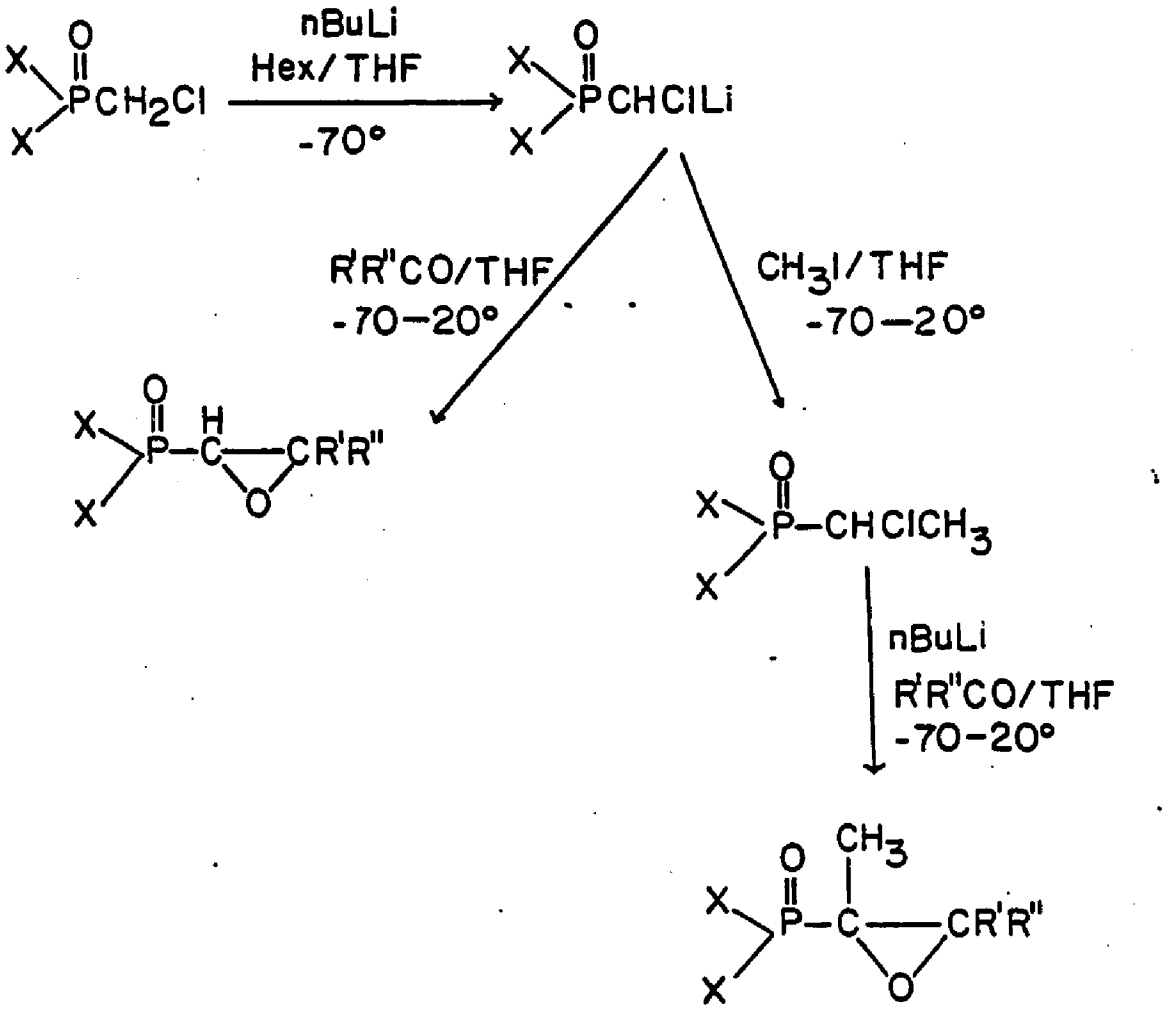
Alpha-substituted 1,2-epoxyphosphonates may be prepared by alkaline treatment of the halohydrins formed by the addition of dialkylphosphonates with halomethyl ketones[31], but the slow rate of reaction and low yields limit the utilization of the reaction.

The Darzens condensation of aromatic aldehydes and aryl and alkyl ketones with dialkylchloromethylphosphonates[32-35] has been found to be effective. But the reaction was found to be ineffective

for the preparation of beta-alkyl and alpha-alkyl or aryl substituted 1,2-epoxyphosphonates[34].

Recently, however Coutrot et. al.[36], have reported successful preparation of a variety of alpha- as well as beta- alkyl substituted 1,2-epoxyphosphonates, as shown below.




Scheme V

X= OEt.

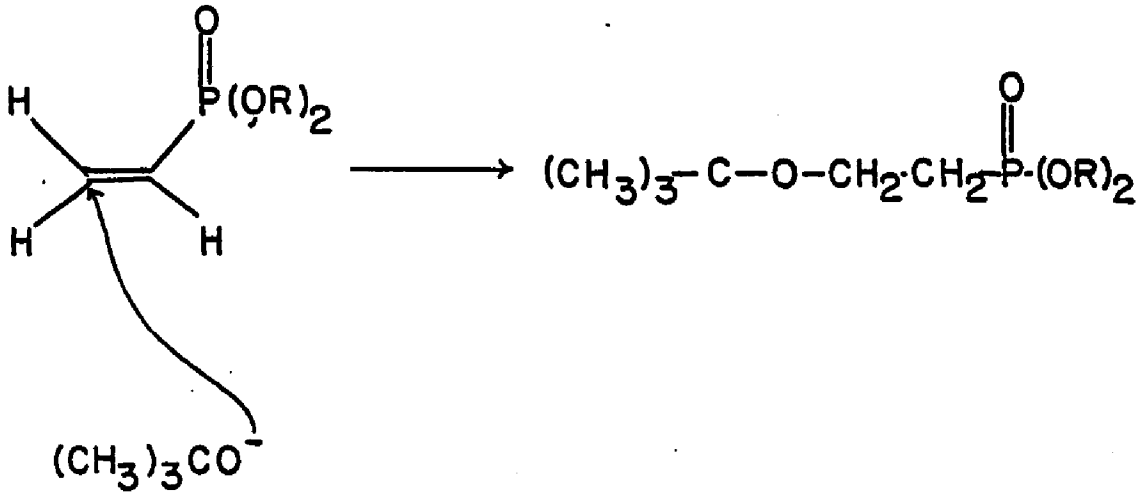
| R'R''CO | Yield % |
|---|---|
| 2-propanone | 80 |
| 3-pentanone | 89 |
| 2,4-dimethyl-3-pentanone | 88 |
| 2-butanone | 85 |
| 3-methyl-2-butanone | 86 |
| 3,3-dimethyl-2-butanone | 75 |
| buten-3-one | 36 |
| 3-methyl-buten-3-one | 75 |
| 1,1-dimethoxy-2-propanone | 76 |
| acetophenone | 51 |

To date this reaction has only been performed with methyl and ethyl esters of chloromethylphosphonic acid.

Direct epoxidation of dialkyl vinylphosphonate can result in side reactions owing to the relative electrophilicity of the double bond. For example, the use of t-butylhydroperoxide has been shown to result in the Michael addition of the butoxide to the olefin as shown [29].

Attempted reaction of diethylvinylphosphonate with buffered peroxytrifluoroacetic acid in dichloromethane [37] and with peracetic acid in ethylacetate [38] gave very little (ca 10%)or no yield of 1,2-epoxyphosphonate. These reagents have been shown to be effective in the epoxidation of alpha-beta unsaturated carboxylic

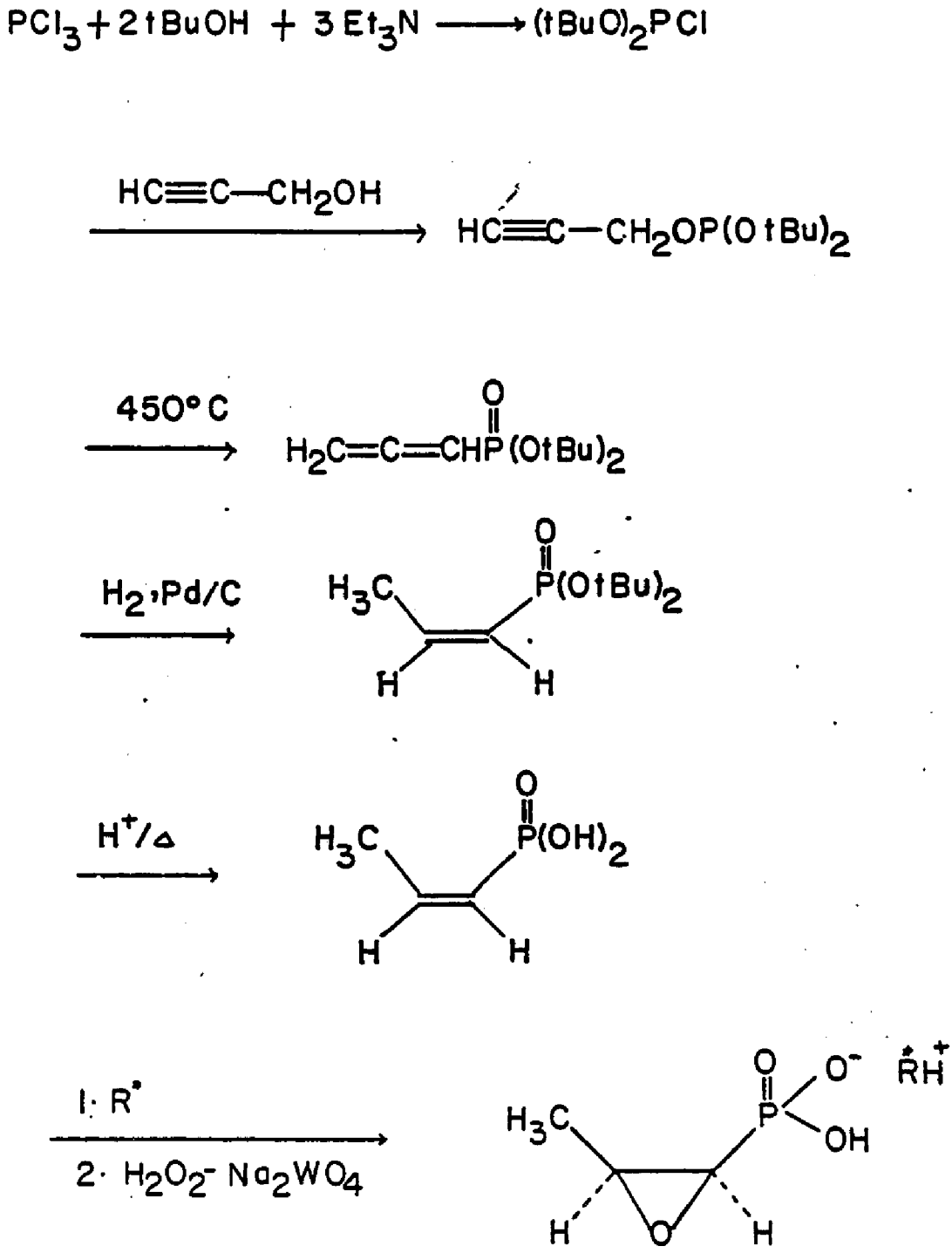
esters[37,38].




Scheme VI

Reaction of diethylvinylphosphonate with methanolic hydrogen peroxide at pH 9.5-10.0[39] resulted in 10% yield of the epoxide[1]. A 62% yield of the 1,2-epoxide was obtained with t-butylhydroperoxide in benzene[40] using Triton B as a catalyst. In addition to the desired epoxide, a significant amount of diethyl 2-t-butoxyethylphosphonate was also formed in this reaction presumably by a Michael addition of t-butoxide.

Direct epoxidation offers a dual advantage. First, the formation of the intermediate vinylphosphonate permits acid catalyzed deprotection prior to epoxidation or removal of the ester following epoxidation by hydrogenation if R=benzyl or phenyl[41]. Secondly, stereospecific vinylphosphonates can be obtained via

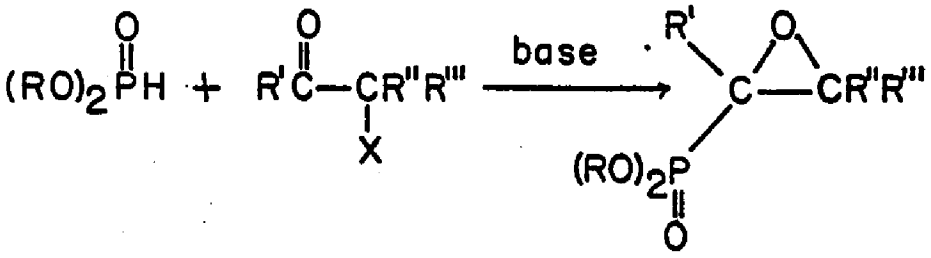


$R^{\bullet} = (+)\ C_6H_5CH(NH_2)CH_3$

Scheme VII

catalytic hydrogenation of the corresponding allenyl[42] or alkynyl[41] phosphonate. Epoxidation of the appropriate isomer can take place assymetrically in the presence of a resolving agent, to isolate the product of the desired absolute steriochemistry as shown in the synthesis of phosphonomycin[42] (scheme VII):

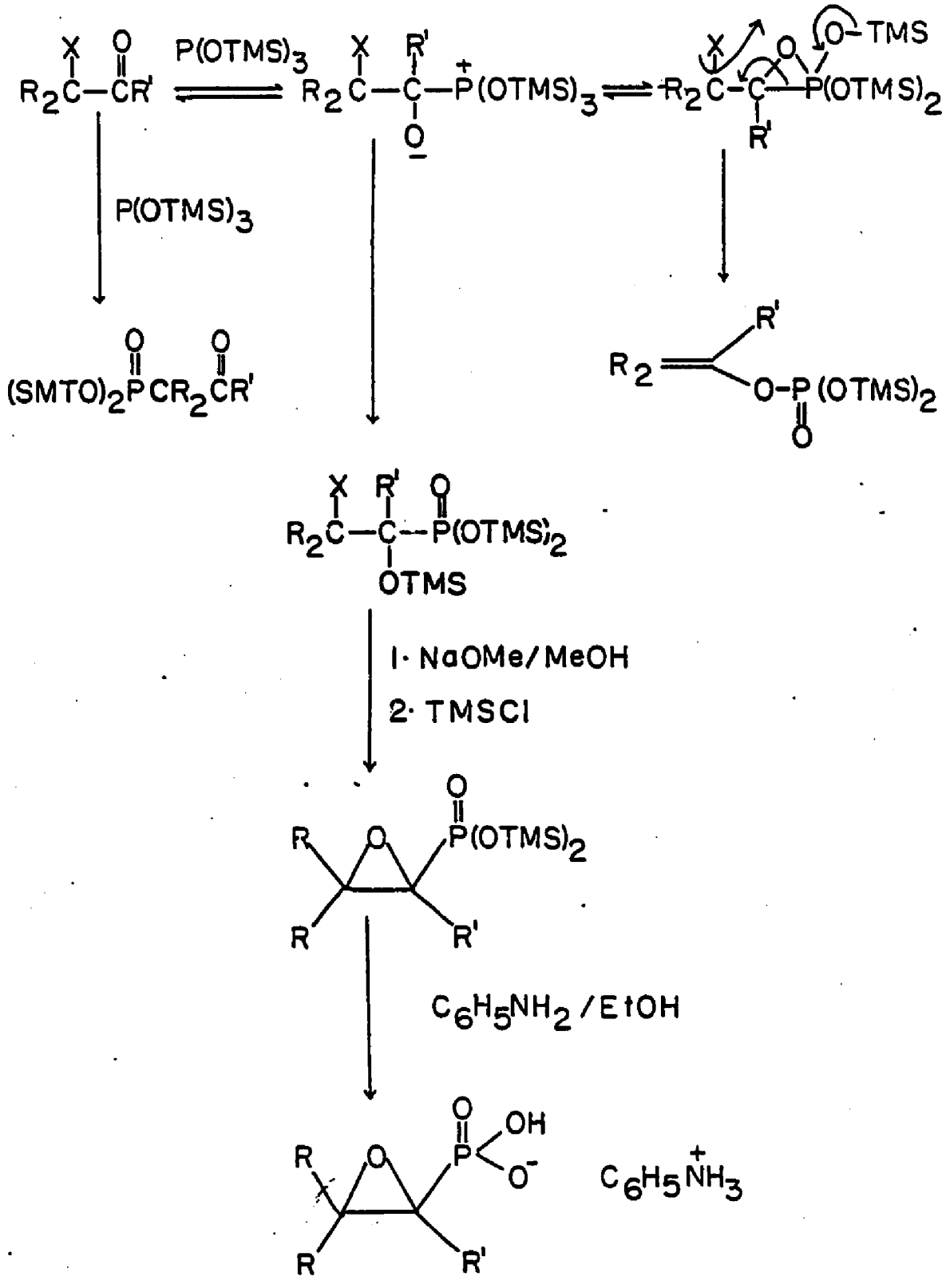
Haake et. al.[43] also reported a facile one step-procedure to 1,2-epoxyphosphonates, in 33-84% yields as shown below in scheme VIII :



R=$CH_3$, $C_2H_5$, $CH_2Ph$;
R'= $CH_3$, t-Bu,
R''=H, $CH_3$,
R'''=H

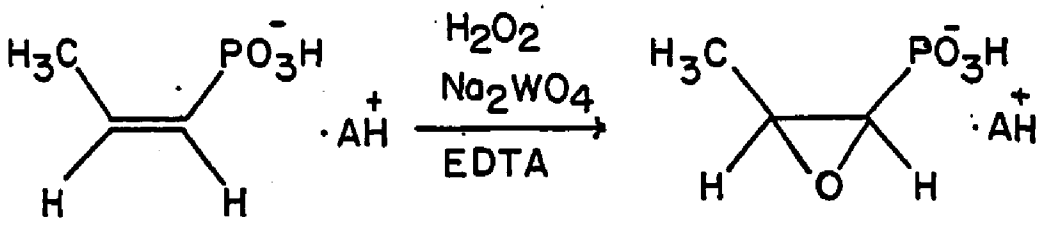
Scheme VIII

In 1979, Sekine et. al.[44] reported the facile hydrolysis of bistrimethylsilyl esters of phosphonic acids by addition of alcohols. They also reported the conversion of halohydrin adducts [10] to the free acids as shown below in scheme IX:


P(OTMS)3
P(OTMS)3
(SMTO)2PCR2CR'
1· NaOMe/MeOH
2· TMSCl
C6H5NH2 / EtOH
C6H5NH3

Scheme IX

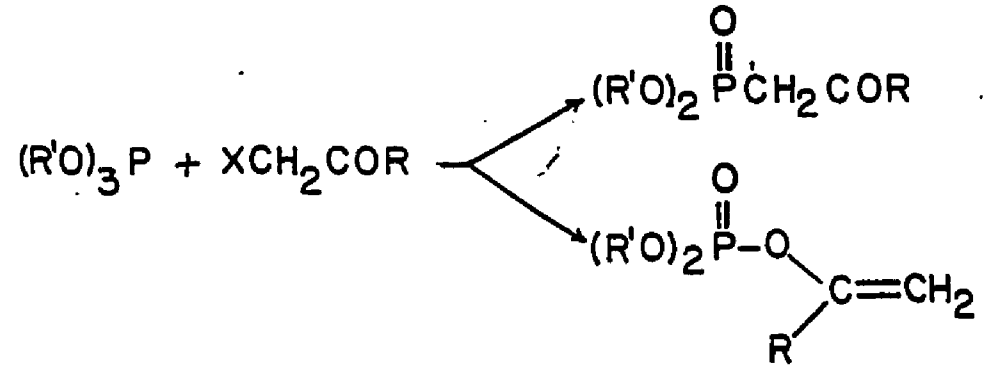
In 1979, Benigni and Trevisan[45] synthesized aminoacid salts of (-)-cis 1,2-epoxypropylphosphonic acid (phosphonomycin) as shown below (scheme X):




A = amino acid

Scheme X

2-Oxophosphonates are important intermediates in the synthesis of enones by the phosphoryl stabilized olefination reaction. 2-Oxophosphonates can in certain instances be prepared from alpha-halogenoketones by the Michaelis-Arbusov reaction.[46] However, the Perkov reaction forming enol phosphates, as shown below (scheme XI), competes. While this reaction can be minimized by varying the reaction conditions, other routes to the 2-oxophosphonates are superior.



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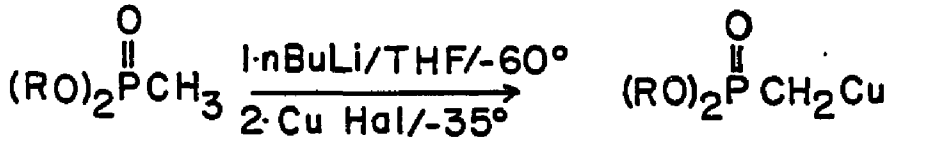
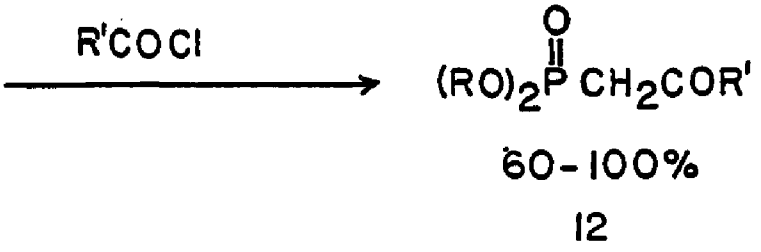
Scheme XI

A more efficient way to prepare 2-oxophosphonates is by acylation of the corresponding alkylphosphonate, using either the acyl halide[47] or the ester[48] as shown below.





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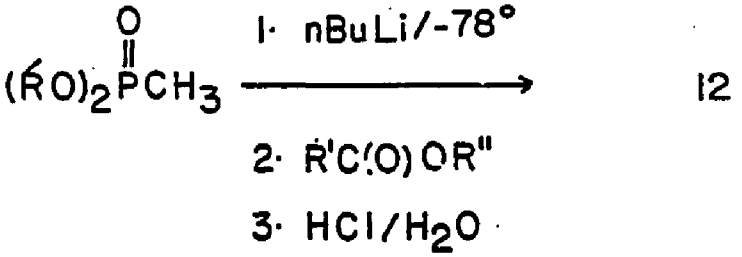
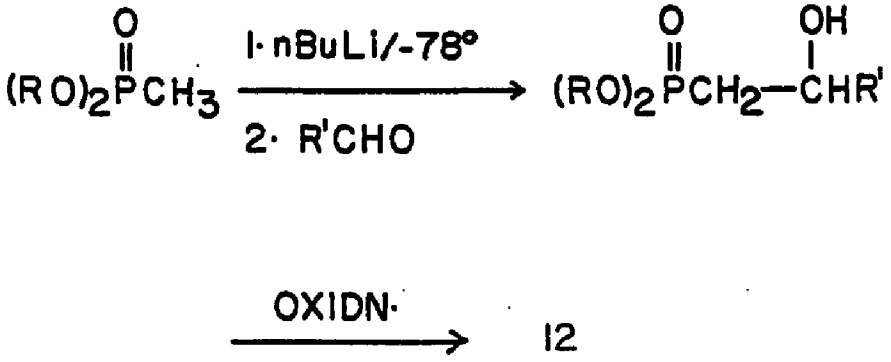


12

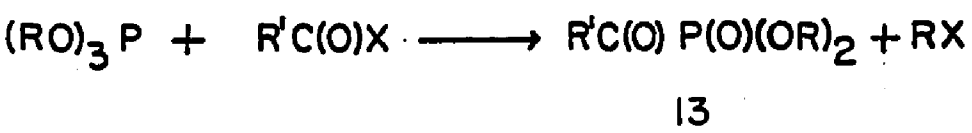
Scheme XII

Further route to make these important intermediates involves reaction of alkylphosphonate anions with aldehydes followed by oxidation of the intermediate beta-hydroxy compound[48], as shown below (scheme XIII).




Scheme XIII

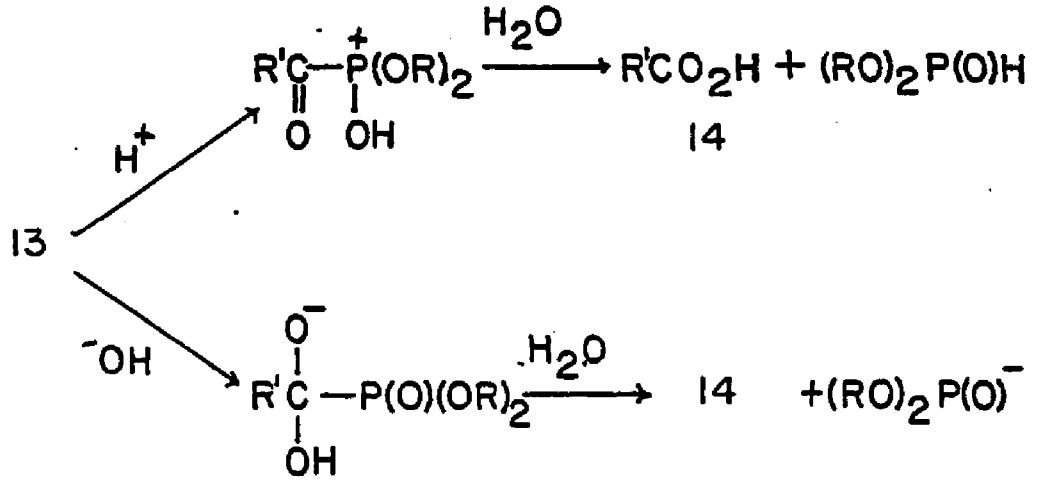
1-Ketophosphonates are readily prepared by the Michaelis-Arbuzov reaction of acyl halides with trialkyl phosphites as shown below[49] (scheme XIV).




Scheme XIV

The high acylating potential of acylphosphonates towards O, N, and C nucleophiles has been recognized[50] and has led to their use as alkoxycarbonylating agents in key steps of the synthesis of prostaglandins[51].

They are highly reactive compounds and are cleaved by acid as well as alkali to phosphites and carboxylic acid derivatives[52,53], presumably through the following mechanism[53].



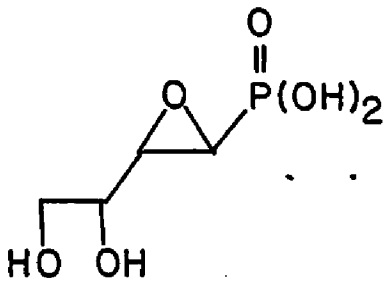

Scheme XV

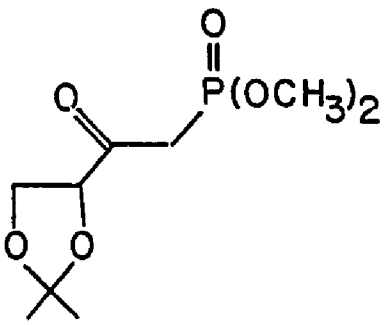
They are more readily cleaved than alpha-hydroxy compounds, and some acyl phosphonates are sensitive to moisture at room temperature[54]. It has been shown that the hemiketal [15] is produced when the 1-ketophosphonate is dissolved in alcohol at room temperature in the absence of acid[52] (scheme XVI).

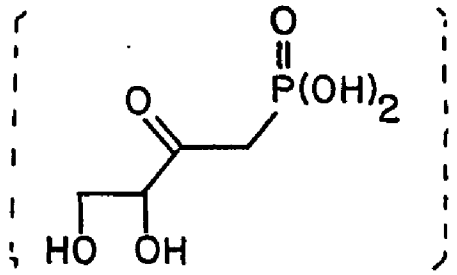

Scheme XVI

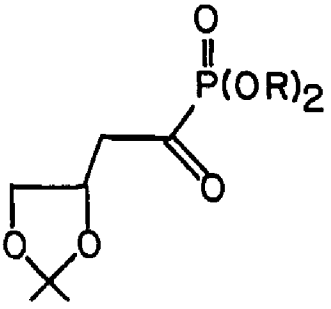
## STATEMENT OF PROBLEM

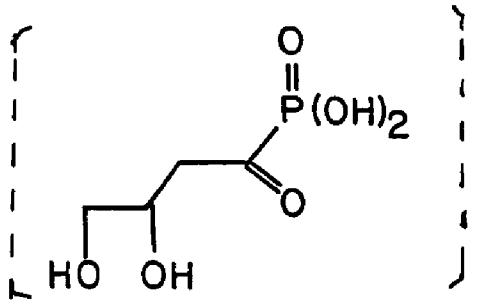
The current project has been concerned with the preparation of analogues of glycerol 3-phosphate which would incorporate 1) a non-labile phosphorus linkage, and 2) a functionality which is capable of irreversibly binding at an enzyme site. Such species would allow affinity label experiments to be designed and performed in enzymatic systems.



The major target to this end was 3,4-dihydroxy-1,2-epoxybutylphosphonic acid, which could be considered an analog of glycerol 3-phosphate and the naturally occuring antibiotic, Phosphonomycin.

Related materials which could serve for this purpose are 3,4-dihydroxy-1-ketobutylphosphonic acid and 3,4-dihydroxy-2-ketobutylphosphonic acid.

# RESULTS AND DISCUSSION

## I. Synthesis of 1,2-epoxyphosphonates:

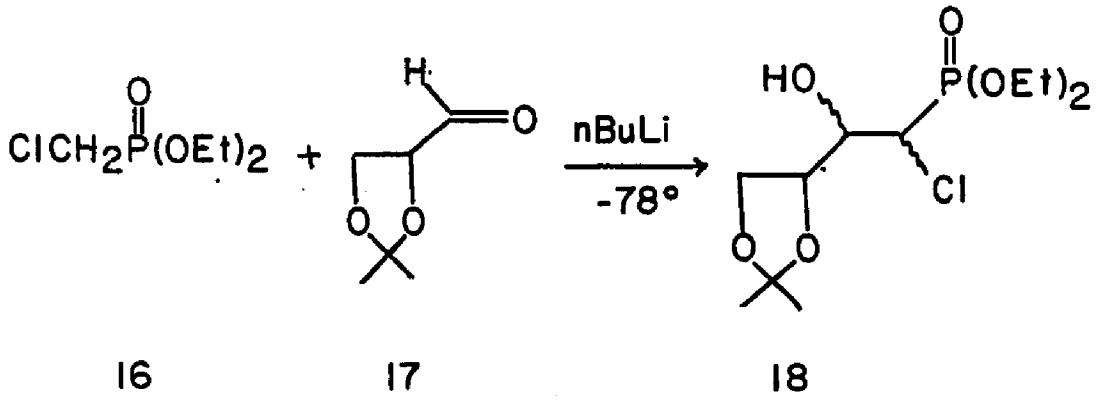
### (a) Attempts via halohydrins:

The Darzens reaction, within the structural limitations discussed, has been found very effective in the synthesis of 1,2-epoxyphosphonates. Numerous examples of its application to the synthesis of dialkyl esters of 1,2-epoxyphosphonic acid have been noted. However, in no case has the reaction been attempted with aryl esters of phosphonic acid. Furthermore, there is but one example of a dealkylation of a dialkyl 1,2-epoxyphosphonate to give the corresponding epoxyphosphonic acid[56].

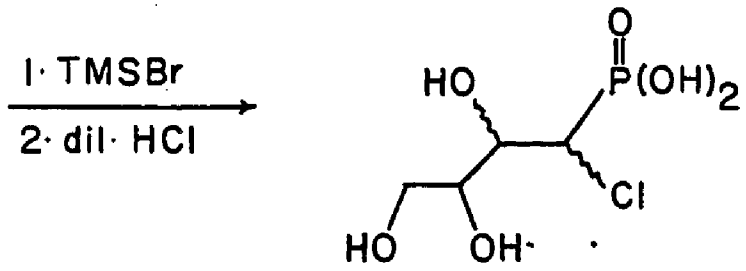
Our initial approach to 1,2-epoxy 3,4-dihydroxybutylphosphonic acid [2] is outlined below in scheme XVII.

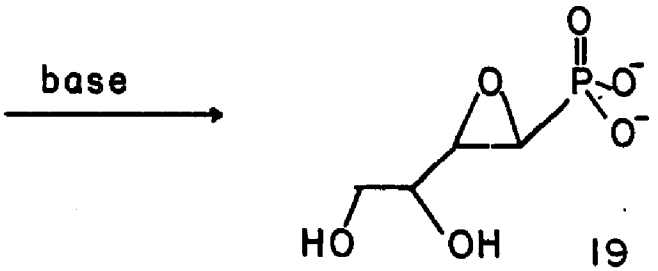
It was desired to fully deprotect the corresponding halohydrin prior to epoxide formation in view of the sensitivity of the oxirane ring alpha to the phosphonate. In this light it was decided that model systems should be examined first in order to develop methodology.

The known diethyl chloromethylphosphonate [16][56a,b] was synthesized by reaction of chloromethyl phosphonic dichloride with 2 equivalents each of ethanol and triethyl amine as shown below in scheme XVIII.




16 17 18

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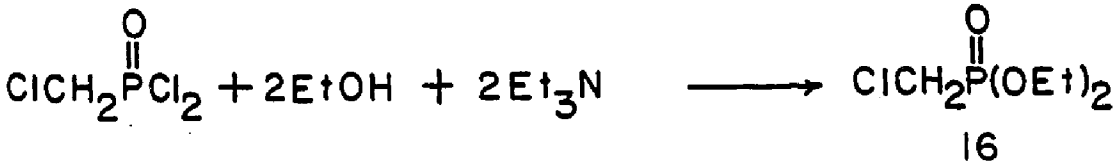
Scheme XVII

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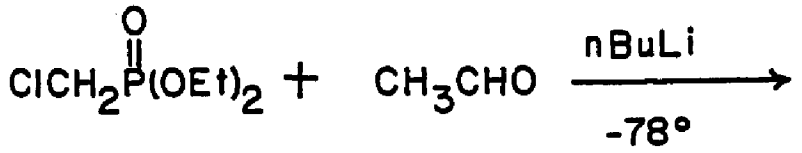
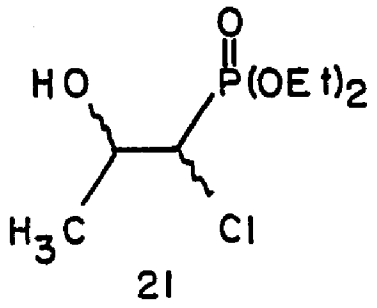
Scheme XVIII

Reaction of the anion generated from diethyl chloromethylphosphonate using nBuLi with acetaldehyde in dry ether at -78 °C, for three hours followed by quenching with water, gave a reaction mixture for which NMR indicated product formation.



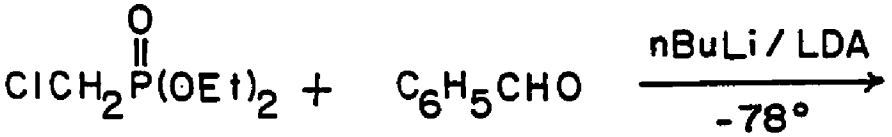

21

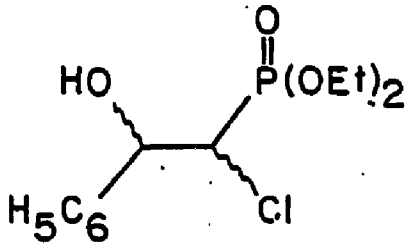
Scheme XIX

Unfortunately, all attempts to purify it by chromatography met with failure. It decomposed on standard silica gel chromatography columns as well as on attempted HPLC.

Similar results were obtained on reaction of lithiated diethyl chloromethylphosphonate, generated using nBuLi or lithium diisopropyl amide [LDA], with benzaldehyde.

Similarly, generation of the anion of diethyl chloromethylphosphonate using t-butyl lithium , and its subsequent reaction with n-pentanal also failed to provide a purifiable product.

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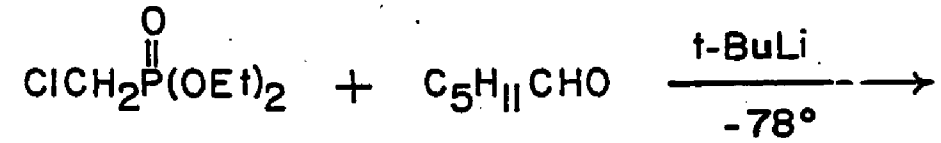
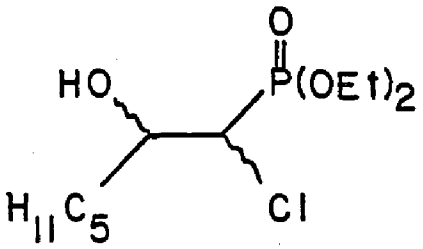
Scheme XX



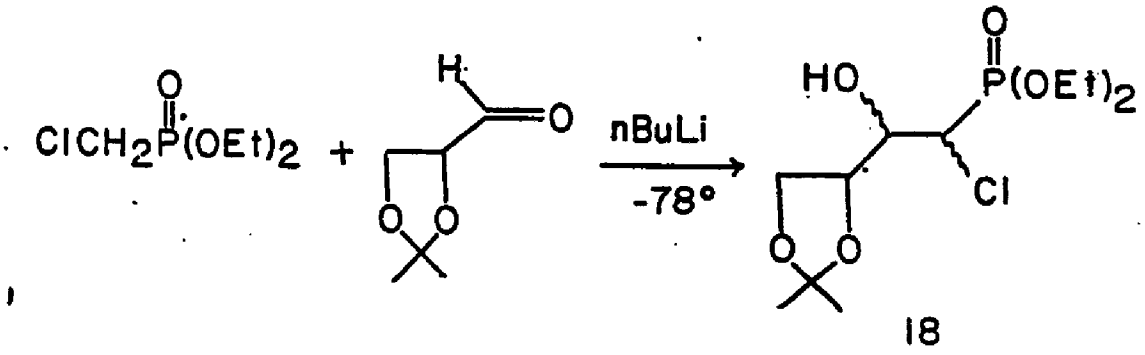




23

Scheme XXI

In 1978, Coutrot and Savignac[36], reported the preparation of 1,2-epoxyphosphonates by the reaction of lithiated diethyl chloromethylphosphonate with various carbonyl compounds. Diethyl chloromethylphosphonate was added to nBuLi in THF/hexane at -70° followed by addition of the carbonyl compound at -70°. After stirring for one hour at -78°, it was warmed to room temperature and stirred overnight.

We have applied this reaction to acetone glyceraldehyde but it was quenched at -78° in order to isolate the halohydrin [18].

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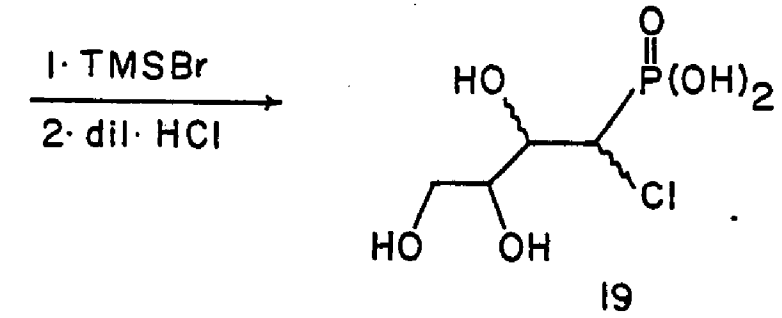


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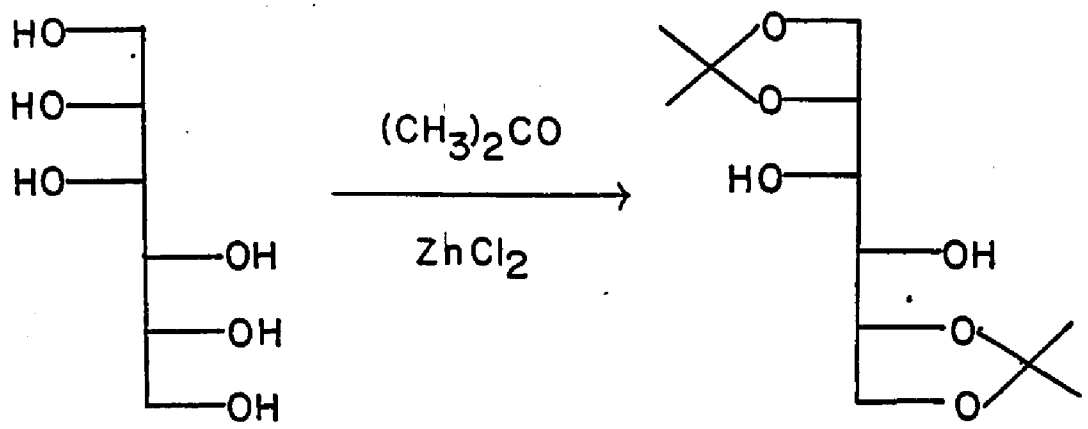
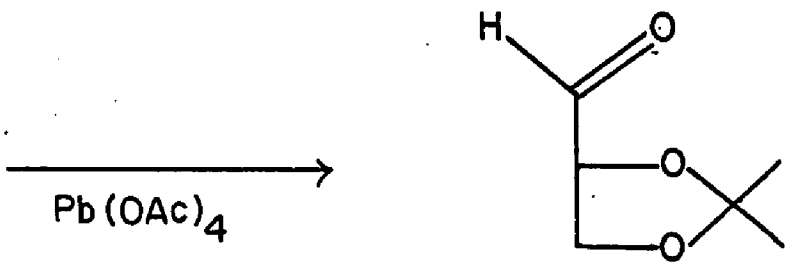
Scheme XXII

Acetone glyceraldehyde [17] was prepared by the method of Baer and Fisher[57] as shown below.




17

Zinc chloride catalyzed acetonization of D-mannitol at room temperature for 16 hr provided 1,2-5,6-diacetone-D-mannitol, which on treatment with lead tetraacetate in dry benzene afforded acetone glyceraldehyde.

Treatment of lithiated diethyl chloromethylphosphonate with acetone glyceraldehyde at -70 to -75 °C for 1 hour followed by quenching with water gave

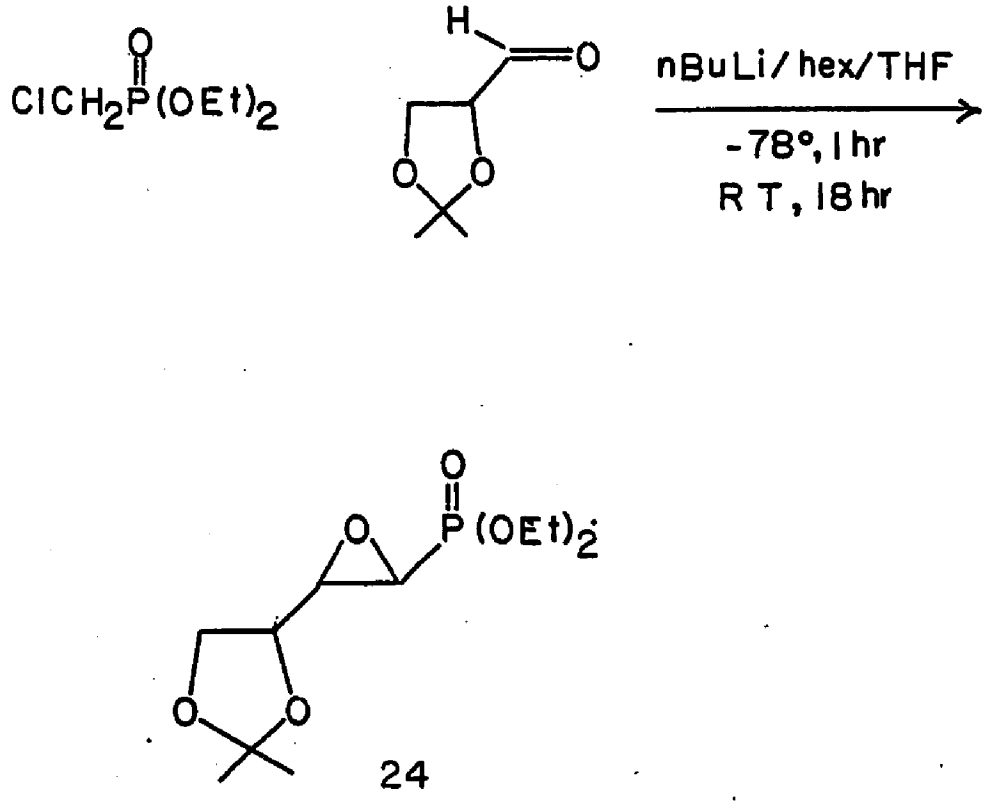
the halohydrin. Attempts to purify it directly were unsuccessful. NMR of this crude material showed presence some starting phosphonate and a multiplet at 5.2 ppm. The mixture was then treated with 1% aq. HCl and extracted with methylene chloride. The aqueous layer was pumped dry to yield a solid which decomposed rapidly. Elemental analysis of this compound was not accurate but did calculate closely with diethyl 1-chloro-3,4-dihydroxy-1-butenylphosphonate as an impurity formed by dehydration of the desired halohydrin.

Attempted treatment of it with excess (ca 5 fold) trimethyl bromosilane resulted in complete decomposition to a black material.

(b). via Darzen's reaction:

(1) with Diethyl chloromethylphosphonate:

Following the failure to obtain the epoxide by the halohydrin route an attempt was made to prepare diethyl 1,2-epoxy-3,4-O-isopropylidene butylphosphonate [24], using Coutrot's conditions, as shown (scheme XXIV).




24

Scheme XXIV

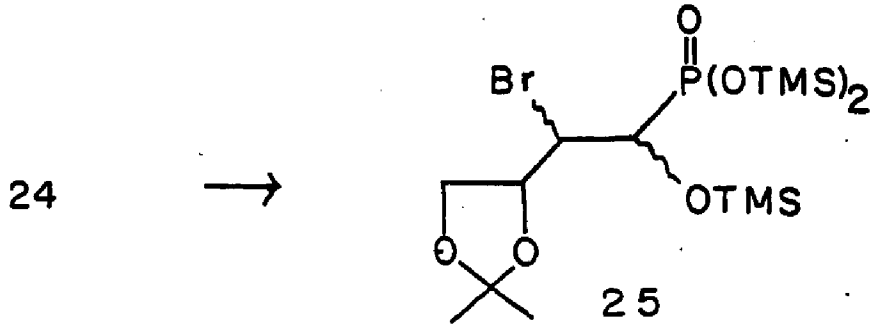
The reaction of lithiated diethyl chloromethylphosphonate with acetone glyceraldehyde was carried out as above and allowed to warm to room temperature with stirring over an 18 hour period. The reaction mixture was then quenched with water and extracted with 1:1 ether-methylene chloride. Product formation was evident by NMR.

Attempted chromatography on silica gel resulted in decomposition. Attempts at HPLC using Lichosorb SI 60

column resulted in numerous peaks. One of these peaks was identified as diethyl chloromethylphosphonate. Decomposition under HPLC conditions was also evident. Fortunately, distillation under reduced pressure provided a fraction comprised of pure diethyl 1,2-epoxy-3,4-O-isopropylidene butylphosphonate, which gave satisfactory spectra and elemental analysis. Remaining diethyl chloromethylphosphonate distilled prior to the product. On injection of the pure sample on the analytical HPLC column, all the peaks of the reaction mixture but the one corresponding to diethyl chloromethyl phosphonate were found, indicating decomposition on the column.

Trimethylbromosilane has been found to be an effective reagent in the cleavage of alkyl esters of phosphonic acids[58]. It was hoped that there would be a difference in the rate of cleavage and the rate of nucleophilic attack on the epoxide by bromide. Unfortunately, treatment of diethyl 3,4-O-isopropylidene 1,2-epoxybutylphosphonate with 2 eq. of trimethylbromosilane at room temperature resulted in attack primarily at the epoxide. This was seen by carrying out the reaction in an NMR tube using $CDCl_3$ as a solvent. Within minutes of mixing the reagents, the protons assigned to the oxirane system had shifted. It is known that nucleophilic attack on 1,2-epoxyphosphonates always occurs at the beta-carbon[29], so the product of reaction

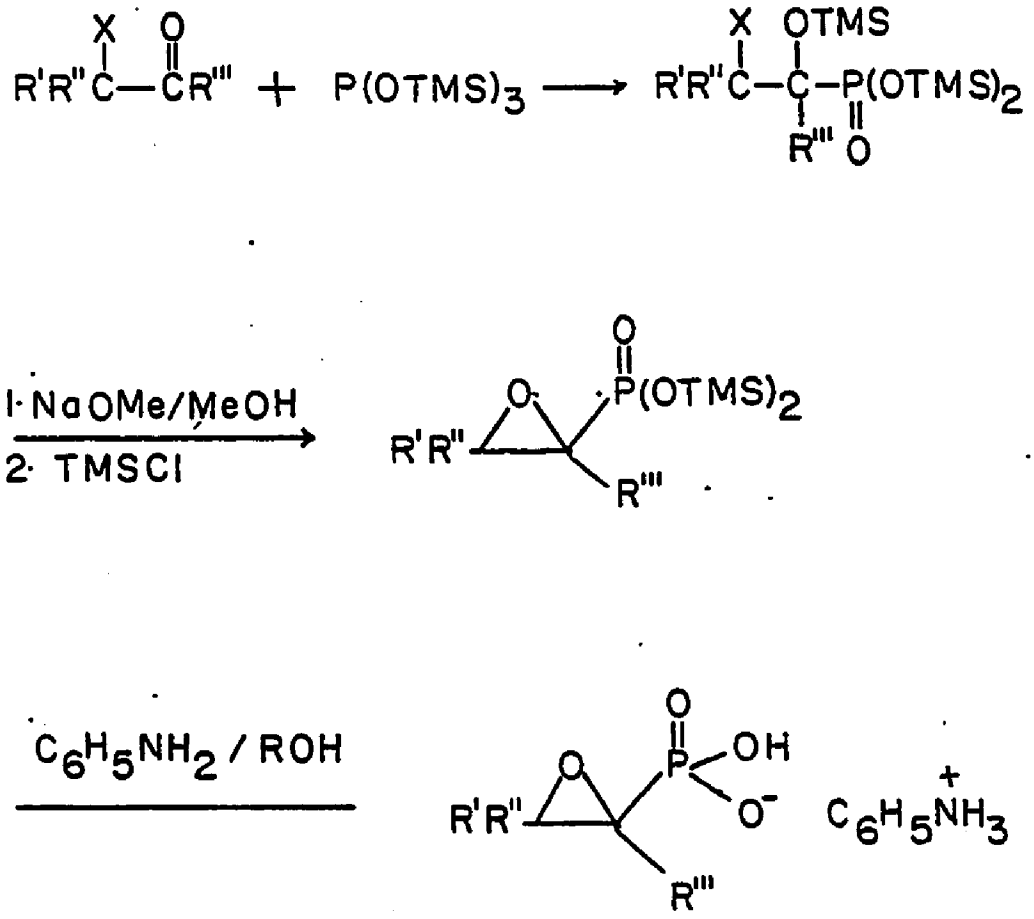
with excess trimethylbromosilane would be ditrimethylsilyl 2-bromo-3,4-O-isopropylidene-1-trimethylsilyloxy butylphosphonate [25]. NMR of this material showed attack at the oxirane and the material was presumed to be [25].




Attempts at cleavage of the acetonide of [24] also resulted in the opening of the epoxide. For example, treatment with saturated ammonium chloride in 90 % methanol overnight at room temperature resulted in attack at the epoxide while the acetonide remained untouched.

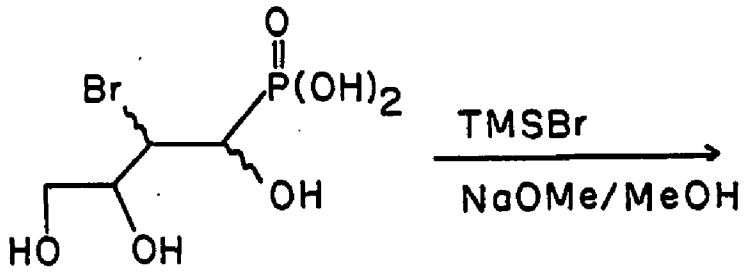
Sekine, *et al*[44]. have demonstrated that trimethyl silylated halohydrins formed by reaction of trimethylsilylphosphite with alpha halocarbonyl compounds can be converted to the corresponding bis (trimethylsilyl) 1,2-epoxy phosphonates by reaction with sodium methoxide in methanol followed by resilylation with trimethylchlorosilane. These can in turn be converted to monoanilinium salts of the epoxyphosphonic acids by

treatment with aniline in alcohol, as shown below in scheme XXV.

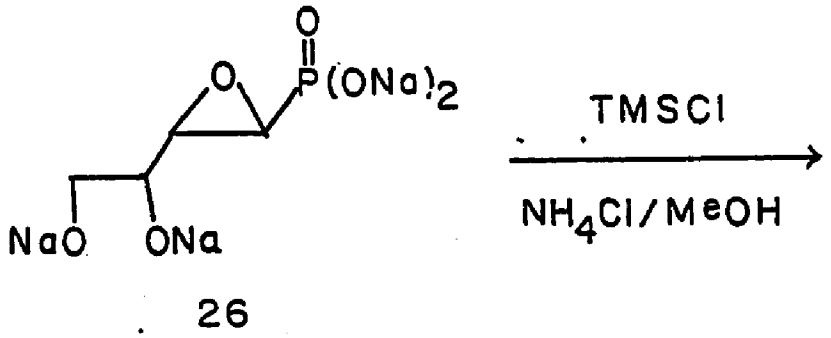


Scheme XXV

This approach was applied to the system at hand as shown below.




25a

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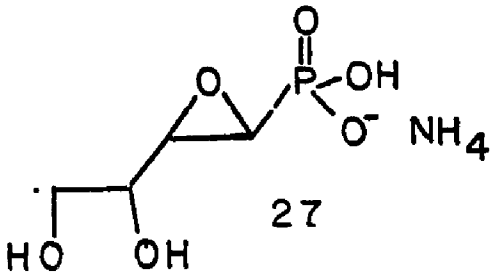


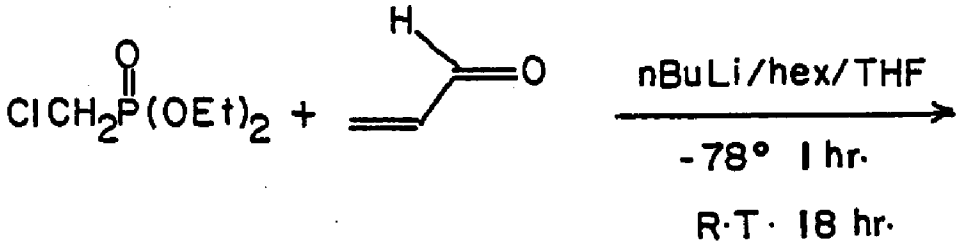

27

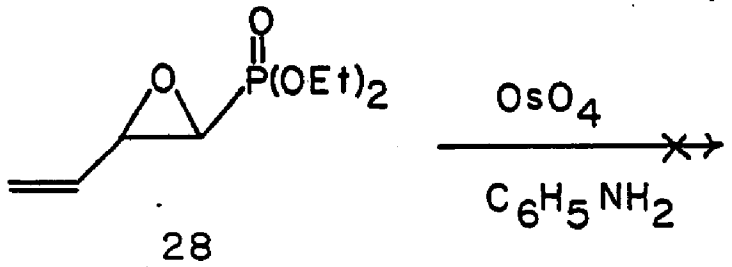
Scheme XXVI

Treatment of [24] with trimethylbromosilane (3 eq.) followed by reaction with 1% aq. HCl gave the 2-bromo-1,3,4-trihydroxybutylphosphonic acid [25a]. Again the structure was presumed on the basis of NMR which confirmed

the cleavage of acetonide.This was treated with 5 eq of bromotrimethylsilane followed by 5 eq. of sodium methoxide in methanol. Two regioisomers are possible,both the 1,2-epoxy and the 2,3-epoxy phosphonates. This mixture was treated with chlorotrimethylsilane. Saturated ammonium chloride in methanol was added and the crystals formed were filtered. This material gave elemental analysis for the trihydrate of the disodium salt of [27].

In order to avoid the possibility of obtaining a mixture of two regioisomers, the following approach was taken.

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Scheme XXVII

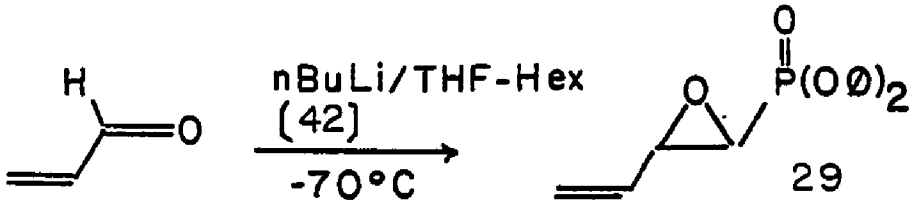
The reaction of lithiated diethyl chloromethyl phosphonate with acrolein at -70 to -75 °C for one hour followed by stirring at room temperature for 18 hours gave

on distillation diethyl 3-butenyl 1,2-epoxy phosphonate [28], which gave satisfactory spectra and elemental analysis. Treatment with 3 eq. of bromotrimethylsilane followed by 3 eq. of sodium methoxide in methanol gave as above disodium salt of 3-butenyl-1,2-epoxyphosphonic acid. Treatment with chlorotrimethylsilane followed by Osmium tetraoxide mediated hydroxylation failed to give any isolable product.

(2) Attempts with diphenyl chloromethylphosphonate:

Phenyl esters of phosphonic acids can be cleaved by hydrogenolysis. Therefore, if the Darzens-type reactions discussed above could be applied to diphenyl chloromethylphosphonate [30], the resulting diphenyl-1,2-epoxyphosphonic acids could possibly be obtained after hydrogenolysis of the ester linkages.

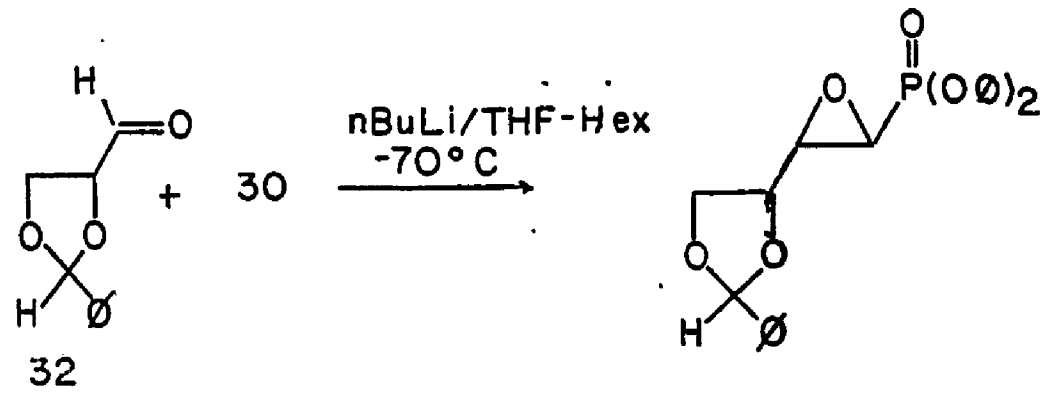
Accordingly, the use of diphenyl chloromethylphosphonate in a Darzen reaction was investigated. The reaction with acrolein would be expected to generate the epoxide [29], which could be hydroxylated with $OsO_4$ and hydrogenolysed with the oxirane ring present.




Scheme XXVIII

The reaction of lithiated diphenyl chloromethylphosphonate with acrolein was performed at -78 °C, as noted for other systems before, and after the usual workup there was obtained from the reaction mixture a solid. This was isolated by chromatography, and also by precipitation from a ether solution by addition of methylene chloride. NMR of this material showed formation of the product. The material was not purifiable completely and so analysis was not obtained.

Another route explored is shown in the scheme below:



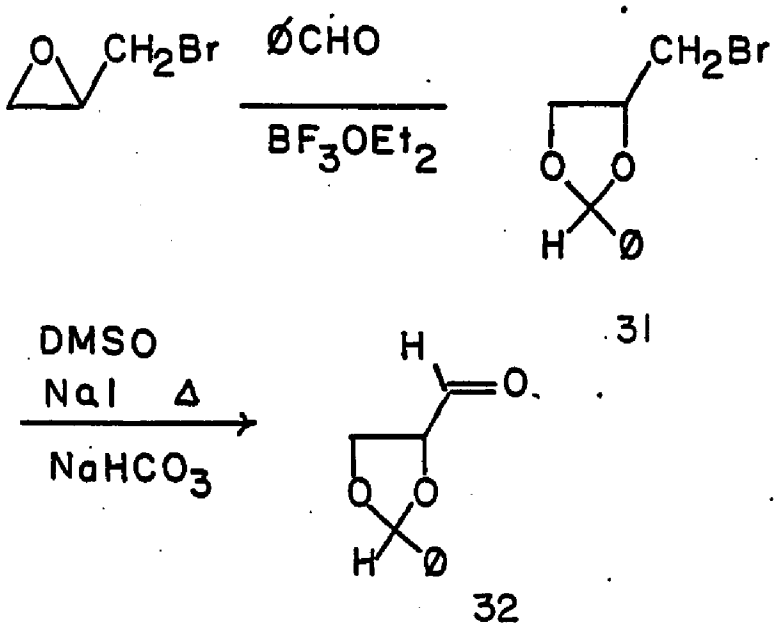

Scheme XXIX

Diphenyl 3,4-O-benzylidene-3,4-dihydroxy-1,2-epoxy phosphonate should be susceptible to hydrogenolysis to generate [2].

Benzylidene glyceraldehyde has been known as an unstable species, not isolated but derivatized[78,79]. It has been synthesized from D-mannitol[79]. Direct benzylidenation of glycerol followed by seperation of the isomers would give 2,3-O-benzylidene glycerol which could

be oxidized. In our hands these methods failed to give the desired product.

Synthesis of benzylidene glyceraldehyde was approached by a novel route as shown below.




Scheme XXX

Epibromohydrin was treated with benzaldehyde in dry chloroform in the presence of a catalytic amount of boron trifluoride etherate at room temperature. Distillation of the reaction mixture gave 2,3-O-benzylidene-1-bromo propane [31][81].

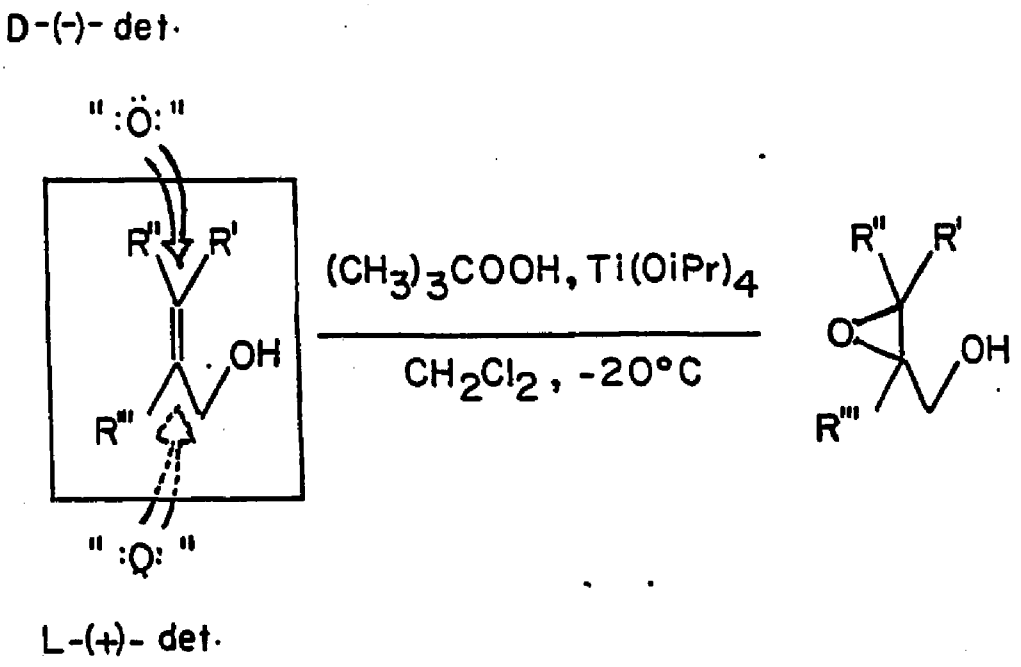
Alkyl iodides have been oxidized directly by treatment with DMSO[80]. Alkyl chlorides and bromides require prior conversion to the tosylate using silver tosylate in order to be so oxidized. We decided to convert

the primary bromide to the iodide insitu, using NaI. Treatment of the bromide [31] with DMSO in the presence of NaI and $NaHCO_3$ at 135 °C, gave the desired aldehyde [32] along with some unreacted bromide. In view of its reported unstability, this was used without purification.

The Darzens reaction of [30] with [32] as shown in the scheme below, gave a mixture in which the aldehyde had been consumed (NMR). Chromatography gave a fraction the NMR of which is in accordance with that of the expected compound.

(c) Direct epoxidation of alkene phosphonates:

Yet another approach to preparation of 1,2-epoxy phosphonates involves direct epoxidation of alkene phosphonates. The advantage of this approach is that it would be possible to cleave or modify the protecting groups on the alkenephosphonate prior to epoxidation. It would also be possible to perform the epoxidation in the presence of chiral auxiliaries in order to isolate the product of desired stereochemistry. One such approach suitable to the present synthetic target would be the Sharpless type epoxidation, in which allylic alcohols are epoxidized using t-butyl hydroperoxide in the presence of optically active tartaric acid esters and titanium tetraalkoxides[61].



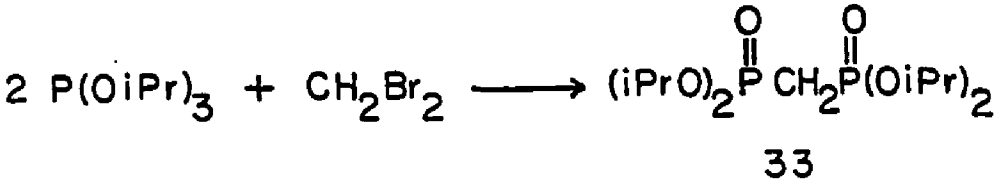

Scheme XXXI

Another approach is to epoxidize alkene phosphonate salts with hydrogen peroxide using chiral counterions [42], for example chiral ammonium ions.

The known diisopropyl 3,4-O-isopropylidene-3,4-dihydroxy-1-butenylphosphonate [34] was synthesised as shown below [62].

Reaction of dibromomethane with triisopropyl phosphite, with removal of the formed isopropyl bromide through a column heated at 65 °C, gave tetraisopropyl methylenebisphosphonate [TIMBP] [33] in good yield [63]. The

anion of TIMBP, generated with nBuLi, on condensation with acetone glyceraldehyde gave [34].

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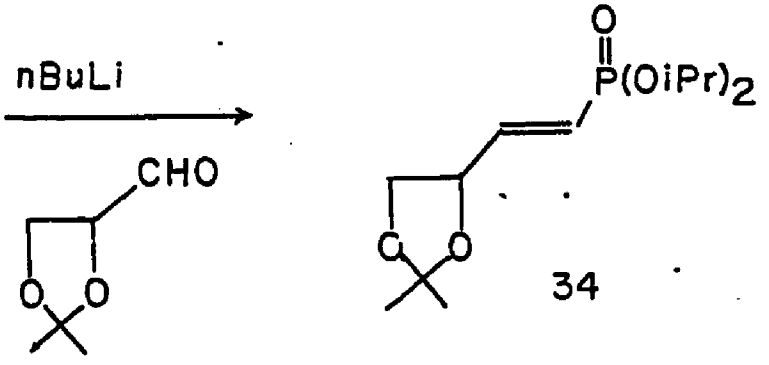
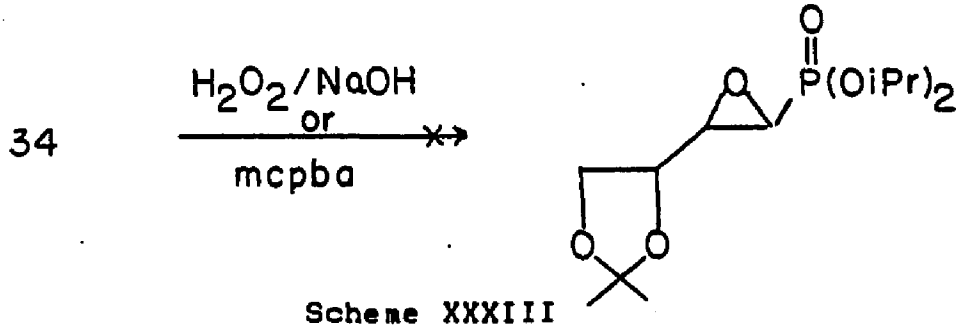



34

Scheme XXXII

Attempted epoxidation of [34] with either hydrogen peroxide/sodium hydroxide or m-chloroperoxybenzoic acid resulted in recovery of the starting vinyl phosphonate.

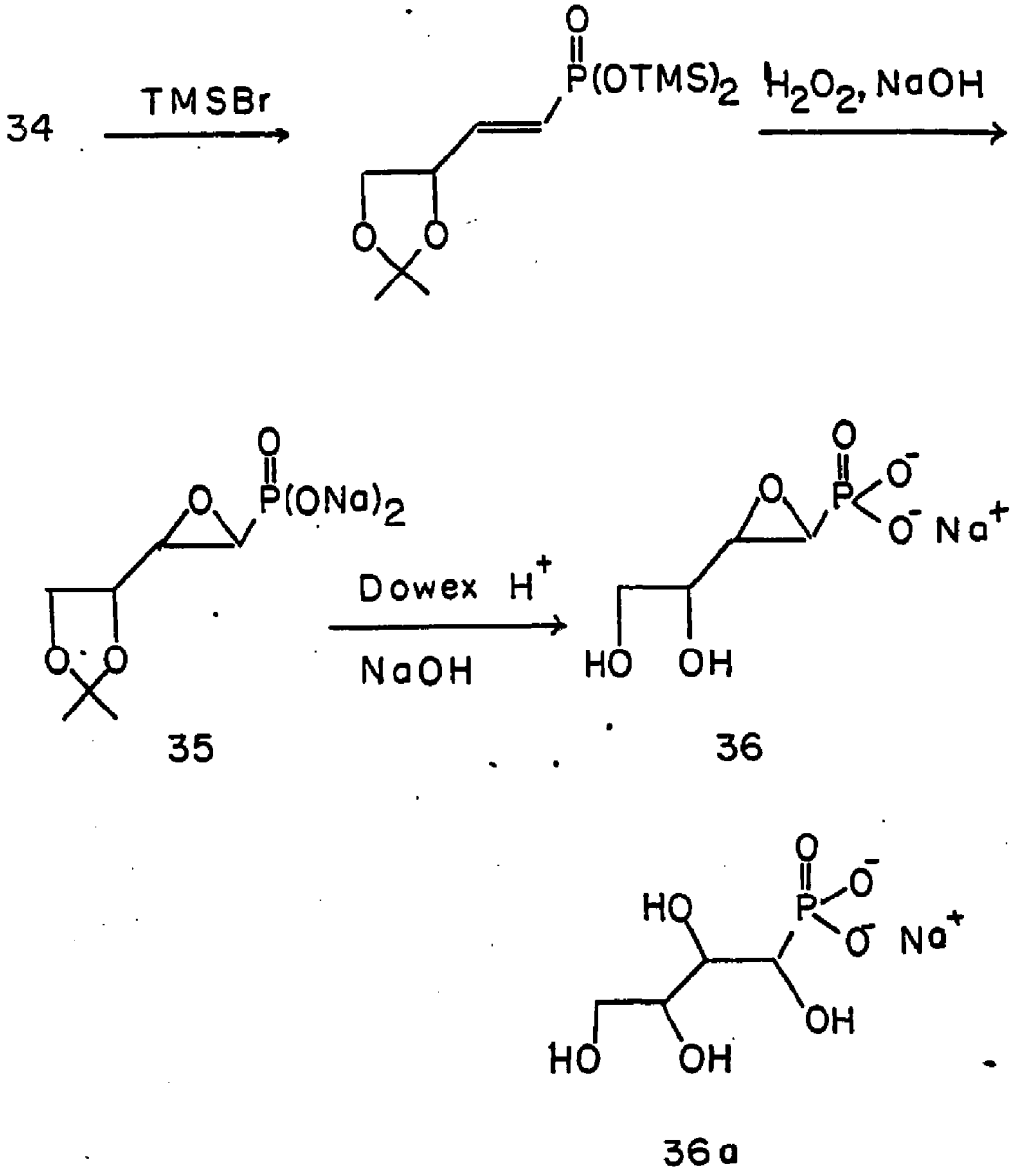



Scheme XXXIII

Previous results in this laboratory[64] have shown that prior conversion of the isopropyl esters of the vinylphosphonate [34] to trimethylsilyl esters followed by reaction with hydrogen peroxide and sodium hydroxide results in oxidation of the double bond.

Treatment of the vinylphosphonate [34], as shown in scheme XXXII with 4 eq. of trimethylbromosilane followed by reaction with hydrogen peroxide and sodium hydroxide, maintaining a pH of 9.5 to 10, in methylene chloride/methanol mixture overnight resulted in formation of a white solid on lypholyzing the aqueous layer. Deacetonization with Dowex 50 in the $H^+$ form at pH 3 followed by treatment with dil. NaOH to pH 7.5, and drying under vacuum resulted in formation of a white hygroscopic compound. This compound analysed for the hydrated form of the desired compound [36a], but was found to be biologically inactive[65].

It was determined by quantitative analysis that the above product was not the desired epoxy diol but the tetrahydroxy compound which would be formed by the water opening of the epoxy compound. NMR of this material did not show any signals between 2.8 and 3.3 ppm which could be assignable to the oxirane protons (for example phosphonomycin[25].




Scheme XXXIV

Repeating the above epoxidation procedure at a pH of 7-7.5 also resulted in formation of the same compound. The same procedure was applied to bis (trimethylsilyl)-3,4-ditrimethylsilyloxybut-1-enyl-1-phosphonate, and yet again the same tetrahydroxy compound resulted.

Failure of the above reaction sequence indicates that the epoxidation must be performed in a nonaqueous solvent

system if the formed epoxide is to survive. This would require an organic soluble substrate with protective groups removable under mild conditions in the presence of the epoxide linkage, and a nonaqueous epoxidation procedure. One such procedure that has been mentioned above is the Sharpless epoxidation. A limitation of this procedure is that epoxidation of allylic alcohols which yield water soluble products proceed with low yields, presumably due to further reaction of the water soluble epoxide with NaOH used during workup. A modified workup has been suggested using saturated NaF and saturated aq. NaCl followed by extraction with organic solvent. Thus it was very desirable that the epoxide have limited water solubility.

It is known that benzyl and phenyl esters of phosphonic acids can be cleaved by hydrogenolysis[14,66]. Benzyl ethers can also be cleaved by hydrogenolysis. So, attempts were made to synthesize diphenyl and dibenzyl esters of the corresponding butenylphosphonic acid. Initial attempts were made starting with 3,4-dihydroxy-but-1-enyl-1-phosphonic acid because of its availability. Treatment of [37] with 3 equivalents of benzyl bromide in dimethyl formamide [DMF] in presence of potassium hydroxide resulted in attack at the double bond. Reaction of the butenylphosphonic acid [37] with 3 eq of nBuLi followed by benzyl bromide also gave none of the desired

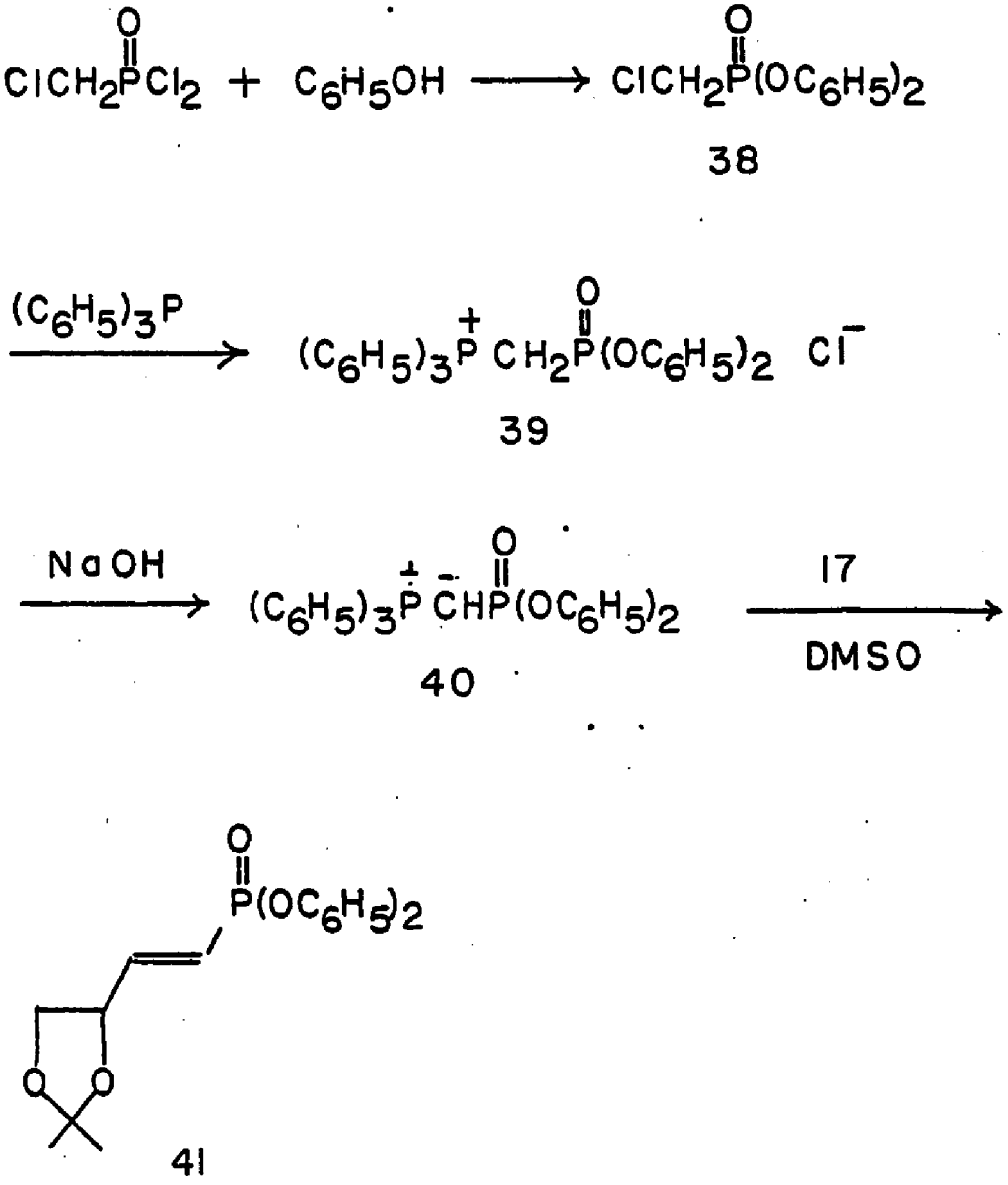
product.

Next, the known[14] diphenyl 3,4-O-isopropylidene-3,4-dihydroxy-but-1-enyl-1-phosphonate [41] was prepared as shown in scheme XXXV.

Reaction of chloromethylphosphonic dichloride with 2 eq of phenol gave on distillation diphenyl chloromethylphosphonate[67]. Treatment with triphenyl phosphine followed by neutralization with sodiumhydroxide gave triphenyphosphoranylidene diphenylphosphonate[68]. Wittig reaction of this with acetone D- glyceraldehyde in dimethyl sulfoxide [DMSO], gave [41](scheme XXXIII).

In a similar fashion reaction of chloromethylphosphonic dichloride with benzyl alcohol in ether in the presence of triethyl amine gave dibenzyl chloromethylphosphonate which was purified by chromatography. Treatment with triphenylphosphine followed by neutralization with NaOH,as above gave triphenylphosphoranylidene dibenzylphosphonate. Unfortunately reaction with acetone D-glyceraldehyde under the same condition as above failed to give the desired product.

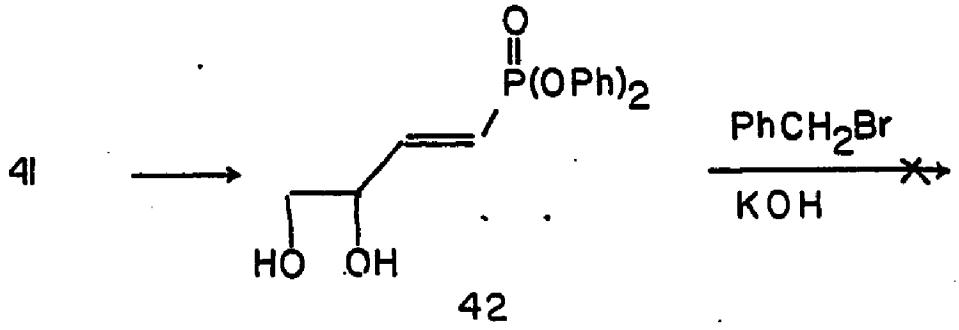
Acid catalyzed hydrolysis of [41] gave diphenyl 3,4-dihydroxy but-1-enyl-1-phosphonate [42]. Sharpless epoxidation on this would not work because the diol functionality would coordinate with the Ti and make attack on the double bond impossible.

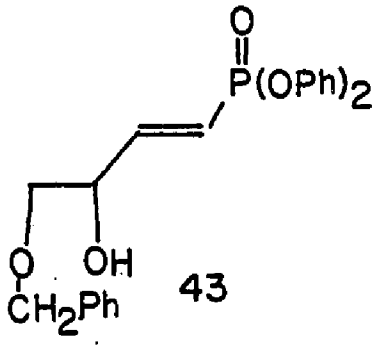


scheme XXXV

It was necessary to block the primary hydroxyl group

of [45] in order to make it a suitable substrate for epoxidation. Our first choice of the blocking group was a benzyl ether which could be removed by hydrogenolysis, possibly along with the phenyl esters in one step. Unfortunately treatment of [45] with benzyl bromide in DMF in the presence of KOH resulted in attack at the double bond and no desired product was observed (scheme XXXVI).

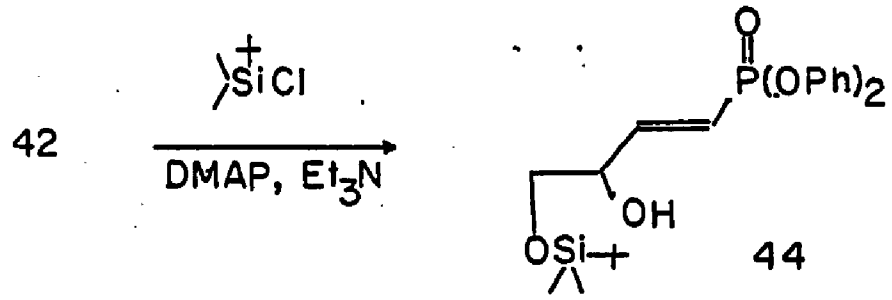



Scheme XXXVI

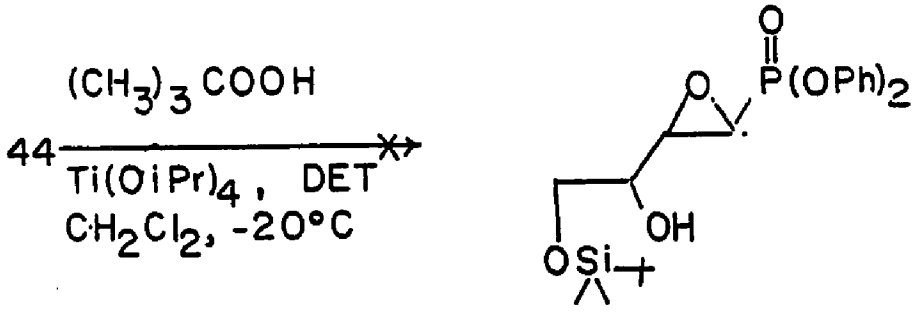
Another blocking group widely used to protect alcohols is the t-butyl dimethyl silyl group, [TBDMS][69]. It can be cleaved selectively with fluoride ion under

mild conditions. Based on the method of Chaudhary and Hernandez[70] the primary hydroxyl group was selectively protected using t-butyl dimethyl silyl chloride in the presence of triethyl amine and dimethyl aminopyridine [DMAP] at room temperature in methylene chloride as shown below in scheme XXXVII. NMR of this material showed 1 t-butyldimethyl silyl group by integration and a broad signal for hydroxyl proton. Other signals also corresponded to the assigned structure. It gave satisfactory analysis.



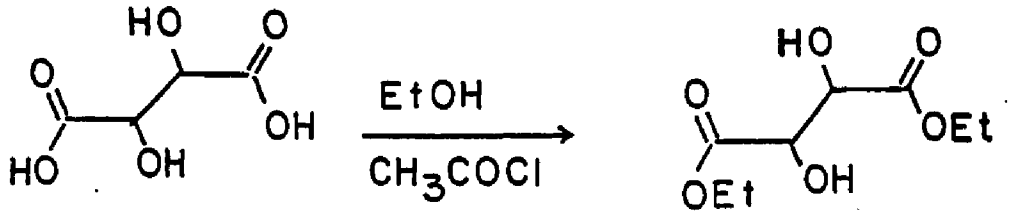

Scheme XXXVII

Sharpless epoxidation of diphenyl 4-t-butyldimethylsilyloxy-3-hydroxy-but-1-enyl-1-phosphonate [44] was carried out as shown below[71].




Scheme XXXVIII

Diethyl tartrate [DET] was prepared by esterification of (+)tartaric acid as shown below, and purified by distillation.




Scheme XXXIX

Anhydrous t-butylhydroperoxide [TBHP] was prepared as a solution in 1,2-dichloroethane by the procedure of Sharpless[72], starting with 70% aq TBHP, removing water azeotropically. Its concentration was determined by NMR integration using the following relation:

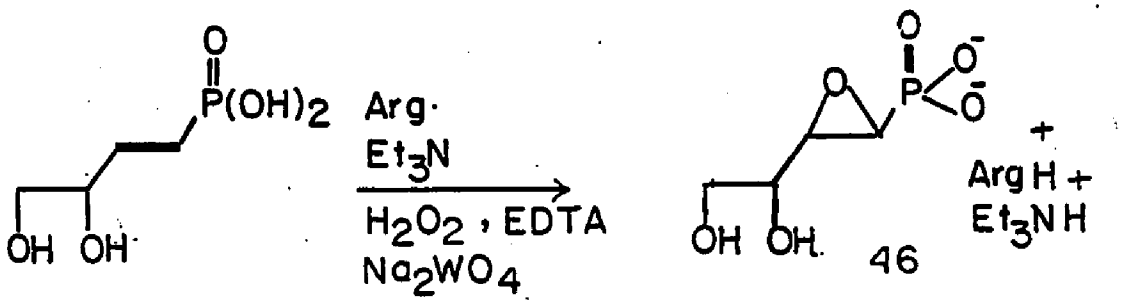
Molarity = A/[(0.10A+(0.18B)]

Where A = integration of tert-butyl resonance (~1.25) and B = integration of dichloroethane resonance (~3.70)

To titanium tetraisopropoxide in dry methylene chloride at -20 °C was added DET followed by the alkene [44] and finally TBHP was added. The mixture was stored at -20 °C for 10 days and poured into saturated NaF solution. The mixture was stirred for 14 hours at room temperature. The aqueous layer was saturated with sodium chloride and

filtered through celite pad to remove titanium salts. Extraction provided a reaction mixture which consisted mainly of the starting alkene. Traces of another compound were observed on TLC. At this point this approach was abondoned.

Failure of the above method led us to explore the possibility of conducting the epoxidation of [37] in aqueous medium after converting it to a amine salt, based on synthesis of phosphonomycin, as a salt of a chiral amine[45]. Epoxidation of 3,4-dihydroxybut-1-enyl-1-phosphonic acid was attempted as shown.

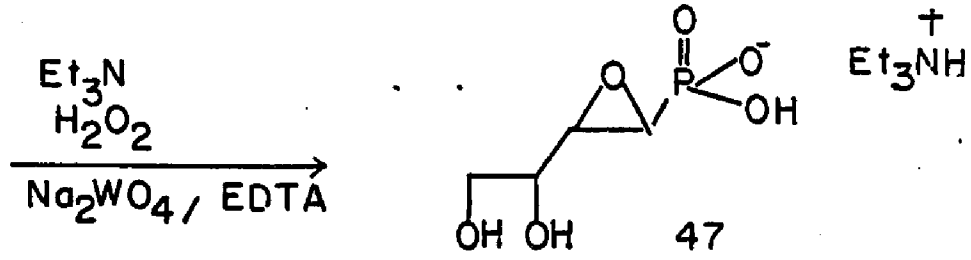



Scheme XXXX

3,4-dihydroxybut-1-enyl-1-phosphonic acid was stirred with l- arginine in 2-propanol at room temperature for one hour. The pH of the resultant mixture was adjusted to 5.5-5.6 with triethyl amine. Sodium tungstate and ethylene diamine tetraacetic acid disodium salt were added at 50 °C. Hydrogen peroxide was added maintaining the temperature

between 50 and 55 °C. The mixture was stirred at 50 °C for one hour and then cooled to 0 °C. The product obtained from this reaction showed that epoxidation had indeed taken place but some triethyl amine was incorporated in the product along with arginine.

It was therefore decided to perform the epoxidation without arginine. The pH of the mixture was adjusted to 5.5-5.6 with triethyl amine and the reaction was performed as shown below (scheme XXXXI).




Scheme XXXXI

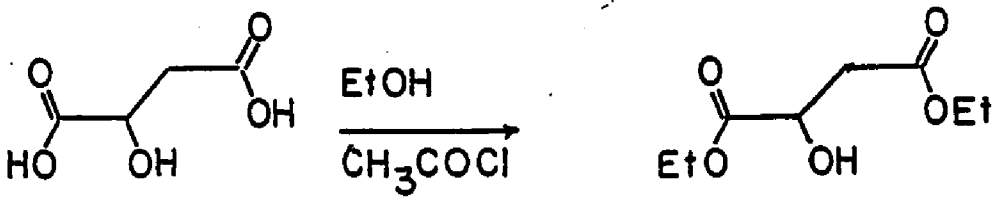
The reaction mixture on cooling deposited crystals which were recrystallized thrice from aqueous ethanol. The NMR spectra supported the postulated reaction as the vinylic proton signal had disappeared and epoxide proton signals were present. A doublet of doublets due to the oxirane proton alpha to phosphorous matches that observed for phosphonomycin[25]. It gave satisfactory analysis.

(d) Attempted preparation 2-halo-3,4-O-isopropylidene-3,4-dihydroxybutanal:

Another approach to 1,2-epoxyphosphonates involves treatment of alpha-halocarbonyl compounds with either tris (trimethylsilyl) phosphite or with dialkylphosphonate anions.

The following approach to the desired epoxyphosphonate was investigated (scheme XXXXII).

l-Malic acid was esterified with methanol acetylchloride system to give dimethyl malate [49][59]. Reduction of [49] with LAH in THF gave (S)-1,2,4-trihydroxy butane . Acetonization was performed with catalysis by p-toluenesulfonic acid to give 3,4-O-isopropylidene-1-butanol [50]. Oxidation of the primary hydroxyl group was achieved using pyridinium chlorochromate in methylene chloride to give 3,4-O-isopropylidene butanal which was purified by distillation. Attempts to halogenate the position alpha to the carbonyl either directly (with $CuCl_2$)[60] or by prior acetalization were not successful.

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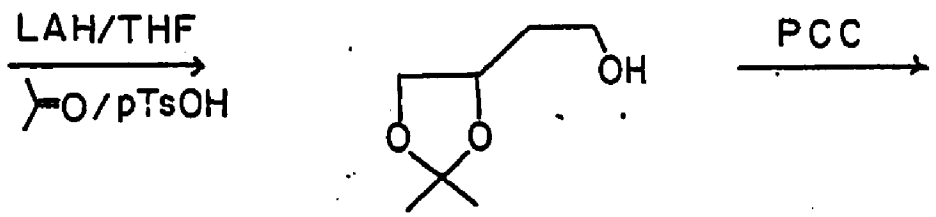


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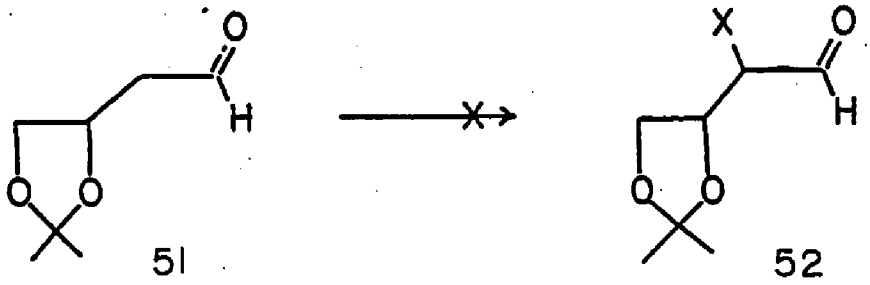
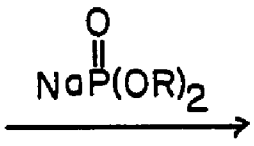


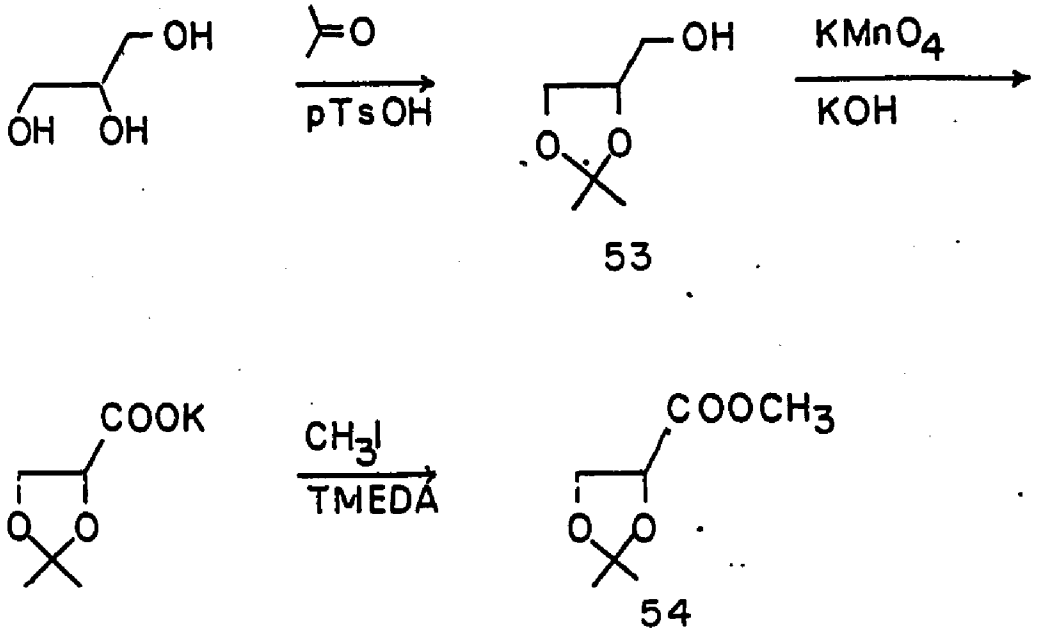

51 52




Scheme XXXXII

II Synthesis of 2-ketophosphonate:

There are available a number of methods for the synthesis of 2-ketophosphonates. In order to synthesize 3,4-dihydroxy butane-2-one-1-phosphonic acid, [3] direct acylation of methylphosphonate seemed to be the best method. This was partly due to the ready availibility of methyl glycerate-2,3-O-acetonide[73] from glycerol by the following route.

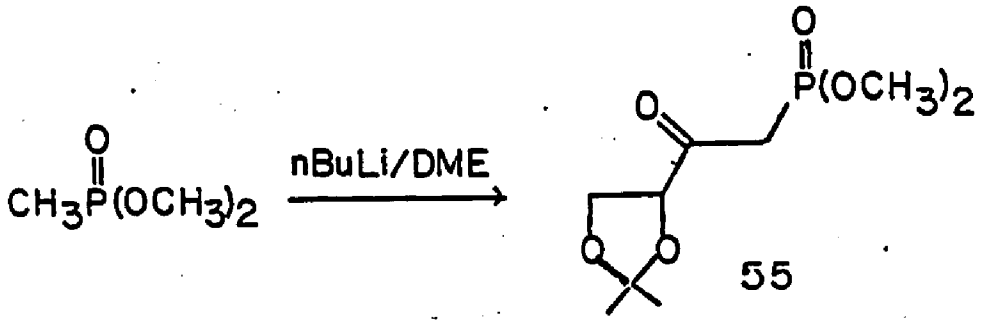



Scheme XXXXIII

Commercial glycerol was converted to glycerol acetonide by reaction with acetone in the presence of p-toluenesulfonic acid. Oxidation of the primary hydroxyl group was achieved using potassium permanganate in the presence of KOH. This yielded potassium glycerate-2,3-O-

acetonide which was methylated with methyl iodide in acetonitrile in the presence of N,N,N',N'-tetramethylethylenediamine [TMEDA] to give methyl glycerate-2,3-O-acetonide [54][73], which was purified by distillation.

Treatment of dimethyl methylphosphonate[74] with nBuLi in dimethoxyethane [DME] at -78 °C, followed by reaction with methyl glycerate-2,3-O-acetonide, gave dimethyl 3,4-O-isopropylidene-3,4-dihydroxy-2-ketobutylphosphonate [55], which exhibited satisfactory spectra and elemental analysis.

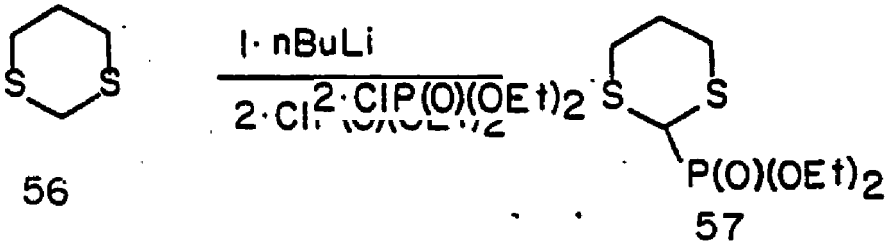



Scheme XXXXIV

Initial attempts to hydrolyse this material failed to give analytically pure sample. This material is being stored in protected form and shall be hydrolyzed immediately prior to biological investigations.

III Attempted synthesis of 1-ketophosphonate:

Owing to the instability of such ketophosphonates, our initial approach to the 1-ketophosphonate involved preparing it in such a manner that the keto group would be protected until the final step. We chose to start with the known diethyl-1,3-dithiane-2-ylphosphonate[75], prepared as follows.



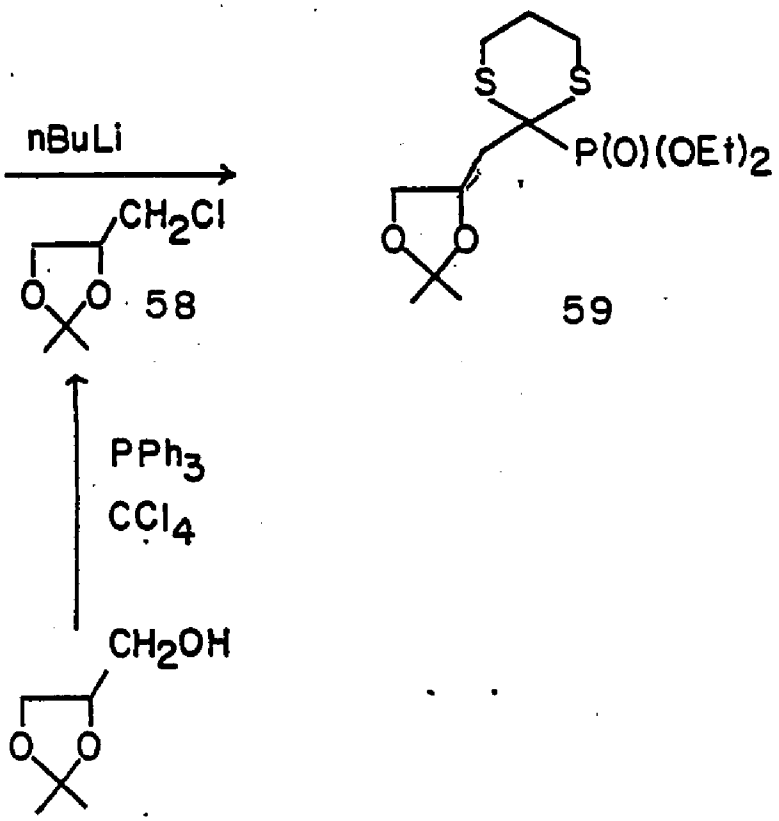

56 57

Scheme XXXXV

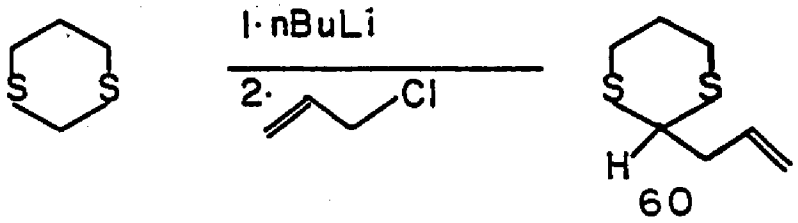
Attempts to alkylate the anion of [57] with 3,4-O-isopropylidene-3,4-dihydroxy-1-chloropropane, prepared as shown below (scheme XXXXVI) were unsuccessful.

We then chose to use allyl halide to provide the 3 carbon fragment which could be hydroxylated.

Treatment of the 1,3-dithiane anion, generated using nBuLi, with freshly distilled allyl chloride gave on distillation under vacuum the known 2-allyl-1,2-dithiane[76] scheme (XXXXVII).



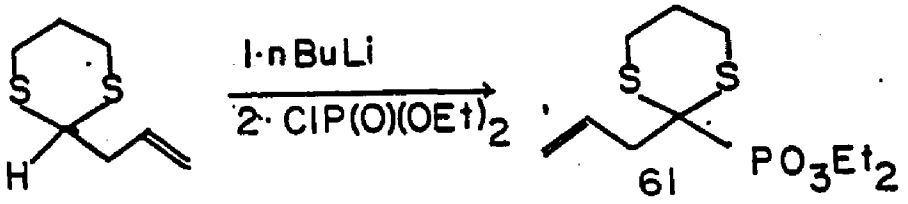

Scheme XXXXVI

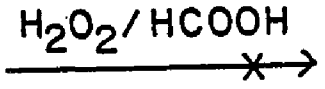



Scheme XXXXVII

Reaction of the anion, generated from 2-allyl-1,3-dithiane using nBuLi in THF at -30 °C for 2.5 hours, with diethyl phosphochloridate gave diethyl 1-(1,3-dithiane-2-

yl)-2-propen-1-ylphosphonate [61]. Product formation was inferred from the NMR and purification was not attempted as it was presumed that simple extraction procedures would suffice to purify the desired compound after hydrolysis in the following steps.



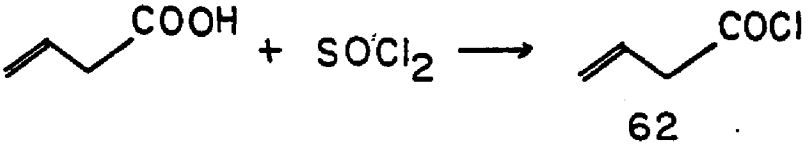




Scheme XXXXVIII

Unfortunately, attempted oxidation using hydrogen peroxide formic acid resulted in simultaneous attack at the sulfur to give an intractable mixture of products.

The most often used method for synthesis of 1-ketophosphonates is the Michaelis-Arbusov reaction of acyl halides with trialkyl phosphites. The reaction of the known 3-butenoyl chloride[77], prepared as shown below, with

triethyl phosphite gave on distillation a mixture of isomeric diethyl-3-butenyl-1-phosphonates. There was distilled material exhibiting NMR corresponding to ethyl protons only. It was deduced that pyrophosphate was formed, and the approach was abandoned.

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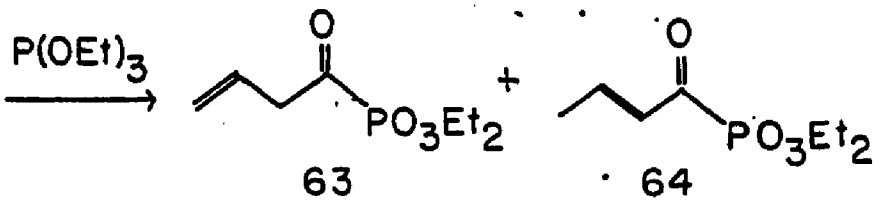


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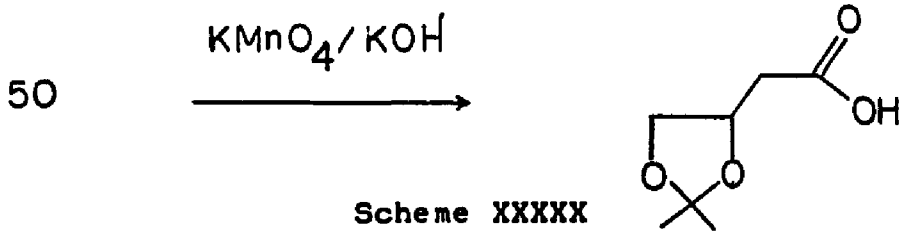
Scheme XXXXIX

Next it was decided to attempt the preparation of 3,4-O-isopropylidene-1-butanoyl chloride and use it in a Michaelis-Arbusov reaction. The starting material for this was the already described 3,4-O-isopropylidene butan-1-ol.




Scheme XXXXX

Unfortunately treatment of [50] with $KMnO_4$-KOH resulted in a mixture of intractable products.

## SUMMARY OF RESULTS

Preparation of the target, 3,4-dihydroxy-1,2-epoxybutylphosphonic acid, as its monotriethylammonium salt has been accomplished. Darzens condensation of diethyl chloromethylphosphonate has been successfully employed in the synthesis diethyl 3,4-O-isopropylidene-3,4-dihydroxy-1,2-epoxybutylphosphonate and diethyl 1,2-epoxy-3-butenylphosphonate. Attempts to prepare dialkyl 1-chloro-2-hydroxyphosphonates in pure form enroute to the target epoxide as well as model structures were unsuccessful.

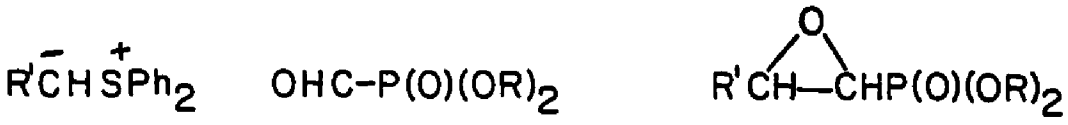
Preparation of the target dimethyl 3,4-O-isopropylidene-3,4-dihydroxy-2-ketobutylphosphonate has been accomplished. The material is to be kept in this form until it is to be used for biochemical purposes, whereupon it will be hydrolysed immediately prior to use.

All attempts to prepare dialkyl 3,4-dihydroxy-1-ketobutylphosphonate were unsuccessful.

A novel procedure for direct conversion of primary bromides to aldehydes via in situ conversion to iodides has been developed.

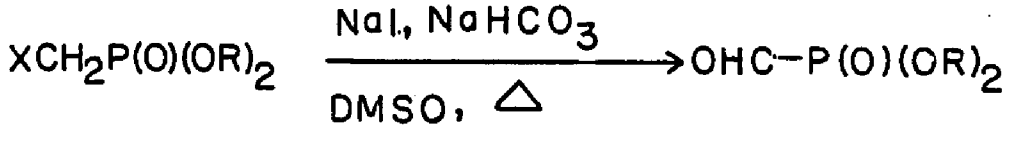
## Suggestions for Future Research

Our interest in 1,2-epoxyphosphonates has led us to search for novel methods for their synthesis. One such method that has received very little attention is the reaction of formyl phosphonate with sulfur ylides.



This method has been mentioned in a patent[82] which gives no details of preparation of formyl phosphonates.

The success of our method of converting primary bromides to aldehydes provided us with a possible method of synthesizing formylphosphonates. Treatment of diethyl chloromethylphosphonate in an NMR tube with NaI and $NaHCO_3$ in DMSO $d_6$ at 130 °C showed conversion to the corresponding aldehyde. Similar results were obtained for diethyl iodomethylphosphonate.



X=Cl, I

R=OEt, Ph

Treatment of diphenyl chloromethylphosphonate as above at 135 °C for 2 hours showed almost complete

consumption of the starting material.

If this method could be used to provide DMSO solutions of formyl phosphonates its reaction with sulfur ylides prepared from halides would provide a general method for the synthesis of 1,2-epoxyphosphonates.

## EXPERIMENTAL

Routine proton spectra were recorded at 60 MHz on a Varien EM360 instrument and the high field proton spectra were obtained on a Brucker-IBM WP200SY instrument. Proton NMR data are reported in parts per million downfield from TMS used as internal standard ( multiplicity s=singlet, d=doublet, t=triplet, dd=doublet of doublets, m=multiplet and bs=broad singlet). Infrared spectra were recorded on a Perkin-Elmer IR598 spectrometer and absorptions are reported in reciprocal centimeters.

Column chromatography was performed in glass columns packed with silica (60-200 mesh, Baker).

THF was dried and distilled from LAH and used immediately. DMSO was distilled under reduced pressure from calcium hydride prior to use. Methylene chloride and triethylamine were distilled from calcium hydride and stored over molecular seives. Methanol was distilled from 4A° and stored over the same. Benzene was dried and distilled from sodium metal just before use. Triisopropyl phosphite, acetaldehyde and benzaldehyde were distilled just before use under inert atmosphere.

Triisopropyl phosphite, l-malic acid, lead tetraacetate, dimethyl methylphosphonate, triphenylphosphine and titanium tetraisoproxide were obtained from Aldrich. Chloromethylphosphonic dichloride and sodium tungstate were obtained from Alfa. Diiodo methane was obtained from

Matheson Coleman and Bell. Hydrogen peroxide (30%) and phenol was obtained from Fisher scientific Co. D-mannitol was obtained form Sigma.

Micro analysis were performed by Mic Anal, Tucson, Arizona.

Preparation of diethylchloromethyl phosphonate [16][56a,b]:

In a 1L flask was placed 15.52 g (0.0927 mol) of chloromethylphosphonic dichloride in 200 mL ether and the mixture was cooled in an ice bath. A mixture of 18.77 g (0.1854 mol) of triethylamine and 6.68 g of absolute ethanol (0.1854 mol) was added dropwise with stirring and cooling. The ice bath was removed after the addition and the mixture was stirred for 2 hours. The white precipitate formed was filtered off and the mixture concentrated under reduced pressure. The residue, on vacuum distillation, gave 8 g ( 46.2 % ) of diethyl chloromethylphosphonate (b.p. 78-93 $^{o}$C/1.1 torr).

Preparation of diethyl 1-chloro-2-hydroxypropylphosphonate [21]:

Diethyl chloromethylphosphonate (2g, 0.1072 mol) was dissolved in 50 mL of anhydrous ether and placed in a 3 neck flask equipped with an addition funnel and a nitrogen inlet tube, and flushed with nitrogen. A 1.7 M solution of nBuLi in hexane (6.3 mL, 0.1072 mol) was added at -78 $^{o}$C and stirred at the same temperature for 1 hour.

Acetaldehyde (freshly distilled) (0.47 g, 0.1072 mol) was added at -78 °C and the mixture stirred at -78 °C for three hours. Ice water (20 mL) was added and the reaction mixture was extracted thrice with 50 mL portions of ether. The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to give 1.72 g of a residue.

Product formation was evident from NMR of the residue (diminished peak of aldehyde, presence of -OH peak ) but purification by chromatography on silica was precluded by product decomposition on the column. This was also true with HPLC using porasil column.

Preparation of diethyl 1-chloro-2-hydroxy-2-phenylethyl-1-phosphonate [22]:

Diethyl chloromethylphosphonate (2g, 0.0107 mol) in 50 mL of anhydrous ether was placed in a 3 neck flask equipped with addition funnel, nitrogen inlet tube, and flushed with nitrogen. A 1.7 M solution of nBuLi (6.3 mL, 0.0107 mol) in hexane was added dropwise at -78 °C and the mixture was stirred at -78 °C for 90 minutes. Freshly distilled benzaldehyde ( 1.137 g, 0.0107 mol) was then added at -78 °C and the mixture was stirred at -78 °C for 1 hour. The cooling bath was removed and after 2 minutes 20 mL of ice water were added. The mixture was extracted thrice with 50 mL portions of ether and the residue after

solvent evaporation was chromatographed on silica, eluting with ethyl acetate followed by ethanol. Again decomposition of product on silica was observed, although product formation was evidenced by NMR.

NMR ($CDCl_3$) : 1.3 (m $C\underline{H}_3$ CH O); 3.1 (dd $C\underline{H}Cl$,J HP=31.2 Hz); 3.5-4.5 (m $C\underline{H}_2$ O); 5.5-6.0 (m $C\underline{H}OHAr$); 6.75 (bs -OH); 7.1-8.0 (Ar$\underline{H}$).

Preparation of diethyl 1-chloro-2-hydroxy-2-phenylethyl-1-phosphonate [22]:

Diisopropyl amine (1.085 g, 0.01072 mol) was dissolved in 25 mL of anhydrous ether and was placed in a 3 neck flask equipped with a condenser, addition funnel, and nitrogen inlet tube, and flushed with nitrogen. The solution was cooled to -23 °C and a 1.7 M nBuLi (6.3 mL, 0.01072 mol) solution in hexane was injected and stirred for 30 minutes . The reaction flask was then cooled to -78 °C and 2 g ( 0.1072 mol) of diethyl chloromethylphosphonate in 15 mL of ether were added dropwise and stirred for 1 hour at -78 °C. Then freshly distilled benzaldehyde (1.085 g, 0.01072 mol) was added dropwise and the mixture was stirred overnight at room temperature. The mixture was treated with 10 % aq acetic acid until the aqueous layer maintained a pH of 3. The layers were then separated and the aqueous layer extracted five times with 50 mL portions of ether. The combined organics were dried over magnesium

sulfate and concentrated. The mixture was chromatographed on silica using 1:1 chloroform-hexane and as in the previous case product decomposition was evident on silica. NMR similar to above.

Preparation of 1,2,5,6-Diacetone D-Mannitol[57]:

A mixture of 300 mL of acetone and 60 g. of zinc chloride was stirred for a few minutes, then filtered. Then, 10 g. of D-mannitol (0.055 mol) were added and the mixture was shaken at room temperature until solution was complete (2 hours). The mixture was stirred overnight at room temperature and then poured into a solution of 70 g. of potassium carbonate in 70 mL water covered by 300 mL of diethyl ether. The mixture was shaken for 30 minutes,then decanted. The residue (zinc carbonate) was washed twice with 100 mL of 1:1 acetone-ether solution and the combined filtrates were concentrated on a rotary evaporator and further dried <u>in vacuo</u> for two hours at 60-70 °C. The residue was refluxed five times for 20 minutes each with 250 mL portions of petroleum ether (b.p. 60-90 °C). The resulting solutions were filtered while hot and then cooled gradually to yield crystals of 1,2,5,6-diacetone D-mannitol, which were filtered and dried.

m.p. 116-19 °C, lit.[57] 119 °C.

Yield : 7 g. (48.5 %).

Preparation of Acetone D-Glyceraldehyde [17][57] :

To a suspension of 1,2,5,6-diacetone D-mannitol (7.8 g,0.0297 mol) in 275 mL of dry benzene (distilled from sodium) was added 13.2 g of lead tetraacetate and the mixture was stirred for 45 minutes (until the sticky precipitate of lead salts were triturated to a fine powder). If on testing with potassium iodide-starch paper lead tetraacetate were still present more diacetone D-mannitol was added. The mixture was filtered and concentrated on the rotary evaporator tc yield acetcne D-glyceraldehyde, which was used immediately due to its tendency to polymerize.

Yield: 7 g (90%).

In some cases residual lead salts remained in the product. These were removed by adding hexane, filtering and concentrating the solution.

Preparation of diethyl 1-chloro-2-hydroxy-3,4-O-isopropylidene-3,4-dihydroxybutylphosphonate [24][36] :

A 1.7 M solution of nBuLi (3.4 mL, 0.0278 mol) in hexane was injected into a 3 neck flask equipped with a nitrogen inlet tube, addition funnel and a thermometer and the mixture was cooled to -20 °C. An equal volume of dry THF was added and the mixture cooled to -70 °C. Diethylchloromethyl phosphonate 1.07 g (0.00575 mol) in 4 mL of THF was added at -75 to -70 °C dropwise. After

stirring this solution for 10 minutes glyceraldehyde acetonide (0.75 g, 0.00575 mol) was added at the same temperature. The mixture was stirred for an hour at -70 °C and then quenched with water. Extraction of this mixture with three portions of 1:1 ether/methylene chloride followed by drying over magnesium sulfate and concentration gave a residue, which showed an NMR signal at 2.1 (bs, OH) but no aldehyde signal.

The above mixture was treated with 1% aq. HCl overnight, then extracted with methylene chloride to remove the unreacted diethyl chloromethylphosphonate. The aqueous layer was lyophilized to yield a grey solid. This was extremely hygroscopic and which turned dark at room temperature.

Analysis for $C_8H_{18}O_6PCl$.

| | Calculated | Found |
|---|---|---|
| C% | 34.73 | 34.92 |
| H% | 06.58 | 06.50 |

The above material was treated with a 5 fold excess of bromotrimethylsilane under a nitrogen atmosphere. The mixture turned dark and sticky, apparently decomposed.

Preparation of diethyl 3,4-O-isopropylidene-1,2-epoxy-3,4-dihydroxybutylphosphonate [24][36]:

A 1.7 M solution of nBuLi (6.7 mL, 0.0115 mol) in hexane

was injected into a 3 neck flask equipped with a nitrogen inlet tube, addition funnel, and a low temperature thermometer, and was cooled to -20 °C. An equal volume of dry THF was added and the mixture was cooled to -70 °C. Subsequently, 2.15 g (0.0115 mol) of diethyl chloromethylphosphonate in 5 ml THF was added at -75 to -70 °C dropwise. After stirring this mixture for 10 minutes a solution of 1.5 g (0.0115 mol) of glyceraldehyde acetonide in 5 mL of THF was added dropwise at -75 to -70 °C. The mixture was stirred for an hour at -70 °C, then brought to room temperature in a few minutes and then stirred at room temperature for 18 hours. Water (15 mL ) was added and the mixture was extracted thrice with 30 mL portions of 1:1 methylene chloride-ether. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give 2.5 g of residue which decomposed on attempted chromatography on either a silica column or HPLC (poracil), as evidenced by NMR. Instead, the product was collected by vacuum distillation. (1.6 g, 126-132 °C/.6 torr).

NMR ($CDCl_3$): 1.2-1.5 (m, 12H, $CH_3CH_2O$, $CH_3$), 2.3-3.4 (m, 2H, oxirane) 3.6-4.5 (m, 7H).

Analysis

| | Calculated | Found |
|---|---|---|
| C% | 47.14 | 46.16 |
| H% | 07.55 | 08.21 |

Reaction of diethyl 3,4-O-isopropylidene-1,2-epoxy-3,4-dihydroxybutylphosphonate with trimethylbromosilane:

The distilled diethyl 3,4-Oisopropylidene-1,2epoxy-3,4-dihydroxybutylphosphonate (0.5 g, 0.00178 mol) was stirred with trimethylbromosilane ( 0.81 g, 0.00534 mol) at room temperature under nitrogen for 2 hours. The mixture was concentrated under reduced pressure.

NMR:

There were two signals due to TMS indicating that the epoxide was attacked! So the reaction was carried out in a NMR tube using excess trimethyl bromosilane and immediately on mixing the two reagents the signals assigned to the epoxide protons shifted. As time went by the ethyl ester portion also changed. The acetonide methyl signals remained unchanged even after three days.

Reaction of bistrimethylsilyl 2-bromo-3,4-O-isopropylidene-1-trimethylsilyloxybutylphosphonate with aq. HCl.

Crude bistrimethylsilyl 2-bromo-3,4-O-isopropylidene-3,4-dihydroxy-1-trimethylsilyloxy butylphosphonate from above was mixed with 25 mL of 1% HCl, 15 mL of ethanol and 10 mL of THF to effect solution which was stirred at room temperature overnight, then concentrated under vacuum. The fact that hydrolysis of the acetonide had ocurred was confirmed by NMR, which showed a complex mixture of

signals from 3.8-4.8 only.

Preparation of 1,2-epoxy-3,4-dihydroxybutylphosphonic acid.

The crude 2-bromo-1,3,4-trihydroxy butylphosphonic acid from above was treated with bromotrimethyl silane (1.36 g, 0.0089 mol) for two hours at room temperature under nitrogen for 2 hours and then concentrated under reduced pressure. Sodium methoxide (0.0089 mol) in methanol was added at room temperature and the mixture stirred overnight under nitrogen. The resulting mixture was dried on a pump to yield a white solid to which was added 100 mL of a saturated solution of ammonium chloride in absolute methanol. The precipitate formed was filtered and pumped dry to give .2 g of residue .

NMR of the residue was inconclusive .

Analysis for $C_4H_{13}O_9PNa_2$ (trihydrate).

| | Calculated | Found |
|---|---|---|
| C% | 17.03 | 17.19 |
| H% | 04.65 | 04.88 |

Preparation of diethyl 1,2-epoxy-3-butenylphosphonate [28] [36] :

To a 250 ml 3 neck flask equipped with a magnetic stirrer, nitrogen inlet tube and an addition funnel cooled to -20 °C was added a 1.7M solution of nBuLi (33mL g, 0.056 mol)

in hexane followed by THF (33 mL). To this was added at -78 °C, dropwise, diethyl chloromethylphosphonate (10 g, 0.054 mol) in 15 mL THF. After stirring this mixture for 10 minutes at -78 °C, freshly distilled acrolein (3 g, 0.054 mol) in 10 mL of THF was added dropwise at -78 °C and stirring was continued for an hour at -78 °C. The cooling bath was then removed and the mixture was allowed to stir for 16 hours at room temperature. Water (40 mL) was then added and the mixture was extracted thrice with 50 mL portions of 1:1 ether/methylene chloride. The organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure to yield 6.5 g of a liquid which on vacuum distillation gave diethyl 1,2-epoxy-3-butenylphosphonate ( 5.6 g, 45.8%, b.p. 92-97 °C/ 0.6 torr).

NMR ($CDCl_3$) 1.35 (t, $CH_3$), 2.7-3.8 (m, oxirane 2H), 4.2 (m, $CH_2$), 5.2-6.4 (m, vinylic 3H).

Analysis for $C_8H_{15}O_4P$.

| | Calculated | Found |
|---|---|---|
| C% | 46.60 | 46.09 |
| H% | 07.33 | 07.68 |

Reaction of diethyl 1,2-epoxy-3-butenylphosphonate with bromotrimethylsilane.

To diethyl 1,2-epoxy-3-butenylphosphonate (0.51 g, 0.00247

mol) was added, under nitrogen, bromotrimethylsilane (1.14 g, 0.00741 mol) at room temperature and the mixture was stirred for 2 hours. The mixture on concentration yielded bistrimethylsilyl 2-bromo-1-trimethylsilyloxy-3-butenyl phosphonate.

NMR indicated again the attack on oxirane affording bis trimethylsilyl 2-bromo-1-trimethylsilyloxy-3-butenylphosphonate ( the symmetrical pattern at 2.7-3.8 assigned to oxirane protons was replaced by a complex multiplet at 3.3-5.5).

Preparation of bistrimethylsilyl 1,2-epoxy-3-butenylphosphonic acid:

Bistrimethylsilyl 2-bromo-1-trimethylsilyloxy-3-butenylphosphonate was treated with anhydrous sodium methoxide (0.38 g, 0.00741 mol) in 5 mL ofmethanol under an atmosphere of nitrogen overnight at room temperature. The mixture was then pumped dry and trimethylchlorosilane (0.88 g,0.00815 mol) was added under nitrogen. After stirring for a few hours at room temperature the mixture was concentrated.

This material was extremely unstable and the NMR on it was inconclusive.

Preparation of tetraisopropyl methylenebisphosphonate [33][63] :

A 500 mL three neck flask was equipped with a magnetic stirrer, a condenser and thermometer. It was charged with 312.4 g (1.5 mol) of triisopropyl phosphite and 87 g. (0.5 mol) of dibromomethane. Water was circulated through the condenser at 65 °C so as to remove isopropyl bromide as it was formed, which was collected in a dry ice trap. The mixture was heated gradually to 185 °C and was maintained at that temperature for two hours. Excess triisopropyl phosphite was removed under reduced pressure and the residue on vacuum distillation, afforded tetraisopropyl methylenebisphosphonate ( b.p. 125-30 °C, 0.2-0.3 torr, lit.[63] 87-89 °C/0.003 torr, 85%).

NMR: (CDCl3), 1.3-1.5 (d,24 H), 2.0-2.7 (t,2H), 4.3-5.0 (m,4H)

Preparation of diisopropyl 3,4-O-isopropylidene-3,4-dihydroxy-1-butenylphosphonate [34][62] :

Tetraisopropyl methylenebisphosphonate (18 g, 0.052 mol) was dissolved in 200 mL of dry heptane in a 3 neck flask equipped with condenser, addition funnel and nitrogen bubbler. To this was added a 1.6 M solution of nBuLi (32.5 mL, 0.052 mol) in hexane at room temperature. The mixture was stirred for 2 hours, then cooled to 0 °C and 6.8 g (0.052 mol) of acetone D-glyceraldehyde in 20 mL of

heptane were added dropwise. The reaction mixture was allowed to warm to room temperature and then refluxed for 2 hours. After cooling to room temperature 500 mL of water were added and the layers were separated. The aqueous layer was extracted twice with 100 mL portions of heptane and the combined organics were dried over magnesium sulfate. Heptane was removed under reduced pressure and [37] was collected by vacuum distillation (b.p. 110-$^{o}_{20}$/0.05 torr, 85%.)

NMR ($CDCl_3$), 1.2-1.5 (m,18H), 3.5-4.9 (t,5H), 5.5-7.1 (m,2H).

Epoxidation of diisopropyl 3,4-O-isopropylidene-3,4-dihydroxy-1-butenylphosphonate:

Diisopropyl 3,4-O-isopropylidene3,4-dihydroxy-1-butenylphosphonate (4g, 0.0137 mol) was placed in a 3 neck flask equipped with a magnetic stirrer, addition funnel, and nitrogen inlet tube. Trimethylbromosilane (16.76 g, 0.055 mol) was added dropwise and the mixture was stirred overnight at room temperature. The mixture was then concentrated to give 5 g of bistrimethylsilyl 3,4-O-isopropylidene-3,4-dihydroxy-1-butenylphosphonate.

The silylated material was dissolved in 20 mL of methylene chloride and 10 mL of methanol and cooled to 0 $^{o}$C. Hydrogen peroxide (30 % v/v) (8 mL) followed by 20 mL of NaOH (0.2 M) was added maintaining the pH =9.5-10.0. The resulting

two phase system was stirred overnight at room temperature and the layers were separated.

The aq. layer was treated with Dowex 50 (H+) to bring the pH to 7-7.5, then filtered and pumped dry to yield a syrup which eventually solidified. This solid was dissolved in water, the pH was adjusted to 3 with Dowex 50 (H+) and the mixture was stirred for 48 hours, then filtered. The pH of the filtrate was adjusted to 7.5 with dilute NaOH and dried under vacuum.

NMR of this material was inconclusive.

The material is extremely hygroscopic and exhibits an elemental analysis in accord with the hydrolysed epoxide, that is 1,2,3,4-tetrahydroxybutylphosphonic acid disodium salt.

Analysis for $C_4H_7O_6PNa_2.3H_2O$.

| | Calculated | Found |
|---|---|---|
| C% | 17.03 | 17.40 |
| H% | 04.64 | 04.52 |

Preparation of diphenyl chloromethylphosphonate (38)[67]:

Chloromethyl phosphonic dichloride (46.8 g, 0.44 mol) and phenol (53 g, 0.88 mol) were dried under vacuum for 2 hours and then heated at reflux under a nitrogen atmosphere at 155°C overnight. The mixture was cooled to room temperature and then slowly reheated to 160°C for 4

hours under 15-16 torr pressure with an air cooled Vigreaux condenser. Hydrogen chloride was trapped over ice cooled NaOH. The residue was distilled under reduced pressure to yield diphenyl chloromethylphosphonate. ( 70g, 66%, 166-69 °C/0.25 torr).

NMR (CDCl3) 3.84 (d, CH2, J H,P=30 Hz), 7.27 (s, Ar 10H).

Preparation of diphenyl triphenylphosphoniummethylidenephosphonate[68]:

Diphenyl chloromethylphosphonate (28.25 g; 0.118 mol) was placed in a 100 mL 3 neck flask under nitrogen and triphenyl phosphine (26.2 g;0.100 mol) was added. The mixture was stirred for 10 minutes and then vacuum dried for 1 hour. The mixture was heated at 165 °C under nitrogen for 4 hours, then cooled to room temperature. A light yellow mass formed. The solid was scraped out using 30 mL of anhydrous ether, filtered through a sintered glass funnel, and washed 6 times with 30 mL portions of ether. This solid was placed in a 500 mL beaker with 200 mL of water. The stirred suspension was treated with 6N NaOH and brought to pH 7 (pH of ppt 9). The white precipitate was filtered and recrystallized from ethyl acetate. (m.p. 145-46 °C lit.[68] 149-50 °C, 60%).

Preparation of diphenyl 3,4-O-isopropylidene-3,4-dihydroxybutenylphosphonate [41][14]:

1,2,5,6-diacetone D-mannitol (3 g, 0.0114 mol) was suspended in 120 mL of dry benzene (distilled from sodium), rapidly mixed with lead tetraacetate (5.08 g.0.0114 mol) and vigorously stirred at room temperature for 2 hours. The precipitated lead salts were filtered and the solvent evaporated under reduced pressure.

The resultant glyceraldehyde acetonide was dissolved in 60 mL of dry DMSO (distilled from calcium hydride) and diphenyl triphenylphosphoniummethylidenephosphonate (8 g, 0.0114 mol) was added. This suspension was refluxed at 80-80 °C (bath temperature) under a nitrogen atmosphere overnight. The reaction mixture was cooled to room temperature and poured into 70 mL of water, and extracted thrice with 75 mL portions of anhydrous ether. Concentration of the organics gave 8 g of a semisolid mixture which was chromatographed on silica using either ethyl acetate (Rf of product 0.63) or 4:1 petroleum ether:ether (Rf 0.4).

Yield 3.0 g, 73%.

NMR matched that in literature[14].

Hydrolysis of diphenyl 3,4-O-isopropylidene-3,4-dihydroxybutenylphosphonate:

Diphenyl 3,4-O-isopropylidene-3,4-

dihydroxybutenylphosphonate (1.5 g; 0.00416 mol) was treated with 25 mL of 1% HCl and 25 mL each of THF and ethanol and stirred at room temperature overnight. THF and ethanol were removed under reduced pressure and the residual aqueous mixture was extracted with 100 mL of chloroform, dried over magnesium sulfate and concentrated. TLC showed presence of some less polar contaminants which were removed by column chromatography, eluting initially with 1:1 hexane-ethylacetate. Diphenyl 3,4-dihydroxybutenylphosphonate [42] was eluted with absolute ethanol (1.1 g, 82.5%).

NMR ($CDCl_3$) 3-4.3 (m, $CH_2O$, $CHO$); 4.4 (bs, OH), 5.8-7.0 (m, vinylic H), 7.3 (ArH).

Preparation of diphenyl 4-(t-butyldimethylsilyloxy)-3-hydroxy-1-butenylphosphonate [44][70]:

To diphenyl 3,4-dihydroxybutenyl-1-phosphonate (0.21 g, 0.007 mol) in 25 mL of methylene chloride was added under an atmosphere of nitrogen 4-DMAP (.0035 g, 0.00028 mol), triethyl amine (0.779 g;0.0077 mol) and t-butyl dimethyl chlorosilane (0.107 g; 0.007 mol). The mixture was stirred overnight at room temperature. Water was added, the layers were separated and the organic layer was dried over magnesium sulfate and concentrated. The residue was chromatographed on silica eluting with 1:1 hexane-ethylacetate, giving a small amount of disilylated

material followed by 0.2 g (70% based on [48]) of diphenyl 4-(t-butyldimethylsilyloxy)-3-hydroxybutenylphosphonate. It gave satisfactory analysis. NMR ($CDCl_3$, 200MHz) 0.8 (s, $SiCH_3$; 0.95 (s, Si-t-butyl); 2.9-3.7 (m, $OCH_2$; OCH); 4.25 (bs, OH); 6.15-7.1 (m, vinylic H), 7.1-7.35 (m, ArH).

Analysis for $C_{22}H_{31}O_5PSi$.

| | Calculated | Found |
|---|---|---|
| C% | 60.81 | 61.09 |
| H% | 06.90 | 07.27 |

Preparation of (+)-diethyl tartarate:

Absolute ethanol (200 mL) was placed in a dry 500 mL round bottom flask equipped with a drying tube and cooled in a ice bath. Acetyl chloride (10 mL) was added dropwise with cooling. (+)-D-Tartaric acid (15 g; 0.1 mol) was added and the mixture was stirred at room temperature overnight. Excess ethanol was removed on a rotary evaporator and the residue was vacuum distilled to give 12 g (58.2%) of d-diethyl tartarate (b.p. 150-153/12 torr).

Attempted epoxidation of diphenyl 4-(-t-butyldimethylsilyloxy)-3-hydroxybutenyl-1-phosphonate [71]:

Freshly distilled dry methylene chloride (15 mL) was placed in a 100 mL round bottom flask under a nitrogen atmosphere and cooled to -23 °C (carbon tetrachloride/Dry

Ice). Titanium tetraisopropoxide (0.327 g.,0.0115 mol) was injected followed by 0.237 g (0.0115 mol) of (+)-diethyl tartarate. After stirring the solution for 5 minutes, 0.5 gm of diphenyl 4-(-t-butyldimethylsilyloxy)-3-hydroxy-1-butenylphosphonate was added, followed by 0.52 mL of a 4.4 M solution of t-butyl hydroperoxide in 1,2-dichloro ethane. The solution was stirred for a few minutes at -23 °C and then stored in a freezer at -20 °C for 5 days. Workup involving treatment with NaF followed by saturation with NaCl, filtration and extraction with methylene chloride yielded a mixture comprised of the starting alkene along with traces of another compound (by TLC).

Preparation of 3,4-dihydroxy-1,2-epoxybutyl-1-phosphonic acid monoarginate [46][45] :

3,4-dihydroxy-1-butenyl-1-phosphonic acid (1.51 g, 0.009 mol) was dissolved in 10 mL of isopropanol. L-(+)-Arginine (0.8 g,0.0045 mol) was added and the mixture was stirred for 1 hour. The pH of the mixture was adjusted to 5.6-5.7 with triethyl amine, and sodium tungstate dihydrate ( 0.05 g, 0.15 mmol) followed by disodium ethylene diamine tetraacetic acid [EDTA] (0.05 g,o.13 mmol) were added. The mixture was heated to 50 °C and hydrogen peroxide (1.2 ml, 30 %) was added maintaining the temperature under 55 °C. The mixture was stirred at this temperature for 1 hour, then cooled to room temperature.

Crystals which formed were filtered and recrystallized from aq. ethanol, giving 0.8 g of a solid. NMR showed dissappearance of the vinylic protons and other signals consistent with oxirane protons. Unfortunately a small amount of triethyl amine was incorporated in the mixture and could not be removed under vacuum.

Preparation of 3,4-dihydroxy-1,2-epoxybutyl-1-phosphonic acid monotriethylammonium salt [47][45] :

3,4-dihydroxybut-1-enylphosphonic acid (0.25 g, 0.00148 mol) was dissolved in 25 mL of isopropanol and the pH of the mixture was adjusted to 5.6 with triethyl amine. Catalytic amounts of sodium tungstate and EDTA were added and the mixture was heated to 50 $^{o}$C. 2 mL of hydrogen peroxide (30 %) was added dropwise, maintaining the temperature below 55 $^{o}$C. The mixture was stirred at 55 $^{o}$C for 2 hours then at room temperature overnight. The mixture, on cooling, deposited crystals which were filtered and recrystallized from aqueous ethanol (0.14 g, 36.8%).

NMR ($D_2O$, 200 MHz) 0.14 (t, $CH_3$); 2.8-3.0 (dd, oxirane 1H, J PH=20Hz), 3.2-4.7 (m, 8H). No vinylic protons were seen.

Analysis for $C_{10}H_{30}O_9PN$ (trihydrate).

| | Calculated | Found |
|---|---|---|
| C% | 35.40 | 35.16 |
| H% | 08.92 | 08.99 |

Preparation of dimethyl 3,4-O-isopropylidene-3,4-dihydroxy-2-ketobutylphosphonate [55][74]:

A 250 mL 3 neck flask equipped with a magnetic stirrer and two pressure equalising addition funnels was flushed with nitrogen and charged with dimethyl methylphosphonate (4.25 g, 0.0342 mol) and dry dimethoxyethane [DME]. After cooling to -78 °C a 1.7 M solution of nBuLi in hexane (20 mL, 0.0342 mol) was added dropwise and the mixture was stirred for 30 minutes. Methyl glycerate 2,3-acetonide (3.65 g, 0.0228 mol) in 10 mL DME was then added dropwise at -78 °C over a period of 30 minutes and the mixture was stirred for a further 30 minutes at the same temperature. The mixture was then warmed to room temperature and stirred overnight. Water (50 mL) was added to the reaction mixture which was then extracted twice with 50 mL portions of chloroform. The aqueous layer was acidified with 1 N HCl (50 mL) then extracted four times with 50 mL portions of chloroform. The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to give 4.8 g (84%) of dimethyl 3,4-O-isopropylidene-3,4-dihydroxy-2-ketobutylphosphonate.

NMR ($CDCl_3$) 1.35,1.45 (s, $CH_3$); 3.85 (d, $CH_2P$) 2.8-4.7 (m, $CH_2O$, CHOC).

Analysis for $C_9H_{17}O_6P$.

| | Calculated | Found |
|---|---|---|
| C% | 42.86 | 42.11 |
| H% | 06.79 | 06.99 |

Preparation of diethyl 1,3-dithiane-2-ylphosphonate [57][75]:

In a 3 neck flask equipped with a stirring bar, two dropping funnels and a nitrogen inlet tube was placed 2 g (0.0166 mole) of sublimed 1,3-dithiane in 50 mL of dry THF. The system was then purged with nitrogen, and a 1.7 M solution of nBuLi in hexane (9.8 mL, 0.166 mol) was added at -40 °C and stirred for 1.5 hour at -25 to -15 °C. Following this, the mixture was cooled to -78 °C and diethyl phosphorochloridate (2.86 g, 0.0166 mol) in 10 mL THF was added dropwise at -78 °C. The mixture was stirred cold for 0.5 hour then allowed to warm slowly to 0 °C, and was quenched with 100 mL of 20 % ammonium chloride solution. The THF was removed under reduced pressure and the residue was extracted twice with 50 mL of chloroform. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on silica eluting with 3:1 hexane: ethyl acetate to give 1.3 g (30%) of diethyl 1,3-dithian-2ylphosphonate.

NMR ($CDCl_3$), 1.4 (t, $CH_3$), 1.8-2.8 (m, 6H), #.6 (d, CHP J =22 Hz), 4.3 (m, $POCH_2$).

Attempted preparation of diethyl 1,3-dithiane-2-phosphonate-2-(2,3-O-isopropylidene-)-propane:

Diethyl 1,3-dithian-2-ylphosphonate (0.5 g, 0.00195 mol) was dissolved in 20 mL of dry THF. Under an atmosphere of nitrogen was added at -40 °C, a 1.6 M solution of nBuLi (1.2 mL, 0.00195 mol). The mixture was stirred for 2 hours at -25 to -15 °C then cooled to -70 °C. 2,3-O-isopropylidene-1-chloropropane (0.3 g, 0.00195 mol) in 2 mL of THF was added and the mixture was stirred at -70 °C for 1 hour, then stored in the freezer for 2 days at -20 °C and finally was quenched with water. Removal of THF and extraction thrice with 25 mL portions of chloroform gave 0.7 g of a mixture.

TLC indicated the presence of only the starting materials.

Preparation of 2-allyl 1,3-dithiane [60][76]:

Sublimed 1,3-dithiane (10 g, 0.088 mol) was dissolved in 150 mL of dry THF in a 250 mL flask equipped with a Claisen head, nitrogen inlet tube, and an addition funnel. The system was purged with nitrogen and cooled to -30 °C (Dry Ice/chloroform:carbon tetrachloride 1:1). A 2.6 M solution of nBuLi in hexane (39.5 mL, 0.1027 mol) was added over a period of 5 minutes and stirring was

continued at -30°C for 2 hours. The solution was then allowed to warm to -10°C and 35 mL of freshly distilled allyl chloride (0.245 mol) was added over a 5 minute period. The solution was then set in a refrigerator (4°C) for 40 hours, then was poured into 150 mL of water and acidified to a pH of 5 with 10% HCl. This mixture was extracted with 200 mL of pentane and 200 mL of ether. The two organic extracts were combined and washed with 100 mL of sodium bisulfite, 5% aq. potasium hydroxide, water, and brine, dried over magnesium sulfate and concentrated by rotary evaporation. Fractional distillation of the residue gave 8 g (60%) of 2-allyl-1,3-dithiane was collected. (120°C at 11 torr, through Vigreaux column).
NMR of this material agreed with that reported[76].

Preparation of diethyl 1-(1,3-dithian-2-yl)-2-propene-1-ylphosphonate.

2-allyl-1,3-dithiane (2 g, 0.01246 mol) was dissolved in 25 mL of dry THF and cooled to -40°C. Under an atmosphere of nitrogen a 2.6 M solution of nBuLi (5 mL, 0.013 mol) in hexane was added and the solution was stirred at -30°C for 2.5 hours. After cooling the solution to -70°C, diethyl phosphorochloridate (2.15 g, 0.0125 mol) was added. The solution was stirred for 1 hour at -70°C then slowly warmed to -10°C and stored at 4°C in the refrigerator. The mixture was poured into water (50 mL)

and extracted with three portions of ether. The combined ether extracts were washed with brine, dried over magnesium sulfate and concentrated to give 2.8 g of a residue. NMR of this material indicated that there was some 2-allyl-1,3-dithiane along with diethyl 1-(1,3-dithian-2-yl)-2-propene-1-ylphosphonate.

NMR ($CDCl_3$), 1.3 (t, $CH_3$), 1.5-3.3 (m, $CH_2$), 3.8-4.4 (m, $POCH_2$), 4.8-6.2 (vinylic H)

This material was used without purification as it would be easier to remove the impurity on hydrolysis of either the protective 1,3-dithiane group or the phosphonate by extraction procedures.

Reaction of diethyl 1-(1,3-dithian-2-yl)-2-propen-1-ylphosphonate with Hydrogen Peroxide:

The above material (1g) was treated with 3.2 mL of 80% formic acid and 0.92 mL of hydrogen peroxide (30%) at 45 °C overnight. The mixture was then dried on the pump to yield 1.2 g of a gummy product which was not entirely soluble in any solvent and was impossible to analyse further.

Preparation of 3-butenoyl chloride[77]:

To thionyl chloride (40 g,.336 mol, distilled from quinoline) heated on a water bath was added during the course of an hour 3-butenoic acid (21.5 g, 0.25 mol). The mixture was stirred at 55 °C for three hours and distilled

to give 18 g (69%) of 3-butenoyl chloride (b.p. 93-95 °C, lit.[77] 93-95/750 torr).

Preparation of diethyl 1-oxo-3-butenylphosphonate:

3-Butenoyl chloride (12 g, 0.114 mol) was cooled in an ice bath and triethyl phosphite (20 g, 0.12 mol) was added dropwise over 2 hours. The mixture was stirred overnight at room temperature then heated at 70 °C for 1 hour. The mixture was then distilled under reduced pressure. 8 g of a material distilled at 101-102 °C/15 torr. NMR of this material showed signals corresponding only to ethyl groups. Presumably tetraethyl pyrophosphate was formed. NMR of the residue showed it to be a mixture of diethyl 1-oxo-3-butenylphosphonate and the isomerized diethyl 1-oxo-2-butenylphosphonate.

NMR ($CDCl_3$, 200 MHz) 1.3 (m, $POCH_2\underline{CH}_3$), 4-4.5 (m, $OC\underline{H}_2$), 2 (dd, $C\underline{H}_2CO$), 5-7.8 (m, vinylic H).

Preparation of potassium glycerate 2,3-acetonide[73]:

Glycerol acetonide (2.93 g, 0.022 mol) was dissolved in water (20 mL) containing potasium hydroxide (1.34 g, 0.024 mol) and oxidized with (~50%) excess aqueous potasium permanganate solution at 0-10 °C until the colour of permanganate remained for 30 minutes. Excess permanganate was decomposed with methanol and the precipitated manganese dioxide was filtered off. The filtrate was

lypholised to yield a white solid which was used without purification.

Preparation of methyl glycerate 2,3-acetonide[73]:
The white solid from above was suspended in acetonitrile (25 mL) and treated with methyl iodide (4.26 g,0.03 mol) in the presence of N,N,N'N'-tetramethylethylenediamine (0.25 g, 0.0002 mol) at 50 °C for 5 hours with vigorous stirring. The mixture was filtered and distilled under reduced pressure to give methyl glycerate 2,3-acetonide ( 50 % from glycerol acetonide, b.p. 70-74 °C/ 15-17 torr, lit.[73] 88 °C/28 torr). NMR of this material matched that in the reference[73].

Preparation of diphenyl 1,2-epoxy-1,3-butenylphosphonate:
A 1.7 M solution of nBuLi in hexane ( 0.0141 mol) was placed in a 3 neck flask under nitrogen. Dry THF (10 mL) was added at -20 °C and the solution was cooled to -70 °C. Diphenyl chloromethylphosphonate (4 g, 0.0141 mol) in 5 mL THF was added and the mixture was stirred for 10 minutes. Freshly distilled acrolein (1 g, 0.0178 mol) in 5 mL of THF was added at -75 to -70 °C, and the mixture was stirred at the same temperature for 1 hour, then warmed to room temperature and stirred for 18 hours. Water (10 mL) was added and the mixture was extracted thrice with 30 mL portions of 1:1 ether/methylene chloride. The combined

organics were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue on silica gel, using an ethyl acetate:ethanol gradient, gave 2 g of a pale yellow solid. This material was found to be insoluble in ether and so was dissolved in methylene chloride and precipitated with ether to give 1.7 g of a white solid. NMR showed the presence of OH and other expected signals but it could not be satisfactorily purified.

Preparation of epibromohydrin benzaldehyde acetal [31]: Epibromohydrin (2 g, 0.0146 mol) was dissolved in chloroform ( 10 mL) and under an atmosphere of nitrogen was added freshly distilled benzaldehyde ( 2 g,0.0188 mol) was added followed by 5 drops of borontrifluoride etherate. The mixture was stirred at room temperature overnight, washed with aq. sodium bisulfite, dried and then concentrated under reduced pressure. Distillation of the residue under reduced pressure gave 2,3-O-benzylidene-1-bromo propane ( 75%,b.p. 105-108 °C/0.5 torr). NMR matches literature[81].

Oxidation of epibromohydrin benzaldehyde acetal [31]: 2,3-O-benzylidene-1-bromo propane (10 g,0.0433 mol) was dissolved in dry DMSO (200 mL) and purged with nitrogen. Sodium bicarbonate (7.2 g,0.0866 mol) and NaI (10 g 0.066

mol) were added and the mixture was heated to 130°C overnight. Water (600 mL) was added and the mixture was extracted thrice with 200 mL portions of ether. The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to give 6.4 g of a mixture. NMR indicated that 2,3-O-benzylidene propanal was formed (aldehyde peak at 9.9 ) and there was some unreacted bromide. Owing to the reported instability[78,79] of this compound it was used without purification.

Preparation of diphenyl 1,2-epoxy-3,4-O-benzylidene-3-4-dihydroxybutylphosphonate[36]:

A 2.6 M solution of nBuLi in hexane (0.0104 mol) was placed in a 3 neck flask under a nitrogen atmosphere and THF (4 mL) was added at -20°C. The solution was then cooled to -70°C and diphenyl chloromethylphosphonate (2.82 g, 0.01 mol) in 5 mL of THF was added dropwise. The mixture was stirred for 15 minutes at -70°C and 2,3-O-benzylidene-2,3-dihydroxypropanal (2.5 g of the mixture from above) was added and the resulting mixture was stirred at -70°C for 2 hours, then warmed to room temperature and stirred for 18 hours. Water (50 mL) was added and the mixture was extracted thrice with 50 mL portions of 1:1 ether/methylene chloride. The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to yield 3.5 g of a

mixture. Chromatography of the residue on silica gel using 4:1 hexane/ether gave 0.8 g of diphenyl 1,2-epoxy-3,4-O-benzylidene-3,4-dihydroxy-1-phosphonate.

NMR of this material showed no aldehyde peak, signals between 2 and 3 assignable to oxirane protons. Product formation was thus inferred but purity was doubtfull.

Preparation of (S)-(-)-dimethyl malate [49][59] :

L-Malic acid (67 g, 0.5 mol) was dissolved in 3% HCl in methanol prepared by adding 25 mL of acetyl chloride to 500 mL of methanol. The solution was stirred under an inert atmosphere overnight at room temperature, then concentrated under reduced pressure and distilled under reduced pressure to give dimethyl malate ( 60%, b.p. 120-124 $^{o}$/15 torr).

Preparation of (S)-1,2,4-butanetriol[59a] :

A solution of (S)-Dimethyl malate (13 g, 0.08 mol) in 15 mL of dry THF was added dropwise to 10.5 g of lithium aluminium hydride in 500 mL of THF and the mixture was refluxed overnight. Water (300 mL) was carefully added and the white precipitate which formed was filtered and washed with four 60 mL portions of dry ethanol. The combined filterates were evaporated to near dryness under vacuum. Short column chromatography of the residue over 50 g silica with graded elution using chloroform ethanol to

remove inorganic material gave 4 g (40 %) of oily (S)-1,2,4-butanetriol[59a].

Preparation of (S)-1,2-O-isopropylidenebutane-1,2,4-triol[59a]:

(S)-1,2,4-butanetriol ( 9 g, 0.084 mol) was stirred in 500 mL acetone in the presence of 400 mg of p-toluenesulfonic acid monohydrate at room temperature for 1.2 hour. Sodium bicarbonate was suspended in the solution and stirred for 10 minutes, then acetone was evaporated to dryness and the residue was extracted with ethyl acetate. After washing with aq. sodium bicarbonate and sodium chloride and drying, the solvent was removed under reduced pressure to give 11 g (90 %) of 3,4-O-isopropylidenebutane-1,2,4-triol.

NMR of this material was in accordance with that in the literature[59a].

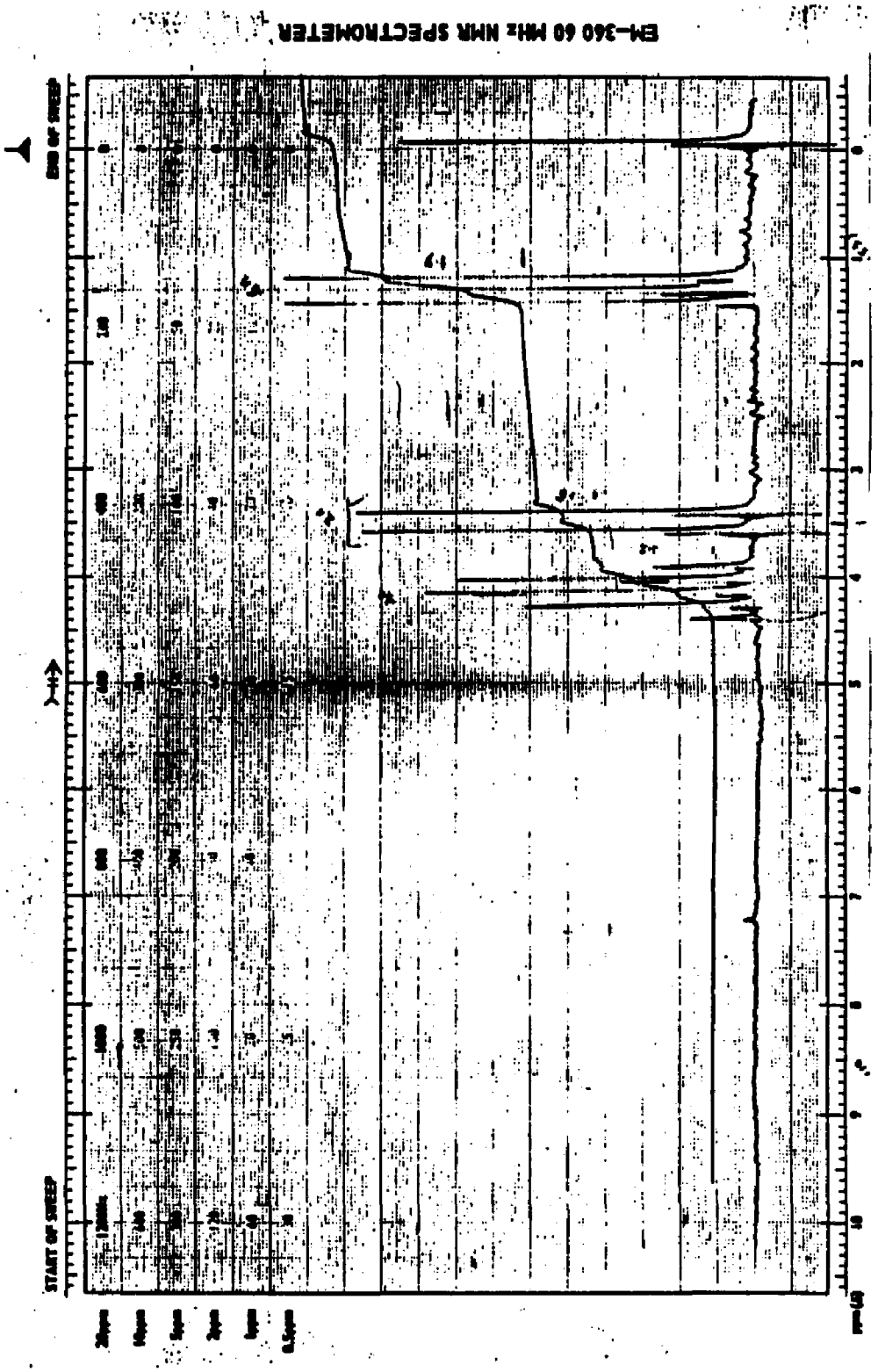
Preparation of (S)-3,4-O-isopropylidene-3,4-dihydroxy-butanal[59a]:

(S)-1,2,-O-isopropylidene-1,2,4-butanetriol (7.3 g, 0.05 mol) in 20 mL of methylene chloride was added to a stirred suspension of pyridinium chlorochromate (16.15 g, 0.075), sodium acetate (1.23 g) and celite (15 g) in 100 mL methylene chloride and stirring was continued at room temperature for 2 hours. Ether (100 mL) was added and the

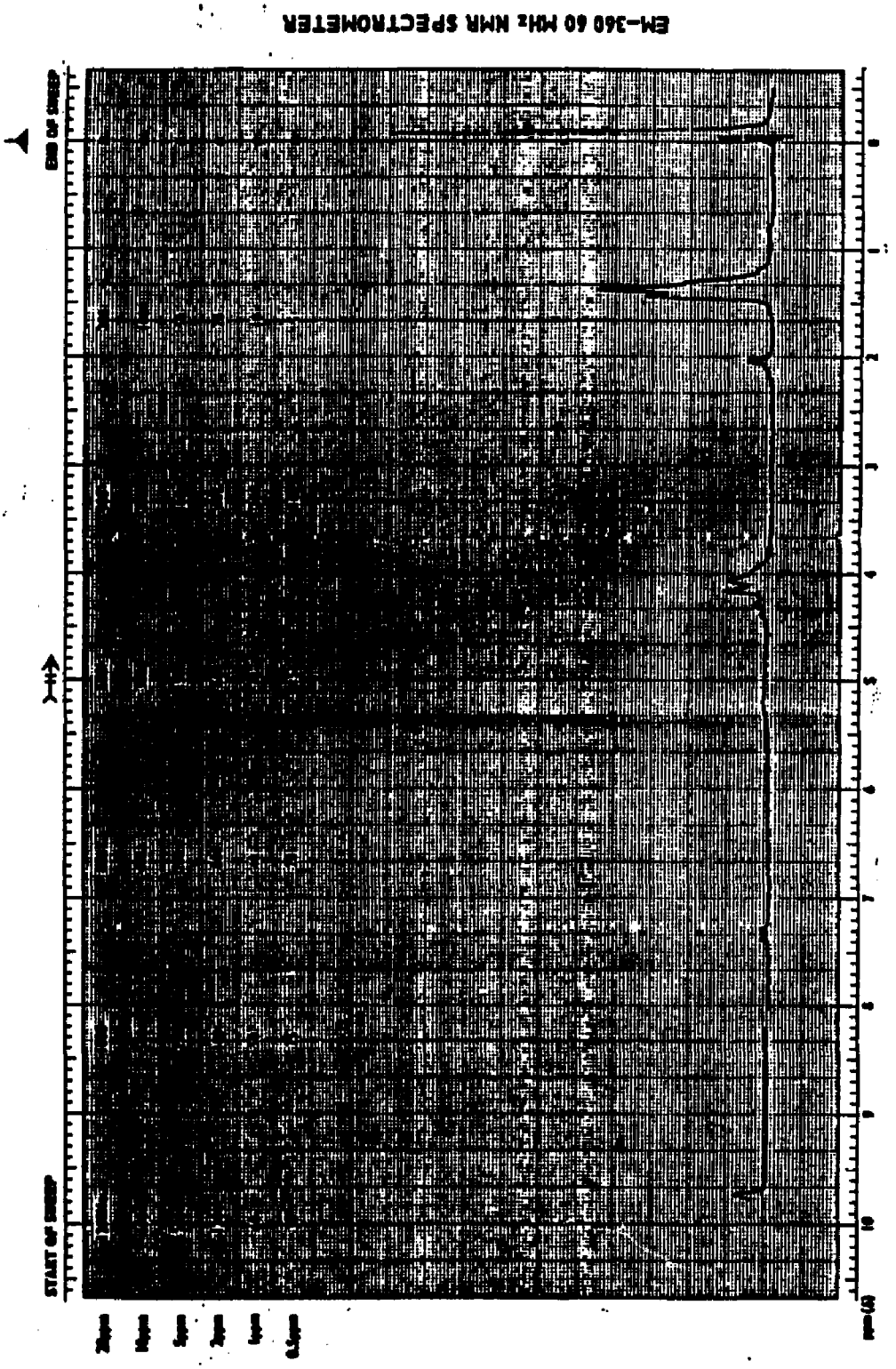
mixture was filtered through florosil. The florosil column was washed three times with 50 mL portions of ether which were combined and concentrated under reduced pressure. The residue, on vacuum distillation, afforded 4 g (36 %) of (S)-3,4-O-isopropylidene-3,4-dihydroxybutanal. NMR of this material was consistent with that reported[59a].

Attempted halogenation of (S)-3,4-O-isopropylidene-3,4-dihydroxybutanal:

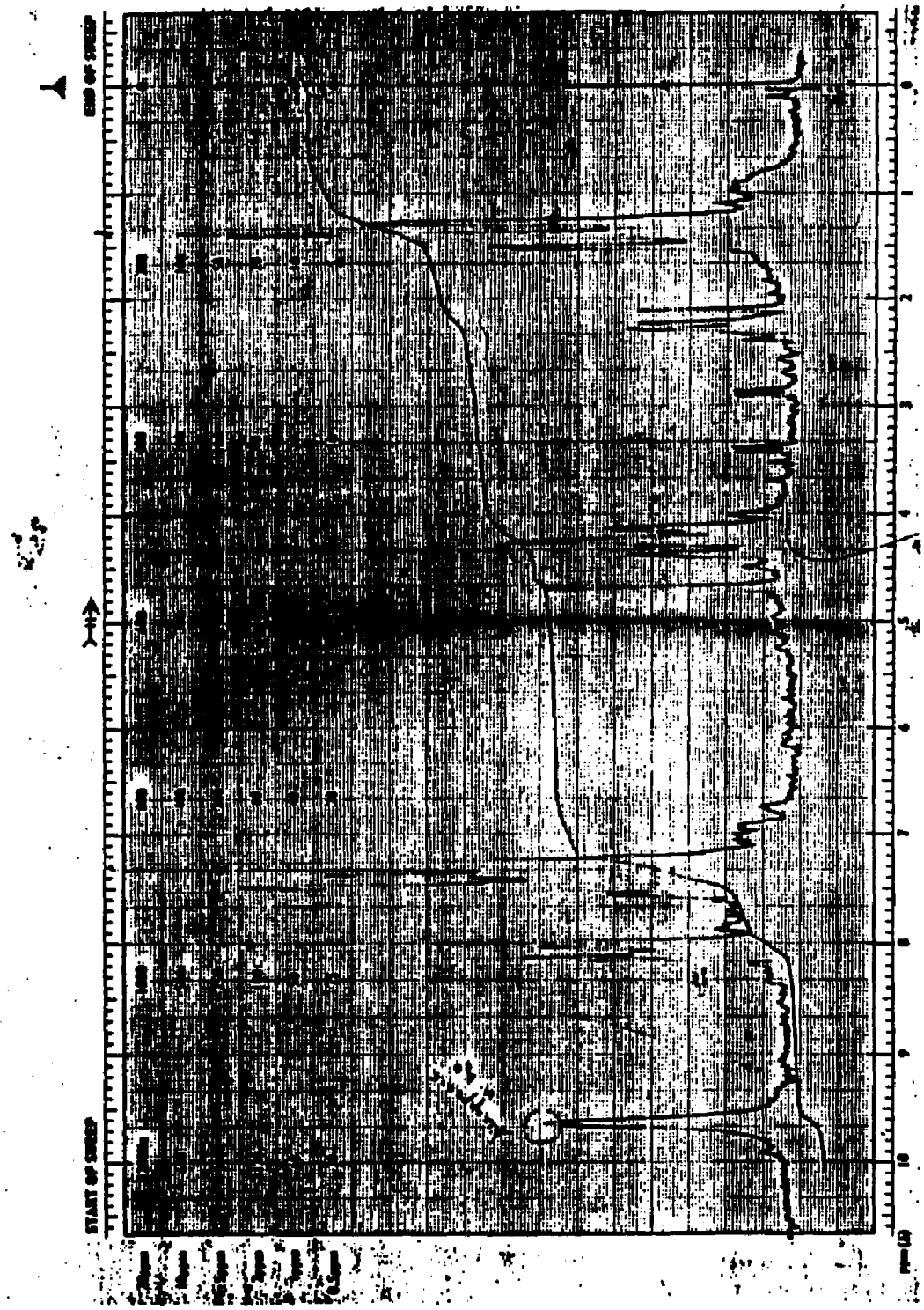
(S)-3,4-isopropylidene-3,4dihydroxybutanal (0.2 g, 0.00139 mol) and cupric chloride dihydrate (0.23 g, 0.00139 mol) were dissolved in 12 mL of 3:1 isopropanol/water in a 50 mL round bottom flask equipped with a magnetic stirrer, reflux condenser. The mixture was refluxed under an atmosphere of nitrogen for 48 hours (bath temperature 96 $^{o}$C). No precipitation was seen and so the approach was abandoned.



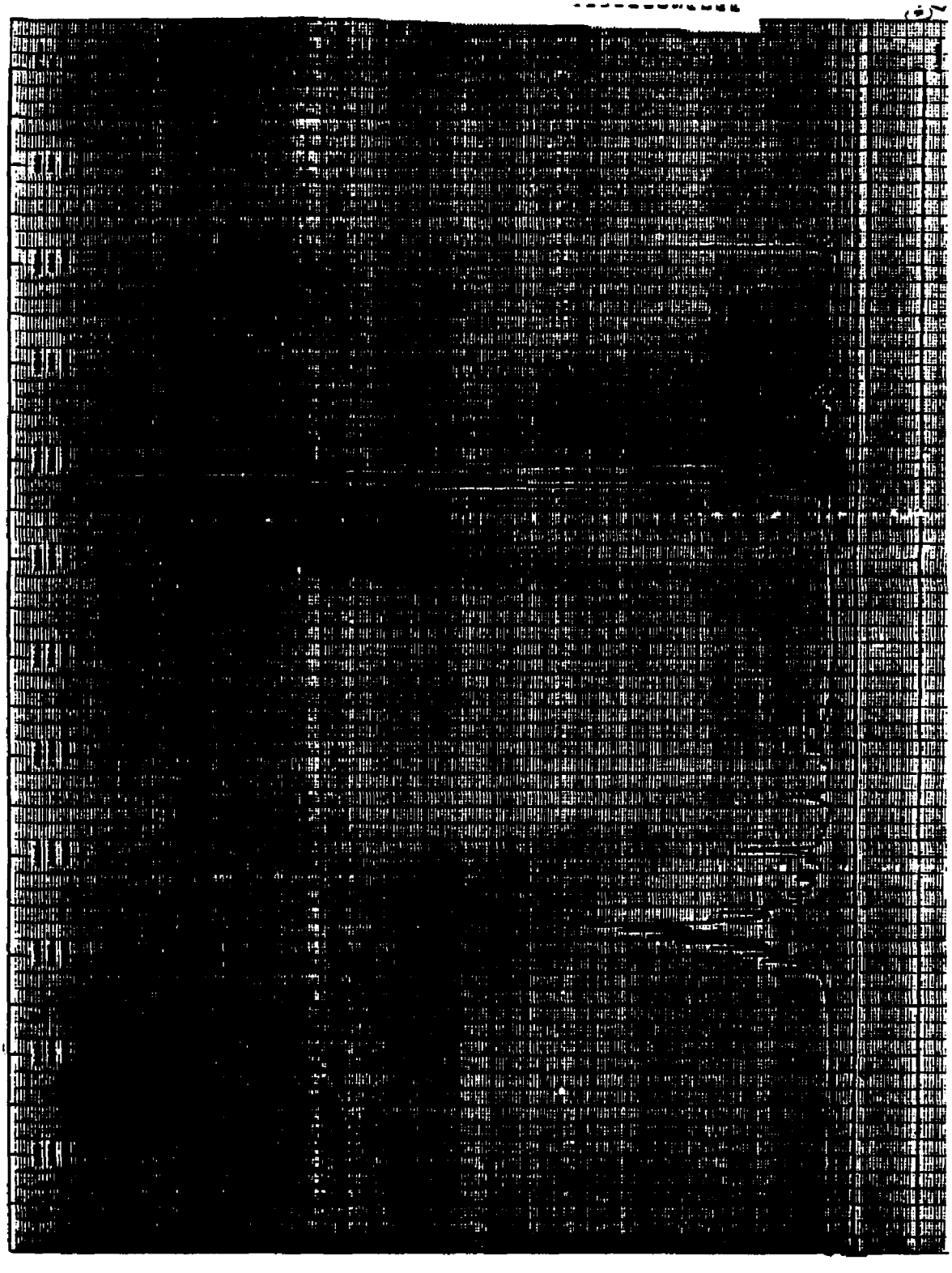

NMR of [16]



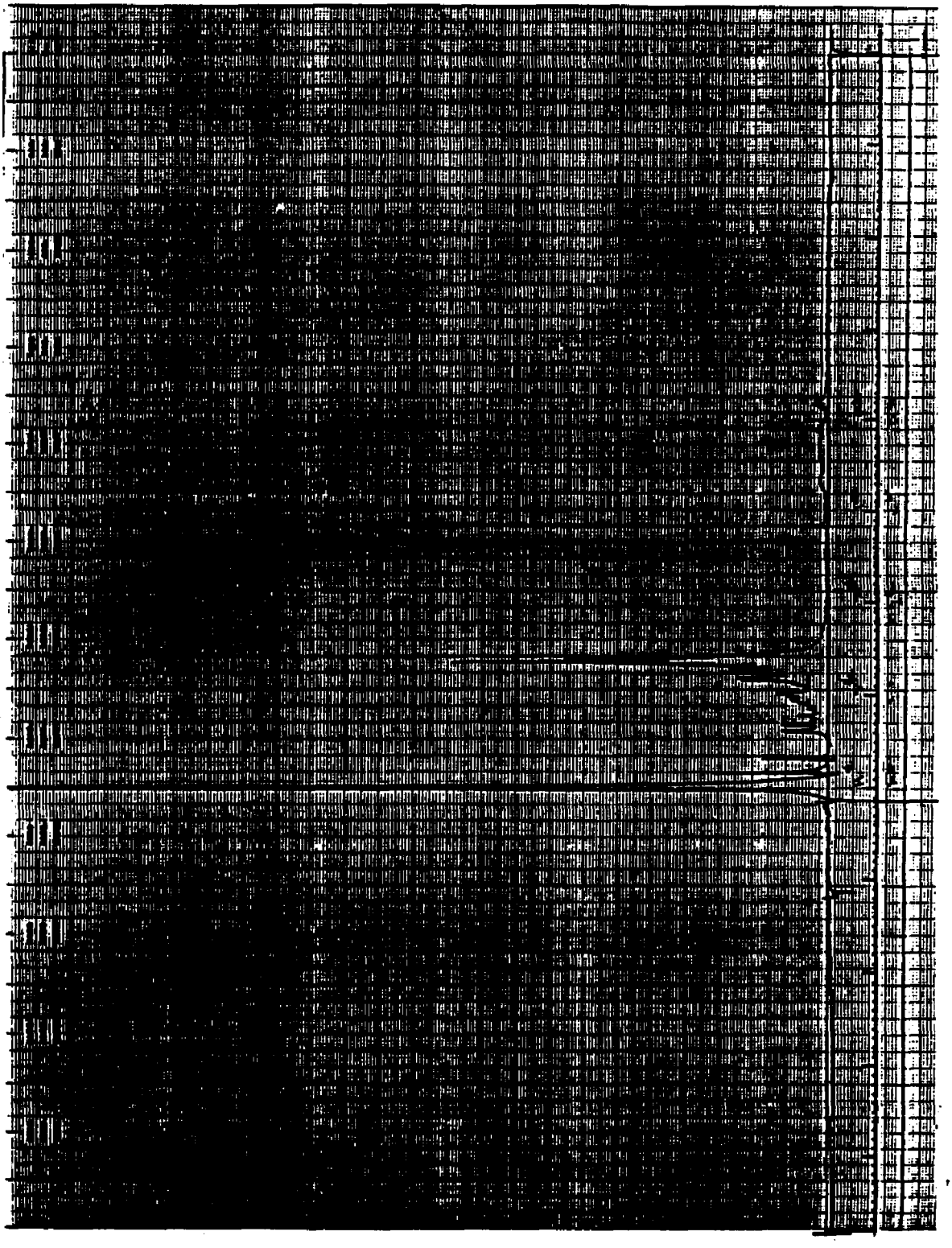

NMR of [17]



NMR of [22]



NMR of [24]

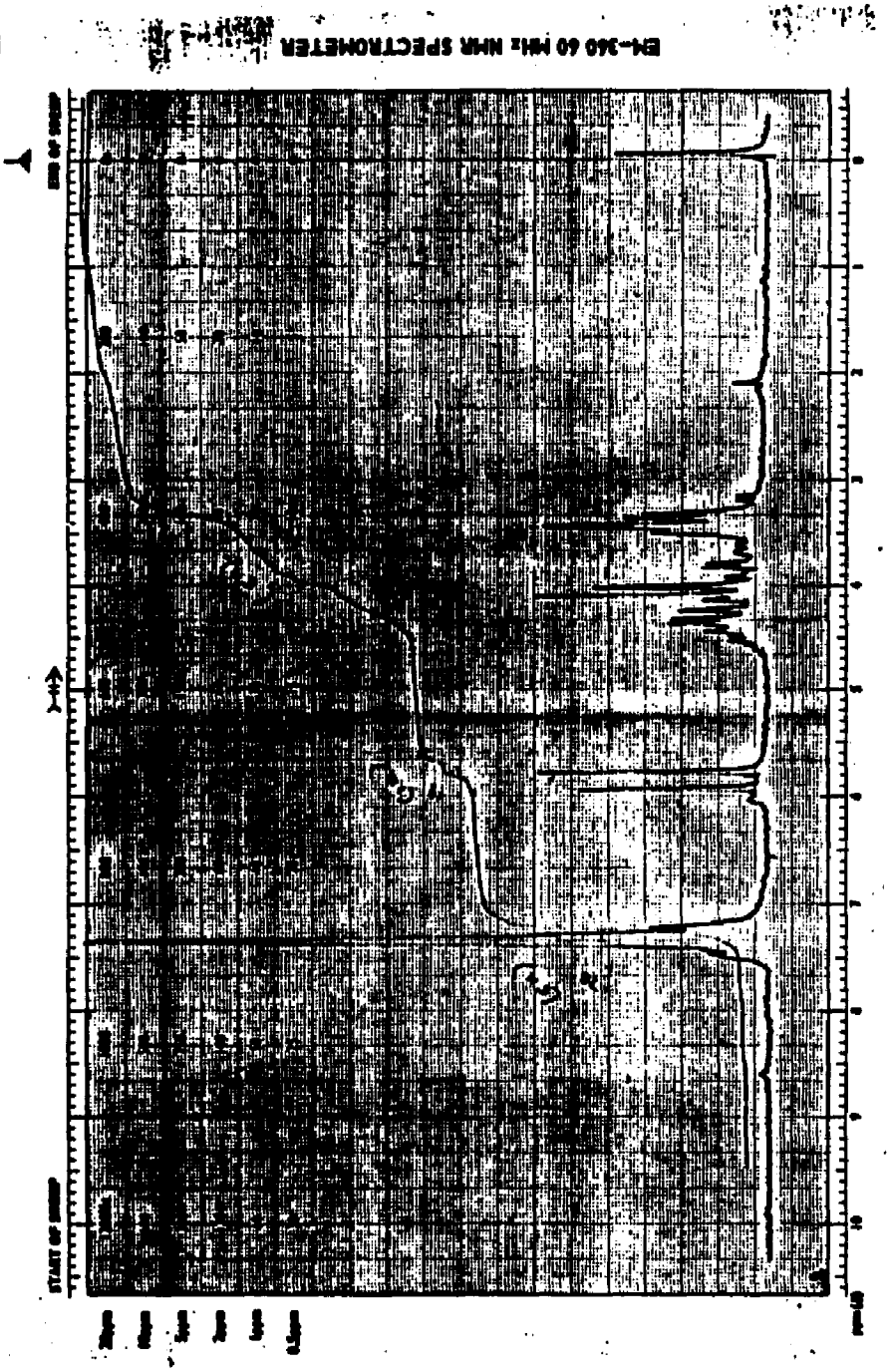


NMR of [25a]

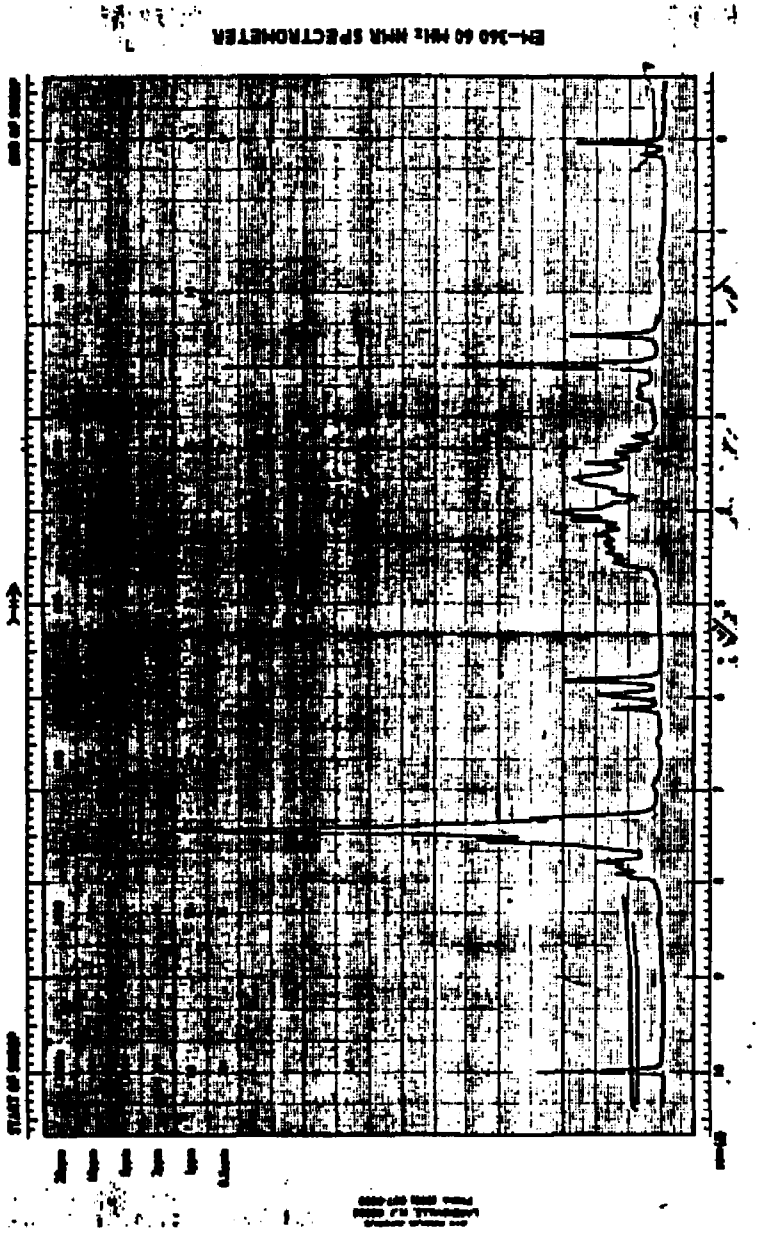
NMR of [28]



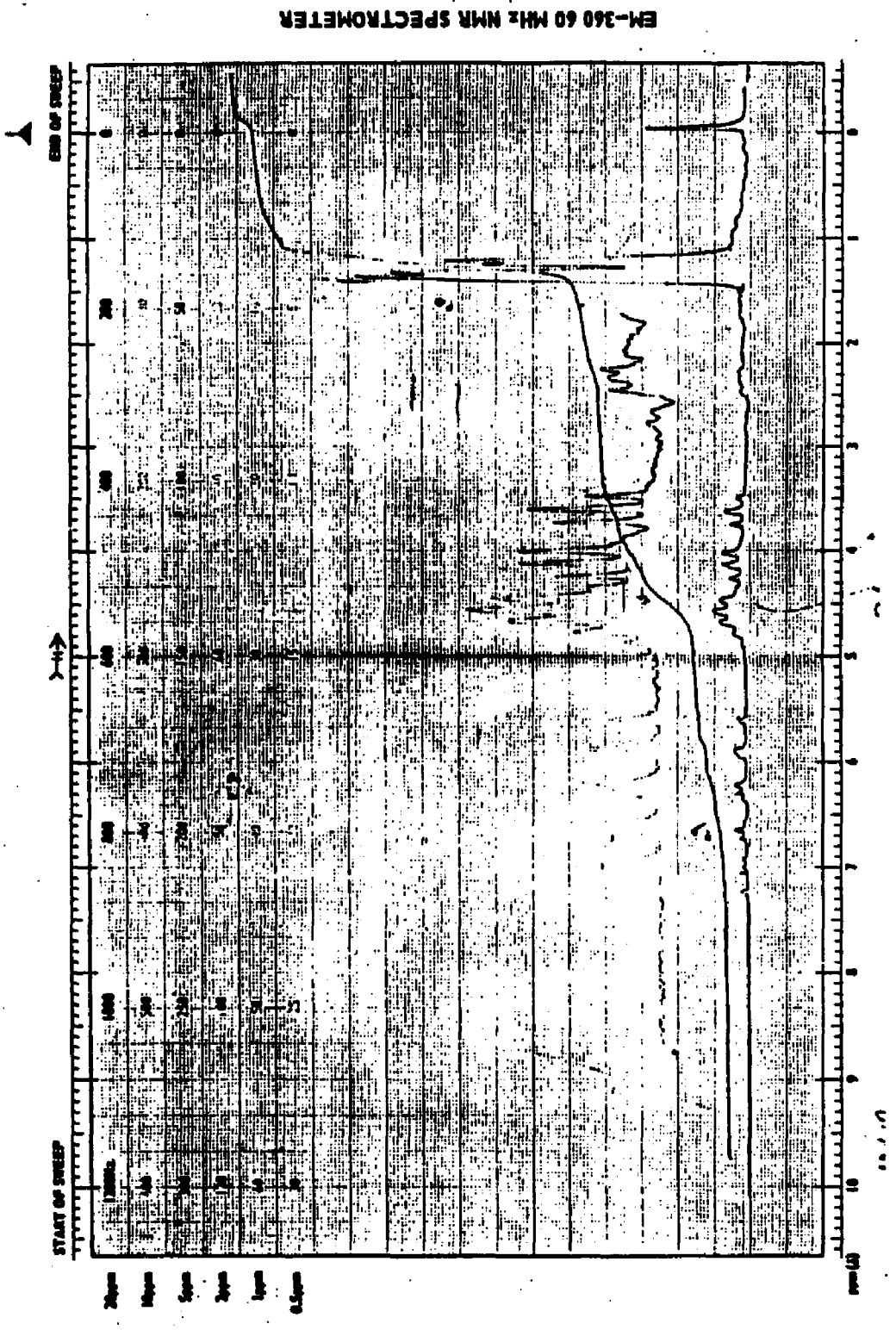
EM-360 60 MHz NMR SPECTROMETER



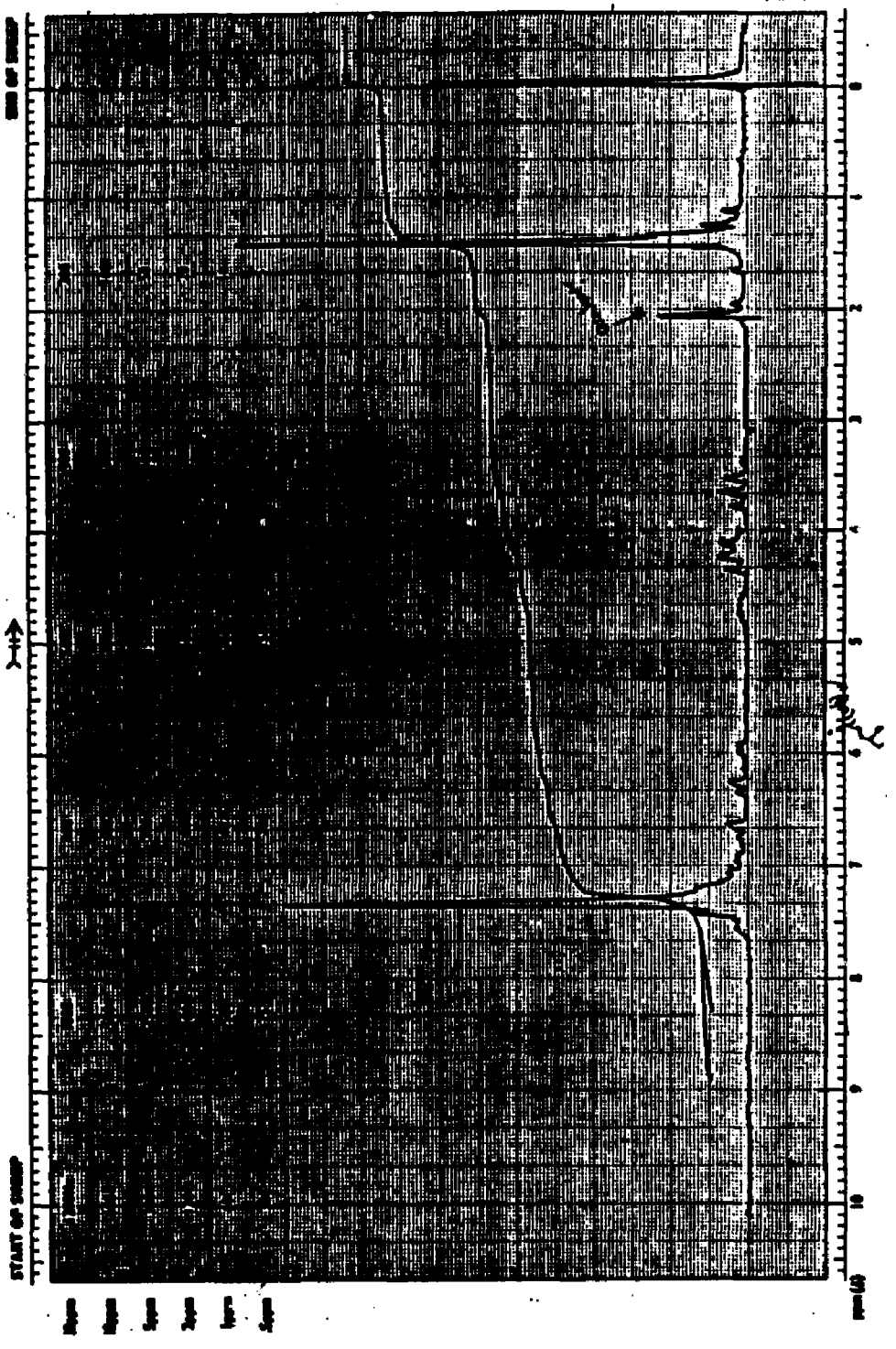
NMR of [31]



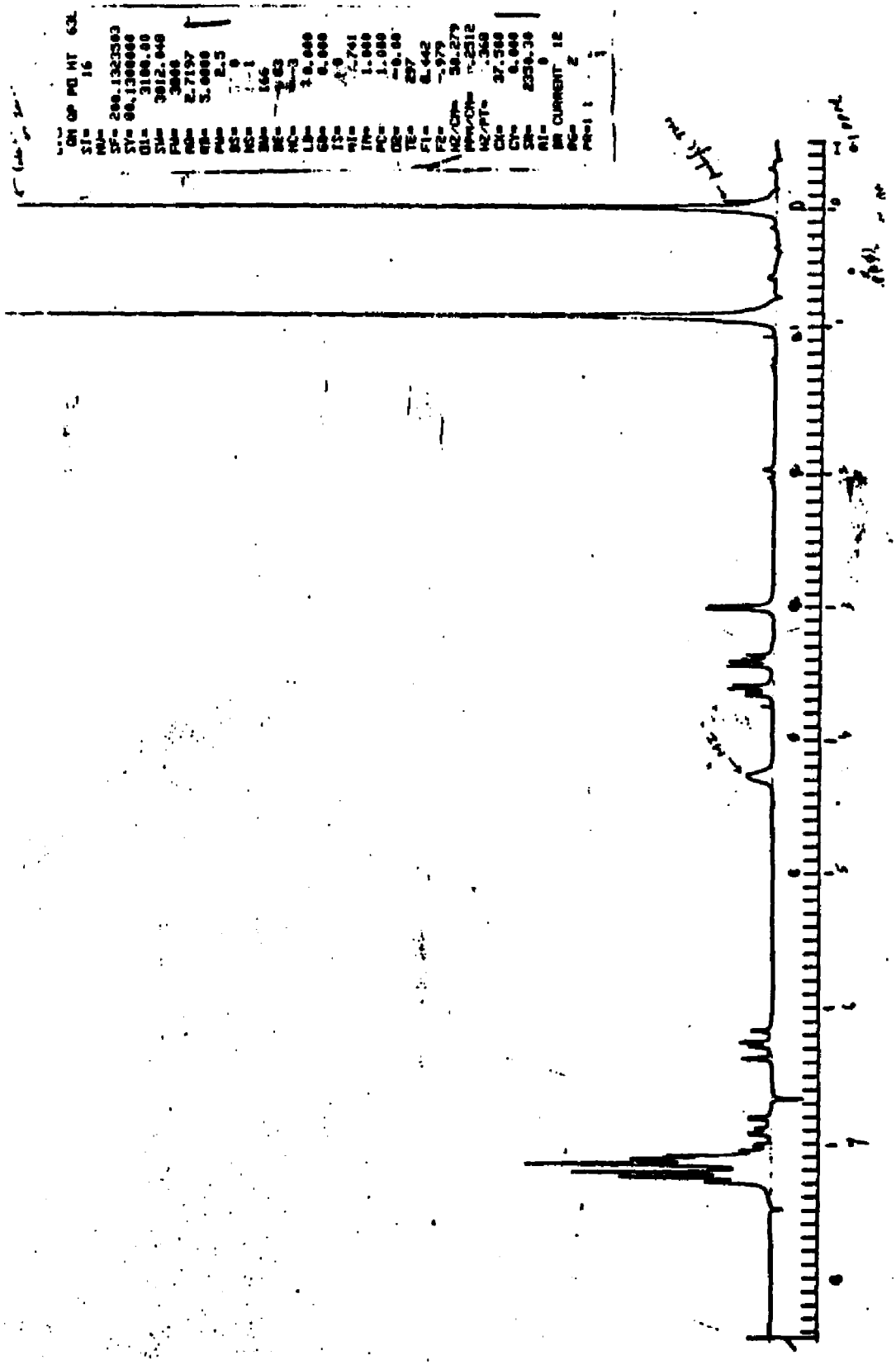

NMR of [32]



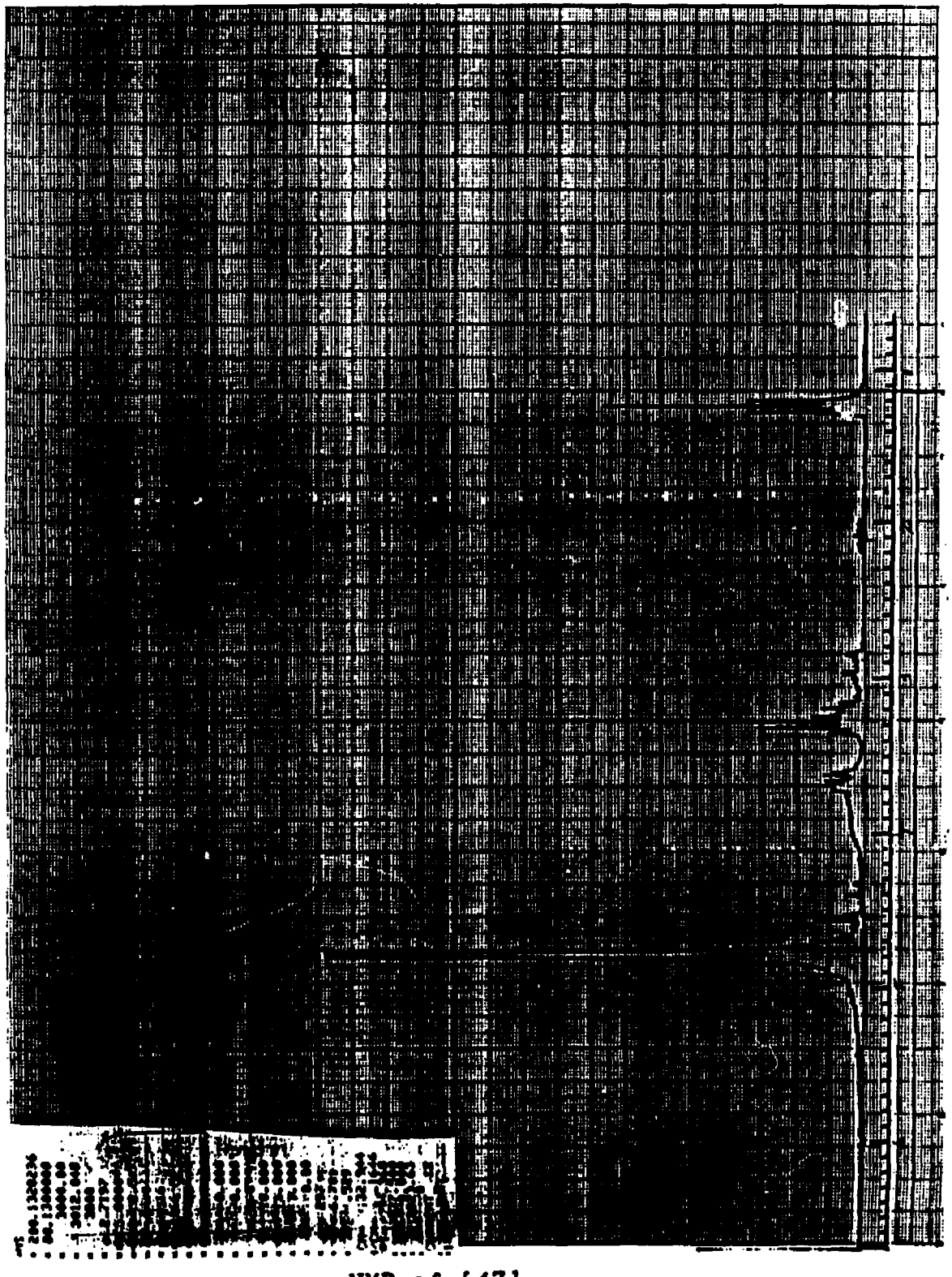

NMR of [34]



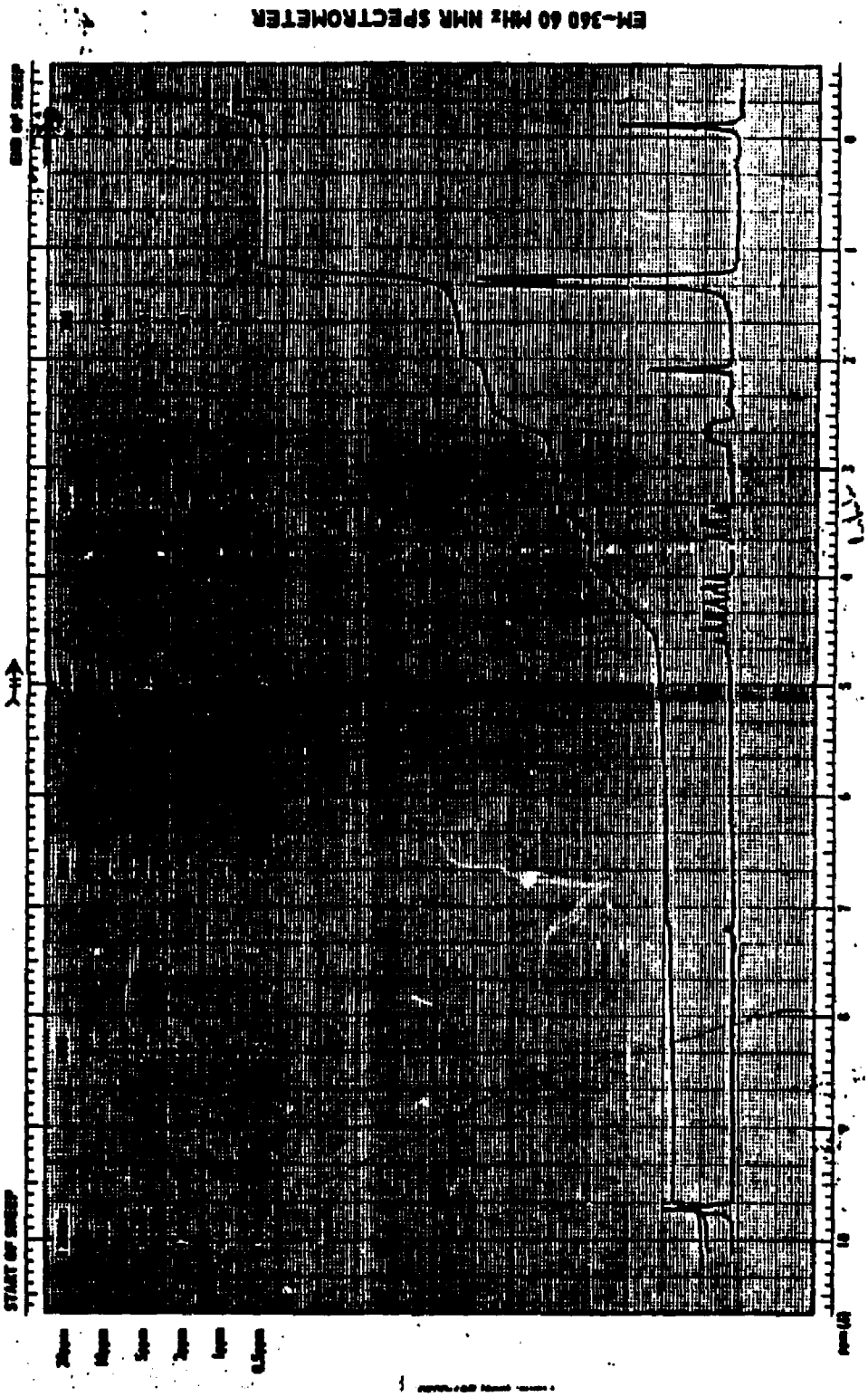
NMR of [41]



NMR of [43]



NMR of [47]

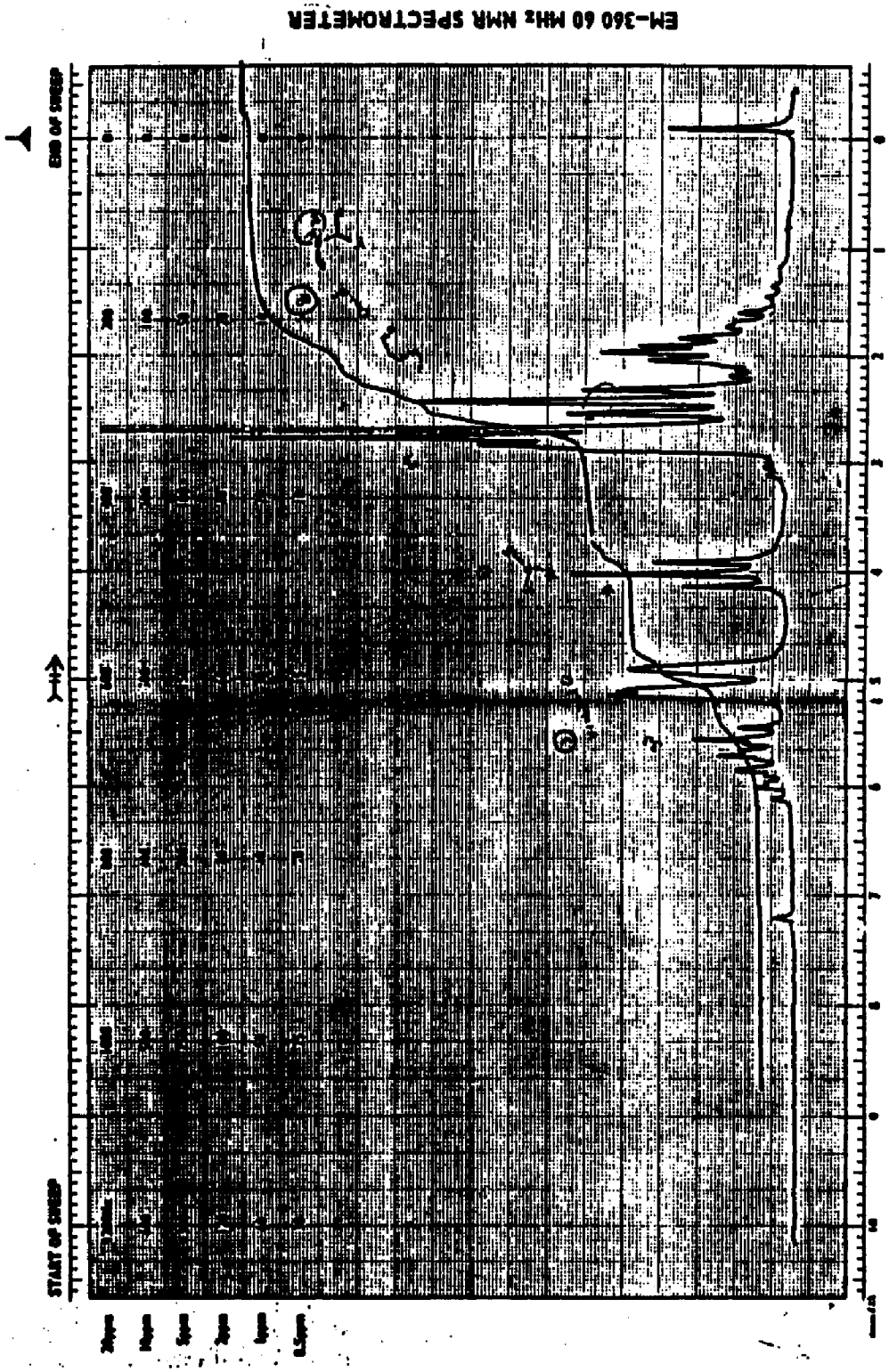



NMR of 51

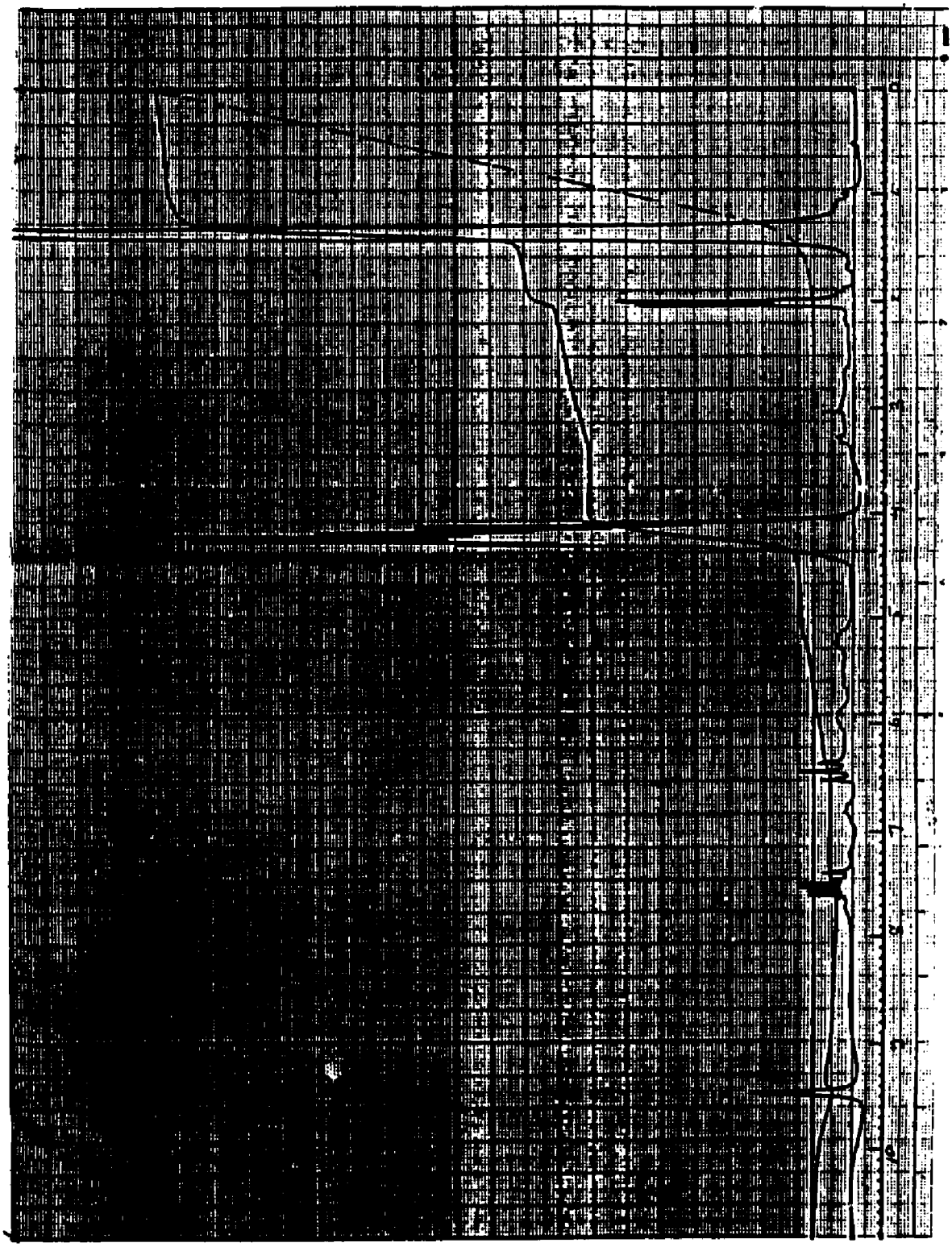
NMR of [55]



EM-360 60 MHz NMR SPECTROMETER




NMR of [60]



NMR of [63+64]

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