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SYNTHESIS AND CHEMISTRY OF 2,2-DISUBSTITUTED 1-ALKENYLPHOSPHONIC DERIVATIVES

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Synthesis and Chemistry of 2,2-Disubstituted 1-Alkenylphosphonic Derivatives

A dissertation submitted by

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Supervisor : Prof. T. A. MODRO

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by

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Department of Chemistry

Submitted for the Degree of Magister Scientiae

SUMMARY

The reaction of 2-methyl-1-pentene with phosphorus pentachloride gave invariably a mixture of products which could not be isomerised to produce single compounds. Similarly, five compounds were obtained following the esterification reaction of the above-mentioned mixture. Base-catalysed isomerisation of the mixtures of the alkenyl phosphonate diesters, as well as attempted standard chromatographic methods, failed to give single compounds. Pure α,β- and β,γ-unsaturated phosphonates have been obtained in high yields by independent, unambiguous routes. Prototropic equilibrium studies on the pure alkenyl phosphonates were carried out and hyperconjugation effects operating in such systems were discussed. A gas chromatographic study of the alkenylphosphonate mixtures and of the pure compounds gave chromatographic data previously unreported for compounds of this type.

OPSOMMING

Die reaksie van 2-metiel-1-penteen met fosfor pentachloried het deurgaans 'n mengsel van produkte opgelewer wat nie geïsomeriseerd kon word tot 'n enkele produk nie. Na esterifikasie van die bogenoemde is 'n mengsel van vyf produkte verkry. Basis-gekataliseerde isomerisasie van die mengsel van alkenielfosfonaat diësters, sowel as standaard chromatografiese tegnieke, was onsuksesvol om enkel produkte te lewer. Hoë opbrengste van suiwer α,β- en β,γ-onversadigde fosfonate is verkry deur van betroubare, onafhanklike metodes gebruik te maak. Prototropiese ekwilibrium studies van die suiwer alkenielfosfonate is uitgevoer en die effek van hiperkonjugasie in dié sisteme is bespreek. Gas chromatografiese studies van die suiwer, sowel as mengsels van alkenielfosfonate het, tot op hede onbekende chromatografiese data opgelewer.

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CHAPTER 1 : INTRODUCTION

1.1 GENERAL

Phosphorus (the Greek equivalent of "light bearer") is the most abundant and most fully studied element in group VA. The simple inorganic chemistry of phosphorus was developed by a large number of chemists during the eighteenth and nineteenth century while the organophosphorus chemistry has got its roots back in 1820 when J. L. Lassaigne (1) reacted alcohol with phosphoric acid. The systematic development of organophosphorus chemistry was initially undertaken by A. Michaelis during the later part of the nineteenth century, followed by Arbusov in the early years of the twentieth century (2,3).

Due to its electronic structure $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^3$, phosphorus is capable of forming defined families of tri-, tetra-, penta-, and hexacoordinated derivatives in which the ligands can be organic or inorganic. In recent years the new and fascinating chemistry of mono- and dicoordinated phosphorus is rapidly developing (4). The ease with which it is possible to progress from the lowest to the highest coordination number [P(III) $\rightarrow$ P(IV) $\rightarrow$ P(V) $\rightarrow$ P(VI)] makes

these organophosphorus reagents useful in general organic synthesis. The important factors in this are (5):

a) the high nucleophilicity of tervalent phosphorus reagents towards a wide range of electrophiles.

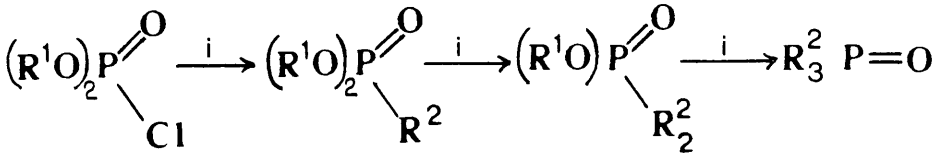
b) the strong bonds that phosphorus forms with oxygen (particularly P=O), sulphur, nitrogen, the halogens, and carbon.

c) the capability of phosphorus to stabilize adjacent anions, best illustrated by the importance of the Wittig ylide in synthesis.

1.2 PHOSPHONIC ACID DERIVATIVES

1.2.1 The Synthesis of Phosphonic Acid Derivatives

The formation of phosphorus-carbon bond from phosphoryl chlorides and organometallic reagents (6) (Scheme 1), is not a convenient route since it is adversly affected by further reaction of the required product and is therefore used to a limited extent only:



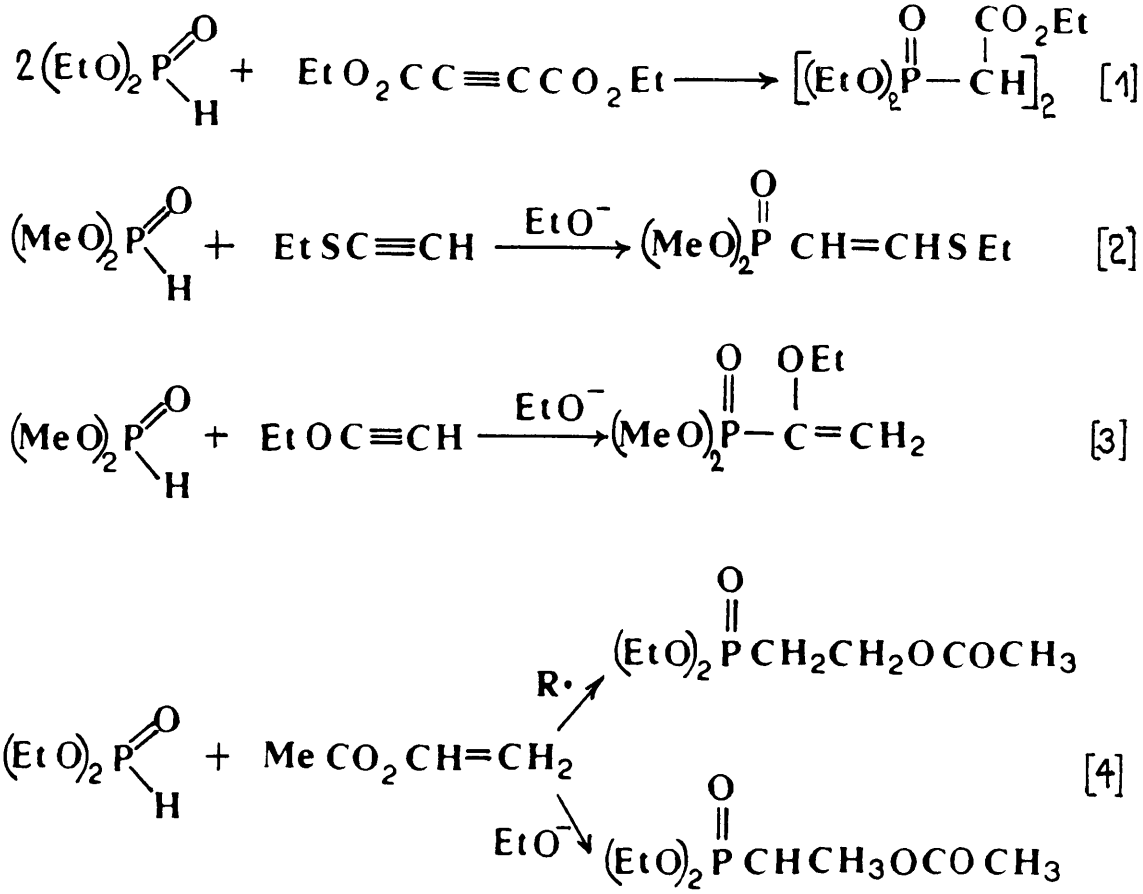
i = R^2MgX or i = R^2Li

SCHEME 1

Three general methods for the preparation of phosphonic acid derivatives are outlined bellow:

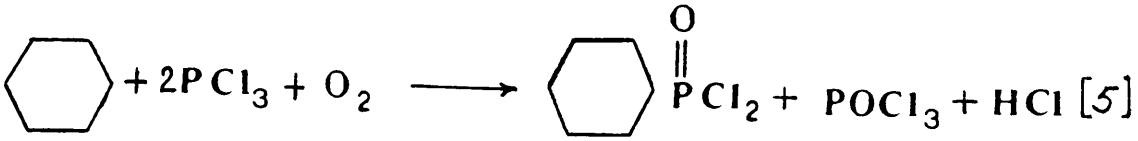
a) Addition of suitable phosphorus intermediates to compounds possessing carbon-carbon double or triple bonds.

Unless the unsaturated bond is highly activated, when no catalyst is necessary (Eq. [1]), addition to a functionally activated bond normally takes place under base-catalysed conditions (Eq. [2] and [3]) or under free-radical conditions, the two reactions leading to isomeric products (Eq. [4]) (7).

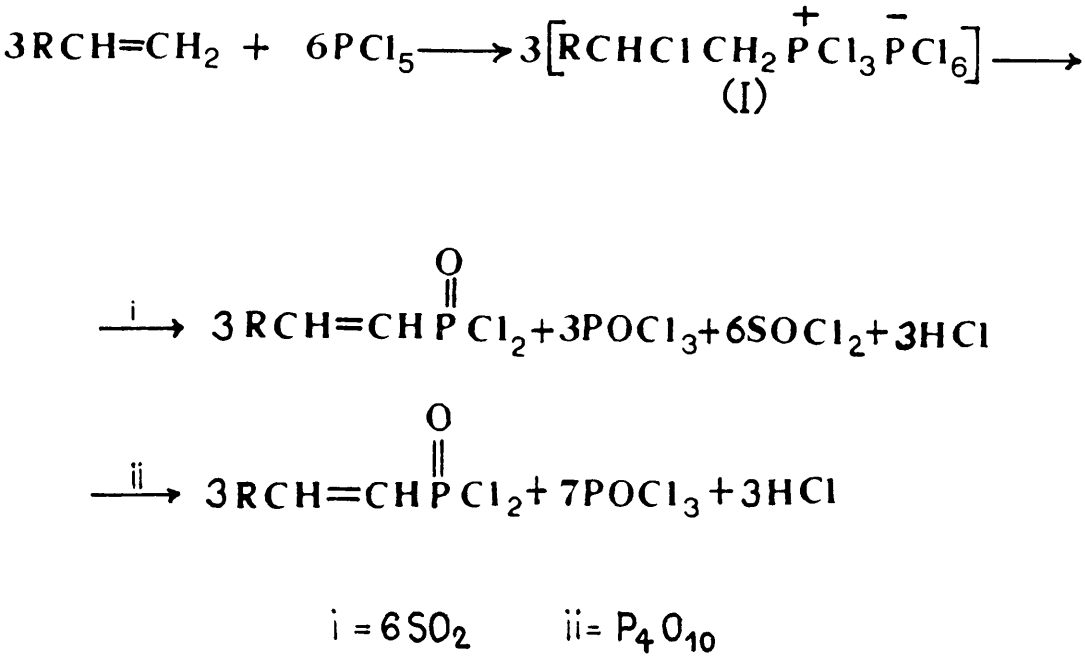


b) The synthesis of phosphonic dihalides by oxidative chlorophosphonation of cyclohexane.

Under ambient conditions, passage of a stream of oxygen through a mixture of cyclohexane and phosphorus trichloride yields the phosphonic dichloride (8) (Eq. [5]).



A more common synthesis, however, is the interaction of an inorganic phosphorus halide and a hydrocarbon, generally unsaturated, in the presence of aluminium trichloride (Scheme 2) (9).

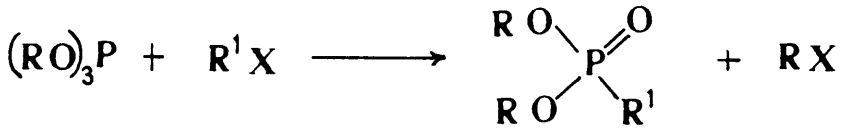


SCHEME 2

On addition of sulphur dioxide or phosphorus pentoxide, the complexes (I) formed when alkenes are treated with phosphorus pentachloride are converted to vinylphosphonic dichlorides (10).

c) The reaction of phosphite triesters with alkylating reagents. The Michaelis - Arbusov reaction

One of the most important transformations of trivalent to pentavalent phosphorus compounds is the conversion of trialkyl phosphites to the thermodynamically more stable phosphonates; the reaction is accompanied by the formation of a phosphorus-carbon bond. This is known as Michaelis-Arbusov reaction and is effected by the action of alkyl halides (Scheme 3).



SCHEME 3

In the present project methods (b) and (c) described above were used in the synthesis of vinyl phosphonates. Therefore, in the following subchapters more attention will be given to these particular routes.

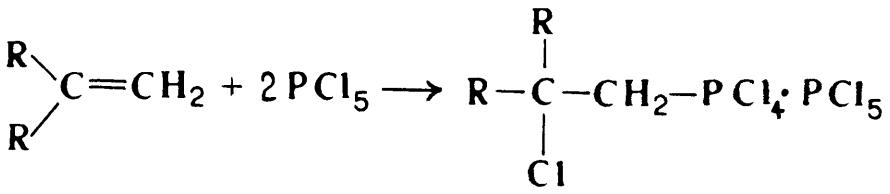
1.2.2 The Synthesis of Phosphonic Dichlorides

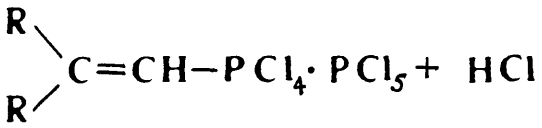
1.2.2.1 Addition of Phosphorus Pentachloride to Alkenes

It was first found by Marsh and Gardner (11, 12) that camphene adds phosphorus pentachloride. Later on, Bergmann and Bondi (13, 14, 15) investigated such reactions and recognized their general principle. They claimed that PCl_5 is added mainly on the α-carbon atom to 1-alkenes unsubstituted at C-1.

Compounds with substituents at α-carbon, like 1,3-diphenylpropene, stilbene, and triphenylethylene, do not react with phosphorus pentachloride according to the desired scheme. However, some cyclic compounds like camphene (11, 12) and indene (13, 16) react normally like 1-olefins.

When an alkene has two alkyl groups linked to β-carbon, one alkoxy residue, alkylmercapto group or one aryl residue, the addition takes place regiospecifically according to Scheme 4. Primary adducts are usually unstable and eliminate HCl to form α,β-unsaturated phosphonic acid tetrachlorides.



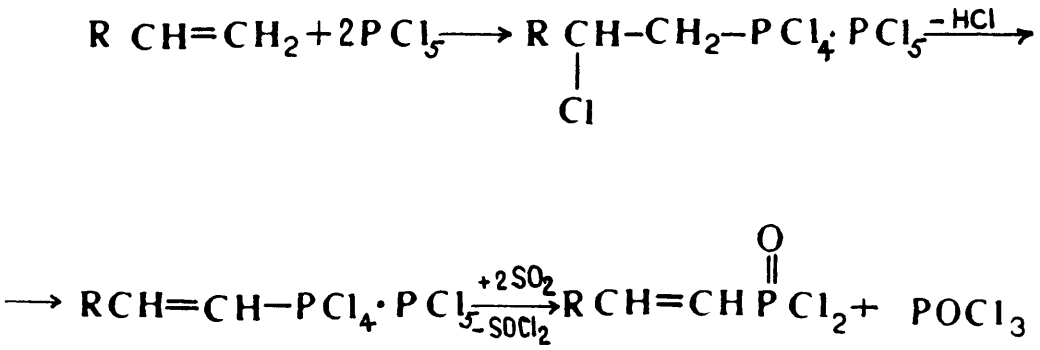


SCHEME 4

Such reactions have been described for 2-methylpropene (14, 17, 18), 2,2,4-trimethyl-1-pentene (18), styrene (13, 15, 17, 19, 20), styrene substituted in the aromatic ring (21), 1,1-diphenylethylene and its substituted derivatives (13, 14, 17), 2-phenylpropene (13), vinyl ether (20, 22), and vinyl thioether (23).

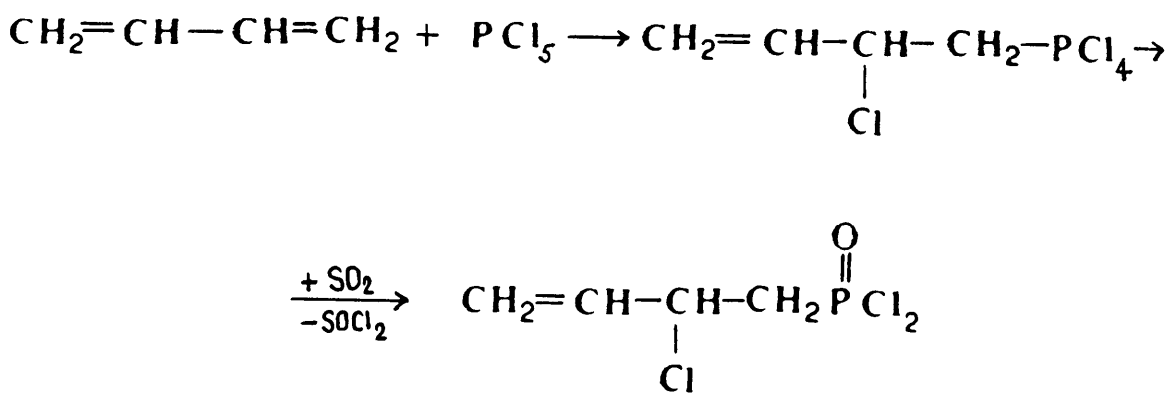
1.2.2.2 Preparation of α,β-Unsaturated Phosphonic Dichlorides from Terminal Double Bond Olefins and PCl_5

The addition of PCl_5 to 1-olefins containing at least one aryl or two alkyl groups at β-carbon leads to phosphonic acid tetrachlorides with PCl_4 substituent. Further treatment of such compounds with SO_2 or with P_4O_{10} leads to elimination of HCl and the formation of α,β-unsaturated phosphonic dichlorides (Scheme 5). Alkyl-vinyl as well as vinyl-aryl ethers and thioethers react analogously (9).



SCHEME 5

Butadiene adds only one molecule of PCl_5. When the adduct is treated with SO_2 (24) or with acetic acid (25, 26) it is transformed into a mixture of compounds in which 2-chloro-3-butenylphosphonic dichloride is the major component (Scheme 6).

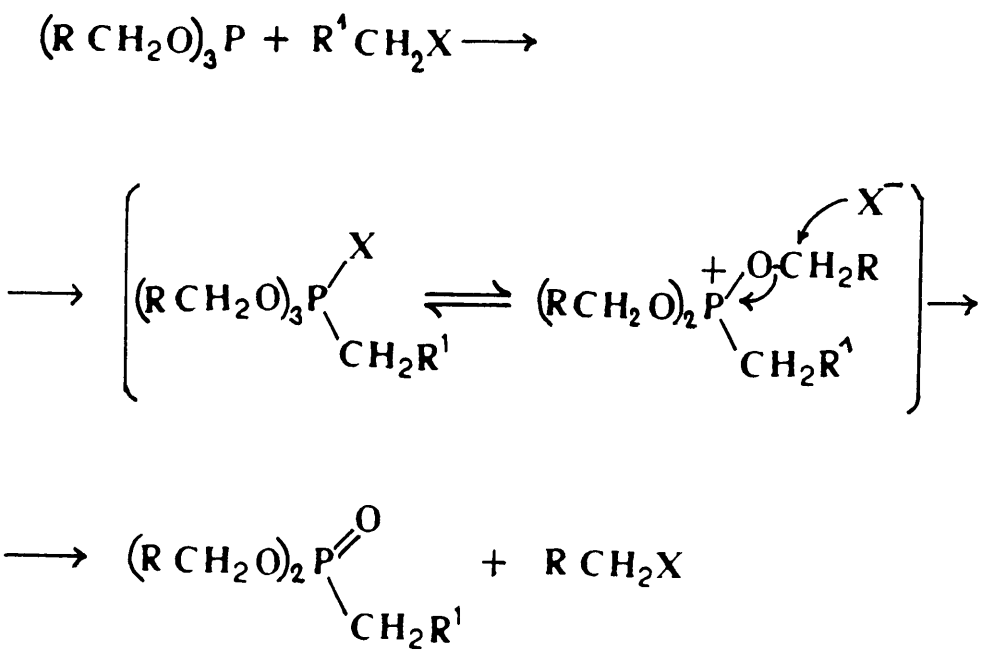


SCHEME 6

1.2.2.3 The Michaelis-Arbusov Reaction

The Michaelis-Arbusov reaction has been known for almost one hundred years (27) and has been extensively reviewed (28-30). In this reaction a C.N.3 compound carrying a P-OR group is converted into a C.N.4 compound with a phosphorus-oxygen double bond (phosphoryl group). A new

carbon-phosphorus bond is formed concurrently. In this reaction, the first formed intermediate is a quaternary quasiphosphonium salt, which can be isolated in some instances. This intermediate undergoes, however, nucleophilic attack at carbon by the anion to give the phosphoryl product (Scheme 7).



SCHEME 7

The driving force of this reaction is the high P=O bond energy ($630KJmol^{-1}$). This reaction generally proceeds by S_N2 attack of the phosphite on carbon followed by an S_N2 reaction of the displaced anion on the alkyl group of the quasiphosphonium intermediate.

The Arbusov reaction is highly stereoselective and often stereospecific. While the effect of the groups attached to P on the relative reactivity of the phosphorus reagent has not been adequately studied, the accumulation of alkyl or aryl groups markedly increases the rate of reaction. Thus, the following reactivity series has been established:

$$(EtO)_3P < (EtO)_2PEt < EtOPEt_2$$

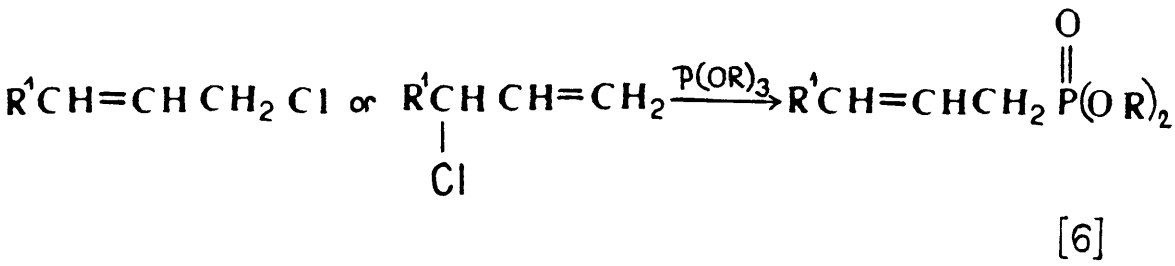
$$(EtO)_3P < (EtO)_2PPh < EtOPPh_2$$

Virtually any halide capable of undergoing bimolecular nucleophilic displacement may enter into the Arbusov reaction. The usual reactivity sequence is:

acyl > primary alkyl > secondary alkyl

iodide > bromide > chloride

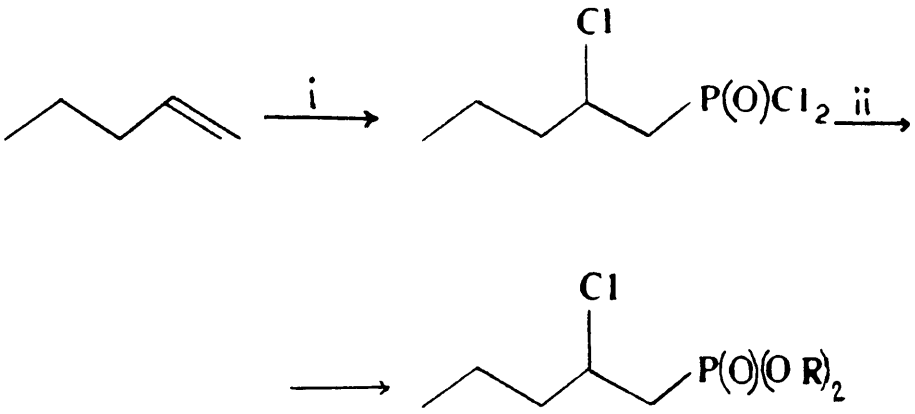
Allylic halides may react normally or with allylic rearrangement depending upon whether the halide is on a terminal carbon (Eq. [6]).



[6]

1.3 WORK LEADING TO THE PRESENT PROJECT

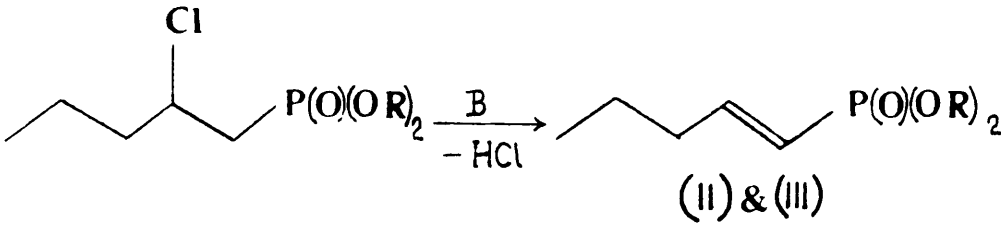
Phosphonic dihalides may be utilized in the synthesis of a wide range of other derivatives (8). Recent work from our laboratory (31) has shown the formation of vinyl phosphonate product (II,III) following the reaction of a phosphonic diester with a strong base. The interaction of an inorganic phosphorus halide and 1-pentene (a straight chain olefin) was the reaction of choice in the synthesis of the phosphonic dihalide (Eq. [7]) (Scheme 8).



[7]

i = PCl_5, C_6H_6, followed by P_4O_{10}

ii = ROH, C_5H_5N, C_6H_6



[8]

(II) R = Et

B = EtONa/EtOH ; EtOK/EtOH

$(EtO)_2Mg$/EtOH ; t-BuOK/t-BuOH

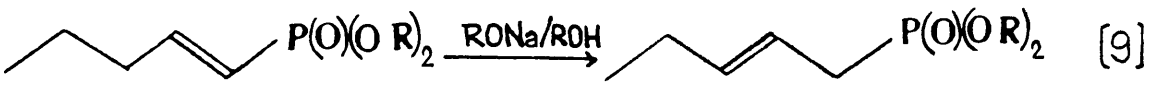
KOH/EtOH ; BuLi/C_6H_{14}

(III) R = Me

B = MeONa/MeOH ; BuLi/C_6H_{14}

SCHEME 8

E-1-pentenylphosphonic ester (α,β-unsaturated ester) was the exclusive product of the elimination reaction (Eq. [8]). It was also shown (31) that when incubated at room temperature in an alcohol containing the corresponding sodium alkoxide, (II) and (III) isomerised completely to the corresponding E-2-pentenyl-1-phosphonic derivatives (IV) and (V) (β,γ - unsaturated ester) (Eq. [9]).



[9]

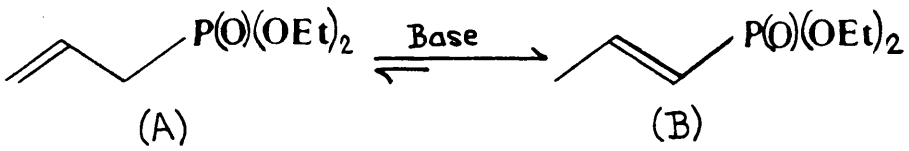
(IV) R = Et

(V) R = Me

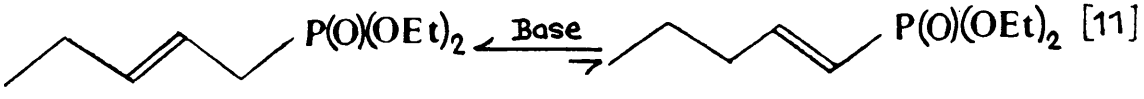
In the present project this work has been extended to include the reaction of an olefin branched in position 2 with PCl_5. We were interested in the addition itself, as well as in the subsequent reaction in which the corresponding phosphonic diesters are formed. Of particular interest was the base-catalysed prototropic isomerisation of the particular phosphonic diesters formed and the effect of the diethylphosphoryl group $(EtO)_2P(O)$ on the olefinic bond, as compared with other similar groups, and with common

factors operating in all alkenes.

The prototropic equilibria in an unsaturated system of the general type presented in Equation [9] have been extensively studied, and some generalizations concerning the relative stabilization (or destabilization) effects of groups X and Y on the adjacent olefinic bond have been formulated (32-34). Little information is, however, available on the effect of dialkoxyphosphoryl group, $P(O)(OR)_2$ on the alkene structure, and the reported results indicate that the preferred location of the alkene bond depends strongly on the detailed structure of the unsaturated phosphonic ester. While simple diethyl 2-propenylphosphonate (A) undergoes complete isomerisation to the 1-propenyl derivative (B) (Eq. [10]) (35), the corresponding pentenyl system (C,D) yields the β,γ-unsaturated isomer as a thermodynamic product (Eq. [11]) (31).

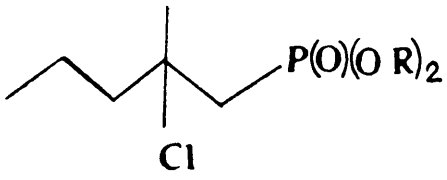


(A) (B) [10]



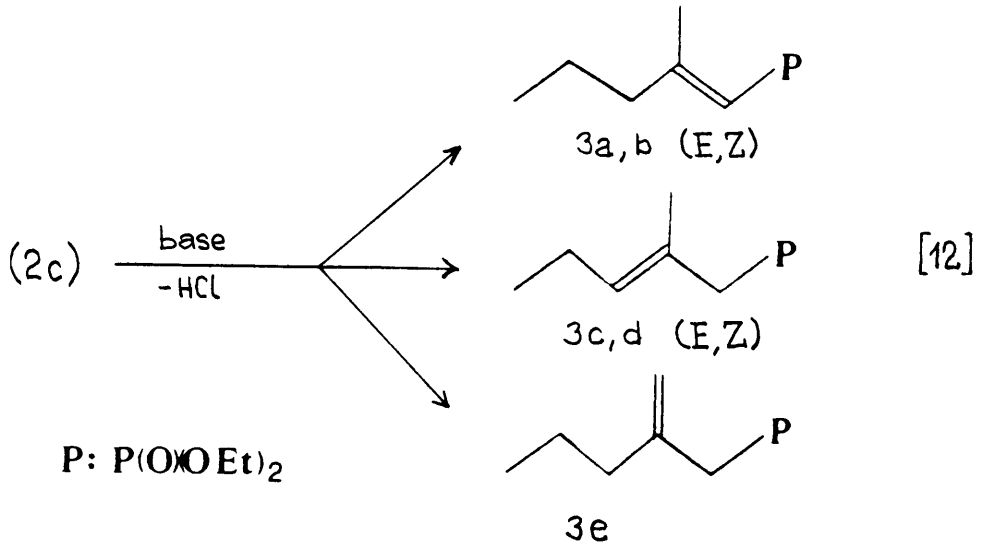
(C) (D) [11]

In this work we attempted to synthesize the diester of 2-chloro-2-methylpentylphosphonate (2c) and to study the course of the base-promoted dehydrohalogenation of this substrate.



(2c)

Elimination of HCl from a molecule of 2c can, in principle, lead to three isomeric unsaturated phosphonates, two of which can exist as a pair of geometrical (E/Z) isomers (Eq. [12]).



[12]

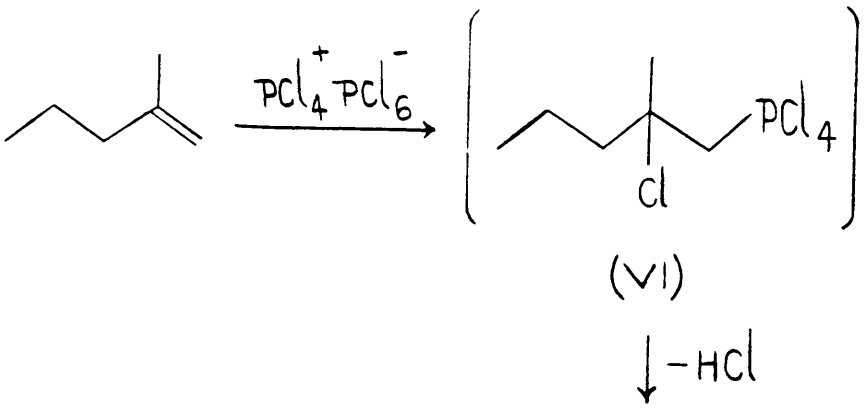
Phosphonates 3a,b 3c,d and 3e differ with respect to the number of carbon atoms and the phosphoryl group directly attached to the olefinic function, as well as the number of allylic hydrogen atoms. Since these three isomeric compounds can be mutually interconvertible via the prototropic equilibrium, we were interested in the determination of their relative abundance under conditions of kinetic and thermodynamic control.

CHAPTER 2 : RESULTS AND DISCUSSION

2.1 THE ATTEMPTED SYNTHESIS OF 2-CHLORO-2-METHYL-PENTYLPHOSPHONIC DICHLORIDE

The product of the reaction of 2-methyl-1-pentene with PCl_5 and P_2O_5 (9) was obtained as a colourless liquid in high yield (70-80%). The liquid is perfectly stable at 4°C but decomposes slowly at room temperature and when exposed to air.

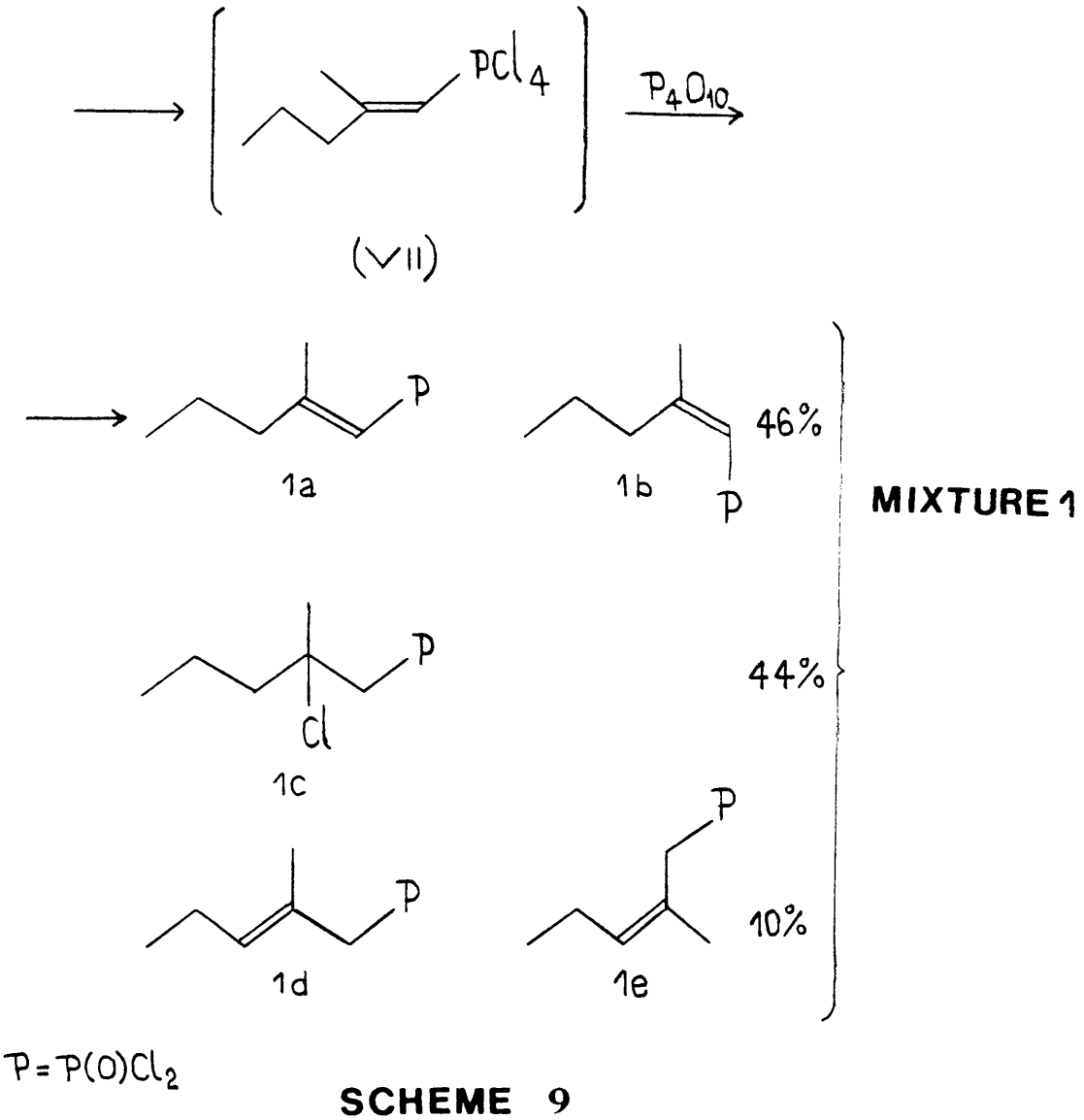
EVIDENCE FOR STRUCTURE. On the basis of ^1H and ^{31}P nmr data it was found that the product of the reaction of 2-methyl-1-pentene with PCl_5 and P_2O_5 in benzene was a mixture (Mixture 1) of five compounds. The reaction takes place according to Scheme 9.



(VI)

↓ -HCl

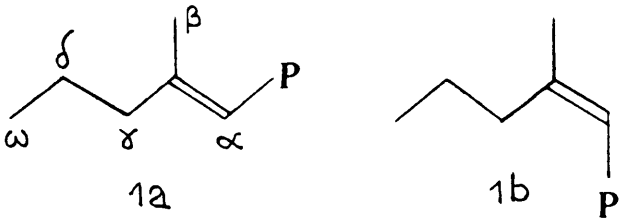
Scheme 9 continues



SCHEME 9

The initial addition of PCl_5 takes place regiospecifically to give an intermediate (VI) (not isolated). This primary adduct is unstable and eliminates HCl to give an α,β-unsaturated phosphonic acid tetrachloride (VII) (also not isolated). Further treatment with P_2O_5 leads to the formation of α,β-unsaturated phosphonic dichlorides (E/Z) (1a,1b) (46%), 2-chloro-2-methylpentylphosphonic dichloride (1c) (44%) and β,γ-unsaturated phosphonic dichloride (E/Z) (1d,1e) (10%). The mixture gave the ^1H nmr spectrum showing characteristic signals of the compounds

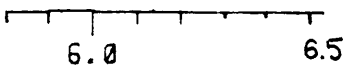
obtained with the expected integration, and the ^{31}P nmr spectrum consisting of five singlets (clearly showing the presence of five phosphorus containing compounds). The low field ^{1}H doublet and triplet for the α,β- and β,γ-unsaturated phosphonic dichloride vinylic protons respectively, are shown in Figure 1.



1a

1b

P=P(O)Cl$_2$



α-CH, δ: 5.86 ppm, J_{H-P} = 38.36 Hz

Fig. 1 continues

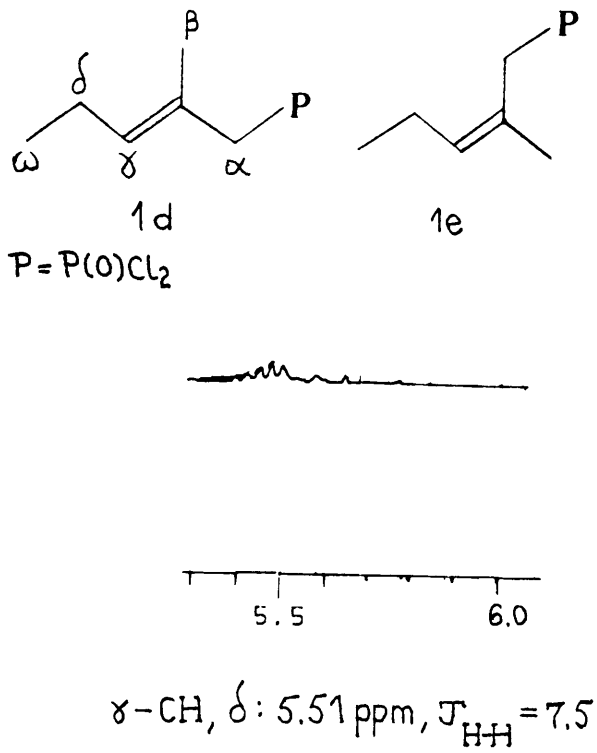


Fig. 1: The α-CH (1a,1b) and γ-CH (1d,1e) resonances from the ^1H nmr spectrum of Mixture 1

The doublet at δ 5.86ppm is due to coupling of the vinylic hydrogen with P (J_{H-P} =38.36Hz) in compounds 1a,1b. At δ 5.51ppm a very small triplet can be observed, this being due to coupling of the vinylic hydrogen with the adjacent CH_2 (J_{H-H} =7.5Hz) in compounds 1d,1e. The low field position of the doublet is explained by the presence of a very strongly electronegative $POCl_2$ group (36) which exerts a deshielding effect on proton α in 1a and 1b.

The fact that the components of this particular mixture belong to the same family of organophosphorus compounds

(phosphonic dichlorides) allowed the integration of ^{31}P nmr signals, thus a quantitative measure concerning each compound in the mixture was obtained (Fig. 2).

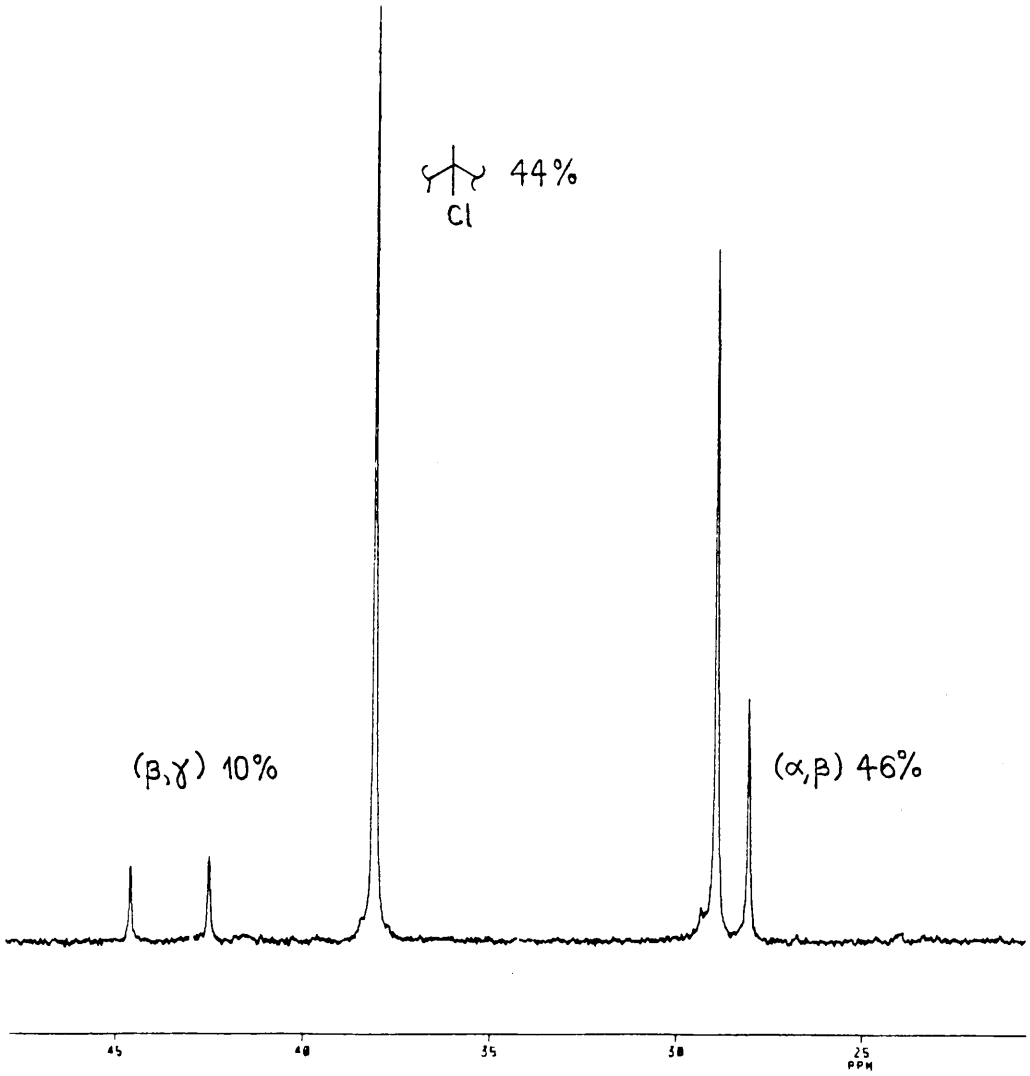


Fig.2: ^{31}P nmr spectrum of Mixture 1

Therefore, a ~1.3:1 mixture of unsaturated chlorides and the 2-chloro (uneliminated) precursor was obtained. It is interesting to notice that the E and Z isomers always appear close to each other in the ^{31}P nmr spectra, but at this early stage of the project it could not be decided which peak corresponds to E or Z isomer. This problem was elucidated later and is explained in Chapter 2 (2.3.1.4).

Since the initial aim was to prepare pure 2-chloro-2-methylpentylphosphonic dichloride, attempts to modify the reaction conditions were made (See Experiment 3.2.12). However, the new reaction conditions used failed to give the expected compound and a similar mixture (Mixture 1a) of uneliminated chloride, α,β- and β,γ-unsaturated compounds was obtained (Fig. 3).

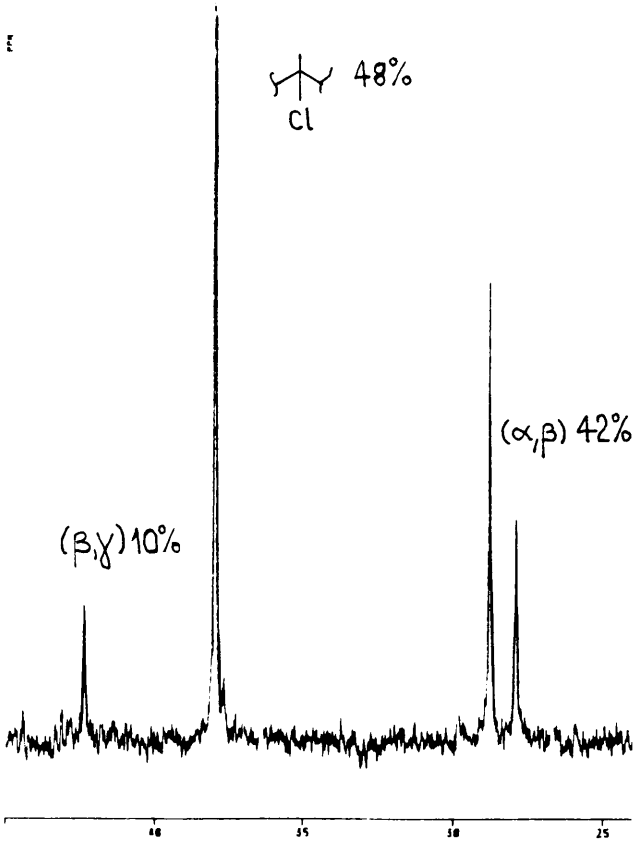


Fig.3: ^{31}P nmr spectrum of Mixture 1a

In the next step, thermal elimination of HCl in Mixture 1a in two different solvents (benzene and CCl_4) was tried. The progress of the reaction was followed by ^{31}P nmr spectroscopy and it was found that after 95h the reaction proceeded very slowly to give only slightly more of α,β-unsaturated phosphonic dichloride than in the initial mixture.

Another attempt was to separate compounds in Mixture 1 by bulb-to-bulb distillation. Since the α,β - and β,γ-unsaturated compounds have a lower molecular weight than the uneliminated chloride (hence should be more volatile), we expected to collect them in the first fraction. The product of the distillation was, however, a mixture of five compounds (Mixture 1b) (Fig. 4) but the amount of uneliminated chloride decreased relatively in favour of the α,β-and β,γ-unsaturated compounds. Therefore, it is possible that the vacuum applied was more effective than thermal elimination in assisting the formation of the unsaturated compounds.

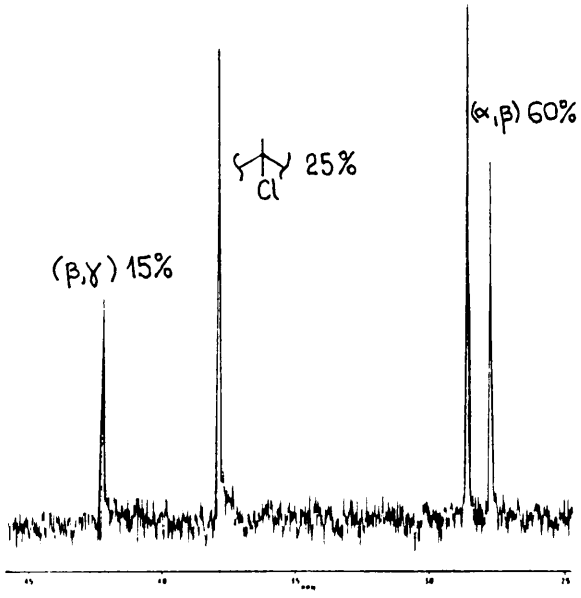


Fig. 4: ^{31}P nmr spectrum of Mixture 1b

2.2 THE ESTERIFICATION REACTION OF ALKENYLPHOSPHONIC DICHLORIDES

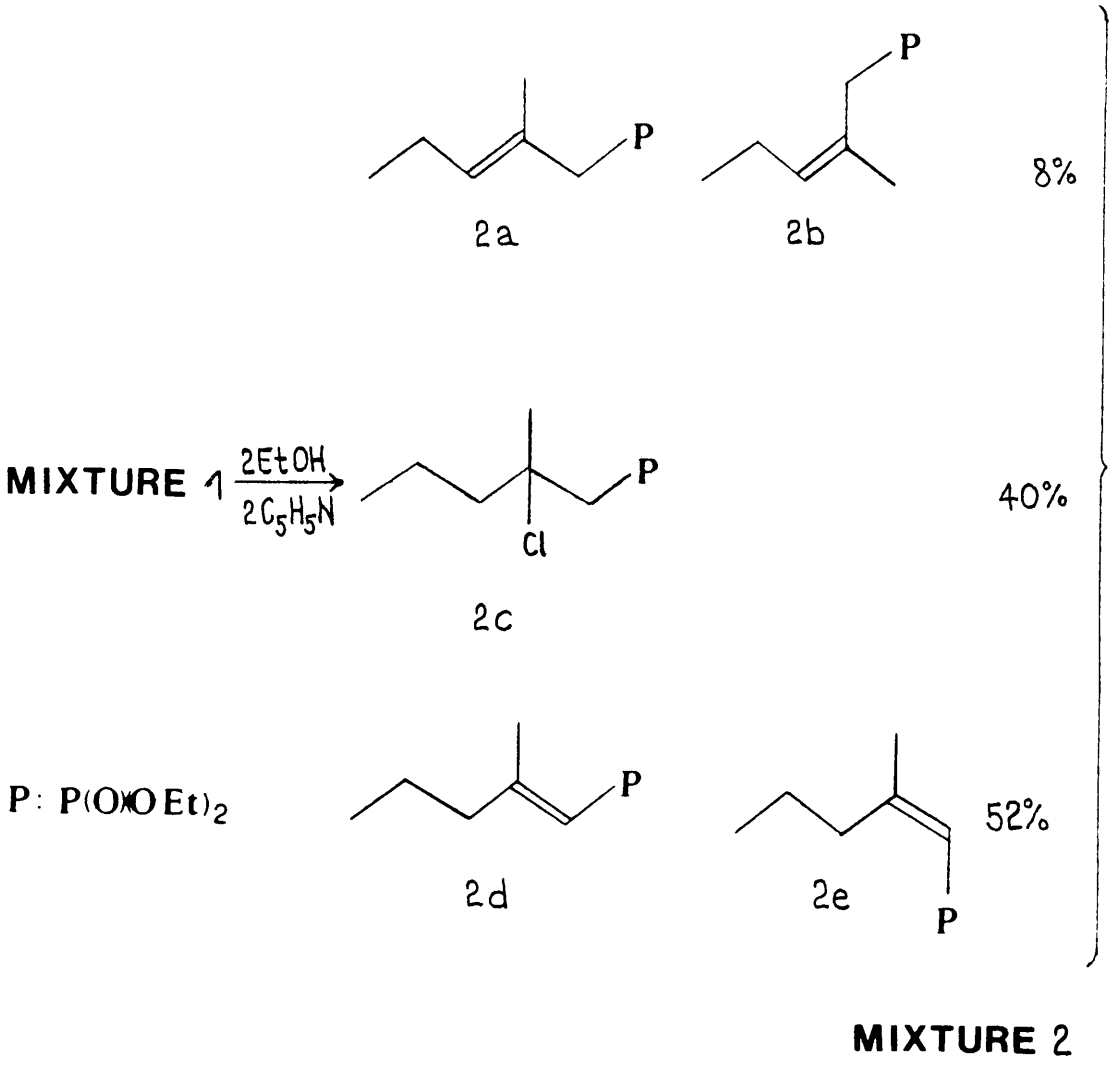
The experiments carried out up to this point showed that pure 2-chloro-2-methylpentylphosphonic dichloride could not be obtained from 2-methyl-1-pentene and PCl_5. Instead, under the reaction conditions used a mixture of five products was always obtained. It follows that the next step (the esterification reaction) should most certainly give a mixture of phosphonic esters.

Vinylphosphonates have been previously synthesized and characterized by a number of authors (31, 37-39); however, the compounds prepared in this project have not been made before. ^{1}H and ^{31}P nmr spectra of vinylphosphonates have also been the subject of numerous studies and the literature survey done clearly shows the interest in these particular compounds (40-49).

A closely related example is the synthesis of phosphonic diester starting from 2-methylpropene (9). Whereas the authors report the formation of one compound only, in the present work it was found that a mixture of five compounds was the outcome of the reaction sequence.

Using the required molar quantity of ethanol and base (2mol equiv.), Mixture 1 was converted into Mixture 2 according to

Scheme 10. The reaction product was obtained as a colourless liquid in a 80% yield and it proved to be both thermally and hydrolytically stable.



SCHEME 10

The ^{31}P nmr spectrum clearly shows the presence of 5 compounds in this mixture (Fig. 5).

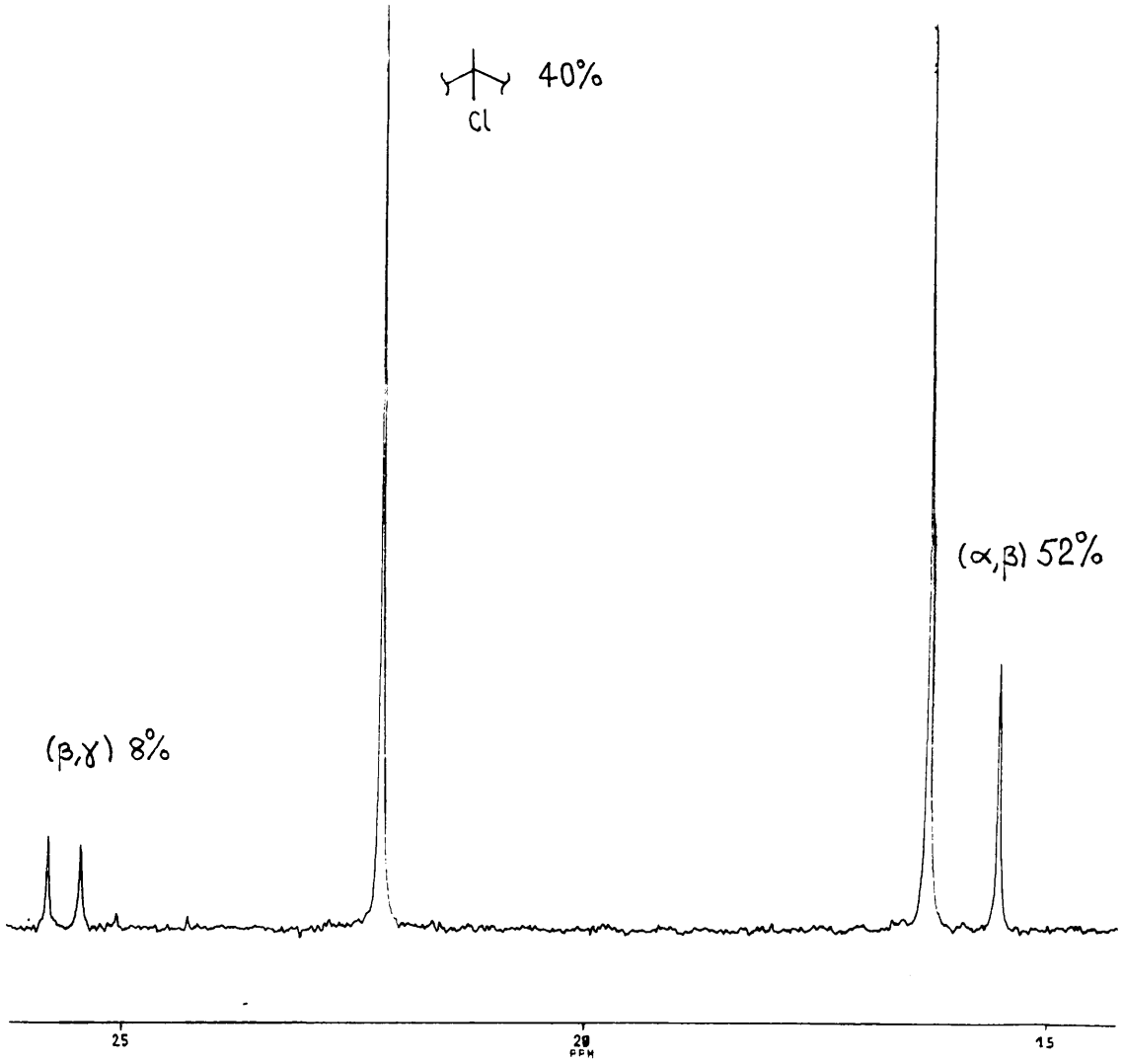
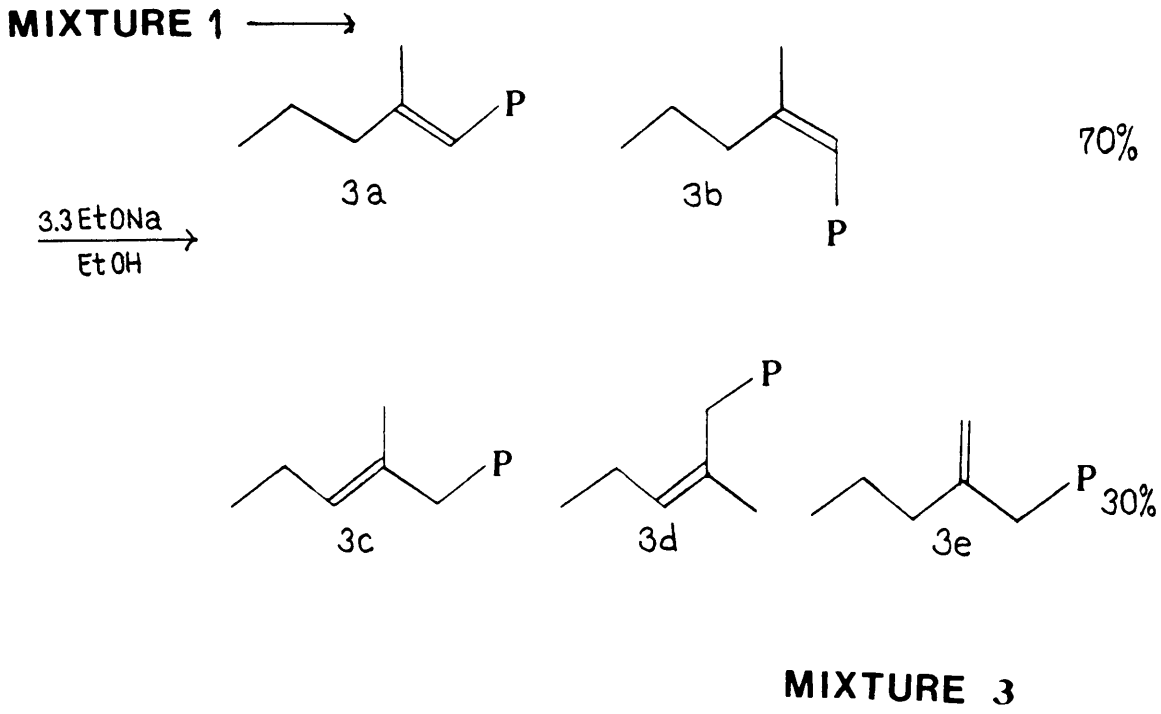


Fig. 5 : ^{31}P nmr spectrum of Mixture 2

There is virtually no change in the composition of the phosphonate mixture and only a slight increase in the α,β-unsaturated product (6%) was noticed. This result indicates that the only reaction that takes place is substitution at phosphorus, resulting in the exchange of two chlorine atoms

by two ethoxy groups. However, when Mixture 1 was treated with stronger base, such as alkoxide ion, only the α,β- and β,γ-unsaturated products were obtained (Scheme 11).



SCHEME 11

A first conclusion is that pyridine is too weak a base to bring about the dehydrohalogenation reaction or any isomerisation of the α,β- to β,γ- or β,γ- to α,β-unsaturated products. When a stronger base, such as EtONa was used, total elimination of HCl took place to give exclusively the α,β- and β,γ-unsaturated compounds.

A new feature of the ^{31}P nmr spectrum of Mixture 3 is the appearance of an extra peak at δ 24.99ppm. This peak was assigned to a β,γ'-unsaturated product which can be formed by isomerisation of the α,β-unsaturated compound (Fig. 6).

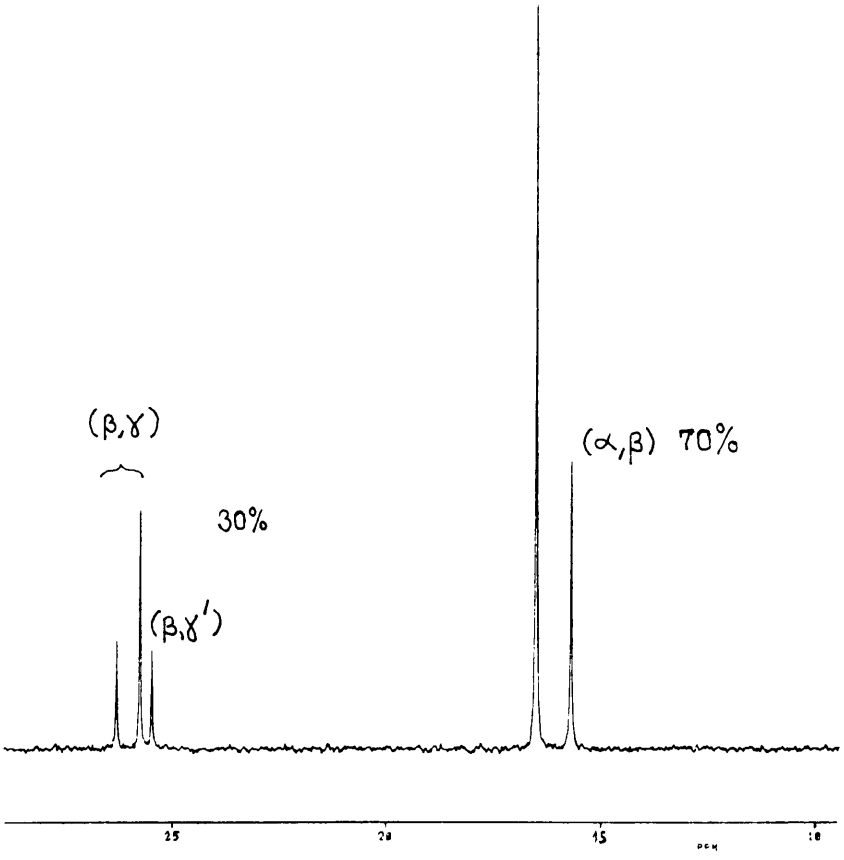
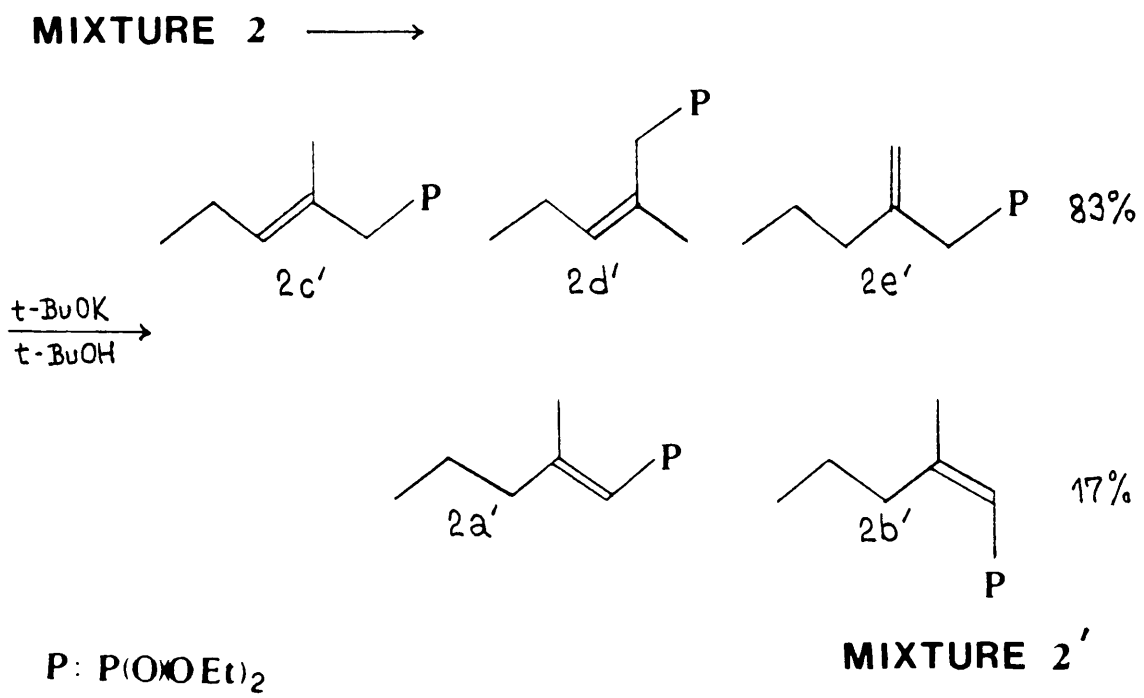


Fig. 6 : ^{31}P nmr spectrum of Mixture 3

When Mixture 2 was incubated at 30°C in t-BuOK/t-BuOH for 70h, complete elimination of HCl followed by isomerisation of α,β - to β,γ -unsaturated phosphonates took place to give a ~(5:1) (β,γ:α,β) mixture of compounds (Scheme 12) (Fig. 7). Similarly, when Mixture 3 was incubated at room temperature in EtONa/EtOH for 70h, isomerisation to β,γ-unsaturated compounds in a (2:1) (β,γ: α,β) ratio was the outcome of the reaction (Scheme 13) (Fig. 8).



SCHEME 12

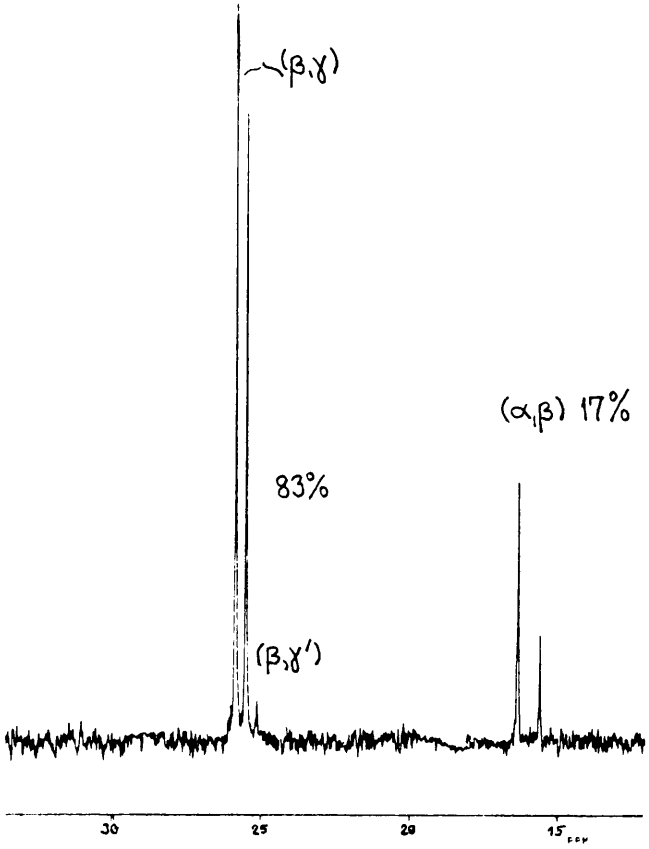
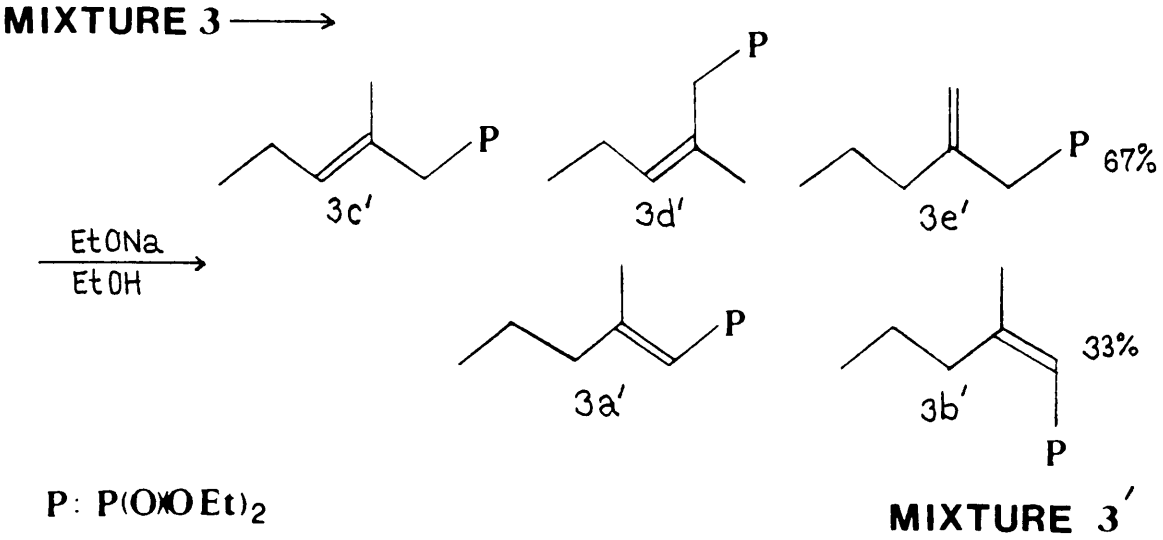


Fig. 7 : ^{31}P nmr spectrum of Mixture 2'



SCHEME 13

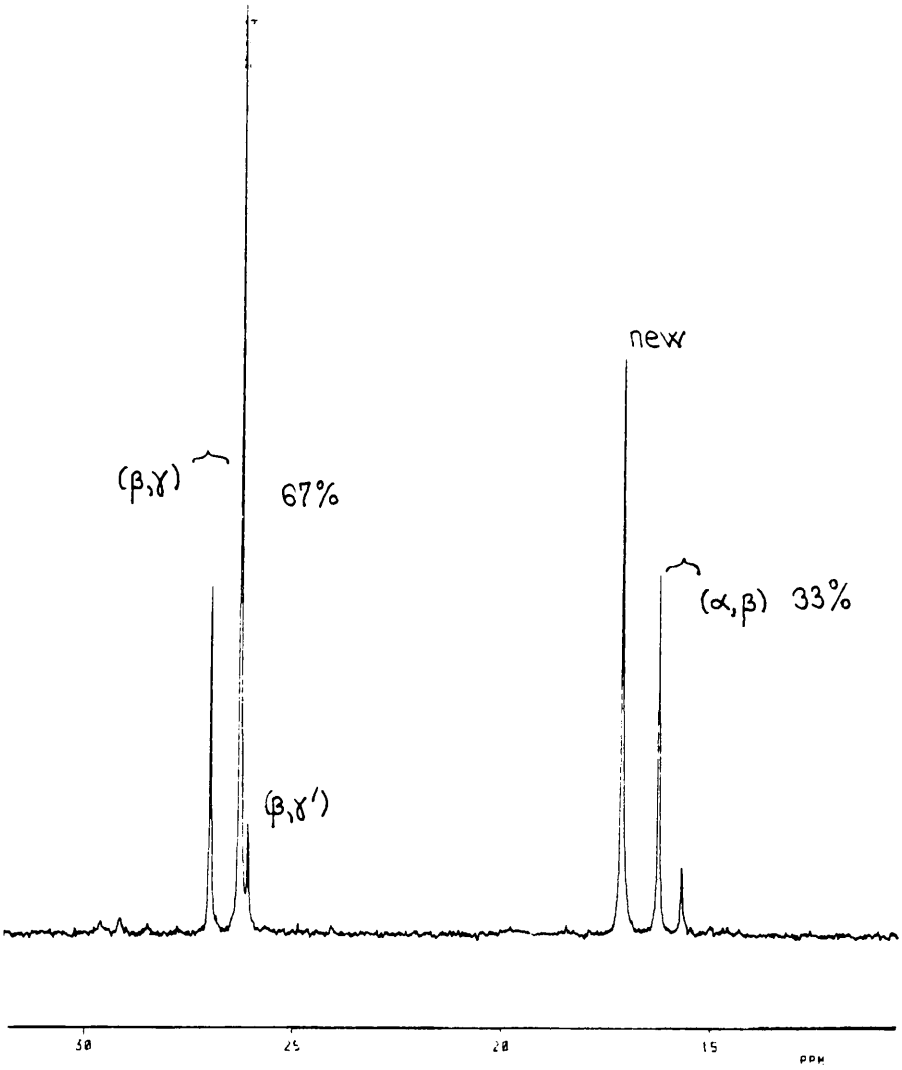
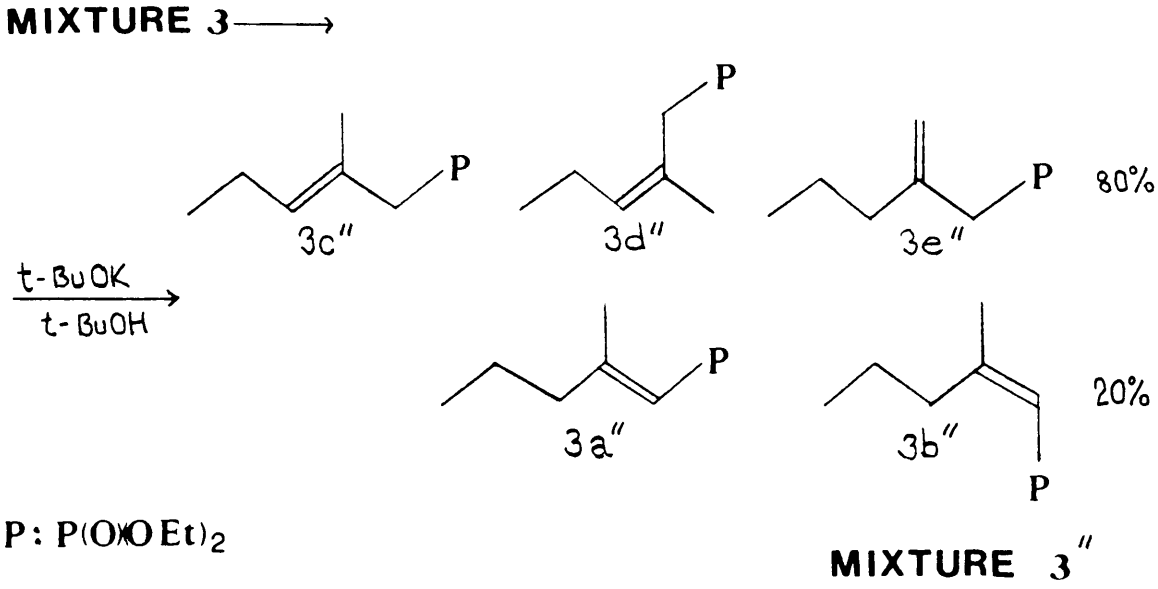


Fig. 8 : ^{31}P nmr spectrum of Mixture 3'

The new peak appearing at δ 17.09ppm was shown to be derived from the dealkylation reaction (formation of this product is given on page 77). The formation of the dealkylation compound can be easily eliminated by using a t-BuOK/t-BuOH mixture as the basic system for the isomerisation reaction. Thus, when Mixture 3 was treated with 1.2mol equiv. t-BuOK/t-BuOH at R.T. for 30h a (4:1) mixture of (β,γ : α,β) unsaturated phosphonates was obtained (Scheme 14) (Fig. 9).



SCHEME 14

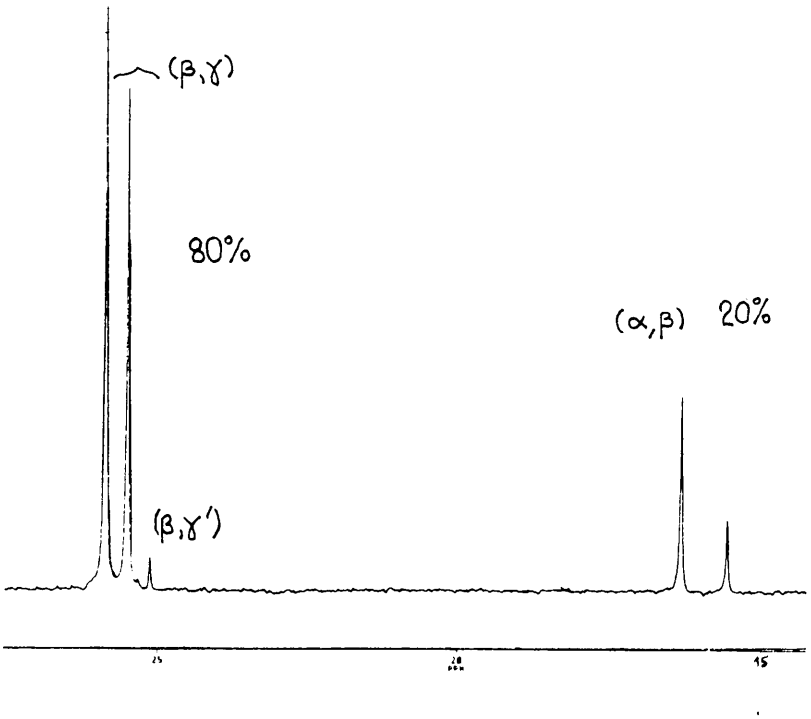
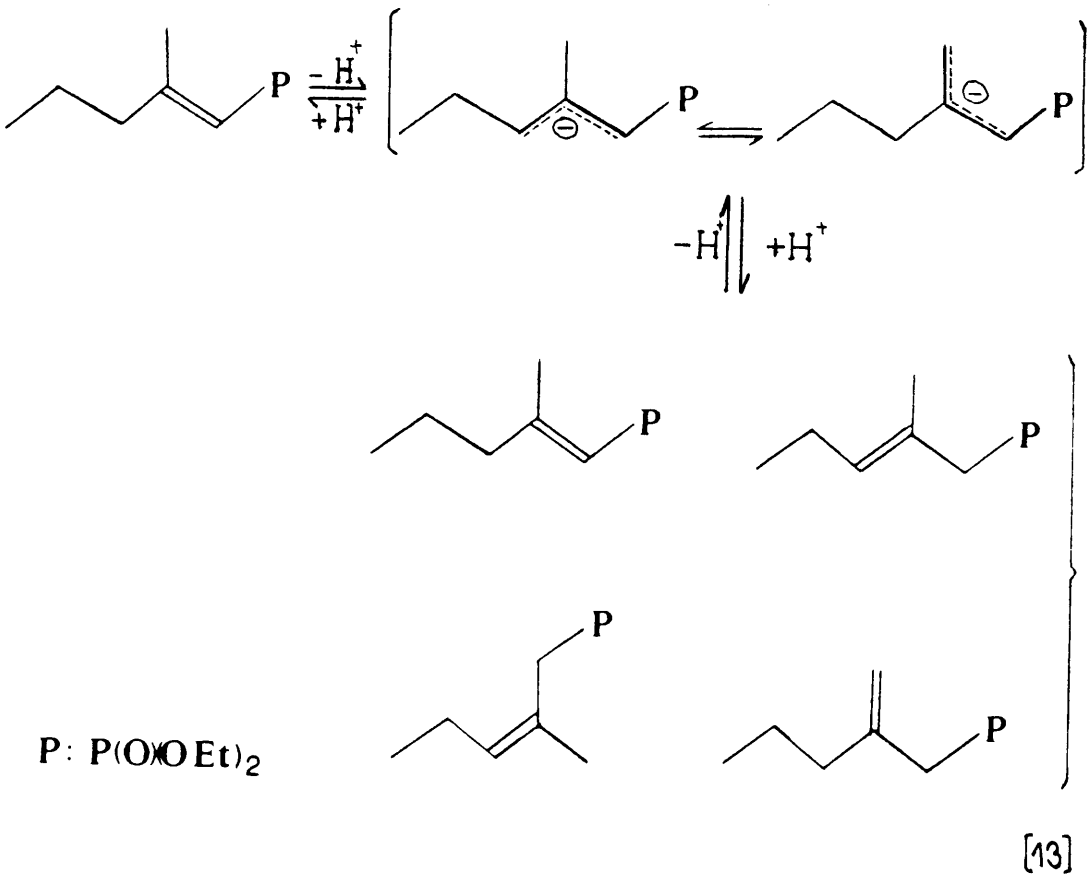


Fig. 9 : ^{31}P nmr spectrum of Mixture 3"

From the above experiments it is clear that isomerisation attempts gave always mixtures of α,β- and β,γ-unsaturated compounds. The present findings are consistent with the results obtained by Ionin and Petrov (50) who reported for diethyl butenylphosphonate the formation of an equilibrium mixture consisting of both α,β- and β,γ-isomers (ratio 1:3). In the case of α,β-unsaturated phosphonic bisamides, $Pr-CH=CH-P(O)(NR_2)_2$, which have also been studied in our laboratory (51), it was found that no isomerisation to β,γ-products took place. This fact was attributed to the weak acidity of the γ-protons which could not be abstracted by the bases used (MeONa/MeOH; t-BuOK/t-BuOH; LDA).

It it obvious that the α,β- and β,γ-unsaturated phosphonates correspond to the kinetic as well as the thermodynamic products of reaction. It is only the ratio in which they are formed that differs. Thus, the kinetic product of the elimination contains more of the α,β-unsaturated isomer, while the thermodynamic one contains more of the β,γ-unsaturated compound.

Isomerisation of α,β- to β,γ-unsaturated phosphonates proceeds via the allylic carbanion intermediate (VIII) according to the following Equation 13.

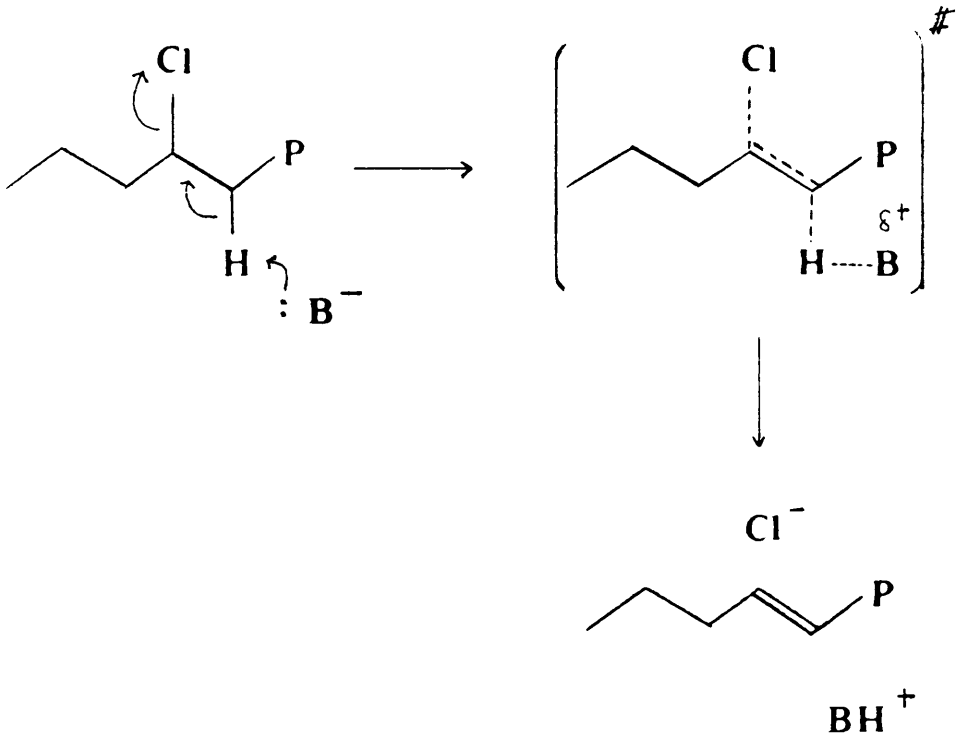


[13]

In the present study, the esterification reaction was carried out also by means of methanol, and results similar to those already discussed for the diethyl pentenylphosphonates were observed.

2.2.1 Elimination Reactions and Hyperconjugation Effects in Diethyl Alkenylphosphonate Mixtures

With an unbranched system (31) base-induced elimination of HCl from the halide takes place via an E2 mechanism to give almost pure α,β-unsaturated phosphonate (Scheme 15).

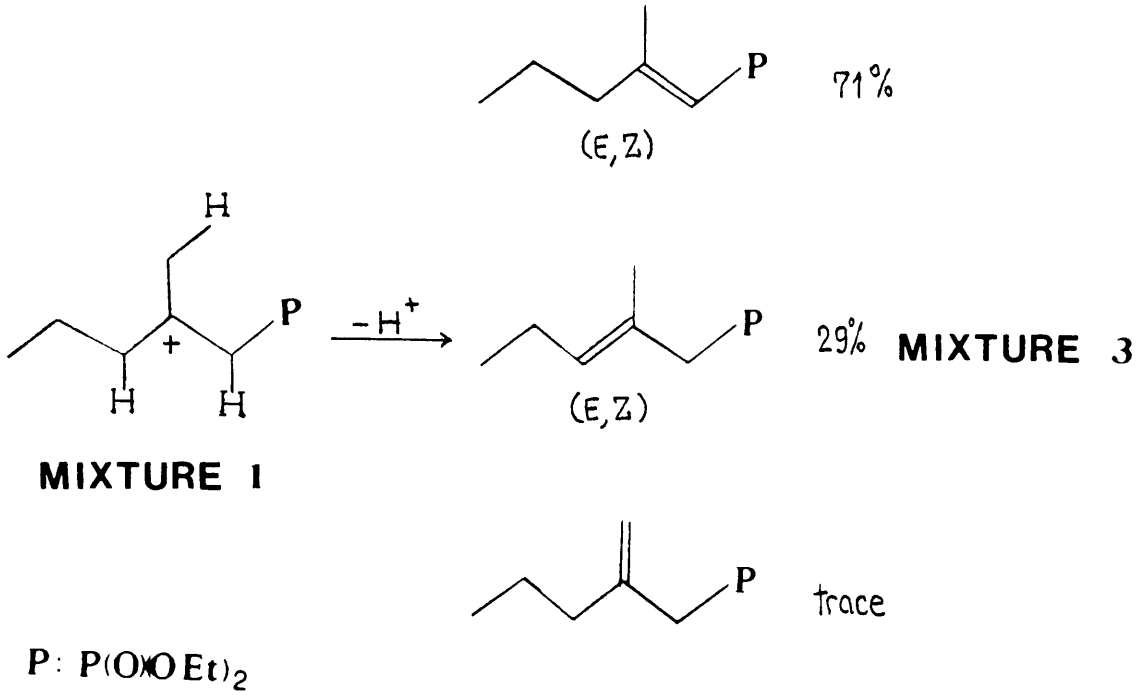


P: $P(O)(OEt)_2$

B: EtO^-

SCHEME 15

The presence in the substrate of an alkyl group that can give rise to relatively stable carbocation, promotes unimolecular elimination. Thus, with alkyl halides, increasing E1 elimination occurs along the series: primary < secondary < tertiary. This sequence reflects the relative stability of the resultant carbocations. Consequently, primary halides almost never undergo E1 elimination (52). It, therefore, follows that elimination of HCl from 2-chloro-2-methylpentylphosphonic ester may take place via an unimolecular solvolytic elimination mechanism according to Scheme 16.



SCHEME 16

Three isomeric products, two of which exist as (E/Z) isomers, were obtained in the above transformation (Mixture 3). When base-catalysed prototropic isomerisation was carried out (t-BuOK/t-BuOH), a new mixture was formed (Mixture 3") (Scheme 14). These results are summarised in Table 1.

Table 1. Product Mixtures 3 and 3"

ISOMERS	MIXTURE 3 % (kinetic)	MIXTURE 3" % (thermodynamic)
(α,β)(E,Z)	71	20
(β,γ)(E,Z)	29	80
(β,γ')	trace	trace

In the kinetic mixture α,β- and β,γ-unsaturated isomers are the major products as compared to β,γ'-isomer which appears as a trace only. This fact can be easily explained by the Zaytsev rules (52) which state that the alkene bearing most alkyl substituents on the double bond carbons will predominate.

As far as the thermodynamic mixture is concerned the same trend as above is observed. However, one has to account for the fact that β,γ-isomer appears as the major component in

the equilibrium mixture. It was found that hyperconjugation effects are to a high degree responsible for this order of preference. Hyperconjugation is dependent on the presence of a hydrogen atom on the carbon atom α- to the unsaturated system. Thus, in the thermodynamic mixture there are seven "hyperconjugable" α-hydrogen atoms in the β,γ-unsaturated isomer compared to five α-hydrogen atoms in the α,β-unsaturated isomer. This results in the preferential formation of the former compound.

The number of carbon atoms attached to the olefinic function may also have an influence on the stability of the product. Thus, the β,γ-unsaturated isomer has three carbon atoms directly bonded to the unsaturated system, while the α,β-unsaturated isomer has only two such carbon atoms.

Similar comparisons were made for different alkenyl phosphonate systems which have been subsequently synthesized in our laboratory. Most of the data obtained is collected in Table 2, the sixth entry being Mixture 3" already discussed. The number of phosphonate groups (one or nil) present on the olefinic function has also been taken into account (53).

When Δ (1,2-2,3) was calculated for each product, two different trends were observed. It was found that a (1,0,1) entry is specific of a mixture consisting of major α,β- and minor β,γ-unsaturated isomer, while (-2,-1,1), (-7,-2,1), and (-3,-1,1) entries are specific of a major β,γ-unsaturated

isomer in a mixture. It is, therefore, clear that hyperconjugation accounts for greater thermodynamic stability of alkenes in which the double bond is not terminal.

Table 2: Prototropic Equilibria of Diethyl Alkenylphosphonates (t-BuOK/t-BuOH, 25°C)

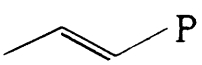
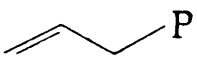
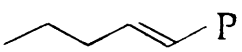
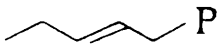
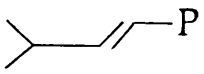
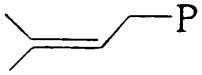
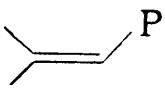
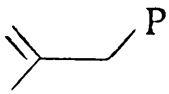
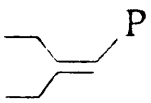
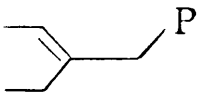
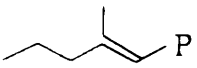
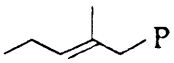
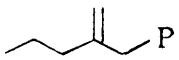
	1,2	2,3	Δ (1,2 - 2,3)
			
%	100	0	
# H, C, P	3, 1, 1	2, 1, 0	1, 0, 1
			
%	10.3 (10.9% add)	78.8	
# H, C, P	2, 1, 1	4, 2, 0	-2, -1, 1
			
%	0.9	99.1	
# H, C, P	1, 1, 1	8, 3, 0	-7, -2, 1
			
%	80.0	20.0	
# H, C, P	6, 2, 1	5, 2, 0	1, 0, 1

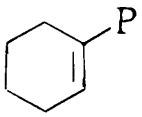
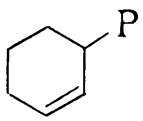
Table 2 continues

%	4.4	95.6		
# H, C, P	4, 2, 1	7, 3, 0		-3, -1, 1

%	12.0	84.1	3.9	
# H, C, P	5, 2, 1	7, 3, 0	4, 2, 0	-2, -1, 1 ; 1, 0, 1

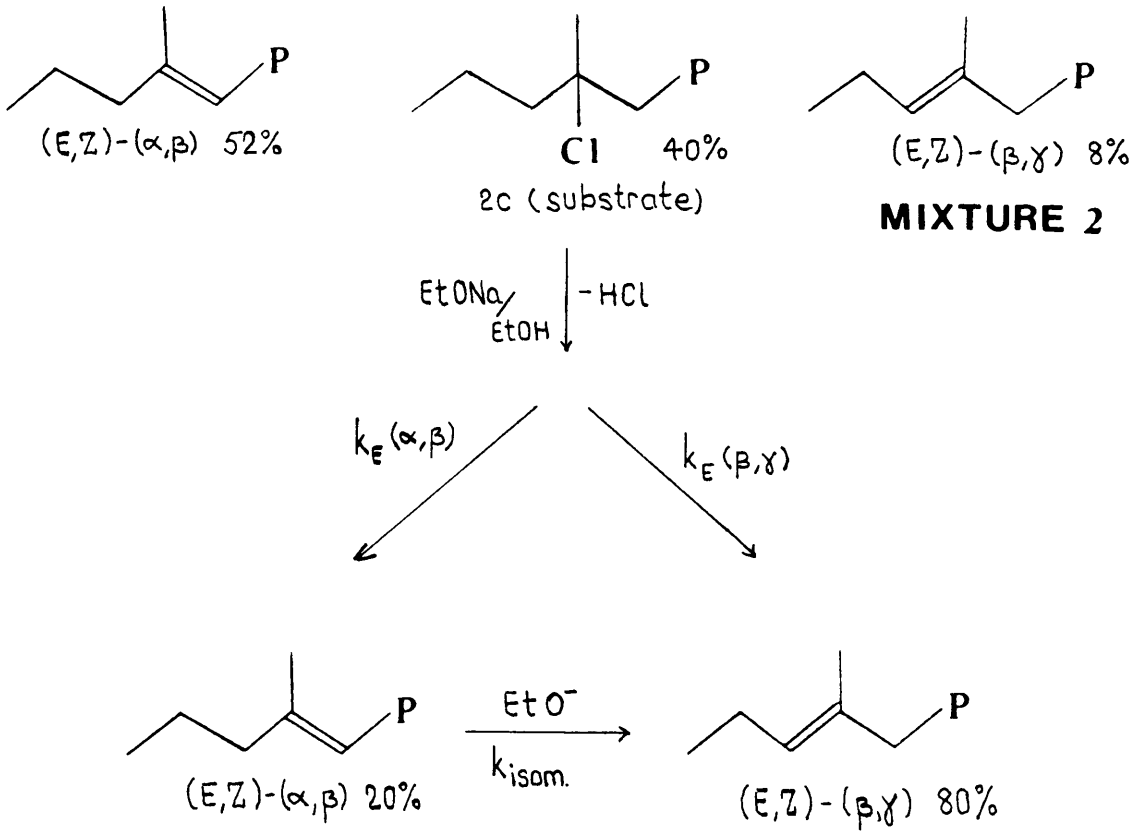



%	95.0	5.0	
# H, C, P	4, 2, 1	3, 2, 0	1, 0, 1

2.2.2 The Conversion Versus Time Study Involving Diethyl Alkenylphosphonate Mixtures

It has been found that when Mixture 1 was treated with an ethanol/pyridine system (2M solution) esterification took place to give a product consisting of five compounds (Mixture 2). When Mixture 1 was treated with EtONa/EtOH,

complete elimination of HCl took place to give solely α,β- and β,γ-unsaturated phosphonates (Mixture 3). However, a more indepth study was undertaken in order to find out more about the progress of the elimination reaction. Therefore, Mixture 2 was further treated with a 2.2M solution of EtONa/EtOH and the reaction was carried out for 120h (Scheme 17).



P: $P(O)OEt)_2$

SCHEME 17

^{31}P nmr spectroscopy was selected to monitor the substrate disappearance and product appearance during the course of the reaction. The data obtained was gathered in a concentration-time plot (Fig. 10) from which the following observations were made:

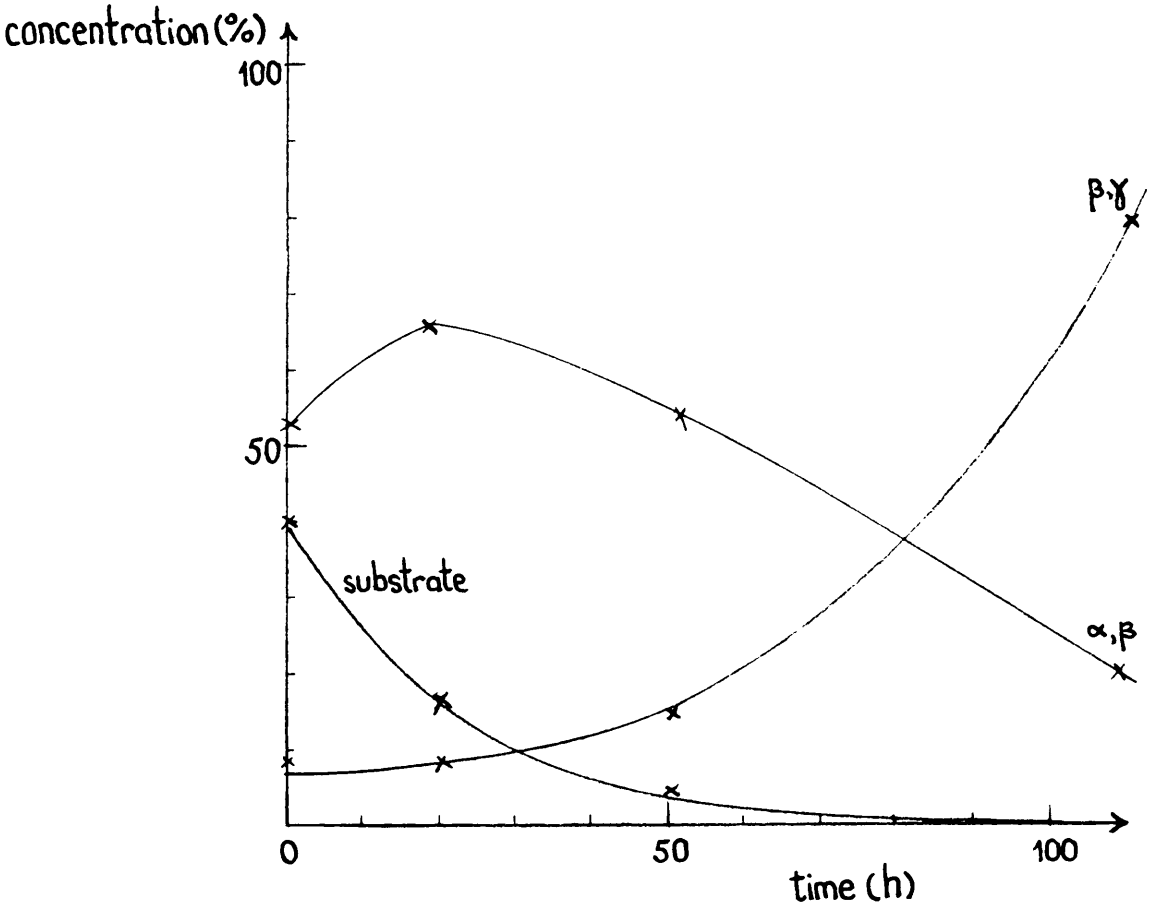


Fig. 10 : The concentration-time plot for the substrate and products obtained from the reaction of Mixture 2 with 2.2M EtONa / EtOH at 25°C

a) α,β-unsaturated isomer shows initially a slight increase, followed by a decrease as the reaction progresses.
b) β,γ-unsaturated isomer shows a constant increase and finally crosses the plot for the α,β-isomer.
c) the decrease of the substrate follows the usual profile for the monotonic decay of a reaction substrate.

The first conclusion drawn from this study is that the rate of the formation of the α,β-unsaturated isomer from the substrate is greater than the rate of its isomerisation to the β,γ-product:

$$k_E(\alpha,\beta) > k_{isom.}$$

Also, in the first stages of the reaction the rate of α,β-isomer formation is greater than the rate of β,γ-isomer formation:

$$k_E(\alpha,\beta) > k_E(\beta,\gamma)$$

Meanwhile, β,γ-unsaturated isomer forms gradually at a slow rate. There are two sources for its formation: (i) dehydrohalogenation of the substrate, and (ii) isomerisation of the α,β-compound. The fact that the plots for the α,β- and β,γ-unsaturated isomers cross each other at a certain point means that they are mutually interconvertible. Complete isomerisation to β,γ-compound was not attained, this being an indication that both isomers are always found in equilibrium with one another.

2.2.3 The Chromatographic Determination of the α,β- and β,γ-Unsaturated Phosphonate Mixtures

Attempts were made to separate the two regioisomers present in some of the mixtures obtained using column chromatography techniques. Thus, when a benzene-ethyl acetate solvent system was used for preliminary TLC tests, two distinctive spots indicating the presence of α,β- and β,γ-unsaturated isomers were observed in Mixture 3". However, when the mixture was chromatographed on a silica column, the compounds failed to give satisfactory separation.

Several fractions were collected from the column, but only those with similar compositions were combined and distilled on a bulb-to-bulb distillation apparatus. ^{31}P nmr spectra obtained on the different portions collected during distillation showed again a mixture of compounds. It was obvious from the above findings that a more effective method was necessary in order to separate the five compounds obtained. Capillary gas chromatography was the method of choice and eventually the full separation was achieved. A comprehensive description of this chromatographic method is given in Appendix 1.

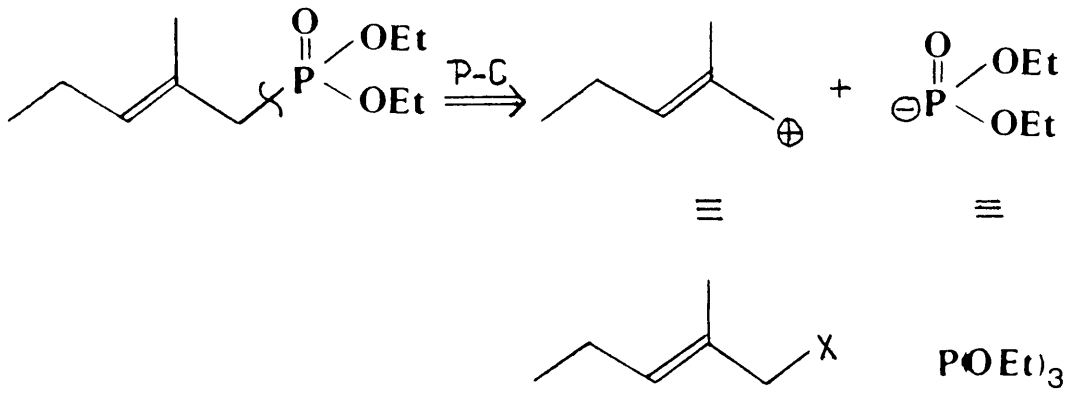
2.3 THE INDEPENDENT SYNTHESIS OF α,β- AND β,γ-UNSATURATED PHOSPHONATES

We have shown that the literature method (9) for preparing phosphonic esters via the addition of PCl_5 to alkenes gave, in the case of 2-methyl-1-pentene, invariably a mixture of products, and the base-catalysed isomerisation did not produce single compounds, but an equilibrium mixture of products. In view of this, we decided to prepare individual compounds of the previously discussed mixtures by independent, unambiguous routes. We intended then to study prototropic equilibria using pure alkenylphosphonates as starting materials.

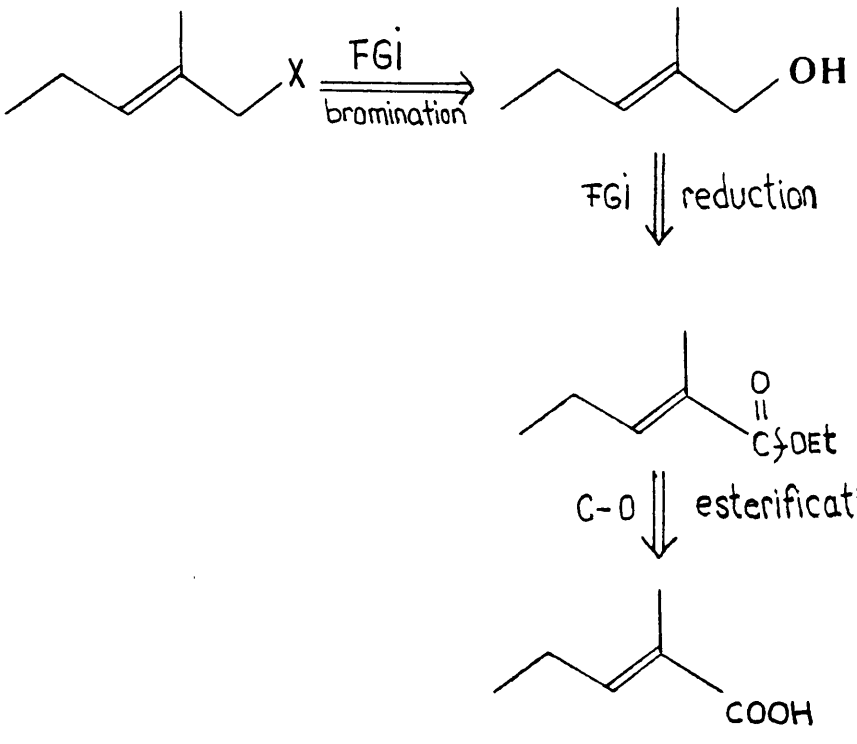
2.3.1 A Retrosynthetic Approach to the Synthesis of E-2-Methyl-2-Pentenylphosphonic Ester

The following disconnection approach was used for this particular synthesis:

ANALYSIS:



[14]

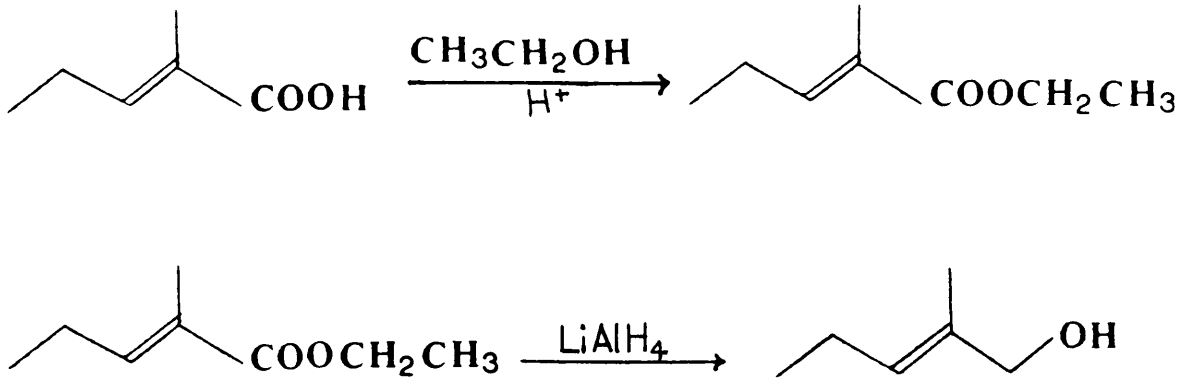


[15]

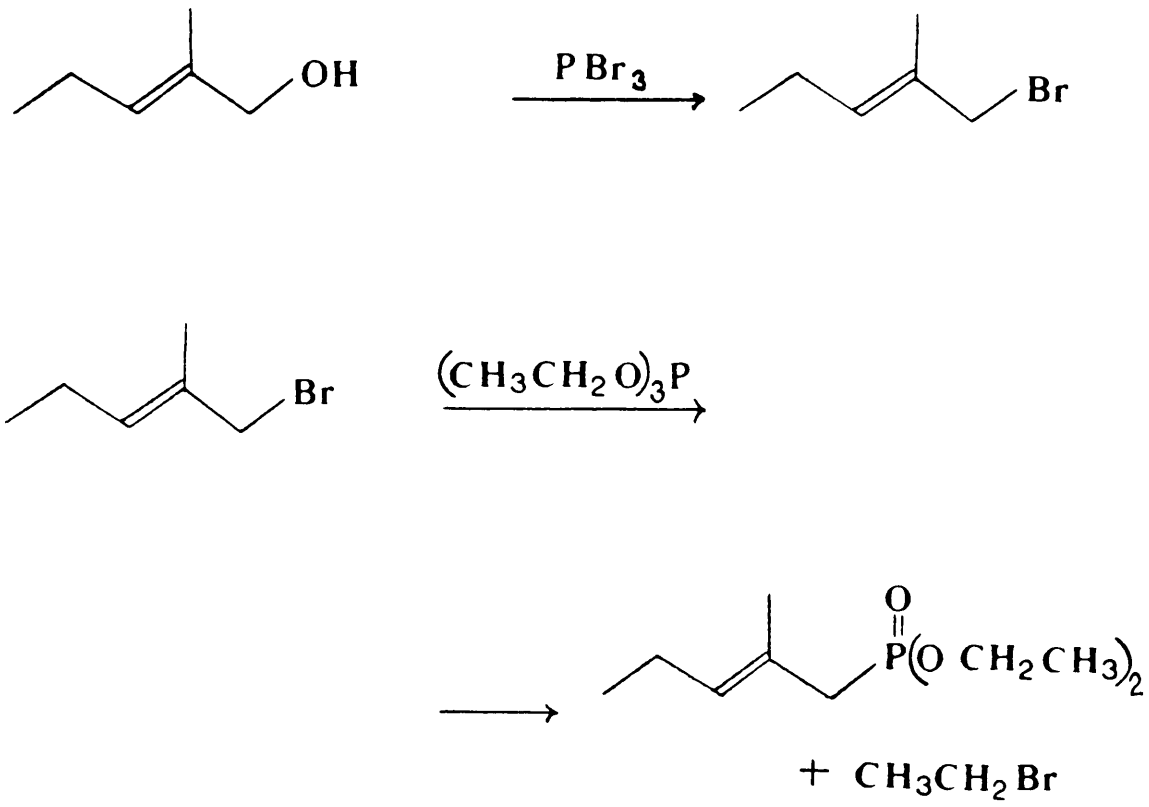
First a bond joining carbon to a heteroatom (P) (Eq. [14]) was disconnected; this approach is fundamental to synthetic design and is a one-group disconnection (54). As usual, the reagent for the cationic synthon is the corresponding halide while for the anionic synthon triethyl phosphite, a commercially available reagent, was chosen. The alkyl halide can be easily made from the corresponding alcohol which, in turn, can be synthesized by reduction of an ester. The latter is obtained from the corresponding carboxylic acid which is also a commerically available compound (Eq. [15]).

Therefore, the following synthetic approach was used in the synthesis of E-2-methyl-2-pentenylphosphonic ester (Scheme 18).

SYNTHESIS:



Scheme 18 continues

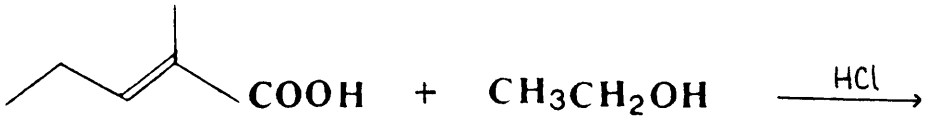


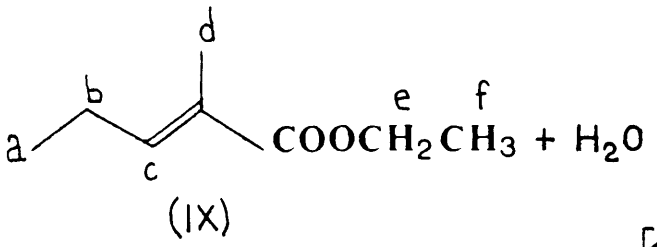
SCHEME 18

Each reaction step in Scheme 18 will be fully discussed in the subchapters that follow, whereas the detailed experimental data will be given in Chapter 3.

2.3.1.1 The synthesis of Ethyl 2-E-Methylpentenoate

The esterification of E-2-methylpentenoic acid was performed using Fisher and Speir method (55) to give a pure product in a good yield (70%) (Eq. [16]).





(IX)

[16]

Thus, the carboxylic acid was treated with ethanol saturated with HCl. The Fisher esterification is one of the best known examples of nucleophilicacyl substitution reactions carried out under acidic conditions. ^{1}H nmr spectrum of compound (IX) showed all the expected signals with the proper integration. On esterification, all signals of the acid moiety moved upfield by ∿0.2ppm while the signals given by

the introduced OEt groups gave the expected multiplets with the right integration. It follows that the triplet at δ 1.27ppm is due to (f) protons, while the quartet at δ 4.16ppm is due to (e) protons (see Appendix 2).

2.3.1.2 The Synthesis of E-2-Methyl-2-Penten-1-Ol

Esters are generally reduced to the alcohol stage quite easily, without side reactions taking place. The classical reducing agent is lithium aluminium hydride and it was discovered by Finholt, Bond, and Schlesinger (56). One of the first studies on reduction of organic compounds (aldehydes, ketones, esters, acid chlorides, and acid anhydrides) by $LiAlH_4$ was done by Nystrom and Brown (57). They have shown that with esters, the reduction proceeded in accordance with Equation 17, to give alcohol in very high yields:

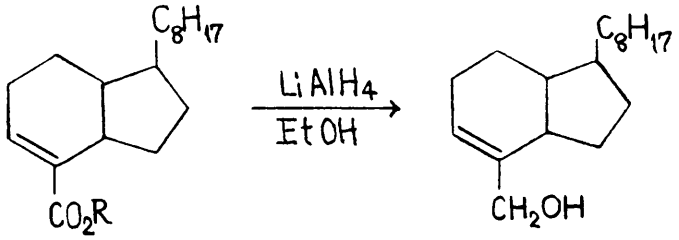
$$2\ RCOOR' + LiAlH_4 \longrightarrow LiAl(OR')_2(OCH_2R)_2 \qquad [17]$$

Although it was pointed out that carbon-to-carbon double bonds in certain unsaturated compounds were hydrogenated by the reagent, Martin, Schepartz, and Daubert (58) obtained

fairly good yield of primary alcohol in the following transformation (Eq. [18]):

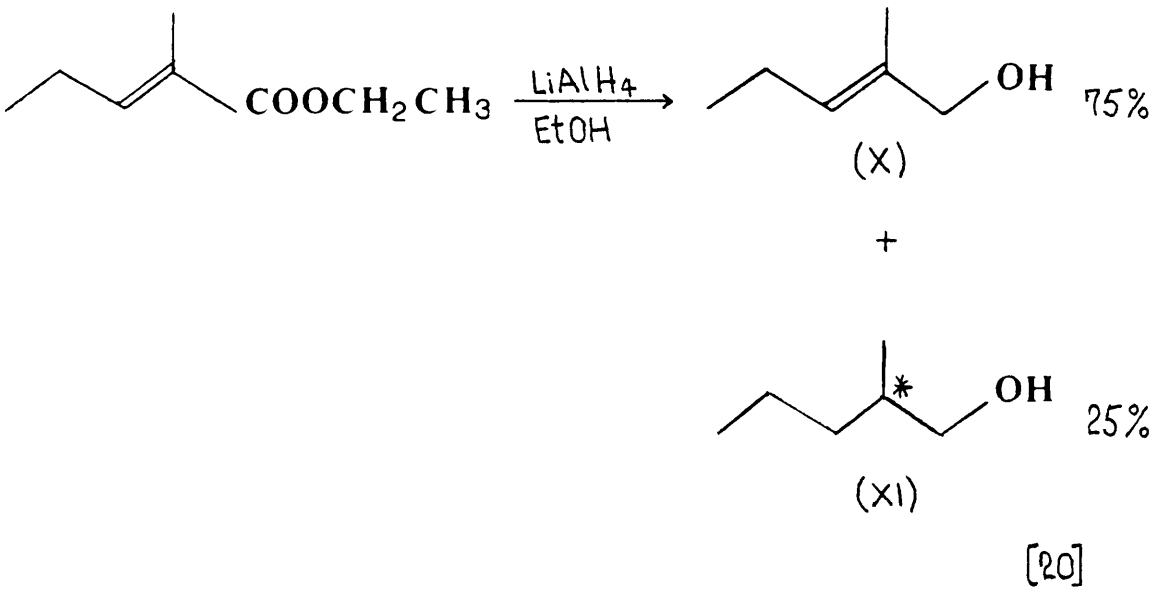
$$R\text{-}CH_2CH{=}CH\text{-}COOC_2H_5 \xrightarrow{LiAlH_4} LiAl(OC_2H_5)_2(OCH_2CH{=}CH\text{-}CH_2R)_2 \xrightarrow[H_2O]{H_2SO_4} R\text{-}CH_2CH{=}CH\text{-}CH_2OH \qquad [18]$$

Later work done by Davidson, Gunther, Waddington-Feather, and Lythgoe (59) contradicted the above findings by showing that reduction of a conjugated ester with $LiAlH_4$ gave only moderate yields of the allylic alcohol (Eq. [19]). They proposed the use of a solution of $LiAlH_4$ to which 1mol of absolute ethanol was added. The effective reagent was presumably lithium aluminium monoethoxyhydride and it proved to be successful for the reduction of other conjugated esters when saturation of the ethylenic link may be a complicating factor.



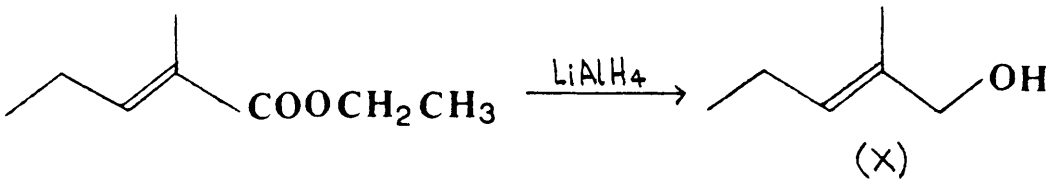
[19]

To some extent, our results proved to be contradictory to the findings of the above-mentioned authors (59). Thus, when a solution of $LiAlH_4$ and absolute ethanol was used, the product was obtained as a mixture of the desired alcohol (X) and the fully reduced compound (XI) (Eq. [20]).

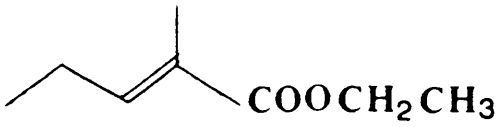


[20]

However, when the method of Nystrom and Brown (57) was used, the allylic alcohol was obtained in good yield (78%) without any trace of compound (XI) (Eq. [21]). In the proton nmr spectrum recorded, the presence of less than 10% of the starting ester was found, but this eventually disappeared in the final step of the synthesis (see Appendix 2).



(X)



(IX) <10%

[21]

2.3.1.3 The Synthesis of E-2-Methyl-1-Bromo-2-Pentene

It has long been recognised that alcohols are converted to alkyl halides by treatment with HX. While the transformation proceeds by a nucleophilic displacement mechanism, different reaction pathways are observed with primary and tertiary alcohols. The following reactivity order has been established:

Tertiary > Secondary > Primary

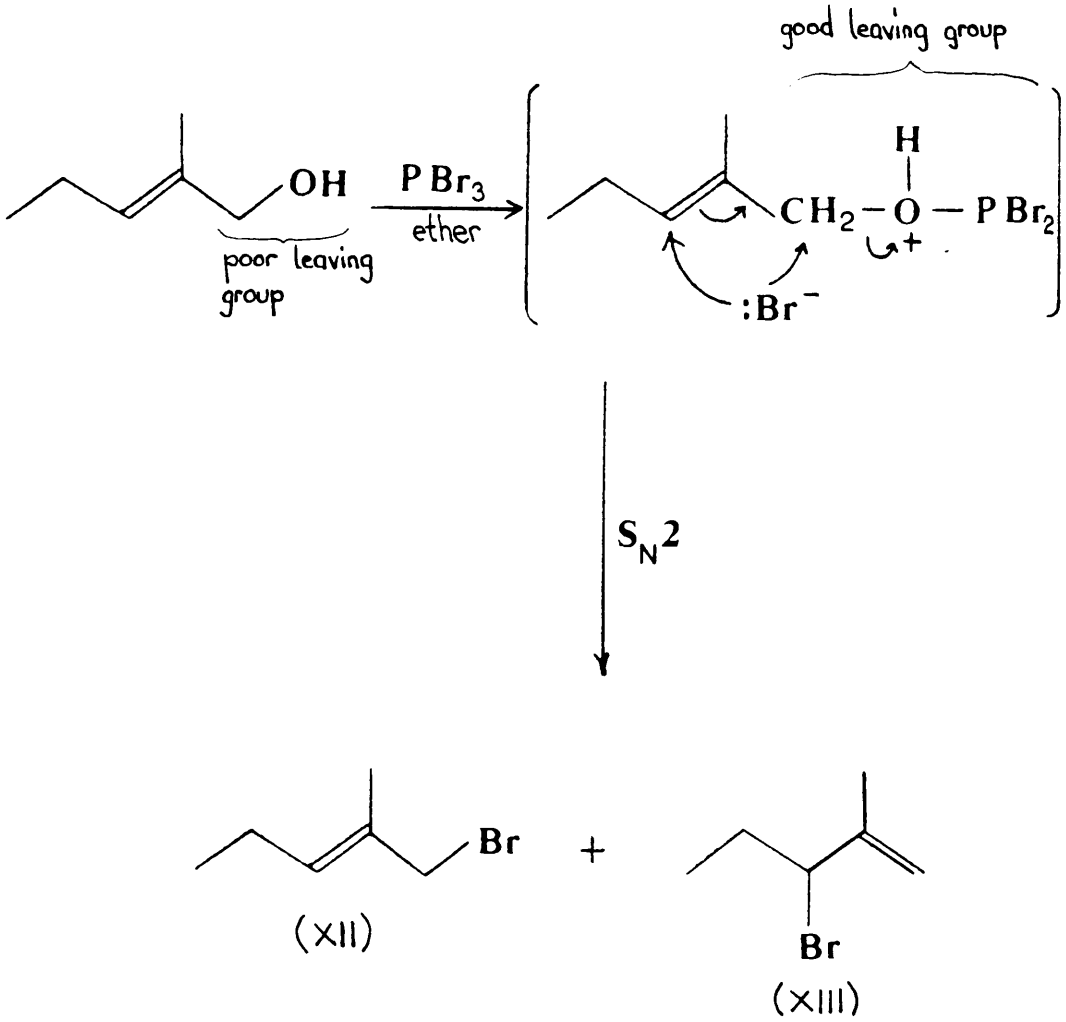
The nucleophilic substitution reaction of halide ions on the protonated alcohol takes place very fast with tertiary alcohols. In this case, a S_N1 process is strongly favoured. Primary alcohols react by a slower S_N2 process, but they can be activated towards displacement by transforming the hydroxyl into a better leaving group (55).

Earlier work done by Young and Lane (60) investigated the composition of butenyl bromides obtained from crotyl alcohol (primary) and methylvinylcarbinol (secondary) by the action of hydrogen bromide or phosphorus tribromide. Using mainly refractive index measurements, they have established that not only does the composition of products actually differ from method to method, but also the product obtained from the primary alcohol is different from that obtained from the secondary alcohol by any given method. Young and Lane (60) have also pointed out that in experiments involving butenyl bromides, it is necessary to work at low temperatures in order to avoid possible rearrangement which might be due to local heating effects.

Using the procedure proposed by Young et al. (60), Goering, Cristol, and Dittmer (61) have successfully converted 3-penten-1-ol to 5-bromo-2-pentene without reporting any rearrangements to the secondary bromide.

In the present work, the same experimental procedure (61) was adopted in order to synthesize E-2-methyl-1-bromo-2-

pentene. A reaction mechanism for this transformation is outlined in Scheme 19.

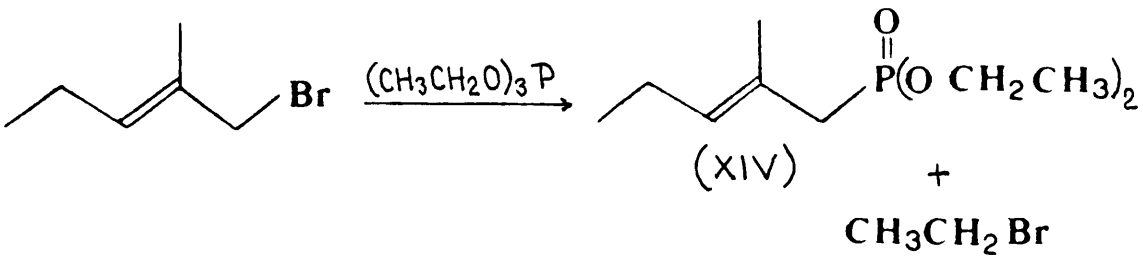


SCHEME 19

The product obtained did not contain any secondary bromide (XIII) and the proton nmr spectrum showed only signals consistent with the expected product (XII). The CH_2 protons next to bromine atom in compound (XII) resonate at δ 3.94ppm and the signal integrates for two protons. The theoretical value for this chemical shift was obtained using Schoolery's rules (62), which permit calculation of a shift position of a methylene group attached to two functional groups by additive effects of the shielding constants. The calculated value of 3.88ppm correlates well with the experimental chemical shift observed for these protons. Again, a trace of the starting ester (IX) was present in the final product (see Appendix 2).

2.3.1.4 The Synthesis of E-2-Methyl-2-Pentenylphosphonic Ester

The β,γ-unsaturated phosphonate was synthesized by the Arbusov procedure (29) and was obtained as a colourless liquid in a very good yield (98%) (Eq. [22]).



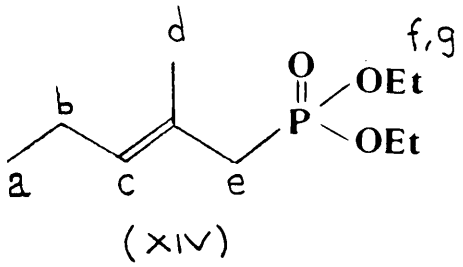
(XIV) + CH_3CH_2Br

[22]

The peak at δ 25.78ppm in the ^{31}P nmr spectrum showed the presence of only one major compound. There was also a very small peak at δ 25.43ppm present in the spectrum; this is an indication of some Z-isomer being formed (see Appendix 3).

Since in the present reaction sequence the starting 2-methyl-2-pentenylphosphonic acid was the E-isomer, a stereoselective synthesis was eventually achieved to give E-2-methyl-2-pentenylphosphonic ester. Therefore, it follows that the signals at δ 25.78ppm and δ 25.42ppm in the phosphorus spectrum of Mixture 3" correspond to the E- and Z-isomers respectively.

The presence of a trace of Z-isomer can be also identified from the proton nmr spectrum of compound (XIV). Thus, a doublet integrating for 2H can be observed at δ 2.47ppm; this clearly belongs to the (e) protons coupled to P in the E-isomer. The small doublet at δ 2.53ppm indicates the presence of some β,γ-unsaturated phosphonate (Z-isomer) (Fig. 11a). Similarly, the peak at δ 1.70ppm due to (d) protons is slightly split, showing again the presence of Z-isomer in the final product (Fig. 11b).



(XIV)

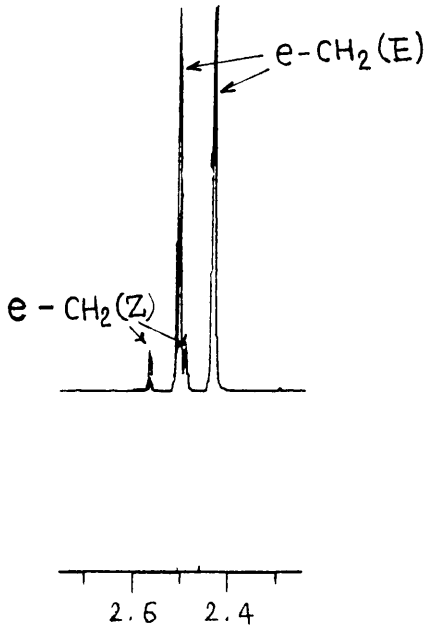


Fig. 11a : The e-CH_2 resonance from the ^1H nmr spectrum of compound (XIV)

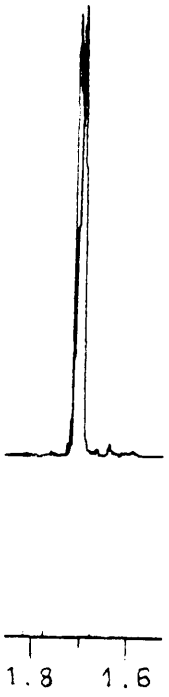
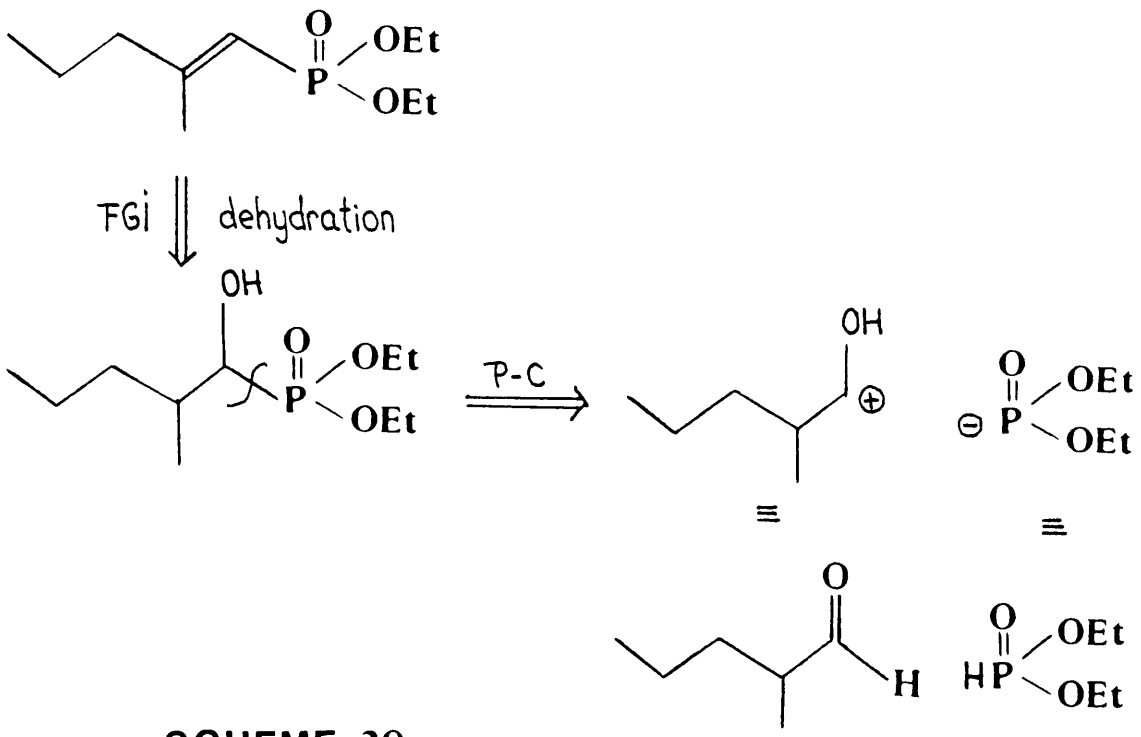


Fig. 11b : The d-CH_3 resonance from the ^1H nmr spectrum of compound (XIV)

2.3.2 A Retrosynthetic Approach to the Synthesis of 2-Methyl-1-Pentenylphosphonic Ester

Although the synthesis designed for the preparation of α,β - unsaturated phosphonate seemed quite straightforward and easy to carry out, difficulties were encountered with the second reaction step, thus the desired product could not be obtained. The following disconnection was the initial approach to this synthesis (Scheme 20).

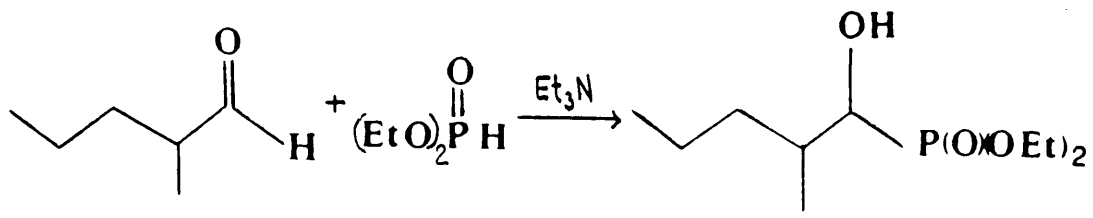
ANALYSIS:



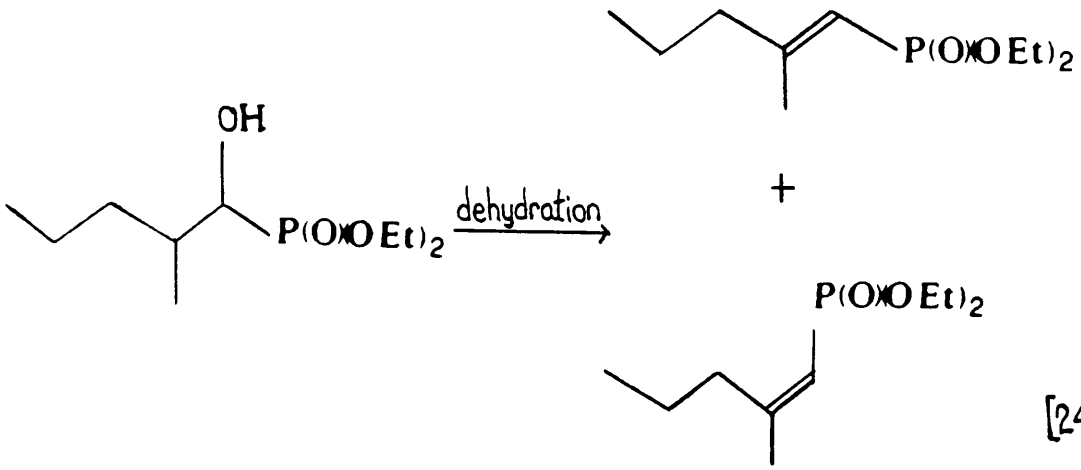
SCHEME 20

Subsequent to the functional interconversion step, the P-C bond was disconnected to give the appropriate synthons. The equivalent for the cationic one is an aldehyde, while for the anionic synthon diethyl phosphite was a suitable reagent. The following synthesis was, therefore, carried out (Scheme 21).

SYNTHESIS:



(XV) [23]



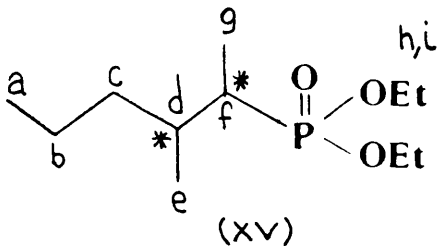
[24]

SCHEME 21

2.3.2.1 The Synthesis of 2-Methyl-1-Hydroxypentyl-phosphonic Ester

2-Methyl-1-hydroxypentylphosphonic ester (XV) was successfully prepared using the Abramov reaction (63,64). In this way 2-methyl-1-pentanal was reacted with diethyl phosphite and triethylamine (ratio, 1:1:0.35) to give a high yield (80%) of the desired product (Eq. [23]).

Due to the presence of two chiral centers (d- and f-C respectively) compound (XV) exists as a pair of diastereomers. Consequently, all the existing signals in the ^{31}P and ^{1}H nmr spectrum should exhibit fine splittings. This trend is clearly observed with signals at δ 0.85ppm and δ 0.99ppm in the proton spectrum ($\Delta\delta$ =0.007) and with the peak at δ 23.21ppm ($\Delta\delta$ = 0.008) in the phosphorus spectrum (Fig. 12a and 12b).



(XV)

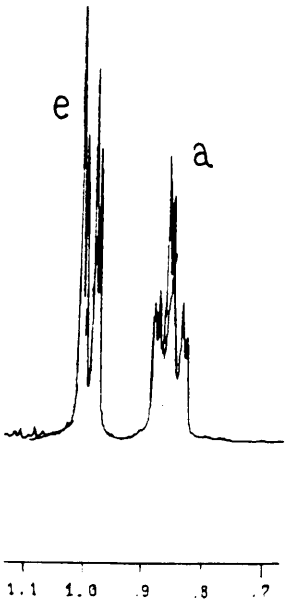


Fig. 12a: The H-H resonances for protons a and e in the ^{1}H nmr spectrum of compound (XV)

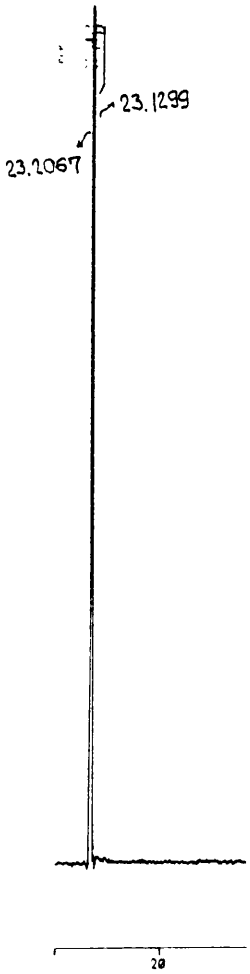


Fig. 12b : The ^{31}P nmr spectrum of compound (xv)

2.3.2.2 The Attempted Dehydration of 2-Methyl-1-Hydroxypentylphosphonic Ester

The reactivity order for the acid-catalysed dehydration of alcohols is the following:

$$R_3COH > R_2CHOH > RCH_2OH$$

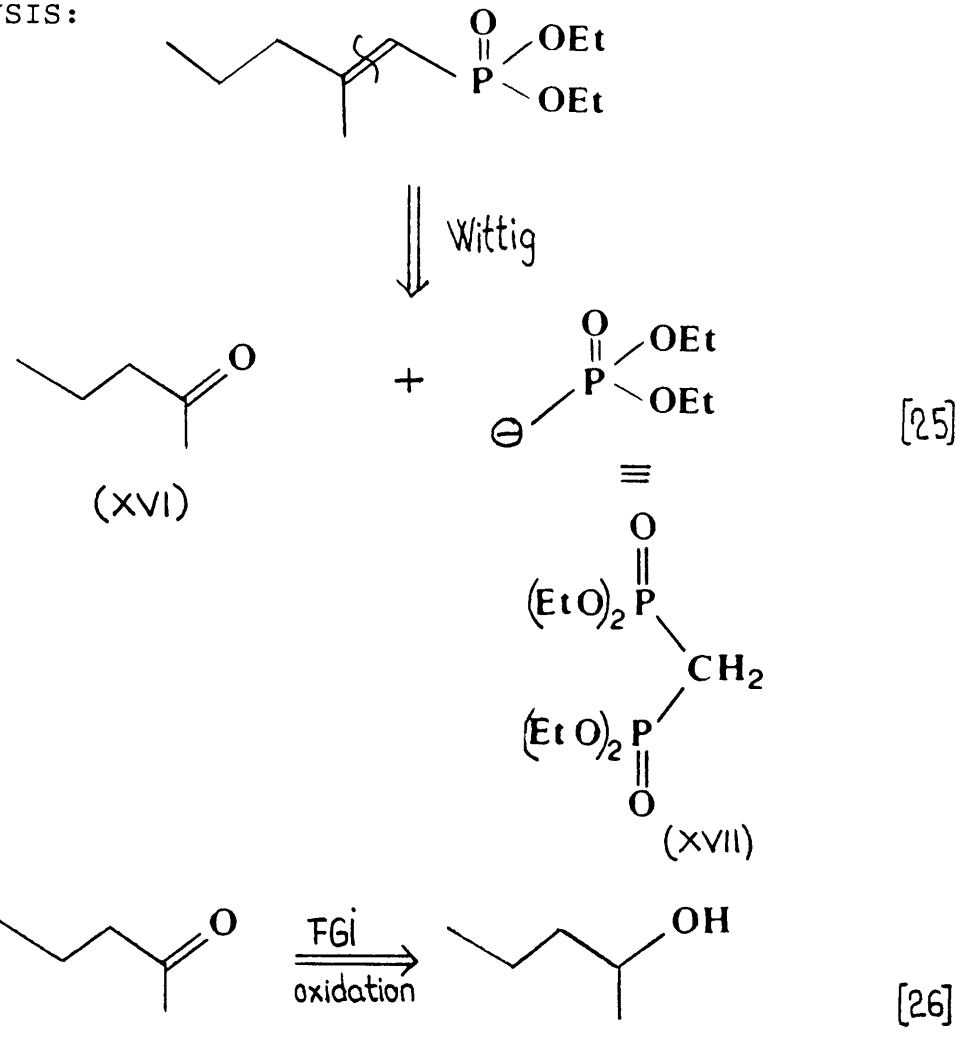
While tertiary alcohols are commonly dehydrated with acid, secondary and primary ones need more severe conditions, this leading sometimes to decomposition of more sensitive molecules. Various dehydrating reagents were used to achieve the required transformation, but the expected α,β-unsaturated phosphonate failed to form (Eq. [24]). When the dehydration was carried out with P_2O_5 in toluene, extensive decomposition took place; with P_2O_5 in benzene only slight elimination could be observed together with some decomposition (loss of the -OEt groups). With a $SOCl_2$ /pyridine system, destruction of the molecule took place while with $SOCl_2$/DMF (65-68) partial exchange of -OH with -Cl was observed.

Following the outcome of the above procedure, a different approach was undertaken. For many years now the alcohol dehydration methods for olefin synthesis have largely been supressed by the Wittig reaction (69). This method gives total control over the position of the double bond and partial control over its geometry. In this process a phosphorus ylide (also called phosphorane)adds to a ketone or aldehyde, yielding a dipolar betaine. The betaine intermediate in the Wittig reaction is unstable and decomposes at temperatures above $0^{\circ}C$ to yield alkene and triphenylphosphine oxide. Numerous reviews on Wittig reactions have been published (70-73) covering both the synthetic and mechanistic aspects of the reaction and

reflecting its importance as a synthetic procedure.

The following disconnection was designed as an alternative to the previous one involving the dehydration step (Scheme 22).

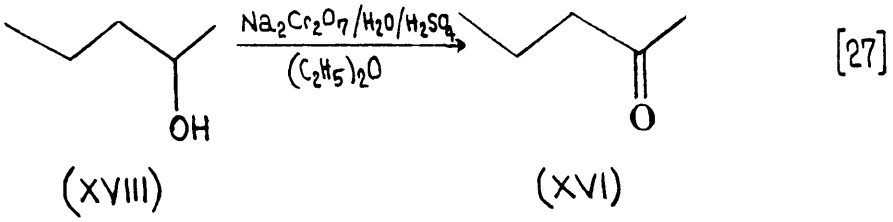
ANALYSIS:



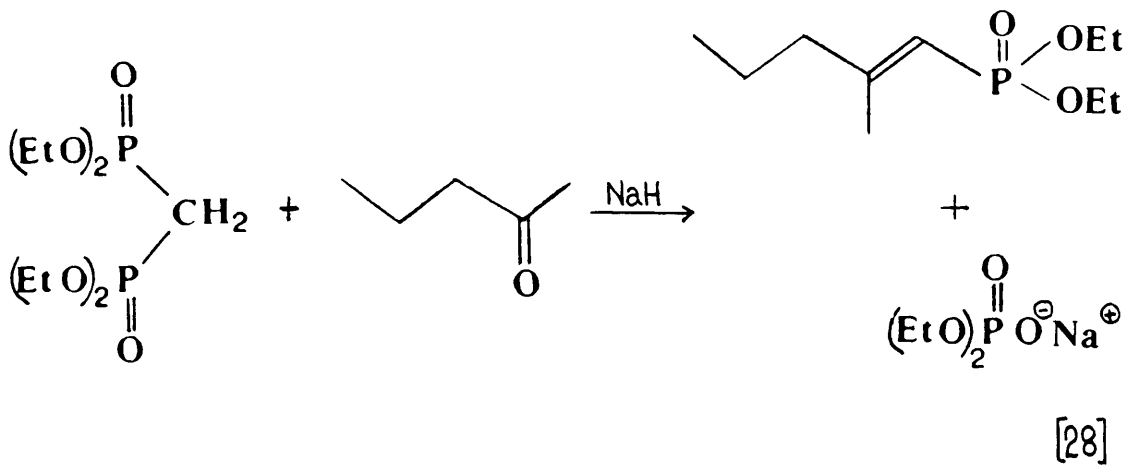
SCHEME 22

The synthesis was carried out with the reagents shown (XVI and XVII) (Eq. [25]) in high yield and high stereoselectivity (Scheme 23).

SYNTHESIS:



[27]



[28]

SCHEME 23

In the following subchapters each reaction step in Scheme 23 will be discussed.

2.3.2.3 The Synthesis of 2-Pentanone

2-Pentanone was easily synthesized in a high yield (94%) from the corresponding secondary alcohol using sodium dichromate as the oxidising reagent (74) (Eq. [27]). The proton nmr spectrum showed signals consistent with the expected product. The singlet at δ 2.48ppm corresponding to the hydroxylic proton (c) as well as the low field multiplet at δ 3.67ppm corresponding to proton (b) disappeared completely, thus indicating the formation of a ketone. Protons (a') (Fig. 13, XVI) giving a doublet in the ^{1}H spectrum of the alcohol (protons a), moved downfield by ~1ppm and appeared as a singlet. This is a consequence of the deshielding effect exerted by the carbonyl group which, to the same extent, influences the other protons in the molecule.

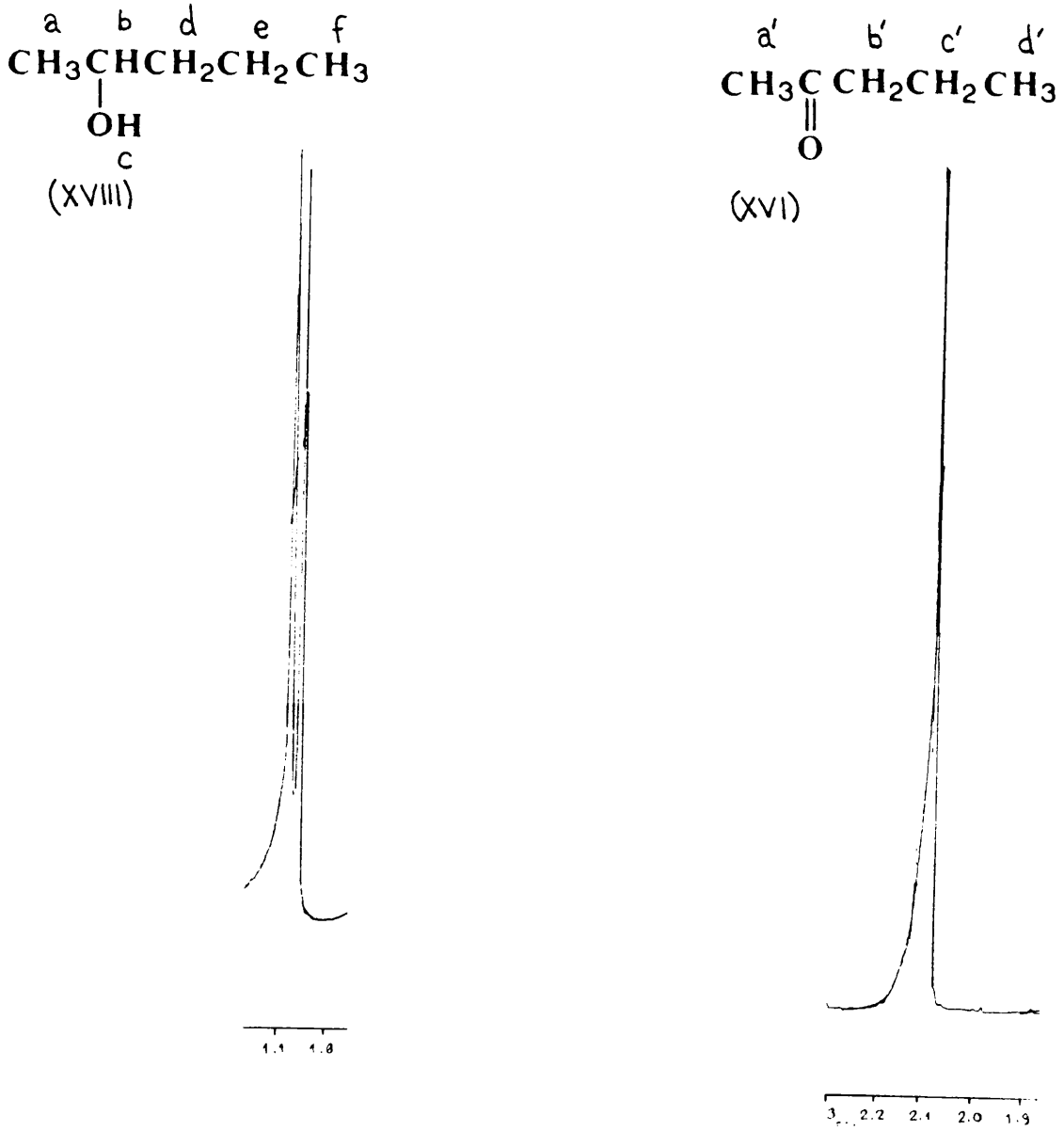
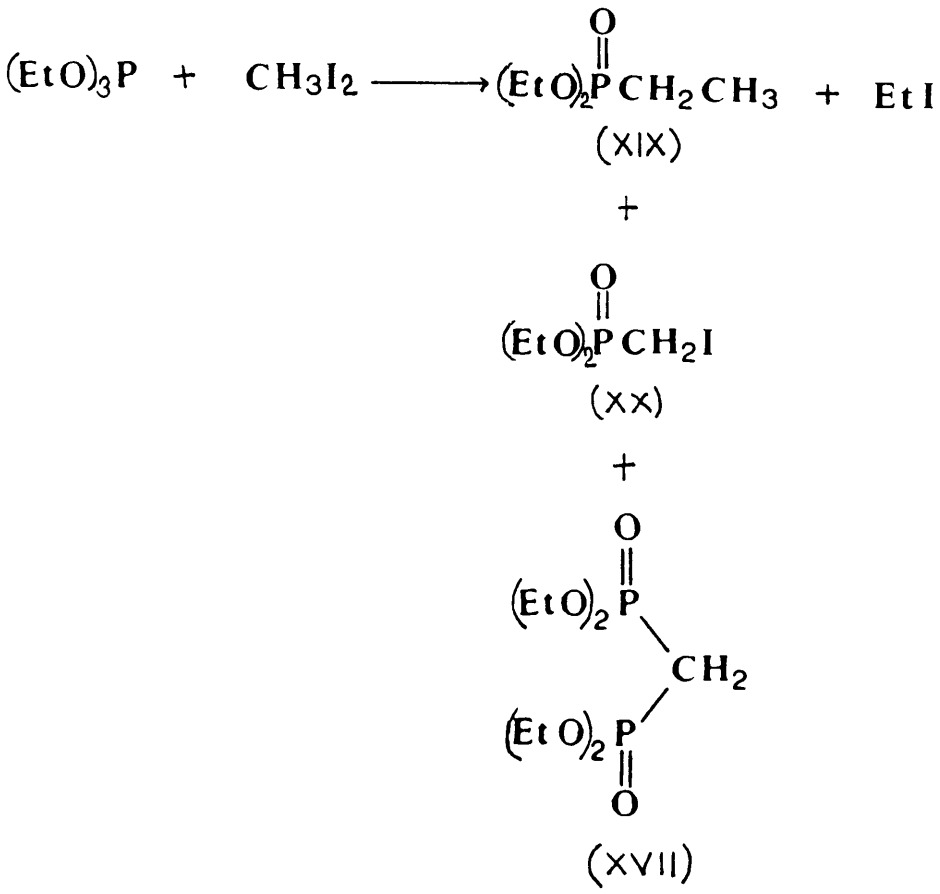


Fig. 13 : The H-H resonances for protons (a) and (a') in the ^1H nmr spectrum of compounds (XVIII) and (XVI)

2.3.2.4 The Synthesis of Tetraethyl Methylenediphosphonate

Tetraethyl methylenediphosphonate was prepared from methylene iodide and triethyl phosphite (75-77) by the

Arbusov-Michaelis reaction. It was obtained in a very pure state, but in low yield (21%) as the third fraction (XVII) collected in the final distillation process (see Appendices 2 and 3). The first fraction consisted mainly of diethyl ethanephosphonate (XIX) (formed by the isomerisation of triethyl phosphite), while the second fraction consisted mainly of diethyl iodomethylenephosphonate (XX) (from the incompleted Arbusov reaction) (Eq. [29]).



[29]

It has been shown (78) that when a 50% excess of the phosphite was used, the yield approaches 30%. A comprehensive account for the mechanistic and reactivity aspects related to this particular reaction is available in the literature (79-81).

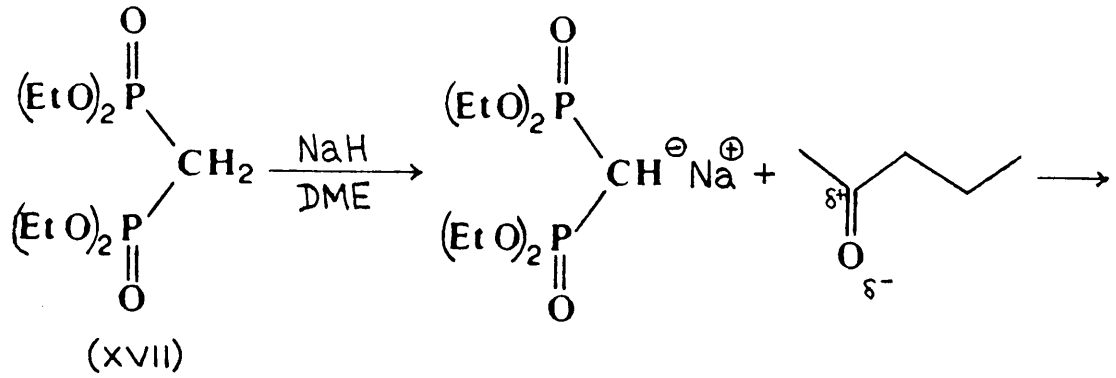
2.3.2.5 The Synthesis of 2-Methyl-1-Pentenylphosphonic Ester

It is obvious that addition of a second P(O)-activating group to a carbon greatly enhances the acidity of hydrogen atoms attached to α-carbon. Therefore, carbanions obtained from compounds activated by two P(O) groups (bisphosphonates) readily react with aldehydes or ketones to give a wide range of vinyl phosphorus compounds.

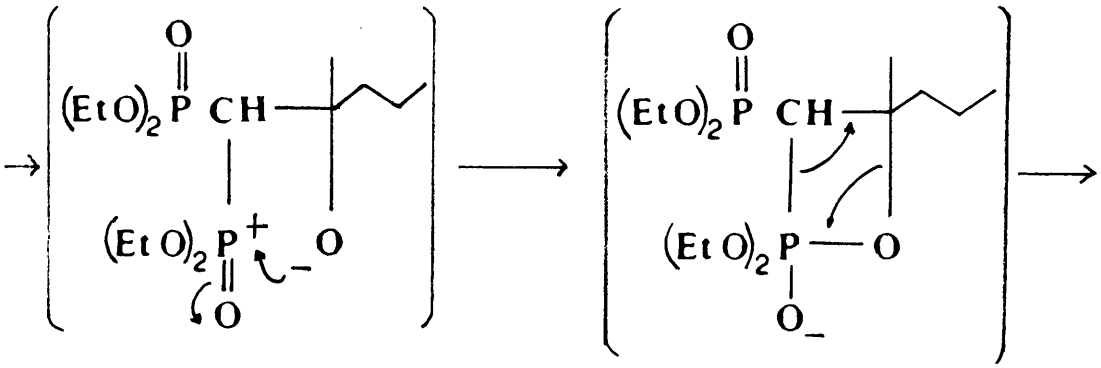
The first example of an olefin synthesis using a carbanion generated from phosphonates was reported by Horner (82). Later on, Wadsworth and Emmons (83) carried out a broad study of this reaction. Boutagy and Thomas (84) have described the mechanistic aspects and the stereochemistry involved in this reaction.

In the present project, 2-methyl-1-pentenylphosphonic ester was obtained in fairly good yields by reacting the anion

derived from tetraethyl methylenediphosphonate with 2-pentanone in a suitable solvent. Variations in the reaction yields were observed when different solvents were used. Thus, with dimethylformamide (85) a 63% yield was obtained, while with 1,2-dimethoxyethane only a 52% yield of the product resulted. A reaction mechanism for this transformation is given in Scheme 24.

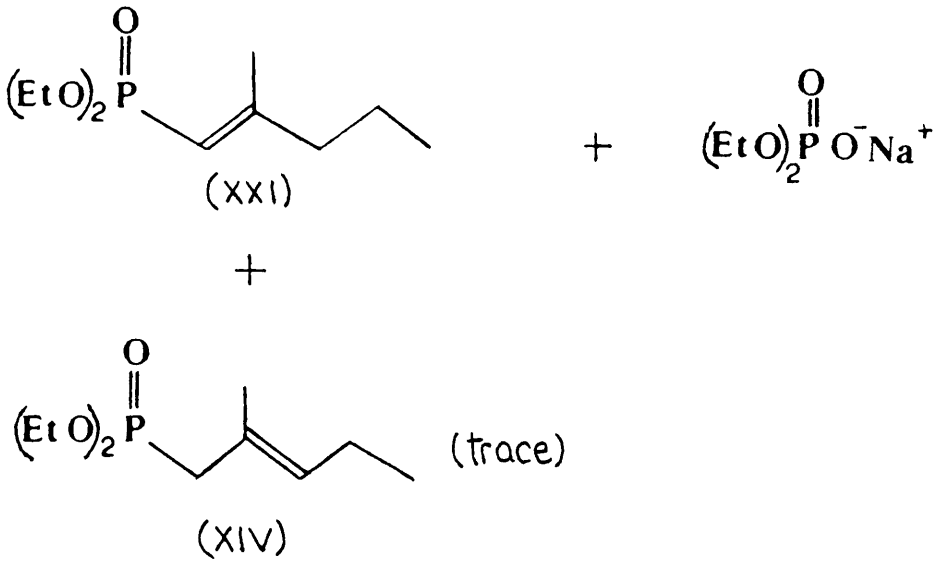


(XVII)



(Y)

Scheme 24 continues



SCHEME 24

In the above scheme the phosphonate anion was easily formed by treating tetraethyl methylenediphosphonate with sodium hydride. Thereafter, it was reacted in situ with 2-pentanone to give the vinylphosphonates (XXI and XIV). The reaction takes place via the betaine intermediate (Y) which rapidly decomposes to give the final product.

Much of the research done on the Horner-Emmons procedure demonstrated that although the reaction is not stereospecific, the formation of the trans-isomer is favoured. Moreover, the trans-isomer often emerges as the

sole reaction product (86-91).

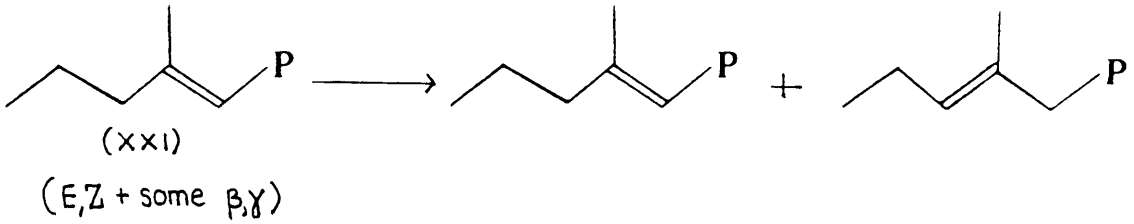
In our synthesis the same trend has been observed, where the E-2-methyl-1-pentenylphosphonic ester was the major product (60%), with some Z-isomer being present as well (25%). Under the basic reaction conditions, corroborated with the long reaction time (thermodynamic conditions), formation of the β,γ-unsaturated isomer could not be avoided, consequently 15% of β,γ-isomer was obtained (see Appendix 3).

2.4 PROTOTROPIC EQUILIBRIA IN 1- AND 2-PENTENYLPHOSPHONIC ESTERS

The work conducted during the earlier stages of the current project showed that isomerisation of Mixture 3 (consisting of major α,β - and minor β,γ-unsaturated phosphonates) leads to a new mixture of compounds in which β,γ-product is the major component. It was, therefore, concluded that these isomeric compounds are mutually interconvertible via the prototropic equilibrium.

Once the α,β - and β,γ-pentenylphosphonic esters have been independently synthesized, one of the points of interest was whether base-induced isomerisation of the pure compounds gives either a single product or a mixture thereof. Prototropic equilibrium studies have been carried out in the

presence of EtONa/EtOH and t-BuOK/t-BuOH systems and the reaction progress was followed by ^{31}P nmr spectroscopy. The results obtained are summarized in Equations 30 and 31.



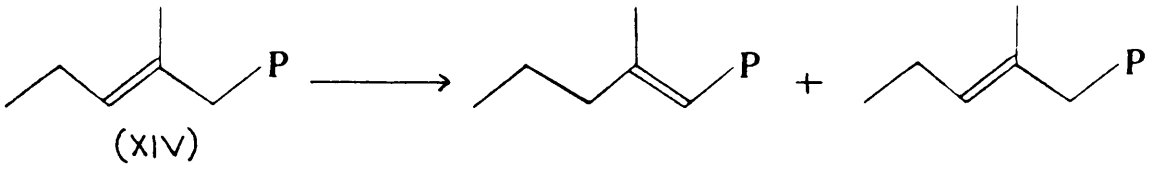
(XXI)

(E,Z + some β,γ)

a) EtONa/EtOH: 21% 79%

b) t-BuOK/t-BuOH: 18% 82%

P: $P(OEt)_2$ [30]



(XIV)

(E,Z)

a) EtONa/EtOH: 15% 85%

b) t-BuOK/t-BuOH: 20% 80%

P: $P(OEt)_2$ [31]

The above results clearly show that mixtures of α,β- and β,γ-unsaturated phosphonates were obtained from isomerisation experiments. The relative abundance of each compound in the mixture is indicated below each component. It was found that the pure α,β-unsaturated substrate isomerises to give major β,γ-phosphonate, while pure β,γ-compound showed an insignificant change after isomerisation, giving only very little of the α,β-isomer. These results agree well with the fact that β,γ-isomer was obtained as a pure compound, following its independent synthesis, and indicate that β,γ-unsaturated phosphonate is both kinetically and thermodynamically favoured compound in this system.

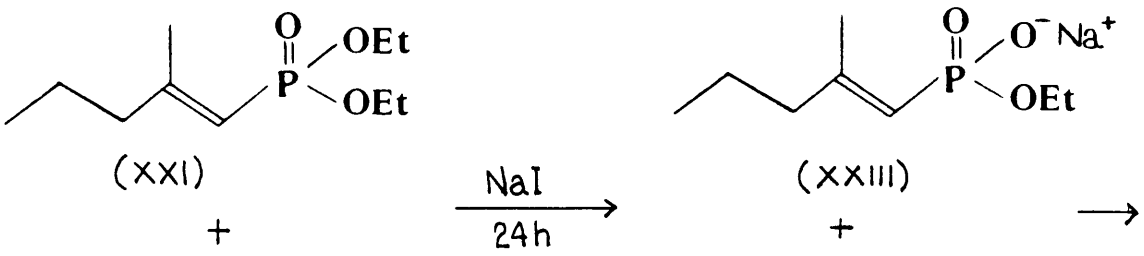
Many examples of equilibria between α,β- and β,γ-unsaturated systems are available in the literature. In this regard, hyperconjugation effects have been studied for acyclic and cyclic unsaturated ketones, esters, carboxylic acid salts, and nitriles (92-96). In the present work, hyperconjugation was found to be mostly responsible for the stability of β,γ-pentenylphosphonic system, this being the first example of such effect described for unsaturated phosphonate derivatives.

Both reaction products in Equations 30 and 31 can be easily identified from the phosphorus nmr spectra obtained. However, besides the expected signals, new sets of peaks

downfield from the α,β - and β,γ-unsaturated phosphonates were observed. A closer look at the integration of these novel peaks, indicates that these side-products appear in a large quantity when EtONa/EtOH base system was used, while decreasing considerably in the presence of t-BuOK/t-BuOH. It was assumed that these new compounds are the dealkylation products and in a subsequent experiment this assumption was confirmed.

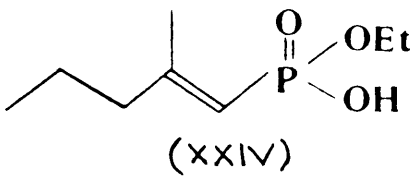
2.4.1 Dealkylation of 2-Methyl-1-Pentenylphosphonic Ester

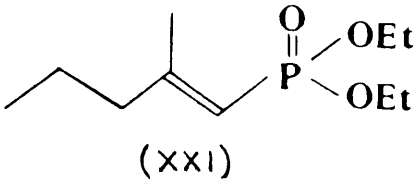
Using a modified procedure (longer reaction time) of the one described by Zervas and Dilaris (97) it was found that when 2-methyl-1-pentenylphosphonic ester was treated with sodium iodide, monodealkylation takes place to give a mixture of the expected product and the starting compound (Eq. [32]).

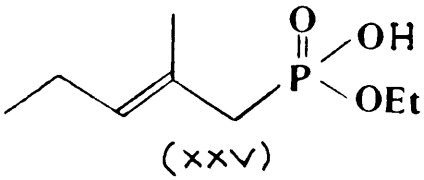


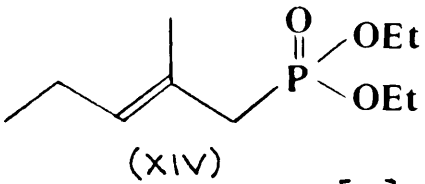
Equation 32 continues

CF_3COOH →


(XXIV)


(XXI)


(XXV)

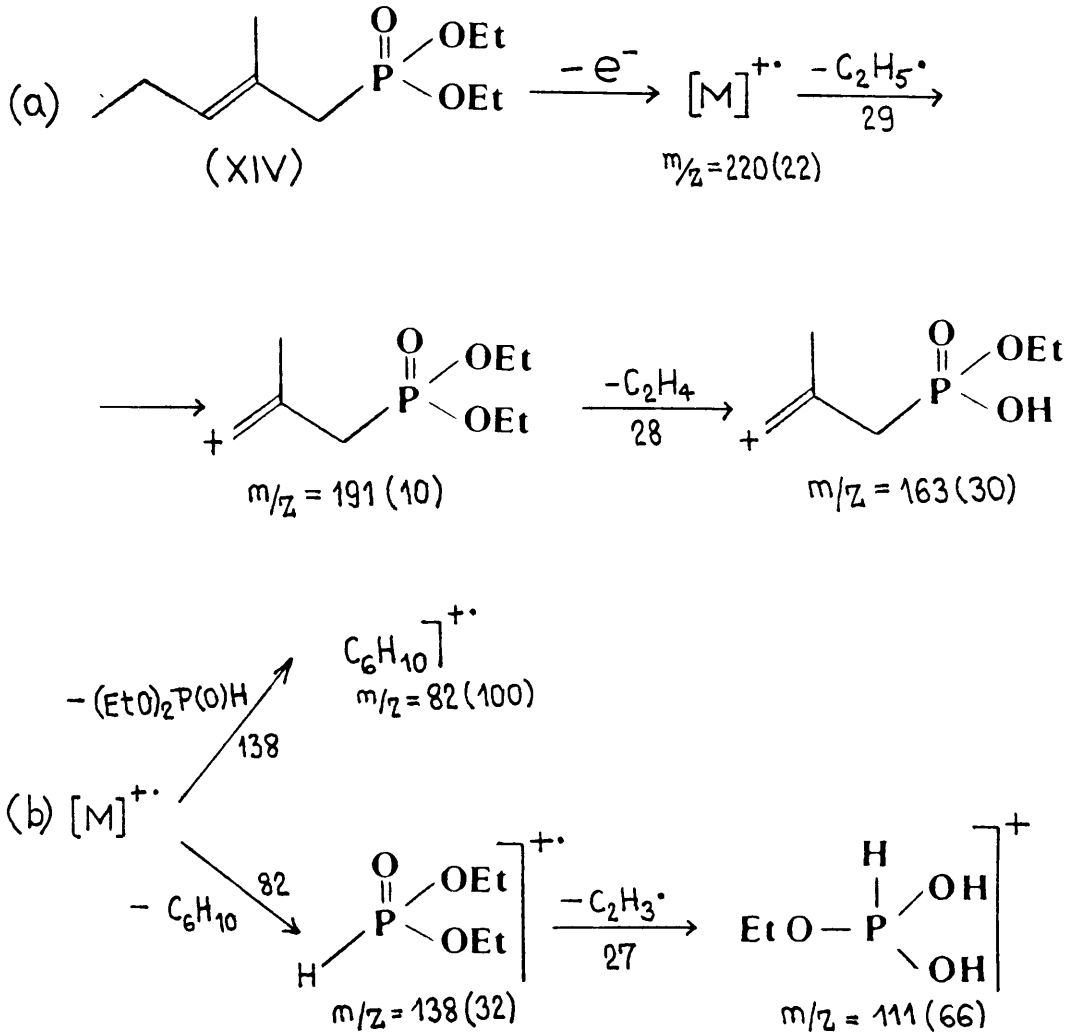

(XIV)

[32]

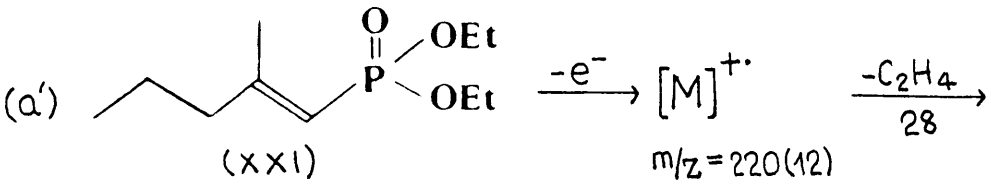
Formation of the anions (XXIII and XXVI) in Equation 32, deactivates the intermediate with respect to a nucleophile and no further dealkylation takes place. Therefore, only monodealkylated compounds (XXIV and XXV) are produced in this reaction. The ^{31}P nmr spectrum clearly showed the presence of new sets of peaks at δ 18.11 and 18.67ppm downfield from α,β-isomer, and 27.58, 28.21 and 28.51ppm downfield from the β,γ-isomer (see Appendix 3). These chemical shifts agree very well with the ones obtained for the new compounds in Equations 30 and 31 (See Experiments 3.2.16 and 3.2.17)

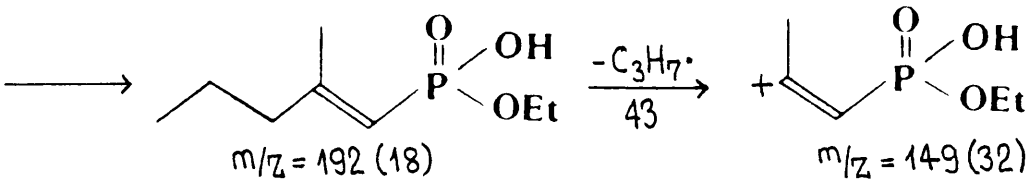
2.5 MASS SPECTROMETRY OF α,β-AND β,γ-PENTENYLPHOSPHONIC ESTERS

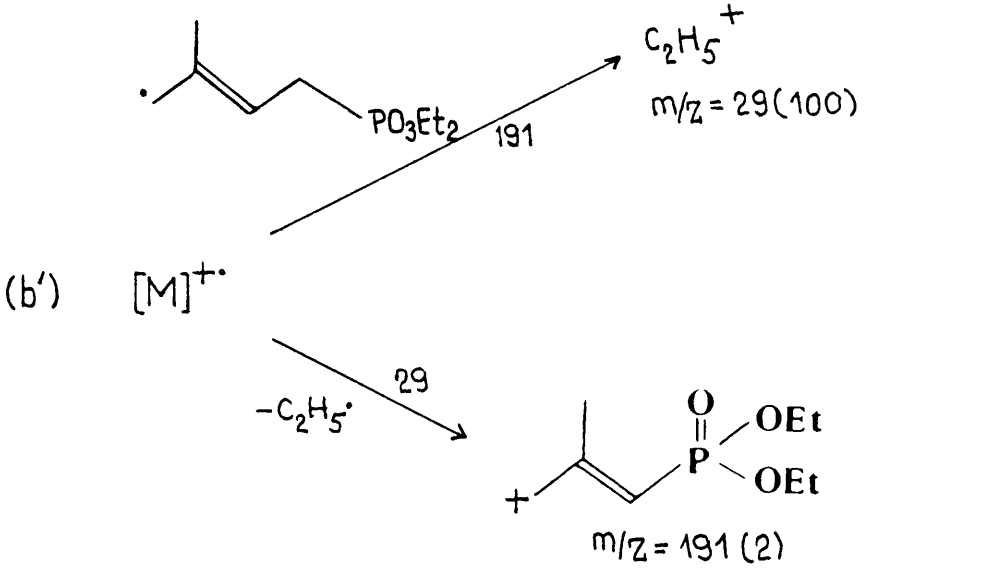
Mass spectra for compounds (XIV) and (XXI) were recorded and the characteristic fragmentation behaviour of these compounds was studied. Selected fragmentation data are described in Schemes 25 and 26 (see Appendix 4 for details).



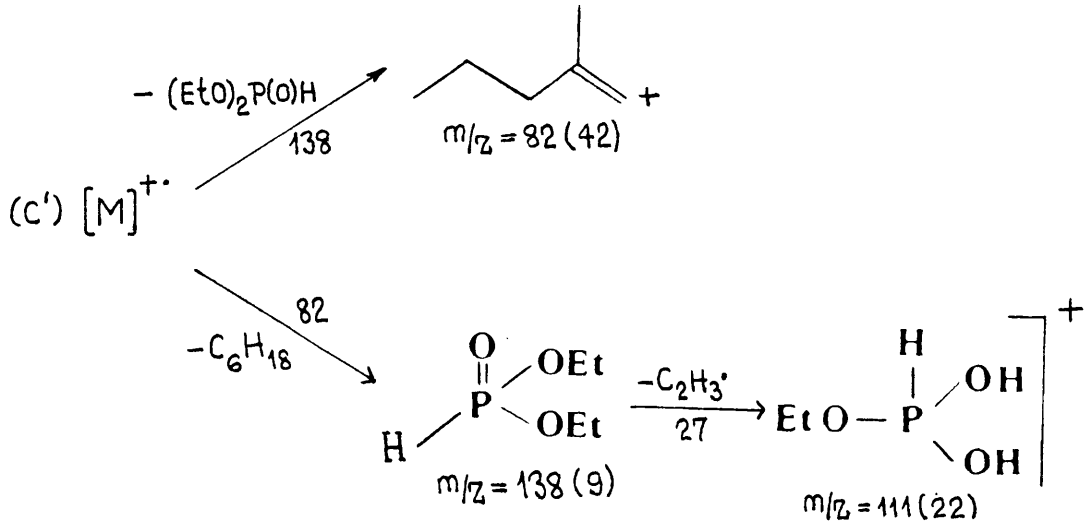
SCHEME 25







Scheme 26 continues



Note : Numbers in brackets represent % relative abundance for m/z fragment ion

SCHEME 26

For both compounds loss of ethylene (C_2H_4) occurs via the typical McLafferty rearrangement (98) to give the expected molecular ion. The α-cleavage steps (b and c') take place with hydrogen migration, while loss of vinyl radical (C_2H_3·) (99) involves a double hydrogen rearrangement.

When Mixture 3 was separated by capillary gas chromatography into its components, the mass spectra recorded for each compound showed exactly the same fragmentation pattern as for the pure compounds described above (see Appendix 4). This correlation indicates once more the power of capillary gas chromatography coupled with mass spectrometry in the separation and identification of complex organic mixtures.

2.6 CONCLUSIONS

In the present project the reaction of 2-methyl-1-pentene with phosphorus pentachloride , as well as the subsequent reaction in which the corresponding phosphonic diesters are formed were investigated. The products obtained were invariably mixtures of five compounds that could not be separated by standard chromatographic techniques. Prototropic equilibrium studies on the above-mentioned unsaturated systems showed the formation of equilibrium mixtures of products.

Two completely new compounds, components of the alkenylphosphonate mixtures, have been synthesized and fully characterized in the present work. These are :

a) E-2-methyl-2-pentenylphosphonic diethyl ester
b) E-2-methyl-1-penthenylphosphonic diethyl ester

The base-catalysed isomerisation of these pure compounds showed that α,β -unsaturated substrate isomerises to give major β,γ -unsaturated phosphonate, while the β,γ-substrate shows very little change after isomerisation, giving only a trace of the α,β -isomer. Hyperconjugation effects were found to be mostly responsible for the stability of the β,γ -unsaturated phosphonates.

A fairly extensive part of this project dealt with capillary gas chromatographic determination of the alkenylphosphonate mixtures. No such data have yet been reported for these particular systems. Mass spectra fragmentation patterns for the pure synthesized alkenylphosphonates were obtained using a GC-MS coupled system.

2.7 FUTURE WORK

Firm evidence for the structure of the β,γ'-unsaturated phosphonate is still required; the independent, unambiguous synthesis of this compound is, therefore, necessary. Prototropic equilibrium studies on β,γ'-unsaturated phosphonate merit further attention.

The reactions of pure synthesized α,β- and β,γ-unsaturated phosphonates with organometallic reagents and other nucleophiles have not been attempted before and deserve investigation.

The importance and wide variety of phosphorus compounds in living systems, makes the unsaturated phosphonates important candidates for a wide range of studies. In view of this it becomes obvious that the role of unsaturated phosphonates as phosphorylating agents merit further investigation.

CHAPTER 3: EXPERIMENTAL

3.1 GENERAL

3.1.1 Solvents and Reagents

All solvents and commercially available reagents were purified before use. Benzene was dried by azeotropic distillation and stored over sodium wire. Ether was pre-dried over calcium chloride, distilled from calcium hydride and stored over sodium wire. Ethanol was distilled from magnesium turnings and stored over 4A molecular sieves. Pyridine and diethylamine were distilled from KOH and stored over KOH pellets. Dichloromethane was distilled from P_2O_5. Solutions of sodium alkoxides and t-BuOK in alcohols were prepared by dissolving the required quantity of sodium and t-BuOK respectively, in the corresponding alcohol under nitrogen with exclusion of moisture. Reagents used were purchased from Aldrich Chemicals, Fluka Chemie AG and BDH Chemicals. MERCK Chloroform-d, min. 99.8% D was used for recording ^{1}H and ^{31}P nmr spectra.

3.1.2 Reaction Conditions

Reactions were carried out with rigorous exclusion of moisture (under nitrogen where necessary).

3.1.3 Purification of Compounds

Products were purified by bulb-to-bulb distillation techniques, using a Buchi GKR-50 glass-tube oven, and by column chromatography on MERCK silica gel 60 (particle size 0.063-0.2 mm). The progress of column chromatographic separation was monitored using thin layer chromatography (MERCK TLC plastic sheets silica gel 60F 254).

3.1.4 Characterization of Compounds

Most compounds were identified by boiling points, TLC behaviour, refractive indices and NMR (^{1}H and ^{31}P) spectra. Refractive indices were determined on a ATAGO 1T refractometer provided with a digital thermometer. NMR spectra were recorded on BRUCKER AC 300FT spectrometer.

Chemical shifts (δ) are given in ppm and measured as follows: ^{1}H relative to TMS (internal standard) and ^{31}P relative to trimethyl phosphate (external standard). Elemental analyses (C, H, N) were performed at the University of Cape Town using a Heraeus Universal combustion analyser.

3.2 SYNTHESES

3.2.1 Preparation of Ethyl 2-E-Methylpentenoate (IX) (55)

A 250 ml round-bottom flask was fitted with a water condenser and drying tube. E-2-methyl-2-pentenoic acid (11g, 9.64×10^{-2} mol) was placed in the flask and absolute ethanol (32 ml) containing 5.7 g dry HCl was added. The mixture was heated under reflux for 4 1/2 h. The solvent was then removed under reduced pressure, diethyl ether (20 ml) was added and the acidic solution was washed with aqueous $NaHCO_3$. The water layer was extracted with diethyl ether (3 x 15 ml) and the organic fractions were combined and dried over $MgSO_4$. Evaporation of the solvent gave the crude ester. The compound was purified by distillation. Yield: 9 g, 70%; bp 165-168°C; n_D^{25} 1.4385; ^{1}H nmr ($CDCl_3$) δ:

1.03 (3H, t, J_{H-H}= 7.51Hz, a), 1.27 (3H, t, J_{H-H}= 7.16Hz, f), 1.80 (3H, s, d), 2.15 (2H, d of q, J_{H-H} = 7.45 Hz, b), 4.16 (2H, q, J_{H-H}= 7.15Hz, e), 6.72 (1H, t, $J_{H\,H}$= 7.41Hz, c)

3.2.2 Preparation of E-2-Methyl-2-Penten-1-Ol (X) (56)

A solution of $LiAlH_4$ (1.22 g, 3.21 x 10^{-2} mol, 25% excess) in ether (30 ml) was placed in a 250 ml two-necked round-bottom flask equipped with reflux condenser and $CaCl_2$ drying tube, dropping funnel and magnetic stirrer bar. Through the dropping funnel a solution of ethyl 2-E-methylpentenoate (7.3 g, 5.13 x 10^{-2} mol) in ether (10 ml) was added at such a rate to produce a gentle reflux. The mixture was stirred for an additional 1 1/2 h. The excess of $LiAlH_4$ was decomposed by dropwise addition of water (20 ml), the mixture was then poured into 50 ml of iced water, and to this was added 100 ml of 10% sulphuric acid; all the salts formed dissolved and the ether layer became neutral. The aqueous layer was extracted with diethyl ether (3 x 20 ml). Evaporation of the dried etheral layer gave the expected product as a colourless oil. Yield: 3.83 g, 78%; ^{1}H nmr ($CDCl_3$) δ : 0.94 (3H, t, J_{H-H}= 7.56Hz, a), 1.55 (1H, s, f), 1.63 (3H, s, d), 2.02 (2H, d of q, J_{H-H}= 7.43 Hz, b), 3.96 (2H, s, e), 5.36

(1H, t, J_{HH}= 7.13Hz, c).

3.2.3 Preparation of E-2-Methyl-1-Bromo-2-Pentene (XII)(61)

A solution of E-2-methyl-2-penten-1-ol (3.4 g, 3.39×10^{-2} mol), pyridine (1 ml, 0.98 g, 1.24×10^{-2} mol), and diethyl ether (5 ml) was placed in a 100 ml round-bottom three-necked flask provided with magnetic stirrer bar, low temperature thermometer, dropping funnel, and air condenser with drying $CaCl_2$ tube. The mixture was cooled to -40 °C and the solution of PBr_3 (3.71 g, 1.3 ml, 1.37×10^{-2} mol) in diethyl ether (5 ml) was added dropwise over a period of 15 min. and keeping the temperature between -35 and -45 °C during the addition. A white precipitate was formed ($C_5H_5NH^+ Br^-$). The mixture was stirred for another 5 min. at - 40°C after the addition was completed. The flask was warmed up to room temperature and stirring was continued for 30 min. The solution was washed with 20ml 10% $NaHCO_3$ and the two layers were separated. The organic phase was washed again with H_2O (15 ml) and extracted with ether. After drying over $MgSO_4$, diethyl ether was removed by distillation under normal pressure to leave behind the desired product as a colourless oil. Yield: 5.1 g, 65%; ^1H nmr ($CDCl_3$) δ: 0.95 (3H, t, J_{HH}

= 7.57Hz, a), 1.73 (3H, s, d), 2.02 (2H, d of q, J_{H-H}= 7.47Hz, b), 3.94 (2H, s, e), 5.57 (1H, t, J_{H-H}= 6.77Hz, c).

3.2.4 Preparation of E-2-Methyl-2-Pentenylphosphonic Ester (XIV) (29)

A mixture of E-2-methyl-1-bromo-2-pentene (3.2 g, 1.96 x 10^{-2} mol) and triethyl phosphite (3.26 g, 3.2 ml, 1.96 x 10^{-2} mol) was placed in a 50ml round-bottom flask with a short column, air condenser, drying tube, and receiver flask immersed in iced water. The mixture was heated on an oil bath (bath temperature 150°C) and EtBr was distilled off. The desired product which was left behind in the reaction vessel was purified by bulb-to-bulb distillation at oven temperature 90-110°C (0.28 mmHg) to give a colourless oil. Yield: 4.22 g, 98%, n_D^{20}: 1.4466; ^{1}H nmr ($CDCl_3$) δ: 0.90 (3H, t, J_{H-H}= 7.5Hz, a), 1.25 (6H, t, J_{H-H}= 7.04Hz, 2 x g), 1.7 (3H, s, d), 2.0 (2H, d of q , J_{H-H}= 7.25Hz, b), 2.47 (2H, d, J_{H-P}= 21.86Hz, e), 4.04 (4H, quint, J_{H-P}= J_{H-H}= 7.10Hz, 2 x f), 5.24 (1H, t, J_{H-H}= 7.02Hz, c); ^{31}P nmr ($CDCl_3$) δ: 25.78. Anal. calcd. for $C_{10}H_{21}O_3P$: C 54.53, H 9.61%; found: C 51.3, H 9.34%. A trace of the Z-isomer was observed as well; ^{31}P nmr ($CDCl_3$) δ: 25.43.

3.2.5 Preparation of 2-Methyl-1-Hydroxypentylphosphonic Ester (XV) (63,64)

A mixture of 2-methyl-1-pentanal (6 g, 7.43 ml, 8.32×10^{-2} mol), diethyl phosphite (11.65 g, 10.89 ml, 8.44×10^{-2} mol), and triethylamine (3 g, 4.1 ml, 2.96×10^{-2} mol, 3 mol equiv) was heated with stirring at 85°C for 2 h. The product was distilled under vacuum to give a colourless oil. Yield: 11.46 g, 80%, bp 124-125°C (0.7 mmHg), n_D^{20} : 1.4458; ^{1}H nmr ($CDCl_3$) δ : 0.85 (3H, t, J_{H-H}= 7.9Hz, a), 0.99 (3H, d, J_{H-H}= 6.93Hz, e), 1.28 (6H, t, J_{H-H}= 7.09Hz, 2 x i), 1.34-1.50 (1H, m, d), 1.65-1.75 (2H, m, c), 1.80-1.98 (2H, m, b), 3.35 (1H, s, g), 3.78 (1H, d of d, J_{H-H}= 3.96Hz, J_{H-P}= 9.0Hz, f), 4.11 (4H, quint, J_{H-H}= J_{H-P}= 7.26Hz, 2 x h); ^{31}P nmr ($CDCl_3$) δ : 23.21.

3.2.6 The Attempted Dehydration of 2-Methyl-1-Hydroxypentylphosphonic Ester (65-68)

(a) A mixture of ∝ -hydroxyphosphonate (XV) (2.38 g, 0.01 mol) and P_2O_5 (1.42 g, 0.01 mol) in dry toluene (40 ml) was heated under reflux for 1 h. The solution was decanted off and washed with 20 ml cold H_2O followed by 30 ml diluted $NaHCO_3$ solution. After solvent evaporation ,the product was obtained as a pale yellow oil. Yield: 0.37 g, 20%. Both ^1H and ^{31}P nmr spectra showed extensive decomposition of the product. The experiment was repeated using benzene as solvent and the same procedure as above was followed. The product obtained showed slight elimination of H_2O accompanied by extensive decomposition.

(b) A mixture of ∝ -hydroxyphosphonate (2.38 g, 0.01 mol) and pyridine (0.79 g, 0.81 ml, 0.01 mol) in dry benzene (10 ml) was added dropwise to a stirred, cold (5°C) solution of $SOCl_2$ (1.19 g, 0.73 ml, 0.01 mol) in benzene (10 ml). The addition was performed over a period of 20 min.; the formation of pyridinium chloride as a white precipitate was observed. The flask was warmed at room temperature and a solution of triethylamine (3.04 g, 4.16 ml, 0.03 mol, 50% excess) was added dropwise (slightly exothermic reaction was

observed), then the mixture was heated under reflux for 30 min. After filtration, washing with 40 ml 5% HCl solution, followed by 3 x 30 ml H_2O, and drying over $MgSO_4$, the solvent was removed giving the product as a dark redish oil. Both ^1H and ^{31}P nmr showed extensive decompositon.

(c) Thionyl chloride (1.19 g, 0.73 ml, 0.01 mol) was added dropwise to a stirred, cold (0 C) solution of α-hydroxyphosphonate (2.38 g, 0.01 mol), and DMF (10 ml). The mixture was stirred at room temperature for 12 h; it was then poured into 150 ml cold H_2O. After extraction of the organic layer, and further washing with $NaHCO_3$ and drying, the solvent was removed to give a yellow oil. Decomposition of the product was again the outcome of this attempted dehydration.

3.2.7 Preparation of 2-Pentanone (XVI) (74)

A 500 ml three-necked flask was equipped with a Liebig condenser with drying tube, thermometer, a dropping funnel, and magnetic stirrer bar. A solution of 2-pentanol (25 g, 0.28 mol) in diethyl ether (90 ml) was placed in the flask and chromic acid solution (141 ml, 0.091 mol) was poured in the dropping funnel. The latter was added dropwise over a

period of 20 min. to the vigorously stirred alcohol solution, keeping the temperature between 25 and 30°C. The stirring was continued for 2 h at room temperature. The mixture was transferred to a separatory funnel, the ether layer was separated, and the dark green aqueous layer was extracted with 4 x 50 ml portions of ether. The combined ether extracts were washed with 40 ml saturated NaCl solution, then the ether layer was dried over $MgSO_4$. After the evaporation of the solvent, the organic residue was distilled to give the desired product as a colourless liquid. Yield: 22.9 g, 94%, bp 101°C (650 mmHg), n_D^{20} : 1,3895; ^1H nmr ($CDCl_3$) δ : 0.88 (3H, t, J_{H-H}= 7.36Hz, d'), 1.56 (2H, q of t, J_{H-H}= 7.34Hz, c'), 2.09 (3H, s, a'), 2.36 (2H, t, J_{H-H}= 7.29Hz, b').

3.2.8 Preparation of Tetraethyl Methylenediphosphonate (XVII) (76,77)

A 250 ml round-bottom flask was equipped with a 30 cm Vigreux column, thermometer, Liebig condenser, and receiving flask with $CaCl_2$ drying tube. Freshly distilled methylene iodide (57 g, 17 ml, 0.21 mol) and triethyl phosphite (105 ml, 101 g, 0.61 mol 50% excess) were added to the flask. The pale yellow mixture was heated rapidly at 160°C by means of a pre-heated oil bath. Soon after heating, a vigorous

reaction took place with rapid evolution of ethyl iodide which was collected in the cooled receiving flask. The reaction mixture was distilled under reduced pressure and four fractions were collected as follows: (i) bp 92-100 °C (20 mmHg), yield: 61 g; (ii) bp 40-75°C (0.35 mmHg), yield: 9 g [these two fractions consisted mainly of diethyl ethanephosphonate (XIX)]; (iii) bp 80-120 °C (0.35 mmHg), yield: 35 g, consisting mainly of diethyl iodomethanephosphonate (XX); (iv) bp 120-125°C (0.35 mmHg), yield: 13.2 g, 21% which was the desired product (XVII), n_D^{20} : 1.4315, literature (77) n_D^{20} : 1.4300; ^{1}H nmr ($CDCl_3$)δ: 1.27 (12H, t, J_{H-H}= 7.03Hz, 2 x a), 2.33 (2H, t, J_{H-P}= 21.04Hz, c), 4.10 (8H, quint, J_{H-H}= J_{H-P}= 7.2Hz, 2 x b); ^{31}P nmr ($CDCl_3$)δ: 17.08.

3.2.9 Preparation of 2-Methyl-1-Pentenylphosphonic Ester (XXI)

Tetraethyl methylenediphosphonate (5.36 g, 0.018 mol) in DME (10 ml) was added dropwise at room temperature to a slurry of sodium hydride (0.48 g, 0.02 mol) in 40 ml DME. The reaction was exothermic with strong evolution of hydrogen. The solution was stirred at room temperature for 15 min.

until the reaction was complete. The solvent was removed and the sodium salt of the bisphosphonate was obtained as a pale yellow glassy material. The salt was dissolved in 20 ml DMF, then 2-pentanone (3.1 g, 0.036 mol, 100% excess) was added. The mixture was heated under reflux for 4 h (120°C oil bath), then it was poured into 150 ml H_2O and extracted with 3 x 60 ml benzene. After drying the organic layer and evaporation of the solvent, the product was obtained as a yellow oil. The compound was purified by bulb-to-bulb distillation at oven temperature 90-100°C (0.4 mmHg) and a colourless oil was obtained. Yield: 2.5 g, 63%, n_D^{20} : 1.4450. From the ^1H and ^{31}P nmr it was obvious that the product contained some β,γ-unsaturated phosphonate (XIV). Thus the following data is a description for the mixture of these compounds. ^1H nmr ($CDCl_3$) δ : 0.87 (6H, t, J_{H-H}= 7.27Hz, a, a'), 1.28 (12H, t, J_{H-H}= 7.0Hz, 2 x g and 2 x g'), 1.45 (2H, q of t, J_{H-H}= 7.44Hz, b), 1.86 (3H, s, d), 2.04 (3H, s, d'), 2.09 (2H, t, J_{H-H}= 7.5 Hz, c), 2.41-2.55 (2H, m, b'), 2.86 (2H, d, J_{H-P}= 22.33Hz, e'), 4.03 (8H, quint, J_{H-H} = J_{H-P}= 7.54Hz, f, f'), 4.89 (1H, t, J_{H-H}= 7.02Hz, c'), 5.32 (1H, d, J_{H-H}= 18.94Hz, e); ^{31}P nmr ($CDCl_3$) δ : 15.52 (Z-XXI), 16.28 (E-XXI), 25.05 (XIV). Anal. calcd. for $C_{10}H_{21}O_3P$: C 54.53, H 9.61%; found: C 51.28, H 10.6%.

3.2.10 Dealkylation Reaction of 2-Methyl-1-Pentenylphosphonic Ester (97)

2-Methyl-1-pentenylphosphonic ester (XXI) (0.97 g, 4.41 x 10^{-3} mol) was dissolved in dry acetone (15 ml). To this solution, NaI (1.32 g, 8.82 x 10^{-3} mol, 2 mol equiv.) was added and the mixture was heated under reflux for 20 min. The mixture was concentrated to half of its original volume and few drops of CF_3COOH were added to form the free acid. The solution solidified completely upon CF_3COOH addition; few drops of H_2O were added and a solution containing some precipitate (CF_3COONa and excess NaI) was obtained. $CHCl_3$ (20 ml) was added and the mixture was filtered. The dried organic layer was evaporated off to give a pale yellow oil. Yield: 0.7 g, 82%; ^{31}P nmr ($CDCl_3$) δ : 15.67 (Z-XXI), 16.47 (E-XXI); δ : 18.11 (Z-XXIV), 18.67 (E-XXIV); δ : 25.43 (β,γ'), 25.72 (Z-XIV), 26.26 (E-XIV), 27.58 (β,γ' of XXV), 28.21 (Z-XXV), 28.51 (E-XXV).

3.2.11 The Attempted Preparation of 2-Chloro-2-Methyl-pentylphosphonic Dichloride (1c) (9)

A 100 ml three-necked flask was equipped with a water condenser (Liebig) with $CaCl_2$ drying tube, thermometer,

stopper, and magnetic stirrer bar. PCl_5 (20.85 g, 0.1 mol) was placed in the flask through the side neck via a powder funnel and dry benzene (15 ml) was added. The suspension was cooled at 15°C and 2-methyl-1-pentene (9 g, 13.2 ml, 0.107 mol) was added dropwise through a dropping funnel. After the addition of only few drops, the mixture solidified rapidly; more benzene was added (20 ml) and the alkene was also diluted with 5 ml benzene. The addition was continued and the temperature was kept constant (15°C). When the alkene addition was completed, the dropping funnel was replaced by a powder funnel through which P_2O_5 (5 g, 0.035 mol) was added. The reaction mixture was heated at 60°C and stirred at this temperature for 3 1/2 h. The heat source was removed and the stirring was continued overnight at room temperature. The solution was filtered through a ground glass sinter funnel and the brown precipitate was washed with 20 ml benzene. The filtrate was evaporated off to remove benzene and $POCl_3$ and the product obtained was purified by bulb-to-bulb distillation at oven temperature 75-95°C (0.25 mmHg) to give a colourless oil. Yield: 16.81g, 78%; ^{31}P nmr clearly shows that the compound obtained is a mixture of five products (1a-1e). ^{31}P nmr ($CDCl_3$) δ : 28.02, 28.89, 46%; δ : 38.04, 44%; δ : 42.47, 44.56, 10%; ^1H nmr ($CDCl_3$) δ : 3.26 (2H, d, J_{H-H}= 14.8Hz), 3.29 (2H, d, J_{H-H}= 17.23Hz), 3.40 (2H, d, J_{H-H}= 18.41Hz) [these doublets correspond to α-CH_2 in 1c and α-CH_2 in 1d/e (E/Z), but no exact assignment could be made]; 5.51 (1H, t, J_{H-H}= 7.5Hz, α-CH_2 in 1d/e), 5.86 (1H, d, J_{H-P}= 38.36Hz, α-CH

in 1a/1b). These data correspond to Mixture 1.

3.2.12 The Attempted Preparation of 2-Chloro-2-Methylpentylphosphonic Dichloride (1c) (Modified Procedure)

The same procedure as above was repeated, with the following modification: after the complete addition of alkene the mixture was stirred at room temperature for 22 h. Thereafter P_2O_5 was added and the stirring was continued for 24 h at room temperature. The same work-up as for Exp. 3.2.11 was performed. The product obtained consisted of a mixture of five compounds in slightly different amounts than the ones obtained in Exp. 3.2.11. ^{31}P nmr ($CDCl_3$) δ: 27.88, 28.74, 42%; 37.94, 48%; 42.32, 44.52, 10%. These data correspond to Mixture 1a.

3.2.13 The Attempted Separation of Compounds in Mixture 1 by Bulb-to-Bulb Distillation

Mixture 1 (3.63 g, 0.014 mol) was distilled on a bulb-to-bulb apparatus. Two fractions were collected at oven

temperatures 75-85°C and 85-110°C (0.4mmHg). Both fractions showed similar compositions. ^{31}P nmr ($CDCl_3$) δ : 27.77, 28.63, 60%; 37.89, 25%; 42.22, 15%. These data correspond to Mixture 1b.

3.2.14 The Esterification Reaction of Mixture 1

Procedure 1

To a solution of ethanol (1.5 ml, 0.02 mol), pyridine (2 ml, 0.02 mol) and dry benzene (8 ml), Mixture 1 (2.0 g, 0.01 mol) in benzene (3 ml) was added dropwise with stirring. The mixture obtained was heated at 50°C for 2 h, then cooled, filtered, and washed with benzene (3 x 5 ml). The organic layer was extracted with aqueous Na_2CO_3 (3 x 15 ml) solution and dried over Na_2SO_4. Removal of solvent gave the crude ester, which was purified on a bulb-to-bulb distillation apparatus at oven temparature 90-120°C (0.3 mmHg). Yield: 1.17 g, 80%. The product obtained was a mixture of five compounds (2a-2e). ^{31}P nmr ($CDCl_3$) δ : 15.51 (2b), 16.27 (2a), 52%, 22.19 (2c), 40%, 25.44 (2e), 25.79 (2d), 8%; ^1H nmr ($CDCl_3$) δ : 4.9 (1H, t, J_{H-H}= 7.01Hz, γ -CH in 2e/2d), 5.32 (1H, d, J_{H-P} = 18.7Hz, α -CH in 2a/2b). These data correspond to Mixture 2. Assignment of peaks was done by

comparison to pure synthesized compounds (XIV) and (XXI).

Procedure 2

Mixture 1 (11.02 g, 4.81 x 10^{-2} mol) in 10 ml ethanol was added dropwise with vigorous stirring and cooling (5-10 °C) to a solution of EtONa (2M) in ethanol. When the addition was completed, the cooling source was removed and the mixture was stirred at room temperature for 24 h. The basic solution was acidified (pH 7) with 2 ml CF_3COOH, and filtered through a ground glass sinter funnel. Water (15 ml) was added and the mixture was extracted with CCl_4(3 x 10ml). After drying ($MgSO_4$) and evaporating the solvent under reduced pressure, the product was purified by bulb-to-bulb distillation at oven temperature 100-125 °C (0.5 mmHg). yield: 8.1 g, 76%. This product was obtained as a mixture of α,β- and β,γ-unsaturated products only. ^{31}P nmr ($CDCl_3$) δ : 15.68 (3b), 16.51 (3a), 71%; 25.46 (3e), 25.75 (3d), 26.30 (3c), 29%; ^{1}H nmr ($CDCl_3$) δ : 4.92 (1H, t, J_{H-H}= 7.02Hz, γ-CH in 3c/3d), 5.32 (1H, d, J_{H-P}= 18.65Hz, α-CH in 3a/3b). These data correspond to Mixture 3. Assignment of peaks was done by comparison to pure synthesized compounds (XIV) and (XXI).

3.2.15 The Attempted Separation of α,β- and β,γ-Unsaturated Phosphonates in Mixture 3'

Mixture 3' [consisting of (E,Z) - (α,β)-unsaturated phosphonates 33% and (E,Z)-(β,γ)-unsaturated phosphonates 67%] (2.2 g, 9.99 x 10^{-3} mol) was dissolved in a benzene : ethyl acetate mixture (4:1) and placed on a column of silica (4.5 x 60 cm). Elution with the following solvents was performed: benzene - ethyl acetate (4:1) (1l) (fractions 1-100); acetone (1l) (fractions 101-200).

Fractions 1-100 were mixed together and evaporated to dryness to give a colourless oil. This was distilled by bulb-to-bulb distillation and three fractions were collected: (i) oven temperature 60-75°C (0.4 mmHg); yield: 0.4 g; ^{31}P nmr ($CDCl_3$) δ : 15.51 (3b'), 16.27 (3a'), 15%; 25.06 (3e'), 25.45 (3d), 26.37 (3c'), 85%; (ii) oven temperature 75-85°C (0.4 mmHg); yield : 0.06 g; ^{31}P nmr ($CDCl_3$) δ : 15.52 (3b'), 16.28 (3a'), 15%; 25.06 (3e'), 25.45 (3d'), 25.81 (3c'), 85%; (iii) oven temperature 85-100°C (0.4 mmHg); yield: 0.06 g; ^{31}P nmr ($CDCl_3$) δ : 15.47 (3b'), 16.23 (3a'), 30%; 25.06 (3e'), 25.41 (3d'), 25.76 (3c'), 70%.

Fractions 101-103 were combined and the solvent was evaporated off leaving behind a colourless oil. Yield: 0.7 g; ^{31}P nmr ($CDCl_3$) δ : 15.52 (3b'), 16.28 (3a'), 20%; 25.06 (3e'), 25.46 (3d'), 25.81 (3c'), 80%. Anal. calcd. for $C_{10}H_{21}PO_3$: C 54.53, H 9.61%; found: C 54.25, H 9.91%.

Fractions 134-152 were combined and concentrated to a small volume (10 ml) on a rotary evaporator and the residual oil was purified by bulb-to-bulb distillation. Two fractions were collected: (i) oven temperature 50-65°C (0.4 mmHg); yield : 0.043 g; ^{31}P nmr ($CDCl_3$) δ : 15.49 (3b'), 16.24 (3a'), 10%; 25.04 (3e'), 25.42 (3d'), 25.78 (3c'), 90%; (ii) oven temperature 70-95°C (0.4 mmHg); yield : 0.23 g; this fraction consists mainly of an unknown compound.

Fractions 152-200 showed, after evaporation of the solvent, the presence of an unknown compound.

Assignment of peaks in Mixture 3' was done by comparison to pure synthesized compounds (XIV) and (XXI).

3.2.16 Isomerisation of 2-Methyl-1-Pentenylphosphonic Ester

(a) EtONa/EtOH

A mixture of 2-methyl-1-pentenylphosphonic ester (0.2 g, 9.08×10^{-4} mol) and EtONa (0.6 ml, 2 mol equiv., 1.95×10^{-3} mol, 3.26M) in ethanol was incubated at room temperature for 120 h. To the above mixture, a drop of F_3CCOOH was added, the solvent was evaporated off, and $CDCl_3$ was added to precipitate $F_3CCOONa$. Few drops of water were added, the mixture was shaken very well and, after the two layers separated completely, the water layer was withdrawn. The organic layer was dried over $MgSO_4$ and then transferred to the nmr tube. ^{31}P nmr ($CDCl_3$) δ : 15.58 (Z-XXI), 16.37 (E-XXI), 18.53 (Z-XXIV), 19.19 (E-XXIV), 21%; 25.22 (β,γ'), 25.58 (Z-XIV), 26.02 (E-XIV), 28.61 (Z-XXV), 28.95 (E-XXV), 79%.

(b) t-BuOK/t-BuOH

A mixture of 2-methyl-1-pentenylphosphonic ester (0.2 g, 9.08×10^{-4} mol) and t-BuOK (0.12 g, 15% excess, 1.76M) in t-butanol was incubated at room temperature for 120 h. The

mixture was worked up in the same way as for 3.2.16 (a). ^{31}P nmr ($CDCl_3$) δ : 15.63 (Z-XXI), 16.43 (E-XXI), 18%, 18.19 (Z-XXIV), 18.8 (E-XXIV), trace; 25.3 (β,γ'), 25.67 (Z-XIV), 26.17 (E-XIV), 82%, 27.72 (β,γ' of XXV), 28.32 (Z-XXV), 28.62 (E-XXV), trace.

3.2.17 Isomerisation of 2-Methyl-2-Pentenylphosphonic Ester

(a) EtONa/EtOH

The same experimental procedure and similar work up as for 3.2.16 (a) was performed. ^{31}P nmr ($CDCl_3$) δ : 15.66 (Z-XXI), 16.46 (E-XXI), 18.29 (Z-XXIV), 18.9 (E-XXIV), 19%; 25.71 (Z-XIV), 26.24 (E-XIV), 28.42 (Z-XXV), 28.75 (E-XXV), 81%.

(b) t-BuOK/t-BuOH

The same experimental procedure and the same work up as for 3.2.16 (a) was performed. ^{31}P nmr ($CDCl_3$) δ : 15.53 (Z-XXI), 16.29 (E-XXI), 20%, 17.54 (Z-XXIV), 18.02 (E-XXIV), trace; 25.49 (Z-XIV), 25.87 (E-XIV), 80%, 27.7 (β,γ' of XXV), trace.

3.2.18 Isomerisation of Mixture 2

Mixture 2 (0.95 g, 3.7×10^{-3} mol) was added to a 1.53M t-BuOK/t-BuOH solution and the mixture obtained was incubated at 30°C for 70 h. After evaporation of the solvent, 10 ml H_2O was added and the mixture was extracted with $CHCl_3$ (3 x 10 ml). After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure, the product was purified by bulb-to-bulb distillation at oven temperature 100-130 °C (0.4 mmHg). Yield: 0.52 g, 63%; ^{31}P nmr ($CDCl_3$) δ : 15.56 (2b'), 16.32 (2a'), 17%; 25.12 (2e'), 25.50 (2d'), 25.87 (2c'), 83%. These data correspond to Mixture 2'.

3.2.19 Isomerisation of Mixture 3

(a) <u>EtONa/EtOH</u>

Mixture 3 (0.05 g, 2.27×10^{-4} mol) was added to a 1M EtONa/EtOH solution and the mixture obtained was incubated at room temperature for 70 h. The same work up as for 3.2.16 (a) was performed. ^{31}P nmr ($CDCl_3$) δ : 15.67 (3b'), 16.22 (3a'), 33%; 17.1 (dealkylated product); 26.06 (3e'), 26.25 (3d'), 26.96 (3c'), 67%. These data correspond to

Mixture 3'.

(b) t-BuOK/t-BuOH

Mixture 3 (0.05 g, 2.27×10^{-4} mol) was added to a 1.3M t-BuOK/t-BuOH solution and the mixture obtained was incubated at room temperature for 30 h. The same work up as for 3.2.16 (a) was performed. ^{31}P nmr ($CDCl_3$) δ : 15.49 (3b"), 16.25 (3a"), 20%; 25.03 (3e"), 25.42 (3d"), 25.78 (3c"), 80%. These data correspond to Mixture 3".

NOTE: Assignment of peaks in Mixtures 2', 3', and 3" was done by comparison to pure synthesized compounds (XIV) and (XXI).

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APPENDIX 1

1. GAS CHROMATOGRAPHY. COLUMNS AND CONDITIONS

CW 20M (carbowax/polyethylene glycol) and SE 30 (polydimethylsiloxane) glass capillary columns were prepared at the Institute for Chromatography of the University of Pretoria. The columns were deactivated and statically coated according to the methods described by Grob (100). Both columns were of 0.4 m film thickness in 0.35 mm i.d. glass tubing with attached flexible fused silica-end pieces (101). 50 m CW 20M and 12.5 m SE 30 were connected with press-fit couplings (102) to get a complete separation of all isomers. One microliter of sample dissolved in AnalaR acetone was injected (sample splitter system used) at the injector temperature 230°C. The carrier gas used was He at linear flow speed of 25 cm s^{-1}. The temperature program used was the following:

$$30^{\circ}C\ (1\ min.) \xrightarrow{10^{\circ}C\ min^{-1}} 160^{\circ}C \xrightarrow{1^{\circ}C\ min^{-1}} 170^{\circ}C\ (isotherm)$$

Mass spectra were recorded on a HP 5988 Quadrupole Mass Spectrometer directly coupled to a HP 5890 Gas

Chromatograph (described above) with He as the carrier gas. The following temperatures were used: source temperature 200 C, GC-MS interface temperature 280 C, analyser temperature 180 C. A full scan was made from 20-500 a.m.u. (2 scans per second).

2. REGIO- AND STEREOISOMER SEPARATIONS BY CAPILLARY GAS CHROMATOGRAPHY

2.1 Qualitative Separation of Mixture 3

Capillary gas chromatography was found to be one of the highest precision methods (103, 104) for the determination of stereoisomeric mixtures. In the present project this method was used for the identification of products in Mixture 3, as well as for the separation of E and Z isomers in compounds (XIV) and (XXI).

The successful determination of closely related compounds was critically dependent on the proper choice of the stationary liquid phase. It was found that when a 25 m SE 30 column was used, an incomplete separation of Mixture 3 was achieved (Fig. 14a). SE 30 is a non-polar phase and separates the components according to their volatility. With

a 50 m CW 20M column, a better but still incomplete resolution was obtained (Fig. 14b). Carbowax is a polar phase which interacts with polarisable groups in the existing compounds, namely the carbon-carbon double bonds and the phosphonate ester groups. This behaviour accounts for the change in the elution order observed with this particular column.

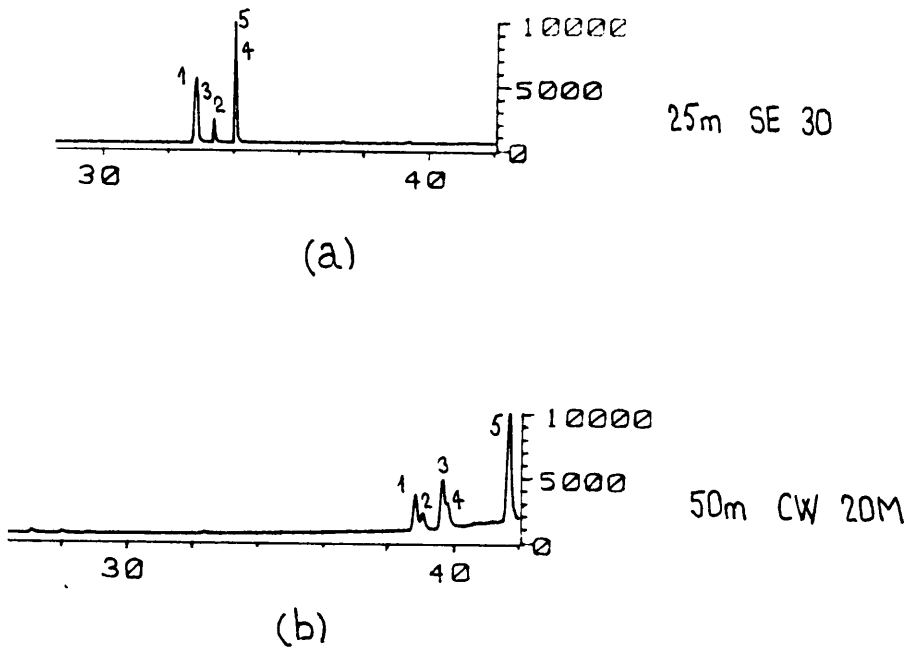

Fig.14 The separation of Mixture 3 on two different glass capillary columns

It was therefore concluded that a better resolution could only be achieved by using a combination of phases. In order to decide on the length of each phase so that when combined they will give a more complete separation, a window diagram (105) (Fig. 15) was constructed. The resultant qualitative separation obtained with two coupled columns is shown in Fig. 16.

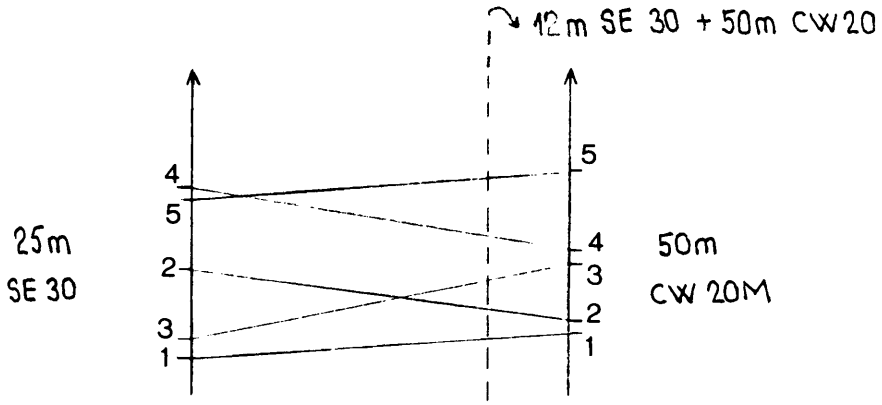

Fig. 15 : The window diagram for the separation of Mixture 3

Fig. 16 : The separation of Mixture 3 on a combination of stationary liquid phases

2.2 Quantitative Determinations of Regio- and Stereoisomers in Compounds (XIV), (XXI), and Mixture 3

Using the same column conditions* as for the qualitative determination of compounds in Mixture 3, the composition of products (XIV) and (XXI) was determined. Thus, the chromatogram recorded for compound (XIV) showed two peaks of different intensity (Fig. 17a). Correlation of these data with the nmr information made possible the unambiguous assignment of these two peaks. Similarly, the chromatogram for compound (XXI) showed the appearance of five peaks (Fig. 17b). This result was quite unexpected in view of the fact that ^{1}H and ^{31}P nmr data showed the presence of three compounds only [(E)-(α,β)-, (Z)-(α,β)-, and (E or Z)-(β,γ)-unsaturated phosphonates]. It is therefore clear that all three β,γ-isomers are present in compound (XXI) [(E)-(β,γ)-, (Z)-(β,γ)-, and (β,γ')-unsaturated phosphonates], however, two of them are found in very low yields (1 and 2%). Finally the composition of Mixture 3 was determined (Fig. 17c) and it was found to be very similar with the one obtained from the ^{31}P nmr data (Scheme 11, p 29). All the above findings are summarized in Table 3.

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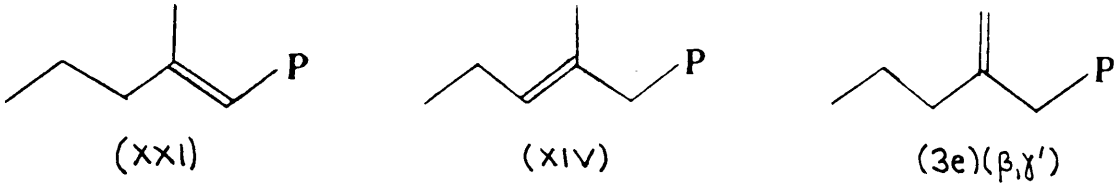
* A flame ionisation detector was used for the quantitative determination

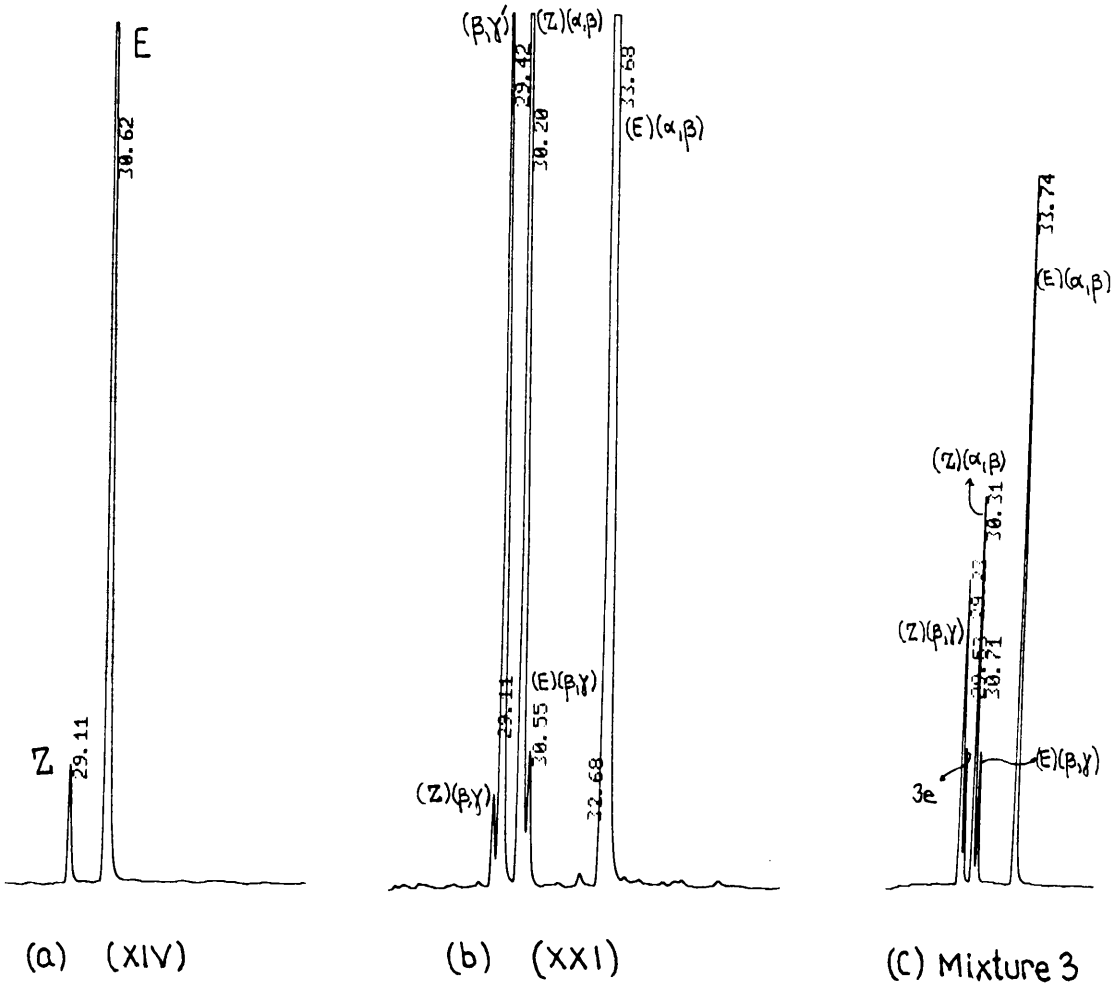
Table 3. Gas Chromatographic Separations of Compounds (XIV), (XXI), and Mixture 3

Compound	Retention Time (min)	%	Components
(XIV)	29.11	7.4	(XIV) Z
	30.62	92.6	(XIV) E
(XXI)	29.11	1.1	(XIV) Z
	29.42	15.2	(β,γ')
	30.20	21.4	(XXI) Z
	30.55	2.0	(XIV) E
	33.68	60.3	(XXI) E
Mixture 3	29.23	15.4	(XIV) Z
	29.53	7.2	3e
	30.31	21.5	(XXI) Z
	30.71	7.4	(XIV) E
	33.74	48.6	(XXI) E



(XXI) (XIV) (3e)(β,γ')

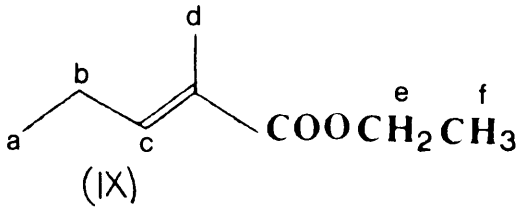
P: $P(O)(OEt)_2$



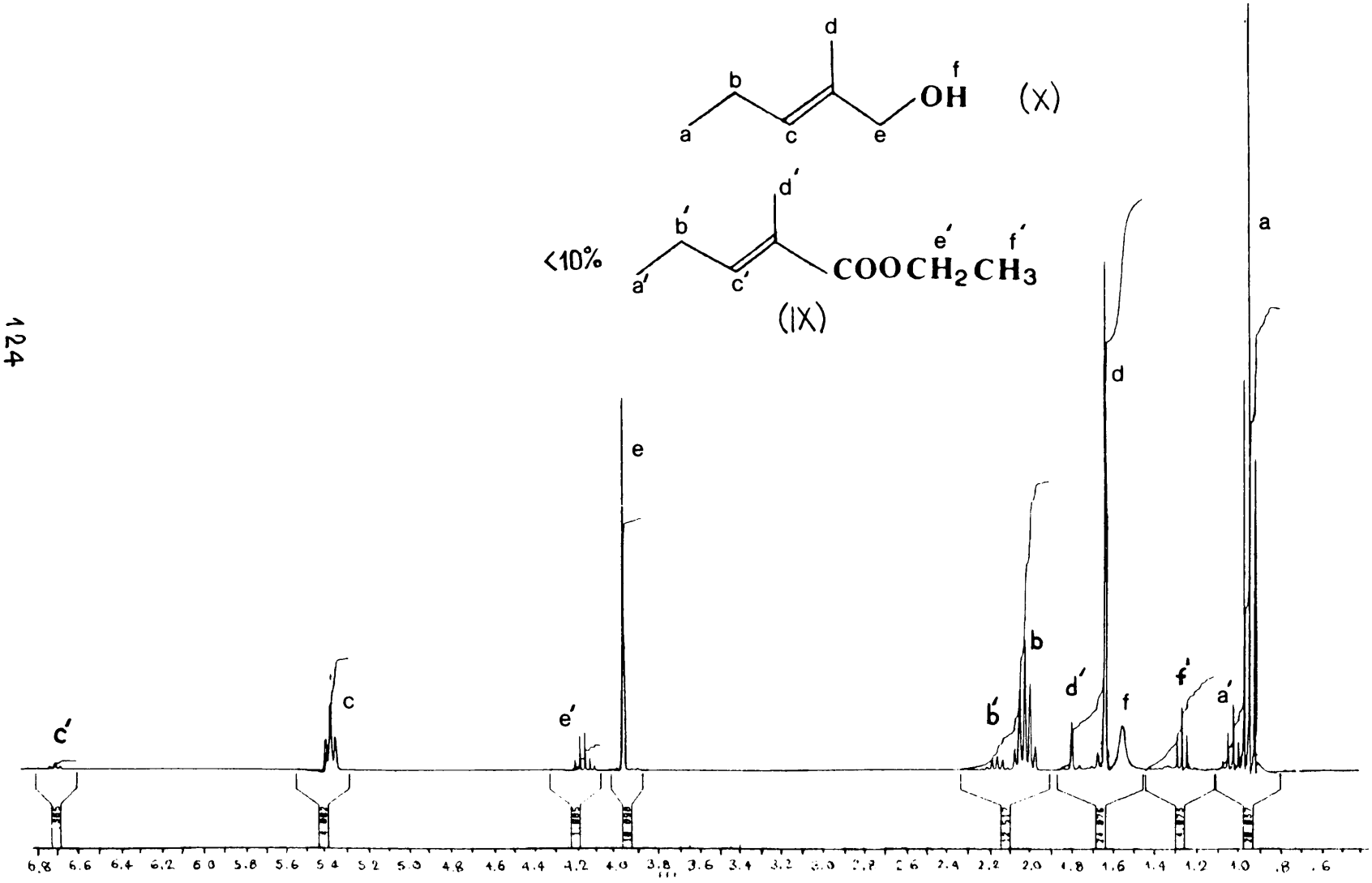
(a) (XIV) (b) (XXI) (C) Mixture 3

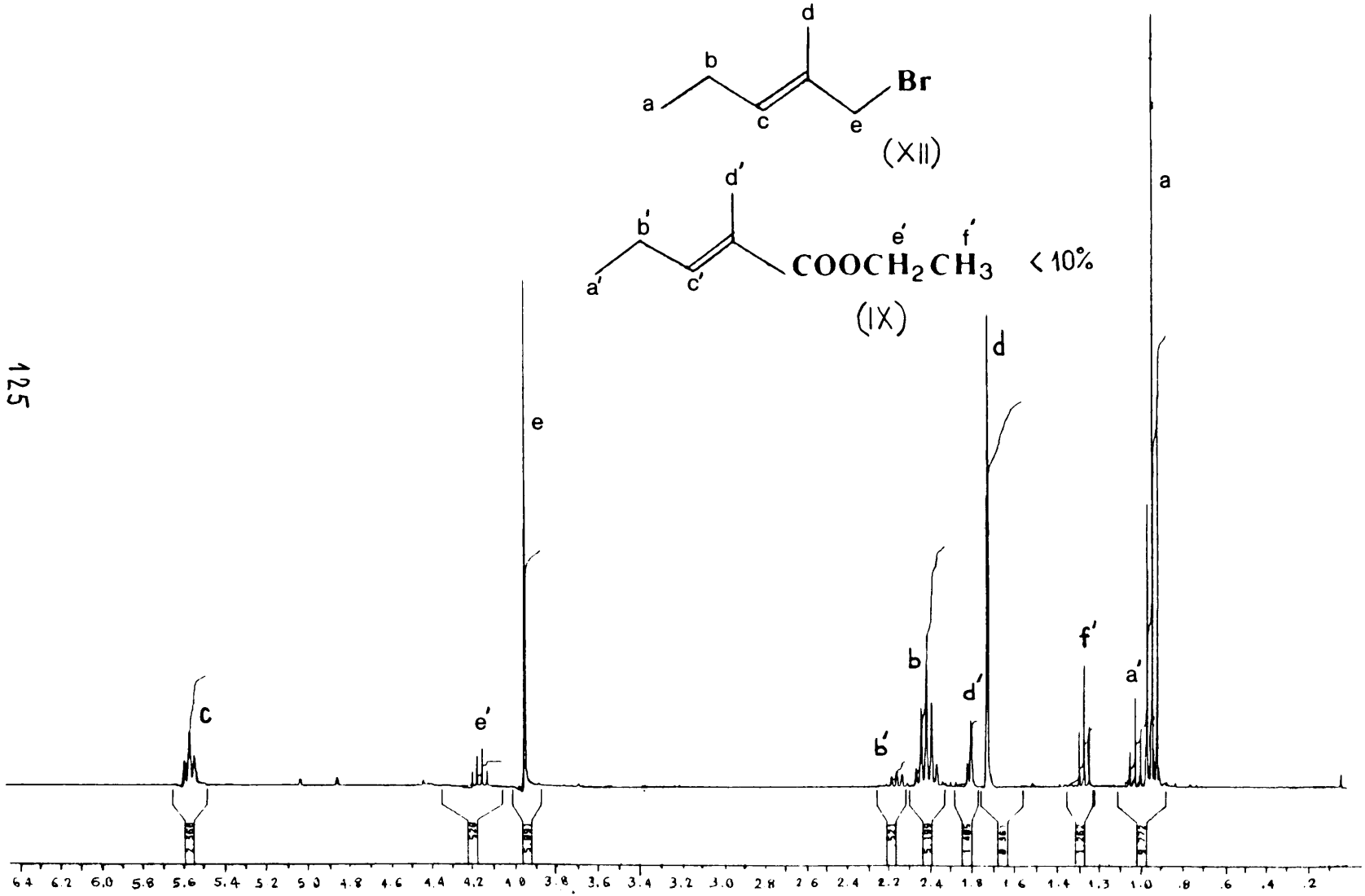
Fig. 17 : Gas chromatograms of compounds (XIV),(XXI), and Mixture 3

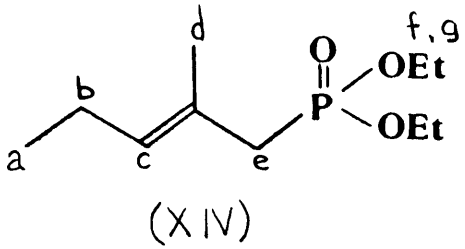
APPENDIX 2 : ^1H NMR SPECTRA



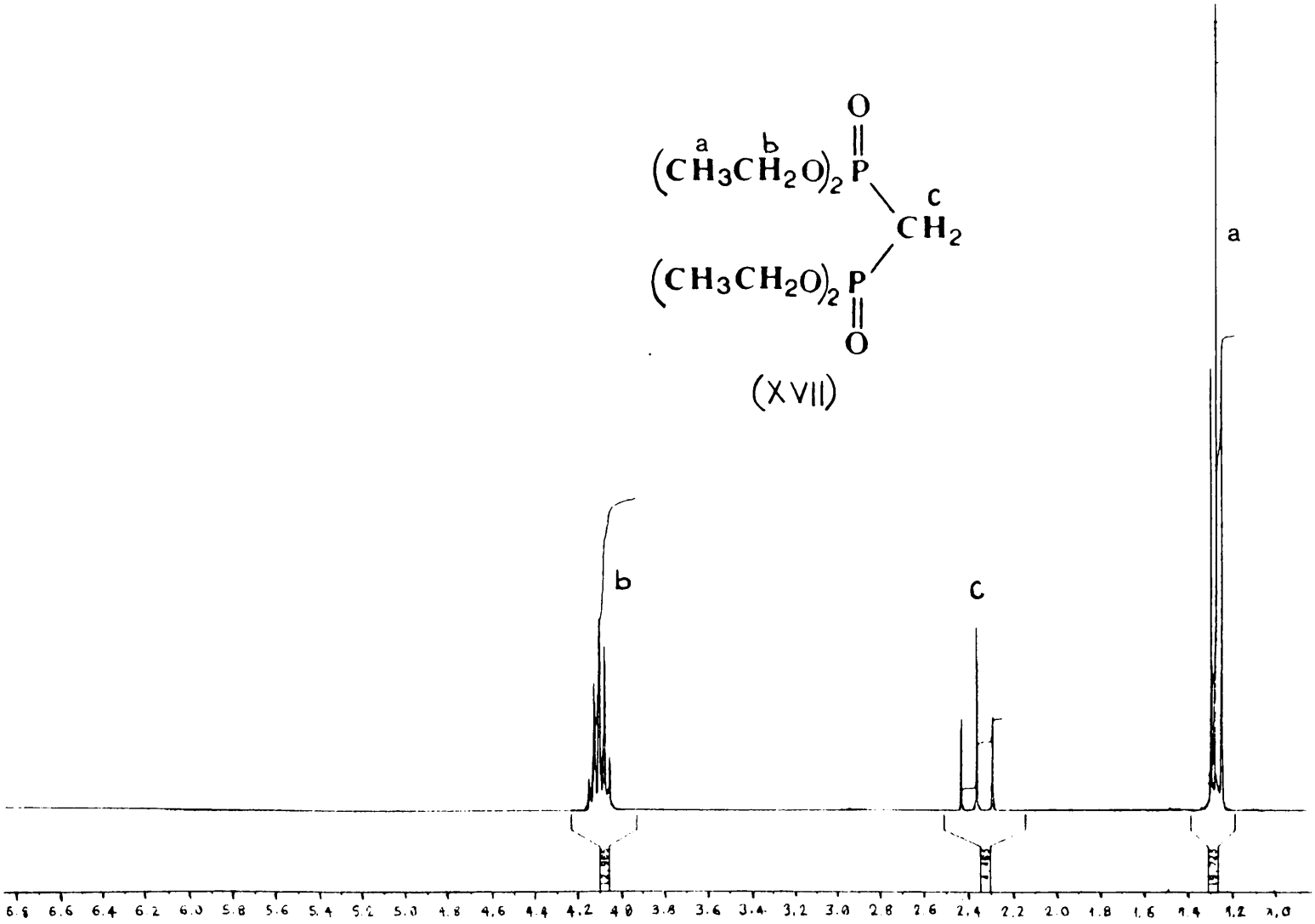
(IX)

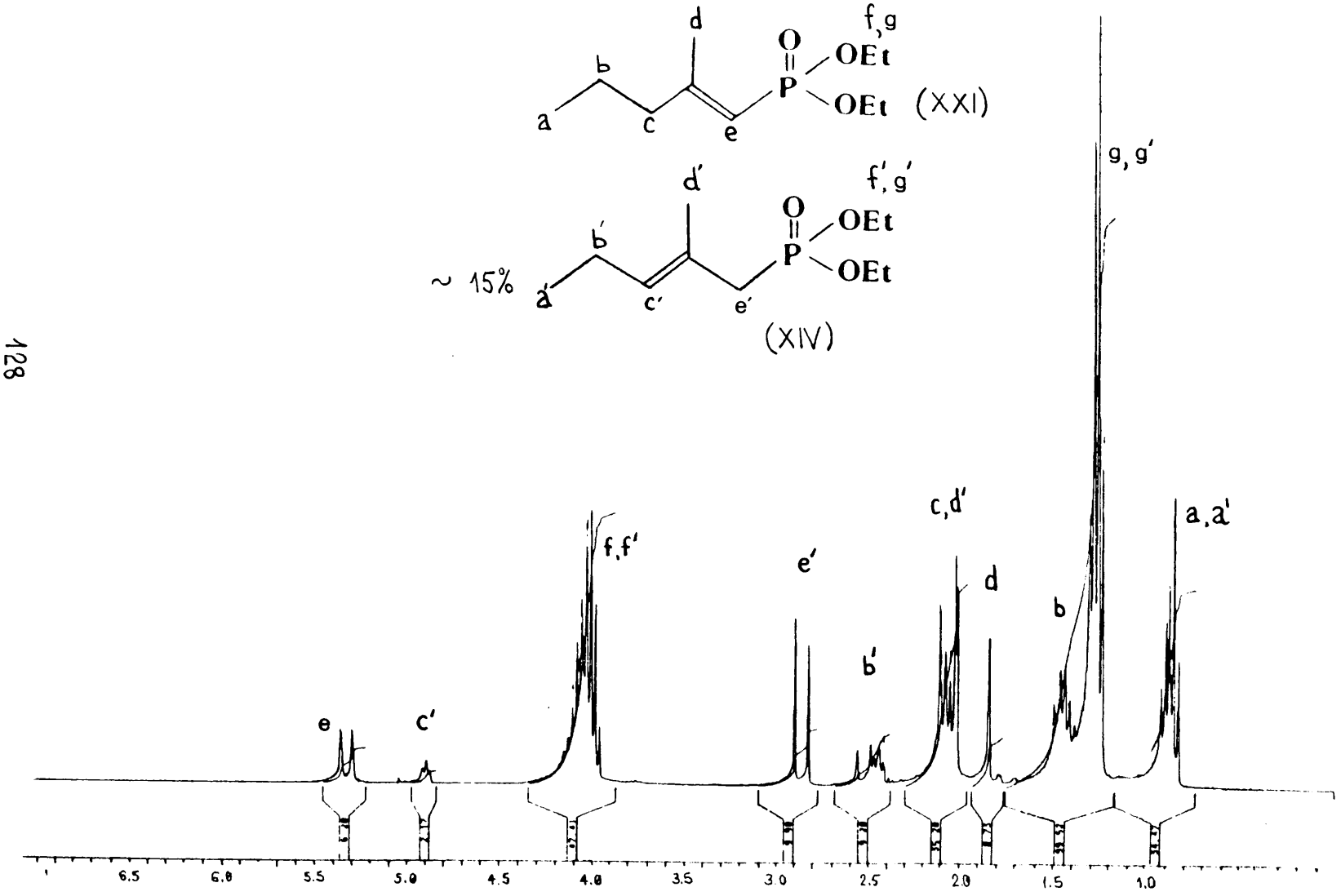




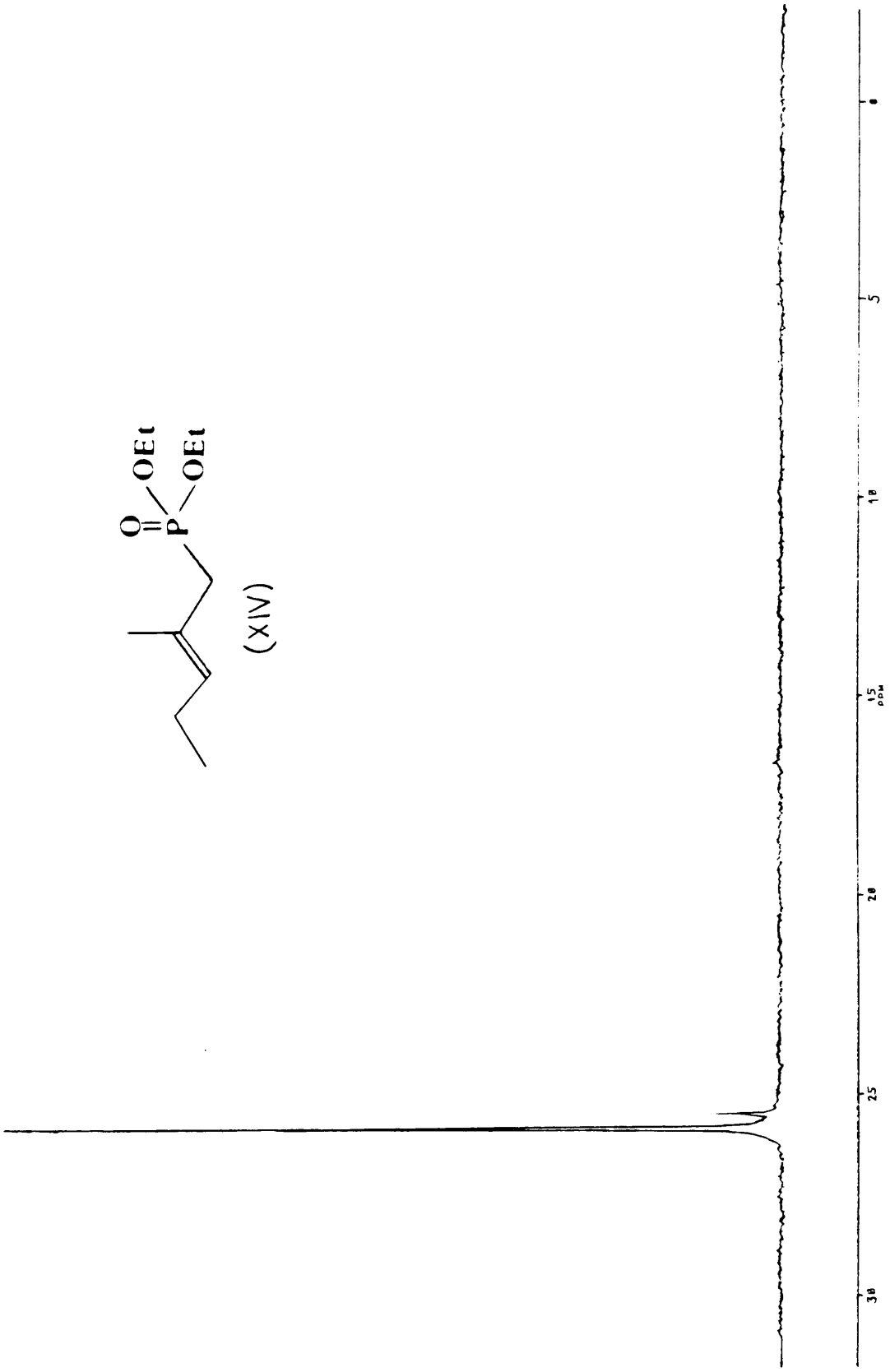


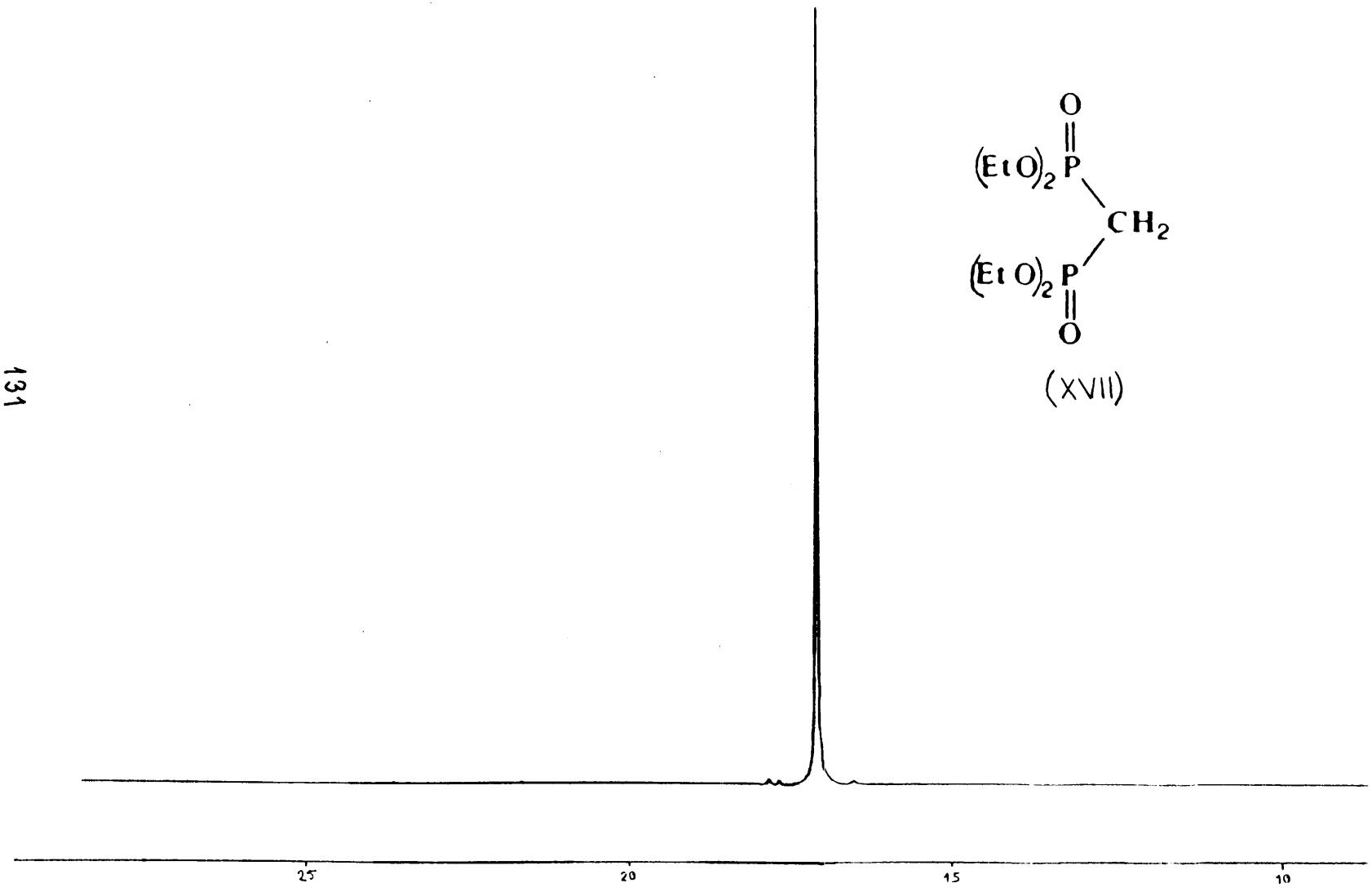
(XIV)



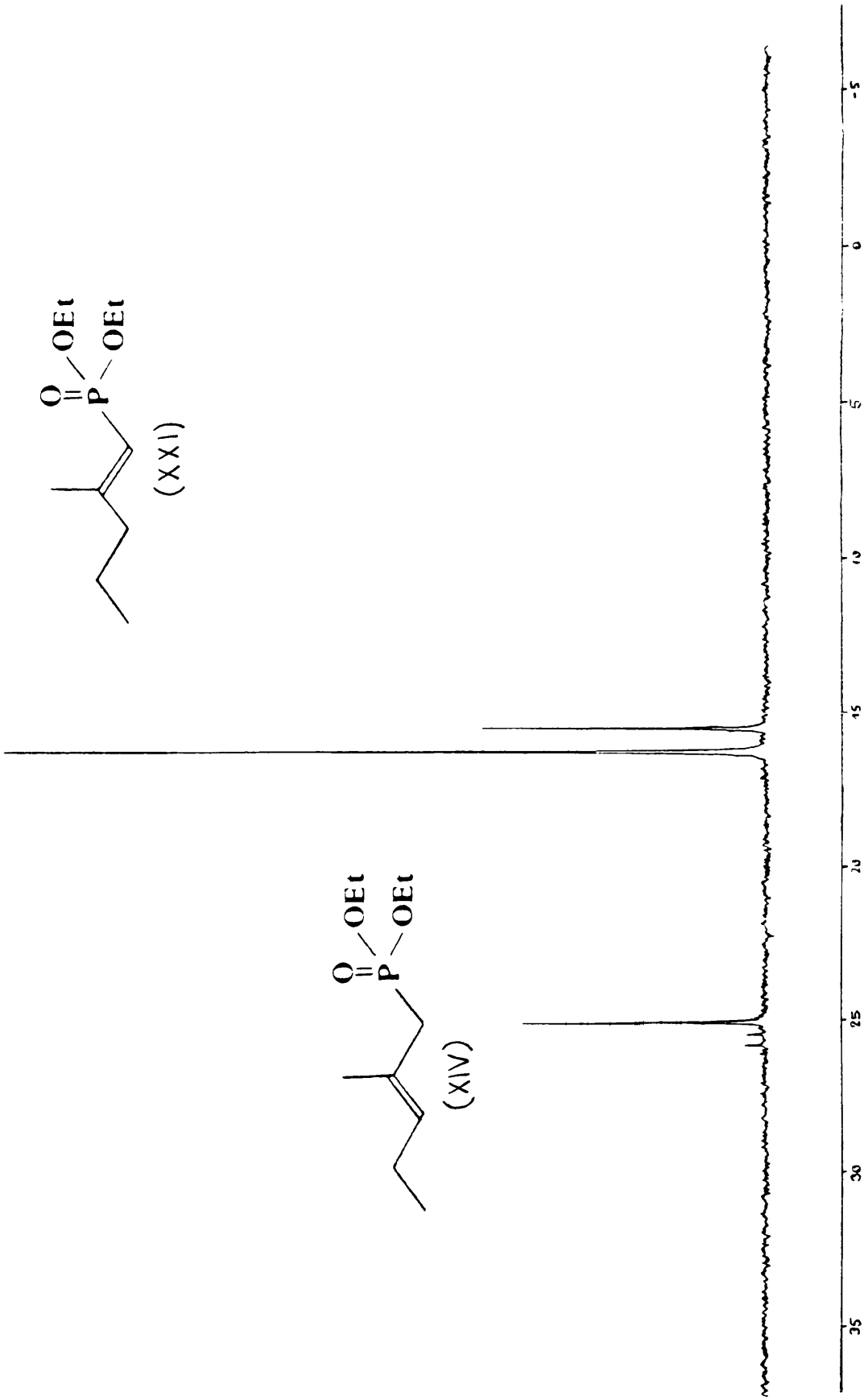


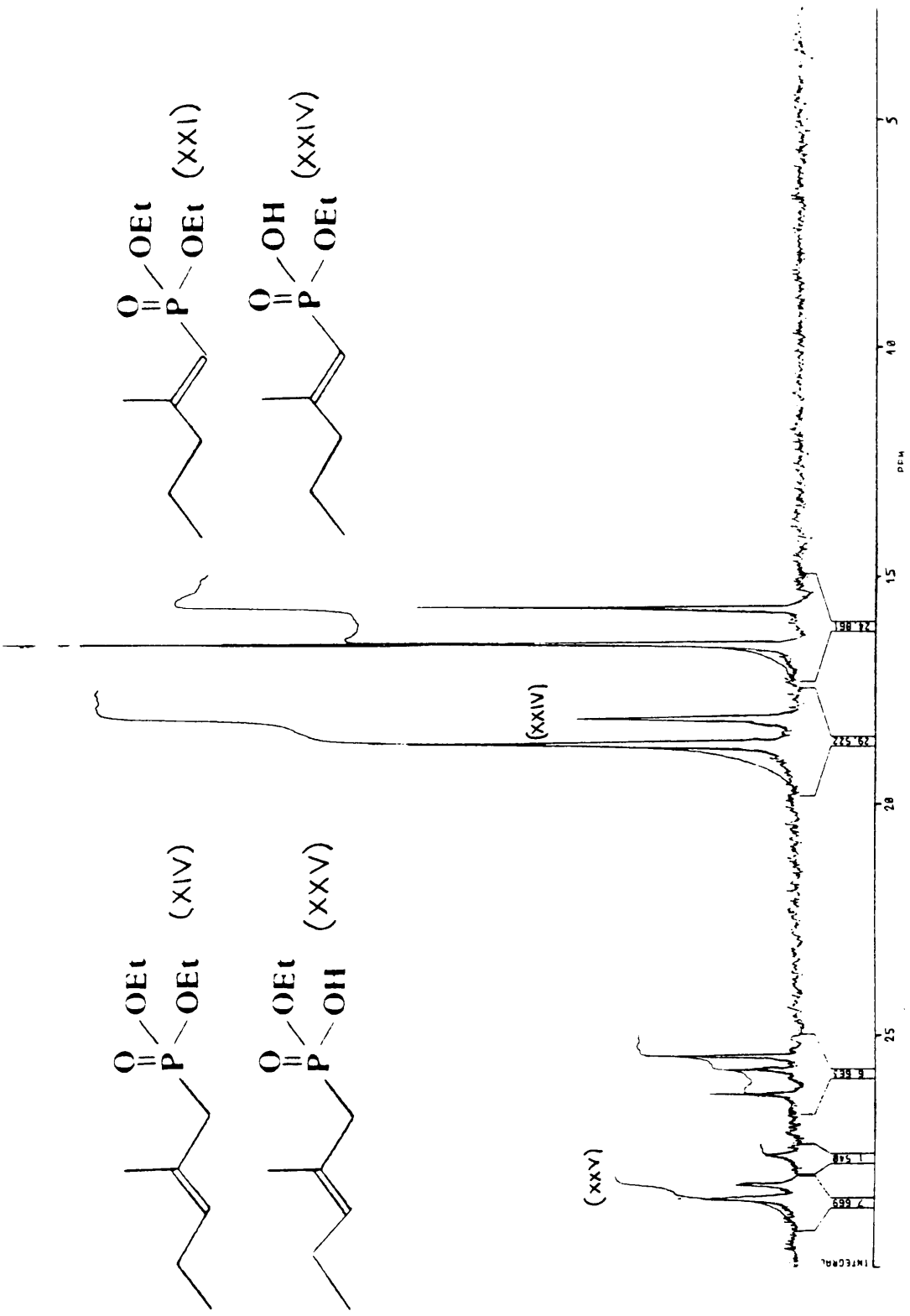
APPENDIX 3 : ^{31}P NMR SPECTRA



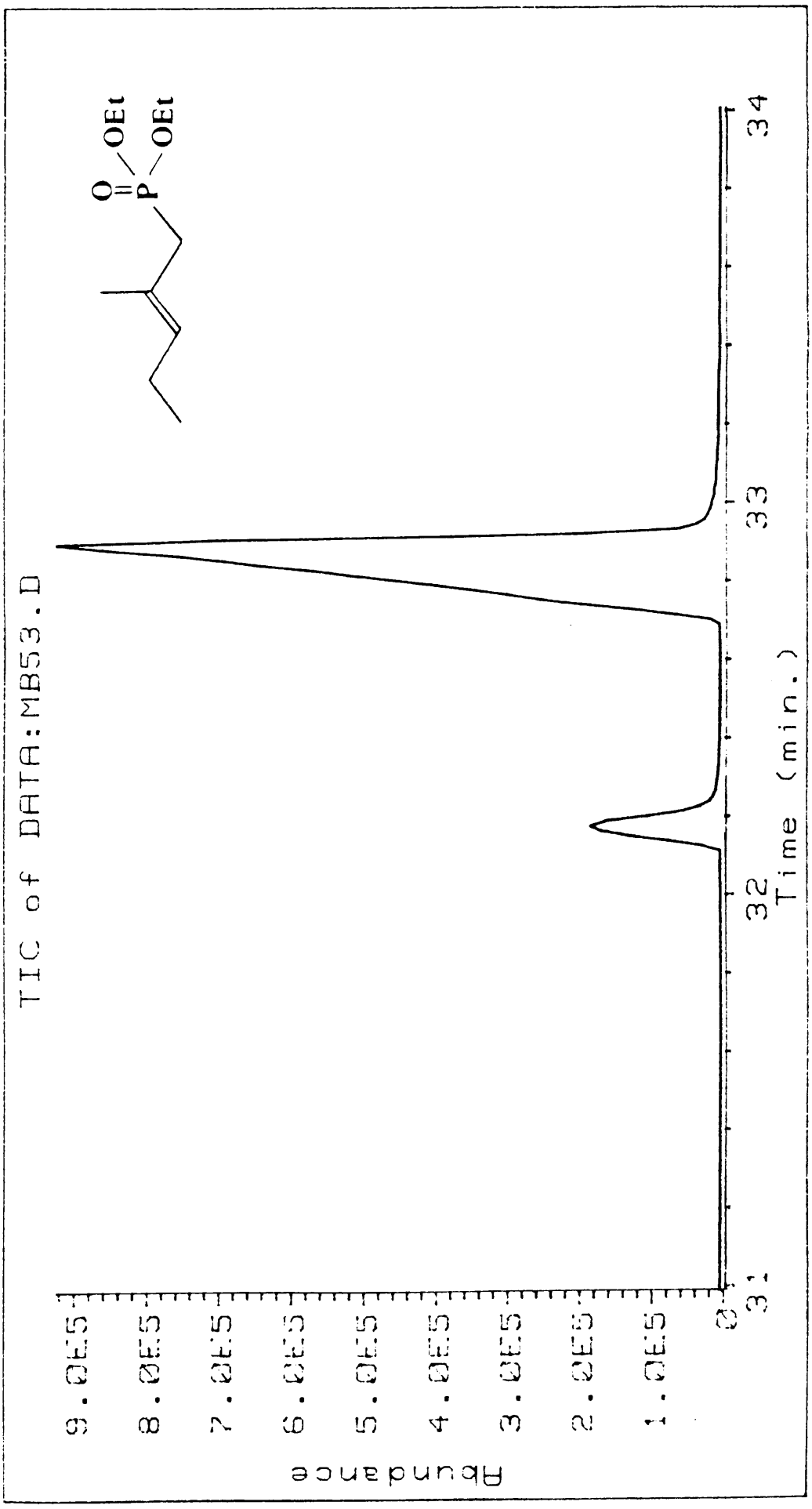


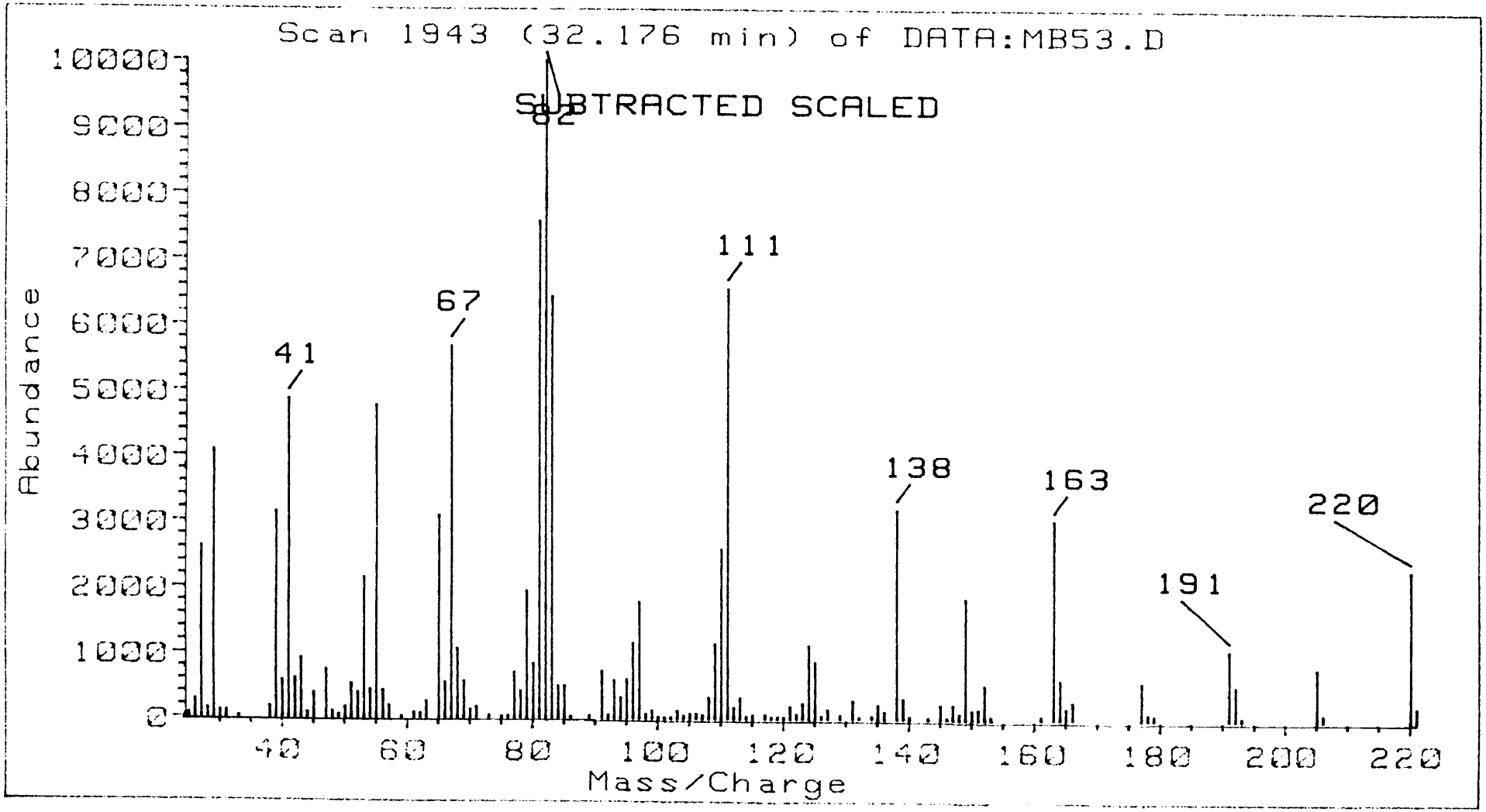
(XVII)

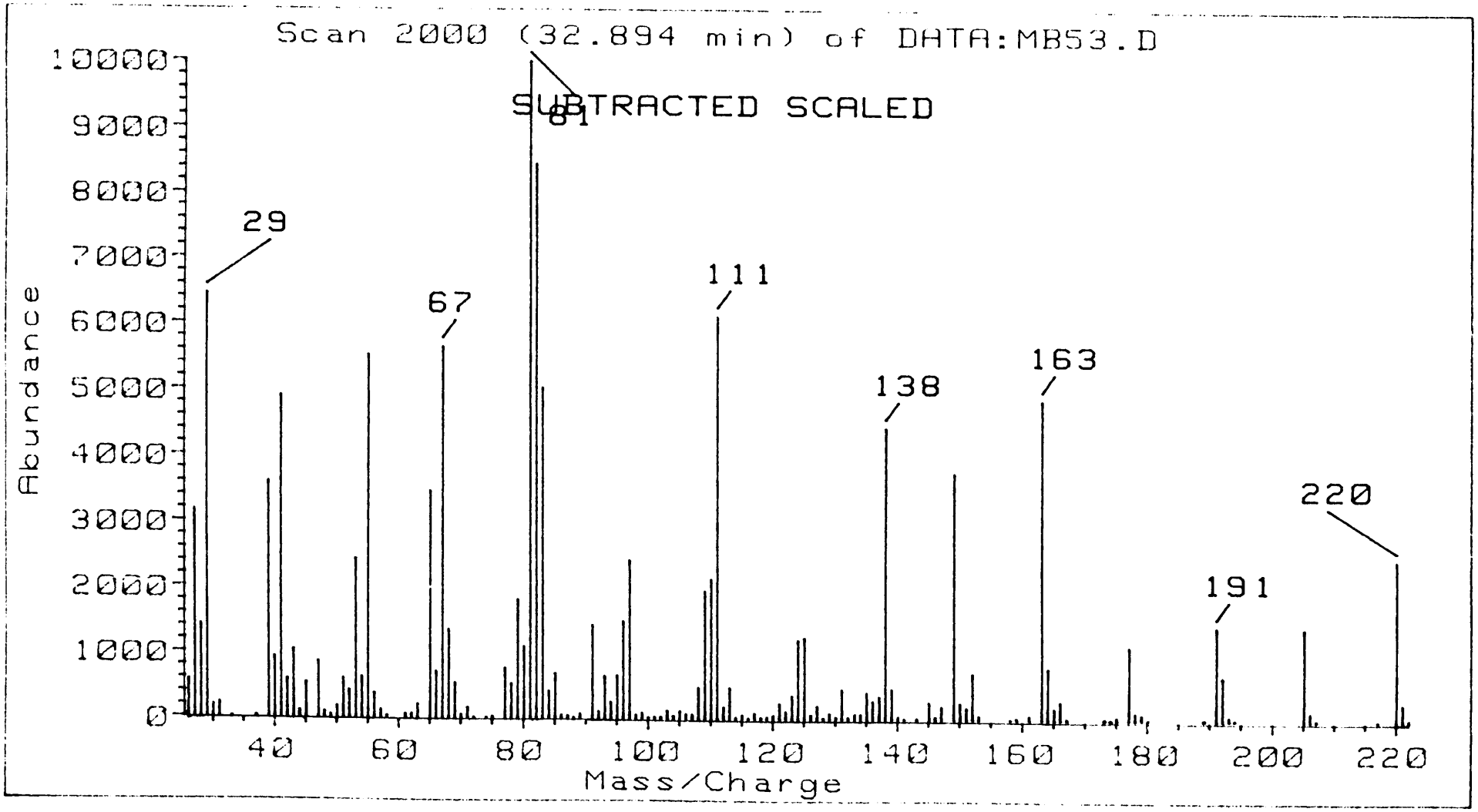




APPENDIX 4 : GAS CHROMATOGRAMS AND MASS SPECTRA







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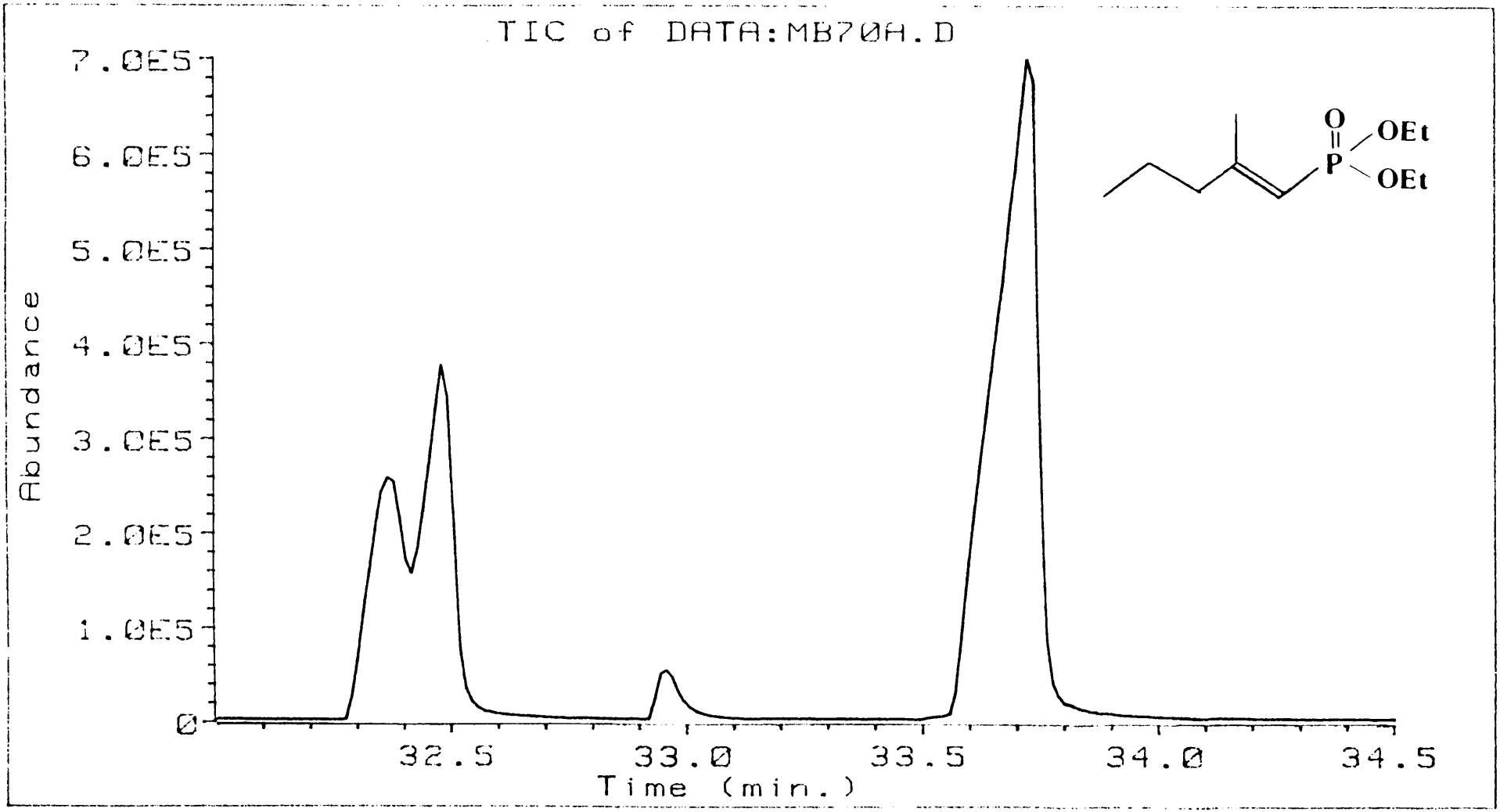

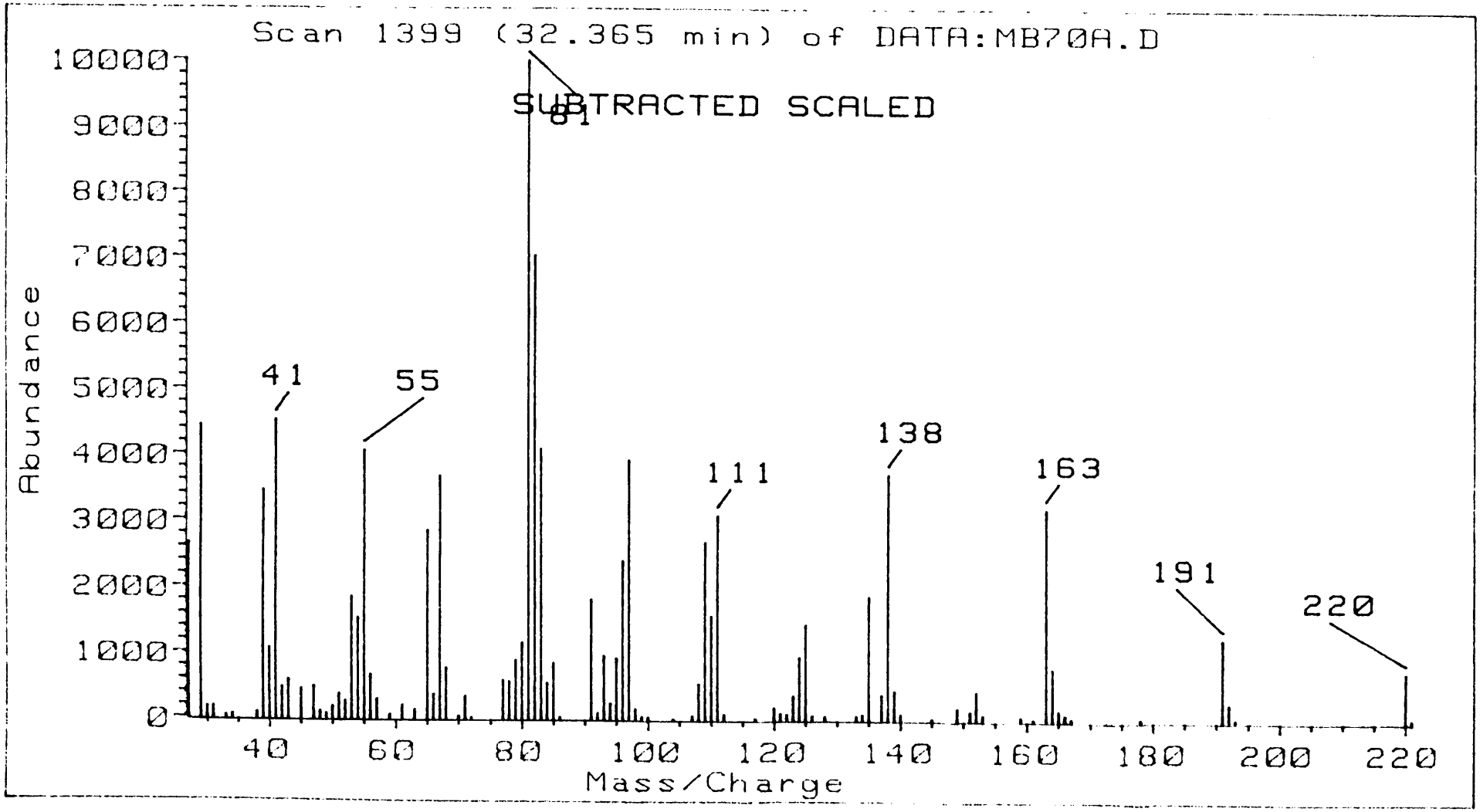

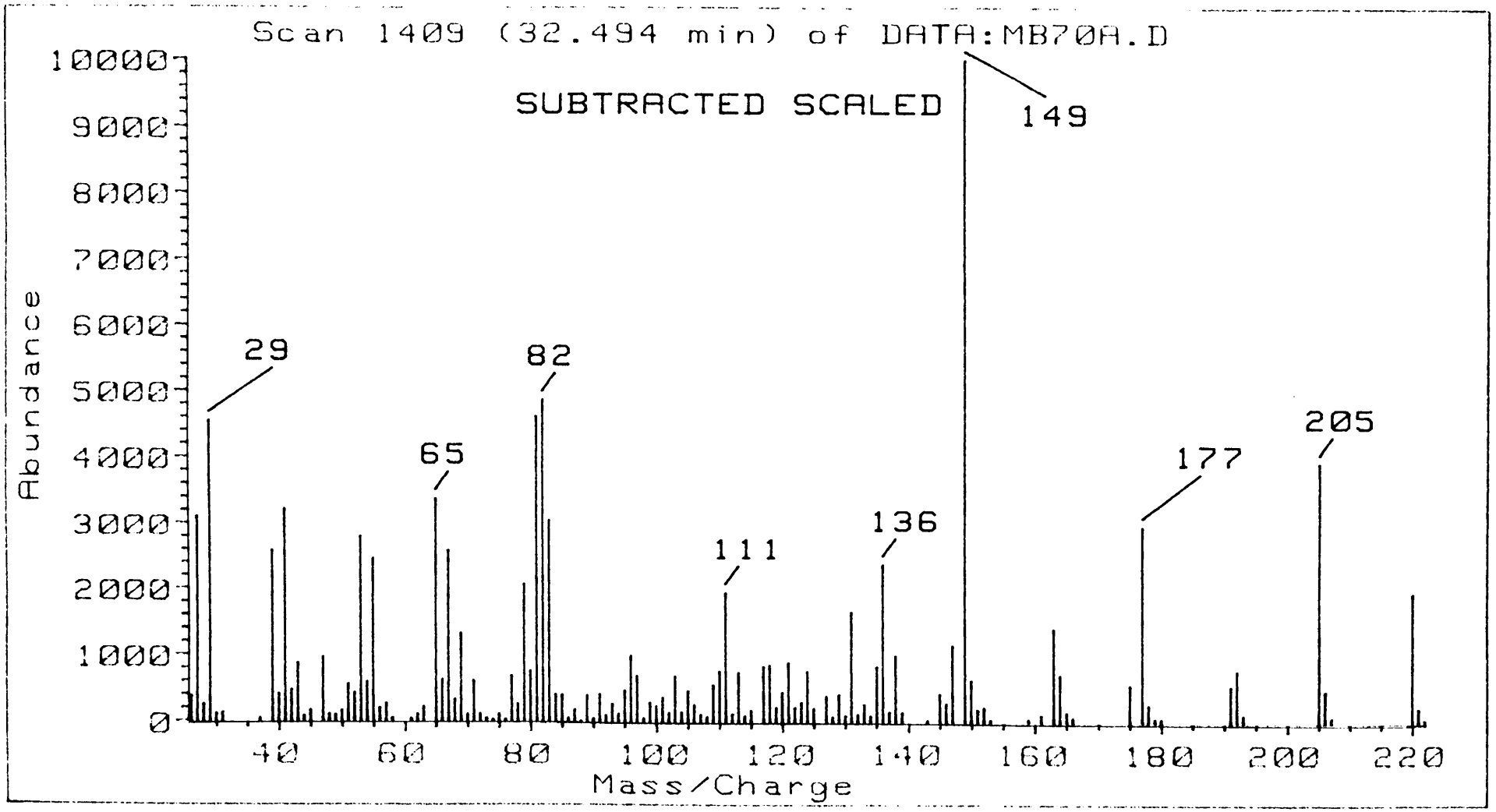

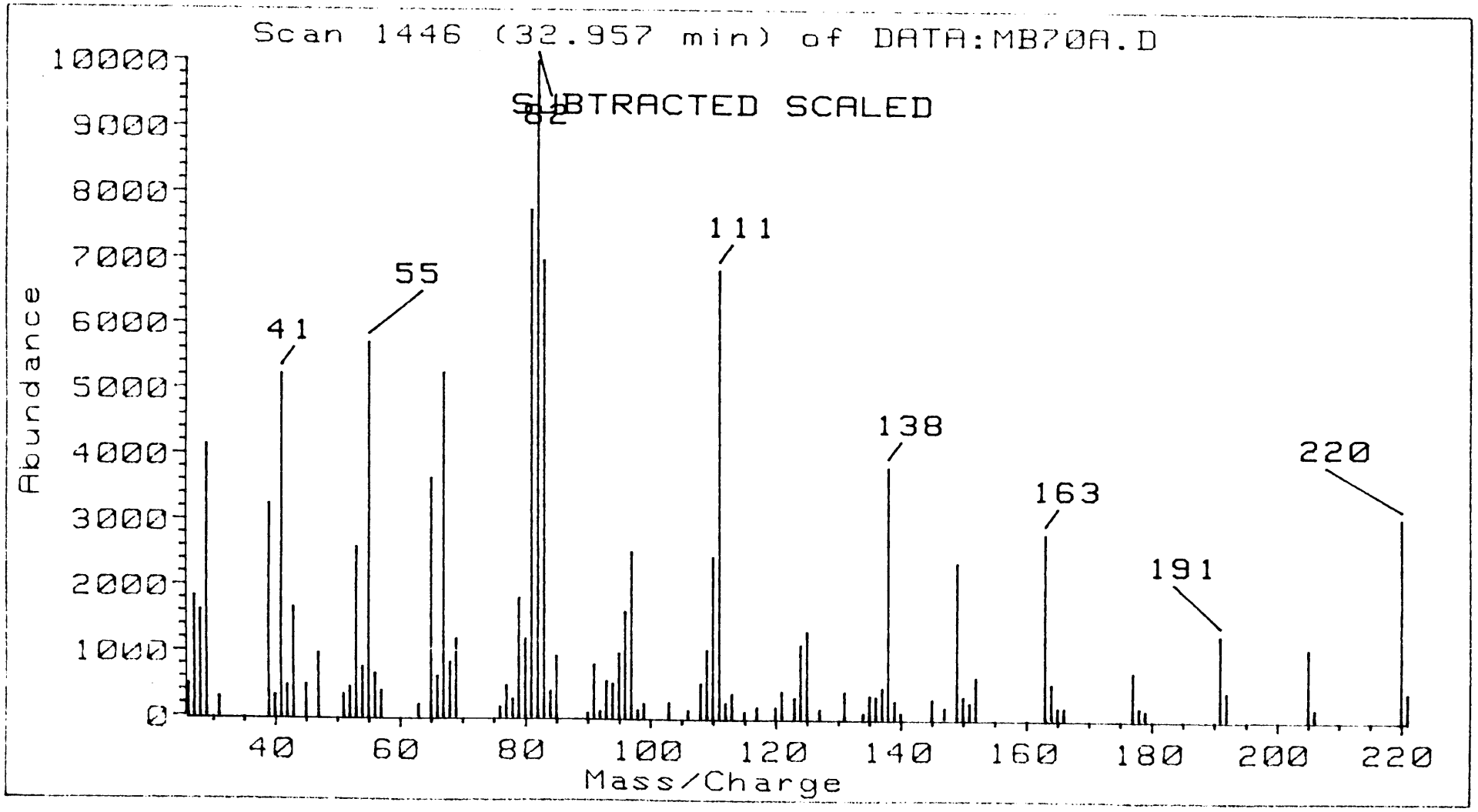

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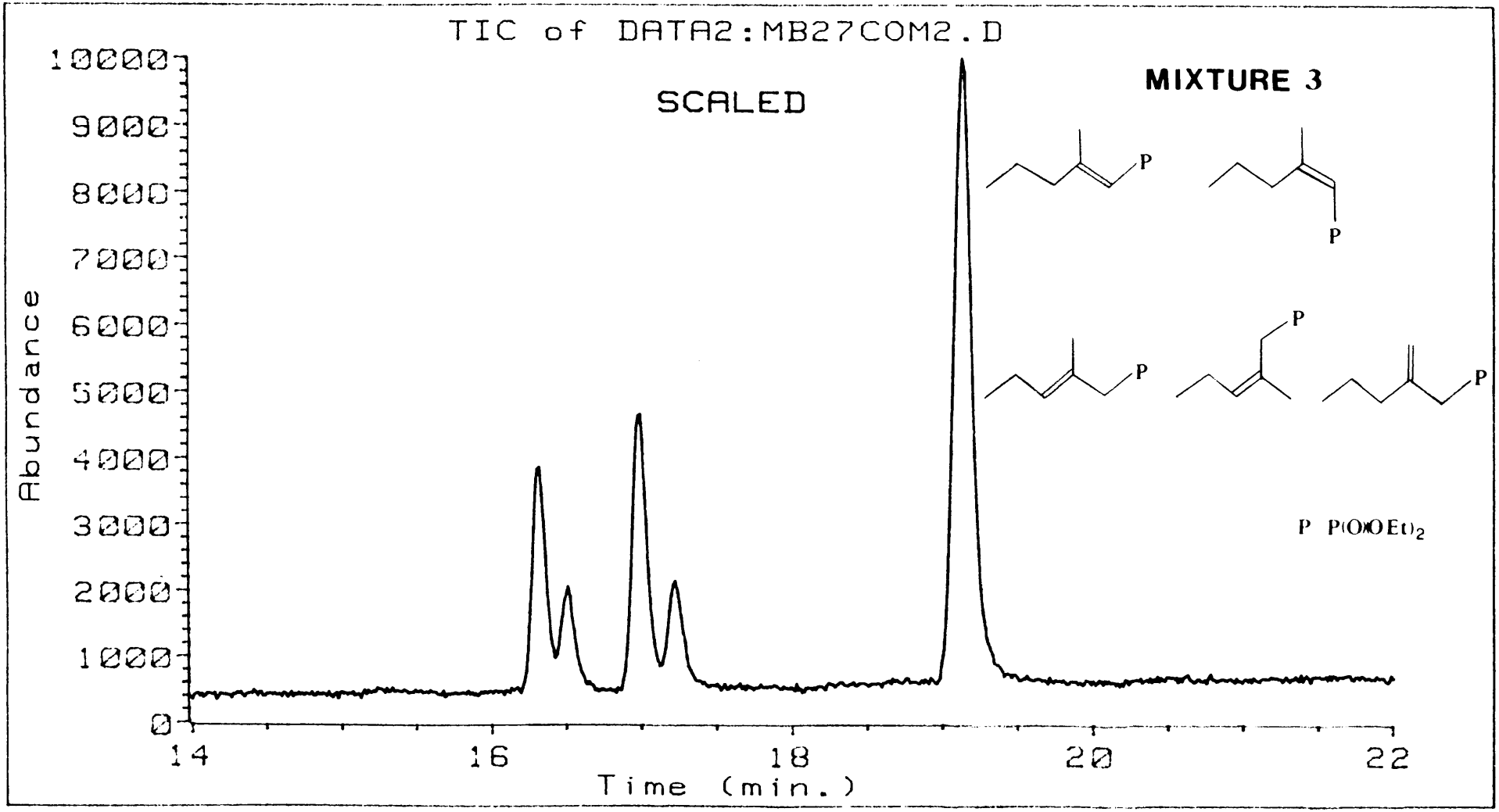

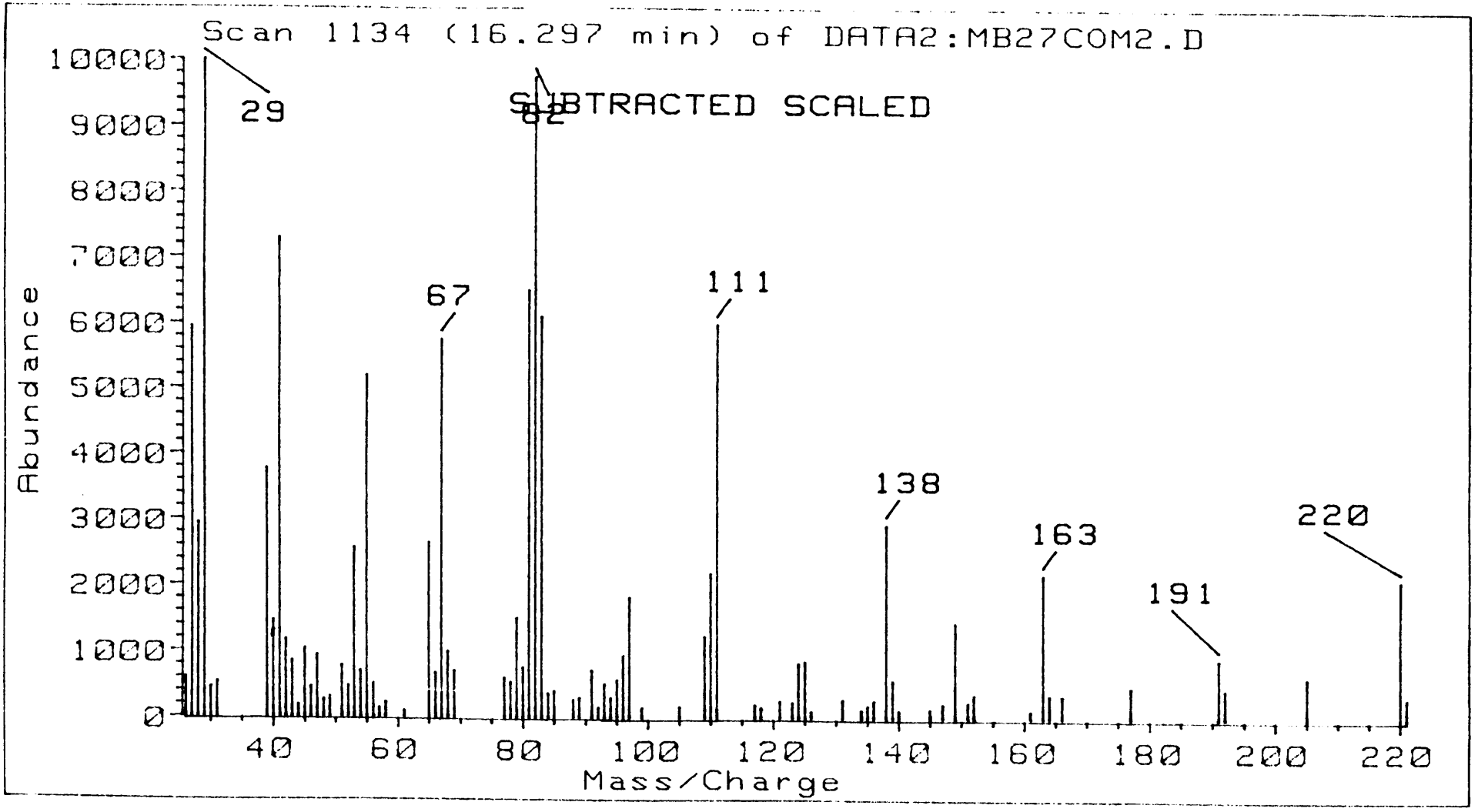

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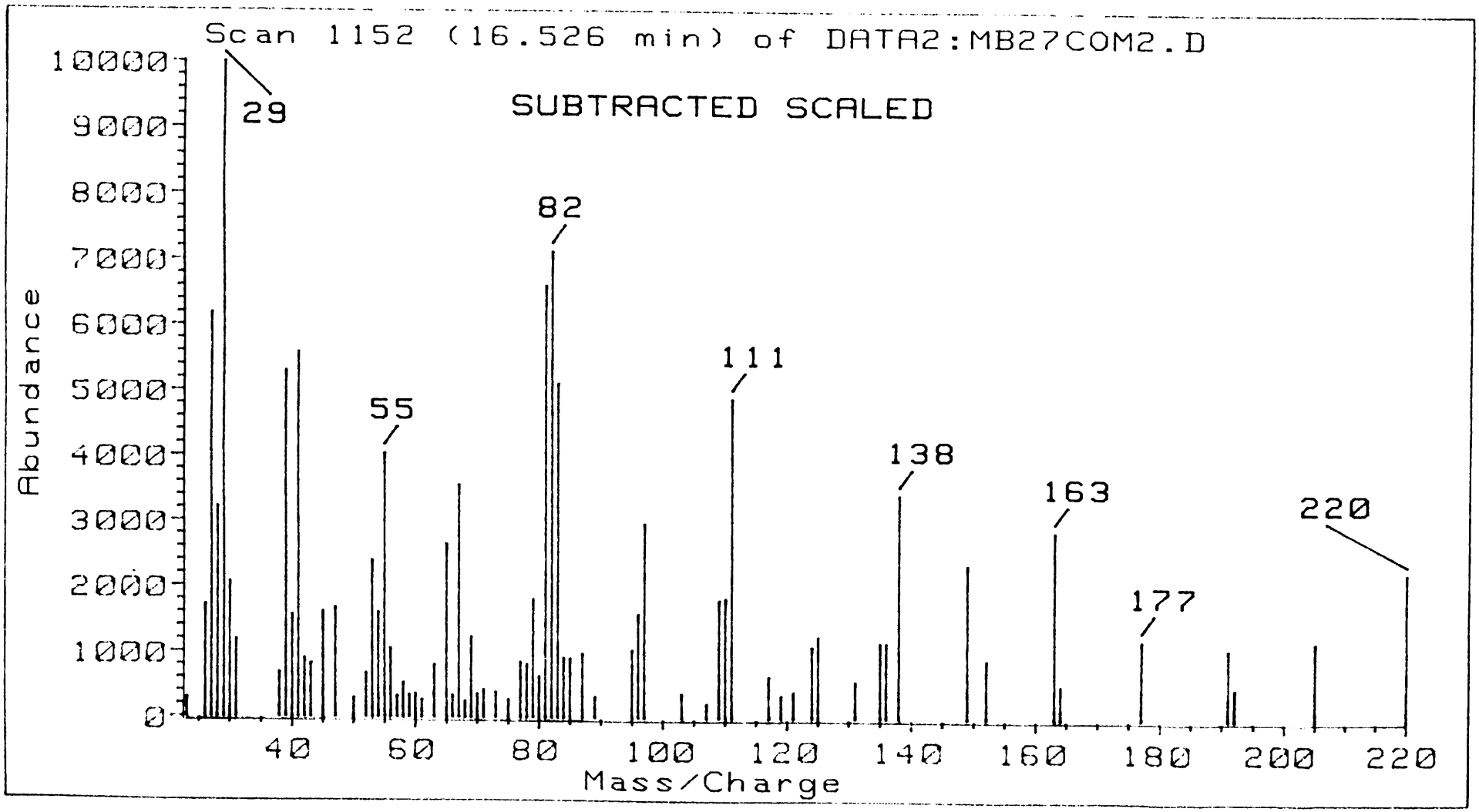

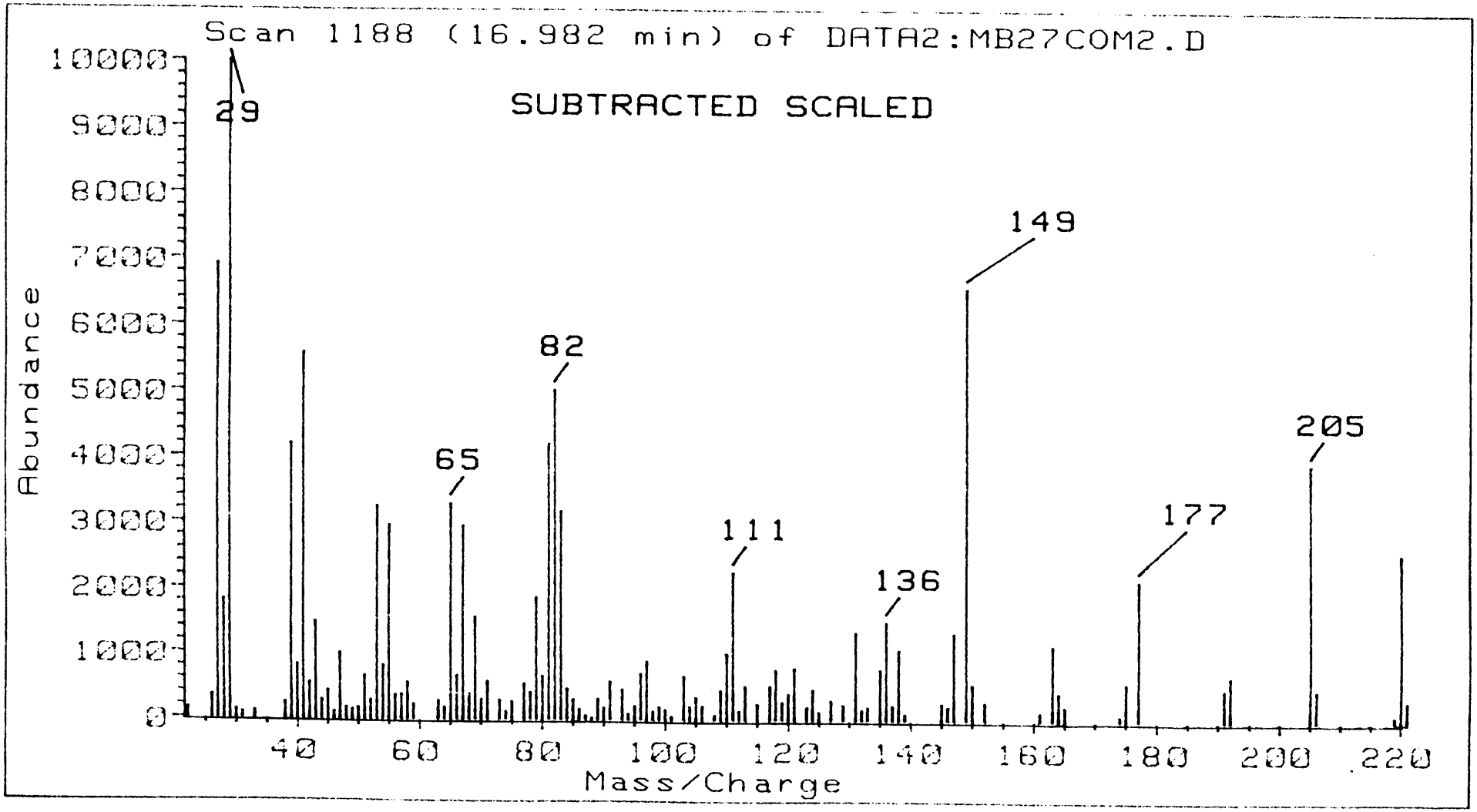

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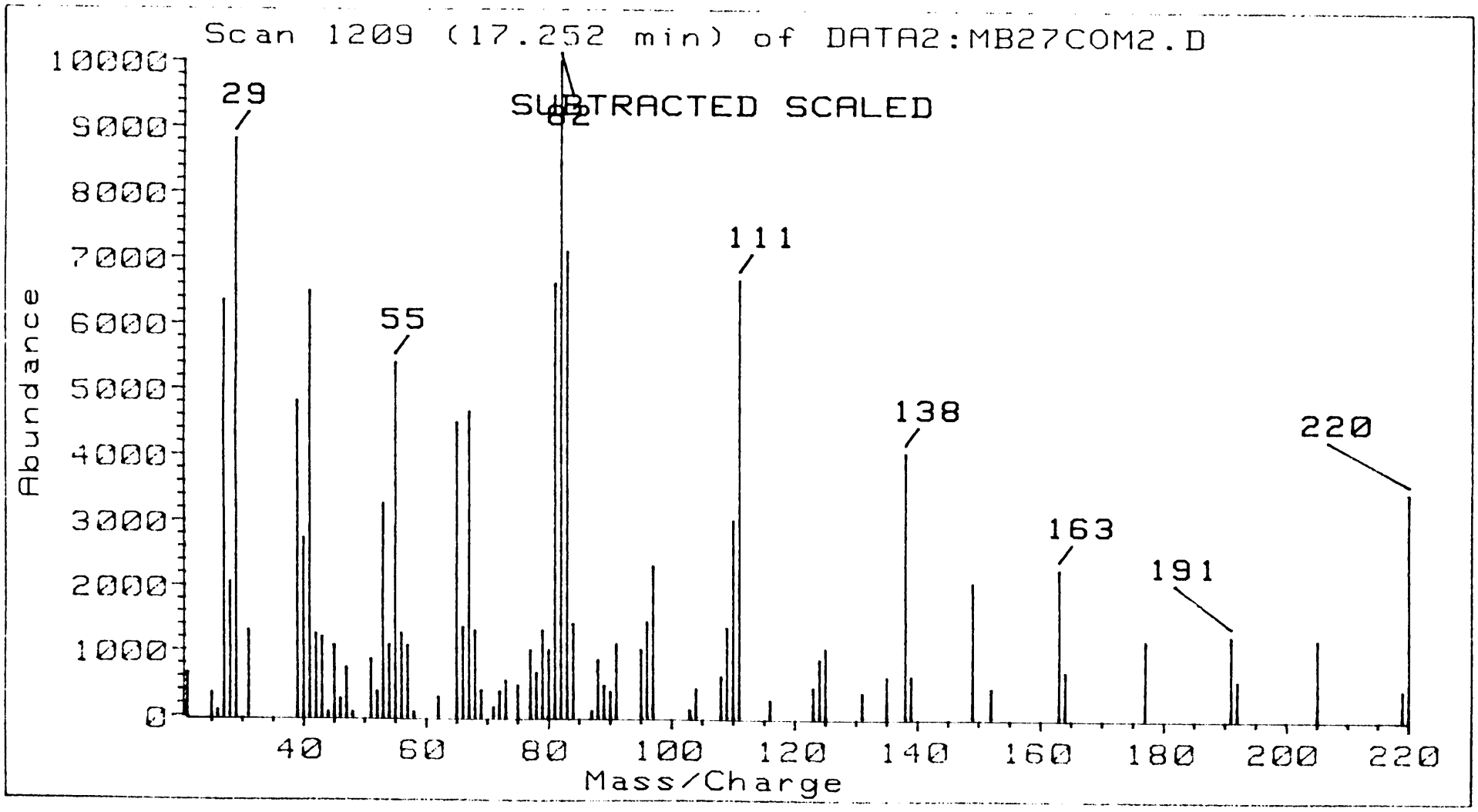

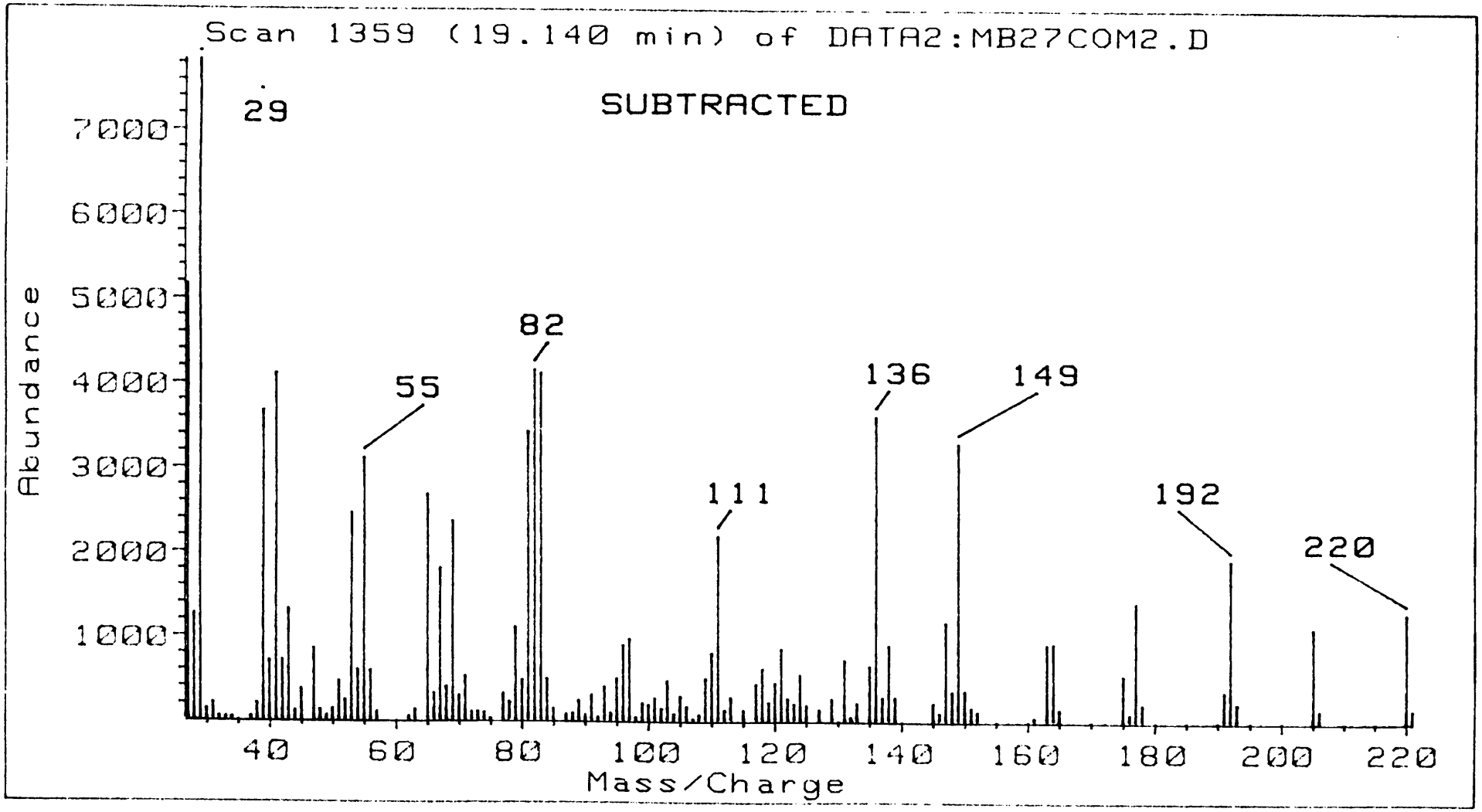

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