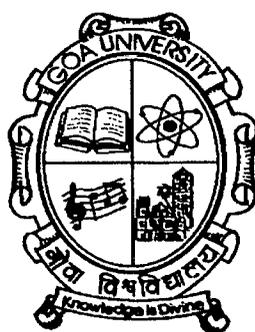


ORGANOPHOSPHORANES *In* ORGANIC SYNTHESES

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MARCH 2005

ORGANOPHOSPHORANES IN ORGANIC SYNTHESES

A Thesis Submitted to
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For the Degree of

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(In Chemistry)

By

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**GOA UNIVERSITY
TALEIGAO PLATEAU
GOA 403 206 INDIA**

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DECLARATION

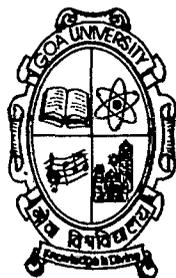
I hereby declare that the matter embodied in this thesis entitled, "Organophosphoranes In Organic Syntheses" is the result of investigations carried out by me, in the Department of Chemistry, Goa University, Goa-India, under the supervision of **Dr. S. G. Tilve**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.


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CERTIFICATE

Certified that the work entitled, “**Organophosphoranes In Organic Syntheses**” presented in this thesis has been carried out by **Mr. Chandan P. Amonkar**, under my supervision and the same has not been submitted elsewhere for the award of a degree.

Goa University
March 2005




(Dr. S. G. TILVE)
Guiding Teacher
Department of Chemistry
Goa University

Examined by

 8th Aug 2005

***We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.
Through the unknown, remembered gate
When the last of earth left to discover
Is that which was the beginning,
At the source of the longest river
The voice of a hidden waterfall.....
Not known, because not looked for,
But heard, half heard, in the stillness
Between two waves of the sea.***

- T. S. Eliot

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Contents

• Chapter 1	
❖ Introduction To Wittig Reaction 01
❖ References 15
• Chapter 2	
❖ Approach Towards Synthesis Of Naphthalene Moiety Of Neocarzinostatin	
Section I	
▪ Approach Towards Synthesis Of Naphthalene Moiety Of Neocarzinostatin Via Vicinal Dicarbonyl Precursor 21
Section II	
▪ A General Approach Towards 4- Methyl-2- Functionalised Naphthalenes 50
❖ Conclusion 98
❖ Experimental 99
❖ References 124

• Chapter 3	
❖ Synthesis Of 3-Substituted-5-Methyl-2(5H)-Furanone 129
❖ Conclusion 202
❖ Experimental 203
❖ References 213
• Chapter 4	
❖ Attempted Syntheses Of Selected Natural Products	
Section I	
▪ Synthesis Of 2-(p-Chlorophenyl) Methylidene -5,5-Dimethyl Cyclopentanone (2), An Intermediate For Potent Fungicide (1) 217
▪ Conclusion 243
▪ Experimental 244
▪ References 254

Section II

- **Attempted Synthesis Of
Laurencione, A Labile
Dihydrofuran Derivatives
From Red Alga, *Laurencia spectabilis* 256**
- **Conclusion 274**
- **Experimental 275**
- **References 278**

Section III

- **Synthesis Of Chaetomellic
Anhydride A 280**
- **Conclusion 297**
- **Experimental 298**
- **References 301**

Section IV

- **Synthetic Studies Of Pyrano
[2,3-*b*] Quinoline Compounds 305**
- **Conclusion 323**
- **Experimental 324**
- **References 328**

DEFINITION OF ABBREVIATIONS***General abbreviations***

Anhy.	Anhydrous
b.p.	Boiling point
Expt.	Experiment
Fig.	Figure
g	Gram
lit.	literature
min.	Minutes
Mmol.	Millimole
m.p.	Melting point
r. t.	Room temperature
Tlc/ tlc	Thin layer chromatography
%	Percentage
°C	Degree Celcius
ml	Milliliter
Conc.	Concentrated
equ/ equiv.	equivalent
hr/ hrs	Hour/ hours
aq	aqueous
dil	dilute
<i>E</i>	Eentegegen (opposite)
<i>Z</i>	Zissamen (together)
<i>R</i>	Rectus
<i>S</i>	Sinister

Compound abbreviations

PPh ₃	triphenyl phosphine
THF	tetrahydrofuran
DMF	Dimethyl sulfoxide
DMD	Dimethyloxirane
Bzl/ Bn	Benzyl
PCC	Pyridinium chlorochromate
LDA	Lithium diisopropylamide
Pd/C	Palladised carbon
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
Na ₂ SO ₄	Sodium sulphate
HCl	Hydrochloric acid
H ₂ SO ₄	Sulphuric acid

HNO ₃	Nitric acid
K ₂ CO ₃	Potassium carbonate
PdCl ₂	Palladium chloride
CuCl	Cuprous chloride
RhCl ₃	Rhodium trichloride
Ra-Ni	Raney nickel
PBr ₃	Phosphorous tribromide
P ₂ O ₅	Phosphorous pentoxide
KBr	Potassium bromide
EtOAc	Ethyl acetate
CDCl ₃	Deuterated chloroform
D ₂ O	Deuterated water
Pet.ether	Petroleum ether
TMS	Trimethylsilane

Spectroscopic abbreviations

I.R.	Infra Red
PMR (¹ H-NMR)	Proton Magnetic Resonance
¹³ C-NMR	Carbon-13 Magnetic Resonance
DEPT	Distortionless Enhancement by Polarisation Transfer
ν_{\max}	Frequency (maximum)
δ	Delta (p.p.m.) chemical shift Relative to tetramethylsilane (δ TMS = 0)
p.p.m	Parts per million
bs	Broad singlet
s	singlet
d	doublet
dd	Doublet of doublets
dddd	Doublet of doublets of doublets of doublets
t	triplet
q	quartet
m	multiplet
Hz	hertz
Ar-H	Aromatic hydrogens
cm ⁻¹	Frequency in wavenumber
HRMS	High resolution Mass spectrum
MS	Mass spectroscopy

General Remarks

All melting and boiling points were measured by normal Thiels tube method and are uncorrected. Distilled solvents used in all cases. Hexanes or pet ether refers to petroleum fraction boiling between 60-80°C. Anhydrous benzene and hexanes were prepared by preliminary washing with conc. H_2SO_4 , drying over fused calcium chloride followed by distillation and final storage over sodium wire. Anhydrous diethylether was prepared by preliminary drying over fused calcium chloride followed by sodium wire, distillation and final storage over sodium wire. Anhydrous chloroform and dichloromethane were obtained by storing over anhydrous calcium chloride followed by distillation and final storage over molecular sieves. Dry acetone was prepared by heating under reflux with successive quantities of $KMnO_4$, followed by distillation and final storage over anhydrous potassium carbonate. Anhydrous dimethylformamide was prepared by storing over anhydrous barium oxide followed by vacuum distillation and final storage over molecular sieves.

Column chromatography was performed on silica gel 60-120 mesh size and TLC on silica gel (13% $CaSO_4$ as binder). IR spectra were recorded on a Shimadzu FT-IR Spectrophotometer, (solids-KBr pellet/ liquids-neat, unless otherwise stated). 1H -NMR and ^{13}C -NMR spectra were recorded on a Bruker-300 MHz instrument. PMR data, using standard notations were presented in the following order: Chemical shift (δ) / Splitting pattern (J = coupling constant) / Relative proton ratio / Assignment. The multiplicities of carbon signals were obtained from DEPT experiments. NMR spectra were obtained in deuterated chloroform unless otherwise noted. Chemical shift values were expressed in δ -units with tetramethylsilane (TMS) as an internal standard. Low resolution mass spectra were recorded on a triple quadrupole MS/MS instrument (Applied Biosystem Inc.) and high resolution mass spectra (HRMS) were recorded on a MicroMass ES-QTOF Mass spectrometer.

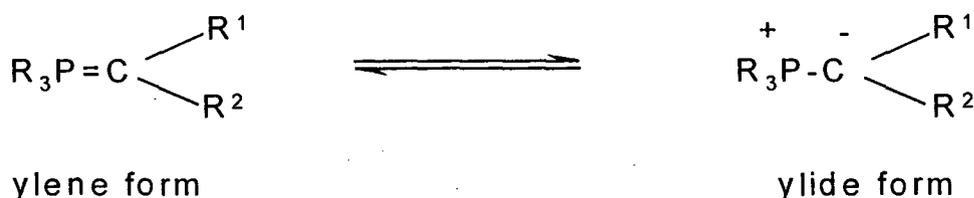
Chapter 1

Introduction To Wittig Reaction

Chapter 1

INTRODUCTION TO WITTIG REACTION**1.1 Introduction**

The reaction of a tertiary phosphine (usually triphenylphosphine) with an alkyl halide gives a phosphonium salt, in which the alpha C-H bonds are sufficiently acidic to be removed by a strong base e.g. organolithium compounds, sodium hydride, sodium amide etc. The resulting anion is believed to be stabilized by overlap between the *p*-orbital at carbon and one of the *d* orbital of the phosphorus atom. The anion could either be written as ylid (ylide) form or ylene form and also frequently termed as phosphorane (Fig. 1).

**Fig. 1**

The reaction between a phosphorane and an aldehyde or a ketone to form a phosphine oxide and an alkene is known as the Wittig reaction (Fig. 2). George Wittig, the German chemist, has first showed the value of this procedure in the synthesis of alkenes. The reaction is easy to carry out and proceeds under mild conditions¹. A valuable feature of the Wittig reaction is that, the mild conditions do not normally promote structural isomerisation, obtaining alkenes in which the position of the double bond is unambiguous.



Fig. 2

Since its discovery² in 1953, the reaction has been extensively studied with respect to structural variation in the phosphonium ylide, in the range of functionalized aldehydes and ketones, in the nature of the bases, the polarity of the solvents that may be used, in the mechanism of the reaction and the factors, which influence the (*E/Z*) ratio. Several papers appeared in this field, which has resulted in a number of review articles.^{1,3} Many thousands of simple and complex syntheses have been effected and the method is widely exploited in research laboratories and in the industrial processes for syntheses in the steroid and carotenoid field.

The reaction generally leads to high yields of di- and tri-substituted alkenes from aldehydes and ketones but, yields of tetra-substituted alkenes from ketones are often poor, owing to steric effect.

1.2 Classification of phosphoranes

There is a marked difference in reactivity of phosphoranes depending upon the nature of R₃ groups. The R₃ groups on the phosphorous could be an alkyl or a phenyl group. If R₃ group is an alkyl group then, the reactivity of phosphorane is more than when R₃ group is phenyl. However, due to the need of a selective generation of phosphorane, in practice, R₃ group is always phenyl.

Depending upon the type of substituents present on alpha carbon atom (R^1 & R^2 ; **Fig. 1**) the phosphoranes are classed into three categories.

Reactive or unstabilized ylide, semi-stabilized ylide and stabilized ylide. When R^1 and R^2 are alkyl and/or hydrogen, the resulting phosphoranes formed are very reactive and highly moisture and oxygen sensitive and hence are termed as reactive or unstable phosphoranes. When one or both (R^1 & R^2) groups are phenyl/allyl the resulting phosphoranes formed are termed as semi-stabilized phosphoranes and when R^1 and/or R^2 groups are electron withdrawing in nature, the phosphoranes obtained can be isolated as crystalline solids and are termed as stabilized phosphoranes.

1.3 Preparation of Phosphoranes

Alkylidene phosphoranes are usually prepared by action of base on alkyltriphenylphosphonium salts. The alkyltriphenylphosphonium salts can be obtained from an alkyl halide and triphenylphosphine (**Fig. 3**).

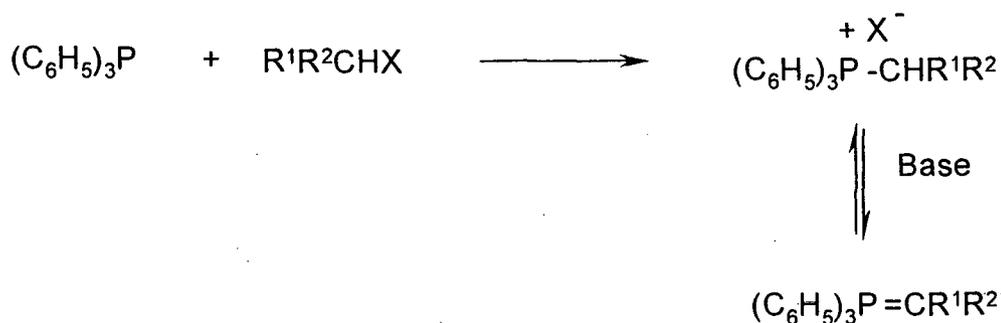


Fig. 3

The phosphonium salt can usually be isolated and crystallized but the phosphorane is generally prepared in solution and used without isolation. Formation of the phosphorane is reversible, and the strength of base

necessary and the reaction conditions depend entirely on the nature of the ylide.

Reactions involving non-stabilized ylides must be conducted under anhydrous conditions and in an inert atmosphere, because these ylides react both with oxygen and with water. Water effects hydrolysis, with the formation of a phosphine oxide and a hydrocarbon.

If the original phosphonium salt is chiral at phosphorus atom, the configuration at the P atom is found to be retained in the related phosphine oxide and the product.

1.4 Synthetic Value Of Wittig Reaction

The value of the Wittig reaction is clearly shown by the fact that it has been used in the synthesis of many alkenes^{1,2,3}, including a considerable number of natural products.

It is a versatile synthesis and can be used for the preparation of mono-, di-, tri-, and tetra-substituted alkenes, and also many cyclic compounds. The carbonyl compound may contain a wide variety of other functional groups such as hydroxyl, ether, ester, halogen and terminal acetylene, which do not interfere with the reaction. In Compounds having keto and ester group, the Wittig reagent reacts with keto group preferentially. Several reactions have been reported, wherein phosphoranes have been reacted with the carbonyl groups of esters⁴, anhydrides⁵ and amides⁶. The mild conditions of the reaction make it an ideal method for the synthesis of sensitive alkenes such as carotenoids and other polyunsaturated compounds.

One especially useful application of the Wittig is in the formation of exocyclic double bonds. The Wittig reaction is the method of choice for converting a cyclic ketone in to an exocyclic alkene, unlike Grignard method which gives endocyclic isomer almost exclusively. The Wittig reaction has been used exclusively in the preparation of variety of methylene steroids⁷, vitamins⁸, carotenoids⁹, terpenoids¹⁰, alkaloids¹¹, several heterocyclic compounds¹² and many natural products like pheromones¹³, prostaglandins¹⁴, etc.

Seebach and coworker¹⁵ have synthesized several macrocyclic compounds by making careful use of phosphoranes.

1.5 Mechanism Of Wittig Reaction ^{1,18,19}

The carbanionoid carbon of the ylide form attacks the electrophilic carbon of the carbonyl group with the formation of an intermediate called 'betaine.

The betaine gives rise to a four-membered cyclic transition state called oxaphosphetane, which finally decomposes to the product alkene and oxide (Fig. 4). The driving force being provided by the formation of the very strong phosphorus-oxygen bond (535 KJmol^{-1}).

Recent low temperature ³¹P-NMR work by Vedejs group suggested¹⁶ no evidence of betaine formation but rather oxaphosphetane¹⁷ formation directly via 2 + 2 addition.

Although the position of the carbon-carbon double bond in an olefin formed by a Wittig reaction may be predicted with certainty, the stereochemistry of the olefin product is sometimes less predictable.

The resonance-stabilized ylide frequently yields *E*-alkene stereoisomer predominantly, in which the carbonyl group is *trans* to the larger group at the beta carbon atom.

With stabilized ylides, formation of the intermediate betaines is reversible, allowing interconversion to the more stable threo form which leads to the *E*-alkene. On the other hand, non-stabilized ylides, usually give more of *Z*-alkene. In this case, the decomposition of the betaine becomes the rate-determining step of the reaction. Here the formation of the betaine is irreversible and conversion into the alkene proceeds mainly from the kinetically favoured erythro betaine (**Fig. 5**).

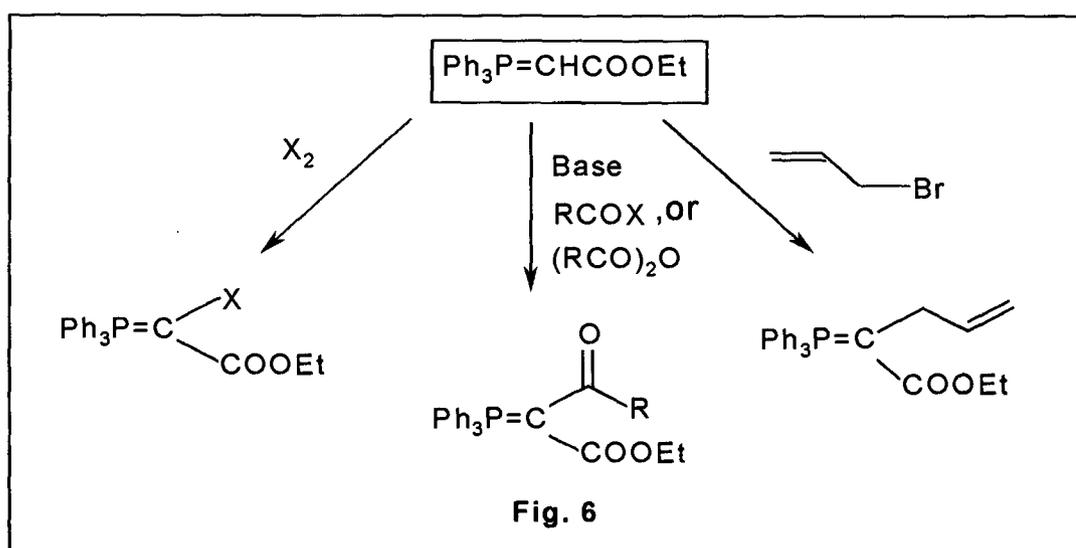
Recent work²⁰ has shown that the steric course of the reactions can be substantially altered by varying the reaction conditions. By proper choice of experimental conditions a high degree of steric control can be achieved. In case of stabilized ylides, the presence of protic solvents or lithium salts gives increase yield of *Z*-alkenes. With non-stabilized ylids, salt free conditions and non-polar solvents give high selectivity for *Z*-alkene. This can be ascribed to the influence of the solvents and additives on the relative stabilities and rates of decomposition of the threo and erythro betaines. The degree of stereoselectivity observed may be influenced by the nature of the substituents both on the ylide and the carbonyl group. The *Z*-isomer of the olefin may be obtained by use of more electrophilic carbonyl reactants, by the use of ylides

derived from triarylphosphines rather than trialkylphosphines, and by the use of non-stabilized alkylidene phosphoranes.

1.7 Preparation Of Complex Phosphoranes

Certain complex phosphoranes cannot be prepared by normal salt method due to the difficulty in preparing starting halo-compounds and also triphenylphosphine might act as a base instead of behaving as a nucleophile, causing the elimination of HX, from an alkyl halide, rather than effecting a substitution. eg. reaction of triphenyl phosphine with α -bromo ketones gave enol phosphonium salt by O-attack instead of acyl phosphorane by C-attack.

The attractive way of making such complex phosphoranes are through alkylation^{21,22,23}, acylation^{24,25,26,27,28} and halogenation²⁹ of simple phosphorane. e.g. stable phosphoranes can be allylated, acylated or halogenated to give modified phosphoranes (**Fig. 6**).



Halophosphoranes can be prepared by making use of stable phosphorane and treating it with halogens or halogenating agents. Such α -halophosphoranes are important precursors to vinyl halides, through Wittig reaction, which, then can be exploited using palladium chemistry for making different types of complex molecules.

1.8 Acylation Of Stable Phosphorane

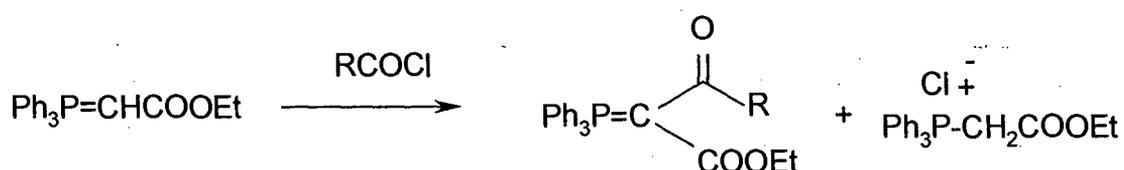


Fig. 7

There are few methods reported in the literature for the acylation of phosphorane at the alpha-carbon. One of the methods is performed by a transylidation.^{30,31} In this type of reaction, normally the yields are around 50% only, as the starting phosphorane itself acts as a base abstracting acidic proton of the salt giving 1:1 mixture of new phosphorane and salt of the starting phosphorane (Fig. 7).

The stoichiometric reaction can be obtained in selective cases by using triethylamine³², two phase system using sodium hydroxide³³, anhydrides³⁴, thioester³⁵ and N-acylimidazole^{36,37}.

Wasserman et al, have reported two modifications³⁸ which overcome these problems and provide mild conditions for carrying out the acylation even in presence of acid-sensitive functional groups. BSA (bis(trimethylsilyl)acetamide) has been employed as a proton scavenger,

which eliminates the need for second equivalent of phosphorane, providing an efficient and general alternative to the acylation of phosphoranes, giving better yields.

In the second modification³⁹, coupling of carboxylic acid has been carried out with stable phosphorane by making use of coupling agent EDCL (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in presence of catalytic amount of DMAP to afford acyl phosphorane in good yields.

Recently, Yadav et al have reported a mild, convenient method for acylation of phosphoranes in good yields, using metal grade zinc⁴⁰.

1.9 Use of Acyl Phosphorane

Keto phosphoranes are versatile intermediates in the synthesis of a variety of functionalized systems. As reported by Cooke⁴¹, reductive removal of triphenylphosphine group⁴² gives beta-keto esters, vinyl derivatives undergo Michael addition of nucleophiles followed by trapping with electrophiles to form alkyl substituent products, and thermolysis provides access to substituted acetylenes⁴³. Acyl substituted phosphoranes have got importance because of their utility in the synthesis of unsaturated ketones and cyclopropane pyrethroids. The acylated stable phosphoranes have not been exploited in olefin synthesis, may be due to extra stability rendered by the second later acyl group there by making them inert towards carbonyl compounds. However, oxidation of acylated phosphoranes yield vicinal carbonyls.

Acyl phosphorane could be considered as tricarbonyl precursor or protected tricarbonyl and it can be readily converted to tricarbonyl system by

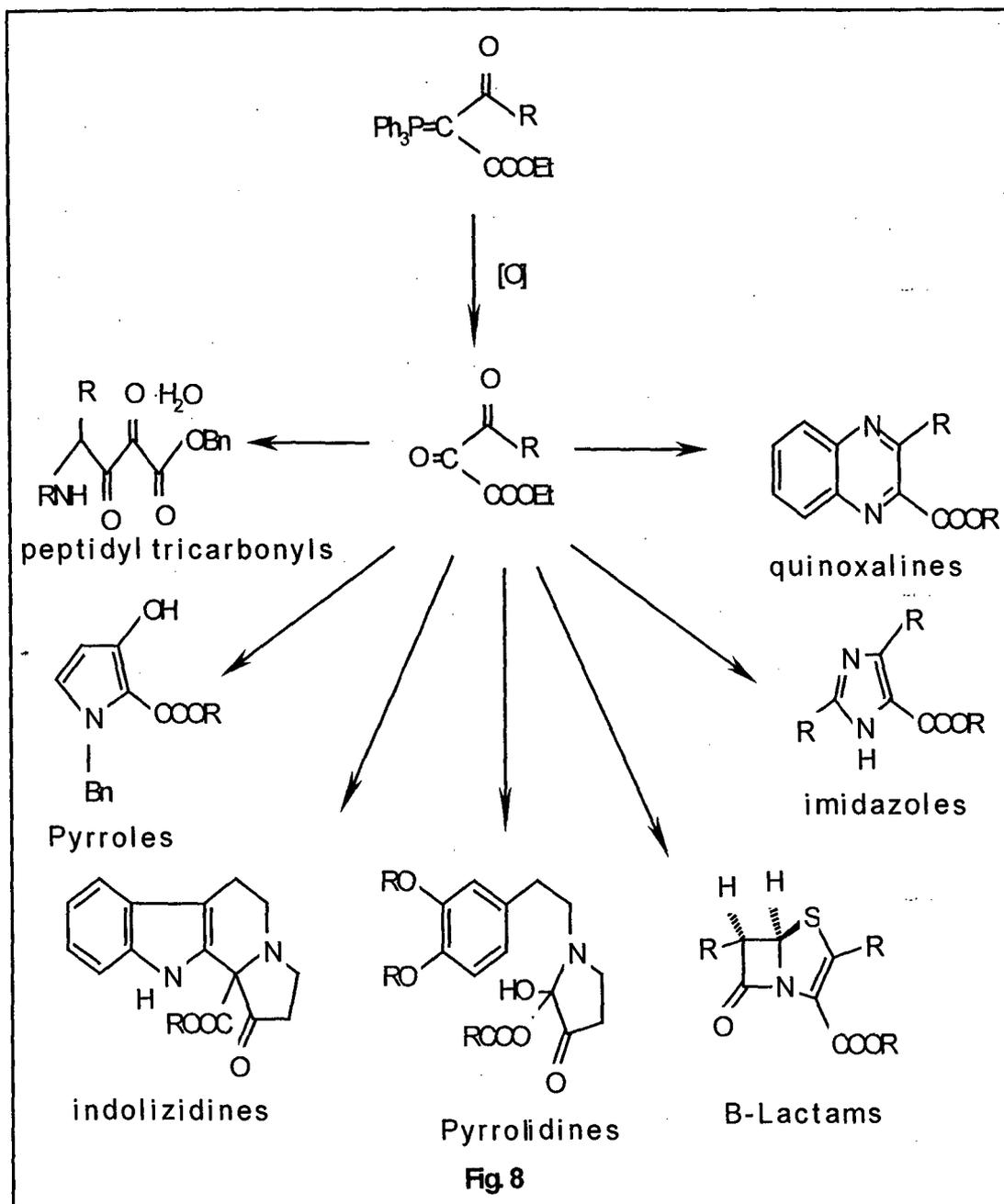
oxidative cleavage of the carbon-phosphorus double bond. Such chemistry has been elegantly exploited by Wasserman *et al*, for synthesizing different natural products⁴⁸. Cleavage of ylides has been accomplished to give tricarbonyl compounds by employing singlet oxygen⁴⁴, ozone⁴⁵, oxone⁴⁶ and DMD⁴⁷, where selective oxidation was desirable, thus protecting other oxidizable functional groups in the phosphorane. Interest in tricarbonyl compounds has risen dramatically in the last few years. The occurrence of this functionality in the powerful immuno-suppressant FK-506 and related antibiotic rapamycin⁴⁹ has led to several strategies for its incorporation into target molecule.

Wasserman has beautifully demonstrated the valuable reactivity patterns of vicinal tricarbonyl compounds in the synthesis of a variety of heterocyclic system (**Fig. 8**). For instance, tricarbonyl compounds have been used to synthesize naturally occurring heterocycles like pyrroles⁵⁰, alkaloids⁵¹, carbazoles⁵², indolizidines⁵³, pyrrolidines⁵⁴, beta-lactam rings⁵⁵, quinoxalines⁵⁶, tricarbonyl systems in FK-506⁵⁷ and rapamycin, imidazole systems⁵⁸, as a part of DuP-532 and cimetidine, enzyme inhibitor peptidyl vicinal tricarbonyls⁵⁹ and many more natural products⁶⁰.

1.10 Alkylation Of Stable Phosphoranes

The alkylation of phosphorus ylides has served two main purposes. It has served as a route to more complex ylides, which often are virtually unavailable by normal salt method. Such ylides can be used in the Wittig reaction for the preparation of 1,1-disubstituted alkenes. The second main role for the alkylation of phosphorus ylides has utilized the ylides as a source

of carbanion with which to form carbon-carbon bonds followed by removal of the phosphorus group⁶¹ (Fig. 9).



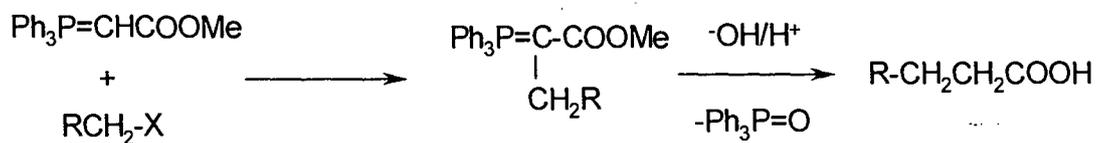
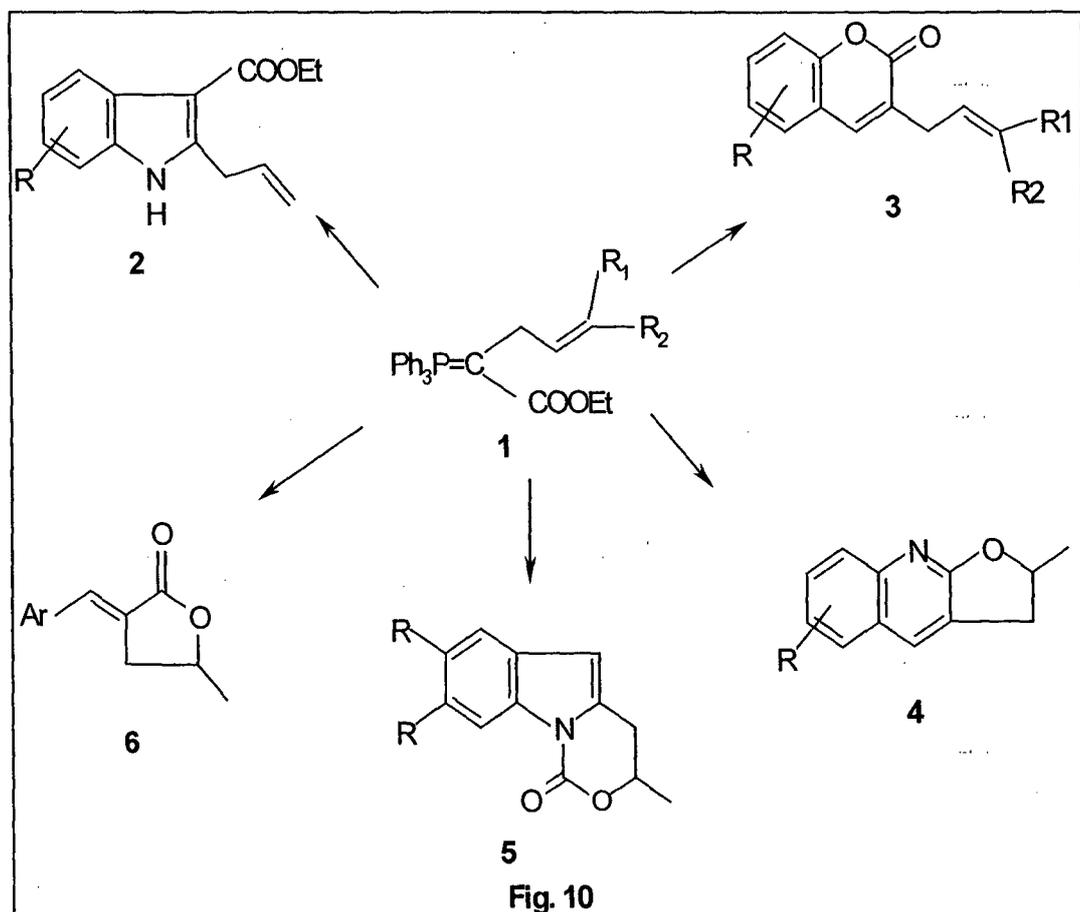
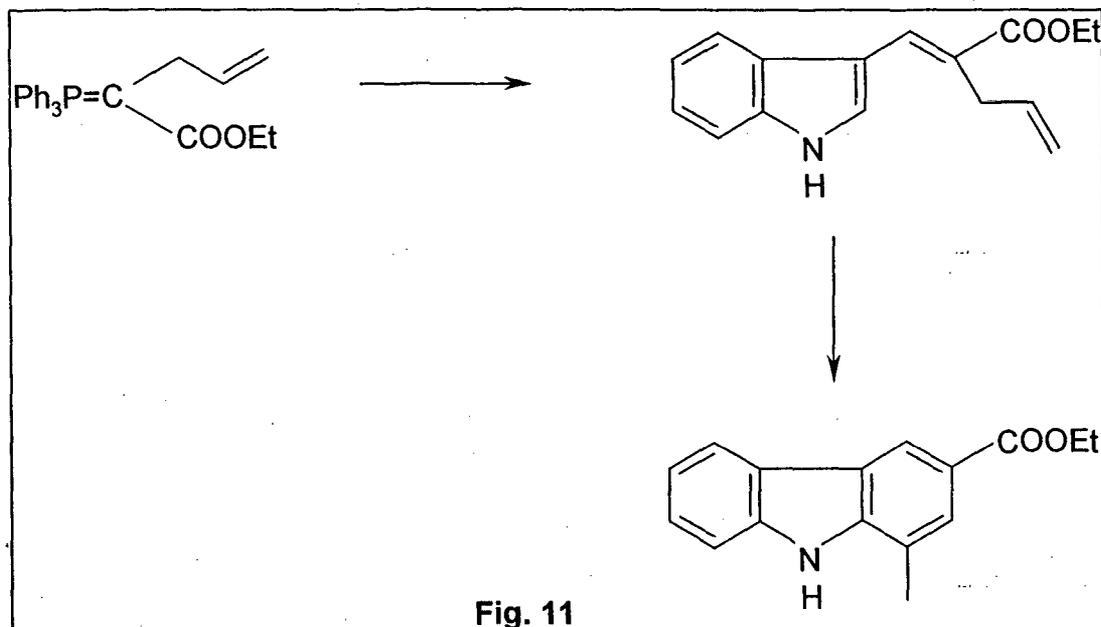


Fig. 9

Mali *et al*⁶², have used allylated phosphorane (1) for the synthesis of heterocycles (Fig. 10), e.g. 2-allyl-3-carboethoxyindoles(2), 3-allylcoumarines(3), furoquinolines(4), oxazinoindole derivatives(5), butyrolactones(6), etc.



In our group, we have used this reagent for the synthesis of carbazole⁶³, precursor to anticancer alkaloid olivacine⁶⁴ (Fig. 11).



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Chapter 2

***Approach Towards Synthesis Of
Naphthalene Moiety Of
Neocarzinostatin.***

Section I

**Approach Towards Synthesis Of
Naphthalene Moiety Of
Neocarzinostatin Via Vicinal Tricarbonyl
Precursor.**

Chapter 2

APPROACH TOWARDS SYNTHESIS OF NAPHTHALENE MOIETY OF NEOCARZINOSTATIN

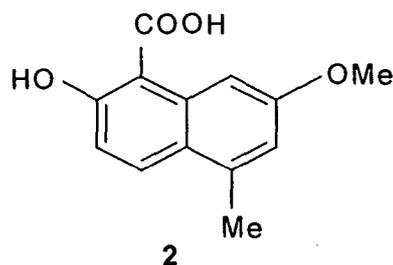
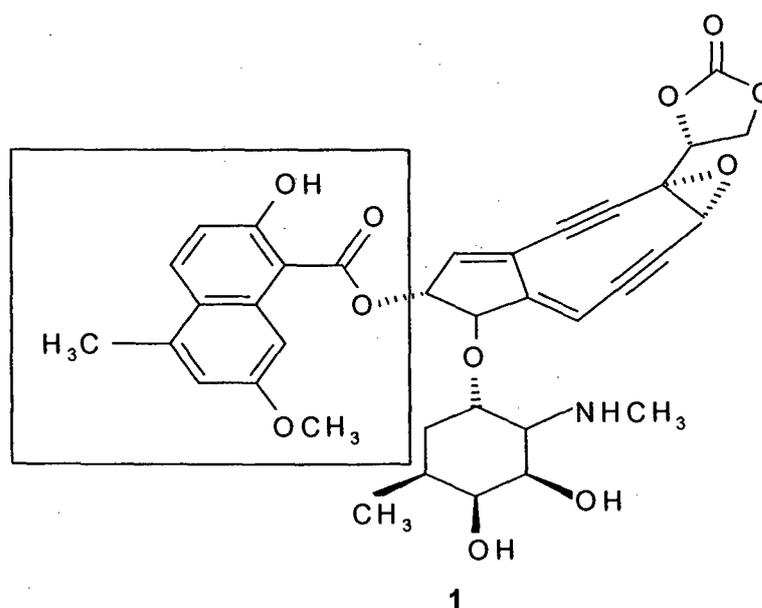
Section I

Approach Towards Synthesis Of Naphthalene Moiety Of Neocarzinostatin Via Vicinal Tricarbonyl Precursor

2.1 Introduction

Neocarzinostatin chromophore, non-protein component of neocarzinostatin, isolated from the culture filtrate of *Streptomyces carzinostaticus*, has attracted considerable interest among synthetic chemists due to its intriguing structural features. This, chromoprotein Neocarzinostatin (NCS)¹ **1**, has shown some promising bioactivity. It is found to be a highly potent antibiotic, antitumor agent². The naphthoate moiety **2** of NCS, has been proposed to play an important role for the specific binding to both NCS apoprotein^{3,4} and to target DNA⁵. It binds to duplex DNA through the coulomb attraction between the positively charged aminosugar moiety and the negatively charged phosphodiester of DNA and also through the interaction of the naphthoate ring between adjacent nucleotide bases. The dienediyne part of NCS is thereby fixed in the groove of double stranded DNA, where it causes severe damage to DNA strand thereby killing the tumor cells⁶.

The naphthoate moiety possesses an active role in DNA cleavage. Compelling evidence has been established that the naphthoic acid ester plays a crucial role in the binding of **1** to DNA by functioning as an intercalating group^{7a}. So, there is a need to prepare the naphthoate moiety in substantial amount which is a requisite for studying the binding mechanism^{7b}, due to this there is a considerable interest among the organic chemists to synthesize this essential acid, 2-hydroxy-7-methoxy-5-methyl-naphthalene-1-carboxylic acid **2**.



2.2 Literature Methods

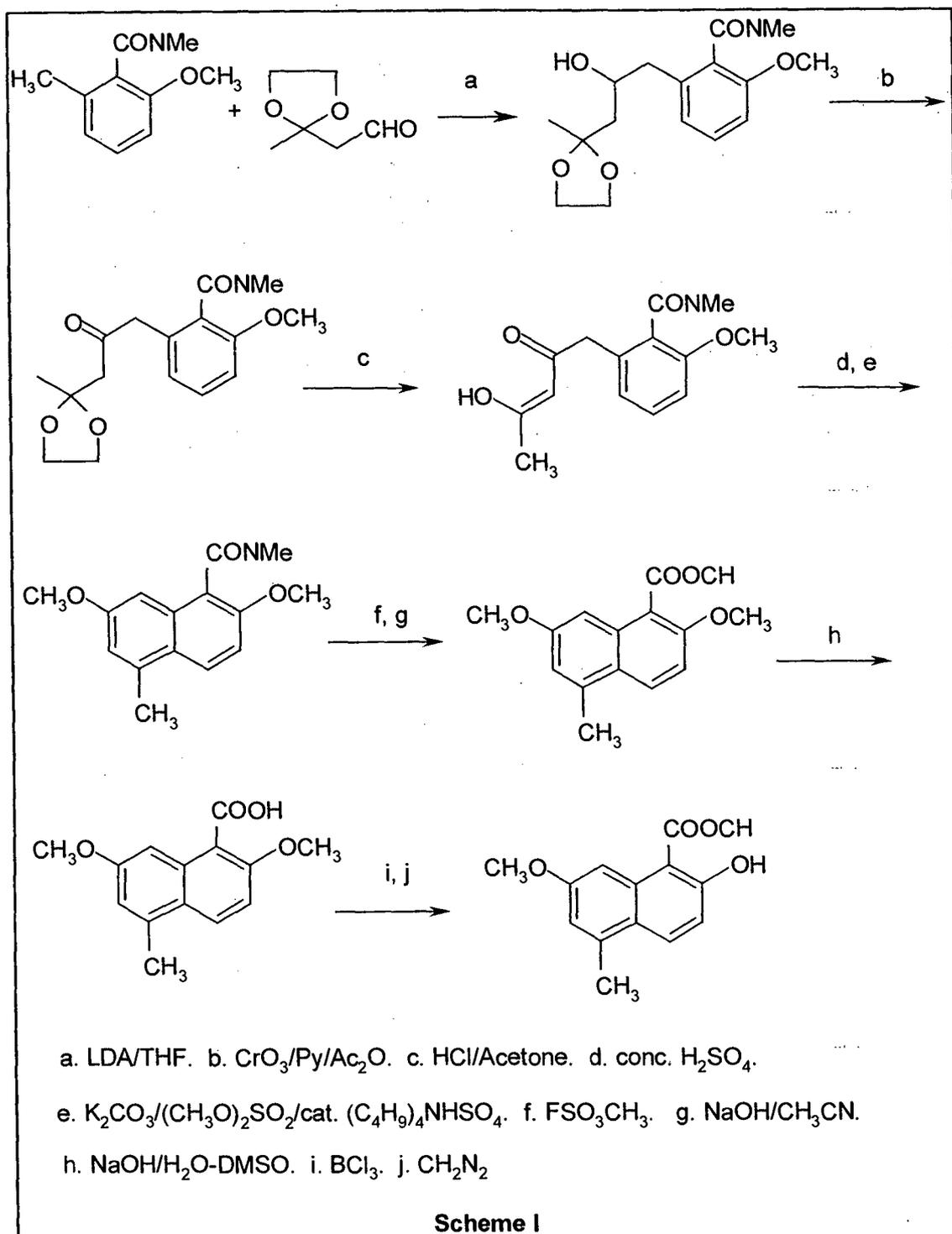
So far this acid **2** had been synthesized non-biomimetically. The different approaches reported are described below.

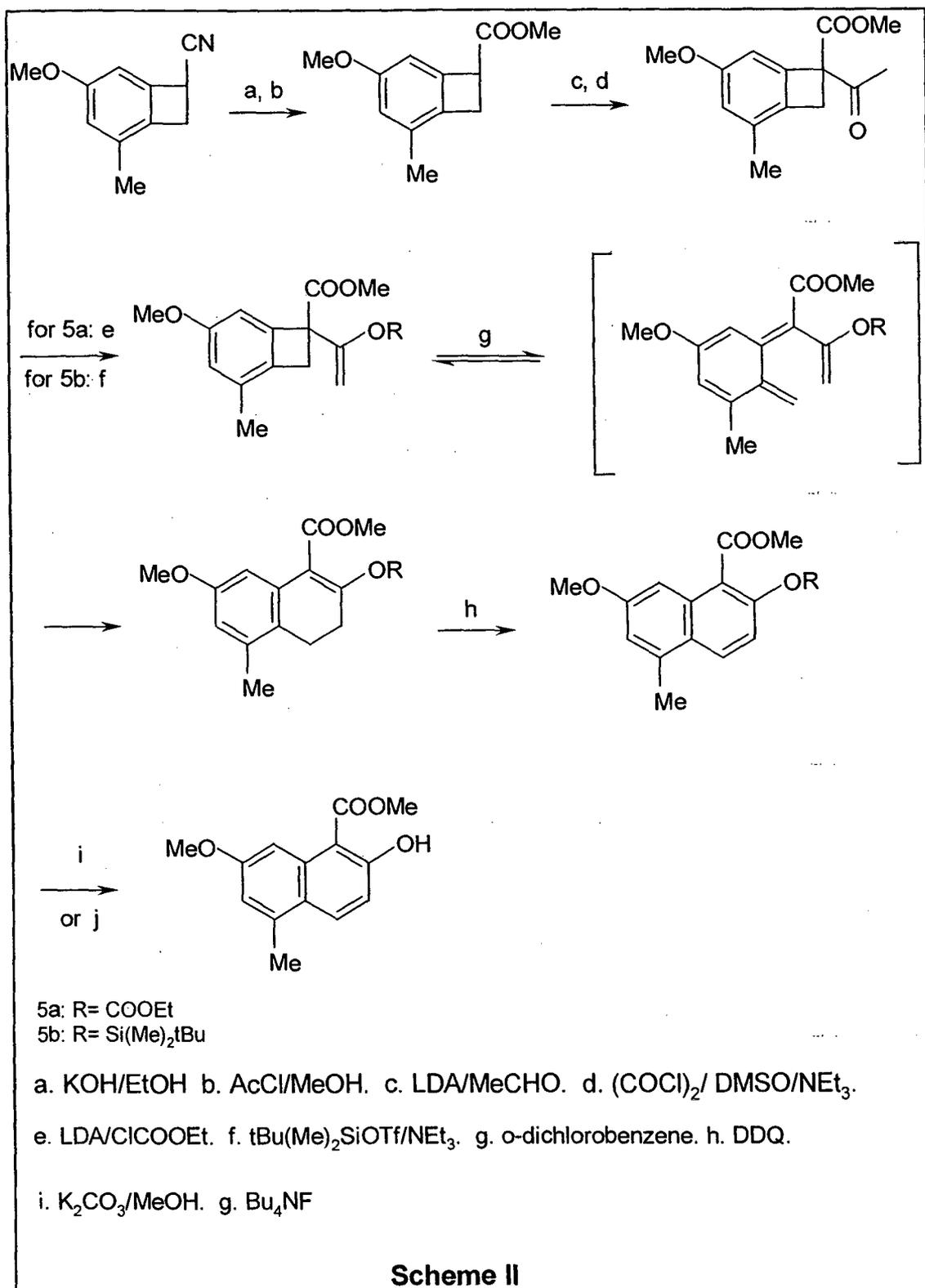
Shibuya *et al*⁸ have achieved the first synthesis of **2** obtaining in 3% yield. Metallation of *o*-toluamide with LDA followed by quenching with 2-methyl-2-(2-oxoethyl)-1,3-dioxolane provided the amide alcohol. Oxidation of alcohol followed by hydrolysis afforded β -diketone. Cyclization followed by methylation yielded dimethyl ether. Alkaline hydrolysis followed by selective demethylation afforded the required hydroxy ester (**Scheme I**).

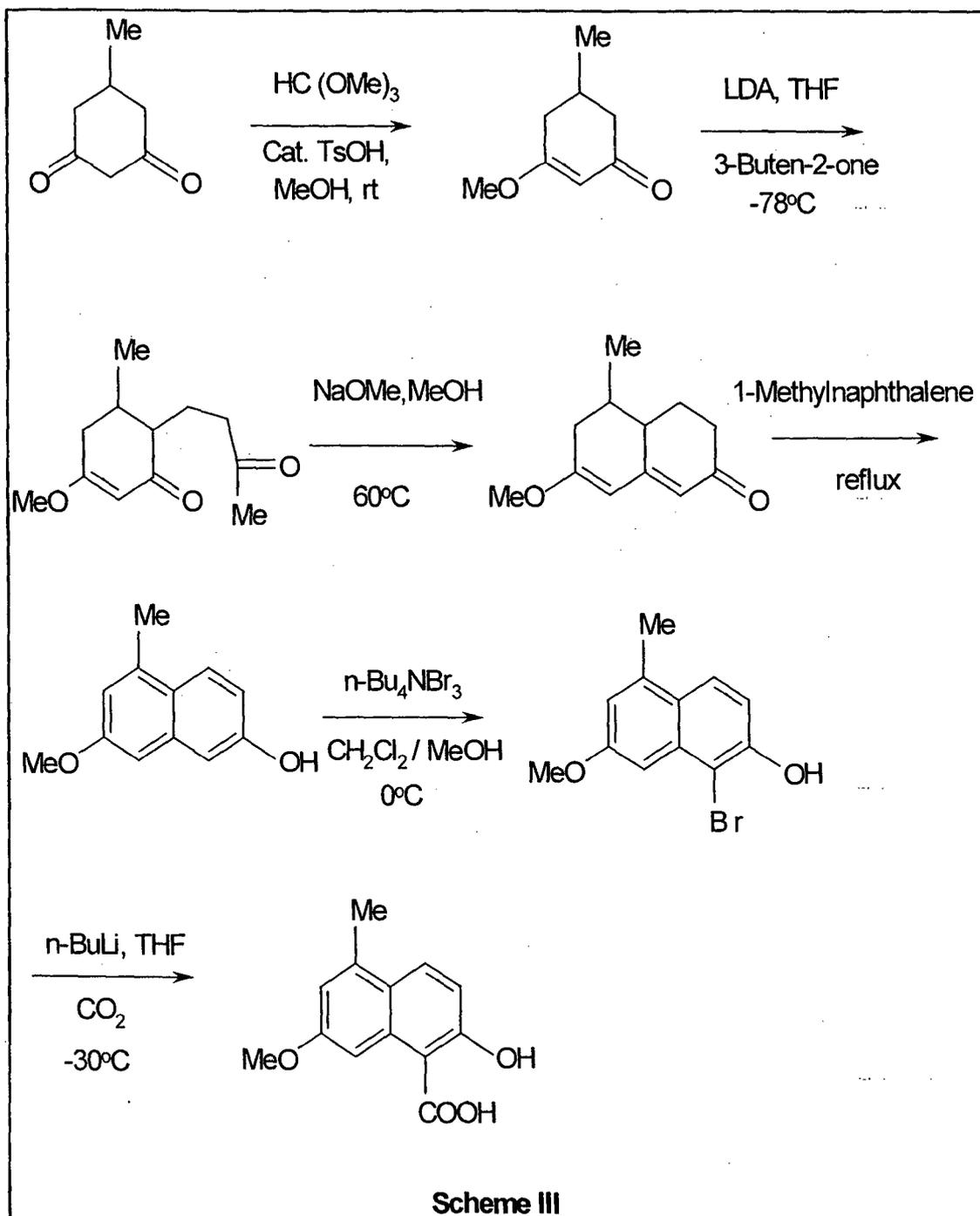
Fukumoto *et al*⁹ have synthesized methyl ester of **2** from 1-cyano-5-methoxy-3-methylbenzocyclobutene in 26% of overall yield.

Thermolysis of 1-carbomethoxy-1-alkenyloxybenzocyclobutene produced the dihydronaphthene, which was easily converted to 2-naphthol by sequential dehydrogenation and deprotection (**Scheme II**).

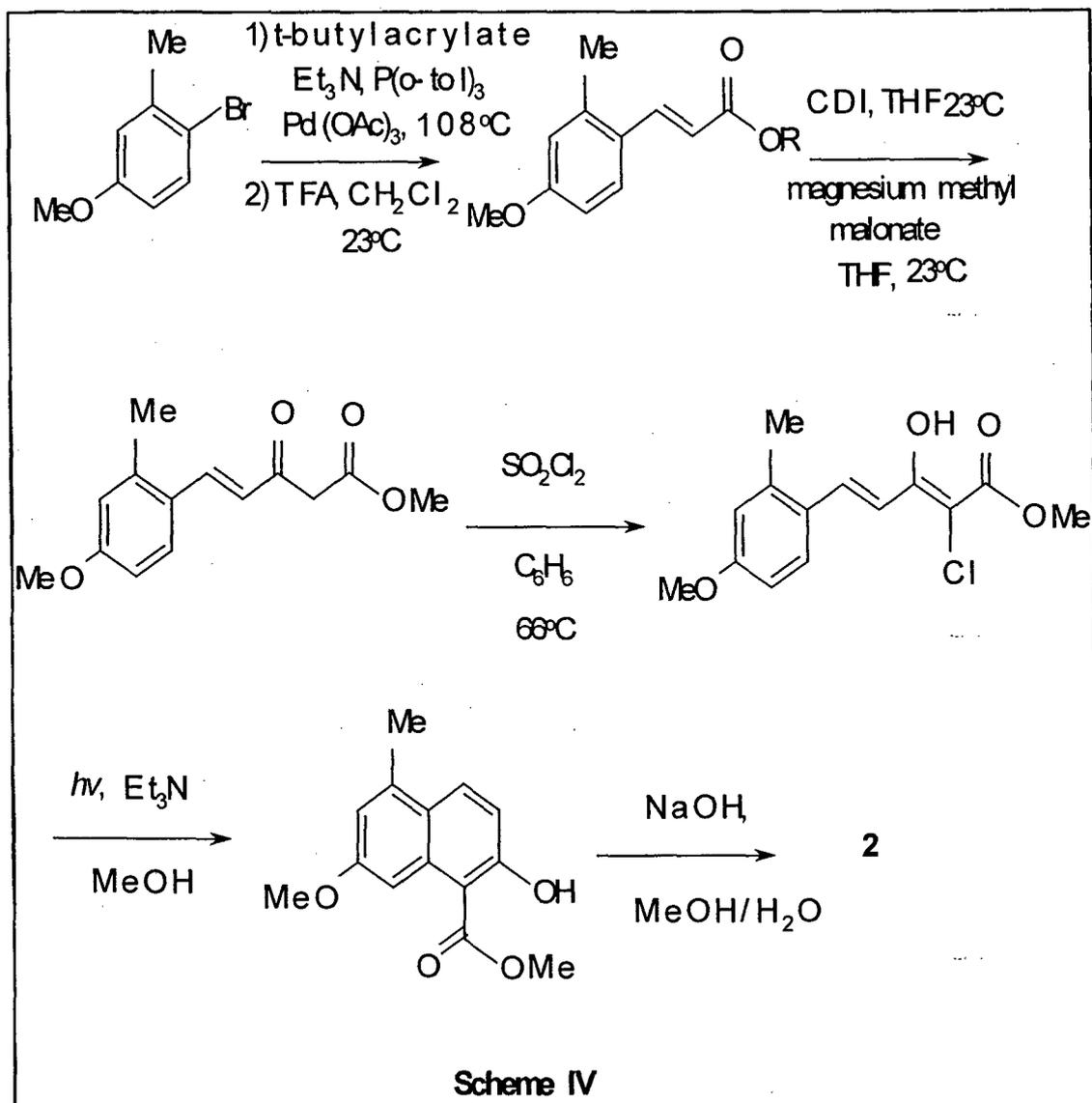
Hirama and coworkers¹⁰ have achieved the total synthesis of neocarzinostatin carboxylic acid (**2**) using expensive methyl cyclohexanedione in 6 steps giving 20% total yield (**Scheme III**).



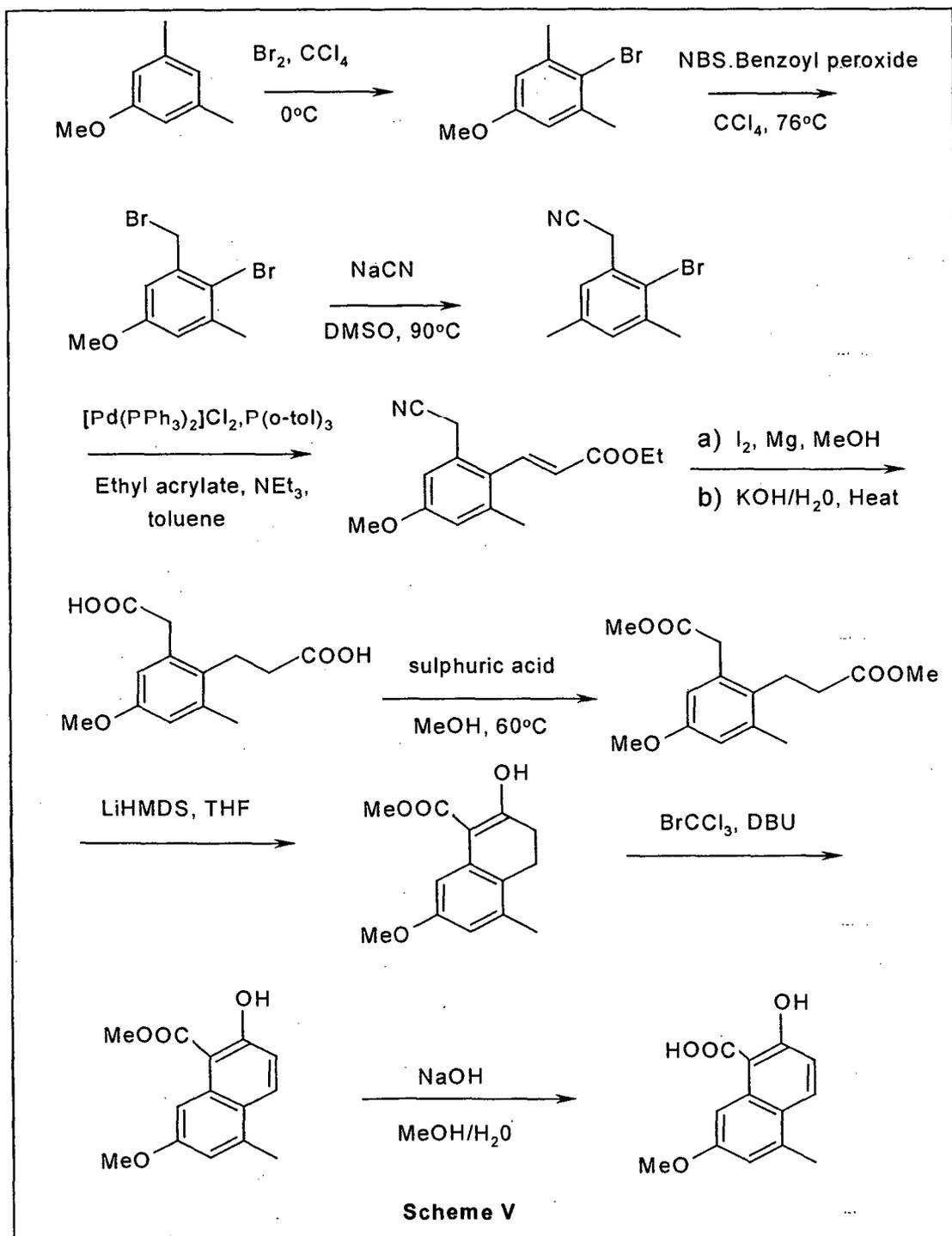




Myer's *et al*¹¹ have obtained (2) from bromoanisole in 9 steps giving 33-37% yields (Scheme IV).



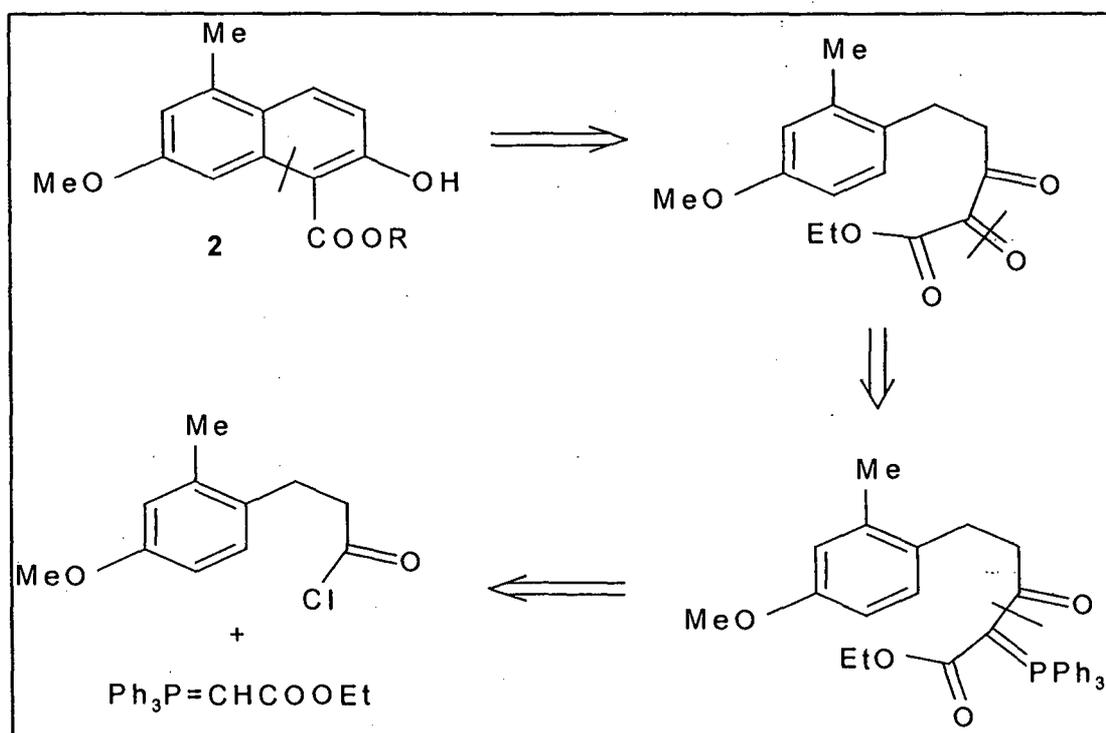
Bruckner *et al*¹² have synthesized this carboxylic acid using dimethyl anisole as a starting compound in 33% overall yield by a nine-step sequence.



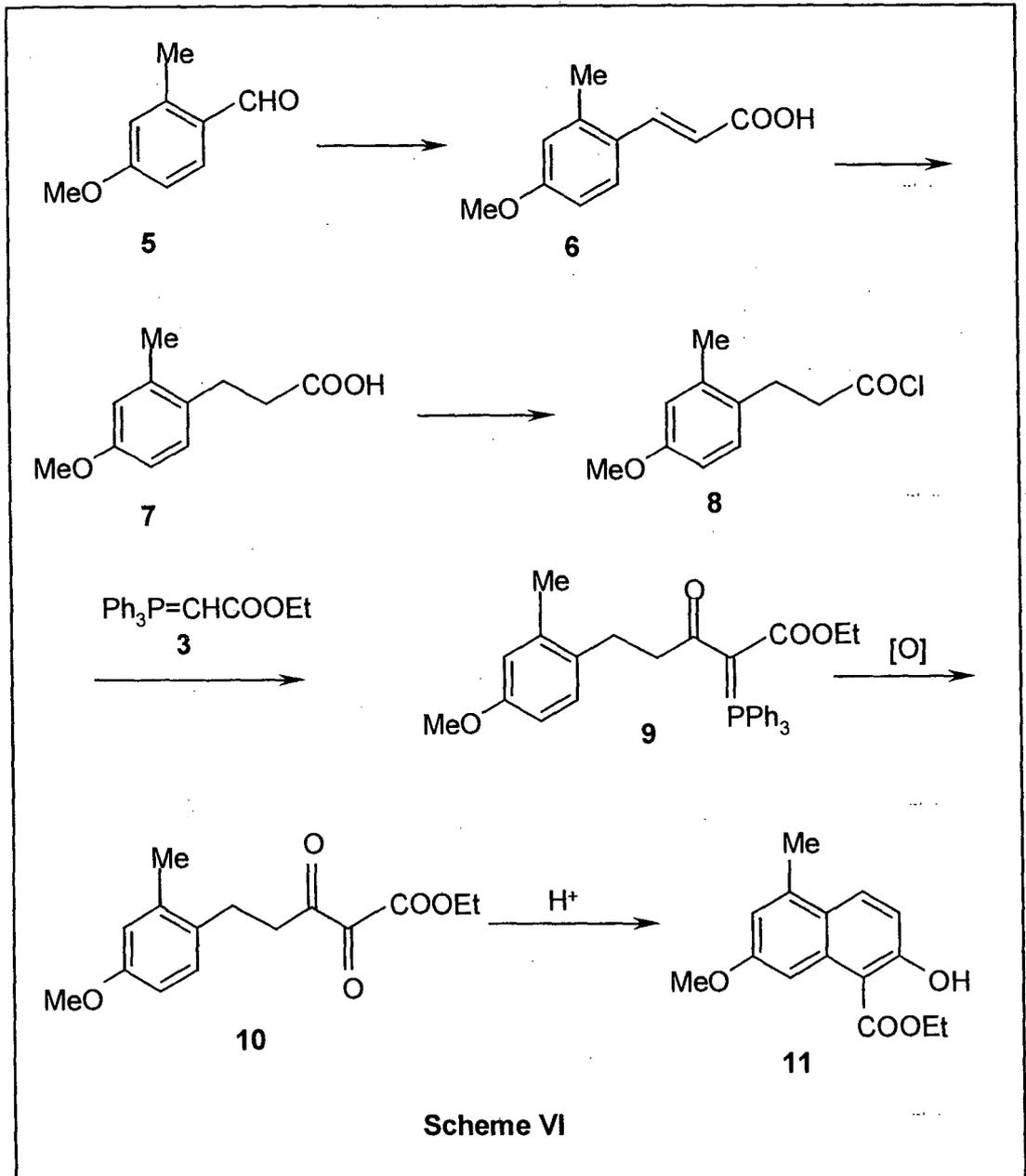
2.3 Our Synthetic Approach

We were interested to use Wasserman approach of vicinal carbonyl precursors for the synthesis of naphthalene moiety of neocarzinostatin.

The retrosynthetic approach towards the synthesis of naphthoic moiety **2**, is depicted below.



We thought that it could be possible to obtain keto-phosphorane **9** by acylation of stable phosphorane **3** using appropriate acid chloride **8**. The acylphosphorane thus formed could be easily oxidized to obtain a tricarbonyl compound by Wasserman approach. Cyclization of this tricarbonyl compound **10**, in acidic medium could give a required naphthalene skeleton **11** (Scheme VI).



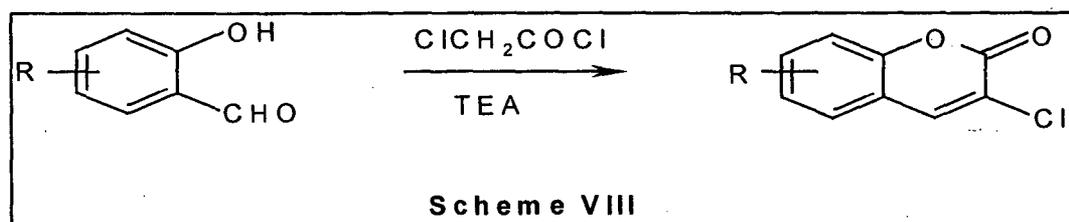
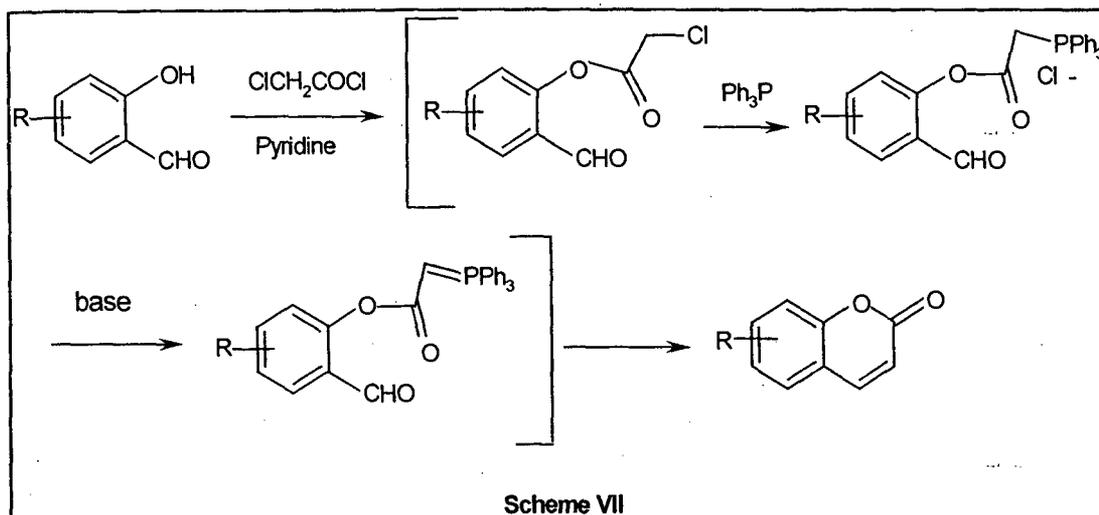
As we have mentioned in chapter 1, during acylation, only 50% yield of acyl-phosphorane is obtained and half equivalent of the phosphorane forms salt^{13,14}.

Of the methods used to overcome this shortcoming, the route reported by Wasserman et al^{15,16} appears to be the best, however, the coupling reagent is very expensive. The method reported by Yadav et al¹⁷ looked quite attractive, but in our hands we could get mere 50% of the acylated product. The method using two phase system,¹⁸ also did not give good yield.

The other method available in the literature uses triethyl amine¹⁹ as a base but as mentioned in chapter 1, this base could not be used with the combination of acid chloride having alpha protons, as it leads to the formation of ketene²⁰, instead of acylphosphorane.

So, we thought of using a base which could avoid the formation of ketene, leading to the formation of acyl phosphorane product.

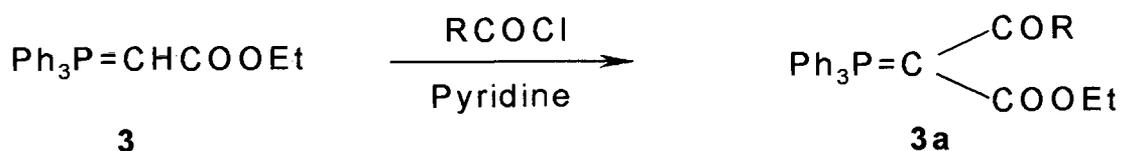
Our group^{21a} had earlier used pyridine instead of triethylamine for the synthesis of coumarin using intramolecular approach (Scheme VII), where as earlier use^{21b} of triethyl amine had resulted in direct formation of 3-chlorocoumarin (Scheme VIII).



Initially, we attempted acylation reaction on stable phosphorane with acid chloride using pyridine as a base.

The required stable phosphorane **3** was prepared by literature method²². The ethyl bromoacetate was mixed with triphenylphosphine in benzene for 12 hours and then treating the phosphorane salt with 2N NaOH to obtain stable phosphorane **3**.

Reaction mixture of acetyl chloride and stable phosphorane **3** one equivalent of each, was refluxed for 3 hours in dry benzene in presence of pyridine. After usual work up, we obtained the acyl-phosphorane **3a** in 76% yield (**Scheme IX**).



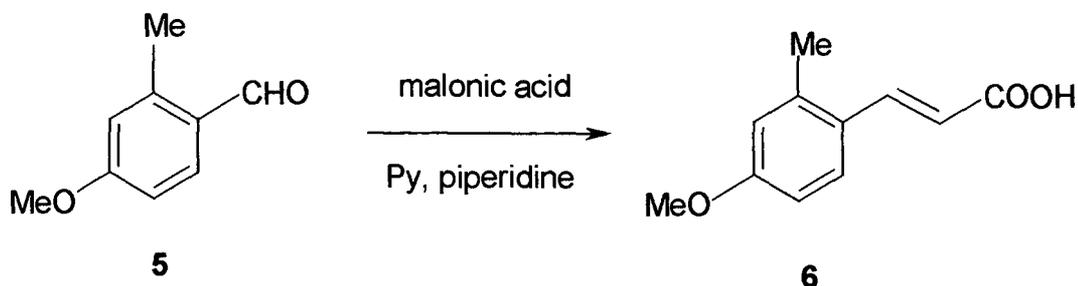
Scheme IX

Similar reaction with benzoyl chloride and chloroacetyl chloride formed the acylated phosphorane in 93 & 79 % yield. However, in few other acyl chlorides tried, the reaction mixture developed dark colour and we had to resort to column chromatography for purification of the acylated product. We also tried K_2CO_3 /acetone reaction condition, where we could not get good yields.

2.4 Attempted synthesis of naphthalene moiety of neocarzinostatin using vicinal dicarbonyl approach.

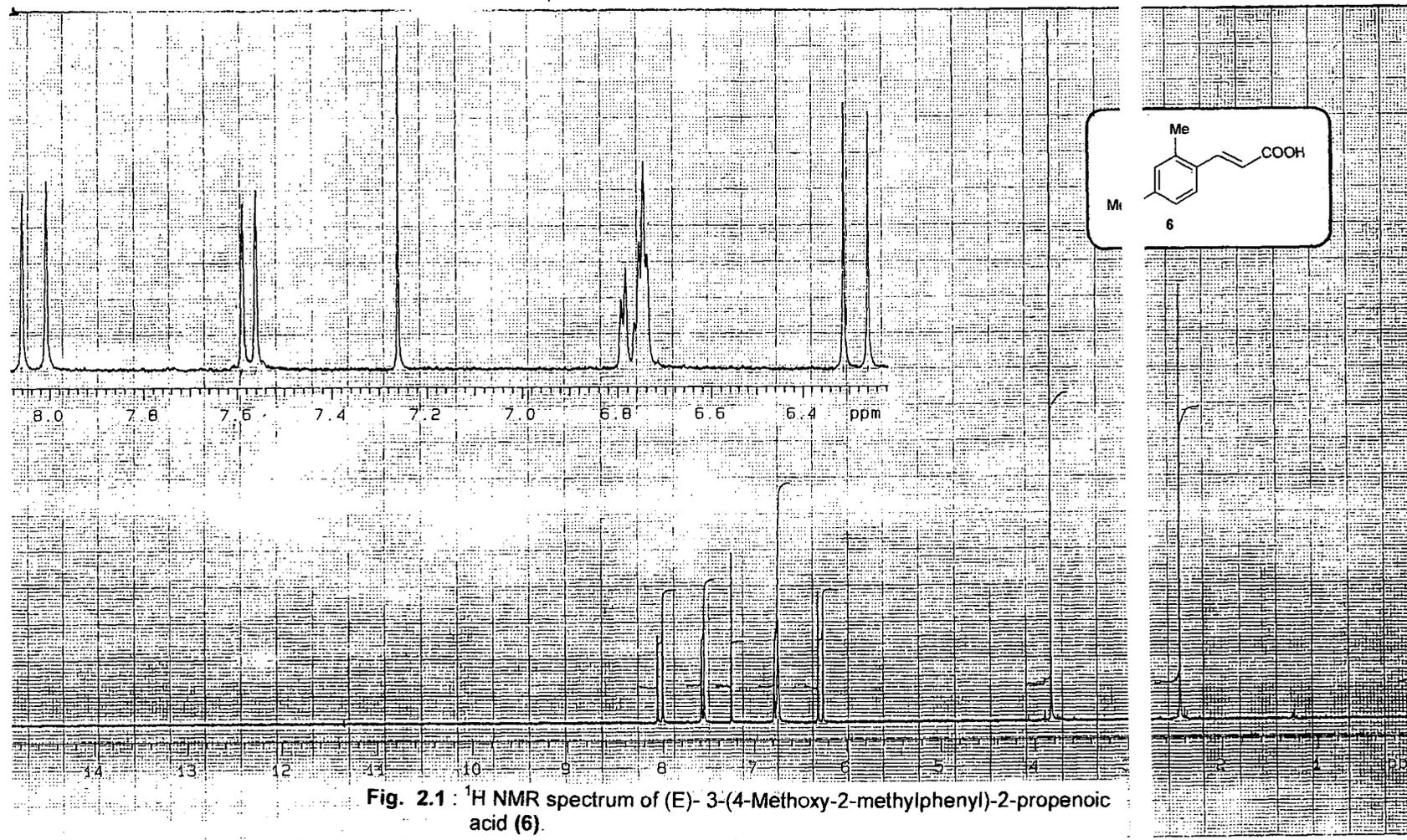
As depicted in **Scheme VI**, we needed acid chloride **8**. We thought of preparing it from 4-hydroxy-2-methyl benzaldehyde **4**, which we had in large amount as a byproduct of Reimer-Tiemann reaction on *m*-Cresol. This aldehyde **4** was to be methylated followed by Knoevenagal-Doebner modification to give the unsaturated acid **6** which on further hydrogenation followed by treatment with oxalyl chloride could give acid chloride **8**.

Thus 4-methoxy-2-methylbenzaldehyde²³ **5** was heated with malonic acid in presence of pyridine and catalytical amount of piperidine. The reaction was completed in 1 hour giving 93% yield of crude product. The recrystallisation of the crude acid was carried out with hot water to afford a yellow solid, which melted at 185°C.



Its IR spectrum showed a broad band at 3420 cm^{-1} presumably due to the carboxylic acid group. The carbonyl absorption was seen at 1680 cm^{-1} as expected.

Its $^1\text{H-NMR}$ (CDCl_3) spectrum (Fig. 2.1) exhibited the signals at δ 2.45 (s, 3H) and δ 3.83 (s, 3H), which was assigned to the CH_3 group attached to the aromatic ring and $-\text{OCH}_3$ group respectively. The peaks at δ 6.30 (d, 1H, $J = 16.8$ Hz) and 8.03 (d, 1H, $J = 16.8$ Hz) may be assigned to the $-\text{CH}=\text{CH}-$ grouping. The high coupling constant ($J = 16.8$ Hz), indicated trans (*E*) geometry of this vinyl system. The signals observed in the region, δ 6.72-6.78 (m, 2H) and at δ 7.58 (d, 1H, $J = 8.2$ Hz), could be assigned to the three aromatic protons. The coupling constant ($J = 8.2$ Hz) indicated *ortho* coupling between the aromatic protons. The high value of coupling constant ($J = 16.8$ Hz) for the olefinic protons suggested *E*-configuration of the acid.

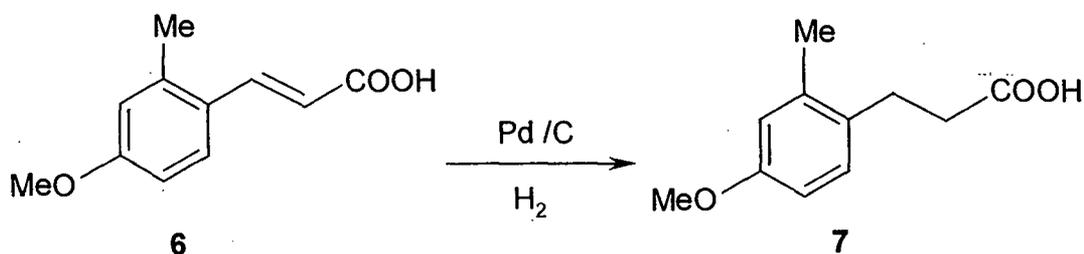


Thus, from the mode of formation and spectral properties, structure **6** was assigned to this compound. The structure was also confirmed further by comparison of its spectral and physical properties reported in literature²⁴.

Comparison of the reported and observed PMR values of compound **6** is given below.

H-atom	Reported values ²⁴	Observed values
	¹ H-NMR (DMSO-d ₆)	¹ H-NMR (CDCl ₃)
s, 3H, (CH ₃)	δ 2.36	δ 2.45
s, 3H, (CH ₃)	δ 3.76	δ 3.83
d, 1H, (CH)	δ 6.36 (<i>J</i> = 16.0 Hz)	δ 6.30 (<i>J</i> = 16.8 Hz)
m, 2H (Ar-H)	δ 6.68-6.84	δ 6.72-6.78
m, 1H (Ar-H)	δ 7.52-7.72	δ 7.58 (d, <i>J</i> = 8.2 Hz)
d, 1H, (CH)	δ 7.80 (<i>J</i> = 16.0 Hz)	δ 8.03 (<i>J</i> = 16.8 Hz)

Our next step was reduction of double bond. This was accomplished by carrying out hydrogenation of the unsaturated acid **6**, dissolved in EtOAc, on a Parr hydrogenator at atmospheric pressure using catalytical amount of 10% palladised charcoal. The reaction was completed after 2 hours, as monitored by tlc. The crude acid was obtained by usual work up.



Recrystallization from hot water furnished shiny white crystals in 95% yield. The melting point of the solid was found to be 102°C, (Lit.^{25a} m.p. 105°C).

Its IR (KBr) spectrum showed bands at 3420 and 1710 cm^{-1} indicating the presence of carboxylic acid group.

Its $^1\text{H-NMR}$ (CDCl_3) spectrum (Fig. 2.2), had signals at δ 2.30 (3H, s) and δ 3.77 (3H, s) attributed to the presence of methyl and methoxy groups in the aromatic ring. The triplets at δ 2.61 (2H, $J = 7.5$ Hz) and δ 2.89 (2H, $J = 7.5$ Hz) could be attributed to the $-\text{CH}_2-\text{CH}_2-$ grouping. The peaks at δ 6.71 (m, 2H) and at δ 7.06 (d, 1H, $J = 8.2$ Hz) could be assigned to the three aromatic protons. The coupling constant ($J = 8.2$ Hz) indicated the ortho coupling between the aromatic proton. The signal at δ 11.41 (s, 1H), which was exchangeable with D_2O , could be due to the acidic proton of the carboxylic group.

Thus, from the mode of formation and spectral properties, structure 7 was assigned to this compound. The structure was also confirmed further by comparison of its spectral and physical properties reported in literature^{25b}.

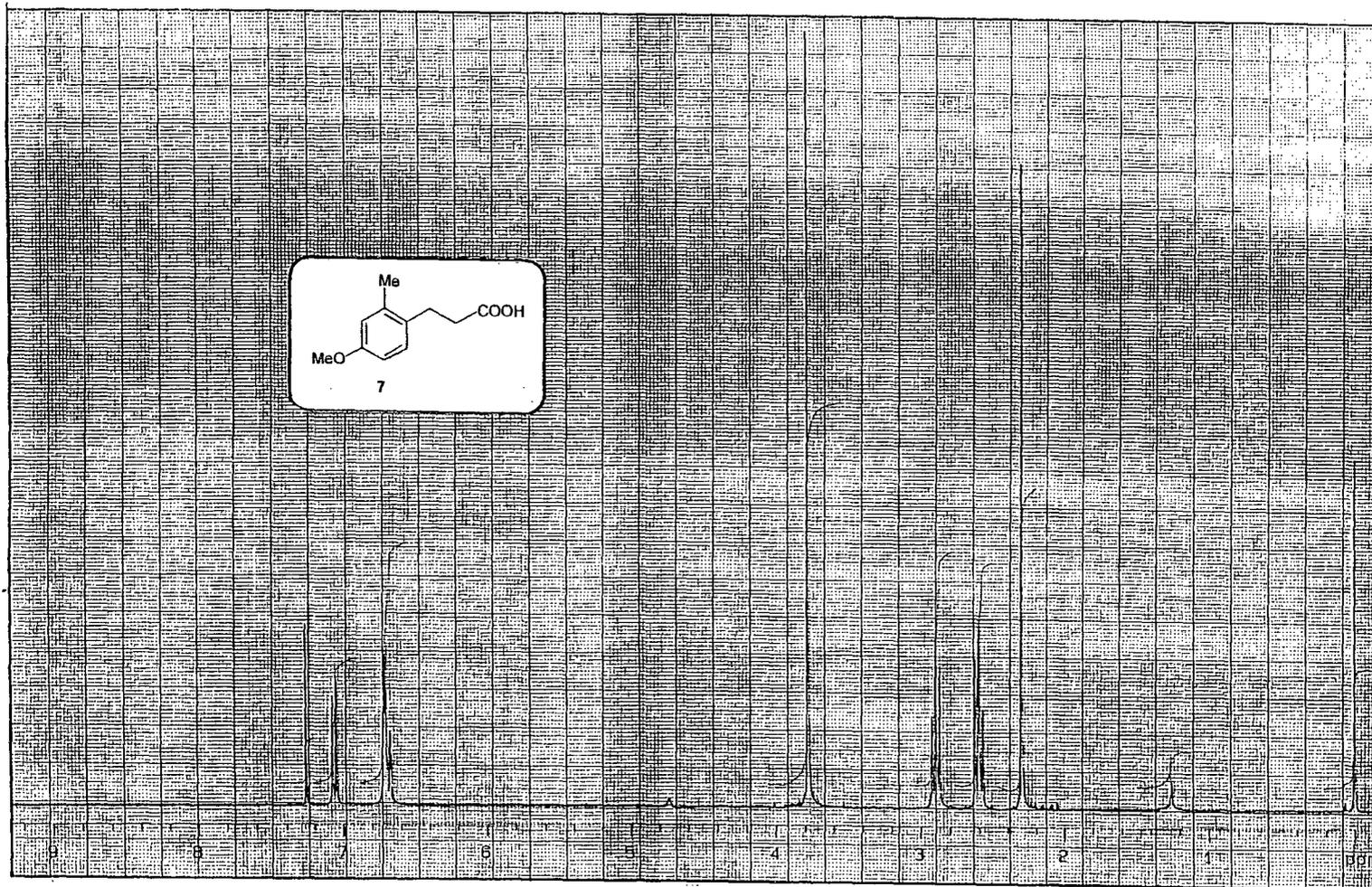
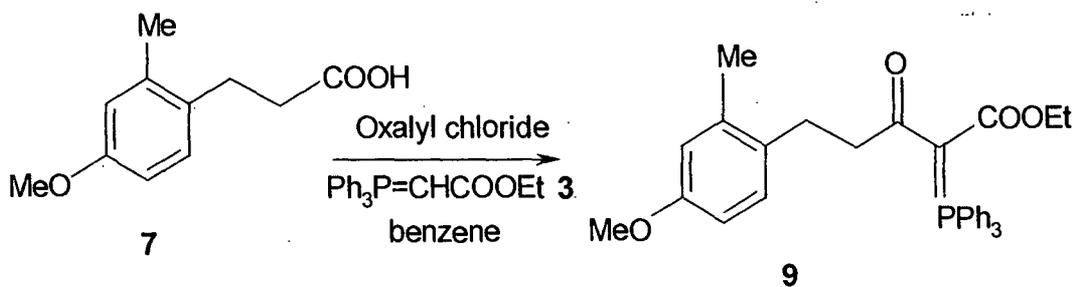


Fig. 2.2 : ^1H NMR spectrum of 3-(4-Methoxy-2-methylphenyl)propionic acid (7).

Comparison of the reported and observed PMR values of compound 7 is given below.

H-atom	Reported values ^{25b} ¹ H-NMR (CDCl ₃)	Observed values ¹ H-NMR (CDCl ₃)
s, 3H, (ArCH ₃)	δ 2.30	δ 2.30
t, 2H, (ArCH ₂)	δ 2.50 (<i>J</i> = 7.5 Hz)	δ 2.61 (<i>J</i> = 7.5 Hz)
t, 2H, (CH ₂ CH ₂)	δ 3.00 (<i>J</i> = 7.5 Hz)	δ 2.89 (<i>J</i> = 7.5 Hz)
s, 3H, (OCH ₃)	δ 3.80	δ 3.77
s, 3H, (Ar-H)	δ 6.50	δ 6.71 (m, 2H, Ar-H) δ 7.06 (d, 1H, <i>J</i> = 8.2 Hz, Ar-H)
s, 1H, (COOH)	δ 11.50	δ 11.41

Our next strategy was to convert this acid 7 to acid chloride 8 and use this acid chloride for acylation of stable phosphorane 3 to get a new acyl phosphorane 9, as such reactions have been reported in literature, as seen in Chapter 1.



The acid chloride **8** was prepared by treating the perhydrocinnamic acid **7** with 1.5 equivalent of oxalyl chloride in dry benzene. The completion of the reaction was determined by tlc. The reaction mixture was concentrated under vacuum, which also removed traces of oxalyl chloride present. This crude product obtained was used for the acylation of stable phosphorane **3** without purification.

The acid chloride **8** was treated with two equivalents of stable phosphorane **3** in dry benzene. The reaction mixture was magnetically stirred at room temperature for 2 hours and then was warmed to 60°C for 1 hour to complete the reaction.

The reaction mixture was decanted to remove salt of parent stable phosphorane, which has been separated out. The filtrate was concentrated and the crude product was purified by column chromatography over silica gel, to obtain a pale yellow solid compound, in 50% yield. The compound was recrystallized in benzene-hexanes. The melting point of the compound was found to be 120°C.

The higher resolution mass spectrum (HRMS) (Fig. 2.3) of the compound had a strong peak at m/z 547.1833 presumably due to $(M+\text{Na})^+$

pseudo ion. The elemental composition of which was determined to be $C_{33}H_{33}O_4P$, ($M + Na^+$): calcd; m/z 547.2014.

The IR spectrum exhibited bands at 1720 and 1660 cm^{-1} , which could be attributed to the presence of ester and conjugated carbonyl group of the compound.

The 1H -NMR ($CDCl_3$) spectrum (Fig. 2.4), showed signals at δ 0.63 (t, 2H, $J = 7.5$ Hz) and at δ 3.72 (q, 3H, $J = 7.5$ Hz), which indicated the presence of OCH_2CH_3 group. A singlet at δ 2.29 integrated for three protons could be attributed to CH_3 group attached to the aromatic ring while the signal observed at δ 4.00 (s, 3H), could be due to the OCH_3 group. The two triplets at δ 2.86 (2H, $J = 7.5$ Hz) and δ 3.17 (2H, $J = 7.5$ Hz) could be attributed to the $-CH_2-$ CH_2- grouping. The signals at δ 6.62-6.27 (m, 2H) and at δ 7.13 (d, 3H, $J = 8.2$ Hz), could be assigned to the protons of 1,2,4-trisubstituted benzene nucleus. The signal displayed at δ 7.40-7.66 (m, 15H) could be assigned to the aromatic protons of the triphenylphosphine moiety.

Based on the mode of formation and spectral details structure 9 was assigned to the compound.

M-11

M-11 60 (1.410) AM (Cen,4, 80.00, Ar,5300.0,556.28,0.40,LS 10); Cm (56:72)

1: TOF MS ES+
2.74e4

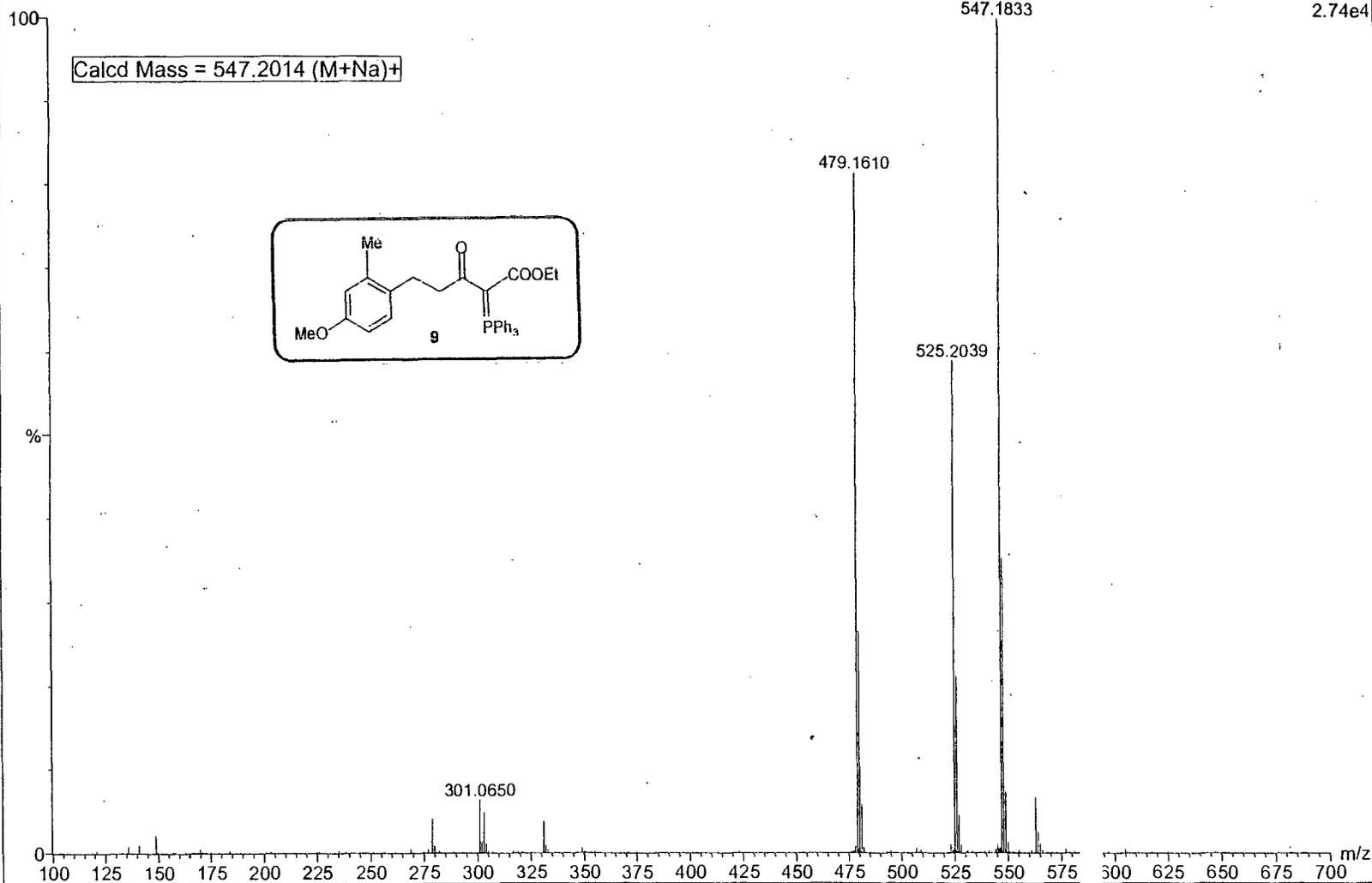


Fig. 2.3 : HRMS of Ethyl 3-oxo-2-(triphenylphosphorylidene)-
(4-methoxy-2-methyl-phenyl)pentanoate (9).

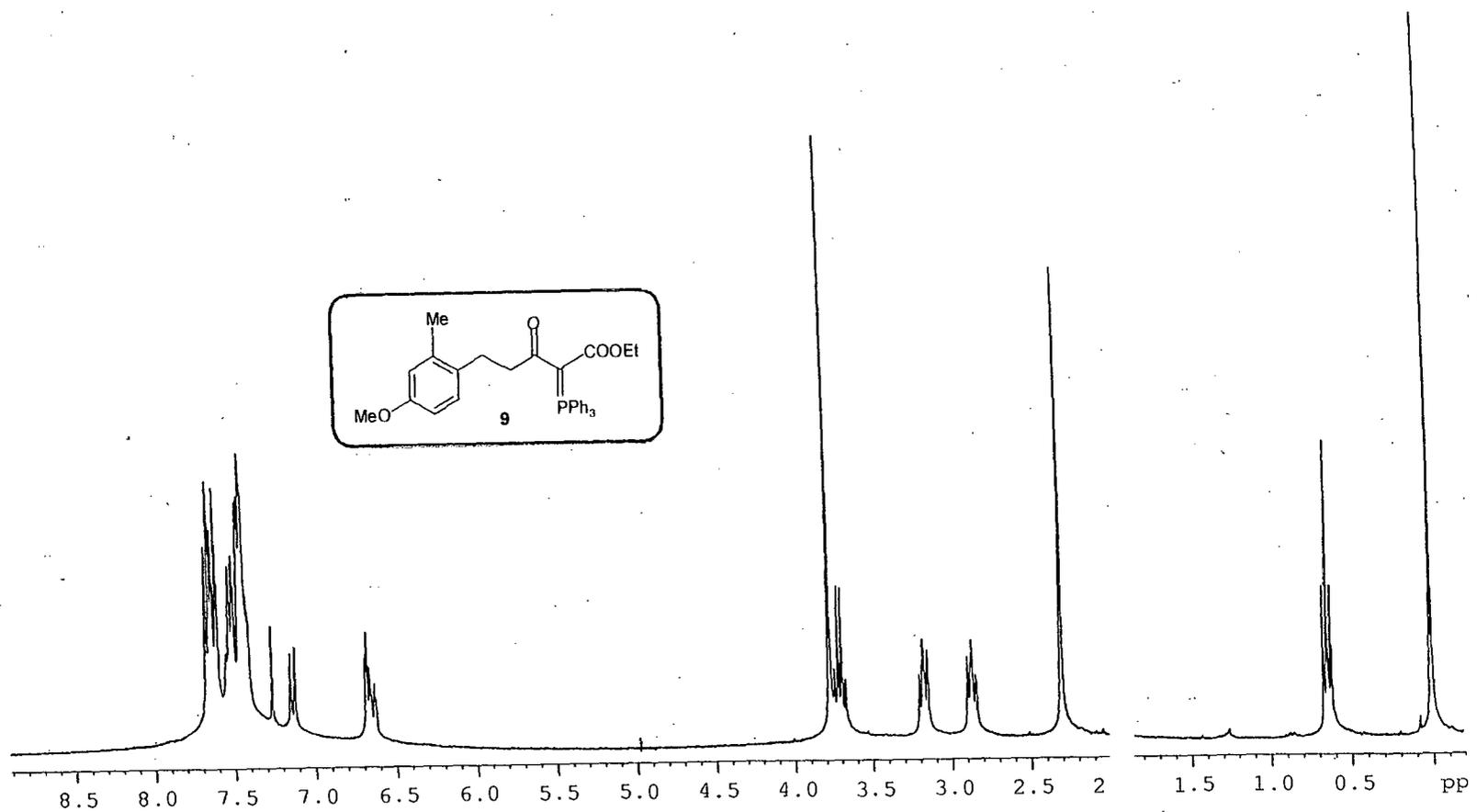
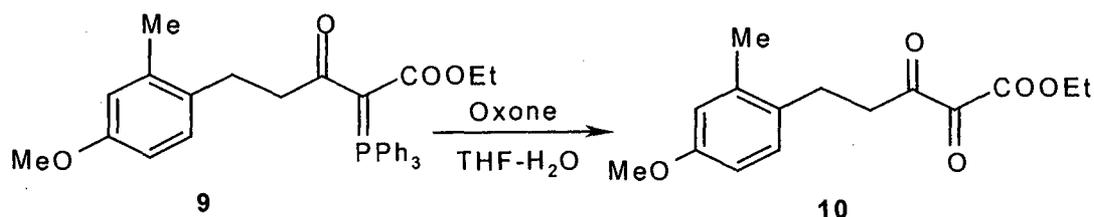


Fig. 2.4 : ^1H NMR spectrum of Ethyl 3-oxo-2-(triphenylphosphoranylidene)-5-(4-methoxy-2-methyl-phenyl)pentanoate (**9**).

As mentioned in chapter 1, it has been well demonstrated by Wasserman *et al* that, such stable acyl-phosphoranes could be easily converted to tricarbonyl compounds. The reagents used are ozone, singlet oxygen and oxone for carrying out such oxidation of acyl-phosphoranes. We chose oxone due to its easy availability.

Thus, Phosphorane **9** was treated with 1.2 equivalent of oxone in THF-water system at room temperature for 12 hours. The tlc indicated the formation of two spots. The lower one was of triphenyl phosphine oxide. The upper spot was separated out by column chromatography over silica gel by using (1:5) ethyl acetate:hexanes as eluent to obtain a yellow solid compound. The yield of purified product was found to be 34%. The recrystallization of the compound was done in benzene-hexanes. The compound melted at 96°C.



The higher resolution mass spectrum (HRMS) (Fig. 2.5) of the compound had strong peaks at m/z 279.0930 and m/z 301.0769, presumably due to $(M+H)^+$ and $(M+Na)^+$ pseudo ions respectively. The elemental composition of which was determined to be C₁₅H₁₈O₅.

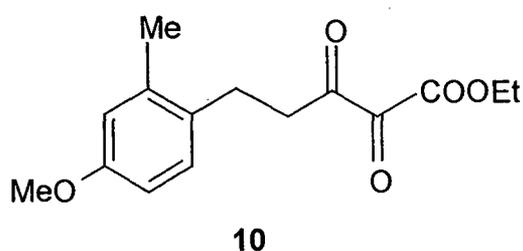
HRMS: m/z calcd for C₁₅H₁₈O₅ (M + H⁺) : 279.1232; found: 279.0939...

m/z calcd for $C_{15}H_{18}O_5$ ($M + Na^+$) : 301.1052; found: 301.0769.

The IR spectrum exhibited a band at 3420 cm^{-1} , which could be assigned to the hydrated middle carbonyl group. A band at 1730 cm^{-1} could be attributed to the carbonyl of ester group.

The $^1\text{H-NMR}$ (CDCl_3) spectrum (**Fig. 2.6**), showed signals at δ 1.22 (t, 2H, $J = 7.2\text{ Hz}$) and at δ 4.30 (q, 3H, $J = 7.2\text{ Hz}$), which indicated the presence of OCH_2CH_3 group. A signal at δ 2.30 (s, 3H), could be attributed to CH_3 group attached to the aromatic ring while another signal observed at δ 3.76 (s, 3H), could be due to the OCH_3 group. The signals at δ 2.61 (t, 2H, $J = 7.5\text{ Hz}$) and δ 2.85 (t, 2H, $J = 7.5\text{ Hz}$) could be attributed to the $-\text{CH}_2-\text{CH}_2-$ grouping. The signals at δ 6.66-6.71 (m, 2H) and at δ 7.05 (d, 3H, $J = 8.2\text{ Hz}$), could be assigned to the protons of 1,2,4-trisubstituted benzene nucleus.

Based on the mode of formation and spectral properties structure **10** was assigned to the compound.



For the synthesis of acid **2** only the last step i.e. acid catalysed ring annulation, as depicted in **Scheme VI**, was remained to be done. We postulated that this ring annulation could take place by the following mechanism (**Scheme X**).

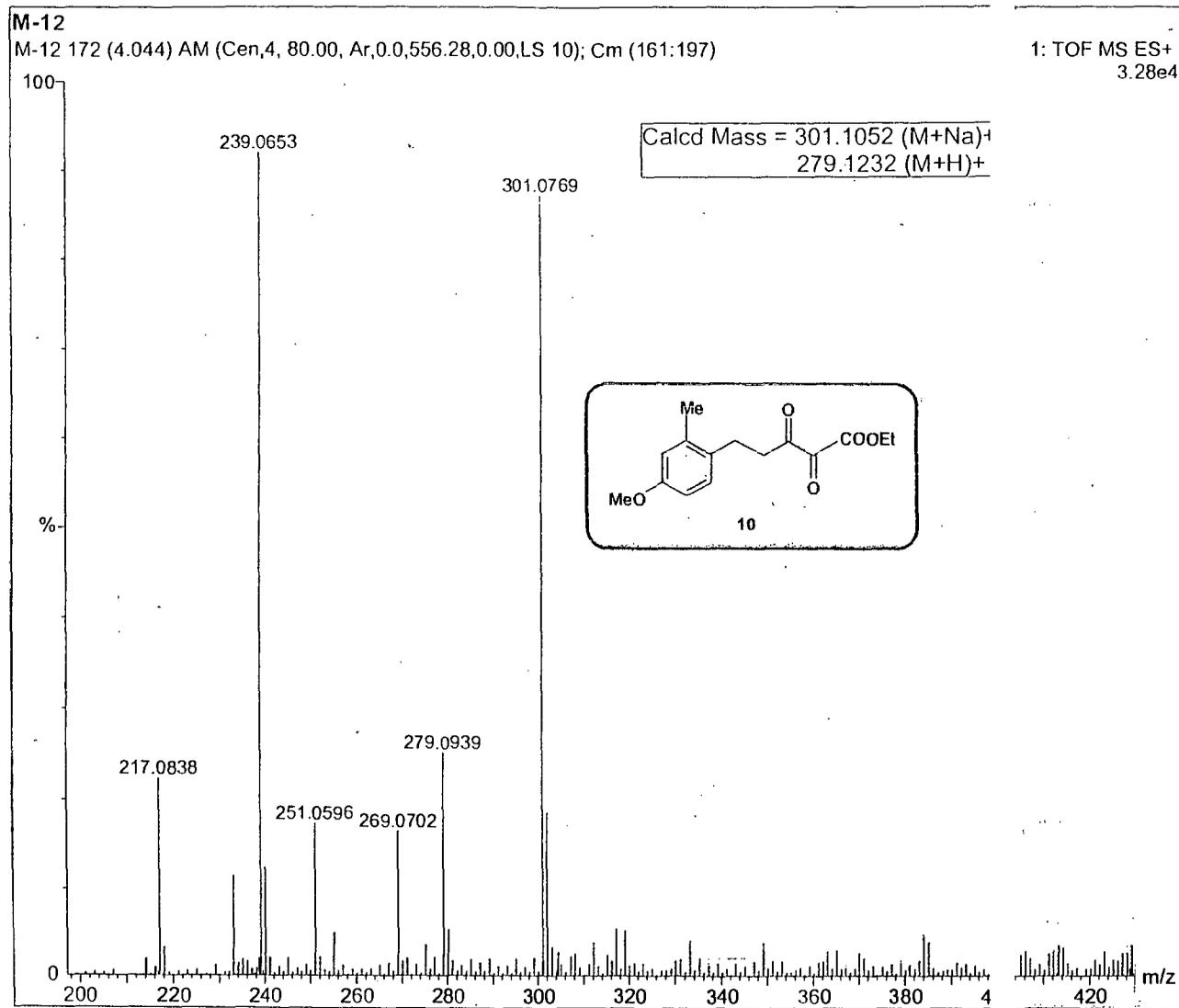


Fig. 2.5 : HRMS of Ethyl 2,3-dioxo-(4-methoxy-2-methyl phenyl)butanoate (10).

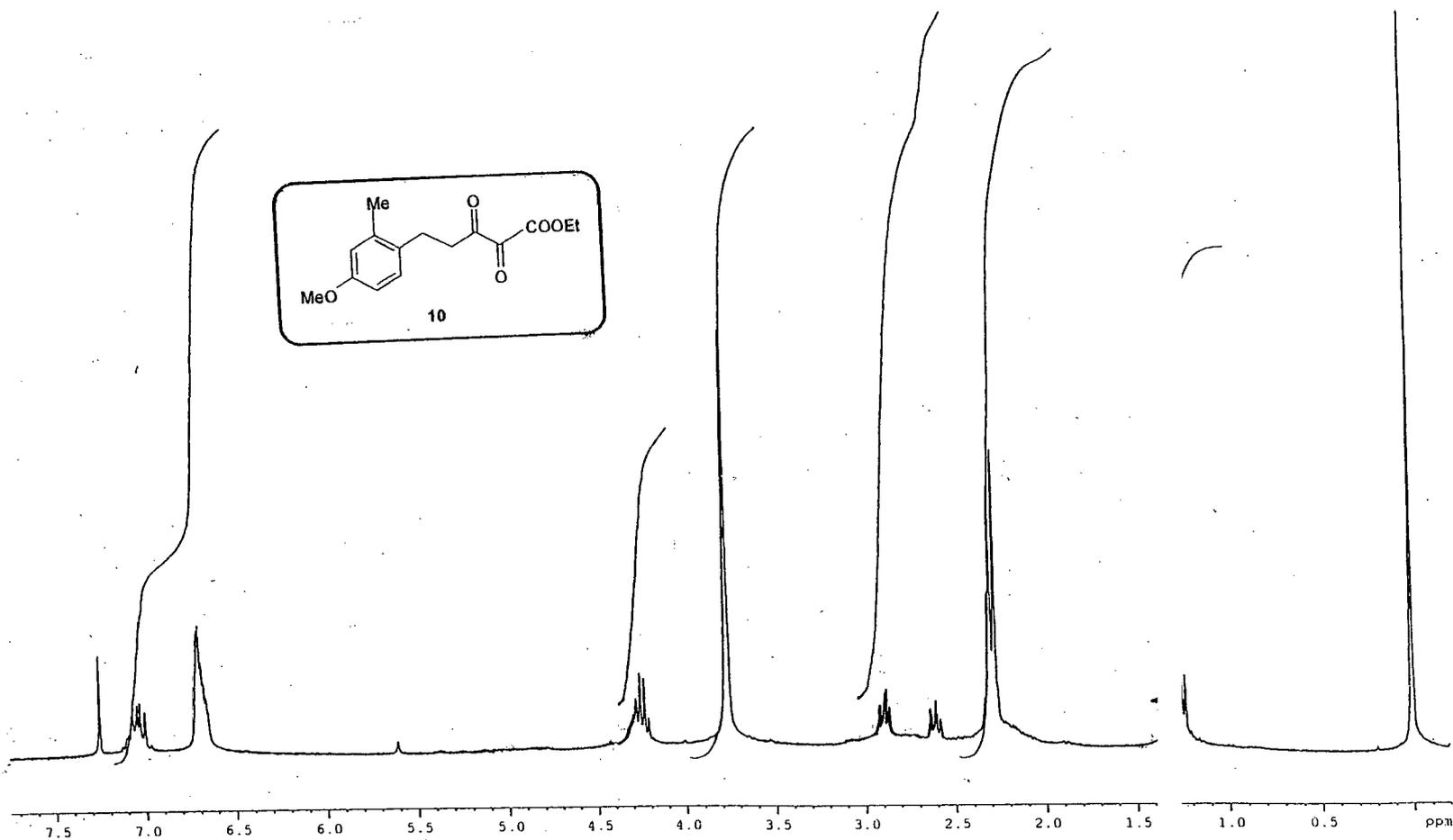
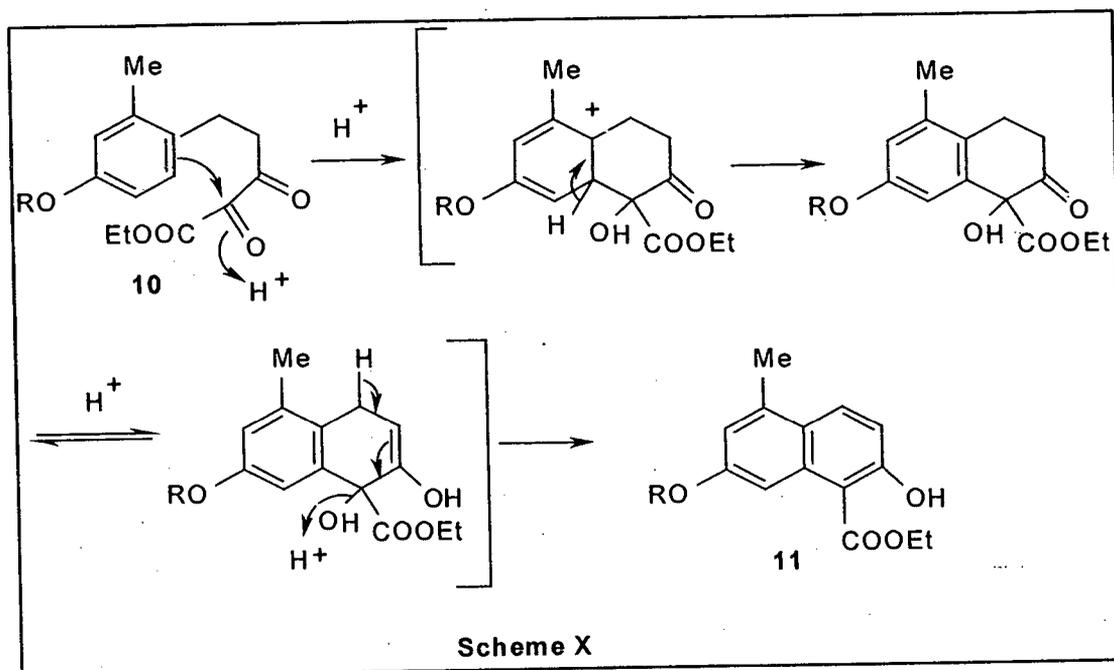


Fig. 2.6 : ¹H NMR spectrum of Ethyl 2,3-dioxo-(4-methoxy-2-methylphenyl)pentanoate (10).



As shown in **Scheme X**, acid catalyzed cyclization of the tricarbonyl compound **10** was attempted as detailed below. The tricarbonyl compound was treated with ice-cold conc. sulphuric acid in an ice bath. The progress of the reaction was monitored on tlc. After 10 min. many spots were observed on tlc indicating that the starting compound must have got decomposed into many products.

In the next attempt, the tricarbonyl compound was refluxed with catalytical amount of PTSA in toluene in a Dean-Stark apparatus assembly, for 15 hours. The tlc of the reaction mixture did not display any new spot indicating that the starting remained unchanged.

It was decided to carry out neat heating of the starting compound in some high boiling solvent. So, the tricarbonyl compound **10** was heated in

diphenyl ether. The tlc did not indicate any change in the starting material, even after refluxing the reaction mixture for 24 hours.

In an another experiment, the mixture of tricarbonyl compound and phosphorous pentoxide was heated on water bath for 12 hours. In this case also, new product formation was not observed.

In an another attempt, the tricarbonyl compound was refluxed with the mixture of hydrobromic acid (48%) and glacial acetic acid for 2 hours. Tlc of the reaction mixture displayed many spots. Separation and purification of the reaction mixture could not be achieved.

In another experiment, the tricarbonyl compound was warmed with PPA at 70°C for 10 minutes. The tlc did not show any new spot other than that of the starting tricarbonyl compound. After usual work up the starting tricarbonyl compound was recovered back.

We could not obtain the desired product through any of these attempts described above. Either, we recovered starting material back or some inseparable decomposed products. So, this route of using tricarbonyl compound (Wasserman chemistry) towards the synthesis of naphthalene **11** was abandoned and a more general and slightly longer route was visualized. This route is described in the section II, of this chapter.

Section II

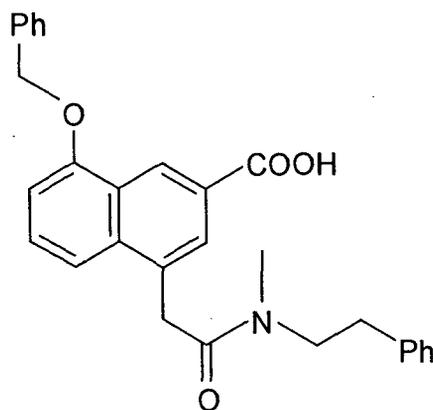
***A General Approach Towards 4-
Methyl-2-Functionalised
Naphthalenes.***

Section II

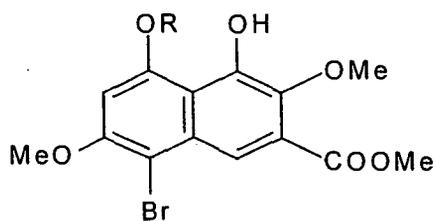
A GENERAL APPROACH TOWARDS 4-METHYL-2-FUNCTIONALISED NAPHTHALENES.**2.5 Introduction**

Substituted naphthalene units are widely encountered in many important naturally occurring biologically active molecules²⁶. There are few naphthalene compounds isolated from nature having a carboxyl group at 2-position.

For instance, the compound **1**, 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid is a high-affinity competitive Leukotriene B₄ (LTB₄)²⁷ receptor antagonist with oral activity and is currently being evaluated for clinical development²⁸.

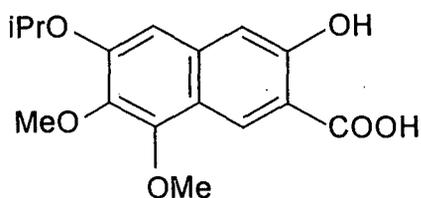
**1**

The substituted naphthalene derivative **2** is a key precursor of naphthalenequinone ring moiety, in the kinase C inhibitor, calphostic C²⁹.



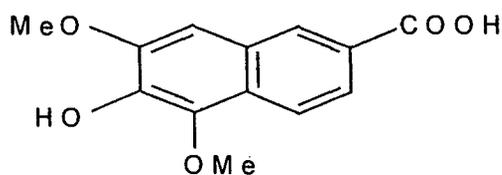
2

Naphthoic acid **3** is a key component of naturally occurring enediyne antitumors, Kedarcidin chromophores^{30b}.

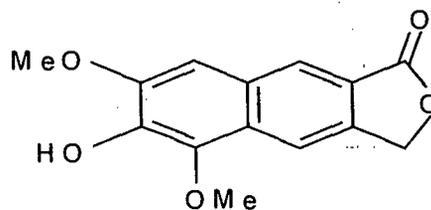


3

The two 2-naphthoic acid derivatives, 6-hydroxy-5,7-dimethoxy-2-naphthoic acid **4** and 6-hydroxy-3-hydroxymethyl-5,7-dimethoxy-2-naphthoic acid lactone **5** have been isolated from the aqueous extract of the heartwood of *Ulmus thomasi*³¹. These lignans, isolated from the extract, are biogenetically interesting due to their *in vivo* dehydrogenative condensation products.



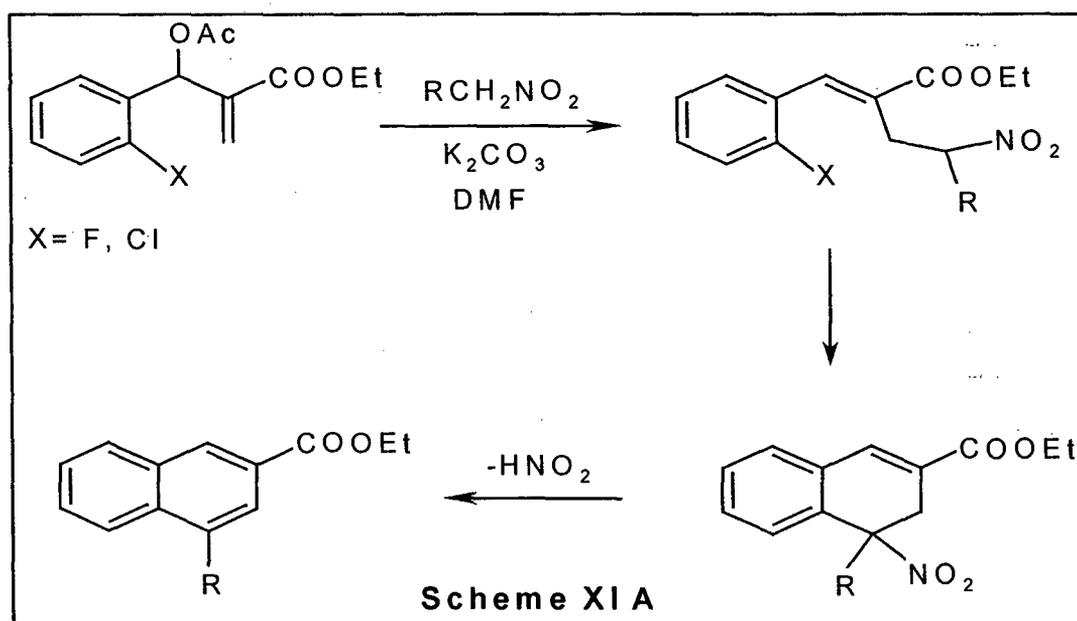
4

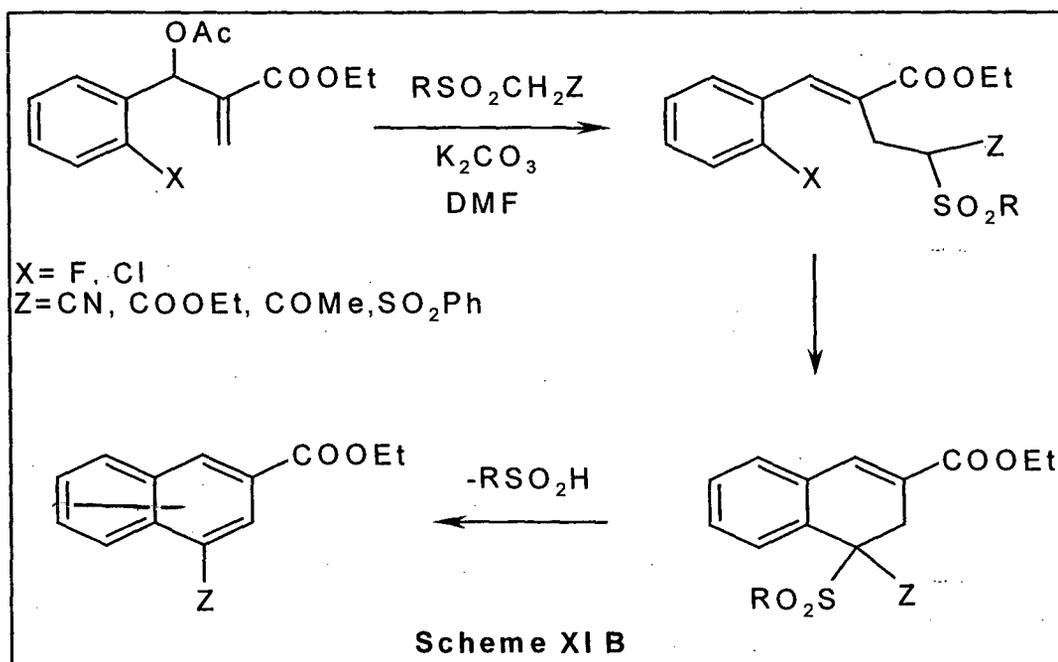


5

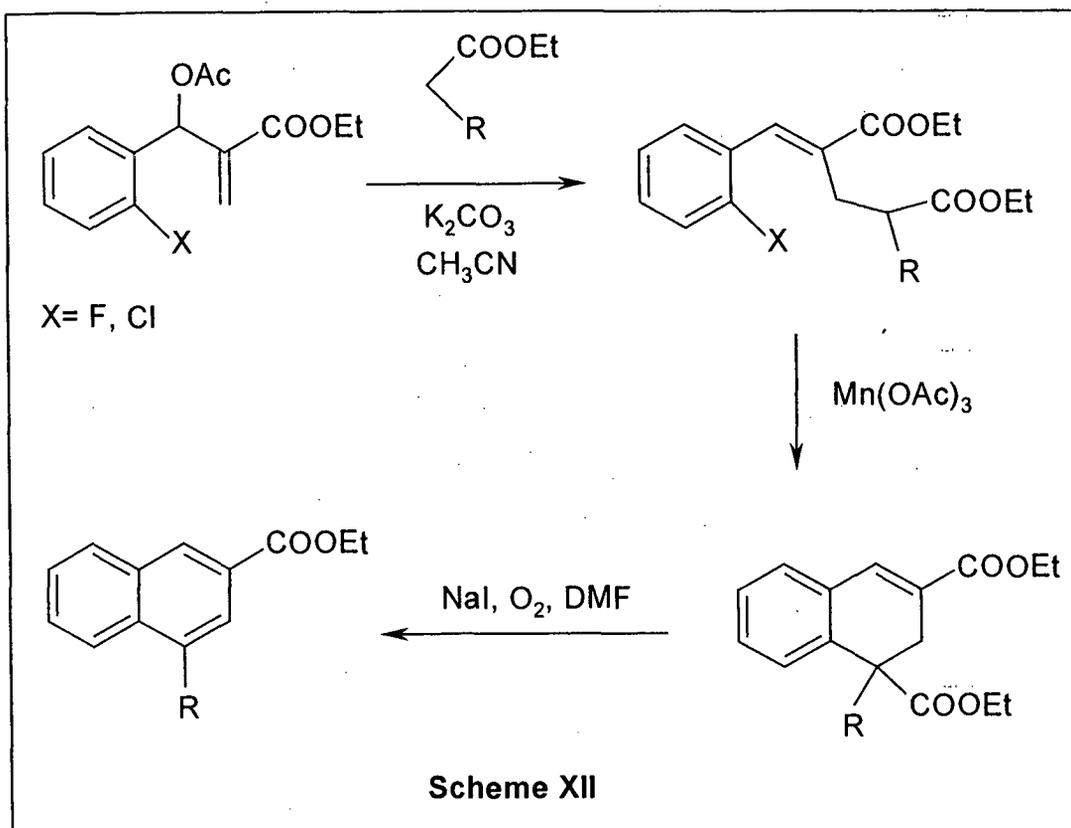
Regioselective synthesis of naphthalene derivatives has been and continues to be of great interest in organic synthesis³² due to the abundance of the skeleton in many biologically important natural products^{32,33a}. Some selected syntheses of 2-functionalized naphthalenes are given below.

Kim and co-workers³³ described a facile synthetic methodology for the synthesis of 2-substituted naphthalenes from the acetates of Baylis-Hillman adducts involving S_N2' type reaction followed by S_NAr elimination (**Scheme XI A & B**).

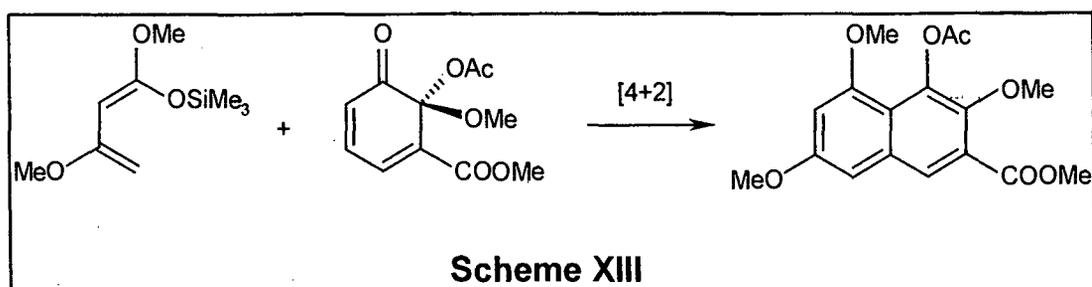




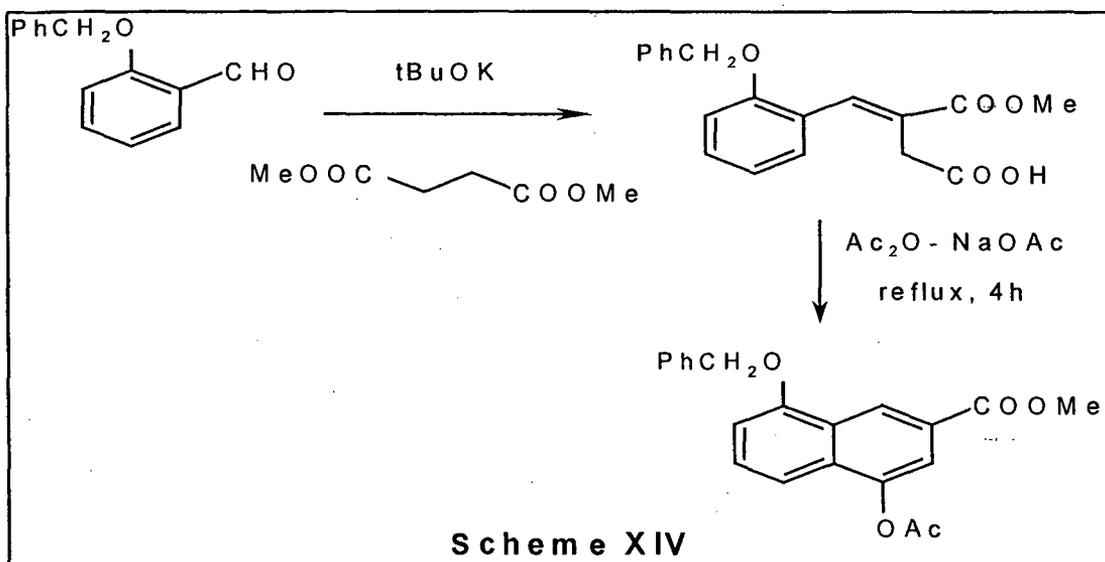
Kim and co-workers³⁴ also developed an alternative method for the synthesis of 1,3-disubstituted naphthalenes from the Baylis-Hillman acetates involving manganese(III) acetate assisted radical cyclization and aromatization as the key step (Scheme XII).



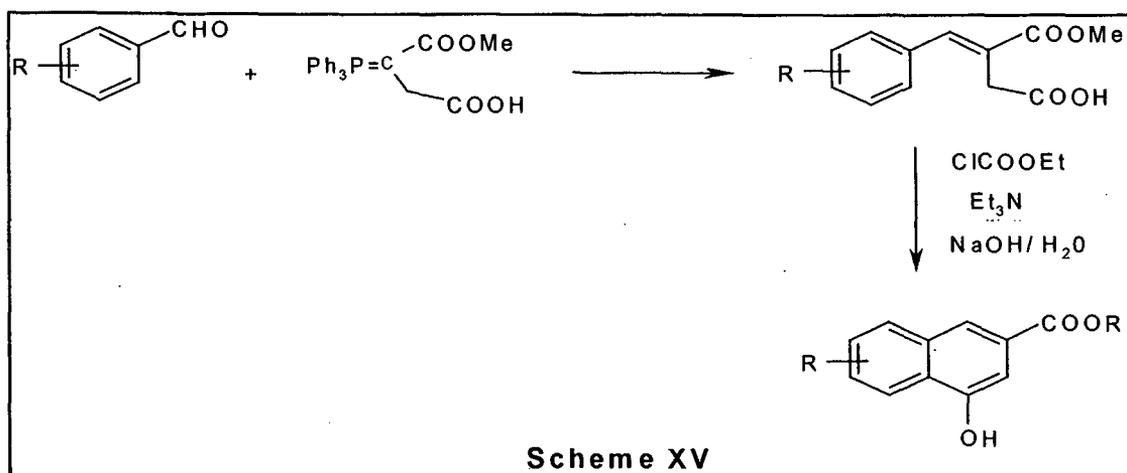
Coleman and coworker²⁹ have reported a procedure to synthesize 2-substituted naphthalene derivatives by employing 4+2 Diels-Alder reaction of quinol with 1,1,3-trioxygenated butadienes (Scheme XIII).



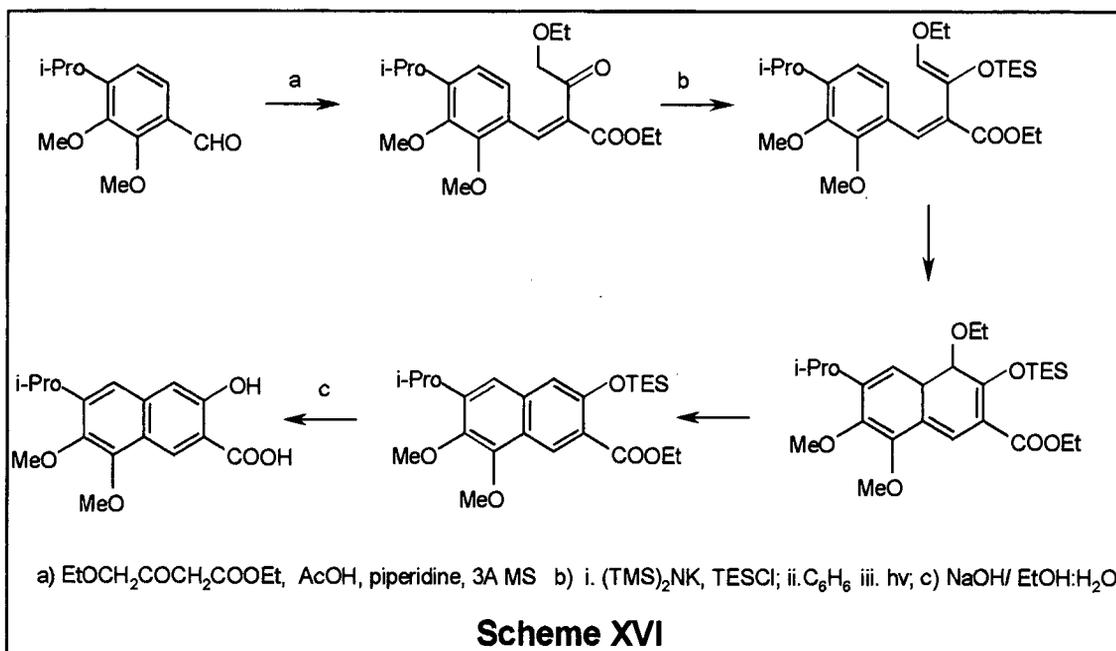
Huang²⁸ *et al* have synthesized naphthalene derivative by Stobbe condensation of *o*-(benzyloxy)-benzaldehyde with dimethylsuccinate followed by cyclization with Ac_2O - NaOAc (Scheme XIV).



Serra^{30a} and coworker have described a synthesis of substituted 4-hydroxy-2-naphthoic acid derivatives by Wittig condensation of aromatic aldehydes followed by benzoannulation. (Scheme XV).

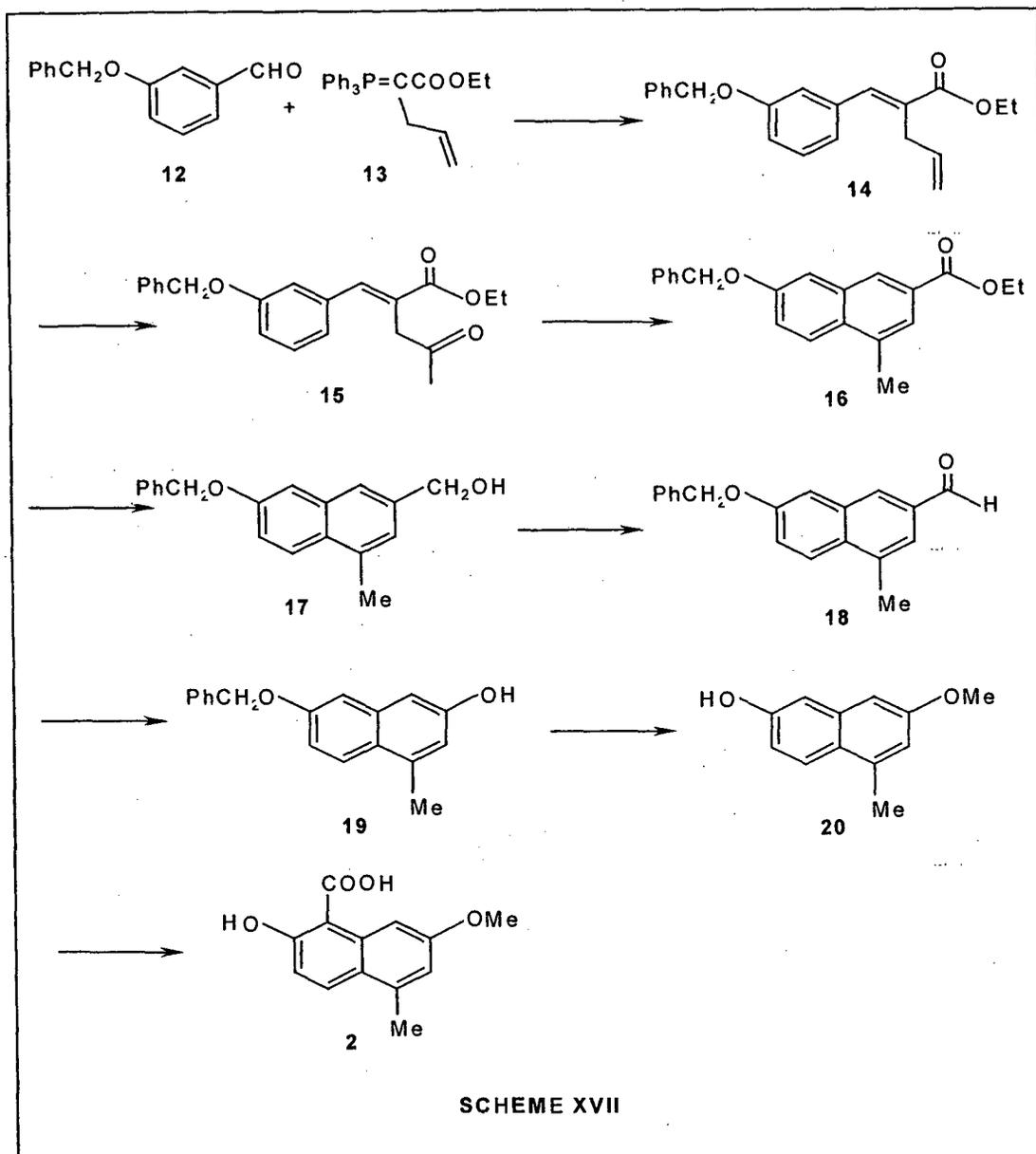


Meyers^{30b} and coworker have reported a synthesis of the naphthoic acid component of kedarcidin chromophore through photochemical and thermal electrocyclic ring closure reactions. (**Scheme XVI**).

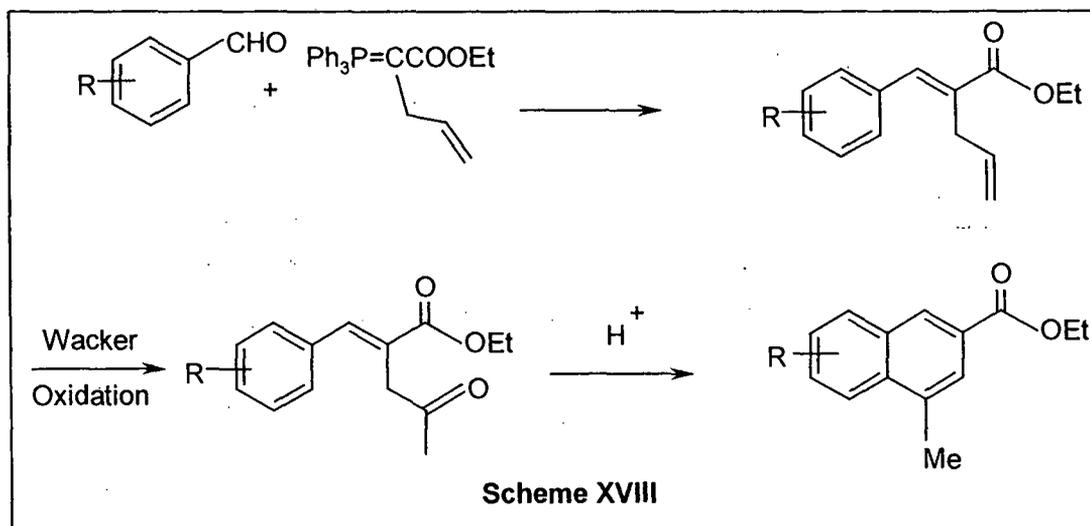


As we were unable to achieve the synthesis of the required naphthalene moiety **2** of neocarzinostatin, in previous section I, we visualized another modified approach.

As depicted in **Scheme XVII**, *m*-benzyloxy benzaldehyde **12** on condensation with phosphorane **13** could give unsaturated ester **14**. The preparation of phosphorane **13** by allylation of stable phosphorane **3** is reported in literature³⁵. The ester **14** on Wacker oxidation could give the keto compound ester **15**. The keto-ester on cyclodehydration then could give naphthalene ester **16**. Functional group transformation of ester function of **16** then could give **2** via reduction of ester group, oxidation and Baeyer-Villiger oxidation.



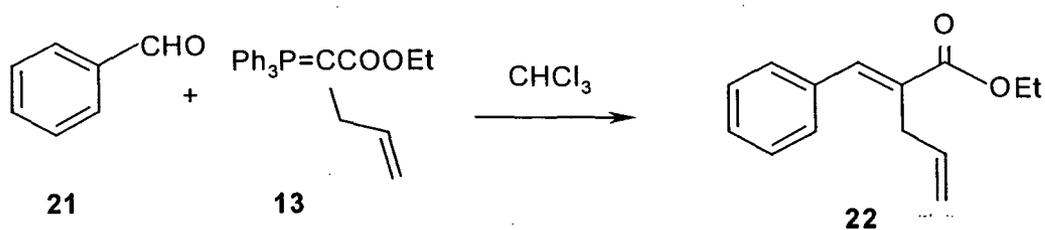
The proposed strategy is divided into two parts. The first part involves synthesis of naphthalene skeleton (**Scheme XVIII**) and second part deals with functional group transformation of the ester functionality.



Thus, to begin with, we targeted ourselves to check the feasibility of ring annulation to get naphthalene ester of type **16** (Scheme XVII).

The first step was to prepare allyl phosphorane **13**. The required allyl phosphorane **13** was prepared by literature method³⁵ involving allylation of stable phosphorane **3**. The allyl bromide was refluxed with stable phosphorane **3** in chloroform for 2 hours and then treating the phosphorane salt with 2N NaOH to obtain stable allyl phosphorane **13**.

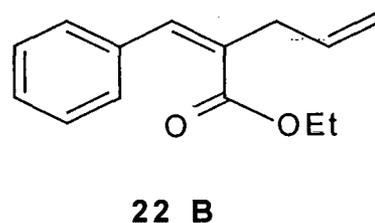
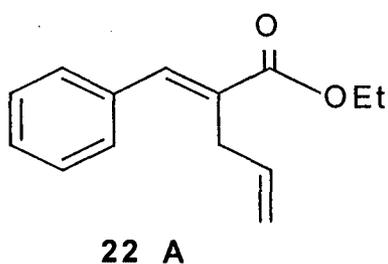
In the next step, we condensed phosphorane **13** with benzaldehyde **21** in chloroform. After 3 hours the TLC showed the disappearance of the starting compounds and two new spots were seen. The lower spot was found to be that of the triphenylphosphine oxide and the upper dark spot was that of the product. It was separated from the crude mixture by silica gel column chromatography to give a sweet smelling liquid in 95% yield, b.p. 136°C, (lit.^{37b} b.p. 135°C).



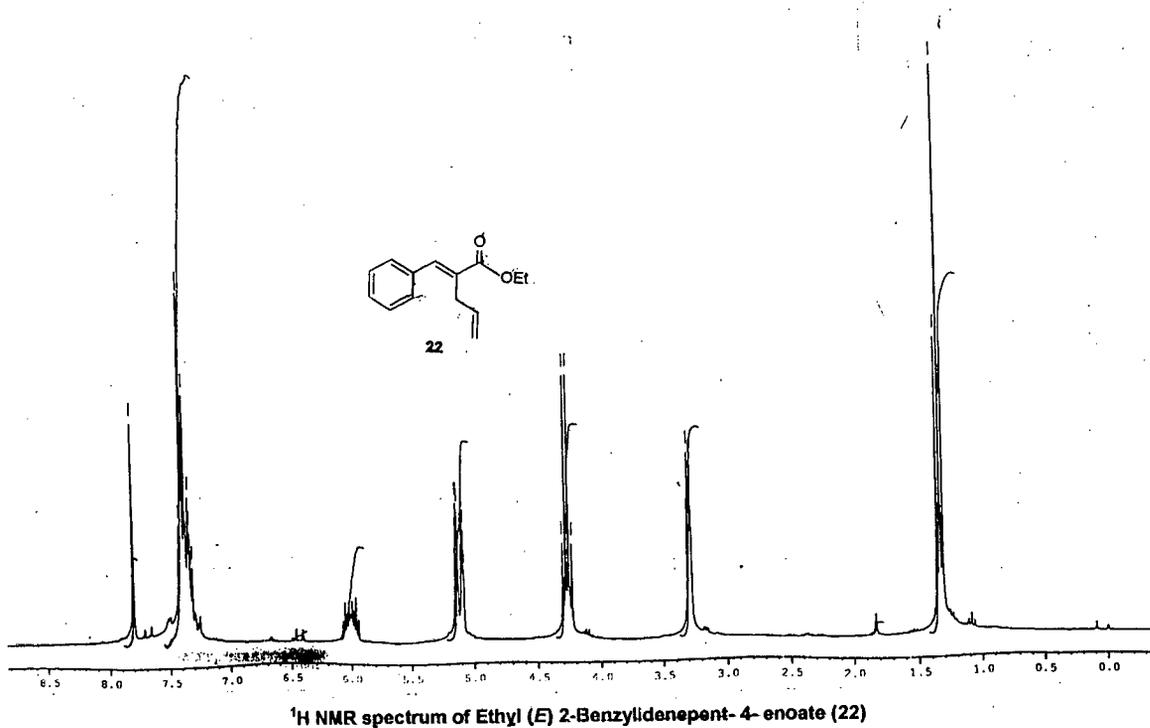
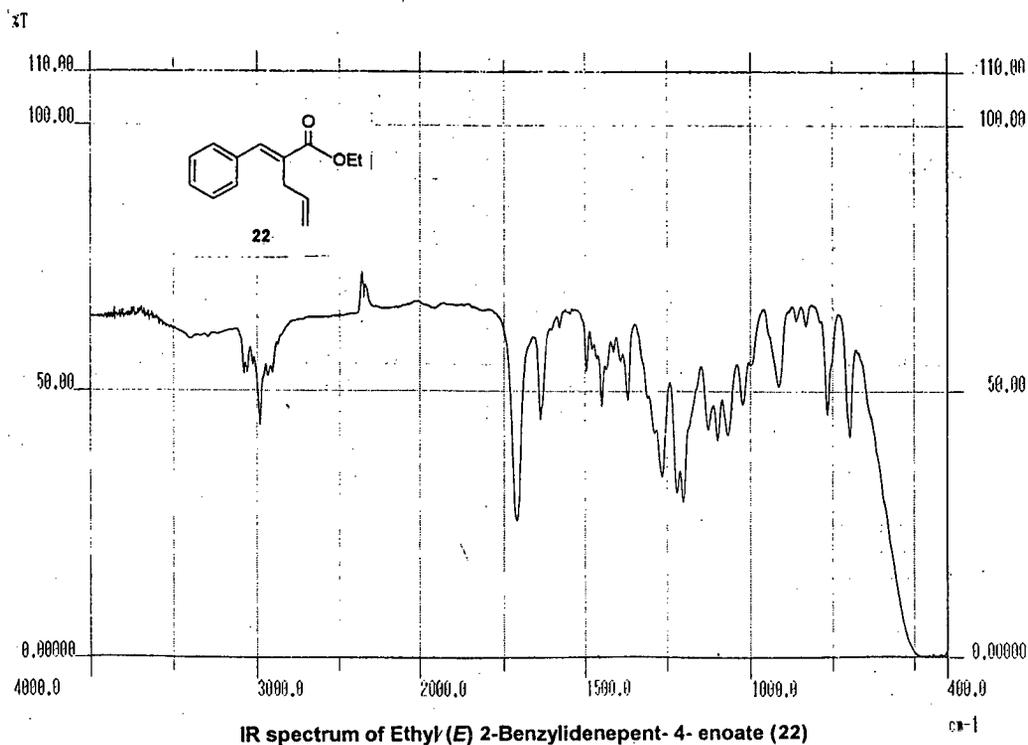
The IR spectrum exhibited a strong band at 1716 cm^{-1} , which could be due to the conjugated carbonyl of the ester group.

PMR spectrum of the compound showed signals at δ 1.33 (t, 3H, $J = 7.2$ Hz) and δ 4.26 (q, 2H, $J = 7.2$ Hz), which could be attributed to $-\text{OCH}_2\text{CH}_3$ group. It also exhibited the characteristic signals of the allyl group ($-\text{CH}_2\text{CH}=\text{CH}_2$) at δ 3.28 (d, 2H, $J = 5.4$ Hz), δ 5.11 (m, 2H) and δ 6.00 (m, 1H). The signal at δ 7.30-7.41 (m, 5H), could be attributed to the aromatic protons of the phenyl ring. The singlet at δ 7.80 integrated for one proton could be assigned to the benzylic proton.

Stereochemistry of the ester 22.



It is well known that the Wittig reaction of the carbonyl compounds provide a mixture of *E* and *Z* isomers. The nature and ratio of *E-Z* isomers depends upon



the phosphorane, reactivity of the carbonyl compound and the solvent used for the reaction. As only one isomer was obtained it was necessary to decide the stereochemistry of the compound.

The product obtained was a trisubstituted olefin. It was necessary to try and decide the stereochemistry by comparison of the chemical shifts with the calculated values of the olefinic protons. The calculated values³⁶ of chemical shifts for the olefinic protons in esters A and B were reported to be δ 7.80 and δ 6.23. As the observed value (δ 7.80) was found to be same as the calculated chemical shift (δ 7.80) for the *E* isomer, the ester may have structure **22A** rather than **22B**.

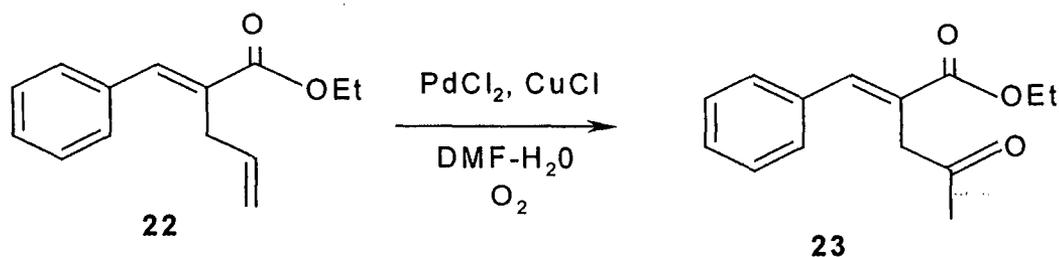
Its ¹³C-NMR (CDCl₃) spectrum showed peaks at δ 60.71 (CH₂) and δ 14.18 (CH₃), which could be assigned, to -OCH₂CH₃ group. Peaks at δ 31.56 (CH₂), 115.55 (CH) and 135.60 (CH₂) could be assigned to -CH₂CH=CH₂ grouping. Peaks at δ 128.47 (CH), 128.48 (CH), 128.33 (CH) and 140.04 (CH) could be attributed to the aromatic carbons. Peaks at δ 167.83 (CO) could be assigned to the conjugated ester carbonyl. The olefinic carbons showed a peak at δ 129.16 (CH). The quaternary carbons appeared at δ 135.43 (C) & 130.47 (C), which could be attributed to one of the carbons of the conjugated ester group and aromatic carbon respectively.

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

Based on the spectral data and mode of formation structure **22A** was assigned to the product obtained. Comparison of the reported³⁷ and observed PMR values of the compound **22A** is given below.

H-atom	Reported values ³⁷ ¹ H-NMR (CDCl ₃)	Observed values ¹ H-NMR (CDCl ₃)
t, 3H, (OCH ₂ CH ₃)	δ 1.45 (J = 7.5 Hz)	δ 1.33 (J = 7.2 Hz)
d, 2H, (-CH ₂ CH=CH ₂)	δ 3.30 (J = 6.0 Hz)	δ 3.28 (J = 5.4 Hz)
q, 2H, (OCH ₂ CH ₃)	δ 4.29 (J = 7.5 Hz)	δ 4.26 (J = 7.2 Hz)
m, 2H (-CH ₂ CH=CH ₂)	δ 4.80-5.18	δ 5.11
m, 1H (-CH ₂ CH=CH ₂)	δ 5.66-6.22	δ 6.00
s, 5H, (Ar-CH)	δ 7.44	δ 7.30-7.41
s, 1H (CH)	δ 7.83	δ 7.80

Now, as we obtained the required ester, it was needed to be converted to keto-ester so that benzoannulation in the next step would be easily achievable. As depicted in the projected synthesis (Scheme XVIII), Wacker reaction³⁸ on this ester having terminal double bond would give the desired keto ester.



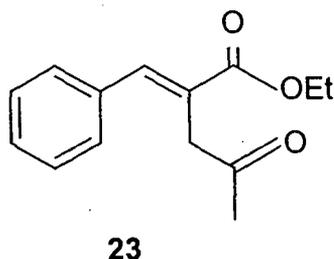
The ester **22** was subjected to the Wacker oxidation using cuprous chloride and palladium chloride in oxygen atmosphere. Initially, oxygen gas was passed through the mixture of CuCl and PdCl₂ in DMF-H₂O solvent system for one hour. Allyl ester was added to this and stirred at room temperature for 10 hours. The progress of the reaction was determined by tlc. The crude product obtained after usual work up was purified by column chromatography over silica gel to obtain a viscous liquid in 75% yield.

The IR spectrum exhibited two strong bands at 1722 and 1706 cm⁻¹, could be due to the presence of conjugated carbonyl of the ester group and the carbonyl of the keto group respectively.

PMR spectrum of the compound showed signals at δ 1.25 (t, 3H, $J = 7.2$ Hz) and δ 4.17 (q, 2H, $J = 7.2$ Hz), which could be attributed to -OCH₂CH₃ group. The two signals at δ 2.17 (s, 3H) and δ 3.53 (s, 2H), could be attributed to the methyl of -COCH₃ group and the methylene of -CH₂COCH₃ group respectively. The signal at δ 7.32-7.18 (m, 5H), could be attributed to the aromatic protons of the phenyl ring. The singlet at δ 7.84 integrated for one proton could be assigned to the benzylic proton.

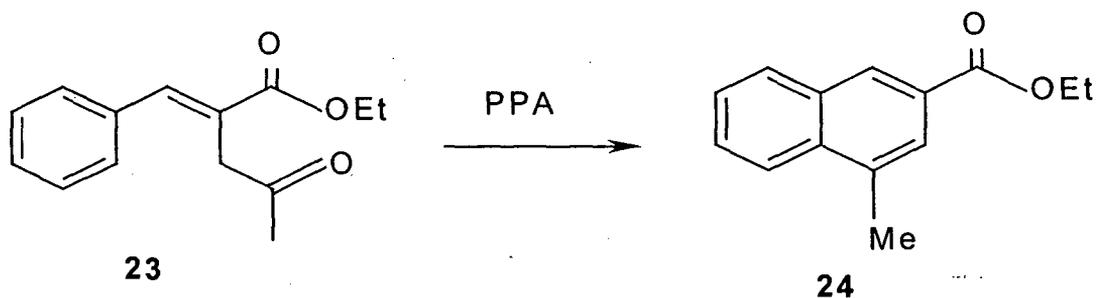
¹³C NMR δ : 14.11 (OCH₂CH₃), 29.97 (CH₃CO), 42.43 (CH₂), 61.07 (OCH₂CH₃), 106.13 (CH), 128.49 (CH), 128.68 (CH₂), 135.10 (C), 141.89 (CH), 153.13 (C), 167.30 (COOEt), 205.94 (CH₃CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.



Based on the spectral data and mode of formation structure **23** was assigned to the product by assuming that the stereochemistry of the olefin was not altered in the sequence.

Next step in the projected synthesis was the ring annulation to build up the naphthalene nucleus. Cyclodehydration of keto-ester would furnish such naphthalene skeleton. We thought of using PPA for the cyclodehydration.



In this case, we added keto ester **24** to the mixture of P_2O_5 and 88% H_3PO_4 (1:3) and the reaction mixture was kept stirring at $70^\circ C$ for 10 min. After quenching the reaction mixture with excess of water it was extracted with ethyl acetate. The EtOAc soluble products were concentrated in a rotavapor and purified by chromatography over a silica gel column yielding a white solid product

in 70% yield. Recrystallization from ethyl acetate-hexanes afforded naphthalene ester **24**, which melted at 52°C; (lit³³. m.p. 51-52°C).

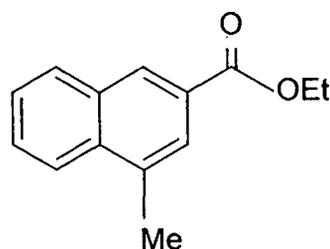
Its IR spectrum showed a strong band at 1722 cm⁻¹ which could be attributed to the carbonyl of aromatic ester.

PMR spectrum of the compound showed signals at δ 1.46 (t, 3H, $J = 7.2$ Hz) and δ 4.45 (q, 2H, $J = 7.2$ Hz), which could be attributed to -OCH₂CH₃ group. The signal observed at δ 2.73 (s, 3H), could be due to benzylic CH₃. The peaks seen at δ 7.52-7.65 (m, 2H), δ 7.93-8.03 (m, 3H) and δ 8.48 (s, 1H), could be assigned to the aromatic protons of the naphthalene ring.

¹³C NMR δ : 14.35 (OCH₂CH₃), 19.25 (CH₃), 60.94 (OCH₂CH₃), 124.00 (CH), 125.56 (CH), 126.16 (CH), 127.21 (C), 127.95 (CH), 129.35 (CH), 129.94 (CH), 132.61 (C), 134.64 (C), 166.85 (COOEt).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

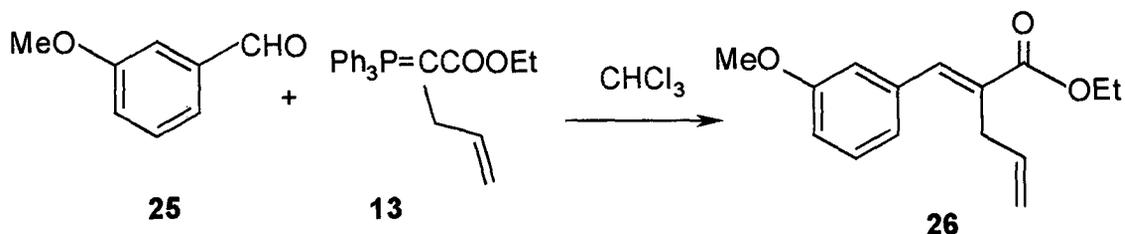
On the basis of mode of formation and spectral data, structure **24** was suggested for this compound.



24

After successful synthesis of 4-methyl-2-functionalised naphthalene we thought of checking the generality of this approach.

When *m*-methoxybenzaldehyde **25** was condensed with phosphorane **13**, an oily liquid product was obtained after the chromatographic purification, in 71% yield.



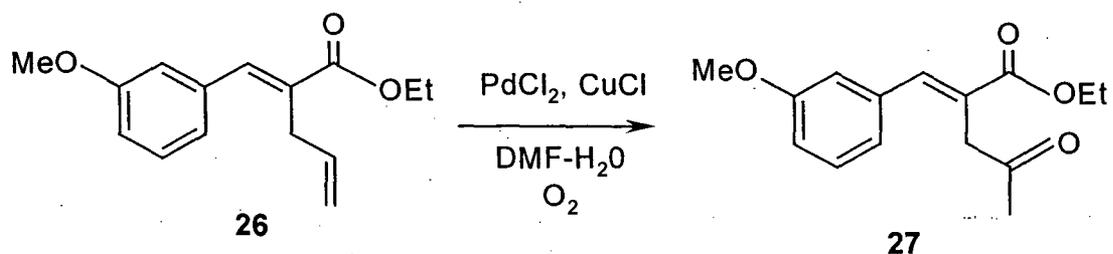
Structure **26** was assigned to the compound based on mode of formation and spectral properties of the compound mentioned below.

IR(ν_{max}): 1715, 1635, 1600 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3)

δ 1.32	t, ($J = 7.2$ Hz)	3H	-OCH ₂ CH ₃
δ 3.26	d, ($J = 5.4$ Hz)	2H	-CH ₂ -CH=
δ 3.89	s	3H	-OCH ₃
δ 4.31	q, ($J = 7.2$ Hz)	2H	-OCH ₂ CH ₃
δ 5.28	m	2H	-CH=CH ₂
δ 6.03	m	1H	-CH=CH ₂
δ 6.95-7.33	m	4H	ArH
δ 7.81	s	1H	Ar-CH=C

The ester **26** was subjected to Wacker oxidation. A viscous liquid obtained, in 77% yield, after chromatographic purification. Based on the mode of formation and spectral properties structure **27** was assigned to the compound.



IR(ν_{\max}): 1722, 1700 cm^{-1}

$^1\text{H-NMR}$: (CDCl_3)

δ 1.33	t ($J = 7.2$ Hz)	3H	-OCH ₂ CH ₃
δ 2.25	s	3H	-COCH ₃
δ 3.62	s	2H	-CH ₂ CO-
δ 3.80	s	3H	-OCH ₃
δ 4.26	q ($J = 7.2$ Hz)	2H	-OCH ₂ -CH ₃
δ 6.86-6.90	m	2H	ArH
δ 7.26-7.31	m	2H	ArH
δ 7.90	s	1H	Ar-CH=C

$^{13}\text{C NMR}$: δ 14.20 (OCH₂CH₃), 29.96 (CH₃), 43.33 (CH₂), 54.99 (CH₃O), 61.34 (OCH₂CH₃), 111.46 (CH), 112.40 (CH), 123.23 (CH), 124.80 (C), 127.73 (C), 142.88 (CH), 148.78 (CH), 149.32 (C), 167.63 (COOEt), 205.65 (CH₃CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

The keto-ester **27** was then cyclised in PPA. A solid was obtained after chromatographic purification in 69% yield. The solid was recrystallized from ethyl acetate-hexanes, which melted at m.p. 55°C. Based on the mode of formation and spectral properties structure **28** was assigned to the compound.



IR(ν_{max}): 1710, 1635, 1600 cm^{-1}

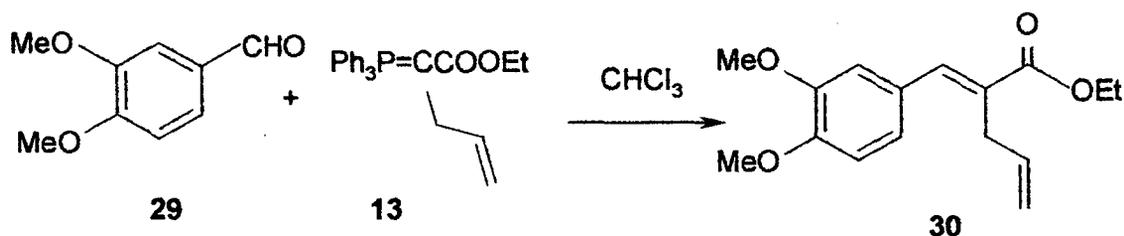
$^1\text{H-NMR}$: (CDCl_3)

δ 1.44	t ($J = 7.2$ Hz)	3H	-OCH ₂ CH ₃
δ 2.69	s	3H	-CH ₃
δ 3.94	s	3H	-OCH ₃
δ 4.42	q ($J = 7.2$ Hz)	2H	-OCH ₂ -CH ₃
δ 7.26-7.29	m	2H	ArH
δ 7.77	s	1H	ArH
δ 7.92	d ($J = 9.0$ Hz)	1H	ArH
δ 8.36	s	1H	ArH

^{13}C NMR: δ 14.30 (OCH_2CH_3), 20.45 (CH_3), 55.67 (OCH_3), 60.78 (OCH_2CH_3), 102.73 (CH), 106.88 (CH), 124.40 (CH), 126.68 (CH), 127.63 (C), 128.73 (CH), 130.22 (C), 133.77 (C), 149.89 (C), 151.52 (C), 168.11 (CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

When 3,4-dimethoxybenzaldehyde **29** was condensed with phosphorane **13**, a viscous liquid product was obtained in 69% yield, after the chromatographic purification. Structure **30** was assigned to the compound, based on mode of formation and by comparison of spectral properties with that of the reported data^{37a}.



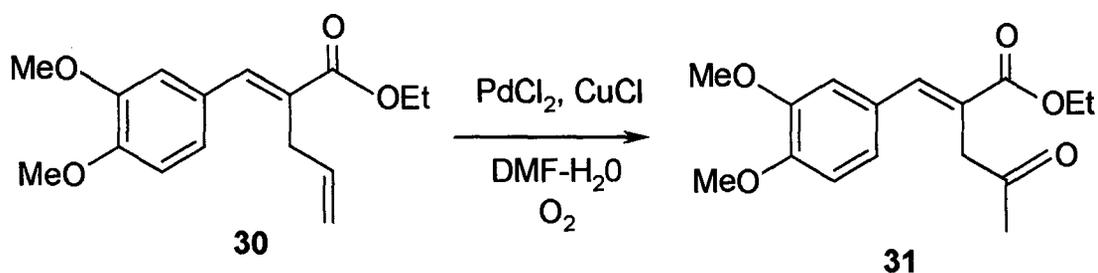
IR(ν_{max}): 1711, 1638, 1606 cm^{-1}

^1H -NMR: (CDCl_3) spectrum (Fig. 2.7)

δ 1.33	t ($J = 7.2$ Hz)	3H	$-\text{OCH}_2\text{CH}_3$
δ 3.33	d ($J = 5.4$ Hz)	2H	$-\text{CH}_2\text{-CH=}$
δ 3.87	s	3H	$-\text{OCH}_3$
δ 3.90	s	3H	$-\text{OCH}_3$
δ 4.27	q ($J = 7.2$ Hz)	2H	$-\text{OCH}_2\text{CH}_3$

δ 5.13	m	2H	-CH=CH ₂
δ 6.03	m	1H	CH ₂ =CH
δ 6.88	d ($J = 8.4$ Hz)	1H	ArH
δ 7.01	t ($J = 8.4, 1.8$ Hz)	2H	ArH
δ 7.76	s	1H	Ar-CH=C

The ester **30** was subjected to Wacker oxidation. A viscous liquid was obtained in 70% yield, after chromatographic purification. Based on the mode of formation and spectral properties structure **31** was assigned to the compound.



The mass spectrum (HRMS) of the compound exhibited a strong peak at m/z 315.2845, presumably due to $(M+Na)^+$ pseudo ion. The elemental composition of the compound was determined to be $C_{16}H_{20}O_5$.

HRMS: m/z calcd for $C_{16}H_{20}O_5$ ($M + Na^+$): 315.3207; found: 315.2845.

IR(ν_{max}): 1722, 1700 cm^{-1}

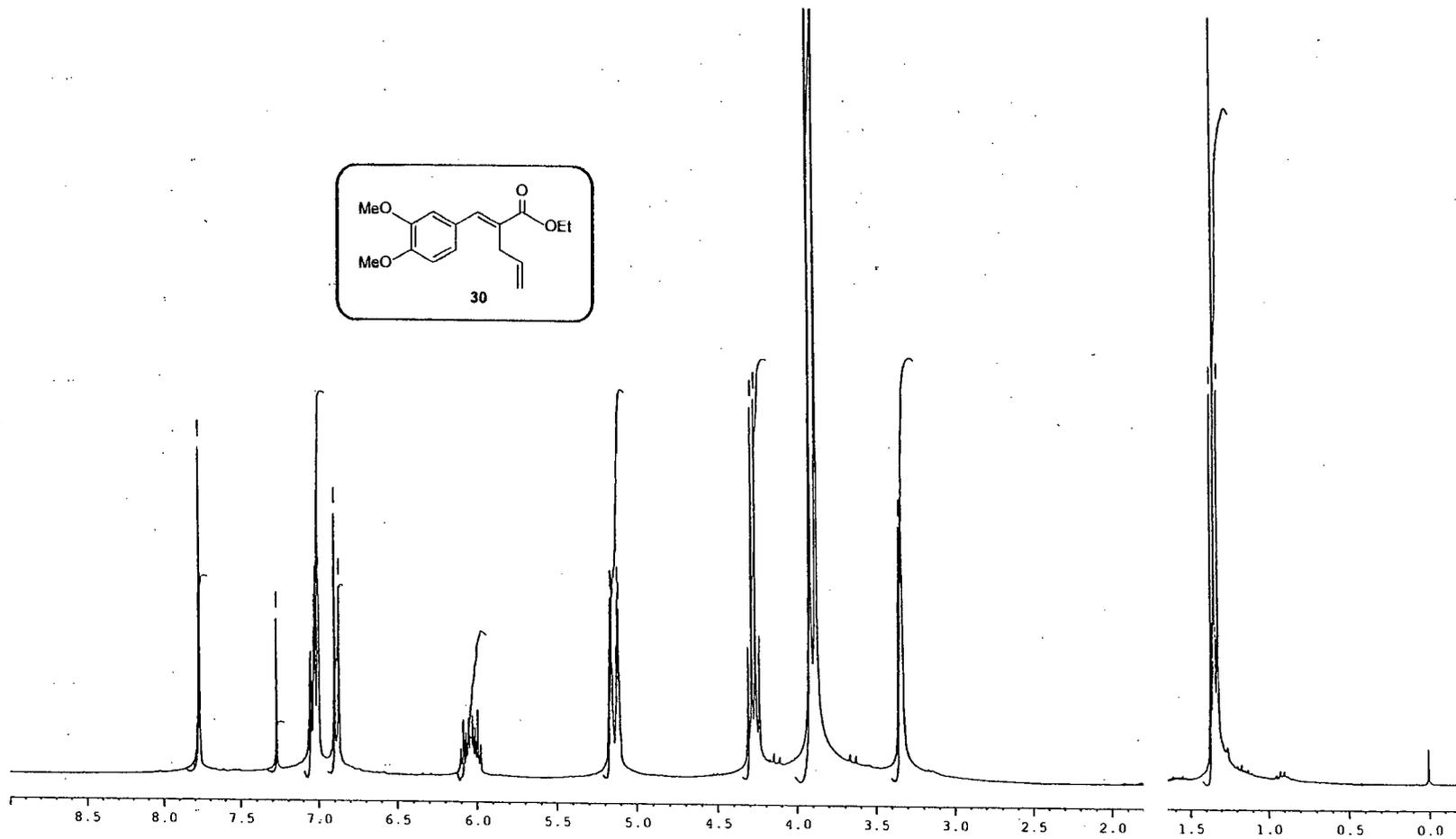


Fig. 2.7 : ¹H NMR spectrum of Ethyl (E)-2-(3,4-dimethoxy-benzylidene)pent-4-enoate (30).

¹H-NMR: (CDCl₃) spectrum (Fig. 2.8)

δ 1.24	t (J = 7.1 Hz)	3H	-OCH ₂ CH ₃
δ 2.17	s	3H	-COCH ₃
δ 3.58	s	2H	-CH ₂ CO-
δ 3.77	s	3H	-OCH ₃
δ 4.17	q (J = 7.1 Hz)	2H	-OCH ₂ CH ₃
δ 6.76-6.84	m	3H	ArH
δ 7.84	s	1H	Ar-CH=C

¹³C NMR spectrum (Fig. 2.9)

δ 14.14 (OCH₂CH₃), 29.89 (CH₃), 42.73 (CH₂), 55.79 (CH₃O), 61.00 (OCH₂CH₃), 110.96 (CH), 112.04 (CH), 122.23 (CH), 124.88 (C), 127.73 (C), 141.98 (CH), 148.78 (C), 149.72 (C), 167.53 (COOEt), 206.45 (CH₃CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

The keto ester **31** was cyclised in PPA. A solid was obtained after chromatographic purification in 70% yield. The solid was recrystallized from ethyl acetate-hexanes, which melted at m.p. 144°C. Based on the mode of formation and spectral properties structure **32** was assigned to the compound.

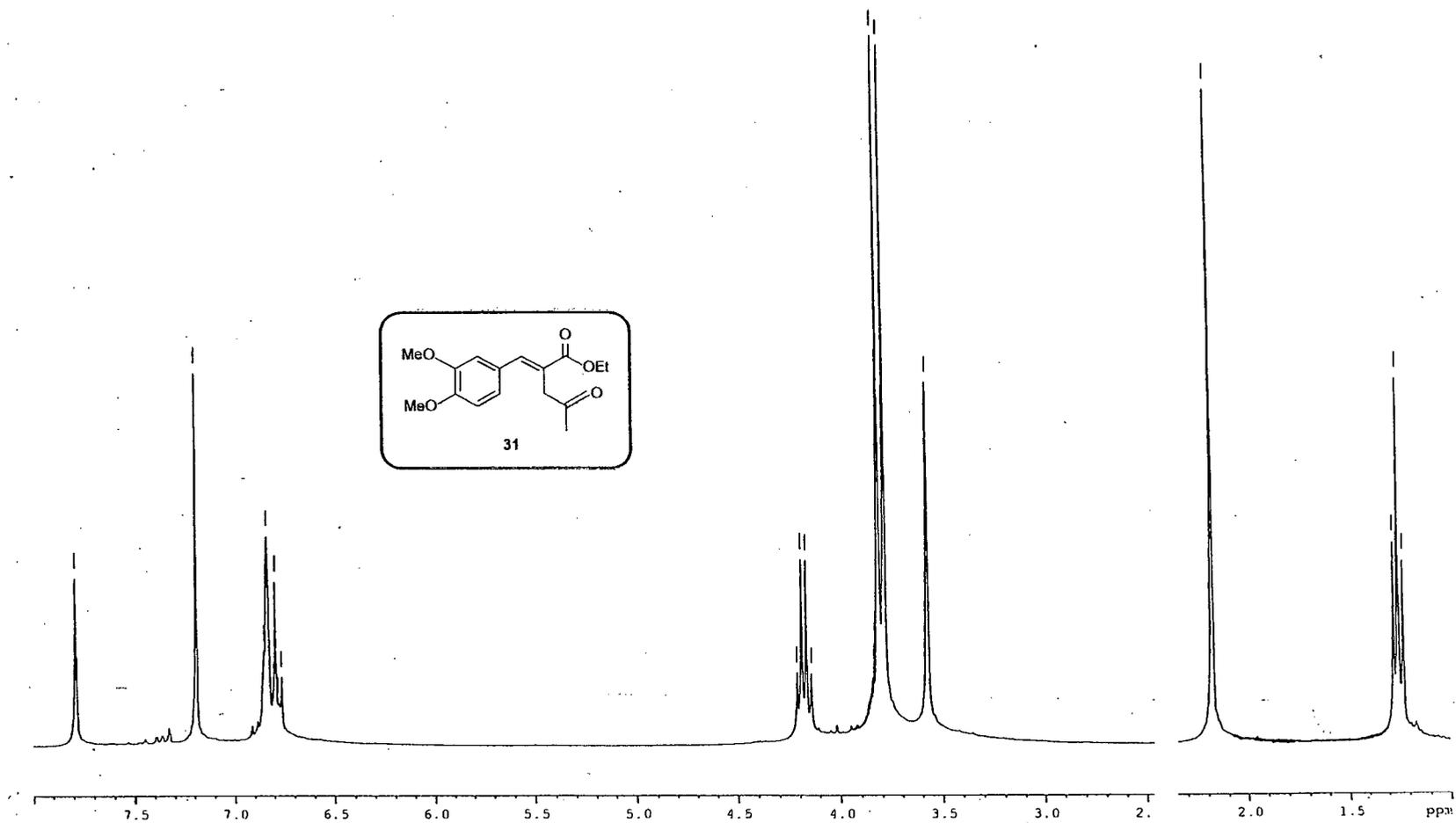


Fig. 2.8 : ¹H NMR spectrum of Ethyl-2-(3,4-dimethoxy-benzylidene)-4-oxopentanoate (31).

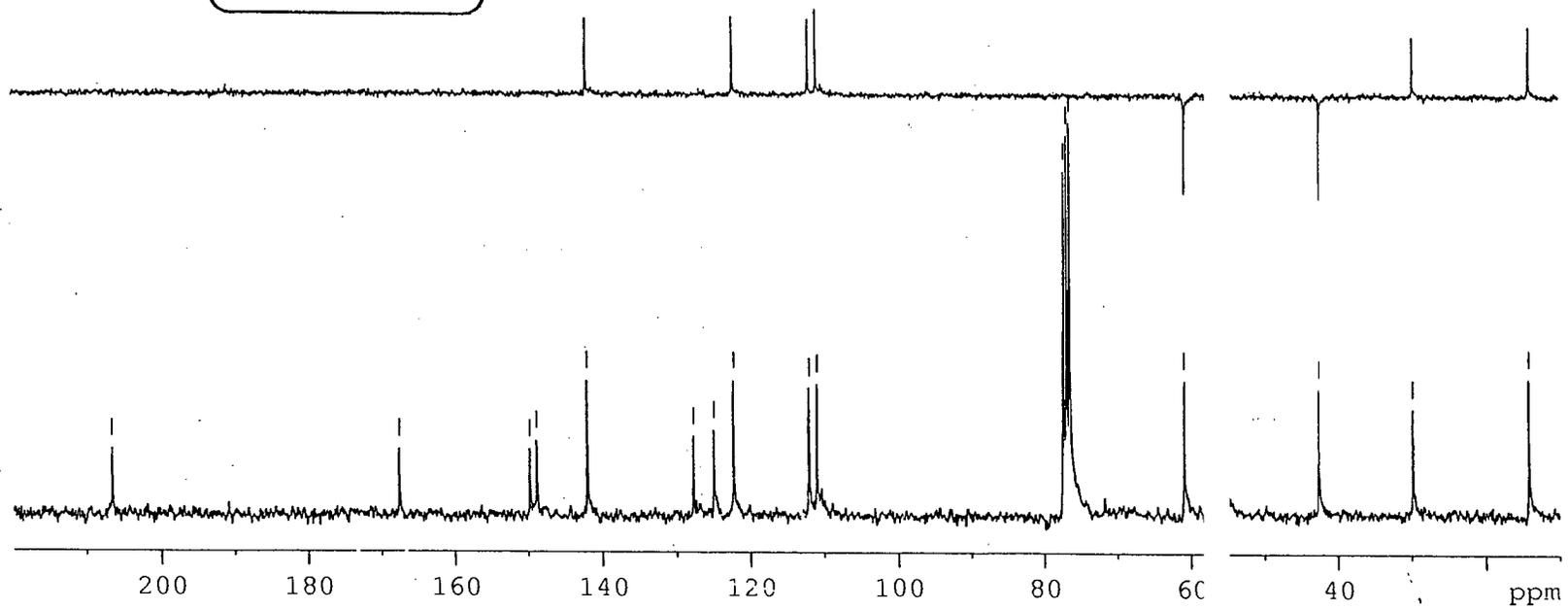
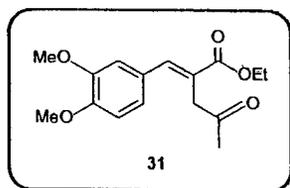
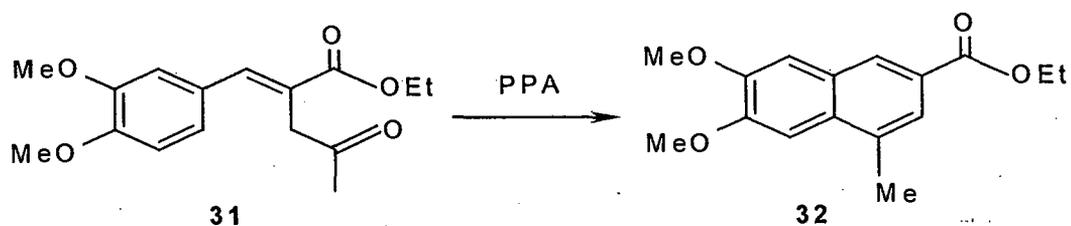


Fig. 2.9 : ^{13}C NMR & DEPT-135 spectrum of Ethyl-2-(3,4-dimethoxy-benzylidene)-4-oxopentanoate (**31**).



The mass spectrum (HRMS) (Fig. 2.10) of the compound exhibited a strong peak at m/z 297.1097, presumably due to $(M+Na)^+$ pseudo ion. The elemental composition of the compound was determined to be $C_{16}H_{18}O_4$.

HRMS: m/z calcd for $C_{16}H_{18}O_4$ ($M + Na^+$) : 297.1103; found: 297.1097.

IR(ν_{max}): 1716 cm^{-1}

$^1\text{H-NMR}$: (CDCl_3) spectrum (Fig. 2.11)

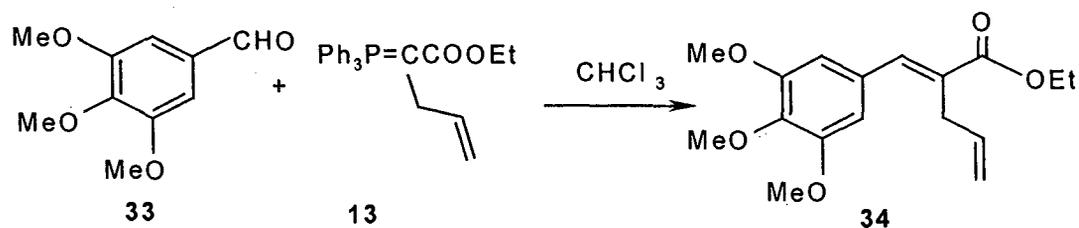
δ 1.43	t ($J = 7.2\text{ Hz}$)	3H	-OCH ₂ CH ₃
δ 2.66	s	3H	-CH ₃
δ 4.01	s	3H	-OCH ₃
δ 4.05	s	3H	-OCH ₃
δ 4.41	q ($J = 7.2\text{ Hz}$)	2H	-OCH ₂ CH ₃
δ 7.20	s	1H	ArH
δ 7.23	s	1H	ArH
δ 7.80	s	1H	ArH
δ 8.33	s	1H	ArH

¹³C NMR spectrum (Fig. 2.12)

δ 14.33 (OCH₂CH₃), 19.47 (CH₃), 55.79 (OCH₃), 60.70 (OCH₂CH₃), 102.73 (CH), 107.98 (CH), 124.42 (CH), 125.62 (C), 127.63 (CH), 128.33 (C), 130.82 (C), 132.78 (C), 149.49 (C), 151.00 (C), 167.05 (CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

When 3,4,5-trimethoxy benzaldehyde **33** was condensed with phosphorane **13** a viscous liquid product was obtained in 65% yield, after the chromatographic purification. Structure **34** was assigned to the compound based on mode of formation and by comparison of spectral properties with that of reported data^{37a}.



IR(ν_{max}): 1711, 1638, 1585 cm^{-1}

M-08

M-08 1 (0.040) AM (Cen,4, 80.00, Ar,5300.0,556.28,0.70,LS 10); Sm (SG, 2x4.00); Cm (1:43)

1: TOF MS ES+
1.53e4

Calcd Mass = 297.103 (M+Na)⁺

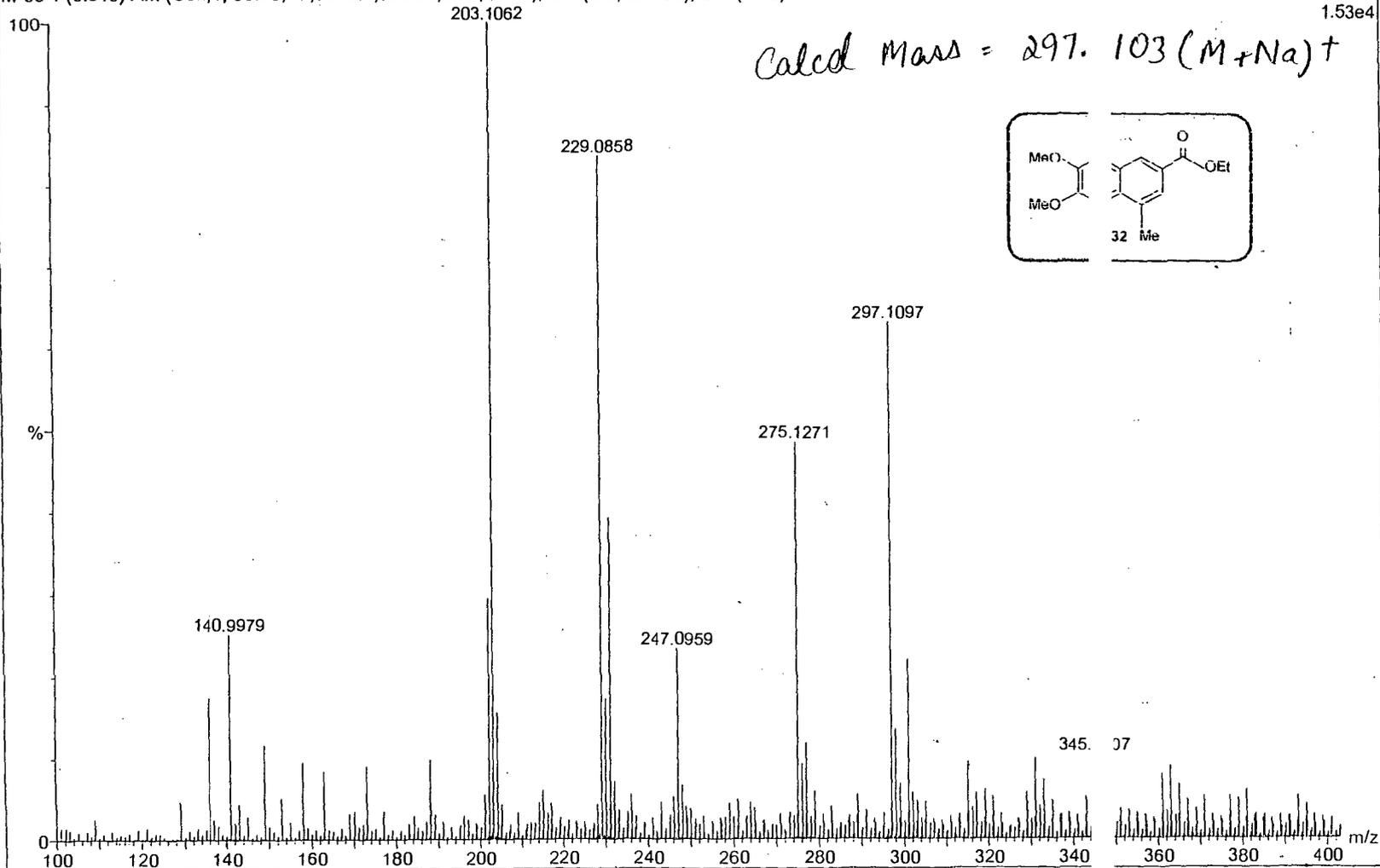
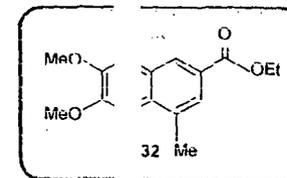


Fig. 2.10 : HRMS of Ethyl- 6,7-dimethoxy- 4-methyl-2-naphthoate (32).

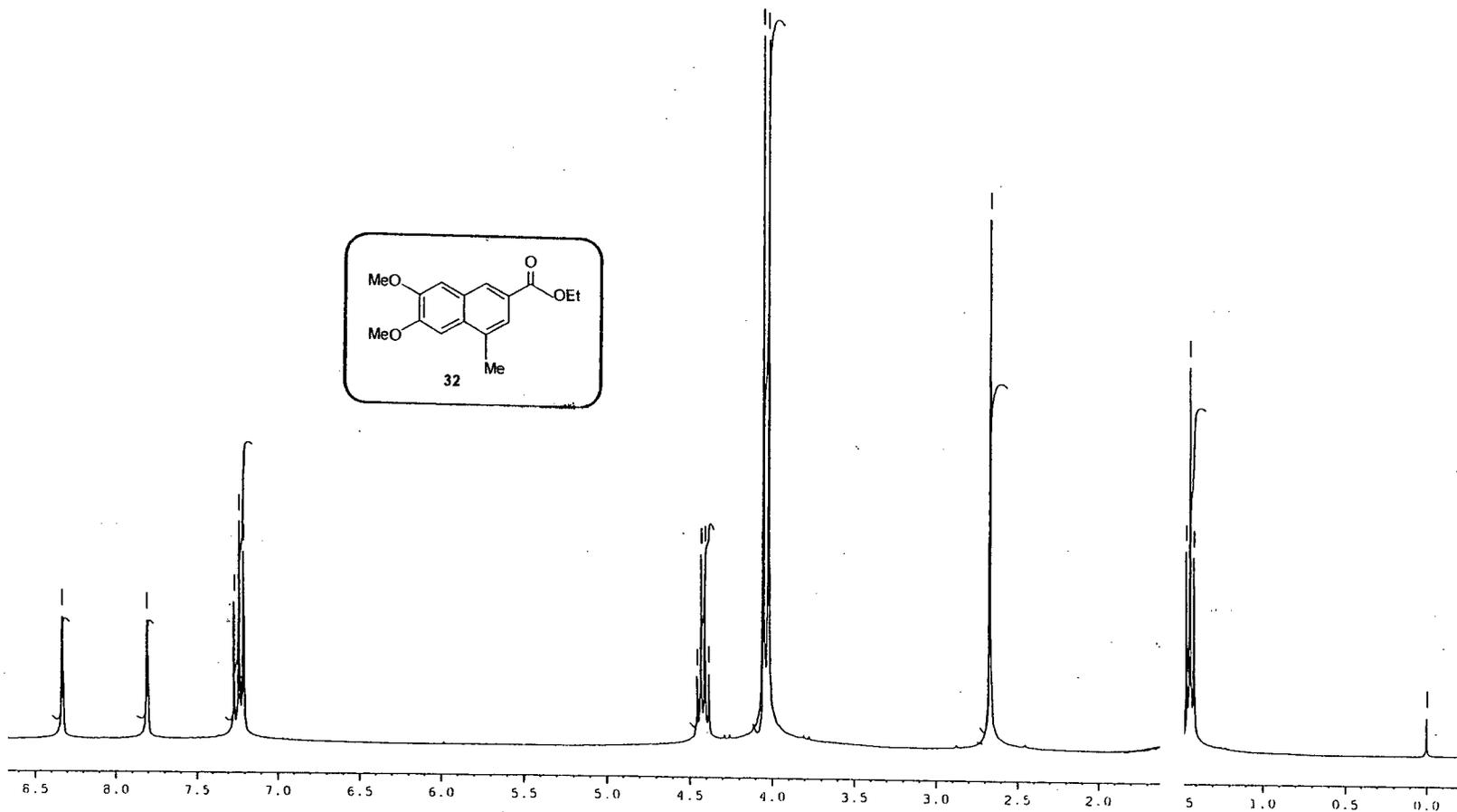


Fig. 2.11 : ¹H NMR spectrum of Ethyl-6,7-dimethoxy-4-methyl-2-naphthoate (32).

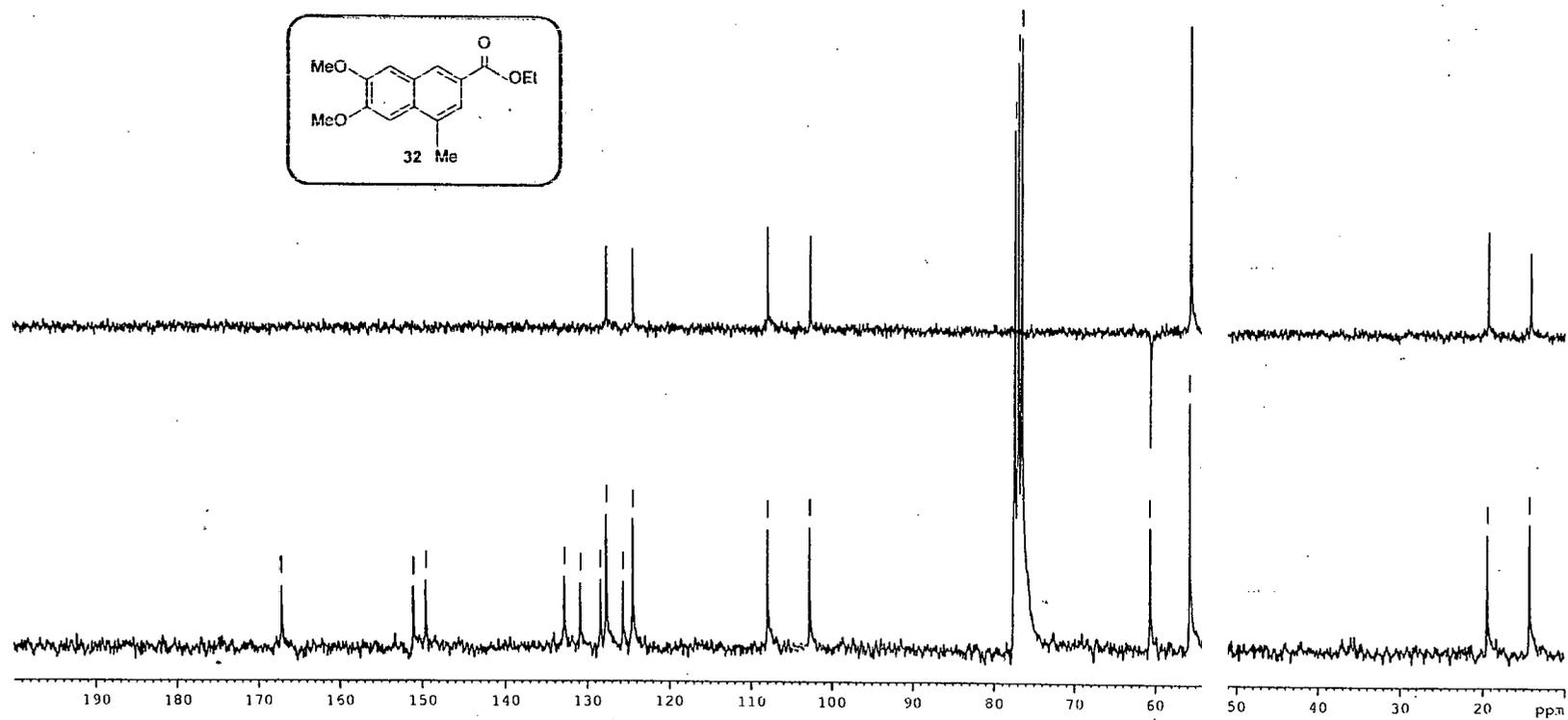
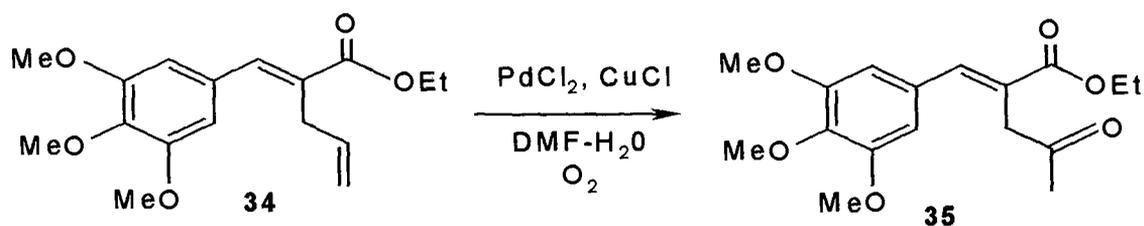


Fig. 2.12 : ^{13}C NMR of Ethyl-6,7-dimethoxy-4-methyl-2-naphthoate (32).

¹H-NMR: (CDCl₃)

δ 1.33	t (<i>J</i> = 7.2 Hz)	3H	-OCH ₂ CH ₃
δ 3.32	d (<i>J</i> = 5.1 Hz)	2H	-CH ₂ -CH=
δ 3.83	s	6H	(- OCH ₃) _{x2}
δ 3.86	s	3H	(- OCH ₃)
δ 4.26	q (<i>J</i> = 7.2 Hz)	2H	-OCH ₂ CH ₃
δ 5.15	m	2H	-CH=CH ₂
δ 6.02	m	1H	-CH=CH ₂
δ 6.66	s	2H	ArH
δ 7.74	s	1H	Ar-CH=C

The ester **34** was subjected to Wacker oxidation. A viscous liquid was obtained in 72% yield, after chromatographic purification. Based on the mode of formation and spectral properties mentioned below, structure **35** was assigned to the compound.

IR(ν_{max}): 1722, 1705 cm⁻¹

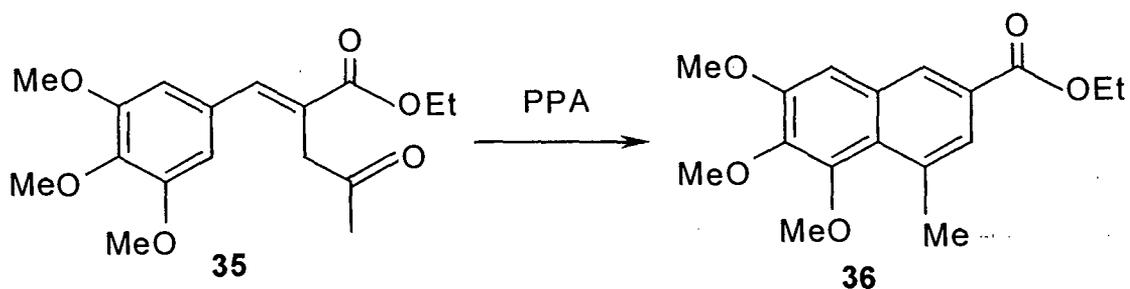
$^1\text{H-NMR}$: (CDCl_3)

δ 1.24	t ($J = 7.1$ Hz)	3H	$-\text{OCH}_2\text{CH}_3$
δ 2.17	s	3H	$-\text{COCH}_3$
δ 3.54	s	2H	$-\text{CH}_2\text{CO}-$
δ 3.73	s	6H	$(-\text{OCH}_3)\times 2$
δ 3.76	s	3H	$-\text{OCH}_3$
δ 4.16	q ($J = 7.1$ Hz)	2H	$-\text{OCH}_2\text{CH}_3$
δ 6.49	s	1H	ArH
δ 7.76	s	1H	Ar-CH=C

$^{13}\text{C-NMR}$: δ 14.12 (OCH_2CH_3), 29.78 (CH_3), 42.77 (CH_2), 56.03 (OCH_3), 60.76 (OCH_3), 61.10 (OCH_2CH_3), 106.09 (CH), 126.13 (C), 130.43 (C), 138.64 (C), 142.18 (CH), 153.10 (C), 167.29 (COOEt), 206.40 (CH_3CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

The final step was to procure naphthalene ester through benzannulation of the keto-ester **35**. This was accomplished by PPA cyclization.



A solid was obtained after chromatographic purification in 66% yield. The solid was recrystallized from ethyl acetate-hexanes, which melted at m.p. 140°C. Based on the mode of formation and spectral properties mentioned below, structure **36** was assigned to the compound.

IR(ν_{\max}): 1720 cm^{-1}

$^1\text{H-NMR}$: (CDCl_3)

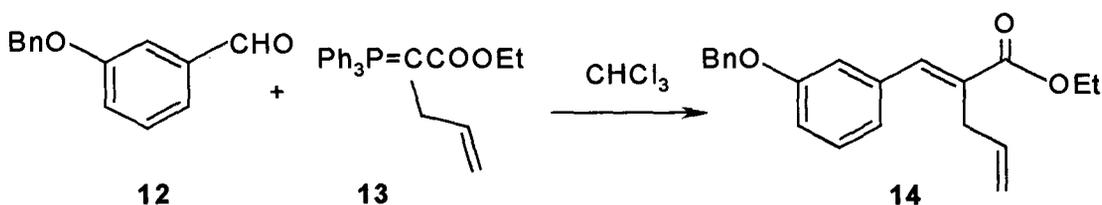
δ 1.43	t ($J = 7.2$ Hz)	3H	$-\text{OCH}_2\text{CH}_3$
δ 2.88	s	3H	$-\text{CH}_3$
δ 3.95	s	3H	$-\text{OCH}_3$
δ 3.98	s	6H	$(-\text{OCH}_3)\times 2$
δ 4.41	q ($J = 7.2$ Hz)	2H	$-\text{OCH}_2\text{CH}_3$
δ 7.06	s	1H	ArH
δ 7.68	s	1H	ArH
δ 8.27	s	1H	ArH

$^{13}\text{C-NMR}$: δ 14.29 (OCH_2CH_3), 23.34 (CH_3), 55.67 (OCH_3), 60.79 (OCH_3), 61.15 (OCH_2CH_3), 104.76 (CH), 125.91 (CH), 126.67 (C), 128.01 (CH), 131.13 (C), 134.27 (C), 143.94 (C), 150.46 (C), 152.66 (C), 166.74 (CO).

The multiplicities of carbon signals mentioned above were obtained from DEPT-135 experiments.

After successfully generalizing the synthesis of these 2-naphthoic acid esters our next target was to synthesize the precursor for the naphthalene segment of neocarzinostatin (**Scheme XVII**).

So, we condensed allyl phosphorane **13** with *m*-benzyloxybenzaldehyde **12** (obtained from *m*-hydroxybenzaldehyde) in chloroform. After about 3 hours, the tlc showed the disappearance of the starting compounds and the formation of two new spots. The lower spot was that of the triphenylphosphine oxide. The upper dark spot was separated from the crude mixture over silica gel column chromatography to give a sweet smelling viscous liquid in 95% yield.



The mass spectrum (HRMS) (**Fig. 2.13**) of the compound exhibited a strong peak at m/z 345.1473, presumably due to $(\text{M}+\text{Na})^+$ pseudo ion. The elemental composition of the compound was determined to be $\text{C}_{21}\text{H}_{22}\text{O}_3$.

HRMS: m/z calcd for $\text{C}_{21}\text{H}_{22}\text{O}_3$ ($\text{M} + \text{Na}^+$): 345.1467; found: 345.1473.

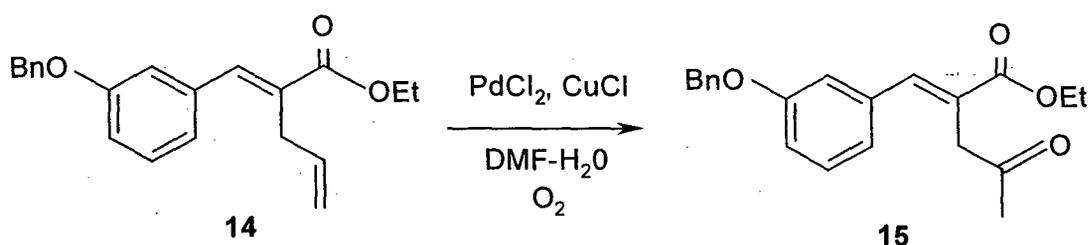
The IR spectrum exhibited a strong band at 1717 cm^{-1} which, could be due to the conjugated carbonyl of the ester group.

PMR spectrum (**Fig. 2.14**) of the compound showed signals at δ 1.30 (t, 3H, $J = 7.2\text{ Hz}$) and δ 4.23 (q, 2H, $J = 7.2\text{ Hz}$), could be attributed to $-\text{OCH}_2\text{CH}_3$ group. The signals exhibited at δ 3.23 (d, 2H, $J = 5.4\text{ Hz}$), δ 5.06 (m, 2H) and δ 5.87-6.00 (m, 1H), could be assigned to allyl group ($-\text{CH}_2\text{CH}=\text{CH}_2$). The signal

observed at δ 4.46 (s, 2H), could be assigned to benzylic group (PhCH₂O-). Peaks at δ 6.90-6.98 (m, 3H) and δ 7.21-7.40 (m, 6H), could be attributed to the aromatic protons of two phenyl rings. The downfield singlet at δ 7.73 integrated for one proton could be assigned to benzylic proton.

Based on above spectral data, structure **14** was assigned to the compound.

In the next step the ester **14** was subjected to the Wacker oxidation. The progress of the reaction was determined by tlc. The crude product obtained after usual work up was purified by column chromatography over silica gel, afforded a viscous liquid as product in 66% yield.



The mass spectrum (HRMS) (Fig. 2.15) of the compound exhibited a strong peak at m/z 361.1420, presumably due to (M+Na)⁺ pseudo ion. The elemental composition of the compound was determined to be C₂₁H₂₂O₄.

HRMS: m/z calcd for C₂₁H₂₂O₄ (M + Na⁺): 345.1467; found: 345.1473.

The IR spectrum exhibited two strong bands at 1722 and 1706 cm⁻¹ indicating the presence of conjugated carbonyl of the ester group and the carbonyl of the keto group respectively.

M-02

M-02 5 (0.114) AM (Gen,4, 80.00, Ar,5300.0,556.28,0.60,LS 10); Cm (1:16)

1: TOF MS ES+
1.97e4

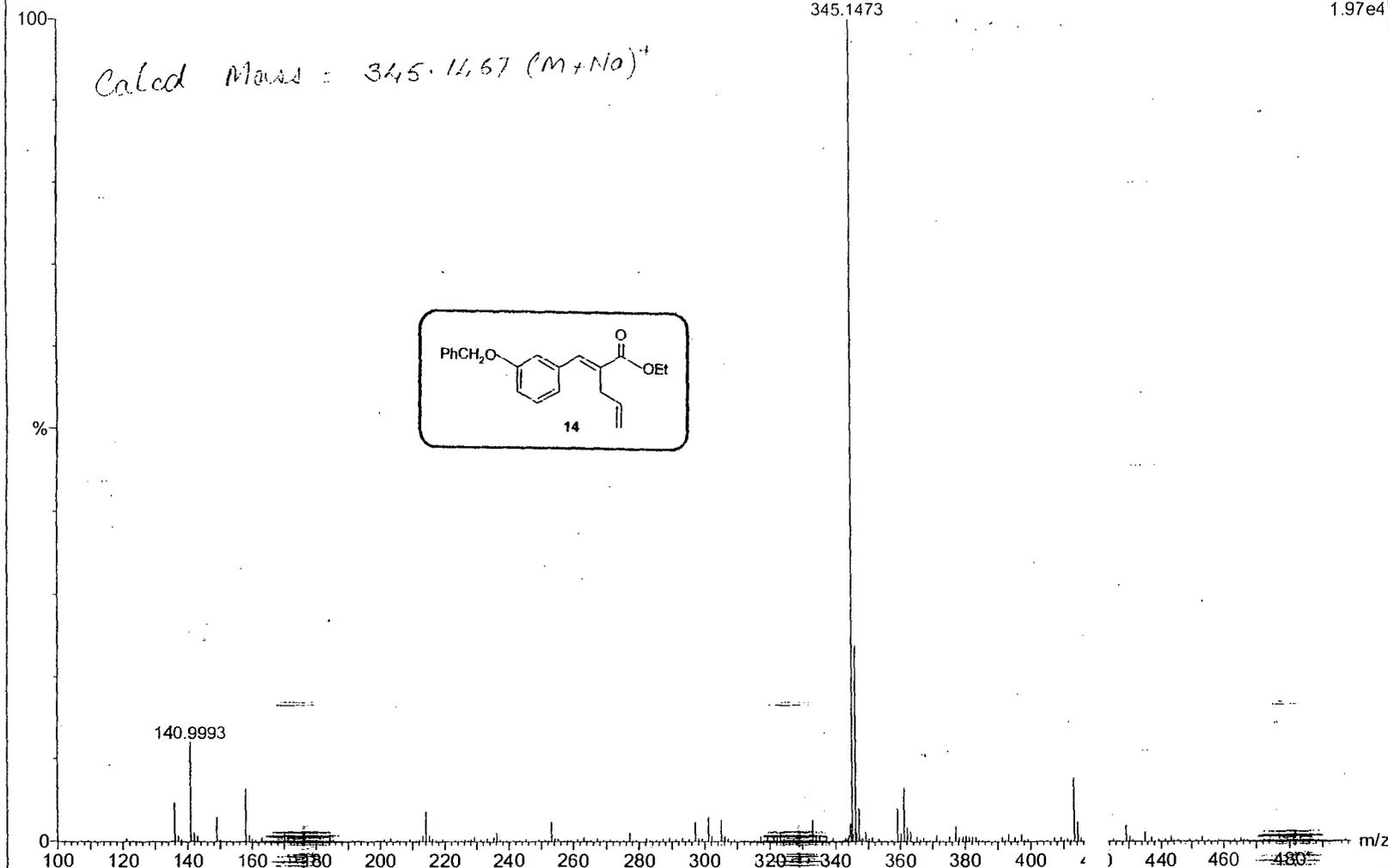


Fig. 2.13 : HRMS of Ethyl (E)-2-(m-benzyloxy-benzylidene)pent-4-enoate (14).

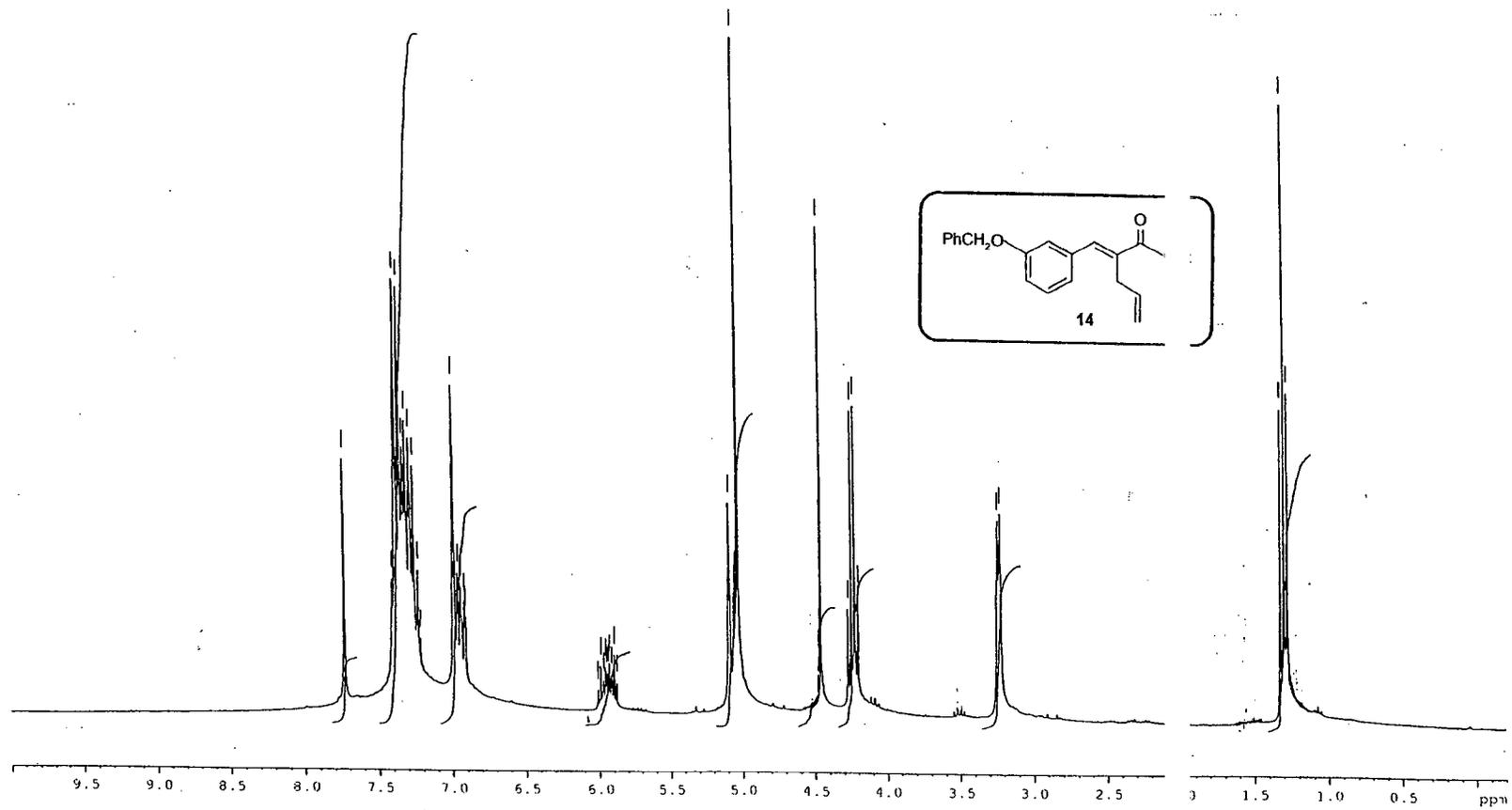


Fig. 2.14 : ^1H NMR spectrum of Ethyl (E)-2-(m-benzoxy-benzylidene)pentenoate (14).

M-06

M-06 97 (2.293) AM (Cen,4, 80.00, Ar,0.0,556.28,0.00,LS 5); Cm (49:108)

1: TOF MS ES+
8.36e4

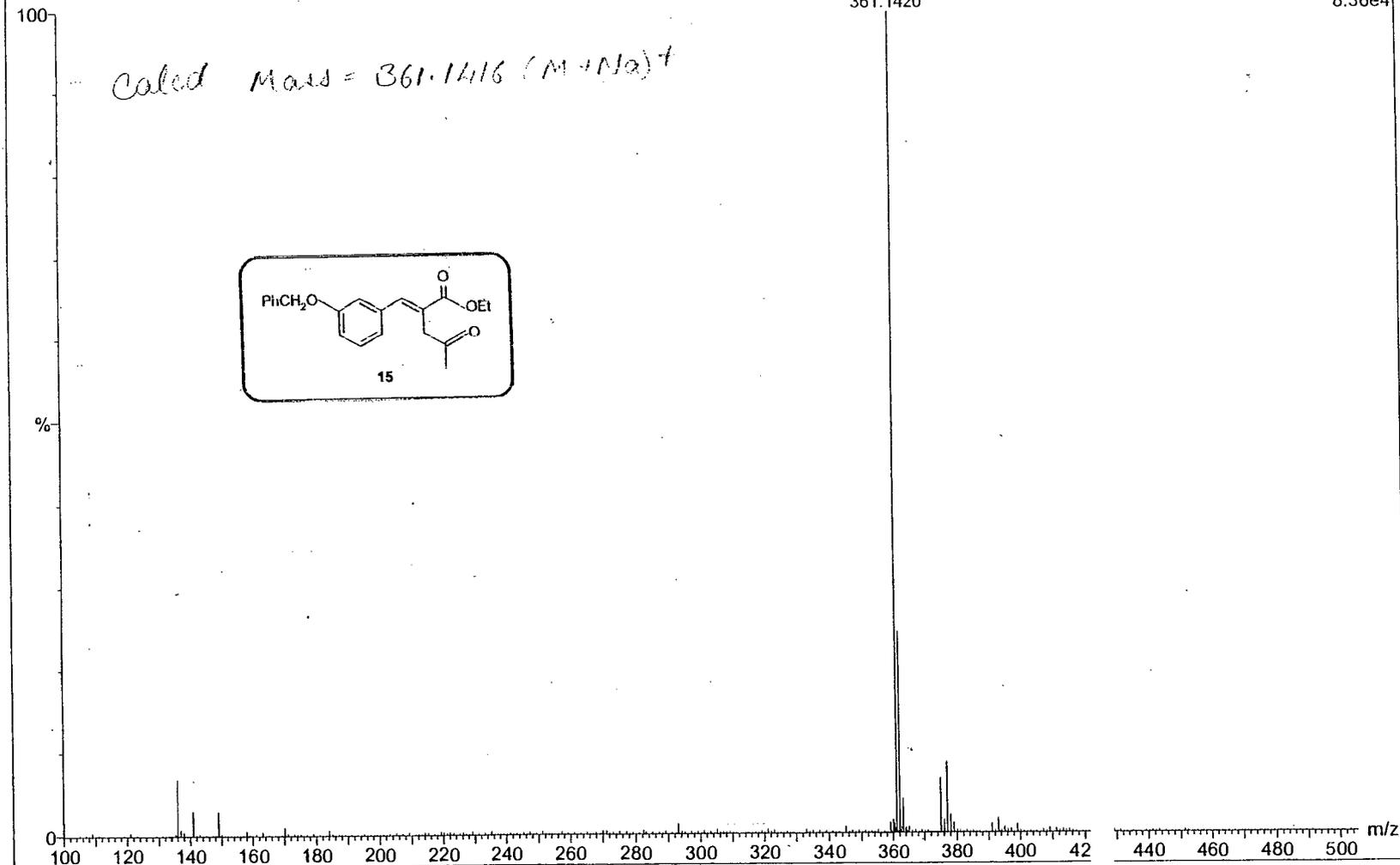
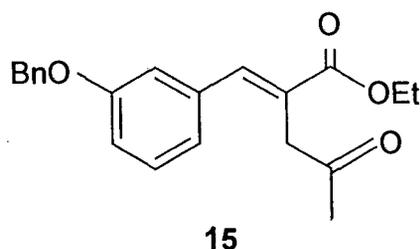


Fig. 2.15 : HRMS of Ethyl-2-(m-benzoxy-benzylidene)-4-oxo-pentanoate (15).

PMR spectrum (Fig. 2.16) of the compound showed signals at δ 1.30 (t, 3H, $J = 6.9$ Hz) and δ 4.21 (q, 2H, $J = 6.9$ Hz), could be attributed to $-\text{OCH}_2\text{CH}_3$ group. The signals exhibited at δ 2.17 (s, 3H) and δ 3.53 (s, 2H), could be attributed to the methyl of $-\text{COCH}_3$ group and the methylene of $-\text{CH}_2\text{COCH}_3$ group. The signal observed at δ 5.02 (s, 2H) could be assigned to benzylic group ($\text{PhCH}_2\text{-O-}$). The signals at δ 6.83-6.93 (m, 3H) and at δ 7.32-7.18 (m, 6H), could be attributed to aromatic protons of the two phenyl rings. The singlet at δ 7.84 integrated for one proton could be assigned to the benzylic proton.

On the basis of mode of formation and spectral data, structure **15** was assigned for this compound



In the next step, we added keto ester **15** to the mixture of P_2O_5 and 88% H_3PO_4 (1:3) and the reaction mixture was kept stirring at 70°C for 10 min. After quenching the reaction mixture with excess of water, it was extracted with ethyl acetate. The crude product obtained after concentrating the solvent was purified over silica gel column chromatography. A white solid product was obtained. Recrystallization from ethyl acetate-hexanes afforded ester **16** (70%, m.p. 181°C).

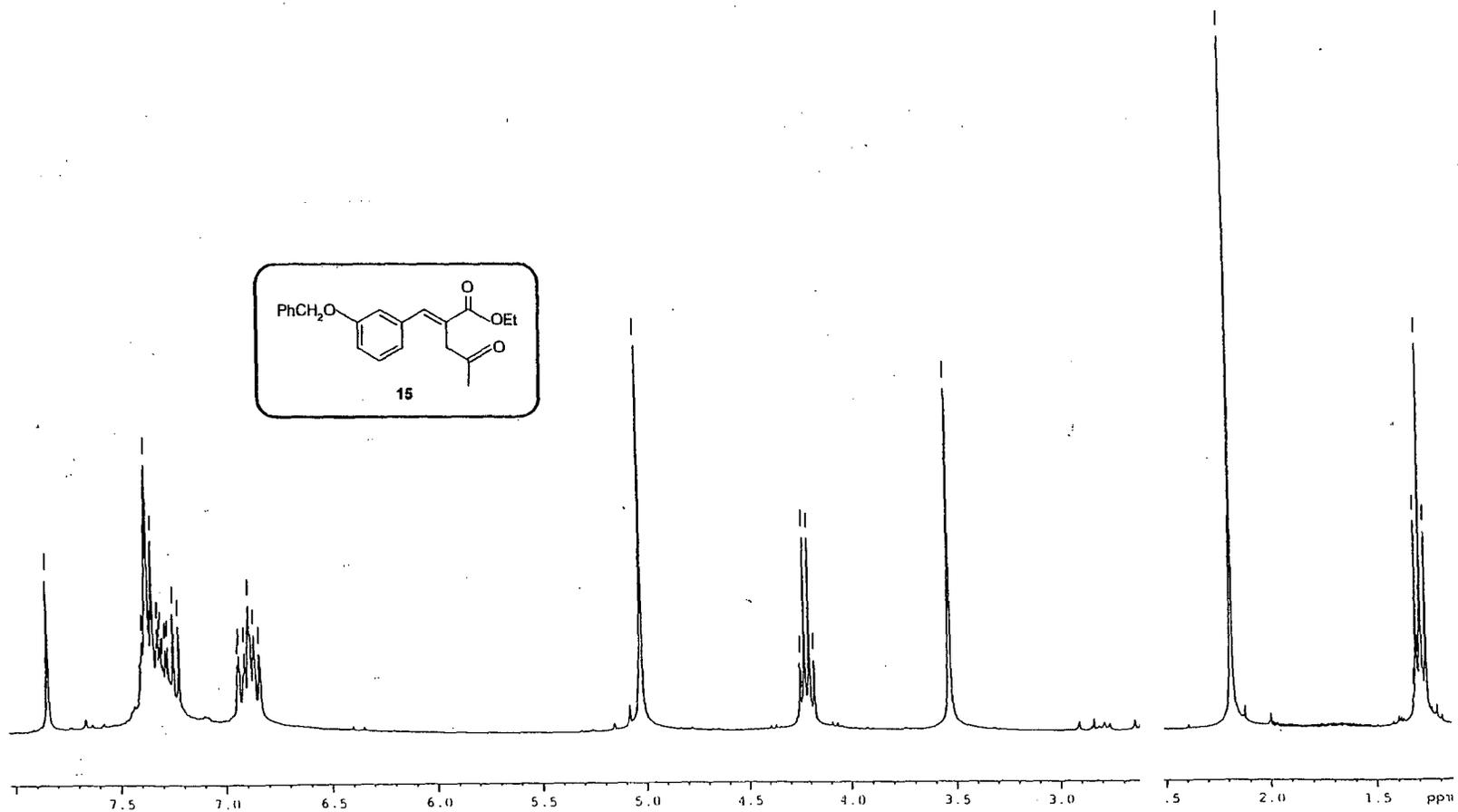
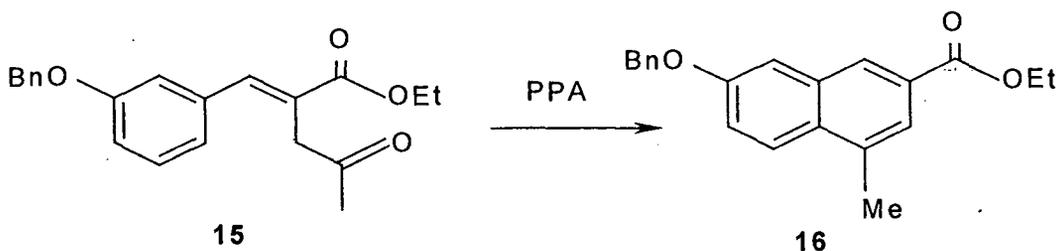


Fig. 2.16: ¹H NMR spectrum of Ethyl-2-(m-benzyloxy-benzylidene)-4-oxo-pentanoate (15).



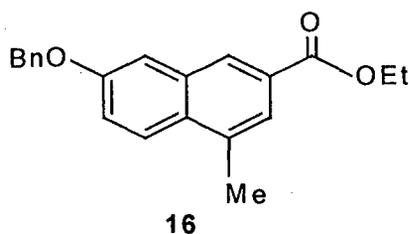
The mass spectrum (HRMS) (Fig. 2.17) of the compound exhibited a strong peak at m/z 343.1283, presumably due to the $(M+Na)^+$ pseudo ion. The elemental composition of the compound was determined to be $C_{21}H_{20}O_3$.

HRMS: m/z calcd for $C_{21}H_{20}O_3$ ($M + Na^+$): 343.1310; found: 343.1283.

Its IR spectrum showed a strong band at 1720 cm^{-1} , which could be attributed to the carbonyl of the aromatic ester.

PMR ($CDCl_3$) spectrum (Fig. 2.18) showed signals at δ 1.33 (t, 3H, $J = 6.9$ Hz) and δ 4.31 (q, 2H, $J = 6.9$ Hz), which could be assigned to the $-OCH_2CH_3$ group of the aromatic ester. The signals observed at δ 2.63 (s, 3H) and δ 4.43 (s, 2H), could be due to benzylic CH_3 and the methylene of benzylic group (Ph- CH_2 -O-). The peaks at δ 7.08-7.19 (m, 7H), δ 7.69 (s, 1H), δ 8.57 (s, 1H) and δ 7.83 (d, 1H, $J = 9.0$ Hz), could be assigned to the aromatic protons.

On the basis of mode of formation and spectral data suggested structure **16** for this compound



M-10

M-10 51' (1.204) AM (Cen,4, 80.00, Ar,5300.0,556.28,0.40,LS 10); Sm (SG, 2x8.00); Cm (47:84)

1: TOF MS ES+
2.41e4

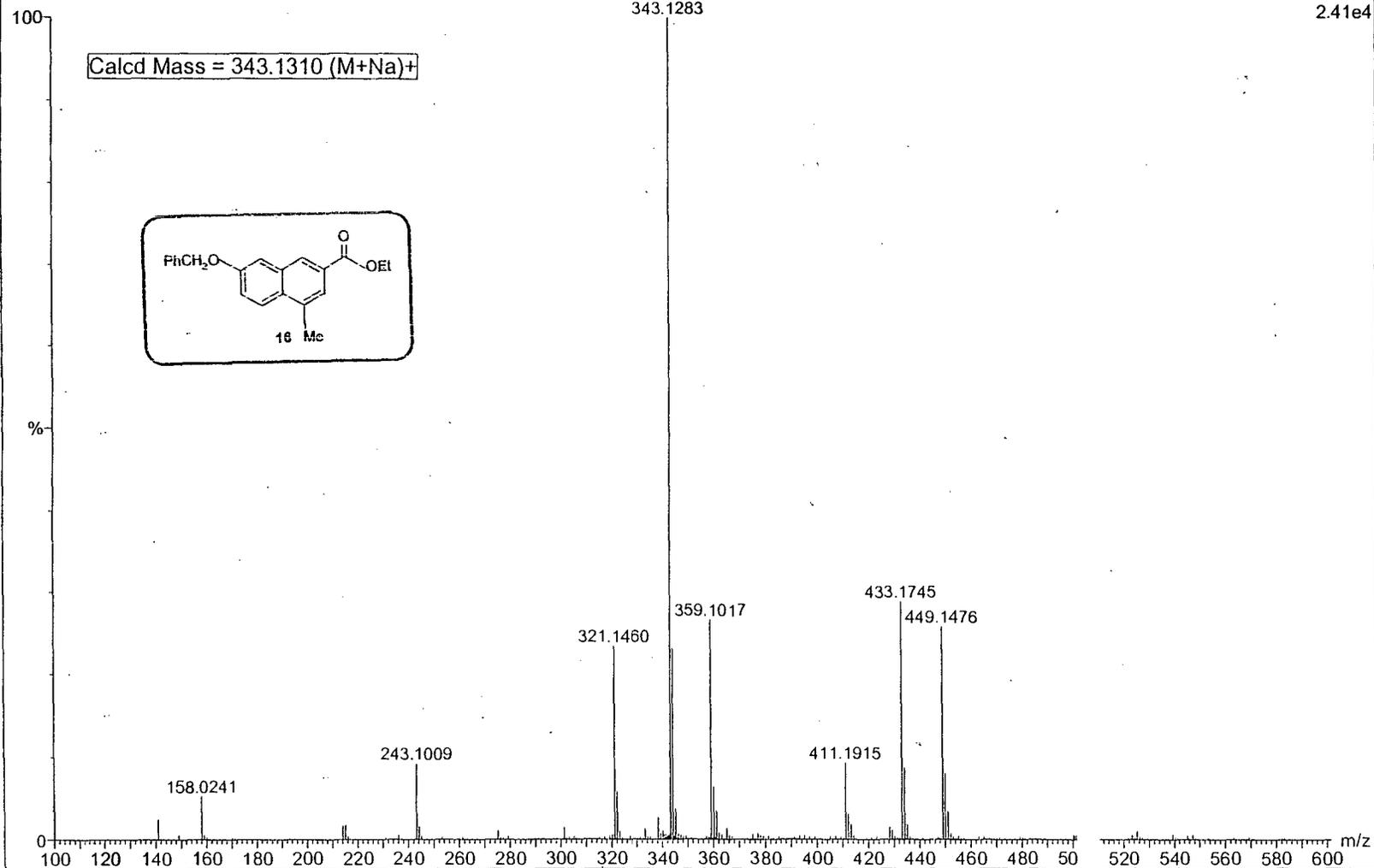


Fig. 2.17 : HRMS of Ethyl-7-benzyloxy-4-methyl-2-naphthoate (16).

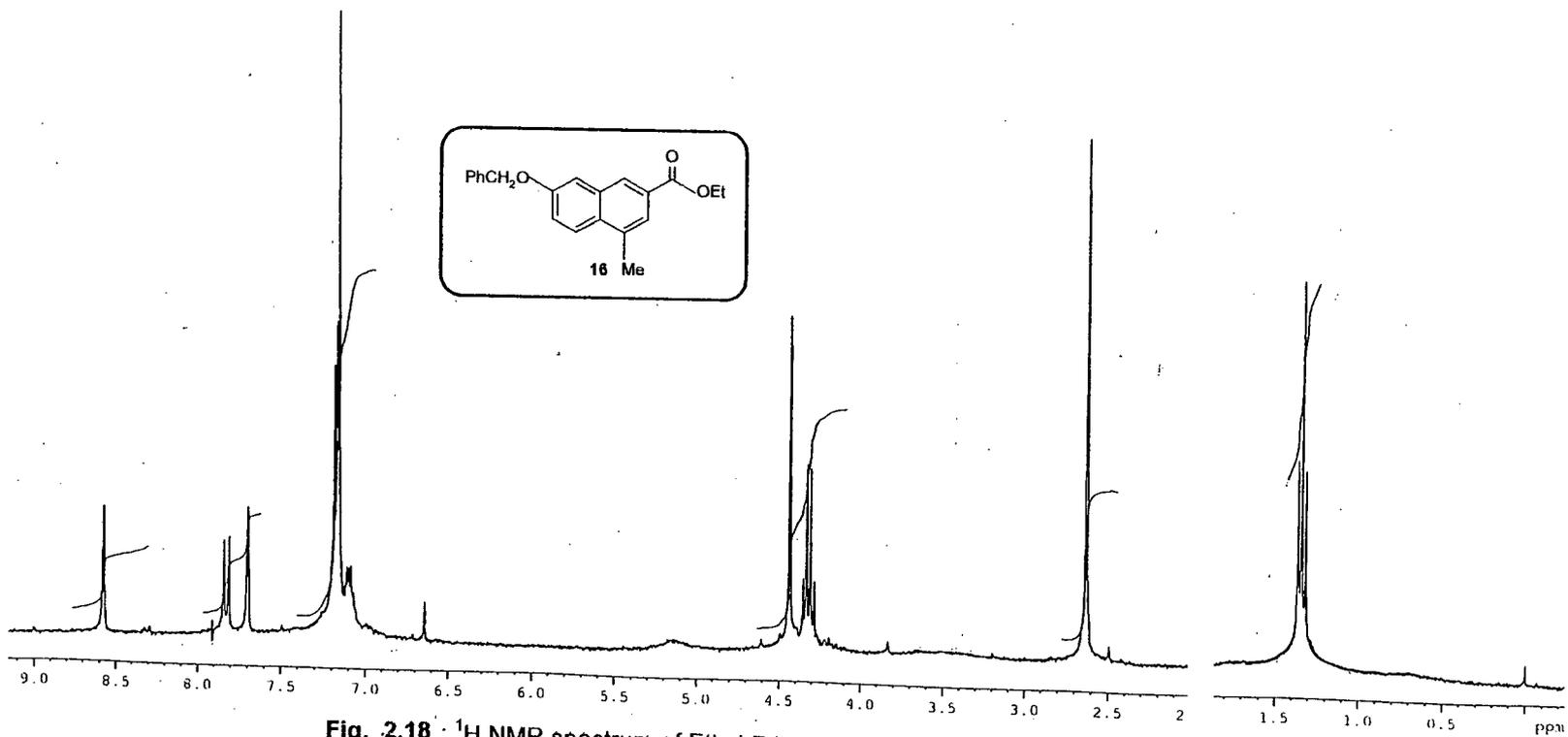
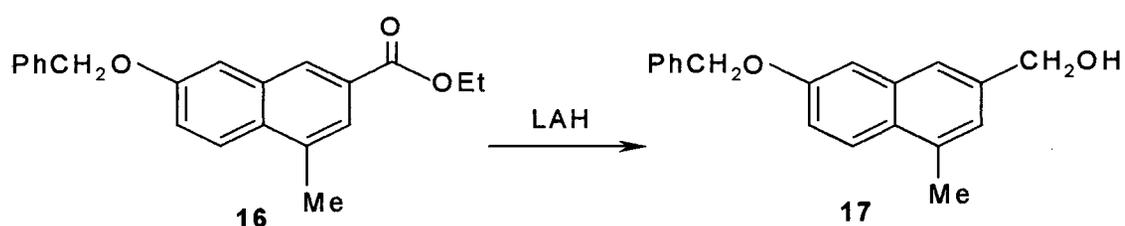


Fig. 2.18 : ¹H NMR spectrum of Ethyl-7-benzyloxy- 4-methyl-2-naphthoate (16)

After successfully achieving the synthesis of this 2-naphthoic acid ester, all we needed to do was functional group transformation as depicted in the **scheme XVII**.

Thus, we converted naphthalene ester **16** to naphthalene alcohol **17** compound. This transformation was accomplished by reducing ester group to alcohol using Lithium aluminium hydride (LAH) in anhydrous diethyl ether. After usual work up and purification of the crude product over silica gel column chromatography yielded a solid product. Recrystallization from ethyl acetate-hexanes afforded alcohol **17** (92%, m.p. 163°C).

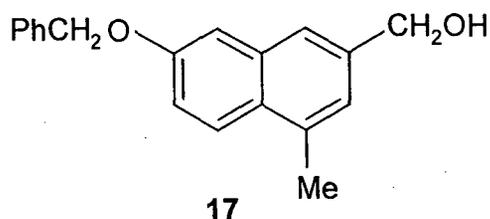


IR(ν_{\max}): 3550, 1600, 1450, 1050 cm^{-1}

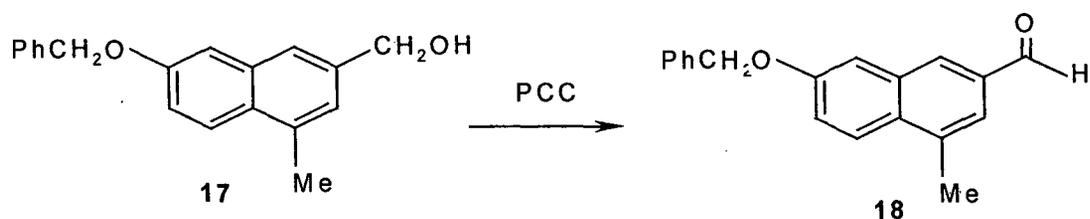
Its IR spectrum revealed a broad band at 3550 cm^{-1} indicating the presence of -OH group.

PMR spectrum of the compound exhibited signals at δ 2.68 (s, 3H) and δ 4.92 (s, 2H), which could be due to the CH_3 group of the aromatic ring and the methylene of the benzylic group ($\text{Ph-CH}_2\text{-O-}$) respectively. It also showed a small broad peak at δ 4.46 (br.s, 1H), which could be assigned to the alcoholic proton OH. The signal observed at δ 4.75 (d, 2H, $J = 5.7$ Hz), could be due to the benzylic group attached to the OH group. The peaks at δ 7.12-7.25 (m, 6H), δ 7.76 (s, 2H), δ 7.97 (s, 1H) and δ 7.87 (d, 1H, $J = 8.7$ Hz), could be assigned to the aromatic protons.

On the basis of mode of formation and spectral data, structure **17** was suggested for this compound



After successfully characterizing the structure for naphthyl alcohol **17**, the oxidation of this primary alcohol was carried out. Pyridinium chlorochromate (PCC) was well known reagent for preparing aldehyde from a primary alcohol without giving any complications.

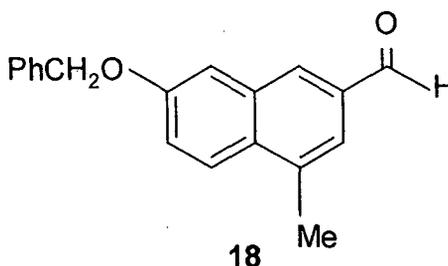


Thus, we added our alcohol to the mixture of slight excess of one equivalent of PCC in dry dichloromethane at room temperature and kept stirring for one hour. After confirming on tlc, the disappearance of the starting compound as well as appearance of the new spot above starting, the reaction mixture was filtered on a celite pad. The crude product obtained after concentration was column chromatographed on silica gel to give a white solid compound. Recrystallization from benzene-hexanes afforded aldehyde **18** (70%, m.p. 142°C).

IR spectrum of the compound showed a strong band at 1695 cm^{-1} , which was assigned, to carbonyl group of aldehyde attached to the ring.

$^1\text{H-NMR}$ spectrum (Fig. 2.19) of the compound displayed signals at δ 2.74 (s, 3H) and δ 4.55 (s, 2H), could be attributed to the benzylic methyl group and the benzylic methylene group ($\text{Ph-CH}_2\text{-O-}$) respectively. Peaks seen at δ 7.20-7.33 (m, 7H), δ 7.67 (s, 1H), δ 8.31 (s, 1H) and δ 7.95 (d, 1H, $J = 9.0\text{ Hz}$), could be assigned to the aromatic protons. The downfield singlet at δ 10.04 for 1 proton could be due to aldehyde proton.

Based on the mode of formation and spectral properties, the structure **18** was assigned to the compound.



Having achieved success in synthesis of naphthaldehyde **18**, our next step was to obtain a naphthol **19**. It was supposed that Baeyer-Villiger oxidation on this aldehyde would furnish us the required phenolic group. Thus, we stirred aldehyde **18** with 1.1 eq. of mcpba in chloroform at room temperature for 10 hours followed by tlc for disappearance of starting spot. The reaction mixture was washed saturated solution of sodium bicarbonate followed by water. The

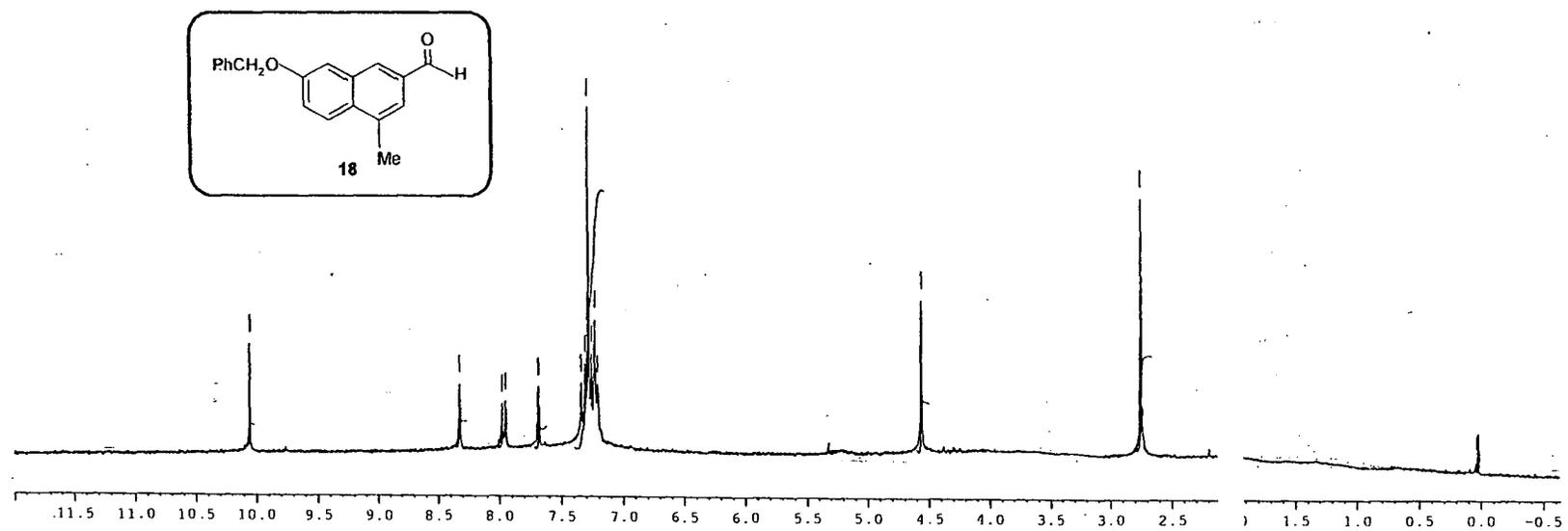


Fig. 2.19: ¹H NMR spectrum of 7-benzyloxy-4-methyl-2-naphthylaldehyde (18)

chloroform layer was concentrated on water bath. But, to our disappointment, there was nothing tangible in the flask. We assumed that the *m*-benzyloxynaphthoic acid must have been formed in the process, which was gone into the bicarbonate washings, along with *m*-chlorobenzoic acid, while doing the work up of the reaction.

To avoid such benzoic acid formation, we adopted a procedure³⁹ where it is claimed that even benzaldehyde which normally gets oxidized with peracids gives Baeyer-Villiger product, i.e. phenol. Thus, We mixed aldehyde **18** in the stirring mixture of H₂O₂ and boric acid at room temperature. The tlc indicated the disappearance of the starting aldehyde spot. The crude product recovered after usual work up was column chromatographed over silica gel. Recrystallization from water afforded a white solid. (88%, m.p. 125°C).

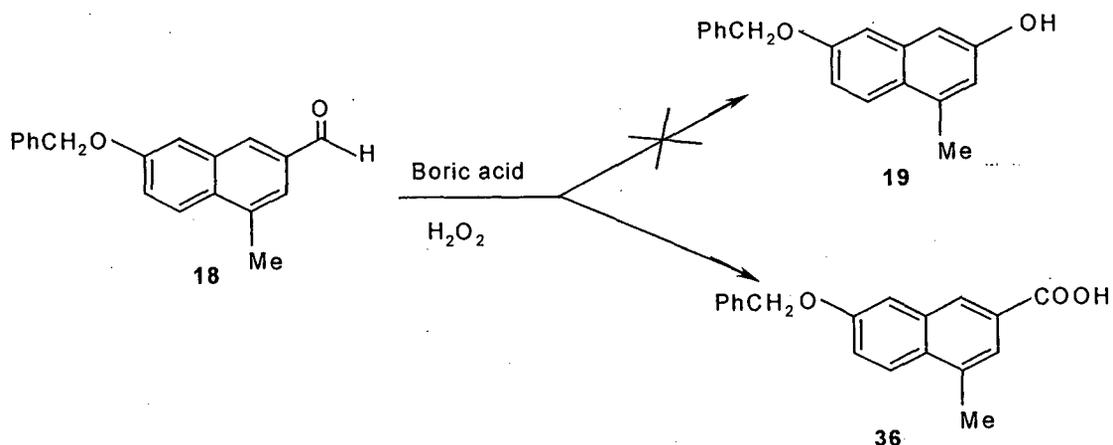
IR spectrum showed a broad band at 3300 cm⁻¹ which could be due to the OH group and it also showed a band in carbonyl region at 1698 cm⁻¹, this could be assigned to the carbonyl group attached to the conjugated system or aromatic ring.

¹H-NMR (CDCl₃) spectrum of the compound displayed signals at δ 2.55 (s, 3H) and δ 5.01 (s, 2H), could be attributed to the benzylic methyl group and the benzylic methylene group (Ph-CH₂-O-) respectively. Peaks seen at δ 7.25-7.34 (m, 6H, δ 7.51 (d, 1H, *J* = 9.0 Hz), δ 7.68 (s, 1H), δ 7.93 (d, 1H, *J* = 9.0 Hz) and δ 8.21 (s, 1H), could be assigned to the aromatic protons. The broad singlet observed at δ 5.56 (s, 1H) could be due to acidic proton.

$^{13}\text{C-NMR}$ (CDCl_3), δ : 19.32 (CH_3), 69.70 (CH_2), 109.55 (CH), 120.21 (CH), 124.84 (CH), 126.04 (CH), 127.49 (CH), 128.19 (CH), 128.85 (CH), 129.31 (C), 132.46 (C), 133.97 (C), 134.24 (C), 156.52 (C), 169.12 (CO)

The multiplicities were obtained from DEPT-135 experiments.

Above, spectral data revealed that the compound could be a naphthoic acid **36** instead of a naphthol **19**.



Thus, in our hands aldehyde **18** could not give us the expected Baeyer-Villiger product, but it got oxidised to corresponding acid.

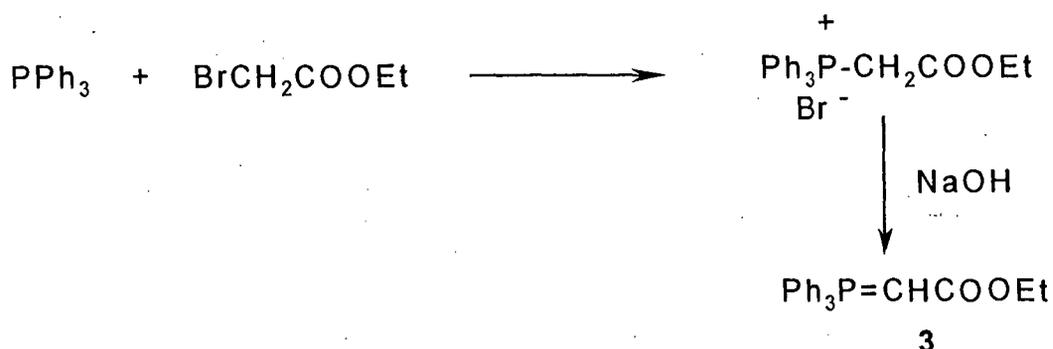
Our attempt of transformation of the ester group of **16** to amino group did not yield due to solubility problems of the intermediate.

2.6 Conclusion

- An attempt has been made to synthesize naphthoic moiety of a highly potent neocarzinostatin, employing Wasserman chemistry, i.e. by synthesizing and using vicinal tricarbonyl compound, to get naphthalene skeleton.
- A convenient and efficient three-step general method towards the synthesis of 2-substituted-4-methyl naphthalene esters has been achieved. Using this method five differently substituted naphthalene esters have been synthesized.
- By using this approach many compounds having naphthalene skeleton could be made available in large quantities and could be used for testing the biological activities.
- An attempt has been made, to extend the above approach to obtain naphthoic moiety of neocarzinostatin by mere functional group transformations.

2.6 Experimental

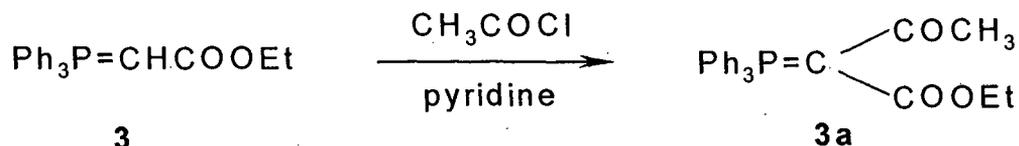
Expt. 2.6.1 : Preparation of triphenyl- α -ethoxycarbonyl methylene-phosphorane (3).



To the solution of triphenylphosphine (15.7 g, 60 mmol) in dry benzene (30 mL) was added a solution of ethyl bromoacetate (11.7 g, 60 mmol) in dry benzene (10 mL) at room temperature, which resulted in an elevation of temperature to about 70°C and the precipitation of salt. After allowing the mixture to cool to room temperature, it was vigorously shaken and left overnight. The separated solid was filtered. Washed with dry benzene and dried.

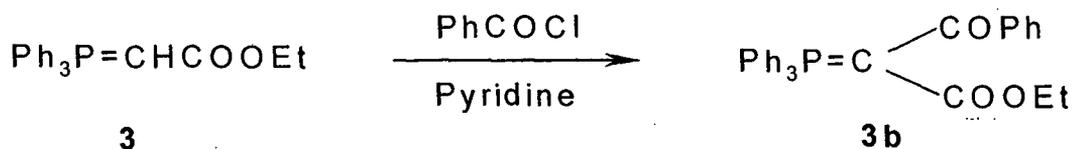
The stirred solution of the above salt in water (150 mL) and benzene (100 mL) was neutralized by 2N sodium hydroxide to a phenolphthalein end point. The benzene layer was separated, dried over anhy. sodium sulphate and concentrated to about 1/3rd volume. Addition of n-hexanes (40-60°C) resulted in the separation of the crystalline product, which was filtered and dried and recrystallized in EtOA-hexanes, to afford triphenylethoxycarbonylmethylene phosphorane 3 (14.6 g, 70%, m.p. 125-126°C), (lit.²² m.p. 125-127°C).

Expt. 2.6.2 : Preparation of Ethyl 3-oxo-2-(triphenylphosphoranylidene)-butanoate⁴⁰ (3a).



To the stirring mixture of phosphorane **3** (0.5 g, 1.4 mmol) in dry benzene (5 mL) and dry pyridine (0.5 mL, 1.4 mmol) was added dropwise, acetyl chloride (0.12g, 0.1 mL, 1.4 mmol) in dry benzene (5 mL) for 10 min. The reaction mixture was then refluxed for 1 hour. Water was added to the reaction mixture and the organic layer was dried over anhydrous sodium sulphate and concentrated to give a white solid, which on recrystallization from benzene afforded **3a** (0.426 g, 76%, m.p. 113°C); IR (ν_{max}): (KBr); 1655, 1555 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.57 (t, $J = 7.5$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 2.39 (s, 3H), 3.66 (q, $J = 7.5$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 7.35-7.60 (m, 15H).

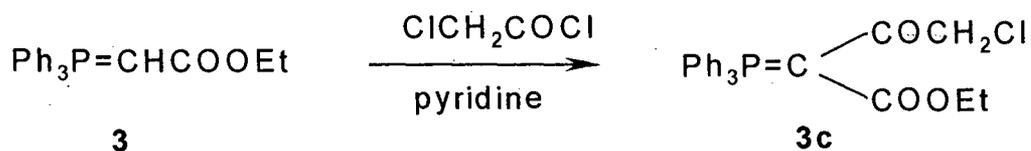
Expt. 2.6.3 : Preparation of Ethyl 3-phenyl-3-oxo-2-(triphenylphosphoranylidene)propionate⁴⁰ (3b).



To the stirring mixture of phosphorane **3** (0.5 g, 1.4 mmol) in dry benzene (5 mL) and dry pyridine (0.5 mL, 1.4 mmol) was added dropwise, benzoyl chloride (0.21 g, 0.17 mL, 1.4 mmol) in dry benzene (5 mL) for 10 min. The reaction mixture was then refluxed for 1 hour. Water was added to the reaction mixture and the organic layer was dried over anhy. sodium sulphate and concentrated to get solid, which on recrystallization from benzene afforded **3b** (0.605 g, 93%, m.p. 124°C); IR (ν_{\max}): (KBr); 1710, 1675 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.56 (t, $J = 7.5$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 3.72 (q, $J = 7.5$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 7.33-7.35 (m, 4H), 7.45-7.53 (m, 8H), 7.69-7.80 (m, 8H).

Expt. 2.6.4 : Preparation of Ethyl 4-chloro-3-oxo-2-

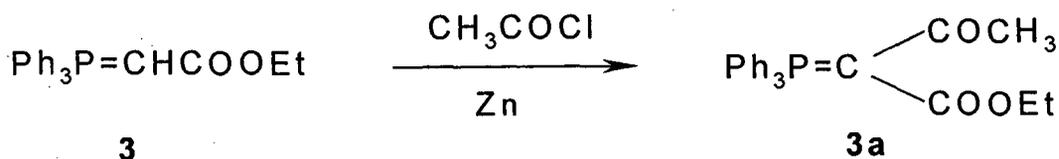
-(triphenylphosphoranylidene)butanoate (3c).



To the stirring mixture of phosphorane **3** (0.5 g, 1.4 mmol) in dry benzene (5 mL) and dry pyridine (0.5 mL, 1.4 mmol) was added dropwise, chloroacetyl chloride (0.16 g, 0.1 mL, 1.4 mmol) in dry benzene (5 mL) for 10 min. The reaction mixture was then refluxed for 1 hour. Water was added to the reaction mixture and the organic layer was dried over anhy. sodium sulphate and concentrated to give a white solid, which on recrystallization from benzene afforded **3a** (0.48 g, 79%, m.p. 128°C); IR (ν_{\max}): (KBr); 1660, 1575 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.56 (t, $J = 7.5$ Hz, 3H, $-\text{OCH}_2\text{CH}_3$), 3.72 (q, $J = 7.5$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 7.33-7.35 (m, 4H), 7.45-7.53 (m, 8H), 7.69-7.80 (m, 8H).

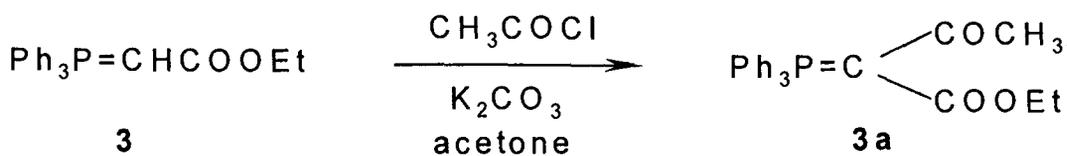
NMR (CDCl₃) : δ 0.65 (t, $J = 7.5$ Hz, 3H, -OCH₂CH₃), 3.73 (q, $J = 7.5$ Hz, 2H, -OCH₂CH₃), 4.78 (s, 2H, -CH₂Cl), 7.43-7.69 (m, 15H).

Expt. 2.6.5 : Preparation of Ethyl 3-oxo-2-(triphenylphosphoranylidene)-butanoate (3a).



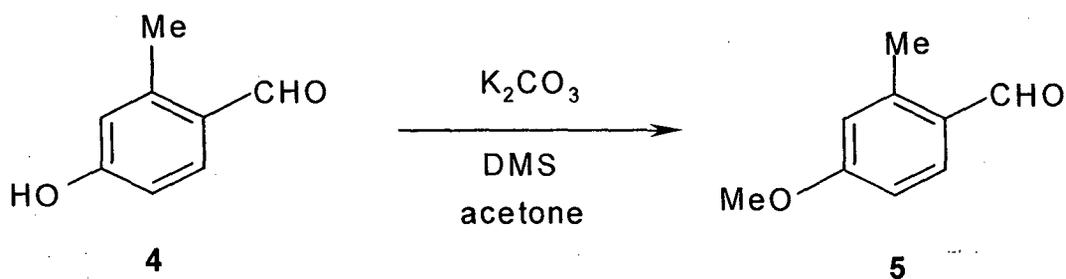
To a solution of acetyl chloride (0.11 mL, 1.4 mmol) in toluene (2 mL), was added activated zinc dust (0.085 g, 1.4 mmol) and the suspension was stirred for 10 min. Then a toluene solution of phosphorane **3** (0.5 g, 1.4 mmol in 20 mL) was added and stirring continued for the given time. The reaction mixture was filtered and the solid washed with ether (10 mL). The combined organic layer was washed with NaHCO₃ solution, water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a white solid, which on recrystallization from benzene afforded the product **3a** (0.278 g, 49%, m.p. 113°C).

Expt. 2.6.6 : Preparation of Ethyl 3-oxo-2-(triphenylphosphoranylidene)-butanoate (3a).



To the stirring mixture of phosphorane **3** (0.5 g, 1.4 mmol) in dry benzene (5 mL) and dry anhy. potassium carbonate (0.39 g, 2.8 mmol) was added dropwise, acetylchloride (0.11 mL, 1.4 mmol) in dry benzene (5 mL) for 10 min. The reaction mixture was then refluxed for 1 hour. Water was added to the reaction mixture, the organic layer was dried over anhy. sodium sulphate and concentrated to get a white solid, which on recrystallization from benzene afforded the product **3a** (0.38 g, 68%, m.p. 113°C).

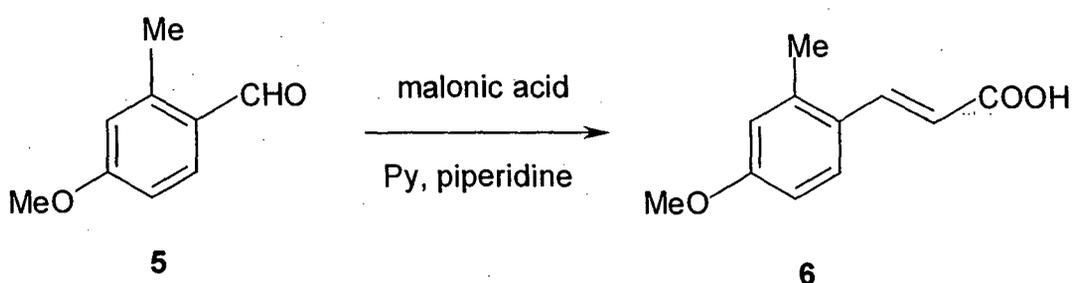
Expt. 2.6.7 : Preparation of 4-methoxy-2-methylbenzaldehyde (5)



To a stirred, well cooled (0°C) solution of 4-hydroxy-2-methylbenzaldehyde **4** (2 g, 14.7 mmol) and anhydrous potassium carbonate (6 g, 44 mmol) in dry acetone (20 mL) was added dimethyl sulphate (1.4 mL, 14.7 mmol) dropwise over a period of 1 hour. After complete addition of dimethyl sulphate the reaction mixture was refluxed for 2 hours. It was then cooled, filtered on ordinary filter paper, washed with acetone (5 mL) and the combined organic solvent was concentrated. The crude product was extracted with diethyl ether, (3 x 10 mL) washed with 2N NaOH, water and the organic layer was dried over

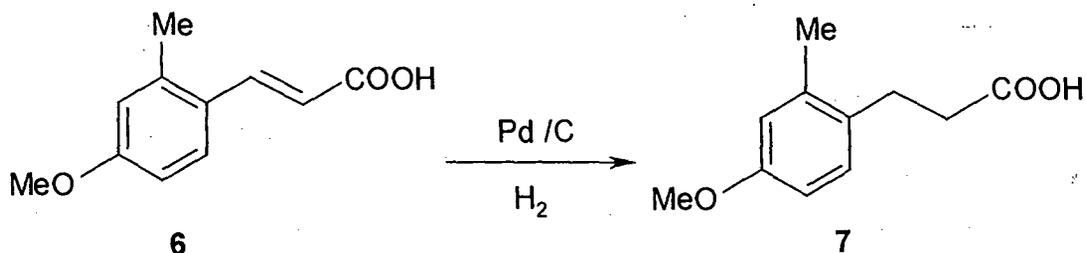
anhydrous sodium sulphate. Concentration of the organic layer afforded a liquid aldehyde **5** (1.8 g, 81%), (Lit.²³ b.p. 140-190°/0.3 mm).

Expt. 2.6.8 : Preparation of (*E*)- 3-(4-Methoxy-2-methylphenyl)-2-propenoic Acid²⁴ (6**).**



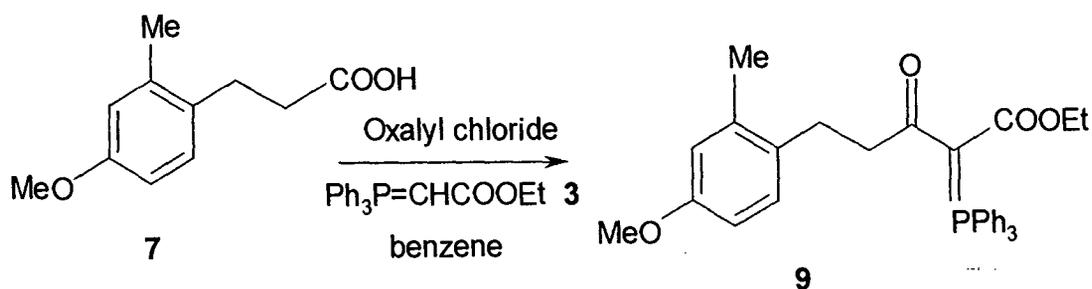
The mixture of p-methoxytolualdehyde **5** (2.4 g, 16 mmol) and malonic acid (3.4 g, 32 mmol) was dissolved in dry pyridine (1.3 mL, 16 mmol) and piperidine (1.4 mL, 14 mmol). The reaction mixture was then refluxed on water bath for 1 hour and then was boiled for another 5 min. on a wire gauze to complete the reaction. The reaction mixture was quenched with 1:1 HCl in excess of water to give a yellow coloured solid, which was then filtered and recrystallized with water to obtain a yellow shiny solid acid **6** (2.86 g, 93%, m.p. 185°C).

**Expt. 2.6.9 : Preparation of 3-(4-Methoxy-2-methylphenyl)-
propionic acid²⁴ (7).**



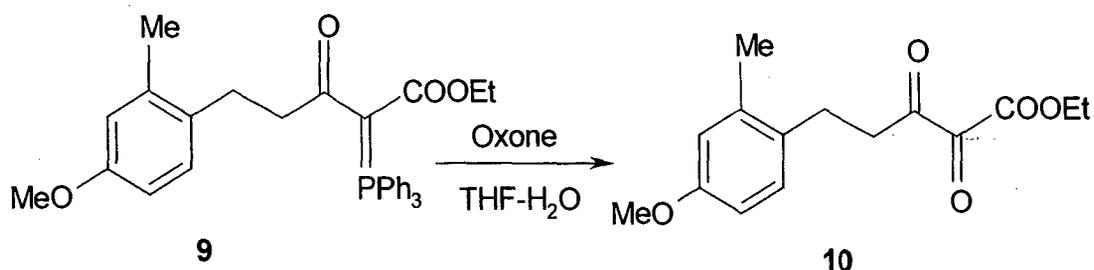
The 4-methoxy-2-methyl-cinnamic acid **6** (0.192 g, 1 mmol) was dissolved in ethyl acetate (10 mL) and to this was added 10% Pd/C (0.02 g, 0.1 mmol). The reaction mixture was subjected to hydrogenation by passing hydrogen gas for 2 hours. The reaction mixture was filtered on fluted filter paper and the filtrate together with washings was concentrated to obtain a white solid. Recrystallization with water afforded acid **7** (0.184 g, 95%), m.p. 102°C, (Lit.^{25a} m.p. 105°C).

**Expt. 2.6.10 : Preparation of Ethyl 3-oxo-2-(triphenylphosphorylidene)-
-5-(4-methoxy-2-methyl-phenyl)pentanoate (9).**



To the stirred solution of 4-methoxy-2-methyl-dihydrocinnamic acid **7** (0.5 g, 2.5 mmol) in dry benzene (10 mL), was added dropwise, oxalyl chloride (0.34 mL, 3.8 mmol) at room temperature for over a period of 30 min. The reaction mixture was then warmed at 40°C for 1 hour. The solvent was then evaporated on vacuum pump. Dry benzene (10 mL) was added to the crude acid chloride **8**. To the stirred reaction mixture was added phosphorane **3** (1.74 g, 5 mmol) in dry benzene (10 mL), dropwise, for over 30 min. The reaction mixture was stirred first at room temperature for 2 hours and then at 60°C for 1 hour. After completion of the reaction, water was added and the reaction mixture was extracted with benzene (2 x 10 mL), washed with water (2 x 5 mL), saturated sodium hydrogen carbonate (2 x 5 mL), water and then the combined organic solvent was dried over anhydrous sodium sulphate and evaporated. The crude product thus obtained was purified by column chromatography over silica gel using EtOAc-hexanes (3:7) as eluent to give a pale yellow solid, which on recrystallization with EtOAc-hexanes afforded acyl-phosphorane **9** (0.785 g, 58%, m.p. 120°C).

Expt. 2.6.11 : Preparation of Ethyl 2,3-dioxo-(4-methoxy-2-methylphenyl)-pentanoate (10).



To the stirred solution of oxone (1.23 g, 2 mmol) in THF (10 mL) and water (5 mL) was added acyl-phosphorane **9** (0.78 g, 1.4 mmol) and the reaction mixture was stirred at room temperature for 12 hours. After the completion of the reaction, water (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 5 mL). The crude product obtained, after evaporation of the solvent, was then purified by column chromatography over silica gel using ethyl acetate: hexanes (1:5) as eluent to afford a yellow solid, which on recrystallization from benzene-hexanes afforded **10** (0.134 g, 34%, m.p. 96°C).

Expt. 2.6.12 : Reaction of Ethyl 2,3-dioxo-(4-methoxy-2-methyl-phenyl)pentanoate (10) with H₂SO₄.

To a flask containing ice-cold ester **10** (0.1g, 0.36 mmol) was added ice cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 10 min. After the completion of reaction, sufficient crushed ice was added to the reaction mixture to make it dilute and the reaction mixture was extracted in diethyl ether (2 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate. The tlc indicated a number of products.

Expt. 2.6.13 : Reaction of Ethyl 2,3-dioxo-(4-methoxy-2-methyl-phenyl)pentanoate (10) with PTSA.

A mixture of tricarbonyl compound **10** (0.1 g, 0.36 mmol) and catalytical amount of p-toluenesulphonic acid (0.01 g) was refluxed in toluene in a Dean-

Stark apparatus assembly for 15 hours. Tlc did not display any change in the starting spot.

Expt. 2.6.14 : Neat heating of Ethyl 2,3-dioxo-(4-methoxy-2-methyl-phenyl)pentanoate (10) in diphenylether .

Tricarbonyl compound **10** (0.1 g, 0.36 mmol) was dissolved in diphenyl ether (5 mL) and the reaction mixture was refluxed for 24 hours under nitrogen atmosphere. No change was observed on tlc.

Expt. 2.6.15 : Reaction of Ethyl 2,3-dioxo-(4-methoxy-2-methyl-phenyl)pentanoate (10) with P₂O₅ .

To the same above reaction mixture was added one equivalent of phosphorus pentoxide (0.05 g, 0.36 mmol) and refluxed for another 12 hours. Tlc did not show any indication of formation of a new spot.

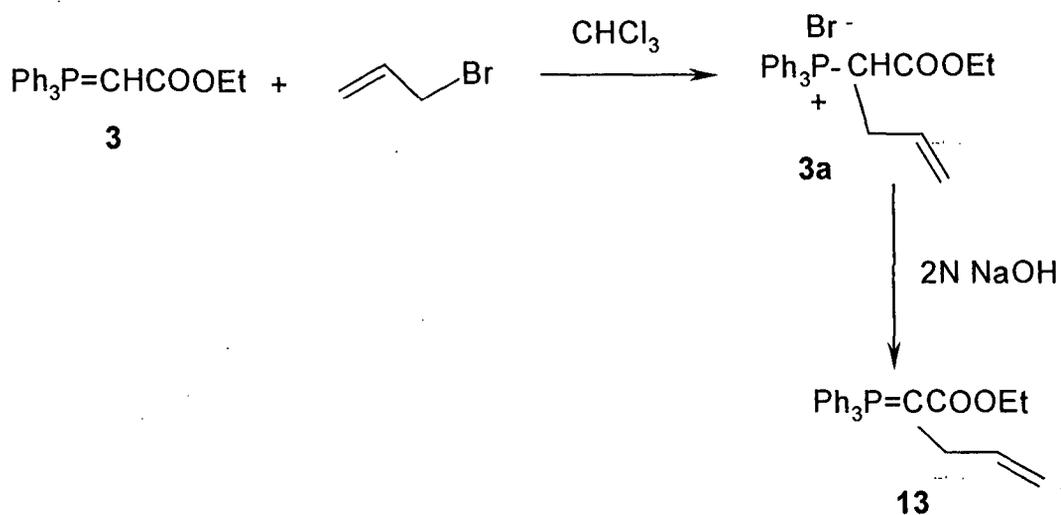
Expt. 2.6.16 : Reaction of Ethyl 2,3-dioxo-(4-methoxy-2-methyl-phenyl)pentanoate (10) with HBr-AcOH .

To the stirred mixture of glacial acetic acid (1.5 mL) and 48% HBr (1 mL) was added tricarbonyl compound **10** (0.1 g, 0.36 mmol) and the reaction mixture was refluxed for 2 hours.

Expt. 2.6.17 : Reaction of Ethyl 2,3-dioxo-(4-methoxy-2-methyl-phenyl)pentanoate (10) with PPA .

A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, tricarbonyl compound **10** (0.1 g, 0.36 mmol) was added in one lot and the mixture was stirred for 10 min. After cooling, crushed ice was added and the reaction mixture was extracted in ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and was concentrated to recover the starting back.

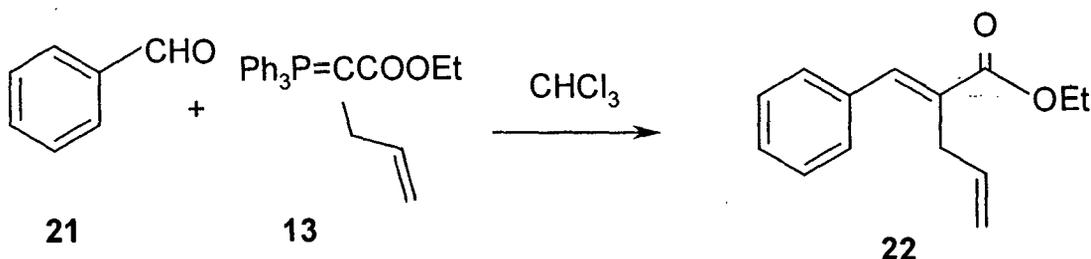
Expt.2.6.18 : Preparation of Carboethoxy-(α -allyl)-methylidene-triphenylphosphorane (13).



A solution of allyl bromide (3.47 g, 2.87 mmol) in chloroform (5 mL) was added to a solution of carboethoxymethylenetriphenyl phosphorane **3** (10 g, 2.87 mmol) in chloroform (20 mL). The reaction mixture was refluxed for 2 hours and the solvent removed under reduced pressure. Hexanes (20 mL) was added to the oily residue, cooled to 0°C and scratched to get a white solid which was filtered and washed with benzene. It was recrystallized from chloroform-hexanes to give the salt **3a** (12.7 g, 94%); m.p. 150-151°C.

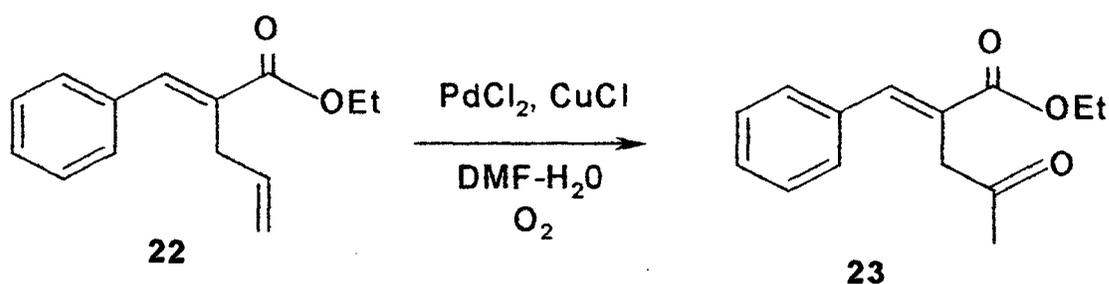
The above salt **3a** was dissolved in water (125 mL) and benzene (100 mL) was added to it. Phenolphthalein (1 or 2 drops) was added to the above solution. Sodium hydroxide solution (2 N) was added to it with stirring till the pink colour persisted. The benzene layer was separated and the aqueous layer was extracted with benzene (50 mL). The combined benzene layer was dried (Na_2SO_4) and solvent removed under reduced pressure to get a crude product. It was recrystallized from benzene-hexanes to furnish phosphorane **13** (5.6 g, 50%, m.p. 122°C); (lit.³⁵ m.p. 122°C).

Expt. 2.6.19 : Preparation of Ethyl (*E*)-2-Benzylidenepent-4-enoate³⁷ (22**).**



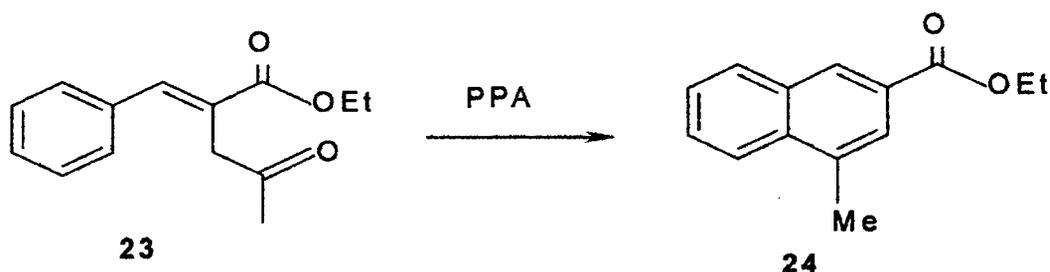
A mixture of benzaldehyde **21** (0.106 g, 1 mmol), allyl phosphorane **13** (0.388 g, 1 mmol) and chloroform (5 mL) was refluxed for 3 hours. Chloroform was evaporated followed by chromatographic separation of the crude product over silica gel using ethyl acetate: hexanes (5:95) as eluent to furnish a liquid ester **22** (0.205 g, 95%), b.p. 136°C, (lit.^{37b} 135 °C).

**Expt. 2.6.20 : Preparation of Ethyl 2-benzylidene-4-oxo-
pentanoate⁴¹ (23).**



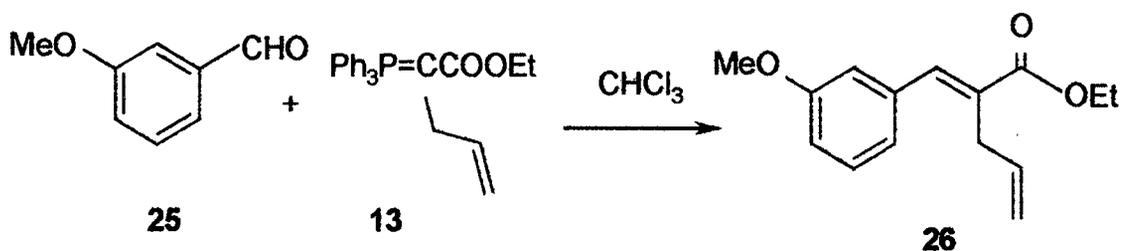
A mixture of cuprous chloride (0.093 g, 1 mmol), palladium chloride (0.018 g, 0.1 mmol) and water (0.2 mL) in dimethylformamide (15 mL) was stirred under oxygen atmosphere for 1 hour. To this reaction mixture, ester **22** (0.216 g, 1 mmol) in DMF (5 mL) was added and the mixture stirred for 10 hours at room temperature. It was then diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude mixture was adsorbed on silica gel and subjected to column chromatography using ethyl acetate: hexanes (1:9) as eluent to afford a viscous liquid keto-ester **23** (0.174 g, 75%).

Expt. 2.6.21 : Preparation of Ethyl 4-methyl-2-naphthoate⁴² (24).



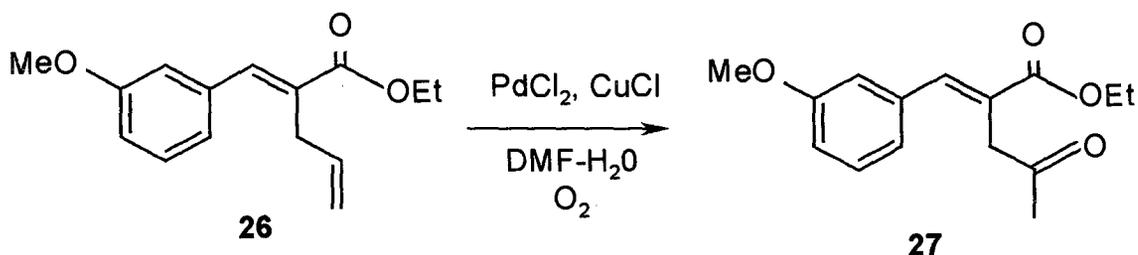
A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, ethyl 2-benzylidene-4-oxopentanoate **23** (0.232 g, 1 mmol) was added in one lot and the mixture was stirred for 10 min. After cooling, crushed ice was added and the reaction mixture was extracted in ethyl acetate (3 x 10 mL). The organic layer was dried over anhydrous sodium sulphate and was concentrated to get the crude product. Column chromatography of crude product using ethyl acetate: hexanes (1:9) as eluent, afforded a white solid. Recrystallization with ethyl acetate- hexanes afforded naphthoic ester **24** (0.150 g, 70%), m.p. 52°C; (lit.³³ m.p. 51-52 °C).

Expt. 2.6.22 : Preparation of Ethyl (*E*)-2-(*m*-methoxy-benzylidene)-4-oxo-pentanoate (26).



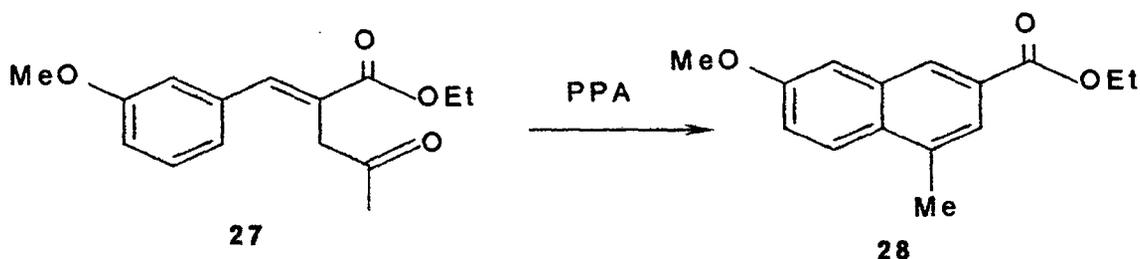
A mixture of *m*-methoxybenzaldehyde **25** (0.136 g, 1 mmol), allyl phosphorane **13** (0.388g, 1mmol) and chloroform (3 mL) was refluxed for 3 hours. Chloroform was evaporated followed by chromatographic separation over silica gel using ethyl acetate: hexanes (5:95) as eluent to furnish a thick liquid ester **26** (0.175 g, 71%).

Expt. 2.6.23 : Preparation of Ethyl 2-(*m*-methoxybenzylidene)-4-oxo-pentanoate (27**).**



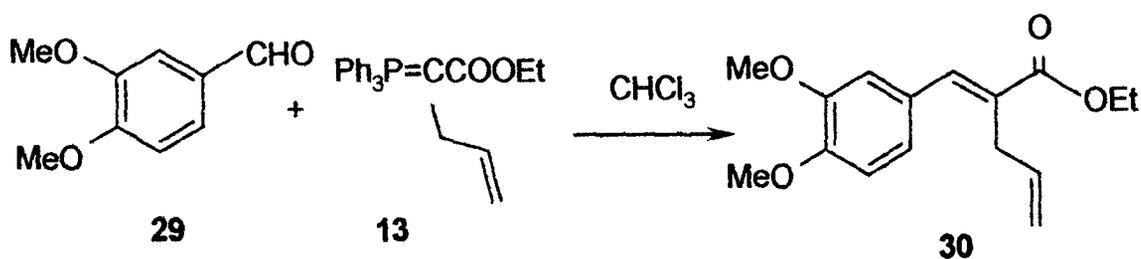
A mixture of cuprous chloride (0.093 g, 1 mmol), palladium chloride (0.018 g, 0.1 mmol) and water (0.2 mL) in dimethylformamide (15 mL) was stirred under oxygen atmosphere for 1 hour. To this reaction mixture, ester **26** (0.246 g, 1 mmol) in DMF (5 mL) was added and the mixture stirred for 10 hours at room temperature. It was then diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude mixture was adsorbed on silica gel and subjected to column chromatography using ethyl acetate: hexanes (1:9) as eluent to afford a viscous liquid keto-ester **27** (0.202 g, 77%).

Expt. 2.6.24 : Preparation of Ethyl 7-methoxy-4-methyl-2-naphthoate (28).



A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, ethyl 2-(*m*-methoxybenzylidene)-4-oxo-pentanoate **27** (0.262 g, 1 mmol) was added in one lot and the mixture was stirred for 10 min. After cooling, crushed ice was added and the reaction mixture was extracted in ethyl acetate (3 x 10 mL). The organic layer was dried over anhydrous sodium sulphate and was concentrated to get the crude product. Column chromatography of crude product using ethyl acetate: hexanes (1:9) as eluent, afforded a white solid. Recrystallization from ethyl acetate-hexanes yielded naphthoic ester **28** (0.168 g, 69%, m.p. 55°C).

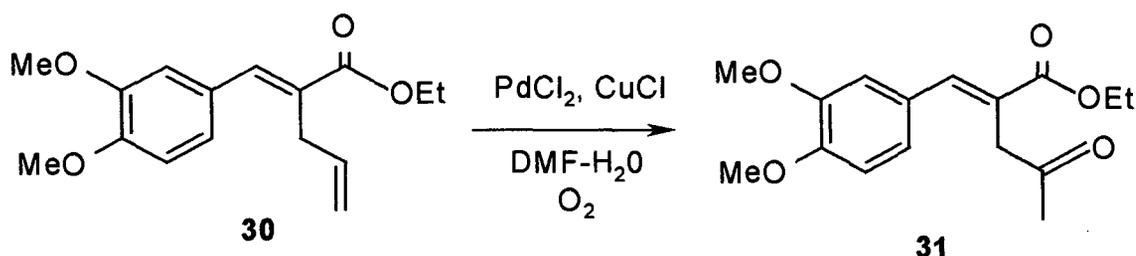
Expt. 2.6.25 : Preparation of Ethyl (*E*)-2-(3,4-dimethoxybenzylidene)-pent-4-enoate³⁷ (30).



A mixture of 3,4-dimethoxybenzaldehyde **29** (0.166 g, 1 mmol), allyl phosphorane **13** (0.388 g, 1 mmol) and chloroform (5 mL) was refluxed for 3 hours. Chloroform was evaporated followed by chromatographic separation over silica gel using ethyl acetate: hexanes (5:95) as eluent, furnished a thick liquid ester **30** (0.191 g, 69%).

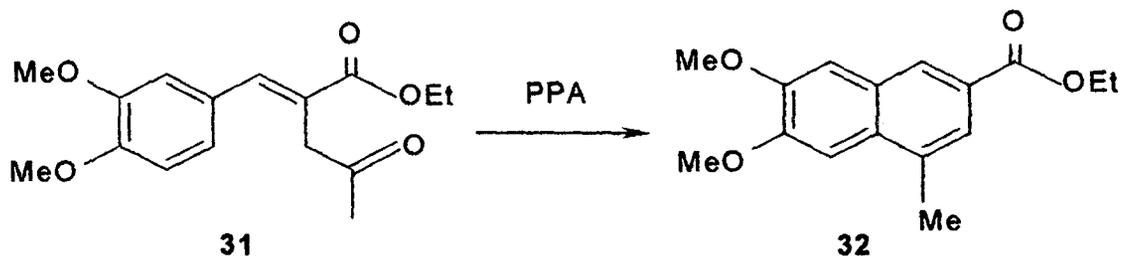
Expt. 2.6.26 : Preparation of Ethyl 2-(3,4-dimethoxybenzylidene)-

-4-oxo-pentanoate (31).



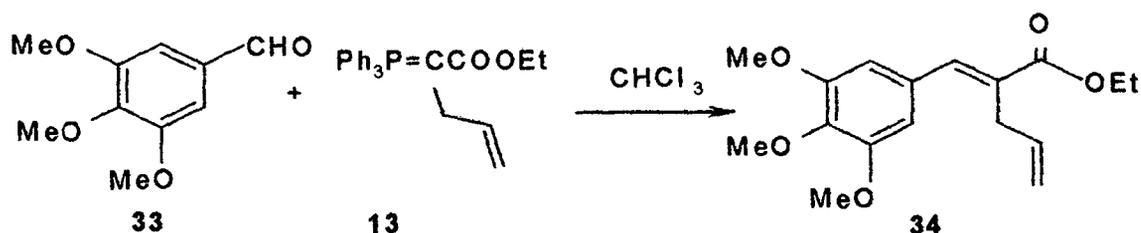
A mixture of cuprous chloride (0.093 g, 1 mmol), palladium chloride (0.018 g, 0.1 mmol) and water (0.2 mL) in dimethylformamide (15 mL) was stirred under oxygen atmosphere for 1 hour. To this reaction mixture, ester **30** (0.276 g, 1 mmol) in DMF (5 mL) was added and the mixture stirred for 10 hours at room temperature. It was then diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude mixture was adsorbed on silica gel and subjected to column chromatography using ethyl acetate: hexanes (1:9) as eluent afforded a viscous liquid keto-ester **31** (0.204 g, 70%).

Expt. 2.6.27 : Preparation of Ethyl 6,7-dimethoxy-4-methyl-2-naphthoate (32).



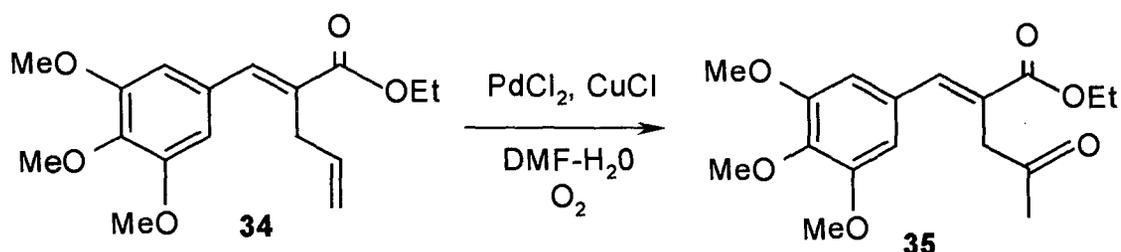
A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, ethyl-2-(3,4-dimethoxybenzylidene)-4-oxo-pentanoate **31** (0.292 g, 1 mmol) was added in one lot and the mixture was stirred for 10 min. After cooling, crushed ice was added and the reaction mixture was extracted in ethyl acetate (3 x 10 mL). The organic layer was dried over anhydrous sodium sulphate and was concentrated to get the crude product. Column chromatography of crude product using ethyl acetate: hexanes (1:9) as eluent, afforded a white solid. Recrystallization with ethyl acetate- hexanes afforded naphthoic ester **32** (0.192 g, 70%, m.p. 144°C).

Expt. 2.6.28 : Preparation of Ethyl (E)-2-(3,4,5-trimethoxybenzylidene)-pent-4-enoate³⁷ (34).



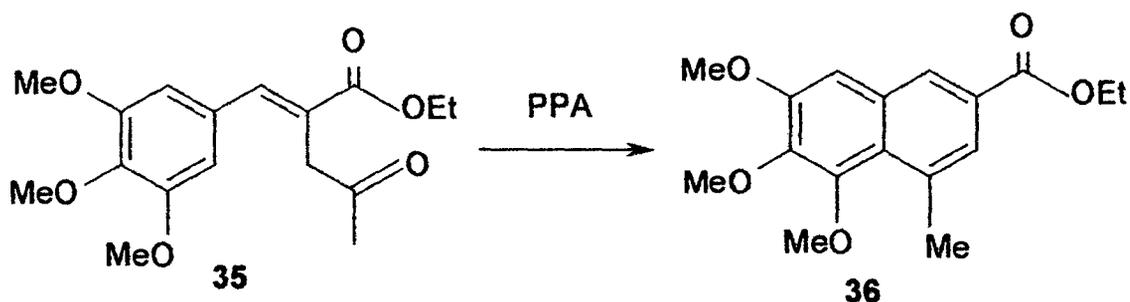
A mixture of trimethoxybenzaldehyde **33** (0.196 g, 1 mmol), allyl phosphorane **13** (0.388 g, 1 mmol) and chloroform (5 mL) was refluxed for 3 hours. Chloroform was evaporated followed by chromatographic separation over silica gel using ethyl acetate: hexanes (5:95) as eluent furnished a thick liquid ester **34** (0.199 g, 65%).

Expt. 2.6.29 : Preparation of Ethyl 2-(3,4,5-trimethoxybenzylidene)-4-oxo-pentanoate (35).



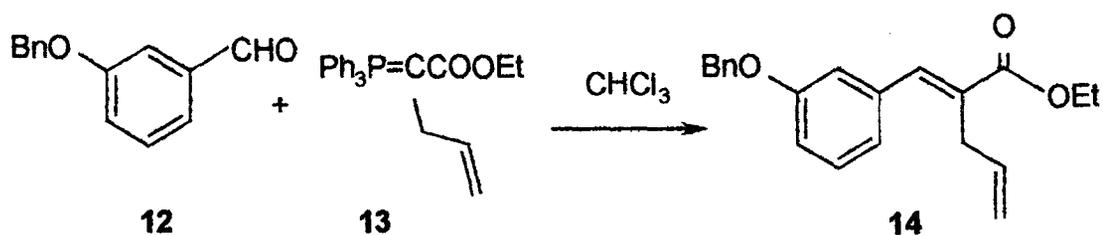
A mixture of cuprous chloride (0.093 g, 1 mmol), palladium chloride (0.018 g, 0.1 mmol) and water (0.2 mL) in dimethylformamide (15 mL) was stirred under oxygen atmosphere for 1 hour. To this reaction mixture, ester **34** (0.306 g, 1 mmol) in DMF (5 mL) was added and the mixture stirred for 10 hours at room temperature. It was then diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude mixture was adsorbed on silica gel and subjected to column chromatography over silica gel using ethyl acetate: hexanes (1:9) as eluent, afforded a viscous liquid keto-ester **35** (0.232 g, 72%).

Expt. 2.6.30 : Preparation of Ethyl 5,6,7-trimethoxy-4-methyl-2-naphthoate (36).



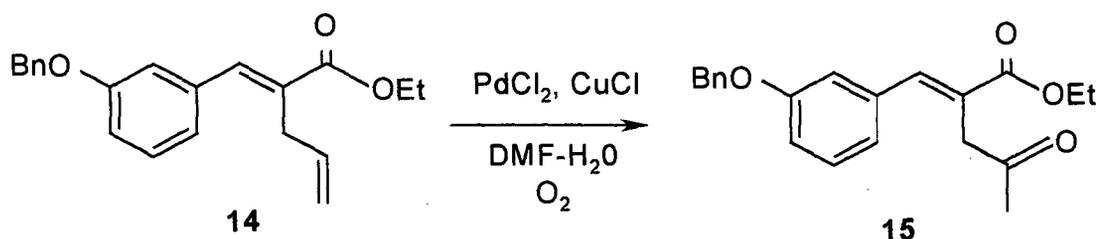
A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, ethyl 2-(3,4,5-trimethoxybenzylidene)-4-oxopentanoate **35** (0.322 g, 1 mmol) was added in one lot and the mixture was stirred for 10 min. After cooling, crushed ice was added and the reaction mixture was extracted in ethyl acetate (3 x 10 mL). The organic layer was dried over anhydrous sodium sulphate and was concentrated to get the crude product. Column chromatography of crude product using ethyl acetate: hexanes (1:9) as eluent, afforded white solid crystals. Recrystallization from ethyl acetate- hexanes yielded naphthoic ester **36** (0.201g, 66%, m.p. 140°C).

Expt. 2.6.31 : Preparation of Ethyl (*E*)-2-(*m*-benzoxybenzylidene)-pent-4-enoate (14).



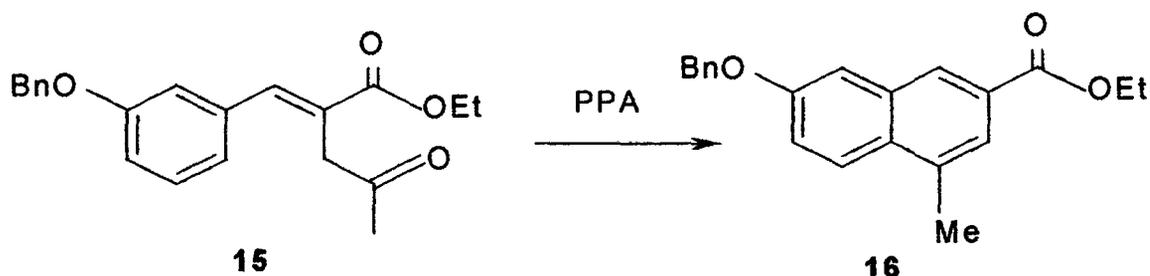
A mixture of *m*-benzoxybenzaldehyde **12** (0.212 g, 1 mmol), allyl phosphorane **13** (0.388 g, 1 mmol) and chloroform (5 mL) was refluxed for 3 hours. Chloroform was evaporated followed by chromatographic separation over silica gel using ethyl acetate: hexanes (5:95) as eluent to furnish a thick liquid ester **14** (0.306 g, 95%).

Expt. 2.6.32 : Preparation of Ethyl 2-(*m*-benzoxy-benzylidene)-4-oxo-pentanoate (15).



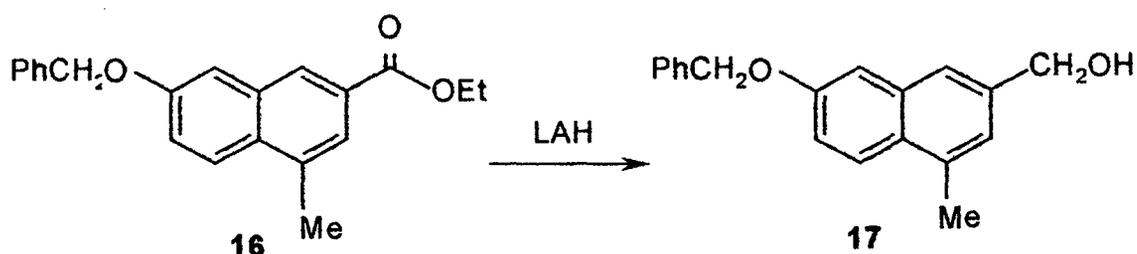
A mixture of cuprous chloride (0.093 g, 1 mmol), palladium chloride (0.018 g, 0.1 mmol) and water (0.2 mL) in dimethylformamide (15 mL) was stirred under oxygen atmosphere for 1 hour. To this reaction mixture, ester **14** (0.322 g, 1 mmol) in DMF (5 mL) was added and the mixture stirred for 10 hours at room temperature. It was then diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated and the crude mixture was adsorbed on silica gel and subjected to column chromatography using ethyl acetate: hexanes (1:9) as eluent, afforded a viscous liquid keto-ester **15** (0.223 g, 66%).

Expt. 2.6.33 : Preparation of Ethyl 7-benzyloxy-4-methyl-2-naphthoate (16).



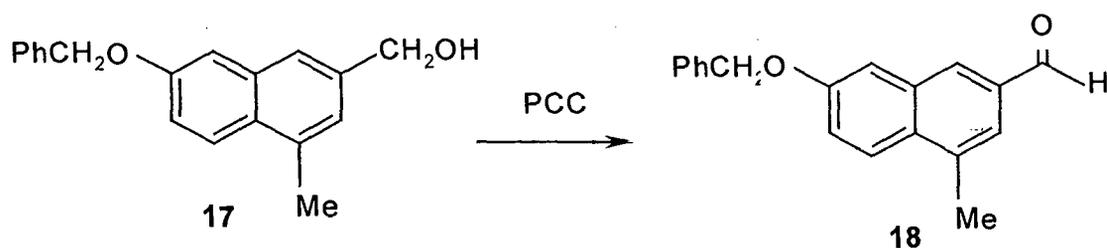
A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, ethyl 2-(*m*-benzyloxybenzylidene)-4-oxopentanoate **15** (0.676 g, 2 mmol) was added in one lot and the mixture was stirred for 10 min. After cooling, crushed ice was added and the reaction mixture was extracted in ethyl acetate (3 x 10 mL). The organic layer was dried over anhydrous sodium sulphate and was concentrated to get the crude product. Column chromatography of crude product using ethyl acetate: hexanes (1:9) as eluent, afforded a white solid. Recrystallization from ethyl acetate-hexanes yielded naphthoic ester **16** (0.448 g, 70%, m.p. 181°C).

Expt. 2.6.34 : Preparation of 7-benzyloxy-4-methyl-2-naphthylalcohol (17).



To a stirred solution of lithium aluminium hydride (0.058 g, 1.5 mmol) in dry diethyl ether (10 mL) was added ester **16** (0.320 g, 1 mmol) in dry diethylether (5 mL) dropwise, at 0°C, over a period of 0.5 hour. The stirring was continued for 2 hours. Ice-cold water (1 mL) was added cautiously to reaction mixture. The white solid separated was filtered off and washed with diethyl ether (2 x 10 mL). The combined organic solvent dried over anhydrous sodium sulphate and concentrated on water bath. The crude product was purified over silica gel column chromatography using ethyl acetate: hexanes (1:4) as eluent to obtain a white solid. Recrystallization from ethyl acetate-hexanes yielded alcohol **17** (0.256 g, 92%, m.p. 163°C).

Expt. 2.6.35 : Preparation of 7-benzyloxy-4-methyl-2-naphthylaldehyde (18).



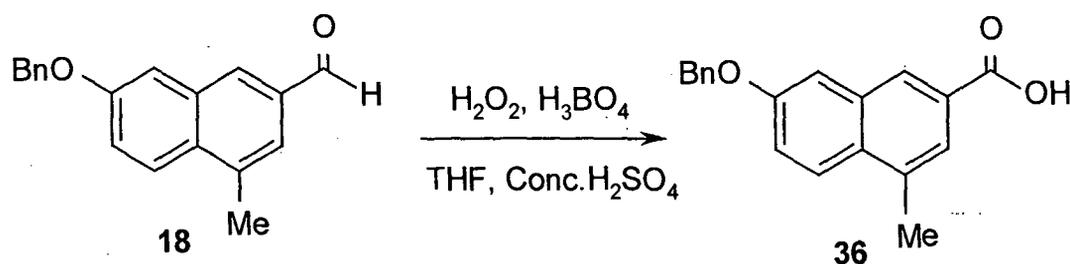
To a magnetically stirred suspension of pyridinium chlorochromate (PCC) (0.258 g, 1.2 mmol) in anhydrous dichloromethane (10 ml) was added alcohol **17** (0.278 g, 1 mmol) in anhydrous dichloromethane (5 ml) at room temperature. The stirring was continued for 1 hour. Diethyl ether (10 ml) was added to the reaction mixture and the supernatant solution was decanted from the black granular solid. The combined organic solutions were passed through a short pad of celite and

the solution was evaporated. The residue obtained was further purified by column chromatography using ethyl acetate: hexanes (3:7) as eluent to give a white solid. Recrystallization from benzene-hexanes afforded aldehyde **18** (0.193 g, 70%, m.p. 142°C).

**Expt. 2.6.36 : Reaction of 7-benzyloxy-4-methyl-2-naphthylaldehyde (18)
with mcpba.**

To the stirring mixture of mcpba (0.146 g, 0.75 mmol) in chloroform (10 mL) was added aldehyde **18** (0.2 g, 0.72 mmol) in chloroform (5 mL) dropwise and the reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was then washed with sat. NaHCO₃ solution (3 x 5 mL) and the chloroform layer was evaporated on water bath. The black tar was obtained after concentration of the organic layer.

**Expt. 2.6.37 : Baeyer-Villiger reaction³⁹ on 7-benzyloxy-4-methyl-2-
-naphthylaldehyde (18).**



To the stirring mixture of boric acid (0.23 g, 3.6 mmol), (30%) hydrogen peroxide (0.18 g, 1.6 mmol) and catalytical amount of concentrated sulphuric acid (0.2 mL) in anhydrous THF (10 mL) was added aldehyde **18** (0.2 g, 0.72

mmol) and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was then refluxed for 3 hours. The solvent was evaporated on water bath and water (10 mL) was added to the reaction mixture. The solid separated out was washed with sat. NaHCO_3 solution (3 x 5 mL), filtered and dried to obtain a solid. Recrystallization from water gave acid **36** (0.216 g, 88%, m.p. 125°C).

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Chapter 3

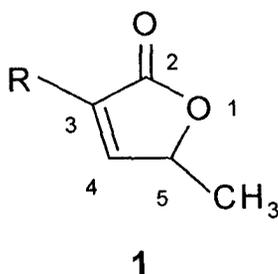
***Synthesis Of 3-Substituted-5-Methyl-
2(5H)-Furanone***

Chapter 3

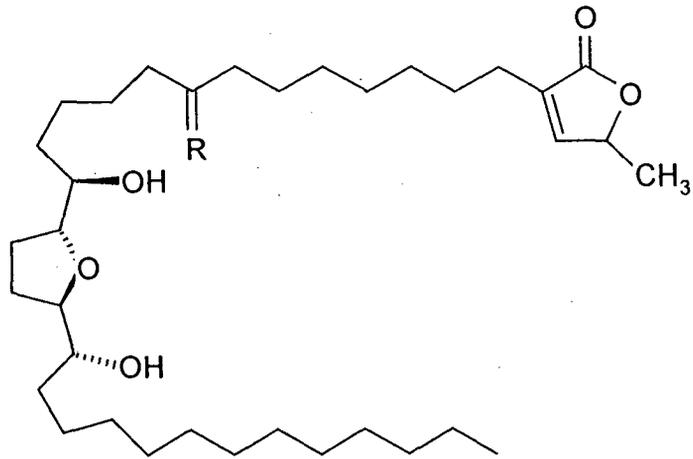
SYNTHESIS OF 3-SUBSTITUTED-5-METHYL-2(5H) FURANONE

3.1. Introduction

The γ -methyl butenolide unit **1**, an unsaturated five-membered lactone is widely encountered in several naturally occurring oxygen heterocycles, comprising both fatty acid and terpenoidal biosynthetic origins¹. Many of these products are isolated from marine animals and territorial plants. The annonaceous acetogenins are the most famous representative members of the butenolides family².

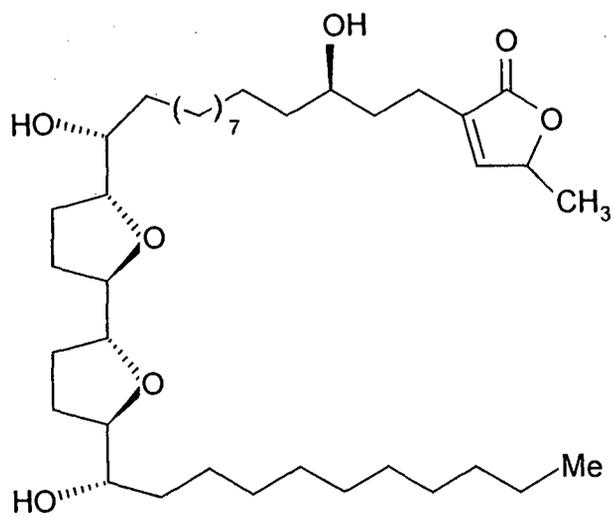


A butenolide is usually a typical 3-substituted -5-methyl-2(5H)-furanone, showing a broad range of biological activity mainly, cytotoxicity, fungicidal activity, antiviral and antibacterial activities, mosquito larvicidal activity, antitumor and pesticidal properties. The 3-substituted-5-methyl-2(5H)-furanone is believed to be one of the essential subunits for the cytotoxicity of the acetogenins³, e.g. corossolone **2**, corossolin **3**, (+) bullatacin **4**.



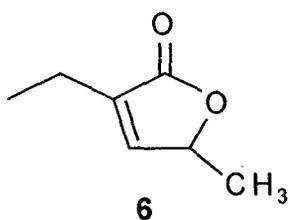
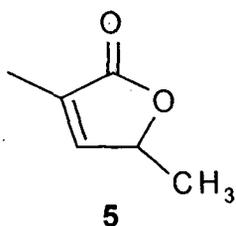
2 R= O; Corossolone

3 R= (R)-OH, H; Corossolin

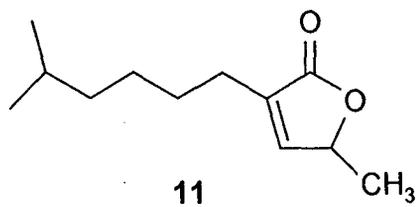
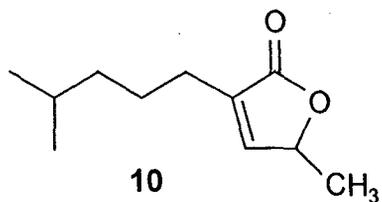
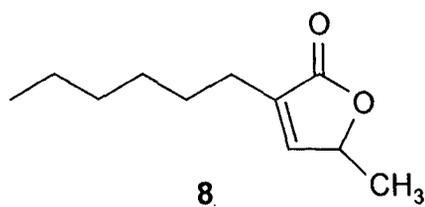
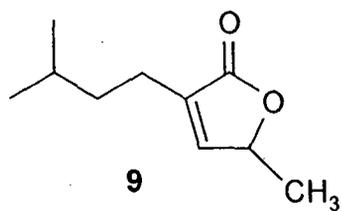
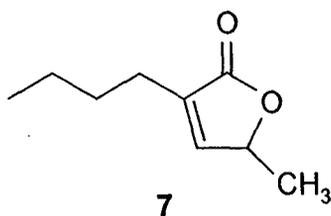


(+) Bullatacin 4

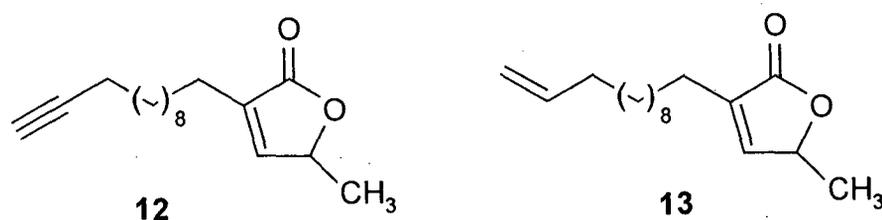
Butenolide **5** is a component of mushroom flavor⁴. Butenolide **6** has fungicidal activity⁵.



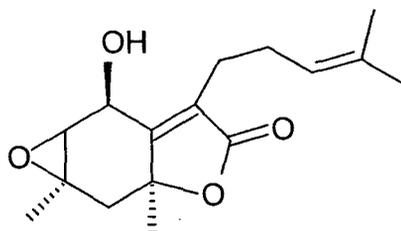
Butenolides **7**, **8**, **9**, **10** and **11** are the volatile lactones isolated from *Streptomyces griseus*⁶.



Butenolides **12** and **13** are isolated from the leaves of *Hortonia* (family Monimiaceae)⁷, both exhibited mosquito larvicidal activity with LC50 values of 0.41 and 0.47 ppm respectively.

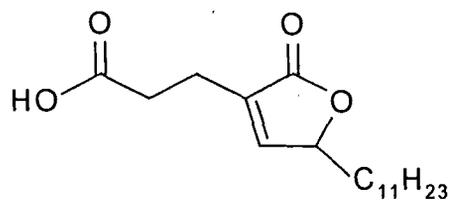


Paniculides **14** constitute a family of highly oxygenated sesquiterpenes isolated from *Andrographis paniculata*⁸.



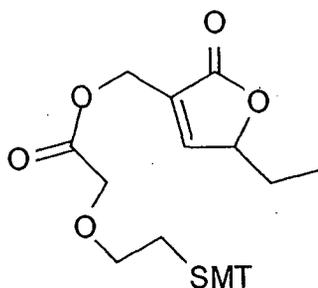
paniculide **14**

Acarenoic **15** is an example of long chain butenolides present in lichens⁹.

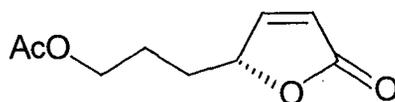


acarenoic acid **15**

Moreover, 2-(5*H*)-furanones are used as intermediates in the synthesis of many products of biological interests, e.g. Butenolide **16** is an useful precursor in the synthesis of ethisolide, isoavenaciolide and avenaciolide, which exhibits potent biological activities¹⁰.

**16**

Butenolide **17** is a key fragment in the synthesis of macrolide amphidinolide, cytotoxic against L120 murine leukemia¹¹.

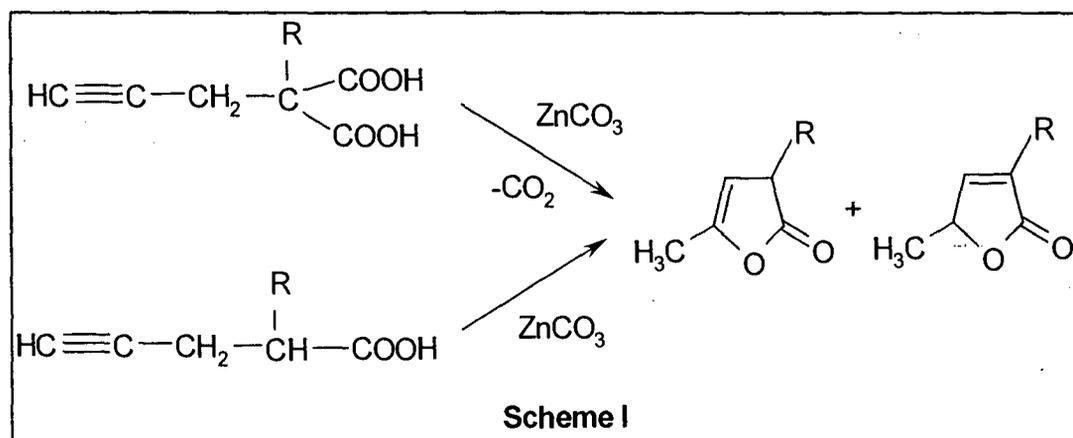
**17**

3.2 Synthesis of 3-substituted-5-methyl butenolide

The wide spread occurrence of γ -methyl butenolide units in a variety of biological active natural products has stimulated considerable interest in the development of new synthesis for their synthesis. They have been utilized for the stereospecific construction of acyclic carbon chains bearing multiple chiral centers, and for the synthesis of a variety of furanoid natural products, due to their easy convertibility to furans^{12,13}.

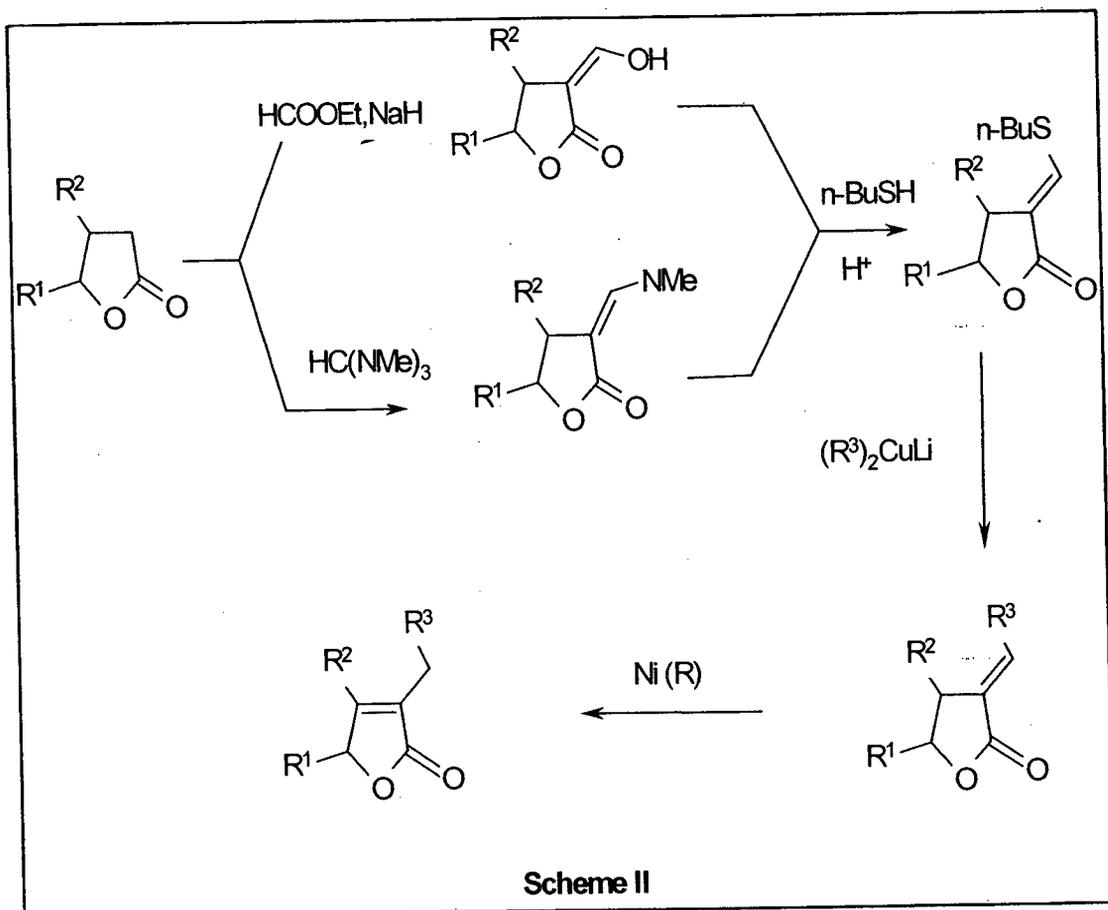
There are many excellent synthetic methods available for the synthesis of butenolides^{9,14-20}. Some of the important methods for the synthesis of 3-substituted-5-methyl butenolides are mentioned below.

Schar²¹ *et al* have synthesized α,β -unsaturated γ -butenolides by cyclizing alkyne diacid and alkyne monoacid in presence of zinc carbonate (Scheme I).

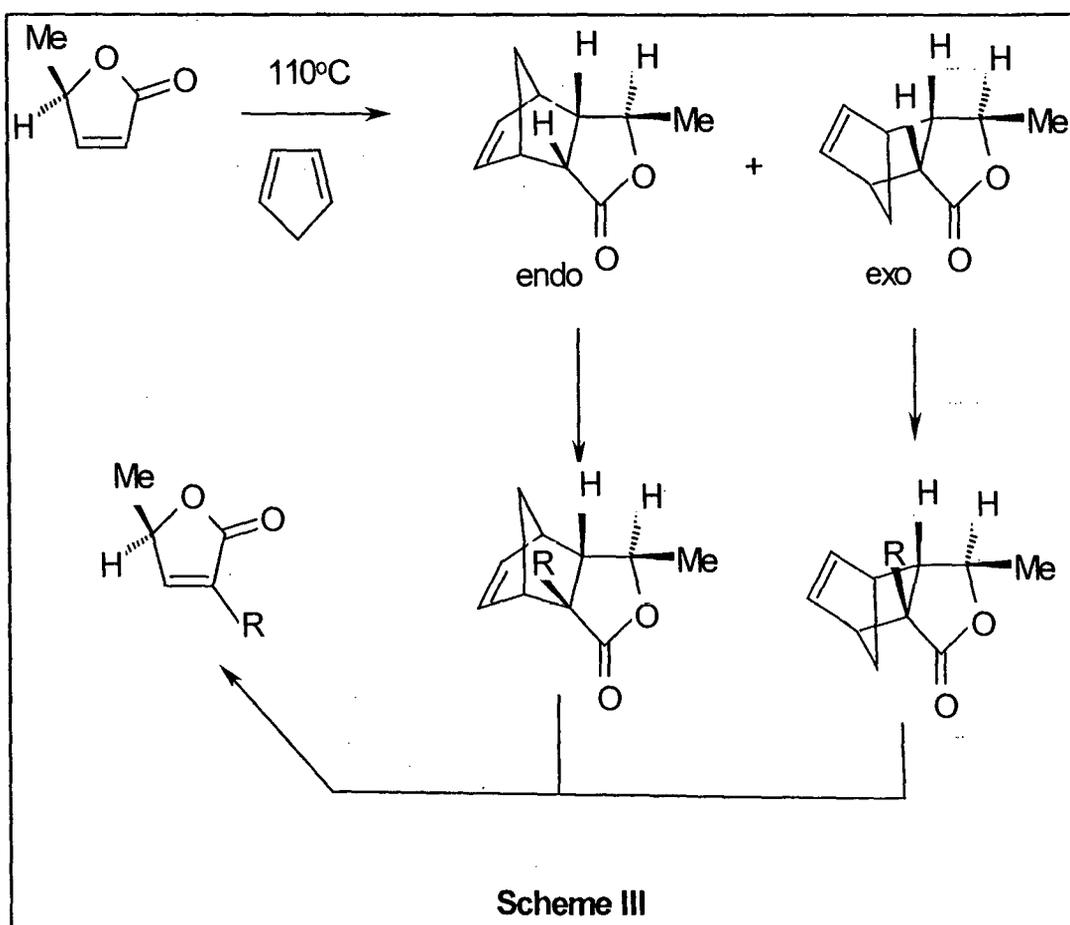


Martin *et al*¹² have reported the synthesis of butenolides by employing readily available γ -butyrolactones. The butyrolactones are converted to vinylogous thiocarbonates by two methods. Formylation of the γ -lactone with ethyl formate and NaH in anhydrous ether gave α -hydroxymethylenes, which were subsequently treated with n-butanethiol, in presence of p-toluenesulfonic acid to give α -n-butylthiomethylene lactones.

In the second method, α -n-butylthiomethylene was prepared by heating γ -lactones with tris(dimethyl-amino) methane to give vinylogous urethanes and treating it with n-butenethiol, in presence of p-toluenesulfonic acid. The α -n-butyl thiomethylene lactones were reacted with lithium dialkylcuprates to obtain α -alkylidene- γ -lactones, which on isomerization using Raney nickel, afforded the desired butenolides (Scheme II).

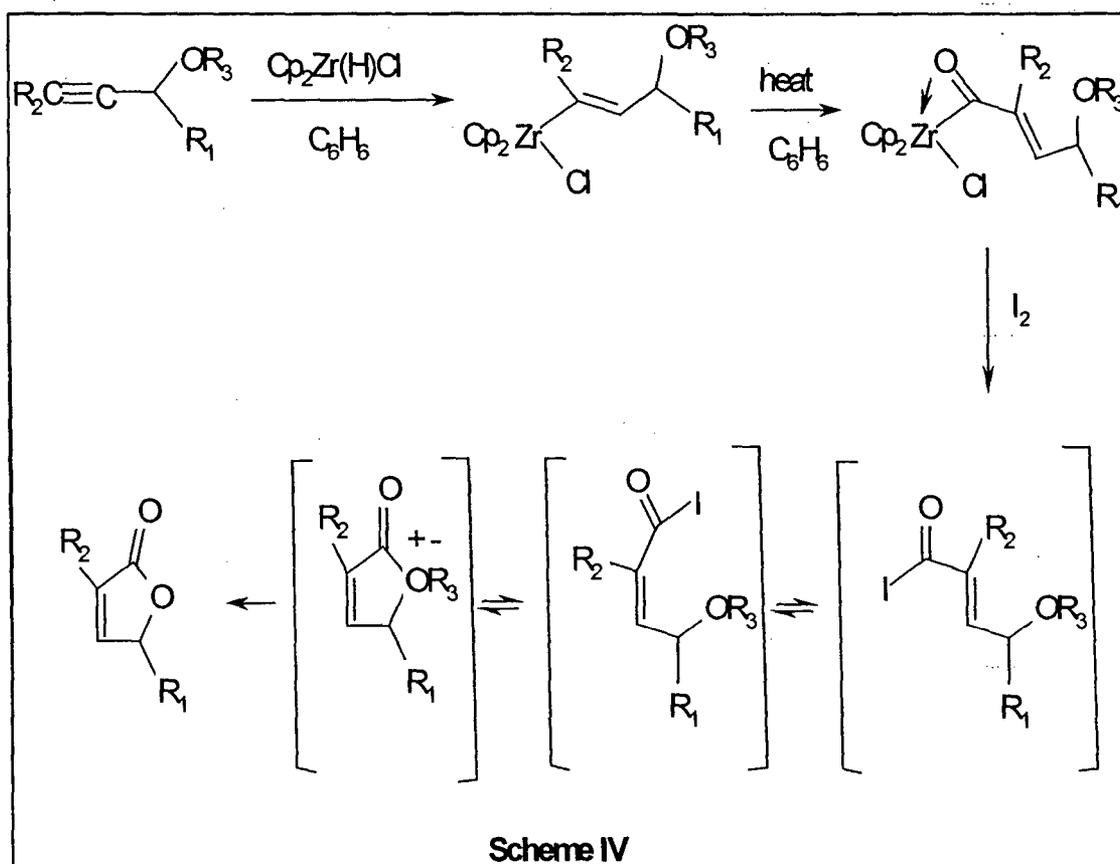


Font and Ortutios method^{6b} involves the alkylation of Diels-Alder adducts obtained from α,β -unsaturated butenolide and cyclopentadiene in presence of LDA and alkyl halide and subsequently, carrying out pyrolysis to yield butenolides (Scheme III).

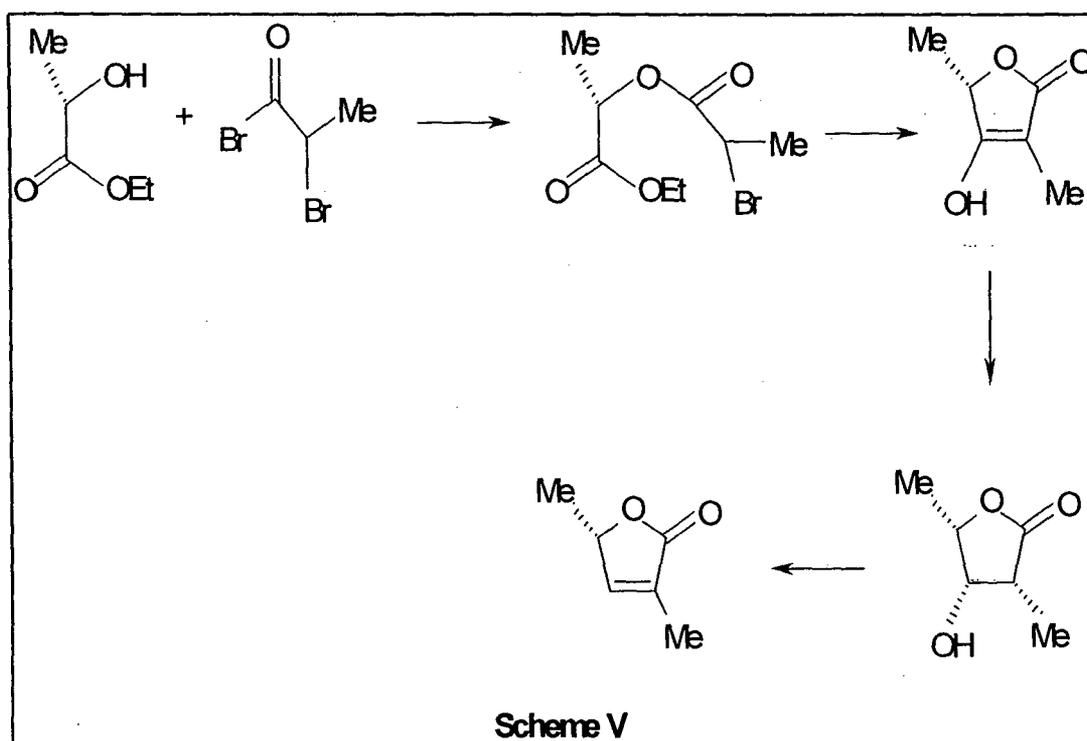


Buchwald and co-workers²² have described a method for the conversion of protected propargylic alcohols into the butenolides. Hydrozirconation of protected propargyl alcohol, provided vinyl zirconocene, which is then carbonylated to give the corresponding acyl zirconocene complex, which on treatment with iodine yielded the butenolide.

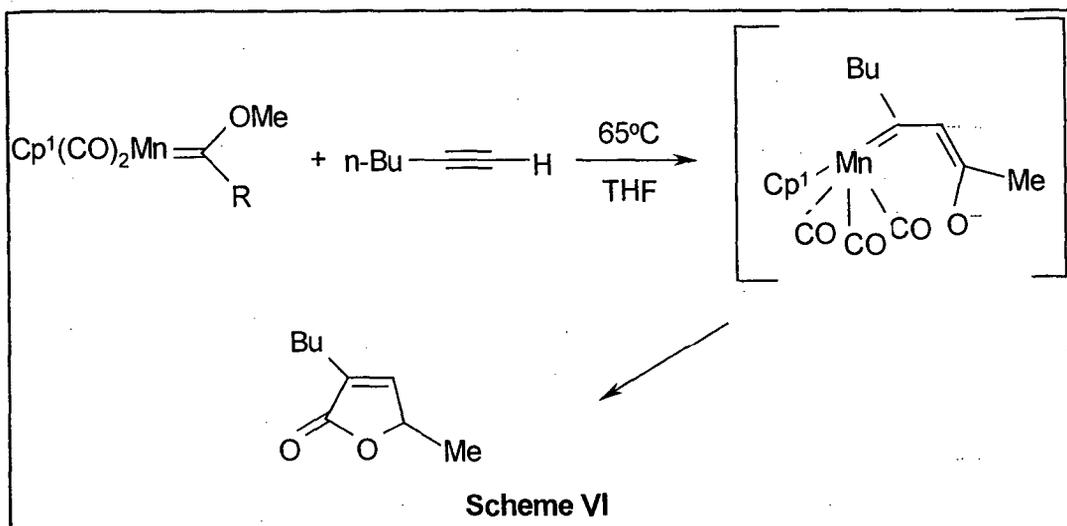
(Scheme IV).



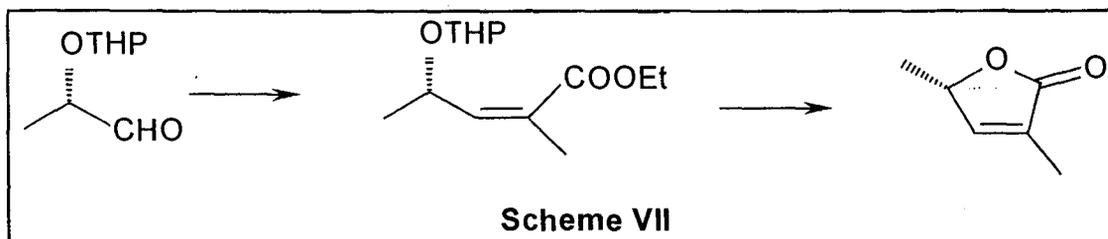
Joullie and Chiarellos method²³ involves preparation of tetronic acid by an intramolecular Grignard reaction, starting from ethyl lactate and then reducing it in presence of Raney nickel to give hydroxyl lactone, Treatment with tosyl chloride, in the presence of triethylamine and dimethylaminopyridine afforded the butenolide (Scheme V).



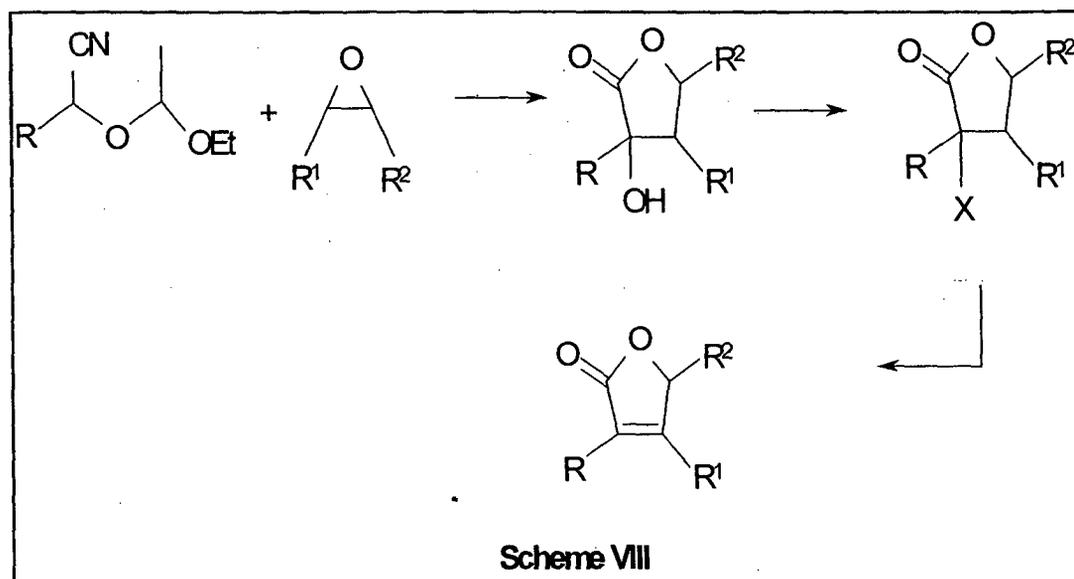
Hoye *et al*²⁴ have described a method, where reaction of manganese carbene complexes in anionic 'lithioxy' version with enynes provided butenolide compounds (Scheme VI).



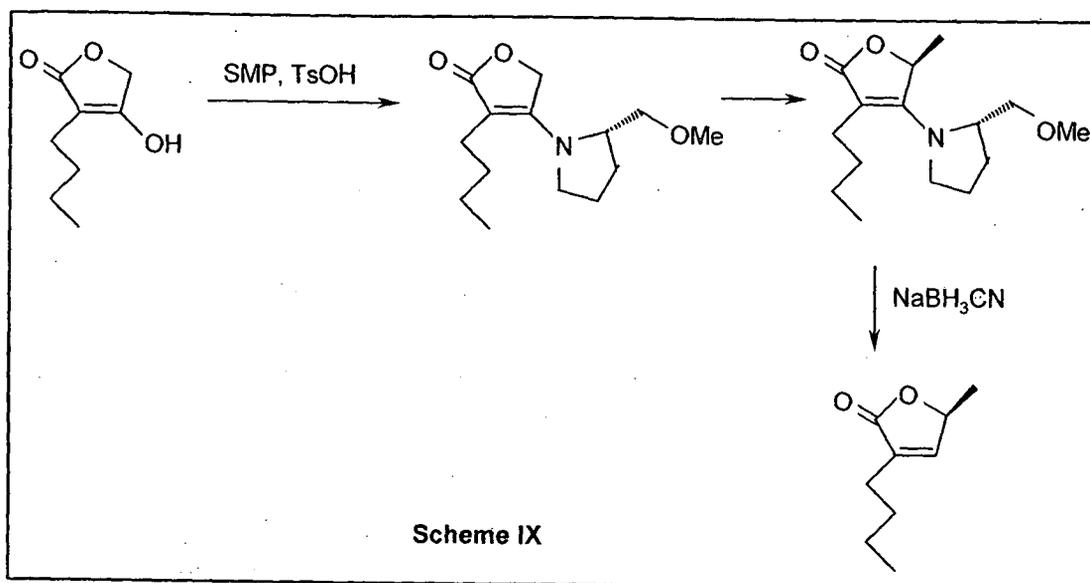
Kang and Lee²⁵ have synthesized butenolide by employing α -O-protected aldehyde derived from ethyl lactate and carrying out Horner-Emmons olefination of the aldehyde with ethyl-2-(dimethylphosphono)-propionate to give unsaturated ester followed by acid hydrolysis (Scheme VII).



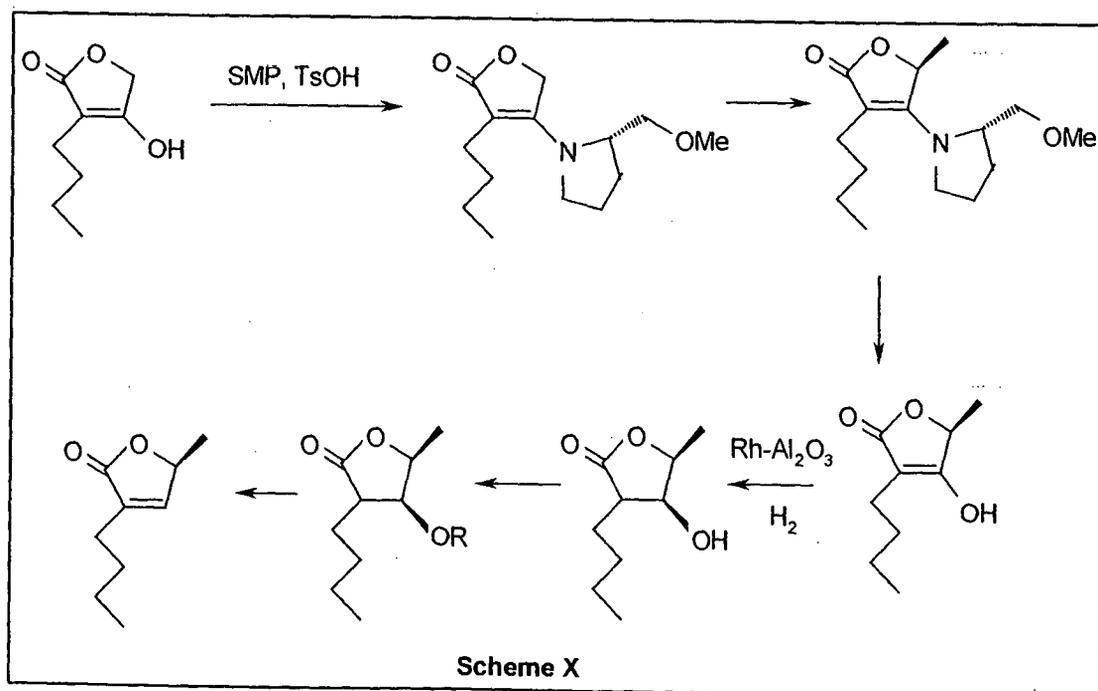
Tamariz *et al*²⁶ have condensed the “*in situ*” generated lithium anion of the protected cyanohydrins with epoxide, followed by acidic hydrolysis to give α -hydroxy- γ -butyrolactones, which were subsequently converted into their halogeno derivatives. Dehydrohalogenation provided α,β -substituted butenolides (Scheme VIII).



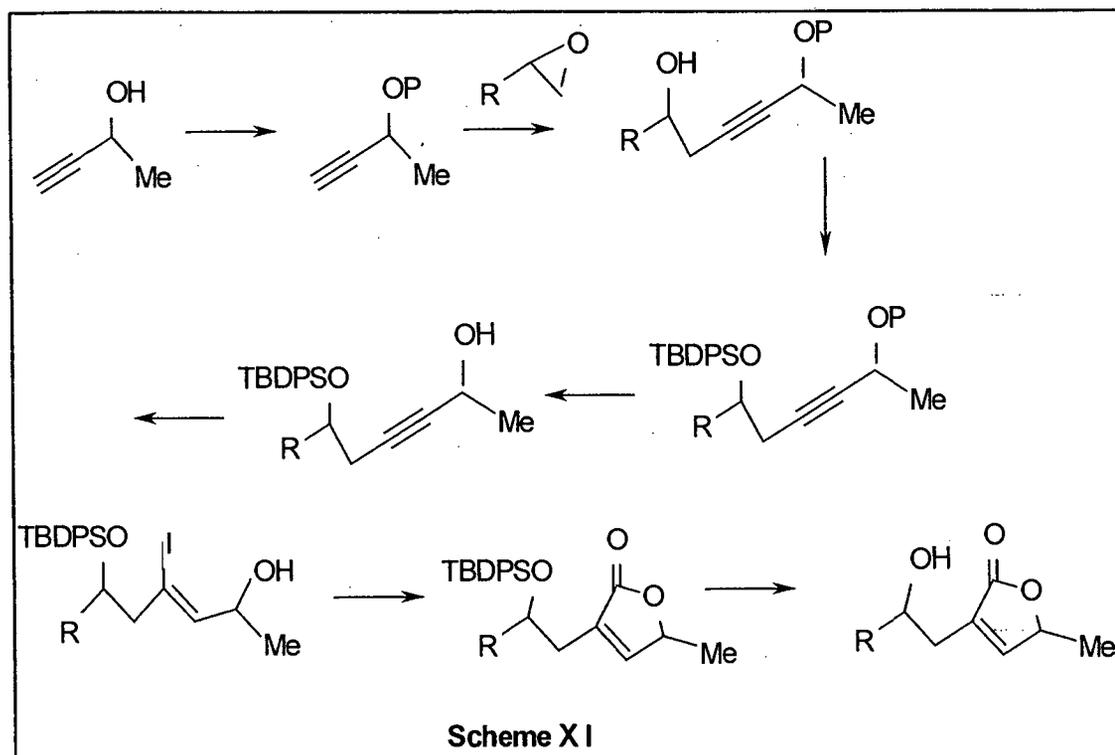
Node and coworkers²⁷ have reported the synthesis of chiral butenolides, by carrying out asymmetric γ -methylation of tetronic acid using (S)-2-methoxymethylpyrrolidine as a chiral auxiliary followed by reduction of enamine with sodium cyanoborohydride (Scheme IX).



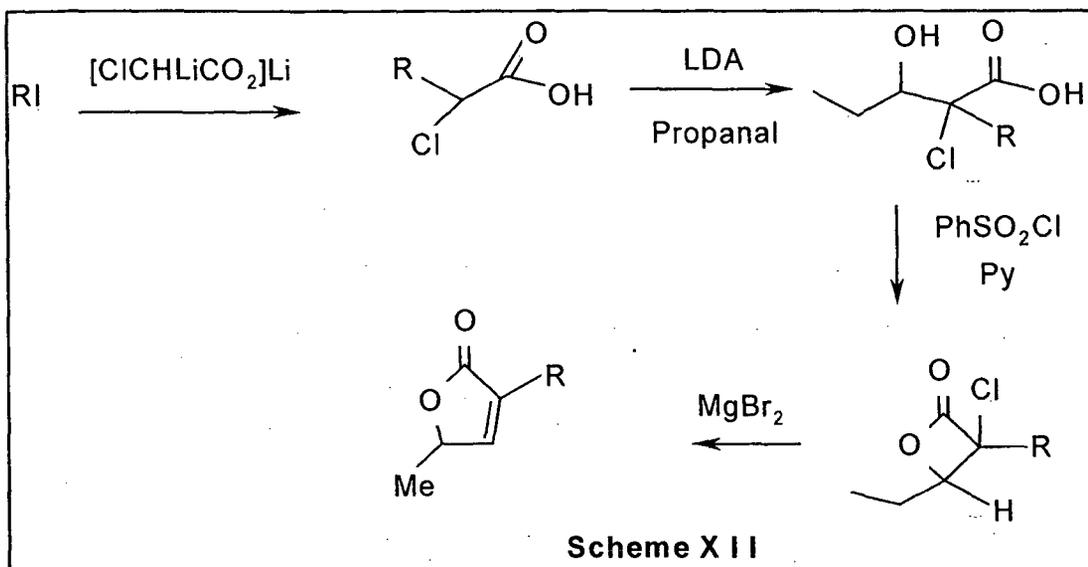
Node and coworkers²⁸, the same group have reported the synthesis of butenolides, by carrying out alkylation at α -position of tetronic acid followed by removal of hydroxyl group by slightly a longer route (**Scheme X**).



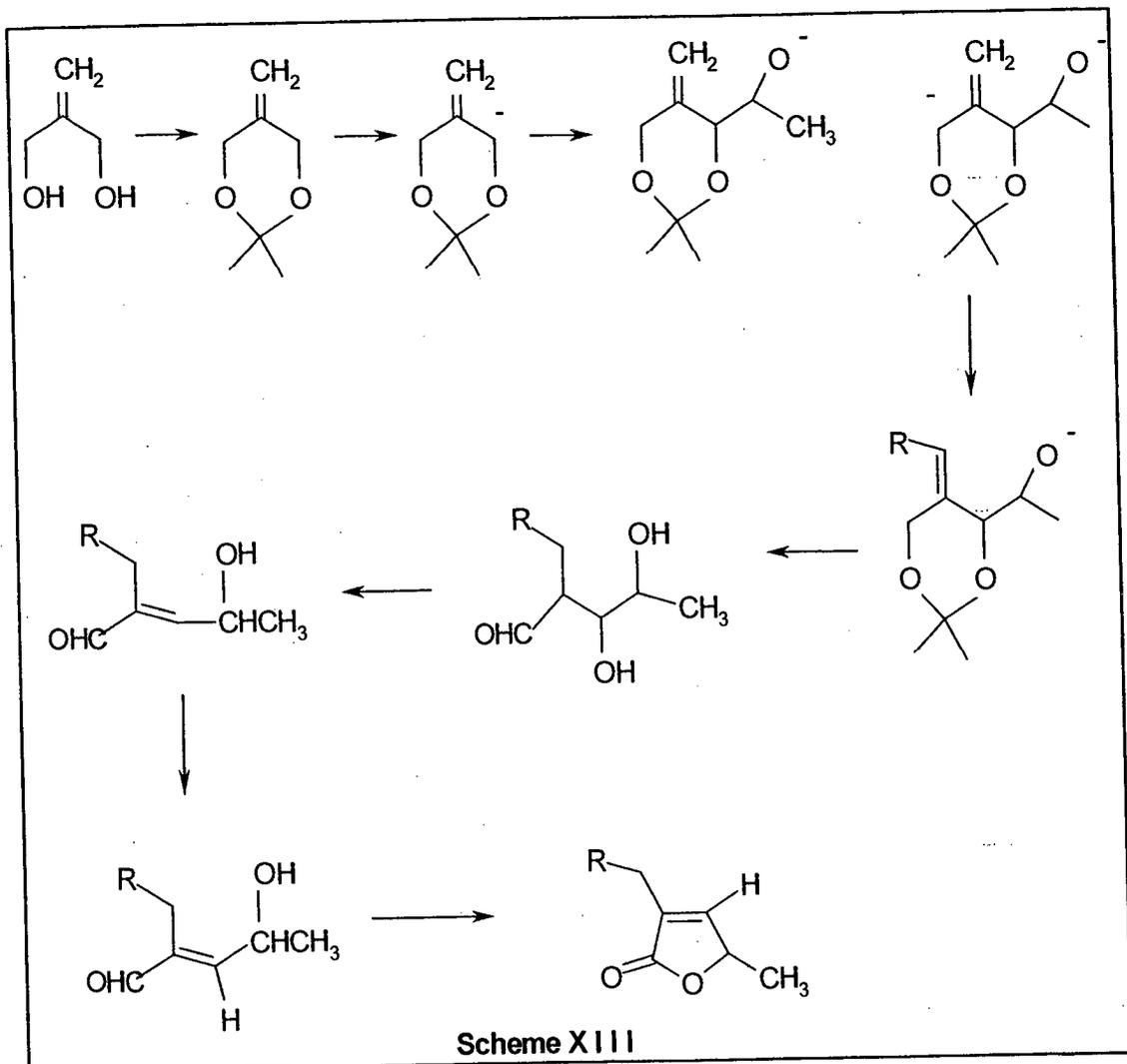
Hoye *et al*²⁹ have synthesized butenolide by employing acetylide derived from 3-butyne-2-ol to prepare propargyl alcohols, which was then converted to vinyl iodides, followed by cyclization (**Scheme XI**).



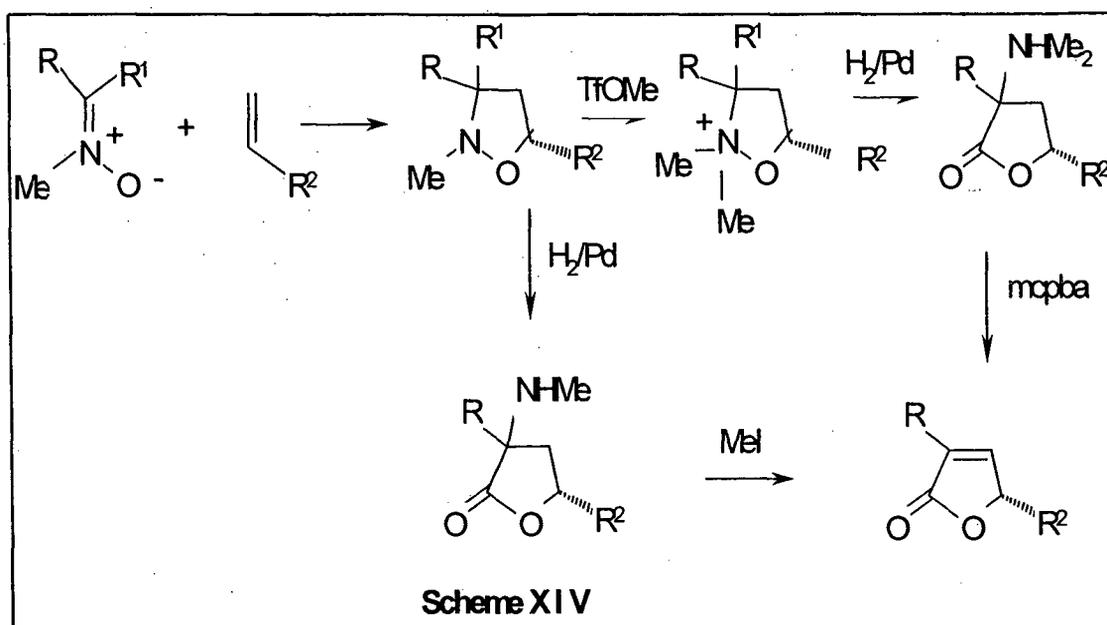
Black *et al*³⁰, reported a four-step synthesis of 3,5-disubstituted butenolides of streptomycetes variety by condensing α -chloro carboxylic acid dianions with propanal to form β -lactones, followed by rearrangement with magnesium bromide (**Scheme XII**).



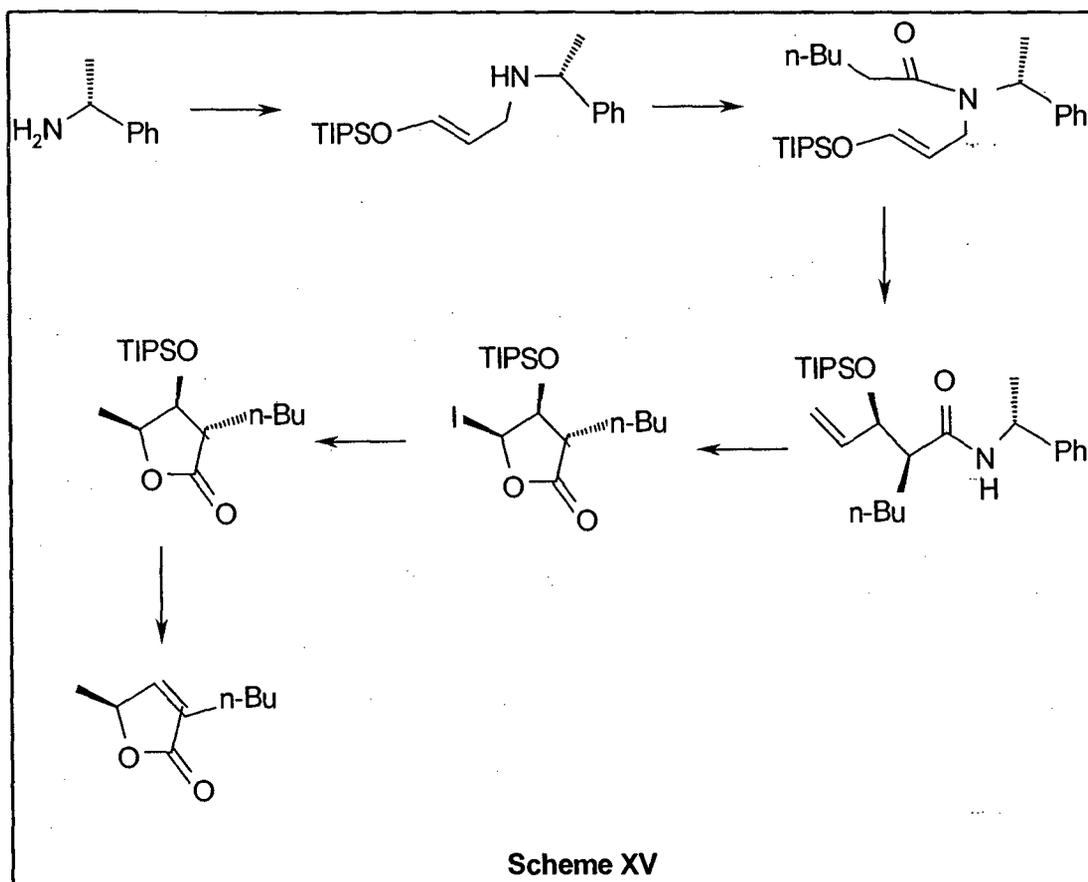
Carlson *et al*³¹ have described the synthetic pathway to volatile streptomyces lactones by making use of anions derived from 2,2-dimethyl-5-methylene-1-3-dioxane. The initial anion formation and the acetaldehyde addition occurs at the α -position and the second anion and alkylation occur at the γ -position. Butenolides were obtained from four membered lactones (**Scheme XIII**).



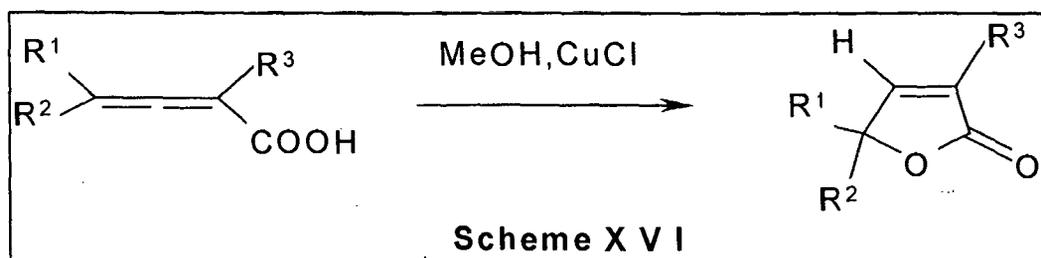
Chiachio and coworkers³² have described the method which involves preparation of isoxazolidines using nitrones and converted isoxazolidines into butenolides by three steps sequence, a) by formation of isoxazolidinium salts, b) hydrogenolysis and c) Cope elimination (**Scheme XIV**).



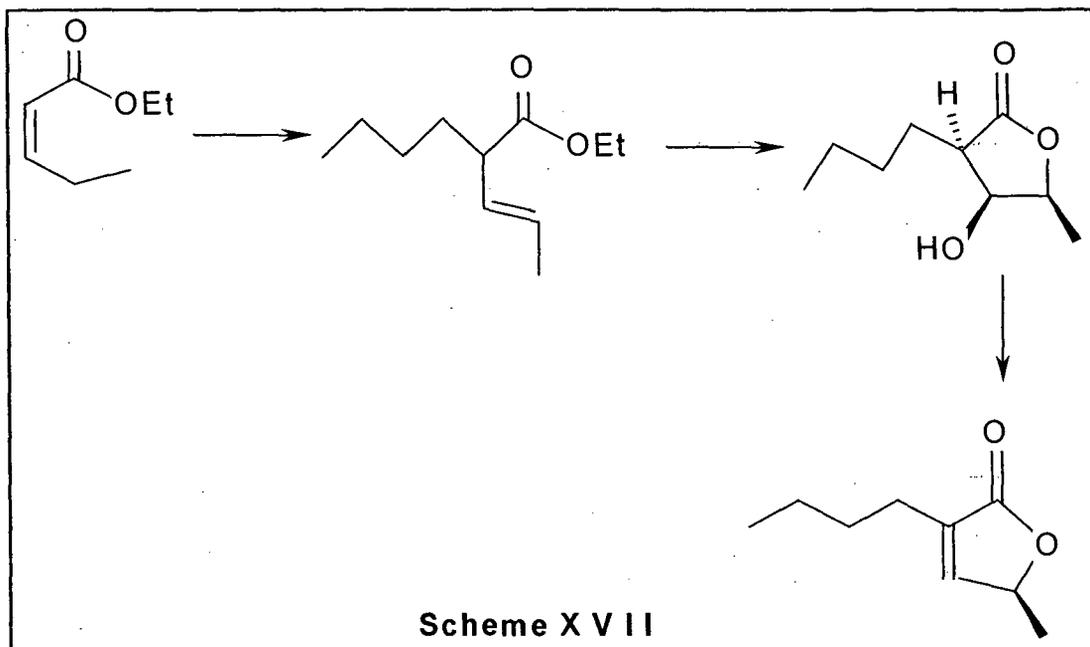
Tsunoda *et al*³³ have developed the asymmetric aza-claisen rearrangement, the thermal [3,3] sigmatropic rearrangement of the enolate of carboxamides and demonstrated its applicability to straightforward short-step synthesis of chiral butenolides (**Scheme XV**).



Ma *et al*³⁴ have developed the CuCl-catalyzed cycloisomerization reaction of 1,2-allenyl carboxylic acid, which provided a cost effective route for the synthesis of α,β -butenolides (Scheme XVI).



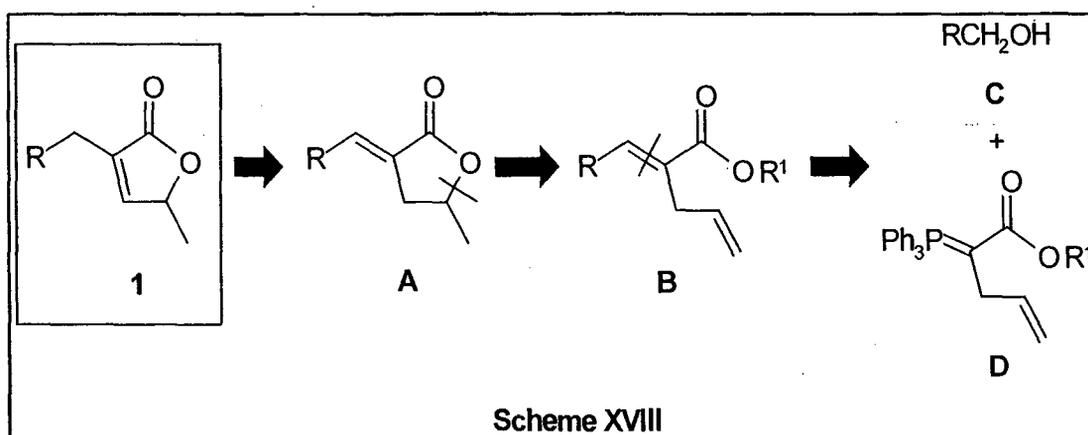
Yao *et al*³⁵ have reported synthesis wherein α -alkylation of ester dienolates were carried out, followed by a subsequent Sharpless dihydroxylation of the β,γ -unsaturated esters. The dehydration of the β -hydroxy lactone afforded the chiral butenolides (Scheme XVII).



3.3 Our Synthetic Strategy

After carefully, going through the literature methods reported for the synthesis of γ -methyl butenolides, we found that, most of these methods are multiple steps or employ costly organometallic reagents or starting materials.

In the present work, we conceptualized as shown in the retrosynthesis below, that the target butenolide could be synthesized by a simple three-step approach (**Scheme XVIII**).

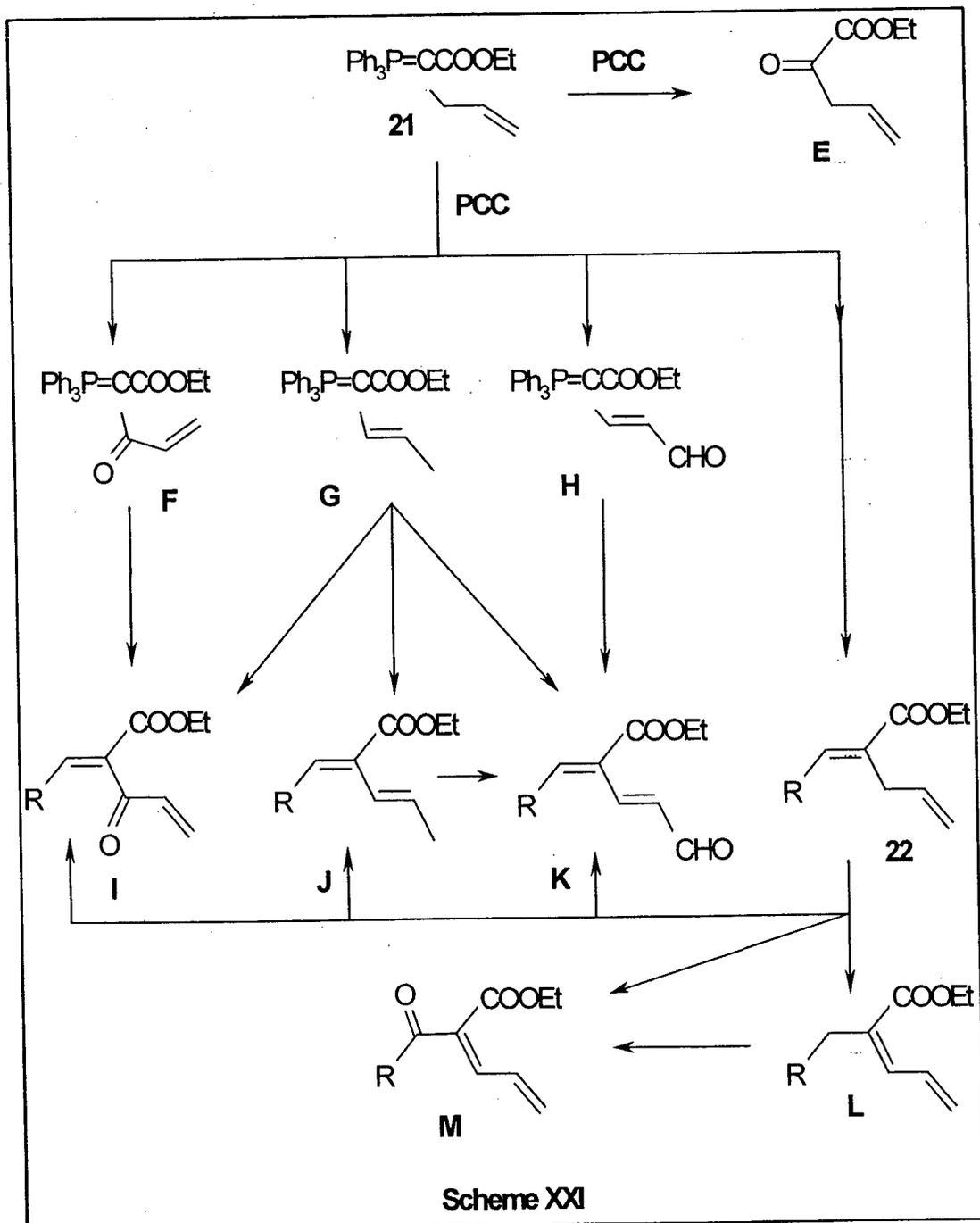


This conceptualization was based on the work reported from our laboratory, which involves domino primary alcohol oxidation-Wittig reaction³⁶ to yield unsaturated ester compounds. In this one pot synthetic strategy, the desired aliphatic alcohols could be oxidized *in situ* and simultaneously condensed with stable phosphoranes to give the α,β -unsaturated compounds (**Scheme XIX**).

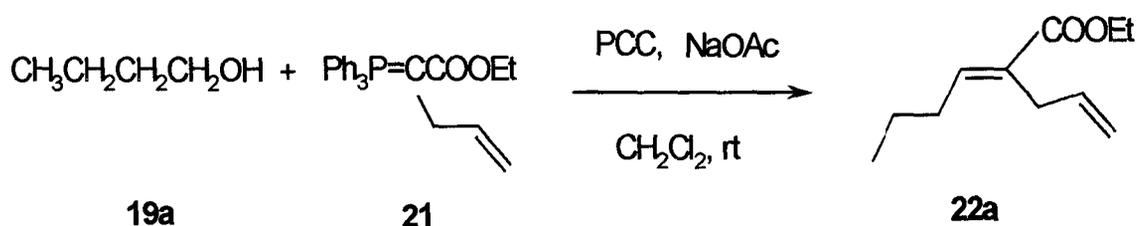
The required allyl phosphorane **21** was prepared by literature³⁷ method and is already been discussed in Chapter 1. As the allyl phosphorane **21** is a functionalised phosphorane, the following possible products were anticipated during the PCC oxidation viz. oxidation of products/phosphorane or isomerisation of double bond. (Scheme XXI), such types of transformations are observed in chromium mediated oxidizing reactions.

The allyl phosphorane **21** in presence of oxidizing agent PCC, itself could get oxidized forming a vicinal dicarbonyl compound **E**. If oxidation of allyl group occurred, then, it could give phosphorane **F** or phosphorane **H**. If isomerisation of double bond takes place, then it could yield phosphorane **G**.

Depending upon the phosphorane formed in this *in situ* one pot reaction condition, the following unsaturated allyl ester products can also be found. Phosphorane **F** could give ester **I**. Similarly, phosphorane **H** could give product **K** and **G** could give product **I**, **J**, and **K**. Phosphorane **21** could give expected ester **22**, which in turn either, could get oxidized to **I**, **K** & **M** or simply the double bond could isomerise to **L** and **J**.



Thus, to begin with, we treated n-butanol **19a** with 1 eq. of allyl phosphorane **21** and 1.2 eq. of PCC and sodium acetate. The reaction mixture was magnetically stirred in dry dichloromethane for one hour. The dark colour change indicated the progress of the reaction. After 1 hr. tlc showed the presence of a new spot along with the spot of triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$). After usual PCC oxidation reaction work up, the crude product obtained was separated by column chromatography over silica gel, using hexanes as eluent, to give a pleasant smelling liquid, in 57% yield.



The ESI mass spectrum had pseudo-molecular $[\text{M}+\text{H}]^+$ ion at m/z 183, corresponding to the elemental composition ($\text{C}_{11}\text{H}_{19}\text{O}_2$), in agreement with the expected structure ($\text{C}_{11}\text{H}_{18}\text{O}_2$). The major fragments at m/z 155(3) $[\text{M} - \text{CO}+\text{H}]^+$, 137(73) $[\text{M} - \text{OEt} + \text{H}]^+$, 109(100) $[\text{M} - \text{COOEt} + \text{H}]^+$, etc, also in agreement with the structure.

Its IR spectrum showed a band at 1716 cm^{-1} which indicated the presence of conjugated carbonyl of ester group.

The $^1\text{H-NMR}$ (CDCl_3) spectrum (**Fig. 3.1**) showed signals at δ 1.29 (t, $J = 7.2$ Hz, 3H) and at δ 4.19 (q, $J = 7.2$ Hz, 2H), indicated the presence of $-\text{OCH}_2\text{CH}_3$ group. The peaks at δ 0.95 (t, $J = 7.5$ Hz, 3H), δ 1.48 (sextet, $J = 7.5$

Hz, 2H,) and δ 2.17 (q, J = 7.5 Hz, 2H) could be assigned to the methyl protons of alkyl group ($\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH=}$) and the two methylene groups ($\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH=}$ & $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH=}$) respectively. The signals at δ 3.07 (br.d, J = 6.0 Hz, 2H), δ 4.99 (m, 2H) and δ 5.81 (m, 1H), indicated the presence of $\text{-CH}_2\text{-CH=CH}_2$ grouping. The peak at δ 6.85 (t, J =7.5 Hz, 1H) was assigned to the olefinic proton ($\text{-CH}_2\text{CH=C}$).

The ^{13}C -NMR (CDCl_3) spectrum (**Fig. 3.2**), displayed the peaks at δ 13.80 (CH_3) and 21.89 (CH_2), could be due to the presence of ($\text{CH}_3\text{-CH}_2\text{-}$) of the alkyl group. The peaks at δ 14.15 (CH_3) and 60.30 (CH_2), could be assigned to carbons of $\text{-OCH}_2\text{CH}_3$ group. The peak at δ 30.46 (CH_2), could be due to the presence of methylene ($\text{-CH}_2\text{-CH=}$) of the alkyl group. The peaks at δ 30.75 (CH_2), 114.84 (CH_2), and 143.45 (CH) could be assigned to the allyl group $\text{-CH}_2\text{CH=CH}_2$. The olefinic carbon CH=C showed the peak at δ 135.55 (CH). The quaternary carbon appearing at δ 130.02 (C) and 167.52 (C) could be assigned to the olefinic carbon CH=C- and the carbonyl carbon C=O of the ester group respectively.

The multiplicities of carbon signals were obtained from DEPT-135 experiments.

Based on the mode of formation and spectral data suggested that the compound could have structure **22a** (*E* isomer) or **22a^l** (*Z* isomer)

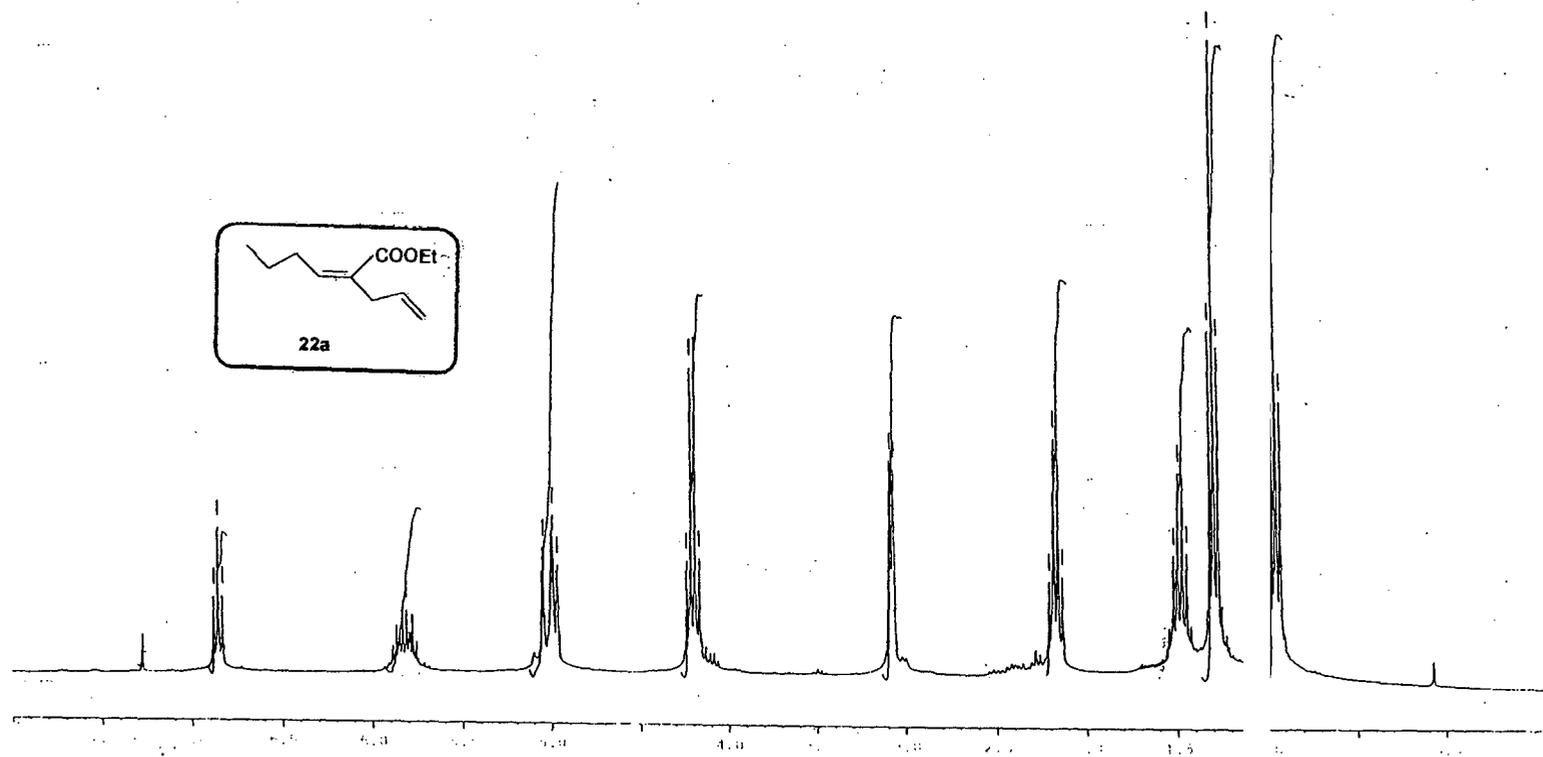


Fig. 3.1 : ¹H NMR spectrum of (E)-Ethyl 2-butylidene-pent-4-enoate (22a)

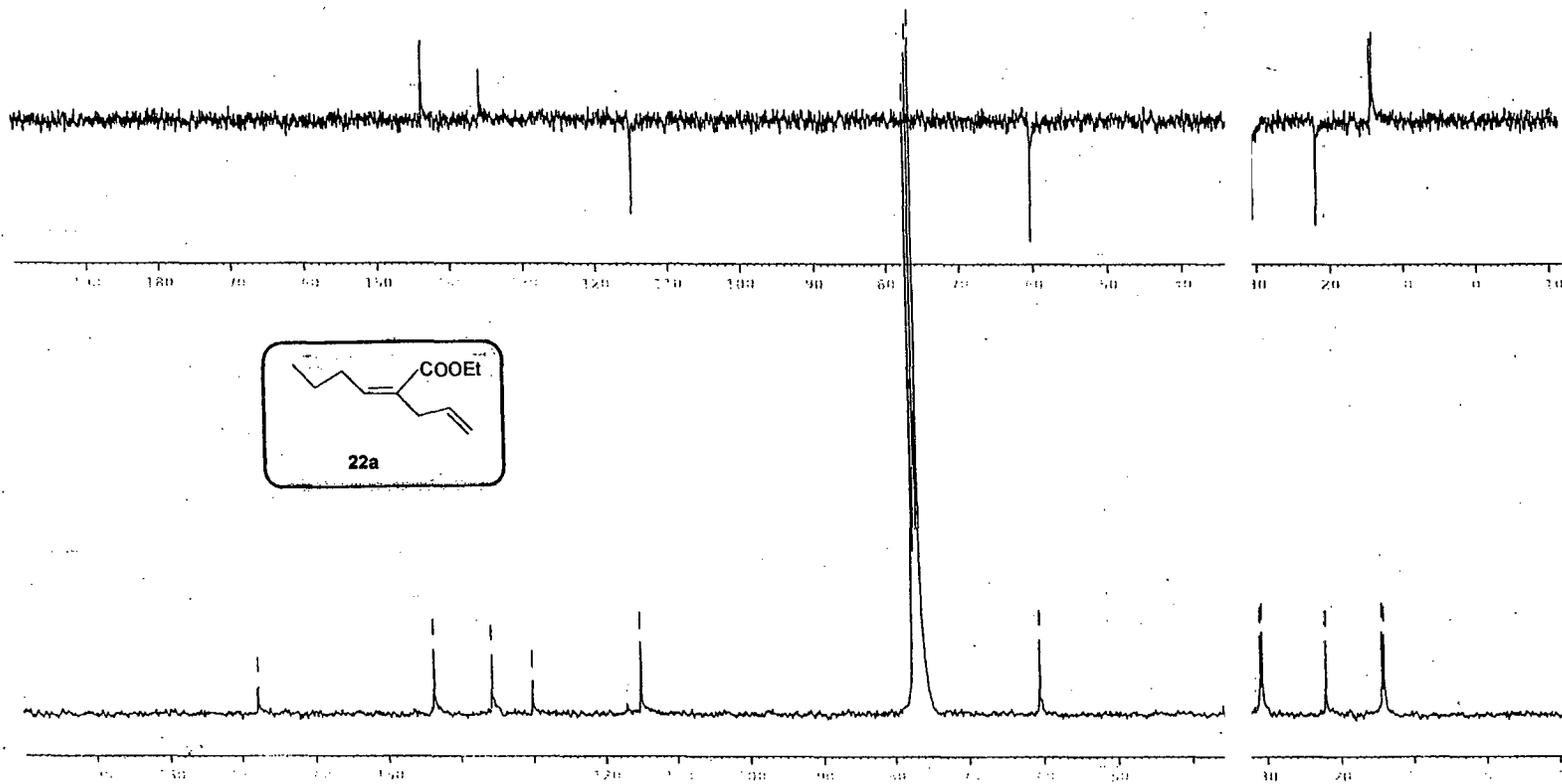
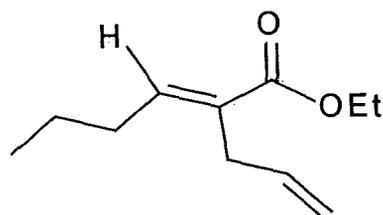
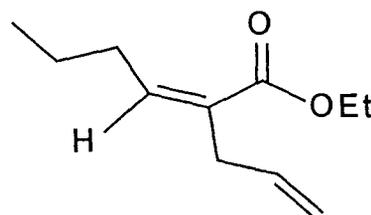


Fig. 3.2 : ^{13}C NMR & DEPT-135 spectrum of (*E*)-Ethyl 2-butylidenepent-4-enoate (22a)

Stereochemistry of the ester 22



22a
E isomer



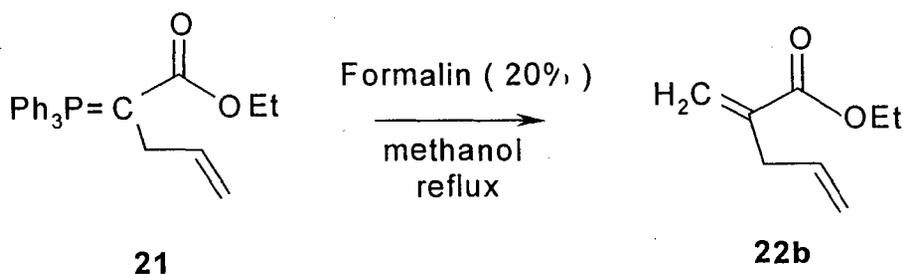
22a'
Z isomer

According to literature, the Wittig reaction on carbonyl compounds is known to provide a mixture of *E* and *Z* isomers of the olefin product. The nature and the ratio of *E-Z* isomers depends upon the reactivities of the carbonyl compound, the phosphorane employed and the solvent used for the reaction. As only one product was obtained it was felt that it was necessary to decide the stereochemistry, whether it was *E* isomer (**22a**) or *Z* isomer (**22a'**).

Since the product was a trisubstituted olefin, the coupling constant of the olefinic protons could not be used to decide the stereochemistry of this ester. The other option would be to compare the chemical shift of the vinyl proton with similar compounds having known *E* and *Z* geometry.

So, it was decided to synthesize the α,β -unsaturated ester **22b** having both the olefinic protons (syn and anti with respect to carboethoxy group). The chemical shift of the two exomethylene protons in the $^1\text{H-NMR}$ spectrum, would then furnish additional information, which will be helpful in assigning the correct stereostructure of the compound **22**.

Hence, the allyl phosphorane **21** was refluxed with aqueous formalin (20%) in methanol for 2 hours. The tlc showed a spot along with the spot of triphenylphosphine oxide. After confirming the disappearance of the starting allylphosphorane on tlc, the reaction mixture was warmed on water bath to remove solvent and after cooling the reaction mixture was extracted with hexanes. The crude product obtained was separated by passing through a column of silica gel, using hexanes as eluent to obtain a pleasant smelling volatile liquid, in 50% yield.



The ESI mass spectrum had pseudo-molecular $[\text{M}+\text{H}]^+$ ion at m/z 141, corresponding to the elemental composition ($\text{C}_8\text{H}_{13}\text{O}_2$), in agreement with the expected structure ($\text{C}_8\text{H}_{12}\text{O}_2$). The major fragments at m/z 113(100) $[\text{M} - \text{CO} + \text{H}]^+$, 95(48) $[\text{M} - \text{OEt} + \text{H}]^+$, 67(36) $[\text{M} - \text{COOEt} + \text{H}]^+$, etc, also in agreement with the structure.

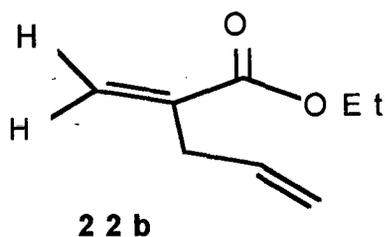
The strong carbonyl peak at 1727 cm^{-1} in the IR spectrum, indicated the presence of unsaturated ester carbonyl.

The $^1\text{H-NMR}$ (CDCl_3) spectrum (**Fig. 3.3**) exhibited signals at δ 1.31 (t, $J = 7.2$ Hz, 3H) and δ 4.22 (q, $J = 7.2$ Hz, 2H), indicated the presence of $-\text{OCH}_2\text{CH}_3$ group. The peaks at δ 3.07 (br.d, $J = 6.6$ Hz, 2H), δ 5.11 (m, 2H) and δ 5.84 (m, 1H), indicated the presence of $-\text{CH}_2\text{CH}=\text{CH}_2$ grouping. The peaks displayed at δ 5.57 (br.s, 1H) and at δ 6.20 (br.s, 1H), indicated the presence of exomethylene protons conjugated to the ester carbonyl.

The ^{13}C NMR (CDCl_3) spectrum (**Fig. 3.4**) exhibited peaks at δ 14.10 (CH_3) & 60.58 (CH_2), which could be assigned to $(-\text{OCH}_2\text{CH}_3)$ group. Peaks at δ 35.82 (CH_2), 116.65 (CH_2) & 135.01 (CH), could be attributed to $(-\text{CH}_2-\text{CH}=\text{CH}_2)$ moiety. The exomethylene and the neighboring quaternary carbons appeared at δ 125.08 (CH_2) and δ 139.18 (C) respectively. The peak at δ 166.86 (C), could be assigned to the carbonyl carbon of conjugated ester.

The multiplicities of carbon signals were obtained from DEPT 135 experiments.

Based on the mode of formation and spectral data, the structure of the compound could be finalized as **22b**.



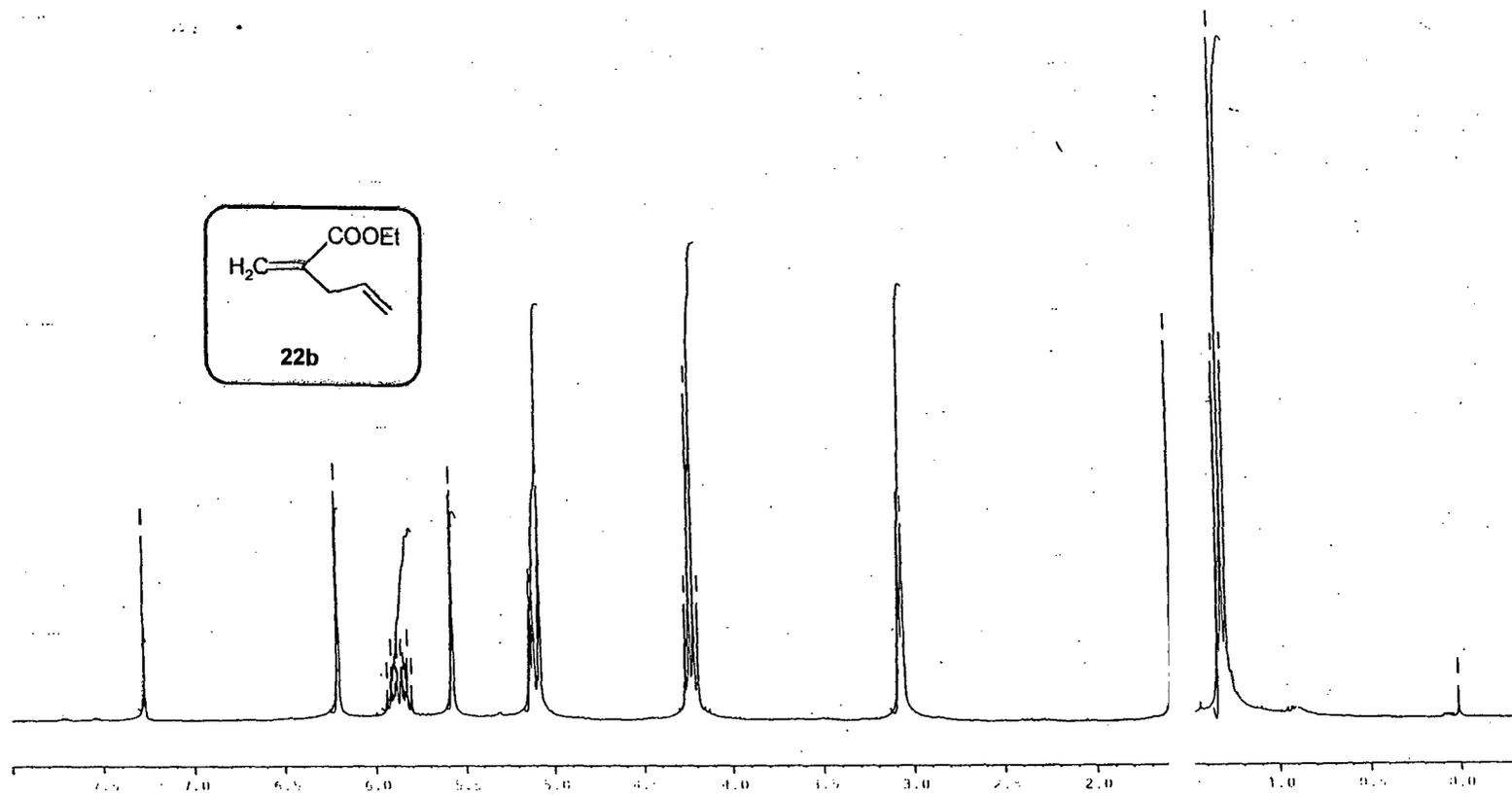


Fig. 3.3 : ¹H NMR spectrum of Ethyl 2-methylenepent-4-enoate (2b)

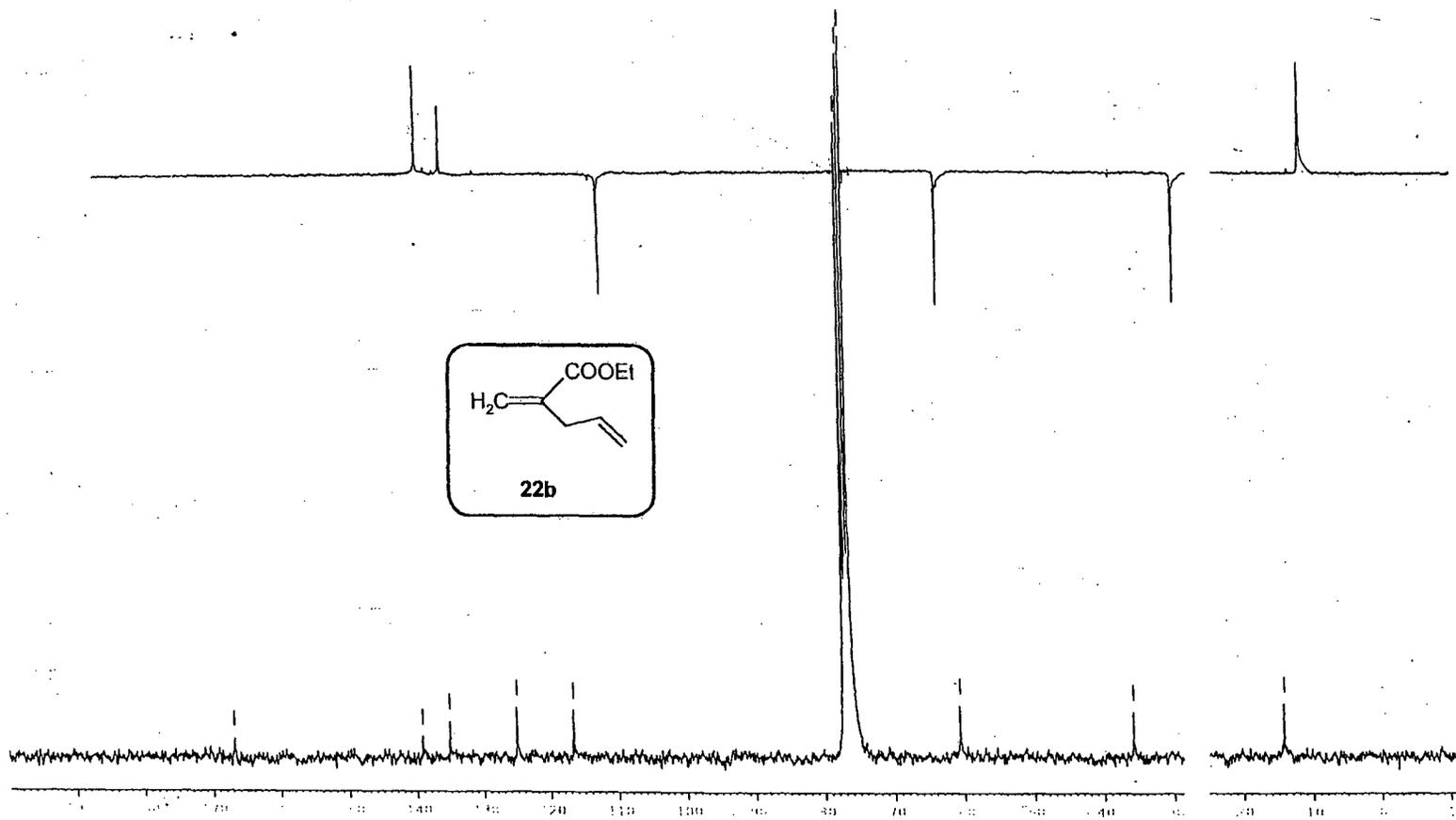
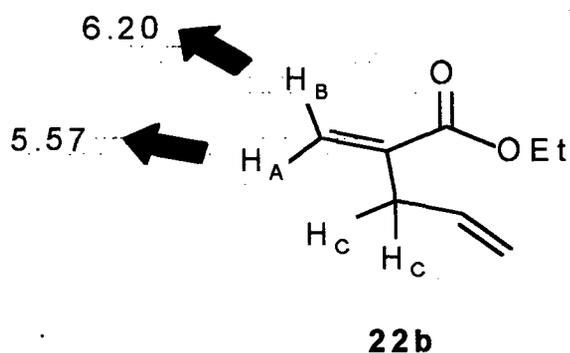
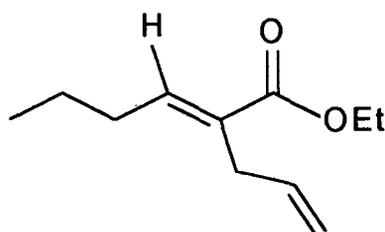


Fig. 3.4 : ^{13}C NMR & DEPT-135 spectrum of Ethyl 2-methylenepent-4-enoate (22b)

The structure **22b** showed two olefinic protons H_A (anti with respect to carboethoxy group) and H_B (syn with respect to carboethoxy group). The H_A proton displayed a broad singlet at δ 5.57 (1H) while, the H_B proton appeared downfield as a broad singlet at δ 6.20 (1H), due to deshielding caused by the carbonyl of carboethoxy group.



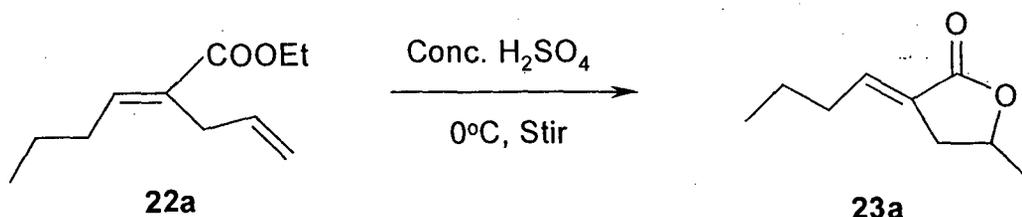
Since the chemical shift (δ 6.85) of the vinyl proton of **22** is closer to that of H_B (δ 6.20) of compound **22b**, the correct structure of the former should be **22a** (*E* isomer).



22a (E isomer)

The second step in the projected synthesis (**Scheme XX**) was to perform cyclisation of the unsaturated ester **22a**.

Ester **22a** was stirred with chilled conc. sulphuric acid at 0°C. After one hour, the reaction mixture was allowed to attain the room temperature. Tlc indicated disappearance of starting compound **22a** from the reaction mixture.



The reaction was quenched by addition of crushed ice and the product was extracted using diethyl ether. The crude product obtained was purified by column chromatography over silica gel using ethyl acetate:hexanes (1:9) as eluent to afford a viscous liquid, in 92% yield.

The ESI mass spectrum had pseudo-molecular $[M+H]^+$ ion at m/z 155, corresponding to the elemental composition ($C_9H_{15}O_2$), in agreement with the expected structure ($C_9H_{14}O_2$). The major fragments at m/z 137(50) $[M - OH_2 + H]^+$, 109(100) $[M - CO - H_2O + H]^+$, etc, also in agreement with the structure.

The IR spectrum exhibited a strong band at 1753 cm^{-1} . This could be due to the carbonyl group of the five membered lactone.

The $^1\text{H-NMR}$ (CDCl_3) spectrum (**Fig. 3.5**) showed peaks at δ 0.95 (t, $J = 7.5\text{ Hz}$, 3H), δ 1.51 (m, 2H), δ 2.16 (m, 2H) and δ 6.73 (br.t, 1H), could be

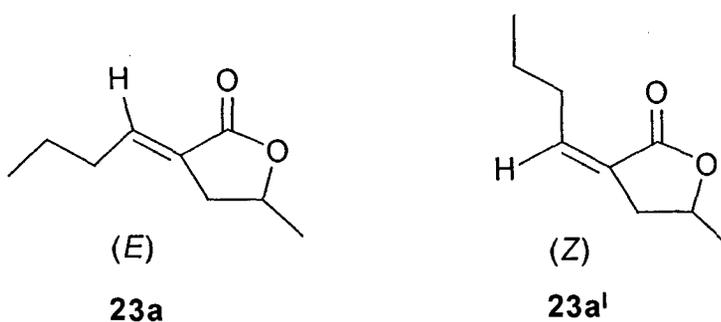
assigned to methyl group ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{}$), two methylene groups ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{}$) & ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{}$) and the olefinic proton ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{}$) respectively. The signals at δ 1.42 (d, $J = 6.3$ Hz, 3H) and δ 4.66 (m, 1H), could be assigned to the protons of $-\text{CHCH}_3$ group, where as the peaks at δ 2.35-2.47 (m, 1H) and δ 2.95-3.06 (m, 1H), could be due to the methylene protons of ($\text{HCH}-\text{CH}$) grouping.

The ^{13}C NMR spectrum (Fig. 3.6)

δ 13.78 (CH_3), 21.47 (CH_2), 22.26 (CH_3), 32.16 (CH_2), 32.91 (CH_2), 73.94 (CH), 126.67 (CH), 140.55 ($=\text{CH}$), 170.72 ($\text{C}=\text{O}$).

The multiplicities of carbon signals were obtained from DEPT 135 experiments.

The above spectral data suggested either structure **23a** or **23a'**, differing in geometries at the double bond i.e. (ester *E* or *Z*).



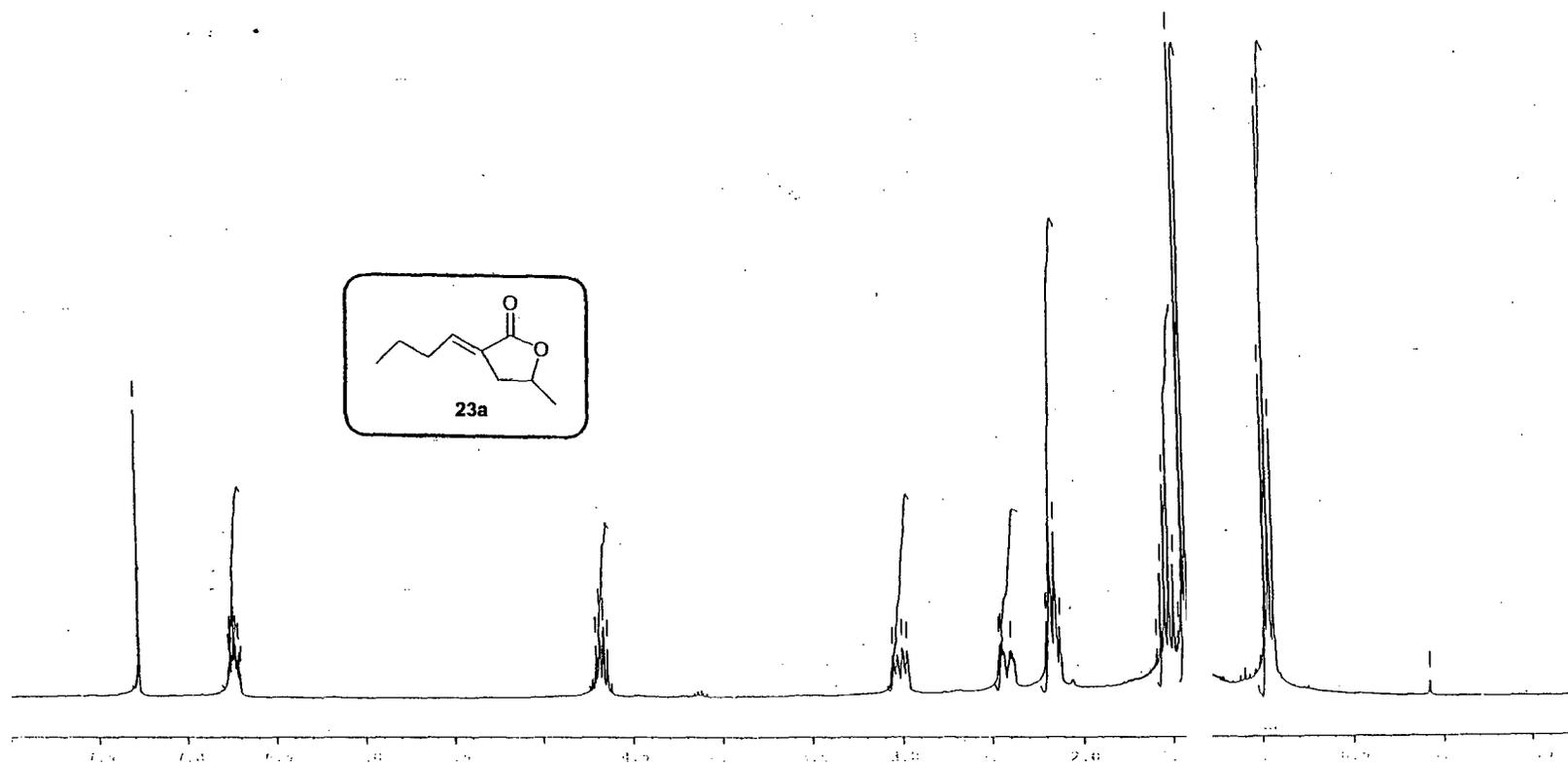


Fig. 3.5 : ¹H NMR spectrum of 5-methyl-3-[(E)-butylidene]-dihydrofuran-2(5H)-one (23a).

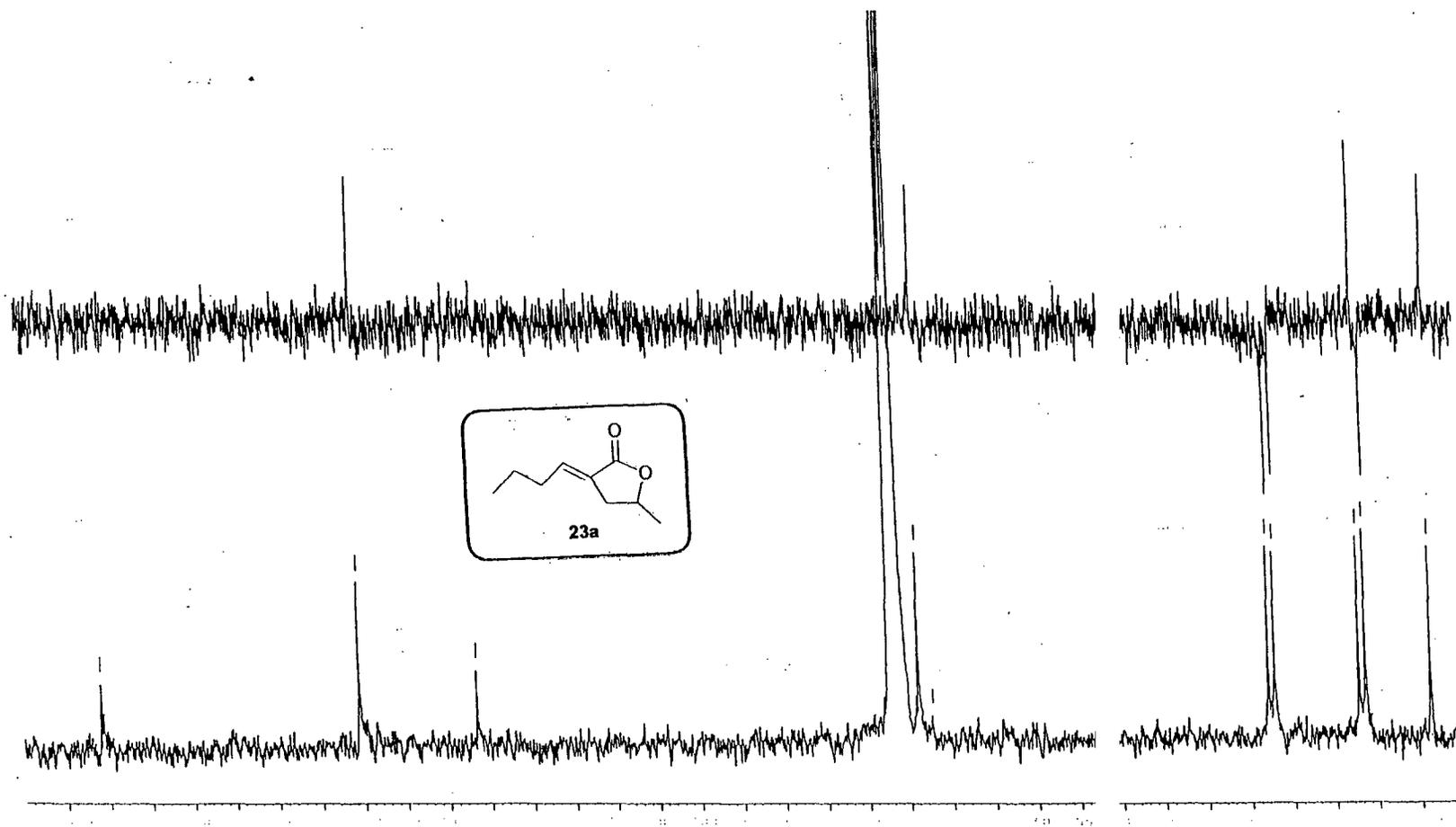


Fig. 3.6 : ^{13}C NMR & DEPT-135 spectrum of 5-methyl-3-[(*E*)-butylidene]-dihydrofuran-2(5H)-one (23a).

Based on the mode of formation, downfield chemical shift (δ 6.73) of the olefin proton (Lit³⁸, chemical shift in case of Z isomer, δ 5.96) and comparison of the data with the literature³⁸ data for the (E) isomer, the structure 23a was assigned to the compound.

The observed and the reported spectral values³⁸ are mentioned below.

Observed spectral values

IR(ν_{\max}): 1753 cm^{-1}

¹H-NMR (CDCl₃): 300 MHz

δ 0.95	t, (J= 7.5 Hz)	3H	-CH ₂ CH ₃
δ 1.42	d, (J= 6.3 Hz)	3H	-CHCH ₃
δ 1.51	m	2H	-CH ₂ CH ₃
δ 2.16	m	2H	-CH ₂ CH=
δ 2.35-2.47	m	1H	-HCHCH
δ 2.95-3.06	m	1H	-HCHCH
δ 4.66	m	1H	-CHCH ₃
δ 6.73	m	1H	=CH

Reported spectral values³⁸

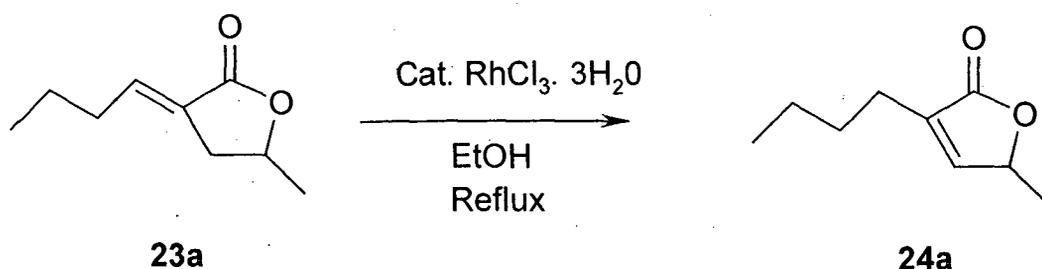
1750 cm^{-1}

¹H-NMR (CCl₄): 100 MHz

δ 0.92	t, (J= 7 Hz)	3H	CH ₃
δ 1.28-1.60	m	5H	CH ₃ -CH ₂
δ 1.96-3.00	m	4H	(2 x CH ₂)
δ 4.42	m	1H	(CH-O-)
δ 6.36	m	1H	CH=C

The last step was to carry out the isomerisation of the exocyclic double bond to the endocyclic double bond, which would give us the desired butenolides skeleton. Literature mentions several methods for such acid catalysed isomerisation of double bond.³⁹ Our initial attempts using Raney Ni¹² was not successful. Another catalyst known to bring such transformations is RhCl₃.3H₂O⁴⁰.

The isomerisation of the exocyclic double bond was carried out by refluxing α,β -unsaturated lactone **23a** with catalytical amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ in degassed absolute alcohol for 24 hours. The crude product was purified by column chromatography over by silica gel using ethyl acetate: hexanes (1:9) as eluent to furnish an oily product, in 77% yield.



The ESI mass spectrum had pseudo-molecular $[\text{M}+\text{H}]^+$ ion at m/z 155, corresponding to the elemental composition ($\text{C}_9\text{H}_{15}\text{O}_2$), in agreement with the expected structure ($\text{C}_9\text{H}_{14}\text{O}_2$). The major fragments at m/z 137(47) $[\text{M} - \text{H}_2\text{O} + \text{H}]^+$, 109(100) $[\text{M} - \text{CO} - \text{H}_2\text{O} + \text{H}]^+$, etc, also in agreement with the structure.

The IR spectrum exhibited a strong band at 1753 cm^{-1} which could be due to the carbonyl group of the five membered lactone.

The $^1\text{H-NMR}$ (CDCl_3) spectrum (Fig. 3.7) showed signals at δ 0.87 (t, $J = 7.5\text{ Hz}$, 3H), δ 1.19-1.53 (m, 4H) and δ 2.22 (t, $J = 7.5\text{ Hz}$, 2H), could be assigned to the methyl group ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$) and methylene groups ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$) & ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$) respectively. The peaks at δ 1.34 (d, $J = 6.0\text{ Hz}$, 3H) and δ 4.95 (q, 1H), could be assigned to the protons of $-\text{CHCH}_3$ group. The signal observed at δ 6.96 (m, 1H) could be assigned to the trisubstituted olefinic proton.

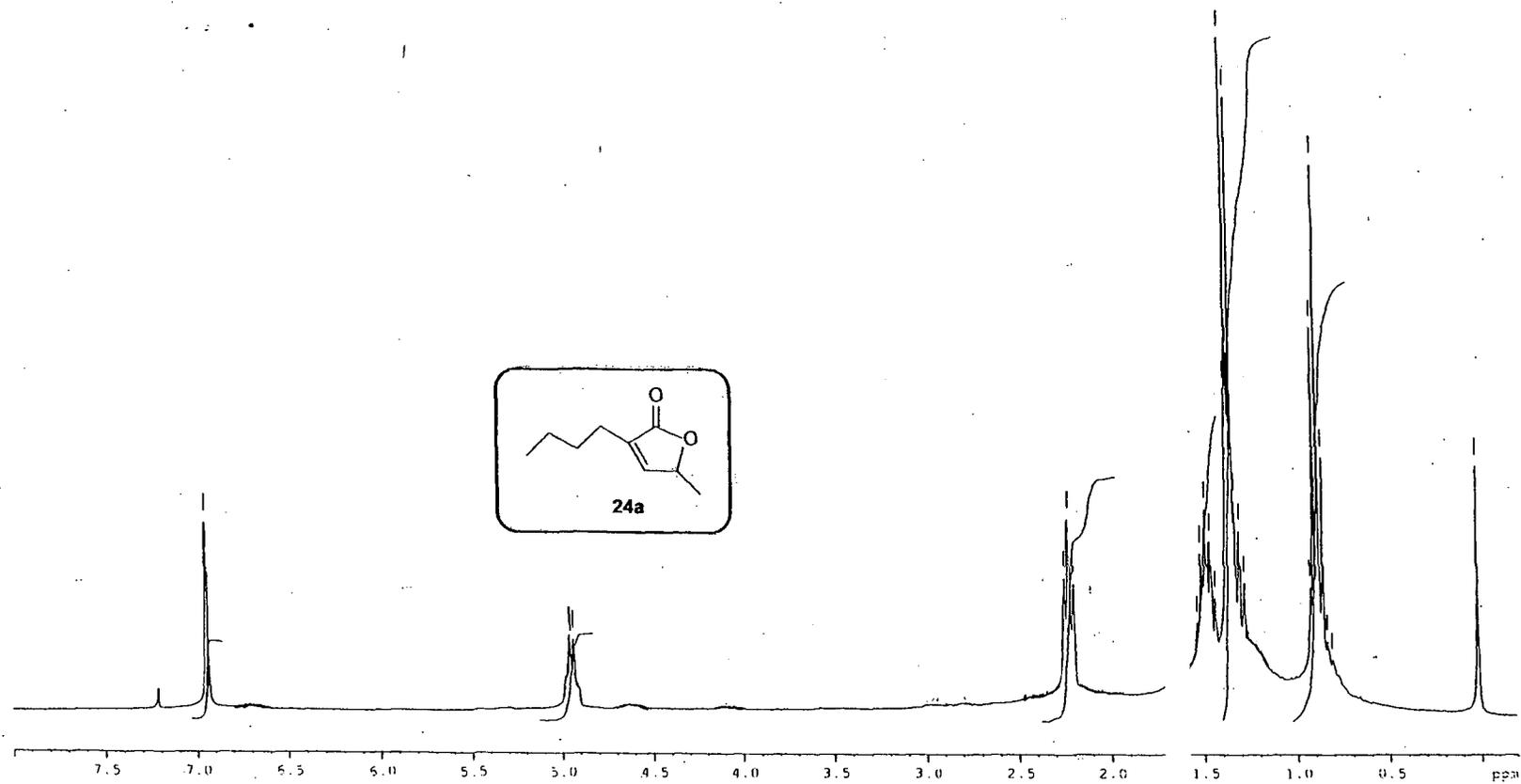


Fig. 3.7 : ^1H NMR spectrum of 3-Butyl-5-methyl-2[5H]-furanone (24a).

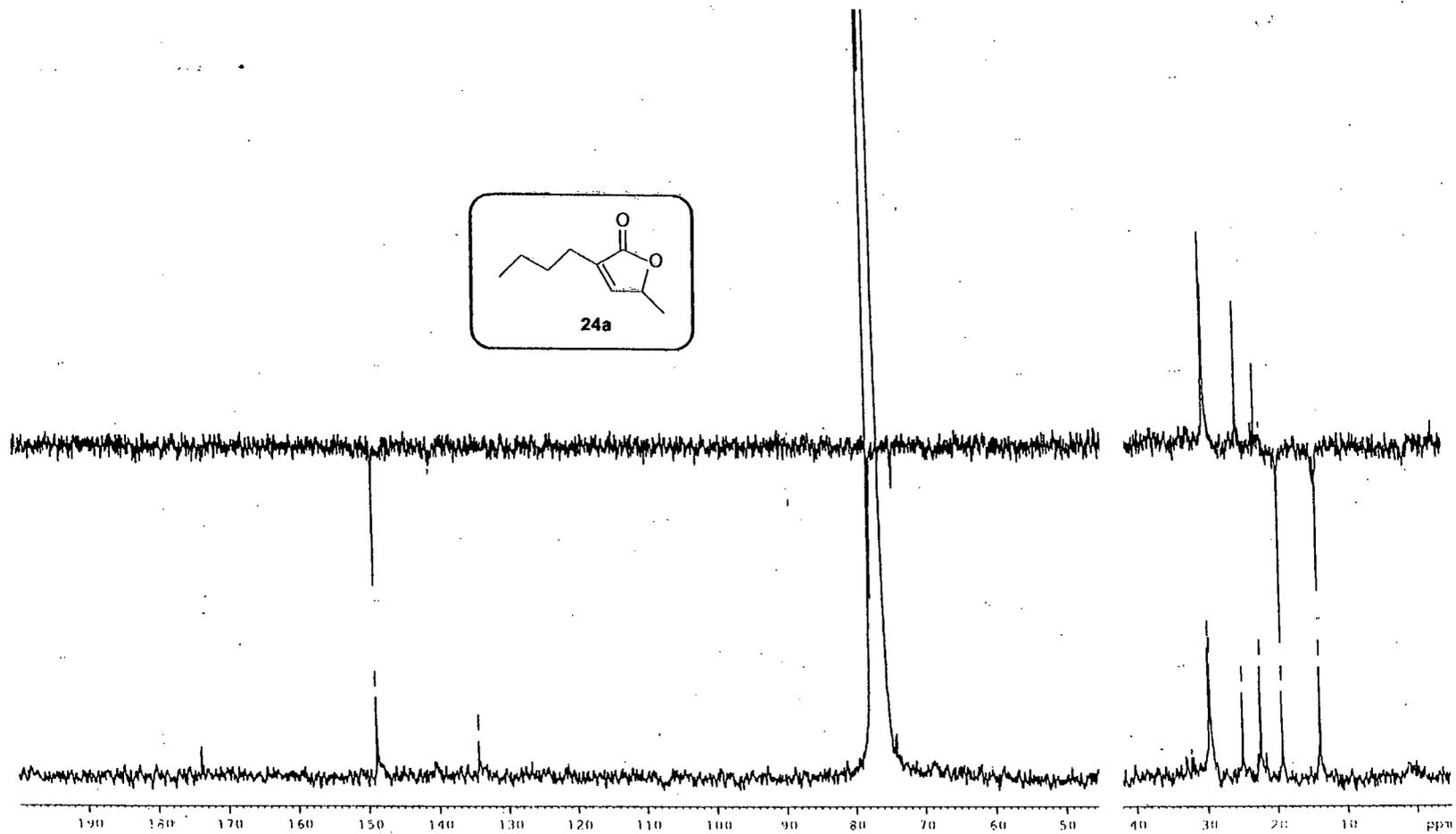


Fig. 3.8 : ^{13}C NMR & DEPT-135 spectrum of 3-Butyl-5-methyl-2[5H]-furanone (24a).

The ^{13}C NMR values are mentioned below (Fig. 3.8).

δ 13.68 (CH₃), 19.13 (CH₃), 22.18 (CH₂), 24.78 (CH₂), 29.43 (CH₂), 75.45 (CH), 134.24 (C), 148.73 (=CH), 173.60 (C=O)

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data the structure **24a** was assigned to the product. The observed spectral values are in close agreement with the reported values⁴¹ for this natural product **7**. The observed and the reported spectral values are mentioned below.

Observed spectral values

Reported spectral values⁴¹

IR(ν_{max}): 1753 cm⁻¹

1750 cm⁻¹

$^1\text{H-NMR}$ (CDCl₃)

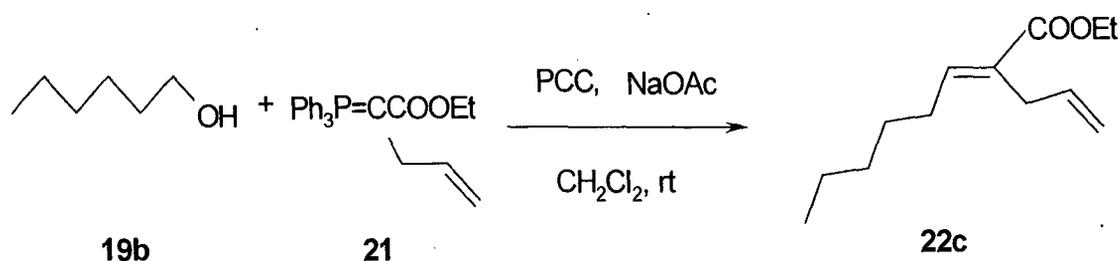
δ 0.87	t, ($J=7.5$ Hz)	3H	-CH ₂ CH ₃	δ 0.92	m	3H
δ 1.19-1.53	m	4H	-CH ₂ CH ₂ -	δ 1.05-1.73	complex absorption	4H
δ 1.34	d, ($J=6.0$ Hz)	3H	-CHCH ₃	δ 1.39	d, ($J=7.21$ Hz)	3H
δ 2.22	t, ($J=7.5$ Hz)	2H	-CH ₂ -	δ 2.23	complex absorption	2H
δ 4.95	q, ($J=7.5$ Hz)	1H	-CHCH ₃	δ 4.96	q, ($J=7.21$ Hz)	1H
δ 6.96	m	1H	=CH	δ 6.96	m	1H

C^{13} NMR (CDCl₃) :

Observed Values	δ 13.68 (CH ₃), 19.13 (CH ₃), 22.18 (CH ₂), 24.78 (CH ₂), 29.43 (CH ₂), 75.45 (CH), 134.24 (C), 148.73 (=CH), 173.60 (C=O)
Reported Values ⁴¹	δ 13.46, 18.94, 22.02, 24.63, 29.33, 77.19, 133.93, 148.90, 173.63

After successfully synthesizing one naturally occurring butenolide **7** using the domino Wittig reaction effectively, we thought of establishing the generality of the reaction by targeting ourselves to the synthesis of two more naturally occurring butenolides **8** and **9**.

So, we treated n-hexanol **19b** with 1 eq. of allyl phosphorane **21** and 1.2 eq. of PCC and sodium acetate. The reaction mixture was magnetically stirred in dry dichloromethane for one hour. The appearance of dark colour for the reaction mixture indicated the progress of the reaction. After 1 h, tlc showed the presence of a new spot along with the spot of triphenylphosphine oxide. After usual PCC oxidation reaction work up the crude product obtained was separated by column chromatography over silica gel using hexanes as eluent, to give a pleasant smelling liquid, in 60% yield.



The high-resolution mass spectrum (HRMS) of the compound had a strong peak at m/z 211.1696, presumably due to $(M+H)^+$ pseudo ion. The elemental composition of which was determined to be C₁₃H₂₀O₂.

HRMS: m/z calcd for C₁₃H₂₀O₂ ($M + H^+$): 211.1698; found: 211.1696.

IR(ν_{\max}): 1722 (s), 1653 (w), 1643 (w) cm⁻¹

^1H NMR spectral data is given below.

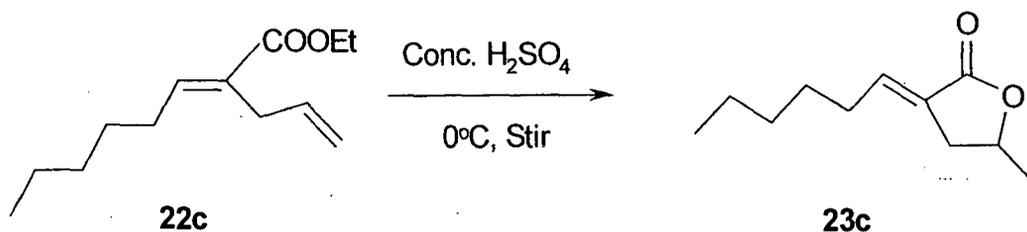
δ 0.82	t, $J = 7.5$ Hz	3H	$-\text{CH}_2\text{CH}_3$
δ 1.11-1.36	m	9H	3x ($-\text{CH}_2-$) & $-\text{OCH}_2\text{CH}_3$
δ 2.11	m	2H	$-\text{CH}_2-\text{C}=\text{}$
δ 3.00	d, $J = 6.0$ Hz	2H	$-\text{CH}_2-\text{CH}=\text{CH}_2$
δ 4.12	q, $J = 7.2$ Hz	2H	$-\text{OCH}_2\text{CH}_3$
δ 4.91	m	2H	$-\text{CH}_2-\text{CH}=\text{CH}_2$
δ 5.74	m	1H	$-\text{CH}_2-\text{CH}=\text{CH}_2$
δ 6.77	t, $J = 7.5$ Hz	1H	$=\text{CH}$

The ^{13}C NMR values are mentioned below.

δ 13.97 (CH_3), 14.28 (CH_3), 22.49 (CH_2), 28.40 (CH_2), 28.54 (CH_2), 30.84 (CH_2), 31.62 (CH_2), 60.44 (OCH_2), 114.96 ($\text{CH}=\text{CH}_2$), 129.86 (C), 135.66 ($\text{CH}=\text{CH}_2$), 143.92 ($=\text{CH}$), 167.69 ($\text{C}=\text{O}$)

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data the structure **22c** was assigned to the ester having *E* geometry.

Ester **22c** was stirred with chilled conc. sulphuric acid at 0°C . After one hour, the reaction mixture was allowed to attain the room temperature. Tlc indicated the disappearance of starting ester. The reaction was quenched by addition of crushed ice and the reaction mixture was extracted with diethyl ether. The crude product obtained was purified by column chromatography over silica gel using ethyl acetate:hexanes (1:9) as eluent to afford an oily liquid, 89% yield.



The high-resolution mass spectrum (HRMS) of the compound had a strong peak at m/z 183.1376, presumably due to $(M+H)^+$ pseudo ion. The elemental composition of which was determined to be $\text{C}_{11}\text{H}_{18}\text{O}_2$.

HRMS: m/z calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$ ($M + H^+$): 183.1385; found: 183.1376.

IR(ν_{max}): 1753 (s), 1685 (w) cm^{-1}

^1H NMR spectral data is given below.

δ 0.90	t, $J = 6.6$ Hz	3H	$-\text{CH}_2\text{CH}_3$
δ 1.25-1.50	m	6H	3x ($-\text{CH}_2-$)
δ 1.42	d, $J = 6.3$ Hz	3H	$-\text{CH}-\text{CH}_3$
δ 2.18	q, $J = 7.2$ Hz	2H	$-\text{CH}_2-\text{CH}=\text{}$
δ 2.40	m	1H	$-\text{HCH}-\text{CH}$
δ 3.00	bdd, $J = 16.8, 7.8$ Hz	1H	$-\text{HCH}-\text{CH}$
δ 4.67	m	1H	$-\text{CH}$
δ 6.73	t, $J = 7.5$ Hz	1H	$=\text{CH}$

The ^{13}C NMR values are mentioned below.

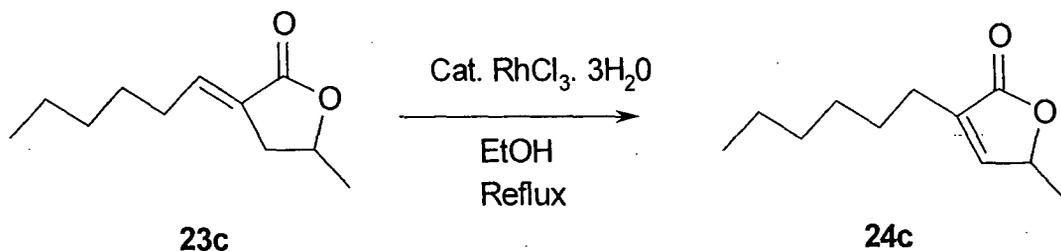
δ 13.91(CH₃), 22.25 (CH₃), 22.40 (CH₂), 27.80 (CH₂), 30.13 (CH₂), 31.43 (CH₂), 32.88 (CH₂), 73.94 (CH), 126.45 (C), 140.87 (=C), 170.96 (C=O).

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data, the structure **23c** was assigned to the product having *E* geometry.

The reported values³⁸ of ^1H -NMR for the compound **23c** is mentioned below.

δ 0.88	m	3H	CH ₃
δ 1.00-1.56	m	9H	CH ₃ & 3 CH ₂
δ 1.98-3.06	m	4H	2 CH ₂
δ 4.50	m	1H	CH-O-
δ 6.44	m	1H	CH=C

The isomerisation was carried out by refluxing α,β -unsaturated lactone **23c** with catalytical amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ in degassed absolute alcohol for 24 hours. The crude product was purified by column chromatography over silica gel using ethyl acetate: hexanes (1:9) as eluent to furnish a viscous liquid product, in 93% yield.



The high-resolution mass spectrum (HRMS) (Fig. 3.9) of the compound had a strong peak at m/z 183.1393, presumably due to $(M+H)^+$ pseudo ion. The elemental composition of which was determined to be $C_{11}H_{18}O_2$.

HRMS: m/z calcd for $C_{11}H_{18}O_2$ ($M + H^+$): 183.1385; found: 183.1393.

IR (neat): 1750 (C=O), 1650 (C=C) cm^{-1} .

1H NMR spectral data is given below (Fig. 3.10).

δ 0.88	t, $J = 6.3$ Hz	3H	-CH ₂ CH ₃
δ 1.26-1.60	m	8H	4x (-CH ₂ -)
δ 1.47	d, $J = 6.6$ Hz	3H	-CH-CH ₃
δ 2.27	t, $J = 7.5$ Hz	2H	=C-CH ₂
δ 5.00	m	1H	-CH-CH ₃
δ 6.99	bd, $J = 0.9$ Hz	1H	=CH

^{13}C NMR spectral data is given below (Fig. 3.11).

δ 14.01 (CH₃), 19.12 (CH₃), 22.51 (CH₂), 22.16 (CH₂), 27.35 (CH₂), 28.82 (CH₂), 31.48 (CH₂), 73.87 (CH), 134.35 (C), 148.83 (=CH), 173.87 (C=O).

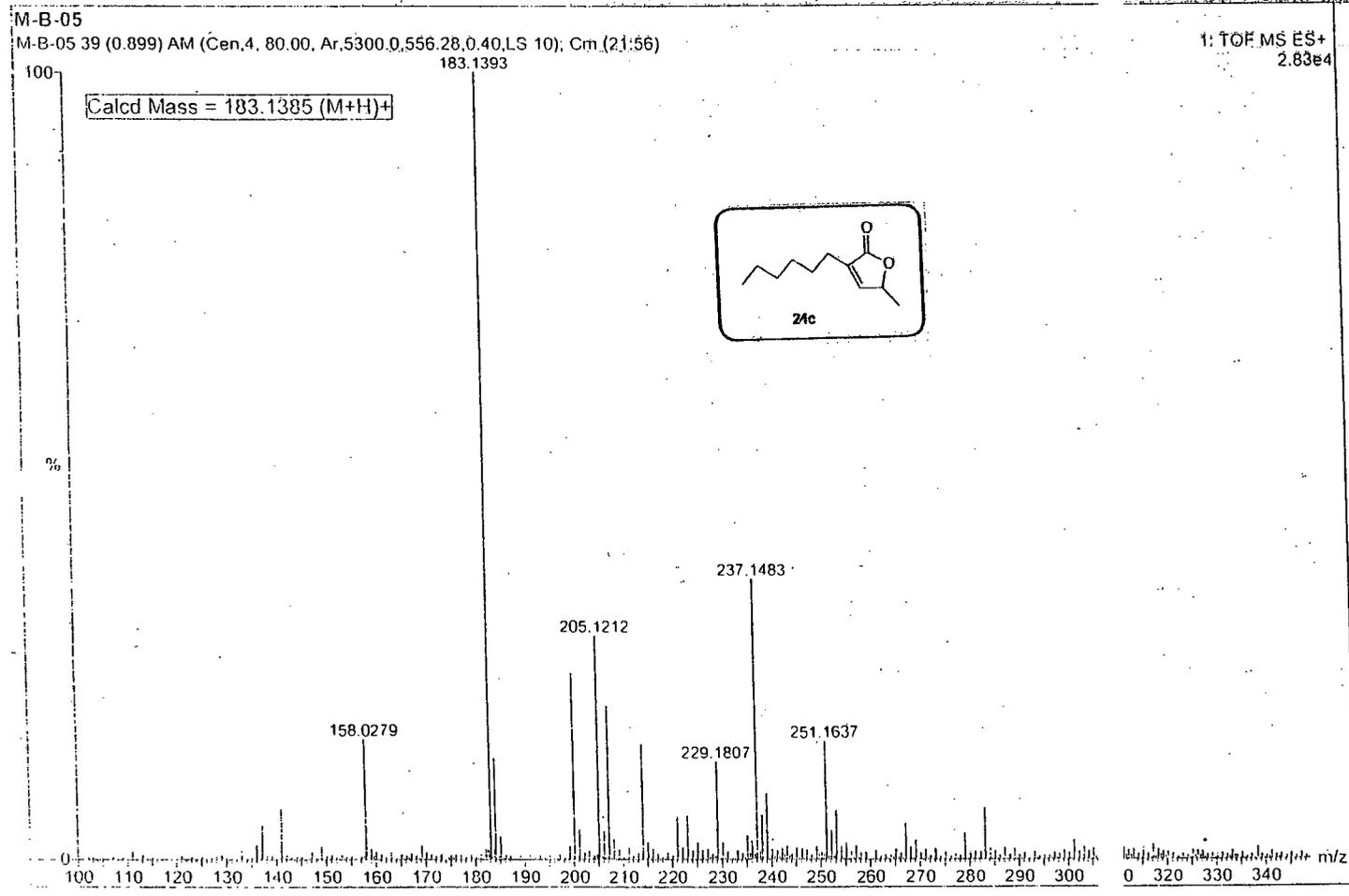


Fig. 3.9 : HRMS of 3-Hexyl-5-methyl-2[5H]-furanone (24c).

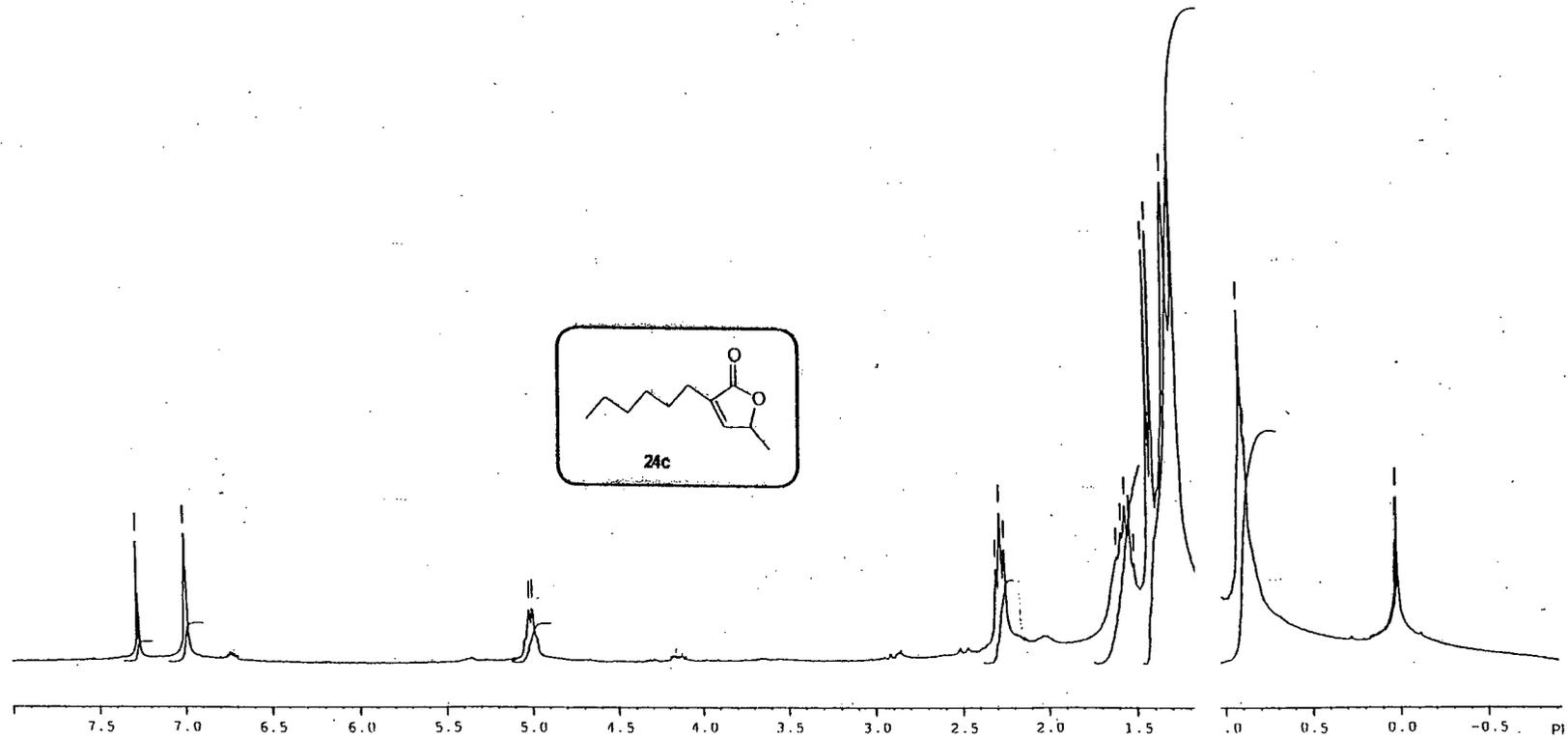


Fig. 3.10 : ^1H NMR spectrum of 3-Hexyl-5-methyl-2[5H]-furanone (24c).

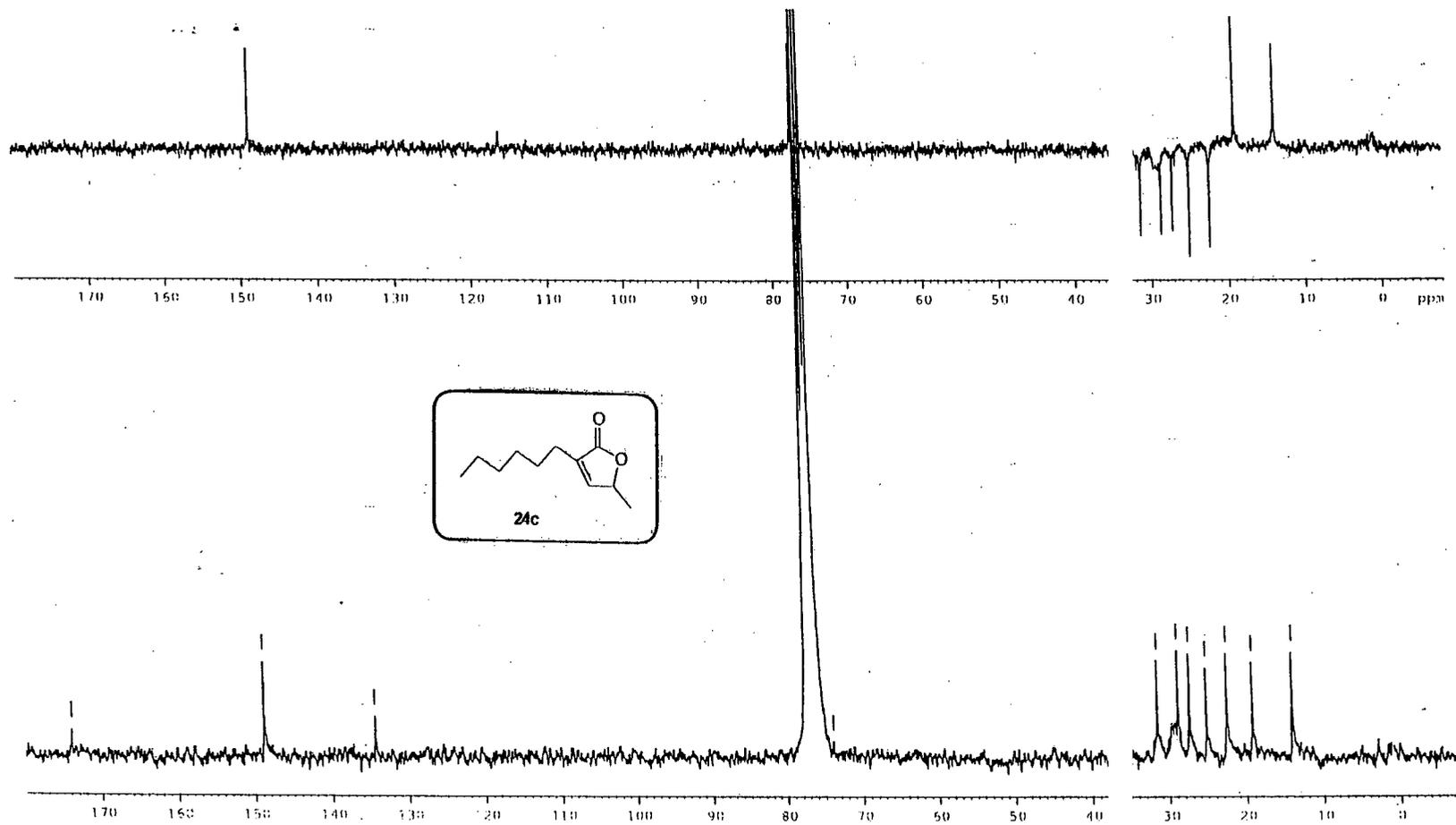
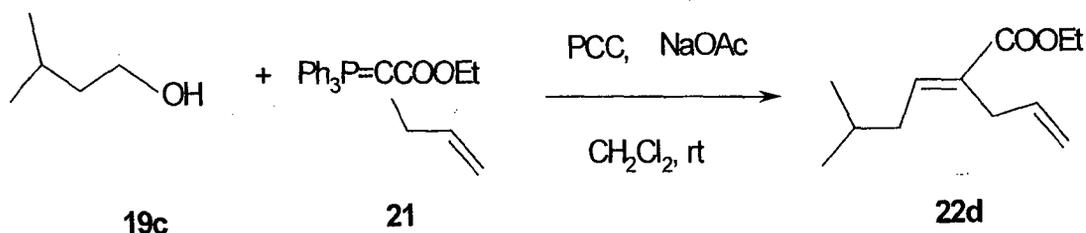


Fig. 3.11 | ^{13}C NMR & DEPT-135 spectrum of 3-Hexyl-5-methyl-2[5H]-furanone (2c).

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data the structure **24c** was assigned to the product.

Towards the synthesis of naturally occurring butenolide **9**, isopentanol **19c** was treated with 1 eq. of allyl phosphorane **21** and 1.2 eq. of PCC and sodium acetate respectively. The reaction mixture was magnetically stirred in dry dichloromethane for one hour. The appearance of dark colour for the reaction mixture indicated the progress of the reaction. After 1 hour, tic indicated the presence of a new spot along with the spot of triphenylphosphine oxide. After usual PCC oxidation reaction work up, the crude product obtained, was separated by column chromatography over silica gel using ethyl acetate: hexanes (1:9), to give a pleasant smelling liquid, in 65% yield.



The high-resolution mass spectrum (HRMS) of the compound had a strong peak at m/z 219.1361, presumably due to $(M+Na)^+$ pseudo ion. The elemental composition of which was determined to be C₁₂H₂₀O₂.

HRMS: m/z calcd for C₁₂H₂₀O₂ + Na ($M + Na^+$): 219.1361; found: 219.1361.

IR(ν_{max}): 1720 (s), 1650 (w) cm⁻¹

^1H NMR spectral data is given below.

δ 0.90	d, $J = 6.6$ Hz	6H	2 x (-CH ₃)
δ 1.22	t, $J = 7.2$ Hz	3H	-OCH ₂ CH ₃
δ 1.69	m	1H	>CH-
δ 2.01	m	2H	-CH ₂ -
δ 2.99	d, $J = 6.0$ Hz	2H	-CH ₂ -CH=CH ₂
δ 4.11	q, $J = 7.2$ Hz	2H	-OCH ₂ CH ₃
δ 4.91	m	2H	-CH ₂ -CH=CH ₂
δ 5.73	m	1H	-CH ₂ -CH=CH ₂
δ 6.79	t, $J = 7.5$ Hz	1H	-CH ₂ -CH=C

The ^{13}C NMR spectral data is given below.

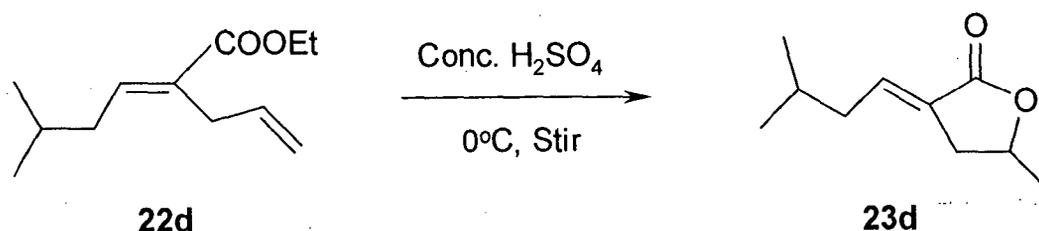
δ 14.23 (CH₃), 22.32 (CH₃), 22.66 (CH₃), 29.08 (CH), 31.58 (CH₂), 37.58 (CH₂),
60.38 (OCH₂), 114.98 (CH=CH₂), 130.48 (C), 135.56 (CH=CH₂), 148.13 (=CH),
167.58 (C=O)

The multiplicities of carbon signals were obtained from DEPT 135 experiments.

Based on the mode of formation and spectral data the structure **22d** was assigned to the ester having *E* geometry.

Ester **22d** was stirred with chilled conc. sulphuric acid at 0°C. After one hour, the reaction mixture was allowed to attain the room temperature. Tlc indicated the disappearance of the starting ester. The reaction mixture was

quenched by adding crushed ice and was extracted with diethyl ether. The crude product obtained, was purified by column chromatography over silica gel using ethyl acetate:hexanes (1: 9) as eluent, to afford an oily liquid, in 90% yield.



The spectral data of the oily liquid is mentioned below.

The high-resolution mass spectrum (HRMS) of the compound had a strong peak at m/z 169.1219, presumably due to $(M+H)^+$ pseudo ion. The elemental composition of which was determined to be $C_{10}H_{16}O_2$.

HRMS: m/z calcd for $C_{10}H_{16}O_2$ ($M + H^+$): 169.1228 ; found: 169.1219.

IR(ν_{max}): 17 53 (s), 1680 (w) cm^{-1}

^1H NMR spectral data is given below.

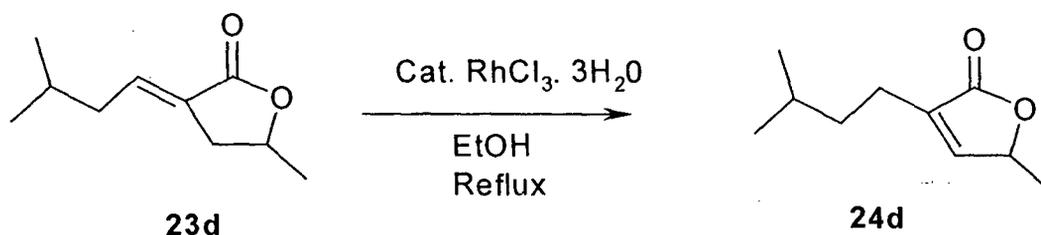
δ 0.94	d, $J = 6.6$ Hz	6H	2 x (- <u>CH</u> ₃)
δ 1.41	d, $J = 6.0$ Hz	3H	-CH- <u>CH</u> ₃
δ 1.81	m	1H	> <u>CH</u>
δ 2.06	t, $J = 6.6$ Hz	2H	- <u>CH</u> ₂ -CH=
δ 2.40	dd, $J = 16.8$ Hz	1H	- <u>H</u> CH-CH
δ 3.00	bdd, $J = 16.8$ & 7.8 Hz	1H	-H <u>CH</u> -CH
δ 4.66	m	1H	- <u>CH</u> -CH ₃
δ 6.76	t, $J = 7.8$ Hz	1H	- <u>CH</u> =C

The ^{13}C NMR spectral data is given below.

δ 22.25 (CH_3), 22.39 (CH_3), 28.09 (CH_3), 33.05 (CH_2), 39.28 (CH_2), 73.93 (CH), 127.17 (C), 139.68 ($=\text{CH}$), 170.86 ($\text{C}=\text{O}$).

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data the structure **23d** was assigned to the product, having *E* geometry.

The isomerisation was carried out by refluxing α,β -unsaturated lactone **23d** with catalytical amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ in degassed absolute alcohol for 24 hours. The crude product was purified by column chromatography over silica gel using ethyl acetate: hexanes (1:9) as eluent, to furnish an oily product, in 94% yield.



The spectral data of the oily liquid is mentioned below.

The high-resolution mass spectrum (HRMS) (Fig. 3.12) of the compound had a strong peak at m/z 169.1232, presumably due to $(\text{M}+\text{H})^+$ pseudo ion. The elemental composition of which was determined to be $\text{C}_{10}\text{H}_{16}\text{O}_2$.

HRMS: m/z calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$ ($\text{M} + \text{H}^+$): 169.1228; found: 169.1232.

IR (neat): 1750 ($\text{C}=\text{O}$), 1650 ($\text{C}=\text{C}$) cm^{-1} .

^1H NMR spectral data is given below (Fig. 3.13).

δ 0.93	d, $J = 6.6$ Hz	6H	2 x (CH ₃)
δ 1.18-1.65	m	3H	-CH ₂ - & -CH-
δ 1.42	d, $J = 6.3$ Hz	3H	-CH-CH ₃
δ 2.28	t, $J = 7.8$ Hz	2H	-CH ₂ -C=
δ 4.99	m	1H	-CH-CH ₃
δ 6.98	d, $J = 1.2$ Hz	1H	=CH

^{13}C NMR spectral data is given below (Fig. 3.14).

δ 19.22 (CH₃), 22.36 (CH₃), 23.12 (CH₃), 27.74 (CH₂), 27.74 (CH₂), 29.69 (CH), 36.41(CH₂), 77.02 (CH), 134.59 (C), 148.65 (=CH), 170.01 (C=O).

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data the structure **24d** was assigned to the product.

The spectral data of the natural product **9** reported in literature⁴² given below is found to be in close agreement with the observed data.

Observed spectral values

Reported spectral values⁴²

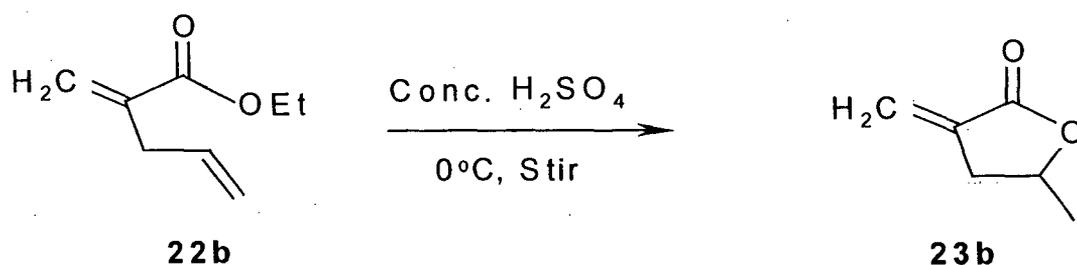
^1H -NMR (CDCl₃)

δ 0.93	d, ($J = 6.6$ Hz)	6H	2 x (CH ₃) ₂	δ 0.95	d, ($J = 6$ Hz)	6H
δ 1.18-1.65	m	3H	CH ₂ - & CH-	δ 1.40	br. d, ($J = 6$ Hz)	3H
δ 1.42	d, ($J = 6.3$ Hz)	3H	-CHCH ₃	δ 2.25	Broad multiplet	2H
δ 2.28	t, ($J = 7.8$ Hz)	2H	-CH ₂ -C=	δ 4.9	Broad multiplet	1H

δ 4.99	m	1H	$-\underline{\text{C}}\text{HCH}_3$	δ 6.9	Narrow multiplet	1H
δ 6.98	d, ($J=1.2$ Hz)	1H	$=\text{CH}$			

The ester **22b** has been prepared earlier to establish the stereochemistry of the ester **22a**. It was realized that cyclization of this ester could give the biologically active butyrolactone⁴³ **23b** and furthermore, naturally occurring butenolide **5** could also be prepared via isomerisation.

The second step was to performed cyclisation of the unsaturated ester **22b**.



We treated ester **22b** with chilled conc. sulphuric acid at 0°C . After one hour, the reaction mixture was allowed to attain the room temperature. Tlc indicated the disappearance of the starting ester. The reaction was quenched by the addition of crushed ice and the reaction mixture was extracted with diethyl ether. The crude product obtained, after work up, was purified by column chromatography over silica gel using ethyl acetate:hexanes (1:9) as eluent, to afford an oily liquid, in 87% yield.

M-B-06

M-B-06 23 (0.526) AM (Cen,4, 80.00, Ar,0.0,556.28,0.00,LS 10); Cm,(1:49-52:77)

1: TOF MS ES+
6.07e3

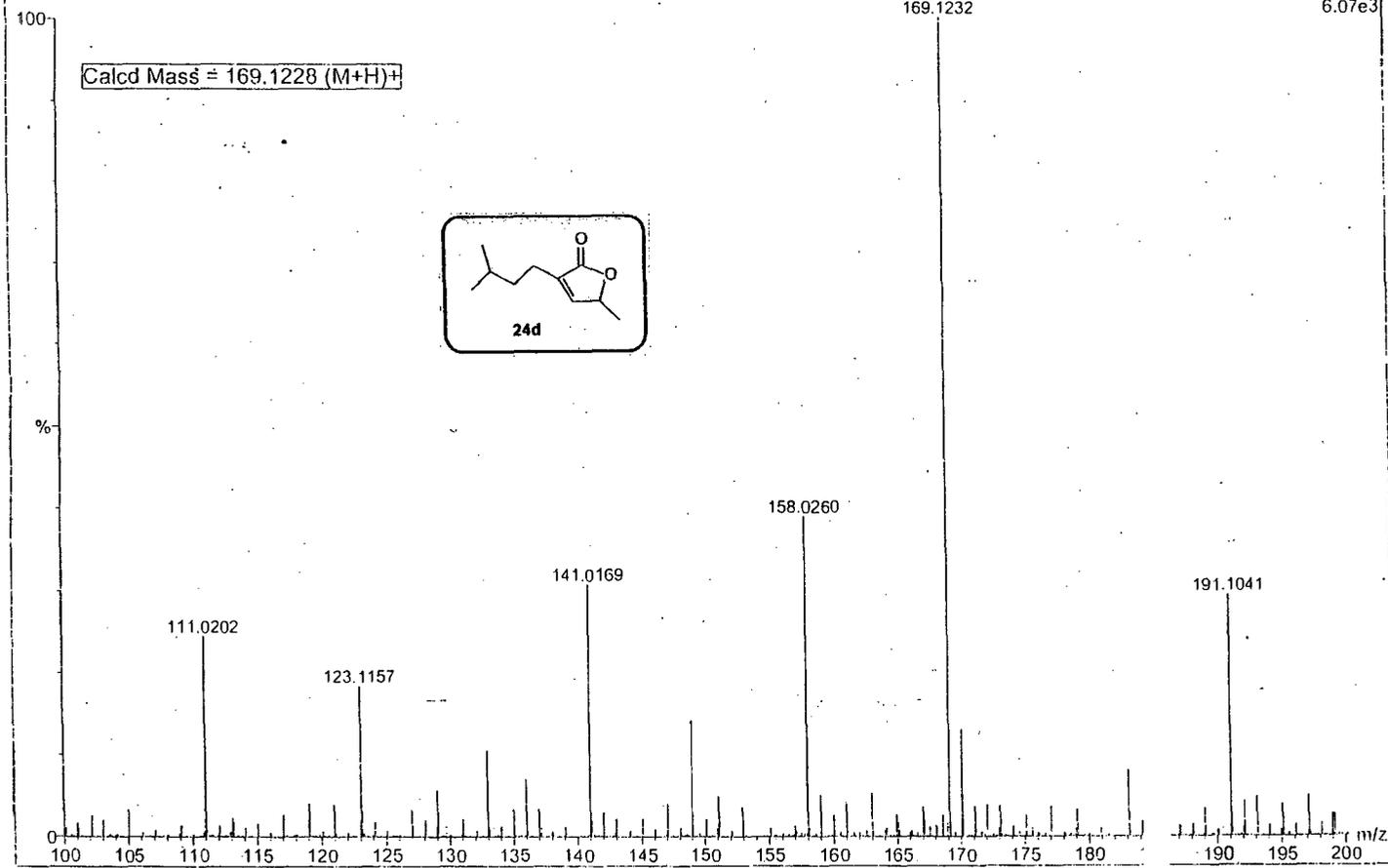


Fig. 3.12 : HRMS of 3-(3-Methyl-butyl)-5-methyl-2[5H]-furanone (24d).

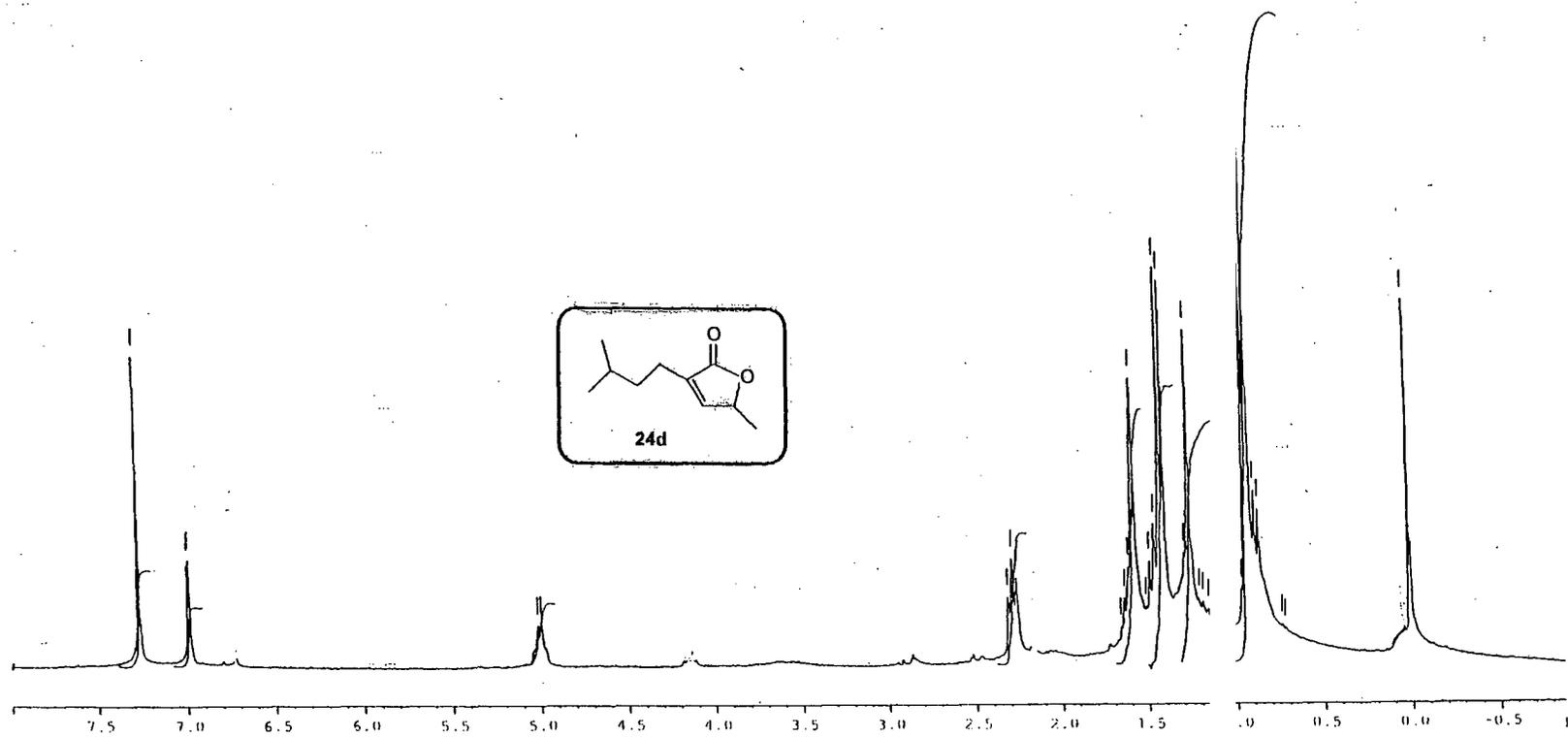


Fig. 3.13 | ^1H NMR spectrum of 3-(3-Methyl-butyl)-5-methyl-2[5H]-furanone (24d).

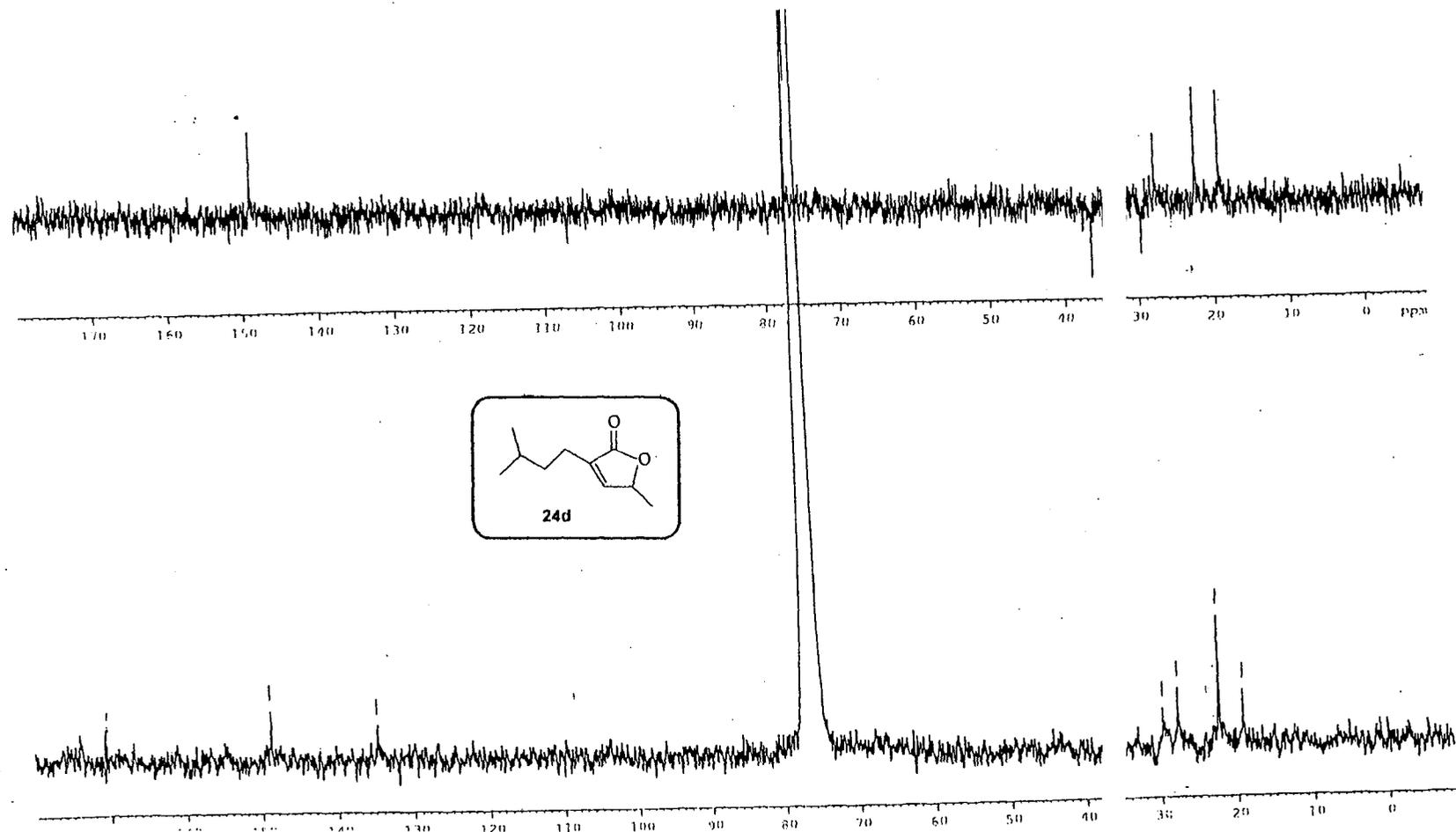
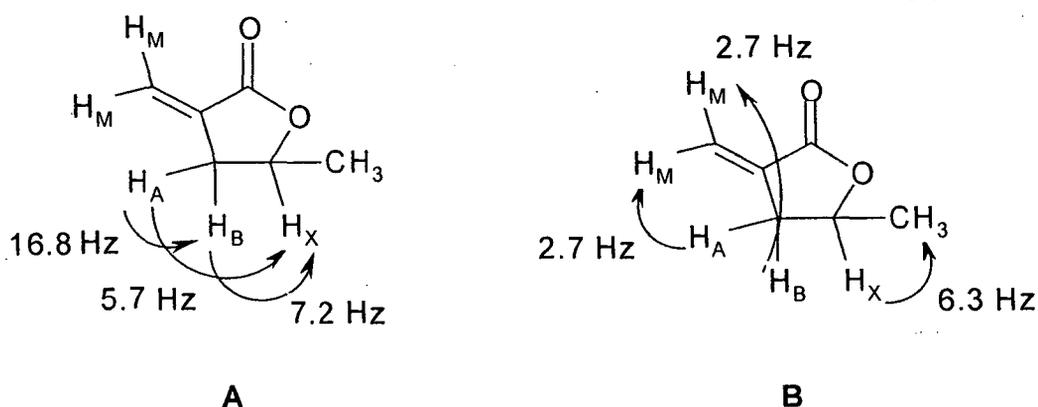


Fig. 3.14 ^{13}C NMR & DEPT-135 spectrum of 3-(3-Methyl-butyl)-5-methyl-2[5H]-furanone (24d).

The ESI mass spectrum had pseudo-molecular $[M+H]^+$ ion at m/z 113, corresponding to the elemental composition $(C_6H_9O_2)$ $[M+H]$, in agreement with the expected structure $(C_6H_8O_2)$. The major fragments at m/z 95(17) $[M - OH_2 + H]^+$, 67(100) $[M - CO - H_2O + H]^+$, etc, also in agreement with the structure.

IR spectrum of the product showed a strong band at 1765 cm^{-1} , which could be assigned, to the carbonyl group of the five-membered lactone.

The $^1\text{H-NMR}$ spectrum (Fig. 3.15) exhibited the signal at δ 1.43 (d, $J = 6.3$ Hz, 3H), indicating the presence of CH_3 group attached to a methine group ($-\text{CHCH}_3$), where as the signal at δ 4.66 (ddq, $J = 7.2$ Hz, 6.3 Hz and 5.7 Hz, 1H) could be assigned to the proton of carbon atom flanked by methylene and methyl groups ($-\text{CH}_2-\text{CH}-\text{CH}_3$). The low field appearance of methane proton (H_X) at δ



4.66 indicated that it could be attached to the carbon having an electron withdrawing atom such as oxygen. The peaks at δ 2.56 (ddt, $J = 16.8$ Hz, 5.7 Hz, & 2.7 Hz, 1H) and δ 3.10 (ddt, $J = 16.8$ Hz, 7.2 Hz, & 2.7 Hz, 1H) was assigned to the two methylene protons (H_A & H_B).

The nature of peaks indicated the presence of ABMX pattern (Fig. A & B). The geminal coupling constant is 16.8 Hz ($H_A H_B$), the vicinal coupling constants are 5.7 Hz and 7.2 Hz ($H_A H_X$ & $H_B H_X$) and the allylic coupling constant is 2.7 Hz ($H_A H_M$ & $H_B H_M$).

The peaks at δ 5.63 (t, $J = 2.7$ Hz, 1H) and δ 6.24 (t, $J = 2.7$ Hz, 1H) were indicated the presence of two methylene protons (H_M), both show allylic coupling with methylene protons H_A and H_B .

The ^{13}C -NMR spectrum (Fig. 3.16) displayed a peak at δ 21.87 (CH_3) could be assigned to the methyl carbon attached to the carbon having the methine proton ($-\text{CH}\underline{\text{C}}\text{H}_3$). The peak at δ 35.09 (CH_2) is assigned to the carbon having methylene protons (H_A and H_B). The low field appearance of the carbon having methine proton (H_X) at δ 73.83 (CH) indicated that it could be attached to the carbon having an electron withdrawing oxygen atom ($-\underline{\text{C}}\text{HCH}_3$). The methylene carbon appeared at δ 121.91 ($\text{CH}=\text{}$). The peak at δ 134.80 (C) indicated the presence of quaternary carbon of the unsaturated carbon next to the carbonyl group. The peak appeared at δ 176.19 (C) could be assigned to the carbon of the carbonyl group of lactone.

The multiplicities of the carbon signals were assigned using DEPT 135 experiments. Based on the mode of formation, spectral data and similarity of the spectral data with that of literature⁴³, we could assign structure **23b** for the compound.

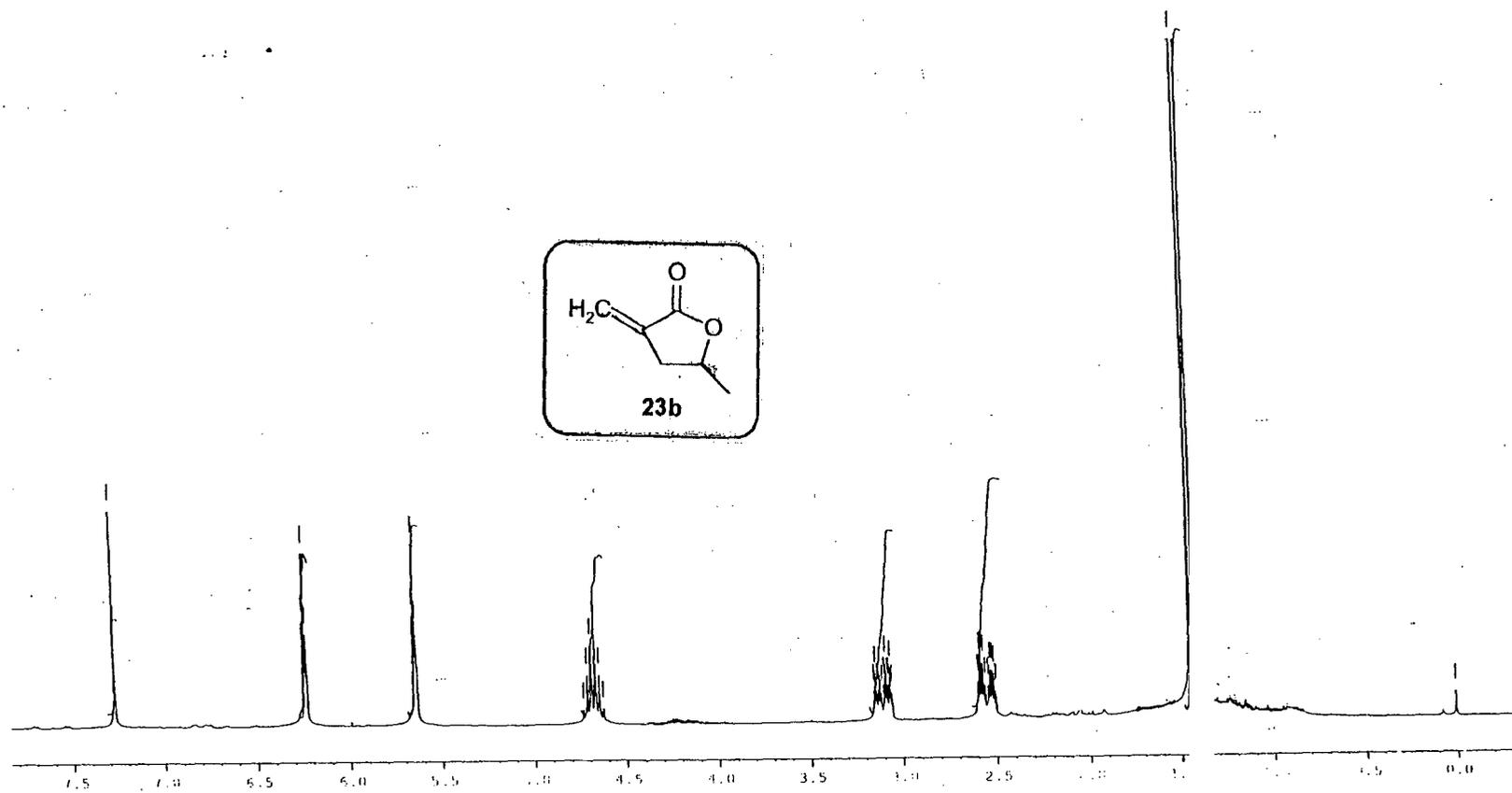


Fig. 3.15 : ¹H NMR spectrum of 5-methyl-3-[(E)-methylidene]-dihydrofuran-2(1H)-one (23b).

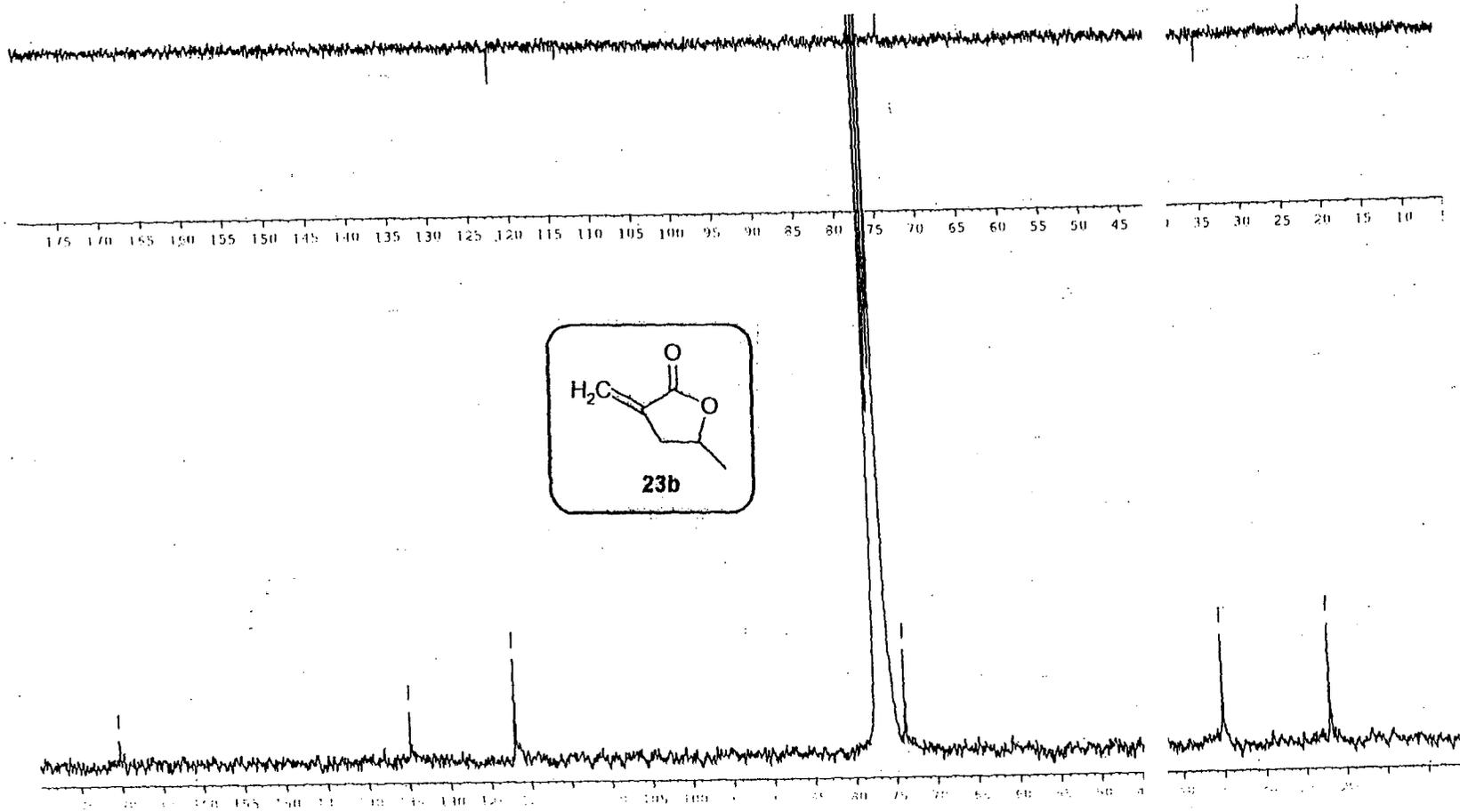


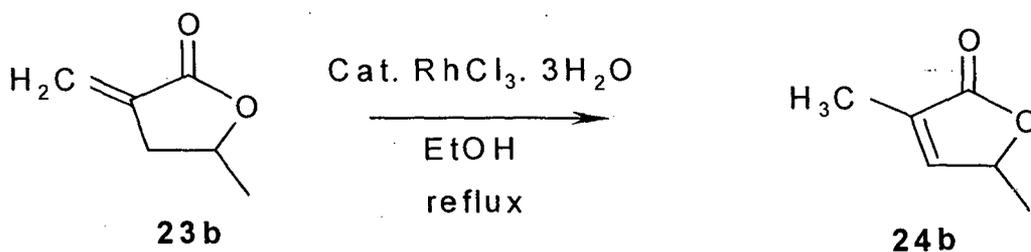
Fig. 3.16: ^{13}C NMR & DEPT-135 spectrum of 5-methyl-3-[(*E*)-methylidene]-dihydro-2(5H)-one (23b).

Observed spectral valuesReported spectral values⁴³¹H-NMR (CDCl₃)

δ 1.43	d, (J = 6.3 Hz)	3H	-CH ₃
δ 2.56	ddt, (J = 16.8 Hz, 5.7 Hz, 2.7 Hz)	1H	-HCH-
δ 3.10	ddt, (J = 16.8 Hz, 7.2 Hz, 2.7 Hz)	1H	-HCH-
δ 4.66	ddq, (J = 7.2 Hz, 6.3 Hz, 5.7 Hz)	1H	-CHCH ₃
δ 5.63	t, (J = 2.7 Hz)	1H	=HCH
δ 6.24	t, (J = 2.7 Hz)	1H	=HCH

δ 1.42	d, (J = 6.0 Hz)	3H	
δ 2.56	ddt, (J = 16.80 Hz, 5.85 Hz, 2.90 Hz)	1H	
δ 3.13	ddt, (J = 16.80 Hz, 7.35 Hz, 2.62 Hz)	1H	
δ 3.70	ddq, (J = 2.62 Hz)	1H	
δ 6.22	Large t, (J = 3.0 Hz)	1H	

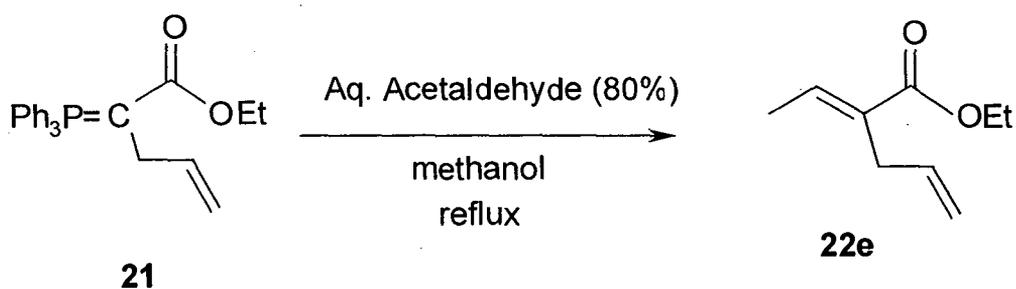
We refluxed α,β -unsaturated lactone **23b** with catalytic amount of RhCl₃·3H₂O in degassed absolute alcohol for 14 hours.



But to our disappointment, the tlc showed many spots indicating the decomposition of the starting. In our hands we could not get the isomerised product.

Subsequently, we attempted synthesis of butenolide **6** a known fungicidal agent, by using commercially available acetaldehyde.

Thus, condensation of aqueous acetaldehyde solution (80%) with allyl phosphorane **21** by refluxing in methanol for 3 hours led to the formation of desired product **22e**. The progress of the reaction was monitored by tlc, which confirmed the disappearance of starting material and appearance of a new spot due to the product, along with the spot of triphenylphosphine oxide. Subsequently, the reaction mixture was warmed on water bath to remove solvent and after cooling, the product was extracted with hexanes. The crude product obtained, was purified by column chromatography over silica gel, using hexanes as eluent, to obtain a pleasant smelling volatile liquid, in 50% yield.



The ESI mass spectrum had pseudo-molecular $[\text{M}+\text{H}]^+$ ion at m/z 155, corresponding to the elemental composition $(\text{C}_9\text{H}_{15}\text{O}_2)$ $[\text{M}+\text{H}]$, in agreement with the expected structure $(\text{C}_9\text{H}_{14}\text{O}_2)$. The major fragments at m/z 127(100) $[\text{M} - \text{CO} + \text{H}]^+$, 109(54) $[\text{M} - \text{OEt} + \text{H}]^+$, 81(39) $[\text{M} - \text{COOEt} + \text{H}]^+$, etc, also in agreement with the structure.

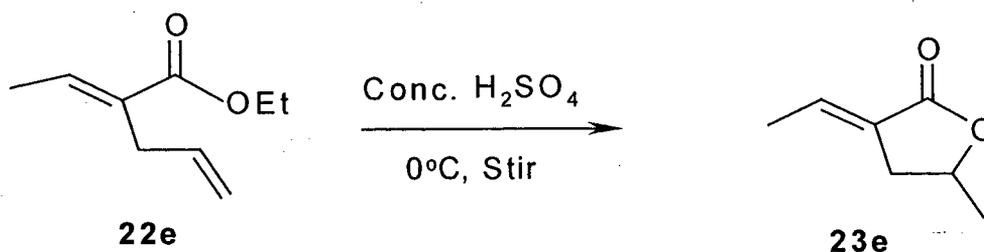
The IR spectrum of the product showed a strong band at 1722 cm^{-1} . This indicated the presence of conjugated carbonyl group of ester.

The $^1\text{H-NMR}$ (CDCl_3) spectrum exhibited the signals at δ 1.28 (t, $J = 7.2$ Hz, 3H) and δ 4.19 (q, $J = 7.2$ Hz, 2H), indicated the presence of ($-\text{OCH}_2\text{CH}_3$) grouping. The appearance of peaks at δ 1.79 (d, $J = 6.9$ Hz, 3H) and δ 6.95 (q, $J = 6.9$ Hz, 1H) were assigned to vinyl methyl protons ($\text{CH}_3\text{-CH=}$) and vinyl proton, adjacent to the methyl group ($\text{CH}_3\text{-CH=}$), respectively. The peaks observed δ 3.08 (br. d, $J = 6.0$ Hz, 2H), δ 5.00 (m, 2H) and δ 5.81 (m, 1H) were assigned to the allyl moiety ($-\text{CH}_2\text{-CH=CH}_2$).

The structure was further confirmed by $^{13}\text{C-NMR}$ (CDCl_3) spectrum, which displayed the peaks at δ 14.12 (CH_3) and δ 60.36 (CH_2) due to ($-\text{OCH}_2\text{CH}_3$) group. The peak at δ 14.21 (CH_3) could be due to the ($\text{CH}_3\text{-CH=}$) methyl carbon, while the peaks at δ 30.45 (CH_2), δ 114.90 (CH_2) and δ 138.28 (CH) could be assigned to the allyl group ($-\text{CH}_2\text{CH=CH}_2$). The trisubstituted olefinic carbon signal appeared at δ 135.19 (CH) where as the peaks appearing at δ 130.95 (C) and δ 167.45 (C) could be assigned to the quaternary carbon and the carbonyl moiety, respectively.

The multiplicities of carbon signals were obtained from DEPT 135 experiments. Based on the mode of formation and spectral data the structure **22d** was assigned to the ester having *E* geometry.

Ester **22d** treated with chilled conc. sulphuric acid at 0°C. After one hour, the reaction mixture was allowed to attain the room temperature. The tlc indicated the disappearance of starting material. The reaction mixture was quenched by the addition of crushed ice and the reaction mixture was extracted with diethyl ether. The crude product obtained, was purified by column chromatography over silica gel, using ethyl acetate:hexanes (1: 9) as eluent, to afford an oily liquid, in 85% yield.



The ESI mass spectrum had pseudo-molecular $[M+H]^+$ ion at m/z 127, corresponding to the elemental composition (C₇H₁₁O₂) $[M+H]$, in agreement with the expected structure (C₇H₁₀O₂). The major fragments at m/z 109(29) $[M - H_2O + H]^+$, 81(100) $[M - CO - H_2O + H]^+$, etc, also in agreement with the structure.

The IR spectrum showed a strong band at 1756 cm⁻¹, which could be assigned to the carbonyl group of five-membered lactone. The cyclised product was further confirmed by its ¹H-NMR and ¹³C-NMR spectra.

¹H NMR (CDCl₃)

δ 1.35	d, $J = 6.3$ Hz	3H	-CH-CH ₃
δ 1.78	dt, $J = 6.3$ Hz	3H	CH ₃ CH=
δ 2.35	ddt, $J = 16.8, 5.2$ & 1.8 Hz (ABXM)	1H	-HCH-CH

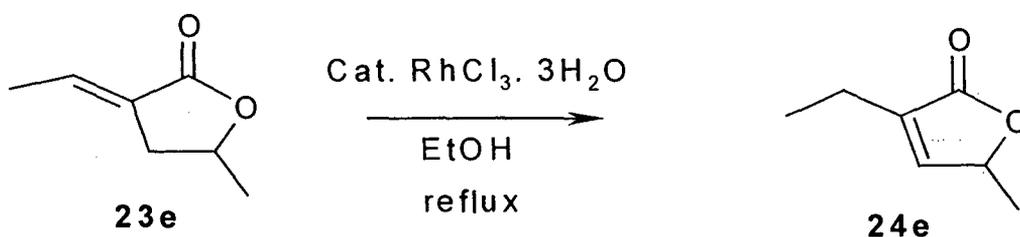
δ 3.01	ddt, $J = 16.8, 7.8 \text{ \& } 2.1 \text{ Hz}$ (ABXM)	1H	-HCH-CH
δ 4.61	ddq, $J = 7.8, 6.3 \text{ \& } 5.2 \text{ Hz}$ (ABX)	1H	-CH-CH ₃
δ 6.71	m,	1H	=CHCH ₃

¹³C NMR spectral data is given below.

δ 15.55 (CH₃CH=), 22.20 (CH₃CH), 32.65 (CH₂), 73.85 (CH₃CH), 127.55 (C), 135.39 (=CH), 170.64 (C=O).

The multiplicities of the carbon signals were assigned using DEPT 135 experiments. Based on the mode of formation and spectral data the structure **23e** was assigned to the product having *E* geometry.

The next step was the isomerisation of the double bond.



The isomerisation of the exocyclic double bond was carried out by refluxing α,β -unsaturated lactone **24e** with catalytical amount of RhCl₃·3H₂O in degassed absolute alcohol for 24 hours. The crude product obtained after usual work up, was purified by column chromatography over silica gel, using ethyl acetate:hexanes (1:9), as eluent, to furnish an oily product, in 92% yield.

The ESI mass spectrum had pseudo-molecular $[M+H]^+$ ion at m/z 127, corresponding to the elemental composition $(C_7H_{11}O_2)$ $[M+H]$, in agreement with the expected structure $(C_7H_{10}O_2)$. The major fragments at m/z 109(100) $[M - H_2O + H]^+$, 99(26) $[M - CO - H_2O + H]^+$, etc, also in agreement with the structure.

The IR spectrum showed a strong band at 1750 cm^{-1} which could be assigned to the carbonyl group of five-membered lactone. The cyclised product was further confirmed by its $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra.

The $^1\text{H-NMR}$ spectrum (Fig. 3.17) is mentioned below.

δ 1.19	t,	$J = 7.2\text{ Hz}$	3H	$-\text{CH}-\underline{\text{C}}\text{H}_3$
δ 1.34	d,	$J = 6.6\text{ Hz}$	3H	$-\text{CH}_2\underline{\text{C}}\text{H}_3$
δ 2.22	q,	$J = 7.2\text{ Hz}$	2H	$-\text{CH}_2\underline{\text{C}}\text{H}_3$
δ 4.94	d,	$J = 6.6\text{ Hz}$	1H	$-\underline{\text{C}}\text{H}-\text{CH}_3$
δ 6.93	m,		1H	$=\underline{\text{C}}\text{H}$

$^{13}\text{C-NMR}$ spectral data is given below (Fig. 3.18).

$^{13}\text{C NMR}$: $\delta = 11.43$ (CH_3), 18.24 (CH_3), 18.98 (CH_2), 77.23 (CH), 134.86 (C), 148.54 ($=\text{CH}$), 173.57 ($\text{C}=\text{O}$).

The multiplicities of the carbon signals were assigned using DEPT 135 experiments. Based on the mode of formation and the close similarity with the literature data, the structure **6** was assigned to the product.

The literature spectral data⁴⁴ of **6** mentioned below is similar to the observed spectral data.

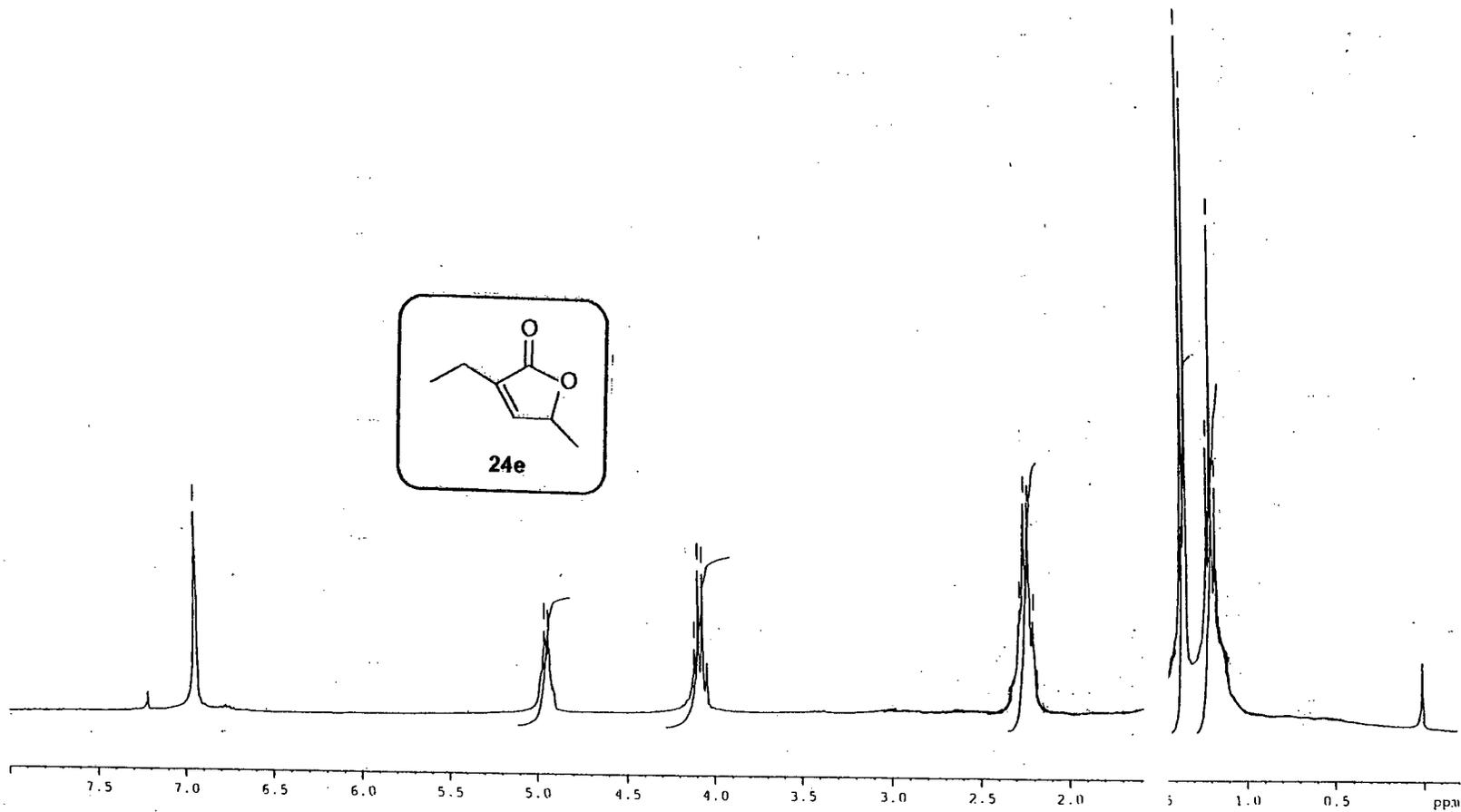


Fig. 3.17: ¹H NMR spectrum of 3-Ethyl-5-methyl-2[5H]-furanone (24e).

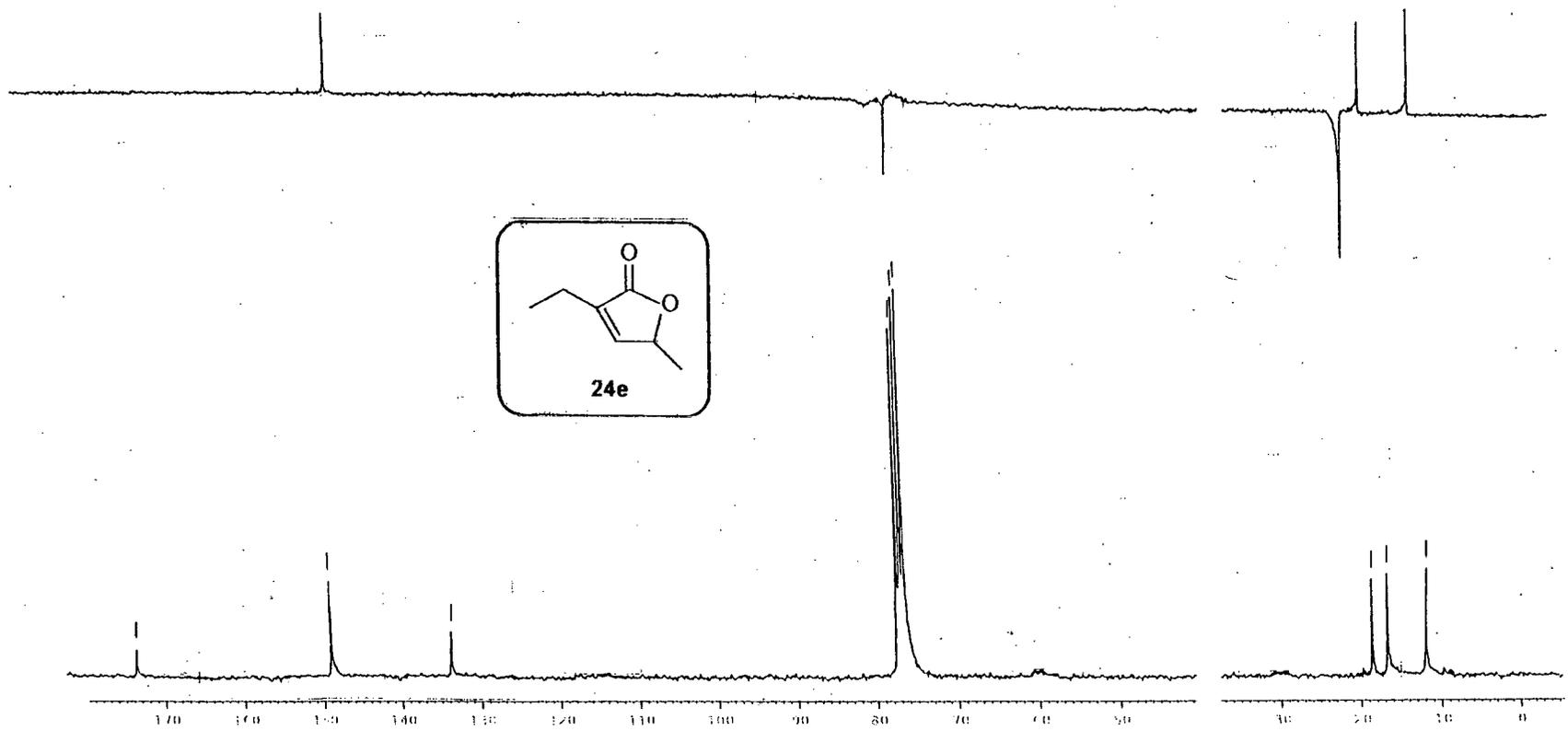


Fig. 3.18: ^{13}C NMR & DEPT-135 spectrum of 3-Ethyl-5-methyl-2-furanone (24e).

Observed spectral values**Reported spectral values⁴⁴**IR(ν_{\max}): 1750 cm^{-1} 1750 cm^{-1} **¹H-NMR (CDCl₃)**

δ 1.19	t, ($J = 7.2$ Hz)	3H	-CH ₂ CH ₃	δ 1.16	t, ($J = 7.20$ Hz)	3H
δ 1.34	d, ($J = 6.6$ Hz)	3H	-CH ₂ CH ₃ -	δ 1.40	d, ($J = 7.21$ Hz)	3H
δ 2.22	q, ($J = 7.2$ Hz)	2H	-CH ₂ -CH ₃	δ 2.23	q, ($J = 7.20$ Hz)	2H
δ 4.94	d, ($J = 6.6$ Hz)	1H	-CHCH ₃	δ 5.00	q, ($J = 7.21$ Hz)	1H
δ 6.93	br.s	1H	=CH	δ 7.01	m	1H

C¹³ NMR (CDCl₃) :

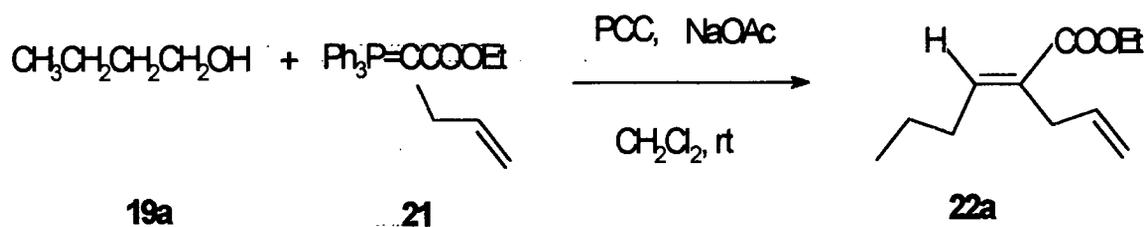
Observed Values	δ 11.43, 18.24, 18.98, 77.23, 134.86, 148.54, 173.57
Reported Values ⁴⁴	δ 11.41, 18.24, 18.77, 77.17, 133.16, 148.33, 173.36

3.4 Conclusion

- A convenient and an operationally facile, three-step synthesis towards (±) 3-substituted-5-methyl butenolides has been achieved.
- We have demonstrated that functionalized Wittig reagent (**21**) can also be used for the domino primary alcohol oxidation-Wittig reaction.
- Using this protocol four volatile *Streptomyces* butenolides are synthesized.
- Synthesis of two naturally occurring butenolides, (±) 3-Hexyl-5-methyl-2[5*H*]-furanone (**24c**) and (±) 3-(3-Methylbutyl)-5-methyl-2[5*H*]-furanone (**24d**) is reported for the first time.

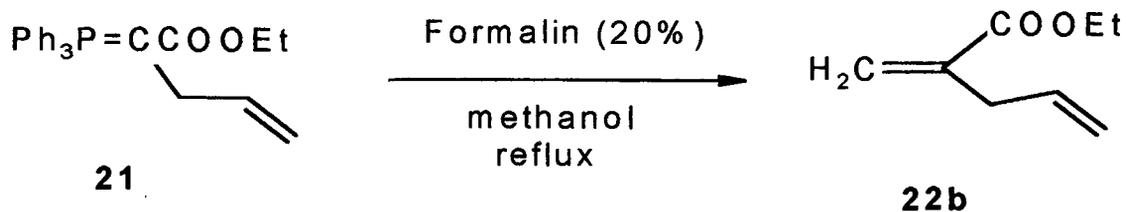
3.5 Experimental

Expt. 3.4.1 : Preparation of (E)-Ethyl 2-butylidenepent-4-enoate (22a)



To a magnetically stirred suspension of pyridinium chlorochromate (3.5 g, 16.2 mmol), anhydrous sodium acetate (1.33 g, 16.2 mmol.) in anhydrous dichloromethane (10 mL) and allyl phosphorane **21** (5.24 g, 13.5 mmol.) was added n-butanol **19a** (1 g, 13.5 mmol.) in anhydrous dichloromethane (5 mL) in one portion at room temperature. After 3h, diethyl ether (5 mL) was added and supernatant solution decanted from the black granular solid. The combined organic solution was then passed through a short pad of celite. The residue obtained after the evaporation of the solvent was further purified by column chromatography using hexanes as eluent to afford a pleasant smelling liquid **22a** (1.402 g, 57%).

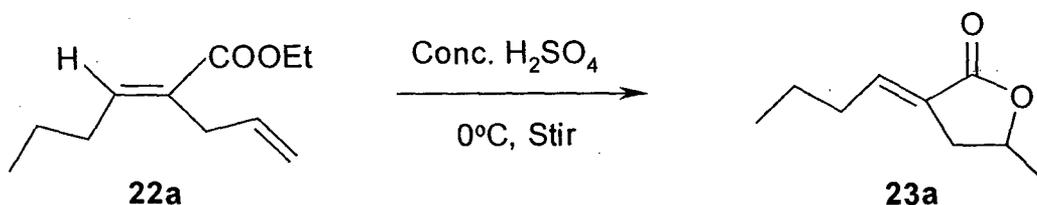
Expt. 3.4.2 : Preparation of Ethyl 2-methylidenepent-4-enoate (22b)



To a solution of allyl phosphorane **21** (0.76 g, 2 mmol.) in methanol (10 mL) was added formalin (20%) **19b** (4 ml, 20 mmol.) and the reaction mixture was refluxed for 2 h. After the completion of reaction methanol was removed under vacuum and hexanes (20 mL) was added and the reaction mixture was shaken vigorously. The hexane layer was separated, evaporated and the resulting crude product was purified by column chromatography over silica gel, using hexanes as eluent, to afford pleasant smelling volatile liquid **22b** (0.137 g, 50%).

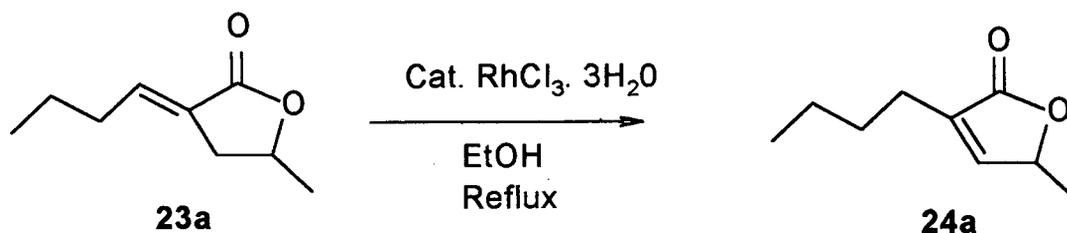
Expt. 3.4.3: Preparation of 5-Methyl-3-[(E)-butylidene]-dihydrofuran-

-2(5H)one³⁸ (23a)



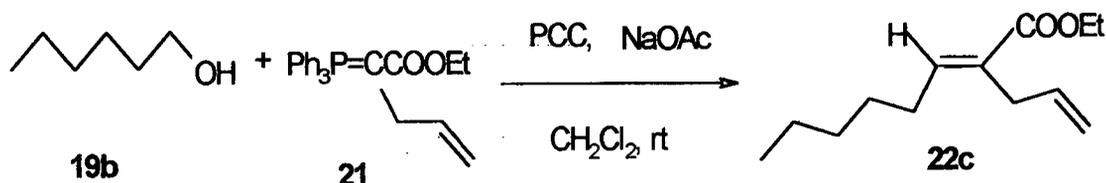
To a flask containing ice-cold ester **22a** (0.5 g, 2.75 mmol) was added ice-cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 1h. Crushed ice was added to the reaction mixture to make it dilute and the reaction mixture was extracted in diethyl ether (5 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate, concentrated and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to yield liquid lactone **23a** (0.389 g, 92%).

Expt. 3.4.4 : Preparation of 3-Butyl-5-methyl-2[5H] furanone⁴¹ (24a)



To a solution of lactone **23a** (0.1 g, 0.65 mmol) in absolute alcohol (10 mL) was added cat. amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (0.01 g, 0.04 mmol) and the reaction mixture was refluxed for 15 h. The reaction mixture was concentrated, adsorbed on silica gel and the crude product was purified by column chromatography over silica gel, using ethylacetate: hexanes (1:9), as eluent to obtain liquid butenolide **24a** (0.077 g, 77%).

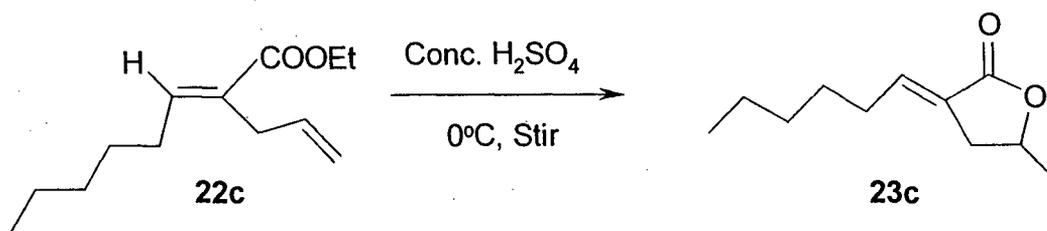
Expt. 3.4.5 : Preparation of (*E*)-Ethyl 2-hexylidene-pent-4-enoate (22c)



To a magnetically stirred suspension of pyridinium chlorochromate (2.587 g, 12 mmol), anhydrous sodium acetate (0.984 g, 12 mmol.) in anhydrous dichloromethane (10 mL) and allyl phosphorane **21** (3.88 g, 10 mmol.) was added n-hexanol **19c** (1 g, 10 mmol.) in anhydrous dichloromethane (5 mL) in one portion at room temperature. The reaction was monitored by tlc. After 3h,

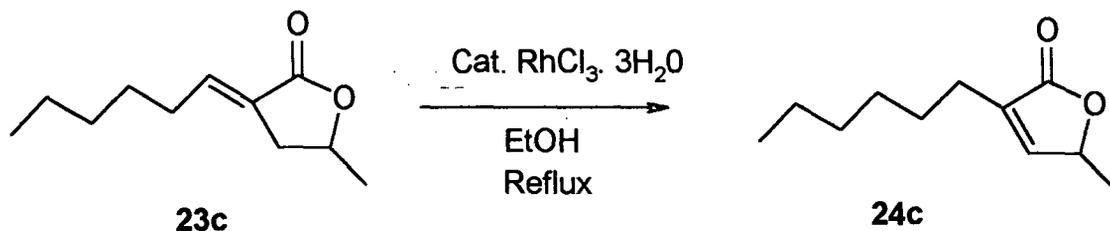
diethyl ether (5 mL) was added and supernatant solution decanted from the black granular solid. The combined organic solution was then passed through a short pad of celite. The residue obtained after the evaporation of the solvent was further purified by column chromatography over silica gel, using hexanes as eluent to afford pleasant smelling liquid **22c** (1.188 g, 60%).

**Expt. 3.4.6 : Preparation of 5-Methyl-3-[(E)-hexylidene]- dihydrofuran-
- 2(5H)one³⁸ (23c)**



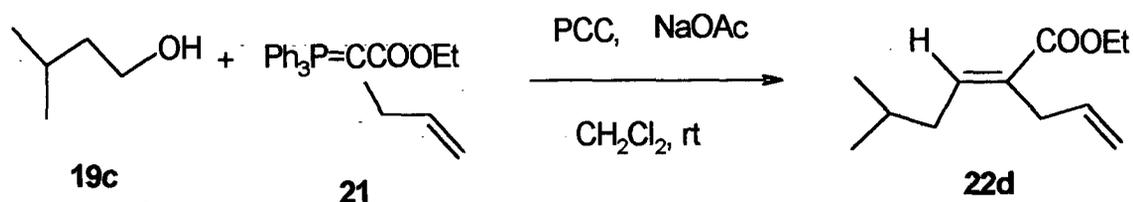
To a flask containing ice-cold ester **22c** (0.5 g, 2.52 mmol) was added ice-cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 1 h. Sufficient crushed ice was added to the reaction mixture to make it dilute and the reaction mixture was extracted in diethylether (5 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate, evaporated and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to yield a liquid lactone **23c** (0.408 g, 89%).

Expt. 3.4.7 : Preparation of 3-Hexyl-5-methyl-2[5H] furanone⁴² (24c)



To a solution of lactone **23c** (0.1 g, 0.55 mmol) in absolute alcohol (10 mL) was added cat. amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (0.01 g, 0.04 mmol) and the reaction mixture was refluxed for 15 h. The reaction mixture was evaporated, adsorbed on silica gel and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to obtain liquid butenolide **24c** (0.093 g, 93%).

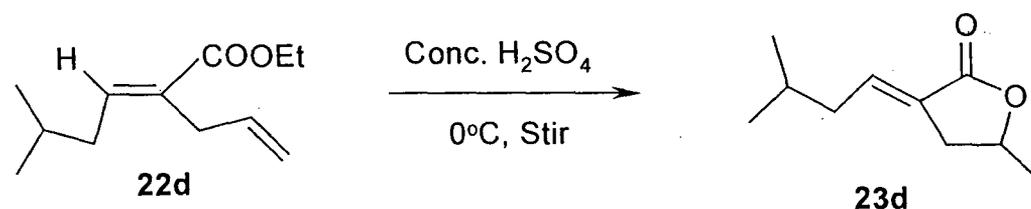
Expt. 3.4.8 : Preparation of (*E*)-Ethyl isobutylidenepent-4-enoate (22d)



To a magnetically stirred suspension of pyridinium chlorochromate (2.94 g, 13.6 mmol), anhydrous sodium acetate (1.12 g, 13.6 mmol.) in anhydrous dichloromethane (10 mL) and allyl phosphorane **21** (4.41 g, 11.4 mmol) was added iso-pentanol **19d** (1 g, 11.4 mmol.) in anhydrous dichloromethane (5 mL)

added iso-pentanol **19d** (1 g, 11.4 mmol.) in anhydrous dichloromethane (5 mL) in one portion at room temperature. After 3 h, diethyl ether (5 mL) was added and supernatant solution decanted from the black granular solid. The combined organic solution was then passed through a short pad of celite. The residue obtained after the evaporation of the solvent was further purified by column chromatography over silica gel, using hexanes as eluent to afford pleasant smelling liquid **22d** (1.45 g, 65%).

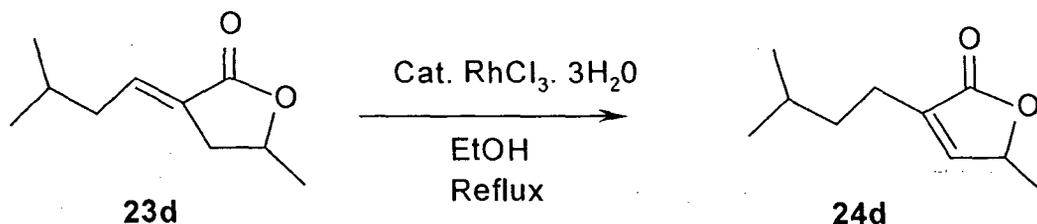
Expt. 3.4.9 : Preparation of 5-Methyl-3-[(E)-3-methyl butylidene]-dihydrofuran-2(5H)-one (23d)



To a flask containing ice-cold ester **22d** (0.5 g, 2.55 mmol) was added ice-cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 1 h. Sufficient crushed ice was added to the reaction mixture to make it dilute and the reaction mixture was extracted in diethyl ether (5 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate, concentrated under vacuum and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to yield liquid lactone **23d** (0.385 g, 90%).

Expt. 3.4.10 : Preparation of 3-(3-Methylbutyl)-5-methyl-2[5H]

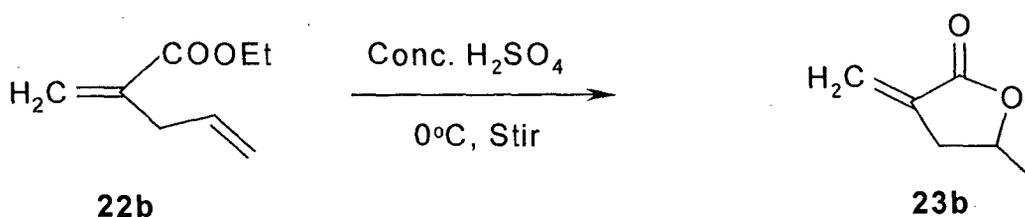
furanone⁴² (24d)



To a solution of lactone **23d** (0.1 g, 0.51 mmol) in absolute alcohol (10 mL) was added cat. amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (0.01 g, 0.04 mmol) and the reaction mixture was refluxed for 15 h. The reaction mixture was evaporated to dryness, adsorbed on silica gel and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to obtain a viscous liquid butenolide **24d** (0.094 g, 94%).

Expt. 3.4.11 : Preparation of 5-Methyl-3-[methylidene]-dihydrofuran-

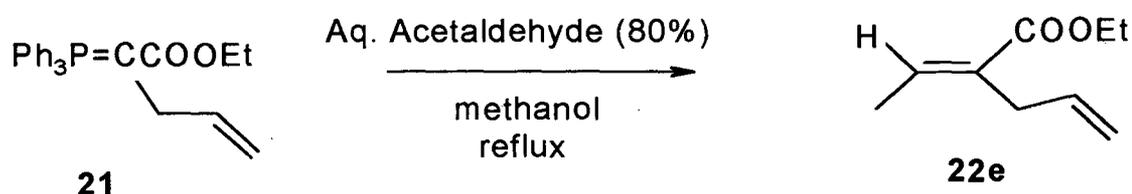
-2(5H)-one⁴³ (23b)



To a flask containing ice-cold ester **22b** (0.1 g, 0.71 mmol) was added ice-cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice

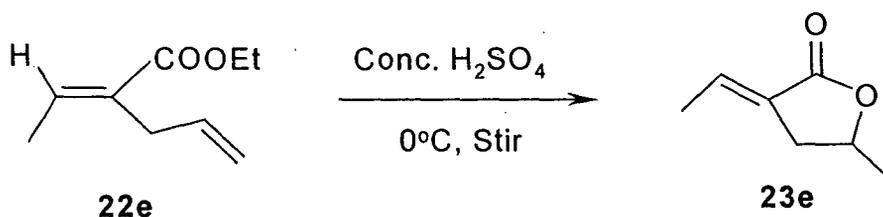
dilute and the reaction mixture was extracted in diethyl ether (5 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate, evaporated and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to yield a viscous liquid lactone **23b** (0.07 g, 87%).

Expt. 3.4.12 : Preparation of (*E*)-Ethyl 2-ethylidenepent-4-enoate (22e**)**



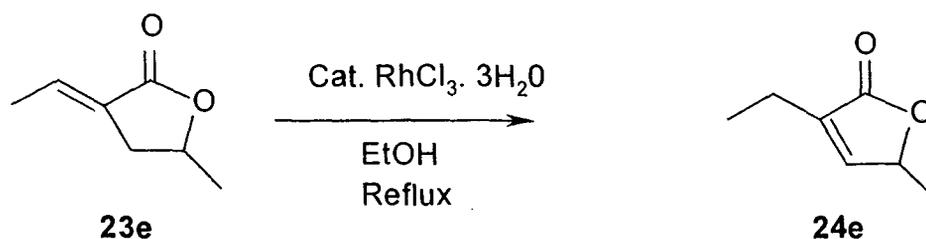
To a solution of allyl phosphorane **21** (0.76 g, 2 mmol.) in methanol (10 mL) was added aq. acetadehyde (80%) **19e** (0.5 ml, 20 mmol.) and the reaction mixture was refluxed for 2 h. Methanol was removed by evaporation, hexanes (20 mL) was added and the reaction mixture was shaken vigorously. The hexane layer was separated, evaporated and the resulting crude product was purified by column chromatography over silica gel, using hexanes as eluent, to afford pleasant smelling volatile liquid **22e** (0.15 g, 50%).

**Expt. 3.4.13 : Preparation of 5-Methyl-3-[(E)-ethylidene]- dihydrofuran-
-2(5H)one (23e)**



To a flask containing ice cold ester **22e** (0.1 g, 0.65 mmol) was added ice-cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 1 h. Sufficient crushed ice was added to the reaction mixture to make it dilute and the reaction mixture was extracted in diethyl ether (5 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate, concentrated and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to yield viscous liquid lactone **23e** (0.07 g, 85%).

Expt. 3.4.14 : Preparation of 3-Ethyl-5-methyl-2[5H] furanone⁴⁴ (24e)



To a solution of lactone **23e** (0.1 g, 0.8 mmol) in absolute alcohol (10 mL) was added cat. amount of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (0.01 g, 0.04 mmol) and the reaction mixture was refluxed for 15 h. The reaction mixture was adsorbed on silica gel and the crude product was purified by column chromatography over silica gel, using ethyl acetate: hexanes (1:9), as eluent to obtain a viscous liquid butenolide **24e** (0.092 g, 92%).

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Chapter 4

***Attempted Syntheses Of Selected
Natural Products***

Section I

***Synthesis Of 2-(p-Chlorophenyl)
Methylidene -5,5-Dimethyl
Cyclopentanone (2), An Intermediate For
Potent Fungicide (1).***

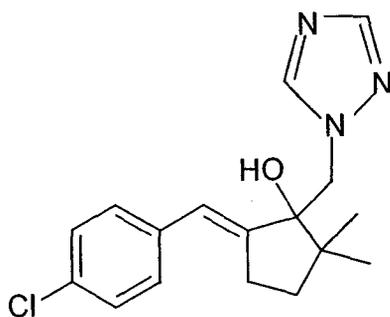
Chapter 4

ATTEMPTED SYNTHESIS OF SELECTED NATURAL PRODUCTS

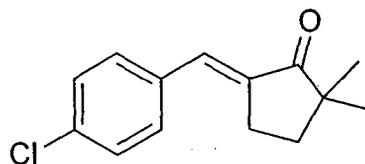
Section I

An Attempted Synthesis Of 2-(*p*-Chlorophenyl) Methylidene-5,5-Dimethyl Cyclopentanone (2), An Intermediate For Potent Fungicide (1).

4.1.1 Introduction



1

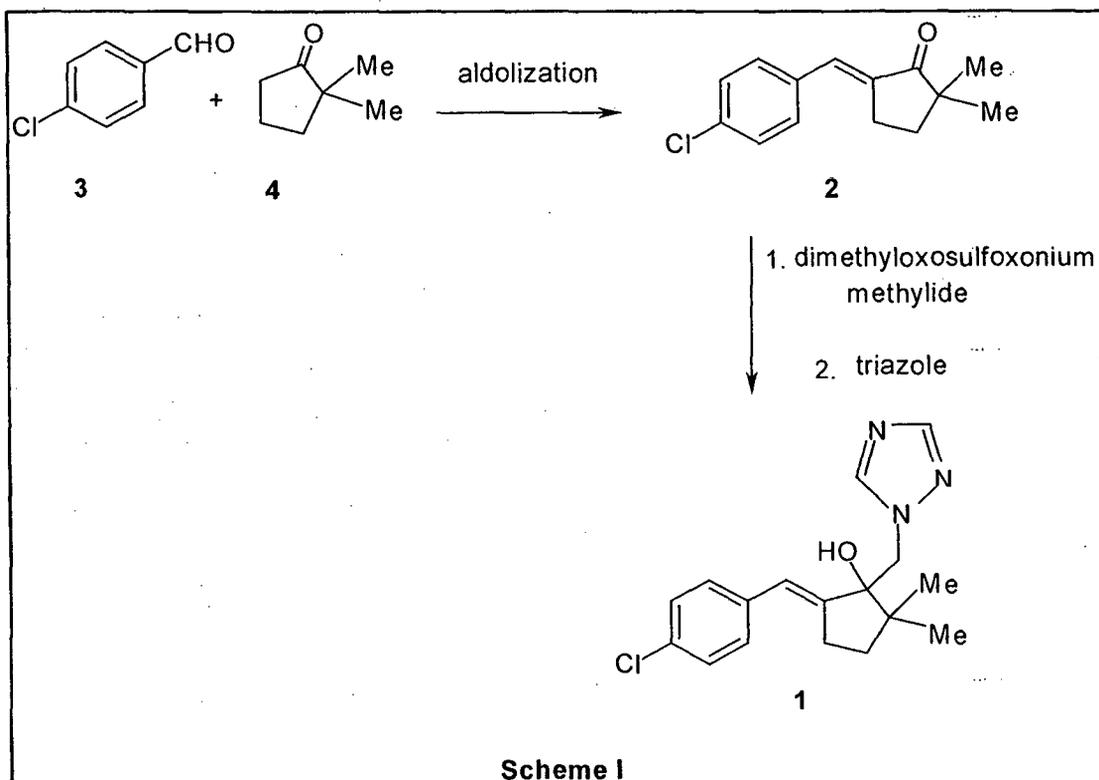


2

Compound **1**¹ is found to be a potent fungicide, mainly used to protect crops against *Botrytis cinera*. Its efficiency has been found to be more than 80%.

The first synthesis of fungicide **1** has been reported by Mugnier *et al*^{2a} in a French patent. Ketone **2** has been obtained by aldolization of 2,2-dimethylcyclopentanone **4** with *p*-chlorobenzaldehyde. The final fungicide **1** is

obtained by condensing ketone **2** with dimethyloxosulfoxonium methylide (Corey ylide) and the resulting product was opened with triazole² (Scheme I)

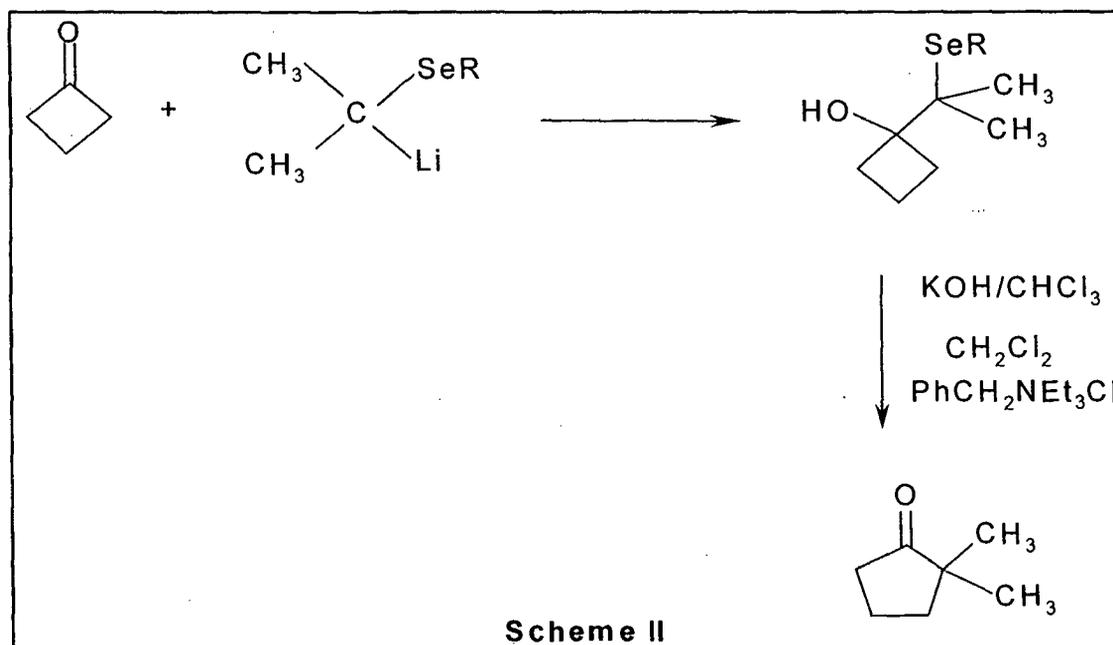


Compound **2**, 2-[(*p*-chlorophenyl)methylidene]-5,5-dimethylcyclopentanone is a key intermediate in the synthesis of fungicide **1** and as mentioned above, is prepared from substituted cyclopentanone **4**. Syntheses of 2,2-disubstituted-1-cyclopentanone **4** can be broadly divided into two general categories. The first type involves the cyclization of appropriately substituted pentenoic acids, dinitriles or diacids. The second method comprises of direct alkylation of cyclopentanone, either in a one or two step fashion, resulting in the formation of 2,2-disubstituted cyclopentanone derivatives.

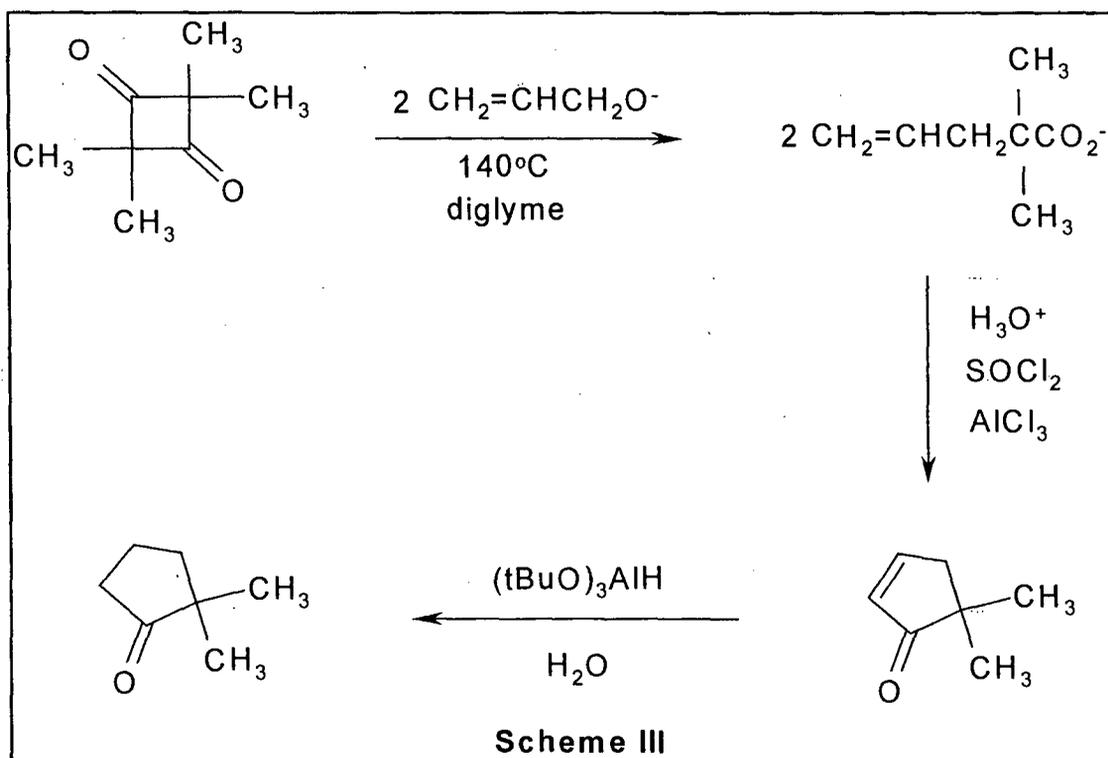
In practice, preparation of ketone **4** has always been cumbersome. Monoalkylation of 2-methylcyclopentanone³ and dimethylation of cyclopentanone⁴ resulted in mixture of polyalkylated cyclopentanones. The separation of desired ketone **4** from the mixture of this polyalkylated cyclopentanones is very difficult. Other methods involve multistep reactions such as, cyclization of methyladipic acid⁵, 5-iodo-2,2-dimethylpentan-2-dimethylpent-4-enal⁶, pinacolic transposition⁷ etc.

Some of the more recent methods for the preparation of 2,2-dimethylcyclopentane **4** are mentioned below.

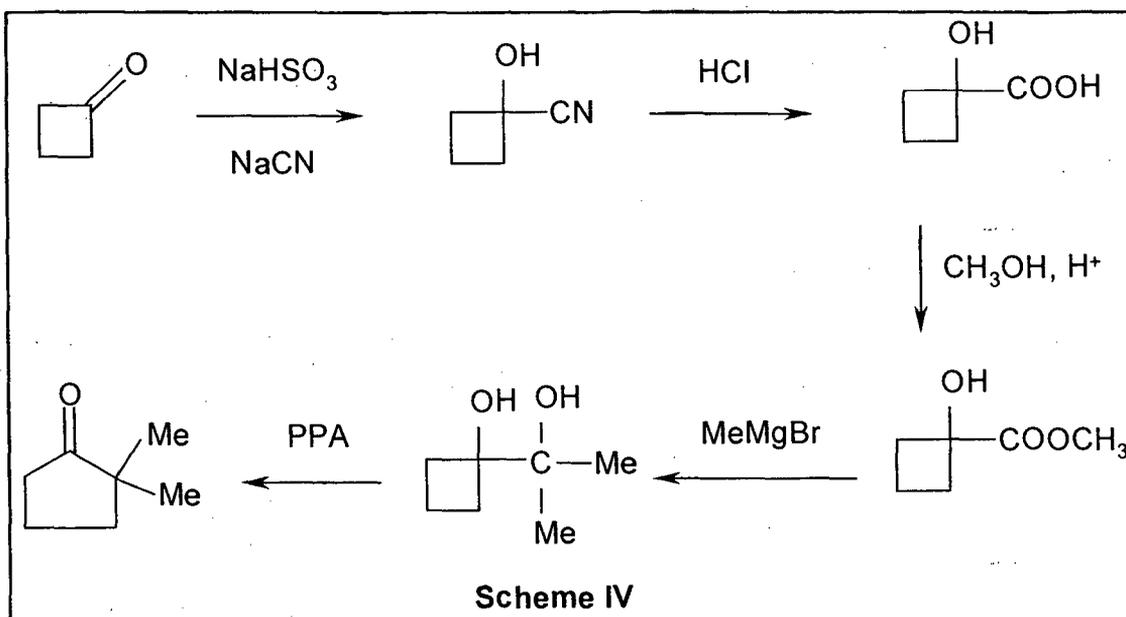
Krief *et al*⁸ have reported reaction of β -hydroxyalkylselenides possessing two alkyl substituents on the carbon bearing the selenenyl moiety with dihalocarbenes generated from haloforms to produce ring enlarged ketones (Scheme II).



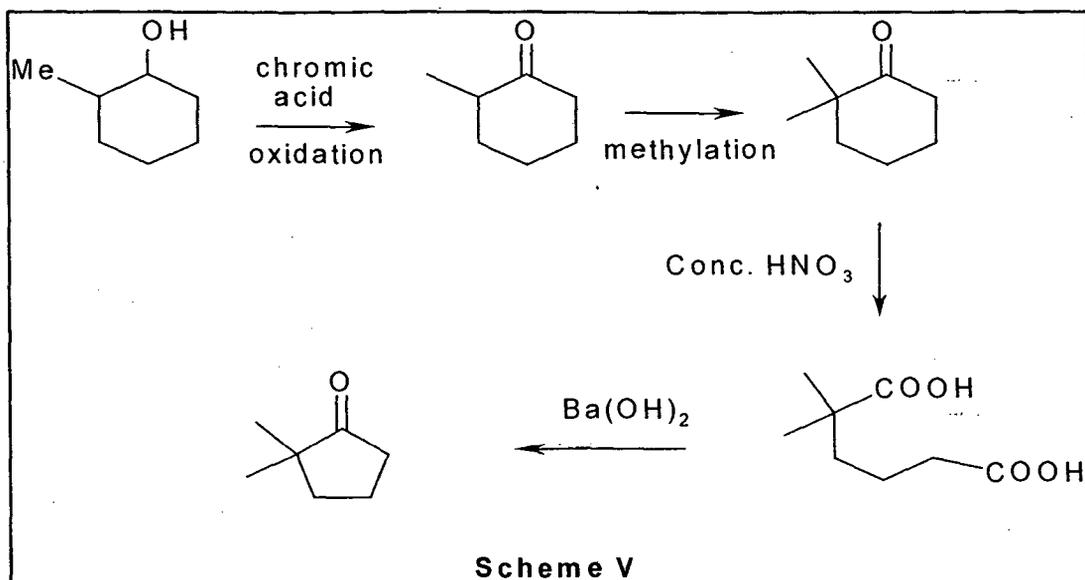
Kopecky and Levine⁹ have accomplished the synthesis of **4** by treating tetramethyl-1,3-cyclobutanedione with two equivalents of allyl oxide anion at 140°C to yield 2,2-dimethyl-4-pentenoic acid, which on intramolecular Friedel-Crafts acylation provided 5,5-dimethyl-2-cyclopentenone. Reduction of this ketone with tri-(t-butoxy)aluminium hydride at -70°C gave 5,5-dimethylcyclopentenone (Scheme III).



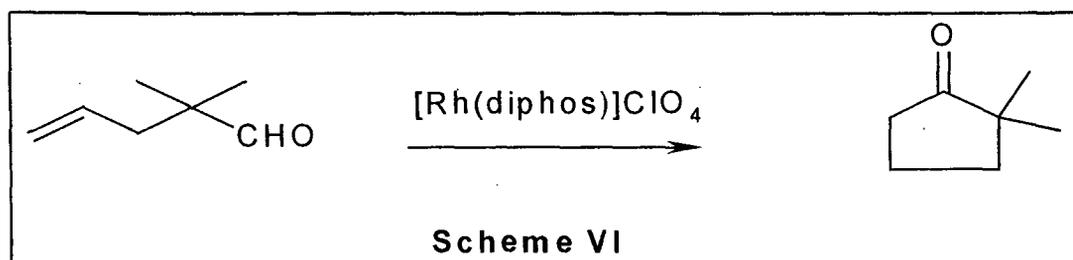
Conley¹⁰ has reported a general route to 2,2-dimethylcyclopentanone **4** in 79% yield, by the ring expansion of the corresponding 1-(disubstituted carbinol)-1-hydroxycyclobutane in polyphosphoric acid (**Scheme IV**).



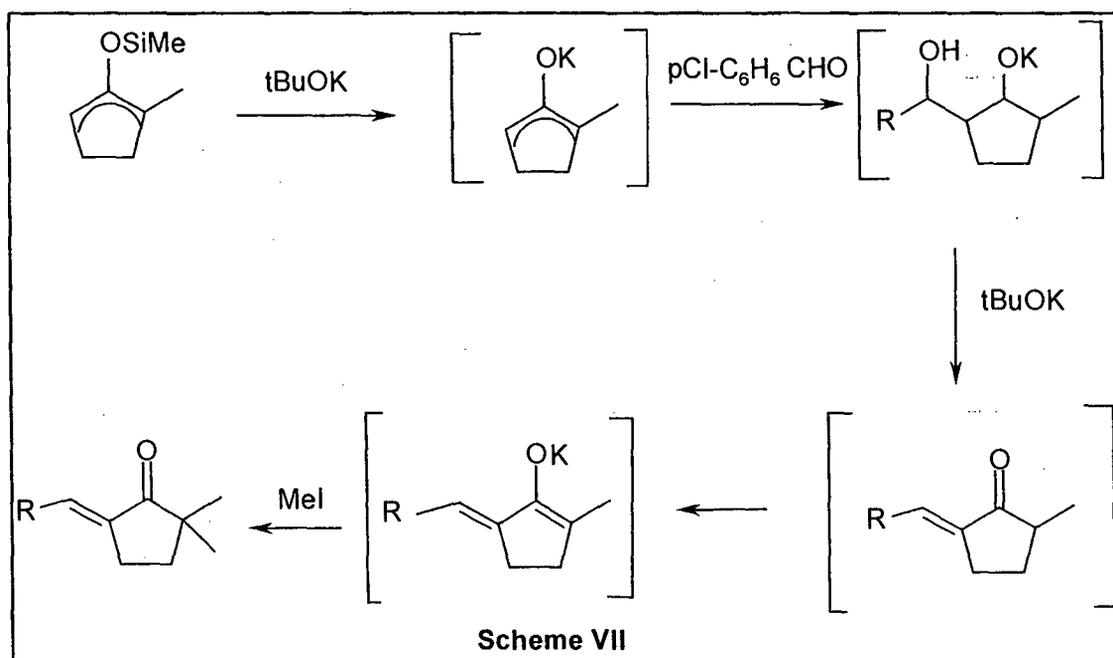
Wilcox and coworker¹¹ have described preparation of this key intermediate **4** from 2-methylcyclohexanol. The steps involved are chromic acid oxidation followed by monomethylation and oxidation under Meerwein-Unkels conditions. The treatment of diacid with $\text{Ba}(\text{OH})_2$ furnished 2,2-cyclopentanone (**Scheme V**).



Bosnich and coworker¹² have reported a reaction which involved conversion of 4-pentenals to cyclopentanones by Rhodium-catalyzed hydroacylation (**Scheme VI**).



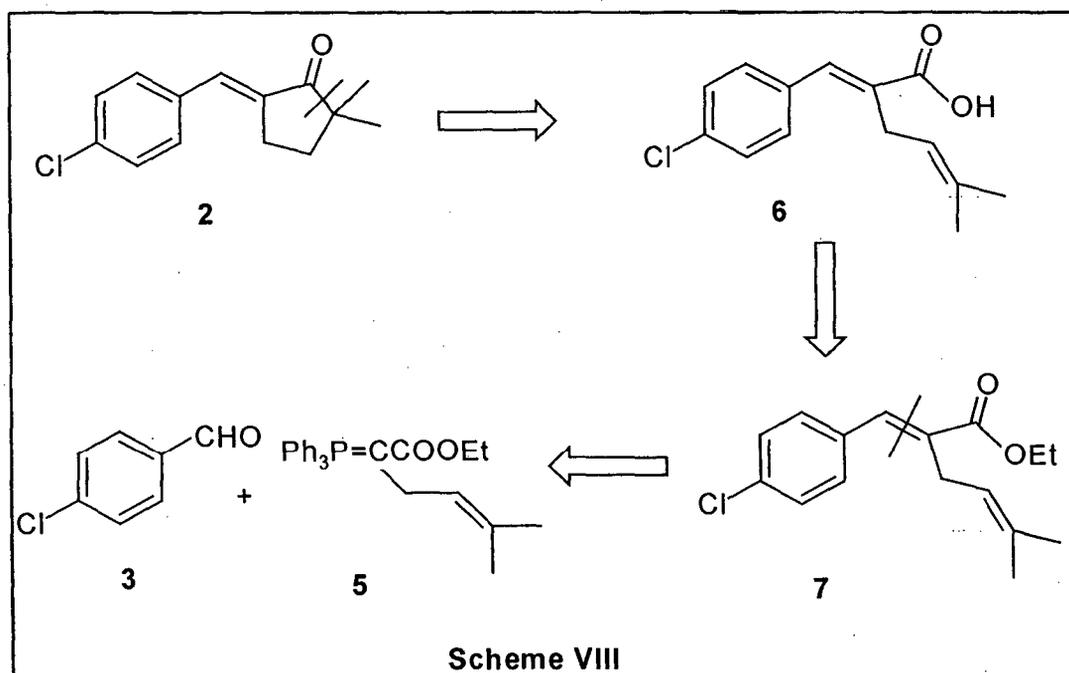
Duhamel *et al*¹³ have achieved synthesis of ketone **2**, in 80% yield, via a novel route involving regioselective aldolization with *p*-chlorobenzaldehyde of 2-methylcyclopentene followed by methylation (**Scheme VII**).



From the various reactions listed above for the preparation of 2,2-dimethylcyclopentanone **4**, a precursor for synthesis of **2**, it can be seen that it is difficult to access and requires a multistep procedure.

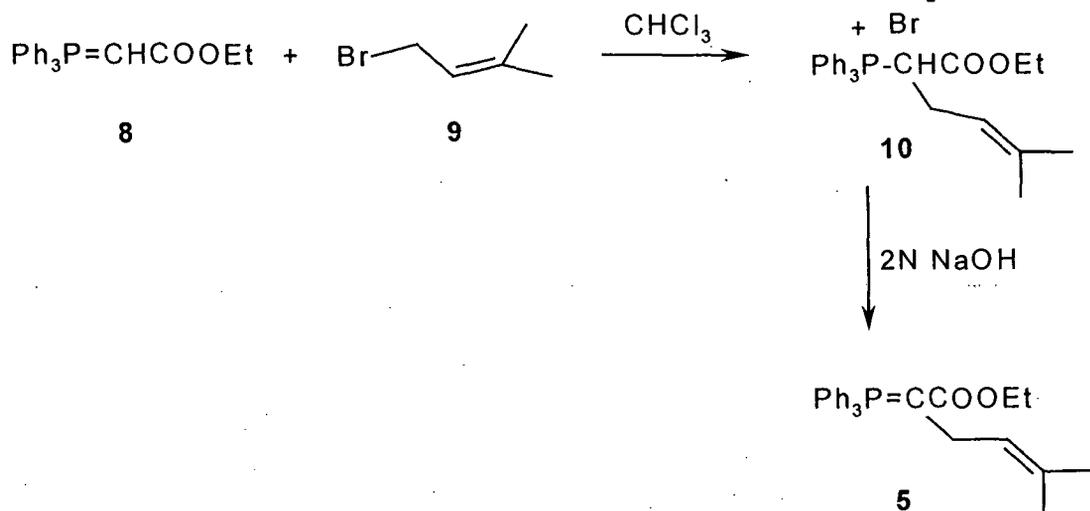
So, we thought of achieving the synthesis of intermediate **2**, using a different approach, wherein the cyclization step would be carried out at the latter stage to synthesize compound **2**, and also using the phosphorane intermediates

that have proven versatile synthones in our hands. The retrosynthesis of the approach is depicted in **Scheme VIII**.

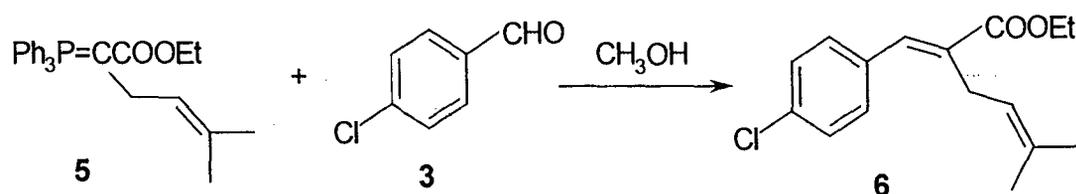


Broadly, the strategy involved was the condensation of prenyl phosphorane **5** with p-chlorobenzaldehyde **3** to obtain α,β -unsaturated ester **6**, which could then be hydrolysed to an acid **7**. Cyclization of this acid **7** would yield the desired ketone **2**.

Our first step was to prepare prenyl phosphorane **5**. This was prepared by the reported method¹⁴. Alkylation of stable phosphorane¹⁵ **8** with prenyl bromide **9** resulted in the phosphorane salt **10** which was then treated with 2N NaOH to obtain the desired phosphorane **5**.



Our next step was to condense this prenyl phosphorane **5** with *p*-chlorobenzaldehyde **3**.

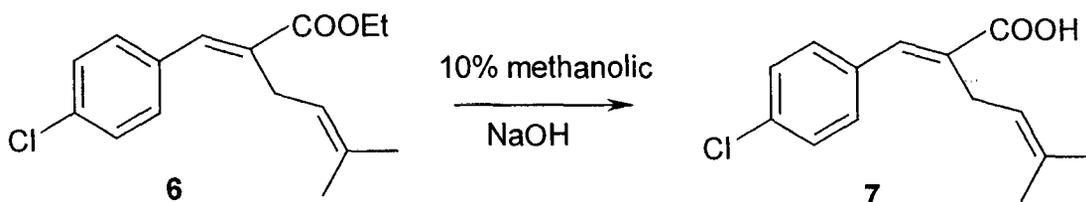


This was accomplished by refluxing *p*-chlorobenzaldehyde **3** with prenyl phosphorane **5** in methanol for 3 hours. Tlc of the reaction mixture showed the disappearance of the starting aldehyde and appearance a new spot along with triphenylphosphine oxide. The crude product was purified by column chromatography over silica gel using EtOAc: hexanes (5:95) as eluent to obtain a pleasant smelling viscous liquid in 95% yield.

Its IR spectrum exhibited a strong band at 1725 cm^{-1} which could be attributed to the carbonyl of the unsaturated ester group.

The $^1\text{H-NMR}$ spectrum (Fig. 4.1.1), showed signals at δ 1.35 (t, $J = 7.2$ Hz, 3H) and δ 4.23 (q, $J = 7.2$ Hz, 2H), which could be attributed to $-\text{OCH}_2\text{CH}_3$ group. The peaks exhibited at δ 1.62 (s, 3H) and δ 1.72 (s, 3H), could be due to the two allylic methyl groups while the peaks observed at δ 3.18 (d, $J = 6.6$ Hz, 2H) and δ 5.12 (t, $J = 1.2$ Hz, 1H), could be assigned to the methylene protons and CH of prenyl group ($-\text{CH}_2\text{CH}=\text{C}<$). The signal at δ 7.34 (m, 4H), could be attributed to aromatic protons of phenyl ring and the peak at δ 7.61 (s, 1H) could be assigned to the benzylic proton. The down field shift of this proton indicated it to be cis to the $-\text{COOCH}_2\text{CH}_3$ group (*E* geometry), hence the ester should have structure 6.

The ester 6 obtained was then hydrolysed by refluxing it with 10% methanolic NaOH for about 4 hours. The reaction mixture was then neutralized with HCl to afford a white solid. Recrystallization with aqueous ethanol furnished compound 7 in 69.6% yield. The solid melted at 190°C .



Its IR spectrum exhibited a broad band at 3500 cm^{-1} and a strong band at 1690 cm^{-1} could be due to the presence of α - β unsaturated carboxylic acid.

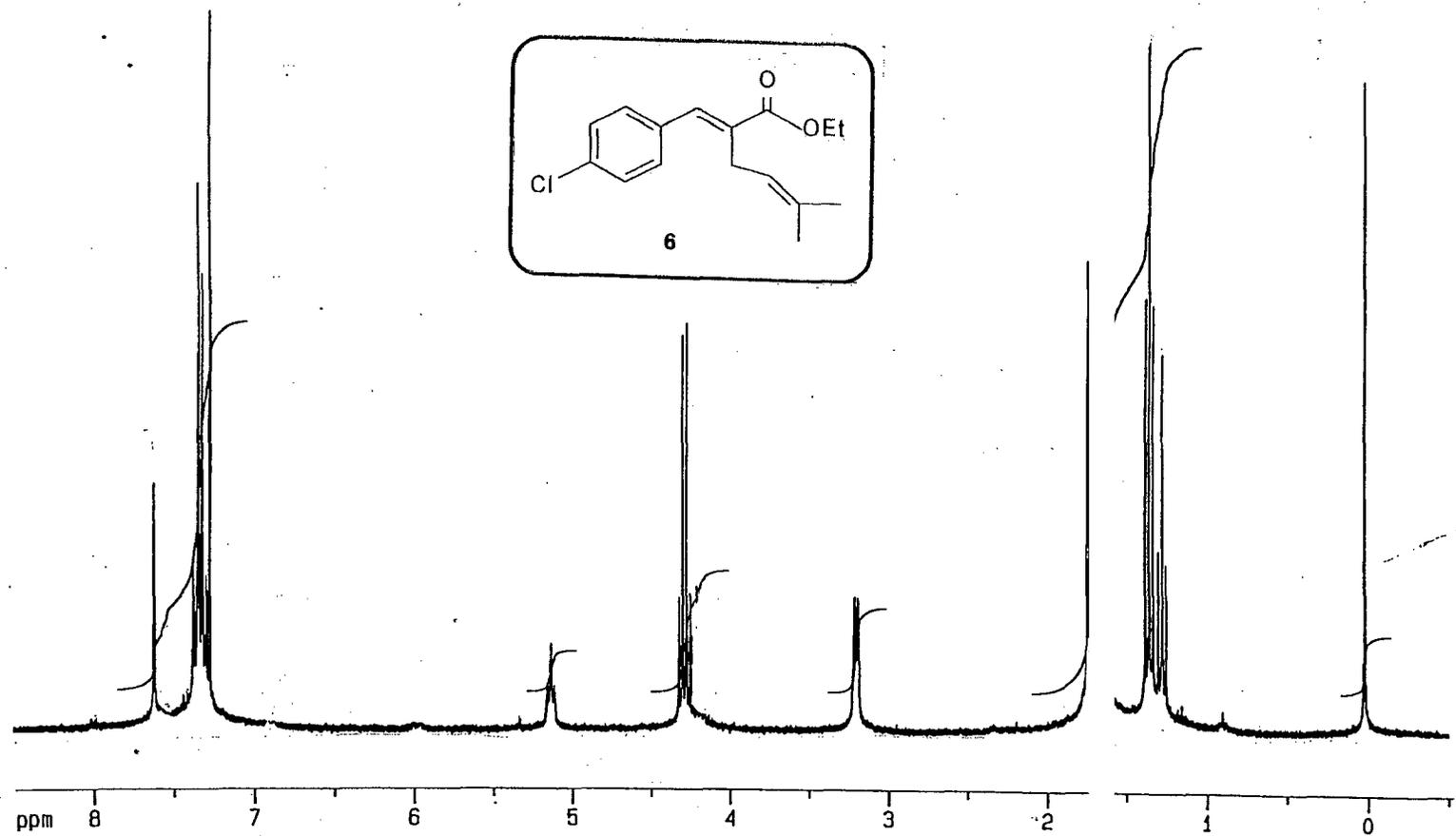


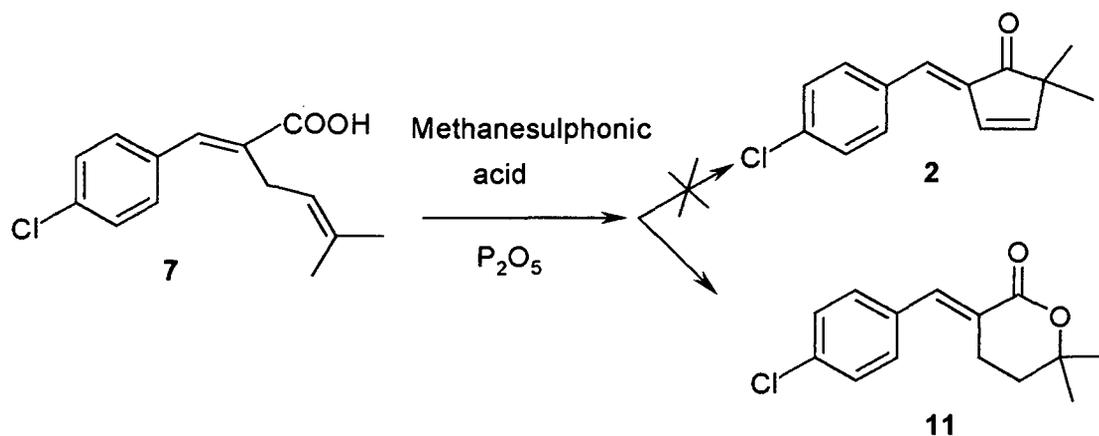
Fig. 4.1.1 : ¹H-NMR of ethyl-2-(p-chloro benzylidene)-5-methyl-1-ene-hexanoate (6)

The ^1H NMR spectrum, showed peaks at δ 1.67 (s, 3H) and δ 1.74 (s, 3H) which could be assigned to the two allylic methyl groups. The signals at δ 3.22 (d, $J = 6.6$ Hz, 2H) and δ 5.15 (t, $J = 1.2$ Hz, 1H) could be assigned to the methylene protons and CH of prenyl group ($-\text{CH}_2\text{CH}=\text{C}<$).

The peak at δ 7.35 (m, 4H) could be attributed to aromatic protons of phenyl ring while the signal at δ 7.76 (s, 1H) could be assigned to the benzylic proton. The down field shift of this proton indicated it to be cis to the $-\text{COOH}$ group (*E* geometry), hence the acid should have structure **7**.

Our last step was to carry out the ring cyclization of the α - β unsaturated acid **7**. In literature, there are few examples where such five membered ketones have been cyclized from alkene-acids, for instance, PPA cyclization¹⁶. Eaton *et al*¹⁷ have reported a novel method for conversion of lactones into ketones using methanesulphonic acid and phosphorous pentoxide. We visualized that, this method would furnish the required ketone **2**.

So, we added acid **7** to the stirred mixture of methane sulphonic acid and phosphorous pentoxide (1:10). The progress of the reaction was monitored by tlc. Tlc showed the appearance of new spot. The crude product obtained was further purified by column chromatography over silica gel using EtOAc: hexanes (5:95) as eluent to obtain a white solid. Recrystallization with EtOAc-hexanes afforded solid **11** in 56% yield. The melting point of the solid was found to be 103°C.



The spectral data of the product **11** is given below.

IR : 1700 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3) : (Fig. 4.1.2)

δ 1.45	s	6H
δ 1.89	t, ($J = 7.2\text{ Hz}$)	2H
δ 2.86	t, ($J = 7.2\text{ Hz}$)	2H
δ 7.39-7.48	m	4H
δ 7.85	br. s,	1H

$^{13}\text{C-NMR}$ (CDCl_3) spectrum : (Fig. 4.1.2')

δ : 22.63 (CH_3), 27.73 (CH_3), 33.03 (CH_2), 80.13 (C), 116.07 (CH), 124.93 (C), 128.77 (CH), 129.12 (C), 131.43 (CH), 133.45 (CH), 135.08 (C), 139.99 (CH), 166.65 (C)

The multiplicities were obtained from DEPT-135 experiments.

The reported¹ spectral data of expected compound **2** is given below.

IR : 1704 cm⁻¹

¹H-NMR (CDCl₃) :

δ 1.10	s	6H
δ 1.83	t, (J = 7.3 Hz)	2H
δ 2.83	d, (J = 2.7, 7.3 Hz)	2H
δ 7.32	s	1H
δ 7.33-7.44	2d, (J = 8.6, 12.6 Hz)	4H

¹³C-NMR (CDCl₃):

δ : 25.6, 35.6, 44.7, 128.8, 131.5, 131.6, 134.0, 134.9, 135.8, 210.9

Comparison of spectral data (IR & ¹H NMR) of compound **2** with that of the observed data for product obtained **11**, could not confirm formation of ketone **2**. So, based on spectral data, structure **11** was assigned for the product.

In PMR spectrum of the product, a downfield broad singlet (br.s, 1H) was seen at δ 7.85, which was not seen in the spectrum of ketone **2**. In ¹³C NMR data, we could observe the difference in the spectra. Signal at δ 44.7 was missing in the product and instead a peak at δ 80.13 was seen. Similarly, the carbonyl group in **2** was seen at δ 210.9, while in the product it was at δ 166.65.

Thus, the H¹NMR spectrum (Fig. 4.1.2), could be assigned to structure **11** as follows. Signal seen at δ 1.45 (br.s, 6H) could be attributed to the two methyl groups while, peaks at δ 1.89 (t, J = 7.2 Hz, 2H) and δ 2.86 (t, J = 7.2 Hz, 2H)

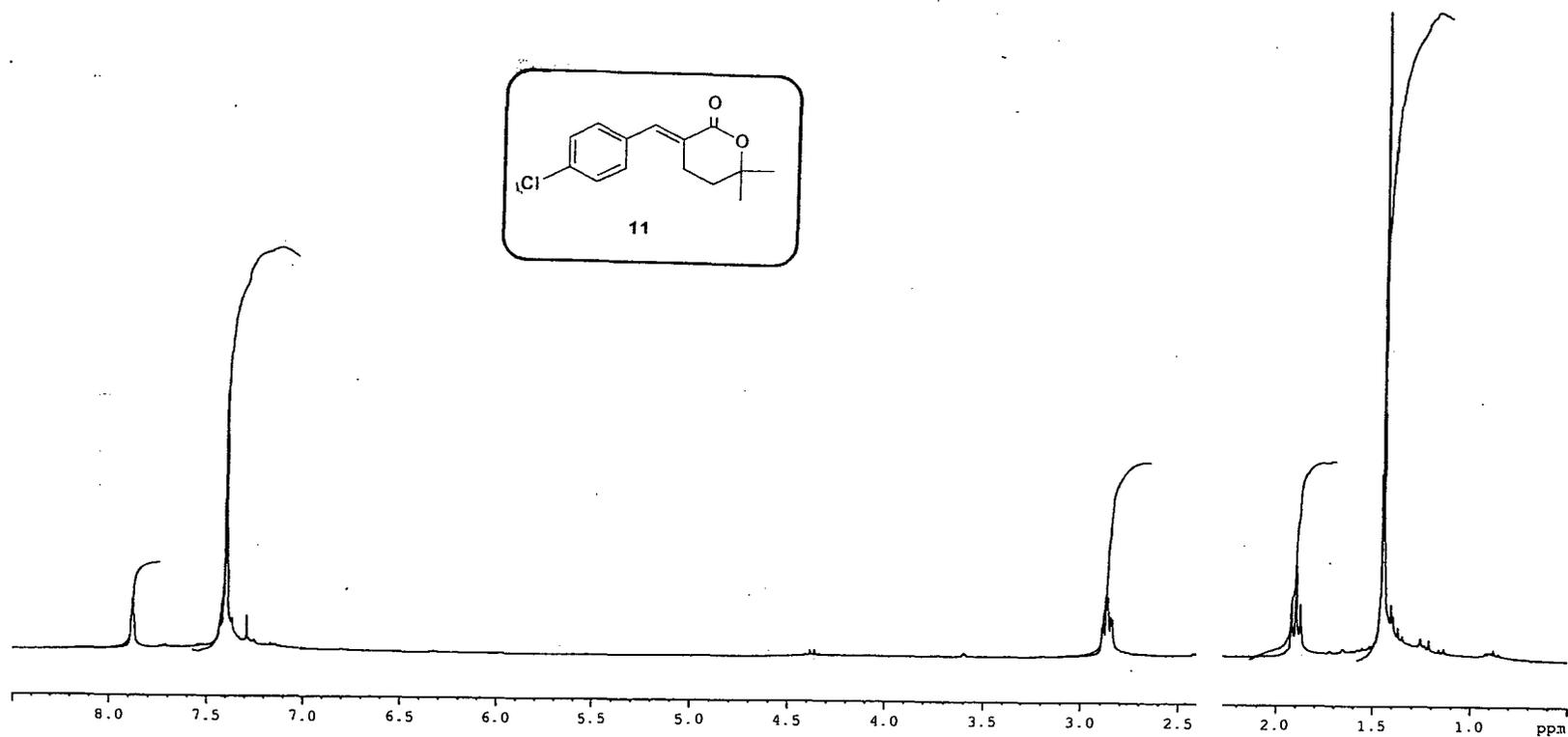


Fig. 4.1.2 : ¹H NMR spectrum of α -(p-chlorobenzylidene)- δ -methyl- δ -lactone (11).

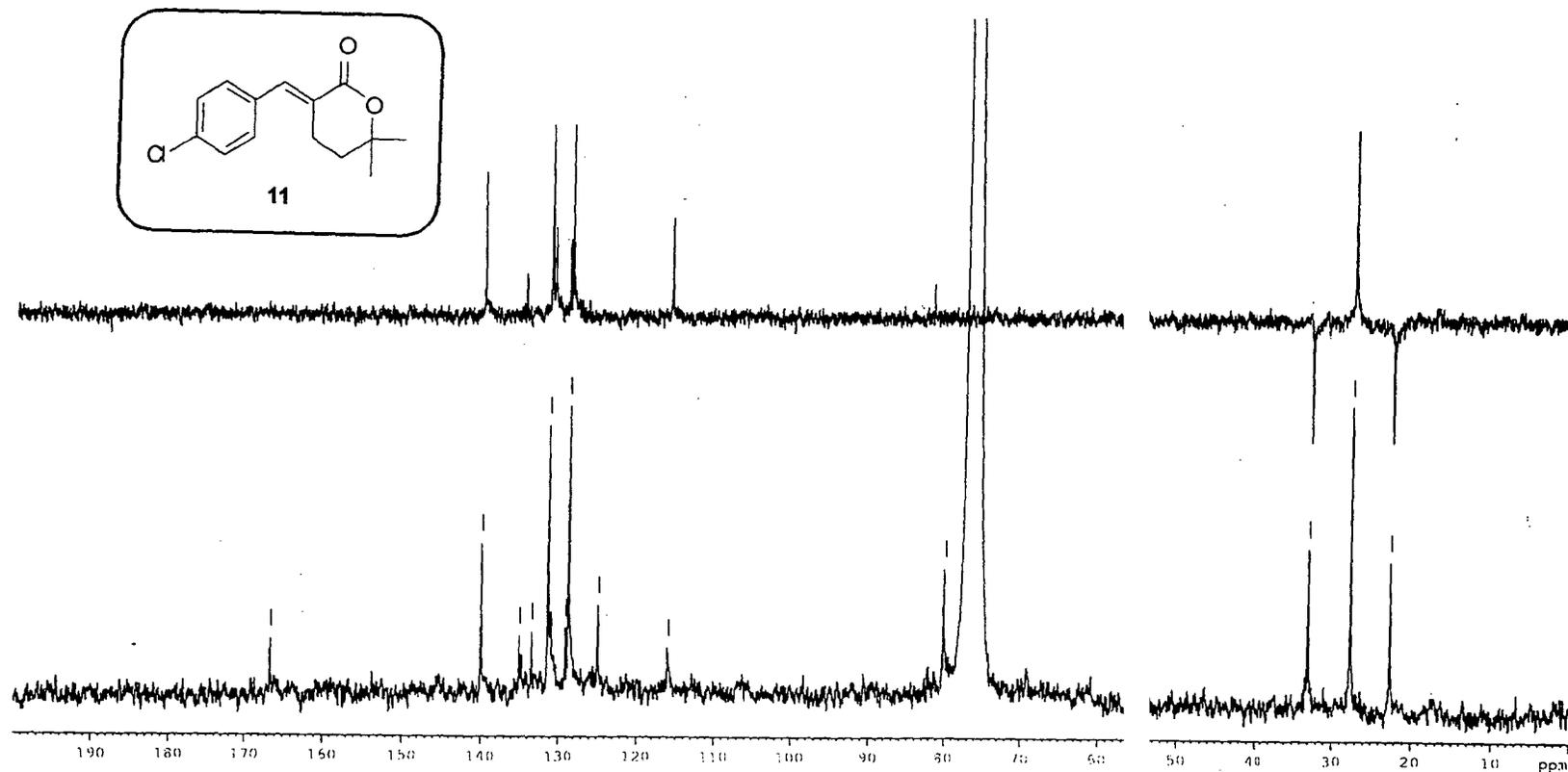
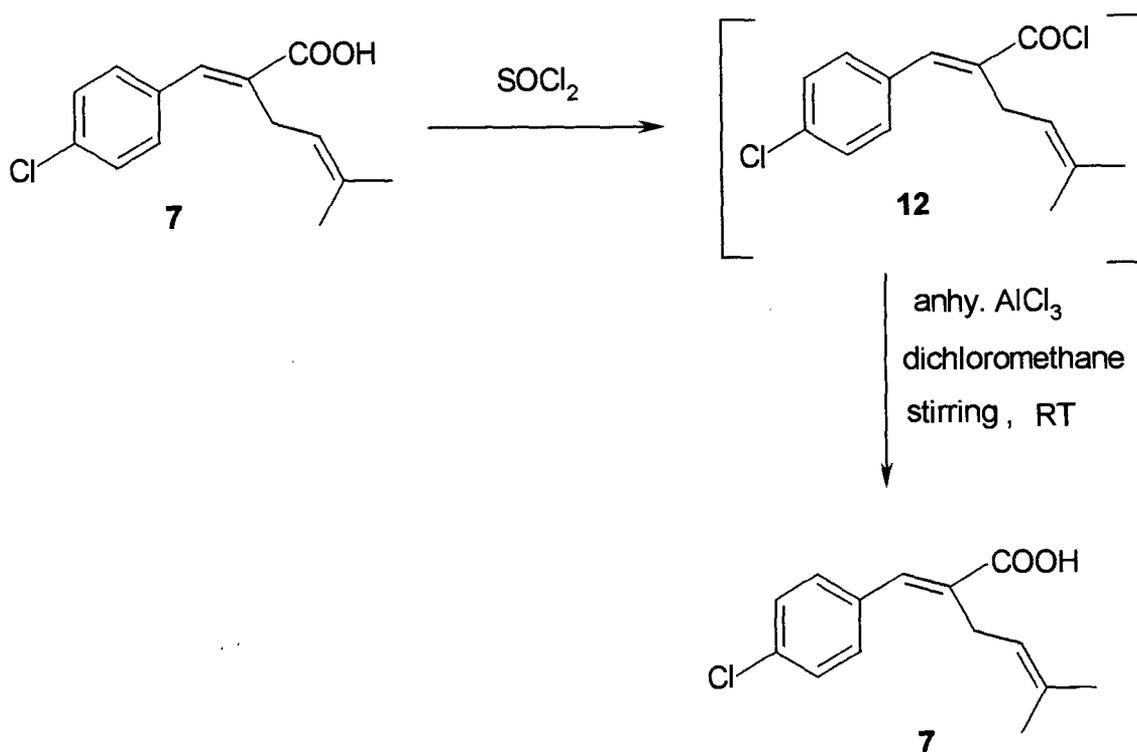


Fig. 4.1.2¹: ^{13}C NMR & DEPT-135 spectrum of α -(p-chlorobenzylidene)- δ -dimethyl- δ -lactone (11).

could be due to the two methylene groups (-CH₂CH₂-). The peak observed at δ 7.39-7.48 (m, 4H) could be attributed to the aromatic protons of phenyl ring while the peak at δ 7.85 (br.s, 1H) could be assigned to the benzylic proton. The down field shift of this proton indicated it to be cis to the carbonyl group (*E* geometry).

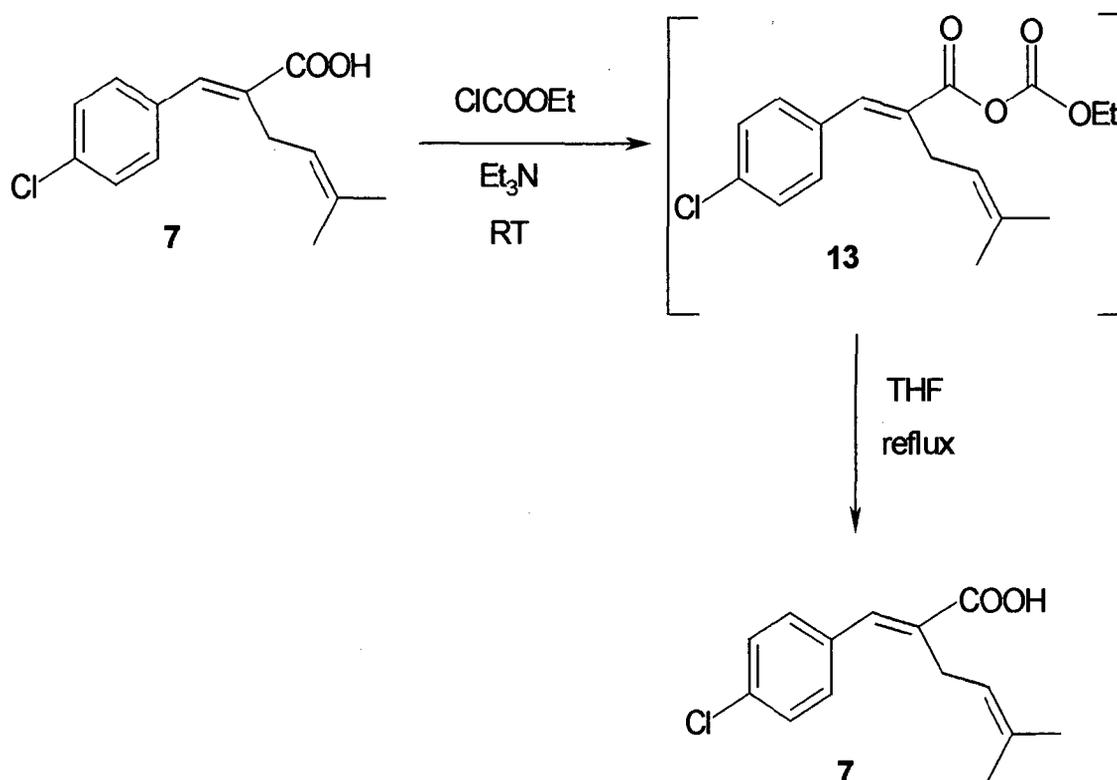
We thought that, perhaps, Friedel-Crafts intramolecular acylation of acid chloride¹⁸ would give the desired cyclopentanone. So, we converted acid **7** to acid chloride **12** by thionyl chloride method. The crude acid chloride **12** obtained without isolation, was treated with anhydrous AlCl₃ in dichloromethane at room temperature. After usual work up, the solid product obtained was recrystallized with aqueous ethanol to afford a white solid in 62% yield, which melted at 190 °C.

This compound was identified as the starting acid **7** based on the physical constant and spectral data.



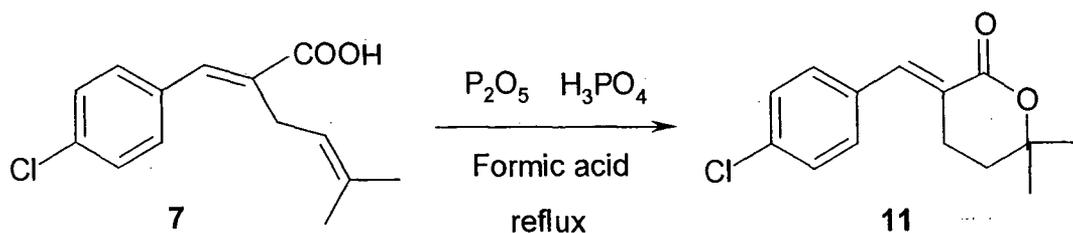
The acid **7** was stirred with ethyl chloroformate in presence of triethylamine at room temperature. The reaction mixture was continued to stir for 2 hours. An aliquot of reaction mixture was tested for Infra Red. The IR spectrum of the compound obtained, displayed bands at 1780 and 1725 cm^{-1} . This indicated the formation of mixed anhydride **13**.

This mixed anhydride **13** was refluxed in THF for 5 h. After work up the compound obtained was crystallized with ethylacetate-hexanes to give a white solid in 79.7% yield, which melted at 190°C.



Physical and spectral properties of the product indicated that the starting acid **7** is recovered back.

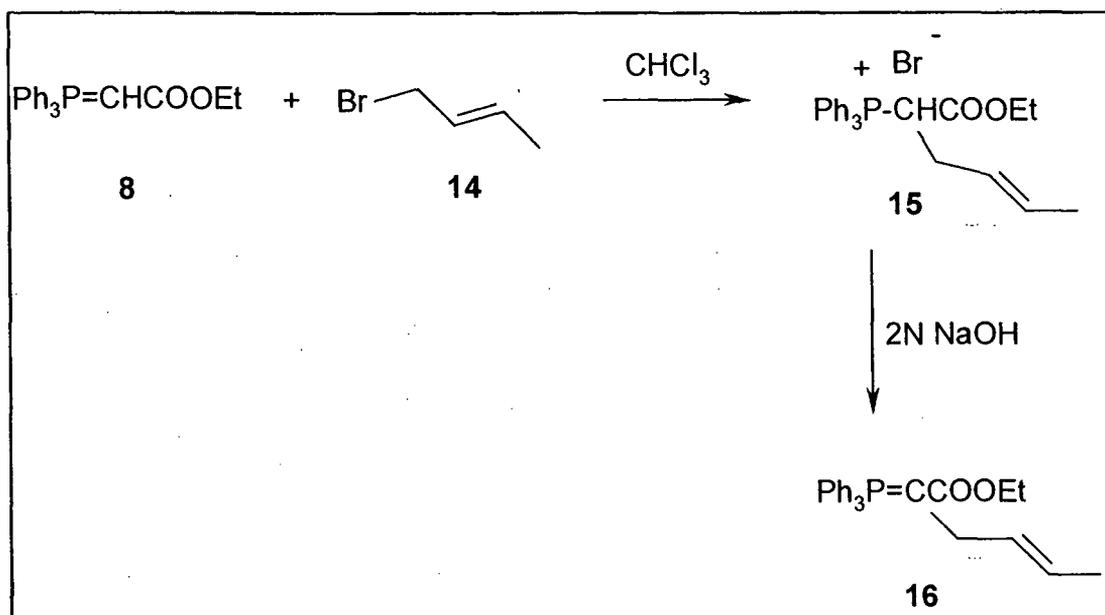
Acid **7** was added to the mixture of phosphoric acid, formic acid and phosphorus pentoxide and the reaction mixture was refluxed. The solid obtained was purified by column chromatography over silica gel using ethylacetate-hexanes. Recrystallization with ethylacetate-hexane afforded solid, which melted at 103°C.



Physical and spectral properties of compound indicated that it is the δ lactone **11**, obtained earlier using methanesulphonic acid and P_2O_5 . It is reported in literature¹⁷ that δ -lactone could be converted to a five membered ketone. We attempted conversion of **11** to ketone by using this method but we obtained the starting δ -lactone **11** back.

We reasoned that the desired product could not be formed, perhaps due to, two methyl groups causing steric hindrance, hence we decided to study this reaction with one methyl group. We synthesized the homoallyl phosphorane **16** in 60% yield, by refluxing the phosphorane **8** with homoallyl bromide **14** in chloroform and then subjecting the salt **15** to dilute sodium hydroxide solution.

The solid obtained was recrystallized with benzene-hexanes and the melting point of the solid was found to be 137°C.



Its IR spectrum exhibited strong bands at 1722 and 1620 cm^{-1} which could be attributed to the carbonyl of unsaturated ester group and to the double bond, respectively.

The ^1H NMR spectrum (Fig. 4.1.3), showed peaks at δ 1.29 (t, $J = 7.2$ Hz, 3H) and δ 4.22 (q, $J = 7.2$ Hz, 2H) which could be attributed to $-\text{OCH}_2\text{CH}_3$ of the ester group, while the peak exhibited at δ 1.65 (d, $J = 4.9$ Hz, 3H), could be due to the crotyl methyl group. The peaks observed at δ 3.14 (d, $J = 3.7$ Hz, 2H), δ 5.48 (m, 2H) could be assigned to the allylmethylene group and two olefinic protons of crotyl group ($-\text{CH}_2\text{CH}=\text{CH}-$). The signal at δ 7.29-7.76 (m, 15H) could be attributed to aromatic protons of three phenyl rings of phosphorane 16.

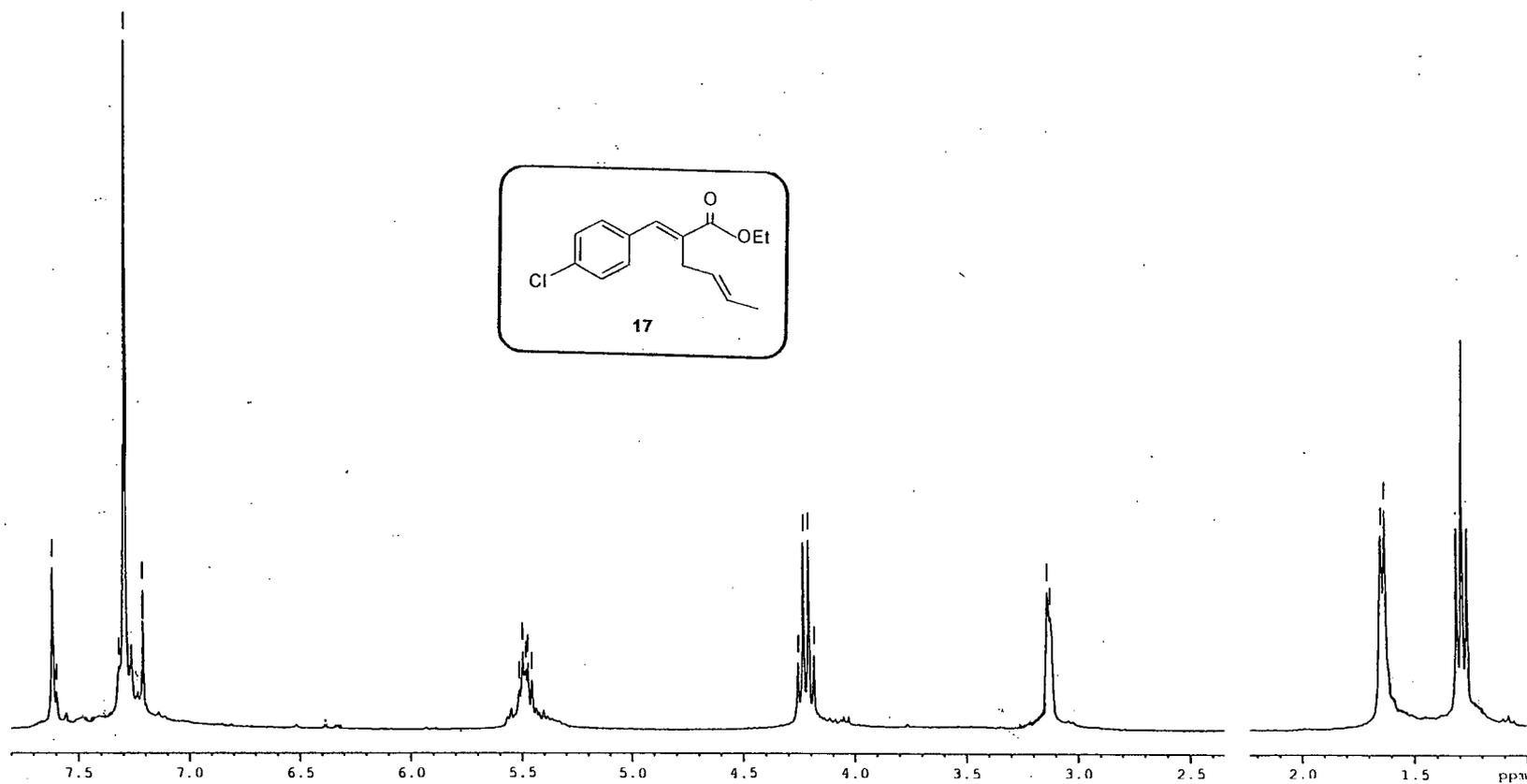
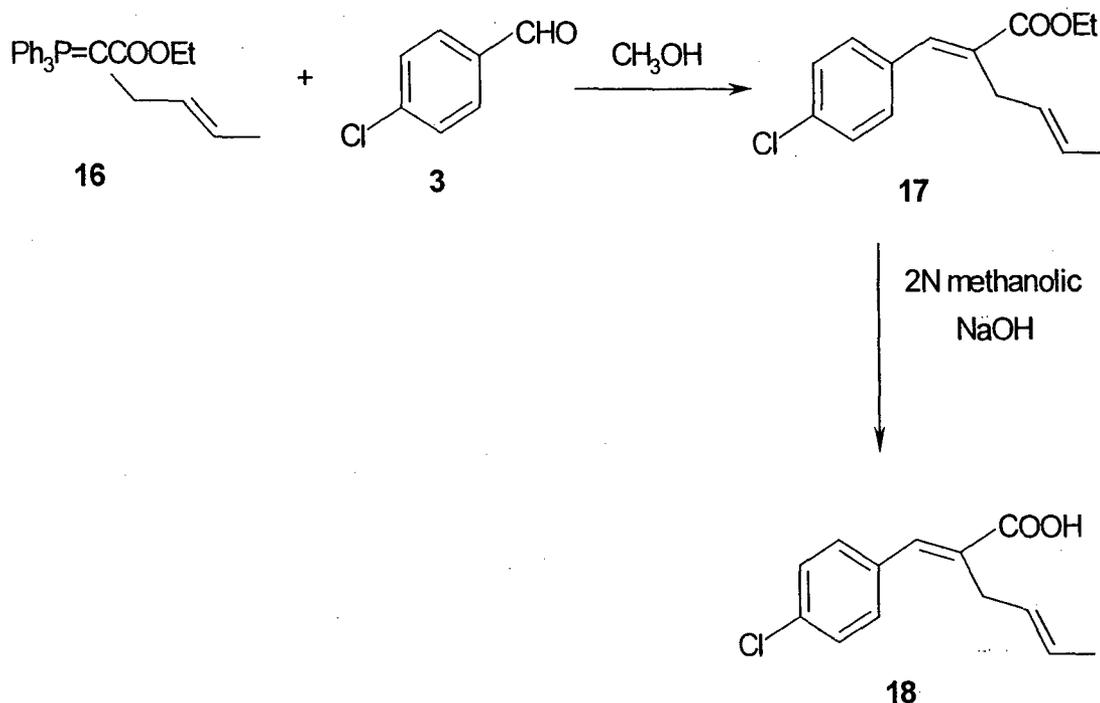


Fig. 4.1.3 : ¹H-NMR of ethyl-2-(p-chloro benzylidene)- 4-ene-hexanoate (17)

This homoallyl phosphorane **16** was condensed with *p*-chlorobenzaldehyde **3** in chloroform. The formation of the product was monitored by tlc. The crude product was separated and purified by column chromatography over silica gel using, EtOAc: hexanes (5:95), as eluent, to yield a pleasant smelling viscous liquid in 91% yield.



Its IR spectrum exhibited a strong band at 1725 cm⁻¹ which could be attributed to the carbonyl of unsaturated ester group.

The H¹NMR spectrum, showed peaks at δ 1.29 (t, *J* = 7.2 Hz, 3H) and δ 4.22 (q, *J* = 7.2 Hz, 2H) which could be attributed to -OCH₂CH₃ of the ester group, while the signal exhibited at δ 1.65 (d, *J* = 4.9 Hz, 3H) could be due to the homoallylic methyl group. The peaks observed at δ 3.14 (d, *J* = 3.7 Hz, 2H) and δ 5.48 (m, 2H), could be assigned to the allyl methylenes protons and two olefinic

protons of homoallylic group (-CH₂CH=CH-), respectively. The peaks at δ 7.29 (br.s, 4H) and δ 7.62 (s, 1H) could be attributed to aromatic protons of phenyl ring and to the benzylic proton. The down field shift of this proton indicated it to be cis to the (-COOCH₂CH₃) group having *E* geometry, hence the ester should have structure **17**.

The ester **17** obtained was then hydrolyzed in methanolic sodium hydroxide to obtain a solid. Recrystallization with aqueous ethanol afforded a white solid **18** in 86% yield, which melted at 168°C.

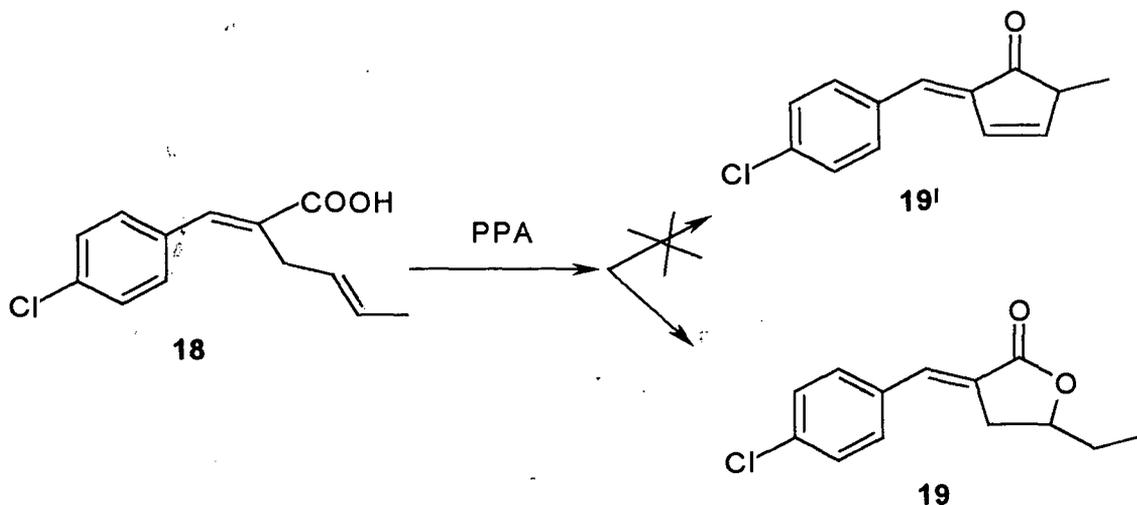
The IR spectrum exhibited a broad band at 3500 cm⁻¹ and a strong band at 1695 cm⁻¹ which could be attributed to the α - β unsaturated carboxylic acid.

The ¹H NMR spectrum, displayed peaks at δ 1.66 (d, *J* = 5.1 Hz, 3H) could be due to the methyl group, while the peaks observed at δ 3.16 (br.s, 2H) and δ 5.51 (m, 2H) could be assigned to the allyl methylenes protons and the two olefinic protons of the crotyl group (-CH₂CH=CH).

The signal at δ 7.35 (br.s, 4H) and δ 7.76 (s, 1H) could be assigned to the aromatic protons and the benzylic proton respectively. Also a peak as broad singlet was seen at δ 4.68 (br.s, 1H, D₂O), exchangeable with D₂O, which could be due to the presence of -COOH proton in the compound. The down field shift of this benzylic proton indicated it to be cis to the (-COOH) group (*E* geometry), hence the compound should have structure **18**.

The acid **18** obtained, was then subjected to the PPA cyclization. The crude product was purified on column chromatography to give a white solid

compound. Recrystallization with ethylacetate-hexanes afforded solid **19** in 67% yield and melted at 110°C.



Its IR spectrum exhibited a strong band at 1748 cm^{-1} . This could be due to the carbonyl of ketone **19'** or of butyrolactone **19**.

The ^1H NMR spectrum (Fig. 4.1.4), displayed peaks at δ 0.99 (t, $J = 4.8$ Hz, 3H) and at δ 1.72 (m, 2H) could be attributed to the (-CH-CH₂-CH₃) group. The signals exhibited at δ 2.75 (dddd, $J = 17.3, 5.5$ & 3.0 Hz, 1H) and δ 3.33 (dddd, $J = 17.5, 7.8$ & 2.8 Hz, 1H) could be assigned to the two protons of methylene group (-CH₂CH-) showing dddd patterns (geminal, vicinal and allylic couplings). The peak observed at δ 4.52 (m, 1H) could be assigned to the proton of the carbon atom attached to the oxygen atom while the peaks observed at δ 7.37 (s, 4H) and δ 7.45 (t, $J = 1.8$ Hz, 1H) could be attributed to aromatic protons of phenyl ring and the benzylic proton which has shown splitting due to long range allylic coupling (CH=C-CH₂-).

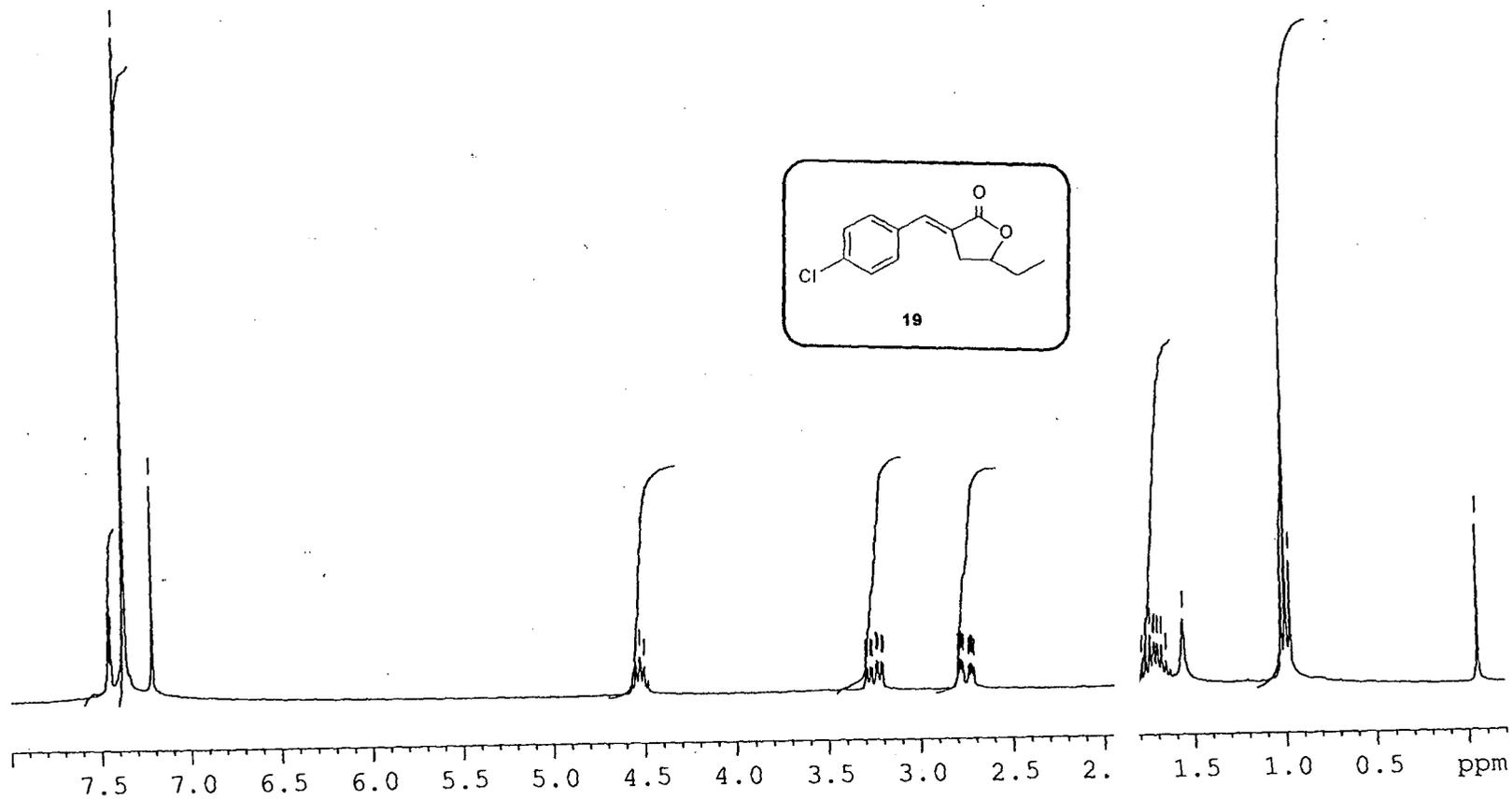
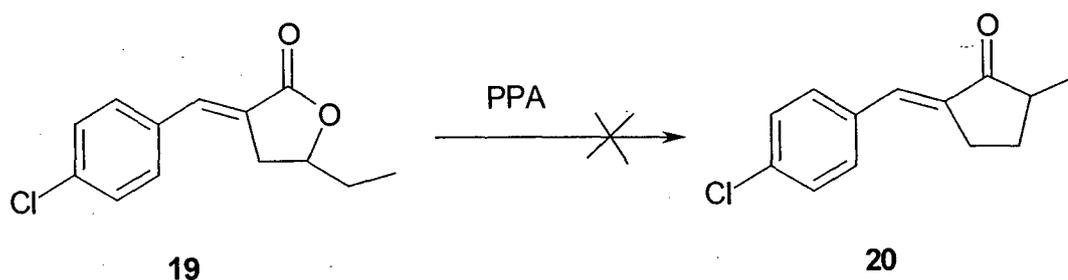


Fig. 4.1.4 : ¹H-NMR of α-(p-chlorobenzylidene)-γ-ethyl-γ-butyrolactone (19)

Based on (^1H NMR) spectral analysis structure **19** was given to the compound.

The expected cyclopentanone product **2** could not be obtained by the above described method, it was thought that perhaps treating this butyrolactone **19** with PPA at higher temperature would yield us the desired cyclopentanone product **20**.



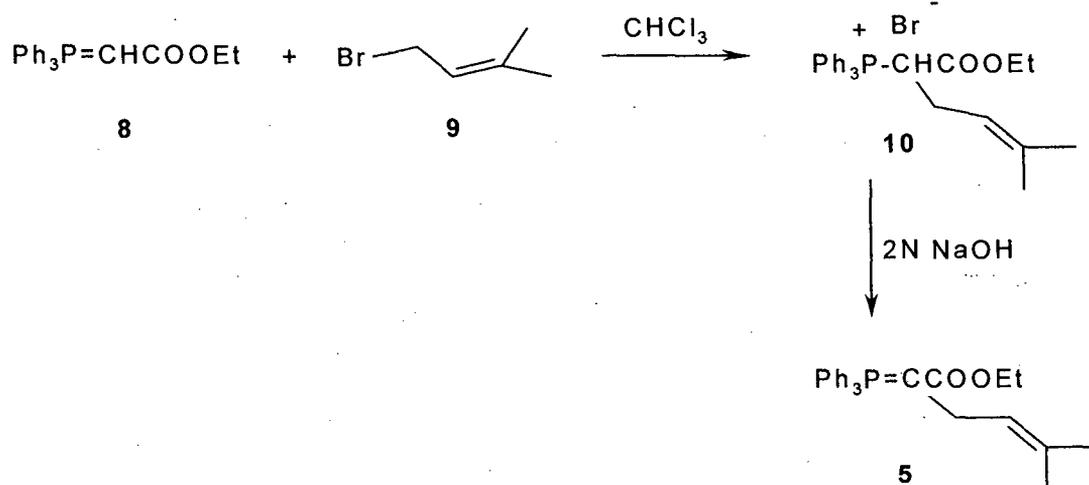
The butyrolactone **19** was subjected to PPA. The reaction mixture was heated at 140°C for 24 h. The reaction was monitored by tlc. The tlc did not show any formation of new spot indicating that the starting compound remained intact.

4.1.2 Conclusion

- An unsuccessful attempt has been made to synthesize 2-[(*p*-chlorophenyl) methylidene] -5,5-dimethylcyclopentanone (**2**).
- During the synthesis using prenyl phosphorane (**5**), formation of δ -lactone was observed. This observation could be exploited to make library of different δ -lactone compounds, using different aldehydes.
- A new crotyl phosphorane **15** has been synthesized. The reagent can be used for the synthesis of γ -ethyl- γ -butyrolactones¹⁹.

4.1.3 Experimental

Expt. 1 : Preparation of Carboethoxy-(α -prenyl)-methylenetriphenyl-phosphorane (5).

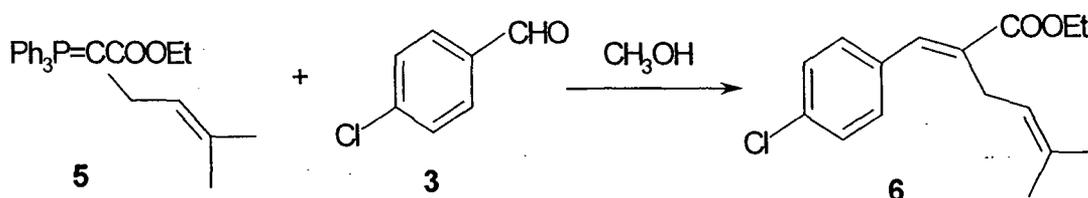


A mixture of prenyl bromide **9** (25 mL) and carboethoxymethylene triphenyl phosphorane¹⁵ **8** (10 g, 2.87 mmol) was refluxed in chloroform (10 mL) for 5 hours and kept overnight at room temperature. It was filtered and the solid was washed with dry ether. On recrystallisation from chloroform: n-hexanes, it furnished salt **10** (8.1g, 60%) m.p.150-151°C.

The salt was dissolved in water (125 mL) and benzene (100 mL) was added to it. Phenolphthalein (1 or 2 drops) was added to it. 2N sodium hydroxide solution was added to it with stirring till pink colour persisted. The benzene layer was separated and the aqueous layer was extracted with benzene (50 mL). The combined benzene layer was dried over anhy. sodium sulphate and the solvent

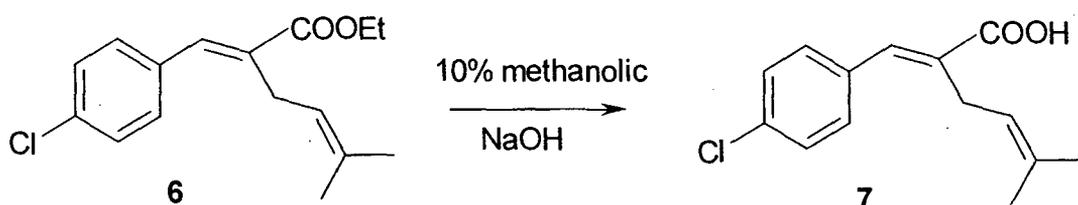
removed under reduced pressure to get a crude product. It was recrystallised from benzene : hexanes to furnish phosphorane **21** (5.6 g, 50%) m.p. 122°C.

Expt. 2 : Preparation of (E) ethyl-2-(p-chlorobenzylidene)-5-methyl-4-ene-hexanoate (6)



A mixture of p-chlorobenzaldehyde (0.212 g, 1 mmol), prenyl phosphorane **5** (0.388 g, 1 mmol) and methanol (5 mL) was refluxed for 3 hours. The solvent was concentrated in vacuum. The crude product was adsorbed on silica gel and purified by column chromatography over silica gel using ethyl acetate:hexanes (5:95) as eluent, to furnish a pleasant smelling viscous liquid **6** (0.306 g, 95%).

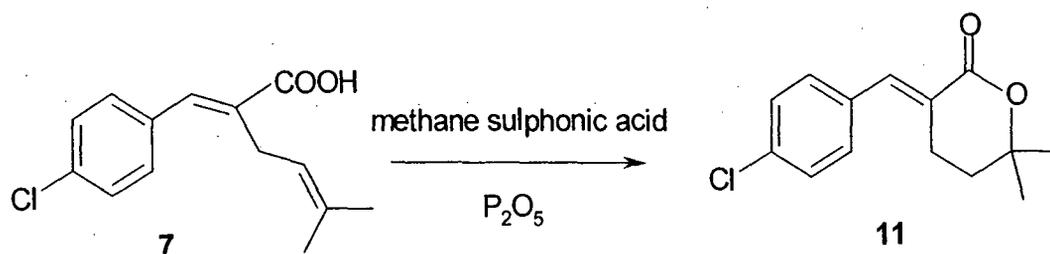
Expt. 3 : Preparation of (E) 2-(p-Chlorobenzylidene)-5-methyl-4-ene-Hexanoic acid (7)



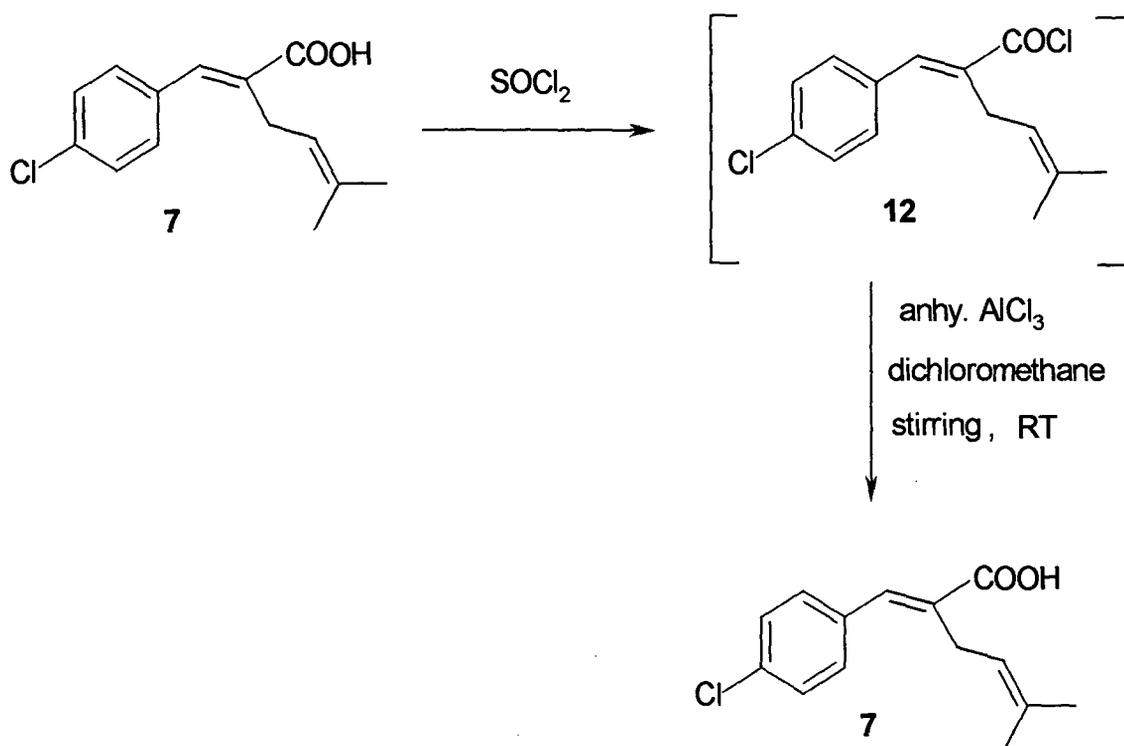
To the solution of prenyl ester **6** (0.278 g, 1mmol) in methanol (10 mL) was added 10% sodium hydroxide (10 mL) and the reaction mixture was refluxed

for four hours. The reaction mixture was evaporated to remove methanol. The reaction mixture was extracted with diethyl ether (3 x 5 mL) and the aqueous layer was neutralized with concentrated hydrochloric acid. The solid obtained was filtered at the pump and dried. The recrystallization was done by aqueous ethanol to yield a white solid **7** (0.174 g, 69.6%, m.p. 190°C).

Expt. 4 : Reaction of acid (7) with Phosphorous pentoxide and p-methane sulphonic acid.

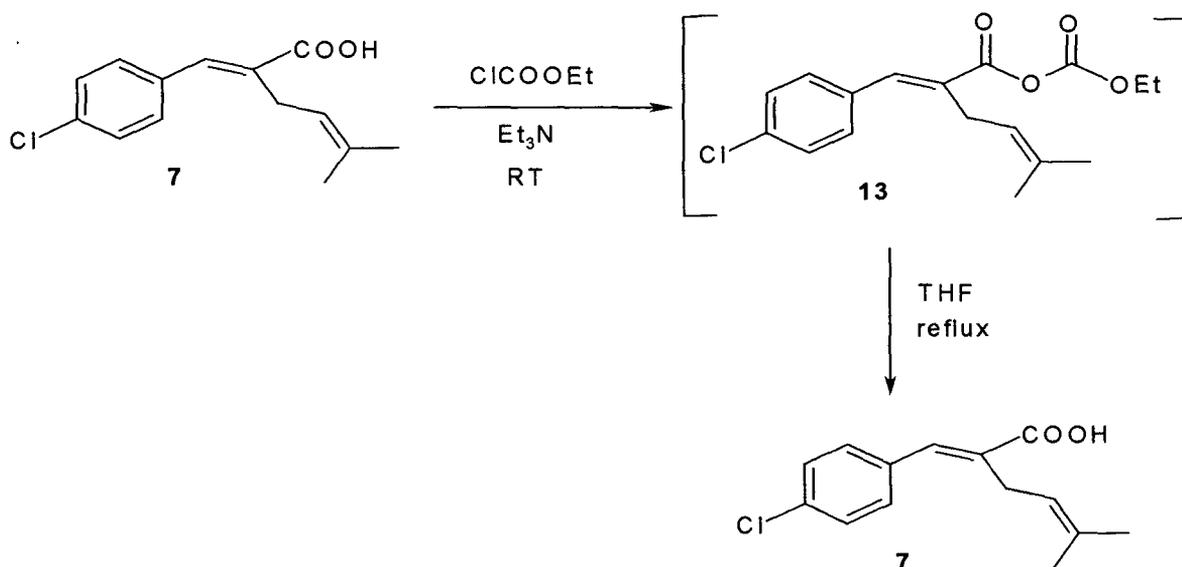


To the stirred p-methanesulphonic acid (2.9 g, 30 mmol) was added phosphorous pentoxide (0.29 g, 2 mmol) in one lot and the resulting mixture was stirred for one hour at room temperature in a moisture free experimental set up. To this was added prenyl acid **7** (0.1 g, 0.4 mmol) and the reaction mixture was continued to stir for two days. The reaction mixture was diluted with ice cold water and extracted with diethyl ether (3 x 5 mL). The solvent was concentrated and the crude product was purified by column chromatography over silica gel using ethyl acetate: hexanes (5:95) to yield a solid. Recrystallization with ethyl acetate-hexanes afforded white solid (0.056 g, 56%, m.p. 103°C).

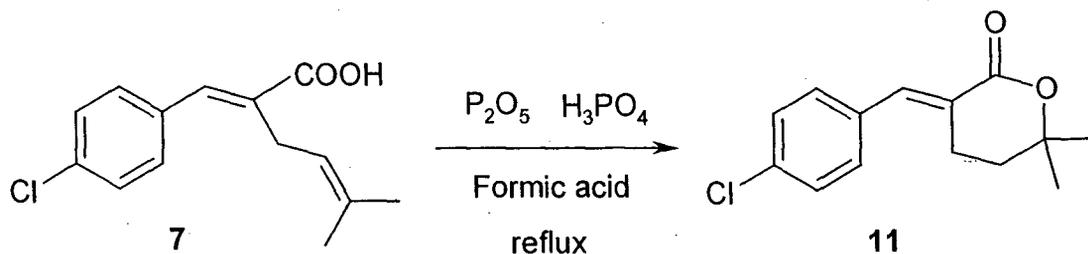


The mixture of prenyl acid **7** (0.1 g, 0.4 mmol) and redistilled thionyl chloride (0.12 g, 1 mmol) was refluxed for 3 hours. The reaction mixture was distilled to remove excess of thionyl chloride. To this was added anhydrous dichloromethane (10 mL) and anhydrous aluminium chloride (0.13 g, 1 mmol) at 0°C. The reaction mixture was allowed to attain the room temperature and stirred for 15 hours. The reaction mixture was diluted with chilled water followed by concentrated HCl. The organic layer was separated, washed with water and concentrated to yield a solid product. Recrystallization with aqueous ethanol yielded white solid (0.062 g, 62%, m.p. 190 °C).

Expt. 6 : Reaction of acid (7) with ethylchloroformate.

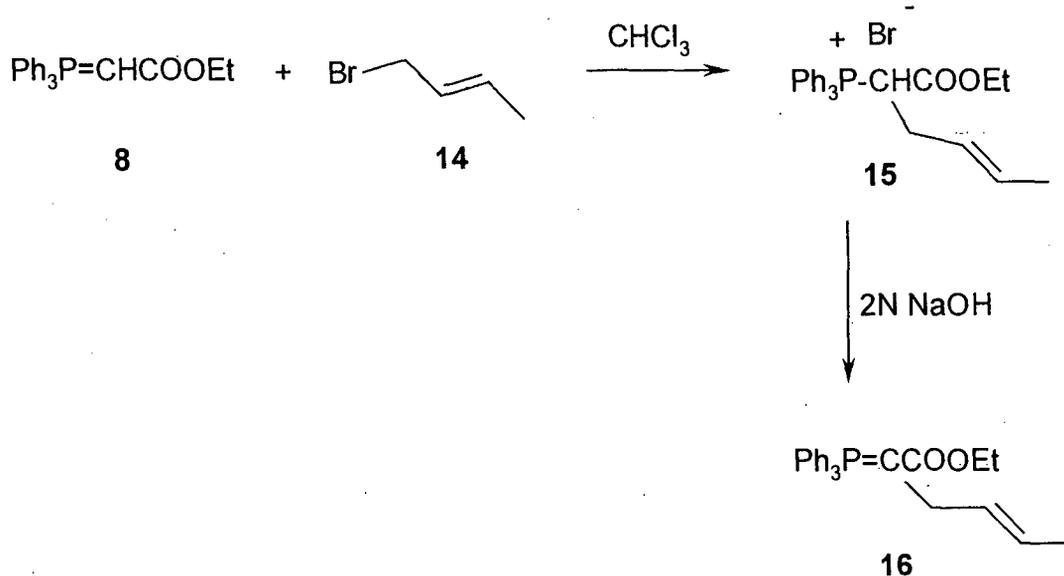


Triethylamine (0.353 g, 3.5 mmol) was added dropwise to the stirring mixture of prenyl acid (0.25 g, 1 mmol) and ethyl chloroformate (0.259 g, 2.4 mmol) in THF (10 mL) in an ice bath. The reaction mixture was allowed to attain the room temperature and was stirred for 2 hours. Finally, the reaction mixture was refluxed for seven hours. The reaction mixture was evaporated at the pump followed by washing with dilute sodium bicarbonate, dilute hydrochloric acid and extracted with ethyl acetate (3 X 5 mL). The solvent was evaporated under reduced pressure to give a white solid. Recrystallization was carried out using ethyl acetate-hexanes (0.167 g, 79.7%, m.p. 190°C).

Expt. 7 : Reaction of acid (7) with PPA and formic acid.

Prenyl acid (0.1 g, 0.4 mmol) was added to the stirring mixture of orthophosphoric acid (0.19 ml, 1 mmol), phosphorous pentoxide (0.1 g, 0.7 mmol) and formic acid (0.15 ml, 1 mmol). The reaction mixture was stirred at 80°C for 15 hours. Chilled water was added to the reaction mixture and extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with sodium bicarbonate and dried over anhydrous sodium sulphate and the reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography over silica gel using ethyl acetate: hexanes (5:95), to yield a white solid compound. Recrystallization with ethyl acetate-hexanes afforded compound **11** (0.086 g, 86%, m.p. 103°C).

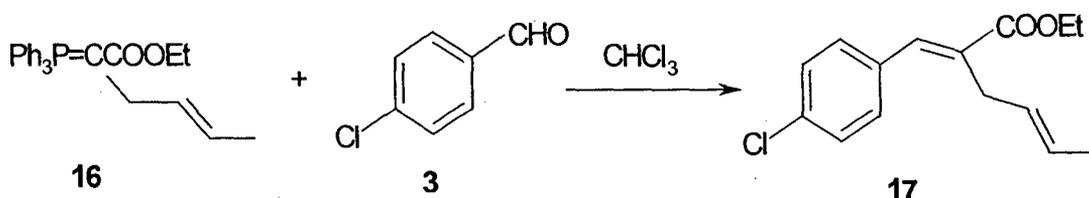
Expt. 8 : Preparation of Carboethoxy-(α -homoallyl)-methylene triphenylphosphorane (16).



A mixture of homoallyl bromide **14** (1.16 g, 0.08 ml, 8.5 mmol) and carboethoxymethylene triphenyl phosphorane **8** (3 g, 8 mmol) was refluxed for 5 hours in chloroform (10 mL) and kept overnight at room temperature. It was filtered and the solid was washed with dry ether. On recrystallisation from chloroform: hexanes it furnished a sticky salt. The salt was dissolved in water (25 mL) and benzene (10 mL) was added to it. Phenolphthalein (1 or 2 drops) was added to it. 2N sodium hydroxide solution was added to it with stirring till pink colour persisted. The benzene layer was separated and the aqueous layer was extracted with benzene (25 mL). The combined benzene layer was dried over anhy. sodium sulphate and the solvent removed under reduced pressure to get a

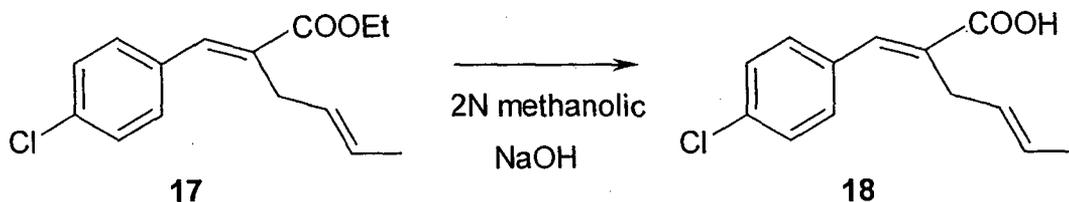
pale yellow solid. Recrystallization with benzene-hexanes afforded phosphorane **16** (2.07 g, 59.8%, m.p. 137°C).

Expt. 9 : Preparation of (E) ethyl-2-(p-chlorobenzylidene)-4-ene-hexanoate (17)



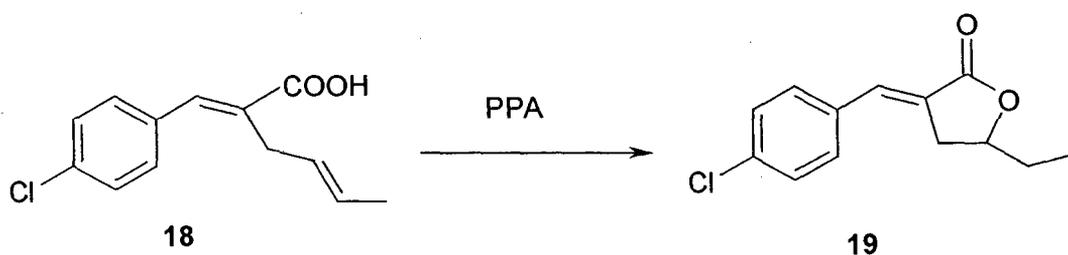
A mixture of p-chlorobenzaldehyde (0.7 g, 5 mmol), phosphorane **16** (2 g, 5 mmol) and chloroform (10 mL) was refluxed for 6 hours. The solvent was concentrated under vacuum and the crude mixture was purified by column chromatography over silica gel using ethyl acetate:hexanes (5:95), as eluent, to furnish a viscous pleasant smelling liquid **17** (1.2 g, 91%).

Expt. 10 : Preparation of (E) 2-(p-Chlorobenzylidene)-4-ene-hexanoic acid (18)



To the solution of homoallyl ester **17** (1.0 g, 3.7 mmol) in methanol (10 mL) was added 10% sodium hydroxide (10 mL) and the reaction mixture was refluxed for one hour. The reaction mixture was evaporated water bath to remove methanol. The reaction mixture was extracted with diethyl ether (3 x 5 mL) and the aqueous layer was neutralized with concentrated hydrochloric acid. The solid obtained was filtered at the pump and dried. The recrystallisation was done by aqueous ethanol to yield a white solid (0.8 g, 86%, m.p. 168°C).

Expt. 11 : Reaction of acid (18) with Polyphosphoric acid.



Homoallyl acid **18** (0.1 g, 0.4 mmol) was added to the commercially available polyphosphoric acid (1 g). The reaction mixture was stirred at 80°C for 15 hours. Chilled water was added to the reaction mixture and extracted with ethyl acetate (3 x 5 mL). The organic layer was washed with sodium bicarbonate and dried over anhydrous sodium sulphate and the reaction mixture was concentrated on water bath. The crude product was purified by column chromatography over silica gel using ethyl acetate: hexanes (5:95) to yield a white solid compound. Recrystallization with ethyl acetate: hexanes afforded solid **19** (0.064 g, 67%, m.p. 110°C).

Expt. 12 : Reaction of Butyrolactone (19) with Polyphosphoric acid.

Butyrolactone **19** (0.1 g, 0.4 mmol) was added to the commercially available polyphosphoric acid (1 g). The reaction mixture was stirred at 140°C for 24 hours. The reaction was monitored on tlc. No new spot was observed on tlc, indicating that the starting material remained intact.

4.1.4 References

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Section II

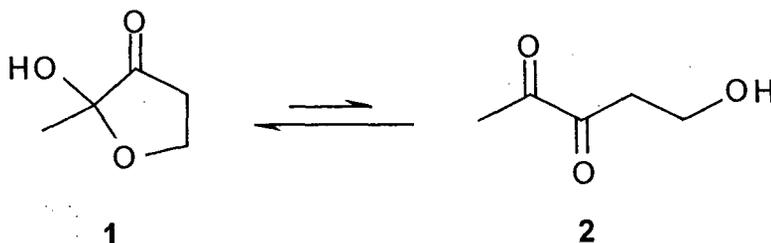
***Attempted Synthesis Of
Laurencione, A Labile
Dihydrofuran Derivatives
From Red Alga, Laurencia
spectabilis***

Section II

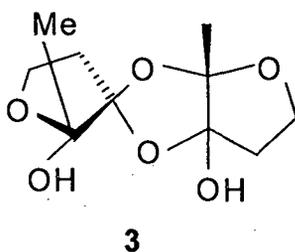
**ATTEMPTED SYNTHESIS OF LAURENCIONE, A LABILE
DIHYDROFURAN DERIVATIVE FROM RED ALGA, LAURENCIA
SPECTABILIS.**

4.II.1 Introduction

Laurencione is a major metabolite of the lipids extract of the marine red alga *Laurencia spectabilis*¹. It mainly occurs as a mixture of two interconverting forms. i.e. (\pm)-2-hydroxy-2-methyldihydrofuran-3(2*H*)-one **1** and the open-chain form 5-hydroxypentane-2,3-dione **2** (ratio, 83:17 in CDCl₃; ¹H NMR).



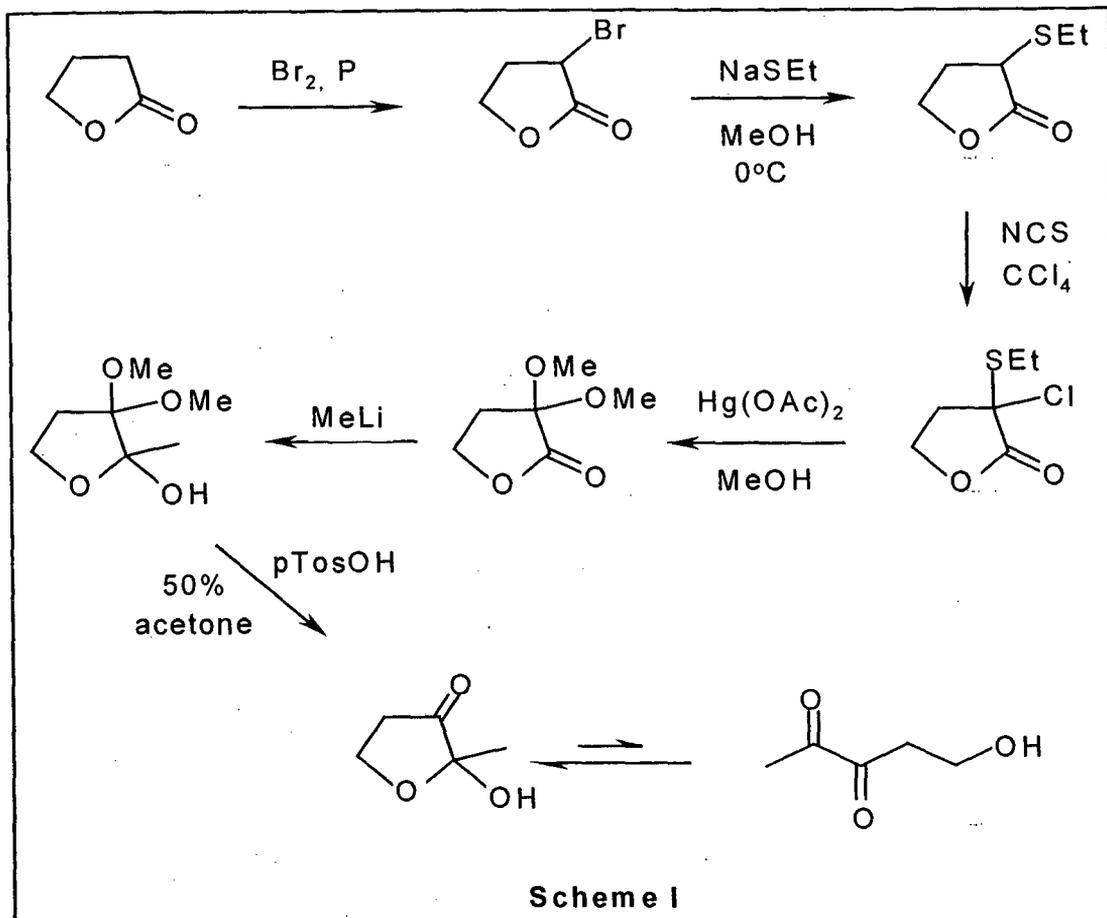
Laurencione is a very labile natural product, which dimerizes to afford a spiro-bis-pinnaketel **3** on contact with silica gel, which has been isolated from *Laurencia pinnatifida*². 5-hydroxypentane-2,3-dione (**2**) has been reported recently as a Strecker degradation product of xylose, but its existence was only established by the isolation of the corresponding quinoxaline derivative³.



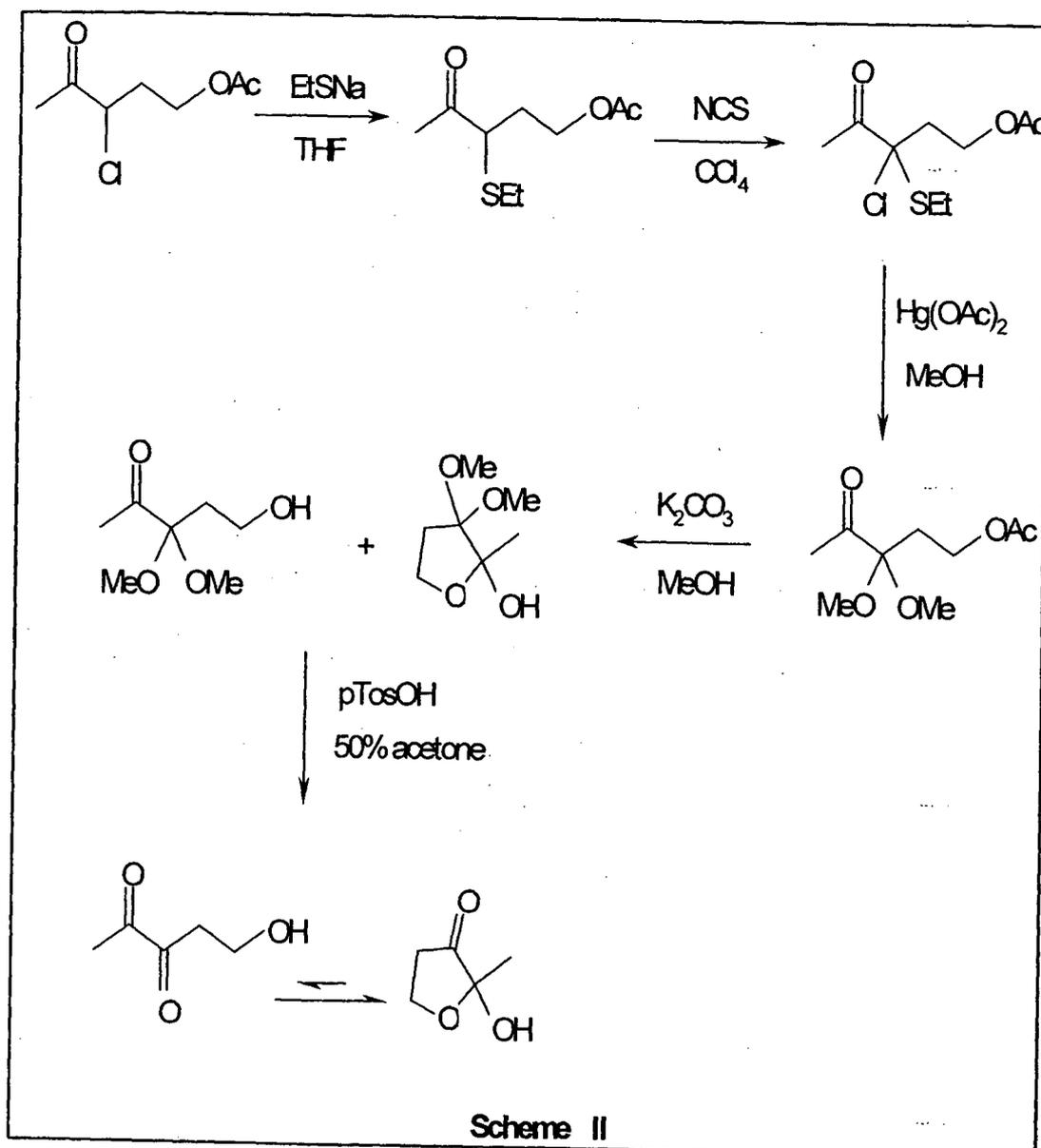
The lability of Laurencione, the peculiar hemiacetal structure and the fact that it is a novel marine product makes it a suitable and challenging target molecule.

After going through the literature, it was found that few synthesis have been reported to prepare the laurencione. De Kimpe *et al* have synthesized Laurencione by various routes, as mentioned below.

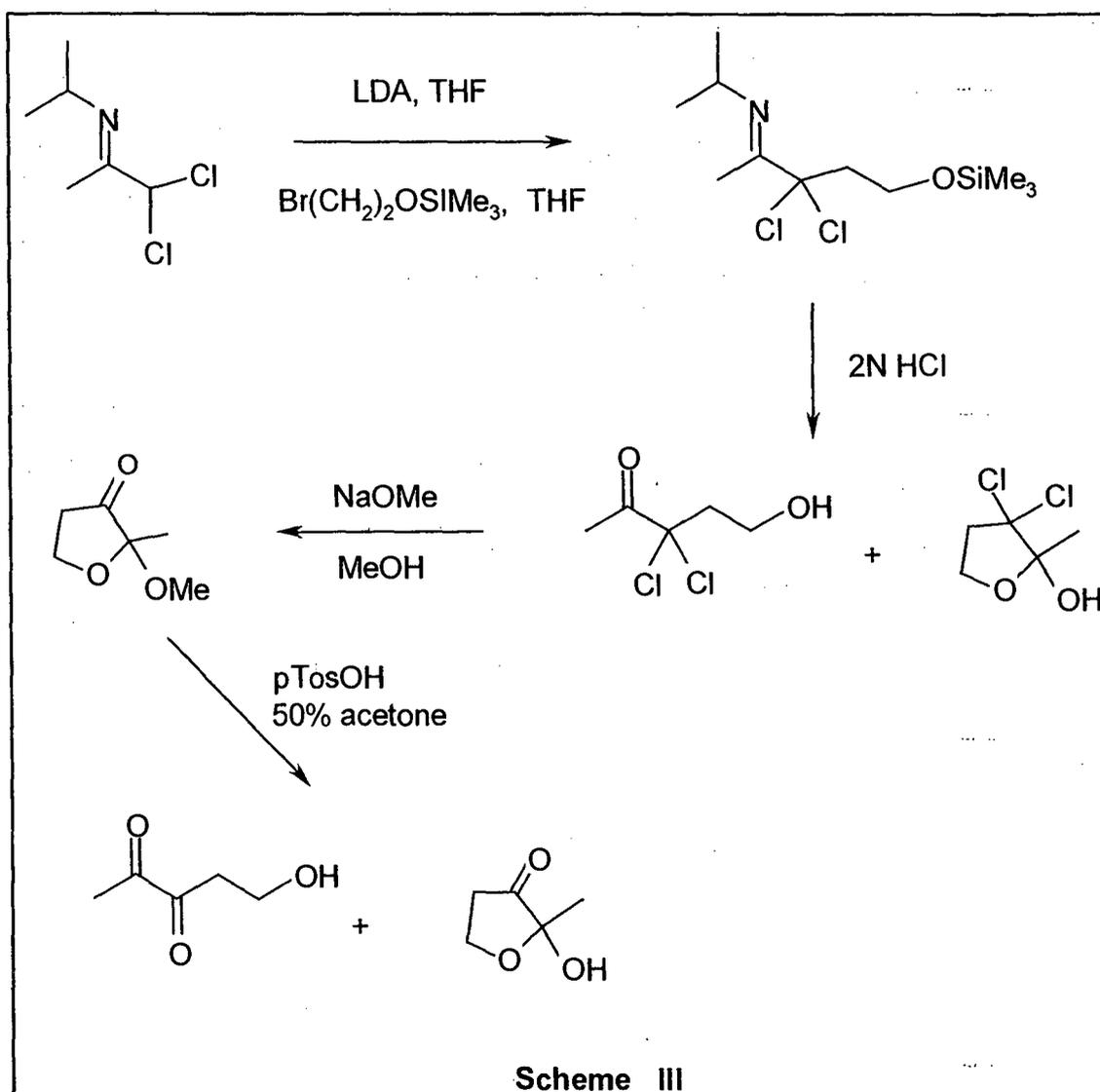
In (Scheme I), De Kimpe *et al*⁴ have reported four different routes for the synthesis of laurencione. The first route employs γ -butyrolactone while maintaining the cyclic structure throughout. The synthesis is comprised of conversion of γ -butyrolactone into α,α -dimethoxy- γ -butyrolactone, addition of methyl lithium across the lactone carbonyl, and acid hydrolysis of the acetal moiety.



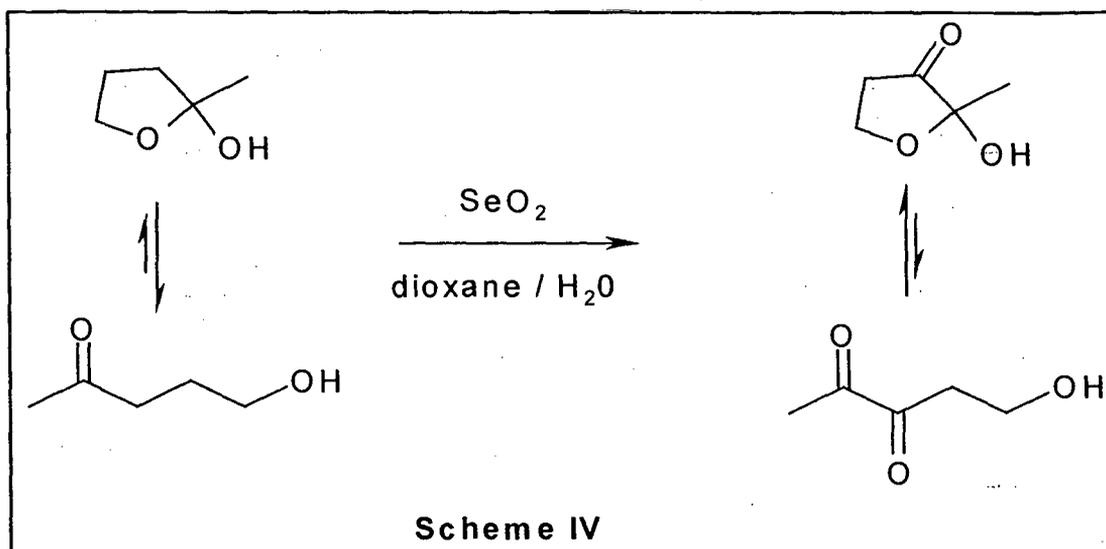
The second route reported⁵ is a straightforward formal synthesis of laurencione, utilizing elaboration of 5-acetoxy-3-chloropentan-2-one as the starting compound. The synthetic route consists of α -sulfenylation, α -chlorination of the resulting β -oxosulfide, Hg^{+2} -catalyzed methanolysis of the γ -acetoxy- α,α -dimethoxy ketone, with subsequent cyclization and acid hydrolysis of the acetal (Scheme II).



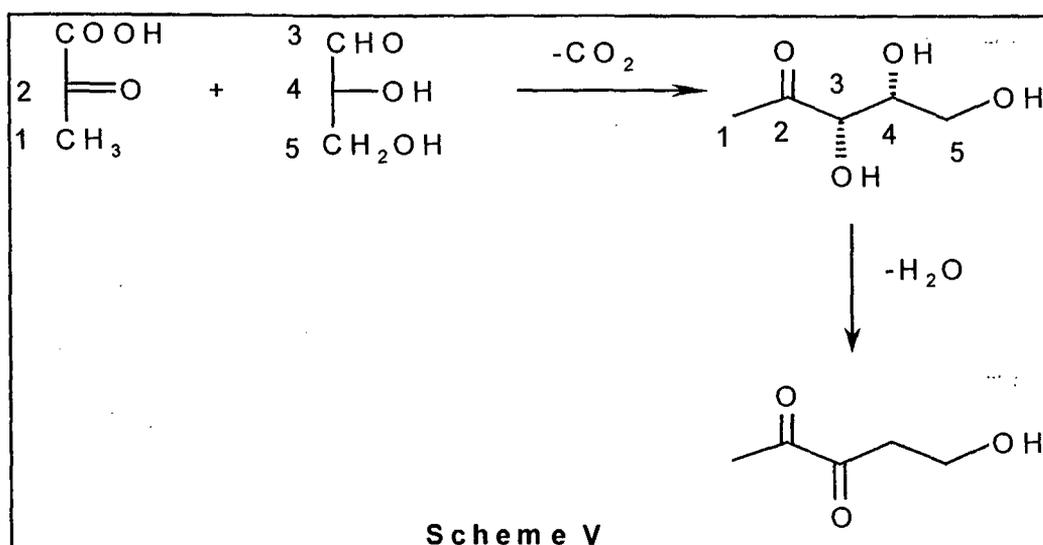
The third route⁵ is an alternative synthesis of laurencione from 1,1-dichloroacetone by a sequence of reactions involving imination, regiospecific β -hydroxyethylation, hydrolysis of the resulting functionalized tetrahydrofuran and final acid hydrolysis of laurencione methyl ether (Scheme III).



In the last route, De kimpe *et al*⁶ have synthesized laurencione from 5-hydroxy-2-pentanone in one step. The oxidation of the γ -hydroxy ketone was carried out by selenium dioxide in aqueous dioxane to afford laurencione in 48% yield (Scheme IV).

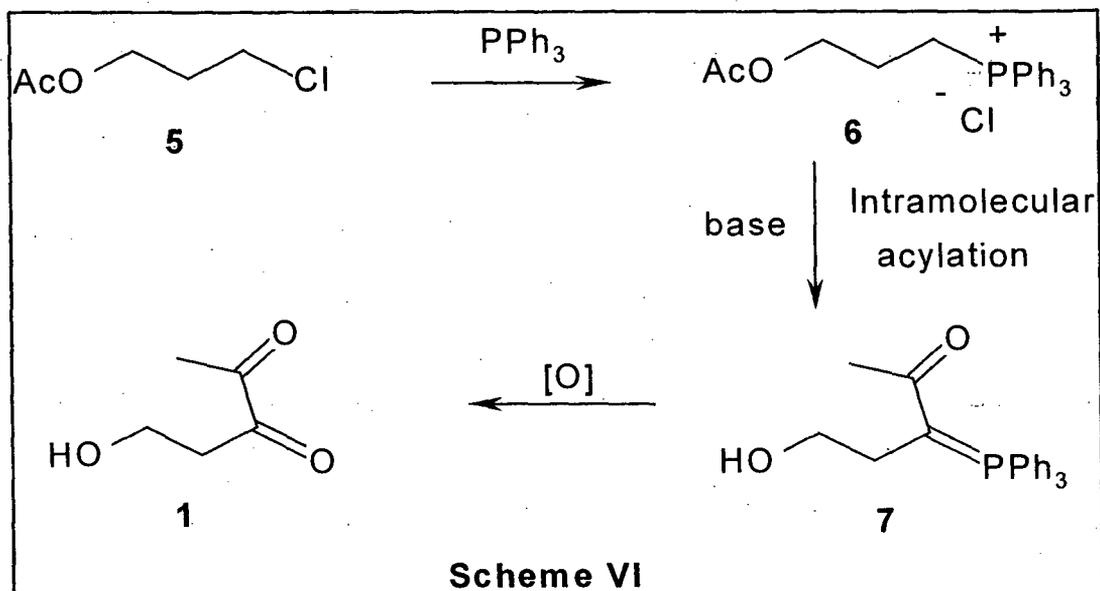


5-Hydroxy-2,3-dione (Laurencione) is also been biosynthesized⁸ from ¹³C labelled pyruvate and D-glyceraldehyde as shown in **Scheme V**.



4.II.2 Our approach

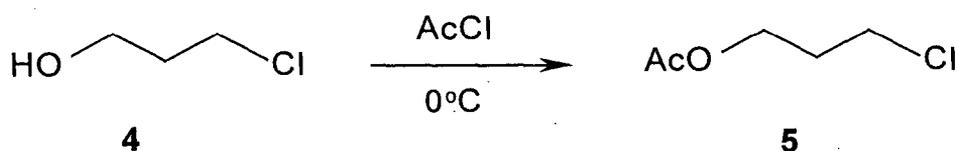
We envisaged a three-step approach towards the preparation of this acid labile marine natural product, laurencione **1**, using Wasserman approach of preparing dicarbonyl compound via intramolecular acylation, as depicted in the **Scheme VI**.



The first step was to prepare the phosphorane salt **6** from 3-chloropropyl acetate **5**. The intramolecular acylation reaction on phosphorane formed from salt **6** would provide acyl-Wittig reagent **7**. The oxidation of phosphoranes⁸⁻¹⁰ is a well-known procedure to get carbonyl compounds as reported by Wasserman. The oxidation of the acyl-phosphorane would furnish us the desired target molecule.

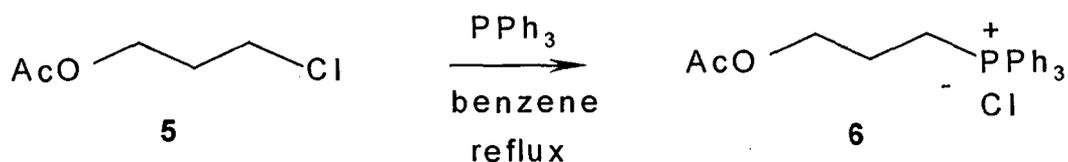
The first step was to accomplish the phosphorane salt of 3-chloropropyl acetate. The 3-chloropropyl acetate **5** was prepared by acetylation of 3-chloropropanol **4** using acetyl chloride. To the stirred 3-chloropropanol **4** was added one equivalent of acetylchloride at 0°C. The reaction mixture was stirred for one hour, after which it was allowed to attain the room temperature. The product was washed with water and extracted in diethyl ether. After giving sodium bicarbonate wash, the organic layer was dried over anhydrous Na₂SO₄ and concentrated to yield a pleasant smelling liquid in 86% yield, b.p.166°C (lit.¹¹ b.p 168 °C).

The IR spectrum of the compound showed a strong band at 1740 cm⁻¹ indicating the presence of ester carbonyl group.

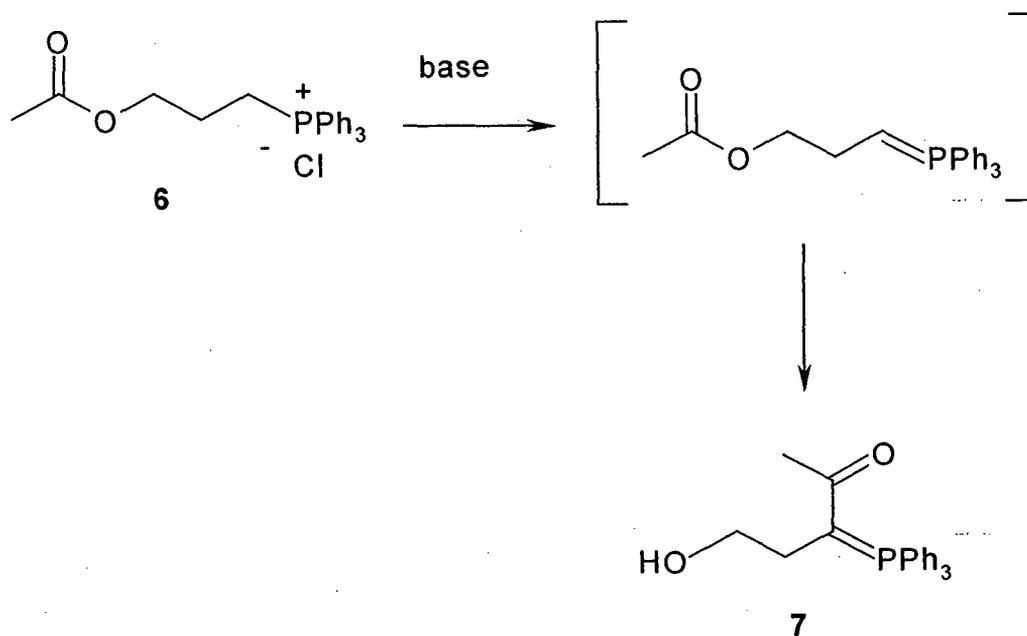


The next step was to obtain the phosphorane salt **6** of 3-chloropropylacetate **5**. This was prepared by treating chloroester **5** with triphenylphosphine in benzene and refluxing it for 10 hours. The white solid separated out, was washed with dry benzene several times to remove excess of triphenylphosphine. The salt **6** was obtained in 43% of yield, (m.p. 216°C).

The IR spectrum displayed a strong band at 1722 cm⁻¹, which could be attributed to the ester carbonyl group.



The next step was to carry out intramolecular acylation reaction of the phosphorane salt 6. Such types of intramolecular acylation condensation are known in literature^{12,13}. It was thought that the treatment of phosphorane salt with a strong base would give ylide, which is being a reactive phosphorane would react intramolecularly to transfer acyl group. This would result in the formation of a new stable phosphorane 7.



So, we treated phosphonium salt **6** with 2 equivalent of base potassium t-butoxide in anhydrous diethylether. To the stirred mixture of salt **6** in anhydrous diethyl ether was added K-t-butoxide in nitrogen atmosphere and moisture-free reaction set up. The yellow colour developed initially, disappeared in the course of time. The tic showed two spots. After six hours of stirring at room temperature the reaction mixture was concentrated to get the crude product. The two products formed were separated and purified on silica gel column chromatography.

The top spot eluted, employing (3:7) ethyl acetate-hexanes to give a sticky substance, having 54% yield. The spectral data of the product is given below.

IR (neat): 3404, 1743 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3) (Fig. 4.2.2),

δ 1.89	t, ($J = 7.5$ Hz)	2H
δ 1.95	s	3H
δ 2.25	m	2H
δ 4.04	t, ($J = 6.2$ Hz)	2H
δ 7.41 -7.72	m	10H

$^{13}\text{C-NMR}$ (Fig. 4.2.3),

δ 20.73 (CH_3), 21.04 (CH_2), 26.75 (CH_2), 64.05 (CH_2O), 128.56 (Ar-C), 130.55 (Ar-C), 131.82 (Ar-C), 133.04 (Ar-C), 170.76 ($\text{C}=\text{O}$).

The multiplicities were obtained from DEPT-135 experiments.

Based on the spectral data of the product mentioned above, indicated that the product could not have structure 7, as anticipated.

The high-resolution mass spectrum (HRMS) (Fig. 4.2.1), of the compound had strong peaks at $m/z = 303.1449$ and $m/z = 326.1352$, presumably due to $(M+H)^+$ and $(M+Na)^+$ pseudo ions respectively. The elemental composition of the compound was determined to be $C_{17}H_{19}O_3P_1$.

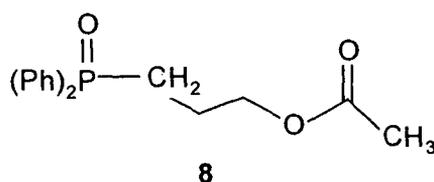
$M/z = \text{calcd. } (C_{17}H_{19}O_3P_1 + H) = 303.1640$; found: $(C_{17}H_{19}O_3P_1 + H) = 303.1449$

calcd. $(C_{17}H_{19}O_3P_1 + Na) = 326.1537$; found: $(C_{17}H_{19}O_3P_1 + Na) = 326.1352$

A strong band at 1743 cm^{-1} in the IR spectrum could be attributed to the carbonyl of ester group.

The $^1\text{H-NMR}$ spectrum (Fig. 4.2.2), showed peaks at $\delta 1.89$ (t, $J = 7.5 \text{ Hz}$, 2H) and $\delta 1.95$ (s, 3H) could be assigned to the methylene protons adjacent to another methylene group and the phosphorous atom ($\text{CH}_2\text{CH}_2\text{P}$) and the methyl group attached to the carbonyl group (CH_3CO), respectively. The signals observed at $\delta 2.25$ (m, 2H) and $\delta 4.04$ (t, $J = 6.2 \text{ Hz}$, 2H), could be due to the methylene flanked by two more methylene groups ($\text{CH}_2\text{CH}_2\text{CH}_2$) and the methylene attached to the electron withdrawing atom such as oxygen atom (CH_2O). The signal at $\delta 7.41\text{-}7.71$ (m, 10H) could be assigned to the aromatic protons of the two phenyl rings attached to the phosphorous atom.

Based on spectral data structure 8 was assigned to the compound.



+TOF MS: 2.617 to 4.501 min from MT20040415162116.wiff
a=3.56251716555172050e-004, t0=-2.04463107224728450e+000, subtracted (0.184 to 0.900 min) Iax: 1306.0 counts

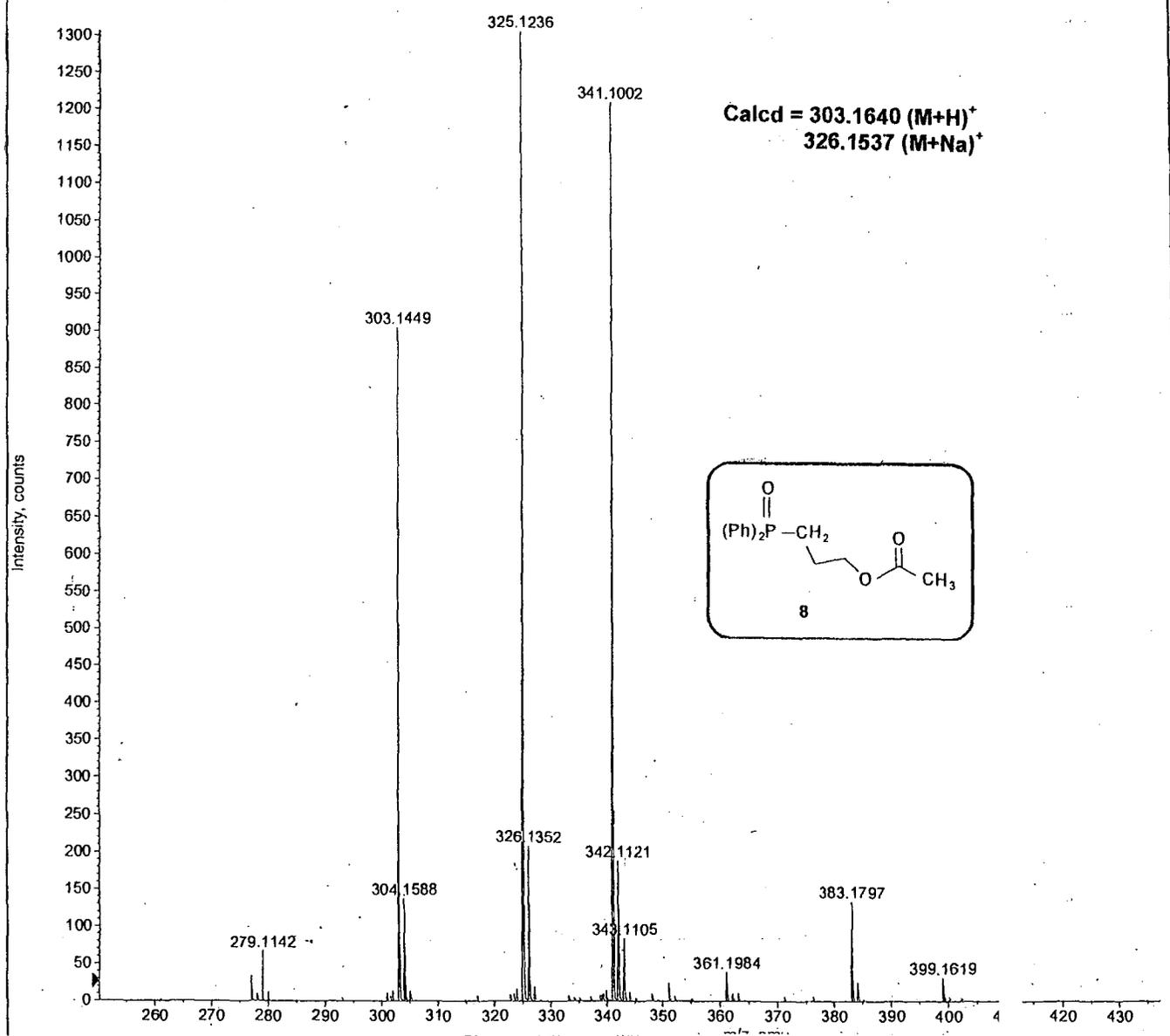


Fig. 4.2.1 : HRMS of Diphenyl-(3-acetoxy-propyl)-phosphine oxide (8)

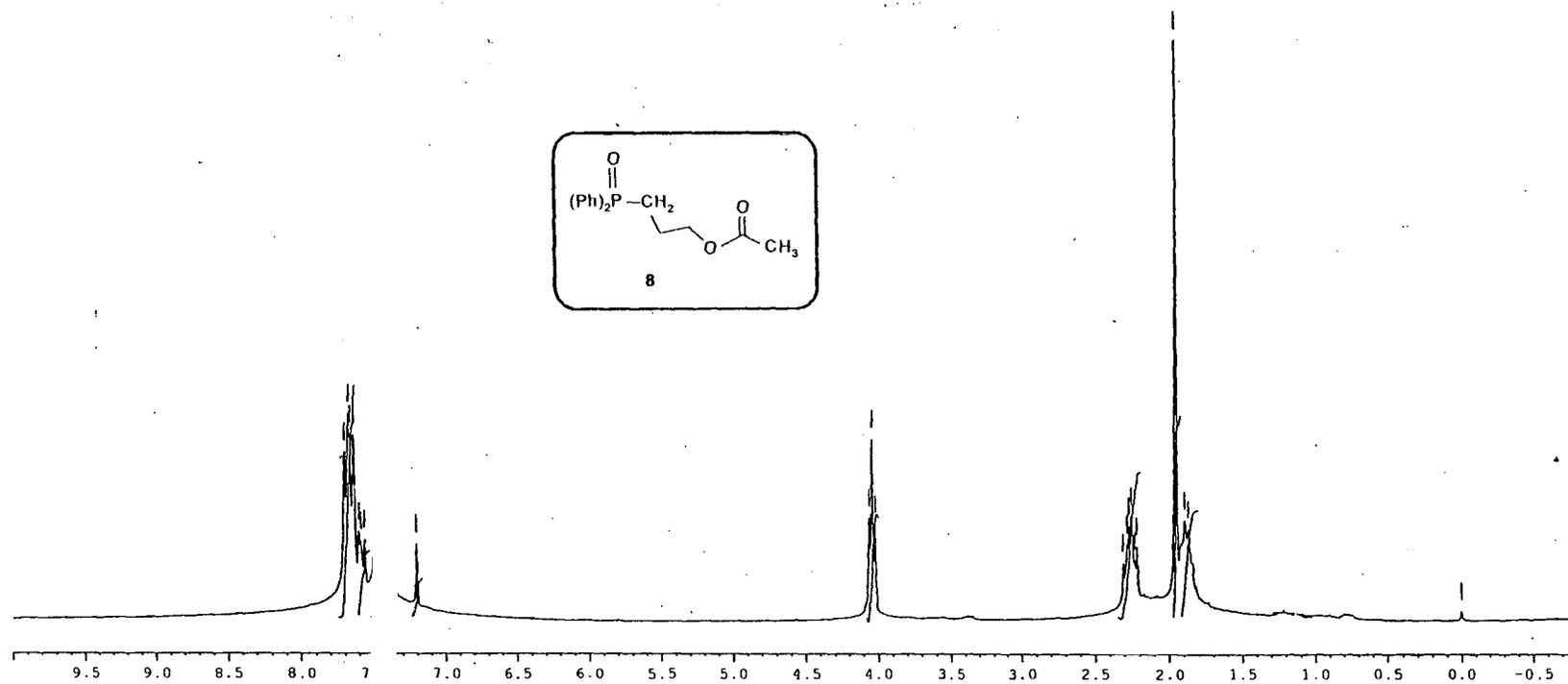


Fig. 4.2.2 : ¹H-NMR of Diphenyl-(3-acetoxy-propyl)-phosphine oxide (8)

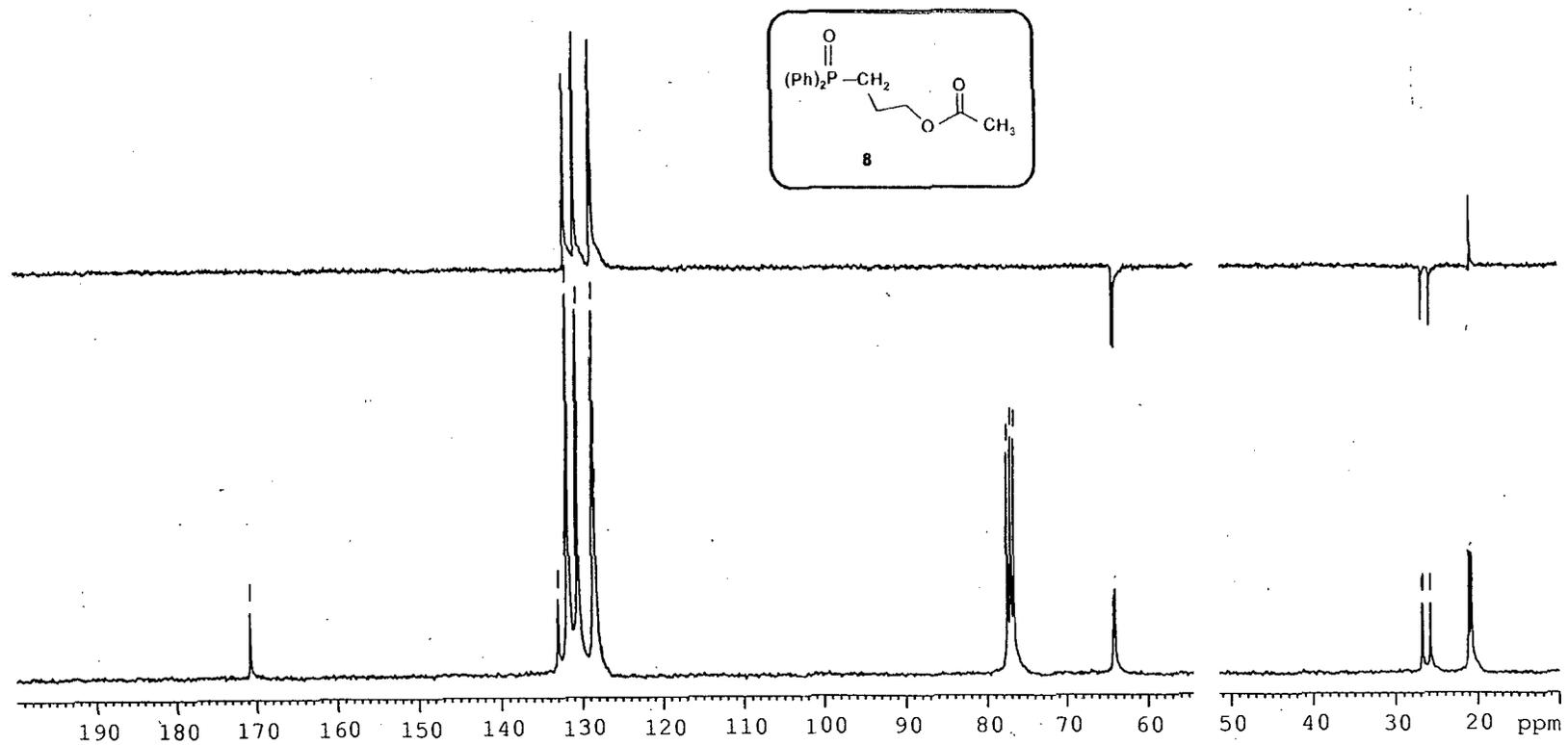


Fig. 4.2.3: ^{13}C -NMR of Diphenyl-(3-acetoxy-propyl)-phosphine oxide (8)

The second spot which was eluted employing (1:1) ethyl acetate-hexanes gave a sticky solid in 22% yield.

The IR spectrum of the compound exhibited a band at 1737 cm^{-1} . This could be assigned to the carbonyl group of ester.

$^1\text{H-NMR}$ (Fig. 4.2.4),

δ 1.84	s	3H	OCOCH ₃
δ 2.10	s	3H	COCH ₃
δ 3.63	t, ($J = 4.5\text{ Hz}$)	2H	CH ₂ -CH ₂ O
δ 3.74	t, ($J = 7.5\text{ Hz}$)	2H	CH ₂ -CH ₂ O
δ 7.43 -7.76	m	15H	15 x (Ar-H)

The $^1\text{H-NMR}$ spectrum showed signals at δ 1.84 (s, 3H) and δ 2.10 (s, 3H), which could be assigned to the methyl protons of -OCOCH₃ group and COCH₃ group, respectively. The peaks exhibited at δ 3.63 (t, $J = 4.5\text{ Hz}$, 2H) and δ 3.74 (t, $J = 7.5\text{ Hz}$, 2H), could be assigned to the methylene protons of (CH₂CH₂O) and (CH₂CH₂O), respectively. The signal displayed at δ 7.3-7.76 (m, 15H) could be assigned to the aromatic protons of triphenylphosphine group (PPh₃).

$^{13}\text{C-NMR}$ (Fig. 4.2.5),

δ 20.85 (COCH₃), 25.29 (OCOCH₃), 27.28 (CH₂), 60.92 (CH₂O), 126.35 (C), 128.49 (Ar-C), 130.67 (Ar-C), 131.56 (Ar-C), 133.29 (Ar-C), 170.80 (OCO), 188.88 (COCH₃).

The multiplicities were obtained from DEPT-135 experiments.

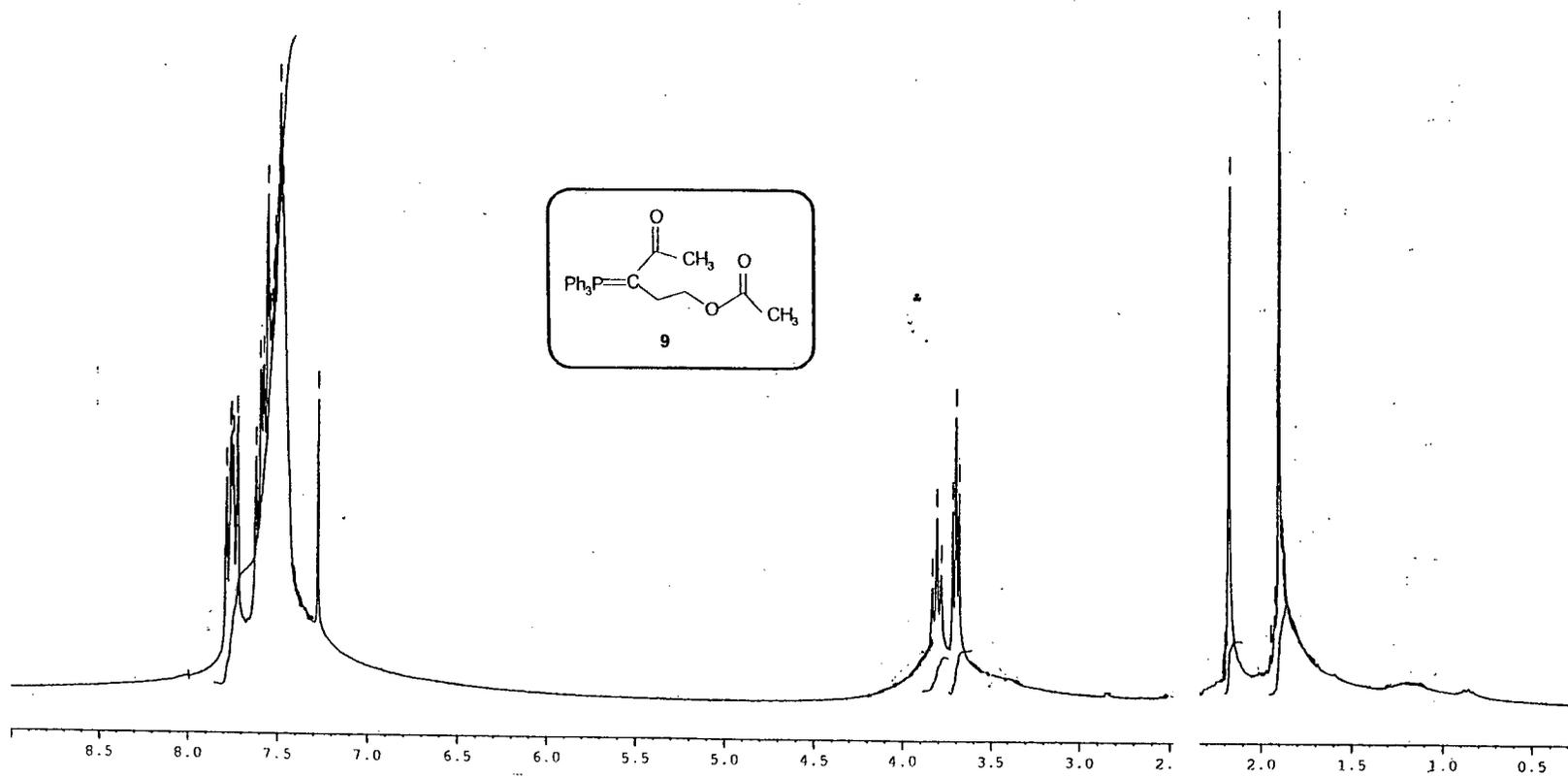


Fig. 4.2.4: ^{13}C -NMR of 3-Acetoxy-1-acetyl-propylenetriphenyl phosphorane (9)

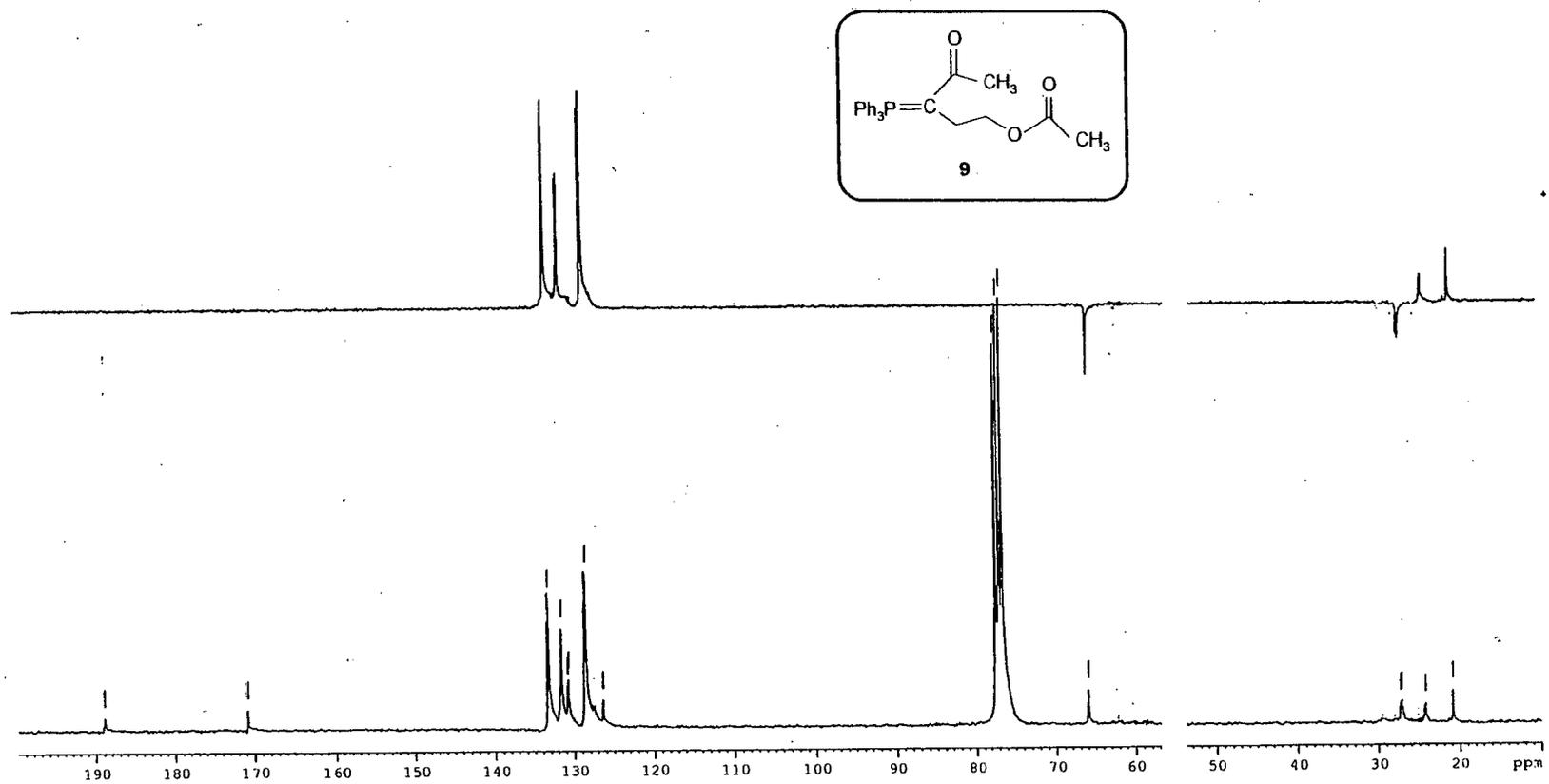
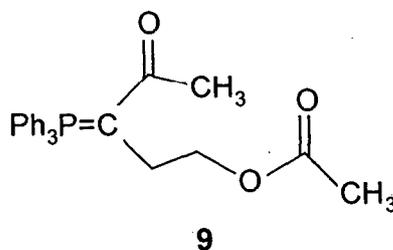


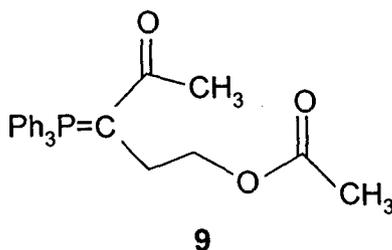
Fig. 4.2.5: ¹H-NMR of 3-Acetoxy-1-acetyl-propylidene triphenyl phosphorane (9)

Based on mode of formation and spectral data structure **9** was assigned to the compound.



As compound **9** was obtained in a very less amount, the same reaction was repeated by changing the solvent and elevating the temperature. To the stirred solution of phosphonium salt **6** in anhydrous t-butanol was added base K-t-butoxide at room temperature in a nitrogen atmosphere and moisture-free set up. After five minutes, the reaction mixture was refluxed for 8 h at 80°C. The resulting product obtained after concentration of solvent was purified on silica gel column chromatography to give a white sticky solid, in 67% yield.

The physical and spectral data was found identical with that of compound **9**.



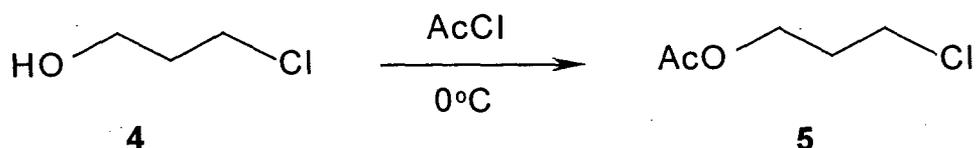
As expected stable hydroxy phosphorane **7**, could not be obtained. The reaction was not proceeded further.

4.11.3 Conclusion

- An attempt has been made to synthesize Laurencione, a labile and challenging marine natural product via vicinal dicarbonyl (Wasserman approach).
- However, the required phosphorane synthesis by intramolecular acylation of Wittig reagent could not be achieved.

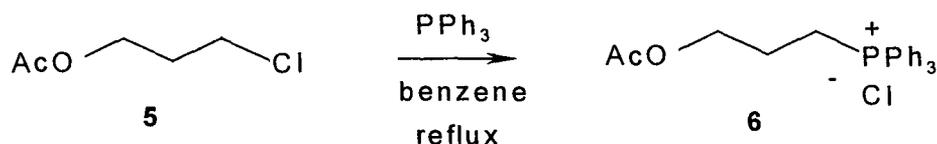
4.II.4 Experimental

Expt. 1 : Preparation of 3-chloropropylacetate (5).



Acetyl chloride (0.83 g, 10.5 mmol) was added dropwise to 3-chloropropanol (1 g, 10.5 mmol) with stirring at 0°C. The reaction mixture was stirred for one hour. After one hour the reaction mixture was allowed to attain room temperature. The reaction mixture was extracted with diethyl ether (3 x 5 mL), washed with water and the organic layer was again washed with saturated solution of sodium bicarbonate. The organic layer was dried over anhydrous Na₂SO₄ and solvent was evaporated on water bath to give a pleasant smelling liquid product (0.863 g, 86.3%), b.p 166°C. (Lit.¹¹ b.p 166°C).

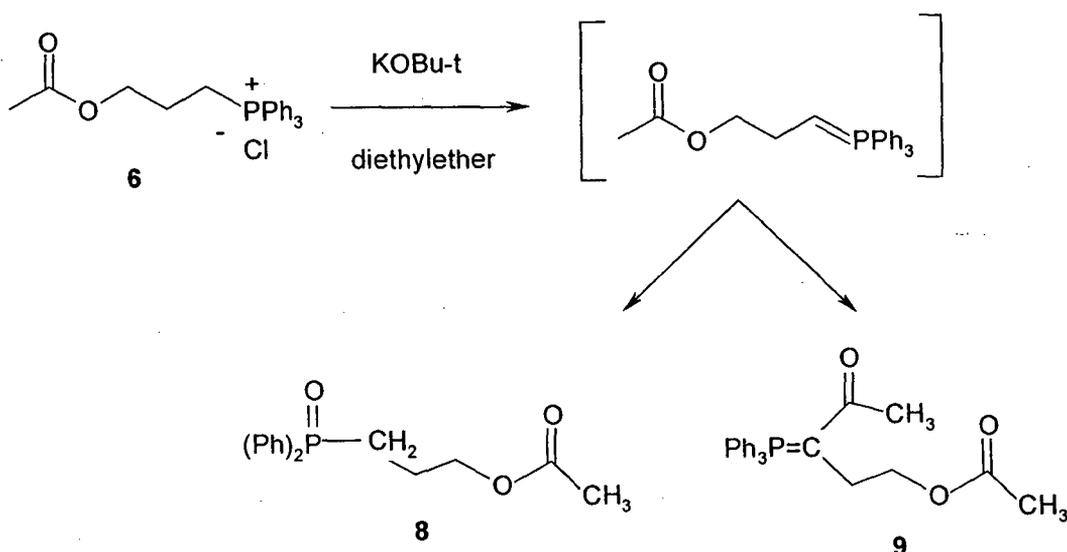
Expt. 2 : Preparation of phosphorane salt (6) of 3-chloropropylacetate¹⁴.



The mixture of 3-chloropropylacetate (1 g, 7.3 mmol) and triphenylphosphine (0.52 g, 7.3 mmol) was refluxed neat for 12 hours. To the

reaction mixture was added dry benzene (10 mL). The white solid formed was washed with dry benzene to remove excess of triphenylphosphine. The product obtained was dried over reduced pressure to yield a hygroscopic white solid. (1.24 g, 43%, m.p. 216°C).

Expt. 3 : Intramolecular Wittig reaction of phosphorane salt (6) of 3- chloropropylacetate.



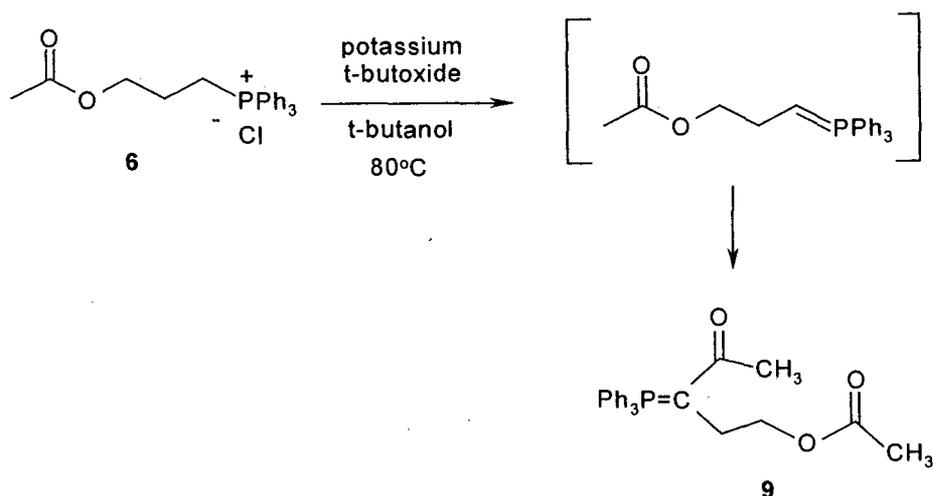
To the stirred solution of phosphorane salt (1 g, 2.5 mmol) in anhydrous diethyl ether (10 mL) was added potassium t-butoxide (0.56 g, 5 mmol) in a nitrogen atmosphere and moisture-free reaction condition at -10°C . The starting yellow colour disappeared after 5 minutes of time. The reaction mixture was allowed to stir at room temperature for another 6 hours. The reaction mixture was evaporated to remove solvent and the crude product obtained was separated on column chromatography. The two products were separated out.

The top spot was eluted out using (3:7) ethyl acetate-hexanes to furnish a sticky solid, diphenyl-(3-acetoxy-propyl)-phosphine oxide **8** (0.4 g, 54%)

3-Acetoxy-1-acetyl-propylidene-triphenyl phosphorane (**9**)

The down spot was eluted out using (1:1) ethyl acetate-hexanes to furnish a sticky solid **9** (0.23 g, 22%)

Expt. 4 : Preparation of 3-Acetoxy-1-acetyl-propylidene-triphenyl phosphorane (**9**)



Potassium t-butoxide (0.56 g, 5 mmol) was added to solution of phosphorane salt (1 g, 2.5 mmol) in anhydrous t-butanol (10 mL). The reaction mixture was refluxed at 80°C for 8 hours. The solvent was concentrated on water bath and the crude reaction mixture was purified over silica gel column chromatography using (1:1) ethyl acetate-hexanes to afford a white semi solid **9** (0.68 g, 67%).

2.II.4 References

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Section III

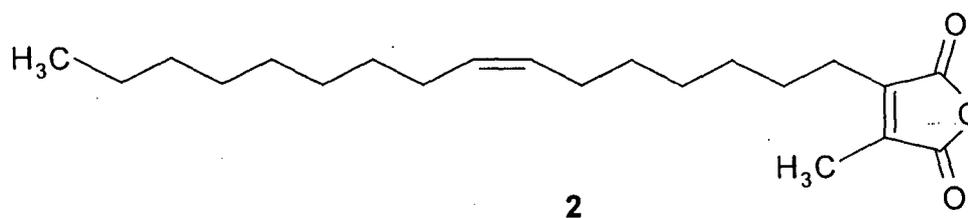
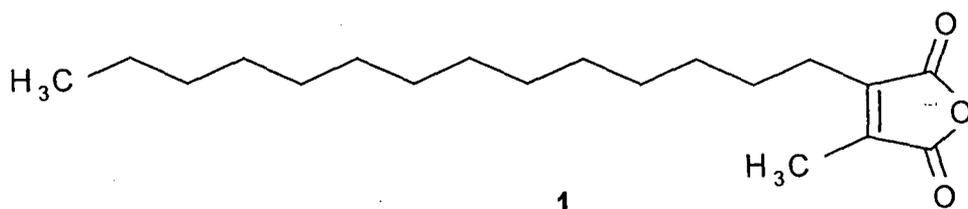
***Synthesis Of Chaetomelic
Anhydride A.***

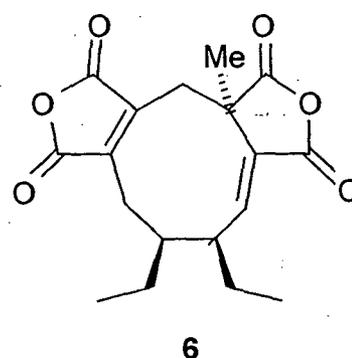
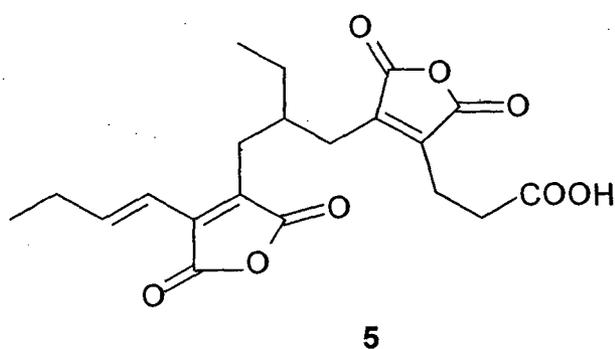
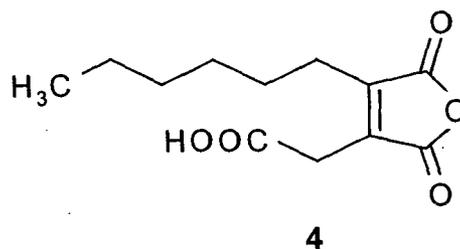
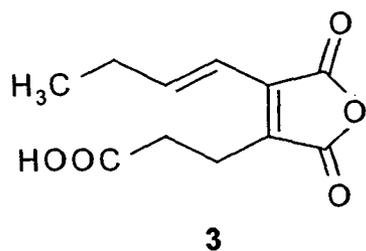
Section III

SYNTHETIC STUDIES OF CHAETOMELLIC ANHYDRIDE A

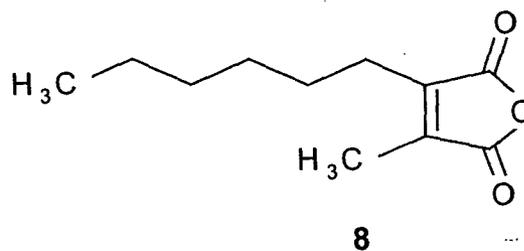
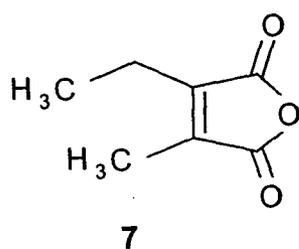
4.III.1 Introduction

A large number of natural products containing a substituted maleic anhydride unit have been reported in the literature. Some of them show wide range of biological activities, including antibacterial^{1,2}, fungicidal³, immuno modulating⁴, plant growth promoting⁵, etc. The simplest form possesses either an alkenyl or an alkyl substituent in one position and either a methyl, carboxymethyl or carboxyethyl substituent in the second position, for instance, Chaetomelic anhydride A **1** and Chaetomelic anhydride B **2** (isolated⁶ from fermentation broth of the coelomycete *Chaetomella acutiseta*), unnamed anhydrides **3**⁷, **4**⁸, the dimer, Cordyanhydride A **5**⁹ and the more complex anhydride, glaucanic acid **6**¹⁰.





Other naturally occurring 2,3-dialkylmaleic anhydrides include 2-ethyl-3-methylmaleic anhydride **7**, isolated from the volatile oil of *Paederia foetida* L¹¹ and from elderberry (*Sambucus nigra* L. fruit, Korsor cultivar)¹², 2-hexyl-3-methylmaleic anhydride **8**, isolated from the essential oil of *Agropyrum repens* rhizome¹³, etc.



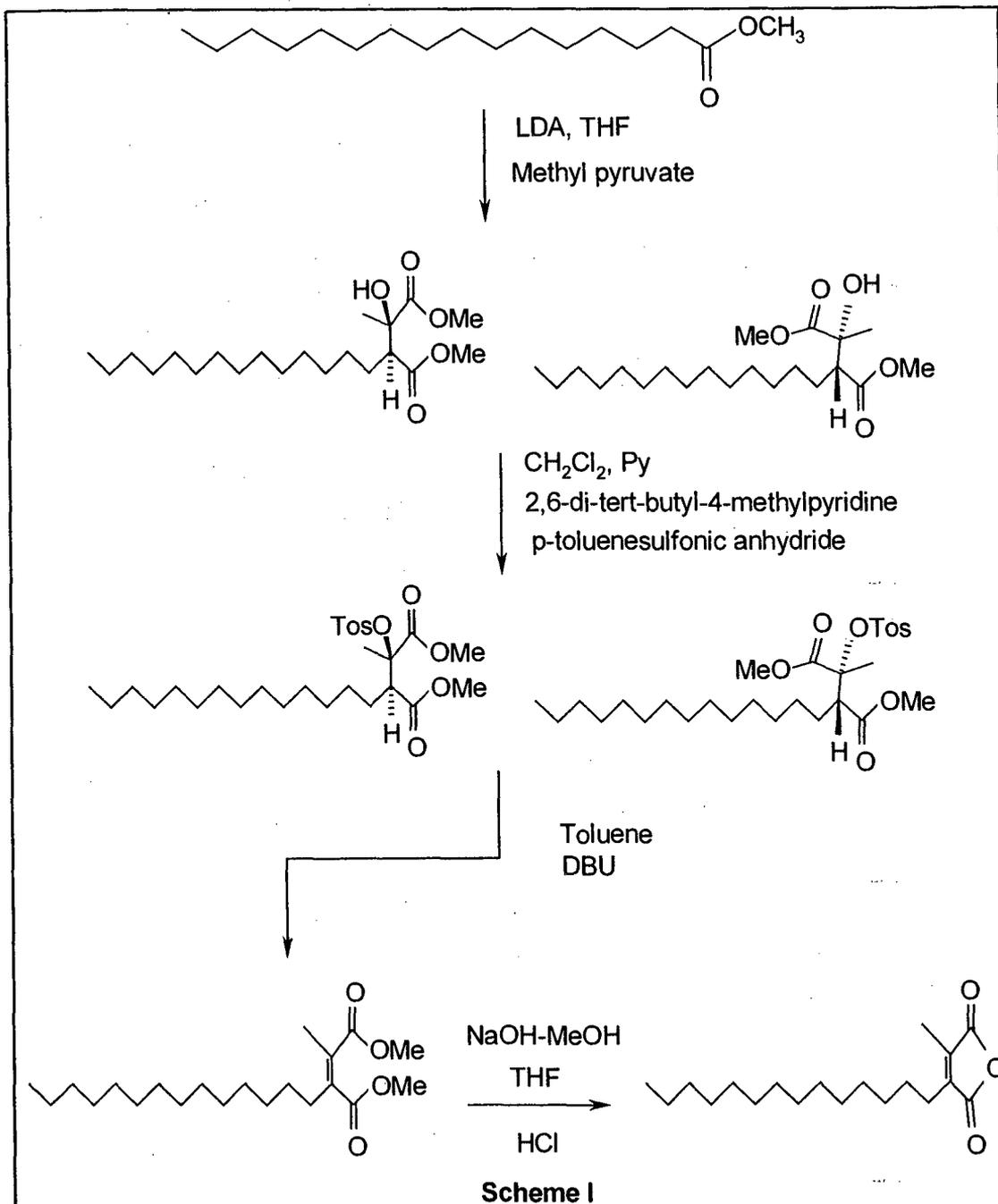
Chaetomelic acid A anhydride (tetradecyl methyl maleic anhydride) **1** has been recently isolated from *Chaetomelic acutisetata*. Its dianionic form is a potent and highly specific inhibitor of ras farnesyl-protein transferase.

Isoprenylation is a critically important post-translational modification that can control protein location and cellular activation²⁶. Addition of C₁₅ farnesyl unit to ras by protein farnesyltransferase (PFTase) is essential for its association with cell membranes and promotion of cell-transforming activity²⁷. Mutated ras genes are found in about 25% of human tumors and are believed to play an important role in human tumor growth²⁸. Recently, PFTase inhibitors were found to reduce the number of tumorigenic phenotypes of cells transformed by ras in both cell culture and animal models²⁹.

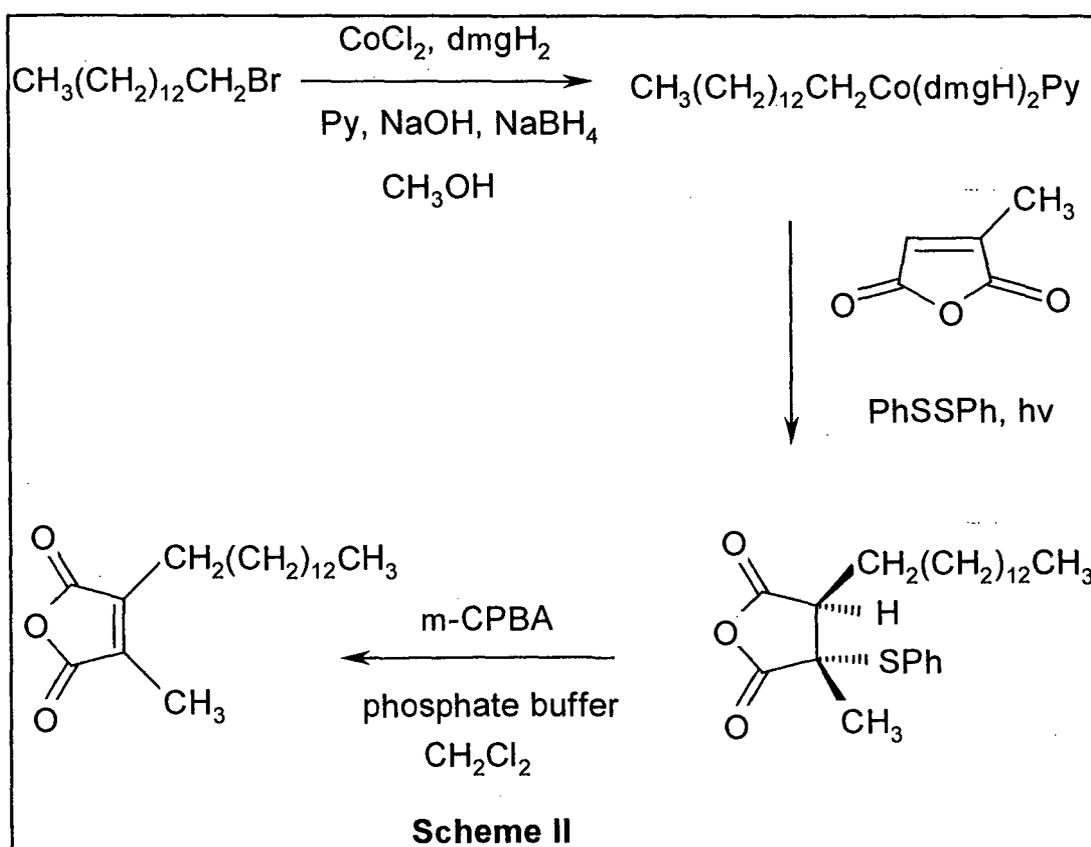
Chaetomelic acid A **1** is a nanomolecular competitive inhibitor of farnesyl pyrophosphate binding the diacid moiety, acts as a stable pyrophosphate mimic³⁰.

4.III.2 Literature methods towards the synthesis of chaetomelic acid A anhydride

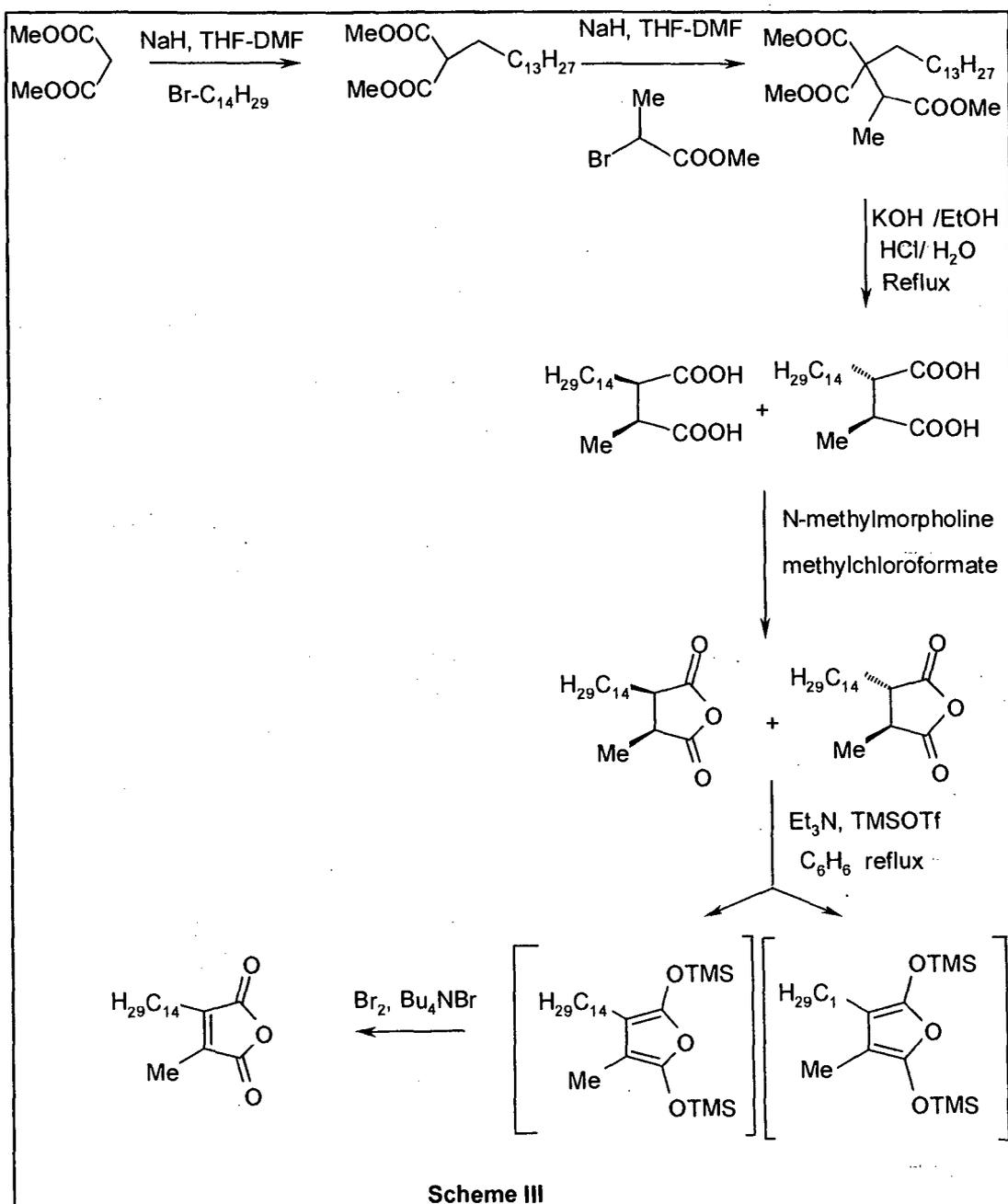
The first biogenetic type synthesis of chaetomelic acid A anhydride was reported by Singh *et al*³¹. It involves aldol condensation of methyl palmitate with methyl pyruvate. Separation of resulting diastereoisomers provided the corresponding anhydrides in 18% overall yield (**Scheme I**).



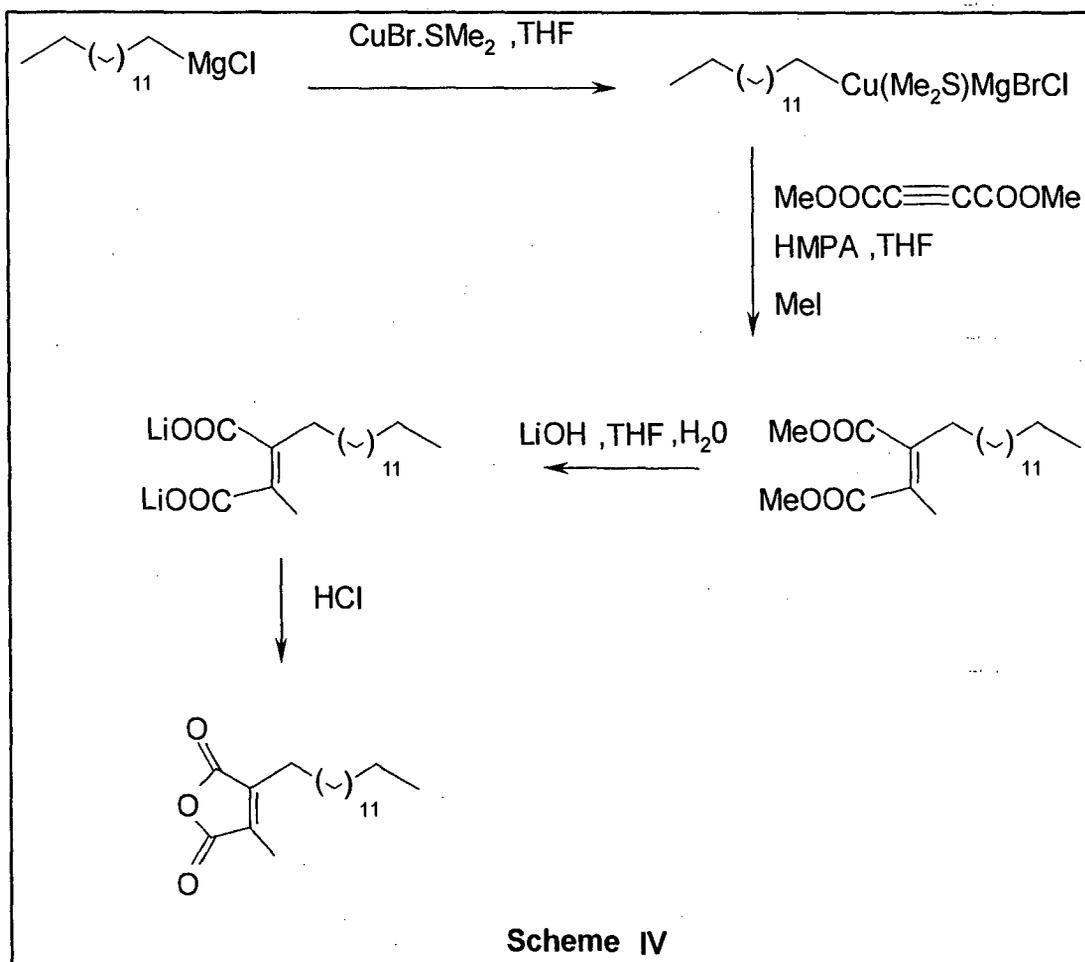
Brandchaud *et al*³² have described a more efficient three-step approach, employing a cobalt-mediated radical coupling strategy, obtaining 64% **1** in overall yield. It involved a doubly chemoselective cross coupling of myristyl cobaloxime with citraconic anhydride and diphenyl disulfide as the key step. Sulfide oxidation followed by syn elimination provided the target molecule (**Scheme II**).



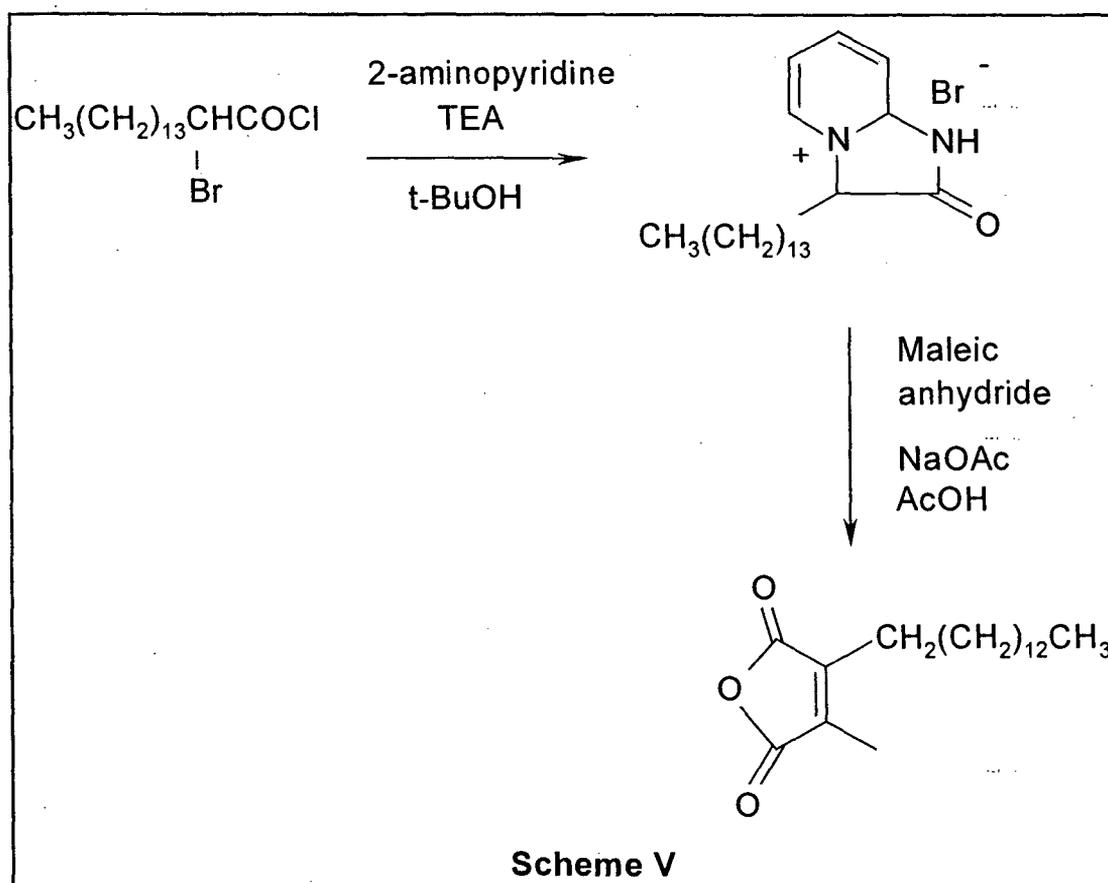
Schauble *et al*³³ have reported a five-step synthesis involving a novel succinate to maleate oxidation with 83% overall yield. Monoalkylation of dimethyl malonate with 1-bromotetradecane afforded monoalkylmalonate, which was subsequently treated with 2-bromopropionate to obtain a triesters. Hydrolysis and decarboxylation of the triesters followed by acidification gave mixtures of diastereomeric erythro and threo succinic acids. These were converted to their anhydrides. The furan derivative obtained was converted to the desired product (Scheme III).



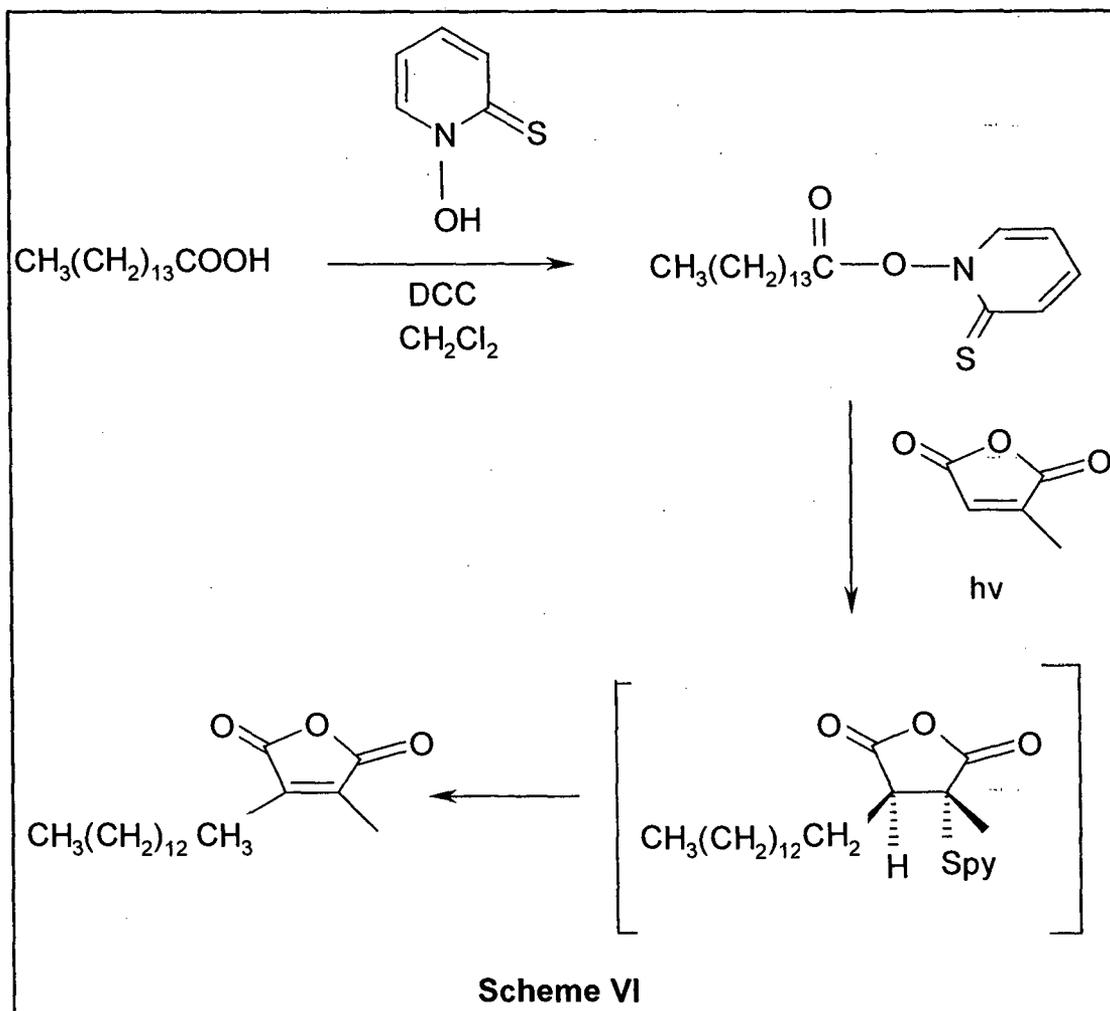
Vederas *et al*³⁴ have reported a two-step stereospecific synthesis giving 77% overall yield. Addition of organocuprates derived from Grignard reagents (e.g. tetradecylmagnesium chloride and CuBr.Me₂S) to dimethylacetylenedicarboxylate (DMAD) in tetrahydrofuran containing hexamethylphosphoramide was followed by capture of the resulting copper enolates with methyl iodide to give dimethyl ester derivative. Hydrolysis with lithium hydroxide generated the corresponding lithium carboxylate, which readily closed to 2,3-disubstituted maleic anhydride upon acid treatment (**Scheme IV**).



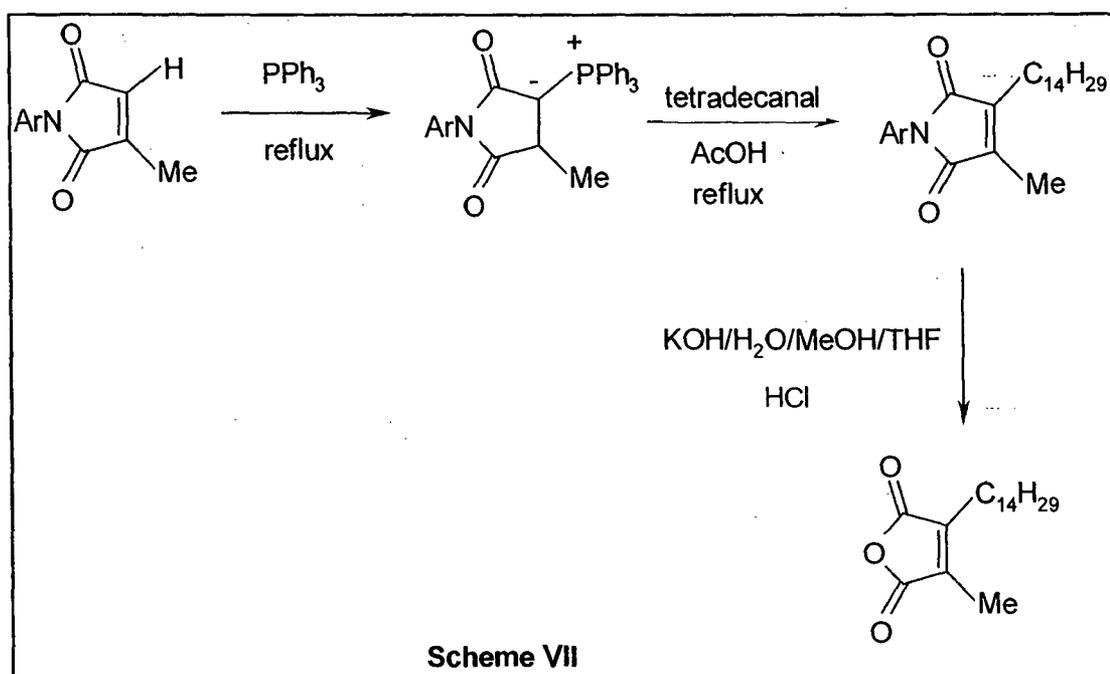
Argade *et al*³⁵ have developed a three-step approach, which employs condensation of tetradecylimidazo pyridinium bromide and maleic anhydride with 62% overall yield. The imidazopyridinium bromide obtained from the reaction of 2-bromopalmitoyl chloride and 2-aminopyridine was reacted with maleic anhydride in the presence of NaOAc/AcOH to form the target molecule (Scheme V).



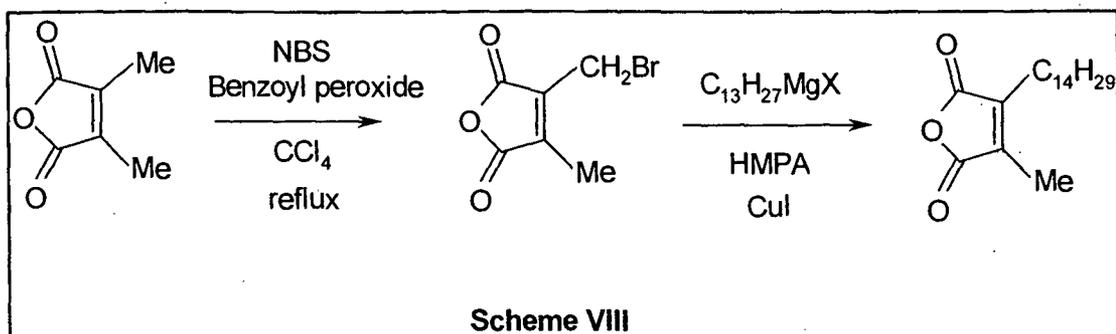
Samadi *et al*³⁶ have synthesized chaetomelic anhydride A in one step by Barton radical decarboxylation, namely, irradiation of thiohydroxamic ester derived from carboxylic acid in the presence of citraconic anhydride (Scheme VI).



Argade *et al*³⁷ have reported another two-step approach to chaetomelic acid anhydride. Methyl-N-p-tolyl(triphenylphosphoranylidene) succinimide obtained from citraconimide was condensed with tetradecanal in refluxing glacial acetic acid. The adduct obtained was then converted to chaetomelic anhydride (Scheme VII).



Argade *et al*³⁸ have also reported an improved, highly chemoselective, two-step approach via copper iodide induced, carbon-carbon coupling of Grignard reagents with (bromomethyl) methylmaleic anhydride obtained from bromination of dimethyl maleic anhydride with NBS to furnish chaetomelic acid A anhydride (Scheme VIII).

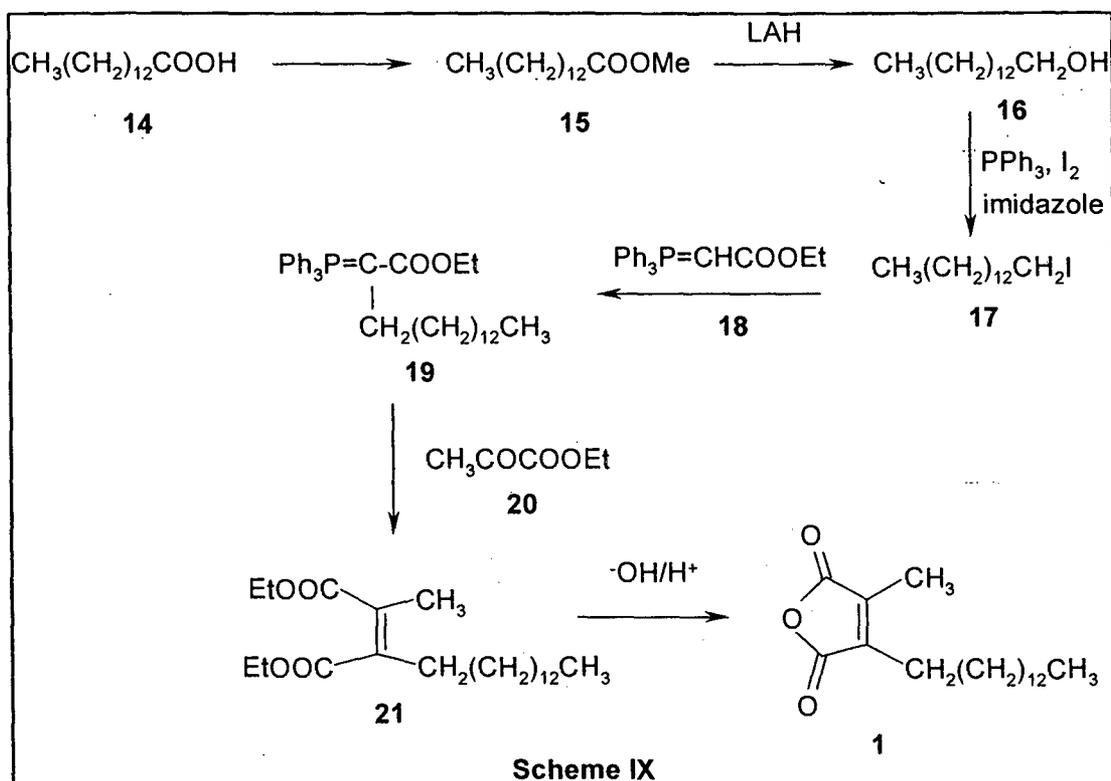


4.III.3 Our Approach

We envisage a simple approach towards the synthesis of Chaetomelic acid anhydride **1** (Scheme IX). Alkylation of stable phosphoranes is well known and have been reported in literature³⁹. However, not much attempts have been made in employing this type of reactions in the organic synthesis.

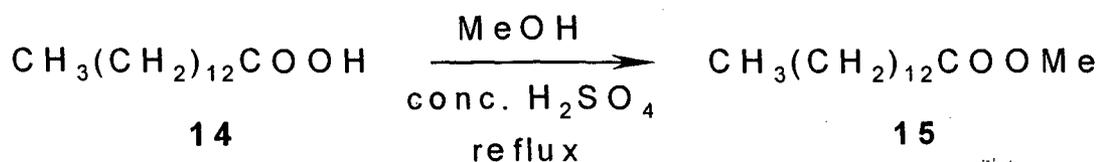
We thought that, alkylation of the stable phosphorane **18** would give a new alkyl phosphorane **19**. The condensation of this new phosphorane **19** with dicarbonyl ester **20** would obtain a diester **21**. Alkaline hydrolysis followed by acid treatment would furnish the required disubstituted maleic anhydride **1**.

As depicted in the Scheme IX we required a long chain alkyl substituent. We used commercially available tetradecanoic acid **14** for this purpose. Our first step was to prepare methyl ester of the acid. This was accomplished by using a reported method^{40a}.



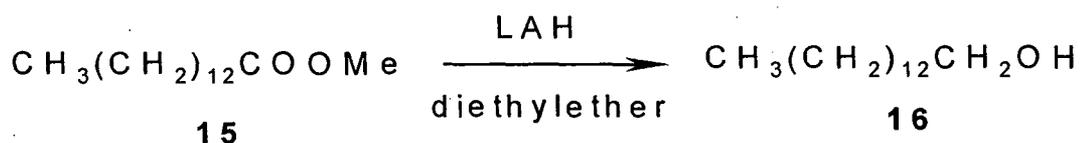
Thus the acid **14** was refluxed in methanol, in presence of catalytical amount of concentrated sulphuric acid for one hour. The crude ester obtained after the usual work up was then purified by column chromatography over silica gel using ethyl acetate:hexanes (5:95) as eluent to afford a liquid ester **15** in 95% yield. The boiling point of the liquid is found to be 323°C , (lit^{40b} b.p. 323°C).

IR : $1745, 1160\text{ cm}^{-1}$.

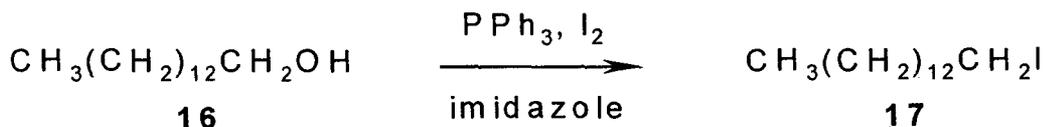


The methyl ester **15** was reduced to long chain alcohol **16** using lithium aluminium hydride (LAH). The methyl myristate **15** was added to a solution of LAH in anhydrous diethyl ether at 0°C. The reaction mixture was stirred for one hour. After usual work up, a crude product was obtained which was purified by column chromatography over silica gel employing ethyl acetate:hexanes (10:90) as eluent to afford a low melting white solid **16** in 98% yield, b.p. 263°C (Lit.^{41a} b.p. 263°C).

IR: 3380 cm⁻¹.

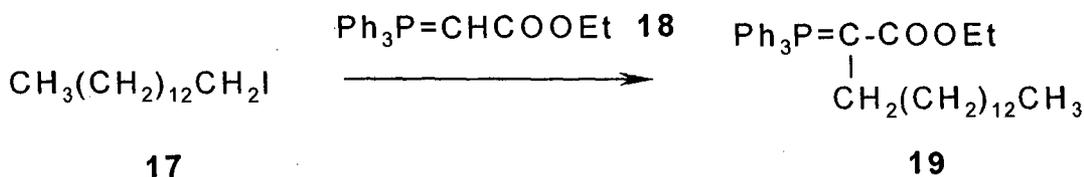


The myristyl alcohol **16**, obtained in the previous step was transformed to myristyl iodide **17**, by a known method^{41b-c}.



The myristyl alcohol **16** was added dropwise to the stirred mixture of triphenylphosphine and imidazole and iodine in acetonitrile at 0°C for 30 min. The reaction mixture was allowed to attain room temperature and was stirred for 8 h. The solvent was evaporated on water bath and the crude mixture was subjected to column chromatography using hexanes as eluent to afford a liquid compound **17** in 46% yield, b.p. 195°/17 mm, (lit.^{41d} b.p. 128°/0.5 mm).

The next step in the projected synthesis was to prepare alkyl phosphorane **19** from the reaction of stable phosphorane^{41e} **18** and myristyl iodide **17**.

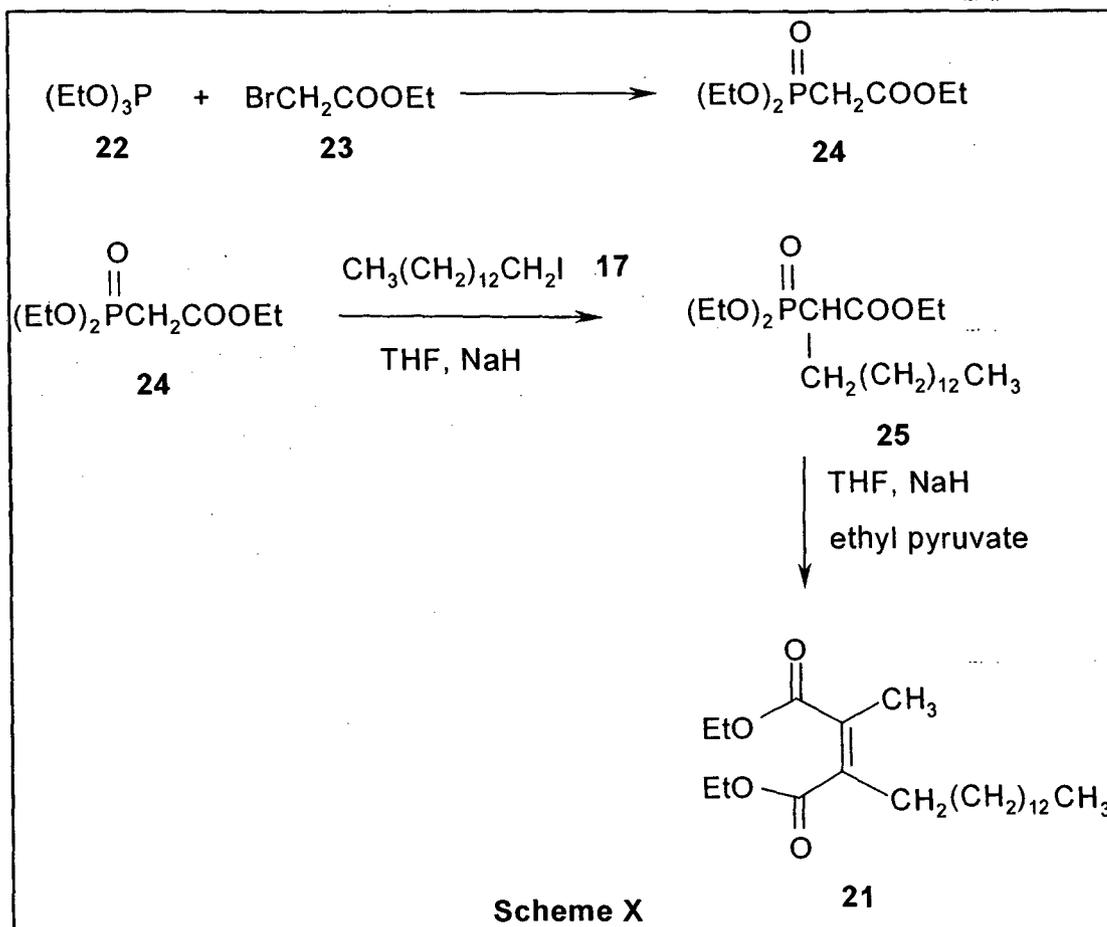


The myristyl iodide **17** was treated with stable phosphorane **18** in chloroform and the reaction mixture was refluxed for 15 hours. The reaction was monitored by tlc. No base spot was observed on tlc, indicating that salt of starting phosphorane **18** was not formed.

The same reaction was tried in anhydrous THF. Tlc showed no new spot formation, even after refluxing the reaction mixture for 12 hours.

The same reaction was carried out without solvent. Neat heating of myristyl iodide and stable phosphorane was carried out for 12 hours. Tlc, again showed no new spot, indicating that alkylation of phosphorane had not taken place.

At this stage, we thought that perhaps, alkylation of phosphonate⁴² **24** would be feasible and the new alkyl phosphonate **25** would serve our purpose in the next step, i.e. condensation of new phosphonate with dicarbonyl compound (Scheme X).



So, the required starting phosphonate **24** was prepared by the known literature procedure⁴³. The ethyl bromoacetate **22** was added dropwise to triethyl phosphite **23**. After 30 min. induction period the temperature rose and ethyl bromide began to distil. The remainder of the ethyl bromoacetate was then added at a rate to maintain the reaction. After complete addition, the reaction mixture was heated at 170°C for 9 hours. Distillation afforded pleasant smelling liquid triethyl phosphonoacetate **24** in 88% yield, b.p 172°C, (Lit.⁴³ b.p 172°C).

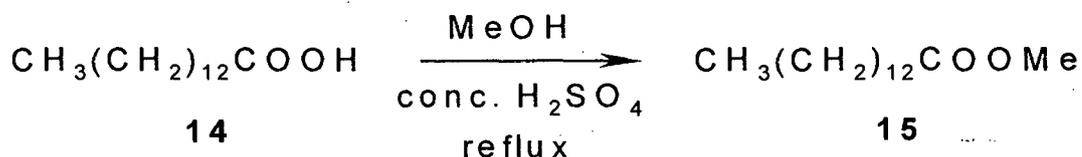
The next step was to carry out the alkylation of the phosphonate. The phosphonate **24**, was added dropwise to the suspension of sodium hydride in anhydrous THF at 0°C. To this, was added myristyl iodide **17** and the reaction mixture was first stirred at room temperature for 6 hours. The course of the reaction was monitored by tlc. The reaction mixture was refluxed for 16 hours. The tlc did not exhibit formation of any new spot indicating that the alkylation reaction has not occurred.

4.III.4 Conclusion

- Alkylation of stable phosphorane **18** and phosphonate **24** with long chain alkyl halide is found to be difficult to achieved though, alkylation with simple alkyl halides are known in literature

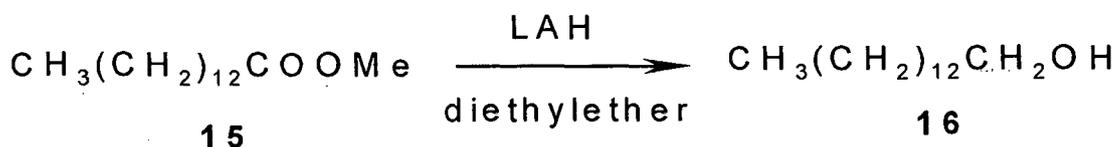
4.III.5 Experimental

Expt. 1 : Preparation of methylmyristate (15)



Tetradecanoic acid **14** (2 g, 9 mmol) was dissolved in methanol (5 mL) and concentrated sulphuric acid (0.5 mL) was added. The reaction mixture was refluxed for 3 hours. The solvent was evaporated on water bath and the reaction mixture was extracted with diethyl ether (3 x 5 mL). The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and concentrated to afford a pleasant smelling liquid. The crude product was purified by column chromatography over silica gel using ethyl acetate:hexanes (5:95) as eluent to obtain **15** (2.1 g, 95%), b.p. 323°C, (lit.^{40b} b.p. 323°C).

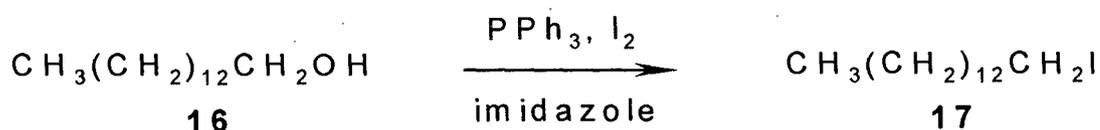
Expt. 2 : Preparation of tertadecyl alcohol (16)



To a stirred solution of Lithium aluminium hydride (0.19 g, 5 mmol) in dry diethyl ether (10 mL) was added ester **15** (1 g, 4.1 mmol) in dry diethyl

ether (5 mL) dropwise, at 0°C, over a period of 0.5 hour. The stirring was continued for 2 hours. Ice-cold water (1 mL) was added cautiously to the reaction mixture. The white solid separated was filtered off and washed with diethyl ether. The combined organic solvent dried over anhydrous sodium sulphate and concentrated on water bath. The crude product was purified over silica gel column chromatography using ethyl acetate:hexanes (1:9) as eluent to obtain a low melting solid alcohol **16** (0.68 g, 98%), b.p. 263°C (Lit.^{41a} b.p. 263°C).

Expt. 3 : Preparation of 1-tetradecyl iodide (17)



1-tetradecanol **16** (4.3 g, 20 mmol) in acetonitrile (5 mL) was added to the stirred mixture of triphenylphosphine (5.26 g, 20 mmol), imidazole (1.36 g, 20 mmol) and iodine (5.08 g, 20 mmol) in acetonitrile (10 mL) at 0°C for 30 min. The reaction mixture was allowed to attain room temperature and kept stirring for another 8 hours. The solvent was evaporated on water bath and the crude mixture was purified by column chromatography over silica gel employing hexanes as eluent to yield liquid **17** (3.0 g, 46%), b.p. 195°/17 mm, (lit.^{41d} b.p. 128°/0.5 mm).

Expt. 4 : Preparation of triethyl phosphonoacetate (24)

Ethyl bromoacetate **22** (7 g, 0.042 mol) was added dropwise to triethyl phosphite **23** (7 g, 0.042 mol). After 0.5 hour induction period the temperature rose and ethyl bromide began to distil. The remainder of the ethyl bromoacetate was then added at a rate to maintain the reaction. After complete addition, the reaction mixture was heated at 170°C for 9 hours. Distillation afforded triethyl phosphonoacetate **24** (7.45 g, 88%), b.p 172°C, (Lit.⁴³ b.p 172°C).

Expt. 5 : Reaction of Myristyl iodide (17) with triethyl phosphonoacetate (24)

To a slurry of 60% NaH (0.22 g, 8.9 mmol) in 10 mL dry THF was added dropwise at 0°C with stirring, triethyl phosphonate **24** (1 g, 4.46 mmol). After the addition the solution was stirred for one hour. Myristyl iodide **17** (1.45 g, 4.46 mmol) in 5 mL THF was added to the slurry and reaction mixture was stirred at room temperature for 6 hours. The tlc did not indicate formation of any new product. The reaction mixture was reflux for 16 hours. Tlc did not indicate formation of any new product.

4.III.6 References

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Section IV

***Synthetic Studies Of Pyrano [2,3-b]
Quinoline Compounds***

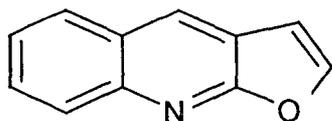
Section IV

Synthetic Studies Of Pyrano [2,3-*b*] quinoline compounds

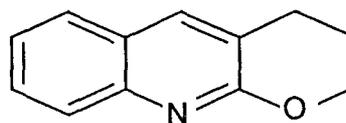
4.IV.1 Introduction

Balfourodedron riedelianum (Rutaceae) is a small Brazilian tree which has been used in folk medicine¹ for the treatment of gastrointestinal ailments. The plant family Rutaceae is known^{2,3} to be a prolific source of pyrano[2,3-*b*]quinoline and furo[2,3-*b*]quinoline alkaloids. These alkaloids have been reported^{4,12a-b} to be associated with interestingly pharmacological as well as biological properties such as antiallergic, anti-inflammatory and estrogenic activities^{12c-e}. Most of the alkaloids isolated from this source are tertiary bases, more commonly furoquinoline alkaloids that typically occur in Rutaceae e.g. skimmianine¹³ 1.

In the case of furo-quinoline alkaloids, the furan ring is fused to *b* bond of quinoline and in case of pyrano-quinolines the pyran ring is fused to the *b* bond of quinoline. These are commonly called as furo [2,3-*b*] quinoline and pyrano [2,3-*b*] quinoline and are represented by structure A and B.



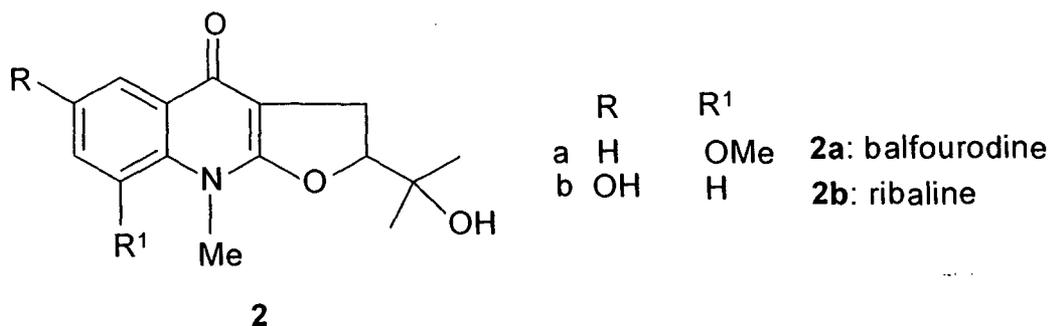
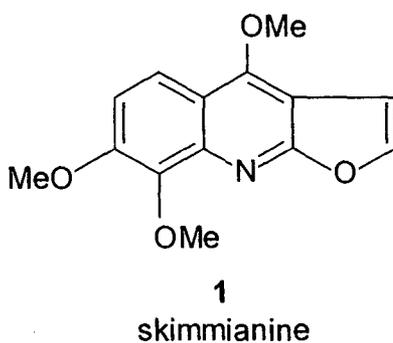
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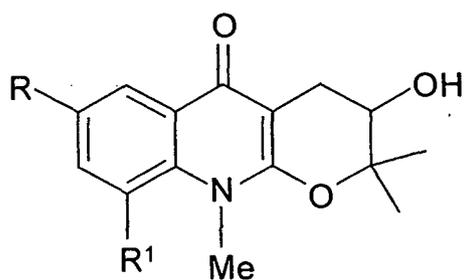


B

Rapoport and Holden¹⁴ have isolated from the trunk bark of Rutaceae contains representatives of dihydrofuro (balfourodine, **2a**), dihydropyrano-4-quinolones (isobalfourodine, **3a**), khaplofoline¹⁵ (**4**) and other related alkaloids e.g. (2-phenyl-1-methyl-4-quinolone and acridone alkaloid named evoxanthine). Much later, a number of minor quinolin-4-one alkaloid, including (+)-ribaline (**2b**) and (-)-ribalinidine (**3c**), have been reported^{16a-b} from the bark of the same tree.

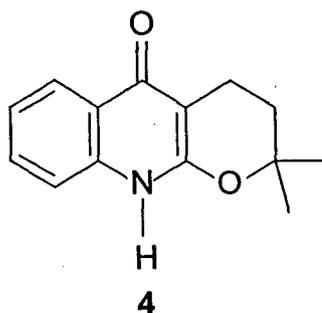
Furthermore, the same authors have characterized two more quaternary alkaloids, O⁴-methylbalfourodinium (**5a**) and ribalinium (**5b**) from the same source.





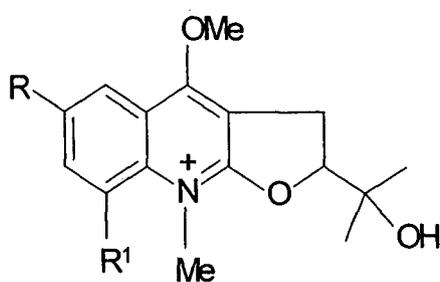
3

	R	R ¹	
a	H	OMe	3a: isobalfourodine
b	H	H	3b: ribalinine
c	OH	H	3c: ribalinidine



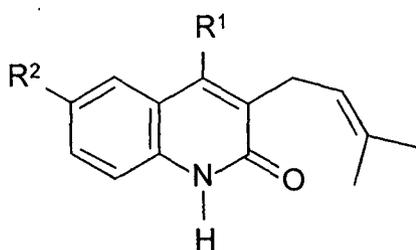
4

khaplofoline



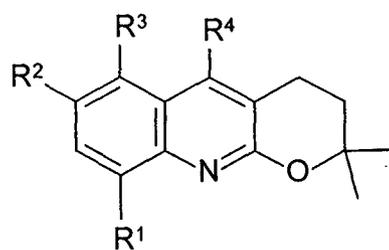
5

	R	R ¹	
a	H	OMe	5a: O⁴-methylbalfourodinium
b	OH	H	5b: ribalinium



6

3-prenyl-2-quinolone



7

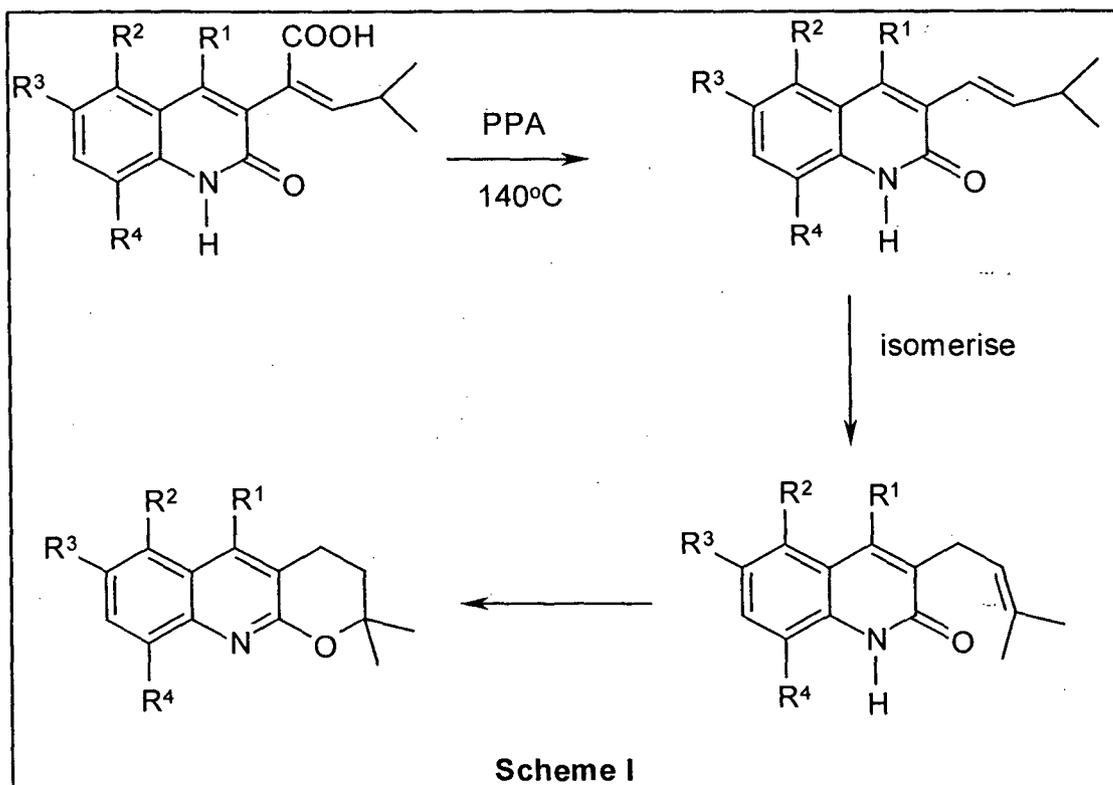
3,4-dihydro-2,2-dimethyl
-2H-pyrano[2,3-b]quinoline.

In this section of the chapter, we have directed our efforts towards developing a general synthesis of pyranoquinoline compounds **7**. Several bioactive alkaloids contain a pyranoquinoline moiety.^{16c}

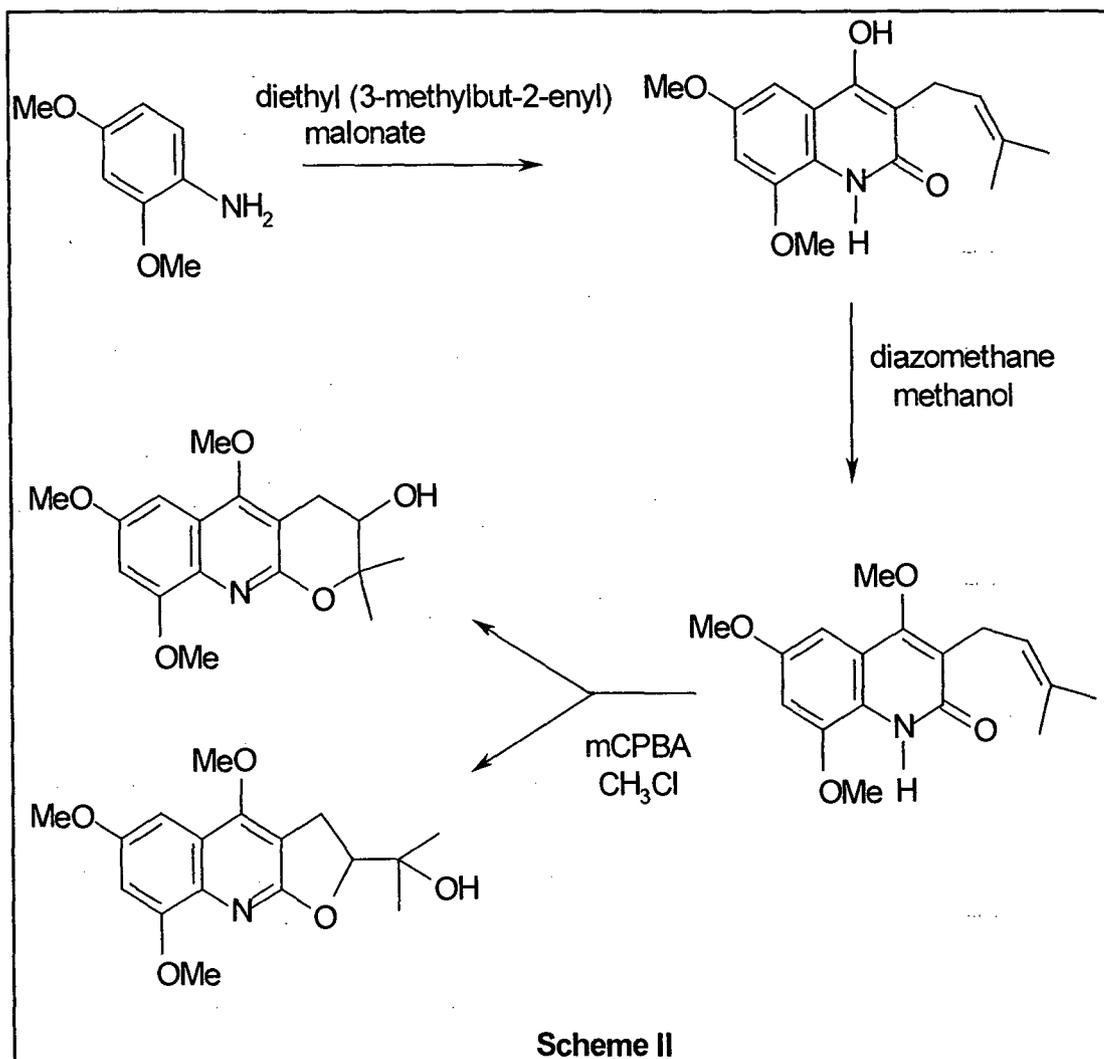
Prenylquinoline **6** is the important precursor towards the synthesis of most of these naturally occurring pyranoquinoline alkaloids and furoquinoline alkaloids. The synthetic method for the preparation of the pyranoquinoline system is based on either oxidative cyclization of 4-hydroxy-3-(3^l-methylbut-1^l-enyl)-2-quinolinones with DDQ¹⁷ or the Prevost reaction of 3-prenyl-2-quinolones¹⁸.

Though, these methods have been fairly satisfactory, the overall yield of the alkaloids was only 15-35%, primarily because the synthesis of the precursor prenylquinolines gave low yields^{19,20} and were often attended with undesired side reactions (such as the formation of unwanted 3-(3^l-methylbut-1^l-enyl)-2-quinolones as the major product²¹).

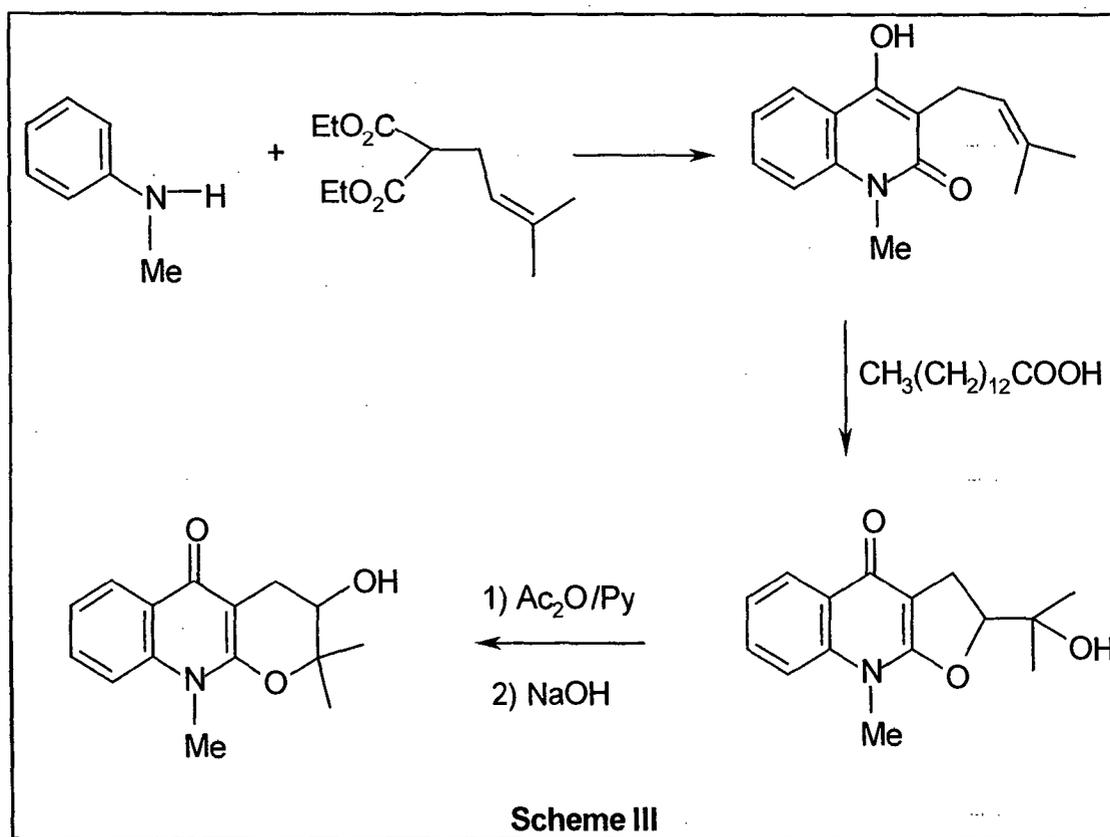
Prasad and Sekar²² have described a method for the preparation of pyranoquinolines using carboxy derivative of the 2-quinolinone as starting material and treating it with polyphosphoric acid at 140°C. Extension and application of this method gave different pyranoquinolines (**Scheme I**).



Grundon *et al*²³ have reacted 2,4-dimethoxyaniline with diethyl (3-methylbut-2-enyl) malonate in boiling diphenyl ether and the product isolated was treated with solution of diazomethane in ether. The 4-hydroxy-2-quinolone obtained was subjected to *m*-chloroperoxybenzoic acid oxidation in chloroform at 0°C to give a mixture of two pyranoquinoline and furoquinoline products in 7:5 ratio. (Scheme II)

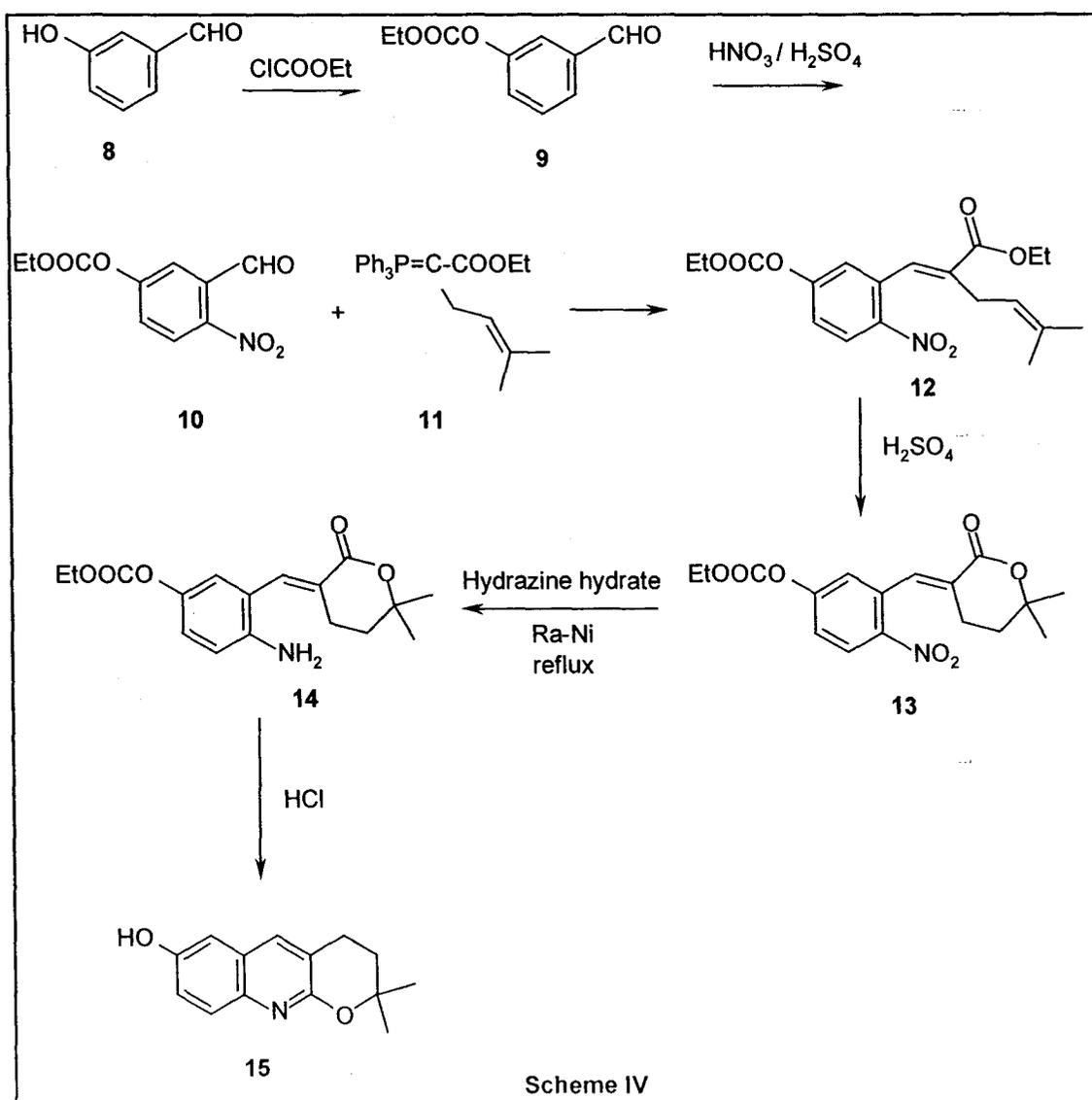


Corral and *et al*²⁴ have reported the synthesis of pyranoquinolone using N-methyl aniline and diethyl-(3-methylbut-2-enyl)-malonate to obtain the prenylquinolone and treating this with dodecanoic acid to give furoquinolone. They also converted the 5-membered furan ring into 6-membered pyran isomer in a facile manner under basic condition (Scheme III).



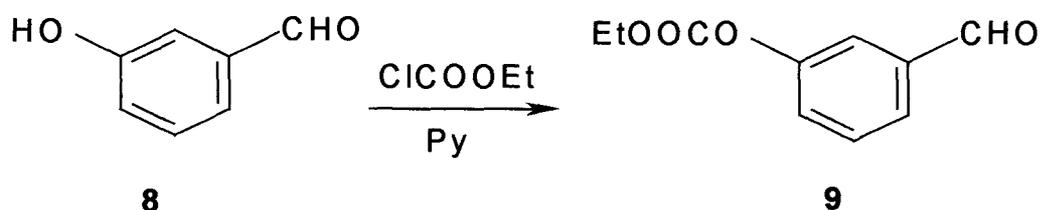
4.IV.2 Our Strategy

The Strategy envisaged was to condense nitroaldehyde **10** with prenyl phosphorane **11** to obtain prenyl ester **12** which would then be subjected to acid catalysed cyclisation to give a δ -lactone **14**. The reduction of nitro group followed by acid treatment would give pyranoquinoline **15**. The strategy visualized is depicted in (Scheme IV).

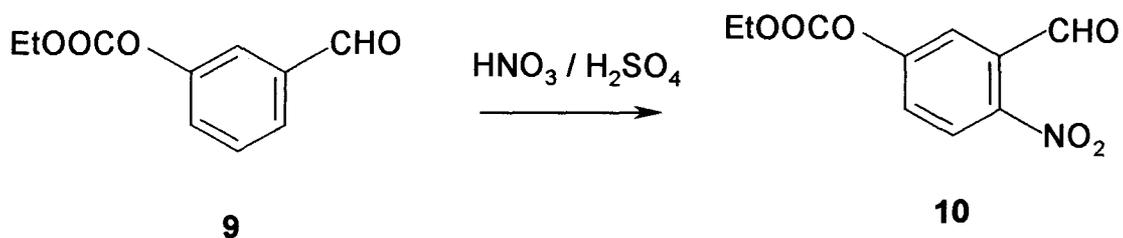


The first step in our projected synthesis involves condensation of 5-substituted-2-nitrobenzaldehyde **10** with prenyl phosphorane **11**. The nitrobenzaldehyde **10** was prepared from the known literature method²⁵.

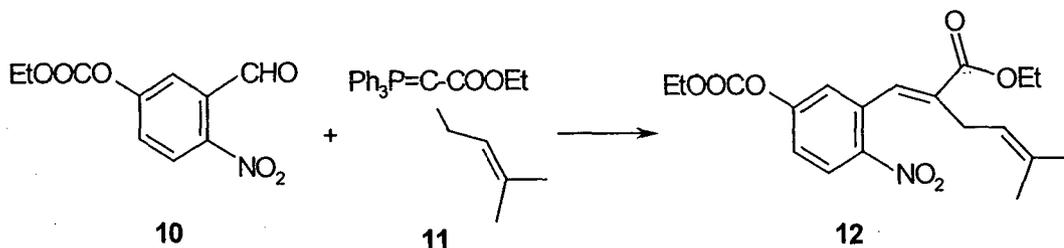
Thus, protection of *o*-hydroxybenzaldehyde **8** was carried out with ethyl chloroformate in presence of pyridine as reported in the literature method. The spectral data of the product was found to be identical with the data reported in the literature²⁵.



The nitration on *O*-protected benzaldehyde **9** was carried out by subjecting the aldehyde to sulphuric acid /nitric acid mixture. After usual work up the crude product was crystallized from hexanes to yield pale yellow needles of ethyl-3-formyl-4-nitrophenyl carbonate **10**. The crystallized product was melted at 61°C . (Lit.²⁵ m.p. $60\text{-}61^\circ\text{C}$).



For the next condensation reaction, we required prenyl phosphorane **11**. The prenyl phosphorane was prepared as per literature method²⁶.



This prenyl phosphorane **11** was condensed with nitrobenzaldehyde **10** in dry benzene. The reaction mixture was refluxed vigorously for 3 hours. The crude product obtained after the usual work up was purified by column chromatography over silica gel using ethyl acetate:hexanes (1:9) as eluent to obtain a pleasant smelling viscous liquid in 82% yield.

The IR spectrum exhibited strong bands at 1770 cm^{-1} which could be attributed to the carbonyl of carbonate group, 1722 cm^{-1} could be attributed to the carbonyl of unsaturated ester group. The bands displayed at 1530 cm^{-1} and 1344 cm^{-1} indicated the presence of nitro group.

The ^1H NMR spectrum (Fig. 4.4.1), showed peaks at δ 1.26-1.43 (m, 6H) and δ 4.19-4.33 (m, 4H), which could be attributed to the two ester groups $2 \times (-\text{OCH}_2\text{CH}_3)$, while the signal at δ 1.64 (s, 6H) could be assigned to two methyls of prenyl group. The peaks observed at δ 2.93 (d, $J = 6.6\text{ Hz}$, 2H) and at δ 4.95 (br.s, 1H) could be assigned to the prenyl moiety $(-\text{CH}_2\text{CH}=\text{C}-)$. The peaks observed at δ 7.15 (d, $J = 2.4\text{ Hz}$, 1H), δ 8.14 (d, $J = 9.0\text{ Hz}$, 1H) and δ 7.29 (dd, $J = 9.0 \& 2.4\text{ Hz}$, 1H) indicated the presence of 1,2,4-trisubstituted aromatic

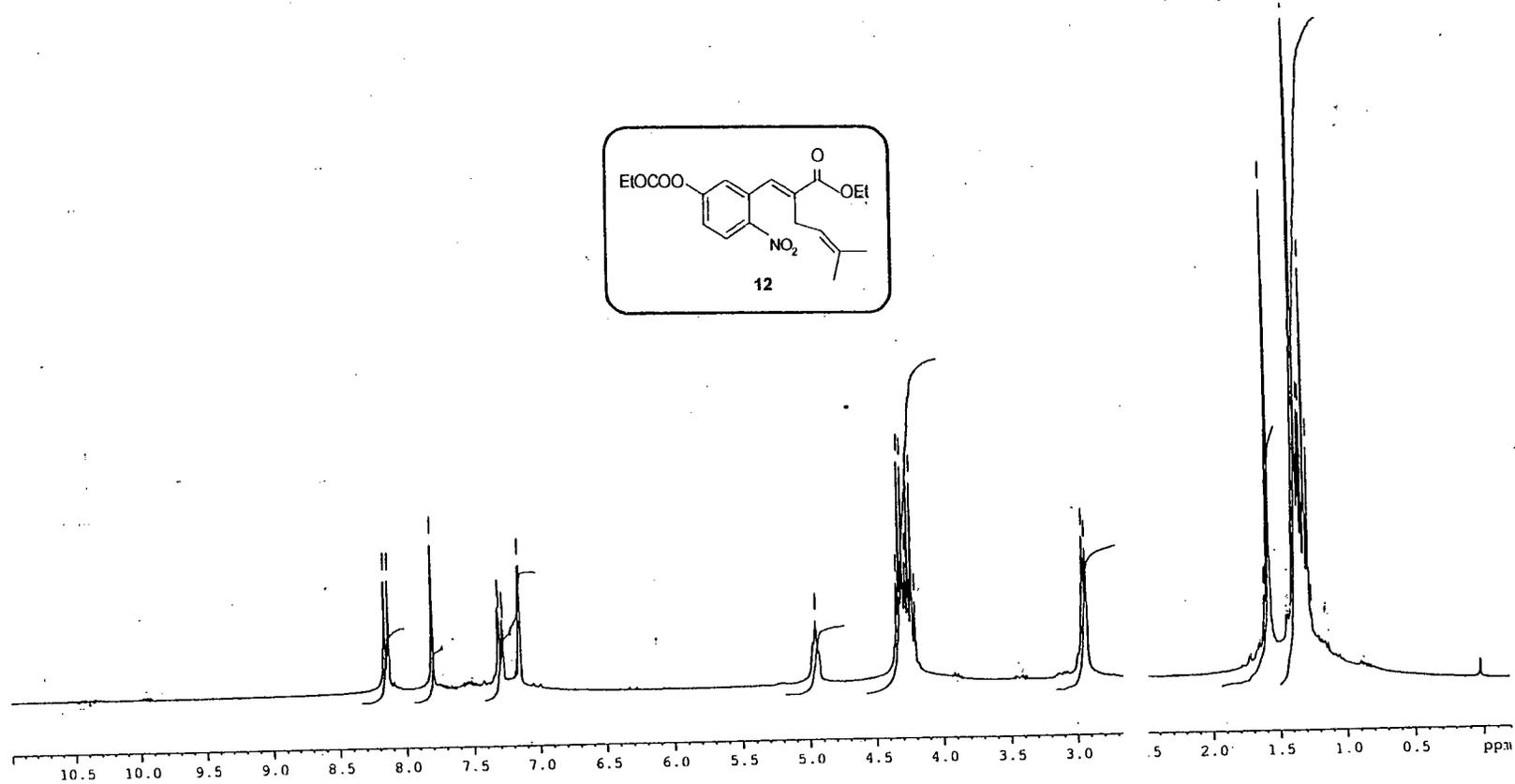


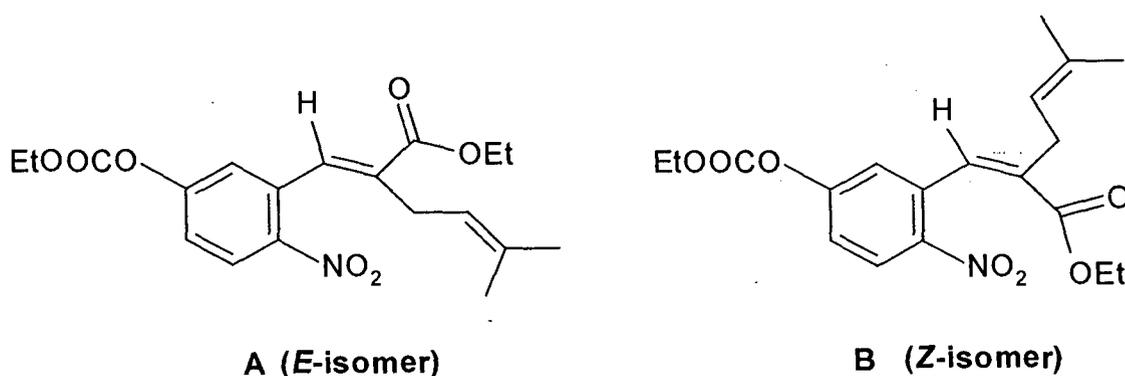
Fig. 4.4.1: ¹H-NMR of ethyl-(α-prenyl)-3(ethyl-formyl carbonate)-2-nitro cinnamate (12).

system, while the signal at δ 7.79 (s, 1H) could be assigned to the benzylic proton.

Stereochemistry of the ester 12.

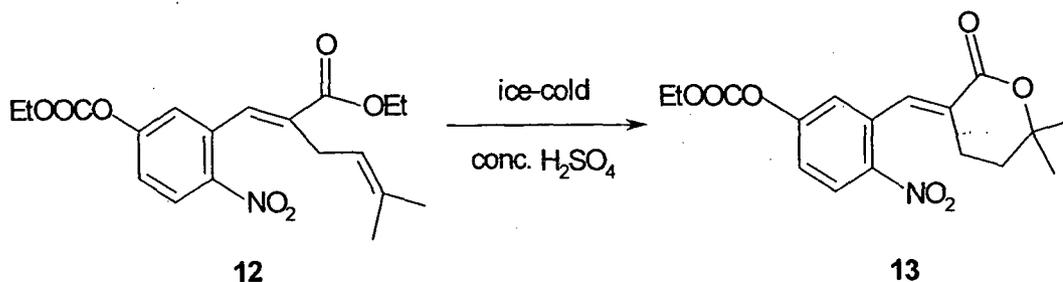
Olefinations of carbonyl compounds by Wittig reaction are known to furnish two geometrical isomers (*E* and *Z*). We have already seen in Chapter III that reaction of carboethoxy-(α -allyl)-methylidenephosphorane with aldehyde gives only *E* isomer.

The nitroester could have structure either **A** (*E*-isomer) i.e. olefinic β -proton lies syn to the carbonyl group of ester or structure **B** (*Z*-isomer) i.e. olefinic β -proton lies anti to carbonyl group of ester.



The structure **A** (*E*-isomer) was assigned to the product by the same analogy as discussed in chapter III.

The pleasant smelling ester **12** was subjected to the concentrated sulphuric acid in an ice-cold condition for one hour to furnish a lactone. The liquid obtained was purified by column chromatography over silica gel using ethyl acetate:hexanes (1:9) as eluent to obtain a viscous liquid in 95% yield.



The IR spectrum exhibited strong bands at 1774 cm^{-1} which could be attributed to the carbonyl of carbonate group, and a band at 1717 cm^{-1} could be attributed to the carbonyl of α,β -unsaturated six membered lactone group. The bands displayed at 1531 cm^{-1} and 1344 cm^{-1} indicated the presence of nitro group.

The ^1H NMR spectrum (Fig. 4.4.2), showed peaks at δ 1.40 (s, 6H), δ 1.78 (t, $J = 6.9\text{ Hz}$, 2H) and δ 2.53 (t, $J = 6.9\text{ Hz}$, 2H) could be attributed to the two methyl groups and two methylene groups ($-\text{CH}_2\text{CH}_2-$) of the six membered lactone, respectively. The signals observed at δ 1.34 (t, $J = 7.2\text{ Hz}$, 3H) and δ 4.30 (q, $J = 7.2\text{ Hz}$, 2H) was assigned to the ester group of the carbonate moiety.

The peaks exhibited at δ 7.18 (d, $J = 2.4\text{ Hz}$, 1H), δ 8.17 (d, $J = 9.0\text{ Hz}$, 1H) and δ 7.32 (dd, $J = 9.0\text{ \& } 2.4\text{ Hz}$, 1H) could be assigned to 1,2,4-trisubstituted aromatic system while the signal at δ 8.03 (s, 1H) was assigned to the benzylic proton.

Based on spectral analysis the product obtained was assigned structure **13** having *E* geometry by assuming that no change in stereochemistry occurred during cyclisation.

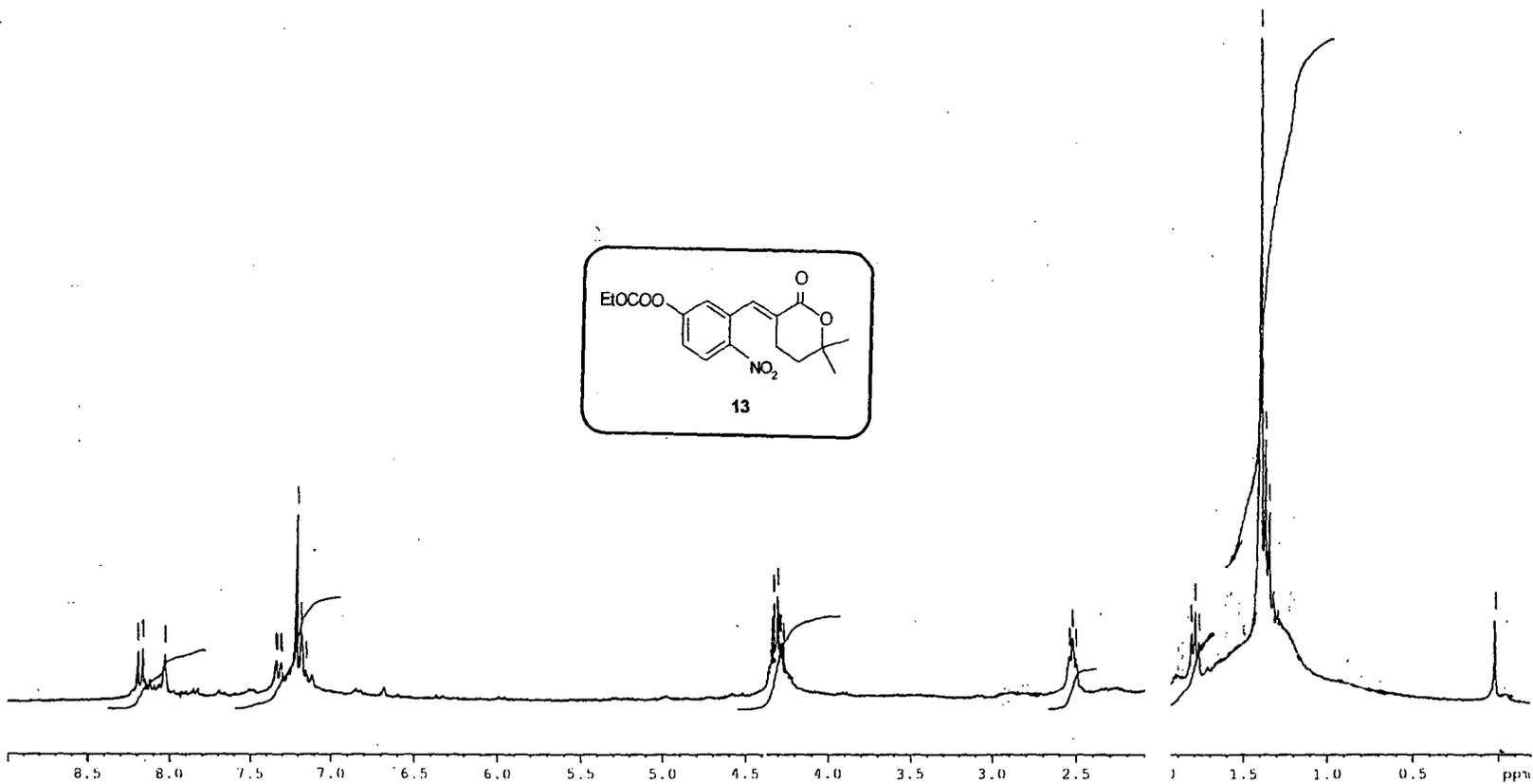
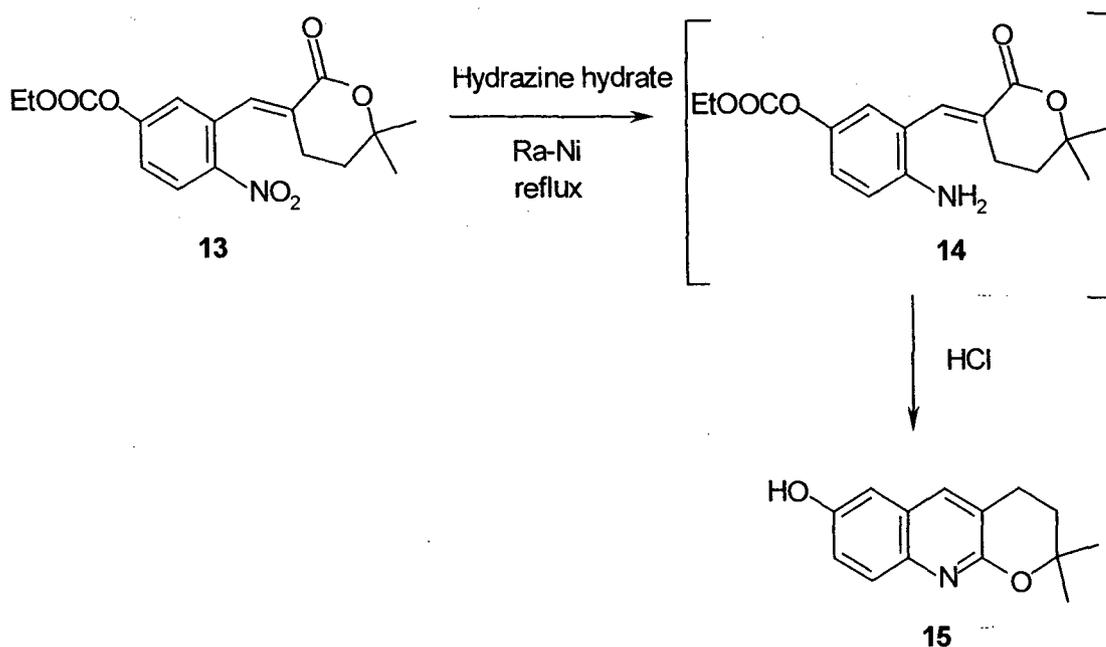


Fig. 4.4.2 : ¹H NMR spectrum of α -3-(ethyl formyl carbonal)-2-nitrobenzylidene- δ -dimethyl- δ -lactone (13).

Our next step was the reduction of nitrolactone **13**. This was accomplished by treating the ester with hydrazine in presence of Raney-nickel and refluxing in ethanol for 15 minutes. The crude product obtained was further refluxed with concentrated hydrochloric acid for 6 hours. Usual work up followed by column chromatographic purification over silica gel using ethyl acetate:hexanes (1:1) as eluent obtained a solid compound. Recrystallization with ethyl acetate-hexanes afforded a white solid, (59%, m.p. 224°C).



The IR spectrum exhibited a broad band at 3300 cm^{-1} was due to the presence of phenolic group. The absence of carbonyl group and nitro group was confirmed by the absence of characteristic bands, as seen in the IR spectrum of compound **13**.

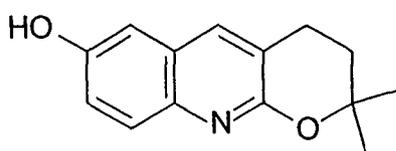
The ^1H -NMR spectrum (Fig. 4.4.3), of the product showed peaks at δ 1.46 (s, 6H), δ 1.93 (t, $J = 6.9$ Hz, 2H) and δ 2.99 (t, $J = 6.9$ Hz, 2H) could be attributed to the two methyl groups and two methylene groups ($-\text{CH}_2\text{CH}_2-$) of the pyran ring, respectively. The small broad singlet at δ 5.58 (br.s 1H) could be the phenolic proton. The peaks at δ 7.03 (d, $J = 2.7$ Hz, 1H), δ 7.21 (dd, $J = 9.0$ & 2.7Hz, 1H), δ 7.73 (s, 1H) and δ 7.76 (s, 1H) could be assigned to the four aromatic protons of quinoline ring.

^{13}C -NMR (Fig. 4.4.4),

δ 22.59 (CH_2), 27.28 (2 x CH_3), 32.39 (CH_2), 70.19 (C), 108.46 (CH), 118.06 (CH), 120.69 (CH), 125.83 (CH), 128.52 (C), 136.16 (C), 141.62 (C), 152.02 (C), 158.20 (C)

The multiplicities were obtained from DEPT-135 experiments.

Based on the spectral data and mode of formation structure **15** was assigned to the compound.



15

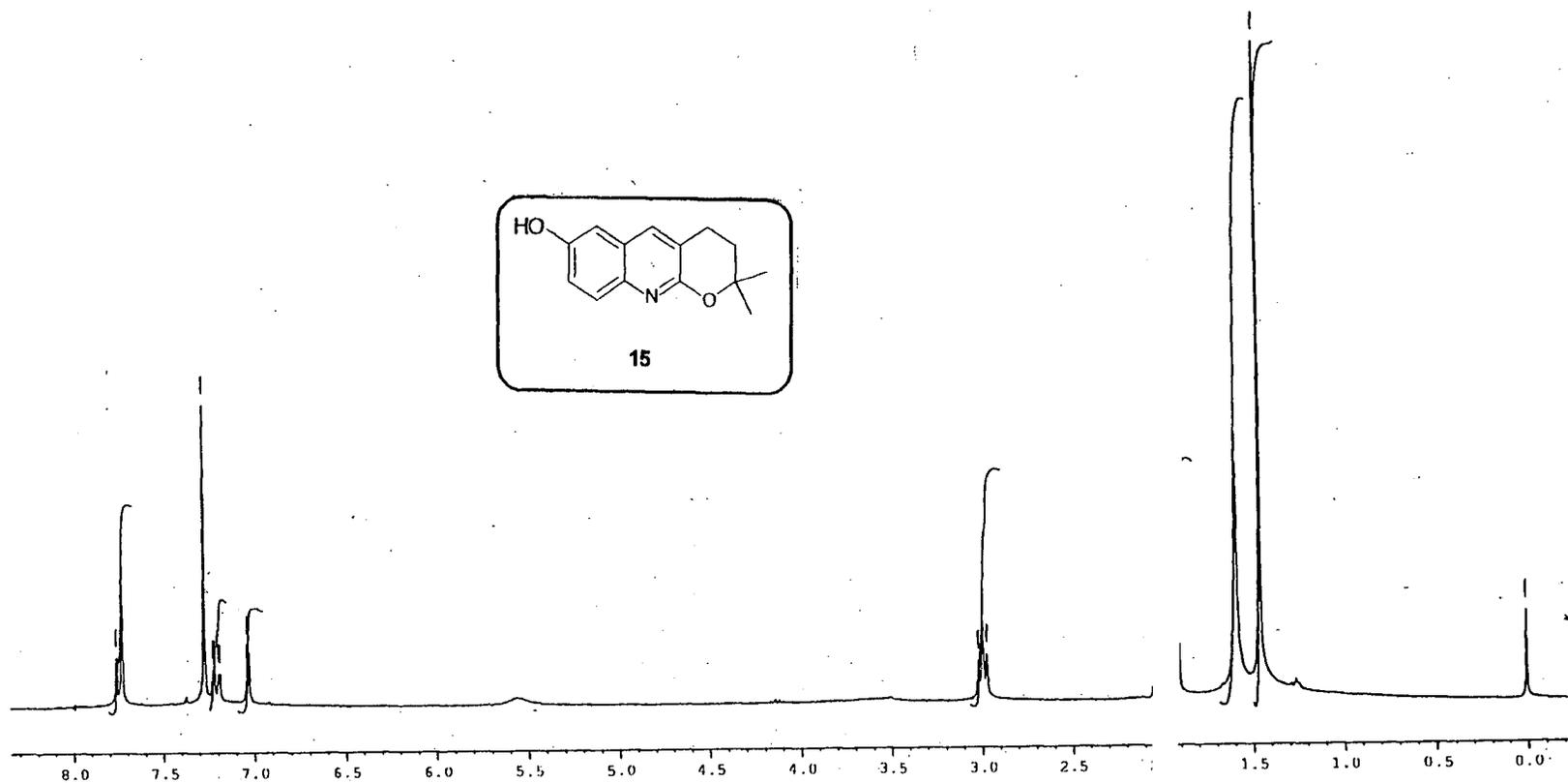


Fig. 4.4.3 : ¹H-NMR of 2,2-dimethyl-3,4-dihydroprano[2,3-b]quinoline (15).

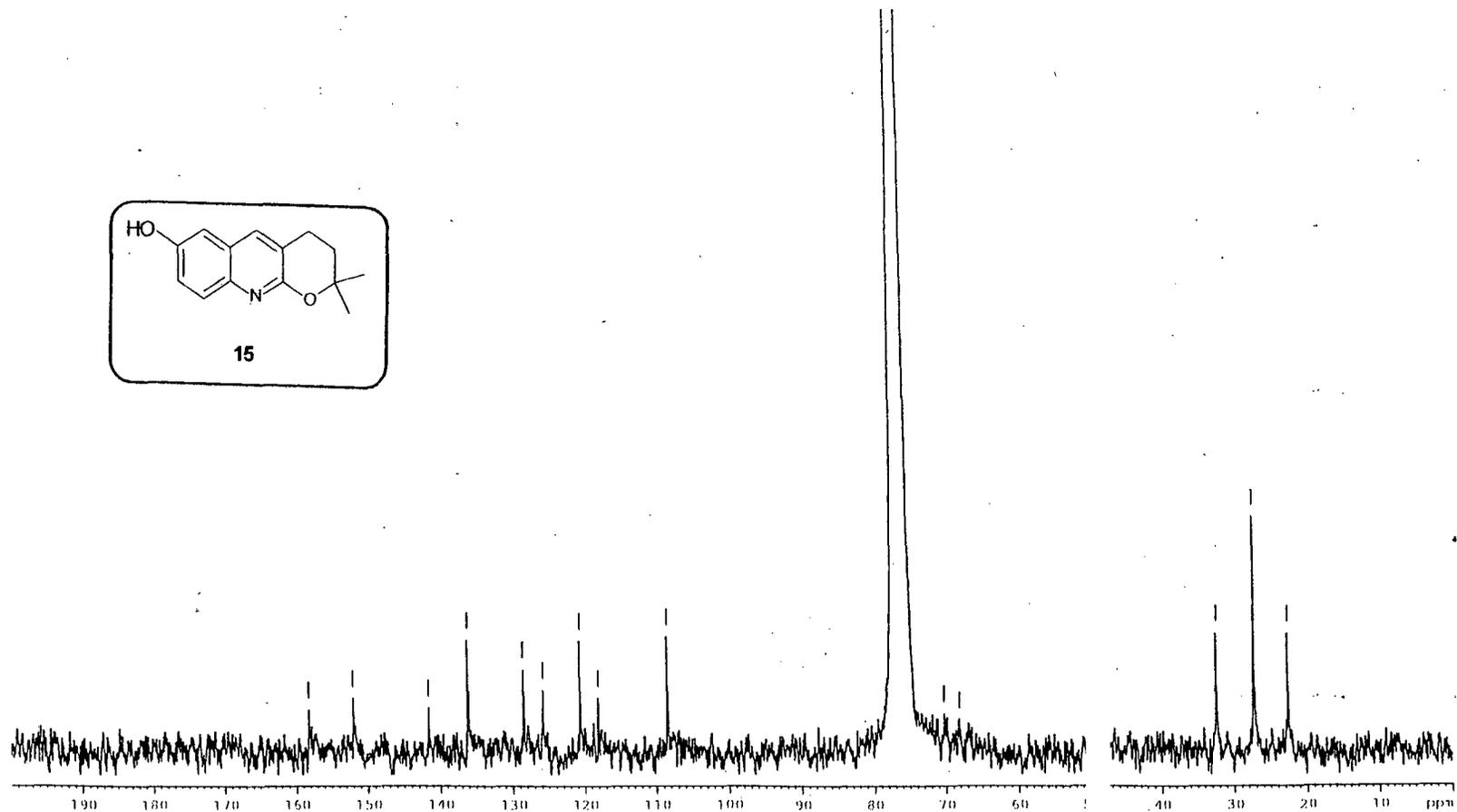
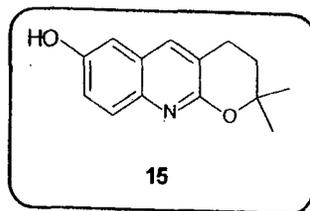


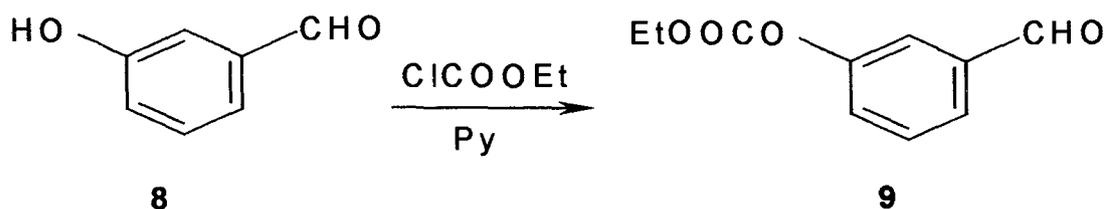
Fig. 4.4.4 : ^{13}C -NMR of 2,2-dimethyl-3,4-dihydroprano[2,3-b]-quinolin (15).

4.IV.3 Conclusion

- A new simple method has been developed for the synthesis of alkaloids having pyranoquinoline skeleton.

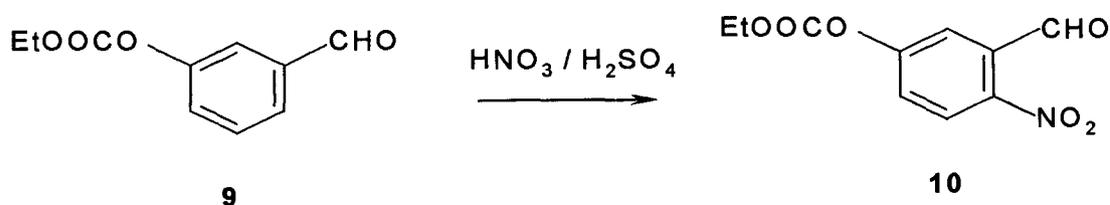
4.IV.4 Experimental

Expt. 1 : Preparation of Ethyl 3-formylphenyl carbonate (9)



3-hydroxybenzaldehyde (15.0 g, 0.123 mol) was dissolved in dry pyridine (100 mL). The solution was cooled in an ice bath and ethyl chloroformate (20 mL) was added dropwise over a period of 30 min. The resulting solution was stirred for 2 hours at room temperature. The product was extracted with diethyl ether (2 x 10 mL) and the ether layer was washed with water, 5% HCl, 5% cold NaOH and again with water. The dried organic extract was evaporated to give the product as dark red syrup **9** (23.0 g, 97%).

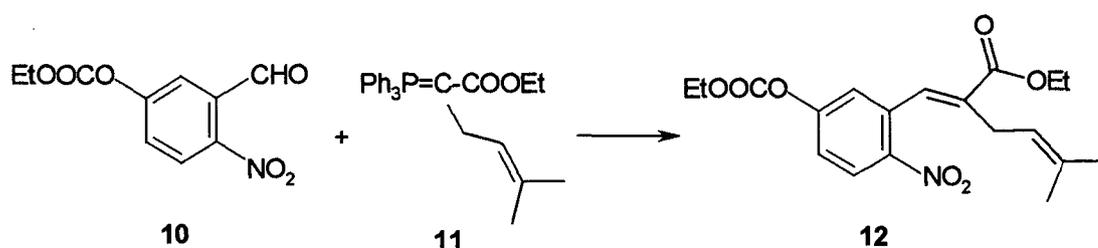
Expt. 2: Preparation of Ethyl 3-formyl-4-nitrophenyl carbonate (10)



Ethyl 3-formylphenyl carbonate (14.0 g, 0.0072 mol) was dissolve in conc. H₂SO₄ (135 mL). The solution was cooled to -5°C and a solution of fuming nitric

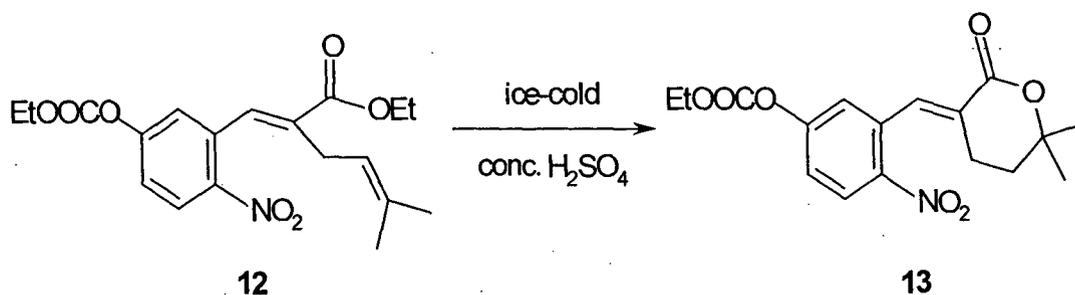
acid (3.44 mL, sp.g.1.49, 0.0814 mol) in 25 mL of conc. Sulphuric acid was added dropwise over 15 min. at -5°C to 0°C . Stirring was continued at -5°C to 0°C for one hour. Water (500 mL) was added dropwise at -10°C and the product was extracted into chlorform. Evaporation of the washed and dried solvent gave a gum which crystallized from hexanes as pale yellow needles **10** (13.0 g, 76%), m.p. 61°C , (Lit.²⁵ m.p. $60-61^{\circ}\text{C}$).

Expt. 3 : Preparation of (E) ethyl (α -prenyl)-3(ethyl-formyl carbonate)-2-nitrocinnamate (12).



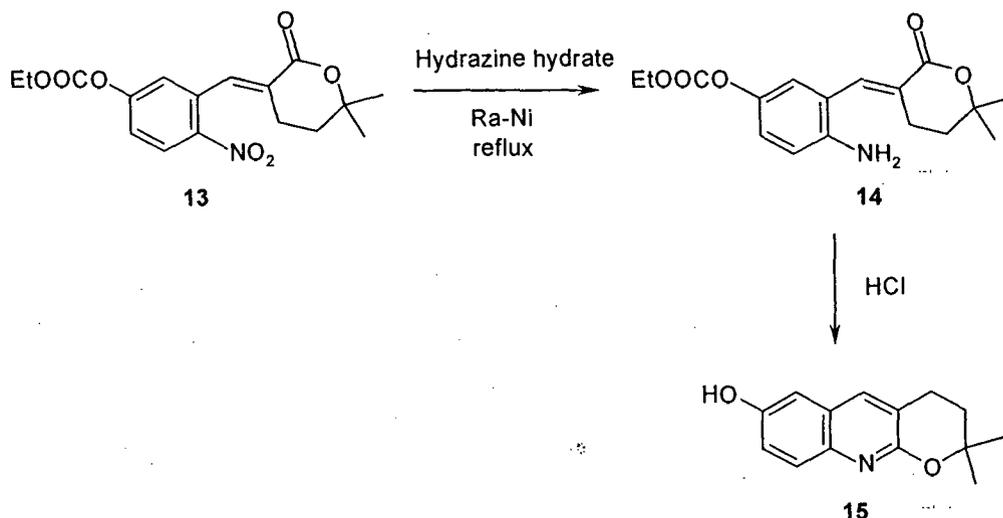
A mixture of ethyl 3-formyl-4-nitrophenyl carbonate **10** (0.239 g, 1 mmol), prenyl phosphorane **11** (0.459 g, 1.1 mmol) was refluxed vigorously in benzene for 3 hours. Chromatographic separation over silica gel using ethyl acetate:hexanes (1:9) as eluent furnished a pleasant smelling viscous liquid **12** (0.308 g, 82 %).

**Expt. 4 : Preparation of (*E*) α -3-(ethyl formyl carbonate)-2- nitrobenzylidene-
- δ -dimethyl- δ -lactone (13).**



To a flask containing ice cold ester (0.376 g, 1 mmol) was added ice cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 1 hour. After the completion of reaction, sufficient crushed ice was added to the reaction mixture to make it dilute and the reaction mixture was extracted in diethyl ether (2 x 5 mL). The combined organic extract was dried over anhydrous sodium sulphate and concentrated to get a viscous liquid. The crude product obtained was purified by column chromatography over silica gel using ethyl acetate: hexanes (1:9) as eluent to yield compound **13** (0.962 g, 95%).

Expt. 5: Preparation of 2,2-dimethyl-3,4-dihydroprano-7-hydroxy-[2,3-b]-quinoline (15).



α -3-(ethylformylcarbonate)-2-nitrobenzylidene- δ -dimethyl- δ -lactone (13)

(0.345 g, 1 mmol) was dissolved in ethanol (15 mL) and hydrazine hydrate (99%, 0.5 mL) was added to it followed by addition of Raney-nickel (~0.1 g). The reaction mixture was refluxed for 10 min., cooled and filtered. The solvent was removed under reduced pressure and 6N HCl (10 mL, AR grade) was added to the residue. The reaction mixture was heated on waterbath for 6 hours. It was cooled to room temperature and washed with dichloromethane (2 x 10 mL). The aqueous layer was cooled to 0°C, basified with liquor ammonia and extracted with dichloromethane (3 x 10 mL). The organic layer was dried over anhydrous sodium sulphate and the crude product obtained was purified by column chromatography over silica gel using ethyl acetate: hexanes (1:1) as eluent. The recrystallization of the product with ethyl acetate-hexanes yielded white solid 15 (0.123 g, 59%, m.p. 224°C).

4.IV.5 References

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