REACTIONS AND REACTIVITY

OF

ALLYLIC AND BENZYLIC

CARBAMATES

by

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DECLARATION

I hereby certify that this research is the result of my own investigation which has not been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed : ....

J.C. LONGLEY

I hereby certify that this statement is correct.

Signed : ....

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ABBREVIATIONS

aq.	:	aqueous
Ar	:	aryl
b.p.	:	boiling point
Boc	:	butoxycarbonyl
Bu	:	butyl
BuLi	:	butyl lithium
d	:	doublet
DABCO	:	1,4-diazabicyclo-[2,2,2]-octane
DCC	:	dicyclohexylcarbodiimide
DDQ	:	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	:	diethyl azodicarboxylate
DIBAL	:	diisobutylaluminium hydride
DMF	:	N,N-dimethylformamide
DMG	:	directed metallation group
DoM	:	directed *ortho* metallation
E^+	:	electrophile
Et	:	ethyl
ether	:	diethyl ether
GC/MS	:	gas chromatography / mass spectrometry
h	:	hour
Δ	:	heat
^{i}Pr	:	isopropyl
LAH	:	lithium aluminium hydride
LDA	:	lithium diisopropylamide
M^+	:	molecular ion
MCPBA	:	3-chloroperoxybenzoic acid
m	:	multiplet
Me	:	methyl
m.p.	:	melting point
min	:	minute

NMR	:	nuclear magnetic resonance
Nu⁻	:	nucleophile
OAc	:	acetate
OAm	:	amide
Ph	:	phenyl
Pr	:	propyl
q	:	quartet
RT, rt	:	room temperature
s	:	singlet, second
sat.	:	saturated
t	:	triplet
TBDMS	:	*tertiary* butyldimethylsilyl
TBDMSCl	:	*tertiary* butyldimethylsilylchloride
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
TMS	:	trimethylsilyl, tetramethylsilane
TMSCl	:	trimethylsilylchloride

SUMMARY

The purpose of this investigation was to study the effect of the carbamate group on the reactions and reactivity of substituted 1,1-diphenylmethane and α,ω-diphenyl allylic compounds. A series of carbamates were prepared and reacted with a variety of electrophiles and nucleophiles.

1-(O-N,N-dimethylcarbamoyloxy)-1,1-diphenylmethane (i) reacted with a variety of electrophiles to afford α-substituted carbamate products (ii).

Reactions of allylic carbamates with electrophiles proceed with substitution at the carbon atom α or γ to the carbamate. 1-(O-N,N-diethylcarbamoyloxy)-1,3-diphenyl-2-propene (iii) only reacted with methyl iodide to afford the γ-substituted product (iv). Reactions of 1-(O-N,N-diethylcarbamoyloxy)-1,5-diphenyl-2,4-pentadiene (v) with electrophiles were all unsuccessful.

Nucleophilic substitution reactions were performed with carbamates (i), (iii) and (v). No success was achieved in the reactions of (i) with nucleophiles. Carbamates (iii) and (v) reacted with a few oxygen nucleophiles to afford allylic ethers with simultaneous elimination of the carbamate group.

Several properties of terminal-diphenyl carbamates have been revealed :

(a)   Benzylic carbamate (i) reacted successfully with a variety of electrophiles. Nucleophilic substitution is not favoured with the benzylic carbamate. This indicates that S_N2 elimination of the carbamate does not occur in this molecule.

(b)   Allylic carbamate (iii) only reacts with methyl iodide indicating that the bulk of the diethyl substituents on the carbamate group, the bulk of the incoming electrophile and the size of the phenyl groups are fundamental to the success of reaction. Methylation occurred only at the γ-position.

(c)   Conjugated allylic carbamate **(v)** did not react with any electrophiles, suggesting that, in addition to the steric factors, the stability offered in the retention of conjugation in the molecule prevented the formation of the electrophilic substitution products.

(d)   Unsymmetrical allylic carbamates **(iii)** and **(v)**, in which the carbamate occupies a benzylic position, are more stable than symmetrical allylic carbamates **(vi)** and **(vii)** which decompose to the corresponding alcohol.

(e)   Nucleophilic substitution of **(iii)** and **(v)** occurred with S_N2' elimination of the carbamate group, the reaction proceeding in a way which faciliates the formation of the most conjugated product possible.

Nucleophilic substitution of **(iii)** with the phenoxide anion resulted in the allyl aryl ether **(viii)**. Several attempts were made to promote the Claisen rearrangement to afford the allylic phenol **(ix)** but without success.

Exploitation of the migrational ability and the leaving group ability of the carbamate moiety were extended to the synthesis of Δ^3-flavene **(xi)** from allylic alcohol **(x)**. Several attempts were made to synthesise **(x)** *via* the Aldol condensation and Grignard reactions. The synthesis of **(xi)** was hindered by the failure to produce allylic alcohol **(x)**.

During the course of these investigations an unexpected decomposition reaction was discovered. The purification by distillation of allylic carbamate **(xii)** afforded allylic amine **(xiii)** in quantitative yield. The driving force for the reaction is the intramolecular S_N2' elimination of the carbamate with the simultaneous loss of carbon dioxide. This reaction may have scope in the synthesis of allylic amines.

(i)

(ii)

(iii)

(iv)

(v)

(vi)

(vii)

(viii)

(ix)

(x)

(xi)

(xii)

(xiii)
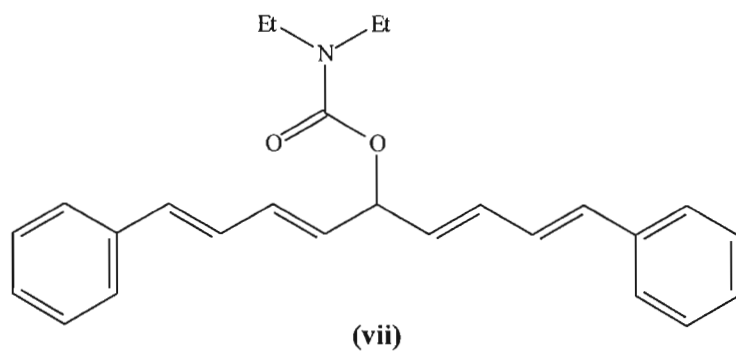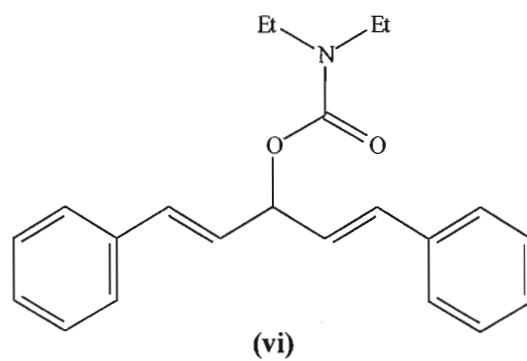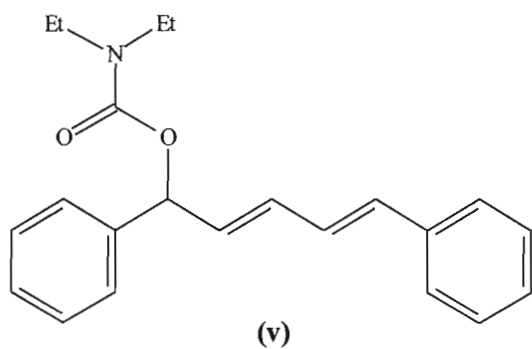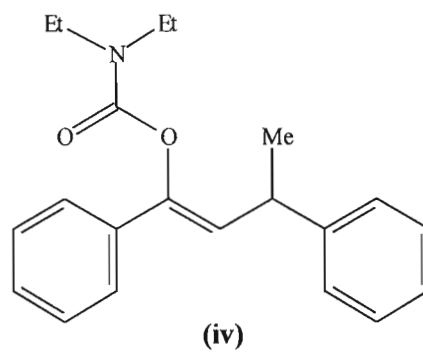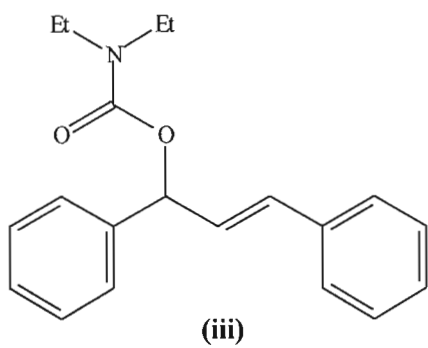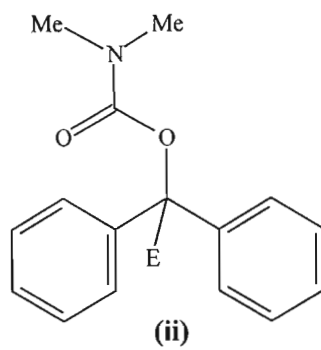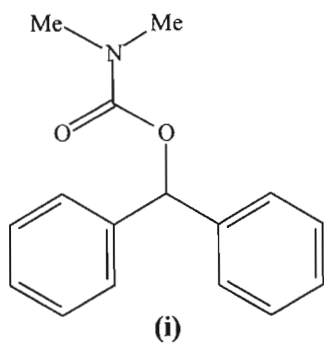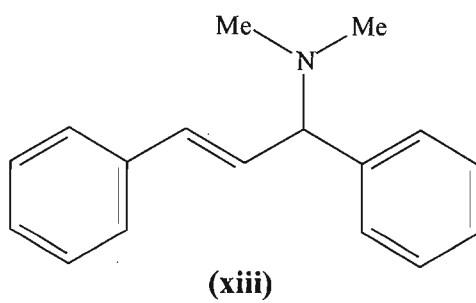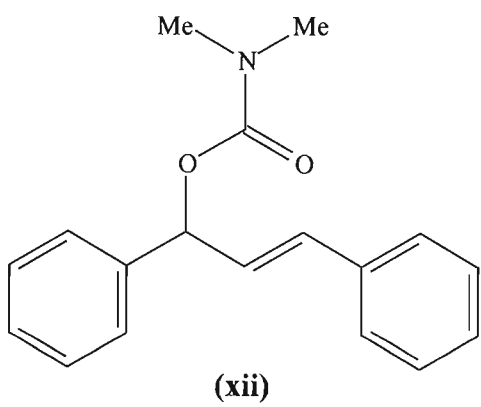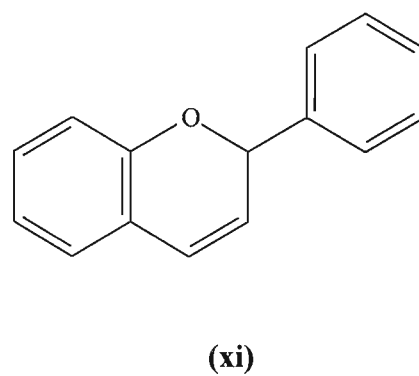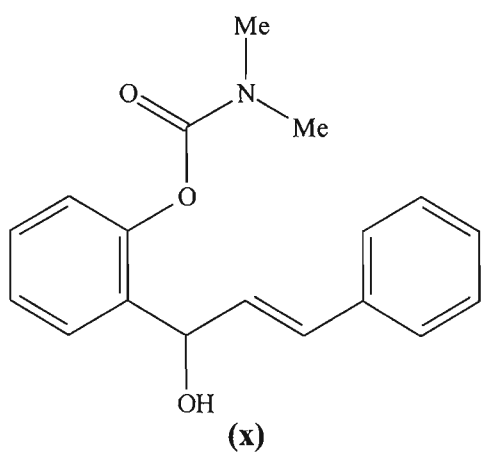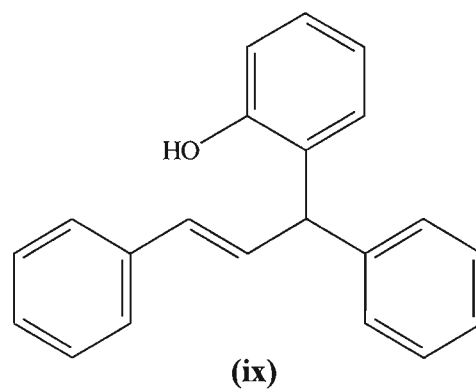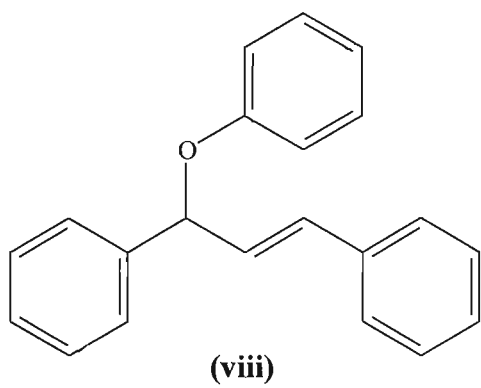
CHAPTER 1 : INTRODUCTION

The prime aim of this project was to investigate the reactions and reactivity of the carbamate functionality **(1)** , in particular its effects on benzylic and allylic systems.
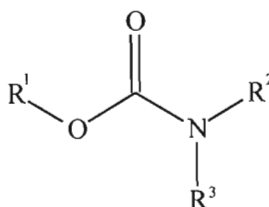
(1)

R^1 = alkyl or aryl

R^2, R^3 = alkyl, aryl or H

The carbamate moiety has been widely studied and exploited in organic synthesis. Our intention was to investigate, develop and exploit the chemistry of benzylic and allylic carbamates and to propose future areas in which such systems might prove to be synthetically useful.

1.0   THE CARBAMATE MOIETY

1.1   NOMENCLATURE

Systematic naming of carbamates is derived from carbamic acid, NH_2COOH, an unstable compound which in acid solution decomposes to afford carbon dioxide and ammonia.[1]

Carbamic acid esters are then referred to as carbamates. Substituents attached to the nitrogen atom are named N-alkyl or aryl while those attached to the oxygen are referred to by their alkyl or aryl IUPAC name. The insecticide carbaryl **(2)** would be systematically named 1-naphthyl-N-methylcarbamate.
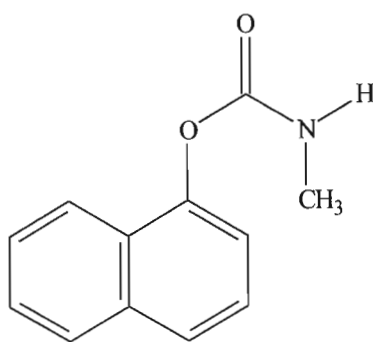
(2)

1.2   APPLICATIONS OF CARBAMATES AS DRUGS AND POISONS

Arguably the most widely encountered application of carbamate compounds is as pesticides. The pharmacological action of carbamates in inhibiting the action of the enzyme, acetylcholinesterase, has facilitated their exploitation both as insecticides and in medicine.

Transmission of nerve impulses at the synapses depends upon the successful and rapid equilibrium between acetylcholine and choline being maintained in the synapse. Subsequent to the transfer of the "nerve message" to the receptor in the post synapse membrane, the acetylcholine is hydrolysed to choline by acetylcholinesterase and so the equilibrium is maintained.

By inhibiting the action of acetylcholinesterase, the nervous system is impeded by the slow hydrolysis of the carbamoylated intermediate, causing an undesirable accumulation of acetylcholine in the synapse, and unless treated, resulting in the death of the affected organism.[2]

The oldest known exploitation of this property of carbamates is believed to be the forced drinking of eserine in the West African witchcraft trials. Esere, or Physostigmine **(3)**, as it has become known, is the main alkaloid derived from the calabar bean *Physostigma bebebosum* and has powerful anti-cholinesterase properties.

(3)

After imbibing the milky potion, the survival of the accused depended not so much on his innocence, but rather on his ability to vomit, so preventing his death which would result from a build up of his own cholinesterase.[3]   Physostigmine has recently been found to be useful in the treatment of Alzheimer's disease.[4,5,6]

Mitomycin C (4) is a highly toxic antitumour antibiotic extracted from *Streptomyces caespitosus*. The molecule contains three recognised carcinostatic groups, an aziridine, a carbamate and a quinone. Mitomycin C and the closely related porfiromycin (5) are clinically administered for the treatment of carcinomas of the breast, lung, colon and stomach.[7]

(4)   (5)

Other medicinal uses of carbamates include antiseptics[12], local anaesthetics[13], anti-convulsants[14], anti-leukaemia agents[12] and muscle relaxants[15].

Carbamates have found extensive application in pest control as insecticides, herbicides, nematocides and fungicides, both as *O*-carbamates and as thio- and dithiocarbamates.[3,8,9,10,11] Of the most well known of these compounds are carbaryl (2), carbofuran (6), aldicarb (7) and propoxur (8).
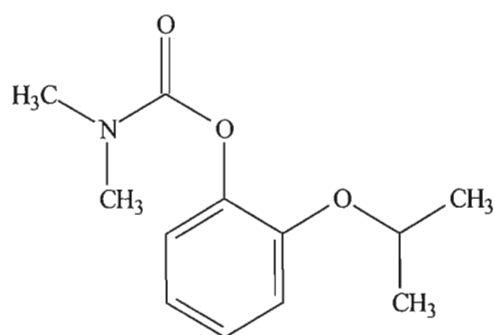
(6)   **(7)**

(8)

Most biologically active carbamate compounds are N-methyl substituted **(6)**, **(7)** or N, N-dimethyl substituted **(8)** compounds. The first carbamate insecticides were introduced by the Geigy Chemical Company in 1951. They were a series of N, N-dimethyl carbamates including Isolan **(9)** and Dimetan **(10)**.
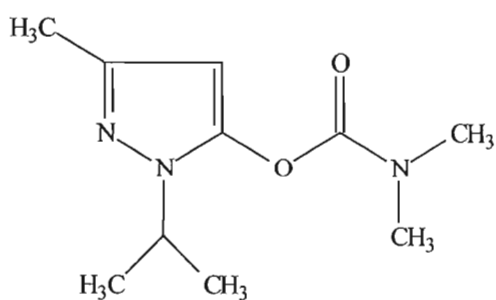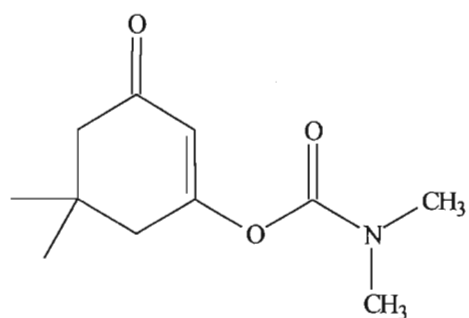
(9)   **(10)**

It was later realised that the N-methyl compounds were more toxic towards insects and in 1956 carbaryl **(2)** was introduced onto the market.[11]

The introduction of carbamates as a group of pesticides, and their subsequent extensive use in the agrochemical industry was encouraged by the need to find effective pest control mechanisms which did not have long soil retention times. It was realised that compounds such as DDT and Dieldrin and their related organochlorine pesticides, although cheap and effective, had long-lasting damaging effects on the environment and affected non-targeted flora and fauna, having been found to have accumulated in successive crop applications.[11]

Carbamates are a group of more selective, more environmentally friendly and yet highly effective pesticides. As they do not remain active in the soil for extended periods under natural conditions they are favoured over organochlorines.

1.3   INDUSTRIAL USES OF CARBAMATES

An ethylcarbamate / formaldehyde mixture has been used in the textile industry to produce a crease resistant finish to fabric.[16] Carbamates have been used in hair conditioners[17], as plasticisers for rubbers[18] and melamine alkyd resins[19], as fuel additives[20], and simple vinyl carbamates are useful monomers for the direct access to transparent polymers and varnishes.[21]

1.4   SYNTHETIC ROUTES TO CARBAMATES

Many syntheses have been developed over the last 150 years. However, few have found favour on a commercial scale owing to the toxicity and difficulties associated with the use of some of the reagents, notably phosgene (11), required in these syntheses.
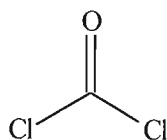
(11)

1.4.1 REACTION OF ALCOHOLS WITH UREAS

Ethyl carbamate was first prepared by Wohler in 1840 from urea and ethanol.[12] This route is the most favoured commercial route to methyl- and ethyl carbamate. The reaction leads to O-substituted carbamates with the liberation of ammonia (**Scheme 1**),


R = Me, Et

Scheme 1

1.4.2 REACTION OF ALKYLCHLOROFORMATES WITH AMINES

This method is a high yielding route to N-alkyl carbamates (**Scheme 2**). The alkylchloroformate is generated from the relevant alcohol and phosgene in the presence of a base. This is then reacted with the primary amine to yield the N-alkylcarbamate.[22,23] The disadvantage of this reaction is the need to use highly toxic phosgene gas.
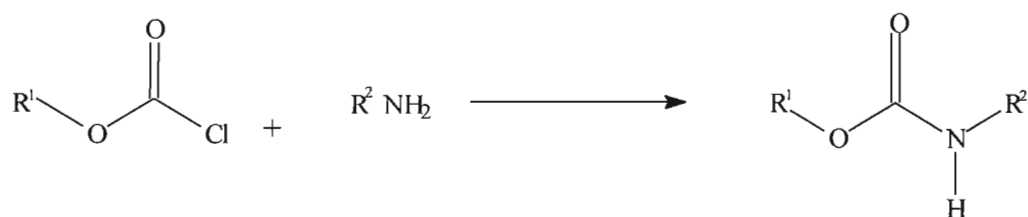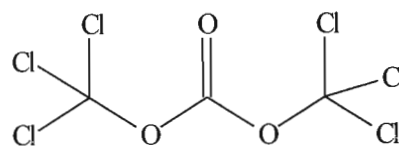

Scheme 2

Recently, alternatives to phosgene have been introduced in the synthesis of chloroformates. Trichloromethyl carbonate ("diphosgene") (**12**) is a liquid. Bis(trichloromethyl) carbonate ("triphosgene") (**13**) is a non-toxic solid with a melting point of 80°C and a boiling point of

206°C. These reagents are far easier to handle and accurately measure than the gaseous phosgene. They have both already been proven to be adequate substitutes for phosgene in the reactions relevant to this discussion.[24,25]
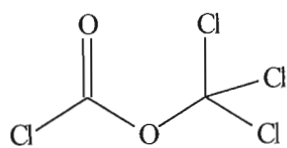
(12)   **(13)**

1.4.3   TRANSESTERIFICATION

The aluminium isopropoxide catalysis of the interchange between ethyl carbamate and benzyl alcohol yields benzyl carbamate **(Scheme 3)**. This method is now used to prepare mono- and dicarbamates from alcohols and diols.[12]   N-substituted or unsubstituted carbamates can be used in the interchange.[26]   The reaction is limited in that it does not work for tertiary alcohols and phenols.

Scheme 3

1.4.4   REACTION OF AMINES WITH CARBONATES

The carbamoylation of tertiary carbinols to unsaturated carbamates by many simple methods fails due to the ease of dehydration, with conjugation in the system compounding the problem further. However, the reaction of the carbinol with phenylchloroformate yields the carbonate. Its subsequent reaction with liquid ammonia results in excellent yields of the carbamate[27] **(Scheme 4)**.
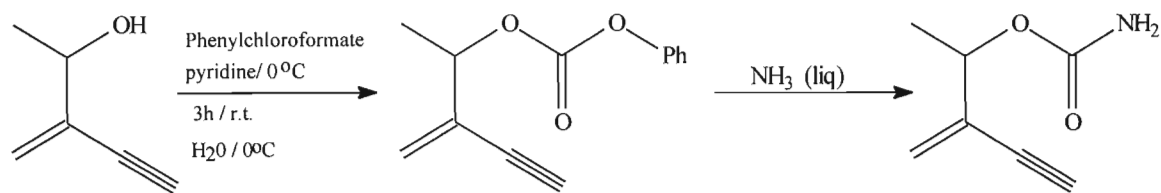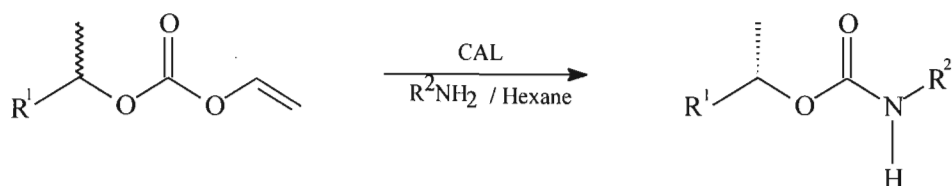
Scheme 4

Similarly, propargylcarbinol and propargylcycloalkanol carbamates have been prepared by reacting phenylchloroformate with the relevant carbinols.[28]

Two specific carbonates, di-(2-pyridyl) carbonate (DPC) **(14)**[29] and N,N-di-succinimyl carbonate (DSC) **(15)**,[30] have been used in the preparation of mixed carbonates which, when reacted with amines, yield the corresponding carbamates. This reaction has been successfully applied to the synthesis of a wide variety of carbamates of sterically hindered amines and alcohols.

(14)   **(15)**
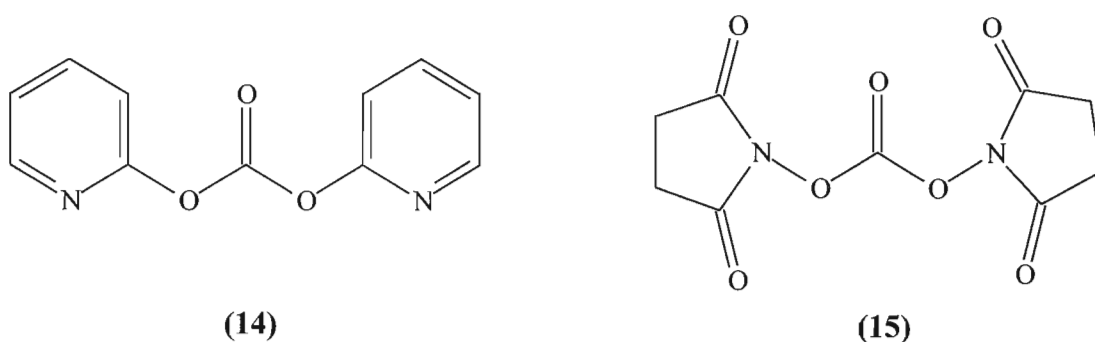
The synthesis of chiral carbamates has been achieved using *Candida antarctica* lipase (CAL) in the mediated resolution of amines with vinyl carbonates[37] **(Scheme 5)**.


R^1, R^2 = alkyl, aryl

Scheme 5

9

1.4.5 REACTION OF CARBAMOYL CHLORIDES WITH ALCOHOLS

This preparation provides a good general route to carbamates. The drawback is the need to use phosgene in the preparation of the carbamoyl chlorides,[12] hence the method is not industrially viable.

N,N-Disubstituted carbamoyl chlorides react with alcohols to yield N,N-disubstituted carbamates. The reaction is believed to proceed *via* one of two possible pathways, namely addition - elimination (concerted displacement of the halide ion by the nucleophile; Path A, **Scheme 6**) or unimolecular loss of Cl⁻ (Path B, **Scheme 6**).

R^1, R^2 = alkyl, aryl
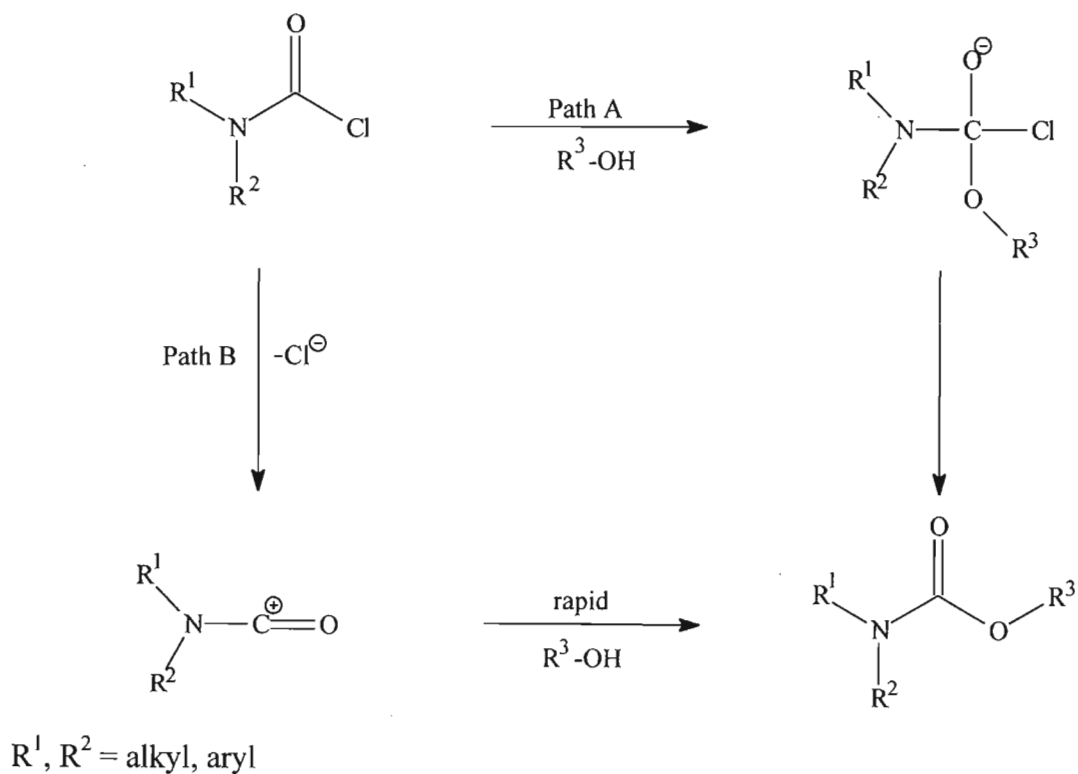
Scheme 6

1.4.6 REACTION OF ISOCYANATES WITH ALCOHOLS

This method is a good route to N-substituted carbamates **(Scheme 7)**. The reaction is rapid and quantitative, being accelerated by the presence of a tertiary amine.[31]
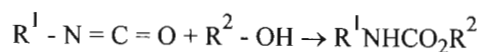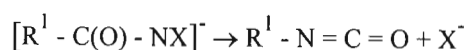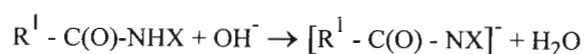
$$R^1 - N = C = O + R^2 - OH \rightarrow R^1 - NH - COOR^2$$
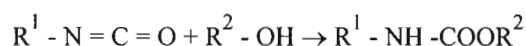
Scheme 7

An extension of this method involves the reaction of sodium cyanate with alcohols. The reaction has been applied to the carbamoylation of primary, secondary and tertiary alcohols, steroids, polyols and phenols as well as mono and polythiols and oximes. Yields of between 60 and 90% were obtained.[32]

1.4.7 HOFMANN REACTION

The reaction of amides, in particular long alkyl amides and amides of α,β-unsaturates, *via* the Hofmann degradation yield, in a dry state, isocyanates which, in alcoholic solution, are converted to the corresponding carbamate[33] **(Scheme 8)**.

$$R^1 - C(O)\text{-}NHX + OH^- \rightarrow [R^1 - C(O) - NX]^- + H_2O$$

$$[R^1 - C(O) - NX]^- \rightarrow R^1 - N = C = O + X^-$$

$$R^1 - N = C = O + R^2 - OH \rightarrow R^1NHCO_2R^2$$

R^1, R^2 = alkyl

X = halide

Scheme 8

Alkoxyurethanes have been prepared from halogen amides by means of reaction of sodium alcoholates with bromine. This method, when applied to $ClCH_2CONH_2$ in ethanol,

afforded ethyl ethoxymethylcarbamate, $EtOCH_2NHCO_2Et$. In a similar fashion methyl methoxymethylcarbamate was obtained.[34]

1.4.8   VINYL CARBAMATES

Vinyl carbamates have been synthesised from terminal alkynes, carbon dioxide and secondary amines using mononuclear ruthenium complexes as catalysts[36] **(Scheme 9)**.
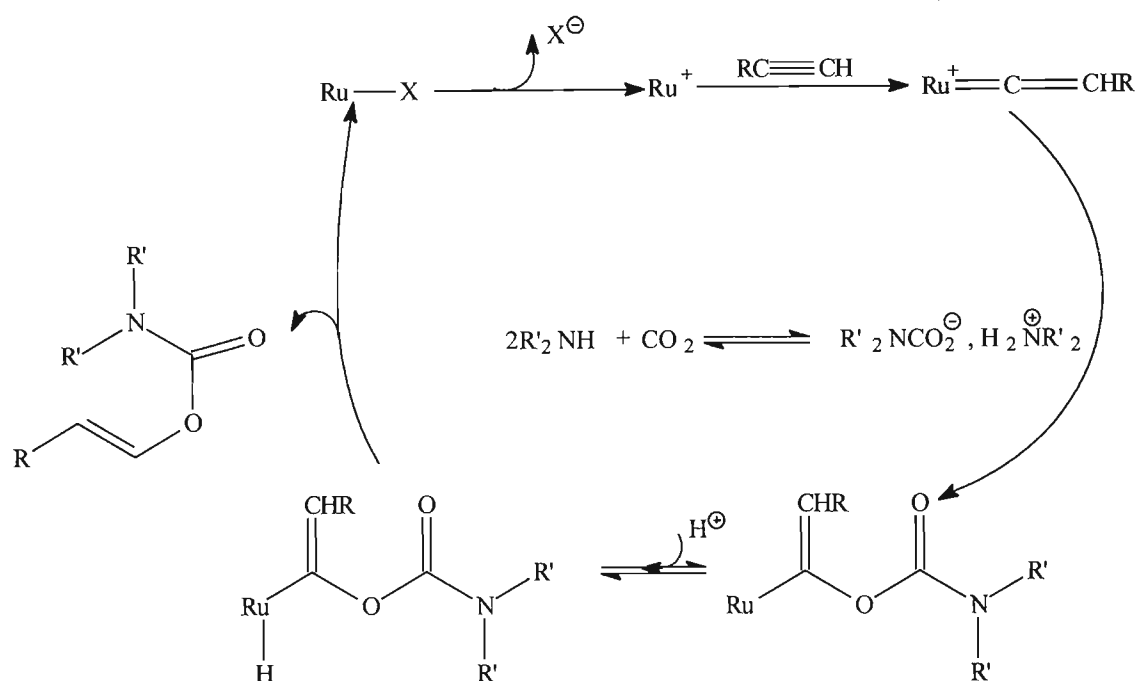
R, R' = alkyl, aryl, H

Scheme 9

It has been suggested that as two equivalents of amine are required per equivalent of alkyne that the reaction proceeds *via* the *in situ* generation of the ammonium carbamate. This then adds to the active end of the alkyne. As the reaction only proceeds with terminal alkynes it has been proposed that the mechanism involves the formation of a ruthenium-vinylidene intermediate. It has also been established that the most efficient catalyst is $[RuCl_2(norbornadiene)]_n$.[21]

This method has been extended to the synthesis of *O*-β-oxoalkylcarbamates **(16)**.[36]

(16)
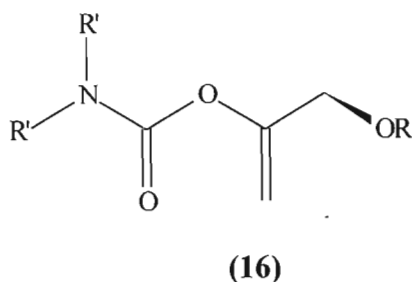
R, R' = alkyl, aryl, H

1.4.9   NOVEL SYNTHESES

A new route to generate the carbamate anion is by the reaction of carbon dioxide with amines and then the addition of an electrophile.[38] Earlier methods involving carbon dioxide employed metal-porphyrin or ruthenium catalysts, but the methods were hindered by polymerisation side reactions and the lack of success with primary amines.[35,39] In addition, high temperatures, long reaction times and high pressures were necessary to facilitate the reactions.[40]

A mild method for the preparation of carbamates, which avoids either the use of phosgene or elevated temperatures, involves the reaction of primary, secondary or aromatic amines with carbon dioxide and a variety of electrophiles at room temperature and atmospheric pressure **(Scheme 10)**. The reaction involves the bubbling of CO_2 gas directly into the reaction mixture containing the amine and electrophile in DMF at room temperature using Cs_2CO_3 as a base.
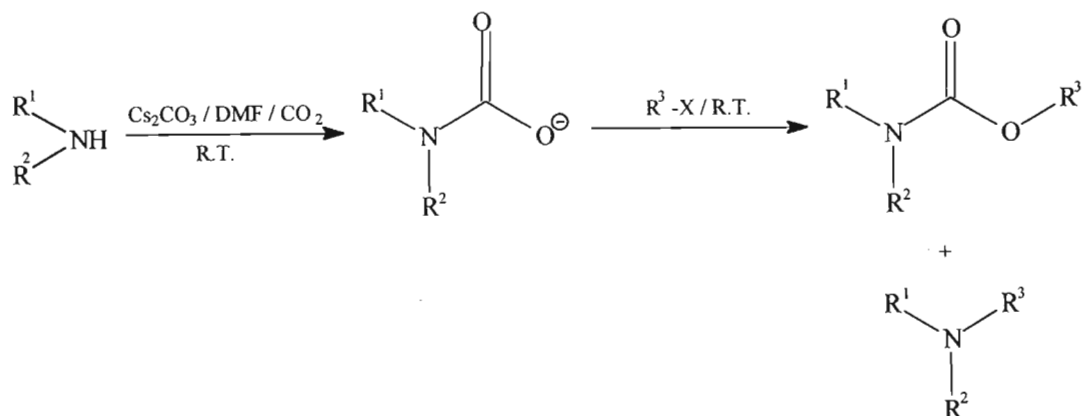
R^1, R^2, R^3 = alkyl

X = halide

Scheme 10

Yields of up to 96% have been obtained in which the preference for the carbamate over the tertiary amine is 97:3. When K_2CO_3 or Na_2CO_3 were used the selectivity was reversed. It is proposed that the Cs^+ ion behaves as a counter ion in the same manner in which it enhances the rate of alkylation of carboxylic acids to the corresponding ester.[41] However, steric hindrance limits the reaction and it has been found to be most successful in the carbamoylation of secondary amines.

1.5   REACTIONS OF CARBAMATES

1.5.1   THERMAL DECOMPOSITION

The thermal stability of carbamates varies according to the extent of N-substitution. The unsubstituted carbamates readily decompose on heating to cyanic acid derivatives, N-substituted carbamates decompose mainly to isocyanates while N,N-disubstituted species are fairly resistant to elevated temperatures.

The decomposition products of unsubstituted carbamates include allophanates, cyanuric acid, and alcohol. The presence of trace amounts of metal salts enhances the rate of decomposition.[12]

N-substituted carbamates decompose on heating to afford isocyanates, alcohols, and minor products of alkenes, CO_2, ureas and carbodiimides. [42a]

N,N-disubstituted carbamates usually do not decompose cleanly on heating. Two exceptions to this trend are the thermal decomposition of ethyl carbazole-9-carboxylate (17) to yield carbon dioxide, ethene and the disubstituted amine (18) (carbazole)[42b] (Scheme 11), and the pyrolysis of the dicarbamate of 1,3-butylene glycol (19) which yields a cyclic urea (20) and an oxazolidone (21). In this reaction C-O bonds are broken and replaced by the formation of stronger C-N bonds[12] (Scheme 12).

(17)   (18)

+

$H_2C \!\!=\!\! CH_2$ + CO_2
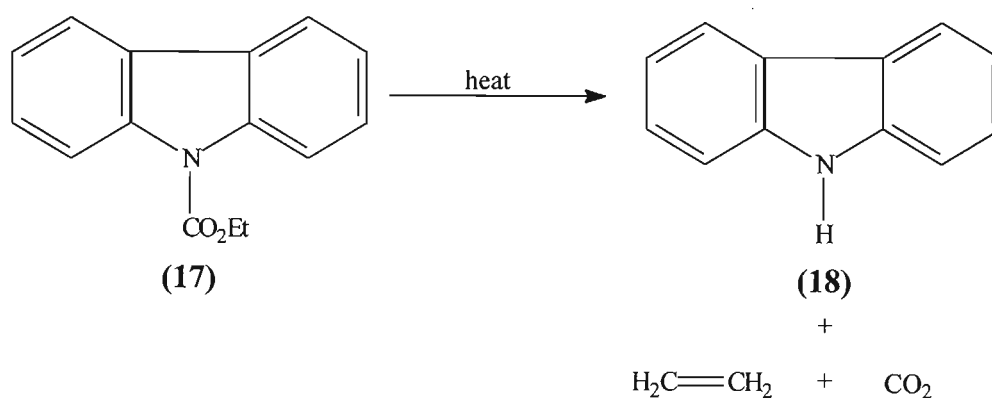
Scheme 11

(19)   (20)   (21)
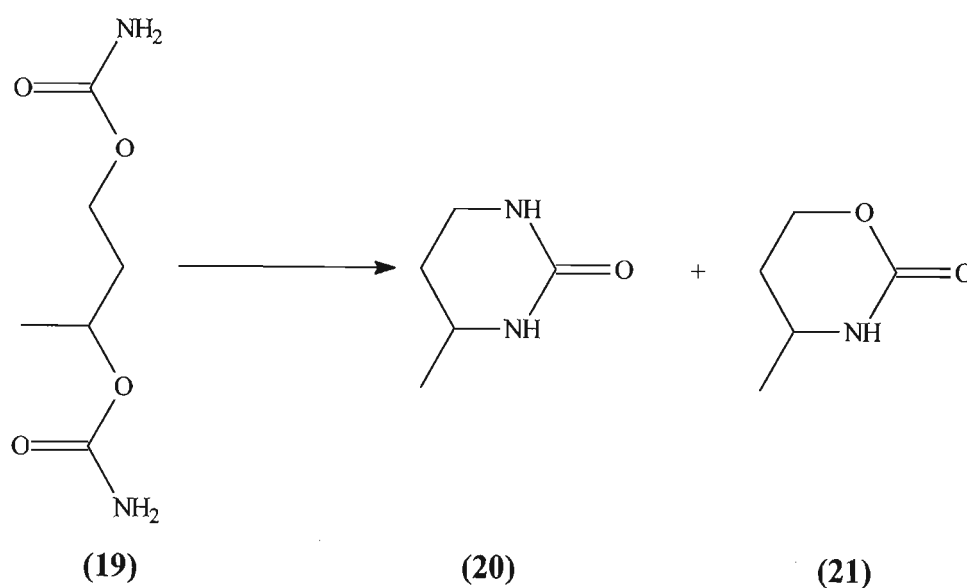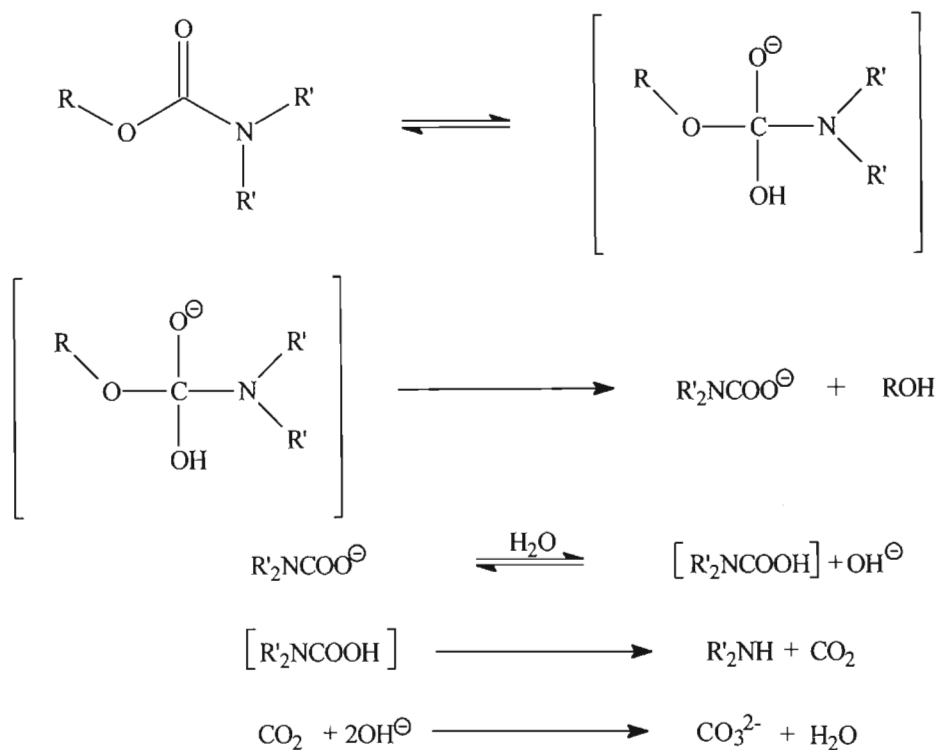
Scheme 12

1.5.2 HYDROLYSIS

Unsubstituted and monosubstituted carbamates derived from aliphatic alcohols and all disubstituted carbamates are hydrolysed in alkaline solution *via* a carbamate anion to an amine, water and carbonate **(Scheme 13)**.[12]

Scheme 13

The hydrolysis of phenol derived carbamates is more rapid and includes the formation of an isocyanate intermediate, the driving force being the formation of the stable phenoxide anion; except in the N-substituted aromatic carbamates which cannot form isocyanate intermediates **(Scheme 14)**. The base hydrolysis of these compounds then proceeds *via* the carbamate anion as illustrated in **Scheme 13**.
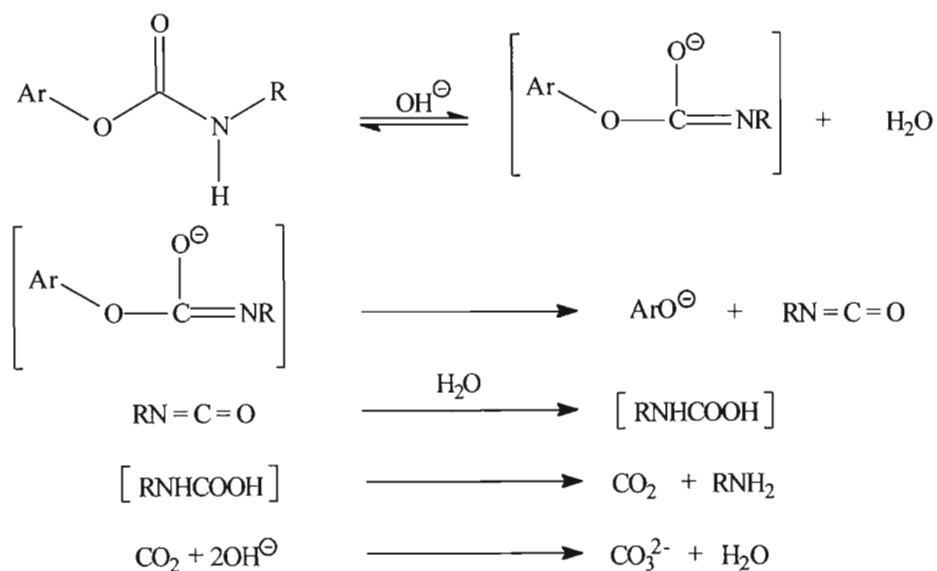
Scheme 14

In acidic media, *e.g.* HBr in glacial acetic acid, carbamates decompose to afford CO_2, amine and an alkyl chloride **(Scheme 15)**. It is believed that the nucleophilic centre of the carbamate is protonated and then the halide ion attacks the alkoxy group.[43]

The ease of hydrolysis of carbamates to hydroxyamines has recently been utilised in the synthesis of the pharmacologically important 1,3-hydroxylamines. Certain cyclic allylic carbamates were produced *via* the Pd(0) catalysed reaction of cyclic carbonates in the presence of isocyanates. Hydrolysis of the carbamate afforded a variety of 3-amino-4-penten-1-ols[8] **(Scheme 16)**.

Scheme 15

(i) 1.2 eq. PPh$_3$
(ii) 1.2 DEAD/THF
0°C to R.T.
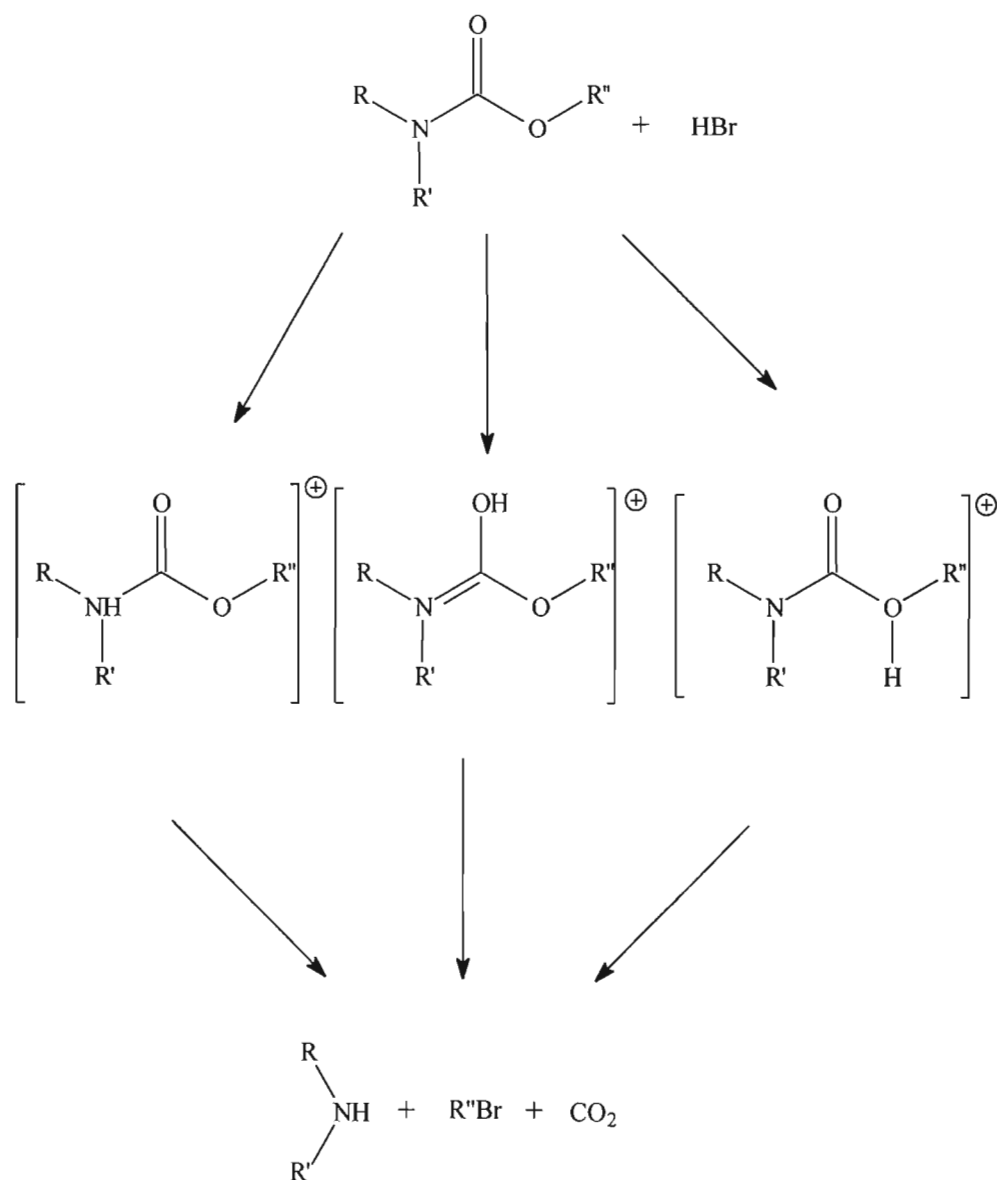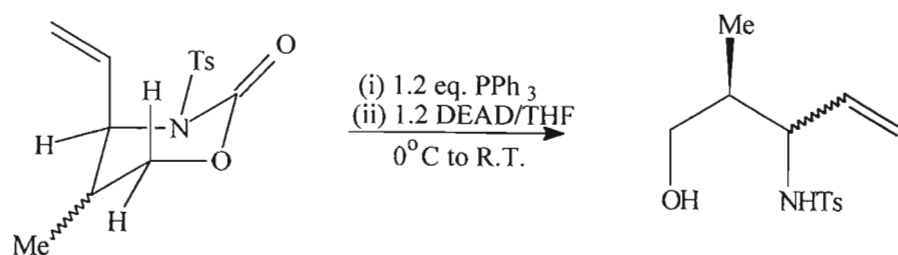
Scheme 16

1.5.3   REACTIONS AT THE ESTER GROUP

Werner[44] revealed in 1918 that heating ethyl carbamate to 150°C in the presence of ammonia afforded the urea (33% yield) and ethanol **(Scheme 17)**.
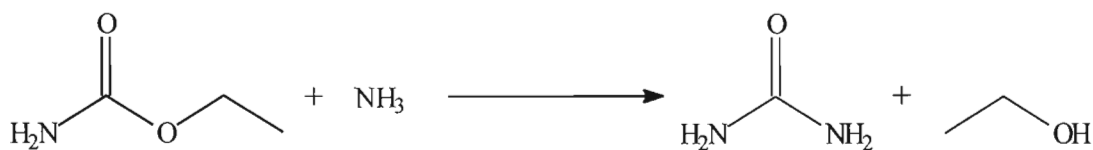
Scheme 17

N,N-dialkylureas were prepared by heating N-alkylcarbamates with the corresponding amines at 150°C[45] **(Scheme 18)**.

$$H_2NCO_2Et \ + \ RNH_2 \longrightarrow H_2NCONHR + EtOH$$

$$H_2NCONHR + RNH_2 \longrightarrow RNHCONHR + NH_3$$

$$RNHCO_2Et \ + \ RNH_2 \longrightarrow RNHCONHR + EtOH$$
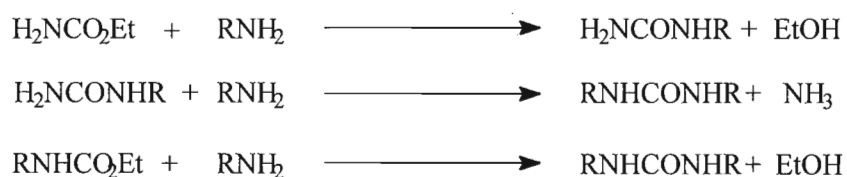
Scheme 18

Reduction **(Scheme 19)** of the carbamate ester group using lithium aluminium hydride (LAH) produced secondary and tertiary methylamines in yields in excess of 80%.[46, 47]
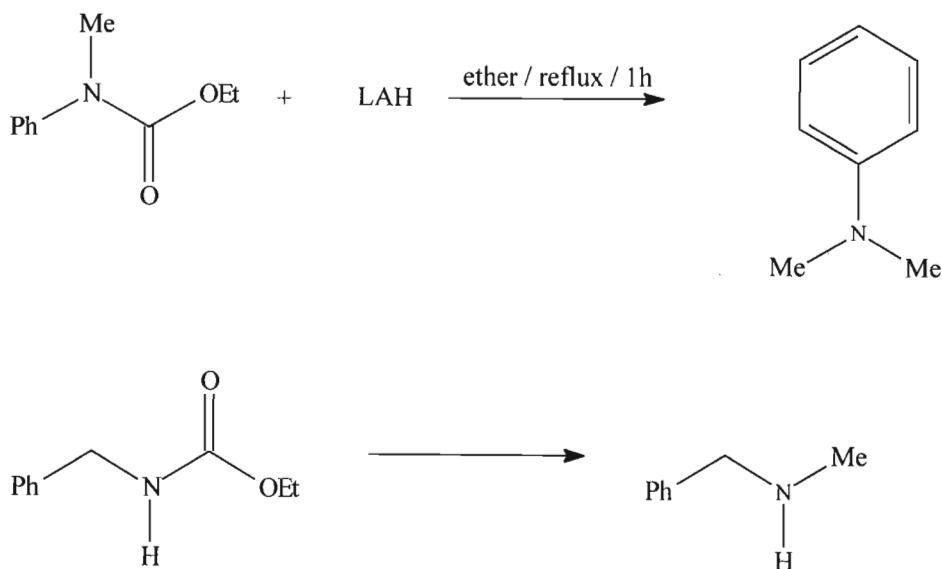
Scheme 19

1.5.4 REACTIONS AT THE AMIDO GROUP

N-unsubstituted and N-monosubstituted carbamates, when treated with base, provide nucleophilic species through the abstraction of the N-proton. Reaction with electrophiles to afford N-substituted carbamates is then facilitated.

Acyl derivatives of ethyl carbamate are best prepared by the action of acid halides or acid anhydrides on the carbamate. Reaction with carboxylic acids and esters are limited.[12]
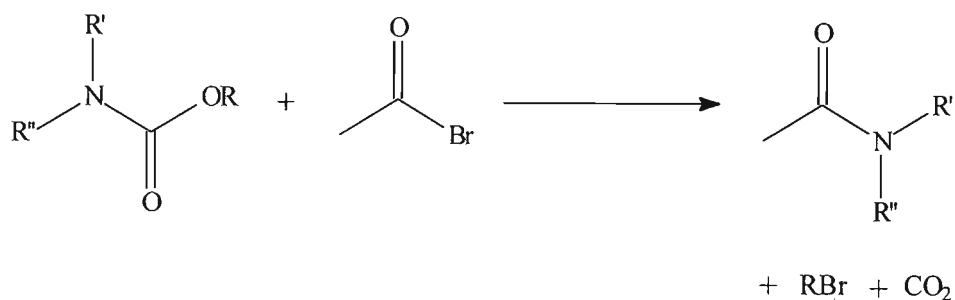
Carbamates react with acetyl bromide **(Scheme 20)** to yield N-substituted acetamides, alkyl or aralkylbromides and carbon dioxide. The highest yields are obtained in reactions involving N,N-dimethylcarbamates, the lowest being in the reaction of ethyl carbamate and benzylcarbamate.[48]

R = Et, CH$_2$Ph;   R', R'' = H, Me, Ph

Scheme 20

The reaction of isopropyl-3,4-dichlorocarbanilate **(22)**, with a slight excess of oxalylchloride in benzene, provides a route to 3-(3,4-dichlorophenyl)oxazolidinetrione **(23)** with the elimination of propylene[49] **(Scheme 21)**.

(22)
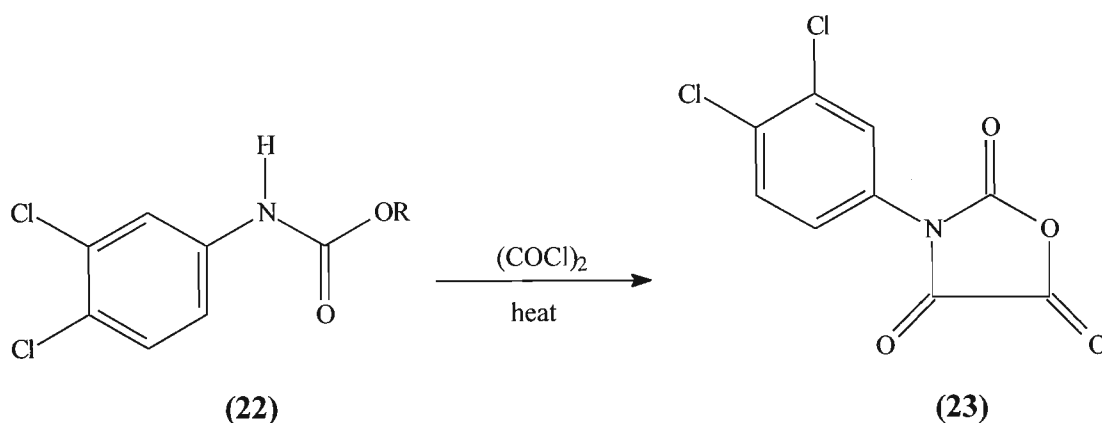
$R = {}^i Pr, {}^s Bu, {}^t Bu, {}^i Bu$, cyclohexyl

(23)

Scheme 21

1.5.5 REACTIONS OF CARBONYL COMPOUNDS WITH CARBAMATES

Benzyl carbamates condense readily with both aliphatic and aromatic aldehydes. One mole of aldehyde reacts with two moles of the carbamate **(Scheme 22)**.[50,51]

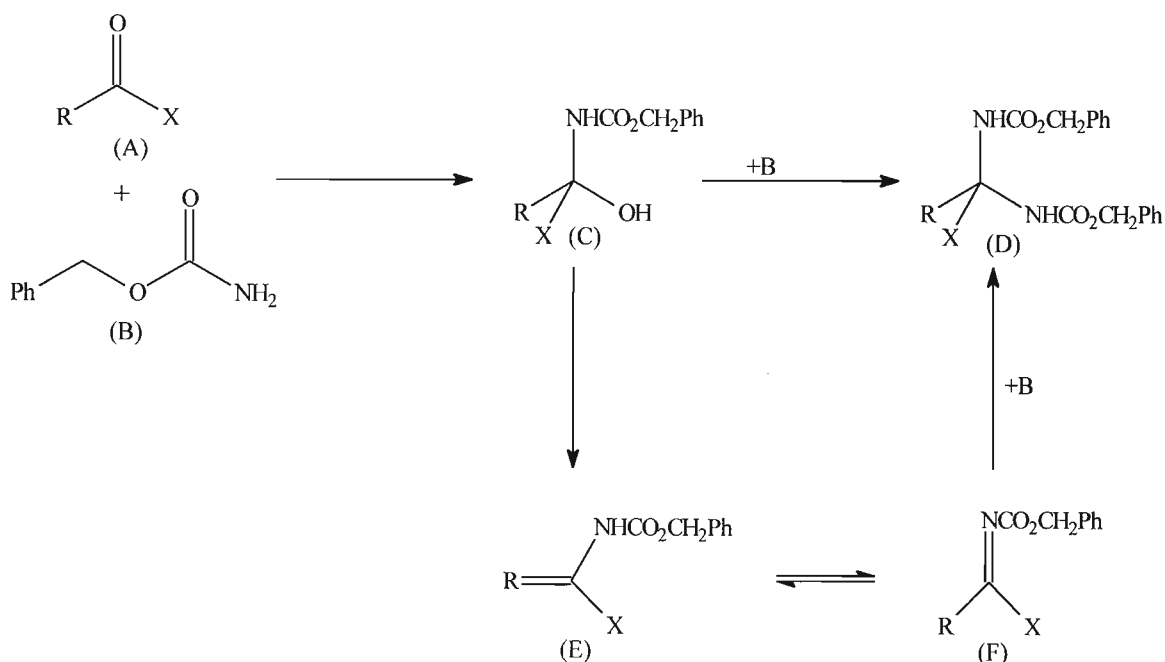When X = H: R = i-Bu, Ph, p-MeC$_6$H$_4$, 3,4-CH$_2$O$_2$C$_6$H$_3$, C$_4$H$_3$O

When X = COOH: R = Me, PhCH$_2$, CH$_2$CH$_2$COOH, Ph.

Scheme 22

The reaction involves the primary addition of the amide portion of the carbamate to the carbonyl compound followed either by direct replacement of the hydroxy group by another amide residue or elimination of water with the formation of unsaturated intermediates to which the second mole of amide may add. Hydrolysis of the products under aqueous acidic conditions regenerates the original carbamate and carbonyl compound. However, the catalytic hydrogenation of the aldehyde products led to the formation of primary amines, while similar treatment of the products of α-keto acids afforded α-amino acids. This provides an elegant route from carbonyl compounds to primary amines and amino acids *via* carbamate intermediates.

Similar reactions involving α,β-unsaturated aldehydes **(Scheme 23)** require three moles of carbamate per mole of aldehyde. This can be ascribed to the 1,2- and 1,4-addition products of the reaction.[23]
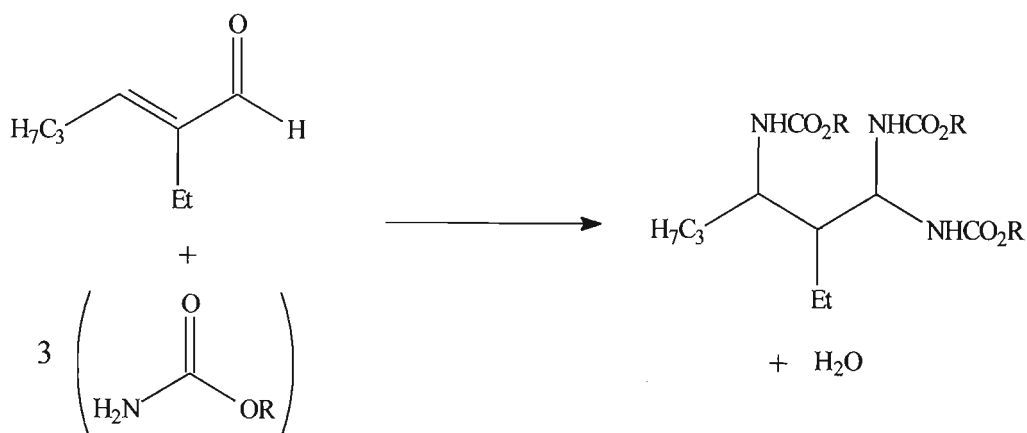
Scheme 23

The exploitation of this reaction led to the preparation of indanone derivatives **(24)** when treating α-ethylcinnamaldehyde with ethyl- and benzylcarbamates[52] **(Scheme 24)**.
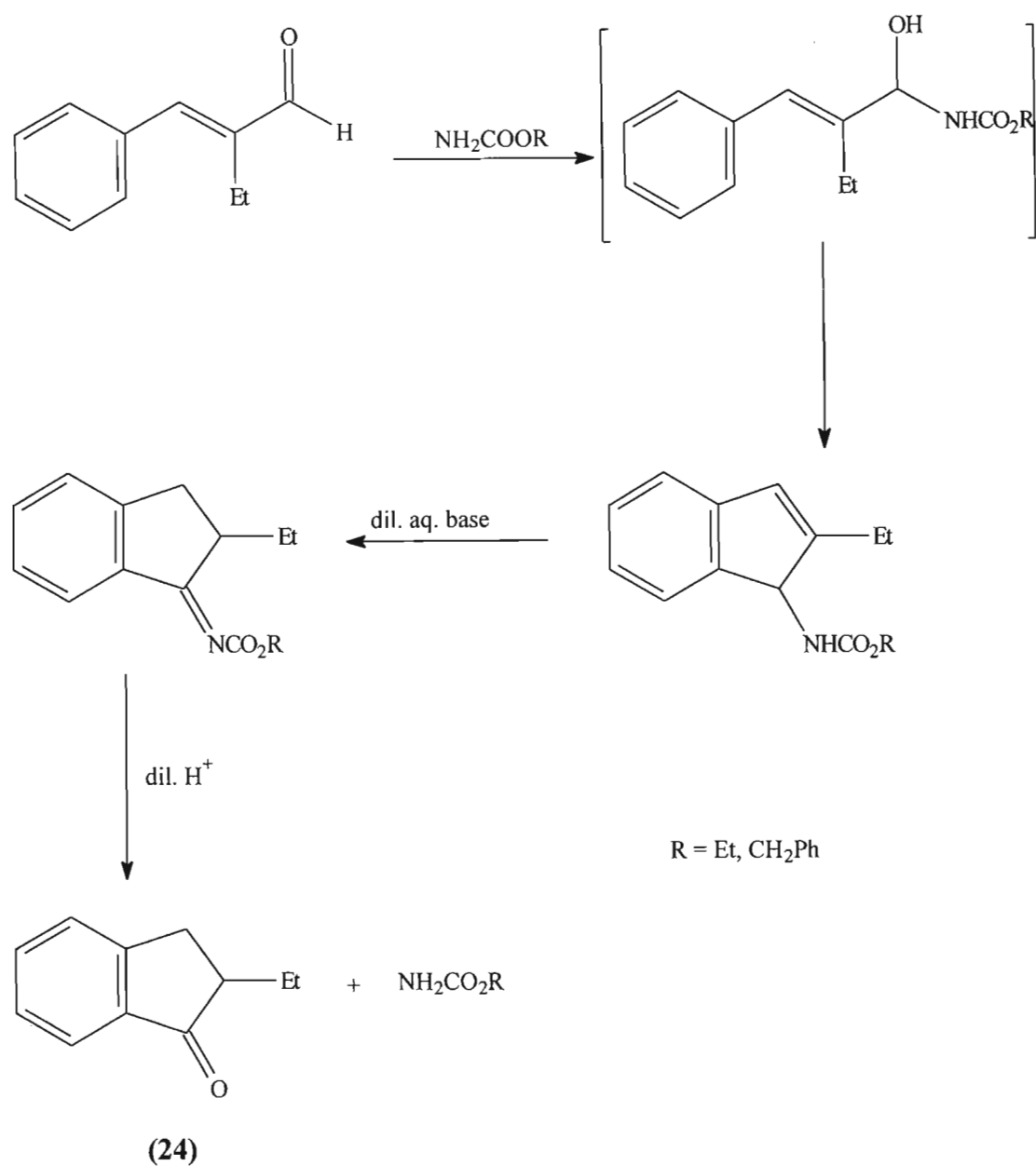
Scheme 24

The presence of a substituent in the α-position of the aldehyde may facilitate ring closure as had previously been observed in the preparation of cyclic ketones.[53]

1.6   CARBAMATES AS SYNTHETIC INTERMEDIATES

1.6.1   CARBAMATES AS PROTECTING GROUPS IN SYNTHESIS

In 1903 Fischer established the importance of protecting groups in successful synthesis. He first used a urethane and chloroacetyl moiety as N-terminal protecting groups in the selective synthesis of peptides. Only later, in 1932, did Bergmann and Zervas report the use of the benzyloxycarbonyl (Z, CbO) group **(25)** in peptide synthesis.[54]

(25)
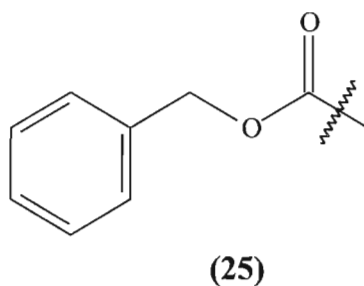
Suitable protecting groups in peptide synthesis prevent the formation of unwanted side products such as oligo- and cyclopeptides. They also prevent the racemization of the activated amino acid. This racemization usually occurs *via* an intermediate oxazolone which forms from N-acyl protected amino acids.[56] This side reaction can be successfully blocked by the use of carbamates as N-terminal protecting groups **(Scheme 25)**.
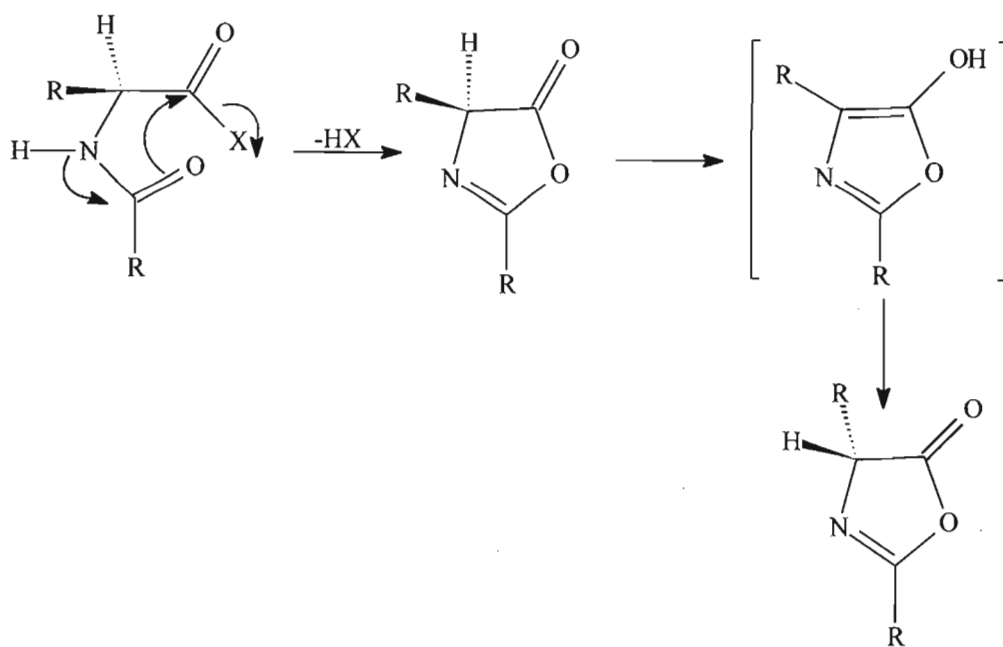
Scheme 25

Probably the most widely applied carbamate protecting group is the tertiary butoxycarbonyl group (t-Boc). It is unaffected during peptide bond formation and can be removed after the reaction is complete by treatment with HCl in dichloromethane, ether or ethyl acetate. Neat trifluoroacetic acid also adequately cleaves the protecting group to leave the desired peptide.[55] During the acid catalysed cleavage, the ^{t}Bu cation is formed which subsequently eliminates a proton to give isobutene as a product of deprotection **(Scheme 26)**. If there is a nucleophile present it may react with the cation to give rise to unwanted side products.
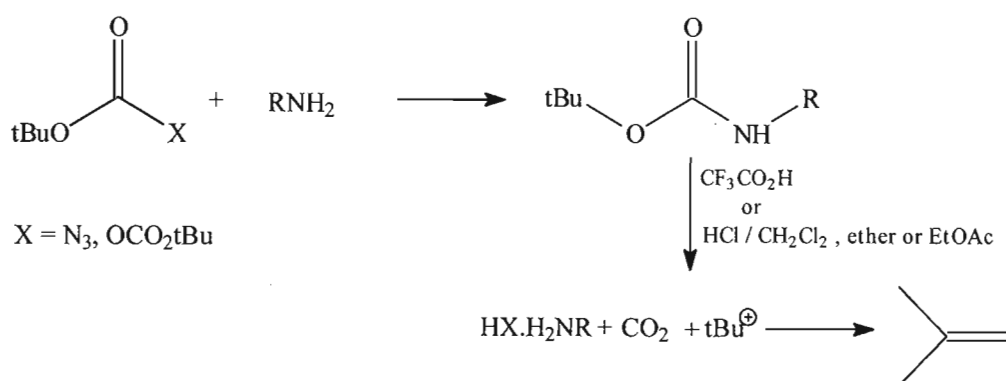
Scheme 26

In order to overcome such possible problems, variants of the Boc group, **(26)** and **(27)** have been developed, building on the positive inductive effects which stabilise the cation formed on deprotection.

Iboc

Adpoc

(26)

(27)
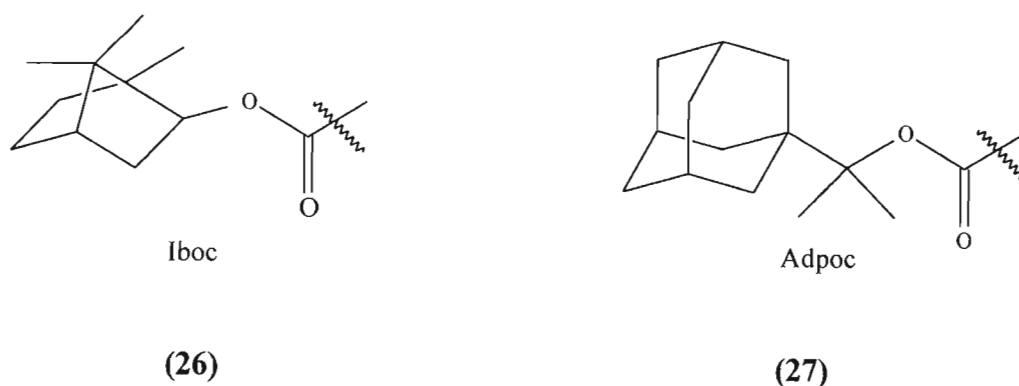
1.6.2 ACTIVATING - STABILISING ABILITY OF THE CARBAMATE GROUP

1.6.2.1 Alpha-Metallation

Alpha-metallations are deprotonations of olefinic, aromatic or other π-systems at the sp^2 carbon atom α to the heteroatom X.[57]

$$X = NR_2, OR, SR, SiR_3$$

Scheme 27

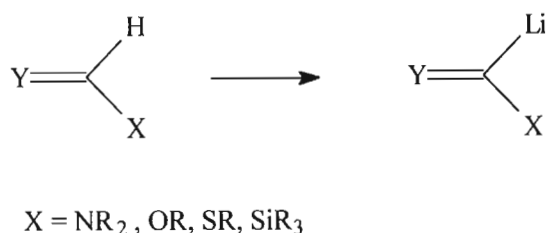Lithiations of this type are far more rapid than β-lithiations which will be discussed in the next section. The inductive effect of the α-activator greatly increases the acidity of the adjacent C-H bond, hence α-lithiations are facile.

Heteroatom substituted allylic anions **(28)** serve as homoenolate anion equivalents.[58]

(28)

$$X=NR_2, OR, SR, SiR_3$$

Homoenolates have been found to be useful intermediates in the synthesis of γ-lactones. Regioselectivity of substitution of these compounds has posed problems in that substitution can occur at the α- and γ-positions. The nature and size of groups attached to the heteroatom, the counter cation, solvent, temperature and reaction time all influence the regioselectivity of the reaction.

In 1980, Hoppe and co-workers[59] established the protection of alcohols as carbamates with the concomitant enhancement of CH acidity to be invaluable in the generation of alkoxycarbanions. The *O*-substituted 1-hydroxy allyl anion **(29)** is a useful synthetic equivalent of homoenolate ions **(30)**. Usually these are attacked at the γ-position **(31)**, the resulting enol ethers then being hydrolysed to the β-substituted carbonyl compounds **(32)**.
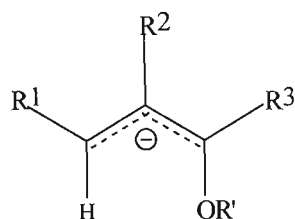
(29)
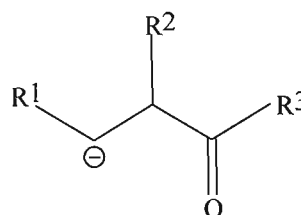
(30)
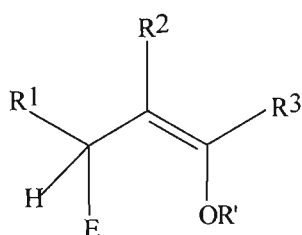
(31)
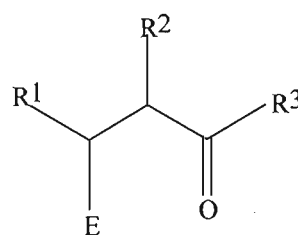
(32)

Previously, allyl-alkyl and allyl-trialkylsilyl enol ethers have been employed to perform this function, but these intermediates are limited to derivatives of **(29)** in which $R^1 = R^3 = H$, due to the low acidity of the α- and γ-substituted allyl ethers.

It has been found that the presence of N,N-dialkylcarbamoyl groups in the ester increases the kinetic acidity of α-protons, by chelation, to the extent that alkyl substituted allyl derivatives can also be deprotonated. Regiospecificity can be influenced by the steric interaction of the alkyl substituents attached to the nitrogen atom of the carbamate, as well as the position of the substituents. Higher substitution of the α-position can be forced by the presence of substituents in the γ-position **(33)**, while γ-substitution can be enhanced by substituents in the α-position **(34)**.

(33)　　　　　　　　　　　　**(34)**
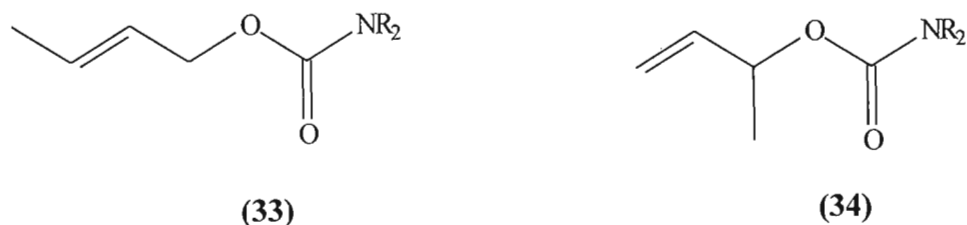
Carbamic acid allyl esters have been successfully substituted in the γ-position in their reaction with carbonyl compounds.[60] The allyl carbamate was deprotonated using n-BuLi. It has been postulated that the reaction proceeds *via* a "tight-ion" pair, **(35)**, in which the lithium counter cation is held at the α-position by complexing with the oxygen of the carbamoyl functionality, hence facilitating reaction of the carbonyl at the γ-position *via* a six-membered transition state **(36)** **(Figure 1)**.

(35)　　　　　　　　　　　　**(36)**
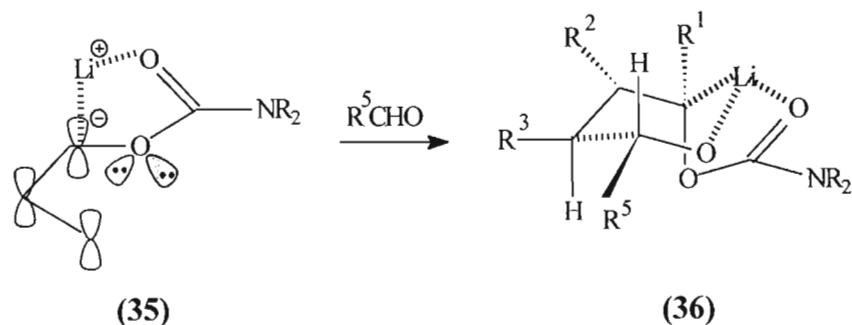
Figure 1

γ-Adducts of 2-butynylcarbamates with aldehydes have been synthesised through metal exchange between lithium and titanium.[61] The homoaldol reaction has been further expanded to yield *syn*-adducts of the γ-hydroxyalkylation of (Z)-2-butenylcarbamates with yields of the major product (E)-*syn*-adduct with d.e.'s higher than 80%. Subsequent methanolysis catalysed by mercury (II) acetate afforded *cis*-γ-lactol methyl ethers, which on Grieco oxidation, yielded β,γ-substituted-γ-lactones.

α-Metallation with metal exchange has been extended to the 1,3-chirality transfer in the reaction of α-chiral 2-alkenylcarbamates with carbonyl compounds.[62] The efficiency of the reaction is enhanced by using lithium diamine complexes[63] such as that prepared from s-BuLi and (-)-sparteine. Subsequent Grieco oxidation affords optically active lactones **(37)** **(Scheme 28)**.
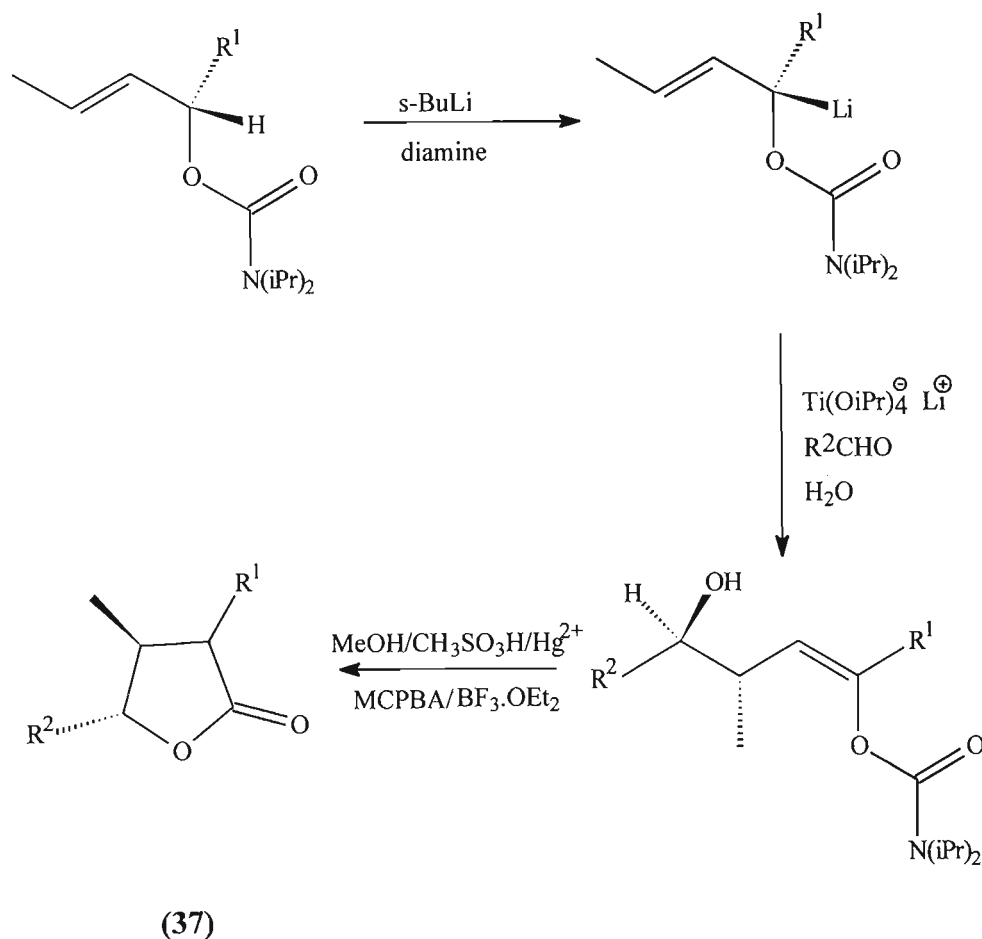
Scheme 28

Carbamate dianions can be produced from N-alkyl and N-aryl substituted carbamates.[64] The carbonyl group of the carbamate function needs to be protected from nucleophilic attack. This can be achieved either by shielding with bulky substituents or by reducing the electrophilicity using lithium salts. The carbamate is doubly deprotonated by BuLi or LDA to give the double lithium salt. On treatment with electrophiles and neutralisation with glacial acetic acid, the predominantly (Z)-γ-adducts (38) with small amounts of the α-allyl esters are produced. The enol esters were then hydrolysed to afford β-substituted carbonyl compounds (Scheme 29).
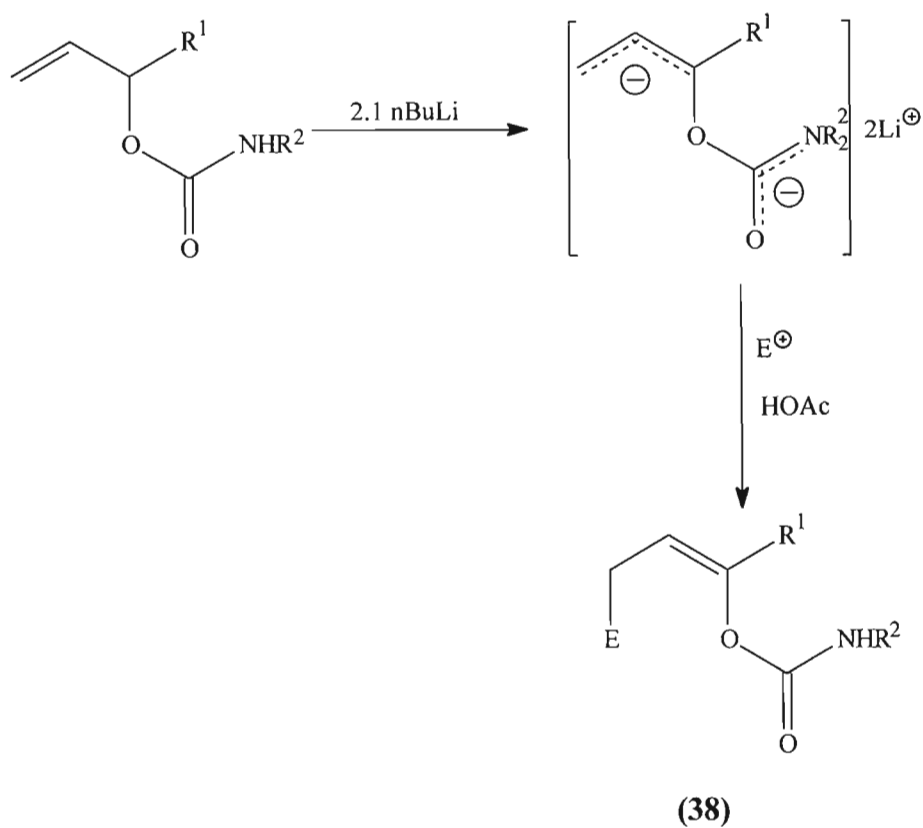
Scheme 29

Tertiary butyl benzyl carbamates **(39)** have provided building blocks to optically active *secondary* and *tertiary* benzyl alcohols.[65] Treatment of the carbamate with 2 equivalents of s-BuLi prior to quenching with electrophiles yielded alkylated carbamates in over 80% yields. Treatment of the substituted carbamate with a further 2 equivalents of s-BuLi and reaction with another electrophile led to disubstituted benzyl carbamates. Cleavage of the carbamate using DIBAL in THF gave excellent yields of chiral alcohols **(40)** **(Scheme 30)**.
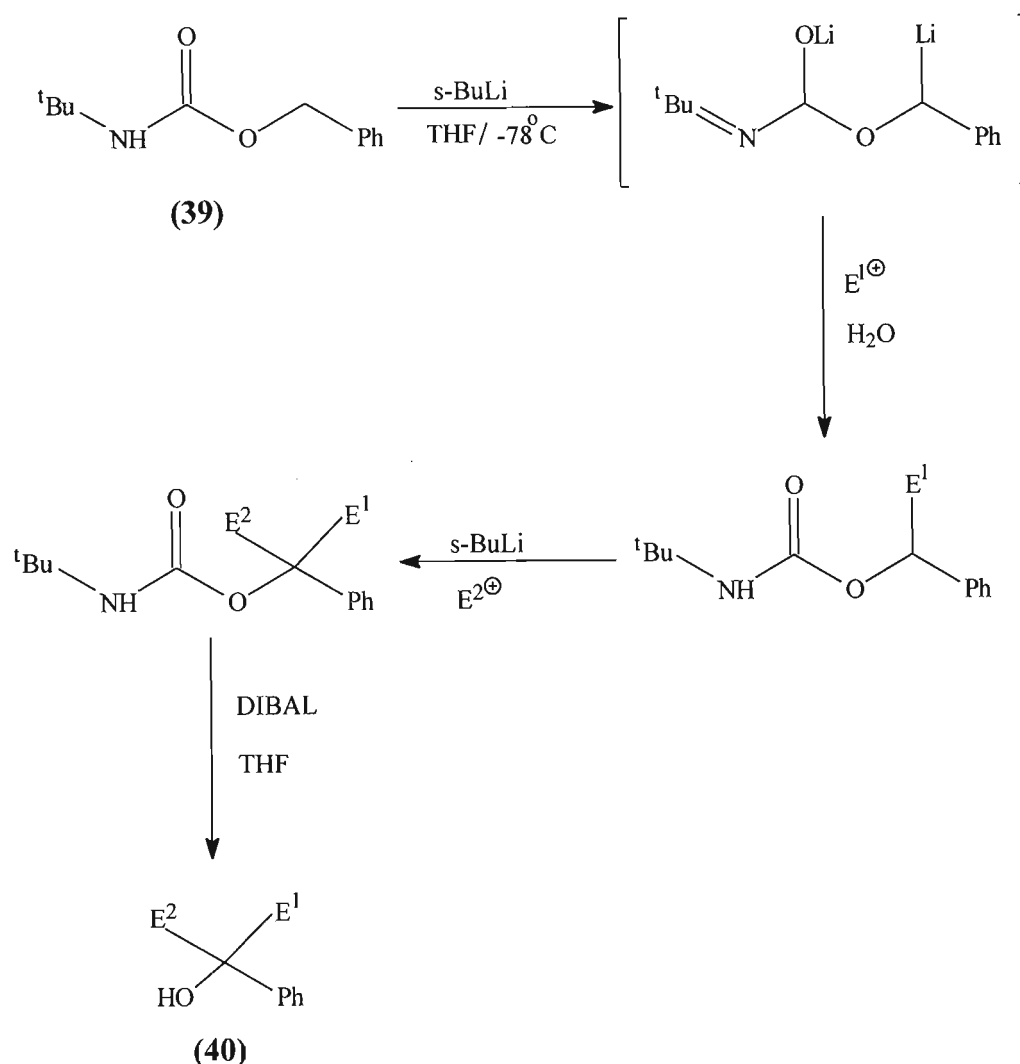
Scheme 30

1.6.2.2 Beta- (*ortho*) Metallation

Directed *ortho* Metallation (DoM) was first discovered independently by Gilman and Bebb[66] and Wittig and Fuhrmann.[67] n-BuLi deprotonated the *ortho* position of anisole leading to the study of such aromatic substitution reactions.

Deprotonation by a strong base occurs at the position *ortho* to the directing metallation group (DMG).[68] It is believed that the reaction is a three step process:

(i) Co-ordination of $(RLi)_n$ to the heteroatom of the DMG. **(41)**

(ii) Deprotonation to give the co-ordinated lithiated species. **(42)**

(iii) Reaction with the electrophile to afford the product **(43)** **(Scheme 31)**.
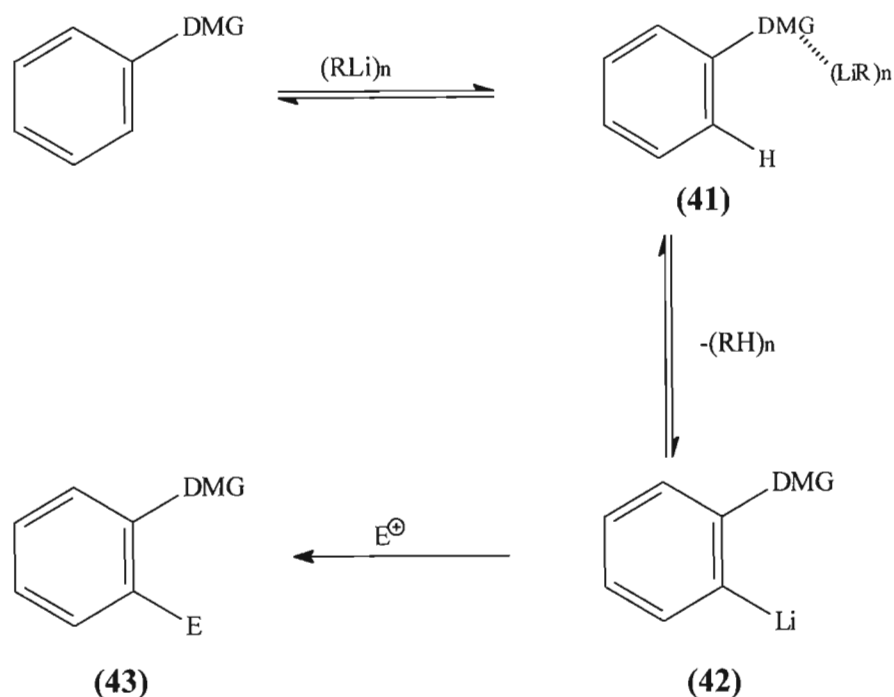
Scheme 31

The DMG must behave as a good co-ordinating site for the alkyllithium and as a poor electrophilic site for attack by the base. Thus, the heteroatom forms an integral part of the DMG. These criteria are satisfied by the carbamate group. The co-ordination of the lithium to the carbamate facilitates good regioselectivity of electrophilic substitution. Subsequent hydrolysis of the *O*-aryl carbamates yields *ortho* substituted phenols. Hydrolysis can be achieved either by treatment with NaOH in aqueous MeOH or by refluxing in LAH/THF and protonating with mild acid.[69]

Carbamate protected phenols allow for *ortho* substitution *via* combined DoM-nucleophilic substitution and this introduces the concept of a 1,2-dipole equivalent (44).[71]
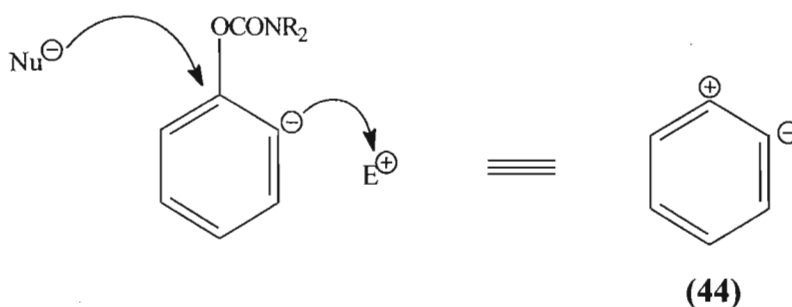
An example of the application of the 1,2-dipole equivalent is shown in **Scheme 32**.
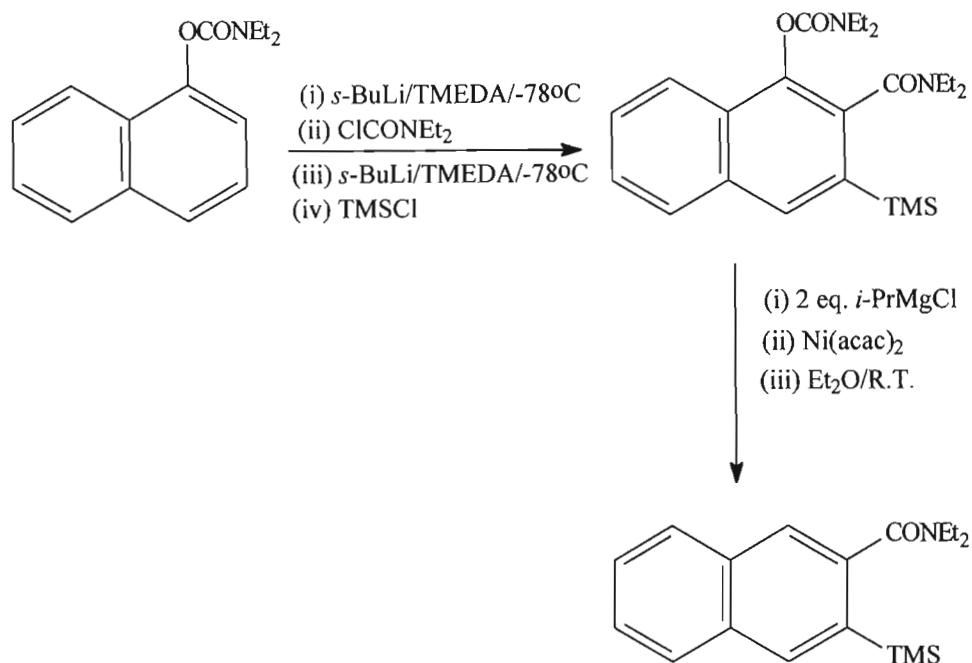
Scheme 32

A Ni(0) catalysed cross coupling reaction has been shown to afford regiospecifically functionalized biaryl compounds **(45)** (**Scheme 33**).[72]

(45)
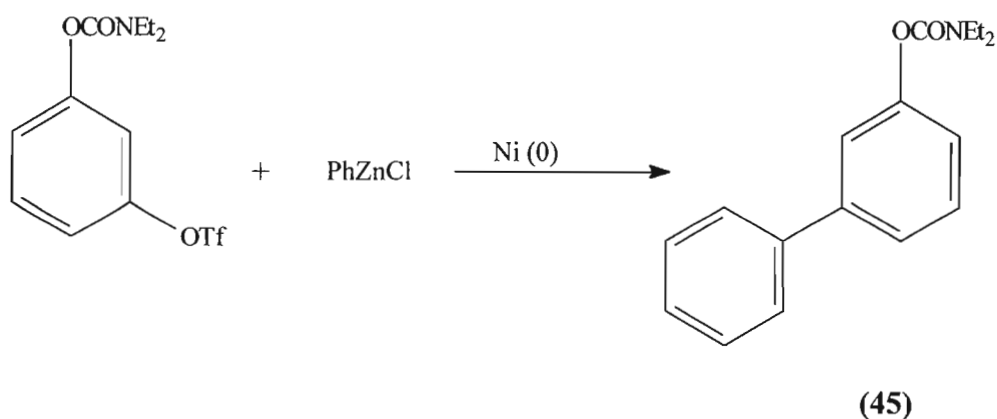
Scheme 33

Alpha-metallated enol carbamates can be regarded as acyl anion equivalents **(46)** and, as such, have been utilised as umpolung synthons in subsequent reactions with electrophiles.[73]

(46)
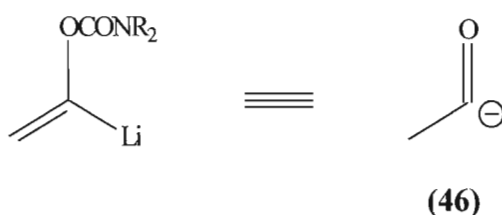
DoM applications have provided synthetic routes to polysubstituted aromatic compounds, polysubstituted pyridines,[70] phenethylamines, steroids, naphthyls, phenanthryls, binaphthyls, pyridines, quinolines and uracils.

1.6.2.3 The Migrational and Leaving Group Ability of the Carbamate Moiety

Recent reports of the migrational ability of the carbamate group describe the migration of the amide portion of the carbamate intramolecularly from one oxygen atom to another. N,N-diethyl vinyl carbamate[73] was deprotonated in the α-position giving the lithium stabilised complex, analogous to the acyl anion synthon (46) mentioned earlier. Reaction with alkyl halides led to normal α-substituted carbamates. However, reaction with aldehydes provided a site for migration of the amide, the driving force being the formation of the more thermodynamically stable enolate.

Snieckus and his co-workers[68] continue to utilise this useful facet of carbamate chemistry. In their discussions on *ortho*-metallation they refer to and make use of the migration of the amide portion of the carbamate from the oxygen atom to the *ortho*-carbon atom **(Scheme 34)**.
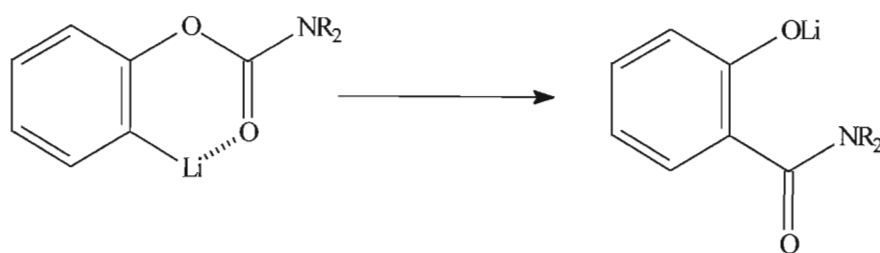
Scheme 34

This migration occurs in the absence of electrophiles and on warming from -78°C to room temperature. This anionic equivalent of the Fries rearrangement is useful in that it involves the transfer of the amide group, which is also a powerful DMG, to an *ortho* site from whence it too can promote further metallation. The same researchers recently exploited this migration in the synthesis of dibenzo[b,d] pyranones **(47)** from biaryl *O*-carbamates[74] **(Scheme 35)**.
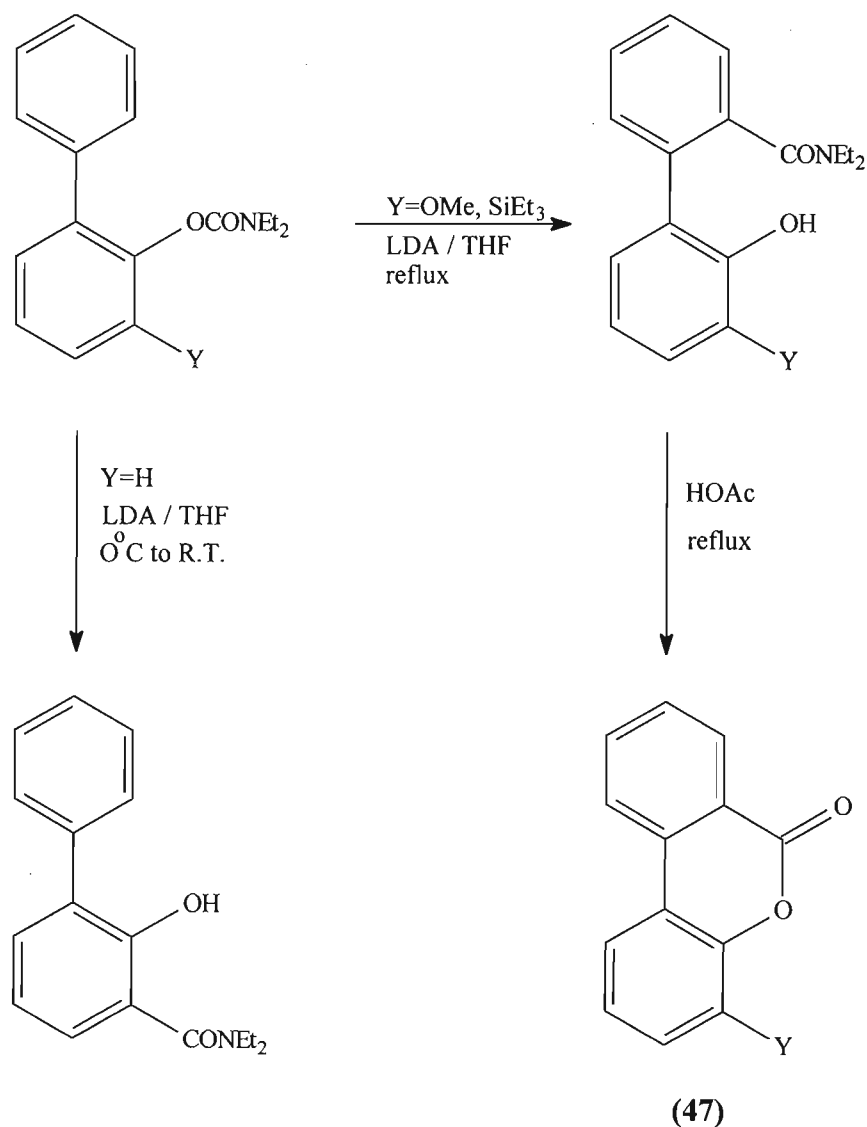
Scheme 35

The migrational ability and the leaving group capability of the carbamate group have been exploited in the synthesis of substituted chromenes **(48)**, coumarins **(49)** **(Scheme 36)**, substituted cyclohexenes **(52)** **(Scheme 38)** and β-amino esters **(53)** **(Scheme 37)**.[75]

Substituted chromenes **(48)** and coumarins **(49)**[75] were synthesised from the DABCO catalysed Baylis-Hillman reaction product of the N,N-dialkylcarbamate of salicylaldehyde and methyl acrylate.
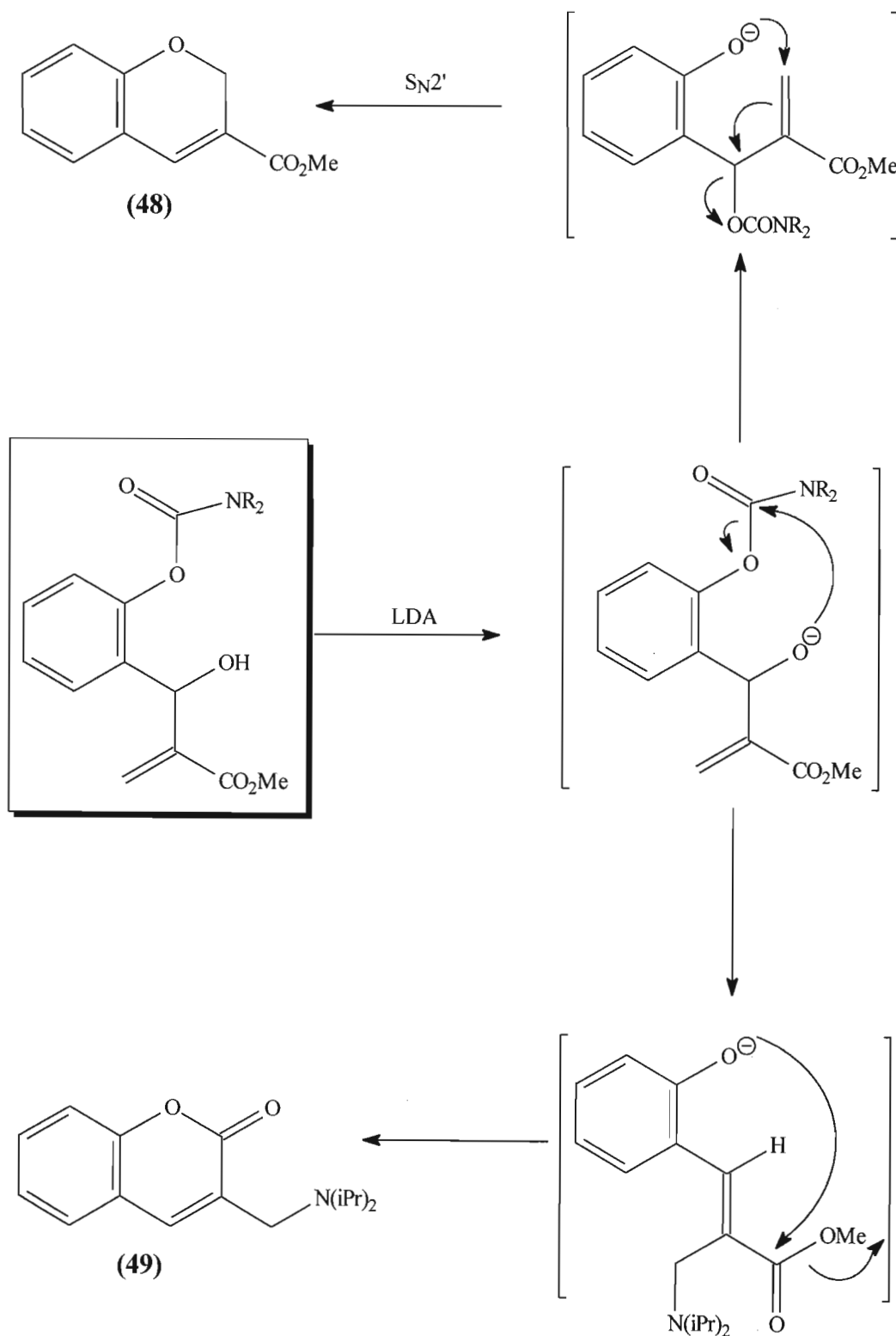
Scheme 36

Intramolecular migration of the carbamate is promoted by the deliberate abstraction of the acidic alcohol proton and cyclization occurs with the S_N2' elimination of the carbamate group.

The leaving group ability of the carbamate functionality can be successfully employed in the cyclization of 2-butenylene dicarbamates **(50)** to give 4-vinyl-2-oxazolidones **(51)** in high yield **(Scheme 37)**.[77] The dicarbamates are readily obtained from the reaction in THF of but-2-en-1,4-diols with a slight excess of isocyanate. Oxidative addition of the dicarbamate to a palladium(0) catalyst forms the cationic π-allylpalladium(II) complex. Proton abstraction from the phenylcarbamoyloxy group followed by intramolecular attack of the nitrogen nucleophile within the intermediate produces the vinyloxazolidone and regenerates palladium(0). An interesting proposal for the mechanism of the reaction includes the *in situ* formation of amide anions during the decarboxylation of carbamates. It is these amide anions which behave as the bases for the abstraction of the proton from carbonucleophiles to afford the cyclized product.
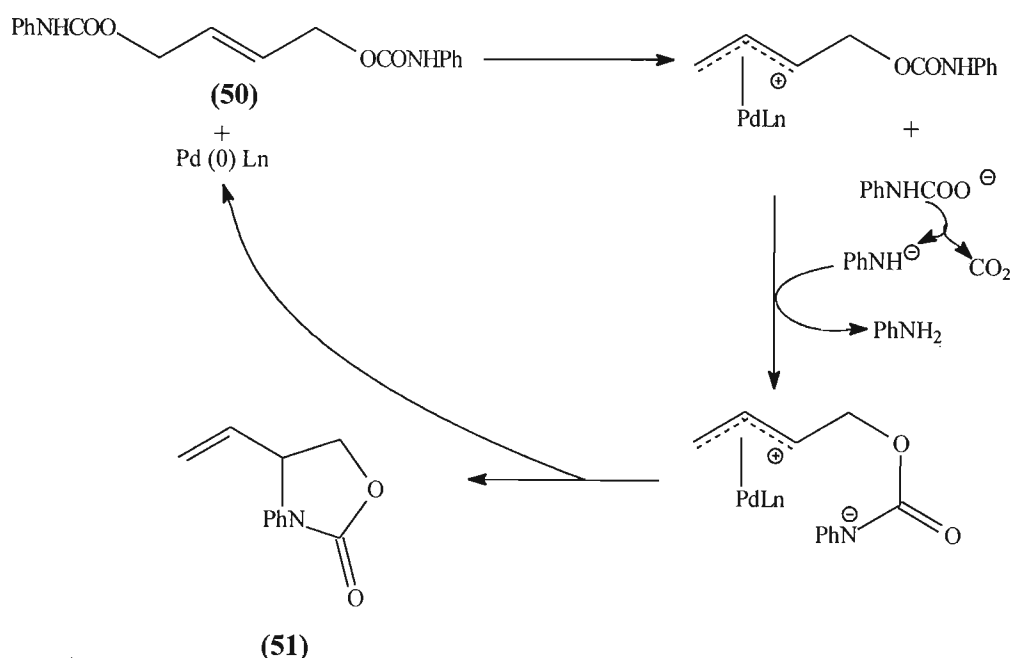
Scheme 37

Alkyl substituted cyclohexenes **(52)** were synthesised *via* DABCO catalysed Diels-Alder reaction from *in situ* prepared allylic carbamates[75] **(Scheme 38)**.
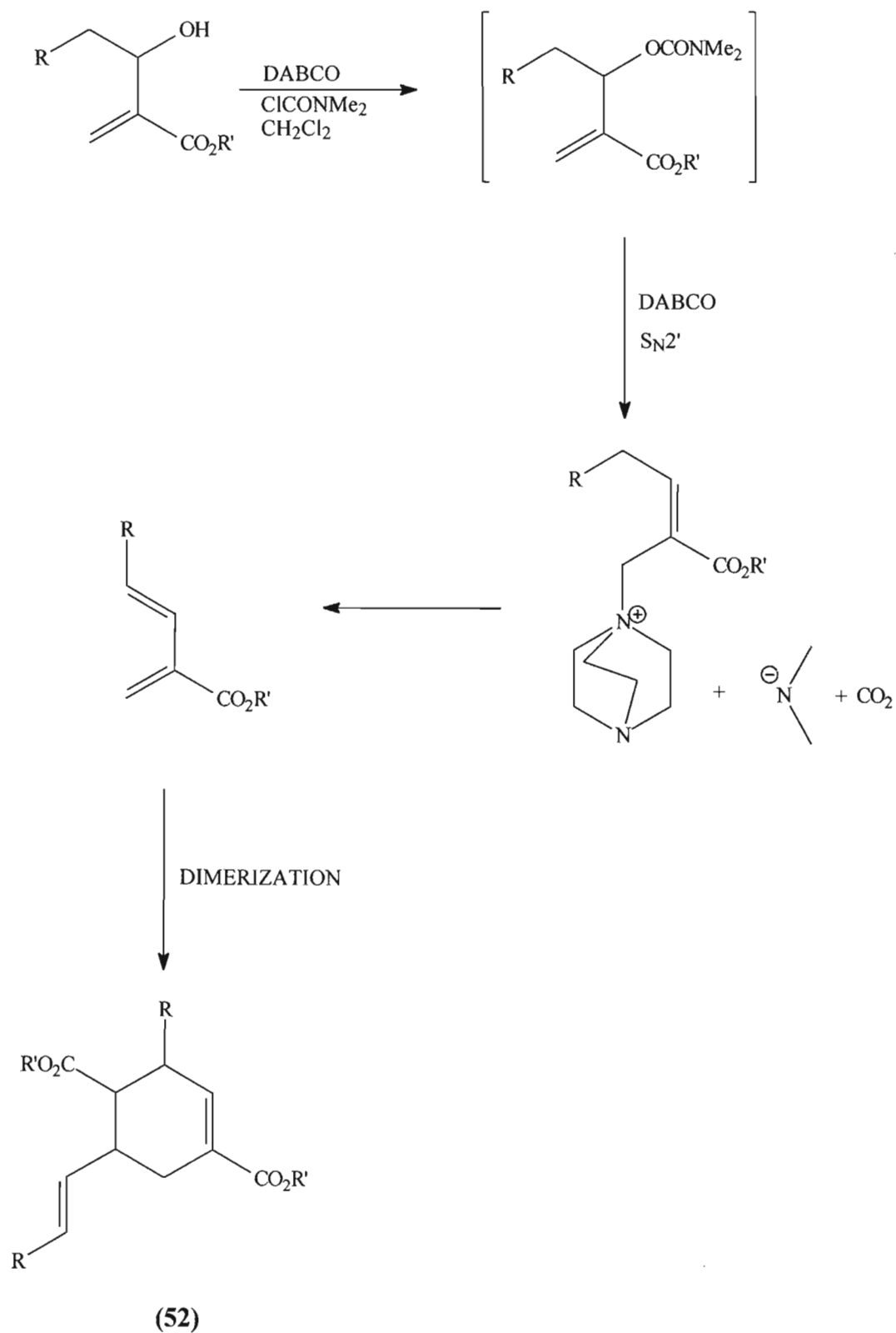
Scheme 38

Similar reactions with aromatic allylic carbamates afforded β-amino esters **(53)** as dimerization could not take place. Instead the eliminated amine portion of the leaving carbamate group nucleophilically attacked the carbon atom coordinated to DABCO which resulted in elimination of the DABCO catalyst **(Scheme 39)**.
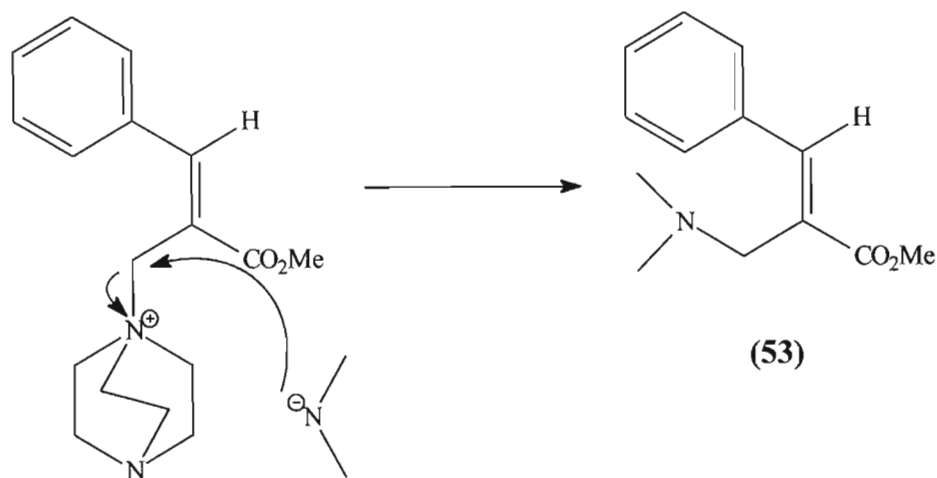
Scheme 39

The concerted elimination of DABCO, as occurs in the reactions with alkyl systems, is impossible due to the absence of an allylic proton.[75]

The [2+2] cycloaddition reaction of cyclic enecarbamates with ketenes provided a short and efficient route to the Geissman-Waiss lactone **(54) (Scheme 40)**, a key precursor to some pyrrolizidine bases such as retronecine **(55)**, in 62% yield.[78] In the reaction the carbamate functionality behaves both as a ketenophile and as a protecting group.

(55)
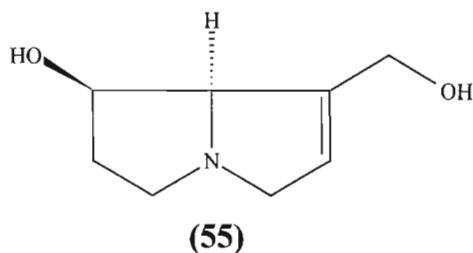
The reaction of cyclic enecarbamate **(56)** with dichloroketene in hexane at room temperature gave the aza-bicyclo-cyclobutanone **(57)**. Dechlorination was carried out

using zinc in acetic acid at room temperature to provide the corresponding aza-bicyclo-cyclobutanone. Ring expansion carried out in dichloromethane using MCPBA, followed by basic workup, yielded the desired bicyclic carbamate γ-lactone **(58) (Scheme 40)**.
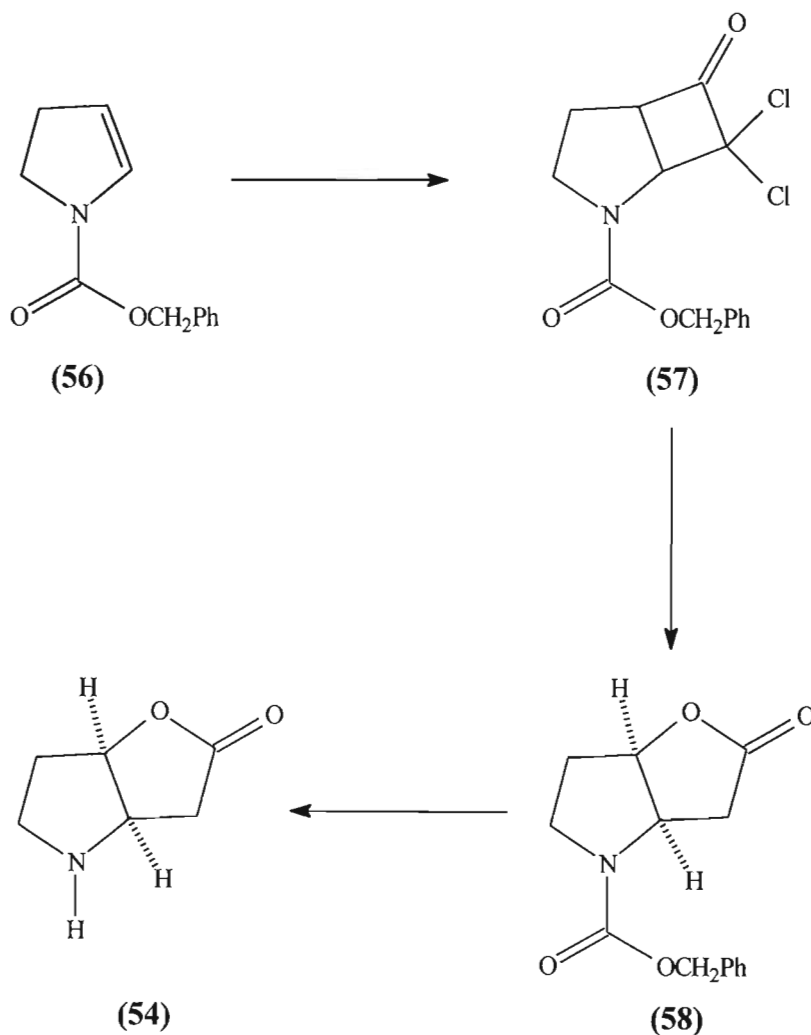
Scheme 40

Hydrolysis of the benzyloxycarbonyl moiety over Pd/C catalyst resulted in the desired Geissman-Waiss lactone **(54)** as the sole product **(Scheme 40)**.

1.7   SUMMARY

The carbamate group has been used in the successful synthesis of a variety of compounds. The synthetic usefulness of the carbamate group as a protecting group, its ability stabilise a carbanion, its leaving group ability and its migrational ability were of particular interest to us.

The use of the carbamate group in the generation of homoenolate anion equivalents, in particular by Hoppe and his co-workers,[59,60,61] prompted us to investigate the usefulness of this work in the electrophilic substitution of 1,1-diphenyl benzylic carbamate **(59)** and α,ω-diphenyl allylic carbamate **(60)** systems.

OCONR$_2$ OCONR$_2$

(59)   **(60)**
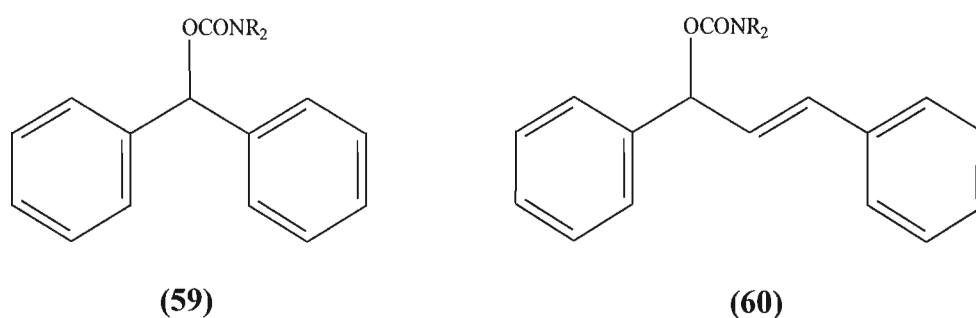
R = alkyl

The leaving group ability of the carbamate group offered a further possible route to the regiospecific functionalization of benzylic- and allylic-α,ω-diphenyl compounds.

The regiospecific functionalization of α,ω-diphenylpolyenes **(61)** is not easy, due to their low reactivity. Would the introduction of a carbamate group facilitate the desired regiospecific functionalization of such compounds **(62)** ?
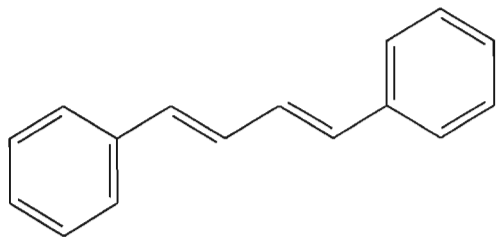
(61)
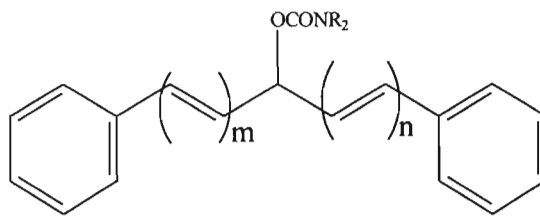
(62)

R = alkyl

m,n = 0, 1, 2...

This chemistry had not previously been studied and so it was necessary to establish the usefulness of the carbamate moiety firstly in the functionalization of 1,1-diphenyl benzylic and terminal diphenyl substituted allylic compounds and then to extend the study to α,ω-diphenylpolyenes.

CHAPTER 2 : DISCUSSION

2.1   INTRODUCTION

"How Far Can a Carbanion Delocalize?"[80a]

The above question is currently stimulating extensive interest in the study of conjugated polyunsaturated molecules. Conjugated polyenes currently enjoy a high profile in the study of non-linear optical conductors in the search for materials suitable for the rapid electronic transfer of information.[80] Conjugated polyenes are found extensively in nature[81], forming part of several pharmacalogically active compounds.[82] Polyene aldehydes have been used as synthetic building blocks for, amongst others, natural products and medicinal compounds,[83] fragrance synthesis,[84] and charge transfer molecules.[80]

The carbamate group has been shown to stabilise a carbanion in benzylic and allylic systems.[59-65] Its versatility has been repeatedly exploited in the synthesis of a variety of compounds. The leaving group ability has been applied in the synthesis of chromenes and coumarins, suggesting that the elimination of the carbamate proceeds *via* a S_N2' mechanism.[75] Many of the recently published studies of intramolecular charge-transfer phenomena and non-linear hyperpolarizability involve α,ω-diaryl systems.[80a-g]

A soliton is a non-dissipative wave. It has been suggested that the delocalization of a carbanion can be modelled on the behaviour of a soliton.[80a] ^{13}C NMR studies of α,ω-diphenylpolyenes indicate that the saturation of delocalization of the carbanion is reached after 31 carbon atoms, excluding the terminal phenyl rings. This suggests that the soliton width is 31 carbon atoms from its point of generation. This hypothesis prompted us to investigate firstly diphenyl benzylic and allylic compounds to establish whether the introduction of a carbamate group would influence the electrophilic regioselectivity of substitution onto the chain or ring and then, if possible, to apply our findings to the regiospecific functionalization of longer diphenyl polyenes.

In addition to the electrophilic studies, we also examined reactions of carbamates with nucleophiles. The aim was to establish the position at which a nucleophile would attack and so shed light on the mechanism of elimination of the carbamate moiety.

2.2   PREPARATION OF STARTING MATERIALS

The most feasible route to the N,N-dialkyl diphenyl-benzylic and -allylic carbamates was to react N,N-dialkylcarbamoyl chloride with the corresponding alcohol precursors. Many of the alcohols were prepared by the reduction of the corresponding α,ω-diphenyl ketone using sodium borohydride.

2.2.1   PREPARATION OF ALLYLIC KETONES

All allylic ketones were prepared using the Aldol condensation. The unsymmetrical ketones (63) were prepared by reacting one equivalent of aldehyde with one equivalent of ketone in aqueous ethanolic sodium hydroxide solution (Scheme 41), while the symmetrical ketones (64) were prepared by the reaction of two equivalents of aldehyde with one equivalent of acetone (Scheme 42). No self-aldol product was isolated.
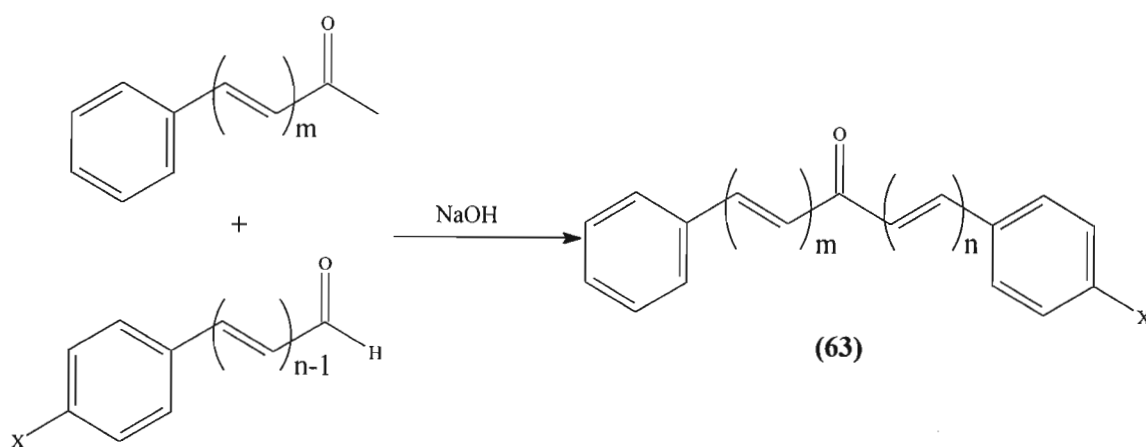
where X=H, NO$_2$ and

m=0, 1

n=1, 2

m ≠ n

Scheme 41
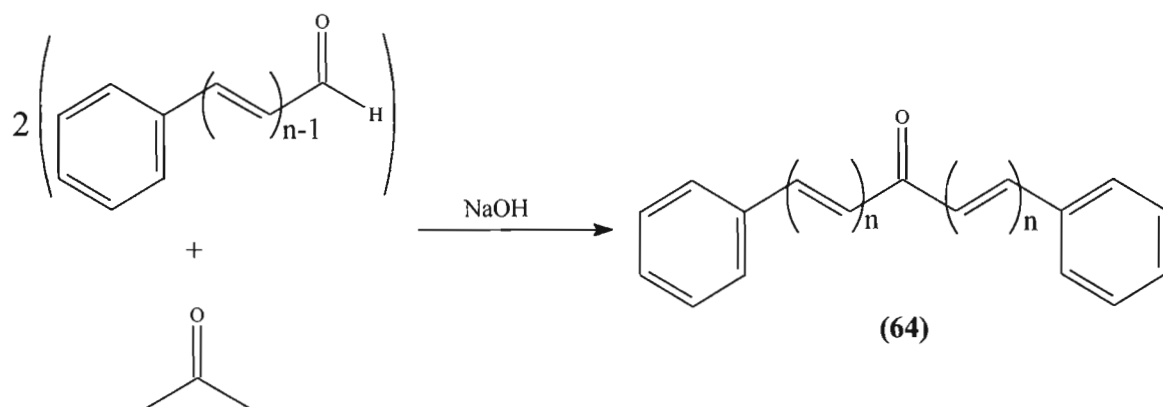
where n=1,2

Scheme 42

Reactions were all fairly rapid and gave good yields **(Table 1)**. All products were crystalline, precipitating out of solution within minutes of the start of the reaction. As the chain length increased so the colour of the compounds tended more towards the red end of the visible spectrum. Again the self-aldol product was not apparent.

Table 1: *Summary of ketones synthesised* [85a,b]

KETONE	m	n	X	% YIELD
63 a	0	1	NO$_2$	94
63 b	0	2	H	75
63 c	1	2	H	75
64 a	-	1	H	81
64 b	-	2	H	66

2.2.2   PREPARATION OF ALCOHOLS

With the exception of 1,3-diphenyl-2-propen-1-ol, which was prepared by the Grignard reaction of phenylmagnesium bromide with cinnamaldehyde in diethyl ether, all alcohols **(65)** were initially prepared by the reduction of the corresponding enones with sodium

borohydride **(Scheme 43)** in moderate to excellent yield **(Table 2).**[86] All products were crystalline.

(65)
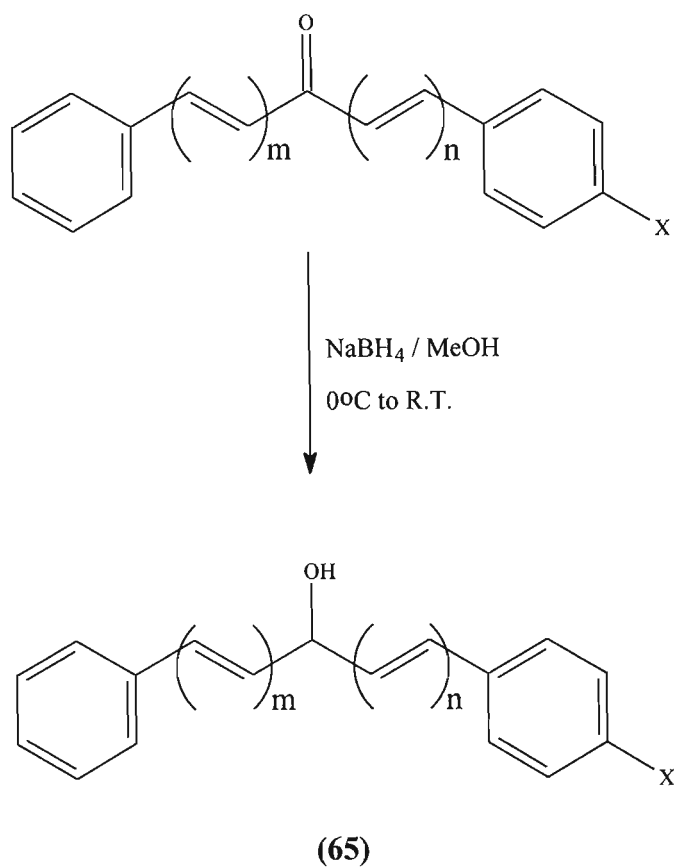
m, n = 0, 1, 2

X= H, NO_2

Scheme 43

Table 2: *Nature and yields of alcohols synthesised*[86, 87, 88]

ALCOHOL	m	n	X	% YIELD
65 a	0	0	H	62
65 b	0	1	H	61
65 c	1	1	H	78
65 d	0	2	H	95
65 e	2	2	H	91
65 f	0	1	NO_2	0

It is interesting to note the higher yields in the reduction of the more conjugated ketones. The competition in the reduction between the double bond and the carbonyl group causes some concern for the synthetic chemist.[85d] It would appear that the preservation of extended conjugation of the molecule enables the selective reduction of the ketone, whereas in shorter chain α,β-unsaturated ketones, this competition may be more significant, resulting in lower yields of the desired product.

The alcohols synthesised were very sensitive to air, light and protic solvents, as had previously been discovered in earlier studies of polyenecarbinols.[85b] In particular, the alcohols in which (m, n) = (1, 2) and (2,2) were very unstable. These compounds undergo allylic rearrangements (Scheme 44) in air and in acidic medium, the hydroxy group migrating from a position within the conjugated chain to the most stable position in the chain, the benzylic position. The formation of the most conjugated isomer perhaps provides a second driving force for the rearrangement. An additional explanation may be the reduction in the degree of polarisation of the C=C double bonds by the carbonyl group with increase in conjugation.

m,n = 1,2
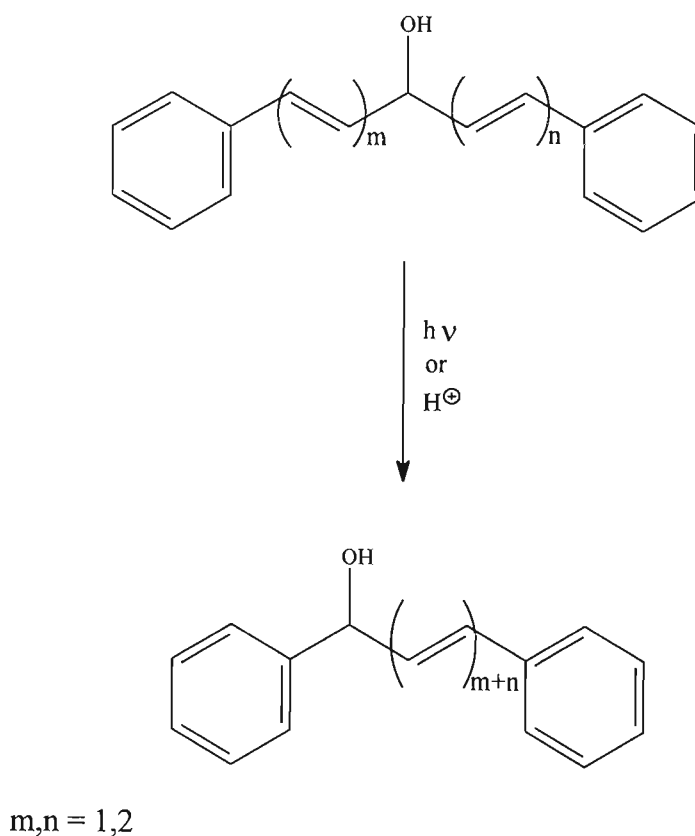
Scheme 44

Therefore the carbinols were stored in sealed containers in a dark refrigerator. Even so, the compounds in which the hydroxy group was in the benzylic position were stable, while those in which the hydroxy group was not in the benzylic position decomposed after some time.

Attempts to synthesise 3-(4'-nitrophenyl)-1-phenyl-2-propen-1-ol by sodium borohydride reduction of the corresponding enone in methanolic solution proved to be futile. Problems with this method of reducing compounds containing nitrogen groups attached to phenyl rings have been encountered.[87] It has been suggested that the nitro group on the phenyl ring can be nucleophilically displaced as nitrite ion by hydride from borohydride ion, the nitro group behaving as a good leaving group. This would require that the oxygen atoms of the nitro group be more towards perpendicular to than coplanar with the ring, hence not participating in resonance stabilisation, and allowing complexation with borohydride to occur at the nitro group.

Several attempts were made to reduce the ketone in a solution of 1:10 v/v MeOH/THF.[88] None proved to be successful. It is believed that the formation of methoxyborohydrides from the reaction of methanol with sodium borohydride occurs *in situ*. The authors suggest that the methoxyborohydrides are more selective than $NaBH_4$, and are suited to reductions of allylic α,β-unsaturated ketones in which conjugation extends into the phenyl ring, the reaction being complete within 20 mins. We isolated quantitative amounts of ketone.

2.2.3 PREPARATION OF CARBAMATES

All carbamates were prepared by the reaction of N,N-dialkylcarbamoyl chloride with the corresponding alcohol in THF **(Scheme 45)**. The alcoholic proton was abstracted using sodium hydride, in so doing generating hydrogen gas and the sodium alkoxide intermediate. Subsequent reaction with the N,N-dialkylcarbamoyl chloride and acidification afforded the desired carbamate after purification.
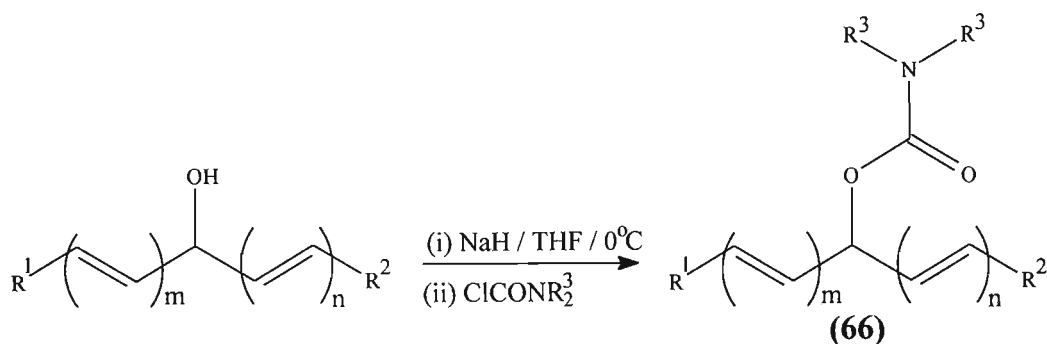
m = 0, 1, 2

n = 0

R^1 = Ph, R^2 = H, Ph, R^3 = Me, Et, ^{i}Pr.

Scheme 45

Although the yield of 1-(O-N,N-diethyl-carbamoyloxy)-3-phenyl-2-propene **(66a)** was good, the yields of the (O-N,N-dialkyl-carbamoyloxy)-α,ω-diphenyl compounds were generally moderate **(Table 3)**. The syntheses of symmetrical α,ω-diphenyl allylic carbamates were inhibited by the lack of stability of the alcohol precursors, as discussed in the previous section.

Table 3: *Summary of carbamates synthesised*

| CARBAMATE	m	n	R^1	R^2	R^3	% YIELD
66 a	1	0	Ph	H	Et	81
66 b	0	0	Ph	Ph	Me	71
66 c	1	0	Ph	Ph	Et	57
66 d	1	0	Ph	Ph	^{i}Pr	54
66 e	2	0	Ph	Ph	Et	67

From the yields of the carbamates, it could be deduced that the nature of the substituents R^1 and R^2 on the allylic alcohol as well as the alkyl substituents, R^3, on the nitrogen atom of the carbamate group, influence the ease of formation of the carbamate. The diphenyl compounds were all produced with lower yields than the O-N,N-diethylcarbamate of cinnamyl alcohol **(66a)**. Both the size of the alkyl groups attached to the nitrogen and the

size and proximity of the phenyl ring to the carbamate group appear to influence the formation of the carbamates. The high yield of (66b) can be attributed to the small steric hindrance offered by the N,N-dimethyl substituents on the carbamate group. One might have expected the yield of this compound to be lower than the others due to the crowding of the central carbon atom by the two phenyl groups. As chain length increases one might expect the steric influence of the phenyl groups to diminish. In comparing the yields of (66c) and (66e) this supposition is proved to be correct. However, when one considers compounds (66b), (66c) and (66d), it could be deduced that the bulk of the substituents on the nitrogen atom have more influence on the yield of the reaction than the phenyl groups.

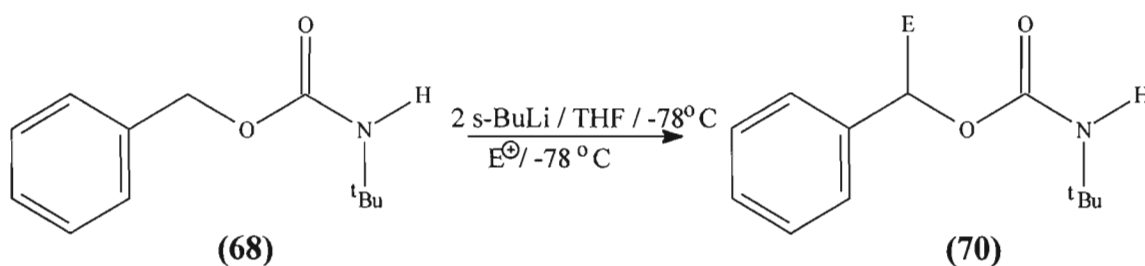## 2.3 ELECTROPHILIC SUBSTITUTION REACTIONS

2.3.1 REACTIONS OF 1-(O-N,N-DIMETHYLCARBAMOYLOXY)-1,1-DIPHENYLMETHANE WITH ELECTROPHILES.

Hoppe and co-workers[59] showed that 1-(O-N,N-diethylcarbamoyloxy)-1-phenylmethane (67) could be successfully substituted with electrophiles via the lithiated homoenolate anion equivalent (Scheme 46). They claim that when the anion was quenched with methyl iodide, the reaction afforded methyl substituted carbamate in 91% yield, and, when trapped with dimethyl carbonate, a yield of 74% was achieved for the methyl ester substituted carbamate.
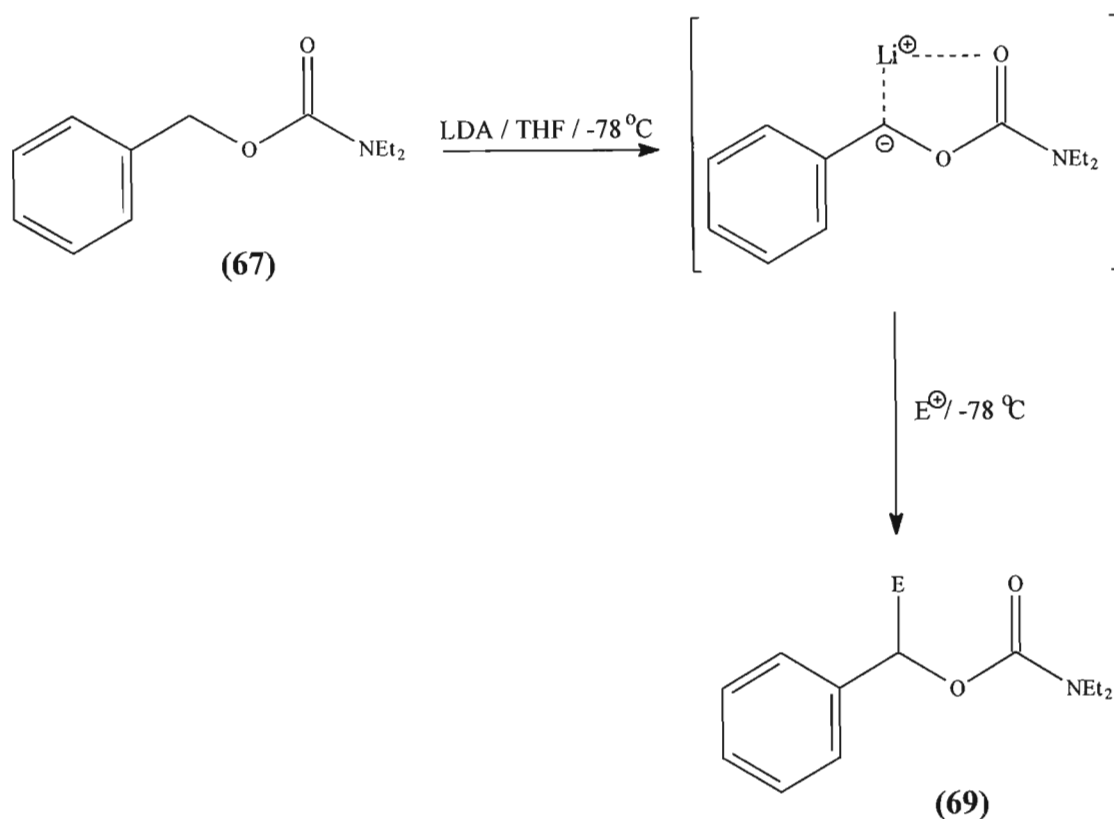
Scheme 46

Barner and Mani[65] investigated similar reactions of electrophiles with N-*tertiary* butyl benzyl carbamate **(68)** in the preparation of asymmetric alcohols **(Scheme 47)**. These experiments demanded the protection of the monosubstituted nitrogen with lithium for the success of the reactions. Whereas Hoppe[59] could use one equivalent of base in the reactions of N,N-dialkyl substituted carbamates, Barner and Mani required two equivalents per equivalent of carbamate. The carbamates were all formed in yields in excess of 80% **(Table 4)**.
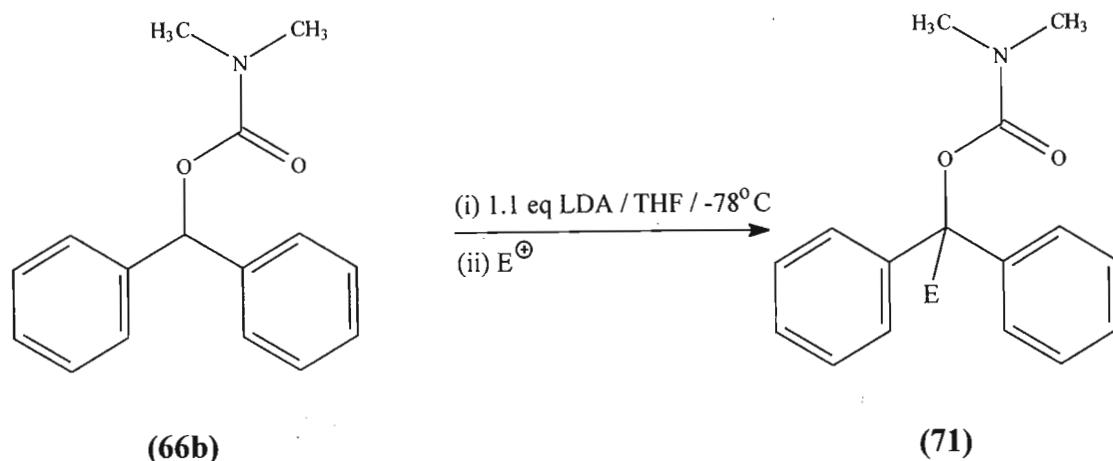

Scheme 47

Table 4 : *Summary of electrophilic substitution reactions of benzyl carbamates.* [59, 65]

CARBAMATE	ELECTROPHILE	% YIELD
69a	MeI	91
70a	MeI	91
70b	$PhCH_2Br$	82
70c	$CH_2=CHCH_2Br$	86
70d	$CH_2=C(CH_2Cl)_2$	89
70e	$ClCH_2CH=CHCH_2Cl$	81
70f	$Br(CH_2)_3Cl$	86
70g	$Br(CH_2)_4Cl$	82
70h	TMSCl	85
70i	PhCHO	88
70j	$ICH_2C(CH_3)_2CHO$	87
70k	$CH_3CHBrCH_2CH_2Br$	82

Electrophilic substitution reactions with **(66b)** were carried out at -78°C. LDA was generated *in situ* in THF and the carbamate added dropwise. Generation of the anion was immediate and could be detected by the bright orange colour associated with the formation of the intermediate. Electrophiles were added dropwise at the same temperature after the anion had been generated **(Scheme 48)**. Reactions are summarised in **Table 5**.

Table 5 : *Electrophilic substitution products of* (66b).

CARBAMATE	ELECTROPHILE	% YIELD
71 a	MeI	71
71 b	$PhCH_2Br$	42
71 c	TMSCl	47
71 d	TBDMSCl	0
71 e	PhCHO	0
71 f	PhCH=CHCHO	37
71 g	$CH_2=CHCOOMe$	0

Scheme 48

Reactions with a variety of electrophiles were carried out. It would appear that the success of the reaction is governed principally by the bulk of the incoming electrophile and its steric interaction with the carbamate.

As in the reactions carried out by Hoppe[59] and Barner and Mani[65], the carbamate is most successfully alkylated **(71a)** using methyl iodide. This would be due to the ease with which methyl iodide can approach the carbanion and be attacked by the electron pair. In the reaction with benzyl bromide **(71b)**, the phenyl ring is far enough away from the carbanion not to prevent reaction from occurring, although the yield is significantly lower than that of the reaction with methyl iodide. Reactions with silicon-containing electrophiles reveal the same tendency, the reaction with the less bulky TMSCl proceeding with limited yield **(71c)**, while the reaction with TBDMSCl does not proceed at all **(71d)**. The bulk of this electrophile is such that it cannot approach the reaction site closely enough to facilitate bond formation.

In their studies of the electrophilic substitution of *tertiary* butyl benzyl carbamate **(70)**, Barner and Mani[65] isolated the product of the reaction with benzaldehyde **(70i)** in 88% yield. Hoppe[60] suggests that the reaction of carbonyl compounds with allylic carbamates proceeds *via* the six-membered transition state **(36)**. For the same transition state model to be applicable to benzyl carbamates and **(66b)**, the electrons within the ring need to be considered to delocalize within the transition state **(Figure 2)**, generating a temporary

positive charge on the ring. The reaction of benzaldehyde with **(66b)** afforded starting materials. In the reaction with the benzyl carbamate the single phenyl ring is spatially removed from the incoming benzaldehyde ring. Hence, steric interaction and electronic repulsion between the rings do not prevent the formation of the transition state **(36)** and the 1,2-addition product. However, in the reaction of **(66b)** with benzaldehyde the three rings interact sterically and the π-electron clouds associated with the aromatic rings probably repel each other. The combination of these two factors would prevent the formation of the transition state **("71e")**.

(36)

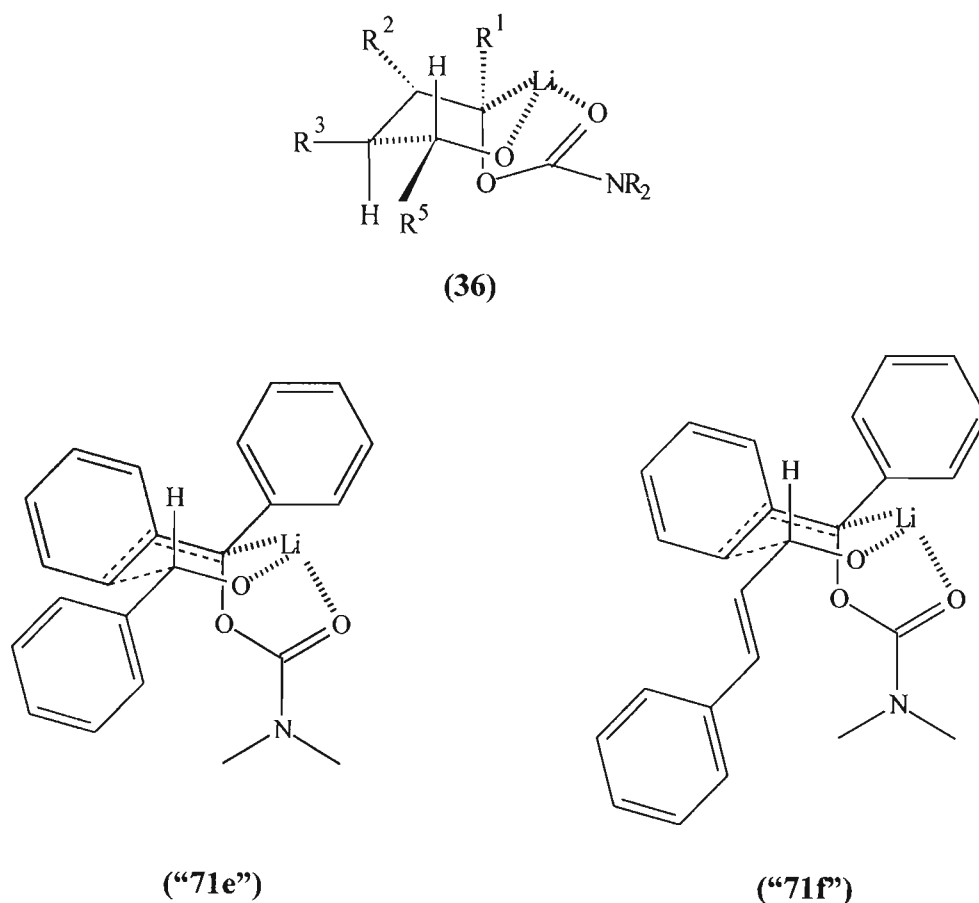

("71e")   **("71f")**

Figure 2

The reaction of **(66b)** with cinnamaldehyde, however, did result in the formation of the 1,2-addition product. The electrophilic carbonyl carbon, unlike in benzaldehyde, is more remote from the phenyl ring. This means that the carbonyl carbon could approach the carbanion sufficiently closely to allow overlap of the orbitals and bond formation to occur. The formation of the product would indicate that the steric interactions between the phenyl rings are more significant than the electronic repulsion between the π-electrons. This can

be argued because the π-electrons of the double bond in cinnamaldehyde and the aromatic π-electrons of the phenyl rings did not prevent the formation of the product. The relative proximities of the atoms and substituents can be seen in the transition state (**"71f"**) (**Figure 2**).

The reaction of (**66b**) with methyl acrylate as Michael acceptor yielded starting materials.

2.3.2 REACTIONS OF 1-(*O*-N,N-DIETHYLCARBAMOYLOXY)-1,3-DIPHENYL-2-PROPENE WITH ELECTROPHILES.

In their studies of homoenolate anion equivalents, Hoppe and co-workers[59, 60, 61] showed that the carbamate group is instrumental in promoting the regiospecific electrophilic functionalization of allylic compounds (**Scheme 49**). No studies were made of terminal-aryl or diaryl allylic carbamates. Numerous reactions have been carried out with a variety of N,N-dialkyl substituted carbamates, N-substituted carbamates and alkyl halides and carbonyl compounds as electrophiles.[59-61,65] The results are summarized in **Table 6**.

Table 6 : *Summary of electrophilic substitutions of allylic carbamates.*[59]

CARBAMATE	R^1	R^2	R^3	R^4	E^+	PRODUCT	% YIELD	$\gamma : \alpha$
72a	H	H	H	Et	PhCH$_2$Br	**73a**	51	95:5
72b	H	H	H	Me	PhCH$_2$Br	**73b, 74b**	54	78:22
72c	H	H	H	^{i}Pr	PhCH$_2$Br	**73c**	63	97: <3
72a	H	H	H	Et	MeI	**73d**	70	95:5
72d	Me	H	H	Et	PhCH$_2$Br	**73e, 74e**	75	47:53
72e	H	Me	H	Et	PhCH$_2$Br	**73f, 74f**	77	85:15
72f	H	H	Me	Et	PhCH$_2$Br	**73g**	79	97:<3
72f	H	H	Me	Et	MeI	**73h**	76	97:<3
72f	H	H	Me	Et	HOAc	**73i**	65	97:<3
66a	Ph	H	H	Et	-	-	-	-
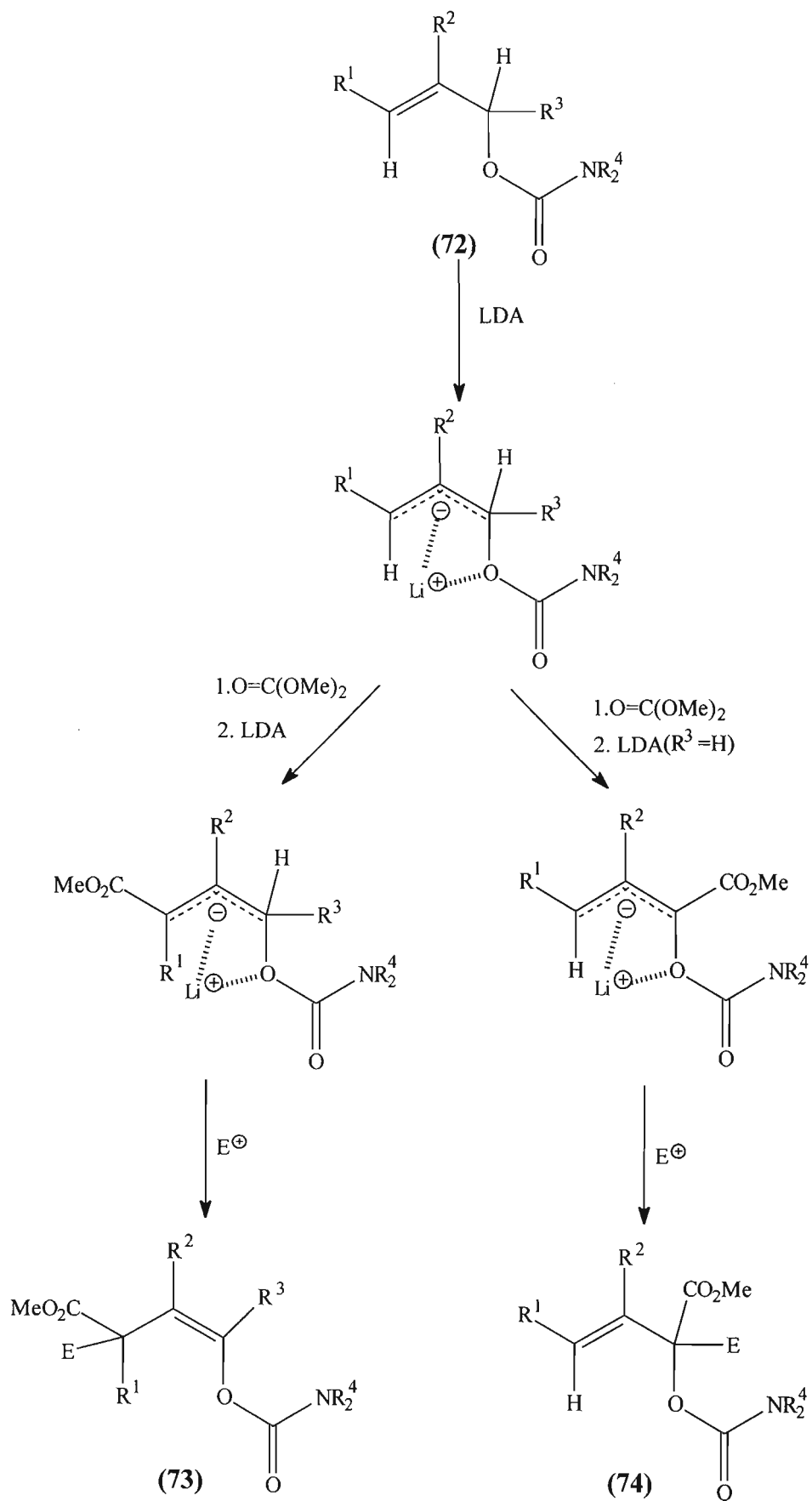
Scheme 49

Initial studies[59] involved first the base abstraction of the α-proton from carbamate (72) and reaction with dimethyl carbonate, and then the removal of the second proton and subsequent reaction with another electrophile. The regioselectivity is governed mainly by the steric interaction of the substituents on the allylic carbamate and the alkyl substituents on the nitrogen atom of the carbamate group itself (73) and (74).

Further studies[61] involved electrophilic substitution reactions with carbonyl compounds (Scheme 50). The reactions were restricted to those with allylic diisopropyl carbamates, the size of the alkyl substituents having been found to preferentially promote γ-substitution over α-substitution. Results are summarised in Table 7.

Table 7 : *Homoaldol reactions with allylic carbamates*[61]

CARBAMATE	R^1	R^2	R^3	R^4	R^5	R^6	% YIELD	$\gamma : \alpha$
72c	H	H	H	H	Me	Me	79	93 : 7
75b	Me	H	H	H	Me_3C	H	93	97 : <3
75b	Me	H	H	H	$Me_2C=CH$	H	60	83 : 17
75c	H	H	Me	H	Me_3C	H	77	97 : <3
75d	H	H	Me	Me	Ph	H	75	95 : <5

A few general deductions can be made from the results obtained by Hoppe and his group.[61] As was established in reactions of benzyl carbamates, the steric interaction between substituents in the alkyl chain, the substituents on the nitrogen atom of the carbamate group and the size of the reacting electrophile influence the yield of reaction. The allylic system, however, offers the electrophile two favourable sites for reaction, namely the carbon atom α to the carbamate, where the carbanion is initially stabilised by the carbamate group, and the allylic carbon atom γ to the carbamate group. It is at this point important to discuss the results published by Hoppe.[61]
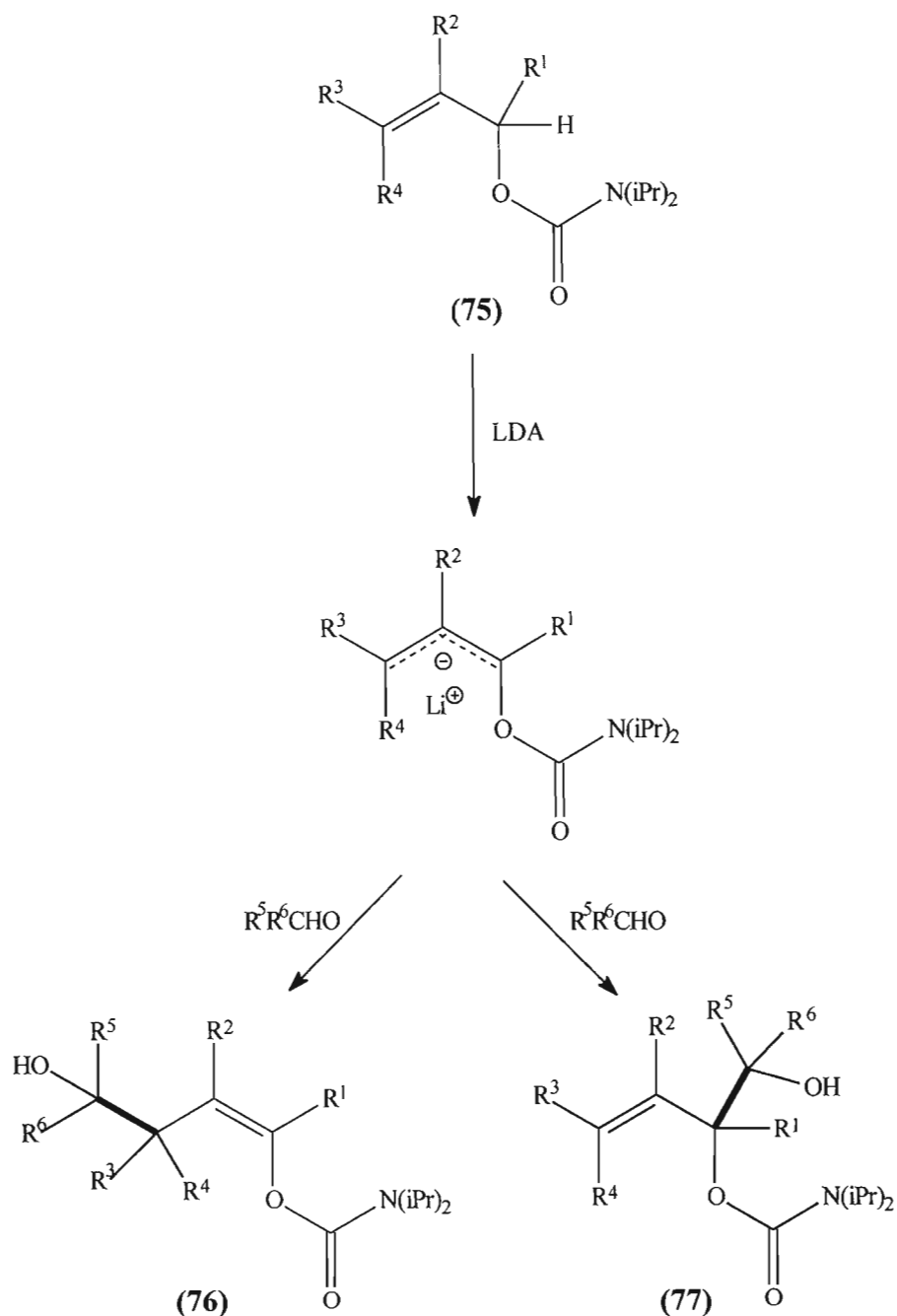
Scheme 50

N,N-diethyl and N,N-diisopropyl carbamates **(72a)** and **(72c)** containing no substituents on the chain react with benzyl bromide to afford, predominantly, the respective γ-adducts **(73a)** and **(73c)**, while the N,N-dimethyl carbamate **(72b)** gives rise to a significant amount of the α-adduct **(74)** as well. The reaction of the N,N-diethyl carbamate **(72a)** with methyl iodide gives predominantly the γ-adduct **(73d)** in higher yield than the electrophilic

substitution with benzyl bromide. These reactions with the same allylic backbone but with differing N,N-dialkyl substituents illustrate the importance of the alkyl substituents on the nitrogen atom on regioselectivity, and the size of the incoming electrophile on overall yield.

The presence of methyl substituents on the chain influence regioselectivity of substitution. Little selectivity is achieved in the reaction of the N,N-diethyl carbamate (72d), in which the methyl substituent is in the γ-position. The positive inductive effect of the methyl group hinders delocalization of the carbanion and the steric hindrance offered to the incoming electrophile forces a slight preference for the α-position. A good selectivity is still obtained in the substitution of N,N-diethyl carbamate (72e) in which the methyl substituent occupies the β-position with benzyl bromide, excellent γ-selectivity is obtained in the reaction of benzyl bromide with N,N-diethyl carbamate (72f) containing an α-methyl substituent. Here the positive inductive effect increases electron density on the α-carbon atom so promoting the migration of the carbanion to the γ-carbon atom while the steric interaction of the methyl group hinders substitution at the α-carbon atom.

The homoaldol reactions reveal a marked tendency towards the formation of the γ-adducts.[61] No comparisons are available with regard to the effect the nitrogen substituents would have on the yields and selectivity of the homoaldol reactions. It is assumed then that the authors, in using only the N,N-diisopropyl carbamates, were trying to promote only γ-substitution rather than study the effect of the size of the carbamate group on the selectivity of the reaction.

Excellent selectivity towards γ-substitution is obtained in the reaction of acetone with N,N-diisopropyl allyl carbamate (72c). The reactions of *tertiary* butyl aldehyde with α-and γ-methyl substituted carbamates (75b) and (75c) result in the same regioselectivity, but the yield in the latter reaction, in which the carbamate contains a methyl substituent in the γ-position, is far lower than the former where the methyl substituent is in the α-position. With γ,γ-disubstituted carbamate (75d), benzaldehyde still reacts at the γ-position. In order to substantiate how the steric factors are overcome to maintain γ-selectivity in the homoaldol reactions, Hoppe[60] proposed the six-membered transition state mentioned in

Chapter 1 **(36) (Figure 1)** (p.27). The reaction of α-methyl substituted carbamate **(75b)** with crotonaldehyde proved to be lower yielding than the other reactions. In addition the selectivity of the reaction was lower, the extended planarity of the aldehyde perhaps allowing the carbonyl carbon to approach the α-carbon atom more closely than is possible for the other aldehydes.

In order to build on the work of previous researchers, and apply their findings to the benzylic/allylic systems, reactions with a similar diversity of electrophiles were carried out with 1-(O-N,N-diethylcarbamoyloxy)-1,3-diphenyl-2-propene **(66c) (Table 8)**.

Table 8 : *Electrophilic substitution reactions of (66c)*

ELECTROPHILE	PRODUCT	% YIELD
MeI	**78a,79a**	55, 0
EtI	**78b,79b**	0, 0
TMSCl	**78c,79c**	0, 0
TBDMSCl	**78d,79d**	0, 0
PhCHO	**78e,79e**	0, 0
PhCH=CHCHO	**78f,79f**	0, 0
CH_2=CHCOOMe	**78g,79g**	0, 0

Reactions with electrophiles were carried out in dry THF at -78°C. In each reaction LDA was used as base and the generation of the carbamate anion was signified by the instant colour change from yellow to cherry red. It was thought that the reactions would proceed in the same manner as those already achieved, the carbamate having substituents R^1=R^2=Ph according to the structure **(72) (Scheme 49)** (p.54). We expected the reactions to follow a similar pathway, resulting in two possible substitution products, the α- (Path A) and γ-adducts (Path B) **(Scheme 51)**.
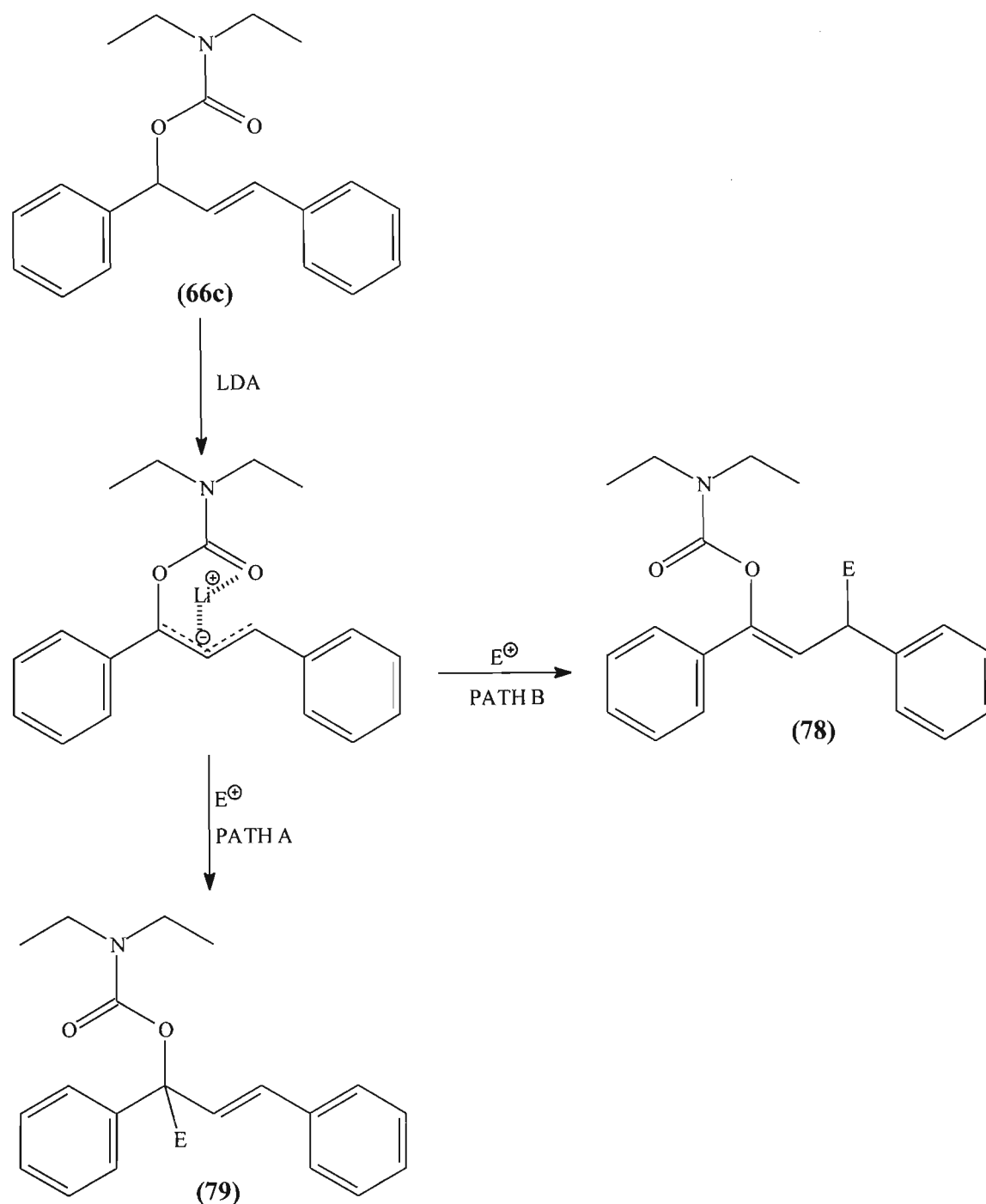
Scheme 51

Electronically there are two possible substitution positions, the α-carbon to the carbamate and the γ-position. However, the only substitution to occur successfully was in the reaction with methyl iodide **(78a)**. On inspection of molecular models it becomes apparent that the system is highly sterically hindered. In the earlier discussions it was apparent that alkyl substituents on the allyl chain did not influence the overall yield of the reaction as significantly as the nitrogen substituents in the carbamate group.

The carbamate contains two terminal phenyl rings, one attached to each of the α- and γ-carbon atoms respectively. The phenyl ring is capable of stabilising a negative charge and possibly participates to some extent in the conjugation of the molecule as a whole. This would not be surprising because we have already seen that the phenyl ring takes part in the formation of the six-membered transition state of the reaction of with cinnamaldehyde (**"71f"**). This possible resonance stabilisation could contribute to the lowering of the nucleophilicity of the carbamate. Methyl iodide is a small and moderately strong electrophile and could overcome the weak nucleophilicity of the carbamate whereas the weaker electrophiles cannot. In addition to the stabilising effects, the size of the phenyl rings results in steric interactions with the alkyl substituents of the carbamate group. This interaction hinders free rotation within the molecule and forces the amide portion of the carbamate group away from the nearer ring and towards the double bond of the allyl system. There exists the possibility also of electronic repulsive forces between the π-electrons of the ring and the lone pairs on the amide oxygen. We know from previous discussions that the size of the substituents on the nitrogen atom have significant steric influence. The two ethyl groups of the carbamate group then rotate in the vicinity of the carbon in the γ-position, hindering the approach for incoming electrophiles. The α-position is blocked by the rotation about the C-O bond.

The γ-position would appear to be the more favourable site for substitution by electrophiles owing to the lower steric factors surrounding the approach to this carbon atom. Of the electrophiles reacted with 1-(O-N,N-diethylcarbamoyloxy)-1,1-diphenyl-2-propene, only the reaction with methyl iodide results in any substitution product, only the γ-substituted product being isolated. The ethyl group of ethyl iodide, TMSCl and TBDMSCl are far too bulky to participate in reaction as their size inhibits their approach to the reaction sites. The proposed six-membered transition state of the reaction of benzaldehyde (**"78e"**) and cinnamaldehyde (**"78f"**) show more hindrance towards these reactions than the corresponding reactions with **(66b)** **(Figure 3)**. This arises due to the larger size of the allyl chain and the larger alkyl substituents on the nitrogen atom of the carbamate.

("78e") ("78f")
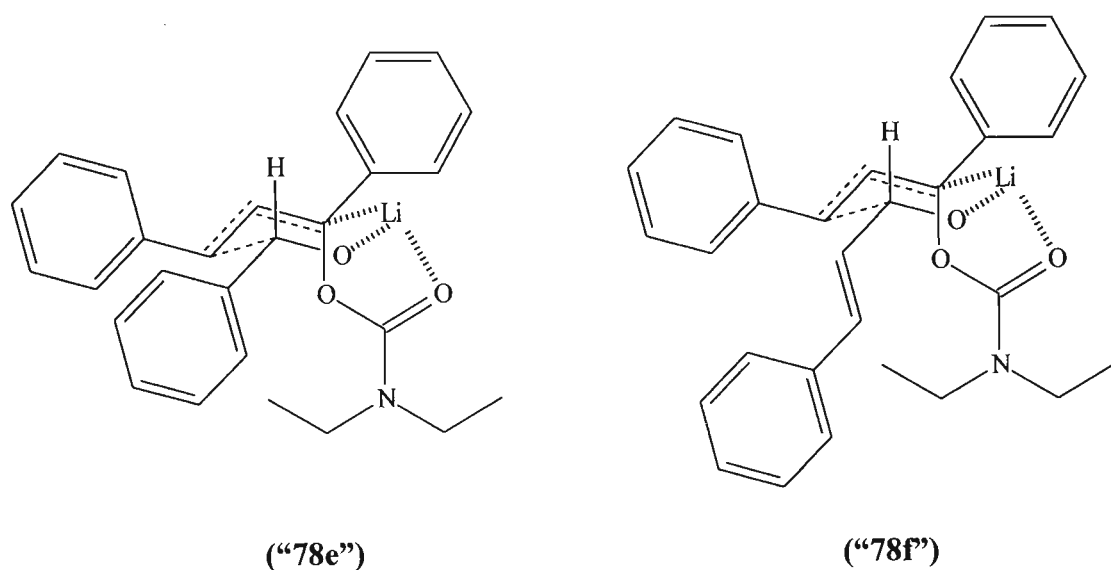
Figure 3

Again the reaction with methyl acrylate proved fruitless, implying that reaction with Michael acceptors is not favourable. It is possible for the acrylate ester to approach both the α- and γ-carbon atoms. The repulsions of lone pairs on the several oxygen atoms and interaction with the π-electrons of the rings might render the formation of the 1,4-addition product unfavourable.

2.3.3 REACTIONS OF 1-(O-N,N-DIETHYLCARBAMOYLOXY)-1,5-DIPHENYL-2,4-PENTADIENE WITH ELECTROPHILES

The extension of the electrophilic substitution reactions was carried out on the conjugated diene 1-(O-N,N-diethylcarbamoyloxy)-1,5-diphenyl-2,4-pentadiene **(66e)**. We believed that the longer chain length of the molecule would provide less steric hindrance to substitution with electrophiles if the substitution was to occur at the benzylic carbon atom in the ξ-position to the carbamate group. We knew already that methyl iodide reacted successfully with the smaller molecule and that larger electrophiles did not. The questions which required answering were : where would substitution occur, would the carbanion be delocalized along the chain; could larger electrophiles successfully substitute the longer conjugated molecule and so indicate that the steric interaction of the carbamate alkyl groups is only significant in positions close to the carbamate group itself?

Molecular models of the carbamate in question reveal that the alkyl groups do not hinder the ξ-carbon atom sterically as is the case with the α- and the γ-carbon atoms. Based on our findings thus far, it was reasonable to expect that substitution might occur in the ξ-position **(81)** **(Scheme 52)**, at least with methyl iodide.

(66e)

(i) Base/THF
(ii) E⊕ -78°C
(iii) NH₄Cl / workup

(81)
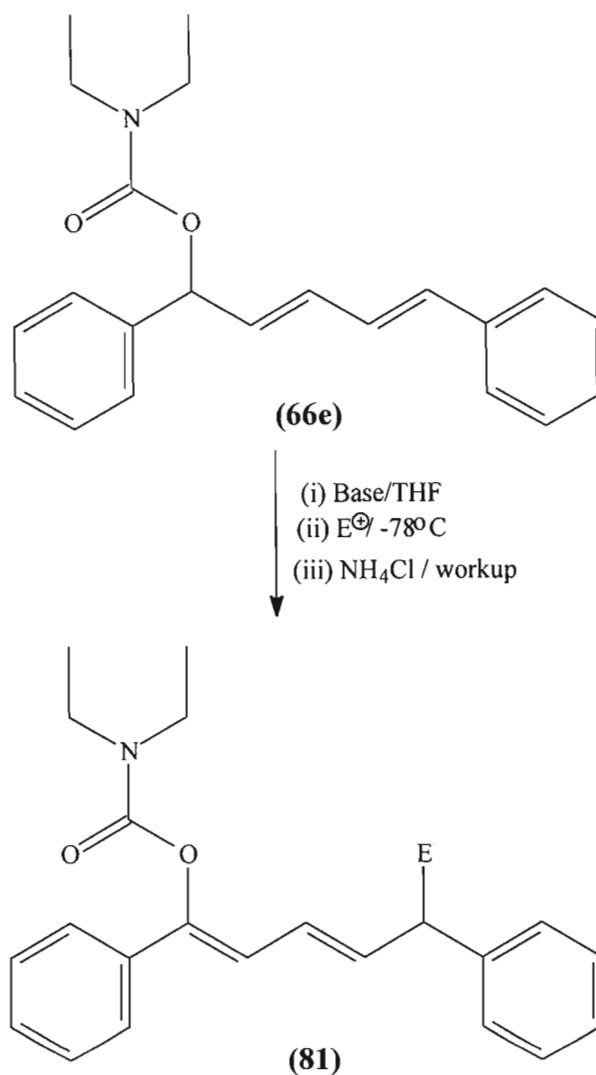
Scheme 52

Several attempts were made to substitute the carbamate with the electrophiles as used in the reactions in the previous section. No reaction resulted in the desired substitution product, in all instances starting materials were isolated. In the previous reactions LDA was generated *in situ* at 0°C then cooled to -78°C for the generation of the carbamate anion and addition of the electrophilic species. LDA and n-butyl lithium were used as bases in the reactions of 1-(*O*-N,N-diethylcarbamoyloxy)-1,5-diphenyl-2,4-pentadiene with the

electrophiles. Possibly LDA was too bulky to abstract the proton. This was not the case as the anion was generated when either base was employed. This was revealed by the immediate change in colour of the solution from orange to intense purple.

The reactions were carried out and quenched at -78°C without success. They were repeated but allowed to warm to room temperature prior to quenching, also without success. The reactions were quenched with water or methanol instead of ammonium chloride to no avail. The solvent was evaporated under reduced pressure without quenching the reaction prior to purification using chromatography. None of the variations in the procedure resulted in the substitution product being isolated.

As has been discussed in the electrophilic substitution reactions in sections 2.3.1 and 2.3.2, the steric interactions of the electrophile, the carbamate molecule and the alkyl groups attached to the nitrogen atom of the carbamate group itself all contribute to the success of the reaction. We suggest from the results of the reactions in this section that the carbanion does not delocalize under the reaction conditions used. This restriction of the lability of charge could be due to the fact that the lithium counter cation strongly chelates with the lone pairs on the carbonyl oxygen atom of the carbamate and the carbanion, restricting the delocalization to between the α- and the γ-carbon atoms, and so also supporting the idea of the six-membered transition state.

This argument does not explain the failure to isolate the γ-substituted methylated product. This product should have formed, the analogue to the product of the reaction of methyl iodide with 1-(O-N,N-diethylcarbamoyloxy)-1,3-diphenyl-2-propene, if the arguments used to explain the previous reactions hold true. We suggest that these arguments remain true for benzylic and allylic systems in which there is no conjugation in the alkyl chain. The failure to substitute in either of the γ- or the ξ-positions suggests that the preservation of conjugation within the molecule, even in the intermediate, prevents the electrophilic substitution from taking place.

2.4 NUCLEOPHILIC SUBSTITUTION REACTIONS

Serendipity has been defined as the "faculty of making happy discoveries by accident."[89] The method which had been employed to synthesise the carbamates in which the carbamate moiety occupies the benzylic position (section 2.2.3, p.46) proved fruitless in the synthesis of the symmetrical carbamates (82) and (83). These compounds are unstable, decomposing to the corresponding alcohol.

(82)

(83)
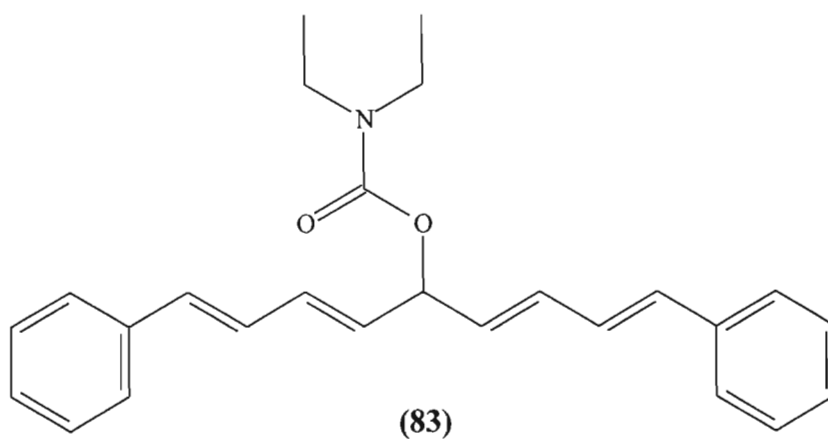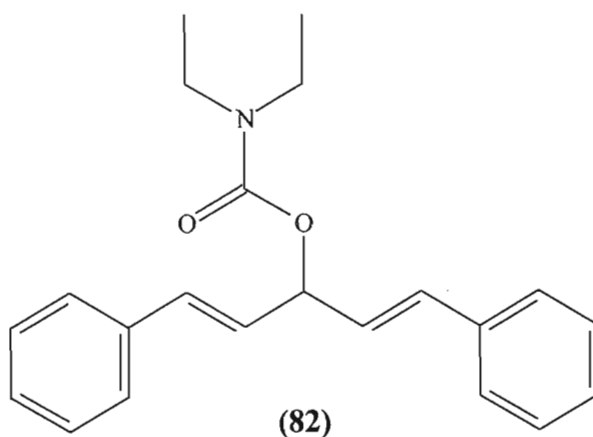
Hence, we attempted to synthesise 3-(*O*-N,N-diethylcarbamoyloxy)-1,5-diethyl-1,4-pentadiene (82) using DABCO as a base catalyst. Instead of isolating the carbamate (82), 1,5-diphenyl-1-methoxy-2,4-pentadiene (84) was obtained. As is the case with symmetrical conjugated diphenyl alcohols, the analogous symmetrical carbamates also appear to be unstable. 60MHz NMR spectra of the crude reaction mixtures suggested that the desired compounds were present, while TLC suggested that more than starting materials were present in the reaction vessel. This was true for all the attempted syntheses of the desired compounds. After purification by chromatography the original alcohol was isolated.

The reaction pathway of nucleophilic substitution involves the S_N2' elimination of the carbamate group with the simultaneous extension of conjugation providing the additional driving force for the reaction **(Scheme 53)**.

$$(i) \text{ DABCO/THF/N}_2$$
$$(ii) \text{ ClCONR}_2$$

$$(i) \text{ MeOH}$$
$$(ii) \text{ workup}$$

(84)
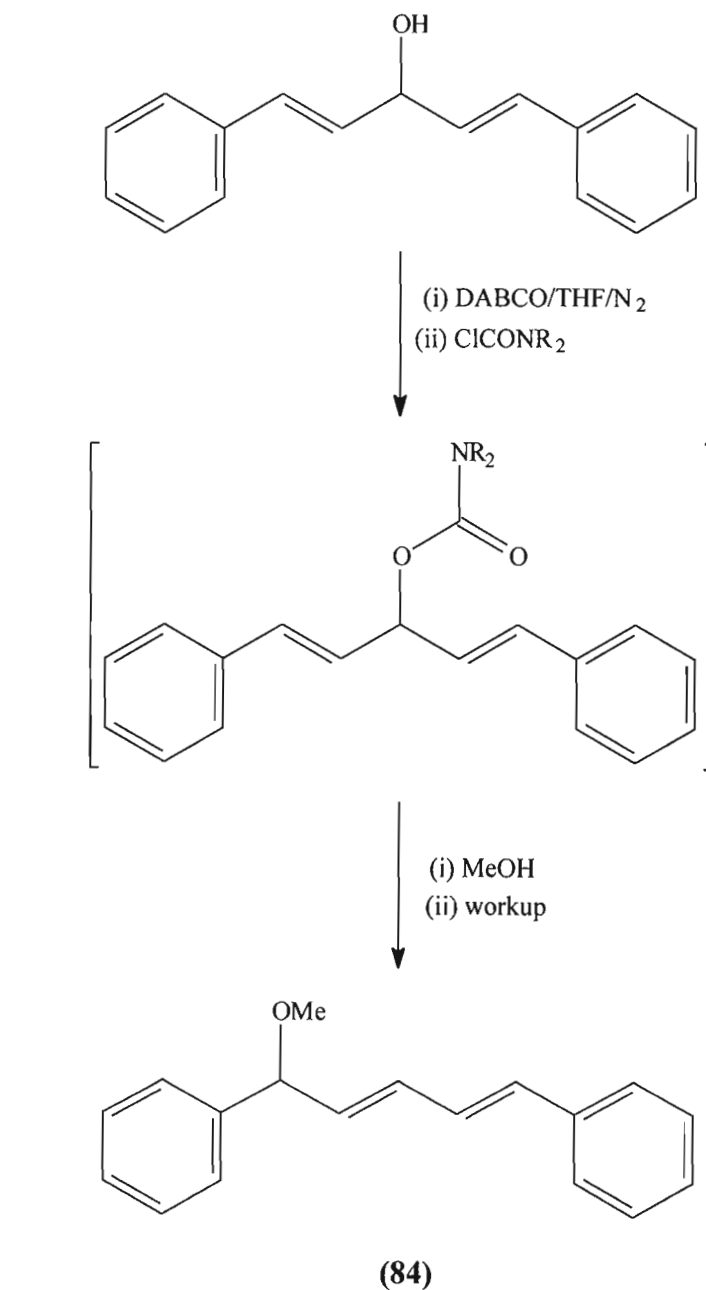
R = Me, Et

Scheme 53

Having postulated that the formation of the methyl ether proceeded *via* the S_N2' mechanism, we then carried out reactions with other nucleophiles and carbamates **(66b)**, **(66c)** and **(66e) (Table 9)**.

Table 9 : *Summary of reactions of nucleophiles with carbamates.*

CARBAMATE	NUCLEOPHILE	% YIELD
(66b)	MeOH	0
(66b)	PhO⁻	0
(66c)	PhOH	0
(66c)	PhO⁻	5.4
(66e)	MeOH	14
(66e)	PhO⁻	0
(66e)	H_2O	35
(66e)	$(^iPr)_2NH$	0
(66e)	$(MeO_2C)_2CH^-$	0
(66e)	EtO⁻	0
(66e)	$^iPrO^-$	0
(66e)	PhNH⁻	0
(66e)	Et_2N^-	0

The reaction of **(66b)** with nucleophiles resulted in no reaction, suggesting that the S_N2 mechanism of reaction is excluded. The reactions with the allylic **(66c)** and conjugated **(66e)** carbamates resulted in nucleophilic substitution reactions occurring with methanol, phenoxide anion and water **(Scheme 54)**. The yields of the reactions are generally low, probably due to steric factors and nucleophilicity. We see that the yields of reaction with oxygen nucleophiles decrease with increase in bulk and decrease in nucleophilicity. No nitrogen nucleophilic substitutions were successful. This might be considered surprising in that the carbon-nitrogen bond is stronger than the carbon-oxygen bond, which indeed did form under similar conditions.

n = 1, 2
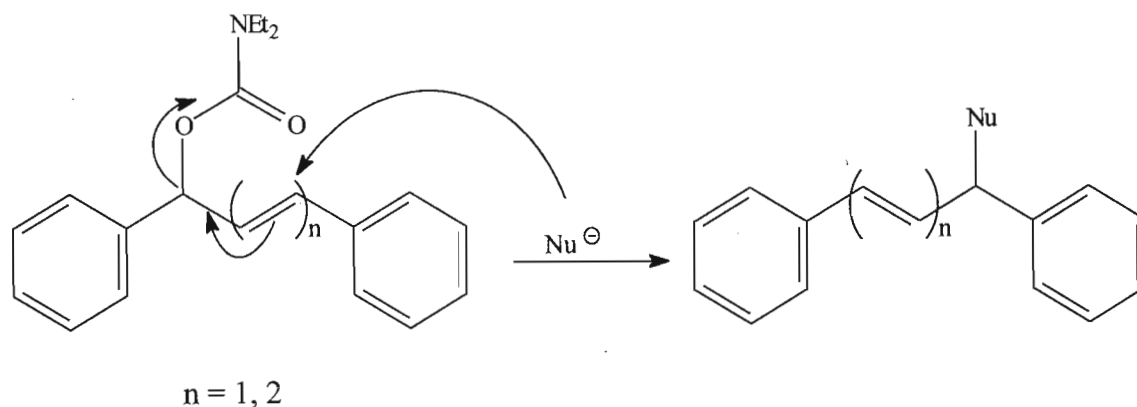
Scheme 54

Successful nucleophilic substitution reactions have been carried out with racemic 1,3-diphenyl acetate **(85)** using palladium catalysts[90] with a variety of ligands and dimethylsodiomalonate in THF under reflux. The (S)-enantiomer **(ent-86)** predominates. Similar reactions with bis(sulphone) afforded substitution products in excellent yields. The authors believe that the palladium catalyst chelates to the allylic acetate permitting the nucleophile to approach from only one side of the molecule, hence in addition to the excellent overall yield, they were able to introduce asymmetry into the product **(Scheme 55)**.

It is interesting to observe that the reactions carried out by these workers involve attack by nucleophiles of quite large size with the elimination of the acetate, which is a good leaving group. The dimethyl sodiomalonate nucleophile did not react successfully with the allylic carbamate **(66e)**, the carbamate being the good leaving group. We know that the carbamate undergoes S_N2' elimination reactions with nucleophiles. However, it could be that the bulk of the carbamate moiety prevents the nucleophile from approaching the site for attack. The use of palladium catalysts could introduce some interesting new chemistry of allylic carbamates in which further asymmetric induction reagents are revealed.
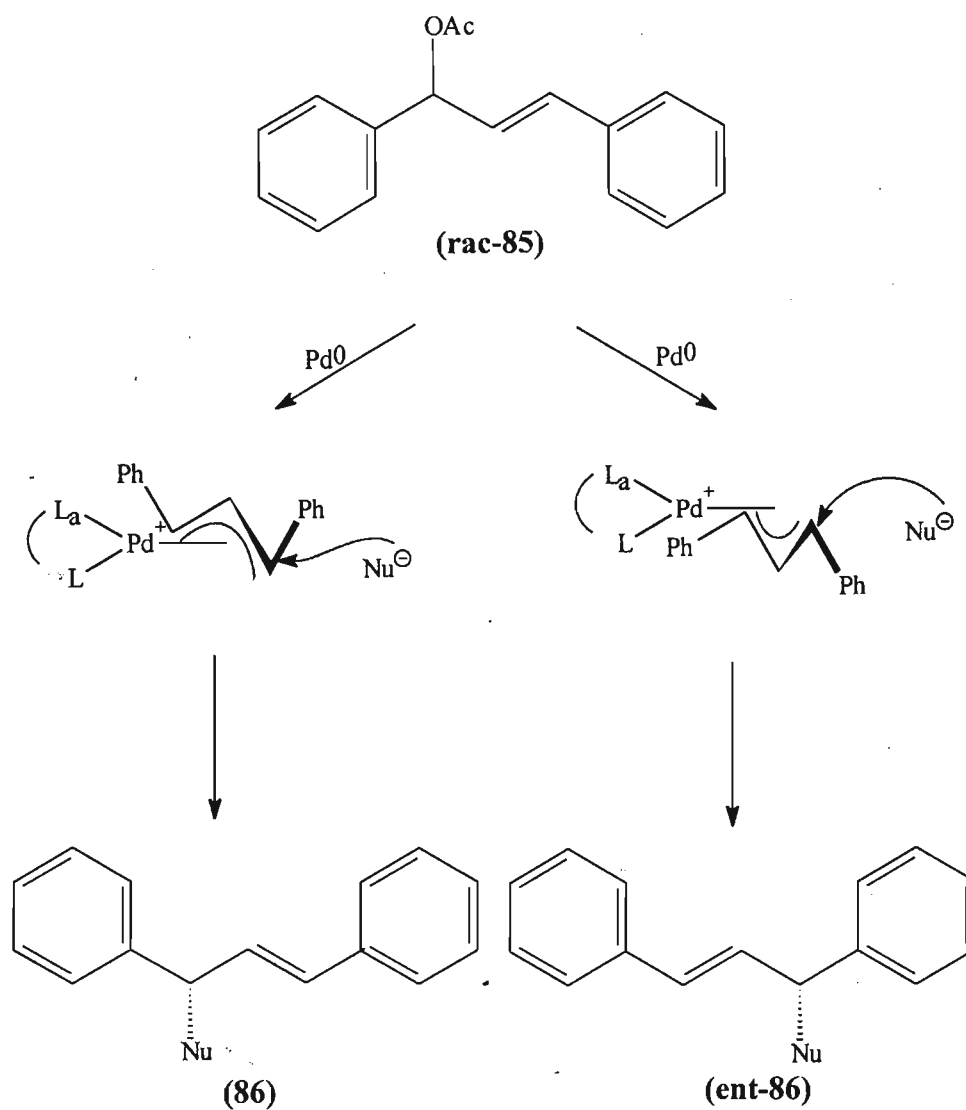
Scheme 55

2.4.1 ATTEMPTED REARRANGEMENTS OF ALLYL PHENYL ETHERS

1,3-Diphenyl-1-phenoxy-2-propene **(87)** is an allyl vinyl ether. It was decided to investigate whether this compound could undergo the Claisen rearrangement, and in so doing provide a new route to substituted phenols **(88)** **(Scheme 56)**.
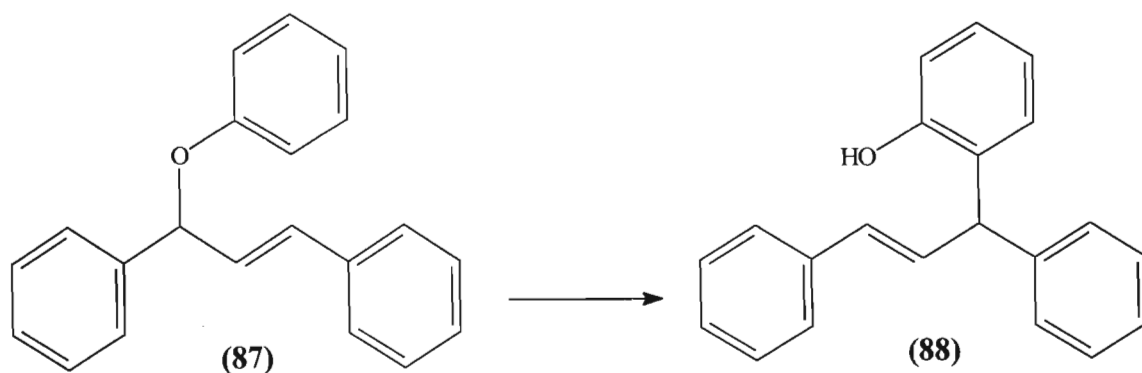
Scheme 56

It had been found in previous studies of the rearrangements of β-alkylallyl aryl ethers[91] and the *ortho*-Claisen rearrangement of cinnamyl *p*-tolyl ethers[92] that the rate of reaction is not influenced significantly by the substituents in the β-position. Allyl-, β-methylallyl- and *t*-butyl allyl phenyl and *p*-methoxyphenyl ethers underwent the Claisen rearrangement in yields of 44% to 56% **(Scheme 57)**.

R = H, Me, ^{t}Bu

X = H, OMe
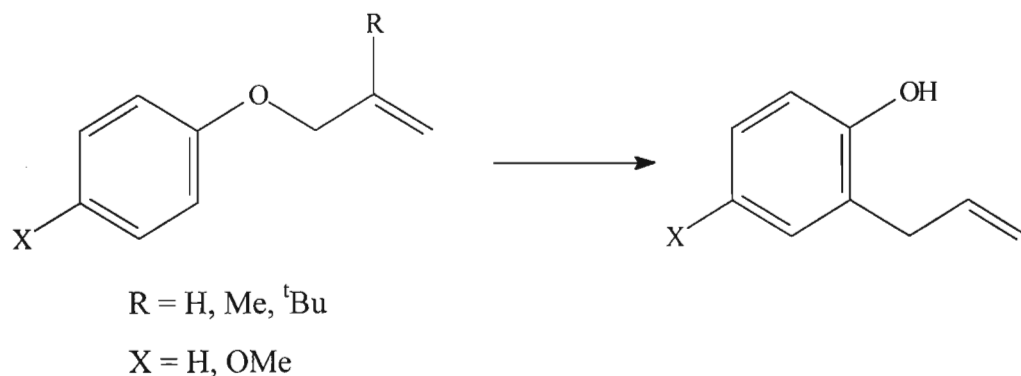
Scheme 57

It was suggested by White and Fife[91] that the α- and γ-allyl substituents do influence the rate of rearrangement. The rearrangement reactions of a variety of *m*- and *p*-X-cinnamyl-*p*-Y-phenyl ethers were studied in which X was an activating or deactivating group while Y in most cases was methyl. Yields on the whole were very high **(Scheme 58)**. Reactions were carried out in Carbitol solution (diethylene glycol monoethyl ether) at 150°C and separated in a mixture of 1:99 methanol : ether on alumina.
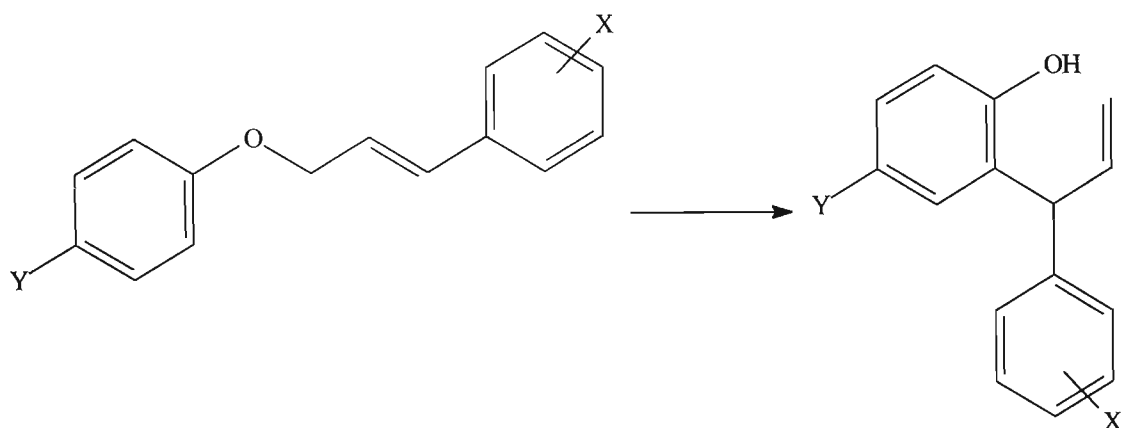
X = H, *m*-Cl, *p*-Cl, *m*-Me, *p*-Me, *m*-OMe, *p*-OMe

m-CN, *p*-CN, *m*-NO$_2$, *p*-NO$_2$.

Y = H, *p*-Me, *p*-OMe

Scheme 58

Reaction of sodium phenoxide with the carbamate **(66c)** resulted in the formation of the allyl aryl ether **(87)**. Several attempts were made to force the rearrangement of **(87)** to take place. Neither refluxing the isolated ether in toluene nor in diglyme under a nitrogen atmosphere in an autoclave promoted the rearrangement. The failure of this reaction supports the findings of White and Fife,[91] who suggest that the rearrangement is enhanced by electron donating groups in both the allyl and phenyl group of the allyl phenyl ether. We tried to force the rearrangement of a compound containing a resonance stabilising phenyl group in the γ-position of the allyl group of the ether.

Attempts to obtain the Claisen rearrangement product of the 1,5-diphenyl-1-phenoxy-2,4-pentadiene allyl vinyl ether were unsuccessful. The substituent in the γ-position being in conjugation with the 5-phenyl ring is even more likely to prevent the rearrangement from occurring than in the rearrangement of **(87)**. In addition, the conjugation of the alkyl chain offers the molecule overall stability; as we have already discussed, the maintenance of this conjugation in these molecules has proved to be extremely difficult to overcome.

2.4.2   ISOLATION OF 1-(N,N-DIMETHYLAMINO)-1,3-DIPHENYL-2-PROPENE (90)

We wished to investigate the influence of the alkyl groups attached to the nitrogen atom of the carbamate group on the electrophilic substitutions in order to vindicate our hypotheses regarding the importance of the steric hindrances of the substituents. In an attempt to prepare 1-(*O*-N,N-dimethylcarbamoyloxy)-1,3-diphenyl-2-propene (89) we unexpectedly isolated 1-(N,N-dimethylamino)-1,3-diphenyl-2-propene (90). The reaction was carried out as in the preparation of the analogous diethyl carbamate (66c) (Section 2.2.3, p.46).

TLC revealed that the desired carbamate was present in the reaction mixture prior to purification by distillation. It has been mentioned that N,N-disubstituted carbamates do not usually decompose on heating.[12]   In carrying out this distillation the carbamate decomposed to afford the allylic amine (90). The mechanism of reaction proposed involves the concerted attack of the allylic position by the lone pairs on the nitrogen atom of the carbamate with simultaneous S_N2' elimination of the carbamate group and evolution of CO_2, the liberation of the gas and the formation of the strong carbon-nitrogen bond probably being the driving forces of the reaction (Scheme 59).

This reaction strongly supports the belief that steric factors are central to the success of the reactions attempted in this work.   In an earlier reaction, diethylamine was reacted with sodium hydride prior to the addition of the carbamate (66c) (Section 2.4, p.66).   This was done to generate a strongly nucleophilic nitrogen species to facilitate the S_N2' elimination of the carbamate group. The reaction did not render the desired allylic amine. We would expect that the nucleophile generated in this reaction is stronger than the amine portion of the dimethyl carbamate (89).   The weaker nucleophile was able to partake in reaction because the lone pair orbital on the nitrogen atom was able to approach the γ-carbon atom more closely than the bulkier diethylamine anion.   Were steric factors not so important, the reaction with diethylamine would probably have proceeded as expected in the nucleophilic substitution reaction.
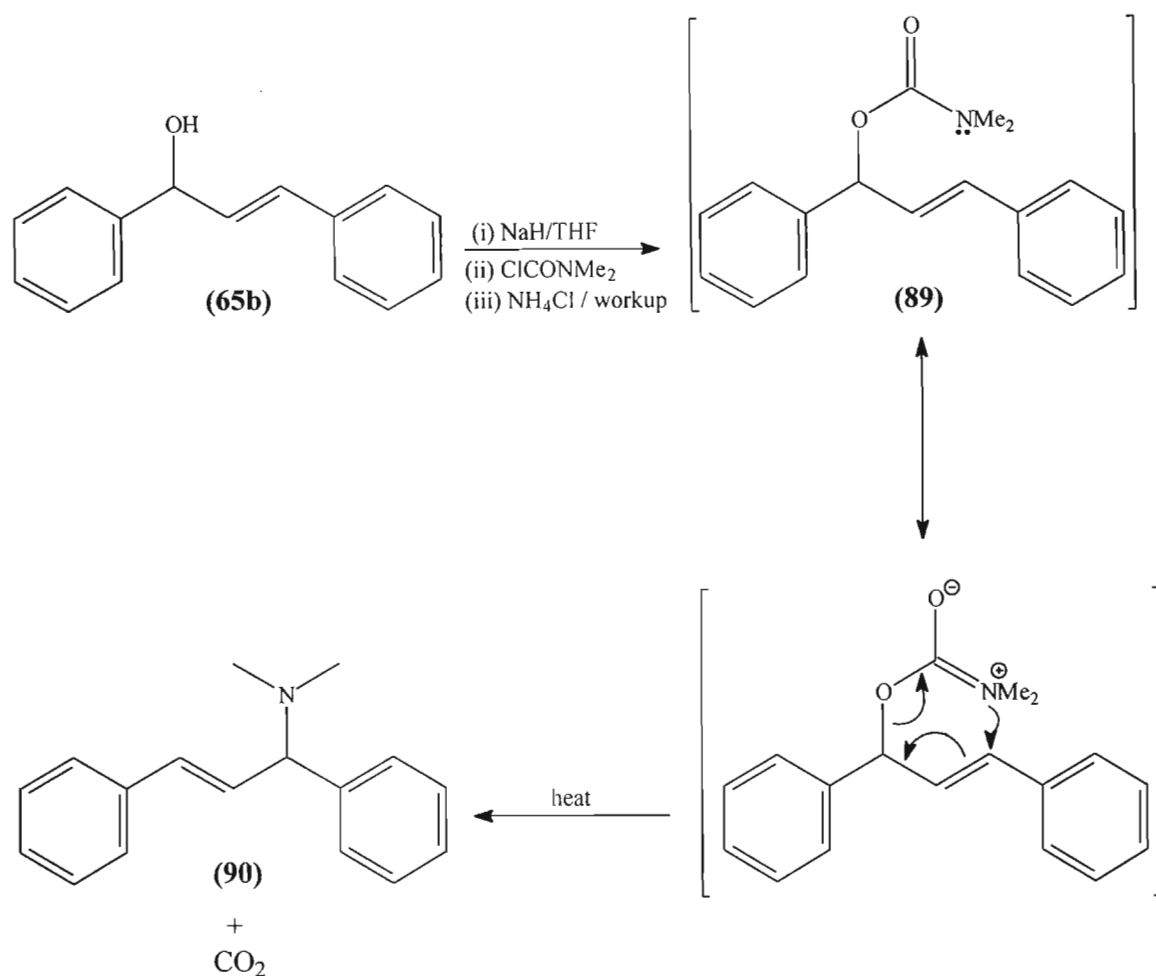
Scheme 59

A study of the proton NMR spectra of the dimethyl carbamates **(66b)**, **(71a)**, **(71c)** and **(71f)** shows that the methyl groups have different chemical shifts, two singlets arising as a result. The different environments arise due to the existence of two resonance structures. As a result, the partial delocalization of π-electrons throughout the amide portion of the carbamate group **(91)** effectively hinders the free rotation about the bond between the carbonyl carbon and the nitrogen atom and renders the group planar. Hence, the methyl groups experience different shielding effects from their environments. However, the ^{1}H NMR spectrum of the allylic amine **(90)** contains a singlet corresponding to the two methyl groups. This indicates that the methyl groups experience the same environment and so there is no restriction to free rotation about the carbon - nitrogen bond.

(91)
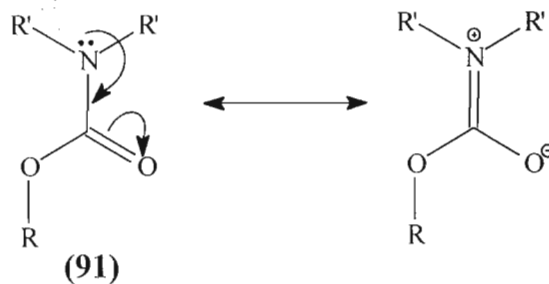
R = Me, Et, ^{i}Pr

R' = allyl alkyl

Similar attempts to produce the allylic amines of **(66c)**, **(66d)** and **(66e)** were unsuccessful. It appears that the carbamates with the larger alkyl groups are more stable to heat in that they neither decompose on distillation nor do they rearrange. It could be that the alkyl groups on these carbamates are too large to allow the nitrogen lone pair orbital to overlap the allylic carbon in a way which promotes the rearrangement. In the case of the diene carbamate **(66e)**, additional resistance to rearrangement is offered by the stability of extended conjugation of the molecule.

2.4.3   ATTEMPTED ROUTES TO 2-PHENYL-2*H*-1-BENZOPYRAN **(92)**

The syntheses of substituted chromenes and coumarins by Janse van Rensburg[75] exploited the migrational and leaving group abilities of the carbamate group (Scheme 35, p.35). It was believed that the 1,3-diphenyl-2-propene carbamate compounds could provide a new route to 2-phenyl-2*H*-1-benzopyran **(92)**, also called Δ^3-flavene, by exploiting these same properties of the carbamate functional group. Three avenues were investigated.

The shortest synthesis of the target molecule appeared to be from the reduced Aldol condensation product of 2'-*O*-carbamoyloxyacetophenone and benzaldehyde **(93)** (**Scheme 60**).

Scheme 60
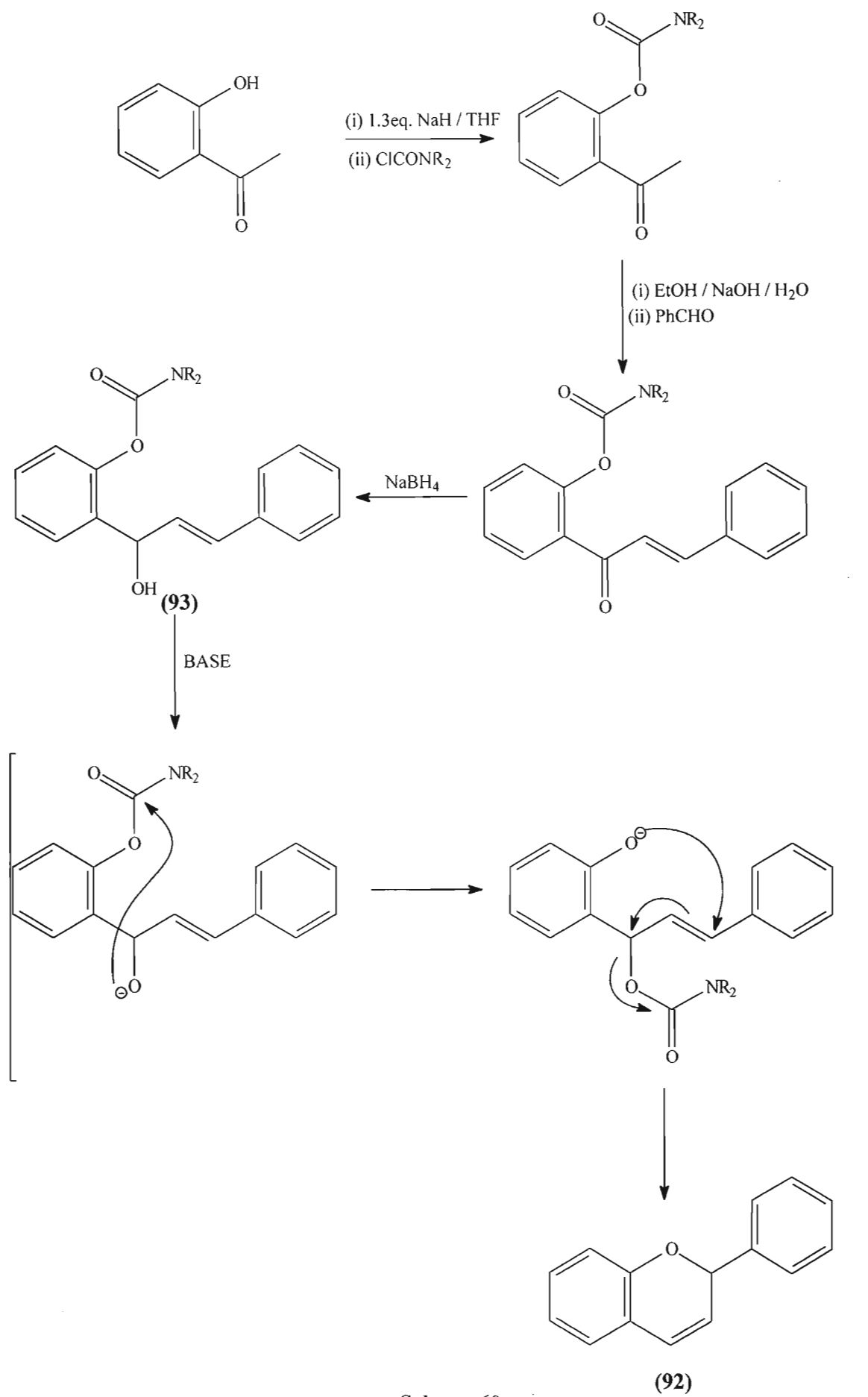
Attempts to synthesise the 2'-(*O*-dialkylcarbamoyloxy)acetophenone did not result in either the dimethyl or the diethyl carbamate when 2'-hydroxyacetophenone was reacted with the respective carbamoyl chloride. The reaction resulted in a complex mixture. Janse van Rensburg[75] succeeded in abstracting the phenolic proton of salicylaldehyde using triethylamine in the synthesis of *O*-N,N-dimethylcarbamoyloxybenzaldehyde. Thus to overcome the problems encountered with sodium hydride, and apply Janse van Rensburg's method to 2'-hydroxyacetophenone, we decided to attempt the reaction with triethylamine as base in dichloromethane. In addition, triethylamine does not pose the problem of paraffin impurity in the reaction mixture associated with sodium hydride. Unfortunately, this method was also to no avail. An alternative route was then sought to synthesise allylic alcohol **(93)**.

2'-hydroxyacetophenone was protected as 2-(acetophenyl) benzoate[93] **(94)**. The base employed in the preparation was triethylamine, and the yield of the reaction was good. Having synthesised this protected species, it was thought that the Aldol condensation with benzaldehyde could now be achieved. Thereafter the protecting group could be removed and then the carbamate group could be added prior to reduction with sodium borohydride to afford **(93) (Scheme 61)**.

Attempts to perform the Aldol condensation afforded a dark orange liquid, which proved to be a complex mixture of products. There could be an element of competition between the Aldol reaction with benzaldehyde and self-aldol reaction with the ketone carbonyl group of the protected ketone **(94)**. However, neither product could be isolated.

The protection of the carbonyl as the ketal and then reaction with carbamoyl chloride to obtain the desired carbamate after deprotection is a further avenue which should be explored. This approach might overcome the problems encountered in the Aldol condensation routes performed in this work.
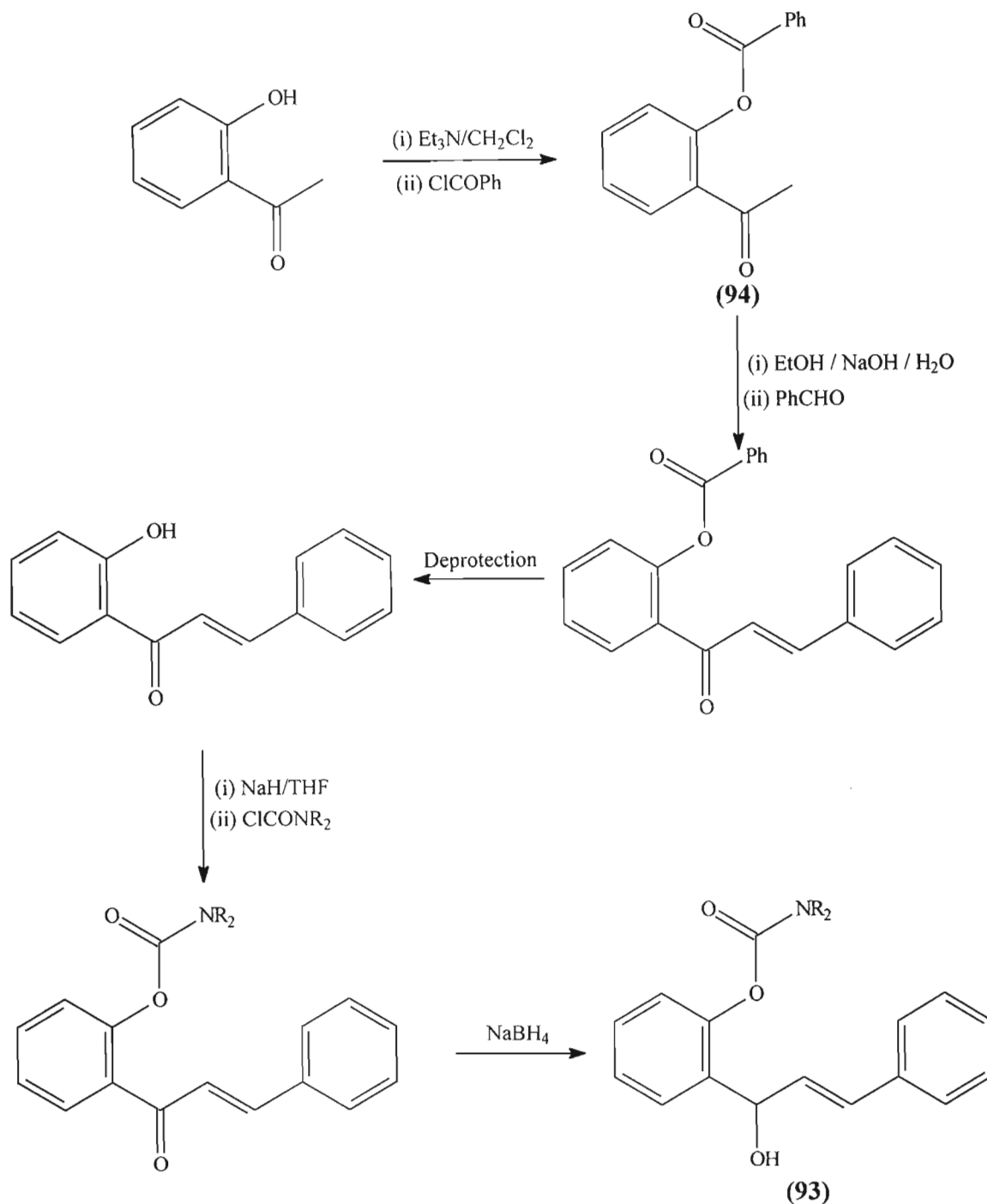
Scheme 61

The third route to **(93)** involved the Grignard reaction of *O*-N,N-dimethylcarbamoyloxybenzaldehyde **(95)** with 2-phenylethenyl magnesium bromide **(96)**. 2'-bromostyrene **(99)**[94] was synthesised by the dehydrohalogenation of 2,3-dibromo-3-phenylpropanoic acid **(98)** which in turn was formed by the bromination of *trans*-cinnamic acid **(97)** **(Scheme 62)**. The Grignard reagent was generated *in situ* from 2'-bromostyrene and magnesium turnings.
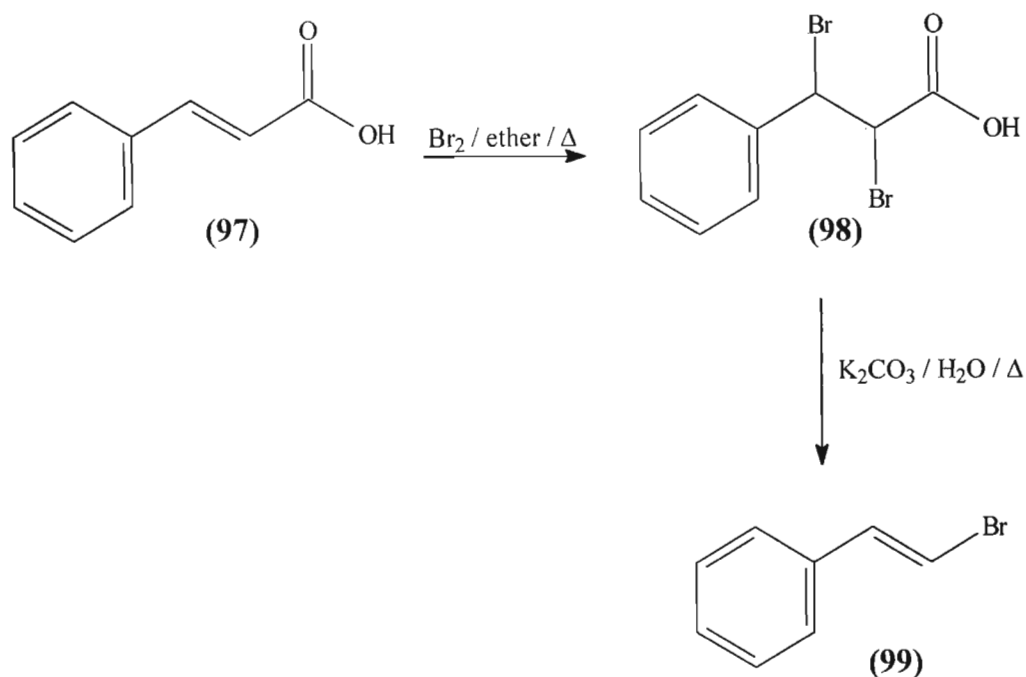
Scheme 62

An earlier method of synthesis of β-chlorostyrene involves the bubbling of chlorine gas through a solution of carbon disulphide and cinnamic acid.[95] An adaptation of this method yields a mixture of *cis*- and *trans*-isomers (*ca.* 70% *trans*).[96] In order to increase the amount of *trans* isomer, this mixture was refluxed in a sodium hydroxide/2-propanol solution before treatment with cold water. This method yielded 97% trans-β-bromostyrene.[96] The procedure which we used does not differ much from those previously accomplished. The main difference is the base utilised. Under strongly alkaline conditions the reaction of 2,3-dibromocinnamic acid leads primarily to 2-bromocinnamic acid. When no base is used or the base is carbonate in aqueous solution, the elimination of CO_2 occurs subsequent to the loss of the benzylic bromine atom yielding a *cis/trans* mixture of 2'-bromostyrene. In acetone, the carbonate reaction results in only the *cis* product.[94]

For the purposes of our reaction it was not necessary to purify the mixture. From ^{1}H NMR it was established that the mixture contained 72% *trans*-2'-bromostyrene.

First attempts at the Grignard reaction failed in ether. Vinyl bromide does not undergo the Grignard reaction readily in ether, but has been successfully carried out in dry THF.[97]

2'-bromostyrene is a substituted vinyl bromide, therefore we attempted the Grignard reaction in dry THF with freshly acid washed and dried magnesium turnings. The Grignard reagent was generated and O-N,N-dimethylcarbamoyloxybenzaldehyde (95) was then added. The reaction was refluxed overnight. Three products were possible, namely the expected Grignard allylic alcohol (100), the carbamate migration product (101), and the desired benzopyran (92) (Scheme 63).
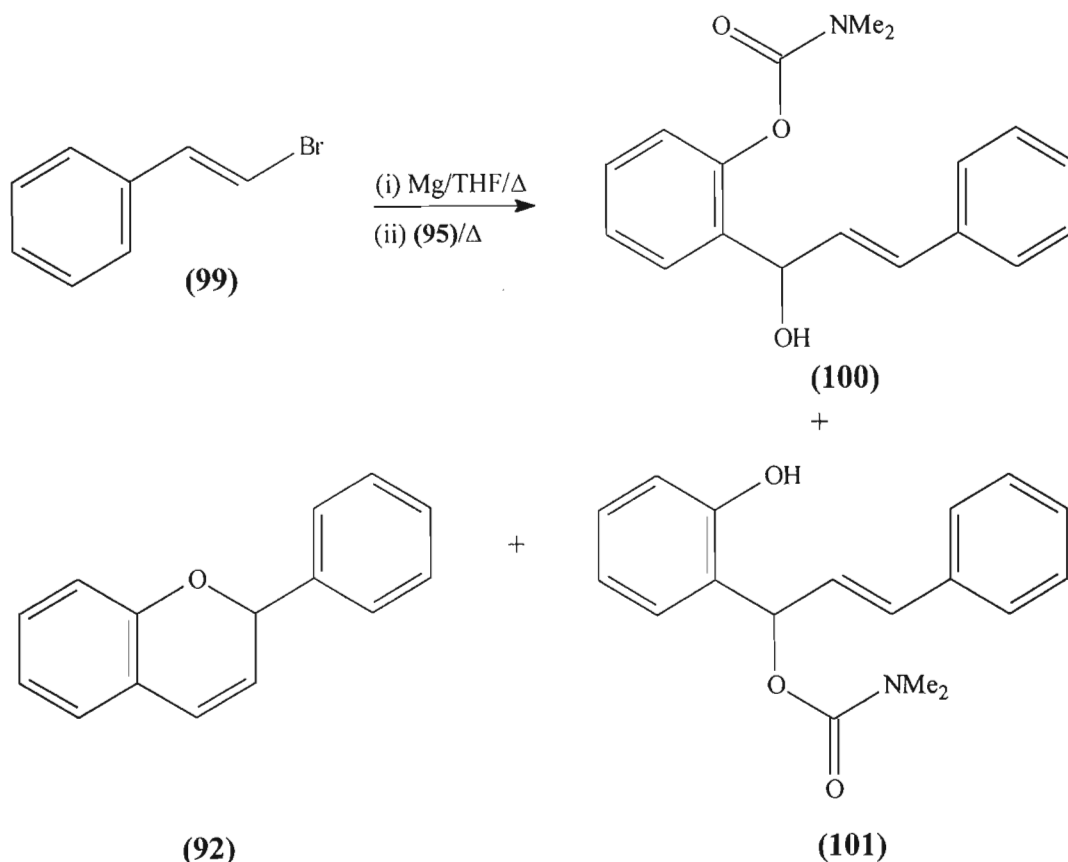
Scheme 63

The products would provide insight into the stability of the intermediates and the rates of migration and elimination of the carbamate group. If (100) predominated it would imply that the rate of protonation of the allyl oxoanion is faster than the migration of the amide. Isolation of predominantly compound (101) would indicate the preference for the more stable phenoxide anion intermediate, the formation of this anion promoting the migration of the amide. If the target molecule (92) predominates then the driving force of the reaction would be the migration and subsequent S_N2' elimination of the carbamate.

None of the above expected products was isolated. Instead, the reaction became a brown, ill-defined mixture of compounds. Grignard reactions with vinyl bromide species often do not proceed with the same ease as with other bromo compounds.[97] The formation of allylic alcohols by reacting 2'-bromostyrene with benzaldehyde have been successfully achieved in excellent yields and with retention of stereochemistry. When (*E*)-2'-bromostyrene is the used as starting compound, the *trans*-1,3-diphenyl-2-propen-1-ol is the resulting product.

Neumann and Seebach[98] treated one equivalent of vinyl bromide with two equivalents of *tertiary* butyl lithium at -120°C and stirred at this temperature for two hours before adding the benzaldehyde (**Scheme 64**). Yields : (*E*)-isomer = 71%; (*Z*)-isomer = 81%.
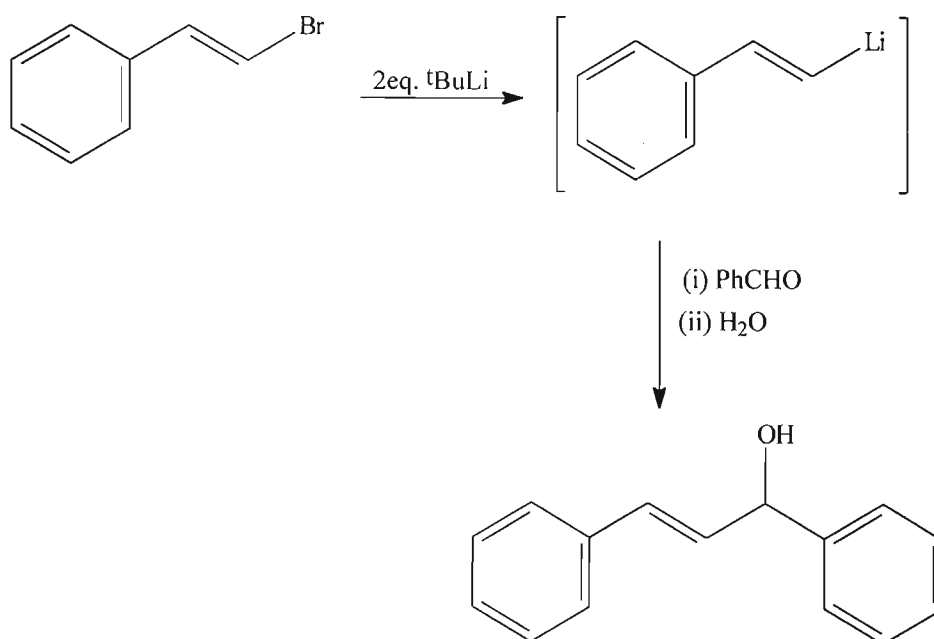
Scheme 64

Further work in the synthesis of allylic alcohols from alkenyl metal compounds was carried out by Takai and co-workers[99](**Scheme 65**). They isolated allylic alcohols from the reactions of vinyl iodides and bromides with carbonyl compounds using $CrCl_2$ in dimethylformamide at room temperature. Yields : (*E*)-isomer = 82%, (*Z*)-isomer = 78%. The authors specifically state that the reaction does not proceed successfully when the chromium reagent is prepared from $CrCl_3$-$LiAlH_4$ and that the reaction does not work in THF. We therefore did not reduce $CrCl_3$ using $LiAlH_4$ and attempt the reaction.
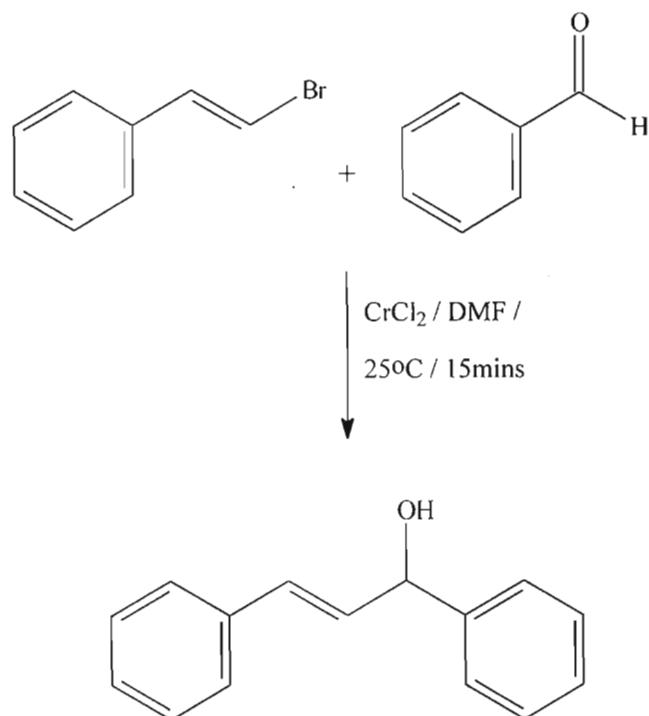
Scheme 65

These two methods were not examined in the reaction of benzaldehyde with 2-(*O*-N,N-dimethylcarbamoyloxy) benzaldehyde due to time constraints and non-availability of the reagents. These methods remain for exploitation in future attempts to produce benzopyrans *via* carbamoylated allylic alcohols like **(93)**.

Benzopyran **(92)** has been prepared by the dehydrogenation of *O*-cinnamylphenol **(102)** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[100] **(Scheme 66)**. The 2-phenyl-2*H*-1-benzopyran was obtained in 40% yield after chromatography through silica gel eluting with hexane. Other substituted flav-3-enes were obtained but in yields of 15-20%.

(102)   **(92)**
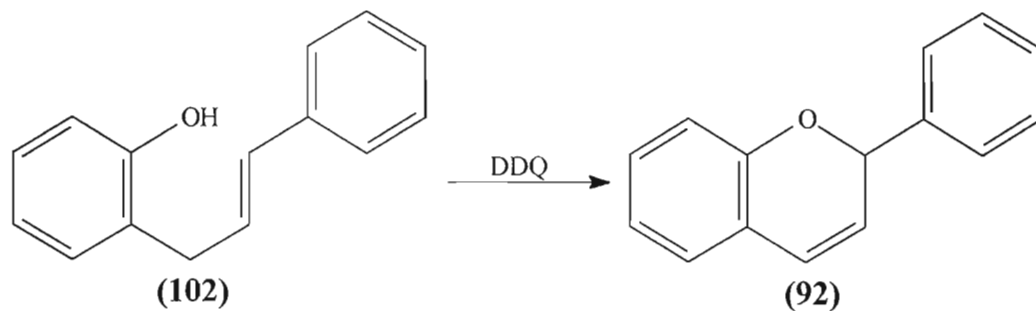
Scheme 66

Target molecule (92) has been elegantly prepared from Δ^2-chromene (103) in excellent yield.[101] The reaction path is outlined in **Scheme 67**.
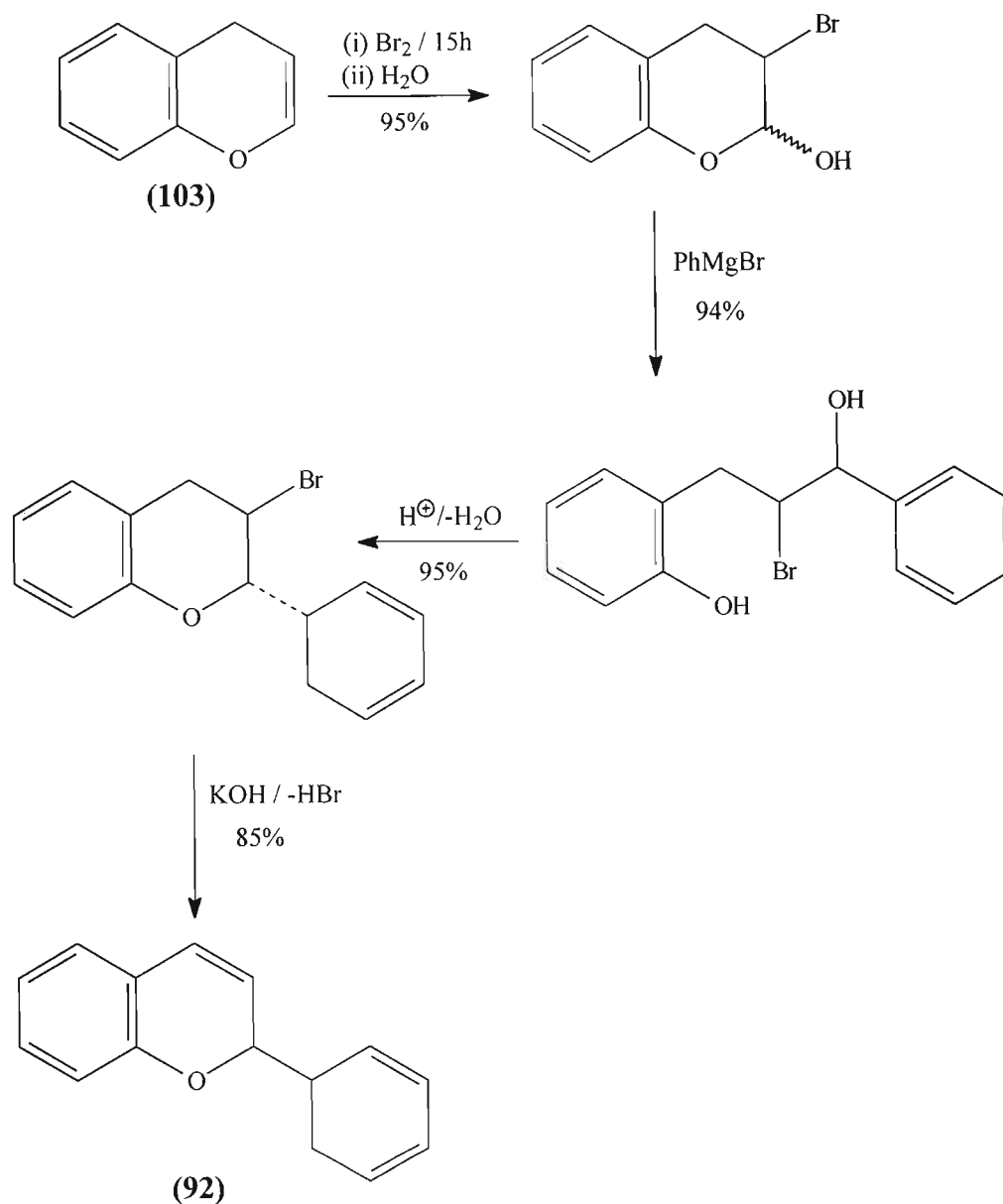
Scheme 67

When comparing the work of Janse van Rensburg[75] (Section 1.6.2.3, p.34) in the synthesis of substituted chromenes (48), we see that the nucleophilic attack takes place at a terminal double bond, where the electrophilicity is enhanced by the presence of the methyl ester in the 2-position. In the system we attempted to cyclize by exploiting the findings in his work, the phenyl group occupies the 3-position and may hinder the attack both sterically and electronically.

2.6 CONCLUSIONS

The following conclusions can be drawn from this work :

1. Unsymmetrical α,ω-diphenyl carbamates in which the carbamate group occupies one of the benzylic positions are more stable than the symmetrical α,ω-diphenyl carbamates.

2. 1-(O-N,N-dimethylcarbamoyloxy)-1,1-diphenylmethane and 1-(O-N,N-diethyl-carbamoyl-oxy)-1,3-diphenyl-2-propene undergo electrophilic substitution reactions. The success of the reaction is determined by the steric hindrance offered by the alkyl substituents on the carbamate group and the bulk of the incoming electrophile.

3. Electrophilic substitution of 1-(O-N,N-dimethylcarbamoyloxy)-1,1-diphenylmethanol takes place at the α-position to the carbamate, not on the phenyl rings. Nucleophilic substitution does not occur. This supports the hypothesis that the carbamate group is not eliminated by the S_N2 mechanism.

4. Electrophilic substitution of 1-(O-N,N-diethylcarbamoyloxy)-1,3-diphenyl-2-propene occurred in the γ-position only with methyl iodide. Larger electrophiles were unsuccessfully reacted. This finding vindicates conclusion 2. Nucleophilic substitutions occur at the γ-position with the elimination of the carbamate group, we propose the S_N2' mechanism. 1-(O-N,N-diethylcarbamoyloxy)- and 1-(O-N,N-diisopropylcarbamoyloxy)-1,3-diphenyl-2-propene are more heat stable than 1-(O-N,N-dimethylcarbamoyloxy)-1,3-diphenyl-2-propene which rearranges to 1-(N,N-dimethylamino)-1,3-diphenyl-2-propene on heating.

5. Electrophilic substitution reactions did not take place with more highly conjugated carbamates. We propose that the carbanion is not delocalized but held by the lithium counter cation between the α- and γ-positions. Conjugation in the diene offers the molecule additional stability against attack by electrophiles. Nucleophilic substitution reactions did occur at the benzylic ξ-position with the elimination of the carbamate group, supporting the idea that maximum conjugation is favoured by the molecule.

2.7   PROPOSED FUTURE WORK

The route to benzopyrans like compound (92) can be explored using carbamates. Firstly, the untried methods discussed for the formation of the allylic alcohol (93) require application. If (93) is isolated then the acidic proton of the alcohol can be formally removed to facilitate the migration of the carbamate. Secondly, the formation of the Δ^3-flavenes can be examined *via* the formation of chromenes from allylic carbamates, as Janse van Rensburg achieved, with subsequent treatment as discussed in the previous section (Scheme 67). The effect of substituents on the progress of the reactions could be established. If α,ω-diphenyl allylic carbamates offer a route to a variety of flav-3-enes, they could provide exciting new precursors to the synthesis of flavonoids and related compounds.

The extension of the electrophilic substitution reactions to longer chain polyenes seems to require modification to the procedures employed in this work. The use of lithium bases to abstract the acidic proton, although effective in the generation of the homoenolate anion equivalent, seem to prevent the delocalization of the carbanion beyond the γ-position. If the carbanion can be generated using another reagent this problem might be overcome.

The additional problem of the steric interference of the alkyl groups on the carbamate functional group could be overcome by using N-alkyl substituted carbamates instead of N,N-dialkyl substituted carbamates. Many of the reactions, both nucleophilic and electrophilic substitution reactions, which failed to result in the expected products might be successful using smaller carbamates.

We need to remove the carbamate group after electrophilic substitution in an attempt to synthesise asymmetric allylic alcohols as performed by Barner and Mani[65] in their studies of the benzylic carbamate. The reaction of 1-(*O*-N,N-dimethylcarbamoyloxy)-1,1-diphenylmethane (66b) with cinnamaldehyde should be extended. This reaction could offer a route to substituted unreactive α,ω-diphenylpolyenes (61).

The effect of the end groups and substituents within the polyene chain require investigation. Could a cyano group in the chain perhaps attract the carbanion past the γ-position and promote more remote functionalization of the carbamate? The effect of the nature and position of electron withdrawing and donor groups might have a bearing on the outcome of the reactions. Some correlation might become apparent between the position of substitution and the effectiveness of the polyene as non-linear conductor.

The reaction of palladium catalysts with allylic carbamates can be compared with the acetate analogues. These reactions may assist in the stereospecific functionalization of allylic carbamates with nucleophiles, as well as providing a possible solution to the steric problem encountered in our work.

The carbamate group has been utilised in the synthesis of several natural products and pharmaceutically active compounds. The work carried out in this study could be applied, although to a limited extent, in the electrophilic and nucleophilic functionalization of such compounds as Vitamin A$_1$ (retinol) (104)[102] and Vitamin A$_2$ (dehydroretinol) (105). The synthesis and functionalization of polyenes such as Rapamycin (106)[82j] and Roxaticin (107)[83d] are a challenge to the synthetic organic chemist. The carbamate group could be found to be a useful tool in such reactions.

(104)

(105)

(106)

(107)
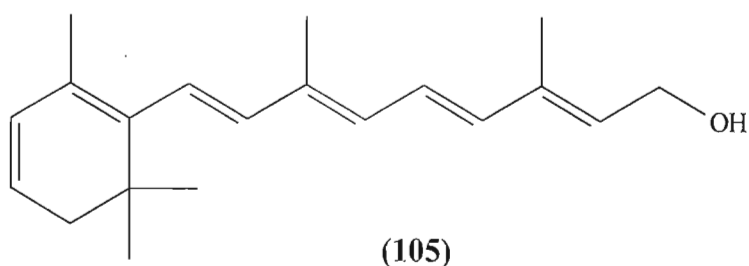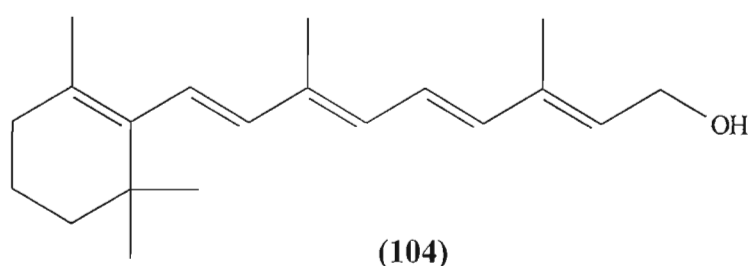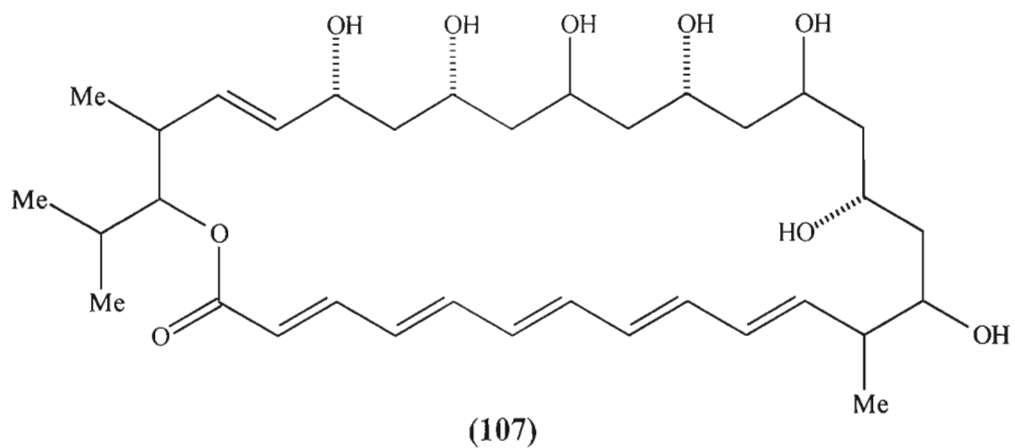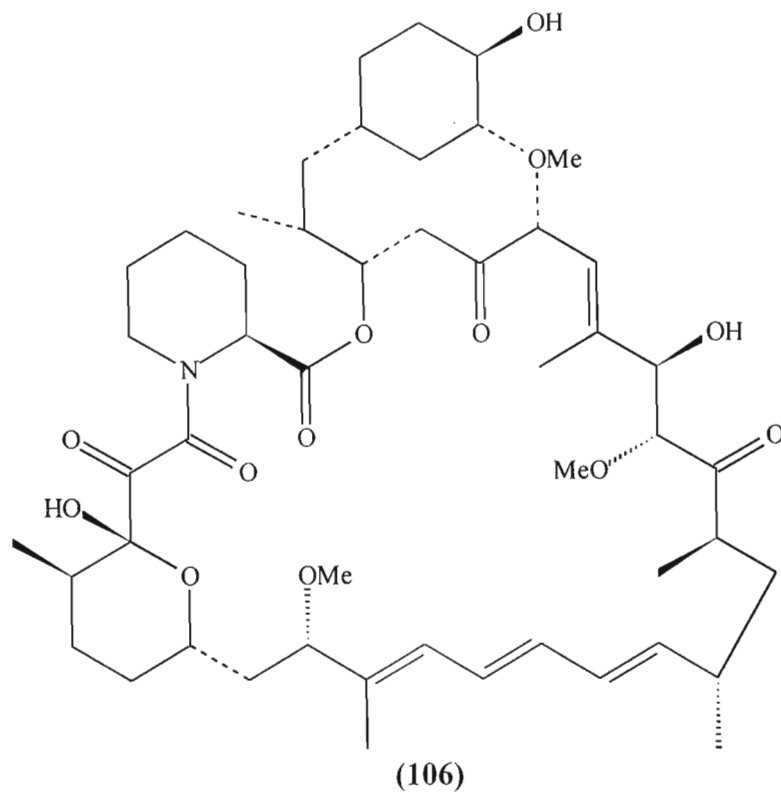
The carbamate group exhibits several properties which enable its use in synthetic organic chemistry. This functional group has been exploited in a variety of syntheses; but many years of research work awaits us to establish the wider, largely unthought of, scope of applicability of the versatile carbamate group in synthetic organic chemistry.

CHAPTER 3 : EXPERIMENTAL

3.1 CHEMICALS AND INSTRUMENTATION

All solvents were distilled according to standard procedures before use.[103] Flash column chromatography was performed using Merck silica gel (200-400 mesh) by the technique of Still *et al.*[104] Pre-coated Kieselgel 60 F_{254} Merck plastic sheets were used for thin-layer chromatography. Centrifugal chromatography was carried out using a Harrison Research Chromatotron Model 7924T on 4mm Merck silica gel (200-400mesh) coated glass plates. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra (^{1}H 200MHz and ^{13}C 50MHz) were recorded on a Varian Gemini 200 instrument and a Varian T60 (^{1}H 60MHz) instrument. All chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard, using $CDCl_3$ as solvent, unless otherwise stated. Mass spectra were recorded on a Hewlett-Packard mass spectrometer (HP5988A). Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyser.

3.2   PREPARATION OF KETONES

(E)-3-(4-Nitrophenyl)-1-phenyl-2-propen-1-one **(63a)**

4-Nitrobenzaldehyde (10.01 g, 66.3 mmol) and acetophenone (7.20 g, 60.0 mmol) were dissolved in ethanol (200 ml) and cooled to 0°C. 10% Aqueous sodium hydroxide (100 ml) was then added slowly. The solution soon turned pink and shortly thereafter dark brown. The reaction was allowed to stir at room temperature for 2 h. The pale white crystals were then filtered. The filtrate was recrystallized first from ethyl acetate and then from ethanol to afford white crystals of (E)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one. (14.32 g, 94.3%) m.p. 148°C. (Found : C, 71.03%; H, 4.52; N, 5.49; $C_{15}H_{11}NO_3$ requires C, 71.15; H, 4.35; N, 5.53); δ_H (200 MHz) : 7.488 - 7.672 (3H, m, Ar-*H*), 7.655 (1H, d, Ar-C*H*), 7.769 - 7.826 (2H, m, Ar-*H*), 7.830 (1H, d, O=C-C*H*), 8.044 (2H, d, Ar-*H*), 8.275 (2H, d, Ar-*H*); δ_C (50 MHz) : 124.201 (d, Ar-*C*), 125.669 (d, Ar-CH=*C*H), 128.519 (d, Ar-*C*), 128.687 (s, Ar-*C*), 128.816, 128.914, 133.374 (3 x d, Ar-*C*), 137.497 (s, Ar-*C*), 141.022 (s, Ar-*C*-NO₂), 141.496 (d, Ar-*C*H=CH), 189.614 (s, *C*=O); *m/z* : 253 (M⁺, 19%), 207 (14), 176 (12), 105 (82), 102 (27), 90 (8), 77 (100), 51 (32).
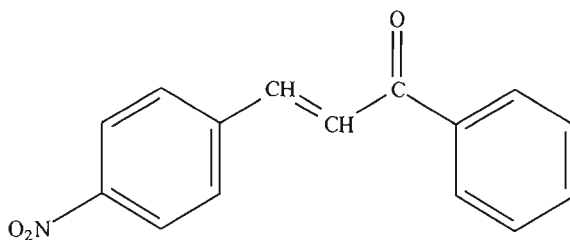
(63a)

(E,E)-1,5-Diphenyl-2,4-pentadien-1-one **(63b)**

Cinnamaldehyde (20.00 g, 19.1ml, 151.5 mmol) and acetophenone (15.00 g, 14.6 ml, 125.0 mmol) were dissolved in ethanol (100 ml). 10% Aqueous sodium hydroxide (20.00 g) was added slowly. The solution almost immediately turned a red brown colour, and crystallization began shortly thereafter. After 2 h the golden yellow crystals were filtered and recrystallized from ethanol to afford pure (E,E)-1,5-Diphenyl-2,4-pentadien-1-one. (21.81g, 75%) m.p. 94°C. δ_H (200 MHz) : 6.944-7.099 (3H, m, Ar-*H*, O=C-C*H*, Ar-CH=C*H*), 7.225-7.648 (9H, m, Ar-*H*, O=C-CH=C*H*, Ar-C*H*), 7.939-7.988 (2H, m, Ar-*H*); δ_C (50 MHz) : 125.286 (d, Ar-CH=*C*H), 126.858, 127.250, 128.326, 128.523, 128.787 (5xd, Ar-*C*), 129.162 (d, Ar-*C*H=CH), 132.606 (d, Ar-*C*), 136.002, 138.112 (2xs, Ar-*C*), 141.851 (d, O=C-*C*H), 144.761 (d, Ar-C(O)-CH=*C*H), 190.294 (s, *C*=O); *m/z* : 234 (M$^+$, 75%), 157 (42), 128 (83), 105 (68), 91 (35), 77 (100), 51 (33).
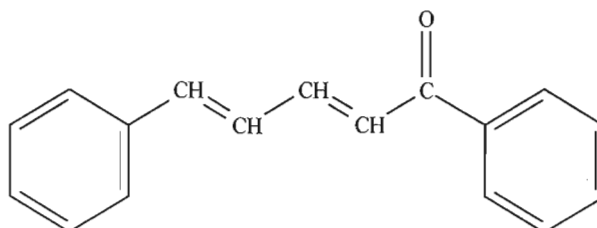
(63b)

(1,4,6E)-1,7-Diphenyl-1,4,6-heptatrien-3-one **(63c)**

Cinnamaldehyde (20.00 g, 19.1 ml, 151.5 mmol) and benzylacetone (21.32 g, 150.0 mmol) were dissolved in ethanol (100 ml). 10% Aqueous sodium hydroxide (20.00 g) was added slowly. The solution immediately became brown in colour, and crystallization began after about 30 s. After 2 h the solution was almost full of orange crystals, these were filtered and recrystallized from ethanol to yield yellow crystals of (1,4,6E)-1,7-diphenyl-1,4,6-heptatrien-3-one. (15.56 g, 75%) m.p. 102°C. δ_H (200MHz) : 6.628 (1H, d, Ar-C*H*=CH-CH), 7.016 (1H, d, Ar-C*H*=CH-C(O)), 7.371 (1H, d, Ar-CH=CH-C(O)-C*H*), 7.693 (1H, d, Ar-CH=C*H*-C(O)), 7.244-7.599 (12H, m, Ar-*H*, Ar-CH=C*H*-C*H*=CH); δ_C (50MHz) : 125.377 (d, Ar-CH=*C*H), 126.898, 127. 292, 128. 852, 129.240 (4xd, Ar-*C*), 128.365 (d, Ar-CH=*C*H), 130.45 (Ar-*C*H=CH-CH), 134.794, 136.050 (2xs, Ar-*C*), 141.754 (d, Ar-CH=CH-CH=*C*H), 143.062 (d, Ar-*C*H=CH-C(O)), 143.510 (d, Ar-CH=CH-*C*H), 189.056 (s, *C*=O); *m/z* : 260 (M$^+$, 68%), 183 (20), 169 (35), 141 (51), 115 (41), 105 (16), 103 (80), 91 (100), 77 (91).
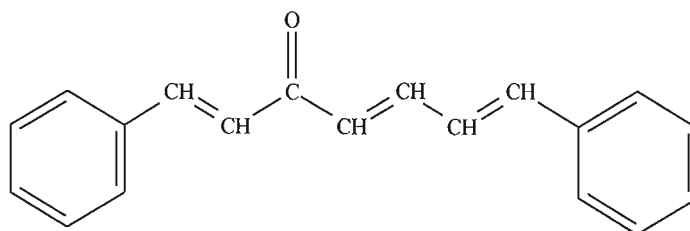
(63c)

(E,E)-1,5-Diphenyl-1,4-pentadien-3-one **(64a)**

Sodium hydroxide (25.00 g, 625.0 mmol) was dissolved in water (250 ml) and ethanol (200 ml) was added to the solution which was then cooled to 0°C in an ice/water bath. Benzaldehyde (26.00 g, 24.8 ml, 250.0 mmol) and acetone (7.50 g, 9.5 ml, 130.0 mmol) were placed in a 500 ml Erlenmeyer flask followed by the alkaline ethanolic solution. The mixture was stirred for a further 15 mins at room temperature and the bright yellow precipitate filtered. The crude product was recrystallized from ethyl acetate to yield bright yellow prisms. (13.34 g, 81%) m.p. 104°C. δ_H (200 MHz) : 7.063 (2H, d, Ar-CH=CH), 7.382 (6H, m, Ar-H), 7.587 (4H, m, Ar-H), 7.727 (2H, d, Ar-CH=CH); δ_C (50 MHz) : 125.347 (d, O=C-CH), 128.358, 128.908, 130.457 (3xd, Ar-C), 134.703 (s, Ar-C), 143.230 (d, Ar-CH=CH), 188.813 (s, C=O); *m/z* : 234 (M$^+$, 40%), 233 (39), 157 (3), 156 (6), 131 (42), 128 (20), 103 (80), 91 (27), 77 (100), 51 (43).
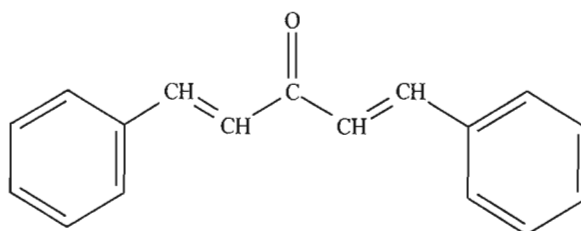
(64a)

(1,3,6,8E)-1,9-Diphenyl-1,3,6,8-nonatetraen-5-one **(64b)**

Sodium hydroxide (200.00 g, 5.0 mol) was dissolved in water (2000 ml) and ethanol (1600 ml) was added to the solution which was then cooled to 0°C in an ice water bath. Cinnamaldehyde (263.90 g, 2.0 mol) and acetone (66.00 g, 1.0 mol) were placed in a 5000 ml flat-bottomed flask followed by the alkaline ethanolic solution. The mixture was stirred for a further 2 h at room temperature and the orange precipitate filtered. The crude product was recrystallized from ethyl acetate to yield bright orange needles. (189.84 g, 66%) m.p. 144°C. δ_H (200 MHz) : 6.562 (2H, d, CH-C=O), 6.935-6.971 (2H, m, CH=CH), 7.251 - 7.540 (12H, m, CH=CH, Ar-H); δ_C (50 MHz) : 126.967 (d, Ar-CH=CH), 127.243, 128.822, 129.002 (3xd, Ar-C), 129.147 (d, Ar-CH=CH), 136.103 (s, Ar-C), 141.439 (d, O=C-CH), 143.011 (d, O=C-CH=CH), 188.912 (s, C=O); *m/z* : No satisfactory results obtained.
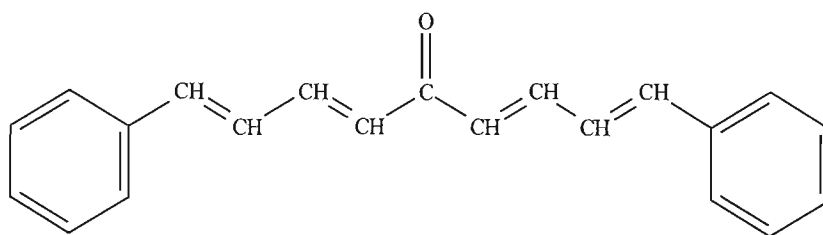
(64b)

2-Acetylphenylbenzoate **(94)**

2-Hydroxyacetophenone (10.00 g, 73.5 mmol) and triethylamine (7.58 g, 75.0 mmol) were dissolved in dichloromethane (100 ml). Benzoyl chloride (10.54 g, 75 mmol) was added at 0°C. The reaction was allowed to stir for 6.5 h at room temperature before being quenched with saturated sodium bicarbonate. The organic layer was then washed twice more with saturated sodium bicarbonate solution and then three times with distilled water. The dichloromethane layer was then dried over anhydrous $MgSO_4$, filtered and the solvent was then removed under vacuum on a rotary evaporator to yield pale pink crystals. These were recrystallized from hexane to afford white needles of pure 2-acetylphenylbenzoate. (11.850 g, 67%) m.p. 78-79°C. (Found : C, 74.84%; H, 5.15; $C_{15}H_{12}O_3$ requires C, 75.00; H, 5.00); δ_H (200 MHz) : 2.531 (3H, s, CH_3), 7.222 (1H, d, Ar-H), 7.347 (1H, t, Ar-H), 7.466-7.676 (4H, m, Ar-H), 7.855 (1H, d, Ar-H), 8.212 (2H, d, Ar-H); δ_C (50 MHz) : 29.742 (q, CH_3), 123.889, 126.152, 128.676, 130.258, 133.397, 133.798 (6xd, Ar-C), 128.198 (s, Ar-C), 131.206 (s, Ar-C), 149.321 (s, Ar-C), 165.117 (s, O-C=O), 197.750 (s, CH_3-C=O); m/z : 240 (M$^+$, 2%), 121 (1), 120 (1), 105 (100), 92 (2), 77 (37), 51 (10), 43 (4).
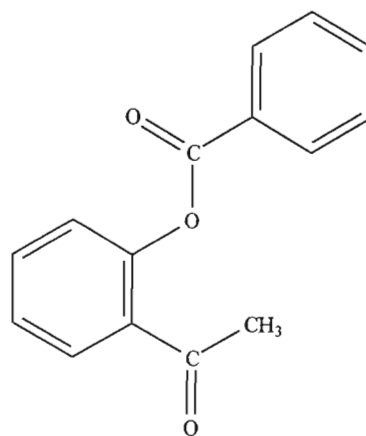
(94)

3.3 PREPARATION OF ALCOHOLS

1,1-Diphenylmethanol (**65a**)

Benzophenone (20.00 g, 110.0 mmol) was dissolved in absolute ethanol (530 ml) in a round bottomed flask. Sodium borohydride (8.08 g, 220.0 mmol) was added portionwise to the solution while being stirred and cooled in an ice/salt water bath until the solution had turned colourless, indicating that all the ketone had reacted. Thereafter the reaction with the excess borohydride was allowed to react for a further 30 mins at room temperature under a nitrogen atmosphere and in diffuse light. The solution was again cooled and 1M sodium hydroxide (250 ml) was added. A thick white precipitate immediately formed. After 2 h the precipitate was filtered, washed with distilled water and lightly pressed. The precipitate was then dissolved in boiling hexane and separated from the water droplets. Colourless crystals precipitated on cooling. The product was filtered after being allowed to precipitate in the fridge overnight to afford pure white needles of 1,1-diphenylmethanol. (33.16 g , 62%). m.p. : 62°C. (Found: C, 84.50%; H, 6.80; $C_{13}H_{12}O$ requires C, 84.80; H, 6.50); δ_H (200MHz) 2.253 (1H, s (broad), O*H*), 5.842 (1H, s, HOC*H*), 7.227-7.416 (10H, m, Ar-*H*); δ_C (50 MHz) 77.646 (d, *C*-OH), 127.510 (d, Ar-*C*), 127.570 (d, Ar-*C*), 128.492 (d, Ar-*C*), 143.748 (s, Ar-*C*); *m/z* 184 (M^+, 37%), 183 (13), 165 (8), 107 (12), 106 (12), 105 (100), 78 (39), 77 (38).
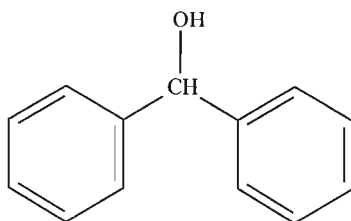
(**65a**)

(E)-1,3-Diphenyl-2-propen-1-ol **(65b)**

A round-botttomed flask containing a stirrer bar was connected *via* a three-necked adaptor to an addition funnel and reflux condenser carrying a $CaCl_2$ guard tube. Magnesium turnings (3.98 g, 163.5 mmol), dry diethyl ether (30 ml) and iodine (1 crystal) were placed into the flask. Into the addition funnel were placed bromobenzene (23.50 g, 150.0 mmol) and dry ether (30 ml). A few drops were added to the magnesium turnings and the stirrer was started. Once the reaction had started the remaining bromobenzene solution, diluted with further ether (60 ml) was added at such a rate as to maintain gentle reflux. After the addition was complete the reaction was refluxed for a further hour. The reaction mixture was then cooled in an ice-bath and a solution of freshly distilled cinnamaldehyde (12.67 g, 96.0 mmol) in ether (20 ml) was added dropwise. The reaction was refluxed for 18h. Thereafter the reaction was quenched with a mixture of ice (30 g) and 1N H_2SO_4 (30 ml). The carbinol was extracted into ether, washed twice with saturated sodium bicarbonate solution and thrice with water. The solvent was evaporated to yield a yellow residue which was dissolved in boiling hexane. Cooling of the solution afforded white needles of (E)-1,3-diphenylprop-2-en-1-ol. (12.35 g, 61%). m.p. : 56 -57°C. δ_H (200MHz) : 2.381 (1H, s (broad), O*H*), 5.320 (1H, d, C*H*-OH), 6.340 (1H, dd, CH(OH)-C*H*=CH), 6.642 (1H, d, CH=C*H*-Ar), 7.169 - 7.426 (10H, m, Ar-*H*); δ_C (50MHz) : 75.034 (d, *C*H(OH)), 126.321, 126.578, 127.733, 128.526, 128.570 (5xd, Ar-*C*), 130.453 (d, Ar-CH=*C*H), 131.467 (d, Ar-*C*H=CH), 136.460 (s, Ar-*C*-CH=CH), 142.711 (s, Ar-*C*-CH(OH); *m/z* : 210 (M$^+$, 28%), 192 (2), 133 (2), 119 (1), 115 (7), 105 (100), 103 (10), 91 (13), 77 (18).
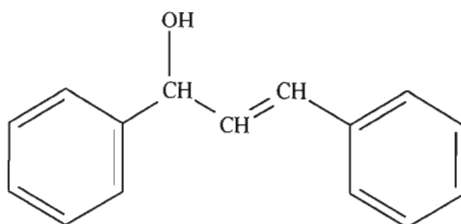
(65b)

(1E,4E)-1,5-Diphenyl-1,4-pentadien-3-ol **(65c)**

(1E,4E)-1,5-Diphenyl-1,4-pentadien-3-one (10.00 g, 42.9 mmol) was dissolved in methanol (200 ml) in a 1000 ml round-bottomed flask. Sodium borohydride (2.05 g, 54.0 mmol) was added portionwise to the solution while being stirred and cooled in an ice/salt water bath until the solution had turned colourless, indicating that all the ketone had reacted. Thereafter the reaction with the excess borohydride was allowed to react for a further 15 mins at room temperature. The solution was again cooled and 1M sodium hydroxide (430 ml) was added. A thick white precipitate immediately formed. After 2 h the precipitate was filtered and washed with distilled water and lightly pressed. The precipitate was then dissolved in diethyl ether and separated from the water droplets. The ether was distilled on a rotary evaporator and the resulting white crystals were collected. (7.81g, 78%). m.p. 66 - 68 °C. δ_H (200MHz) : 1.873 (1H, s (broad) OH), 4.994 (1H, t, CH(OH)), 6.313 (2H, dd, CH(OH)-CH=CH), 6.675 (2H, Ar-CH=CH), 7.207-7.436 (10H, m, Ar-H); δ_C (50 MHz) : 73.490 (d, CH(OH)), 126.487 (d, Ar-C), 127.704 (d, CH(OH)-CH), 128.500 (d, Ar-CH=CH), 130.279, 130.680 (2xd, Ar-C), 136.435 (s, Ar-C); *m/z* : No satisfactory results obtained.
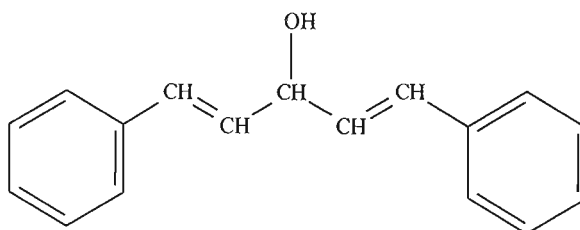
(65c)

(E,E)-1,5-Diphenyl-2,4-pentadien-1-ol **(65d)**

<u>Method A</u>

(E,E)-1,5-Diphenyl-2,4-pentadien-1-one (10.00 g, 42.7 mmol) was dissolved in methanol (250 ml). The solution was cooled to 0°C in an ice-water bath and sodium borohydride (3.00 g, 79.0 mmol) was added portionwise. The solution was stirred until it turned colourless and then cooled on an ice/salt water bath and sodium hydroxide (1M, 400 ml) was added slowly. The resulting white precipitate was filtered, washed with water and lightly pressed. The precipitate was dissolved in boiling hexane and separated from the residual water to afford white needles of (E,E)-1,5-diphenyl-2,4-pentadien-1-ol on cooling. (9.58g, 95%). m.p. : 78 - 80°C. δ_H (200 MHz) : 2.152 (1H, s, O*H*), 5.281 (1H, d, HO-C*H*), 5.970 (1H, dd, CH=C*H*-CH(OH)), 6.385-6.831 (3H, m, CH=C*H*-C*H*=C*H*-Ar), 7.168 - 7.408 (10H, m, Ar-*H*); δ_C (50MHz) : 74.811 (d, *C*H(OH)), 126.368, 127.629, 127.748, 128.045, 128.589 (5xd, Ar-*C*), 126.282 (d, Ar-CH=*C*H),130.927 (d, CH(OH)-CH=*C*H), 133.177 (d, Ar-*C*H=CH), 135.483 (d, CH(OH)-*C*H=CH), 137.034 (s, Ar-*C*), 142.745 (s, Ar-*C*); *m/z* : 236 (M$^+$, 10%), 131 (8), 128 (9), 117 (15), 115 (14), 105 (100), 91 (19), 77 (26), 55 (10), 43 (11).
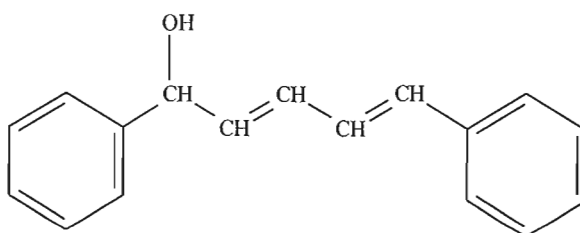
(65d)

<u>Method B</u>

To a solution of 1,5-diphenyl-1,4-pentadien-3-ol (2.0 g, 8.44 mmol) in THF (40 ml) under nitrogen was added DABCO (1.01 g, 9.0 mmol). The reaction mixture was cooled to 0°C and N,N-diethylcarbamoyl chloride (1.23 g, 1.15 ml, 9.0 mmol) in THF (10 ml) was added dropwise. The reaction mixture was then stirred overnight at room temperature and quenched with 15% HCl (40 ml). The organic layer was extracted into diethyl ether, dried over anhydrous MgSO$_4$ and recovered after filtration of the drying agent. The solvent was

removed under reduced pressure to afford a white crystals. Recrystallization was carried out from petroleum ether (60-80°C) yielding **(65d)**. (0.70 g, 35%).

(E,E,E,E)-1,9-Diphenyl-1,3,6,8-nonatetraen-5-ol **(65e)**

(E,E,E,E)-1,9-Diphenyl-1,3,6,8-nonatetraen-5-one (10.00 g, 35.0 mmol) was dissolved in methanol (250 ml). The solution was cooled to 0°C in an ice-water bath and sodium borohydride (3.00 g, 79.0 mmol) was added portionwise. The solution was stirred until it turned pale yellow. The reaction was allowed to warm to room temperature and stirred for a further 15 mins and then again cooled on an ice/salt water bath and sodium hydroxide (1M, 350 ml) was added slowly. The resulting yellow precipitate was filtered, washed with water and lightly pressed. After 2 h the precipitate was dissolved in diethyl ether and separated from the remaining water droplets. The ether was evaporated under vacuum and the resulting yellow crystals collected. (9.17 g, 91%) m.p. : 104°C. δ_H (200 MHz) : 4.835 (1H, d, HO-C*H*), 4.885 (1H, s, O*H*), 5.888 (2H, dd, CH=C*H*-CH(OH)), 6.393-6.883 (6H, m, CH=C*H*-C*H*=C*H*-Ar), 7.208-7.442 (10H, m, Ar-*H*); δ_C (50MHz) : 73.087 (d, *C*H(OH)), 126.379 (d, Ar-CH=*C*H), 127.644, 128.036, 128.584 (3xd, Ar-*C*), 131.223 (d, CH(OH)-CH=*C*H), 133.214 (d, Ar-*C*H=CH), 134.149 (d, CH(OH)-*C*H=CH), 136.991 (s, Ar-*C*); *m/z* : No satisfactory results obtained.
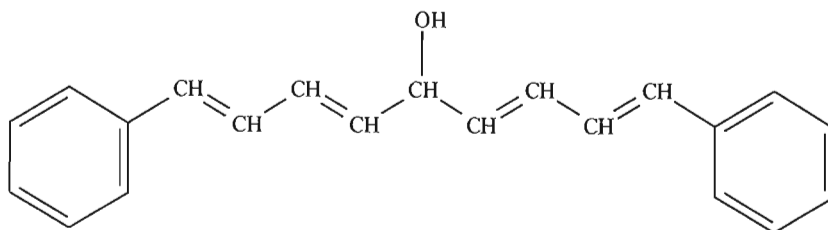
(65e)

3.4 PREPARATION OF CARBAMATES

(E)-1-(O-N,N-Diethylcarbamoyloxy)-3-phenyl-2-propene **(66a)**

To a suspension of sodium hydride (1.27 g (80% in paraffin), 42.4 mmol) in THF (18.75 ml) was slowly added cinnamyl alcohol (3.37 g, 25.0 mmol) while cooling the flask in an ice bath. The reaction was allowed to warm to room temperature and stirred at this temperature for 30 mins. After cooling again to 0°C, N,N-diethylcarbamoyl chloride (3.39 g, 25.0 mmol) was added dropwise and the reaction mixture then stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride, the products were extracted into ether and dried over anhydrous magnesium sulphate. The solvent was removed under vacuum to afford a light yellow oil. (4.69 g, 81%); δ_H (200MHz) : 1.116 (6H, t, N(CH$_2$CH_3)$_2$), 3.279 (4H, q, N(CH_2CH$_3$)$_2$), 4.730 (2H, d, CH_2OCO(CH$_2$CH$_3$)$_2$), 6.226-6.336 (1H, m, CH=CH-CH$_2$), 6.612 (1H, d, Ar-CH=CH), 7.206-7.398 (6H, m, Ar-H) ; δ_C (50 MHz) : 14.030, 14.146 (2xq, N(CH$_2$CH_3)$_2$), 41.723, 41.782 (2xt, N(CH_2CH$_3$)$_2$), 65.540 (t, CH_2OCO(CH$_2$CH$_3$)$_2$), 124.537, 126.552, 127.831 (3xd, Ar-C), 127.831, 128.541 (2xt, CH=CH), 136.470 (s, Ar-C), 155.676 (s, OC=O); *m/z* : 233 (M$^+$, 7%), 133 (1), 117 (100), 115 (35), 100 (25), 91 (14), 77 (5), 72 (10), 42 (9).
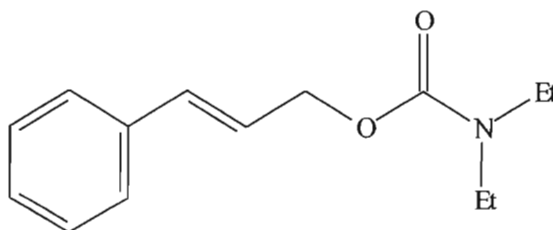
(66a)

1-(O-N,N-Dimethylcarbamoyloxy)-1,1-diphenylmethane **(66b)**

To a suspension of sodium hydride (1.80 g (80% in paraffin), 60.0 mmol) in THF (200 ml) was slowly added 1,1-diphenylmethanol (10.00 g, 54.4 mmol) while cooling the flask in an ice bath. The reaction was allowed to warm to room temperature and stirred in a nitrogen atmosphere at this temperature for 30 mins. The solution was again cooled to 0°C, and N,N-dimethylcarbamoyl chloride (6.54 g, 5.60 ml, 61.0 mmol) was added dropwise and the reaction mixture then stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride and the products were extracted into diethyl ether. The ether layer was dried over anhydrous magnesium sulphate and filtered. The solvent was removed under vacuum to afford a white crystalline mass. Separation on silica gel eluting with 3:2 hexane:ether and subsequent removal of the solvent under vacuum yielded white crystals. (9.84 g, 71%); m.p. 55°C. (Found : C, 75.05%; H, 6.73; N, 5.50; $C_{16}H_{17}NO_2$ requires C, 75.29; H, 6.67; N, 5.49); δ_H (200MHz) : 2.984 (6H, d, N(CH_3)$_2$), 6.802 (1H, s, OCH), (10H, m, Ar-H); δ_C (50MHz) : 35.996, 36.559 (2xq, N(CH$_3$)$_2$), 77.754 (d, OCH), 126.958, 127.649, 128.420 (3xd, Ar-C), 141.009 (s, Ar-C), 156.376 (s, OC=O); m/z : 255 (M$^+$, 11%), 211 (2), 167 (100), 139 (3), 134 (12), 105 (3), 91 (1), 77 (5), 72 (8).
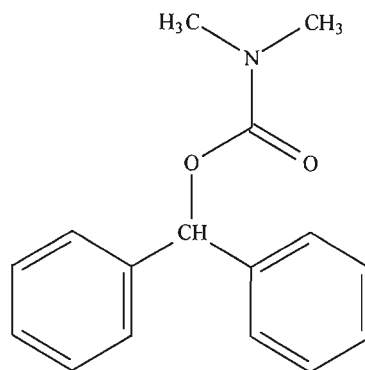
(66b)

(E)-1-(O-N,N-Diethylcarbamoyloxy)-1,3-diphenyl-2-propene **(66c)**

To a suspension of sodium hydride (0.90 g (80% in paraffin), 30.0 mmol) in THF (100 ml) at 0°C was slowly added (E)-1,3-diphenyl-2-propen-1-ol (5.00 g, 23.8 mmol). The reaction was allowed to warm to room temperature and stirred in a nitrogen atmosphere at this temperature for 30 mins. The solution was again cooled to 0°C, and N,N-diethylcarbamoyl chloride (4.07 g, 3.80 ml, 30.0 mmol) was added dropwise and the reaction mixture then stirred at room temperature for 3.5 h. The reaction was quenched with saturated ammonium chloride and the products were extracted into diethyl ether. The ether layer was dried over anhydrous magnesium sulphate and filtered. The solvent was removed under vacuum to afford a thick yellow oil. Separation by centifugal chromatography on silica gel eluting with 9:1 hexane:ether and subsequent removal of the solvent under vacuum yielded a thick yellow oil. (4.18 g, 57%); b.p. 210°C/0.4 mmHg. (Found : C, 77.96%; H, 7.51; N, 4.46; $C_{20}H_{23}NO_2$ requires C, 77.67; H, 7.44; N, 4.53) δ_H (200MHz) : 1.116 (6H, t (broad), $N(CH_2CH_3)_2$), 3.317 (4H, q (broad), $N(CH_2CH_3)_2$), 6.302-6.420 (2H, m, C*H*=C*H*), 6.630 (1H, d, Ar-C*H*-CH), 7.189-7.443 (10H,m, Ar-*H*); δ_C (50MHz) : 13.500, 14.200 (2xq, $N(CH_2CH_3)_2$), 41.700, 41.800 (2xt, $N(CH_2CH_3)_2$), 76.116 (d, OCH), 126.637, 126.832, 127.803, 128.487, 128.563 (5xd, Ar-*C*), 127.829, 131.807 (2 x d, *C*H=*C*H) 136.373, 140.096 (2xs, Ar-*C*), 154.944 (s, O*C*=O); *m/z* : 309 (M⁺, 2%), 204 (2), 193 (12), 131 (1), 116 (1), 105 (11), 100 (100), 91 (6), 77 (12), 72 (41), 44 (9).
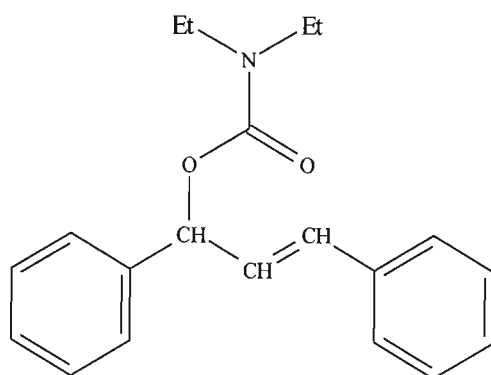
(66c)

1-(O-N,N-Diisopropylcarbamoyloxy)-1,3-diphenyl-2-propene (**66d**)

To a suspension of sodium hydride (0.48 g (50% in paraffin), 10.0 mmol) in THF (50 ml) at 0°C was slowly added (E)-1,3-diphenyl-2-propen-1-ol (1.02 g, 4.8 mmol). The reaction was allowed to warm to room temperature and stirred in a nitrogen atmosphere at this temperature for 30 mins. The solution was again cooled to 0°C, and N,N-diisopropylcarbamoyl chloride (1.64 g, 10.0 mmol) was added dropwise and the reaction mixture then stirred at room temperature for 3.5 h. The reaction was quenched with saturated ammonium chloride and the products were extracted into diethyl ether. The ether layer was dried over anhydrous magnesium sulphate and filtered. The solvent was removed under vacuum to afford a thick yellow oil. Separation by centifugal chromatography on silica gel eluting with 9:1 hexane:ether and subsequent removal of the solvent under vacuum yielded a thick yellow oil. (0.88 g, 54%); b.p. 220°C/0.35 mmHg. (Found : C, 78.62%; H, 7.79; N, 3.91; $C_{22}H_{27}NO_2$ requires C, 78.34; H, 8.01; N, 4.15) δ_H (200MHz) : 1.224 (12H, d (broad), N(CH(CH_3)$_2$)$_2$), 3.800-4.100 (2H, (broad), N(CH(CH$_3$)$_2$)$_2$), 6.327-6.446 (2H, m, CH=CH), 6.512 (1H, d, Ar-CH-CH), 7.212-7.454 (10H, m, Ar-H); δ_C (50MHz) : 20-22 (4xq,(broad), N(CH(CH$_3$)$_2$)$_2$), 44-45 (2xd,(broad), N(CH(CH$_3$)$_2$)$_2$), 76.668 (d, OCH), 126.662, 127.020, 127.756, 128.391, 128.492 (5xd, Ar-C), 127.812, 31.821 (2 x d, CH=CH) 136.462, 140.134 (2 x s, Ar-C), 154.944 (s, OC=O); m/z : 337 (M$^+$,2%), 193 (100), 128 (23), 115 (76), 105 (5), 91 (23), 86 (22), 77 (7), 70 (8).
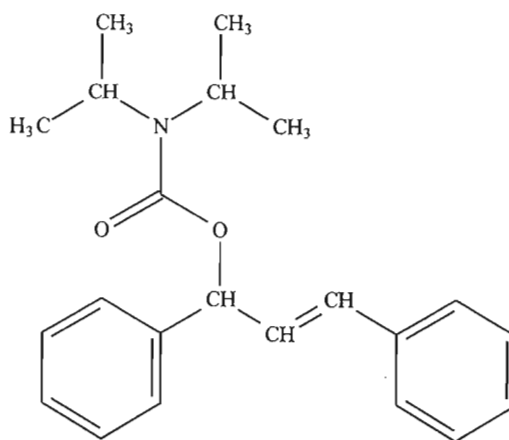
(**66d**)

1-(O-N,N-Diethylcarbamoyloxy)-1,5-diphenyl-2,4-pentadiene **(66e)**

To a suspension of sodium hydride (0.80 g (80% in paraffin), 26.7 mmol) in THF (100 ml) at 0°C was slowly added 1,5-diphenyl-2,4-pentadien-1-ol (5.00 g, 21.1 mmol). The reaction was stirred at room temperature for 30 mins in a nitrogen atmosphere. The solution was again cooled to 0°C, and N,N-diethylcarbamoyl chloride (3.62 g, 3.40 ml, 26.7 mmol) was added dropwise while stirring under nitrogen. The reaction mixture was then stirred at room temperature for 2 h during which the contents of the reaction vessel had become red-brown. The reaction was quenched with saturated ammonium chloride, the organic layer turned yellow upon quenching. The products were extracted into diethyl ether and dried over anhydrous magnesium sulphate and filtered. The solvent was removed under vacuum to afford an orange liquid. Separation by centifugal chromatography on silica gel eluting with 9:1 hexane:ether and subsequent removal of the solvent under vacuum yielded a thick orange oil. (4.83 g, 67%); b.p. 235°C/3 mmHg. δ_H (200MHz) : 1.177 (6H, t, (broad), N(CH$_2$CH_3)$_2$), 3.321 (4H, q, (broad), N(CH_2CH$_3$)$_2$), 5.968 (1H, dd, CH=CH-CHO), 6.314 (1H, d, CHO), 6.337-6.824 (3H, m, Ar-CH=CH-CH=CH), 7.158-7.403 (10H, m, Ar-H); δ_C (50MHz) : 13.702, 14.219 (2xq, N(CH$_2$CH$_3$)$_2$), 41.272, 41.381 (2xt, N(CH$_2$CH$_3$)$_2$), 76.409 (d, CHO), 126.372 (d, Ar-CH=CH), 126.822, 127.645, 127.797, 127.994, 128.499, 128.575 (6xd, Ar-C), 132.166 (d, OCH-CH=CH), 132.560 (d, Ar-CH=CH), 133.500 (d, OCH-CH=CH), 137.019, 140.066 (2xs, Ar-C), 154.976 (OC=O); *m/z* : 291 (M-44, 68%), 262 (23), 219 (88), 215 (20), 204 (19), 141 (24), 129 (18), 115 (35), 104 (18), 91 (100), 77 (10), 44 (27).
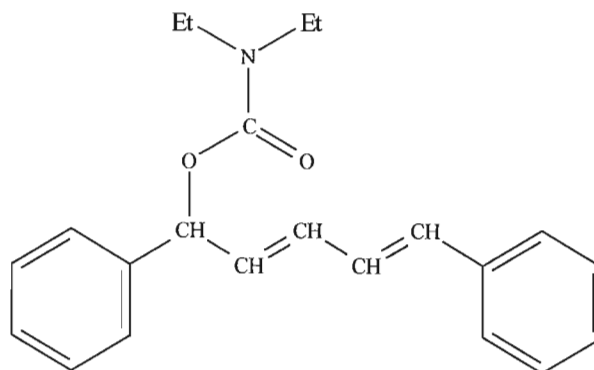
(66e)

O-N,N-Dimethylcarbamoyloxybenzaldehyde (**95**)

To a stirred solution of salicylaldehyde (9.65 g, 8.42 ml, 79.0 mmol) and triethylamine (11.20 g, 15.3 ml, 100.0 mmol) in anhydrous CH_2Cl_2 (125 ml) at 0°C under nitrogen was added dropwise N,N-dimethylcarbamoyl chloride (10.14 g, 94.0 mmol). The reaction was stirred at 0°C for 3 h, the mixture was then allowed to warm to room temperature before washing successively with 2N HCl (70 ml), sat. $NaHCO_3$ (70 ml) and water (70 ml). The organic phase was separated from the aqueous phase and dried over anhydrous $MgSO_4$. After filtering to remove the drying agent, the solvent was removed under reduced vacuum and the product purified by distillation. (13.87 g, 91%) b.p. 130-132°C/3mmHg;

δ_H (200MHz) : 3.012, 3.140 (6H, 2xs, N(CH_3)$_2$), 7.200-7.897 (4H, m, Ar-H), 10.182 (1H, s, CHO); δ_C (50MHz) : 36.551, 36.819 (2xq, N(CH$_3$)$_2$), 123.656, 125.757, 129.739, 135.185 (4xd, Ar-C), 128.417 (s, COCON) 152.948 (s, CCHO), 154.196 (s, OCON), 188.878 (d, CCHO); *m/z* : 193 (M$^+$, 3%), 165 (1), 149 (2), 121 (19), 105 (2), 92 (2), 77 (3), 72 (100), 56 (4), 42 (8).
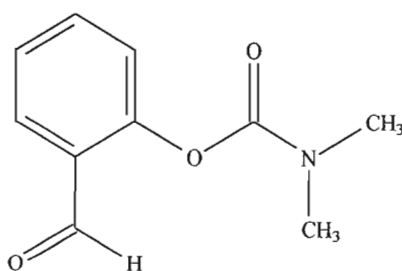
(**95**)

3.5 PREPARATION OF ELECTROPHILICALLY SUBSTITUTED CARBAMATES.

1-(O-N,N-Dimethylcarbamoyloxy)-1,1-diphenyl-1-methylmethane. **(71a)**

To a solution of diisopropylamine (0.32 ml, 2.3 mmol) in THF (10 ml) at 0°C under nitrogen was added dropwise n-BuLi in hexane (1.37M, 1.67 ml, 2.3 mmol). The mixture was stirred at 0°C for 1 h and then cooled to -78°C. A solution of O-N,N-dimethylcarbamoyloxy-1,1-diphenylmethane (0.50 g, 2.0 mmol) in THF (5 ml) was added dropwise. The solution instantly became bright orange in colour indicating the generation of the benzylic carbamate anion. The solution was stirred at -78°C for 30 mins. Iodomethane (0.15 ml, 2.4 mmol) was added dropwise. The solution immediately turned yellow. The reaction mixture was stirred at -78°C for 2.5 h and then allowed to warm to room temperature before quenching with sat. NH_4Cl. The reaction products were extracted into diethyl ether, the ether layer dried over anhydrous $MgSO_4$, and recovered after filtering off the drying agent. The solvent was removed under reduced pressure to leave a viscous yellow liquid. Separation on silica gel using centrifugal chromatography and eluting with a 4:1 solution of hexane/ether afforded, after evaporation of the solvent, orange crystals. (0.37 g, 71%). m.p. 93°C. (Found : C, 76.02%; H, 7.03; N, 5.20; $C_{17}H_{19}NO_2$ requires C, 75.84%, H, 7.06; N, 5.20) δ_H (200MHz) : 2.223 (3H, s, CCH_3), 2.861, 3.054 (6H, 2xd, N(CH_3)$_2$), 7.183-7.348 (10H, m, Ar-H); δ_C (50MHz) : 27.558 (q, CCH_3), 36.302 (q, N(CH$_3$)$_2$), 83.997 (s, Ar-C-Ar), 125.811, 126.506, 126.885, 128.048, 128.393 (5xd, Ar-C), 146.358 (s, Ar-C), 154.781 (s, OCON); m/z : 181, (M-88, 15%), 180 (100), 165 (84), 152 (12), 115 (5), 102 (11), 89 (32), 77 (21), 63 (8), 51 (11).
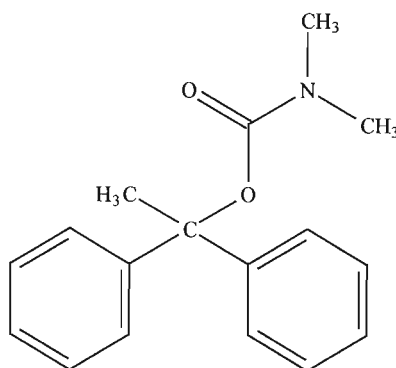
(71a)

1-Benzyl-1-(O-N,N-dimethylcarbamoyloxy)-1,1-diphenylmethane. **(71b)**

To a solution of diisopropylamine (0.32 ml, 2.3 mmol) in THF (10 ml) at 0°C under nitrogen was added dropwise n-BuLi in hexane (1.37M, 1.67 ml, 2.3 mmol). The mixture was stirred at 0°C for 1h and then cooled to -78°C. A solution of *O*-N,N-dimethylcarbamoyloxy-1,1-diphenylmethane (0.50 g, 2.0 mmol) in THF (5 ml) was added dropwise. The solution instantly became bright orange in colour indicating the generation of the benzylic carbamate anion. The solution was stirred at -78°C for 30 mins. Benzyl bromide (0.29 ml, 2.4 mmol) was added dropwise. The solution immediately turned light orange. The reaction mixture was stirred at -78°C for 2.5 h and then allowed to warm to room temperature before quenching with sat. NH$_4$Cl. The reaction products were extracted into diethyl ether, the ether layer dried over anhydrous MgSO$_4$, and recovered after filtering off the drying agent. The solvent was removed under reduced pressure to leave a viscous yellow liquid. Separation on silica gel using centrifugal chromatography and eluting with a 4:1 solution of hexane/ether afforded, after evaporation of the solvent, white crystals. (0.28 g, 42%) m.p. 55°C. (Found : C, 79.96%; H, 6.85; N, 4.22; C$_{23}$H$_{23}$NO$_2$ requires C, 80.00%; H, 6.67; N, 4.06); δ_H (200MHz) : 2.871 (6H, s, N(CH_3)$_2$), 4.071 (2H, s, Ar-CH_2) 7.066-7.357 (15H, m, Ar-H); δ_C (50MHz) : 36.211, 36.448 (2xq, N(CH$_3$)$_2$), 43.233 (t, Ar-CH$_2$) 85.306 (s, Ar-C-Ar), 126.199, 126.302, 126.796, 126.940, 127.298, 127.645, 127.875, 128.415, 130.593 (9xd, Ar-C), 136.111, 145.462 (2 x s, Ar-C), 154.699 (s, OCON); *m/z* : 256, (M-88, 100%), 254 (7), 178 (61), 165 (28), 120 (28), 113 (21), 107 (6), 91 (6), 77 (8).
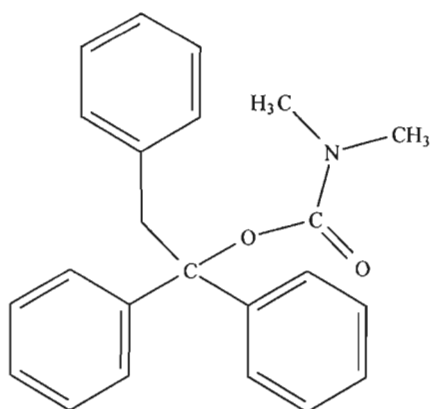
(71b)

1-O-N,N-Dimethylcarbamoyloxy-1,1-diphenyl-1-trimethylsilylmethane. (**71c**)

To a solution of diisopropylamine (0.32 ml, 2.3 mmol) in THF (5 ml) at 0°C under nitrogen was added dropwise n-BuLi in hexane (1.38M, 1.66 ml, 2.3 mmol). The mixture was stirred at 0°C for 30 mins and then cooled to -78°C. A solution of *O*-N,N-dimethylcarbamoyloxy-1,1-diphenylmethane (0.50 g, 2.0 mmol) and trimethylsilyl chloride (0.30 ml, 2.4 mmol) in THF (2 ml) was added dropwise. The solution instantly became bright orange in colour indicating the generation of the benzylic carbamate anion. The reaction mixture was stirred at -78°C for 1 h and then allowed to warm to room temperature during which time the reaction mixture became brown. The reaction was quenched with sat. NH$_4$Cl. The yellow organic phase was extracted into diethyl ether, the ether layer dried over anhydrous MgSO$_4$, and recovered after filtering off the drying agent. The solvent was removed under reduced pressure to leave a viscous yellow oil. Separation on silica gel using centrifugal chromatography and eluting with a 9:1 solution of hexane/ether and evaporation of the solvent afforded white crystals. (0.30 g, 47%) m.p. 65°C. (Found : C, 69.49%; H, 7.56; N, 4.28; C$_{19}$H$_{25}$NO$_2$Si requires C, 69.72%; H, 7.65; N, 4.28) δ_H (200MHz) : 0.084 (9H, s, Si(C*H$_3$*)$_3$), 2.924, 3.143 (6H, 2xs, N(C*H$_3$*)$_2$), 7.192-7.340 (10H, m, Ar-*H*); δ_C (50MHz) : 0.161 (q, Si(CH$_3$)$_3$), 36.404, 36.601 (2xq, N(CH$_3$)$_2$), 84.340 (s, Ar-*C*-Ar), 126.194, 126.219, 126.246, 127.842, 127.870, 127.897, (6xd, Ar-*C*), 143,722 (s, Ar-*C*), 155.865 (s, OCON); *m/z* : 327 (M$^+$, 3%), 312 (4), 255 (2), 178 (1), 165 (6), 146 (100), 105 (2), 102 (15), 77 (2).
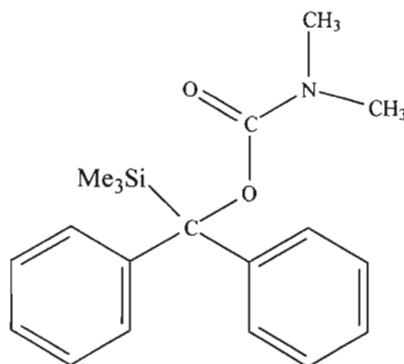
(**71c**)

1-(O-N,N-Dimethylcarbamoyloxy)-2-hydroxy-1,1,4-triphenyl-3-butene. **(71f)**

To a solution of diisopropylamine (0.32 ml, 2.3 mmol) in THF (10 ml) at 0°C under nitrogen was added dropwise n-BuLi in hexane (1.37M, 1.67 ml, 2.3 mmol). The mixture was stirred at 0°C for 0.5 h and then cooled to -78°C. A solution of *O*-N,N-dimethylcarbamoyloxy-1,1-diphenyl methane (0.50 g, 2.0 mmol) in THF (5 ml) was added dropwise. The solution instantly became bright orange in colour indicating the generation of the benzylic carbamate anion. The solution was stirred at -78°C for 30 mins. Cinnamaldehyde (0.30 ml, 2.4 mmol) was added dropwise. The solution turned yellow. The reaction mixture was stirred at -78°C for 1.5 h and then allowed to warm to room temperature before quenching with sat. NH₄Cl. The reaction products were extracted into diethyl ether, the ether layer dried over anhydrous MgSO₄, and recovered after filtering off the drying agent. The solvent was removed under reduced pressure to leave a light yellow solid. Recrystallization from ethyl acetate afforded the white crystals (0.28 mg, 37%). m.p. 63°C. (Found : C, 77.41%; H, 6.44; N, 3.53; $C_{25}H_{25}NO_3$ requires C, 77.52%; H, 6.46; N, 3.62) δ_H (200MHz) : 2.734, 2.858 (6H, 2xs, N(CH_3)₂), 6.125-6.322 (2H, m, Ar-CH=CH), 6.588 (1H, d, CHOH), 7.167-7.607 (16H, m, Ar-H, OH); δ_C (50MHz) : 36.211, 36.448 (2xq, N(CH₃)₂), 78.945 (d, CHOH), 80.040 (s, Ar-C-Ar), 127.114, 127.140 (2xd, CH=CH), 124.031, 126.156, 126.352, 126.666, 127.813, 128.141, 128.164, 128.381, 134.689 (9xd, Ar-C), 136.379, 143.288, 144.767 (3xs, Ar-C), 155.699 (s, OCON); *m/z* : 298, (M-88, 34%), 115 (50), 105 (100), 91 (56), 77 (80), 44 (36).
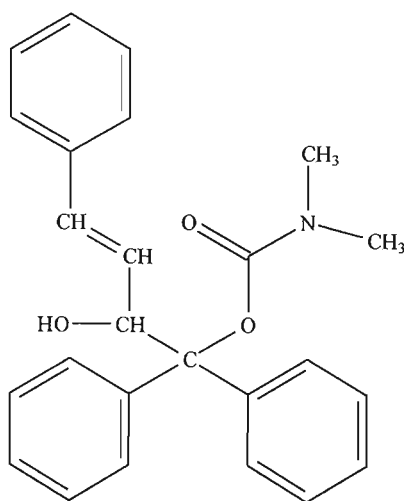
(71f)

1-O-N,N-Diethylcarbamoyloxy-3-methyl-1,3-diphenyl-1-propene. **(78a)**

To a solution of 1-(E)-*O*-N,N-diethylcarbamoyloxy-1,3-diphenyl-2-propene (0.25 g, 0.8 mmol) in THF (5 ml) at -78°C under nitrogen was added dropwise n-BuLi in hexane (1.06M, 0.84 ml, 0.9 mmol). The solution immediately turned cherry red indicating the generation of the allylic carbamate anion. The solution was stirred at -78°C for 1 h. Iodomethane (0.10 ml, 1.2 mmol) was added dropwise. The solution immediately turned bright orange. The reaction mixture was stirred at -78°C for 1.5 h during which time the solution became yellow then allowed to warm to room temperature before being quenched with sat. NH$_4$Cl. The reaction products were extracted into diethyl ether, the ether layer dried over anhydrous MgSO$_4$, and recovered after filtering off the drying agent. The solvent was removed under reduced pressure to leave a viscous yellow liquid. Separation on silica gel using centrifugal chromatography and eluting with a 9:1 solution of hexane/ethyl acetate afforded, after evaporation of the solvent, a yellow oil. (0.14 g, 55%).

δ_H (200MHz) : 1.144, 1.245 (6H, 2xt, N(CH$_2$C*H*$_3$)$_2$), 1.455 (3H, d, Ar-CH-C*H*$_3$), 3.353 (4H, m, N(C*H*$_2$CH$_3$)$_2$), 3.858 (1H, m, Ar-C*H*-CH), 5.873 (1H, d, Ar-CH=C*H*), 7.1633-7.432 (10H, m, Ar-*H*); δ_C (50MHz) : 13.402, 14.457 (2xq, N(CH$_2$*C*H$_3$)$_2$), 21.279 (q, Ar-CH-*C*H$_3$), 36.475 (d, Ar-*C*H-CH$_3$), 41.825, 42.107 (2xt, N(*C*H$_2$CH$_3$)$_2$), 122.654 (d, CH$_3$-*C*H-CH=C(OAm)), 124.557, 126.118, 126.986, 127.907, 128.344, 128.425 (6xd, Ar-*C*), 135.858, 145.508 (2xs, Ar-*C*), 145.398 (s, Ar-*C*(OAm)=CH), 153.411 (s, O*C*ON); *m/z* : 323 (M$^+$, 1%), 218 (1), 207 (8), 191 (2), 131 (1), 129 (1), 118 (2), 105 (14), 100 (100), 91 (2), 77 (11).
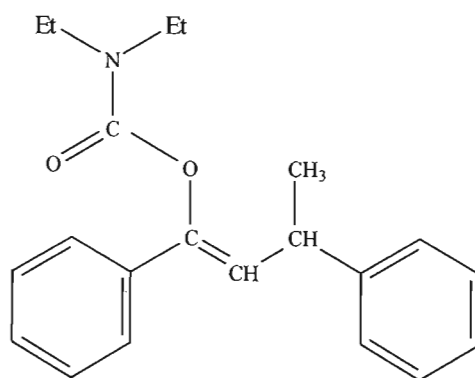
(78a)

3.6   PREPARATION OF ALLYLIC ETHERS

1,5-Diphenyl-1-methoxy-2,4-pentadiene. **(84)**

To a solution of 1,5-diphenyl-1,4-pentadien-3-ol (1.01 g, 4.2 mmol) in THF (20 ml) under nitrogen was added DABCO (1.42 g, 12.7 mmol). The reaction mixture was cooled to 0°C and N,N-diethylcarbamoyl chloride (0.64 g, 0.55 ml, 6.0 mmol) in THF (10 ml) was added dropwise. The reaction mixture was then stirred overnight at room temperature and quenched with sat. NH_4Cl. The organic layer was extracted into diethyl ether, dried over anhydrous $MgSO_4$ and recovered after filtration of the drying agent. The solvent was removed under reduced pressure to afford a light yellow liquid. The liquid was dissolved in a solution of 18:1:1 hexane/ether/methanol and separation by centrifugal chromatography on silica gel afforded a colourless viscous oil which on prolonged exposure to daylight turned light green. (0.15 g, 14%). δ_H (200MHz) : 3.337 (3H, s, O-CH_3), 4.714 (1H, d, Ar-CH-OCH$_3$), 5.883 (1H, dd, Ar-CH(OCH$_3$)-CH), 6.339-6.826 (3H, m, Ar-CH=CH-CH), 7.154-7.407 (10H, m, Ar-H); δ_C (50MHz) : 56.393 (q, OCH$_3$), 83.990 (d, Ar-CH-OCH$_3$), 126.342, 126.793, 127.581, 127.688, 128.157, 128.504, (6xd, Ar-C), 128.568 (d, Ar-CH=CH), 131.826 (d, CH(OH)-CH=CH), 132.980 (d, Ar-CH=CH) 134.190 (d, CH(OH)-CH=CH), 137.065, 141.085 (2xs, Ar-C); *m/z* : 250 (M$^+$, 39), 219 (16), 159 (65), 128 (35), 121 (18), 115 (61), 105 (65), 103 (15), 91 (100), 77 (55).
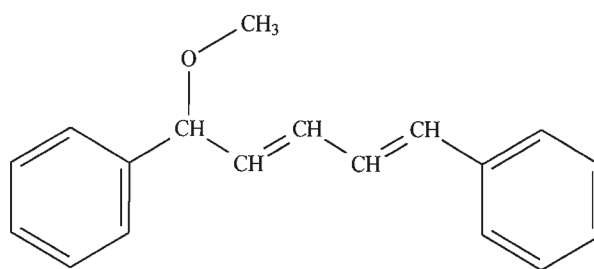
(84)

1,3-Diphenyl-1-phenoxy-2-propene **(87)**

To a stirred suspension of sodium hydride (0.11 g (80% in paraffin), 3.7 mmol) in THF (25 ml) was added phenol (0.32 g, 3.4 mmol) at room temperature. The reaction was stirred at this temperature for 30 mins. The reaction mixture was then cooled to $0^{\circ}C$ and 1-*O*-N,N-diethylcarbamoyloxy-1,3-diphenyl-2-propene (1.00 g, 3.2 mmol) was added portionwise. The reaction mixture was then stirred at room temperature for 2 h and quenched with sat. NH_4Cl. The organic layer was extracted into diethyl ether, dried over anhydrous $MgSO_4$ and recovered after filtration of the drying agent. The solvent was removed under reduced pressure to afford a light yellow liquid. Separation by centifugal chromatography on silica eluting with a 9:1 hexane/ether solution afforded a white solid. (0.05g, 5.4%) m.p. $69^{\circ}C$. (Found : C, 87.87%; H, 6.31; $C_{21}H_{18}O$ requires C, 88.11%; H, 6.29) δ_H (200MHz) : 5.793 (1H, d, Ar-C*H*-O-Ar), 6.428 (1H, dd, CH=C*H*-CH), 6.669 (1H, d, Ar-C*H*=CH), 6.860-7.004, 7.164-7.487 (15H, 2xm, Ar-*H*); δ_C (50MHz) : 80.665 (d, Ar-CH-OAr), 116.197, 121.003, 129.261 (3xd, O-Ar-*C*), 126.521, 126.630, 126.721, 127.840, 128.434, 128.503, 128.676 (7xd, Ar-*C*), 129.348 (d, Ar-*C*H-O-Ar), 131.466 (d, Ar-*C*H=CH), 136.302, 140.309 (2xs, Ar-*C*), 157.883 (s, O-Ar-*C*); *m/z* : 209 (M-77, 10%), 192 (94), 181 (6), 178 (39), 165 (30), 131 (15), 121 (24), 115 (100), 105 (64), 91 (38), 77 (49).
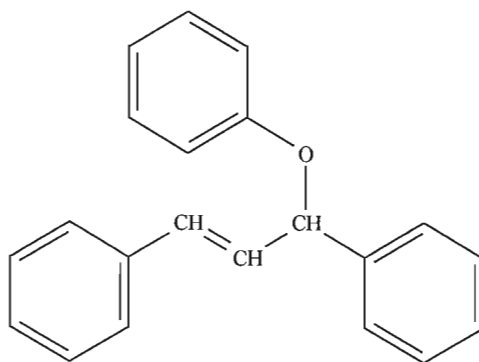
(87)

3.7 SYNTHESIS OF ALLYLIC AMINE

1-(N,N-Dimethylamino)-1,3-diphenyl-2-propene. **(90)**

To a suspension of sodium hydride (1.44 g (50% in paraffin), 30.0 mmol) in THF (100 ml) at 0°C was slowly added (E)-1,3-diphenyl-2-propen-1-ol (5.00 g, 23.8 mmol). The reaction was allowed to warm to room temperature and stirred in a nitrogen atmosphere at this temperature for 1 h. The solution was again cooled to 0°C, and N,N-dimethylcarbamoyl chloride (3.21 g, 2.75 ml, 30.0 mmol) was added dropwise and the reaction mixture then stirred at room temperature for 2 h. The reaction was quenched with saturated ammonium chloride and the products were extracted into diethyl ether. The ether layer was dried over anhydrous magnesium sulphate and filtered. The solvent was removed under vacuum to afford a thick yellow oil. Distillation of the oil using a Kugelrohr afforded a colourless liquid. (4.19 g, 59%); b.p. 235°C/5mmHg. (Found : C, 85.89%; H, 7.99; N, 5.65; $C_{17}H_{19}N$ requires C, 86.08; H, 8.02; N, 5.91) δ_H(200MHz) : 2.229 (6H, s, N(CH_3)$_2$), 3.687 (1H, d, Ar-CH-N(CH$_3$)$_2$), 6.350 (1H, dd, Ar-CH=CH), 6.549 (1H, d, Ar-CH-CH), 7.163-7.410 (10H, m, Ar-H); δ_C (50MHz) : 43.870 (q, N(CH$_3$)$_2$), 75.328 (d, CH-N(CH$_3$)$_2$), 126.315, 127.126, 127.394, 127.769, 128.448, 128.532 (6xd, Ar-C), 131.989, 136.916 (2 x d, CH=CH) 136.847, 142.389 (2xs, Ar-C); *m/z* : 237 (M$^+$, 21%), 193 (62), 178 (19), 160 (34), 134 (16), 115 (100), 103 (4), 91 (44), 77 (11), 65 (9), 42 (11).
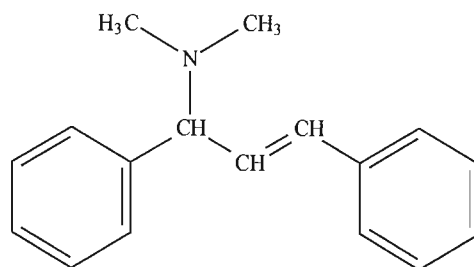
(90)

3.8 PREPARATION OF BROMO-COMPOUND PRECURSORS

2,3-Dibromo-3-phenylpropanoic acid. **(98)**

3-Phenyl-2-propenoic acid (15.00 g, 101.4 mmol) was placed in a 500 ml round-bottomed flask and 150 ml diethyl ether was added. Bromine (27 ml, (20% v/v in ether), 211.2 mmol) was added to the flask in several small portions, stirring with a glass rod after each addition. The acid slowly dissolved resulting in a dark orange solution. The flask was then attached to a distillation head *via* a short fractionating column. The reaction mixture was heated gently on a heating mantle until all the ether had been collected. The heat was then removed and the contents of the flask allowed to cool and solidify. Ice cold water (100 ml) was added to the flask and the crystal mass broken up with a spatula. The crystals were then collected by filtration in a Buchner funnel, washed with several portions of cold water and dried at 100°C in an oven to afford white crystals of 2,3-dibromo-3-phenylpropanoic acid. (25.45 g, 81%). m.p. 195-197°C. δ_H (200MHz) : (acetone) 5.180 (1H, d, Ar-C*H*(Br)), 5.495 (1H, d, HOC(O)C*H*(Br)), 7.415 (3H, m, Ar-*H*), 7.660 (3H, m, Ar-*H*, C(O)O*H*); δ_C (50MHz) : 47.525 (d, Ar-CH-Br), 52.087 (d, Ar-CH(Br)-CH(Br)), 128.943, 129.140, 129.605, 130.005 (4xd, Ar-*C*), 139.164 (s, Ar-*C*) 169.088 (s, O=*C*-OH); *m/z* : 184, (M-126, 57%), 182 (62), 103 (100), 91 (3), 81 (1), 79 (1), 77 (34), 63 (4), 51(1), 39 (1).
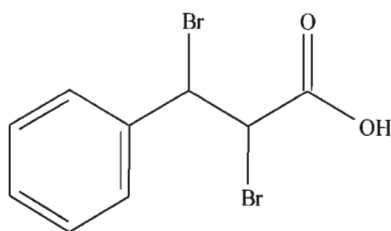
(98)

1-Bromo-2-phenylethene (**99**)

2,3-Dibromo-3-phenylpropanoic acid (25.45 g, 82.6 mmol) was placed in a 1000 ml Erlenmeyer flask. Anhydrous potassium carbonate (25.50 g, 185.8 mmol) was placed in a 500 ml beaker and dissolved in water (225 ml). The basic solution was added to the 2,3-dibromo-3-phenylpropanoic acid and the reaction mixture heated to a gentle boil. The solid dissolved and a light yellow oil formed. The reaction was maintained at the boil for 15 mins and then cooled in an ice/water mixture. The reaction products were extracted into diethyl ether, dried over anhydrous $MgSO_4$. The drying agent was filtered off and the ether was removed under reduced pressure to afford a strong, sweet smelling yellow liquid. (5.61 g, 37%; *cis:trans* 28:72). yellow liquid. δ_H (200MHz) : 6.392 (1H, d J 8.2Hz, Ar-CH=C*H*Br(*cis*)), 6.720 (1H, d J 14Hz, Ar-CH=C*H*Br(*trans*)), 7.030 (1H, d J 8.2Hz, Ar-C*H*=CHBr(*cis*)), 7.071 (1H, d J 14Hz, Ar-C*H*=CHBr(*trans*)), 7.178-7.385 (5H, m, Ar-*H*(*trans*)), 7.641-7.691 (5H, m, Ar-*H*(*cis*)); δ_C (50MHz) : 106.491 (d, Ar-CH=CH-Br), 137.073 (d, Ar-*C*H=CHBr), 126.031, 128.197, 128.718, (3xd, Ar-*C*), 135.809 (s, Ar-*C*); *m/z* : 184 (M^+, 43) , 182 (M^+, 44), 103 (100), 91 (2), 81 (3), 79 (3), 77 (53), 63 (13), 51 (31), 39 (7).
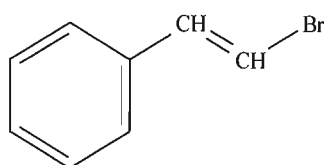
(**99**)

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APPENDIX : ¹H AND ¹³C NMR SPECTRA
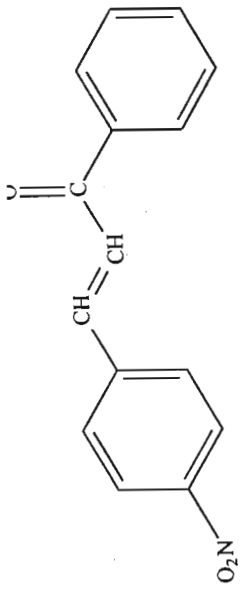
(63a)

(63a)

(63b)

(63b)

(63c)

(63c)

(64a)

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CH
CH
C
O
CH
CH

(64a)

(64b)

(64b)

180 160 140 120 100 80 60 40 20 PPM 0

(65a)

OH
|
CH

(65a)

(65b)

(65b)

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(65c)

(65c)

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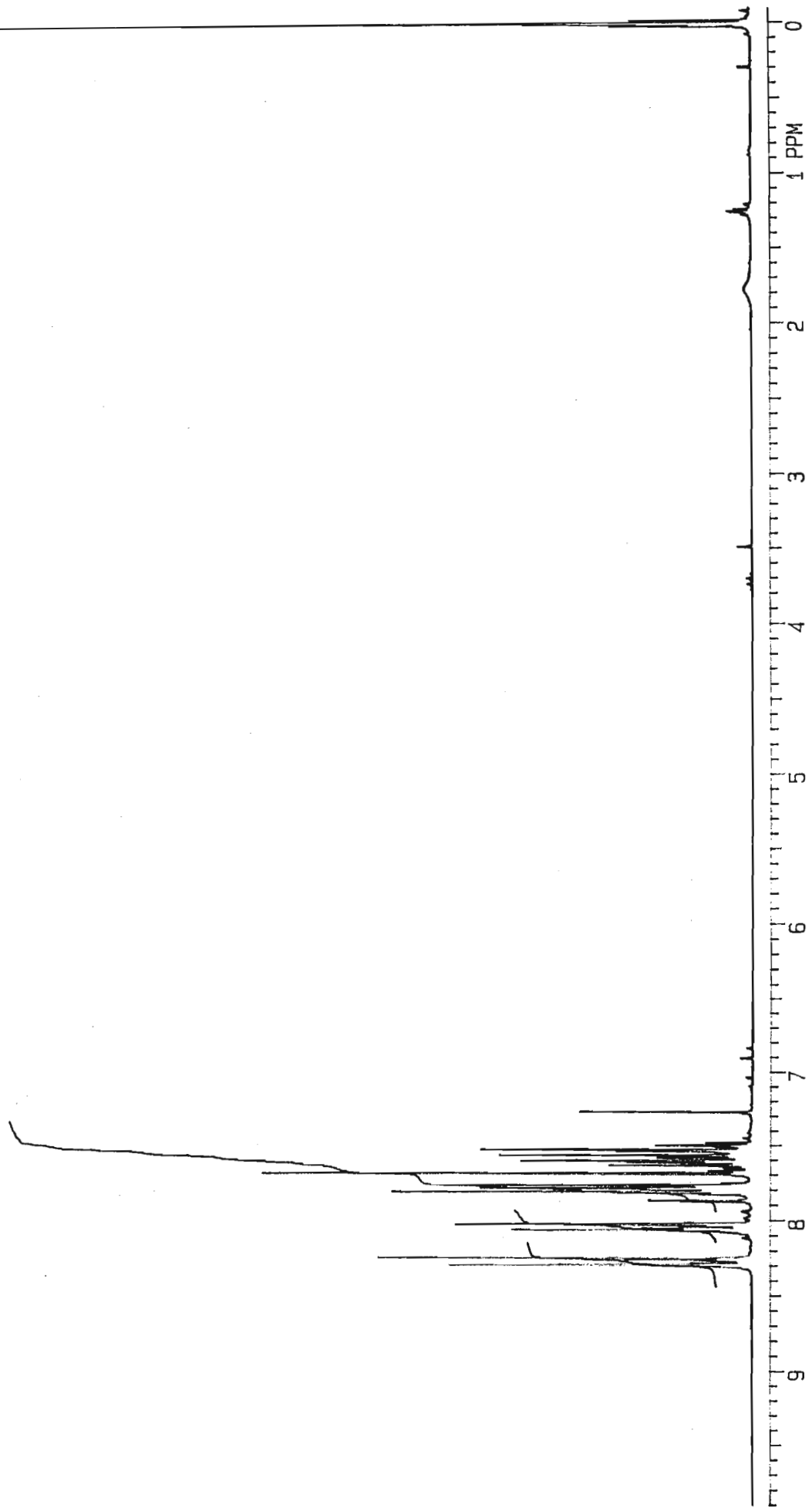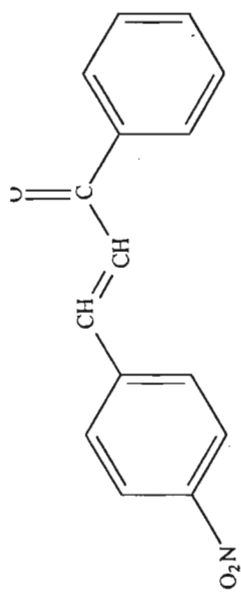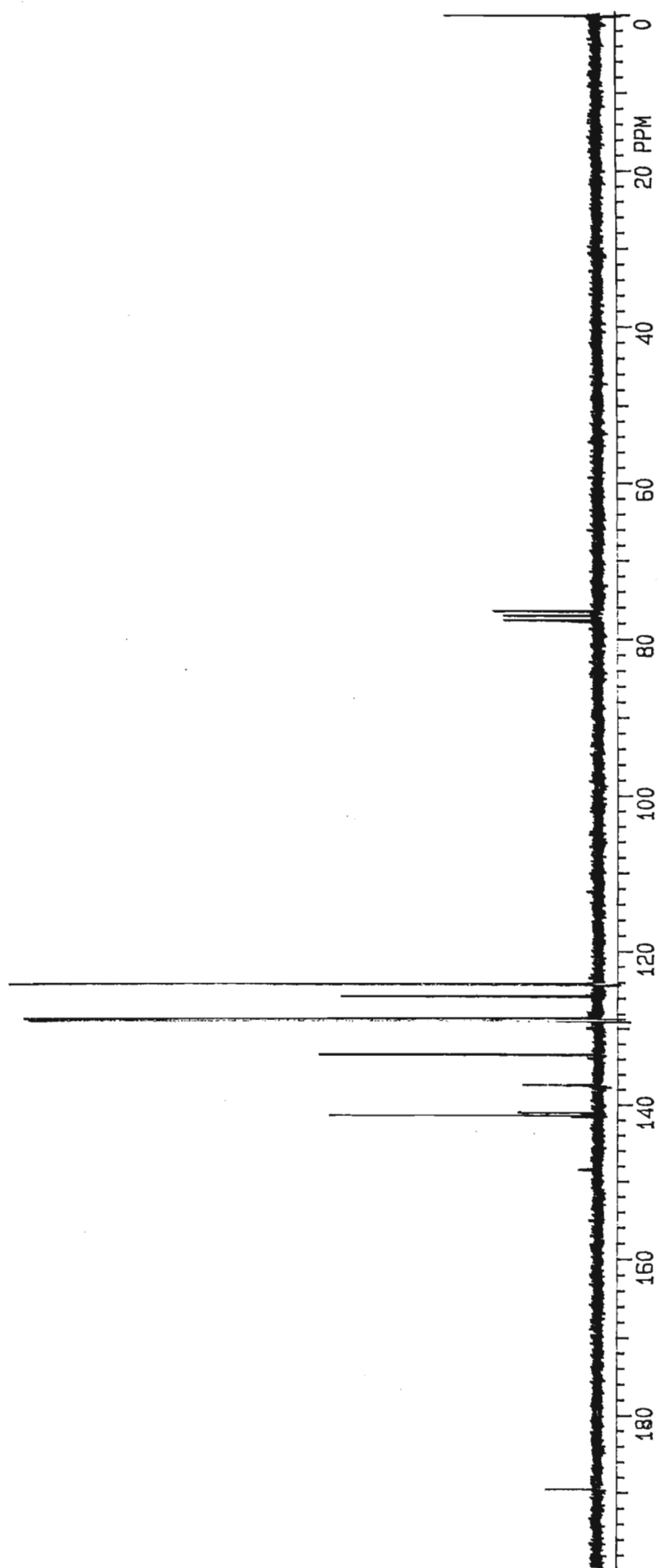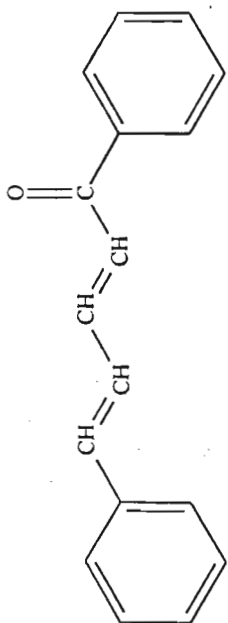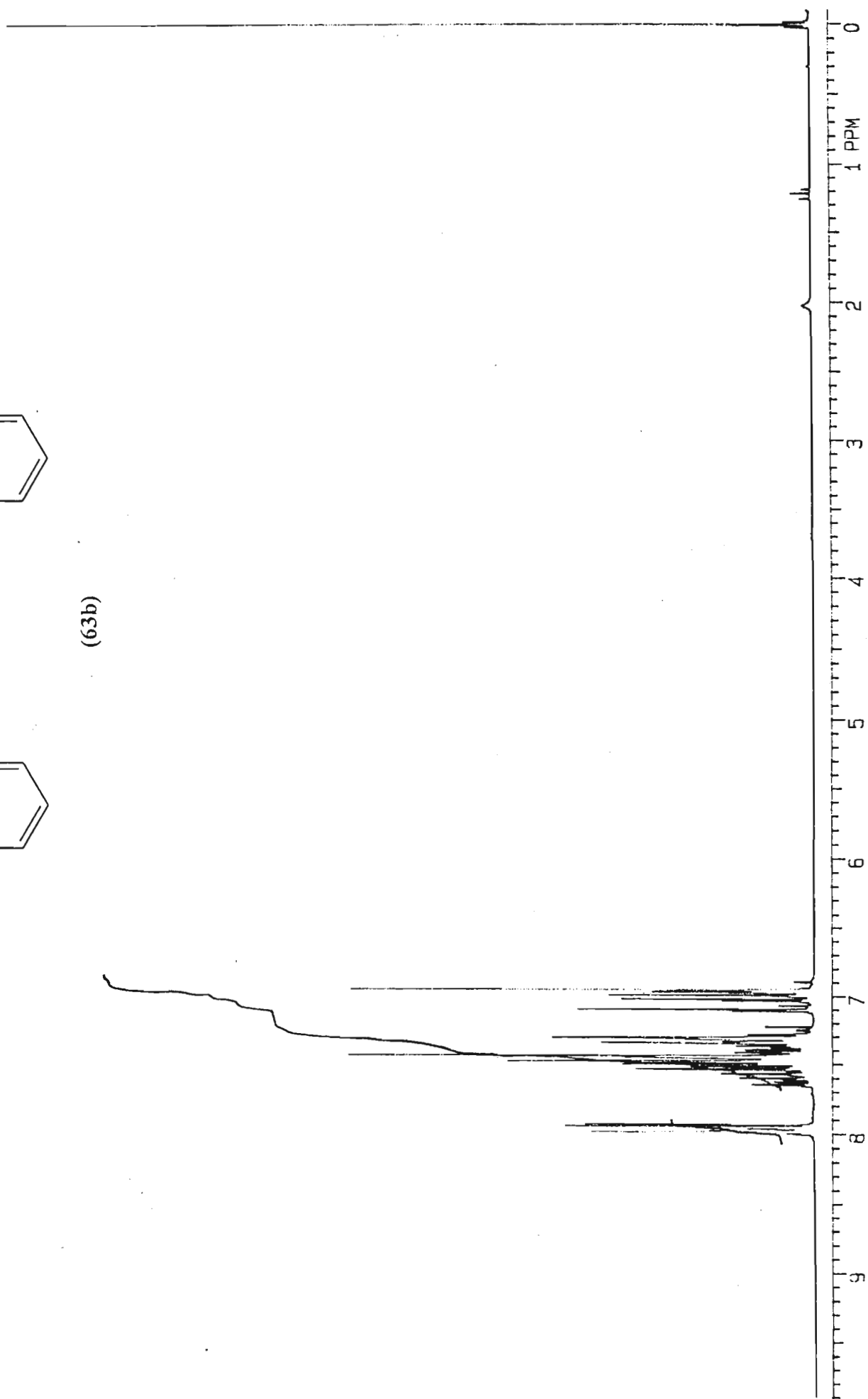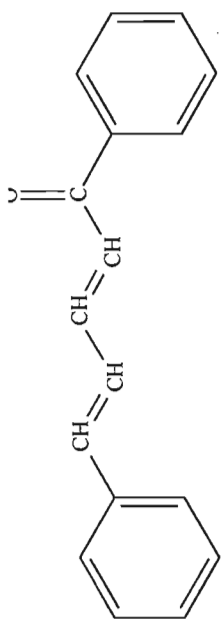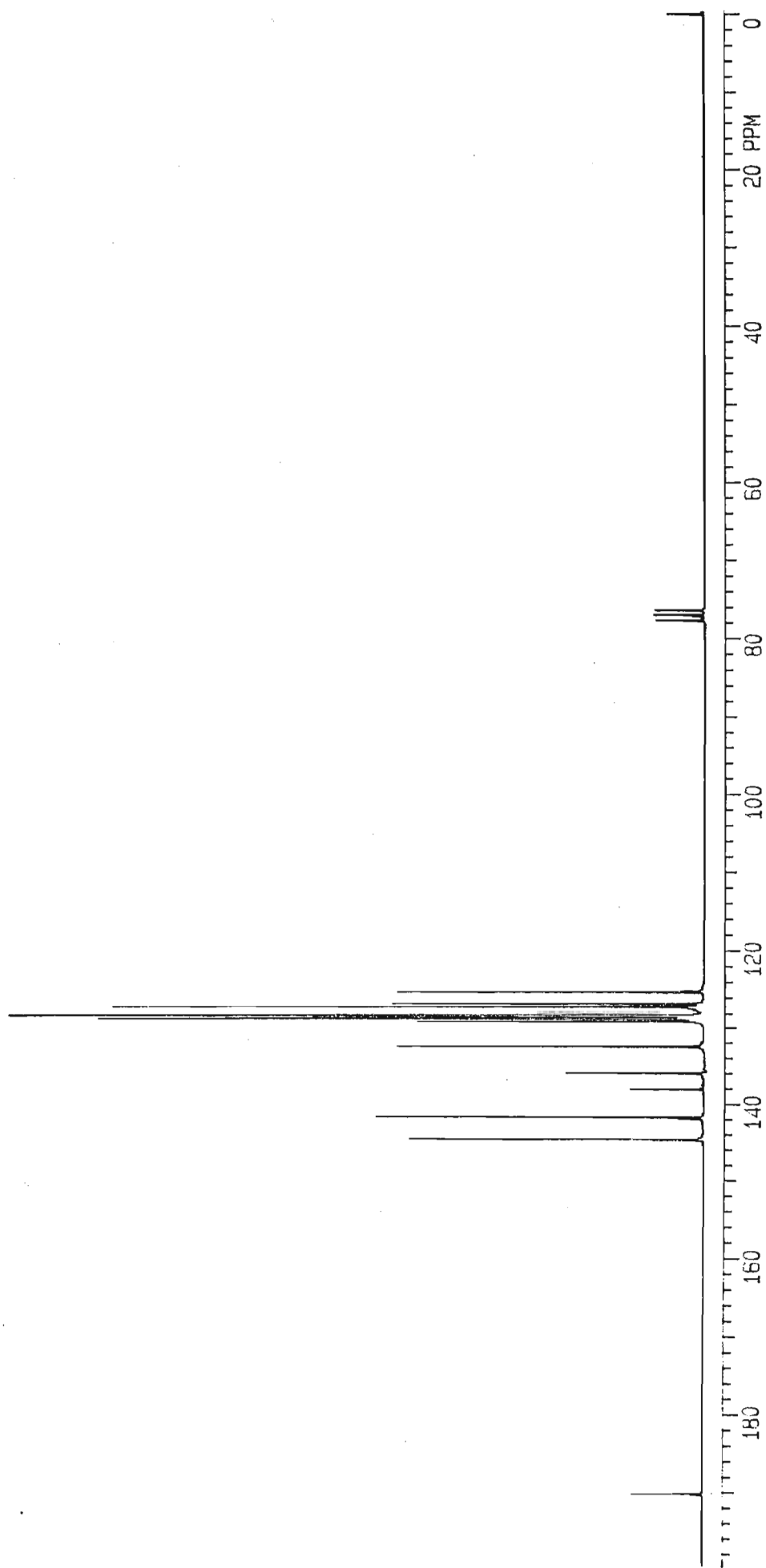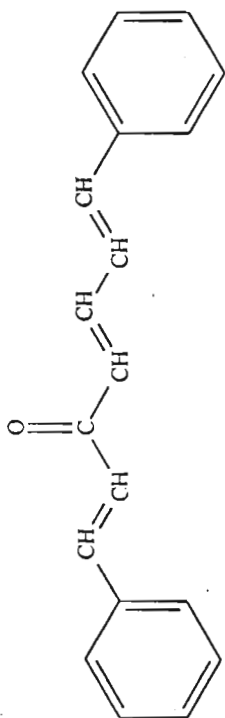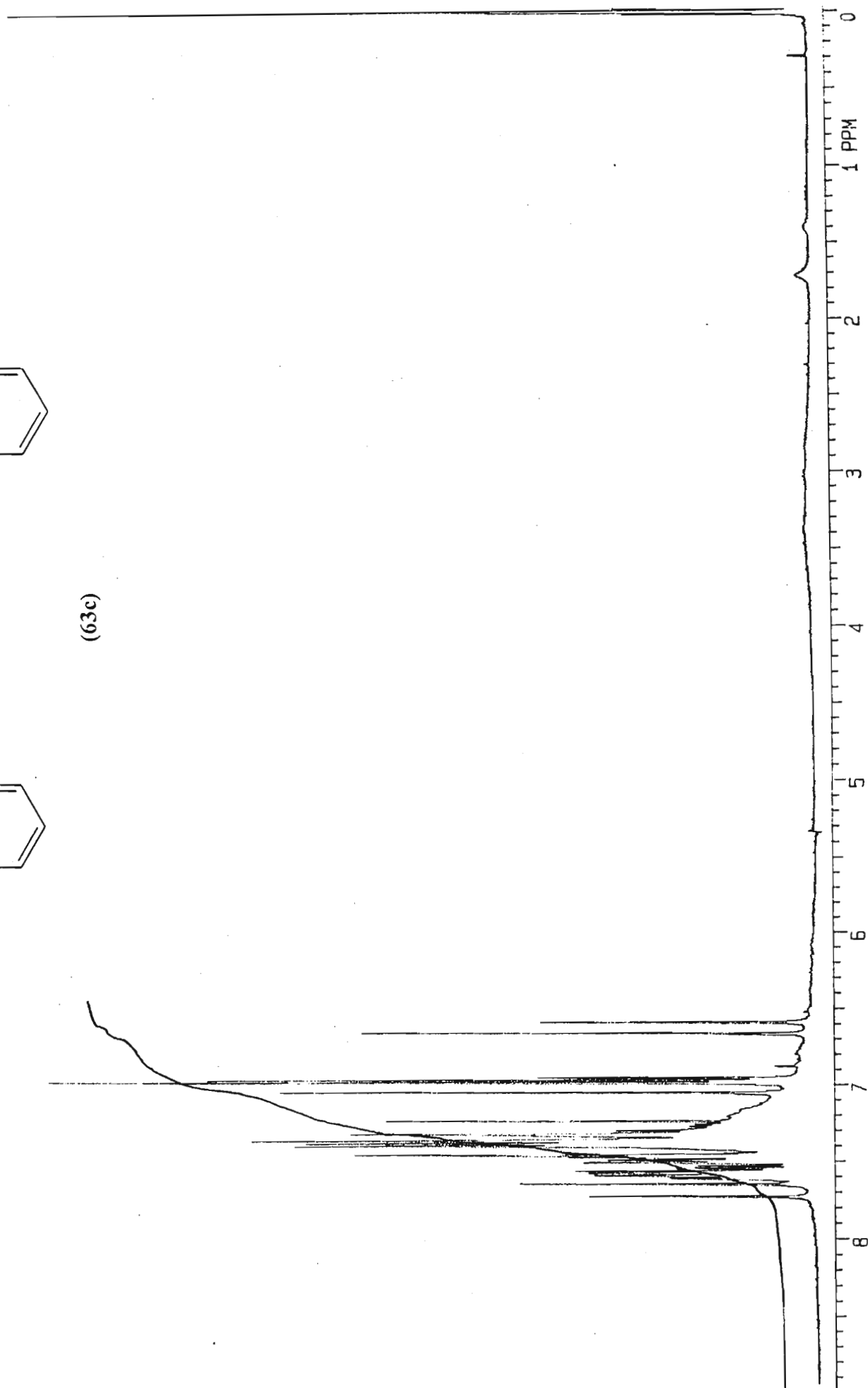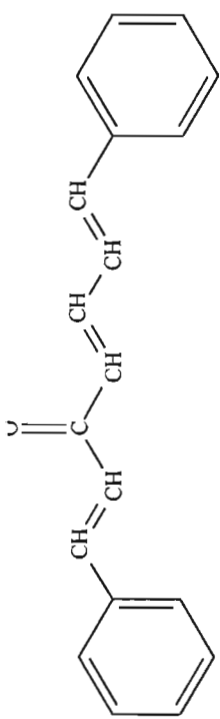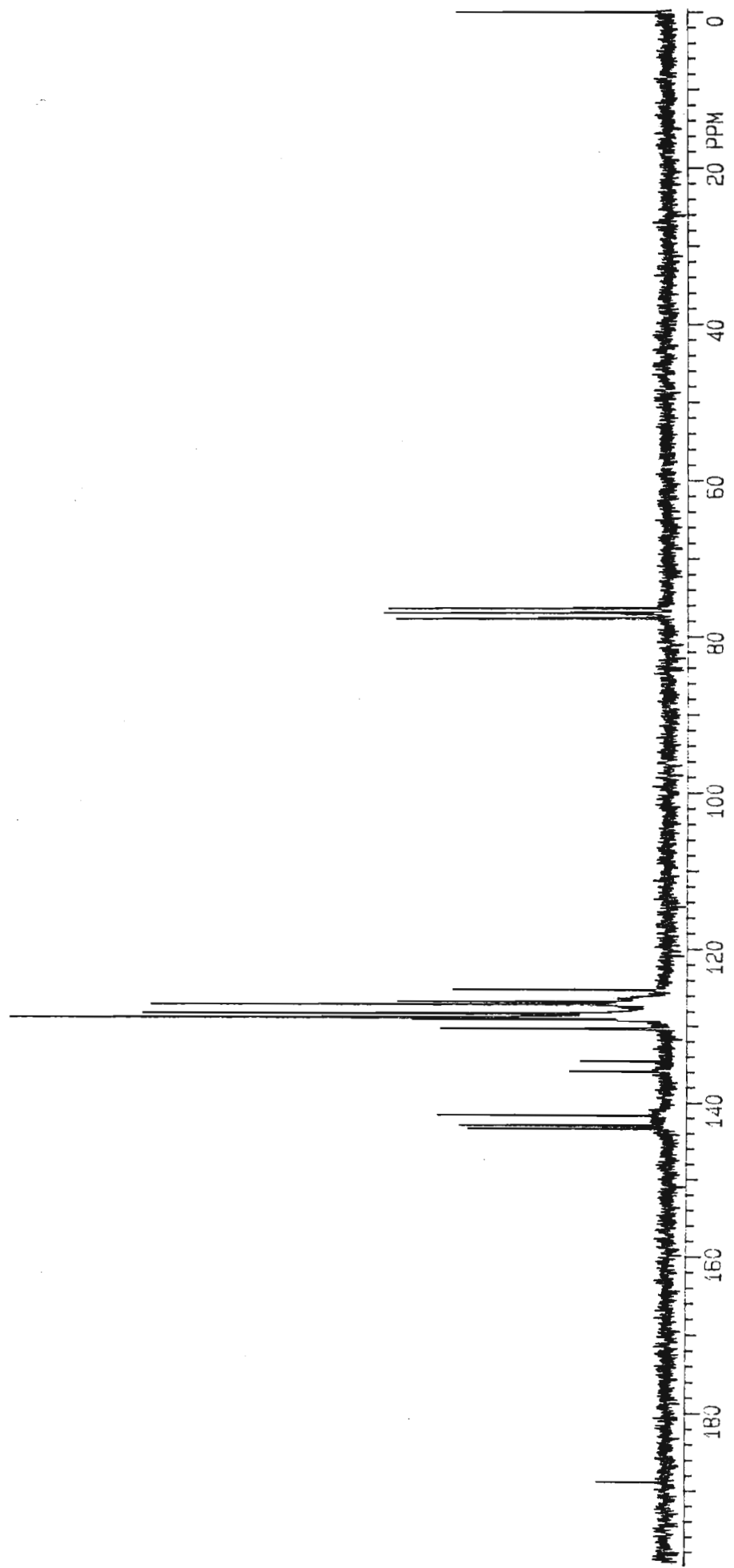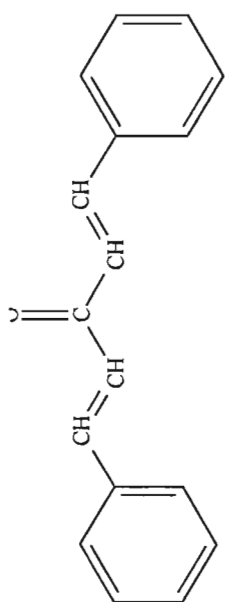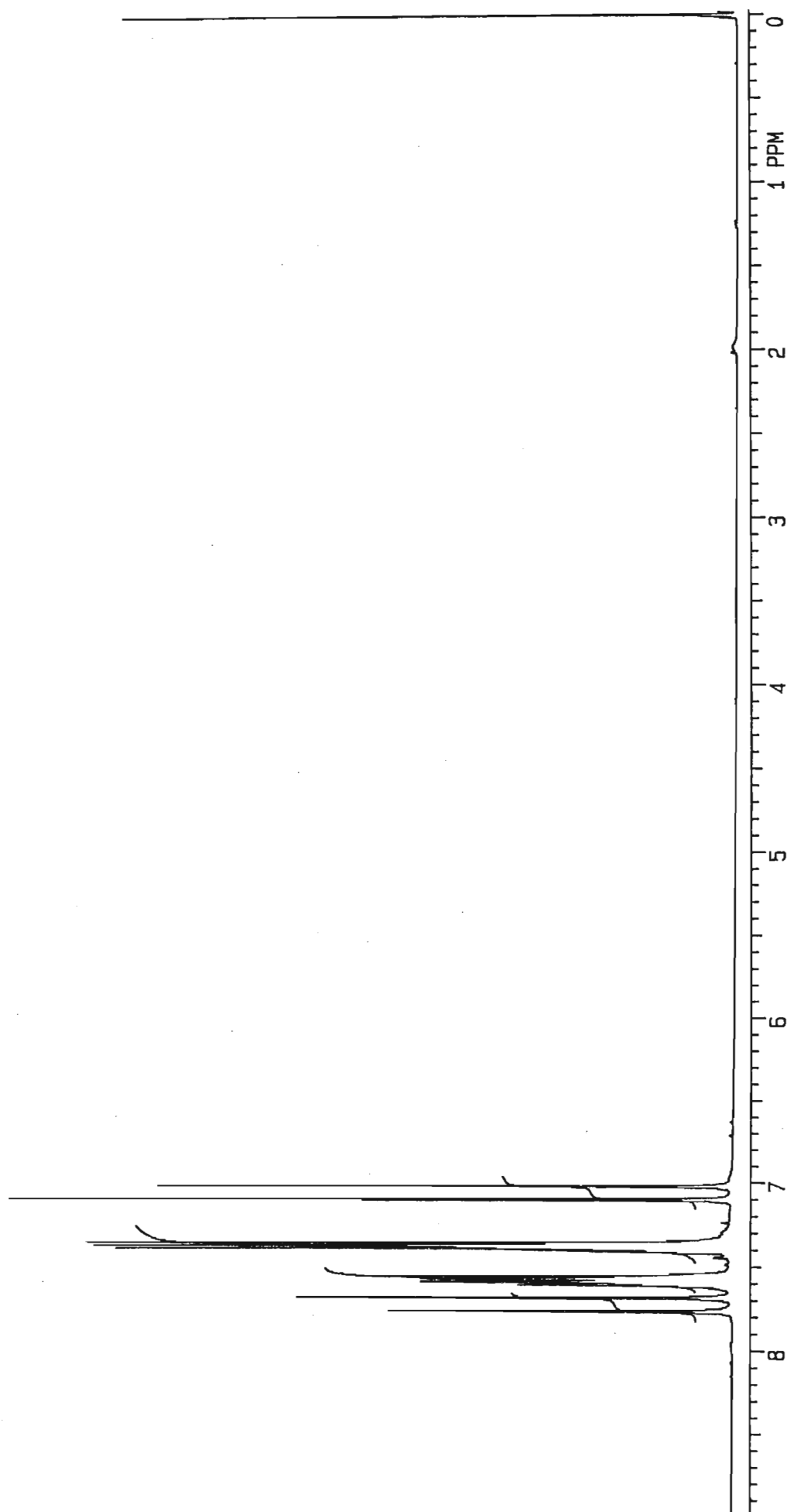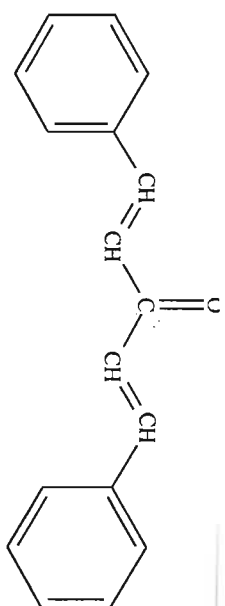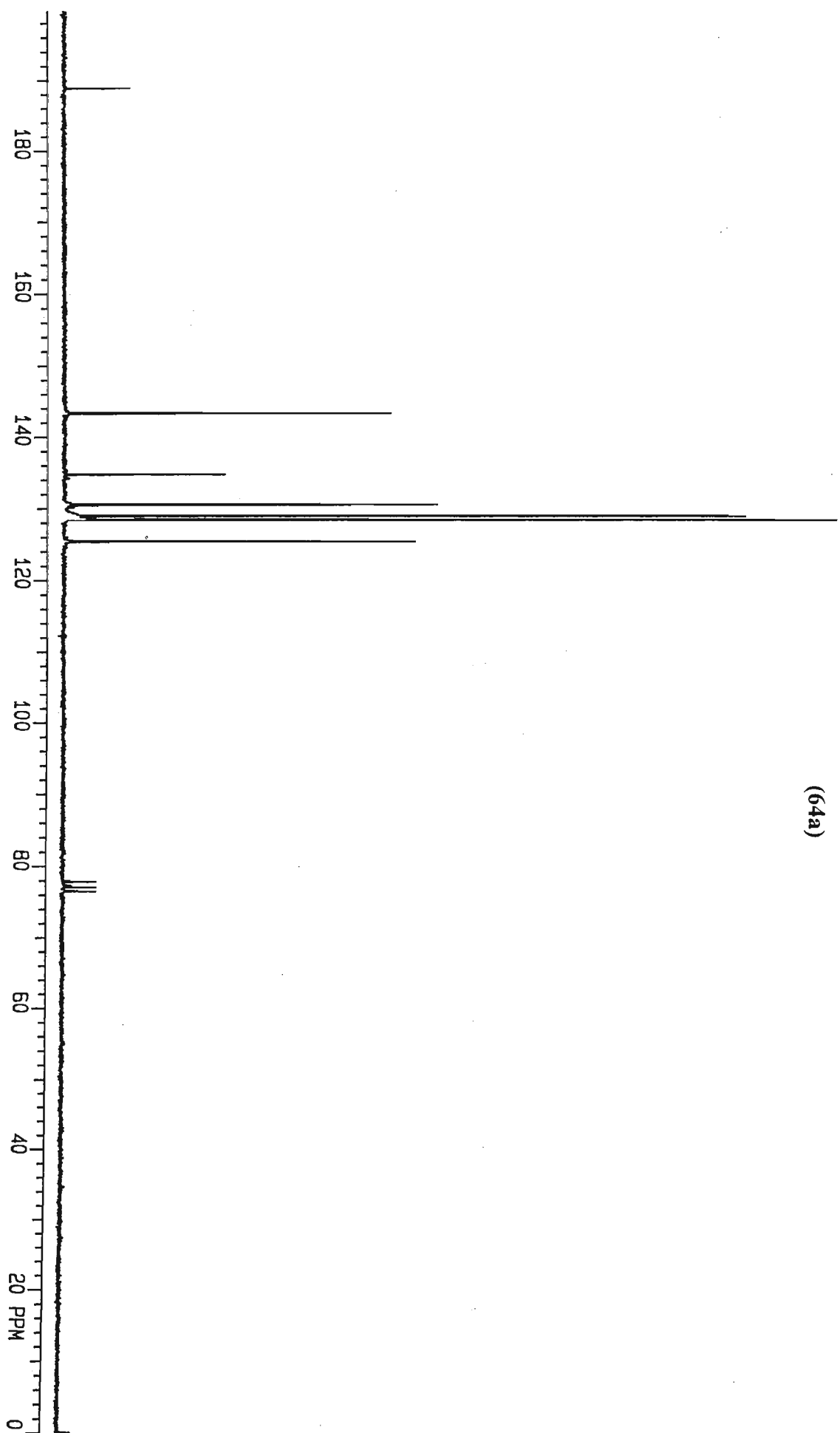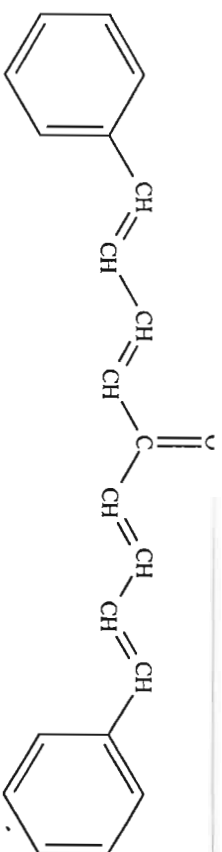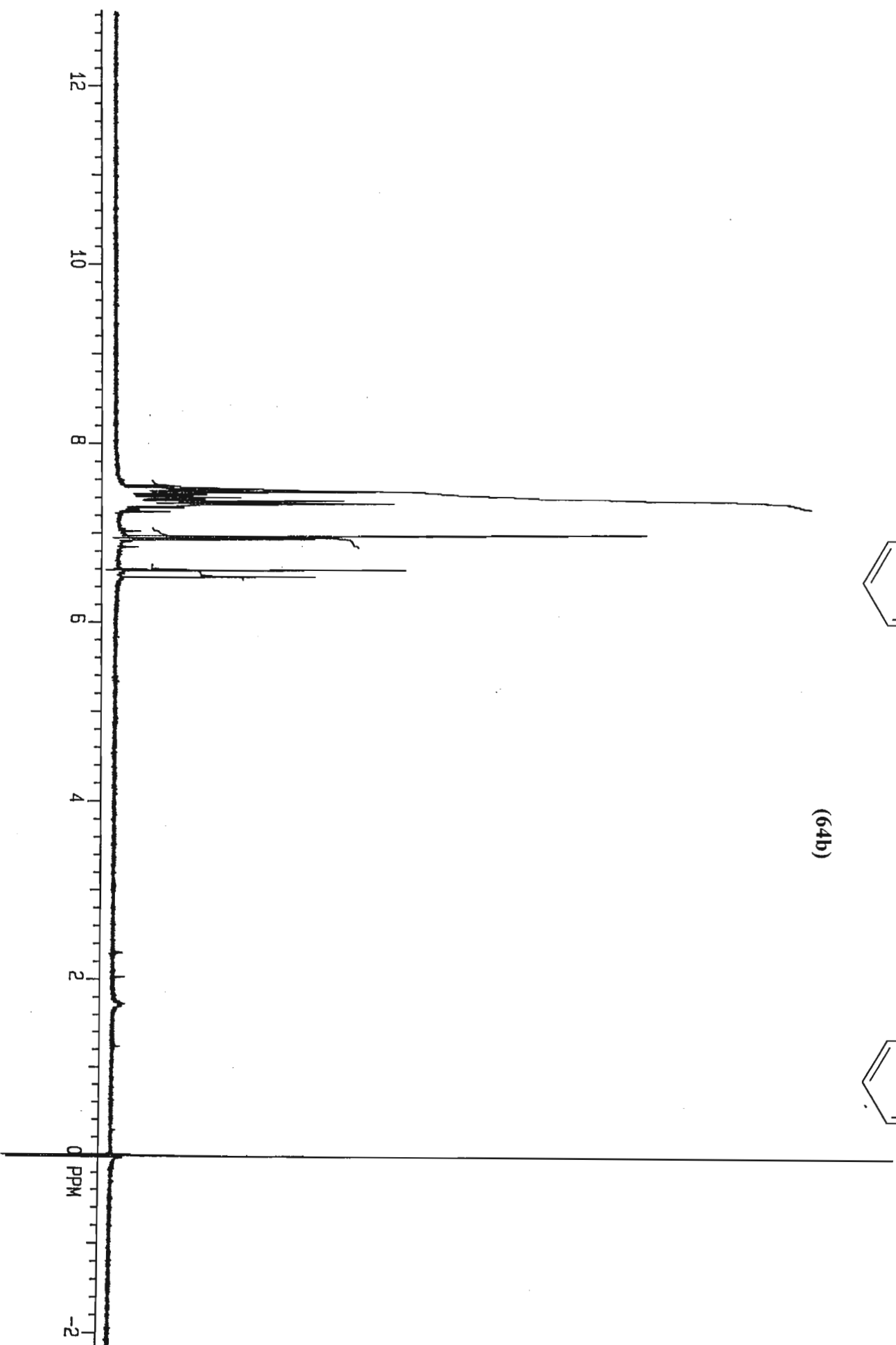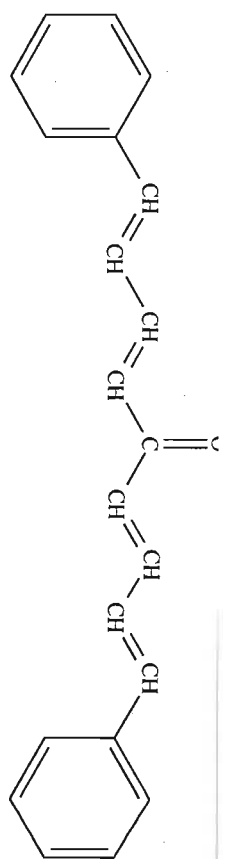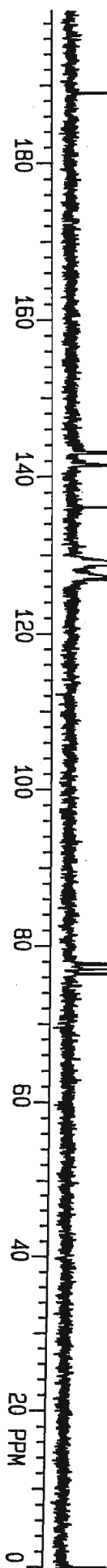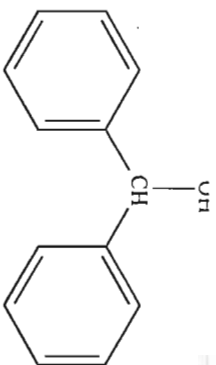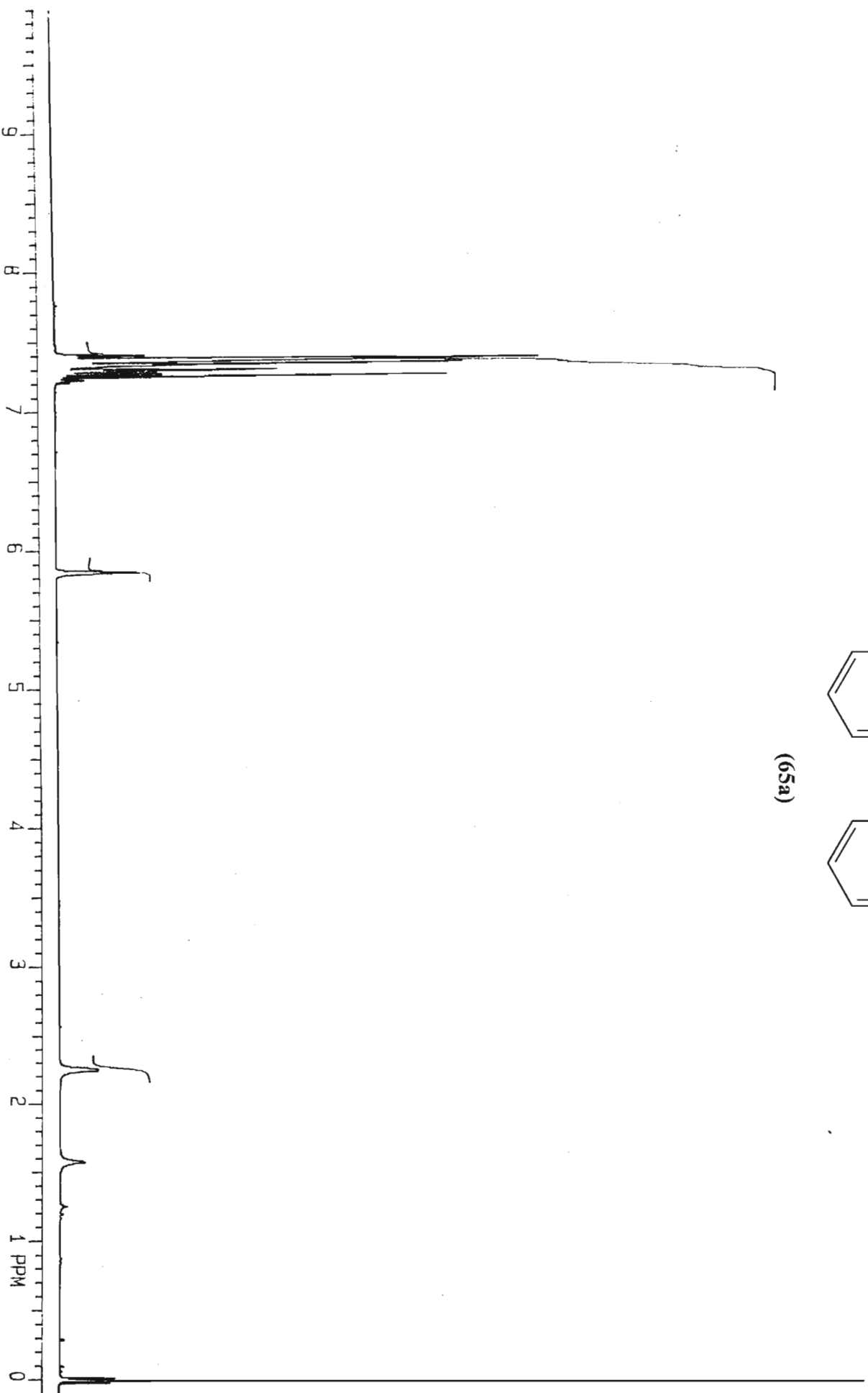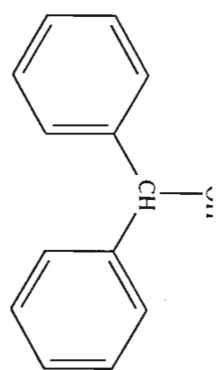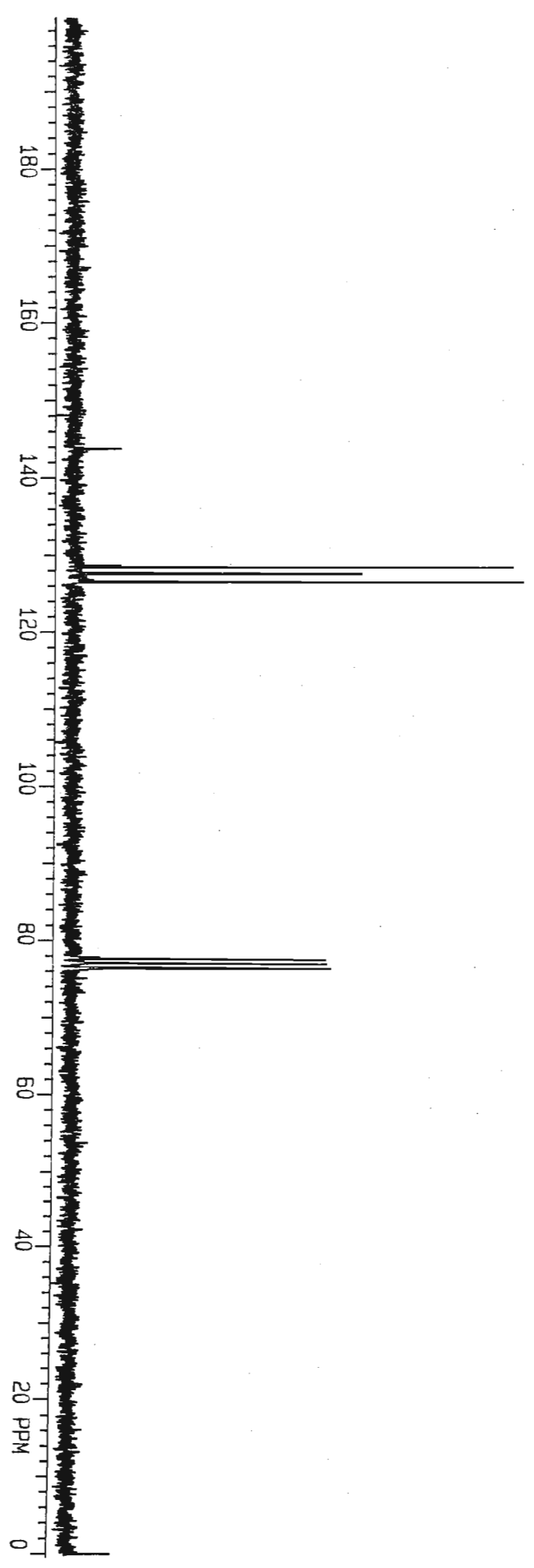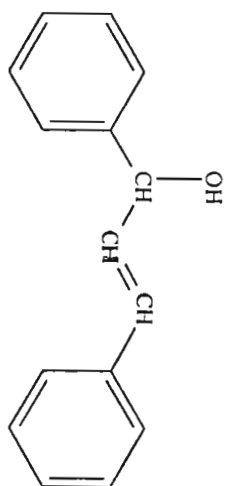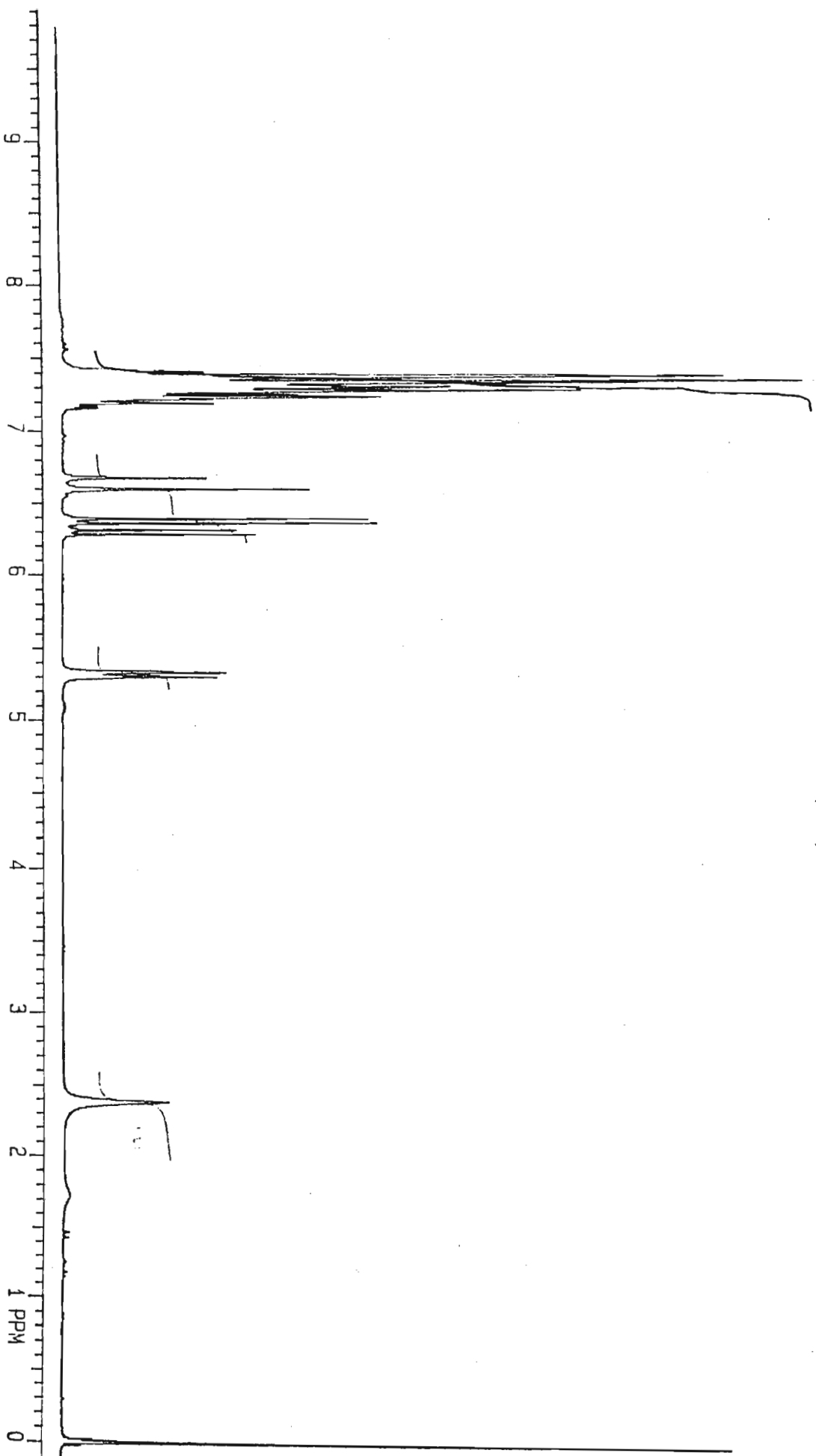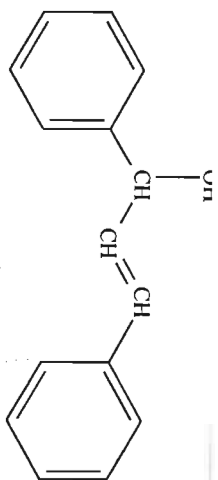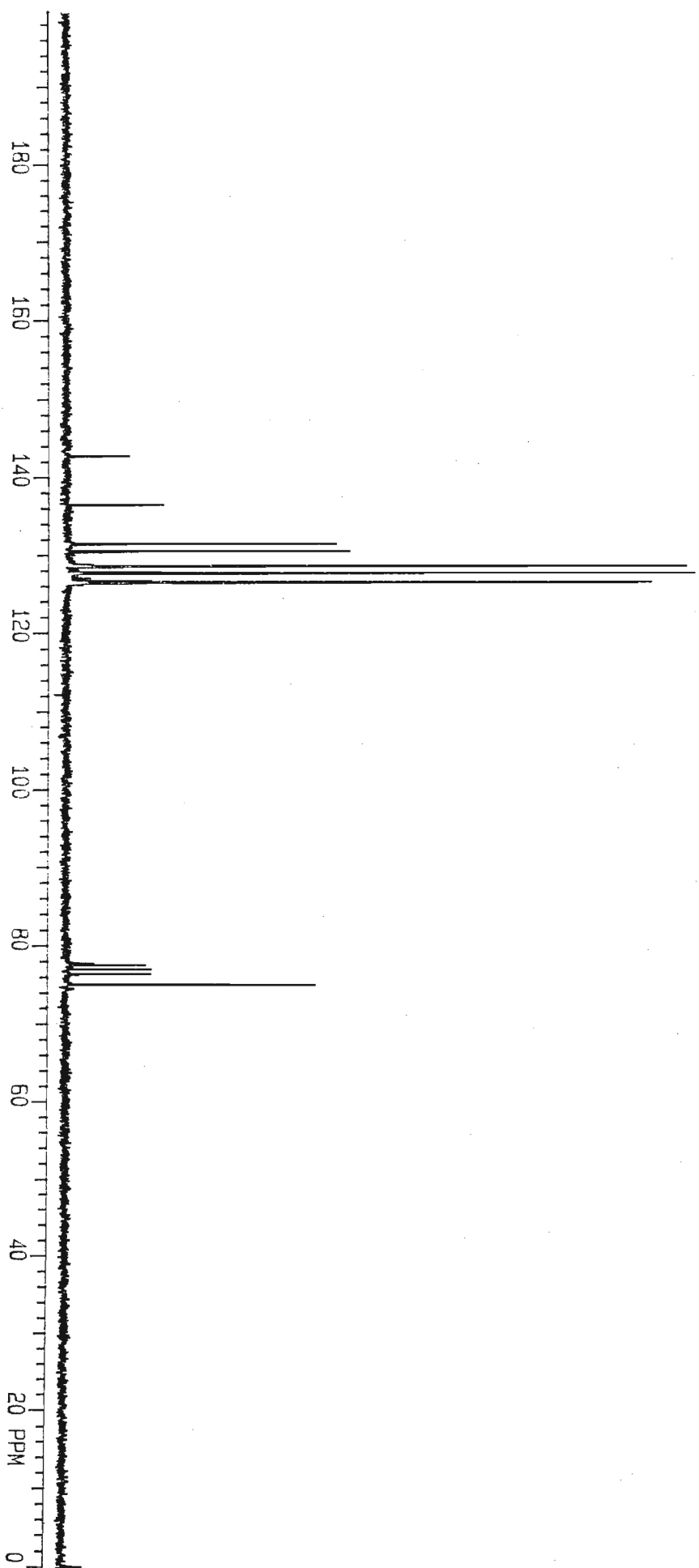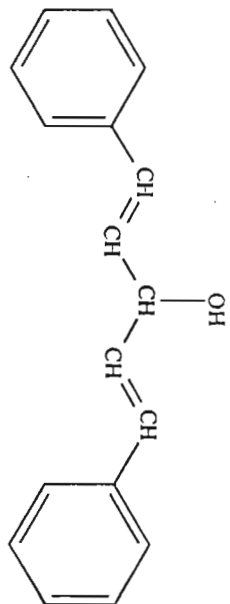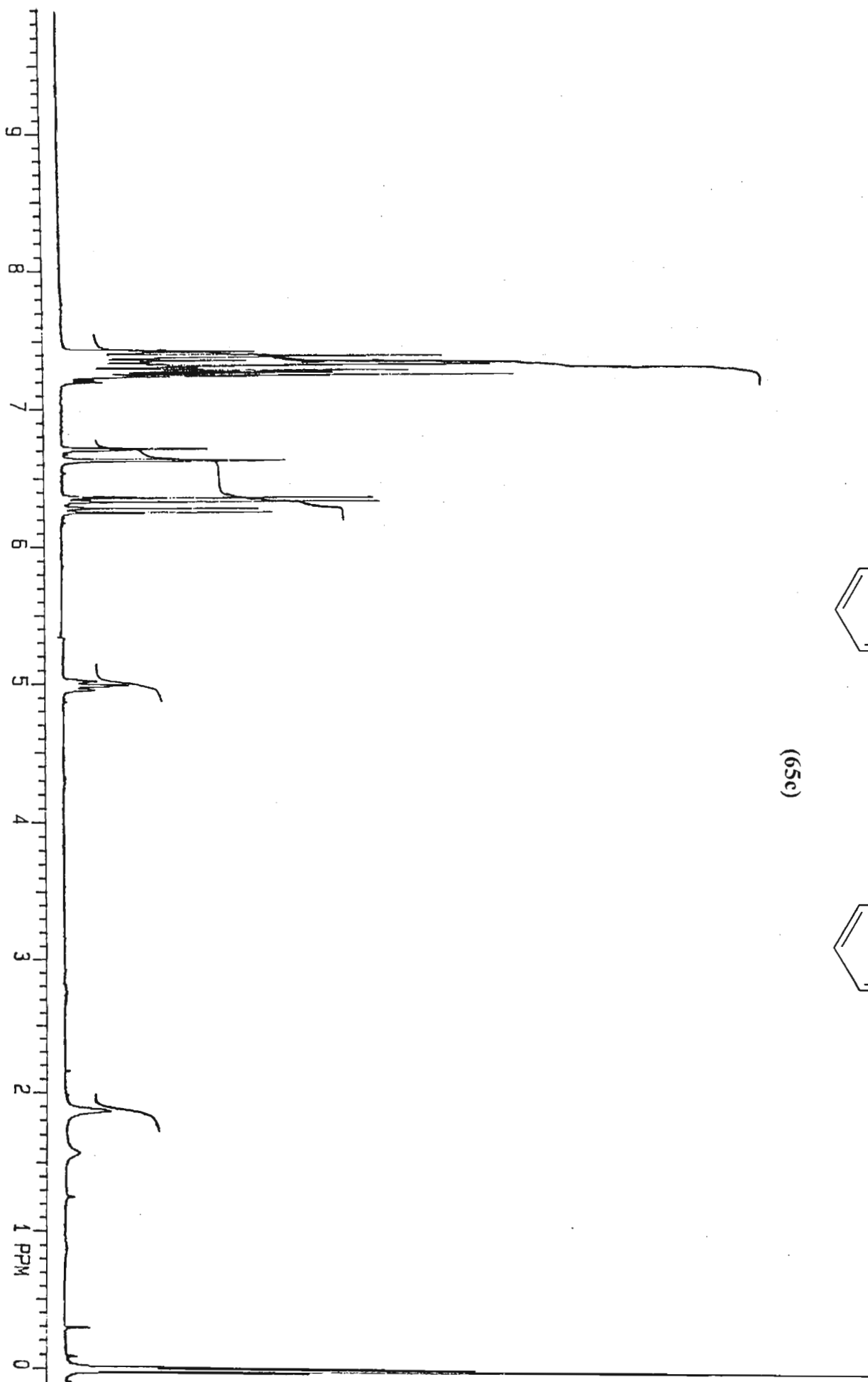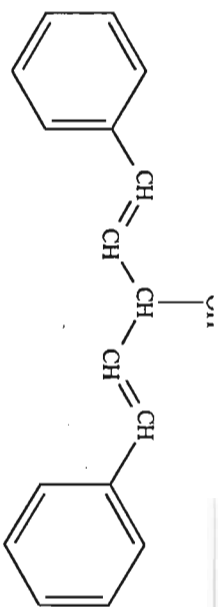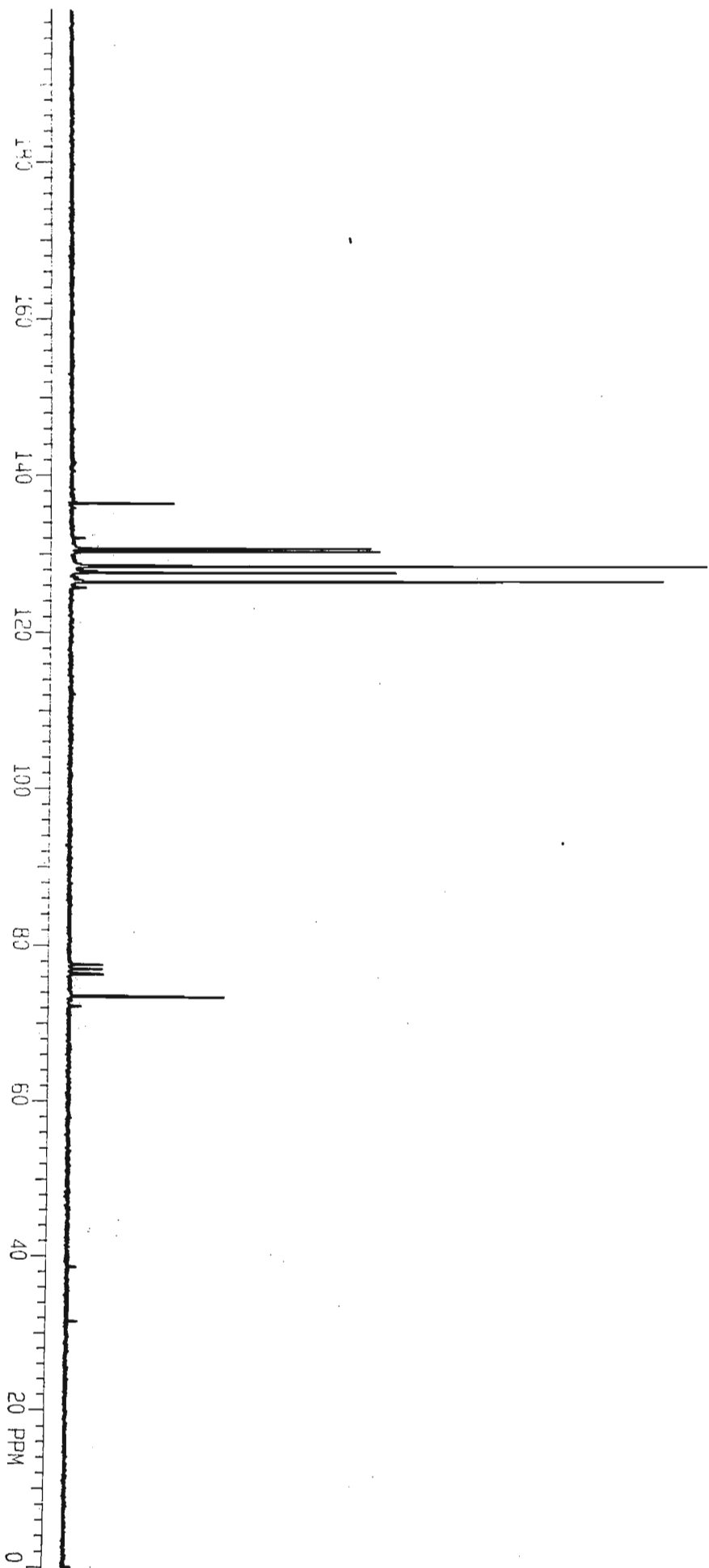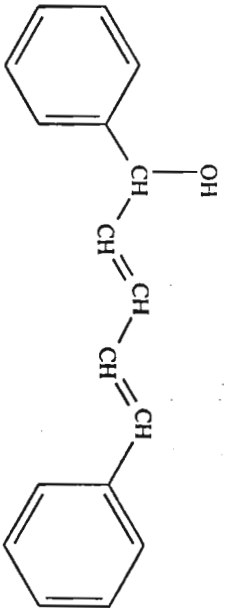
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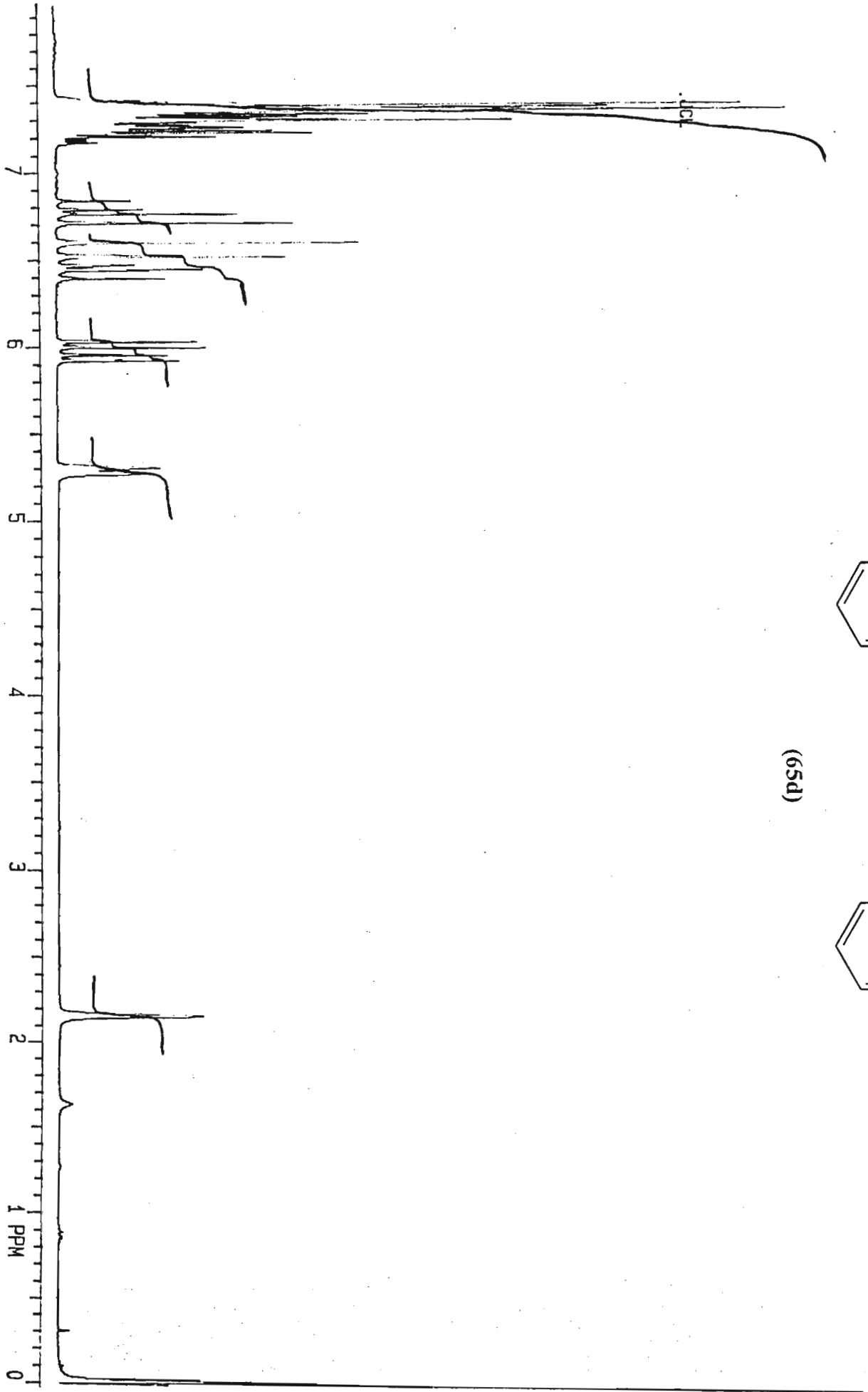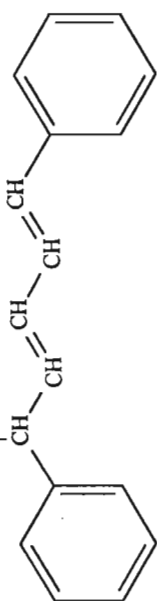
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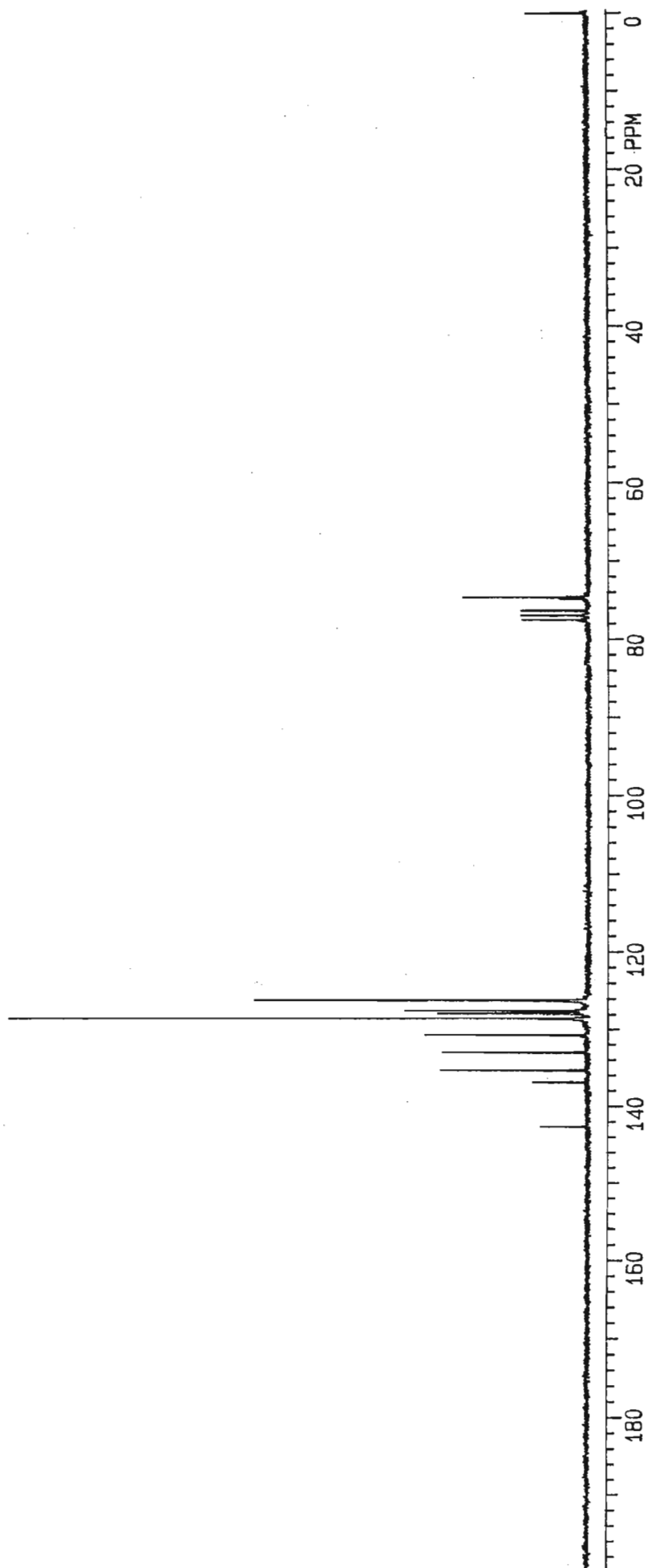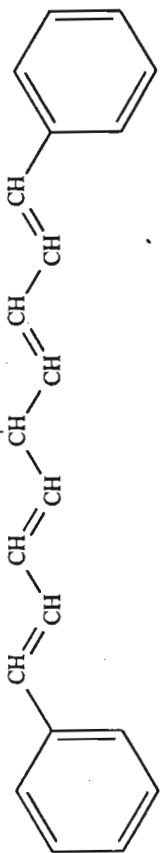
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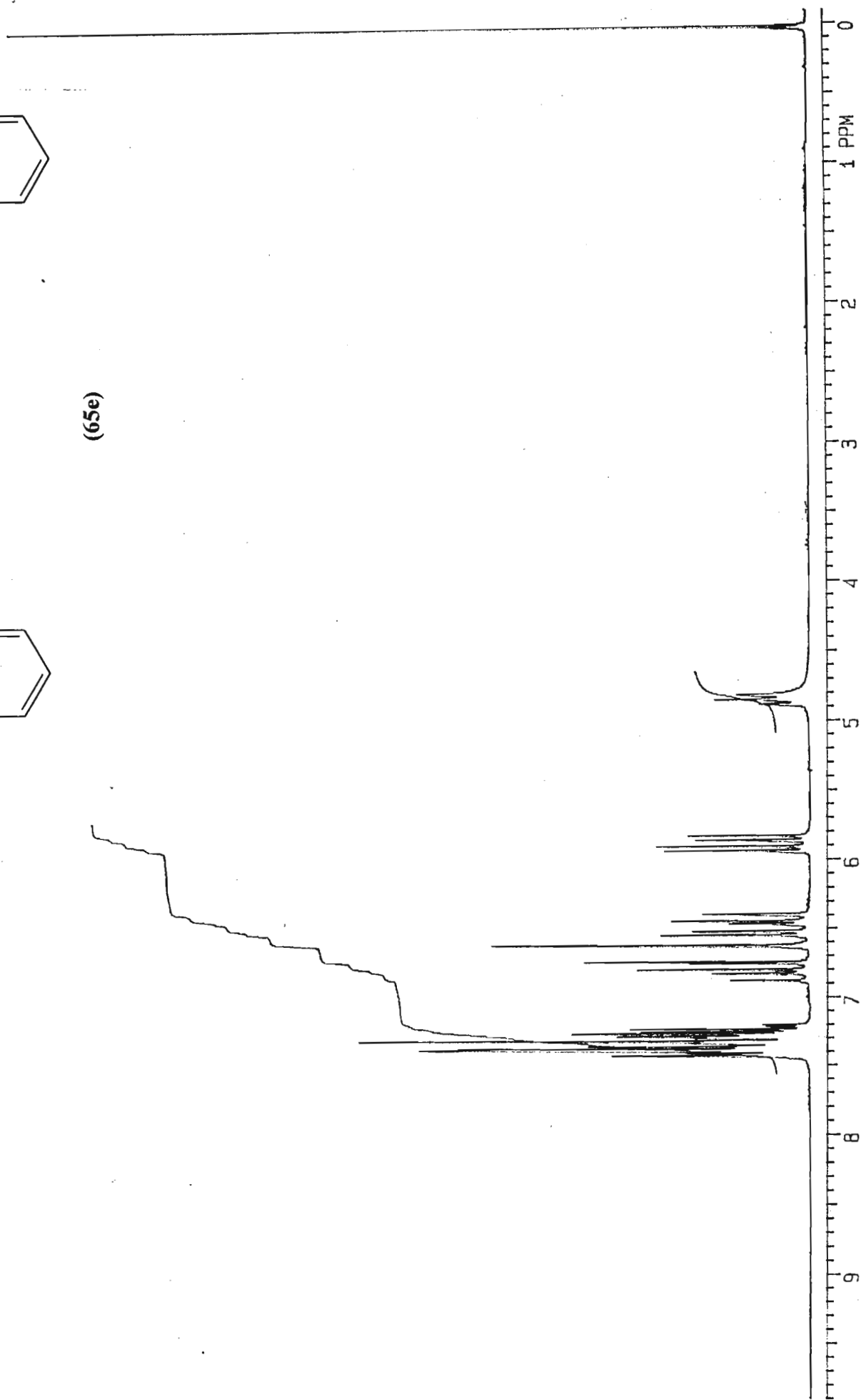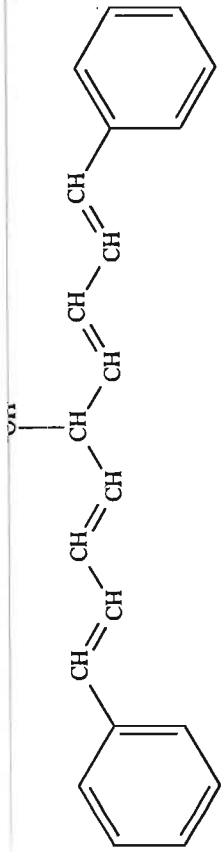
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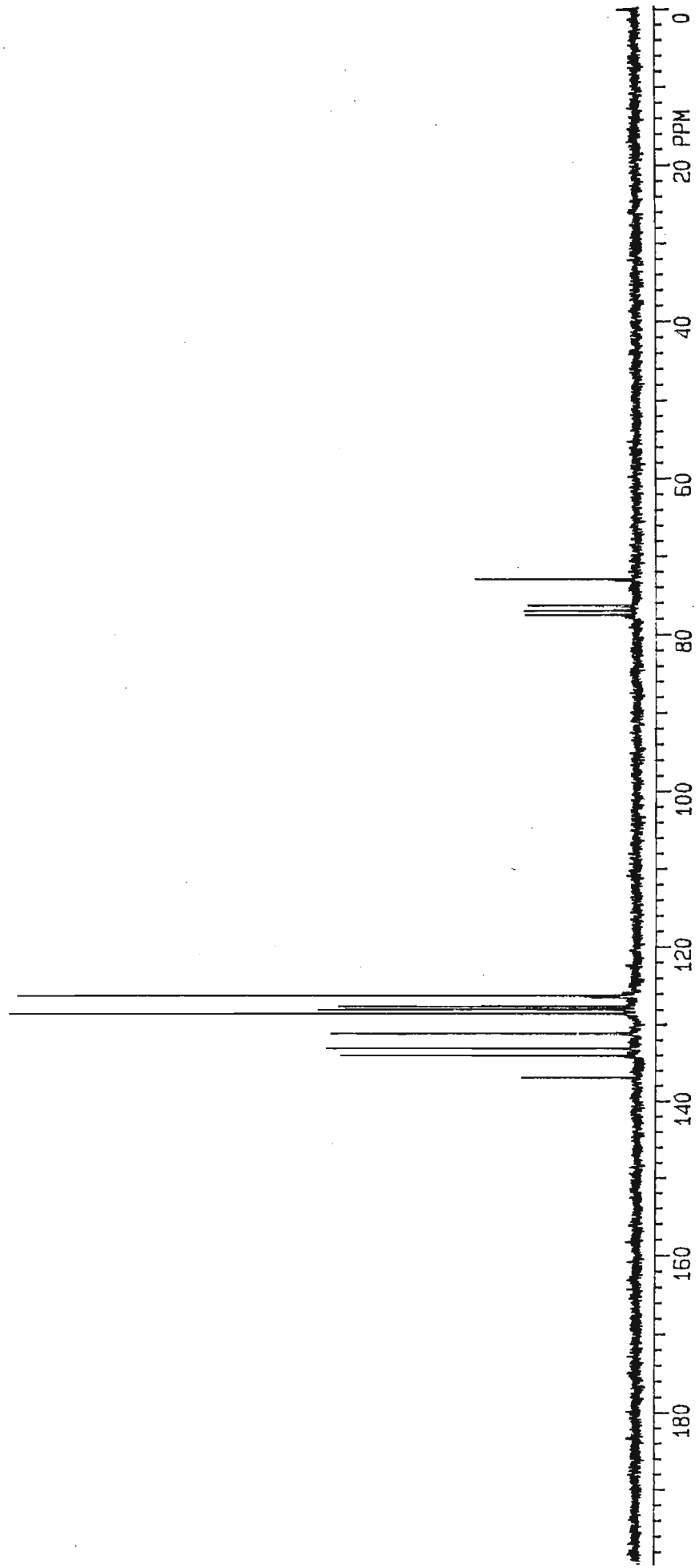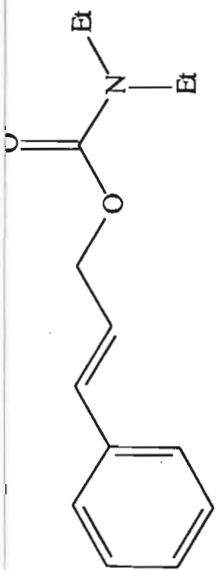
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(66b)

(66b)

(66c)

(66c)
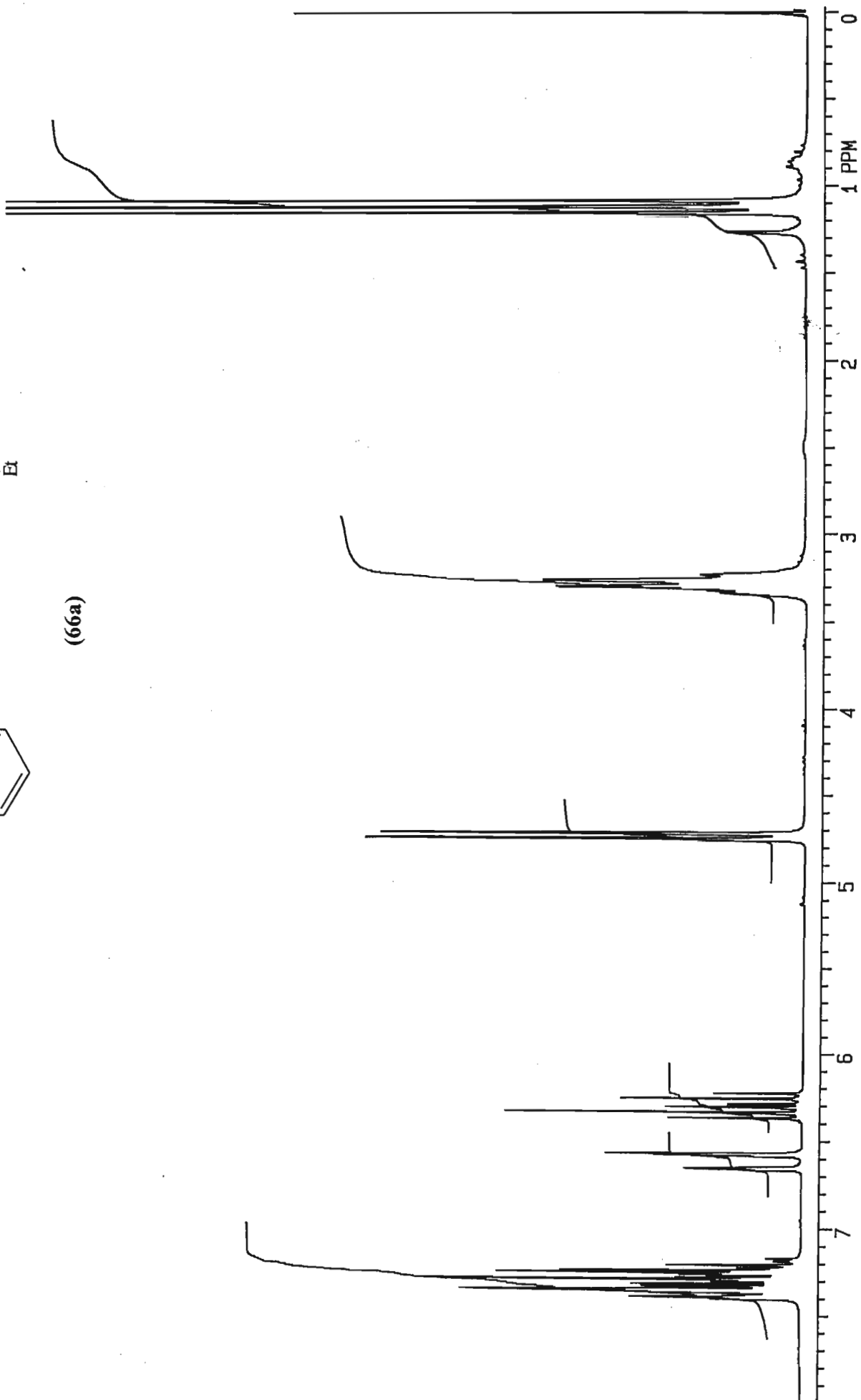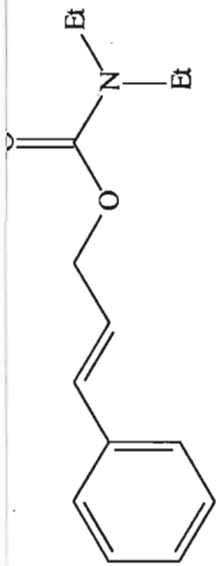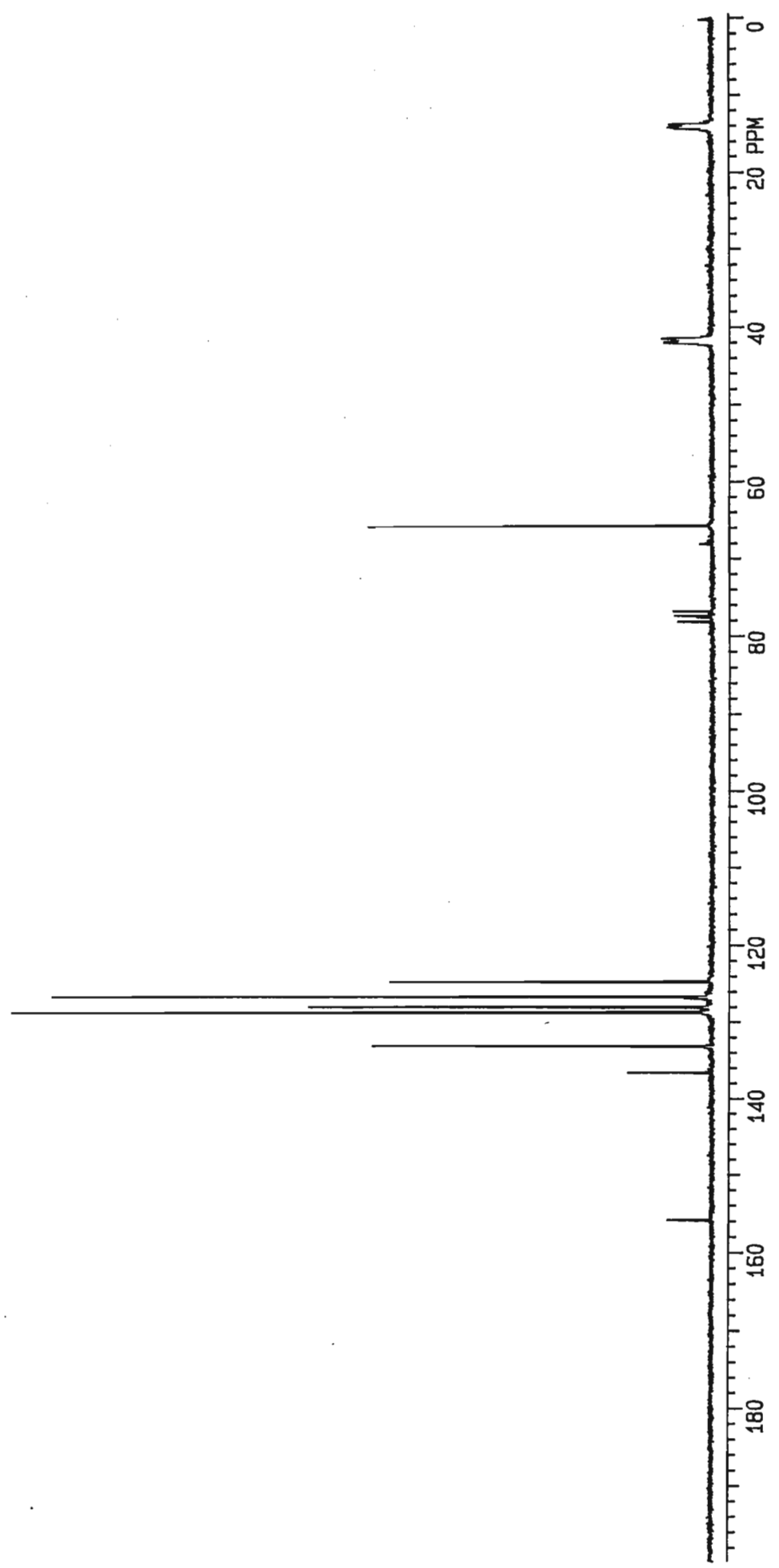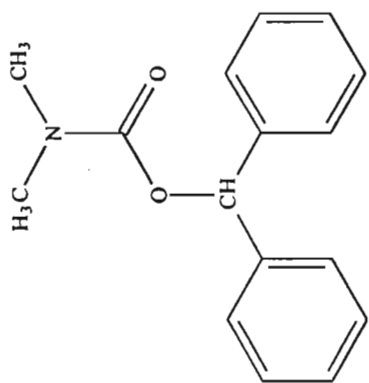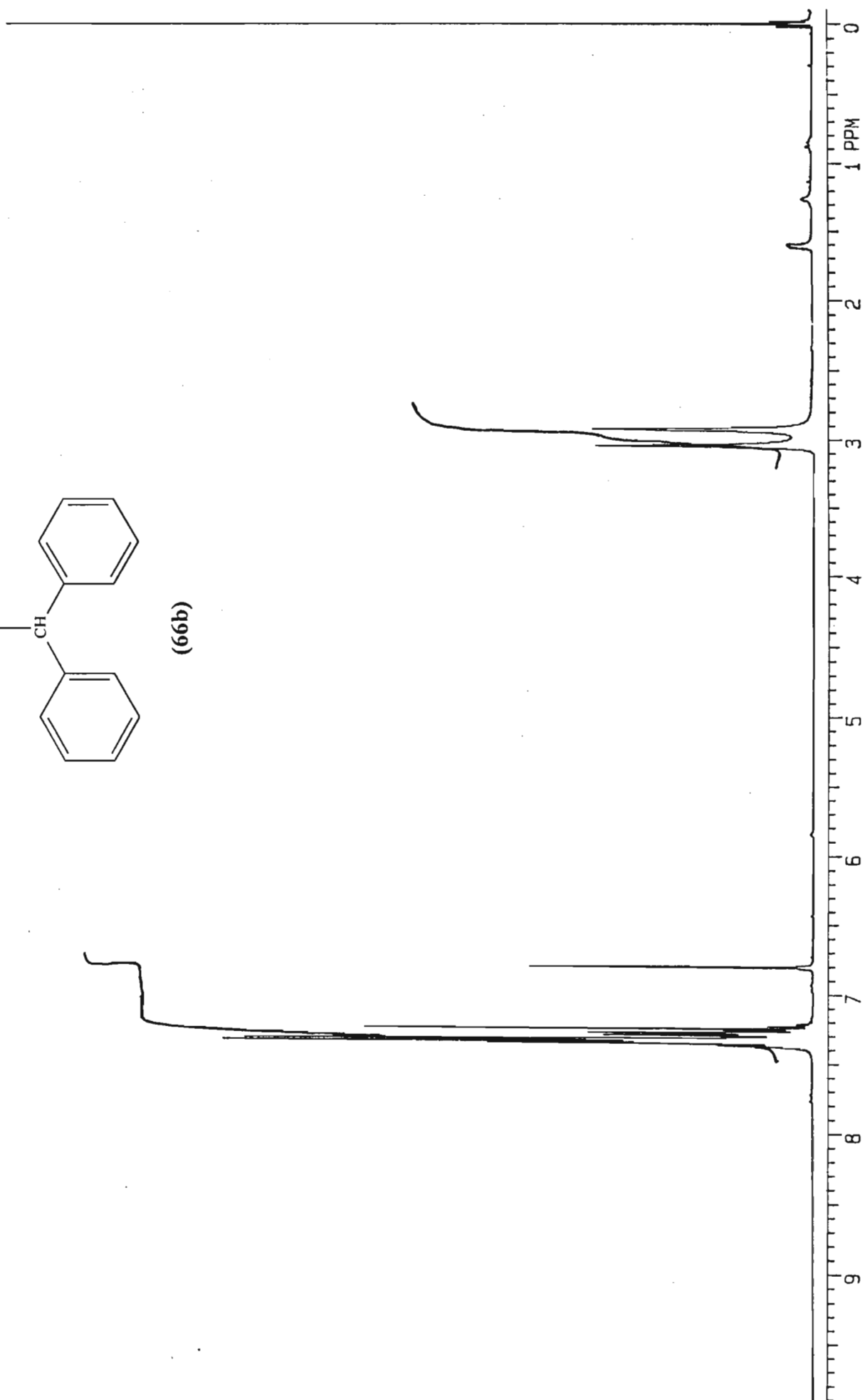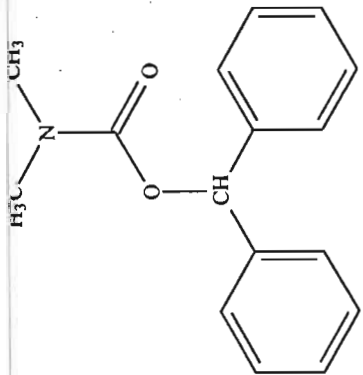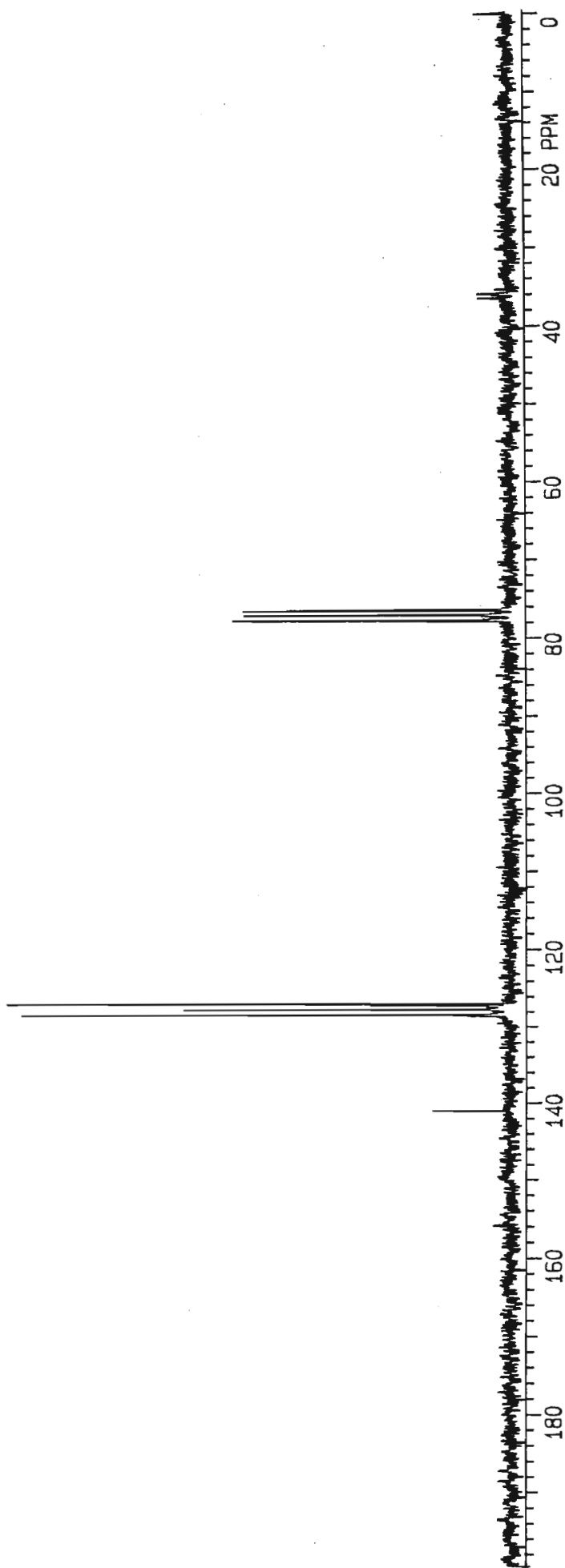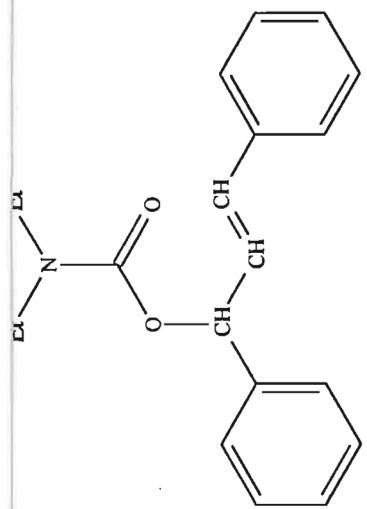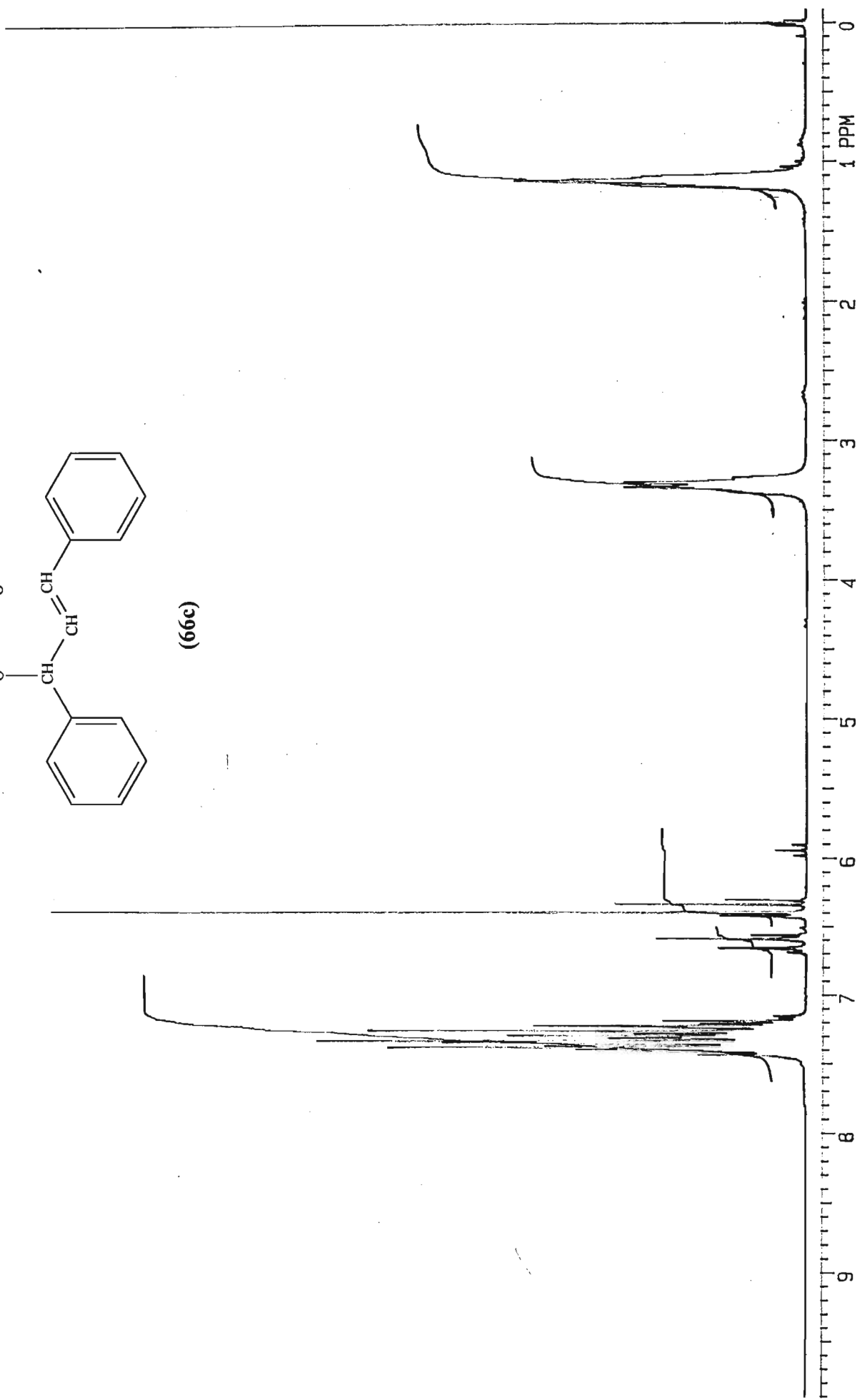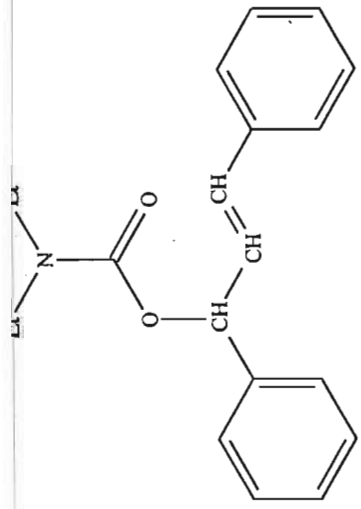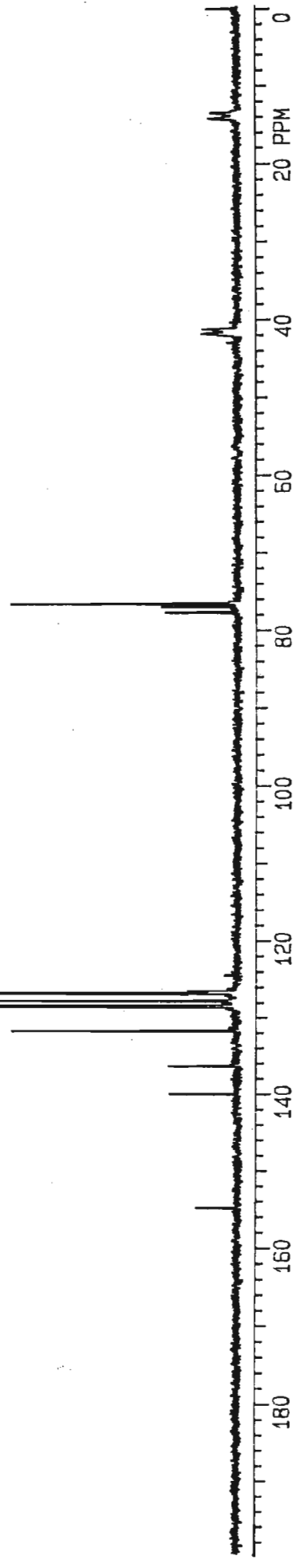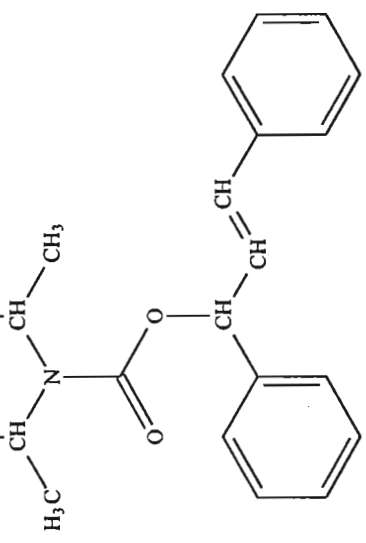
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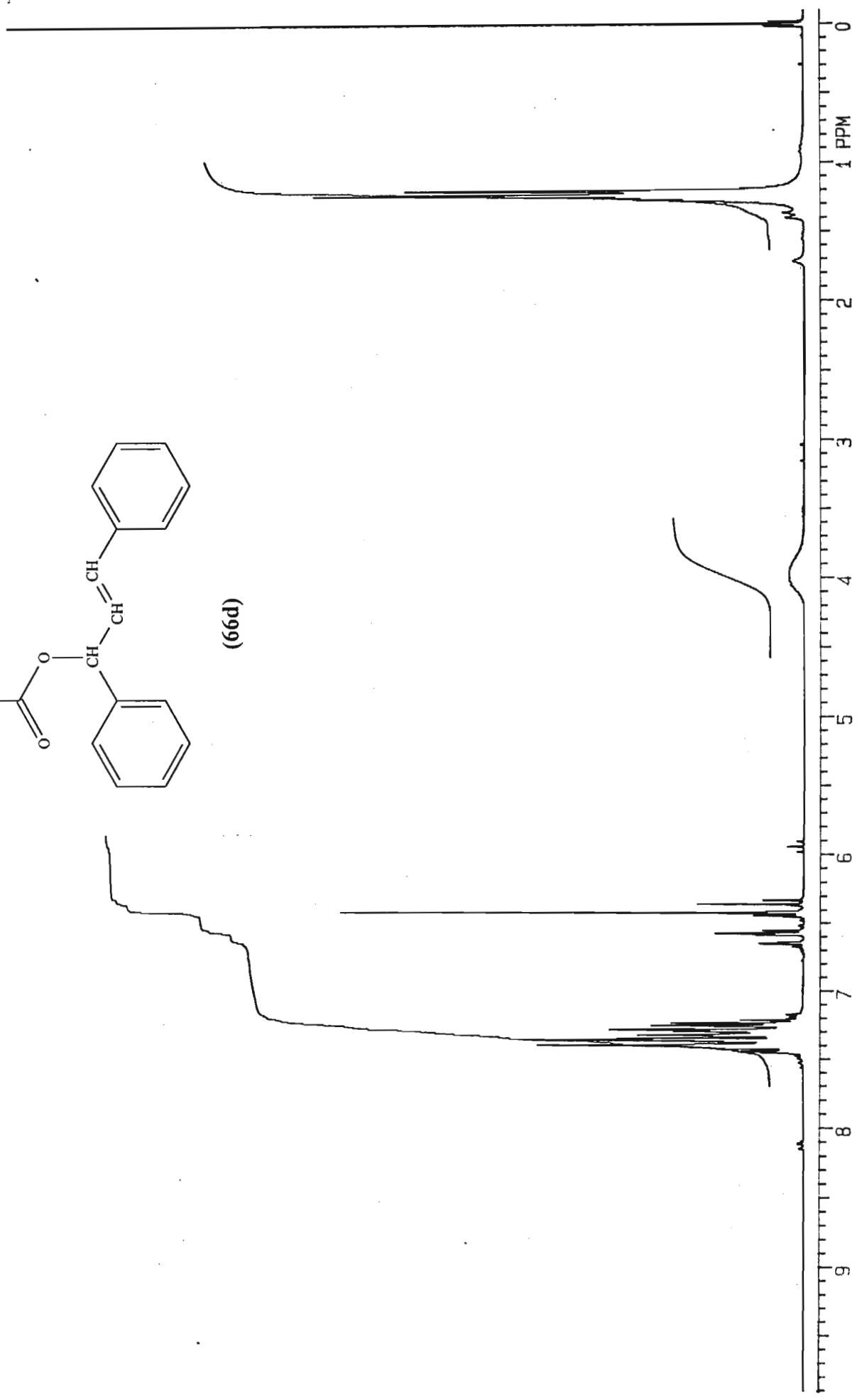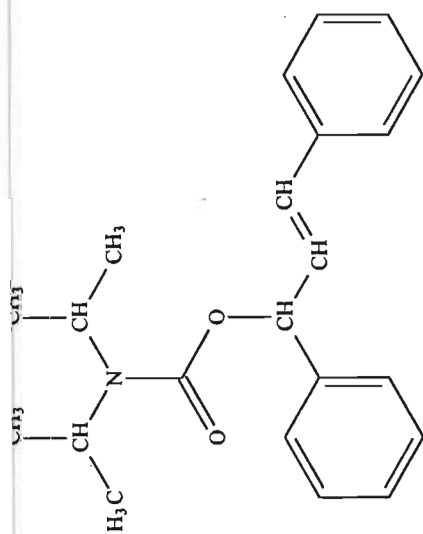
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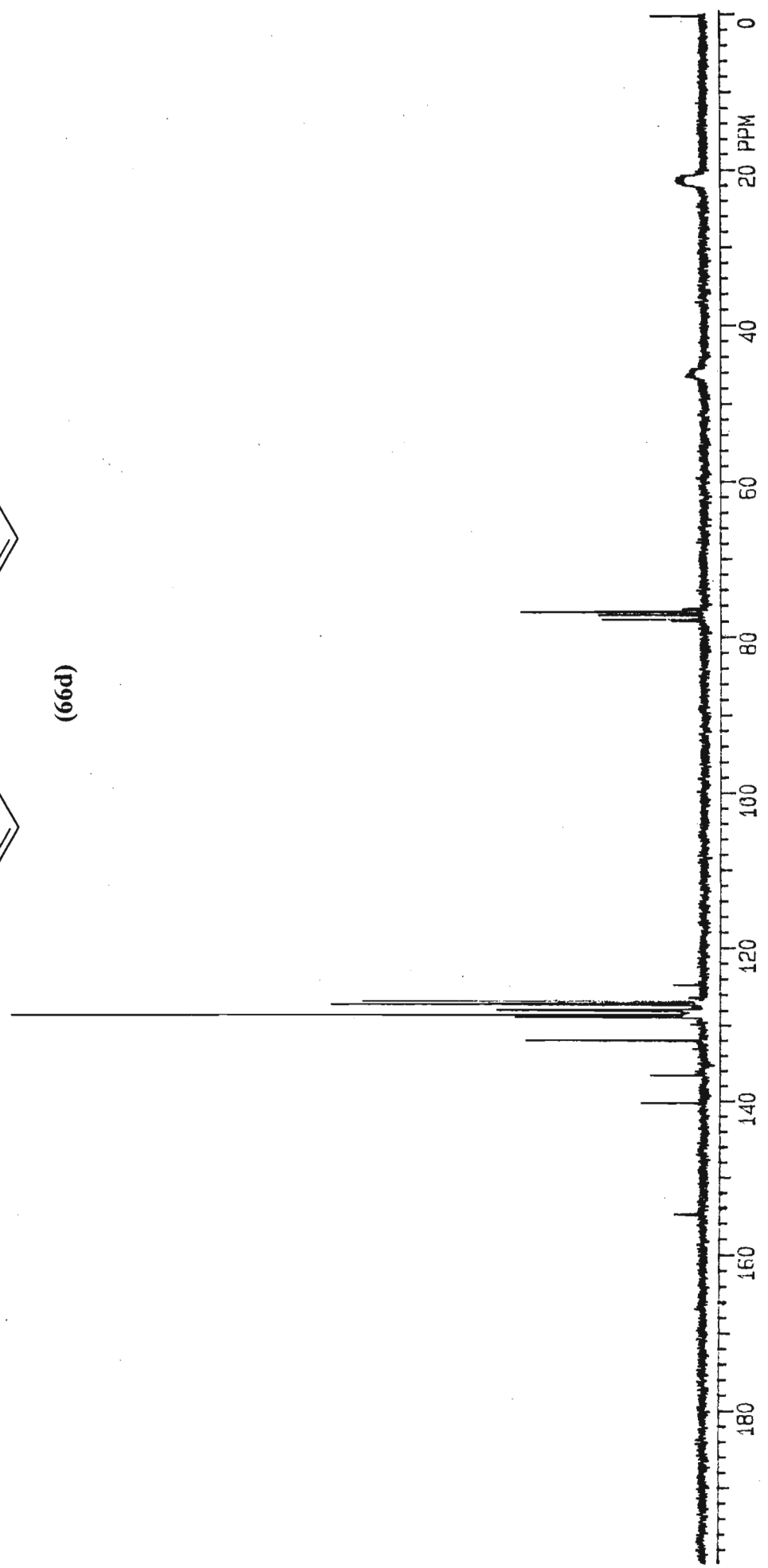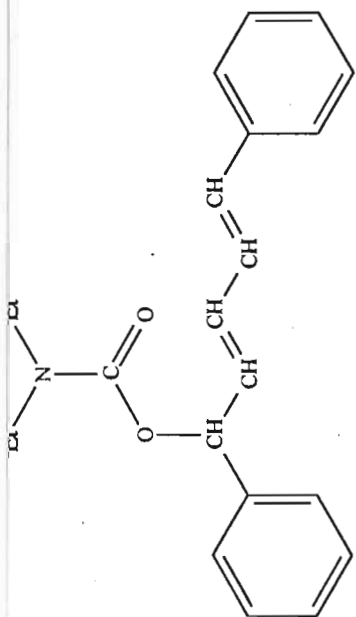
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(66e)

(71a)

(71a)

(71b)

(71b)

(71c)

CH$_3$

CH$_3$

(71c)

Me$_3$Si

120

140

160

180

(71f)
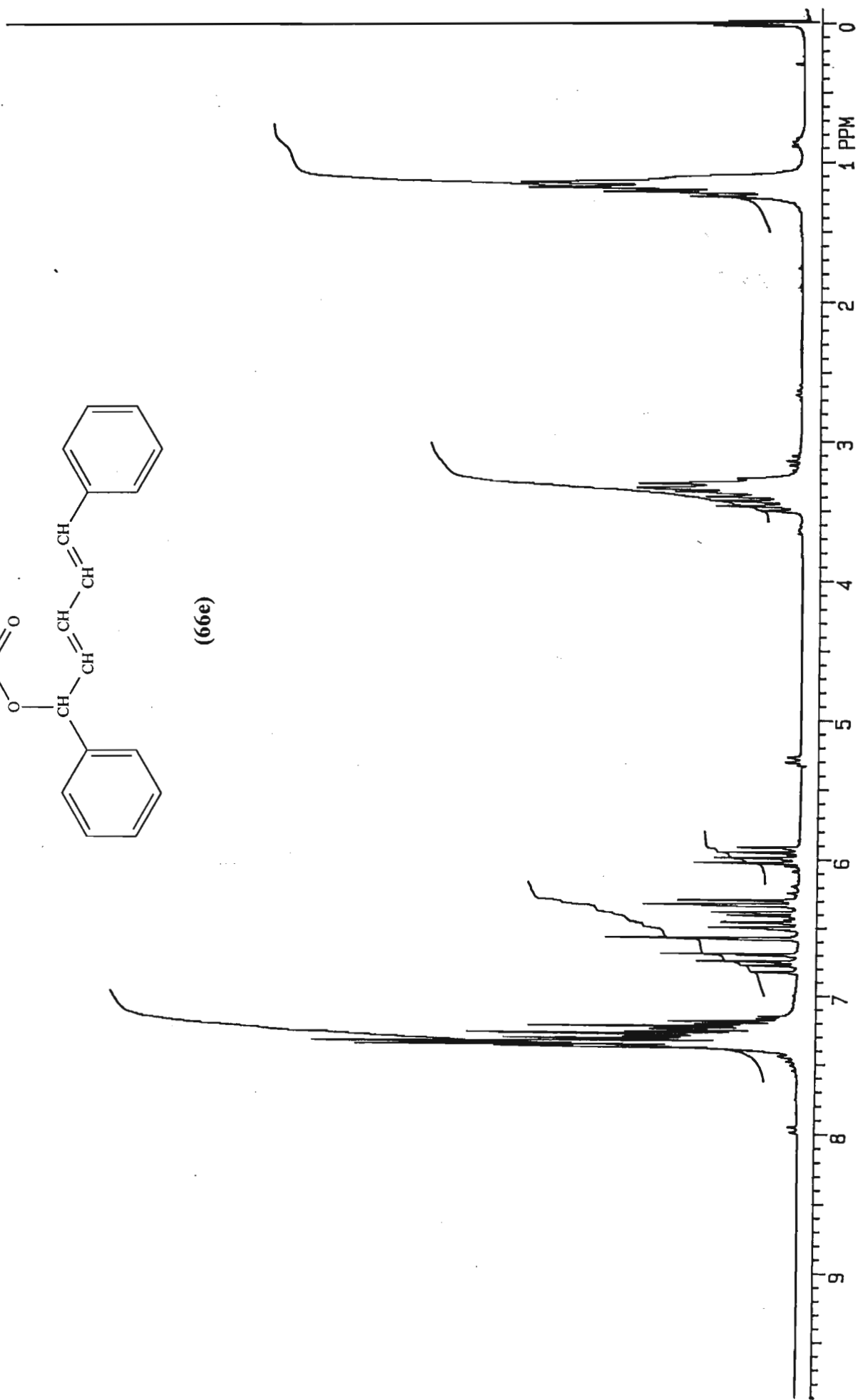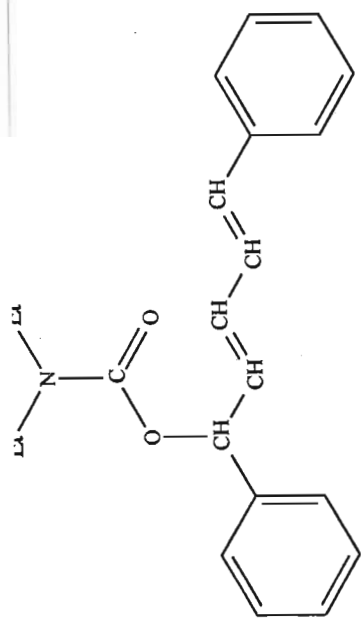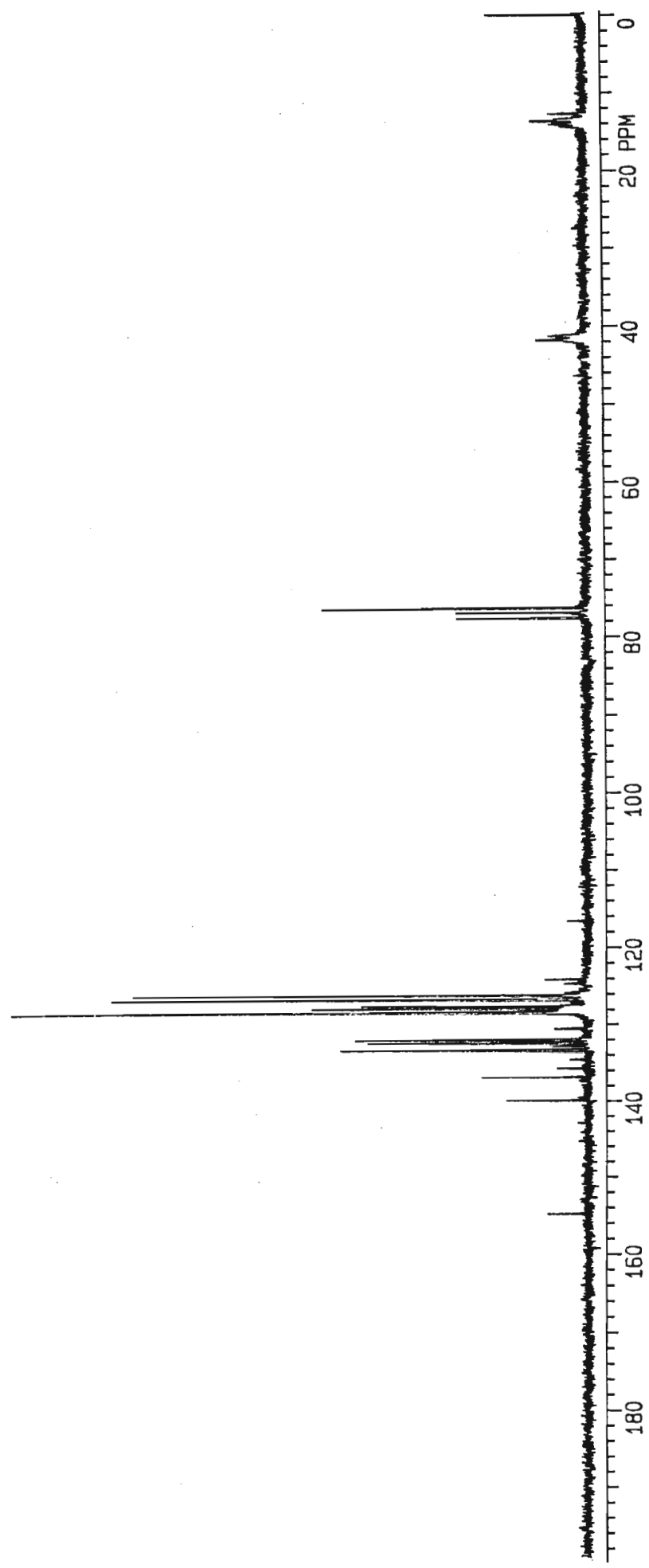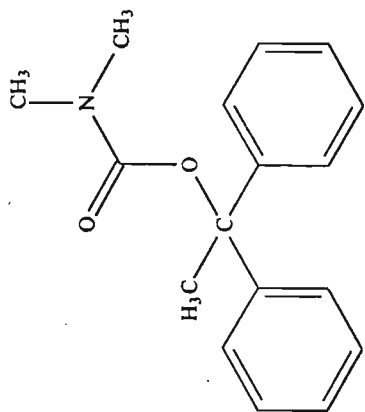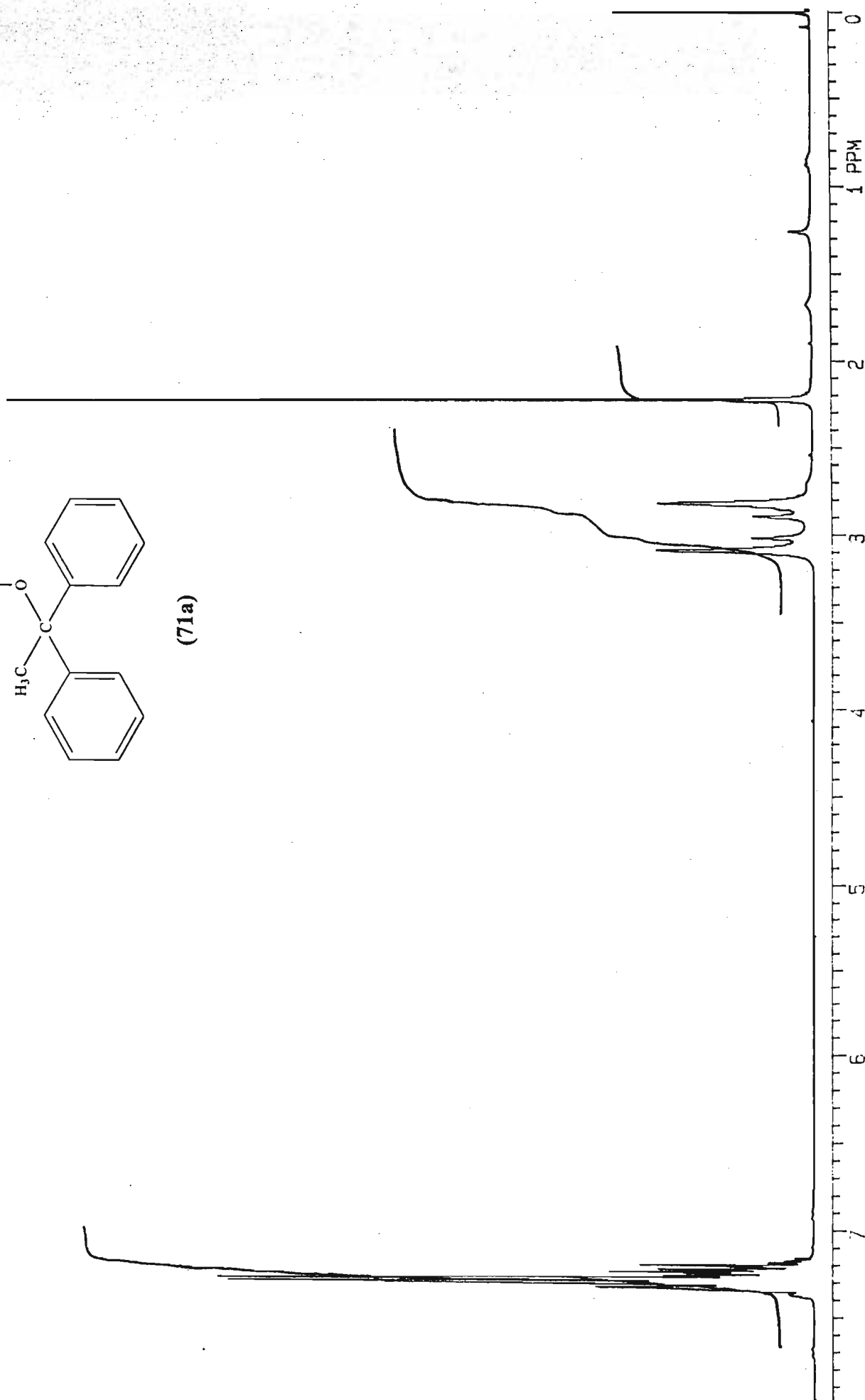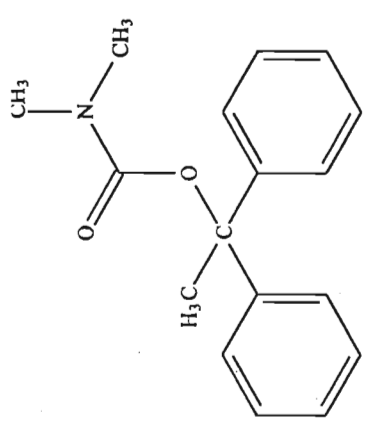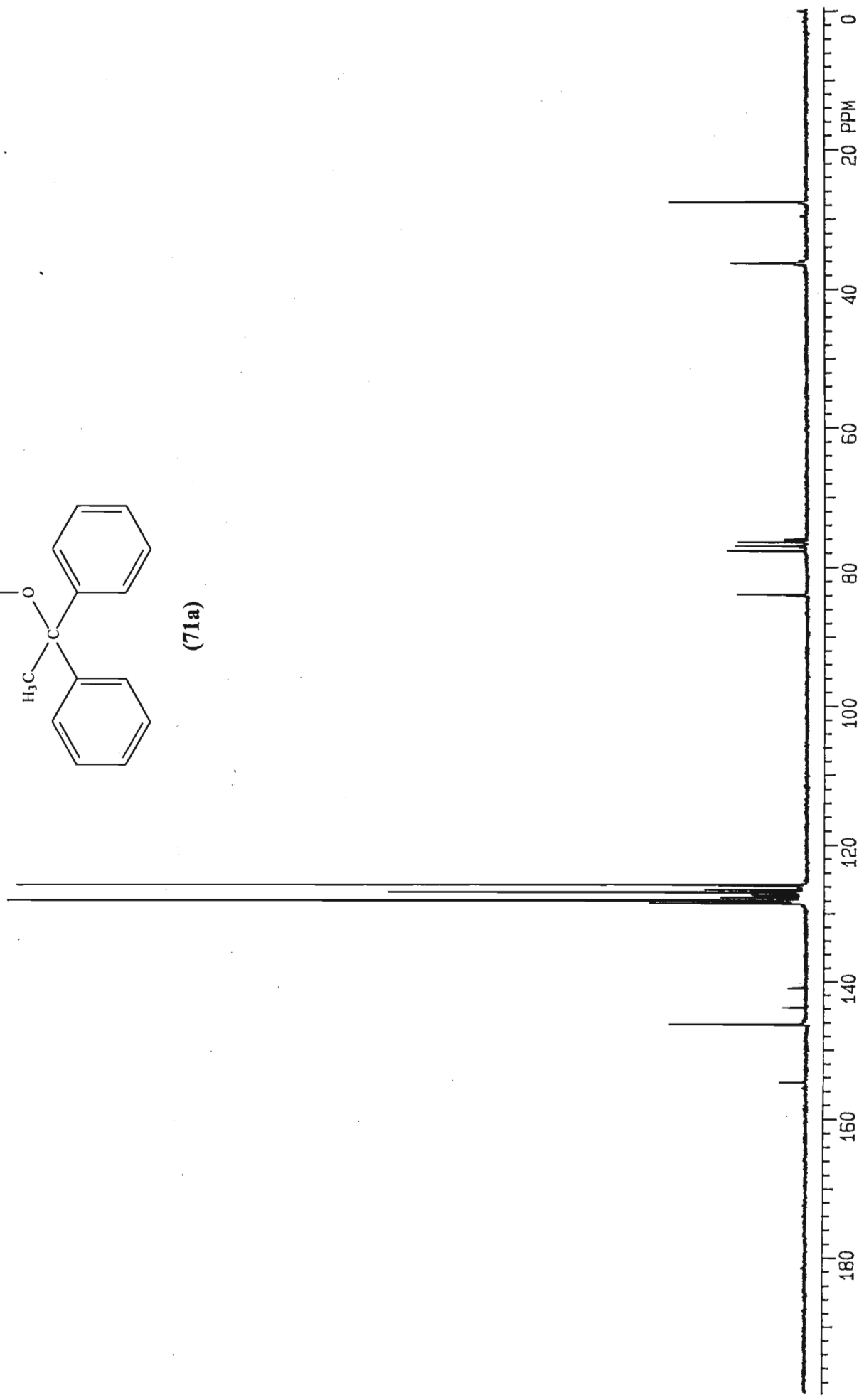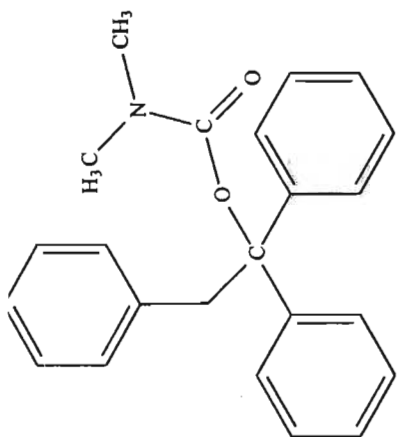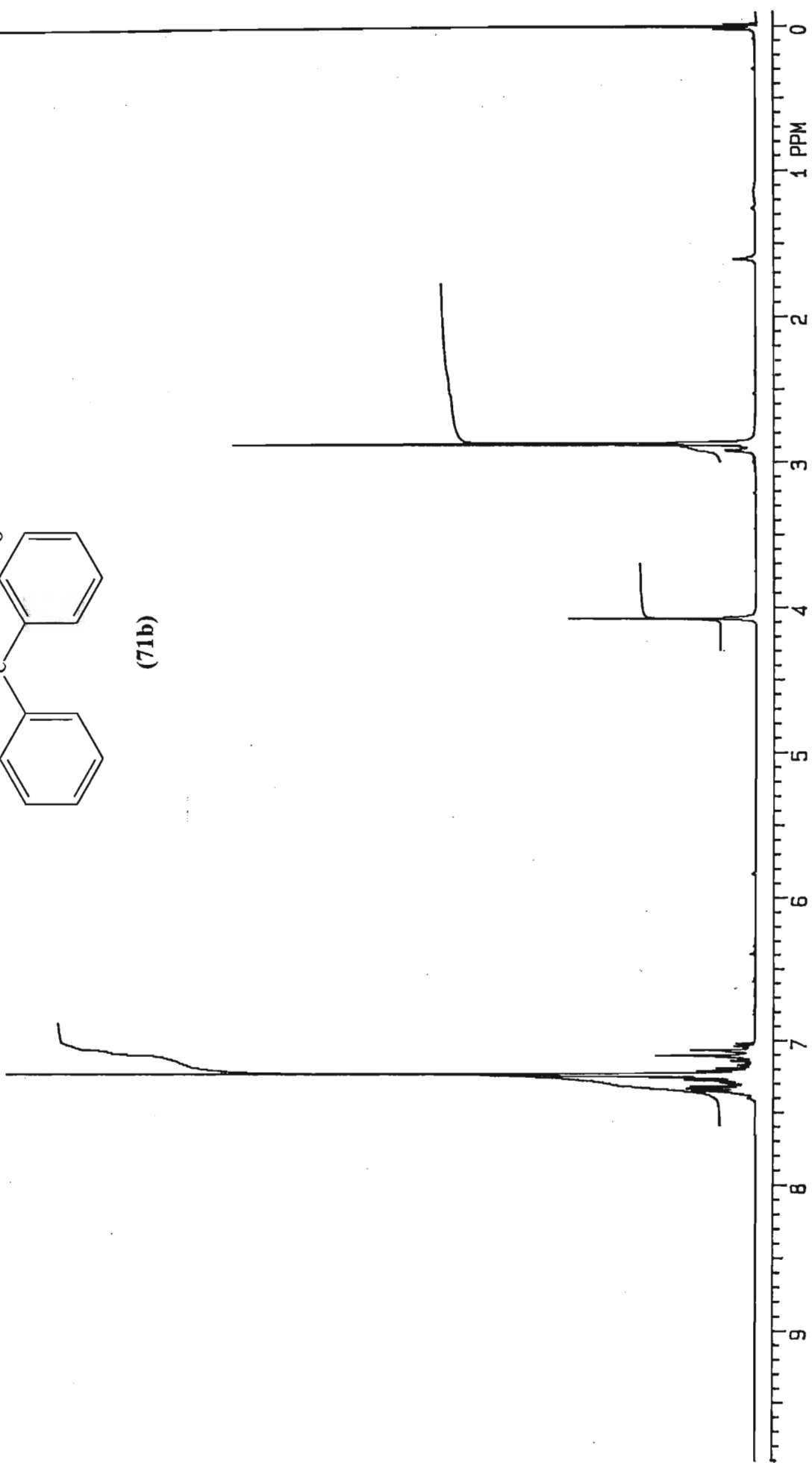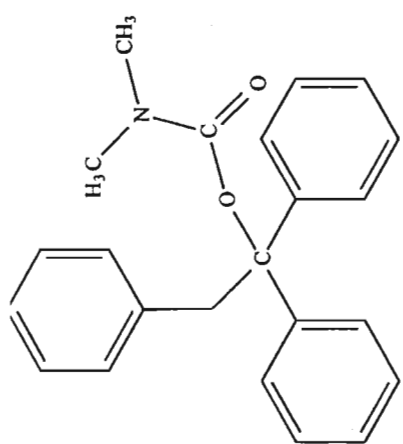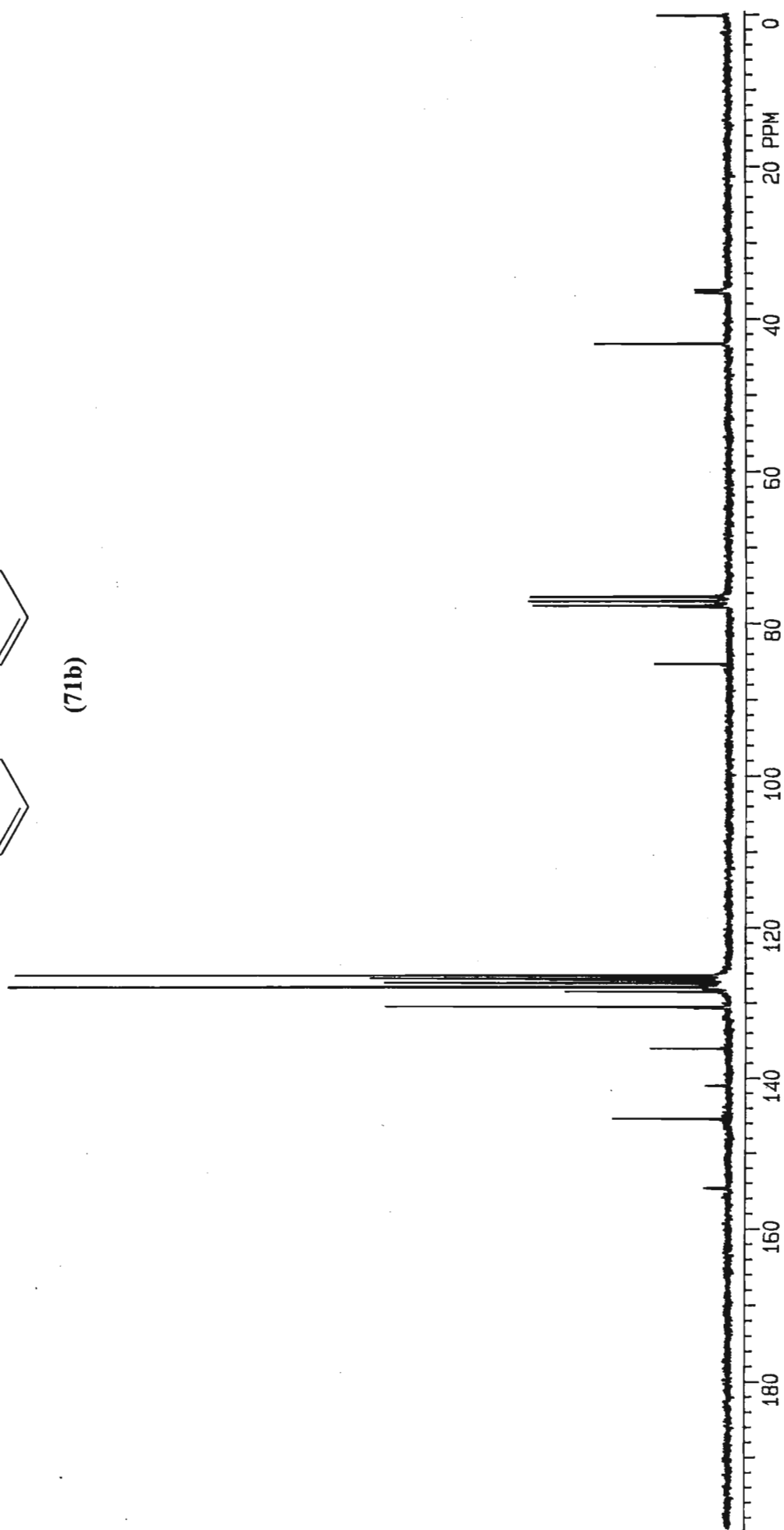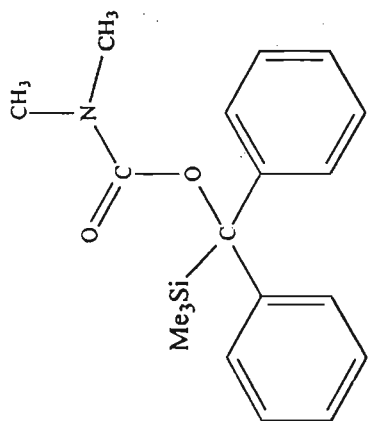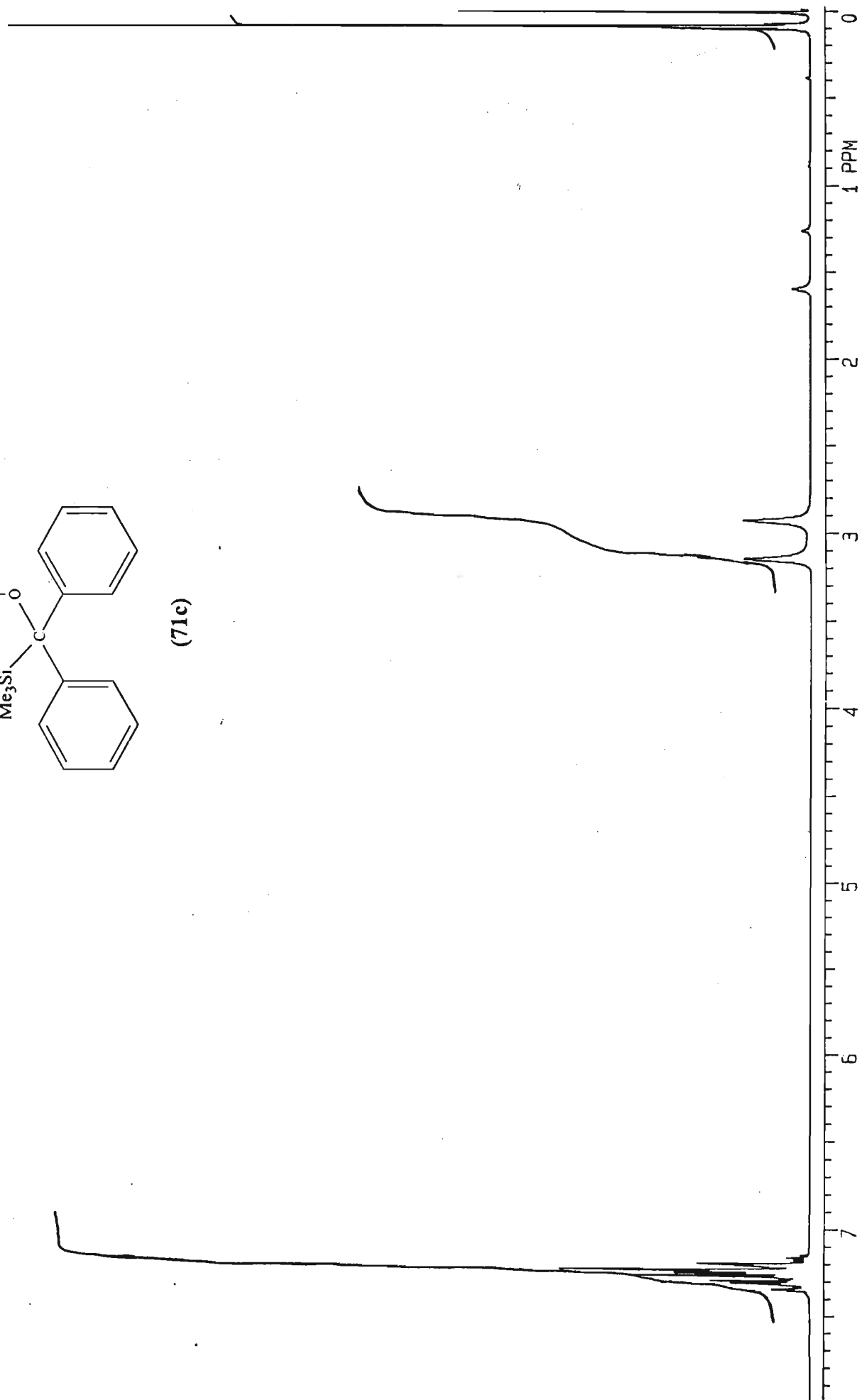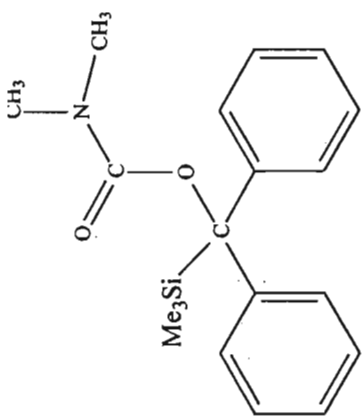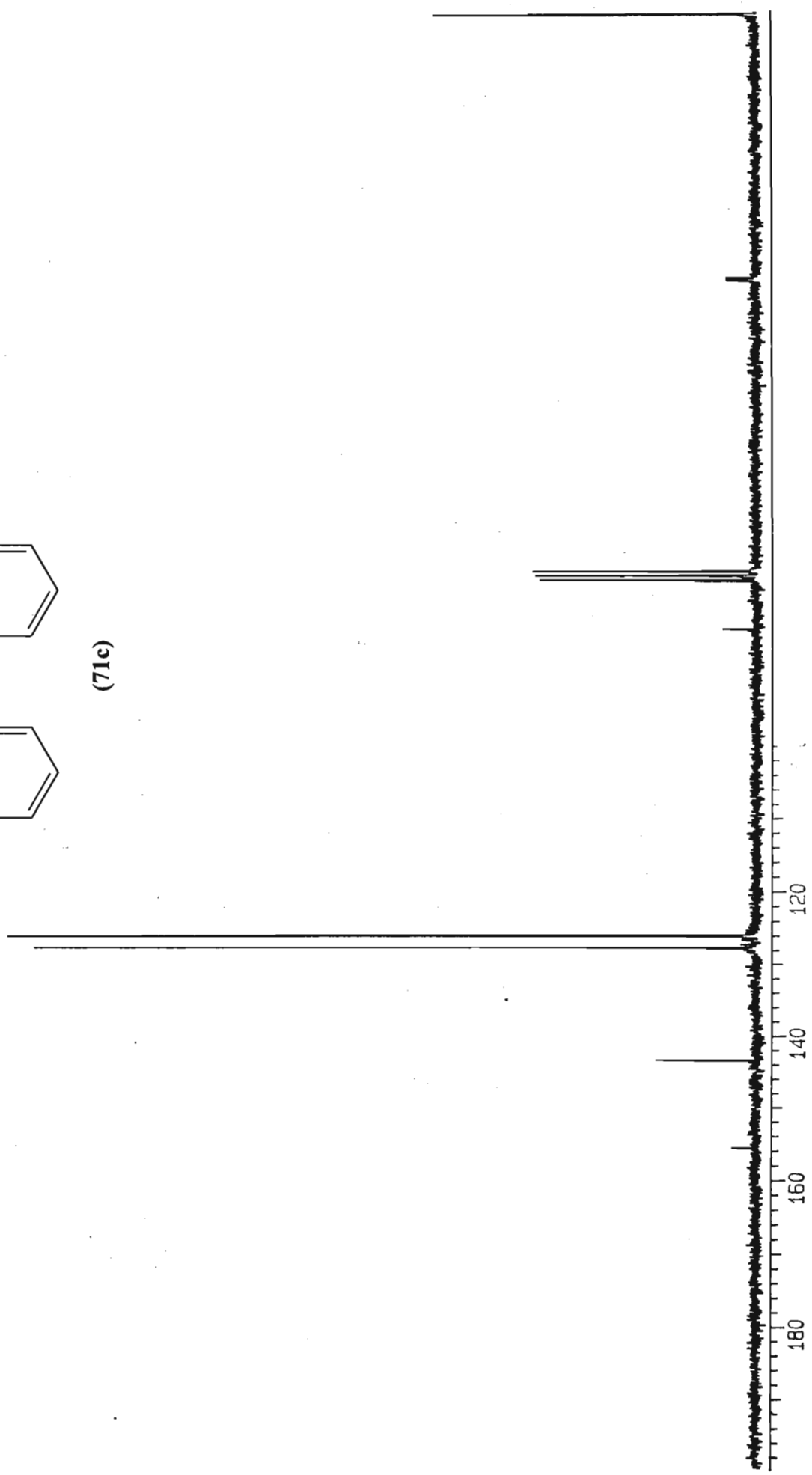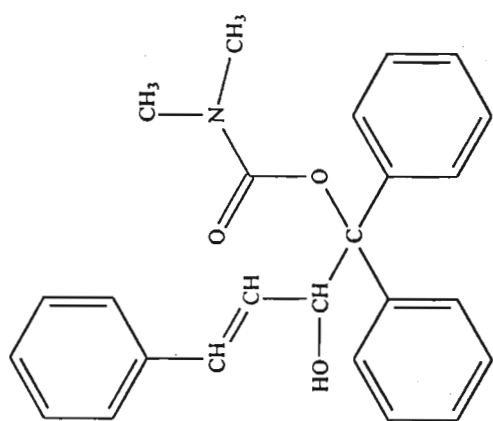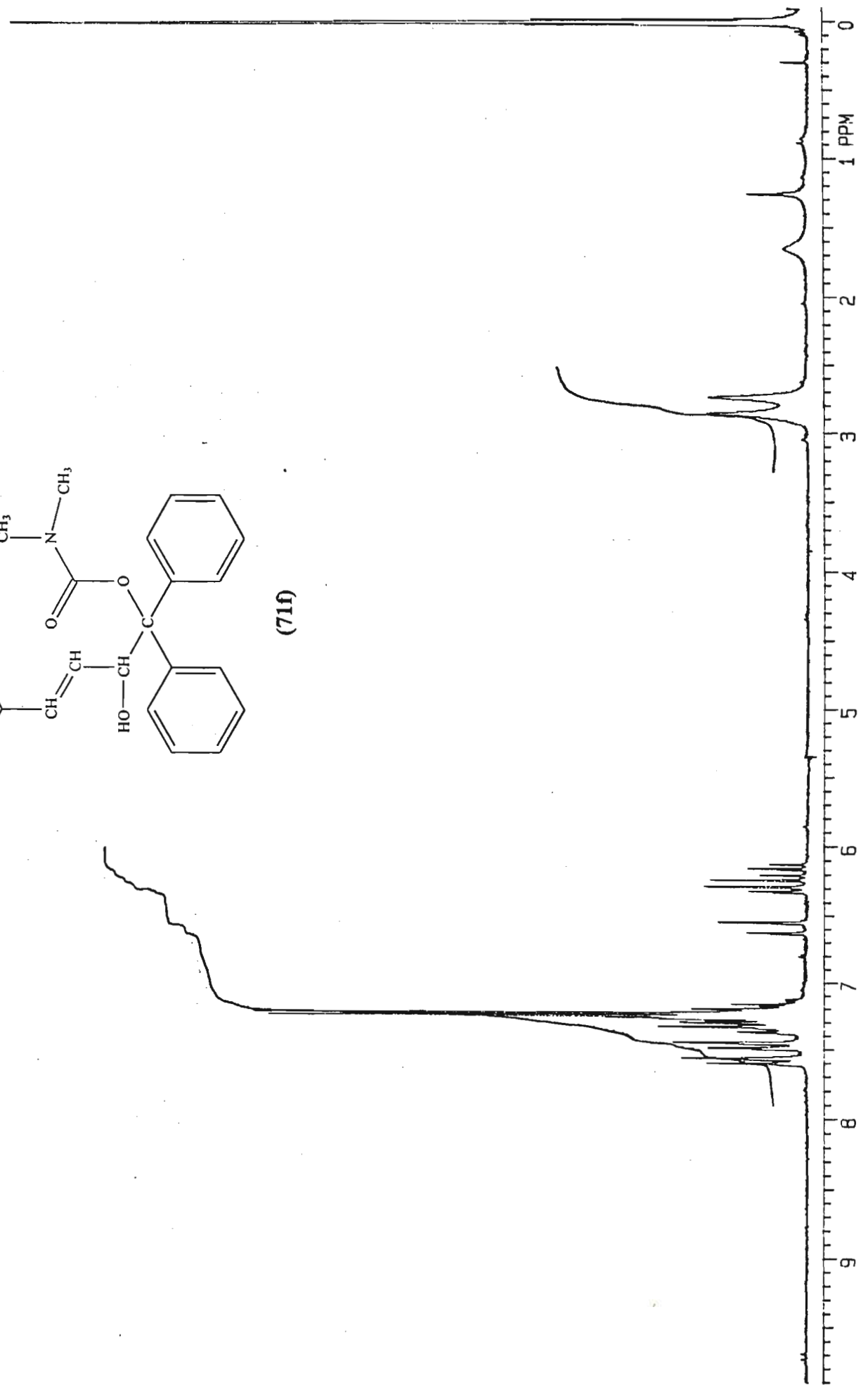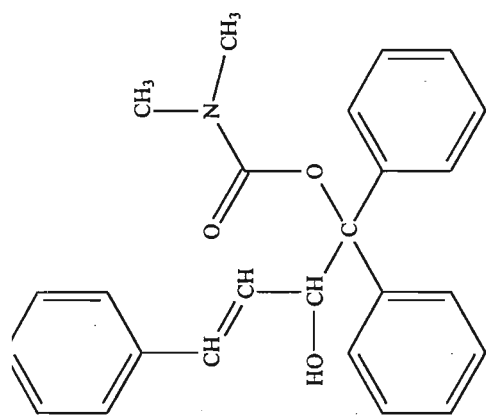
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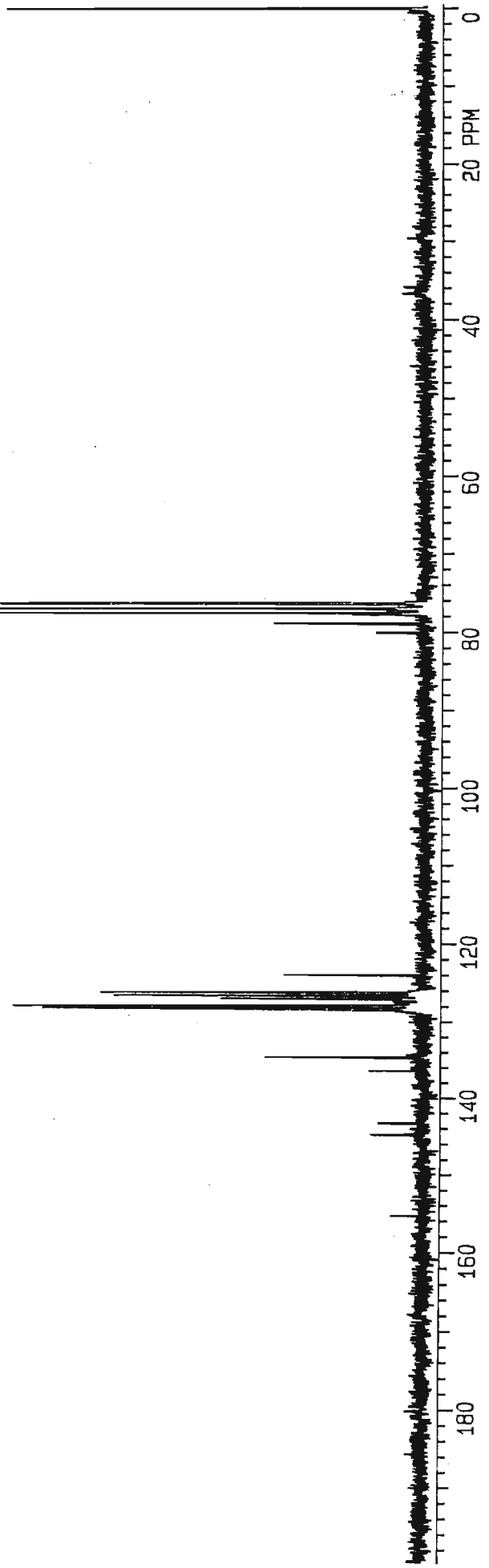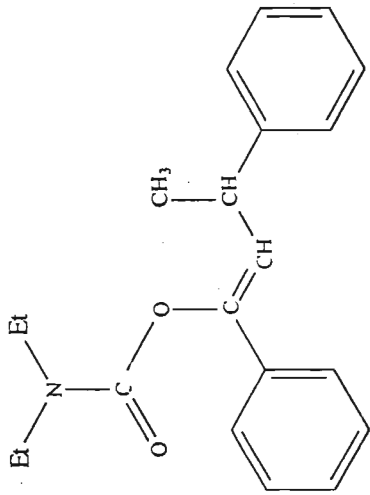
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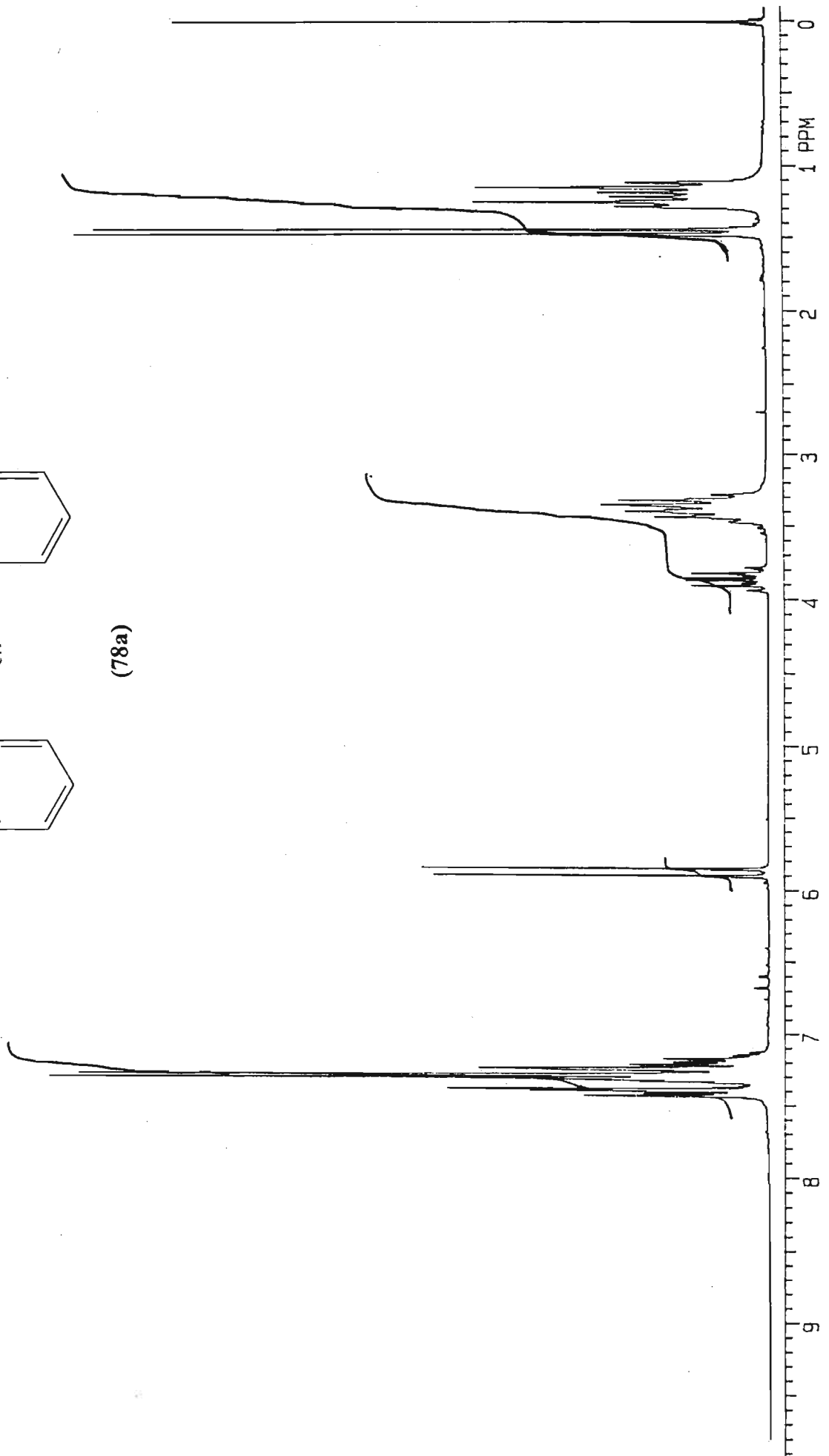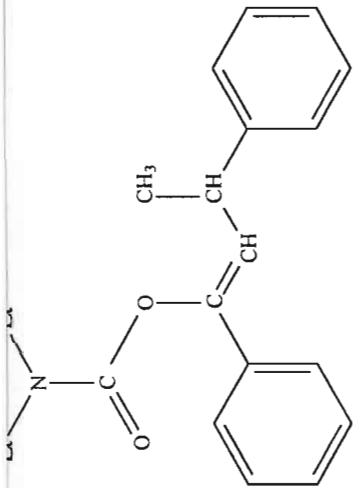
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(84)

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(90)

(90)

(94)

(94)

CH₃ CH₃

(95)

(95)

(98)

(98)

(99)

1 PPM

(99)