TERTIARY AMINE-CATALYSED DIELS-ALDER REACTIONS

by

DARRYL DOMINIC KADER
B.Sc. (Natal), B.Sc. (Hons) (Rhodes)

A thesis submitted in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE,

University of Natal

Department of Chemistry and Chemical Technology
University of Natal
Pietermaritzburg

January 1995

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 : .....

D.D. KADER

I hereby certify that this statement is correct.

Signed : .....

DOCTOR N.D. EMSLIE

SUPERVISOR

Department of Chemistry and Chemical Technology

University of Natal

Pietermaritzburg

January 1995

CONTENTS

ACKNOWLEDGEMENTS

I wish to thank my supervisor Dr. Neville Emslie for his guidance throughout this work. His open door led to countless hours of discussions, his enthusiastic support of new ideas were continued inspiration and encouragement to me. To my co-supervisor Professor S.E. Drewes, I extend my thanks for his encouragement.

To my colleagues I extend my thanks for the healthy working environment which they created, an environment of free discussion, hard work and good humour. Also for their encouraging words and time spent in the proof-reading of this document.

I extend my gratitude to the following people whose efforts were a necessary part of this work :

Mr. M. Watson for the many NMR and GC/MS experiments he carried out and for the invaluable maintenance work on these intruments which enabled the characterization of our compounds;
Mrs. Zoë Hall for the many NMR and GC/MS experiments she performed throughout the course of this work;
Messrs. M. Somaru and H. Dessai for the elemental analyses;
Mr. W. Zondi who was always quick to assist in any way he could;
Mr. P. Forder for glassblowing;
Mr. D. Crawley and Mr. C. Morewood and their staff.

I am indebted to my fiancée Karen and to my parents for their love, support and encouragement during the course of this work.

I gratefully acknowledge the Foundation for Research Development and the University of Natal for their financial support of this research.

ABBREVIATIONS

abs.	:	absolute
aq.	:	aqueous
Ar	:	aryl
atm.	:	atmosphere
b.p.	:	boiling point
br	:	broad
Bu	:	butyl
cat.	:	catalytic
conc.	:	concentrated
d	:	doublet, days
dil.	:	dilute
dd	:	doublet of doublets
DDQ	:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dt	:	doublet of triplets
dq	:	doublet of quartets
DABCO	:	1,4-diazabicyclo-[2,2,2]-octane
DMAP	:	4-dimethylaminopyridine
e.e.	:	enantiomeric excess
eq.	:	equivalents
Et	:	ethyl
GC	:	gas chromatography
h	:	hour/s
Δ	:	heat
M^+	:	molecular ion
MCPBA	:	*meta*-chloroperbenzoic acid
m	:	multiplet
Me	:	methyl
m.p.	:	melting point

min	:	minute
MsCl	:	mesoylchloride
n-BuLi	:	normal butyl lithium
NMM	:	*N*-methylmaleimide
NMR, nmr	:	nuclear magnetic resonance
OAc	:	acetate
OTs	:	tosylate
Ph	:	phenyl
q	:	quartet
rt	:	room temperature
s	:	singlet
sat.	:	saturated
t	:	triplet
^{t}Bu	:	tertiary butyl
TMS	:	tetramethylsilane

SUMMARY

In recent years, increasing interest has been placed on the development of special physical and catalytic methods for improving the rate and selectivity of Diels-Alder cycloaddition reactions. However, little has been published regarding the use of tertiary amines as catalysts in Diels-Alder reactions.

This investigation describes the use of tertiary amines, including DABCO, Et_3N, quinuclidine, quinuclidinol and the natural products quinine, quinidine, sparteine and brucine as catalysts in intermolecular Diels-Alder reactions. The investigation was also extended to the use of PPh_3 and $P(OEt)_3$ as possible catalysts.

Initial work involved the DABCO-catalysed (0.1 eq.) Diels-Alder reaction between cyclopentadiene and methyl acrylate in dichloromethane. After establishing the conditions (22 °C, 2 d) for further reactions, the investigation was extended to the use of the above-mentioned tertiary amines. Based on the yields and *endo:exo* ratios obtained, it was evident that DABCO, the least sterically hindered of the tertiary amines used, was the catalyst of choice for further work.

Various α,β–unsaturated monosubstituted dienophiles (*e.g.* methyl vinyl ketone and acrolein) underwent cycloaddition reactions with cyclopentadiene, in the presence of DABCO. Easy work-up of the reaction mixtures afforded high yields of the cycloadduct with good *endo* selectivity. In contrast, sterically hindered disubstituted dienophiles displayed poor reactivity in DABCO-catalysed Diels-Alder reactions.

The aliphatic dienes, isoprene and 2,3-dimethyl-1,3-butadiene were poorly reactive in DABCO-catalysed cycloaddition reactions with methyl acrylate.

Reaction rates were dramatically enhanced when reactions were carried out under sonication (ultrasound).

Using water as the solvent had a negative effect on the rate of reaction. Lower yields of cycloadduct were obtained than in the corresponding reactions with dichloromethane as the solvent.

The catalytic behaviour of DABCO was further demonstrated in the attempted Diels-Alder cycloaddition reactions between cyclopentadiene and Baylis-Hillman derived allylic esters. Instead of the expected cycloadduct forming, substituted cyclohexenes were isolated. A mechanism for the formation of the cyclohexene product is proposed.

DABCO-catalysed Diels-Alder cycloaddition reactions are proposed to proceed *via* a non-concerted mechanism involving an ion pair intermediate.

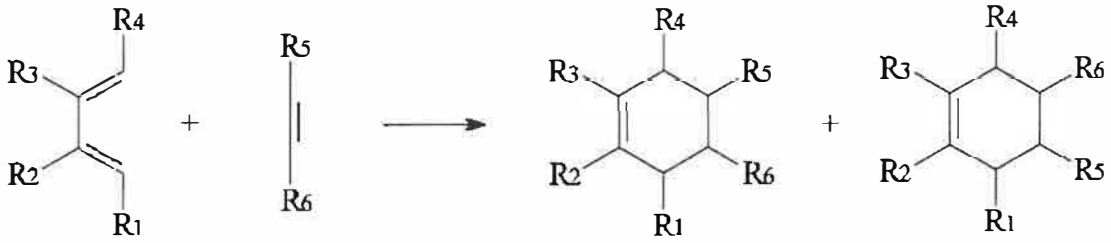
CHAPTER 1: INTRODUCTION

The Diels-Alder reaction constitutes one of the most frequently employed synthetic methods involving a pericyclic 6-electron process. This reaction results in the high regio-, diastereo-, and enantioselective construction of 6-membered and polycyclic ring systems which are of fundamental interest in organic chemistry.[1] In view of the outstanding importance of this method in the preparation of natural products, and hence also of physiologically active molecules (*e.g.* steroidal hormones), increasing interest has been placed in recent years on the development of physical and catalytic methods for the purpose of improving the rate and/or selectivity of these [4π+2π] cycloadditions.

This review outlines the regioselectivity and stereochemistry of the Diels-Alder reaction and also describes physical (*i.e.* pressure and thermal conditions) and catalytic methods which enhance the rate and/or regio- and stereoselectivity as well as the π-diastereofacial selectivity of Diels-Alder reactions in synthetic organic chemistry.

1.1 REGIOCHEMISTRY OF THE DIELS-ALDER REACTION

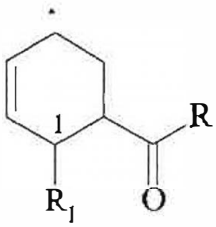
In principle, the reaction of an unsymmetrical diene (**1**) with an unsymmetrical dienophile (**2**) can result in a mixture of two regioisomeric adducts (**3**) and (**4**), but in practice one predominates. Their relative proportions depend on the individual nature of, and on the interplay between, substituent effects (Scheme 1).



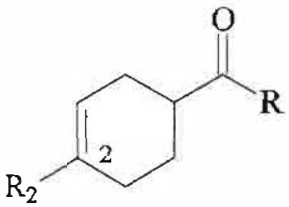
(1) **(2)** **(3)** **(4)**

Scheme 1

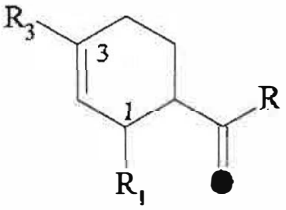
These orientation effects are governed largely by the atomic orbital coefficients at the termini of the conjugated systems concerned. Hence in a 'normal' Diels-Alder reaction a diene substituent at C-1 directs addition of the carbonyl-conjugated alkene towards the *ortho* product (**5**), whereas a C-2 substituent favours the *para* product (**6**).



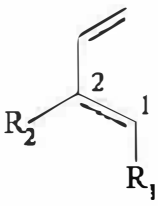
(5)



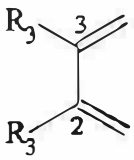
(6)



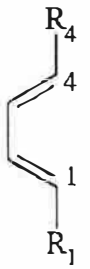
(7)



(8)



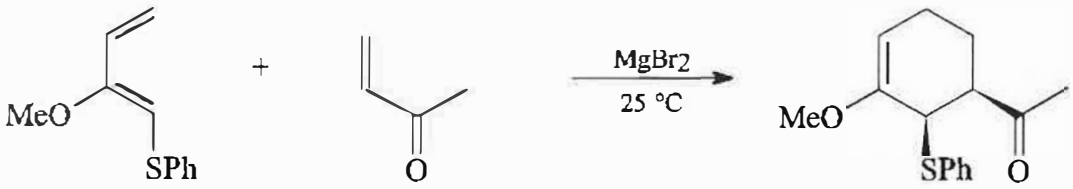
(9)



(10)

The individual directive effects of substituents are synergistic with 1,3-disubstituted dienes (*e.g.* favouring the formation of regioisomer (**7**)), but antagonistic with 1,2- (**8**), 2,3- (**9**) and 1,4- (**10**) disubstituted dienes. The magnitude of the directing effects differs from one substituent to another (*e.g.* SAr > OR > SiR_3) and also with their position on the diene. Similarly for the dienophile, the regiocontrol effect of a substituent R_5 can outweigh that of R_6 in 1,2-disubstituted dienophiles (**2**) (*e.g.* Me < SO_2Ar < NO_2 > CO > Me).

Substituent effects can be exploited to obtain adducts of unusual orientation. This can be accomplished through the use of dienes or dienophiles bearing temporary substituents which control the regiochemistry of the addition and are removed thereafter. For example, the regioselective control of the phenylthio group in the reaction of 2-methoxy-1-phenylthiobutadiene (**11**) and methyl vinyl ketone (**12**) in which the methoxy group is *meta* to the carbonyl group of the dienophile (Scheme 2). The reaction of 2-methoxybutadiene itself with methyl vinyl ketone gives the *para* isomer.[2]



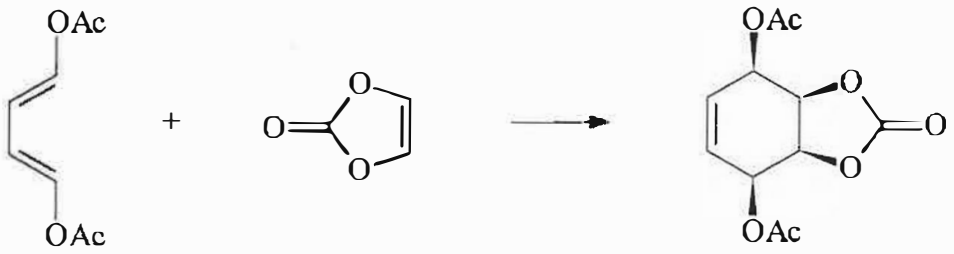
(11) **(12)**

Scheme 2

1.2 STEREOCHEMISTRY OF THE DIELS-ALDER REACTION

The high stereoselectivity of the Diels-Alder reaction has led to its widespread application in the synthesis of complex natural products such as cholestanol,[3] cortisone,[4] reserpine[5] and cantharidin.[6] It should be noted, however, that the high stereoselectivity applies only to the kinetically controlled reaction and may be lost by epimerisation of the product or starting materials, or by facile easy dissociation of the adduct allowing thermodynamic control of the reaction. These factors are fully discussed in a review by Martin and Hill.[7]

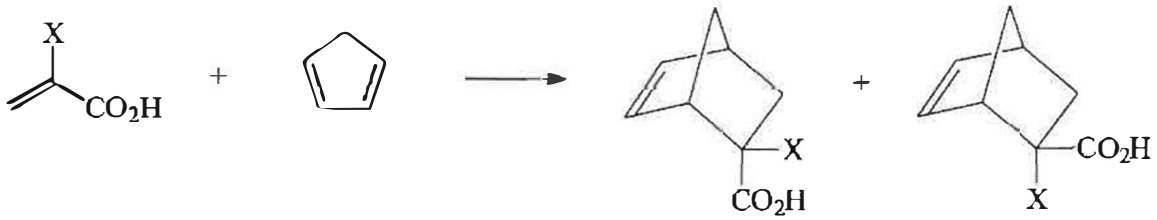
The stereochemistry of the main product can generally be predicted on the basis of the *cis* and *endo* rules. According to the more generally applicable *cis* rule, the relative stereochemistry of the substituent groups on the diene and the dienophile is maintained in the product of cyclo-addition. The *endo* rule which only applies to the kinetic products of the reaction is strictly obeyed only in the addition of cyclic dienes (*e.g.* cyclopentadiene) to cyclic dienophiles (*e.g.* maleic anhydride). It states that the diene and dienophile arrange themselves in parallel planes and that the most stable transition state is that in which maximum orbital overlap occurs. The simultaneous operation of the *cis* and *endo* rules is illustrated in the reaction of 1,4-diacetoxybutadiene (**13**) with ethylene carbonate (**14**) to give the cycloadduct (**15**) (Scheme 3).



(**13**) (**14**) (**15**)

Scheme 3

In the addition of open-chain dienophiles to cyclic dienes, the *endo* rule is not always obeyed and the composition of the mixture obtained may depend on the precise structure of the dienophile and reaction conditions. This is illustrated by Martin and Hill[7] in the addition of α-substituted acrylic acid (**16**) to cyclopentadiene (**17**) (Scheme 4; Table 1). The product ratio varies depending on the nature of the group X. With acrylic acid, the proportiou of *endo* adduct formed was noticeably increased by the presence of Lewis acid catalysts.[8]



(16) **(17)** *(endo)* *(exo)*

Scheme 4

Table 1 Proportion of *endo* and *exo* acids formed in the addition of α-substituted acrylic acids to cyclopentadiene (Scheme 4).

X	***endo* acid**	***exo* acid**
H	75	25
CH_3	35	65
C_2H_5	-	100
C_6H_5	60	40
Br	30	70

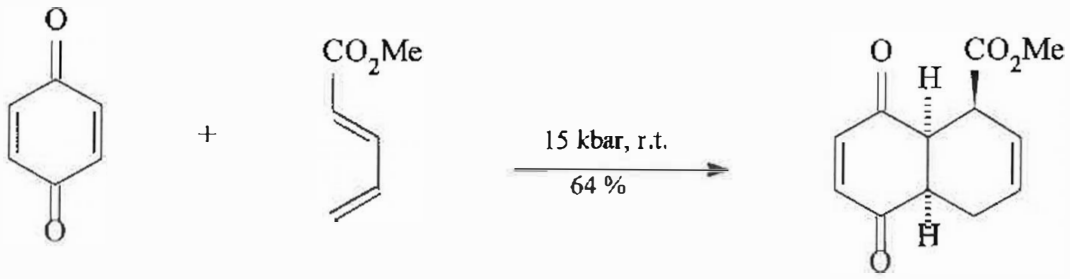
1.3 ACCELERATION AND SELECTIVITY ENHANCEMENT OF THE DIELS-ALDER REACTION BY SPECIAL AND CATALYTIC METHODS

1.3.1 USE OF HIGH PRESSURE

The intermolecular Diels-Alder reaction exhibits a large negative volume of activation (approx. -25 to 45 $cm^3.mol^{-1}$) together with a large negative volume of reaction.[9] Thus, the use of high pressure (10-20 kbar; 1 kbar = 986.9 atm.) for accelerating Diels-Alder reactions and to shift the reaction equilibrium towards the cycloadducts, has been relatively well explored. These effects are particularly useful to promote otherwise slow [4+2]

cycloadditions involving heat or Lewis acid sensitive and/or relatively unreactive substrates.[10]

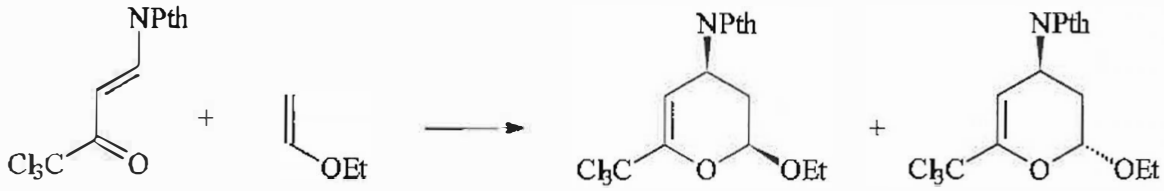
High pressure effects also suppress cyclo-reversion reactions which are either thermodynamically favoured or would interfere with kinetically controlled stereochemistry. For example, the Diels-Alder reaction of 1,4 benzoquinone (**18**) with methyl 2,4-pentadienoate (**19**) to furnish (**20**) proceeds in good yield (64 %) at room temperature under 15 kbar pressure with a reaction time of 18 hours (Scheme 5).[11] At atmospheric pressure the yield is significantly lower (24 h at 80°C; 28 %).



(18) **(19)** **(20)**

Scheme 5

The increased *endo* selectivity of reactions conducted under high pressure can also be exploited in synthesis. This is well illustrated in the cycloaddition of the enamino ketone (**21**) and the ethyl vinyl ether, which provides access to 3-amino sugars. The proportion of *endo* adduct (**22**) was greatly increased at a lower temperature under pressure (Scheme 6).[12]



(21) **(22)** **(23)**

NPth = Naphthyl

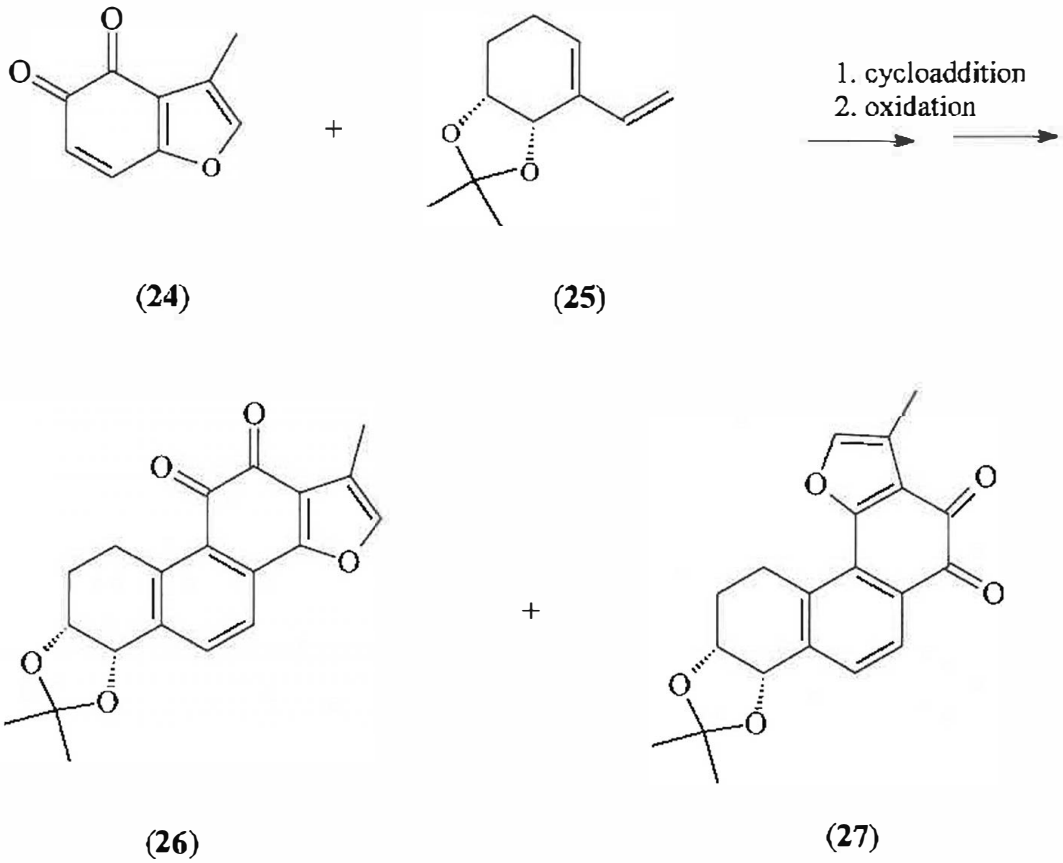
	(22) : (23)
90 °C, 1 bar,	ratio 1.67 : 1
0.5 °C, 6 kbar,	ratio 13.6 : 1

Scheme 6

1.3.2 USE OF ULTRASOUND (SONOCHEMISTRY)

The application of ultrasound (typical range 20 to 850 kHz) has now been established as a general method to accelerate a variety of chemical reactions. Sound waves in solution induce "cavitation", *i.e.* the rapid growth and sudden collapse of bnbbles within the liquid, generating high pressures and temperatures. The efficiency of bubble collapse can be influenced by vapour pressure, temperature, thermal conductivity, surface tension and viscosity, ultrasonic frequency, acoustic intensity, shape of the reaction vessel, and volume of the liquid.[13] The application of ultrasonic acceleration to Diels-Alder reactions is undergoing continuous expansion.

Lee and Snyder[14] reported the convenient ultrasound promoted regioselective cycloaddition of 3-methyl-4,5-benzofurandione (**24**) with the diene (**25**) (Scheme 7; Table 2). Comparison of entries 2/3 indicate similarities of the yields and product ratios (**26**)/(**27**), obtained at 10 kbar (entry 2) and on sonication (entry 3). The latter was attributed to the high pressures and temperatures (up to 1 kbar and 500 K) induced by the ultrasound-induced cavities. Deketalization of the major aromatized regioisomer (**26**) gave the natural product tanshindiol B.



(24) (25)

(26) (27)

Scheme 7

Table 2 Ultrasound promoted Diels-Alder Reactions: Influence on Yield and Regiochemistry [a] (Scheme 7).

Entry	Reaction Conditions	Yield (%) (26)+(27)	Ratio (26)/(27)
1	Benzene, reflux, 8h	51	50:50
2	Toluene, 10 kbar, r.t., 1h	73	87:13
3	Neat, ultrasound, 45°C, 2h	76	83:17

[a] Aromatization of the initial Diels-Alder products occurred under oxygen with SiO_2 or on heating with DDQ in benzene.

1.3.3 USE OF MICROWAVE IRRADIATION

Microwave heating techniques for "dry" organic reactions have recently been developed by Villemin[15] and Mingos.[16] Inorganic oxides (*e.g.* alumina, silica), acidic clays (*e.g.* montmorillonite K10 or KSF) were used as the reaction carriers. Recently Zhu and co-workers[17] reported the first work on microwave-induced Diels-Alder reactions at atmospheric pressure, in the absence of solvent and any inorganics as catalyst carriers. Reaction times were dramatically reduced and good yields were obtained for the reaction between anthracene and maleic anhydride (3 min; 90.4 %), and *trans*, *trans*-1,4-diphenyl-1,3-butadiene and maleic anhydride (3 min; 84,8 %) (Table 3).

Table 3 Comparison of results of the reaction between *trans*, *trans*-1,4-diphenyl-1,3-butadiene and maleic anhydride reacted under different conditions.

Solvent	Procedure followed	Reaction time	Yield (%)
Xylene	Classical	7 hours	88.2
Acetic anhydride	Microwave	32 min.	78
Benzaldehyde	Microwave	1 hour	75
Mono chlorobenzene	Microwave	10 min.	27
No solvent	Microwave "dry reaction"	3 min.	84.8

It has been found that as long as one of the reactants has strong polarity (such as maleic anhydride, dielectric constant 50, at 60°C), microwave energy can be transferred directly into internal energy of the molecules within a shorter time. The activation of the reactants dramatically accelerates the reaction rate.

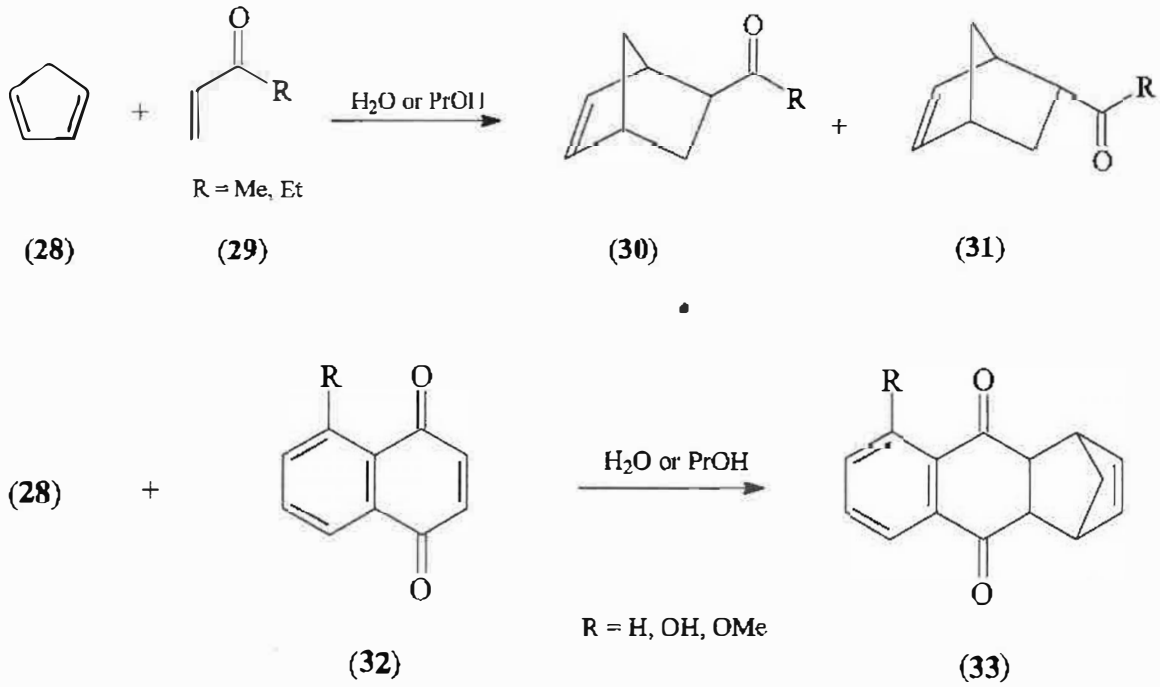
1.3.4 USE OF SPECIAL SOLVENT EFFECTS

For a wide range of solvent systems, both the rate constants and the stereoselectivities of Diels-Alder reactions are only moderately sensitive to changes in the nature of the solvent.[18] Nevertheless, the pioneering work of Breslow and co-workers[19a,b,c] demonstrated dramatic reaction acceleration in aqueous solution. The rate enhancement, paralleled by an increase of *endo:exo* selectivity was ascribed to (a) the hydrophobic or solvophobic packing of the diene and dienophile, respectively, (b) entropy-driven aggregation processes[20] and (c) the high internal pressure of water-similar solvent systems.[21,22]

According to the frontier molecular orbital theory (FMO) approach adopted by Desimoni and co-workers,[23] the interaction between the solvent, acting as an electrophile, and the dienophile, generates a chemical species of the latter with a lowered lowest unoccupied molecular orbital (LUMO) energy. For example, hydrogen-bonding interaction between electron lone pairs on the dienophile and acidic hydrogen atoms of the solvent enhance the reactivity of the dienophile and thus accelerate the rate of reaction.

1.3.4.1 REACTIONS IN AQUEOUS SYSTEMS

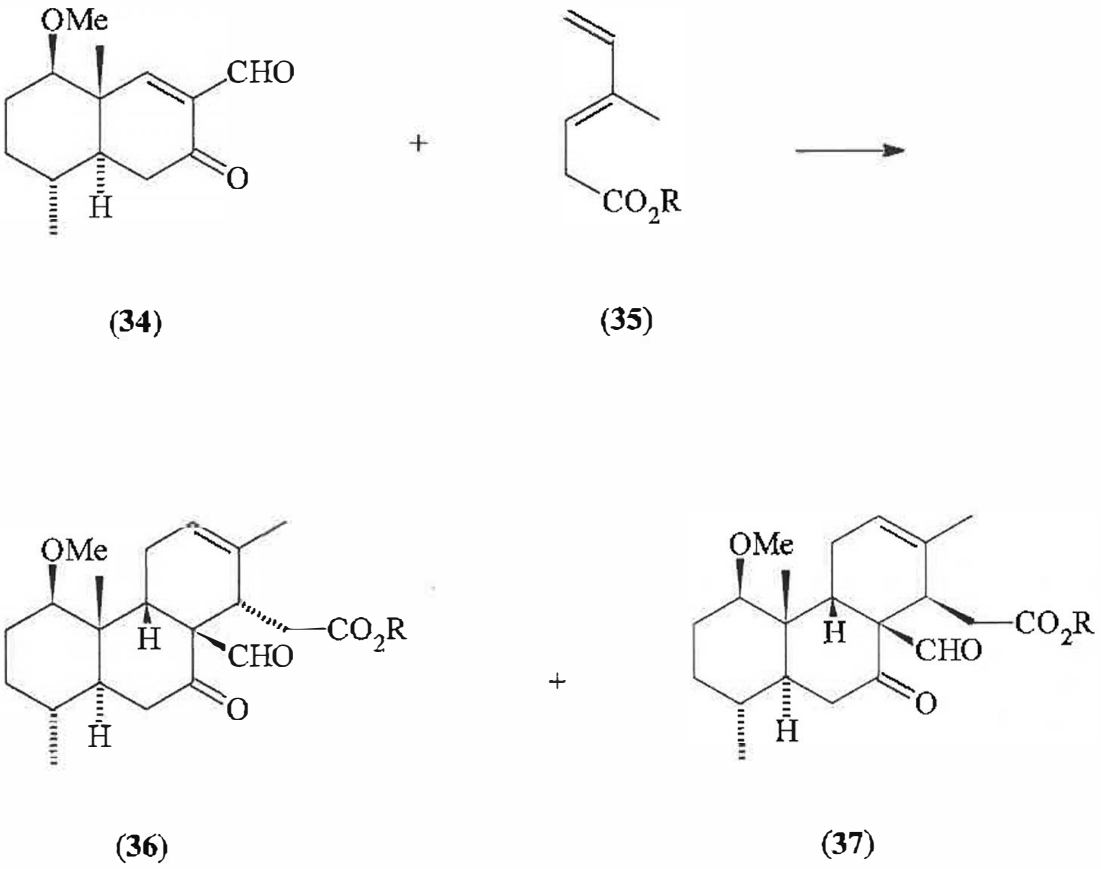
Kinetic measurements on the reactions of cyclopentadiene (**28**) with the alkyl vinyl ketones (**29**) and the 5-substituted 1,4-naphthoquinones (**32**) have been performed in water, in monohydric alcohols, and in highly aqueous solutions containing monohydric alcohols and other organic cosolvents (Scheme 8).[24]



Scheme 8

The reactions are 200 to 5800 times faster in water than in propanol with *endo* preference observed. These typical rate enhancements in water and in highly aqueous binary mixtures are significantly sensitive to substituent effects.[24] For example, an increase of the rate constant in water as the medium is observed in changing the substituent R in (**32**) from H to OH to OCH_3. This can be related to the increasing hydrophobicity of the dienophiles.

In context with synthetic work on quassinoids, Grieco and co-workers[25] found an even more significant rate enhancement of aqueous Diels-Alder reactions when the diene contained a suitably placed ionic substituent (Scheme 9, Table 4). The concentration-dependent increase of rate, yield and *endo* selectivity observed, particularly with the sodium salt of the dienoic acid (**35**) in water (entry 3), was assigned to an entropically favourable interaction of the reactants within an aggregate.



(34) **(35)**

(36) **(37)**

Scheme 9

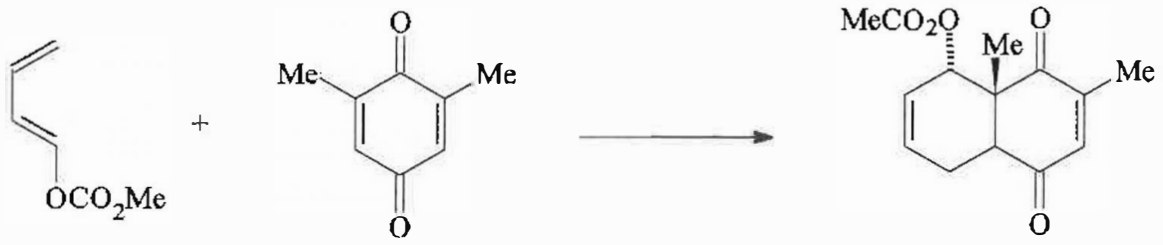
Table 4 Aqueous aggregation-promoted Diels-Alder reactions of Quassinoid Intermediates at Room Temperature (Scheme 9).

Entry	R	Solvent	Concentration of diene	Time (h)	Yield (%) (36) + (37)	Ratio (36)/(37)
1a	Et	C_6H_6	1.0 M	288	52	46:54
2a	Et	H_2●	1.0 M	168	82	57:43
3b	Na	H_2O	2.0 M	5	~100	75:25
4b	Na	H_2O	0.1 M	120	46	47:53

1.3.4.2 REACTIONS OF NON-AQUEOUS POLAR OR WATER-LIKE SYSTEMS

Various studies have shown the value of aqueous microemulsions as reaction media.[26a,b] With the lack of solubility of many reagents in water, non-aqueous microemulsions were examined to enhance solubility and reactivity in such non-homogenous media. Substituting formamide for water exhibited good selectivity and high cycloadduct yield.[27a,b] Similar to reactions in water, the use of other solvents with high dielectric constants favours the formation of the *endo* isomer, probably due to solvophobic interaction.

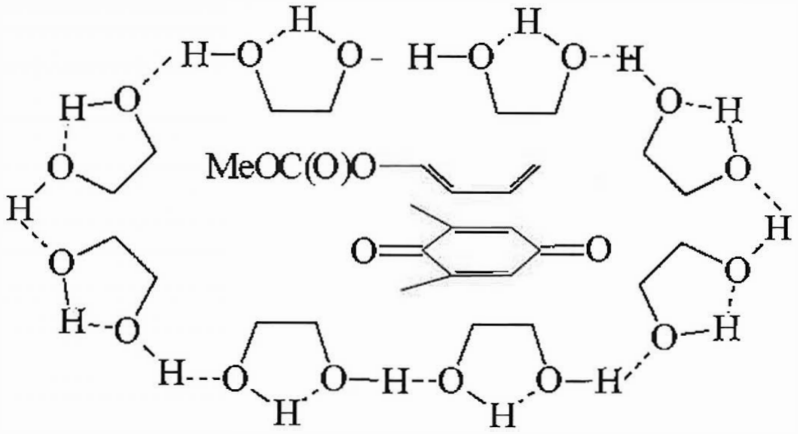
The rate of intermolecular Diels-Alder reactions involving relatively hydrophobic dienes and dienophiles such as (**38**) and (**39**), are significantly increased when the reactions are carried out in pure ethylene glycol (Scheme 10). No reaction was observed in water, presumably due to the total insolubility of (**38**) in water.



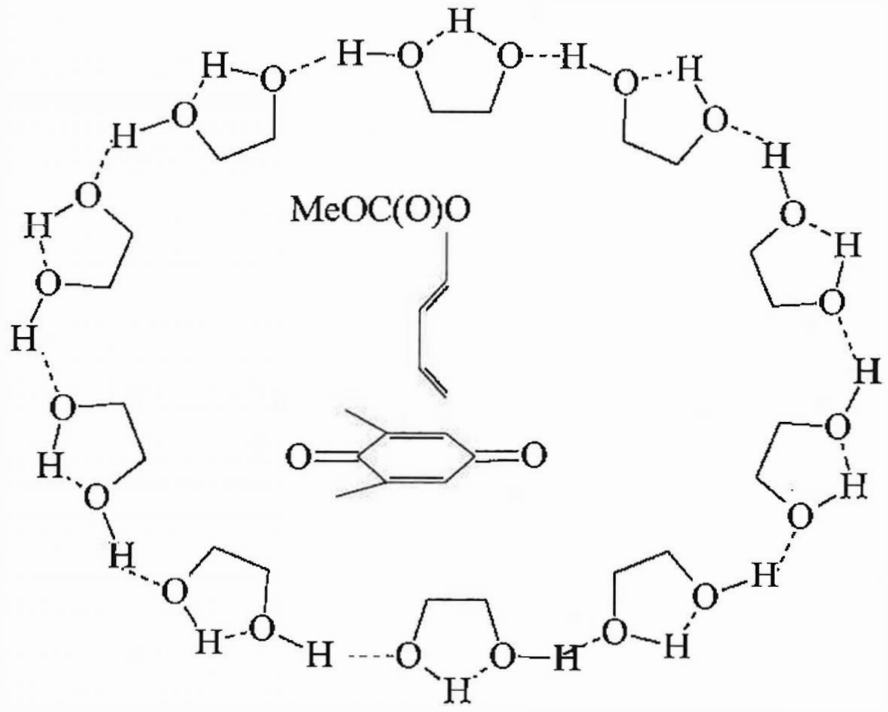
(**38**) (**39**) (**40**)

Scheme 10

The rate enhancement relative to benzene (26:1) is more easily understood in terms of the molecular aggregation phenomena.[28] In addition to the facility for extensive hydrogen bonding, ethylene glycol possesses the capability for solubilization of hydrophobic dienes and dienophiles. Molecular aggregation should be favoured for the π-stack arrangement of the reactants of type (**A**) as compared to the end-on arrangement of type (**B**) (Figure 2). In the reagent aggregate (**A**), the volume is minimised. The relative concentrations of product arrangements of diene and dienophile are larger for type (**A**) and, as a consequence, the observed reaction rates are higher.



(A)



(B)

Figure 2 (**A**) π-Stacked arrangement and (**B**) end-on arrangement

Sauer and Braun[29] first investigated the influence of lithium perchlorate ($LiClO_4$) in diethyl ether on the *endo:exo* ratio of the Diels-Alder reaction of cyclopentadiene with methyl

acrylate. This reaction served as a model system for a general survey of the polarity of $LiClO_4$-diethyl ether solutions. An increase in the concentration of $LiClO_4$ in the system was accompanied by increased formation of the *endo* product. Hence, it was concluded that the presence of this salt should accelerate reactions with polar transition states. On addition of $LiClO_4$ to diethyl ether, the polarity of the system can be increased by up to 20 dielectric units.

In addition to these results, Grieco and co-workers[30,31] reported large accelerations of Diels-Alder reactions performed in the presence of a 5 molar solution of $LiClO_4$ in diethyl ether. The accelerating effect of this solution can be visualized in analogy to the reaction in water by the creation of an "inner pressure" caused by a change in solvent structure which induces a "compression" of the reactants.

Dailey and co-workers[32] presented evidence that the rate accelerations in $LiClO_4$-diethyl ether may be due to a Lewis acid catalysis effect by the lithium cation. The second order rate constants of the Diels-Alder reaction between 9,10-dimethylanthracene and acrylonitrile in diethyl ether were found to depend on the lithium ion concentration. The authors' hypothesis for a "lithium ion-induced effect" was based on the fact that , in general, Diels-Alder reactions which are susceptible to Lewis acid catalysis, can also be accelerated by increasing the concentration of lithium ions.

1.3.5 CATALYSED DIELS-ALDER REACTIONS

1.3.5.1 INORGANIC HETEROGENOUS CATALYSTS

Several inorganic solids, such as silica gel, magnesium silicate, alumina, zeolites (molecular sieves, pore diameter 4Å), and clays have been reported to catalyse Diels-Alder reactions. The use of transition metal-exchanged zeolites is limited either to materials which are small enough to enter and leave the zeolite pores, or to materials which can be strongly bound to the outside surface of the zeolite.[34] The layered nature of clay minerals, which allows expansion of the interlamellar space if required, places fewer restrictions on the size and shape of molecules which may enter the clay and reach the active site for reactions. Laszlo and Luchetti[35] showed that mixed aqueous/organic solvent environment created in their acid-activated clay samples (K10) accelerated Diels-Alder reactions with methyl vinyl ketone and cyclopentadiene. They achieved rate increases of up to 7-8 fold with Fe^{3+}-exchanged K10 and of 3-4 fold with non-exchanged K10.

Results of [4+2] cycloadditions in the presence of chromatographic adsorbents such as silica and alumina parallel those observed for Diels-Alder reactions in the presence of zeolites and modified clays. Some of the solids obtained contain strong Lewis acid sites and are efficient catalysts in reactions of carbonyl-containing dienophiles.[36]

1.3.5.2 ACID CATALYSTS

Many Diels-Alder reactions are accelerated by Brönsted or Lewis acids via protonation or complexation of the dienophile. According to the FMO theory, a significant lowering of the LUMO energy of the dienophile is responsible for the acceleration and enhanced selectivity usually observed in a highest occupied molecular orbital (HOMO)-(diene)-LUMO (dienophile) controlled step (Figure 3).

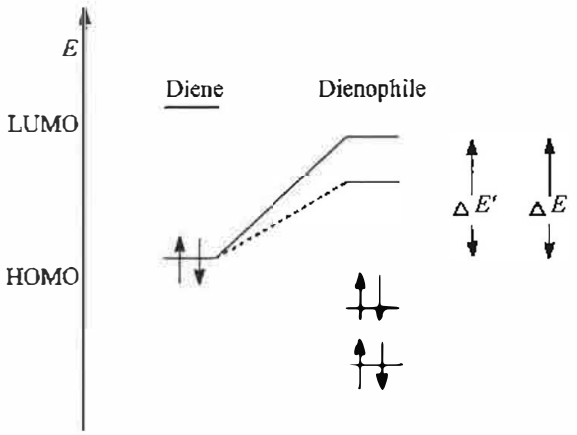
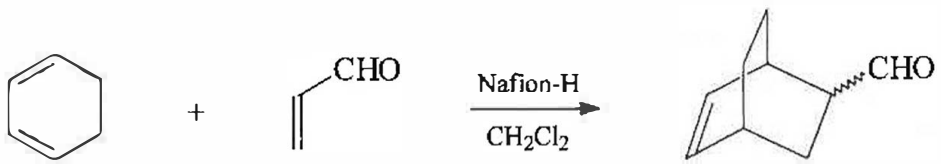


Figure 3

1.3.5.2.1 BRÖNSTED ACIDS

Diels-Alder reactions of cyclopentadiene with ethyl acrylate, methyl vinyl ketone and acrylonitrile in the presence of acetic acid, trichloroacetic acid, dichloroacetic acid and bromoacetic acid have been studied. All these Brönsted acids accelerate Diels-Alder reactions, with trichloroacetic acid being most effective. However, the *endo* transition state is not favoured in the reactions with acrylonitrile.

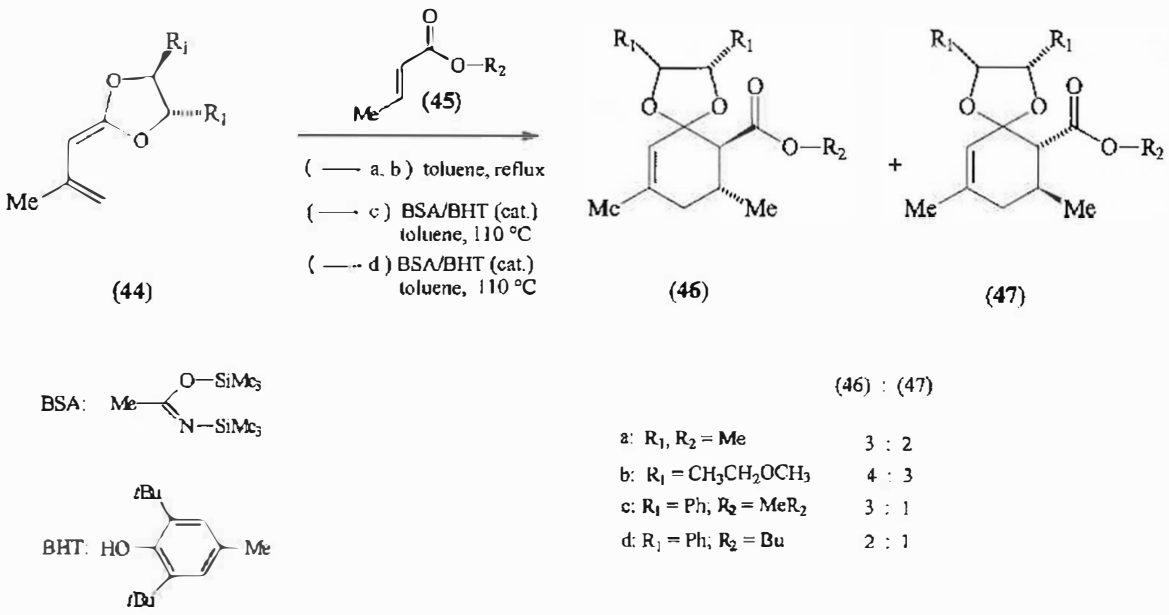
In general, Brönsted acid-catalysed [4+2] cycloadditions have received only limited attention, although Olah and co-workers[37] had reported that Nafion-H, a perfluorinated resin-sulphonic acid, is a highly efficient catalyst. While the uncatalyzed reaction of 1,3-cyclohexadiene (**41**) and acrolein (**42**) yields 25 % of adduct (**43**) (100 °C for 3.5 h), Nafion-H catalysis yields 88 % after stirring for 40 h at 25 °C (Scheme 11).



(41) **(42)** **(43)**

Scheme 11

Boehler and Konopelski[38] used a mixture of 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) and *N,O*-bis (trimethylsilyl) acetamide (BSA) to catalyse asymmetric Diels-Alder reactions. For example, enantiomerically pure vinyl ketene acetals such as (**44**) reacted with dienophiles (**45**) to give the isomeric cycloadducts (**46**) and (**47**) (Scheme 12). The facial selectivity of the reaction is modest when the substituents in (**44**) are small. The presence of a bulky phenyl group (R^1 = Ph) results in an increased diastereomeric excess. The application of high pressure also increased the selectivity in the reactions with (**44**). Variation of the solvent polarity and the use of Lewis acid catalysts did not influence the outcome of the reaction.



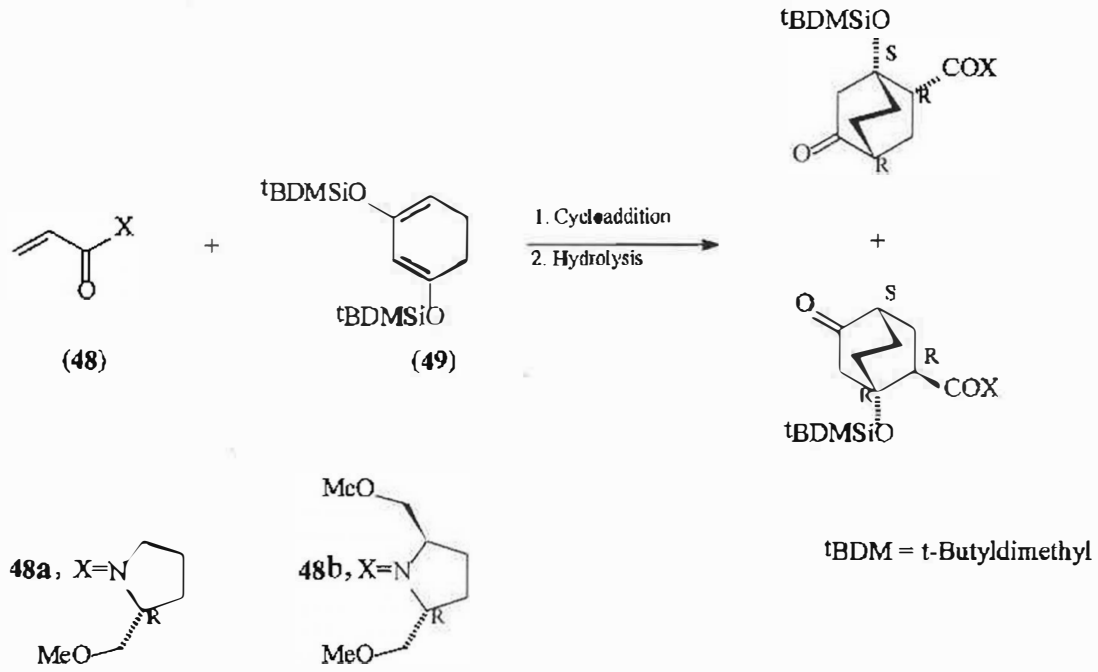
Scheme 12

1.3.5.2.2 LEWIS ACIDS AND RELATED CATALYSTS

Lewis acid-catalysed cycloadditions not only proceed more rapidly than their thermal counterparts but also exhibit greater regio- and stereoselectivity. In the reaction of methyl vinyl ketone with isoprene the proportion of *para* adduct increased from 71:29 in the

uncatalysed reaction, to 93:7 in the presence of tin chloride. Many other examples of this effect have been reported using common Lewis acids such as $TiCl_4$, $ZnCl_2$ (complexed with ethers), $ZnBr_2$, BF_3 (including ether complexed), Et_2AlCl, $EtAlCl_2$, achiral and chiral lanthanide complexes [*e.g.* Eu (III) and Yb (III) complexes].

In general, the *endo:exo* ratio is controlled by the choice of catalyst. For example, cycloaddition reactions of the 1,3-bis siloxycyclohexadiene (**49**) with chiral acrylamides (**48**), derived from chiral pyrrolidines, occur with high *endo:exo* diastereofacial selectivities (Scheme 13; Table 5).[39]



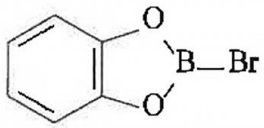
Scheme 13

Table 5, shows that the reaction ratios favour the *endo* isomer when *tert* - butyldimethylsilyl triflate (*t*-$BuMe_2SiOTf$) is used as the catalyst and the *exo* isomer when $Eu(FOD)_3$ is the catalyst. The thermal reaction (performed at 170 °C) also yielded the *exo* isomer as the major product although selectivity was lower.

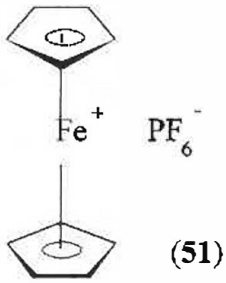
Table 5 Reactions of the diene (**49**) with the acrylamides (**48a**) and (**48b**).

Dienophile	Catalyst (10% molar)	Solvent	Temp (°C)	Time	Yield (%)	*Endo:exo* ratio	% de of *endo*	% de of *exo*
a	*t*-$BuMe_2SiOTf$	CH_2Cl_2	-60	30min	87	84:16	77	96
a	$Eu(fod)_3$	toluene	80	24h	90	0:100		25
b	none	toluene	170[a]	64h	66	23:77	13	74
b	*t*-$BuMe_2SiOTf$	toluene	20	40min	75	70:30	>98	98
b	*t*-$BuMe_2SiOTf$	toluene	-60	3h	60	87:13	>98	>98
b	*t*-$BuMe_2SiOTf$	CH_2Cl_2	-60	30min	96	88:12	>98	>98
b	$Eu(fod)_3$	toluene	80	66h	98	0:100		90

Kelly and co-workers[40] have used Lewis acid catalysts such as 2-bromo-1,3,2-benzodioxaborole (**50**) and the milder ferrocenium hexafluorophosphate (**51**) to accelerate Diels-Alder reactions of cyclic and acyclic carbodienes with dienophiles bearing a carbonyl or ester functional group. Reactions of acrylonitrile however are not influenced by these catalysts.



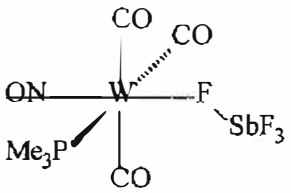
(50)



(51)

Traditional Lewis acids such as BX_3, AlX_3, TiX_4 and SnX_4 do, however, have several undesirable characteristics. These include their extreme sensitivity to water, which is one of the reasons why they are often employed at high catalytic loadings (usually 20 mol. %). Also, binding between these Lewis acids and the oxygen atoms of the dienophile and of the product is generally thermodynamically strong and, in some cases, exchange may be kinetically slow. For this reason, organometallic Lewis acids, particularly organotransition metal complexes as Lewis acid catalysts, have become useful in numerous chemical reactions.[41]

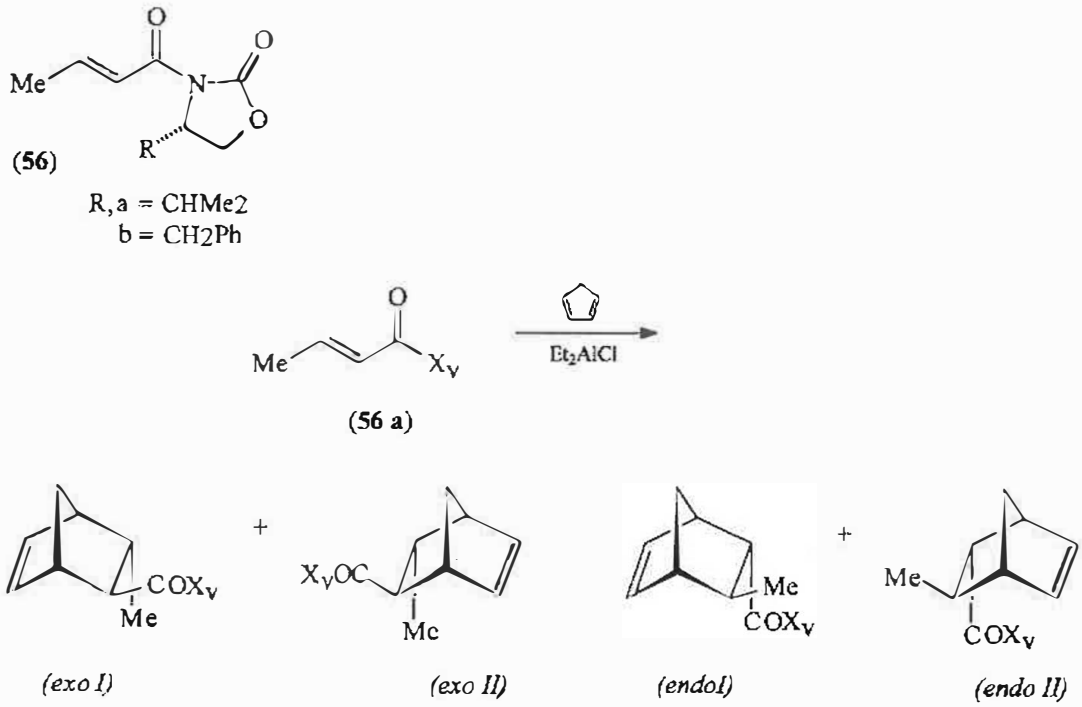
Hersh and co-workers[42] have reported that [4+2] cycloaddition reactions between butadiene or cyclopentadiene and α,β-unsaturated enones are also induced by as little as 0.1 mol. % of the tungsten nitrosyl Lewis acid (**55**). On the basis of an X-ray crystal structure analysis of a Lewis acid-dienophile adduct it was suggested that the catalytic activity of (**55**) is due solely to its Lewis acidity.



(**55**)

Collin and Van de Weghe[43] reported the use of diiodosamarium (SmI_2) for Diels-Alder reactions between cyclopentadiene or isoprene with various dienophiles such as methyl vinyl ketone and maleic anhydride and α,β-unsaturated aldehydes. Compared to other lanthanide derivatives, SmI_2 displays a broad activity : the lanthanide (III) chlorides do not catalyse the reaction of cyclopentadiene with maleic anhydride, and $Yb(fod)_3$ does not induce any reaction between cyclopentadiene and α, β-unsaturated ketones. Reactions of methyl vinyl ketone with SmI_2 are higher yielding than with ytterbium triflate ($Yb(OTf)_3$) and require a smaller amount of catalyst.[44]

The application of chiral auxiliaries incorporated into the dienophile has been widely studied. In some cases, high π-diastereofacial selectivity is induced by the complexation of a chiral dienophile with an appropriate Lewis acid.[45] Evans and co-workers[46] have described the application of chiral α,β-unsaturated *N*-acyloxazolidinones as highly reactive and diastereoselective dienophiles in dialkylaluminium chloride-promoted Diels-Alder reactions. The cycloaddition of the crotyl imide (**56a**), bearing the (*S*)-valinol-derived oxazolidinone, with cyclopentadiene in the presence of diethylaluminium chloride, affords both high levels of *endo* diastereoselection (17:1) and the highest combined *endo:exo* ratio (50:1) of all the Lewis acids screened (Scheme 13).[46]

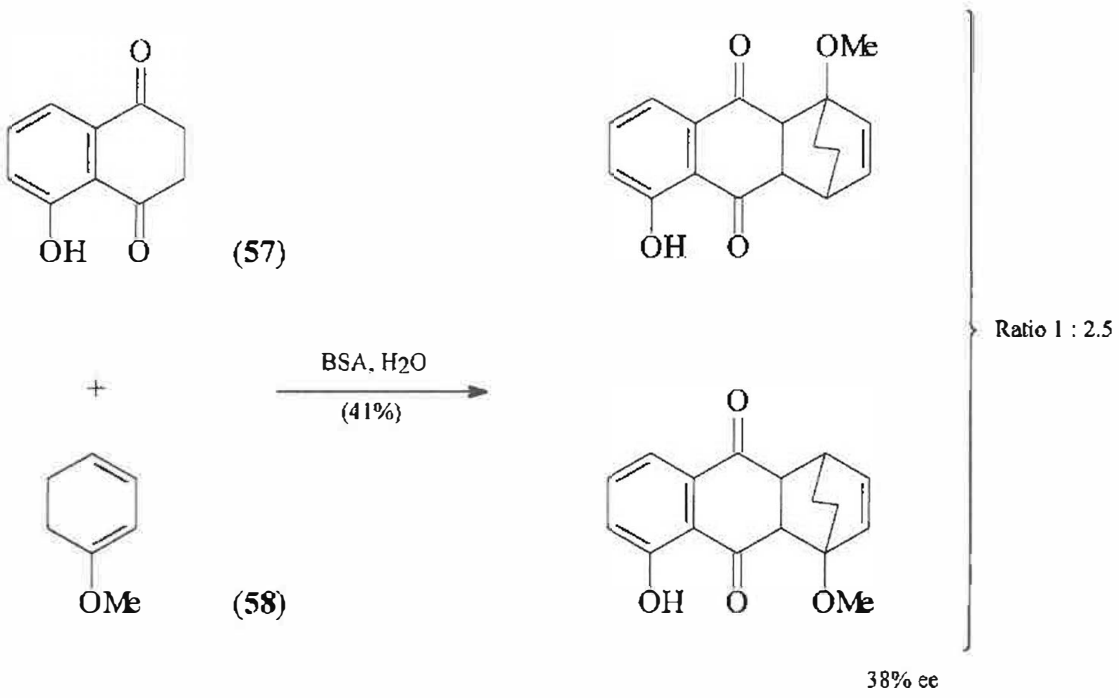


Xv = (S)-valinol-derived oxazolidinone

Scheme 13

1.3.5.3 PROTEIN, ANTIBODY AND ENZYME CATALYSIS

BSA (Bovine Serum Albumin, 5 % equiv) in water catalyses the Diels-Alder reaction between juglone (**57**) and 1-methoxycyclohexadiene (**58**) (Scheme 14).[47] While the regiochemistry of the reaction is unaffected by the protein catalyst, an enantioselectivity of 38 % is observed for the major regioisomer. Interaction between juglone and BSA can be shown by circular dichroism. If the hydroxy group of juglone is protected as an *n*-octyl ether, no interaction with BSA occurs, possibly due to steric reasons. Thus, the Diels-Alder reaction occurs without stereoselectivity.



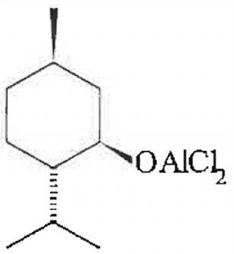
Scheme 14

Biocatalysts, for example Baker's yeast, have also been shown to catalyse Diels-Alder reactions between cyclopentadiene and fumarate derivatives.[48] In contrast to the usual *endo* selectivity, the *exo* cycloadducts are preferentially formed.

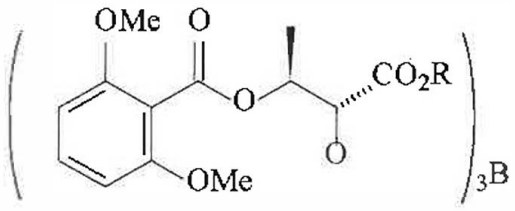
Hilvert and co-workers[49] have reported antibody-catalysed Diels-Alder cycloadditions, and *N*-ethylmaleimide. The authors are currently extending this concept to include other [4+2] cycloadditions.

1.3.5.4 THE GENERAL ACCELERATION AND π- DIASTEREOFACIAL SELECTIVITY IN ASYMMETRIC DIELS-ALDER REACTIONS WITH CHIRAL CATALYSTS

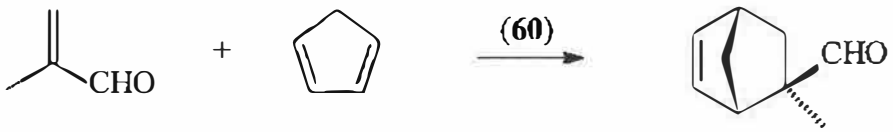
Optically active Lewis acids were first used as catalysts in asymmetric Diels-Alder reactions by Koga and co-workers.[50] The cycloaddition of cyclopentadiene with methacrolein was catalysed by the chiral aluminium compound (**59**) to afford the product in a reasonable e.e. of 72 %. Since then, it has been found that the reaction is best catalysed by the borate (**60**) which yields the product in an e.e. of 96 % (Scheme 15).[51a,b]



(**59**)

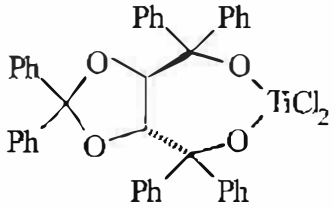


(**60**)

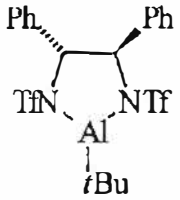


Scheme 15

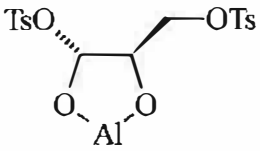
Almost complete π- face stereodifferentiation in Lewis acid-catalysed Diels-Alder reactions has been achieved by applying a chiral dienophile.[46] In contrast to this approach, the use of chiral catalysts such as the titanium complex (**61**),[52] the aluminium complexes (**62**)[53] and (**63**)[54] for the reaction of crotonic acid derivatives (**64**) with cyclopentadiene afford (**65**) with good chiral control with e.e.'s of 91, 95, and 97 % , respectively (Scheme 16).



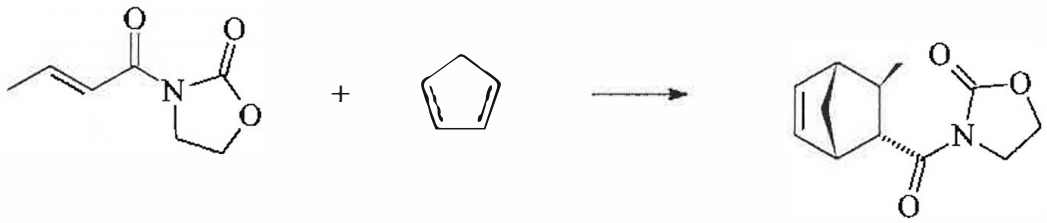
(61)



(62)



(63)



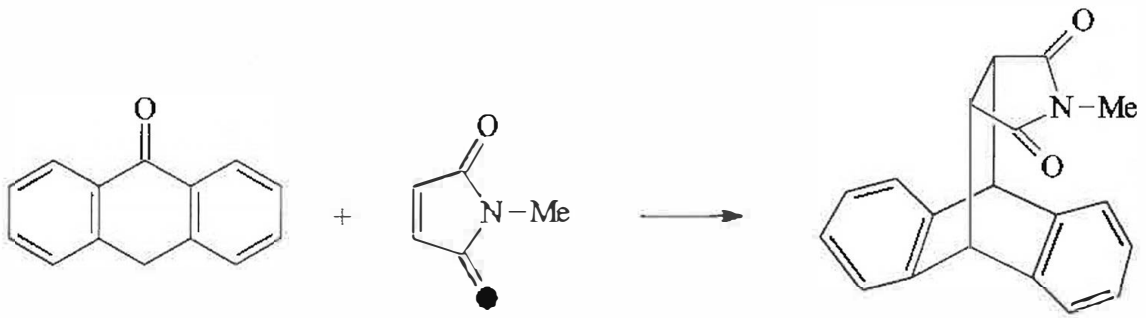
(64) (65)

Scheme 16

More recently, the use of ytterbium trifluoromethanesulphonate (triflate)[55] and scandium triflate[56] as chiral catalysts have afforded products with e.e.'s of 95 and 97 %, respectively.

1.3.5.5 BASE CATALYSIS

In 1989, Rickborn and co-workers[57a,b] reported the first evidence for a base-catalysed Diels-Alder reaction. In the presence of triethylamine, anthrone **(66)** functions as a reactive diene with various dienophiles, *e.g.*, with *N*-methylmaleimide **(67)**, the cycloadduct **(68)** formed (Scheme 15). This was ascribed to an oxyanion acceleration, presumably *via* the enolate of **(66)**.



(66) **(67)** **(68)**

Scheme 17

Kagan and co-workers[58] furthered this work using chiral amines as catalysts and were able to isolate optically active cycloadducts in high yield. Base-catalysed reactions will be discussed in Chapter 2.

CHAPTER 2: DISCUSSION

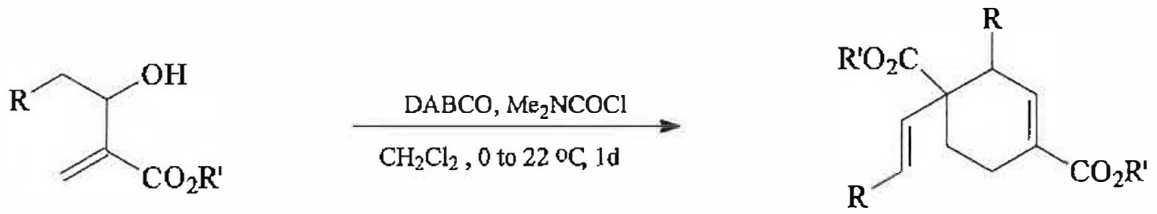
The discussion consists of three parts - A, B and C.

PART A

2.1 TERTIARY AMINE-CATALYSED DIELS-ALDER REACTIONS

2.1.1 INTRODUCTION

Working in our laboratories, Janse van Rensburg[59] reported an efficient synthesis of substituted cyclohexenes (**73**) using allylic alcohols (**69**) derived from the Baylis-Hillman reaction (Scheme 18).



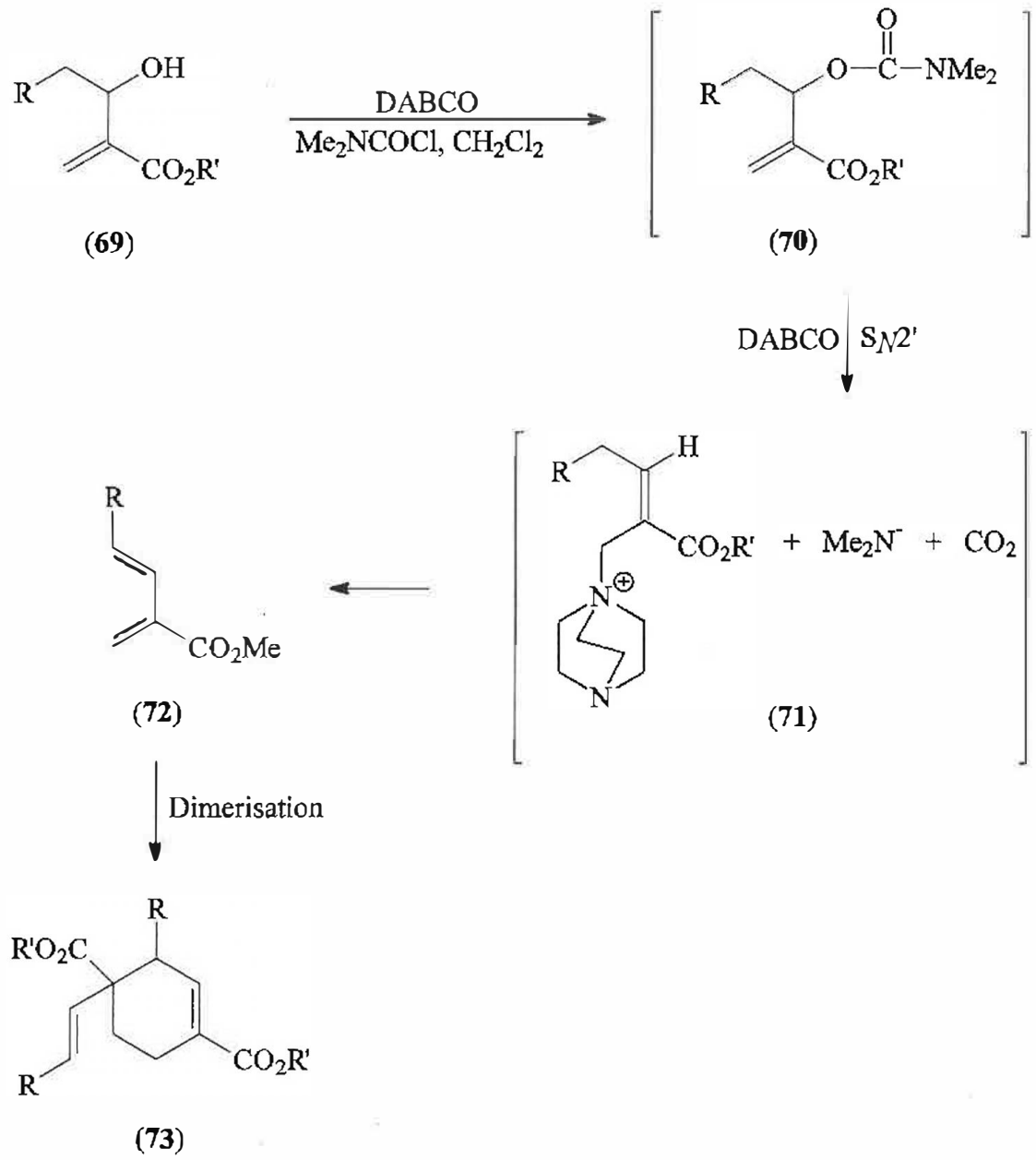
(69) **(73)**

R = H , CH_3 , CH_2CH_3

R' = CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$

Scheme 18

The proposed mechanism for the formation of the substituted cyclohexene (**73**) is shown in Scheme 19.



Scheme 19

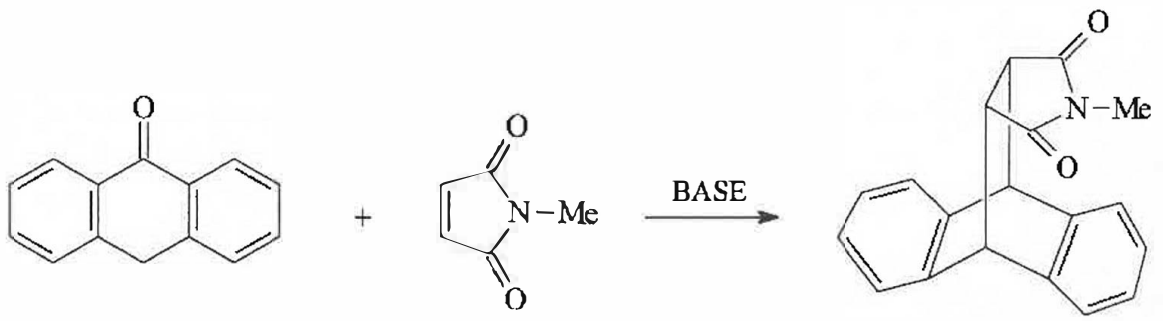
The mechanism involves the formation of an allylic carbamate intermediate (**70**) from the allylic alcohol (**69**) (Scheme 19). The allylic carbamate (**70**) then reacts rapidly with

DABCO in an S_N2' reaction affording the ammonium salt (**71**). The formation of the dimethyl amine anion and carbon dioxide is a result of the spontaneous decomposition of the carbamate leaving group.

The subsequent formation of the diene ester (**72**) results from the concerted elimination of DABCO. Dimerisation then proceeds *via* a Diels-Alder-type cycloaddition reaction affording the substituted cyclohexene (**73**).

It is evident from the reaction conditions outlined in Scheme 18 that the formation of the substituted cyclohexenes (**73**) from allylic alcohols (**69**), *via* an intermolecular Diels-Alder cycloaddition reaction, proceeds under unexpectedly mild reaction conditions. Janse van Rensburg[59] subsequently speculated that due to the mild reaction conditions, the formation of the cyclohexene adduct (**73**) *via* the Diels-Alder cycloaddition may have been DABCO-assisted.

From the literature, it is evident that base-catalysed Diels-Alder reactions have received little attention thus far. In 1989, Rickborn and co-workers[57a,b] reported the first base-catalysed Diels-Alder reaction. In preliminary work, anthrone (**74**) was reported to react as a masked diene with *N*-methylmaleimide (NMM) (**75**) when the reaction was carried out in DMF, Et_3N, or pyridine, to afford the cycloadduct (**76**), exclusively (Scheme 20).



(**74**) (**75**) (**76**)

Scheme 20

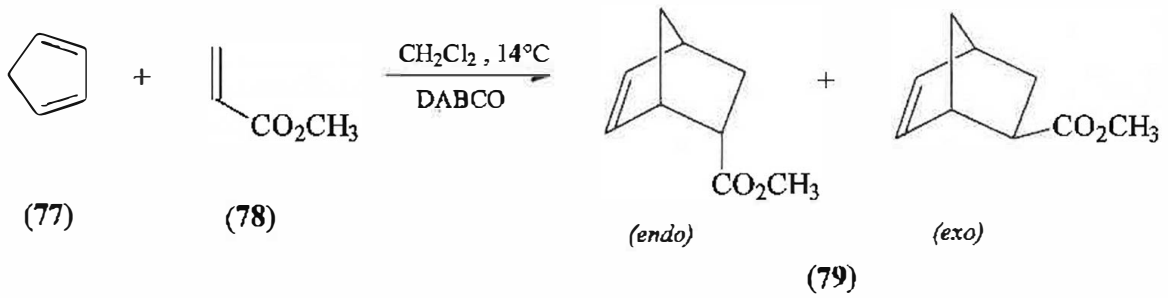
It was found that the rate and course of the reaction was sensitive to the base employed. For example, primary amines *i.e.* isopropylamine were more efficient catalysts than Et_3N, but, also consumed the dienophile by conjugate addition under certain conditions. Efforts to increase the rate of cycloaddition by employing stronger bases, for example, NaOMe in MeOH, afforded Michael adducts rather than cycloadducts.

Kagan and co-workers,[58] encouraged by the work of Rickborn and co-workers,[57a,b] set up conditions allowing chiral amines, such as alkaloids, to catalyse the reaction between anthrone (**74**) and NMM (**75**) (Scheme 20).

The encouraging results obtained by Janse van Rensburg[59] and the results obtained above, prompted an in-depth investigation as to whether DABCO could be used as a catalyst in intermolecular Diels-Alder cycloaddition reactions.

2.1.2 THE USE OF DABCO AS A CATALYST FOR THE PROMOTION OF INTER-MOLECULAR DIELS-ALDER CYCLOADDITION REACTIONS

We initiated this investigation by comparing the reaction rates of uncatalysed Diels-Alder reactions with those containing a catalytic amount of DABCO (0.1 eq.). These reactions were carried out in dichloromethane at ambient temperature (14 °C) using the reactive cyclopentadiene (**77**) as the diene and the monosubstituted dienophile methyl acrylate (**78**) (Scheme 21).



(**77**) (**78**) *(endo)* *(exo)* (**79**)

Scheme 21

Table 8 Results for the uncatalysed and DABCO-catalysed Diels-Alder reaction.

Reaction	Reaction time	Catalyst	% Yield (79)	*Endo:Exo*
a	18 h	-	4	76:24
b	18 h	DABCO	52	76:24

It is evident from the results obtained (Table 8) that the reaction conducted in the presence of DABCO showed an enhanced reaction rate (based on the yield of cycloadduct formed) over the uncatalysed reaction. The above investigation thus established that the Diels-Alder cycloaddition reaction was DABCO-catalysed.

2.1.3 THE EFFECT OF TIME AND TEMPERATURE ON THE REACTION RATE

When the reaction (Scheme 21, page 30) was allowed to proceed for 2 days the yield improved moderately. It was subsequently found that a moderate increase in the reaction temperature also improved the overall yield of the reaction. The results of this investigation are summarised in Table 9.

Table 9 Rate enhancement of DABCO-catalysed reactions.

Reaction	Temperature (°C)	Reaction time	% Yield (79)
a	14	2 d	57
b	22	2 d	66

2. 1.4 THE EFFECT OF OTHER TERTIARY AMINES AS CATALYSTS IN THE DIELS-ALDER CYCLOADDITION REACTION

In a comprehensive review by Drewes and Roos[60] other tertiary amines were found to catalyse the Baylis-Hillman reaction. Further investigations in our laboratories showed that various tertiary amines were successful catalysts for allylic rearrangements.[61]

In light of this we extended our investigation to the use of tertiary amines, other than DABCO, as potential catalysts for intermolecular Diels-Alder cycloaddition reactions. The reactions studied involved the use of the reactive cyclopentadiene (**77**) and methyl acrylate (**78**) as the dienophile. The reaction conditions established in section 2.1.3 page 31 (*i.e.* 22 °C, 2 d), were used. The results are summarised in Table 10 referring to Scheme 21 on page 30.

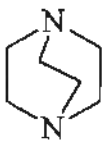
Table 10 The effect of various tertiary amine catalysts in the reaction between cyclopentadiene (**77**) and methyl acrylate (**78**).

Catalyst	**Reaction Time**	**% Yield (79)**	***Endo:Exo***	
			(NMR)	**(GC)**
DABCO	2 d	66	80:20	76:24
quinuclidine	2 d	60	-	78:22
quinuclidinol	2 d	48	-	77:23
Et_3N	2 d	44	78:22	80: 20
quinidine	2 d	42	80:20	82: 18
quinine	2 d	37	80:20	80:20
sparteine	2 d	35	79:21	77:23
brucine	2 d	32	80:20	77:23

It is evident from the results obtained (Table 10) that the rate of cycloadduct formation with the tertiary amine catalysts is directly related to steric factors present in the amines.

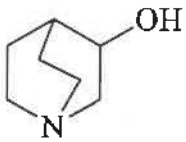
The least sterically hindered tertiary amines, *i.e.* DABCO and quinuclidine, afforded the highest yields of cycloadduct (**79**) (Scheme 21, page 30). The low yields obtained when using the natural product tertiary amines, namely quinidine, quinine, sparteine and brucine as catalysts, can be rationalised in terms of their steric bulkiness (Fig 4). These results are analogous to those reported by Drewes and Roos[60] on the Baylis-Hillman reaction, and Mason[61] on allylic rearrangement reactions. Their low yields were also attributed to steric hindrance.

In contrast to these observations, the *endo/exo* selectivities of the cycloadduct (**79**) were not significantly influenced by the steric nature of the tertiary amines used.

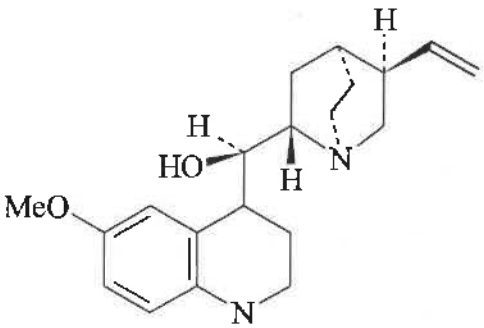


DABCO

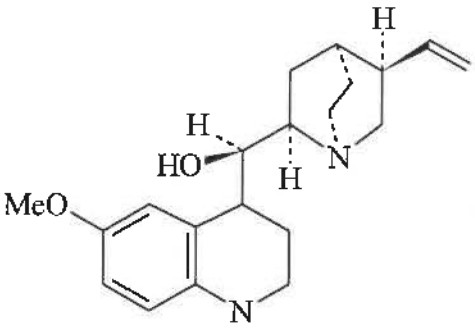
QUINUCLIDINE



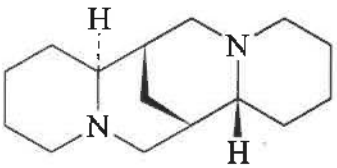
QUINUCLIDINOL



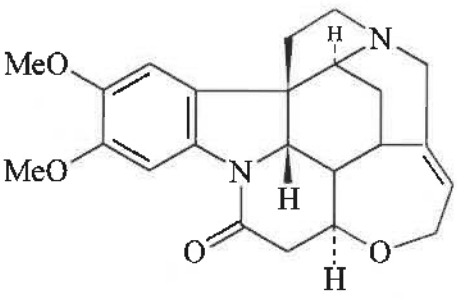
QUINIDINE



QUININE



SPARTEINE



BRUCINE

Figure 4

2.1.5 PHOSPHINE AND PHOSPHITE-CATALYSED DIELS- ALDER REACTIONS

Work done by Baylis and Hilman[62] has demonstrated that besides various tertiary amines, various phosphines and phosphites have also been successfully employed in catalysing the Baylis-Hillman reaction. Owing to the relatively sterically unhindered nature of the lone pair on the phosphorus atom and knowing that the Diels-Alder reaction favours the relatively sterically unhindered tertiary amine *i.e.* DABCO, we envisaged similar catalytic properties using PPh_3 and $P(OEt)_3$. The reactions studied involved the use of cyclopentadiene (**77**) and methyl acrylate (**78**) as the dienophile. The results are summarised in Table 11 referring to Scheme 21 on page 30.

Table 11 The effect of PPh_3 and $P(OEt)_3$ in the reaction between cyclopentadiene (**77**) and methyl acrylate (**78**).

Catalyst	**Reaction time**	**% Yield (79)**	***Endo:Exo***
$P(OEt)_3$	2 d	47	79:21
PPh_3	2 d	30	70:30

The rate of cycloadduct formation for the PPh_3 and $P(OEt)_3$ catalysed Diels-Alder reactions are significantly lower than the DABCO catalysed reaction (Table 10, Page 32).

From the above investigations it is evident that DABCO, the sterically least hindered tertiary amine, is the catalyst of choice for further investigations. To establish the generality of DABCO as a catalyst for Diels-Alder cycloaddition reactions, it was decided to extend this investigation into the use of various dienes and dienophiles.

2.1.6 FURTHER STUDIES OF THE DABCO-CATALYSED DIELS-ALDER CYCLO-ADDITION REACTIONS WITH VARIOUS DIENOPHILES

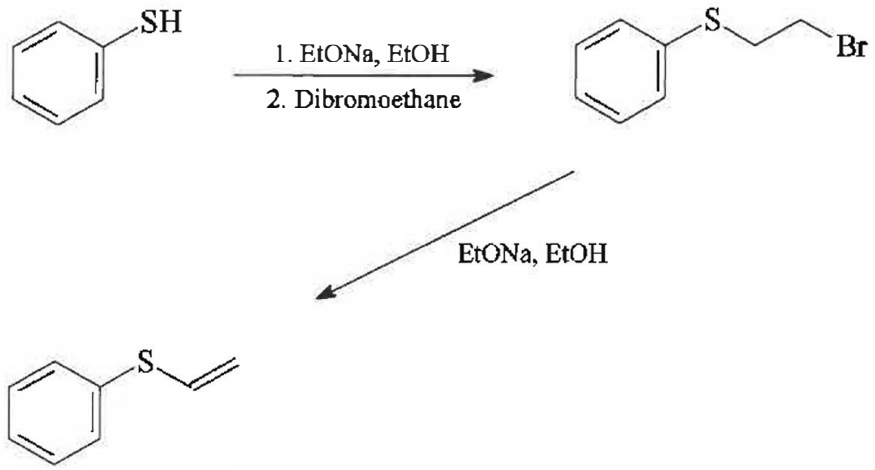
2.1.6.1 INTRODUCTION

In a normal Diels-Alder reaction, the rate of reaction is determined largely by the degree of interaction between an electron-deficient dienophile and an electron-rich diene. The most commonly encountered activating substituents on dienophiles are CO, COR, CO_2R, CN and NO_2 in conjugation with the double or triple bond. The initial work carried out in this investigation involved the use of the following dienophiles, namely methyl acrylate, methyl vinyl ketone, acrylonitrile, acrolein, crotonaldehyde and methylcrotonoate. Other more complex dienophiles were synthesised in order to determine the effects of their bulkiness on the reaction rate.

2.1.6.2 SYNTHESIS OF THE COMPLEX DIENOPHILES

2.1.6.2.1 PREPARATION OF PHENYL VINYL SULPHOXIDE

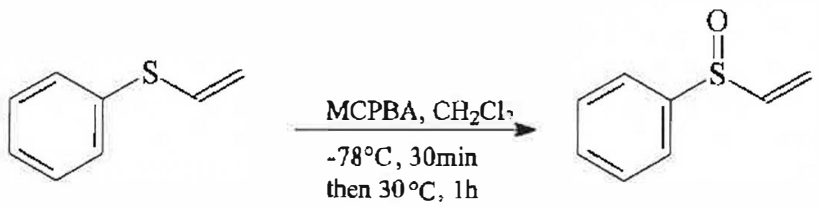
Phenyl vinyl sulphoxide (**81**) was prepared from the thiophenol-derived phenyl vinyl sulphide (**80**) according to the method of Paquette and Carr[63] (Scheme 23). Phenyl vinyl sulphide is unstable at room temperature and slowly decomposes to a dark yellow oil. Decomposition was retarded by storage under nitrogen at 0 °C.



(80) *52%*

Scheme 23

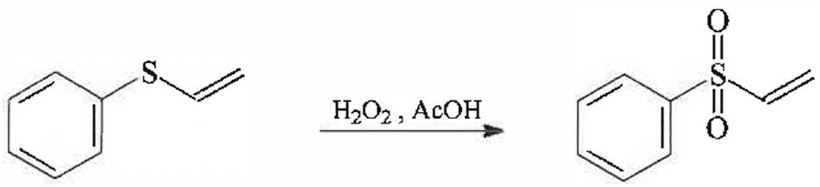
Phenyl vinyl sulphoxide (**81**) was synthesised by the oxidisation of phenyl vinyl sulphide (**80**) using MCPBA (Scheme 24).



(80) **(81)** *55%*

Scheme 24

Although phenyl vinyl sulphone (**82**) has been reported to serve well as a regioselective synthetic ethylene equivalent or terminal alkene in Diels-Alder reactions, we could not utilise this sulphone dienophile, as, the well known literature procedure involving the reaction of phenyl vinyl sulphide (**80**) with glacial acetic acid and hydrogen peroxide was unsuccessful (Scheme 25).[63]



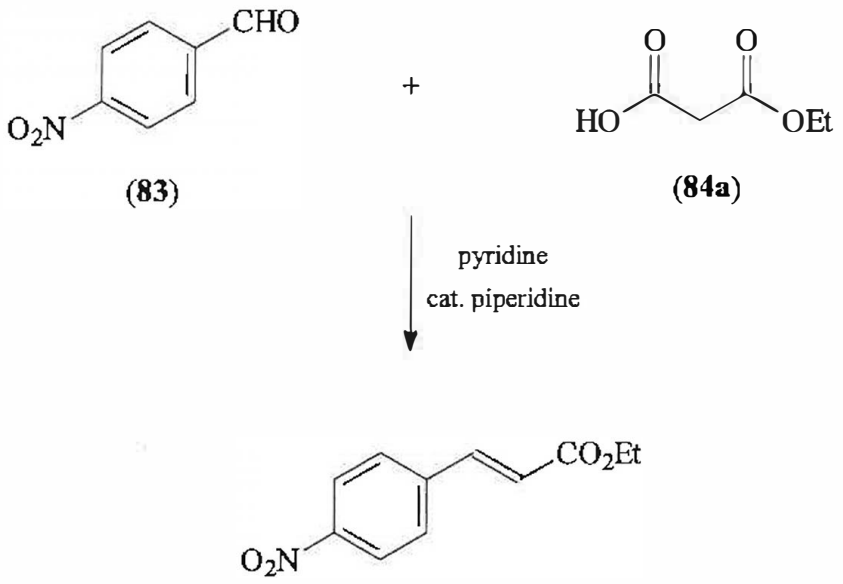
(80) **(82)**

Scheme 25

From a literature search, a more efficient method for the oxidation of sulphides to sulphones became evident.[64] This method involves the use of tetrapropylammonium perruthenate (TPAP) [$(CH_3CH_2CH_2)_4NOH$] to catalyse the oxidation reaction. This procedure, unfortunately, could not be employed as the reagents required for the synthesis of TPAP were unavailable.

2.1.6.2.2 PREPARATION OF ETHYL-*para*-NITROCINNAMATE

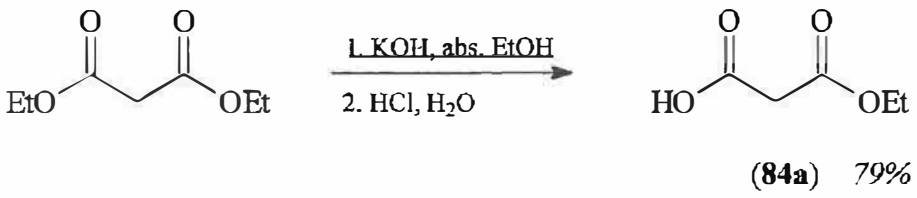
Ethyl-*para*-nitrocinnamate (**84b**) was prepared using the method of preparation for cinnamic acid.[65a] *Para*-nitrobenzaldehyde (**83**) was reacted with ethylmalonic acid (**84a**) in a condensation reaction, using, a mixture of pyridine and a catalytic amount of piperidine as the base system (Scheme 26). This base system also conveniently acted as the reaction solvent, allowing the reaction mixture to be heated to permit decarboxylation.



(84b) *86%*

Scheme 26

Ethyl malonic acid (**84a**) was readily prepared by the partial hydrolysis of diethyl malonate with potassium hydroxide in absolute ethanol, followed by acidification of the potassium salt (Scheme 27).[66]

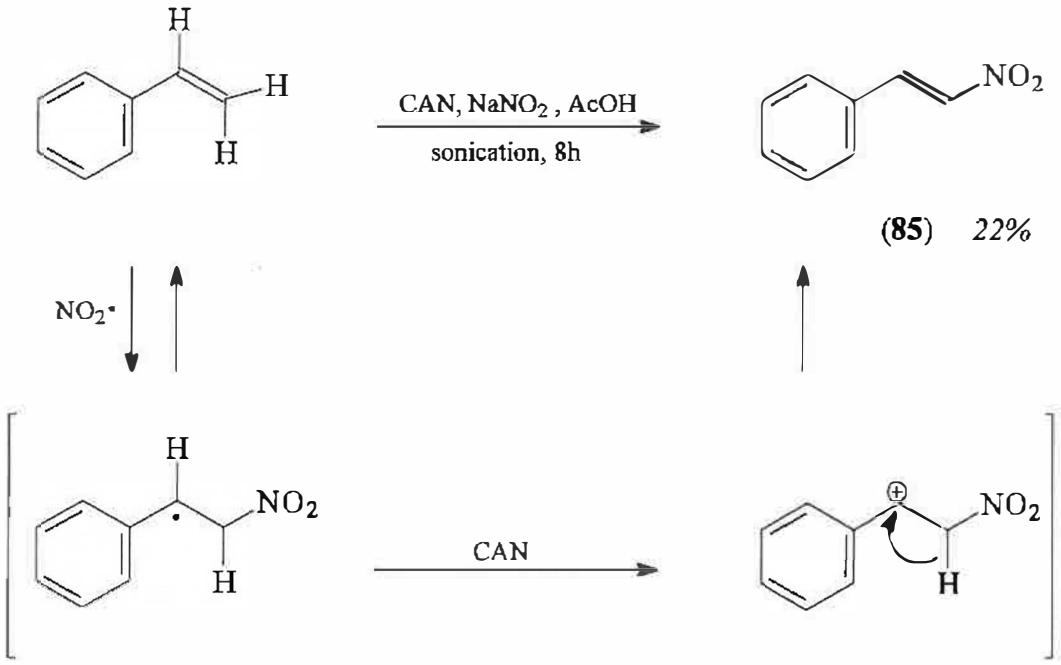


(84a) *79%*

Scheme 27

2.1.6.2.3 PREPARATION OF β-NITROSTYRENE

A new literature method for the nitration of alkenes to α, β-unsaturated nitroalkanes was employed in the synthesis of β-nitrostyrene (**85**) (literature yield 88%).[67] Styrene was treated with sodium nitrate, cerium (IV) ammonium nitrate (CAN) and glacial acetic acid in chloroform (Scheme 28).



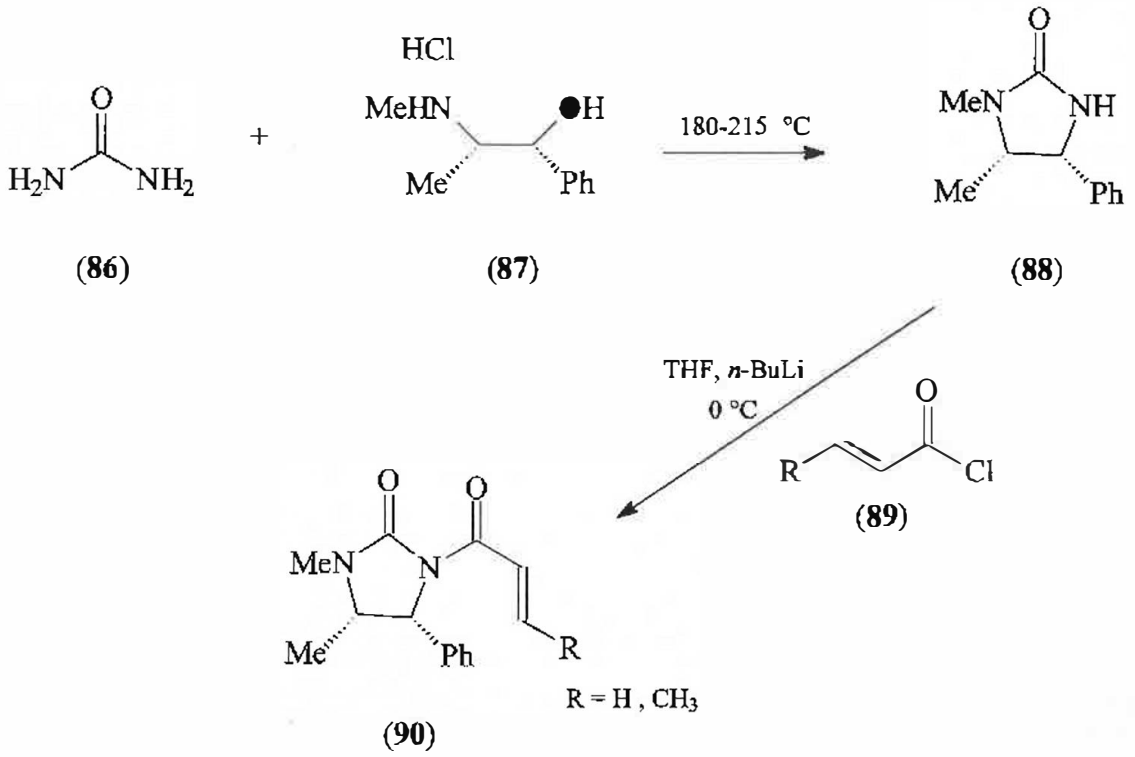
Scheme 28

Sonication of the reaction mixture in a sealed tube increases the concentration of NO_2 radicals generated. After these radicals react with the alkene substrate, CAN oxidizes the resultant carboradical intermediate *in situ* to afford the corresponding carbocationic species. Finally, elimination of the proton α to the nitro group affords β-nitrostyrene.

2.1.6.2.4 PREPARATION OF *N*-ACYL IMIDAZOLIDIN-2-ONES

In our laboratory, Roos and Jensen[68] reported the use of α,β-unsaturated N-acyl-imidazolidin-2-ones as efficient chiral auxiliaries in Lewis acid catalysed Diels-Alder reactions. It was decided to extend the use of these auxiliaries to tertiary amine catalysed Diels-Alder reactions. The *N*-acryloyl and *N*-crotonyl dervatives used in this investigation were prepared by Karina Jensen, a fellow student in our laboratory.

Urea (**86**) and ephedrine hydrochloride (**87**) were fused together using the Close fusion[69] method to afford ephedrine-imidazolidin-2-one (**88**) (Scheme 29). Treatment of (**88**) with acryloyl or crotonyl chloride (**89**) yielded the corresponding α,β-unsaturated derivatives (**90**).

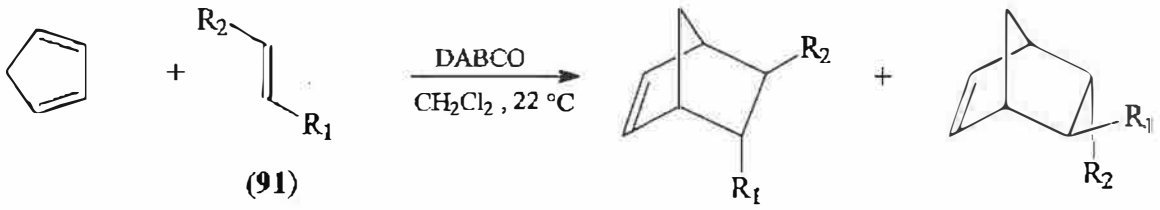


(**86**) (**87**) (**88**) (**89**) (**90**)

Scheme 29

2.1.6.3 DABCO-CATALYSED DIELS-ALDER REACTIONS USING VARIOUS DIENOPHILES

The results of this investigation are summarised in Table 12 referring to Scheme 30. (Note: all reactions involved the use of cyclopentadiene as the diene and 0.1 eq. of DABCO.)



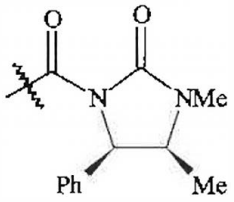
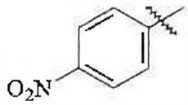
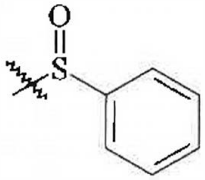
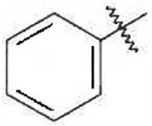
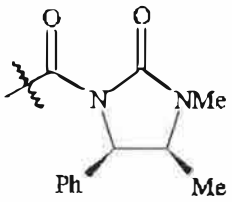
(91)

(endo) *(exo)*

(92)

Scheme 30

Table 12 DABCO-catalysed Diels-Alder reactions of cyclopentadiene with various dienophiles at 22 °C in CH_2Cl_2 (Scheme 30, page 42).

91	R_1	R_2	Time	% Yield (92)	*Endo:Exo* *
a	CN	H	2 d	81	65:35
b	$COCH_3$	H	2 d	76	81:19
c	CHO	H	2 d	72	80:20
d		H	5 d	68	69:31
e	CO_2Et		2 d	66	67:33
f	H	CO_2CH_3	2 d	66	76:24
g		H	3 d	3	77:23
h	CO_2CH3	CH_3	2 d	3	N/R
i	CHO	CH_3	2 d	3	N/R
j	NO_2		2 d	N/R	N/R
k		CH_3	5 d	N/R	N/R

N/R = no result. Dienophile unreactive in DABCO-catalysed Diels-Alder reaction.

* Obtained from GC analysis.

An inspection of Table 12 reveals that DABCO-catalysed cycloaddition reactions with cyclopentadiene are favoured when the dienophile is monosubstituted. This is well illustrated in entries a, b, c, d and f in which the dienophiles, namely acrylonitrile, methyl vinyl ketone, acrolein, *N*-acryloyl-imidazolidin-2-one and methyl acrylate display good reaction rates. The good reactivity of these relatively sterically unhindered dienophiles can be rationalised in terms of their good electron withdrawing substituents.

In contrast to the monosubstituted dienophiles, disubstituted dienophiles, with the exception of ethyl-*para*-nitrocinnamate (entry e), were less reactive (entries h and i) or unreactive (entries j and k). The poor reactivity of methyl crotonate (entry h) and crotonaldehyde (entry i) can be attributed to the steric hindrance of the methyl group reducing the catalytic activity of the relatively bulky tertiary amine *i.e.* DABCO.

The literature reveals that *para*-substituted cinnamic acids, esters, amides and acid chlorides display good reactivity with cyclopentadiene in thermal Diels-Alder reactions.[70] The *endo* selectivity was reported to increase as the *para* substituent varied in the order methyl < hydrogen < chloro < nitro, while the overall reaction rate increased with an increase in the electron withdrawing nature of the dienophile. In conjunction with the sterically unhindered nature of the phenyl ring, the above factors contribute to the good reaction rate and high *endo* selectivity of ethyl-*para*-nitrocinnamate (entry e) in the DABCO-catalysed Diels-Alder cycloaddition reaction with cyclopentadiene.

The low reactivity of phenyl vinyl sulphoxide has been reported in the Baylis-Hillman reaction[62] as well as in Diels-Alder reactions.[1] Thus, it was not unusual that phenyl vinyl sulphoxide (entry g) displayed poor dienophilicity in the attempted DABCO-catalysed Diels-Alder cycloaddition reaction.

Roos and Jensen[68] reported high levels of diastereoselectivity and good yields of cycloadduct (70-80%) in Lewis acid catalysed (diethylammonium chloride) Diels-Alder reactions between cyclopentadiene and the *N*-acryloyl- and *N*-crotonyl-imidazolidin-2-ones

(70-80% yields with *endo:exo* ratios of <6:1 and 15:1 respectively). The high *endo* selectivity was rationalised in terms of the Cα-si face selectivity of the Lewis acid catalysed Diels-Alder reaction and the good complexing ability of the Lewis acid catalyst (Figure 5).

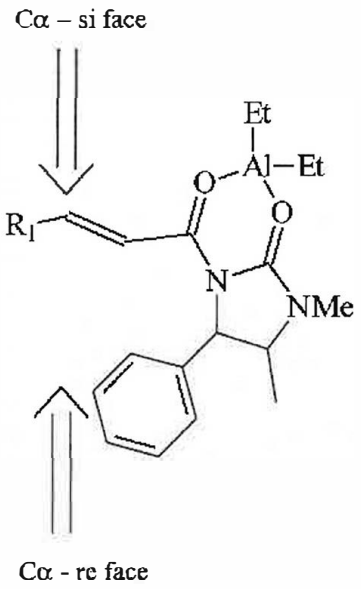


Figure 5

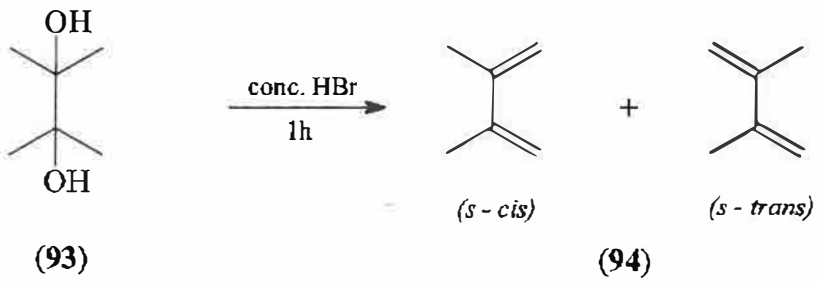
In contrast to the results obtained by Roos and Jensen,[68] the *N*-crotonyl derivative (entry k) was unreactive in the DABCO-catalysed reaction. Again the result can be attributed to the steric nature of the crotonyl group in the dienophile. The DABCO-catalysed Diels-Alder reaction of the unhindered N-acryloyl derivative (entry d) was successful. A rate enhancement was observed for this reaction when 0.2 equivalents of DABCO and 3 equivalents of cyclopentadiene were employed (85%, 3 d, 63:37 *endo:exo*). The low *endo* selectivity in the DABCO-catalysed Diels-Alder reaction can be ascribed to the lack of co-ordination of the catalyst and the dienophile.

2.1.7 FURTHER STUDIES OF THE DABCO-CATALYSED DIELS-ALDER CYCLO-ADDITION REACTIONS WITH VARIOUS DIENES

A wide range of dienes, including cyclic and aliphatic dienes, take part in the Diels-Alder reaction. In normal Diels-Alder reactions, an essential condition for the reaction is that the diene has, or can, adopt a *cisoid* conformation. Having established the high reactivity of cyclopentadiene in DABCO catalysed Diels-Alder reactions, it was decided to extend this investigation to the less reactive dienes, *i.e.* 2-methyl-1,3-butadiene (isoprene) and 2,3-dimethyl-1,3-butadiene.

2.1.7.1 SYNTHESIS OF 2,3-DIMETHYL-1,3-BUTADIENE

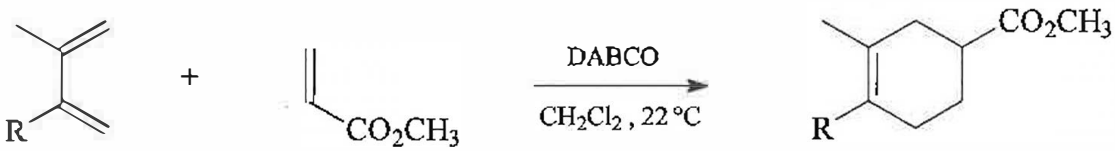
2,3-Dimethyl-1,3-butadiene (**94**) was prepared by stirring 2,2-dimethylbutane-2,3-diol, (Pinacol) (**93**) with *conc.* hydrobromic acid for 1 hour (Scheme 31).[65b] The acid catalysed elimination of two molecules of water from pinacol afforded, after extraction and fractional distillation, 2,3-dimethyl-1,3-butadiene (predominantly *cis*, 52%).



Scheme 31

2.1.7.2 DABCO-CATALYSED DIELS-ALDER REACTIONS USING VARIOUS DIENES

The results of this investigation are summarised in Table 13 referring to Scheme 32. (Note: all reactions initiated involved the use of methyl acrylate as the dienophile and 0.1 eq. of DABCO).



R = H, CH_3

(95) **(96)**

Scheme 32

Table 13 DABCO-catalysed reactions using various dienes.

95	R	Reaction Time	% Yield (96)
a	H	2 d	-
b	CH_3	2 d	4

From Table 13 it is evident that the dienes used are poorly reactive in DABCO-catalysed Diels-Alder reactions. The reason for this poor reactivity is unknown.

2.1.8 DABCO-CATALYSED AQUEOUS DIELS-ALDER REACTIONS

Sauer and Braun[29] first investigated the influence of $LiClO_4$ in diethyl ether on the *endo:exo* ratio of the Diels-Alder reaction of cyclopentadiene with methyl acrylate. This reaction served as a model system for a general survey of the polarity of aqueous $LiClO_4$/diethyl ether solutions. Grieco and co-workers[31] reported large accelerations of the

Diels-Alder reaction in the presence of a 5 molar aqueous solution of $LiClO_4$ in diethyl ether. The acceleration effect reported is analogous to that in water with the creation of an "inner pressure" caused by the change in solvent structure which induces a "compression" of the reactants.

With the knowledge that Diels-Alder reactions can be accelerated in aqueous solutions, it was decided to use water as the solvent system in the DABCO-catalysed reaction of cyclopentadiene with methyl acrylate (Scheme 21, page 30). We envisaged that the yield and stereoselectivity of this reaction would dramatically improve in the aqueous medium. The result of this aqueous reaction is recorded in Table 14, together with the results of the reaction conducted in dichloromethane (Table 9, page 31).

Table 14 DABCO-catalysed aqueous Diels-Alder reaction between cyclopentadiene and methyl acrylate.

Catalyst	**Solvent**	**Reaction Time**	**% Yield (88d)**	***Endo:Exo***
DABCO	CH_2Cl_2	2d	66	66:34
DABCO	H_2O	2d	48	66:34

The results showed a decrease in product yield for the reactions conducted in water as opposed to dichloromethane. This increase in polarity of the solvent, *i.e.* from dichloromethane to water, had a negative effect on the Diels-Alder cycloaddition reaction. The reduced reaction rate displayed in water is not in keeping with the usually high rates of cycloaddition reported in aqueous Diels-Alder reactions. This result can be rationalised in terms of hydrogen bonding occurring between DABCO and water reducing the catalytic activity of the tertiary amine.

2.1.9 DABCO-CATALYSED ULTRASOUND-PROMOTED DIELS-ALDER REACTIONS

The application of ultrasound-promoted Diels-Alder reactions is undergoing continuous expansion. Lee and Snyder[14] reported the use of ultrasound-promoted cycloaddition reactions in the preparation of several biologically active metabolites of Chinese traditional medicine.

In this investigation we hoped to accelerate the rate of the DABCO-catalysed reaction between cyclopentadiene and methyl acrylate (Note: the temperature of the ultrasound bath increased from 22 to 48 °C after 3h). The results of this investigation are summarised in Table 15 referring to Scheme 21 on page 30.

Table 15 DABCO-catalysed ultrasound-promoted Diels-Alder reaction between cyclopentadiene and methyl acrylate.

Reaction	**Catalyst**	**Reaction Time**	**% Yield (79)**	***Endo:Exo***
a	DABCO	3 h	59	71:29
b	-	3 h	10	68:32

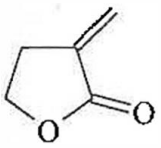
From a comparison of the results observed in Table 8, page 31, it is evident that the rates of cycloaddition are ultrasound-promoted. This can be attributed to the increase in temperature (22 to 48 °C) and pressure of the reaction mixture as a result of cavitation (*i.e* the sudden growth and sudden collapse of bubbles). The slightly higher *exo* selectivity observed in Table 15 can be rationalised in terms of the thermodynamically favoured *exo* conformation at higher temperatures.

PART B

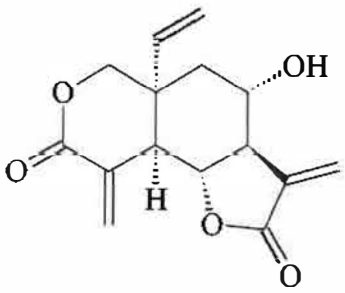
2.2 SYNTHESIS OF SUBSTITUTED CYCLOHEXENES *VIA* A DABCO-CATALYSED DIELS-ALDER CYCLOADDITION REACTION

2.2.1 INTRODUCTION

In a review, Yu and Helquist,[71] have demonstrated that the acrylate unit and related groups occur as structural features in a large number of naturally occurring compounds, many of which possess useful biological activity. Included among these compounds are various classes of unsaturated carboxylic acids, esters and lactones. The most commonly occurring acrylate derivatives are the α-methylene lactones to which much research has been devoted as a result of their anti-tumour properties. Examples of such compounds are tulipalin A (**97**),[72] and the more complex vernolepin (**98**).[73]



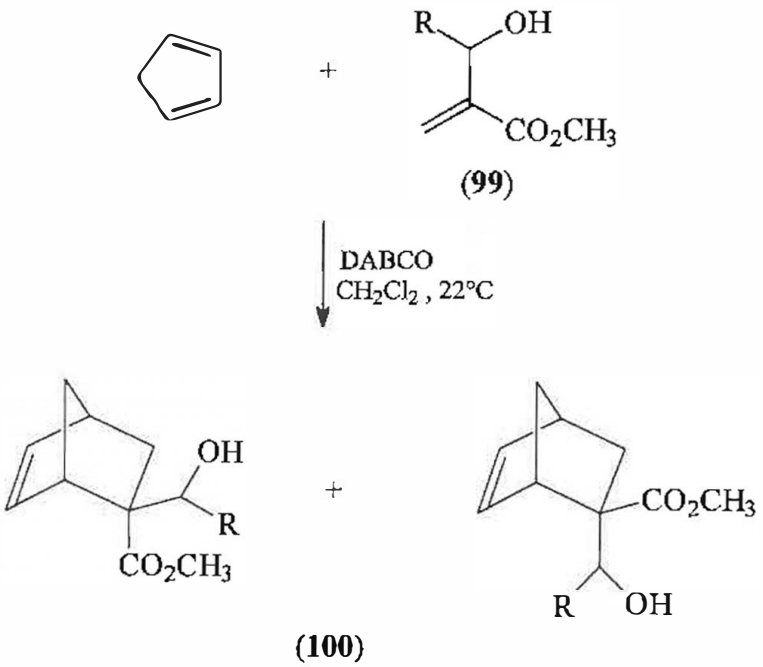
(**97**)



(**98**)

Acrylate systems also possess acceptor and dienophile properties which make them valuable intermediates in the construction of complex organic molecules, as shown by Drewes and co-workers, who used the DABCO catalysed coupling of aldehydes and acrylate esters, as reported by Baylis and Hillman,[62] in their syntheses of integerrinecic,[74] senecivernic,[75] and retronecic acids.[76]

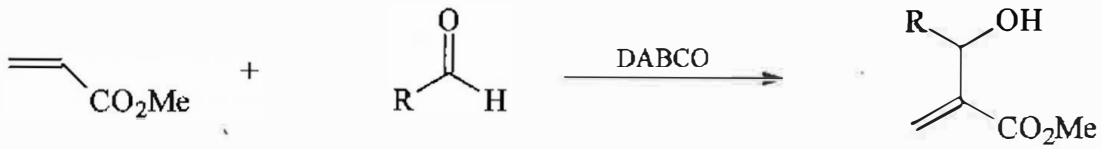
In this investigation we hoped to extend the synthetic utility of α-hydroxy alkyl acrylates (allylic alcohols derived from the Baylis-Hillman reaction) by using them as potential dienophiles in our already established DABCO-catalysed Diels-Alder cycloaddition reactions (Scheme 33).



Scheme 33

2.2.2 THE BAYLIS-HILLMAN REACTION

The required allylic alcohols were prepared *via* the Baylis-Hillman reaction which constitutes, in this case, the DABCO-catalysed coupling of methyl acrylate and an aldehyde (**101**) (Scheme 34, page 52). The reaction conditions of Ameer[77] and Drewes and co-workers[78] were employed in the synthesis of the allylic alcohols (**102**) derived from the corresponding aldehydes (**101**) (Table 16, page 52).



(101)

R = CH_3 , CH_3CH_2 , Ph

(102)

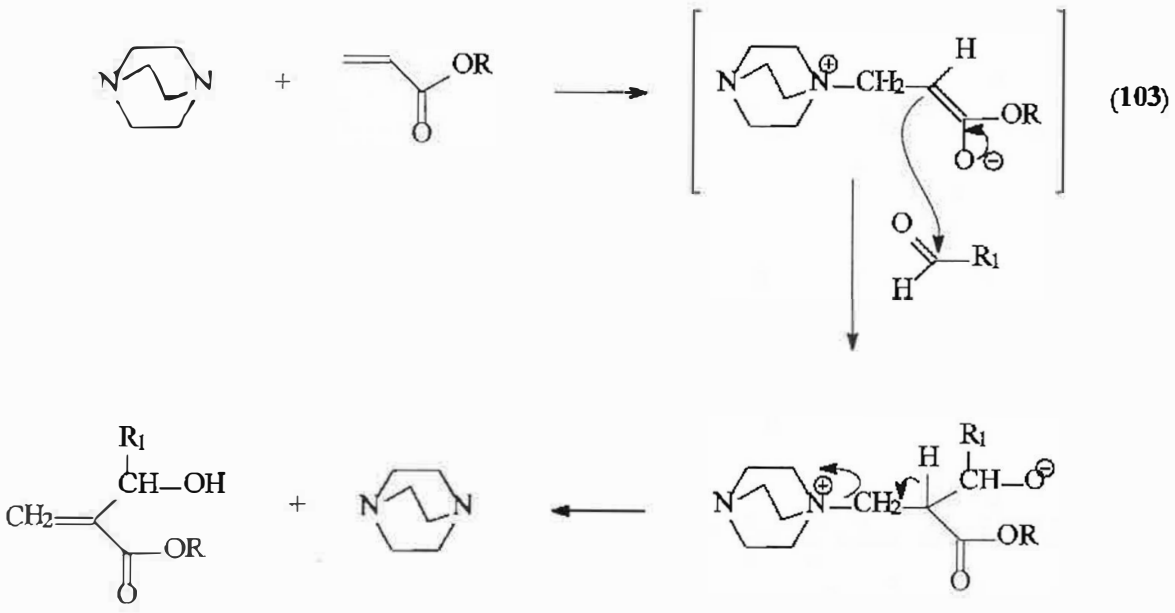
Scheme 34

Table 16 Yield of Baylis-Hillman derived allylic alcohols (**102**).

	Aldehyde (101)	**% Yield (102)**	**Reaction Time***
a	CH_3CHO	75	7 d
b	CH_3CH_2CHO	75	7 d
c	PhCHO	70	40 d

* Reaction times were not optimised. Using excess DABCO has been found to reduce the reaction time.

Hoffman and Rabe[79] outlined the mechanism of the Baylis-Hillman reaction to involve the Michael addition of DABCO to an α,β-unsaturated carbonyl forming a zwitterionic intermediate (**103**) which in turn reacts with an aldehyde (Scheme 35).



(103)

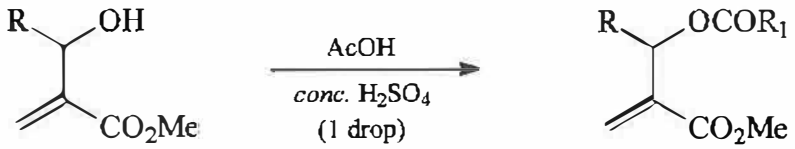
Scheme 35

2.2.3 ATTEMPTED DABCO-CATALYSED DIELS-ALDER REACTIONS USING THE ALLYLIC ALCOHOLS AS POTENTIAL DIENOPHILES

The allylic alcohols (**102**), cyclopentadiene and DABCO (0.1 eq.) were reacted according to the procedure outlined in Scheme 33 on page 51. These reactions were found to be unsuccessful, as after the usual reaction time, the allylic alcohol was isolated in quantitative yield. Again the result can be rationalised in terms of possible co-ordination (H-bonding) between DABCO and the hydroxyl group of the allylic alcohol. It was then decided to overcome this problem by protecting the allylic alcohol as its allylic ester derivative.

2.2.4 PREPARATION OF ALLYLIC ESTERS

The allylic esters (**104a, c**) were prepared in good yield using the method of Drewes and Emslie (Scheme 36 a, Table 17).[74]

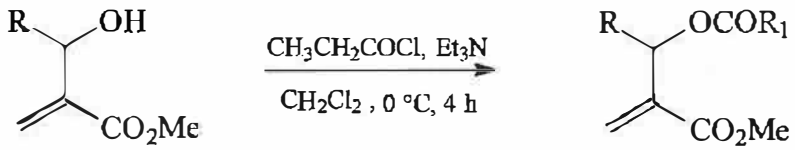


(102) **(104)**

R = CH_3, Ph
R_1 = CH_3

Scheme 36 a

The allylic propionate (**104b**) was prepared from reacting the allylic alcohol (**102b**) with Et_3N and propionyl chloride (Scheme 36 b, Table 17).



(102 b) **(104 b)**

R = CH_3CH_2
R1 = CH_2CH_3

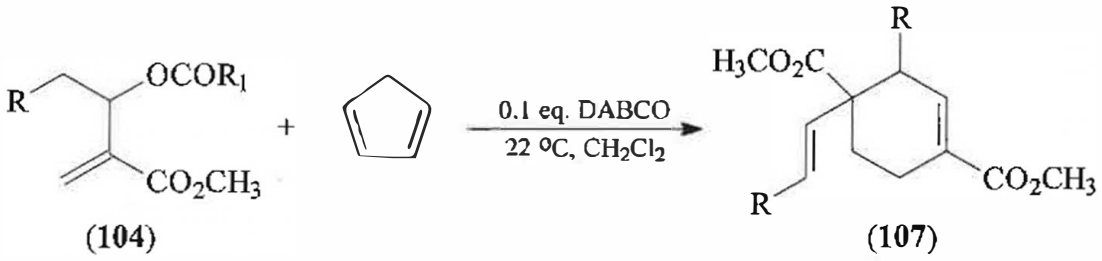
Scheme 36 b

Table 17 Yield of allylic esters (**104**) derived from allylic alcohols(**102**).

Allylic alcohol (102)	R	R_1	% Allylic ester (104)
a	CH_3	CH_3	68
b	CH_3CH_2	CH_2CH_3	78
c	Ph	CH_3	60

2.2.5 SYNTHESIS OF SUBSTITUTED CYCLOHEXENES

Attempted DABCO-catalysed reactions of these allylic esters (**104**) with cyclopentadiene in dichloromethane did not afford the expected cycloadducts (**100**) (Scheme 33, page 51). Instead, we isolated substituted cyclohexene derivatives (Scheme 37, Table 18).



Scheme 37

Table 18 Results for the formation of substituted cyclohexenes (**107**).

Allylic ester (104)	R	Reaction time	% yield (107)
a	H	2 d	28
b	Me	2 d	23
c	H	2 d	-

Janse van Rensburg[59] demonstrated the formation of substituted cyclohexenes (**73**) from allylic carbamate intermediates (**70**) (Scheme 19, page 28). The substituted cyclohexenes shown in Table 18 were found to be identical to those of Janse van Rensburg.[59]

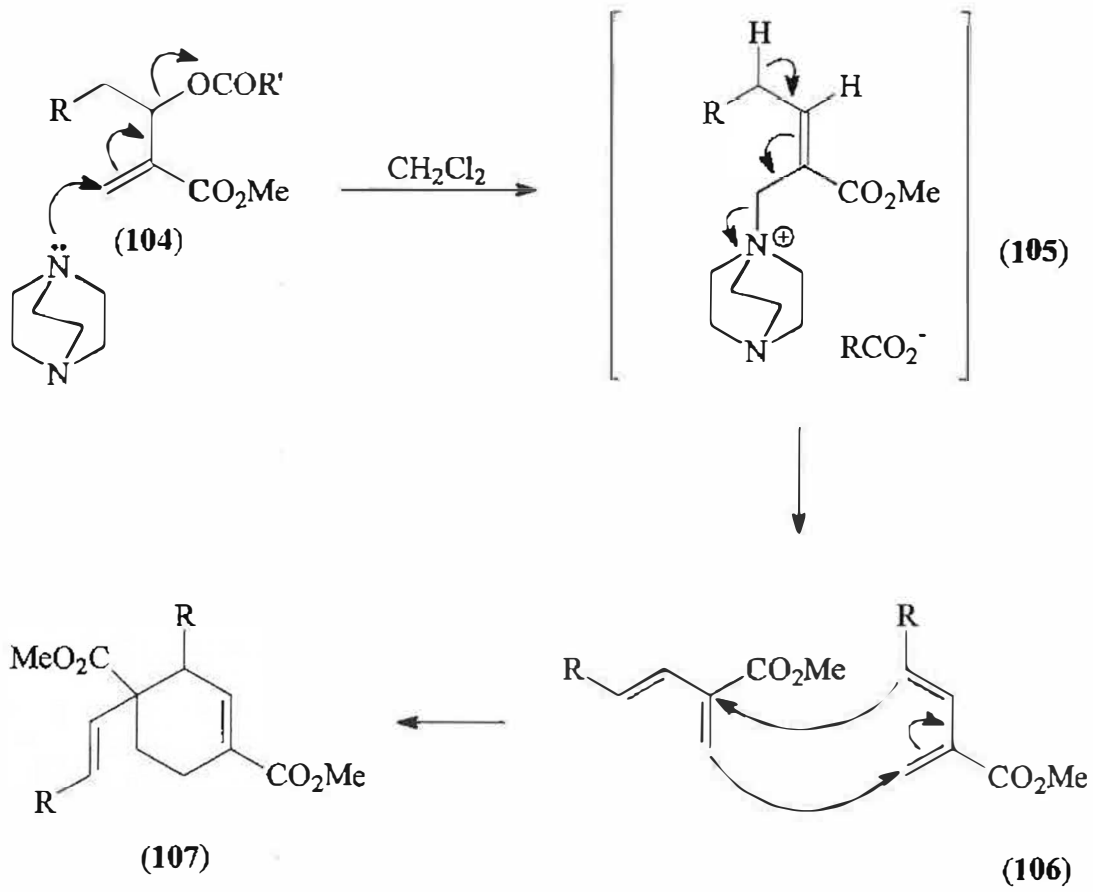
The mechanism proposed by Janse van Rensburg[59] prompted us to repeat the reaction outlined in Scheme 37 in the absence of cyclopentadiene, with DABCO (1 eq.) and under reflux conditions. Both reactions afforded the expected substituted cyclohexene derivatives (**107**) in slightly improved yields.

Table 19 Thermal reactions to enhance the rate of cyclohexene (**107**) formation.

Allylic ester (104)	**R**	**Reaction time**	**% yield (107)**
a	H	4 h	53
b	Me	4 h	50
c	Ph	4 h	-

2.2.6 MECHANISM

The proposed mechanism for the formation of the substituted cyclohexenes (**107**) using the allyllic esters derived from the Baylis-Hillman reaction is illustrated in Scheme 38. It must be emphasised however, that the proposed mechanism is analogous to that proposed by Janse van Rensburg[59] (Scheme 19, page 28) except for an ion pair intermediate (**105**) (Scheme 38).

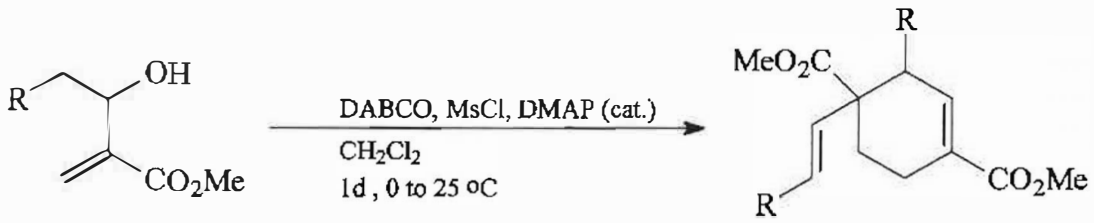


Scheme 38

The mechanism outlined above involves the S_N2' reaction of DABCO with the allylic ester (**104**) resulting in the loss of the ester group to afford an ion pair (**105**). Evidence of the formation of a very similar intermediate is given in the mechanism of the Baylis-Hillman reaction (Scheme 35, page 53). The concerted elimination of DABCO results in the formation of the highly reactive 1,3-butadiene (**106**) which spontaneously dimerises to afford the substituted cyclohexene derivative (**107**).

It has been demonstrated, however, in this thesis, that the speculated DABCO assisted Diels-Alder cycloaddition reaction in the formation of the substituted cyclohexene (**107**) (Scheme38) and (Scheme 19, page 28) is in fact a DABCO-catalysed dimerisation reaction.

The literature reveals only one other example resulting in the formation of substituted cyclohexenes (analogous to those of Janse van Rensburg[59] and those described in this thesis) from allylic alcohols derived from the Baylis-Hillman reaction.[79] In this paper Hoffmann[80] describes the formation of substituted cyclohexenes from allylic alcohols *via* a mesylation/elimination reaction involving the use of DABCO (Scheme 39).



(108)

R = H
R = CH_3

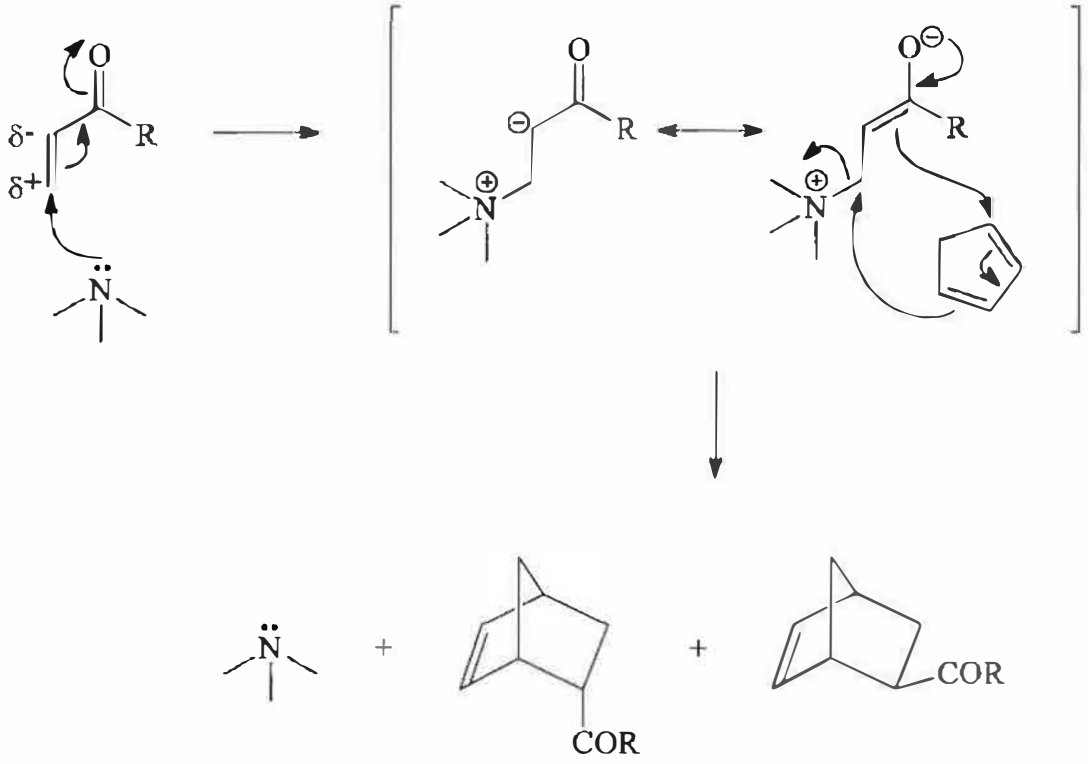
(109)

Scheme 39

PART C

2.3 THE MECHANISM FOR THE TERTIARY AMINE-CATALYSED DIELS-ALDER REACTION

The proposed mechanism for the tertiary amine-catalysed Diels-Alder reaction is outlined in Scheme 40.



Scheme 40

The mechanism outlined above involves the Michael addition of the tertiary amine to the α, β-unsaturated carbonyl. The zwitterion intermediate formed, then spontaneously reacts with the diene in a non-concerted Diels-Alder reaction, with the concerted elimination of the tertiary amine to afford the respective cycloadducts. This mechanism can also be extended to tertiary phosphines and phosphites.

2.4 CONCLUSION

From this investigation it is clearly evident that tertiary amines, in particular the less sterically hindered DABCO, catalyse intermolecular Diels-Alder reactions under mild reaction conditions. These catalysts however, display poor reactivity in cycloaddition reactions with disubstituted dienophiles and under aqueous conditions *e.g.* water. Reaction rates are noticeably increased when subjecting the reactions to ultrasound.

A non-concerted Diels-Alder mechanism is proposed which proceeds *via* an activated ion pair intermediate. The lower yields and poor *endo* selectivity observed with these catalysts as opposed to Lewis acid catalysts, is possibly due to the lack of metal ion co-ordination proposed for the enhanced selectivity in Lewis acid catalysed reactions.

Although the reaction rates are slow, the mild reaction conditions and ease of workup of DABCO-catalysed reactions warrant further investigation into the use of this catalyst with acid sensitive substrates.

CHAPTER 3: EXPERIMENTAL

3.1 CHEMICALS AND INSTRUMENTATION

Solvents and liquid reagents were dried using standard techniques and distilled prior to use.[81] Preparative column chromatography was performed using the technique of Still and co-workers[82] on Merck silica gel 60 (230-400 mesh). 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 (7924T) on 4mm Merck silica gel (200-400 mesh) coated glass plates. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. NMR spectra (^{1}H 200 MHz and ^{13}C 50 MHz) were recorded on a Varian Gemini 200 instrument and a Varian T60 (^{1}H 60 MHz) instrument. All chemical shifts are reported in ppm downfield from TMS as internal standard, using $CDCl_3$ as the solvent. Mass spectra were recorded on a Hewlett-Packard mass spectrometer (HP5988A), linked to a gas chromatograph (Column type : HP-1). Ultrasound reactions were conducted in a Bandelin Sonorex (TK 52) 120 W ultrasound bath. Diastereomeric ratios (*i.e. endo:exo* ratios) were determined by gas chromatographic-mass spectrometry and NMR spectroscopy. Chemical shifts denoted in square brackets are that of minor diastereomers.

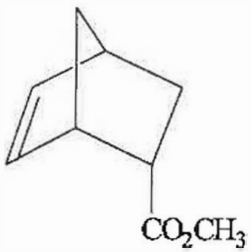
3.2 PREPARATIONS

3.2.1 TERTIARY AMINE, PHOSPHINE AND PHOSPHITE-CATALYSED DIELS-ALDER REACTIONS WITH CYCLOPENTADIENE AND METHYL ACRYLATE

5-Carbomethoxy-2-norbornene (79)

(a) DABCO-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent afforded 5-carbomethoxy-2-norbornene (**79**) as a yellow oil (1.51 g, 66%). *Endo:exo ratio* (^{1}H nmr = 80:20 (δ3.61:δ3.69); GC = 76:24). δ_H (200 MHz): 1.25-1.97 (4H, 3 x m, C*H*CH_2CH, C*H*CHCO, CHC*H*$_2$CH), 2.18 (acetone), 2.90 (1H, m, C*H*CO_2CH_3), 3.04 and 3.20 (2H, 2 x br s, bridgehead *H*), 3.61 [3.69] (3H, s, OCOC*H*$_3$), 5.90 and 6.18 (2H, 2 x m, C*H*=C*H*); δ_C (50 MHz): 29.25 [30.34] (t, *C*H_2CHCO), 41.63 [42.52] (d, *C*HCO_2CH_3), 42.97 [43.17] (d, CH_2*C*HCH_2), 45.66 [46.58] (d, *C*HCHCO), 46.36 (t, *C*H_2CHCH_2), 49.62 (t, CH_2CHCH_2), 51.47 [51.70] (q, CO_2CH_3), 132.37 [135.73] (d, *C*H=CH), 137.73 [138.04] (d, CH=*C*H), 175.21 [176.70] (s, *C*O_2CH_3); *m/z*: 152 (M^+, 16%), 121 (12), 87 (16), 77 (8), 66 (100).



(79)

Quinuclidine-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and quinuclidine (0.17 g, 1.50 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (1.37 g, 60%). *Endo:exo ratio* (GC = 78:22); *m/z*: 152 (M^+, 22%), 121 (11), 87 (14), 77 (9), 66 (100).

Quinuclidinol-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and quinuclidinol (0.19 g, 1.50 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (1.09 g, 48%). *Endo:exo ratio* (GC = 77:23); *m/z*: 152 (M^+, 5%), 87 (11), 67 (5), 66 (100).

Triethylamine-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and triethylamine (0.15 g, 1.50 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using 20% diethyl ether/hexane as the eluent to afford 5-carbomethoxy-2-norbornene (1.00 g, 44%). *Endo:exo ratio* (^{1}H nmr = 78:22; GC = 80:20); *m/z*: 152 (M^+, 8%), 121 (5), 87 (11), 67 (5), 66 (100).

Quinidine-catalysed reaction

Cyclopentadiene (0.50 g, 7.50 mmol), methyl acrylate (0.65 g, 7.50 mmol) and quinidine (0.24 g, 0.75 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (0.48 g, 42%). *Endo:exo ratio* (^{1}H nmr = 80:20; GC = 82:18); *m/z*: 152 (M^+, 7%), 121 (5), 87 (9), 77 (5), 66 (100).

Quinine-catalysed reaction

Cyclopentadiene (0.50 g, 7.50 mmol), methyl acrylate (0.65 g, 7.50 mmol) and quinine (0.24 g, 0.75 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (0.43 g, 37%). *Endo:exo ratio* (^{1}H nmr = 80:20; GC = 80:20); *m/z*: 152 (M^+, 8%), 121 (7), 87 (11), 67 (7), 66 (100).

Sparteine-catalysed reaction

Cyclopentadiene (0.50 g, 7.50 mmol), methyl acrylate (0.65 g, 7.50 mmol) and sparteine (0.18 g, 0.75 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (0.40 g, 35%). *Endo:exo ratio* (^{1}H nmr = 79:21; GC = 77:23); *m/z*: 152 (M^+, 8%), 121 (8), 87 (11), 77 (8), 66 (100).

Brucine-catalysed reaction

Cyclopentadiene (0.50 g, 7.50 mmol), methyl acrylate (0.65 g, 7.50 mmol) and brucine (0.30 g, 0.75 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (0.37 g, 32%). *Endo:exo ratio* (^{1}H nmr = 80:20; GC = 77:23); *m/z*: 152 (M^+, 8%), 121 (5), 87 (11), 77 (8), 66 (100).

Triethylphosphite-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and triethylphosphite (0.25 g, 1.50 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using 20% diethyl ether/hexane as the eluent to afford 5-carbomethoxy-2-norbornene (1.08 g, 47%). *Endo:exo ratio* (GC = 79:21); *m/z*: 152 (M^+, 38%), 121 (22), 87 (19), 77 (8), 66 (100).

Triphenylphosphine-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and triphenylphosphine (0.40 g, 1.50 mmol) were treated according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (0.68 g, 30%). *Endo:exo ratio* (GC = 70:30); *m/z*: 152 (M^+, 5%), 87 (11), 67 (5), 66 (100).

Aqueous DABCO-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to water (2 ml) at 0 °C in a 10 ml round-bottomed flask The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. After work-up according to the procedure described in reaction (a), the crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (1.09 g, 48%). *Endo:exo ratio* (GC = 66:34); *m/z*: 152 (M^+, 5%), 87 (11), 67 (5), 66 (100).

Ultrasound-promoted DABCO-catalysed reaction

Cyclopentadiene (1.00 g, 15.00 mmol), methyl acrylate (1.29 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture was then placed in an ultrasound bath for a further 3 h (22 - 48 °C) and then worked-up according to the procedure described for reaction (a). The crude product was purified on a silica gel column using chloroform as the eluent to afford 5-carbomethoxy-2-norbornene (1.35 g, 59%). *Endo:exo ratio* (GC = 71:29); *m/z*: 152 (M^+, 5%), 87 (11), 67 (5), 66 (100).

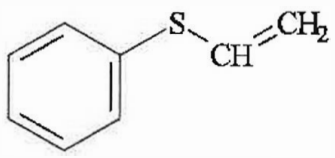
3.2.2 DABCO-CATALYSED DIELS-ALDER REACTIONS WITH VARIOUS DIENOPHILES

3.2.2.1 PREPARATION OF DIENOPHILES

Phenyl vinyl sulphide (80)

Sodium metal (2.30 g, 0.10 mol), cut into small pieces, was added with stirring to EtOH (50 ml) in a 250 ml, 3-necked, round-bottomed flask fitted with a magnetic stirrer, condenser, addition funnel and nitrogen inlet tube. When conversion to sodium ethoxide was complete (15 min) the thiophenol (11.00 g, 0.10 mol) was added dropwise (15-20 min) to the cloudy, grey sodium ethoxide solution. The reaction mixture warmed spontaneously and became clear brown. When the solution cooled to 25 °C, it was transferred by a stainless steel canula over 30 min to a stirred solution of 1,2-dibromoethane (22.00 g, 0.15 mol) in ethanol (14 ml) contained in a 500 ml, 3-necked round-bottomed flask, equipped with a mechanical stirrer, reflux condenser and septum, nitrogen inlet and internal thermometer. The reaction temperature was maintained at 25-30 °C by cooling with an ice bath. The mixture was stirred under nitrogen (36 min) and treated for an additional 30 min with ethanolic sodium ethoxide prepared from sodium metal (4.00 g, 0.17 mol) and EtOH (90 ml). The resulting mixture was stirred at reflux for (8 h), cooled and treated with benzene (75 ml) and water (75 ml). The organic layer was separated and washed with water (2x 50 ml), brine (100 ml) and dried over anhydrous magnesium sulphate and the solvent removed. Distillation of the resulting yellow oil afforded phenyl vinyl sulphide (**80**) (7.06 g, 52%). b.p. 95 °C/ 0.5 mmHg. Due to its instability, the product was stored in a Schlenk tube under nitrogen at 0 °C. δ_H (200 MHz): 5.36 (2H, dd, J = 10 and 18 Hz, CH=CH_2), 6.48 (1H, dd, J = 10 and 18Hz, CH=CH$_2$), 7.35 (5H, m, Ar-H); δ_C (50 MHz): 115.39 (t, SCH=CH_2), 127.02, 129.05 and 130.81 (3 x d, Ar-CH), 131.81 (d, SCH=CH$_2$),

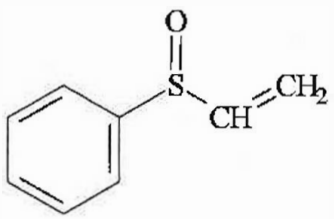
134.19 (s, Ar-*C*); *m/z*: 136 (M^+-1, 76%), 109 (14), 91 (100), 77 (28), 65 (32), 51 (39), 39 (19).



(80)

*Phenyl vinyl sulphoxide (**81**)*

A 250 ml, 3-necked, round-bottomed flask equipped with a dropping funnel and magnetic stirrer was charged with phenyl vinyl sulphide (3.00 g, 0.02 mol) and dichloromethane (45 ml). The solution was stirred and cooled to -78 °C while a solution of MCPBA (3.80 g, 0.02 mol) in dichloromethane (100 ml) was added dropwise over 30 min. The mixture was stirred and warmed to room temperature for 1 h in a water bath at 30 °C and then extracted with dichloromethane (3x 50 ml). The organic extracts were washed with water (3x 50 ml) and dried over anhydrous magnesium sulphate and the solvent removed. The crude product was separated on a silica gel column using 3% ethyl acetate/chloroform as the eluent to afford phenyl vinyl sulphoxide (**81**) (1.72 g, 55%). δ_H (200 MHz): 5.87-6.24 (2H, dd, J = 9.5 and 16.5 Hz, CH=CH_2), 6.54-6.67 (1H, dd, J = 9.5 and 16.5 Hz, CH=CH_2), 7.49-7.61 (5H, m, Ar-*H*); δ_C (50 MHz): 120.70 (t, CH=CH_2), 120.70 (d, CH=CH_2), 124.63, 129.44 and 131.25 (3 x d, Ar-CH), 142.87 (s, Ar-*C*); *m/z*: 152 (M^+, 14%), 135 (16), 104 (100), 91 (14), 78 (62), 65 (19), 51 (57).

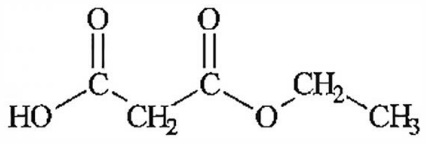


(81)

Ethyl malonic acid ***(84a)***

Diethyl malonate (25.00 g, 0.16 mol) in absolute ethanol (100 ml) was placed in a 3-necked 500 ml round-bottomed flask fitted with a dropping funnel, condenser with $CaCl_2$ drying tube and magnetic stirrer. Potassium hydroxide (8.75 g, 0.16 mol) in absolute ethanol (100 ml) was added dropwise with stirring at rt. The mixture was stirred for a further 2 h and then allowed to stand overnight. The mixture was then heated to boiling and the precipitate of potassium ethyl malonate filtered off. The potassium ethyl malonate was washed with diethyl ether (3x 25 ml) and dried under reduced pressure at rt (20.22 g, 75%).

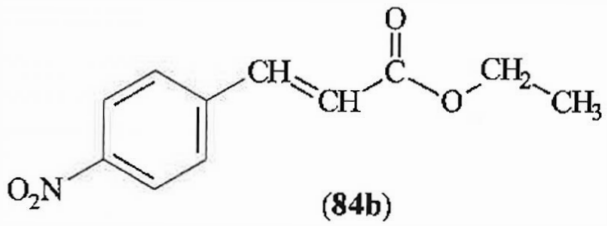
Potassium ethyl malonate (20.00 g, 0.12 mol) in water (20 ml) was then placed in a 100 ml 3-necked round-bottomed flask fitted with a dropping funnel, thermometer and magnetic stirrer. The mixture was cooled in an ice bath and *conc.* HCl (15 ml) was added dropwise over 30 min. The precipitate of KCl was filtered off and washed with diethyl ether 3x 25 ml). The combined ether extracts were dried over anhydrous magnesium sulphate and the solvent removed. The residue was dried at 50 °C under reduced pressure to afford ethyl malonic acid (**84a**) (12.50g, 79%). m.p. 26-29 °C; δ_H (60 MHz): 1.27 (3H, t, J = 6 Hz, OCH_2CH_3), 3.43 (2H, s, $COCH_2CO$), 4.20 (2H, q, J = 6 Hz, OCH_2CH_3), 10.70 (1H, s, CO_2H); *m/z*: 132 (M^+, <1%), 105 (54), 87 (100), 56 (24), 43 (16).



(84a)

Ethyl para-*nitrocinnamate* ***(84b)***

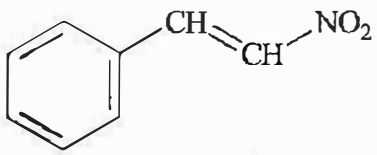
A mixture of ethyl malonic acid (3.96 g, 30.00 mmol) in pyridine (6 ml) in a 100 ml conical flask was gently heated on a hot water bath. Nitrobenzaldehyde (4.56 g, 30.00 mmol) and a catalytic amount of piperidine (10 drops) were added to the flask and the resultant mixture heated until the evolution of carbon dioxide appeared complete (45 min). The mixture was allowed to cool to rt, extracted with diethyl ether (3x 30 ml) and washed with 2M HCl (20 ml), *dil.* H_2SO_4 (20 ml) and finally with water (3x 30 ml). The organic layer was then dried over anhydrous magnesium sulphate. Removal of the solvent afforded crystalline ethyl-*p*-nitrocinnamate (**84b**) (5.70g, 86%). m.p. 138-140 °C; δ_H (200 MHz): 1.36 (3H, t, OCH_2CH_3), 4.28 (2H, q, OCH_2CH_3), 6.61 and 7.70 (2H, 2 x d, J = 16 Hz, C*H*=C*H*), 7.70 and 8.29 (4H, 2 x d, J = 9 Hz, Ar-C*H*); δ_C 50 MHz: 14.27 (q, CH_2CH_3), 61.02 (t, CH_2CH_3), 122.56 (d, CH=*C*HCO), 124.17 and 128.62 (2 x d, Ar-*C*H), 140.57 (s, Ar-*C*), 141.61 (d, *C*H=CHCO), 166.04 (s, Ar-*C*NO_2); *m/z*: 221 (M^+, 8%), 176 (53), 130 (53), 118 (16), 102 (100), 76 (53), 51 (58).



(84b)

β-*Nitrostyrene (**85**)*

Styrene (1.00 g, 9.62 mmol, 1 eq.) was treated with sodium nitrate (6.63 g, 96.15 mmol, 10eq.), cerium ammonium nitrate (CAN) (10.54 g, 19.23 mmol, 2eq.) and glacial acetic acid (3.69 g, 115.38 mmol, 12eq.) in chloroform (137 ml) in a thick-walled sealed tube. After sonication (8 h) at 25-70 °C, the mixture was allowed to cool to rt, extracted with chloroform (3x 50 ml) and washed with sat. NaCl. The organic layer was dried over anhydrous magnesium sulphate and the solvent removed. The crude product was chromatographed on silica, using 10% diethyl ether/hexane as the eluent, to afford β-nitrostyrene (**85**) (0.29g, 22%). m.p. 56-58 °C; δ_H (200 MHz): 7.49-7.60 (1H, superimposed d, J = 13.7 Hz, C*H*=CHNO$_2$), 8.05 (1H, d, J = 13.7 Hz, CH=C*H*NO$_2$), 7.49-7.60 (5H, m, Ar-C*H*); δ_C (50 MHz): 128.78, 129.15 and 129.26 (3 x d, Ar-*C*H), 131.93 (d, CH=*C*HNO$_2$), 139.08 (d, *C*H=CHNO$_2$), 137.11 (s, Ar-*C*); *m/z*: 149 (M^+, 59%), 132 (19), 119 (5), 102 (69), 91 (59), 77 (100), 65 (21), 51 (39).

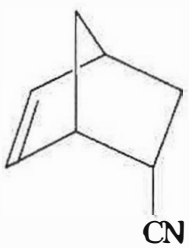


(85)

3.2.2.2 PREPARATION OF DIELS-ALDER CYCLOADDUCTS

*5-Carbonitrile-2-norbornene (**91a**)*

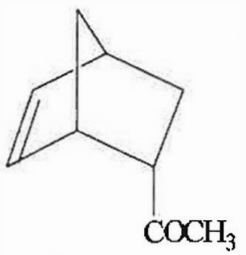
Cyclopentadiene (1.00 g, 15.00 mmol), acrylonitrile (0.79 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. at 0 °C in a 10 ml round-bottomed flask The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and purification of the crude product on a silica gel column using chloroform as the eluent afforded 5-carbonitrile-2-norbornene (**91a**) as a yellow oil (1.45g, 81%). *Endo:exo ratio* (GC = 65:35); δ_H (200 MHz): 1.1-2.2 (4H, 3 x m, C*H*CH_2CH, CHC*H*$_2$CH, C*H*CHCN), 2.1 (acetone), 2.75 (1H, m, C*H*CN), 2.95-3.18 (2H, 2 x br s, bridgehead *H*), 5.90-6.30 (2H, 3 x m, C*H*=C*H*); δ_C (50 MHz) 27.18 (d, *C*HCN), 32.48 [32.21] (t, *C*H_2CHCN), 42.38 [41.83] (d, *C*HCH_2), 45.75 [47.45] (d, *C*HCHCN), 48.52 [47.17] (t, *C*H_2CHCH_2), 121.71 [121.92] (s, *C*N), 132.73 [134.04] and 138.12 [138.86] (2 x d, *C*H=*C*H); *m/z* 119 (M^+, 7%), 104 (7), 91 (7), 79 (6), 77 (6), 66 (100).



(91a)

*5-Acetyl-2-norbornene (**91b**)*

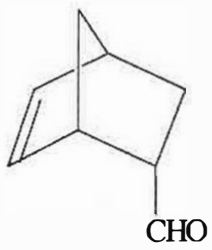
Cyclopentadiene (1.00 g, 15.00 mmol), methyl vinyl ketone (1.05 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. at 0 °C in a 10 ml round-bottomed flask The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and purification of the crude product on a silica gel column using chloroform as the eluent afforded 5- acetyl-2-norbornene (**91b**) as a yellow oil (1.55 g, 76%). *Endo:exo ratio* (GC = 81:19); δ_H (200 MHz): 1.22-1.74 (4H, 3 x m, C*H*CH_2CH, CHC*H*$_2$CH, C*H*CHCOCH_3), 2.1 (acetone), 2.05 [2.12] (3H, s, CO*CH*$_3$), 2.80 and 3.16 (2H, 2 x br s, bridgehead *H*), 2.90 (1H, m, C*H*COCH_3), 5.78 and 6.18 (2H, 2 x m, C*H*=C*H*); δ_C (50 MHz): 27.37 (t, *C*H_2CHCO), 29.18 (q, CO*CH*$_3$), 42.65 (d, *C*HCHCO), 45.83 (d, *C*HCH_2), 49.93 (t, *C*H_2CHCH_2), 52.30 (d, *C*HCOCH_3), 131.22 and 137.80 (2 x d, *C*H=*C*H); *m/z*: 136 (M^+, 31%), 93 (26), 77 (26), 66 (100), 58 (10), 43 (22).



(91b)

*5-Carboxaldehyde-2-norbornene (**91c**)*

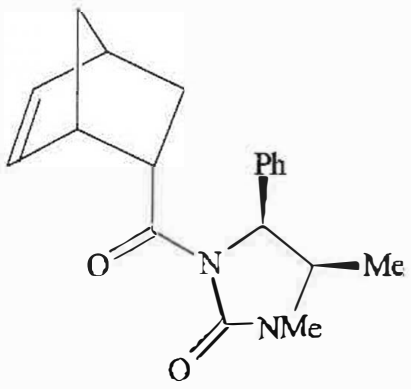
Cyclopentadiene (1.00 g, 15.00 mmol), acrolein (0.84 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. After removal of the solvent, the crude product was chromatographed on silica using 20% diethyl ether/hexane as the eluent to afford 5-carboxaldehyde-2-norbornene (**91c**) (1.30g, 72%). *Endo:exo ratio* (GC = 80:20). δ_H (200 MHz): 1.20-2.01 (4H, 3 x m, C*H*CH_2CH, CHC*H*$_2$CH, C*H*CHCHO), 2.90 (1H, m, C*H*CHO), 2.98 and 3.26 (2H, 2 x br s, bridgehead *H*), 5.9-6.25 (2H, 2 x m, C*H*=C*H*), 9.4 [9.8] (1H, d, J = 2.7 Hz, C*H*O); δ_C (50 MHz): 27.53 [27.06] (t, *C*H_2CHCHO), 42.71 [41.80] (d, *C*HCHCO), 44.97 [44.23] (d, *C*HCH_2), 49.52 [45.82] (t, *C*H_2CHCH_2), 52.19 (d, *C*HCHO), 131.76 [135.26] and 138.08 [138.55] (2 x d, *C*H=*C*H),), 205.06 [204.05] (d, *C*HO); *m/z* 122 (M^+, 11%), 93 (6), 91 (10), 77 (12), 66 (100), 51 (5), 39 (13).



(91c)

*5-(4R,5S)-1,5-Dimethyl-4-phenyl-3-((2'R, 3'R, 6'S, 7'S)-2-norbornene (**91d**)*

(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-3-prop-2'-enoylimidazolidin-2-one (0.30 g, 2.20 mmol), cyclopentadiene (0.14 g, 2.20 mmol) and DABCO (0.02 g, 0.22 mmol) were added to dichloromethane (5 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture under nitrogen, was left to stir for 15 min. and then a further 5 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and purification of the crude product on a silica gel column using chloroform as the eluent afforded white crystalline 5-(4*R*,5*S*)-1,5-dimethyl-4-phenyl-3-((2'*R*, 3'*R*, 6'*S*, 7'*S*)-2-norbornene (**91d**) (0.46 g, 68%). m.p. 167 °C. $[\alpha]_D^{21}$: -221.56° (*c* 1.897, $CHCl_3$). *Endo:exo ratio* (GC = 69:31). δ_H (200 MHz): 0.80 (3H, d, $CHCH_3$), 1.38-1.82 (4H, 3 x m, $CHCH_2CH$, $CHCH_2CH$, $CHCHCO$), 2.84 (3H, s, NCH_3), 3.30 and 3.40 (2H, 2 x br s, bridgehead *H*), 3.90 (1H, m, $CHCH_3$), 4.20 (1H, m, *CH*CO), 5.25 (1H, d, C*H*-Ph), 5.39 and 6.04 (2H, 2 x m, *CH*=*CH*), 7.27 (5H, m, Ar-*CH*); δ_C (50 MHz): 15.06 [14.07] (q, CCH_3), 28.25 [28.14] (q, NCH_3), 28.72 [29.48] (t, CH_2CHCO), 53.90 [42.88] (d, *C*HCO), 43.34 [43.02] (d, $CH_2CHCH{=}CH$), 46.87 [46.65] (d, $CHCH{=}CH$), 50.05 [50.15] (t, CH_2CHCH_2), 59.27 [59.79] (d, C*H*-Ph), 126.86, 127.03 and 128.40 (3 x d, Ar-*C*H), 131.20 [131.66] and 137.60 [137.66] (2 x d, *C*H=*C*H), 136.87 (s, Ar-*C*), 155.90 (s, N-*C*O-N), 173.78 (s, N-*C*OCH); *m/z*: 310 (M^+, 76%), 245 (100), 189 (57), 132 (73), 91 (38), 55 (51).



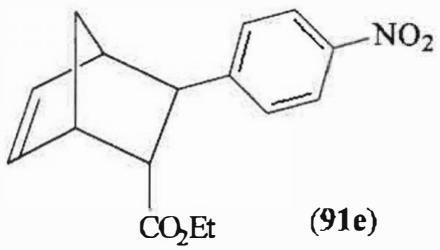
(91d)

DABCO-catalysed rate enhanced reaction

(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-3-prop-2'-enoylimidazolidin-2-one (0.19 g, 0.78 mmol, 1eq.), cyclopentadiene (0.15 g, 2.34 mmol, 3eq.) and DABCO (0.02 g, 0.15 mmol) were treated according to the procedure used in the preceding reaction to afford after 3 d, 5-(4*R*,5*S*)-1,5-dimethyl-4-phenyl-3-((2'*R*, 3'*R*, 6'*S*, 7'*S*)-2-norbornene (0.20 g, 85%). *Endo:exo ratio* (GC = 63:37). *m/z*: 310 (M^+, 24%), 245 (57), 189 (49), 132 (73), 77 (43), 55 (100).

*5-Carboethoxy-6-*para*-nitrobenzene-2-norbornene (**91e**)*

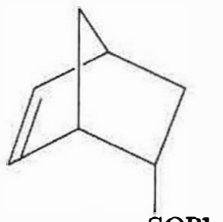
Ethyl-*para*-nitrocinnamate (1.65 g, 7.50 mmol), cyclopentadiene (0.50 g, 7.50 mmol), and DABCO (0.08 g, 0.75 mmol) were added to dichloromethane (5 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. The crude product was chromatographed on silica, using 20% diethyl ether/hexane as the eluent, to afford the yellow crystalline 5-carboethoxy-6-*para*-nitrobenzene-2-norbornene (**91e**) (1.42g, 66%). m.p. 112-115 °C. *Endo:exo ratio* (GC = 67:33); δ_H (200 MHz): 1.28 (3H, t, OCH_2CH_3), 1.70 (1H, m, CHCHPh), 1.87 (1H, d, CHPh), 2.52 (1H, t, CHCHCO), 3.22 (2H, 2 x br s, bridgehead *H*), 3.81 (1H, m, $CHCO_2$), 4.17 (2H, q, OCH_2CH_3), 6.0-6.4 (2H, m, CH=CH), 7.34 and 8.10 [7.50 and 8.17] (4H, dd, *J* = 8 Hz, Ar-CH); δ_C (50 MHz): 14.27 (q, OCH_2CH_3), 46.26 [47.21] (d, CHPh), 47.44 [47.72] (d, CHCHCO), 48.14 [48.10] (t, CH_2CHCH), 48.35 [48.69] (d, CHCO), 50.88 [52.70] (d, CHCHPh), 60.96 [60.77] (t, OCH_2CH_3), 123.27, 123.67, 128.57 and 128.63 (d, ArCH), 135.31 [134.99] and 137.41 [138.71] (2 x d, CH=CH), 151.09 [152.41] (s, ArC), 174.80 [173.63] (s, CO); *m/z*: 287 (M^+, <1%), 222 (7), 176 (5), 152 (3), 102 (3), 67 (7), 66 (100).



(91e)

*5-Phenylsulphoxide-2-norbornene (**91g**)*

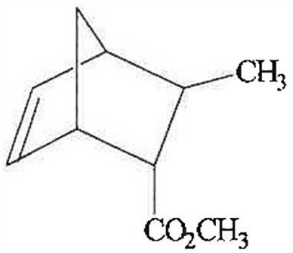
Cyclopentadiene (0.25 g, 3.90 mmol), phenyl vinyl sulphoxide (0.39 g, 2.60 mmol) and DABCO (0.03 g, 0.26 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture under nitrogen, was left to stir for 15 min. and then a further 3 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and GC/MS analysis of the crude product revealed predominantly phenyl vinyl sulphoxide with traces of 5-phenylsulphoxide-2-norbornene **(91g)** (GC = 0.02 g, 3%). *Endo:exo ratio* (GC = 77:23); *m/z*: 218 (M^+, 5%), 136 (14), 93 (100), 77 (78). No satisfactory nmr results were obtained.



(91g)

*5-Carbomethoxy-6-methyl-2-norbornene (**91h**)*

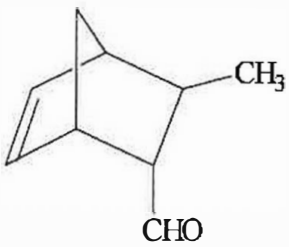
Cyclopentadiene (1.00 g, 15.00 mmol), methyl crotonoate (1.50 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and attempted purification of the crude product on a silica gel column using chloroform as the eluent afforded a mixture of 5-carbomethoxy-6-methyl-2-norbornene (**91h**) and methyl crotonoate. Product yield (GC = 0.08g, 3%). *m/z*: 166 (M^+, <1%), 101 (26), 66 (100), 39 (11). No satisfactory nmr results were obtained.



(91h)

*5-Carboxaldehyde-6-methyl-2-norbornene (**91i**)*

Cyclopentadiene (1.00 g, 15.00 mmol), crotonaldehyde (1.05 g, 15.00 mmol) and DABCO (0.17 g, 1.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The mixture under nitrogen, was left to stir for 15 min. and then a further 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and attempted purification of the crude product on a silica gel column using chloroform as the eluent afforded a mixture of 5-carboxaldehyde-6-methyl-2-norbornene (**91i**) and other components (0.06 g, 3%). *m/z*: 136 (M^+, 19%), 118 (4), 107 (5), 91 (11), 79 (12), 37 (100). No satisfactory nmr results were obtained.

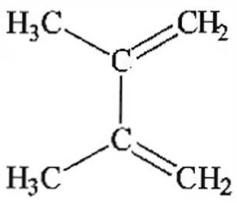


(91i)

3.2.3 DABCO-CATALYSED DIELS-ALDER REACTIONS USING VARIOUS DIENES

3.2.3.1 PREPARATION OF 2,3-DIMETHYL-1,3-BUTADIENE (**94**)

To 2,3-dimethylbutane-2,3-diol (11.80 g, 0.10 mol) in a 50 ml round-bottomed flask with a stirrer bar, was added *conc*. HBr (1.5 ml) and the mixture stirred for 1 h. The stirrer was removed and the flask equipped for distillation. The mixture was slowly distilled until the temperature reached 95 °C. The two phase distillate was transferred to a separating funnel and the aqueous phase removed. The organic phase was washed with water (3 ml) and dried over anhydrous magnesium sulphate. The mixture was then filtered into a 10 ml round-bottomed flask through a small filter funnel plugged lightly with glass wool. Slow distillation of the mixture afforded 2,3-dimethyl-1,3-butadiene (**94**) (4.26g, 52%). b.p. 68 °C. δ_H (200 MHz): 1.92 (6H, s, 2 x CC*H*$_3$), 5.06 (4H, 2 x s, 2 x C=C*H*$_2$); δ_C (50 MHz): 20.54 (q, C*C*H$_3$), 112.99 (t, C=*C*H$_2$), 143.35 (s, *C*=CH$_2$); *m/z*: 82 (M^+, 59%), 79 (11), 67 (100), 54 (27), 41 (41), 39 (54).

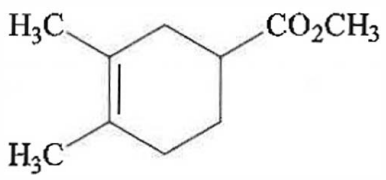


(**94**)

3.2.3.2 PREPARATION OF DIELS-ALDER CYCLOADDUCTS

*1-Carbomethoxy-3,4-dimethylcyclohex-3-ene (**96b**)*

2,3-Dimethyl-1,3-butadiene (0.50 g, 6.08 mmol), methyl acrylate (0.52 g, 6.08 mmol) and DABCO (0.07 g, 0.61 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The flask was fitted with a septum and the mixture stirred under nitrogen for 15 min. The mixture was then stirred for 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. Removal of the solvent and purification of the crude product on a silica gel column using 5% ethyl acetate/chloroform as the eluent afforded 1-carbomethoxy-3,4-dimethyl-cyclohex-3-ene (**95b**) in low yield (0.04g, 4%). *Endo:exo ratio* (GC = > 99% *endo*); δ_H (200 MHz): 0.85, 1.99 and 2.15 (6H, 3 x m, 3 x CH_2), 1.62 (6H, s, 2 x CH_3), 3.68 (3H, s, CO_2CH_3); δ_C (50 MHz): 18.85 and 18.98 (2 x q, C=CCH_3), 25.85 (t, CH_2CHCO), 31.00 (t, CCH_2CH_2), 33.73 (t, CCH_2CH), 40.12 (d, CHCO), 51.58 (q, CO_2CH_3), 123.89 and 131.72 (2 x s, C=C), 176.50 (s, CO); *m/z*: 168 (M^+, 22%), 136 (14), 108 (100), 93 (92), 77 (19), 67 (32).



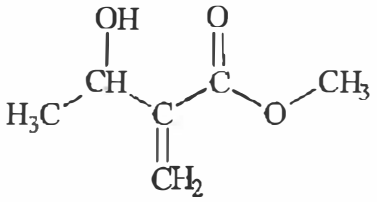
(96b)

3.2.4 SYNTHESIS OF SUBSTITUTED CYCLOHEXENES

3.2.4.1 PREPARATION OF ALLYLIC ALCOHOLS

*Methyl 3-hydroxy-2-methylenebutanoate (**102a**)*

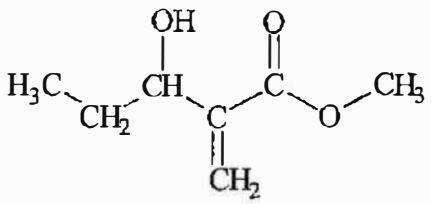
A mixture of acetaldehyde (5.50 g, 0.13 mol), methyl acrylate (7.50 g, 0.09 mol) and DABCO (2.50 g, 0.02 mol) was stirred in a stoppered flask at room temperature for 7 d. The mixture was diluted with diethyl ether (25 ml) and washed with 3M HCl (2x 25 ml), 10% *aq.* $NaHCO_3$ (2x 25 ml) and finally saturated with *aq.* NaCl (25 ml). The organic phase was dried with anhydrous magnesium sulphate and distilled to afford methyl 3-hydroxy-2-methylenebutanoate (**102a**) (8.50 g, 75 %). b.p. 65 °C/10 mmHg; δ_H (200 MHz): 1.35 (3H, d, J = 6.4 Hz, CH-CH_3), 3.34 (1H, s, O*H*), 3.78 (3H, s, CO_2CH_3), 4.63 (1H, q, C*H*-CH_3), 5.89 and 6.21 (2H, 2 x d, J = 1.2 and 0.75 Hz, CH_2=C); δ_C (50 MHz): 22.37 (q, CH-*C*H_3), 51.90 (q, CO_2CH_3), 66.68 (d, $CH_3CH(OH)$), 124.06 (t, CH_2=C), 143.88 (s, *C*=CH_2), 167.08 (s, *C*O); *m/z*: 129 (M^+-1, <1%), 115 (64), 83 (100), 55 (45).



(**102a**)

*Methyl 3-hydroxy-2-methylenepentanoate (**102b**)*

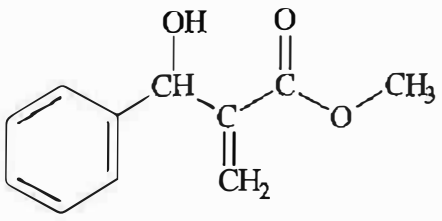
Propionaldehyde (7.30 g, 0.13 mol), methyl acrylate (7.50 g, 0.09 mol) and DABCO (2.50g, 0.02 mol) were treated for 7 d according to the procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate (**102a**). Distillation of the organic layer afforded methyl 3-hydroxy-2-methylenepentanoate (**102b**) (9.42 g, 75%). b.p. 80 °C/ 6 mmHg; δ_H (200 MHz): 0.90 (3H, t, CH_2CH_3), 1.68 (2H, m, CH_2CH_3), 3.34 (1H, s, O*H*), 3.77 (3H, s, CO_2CH_3), 4.34 (1H, t, C*H*OH), 5.82 and 6.24 (2H, 2 x d, J = 0.94 and 0.76 Hz, CH_2=C); *m/z*: 144 (M^+, <1%), 115 (74), 83 (100), 55 (27).



(102b)

*Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**102c**)*

A mixture of benzaldehyde (13.30 g, 0.13 mol), methyl acrylate (7.50 g, 0.09 mol) and DABCO (2.50 g, 0.02 mol) were treated for 40 d according to the procedure described for the preparation of methyl 3-hydroxy-2-methylenebutanoate (**102a**). Distillation of the residual organic oil afforded methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**102c**) (11.70 g, 70%). b.p. 72-75 °C/0.5 mmHg; δ_H (200 MHz): 3.59 (3H, s, CO_2CH_3), 3.60 (1H, s, O*H*), 5.47 (1H, s, PhC*H*), 5.83 and 6.27 (2H, 2 x d, J = 1.26 and 0.90 Hz, CH_2=C), 7.27 (5H, m, Ar-*H*); δ_C (50 MHz): 51.82 (q, CO_2CH_3), 72.64 (d, (OH)CH-Ar), 125.65 (t, CH_2=C), 126.71, 127.70 and 128.31 (3x d, Ar-*C*), 141.43 (s, Ar-*C*), 142.14 (s, CH_2=*C*), 166.64 (s, CO_2CH_3); *m/z*: 192 (M^+, 16%), 160 (20), 132 (46), 105 (100), 77 (7 0), 55 (16).

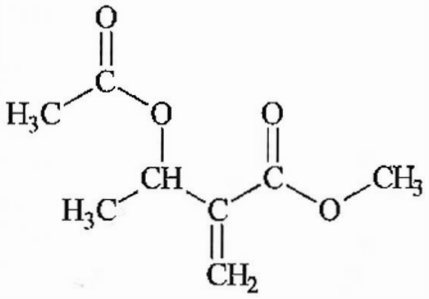


(**102c**)

3.2.4.2 PREPARATION OF ALLYLIC ESTERS

*Methyl 3-acetoxy-2-methylene butanoate (**104a**)*

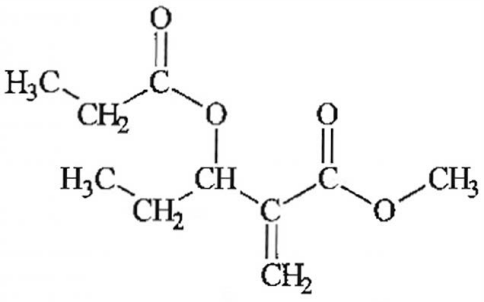
Methyl 3-hydroxy-2-methylenebutanoate (3.00 g, 0.02 mol) was added to acetic anhydride (5.00 g, 0.06 mol) to which had been added 1 drop of *conc.* H_2SO_4. The mixture was stirred for 30 min at rt and then extracted with chloroform (3x 25 ml). The combined organic extracts were neutralised with 2M NaOH and then washed with water (3x 25 ml). The separated organic phase was dried over anhydrous magnesium sulphate and the solvent removed. The crude product was purified on a silica gel column using 30% diethyl ether/hexane as the eluent to afford methyl 3-acetoxy-2-methylene butanoate (**104a**) (2.70 g, 68%). δ_H (200 MHz): 1.42 (3H, d, CH-CH_3), 2.08 (3H, s, COCH_3), 3.78 (3H, s, CO_2CH_3), 5.72 (1H, q, C*H*-CH_3), 5.83 and 6.29 (2H, 2 x d, J = 0.94 and 0.76 Hz, CH_2=C); δ_C (50 MHz): 20.22 (q, OCH*C*H_3), 21.15 (q, OCO*C*H_3), 51.97 (q, CO_2CH_3), 68.20 (d, *C*H-CH_3), 124.71 (t, *C*H_2=C), 141.10 (s, CH_2=*C*), 165.71 (s, *C*O_2CH_3), 169.76 (s, O*C*OCH_3); *m/z*: 172 (M^+-43, 14%), 97 (16), 81 (11), 55 (14), 43 (100).



(104a)

*Methyl 3-propionoxy-2-methylenepentanoate (**104b**)*

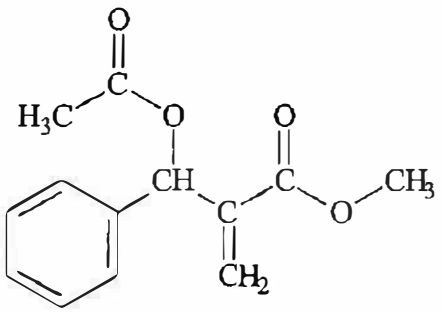
A mixture of methyl 3-hydroxy-2-methylenepentanoate (3.00 g, 0.02 mol) and Et_3N (2.12 g, 0.02 mol) in dry CH_2Cl_2 was cooled to 0 °C in an ice-bath. Propionyl chloride (1.93 g, 0.02 mol, 1.8 ml) was added dropwise with stirring. The mixture was maintained at 0 °C for 30 min and then at rt for 4 h. The mixture was washed with 3M HCl (3x 25 ml), 10% *aq*. $NaHCO_3$ (25 ml) and finally saturated *aq*. NaCl (25 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed. The residue was distilled to afford methyl 3-propionoxy-2-methylenepentanoate (**104b**) (3.27 g, 78%). b.p. 80 °C/6 mmHg; δ_H (200 MHz): 0.91 (3H, t, CH_3CH_2CH), 1.15 (3H, t, $O_2CCH_2CH_3$), 1.75 (2H, m, CH_3CH_2CH), 2.37 (2H, q, $O_2CCH_2CH_3$), 3.78 (3H, s, CO_2CH_3), 5.60 (1H, m, CHO), 5.77 and 6.30 (2H, 2 x d, J = 0.94 and 0.76 Hz, CH_2=C); δ_C (50 MHz): 9.17 (q, $O_2CCH_2CH_3$), 9.55 (q, $CHCH_2CH_3$), 27.27 (t, $CHCH_2CH_3$), 27.74 (t, $O_2CCH_2CH_3$), 51.97 (q, CO_2CH_3), 72.58 (d, CHO), 125.15 (t, CH_2=C), 140.00 (s, CH_2=C), 165.82 (s, CO_2CH_3), 173.41 (s, $O_2CCH_2CH_3$); *m/z*: (M^+-57, 35%), 126 (13), 111 (36), 67 (39), 57 (100), 55 (16).



(104b)

*Methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**104c**)*

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (5.00 g, 0.03 mol) and acetic anhydride (8.10 g, 0.09 mol) were treated according to the procedure described for the preparation of methyl 3-acetoxy-2-methylene butanoate (**104a**) to afford methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**104c**) (3.69 g, 60%). δ_H (200 MHz): 2.08 (3H, s, $OCOCH_3$), 3.68 (3H, s, CO_2CH_3), 5.86 and 6.39 (2H, 2 x d, J = 0.94 and 0.86 Hz, CH_2=C), 6.69 (1H, s, Ph-C*H*-O), 7.34 (5H, m, Ar-*H*); δ_C (50 MHz): 21.03 (q, $OCOCH_3$), 51.95 (q, CO_2CH_3), 73.08 (d, Ph-*C*H-O), 125.74 (t, CH_2=C), 127.66, 128.38 and 128.45 (3 x d, Ar-*C*H), 137.78 (s, Ar-*C*), 139.64 (s, CH_2=*C*), 165,35 (s, CO_2CH_3), 169.35 (s, $OCOCH_3$); *m/z*: 234 (M^+, <1%), 191 (79), 159 (36), 115 (93), 105 (100), 77 (50), 43 (67).

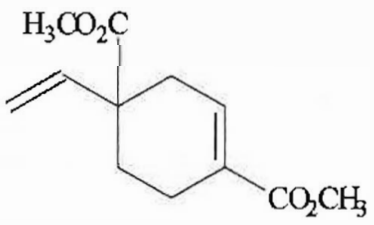


(**104c**)

3.2.4.3 PREPARATION OF CYCLOHEXENES

*Dimethyl 4-(1-ethenyl)-1-cyclohexene-1,4-dicarboxylate (**107a**)*

Methyl 3-acetoxy-2-methylene butanoate (1.29 g, 7.50 mmol), cyclopentadiene (0.50 g, 7.50 mmol) and DABCO (0.08 g, 0.75 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The flask was fitted with a septum and the mixture stirred under nitrogen for 15 min. The mixture was then stirred for 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. The crude product was chromatographed on silica, using 20% diethyl ether/hexane as the eluent, to afford dimethyl 4-(1-ethenyl)-1-cyclohexene-1,4-dicarboxylate (**107a**) (0.39 g, 23%). δ_H (200 MHz): 1.75-2.25 (4H, m, CH_2CH_2), 2.31-2.78 (2H, m, CH_2CH), 3.59 and 3.61 (6H, 2 x s, 2 x CO_2CH_3), 5.09 (2H, superimposed dd, J = 10.7 and 13.6 Hz, CH_2=CH), 5.76 (1H, dd, J = 10.7 and 13.6 Hz, CH_2=C*H*), 6.98 (1H, m, CH_2=C*H*); δ_C (50 MHz): 21.76 and 29.50 (2 x t, CH_2CH_2), 32.16 (t, CH_2CH), 51.57 and 52.26 (2 x q, 2 x OCH_3), 115.19 (t, CH_2=C), 129.37 (s, ArC), 137.02 (d, CH_2CH), 139.42 (d, CH_2=CH), 167.23 (s, CH=CCO_2CH_3), 174.72 (s, CCO_2CH_3); *m/z*: 224 (M^+, 3%), 192 (46), 165 (54), 133 (100), 105 (97), 77 (41), 59 (57).

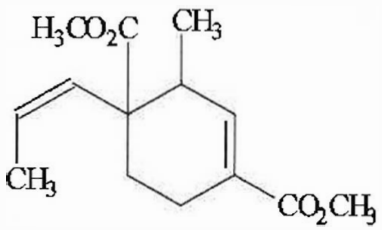


(107a)

Methyl 3-acetoxy-2-methylene butanoate (1.29 g, 7.50 mmol) and DABCO (0.84 g, 7.50 mmol) were added to dichloromethane (25 ml) and the mixture refluxed for 4 h. The crude reaction mixture was worked up according to the procedure outlined in the previous preparation of (**107a**) to afford dimethyl 4-(1-ethenyl)-1-cyclohexene-1,4-dicarboxylate (0.89 g, 53%).

*Dimethyl 3-methyl-4-(1-propenyl)-1-cyclohexene-1,4-dicarboxylate (**107b**)*

Methyl 3-acetoxy-2-methylene butanoate (1.29 g, 7.50 mmol), cyclopentadiene (0.50 g, 7.50 mmol) and DABCO (0.84 g, 7.50 mmol) were added to dichloromethane (2 ml) at 0 °C in a 10 ml round-bottomed flask. The flask was fitted with a septum and the mixture stirred under nitrogen for 15 min. The mixture was then stirred for 2 d in a water bath at 22 °C. The mixture was then poured into a separating funnel, diluted with dichloromethane (20 ml) and washed with 10% HCl (3x 15 ml); 10% $NaHCO_3$ (3x 15 ml) and finally water (3x 25 ml). The organic layer was dried over anhydrous magnesium sulphate. The crude product was chromatographed on silica, using 20% diethyl ether/hexane as the eluent, to afford dimethyl 3-methyl-4-(1-propenyl)-1-cyclohexene-1,4-dicarboxylate (**107b**) (0.43 g, 23%). *Diastereomeric ratio* (GC = 80:20). δ_H (200 MHz): 0.97 [0.99] (3H, d $CHCH_3$), 1.64-2.35 (4H, m, CH_2CH_2), 1.72 (3H, d, CH_3CH=CH), 3.00 (1H, m, $CHCH_3$), 3.65 [3.68] (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 5.43 (1H, dd, J = 16 Hz, CH=$CHCH_3$), 5.53 (1H, dq, J = 16 and 5 Hz, CH=$CHCH_3$), 6.93 (1H, m, CH_3CHCH); δ_C (50 MHz): 16.20 [16.93] (q, CH_3), 18.28 [18.23] (q, CH_3), 22.57 [21.57] and 24.72 [23.97] (2 x t, CH_2CH_2), 35.59 [36.82] (d, CHCH=C), 50.17 (s, $CCHCH_3$), 51.57 (q, OCH_3), 52.12 (q, OCH_3), 126.45 (d, CH=$CHCH_3$), 128.00 (s, CH=CCO_2CH_3), 131.42 (d, CHCH=C), 143.71 (d, CH_2=$CHCH_3$), 167.61 (s, CH=CCO_2CH_3), 174.63 (s, CCO_2CH_3); *m/z*: 252 (M^+, 10%), 193 (57), 161 (98), 133 (76), 126 (100), 111 (67), 91 (62).



(107b)

Methyl 3-acetoxy-2-methylene butanoate (0.50 g, 2.90 mmol) and DABCO (0.33 g, 2.90 mmol) were added to dichloromethane (20 ml). The mixture was refluxed for 4 h and then worked up according to the procedure outlined in the previous preparation of (**107b**), to afford dimethyl 3-methyl-4-(1-propenyl)-1-cyclohexene-1,4-dicarboxylate (0.34 g, 53%).

CHAPTER 4: REFERENCES

1. W. Carruthers, *Cycloaddition reactions in Organic Synthesis*. Tetrahedron Organic Chemistry Series Vol. 8, Pergamon Press, Elmsford, NY, 1990.

2. T. Cohen and Z. Kosarych, *J. Org. Chem.*, **1982**, *47*, 4005.

3. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc.*, **1952**, *74*, 4223.

4. L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *J. Am. Chem. Soc.*, **1952**, *74*, 4974.

5. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, *Tetrahedron*, **1958**, *2*, 1.

6. G. Stork, E. E. van Tamelen, L. J. Friedman and A. Burgstähler, *J. Am. Chem. Soc.*, **1975**, *75*, 384.

7. J. G. Martin and R. K. Hill, *Chem. Rev.*, **1961**, *61*, 537.

8. (a) J. Sauer and J. Kredel, *Tetrahedron Lett.*, **1966**, 731.

   (b) J. Sauer and J. Kredel, *Tetrahedron Lett.*, **1966**, 6359.

9. K. Matsumoto and A. Sera, *Synthesis*, **1985**, 999.

10. W. J. Le Noble and T. Asaro, *Chem. Rev.*, **1978**, *78*, 407.

11. W. G. Dauben and W. R. Baker, *Tetrahedron Lett.*, **1982**, *23*, 2611.

12. L. F. Tietze, T. Hübsch, E. Voss, M. Buback and W. Tost, *J. Am. Chem. Soc.*, **1988**, *110*, 4065.

13. R. F. Abdulla, *Aldrichemica Acta*, **1988**, *21*, 31.

14. J. Lee and J. K. Snyder, *J. Org. Chem.*, **1990**, *55*, 4995.

15. A. Benalloum, B. Labiad and D. Villemin, *J. Chem. Soc., Chem. Commun.*, **1989**, 386.

16. D. R. Baghurst and D. M. Mingos, *J. Organomet. Chem.*, **1990**, 57, 384.

17. R. Zhu, P. Hong and S. Dai, *Synth. Commun.*, **1994**, *24*, 2417.

18. J. Sauer and R. Sustmann, *Angew. Chem., Int. Ed. Engl.*, **1980**, *19*, 779.

19. (a) D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **1980**, *102*, 7819.

(b) R. Breslow, U. Maitra and D.C. Rideout, *Tetrahedron Lett.*, **1983**, *24*, 1901.

(c) R. Breslow and U. Maitra, *Tetrahedron Lett.*, **1984**, *25*, 1239.

20. P. A. Grieco and K. S. Yoshida, *Chem. Lett.*, **1985**, 155.

21. P. A. Grieco and J. Lucchefi, *Tetrahedron Lett.*, **1984**, *25*, 2147.

22. A. Lubineau and E. Meyer, *Tetrahedron Lett.*, **1988**, *44*, 6065.

23. G. Desimoni, G. Faita, P. Righetti, N. Tornaleti and M. Visigalli, *J. Chem. Soc. Perkin Trans. 2.*, **1989**, 437.

24. W. Blokziji, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **1991**, *113*, 4241.

25. P. A. Grieco, P. Garner and Z-M. He, *Tetrahedron Lett.*, **1983**, *27*, 1897.

26. (a) I. Rico, M.T. Maurette, E. Oliveros, M. Reviere and A. Lattes, *Tetrahedron*, **1980**, *36*, 1779.

(b) R. Fargues-Sakellariov, M. T. Maurette, E. Oliveros, M. Reviere and A. Lattes, *Tetrahedron*, **1984**, *40*, 2381.

27. (a) A. Samii Ahmod-Zadeh, A. de Savignac, I. Rico and A. Lattes, *Tetrahedron*, **1985**, *41*, 3683.

(b) A. Lattes, I. Rico, A. de Savinac and A. Samii Ahmod-Zadeh, *Tetrahedron*, **1987**, *43*, 1725.

28. T. Dunams, W. Hoekstra, M. Pentaleri and D. Liotta, *Tetrahedron Lett.*, **1988**, *29*, 3745.

29. R. Braun, F. Schuster and J. Sauer, *Tetrahedron Lett.*, **1986**, *27*, 1285.

30. P. A. Grieco, *Aldrichemica Acta*, **1991**, *24*, 59.

31. P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, **1990**, *112*, 4595.

32. M. A. Forman and W. P. Dailey, *J. Am. Chem. Soc.*, **1991**, *113*, 2761.

33. D. A. Jaegar and C. E. Tucker, *Tetrahedron Lett.*, **1989**, *30*, 1785.

34. W. Hölderich, M. Hesse and F. Näumann. *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 266.

35. (a) P. Laszlo and J. Luchetti, *Tetrahedron Lett.*, **1984**, *25*, 2147.

(b) P. Laszlo and J. Luchetti, *Tetrahedron Lett.*, **1985**, *25*, 1567.

(c) P. Laszlo and J. Luchetti, *Tetrahedron Lett.*, **1985**, *25*, 4387.

36. C. Cativiela, J. M. Fraile, J. I. Garcia, J. A. Mayoral, E. Pires and A. J. Royo, *Tetrahedron*, **1993**, *49*, 4073.

37. G. A. Olah, P. S. Iyer and G. K. S. Prakash, *Synthesis*, **1986**, 513.

38. M. A. Boehler and J. P. Konopelski, *Tetrahedron*, **1991**, *47*, 4519.

39. H. Lamcy-Schelkens and L. Ghosez, *Tetrahedron Lett.*, **1989**, *30*, 5891.

40. T. R. Kelly, S. M. Maity, P. Meghani and N. S. Chandrakumar, *Tetrahedron Lett.*, **1989**, *30*, 1357.

41. W. Beck and K. Sünkel, *Chem. Rev.*, **1988**, *88*, 1405.

42. R. V. Honeychuck, P. V. Bonnesen, J. Farahi and W. H. Hersh, *J. Org. Chem.*, **1987**, *52*, 5293.

43. J. Collin and P. Van de Weghe, *Tetrahedron Lett.*, **1994**, *35*, 2545.

44. S. Danishefsky and M. Bednarski, *Tetrahedron Lett.*, **1985**, *26*, 2507.

45. W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **1984**, *23*, 876.

46. D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, **1988**, *110*, 1238.

47. S. Colanna, A. Manfredi and R. Annunziata. *Tetrahedron Lett.*, **1988**, *29*, 3347.

48. K. R. Rao, T. N. Srinivasan and N. Bhanumathi, *Tetrahedron Lett.*, **1990**, *31*, 5959.

49. D. Hilvert, K. Hill, K. D. Nared and M-T. M. Auditor, *J. Am. Chem. Soc.*, **1989**, *111*, 9261.

50. S. Hashimoto, N. Komeshima and K. Koga, *J. Chem. Soc., Chem. Commun.*, **1979**, 437.

51. (a) K. Furuta, Y. Miwa, K. Iwanaga and H.Yamamoto, *J. Am. Chem. Soc.*, **1988**, *110*, 6254.

(b) K. Furuta, Y. Miwa, S. Shimizu and H.Yamamoto, *J. Org. Chem.*, **1989**, *54*, 1481.

52. K. Narasaka, M. Inova and N. Okada, *Chem.. Lett.*, **1986**, 1109.

53. E. J. Corey, R. Imwinkelried, S. Pikul and Y. B. Xiang, *J. Am. Chem. Soc.*, **1989**, *111*, 5493.

54. C. Chapius and J. Jurczak, *Helv. Chim. Acta*, **1987**, *70*, 436.

55. S. Kobayashi, I. Hachiya, H. Ishatani and M. Araki, *Tetrahedron Lett.*, **1993**, *34*, 4535.

56. S. Kobayashi, M. Araki and I. Hachiya, *J. Org. Chem.*, **1994**, *59*, 3759.

57. (a) M. Koerner and B. Rickborn, *J. Org. Chem.*, **1989**, *54*, 6.

(b) M. Koerner and B. Rickborn, *J. Org. Chem.*, **1990**, *55*, 2662.

58. O. Riant and H. B. Kagan, *Tetrahedron Lett.*, **1989**, *30*, 7403.

59. D. Janse Van Rensberg, *M. Sc. Thesis*, University of Natal, 1994.

60. S. E. Drewes and G. H. P. Roos. *Tetrahedron*, **1988**, *44*, 4653.

61 P. H. Mason, *M. Sc. Thesis*, University of Natal, 1992.

62. A. B. Baylis and M. E. D. Hillman, German Patent 2155113, **1972**, *Chem. Abs.*, *77*, 34174 q.

63. L. A. Paquette and R. V. C. Carr, *Org. Synth.*, **1981**, 157.

64. W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, **1987**, 1625.

65.. L. M. Harwood and C. J. Moody, *Experimental Organic Chemistry, Principles and Practice*. Blackwell Scientific Publications, Butler and Tanner Ltd. UK, 1990, (a) 557, (b) 627.

66. R. E. Strube, *Organic Syntheses*, Collective Volume IV, 263.

67. J. R. Hwu, K-L. Chen and S. Ananthan, *J. Chem. Soc., Chem Comm.*, **1994**, 1425.

68. K. N. Jensen and G. H. P. Roos, *Tetrahedron Asymm.*, **1992**, *3*, 1553.

69. W. J. Close, *J. Org. Chem.*, **1950**, *15*, 1131.

70. C. S. Rondestvedt and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **1955**, *77*, 4878.

71. L-C. Yu and P. Helquist, *J. Org. Chem.*, **1981**, *46*, 4536.

72. R. Tschesche, F-J. Kammerer and G. Wulff, *Chem. Ber.*, **1969**, *102*, 2057.

73. S. M. Kupchan, R. J. Hemingway, D. Werner and A. Karim, *J. Org. Chem.*, **1969**, *34*, 3903.

74. S. E. Drewes and N. D. Emslie, *J. Chem. Soc., Perkin Trans I.*, **1982**, 2079.

75. F. Ameer, S. E. Drewes, M. S. Houston-McMillan and P. T. Kaye, *S. Afr. J. Chem.*, **1986**, *39*, 57.

76. F. Ameer, S. E. Drewes, R. F. A. Hoole, P. T. Kaye and A. T. Pitchford, *J. Chem. Soc., Perkin Trans I.*, **1985**, 2713.

77. F. Ameer, *Ph.D. Thesis*, University of Natal, 1985.

78. F. Ameer, S. E. Drewes, S. Freese and P. T. Kaye, *Synth. Commun.*, **1988**, *18*, 495.

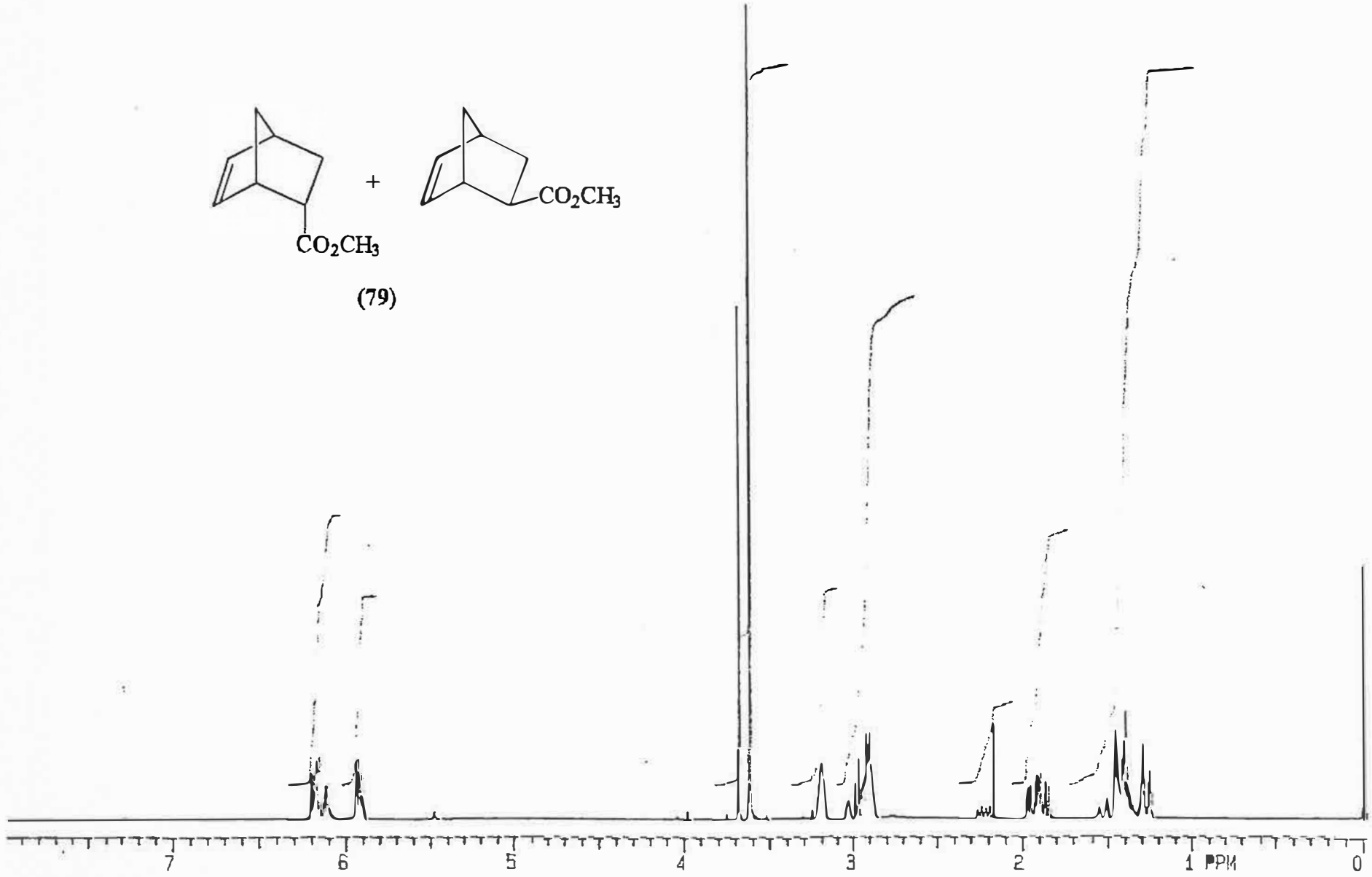
79. H. R. Hoffman and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, **1983**, *22*, 795.

80. W. Poly, D. Schumburg and H. M. R. Hoffmann, *J. Org. Chem*, **1988**, *53*, 3701.

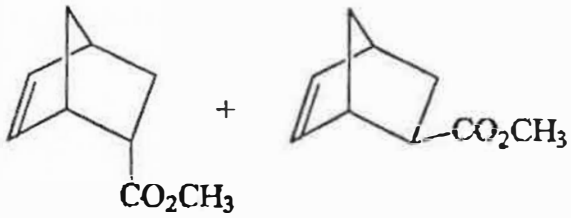
81. D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, 2nd ed., Pergamon, Oxford, 1980.

82. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **1987**, *43*, 2923.

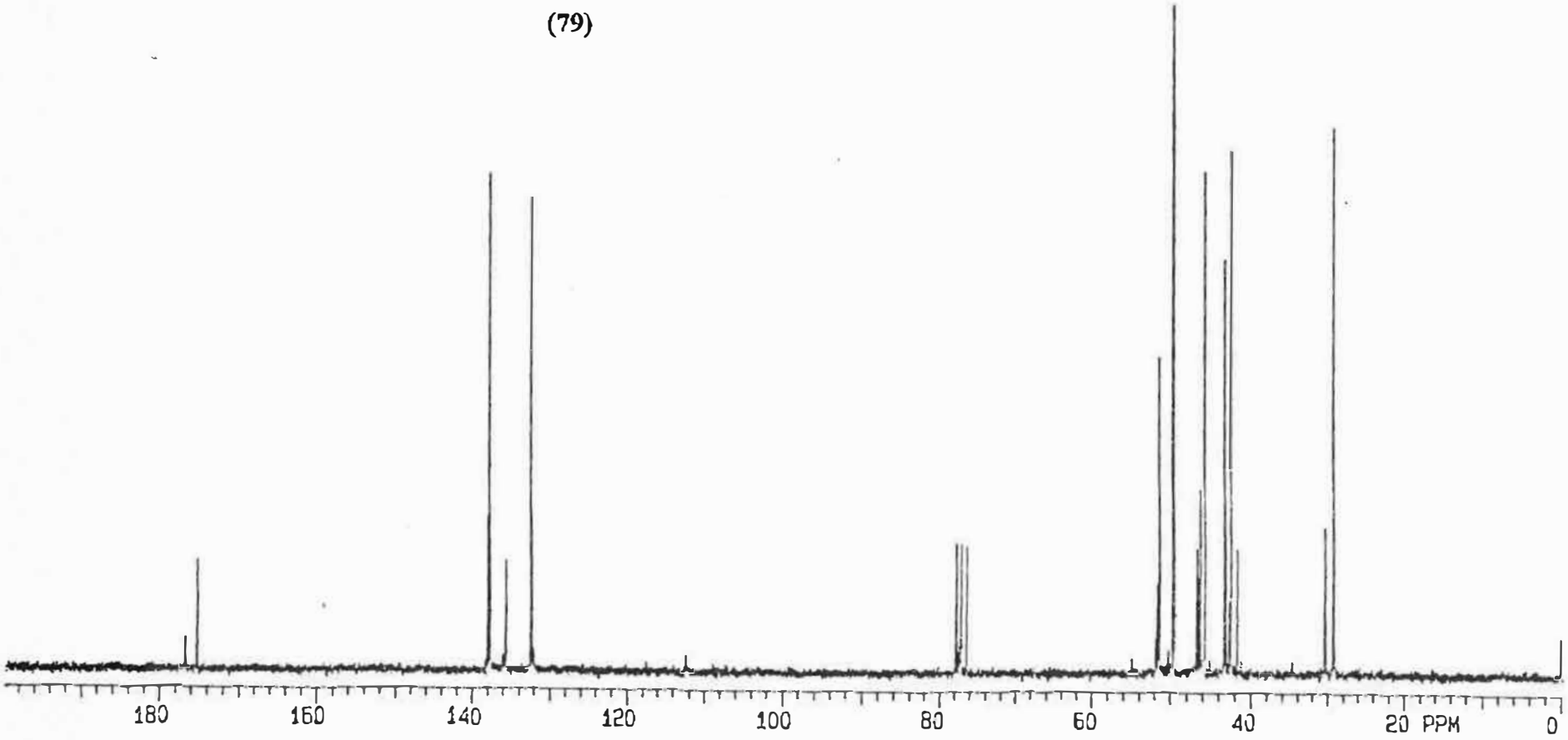
APPENDIX : ^{1}H AND ^{13}C NMR SPECTRA

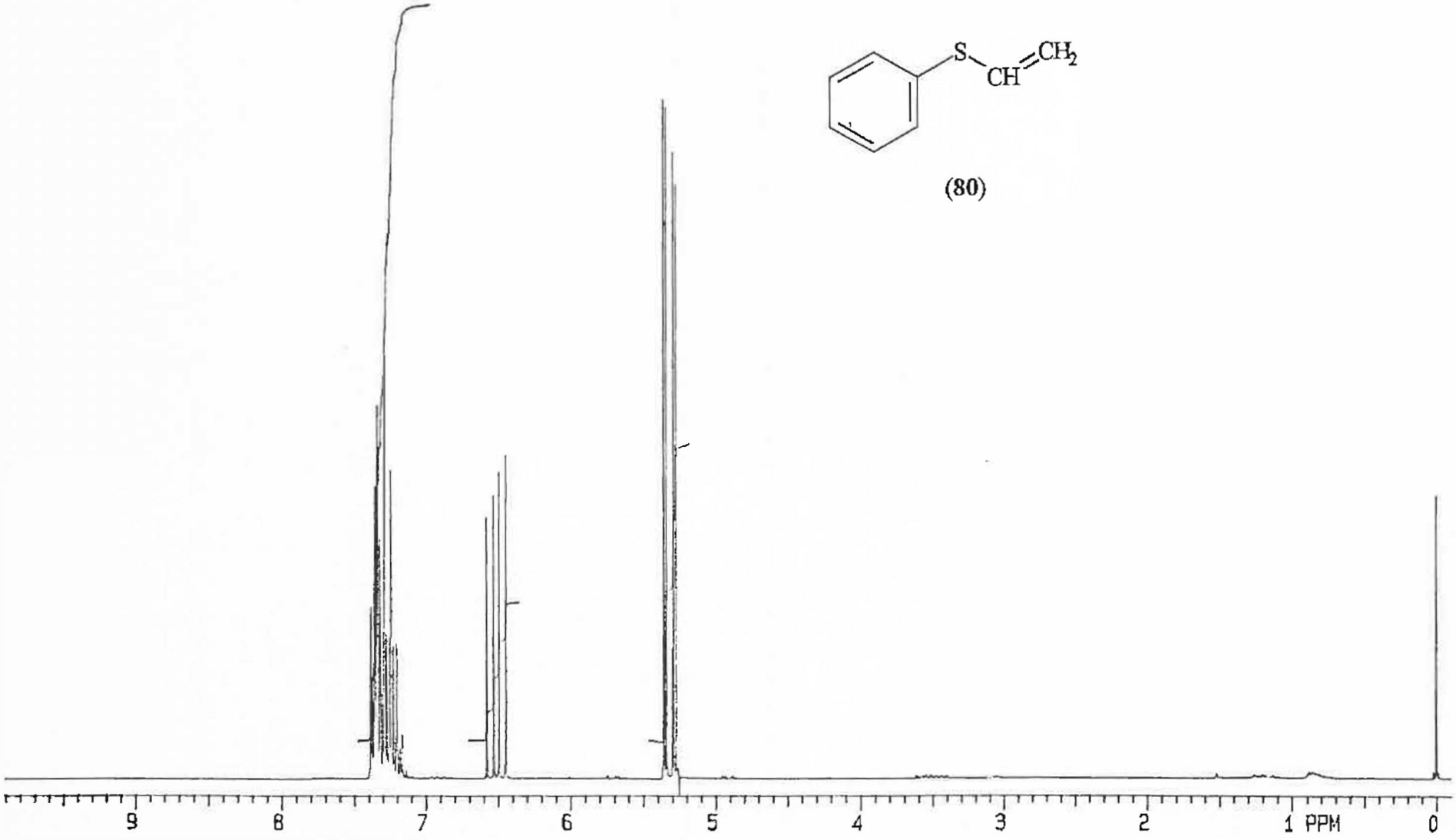


(79)

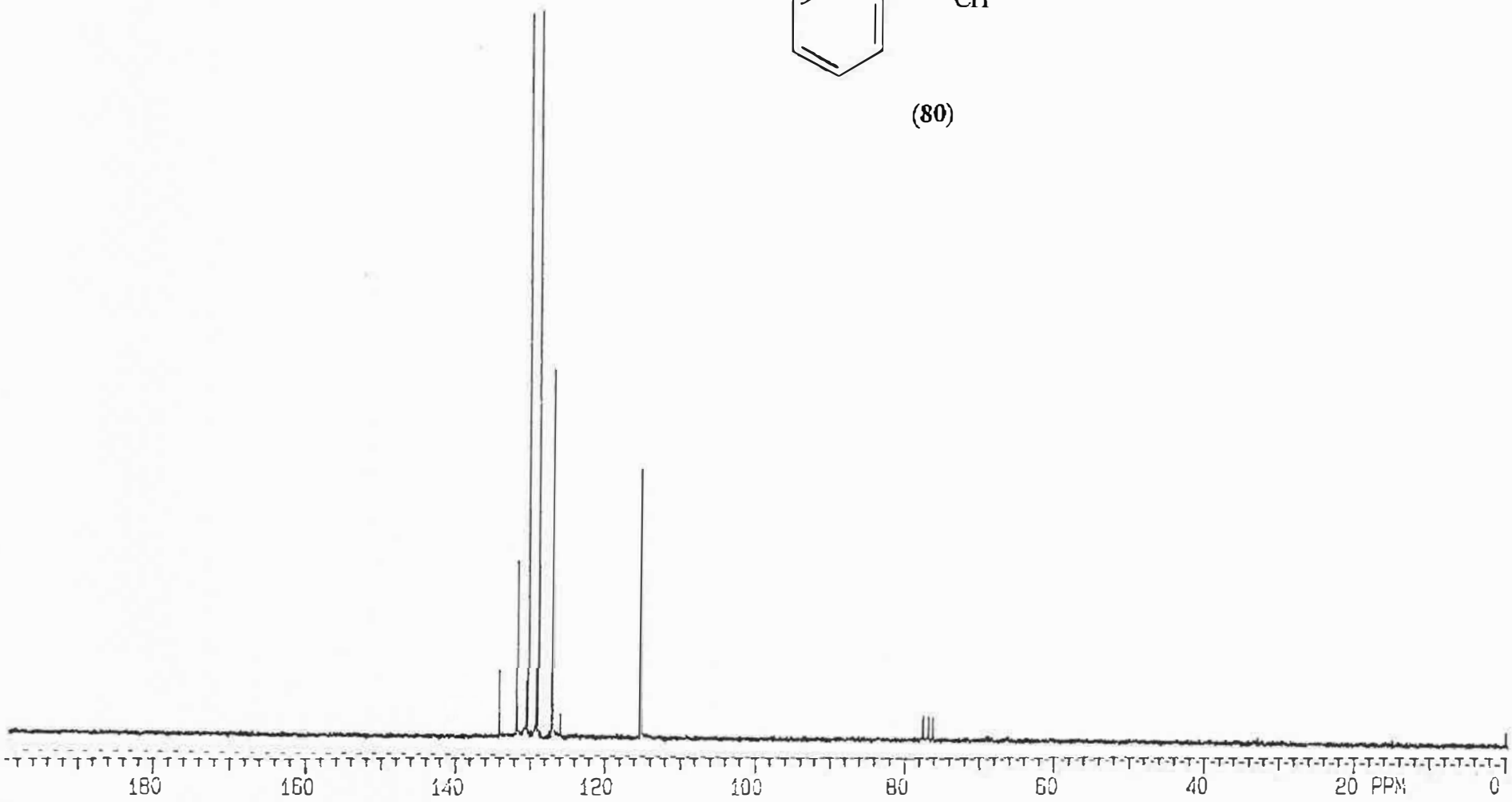


(79)

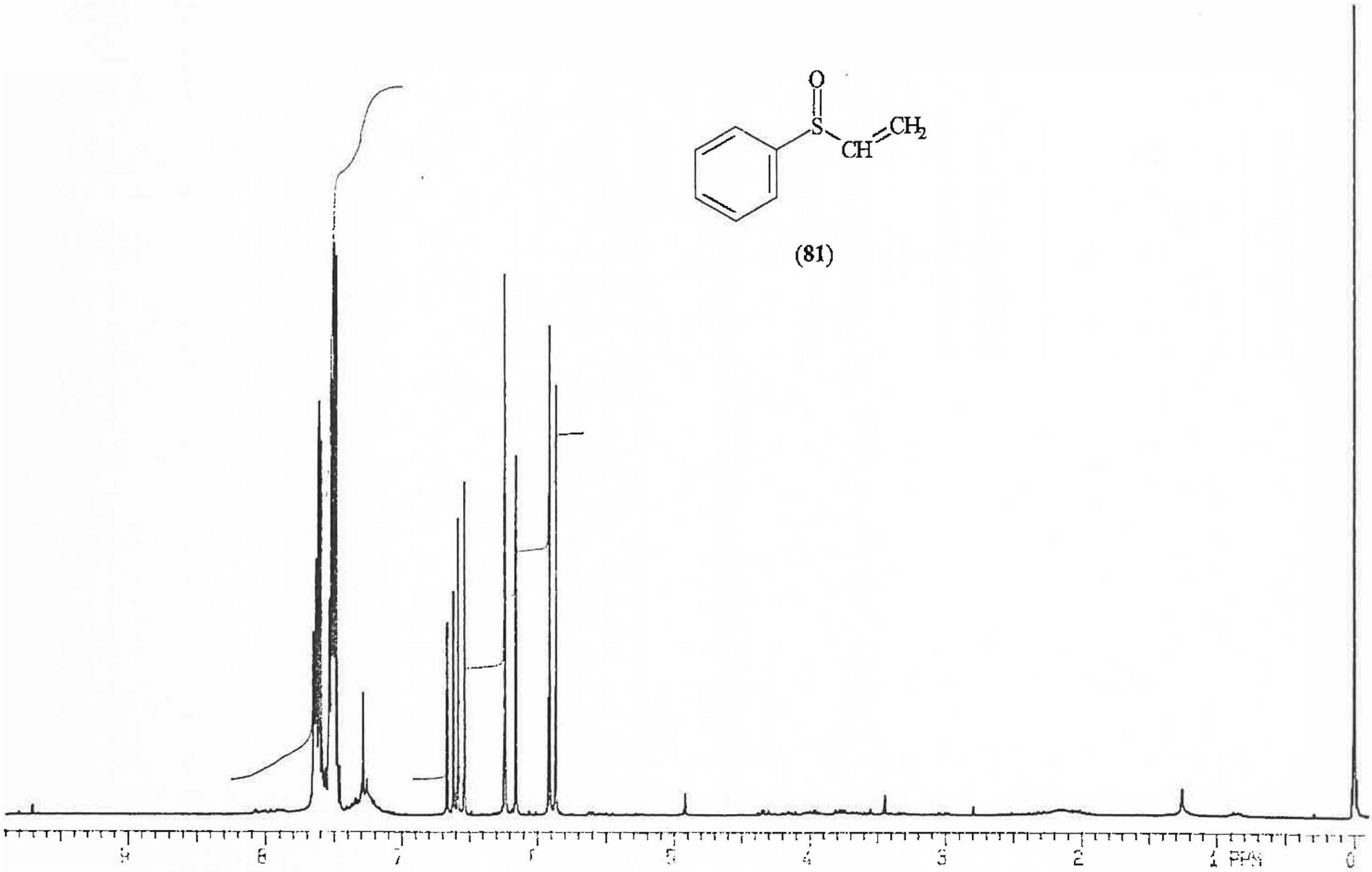




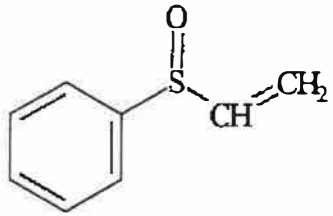
(80)



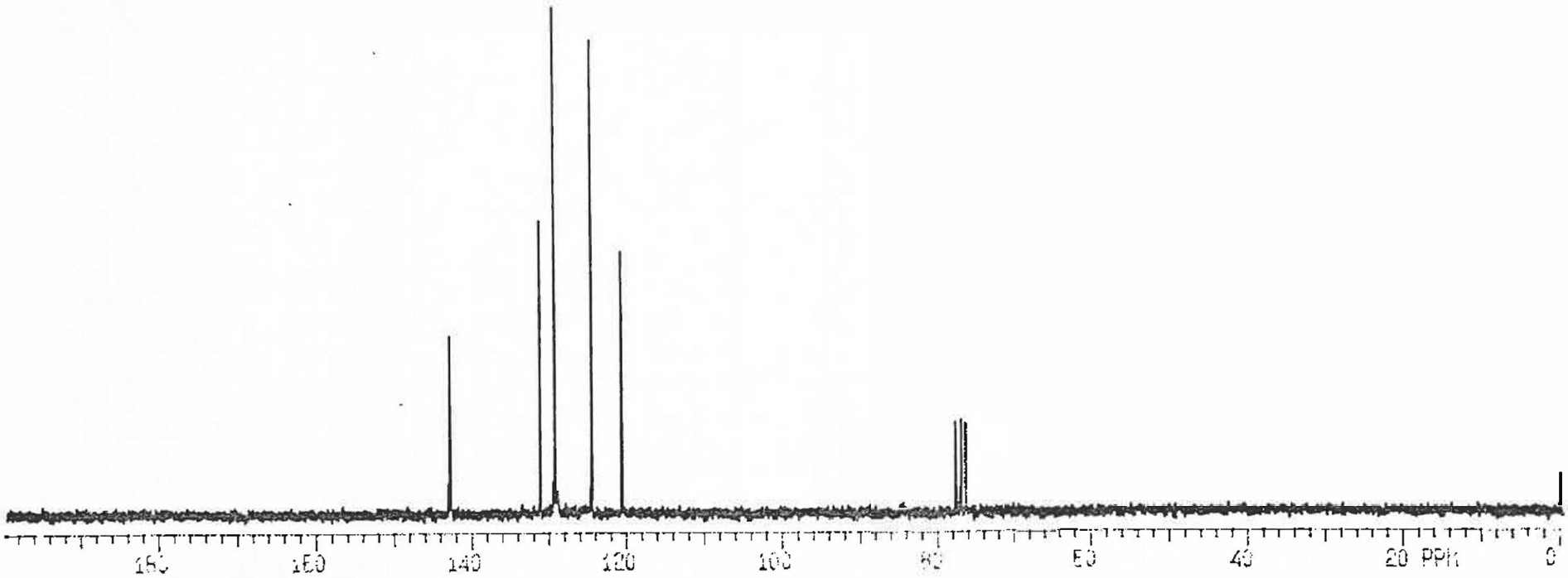
(80)

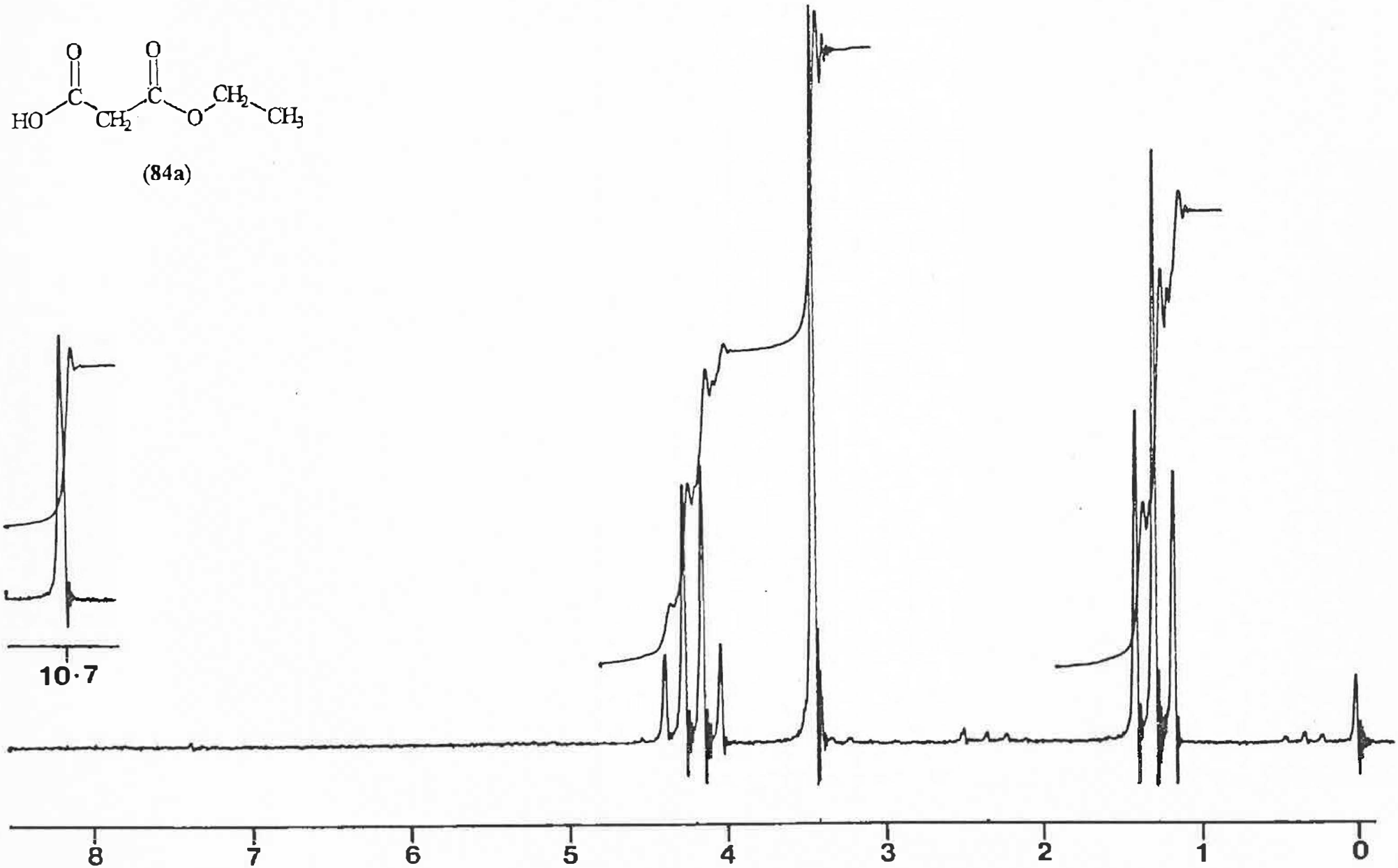


(81)



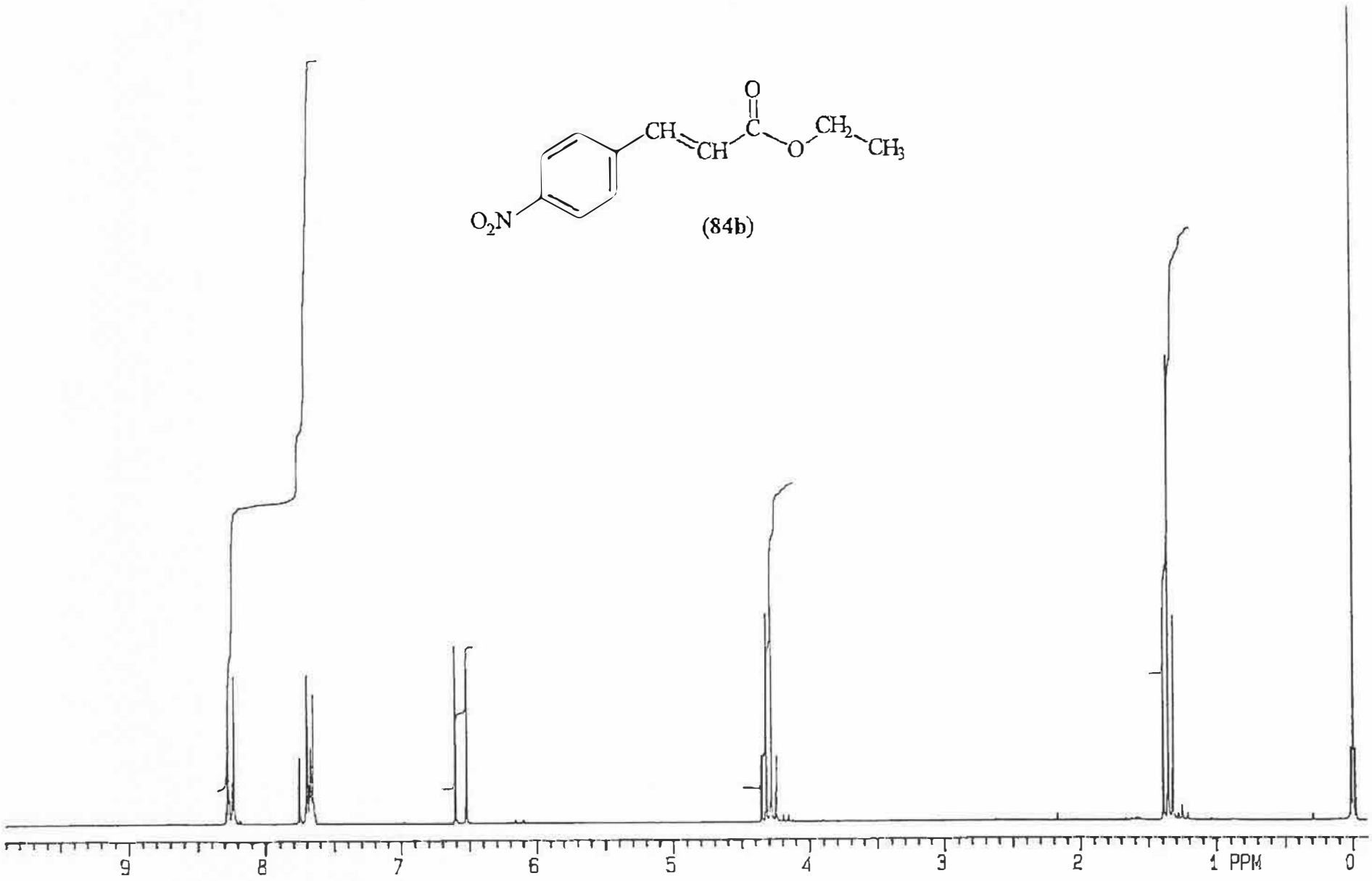
(81)



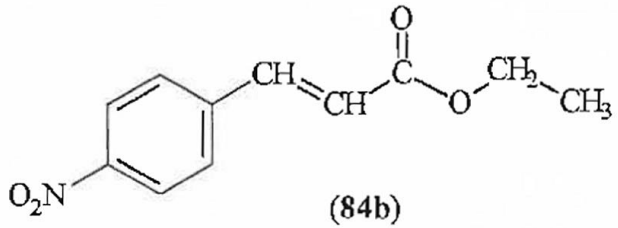


(84a)

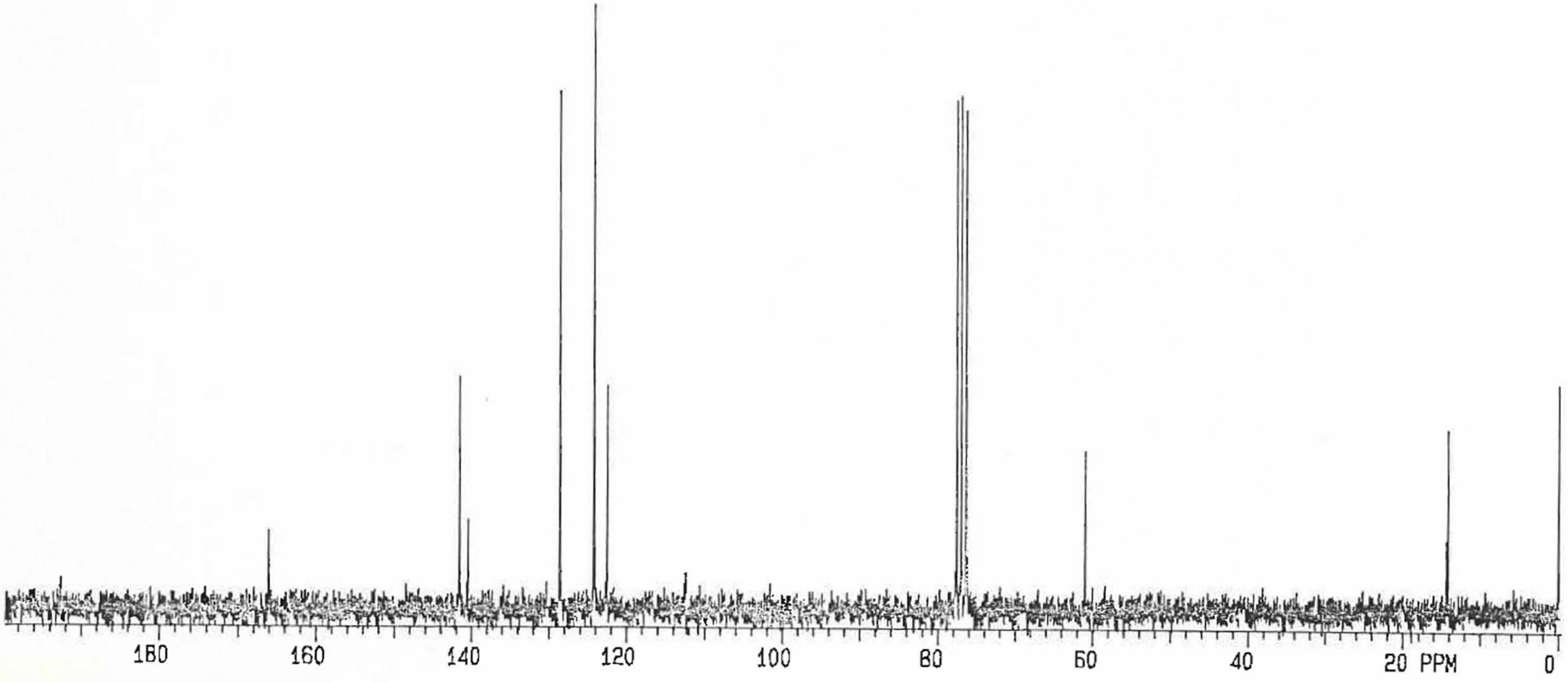
H^1 n.m.r. spectrum (60MHz; $CDCl_3$/TMS)

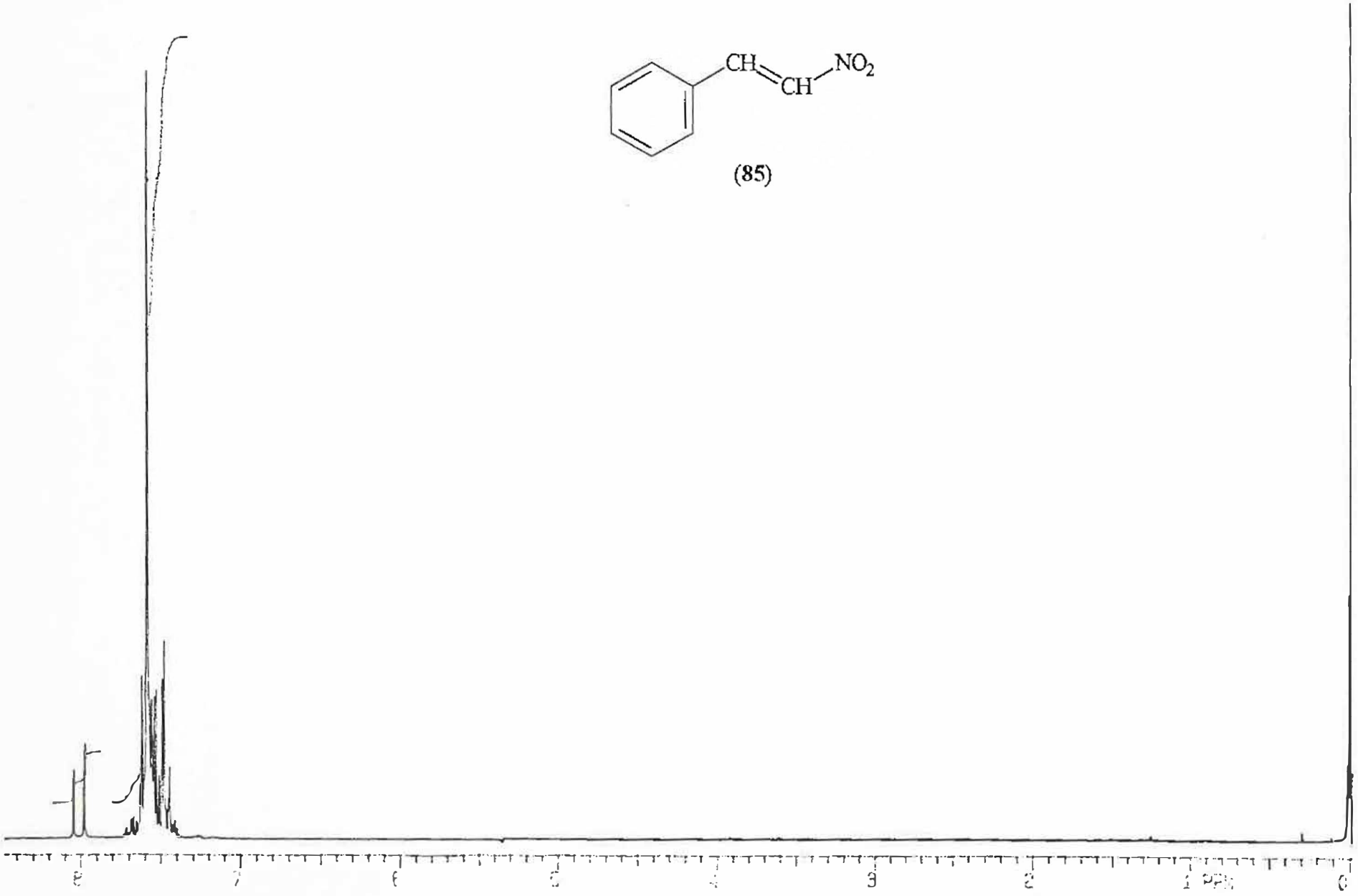


(84b)

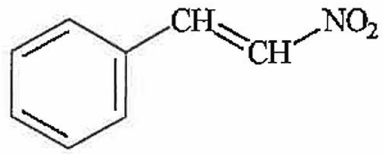


(84b)

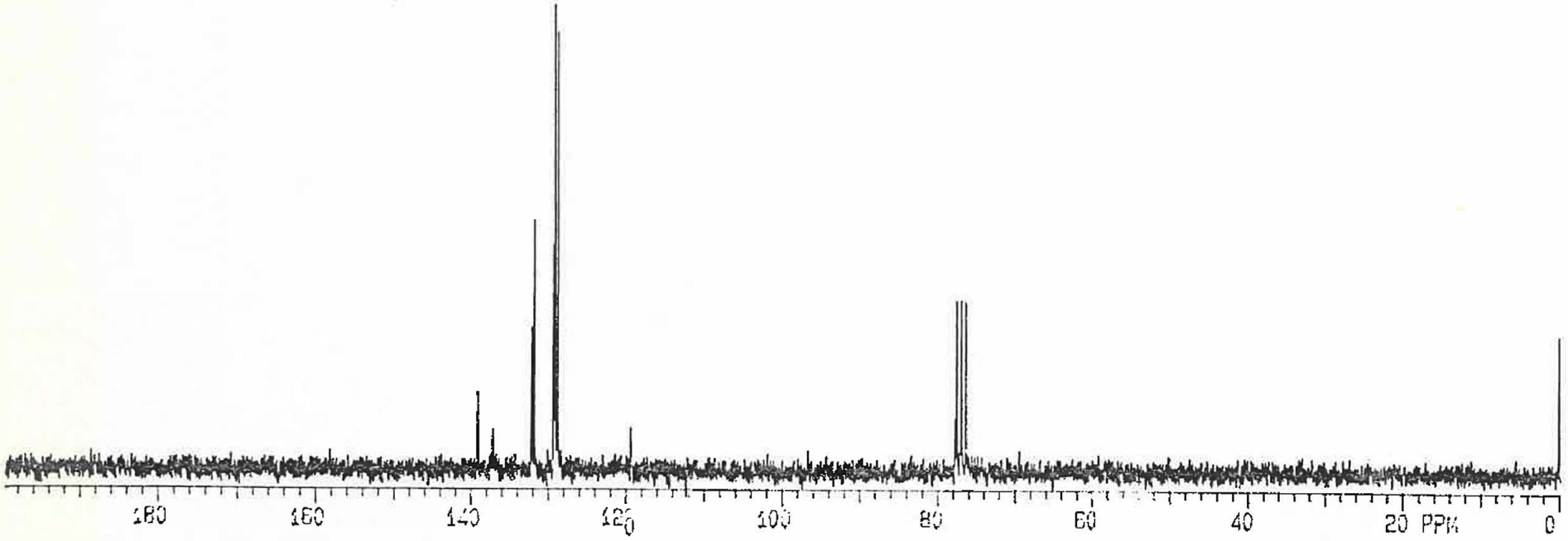




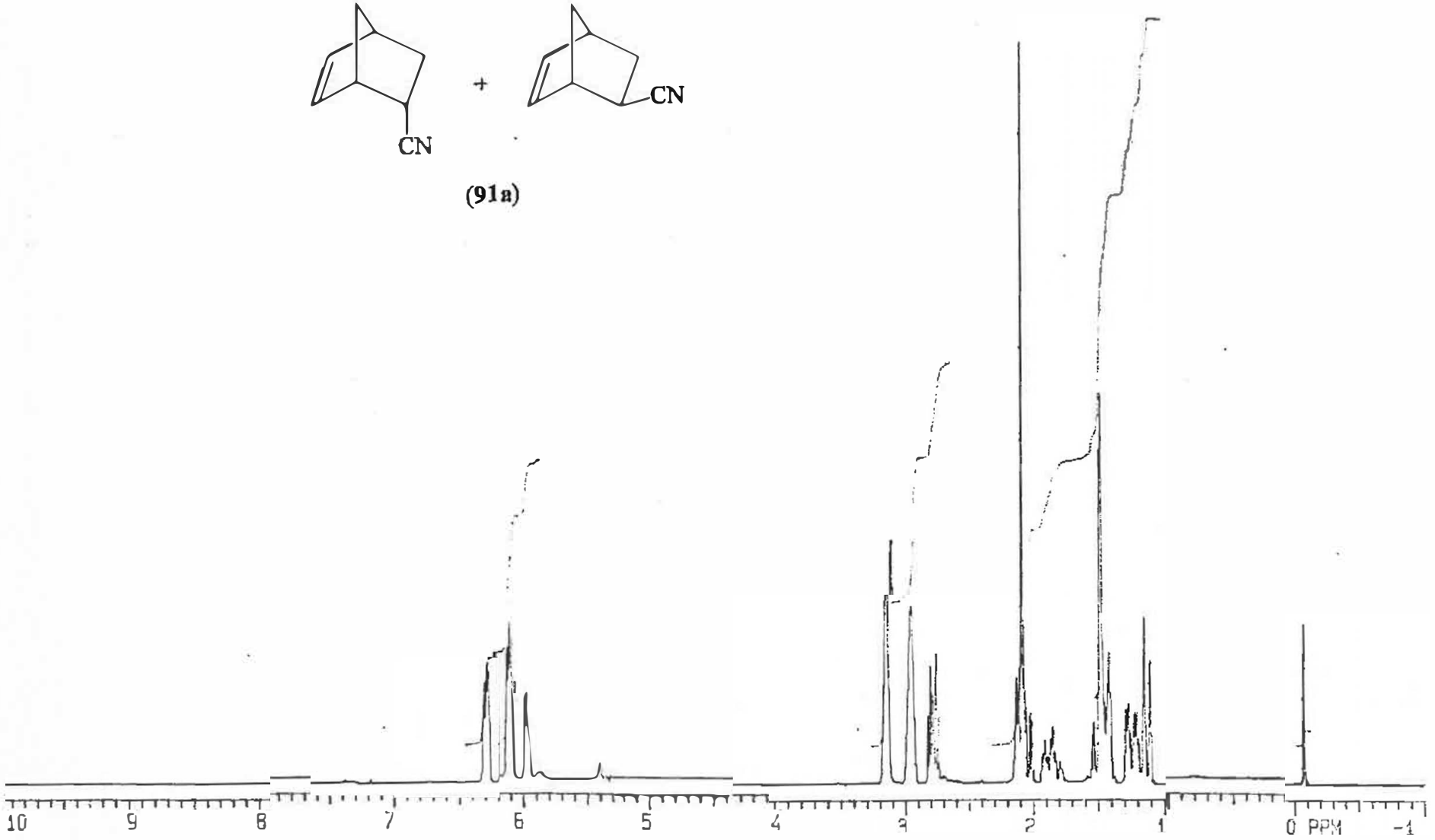
(85)

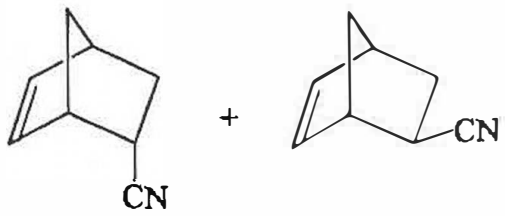


(85)

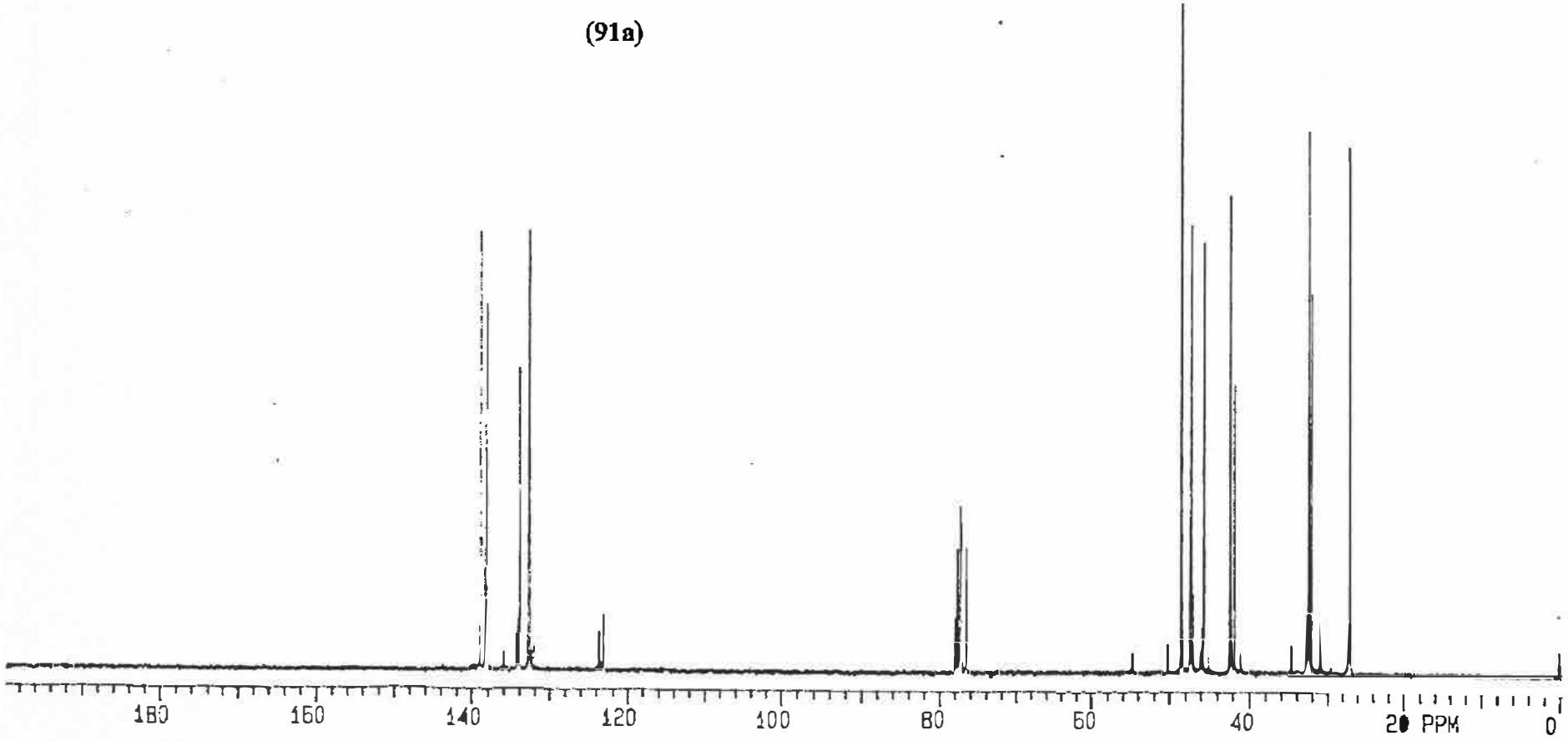


(91a)

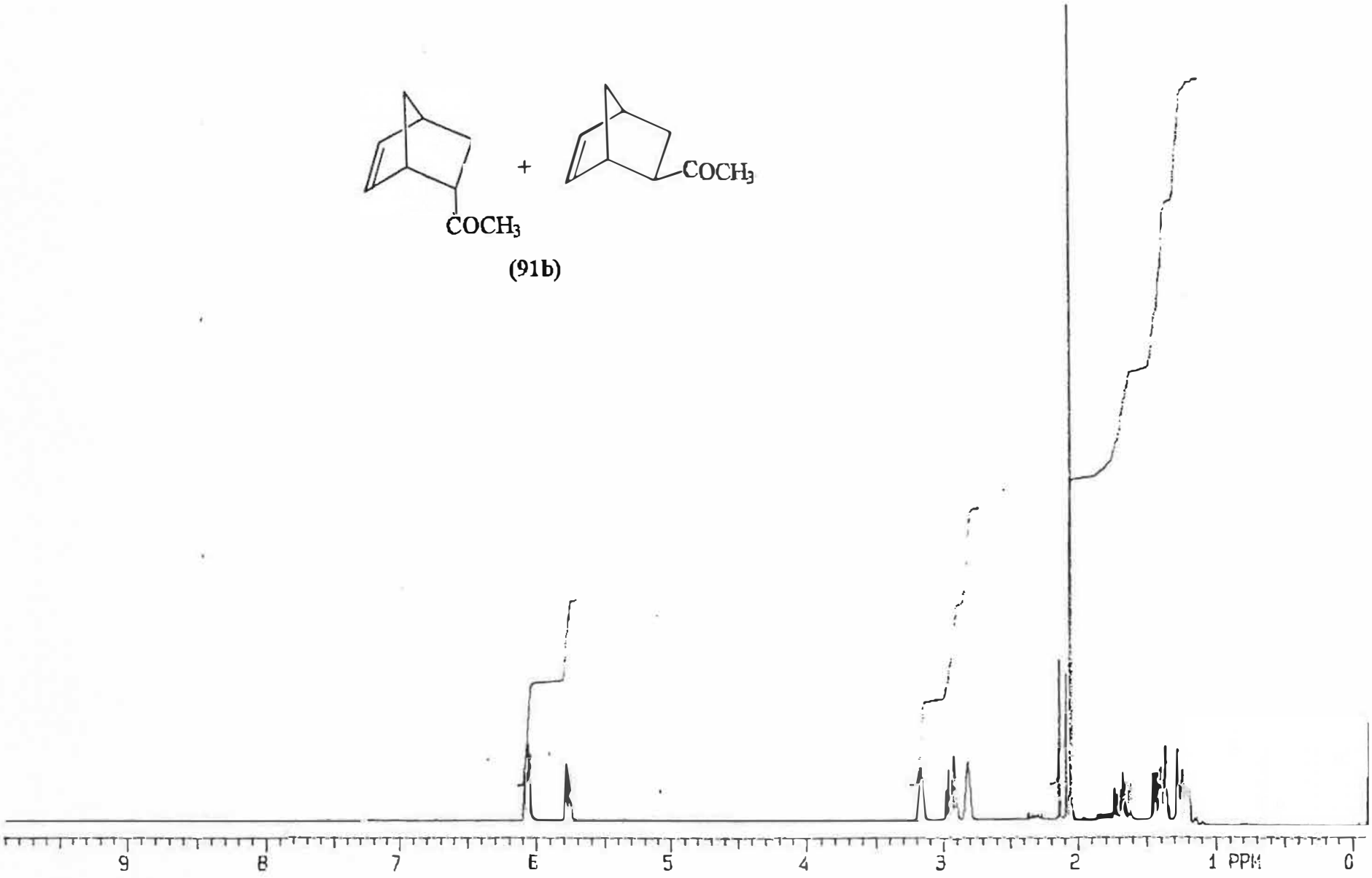


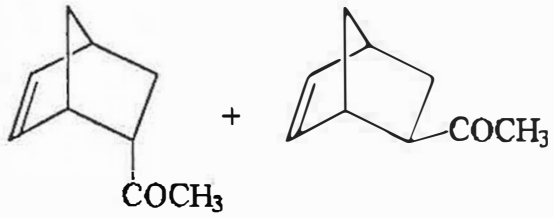


(91a)

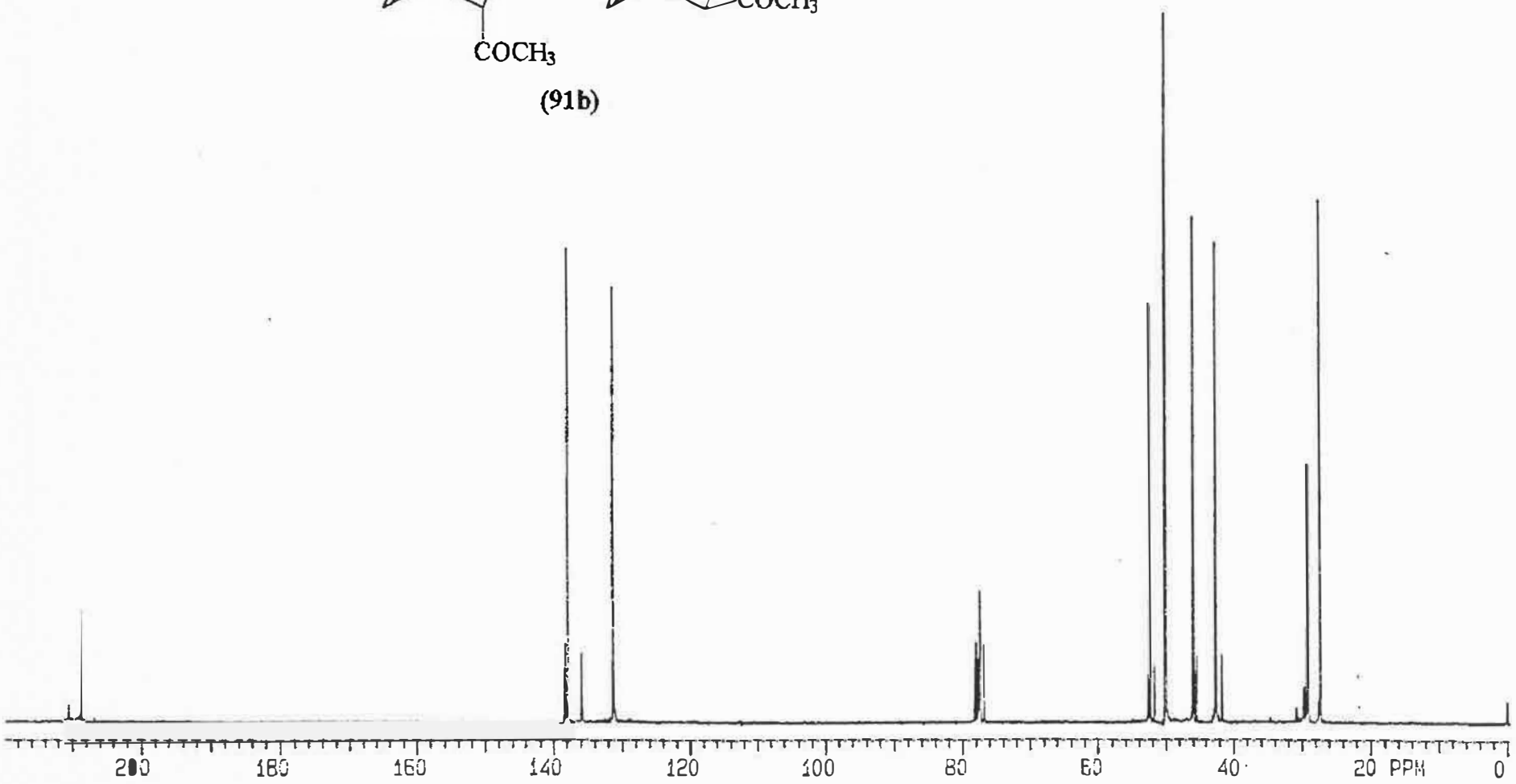


(91b)

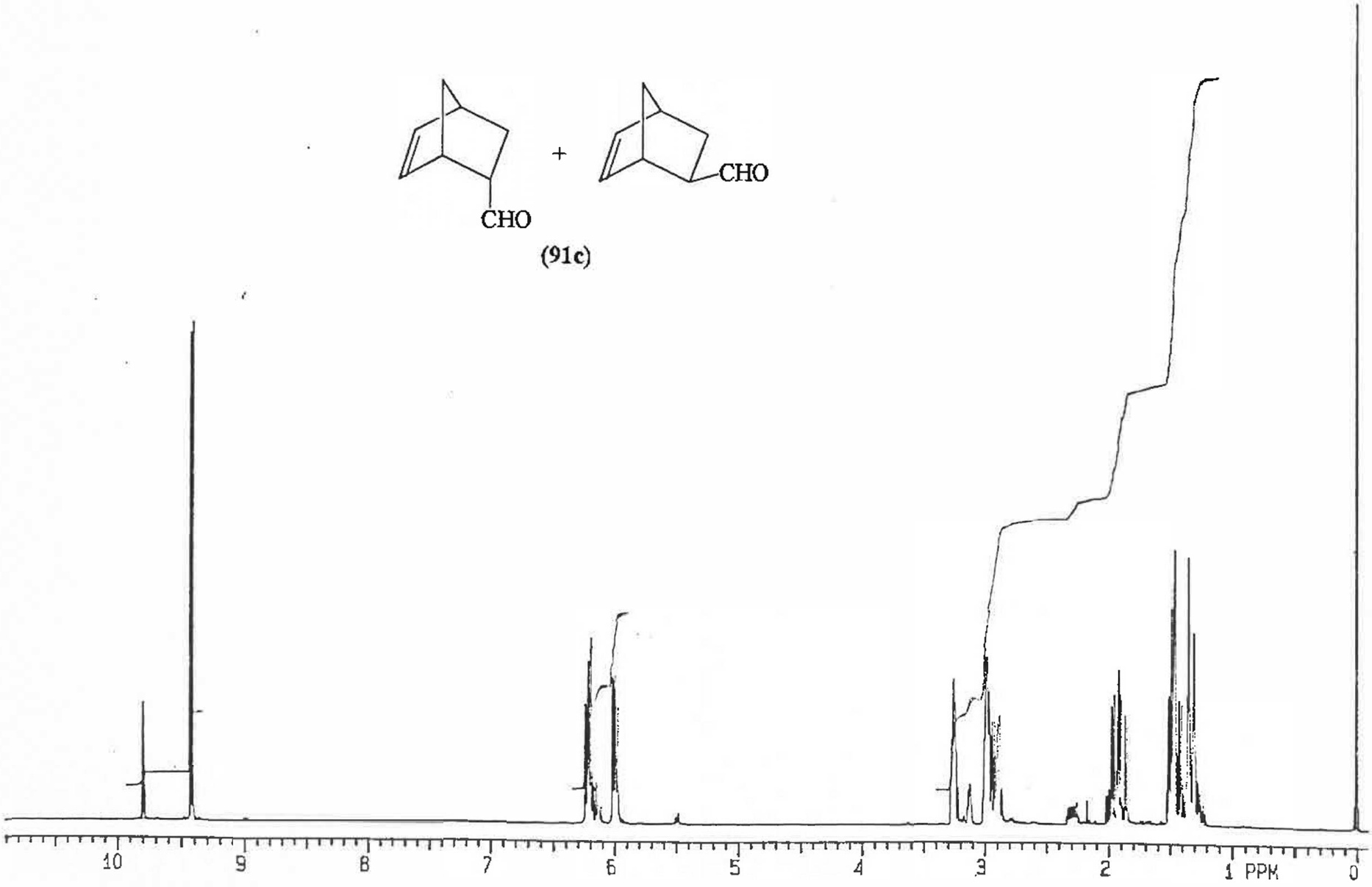


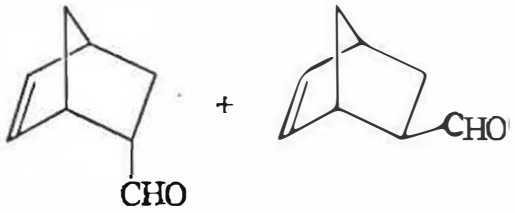


(91b)

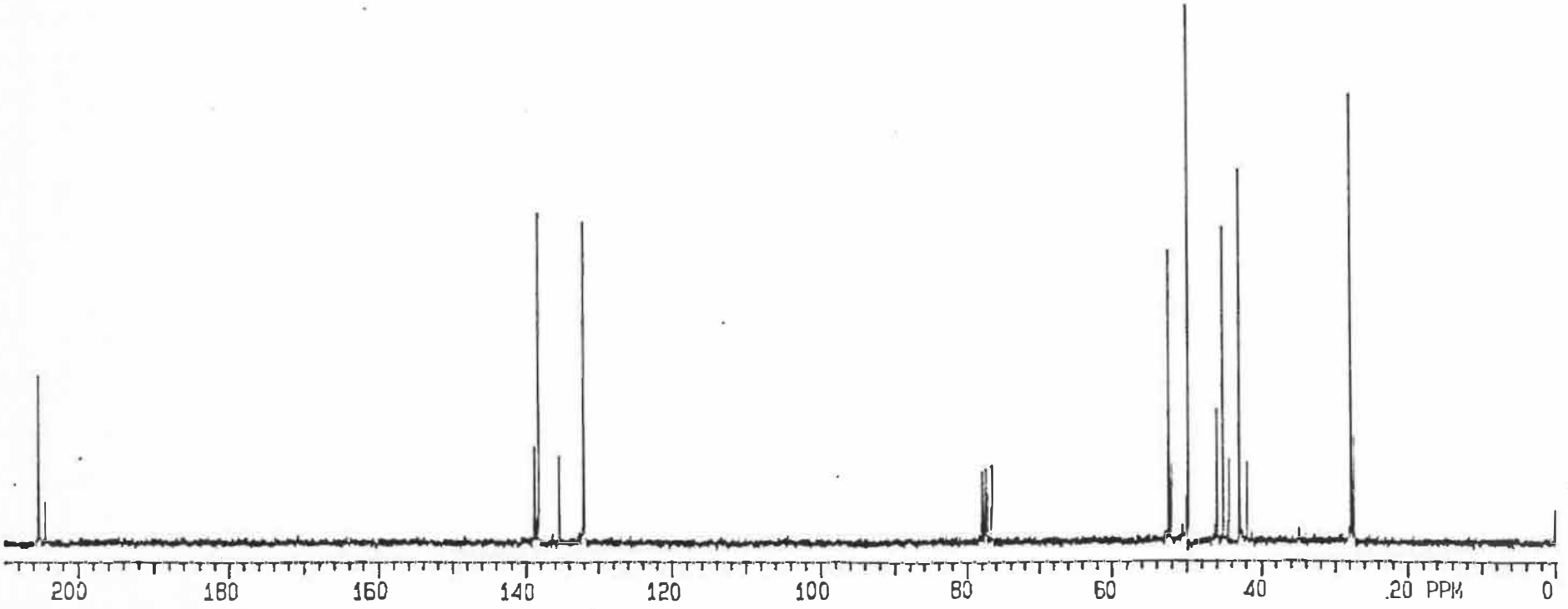


(91c)



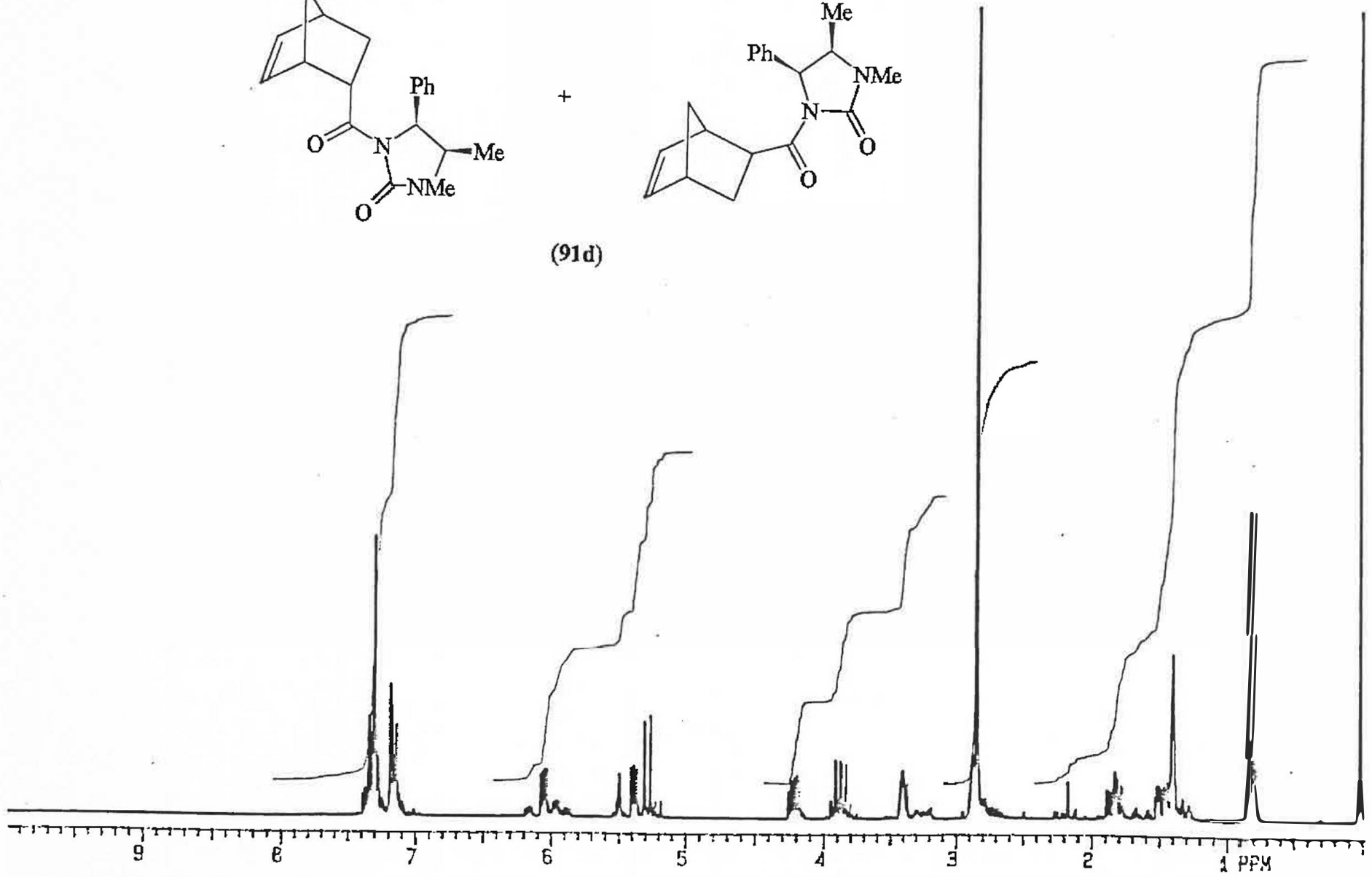


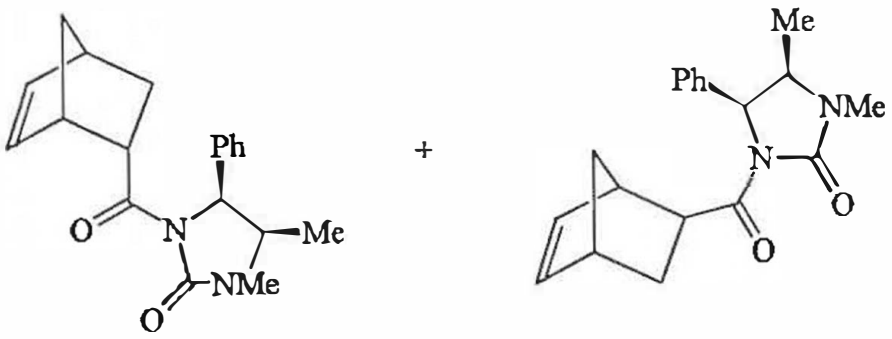
(91c)



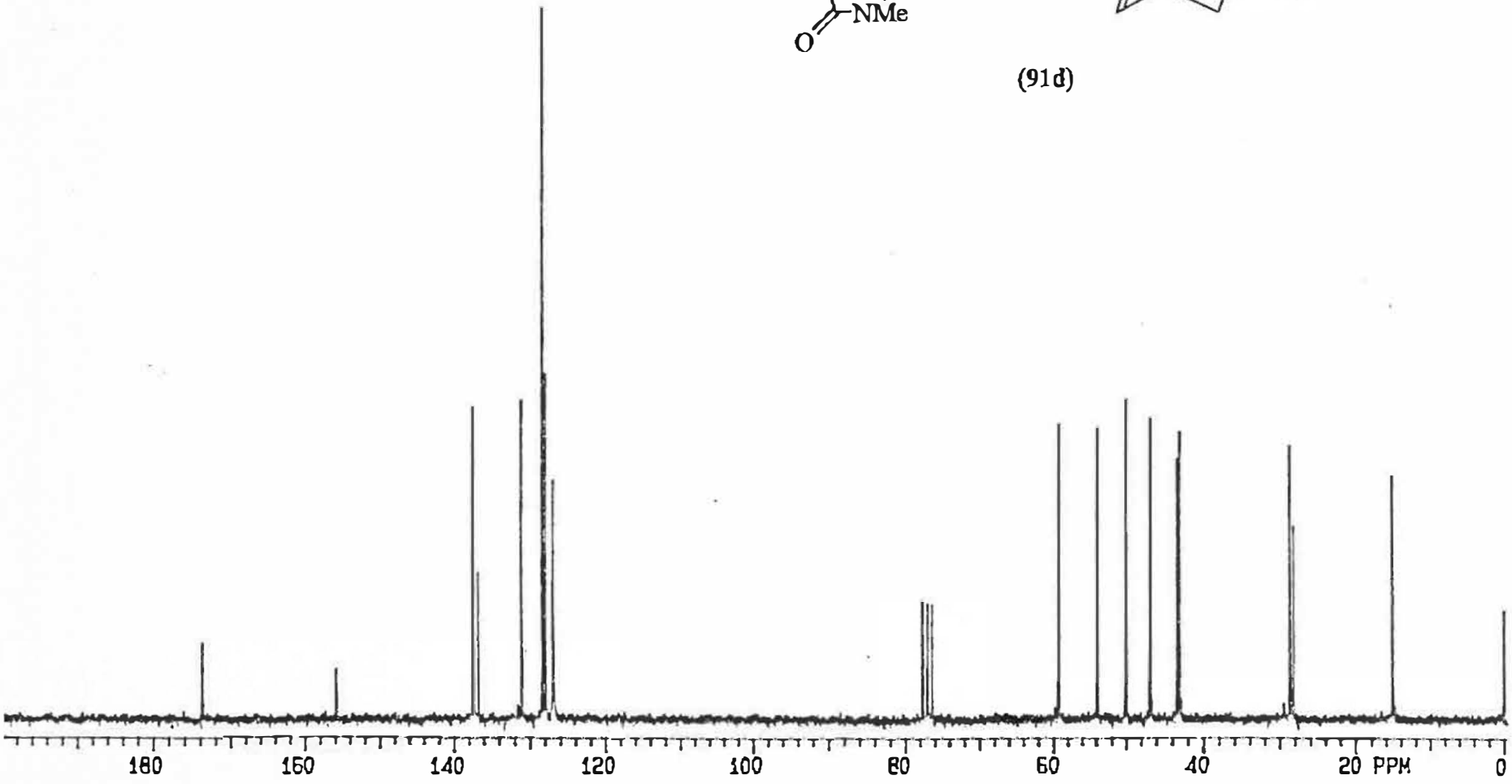
+

(91d)



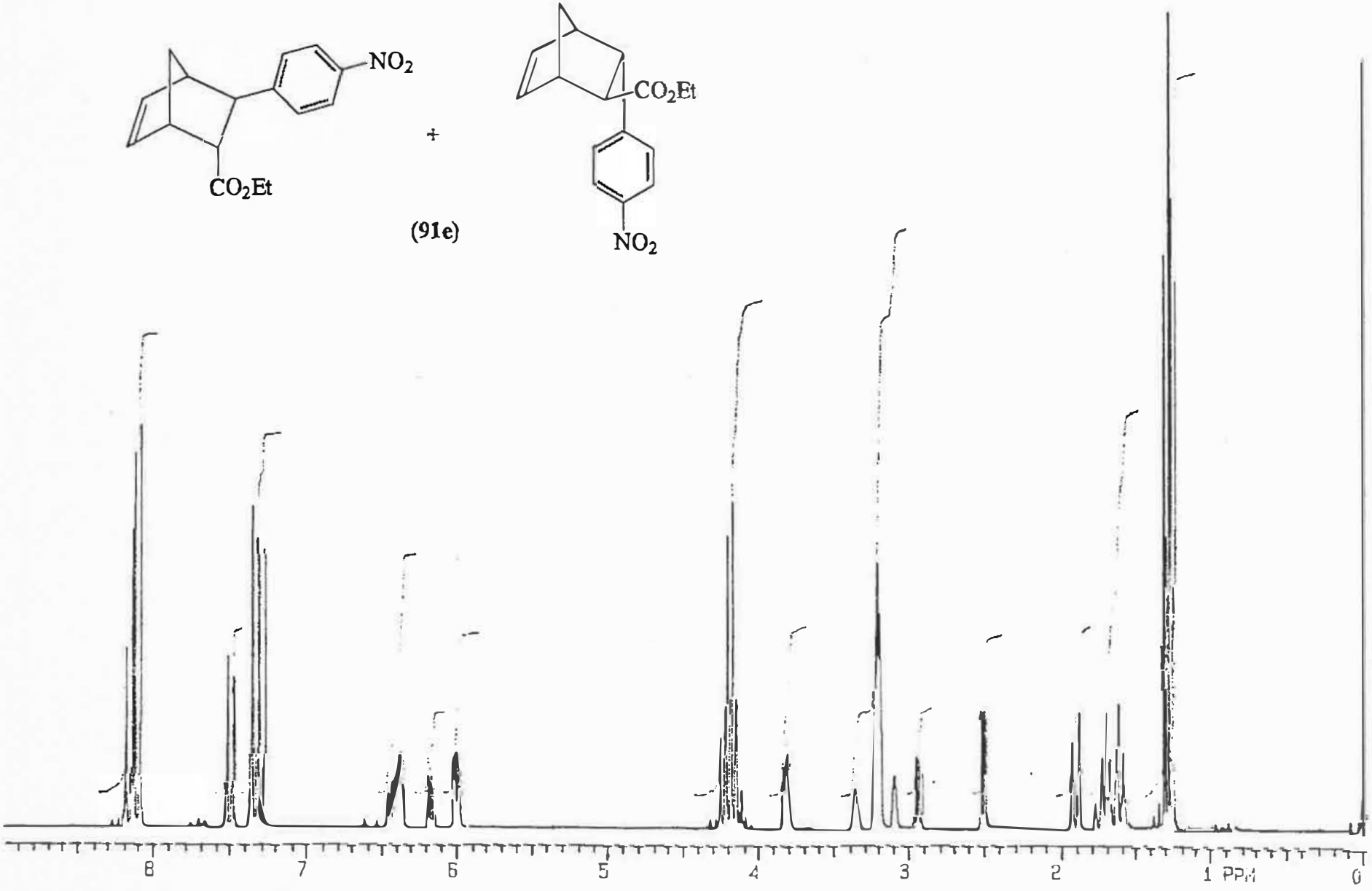


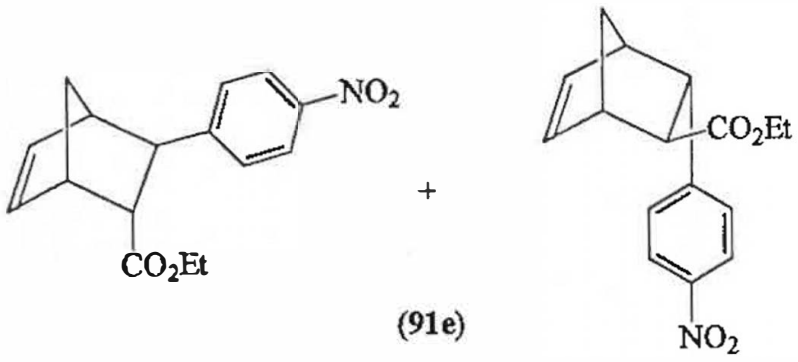
(91d)



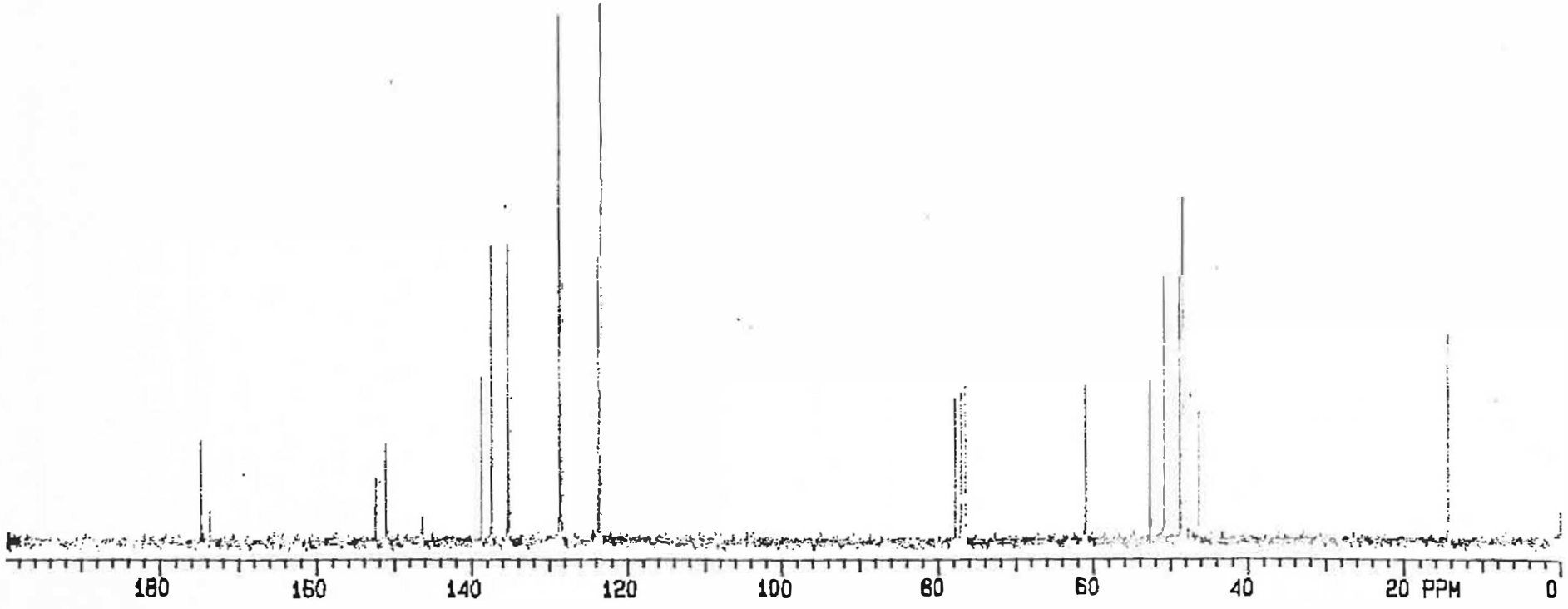
+

(91e)

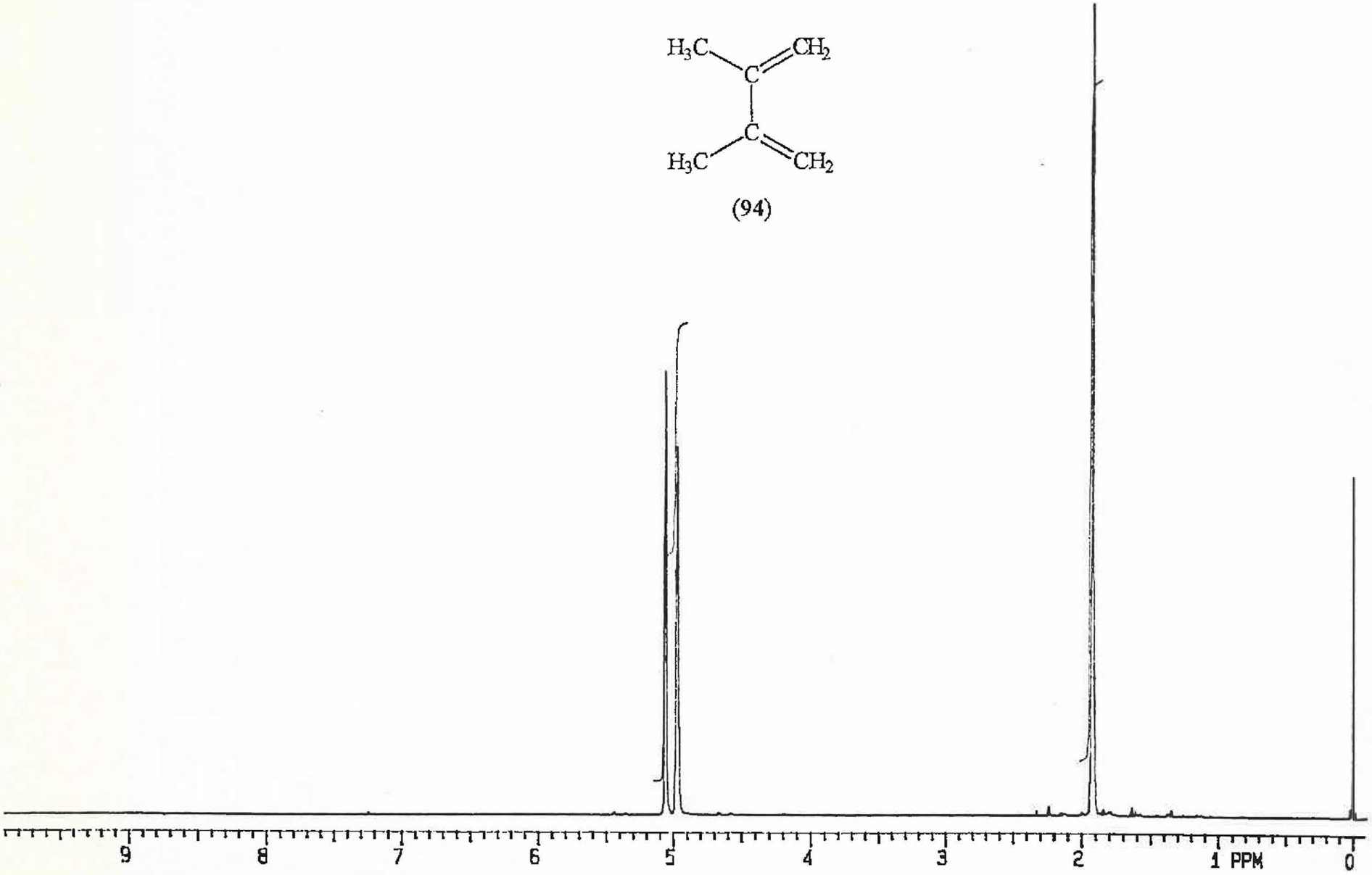


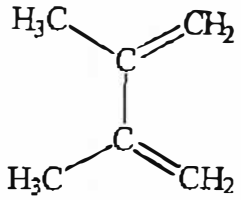


(91e)

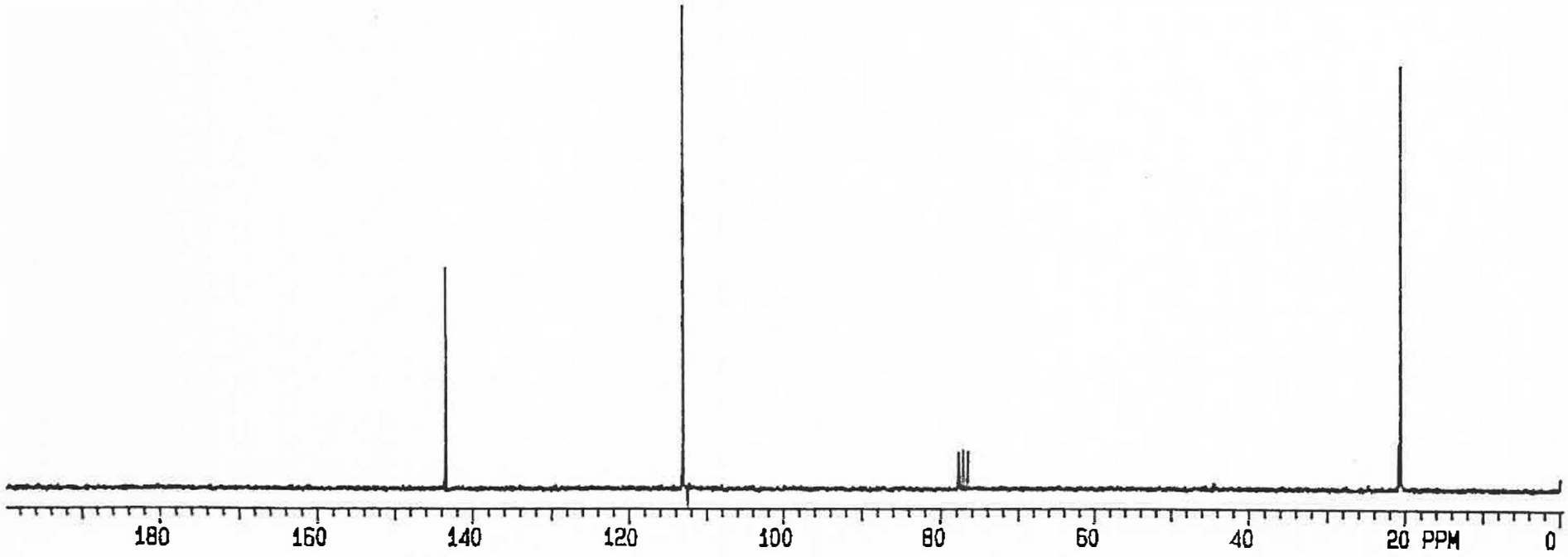


(94)

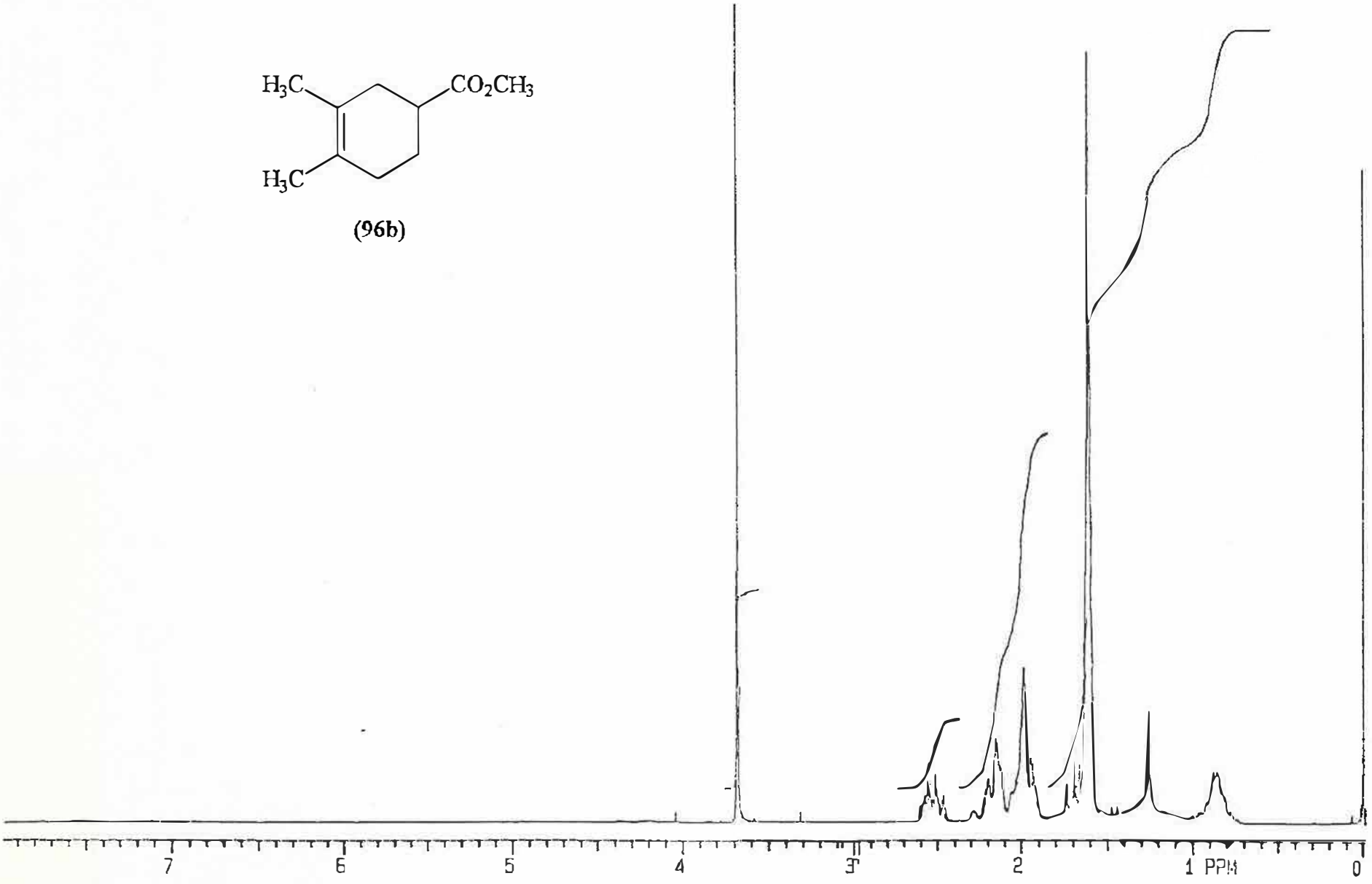


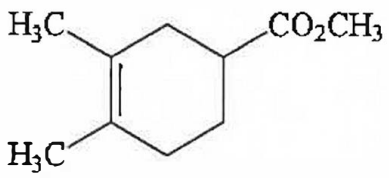


(94)

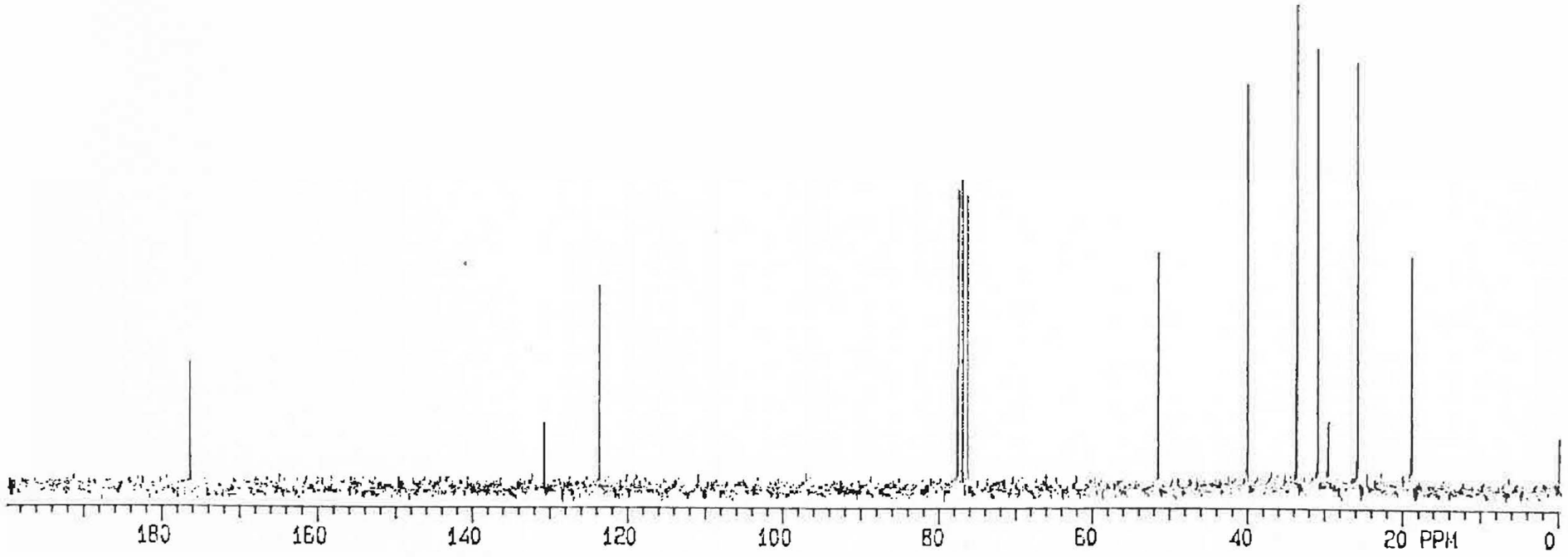


(96b)

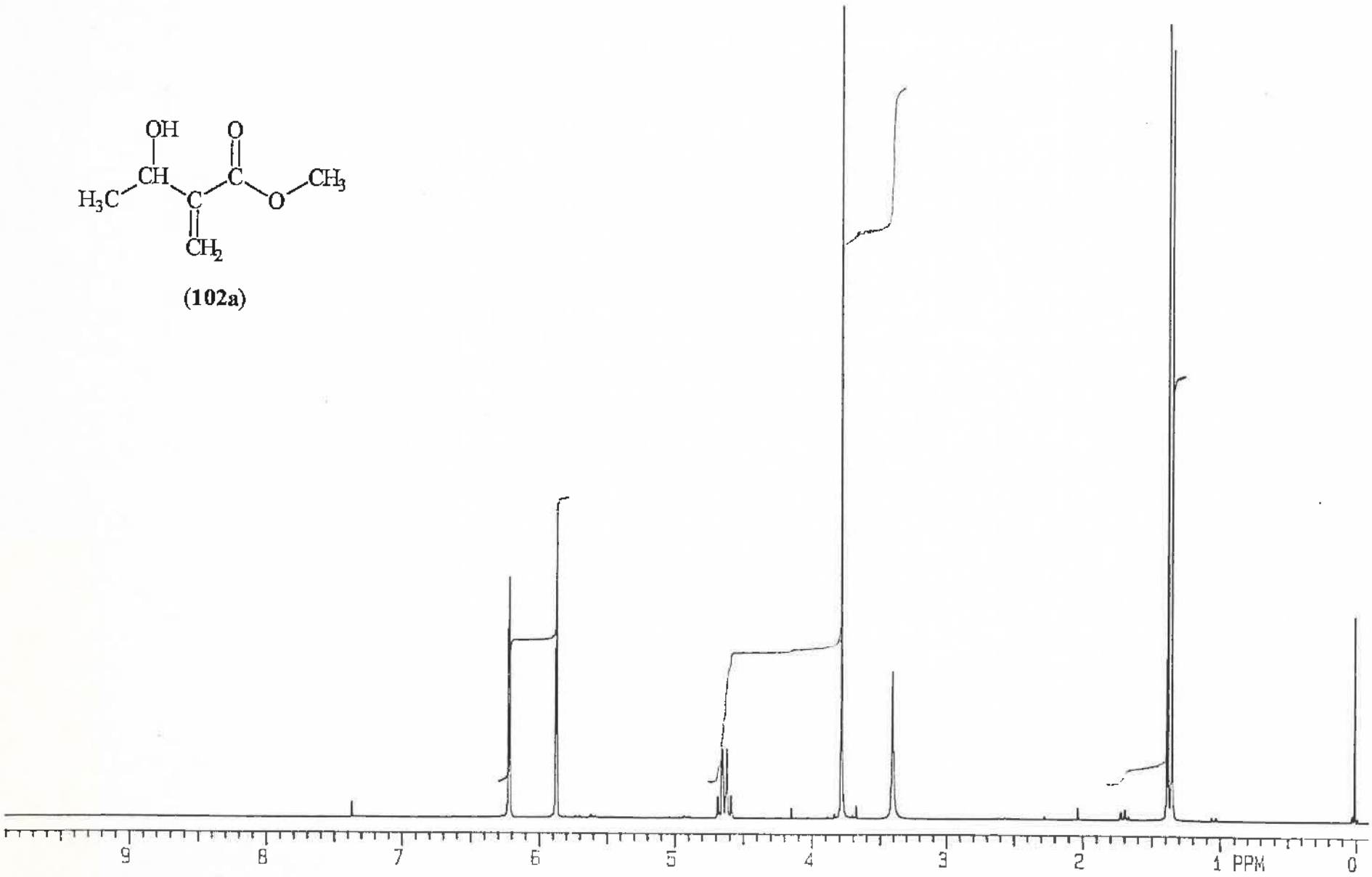


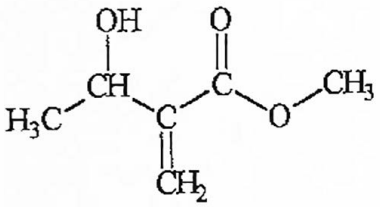


(96b)

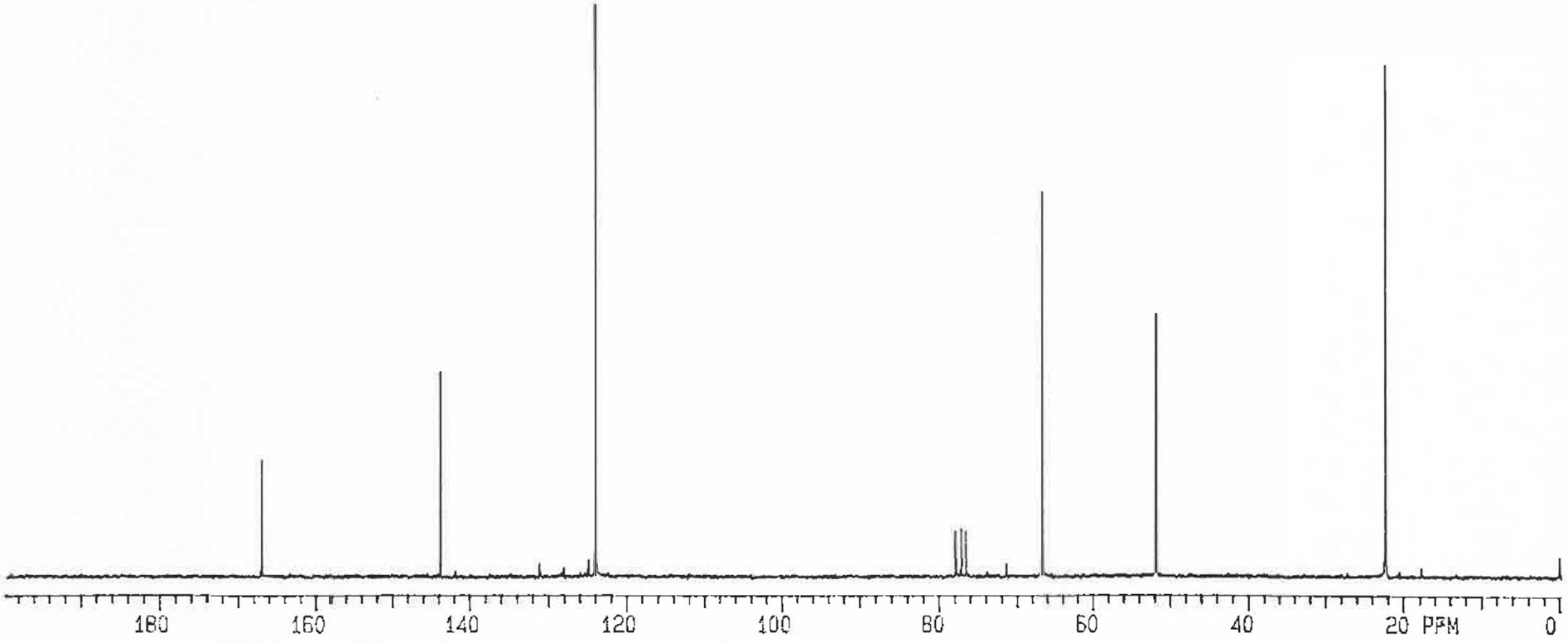


(102a)

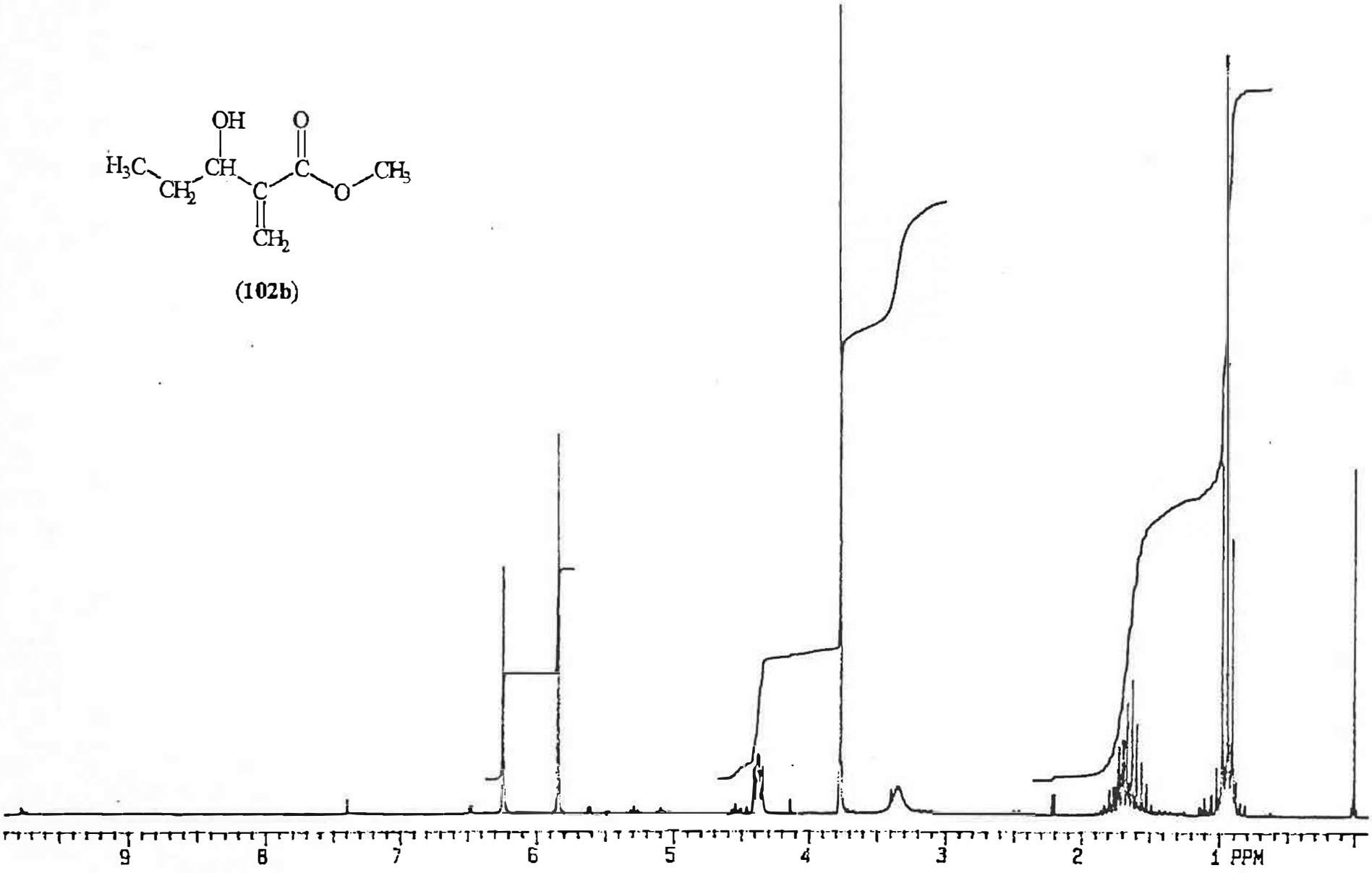


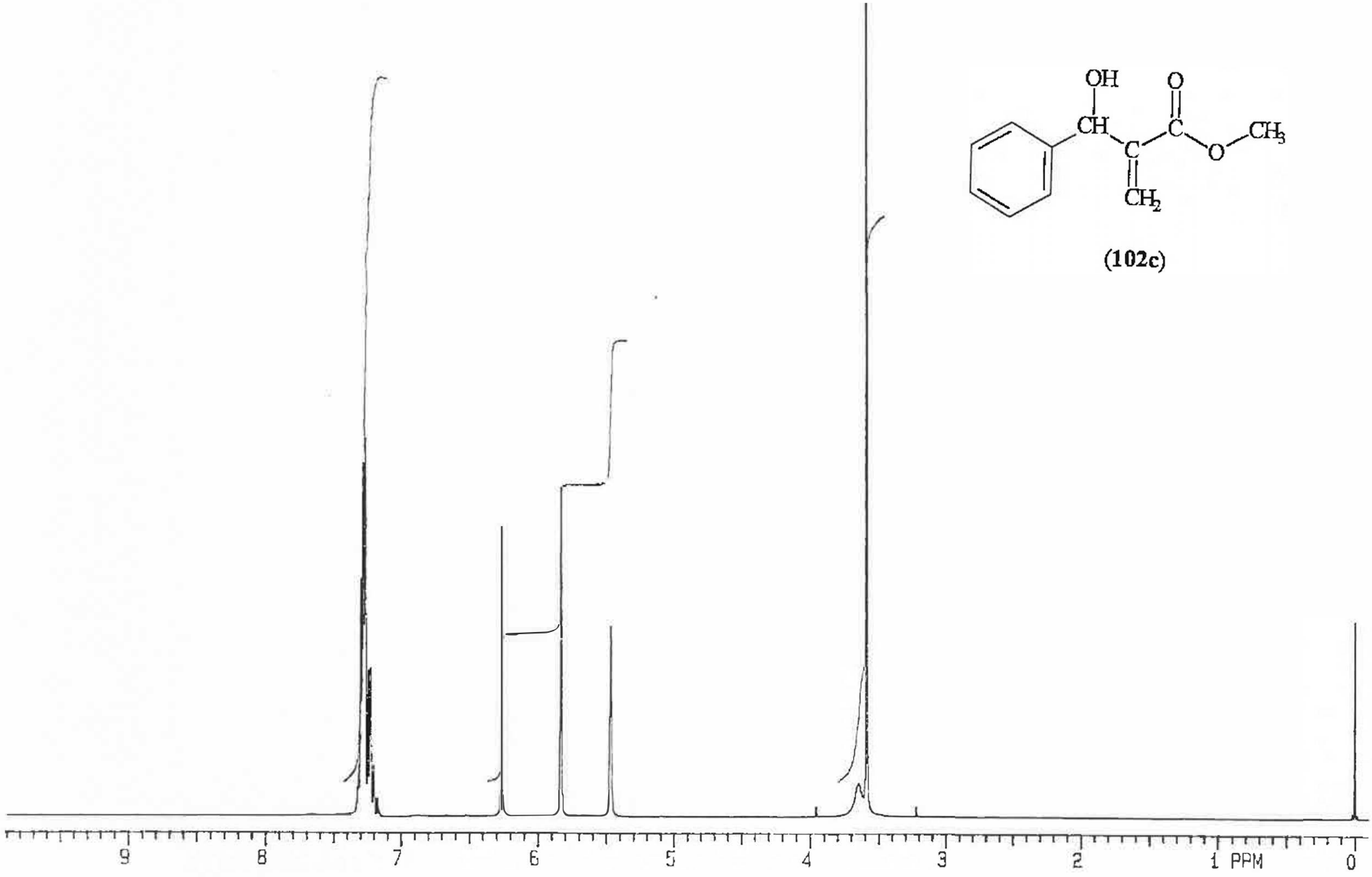


(102a)



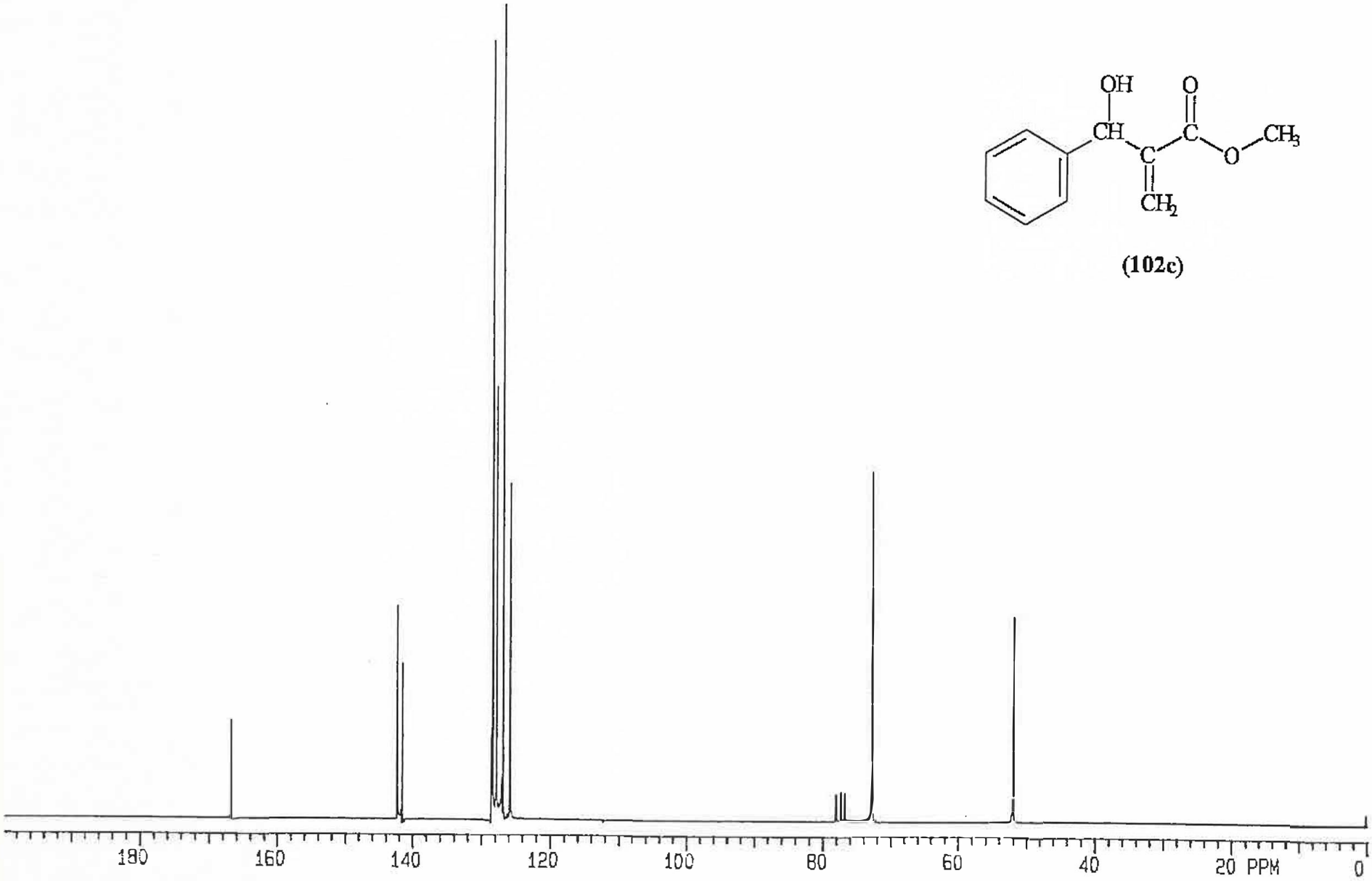
(102b)

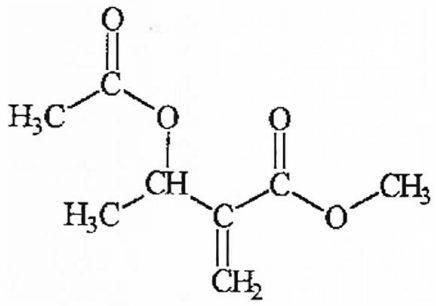




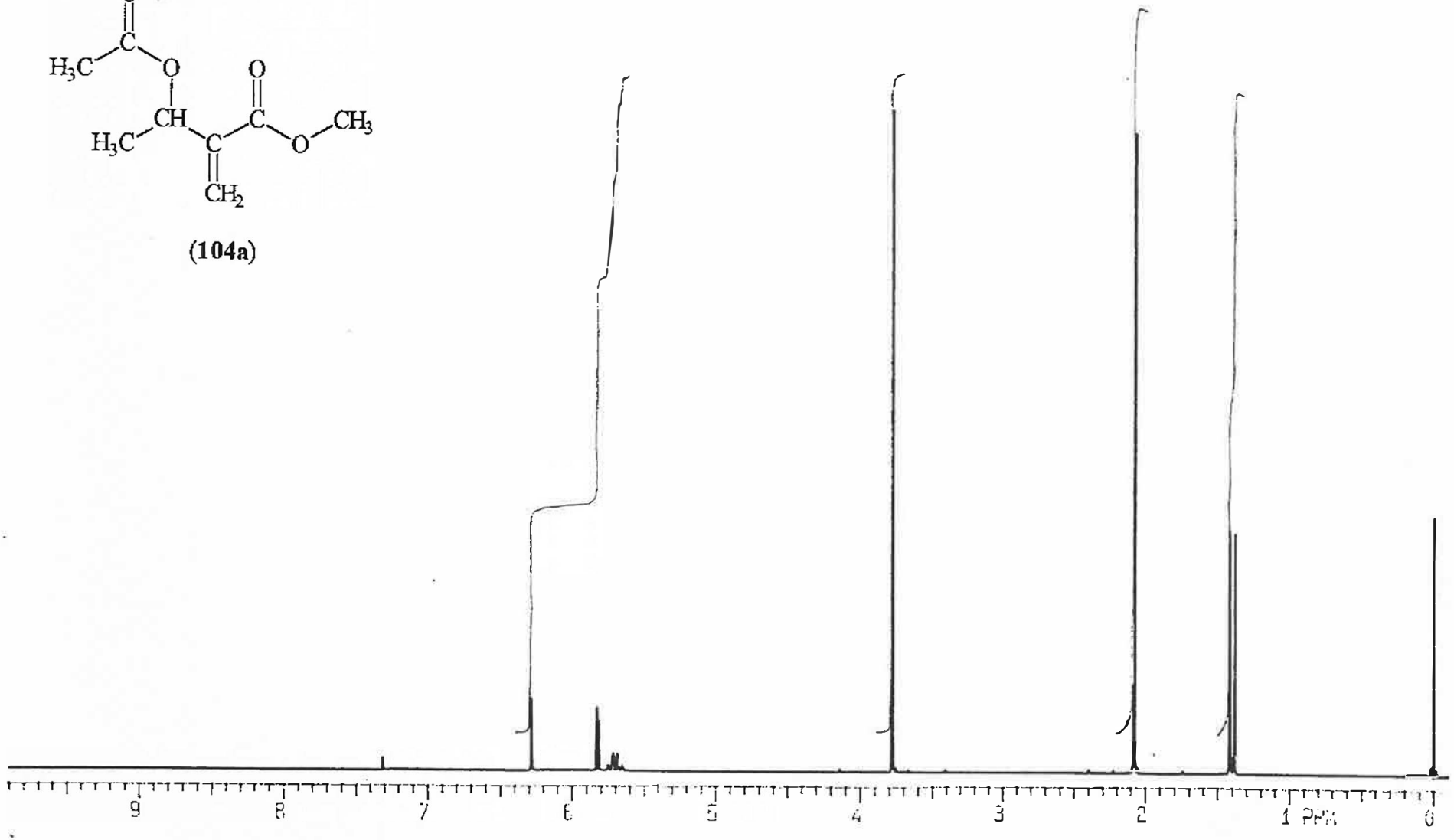
(102c)

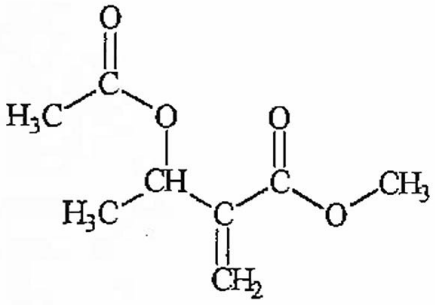
(102c)



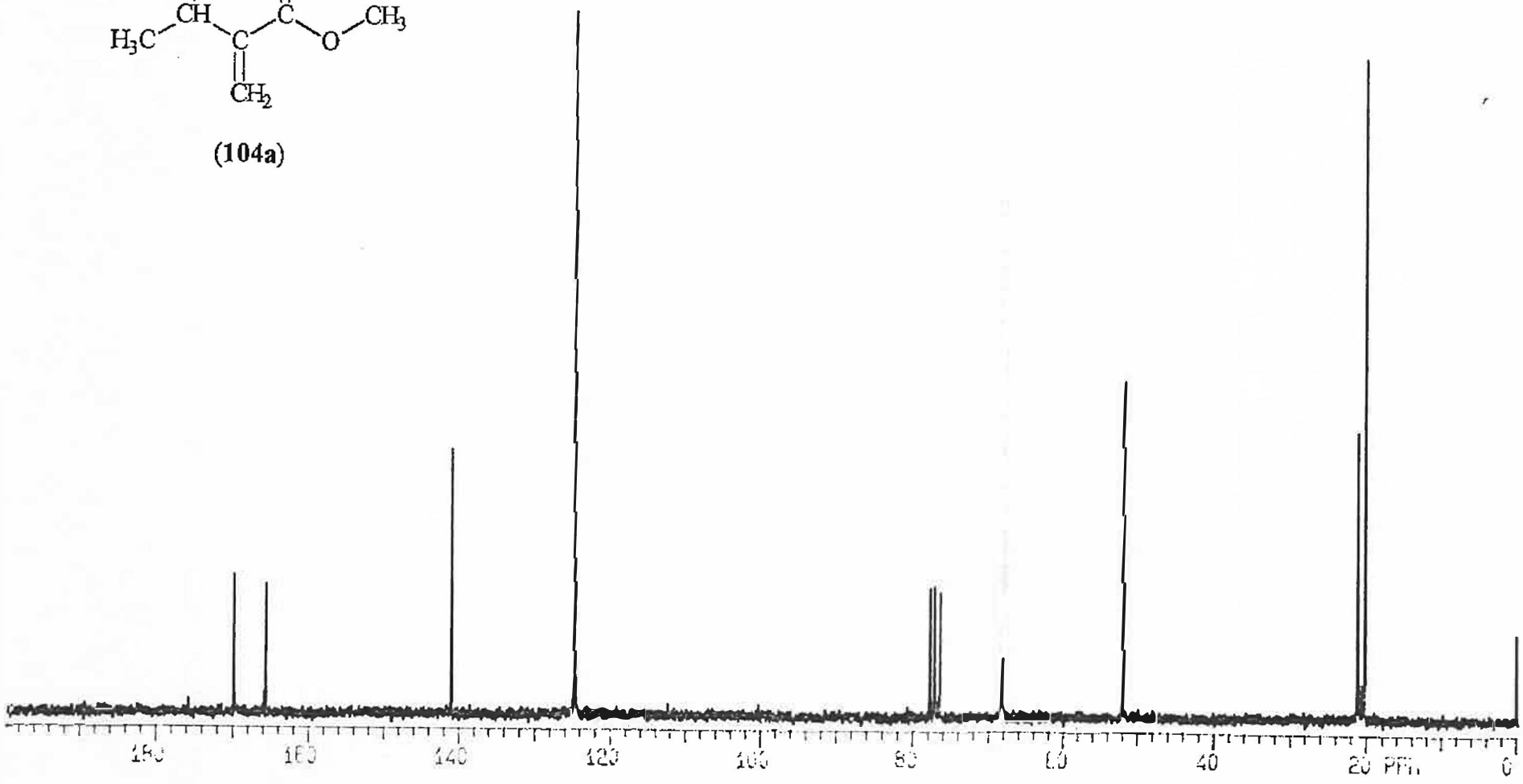


(104a)

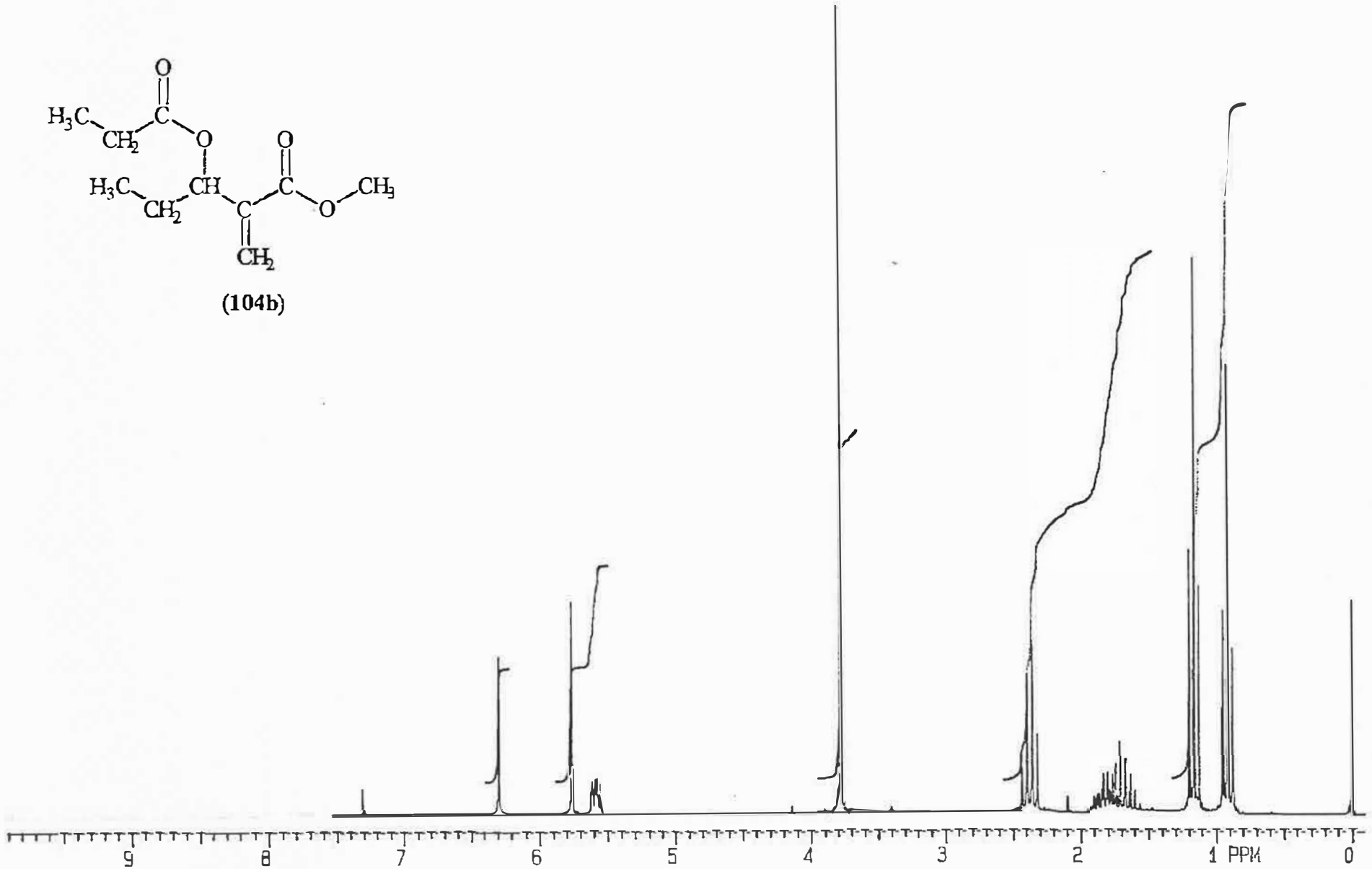


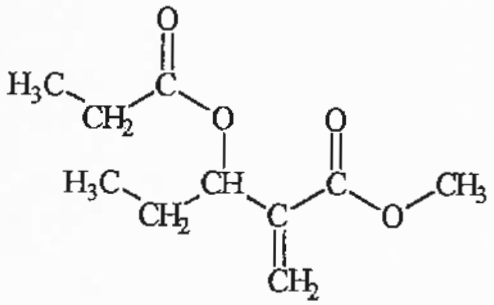


(104a)

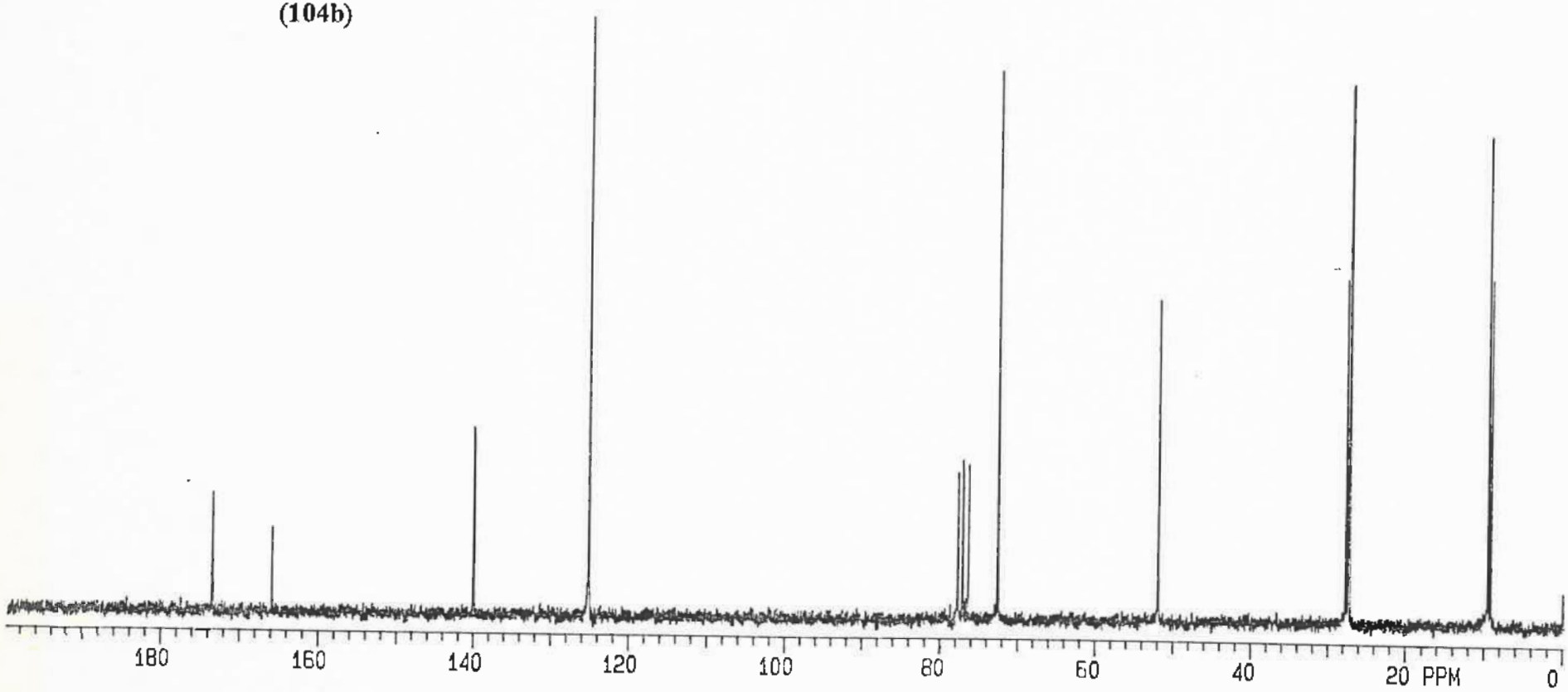


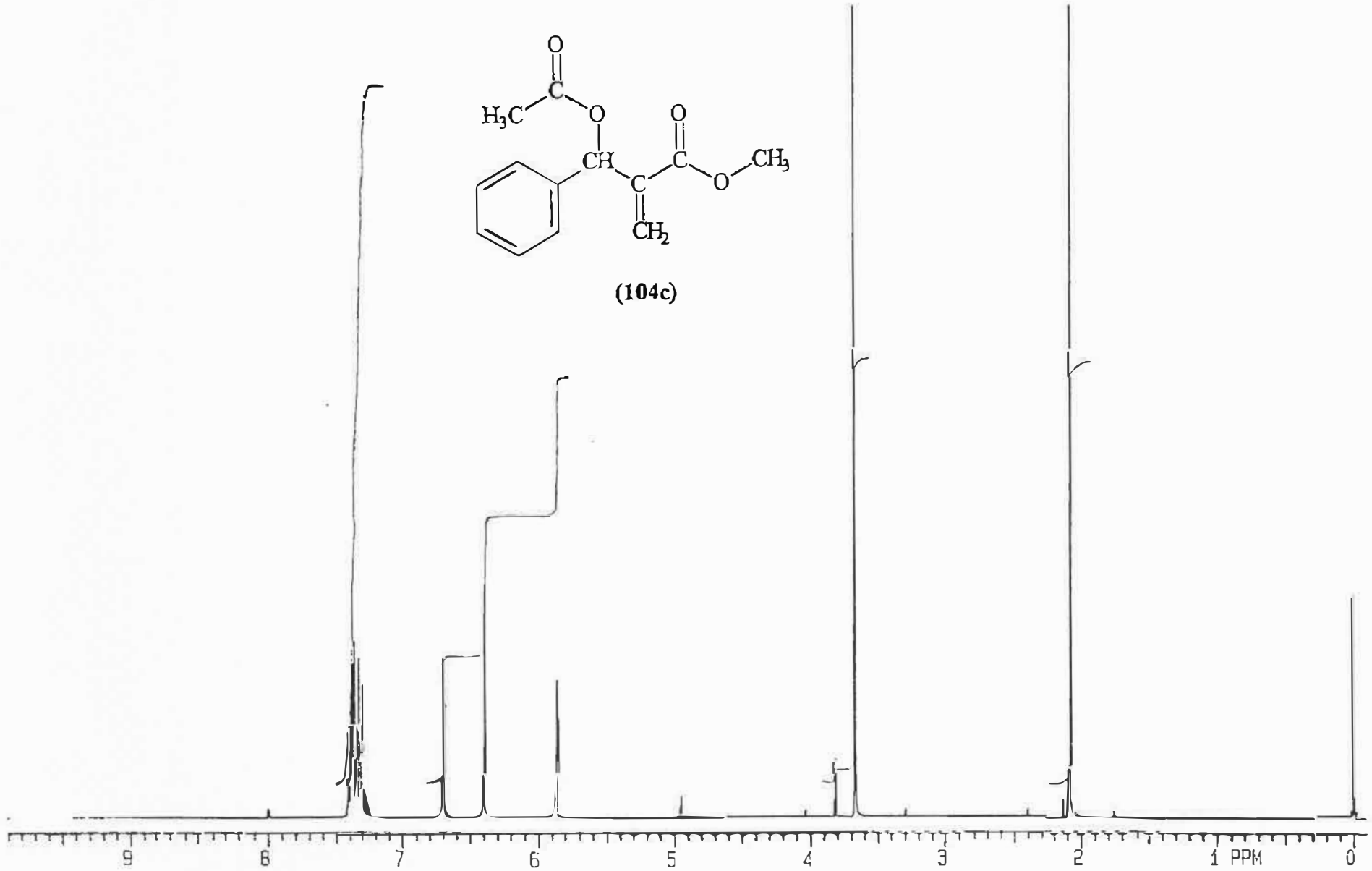
(104b)



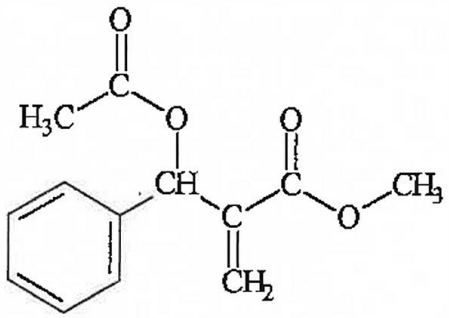


(104b)

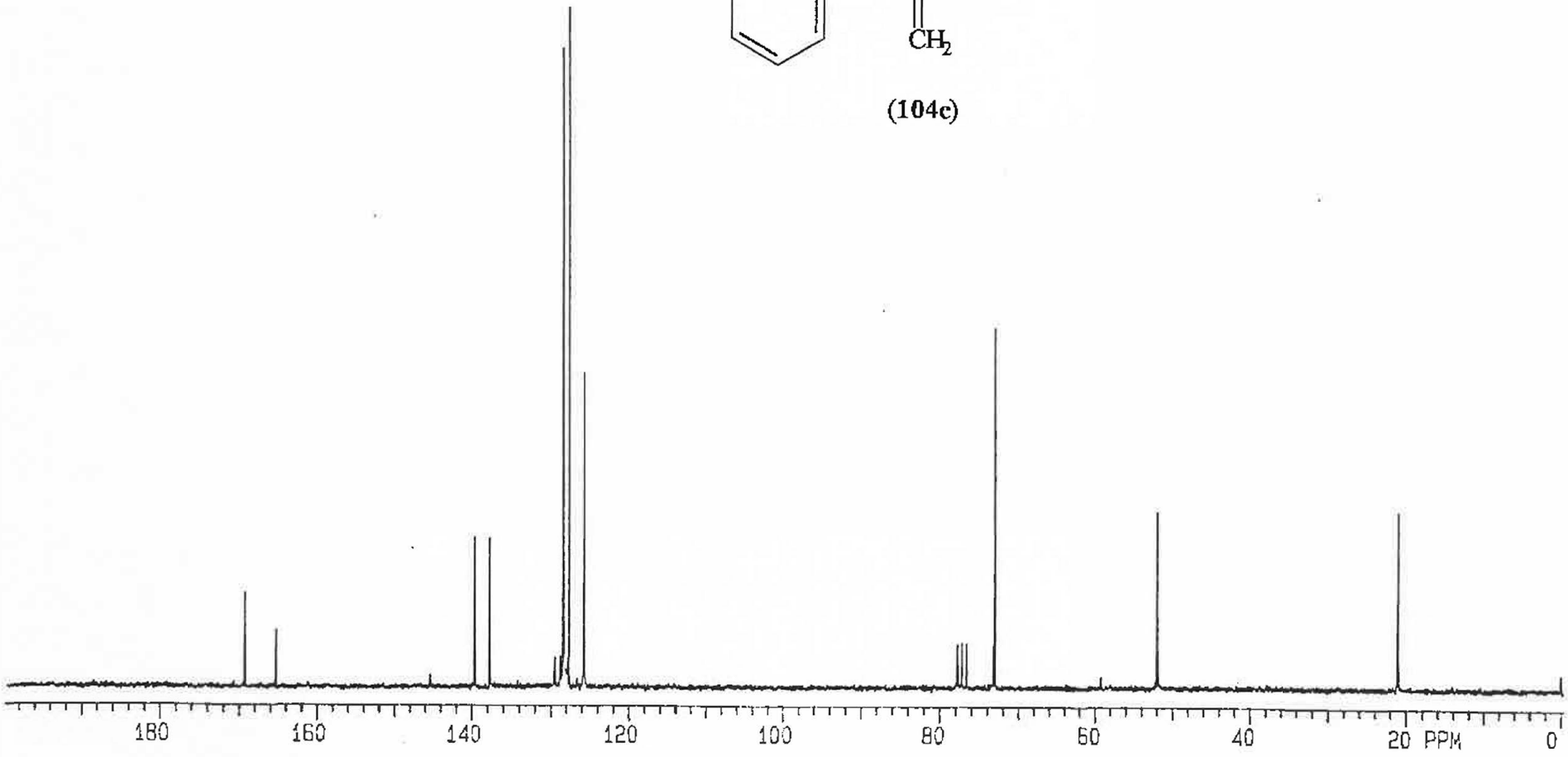




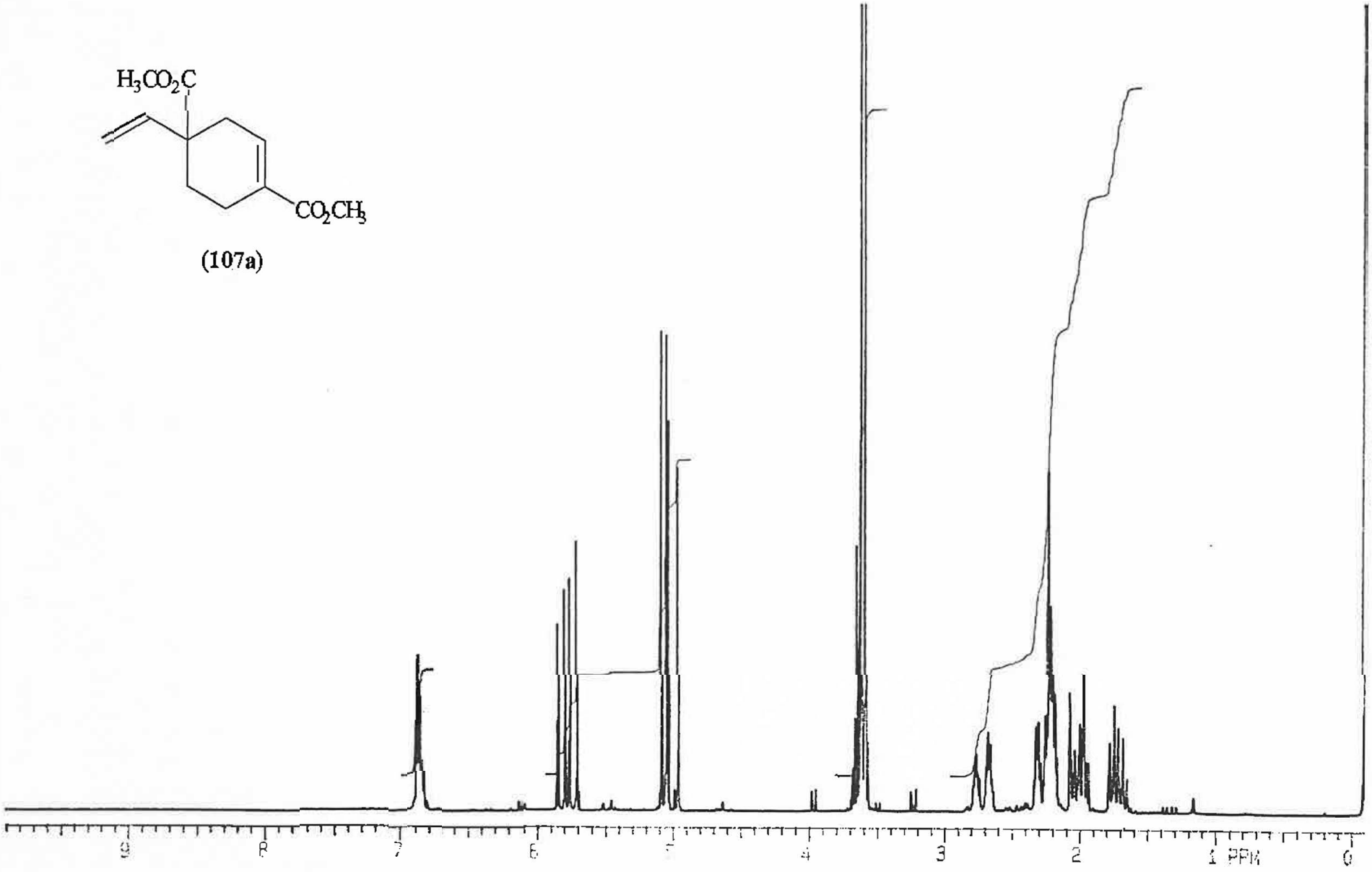
(104c)

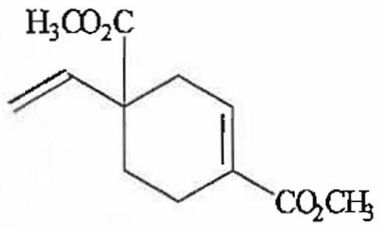


(104c)

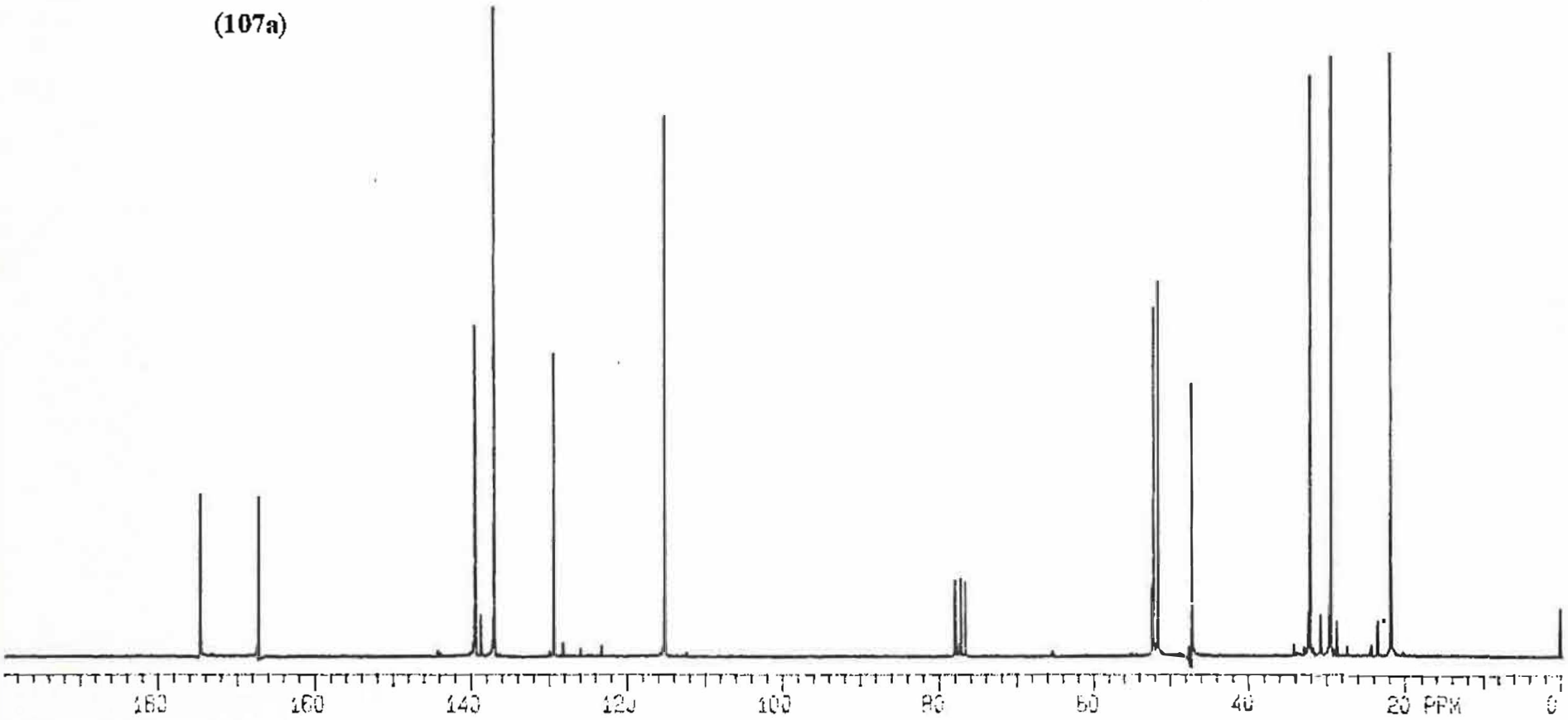


(107a)

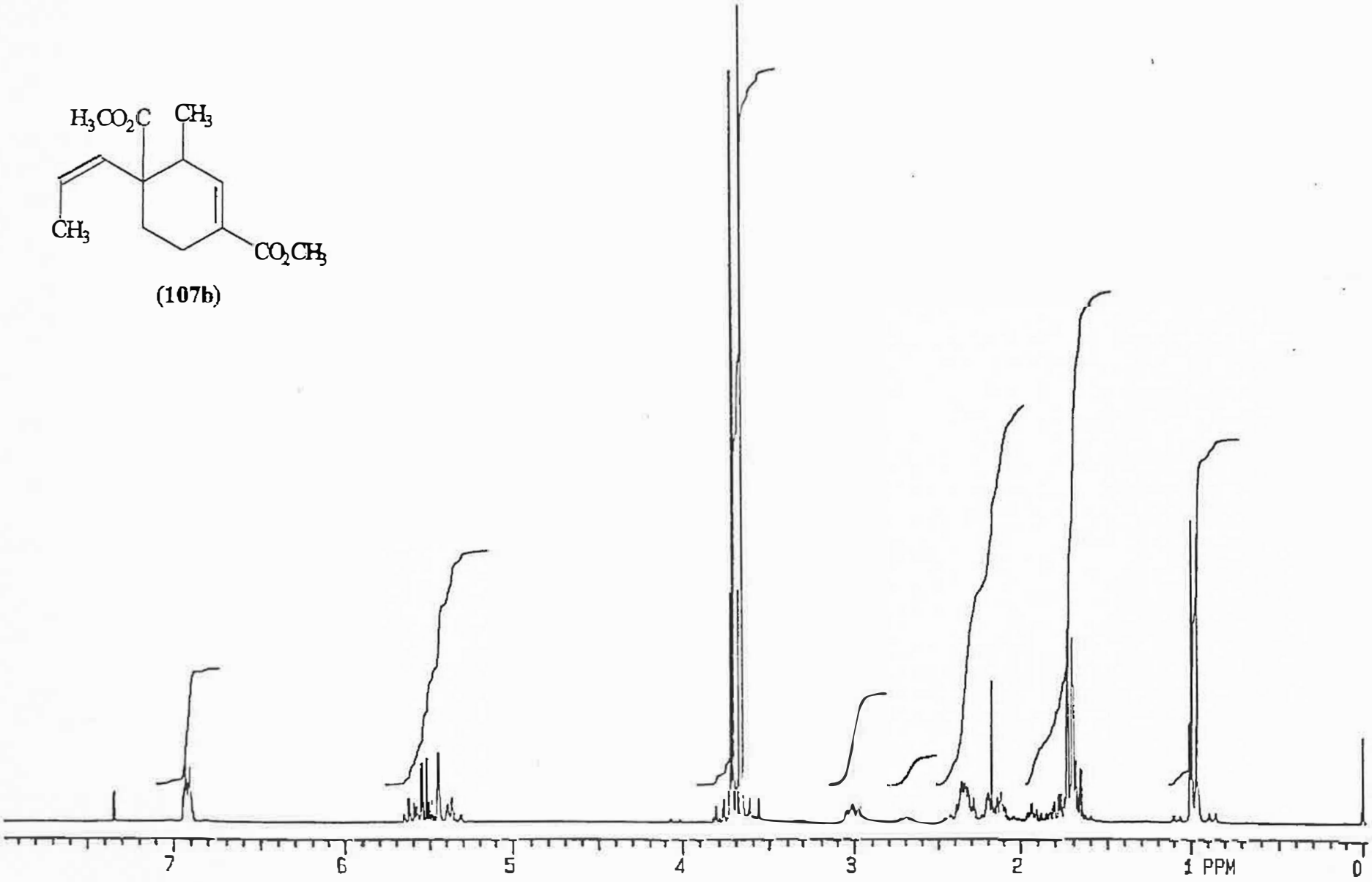


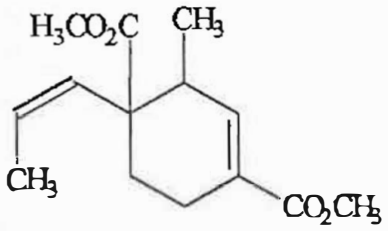


(107a)



(107b)





(107b)