STEREOCHEMICAL ASPECTS OF
THE BAYLIS-HILLMAN REACTION

by

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DECLARATION

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

Signed: ....

A. A. KHAN

I hereby certify that this statement is correct.

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ACKNOWLEDGEMENTS

ABBREVIATIONS

Ar	aryl
b.p.	boiling point
Bn	benzyl
BOC	^{t}butyloxycarbonyl
BQBR	N-benzyl quininium bromide
br	broad
Bu	butyl
CHP	cumyl hydroperoxide
CI	chemical ionisation
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,8-diazabicyclo[4.3.0]non-5-ene
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DET	diethyl tartrate
DIP	direct insertion probe
DIPAMP	(R,R)-1,2-bis[(2-methoxyphenyl)phenyl-phosphino]ethane
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
EI	electron impact
Et	ethyl
Et$_2$O	diethyl ether
EtOAc	ethyl acetate
EuFOD	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione
Eu(hfc)$_3$	tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium
HMPT	hexamethylphosphoric triamide
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MOM	methoxymethoxy

m.p.	melting point
NOE	nuclear overhauser effect
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
QDL	3-quinuclidinol
s	singlet
t	triplet
t	tertiary
TBHP	^{t}butyl hydroperoxide
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	tetramethylsilane
p-TsOH	p-toluenesulphonic acid

SUMMARY

The Baylis-Hillman reaction involves the coupling of an α,β-unsaturated system (i) (R = ester or related system) and an electrophile (ii) (usually an aldehyde, R_2 = H) in the presence of a catalyst to yield products of type (iii) (Equation 1). This investigation focused on methods of achieving chiral induction using this reaction. An alternative indirect procedure of producing (iii) was also investigated.

$$
\underset{(i)}{\overset{H}{\underset{R}{\diagdown}}} \quad + \quad \underset{(ii)}{\underset{R_2}{\overset{R_1}{\diagdown}}}{=}O \quad \xrightarrow{\text{catalyst}} \quad \underset{(iii)}{\overset{OH}{\underset{R}{\diagdown}}R_1 R_2}
$$
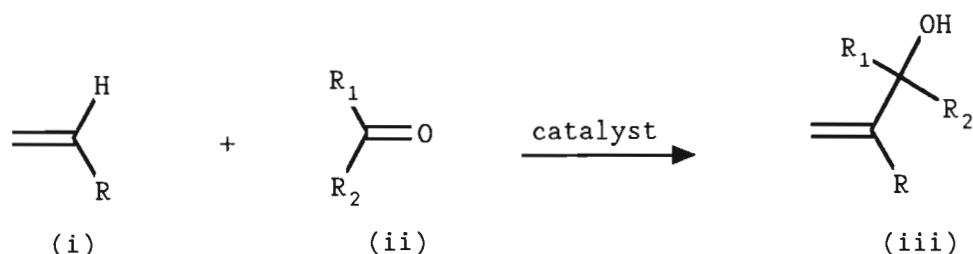
Equation 1.

Hydrolysis of the racemic product (iv) afforded the corresponding acid (v) which could be resolved. The laevorotatory enantiomer of (v) was established to have the 3R configuration by x-ray crystallography and by chemical interconversion. Both the methyl and ^{t}butyl esters of (v) were also laevorotatory for the 3R configuration.

Reaction of (+)-pantolactone acrylate (vi) with aliphatic aldehydes did not afford the expected products, but instead, 2,6-disubstituted-5-methylene-1,3-dioxan-4-ones (vii) were obtained via a novel cyclisation. The cyclisation is highly diastereoselective (>78% de) and NOE experiments showed that the substituents at the 2 and 6 positions adopt a cis configuration.

Aldehydes bearing electron-withdrawing groups did not afford the corresponding dioxanones (vii). The cyclisation appears to be dependent on the nucleophilicity of the resulting oxyanion which in turn depends on the inductive effects that operate.

Several features of dioxanones (vii) were uncovered:

(a)   Reaction of (vi) with one equivalent of an aldehyde
      followed by reaction with another aldehyde afforded
      "mixed" dioxanones (viii) ($R_1 \neq R_2$).
(b)   Unusual results were obtained when dioxanones (vii) were
      hydrogenated. Instead of obtaining the saturated products
      (ix), only the isomerised products (x) were formed
      quantitatively.
(c)   Dioxanones (vii) were relatively stable to acid hydrolysis.
      However, under reflux conditions in acidic medium, they
      were successfully hydrolysed to the corresponding acids
      (xi).

Chiral esters such as the 8-phenylmenthyl acrylate derivative
(xii) and its cyclohexyl analogue (xiii) were also employed as
chiral auxiliaries. The former proved to be the more successful
reagent and afforded diastereoselectivities varying from low (2%
for acetaldehyde) to moderate (70% for trichloroacetaldehyde).

Induction of chirality *via* the readily accessible amino aldehyde
(xiv) prompted the synthesis of sphingosine analogues using the
Baylis-Hillman reaction. Chemical yields were good but it was
not possible to prevent racemisation under the extended reaction
times.

An alternative procedure for producing products of type (iii)
involves 1,4-addition of secondary amines and an aldol reaction
of the resulting β-amino ester. Oxidative elimination of the
amine unmasks the substituted acrylic ester. Three chiral
secondary amines (xv)-(xvii) were used for the dual purpose of
acting as N-containing masking groups and as chiral
auxiliaries. The products were obtained with poor to good
enantioselection (0-58% ee).

The crotonate system only reacts in the Baylis-Hillman reaction

under extreme conditions (2-10kbar). Extension of the chiral masking method to the crotonate system afforded diastereomers which were separated. Reaction of each diastereomer separately with aromatic aldehydes afforded the products with fair to good enantioselectivities (10-56%). In all cases the products were obtained with high selectivity (>90%) towards the E-isomer.

During the course of these investigations a novel rearrangement was uncovered. When pantolactone propanoate (xviii) was allowed to react with benzaldehyde, the novel furopyranone (xix) was produced. This results from an interesting example of a tertiary ketol rearrangement.
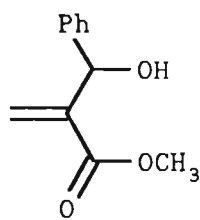
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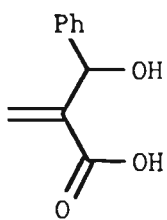
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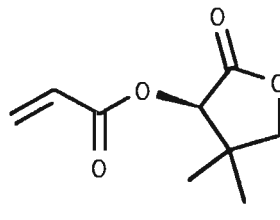
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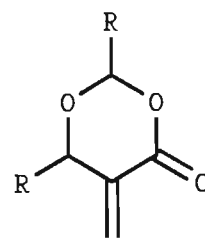
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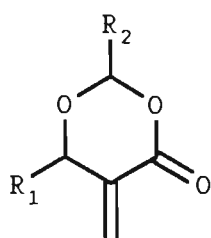
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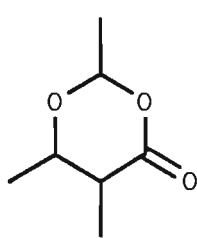
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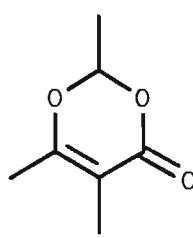
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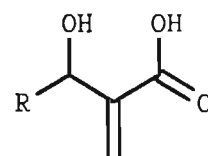
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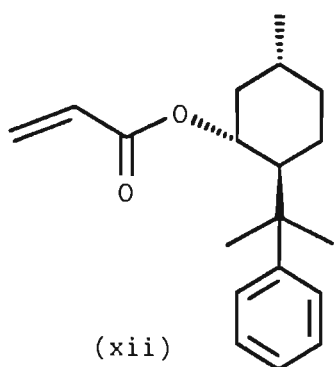
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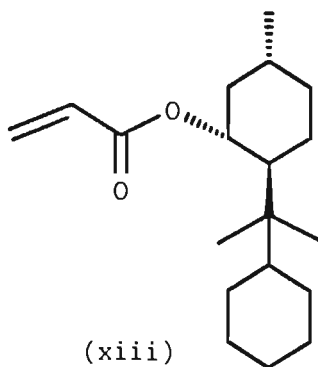
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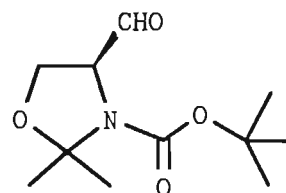
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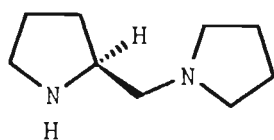
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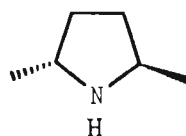
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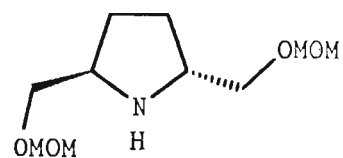
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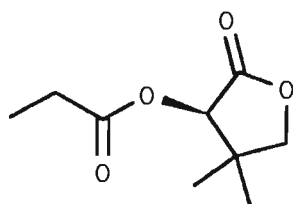
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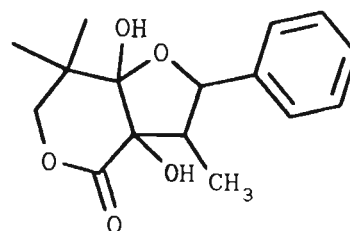
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LIST OF PUBLICATIONS WHICH HAVE
APPEARED FROM THIS THESIS

1. S. E. Drewes, N. D. Emslie, N. Karodia and A. A. Khan, *Chem. Ber.*, 1990, **123**, 1447.

2. M. Brand, S. E. Drewes, N. D. Emslie and A. A. Khan, *Synth. Commun.*, 1991, **21**, 727.

3. S. E. Drewes, N. D. Emslie, J. S. Field, A. A. Khan and N. Ramesar, *Tetrahedron Asymm.*, 1992, **3**, 255.

4. S. E. Drewes, A. A. Khan and K. Rowland, *Synth. Commun.*, 1992, **22**, in press.

1. INTRODUCTION.

The concept of stereochemical control in organic chemistry is the primary focus of activity for many of the leading researchers in both the academic and industrial communities. In recent years, interest in the synthesis of pure enantiomers has gained new impetus as a result of the increasing awareness of the importance of optical purity in the context of biological activity.[1] Many of the biologically active compounds have one or more chiral centres, the specific activity being related to only one stereoisomer, for example, (R,R)-Chloramphenicol (1) is a known antibacterial agent while the (S,S)-stereoisomer is inactive. Thus, enantioselective synthesis, which leads to commercially useful compounds, is an important task facing the synthetic chemist.[2,3]

$$O_2N-\langle\rangle-CH(OH)-CH(NHCOCHCl_2)-CH_2OH$$
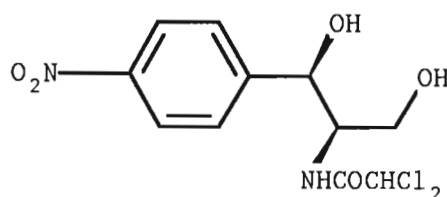
(1)

Asymmetric synthesis has been known for over eighty years. Morrison and Mosher[4] describe an asymmetric synthesis as a reaction in which "an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts." Since this excellent monograph by Morrison and Mosher,[4] many reviews have been published on asymmetric synthesis,[1,5-9] highlighting the tremendous progress made in this area.

The basis of synthetic routes to enantiomerically pure compounds involves the two major classes of stereoselectivity:[9]

(a) producing one enantiomer in preference to another, that is

enantioselectivity; and

(b) producing one diastereomer rather than another, that is diastereoselectivity.

The criteria for a good asymmetric synthesis have been described as follows:[10,11]

(a) It must lead to the desired enantiomer in high optical as well as chemical yield.

(b) The chiral product must be readily separable from the chiral auxiliary.

(c) The chiral auxiliary should be readily available, and unless it is very much cheaper than the desired product, it must be capable of being recovered in good yield and undiminished optical purity.

(d) It should be possible to synthesise both enantiomers of the product selectively.

Besides asymmetric synthesis, three other common strategies for the synthesis of homochiral compounds exist:

(1) RESOLUTION.[12-15] This involves the use of a naturally occurring homochiral compound to convert a racemic mixture into a mixture of diastereomers with different physical and/or chemical properties which may then be separated.

(2) HOMOCHIRAL REACTANTS.[16-18] The "chiral pool" denotes the abundant natural availability of homochiral compounds and avoids any problem of resolution and asymmetric induction. There are many syntheses in which the asymmetric centres in an enantiomerically pure product have been derived from the "chiral pool."

(3) ENZYMES.[19-22] These catalytic proteins that control the rates of most biological reactions under very mild conditions and often with complete stereochemical control are being widely used in the synthesis of homochiral compounds.

1.1. ACRYLATE AND RELATED SYSTEMS.

In a recent review, Yu and Helquist[23] have demonstrated that the acrylate unit and related groups are found as structural features of a very large number of naturally occurring compounds, many of which possess useful biological activity.[24] Included among these compounds are various classes of unsaturated carboxylic acids, esters, lactones and lactams. The most commonly occurring acrylate derivatives are the α-methylene lactones to which much research has been devoted as a result of their cytotoxicity and tumour-inhibitory properties. These compounds may be simple, for example tulipalin A (2),[25] or more complex, for example vernolepin (3).[26]
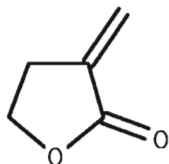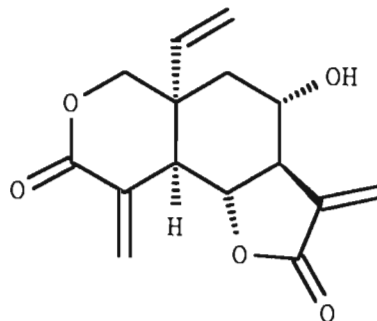
(2)   (3)

Other important compounds possessing the acrylate or related unit include: conocandin (4)[27] (a fungistatic antibiotic), the sesquiterpene gerin (5)[28] (which causes contact dermatitis in humans) and the tremetone derivative (6).[29]
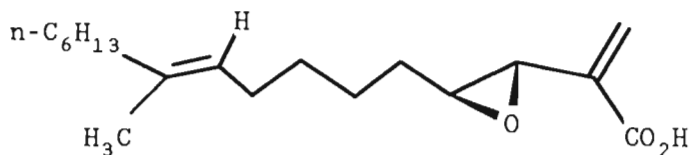
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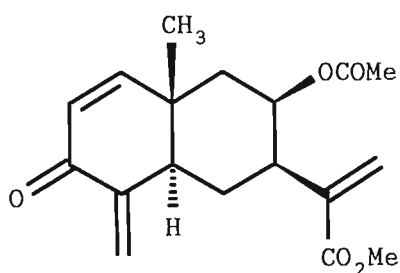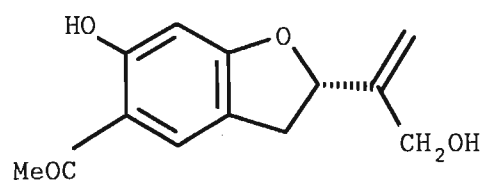
(5)   (6)

Acrylate systems also possess acceptor and dienophile properties which make them valuable intermediates in the construction of complex molecules.

1.2. METHODS FOR THE SYNTHESIS OF ACRYLATE SYSTEMS.

The most obvious method for the synthesis of α-substituted acrylates (9) is an aldol condensation of an α-unsubstituted acrylic system (7) with an electrophile (8) (Scheme 1). This may be achieved by:

(1)   a direct procedure involving a formal vinyl carbanion or
(2)   by making use of an acrylate anion equivalent.

(7)   (8)   (9)
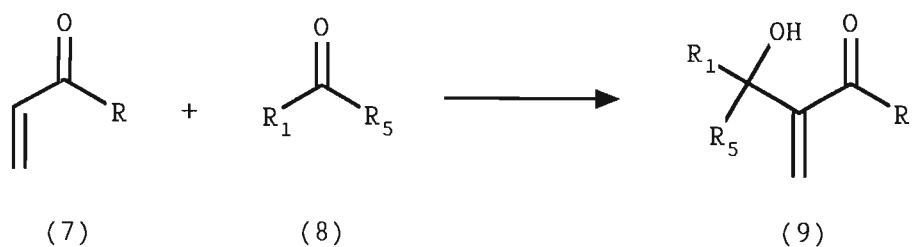
Scheme 1.

1.2.1. DIRECT INTRODUCTION: FORMAL ACRYLATE ANION.

The direct generation of a vinyl carbanion from an α-unsubstituted acrylate using LDA or LTMP as the base has been studied by Feit *et al..*[30] A severe limitation of this method is the facile anionic polymerisation of the acrylate.

A more successful direct method was reported by Marino and co-workers[31] and utilised vinyl cuprates. These reagents react at low temperature with a variety of electrophiles to give the desired products in good yield.

A milder and higher yielding direct procedure for the synthesis of α-substituted acrylic systems will be discussed later (Section 1.3).

1.2.2. ACRYLATE ANION EQUIVALENTS.

Several metal enolates have been used as synthetic equivalents of the acrylate anion with alkyl halides[23,32,33] and aldehydes.[34,35] Baraldi *et al.*[32] described an efficient preparation of α-substituted acrylic esters based on the Dieckmann-Michael retrograde reactions of the C-alkylation products of 4-methoxy carbonylthiolan-3-one (10) (Scheme 2). The α-substituted acrylic esters (12) were smoothly generated from the alkylated products (11) by a base promoted fragmentation.

Scheme 2.

Reagents: (i) RX, K_2CO_3, Me_2CO

(ii) 5% NaOH
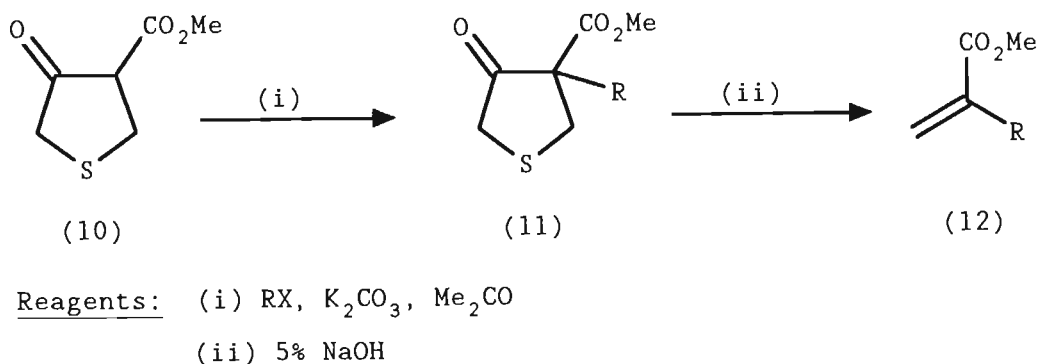
Perhaps the simplest and most elegant procedure for generating an acrylate anion equivalent was developed by Yu and Helquist.[23,33] Their method is based upon the use of an acrylate synthon of the general structure $ZCH_2CH_2CO_2R$ in which the group Z, after appropriate modification, may ultimately serve as a leaving group in an elimination reaction to unmask the acrylic system.

Their reagent, methyl 3-(dimethylamino)propionate (13), is conveniently obtained in large quantities from dimethylamine and methyl acrylate- two relatively inexpensive starting materials. The enolate (14) was generated with LDA and was found to be quite stable, possibly due to its existence as the chelated species (14a). The intermediate (14) reacts with alkyl halides to produce the corresponding 2-substituted propionates (15) which are actually Mannich base derivatives- a very useful class of compounds.[36] Deprotection of the alkylation products (15) was accomplished in two steps:- quarternisation of the nitrogen with methyl iodide followed by elimination by treatment with DBN, yielded the 2-substituted acrylates (16) (Scheme 3).
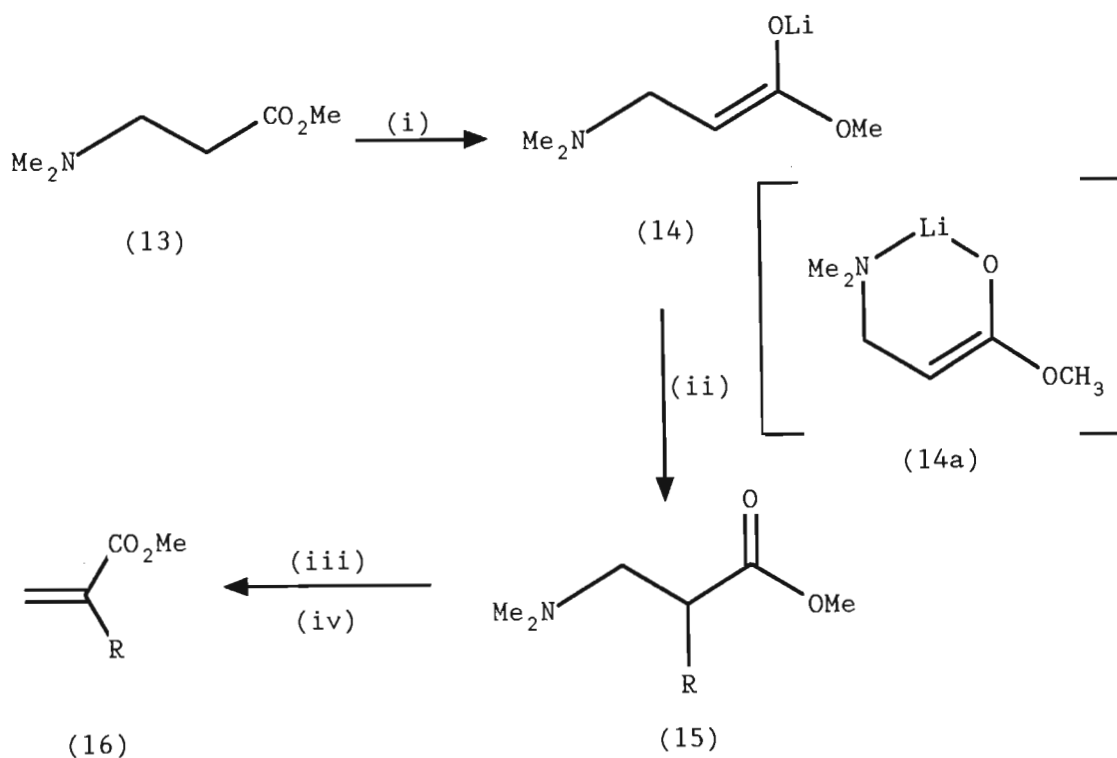
Reagents: (i) LDA (ii) RX, THF, HMPT, -78 to 25°C

(iii) CH₃I, CH₃OH, (iv) DBN, benzene, reflux.

Scheme 3.

Scolastico and co-workers[37] extended the use of compound (13), which had previously been used only in alkylation reactions, with simple aliphatic aldehydes, thus demonstrating its feasibility in aldol-type reactions. However, milder conditions than those described by Yu and Helquist[23,33] had to be used for the elimination step.

A logical extension of this approach would be the use of *chiral* N-containing auxiliary groups which may be eliminated after aldol-type condensation with aldehydes and ketones. These would yield 2-(α-hydroxy)alkyl and aryl acrylate derivatives stereoselectively.

1.3. THE BAYLIS-HILLMAN REACTION.

As was mentioned earlier (Section 1.2.1.), another direct method for the synthesis of substituted acrylic systems (18) exists. This reaction, which involves the coupling of certain electrophiles (8) (mostly aldehydes, R_5=H) and an α,β-unsaturated system (17) in the presence of a catalyst has found wide application in synthesis in recent years (Scheme 4).
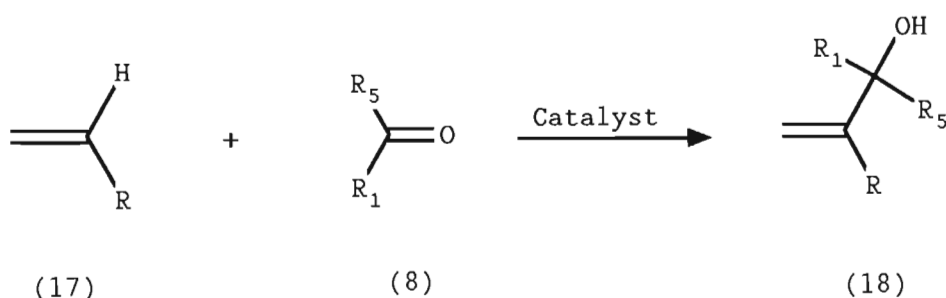
Scheme 4.

The reaction between certain aldehydes and acrylic esters or acrylonitrile in the presence of tricyclohexylphosphine was first reported by Morita *et al.*.[38] A significant drawback, however, was the low conversion of this reaction, as the phosphine catalyst was rapidly deactivated due to its susceptibility to air oxidation. In 1972, Baylis and Hillman[39] then published in a patent, the successful coupling of such systems by making use of sterically hindered tertiary amines as catalysts.

Primarily, Baylis and Hillman[39] reported that the α,β-unsaturated system (17) may be an acrylic ester (R=$COOR_2$), an acrylic nitrile (R=C$\equiv$N), an amide (R=CO(NR$_3$)$_2$), or a ketone (R=COR_4). In both the unsaturated compound (17) and the aldehyde (8) (R_5=H), the groups R_1, R_2, R_3 and R_4 (Scheme 4) may be simple or highly substituted aliphatic or aromatic chains. In the

original patent, Baylis and Hillman[39] reported the use of DABCO, pyrrocoline and quinuclidine as catalysts. Of these, DABCO is by far the most widely used.

In a recent review, Drewes and Roos[40] found it appropriate to refer to this general sequence as the Baylis-Hillman reaction, in deference to the pioneering work of these two researchers. This review covers the literature up to the time of printing. Since then, a steady stream of publications has appeared on the subject and the name Baylis-Hillman has met with general acceptance. Recent papers in the field will be reviewed briefly.

1.3.1.   REACTANTS AND APPLICATIONS.

1.3.1.1.   THE α,β-UNSATURATED SYSTEM.

In the original patent,[39] Baylis and Hillman reported that the α,β-unsaturated system may be an ester, nitrile, amide or ketone. However, activated vinyl systems other than these have also been found to participate in Baylis-Hillman type reactions.

Auvray *et al.*[41] have shown that phenyl vinyl sulphone (19) reacts with various aldehydes in the presence of a catalytic amount of DABCO, furnishing the corresponding allylic alcohols (20) in good yield. These were readily converted to the corresponding acetates (21) and the allylically rearranged bromides (22) which were in turn allowed to react with nucleophiles (Scheme 5).
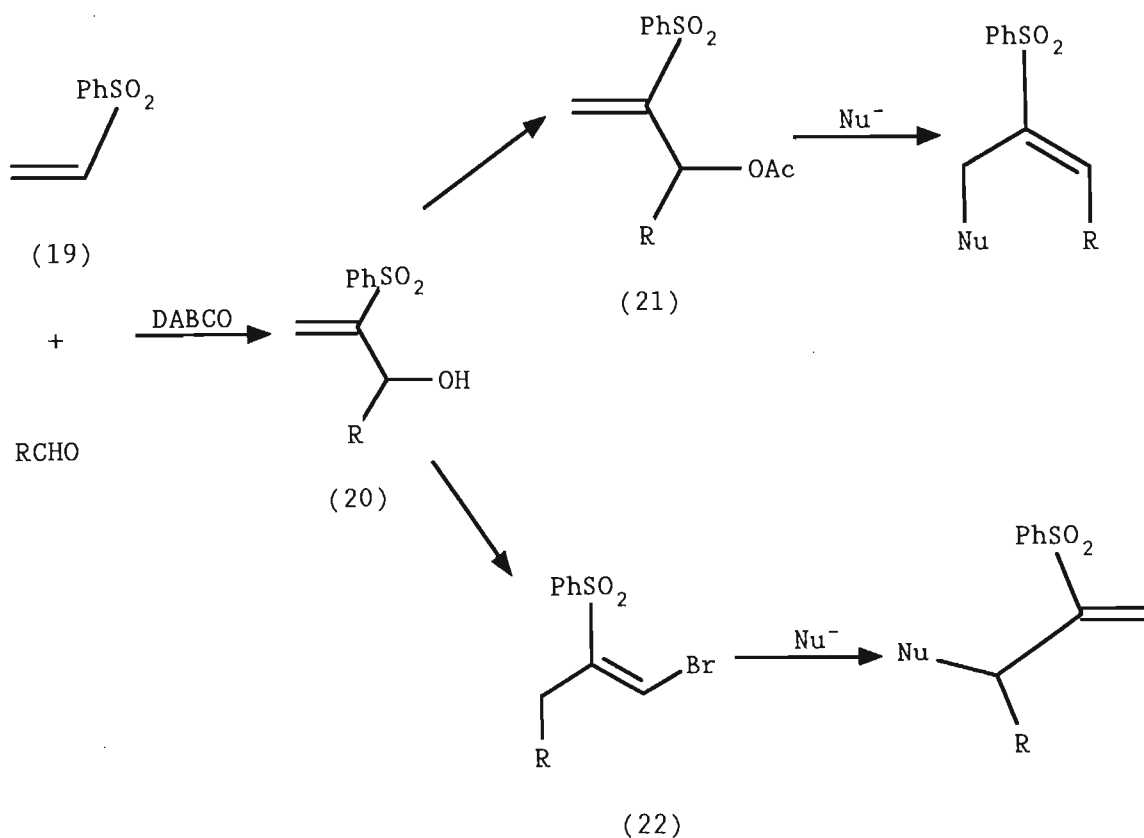
Scheme 5.

Hoffmann and Weichert[42] have extended the use of compounds of type (20), also derived from the Baylis-Hillman reaction, by oxidising them to the corresponding α-methylene-β-keto sulphones which were subsequently used in a wide variety of synthetic applications.

More recently, Villiéras and co-workers[43] have shown that diethyl vinylphosphonate (23) may be used in the Baylis-Hillman reaction to yield α-hydroxyalkyl vinylphosphonates (24) (Scheme 6). However, the reactions were very slow and the authors attribute this to the weak electrophilicity of the substrate.
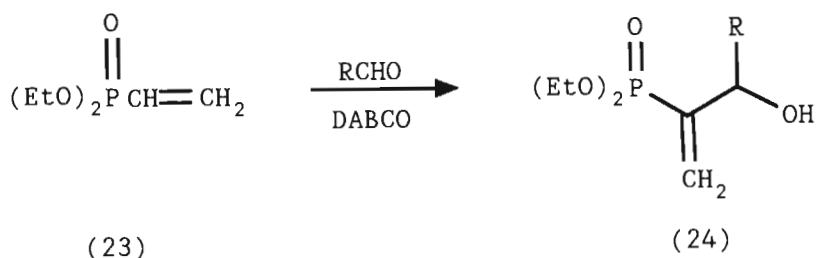
Scheme 6.

1.3.1.2. THE ELECTROPHILE.

In the original patent[39] the electrophile was restricted to aldehydes only. Since then however, several other electrophiles have been used successfully in the Baylis-Hillman reaction.

Perlmutter and Teo[44] achieved the desired products by coupling ethyl acrylate to N-(para-toluenesulphonyl)imines of aromatic aldehydes (25) in the presence of DABCO. Subsequently, Yamamoto et al.[45] found that the amine catalysed reaction of acrylates with methyl benzylidenecarbamate (26) was much faster than that with common aldehydes.
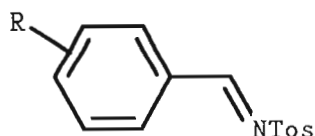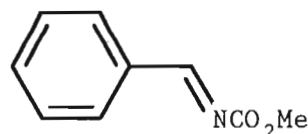
Hill and Isaacs[46] have demonstrated that the Baylis-Hillman reaction is promoted by elevated pressures. They have also shown that by using very high pressures, it is possible to include ketones as electrophiles in the Baylis-Hillman reaction. Thus, acetone reacted with methyl acrylate in the presence of DABCO at 5 kbar to yield the expected product in 75% yield after only two hours.

Basavaiah[47] has used α-keto esters as the electrophilic partner in coupling reactions with either acrylonitrile or methyl acrylate in the presence of DABCO. Hoffmann[48] used the Baylis-Hillman reaction of methyl acrylate and methyl pyruvate as a key step in the two step synthesis of dimethyl 2,3-dimethylene-butanedioate. This compound has served as a Diels-Alder diene[49] and, in the form of free 2,3-dimethylenebutanedioic acid, as a building block for α-methylene-γ-butyrolactones.[50]

Recently, Drewes and co-workers[51] studied the reaction of a series of α,β-unsaturated aldehydes with methyl acrylate using 3-hydroxyquinuclidine as the catalyst. The multifunctional products from these reactions are useful synthetic intermediates in their own right but, in addition, mild oxidation of the secondary alcohol should afford substrates which will:

   (a) decarboxylate to vinyl ketone derivatives and
   (b) undergo intramolecular Diels-Alder reactions.

Basavaiah and co-workers[52] have demonstrated the use of diethyl-ketomalonate as the electrophile in the Baylis-Hillman reaction. Reaction times were found to be much shorter than for aldehydes and the reaction with methyl acrylate is complete in four hours even in a one molar solution in THF. A similar reaction of methyl acrylate with aldehydes takes between eighteen hours and seven days.

1.3.2. SYNTHETIC APPLICATIONS OF THE
BAYLIS-HILLMAN REACTION.

Recently, Masuyama et al.[53] have shown that ethyl 2-(hydroxy-methyl)acrylate derivatives serve as reagents for 2-ethoxy-carbonyl allylation of carbonyl compounds by using $PdCl_2(PhCN)_2$-$SnCl_2$ to produce α-methylene-γ-butyrolactones

diastereoselectively. A detailed study using a wide variety of aldehydes afforded the *syn* products with selectivities of 90-100% (Scheme 7).
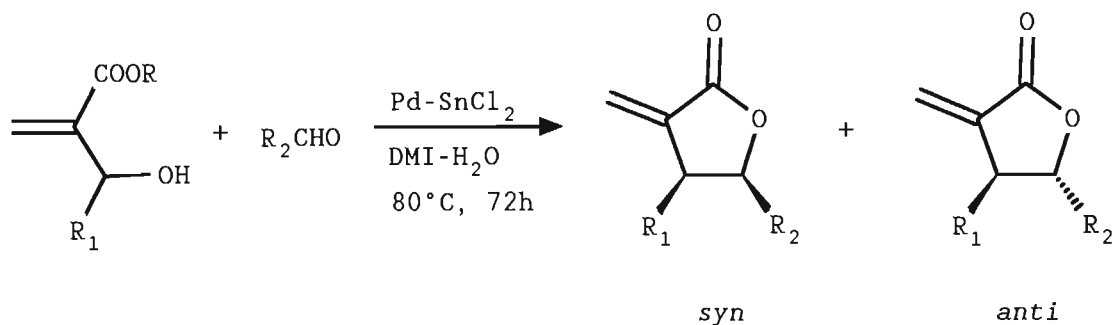
Scheme 7.

Hoffmann and co-workers[54] have made some interesting observations using the Baylis-Hillman reaction. Suitably functionalised aldehydes were found to enter into interesting tandem processes, for example, 2-phenylethanal, which enolises more readily than a simple aliphatic aldehyde, was found to react with methyl acrylate (30) in the presence of DABCO to give not only the expected product (27) in 17% yield but also compound (28) in 40% yield.

(27)

(28)
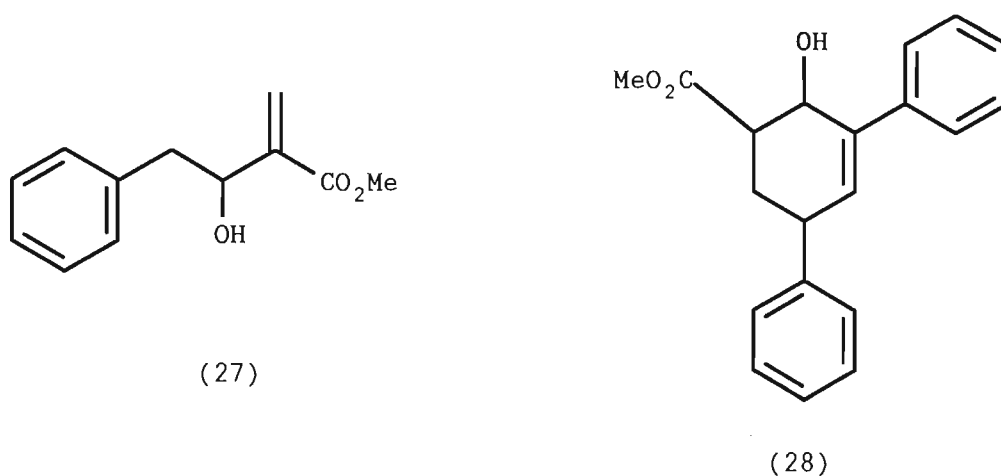
The formation of the cyclohexenol (28) was interpreted as a

[2+2+2] cycloaddition,[55] which is brought about sequentially by:
(1) aldol addition, (2) aldol dehydration and intermolecular
addition of the d^4-dienolate donor, and finally, (3) intra-
molecular aldol addition. The cyclohexenol moeity of compound
(28) was aromatised by oxidation with $BaMnO_4$ to yield compound
(29) (Scheme 8).
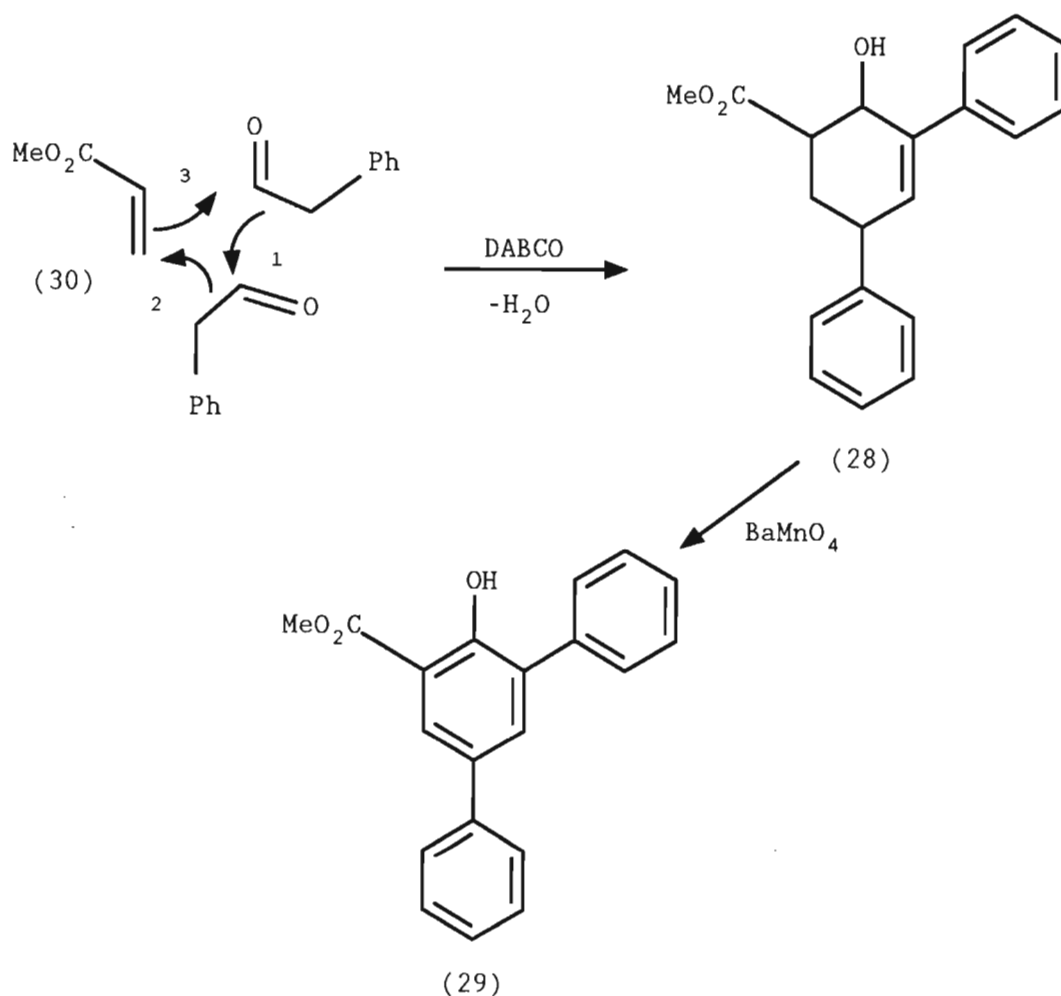
Scheme 8.

Aldehydes with a second donor group 1,4 and 1,5 to the formyl
group were also investigated.[54] The ester aldehyde (31), for
example, reacted with methyl acrylate (30) in the presence of
DABCO to yield compound (32) (40%), which, under the reaction
conditions, partially lactonised to compound (33).

(31)   (32)   (33)
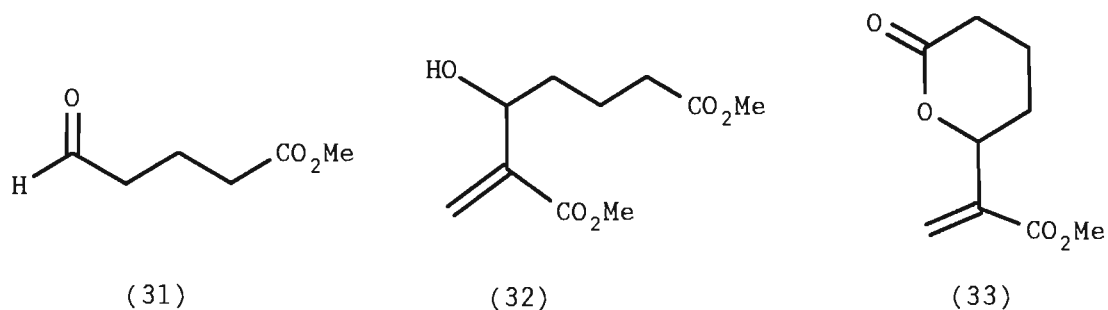
When ᵗbutyl acrylate (34) was used instead of methyl acrylate (30), the corresponding coupling product was only obtained in 14% yield. The cyclohexenecarboxylic acid (35) was found to be a major product. Its formation was rationalised by: (1) Michael addition, (2) Michael addition, (3) intramolecular aldol reaction, (4) 6-exo-trig lactonisation, and finally, (5) formation of the cyclohexene double bond with the liberation of the carboxylic acid. Steps (4) and (5) terminate the [2+2+2] cycloaddition in a novel way (Scheme 9).
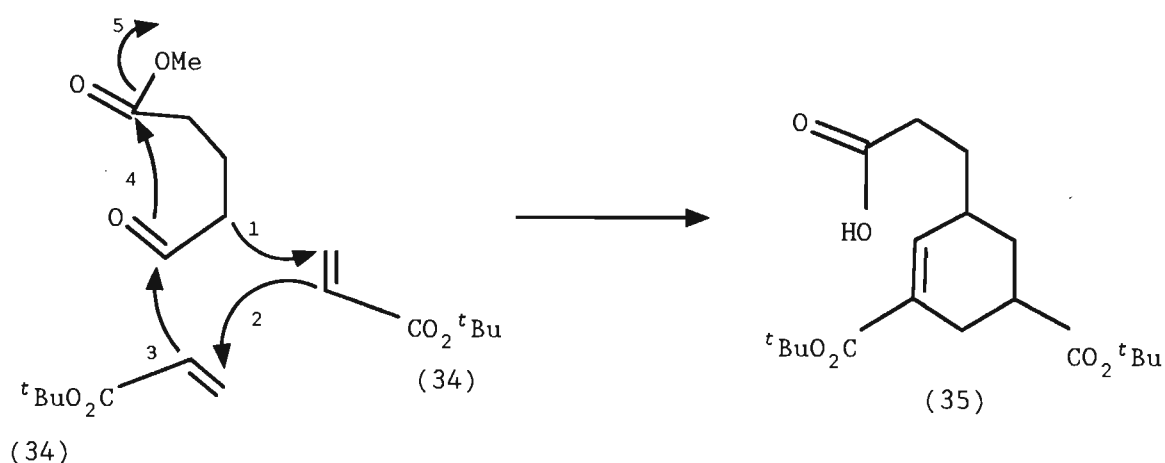
Scheme 9.

Several other interesting features of the Baylis-Hillman reaction emerge from this paper.[54]

Jungheim and Sigmund[56] recently described a new class of

synthetic γ-lactam antibacterial agents which exhibit a broad spectrum of antibacterial activity. Subsequently, Jungheim[57] reported on the synthesis of bicyclic pyrazolidinones with carbapenem type side chains. The requisite pyrazolidine starting materials were obtained in one step from the condensation of anhydrous hydrazine with Baylis-Hillman derived substituted acrylates.

Recently, Bode and Kaye[58] described a new synthesis of indolizines *via* thermal cyclisation of 2-pyridyl derivatives. Attempted distillation of one of the Baylis-Hillman products, methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (36), afforded a colourless solid, which was identified as methyl indolizine-2-carboxylate (37).[59] The authors propose that a possible nucleophilic addition-elimination sequence led to the transformation product (Scheme 10).
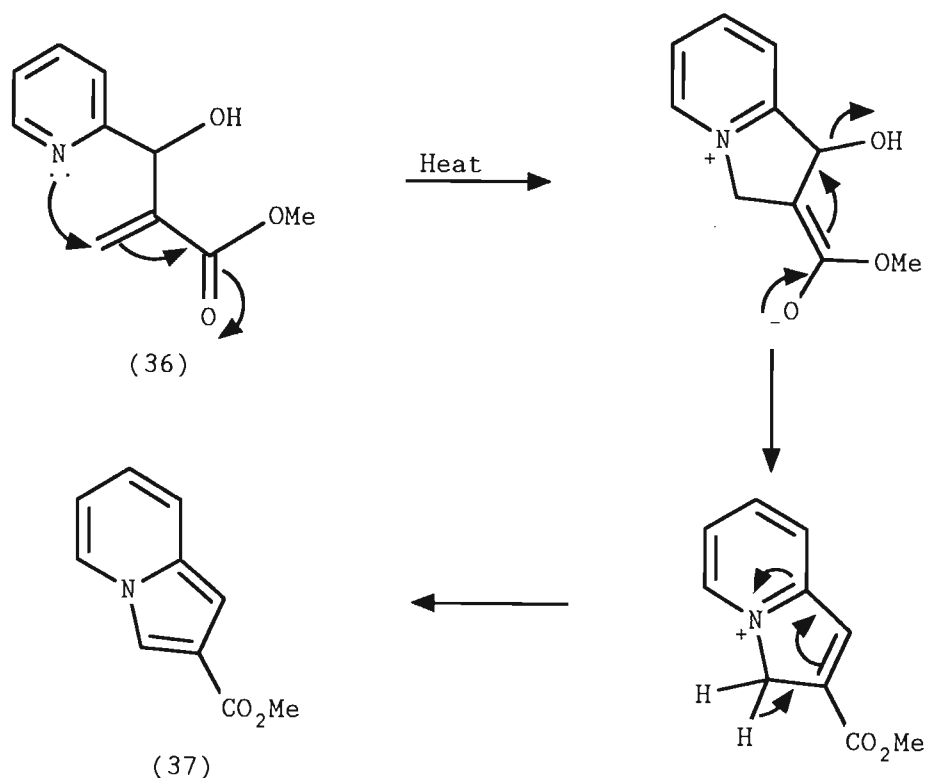
Scheme 10.

In another interesting paper, Kaye and co-workers[60] have described the synthesis of a coumarin derivative (40) *via* the Baylis-Hillman reaction. Extension of their work on indolizines[58] involved the attempted synthesis of the chromene system (39) from the salicylaldehyde-derived analogue (38) (Scheme 11). However, the expected product was not isolated, but instead, the sole colourless crystalline coumarin derivative (40) was identified by x-ray crystallography.
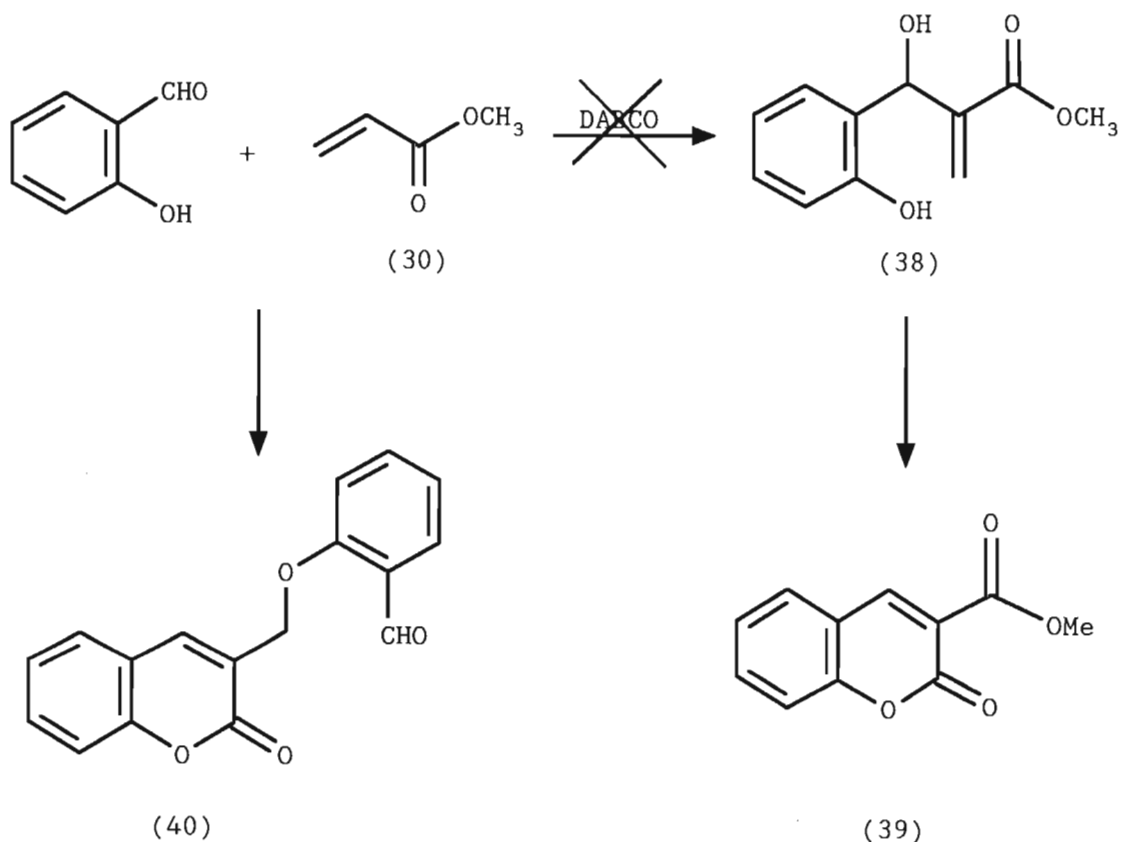
Scheme 11.

This interesting transformation is thought to proceed *via* a tandem four-phase sequence involving: (1) Baylis-Hillman reaction, (2) intramolecular transesterification, (3) dehydration and (4) nucleophilic substitution (Scheme 12).
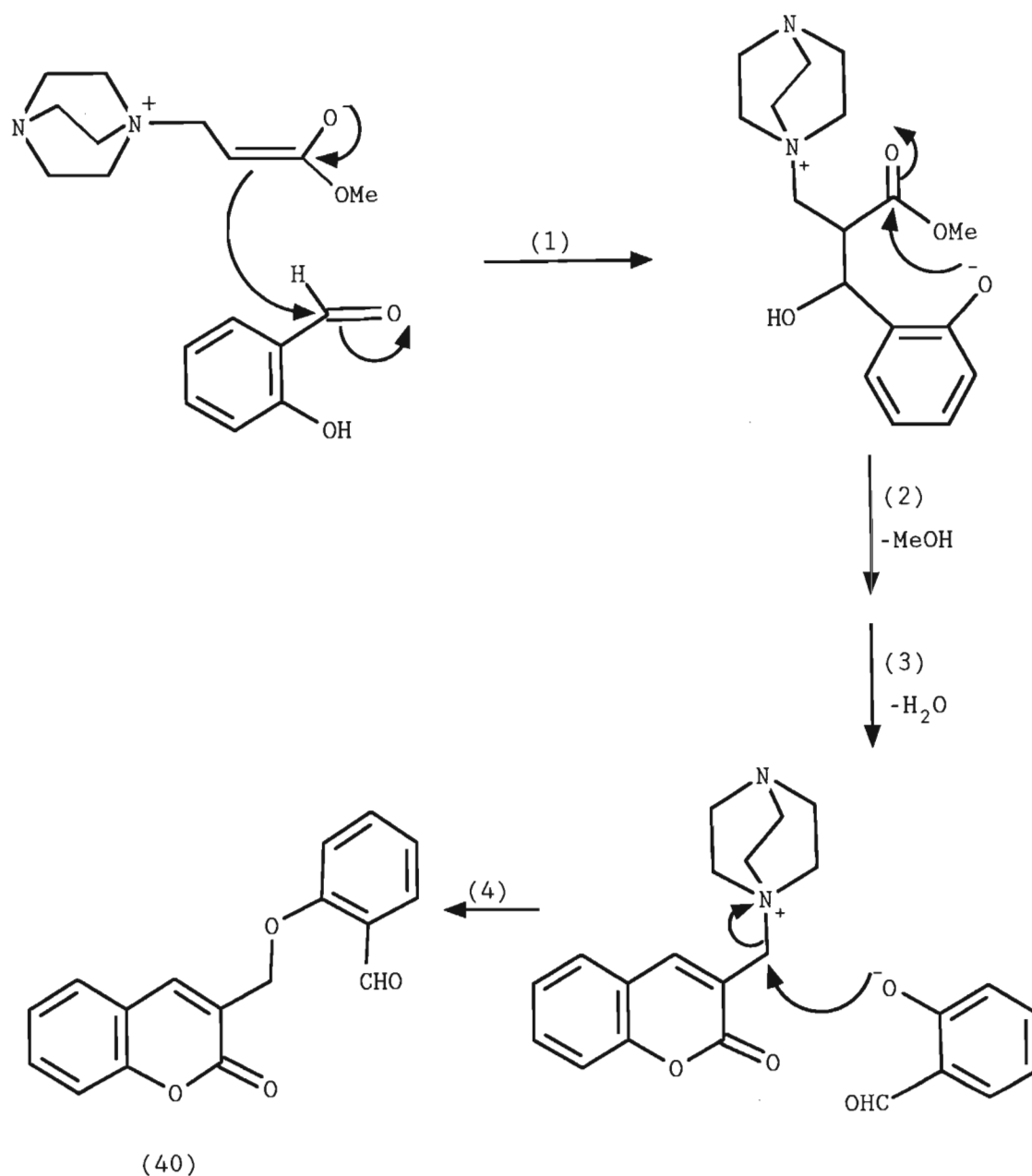
Scheme 12.

Adam and co-workers[61] have recently reported on the synthesis of α-methylene β-lactones, a novel class of heterocycles. Two synthetic methods were developed for the synthesis of these heterocycles. The more attractive method involves the one step transformation of a Baylis-Hillman product to the target molecule (41) (Scheme 13).
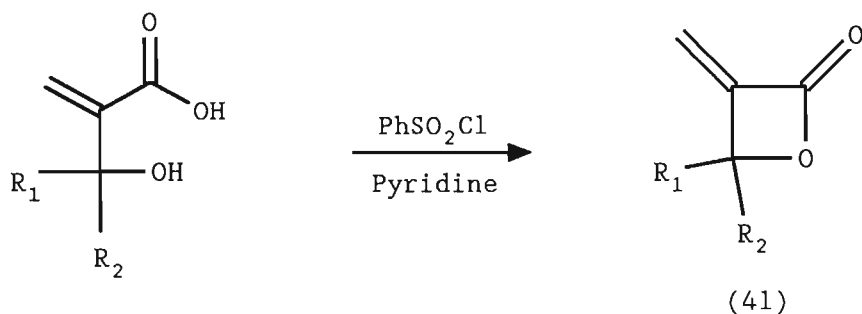
Scheme 13.

More recently Caubère and co-workers[62] investigated the use of dialdehydes in the Baylis-Hillman reaction with the aim of selectively performing mono- (42) or bis-condensations (43) as shown in Scheme 14.
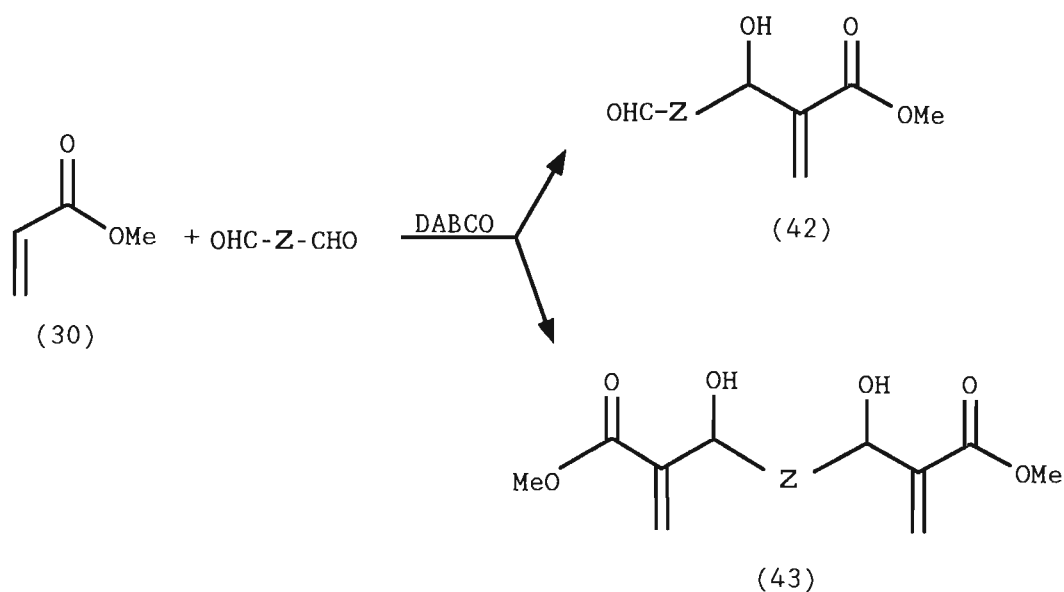
$Z = o,m,p-C_6H_4;\ 4,4'-,\ 3,3'-C_6H_4-C_6H_4;$
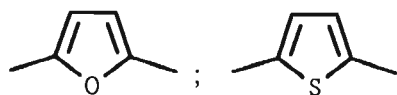
Scheme 14.

Having optimised the conditions the authors were able to select-
ively obtain the mono- (42) or the bis-condensation product
(43). Two interesting results are worthy of note. When the
dialdehyde (44) was used, intramolecular hemiacetalisation led
to the hydroxy dihydroisobenzofuran derivative (45). The same
reaction was observed with dialdehyde (46) which afforded the
hydroxy tetrahydropyran derivative (47) (Scheme 15).

(44)   (30)   (45)

OHC-(CH₂)₃-CHO   +   OMe   DABCO

(46)   (30)   (47)
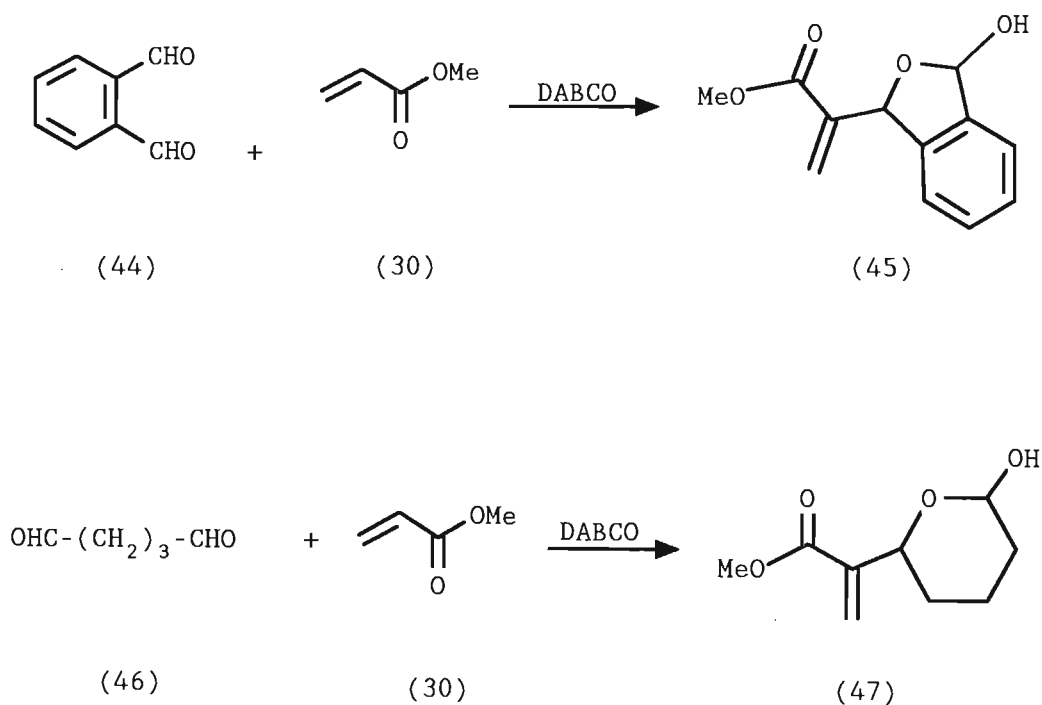
Scheme 15.

Clerocidin (48)[63] and terpentecin (49)[64] exhibit antibiotic and
antitumour activities which may well be associated with their
sidechains.[65]
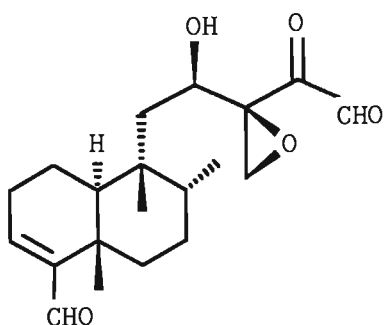
(48)
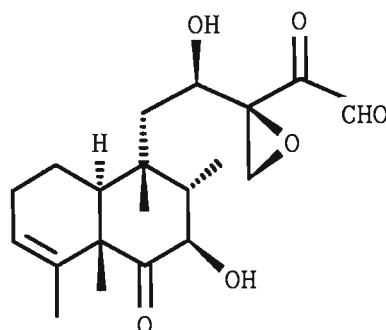
(49)
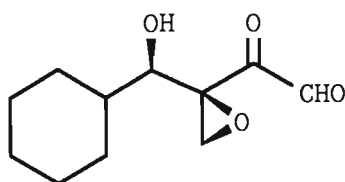
(50)

In connection with their structure-activity studies, Ollis and co-workers[66] required a flexible route towards clerocidin (48) and its structural analogues. The synthesis of suitable precursors of the carboxylic decalin portion had been completed at this stage.[67] Studies towards the diastereospecific synthesis of the model compound (50) were undertaken. Hydroxy-enones (51) derived from the Baylis-Hillman reaction of methyl vinyl ketone and aldehydes, provided the substrates for the examination of diastereoselection in the epoxidation of these olefins (Scheme 16). The desired *syn*-selectivity was achieved under Sharpless conditions.[68] The results are shown in Table 1.

(51)   (52)-*syn*   +   (53)-*anti*
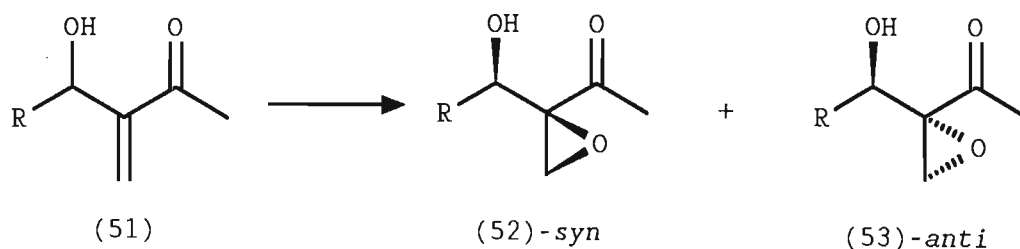
Scheme 16.

Table 1.

R	CONDITIONS	YIELD	*syn/anti*
c-hexyl	H_2O_2/NaOH/MeOH/0°C	76	40 : 60
c-hexyl	TBHP/NaOH/MeOH/-40°C	70	33 : 67
c-hexyl	BQBR/CHP/Tol/NaOH/-20°C	78	40 : 60
c-hexyl	MCPBA/CH_2Cl_2/20°C/3 days	-	-
c-hexyl	$Ti(O^iPr)_4$/TBHP/CH_2Cl_2/-15°C	78	100
Me	$Ti(O^iPr)_4$/TBHP/CH_2Cl_2/-15°C	63	100
Et	$Ti(O^iPr)_4$/TBHP/CH_2Cl_2/-15°C	72	100
iPr	$Ti(O^iPr)_4$/TBHP/CH_2Cl_2/-15°C	70	100

Prompted by these results, Ollis and co-workers[69] undertook a detailed study of the reaction, using various electron-deficient olefins, in order to delineate the structural features required in the starting material for its successful epoxidation. From these investigations Ollis and co-workers[69] observed that blocking the hydroxyl functionality totally inhibits the epoxidation reaction. It is proposed that initial coordination of the titanium complex with the hydroxyl group is necessary for subsequent reaction to ensue. Interestingly, kinetic resolution of hydroxyenone (51) (R=cyclohexyl) led to the optically active epoxide (52) (R=cyclohexyl) with an ee of 23%. The recovered starting material was also found to be optically active (22% ee). Further results in this area were recently published by Ollis and co-workers.[70]

The Baylis-Hillman reaction has also found its place in natural product synthesis. Drewes and co-workers[71,72] have used inter-

mediates derived from the Baylis-Hillman reaction to synthesise integerrinecic acid (54)[71] and retronecic acid (55).[72]

(54)

(55)
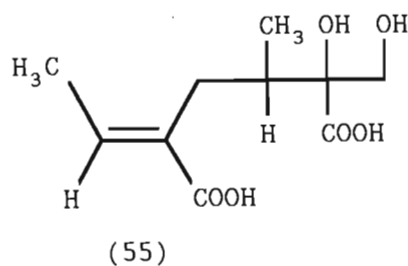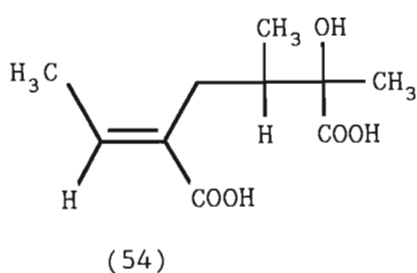
Hoffmann and Rabe[73a] have likewise synthesised mikanecic acid (56) using a Baylis-Hillman product as a key intermediate.

(56)
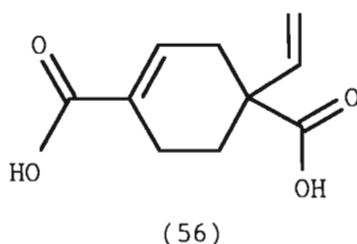
It is clear that the Baylis-Hillman reaction has made its mark on organic chemistry. Since the product of this reaction bears a chiral centre, the area of asymmetric synthesis using the Baylis-Hillman reaction beckons.

1.4.   STEREOCHEMICAL ASPECTS OF THE BAYLIS-HILLMAN REACTION.

The reaction of an activated α,β-unsaturated vinyl system with an electrophile, barring formaldehyde and symmetrical ketones, yields a product (18) which contains at least one asymmetric carbon β to the carbonyl or nitrile functionality.

R = $-COOR_2$, $-C \equiv N$, $-CON(R_3)_2$, $-COR_4$, $-SO_2Ph$, $(EtO_2)P = O$
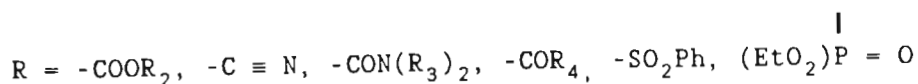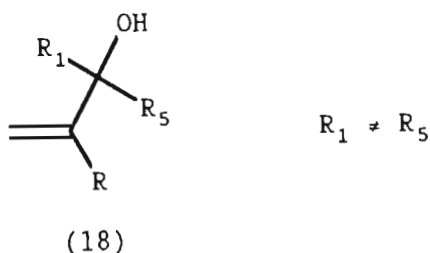
It is a well known fact, that if the reagents and reaction conditions are all achiral, the product must be a racemic mixture. That is, no optically active material can be created if all starting materials and conditions are optically inactive.[74]

To introduce optical activity into the product of the Baylis-Hillman reaction there exists five possible modes of chiral induction. These involve the use of:

(a) Optically active electrophiles.
(b) Optically active α,β-unsaturated substrates.
(c) Chiral solvents.
(d) Chiral catalysts.
(e) Combinations of the above chiral directors.

1.4.1.   THE USE OF OPTICALLY ACTIVE ALDEHYDES.

The accepted mechanism of the Baylis-Hillman reaction involves a Michael addition of the catalyst to the α,β-unsaturated substrate, followed by nucleophilic attack on the prochiral electrophile and subsequent elimination of the catalyst.[40,73b] The generated carbanion should attack the electrophile at the less sterically hindered face (Figure 1). The consequence of this would be asymmetric induction at the newly formed chiral centre.
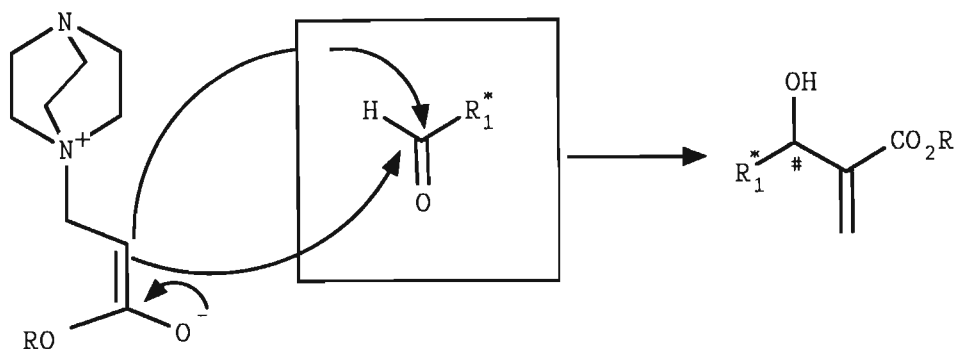
Figure 1.

1.4.1.1. THE USE OF CHIRAL α-ALKOXY ALDEHYDES.

An electrophile, with a chiral directing group adjacent to the site of reaction, would be the most likely choice for good asymmetric induction.   During the course of their studies towards the total synthesis of the antibiotic conocandin (4), Scolastico and co-workers[37] became interested in developing a method for the stereoselective synthesis of *anti*[75] (*threo*)[76] esters of general formula (58) (SCHEME 17). The most straight-forward way to achieve this goal was thought to be an aldol-type condensation between a chiral α-alkoxy aldehyde and a synthetic equivalent of the acrylate-anion (Section 1.2.2.).

(57) R_3 = OR_4 (58)
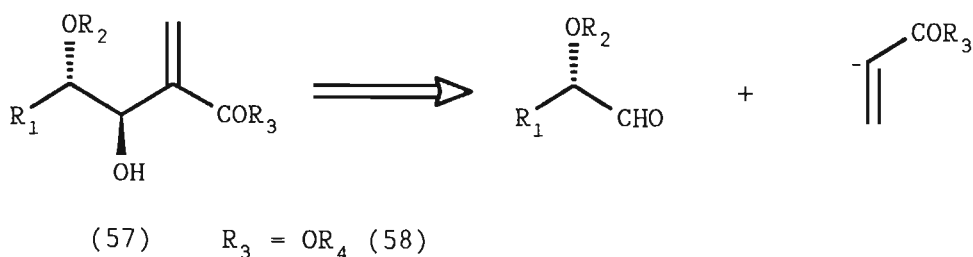
Scheme 17.

Drewes *et al.*[77] applied this approach by using chiral α-alkoxy aldehydes   in   the   stereoselective   synthesis   of   α-methylene-

β-hydroxy-γ-alkoxy ketones (57) and esters (58) *via* the Baylis-Hillman reaction. The yields, although not optimised, were within the synthetically useful range and the coupling of these aldehydes with vinyl carbanions proceeded with reasonable diastereoface selectivity. The results are summarised below (Scheme 18 and Table 2).
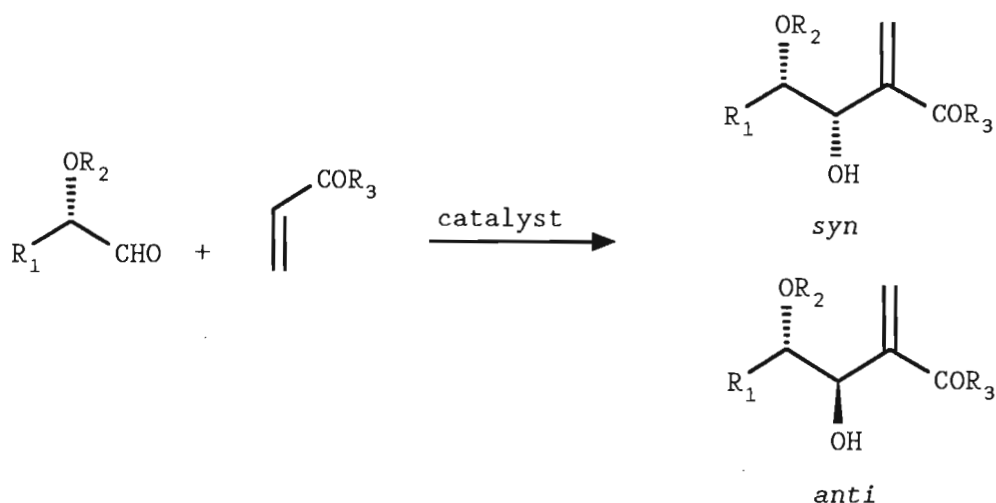
Scheme 18.

Table 2.

R$_1$	R$_2$	R$_3$	CATALYST	TIME	*anti/syn*	YIELD %
Me	Bn	OMe	A	14d	60 : 40	65
Me	MOM	OMe	A	4d	70 : 30	55
Me	MOM	OMe	B	36h	72 : 28	60
Me	MOM	Me	A	2h	71 : 29	54
Me	MOM	Me	B	<20m	71 : 29	80
Me	MOM	Me	B	2h	71 : 29	80
Ph	MOM	Me	A	6d	62 : 38	70

A = DABCO   B = 3-Hydroxyquinuclidine

The coupling of three aldehydes with either one of two activated vinyl systems (an ester or a ketone) in the presence of either one of two catalysts was studied. Catalyst B and the vinyl ketone function were established as important determinants of reaction rate whilst not affecting the selectivity. The *syn/anti* ratios were determined by ^{1}H NMR using EuFOD shift reagent where necessary and assignments were made according to published data.[37] The observed outcome of predominant *anti*-selectivity was explained using Felkin's model[78] (Figure 2). The absence of the "more usual" coordinating metal counterion gave the authors reasonable confidence in this proposal.
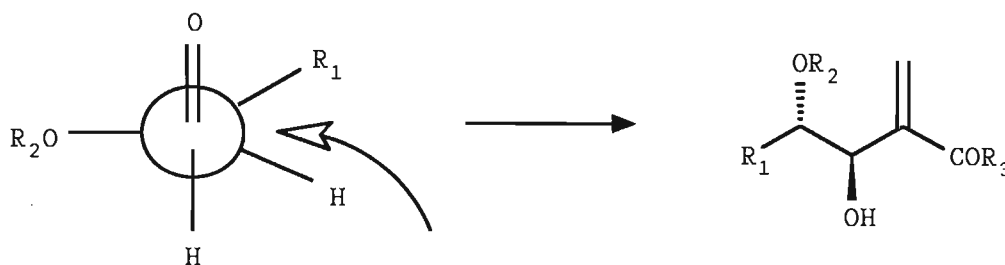
Figure 2.

The selectivities obtained *via* the Baylis-Hillman reaction[77] are comparable to those obtained by Scolastico and co-workers.[37] There are, however, three advantages associated with the Baylis-Hillman reaction:-

(1) The problems of working at low temperatures are avoided.
(2) The Baylis-Hillman reaction obviates the need for masking agents.
(3) The reagents are cheaper.

1.4.1.2. THE USE OF CHIRAL β-ALKOXY ALDEHYDES.

The use of enzymes[19-22] has attracted considerable interest because of the mild conditions required and the high stereochemical control they exhibit. β-Hydroxy esters are readily available by the microbial reduction of β-oxoesters.[79] The yeast reduction of ethyl acetoacetate to afford S-ethyl-3-hydroxybutyrate (59) exemplifies this[80] (Scheme 19).
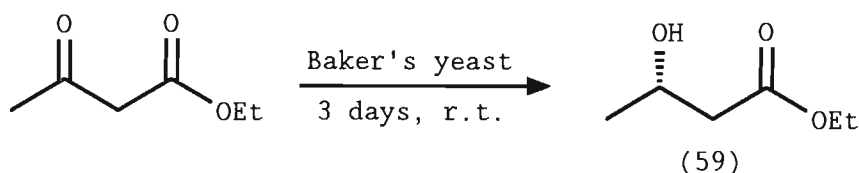
Scheme 19.

Drewes and co-workers[81] saw this as a route to optically pure β-alkoxy aldehydes, which could be substituted or unsubstituted α to the carbonyl. Initial investigations using α-unsubstituted β-alkoxy aldehydes gave promising results (Scheme 20 and Table 3).
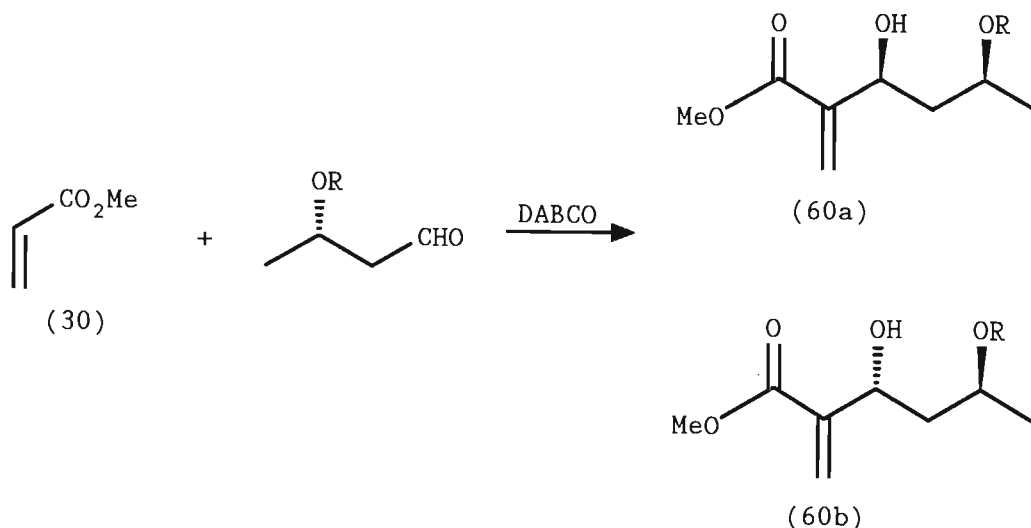
Scheme 20.

Table 3.

R	YIELD	%de
CH_3OCH_2-	65	86
$PhCH_2-$	70	51

Comparison of the result for entry 1 with the analogous result for α-alkoxy aldehydes (Table 2, entry 2) shows a marked increase in the diastereoselectivity for β-alkoxy aldehydes. Since the chiral centre in β-alkoxy aldehydes is one carbon away from the prochiral reaction centre, one would expect the diastereofacial selectivity to be less pronounced than that of the α-alkoxy aldehydes. The results indicate the opposite.

An intramolecular chelation between the methylene group of the protecting group and the carbonyl oxygen to form a six-membered "ring" is proposed.[82] However, the fact that the methylene group occurs between two electronegative oxygen atoms, thus rendering it electron deficient, is thought to be instrumental in the formation of the "ring" (Figure 3). The attacking nucleophile is expected to approach predominantly from the side remote to the methyl group.
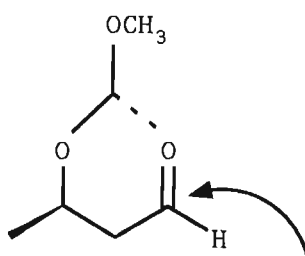
Figure 3.

An interesting extension of the γ-alkoxy-(α-hydroxyalkyl)-acrylates was that they could be transformed into highly functionalised tetrahydrofuran derivatives.[81] Thus, methyl 5-(benzyloxy)-3-hydroxy-2-methylenehexanoate (60a) was cyclised under thermodynamic control conditions using the iodoetheri-fication technique to afford the tetrahydrofuran derivative (61) (Scheme 21).
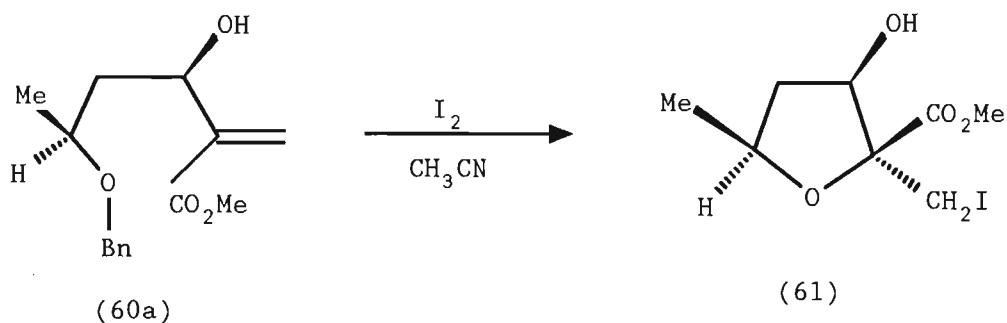
Scheme 21.

Studies using α-substituted β-alkoxy aldehydes were not as successful.[82] The coupling of these aldehydes with methyl acrylate (30) gave largely the 3-hydroxy dimethylene ester (62) (Scheme 22) which was found to be racemic. Only traces of the desired products were obtained.
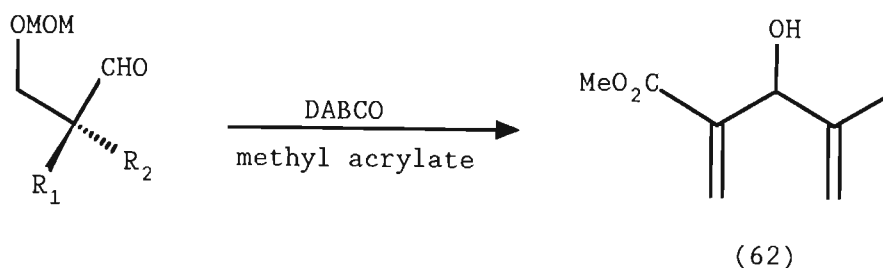
Scheme 22.

It is proposed[82] that the α-substituted β-alkoxy aldehydes afford methyl acrolein (63) by the elimination of the methoxymethyl group. Aldehyde (63) then reacts with methyl acrylate in a classical Baylis-Hillman reaction to afford the product (62).

(63)
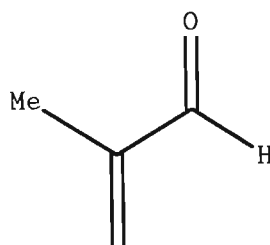
1.4.1.3. THE USE OF α-AMINO ALDEHYDES.

α-Amino aldehydes have been widely used in stereocontrolled aldol reactions because of the potentially useful multi-functional molecules that result.[83] Because of the high anti-diastereoselectivity obtained with α-alkoxy aldehydes,[77] Manickum and Roos[84] were prompted to examine the analogous protected amino aldehydes under the Baylis-Hillman approach. The results are summarised below (Scheme 23 and Table 4).
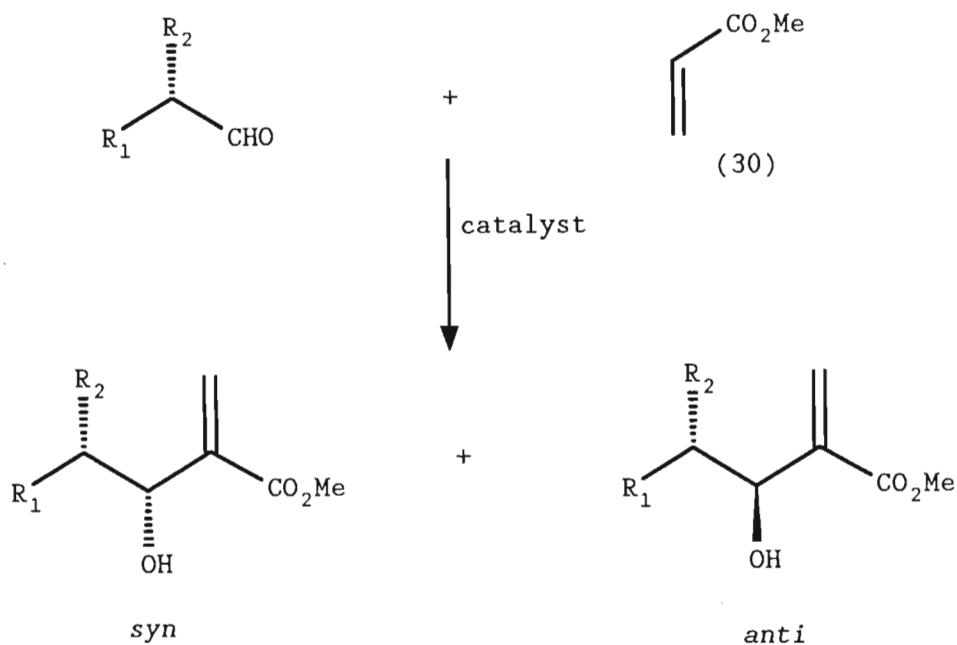
Scheme 23.

Table 4.

R_1	R_2	CATALYST	*anti/syn*	YIELD
Me	$N(CH_2Ph)_2$	B	-	-
Me	$N(CH_2Ph)_2$	A	72 : 28	71
Bn	$N(CH_2Ph)_2$	A	70 : 30	80
Me	N-phthaloyl	A	55 : 45	30
Me	NH^tBOC	A	26 : 74	80
Me	NH^tBOC	A	29 : 71	76
$-(CH_2)_4N-SO_2Ph$		A	88 : 12	55

A = DABCO   B = 3-HYDROXYQUINUCLIDINE

The observed reactivity of the aldehydes was as anticipated,
with those having electron withdrawing N-protection showing
greater reactivity. As expected, the observed diastereo-
selectivity was also dependent on the type of nitrogen
protection. Thus, the *anti*-diastereoselectivity was
rationalised in terms of the Felkin-Anh open chain model[78,85]
and followed that obtained with the α-alkoxy aldehydes.[77]

The reversal of selectivity with the NH^{t}BOC aldehyde was
rationalised in terms of the hydrogen bonded species (FIG. 4)
and is in accordance with earlier reports[83,86] where a proton-
bridged Cram cyclic model[87] is said to account for the *syn*
stereochemical outcome.
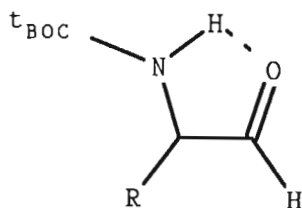
Figure 4.

1.4.1.4. THE USE OF OTHER CHIRAL ALDEHYDES.

Recently, Isaacs and co-workers[88] examined the reaction of two
chiral aldehydes with acrylonitrile and ethyl acrylate under
high pressure. However, only small degrees of enantiomeric
discrimination were observed. Furthermore, at atmospheric
pressure no enantiomeric excesses were observed at all. Isaacs
proposes that the discriminatory part of the molecules are too
remote from the reaction site to be effective.

1.4.2. THE USE OF CHIRAL SOLVENTS.

Solvents are not generally used in the Baylis-Hillman reaction
since they adversely affect the rate of reaction. Almost
invariably the aldehyde or acrylic partner, depending on which
is more volatile, is used in excess to dissolve the catalyst.
However, Kaye and co-workers,[89] in their rate enhancement
studies, found that the addition of hydroxylated species, for
example methanol, significantly reduced the reaction time.

These findings prompted Isaacs[88] to investigate the effects of
chiral hydroxylated solvents on asymmetric induction in the
Baylis-Hillman reaction. However, an ee of only 3% was obtained
when (+)-ethyl lactate was used as a chiral solvent.

1.4.3. THE USE OF CHIRAL CATALYSTS.

The use of chiral chemical catalysts is still a relatively new
area but recent developments in this field point to rich
possibilities for the future. Two examples which demonstrate
the importance of this method of asymmetric synthesis are the
catalytic version of the Sharpless epoxidation[68] and the use of
chiral organometallic reagents in asymmetric hyrogenations.[90]
Since the Baylis-Hillman reaction is catalysed by tertiary
amines which are abundantly available in optically pure form, a
study of asymmetric synthesis using chiral catalysis is not
unexpected.

Wynberg[91] has had some success using quinine (64) as a chiral
catalyst in the reaction between diethyl zinc and aromatic
aldehydes. Thus, Wynberg demonstrated that benzaldehyde afforded
(R)-(+)-1-phenylpropanol with an ee of 68% while 2-ethoxy-

benzaldehyde afforded the corresponding product with an ee of 92% (Scheme 24).

R = H   68% ee

R = OEt   92% ee
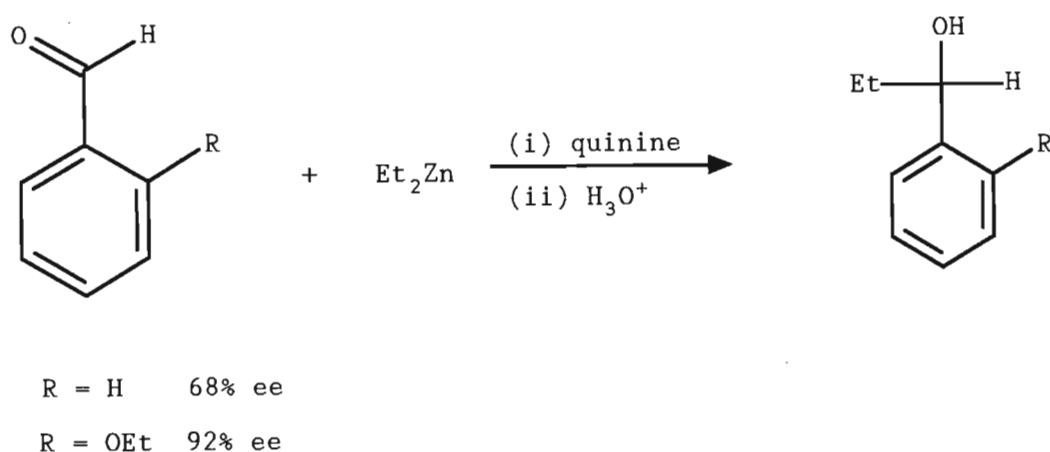
Scheme 24.

Preliminary studies, which were prompted by Wynberg's[91] positive results, were undertaken by Drewes and Roos.[40] The chiral catalysts (64)-(68) were chosen specifically because of the presence of the hydroxyl functionality. Kaye and co-workers[89] had speculated on the possibility of hydrogen bonding stabilisation to account for the rate enhancement of 3-hydroxyquinuclidine over DABCO. It was anticipated that the hydroxyl functionality in the chiral catalysts would not only positively affect the rate of the reaction but also the stereochemical outcome. However, preliminary results were disappointing in the sense that only low enantiomeric excesses were obtained (Table 5).
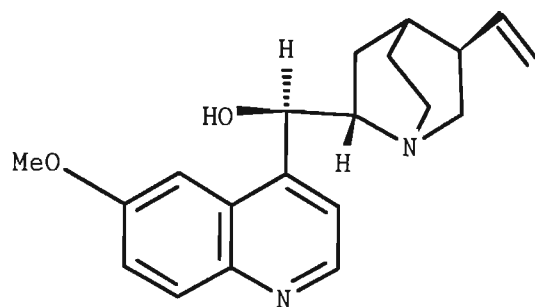
(64)
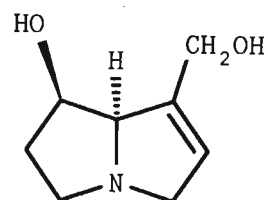
(65)
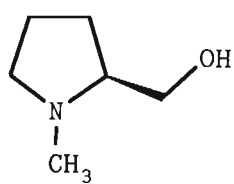
(66)

(67)

(68)

Table 5.

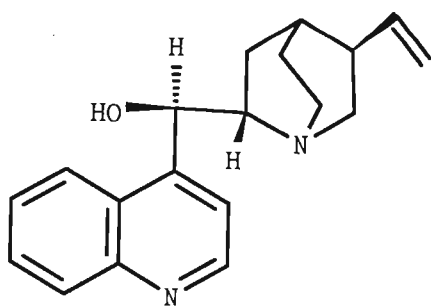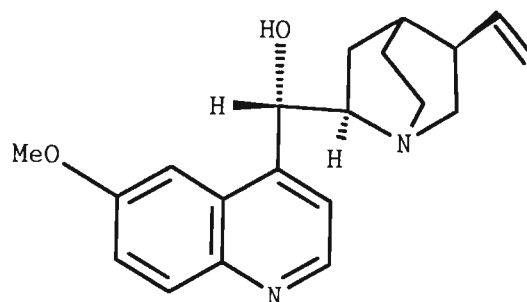| CATALYST	ALDEHYDE	SUBSTRATE	TIME(d)	%ee
Brucine	CH_3CHO	MVK	4.75	8
(62)	CH_3CHO	MVK	4.5	8
(63)	$4-NO_2-C_6H_4CHO$	MVK	30	0
(63)	$4-NO_2-C_6H_4CHO$	MA	30	11
(64)	CH_3CHO	MVK	4	0
(65)	CH_3CHO	MVK	4.5	10
(66)	CH_3CHO	MVK	7	12

MVK = methyl vinyl ketone   MA = methyl acrylate

Isaacs[88] has also investigated the use of chiral catalysts under high pressure conditions in the reaction of acrylonitrile and acetaldehyde. The results were also poor and Isaacs proposes that the chiral base, attached to the β-carbon, is too remote from the reaction site to influence the stereochemistry to any extent. A further disadvantage was that the chiral bases were all poor catalysts and yields were very low, even zero.

In a recent paper, Fráter and co-workers[92] described the first intramolecular Baylis-Hillman reaction. The cyclopentenol (70) was required as a synthetic intermediate in one of their programs. They envisaged that an intramolecular Baylis-Hillman reaction of the α,β-unsaturated-ε-keto ester (69) would yield the target molecule (70) (Scheme 25).
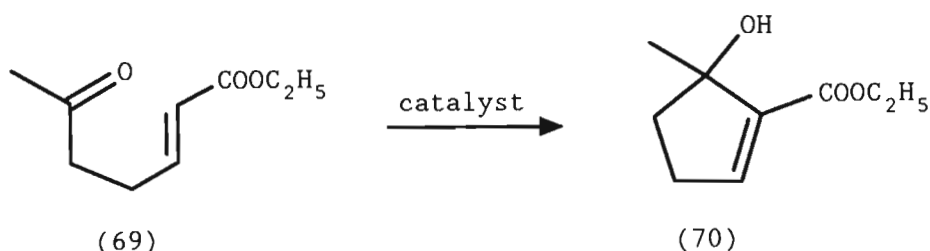
Scheme 25.

Several catalysts, including chiral ones, were used under various conditions in order to effect the cyclisation. It was found that contrary to the nitrogen-bases, phosphines[38] turned out to be the useful catalysts in this reaction. Of the chiral phosphine catalysts (71) and (72), only catalyst (72) afforded the desired product with an ee of only 14%.

$$R = C_6H_5 \quad (71)$$

$$R = c\text{-}C_6H_{11} \quad (72)$$
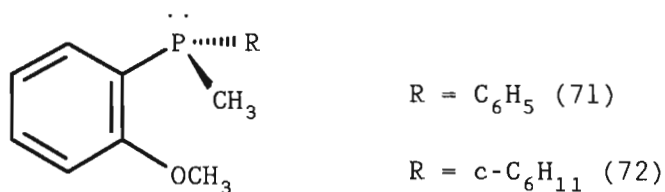
The extension of the above methodology to the case where a six-membered cyclopentenol would result, was also disappointing. Again, the nitrogen-bases, including DABCO, were unable to catalyse the intramolecular Baylis-Hillman reaction of (73) to the product (74) (Scheme 26). Even in this case the chiral catalysts were unable to afford the product with appreciable optical activity.

(73)   (74)
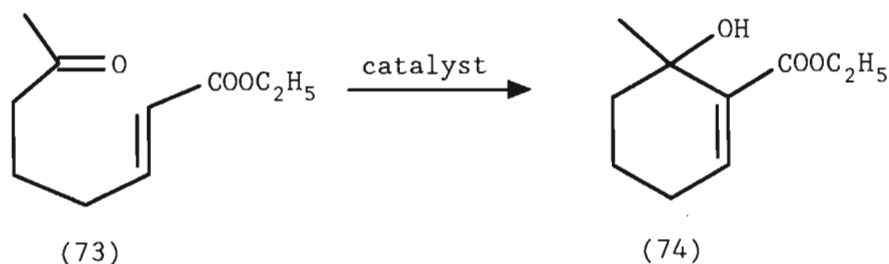
Scheme 26.

DABCO and quinuclidine are by far the most widely used catalysts in the Baylis-Hillman reaction.[40] In the recent literature, a steady stream of publications have reported on the synthesis of substituted DABCO's and quinuclidines. These catalysts, and the fact that more bulky aldehydes have not been used, ensures that this line of research is far from exhausted.

In 1989, Corey[93] described an efficient stereospecific synthesis of *trans*-2,6-diphenylquinuclidine (75) together with an efficient resolution of (75) into pure enantiomers- a potentially useful catalyst for the Baylis-Hillman reaction.

(75)
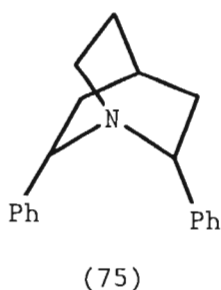
Sharpless[94] cites the Baylis-Hillman reaction when he reports on an efficient synthesis of enantiopure *trans*-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane (76) from stilbene diamine.
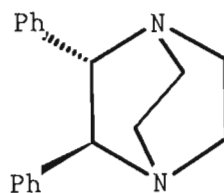
(76)

In a more recent paper, Soai and co-workers[95] speculate on the use of chiral DABCO's as base catalysts in organic reactions. Again, the Baylis-Hillman reaction is referred to in this context. Their compound, [(2S,5S)-2,5-bis(phenylmethyl)-1,4-diazabicyclo[2.2.2]octane (77) was synthesised from a chiral piperazine.
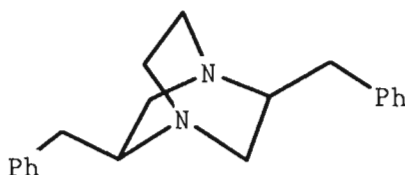

(77)

Chiral organometallic catalysts, particularly those based on rhodium and ruthenium, are finding wide application in asymmetric synthesis.[96,97] Matsuda[98] has recently described the rhodium (I) or ruthenium (II) catalysed direct coupling of vinyl ketones with aldehydes and subsequent reduction to give aldol derivatives anti-selectively.

Prompted by Matsuda's[98] results, Raab and Roos[99] are currently investigating the use of chiral rhodium and ruthenium catalysts in the Baylis-Hillman reaction. Preliminary results indicate that these catalysts are more effective chiral inducers than the nitrogen-based chiral catalysts.

1.4.4. THE USE OF CHIRAL ACRYLIC SYSTEMS.

Since this aspect of asymmetric synthesis *via* the Baylis-Hillman reaction is one of the subjects of this study, it will be covered in the DISCUSSION (Section 2.3.1.).

1.4.5. THE USE OF COMBINATIONS OF CHIRAL DIRECTORS.

The use of two homochiral reactants, that is, a substrate and a reagent, is a possible method of achieving high optical yields. This would constitute a double asymmetric synthesis as described by Masamune *et al.*.[100] If the two homochiral reactants form a matched pair, that is, they work synergistically, there is rich possibility of achieving high asymmetric induction.

To date there have been no publications on such a study. However, work in progress in these laboratories[101] involves the use of chiral α-alkoxy aldehydes and chiral acrylic systems in the context of double asymmetric induction.

2. DISCUSSION.

2.1. AIMS OF THIS INVESTIGATION.

In its simplest form the Baylis-Hillman reaction[40] involves the
coupling of methyl acrylate (30) with an aldehyde in the
presence of the tertiary amine, DABCO, to afford 2-(α-hydroxy)-
alkyl and aryl acrylates (78) (Scheme 27).
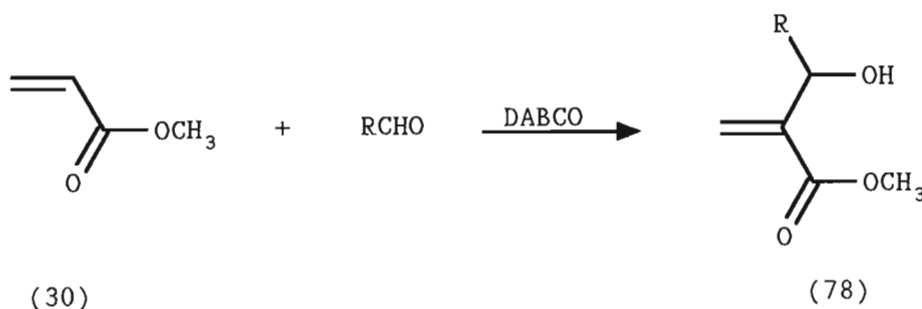
Scheme 27.

For R≠H, the carbon bearing the hydroxyl group is an asymmetric
centre and several possibilities exist for chiral induction in
the product (Section 1.4.). Various authors[40,88,102,103] have
attempted to induce chirality in the reaction product. However,
in no instance was it possible to designate the absolute
configuration of the major stereoisomer unambiguously. Since
benzaldehyde is commonly used as the electrophilic partner in
the Baylis-Hillman reaction, and the resultant 2-(α-hydroxy)-
benzyl acrylate may be hydrolysed to the acid, resolution could
afford one Baylis-Hillman product in homochiral form. The
determination of its absolute configuration would be beneficial
to future asymmetric studies.

One method of achieving asymmetric synthesis using the Baylis-
Hillman reaction is *via* chiral acrylic substrates. Chiral
acrylic esters are readily available from a wide variety of
commercially and synthetically produced chiral alcohols.

Another method of achieving stereoselectivity in the Baylis-Hillman reaction is by making use of chiral aldehydes. Amino acids are readily available with high enantiomeric purity and provide ready access to protected amino aldehydes by reduction. Chiral cyclic amino aldehydes are particularly attractive electrophiles for asymmetric synthesis.[104]

There are many indirect methods of obtaining the Baylis-Hillman product (Section 1.2.2.). An attractive procedure[23] involves the use of amines to mask the acrylic compound. After appropriate modification, the amine is eliminated, hence unmasking the acrylic compound. Scolastico and co-workers[37] have used this approach in aldol-type reactions. A logical extension of this approach would be the use of chiral N-containing masking agents which, after aldol condensation and elimination of the chiral auxiliary, would afford the Baylis-Hillman product stereoselectively.[102]

Since the original patent by Baylis and Hillman,[39] a number of other reactants have been used in this base catalysed coupling reaction (Section 1.3.1.). Attempts to include the crotonic system were unsuccessful, but this was achieved by Hill and Isaacs[46] using high pressures (2-10 kbar). However, even under these extreme conditions, the reaction times were long and yields were poor. An alternative method for obtaining the Baylis-Hillman product of crotonic derivatives would be *via* the masking method.[23,37,102]

The aims of this investigation were thus:

(a) To resolve the Baylis-Hillman product resulting from the reaction of methyl acrylate (30) with benzaldehyde and to determine the absolute configuration of this compound.

(b) To investigate the use of chiral acrylic esters as chiral directors in the Baylis-Hillman reaction.

(c) To investigate chiral cyclic amino aldehydes as chiral inducers in the Baylis-Hillman reaction.

(d) To extend the use of chiral acrylate masking agents with a view to increasing the optical yields of the products.

(e) To extend the chiral masking methodology to the crotonic system.

2.2. RESOLUTION AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF 3-HYDROXY-2-METHYLENE-3-PHENYLPROPANOIC ACID (81)

2.2.1. CLASSICAL RESOLUTION.

In the absence of a chiral environment, the product of the Baylis-Hillman reaction is obviously a racemate. The reaction of methyl acrylate (30) and benzaldehyde (79) in the presence of DABCO, affords (±)-methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80) which may be hydrolysed to (±)-3-hydroxy-2-methylene-3-phenylpropanoic acid (81) (Scheme 28).
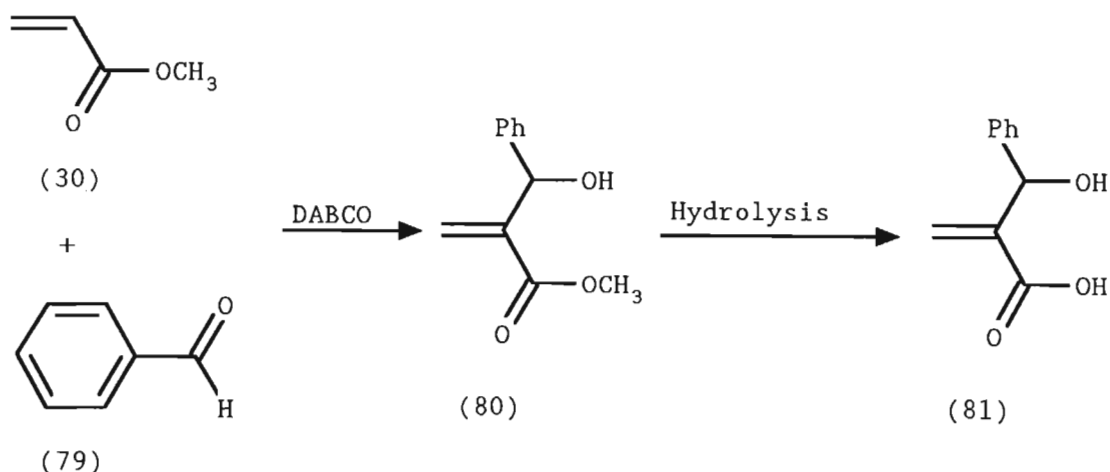
Scheme 28.

Despite its "low technology" image, classical resolution is widely used industrially and in particular, furnishes a large proportion of those optically active drugs which are not derived from natural products. A representative group of such drugs shows that 65% of them owe their optical activity to classical resolution.[14]

Classical resolution becomes particularly attractive when it can be combined with *in situ* racemisation in a crystallisation-induced asymmetric transformation - a process designated "deracemisation".[105] It is then possible to get almost complete conversion to the required enantiomer - precipitation of one diastereomer drives the equilibrium in favour of that isomer.

Although Wilen *et al.*[106] have provided guidelines which permit a rational approach to resolutions with a high probability of success, the crucial step is finding the ideal resolving agent, mostly by trial and error.

2.2.2. KINETIC RESOLUTION.

In this process,[107] one of the enantiomers (A) of a racemate (AB) is more readily converted to the product. Kinetic resolution may be realised by chemical or enzymic methods - in the former case the reaction may be either catalytic or stoichiometric.

In 1985, Brown and Cutting[108] reported on the effective kinetic resolution in the asymmetric hydrogenation of α-(hydroxyalkyl)-acrylic esters obtained *via* the Baylis-Hillman reaction. The rhodium complex of the optically active DIPAMP ligand was used as the catalyst for the reduction. Superior results were obtained when substrates bearing phenyl or furan rings were hydrogenated. Thus, compounds (80) and (82) were reduced
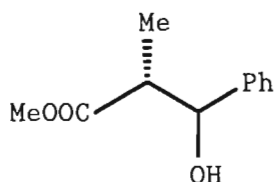
exclusively to compounds (83) and (84) respectively. The maximum discrimination between enantiomers was 6.5:1, and this required reduction to >70% for recovery of the starting materials with better than 90% ee.
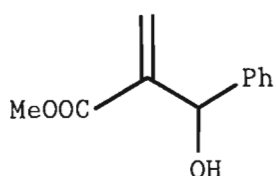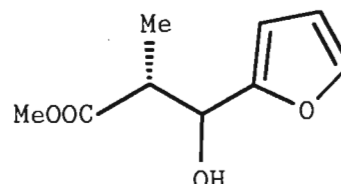

(80)
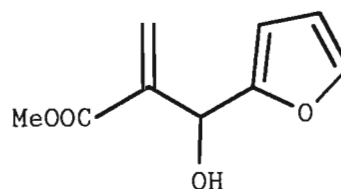
(82)

(83)

(84)

Recently Burgess and Jennings[109] reported on biocatalytic resolutions of α-methylene-β-hydroxy esters and ketones which were prepared by the Baylis-Hillman reaction. The resolutions were achieved *via* lipase mediated irreversible acylations (Scheme 29). The authors found that enantiodiscrimination by the enzyme was high when R_2 was a long chain. Enantiomeric excesses for compounds (86) with varying R_1 and R_2 groups were in the range of 52 to >95%. The absolute configurations were assigned only tentatively by hydrogenation of one of the products and comparing it to a known compound.

(85)   *Pseudomonas* AK
        vinyl acetate
        hexane, 25°C

(86)   +   (87)
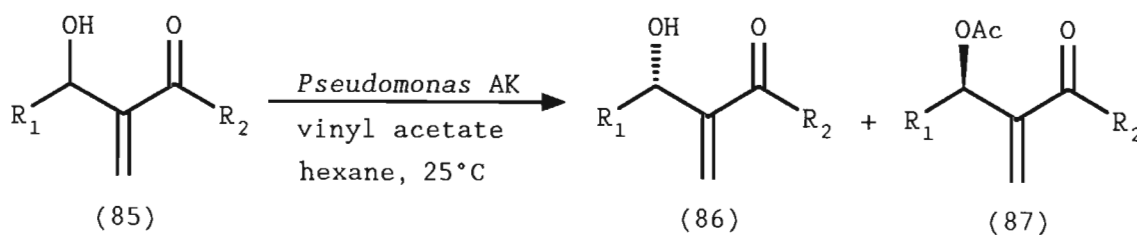
Scheme 29.

2.2.3. RESOLUTION OF 3-HYDROXY-2-METHYLENE-
3-PHENYLPROPANOIC ACID (81).

The desired acid (81) was obtained by hydrolysis of the corres-
ponding ester (80) by conventional methods.[111]

OH   O

Ph   OH
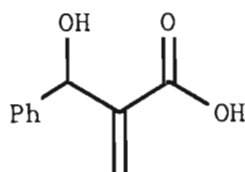
(81)

In 1959, Clarke[112] reported on the resolution of racemic
β-hydroxybutyric acid using quinine (64) as the chiral amine.
Since compound (81) is also a β-hydroxy acid, this seemed to be
a particularly attractive solution for our purposes. Unfor-
tunately, Clarke's procedure did not afford any separable
diastereomeric salts. Use of a wide variety of resolving
agents, which included brucine, ephedrine and 1-phenylethyl-
amine, proved to be no more successful.

In 1971, Boyle[113] described some of the commonly used resolving
agents for the resolution of acids. Among these was D-(-)-*threo*
-2-amino-1-(4-nitrophenyl)-1,3-propanediol   (88)   which   is
commercially available. When compound (81) was treated with
(88) in acetone/chloroform, predominantly one diastereomer of
the salt (89) crystallised on cooling. Repeated recrystalli-
sation of the salt (89) from acetone/chloroform afforded a white
crystalline solid which had a constant melting point (99°C) and
optical rotation ($[\alpha]_D$ = -23.5° (c1.05, CH_3OH)). However, the
enantiohomogeneity of the liberated acid (81) was yet to be
determined.

(88)

(89)
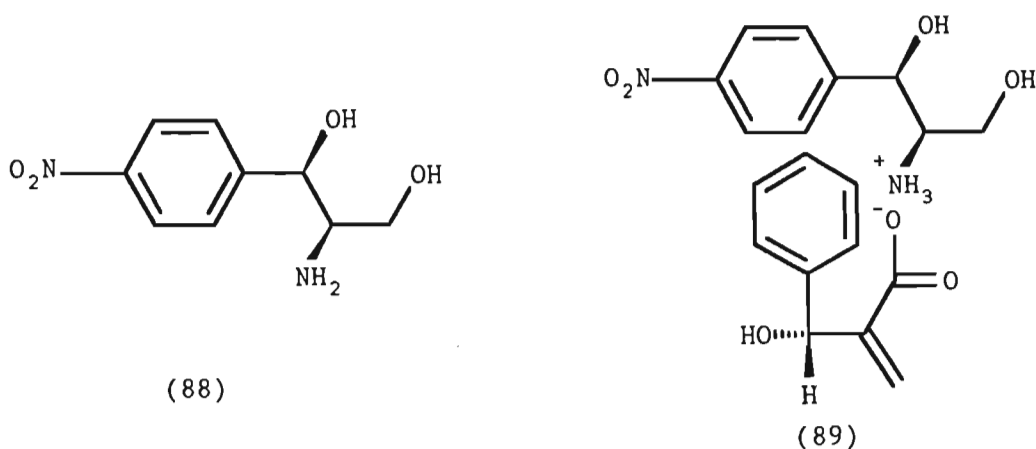
To establish its homochirality, NMR spectroscopy using chiral shift reagents was employed on the corresponding methyl ester (80). Conversion of the "resolved" acid (81) to the "resolved" methyl ester (80) by conventional[111] esterification methods was unsuccessful. However, the DCC procedure[114] afforded "resolved" ester (80) in good (75%) yield.

Addition of Eu(hfc)$_3$ to an NMR sample of racemic-(80) resulted in a downfield shift of the methoxy and vinyl signals. When the methoxy signal had shifted to about 4 ppm, it clearly separated into two signals of equal intensity for each of the enantiomers. Similarly, each of the vinyl protons also showed signals of equal intensity for both enantiomers (Figure 5a).
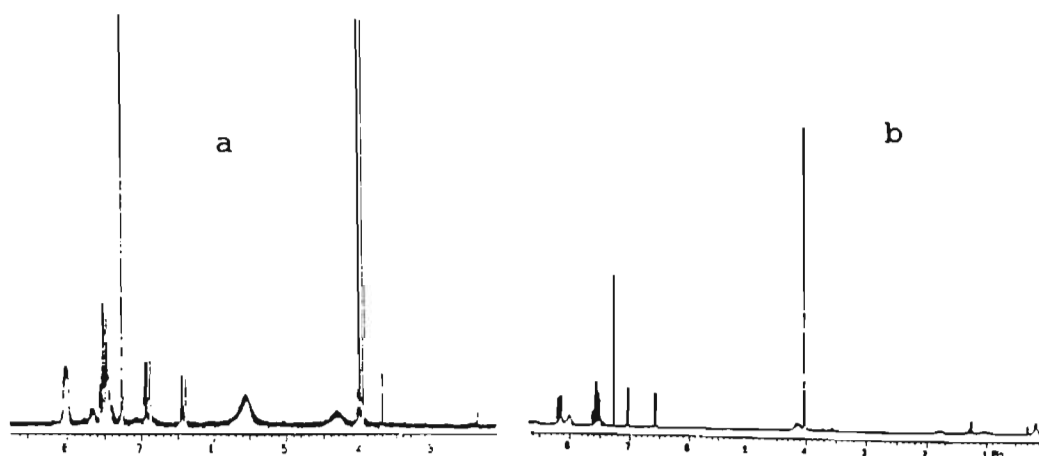

Figure 5.

Shift experiments on "resolved"-(80) using the exact conditions employed for racemic-(80) indicated that the resolution had been successful. Addition of Eu(hfc)$_3$ even after the methoxy signal was beyond 4 ppm, showed no trace of the other enantiomer (Figure 5b).

Thus, the salt (89) (m.p. 99°C, $[\alpha]_D^{25}$ = -23.5° (c1.05, CH$_3$OH)), the liberated acid (81) (m.p. 79°C, $[\alpha]_D^{25}$ = -23.2° (c1.05, CHCl$_3$)) and the methyl ester (80) (m.p. 52°C, $[\alpha]_D^{26}$ = -111.1° (c1.11, CH$_3$OH) are homochiral.

(80)   (81)
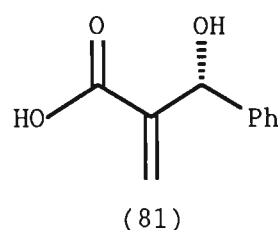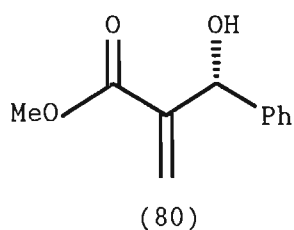
Frequently,[102] ^{t}butyl esters of acrylic systems are prepared because of the steric bulk that accompanies them. Initial attempts to prepare this ester (90), including *via* the DCC method,[114] were unsuccessful. Success was achieved by the isobutylene method.[115] The homochiral tertiary butyl ester (90) had $[\alpha]_D^{26}$ = -93.2° (c1.09, CH$_3$OH).

(90)
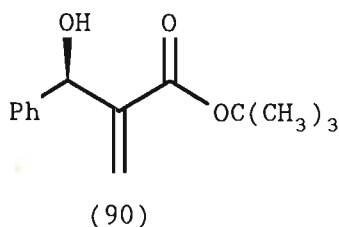
2.2.4. DETERMINATION OF ABSOLUTE CONFIGURATION:

2.2.4.1. BY X-RAY CRYSTALLOGRAPHY.

The homochiral acid (81) is a crystalline solid. A single crystal suitable for x-ray analysis was readily obtained from chloroform/carbon tetrachloride. The use of x-ray crystallography for the determination of absolute configuration is well documented.[116,117] The x-ray structure of the resolved acid (81) is shown below (Figure 6), but the absolute configuration determination, even when using a Cu-tube, was unsuccessful.[118] Attempts to incorporate heavy metals to facilitate the absolute configuration determination did not provide suitable crystals for x-ray analysis.
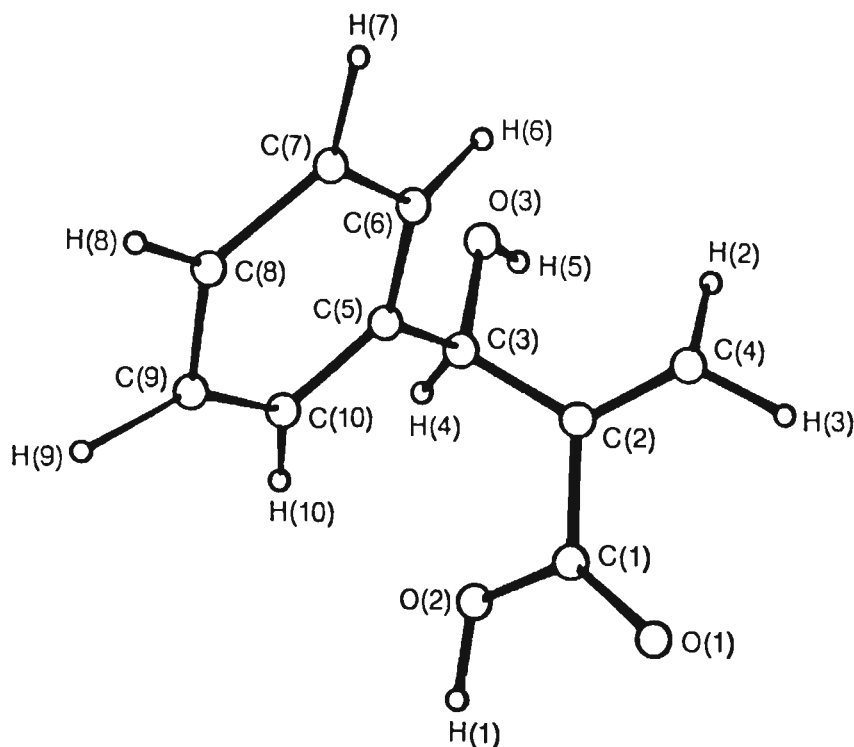

Figure 6.

The homochiral salt (89) is also highly crystalline and would allow the determination of the absolute configuration of the acid portion since the two chiral centres of the resolving agent (88) are of known configuration. Recrystallisation from hot water afforded suitable crystals which permitted x-ray analysis of compound (89) (Figure 7).
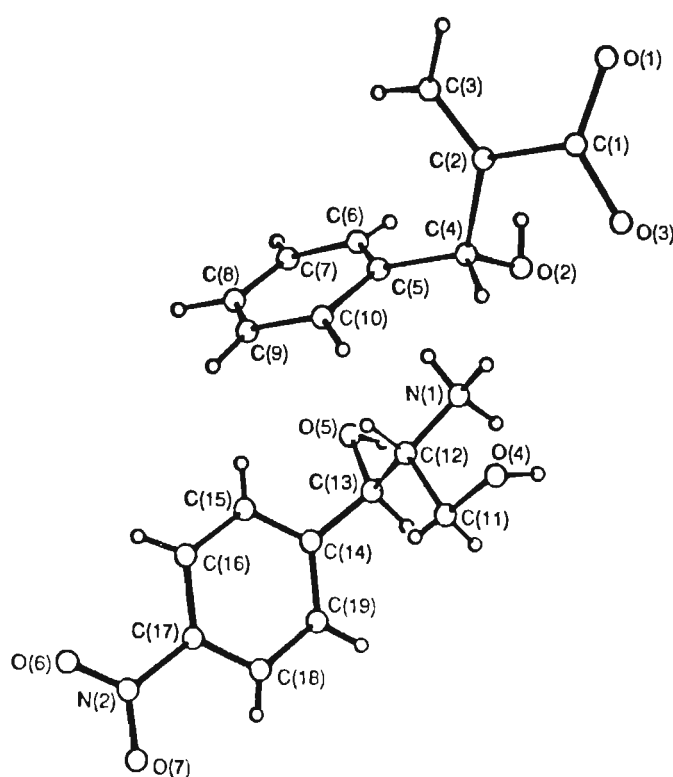

Figure 7.

The absolute configuration at C(3) [C(4) in Figure 7] of the acid (81) was established as R by noting that the configuration at C(13) (Figure 7) is fixed as R. The laevorotatory enantiomer of (81) thus has the 3R configuration.[119,120]

Since the priorities of the groups around the chiral centre of (81) do not change upon esterification, both the laevorotatory esters (80) and (90) also have the 3R configutation.[119,120]

2.2.4.2. BY CHEMICAL INTERCONVERSION.

In a recent series of papers, Oppolzer[121,122] has reported on asymmetric alkylations, acylations and aldolisations using chiral sultam auxiliaries. One of these products (91), of known absolute configuration, may be obtained by hydrogenation of the homochiral methyl ester (80) (Scheme 30).
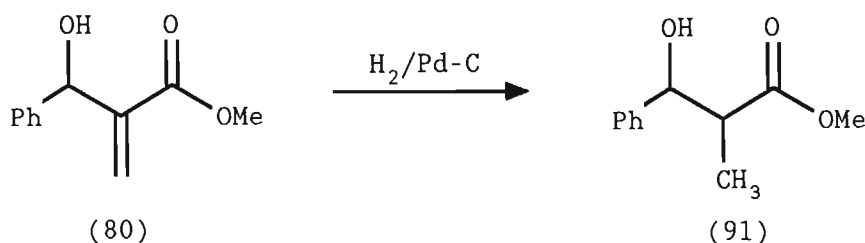
Scheme 30.

Since the chiral centre at C(3) of (80) is unaffected, only two possible diastereomers may result upon hydrogenation. If it is accepted that the absolute configuration at C(3) in (80) is 3R (Section 2.2.4.1.), then the two possible diastereomers would be (2R,3S) and (2S,3S) respectively. The change in absolute configuration of 3R in (80) to 3S in (91) is due to the change in priorities around the chiral centres.

Compound (91) was obtained as a mixture of diastereomers upon hydrogenation of (80) using the procedure of Matsuda and co-workers.[98] Separation by column chromatography afforded diastereomers (91a) ($[\alpha]_D^{21}$ = -57.9° (c1.1, $CHCl_3$)) and (91b) ($[\alpha]_D^{21}$ = -22.8° (c1.2, $CHCl_3$)) (Scheme 31).
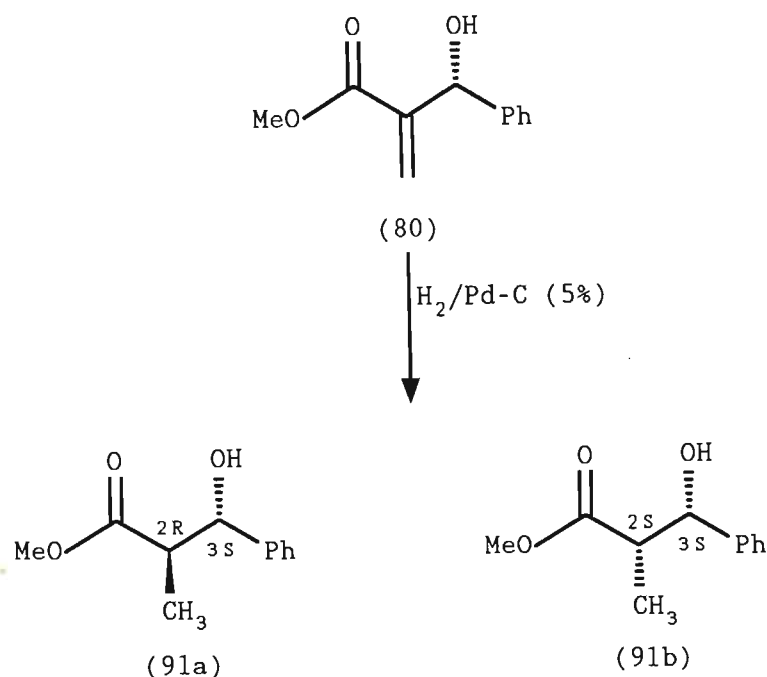
Scheme 31.

Oppolzer[121,122] quotes the optical rotations for the diastereo-
meric forms of (91) as follows:

(2S,3R) $[\alpha]_D$ = +58.9°

(2S,3S) $[\alpha]_D$ = -20.8°

(2R,3R) $[\alpha]_D$ = +23.5°   lit.[123] $[\alpha]_D$ = +23.2°

Hence the antipode of the (2S,3R) diastereomer, that is, the
(2R,3S) antipode would have $[\alpha]_D$ ≈ -58.9°.

Comparison of these optical rotations with those of (91a) and
(91b) confirms that (91a) is the (2R,3S) diastereomer and (91b)
is the (2S,3S) diastereomer and this confirms that the absolute
configuration of (80) is 3R.

The above findings have recently been published.[120]

2.3. ASYMMETRIC SYNTHESIS USING THE BAYLIS-HILLMAN REACTION.

2.3.1. THE USE OF CHIRAL ACRYLIC ESTERS.

Chiral acrylic esters have found wide application in asymmetric synthesis particularly in the area of asymmetric Diels-Alder reactions.[124-126] They are also suitable substrates for asymmetric synthesis *via* the Baylis-Hillman reaction (Section 1.4.4.). Basavaiah and co-workers[103] have published their results on this subject.

In the first instance, Basavaiah and co-workers[103] investigated the applicability of the readily available (-)-menthyl acrylate (92). Brown and co-workers[127] were actually the first group to report on the use of both enantiomers of (92) in the Baylis-Hillman reaction. However, their primary focus was to use these products in directed homogeneous hydrogenation studies.
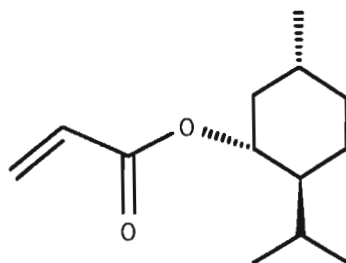

(92)

Using (-)-menthyl acrylate (92) as the substrate, Basavaiah[103] found the diastereoselectivities of the products to be in the range of 7-20% (Table 6, entries 1-5). In this series the best results were obtained when propionaldehyde and furfural were used as the electrophiles (Table 6, entries 2 and 4).

With a view to achieving higher diastereoselectivities, Basavaiah[103] investigated the chiral acrylates (93) and (94) which were readily obtained from the corresponding chiral alcohols.[128] Again, propionaldehyde gave the highest diastereo-selection (Table 6, entries 7 and 9). Benzaldehyde on the other hand, resulted in low diastereoselectivities (Table 6, entries

5,8 and 10).
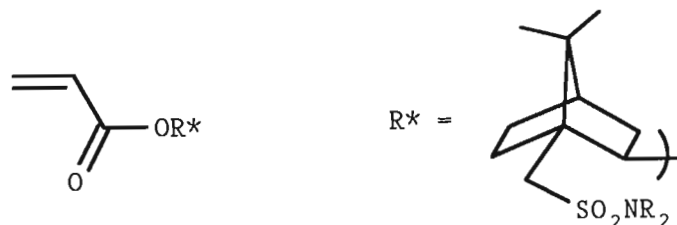
R = -CH(CH$_3$)$_2$ (93)

R = -c-hexyl (94)

Table 6.

| ENTRY	ACRYLATE	ALDEHYDE	YIELD %	de %
1	(92)	CH$_3$CHO	83	11
2	(92)	CH$_3$CH$_2$CHO	78	16
3	(92)	(CH$_3$)$_2$CHCHO	77	7
4	(92)	Furfural	85	20
5	(92)	C$_6$H$_5$CHO	89	15
6	(93)	CH$_3$CHO	70	30
7	(93)	CH$_3$CH$_2$CHO	70	42
8	(93)	C$_6$H$_5$CHO	84	15
9	(94)	CH$_3$CH$_2$CHO	45	70
10	(94)	C$_6$H$_5$CHO	80	25

In general, the diastereoselectivities obtained by Basavaiah and co-workers[103] are low except for entries 7 and 9 (Table 6). The authors did not speculate on the significance of their results.

2.3.1.1. USE OF (R)-(+)-PANTOLACTONE ACRYLATE (96).

In 1985, Helmchen and co-workers[129] used the chiral acrylate derived from (R)-(+)-pantolactone (95) in asymmetric Diels-Alder reactions. Very high diastereofacial selectivities were obtained when it was treated with cyclopentadiene and butadiene.
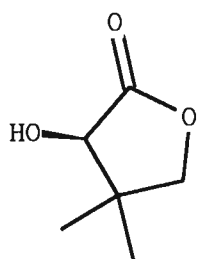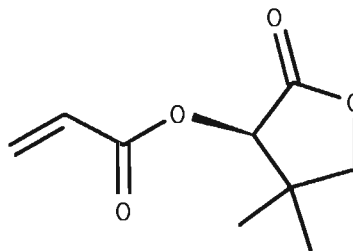
(95)   (96)

Prompted by Helmchen's[129] positive results and the fact that (R)-pantolactone (95) is commercially available, it was selected for asymmetric investigations. (R)-(+)-pantolactone acrylate (96) was obtained in good yield using Helmchen's procedure.[129]

Initial experiments involved the reaction of (96) with acetaldehyde in the presence of DABCO (20 mass% of (96)). Because of the volatility of acetaldehyde, it is usually used in excess and this assists to dissolve the catalyst. Within 20 minutes a white precipitate resulted. Tlc revealed the total consumption of the starting acrylic ester (96). Three compounds, namely, the catalyst DABCO, the alcohol pantolactone (95) and an unknown compound were identified.

The unknown compound was readily separated from the mixture by chromatography. ^{1}H and ^{13}C NMR indicated the presence of two methyl groups, a methylene group, two methine groups and two quarternary carbon atoms. This information, together with mass spectrometry and microanalysis, pointed towards structure (97).

(97)
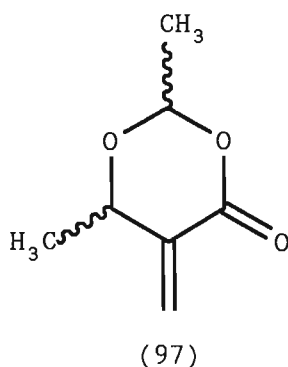
The proposed mechanism for the formation of (97) involves initial reaction of pantolactone acrylate (96) with one equivalent of acetaldehyde to afford intermediate (98) (Scheme 32). Further reaction produces a hemiacetal (99) which undergoes an intramolecular transesterification to afford the dioxanone (97) in 84% yield. The alcohol liberated during the transesterification is recovered as the optically pure compound (95).
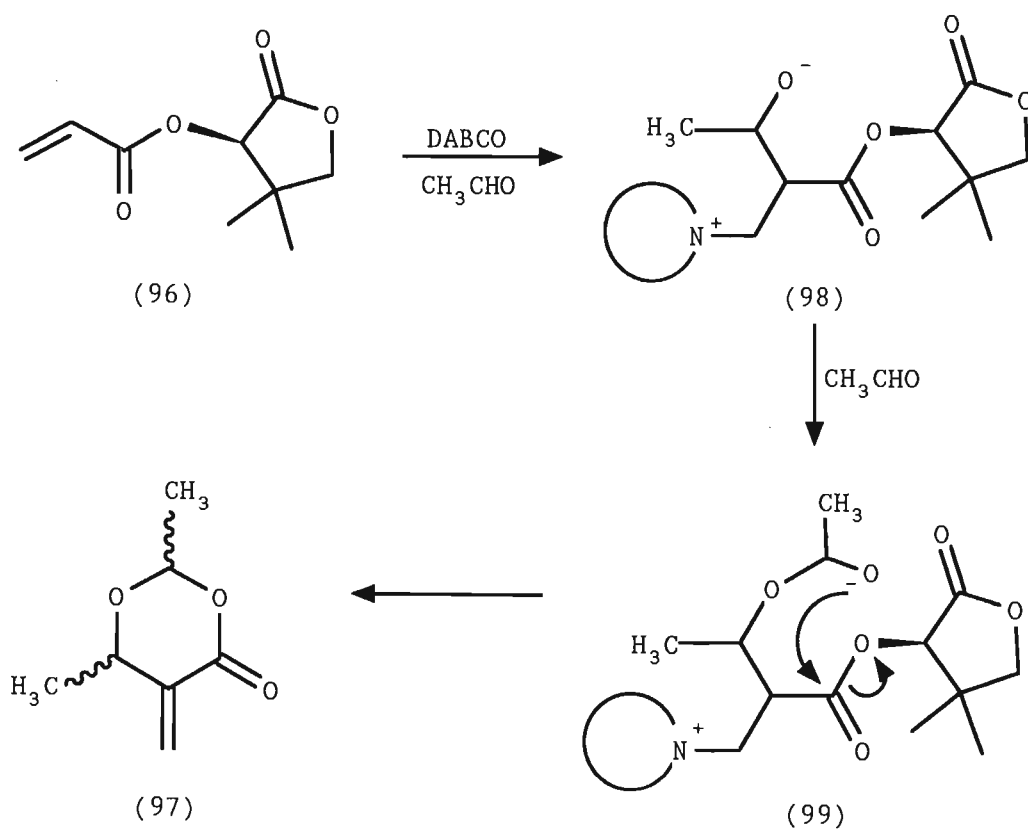
Scheme 32.

An interesting feature in the gas chromatograph/mass spectrum of
(97) is the presence of two separable peaks, both having the
same molecular ion and fragmentation pattern. These were
clearly diastereomers and the cyclisation was highly diastereo-
selective (87% de). Surprisingly, NMR did not indicate the
presence of diastereomers.

Preliminary results in this area have been published.[130]

The importance of this novel cyclisation towards the synthesis
of 1,3-dioxan-4-ones is borne out by the numerous publications
that have emerged concurrently and independently on the
synthesis and synthetic potential of these highly functionalised
molecules.[132-149]

## 2.3.1.1.1. RELATED WORK ON 1,3-DIOXAN-4-ONES.

In 1970 Äyräs and Pihlaja[131] reported on the preparation of
1,3-dioxan-4-one and its methyl derivatives. Prior to this,
with the exception of two noteworthy reports, very little
attention had been paid to these compounds. The report by Kahn
and Cohen[132] investigated the effect of 2,2,6-trimethyl-4-oxo-
1,3-dioxane on cation transfer in incubated cold-stored human
erythrocytes. The other report by Hennes and Gundiger[133]
involved the synthesis of some chlorinated derivatives from
chloral hydrate and a chlorinated 3-hydroxyacid.

Äyräs and Pihlaja[131] gained access to 1,3-dioxan-4-ones (101) by
condensing 3-hydroxyacids (100) with appropriate aldehydes in
slightly acid medium (Scheme 33). Several derivatives of type
(101) were synthesised in varying yields (10-81%), some of which
were isolated as mixtures of isomers.
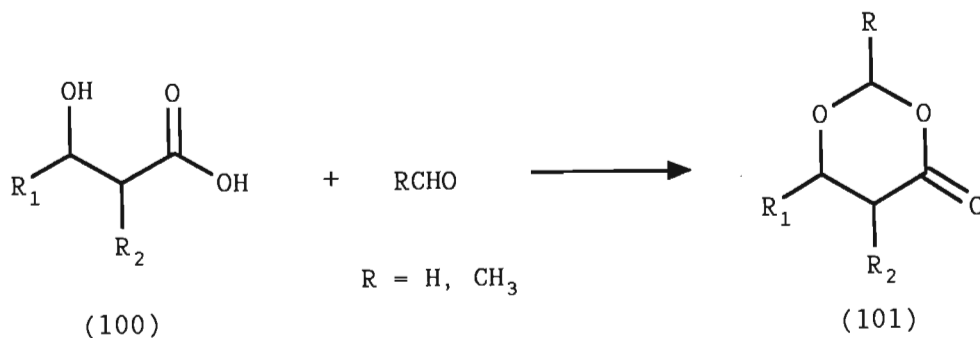
Scheme 33.

Seebach and co-workers[134] produced a series of dioxanones (103) from various aldehydes and (R)- or (S)-3-hydroxybutanoic acid (102) which were obtained from poly(hydroxybutanoate) (R-(102)) or by the yeast reduction of acetoacetic acid (S-(102)) (Scheme 34 and Table 7).
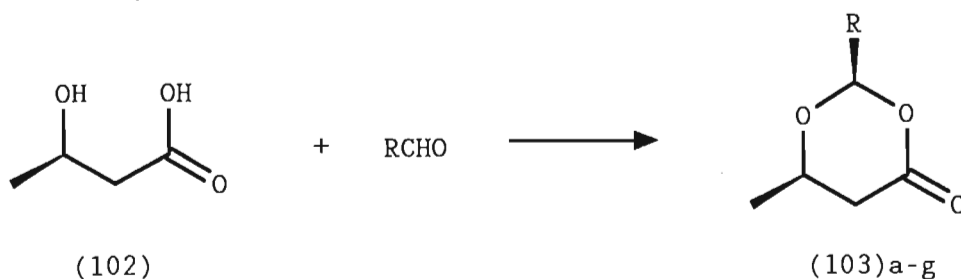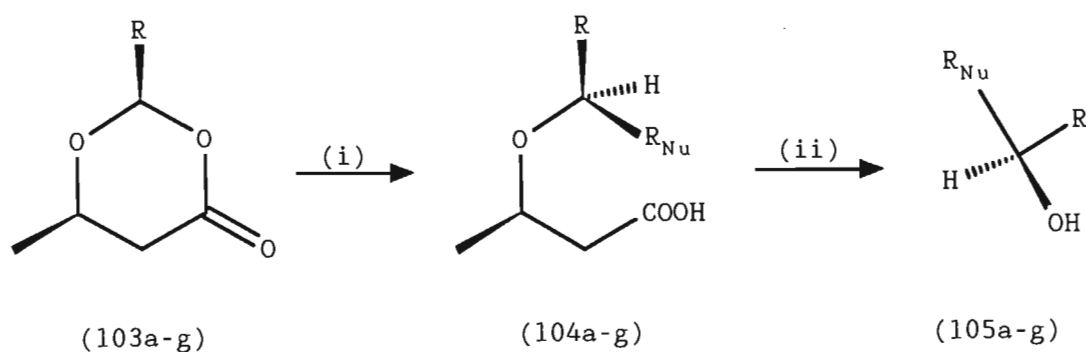

Scheme 34.

Table 7.

PRODUCT (103)	R	YIELD %
(a)	CH_3	60
(b)	$CH(CH_3)_2$	61
(c)	$C(CH_3)_3$	40
(d)	$n\text{-}C_7H_{15}$	71
(e)	$(CH_2)_2C_6H_5$	66
(f)	$n\text{-}C_8H_{17}$	66
(g)	CCl_3	50

When the dioxanones (103a-g) were treated at -75°C with a silyl nucleophile, Me₃SiR_Nu, and titanium tetrachloride or isopropoxy-titanium trichloride, the corresponding β-alkoxy acids (104) were produced in high yields and excellent diastereoselec-tivities. Treatment of the acids (104) with excess LDA afforded the corresponding optically active alcohols (105) with >90% ee (Scheme 35)).


(103a-g)   (104a-g)   (105a-g)

Reagents: (i) a) Me₃SiR_Nu, CH₂Cl₂, -75°C.

          b) Cl₃TiX, -75°C to RT.   c) H₂O

(ii) LDA/THF, -30°C to RT.

Scheme 35.

Following the above report, Seebach and co-workers[135-149] exploited the synthetic potential of 1,3-dioxan-4-ones. The alcohols (105) were derived from reaction at position two of the dioxanones. Subsequent reports described reactions at positions five and six of the dioxanones leading to interesting products. Some examples will be described.

Using (103c), Seebach and co-workers[135] were able to generate the lithium enolate (106) which was found to be resistant to β-elimination[150] at -75°C. Alkylation of (106) produced 5,6-*trans*-disubstituted dioxanones (107) diastereoselectively, demonstrating reaction at position 5 (Scheme 36).
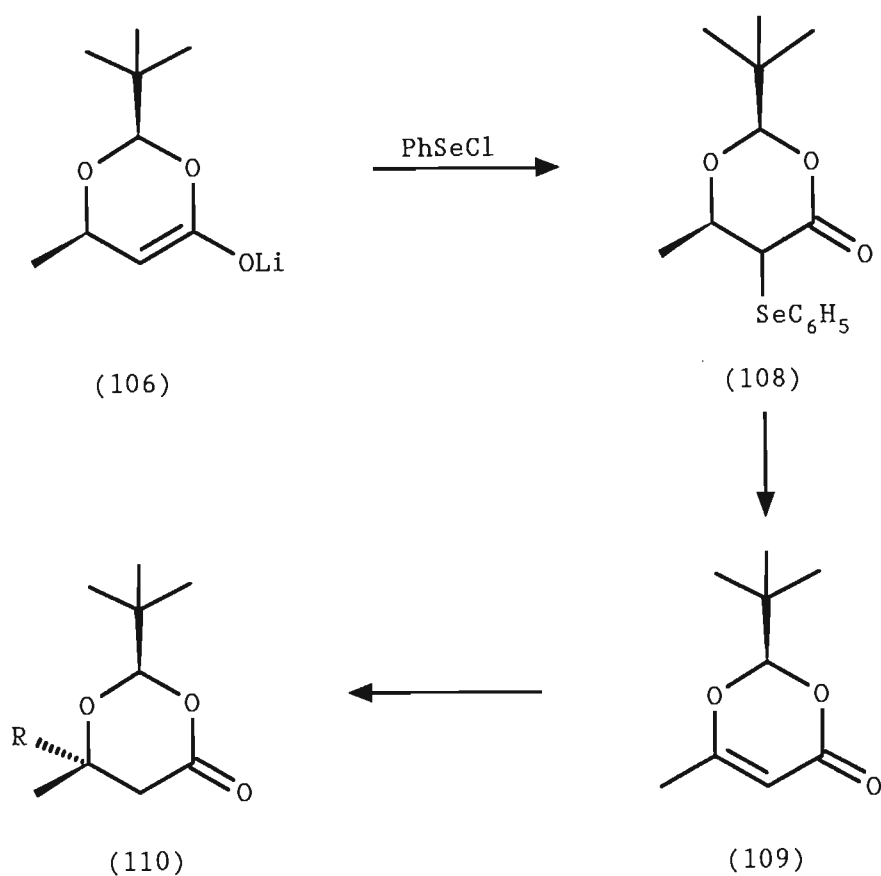

(103c)   (106)   (107)
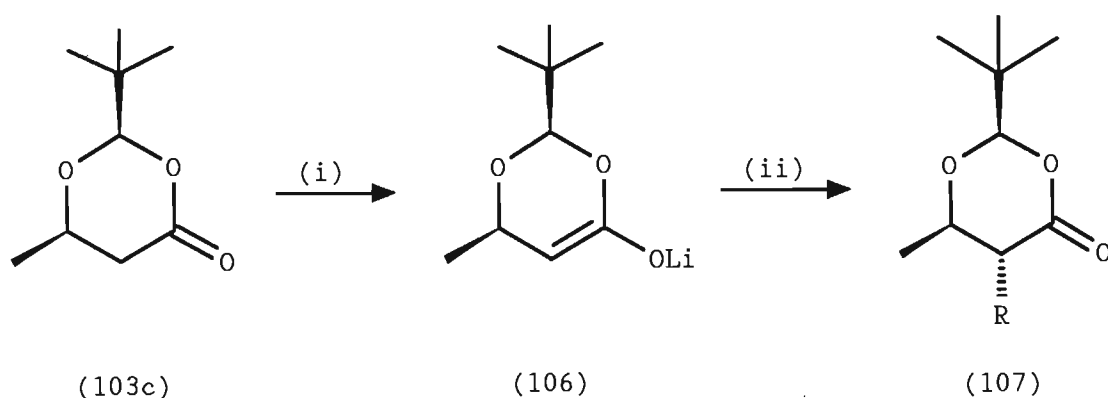
Reagents: (i) LDA, THF, -75°C.

             (ii) RX

Scheme 36.

The enolate (106) was selenated with phenylselenyl chloride to produce (108) which, after oxidation, spontaneously eliminated to (109). Michael addition of dialkyl cuprates led to single products (110) containing a new persubstituted stereogenic centre at C(6) (Scheme 37).

Scheme 37.

Recently, Seebach and Amberg[141] described the synthesis and reactivity of the α-benzylidene derivative (111). This compound was subjected to direct Michael additions of silyl groups and, in each case, only a single stereoisomer (112) of the possible Michael adducts was formed (Scheme 38).

(111)   (112)
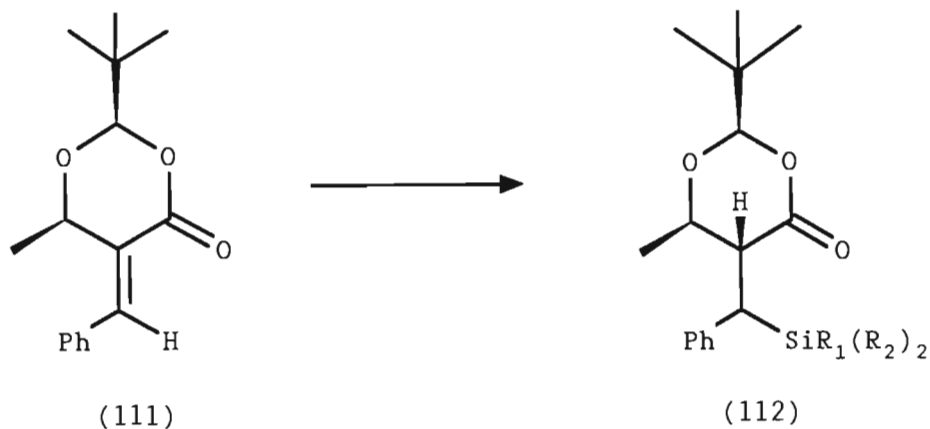
Reagents: (i) ClSiR$_1$(R$_2$)$_2$ (ii) Bu$_2$Cu(CN)Li$_2$,   -75°C, THF

               (iii) NH$_3$/H$_2$O   (iv) H$^+$ or F$^-$

Scheme 38.

Seebach and Amberg followed this up with several papers describing the reactivity of dioxanones.[143-145]

The 2,6-dialkyl-5-methylene-1,3-dioxan-4-one (97) prepared in this study, resembles Seebach's dioxanone (111). Seebach[143] did in fact produce a dioxanone (113) bearing a terminal double bond by a procedure involving selenation and oxidative elimination (Scheme 39).

(113)
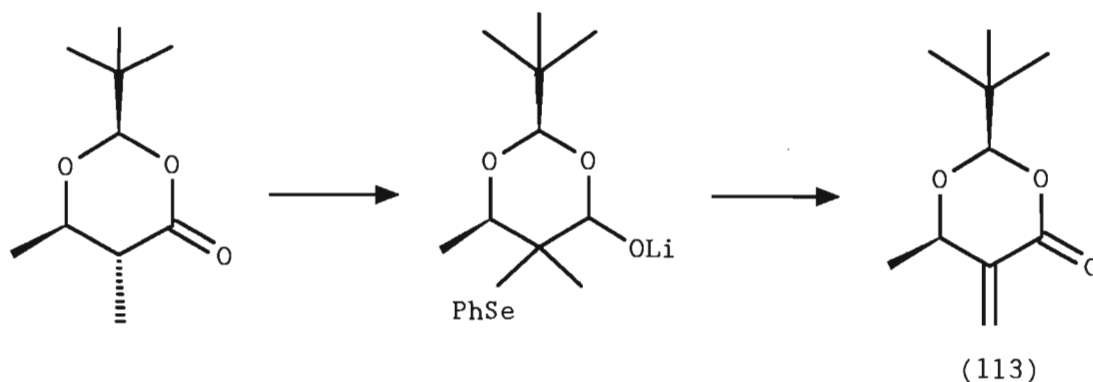
Scheme 39.

In an alternative route, Seebach and Amberg[144] described the synthesis of (113) *via* reaction of the hydrolysis product of the methyl acrylate/acetaldehyde Baylis-Hillman reaction with pivalaldehyde.

2.3.1.1.2. REACTION OF PANTOLACTONE ACRYLATE (96) WITH OTHER ALDEHYDES.

Several aldehydes were investigated in the Baylis-Hillman reaction of pantolactone acrylate (96). Since the cyclisation to the dioxanone occurred so readily with acetaldehyde, an investigation of this method of producing 1,3-dioxan-4-ones with a view to establishing the requirements and constraints of this novel cyclisation reaction, was undertaken. Therefore, all reactions involving acrylate (96) were conducted using 20 mass% DABCO (based on (96)) and >2 equivalents of the aldehyde.

In the first instance, a series of acyclic aliphatic aldehydes were examined to establish the generality of the cyclisation to the substituted 1,3-dioxan-4-ones (114). In all cases, the desired product (114a-c) was isolated in high yield and very good diastereoselectivity (78-87%) (Scheme 40).
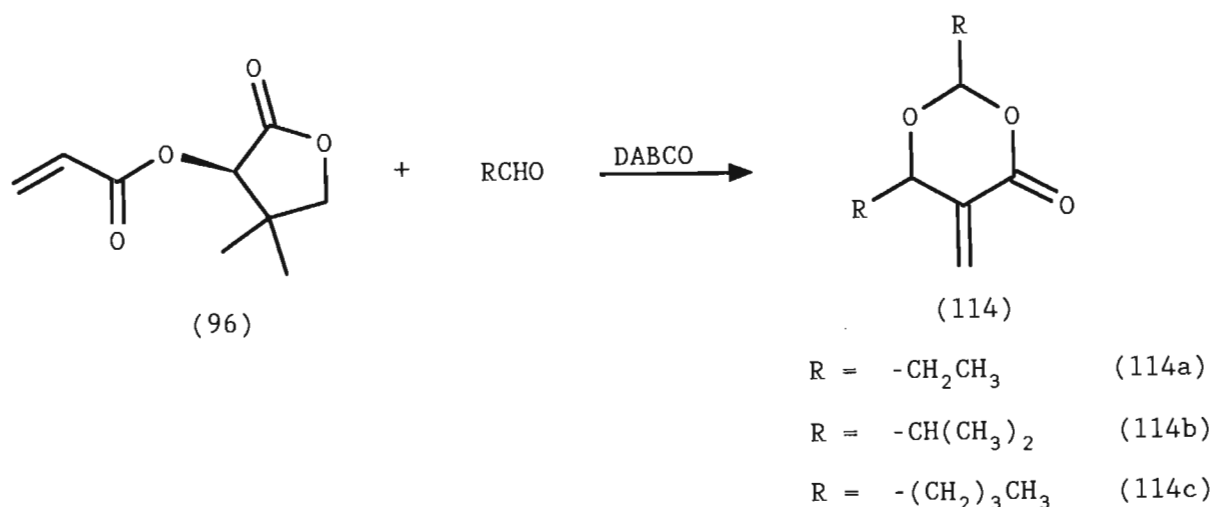
Scheme 40.

The study was extended to aromatic aldehydes starting with benzaldehyde (79). In this case, the expected 1,3-dioxan-4-one (115) was not formed. Instead, the "normal" Baylis-Hillman product (116) was isolated in good yield but very poor diastereoselection (2% de).
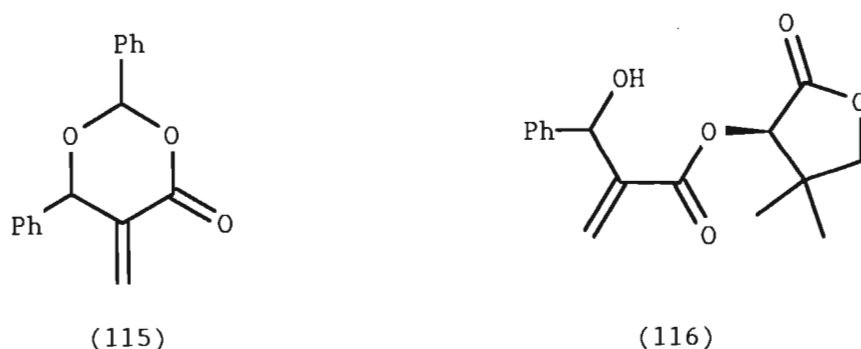
Since the steric bulk of an isopropyl group is normally considered to be greater than that of a benzyl substituent,[151] the phenyl group should not hinder the cyclisation. In order to totally exclude steric influences on the cyclisation process, pantolactone acrylate (96) was allowed to react with cyclohexanecarboxaldehyde under the same conditions. The expected dioxanone (117) was obtained in good yield with a de of 86%.

(117)
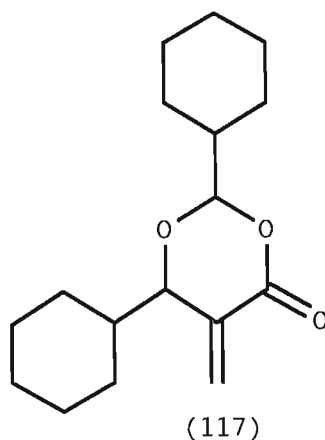
The above findings indicate that the reason for the phenyl derivative not being able to cyclise is not a steric effect but possibly an electronic one. A possible explanation is that the cyclisation process is dependent on the nucleophilicity of the oxyanion of intermediate (118) which in turn depends on the nature of R. March[74] describes the order of nucleophilicity for a few examples as follows:

$$NH_2^- > \underline{RO}^- > OH^- > R_2NH > \underline{ArO}^- > NH_3 > \text{pyridine} > F^- > H_2O.$$
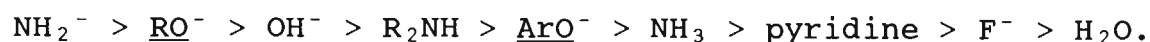
If this is extrapolated to the present situation, then the nucleophilicity order would be expected to be:

R = alkyl
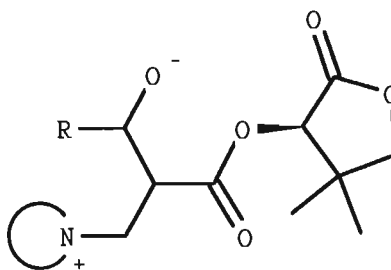
(118)

The above proposal may also be explained in terms of the inductive effects that operate. Alkyl groups are usually regarded as electron donating (+I) while Ph groups are associated with a -I effect.[74] The inductive effect that is operating affects the nucleophilicity of the oxyanion and hence dictates whether or not cyclisation will occur.

In order to find support for the above proposal, trichloro-acetaldehyde was used. This aldehyde is very reactive and has the negative inductive influence (-I) of the three chlorine atoms associated with it. In this instance, the conventional Baylis-Hillman product (119) was isolated in excellent yield (83%) and reasonable diastereoselection (48% de) but without a trace of the expected dioxanone (120). It seems reasonable to propose that the cyclisation to the dioxanone is influenced by the nature of the inductive effect that is operating.
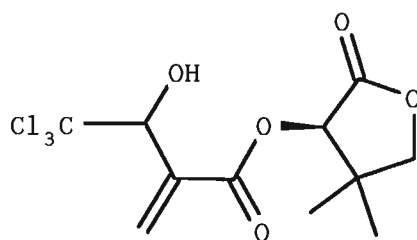
(119)
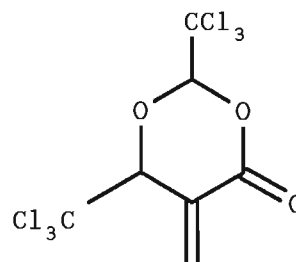
(120)

The results for the reactions that led to dioxanones together with the yields and diastereomeric excesses are summarised in Table 8.

Table 8.

(96)
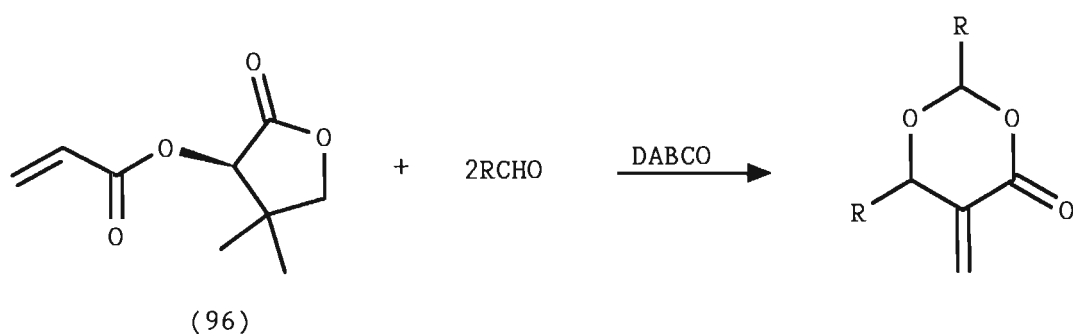
ENTRY	R	YIELD %	de %
1	CH_3	84	87
2	CH_2CH_3	89	78
3	$CH(CH_3)_2$	78	81
4	$(CH_2)_3CH_3$	77	78
5	c-hexyl	61	86

Table 9 summarises the reactions that resulted in conventional Baylis-Hillman products.

Table 9.

(96)

ENTRY	RCHO	YIELD %	de %
1	PhCHO	81	2
2	Cl_3CHO	83	48

The product (119) (Table 9, entry 2) is a white crystalline solid. Attempts to separate the major diastereomer from the 74:26 mixture by recrystallisation were unsuccessful. However, recrystallisation from chloroform furnished the minor diastereomer exclusively ($[\alpha]_D^{27}$ = -8.6° (c0.74, $CHCl_3$)). The crystals were suitable for x-ray analysis of the compound (Figure 8).[152]

Figure 8.

From the x-ray diagram and the fact that the absolute configuration of C(6) (Figure 8) is fixed as R, the absolute configuration of the newly formed centre C(3) [C(2) in Figure 8] of the minor diastereomer was determined to be 3S. Hence the major diastereomer has the 3R configuration. This result will be used in future discussions.

2.3.1.1.3. SYNTHESIS OF MIXED DIOXANONES.

In all the cases discussed so far, the substituents at the 2 and 6 positions of the dioxanones (121) were derived from the same aldehyde ($R_1 = R_2$). It would obviously be of interest to see whether cases of $R_1 \neq R_2$ could be synthesised. In Seebach's[134] dioxanones (Scheme 34), which derive from 3-hydroxybutanoic acid (102), the substituent at the 6 position (R_1) is fixed by the hydroxyacid (102). Only the substituent at the 2 position may be varied depending on the aldehyde used.

(121)
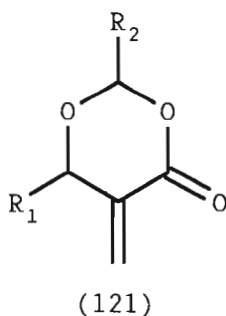
The mechanism proposed earlier (Scheme 32) suggests that disubstitution ($R_1 \neq R_2$) is a possibility leading to "mixed" dioxanones (Scheme 41).
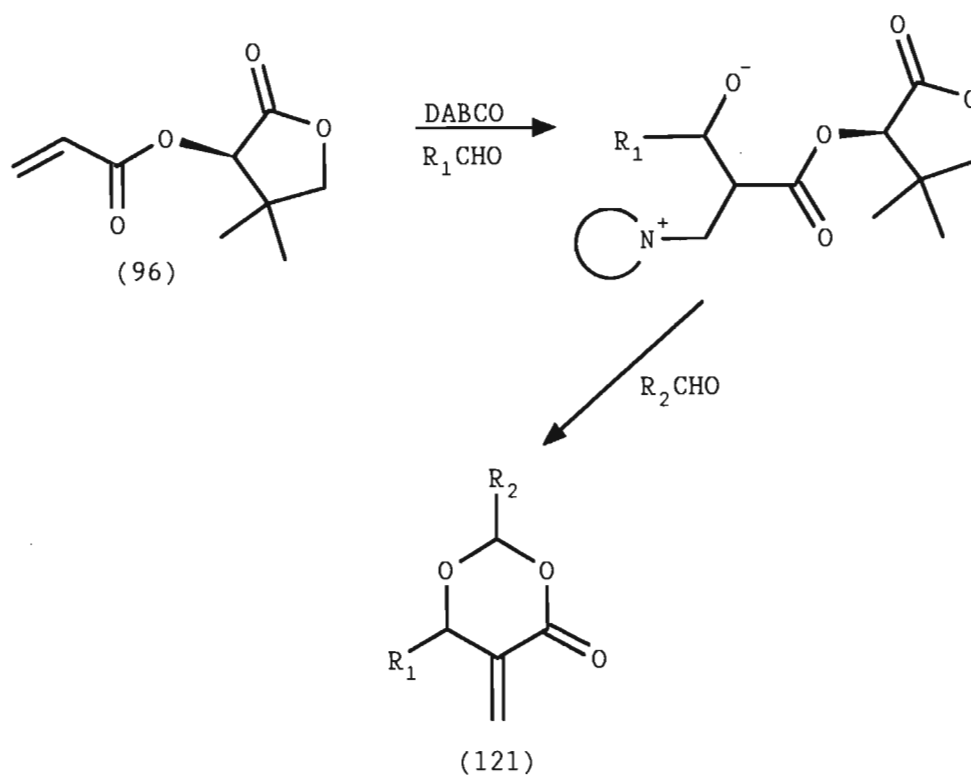
Scheme 41.

Indeed, when acrylate (96) was allowed to react overnight with one equivalent of cyclohexanecarboxaldehyde, followed by treatment with one equivalent of acetaldehyde, the mixed dioxanone (122) was obtained in 52% yield and a de of 83%. The lower yield is due to the fact that some (117) was formed .

(122)

(117)
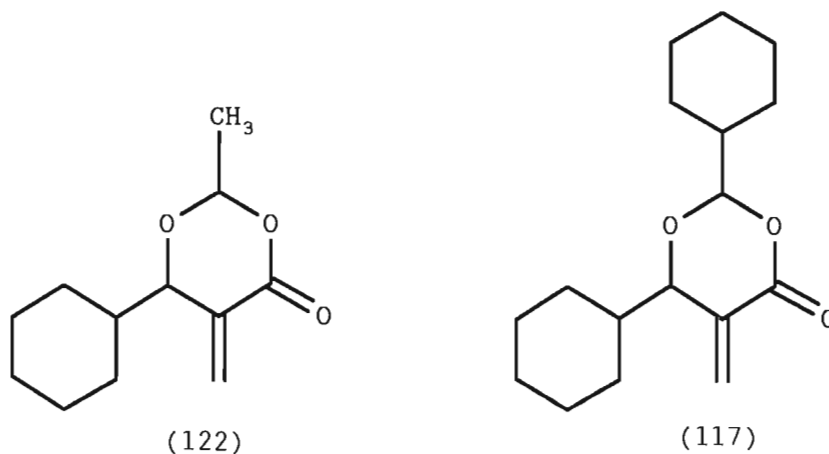
The above reaction was repeated using isobutyraldehyde as the second aldehyde. Dioxanone (123) was produced with a diastereomeric excess of 78%. These results, together with those in a preliminary publication,[130] makes this a useful entry into the synthesis of 2,6-disubstituted-5-methylene-1,3-dioxan-4-ones (121) with the substituents at the 2 and 6 positions varying depending on the aldehydes used.

(123)
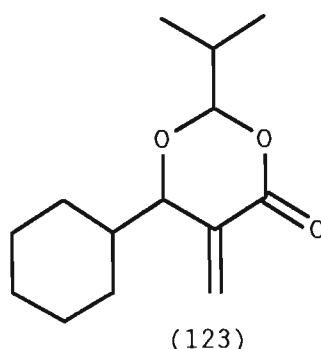
2.3.1.1.4. CONFORMATIONAL AND CONFIGURATIONAL STUDIES.

From GC/MS and NMR data it is evident that the cyclisation to the dioxanones is highly diastereoselective. Initial investigations were concerned with establishing the relationship of the alkyl substituents at the 2 and 6 positions, that is, whether the cyclistion is *cis* or *trans* selective.

Preliminary investigations involved the comparison of ^1H and ^{13}C NMR shifts of dioxanone (97) to closely related compounds prepared by Anteunis and Camerlynck[153] and Äyräs and Pihlaja.[154] Table 10 compares the NMR data of (97) to those presented more recently by Seebach[137] for compounds (124) and (125). The absence of the exocyclic methylene group in (124) and (125) must be taken into account. However, ^{13}C NMR shifts suggest that (97) is the *cis* isomer and that compounds similar to (97) take on a flattened chair conformation.[153]

Table 10.
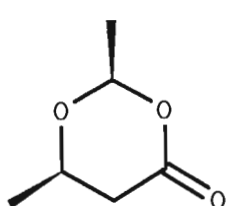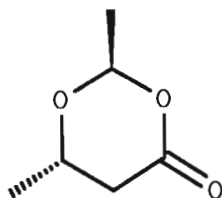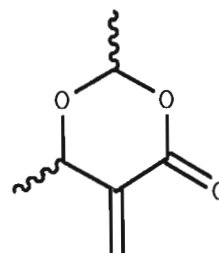
COMPOUND	H-C$_2$	H-C$_6$	C-2	C-6
(124)	5.45	3.97-4.08	70.15	100.19
(125)	5.61	-	66.74	94.53
(97)	5.54	4.65-4.71	73.57	99.03

NOE experiments on dioxanones would allow the determination of the positions of the alkyl substituents relative to each other. Seebach and co-workers[137,149] have indeed used NOE experiments to determine the configurations of their dioxanones and have established the *cis* relationship of the substituents at the 2 and 6 positions.

Three substrates, namely, two from the alicyclic aldehyde series ((97) and (114b)) and the one derived from cyclo-hexanecarboxaldehyde (117), were examined for NOE effects.

(97)   (114b)   (117)
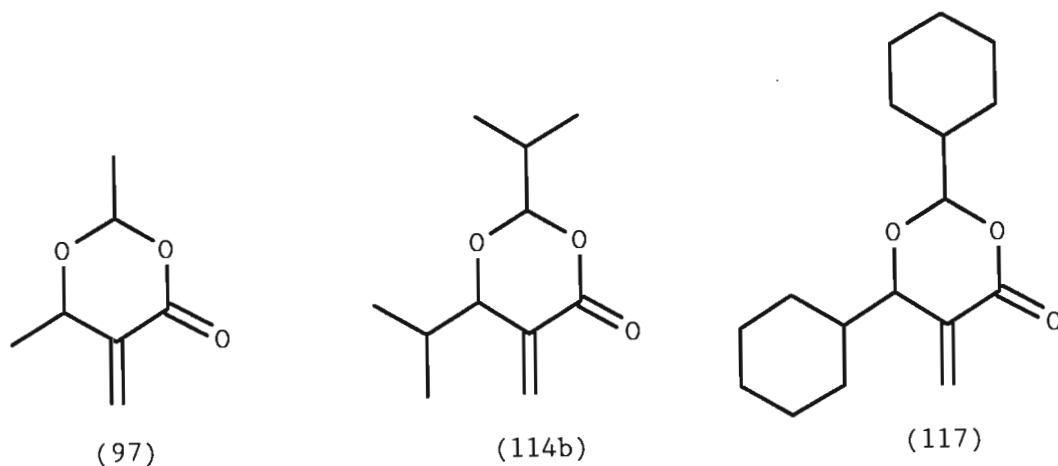
In all cases, irradiation of the proton at position 2 of the major diastereomer resulted in a positive NOE for the corresponding proton at the 6 position. Irradiation of the proton at the 6 position resulted in the same effect on the signal at position 2 (Figure 9).

\# Frequency of irradiation

* Positive NOE
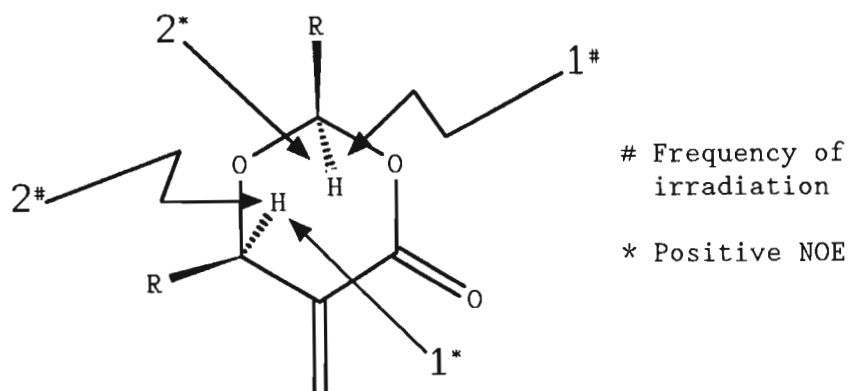
Figure 9.

The above results, together with the NMR shift correlations, allows the conclusion that the dioxanones adopt a *cis* configuration and that the cyclisation is highly *cis* selective.

Assuming the above arrangement, then the possible diastereomers would be 2R6R, 2S6S, 2R6S and 2S6R. Since the RR/SS pair and RS/SR pair are enantiomers, the observed diastereomeric excesses arise from the excess of the RR/SS pair (diastereomer 1) over

the RS/SR pair (diastereomer 2) or *vice versa*. The *cis* configurations of the dioxanones allows the deduction that the observed diastereomeric excesses are due to the excess of the RR/SS pair over the RS/SR pair.

2.3.1.1.5. REACTIONS OF DIOXANONES.

2.3.1.1.5.1. ISOMERISATION OF THE EXOCYCLIC DOUBLE BOND.

In a review article, Hubert and Reimlinger[155] described the isomerisation of exocyclic olefins to the endocyclic isomers. The authors state that endocyclic olefins are as a rule more stable. Several examples of this type of isomerisation are described in this review[155] and a later one by the same authors.[156] These migrations have also been observed in steroids in the presence of hydrogenation catalysts.[157]

During conformational studies of 5-alkylidene-1,3-dioxanes, Anteunis and Camerlynck[153] subjected compound (126) to hydrogenation using Pt as the catalyst. This produced compounds (127) and (128) (Scheme 42). The dioxin (128) was the minor product and was resistant to further hydrogenation.

(126)   (127)   (128)
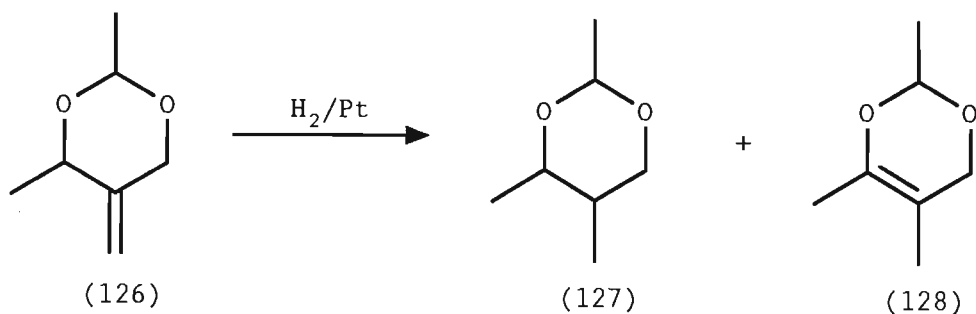
Scheme 42.

In view of the above findings, dioxanone (97) was hydrogenated using Pd-C as the catalyst. If the reaction was to follow that of Anteunis and Camerlynck[153] (Scheme 42), then the products (129) and (130) would be expected (Scheme 43).

(97)   H₂/Pd-C   (129)   +   (130)
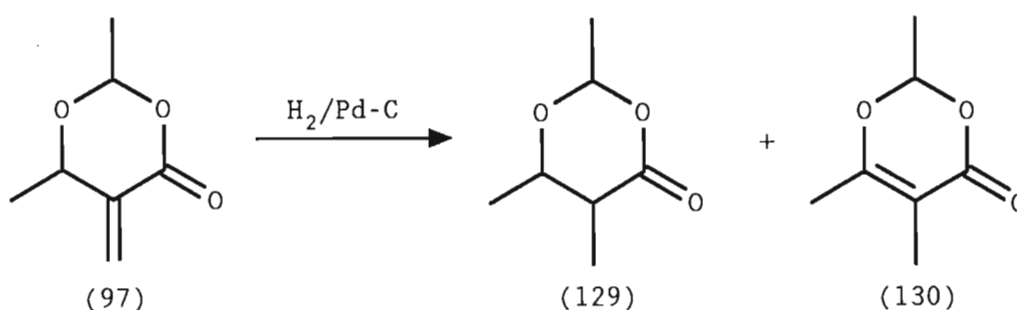
Scheme 43.

However, tlc revealed that the starting material (97) was totally transformed to the dioxinone (130) without a trace of the saturated compound (129). Compound (130) was resistant to further hydrogenation. Seebach[144] has also used this method to produce compound (131) from (113).

(113)   (131)
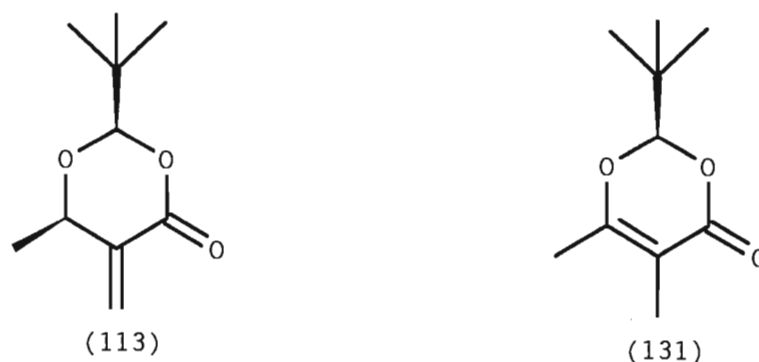
In order to establish the generality of the observed isomerisation, compounds (114b) and (117) were subjected to the same conditions. The corresponding dioxinones (132) and (133) were produced quantitatively.
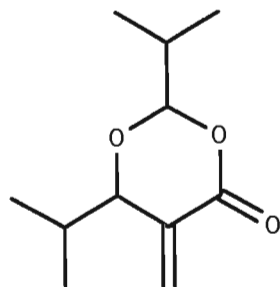
(114b)
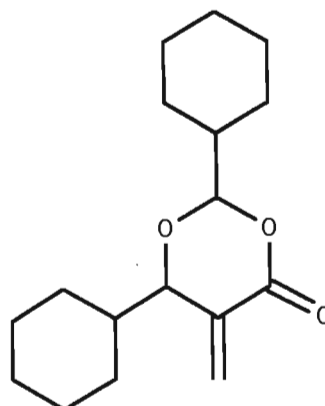
(117)
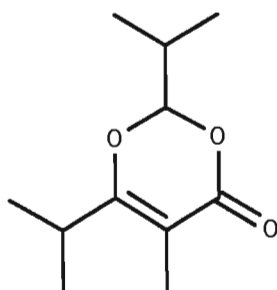
(132)
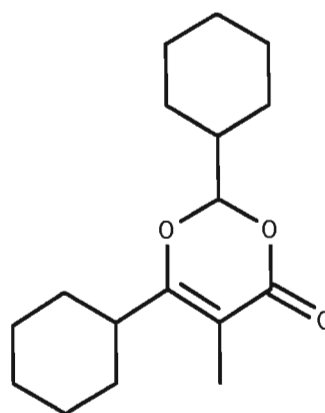
(133)

The isomerisation of the double bond destroys the chiral centre at C(6). If the contributions of the minor diastereomers are ignored, then the use of chiral shift reagents should allow the determination of enantiomeric excesses. These were determined using Eu(hfc)$_3$ and were not nearly as high as the de's of the corresponding dioxanones (Table 11). However, there seems to be a steady increase in ee as the steric bulk of the aldehyde increases from acetaldehyde to cyclohexanecarboxaldehyde.

Table 11.

ENTRY	COMPOUND	ee %
1	(130)	10
2	(132)	22
3	(133)	39

From the x-ray structure of compound (119) (Figure 8), it was deduced that the major diastereomer had the 3R configuration. If attack of the DABCO-pantolactone acrylate adduct occurs from the same side during dioxanone formation, then the intermediate (134) is expected to have the 3S diastereomer in excess (R changes to S purely as a result of priorities of substituents).
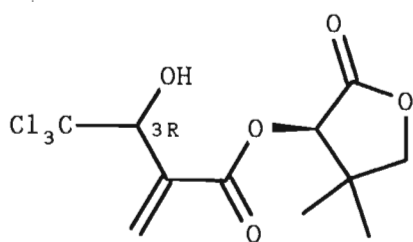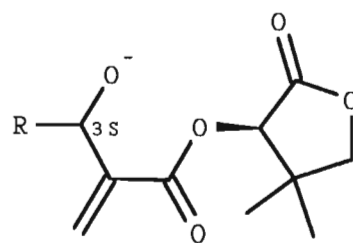
(119)   (134)

Reaction of intermediate (134) with a second equivalent of aldehyde followed by transesterification affords the dioxanones. It has already been established that the de's result from the excess of the RR/SS pair over the RS/SR pair (Section 2.3.1.1.4.). If the contributions of the minor diastereomers are ignored, then the ee's observed are due to the excess of the SS enantiomer over the RR enantiomer.

2.3.1.1.5.2. HYDROLYSIS OF DIOXANONES.

The reaction of pantolactone acrylate (96) with certain aldehydes seems to favour dioxanone formation. Indeed, when (96) is allowed to react with one equivalent of acetaldehyde under Baylis-Hillman conditions, a mixture of the conventional product (135) and the dioxanone (97) is produced. The lower yields obtained for mixed dioxanones (Section 2.3.1.1.3.) resulted from the formation of some dioxanone purely from the first aldehyde used.

(135)   (97)
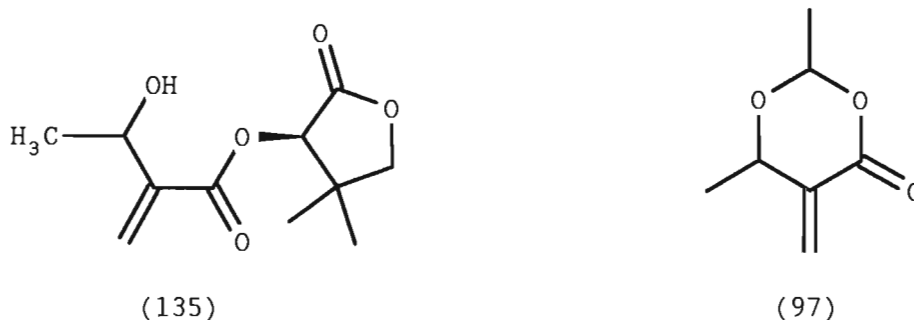
The conventional Baylis-Hillman products can also be produced from the dioxanones by hydrolysis and esterification. The esterification of the Baylis-Hillman derived hydroxyacid (81) by the DCC method[114] has already been described (Section 2.2.3.).

Seebach and Amberg[144] have described a general procedure for the hydrolysis of 5-alkyl or aryl 1,3-dioxan-4-ones. The dioxanones were hydrolysed to the corresponding α-alkyl or aryl hydroxy-acids in good yield (Scheme 44).

3N HCl/THF

(136)
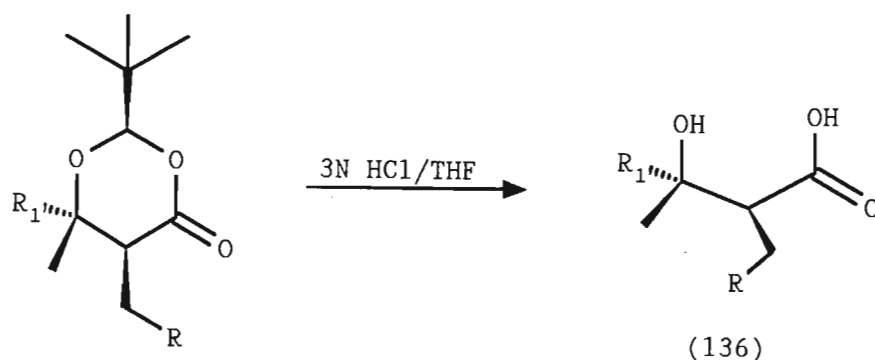
Scheme 44.

The dioxanones produced in this study all have a terminal methylene group α to the carbonyl functionality, that is, at position 5. This makes them prone to decomposition and polymerisation, hence milder hydrolysis methods are required.

In the first instance, three dioxanones ((97), (114b) and (117)) were treated with p-toluenesulphonic acid in chloroform at room temperature. After several days no hydrolysis had occurred. Increasing the amount of p-TsOH did not influence the reaction.
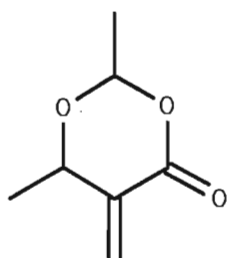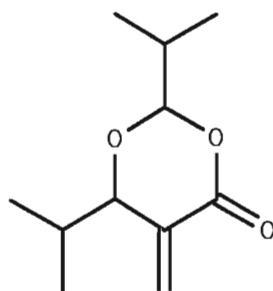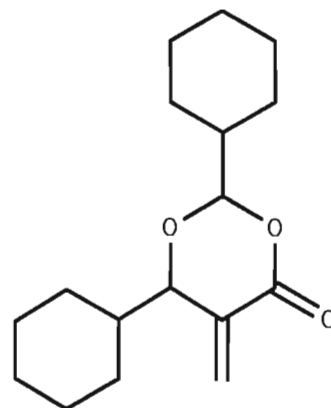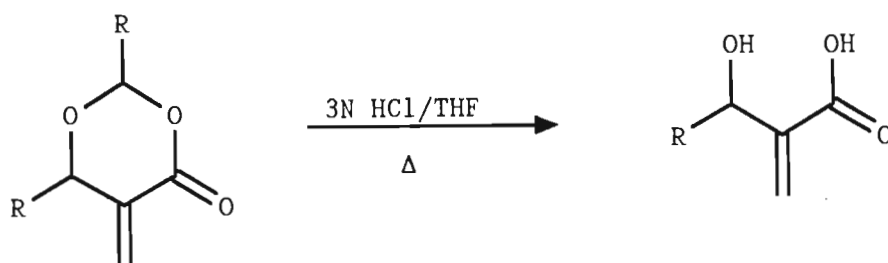

(97)   (114b)   (117)

Using Seebach's method,[144] it was found that the hydrolysis did occur but the reaction did not go to completion so that reflux conditions were used as a last resort. Table 12 summarises the results obtained.

Table 12.

SUBSTRATE	R	PRODUCT	YIELD
(97)	CH_3	(137a)	76
(114b)	$CH(CH_3)_2$	(137b)	55
(117)	$c\text{-}C_6H_{11}$	(137c)	56

The yields obtained for the α-methylene-β-hydroxyacids (137) are lower than those obtained by Seebach[144] possibly due to polymerisation and decomposition.

The determination of ee's at position 6 of the dioxanones is possible by esterification[114] of the acids (137) followed by shift experiments.

2.3.1.2.   USE OF (-)-8-PHENYLMENTHYL ACRYLATE (139).

Basavaiah and co-workers[103] (Section 2.3.1.) obtained fair results with (-)-menthyl acrylate (92) in stereochemical studies of the Baylis-Hillman reaction.

Recently, 8-phenylmenthol (138), originally prepared by Corey and Ensley,[158] has been used to good effect in asymmetric

synthetic studies.[158-163]
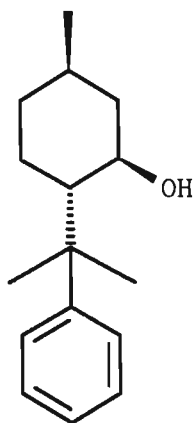
(138)

d'Angelo and Maddaluno[161] obtained high diastereoselectivities through high-pressure-induced addition of amines to α,β-ethylenic esters. The best results were achieved when esters derived from 8-phenylmenthol (138) and 8-(β-naphthyl)menthol were used. The stereochemical outcome of the reaction was explained using the "π-stacking" model previously proposed by Oppolzer,[163] in which the aryl group of the inductor shields one face of the crotonate unit, thereby directing the amine addition to the other face (Figure 10).
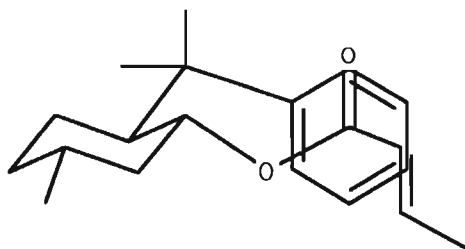
Figure 10.

It was hoped that the above "π-stacking" would operate when 8-phenylmenthyl acrylate (139) is used as the substrate in asymmetric Baylis-Hillman reactions. The proposed mechanism of the Baylis-Hillman reaction[40,73b] involves an intermediate (Figure 11) which has the necessary requirements for such

"π-stacking" to exist.
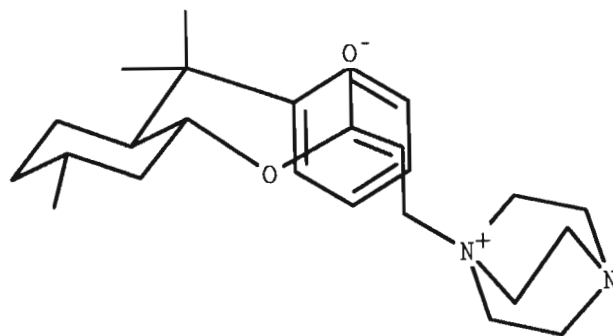
Figure 11.

The synthesis of the chiral auxiliary, 8-phenylmenthol (138), has been described by several authors.[158,164,165] The method of Ort[165] is particularly attractive because of its simplicity. (-)-8-phenylmenthyl acrylate (139) was obtained using Helmchen's[129] method.

(139)
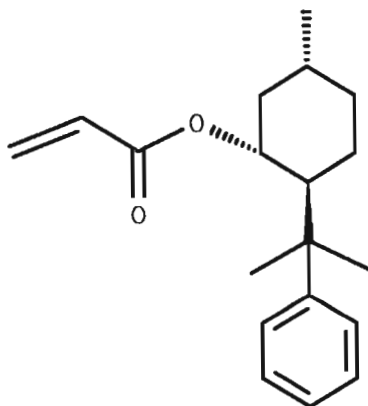
Basavaiah and co-workers[103] (Section 2.3.1.) obtained the best selectivities with the chiral acrylates (92), (93) and (94) when propionaldehyde and furfuraldehyde were used as the electrophiles. When (139) was allowed to react with propionaldehyde in the presence of one equivalent of DABCO, the desired product (140b) was obtained in excellent yield (81%) and good diastereoselectivity (65% de). However, the reaction with furfuraldehyde afforded the product (140g) in 59% yield and disappointing

diastereoselectivity (30% de).

Basavaiah's results[103] (Table 6, entries 5, 8 and 10) show that the diastereoselectivities obtained with benzaldehyde were poor (15-25% de). When (139) was allowed to react with benzaldehyde, the product (140e) was obtained in good yield (82%) and a de of 35%. Although this represents an increase in selectivity over Basavaiah's[103] acrylates, it is not substantial.

From the results of pantolactone acrylate (96), it was evident that the best result was achieved with trichloroacetaldehyde as the electrophile. Indeed, when (139) and this aldehyde reacted under Baylis-Hillman conditions, the product (140a) was obtained with good diastereoselectivity (70% de).

(-)-8-Phenylmenthyl acrylate (139) was subsequently allowed to react with several aldehydes in the presence of one equivalent of DABCO (Scheme 45). The results obtained are tabulated below in order of decreasing diastereomeric excess (Table 13).
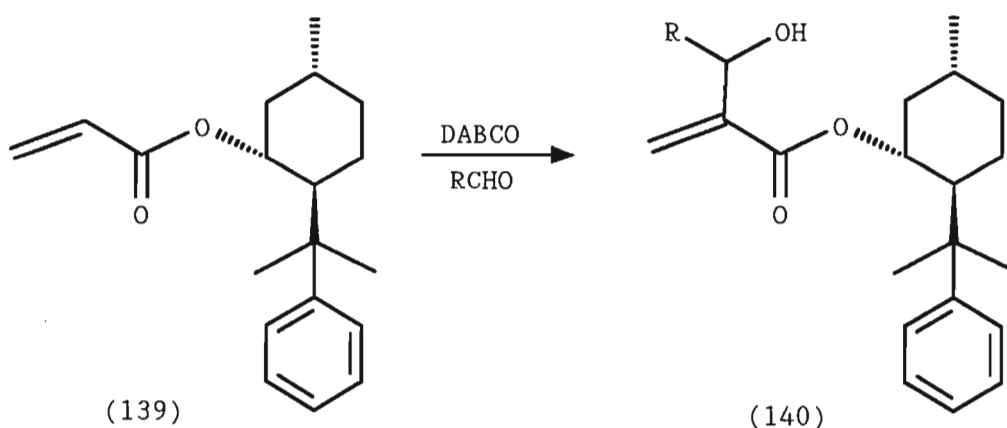
Scheme 45.

Table 13.

ENTRY	COMPOUND	R	de %
1	(140a)	CCl_3	70
2	(140b)	CH_2CH_3	65
3	(140c)	$p-NO_2Ph$	60
4	(140d)	$CH(CH)_2$	42
5	(140e)	Ph	35
6	(140f)	c-hexyl	31
7	(140g)	furyl	30
8	(140h)	CH_3	2

The above results, except for entry 8, represent a marked increase in diastereoselectivities compared to those reported by Basavaiah.[103]   However, there does not seem to be a logical pattern to explain the results, for example, steric bulk of the aldehyde resulting in higher de's.   The same can be said of Basavaiah's results.[103]

The significance of the above results, together with those of other acrylates studied, will be discussed later (Section 2.3.2) in the context of recent findings by Fráter and co-workers[92] and Isaacs and co-workers.[88]

2.3.1.3.   USE OF (-)-8-CYCLOHEXYLMENTHYL ACRYLATE (146).

Recently, Drewes and co-workers[166] reported on the synthesis of highly crystalline, enantiomerically pure aldols by utilisation of the (-)-ephedrine derived N-acylimidazolidin-2-one (141). However, whilst this auxiliary showed excellent selectivity with aromatic aldehydes (de ≥ 96%, >99% after recrystallisation), the

results with aliphatic aldehydes were disappointing (for example, CH_3CHO 10%de, i-PrCHO 60%de, c-$C_6H_{11}CHO$ 70%de).
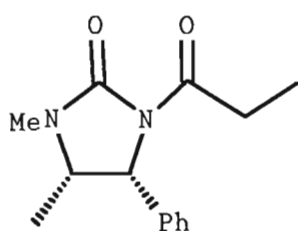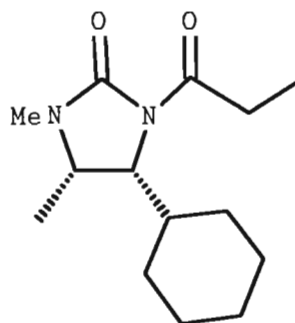
(141)   (142)

More recently, Drewes *et al.*[167] described that the solution to this problem lies in hydrogenation[168] of the auxiliary (141) to its cyclohexyl derivative (142). Using (142), diastereomeric excesses of >90% were achieved with aliphatic aldehydes. In addition, check reactions revealed no loss of selectivity with aromatic aldehydes.

On the other hand, Evans and co-workers[151] found that hydrogenation of the auxiliary (143) to the cyclohexyl derivative (144) led to a significant decrease in diastereoselectivity in cyclo-addition reactions with isoprene.
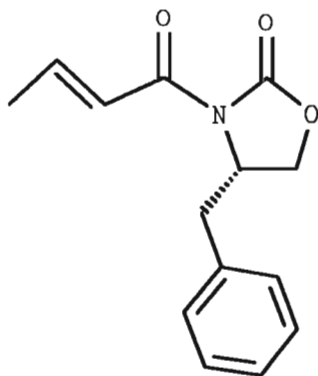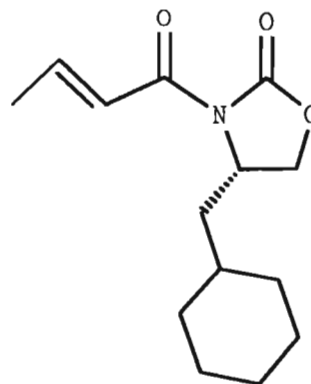
(143)   (144)

The phenyl ring of 8-phenylmenthol(138) was nonetheless hydrogenated[168] to produce (-)-8-cyclohexylmenthol (145), in the hope that the corresponding acrylate (146) would result in an

increase in diastereoselectivity in keeping with the findings of
Drewes *et al..*[167]

(145)   (146)
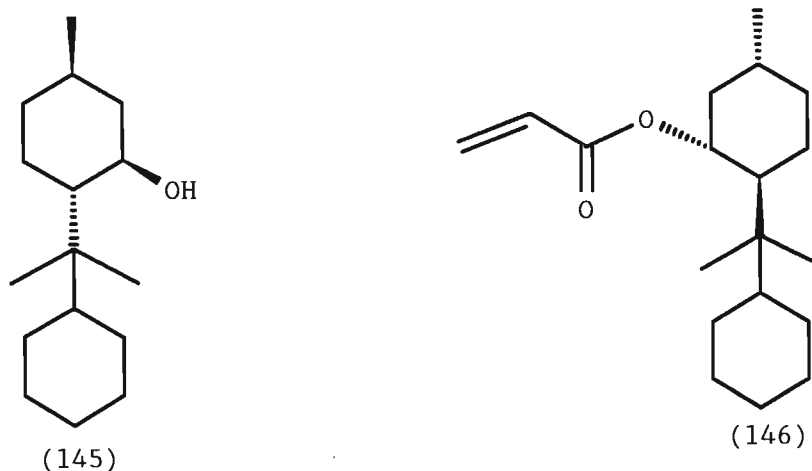
In the first instance, acrylate (146) and trichloroacetaldehyde
were allowed to react under Baylis-Hillman conditions. The
expected product (147a) was obtained in satisfactory yield (58%)
but a disappointing de of 62%. Surprisingly, the reaction with
propionaldehyde, which usually afforded good de's (cf. Tables 6
and 13), yielded the product (147b) with a de of only 35%. The
results of the reaction of (146) with various aldehydes are
summarised below (Scheme 46 and Table 14).

(146)   (147)
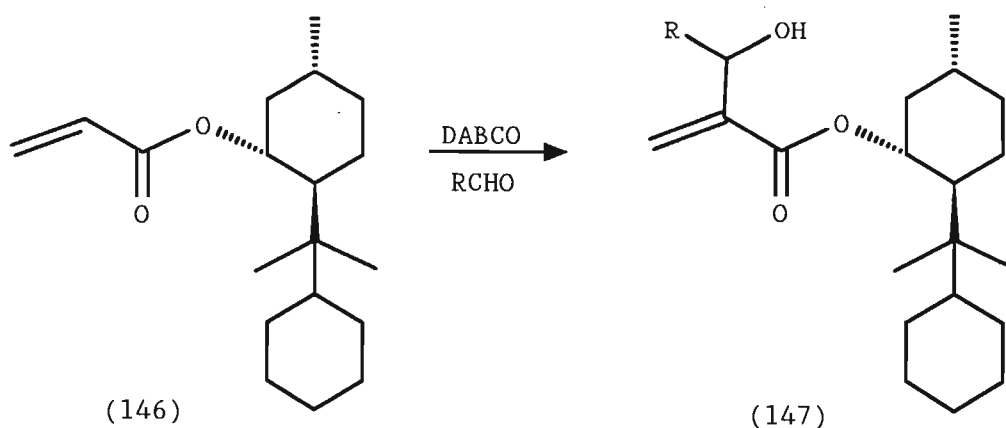
Scheme 46.

Table 14.

ENTRY	COMPOUND	R	de %
1	(147a)	CCl_3	62
2	(147b)	CH_2CH_3	35
3	(147c)	c-hexyl	35
4	(147d)	$p-NO_2Ph$	17
5	(147e)	Ph	13
6	(147f)	CH_3	4

On the whole, the results obtained using (146) are inferior to those when 8-phenylmenthol acrylate (139) was used as the chiral substrate despite the increased steric bulk that accompanies (147).

2.3.2. INTERPRETATION OF THE RESULTS OF CHIRAL ACRYLATES AS SUBSTRATES IN THE BAYLIS-HILLMAN REACTION.

Thus far, the relatively poor stereochemical control observed in the Baylis-Hillman reaction may possibly be attributed to the absence of any chelating metals in the reaction. One could reasonably expect a the non-chelation control model to be operative. However, there does not seem to be any logical pattern in the results obtained based on, for example, steric bulk of the aldehydes. Even the results obtained by Basavaiah[103] seem to indicate that the stereochemical outcome of the reaction is independent of the size of the aldehyde. For example, the de obtained for the product from the reaction of

(-)-menthyl acrylate (92) and isobutyraldehyde was less than half that when the same acrylate (92) reacted with the less bulky propionaldehyde.

Hill and Isaacs[46] demonstrated that the Baylis-Hillman reaction is promoted by elevated pressures. Indeed, in many cases no product was formed at atmospheric pressure even after several weeks, while good yields were obtained overnight at 7-8 kbar. Recently, Isaacs and co-workers[88] described several methods of asymmetric induction. However, the main part of these investigations involved very high pressures (5-8 kbar) and some interesting results will be discussed.

Isaacs'[88] studies using chiral acrylic esters are not readily rationalised. Only modest degrees of chiral discrimination were found in reactions between acetaldehyde and chiral acrylic esters. This is attributed to the small size of the side chain which precludes much stereochemical differentiation. For example, (-)-menthyl acrylate (92) reacted with acetaldehyde at 7 kbar to afford the product with a de of 16% (cf. Basavaiah's result of 11% de at atmospheric pressure).[103]

The really significant observation of 95-100% discrimination occurred when aromatic aldehydes reacted with chiral acrylic esters.[88] In the best example studied, the reaction between benzaldehyde (79) and (-)-menthyl acrylate (92) under high pressure (7.5 kbar), only one diastereoisomeric product was detected by HPLC. The same reaction at atmospheric pressure afforded a mixture of diastereomers and the de was only 22% (cf. Basavaiah's[103] result of 15% de for the same reaction). Similar high de's were obtained for the p-methyl and p-ethyl benzaldehydes reacting at 7 kbar though neither naphthaldehyde nor the furan or thiophene aldehydes performed as well.

Isaacs and co-workers[88] report a de of 86% when 8-phenylmenthyl acrylate (139) reacted with benzaldehyde (79). This is more

than double the de of 35% observed in this work (Table 13) for the same reaction at atmospheric pressure. It is evident that the high pressures employed by Isaacs and co-workers[88] have a positive effect on the stereochemical outcome of the reaction.

An interesting feature of the high pressure Baylis-Hillman reactions in which Isaacs[88] obtained de's of >80%, is the low yields of the products obtained (<42%). For example, comparison of the results when (-)-menthyl acrylate (92) and benzaldehyde reacted at 0.001 kbar ($\approx$atmospheric pressure) to those when the same reaction was conducted at 7.5 kbar (Table 15) reveals the following:

(a) The de of 22% at atmospheric pressure increases nearly five fold to 100% at 7.5 kbar.
(b) The reaction time was 21 hours at high pressure as opposed to 1150 hours at atmospheric pressure.
(c) The yield of the product at atmospheric pressure is 93% while that at 7.5 kbar is only 42%.

Table 15.

ACRYLATE	ALDEHYDE	PRESSURE (kbar)	TIME (h)	YIELD	de %
(92)	PhCHO	0.001	1150	93	22
(92)	PhCHO	7.5	21	42	100

The above results seem to indicate that the stereochemical outcome of the reaction is time dependent. The yields of <50% for the cases where the de's were >50% seem to imply some kind of "kinetic resolution." Definite conclusions would require further experimentation.

Consideration of the results from this work (Tables 9, 13, 14)

seem to imply that the de's depend on the reactivity of the aldehydes. Trichloroacetaldehyde is by far the most reactive aldehyde used, and indeed, the de's obtained for all three acrylates used in this work ((96), (139) and (146)) were best with this aldehyde.

There are, however, anomalies to the above generalisation. Furfuraldehyde is very reactive in the Baylis-Hillman reaction, but, the de obtained when it reacted with acrylate (139) was low (Table 13), as was the de of the product when acrylate (146) and p-nitrobenzaldehyde were allowed to react.

Another point that is evident from this study (Tables 13 and 14) as well as Basavaiah's work[103] (Table 6), is that the de's obtained when propionaldehyde was used as the electrophile are generally high. In the absence of any significant steric bulk, it seems likely that its reactivity plays a significant role. Unfortunately, Isaacs[88] did not use this aldehyde in any of his experiments for comparisons to be made.

Fráter and co-workers[92] also studied stereochemical aspects of the Baylis-Hillman reaction (Section 1.4.). However, only very low ee's were obtained when compound (70) was produced from (69) *via* the Baylis-Hillman reaction. The authors found that treatment of pure (70) with the catalyst resulted in an equilibrium concentration of 65% of (70) and 35% of the starting material (69).
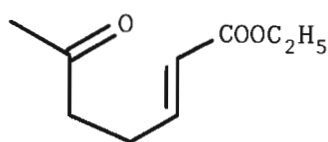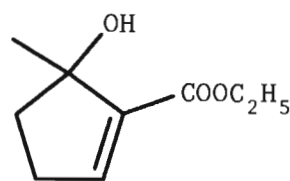
(69)   (70)

The above findings prompted Fráter[92] to investigate the effect of the catalyst on a conventional Baylis-Hillman product (148).

Thus, when (148) was treated with 0.25 equivalents of DABCO, an equilibrium mixture of 87% of (148) and 13% Of benzaldehyde (79) was detected.

(148)
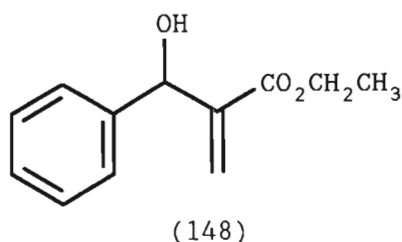
Fráter[92] attributes the low ee's in his experiments and also in earlier attempts[40,103] to the reversibility of the ring-closure, or more generally of the C-C bond formation.

At this point in time an interpretation of the stereochemical outcome of the Baylis-Hillman reaction may not be made conclusively. Further investigations, bearing in mind the effect of pressure, the reversibility of the reaction and the effect of temperature, require thorough investigation.

2.3.3. THE USE OF CHIRAL CYCLIC AMINO ALDEHYDES IN THE BAYLIS-HILLMAN REACTION.

Asymmetric synthesis is always more meaningful if it leads to a target molecule with biological activity. Organic molecules owe their biological activity to a variety of structural features, for example, to a specific arrangement of structural subunits or to a specific functionality. Increasingly, the value of structural analogues of biologically active compounds is being appreciated.[169]

The synthesis of glycosphingolipids, which are major membrane constituents, has gained increasing interest because of the aim to understand the role and function of biological

membranes.[170,171] The backbone component of sphingolipids is almost invariably the long chain base, sphingosine, which is usually present as its D-(+)-(2S,3R)-erythro isomer (149).[172] Current interest in this compound, and analogues of it, is high on account of its reported anti-tumor properties.[173]

(149)
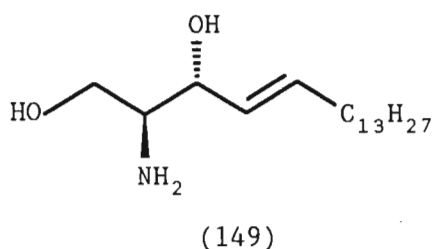
A recent report by Koskinen and Krische[174] describes the synthesis of the sphingosine skeleton starting from serine. Potentially, the Baylis-Hillman reaction lends itself to the synthesis of analogues of sphingosine, and this was investigated.

In 1987, Garner and Park[175] described the synthesis and configurational stability of differentially protected β-hydroxy-α-amino aldehydes. One of these aldehydes (150), prepared from serine, is a suitable aldehyde to produce a sphingosine analogue. Indeed, similar aldehydes have been used by Dondoni and co-workers[176] for the synthesis of sphingosine derivatives.

(150)
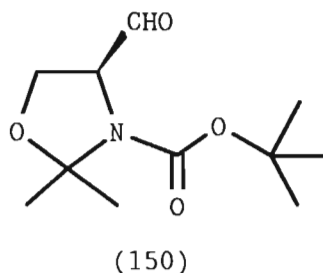
In this study, the projected synthesis of the sphingosine analogue (152) involves the Baylis-Hillman reaction of methyl acrylate (30) and Garner's aldehyde (150) to afford the product (151) which can then be deprotected to the sphingosine analogue

(152) (Scheme 47). The deprotection step has been successfully achieved on similar compounds by Dondoni and co-workers.[176]
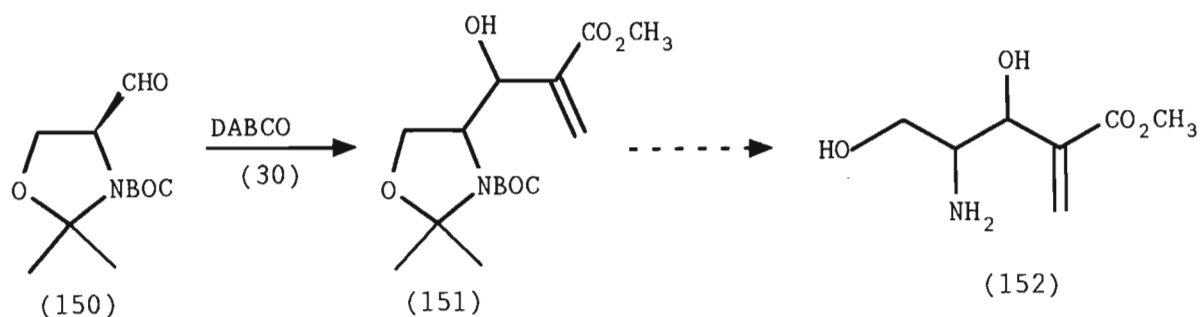
Scheme 47.

The crucial step of this synthesis, that is, the reaction of (150) with methyl acrylate (30) in the presence of DABCO, proceeded in good yield to (151) and was complete in 7 days at room temperature. ^{1}H NMR spectroscopy indicated a mixture of diastereomers with a de of 72%.

Manickum and Roos[84] (Section 1.4.1.3.) investigated variously N-protected α-amino aldehydes in the Baylis-Hillman reaction and the observed diastereoselectivities were found to be dependent on the type of nitrogen protection. Dondoni and co-workers[176] described the stereochemistry and synthetic utility of the addition of 2-(trimethylsilyl)thiazole to various N-protected α-amino aldehydes. Both these groups[84,176] rationalised their results by making use of the Felkin-Anh[78,85] model for asymmetric induction.

Dondoni and co-workers[176] found that reaction of (150) with the thiazole was *anti*-diastereoselective in agreement with the Felkin-Anh model.[18,85] Using the precedent of Dondoni and co-workers[176] and Manickum and Roos,[84] the major diastereomer of (151) was expected to be the *anti*-diastereomer. Unfortunately, correlations by coupling constants could not be used because of broad peaks in the crucial area of the ^{1}H NMR spectrum of (151).

Recently, Roos and Watson[177] have reported on the rapid *in situ* determination of diastereomeric ratios of alcohols by ^{1}H NMR spectroscopy. The method involves derivatisation of the alcohol with trichloroacetylisocyanate resulting in the appearance of the carbamate NH singlets in the usually uncluttered δ8.5-10 region of the spectrum.

Roos and co-workers[178] have extended the above method as a diagnostic tool for the determination of *syn* and *anti* hydroxy systems. A wide variety of systems were studied and the following relationship, $\delta NH_{(syn)} > \delta NH_{(anti)}$, was established. All of these *syn/anti* assignments were corroborated by the more traditional spectral methods or from the literature.

Using the trichloroacetylisocyanate method described above,[177,178] the major diastereomer of (151) was indeed found to be the *anti* isomer. This correlates with the results of Dondoni and co-workers[176] as well as the predicted stereo-chemical outcome using the Felkin-Anh model.[78,85]

The major diastereomer of (151) was readily separated by column chromatography. However, the specific rotation of the pure *anti* diastereomer was very low (*ca.* 1°) and this implied that racemisation may have occurred during the Baylis-Hillman reaction. Attempts to prove this by shift experiments were largely unsuccessful, mostly because of the poor resolution of the peaks in the ^{1}H NMR spectrum of (151).

In 1989, Jurczak and Gołębiowski[104] reviewed the use of optically active N-protected α-amino aldehydes in organic synthesis. They reported that these aldehydes are relatively unstable both chemically and configurationally, particularly in solution. It is recommended that these compounds be used immediately after preparation, but, if purification is necessary, then flash chromatography[179] is suggested.

In the light of the above statements, it seems likely that under the extended period of reaction, racemisation occurs. However, in the absence of any direct evidence, it was decided that another cyclic amino aldehyde should be investigated. The suggestion of Jurczak and Gołębiowski[104] that the aldehyde should be used immediately after preparation was also heeded.

Thurston and Langley[180] provided a procedure which gave ready access to pyrrolidine-2-carboxaldehydes. Using the procedure described for the synthesis of N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde, the corresponding previously unreported 4-nitrobenzoyl isomer (153) was obtained as shown below (Scheme 48).

Reagents: (i) K_2CO_3, p-NO_2-C_6H_4COCl
          (ii) PCC
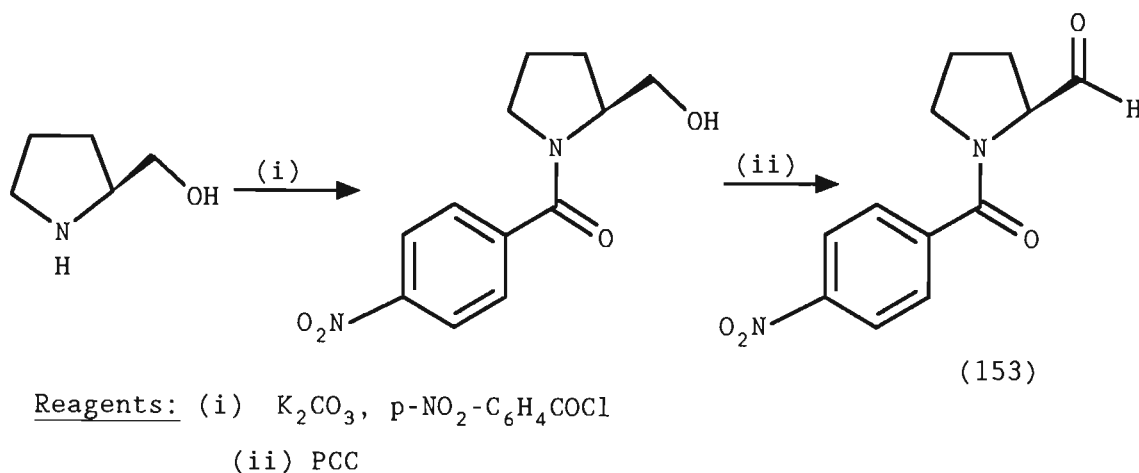
Scheme 48.

The chiral cyclic amino aldehyde (153) was allowed to react with methyl acrylate (30) under the same conditions described for (150). Again, the reaction proceeded smoothly at ambient temperature and afforded (154) in good yield and a de of 50%.

(154)
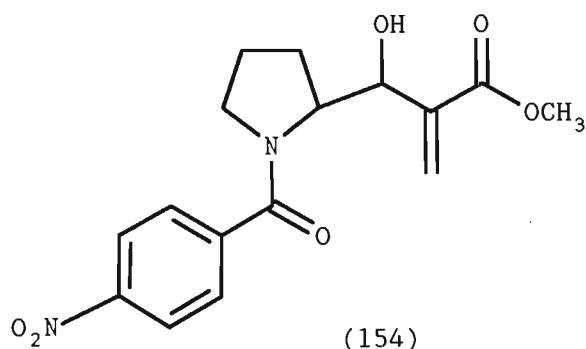
The major diastereomer was isolated by chromatography but again the specific rotation was low (*ca.* 1°). In this instance, shift studies using Eu(hfc)₃ clearly indicated that racemisation had occurred. It seems likely that DABCO is sufficiently basic to abstract the α-proton of the amino aldehydes leading to loss of chirality. Evidence in support of this observation comes from the work of Drewes[86] who reports that the cyclic derivative (156) was obtained during attempts to protect proline (155) at the acid and amine functionalities (Scheme 49). Drewes states that this product can only form if deprotonation occurs at the α-position.
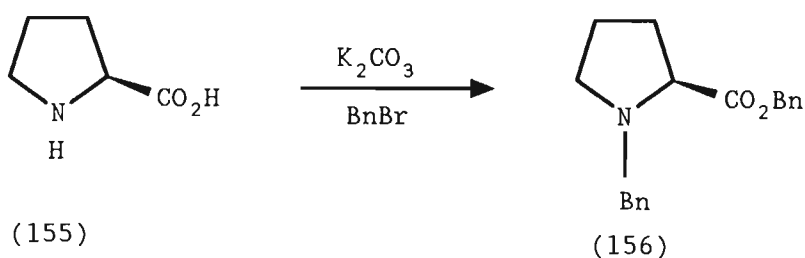
Scheme 49.

A recent publication by Giannis and Henk[181] provides a possible solution to this dilemma and future investigations will involve the use of their aldehyde (157). These authors[181] describe the synthesis of analytically pure N-ᵗbutyloxycarbonyl-L-serinal (157) in three steps from commercially available D-glucosamine hydrochloride. The authors state that "the crystalline and highly functionalised aldehyde (157) is chemically and

configurationally stable at room temperature. Its physical data
remains unchanged for at least 6 months."
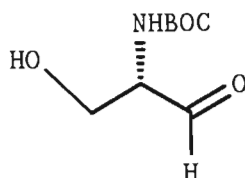
(157)

The above aldehyde (157) has three advantages in the context of
this work:

   (a) It is chemically and configurationally stable and the
       problem of racemisation may be eliminated.
   (b) It would afford the sphingosine analogue (152) directly-
       obviating any deprotection.
   (c) The free hydroxy may promote the reaction as revealed
       by rate studies.[89]

2.4.   THE USE OF CHIRAL MASKING AGENTS.

The Baylis-Hillman product may also be obtained by making use of
the so-called masked acrylate utilised by Yu and Helquist.[23,33]
This method, which had previously been used in alkylations, was
extended by Scolastico and co-workers[37] to include aldol-type
reactions.   Drewes and co-workers[182] followed this up with a
paper describing the synthesis of 2-substitiuted 2-propenoic
acid esters *via* the reaction of masked acrylates with carbonyl
compounds.

A logical extension of the above is to exploit this route for
preparing chiral compounds. Drewes and co-workers[102] used the
commercially available (S)-(+)-2-pyrrolidinemethanol(158) as the
"internal" chiral masking agent.   Initial investigations

involved the reaction of selected aldehydes with the masked acrylate derivative (159) (Scheme 50). However, low ee's were obtained (Table 16) and the authors attribute this to the large distance (1,6) between the inducing centre of chirality and the newly formed asymmetric centre. A substantial improvement in ee was observed when the bulkier ^{t}butyl ester was employed (Table 16).
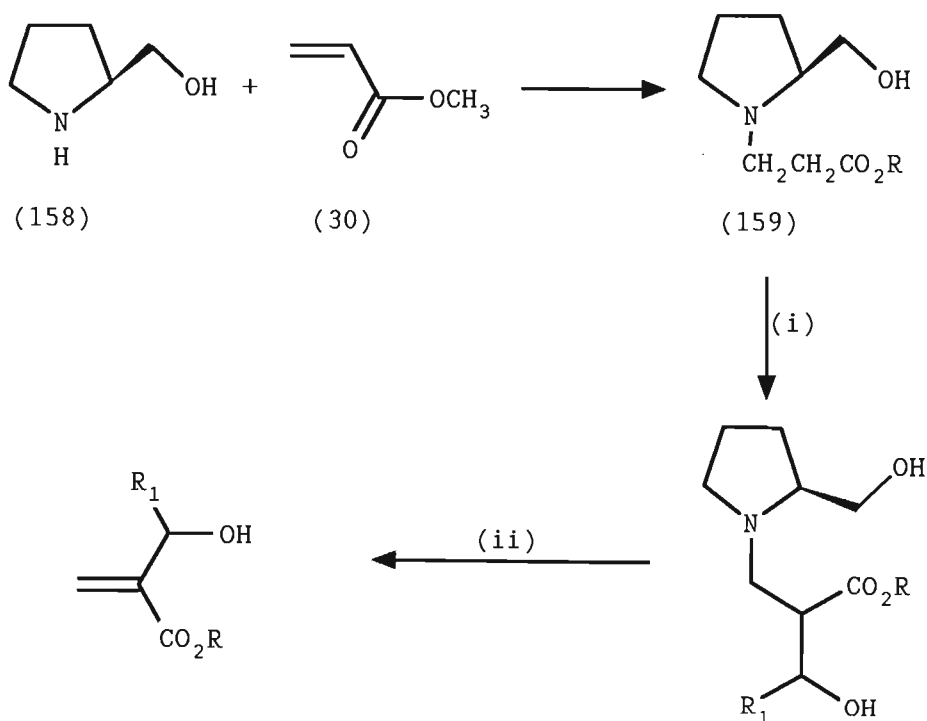
Reagents: (i) 2LDA, R_1CHO

(ii) MCPBA, Basic Al_2O_3

Scheme 50.

Table 16.

ENTRY	R	R$_1$	T°C	ee %
1	CH$_3$	Ph	-100 to 25	8
2	C(CH$_3$)$_3$	Ph	-100 to 25	45
3	C(CH$_3$)$_3$	p-NO$_2$-C$_6$H$_4$	-100	23
4	C(CH$_3$)$_3$	p-NO$_2$-C$_6$H$_4$	-100 to 25	37
5	C(CH$_3$)$_3$	p-OMe-C$_6$H$_4$	-100	50
6	C(CH$_3$)$_3$	p-OMe-C$_6$H$_4$	-100 to 25	65
7	C(CH$_3$)$_3$	p-OMe-C$_6$H$_4$	25	75

2.4.1. (S)-(+)-1-(2-PYRROLIDINYLMETHYL)PYRROLIDINE (160).

The object of this investigation was to explore the use of other chiral masking agents with a view to increasing the ee's obtained so far. The primary aim of this study was to replace the hydroxyl functionality of prolinol (158) with a more bulky group. To this end, the commercially available (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (160) was the ideal candidate.
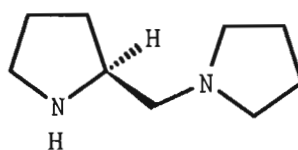
(160)

Since the chiral amine (160) was only available in small quantities and the masked ^{t}butyl acrylic ester is known to produce higher ee's,[102] these investigations were focused on this system. Also, the results obtained by Drewes and co-workers[102] showed highest ee's for aromatic aldehydes.

The chiral amine (160) reacted smoothly with ^{t}butyl acrylate (34) to yield the β-aminopropionate (161) in high yield (80%) following the procedure of Rouvier and co-workers.[183]

(161)   (162)

Compound (161) was treated with LDA and subsequently allowed to react with benzaldehyde (79). The crude aldol product (162) was treated directly with MCPBA followed with basic alumina to eliminate the chiral auxiliary. The expected product (90) was obtained in good yield (69%), a much improved ee of 56% (cf. the ee of 45% of Drewes and co-workers[102]) and a specific rotation of $[\alpha]_D^{24}$ = +55.7° (c1.01, MeOH). From earlier correlations (Section 2.2.) one can infer that the absolute configuration of the major enantiomer of (90) is 3S.

(90)   (163)

Drewes and co-workers[102] obtained their best results when p-methoxybenzaldehyde was used as the electrophile. Under analagous conditions, reaction of this aldehyde with (161) afforded the product (163) in good yield (66%) and an ee of 58%- a slight improvement over the above result but lower than the

previously reported one.[102] The specific rotation, $[\alpha]_D^{24}$ = +62.8° (c1.0, MeOH), shows that the major enantiomer of (163) is dextrorotatory as was the case for (90). Since attack of the enolate of (161) is expected to occur from the same side for both aldehydes, one can infer that the dextrorotatory enantiomer of (163) would also have the 3S configuration.

2.4.2. (2R,5R)-(+)-*TRANS*-2,5-DIMETHYLPYRROLIDINE (164).

In a recent review Whitesell[184] states that, in the majority of scenarios for absolute stereochemical control, the presence of a C_2 symmetry axis within a chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing diastereomeric transition states. Indeed, many successful asymmetric synthetic studies have employed C_2 symmetric chiral auxiliaries,[184] a large number of which are amines.[185-194]

Whitesell[185,186] obtained excellent results when the C_2 symmetric (+)-*trans*-2,5-dimethylpyrrolidine (164) was used as the amine component in enamine alkylations. This prompted an investigation of (164) as a chiral masking agent.

The procedure of Masamune *et al.*[195] was employed for the synthesis of the chiral auxiliary (164) (Scheme 51). A crucial step involved the bakers yeast reduction of 1,5-hexanedione (165) to the corresponding diol (166).[196] Compound (164) was converted to the hydrochloride salt (169) and had satisfactory physical properties, m.p. 199-201°C and $[\alpha]_D^{25}$ = +5.31° (c1.54, CH_2Cl_2) (lit.[195] m.p. 200-203°C and $[\alpha]_D^{24}$ = +5.57° (c.3.0, CH_2Cl_2).
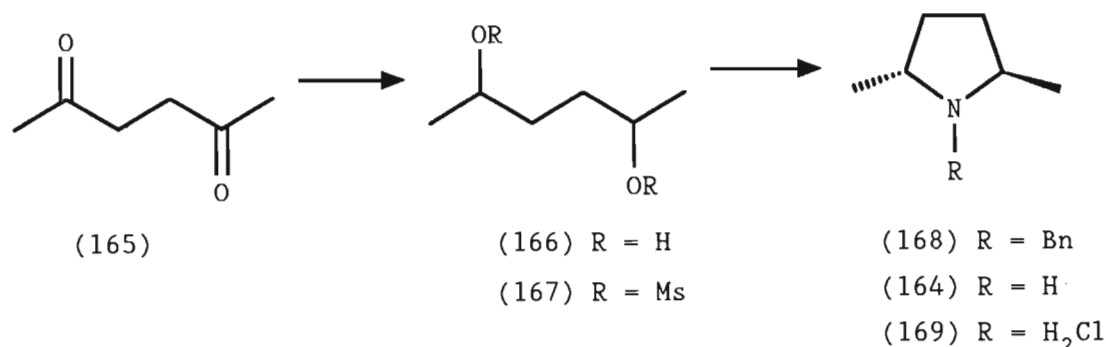
Scheme 51.

The amine (164) reacted smoothly with methyl acrylate (30) to afford the masked acrylate (170). However, the conversion procedure to the substituted acrylate with benzaldehyde (79) yielded the product (80) without any stereoselectivity (ee ≈ 0). When p-methoxybenzaldehyde was employed as the electrophile, the ee of the product (171) was only 1%.
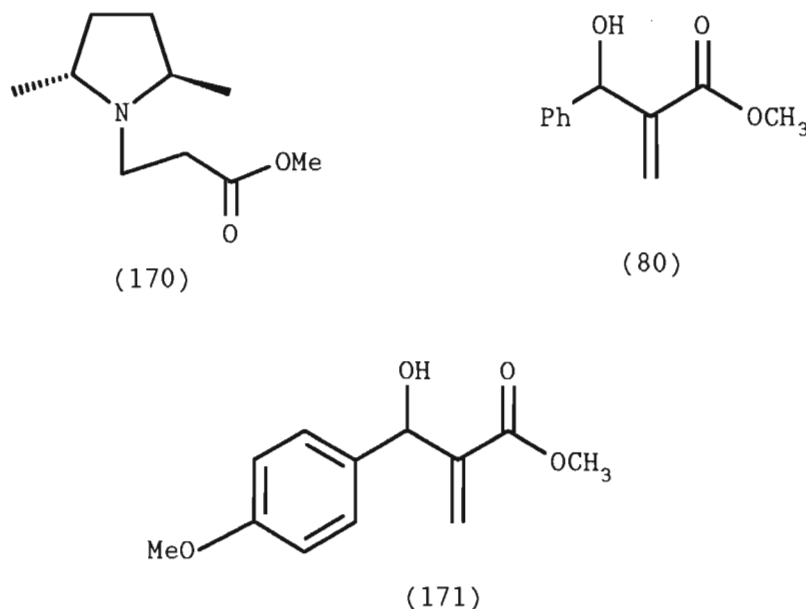
The reaction between ᵗbutyl acrylate (34) and the amine (164) afforded the desired product (172) in good yield. When (172) was allowed to react with benzaldehyde (79) under the conditions described by Drewes and co-workers,[102] the product (90) was obtained with an ee of 15%. The same reaction with p-methoxy-

benzaldehyde yielded (163) with an ee of 17%.

(172)

(90)

(163)
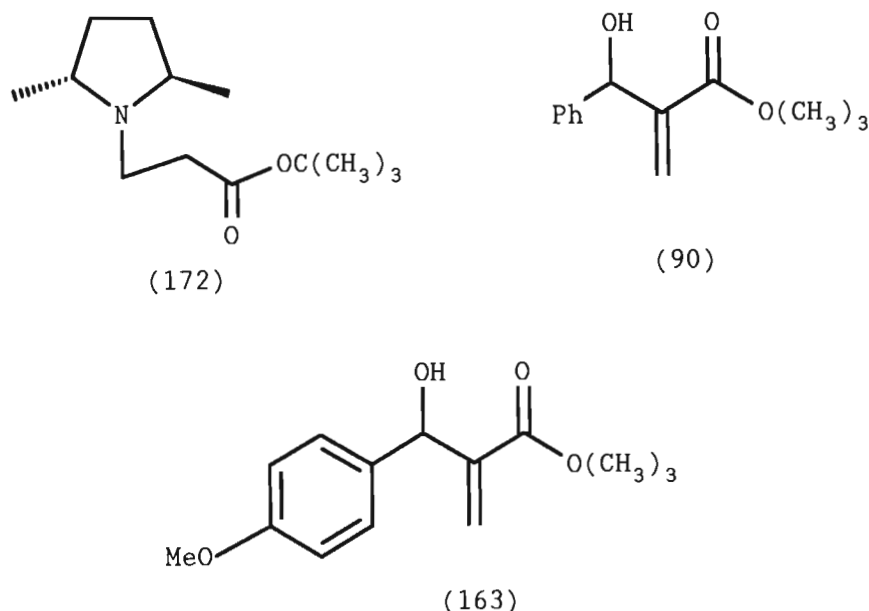
Compound (164) is thus not a suitable chiral masking agent for the present reaction. Several reasons are possible for the low ee's obtained:

(a) The large distance (1,6) between the inducing centre of chirality and the newly formed chiral centre.[102]

(b) The substituents at the 2 and 5 positions, being methyl, are not bulky enough.

(c) Possibly, the absence of heteroatoms on the substituents precludes the chelation proposed for prolinol (158).[197]

2.4.3. (2S,5S)-(-)-*TRANS*-BIS(METHOXYMETHOXYMETHYL)PYRROLIDINE (173).

(2R,5R)-*trans*-2,5-Dimethylpyrrolidine (164) seemed to be a poor choice as a chiral masking agent. However, there are several other C_2 symmetric amines which give excellent stereocontrol. *Trans*-2,5-Bis(methoxymethoxymethyl)pyrrolidine (173) was used with great success by Katsuki and co-workers.[189-194] During asymmetric α-alkylations of amides of (173) with several

alkyl halides, very high de's (>96%) were obtained.[189]

(173)
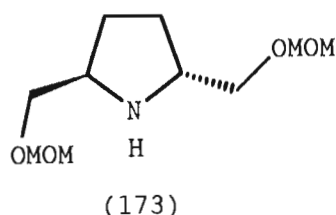
In this study, compound (173) was expected to be a good chiral masking agent since:

(a) The presence of the oxygen atoms on the substituents were expected to provide chelation sites as proposed for (158)[197].

(b) The methoxymethoxymethyl substituents are significantly bulky to have an effect on the stereochemical outcome.

The synthesis of the chiral auxiliary (173) was accomplished by a combination of the procedures described by Katsuki[189] and Ghosez.[198] Racemic *cis*-N-benzyl-2,5-bis(ethoxycarbonyl)pyrrolidine was prepared from *meso*-α,α-dibromoadipate[199] and benzylamine following the procedure of Cignarella and Nathansohn.[200] The *cis*-isomer was transformed to the required *trans*-isomer (174) using the procedure of Lowe and Ridley.[201] Hydrolysis of (174) to the diacid (dl-175) followed by resolution with ephedrine and esterification afforded the (S,S)-diester (176). Reduction of (176) to the diol (177) followed by protection of the hydroxyl groups as the MOM ethers afforded the N-protected compound (178).[37] The target molecule (173) was obtained by hydrogenation of (178) (Scheme 52).
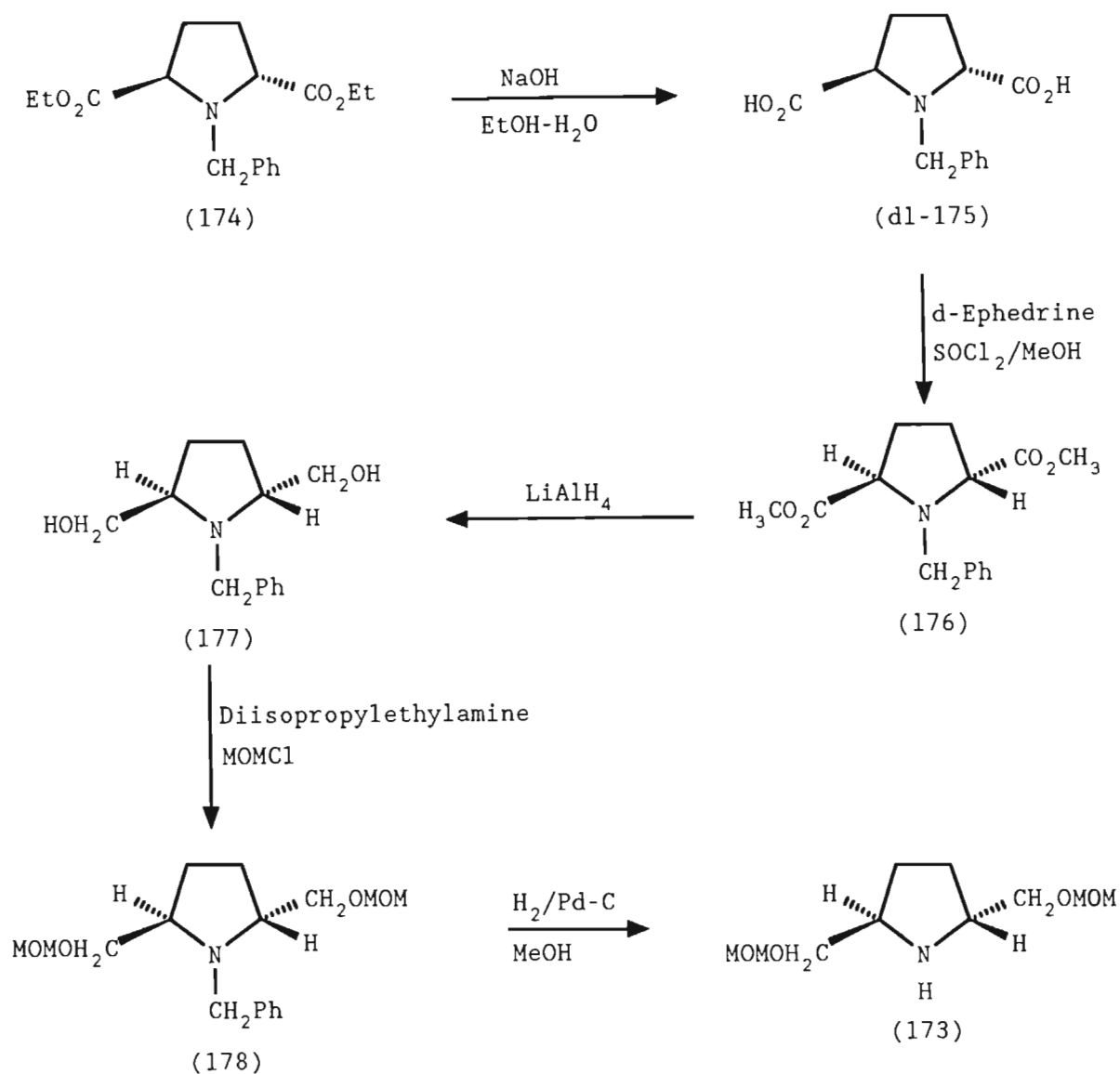
Scheme 52.

The 1,4-addition of (173) to methyl acrylate (30) was surprisingly difficult to achieve and the reaction was incomplete after 24 hours. Even the addition of Lewis acid catalysts[202] gave only poor yields, but this improved after refluxing for several hours giving the product (179).

(179)   (80)
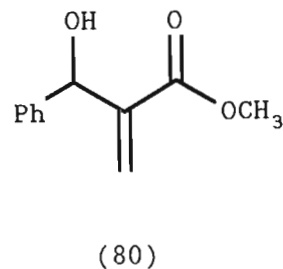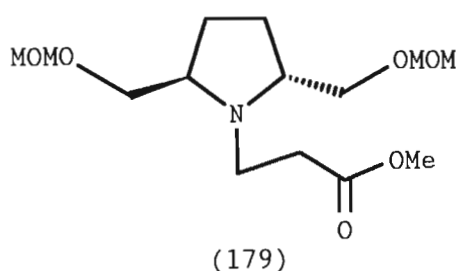
When the enolate of (179) was allowed to react with benzaldehyde in the usual manner,[102] the desired product (80) was obtained with an ee of 32%. This represents a 4-fold increase in ee over that obtained by Drewes and co-workers[102] for the analagous reaction using prolinol (158) as the chiral masking agent, but this is still disappointingly low. However, from previous studies[102,197] and from this work, the ^{t}butyl ester is known to significantly enhance the stereochemical outcome of the reaction.

Unfortunately, all attempts to effect the 1,4-addition of (173) to ^{t}butyl acrylate (34) were unsuccessful. Even prolonged reaction in the presence of Lewis acid catalysts[202] under reflux conditions did not yield the desired product. It seems likely, and indeed molecular models suggest, that the steric bulk of the ^{t}butyl group and the substituents at the 2 and 5 positions of (173), are responsible for the failure of the reaction.

Future work in this area will involve the use of the chiral acrylic amide (180) which can then be masked with achiral amines. In the light of the excellent results obtained by Katsuki and Yamaguchi[203] during aldol reactions of amide enolates bearing trans-2,5-disubstituted pyrrolidines as chiral auxiliaries, this is a very promising route. The option of using chiral amines to mask (180) opens a whole new area of investigation.
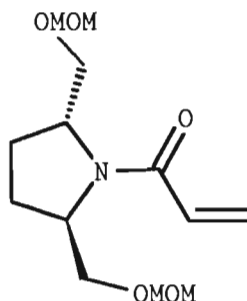
(180)

2.5.   THE CROTONATE SYSTEM.

Under normal conditions the Baylis-Hillman reaction is not applicable to the crotonate system. This could possibly be due to a steric effect or due to the inductive effect of the methyl group on the β-carbon atom. However, Hill and Isaacs[46] were able to include the crotonate system as a substrate in their studies by using pressures of up to 10kbar. Since these pressures are not generally attainable in normal laboratories, an alternative route was investigated.

Preliminary investigations into extending the masked acrylate methodology to the crotonate system by Brand,[197] working in these laboratories, gave promising results. An aldol reaction of the achiral crotonate synthon (181) with benzaldehyde (79) demonstrated the reactivity of the system (Scheme 53).
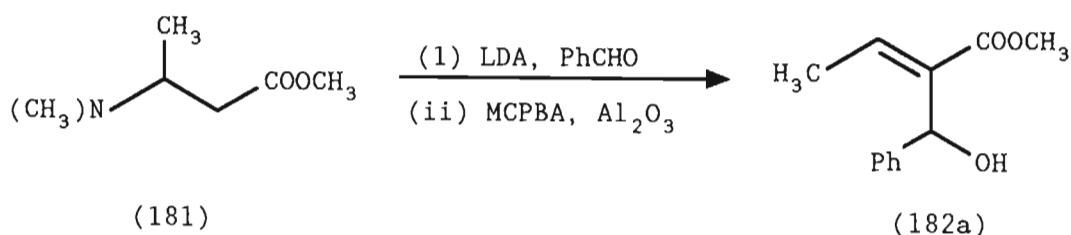
Scheme 53.

Brand[197] had also extended this methodology to the use of a chiral masking agent. In this instance, the commercially available (S)-prolinol (158) afforded the corresponding masked crotonate (183) as a 60 : 40 mixture of diastereomers. Deprotonation of (183) containing the 60 : 40 mixture, and subsequent condensation with p-nitrobenzaldehyde proceeded in good yield. Elimination of the chiral auxiliary afforded the β-hydroxy crotonate (182c) with an ee of 18%.

(183)

(182c)
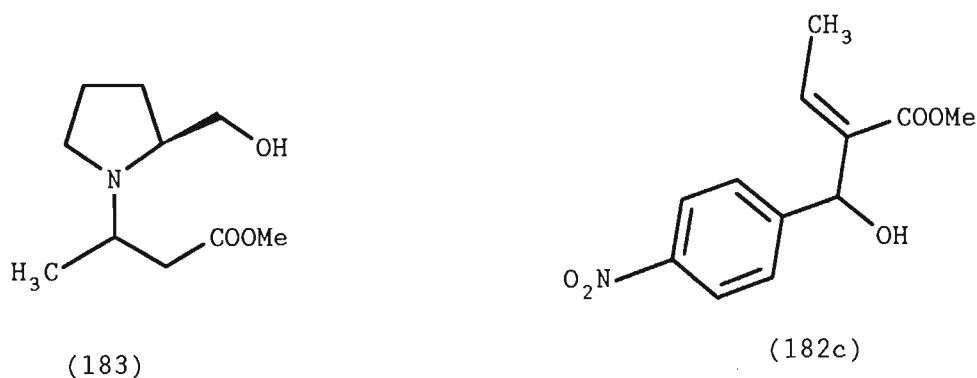
The possibility of separating the 60 : 40 diastereomeric mixture was also investigated by Brand.[197] The separation was achieved by column chromatography using MeOH/CHCl$_3$ (1 : 10). Experiments on the separate diastereomers gave promising results and the object of this study was to pursue this line of research.

The two diastereomers obtained from the separation of the mixture will be referred to as diastereomer (183a) and (183b). Diastereomer (183a) eluted first and is distinguishable from (183b) by the doublet for the crotyl CH$_3$ at 1.00 ppm in the ^{1}H NMR spectrum. The corresponding signal occurs at 1.17 ppm for (183b).

Each diastereomer was separately allowed to react with three aromatic aldehydes according to the procedure of Drewes and co-workers[102] (Scheme 54).
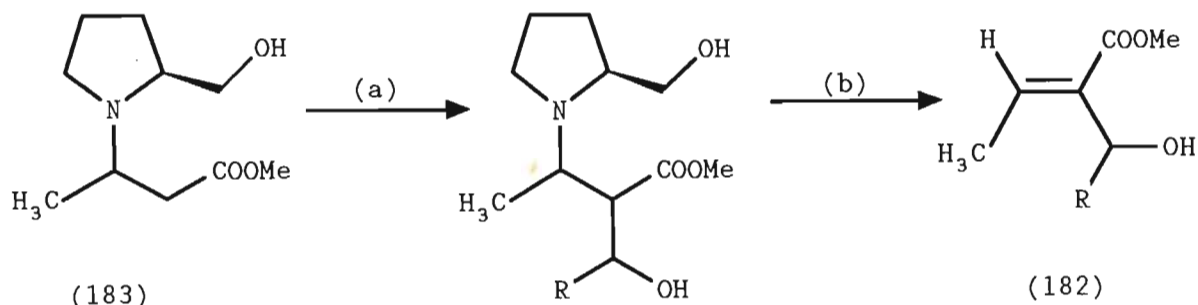
Reagents: (a) (i) LDA, (ii) RCHO, (iii) H_3O^+

(b) (i) MCPBA, (ii) Basic Alumina

R = Ph (182a)

R = p-OMeC$_6$H$_4$ (182b)

R = p-NO$_2$C$_6$H$_4$ (182c)

Scheme 54.

When benzaldehyde (79) was allowed to react with (183a), the expected product (182a) was obtained in fair yield (45%) and an ee of 35%. Diastereomer (183b) yielded (182a) with an ee of 50%. Preliminary results have been published.[204]

It seems likely that the chiral centre at C(3) as well as the one on the auxiliary (158) are both involved in the stereochemical outcome of the reaction. In the case of (183a) the chiral centre on the pyrrolidine ring seems to counteract the inducing effect of the one at C(3). This can be likened to a "mismatched" pair in Masamune's[100] description of double asymmetric synthesis.

Extension of the above methodology to other aromatic aldehydes disproved the above explanation (Table 17).

Table 17.

ALDEHYDE	PRODUCT	%ee with (183a)	%ee with (183b)
PhCHO	(182a)	35	50
p-OMeC$_6$H$_4$CHO	(182b)	56	41
p-NO$_2$C$_6$H$_4$CHO	(182c)	25	10

In all cases, the product (182) was obtained with high selectivity (>90%) towards the E-isomer and no formation of terminal alkene was observed. The assignment of the E configuration is based on the observation that the ^{1}H NMR chemical shift of the vinylic proton is very far downfield (>7 ppm). This is in good agreement with data obtained from closely-related compounds,[205,206] all of which reflect H-bonding of the vinylic proton with the ester carbonyl. The ^{13}C NMR shift of the vinylic methyl group also corresponds to that found in structurally related necic acid derivatives.[207]

2.6. THE SYNTHESIS OF A TETRAHYDROFURAN DERIVATIVE (187) *VIA A* NOVEL CYCLISATION.

The unusual reaction of pantolactone acrylate (96) with certain aldehydes, leading to dioxanone formation (Section 2.3.1.1.), prompted a further investigation of this system. It was hoped that by using the masked acrylate method,[23,33,102,182] even reaction with benzaldehyde (79) would result in dioxanone formation.

A simple aliphatic ester (184) was chosen as a model system.

This would obviate the need for masking and deprotection of the acrylate during initial investigations.
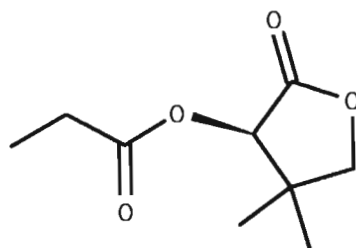
(184)

The ester (184) was treated with LDA followed by two equivalents of benzaldehyde (79) with the aim of producing the dioxanone (185) (Scheme 55). By using the appropriate masked acrylate under analagous conditions, followed by elimination of the amine, the corresponding methylene dioxanone (115) may be produced.

(184)

R = CH$_3$ (185)

R = CH$_2$ (115)
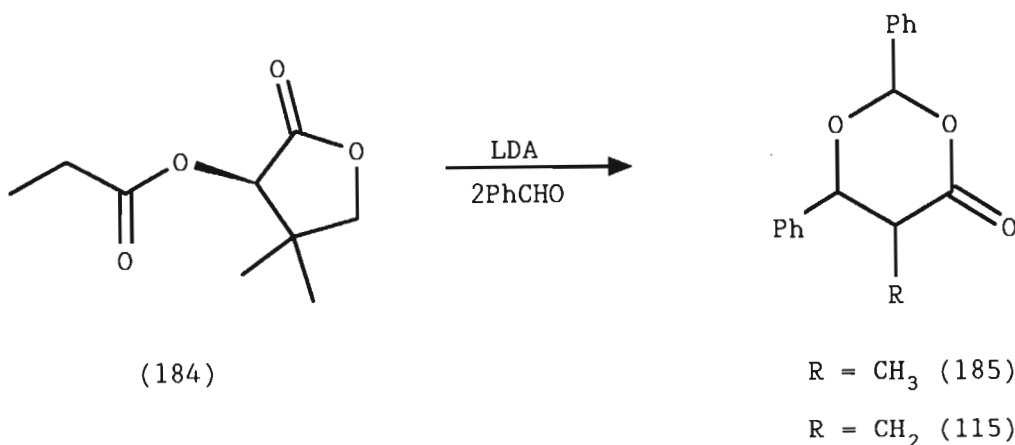
Scheme 55.

When ester (184) was treated as described an unusual result was found. The reaction mixture consisted of several minor components together with one major component which was not easily separable. During chromatographic separation of the mixture, the major component fortunately crystallised in the collection tubes. The crystalline material, which was expected to be

dioxanone (185) was isolated and purified. From the spectral data it was obvious that this compound was not dioxanone (185).

The other possibility would be the formation of the simple aldol condensation product (186). Indeed, the elemental analysis and molecular ion of this crystalline material were consistent with that of (186). However, NMR data did not support this.
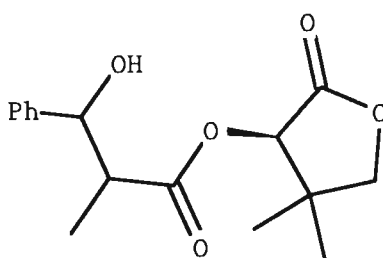
(186)

Examination of the NMR data of the unknown crystalline compound showed that there were three methyl groups, a single methylene group and five methine groups. Furthermore, ^{13}C NMR indicated the presence of five carbons bearing no hydrogens. If the two aromatic methine groups that are equivalent are added, this gives a total of sixteen carbon atoms which is consistent with the molecular formula of (186), that is $C_{16}H_{20}O_5$. The unknown compound has one less methine group compared to (186). Instead, it has an extra quarternary carbon atom. This implies that the unknown evolves from some kind of rearrangement of (186).

Infra-red spectroscopy indicated the presence of hydroxyl groups. Although COSY and HETCOR spectra provided further useful information, it was not possible to assign a structure that was consistent with all the data.

Fortunately, suitable crystals were obtained from benzene which permitted x-ray analysis of the unknown compound (Figure 12). The unknown compound (187) is indeed an isomer of (186).
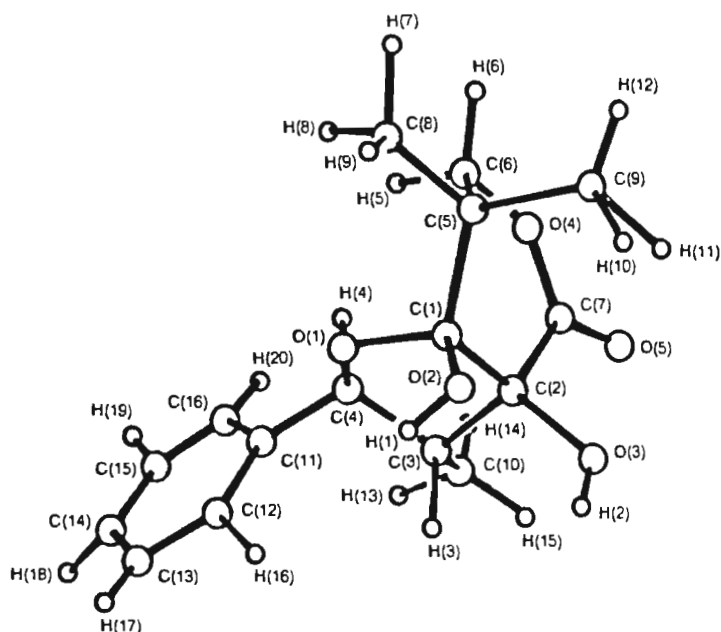
Figure 12.

The tetrahydrofuran derivative (187) bears a striking resemblance to a crystalline compound isolated from the bark of an unnamed *Polyalthia* species by Loder and Nearn.[209] This compound, 3-hydroxy-2-phenyl-2,3,3a,7a-tetrahydro-5H-furo[3,2b]pyran-5-one (188), was given the name altholactone by the authors.

(187)

(188)
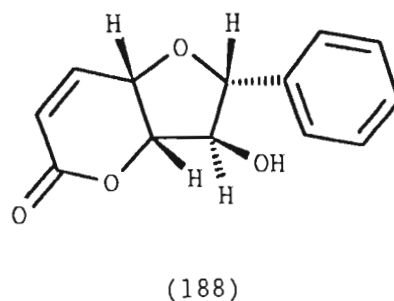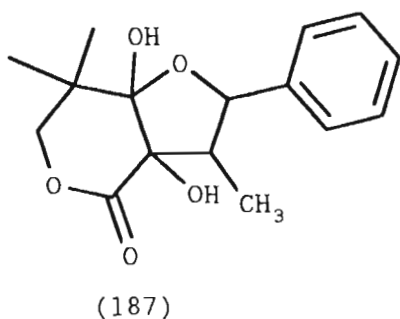
It is proposed that LDA produces a dianion which, after condensation with benzaldehyde (79), produces the intermediate (189) (Scheme 56) which rearranges to (190). Intermediate (191) is produced from (190) as shown in Scheme 56. The final step of the proposed mechanism is simply the cyclisation of the alkoxy anion onto the ketone which, upon work up, affords the diol (187).*
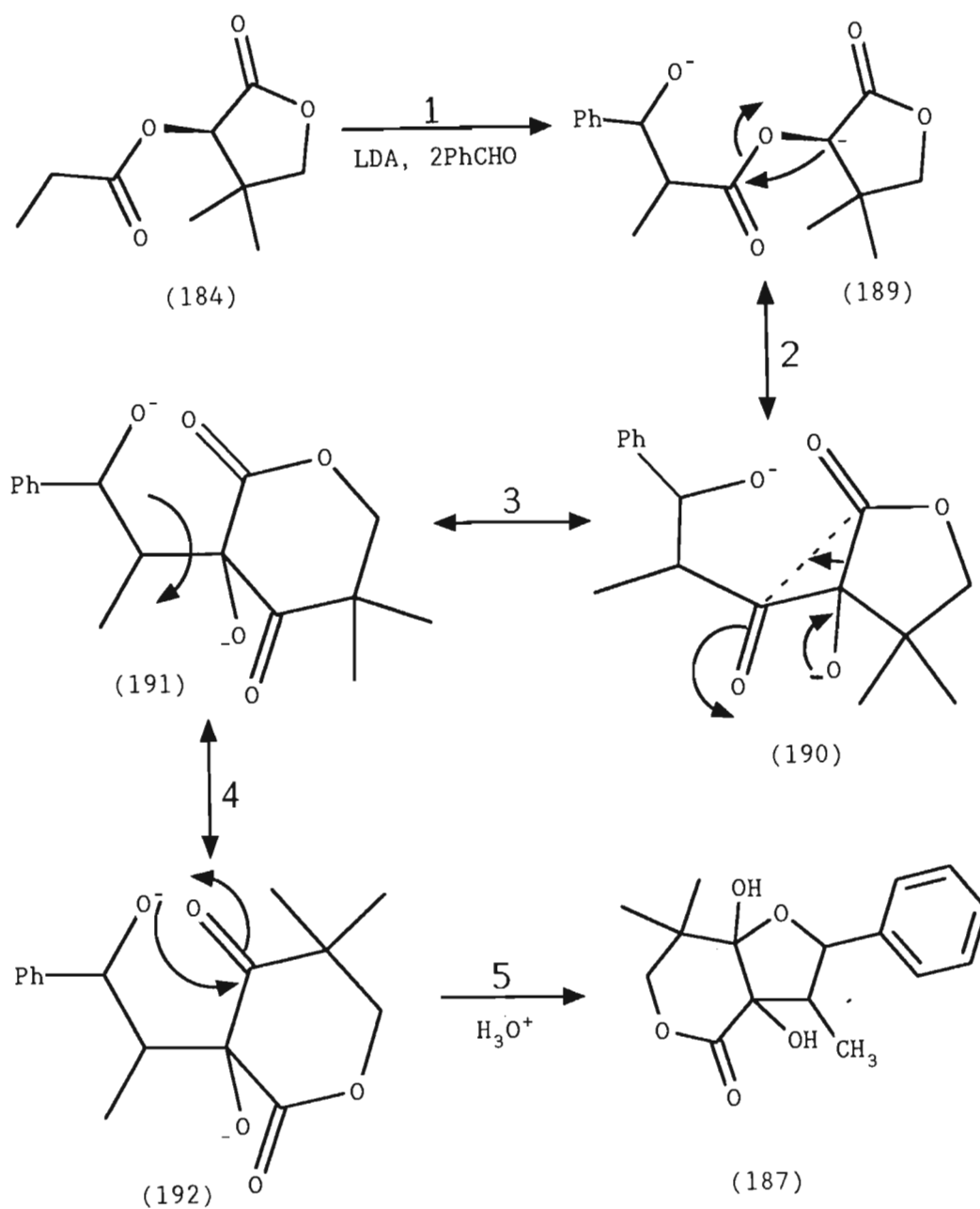
Scheme 56.

The formation of the dianion leading to intermediate (189) may be justified as follows:

(a) The condensation with benzaldehyde (79) does indeed occur at the correct site indicating that this carbanion does form.

(b) The lack of optical activity in (187) implies that the chiral centre of (184) is destroyed at the very outset, and this is possible if the dianion is formed.

The formation of intermediate (190) from (189) (Step 2) is not an unusual reaction and, in fact, is the formation of a ketone (190) by carbanion attack on an ester bearing a good leaving group. The pantolactone moiety is indeed a good leaving group which is precisely the reason that allowed dioxanone formation (Section 2.3.1.1.).

Step 3 is a novel example of the tertiary ketol rearrangement.[210] This rearrangement (Scheme 57) occurs upon the treatment of a tertiary alcohol containing an α-oxo group, with base. Proton abstraction by the base affords intermediate (193) which rearranges to (194) as shown below.

(193)   (194)
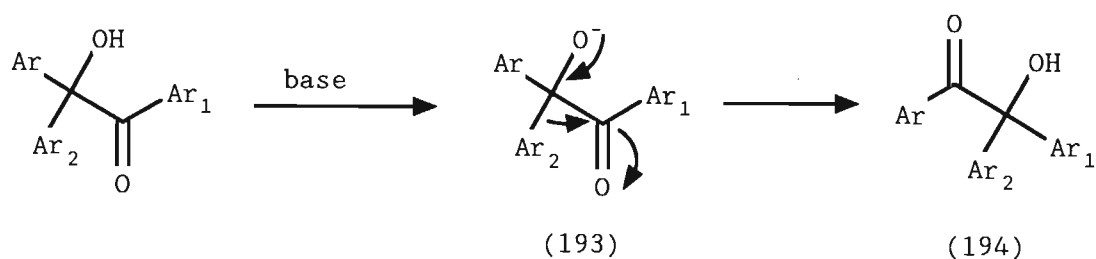
Scheme 57.

Since an intermediate such as (193) can also be produced when one equivalent of a Grignard reagent is added to a benzil or a substituted benzil, rearrangement products can be obtained either by addition of Grignard reagents to benzils (Scheme 58) or by treatment of a tertiary keto-alcohol with base (Scheme 57).[210]
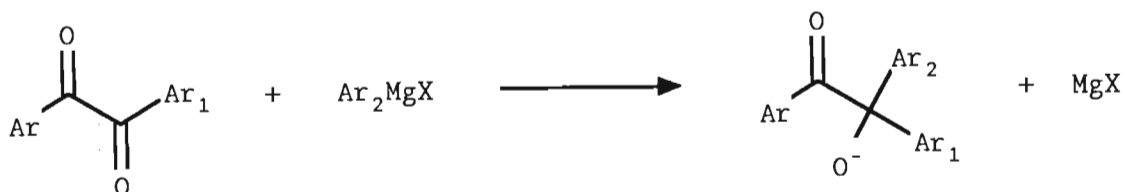
Scheme 58.

The tertiary ketol rearrangement is not restricted to benzoins but has also been observed with acyloins.[210] Rearrangements of the latter type are described in the steroid field.[211] An example of such a tertiary ketol rearrangement, which results in ring enlargement as for (191), is depicted below (Scheme 59).
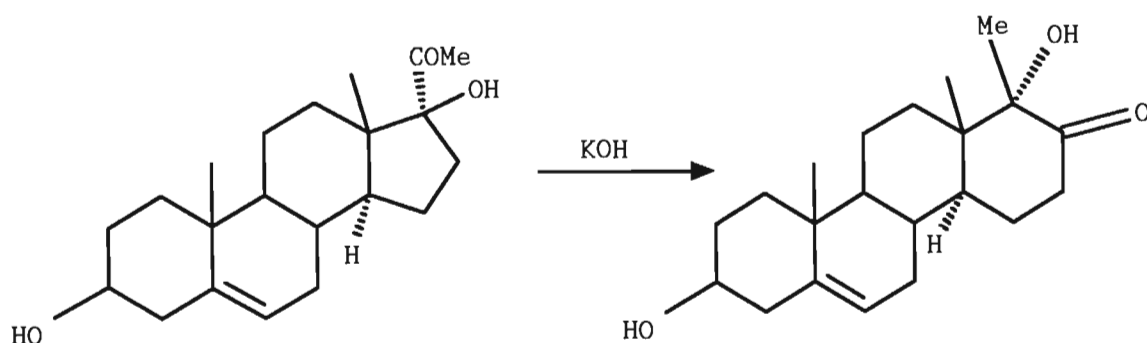
Scheme 59.

Intermediate (190) possesses all the requirements for the tertiary ketol rearrangement. The only difference is that the migratory group is an ester group as opposed to an aryl group (Scheme 57) or an alkyl group (Scheme 59). It seems reasonable to propose that (191) is formed by such a rearrangement.

Several experiments were conducted in order to substantiate the proposed mechanism. However, no meaningful conclusions could be reached. For example, using two equivalents of LDA did not improve the yield of (187). Also, attempts to quench the

proposed dianion with D_2O led to a mixture of compounds which proved difficult to isolate in significant quantities. However, from the ^1H NMR spectrum of the mixture, it was evident that the proton on the pantolactone moiety was indeed abstracted. The absence of any optical activity in (187) supports this idea.

2.7. CONCLUSION.

This study has focused on various stereochemical aspects of the Baylis-Hillman reaction. A considerable number of interesting features have been uncovered and provide ample scope for further pursuits.

3. EXPERIMENTAL.

3.1. INSTRUMENTATION AND CHEMICALS.

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were determined using Perkin-Elmer 240B and 2400 elemental analysers. NMR spectra ([1]H 200MHz and [13]C 50MHz) were recorded on a Gemini 200 instrument, and unless specified to the contrary, $CDCl_3$ was used as the solvent and TMS as the internal standard. Mass spectra were recorded on a Hewlett-Packard gas chromatographic-mass spectrometer (HP5988A) and a Varian high resolution mass spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Infra-red spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Kieselgel 60 F_{254} Merck plastic sheets were used for thin-layer chromatography. Preparative column chromatography was performed using the technique of Still *et al.*[179] on Merck silica gel 60 (230-400 mesh). Solvents were dried using standard techniques[212] and distilled prior to use. Low temperatures were maintained using CO_2-solvent baths according to the procedure of Phipps and Hume.[213] Diastereomeric excesses were determined either by NMR spectroscopy or by gas chromatographic-mass spectrometry while enantiomeric excesses were determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ shift reagent. Chemical shifts for NMR spectroscopy denote those of the major diastereomer. Shifts of minor diastereomers are denoted in square ([]) brackets. NMR spectra are bound separately and are available on request.

3.2. PREPARATIONS.

The preparation of compounds will be reported in this section under the same headings and section numbers reported in Section 2. Thus, Section 3.2.2.1. refers to compounds mentioned in Section 2.2.1.. This will enable cross-referencing between the preparation of a compound and the relevant discussion.

3.2.2. RESOLUTION AND DETERMINATION OF ABSOLUTE CONFIGURATION OF 3-HYDROXY-2-METHYLENE-3-PHENYLPROPANOIC ACID (81).

3.2.2.1. CLASSICAL RESOLUTION.

(±)-Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80).

$C_{11}H_{12}O_3$

MW = 192

(80)
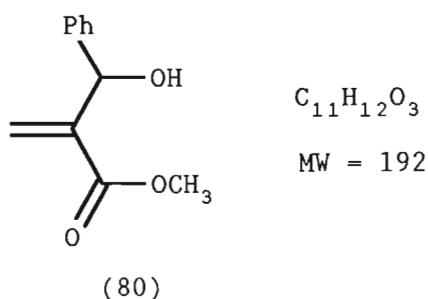
Methyl acrylate (30) (10g, 0.116mol) and benzaldehyde (79) (10g, 0.094mol) were allowed to react overnight in the presence of DABCO (10.57g, 0.094mol). The reaction mixture was diluted with ether and washed successively with 2N HCl, saturated $NaHCO_3$ and water. After evaporation of the solvent and excess methyl acrylate (30), the crude product was purified by flash chromatography on silica gel with Et_2O-Hexane (3:7) yielding (80) (16g, 88%), m.p. 54°C; δ_H 3.58 (3H, s, -OCH_3), 3.81 (1H, br s, -CH-OH), 5.47 (1H, br s, -CH-OH), 5.81 and 6.26 (2H, 2xm, CH_2=C-), 7.20-7.31 (5H, m, PhH's); δ_C 51.81 (q, -OCH_3), 72.56 (d, -CH-OH), 125.60 (t, CH_2=C-), 126.74 (d, 2 x o-PhCH's), 127.69 (d, p-PhCH), 128.30 (d, 2 x m-PhCH's), 141.46 (s, Ph quarternary), 142.20 (s, CH_2=C-) and 166.64 (s, -COOMe); m/z(EI) 192(M$^+$, 23%), 160(23), 105(100), 79(44) and 77(59).

3.2.2.3. RESOLUTION OF 3-HYDROXY-2-METHYLENE-3-PHENYLPROPANOIC ACID (81).

(±)-3-Hydroxy-2-methylene-3-phenylpropanoic acid (81).

$$C_{10}H_{10}O_3$$

$$MW = 178$$

(81)
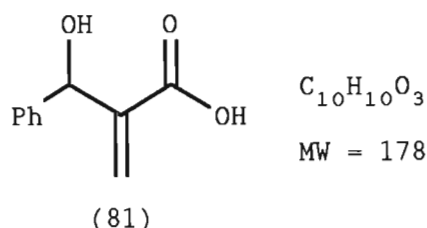
To methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80) (16g, 0.083mol) in ethanol (30ml) was added KOH (6g, 0.107mol) in water (150ml). The mixture was refluxed for 3 hours, the ethanol evaporated, and unreacted ester extracted (Et_2O). The aqueous phase was acidified to pH 2 and was extracted with Et_2O (3 x 100ml) to yield (81) (11.95g, 75%), m.p. 78-79°C (from $CHCl_3/CCl_4$) (Found: C, 67.45; H, 5.8. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.6%); δ_H 5.50 (1H, s, -CH-OH), 5.90 and 6.48 (2H, 2 x m, CH_2=C-), 7.23-7.32 (7H, m and overlapping br s, PhH's and OH's); δ_C 72.82 (d, -CH-OH), 126.63 (d, 2 x o-PhCH's), 128.02 (d, p-PhCH), 128.52 (d, 2 x m-PhCH's), 128.61 (t, CH$_2$=C-), 140.84 (s, Ph quarternary), 141.24 (s, CH$_2$=C-) and 171.09 (s, -COOH); m/z(EI) 178 (M$^+$, 47%), 177(46), 160(19) 132(48), 105(100), 77(63) and 55(16).

(-)-(R,R)-2-Amino-1-(4-nitrophenyl)propan-1,3-diol salt of
3-hydroxy-2-methylene-3-phenylpropanoic acid (89).

$C_{19}H_{22}N_2O_7$

MW = 390

(89)
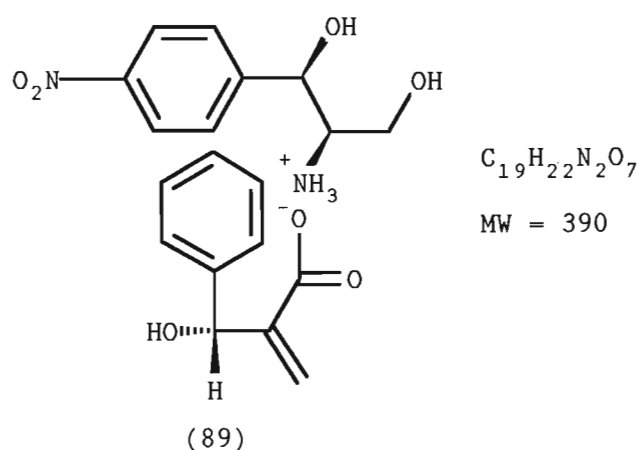
The acid (81) (5.34g, 0.03mol) and the amino diol (88) (6.36g, 0.03mol) were dissolved in a minimum amount of acetone. The mixture was refluxed for 5 minutes, diluted to twice the volume with chloroform, and refrigerated overnight. Filtration yielded (89) (4.4g, 38%) (m.p. 97°C, $[\alpha]_D$ = -20° (MeOH)). The salt was recrystallised (acetone/chloroform) to constant m.p. and optical rotation yielding (89) (3.5g, 30%), m.p. 99°C (Found: C, 58.5; H, 5.5; N, 7.1. $C_{19}H_{22}N_2O_7$ requires C, 58.5; H, 5.6; N, 7.2%); $[\alpha]_D^{25}$ = -23.5° (c1.05, MeOH); δ_H(CD$_3$COCD$_3$) 3.16 (1H, m, -CH-N-), 3.75 (2H, m, -CH_2-OH), 4.84 (1H, d, -CH-CH-OH), 5.59 (1H, s, Ph-CH-OH), 6.01 and 6.27 (2H, 2 x m, CH_2=C-), 7.19-7.42 (5H, m, PhH's), 7.63-7.74 and 8.18-8.26 (4H, 2 x m, p-NO$_2$-C$_6$H$_4$); δ_C(CD$_3$COCD$_3$) 59.26 (t, -CH_2-OH), 68.40 (d, -CH-N-), 72.74 (d, NO$_2$-Ph-CH-), 80.38 (d, Ph-CH-), 124.45 (t, CH_2=C-), 124.67, 128.30, 128.42, 128.47 and 129.28 (5 x d, Ar CH's), 143.95, 145.18, 148.05 and 150.70 (4 x s, -C=CH$_2$ and Ar quarternary carbons), 167.80 (s, -C=O).

(-)-3-Hydroxy-2-methylene-3-phenylpropanoic acid (81).

$C_{10}H_{10}O_3$

MW = 178

(81)
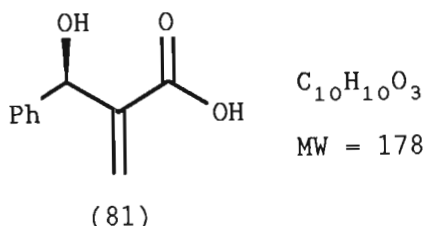
Salt (89) (3.5g, 8.97mmols) was treated with 1.1 equivalents of 2N NaOH. The resolving agent (88) was recovered by filtration and the aqueous phase was cooled to 0°C and acidified to pH3 with 2N HCl. Extraction with Et_2O (3 x 50ml) afforded the homochiral acid (81) (1.2g, 75%), m.p. 79°C (from $CHCl_3/CCl_4$); $[\alpha]_D^{25} = -23.2°$ (c1.05, $CHCl_3$). Spectral data identical to (±)-(81).

(-)-Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80).

$C_{11}H_{12}O_3$

MW = 192

(80)
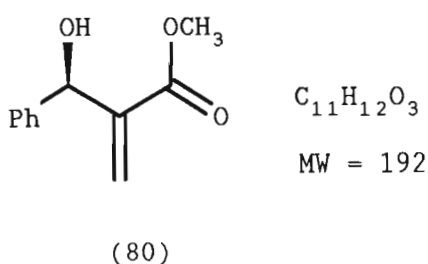
To a stirred solution of (-)-(80) (1.78g, 10mmol) in anhydrous CH_2Cl_2 (10ml) was added DMAP (50mg) and MeOH (2ml, 49mmol). The mixture was cooled to 0°C and DCC ((2.063g, 10mmol) was added in portions. The mixture was allowed to stir at this temperature for 5 minutes and at 20°C for 3 hours. Precipitated urea was filtered off and the filtrate was washed sequentially with 0.5N HCl, saturated $NaHCO_3$ and water. The crude product was purified by column chromatography with Et_2O/hexane (1:1) and yielded (-)-(80) (1.44g, 75%); m.p. 54°C; $[\alpha]_D^{26} = -111.1°$ (c1.11, MeOH). Spectral data is identical to (±)-(80).

(-)-ᵗButyl 3-hydroxy-2-methylene-3-phenylpropanoate (90).

(90)
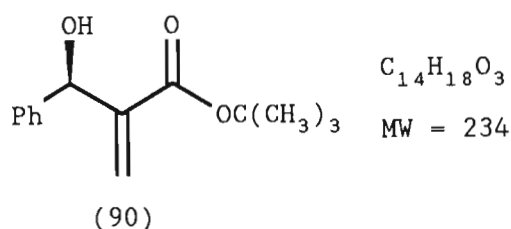
A stirred solution of the homochiral acid (-)-(81) (1.78g, 10mmol) in Et_2O (10ml) was treated with conc. H_2SO_4 (3 drops) and an excess of isobutylene.[115] Stirring was continued for 24 hours in a pressure bottle. The bottle was chilled and the contents were transferred to a separatory funnel containing ice-cold 2N NaOH. Extraction with diethyl ether afforded the crude product which was purified by column chromatography (Et_2O/hexane). A close-running impurity had to be removed using a chromatotron (10% Et_2O/hexane) and yielded (90) (1.2g, 51%); $[\alpha]_D^{26}$ = -93.2° (c1.09, MeOH); δ_H 1.35 (9H, s, 3 x $-CH_3$), 3.55 (1H, br s, $-OH$), 5.44 (1H, br s, $-CH-OH$), 5.75 and 6.22 (2H, 2 x m, $CH_2=C-$), 7.22-7.34 (5H, m, PhH's); δ_C 27.94 (q, 3 x CH_3's), 73.54 (d, $-CH-OH$), 81.66 (s, $-C-(CH_3)_3$), 125.34 (t, $CH_2=C-$), 126.53, 127.66 and 128.33 (d, PhCH's), 141.59 (s, Ar quarternary), 143.37 (s, $-C=CH_2$) and 165.45 (s, $-C=O$); m/z(EI) 234(M^+, 15%), 177(54%), 132(65%) and 105(100%).

3.2.2.4. DETERMINATION OF ABSOLUTE CONFIGURATIONS:

3.2.2.4.2. BY CHEMICAL INTERCONVERSION.

(2R,3S) and (2S,3S)-Methyl 3-hydroxy-2-methyl-3-phenylpropanoate (91a) and (91b).

(91a)   (91b)

$C_{11}H_{14}O_3$

MW = 194
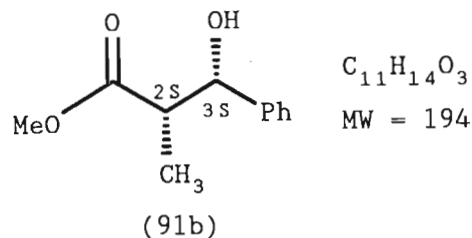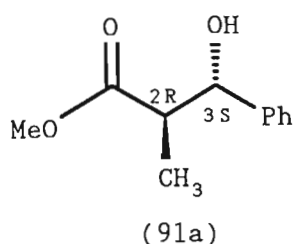
(−)-Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80) (0.576g, 3mmol) in MeOH (10ml) was treated with a catalytic amount of Pd/C. The mixture was hydrogenated until all the starting material (80) was consumed. Filtration of the catalyst and removal of the solvent yielded a mixture of the (2S,3S) and the (2R,3S) isomers (0.56g, 96%). The mixture was separated by column chromatography using Et_2O/hexane (1:9) to afford (2S,3S)-(91) (0.25g, 43%) and (2R,3S)-(91) (0.23g, 40%).

Data for (2R,3S)-(91) $[\alpha]_D^{21}$ = −57.9° (c1.1, $CHCl_3$); δ_H 0.98 (3H, d, −CH-CH_3), 2.80 (1H, dq, −CH-CH_3), 3.16 (1H, br s, −OH), 3.71 (3H, s, −OCH_3), 4.72 (1H, d, Ph-CH-), 7.27-7.36 (5H, m, PhH's); δ_C 14.43 (q, −CH-CH_3), 47.15 (d, −CH-CH_3), 51.93 (q, −OCH_3), 76.38 (d, −CH-OH), 126.69, 128.05 and 128.47 (3 x d, PhCH's), 141.55 (s, Ph quarternary) and 176.29 (s, −C=O); m/z(EI) 194(M^+, 4%), 107(61), 88(100), 79(44) and 77(33).

Data for (2S,3S)-(91) $[\alpha]_D^{23}$ = −22.8° (c1.2, $CHCl_3$); δ_H 1.12 (3H, d, −CH-CH_3), 2.77 (1H, dq, −CH-CH_3), 3.16 (1H, br s, −OH), 3.64 (3H, s, −OCH_3), 5.06 (1H, d, Ph-CH-) and 7.23-7.34 (5H, m, PhH's); δ_C 10.81 (q, −CH-CH_3), 46.49 (d, −CH-CH_3), 51.86 (q, −OCH_3), 73.68 (d, −CH-OH), 125.95, 127.47 and 128.23 (3 x d, PhCH's), 141.50 (s, Ph quarternary) and 176.11 (s, −C=O); m/z(EI) 194(M^+, 5%), 107(67), 88(100), 79(47) and 77(34).

3.2.3. ASYMMETRIC SYNTHESIS USING THE BAYLIS-HILLMAN REACTION.

3.2.3.1. THE USE OF CHIRAL ACRYLIC ESTERS.

3.2.3.1.1. USE OF (R)-(+)-PANTOLACTONE ACRYLATE (96).

GENERAL PROCEDURE 1: SYNTHESIS OF CHIRAL ACRYLIC ESTERS.

Acryloyl chloride (11.3g, 0.125mol) was added to a stirred cold (-24°C) solution of the chiral alcohol (0.100mol) and triethyl-amine (15.2g, 0.150mol) in dry CH_2Cl_2 (125ml) over one hour under nitrogen. After stirring at -24°C for 4.5 hours, the mixture was allowed to warm up to room temperature and was washed successively with 1N HCl (70ml), saturated $NaHCO_3$ (70ml) and water (70ml). The organic phase was dried and the solvent evaporated. The product was purified by distillation or column chromatography.

Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl prop-2-enoate (96).

$C_9H_{12}O_4$

MW = 184

(96)
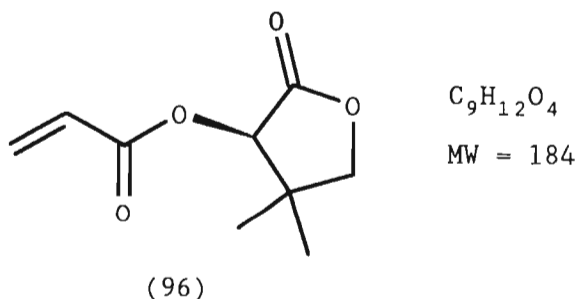
D-pantolactone (13g, 0.0999mol) was treated according to General Procedure 1. Distillation afforded pure (96) (15.64g, 85%), b.p. 83-85°C/0.1mmHg (lit.[129] 84°C/0.1mmHg); $[\alpha]_D^{21}$ = +6.5° (c1.3, CH_2Cl_2); δ_H 1.14 (3H, s, -CH_3), 1.23 (3H, s, -CH_3), 4.08 (2H, s, -O-CH_2-), 5.46 (1H, s, -O-CH-C=O) and 5.97-6.69 (3H, m, CH_2=CH-); δ_C 19.92 and 23.03 (2 x q, 2 x -CH_3), 40.17 (s, -C-(CH_3)$_2$), 75.35 (d, -O-CH-C=O), 76.43 (t, -O-CH$_2$-), 127.39 (d, CH$_2$=CH-), 133.27 (t, CH$_2$=C-), 165.30 (s, -C=O), 172.88 (s, ring -C=O); m/z(EI) 184(M$^+$,1%), 100(7), 85(6), 83(4) and 55(100).

GENERAL PROCEDURE 2: BAYLIS HILLMAN REACTION OF PANTOLACTONE ACRYLATE (96) WITH ALDEHYDES.

A mixture of pantolactone acrylate (96) (0.5g, 2.72mmol), the aldehyde (2.5 equivalents) and DABCO (0.1g, 20mass%) was allowed to stir in a sealed vessel at room temperature. The reactions were monitored by tlc and/or ^{1}H NMR spectroscopy. Excess aldehyde was removed under reduced pressure and the products were purified by flash chromatography on silica gel.

2,6-Dimethyl-5-methylene-1,3-dioxan-4-one (97).

$C_7H_{10}O_3$

MW = 142

(97)
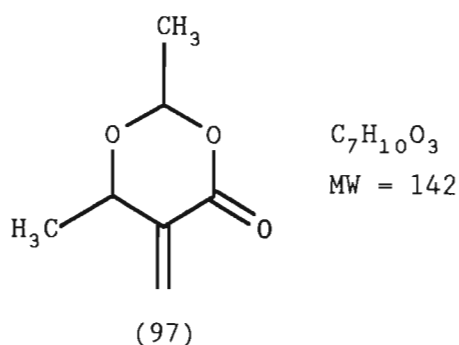
According to General Procedure 2 using acetaldehyde (0.3g, 6.8mmol). The reaction mixture was subjected to chromatography (Et_2O/hexane) and yielded pure (97) (0.325g, 84%) (Found: C, 59.1; H, 7.1. $C_7H_{10}O_3$ requires C, 59.15; H, 7.1%); $[\alpha]_D^{22} = -5.6°$ (c2.1, $CHCl_3$); δ_H 1.49 (3H, d, J5.2, 6-CH_3), 1.52 (3H, d, J6.3, 2-CH_3), 4.68 (1H, m, J6.3, 6-H), 5.54 (1H, q, J5.2, 2-H), 5.63 and 6.51 (2H, 2 x dd, CH_2=C-); δ_C 20.38 (q, 6-CH_3), 20.99 (q, 2-CH_3), 74.30 (d, 6-CH-), 99.87 (d, 2-CH-), 126.06 (t, CH$_2$=C-), 138.06 (s, -C=CH$_2$) and 163.77 (s, -C=O); m/z(EI) 142(M$^+$, 3%), 127(17), 83(30), 54(100) and 43(40).

3.2.3.1.1.2. REACTION OF PANTOLACTONE ACRYLATE (96) WITH OTHER ALDEHYDES.

2,6-Diethyl-5-methylene-1,3-dioxan-4-one (114a).

$C_9H_{14}O_3$

MW = 170
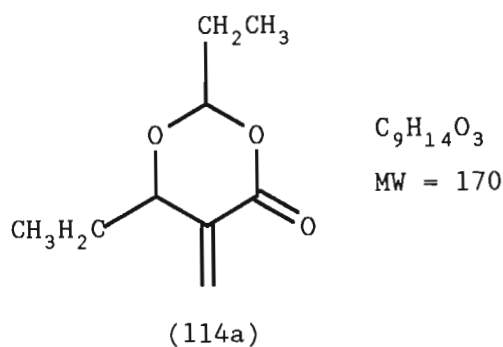
(114a)

According to General Procedure 2 using propionaldehyde (0.395g, 6.8mmol). The reaction mixture was subjected to chromatography using EtOAc/hexane (1:4) and yielded pure (114a) (0.325g, 89%) (Found: 170.09360, $C_9H_{14}O_3$ requires 170.09428); $[\alpha]_D^{26} = -5.34°$ (c1.03, $CHCl_3$); δ_H 1.02 (6H, 2 x overlapping t, 2 x $-CH_3$), 1.62-1.99 (4H, 2 x overlapping m, 2 x $-CH_2-$), 4.54[4.61] (1H, m, 6-$CH-$), 5.28[5.36] (1H, t, 2-$CH-$), 5.61 and 6.49 (2H, 2 x dd, CH_2=C-); δ_C 7.39[7.41] (q, 6-CH_2-CH_3), 8.89[9.01] (q, 3-CH_2-CH_3), 27.64[26.70] (t, 6-CH_2-), 28.02[27.62] (t, 2-CH_2-), 78.50 (d, 6-$CH-$), 102.68[98.10] (d, 2-$CH-$), 125.41[126.45] (t, CH_2=C), 136.87 (s, $-C$=CH$_2$) and 164.19 (s, $-C$=O); m/z(EI) 170(M$^+$, 1%), 141(48), 95(25), 83(100), 67(73), 68(44) and 43(40).

2,6-Diisopropyl-5-methylene-1,3-dioxan-4-one (114b).

$$CH(CH_3)_2$$

$C_{11}H_{18}O_3$

MW = 198
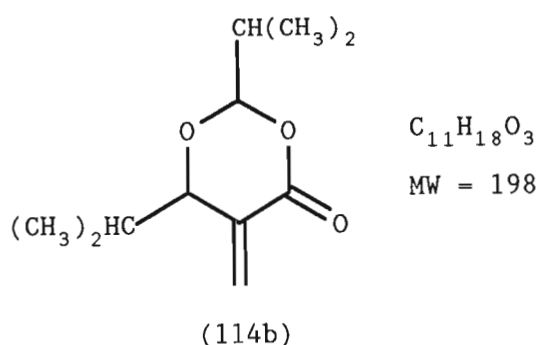
(114b)

According to General Procedure 2 using isobutyraldehyde (0.49g, 6.8mmol). The reaction mixture was subjected to chromatography using EtOAc/hexane (1:4) and yielded pure (114b) (0.42g, 78%) (Found: 198.1233, $C_{11}H_{18}O_3$ requires 198.12558); $[\alpha]_D^{25} = -18.7°$ (c1.03, CHCl$_3$); δ_H 0.9, 1.01, 1.02 and 1.05 (12H, 4d, 4 x -CH_3), 1.93-2.18 (2H, 2 x overlapping m, 2-CH-CH-(CH$_3$)$_2$), 4.48 (1H, m, 6-CH-), 5.03[5.24] (1H, d, 2-CH-), 5.56 and 6.44[6.55] (2H, 2 x dd, CH_2=C-); δ_C 15.47 and 16.01 (2 x q, 6-CH-CH(CH_3)$_2$), 16.18 and 18.61[18.78] (2 x q, 2-CH-CH(CH_3)$_2$), 32.26[29.45] (d, 6-CH-CH(CH$_3$)$_2$), 33.59[32.36] (2-CH-CH(CH$_3$)$_2$), 81.54[80.46] (d, 6-CH), 104.07[102.01] (d, 2-CH), 125.31[127.70] (t, CH_2=C), 136.63[134.30] (s, C=CH$_2$) and 165.46 (s, C=O); m/z(EI) 198(M$^+$, 1%), 156(26), 155(33), 109(29), 84(29), 83(100), 67(38), and 56(22).

2,6-Dibutyl-5-methylene-1,3-dioxan-4-one (114c).

$$CH_2(CH_2)_2CH_3$$

$$CH_3(CH_2)_2H_2C$$

$$C_{13}H_{22}O_3$$
MW = 226
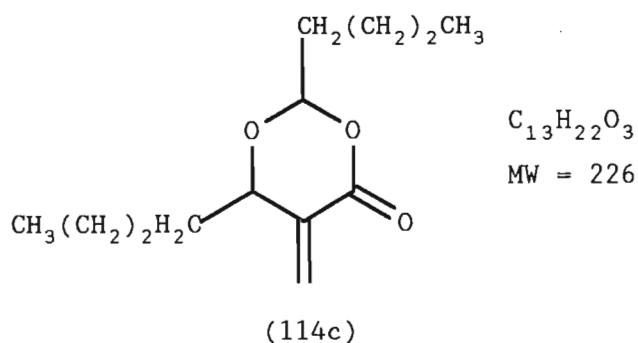
(114c)

According to General Procedure 2 using valeraldehyde (0.585g, 6.8mmol). The reaction mixture was subjected to chromatography using EtOAc/hexane (1:4) and yielded pure (114c) (0.47g, 77%) (Found: C, 68.9; H, 9.8. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.8%); $[\alpha]_D^{22}$ = -12.7° (c0.87, CHCl$_3$); δ_H 0.92 (6H, 2 x overlapping t, 2 x -CH$_3$), 1.30-1.51 (8H, m, -C(2)-CH$_2$(CH$_2$)$_2$CH$_3$ and -C(6)-CH$_2$(CH$_2$)$_2$CH$_3$) 1.68-1.86 (4H, 2 x m, -C(2)-CH$_2$- and -C(6)-CH$_2$-), 4.55[4.68] (1H, m, 6-CH), 5.31[5.42] (1H, t, 2-CH), 5.60 and 6.46 (2H, 2 x d, CH$_2$=C-); δ_C 13.92 and 13.97 (2 x q, 2 x CH$_3$), 22.41, 22.57, 25.30[25.35] and 26.80[27.20] (4 x t, -C(2)-CH$_2$(CH$_2$)$_2$CH$_3$ and -C(6)-CH$_2$(CH$_2$)$_2$CH$_3$), 34.21 (t, 6-CH-CH$_2$-), 34.81 (t, 2-CH-CH$_2$-), 77.86 (d, 6-CH-), 102.38[97.46] (d, 2-CH-), 125.61[126.20] (t, CH$_2$=C-), 137.26[136.31] (s, -C=CH$_2$) and 164.12 (s, -C=O); m/z(EI) 226(M$^+$, 0.1%), 169(59), 123(24), 95(39), 83(100), 81(26) and 55(17).

2,6-Dicyclohexyl-5-methylene-1,3-dioxan-4-one (117).

$C_{17}H_{26}O_3$

MW = 278

(117)
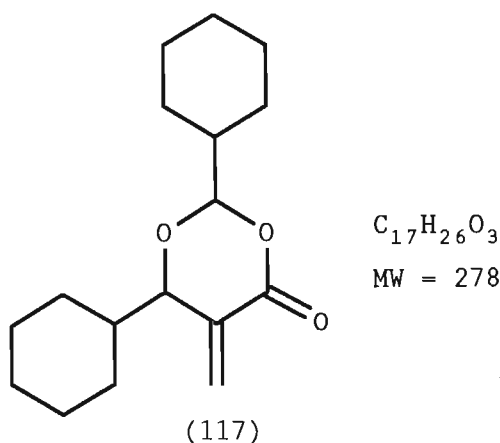
According to General Procedure 2 using cyclohexanecarboxaldehyde (0.763g, 6.8mmol). The reaction mixture was subjected to chromatography using EtOAc/hexane (1:3) and yielded pure (117) (0.46g, 61%) (Found: C, 73.29; H, 9.34. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.41%); $[\alpha]_D^{21}$ = -27.4° (c1.08, CHCl$_3$); δ_H 1.09-1.83 (22H, 2 x *cyclohexyl* ring protons), 4.42[4.26] (1H, m, 6-C*H*), 4.98[5.22] (1H, d, 2-C*H*), 5.53[5.49] and 6.39[6.52] (2H, 2 x dd, C*H*$_2$=C); δ_C 25.62, 25.63, 25.98, 26.18, 26.29, 26.31, 26.41, 26.42, 26.63 and 29.08 (10 x t, *cyclohexyl* C*H*$_2$'s), 41.75 (d, 6-CH-*C*H-), 43.69 (d, 2-CH-*C*H), 81.72 (d, 6-*C*H-), 103.9 (d, 2-*C*H-), 125.40 (t, *C*H$_2$=C-), 136.65 (s, -*C*=CH$_2$) and 165.69 (s, -*C*=O); m/z(CI) 279(M$^+$ + 1); (EI) 196(36%), 195(35), 149(30), 96(100), 95(36), 83(69), 81(58), 55(71) and 41(33).

Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl 3-hydroxy-2-methylene-3-phenylpropanoate (116).

$C_{16}H_{18}O_5$

MW = 290
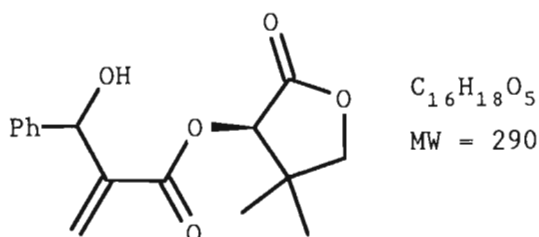
(116)

According to General Procedure 2 using benzaldehyde (0.72g, 6.8mmol). The reaction mixture was subjected to chromatography using EtOAc/hexane (2:3) and yielded pure (116) (0.64g, 81%), de 2%, m.p. 49-52°C (Found: 290.1182, $C_{16}H_{18}O_5$ requires 290.1154); $[\alpha]_D^{28} = +8.2°$ (c0.92, CHCl$_3$); δ_H 0.90[0.91] and 1.09[1.10] (6H, 2 x s, 2 x CH_3's), 2.90 (1H, br d, -OH), 3.99[4.01] (2H, s, -CH_2-O-), 5.34[5.36] (1H, s, ring -CH-), 5.62 (1H, br d, -CH-OH), 6.02 and 6.49[6.53] (2H, 2 x m, CH_2=C-) and 7.27-7.41 (5H, m, PhH's); δ_C 19.64 and 22.91 (2 x q, 2 x CH_3), 40.38[40.41] (s, -C-(CH$_3$)$_2$), 72.65[73.21] (d, ring -CH-O-), 75.49 (d, -CH-OH), 76.21 (t, ring -CH$_2$-), 126.36, 126.96 and 128.49 (d, PhCH's), 128.09(t, CH$_2$=C-), 140.8[140.9] (s, Ph quarternary carbon), 141.03[141.14] (s, -C=CH$_2$), 164.74 (s, ring -C=O) and 172.21 (s, -C=O); m/z(EI) 290(M$^+$, 13%), 177(43), 169(28), 160(82), 159(52), 132(100), 115(40), 105(65) and 99(64).

Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl 4,4,4-trichloro-3-hydroxy-2-methylenebutanoate (119).

$C_{11}H_{13}Cl_3O_5$

$MW = 331$
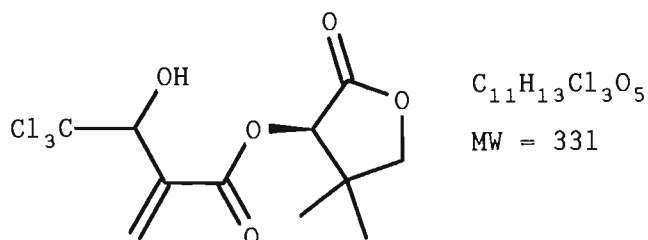
(119)

According to General Procedure 2 using trichloroacetaldehyde (1.00, 6.8mmol). The reaction mixture was subjected to chromatography using EtOAc/hexane (2:3) and yielded pure (119) (0.75g, 83%), de 48%, m.p. 115-120°C (Found: C, 39.69; H, 3.92. $C_{11}H_{13}Cl_3O_5$ requires C, 39.85; H, 3.95%); recrystallisation from $CHCl_3$ afforded the pure minor diastereomer, m.p. 165°C $[\alpha]_D^{21} = -8.6°$ (c1.1, $CHCl_3$); δ_H 1.18 and 1.24 (2 x 3H, 2 x s, 2 x -CH_3), 3.94 (1H, d, -OH), 4.09 (2H, dd, ring -CH_2), 4.53 (1H, br d, -OH), 5.34 (1H, br d, -CH-OH), 5.48 (1H, s, ring -CH-), 6.44 and 6.79 (2H, 2 x d, CH_2=C-); δ_C 20.01 and 23.03 (2 x q, 2 x -CH_3), 40.54 (s, ring -C-(CH$_3$)$_2$), 75.87 (d, ring -CH-), 76.18 (t, ring -CH_2-), 79.95 (d, -CH-OH), 101.95 (s, -CCl$_3$), 133.82 (t, CH_2=C-), 134.58 (s, -C=CH$_2$), 165.23 (s, ring -C=O) and 171.81 (s, -C=O); m/z(CI) 332(M$^+$ + 1); (EI) 303(5%), 213(62), 165(94), 113(100) and 83(62).

3.2.3.1.1.3. SYNTHESIS OF MIXED DIOXANONES.

GENERAL PROCEDURE 3: SYNTHESIS OF MIXED DIOXANONES.

A mixture of pantolactone acrylate (96) (0.68g, 3.7mmol), cyclo-hexanecarboxaldehyde (0.41g, 3.66mmol) and DABCO (0.136g, 1.21mmol) was allowed to stir overnight in a sealed vessel at room temperature. The second aldehyde (3.7mmol) was added and the mixture was allowed to stir for a further 24 hours. The products were isolated by flash chromatography on silica gel.

6-Cyclohexyl-2-methyl-5-methylene-1,3-dioxan-4-one (122).

$C_{12}H_{18}O_3$

MW = 210

(122)
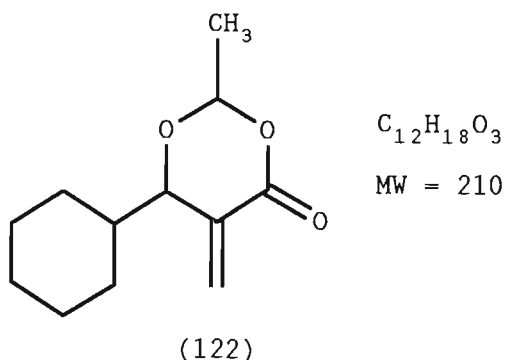
According to General Procedure 3 with acetaldehyde (0.163g, 3.7mmol) as the second aldehyde. Purification by flash chromatography afforded the pure product (122) (0.403g, 52%) (Found: C, 68.78; H, 8.68. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.63); $[\alpha]_D^{26}$ = -10.9° (c1.05, CHCl$_3$); δ_H 1.09-1.84 (11H, *cyclohexyl* H's), 1.51 (3H, d, J5, -CH$_3$), 4.49 (1H, m, 6-CH-), 5.40 (1H, q, J5, 2-CH-), 5.56 and 6.40 (2H, 2 x dd, CH$_2$=C-); δ_C 20.42 (q, -CH$_3$), 25.93-28.84 (5 x t, *cyclohexyl* -CH$_2$'s), 43.54 (d, *cyclohexyl* -CH-), 81.61 (d, 6-CH-), 98.26 (d, 2-CH-), 125.34 (t, CH$_2$=C-), 136.23 (s, -C=CH$_2$) and 165.41 (s, -C=O); m/z(CI) 211(M$^+$ + 1); (EI) 209(M$^+$ - 1, 0.2%), 128(88), 84(100), 83(32) and 55(17).

6-Cyclohexyl-2-isopropyl-5-methylene-1,3-dioxan-4-one (123).

$C_{14}H_{22}O_3$

MW = 238

(123)
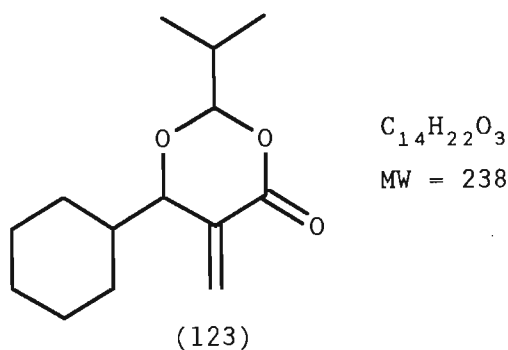
According to General Procedure 3 with isobutyraldehyde (0.267g, 3.7mmol) as the second aldehyde. Purification by flash chromatography afforded the pure product (123) (0.44g, 50%) (Found: C, 70.30; H, 9.46. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30); $[\alpha]_D^{24} = -16.1°$ (c1.02, $CHCl_3$); δ_H 0.99 and 1.03 (6H, 2 x d, 2 x CH_3), 0.98-2.09 (11H, m, *cyclohexyl H's*), 4.45[4.25] (1H, m, 6-C*H*-), 4.99[4.96] (1H, d, 2-C*H*-), 5.54[5.49] and 6.40[6.53] (2 x 1H, 2 x m, CH_2=C-); δ_C 16.11 and 16.26 (2 x q, 2 x -CH_3), 25.55-29.09 (t, *cyclohexyl* -CH_2's), 32.23 (d, -C*H*-(CH_3)$_2$), 41.63 (d, *cyclohexyl*-C*H*), 81.66 (d, 6-C*H*-), 104.33 (d, 2-C*H*-), 125.46 (t, CH_2=C-), 136.63 (s, -C=CH_2) and 165.68 (s, -C=O); m/z(CI) 239(M$^+$+ 1); (EI) 237(M$^+$ - 1, 0.2%), 95(13), 156(100), 84(77) and 55(14).

3.2.3.1.1.5.   REACTIONS OF DIOXANONES.

3.2.3.1.1.5.1.   ISOMERISATION OF THE EXOCYCLIC DOUBLE BOND.

GENERAL PROCEDURE 4: ISOMERISATION OF THE EXOCYCLIC DOUBLE BOND.

The dioxanone (1g) in MeOH (10ml) was treated with a catalytic amount of Pd/C.   The mixture was hydrogenated until all the starting dioxanone was consumed.   Filtration, evaporation of the solvent and column chromatography afforded the pure dioxin-4-ones.

2,5,6-Trimethyl-2H,4H-1,3-dioxin-4-one (130).

$C_7H_{10}O_3$

MW = 142

(130)
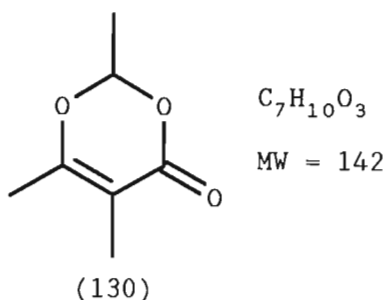
According to General Procedure 4 using (97) which yielded (130) (0.85g, 85%) (Found: C, 59.20; H, 7.12. $C_7H_{10}O_3$ requires C, 59.15; H, 7.09%); $[\alpha]_D^{24} = +30.7°$ (c1.1, CHCl$_3$); δ_H 1.62 (3H, d, C(2)-CH_3), 1.83 and 2.04 (2 x 3H, 2 x s, C(5)-CH_3 and C(6)-CH_3), 5.54 (1H, q, C(2)-H); δ_C 10.59 (q, C(5)-CH_3), 16.99 (q, C(6)-CH$_3$), 19.55 (q, C(2)-CH_3), 97.48 (d, C(2)-CH), 102.77 (s, C(5)), 164.74 (s, C(6)) and 166.83 (s, -C=O); m/z(EI) 142(M$^+$, 32%), 98(76), 83(65), 70(86), 56(41) and 43(100).

2,6-Diisopropyl-5-methyl-2H,4H-1,3-dioxin-4-one (132).

$C_{11}H_{18}O_3$

MW = 198
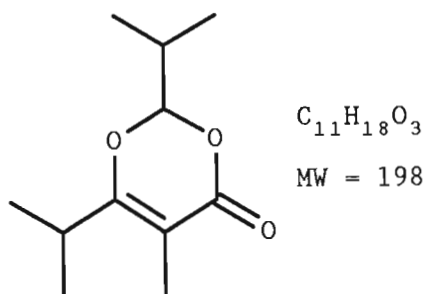
(132)

According to General Procedure 4 using (114b) which yielded (132) (0.86g, 86%) (Found: C, 66.84; H, 9.39. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%); $[\alpha]_D^{24} = +48.3°$ (c0.9, CHCl$_3$); δ_H 1.05-1.16 (12H, 4 x d, 4 x CH_3), 1.84 (3H, s, C(5)-CH_3), 2.15 (1H, m, C(6)-CH-(CH$_3$)$_2$), 2.89 (1H, m, C(2)-CH-(CH$_3$)$_2$), 5.05 (1H, d, C(2)-H); δ_C 9.93 (q, C(5)-CH$_3$), 15.98, 16.26, 18.54 and 19.55 (4 x q, *isopropyl*-CH$_3$'s), 29.38 (d, C(4)-CH-(CH$_3$)$_2$), 31.44 (d, C(2)-CH-(CH$_3$)$_2$), 100.44 (s, C(5)), 103.14 (d, C(2)), 165.19 (s, -C(6)-) and 173..01 (s, -C=O); m/z(EI) 198(M$^+$, 4%), 127(22), 126(30), 98(11), 83(100) 71(13) and 43(7).

2,6-Dicyclohexyl-5-methyl-2H,4H-1,3-dioxin-4-one (133).

$C_{17}H_{26}O_3$

MW = 278

(133)
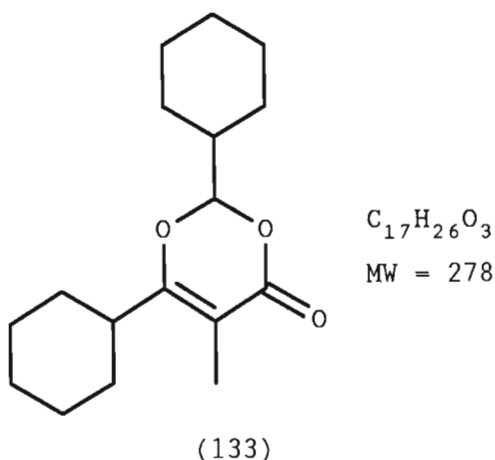
According to General Procedure 4 using (117) which yielded (133) (0.97g, 97%), m.p. 54-55°C (Found: C, 73.07; H, 9.59. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.41%); $[\alpha]_D^{25}$ = +45.5° (c0.7, CHCl$_3$); δ_H 1.05-1.91 (21H, m, *cyclohexyl H's*), 1.83 (3H, s, C(5)-CH_3), 2.53 (1H, m, C(6)-*cyclohexyl-CH-*), 5.05 (1H, d, C(2)-*H*); δ_C 9.98 (q, C(5)-CH$_3$), 25.45-29.45 (10 x t, *cyclohexyl* CH$_2$'s), 39.52 (d, C(6)-*cyclohexyl-CH-*), 40.70 (d, C(2)-*cyclohexyl-CH-*), 100.62 (s, *C*(5)), 102.50 (d, *C*(2)), 165.18 (s, *C*(6)), 172.56 (s, -*C*=O); m/z(EI) 278(M$^+$, 6%), 167(97), 137(26), 111(36), 98(69), 83(100) and 55(18).

3.2.3.1.1.5.2. HYDROLYSIS OF DIOXANONES.

GENERAL PROCEDURE 5: HYDROLYSIS OF DIOXANONES.

The dioxanone (1g) was dissolved in THF (10ml) and 3N HCl (1ml) was added. The mixture was allowed to stir at room temperature for 24 hours. Tlc revealed that the hydrolysis was incomplete, so the mixture was refluxed for 1 hour. The products were isolated by column chromatography.

3-Hydroxy-2-methylenebutanoic acid (137a).

$C_5H_8O_3$

MW = 116
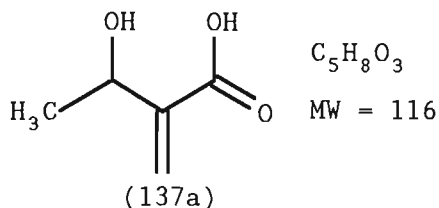
(137a)

According to General Procedure 5 using (97) (1g, 7.04mmol) yielded pure (137a) (0.62g, 76%), m.p. 43-46°C (Found: C, 51.89; H, 7.14. $C_5H_8O_3$ requires C, 51.72; H, 6.94%); $[\alpha]_D^{20} \approx 0°$; δ_H 1.41 (3H, d, $-CH_3$), 4.67 (1H, q, CH_3-CH-), 5.95 and 6.37 (2H, 2 x s, $CH_2=C-$), 7.18 (2H, br s, 2 x $-OH$); δ_C 22.02 (q, $-CH_3$), 67.06 (d, CH_3-CH-), 126.89 (t, $CH_2=C-$), 143.23 (s, $-C=CH_2$) and 171.43 (s, $-COOH$); m/z(DIP) 101(M^+-15, 12%), 98(7), 83(30), 73(16), 71(18), 57(20), 55(36), 45(68) and 43(100).

3-Hydroxy-4-methyl-2-methylenepentanoic acid (137b).

$C_7H_{12}O_3$

MW = 144
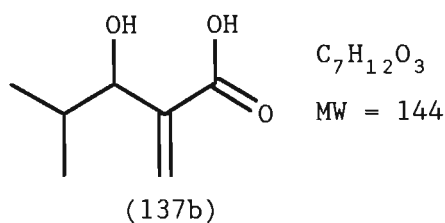
(137b)

According to General Procedure 5 with (114b) (0.6g, 3.03mmol) yielded pure (137b) (0.238g, 55%), m.p. 54-56°C (Found: C, 58.04; H, 8.30. $C_7H_{12}O_3$ requires C, 58.32; H, 8.39%); $[\alpha]_D^{23}$ = -0.91° (c0.55, CHCl$_3$); δ_H 0.90 and 0.97 (6H, 2 x d, 2 x -CH_3), 1.97 (1H, m, -CH-(CH$_3$)$_2$), 4.12 (1H, d, -CH-OH), 5.89 and 6.43 (2H, 2 x d, CH_2=C-), 5.4-6.5 (2H, br s, 2 x -OH); δ_C 17.54 and 19.61 (2 x q, 2 x -CH$_3$), 32.61 (d, -CH-(CH$_3$)$_2$), 77.49 (d, -CH-OH), 128.65 (t, CH$_2$=C-), 140.57 (s, -C=CH$_2$) and 171.31 (s, -COOH); m/z(DIP,CI) 145(M$^+$+1); (DIP,EI) 126(M$^+$-18, 4%), 102(71), 101(74), 84(100), 83(97), 71(44), 56(51) and 55(36).

3-Cyclohexyl-3-hydroxy-2-methylenepropanoic acid (137c).

$C_{10}H_{16}O_3$

MW = 184
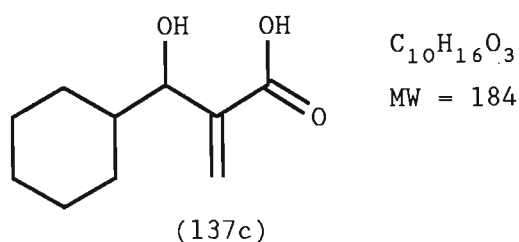
(137c)

According to General Procedure 5 using (117) (0.6g, 2.16mmol) which yielded pure (137c) (0.222g, 56%), m.p. 88-90°C (Found: C, 65.17; H, 8.91. $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%); $[\alpha]_D^{23}$ = -0.91° (c0.55, CHCl$_3$); δ_H 0.88-2.05 (11H, m, *cyclohexyl H's*), 4.12 (1H, d, -C*H*-OH), 5.84 and 6.42 (2H, 2 x d, C*H$_2$*=C-), 6.51-7.25 (2H, br s, 2 x -O*H*); δ_C 25.88, 26.05, 26.31, 28.80 and 29.88 (5 x t, *cyclohexyl* CH$_2$'s), 42.22 (d, *cyclohexyl* CH-), 77.06 (d, -CH-OH), 128.76 (t, CH$_2$=C-), 140.20 (s, -*C*=CH$_2$) and 171.30 (s, -*C*OOH); m/z(DIP, EI) 184(M$^+$, 0.2%), 102(100), 84(53), 83(41), and 55(47).

3.2.3.1.2. THE USE OF (-)-8-PHENYLMENTHYL ACRYLATE (139).

(-)-8-Phenylmenthol (138).

$C_{16}H_{24}O$

MW = 232

(138)
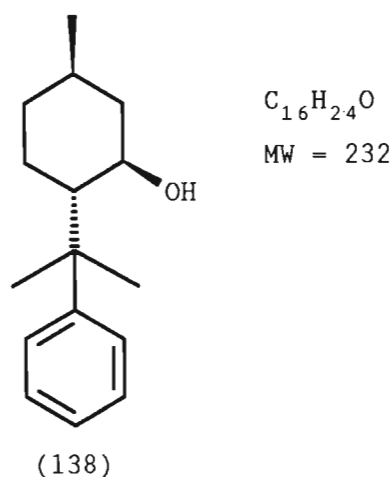
(-)-8-Phenylmenthol (138) was synthesised according to the procedure of Ort.[165] All the physical data was consistent with those described. $[\alpha]_D^{21}$ = -26.3° (c1.80, EtOH) (lit.[165] $[\alpha]_D^{21}$ = -26.4° (c1.80, EtOH); δ_H 0.76-1.90 (9H, m, *cyclohexyl H's* + -O*H*), 0.88 (3H, d, -CH-C*H₃*), 1.29 and 1.42 (6H, 2 x s, -C-(C*H₃*)₂), 3.53 (1H, m, -C*H*-OH), 7.15-7.43 (5H, m, Ph*H's*); δ_C 22.07 and 24.22 (2 x q, 2 x -*C*H₃), 26.53 (t, *cyclohexyl CH₂-*), 28.86 (q, -*C*H₃), 31.59 (d, *cyclohexyl CH-*), 34.97 (t, *cyclohexyl CH₂-*), 39.87 (s, -*C*-(CH₃)₂), 45.46 (t, *cyclohexyl CH₂-*), 54.32 (d, *cyclohexyl CH-*), 73.16 (d, -*C*H-OH), 126.13, 126.17 and 128.82 (d, Ph *C*H's) and 151.76 (s, Ph quarternary); m/z(EI) 232 (M⁺, 5%), 214(7), 119(100) and 91(19).

(-)-8-Phenylmenthyl prop-2-enoate (139).

$C_{19}H_{26}O_2$

MW = 286

(139)
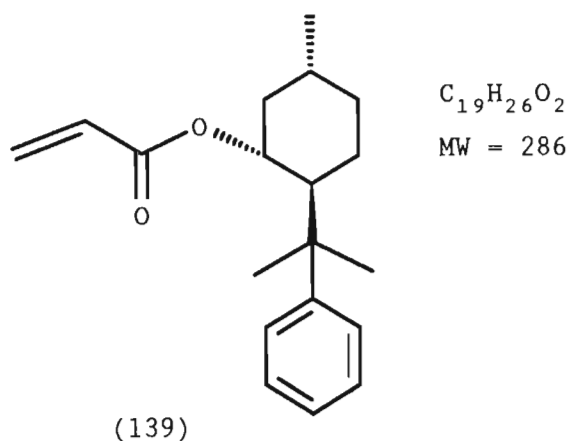
According to General Procedure 1 using (-)-8-phenylmenthol (138) (9.28g, 40mmol) which, after column chromatography using Et_2O/hexane (1:10), yielded (139) (9.75g, 85%) (Found: 286.1948. $C_{19}H_{26}O_2$ requires 286.1933); $[\alpha]_D^{24} = -17.4°$ (c1.1, $CHCl_3$); δ_H 0.81-2.11 (8H, m, *cyclohexyl H's*), 0.86 (3H, d, -CH-C*H₃*), 1.22 and 1.30 (6H, 2 x s, -C-(C*H₃*)₂), 4.88 (1H, dt, ring-C*H*-O-), 5.53-6.08 (3H, m, C*H₂*=C*H*-), 7.07-7.29 (5H, m, Ph*H's*); δ_C 21.85 and 25.36 (2 x q, 2 x -CH₃), 26.67 (t, *cyclohexyl* CH₂-), 27.68 (q, -CH₃), 31.35 (d, *cyclohexyl* CH-), 34.66 (t, *cyclohexyl* CH₂-), 39.78 (s, -C-(CH₃)₂), 41.73 (t, *cyclohexyl* CH₂-), 50.64 (d, *cyclohexyl* CH-), 74.72 (d, ring-CH-O-), 125.32, 125.72 and 128.33 (d, Ph CH's), 129.23 (d, -CH=CH₂), 130.27 (t, CH₂=CH-), 151.96 (s, Ph quarternary) and 165.85 (s, -C=O); m/z(EI) 286 (M⁺, 8%), 214(15), 119(100), 91(19) and 55(12).

GENERAL PROCEDURE 6: BAYLIS-HILLMAN REACTION OF (139).

(-)-8-Phenylmenthyl acrylate (139) (0.572g, 2mmol) was treated with the aldehyde (1.5eq.) and DABCO (0.225g, 2mmol). In some cases, chloroform had to be added to homogenise the mixture. The reaction mixture was allowed to stir in a sealed vessel for 14 days, at which time the products were isolated by column chromatography.

8-Phenylmenthyl 4,4,4-trichloro-3-hydroxy-2-methylenebutanoate (140a).

$C_{21}H_{27}Cl_3O_3$

MW = 432
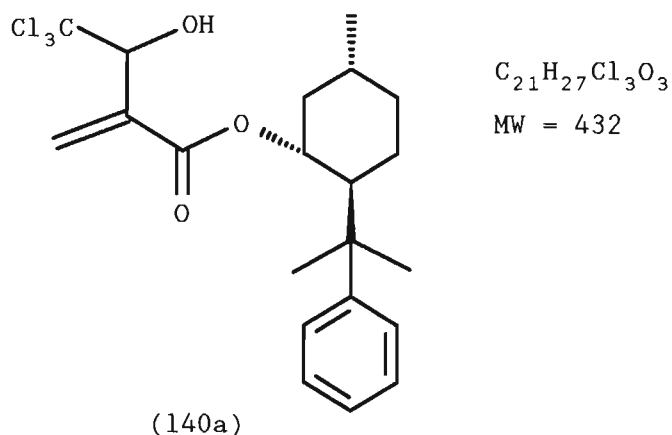
(140a)

According to General Procedure 6 using trichloroacetaldehyde which, after column chromatography with Et_2O/hexane (3:8), yielded (140a) (0.50g, 58%) (Found: 432.10184. $C_{21}H_{27}Cl_3O_3$ requires 432.10256); $[\alpha]_D^{22}$ = -45.7° (c0.5, $CHCl_3$); δ_H 0.80-2.29 (8H, m, *cyclohexyl H's*), 0.87 (3H, d, $-CH-CH_3$), 1.18 and 1.28 (6H, 2 x s, $-C-(CH_3)_2$), 4.89 (1H, dt, ring-C*H*-O-), 4.95[4.62] (1H, d, -C*H*-OH), 5.44[4.45] (1H, d, -O*H* (D_2O exchange)), 5.58 and 5.81[5.87] (2H, 2 x s, CH_2=C-), 7.03-7.28 (5H, m, Ph*H's*); δ_C 21.77, 24.61[23.85] and 28.33 (3 x q, 3 x $-CH_3$), 26.57, 34.52 and 41.12 (3 x t, *cyclohexyl* CH_2's), 134.12 (t, CH_2=C-), 31.27, 50.21, 76.45 and 82.41 (4 x d, *cyclohexyl* CH-'s and CH-OH), 125.25[124.98], 125.55 and 128.50 (d, Ph CH's), 39.42 (s, $-C-(CH_3)_2$), 102.47[102.35] (s, $-C-Cl_3$), 132.92[134.10] (s, $-C=CH_2$), 151.61[152.01] (s, Ph quarternary) and 165.84[165.53] (s, -C=O); m/z(CI) 433 (M⁺+1); (EI) 315(0.5%), 214(3), 119(100), 105(12), 91(20) and 55(4).

8-Phenylmenthyl 3-hydroxy-2-methylenepentanoate (140b).

$C_{22}H_{32}O_3$

MW = 344
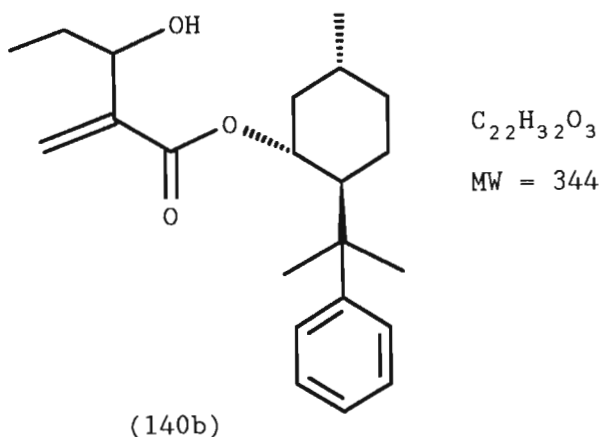
(140b)

According to General Procedure 6 using propionaldehyde which, after column chromatography with Et_2O/hexane (1:4), yielded (140b) (0.56g, 81%) (Found: C, 76.76; H, 9.52. $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36%); $[\alpha]_D^{25}$ = -46.8° (c0.52, $CHCl_3$); δ_H 0.82-2.16 (10H, m, *cyclohexyl H's* and $-CH_2CH_3$), 0.88 (3H, d, ring-CH-CH_3), 0.92 (3H, t, $-CH_2CH_3$), 1.21 and 1.30 (6H, 2 x s, $-C-(CH_3)_2$), 2.75 (1H, br s, $-CH-OH$), 4.07[3.89] (1H, poorly resolved m, $-CH-OH$), 4.91 (1H, dt, ring-CH-O-), 5.44 and 5.51[5.63] (2H, 2 x s, CH_2=C-), 7.06-7.29 (5H, m, PhH's); δ_C 10.32, 21.84, 25.71[24.55] and 27.72[28.10] (4 x q, 4 x $-CH_3$), 26.77, 34.64 and 41.69 (3 x t, *cyclohexyl* CH_2's), 29.04 (t, $-CH_2CH_3$), 125.53, (t, CH_2=C-), 31.41 and 50.45 (2 x d, 2 x ring-CH-'s), 73.71 (d, $-CH-OH$), 75.28 (d, ring-CH-O-), 125.43, 125.74 and 128.45 (d, Ph CH's), 39.80 (s, $-C-(CH_3)_2$), 142.01[142.45] (s, $-C=CH_2$), 151.90 (s, Ph quarternary) and 166.31 (s, $-C=O$); m/z(CI) 345(M$^+$+1); (EI) (214, 4%), 119(100), 105(13), 91(19) and 55(3).

8-Phenylmenthyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)-propanoate (140c).

$C_{26}H_{31}NO_5$

MW = 437
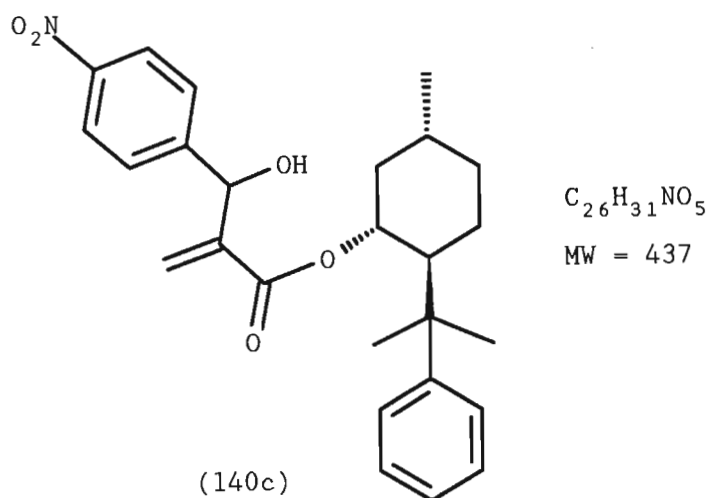
(140c)

According to General Procedure 6 using 4-nitrobenzaldehyde which, after column chromatography yielded (140c) (0.57g, 65%) (Found: C, 71.10; H, 7.04; N, 3.10. $C_{26}H_{31}NO_5$ requires C, 71.37; H, 7.14; N, 3.20%); $[\alpha]_D^{24}$ = -11.9° (c0.50, CHCl$_3$); δ_H 0.71-1.89 (7H, m, *cyclohexyl H's*), 0.82 (3H, d, ring-CH-CH_3), 1.16 and 1.24 (6H, 2 x s, -C-(CH$_3$)$_2$), 2.10 (1H, dt, ring-CH-CH-O-), 3.04 (1H, d, -CH-OH), 4.84 (1H, dt, ring-CH-O-), 5.01 (1H, br d, -CH-OH), 5.55 and 5.69 (2H, 2 x m, CH_2=C-), 7.08-7.27 (5H, m, PhH's), 7.45 and 8.15 (4H, 2 x m, NO$_2$-PhH's); δ_C 21.76, 23.58 and 29.32 (3 x q, 3 x -CH$_3$), 26.43, 34.53 and 41.47 (3 x t, *cyclohexyl* CH$_2$'s), 126.83 (t, CH$_2$=C-), 31.31, 50.39, 72.10 and 76.59 (4 x d, 3 x ring-CH-'s and -CH-OH), 123.80, 125.26, 125.70, 127.85 and 128.51 (d, Ar CH's), 39.52 (s, -C-(CH$_3$)$_2$), 141.43 (s, -C=CH$_2$), 147.73, 149.27 and 152.48 (3 x s, aromatic quarternary carbons) and 165.42 (s, -C=O); m/z(CI) 438(M$^+$+1); (EI) 318(1%), 215(2), 119(100), 105(13) and 91(16).

8-Phenylmenthyl 3-hydroxy-4-methyl-2-methylenepentanoate (140d).

$C_{23}H_{34}O_3$

MW = 358
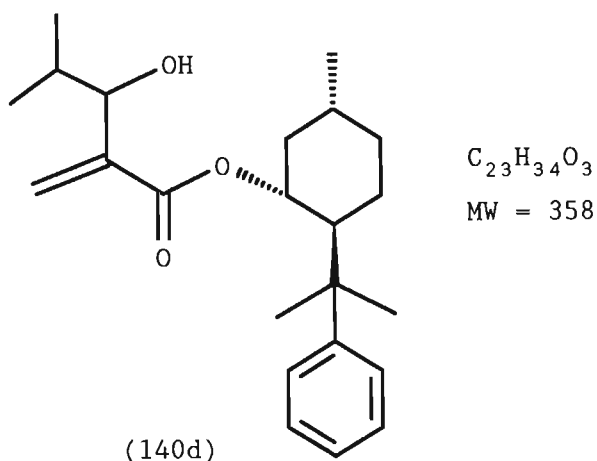
(140d)

According to General Procedure 6 using isobutyraldehyde which, after column chromatography with Et_2O/hexane (1:4), yielded (140d) (0.545g, 76%) (Found: C, 76.81; H, 9.68. $C_{23}H_{34}O_3$ requires C, 77.05; H, 9.56%); $[\alpha]_D^{24}$ = -45.6° (c0.50, $CHCl_3$); δ_H 0.80-2.20 (9H, m, *cyclohexyl H's* and $-CH-(CH_3)_2$), 0.83, 0.87 and 0,96 (9H, 3 x d, ring-CH-CH_3 and $-CH-(CH_3)_2$), 1.21[1.20] and 1.30 (6H, 2 x s, $-C-(CH_3)_2$), 2.72 (1H, d, $-CH-OH$), 3.85[3.75] (1H, dd, $-CH-OH$), 4.89 (1H, dt, ring-$CH-O-$), 5.43[5.49] and 5.51[5.66] (2H, 2 x d, $CH_2=C-$), 7.08-7.30 (5H, m, Ph$H's$); δ_C 18.19[17.31], 19.73[19.62], 21.83, 26.18 and 27.34[28.10] (5 x q, 5 x $-CH_3$), 26.86[25.31], 34.66 and 41.61 (3 x t, *cyclohexyl* $CH_2's$), 126.85[125.98] (t, $CH_2=C-$), 31.42, 32.95[32.88], 50.42, 75.45[75.38] and 78.89 (5 x d, 3 x ring-CH-'s, $-CH-(CH_3)_2$ and $-CH-OH$), 125.47, 125.77 and 128.46 (d, Ph CH's), 39.74 (s, $-C-(CH_3)_2$), 140.68[141.58] (s, $-C=CH_2$), 151.39[151.52] (s, Ph quarternary) and 165.90 (s, $-C=O$); m/z(CI) 359(M^++1); (EI) 315(3%), 215(14), 214(12), 119(100), 105(18) and 91(17).

8-Phenylmenthyl 3-hydroxy-4-phenylpropanoate (140e).

$C_{26}H_{32}O_3$

MW = 392
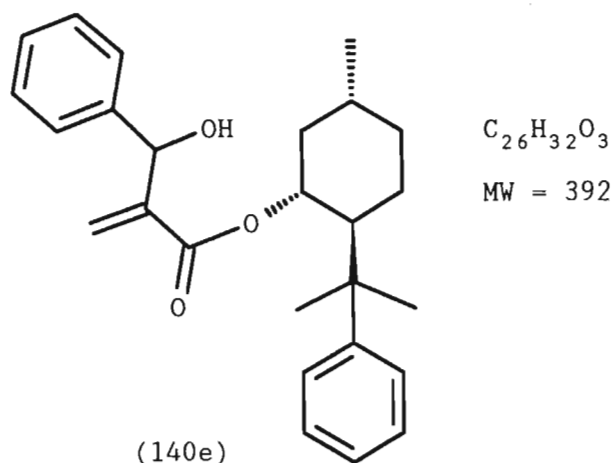
(140e)

According to General Procedure 6 using benzaldehyde (79) which, after column chromatography with Et_2O/hexane (3:8), yielded (140e) (0.64g, 82%) (Found: 392.2353. $C_{26}H_{32}O_3$ requires 392.2351); $[\alpha]_D^{25}$ = +10.8° (c0.50, $CHCl_3$); δ_H 0.59-2.08 (8H, m, cyclohexyl H's), 0.77 (3H, d, -CH-CH_3), 1.13 and 1.21 (6H, 2 x s, -C-(CH_3)_2), 2.95 (1H, d, -CH-OH), 4.78 (1H, dt, ring-CH-O-), 4.91 (1H, d, -CH-OH), 5.59 and 5.74 (2H, 2 x m, CH_2=C-), 7.05-7.31 (10H, m, PhH's); δ_C 21.72, 24.40 and 28.46 (3 x q, 3 x -CH_3), 26.47, 34.51 and 41.17 (3 x t, cyclohexyl CH_2's), 125.10 (t, CH_2=C-), 31.16, 50.42, 72.53 and 75.07 (3 x d, 3 x ring-CH-'s and -CH-OH), 125.23, 125.65 127.17, 127.93, 128.38 and 128.50 (d, Ph CH's), 39.39 (s, -C-(CH_3)_2), 141.47 (s, -C=CH_2), 142.19 and 151.65 (2 x s, 2 x Ph quarternary) and 165.21 (s, -C=O); m/z(CI) 392(M⁺), 391(M⁺-1); (EI) 273(1%), 214(6), 161(6), 119(100), 105(16) and 91(22).

8-Phenylmenthyl 3-cyclohexyl-3-hydroxy-2-methylenepropanoate (140f).

$C_{26}H_{38}O_3$

MW = 398
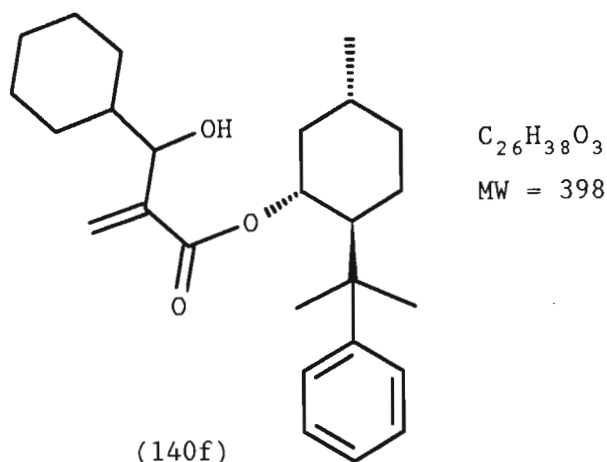
(140f)

According to General Procedure 6 using cyclohexanecarboxaldehyde which, after column chromatography, yielded (140f) (0.53g, 67%) (Found: C, 78.06; H, 9.65. $C_{26}H_{38}O_3$ requires C, 78.35; H, 9.61%); $[\alpha]_D^{25}$ = -37.2° (c0.50, CHCl$_3$); δ_H 0.75-2.35 (19H, m, *menthyl and cyclohexyl H's*), 0.87[0.88] (3H, d, -CH-CH_3), 1.21[1.20] and 1.30 (6H, 2 x s, -C-(CH$_3$)$_2$), 2.25[2.75] (1H, d and br s, -CH-OH), 3.69[3.85] (1H, br s, -CHOH), 4.88 (1H, dt, ring-CH-O-), 5.39[5.45] and 5.52[5.63] (2H, 2 x m, CH_2=C-), 7.07-7.27 (5H, m, PhH's); δ_C 21.83, 26.21 and 27.29 (3 x q, 3 x -CH$_3$), 26.00, 26.12, 26.48, 28.79, 30.10, 34.63 and 41.61 (8 x t, *cyclohexyl* CH$_2$'s), 126.89[125.99] (t, CH$_2$=C-), 31.41, 42.57, 50.38, 75.44 and 78.29 (5 x d, 3 x *menthyl*-CH-'s, 1 x *cyclohexyl* CH's and -CH-OH), 125.47, 125.75 and 128.43 (d, Ph CH's), 39.73 (s, -C-(CH$_3$)$_2$), 140.39[140.78] (s, -C=CH$_2$), 151.32 (s, Ph quarternary) and 166.02[165.99] (s, -C=O); m/z(CI) 397(M$^+$-1); (EI) 315(1%), 279(1), 215(13), 214(6), 167(5), 119(100), 105(32), 91(22) and 55(4).

8-Phenylmenthyl 3-(2-furyl)-3-hydroxy-2-methylenepropanoate (140g).

$C_{24}H_{30}O_4$
MW = 382
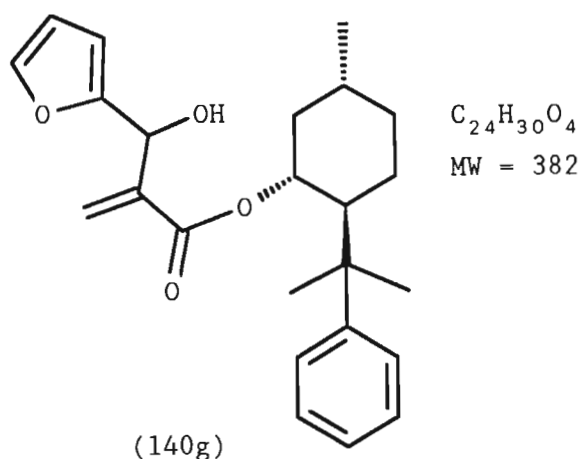
(140g)

According to General Procedure 6 using furfuraldeyde which, after column chromatography, yielded (140g) (0.45g, 59%) (Found: C, 75.10; H, 8.08. $C_{24}H_{30}O_4$ requires C, 75.36; H, 7.91%); $[\alpha]_D^{24}$ = +0.9° (c0.50, CHCl₃); δ_H 0.70-1.81 (7H, m, *menthyl H's*), 0.84 (3H, d, -CH-C*H₃*), 1.19 and 1.29 (6H, 2 x s, -C-(C*H₃*)₂), 2.07 (1H, dt, ring-C*H*-CH-O-), 2.81 (1H, d, -C*H*-O*H*), 4.87 (1H, dt, ring-C*H*-O-), 4.94 (1H, d, -C*H*-OH), 5.68 and 5.83 (2H, 2 x m, C*H₂*=C-), 6.13 and 6.30 (2H, 2 x m, 2 x furyl-C*H's*), 7.10-7.28 (5H, m, Ph*H's*) and 7.34 (1H, m, furyl-O-C*H*-); δ_C 21.79, 24.28 and 28.67 (3 x q, 3 x -CH₃), 26.52, 34.57 and 41.36 (3 x t, *cyclohexyl* CH₂'s), 126.28 (t, CH₂=C-), 31.29, 50.43, 66.70 and 75.25 (4 x d, 3 x *menthyl*-CH-'s and -CH-OH), 107.36 and 110.61 (2 x d, furyl-CH's), 125.22, 125.74 and 128.50 (d, Ph CH's), 142.10 (d, furyl-O-CH-), 39.49 (s, -C-(CH₃)₂), 139.66 (s, -C=CH₂), 151.87 (s, Ph quarternary) 154.35 (s, furyl-C-CH-) and 165.03 (s, -C=O); m/z(CI) 382(M⁺); (EI) 263(1%), 214(4), 199(3), 168(22), 119(100), 105(45), 97(9), 91(22) and 55(3).

8-Phenylmenthyl 3-hydroxy-2-methylenebutanoate (140h).

$C_{21}H_{30}O_3$

MW = 330
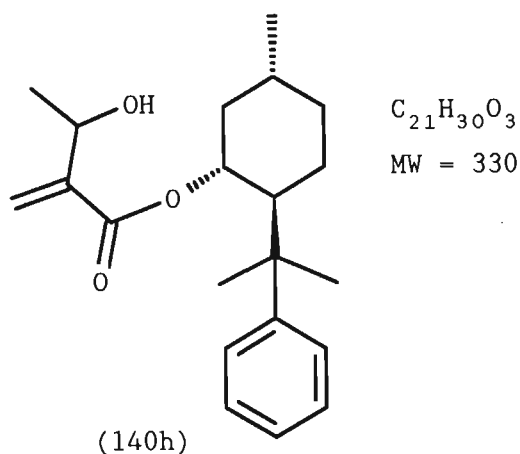
(140h)

According to General Procedure 6 using acetaldehyde which, after column chromatography with Et_2O/hexane (1:4), yielded (140h) (0.48g, 73%) (Found: C, 76.60; H, 9.24. $C_{21}H_{30}O_3$ requires C, 76.33; H, 9.15%); $[\alpha]_D^{23}$ = -47.1° (c0.50, $CHCl_3$); δ_H 0.84-2.16 (8H, m, menthyl *H*'s), 0.88 (3H, d, -CH-C*H₃*), 1.21 and 1.31 (6H, 2 x s, -C-(CH_3)₂), 1.30 (3H, d, C*H₃*-CH-OH), 2.85[2.56] (1H, d, -CH-O*H*), 4.33[4.19] (1H, dd, -C*H*-OH for 2 diastereomers), 4.92 (1H, dt, ring-C*H*-O-), 5.47[5.50] and 5.52[5.60] (2H, 2 x m, C*H₂*=C-), 7.04-7.29 (5H, m, Ph*H*'s); δ_C 21.72[21.88], 21.82, 25.46[25.20] and 27.91 (4 x q, 4 x -CH_3), 26.72, 34.62 and 41.73 (3 x t, cyclohexyl CH_2's), 124.43[124.15] (t, CH_2=C-), 31.40 and 50.46 (2 x d, 2 x menthyl-CH-'s), 67.32[66.84] (d, -CH-OH), 75.24[75.11] (d, ring -C*H*-O-), 125.38[125.34], 125.72 and 128.44 (d, Ph C*H*'s), 39.75 (s, -*C*-(CH_3)₂), 143.33[144.02] (s, -*C*=CH₂), 151.91[151.93] (s, Ph quarternary) and 166.30 (s, -*C*=O); m/z(CI) 331(M⁺+1); (EI) 214(5%), 119(100), 91(15), 81(4) and 55(2).

3.2.3.1.3. USE OF (-)-8-CYCLOHEXYLMENTHYL ACRYLATE (146).

(-)-8-Cyclohexylmenthol (145).

C$_{16}$H$_{30}$O
MW = 238

(145)
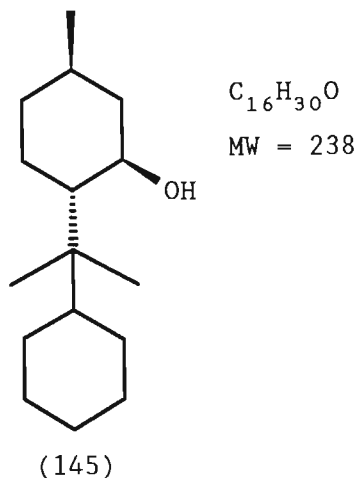
A mixture of (-)-8-phenylmenthol (138) (5g, 21.6mmol), RhCl$_3$.3H$_2$O (0.1g), aliquat-336 (0.22g), H$_2$O (5ml) and dichloroethane (5ml) was shaken at 2-3atm of H$_2$ overnight. The mixture was diluted with ether, filtered and the solvents evaporated. The residue was filtered through a column of silica gel by eluting with Et$_2$O. Purification by column chromatography using Et$_2$O/hexane (1:9) yielded pure (145) (5.03g, 98%) (Found: C, 80.52; H, 12.49. C$_{16}$H$_{30}$O requires C, 80.61; H, 12.68%); [α]$_D$^{30} = -18.96° (c1.06, CHCl$_3$); δ$_H$ 0.71-1.95 (20H, m, *menthyl and cyclohexyl H's + -OH*), 0.80 and 0.97 (6H, 2 x s, -C-(CH$_3$)$_2$), 0.89 (3H, d, ring-CH-CH$_3$), 3.59 (1H, dt, ring-CH-OH); δ$_C$ 21.33, 22.12 and 22.64 (3 x q, 3 x -CH$_3$), 25.71, 27.16, 27.25, 27.44, 27.47, 27.52, 35.24 and 47.24 (8 x t, 3 x *menthyl* CH$_2$'s and 5 x *cyclohexyl* CH$_2$'s), 31.80 45.26, 49.53 and 73.22 (4 x d, 3 x *menthyl*-CH-'s and 1 x *cyclohexyl*-CH-), 37.58 (s, -C-(CH$_3$)$_2$); m/z(EI) 238(M$^+$, 05%), 154(6), 137(40), 125(44), 124(50), 95(43), 83(46), 81(70), 69(65) and 55(100).

(-)-8-Cyclohexylmenthyl prop-2-enoate (146).

C$_{19}$H$_{32}$O$_2$

MW = 292

(146)
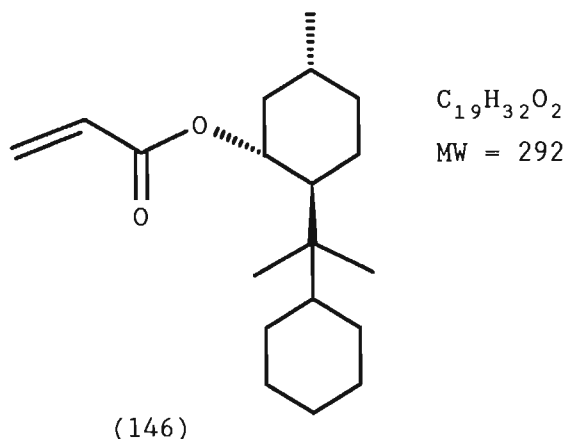
According to General Procedure 1 using (145) (4.5g, 18.91mmol) yielded after column chromatography with Et$_2$O/hexane (1:19) (146) (4.86g, 88%) (Found: 292.24020. C$_{19}$H$_{32}$O$_2$ requires 292.24022); $[\alpha]_D^{24}$ = -47.4° (c1.04, CHCl$_3$); δ_H 0.71-2.04 (19H, m, *menthyl* and *cyclohexyl H's*), 0.73 and 0.79 (6H, 2 x s, -C-(CH_3)$_2$), 0.88 (3H, d, ring-CH-CH_3), 4.92 (1H, dt, ring-CH-O-), 5.78-6.43 (3H, CH_2=CH-); δ_C 21.32, 21.90 and 22.13 (3 x q, 3 x -CH$_3$), 25.74, 27.08, 27.25, 27.37, 27.48, 27.51, 34.90 and 42.15 (8 x t, 3 x menthyl CH$_2$'s and 5 x cyclohexyl CH$_2$'s), 130.68 (t, CH$_2$=CH-), 31.31, 45.14, 46.00 and 75.42 (4 x d, 3 x menthyl-CH-'s and 1 x cyclohexyl-CH-), 129.80 (d, -CH=CH$_2$), 37.46 (s, -C-(CH$_3$)$_2$) and 165.39 (s, -C=O); m/z(CI) 293(M$^+$+1); (EI) 220(1%), 137(39), 125(70), 124(88), 109(14), 96(43), 95(28), 81(92), 69(64) and 55(100).

GENERAL PROCEDURE 7: BAYLIS-HILLMAN REACTION OF (146).

Acrylate (146) (0.584g, 2mmol) was treated with the aldehyde (1.5eq) and DABCO (0.225g, 2mmol). In some cases, chloroform had to be added to homogenise the mixture. The mixture was allowed to stir in a sealed vessel for 14 days, at which time the products were isolated by column chromatography.

8-Cyclohexylmenthyl 4,4,4-trichloro-3-hydroxy-2-methylene-butanoate (147a).

$C_{21}H_{33}Cl_3O_3$

MW = 356
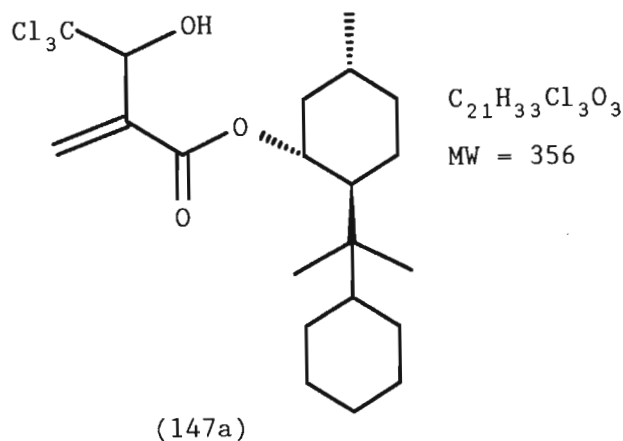
(147a)

According to General Procedure 7 using trichloroacetaldehyde, which, after purification by column chromatography using Et_2O/hexane (1:4) yielded pure (147a) (0.51g, 58%) (Found: C, 57.60; H, 7.65. $C_{21}H_{33}Cl_3O_3$ requires C, 57.34; H, 7.56%); $[\alpha]_D^{26} = -31.1°$ (c0.50, $CHCl_3$); δ_H 0.75-2.05 (19H, m, *menthyl* and *cyclohexyl H's*), 0.73 and 0.78 (6H, 2 x s, $-C-(CH_3)_2$), 0.89 (3H, d, ring-CH-CH_3), 4.95 (1H, dt, ring-CH-O-), 4.96 (1H, d, -CH-OH), 5.95 (1H, d, -OH by D_2O exchange), 6.13 and 6.56 (2H, 2 x d, CH_2=C-); δ_C 21.30, 21.84 and 22.05 (3 x q, 3 x -CH_3), 25.82, 26.98, 27.14, 27.20, 27.40, 27.41, 34.80 and 41.63 (8 x t, 3 x *menthyl* CH_2's *and* 5 x *cyclohexyl* CH_2's), 134.00 (t, CH_2=C-), 31.31, 45.01, 45.77, 77.16 and 84.39 (5 x d, 3 x *menthyl-CH-'s*, 1 x *cyclohexyl-CH-* and -CH-OH), 37.40 (s, $-C-(CH_3)_2$), 102.49 (s, -CCl_3), 133.60 (s, -C=CH_2) and 166.48 (s, -C=O); m/z(CI) 357(M^++1); (EI) 221(17%), 219(19), 137(96), 125(100), 124(95), 95(44), 81(78), 69(47) and 55(39).

8-Cyclohexylmenthyl 3-hydroxy-2-methylenepentanoate (147b).

C$_{22}$H$_{38}$O$_3$

MW = 350
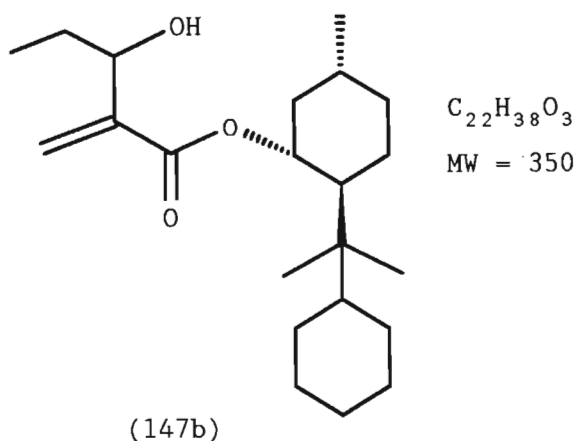
(147b)

According to General Procedure 7 using propionaldehyde, which, after purification by column chromatography using Et$_2$O/hexane (1:4) yielded pure (147b) (0.525g, 75%) (Found: C, 75.54; H, 10.93. C$_{22}$H$_{38}$O$_3$ requires C, 75.38; H, 10.93%); $[\alpha]_D^{25}$ = -55.3° (c0.51, CHCl$_3$); δ_H 0.74 and 0.78 (6H, 2 x s, -C-(CH$_3$)$_2$), 0.81-2.01 (27H, m, *menthyl* and *cyclohexyl* H's, ring-CH-CH$_3$ and -CH$_2$CH$_3$), 3.10[2.64] (1H, d, -OH), 4.25[4.38] (1H, m, -CH-OH), 4.96 (1H, dt, ring-CH-O-), 5.75[5.81] and 6.16[6.19] (2H, 2 x d, CH$_2$=C-); δ_C 10.32[10.28], 21.42, 21.89 and 22.29 (4 x q, 4 x -CH$_3$), 25.80, 27.04, 27.19, 27.39, 27.44, 27.45, 29.21, 34.87 and 42.05 (9 x t, 3 x *menthyl* CH$_2$'s, 5 x *cyclohexyl* CH$_2$'s and 1 x -CH$_2$CH$_3$), 125.38[124.65] (t, CH$_2$=C-), 31.36, 44.96, 46.04, 74.37[73.11] and 75.86 (5 x d, 3 x *menthyl*-CH-'s, 1 x *cyclohexyl*-CH- and -CH-OH), 37.34 (s, -C-(CH$_3$)$_2$), 142.58[143.26] (s, -C=CH$_2$) and 165.99 (s, -C=O); m/z(CI) 350(M$^+$), 351(M$^+$+1), 349(M$^+$-1); (EI) 267(M$^+$-cyclohexyl, 10%), 137(53), 131(96), 124(73), 113(100), 95(56), 81(67), 69(50), 67(30) and 55(35).

8-Cyclohexylmenthyl 3-hydroxy-2-methylene-3-(4-nitrophenyl)-propanoate (147d).

$C_{26}H_{37}NO_3$

MW = 443

(147d)

According to General Procedure 7 using 4-nitrobenzaldehyde which, after purification by column chromatography using Et_2O/hexane (3:7) yielded pure (147d) (0.56g, 63%) (Found: C, 70.52; H, 8.38; N, 3.14. $C_{26}H_{37}NO_5$ requires C, 70.40; H, 8.41; N, 3.16 %); $[\alpha]_D^{24}$ = -46.3° (c0.55, $CHCl_3$); δ_H 0.67 and 0.68 (6H, 2 x s, $-C-(CH_3)_2$), 0.80-1.89 (19H, m, *menthyl* and *cyclohexyl H's*), 0.85 (3H, d, ring-$CH-CH_3$), 3.42 (1H, d, $-OH$), 4.89 (1H, dt, ring-$CH-O-$), 5.66 (1H, d, $-CH-OH$), 5.90 and 6.33 (2H, 2 x m, $CH_2=C-$), 7.56 and 8.19 (4H, 2 x m, Ar *H's*); δ_C 21.33, 21.82 and 22.22 (3 x q, 3 x $-CH_3$), 25.71, 26.98, 27.12, 27.34, 27.40, 27.47, 34.74 and 41.97 (8 x t, 3 x *menthyl* CH_2's + 5 x *cyclohexyl* CH_2's), 126.52 (t, $CH_2=C-$), 31.29, 44.96, 45.97, 72.86, and 76.50 (5 x d, 3 x *menthyl*-CH-'s, 1 x *cyclohexyl*-CH- and -CH-OH), 123.95 and 127.80 (d, Ar CH's), 37.28 (s, $-C-(CH_3)_2$), 142.11 (s, $-C=CH_2$), 147.80 and 148.81 (s, aromatic quarternary carbons) and 165.23 (s, $-C=O$); m/z(CI) 444(M^++1); (EI) 207(15%), 177(13), 160(19), 137(77), 125(100), 124(84), 123(24), 95(54), 83(64), 81(74), 69(60), 67(30) and 55(28).

8-Cyclohexylmenthyl 3-hydroxy-2-methylene-3-phenylpropanoate (147e).

$C_{26}H_{38}O_3$
MW = 398
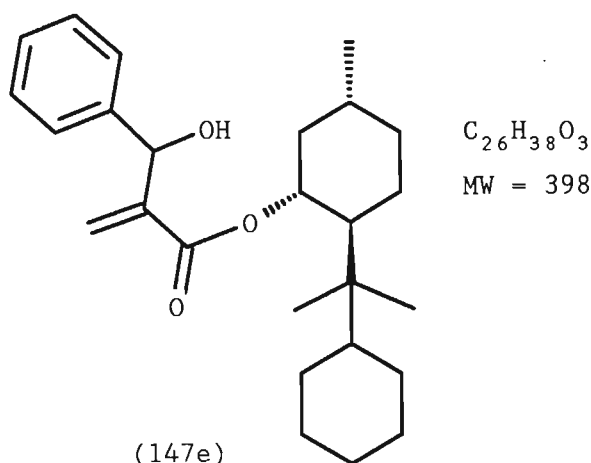
(147e)

According to General Procedure 7 using benzaldehyde which, after purification by column chromatography using Et_2O/hexane (3:7) yielded pure (147e) (0.60g, 75%) (Found: C, 78.19; H, 9.65. $C_{26}H_{38}O_3$ requires C, 78.35; H, 9.61%); $[\alpha]_D^{24}$ = -34.3° (c0.51, $CHCl_3$); δ_H 0.72-1.89 (19H, m, *menthyl* and *cyclohexyl H's*), 0.64 and 0.65 (6H, 2 x s, $-C-(CH_3)_2$), 0.81[0.84] (3H, d, ring-CH-C*H₃*), 3.37[3.73] (1H, d, -O*H*), 4.81 (1H, dt, ring-C*H*-O-), 5.45[5.53] (1H, d, -C*H*-OH), 5.73[5.88] and 6.23[6.24] (2H, 2 x m, C*H₂*=C-), 7.19-7.36 (5H, m, Ar *H's*); δ_C 21.24, 21.82 and 22.03[22.06] (3 x q, 3 x $-CH_3$), 25.68, 27.00, 27.08, 27.32, 27.33, 27.42, 34.77 and 41.72 (8 x t, 3 x *menthyl* CH_2's + 5 x *cyclohexyl* CH_2's), 124.77[126.52] (t, CH_2=C-), 31.18[31.21], 44.85, 45.78, 73.15[73.94], and 75.84[76.02 (5 x d, 3 x *menthyl*-CH-'s, 1 x *cyclohexyl*-CH- and -CH-OH), 126.63[127.86] 127.18[128.07] and 128.62 (d, Ar C*H's*), 37.18 (s, $-C-(CH_3)_2$), 141.40[143.10] (s, -*C*=CH₂), 142.60 (s, aromatic quarternary) and 165.41[165.74] (s, -*C*=O); m/z(CI) 398(M⁺), 397(M⁺-1); (EI) 297(4%), 179(17), 161(100), 137(65), 125(54), 124(62), 117(36), 115(41), 111(43), 97(33), 95(58), 81(75) and 55(43).

8-Cyclohexylmenthyl 3-hydroxy-2-methylenebutanoate (147f).

$C_{21}H_{36}O_3$
MW = 336
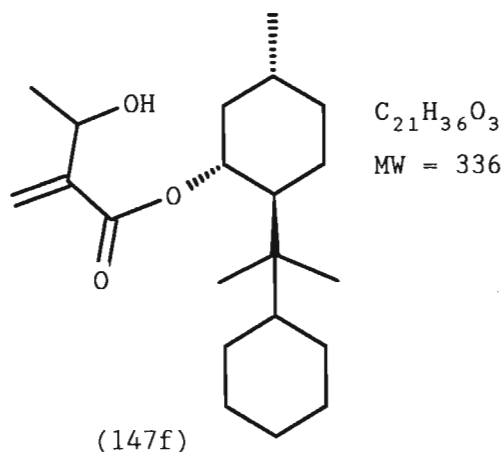
(147f)

According to General Procedure 7 using acetaldehyde which, after purification by column chromatography using Et_2O/hexane (2:8) yielded pure (147f) (0.585g, 87%) (Found: C, 74.99; H, 11.08. $C_{21}H_{36}O_3$ requires C, 74.95; H, 10.78%); $[\alpha]_D^{23}$ = -57.4° (c0.50, $CHCl_3$); δ_H 0.75-2.04 (19H, m, *menthyl* and *cyclohexyl H's*), 0.74 and 0.78 (6H, 2 x s, $-C-(CH_3)_2$), 0.89 (3H, d, ring-CH-CH_3), 1.39[1.38] (3H, d, $-CH-CH_3$), 2.98[2.75] (1H, d, -O*H*), 4.62 (1H, m, -C*H*-OH), 4.96 (1H, dt, ring-C*H*-O-), 5.79[5.83] and 6.15 (2H, 2 x m, CH_2=C-); δ_C 21.36, 21.89, 21.98[22.20] and 22.31 (4 x q, 4 x $-CH_3$), 25.75, 27.03, 27.15, 27.36, 27.37, 27.44, 34.84 and 42.10 (8 x t, 3 x *menthyl* CH_2's + 5 x *cyclohexyl* CH_2's), 123.74[124.25] (t, CH_2=C-), 31.34, 44.94, 46.04, 67.28[67.79], and 75.81[75.89] (5 x d, 3 x *menthyl*-CH-'s, 1 x *cyclohexyl*-CH- and -CH-OH), 37.32 (s, $-C-(CH_3)_2$), 144.03[144.50] (s, -*C*=CH_2) and 165.88[165.99] (s, -*C*=O); m/z(CI) 337(M$^+$+1), 336(M$^+$); (EI) 253(6%), 137(45), 124(58), 117(100), 99(62), 97(9), 81(61), 69(30) and 55(21).

3.2.3.3. THE USE OF CHIRAL CYCLIC AMINO ALDEHYDES IN THE BAYLIS-HILLMAN REACTION.

GENERAL PROCEDURE 8: BAYLIS-HILLMAN REACTION OF CHIRAL CYCLIC AMINO ALDEHYDES

The aldehyde (1eq), DABCO (1eq) and methyl acrylate (3eq) were stirred together in a sealed vessel at room temperature for 7 days. Excess methyl acrylate was removed under reduced pressure. The crude products were purified by column chromatography.

Methyl 3-hydroxy-3-(4-(1,1-dimethylethyl 2,2-dimethyl-3-oxazolidinecarboxylate))-2-methylenepropanoate (151).

$C_{15}H_{25}NO_6$

MW = 315

(151)
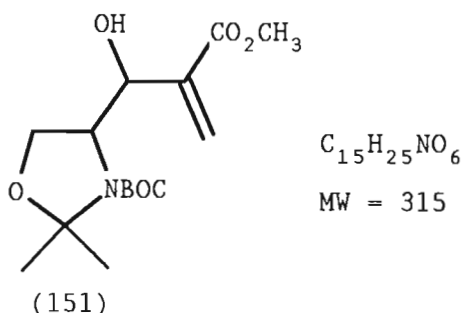
According to General Procedure 8 using Garner's aldehyde (150)[175] (2.5g, 10.9mmol) which, after purification by column chromatography using hexane/EtOAc (3:2), yielded pure (151) (2.92g, 85%) (Found: 315.1658. $C_{15}H_{25}NO_6$ requires 315.1675). The major(*anti*) diastereomer was obtained by chromatography using hexane/EtOAc (3:2); $[\alpha]_D^{24} = -1.9°$ (c0.54, CHCl$_3$); δ_H 1.49 (9H, s, -C-(CH$_3$)$_3$), 1.51 and 1.52 (6H, 2 x br s, -C-(CH$_3$)$_2$), 3.79 (3H, s, -OCH$_3$), 3.91 (1H, br t, ring-C*H*-), 4.09-4.24 (2H, m, ring-O-C*H*$_2$-), 4.45-4.68 (2H, m, -C*H*-O*H*), 5.78 and 6.26 (2H, br s, C*H*$_2$=C-); δ_C 24.04, 27.02 and 28.35 (3 x q, 1 x -C-(CH$_3$)$_3$ and 2 x -C-(CH$_3$)$_2$), 52.05 (q, -OCH$_3$), 61.81 (d, -CH-N-), 65.03 (t, -CH$_2$-O-), 74.15 (d, -CH-OH), 80.94 and 94.35 (2 x s, -C-(CH$_3$)$_2$ and -C-(CH$_3$)$_3$), 126.94 (t, CH$_2$=C-), 140.17 (s,

$-C=CH_2$), 153.7 (s, $-N-C=O$) and 167.53 (s, $-C=O$); m/z(EI) 315(M^+, 1%), 242(1), 200(18), 184(7), 144(21), 116(22), 115(21), 100(100), 84(21) and 83(49).

(2S)-N-(4-Nitrobenzoyl)pyrrolidine-2-carboxaldehyde (153).

$C_{12}H_{12}N_2O_4$

MW = 248

(153)
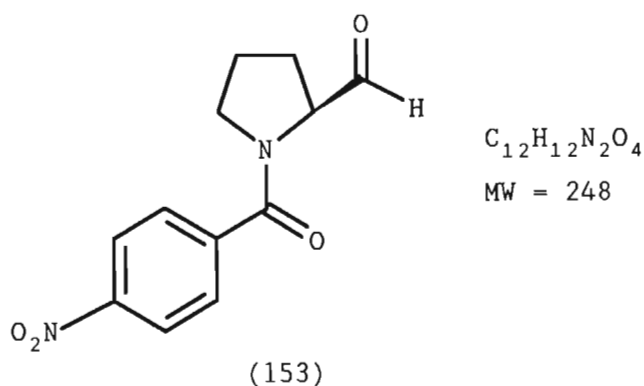
Compound (153) is a new compound which was prepared by Thurston and Langley's procedure[180] for the 2-nitrobenzoyl isomer. Purification by column chromatography using MeOH/CHCl$_3$ (1:4) afforded pure (153) (55%), m.p. 74-76°C (Found: 248.0787. $C_{12}H_{12}N_2O_4$ requires 248.0797); $[\alpha]_D^{20}$ = -86.9° (c1.20, CHCl$_3$); δ_H 1.91-2.36 (4H, m, $-CH_2CH_2-$), 3.46-3.68 (2H, m, $-N-CH_2-$), 4.69-4.76 (1H, m, $-N-CH-$), 7.72-7.81 and 8.25-8.34 (4H, 2 x m, ArH's) (signals of minor rotamer also visible); δ_C 25.53 and 26.07 (2 x t, $-CH_2-CH_2-$), 49.98 (t, $-N-CH_2-$), 65.27 (d, $-N-CH-$), 123.76 and 128.38 (2 x d, ArCH's), 141.71 and 148.72 (s, Ar quarternary carbons), 167.91 (s, $-N-C=O$) and 198.21 (s, $-CHO$); m/z(EI) 248(M^+, 2%), 219(43), 150(100), 104(29) and 76(17).

Methyl 3-hydroxy-2-methylene-3-(2-(N-4-nitrobenzoyl)pyrroli-
dinyl)propanoate (154).

$C_{16}H_{18}N_2O_6$

MW = 334

(154)
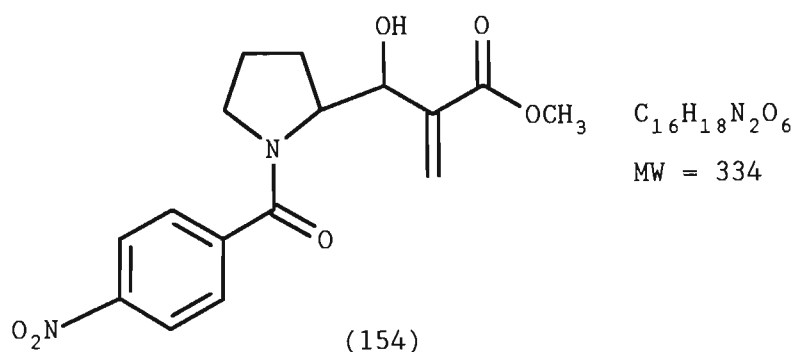
According to General Procedure 8 using (153) (2.48g, 10mmol) which after purification by column chromatography with hexane/EtOAc yielded (154) (2.51g, 75%); 50%de. The major diastereomer was separated using hexane/EtOAc (1:1) to yield white needles, m.p. 129°C (Found: 334.1200. $C_{16}H_{18}N_2O_6$ requires 334.1165); $[\alpha]_D^{23}$ = -1.02° (c1.10, CHCl$_3$); δ_H 1.62-2.07 (4H, m, -CH_2CH_2-), 3.28-3.52 (2H, m, -N-CH_2-), 3.80 (3H, s, -OCH_3), 4.52-4.61 (2H, m, -N-CH- + overlapping -OH), 4.90 (1H, br d, -CH-OH), 5.90 and 6.22 (2H, 2 x s, CH_2=C-), 7.60-7.69 and 8.19-8.26 (4H, 2 x m, ArH's); δ_C 24.90 and 25.45 (2 x t, -CH$_2$-CH$_2$-), 51.19 (t, -N-CH$_2$-), 51.99 (q, -OCH$_3$), 61.38 (d, -N-CH-), 70.02 (d, -CH-OH), 123.65 and 128.36 (2 x d, ArCH's), 126.42 (t, CH$_2$=C-), 140.14 (s, -C=CH$_2$), 142.75 and 148.47 (s, Ar quarternary carbons), 166.74 (s, -COOCH$_3$), 168.51 (s, -N-C=O); m/z(EI) 303(M$^+$ - -OCH$_3$, 1%), 219(53), 150(100), 120(6), 104(27) 92(9), 83(7), 76(12) and 55(3).

3.2.4. THE USE OF CHIRAL MASKING AGENTS.

3.2.4.1. (S)-(+)-1-(2-PYRROLIDINYLMETHYL)PYRROLIDINE (160).

GENERAL PROCEDURE 9: THE MICHAEL ADDITION OF SECONDARY AMINES TO ACRYLATES AND CROTONATES.

The α,β-unsaturated ester (1.1eq) was added dropwise to a stirred solution of the secondary amine (1eq) in ether (10ml/g) at 0°C. Stirring was continued until tlc showed that the starting material was consumed. The products were isolated by column chromatography using MeOH/CHCl$_3$ (1:10).

(S)-(-)-^{t}Butyl 3-N-(1-(2-pyrrolidinylmethyl)pyrrolidinyl)-propanoate (161).

$C_{16}H_{30}N_2O_2$

MW = 282
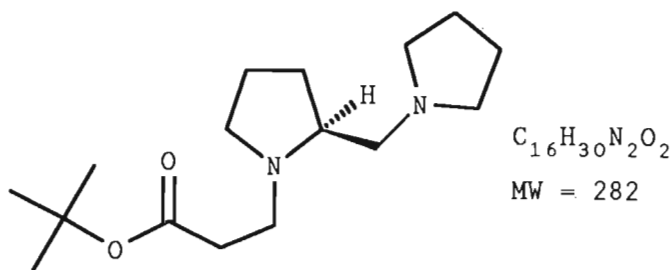
(161)

According to General Procedure 9 using (160) and ^{t}butyl acrylate (34) which, after column chromatography, yielded (161) (80%) (Found: C, 67.97; H, 10.72; N, 9.96. $C_{16}H_{30}N_2O_2$ requires C, 68.04; H, 10.71; N, 9.92%); $[\alpha]_D^{28}$ = -84.4° (c0.61, CHCl$_3$); δ_H 1.44 (9H, s, -C-(CH$_3$)$_3$), 0.55-2.77 and 3.02-3.25 (21H, 10 x CH$_2$'s and 1 x -N-CH-); δ_C 28.16 (q, -C-(CH$_3$)$_3$), 22.85, 23.45, 24.46, 30.62, 35.38, 50.66, 54.09, 55.08, 55.09 and 61.95 (10 x t, 10 x CH$_2$'s), 63.45 (d, -N-CH-), 80.18 (s, -C-(CH$_3$)$_3$) and 172.01 (s, -C=O); m/z(EI) 282(M$^+$, 0.5%), 198(54), 142(100), 96(14) and 84(40).

GENERAL PROCEDURE 10: THE ALDOL REACTION OF MASKED ACRYLATES AND ELIMINATION OF THE MASKING AGENT.

To a solution of LDA (1.2eq) in THF (0.3M) at 0°C under nitrogen was added the β-amino ester (1eq). The mixture was stirred at this temperature for 30 minutes, cooled to -78°C and a solution of the aldehyde (1eq) in THF (2ml/mmol) was added. After 45 minutes at this temperature, the reaction was quenched with saturated NH$_4$Cl and extracted with ether followed by chloroform. The combined extracts were dried (MgSO$_4$) and the solvents evaporated. The crude product in chloroform (0.5M) was treated with a solution of MCPBA (10% molar excess) in chloroform (10ml/g) and the mixture was allowed to stir overnight. Basic alumina (70-290mesh) (2g/mmol) was added and the mixture was stirred for one hour. Elution from a column of alumina (10x mass of combined starting materials) afforded the crude α,β-unsaturated esters which were purified by column chromatography on silica gel using Et$_2$O/hexane.

^{t}Butyl 3-hydroxy-2-methylene-3-phenylpropanoate (90).

$C_{14}H_{18}O_3$

MW = 234

(90)
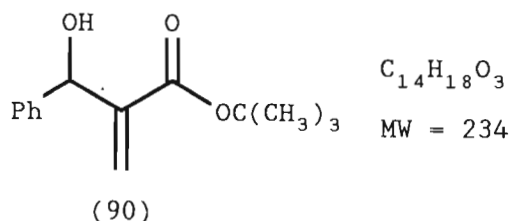
According to General Procedure 10 using (161) and benzaldehyde (79), which yielded (90) (69%); 56%ee; $[\alpha]_D^{24}$ = +55.7° (c1.01, MeOH). Physical properties were identical to (90) (Section 3.2.2.3.).

Butyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate (163).

(163)

$C_{15}H_{20}O_4$

MW = 264
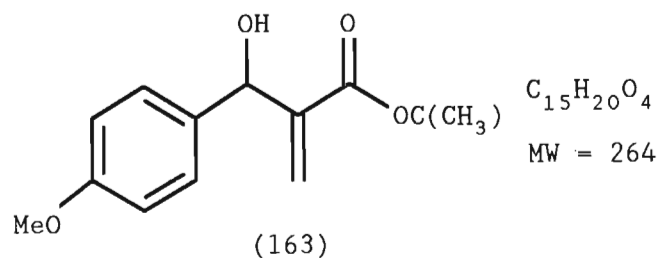
According to General Procedure 10 using (161) and 4-methoxybenzaldehyde yielded (163) (66%); 58%ee; $[\alpha]_D^{25}$ = +62.8° (c1.00, MeOH); δ_H 1.39(9H, s, -C-$(CH_3)_3$), 3.14 (1H, d, -OH), 3.78 (3H, s, -OCH_3), 5.44 (1H, d, -CH-OH), 5.74 and 6.23 (2H, 2 x m, CH_2=C-), 6.86 and 7.27 (4H, m, ArH's); δ_C 28.03 (q, -C-$(CH_3)_3$), 55.38 (q, -OCH_3), 73.13 (d, -CH-OH), 81.48 (s, -C-$(CH_3)_3$), 113.67 and 127.88 (2 x d, Ar CH's), 124.72 (t, CH_2=C-), 133.83 and 159.06 (2 x s, Ar quarternary carbons), 143.65 (s, -C=CH$_2$) and 165.70 (s, -C=O); m/z(EI) 264(M$^+$, 1%), 208(25), 135(100), 108(19) and 77(11).

3.2.4.2. (2R,5R)-(+)-*TRANS*-2,5-DIMETHYLPYRROLIDINE (164).

(2R,5R)-(+)-trans-2,5-Dimethylpyrrolidine (164).
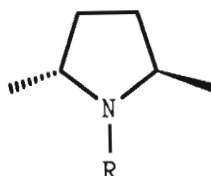
(164) R = H
(169) R = H$_2$Cl

The procedure of Masamune *et al.*[195] was employed. The chiral auxiliary (164) was converted to the hydrochloride salt (169), m.p. 199-201°C (lit.[195] 200-203°C); $[\alpha]_D^{24}$ = +5.31° (c1.54, CH$_2$Cl$_2$) (lit.[195] $[\alpha]_D$ = +5.47° (c3.0, CH$_2$Cl$_2$). Spectral data were identical to those described.[195]

Methyl 3-N-(2,5-dimethylpyrrolidin-1-yl)propanoate (170).

C$_{10}$H$_{19}$NO$_2$

MW = 185

(170)
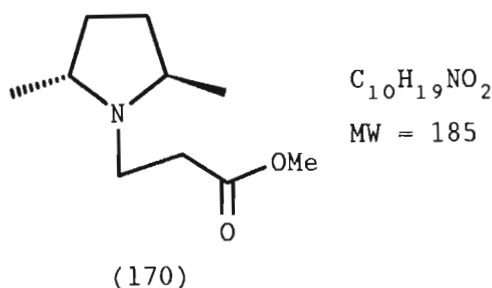
According to General Procedure 9 using (164) which, after purification by column chromatography, yielded (170) (80%) (Found: 185.14131. C$_{10}$H$_{19}$NO$_2$ requires 185.14157); $[\alpha]_D^{22}$ = -98.2° (c1.03, CHCl$_3$); δ_H 0.97 (6H, d, 2 x ring-CH$_3$'s), 1.27-1.48, 1.89-2.11, 2.43-2.75 and 2.88-3.13 (10H, 4 x m, 4 x CH$_2$'s + 2 x CH's), 3.68 (3H, s, -OCH$_3$); δ_C 16.74 (q, 2 x ring-CH$_3$'s), 30.84, 34.08, 42.95 (t, 4 x -CH$_2$'s), 51.69 (q, -OCH$_3$), 55.17 (d, 2 x ring-CH's) and 173.17 (s, -COOMe); m/z(EI) 185(M$^+$, 9%), 170(84), 112(100), 96(39) and 69(17).

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80).

$C_{11}H_{12}O_3$

MW = 192

(80)
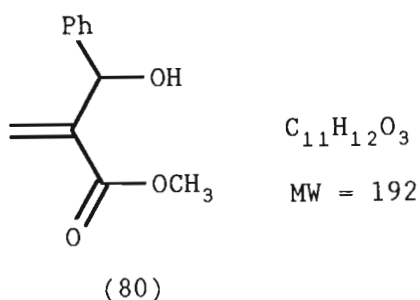
According to General Procedure 10 using (170) and benzaldehyde (79), which yielded (80) (75%); 0%ee;. Spectral data identical to (80) (Section 3.2.2.1.).

Methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate (171).

$C_{12}H_{14}O_4$

MW = 222

(171)
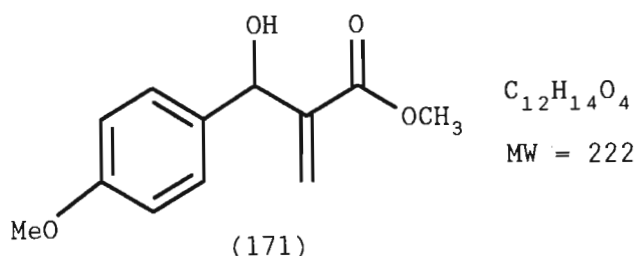
According to General Procedure 10 using (170) and 4-methoxy-benzaldehyde which yielded pure (171) (70%); 1%ee; δ_H 3.05 (1H, d, -OH), 3.70 (3H, s, -COOCH$_3$), 3.78 (3H, s, -PhOCH$_3$), 5.51 (1H, d, -CH-OH), 5.86 and 6.31 (2H, 2 x m, -C=CH$_2$), 6.84-7.30 (4H, dd, ArH's); δ_C 52.07 (q, -COOCH$_3$), 55.40 (q, Ph-OCH$_3$), 72.89 (d, -CH-OH), 114.14 and 128.30 (d, Ar -CH's), 125.92 (t, CH$_2$=C-), 133.48 (s, Ar quarternary), 142.18 (s, -C=CH$_2$), 159.19 (s, Ar quarternary) and 166.78 (s, -C=O); m/z(EI) 222(M$^+$, 17%), 190(13), 162(15), 137(42), 135(100), 108(41), 94(21) and 77(35).

tButyl 3-N-(2,5-dimethylpyrrolidinyl)propanoate (172).

$C_{13}H_{25}NO_2$

MW = 227

(172)
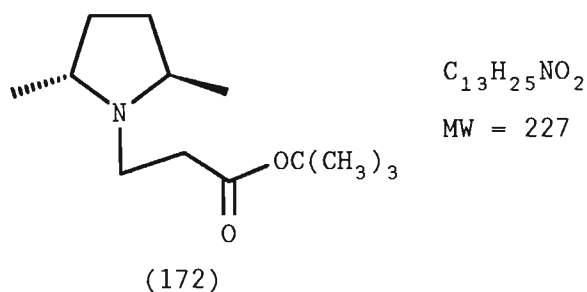
According to General Procedure 9 using (164) and *t*butyl acrylate (34) yielding (172) (75%) (Found: 227.1884. $C_{13}H_{25}NO_2$ requires 227.18852); $[\alpha]_D^{23}$ = -82.2° (c1.02, CHCl$_3$); δ_H 0.97 (6H, d, 2 x ring-CH_3's), 1.45 (9H, s, -C-(CH_3)$_3$), 1.25-1.44, 1.88-2.09, 2.34-2.68 and 2.85-3.11 (10H, m, 4 x -CH_2- + 2 x -N-CH-CH$_3$); δ_C 16.70 (q, ring-CH_3), 28.19 (q, -C-(CH$_3$)$_3$), 30.83, 35.44, 43.18 (t, 4 x -CH$_2$'s), 55.12 (d, ring -CH's), 80.13 (s, -C-(CH$_3$)$_3$) and 172.17 (s, -C=O); m/z)EI) 227(M$^+$, 5%), 212(11), 170(9), 156(96), 112(100), 96(13) and 84(13).

tButyl 3-hydroxy-2-methylene-3-phenylpropanoate (90).

$C_{14}H_{18}O_3$

MW = 234

(90)
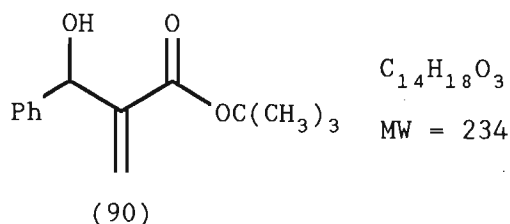
According to General Procedure 10 using (172) and benzaldehyde (79). The yield of (90) was (70%); 15%ee. Spectral data was identical to (90) (Section 3.2.2.3.).

Butyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate (163).

$C_{15}H_{20}O_4$

MW = 264

(163)
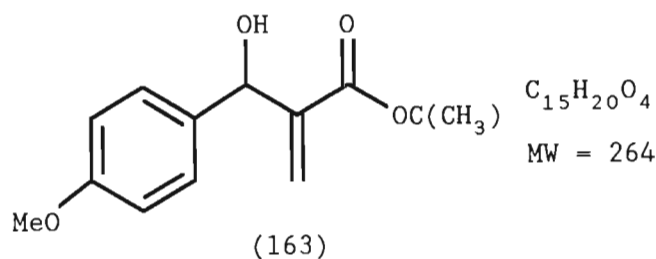
According to General Procedure 10 using (172) and 4-methoxybenzaldehyde. The yield of (163) was (68%); 17%ee. Spectral data was identical to (163) (Section 3.2.4.1.).

3.2.4.3. (2S,5S)-(-)-*TRANS*-BIS(METHOXYMETHOXYMETHYL) PYRROLIDINE (173).

(2S,5S)-trans-Bis(methoxymethoxymethyl)pyrrolidine (173).

(173)
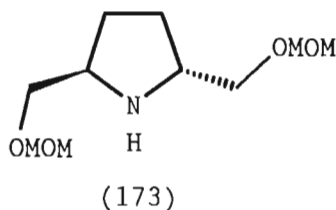
The synthesis of (173) was accomplished by a combination of the procedures described by Katsuki[189] and Ghosez.[198] $[\alpha]_D^{24}$ = -4.2° (c1.10, EtOH) (lit.[189] $[\alpha]_D^{24}$ = +4.32 (c4.0, EtOH) for the antipode).

*Methyl 3-N-(2,5-Bis(methoxymethoxymethyl)pyrrolidin-1-yl)
propanoate (179).*

$C_{14}H_{27}NO_6$

MW = 305

(179)
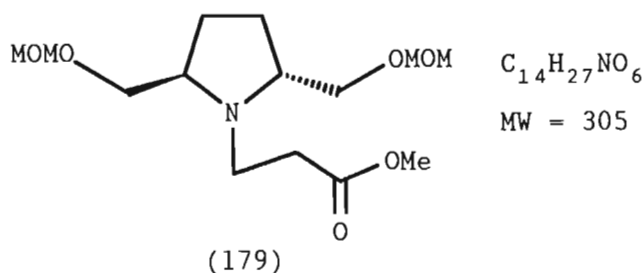
According to General Procedure 9 using (173) and methyl acrylate
(30).   Purification by chromatography yielded (179) (65%)
(Found: 305.1818. $C_{14}H_{27}NO_6$ requires 305.1838); $[\alpha]_D^{24} = -55.5°$
(c0.50, CHCl$_3$); δ_H 3.36 (6H, s, 2 x -CH$_2$-O-CH$_3$), 3.67 (3H, s,
-COOCH$_3$), 4.61 (4H, s, 2 x -O-CH$_2$-O-CH$_3$), 1.59-1.75, 1.86-2.09,
2.45-2.69 and 2.96-3.60 (14H, m, 6 x -CH$_2$'s + 2 x -N-CH-);
δ_C 51.65 and 55.47 (2 x q, 3 x -CH$_3$), 27.23, 34.40, 43.93, 69.17
and 97.02 (t, -CH$_2$'s), 60.48 (d, 2 x -N-CH-) and 173.08 (s,
-C=O); m/z(EI) 305(M$^+$, 0.2%), 244(6), 230(100), 198(11), 154(7),
112(7), 94(13) and 45(36).

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (80).

$C_{11}H_{12}O_3$

MW = 192

(80)
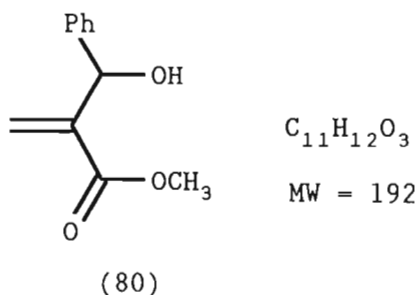
According to General Procedure 10 using (179) and benzaldehyde
(79), which yielded (80) (60%); 32%ee;. Spectral data identical
to (80) (Section 3.2.2.1.).

3.2.5.   THE CROTONATE SYSTEM.

Methyl 3-N-(2-hydroxymethylpyrrolidin-1-yl)butanoate (183).

$C_{10}H_{19}NO_3$

MW = 201
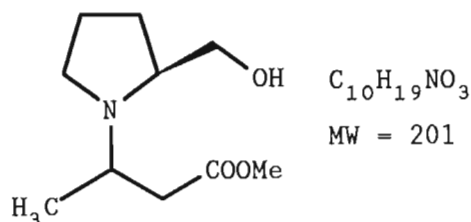
(183)

According to General Procedure 9 yielding (183) (80%) as a 60:40 mixture of the 2 possible diastereomers. These were separated by column chromatography using MeOH/CHCl$_3$ (1:10). Diastereomer (183a) eluted first.

DATA for (183a): (Found: C, 59.57; H, 9.32; N, 6.90. $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.51; N, 6.96%); $[\alpha]_D^{26}$ = -46.1° (c2.0, CHCl$_3$); δ_H 1.00 (3H, d, -CH-CH_3), 1.60-1.80 (4H, m, ring-(CH_2)$_2$-), 2.17-2.66 (3H, m, -N-CH_2- and ring-N-CH-), 2.75-3.06 (3H, m, -CH_2-CO- and -OH), 3.25-3.65 (3H, m, -CH_2O- and CH$_3$-CH-) and 3.69 (3H, s, -OCH_3); δ_C 12.20 (q, -CH$_3$), 24.33 (t, -CH$_2$CH$_2$CH$_2$-), 28.17 (t, ring-CH-CH$_2$-), 41.33 (t, -CH$_2$-CO-), 44.78 (t, -N-CH$_2$-), 50.37 (d, -N-CH-CH$_3$), 51.77 (q, -OCH$_3$), 60.67 (d, ring-CH-), 63.27 (t, -CH$_2$-OH) and 173.18 (s, -C=O); m/z(EI) 201(M$^+$, 15%), 170(100), 128(26) and 70(68).

DATA for (183b): $[\alpha]_D^{26}$ = -5.9° (c1.06, CHCl$_3$); δ_H 1.17 (3H, d, -CH-CH_3), 1.61-1.93 (4H, m, ring-(CH_2)$_2$-), 2.20-2.65 (3H, m, -N-CH_2- and ring-N-CH-), 2.87-3.05 (2H, m, -CH_2-CO-), 3.14(1H, s, -OH), 3.22-3.61 (3H, m, -CH_2O- and CH$_3$-CH-) and 3.69 (3H, s, -OCH_3); δ_C 19.62 (q, -CH$_3$), 24.22 (t, -CH$_2$CH$_2$CH$_2$-), 27.62 (t, ring-CH-CH$_2$-), 36.54 (t, -CH$_2$-CO-), 48.18 (t, -N-CH$_2$-), 51.75 (d, -N-CH-CH$_3$), 51.83 (q, -OCH$_3$), 59.85 (d, ring-CH-), 63.3 (t, -CH$_2$-OH) and 173.32 (s, -C=O); m/z(EI) 201(M$^+$, 2%), 170(100), 128(56) and 70(91).

GENERAL PROCEDURE 11:   THE ALDOL REACTION OF MASKED CROTONATES AND ELIMINATION OF THE AMINE.

To a solution of LDA (2.4eq) was added either (183a) or (183b) (1eq) at 20°C under nitrogen. The mixture was stirred at this temperature for 30 minutes, cooled to -78°C and a solution of the aldehyde (1eq) in THF (2ml/mmol) was added. After 45 minutes at this temperature the reaction was quenched with saturated NH_4Cl and extracted with Et_2O followed by $CHCl_3$. The combined extracts were dried ($MgSO_4$) and the solvents evaporated. To the residue in $CHCl_3$ was added MCPBA (10% molar excess in $CHCl_3$) and the mixture was allowed to stir overnight. Basic alumina (2g/mmol) was added and stirring was continued for one hour. Elution from a column of alumina (10 x the mass of the combined starting materials) afforded the crude products which were purified by column chromatography.

Methyl (E)-2-(1-phenylhydroxymethyl)but-2-enoate (182a).

$C_{12}H_{14}O_3$

MW = 206
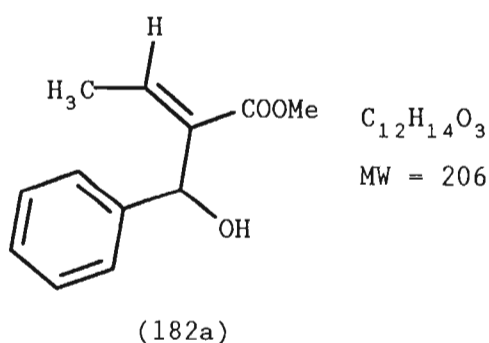
(182a)

According to General Procedure 11 using (183a) and benzaldehyde (79) which yielded (182a) (55%); 35%ee; (Found: 206.09511. $C_{12}H_{14}O_3$ requires 206.09428); $[\alpha]_D^{25}$ = +56.6° (c1.13, $CHCl_3$); δ_H 1.96 (3H, d, $-CH-CH_3$), 3.65 (3H, s, $-O-CH_3$), 4.26 (1H, d, $-OH$), 5.73 (1H, d, $-CH-OH$), 7.09 (1H, q, $CH_3CH=$), 7.15-7.39 (5H, m, PhH's); δ_C 14.32 (q, $CH_3-CH=$), 51.94 (q, $-OCH_3$), 69.40 (d, $-CH-OH$), 125.57, 127.46 and 128.69 (d, PhCH's), 133.42 (s, Ph quarternary), 140.48 (d, $CH_3CH=$), 142.72 (s, $CH_3CH=C-$) and

167.55 (s, $-C$=O); m/z(EI) 206(M^+, 34%), 146(58), 105(100) and 77(50).

The same reaction using (183b) and benzaldehyde (79) yielded (182a) (45%); 50%ee; $[\alpha]_D^{25}$ = -68.7° (c0.96, $CHCl_3$).

Methyl (E)-2-(1-(4-methoxyphenyl)hydroxymethyl)but-2-enoate (182b).

(182b)

$C_{13}H_{16}O_4$

MW = 236
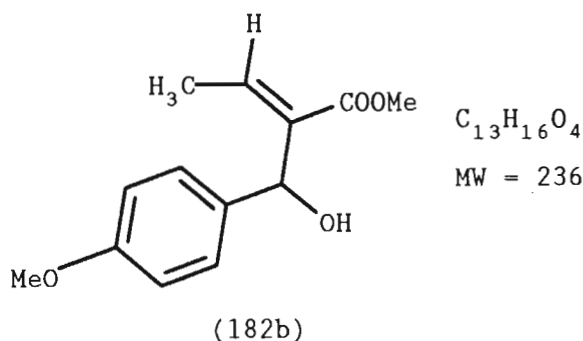
According to General Procedure 11 using (183a) and 4-methoxy-benzaldehyde which yielded (182b) (49%); 56%ee; (Found: C, 66.10; H, 6.85. $C_{13}H_{16}O_4$ requires C, 66.09; H, 6.83%); $[\alpha]_D^{22}$ = +103.2° (c0.52, $CHCl_3$); δ_H 1.95 (3H, d, $-CH-CH_3$), 3.68 (3H, s, $-COO-CH_3$), 3.78 (3H, s, $Ph-O-CH_3$), 4.21 (1H, d, $-OH$), 5.68 (1H, d, $-CH-OH$), 6.86 and 7.28 (4H, m, ArH's) 7.06 (1H, q, CH_3CH=); δ_C 14.27 (q, CH_3-CH=), 51.96 (q, $-COOCH_3$), 55.37 (q, $Ph-O-CH_3$), 69.17 (d, $-CH-OH$), 114.05 and 126.86 (d, $ArCH$'s), 133.47 (s, Ar quarternary), 134.83 (s, CH_3CH=$C-$), 140.18 (d, CH_3CH=$C-$) 158.70 (s, aromatic quarternary) and 167.65 (s, $-C$=O); m/z(EI) 236(M^+, 22%), 176(27), 135(100) 109(31) and 77(37).

The same reaction using (183b) and 4-methoxybenzaldehyde yielded (182b) (47%); 41%ee; $[\alpha]_D^{24}$ = -69.9° (c0.52, $CHCl_3$).

Methyl (E)-2-(1-(4-nitrophenyl)hydroxymethyl)but-2-enoate (182c).

(182c)

$C_{12}H_{13}NO_5$

MW = 251
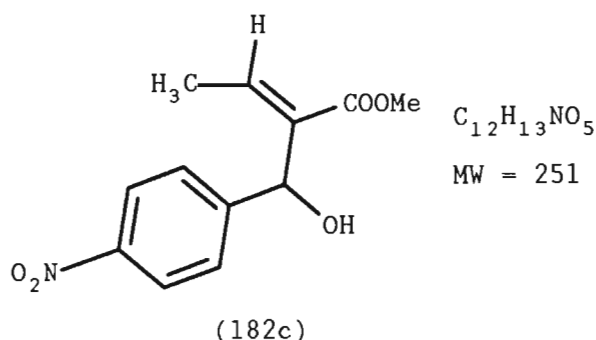
According to General Procedure 11 using (183a) and 4-nitrobenzaldehyde which yielded (182c) (50%); 25%ee; (Found: C, 57.32; H, 5.26; N, 5.51. $C_{12}H_{13}NO_5$ requires C, 57.37; H, 5.22; N, 5.58%); $[\alpha]_D^{24}$ = +71.5° (c0.51, $CHCl_3$); δ_H 2.04 (3H, d, -CH-CH_3), 3.69 (3H, s, -O-CH_3), 4.26 (1H, d, -OH), 5.79 (1H, d, -CH-OH), 7.19 (1H, q, CH_3CH=), 7.54 and 8.18 (4H, m, ArH's); δ_C 14.54 (q, CH$_3$-CH=), 52.22 (q, -COOCH$_3$), 68.90 (d, -CH-OH), 123.96 and 126.50 (d, ArCH's), 132.62 (s, Ar quarternary), 141.84 (d, CH_3CH=C-), 147.08 and 150.38 (2 x s, Ar quarternary and -C=CH-CH$_3$) and 167.65 (s, -C=O); m/z(EI) 251(M$^+$, 15%), 234(60), 191(99) 150(100) 97(57) and 69(65).

The same reaction using (183b) and 4-nitrobenzaldehyde yielded (182c) (51%); 10%ee; $[\alpha]_D^{24}$ = +24.2° (c0.52, $CHCl_3$).

2.6. THE SYNTHESIS OF A TETRAHYDROFURAN DERIVATIVE (187) *VIA* A NOVEL CYCLISATION REACTION.

Tetrahydro-4,4-dimethyl-2-oxo-3-furanyl propanoate (184).

$C_9H_{14}O_4$

MW = 186

(184)
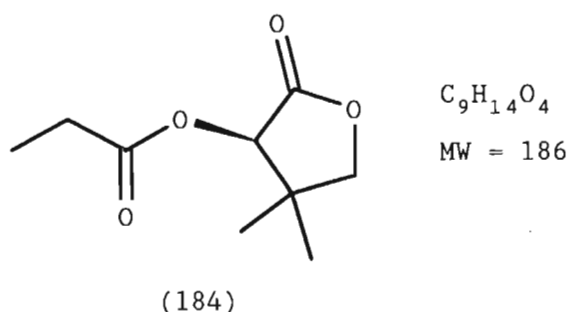
To a stirred solution of pantolactone (4.3g, 0.033mol) and triethylamine (7ml, 0.05mol) in CH_2Cl_2 (40ml) at 0°C was added propionyl chloride (4ml, 0.046mol) over 20 minutes. The contents were stirred at this temperature for 4 hours and washed sequentially with 1N HCl (25ml), saturated $NaHCO_3$ (25ml) and water (25ml). Evaporation of the solvent afforded the crude product which was distilled to yield pure (184) (5.90g, 96%), b.p. 99-100°C/3.15mmHg; (Found: 186.0881. $C_9H_{14}O_4$ requires 186.08919); $[\alpha]_D^{24}$ = -13.9° (c1.1, $CHCl_3$); δ_H 1.17 and 1.21 (6H, 2 x s, ring-CH_3's), 1.21 (3H, t, -CH_2-CH_3), 2.49 (2H, q, -CH_2CH$_3$), 4.01 (2H, s, ring-CH_2), 5.39 (1H, s, ring-CH-); δ_C 9.01 (q, -CH_2CH$_3$), 19.87 and 23.01 (2 x q, ring-CH_3's), 27.22 (t, -CH_2CH$_3$), 40.19 (s, ring-C-(CH$_3$)$_2$), 74.84 (d, ring-CH-), 76.19 (t, ring-CH_2-), 172.57 and 173.29 (2 x s, 2 x -C=O); m/z(EI) 186(M$^+$, 1%), 57(100).

Hexahydro-3a,7a-dihydroxy-3,7,7-trimethyl-2-phenyl-4H-furo[3,2-c]pyran-4-one (187).

$C_{16}H_{20}O_5$

MW = 292
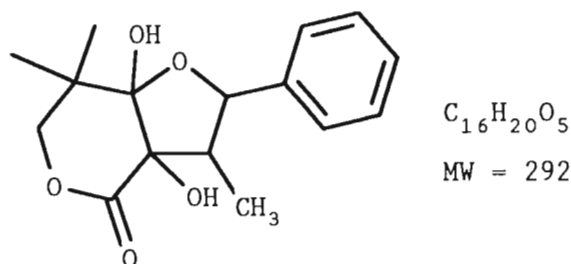
(187)

To a solution of LDA (6.6mmol) in THF (15ml) was added the ester (184) (1.116g, 6mmol) in THF (5ml) at -78°C. The mixture was allowed to stir at this temperature for 30 minutes at which time benzaldehyde (0.637g, 6mmol) was added. The mixture was allowed to stir at this temperature for 30 minutes after which it was allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O followed by $CHCl_3$. The mixture was subjected to column chromatography (Et_2O/hexane) yielding (187) (0.52g, 30%), m.p. 149°C (Found: C, 65.75; H, 6.93. $C_{16}H_{20}O_5$ C, 65.74; H, 6.89%); $[\alpha]_D^{25}$ = 0°; γ/cm^{-1} 3300 and 3390 (OH); δ_H 0.99 (3H, d, CH_3-CH-), 1.12 (6H, s, 2 x ring-CH_3's), 2.46 (1H, m, -CH-CH$_3$), 3.96 and 4.43 (2H, dd, J11, ring-CH_2-), 4.03 and 4.07 (2H, s and br s, 2 x -OH), 4.35 (1H, d, Ph-CH-), 7.26-7.41 (5H, m, Ph*H*'s); δ_C 10.59 (q, -CH-CH$_3$), 17.81 and 19.98 (2 x q, ring-CH_3's), 39.47 (s, ring-C-(CH$_3$)$_2$), 53.39 (d, -CH-CH$_3$), 76.42 (t, ring-CH_2-), 81.88 (s, -C-(OH)-C=O), 84.97 (d, Ph-CH-), 103.25 (s, -C-(OH)-O-), 126.45, 128.43 and 128.60 (d, 2 x Ar -CH's), 139.53 (s, Ar quarternary) and 172.69 (s, -C=O); m/z 292(M$^+$, 1%).

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Appendix: ^{1}H and ^{13}C NMR spectra.

NOTE: The ^{1}H and ^{13}C NMR spectra appear here in the same sequence as that of the EXPERIMENTAL (Section 4).
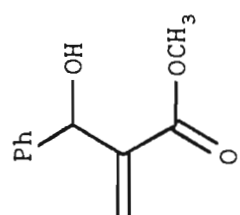
$C_{11}H_{12}O_3$

MW = 192
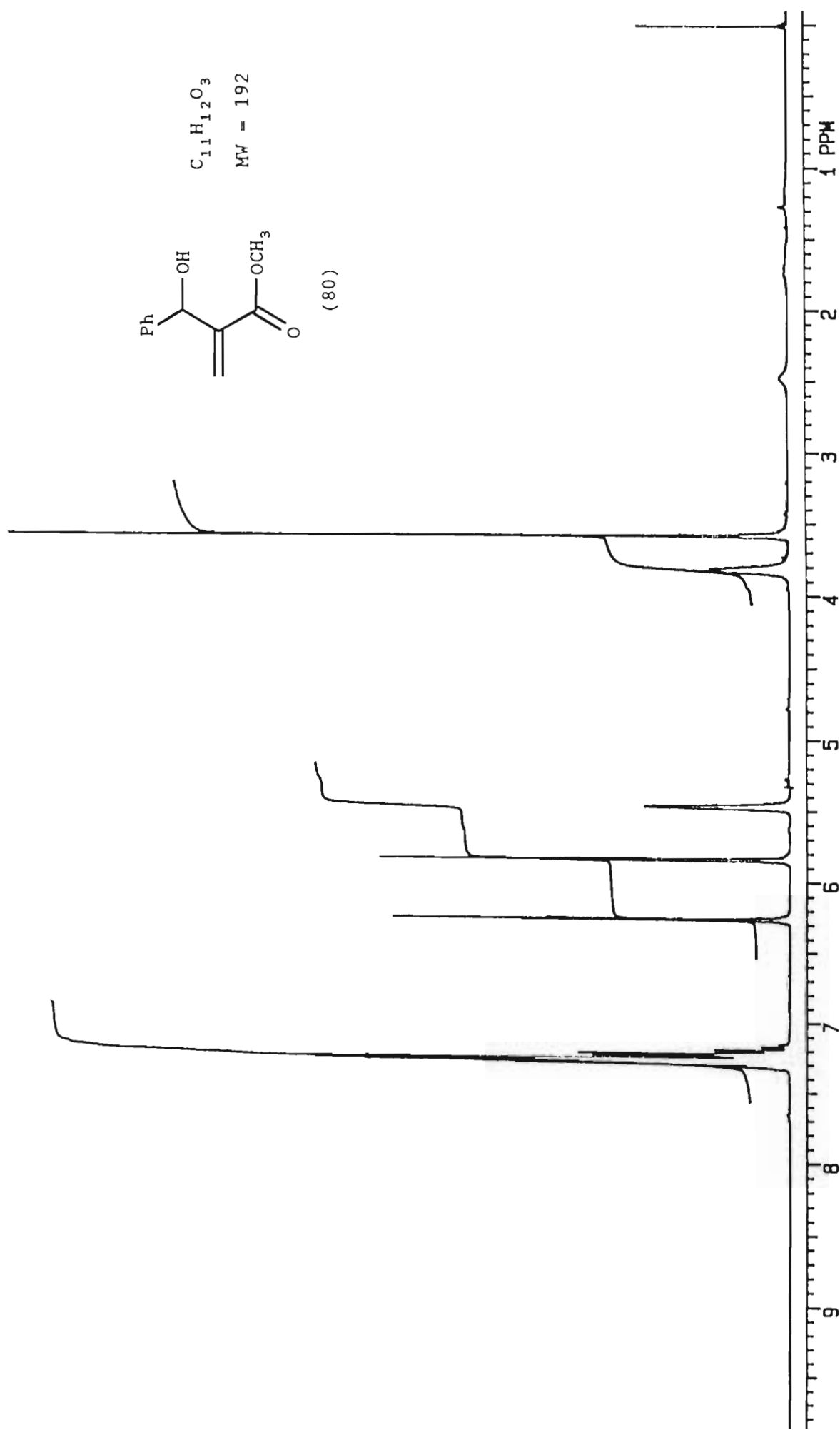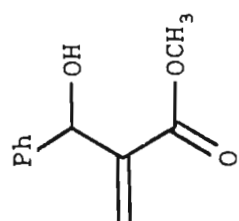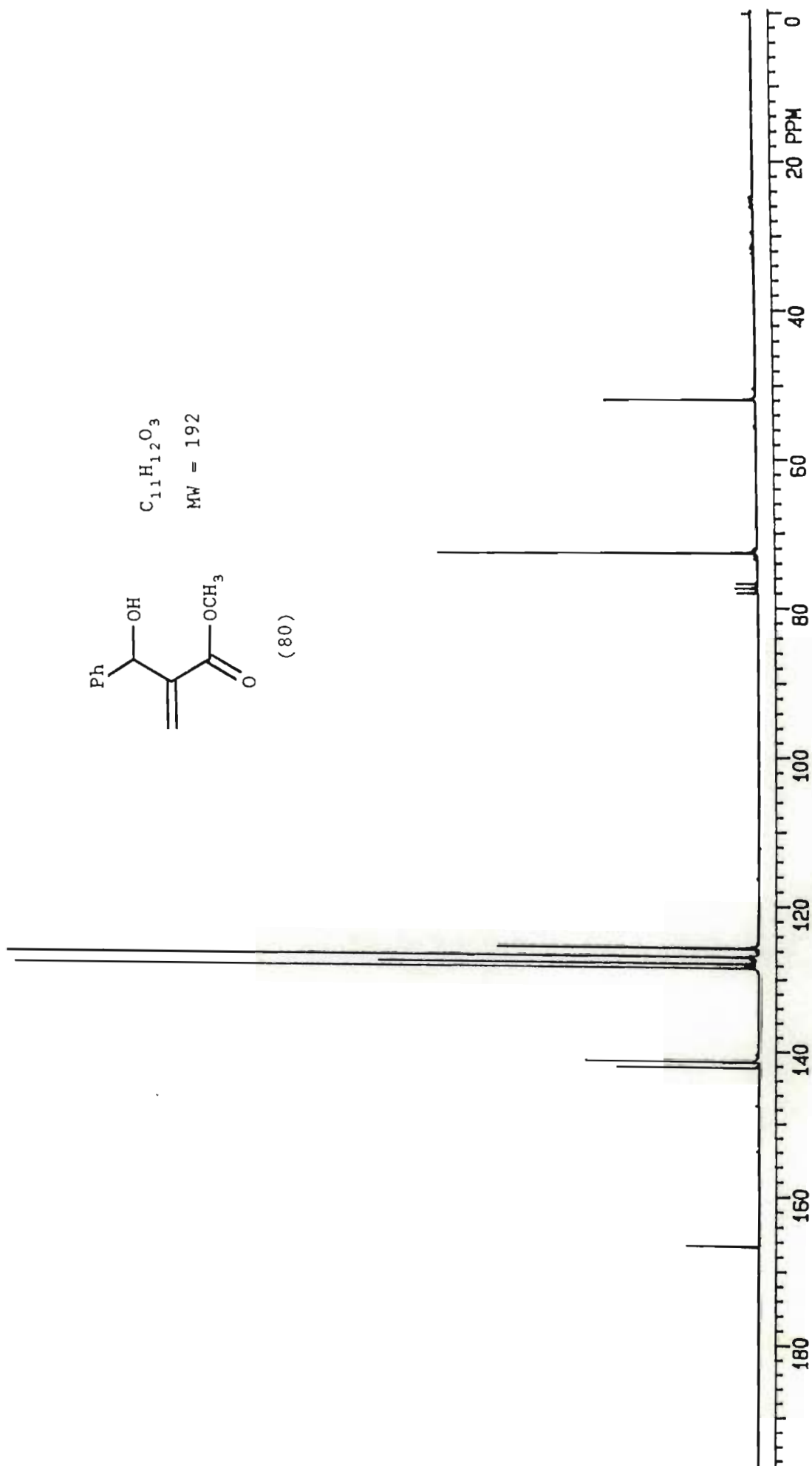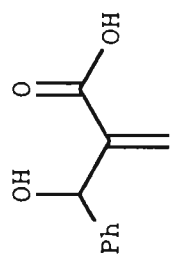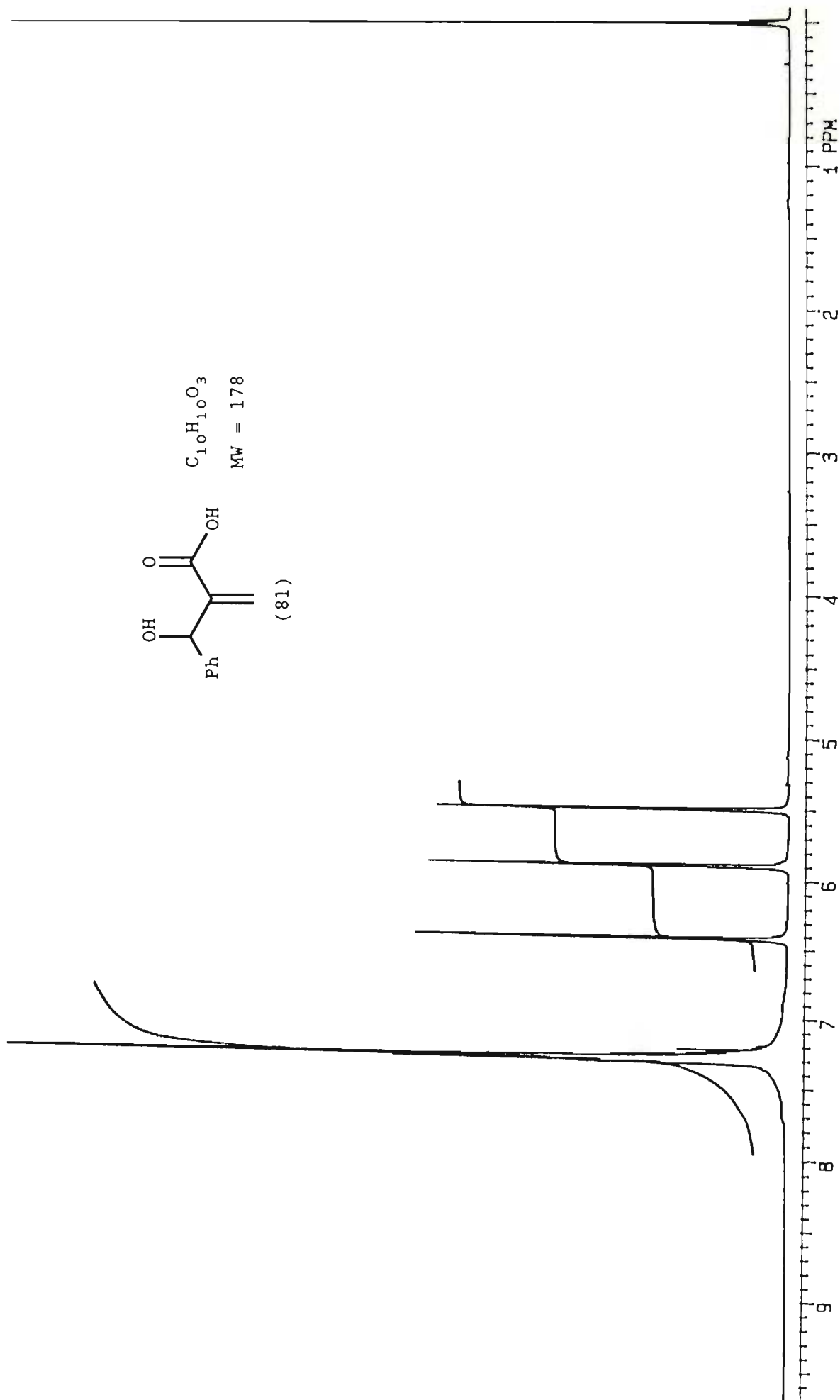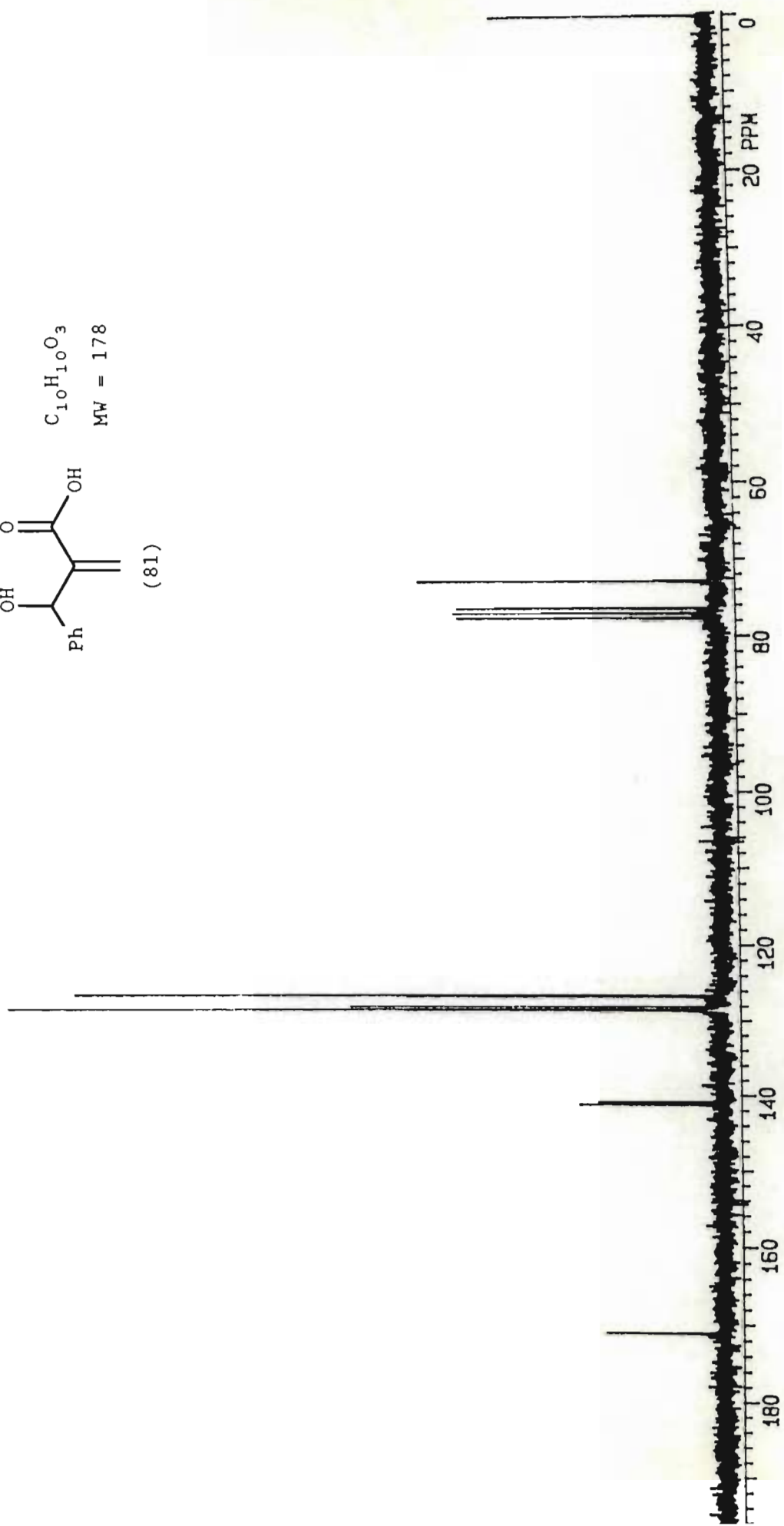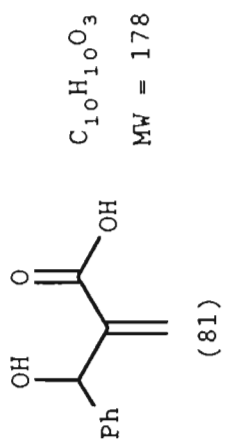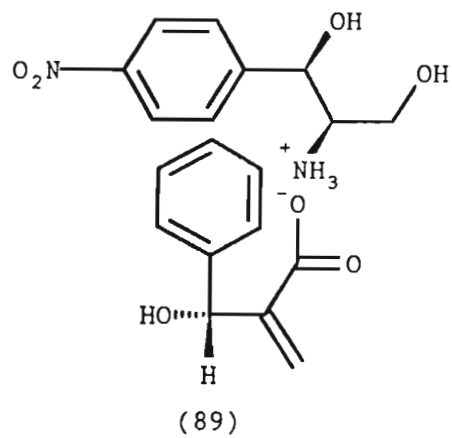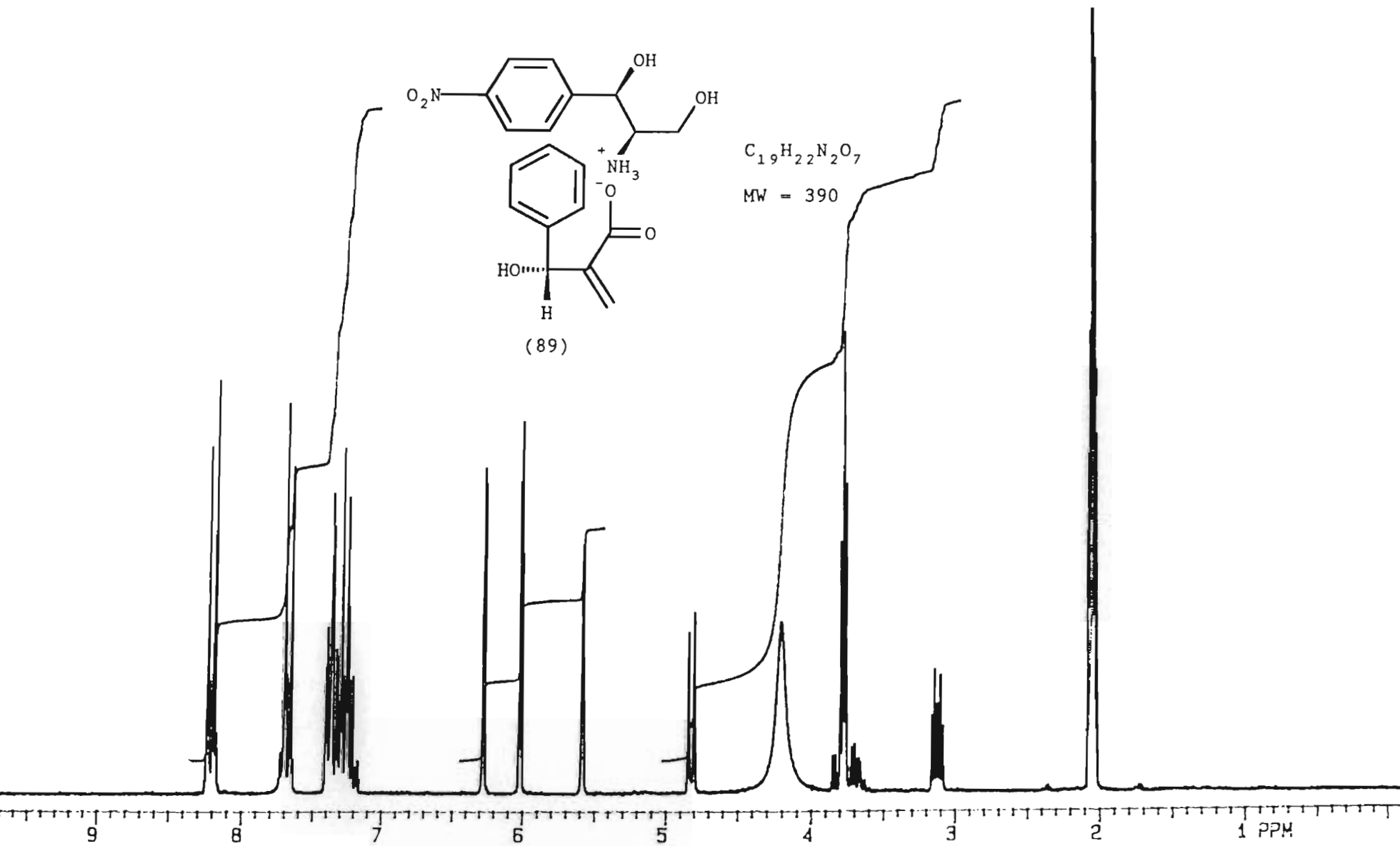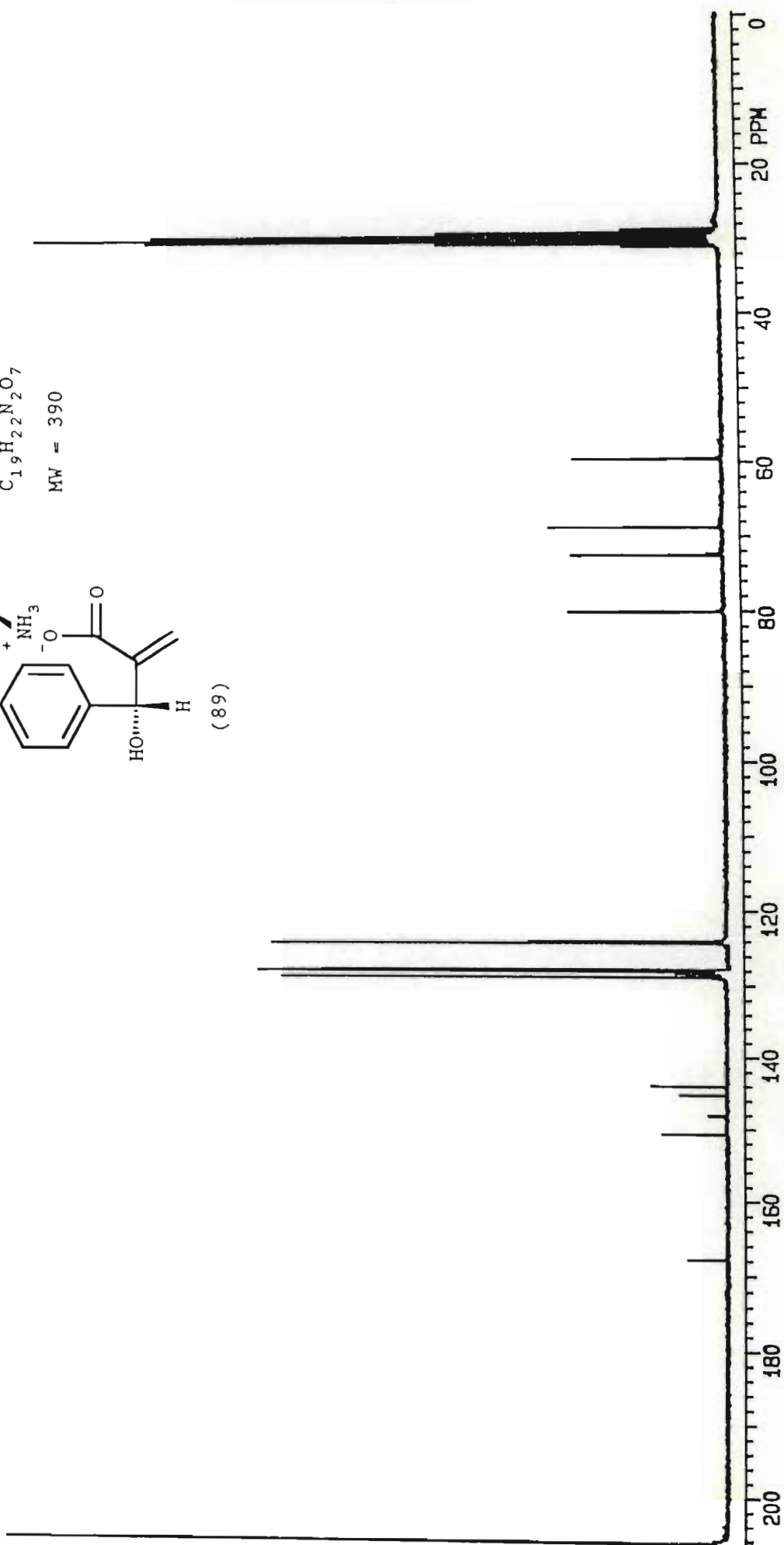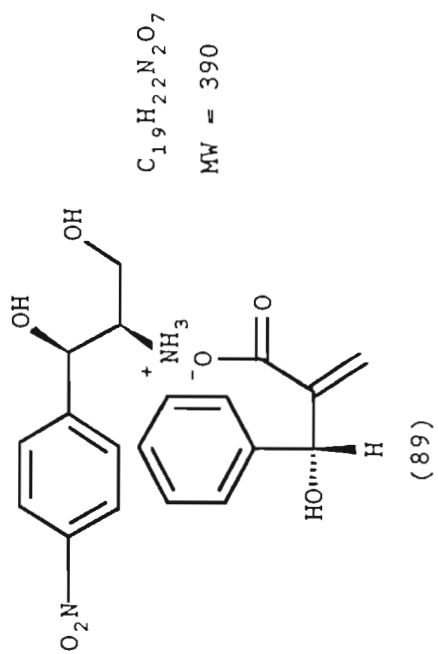
Ph —— OH

OCH$_3$

O

(80)

1 PPM 2 3 4 5 6 7 8 9

$C_{11}H_{12}O_3$

MW = 192

Ph—CH(OH)—C(=CH_2)—CO—OCH_3
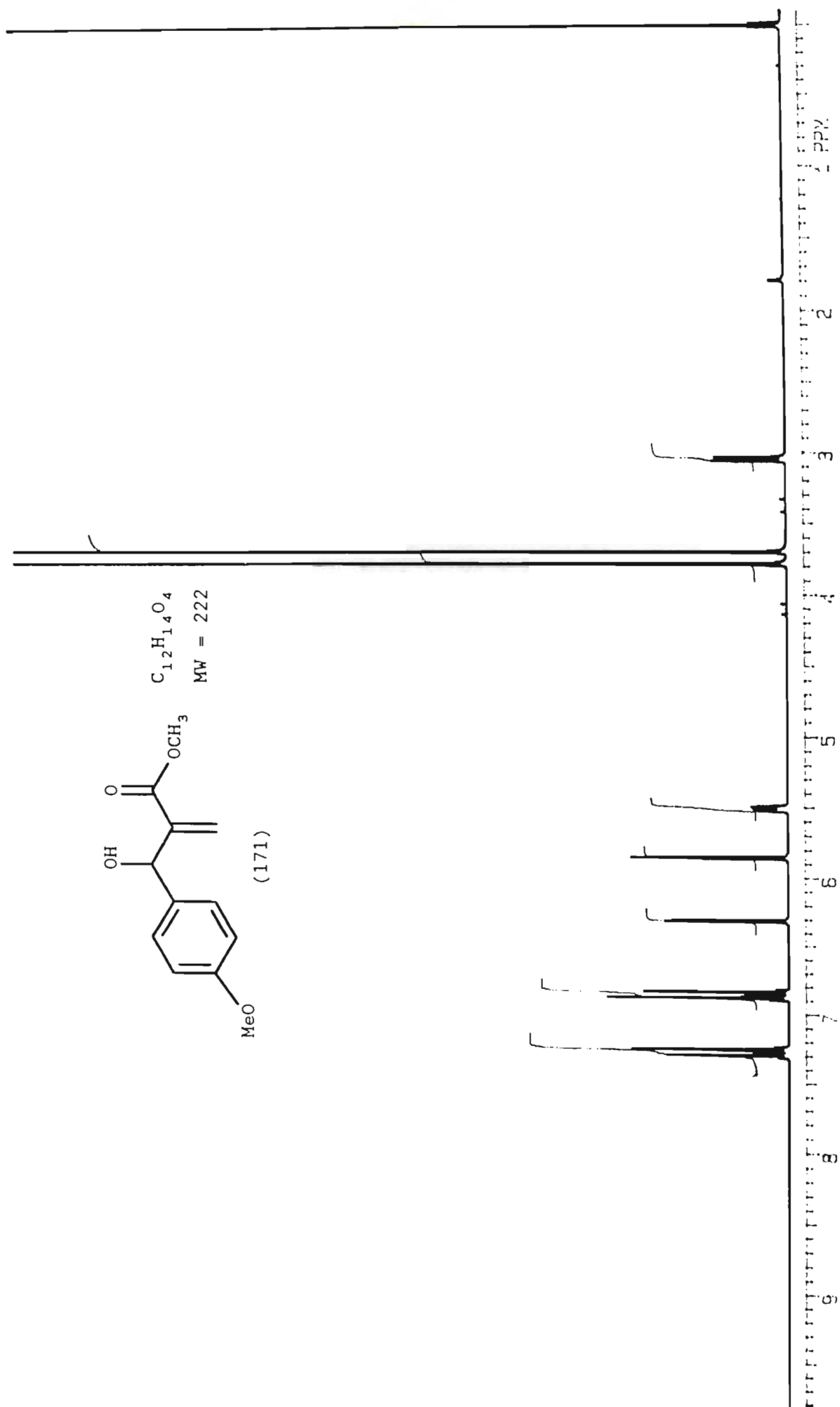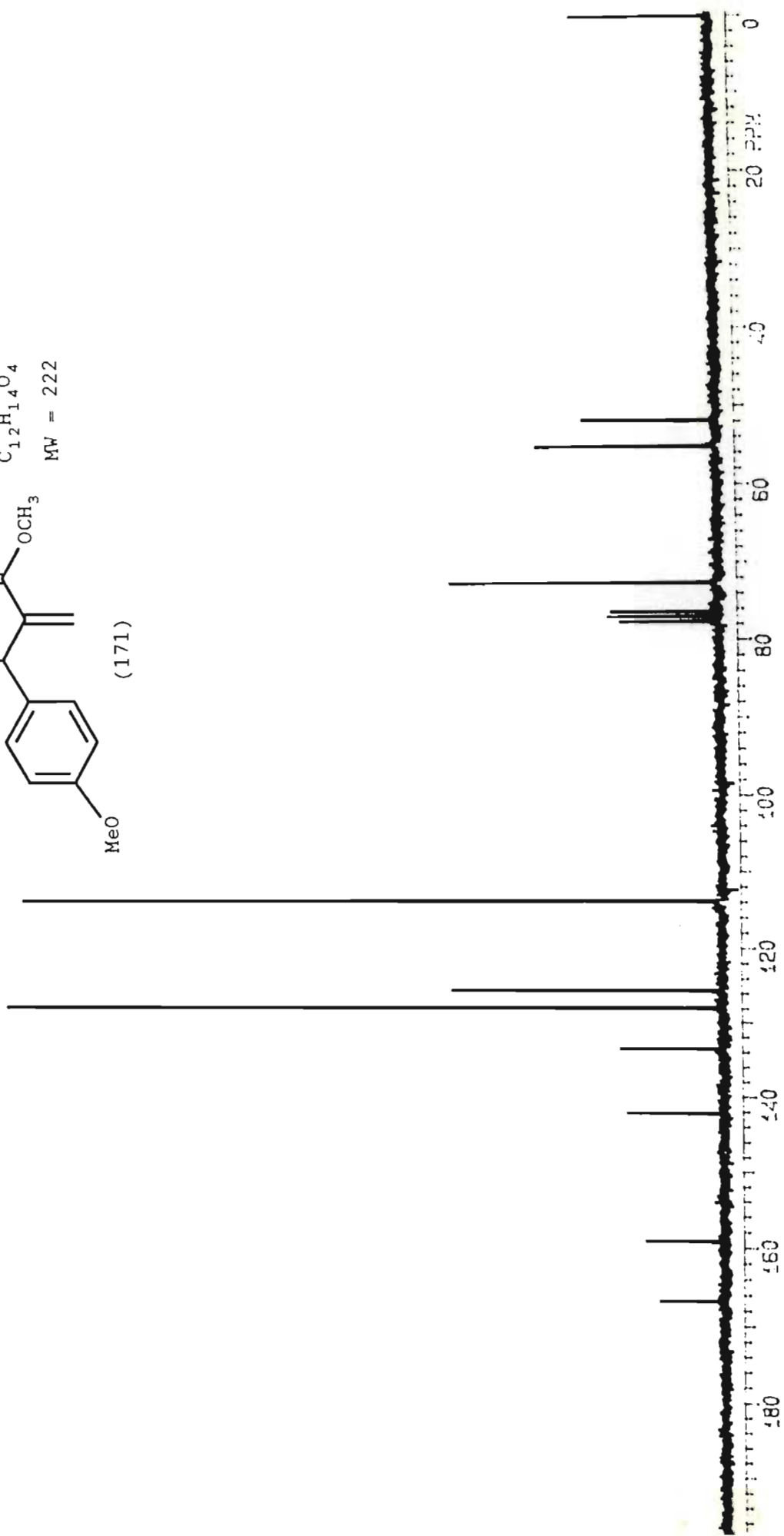
(80)

$C_{10}H_{10}O_3$

MW = 178

(81)

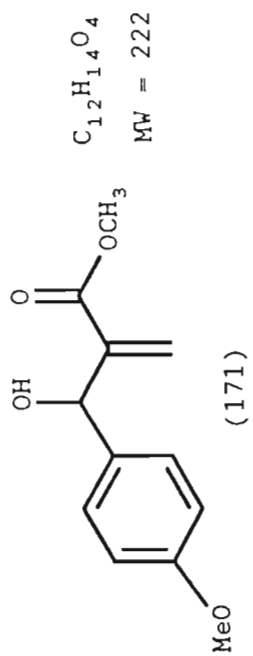Structure: a compound with a phenyl group (Ph), a CH bearing an OH, attached to a carbon with an exocyclic double bond (=CH$_2$), and a carboxylic acid group (C(=O)OH).

1 PPM

$C_{10}H_{10}O_3$

MW = 178

(81)

O_2N

OH

OH

$\overset{+}{N}H_3$

$\overset{-}{O}$

O

HO

H

(89)

$C_{19}H_{22}N_2O_7$

MW = 390

$C_{19}H_{22}N_2O_7$

MW = 390

(89)

$C_{14}H_{18}O_3$

MW = 234

(90)

1 PPM

$C_{14}H_{18}O_3$

MW = 234

OC(CH$_3$)$_3$

O

OH

Ph

(90)
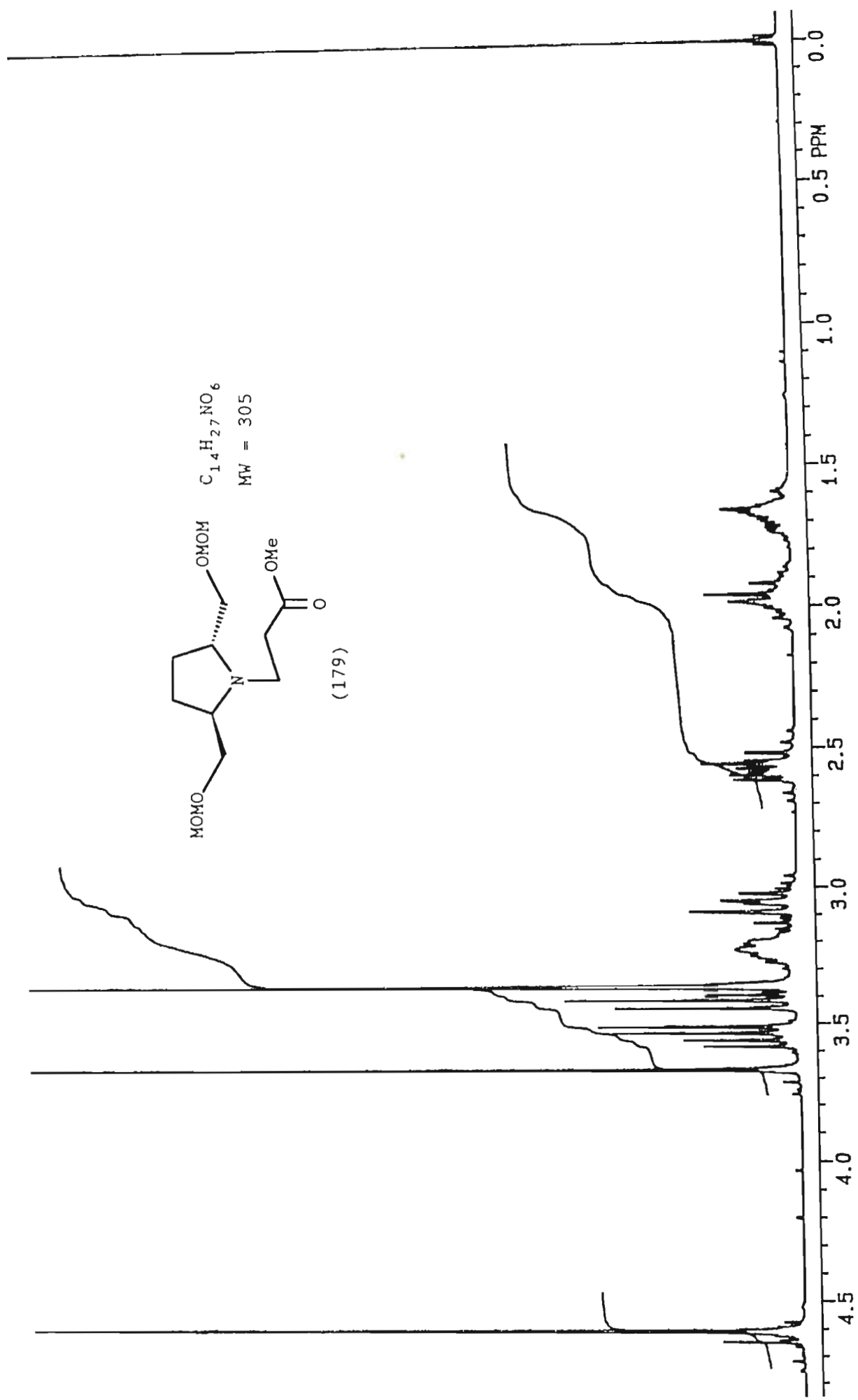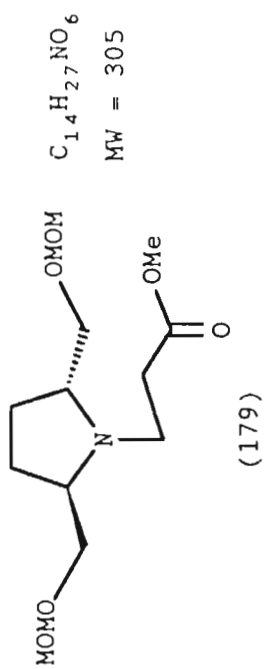
$C_{11}H_{14}O_3$
MW = 194

OH
2R 3S Ph
MeO
O
CH$_3$
(91a)

$C_{11}H_{14}O_3$
MW = 194

OH
Ph
3S
2R
CH_3
O
MeO
(91a)

$C_{11}H_{14}O_3$

MW = 194

OH

Ph

2S 3S

CH$_3$

O

MeO

(91b)

$C_{11}H_{14}O_3$
MW = 194

(91b)

$C_9H_{12}O_4$
MW = 184

(96)

1 PPM

$C_9H_{12}O_4$

MW = 184

(96)

$C_7H_{10}O_3$
$MW = 142$

(97)

$C_7H_{10}O_3$

MW = 142

(97)
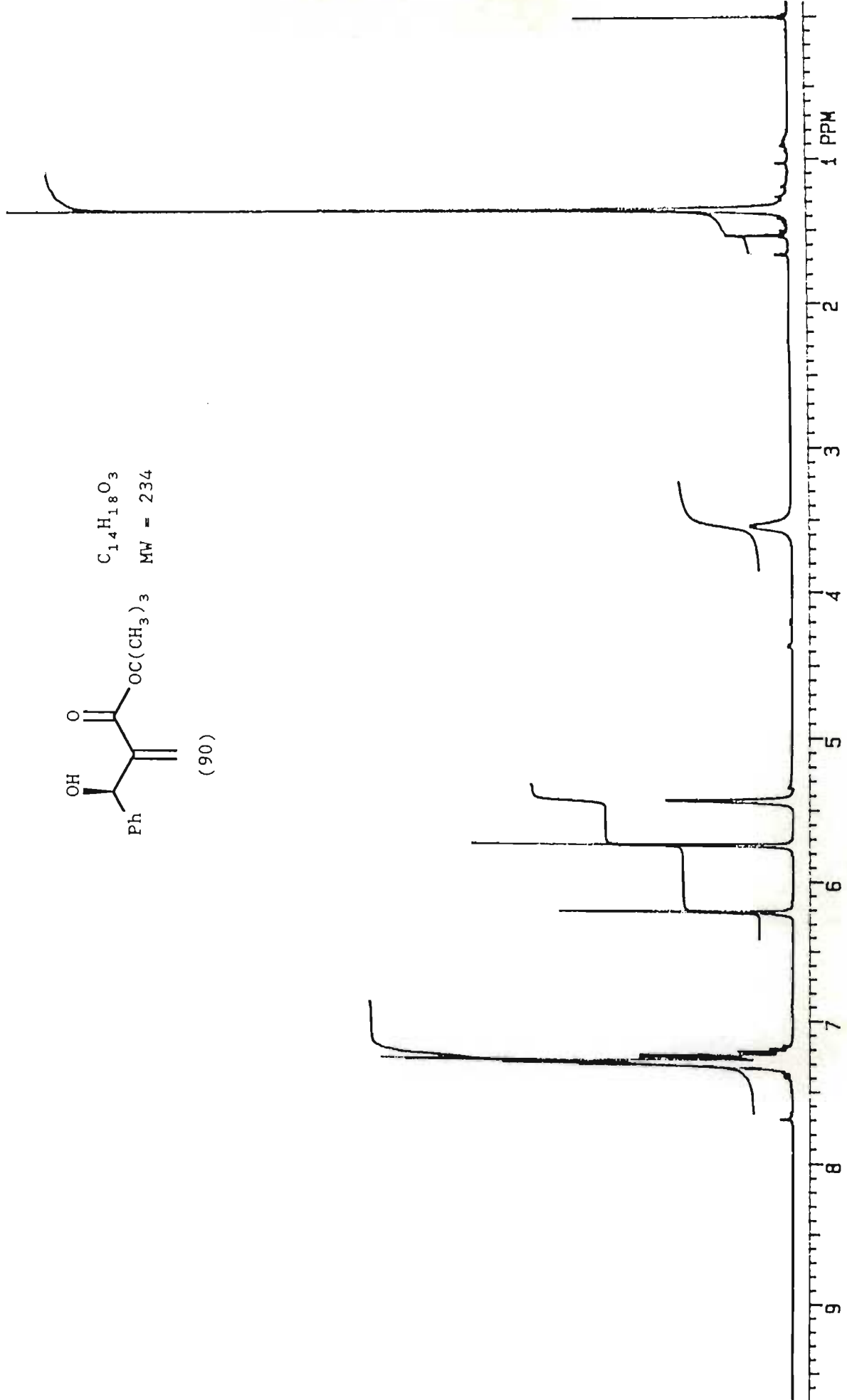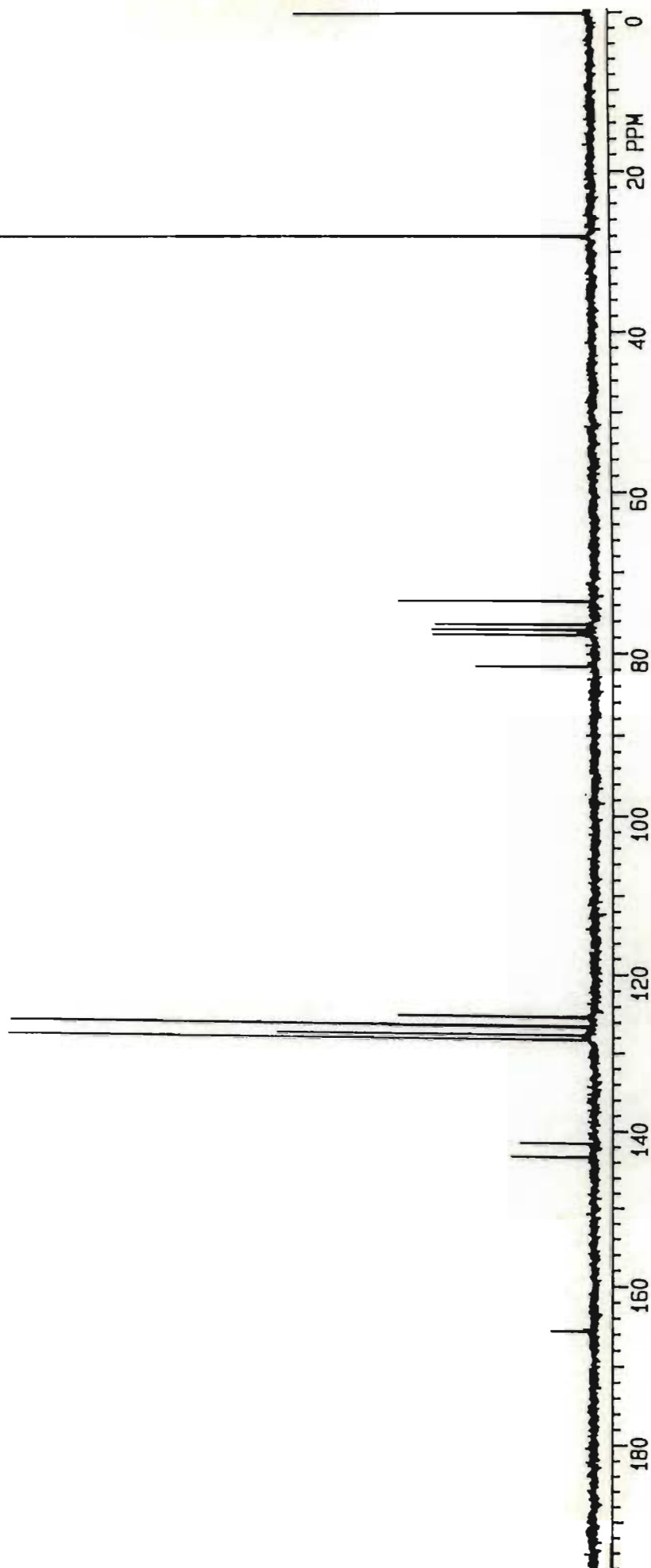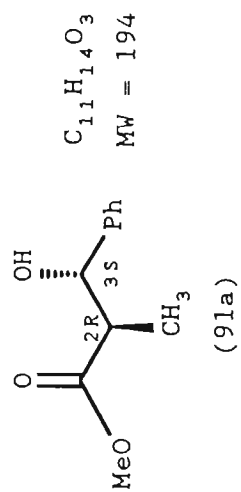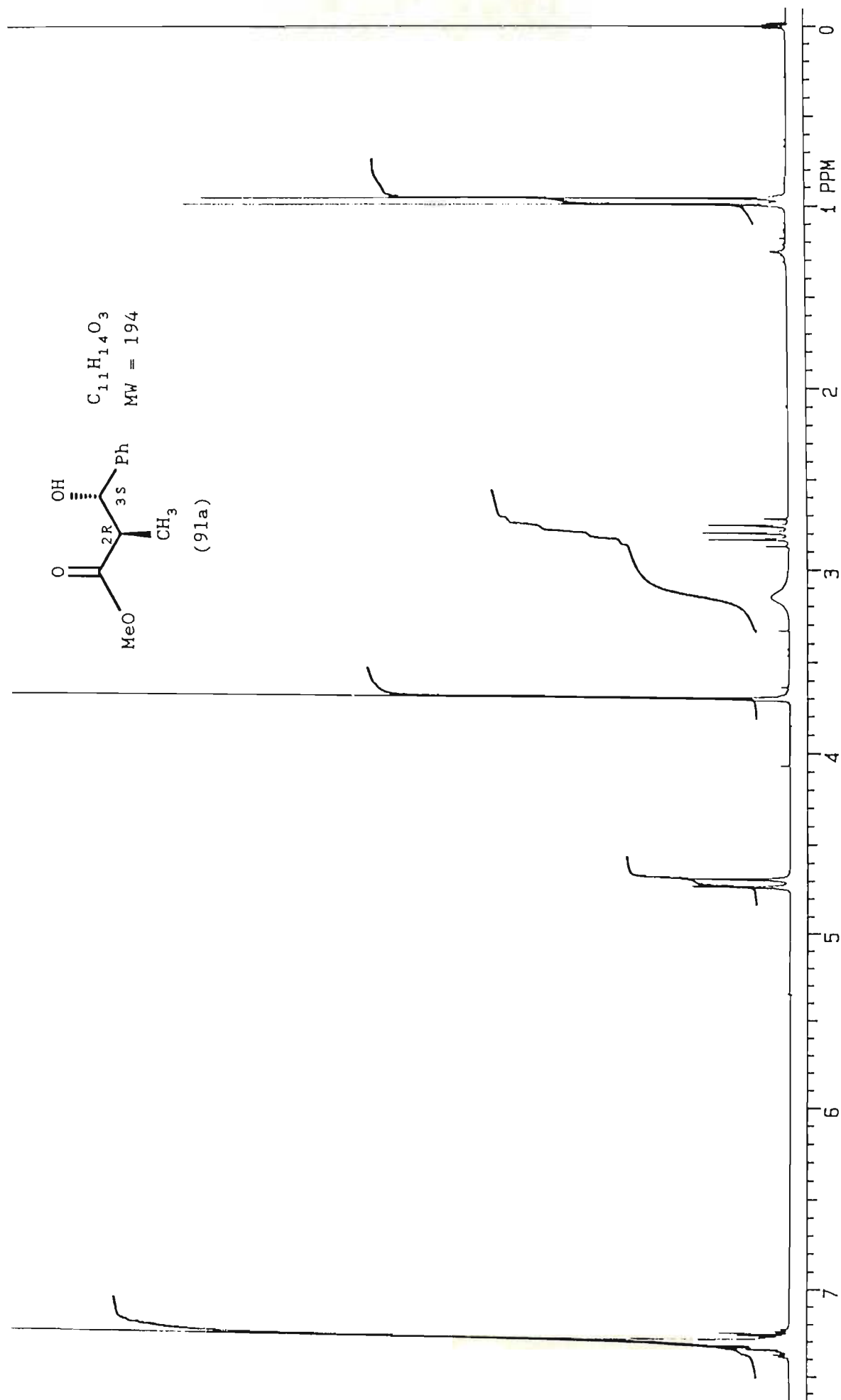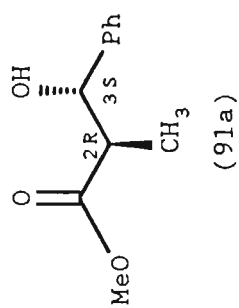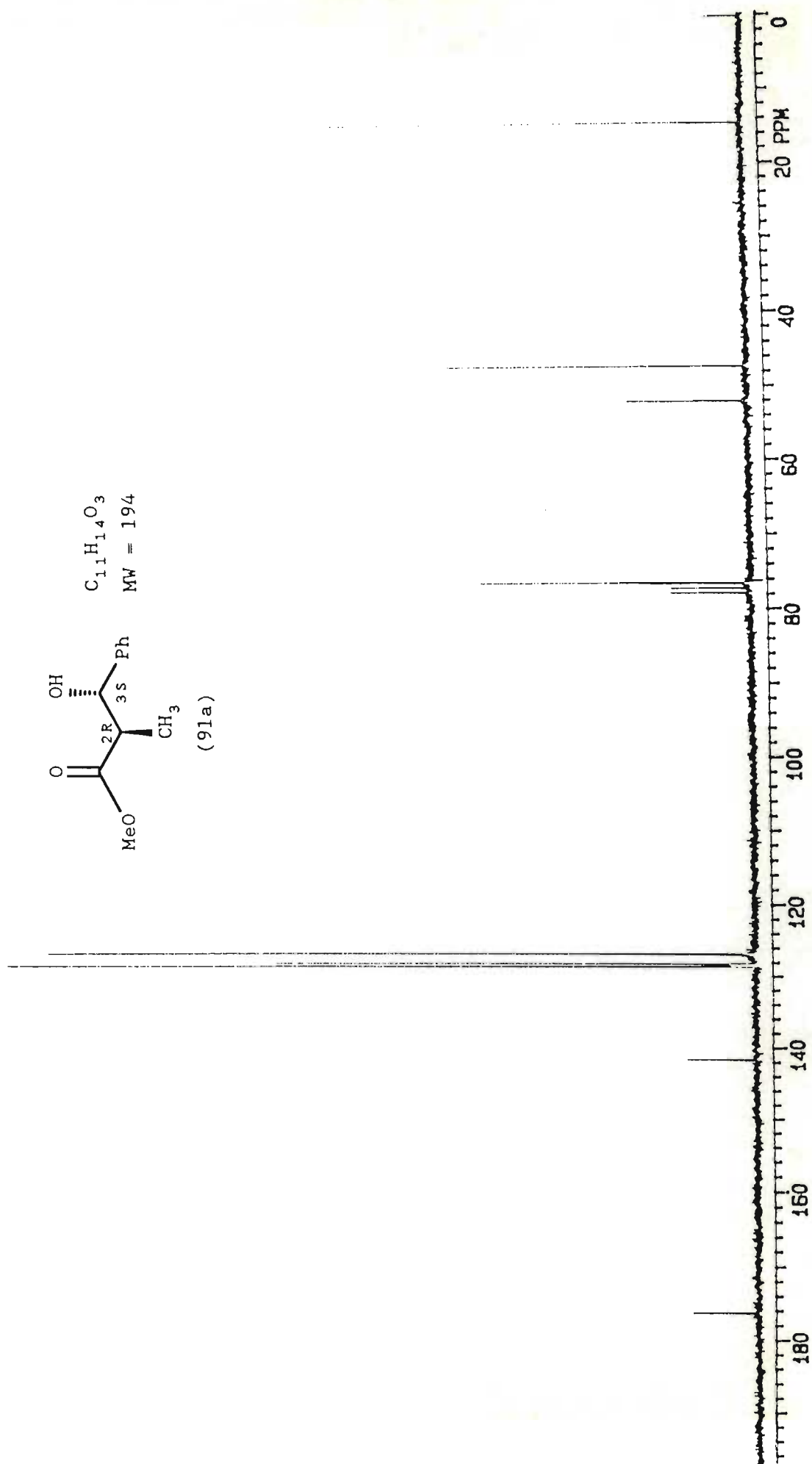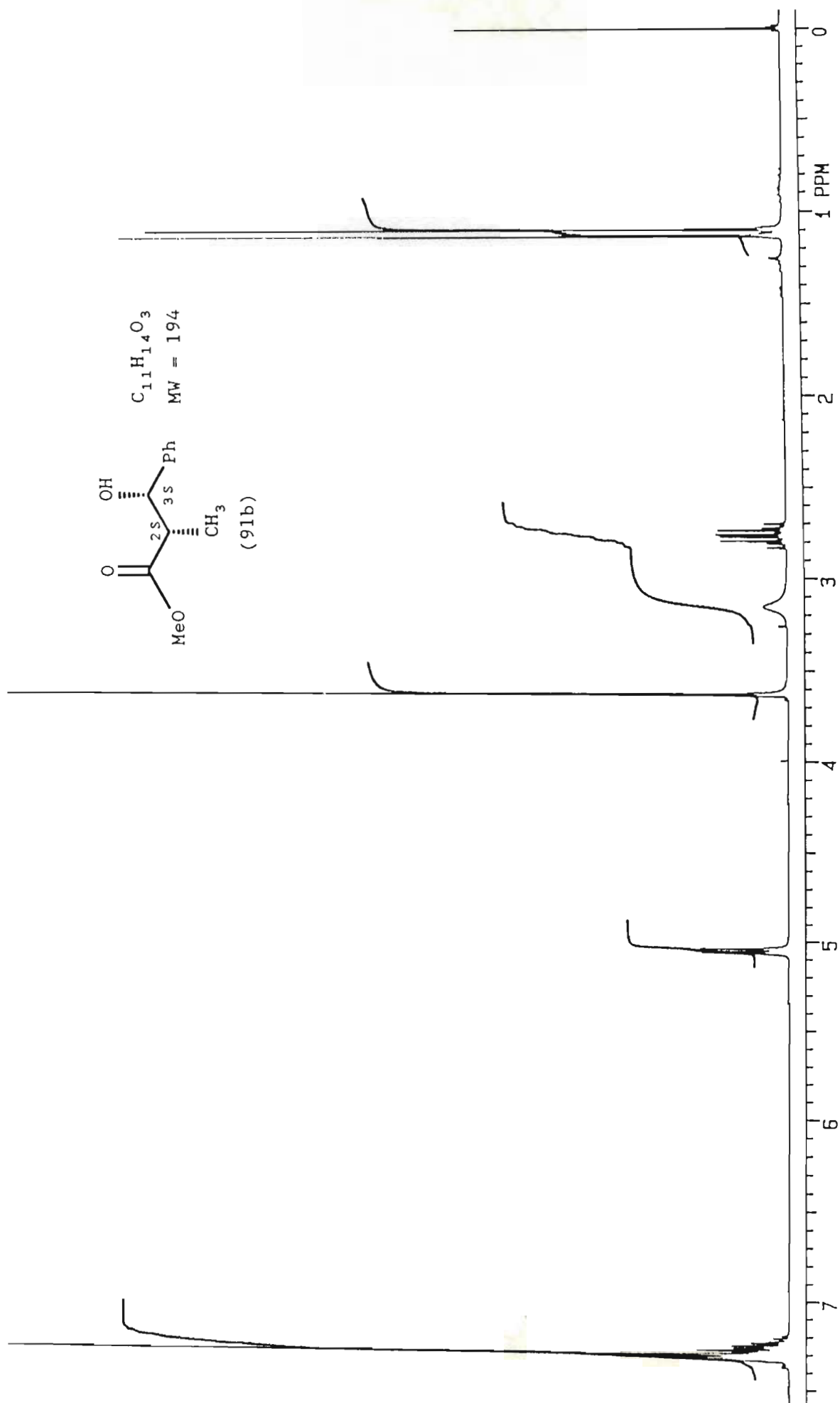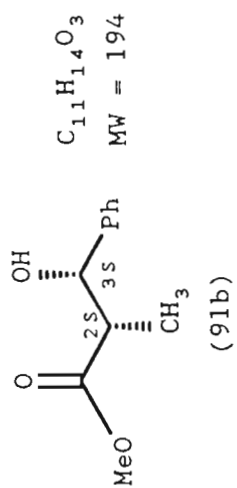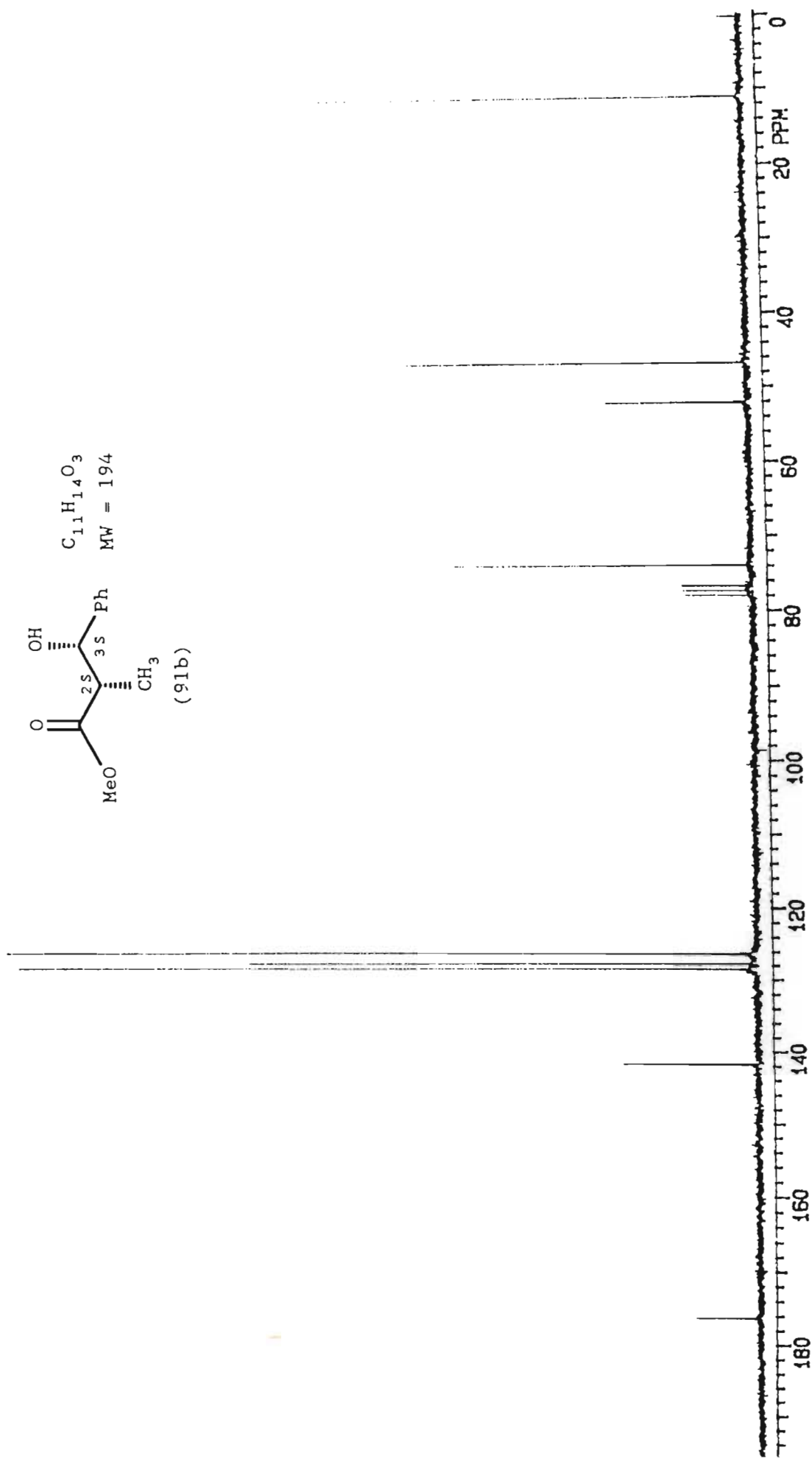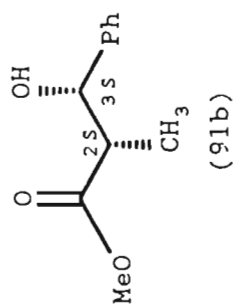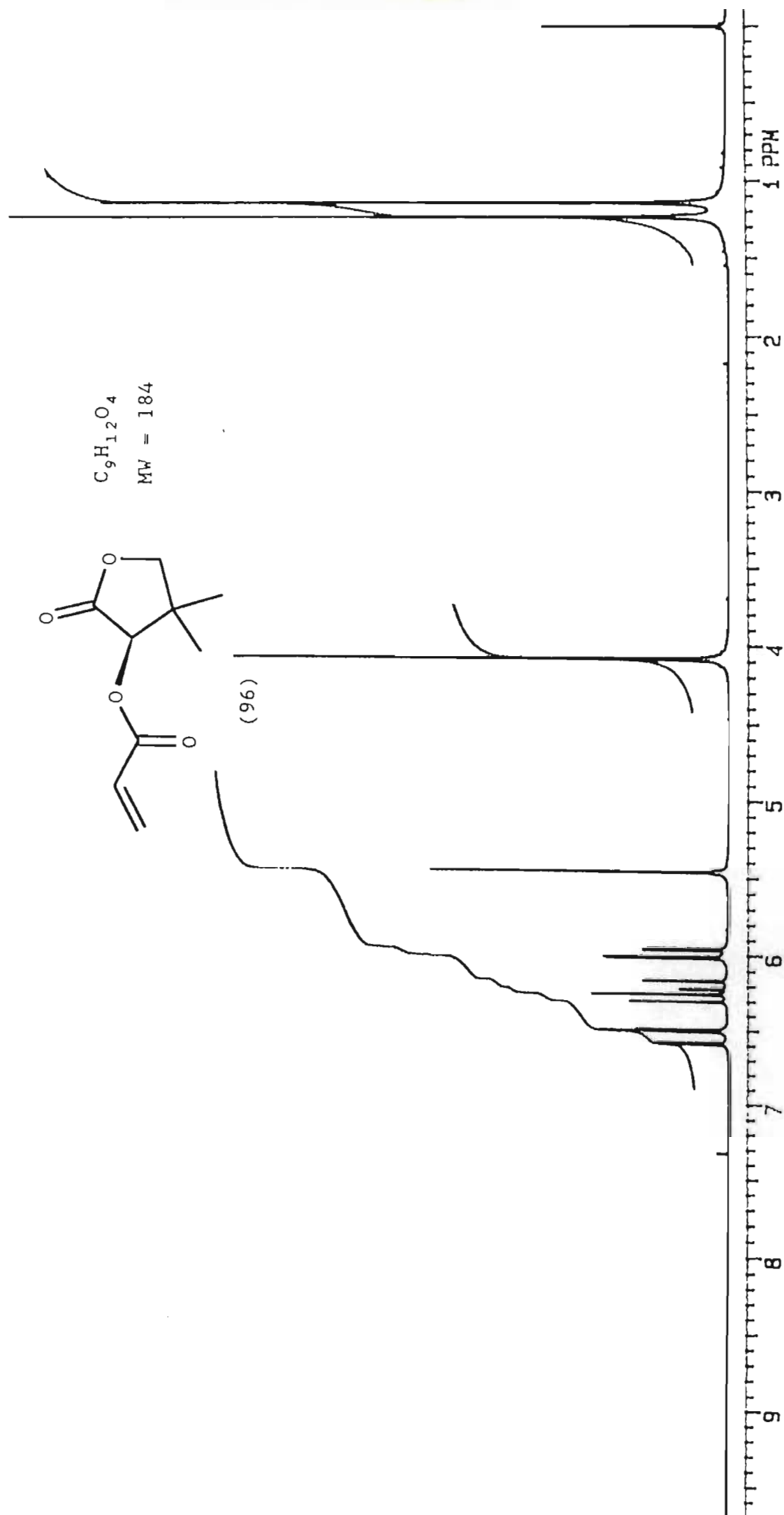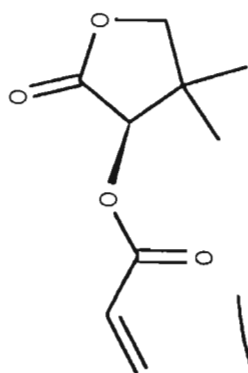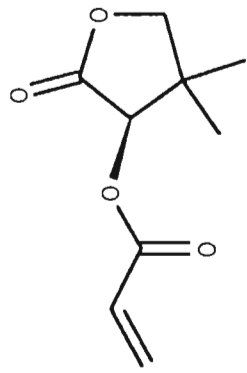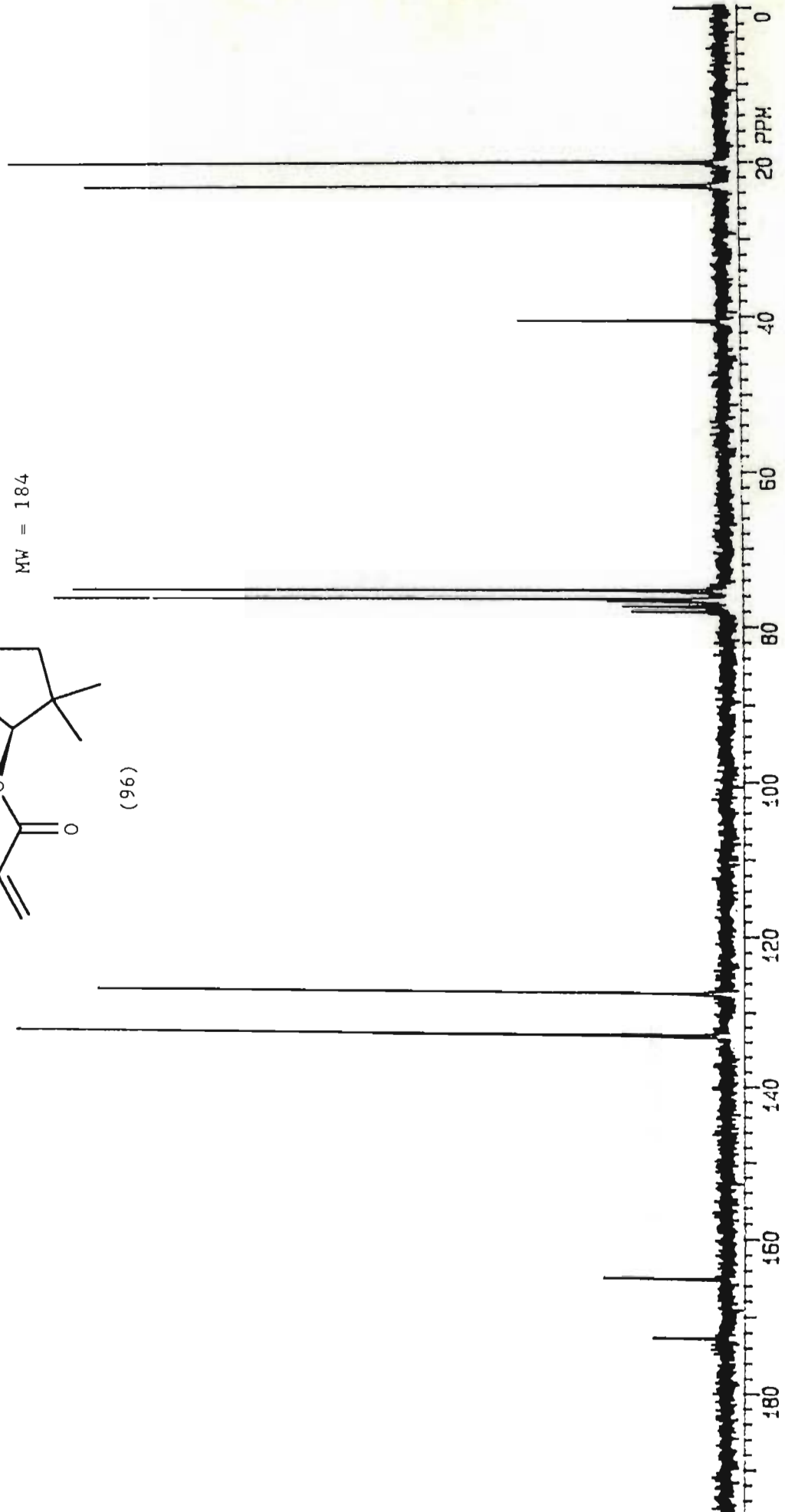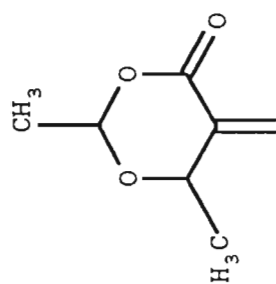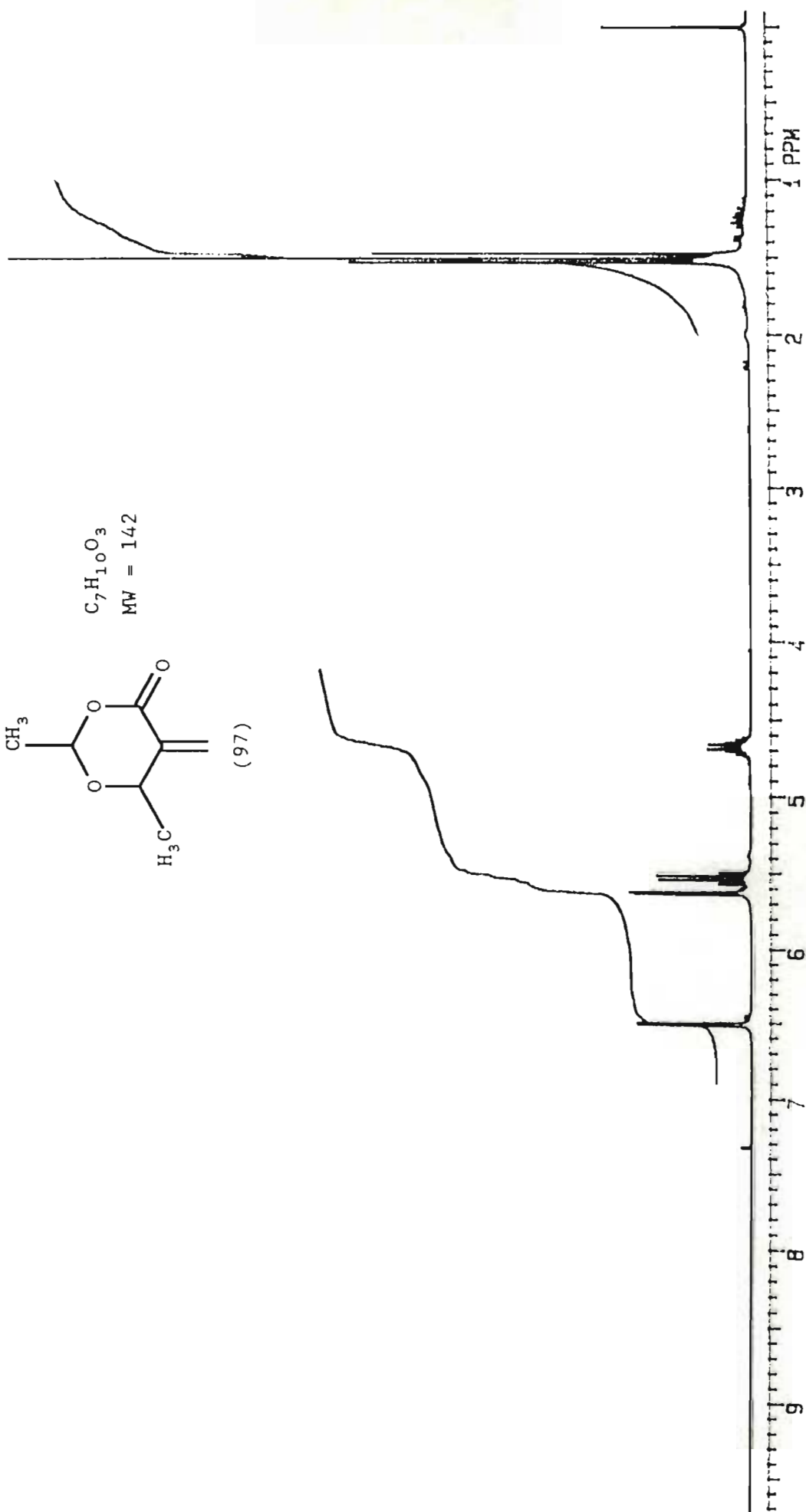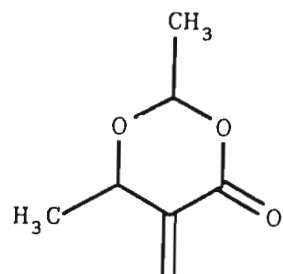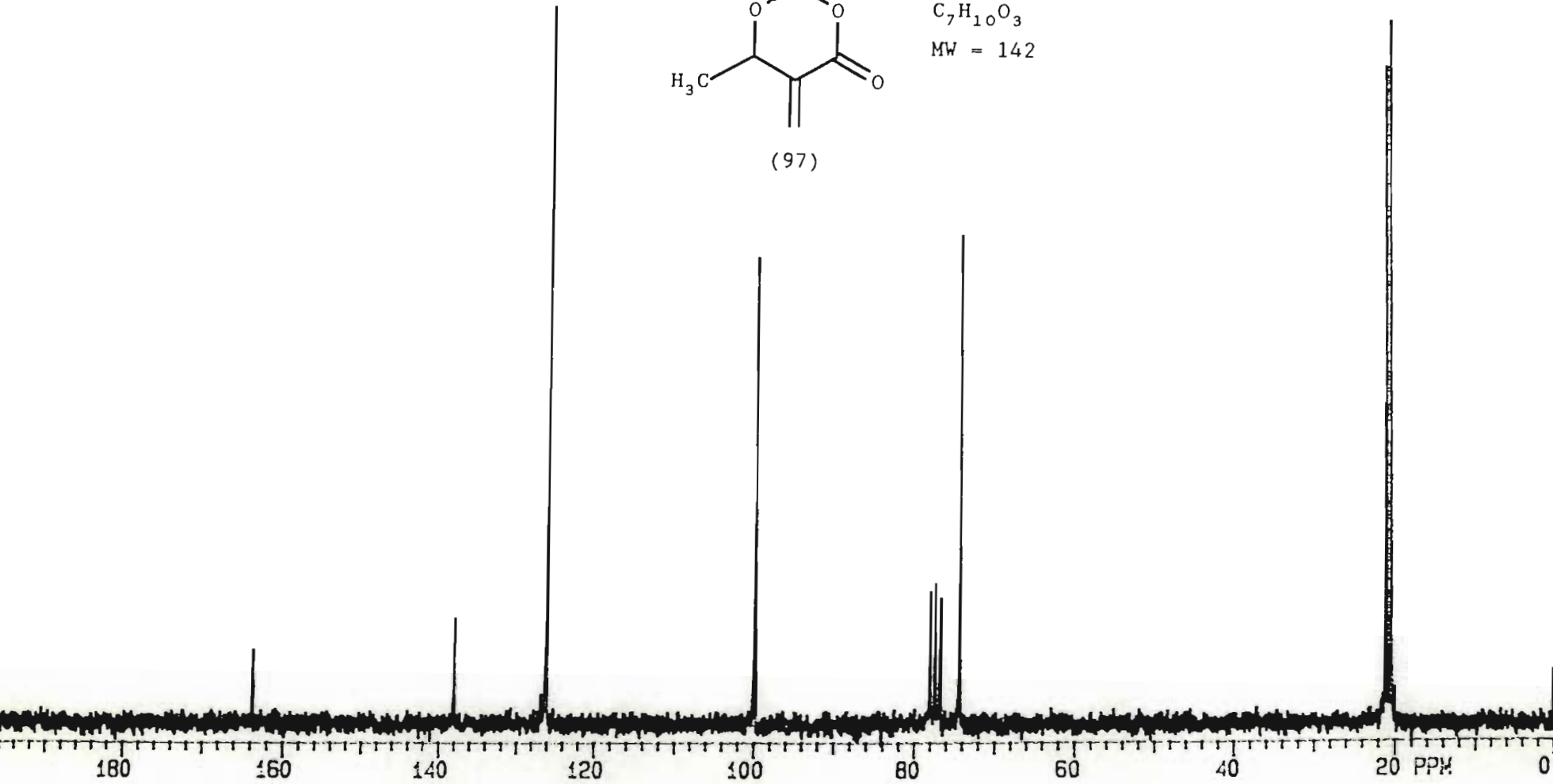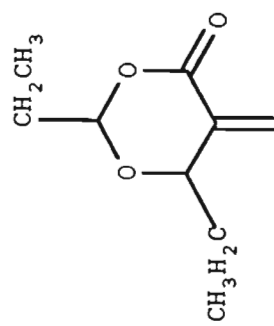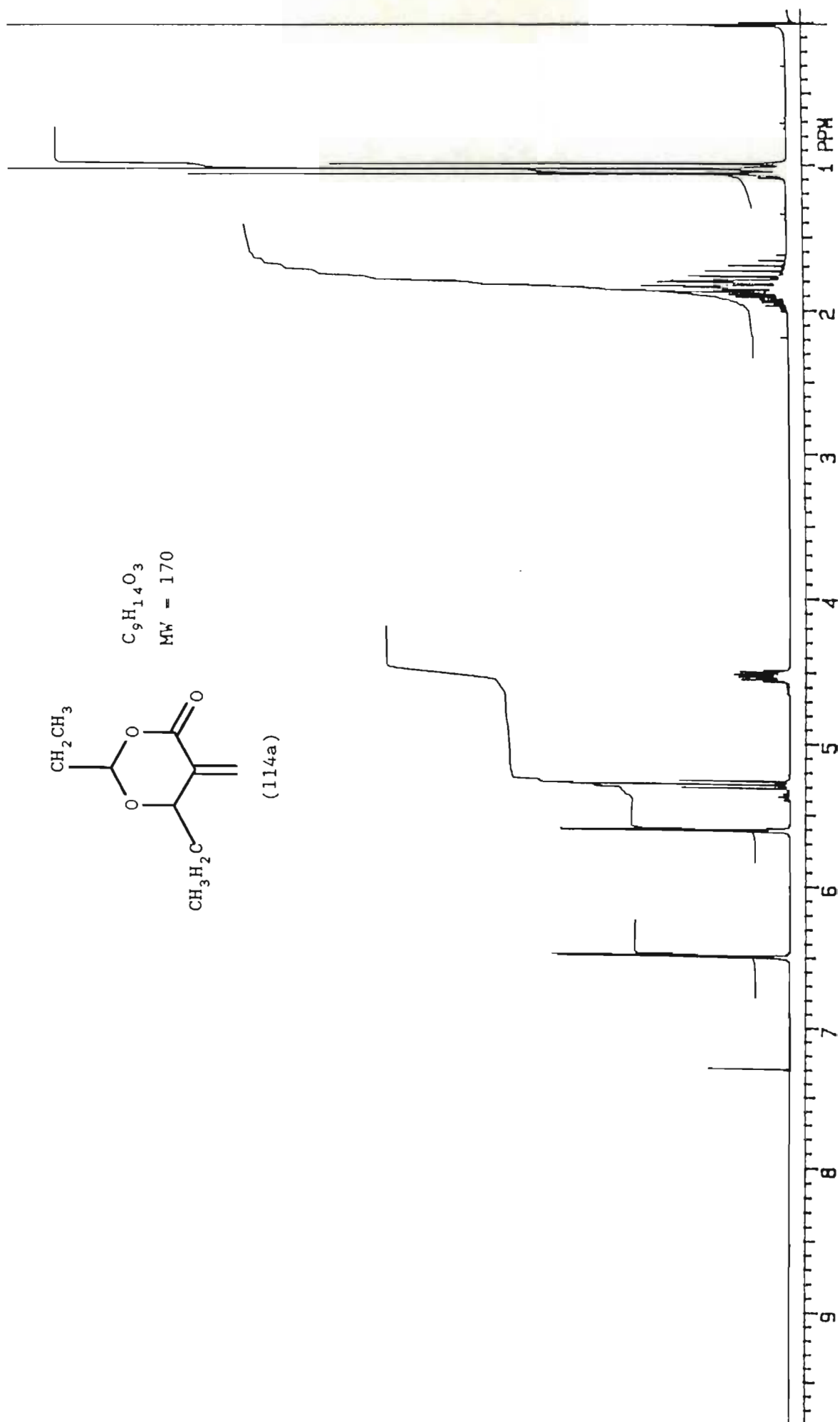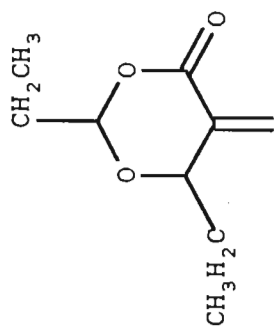
$C_9H_{14}O_3$
MW = 170

(114a)

$C_9H_{14}O_3$
$MW = 170$

(114a)

$C_{11}H_{18}O_3$

MW = 198

(114b)

1 PPM

$C_{11}H_{18}O_3$

MW = 198

(114b)

$C_{13}H_{22}O_3$

MW = 226

(114c)

CH$_2$(CH$_2$)$_2$CH$_3$

CH$_3$(CH$_2$)$_2$H$_2$C

$C_{13}H_{22}O_3$

MW = 226

$CH_2(CH_2)_2CH_3$

$CH_3(CH_2)_2H_2C$
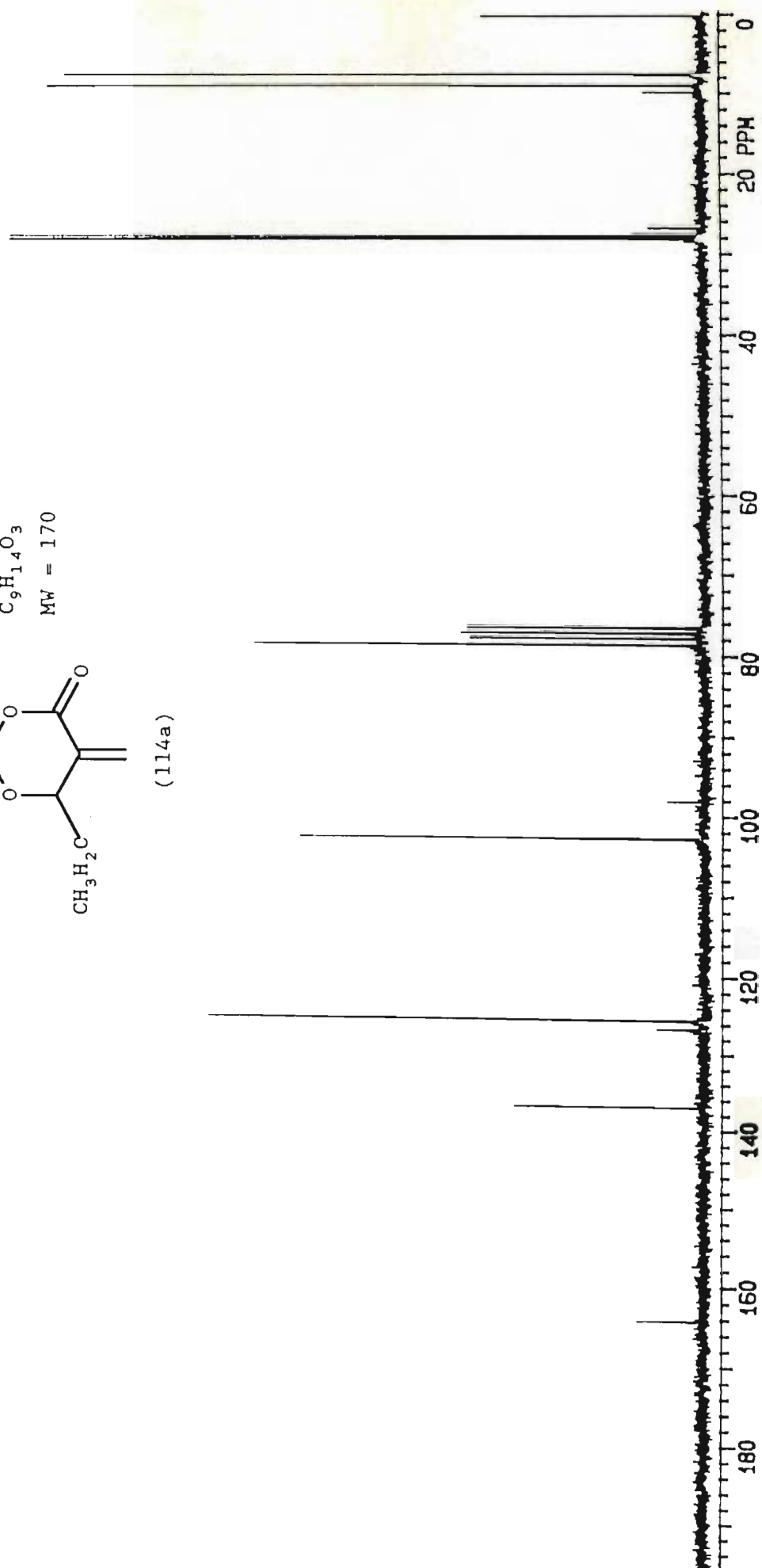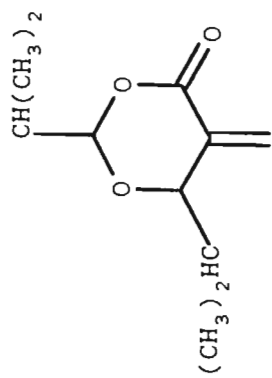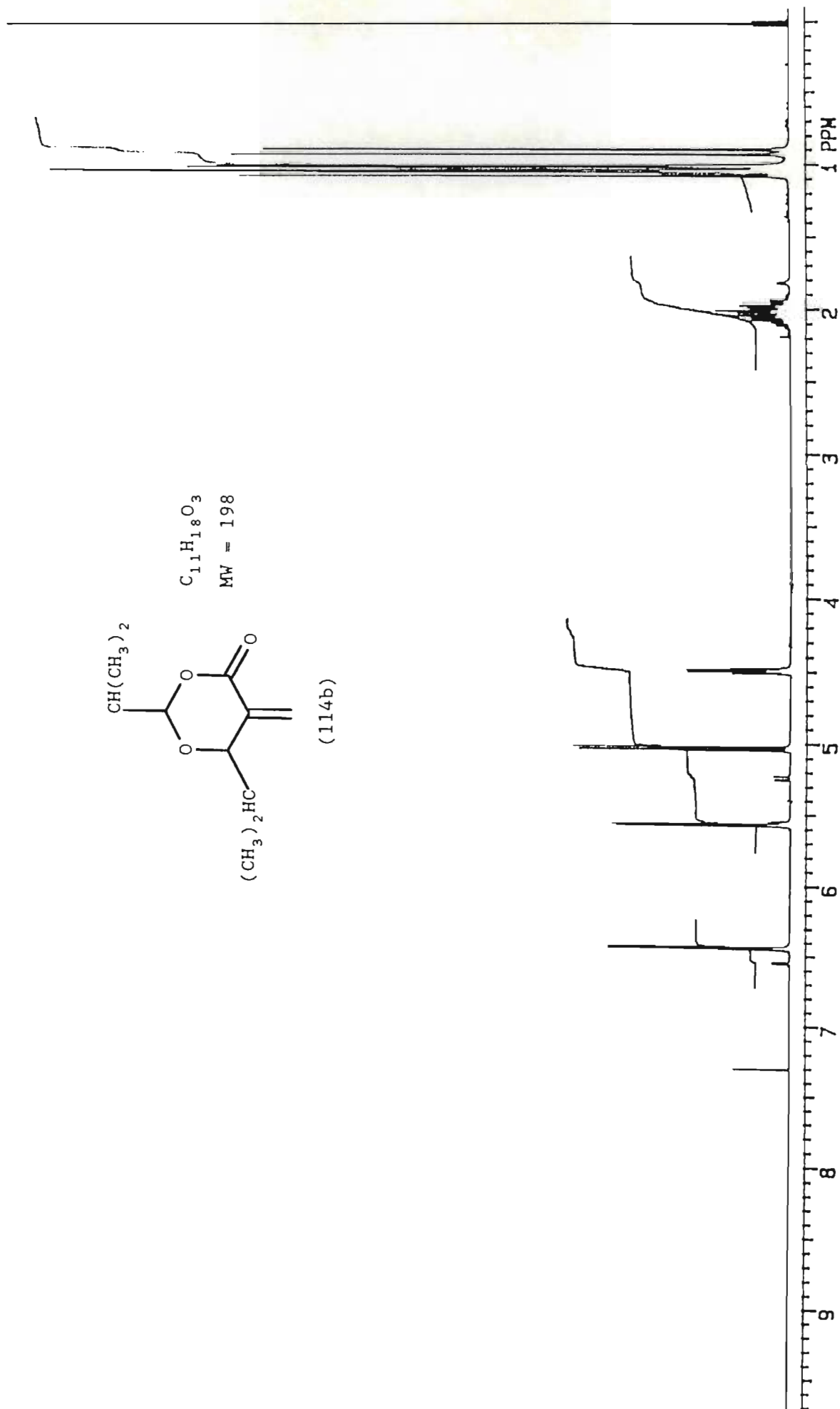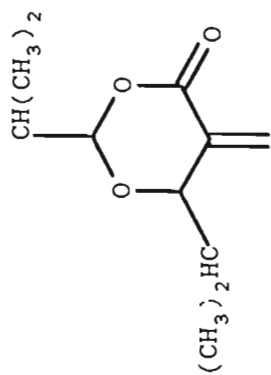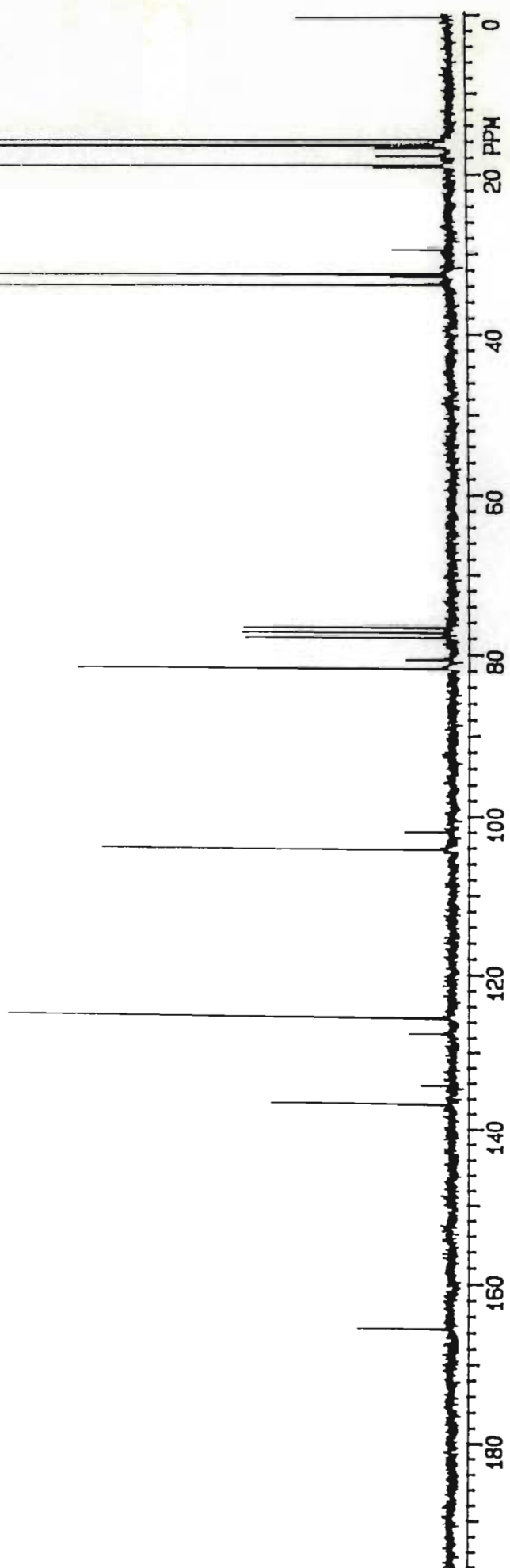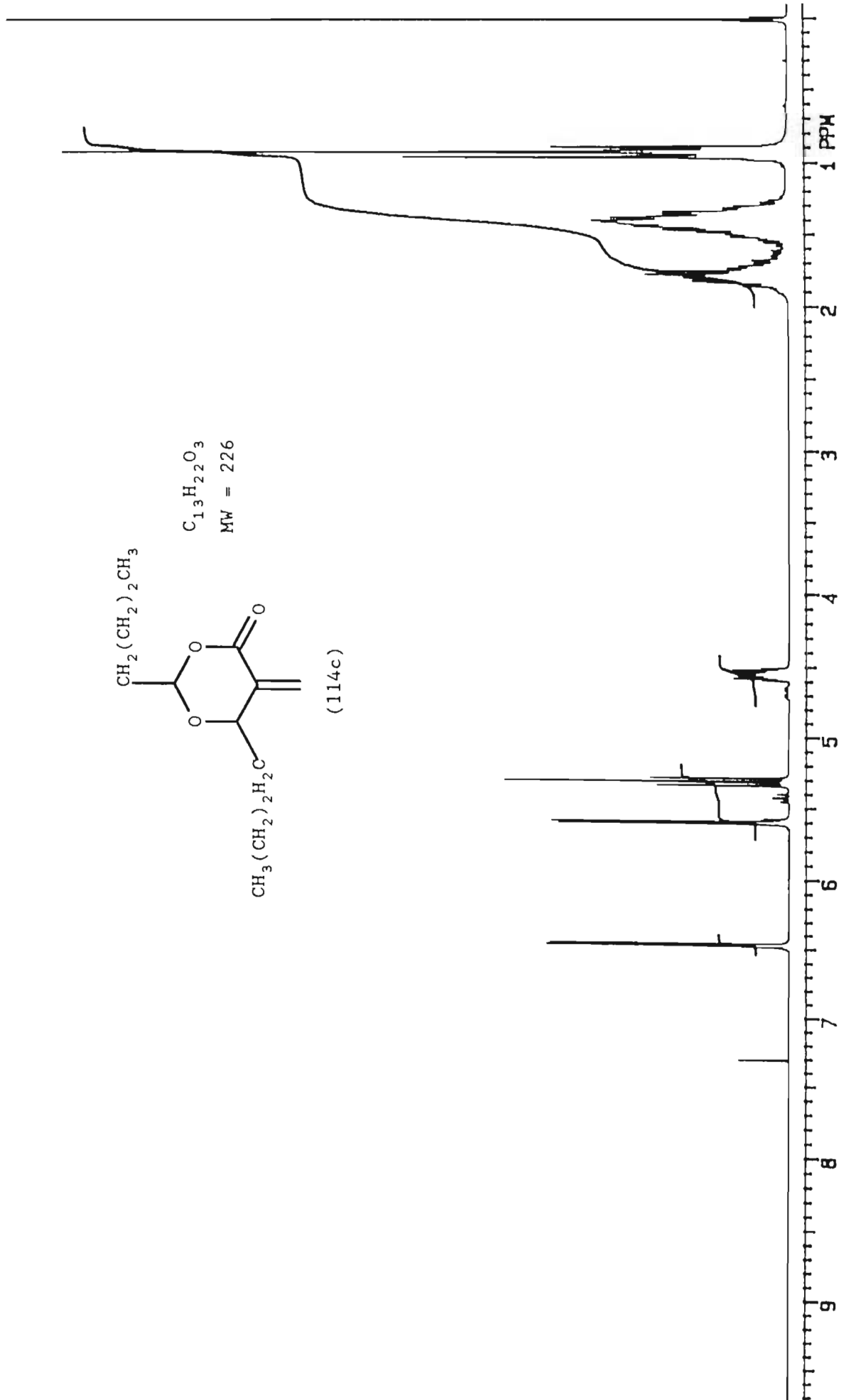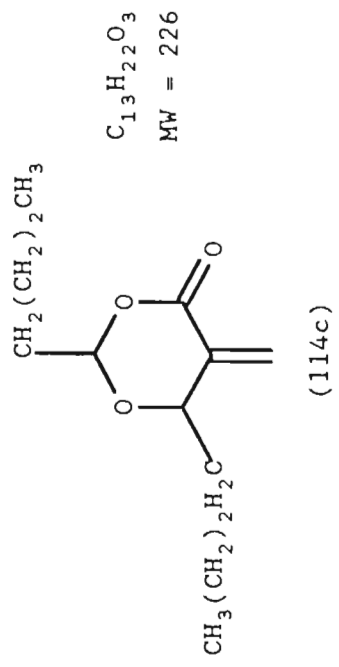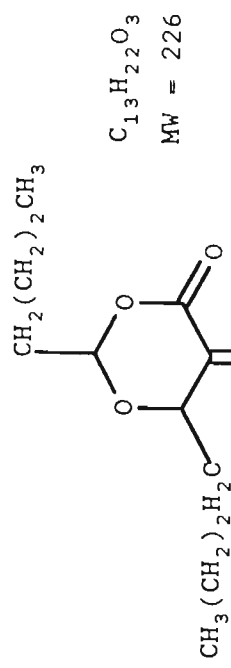
(114c)

$C_{17}H_{26}O_3$
MW = 278

(117)

1 PPM
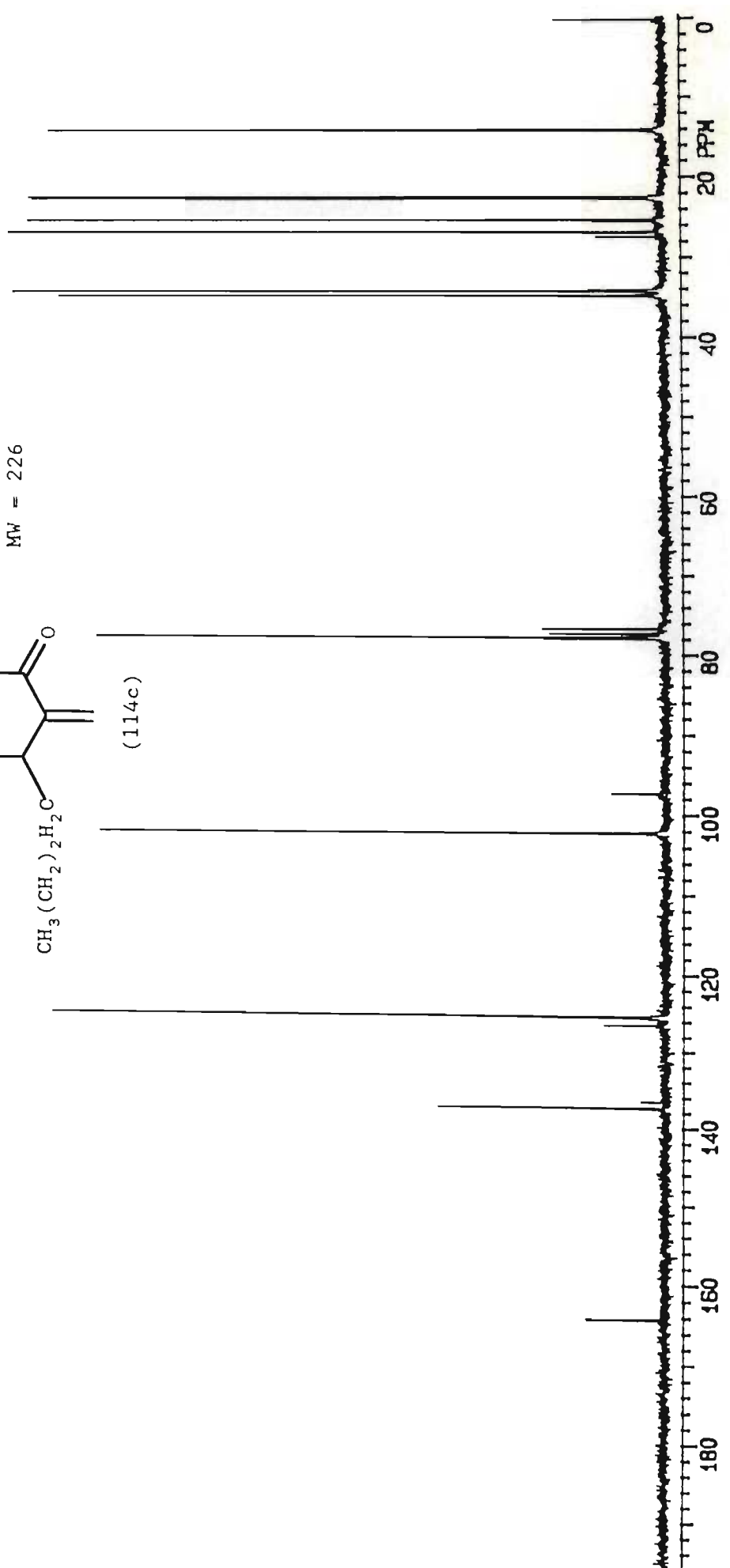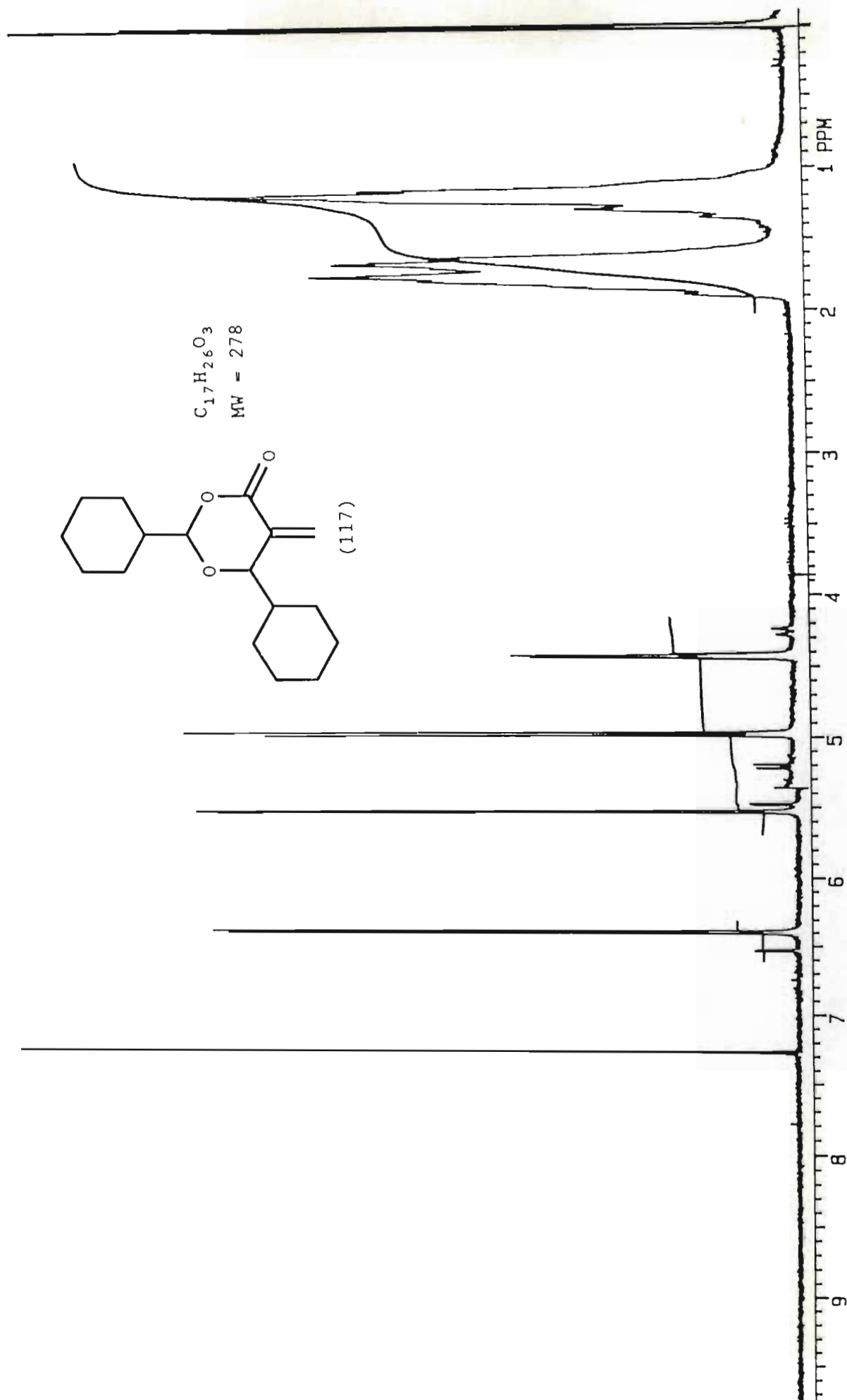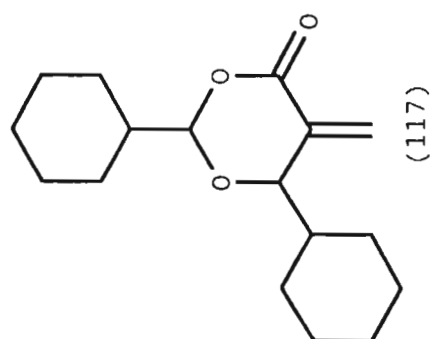
$C_{17}H_{26}O_3$
MW = 278

(117)

$C_{16}H_{18}O_5$
$MW = 290$

(116)

$C_{22}H_{38}O_3$

MW = 350
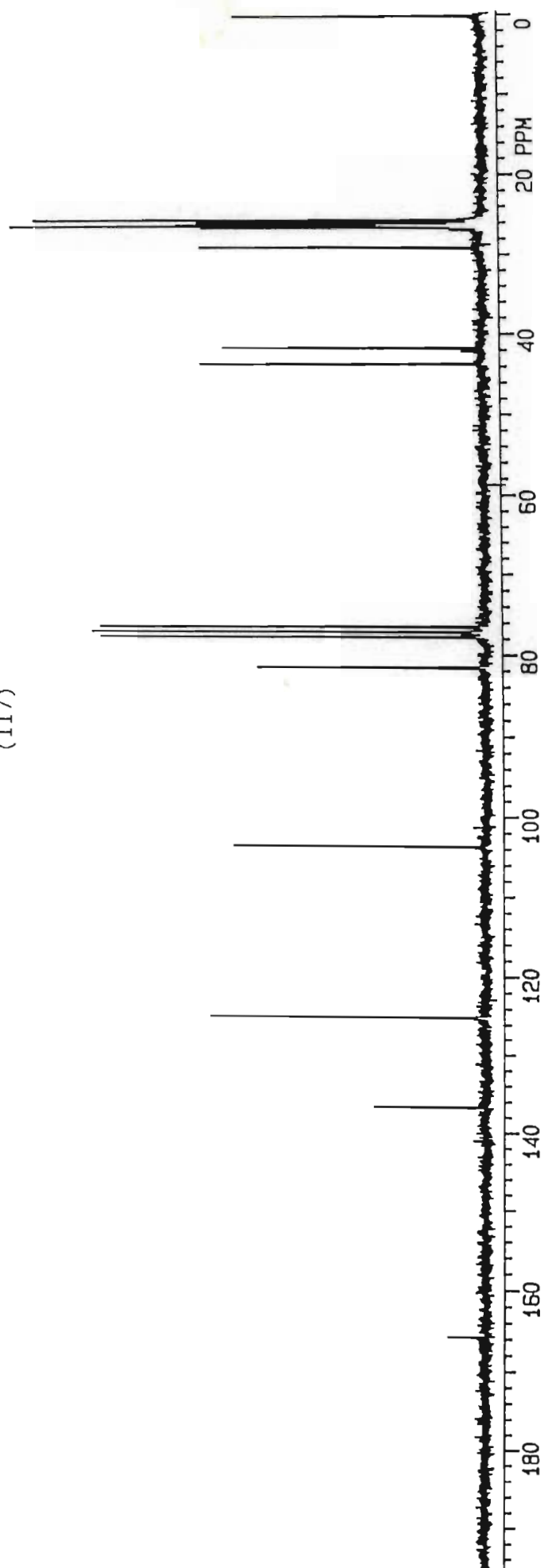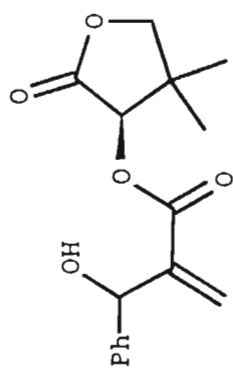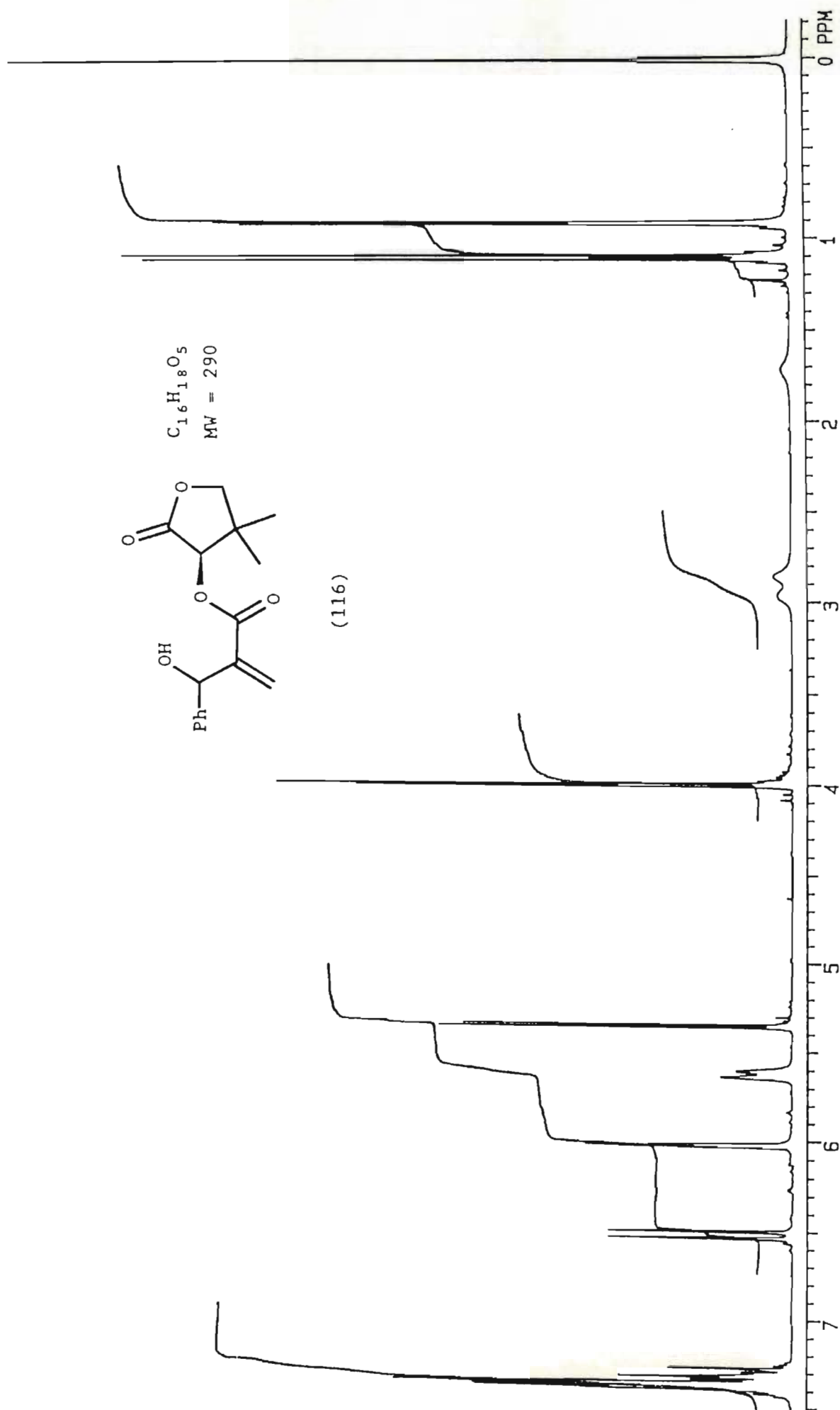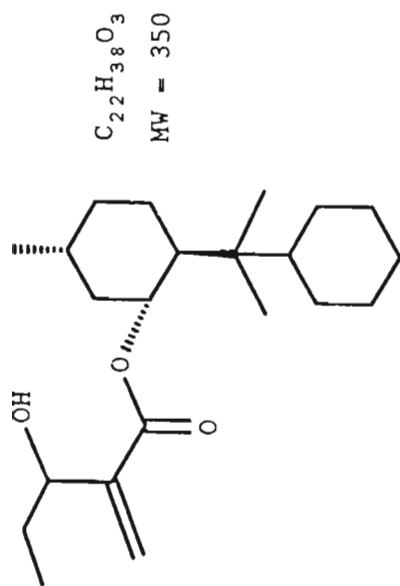
(147b)
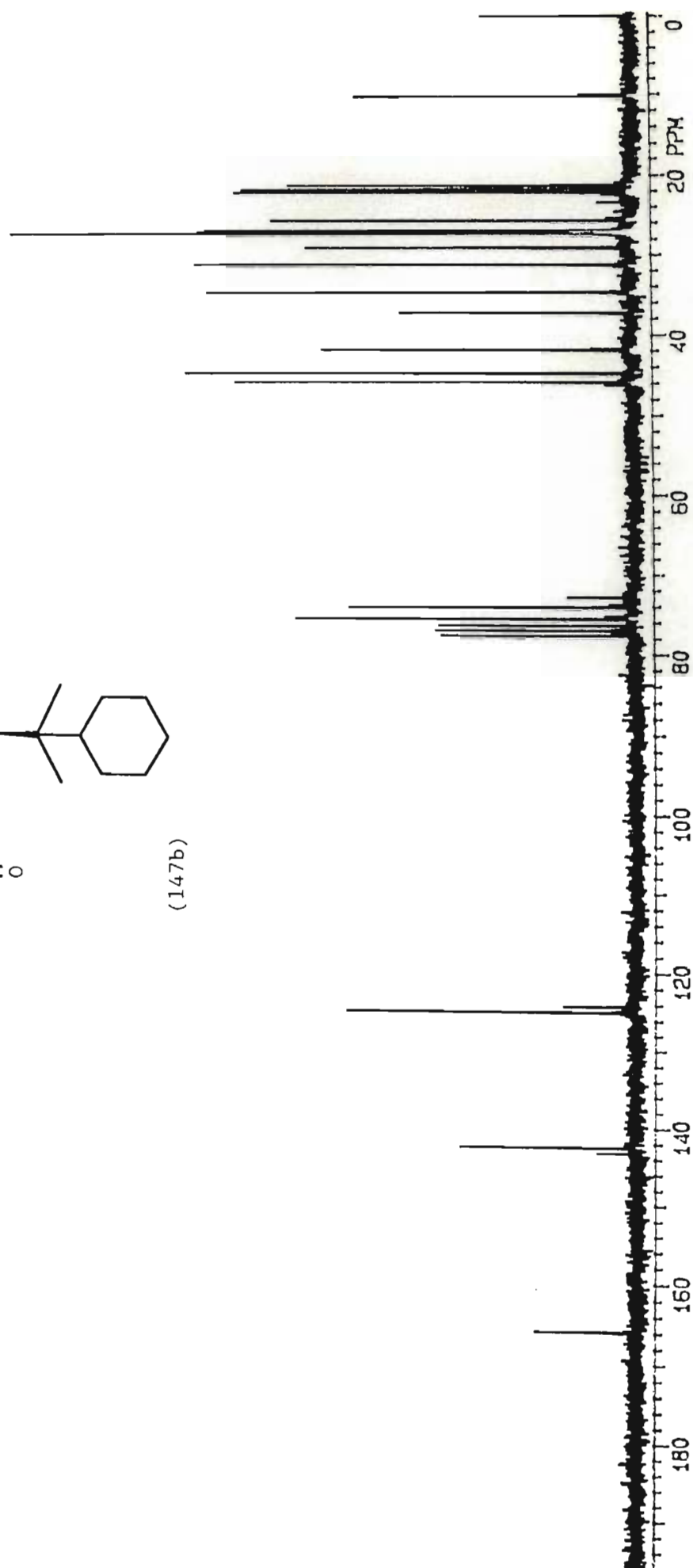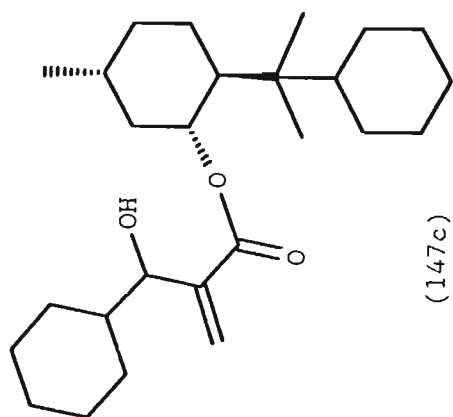
$C_{26}H_{44}O_3$
MW = 404

(147c)

$C_{26}H_{44}O_3$

$MW = 404$

(147c)

$C_{26}H_{37}NO_3$

MW = 443

(147d)

$C_{16}H_{18}O_5$

MW = 290

(116)

$C_{11}H_{13}Cl_3O_5$

MW = 331

(119)
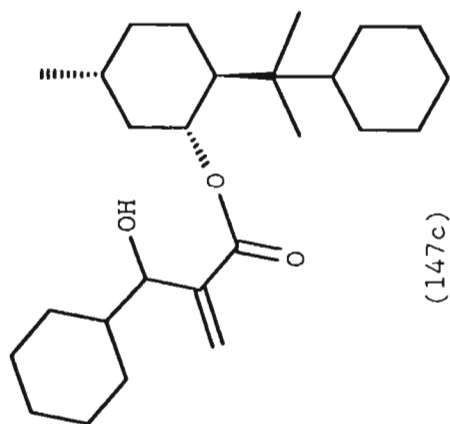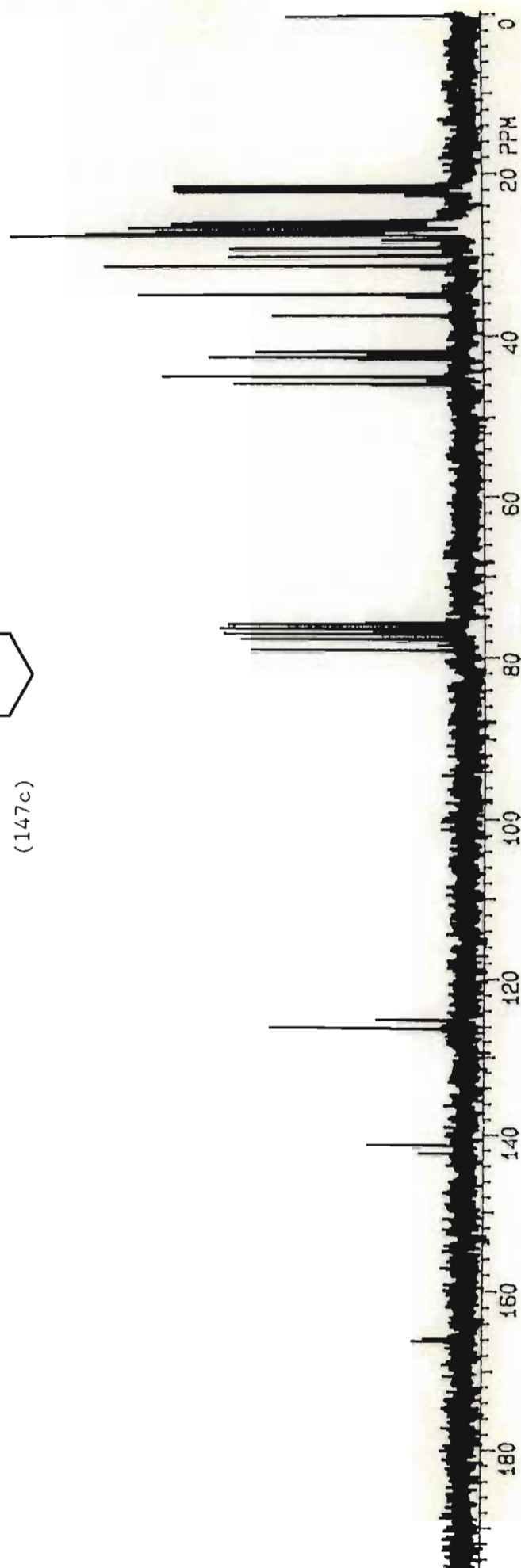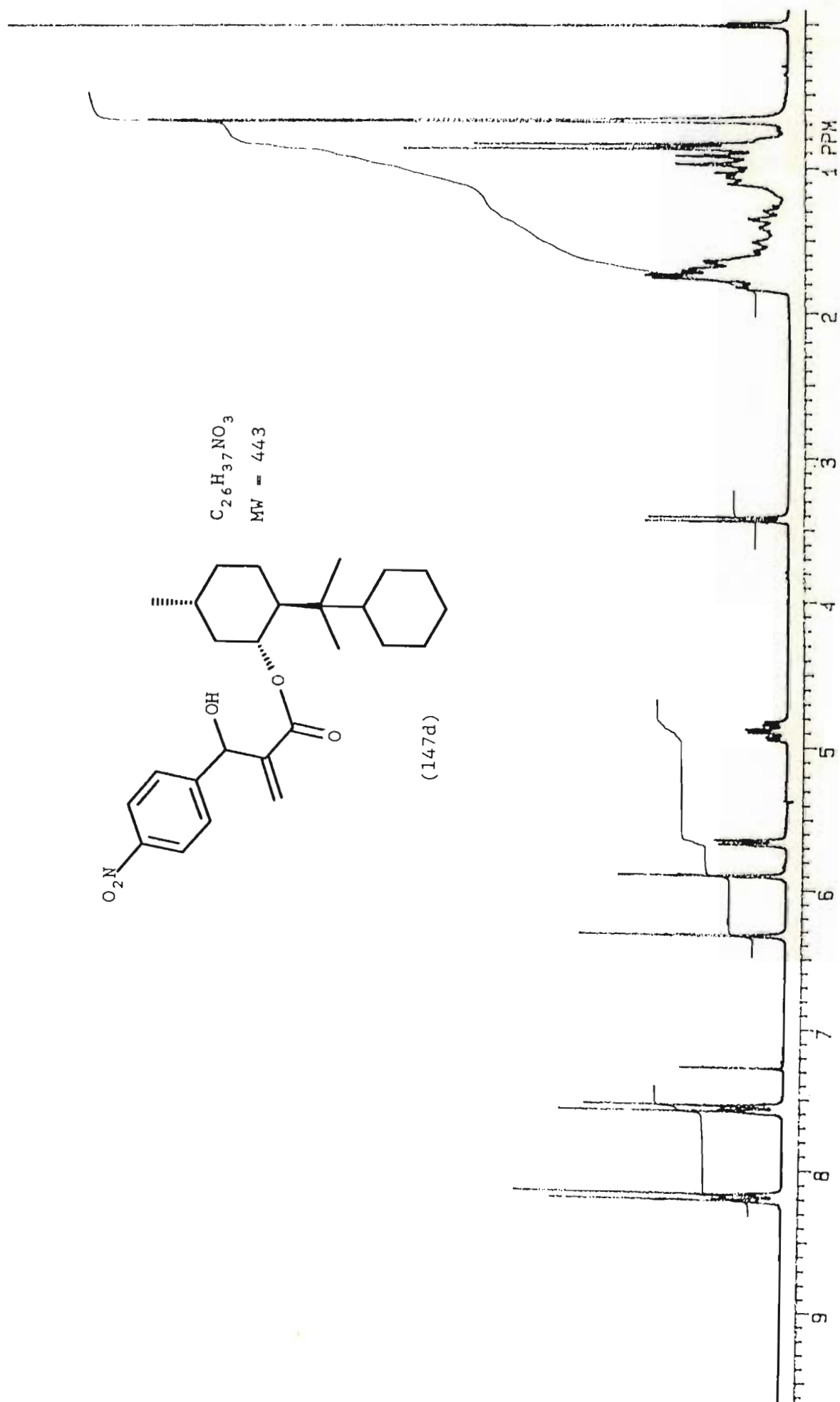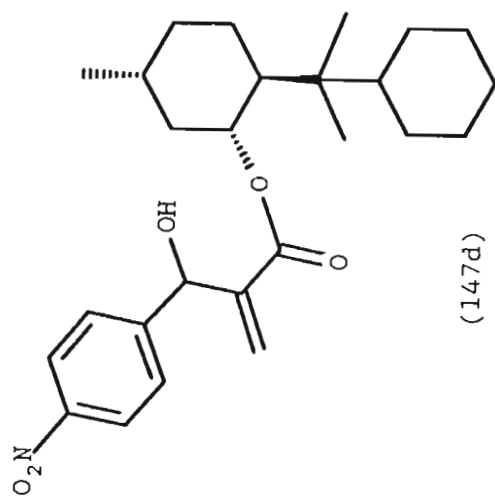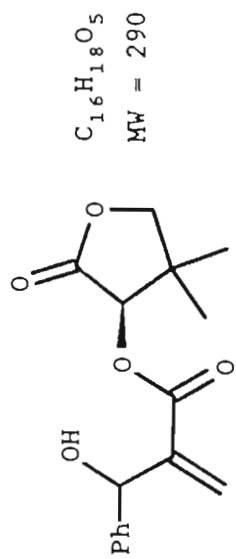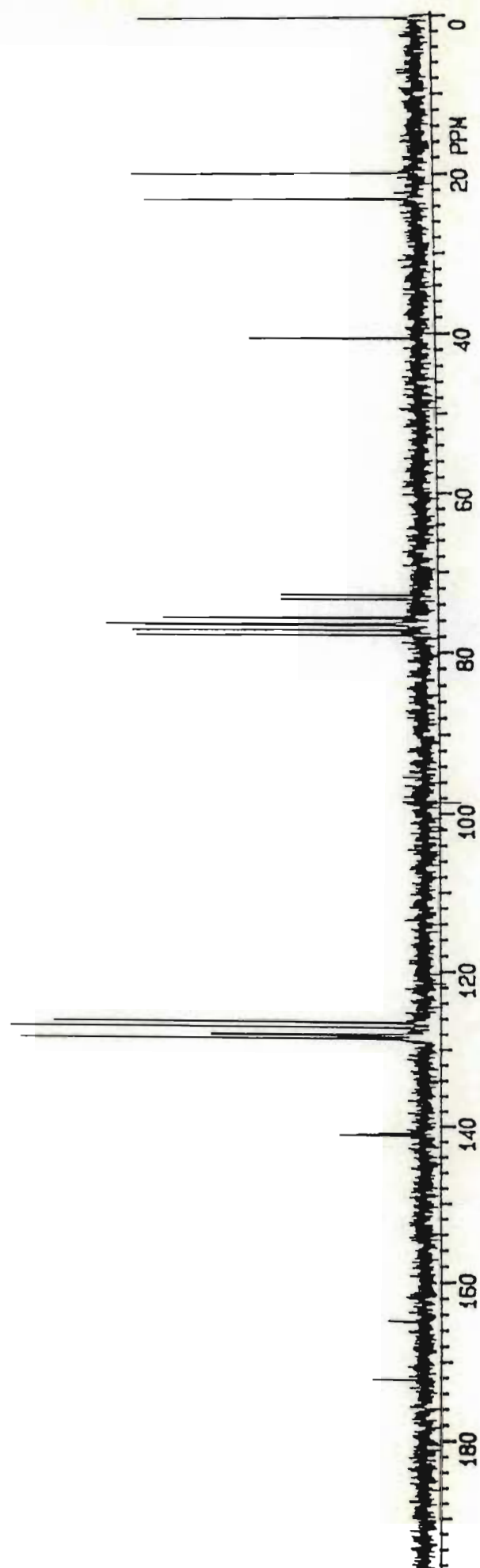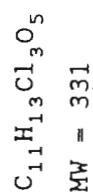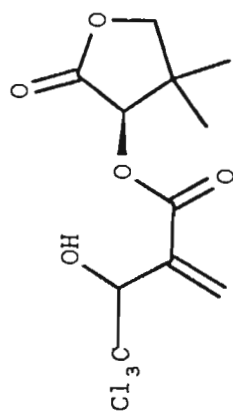
$C_{11}H_{13}Cl_3O_5$

MW = 331

(119)
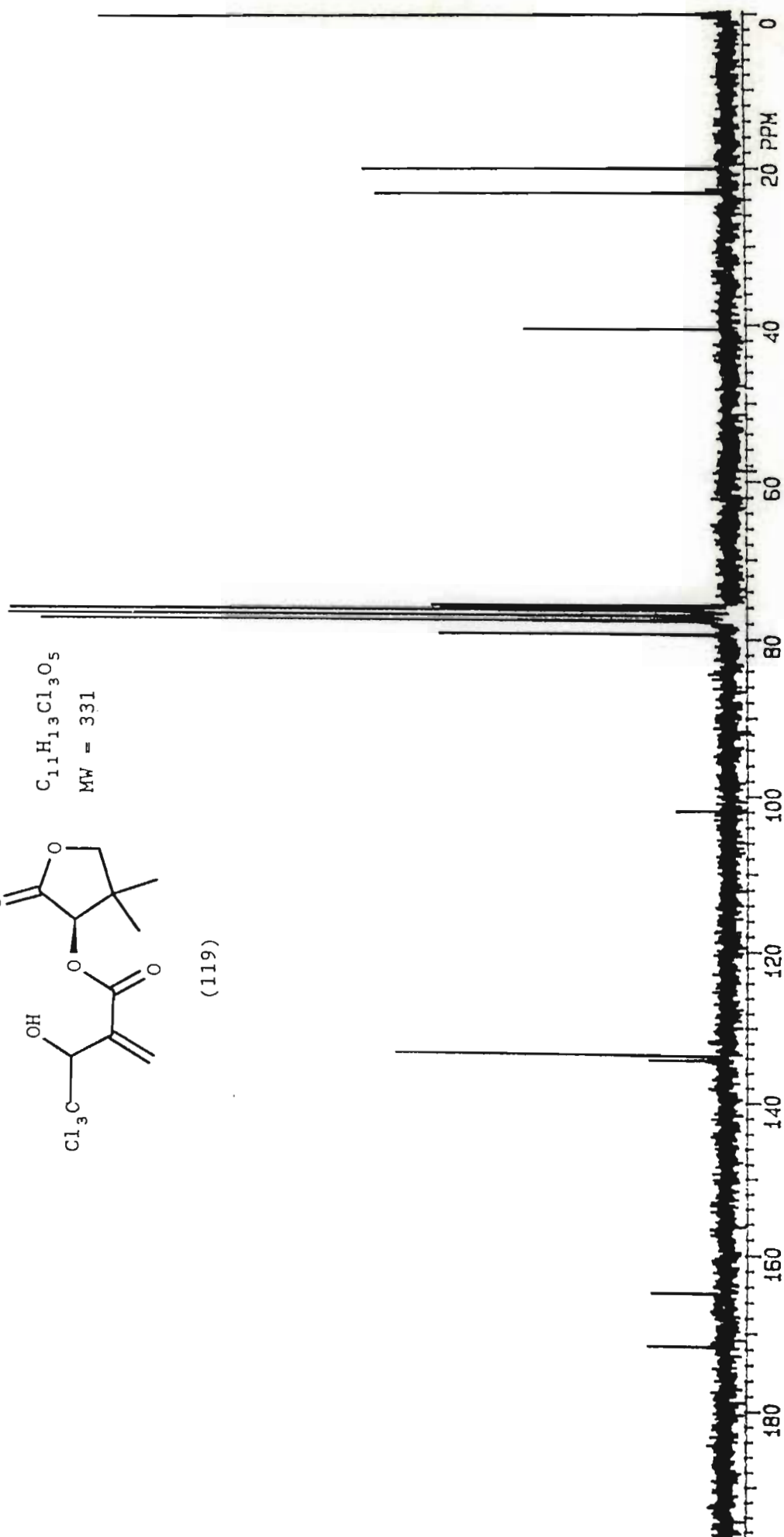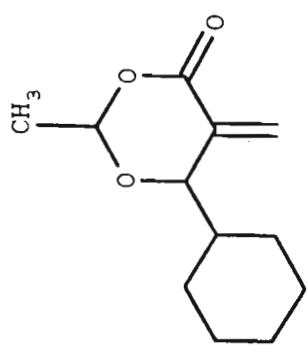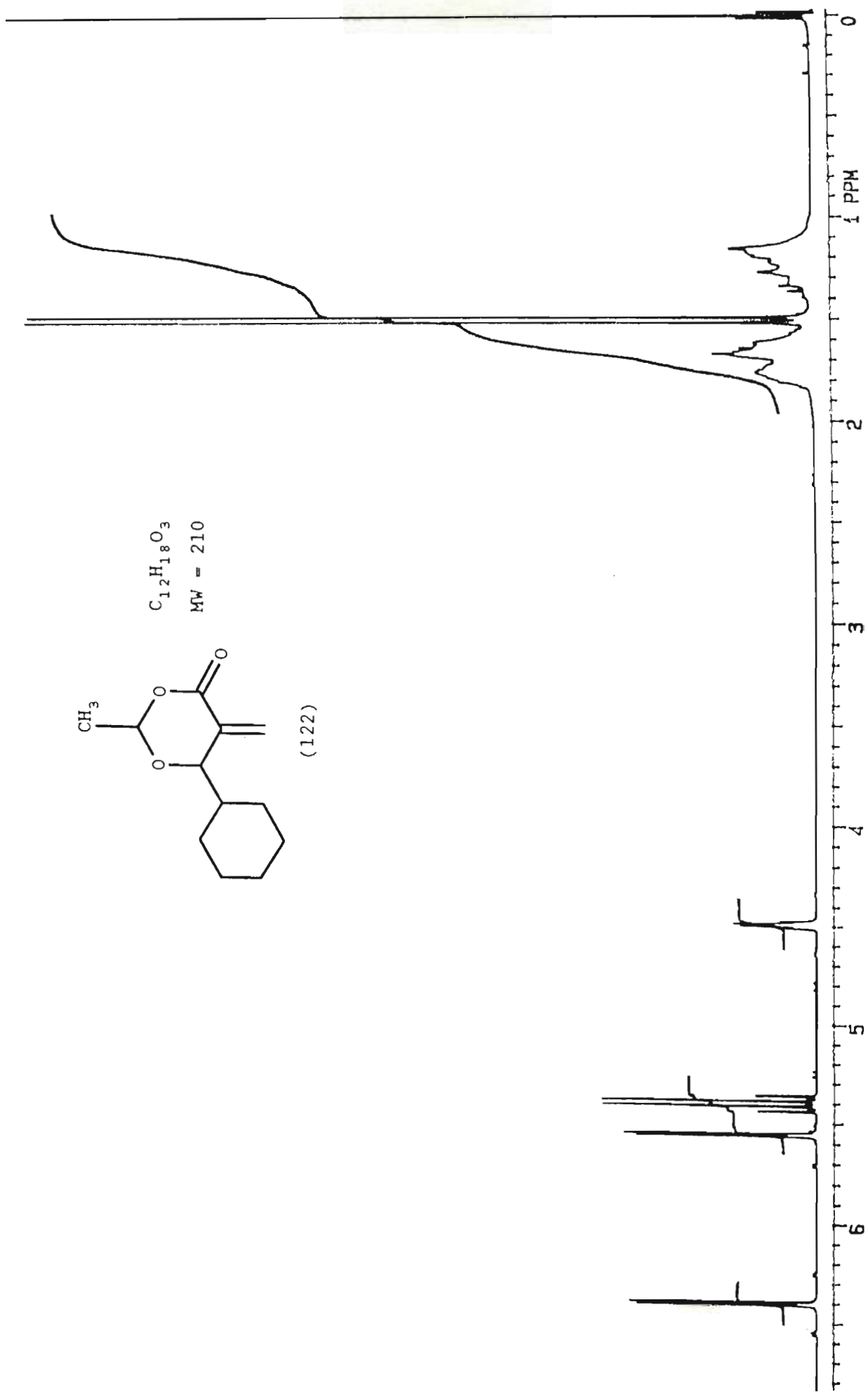
$C_{12}H_{18}O_3$

MW = 210

(122)
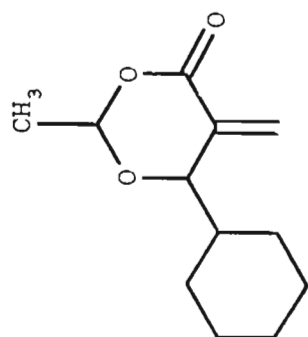
$C_{12}H_{18}O_3$

$MW = 210$

(122)
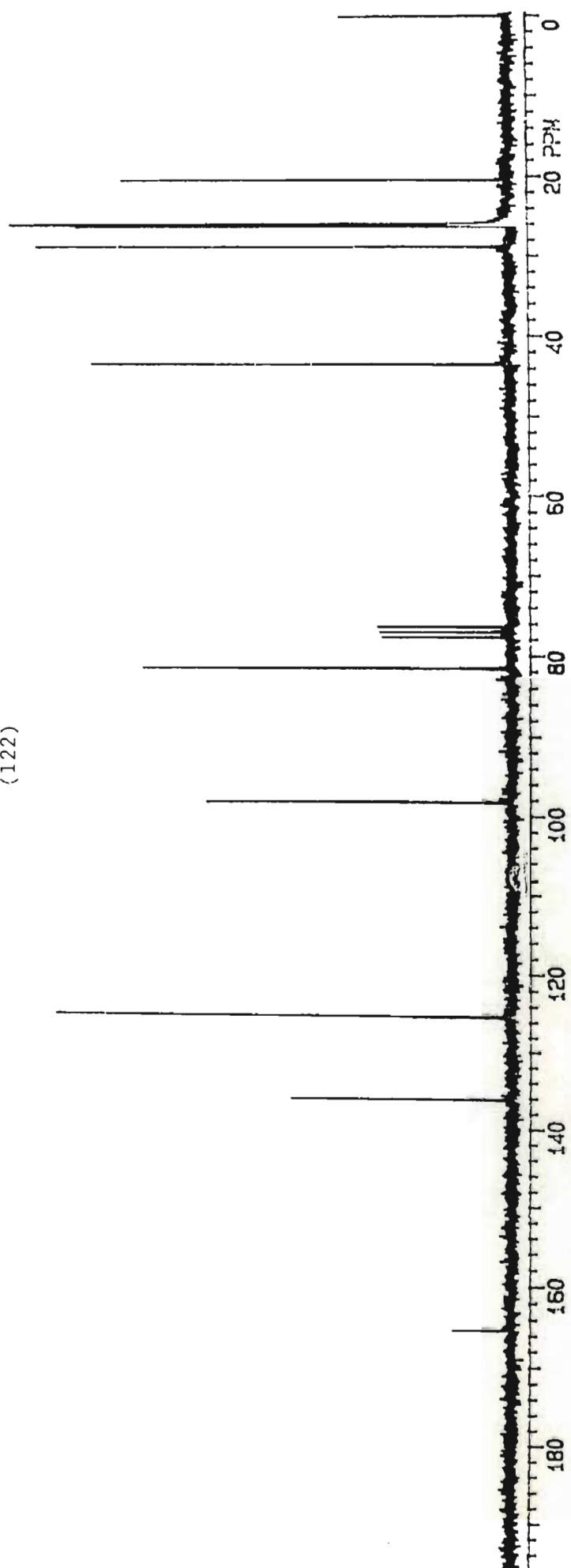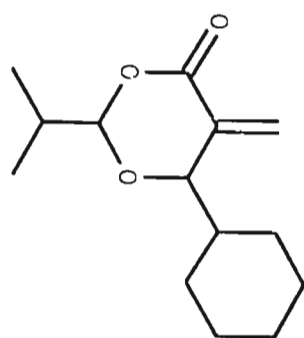
$C_{14}H_{22}O_3$

MW = 238

(123)
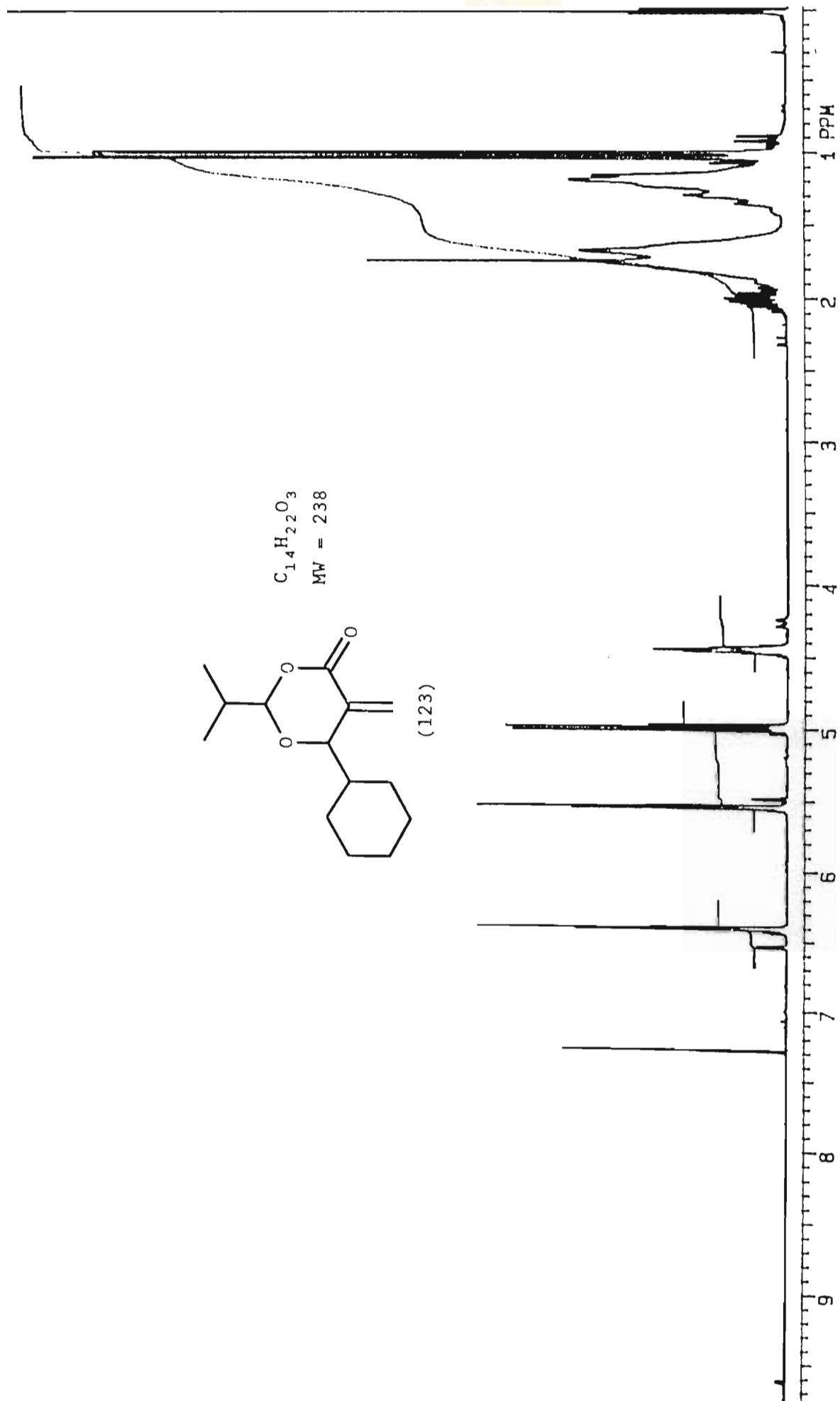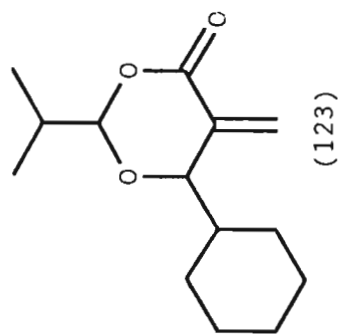
$C_{14}H_{22}O_3$
MW = 238
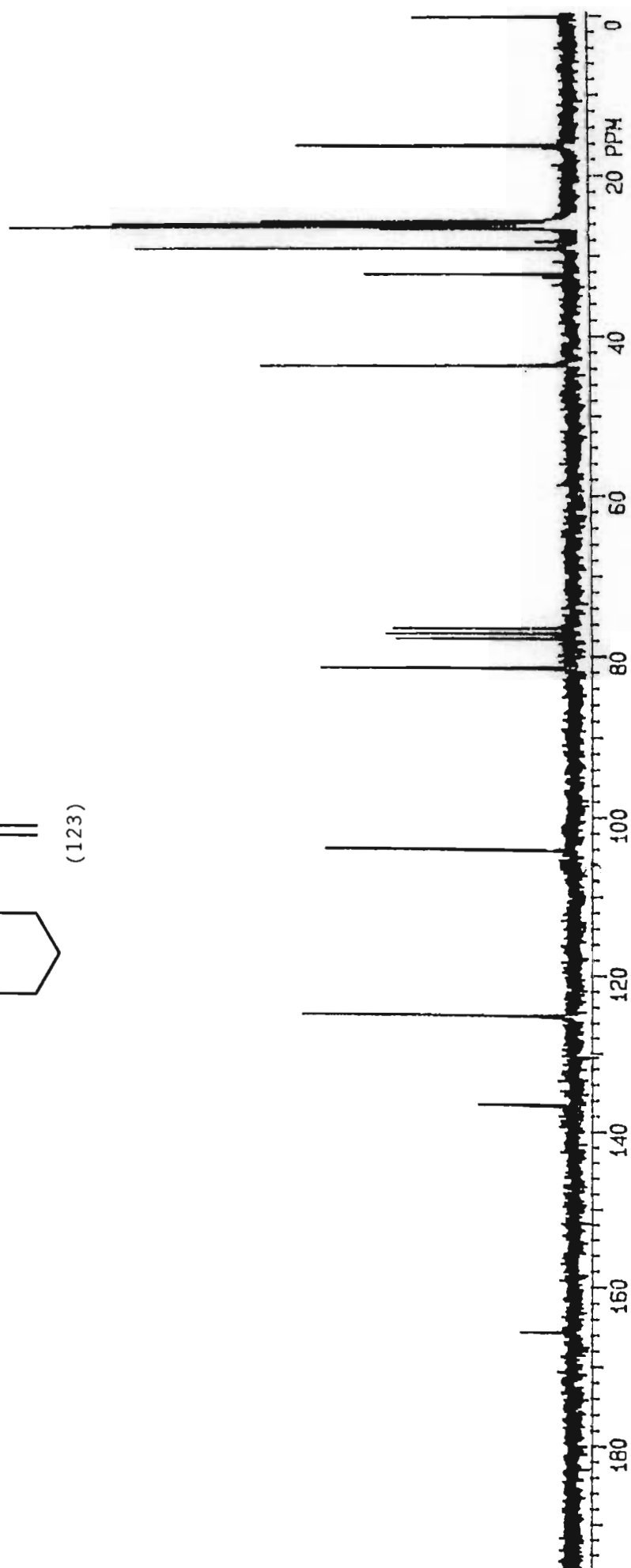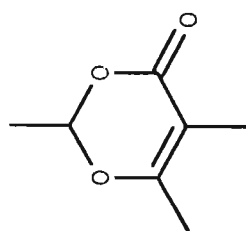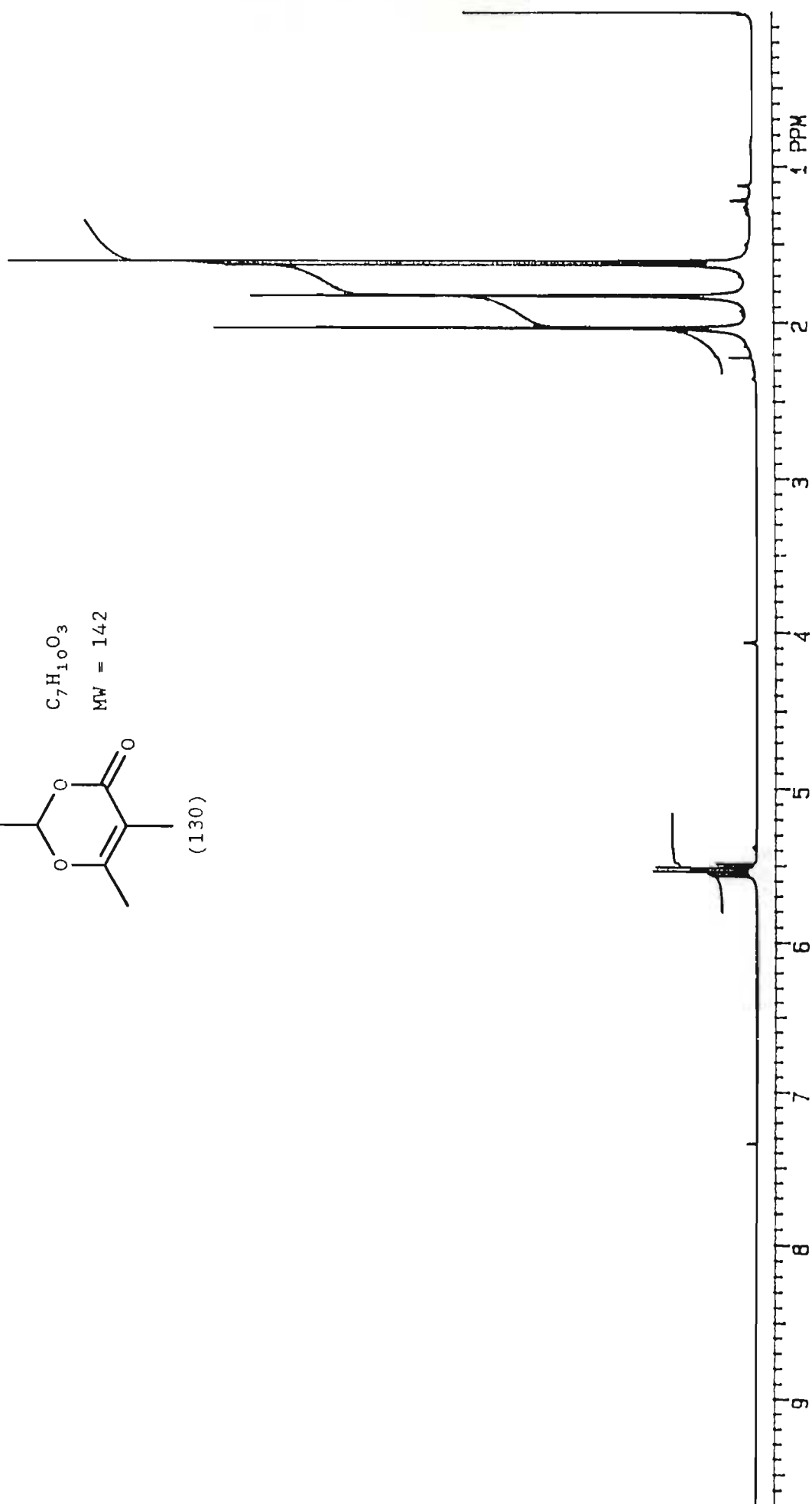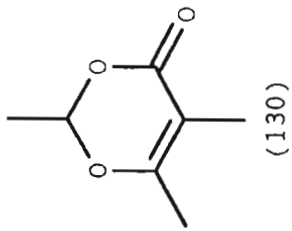
(123)

$C_7H_{10}O_3$

MW = 142

(130)

PPM

$C_7H_{10}O_3$

MW = 142

(130)

$C_{11}H_{18}O_3$

MW = 198

(132)

$C_{11}H_{18}O_3$

MW = 198

(132)

$C_{17}H_{26}O_3$
MW = 278

(133)

$C_{17}H_{26}O_3$
MW = 278

(133)

$C_5H_8O_3$

$MW = 116$

(137a)

$C_5H_8O_3$

MW = 116
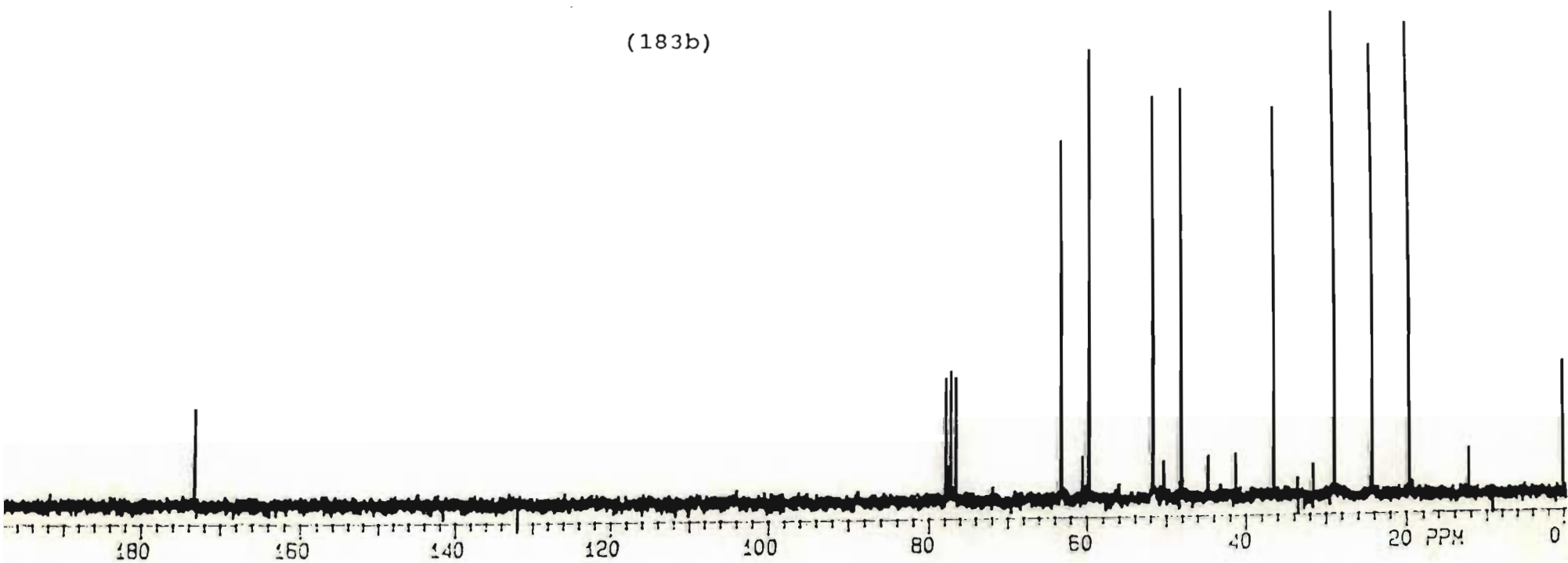
(137a)

$C_7H_{12}O_3$

MW = 144

(137b)

0 PPM
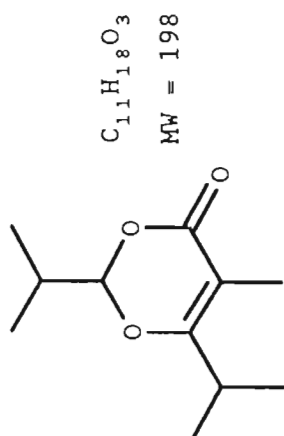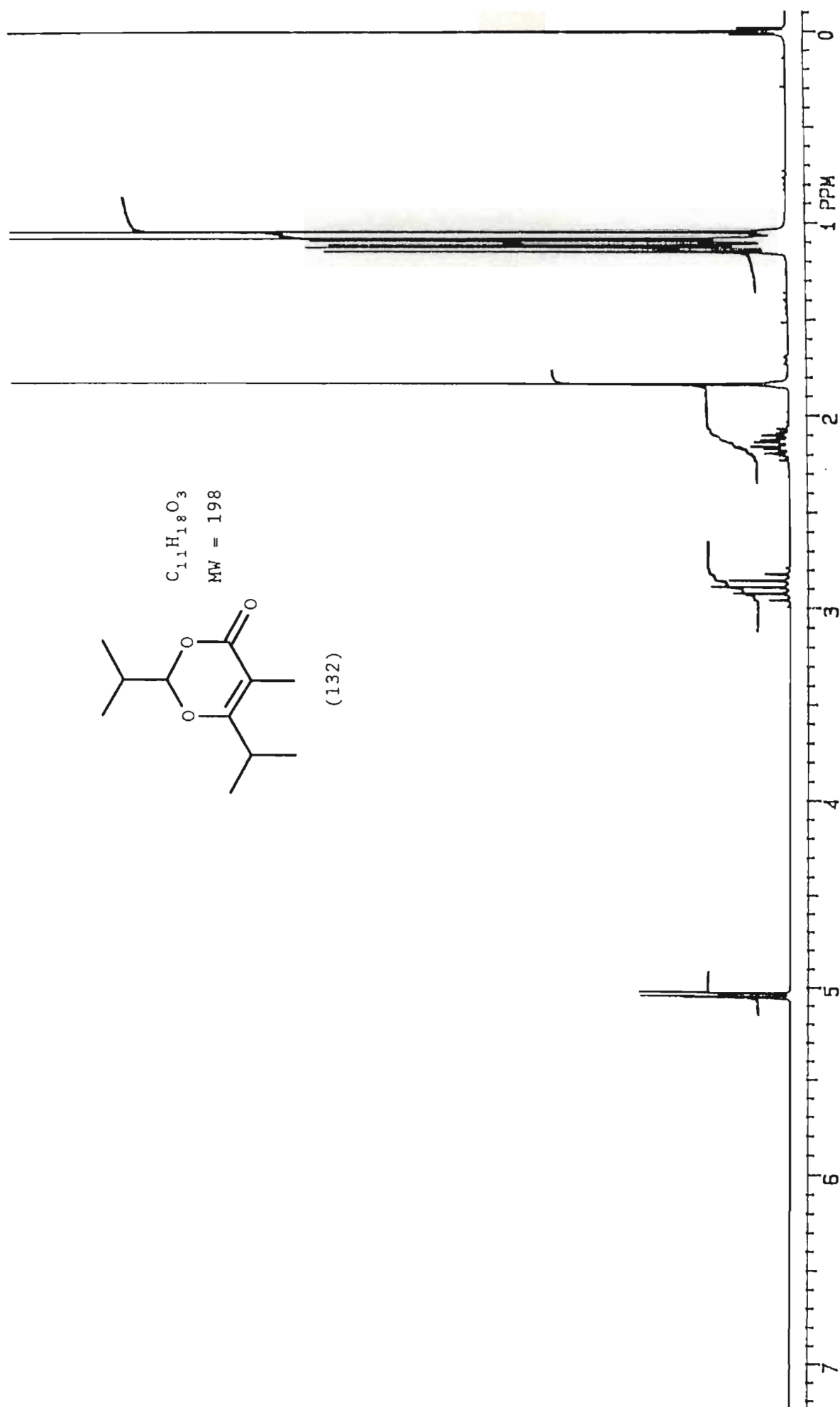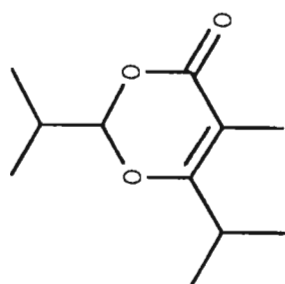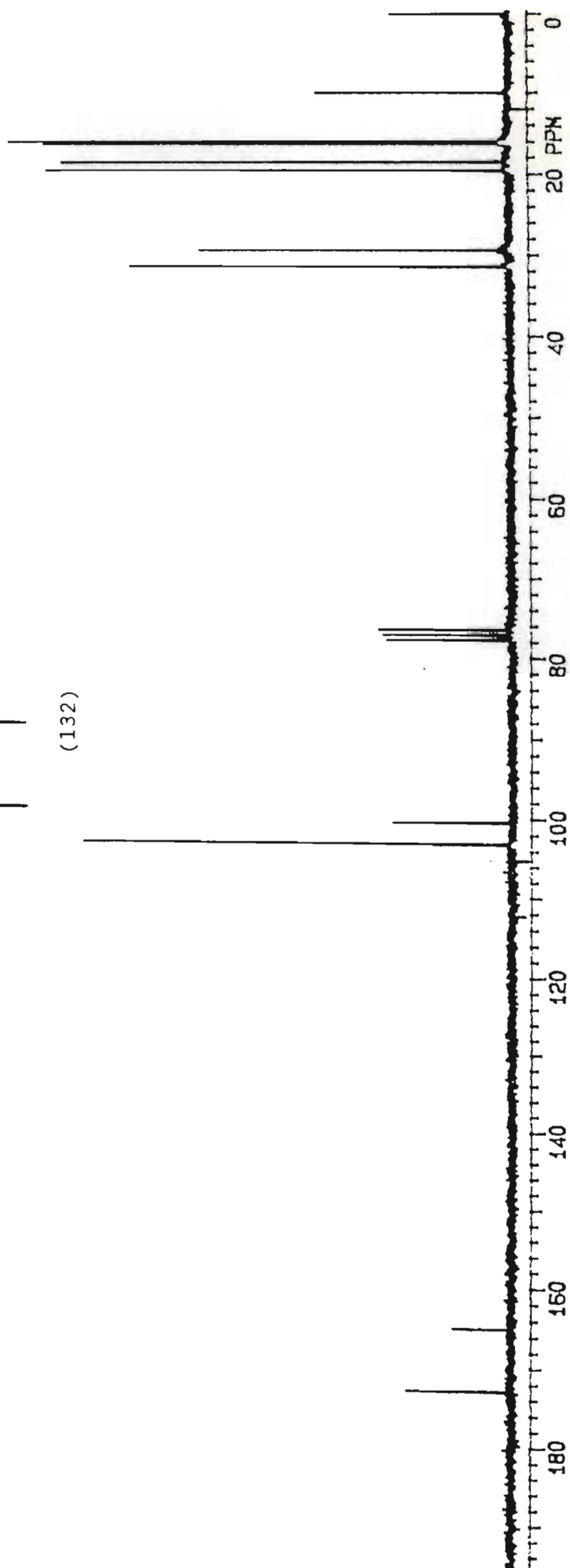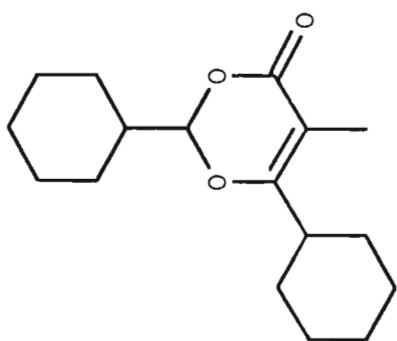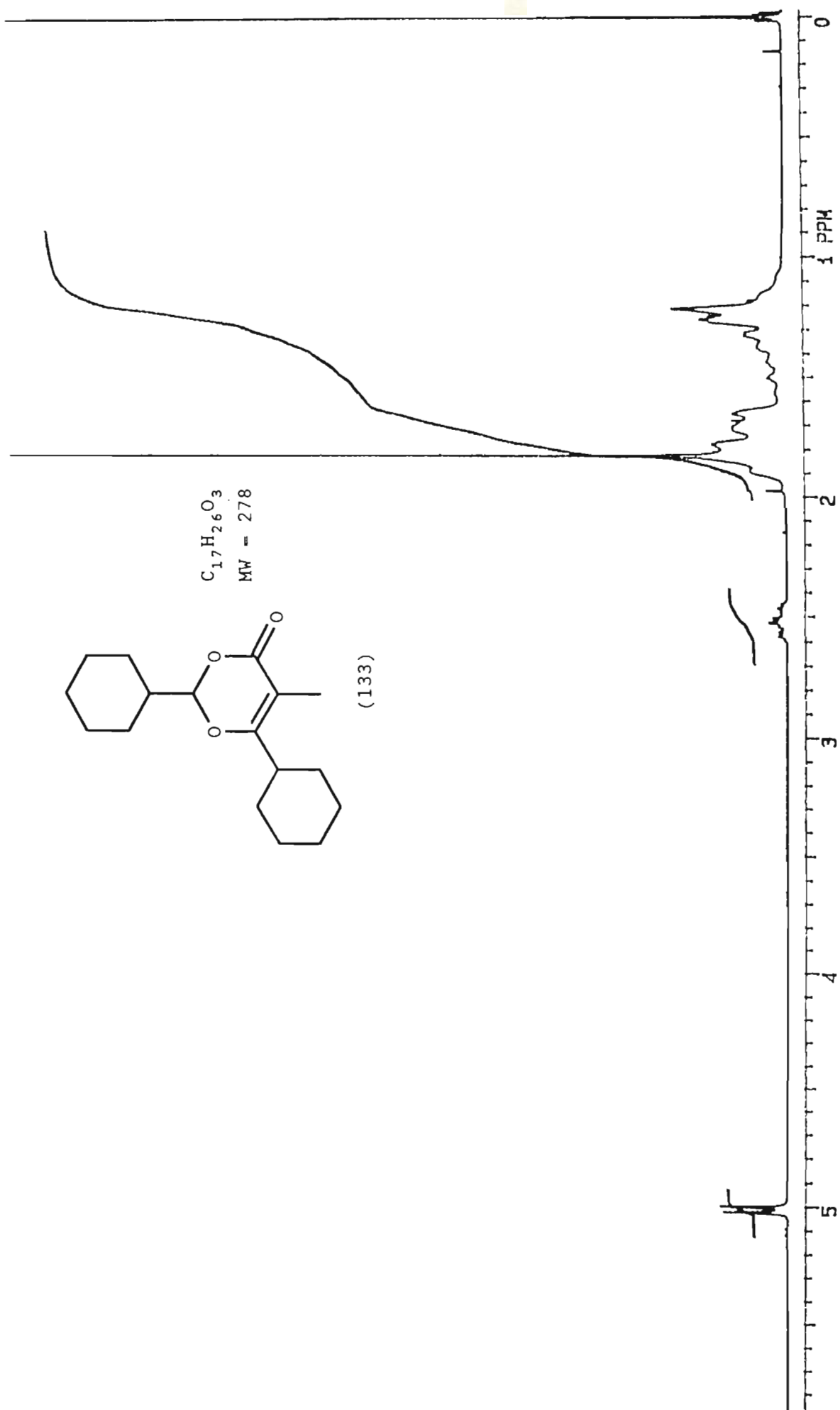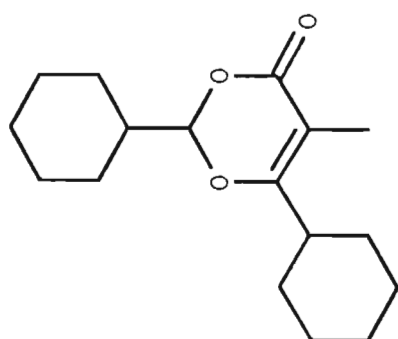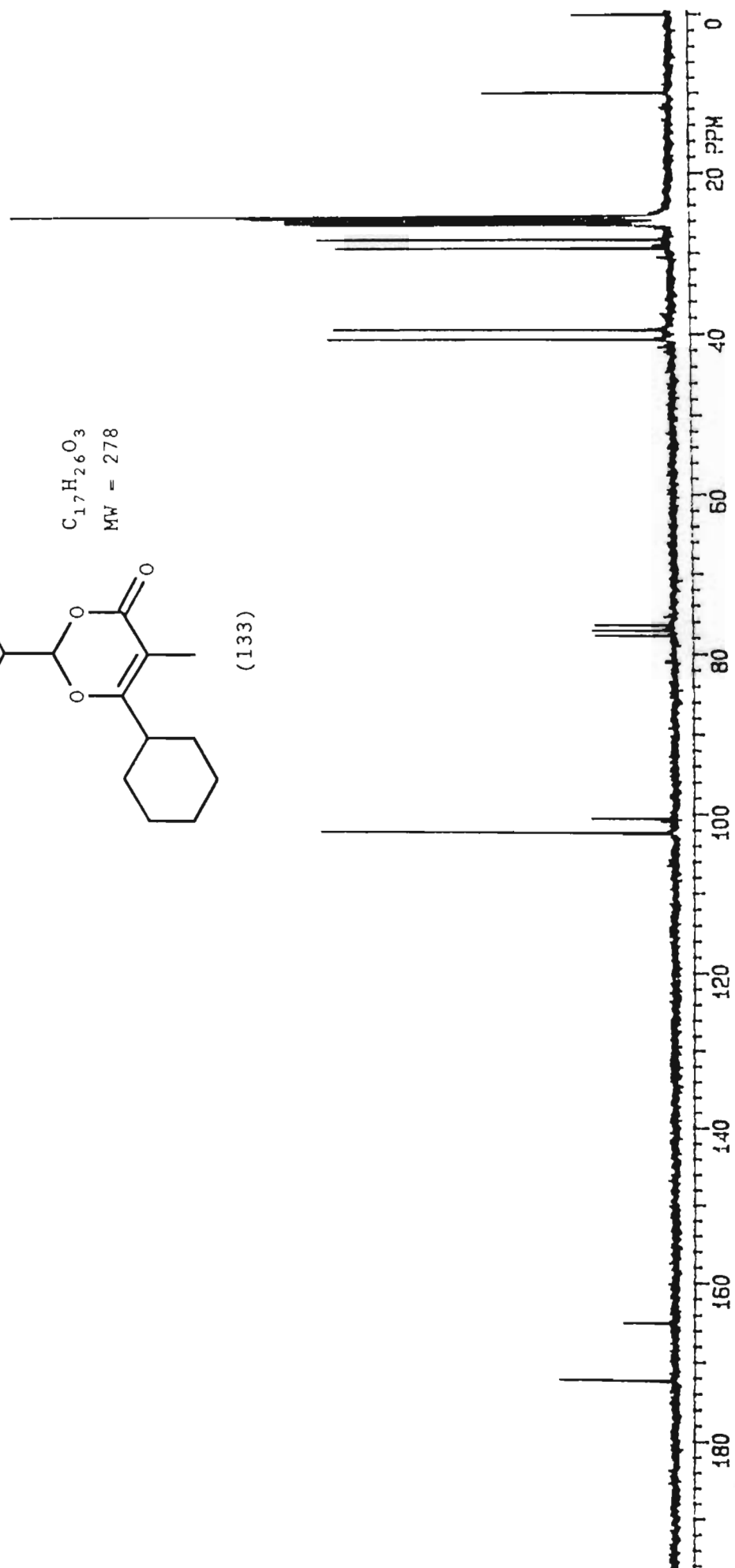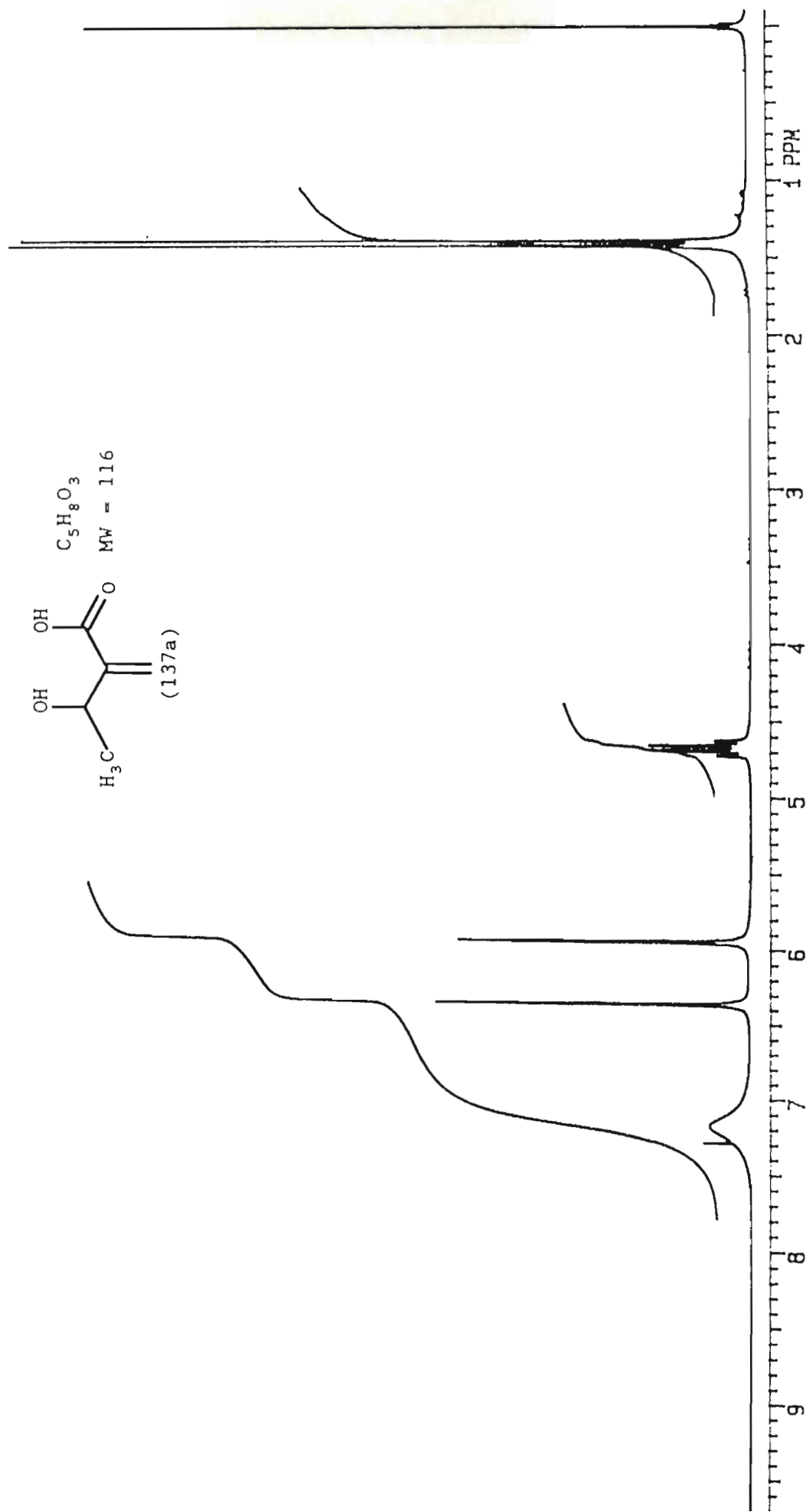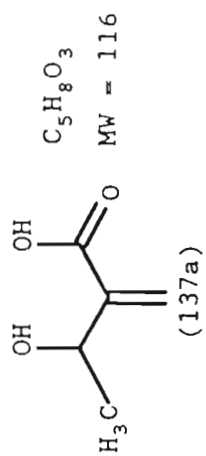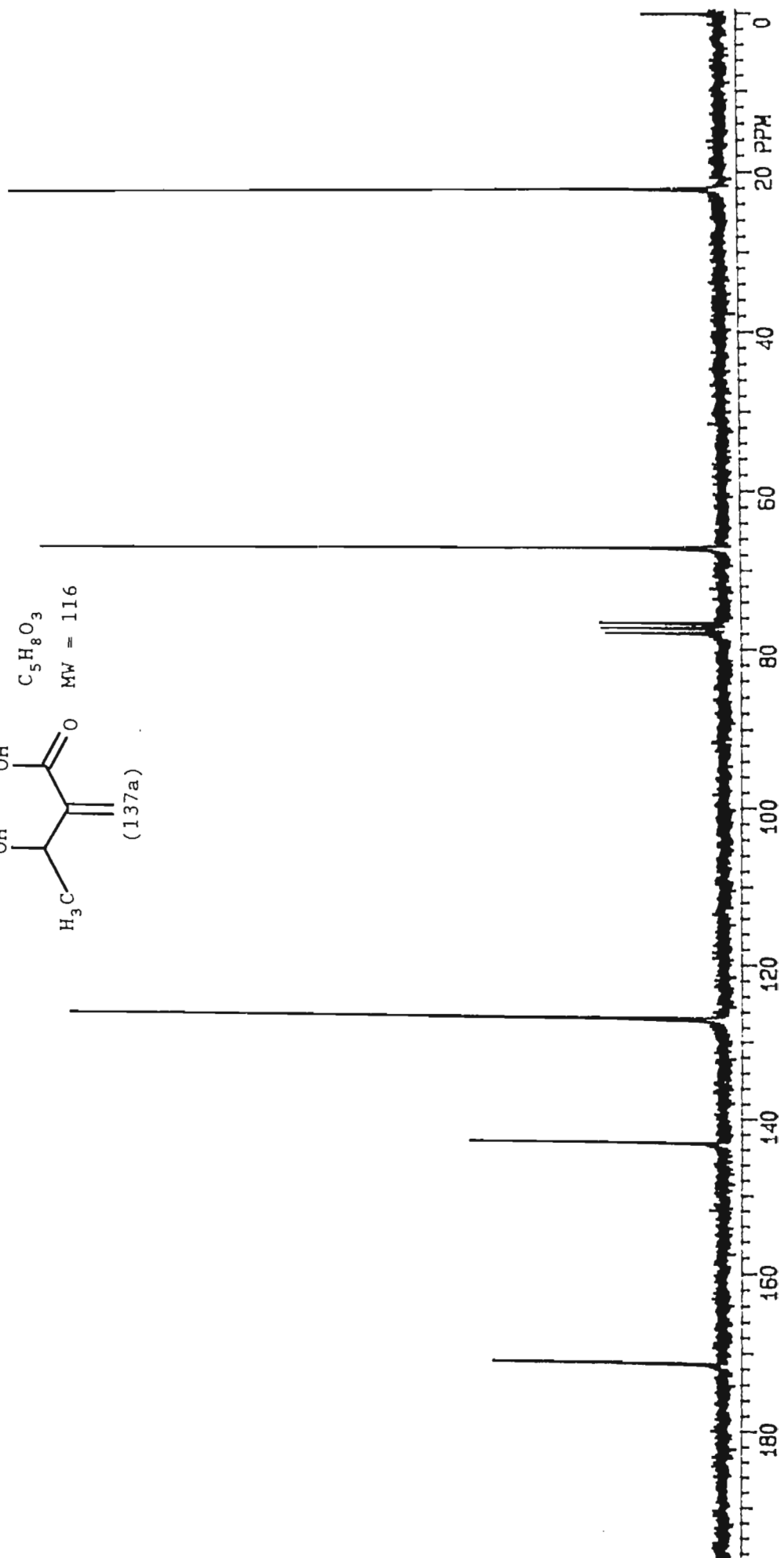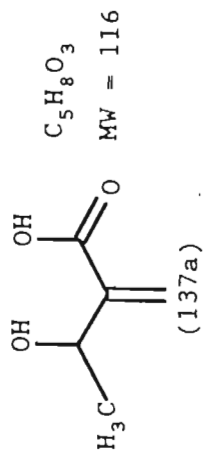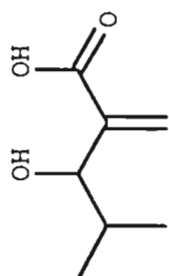
$C_7H_{12}O_3$
MW = 144

(137b)
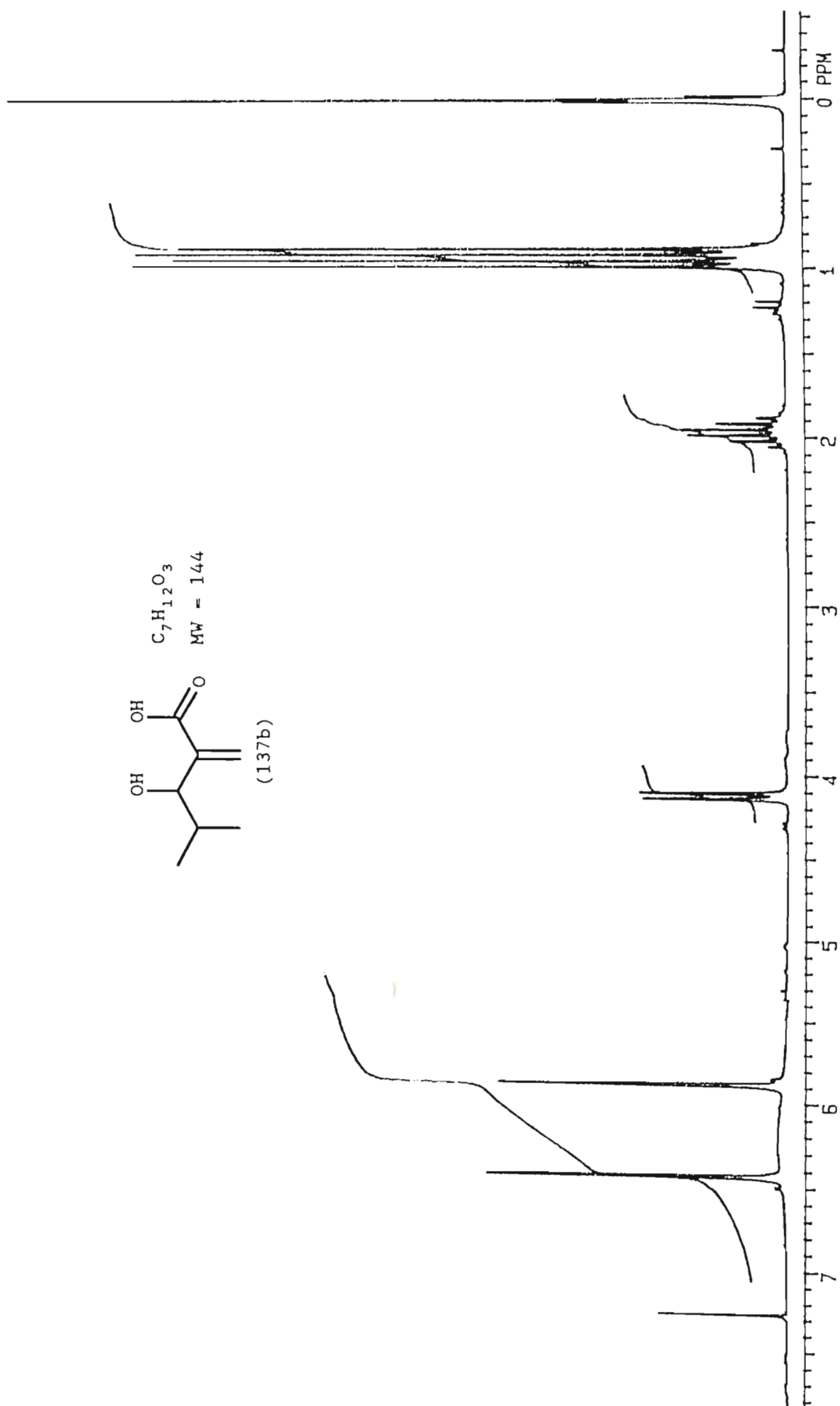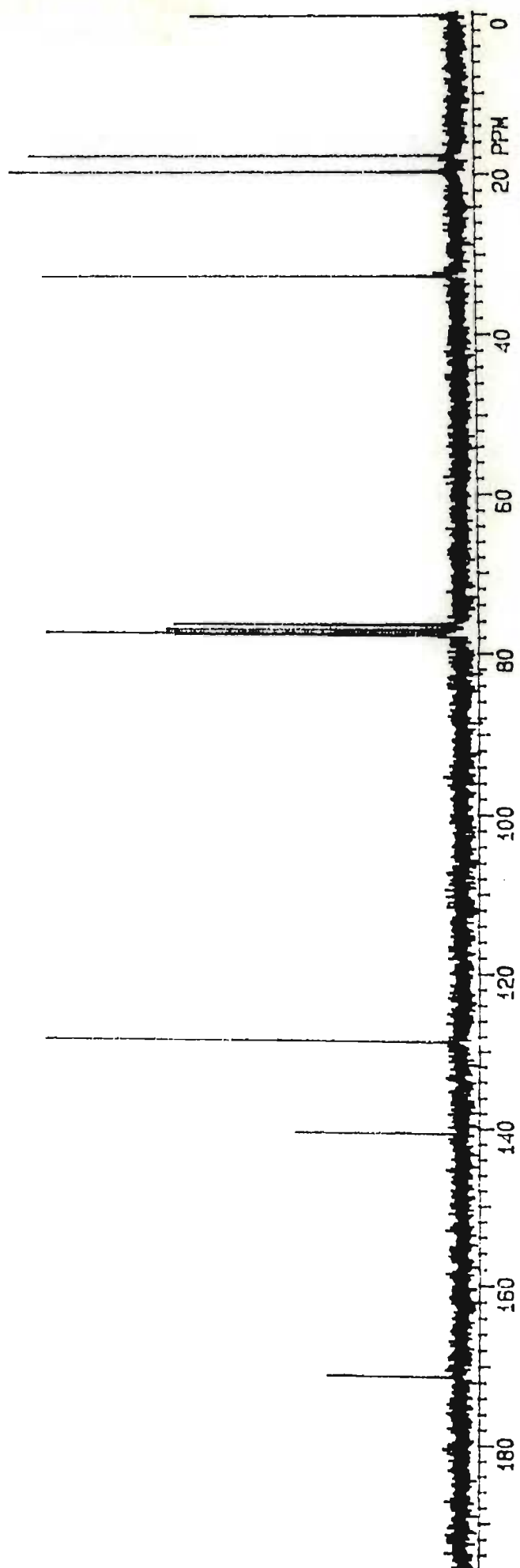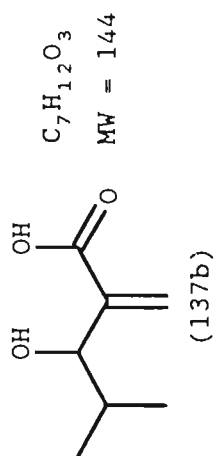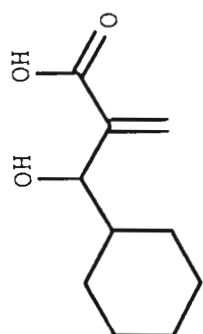
$C_{10}H_{16}O_3$
MW = 184

(137c)
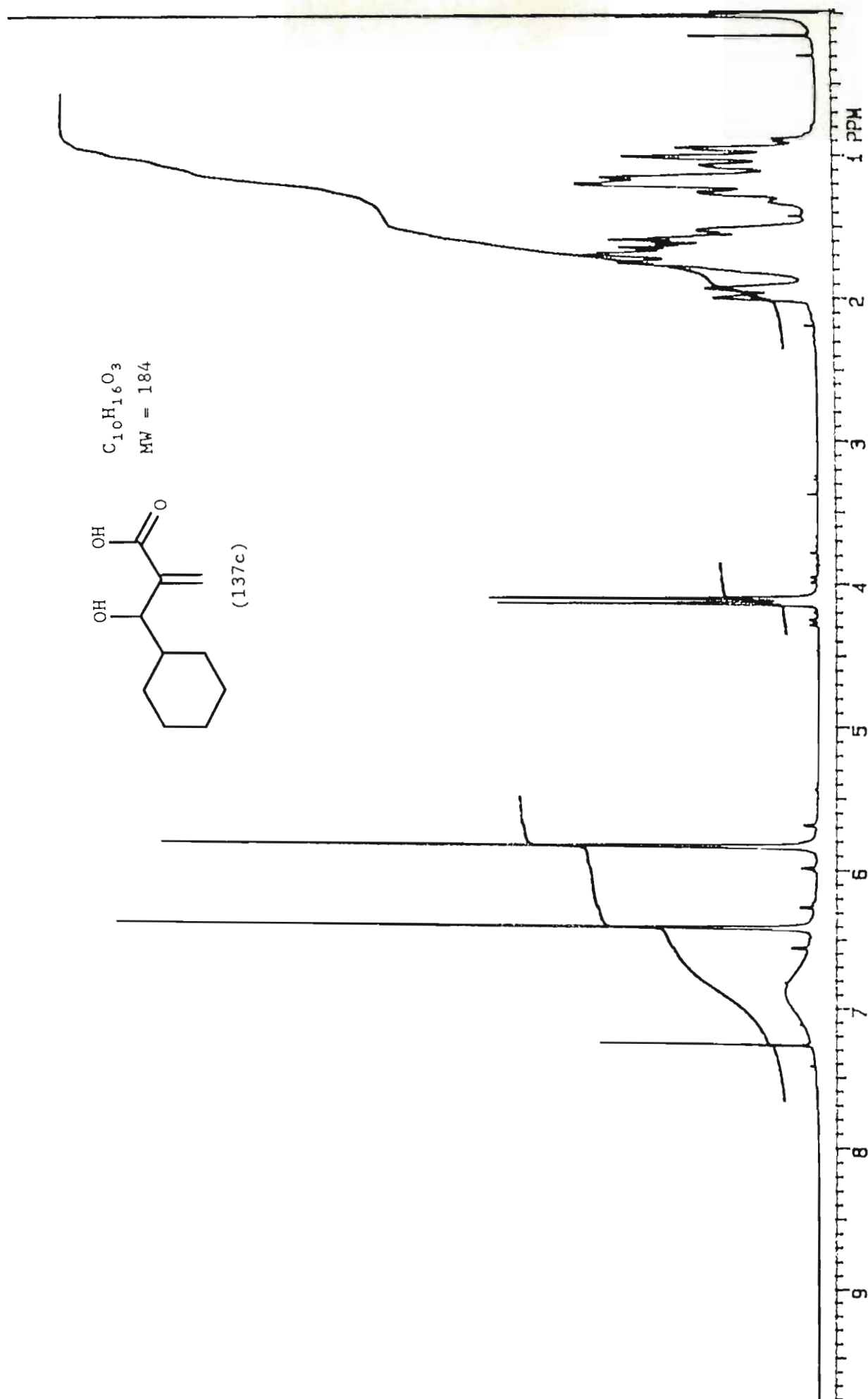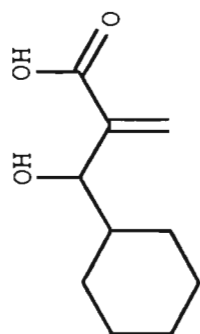
$C_{10}H_{16}O_3$

MW = 184

(137c)

$C_{16}H_{24}O$

MW = 232

(138)

$C_{16}H_{24}O$

$MW = 232$

(138)

$C_{19}H_{26}O_2$
MW = 286

(139)

$C_{19}H_{26}O_2$
$MW = 286$

(139)

$C_{21}H_{27}Cl_3O_3$

MW = 432

(140a)

Cl$_3$C $-$ CH(OH) ... OH
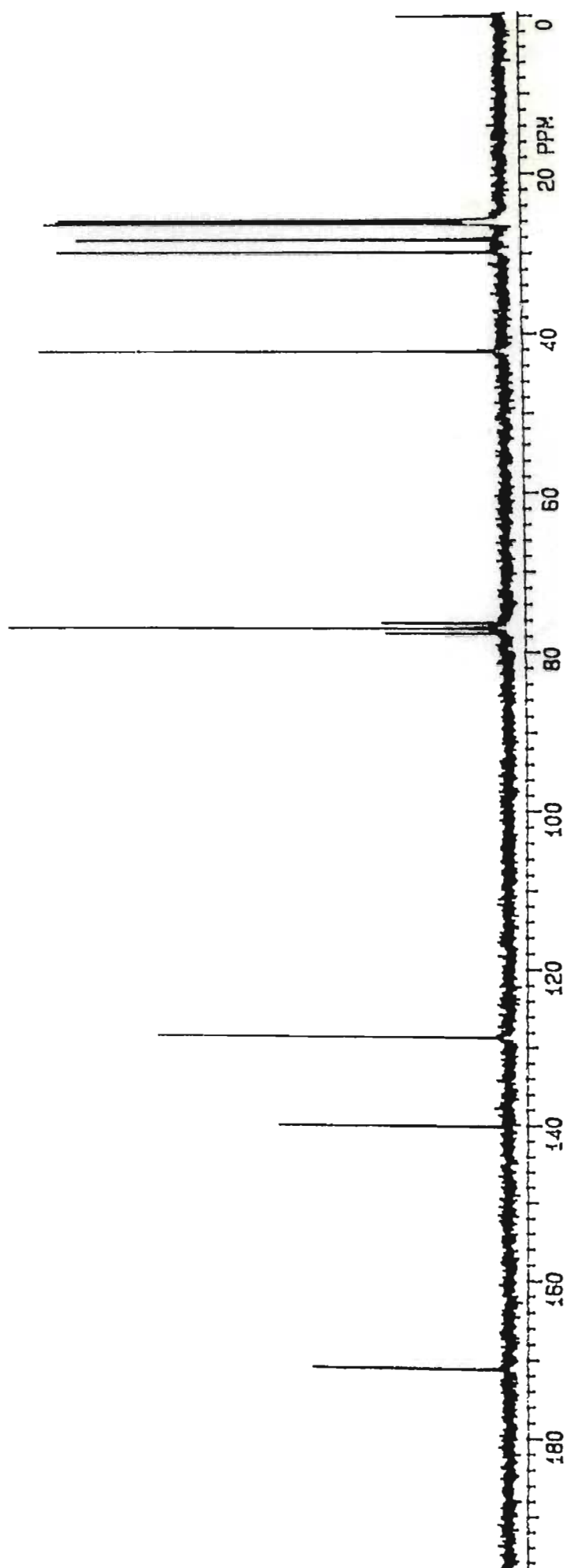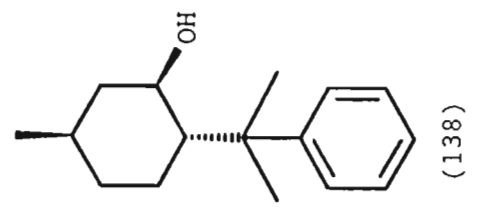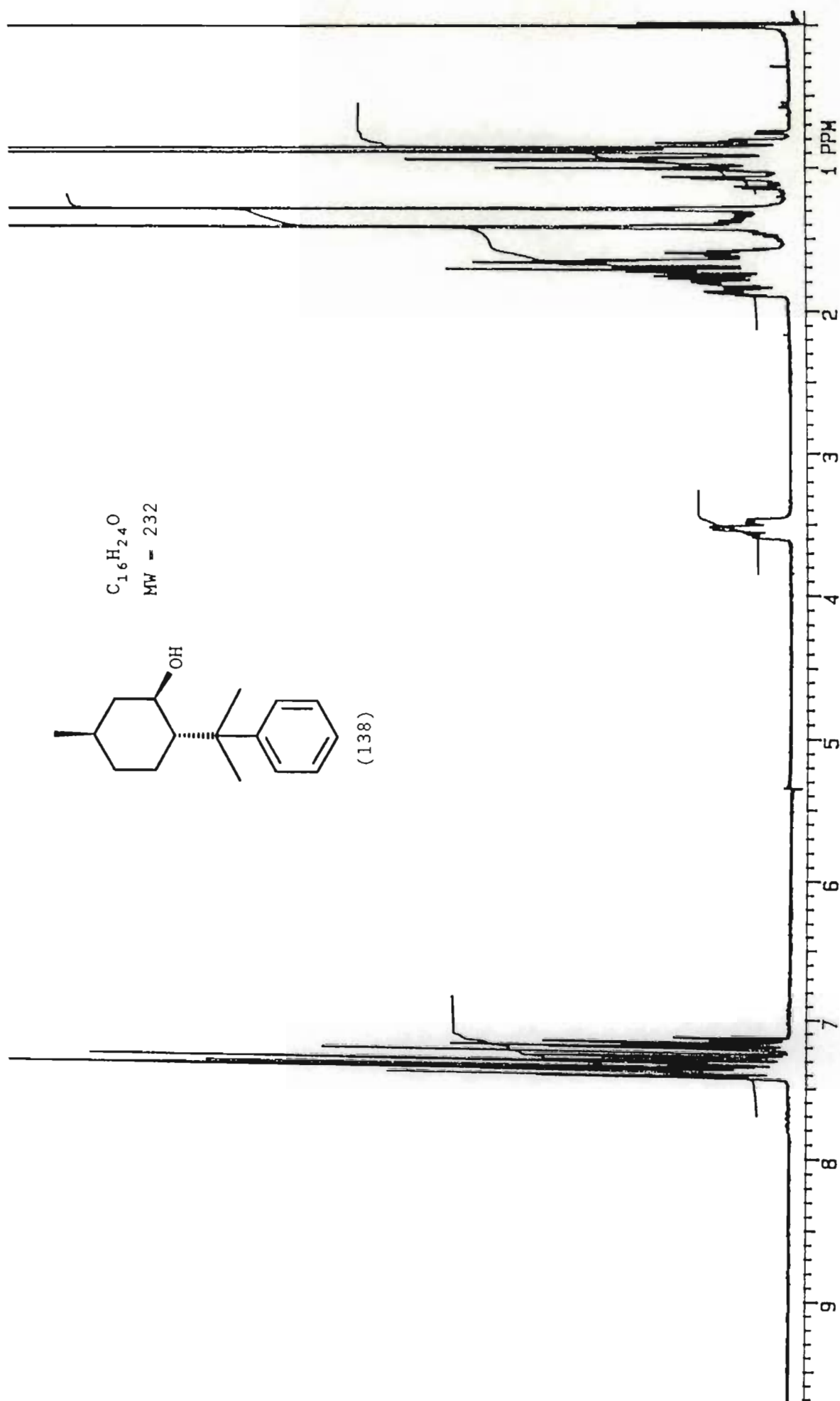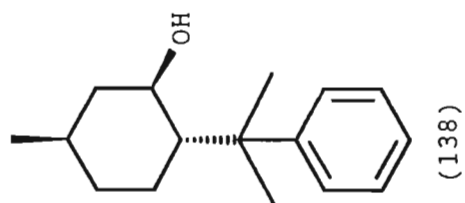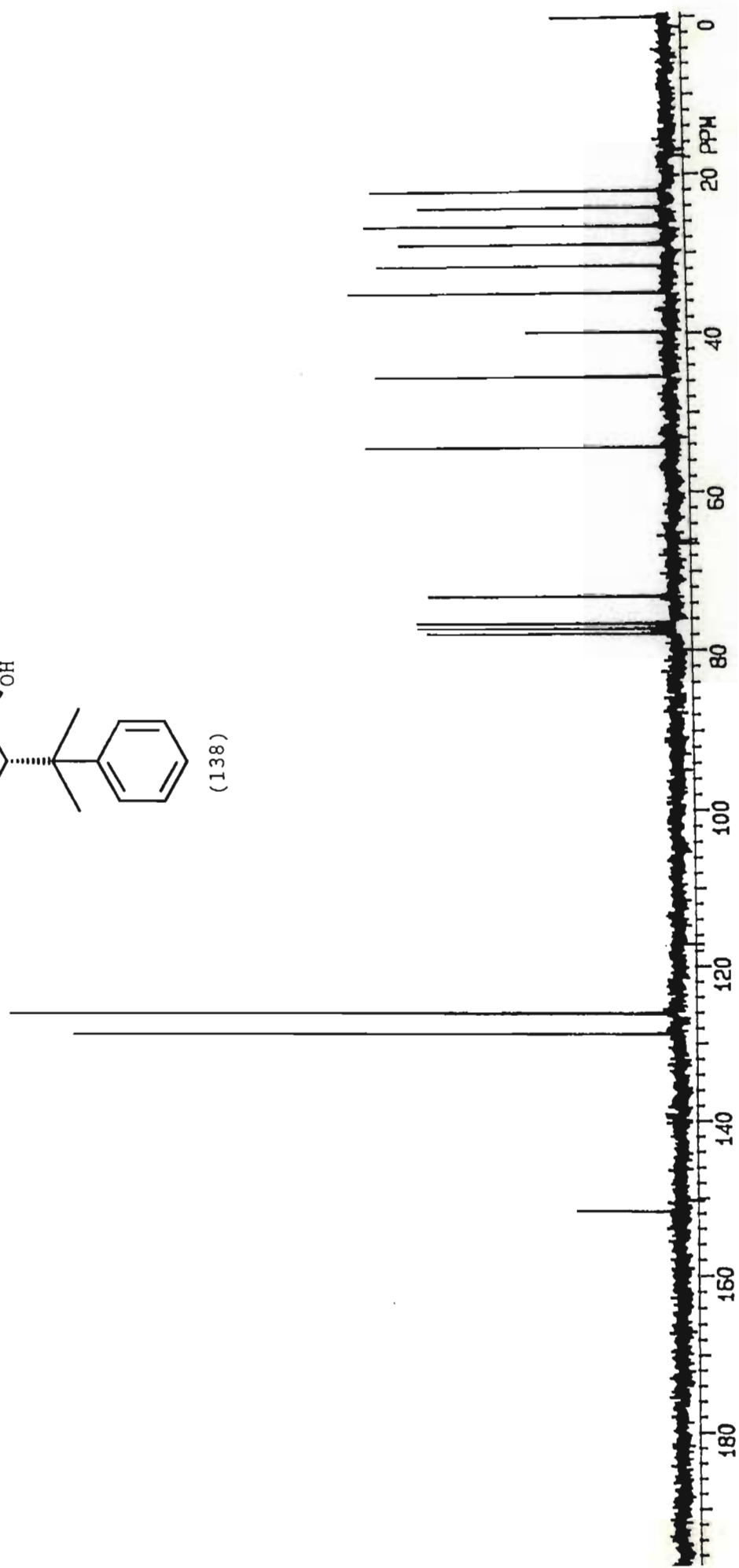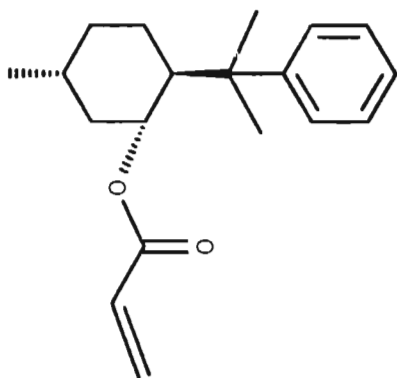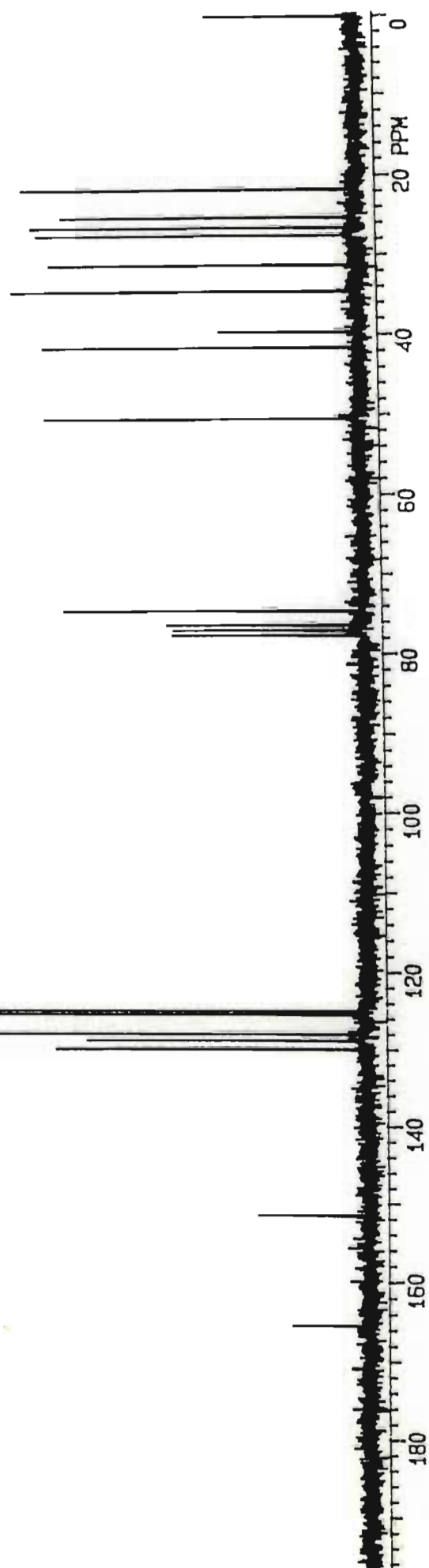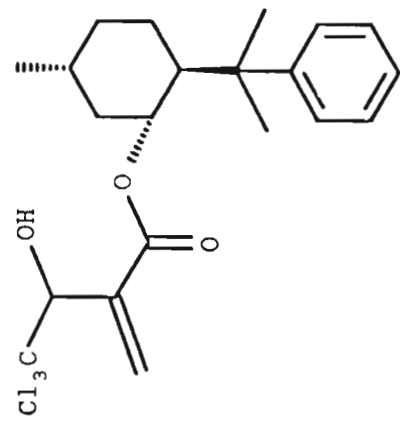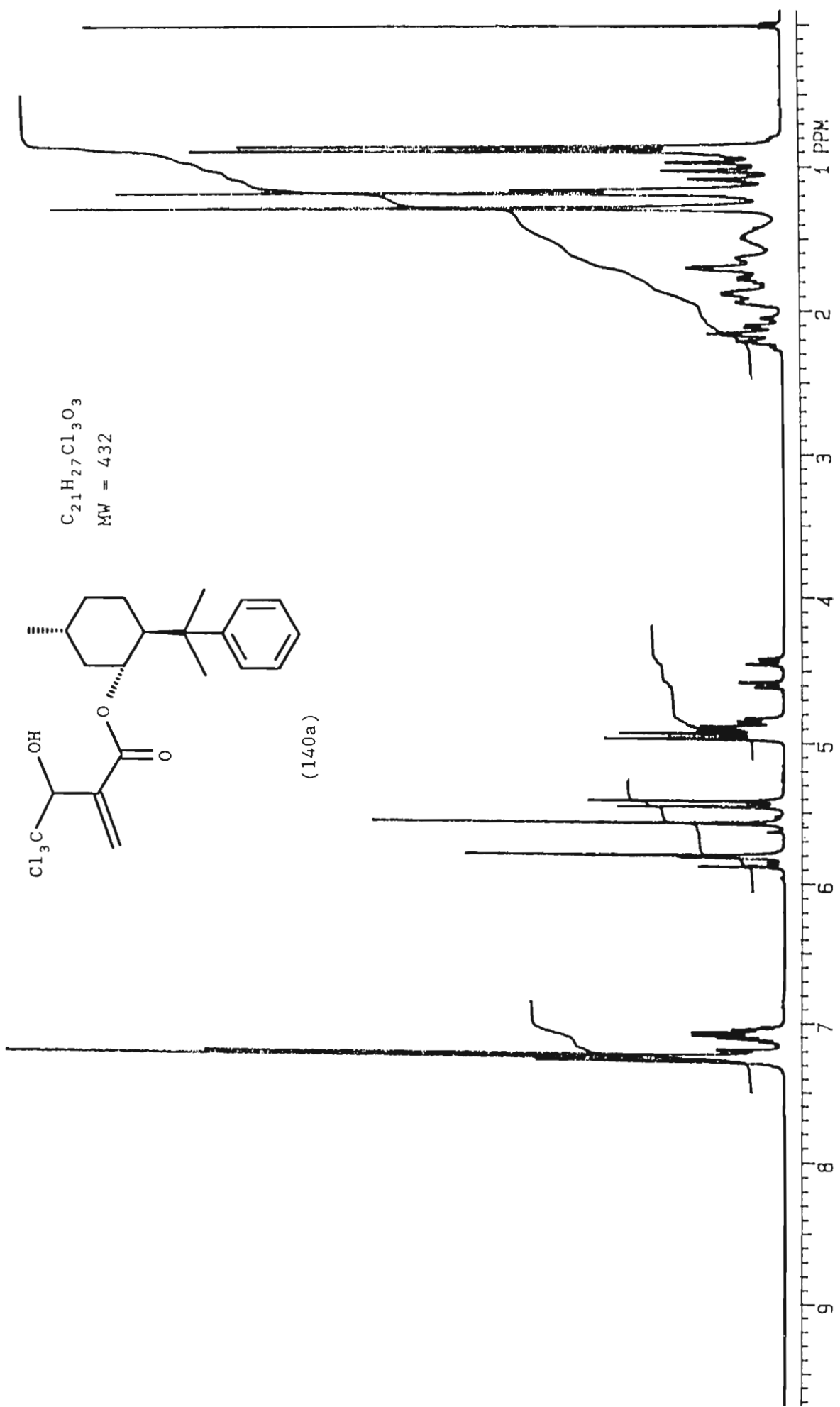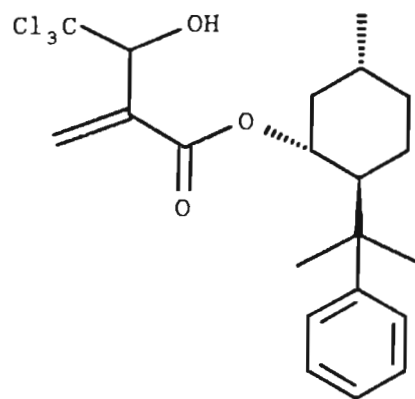
C$_{21}$H$_{27}$Cl$_3$O$_3$

MW = 432

(140a)
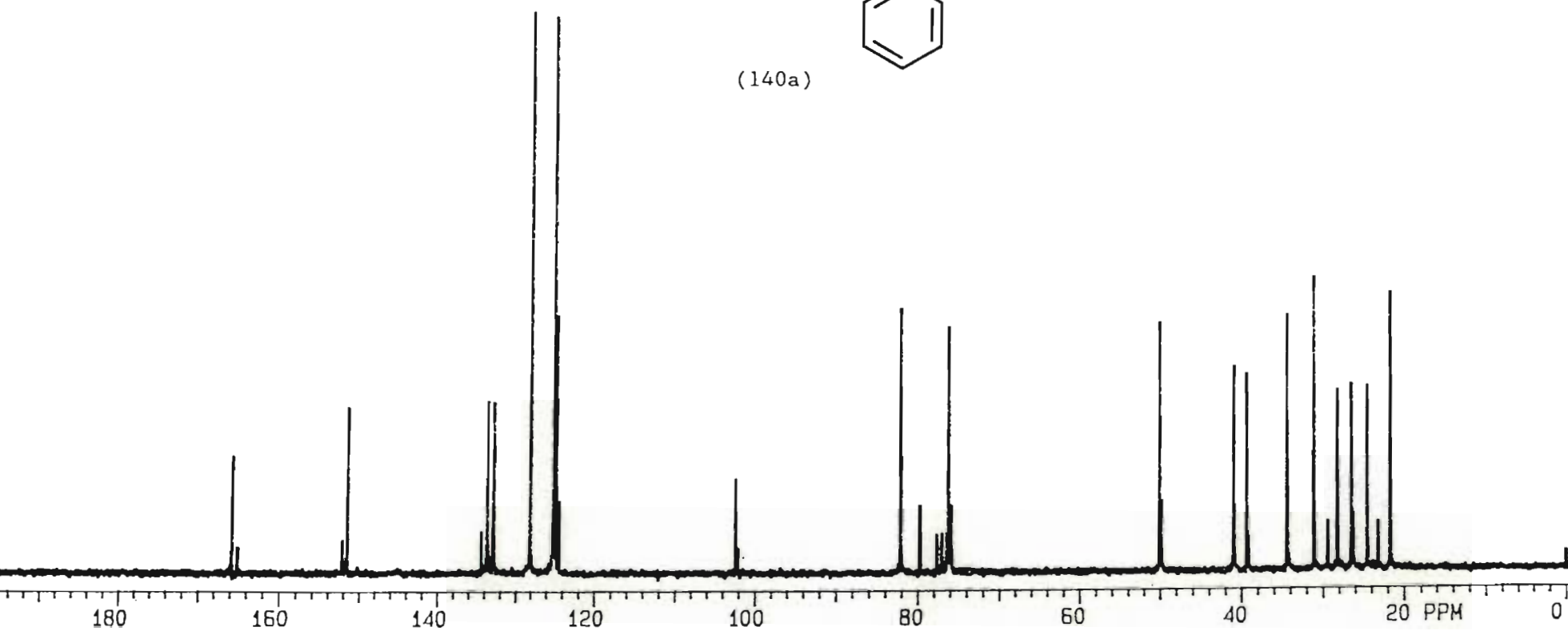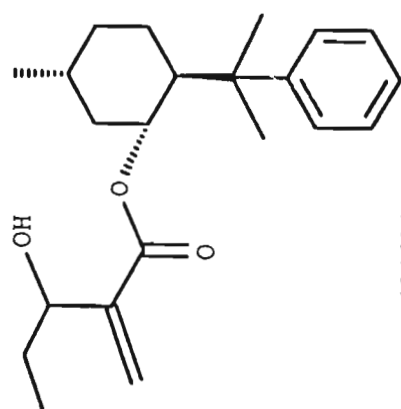
$C_{22}H_{32}O_3$
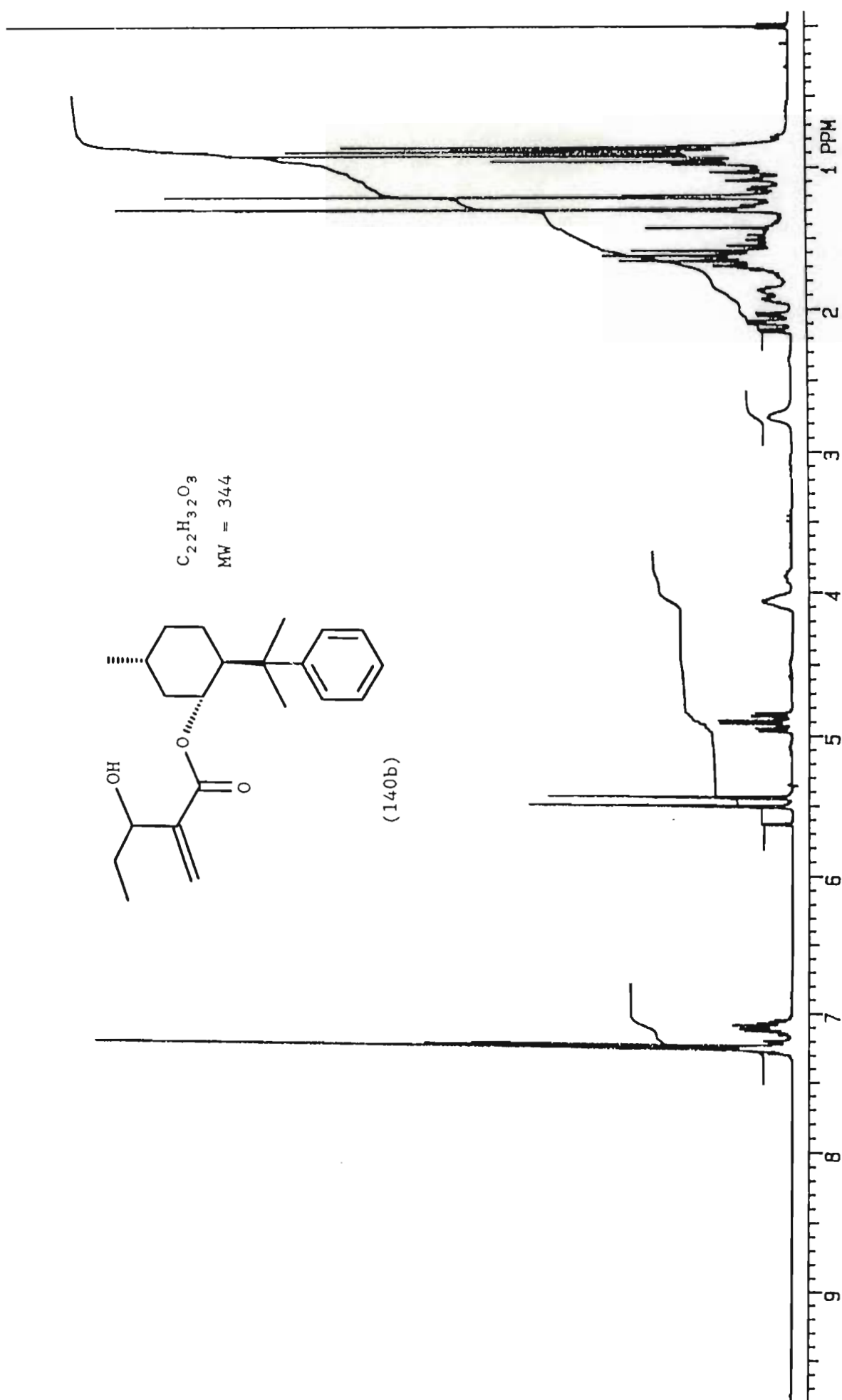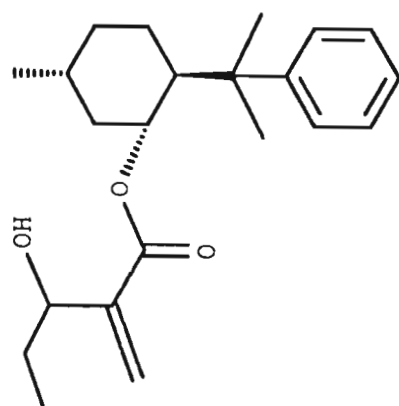
MW = 344

(140b)

$C_{22}H_{32}O_3$

MW = 344

(140b)
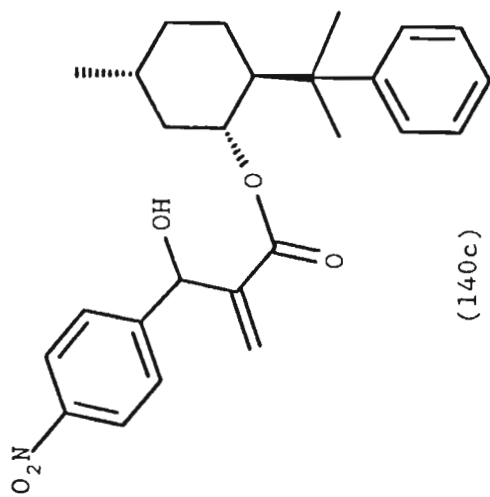
$C_{26}H_{31}NO_5$

MW = 437
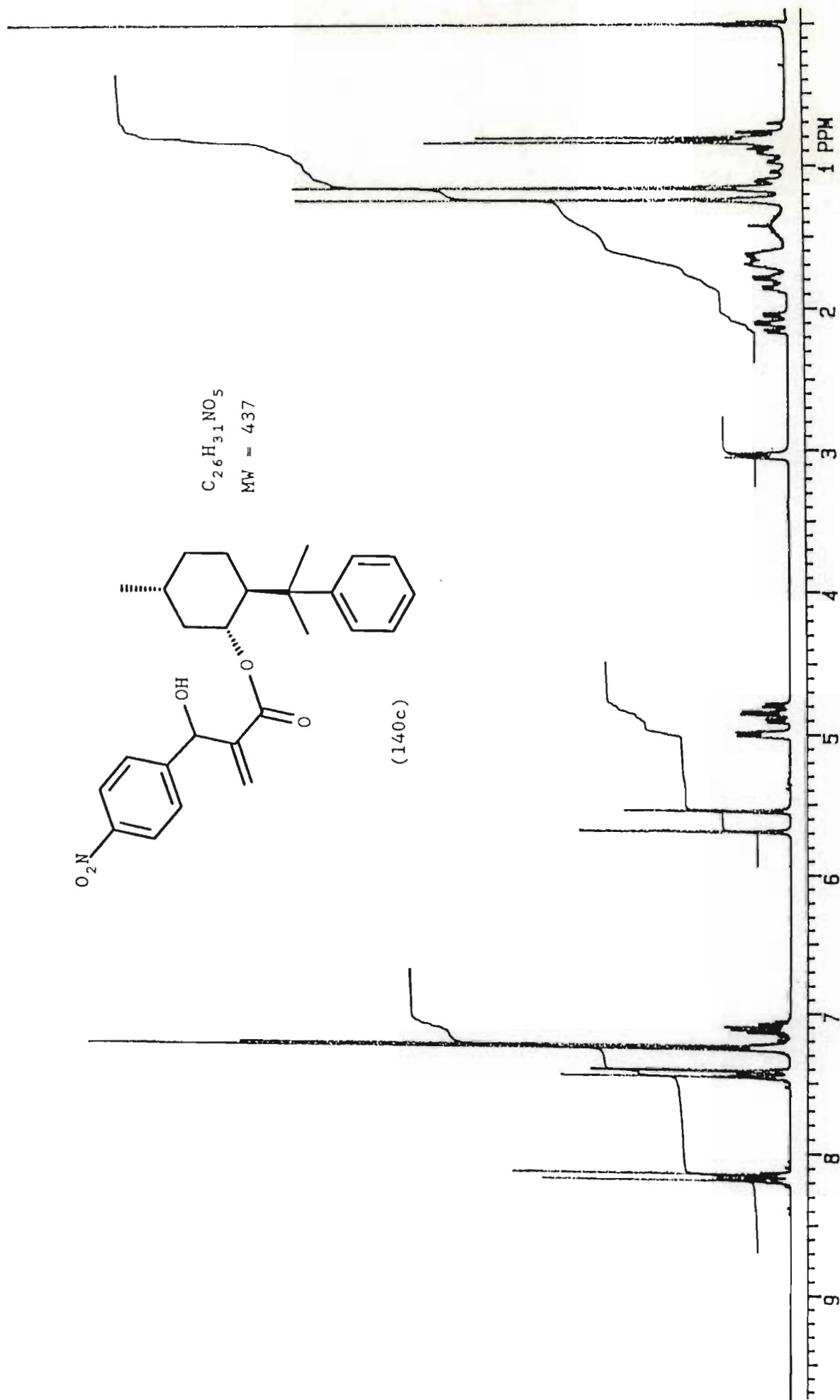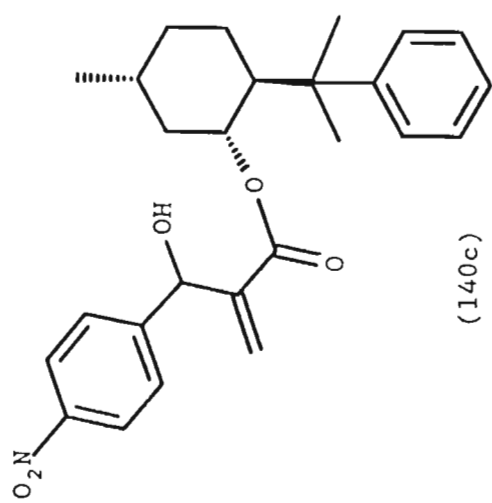
(140c)

$C_{26}H_{31}NO_5$

MW = 437

(140c)
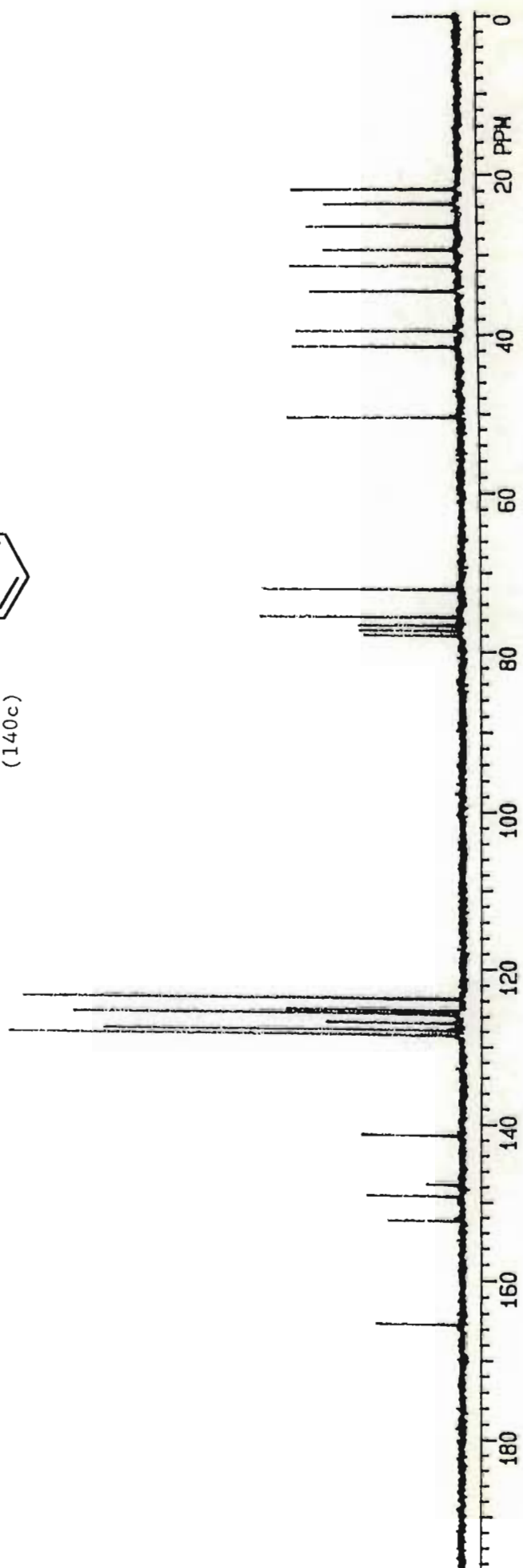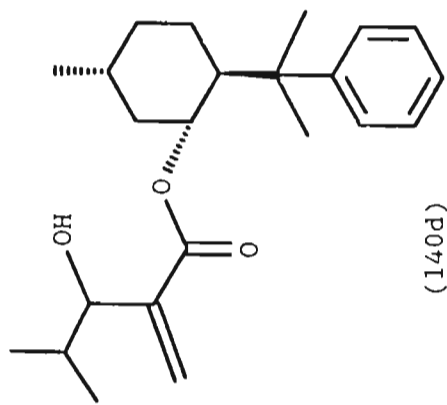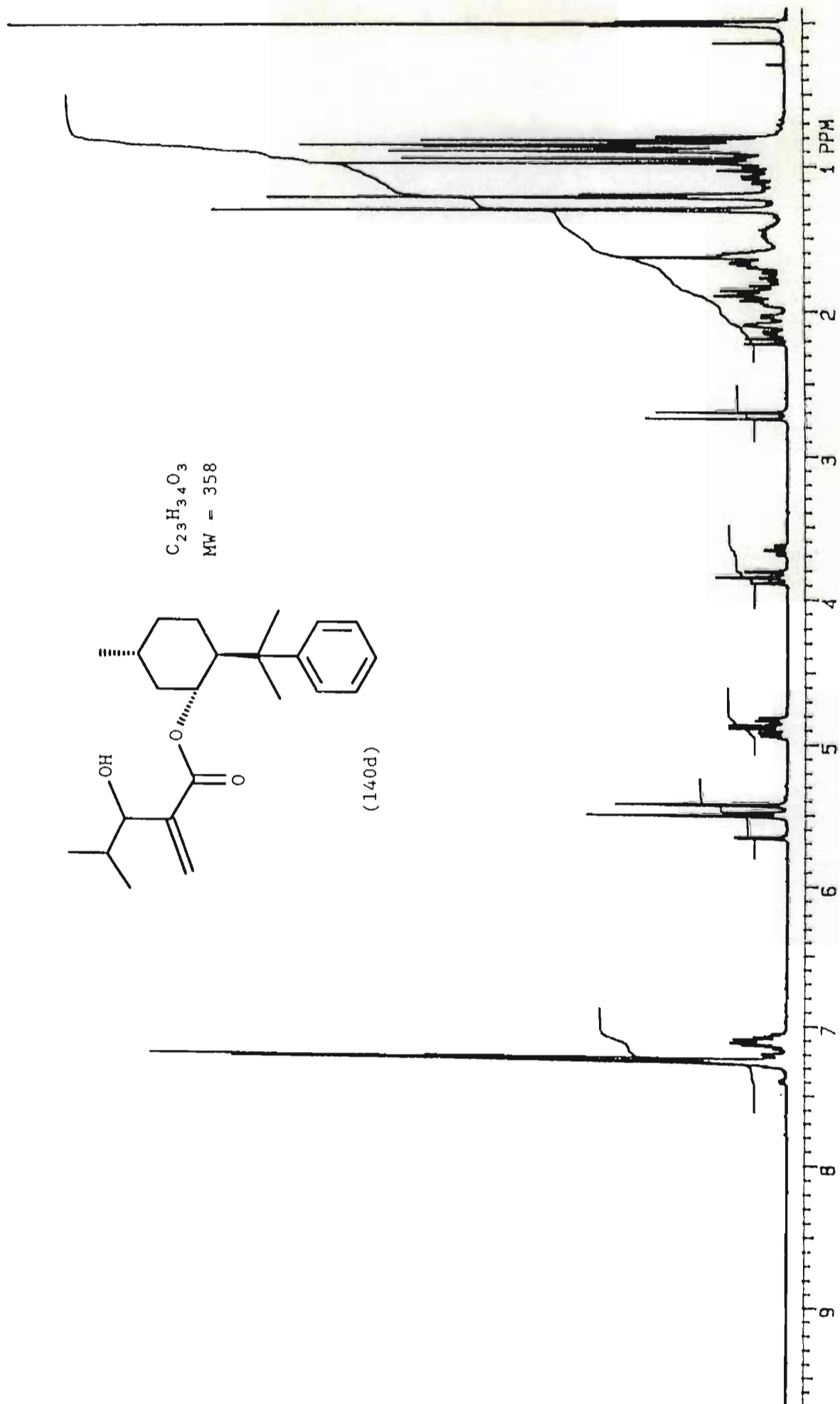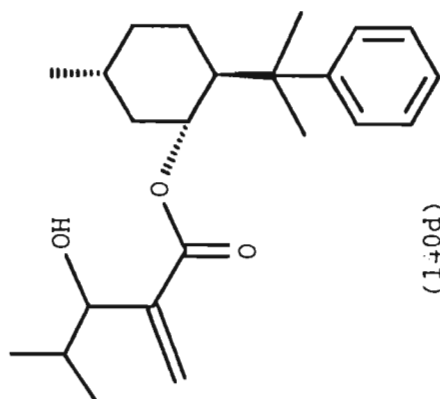
$C_{23}H_{34}O_3$
MW = 358

(140d)

$C_{23}H_{34}O_3$
MW = 358

(1+0d)
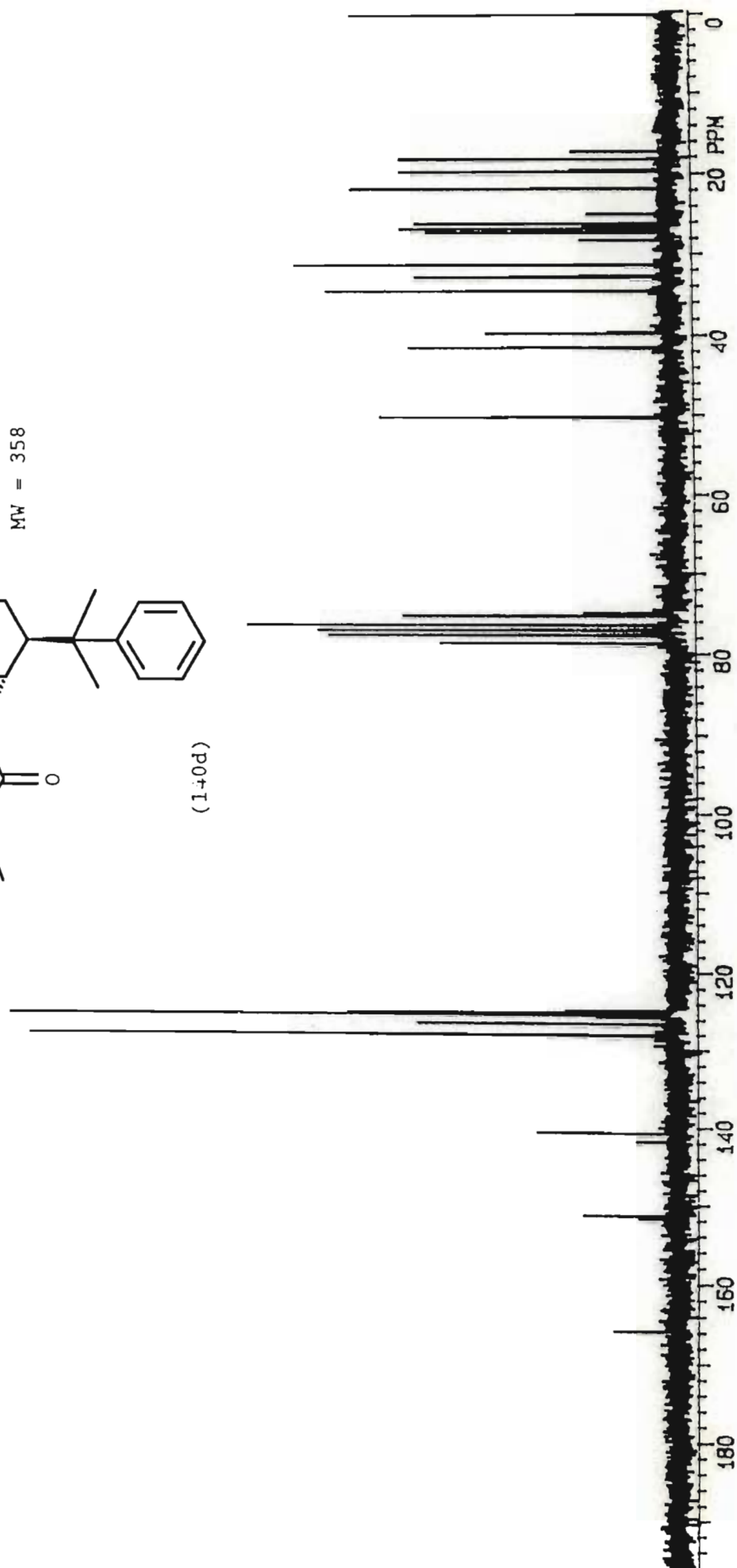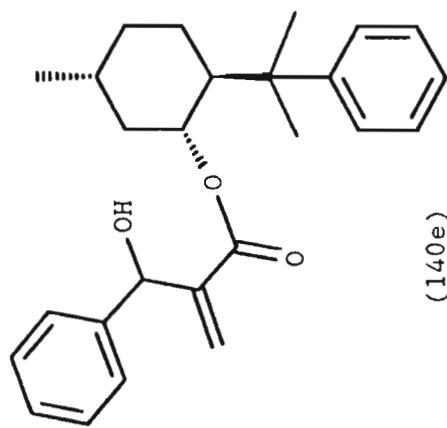
$C_{26}H_{32}O_3$

$MW = 392$

(140e)
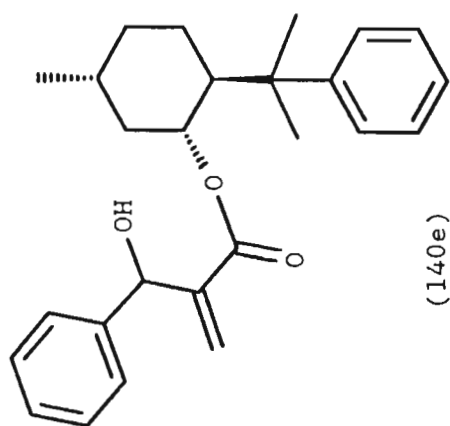
$C_{26}H_{32}O_3$
MW = 392

(140e)

$C_{26}H_{38}O_3$
$MW = 398$
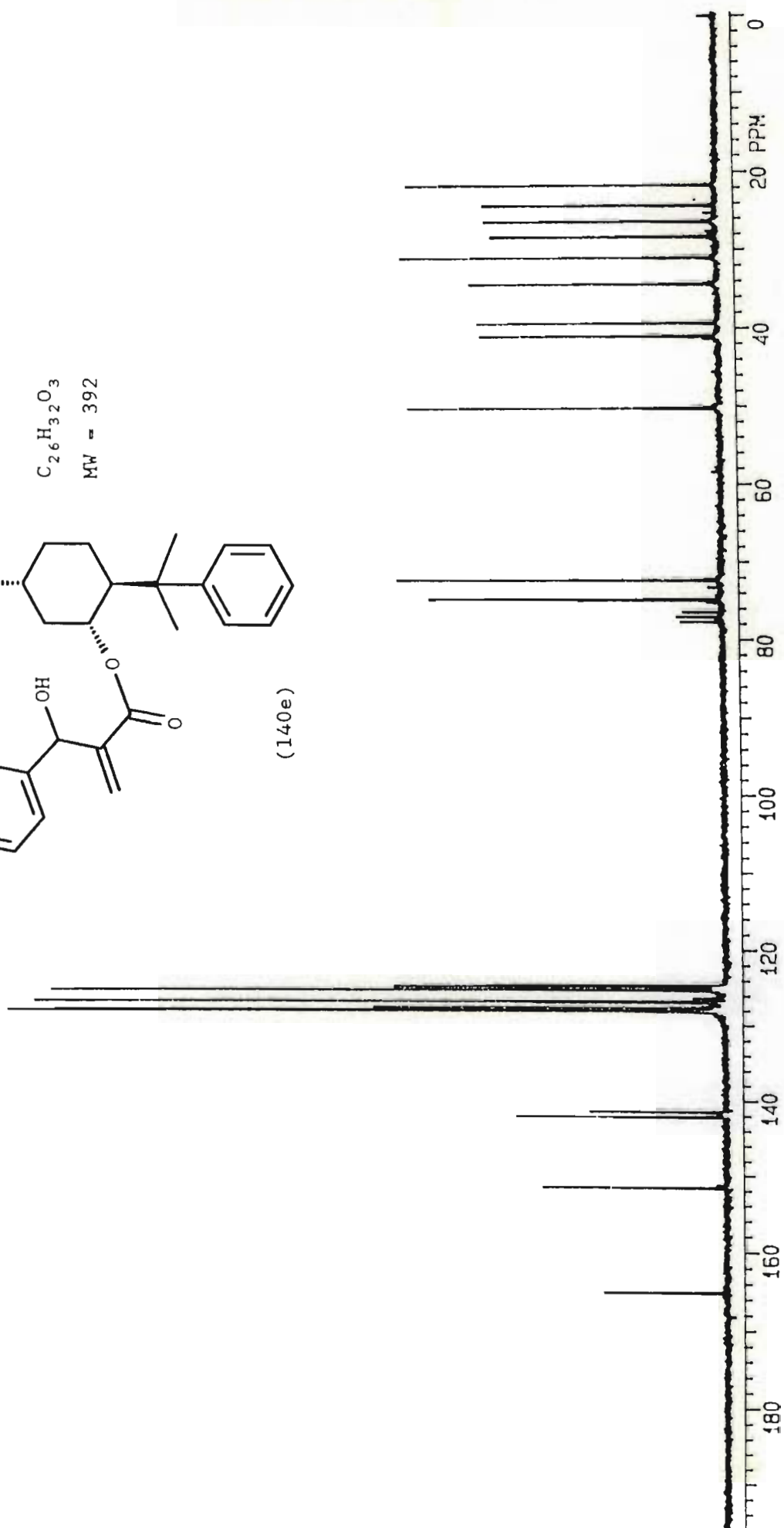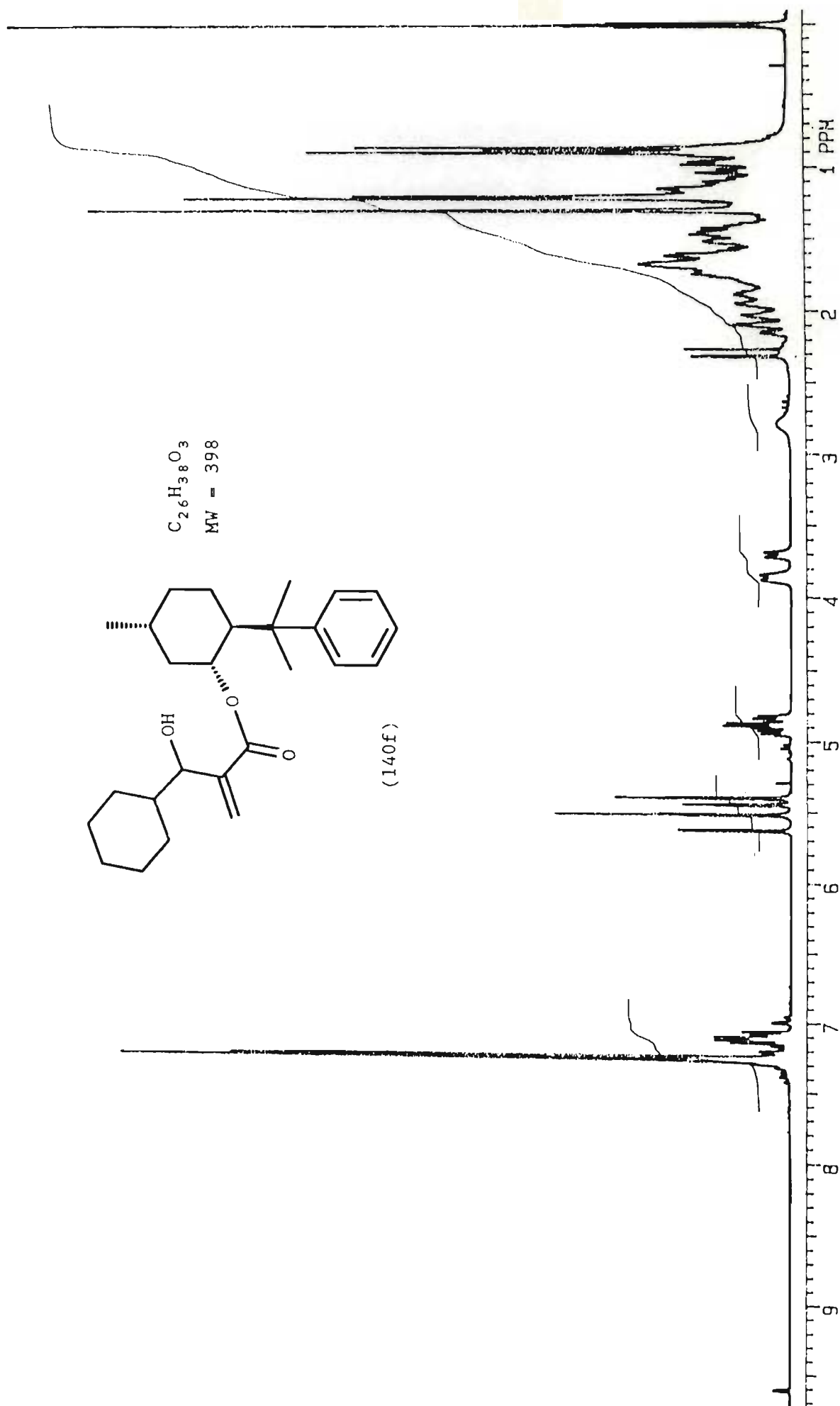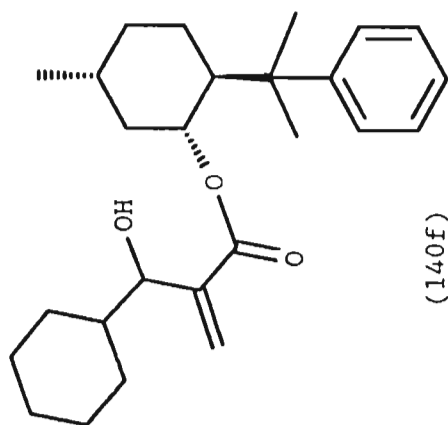
(140f)
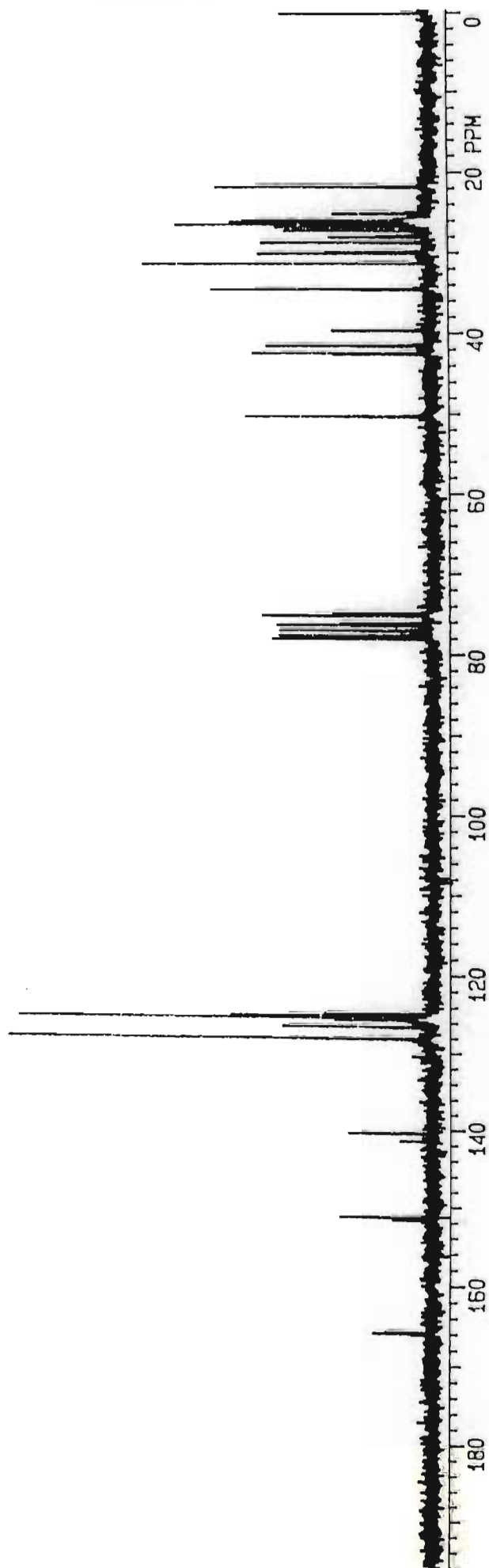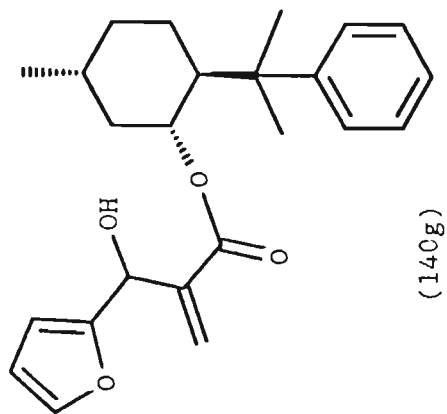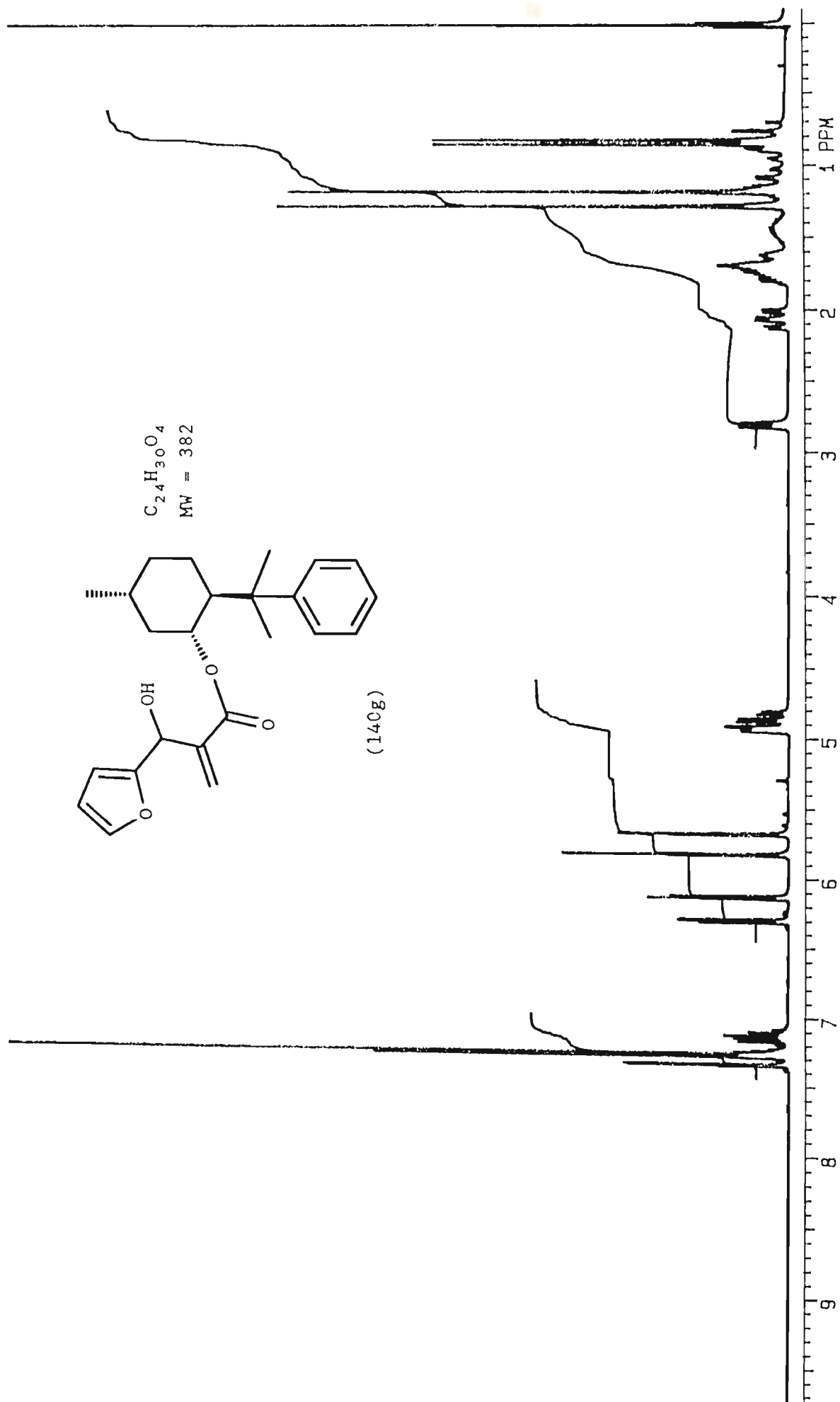
$C_{26}H_{38}O_3$
MW = 398

(140f)

$C_{24}H_{30}O_4$
MW = 382
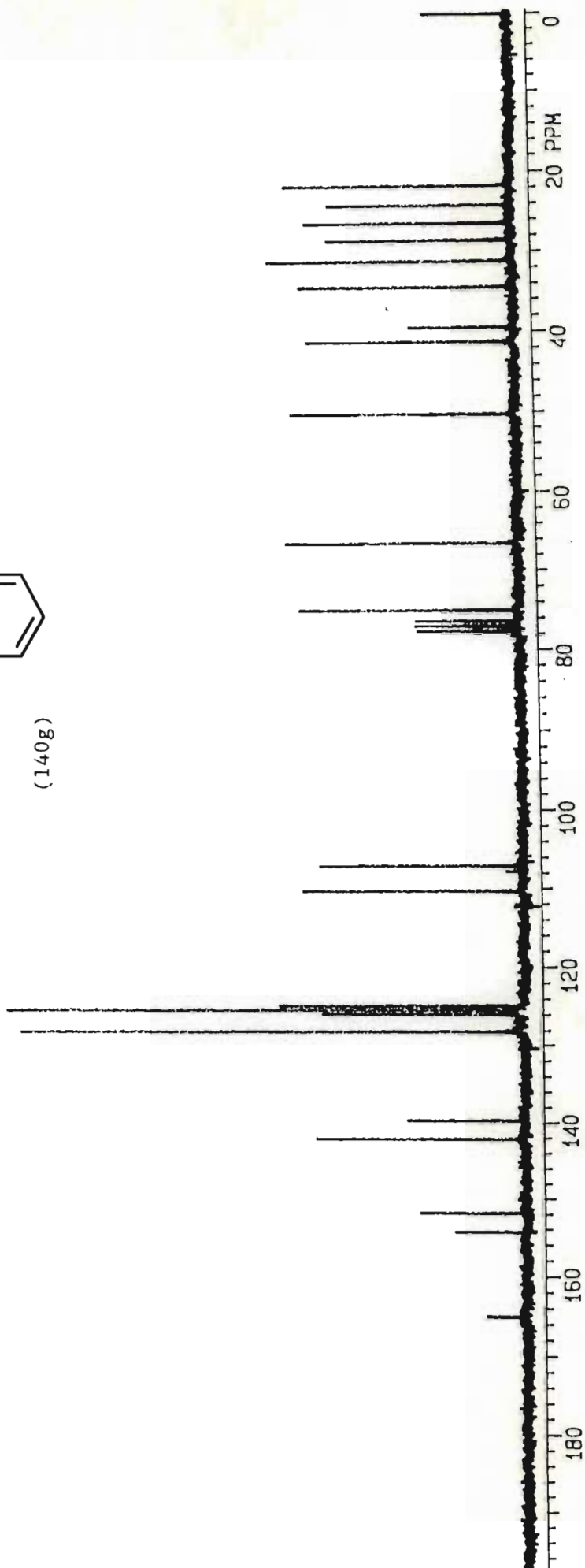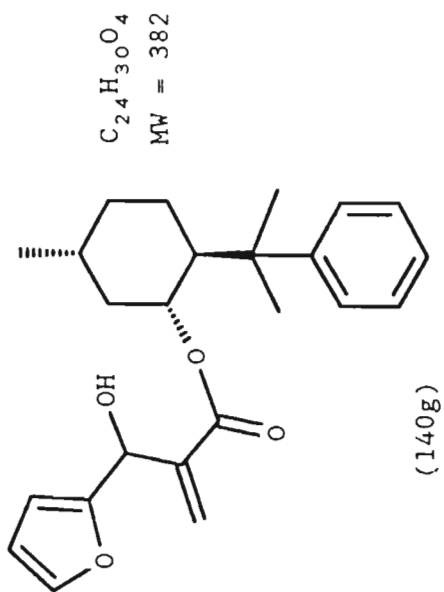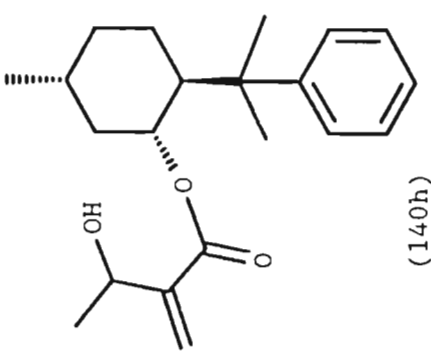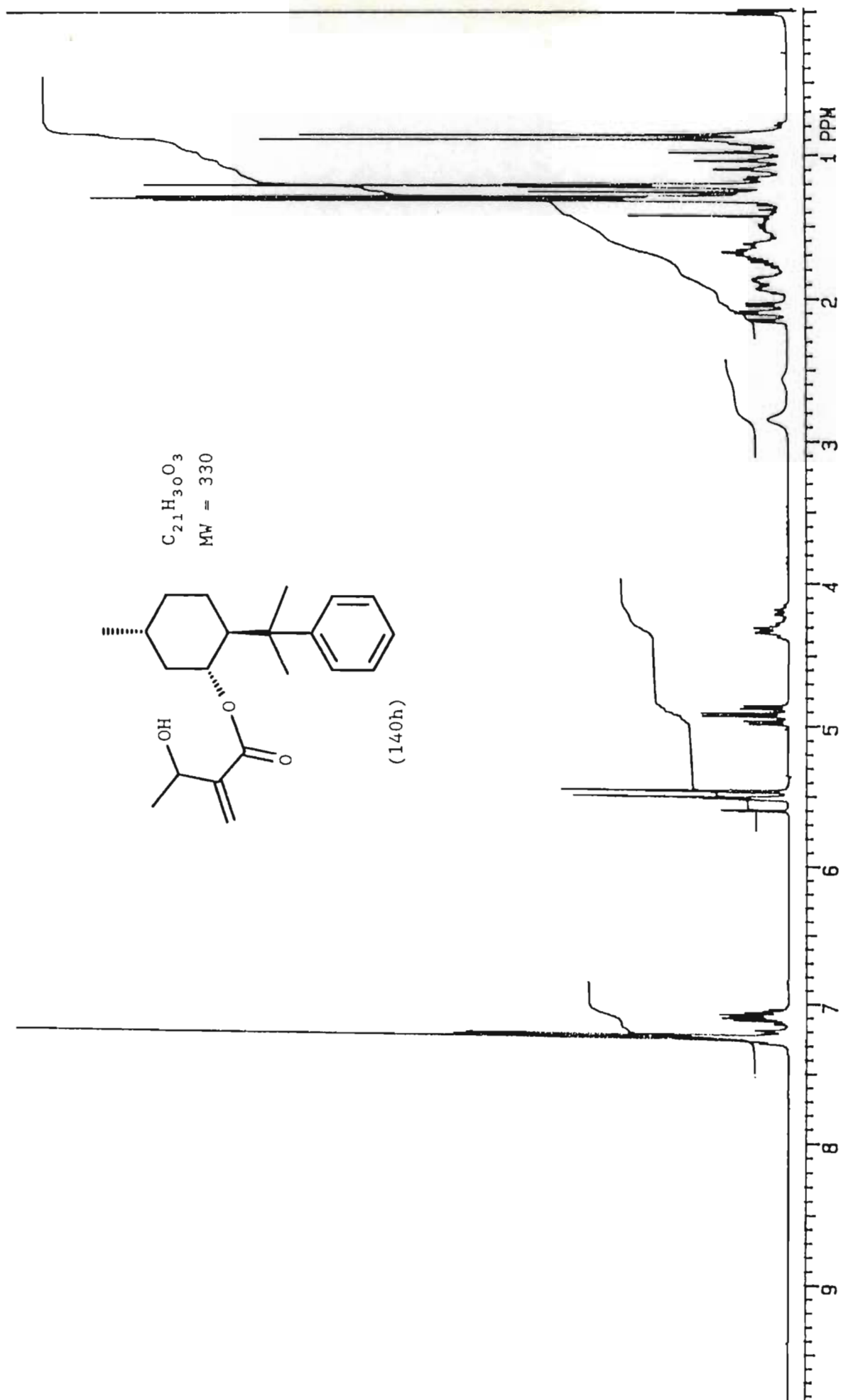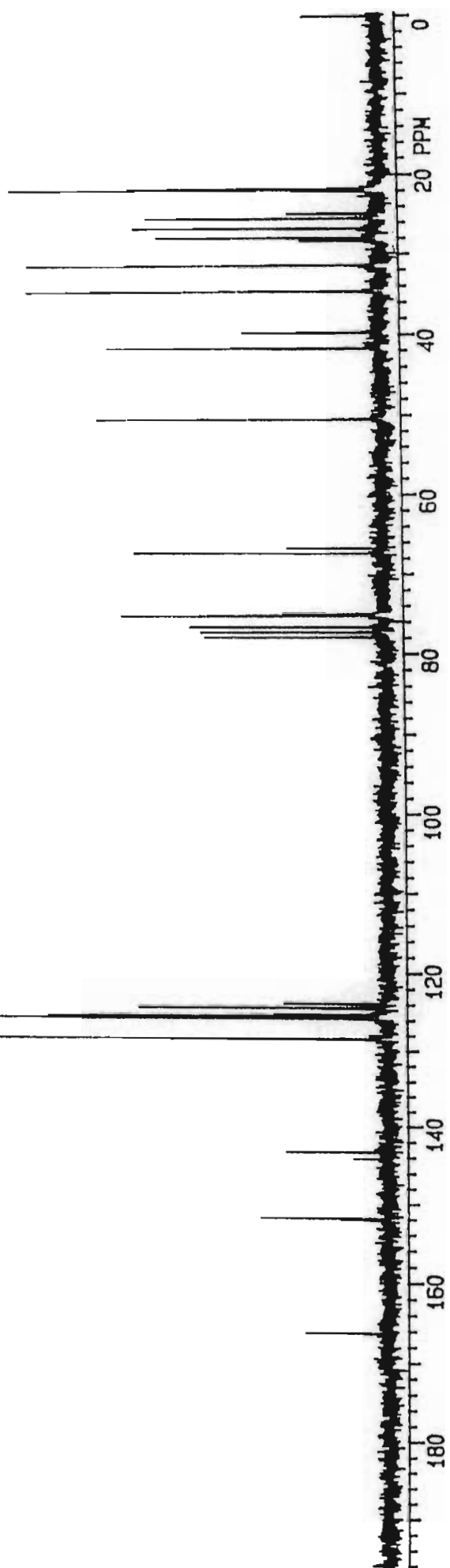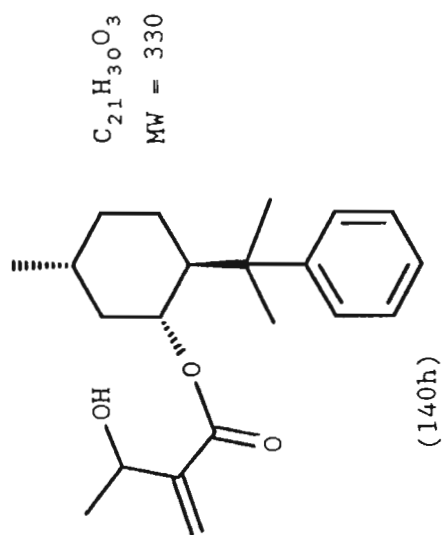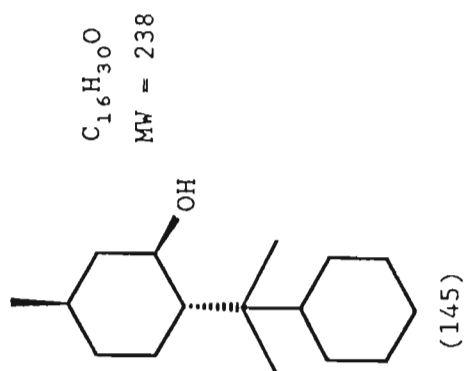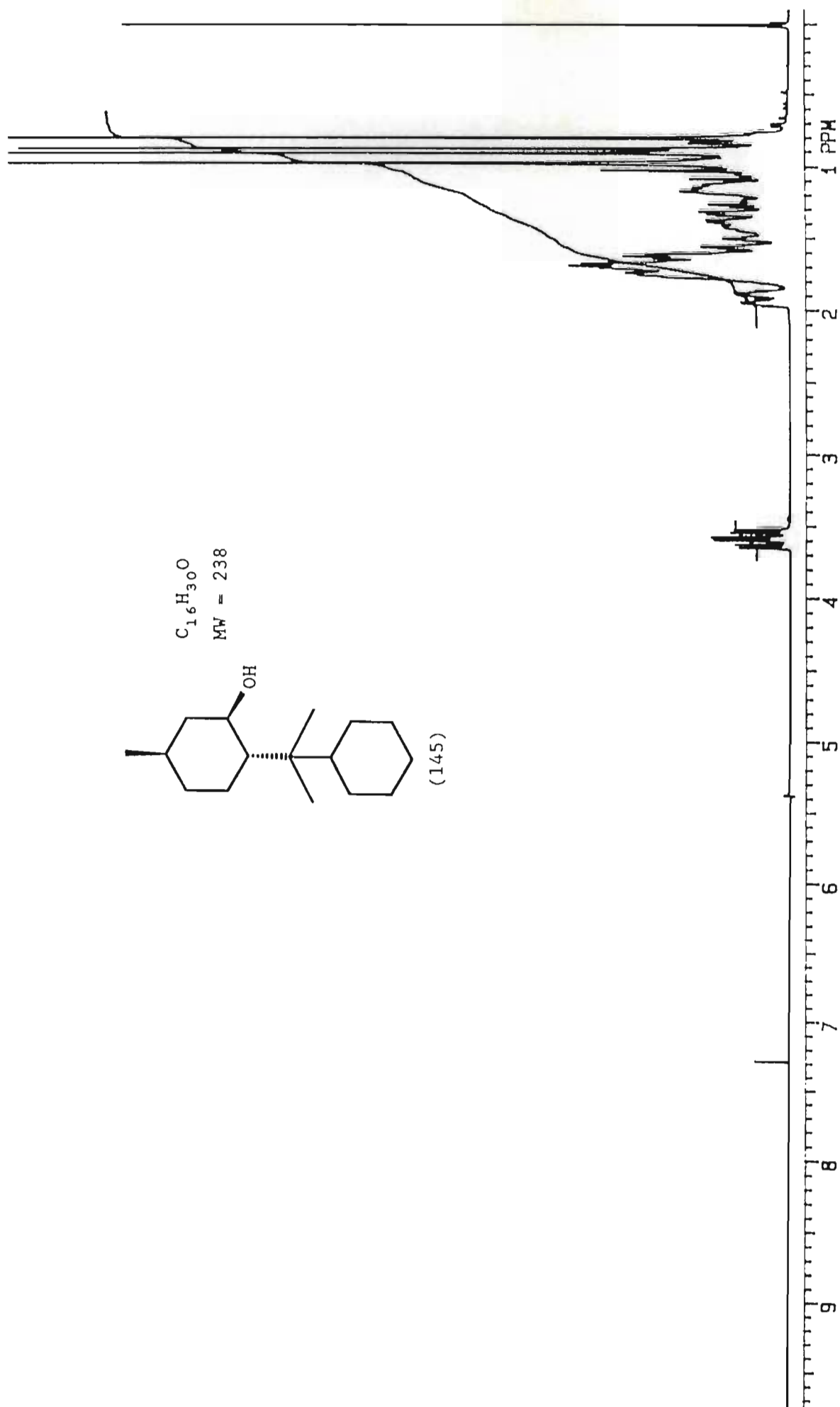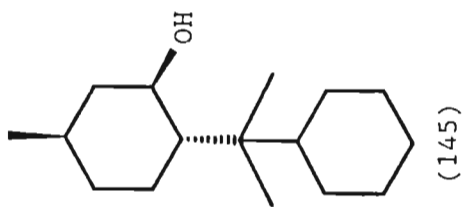
(140g)

$C_{24}H_{30}O_4$
MW = 382

(140g)

$C_{21}H_{30}O_3$

MW = 330

(140h)

$C_{21}H_{30}O_3$

MW = 330

(140h)

$C_{16}H_{30}O$

MW = 238

OH

(145)

9   8   7   6   5   4   3   2   1 PPM

$C_{16}H_{30}O$

MW = 238

OH

(145)

$C_{19}H_{32}O_2$
MW = 292

(146)

1 PPM

$C_{19}H_{32}O_2$
MW = 292

(146)

$C_{21}H_{33}Cl_3O_3$

$MW = 356$

(147a)

$C_{21}H_{33}Cl_3O_3$

MW = 356

(147a)

$C_{22}H_{38}O_3$

MW = 350

(147b.)

$C_{26}H_{37}NO_3$
MW = 443

(147d)

$C_{26}H_{38}O_3$

MW = 398

(147e)

$C_{26}H_{38}O_3$
MW = 398

(147e)

$C_{21}H_{36}O_3$
$MW = 336$

(147f)

$C_{21}H_{36}O_3$

MW = 336

(147f)

$C_{15}H_{25}NO_6$

MW = 315

(151)

$C_{15}H_{25}NO_6$
MW = 315

(151)

$C_{12}H_{12}N_2O_4$
MW = 248

(153)

1 PPM
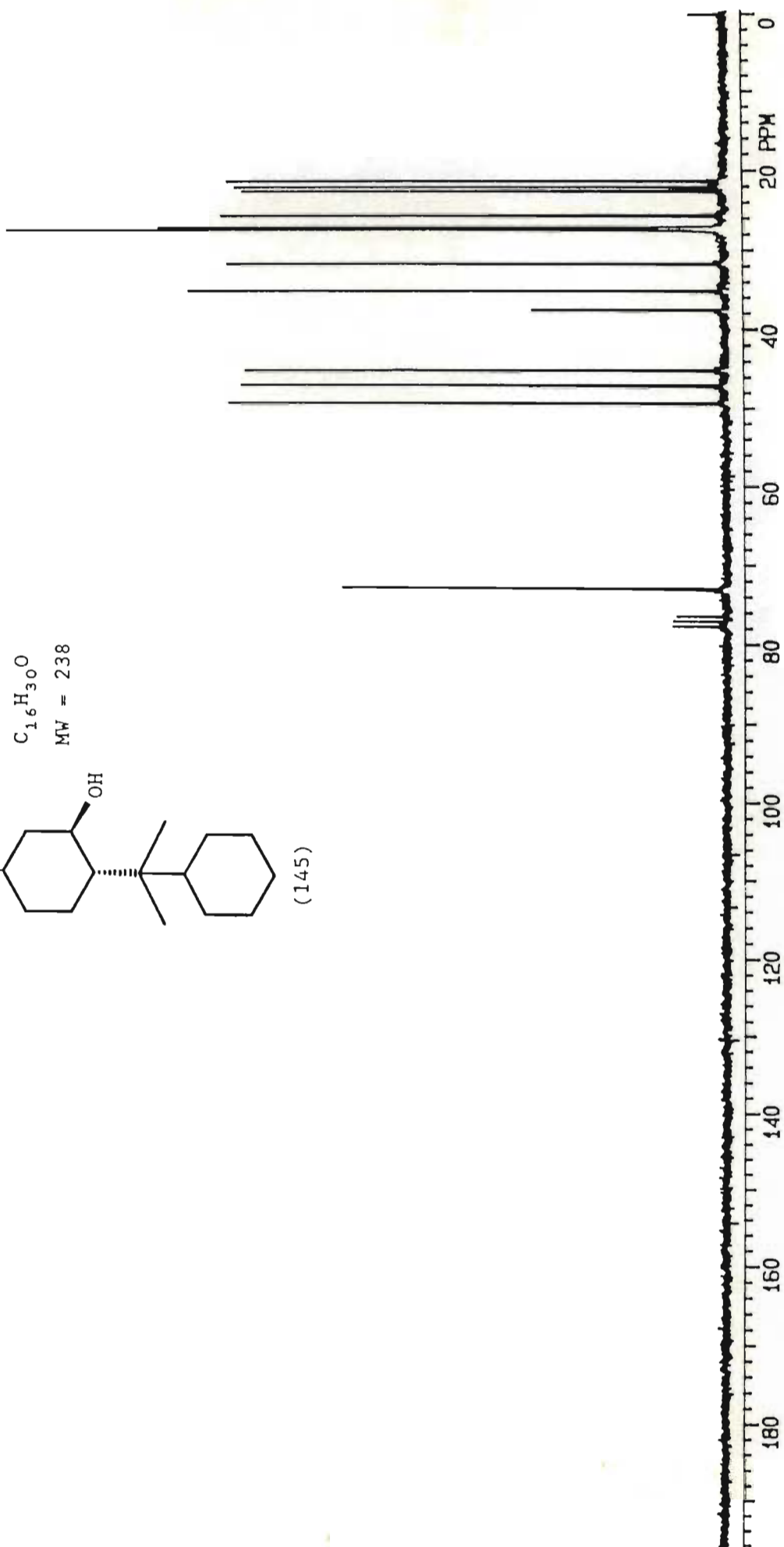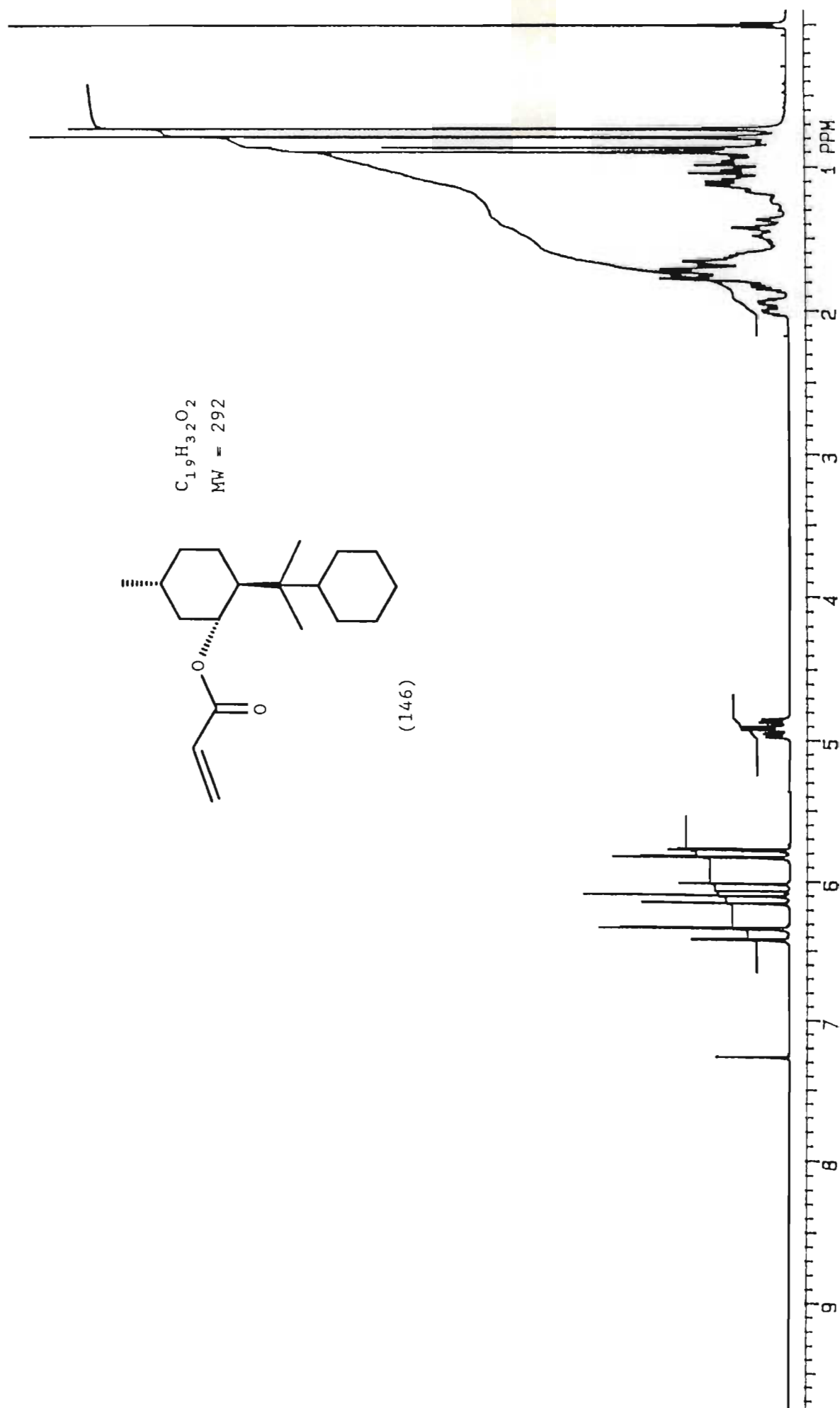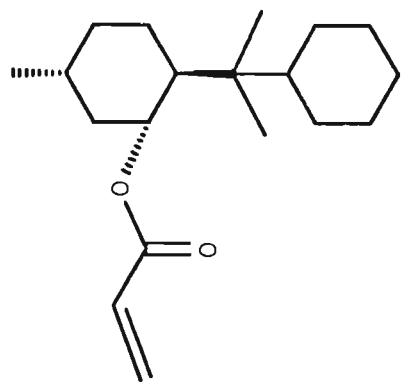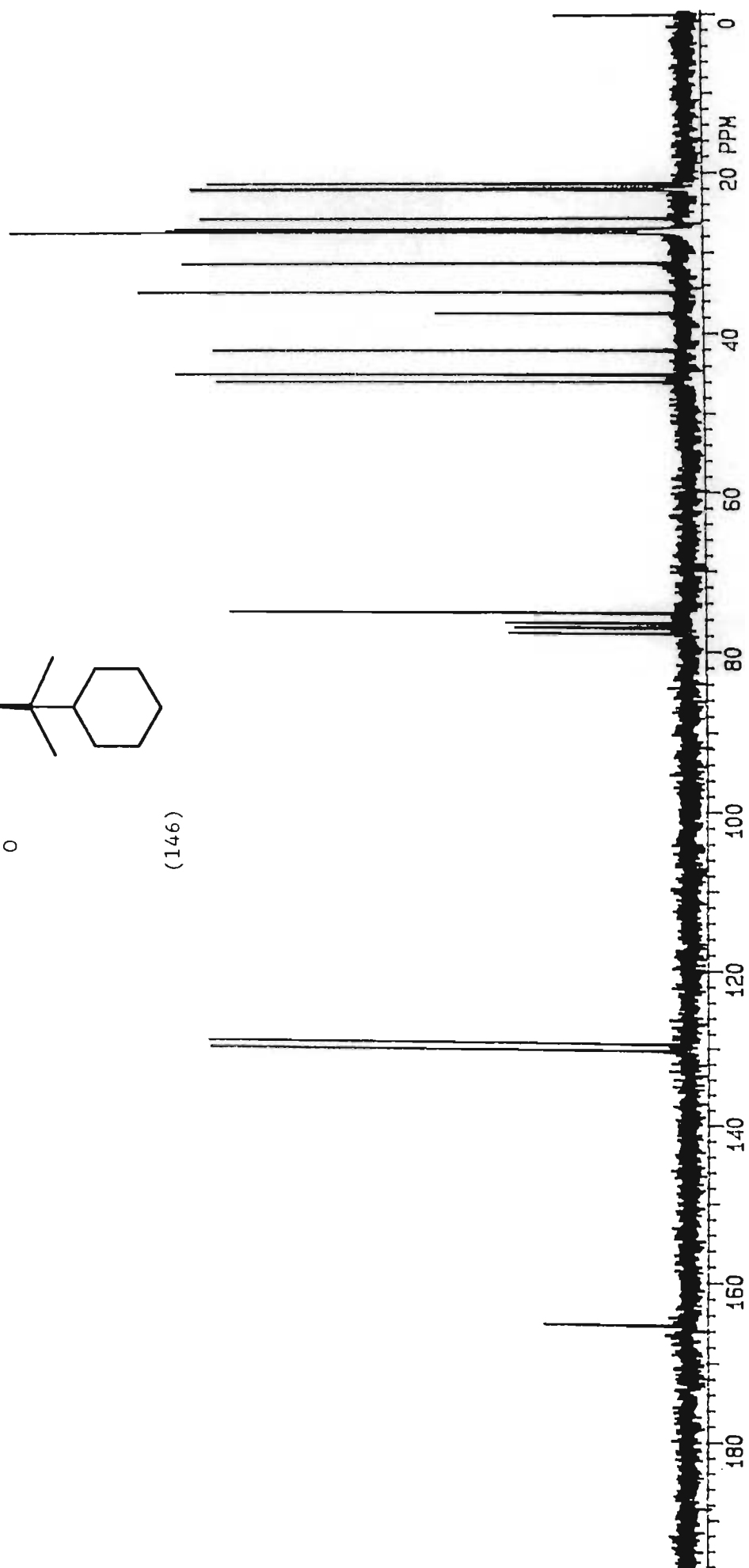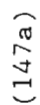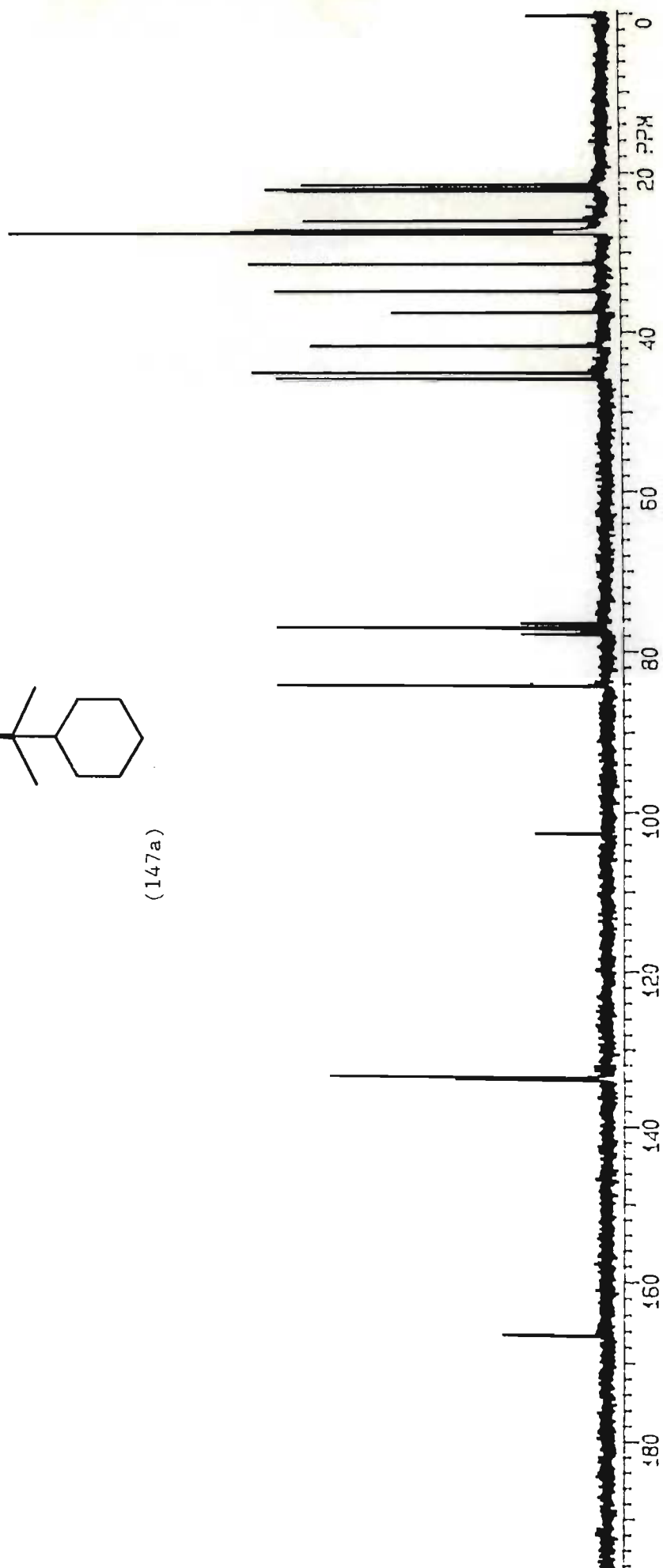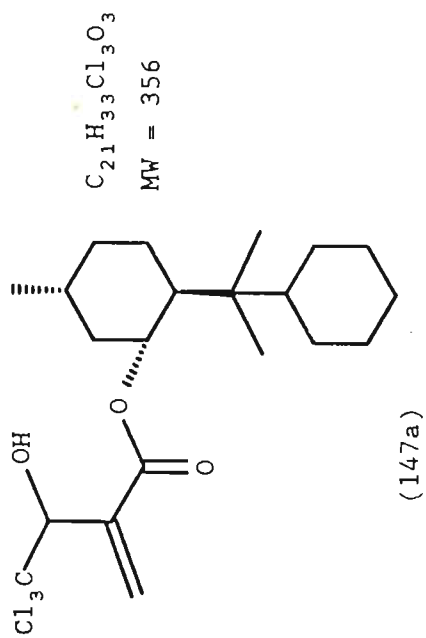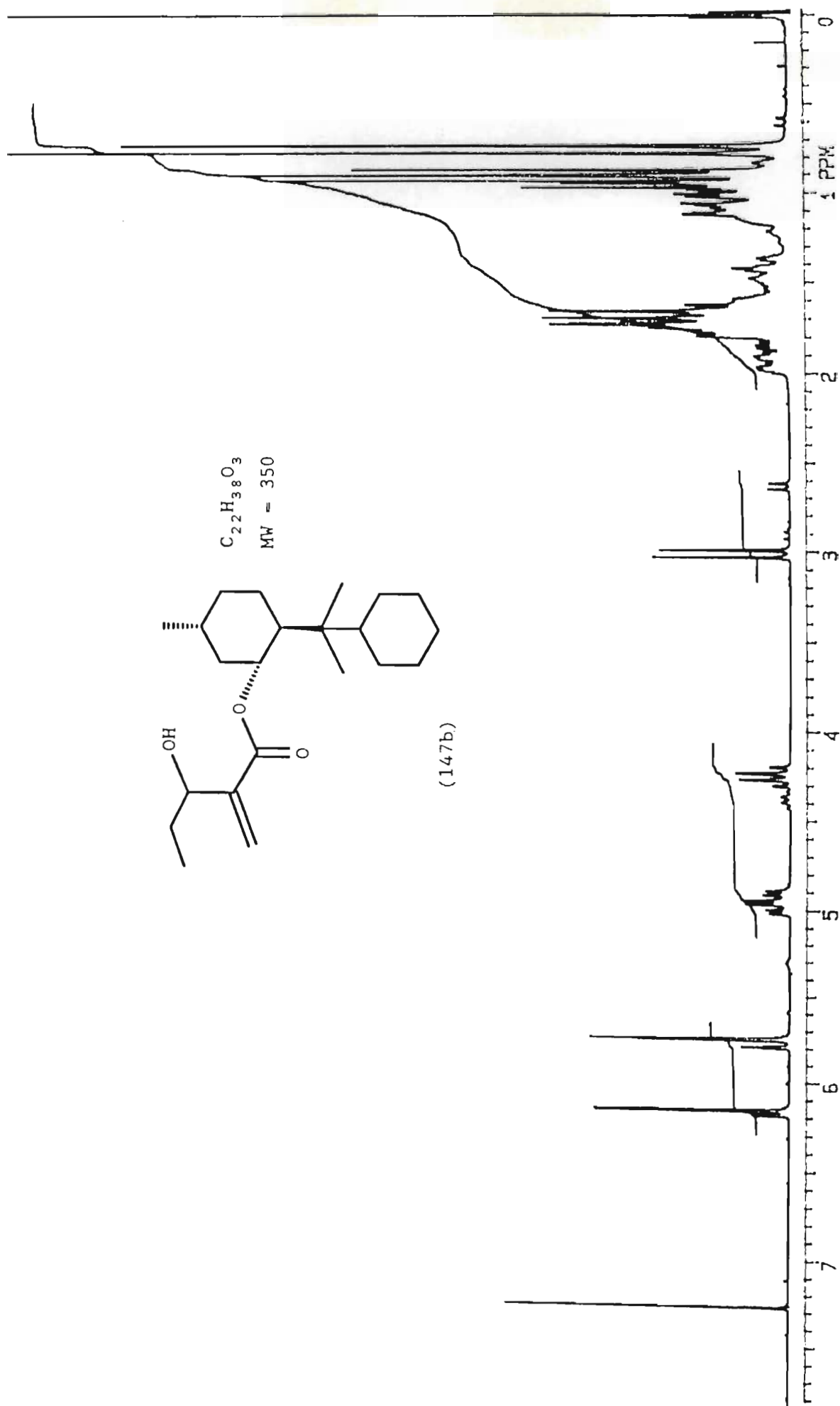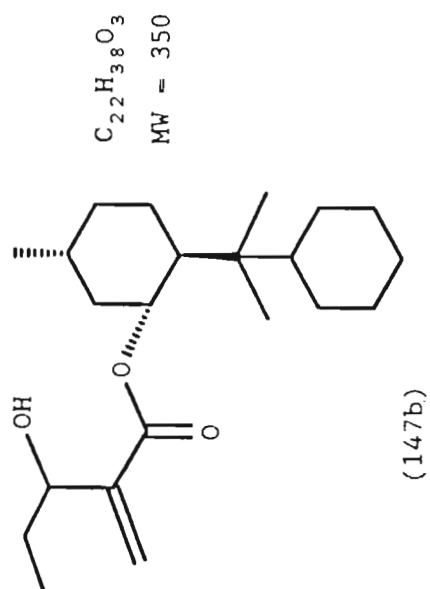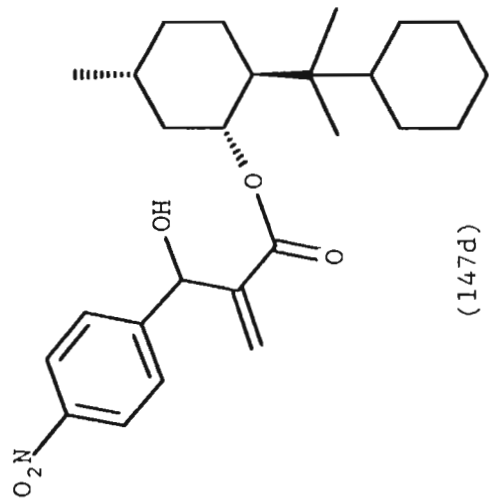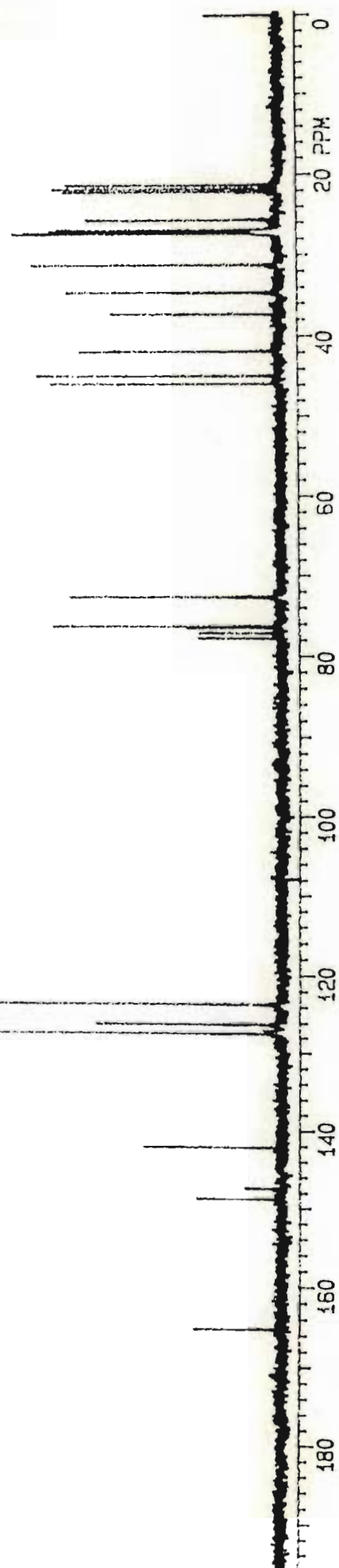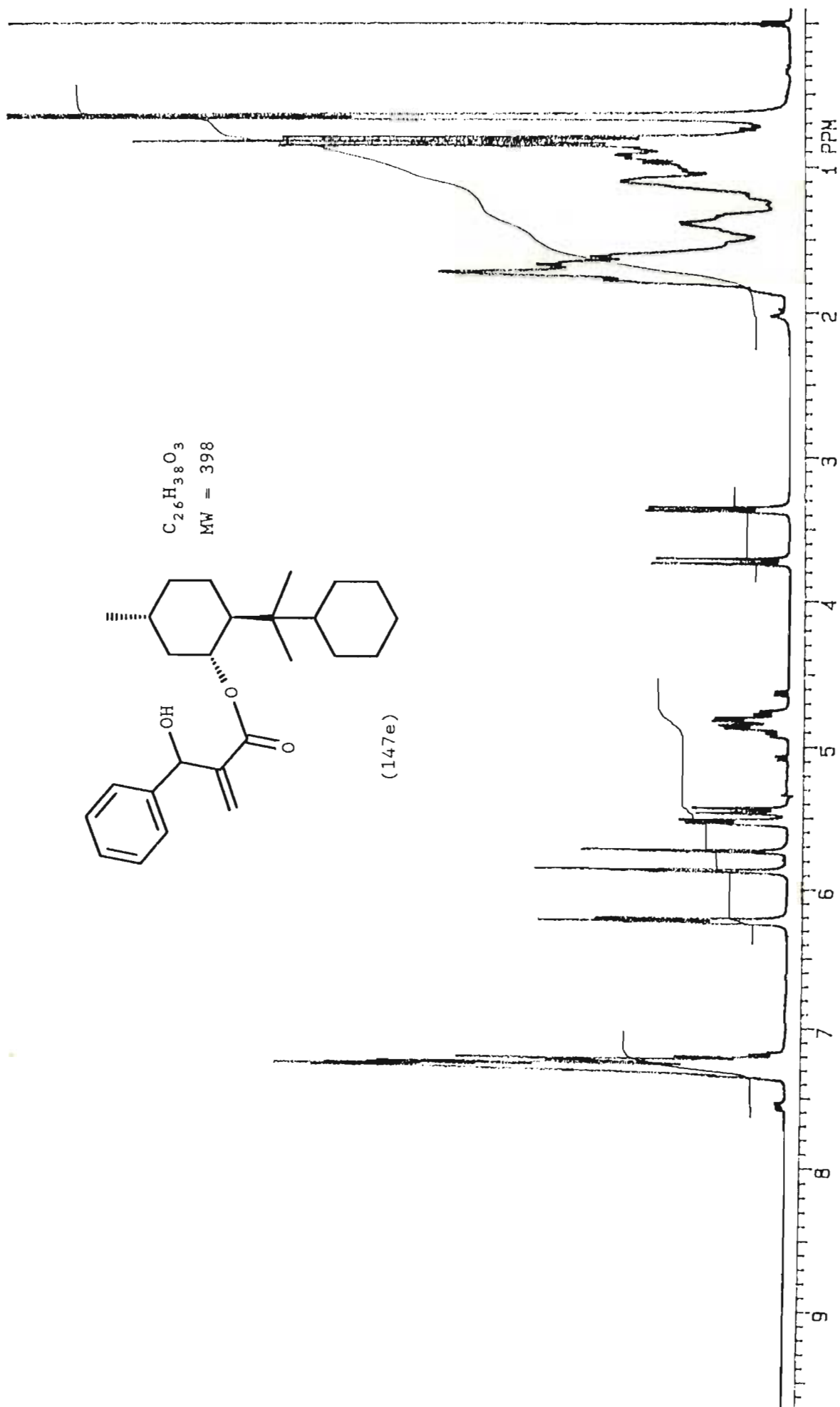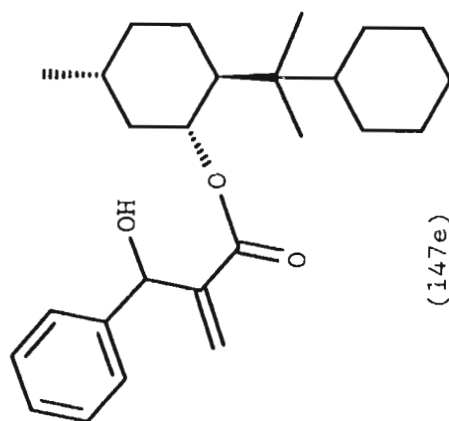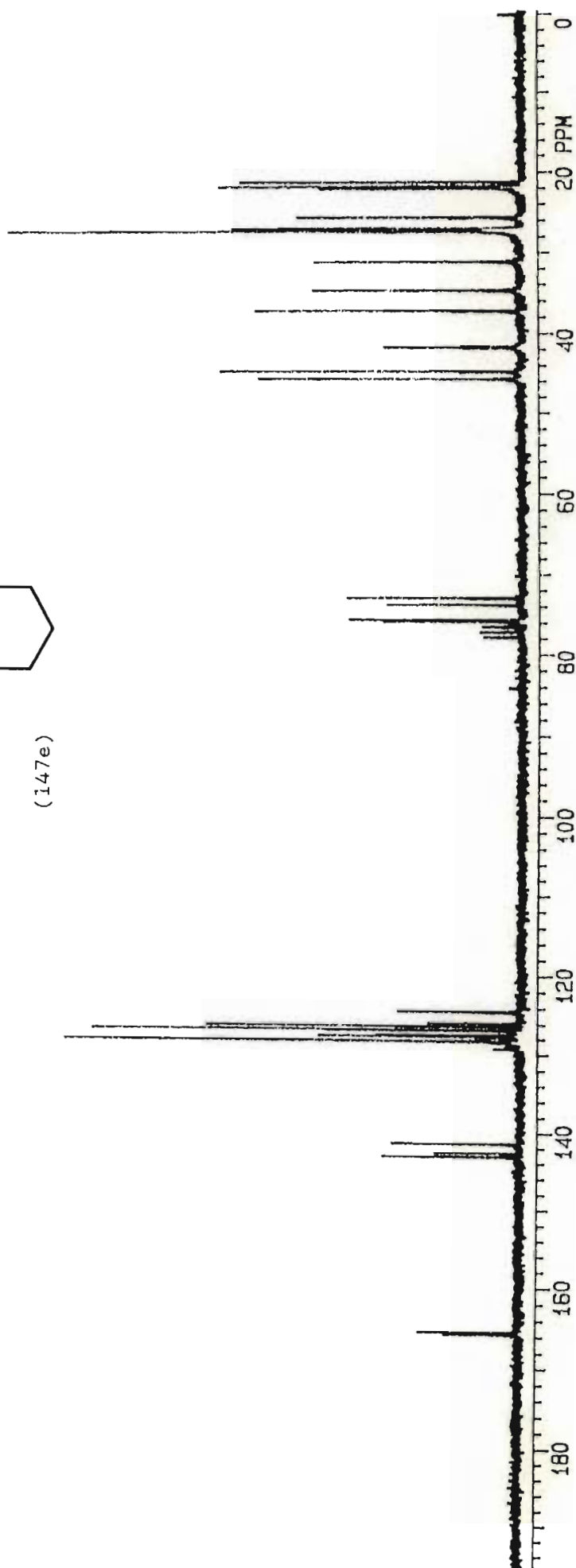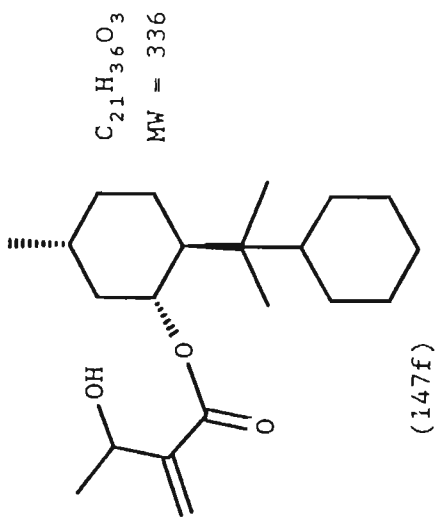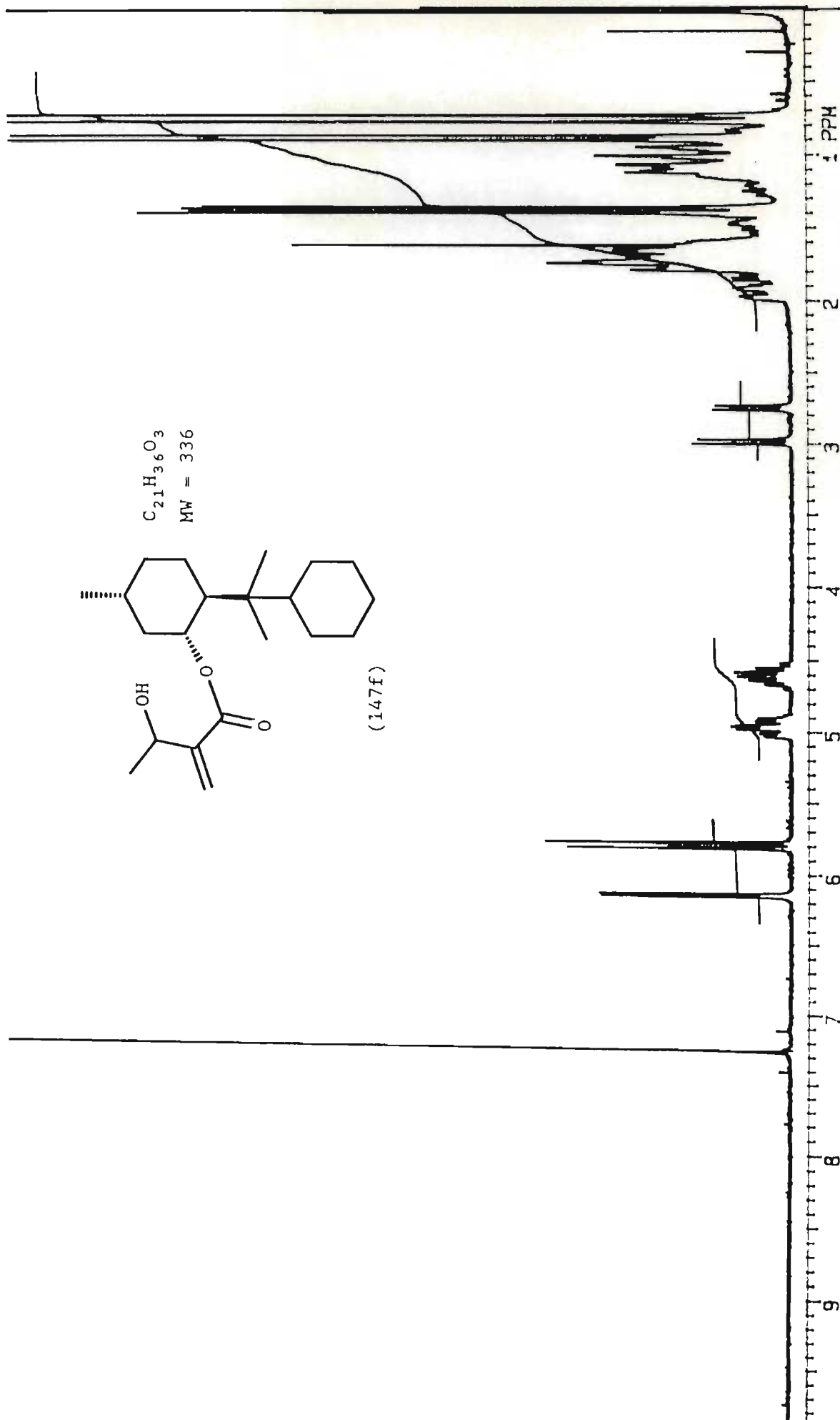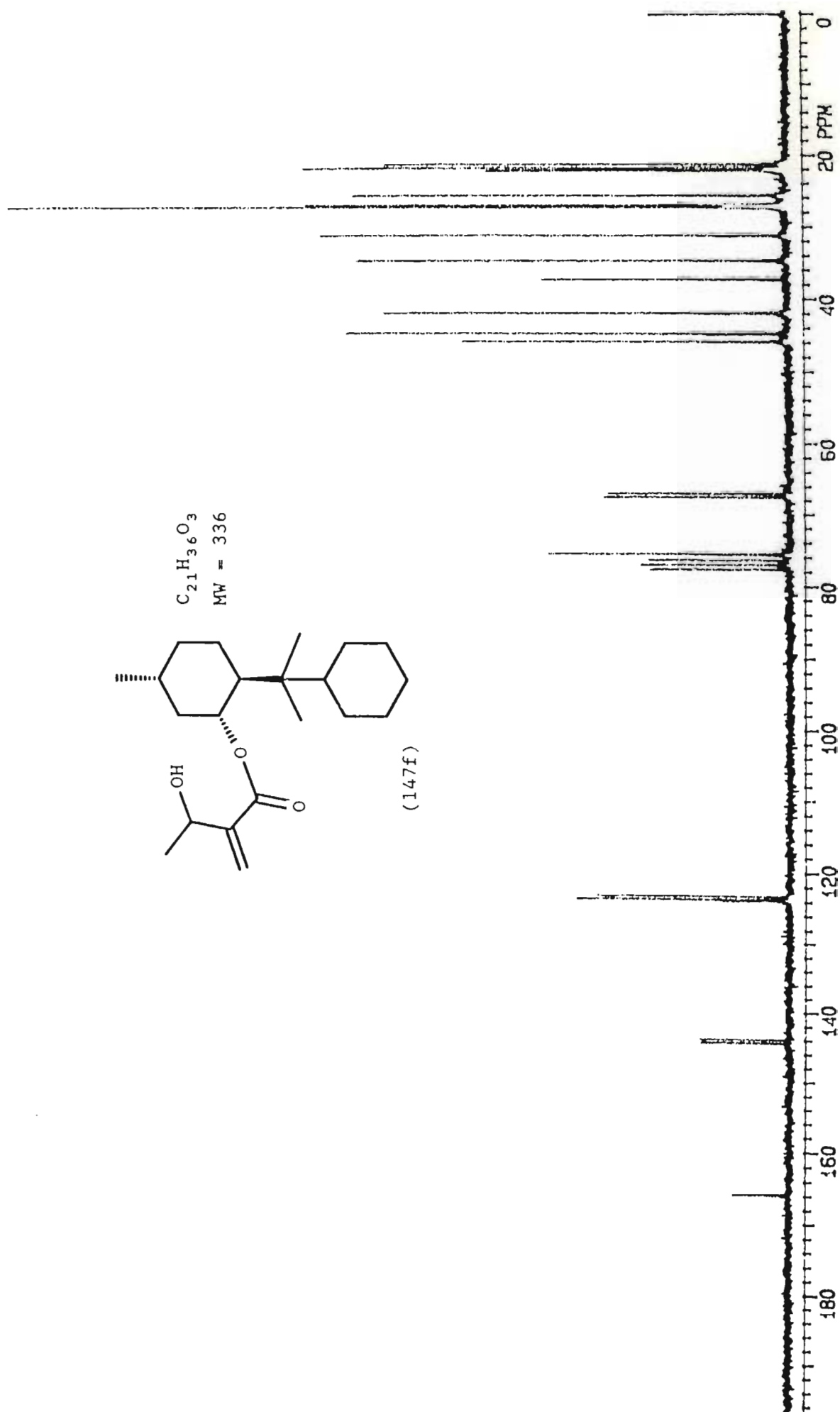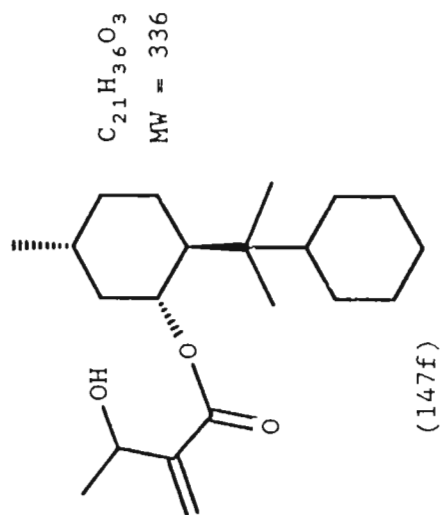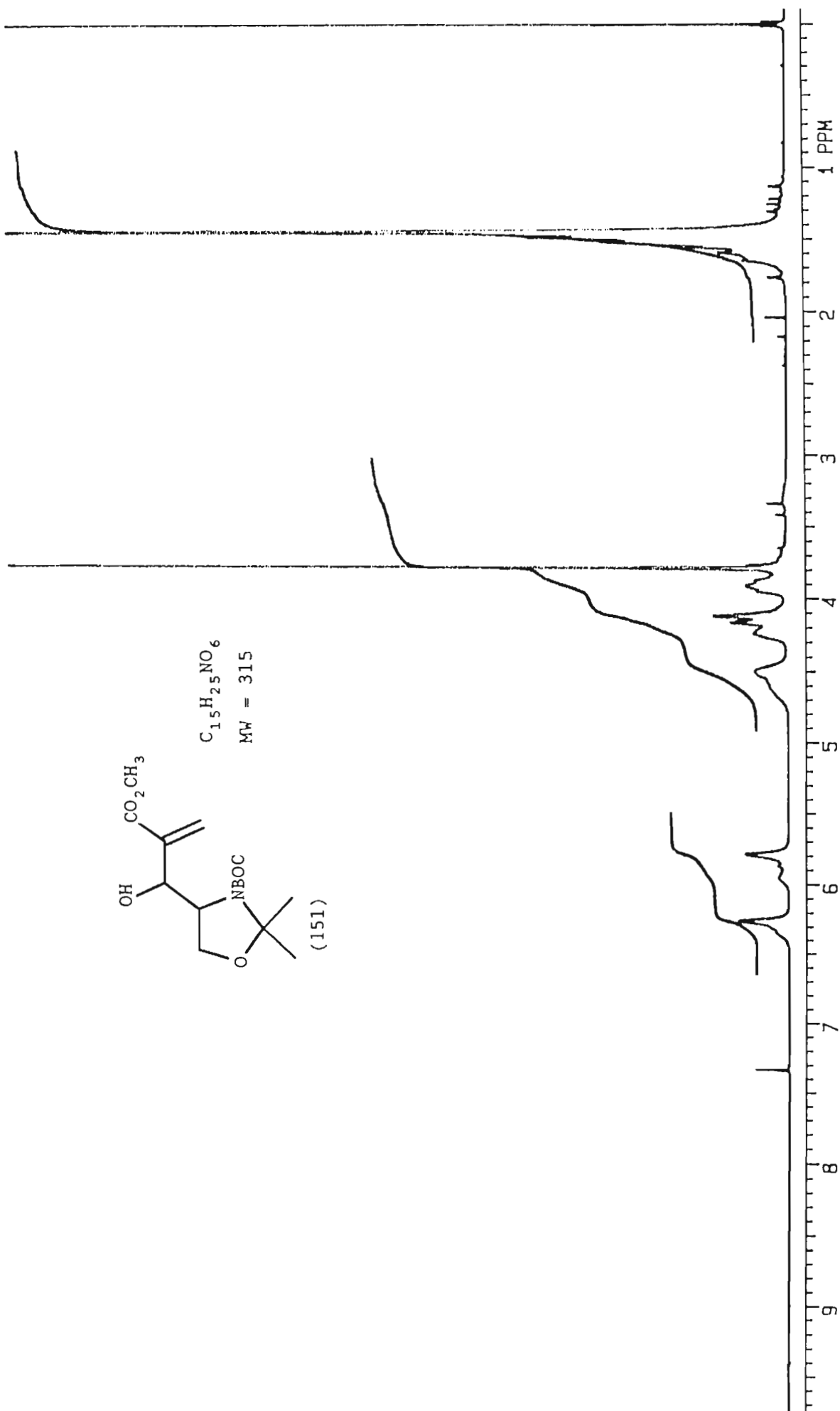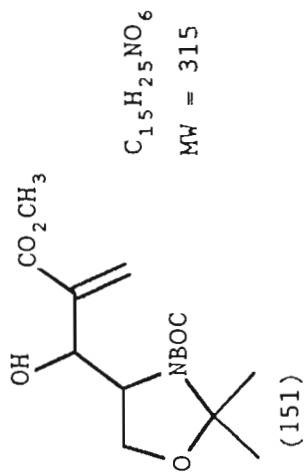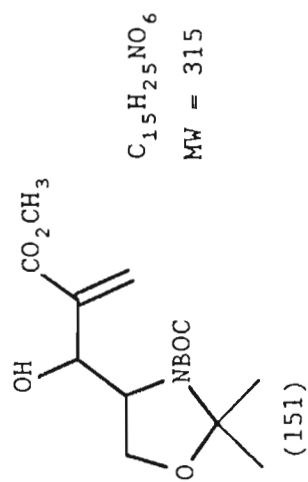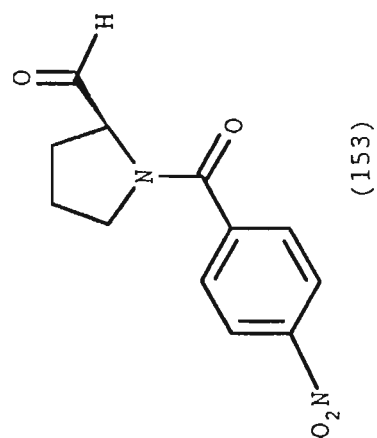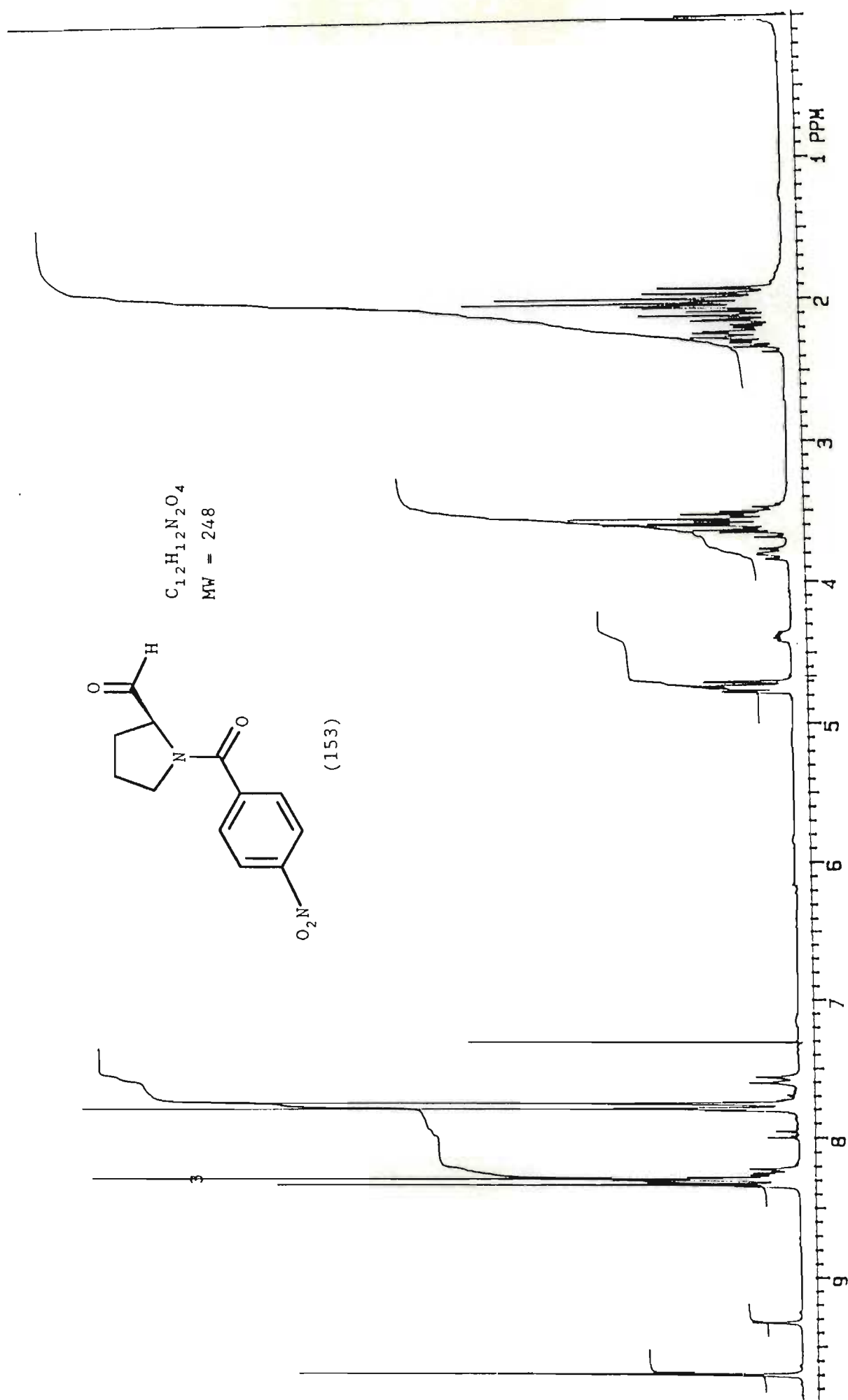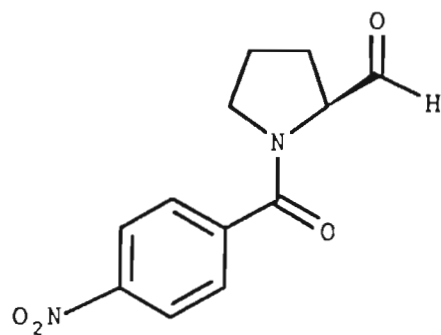
$C_{12}H_{12}N_2O_4$

MW = 248

(153)

$C_{16}H_{18}N_2O_6$

MW = 334
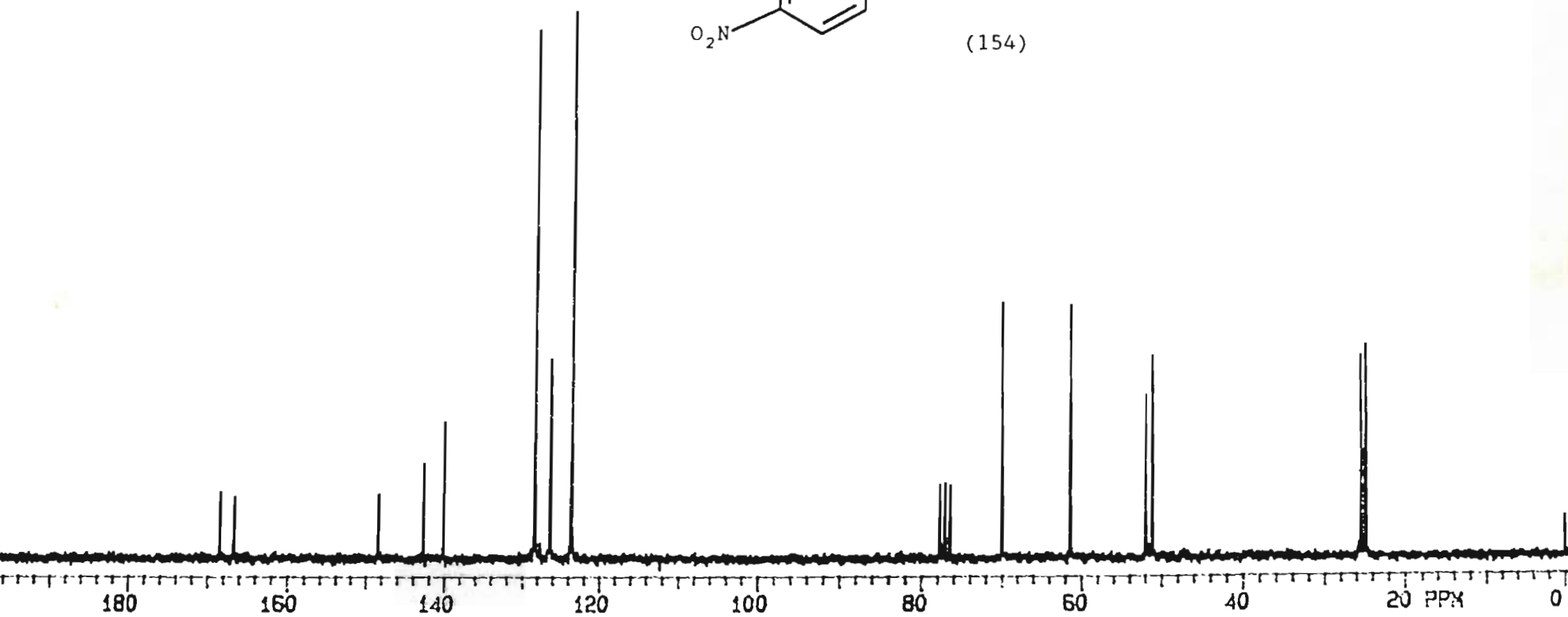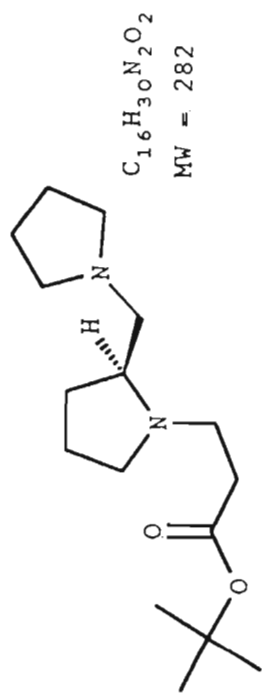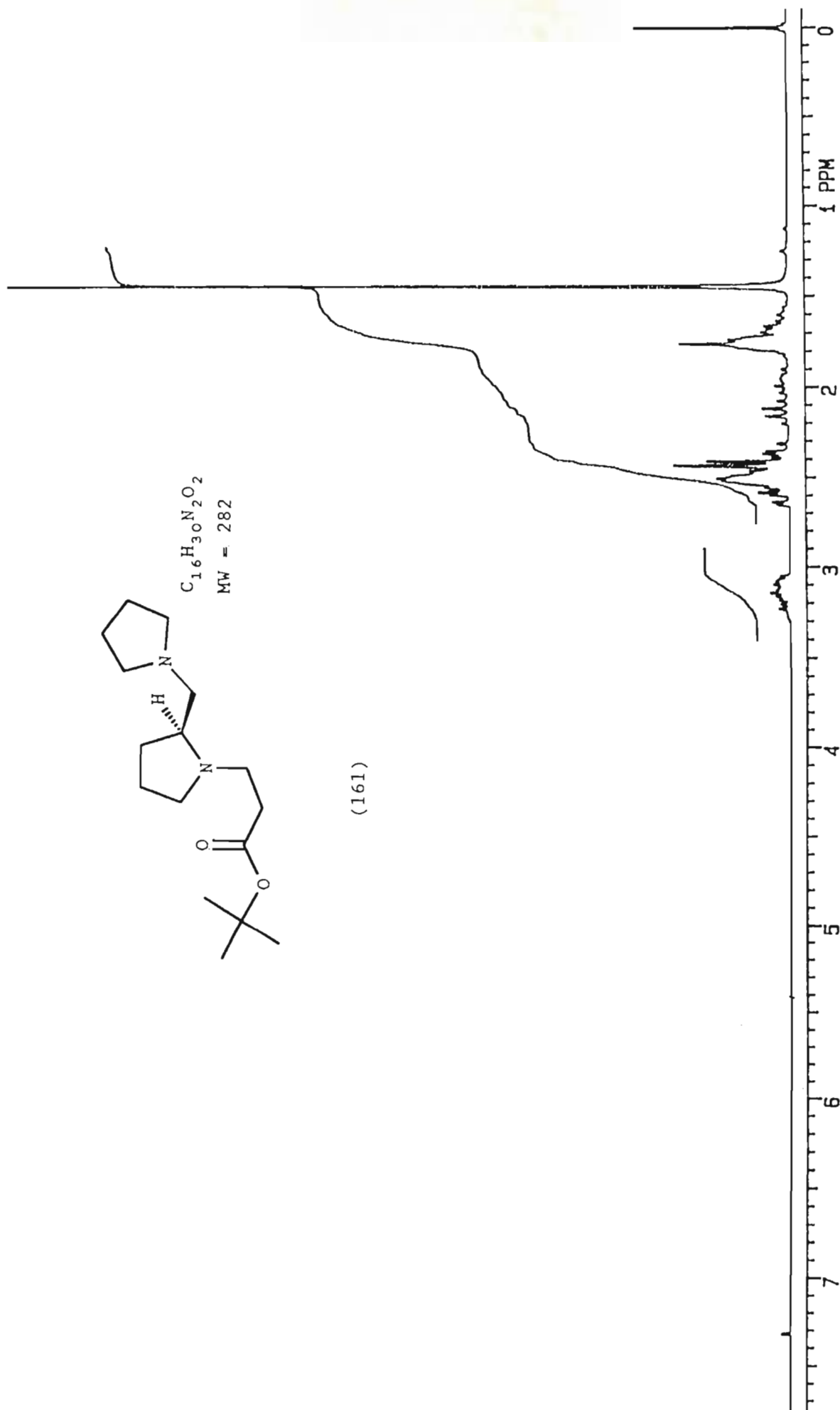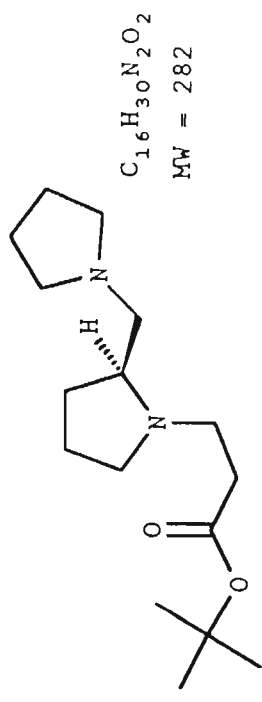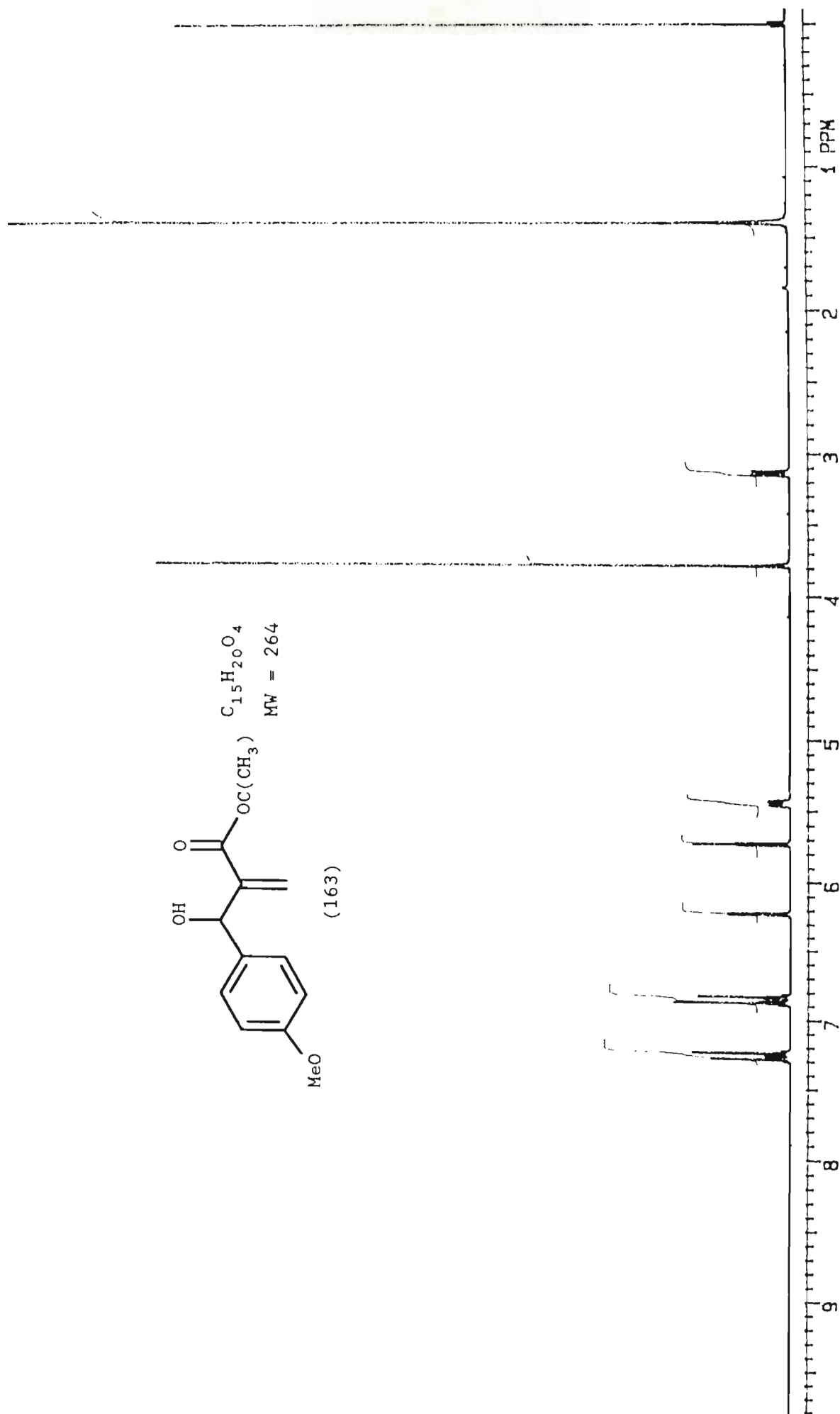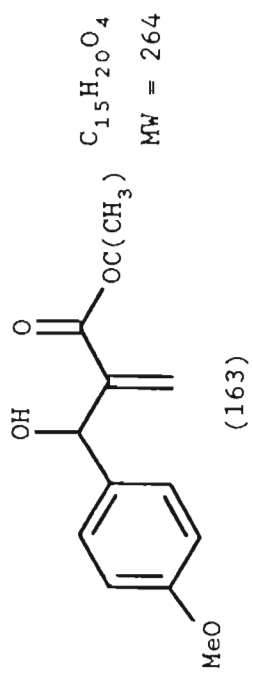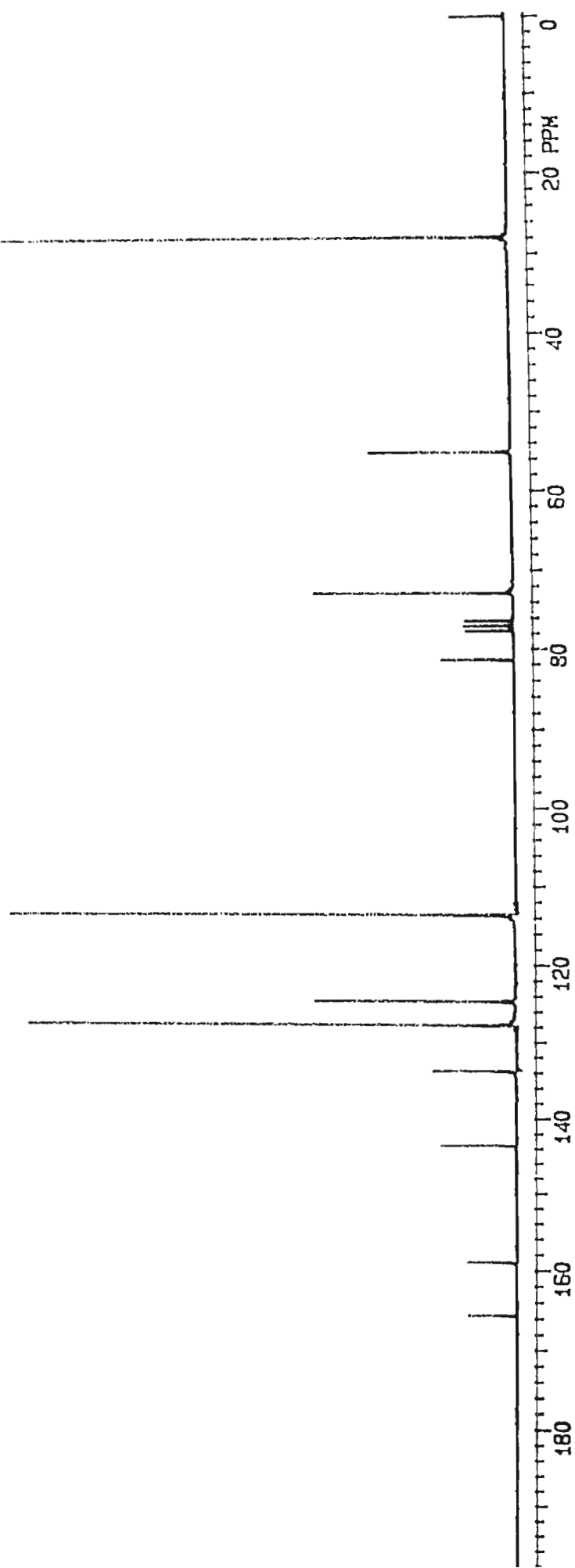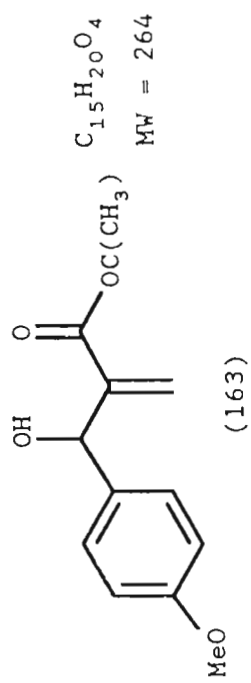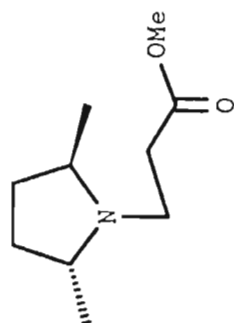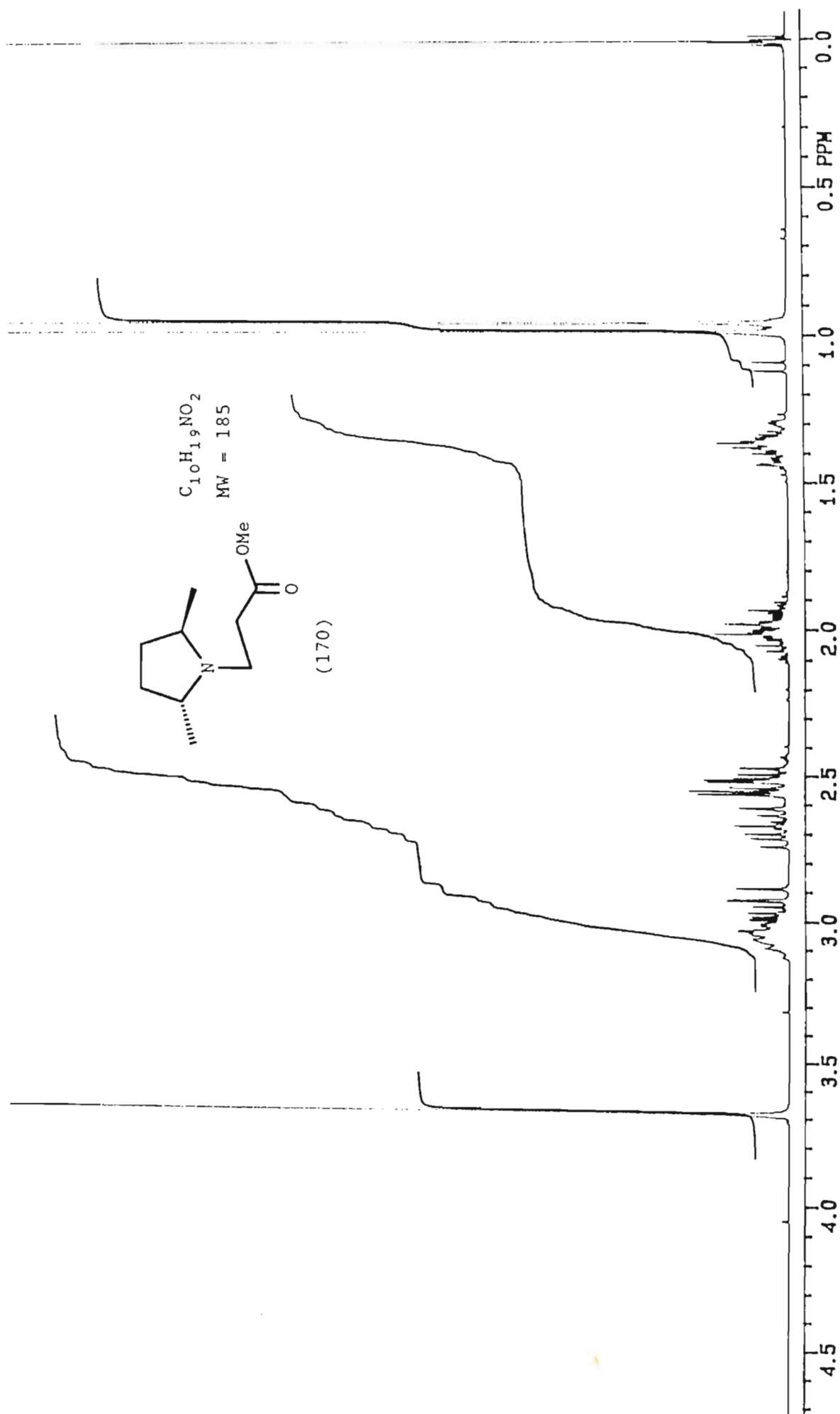
(154)

$C_{16}H_{18}N_2O_6$

MW = 334

(154)

$C_{16}H_{30}N_2O_2$

MW = 282

(161)

$C_{16}H_{30}N_2O_2$

MW = 282

(161)

$C_{15}H_{20}O_4$

MW = 264

OC(CH_3)

(163)

1 PPM

$C_{15}H_{20}O_4$

MW = 264

OC(CH$_3$)

(163)

$C_{10}H_{19}NO_2$
MW = 185

OMe

O

(170)

$C_{10}H_{19}NO_2$

MW = 185

OMe

O

(170)

$C_{12}H_{14}O_4$

MW = 222

(171)

$C_{12}H_{14}O_4$

MW = 222

(171)

$C_{13}H_{25}NO_2$

MW = 227

OC(CH$_3$)$_3$

(172)

$C_{13}H_{25}NO_2$

MW = 227

OC(CH₃)₃ → $OC(CH_3)_3$

(172)

$C_{14}H_{27}NO_6$

MW = 305

(179)

$C_{14}H_{27}NO_6$

MW = 305

(179)

$C_{10}H_{19}NO_3$
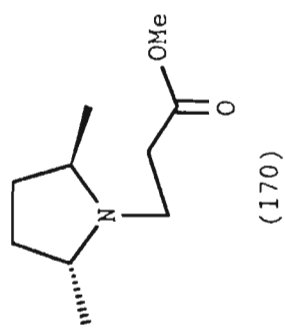
MW = 201

(183a)
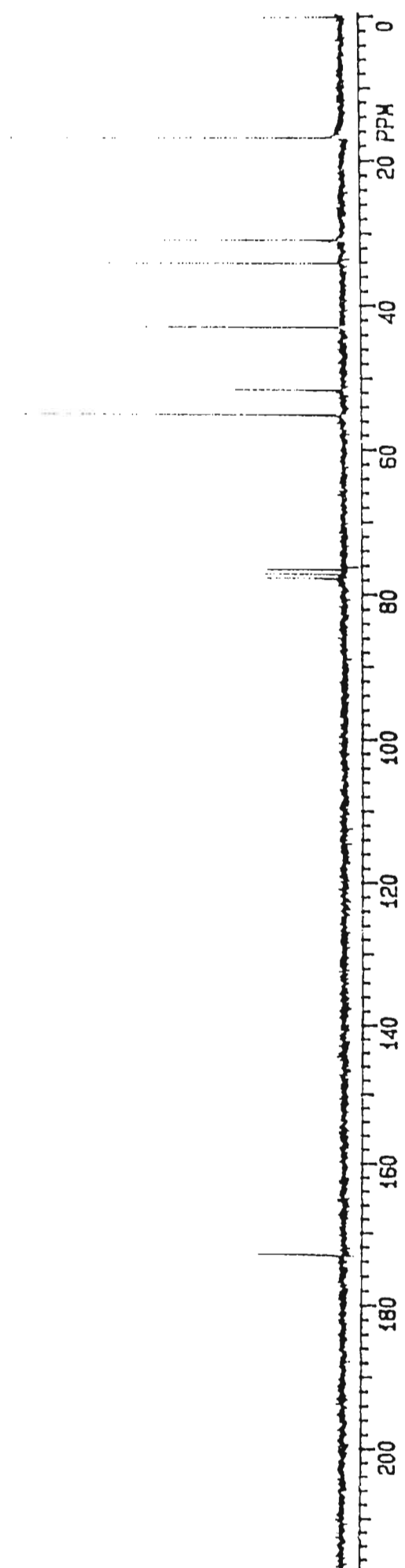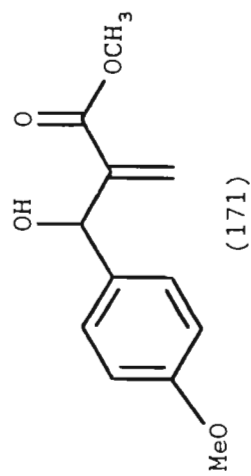
C₁₀H₁₉NO₃

MW = 201
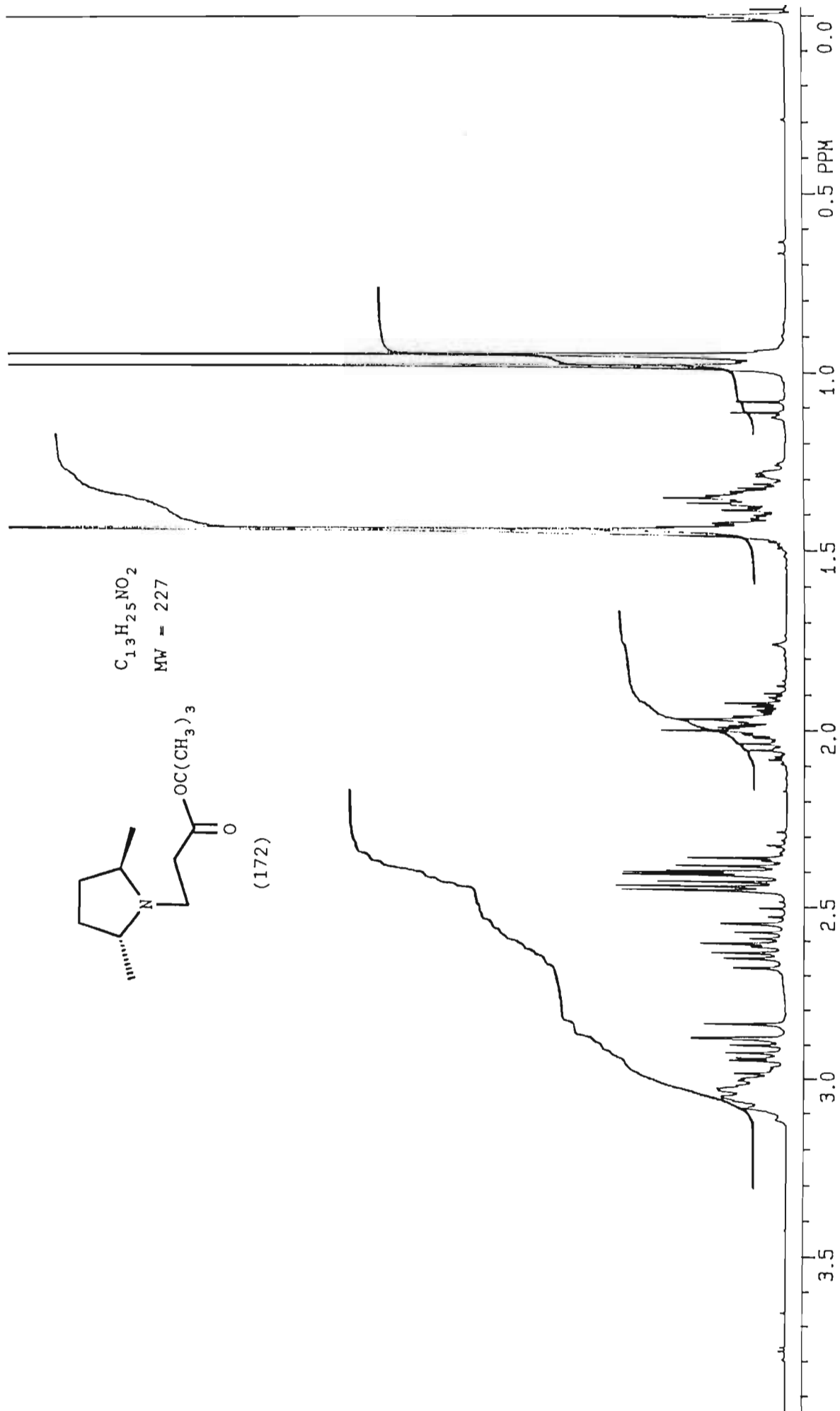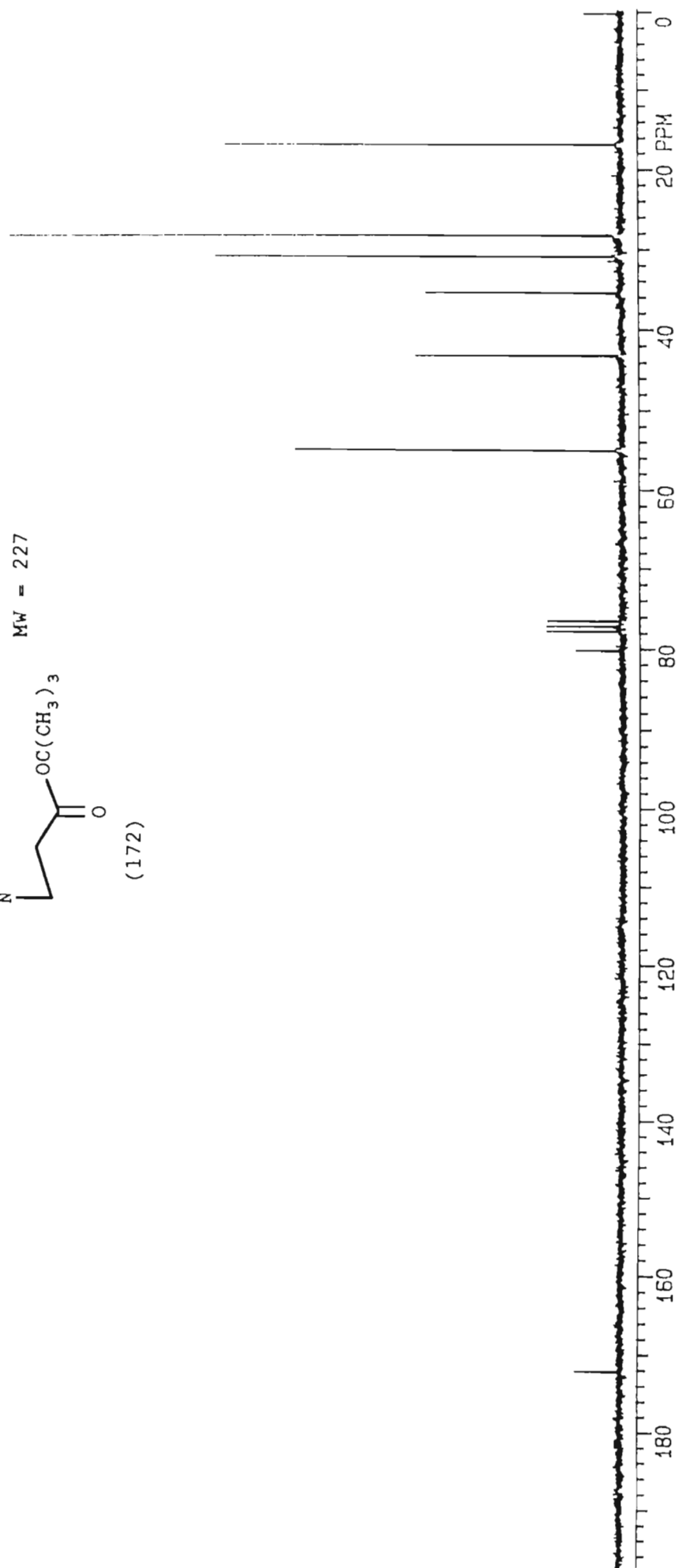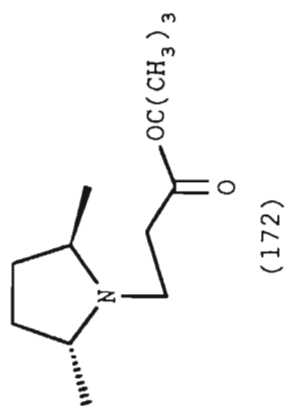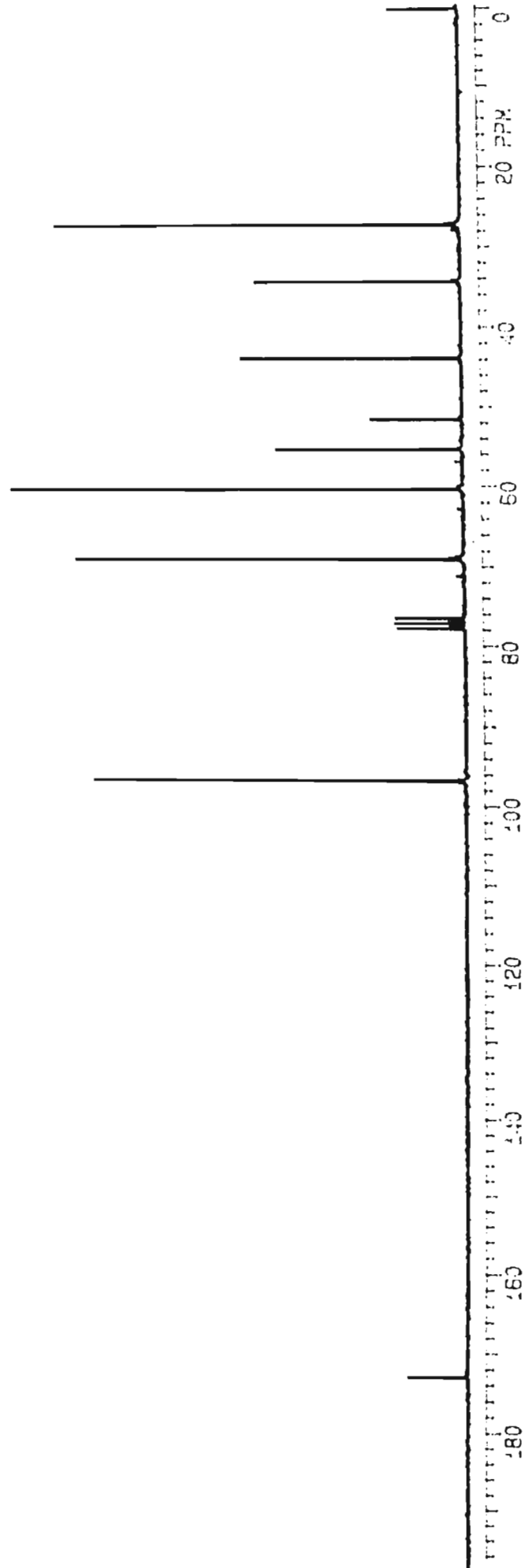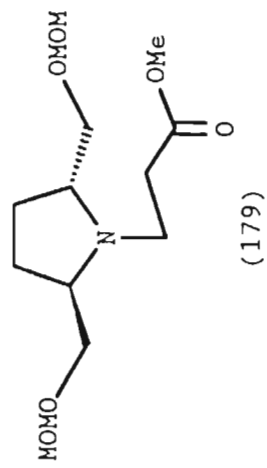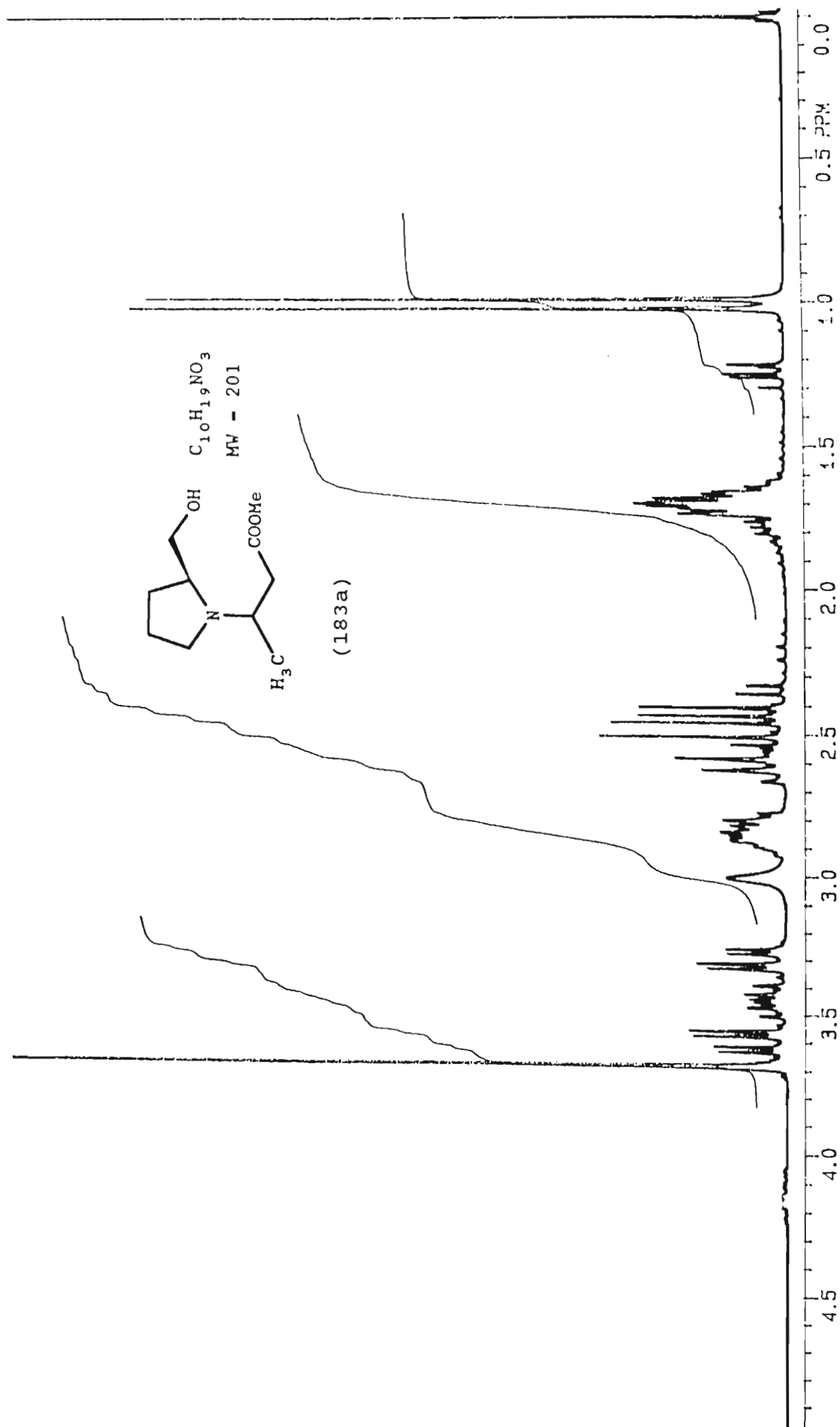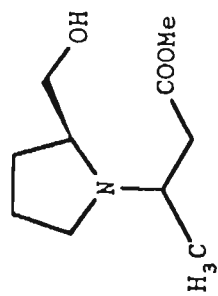
(183a)

$C_{10}H_{19}NO_3$

MW = 201
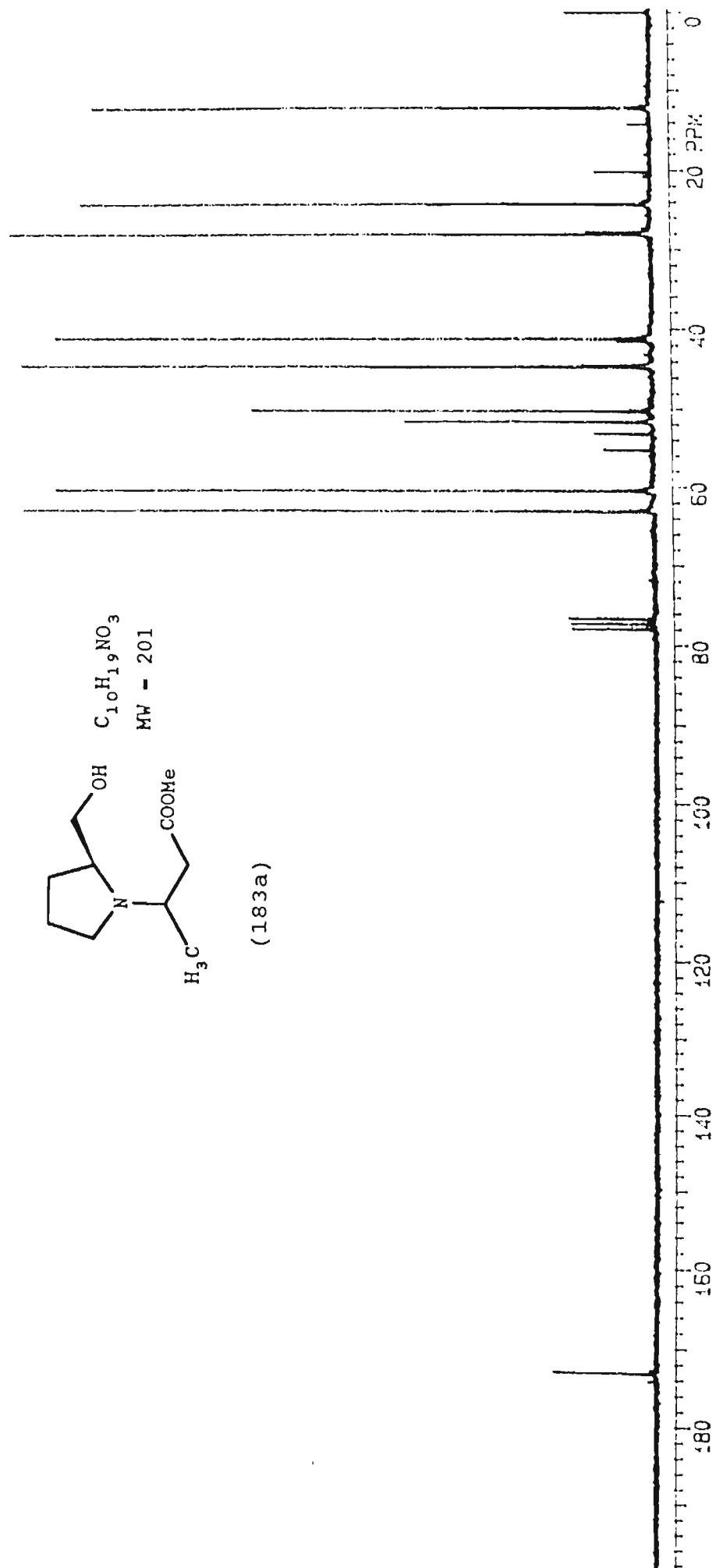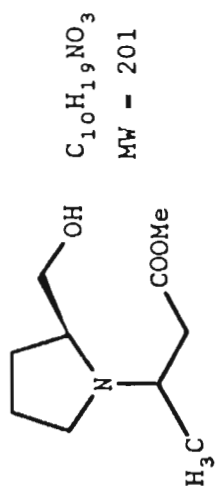
$C_{10}H_{19}NO_3$

MW – 201

(183b)

$C_{10}H_{19}NO_3$

MW — 201

(183b)

H₃C—CH=C(—COOMe)—CH(OH)—C₆H₅

$C_{12}H_{14}O_3$

MW = 206

(182a)

COOMe $C_{12}H_{14}O_3$

MW = 206

H

H$_3$C

OH

(182a)

COOMe

H

H₃C

OH

MeO

$C_{13}H_{16}O_4$

MW = 236

(182b)

$C_{13}H_{16}O_4$

MW = 236

(182b)

$C_{12}H_{13}NO_5$

MW = 251

(182c)

(182c)

$C_{12}H_{13}NO_5$

MW = 251

$C_9H_{14}O_4$

MW = 186

(184)

1 PPM

$C_9H_{14}O_4$

MW = 186

(184)

$C_{16}H_{20}O_5$

MW = 292

(187)

$C_{16}H_{20}O_5$

MW = 292

(187)