A STEREOSELECTIVE SYNTHESIS OF THE TETRACYCLIC QUASSINOID FRAMEWORK

by

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We accept this thesis as conforming
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ABSTRACT

A new synthetic route to the tetracyclic framework of the quassinoids, Compound **80**, was developed. This new route, starting from 2-cyclohexene-1-one **41** via 2-bromo-1-vinylcyclohexenyl acetate **42** and (*E,E*)-6-(7-methoxycarbonyl-6-heptenylidene)-1-cyclohexene-1-carboxaldehyde **78** as intermediates, employed a diene-transmissive Diels-Alder cycloaddition as the key reaction and could be used for the total synthesis of quassinoid compounds. The formation of the ABD rings in the quassinoid skeleton was achieved in one step for the first time based on this new synthetic methodology.

The δ-lactone D ring formation with stereochemical control was investigated through the racemic (*E*)-3-methyl-6-propylidene-1-cyclohexene-1-carboxaldehyde **37** and (3S,4R)-(*E*)-6-propylidene-3,4-dihydroxy-O,O'-isopropylidene-1-cyclohexene-1-carboxaldehyde **39** using an inverse electron demand hetero Diels-Alder cycloaddition. The structures of the formed cycloadducts **38a** and **40a** revealed that the D ring formation could be stereochemically controlled by introducing a proper substituent at C-13 in the C ring.

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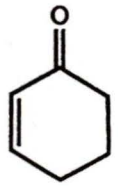

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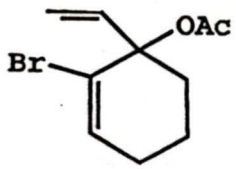

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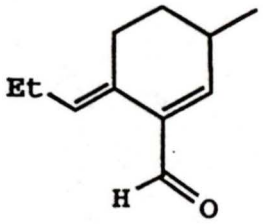

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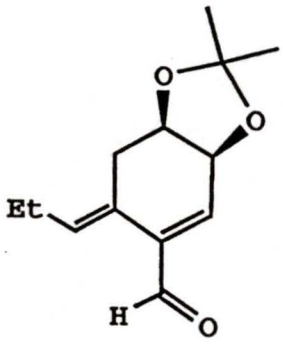

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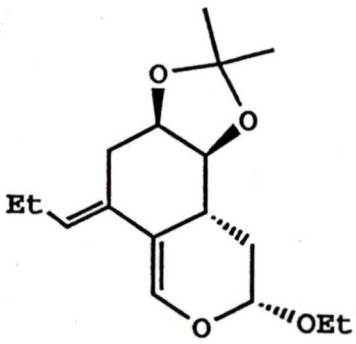
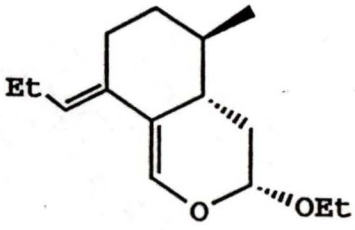


40a



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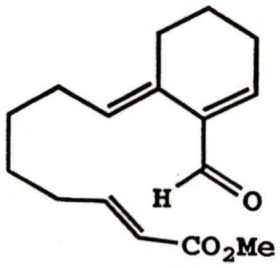

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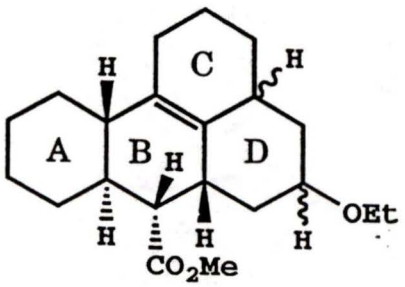

80

TABLE OF CONTENTS

LIST OF FIGURES

FIGURE PAGE

LIST OF ABBREVIATIONS

^{13}C NMR	carbon-13 nuclear magnetic resonance
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
DTDAC	diene-transmissive Diels-Alder cycloaddition
Et	ethyl
GC	gas chromatography
^{1}H NMR	proton nuclear magnetic resonance
br	broad
d	doublet
dd	doublet of doublets
dt	doublet of triplets
m	multiplet
q	quartet
qi	quintet
s	singlet
t	triplet
IR	infrared spectrum
ms	medium strong
s	strong
w	weak
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrum
LUMO	lowest unoccupied molecular orbital
Me	methyl
mp	melting point

MS	mass spectrum
CI	chemical ionization
EI	electron impact
S_N2'	bimolecular nucleophilic substitution with allylic rearrangement
THF	tetrahydrofuran
TS	transition state

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Last but not the least, I wish to thank my parents, my wife and all of the family members for their deep loving encouragement and patience.

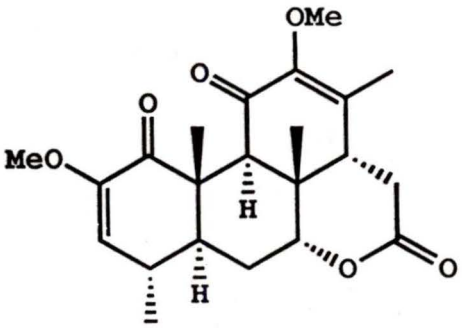
CHAPTER ONE
INTRODUCTION

1.1 General Features of Quassinoids

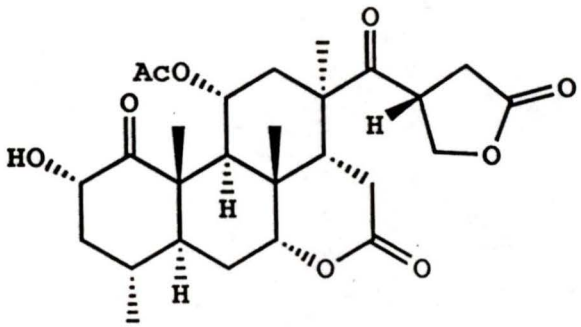
"Quassinoid" is a generic name for a complex family of degraded triterpenes that were originally discovered as the bitter principles of simaroubaceous plants, such as *Pecraena excelsa* Lindt., *Quassia amara* L. and *Jamaica quassia*, and are sometimes called *simaroubolides*. Interest in the synthesis of these natural compounds has increased significantly in the last twenty years due in part to the fact that the American National Cancer Institute found in the early 1970's that certain quassinoids displayed marked antileukemic activity.[1a] More recently, other biological properties have been found, such as antiviral, antimalarial, antifeedant and anti-amoebicidal activities.[1b] Rapid advances in structural studies have led to the isolation and characterization of nearly 100 quassinoids. The structural diversity and biological importance of these natural triterpenoids have made them attractive synthetic targets. Representative examples of quassinoids are shown in Figure 1.

The quassinoids can be divided into five groups according to their basic skeletons. The numbering and stereochemistry of these skeletons are shown in Figure 2. In these five basic skeletons, the number and positions of the methyl groups are the same, and all the quassinoids identified so far have only one methyl group at C-4.

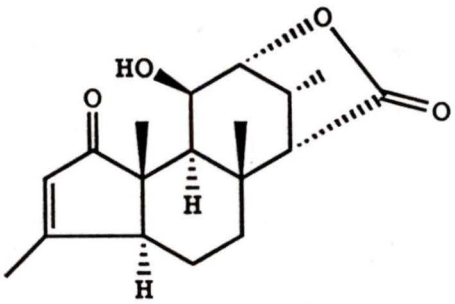
Most of the quassinoids are C_{20}-compounds of the basic picrasane skeleton (**Type I**), seven are C_{19}-compounds of **Type II**, three are C_{18}-



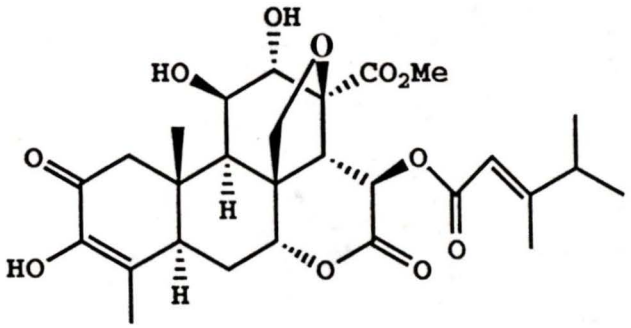
1
Quassin



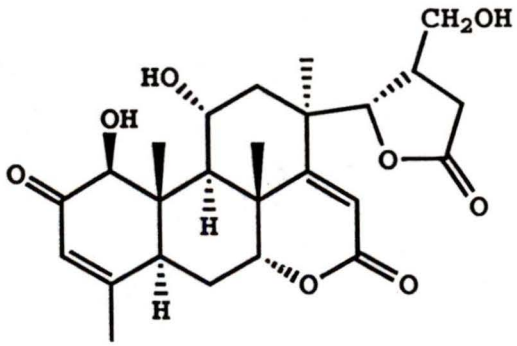
2
Simarolide



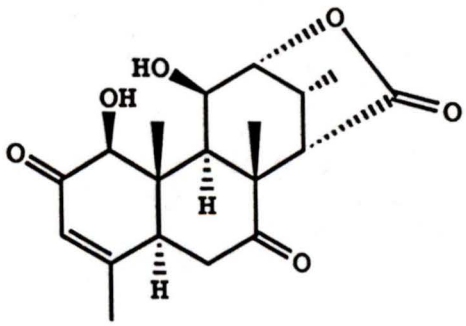
3
Laurycolactone



4
Bruceantin

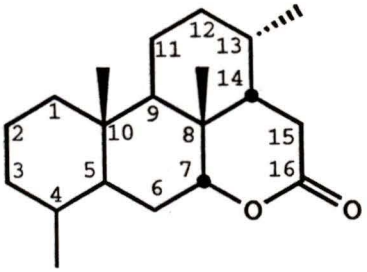


5
Soulameolide

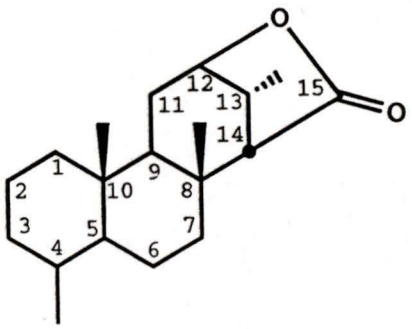


6
Eurycomalactone

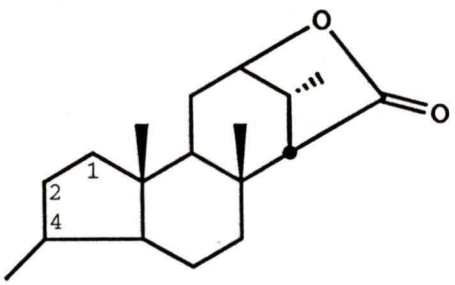
Figure 1. Representative examples of quassinoids



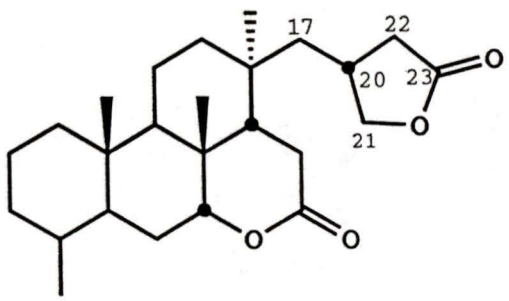
Type I (C_{20})



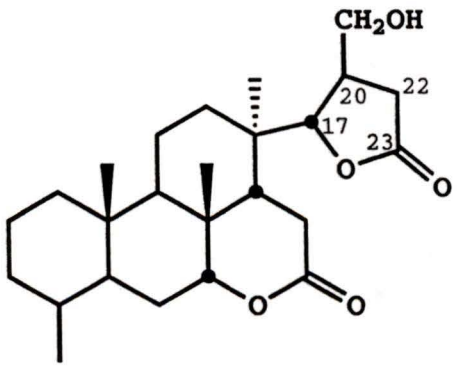
Type II (C_{19})



Type III (C_{18})



Type IV (C_{25})



Type V (C_{25})

Figure 2. The five types of quassinoid skeletons

compounds of **Type III**, three C_{25} of **Type IV** and three C_{25} of **Type V**.

Among the quassinoids, the C_{20} picrasane skeleton occupies a prominent position due to its numerical superiority and diverse biological activities. It can be further divided into three groups on the basis of the presence of an additional bridge in ring C in the form of a hemiketal (**Group A**), an ether (**Group B**), or no additional bridge (**Group C**) as shown in Figure 3.[2]

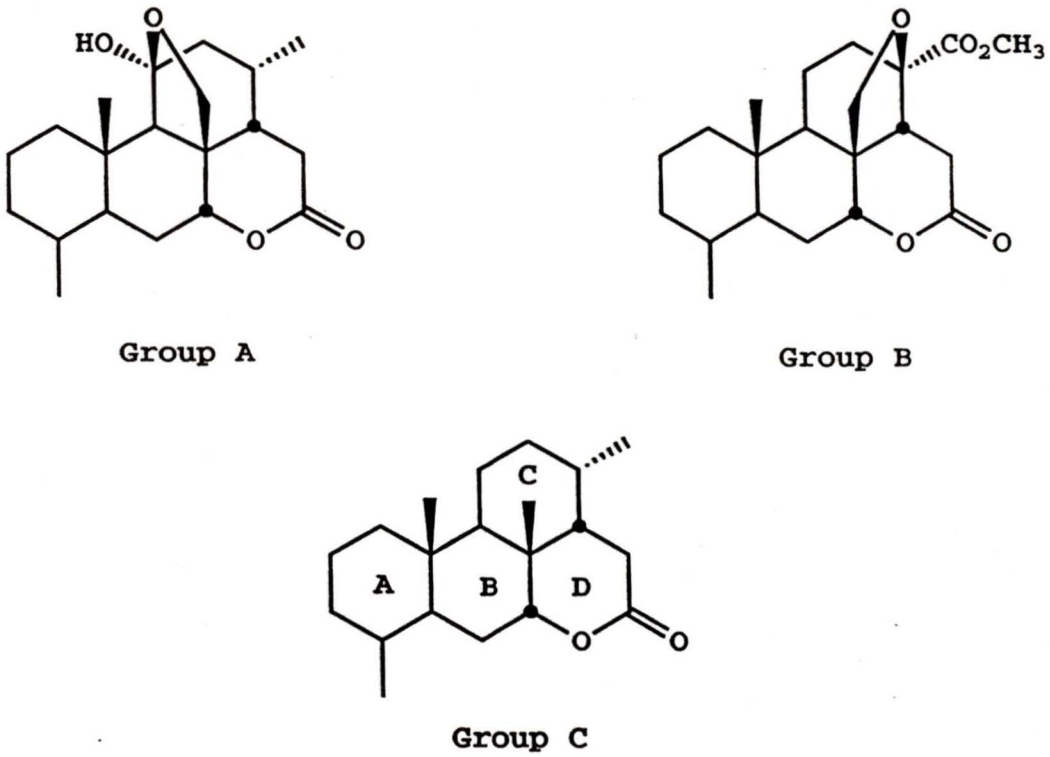
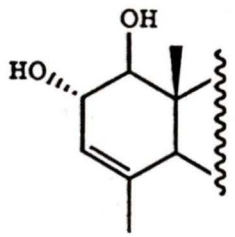


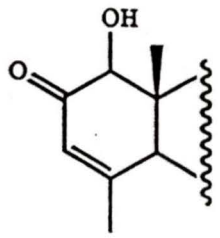
Figure 3. Structural groups of Type I C_{20}-quassinoids

The δ-lactone ring D may have a hydroxyl group at C-15 which is generally esterified with various fatty acids of low molecular weight (ethanoic, 2-methybutanoic, 3-methylbutanoic, 3-methyl-2-butenoic, 2-hydroxy-2-methylbutanoic or 3,4-dimethyl-4-hydroxypentanoic acid).

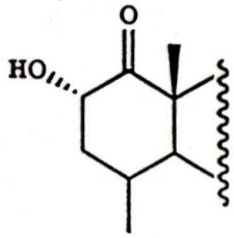
Ring A may have the structure (a), (b), (c), (d), or (e) as shown below.



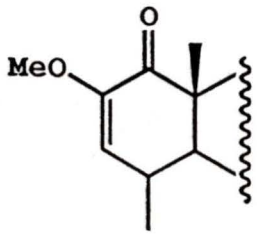
(a)



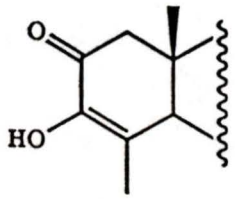
(b)



(c)



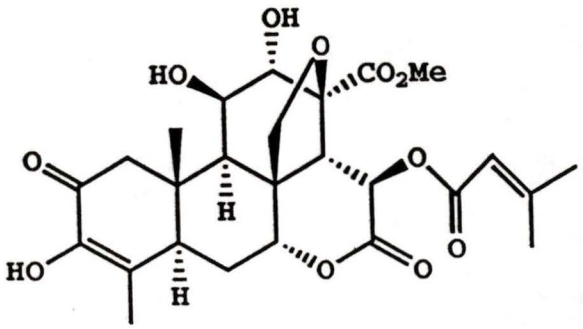
(d)



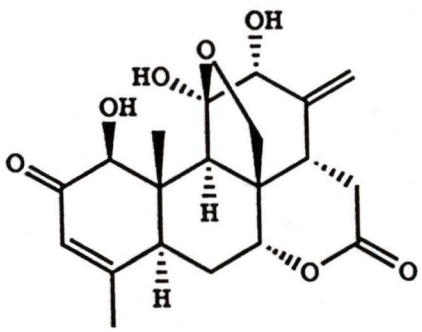
(e)

1.2 Structure and Biological Activity

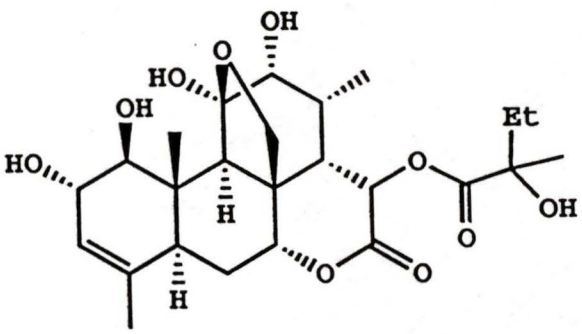
As mentioned above, there are a great number of compounds in the family of quassinoids; but it was indicated that only compounds of type I skeleton (C_{20}-quassinoids) have demonstrated antileukemic activity.[2] A number of the simaroubaceous principles of this type are known as effective antiamoebic agents. Certain quassinoids display *in vivo* antileukemic and antiviral activity. Several quassinoids related to brusatol[3] **7** display anti-inflammatory activity. Extracts of many Simarouba species including *Castela nicholsoni* or *Chaparro amargoso* (Caslamargina), containing ailanthone **8** or glaucarubin **9**, show amoebicidal activity and have long been used by local people in Mexico, China and elsewhere to treat fevers, dysentery and amebiasis.[1b] Bruceantin **4** demonstrated activity against



7
Brusatol



8
ailanthone



9
Glaucarubin

tumors, Colon 38, leukemia, and B16 melanoma systems in mice over a wide dosage range and has been on clinical trial as an antineoplastic agent in the United States for several years.[2,4,5,6,7] The antileukemic activity of bruceantin **4** has been correlated with its ability to suppress DNA and protein synthesis in P-388 lymphocytic leukemic cells[8]. Some quassinoids with different structures have been tested and display antifeedant and insecticidal properties[1b].

According to structure-activity relationship studies,[2] it was found that in both Group A and Group B, the compounds with esters at C-15 or C-6 are potent agents against P-388 leukemia cells (PS). The 3,4-unsaturated-2-

ketone in ring A and the free hydroxyl at C-12 are important for maximal activity. These and other essential features for antileukemic activity of quassinoids, such as the oxomethane bridge, are shown in Figure 4.

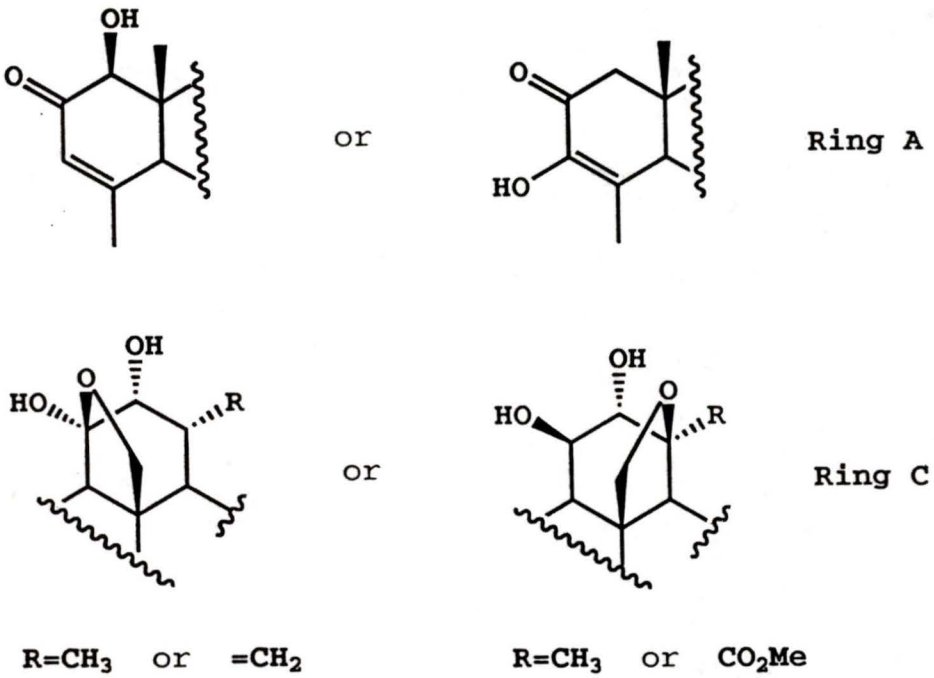


Figure 4. Essential features for antileukemic activity of quassinoids

The quassinoids of Group C were all inactive in the tumor system tested.

1.3. Synthetic Approaches to Quassinoids

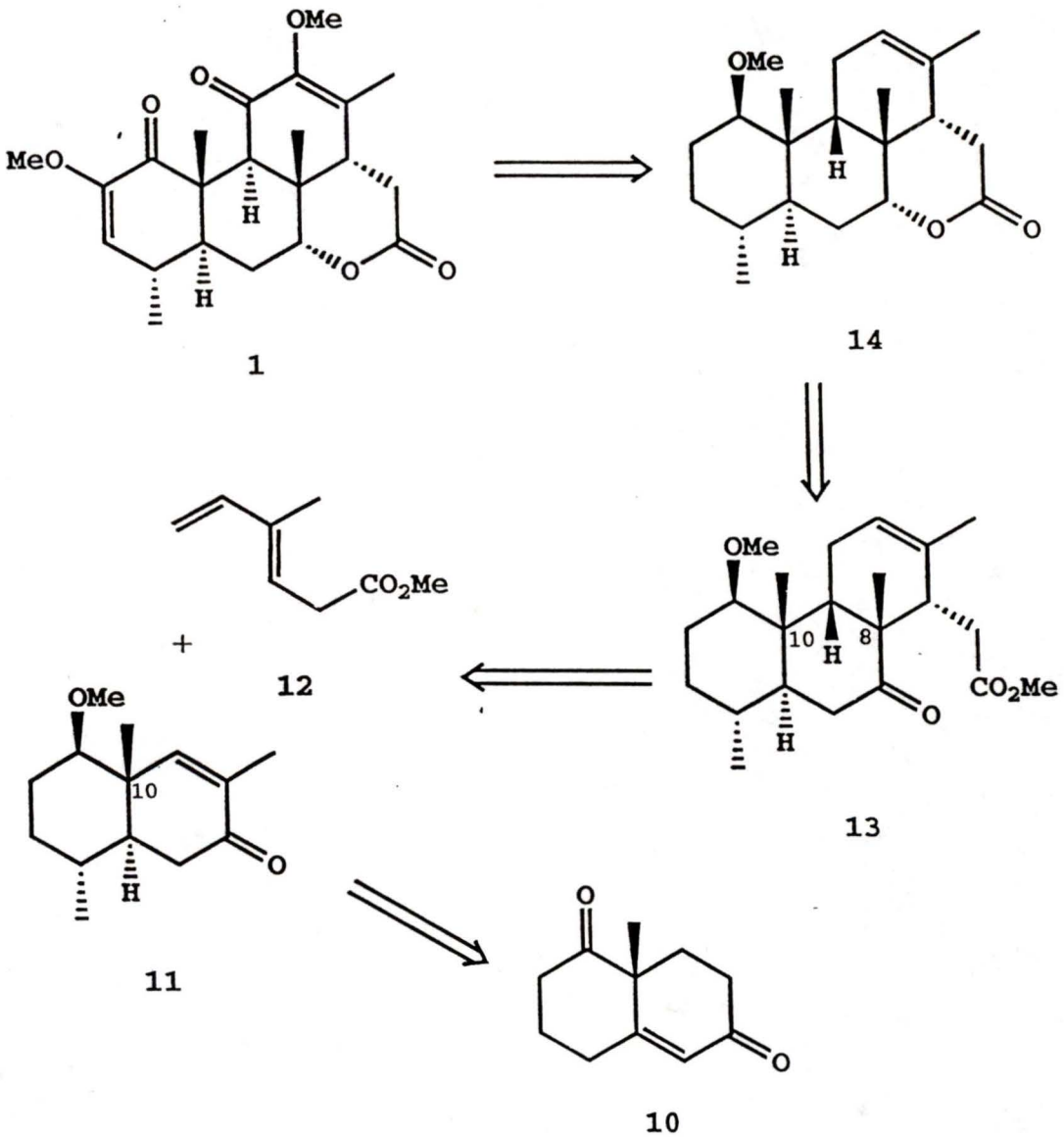
The broad spectrum of biological activities of the quassinoids and their highly oxygenated carbon skeletons with a complex array of stereochemical features have stimulated a great deal of synthetic activity among several research groups. Although a number of approaches towards their synthesis have been described,[1b,9] only recently have the efforts in the quassinoid area culminated in total syntheses.[10,11,12] The complex array of

stereocenters and the large number of oxygenated functional groups combine to make their synthesis difficult.

1.3.1. Grieco's Synthesis of Quassin

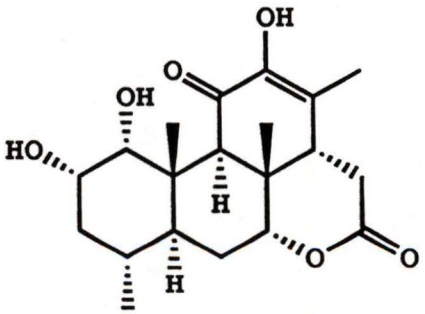
Grieco and coworkers synthesized quassin **1** in 1980,[11] nearly twenty

Scheme 1

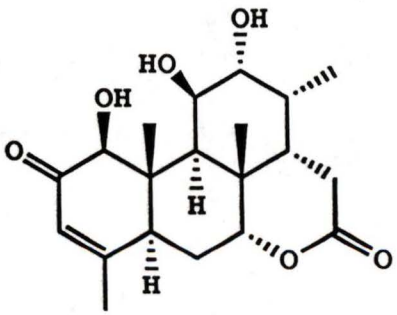


years after its structure was elucidated.[13] He has also reported the total synthesis of castelanolide **15**[14] and klaineanone **16**.[10] A brief retroanalysis of Grieco's route to quassin **1** is shown in Scheme 1.

The enone **11** was prepared through 10 reactions from the Wieland-Miescher ketone **10**. The ketone **13** was obtained via an intermolecular Diels-Alder reaction which relied on the C-10β angular methyl to direct the diene **12** approaching the double bond from the α-face of **11** and provide **13** with the correct syn-relationship between the C-8 and C-10 angular methyl groups. Reduction of the C-7 ketone in **13** furnished the tetracyclic δ-lactone **14** which possessed the complete framework of quassin with the correct relative stereochemistry at all chiral centers with the exception of the configuration at C-9. The next phase of synthesis focused on the correction of the C-9β(H) stereochemistry. The synthesis of quassin **1** was completed in 8 steps from the tetracyclic δ-lactone **14**. Castelanolide **15** was also derived from **14** in 15 steps and klaineanone **16** in 17 steps.



15
Castelanolide



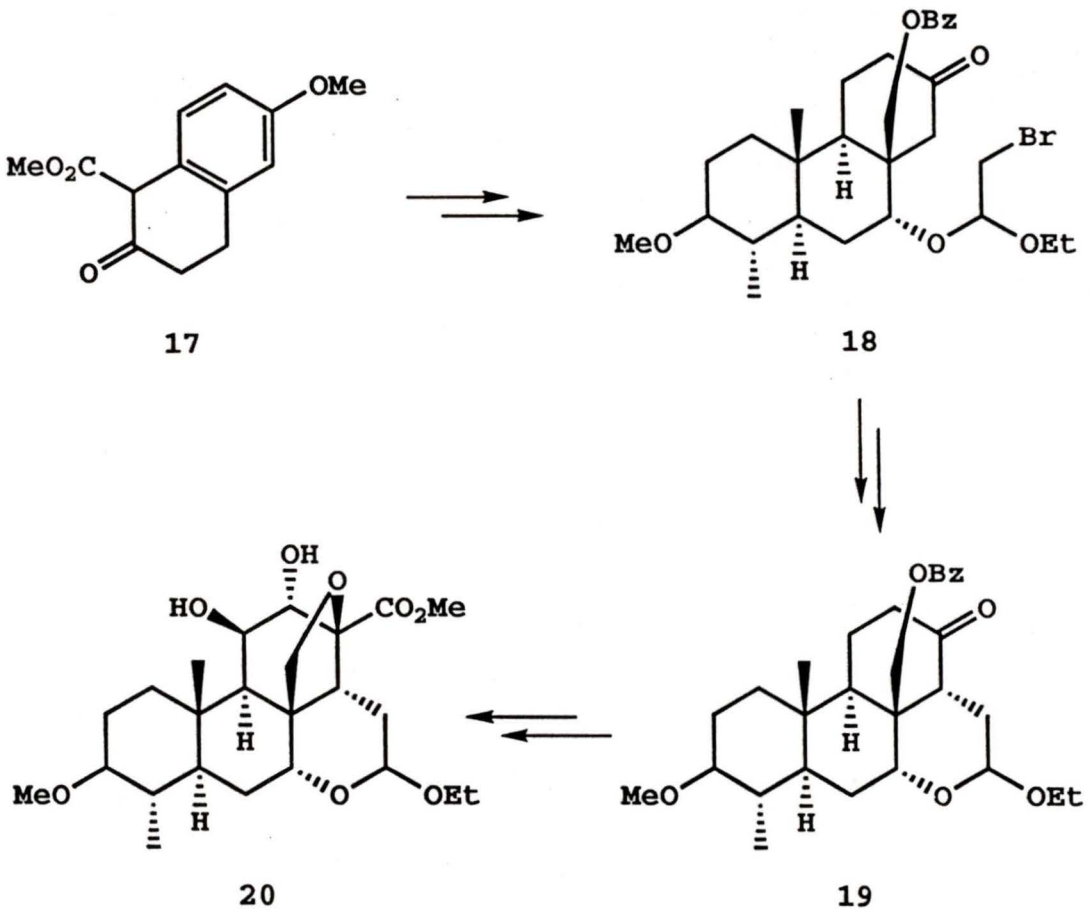
16
Klaineanone

1.3.2. Other Synthetic Methods

Fuchs and coworkers synthesized a pentacyclic ABCDE bruceantin intermediate **20** using more than 25 reactions starting from **17** (see Scheme 2).[15] One key transformation involved the intramolecular alkylation of the

ketone **18** by a β-bromoacetal moiety to afford tetracyclic acetal **19**, which was then converted to pentacyclic compound **20** in 9 steps.

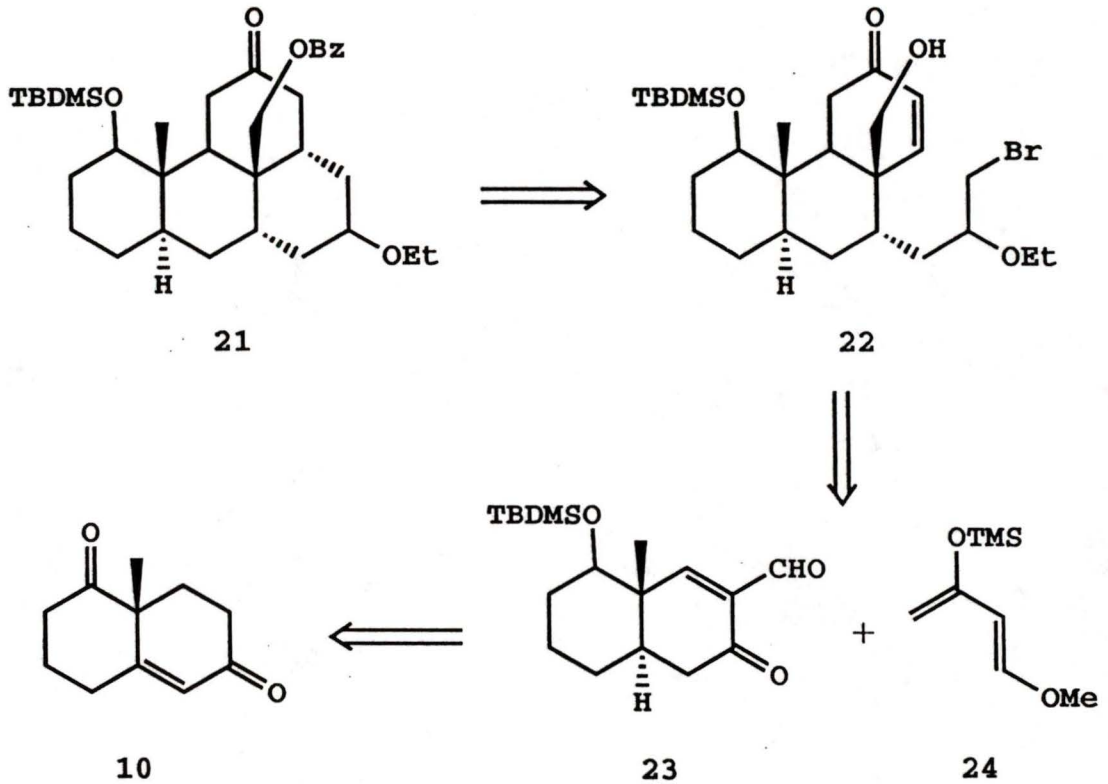
Scheme 2



Watt and his colleagues developed a synthetic approach for assembling the ABCD rings of quassinoids via an intermolecular Diels-Alder reaction of **23** with **24** and a free-radical cyclization of β-bromoacetal **22** as the key reactions and obtained the tetracyclic compound **21** (see Scheme 3).[16]

As mentioned above, the quassinoids have provided a fertile ground for the development of new reagents, procedures and reactions. However, among the ever growing number of new procedures in the literature, only

Scheme 3



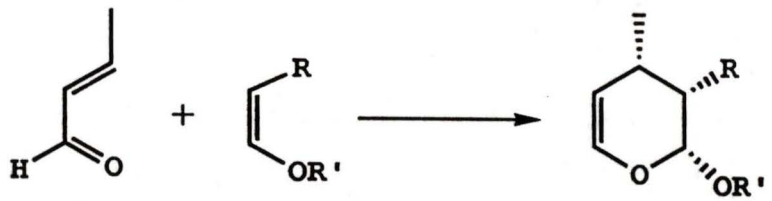
few culminated in total syntheses. No single reaction has probably been more frequently used than the Diels-Alder cycloaddition as a key reaction to construct the quassinoid framework. Successful examples include using intermolecular Diels-Alder reactions to make the B ring[17] and the C ring[18], using intramolecular routes to introduce the CD rings[19] and the BC rings[20].

1.4. A Brief Review of Diels-Alder Cycloadditions Pertinent to Our Synthetic Approach to Quassinoids

1.4.1. The Hetero Diels-Alder Cycloaddition

This reaction is a type of [4+2]-cycloaddition where one or more carbon atoms of the diene and/or dienophile have been replaced by hetero atoms, such as oxygen or nitrogen. For the formation of a dihydropyran derivative, one possible heterodiene is an α,β-unsaturated carbonyl compound, sometimes called an oxadiene, reacting with an electron rich alkene. The reaction belongs to the inverse electron-demand Diels-Alder reaction type and has been widely investigated.[21]

Studies have shown that the reaction between an α,β-unsaturated aldehyde and a β-substituted vinyl ether gives a mixture of two diastereomers with the all *cis* isomer generally predominating.[22]



The stereochemistry suggests a concerted mechanism in which the *endo* transition state is preferred (Figure 5). With a cis vinyl ether, the *exo* adduct may be favored if the **R** group is large. The regiochemistry is consistant with the FMO theory.[23]

It has been found that some Lewis acids catalyze the reaction and dramatically reduce both reaction temperature and reaction time.[24] The catalyst chelates the carbonyl oxygen to form an n,π^*-type molecular complex. Formation of the n,π^*-complex can increase the difference in

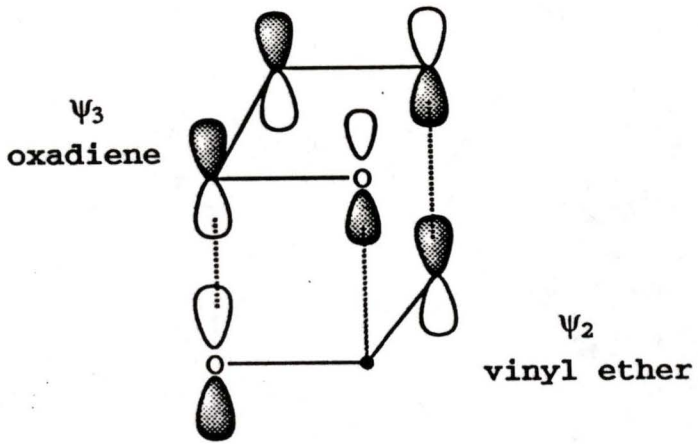


Figure 5. Endo transition state showing the HOMO/LUMO interaction and secondary orbital overlap between the oxadiene and vinyl ether.

energies between the isomeric transition states and hence lead to an increase in selectivity.[25] Moreover, with Lewis acid catalysts, the proportion of endo adduct is considerably increased.

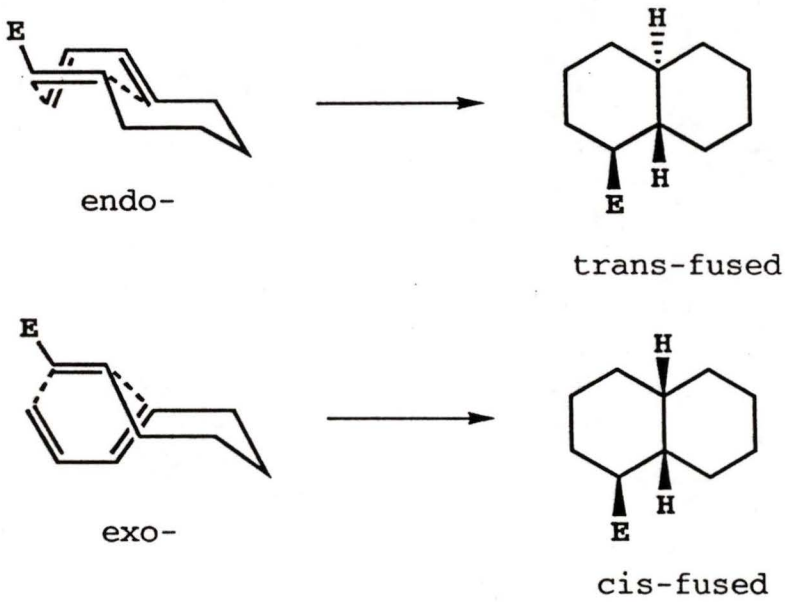
One such catalyst is a soluble lanthanide complex, $Yb(Fod)_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium).[24] It is a mild catalyst and allows for survival of fragile but valuable functional groups both in the reactants and in the cycloadduct. Moreover, only a few mole percent of catalyst is sufficient for a reasonable reaction rate at room temperature.

1.4.2. The Intramolecular Diels-Alder Reaction

The intramolecular Diels-Alder reaction has been widely used to construct bicyclic [4.4.0] ring systems and is suitable for the formation of the AB rings of the quassinoids.

According to the literature,[26] the cycloaddition of *E,E*-1,3,9-decatriene systems proceeds via either of a chair-like *endo* or *exo* transition state, which leads to a mixture of trans- and cis-fused adducts, respectively, with a preference for the former (Scheme 4).

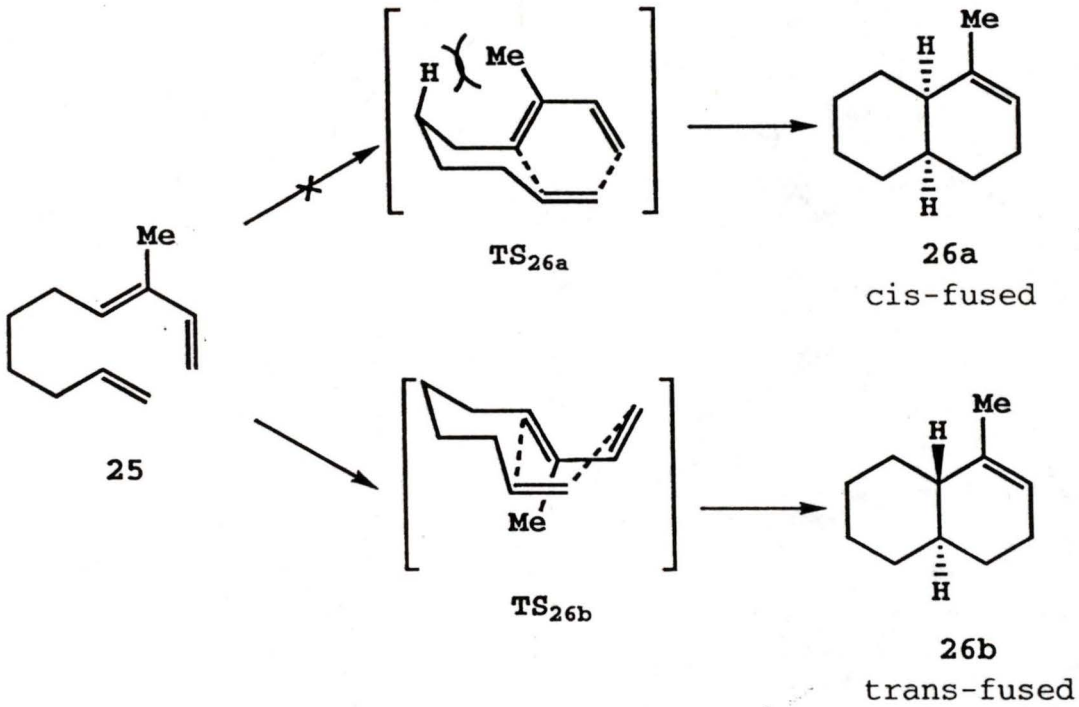
Scheme 4



However, substituents and adjacent rings can markedly alter the ratio of trans- and cis-fused adducts. 3-Methyl-1,3,9-decatriene **25** cyclized to give trans-2-methyl-bicyclo[4.4.0]dec-2-ene **26b** as the only product in 95% yield.[27] The exclusive formation of trans-product may be attributed to the development of severe nonbonded interactions in the transition state TS_{26a} leading to the cis-isomer (Scheme 5).

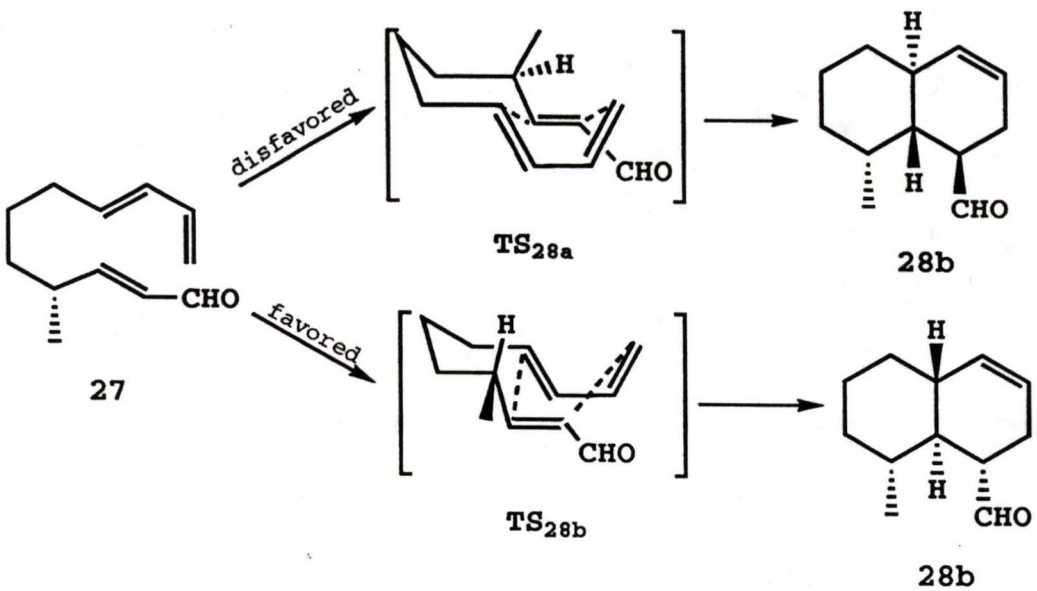
Marshill et al. indicated that a methyl substituent at the C-4 position of enal **27** exerted a powerful directing influence on the mode of cycloaddition.[28] The tendency of the methyl group to adopt an equatorial

Scheme 5



disposition in the transition state favored the formation of compound **28b** (Scheme 6).

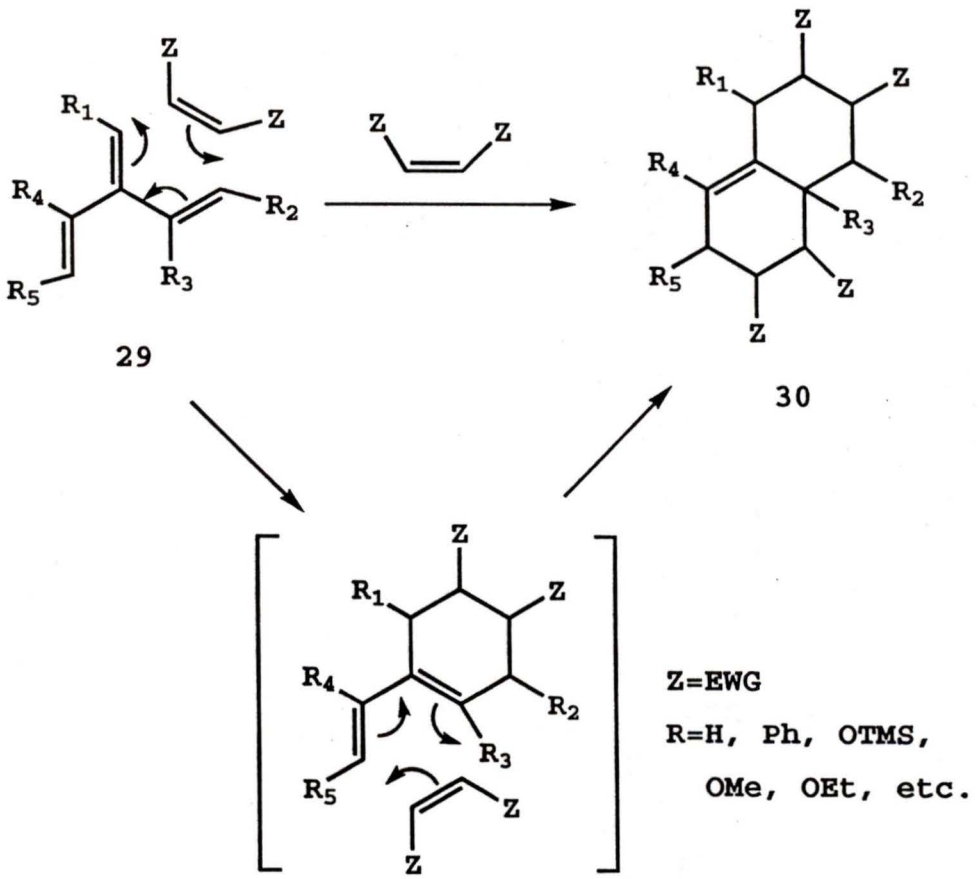
Scheme 6



1.4.3. The Diene Transmissive Diels-Alder Reaction of Cross Conjugated Trienes

Two dienophiles reacting, via two sequential Diels-Alder reactions, with a cross-conjugated triene **29**, leads to a fused ring adduct **30**. This reaction, referred to as "diene-transmissive Diels-Alder cycloaddition" (DTDAC), was investigated by Tsuge and coworkers[29] and is outlined in Scheme 7.

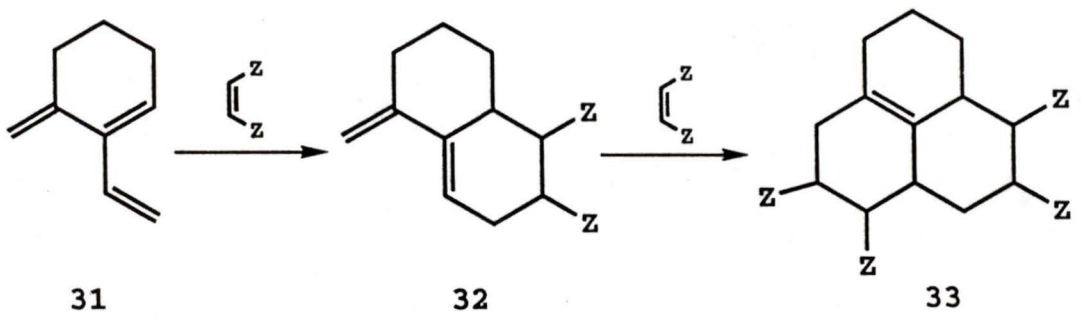
Scheme 7



The initial [4+2]-cycloaddition across a diene part of the triene produces a ring and an endocyclic double bond which forms a new diene unit with the spectator olefin. The newly formed diene then reacts with the second dienophile to afford the bicyclic compound **30**.

Although the DTDAC has high potential for the construction of complex polycyclic molecules, the reaction suffers from the thermal instability of the acyclic trienes involved and from the lack of regiocontrol in the reaction, which severely limits its application in organic synthesis. However, if the triene is constrained around a ring system as shown in Scheme 8, the polycyclic adduct **33** could be formed in a completely regiocontrolled fashion because only two of the double bonds in triene **31** can adopt an *s*-cis conformation and react with a dienophile in the initial reaction.

Scheme 8



31 32 33

Z=EWG

This is the strategy we chose to use for the construction of the tetracyclic quassinoid framework as described in the following section.

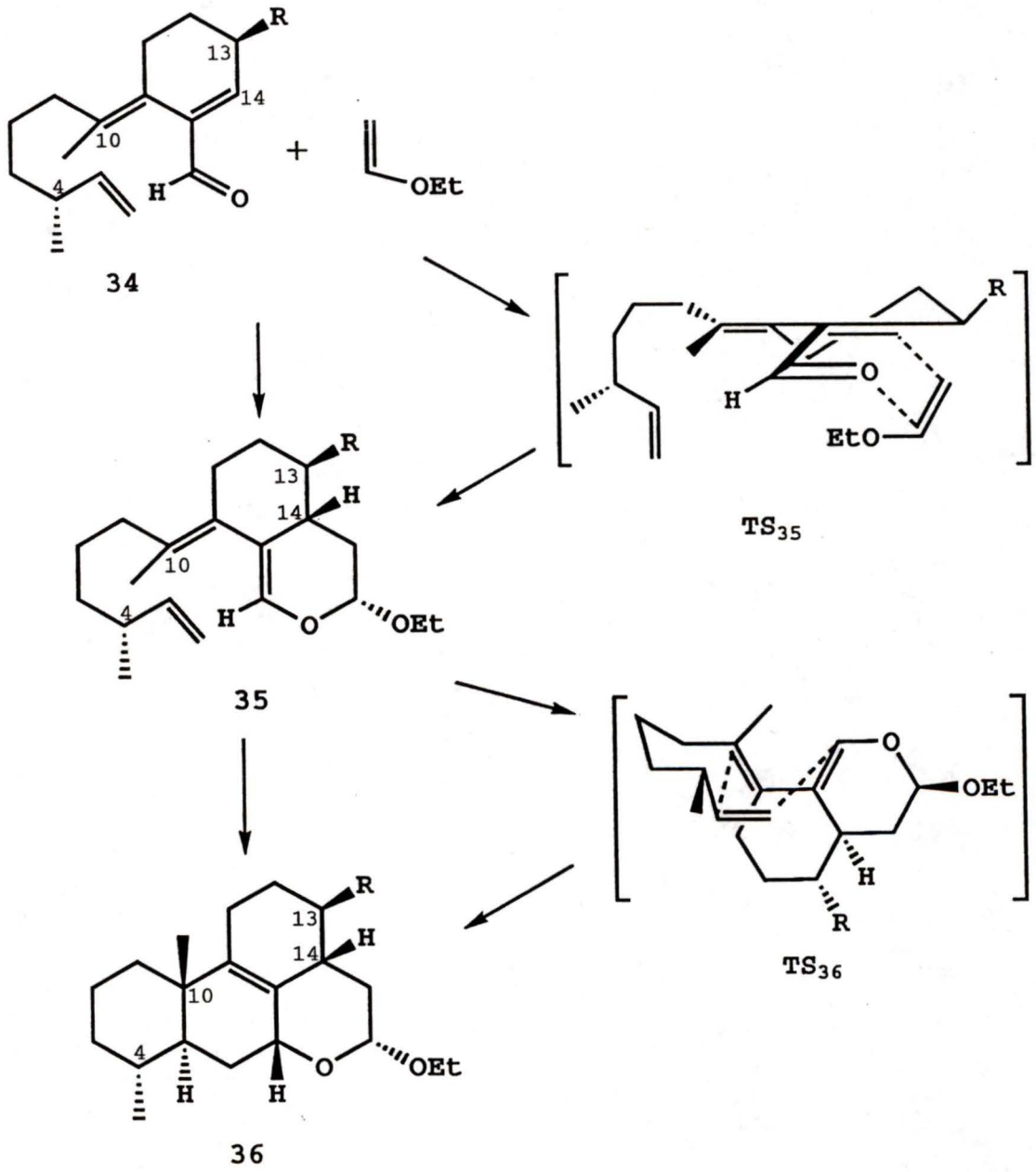
1.5. A New Synthetic Route to the Quassinoid Skeleton via a Diene-Transmissive Diels-Alder Strategy

1.5.1. Synthetic Route to the Tetracyclic Nucleus of the C_{20}-Quassinoid

As mentioned before, the basic structure of most quassinoids comprise the C_{20} tetracyclic skeleton of Type I (cf. Figure 2). Of primary importance

to the synthesis of these compounds is the formation of this tetracyclic framework with the correct stereochemistry at the ring junctions and the substituents. We envisaged using a "diene-transmissive" methodology which involves two tandem Diels-Alder cycloaddition reactions for the rapid formation of the tetracyclic nucleus: a hetero Diels-Alder reaction for the

Scheme 9



δ-lactone D ring and an intramolecular Diels-Alder reaction for the A and B rings. This design could perhaps be one of the shortest ways to synthesize the tetracyclic carbon skeleton of quassinoids. Our approach is described in Scheme 9.

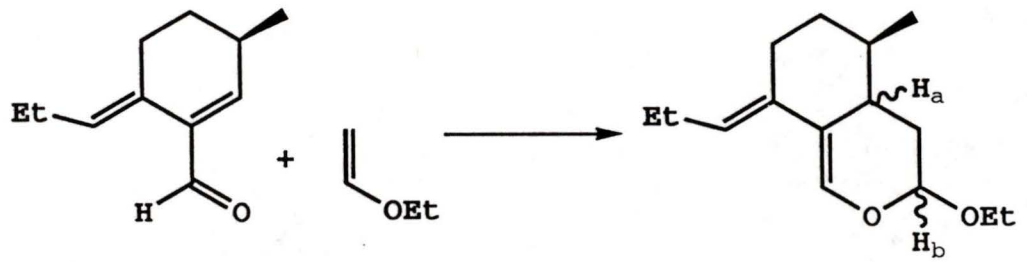
In this synthetic route, firstly, the substituent **R** at C-13 of trienal **34** should direct the approach of dienophile to the other face of the conjugated oxadiene plane ($\mathbf{TS_{35}}$ in Scheme 9) and therefore control the hetero Diels-Alder reaction to form bicyclic triene **35** with the correct stereochemistry at C-14. Secondly, the AB ring closing via an intramolecular Diels-Alder reaction should prefer a chair-like transition state, $\mathbf{TS_{36}}$, where the methyl group at C-4 adopts an equatorial configuration as discussed before (cf. Scheme 6) to form a tetracyclic compound **36** stereoselectively.

1.5.2. Feasibility Studies

To test the feasibility of our synthetic strategy, the racemic molecule **37**, having a methyl at the carbon adjacent to the endocyclic double bond, and the chiral molecule **39** were chosen as model compounds to investigate the δ-lactone ring formation with stereochemical control (Scheme 10). Trienal **43** was prepared to investigate the DTDAC methodology for the C_{20}-quassinoid skeleton formation (Scheme 11). In this model study, we omitted the methyl groups at C-4 and C-10 (cf. Scheme 9) in order to simplify their synthesis. Model studies that include these methyl groups will be described elsewhere.

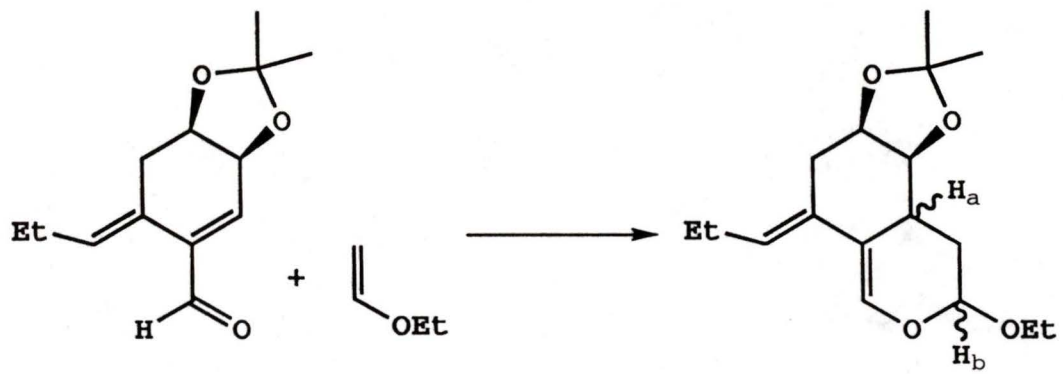
In the retrosynthetic route to precursor **43** (Scheme 11), the key reaction involved is a cuprate addition on allylic acetate **42**.[30,31] This reaction was discovered by Rona et al. and involves an allylic acetate

Scheme 10



37

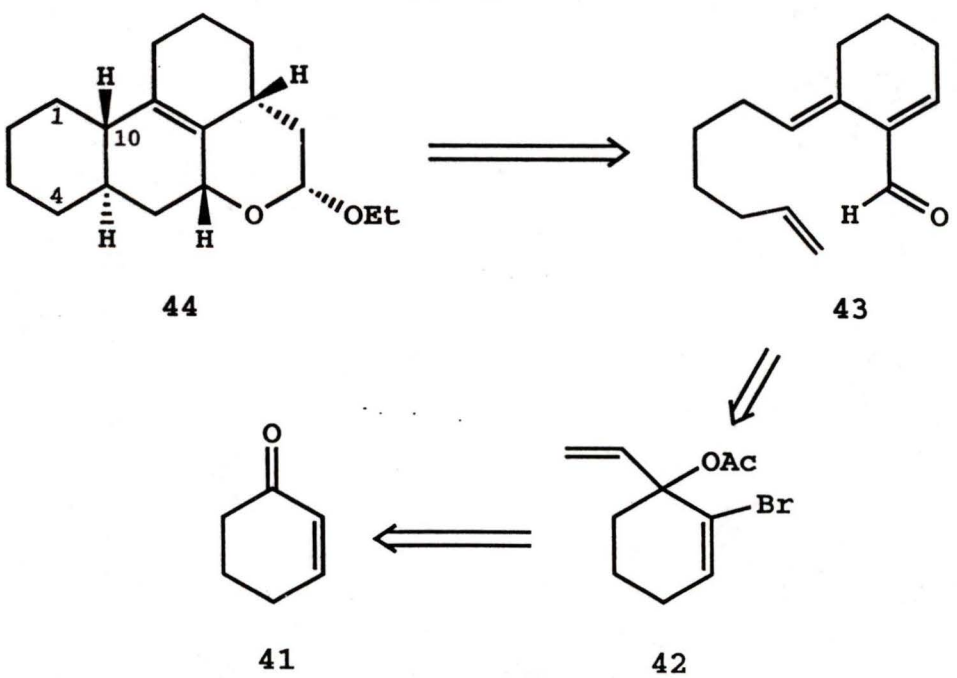
38a β-H_a, β-H_b
38b α-H_a, α-H_b



39

40a β-H_a, β-H_b
40b α-H_a, α-H_b

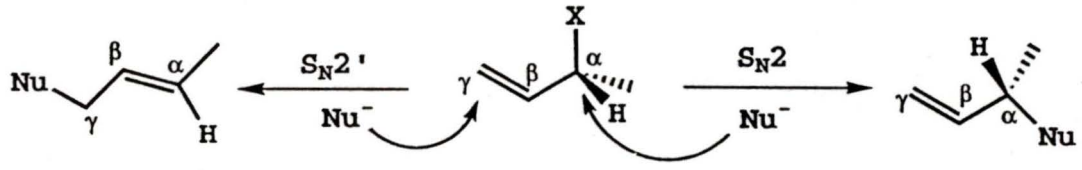
Scheme 11



44 43

41 42

reacting with an organocopper species to give an alkene.[32] This reaction may proceed via a S_N2 or S_N2' mechanism depending on the nature of the leaving group **X** and the substitution on the alkene.



In general, S_N2' alkylations of allylic esters with organocuprate reagents proceed through γ-attack via an anti pathway and give the (E)-alkene as the major product. A better rationalization of the results is perhaps in terms of the π-allyl copper complex (Figure 6)[31]. Unlike most carbon nucleophiles, such as Grignard and organolithium reagents, organocopper(I) reagents contain a metal with a filled set of d-orbitals. The electron density in the orbitals tends to diffuse due to electron-electron repulsion in the d^{10} system. Nucleophilic attack by R_2Cu^- probably gives such a transition state that a filled d- orbital interacts with the LUMO (π*)

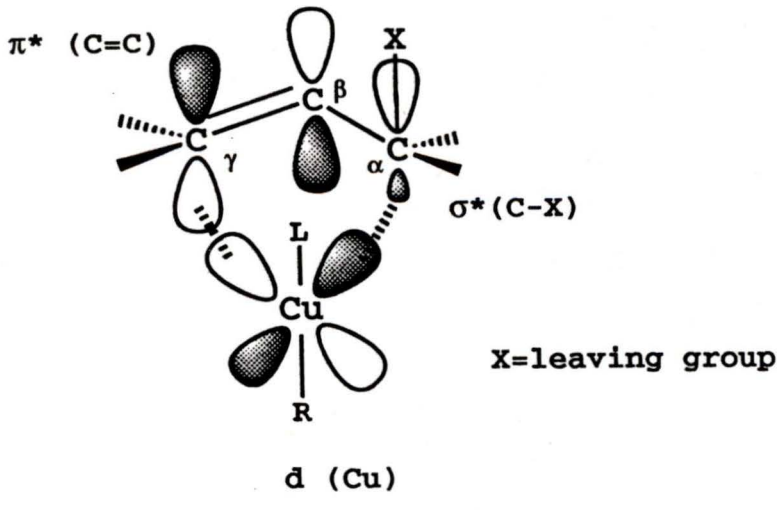


Figure 6. Transition state of the S_N2' reaction.

of the double bond at the γ-carbon and simultaneously, to a considerably smaller extent, with the antibonding orbital (σ*) of C-X bond at the backside of the α-carbon[31]. Such a transition state requires that the C_α-X bond be nearly parallel to the *p*-orbitals of C_β and C_γ (Figure 6).

The reason for yielding the S_N2' product rather than the S_N2 could be illustrated with the theory of hard-soft acids and bases.[33] Most cuprate reagents are believed to be soft bases. Treating allylic acetate as an acid, it will be found that the α-carbon is a relatively harder acid than the γ-carbon[34]. According to the hard-soft acid and base theory, the soft prefers to react with the soft and therefore the R group transfers from Cu to the γ-carbon.

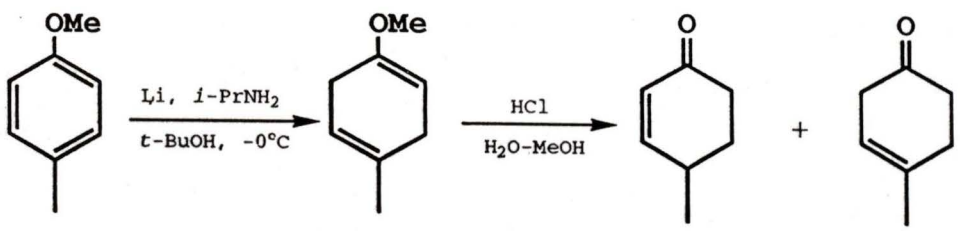
CHAPTER TWO
RESULTS AND DISCUSSION

2.1. Investigation of the δ-Lactone Formation

2.1.1. synthesis of precursors 53 and 37

As discussed earlier in Chapter One, the key reaction in our synthetic methodology is the Diels-Alder cycloaddition (see Scheme 9). In this section, the synthesis of dienealdehydes **53** and **37**, the precursors to bicyclic compounds **54** and **38**, will be described. We envisaged using these precursors in an intermolecular hetero Diels-Alder reaction as a means to construct the δ-lactone D ring of quassinoids. The synthetic route to these two precursors is shown in Scheme 12 and 13.

Scheme 12

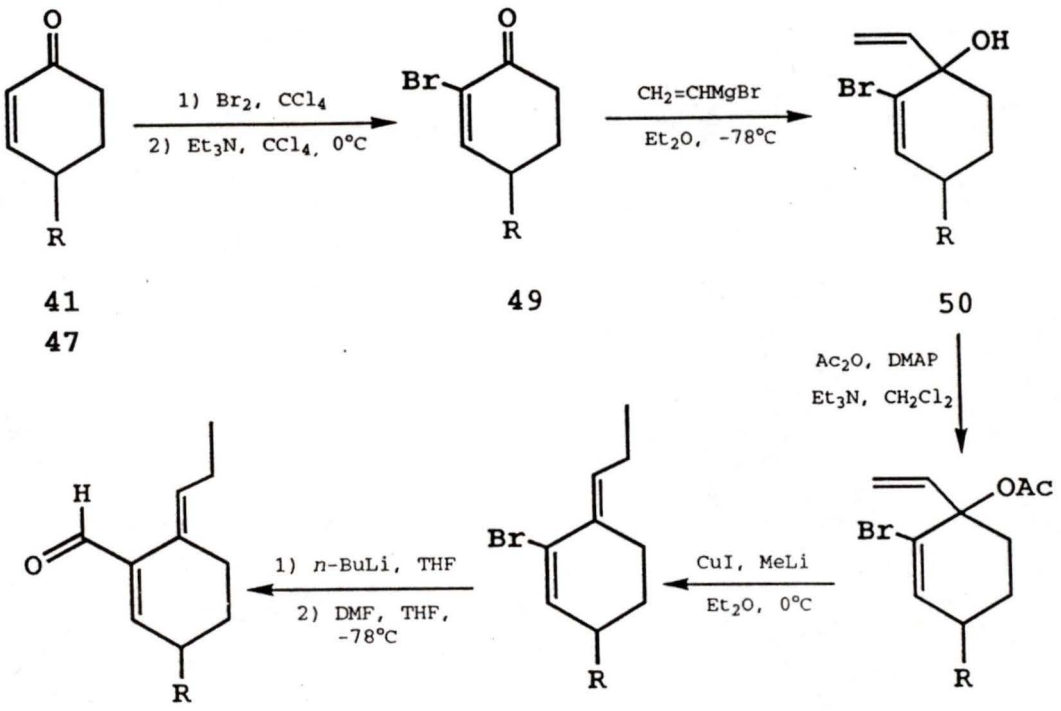


45 **46** **47** **48**

Racemic enone **47** (**R=Me**) was prepared via a modified Birch reduction[35a] of *p*-methylanisole **45** with a lithium isopropylamine-*t*-butanol combination at 0°C followed by hydrolysis of the reduced product **46**[35b] to give enones **47** and **48** in a 1:1 ratio (Scheme 12).

Enone **41** and **47** were first brominated and then dehydrobrominated to afford bromoketone **49a** (77%) and **49b** (64%).[36] Dienol **50a** (73%) and **50b**

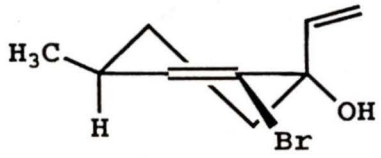
Scheme 13



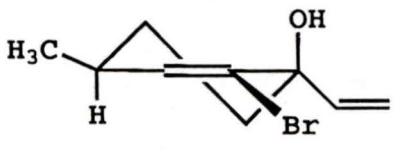
41, 49-50a, 42, 52a, 53: R=H

47, 49-50b, 51, 52b, 37: R=CH_3

(84%) were obtained by reacting **49a** and **49b** with vinylmagnesium Bromide at -78°C. With a methyl group at C-4, **49b** formed two diastereomers ***E*-50b** and ***Z*-50b**. The ^1H NMR spectrum of the crude product **50b** showed that the ratio of these two diastereomers was 3:1. We believed that the major product was ***Z*-50b** resulting from attack of the vinyl Grignard reagent from the least



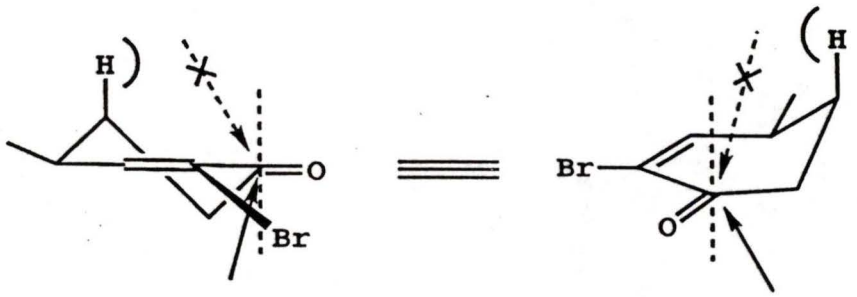
E-50b



Z-50b

hindered equatorial face of Bromoketone **49b** in the conformation shown in Scheme 14.

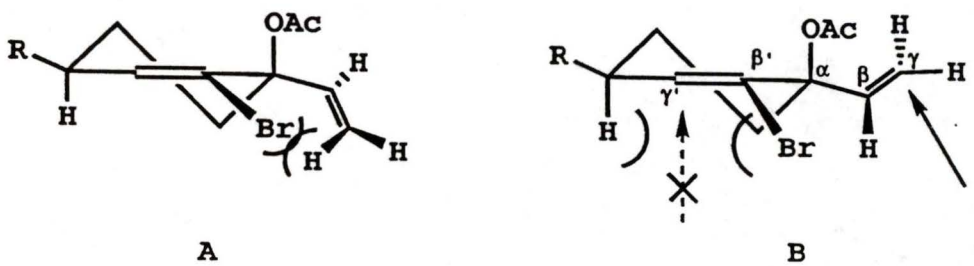
Scheme 14



The esterification of alcohols **50a** and **50b** with acetic anhydride as well as DMAP at room temperature afforded the acetate **42** and **51**.[37] The high catalytic activity of DMAP was used for our sterically hindered tertiary alcohol.

Bromodienes **52a** and **52b** were synthesized by S_N2' displacement of acetates **42** and **51** with lithium dimethylcopper at 0°C. The reaction proceeded with high regio- and stereoselectivity. Firstly, the reaction of the cuprate reagent with both allylic acetates proceeded via a S_N2' mechanism[30,32] with methyl anti γ-attack[31] rather than direct α-attack via a S_N2 displacement (Scheme 15). Secondly, no compound produced by γ'-attack at the endo double bond was detected (see **B** in Scheme 15). This

Scheme 15



R=H, or CH_3

regioselectivity was mainly due to the bulky bromide substituent at the β'-carbon on the trisubstituted double bond (see configuration **B**). Thirdly, the reaction produced the E-isomer stereoselectively.[38] This selectivity can also be explained by the effect of the bulky bromide substituent. In order to allow an S_N2' process the vinyl group had to adopt conformation **A** or **B** where the plane of the double bond is perpendicular to the C-O bond of the acetate.[31,39] In the case of compound **42** or **51**, configuration **B** is expected to be energetically favored because in **A** the vinyl hydrogens experience steric repulsion by the bromine atom. The E-configuration of **52a** was proved indirectly by NOE experiment on compound **53** (*vide infra*).

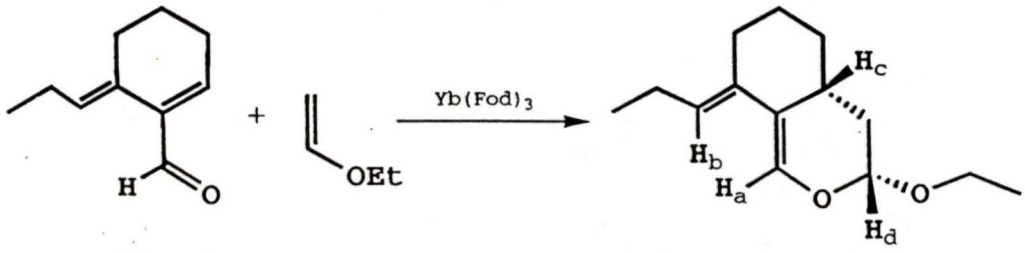
The precursor dienealdehydes **53** and **37** were formed in a way similar to that described by Smith.[36] In our procedure, bromodiene **52** was treated with *n*-butyllithium in THF at -78°C followed by addition of dimethylformamide (DMF) to afford dienal **53** (58%) and **37** (72%). The NOE spectrum of **53** indicated that there was a large enhancement between the aldehyde hydrogen and two vinyl hydrogens and therefore confirmed the E-geometry of **52**.

2.1.2. Reaction of 53 and 37 with Ethyl Vinyl Ether

With compound **53** in hand, we tested the feasibility of the inverse-electron demand Diels-Alder cycloaddition in this cyclic cross-conjugated formyldiene system. Danishefsky and Bednarski found that certain lanthanide complexes had the capacity to catalyze a variety of hetero Diels-Alder reactions.[24] The mild experimental conditions were helpful in promoting the survival of valuable functionalities in the dienophile, diene and adduct. Formyldiene **53** reacted with ethyl vinyl ether under $Yb(Fod)_3$

catalysis at room temperature to give bicyclic adduct **54** in 90% yield (Scheme 16).

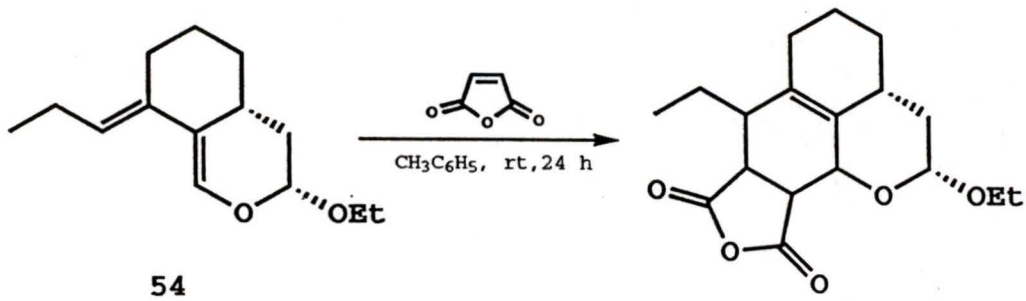
Scheme 16



53 **54**

As expected, the reaction was stereospecific and gave rise to the endo adduct **54** only.[24] The structure of **54** was deduced from its ^1H NMR spectrum which showed one doublet at δ 6.30 (J=1.9 Hz) for H_a (allylic coupling with H_c), one doublet of triplets at δ 5.22 (J=7.2, 2.2 Hz) for H_b, and one doublet of doublets at δ 4.78 (J=9.6, 1.8 Hz) for H_d. The IR spectrum also displayed a conjugated C=C stretch at 1640 and 1625 cm^{-1}. In addition to the formation of a dihydropyran, this hetero Diels-Alder cycloaddition also produced an endocyclic double bond, conjugated with the existing olefin to give a new diene. The newly formed diene underwent a Diels-Alder reaction with maleic anhydride, an electron poor dienophile, in toluene at

Scheme 17

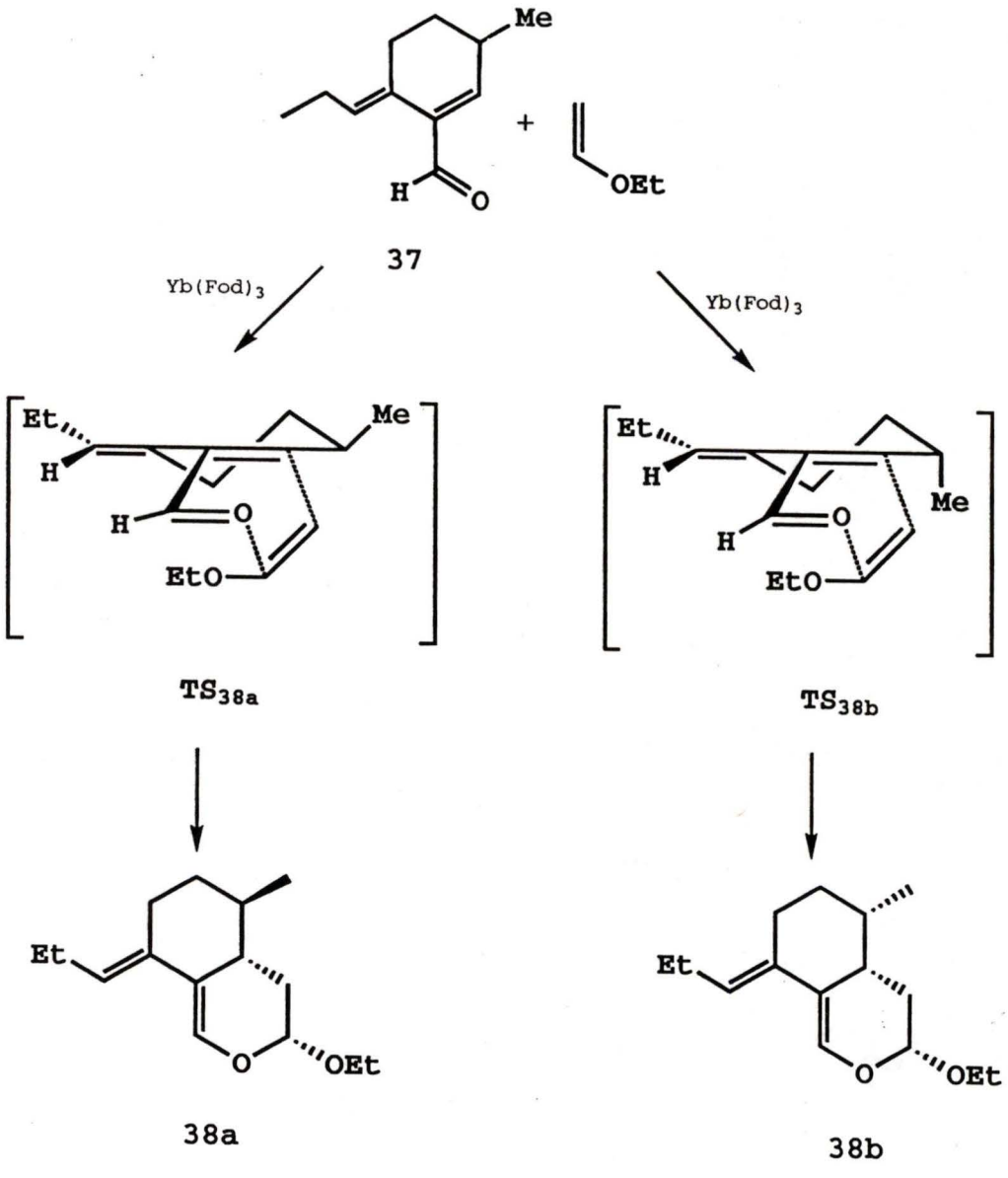


54 **55**

room temperature for 24 h to form the cycloadduct **55** in 92% yield (Scheme 17).

The result of this reaction showed promise for our strategy via the DTDAC to construct the tetracyclic framework of quassinoids.

Scheme 18



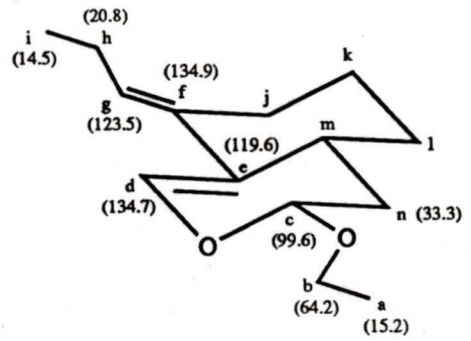
To test the dihydropyran formation with stereocontrol at C-14, we examined the reaction of racemic formyldiene **37** with ethyl vinyl ether. A 3.5:1 mixture of inseparable stereoisomers **38a** and **38b** was obtained, after column chromatography, in 87% chemical yield (Scheme 18). The ratio was determined by ^{1}H NMR as well as GC. We believe that the major product is **38a** and that the reaction of **37** with ethyl vinyl ether occurred via a preferred *endo* transition state $\mathbf{TS_{38a}}$ with the dienophile approaching the oxadiene from the opposite side to the methyl.

We could not determine the stereochemistry of **38a** from its NOE or NOESY spectra because of overlapping resonances. However, we assigned the stereochemistry of **38a** and **38b** by comparing the ^{13}C NMR spectra of the different Diels-Alder adducts **38a**, **38b**, **54**, **40a** (see section 2.2 for its synthesis) and **69** (see section 2.3 for its synthesis).[40]

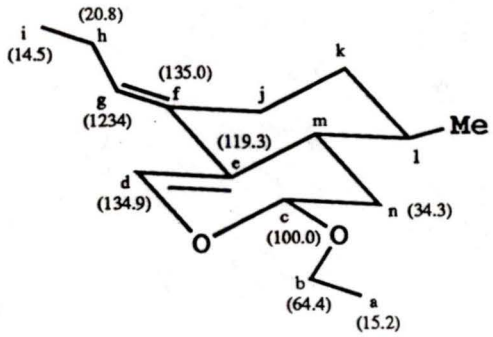
It was found the ^{13}C chemical shift value of C_a--C_i in the adducts, **38a**, **38b**, **54**, **40a** and **69**, were almost the same (see Figure 7). The discrepancies of shift value between **38a** and **38b** at C_j, C_k, C_l, C_m and methyl carbon were due to the methyl group being equatorial or axial. Comparing experimental and calculated values, we assigned the stereochemistry of the major compound **38a** and minor compound **38b**. The calculated values were obtained from taking the ^{13}C chemical shifts in **54** as base values and adding or subtracting the correction factor for equatorial or axial methyl[40]. The results are listed in table 1.

As shown in the table, both calculated and experimental values are close, except perhaps for C_l in **38b**.

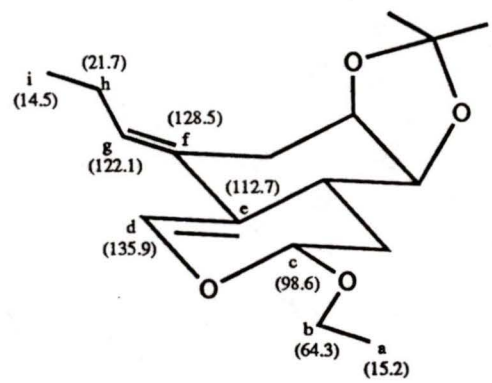
Compounds **38a** and **38b** were not as stable as **54** and isomerized slowly even at 0°C. ^{1}H NMR spectrum of the mixture of isomers showed the



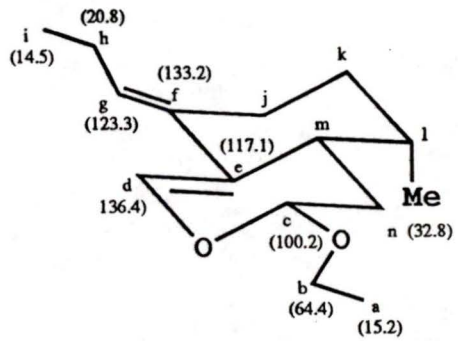
54



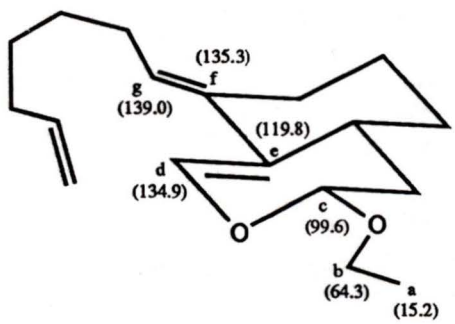
38a



40a



38b



69

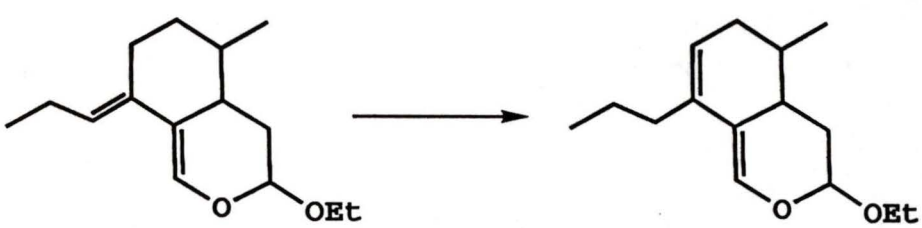
Figure 7. ^{13}C chemical shifts of compounds **38a**, **38b**, **54**, **40a** and **69**.

Table 1. Experimental and calculated values[40] of ^{13}C chemical shift for **38a** and **38b**

carbon	**54** (δ)	**38a** (δ)		**38b** (δ)	
No.	base	calcd.	expt.	calcd.	expt.
C_j	27.7	27.7	27.6	22.3	21.6
C_k	25.2	34.1	34.7	30.3	32.4
C_l	36.5	42.1	40.5	37.6	30.6
C_m	34.0	42.9	38.7	39.2	37.6
Me		20.3	19.8		
Me				12.0	12.8

chemical shifts of the two vinyl protons of **38a** moving to lower field from δ 6.30 (d, J=1.9 Hz) and δ 5.23 (td, J=7.2, 2.2 Hz) to δ 6.40 (d, J=1.9 Hz) and δ 5.35 (bd, J=4.8 Hz). We thought the final isomer to be **56** where the exocyclic double bond migrated to the endocyclic position (scheme 19). GC-MS indicated compounds **56** and **38** had the same molecular weight, but unfortunately, the two isomers were inseparable and we could not fully characterize compound **56**.

Scheme 19

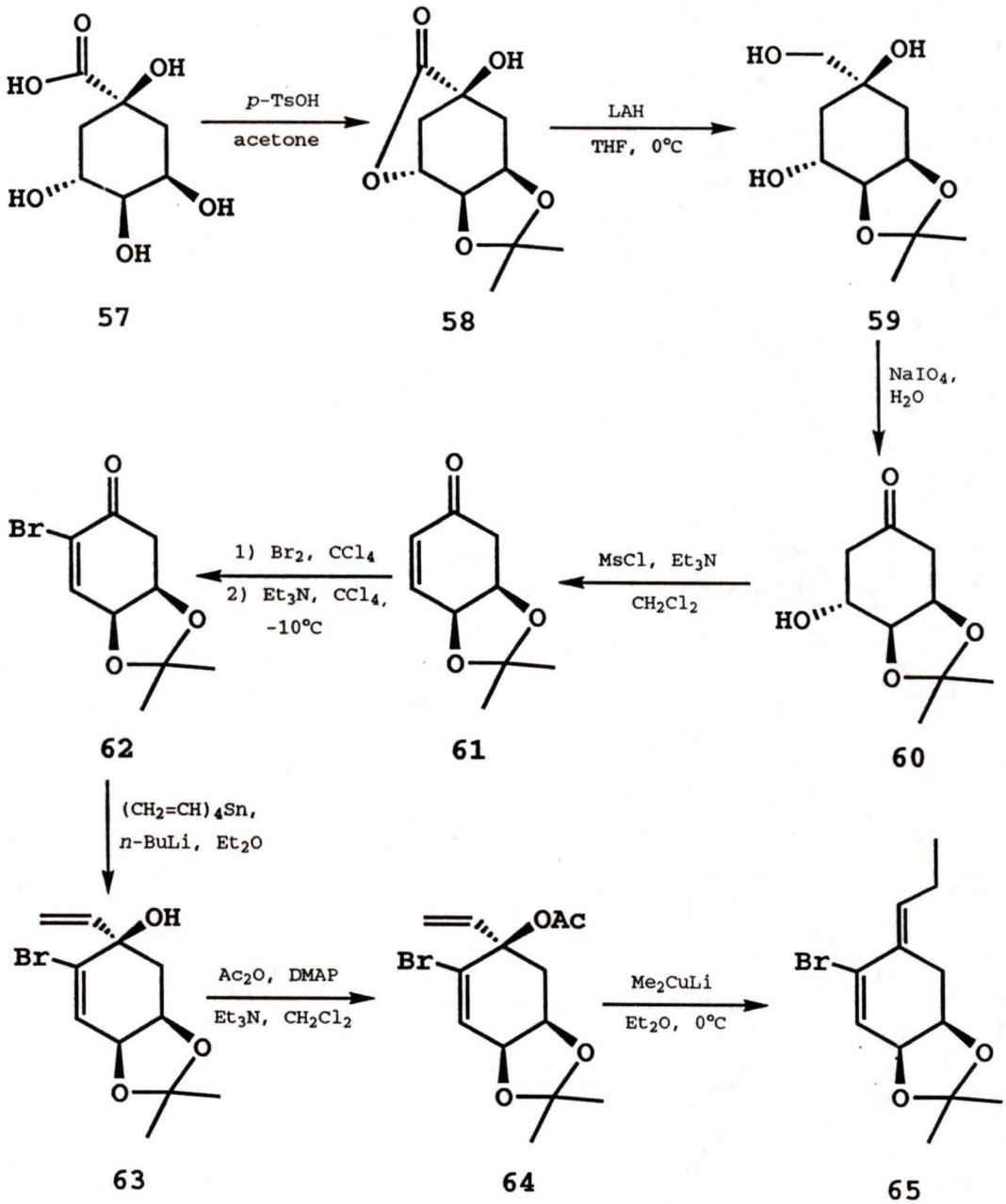


38 56

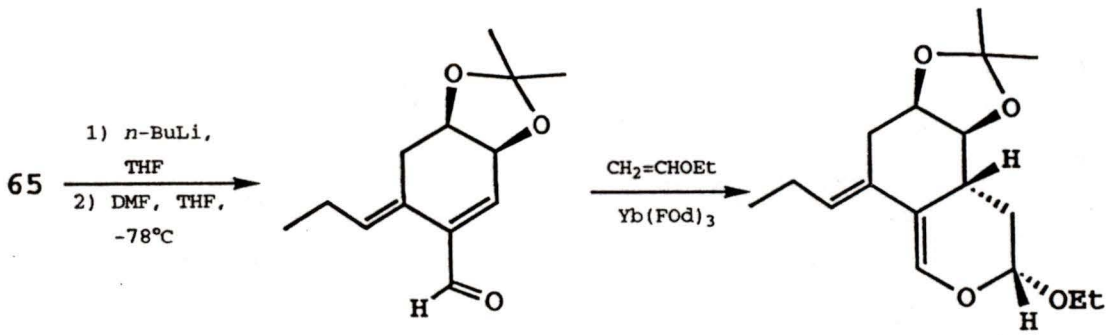
2.2. Synthesis of an Optically Active δ-Lactone Ring

The optically pure compound D-(-)-quinic acid **57** was chosen as a starting material and the synthetic route is shown in Scheme 20.

Scheme 20



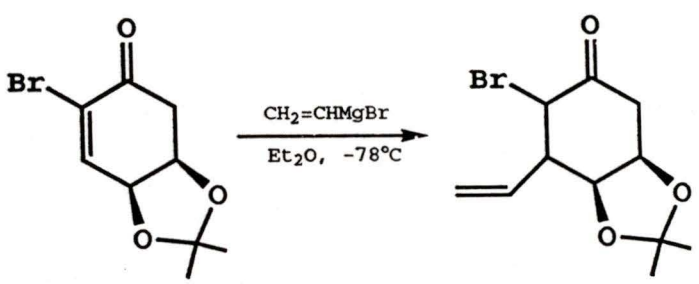
Scheme 20 (cntd)



39 40a

Optically pure enone **61** was prepared from **57** in four steps using a similar procedure as that of Trost[41a] and Danishefsky.[41b] Treatment of **57** with *p*-toluenesulfonic acid in acetone at room temperature gave the acetonide concurrently with lactonization to afford **58** in 95% yield. Reduction of lactone **58** with LAH in THF followed by oxidative cleavage of the resulting vicinal diol **59** with $NaIO_4$ in a phosphate buffer (pH=7) produced ketone **60** in 50% overall yield. Elimination of the hydroxyl group in **60** with methanesulfonyl chloride-triethylamine afforded enone **61** in 88% yield. Bromination-dehydrobromination of enone **61** produced bromoketone **62** in 70% yield. However, using vinylmagnesium bromide to convert enone **62** to allylic alcohol **63** failed. Instead of obtaining **63**, the reaction gave mainly the 1,4-addition product **66** (see Scheme 21) even in the presence of

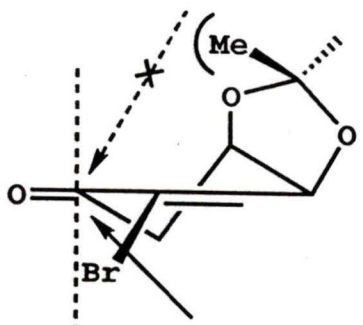
Scheme 21



62 66

excess anhydrous cerium trichloride which is known to favor the 1,2-addition of Grignard reagent to unsaturated carbonyls[42]. Chelation of magnesium to the isopropylidene oxygen, which delivered the reagent to the olefin site, was presumably the cause of this unexpected Michael addition. Vinyllithium, on the other hand, reacted with **62** in diethyl ether to afford mainly the 1,2-addition product **63** in 53% yield and traces of the 1,4-addition compound (Scheme 20).

Unlike **49b** giving two diastereomeric alcohols upon addition of vinylmagnesium bromide, enone **62** formed a single alcohol **63**. The stereoselectivity of the reaction could be due to the steric hindrance of the acetonide to the attack of vinyllithium on the carbonyl from the same side.



The ^{1}H NMR spectrum indicated that there is a long range W coupling between the hydroxyl hydrogen (δ=3.81) and the vinyl hydrogen (δ=5.70) with

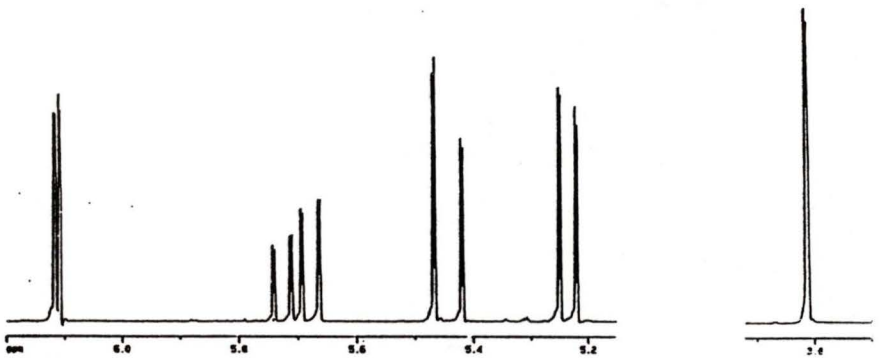
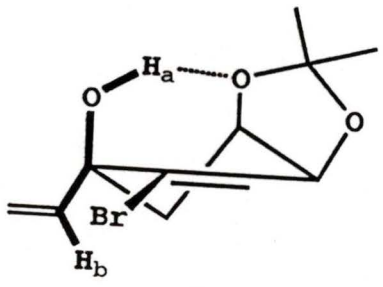


Figure 8. The ^{1}H NMR spectrum of **63**

a coupling constant J=1.2 Hz (Figure 8). This means that the hydroxyl proton H_a is likely to be fixed in a particular position and proton exchange between alcohol molecules is very slow, so that the NMR spectrometer could observe this spin-spin splitting. This may be explained if the hydroxyl hydrogen is involved in an intramolecular hydrogen bond with the isopropylidene oxygen as shown in the configuration of **63** below.



63

In this intramolecular hydrogen bonding, H_a and H_b can be arranged in a W pattern. This configuration of **63** was also confirmed by MM2 calculations.[43]

Acetylation of alcohol **63** was easier than its analogs **50a** and **50b**, and gave allylic acetate **64** in 94% yield. S_N2' displacement of **64** with lithium dimethylcopper(I) gave a 49% yield of *E*-exocyclic olefin **65**[30,32]. The metal-halogen exchange reaction followed by trapping of the resulting vinyl anion with DMF was then used, as before, to convert **65** to the desired aldehyde **39** in 74% yield (see Scheme 20).

The ytterbium-catalyzed cycloaddition of **39** with ethyl vinyl ether and then purification, after work-up with water, produced the desired cycloadduct **40a** in a 66% pure yield and 12% of an inseparable mixture of two by-products (GC determination). No definite structures could be assigned to either of the minor compounds, though one of them could

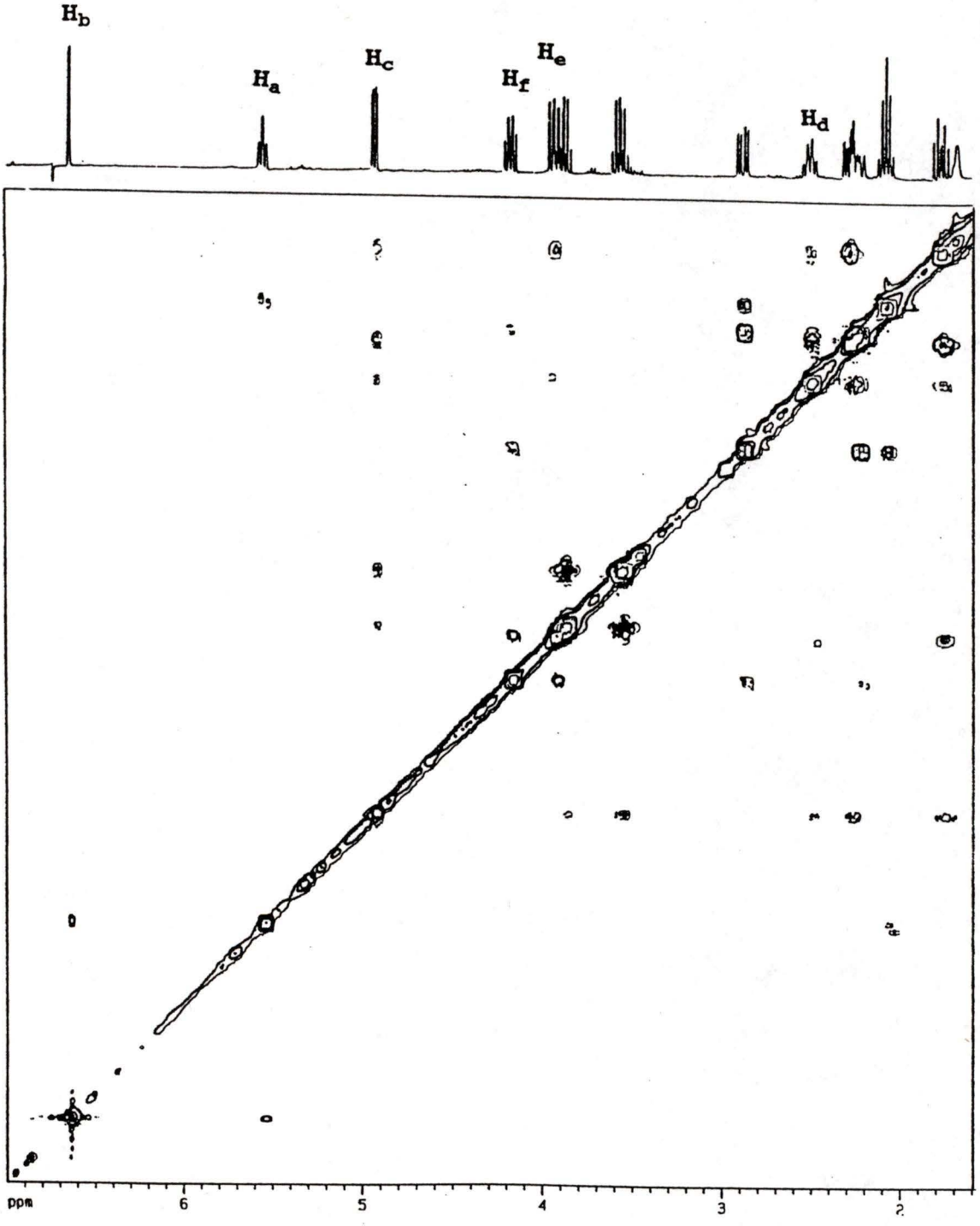
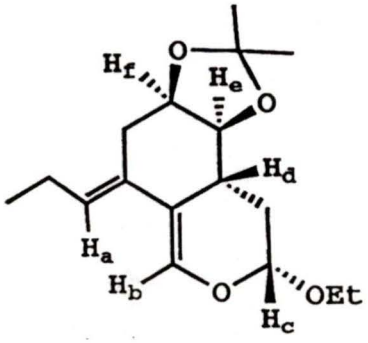
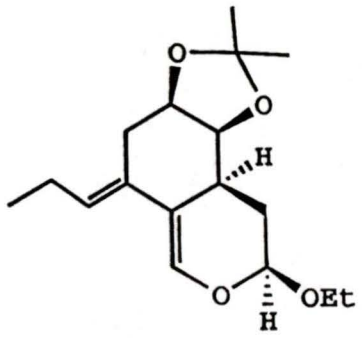


Figure 9. ^{1}H NOESY spectrum of **40a**.

perhaps be the isomer **40b** based on ^{1}H NMR.



40a



40b

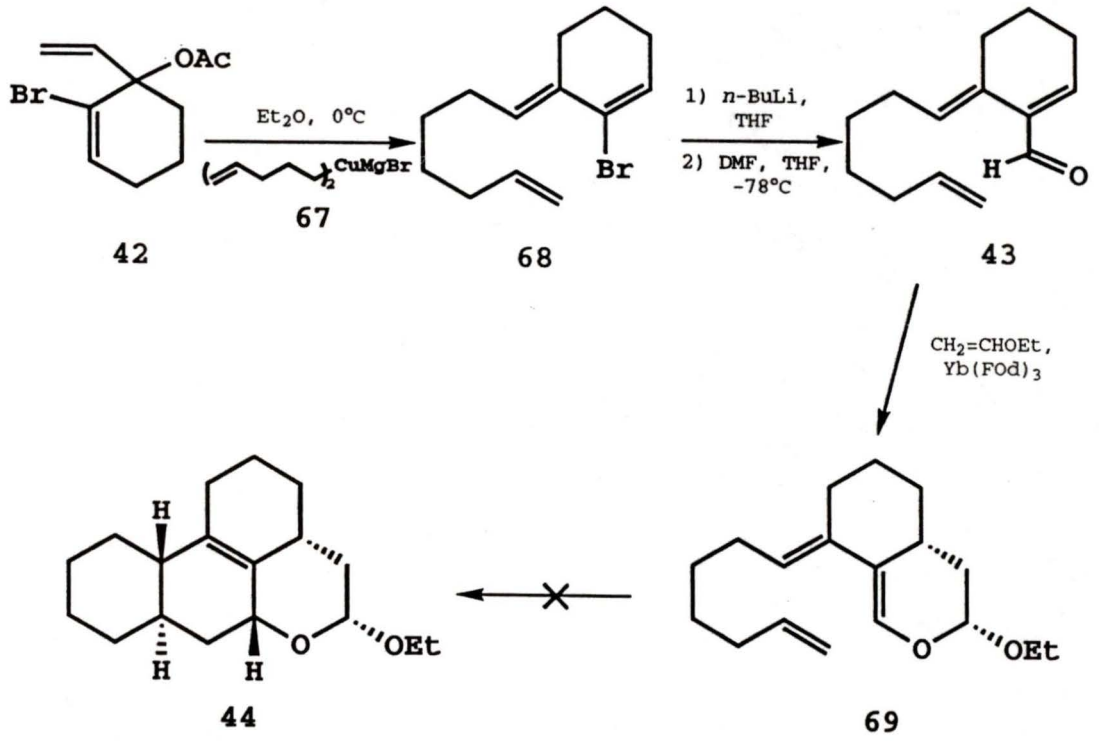
However, the stereochemistry of the adduct **40a** was unambiguously established from its ^{1}H NMR, COSY and NOESY spectra. The NOESY showed positive enhancements between H_a (δ 5.53) and H_b (δ 6.63) and therefore confirmed the *E*-geometry of the propylidene group (see Figure 9). The strong positive enhancement between H_c (δ 4.91) and H_d (δ 2.5-2.43) as well as between H_e (δ 3.91) and H_f (δ 4.15) indicated H_c-H_d and H_e-H_f must be cis. No enhancement between H_d and H_f and a weak enhancement between H_d and H_e also confirmed their trans arrangement. All of these are in accord with the proposed structure of **40a**.

The structure of **40a** indicates, as expected, that the acetonide substituent is able to direct the attack of ethyl vinyl ether from the opposite face of the molecule by steric hindrance. This stereoselective synthesis of cycloadduct **40a** is a particularly interesting model because the product is optically active and contains useful functionalities for further elaboration of the C ring in the quassinoids.

2.3. Investigation of a Synthetic Route to the Tetracyclic Skeleton of Quassinoids

Synthesis of the tetracyclic skeleton of quassinoids was first investigated from **42** following the route shown in Scheme 22.

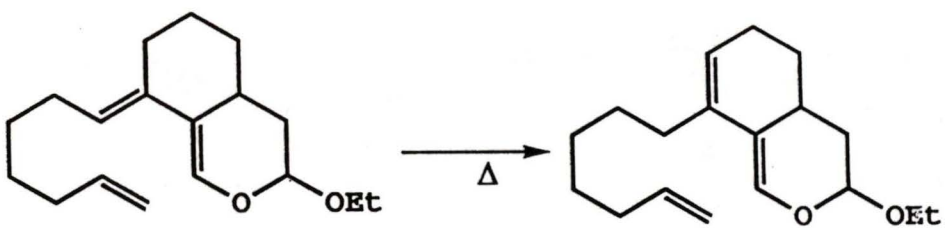
Scheme 22



Di(4-pentenyl)copper(I) magnesium bromide **67** was prepared by the reaction of 1-bromo-4-pentene with magnesium in diethyl ether and then addition of the resulting Grignard reagent to a suspension of copper(I) iodide in diethyl ether at 0°C. The prepared organocopper solution was reacted with **42** in situ to afford bromotriene **68** in 81% yield. Once more, the metal-halogen exchange reaction was used to convert **68** to aldehyde **43** in 67% yield. The inverse electron-demand Diels-Alder reaction of **43** with ethyl vinyl ether gave a 91% yield of the bicyclic adduct **69**.

At first we envisaged that **69** would undergo an intramolecular Diels-Alder reaction upon heating to give tetracyclic compound **44**. The diene in **69** was fixed in the *s*-cis configuration favoring a Diels-Alder cycloaddition. However, all attempts to make **44** from **69** was unsuccessful. Refluxing **69** in toluene resulted in the isomerization of the starting material to the endocyclic olefin **70** (Scheme 23). Heating **69** to 180°C in a sealed tube, either in neat or in a toluene solution with triethylamine and methylene blue produced unknown by-products. Stirring the solution of **69** in 2,2,2-trifluoroethanol, catalyzed by $(Ph_3P)_3RhCl$, overnight at 55°C showed no reaction.[44]

Scheme 23

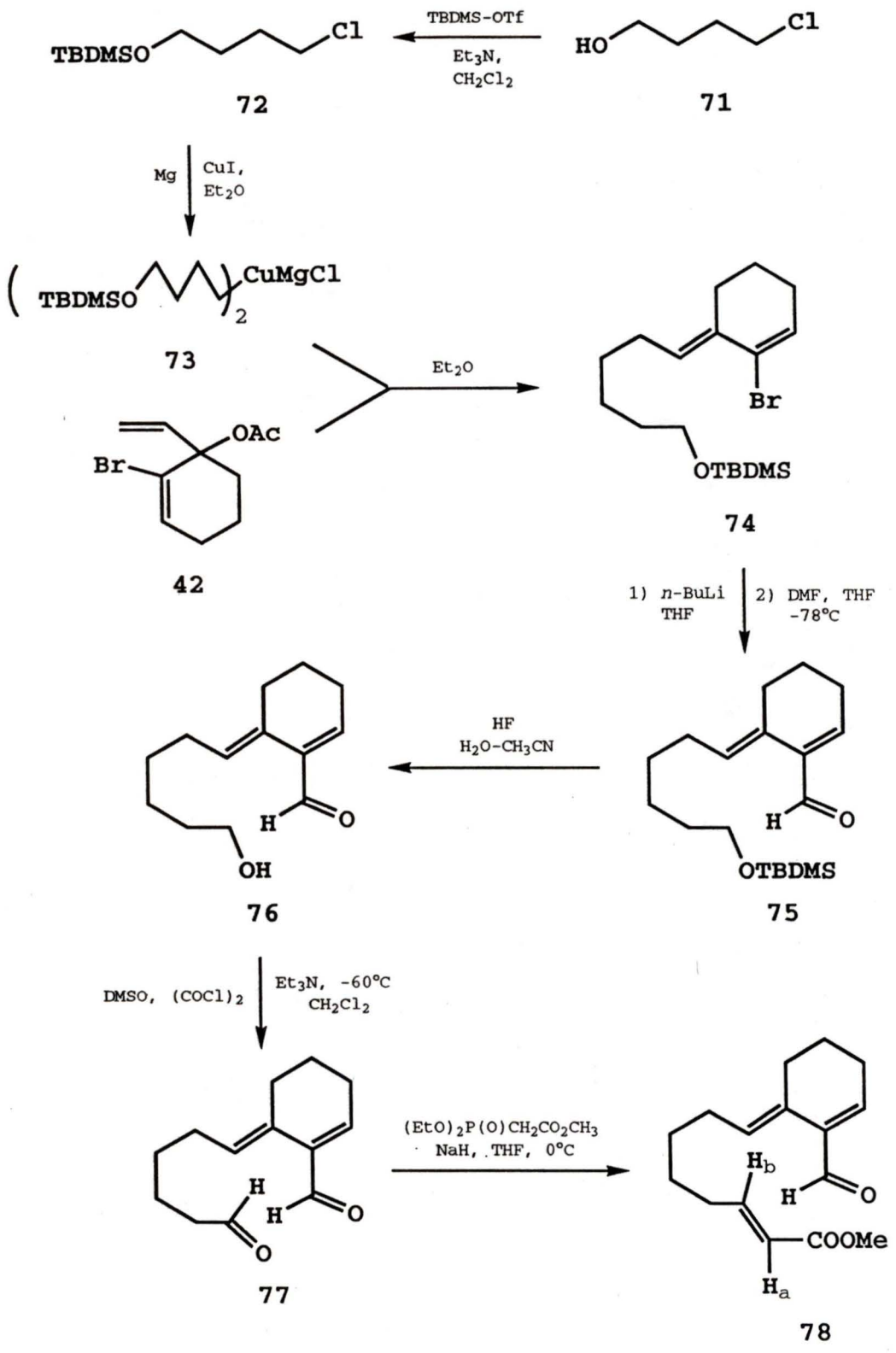


69 **70**

However, from the reaction of diene **54** with maleic anhydride (cf. Scheme 17) it was apparent that we could form the desired tetracyclic compound by activating the dienophile with an electron-withdrawing group. Based on that result, a new compound **78**, precursor to the tetracyclic compound **80**, was designed and the synthetic route is shown in Scheme 24.

73 was prepared from 4-chloro-1-butanol **71**. Protection of the hydroxyl group in **71** with *t*-butyldimethylsilyl trifluoromethanesulfonate[45] gave **72**. Refluxing of **72** with Mg in diethyl ether followed by addition of the resulting

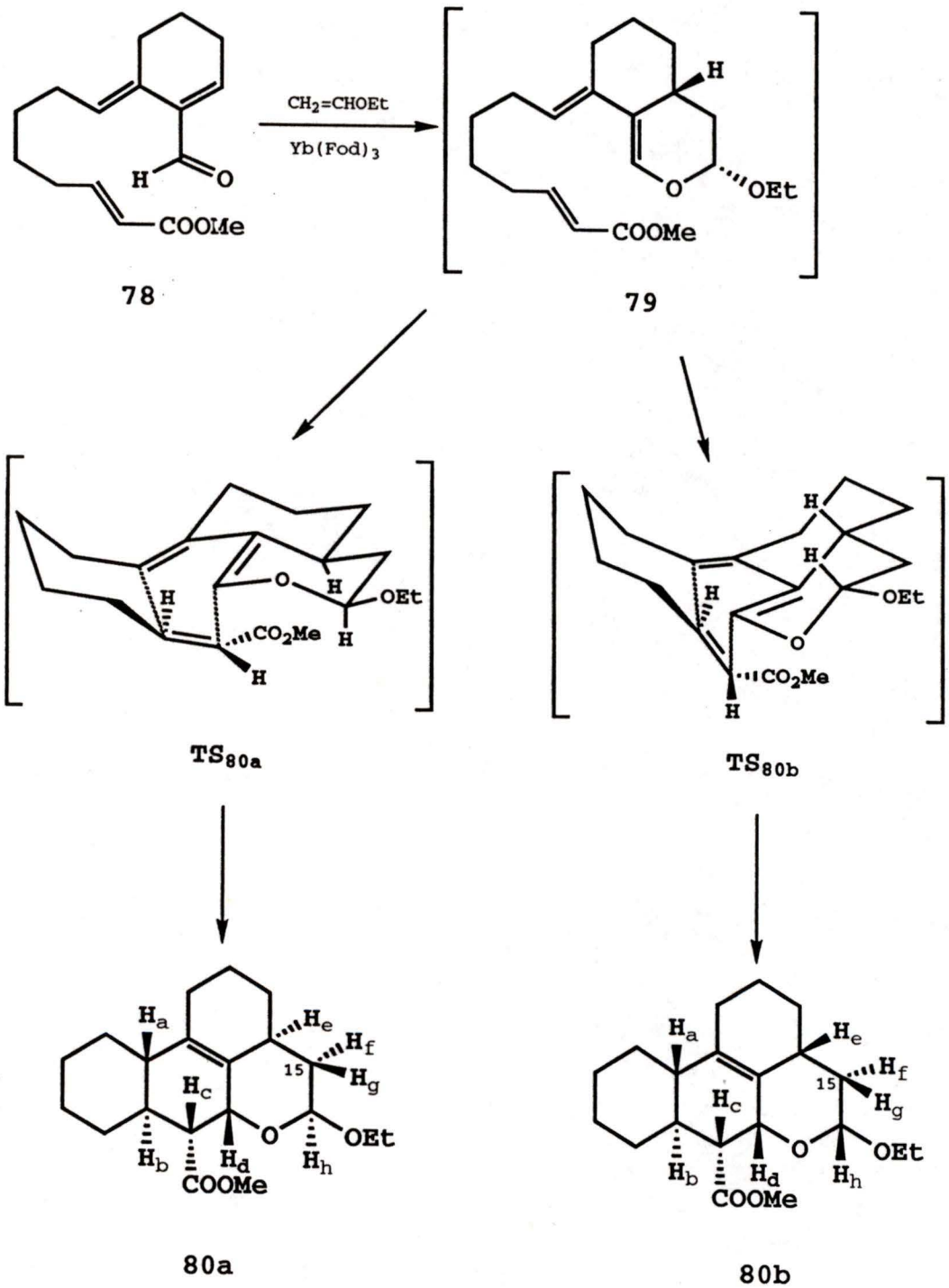
Scheme 24


TBDMS-OTf
Et3N,
CH2Cl2
TBDMSO
Cl
HO
Cl
72
71
Mg
CuI,
Et2O
TBDMSO
CuMgCl
2
73
Et2O
OAc
Br
42
Br
OTBDMS
74
1) n-BuLi
THF
2) DMF, THF
-78°C
HF
H2O-CH3CN
H
O
OH
76
H
O
OTBDMS
75
DMSO, (COCl)2
Et3N, -60°C
CH2Cl2
H
H
O
O
77
(EtO)2P(O)CH2CO2CH3
NaH, THF, 0°C
Hb
H
O
COOMe
Ha
78

Grignard reagent solution to a suspension of copper(I) iodide in Et_2O gave a solution of **73** which reacted with **42** to produce compound **74** and an inseparable impurity. The ^1H and ^{13}C NMR spectra suggested that the impurity was *t*-butyldimethylsilyl butyl ether which had no effect on the next reaction. Direct lithium-bromine exchange of **74**, followed by trapping of the resulting vinyl anion with DMF, afforded aldehyde **75** in 80% overall yield from **42**. Conversion of *t*-butyldimethylsilyl ether **75** to alcohol **76** with tetra-*n*-butylammonium fluoride was unsuccessful due to the fact that the fluoride ion in THF is a sufficiently strong base to react with the cyclic unsaturated aldehyde system in **75**.[45] Aqueous hydrofluoric acid in acetonitrile was very efficient at removing the silyl group to form **76** in 92% yield. Swern oxidation[46] of the resulting primary alcohol **76** produced dialdehyde **77** in 85% yield. The structure of **77** was deduced from its ^1H NMR and IR spectra. The IR spectrum gave two very strong peaks at 1725 cm^{-1} (for saturated aldehyde) and 1695 cm^{-1} (for unsaturated aldehyde). The ^1H NMR showed a singlet at δ 9.38 (for unsaturated aldehyde proton) and a triplet at δ 9.66 (for saturated aldehyde proton). The α,β-unsaturated ester **78** was obtained via a Wadsworth-Emmons reaction of **77** with exactly one equivalent of methyl diethylphosphonoacetate at 0°C. The reaction was chemoselective and only the saturated aldehyde in the side chain was involved in the reaction, because the α,β-unsaturated aldehyde is less reactive. The reaction was also stereoselective and produced the α,β-unsaturated ester **78** with the E-configuration in 87% yield. The E-geometry of the α,β–unsaturated ester was confirmed from its ^1H NMR coupling constants of J=15.7 Hz for the two vinyl protons, H_a and H_b.

The ytterbium-catalyzed, inverse-electron demand, Diels-Alder

Scheme 25


CH2=CHOEt
Yb(Fod)3
H
O
COOMe
78
OEt
79
CO2Me
TS80a
TS80b
Ha
He
Hf
Hg
15
Hc
Hb
Hd
Hh
80a
80b

reaction of **78** with ethyl vinyl ether at room temperature first gave bicyclic ester **79** which was immediately, as predicted, followed by an IMDAC via two chair-like transition states $\mathbf{TS_{80a}}$ and $\mathbf{TS_{80b}}$ to afford a 6:1 mixture of the tetracyclic compounds **80a** and **80b** in 87% yield (see Scheme 25). The ratio was determined by GC and proton NMR. The structure of the major product **80a** was confirmed by proton NMR, NOE and X-ray crystallography. The NOESY spectrum indicated positive enhancements between H_c-H_d, H_d-H_g, H_f-H_h, and no enhancement between H_b-H_c. Given these results and the fact that H_a-H_d must be *cis* and H_b-H_c must be *trans*, we can deduce the structure **80a** for the major isomer. This was confirmed by NOE difference experiments and supported by a constant of 9.3 Hz between H_b-H_c and H_c-H_d. The observation reflects that the intramolecular Diels-Alder cycloaddition proceeded via an endo transition state as we predicted.

Although the minor isomer could not be obtained in the pure form, the ^1H NMR spectrum of the mixture displays coupling constants of 12.5 Hz for

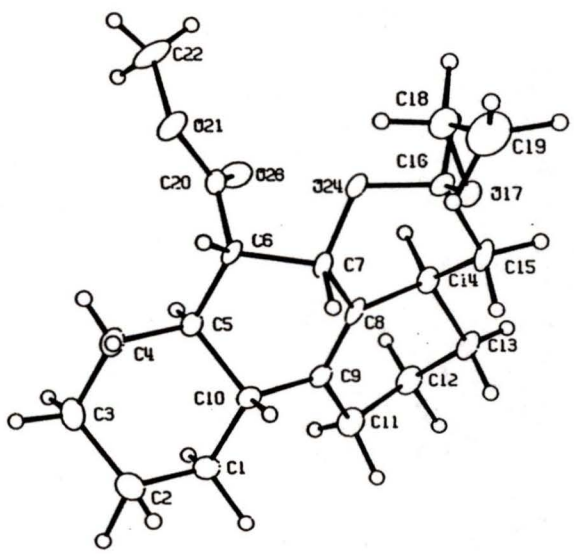


Figure 10. An ORTEP drawing of **80a**

H_{b-c}, 6.5 Hz for H_{c-d}, 9.8 Hz for H_{f-h} and 2.5 Hz for H_{g-h} indicating that the structure of this isomer must be **80b**.

The result of this reaction indicated that our synthetic route to the tetracyclic skeleton of quassinoids was indeed viable.

The X-ray structure analysis of **80a** was carried out in this department and an ORTEP drawing of the molecular structure is shown in Figure 10.

The four rings of **80a** have different topology in the solid state. Ring A takes a chair conformation, but ring D adopts a boat conformation. With the endocyclic double bond, both ring B and C have the half-chair conformation. The X-ray structure shows that ethoxyl group at C_{16} is axial and H_h is equatorial. ^1H NMR suggests that this conformation is also retained in solution. A clearer conformation is drawn in Figure 11.

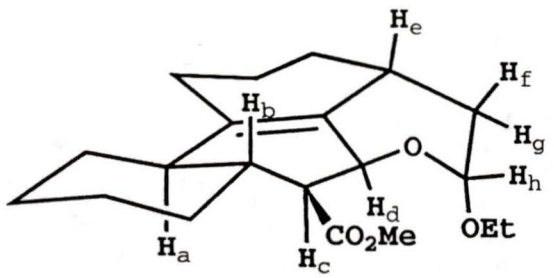


Figure 11. Conformation of **80a**
(enantiomer shown)

CHAPTER THREE
CONCLUSION

A new synthetic route to the tetracyclic framework of the quassinoids was developed. This new route employed a diene-transmissive Diels-Alder cycloaddition as the key reaction and could be used for the total synthesis of quassinoid compounds. The formation of the ABD rings in the quassinoid skeleton was achieved in one step for the first time based on this new synthetic methodology. An X-ray structure determination of **80a** revealed the topology of the molecule and showed that each ring had a different conformation.

Formation of the δ-lactone D ring with stereochemical control was investigated from the racemic 4-methyl-2-cyclohexen-1-one **47** and D-(-)-quinic acid **57** through some selected reactions. It was found that the inverse electron-demand hetero Diels-Alder cycloaddition could be stereochemically controlled by introducing a proper substituent at C-13 in the C ring, such as that in **37** and **39**, and could be used to construct the D ring with the desired stereochemistry.

Although the stereochemistry at C-14 in **80a** is opposite that of quassinoids with respect to the other chiral centers, we believe that it should be possible to correct this by placing chiral centers on the acyclic chain in an analog of **78**. Such chiral centers would control the absolute stereochemistry at C-5, 6, 7 and 10 by adopting an equatorial position in the transition state analog to $\mathbf{TS_{36a}}$ (cf. Scheme 9). Since we have shown that we can control the absolute stereochemistry at C-14 (see section 2.2) and since the chiral centers discussed above should exert a far larger control over the

stereochemistry of the IMDAC, we expect to obtain full control over all chiral centers in higher analogs of **80**. This is in progress in our laboratories.

CHAPTER FOUR
EXPERIMENTAL

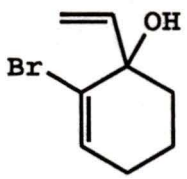
General Procedure.

All reactions were performed under an atmosphere of argon except where otherwise stated. Reactions requiring anhydrous conditions were performed in oven-dried or flame-dried glassware which were flushed several times with argon. Solvents were distilled before use: toluene, diethyl ether and tetrahydrofuran were distilled over sodium-benzophenone; dichloro-methane, dimethylsulfoxide, triethylamine and carbon tetrachloride were fractionated over calcium hydride. The term "*in vacuo*" refers to solvent removal via a Büchi rotoevaporator at water aspirator pressure. Preparative thin-layer chromatography (TLC) was performed on aluminum plates coated with 0.2 mm of silica gel (EM Separations, Art. 5554, DC-Alufolien Kieselgel 60 F_{254}). Flash column chromatography was performed on silica gel Kieselgel 60 from EM Science (particle size: 0.040--0.063 mm, 230-400 mesh ASTM).

Proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined at room temperature on a Brüker WM 250 (250 MHz) spectrometer or a Brüker AMX 360 (360 MHz) spectrometer with $CDCl_3$ as solvent and the solvent residue $CHCl_3$ peak (^{1}H NMR 7.24 ppm and ^{13}C NMR 77.0 ppm) for calibration. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; qi, quintet; m, multiplet; br, broad. Infrared

spectra (IR) were determined on Perkin-Elmer 1330 Infrared Spectrophotometer using $CHCl_3$ as solvent in sodium chloride cavity cells. Mass spectra were recorded on a Finnigan 3300 Gas Mass Spectrometer with 70eV electron impact ionization or using methane as a carrier gas for chemical ionization. High resolution mass spectra and gas chromatography-mass spectra were recorded on a CONCEPT-H Double Focusing Magnetic Mass Spectrometer with 70eV electron impact ionization and 30 M nonpolar fused silica column. Melting points are uncorrected and were determined on a Reichert 7905 melting point apparatus by using open capillary tubes. Gas chromatography were conducted on a Perkin-Elmer Autosystem Gas Chromatograph using a 15 M, 25μ DB-1 capillary column connected to a FID detector with electronic integration.

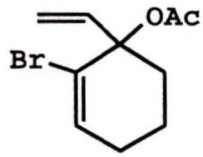
2-Bromo-1-vinyl-2-cyclohexen-1-ol (50a)



2-Bromo-2-cyclohexen-1-one **49a** [36] (4.35 g, 24.9 mmol) in diethyl ether (40 mL) was added slowly to a solution of vinylmagnesium bromide (1M in THF, 50 mL) in diethyl ether (300 mL) at -78°C. The mixture was stirred for 30 min at -78°C and quenched with saturated aqueous ammonium chloride (150 mL). The aqueous phase was extracted with diethyl ether (2x100 mL). The combined organic layers were washed with brine (100 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* and the product was purified by flash column chromatography eluting with hexanes-ethyl acetate 5:1 to yield pure **50a** as a colorless oil (3.69 g, 73%). ^{1}**H**

NMR: 6.14 (t, 1H, J=4.1 Hz), 5.75 (dd, 1H, J=17.2, 10.6 Hz), 5.22 (dd, 1H, J=17.2, 1.2 Hz), 5.11 (dd, 1H, J=10.6, 1.2 Hz), 2.61 (s, 1H), 2.05-1.96 (m, 2H), 1.83 (dd, 2H, J=6.0, 4.6 Hz), 1.68-1.52 (m, 2H); **^{13}C NMR**: 141.8 (d), 132.5 (d), 128.1 (s), 114.5 (t), 74.1 (s), 37.0 (t), 27.6 (t), 18.5 (t); **IR:**3560 (ms), 3540-3360 (br, w), 3090 (w), 3010 (ms), 1635 (ms), 1050 (ms) cm^{-1}; **MS m/z** (relative intensity): 204 (M$^+$, ^{81}Br, 10), 202 (M$^+$, ^{79}Br, 11), 177 (51), 175 (63), 123 (100); **HRMS** calcd for $C_8H_{11}O^{81}Br$: 203.9973, found: 203.9961; calcd for $C_8H_{11}O^{79}Br$: 201.9993, found: 201.9986.

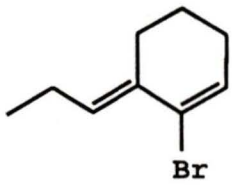
2-Bromo-1-vinyl-2-cyclohexen-1-yl Acetate (42)



Acetic anhydride (1.55 g, 15.2 mmol) was added to a mixture of 2-bromo-1-vinyl-2-cyclohexen-1-ol **50a**, 4-dimethyl-aminopyridine (0.19 g, 1.6 mmol) and triethylamine (1.90 g, 19 mmol) at rt. Dichloromethane (2.8 mL) was added to dissolve the 4-dimethylaminopyridine. The reaction mixture was stirred for 21 h at rt and then diluted with diethyl ether (10 mL). The solution was washed with 1 N hydrochloric acid (10 mL) and saturated aqueous sodium hydrogen carbonate (10 mL). The aqueous layers were separated and extracted with diethyl ether (2x10 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous magnesium sulfate. Solvent evaporation *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (9:1) produced 1.45 g of **42** as an oil (78%). **^{1}H NMR**: 6.30 (dd, 1H, J=5.3, 2.9 Hz), 5.90 (dd, J=17.4, 10.7 Hz), 5.29 (d, J=17.4 Hz), 5.28 (d, 1H, J=10.7 Hz), 2.62 (dt, 1H, J=12.6, 4.3 Hz),

2.30-1.98 (m, 3H), 2.07 (s, 3H), 1.81-1.62 (m, 2H); **^{13}C NMR**: 168.9 (s), 137.4 (d), 133.7 (d), 122.9 (s), 115.9 (t), 82.6 (s), 32.2 (t), 27.1 (t), 21.9 (q), 19.1 (t); **IR:** 3090 (w), 3010 (ms), 1735 (s), 1640 (ms), 1370 (s), 1245 (s), 1195 (s) cm^{-1}; **MS m/z** (relative intensity): no M^+, 186 (60), 184 (72), 105 (100), 104 (15), 103 (24); **HRMS** calcd for $C_8H_9{}^{81}Br(-CH_3CO_2H)$: 185.9868, found: 185.9863; calcd for $C_8H_9{}^{79}Br(-CH_3CO_2H)$: 183.9888, found: 183.9887.

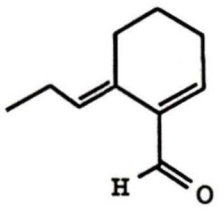
(E)-2-Bromo-1-propylidene-2-cyclohexene (52a)



An ethereal solution of methyllithium (12.3 mL, 1.4 M, 17.2 mmol) was added to a suspension of freshly purified copper iodide (1.60 g, 8.6 mmol) in diethyl ether (30 mL) at 0°C. A solution of acetate **42** (1.05 g, 4.3 mmol) in diethyl ether (30 mL) was then added and a yellow precipitate appeared immediately. Stirring was continued for 30 min. The reaction was then quenched with saturated aqueous ammonium chloride (100 mL). The aqueous phase was separated and extracted with diethyl ether (3x40 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes yielded **52a** as a colorless oil (0.74 g, 86%). **^{1}H NMR**: δ 6.21 (t, 1H, J=4.4 Hz), 5.85 (t, 1H, J=6.1 Hz), 2.41 (t, 2H, J=6.2 Hz), 2.22-2.09 (m, 4H), 1.71 (qi, 2H, J=6.2 Hz), 1.00 (t, 3H, J=7.5 Hz); **IR:** 3005 (w), 1595 (w), 1375 (w) cm^{-1}; **MS m/z** (relative intensity): 202 (M^+, ^{81}Br, 92), 200 (M^+, ^{79}Br, 100), 187 (53), 185 (57), 121 (70),

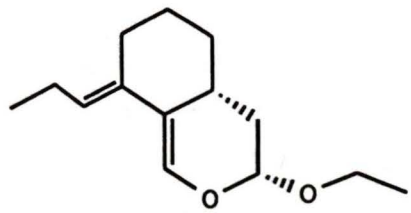
105 (36), 93 (45); **HRMS** calcd for $C_9H_{13}{}^{81}Br$: 202.0181, found: 202.0191; calcd for $C_9H_{13}{}^{79}Br$: 200.0201, found: 200.0191.

(E)-6-propylidene-1-cyclohexenecarboxaldehyde (53)



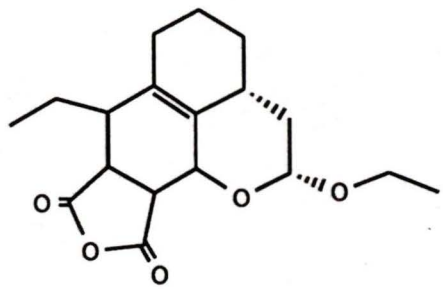
Bromide **52a** (0.74 g, 3.7 mmol) in tetrahydrofuran (10 mL) was added dropwise to a solution of *n*-butyllithium in hexane (2.5 M, 3 mL, 7.5 mmol) at -78°C. The reaction mixture was stirred for 30 min and then N,N-dimethylformamide (2.00 g, 27.4 mmol) was added at -78°C. It was stirred for another 5 h at -78°C and quenched with saturated aqueous ammonium chloride (20 mL). The aqueous layer was separated and extracted with diethyl ether (3x15 mL). The combined organic portions were washed with brine (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the product was purified by flash column chromatography eluting with hexanes-ethyl acetate (9:1) to give a colorless oil (0.32 g, 58%). **^{1}H NMR**: δ 9.47 (S, 1H), 6.63-6.59 (m, 2H), 2.41 (q, 2H, J=6.1 Hz), 2.32 (bt, 2H, J=6.3 Hz), 2.13 (qi, 2H, J=7.5 Hz), 1.71 (qi, 2H, J=6.3 Hz), 0.99 (t, 3H, J=7.5 Hz); **^{13}C NMR**: 194.0 (d), 151.7 (d), 138.2 (s), 131.4 (d), 128.0 (s), 27.1 (t), 24.9 (t), 21.7 (t), 21.0 (t), 13.8 (q); **IR:**3030 (w), 3010 (w), 2725 (w), 1690 (s), 1635 (w), 1595 (w) cm^{-1}; **MS m/z** (relative intensity): 150 (M^+, 65), 149 (100), 135 (32), 121 (15), 107 (42), 93 (36), 91 (49); **HRMS** calcd for $C_{10}H_{14}O$: 150.1045, found: 150.1053.

(±)-4-Ethoxy-10-propylidene-3-oxabicyclo[4.4.0]dodec-1-ene (54)



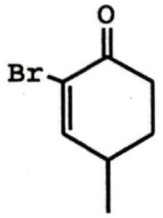
Aldehyde **53** (73 mg, 0.49 mmol) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (63 mg, 0.06 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 3 days at rt. The excess ethyl vinyl ether was removed *in vacuo* and the residue was purified by flash column chromatography eluting with hexanes-ethyl acetate (20:1) to yield the product **54** as a colorless oil (97.8 mg, 90%). **^{1}H NMR**: δ 6.30 (d, 1H, J=1.9 Hz), 5.22 (td, 1H, J=7.2, 2.2 Hz), 4.78 (dd, 1H, J=9.6, 1.8 Hz), 3.90 (dq, 1H, J=9.5, 7.0 Hz), 3.53 (dq, 1H, J=9.5, 7.0 Hz), 2.53 (br.d, 1H, J=13.6 Hz), 2.27-2.19 (m, 1H), 2.15-1.58 (m, 6H), 1.46 (ddd, 1H, J=12.9, 11.2, 9.9 Hz), 1.31-1.10 (m, 2H), 1.21 (t, 3H, J=7.0 Hz), 0.92 (t, 3H, J=7.7 Hz); **^{13}C NMR**: 134.9 (d), 134.7 (s), 123.5 (d), 119.6 (s), 99.6 (d), 64.3 (t), 36.5 (t), 34.0 (d), 33.3 (t), 27.7 (t), 25.2 (t), 20.8 (t), 15.2 (q), 14.5 (q); **IR:** 3005 (w), 1640 (ms), 1625 (ms), 1380 (ms), 1140 (s), 1120 (s), 1070 (ms) cm^{-1}; **MS m/z** (relative intensity): 222 (M+, 23), 149 (11), 122 (14), 117 (10), 105 (16). 97 (11), 95 (15), 93 (15); **HRMS** calcd for $C_{14}H_{22}O_2$: 222.1621, found: 222.1641.

(±)-Tetracyclic Compound 55



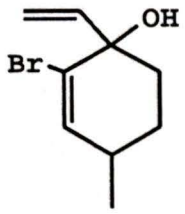
Diene **54** (24 mg, 0.11 mmol) and maleic anhydride (16 mg, 0.16 mmol) were dissolved in toluene (0.6 mL). The solution was stirred at rt for 24 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography eluting with hexanes-ethyl acetate (3:1) to yield the product **55**(32 mg, 92%) as a white solid. **mp:** 168.5-170.5°C; **^{1}H NMR**: δ 5.11 (t, 1H, J=7.1 Hz), 4.38-4.36 (m, 1H), 3.81 (dq, 1H, J=9.8, 7.1 Hz), 3.55 (dd, 1H, J=9.2, 7.7 Hz), 3.52 (dq, 1H, J=9.8, 7.1 Hz), 3.39 (dd, 1H, J=9.2, 5.0 Hz), 2.26-2.13 (m, 1H), 2.08-1.92 (m, 3H), 1.87-1.76 (m, 3H), 1.43-1.25 (m, 1H), 1.18 (t, 3H, J=7.1 Hz), 1.15-1.07 (m, 1H), 1.04 (t, 3H, J=7.3 Hz), 0.98-0.82 (m, 1H); **^{13}C NMR**: δ 171.2 (s), 169.1 (s), 134.9 (s), 131.3 (s), 97.7 (d), 64.0 (d), 63.2 (t), 44.5 (d), 41.8 (d), 39.3 (d), 36.2 (t), 29.3 (d), 28.7 (t), 25.0 (t), 22.0 (t), 20.0 (t), 15.2 (q), 12.4 (q); **IR:** 1850 (ms), 1780 (s), 1060 (s), 975 (s) cm^{-1}; **MS m/z** (relative intensity): 320 (M^+, 2), 274 (87), 246 (50), 222 (100), 202 (8), 175 (35), 173 (25); **HRMS** calcd for $C_{18}H_{24}O_5$: 320.1624, found: 320.1642.

(±)-2-Bromo-4-methyl-2-cyclohexen-1-one (49b)



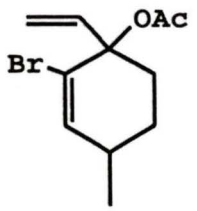
Bromine (1.45 g, 9.1 mmol) in dry carbon tetrachloride (15 mL) was added dropwise to a solution of 4-methyl-2-cyclohexen-1-one **47**[35] (1.01 g, 9.1 mmol) in dry carbon tetrachloride (15 mL) at -10°C. The reaction mixture was stirred 10 min at -10°C, then triethylamine (1.59 g, 15.7 mmol) in dry carbon tetrachloride (10 mL) was added slowly. The reaction mixture was stirred for another 3 h at 0°C and filtered, washing with carbon tetrachloride. The filtrate was washed with 1 N hydrochloric acid (20 mL) and saturated aqueous sodium bicarbonate (20 mL). The aqueous layers were separated and extracted with diethyl ether (2x20 mL). The combined organic portions were washed with saturated sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the product was purified by flash column chromatography eluting with hexanes-ethyl acetate (4:1) to give 1.11 g of bromoketone **49b** as a colorless oil (64%). **^{1}H NMR**: 7.23 (d, 1H, J=2.4 Hz), 3.50-3.37 (m, 2H), 3.28 (ddd, 1H, J=14.0, 10.4, 4.0 Hz), 3.01-2.91 (m, 1H), 2.69-2.56 (m, 1H), 2.17 (d, 3H, J=6.0 Hz); **^{13}C NMR**: 156.4 (d), 123.1 (s), 115.1 (s), 36.9 (t), 34.2 (d), 30.6 (t), 20.0 (q); **IR:** 3020 (ms), 1695 (s) 1595 (ms), 1380 (w) cm^{-1}; **MS m/z** (relative intensity): 190 (M^+, ^{81}Br, 77), 188 (M^+, ^{79}Br, 71), 162 (18), 160 (15), 148 (18), 146 (16), 135 (13), 133 (15), 109 (100); **HRMS** calcd for $C_7H_9O^{81}Br$: 189.9817, found: 189.9796; calcd for $C_7H_9O^{81}Br$: 187.9837, found: 187.9793.

(±)-2-Bromo-4-methyl-1-vinyl-2-cyclohexen-1-ol (50b)



The same procedure as for compound **50a** except that 2-bromo-4-methyl-2-cyclohexen-1-one **49b** (1.06 g, 5.6 mmol) in diethyl ether (10 mL) was added to a solution of vinylmagnesium bromide (17 mL) in diethyl ether (100 mL); Flash column chromatography eluting with hexanes-ethyl acetate (3:1) yielded 1.03g (84%) of a 3:1 ratio of two isomers cis/trans-**50b**. **Major isomer**: **^{1}H NMR**: δ 6.09 (dd, 1H, J=2.8, 1.0 Hz), 5.84 (dd, 1H, J=17.3, 10.6 Hz), 5.26 (dd, 1H, J=17.3, 1.0 Hz), 5.22 (dd, 1H, J=10.6, 1.0 Hz), 2.33 (m, 1H), 2.24 (s, 1H), 2.01 (ddd, 1H, J=13.0, 5.4, 3.1 Hz), 1.89 (dt, 1H, J=13.0, 3.1 Hz), 1.80 (m, 1H), 1.29 (m, 1H), 1.00 (d, 3H, J=7.1 Hz); **^{13}C NMR**: δ 141.5 (d), 138.5 (d), 128.0 (s), 115.7 (t), 74.7 (s), 36.3 (t), 33.8 (d), 27.7 (t), 20.8 (q); **IR:** 3620-3500 (br), 3090 (w), 1635 (w) 1370 (ms) cm^{-1}; **MS m/z** (relative intensity): 218 (M^+, ^{81}Br, 8), 216 (M^+, ^{79}Br, 9), 200 (22), 198(19), 191 (27), 189 (30), 176 (32), 174 (37), 137 (100); **HRMS** calcd for $C_9H_{13}O^{81}Br$: 218.0130, found: 218.0112; calcd for $C_9H_{13}O^{79}Br$: 216.0150, found: 216.0160; **Minor isomer**: **^{1}H NMR**: δ 6.11 (d, 1H, J=3.0 Hz), 5.82 (dd, 1H, J=17.2, 10.6 Hz), 5.34 (dd, 1H, J=17.2, 1.1 Hz), 5.20 (dd, 1H, J=10.6, 1.1 Hz), 2.27 (m, 1H), 2.21 (s, 1H), 1.99 (ddd, 1H, J=14.1, 7.9, 3.2 Hz), 1.84-1.71 (m, 2H), 1.45 (m, 1H), 1.05 (d, 3H, J=7.1 Hz); **^{13}C NMR**: δ 142.7 (d), 138.7 (d), 127.9 (s), 114.3 (t), 74.0 (s), 35.7 (t), 33.6 (d), 26.7 (t), 20.4 (q).

(±)-2-Bromo-4-methyl-1-vinyl-2-cyclohexen-1-yl acetate (51)



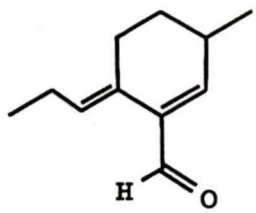
The same procedure as for compound **42** except that acetic anhydride (0.94 g, 9.3 mmol), 2-bromo-4-methyl-1-vinyl-2-cyclohexen-1-ol **50b** (1.01g, 4.7 mmol), 4-dimethylaminopyridine (0.11 g, 0.93 mmol) and triethylamine (1.18 g, 11.6 mmol) were used; Flash column chromatography eluting with hexanes-ethyl acetate (9:1) produced 0.85 g of acetate **51** as an oil (70%). **^{1}H NMR**: δ 6.14 (dd, 1H, J=2.3, 1.2 Hz), 5.88 (dd, 1H, J=17.5, 10.6 Hz), 5.28 (dd, 1H, J=17.5, 0.9 Hz), 5.28 (dd, 1H, J=10.6, 0.9 Hz), 2.62 (ddd, 1H, J=14.1, 12.7, 1.4 Hz), 2.47-2.36 (m, 1H), 2.07 (s, 3H), 2.01 (dt, 1H, J=14.1, 1.4 Hz), 1.82-1.74 (m, 1H), 1.37-1.26 (m, 1H), 1.00 (d, 3H, J=7.1 Hz); **IR:**3090 (w), 3020 (w), 1740 (s), 1640 (w) 1370 (s), 1245 (s), 1210 (s) cm^{-1}; **MS m/z** (relative intensity): no M^+, 198 (100), 196 (98), 117 (67), 115 (54); **HRMS** calcd for $C_9H_9{}^{81}Br$: 197.9868, found: 197.9887; calcd for $C_9H_9{}^{81}Br$: 195.9877, found: 195.9889.

(±)-(E)-2-Bromo-4-methyl-1-propylidene-2-cyclohexene (52b)

The same procedure as for compound **52a** except that methyllithium (1.4 M, 8.8 mL, 12.4 mmol), cuprous iodide (1.18 g, 6.2 mmol) in diethyl ether (30 mL) and acetate **51** (0.80 g, 3.1 mmol) in diethyl ether (30 mL) were

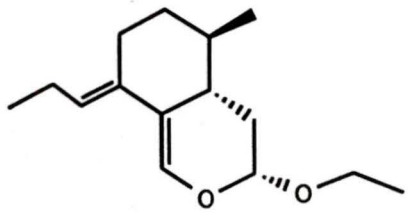
used. Flash column chromatography eluting with hexanes-ethyl acetate (15:1) yielded **52b** as a colorless oil (0.48 g, 72%).**^{1}H NMR:** δ 6.05 (d, 1H, J=3.2 Hz), 5.85 (t, 1H, J=7.3 Hz), 2.62 (dt, 1H, J=14.9, 4.7 Hz), 2.46-2.35 (m, 1H), 2.23 (bt, 1H, J=14.0 Hz), 2.12 (dqi, 2H, J=7.6, 3.2 Hz), 1.88-1.81 (m, 1H), 1.35-1.23 (m, 1H), 1.02 (d, 3H, J=7.1 Hz), 1.00 (t, 3H, J=7.6 Hz); **IR:** 3010 (m), 1590 (w), 1375 (w) cm^{-1}; **MS m/z** (relative intensity): 216 (M^+, ^{81}Br, 76), 214 (M^+, ^{79}Br, 72), 201 (32), 199 (40), 135 (100), 120 (19). **HRMS** calcd for $C_{10}H_{15}{}^{81}Br$: 216.0337, found: 216.0357; calcd for $C_{10}H_{15}{}^{81}Br$: 204.0357, found: 204.0380.

(±)-(E)-3-methyl-6-propylidene-1-cyclohexenecarbox aldehyde (37)



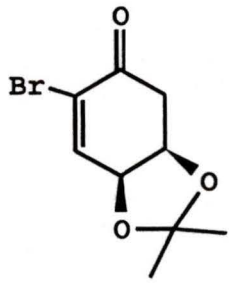
The same procedure as for compound **53** except that bromide **52b** (0.40 g, 1.8 mmol) in tetrahydrofuran (20 mL), *n*-butyllithium (2.5 M in hexane 1.10 mL, 2.8 mmol) and N,N-dimethylformamide (0.54 g, 7.4 mmol) were used. Flash column chromatography eluting with hexanes-ethyl acetate (15:1) gave **37** as a colorless oil (0.22 g, 72%). **^{1}H NMR**: δ 9.47 (s, 1H), 6.62 (t, 1H, J=7.1 Hz), 6.40 (d, 1H, J=3.1 Hz), 2.58-2.51 (m, 2H), 2.16-2.06 (m, 3H), 1.91-1.83 (m, 1H), 1.32-1.21 (m, 1H), 1.12 (d, 3H, J=7.2 Hz), 0.99 (t, 3H, J=7.5 Hz); **^{13}C NMR**: δ 194.3 (d), 157.1 (d), 137.1 (s), 131.6 (d), 128.1 (s), 32.2 (d), 30.2 (t), 24.2 (t), 21.2 (t), 20.2 (q), 13.9 (q); **IR:** 3030 (w), 3015 (w), 1730 (w), 1690 (s), 1635 (w), 1590 (ms) cm^{-1}. **MS m/z** (relative intensity): 164 (M^+, 26), 149 (100), 131 (21), 119 (26), 107 (24), 105 (36); **HRMS** calcd for $C_{11}H_{16}O$: 164.1202, found: 164.1200.

(±)-(4E,6S,7R)-(E)-4-Ethoxy-7-methyl-10-propylidene-3-oxabicyclo[4.4.0]-dodec-1-ene (38a)



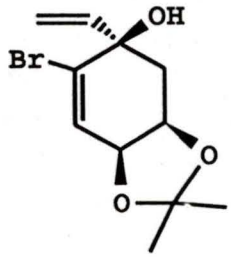
The same procedure as for compound **54** except that the solution of the aldehyde **37** (75 mg, 0.46 mmol) and tris(6,6,7,7,8, 8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (73 mg, 0.07 mmol) in ethyl vinyl ether (2 mL) was stirred for 7.5 days. Flash column chromatography eluting with hexanes-ethyl acetate (40:1) yielded a 3.5:1 mixture of **38a** and **38b** as an oil (94 mg 87%). **Major isomer:** ^{1}**H NMR**: δ 6.30 (d, 1H, J=1.9 Hz), 5.23 (td, 1H, J=7.2, 2.2 Hz), 4.76 (dd, 1H, J=9.8, 1.8 Hz), 3.92 (dq, 1H, J=9.5, 7.1 Hz), 3.54 (dq, 1H, J=9.5, 7.1 Hz), 2.57-2.51 (m, 1H), 2.18 (ddd, 1H, J=13.3, 6.3, 1.8 Hz), 2.09-1.77 (m, 4H), 1.75-1.67 (m, 2H), 1.40 (ddd, 1H, J=12.8, 11.2, 9.8 Hz), 1.22 (t, 3H, J=7.1 Hz), 1.16-1.07 (m, 1H), 0.93 (t, 3H, J=7.5 Hz), 0.92 (d, 3H, J=6.4 Hz);^{13}**C NMR**: δ 135.0 (s), 134.9 (d), 123.4 (d), 119.3 (s), 100.0 (d), 64.4 (t), 40.5 (d), 38.7 (t), 34.7 (t), 34.3 (t), 27.6 (t), 20.8 (t), 19.8 (q), 15.2 (q), 14.5 (q); **IR:** 3060 (w), 3010 (ms), 1640 (s), 1625 (s), 1375 (s), 1135 (s), 1115 (s), 1095 (s), 1055 (s), cm^{-1}; **MS m/z** (relative intensity): 236 (M^+, 100), 191 (35), 149 (24), 147 (9), 131(11); **HRMS** calcd for $C_{15}H_{24}O_2$: 236.1777, found: 236.1767.

(4S,5R)-2-Bromo-4,5-dihydroxy-*O,O'*-isopropylidene-2-cyclohexen-1-one (62).



The same procedure as for compound **51** except that bromine (3.33 g, 20.8 mmol) in carbon tetrachloride (50 mL), conjugated ketone **61** (3.50 g, 20.8 mmol) in carbon tetrachloride (50 mL) and triethylamine (3.58 g, 35.4 mmol) in carbon tetrachloride (35 mL) were used. Flash column chromatography eluting with hexanes-ethyl acetate (2:1) gave **62** as a white solid (3.6 g, 70%): mp 101.5-103.5°C. **^{1}H NMR**: δ 7.06 (dd, 1H, J=3.0, 1.8 Hz), 4.73 (dd, 1H, J=4.9, 3.0 Hz), 4.69-4.63 (m, 1H), 3.14 (dd, 1H, J=17.5, 2.6 Hz), 2.77 (dd, 1H, J=17.5, 3.6 Hz), 1.36 (s, 6H); **^{13}C NMR**: 187.3 (s), 146.1 (d), 123.7 (s), 110.0 (s), 73.2 (d), 72.7 (d), 38.4 (t), 27.5 (q), 26.2 (q); **IR:** 3020 (w), 1700 (s), 1610 (ms), 1380 (ms), 1365 (ms), 1220 (s), 1160 (ms), 1060 (s) cm^{-1}; **MS m/z** (relative intensity):no M^+, 233 (14), 231 (23), 219 (21), 191 (93), 189 (94), 163 (82), 161 (91); $[\alpha]_D$ -18.63° (c 1.83, $CHCl_3$); **HRMS** calcd for $C_8H_8O_3{}^{81}Br(-CH_3)$: 232.9636, found: 232.9630; calcd for $C_8H_8O_3{}^{79}Br(-CH_3)$: 230.9656, found: 230.9653.

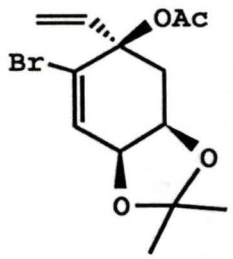
(1R,4S,5R)-2-Bromo-4,5-dihydroxy-*O,O'*-isopropylidene-1-vinyl-2-cyclohexen-1-ol (63).



A solution of *n*-butyllithium (1.6 M in hexanes, 6.1 mL, 9.8 mmol) and diethyl ether (50 mL) was added to tetravinyltin (0.62 g, 2.7 mmol) at 0°C. The reaction mixture was stirred at rt for 40 min. Then bromoketone **62** (1.22 g, 4.9 mmol) in diethyl ether (50 mL) was added slowly to the solution at -78°C. The mixture was stirred for 60 min at -78°C and quenched with saturated aqueous ammonium chloride (60 mL). The aqueous layer was separated and extracted with diethyl ether (2x60 mL). The combined organic layers were washed with brine (50 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo*. The product was then purified by flash column chromatography eluting with hexanes-ethyl acetate (3:1) to yield alcohol **63** as white crystals (0.71 g, 53%). **mp:** 55-57°C. **^{1}H NMR**: δ 6.11 (dd, 1 H, J=3.1, 1.0 Hz), 5.70 (ddd, 1H, J=17.1, 10.6, 1.2 Hz), 5.44 (dd, 1H, J=17.1, 1.3 Hz), 5.23 (dd, 1H, J=10.6, 1.3 Hz), 4.51 (dd, 1H, J=8.3, 3.1 Hz), 4.48-4.45 (m, 1H), 3.81 (d, 1H, J=1.2 Hz), 2.40 (dd, 1H, J=15.0, 4.5 Hz), 2.11 (dd, 1H, J=15.0, 2.5 Hz), 1.46 (s, 3H), 1.35 (s, 3H); **^{13}C NMR**: δ 140.8 (d), 131.7 (s), 128.9 (d), 115.1 (t), 110.3 (s), 73.7 (d), 72.4 (s), 72.4 (d), 37.5 (t), 28.0 (q), 26.5 (q); **IR:**($CHCl_3$) 3600-3400 (br), 3030 (w), 3010 (ms), 1630 (w), 1380 (ms), 1360 (ms), 1220 (s), 1165 (ms), 1045 (s) cm^{-1}; **MS m/z** (relative intensity): no M^+, 261 (63), 259 (63), 219 (15), 201 (99), 199(95), 173 (15), 137(100), 92 (24), 93 (33);

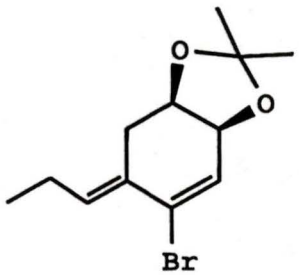
$[\alpha]_D$ -36.29° (c 1.78, $CHCl_3$); **HRMS** calcd for $C_{10}H_{12}O_3{}^{81}Br$ (-CH_3): 260.9950, found: 260.9940; calcd for $C_{10}H_{12}O_3{}^{79}Br$ (-CH_3): 258.9970, found: 258.9975.

(1R,4S,5R)-1-Acetoxy-2-bromo-4,5-dihydroxy-*O,O'*-isopropylidene-1-vinyl-2-cyclohexene (64).



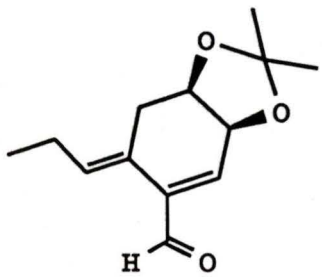
The same procedure as for compound **42** except that acetic anhydride (0.85 g, 8.4 mmol), alcohol **63** (1.15 g, 4.2 mmol), 4-dimethylaminopyridine (0.10 g, 0.84 mmol) and triethylamine (1.48 g, 14.7 mmol) were used. Flash column chromatography eluting with hexanes-ethyl acetate (3:1) produced a white solid (1.25 g, 94%). **mp:** 88.5-90°C. **^{1}H NMR**: δ 6.40 (d, 1H, J=4.4 Hz), 5.84 (dd, 1H, J=17.2, 10.7 Hz), 5.29 (d, 1H, J=10.7 Hz), 5.27 (d, 1H, 17.2 Hz), 4.39 (dd, 1H, J=6.0, 4.4 Hz), 4.28 (ddd, 1H, J=10.4, 6.0, 5.0 Hz), 2.83 (dd, 1H, J=12.4, 10.4 Hz), 2.29 (dd, 1H, J=12.4, 5.0 Hz), 2.07 (s, 3H), 1.47 (s, 3H), 1.33 (s, 3H); **IR:** 3100 (w), 3020 (ms), 1750 (s), 1645 (w), 1390 (ms), 1375 (s), 1240 (s), 1170 (s), 1065 (s), 1025 (ms) cm^{-1}; **MS m/z** (relative intensity): no M^+, 303 (9), 301 (9), 261 (17), 237 (20), 179 (30), 137 (100); $[\alpha]_D$ +60.60 (c 0.34, $CHCl_3$); **HRMS** calcd for $C_{12}H_{14}O_4{}^{81}Br$ (-CH_3): 303.0055, found: 303.0050; calcd for $C_{12}H_{14}O_4{}^{79}Br$ (-CH_3): 301.0075, found: 301.0062.

(*E*)-(1S,6R)-3-Bromo-1,6-dihydroxy-*O,O'*-isopropylidene-4-propylidene-2-cyclohexen-1-ol (65)



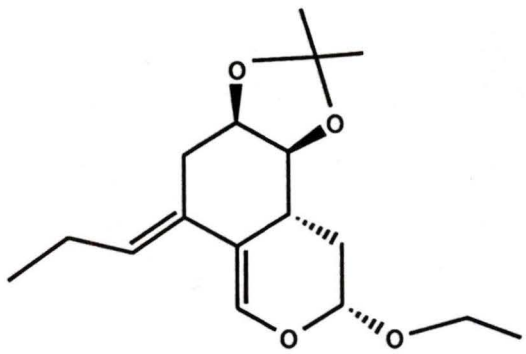
The same procedure as for compound **52a** except that methyllithium (1.4 M, 10.6 mL, 14.9 mmol), copper iodide (1.42 g, 7.4 mmol) in diethyl ether (60 mL) and acetate **64** (1.18 g, 3.7 mmol) in diethyl ether (60 mL) were used. Flash chromatography eluting with hexanes-ethyl acetate (5:1) yielded compound **65** as a colorless oil (0.50 g, 49%). **^{1}H NMR**: δ 6.09 (t, 1H, J=7.2 Hz), 6.05 (d, 1H, J=3.6 Hz), 4.54 (t, 1H, J=4.5 Hz), 4.35 (q, 1H, J=4.5 Hz), 2.87 (dd, 1H, J=15.5, 4.9 Hz), 2.51 (bd, 1H, J=15.5 Hz), 2.16 (qi, 2H, J=7.2 Hz), 1.38 (s, 3H), 1.34 (s, 3H), 1.02 (t, 3H, J=7.2 Hz); **^{13}C NMR**: δ 137.2 (d), 127.2 (d), 127.1 (s), 126.5 (s), 109.3 (s), 73.5 (d), 72.1 (d), 28.3 (t), 28.0 (q), 26.5 (q), 21.3 (t), 13.7 (q); **IR:**3010 (ms), 1640 (w), 1605 (w), 1380 (s), 1370. (ms), 1230 (s) 1160 (ms), 1060 (s), 1040 (s) cm^{-1}; **MS m/z** (relative intensity): 274 (53, M^+, ^{81}Br), 272 (51, M^+, ^{79}Br), 259 (69), 257 (64), 216 (43), 214 (42), 188(66), 173 (41), 171 (42), 151 (76), 107 (84), 91 (100); $[\alpha]_D$ -18.83° (c 1.03, $CHCl_3$); **HRMS** calcd for $C_{12}H_{17}O_2{}^{81}Br$: 274.0392, found: 274.0402, calcd for $C_{12}H_{17}O_2{}^{79}Br$: 272.0412, found: 272.0422.

(3S,4R)-(E)-6-propylidene-3,4-dihydroxy-O,O'-isopropylidene-1-cyclohexene-1-carboxaldehyde (39)



The same procedure as for compound **53** except that *n*-butyllithium (2.5 M in hexanes, 0.23 mL, 0.57 mmol) was added to bromide **65** (120 mg, 0.44 mmol) in tetrahydrofuran (6 mL) and dimethylformamide (0.13 g, 1.76 mmol) was used. Flash column chromatography eluting with hexanes-ethyl acetate (4:1) gave **39** as a colorless oil (72 mg, 74%). **^{1}H NMR**: δ 9.52 (s, 1H), 6.59 (t, 1H, J=7.3 Hz), 6.28 (d, 1H, J=3.4 Hz), 4.68 (dd, 1H, J=5.5, 3.3 Hz), 4.37 (q, 1H, J=4.8 Hz), 2.71 (dd, 1H, J=15.4, 5.3 Hz), 2.44 (dm, 1H, J=15.4 Hz), 2.20-2.06 (m, 2H), 1.32 (s, 3H), 1.29 (s, 3H), 0.97 (t, 3H, J=7.4 Hz); **^{13}C NMR**: δ 193.0 (d), 143.5 (d), 138.2 (s), 136.1 (d), 123.4 (s), 109.4 (s), 72.7d (), 71.7 (d), 28.1 (t), 27.9 (q), 26.2 (q), 21.4 (t), 13.8 (q); **IR:**3015 (w), 3005 (ms), 2735 (w), 1705 (s), 1645 (w), 1605 (w), 1385 (s), 1375 (s), 1240 (s), 1230 (s), 1160 (ms), 1055 (s), 1035 (ms) cm^{-1}; **MS m/z** (relative intensity): 222 (M^+, 5), 207 (4), 165 (12), 164 (100), 149 (20), 147 (78), 136 (21), 135 (19), 121 (37), 93 (27), 91 (49); $[\alpha]_D$ +55.61° (c 1.30, $CHCl_3$); **HRMS** calcd for $C_{13}H_{18}O_3$: 222.1256, found: 222.1257.

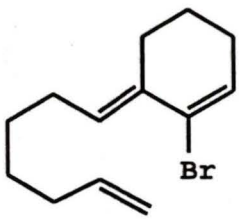
(4R,6R,7S,8R)-(E)-4-Ethoxy-7,8-dihydroxy-*O,O'*-isopropylidene-10-propylidene-3-oxabicyclo[4.4.0]dodec-1-ene (40a)



The aldehyde **39** (51 mg, 0.23 mmol) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (36 mg, 0.03 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 7 days at rt. Then, brine (2 mL) was added to the solution and stirred for 2 h. The aqueous layer was extracted with diethyl ether (2x5 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*. The product was then purified by flash column chromatography eluting with hexanes-ethyl acetate (6:1) to give 44.6 mg of pure **40a** as an oil (66%) and 12% of a mixture of two unidentifiable compounds. **^{1}H NMR**: 6.63 (d, 1H, J=2.1 Hz), 5.53 (td, 1H, J=7.5, 1.1 Hz), 4.91 (dd, 1H, J=7.9, 2.4 Hz), 4.15 (dt, 1H, J=9.1, 6.6 Hz), 3.91 (dd, 1H, J=9.1, 7.1 Hz), 3.85 (dq, 1H, J=9.5, 7.1 Hz), 3.54 (dq, 1H, J=9.5, 7.1 Hz), 2.85 (ddd, 1H, J=14.3, 6.6, 1.0 Hz), 2.51-2.43 (m, 1H), 2.25 (ddd, 1H, J=13.5, 6.7, 2.4 Hz), 2.23-2.16 (m, 1H), 2.04 (dqi, 2H, J=7.5, 1.0 Hz), 1.73 (dt, 1H, J=13.5, 7.9 Hz), 1.45 (s, 3H), 1.31 (s, 3H), 1.20 (t, 3H, J=7.1 Hz), 0.94 (t, 3H, J=7.5 Hz); **^{13}C NMR**: 135.9 (d), 128.5 (s), 122.1 (d), 112.7 (s), 108.5 (s), 98.6 (d), 79.1 (d), 73.9 (d), 64.3 (t), 34.6 (q), 31.9 (t), 29.5 (t), 27.6 (q), 24.9 (q), 21.1 (t), 15.2 (q), 14.5 (q); **IR:** 3035 (w), 3010 (w), 1625 (s), 1596 (w), 1385 (ms), 1235 (s) 1160 (s), 1125 (s), 1060 (s)

cm^{-1}; **MS m/z** (relative intensity): 294 (M^+, 100), 173 (33), 164 (53), 147 (41), 145 (34), 135 (62), 91 (40); $[\alpha]_D$ -0.34° (c 1.17, $CHCl_3$); **HRMS** calcd for $C_{17}H_{36}O_4$: 294.1832, found: 294.1822.

(E)-2-Bromo-1-(6-hepten-1-ylidene)-2-cyclohexene (68)

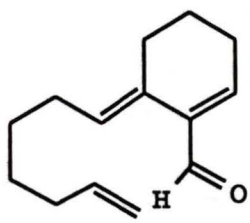


A solution of 5-bromo-1-pentene (2 g, 13.4 mmol) in diethyl ether (8.4 mL) was charged in a dropping funnel and 1 mL of the solution was added to a flask containing freshly activated magnesium (0.35 g, 14.4 mmol) and diethyl ether (5 mL) at rt. When the reaction started the remaining solution was added dropwise to the flask. After the addition was finished, the temperature was raised and the reaction mixture was refluxed for 6 h.

The solution of prepared 4-pentenyl magnesium bromide (10 mL, 10 mmol) was added to a suspension of dry copper iodide (0.95 g, 5 mmol) in diethyl ether (30 mL) at 0°C. The mixture was stirred for 10 min and then acetate **42** (0.66 g, 2.5 mmol) in diethyl ether (30 mL) was added. A yellow precipitate appeared immediately. The reaction mixture was stirred for 1 h at 0°C and quenched with saturated aqueous ammonium chloride (60 mL). The aqueous phase was separated and extracted with diethyl ether (2x30 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash column chromatography eluting with hexanes yielded compound **68** as a colorless oil (0.55 g, 81%). **^{1}H NMR**: δ 6.19 (t, 1H,

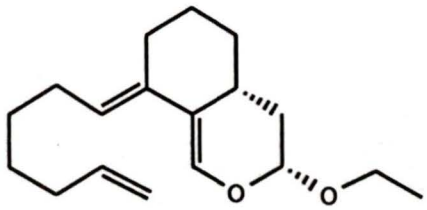
J=4.5 Hz), 5.89-5.63 (m, 1H), 5.04-4.89 (m, 2H), 2.42 (dt, 2H, J=6.2, 1.5 Hz), 2.22-2.00 (m, 6H), 1.70 (qi, 2H, J=6.2), 1.40 (qi, 4H, J=3.6 Hz); **IR:** 3080 (w), 3010 (w), 1640 (ms), 1595 (w) cm^{-1}; **MS m/z** (relative intensity): 256 (M^+, ^{81}Br, 90), 254 (M^+, ^{79}Br, 96), 215 (60), 213 (45), 187 (72), 185 (68), 175 (29); **HRMS** calcd for $C_{13}H_{19}{}^{81}Br$: 256.0651, found: 256.0648; calcd for $C_{13}H_{19}{}^{79}Br$: 254.0671, found: 254.0680.

(E)-6-(6-hepten-1-ylidene)-1-cyclohexene-1-carboxaldehyde (43)



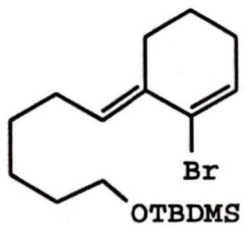
The same procedure as for compound **53** except that bromide **68** (0.52 g, 2.0 mmol) in tetrahydrofuran (25 mL), *n*-butyllithium (2.5 M, in hexane, 1.3 mL, 3.1 mmol) in tetrahydrofuran (1 mL)and dimethylformamide (0.60 g, 8.2 mmol) were used. Flash column chromatography eluting with hexanes-ethyl acetate (15:1) gave **43** as a colorless oil (0.30 g, 67%). **^{1}H NMR**: δ 9.46 (s, 1H), 6.62-6.57 (m, 2H), 5.76 (ddt, 1H, J=17.1, 10.3, 6.7 Hz), 4.95 (ddd, 1H, J=17.1, 3.6, 1.8 Hz), 4.89 (dm, 1H, J=10.2 Hz), 2.40 (q, 2H, J=6.3 Hz), 2.30 (dt, 2H, J=6.3, 1.4 Hz), 2.10 (q, 2H, J=7.0 Hz), 2.02 (qm, 2H, J=6.7 Hz), 1.69 (qi, 2H, J=6.3 Hz), 1.45-1.34 (m, 4H); **^{13}C NMR**: δ 194.0 (d), 161.8 (d), 138.9 (d), 138.2 (s), 129.9 (d), 128.6 (s), 114.2 (t), 33.6 (t), 28.8 (t), 28.6 (t), 27.6 (t), 27.1 (t), 25.1 (t), 21.8 (t); **IR:**3040 (w), 3010 (ms), 1730 (w), 1690 (s), 1640 (ms), 1590 (ms) cm^{-1}; **MS m/z** (relative intensity): 204 (M^+, 23), 203 (100), 163 (62), 135 (45), 121 (24); **HRMS** calcd for $C_{14}H_{20}O$: 204.1515, found: 204.1520.

(E)-4-Ethoxy-10-(6-hepten-1-ylidene)-3-oxabicyclo[4.4.0]dodec-1-ene (69)



The aldehyde **43** (0.22 g, 1.1 mmol) and catalyst tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (0.18 g, 0.17 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 4 days at rt. The excess ethyl vinyl ether was removed *in vacuo* and the residue was purified by flash column chromatography eluting with hexanes-ethyl acetate (15:1) to yield the triene **69** as a slightly yellow oil (0.27 g 91%). **^{1}H NMR**: δ 6.31 (d, 1H, J=1.9 Hz), 5.78 (ddt, 1H, J=17.0, 10.3, 6.7 Hz), 5.23 (dt, 1H, 7.3, 2.3 Hz), 4.97 (ddd, 1H, J=17.1, 3.7, 1.7 Hz), 4.91 (dm, 1H, J=10.2 Hz), 4.78 (dd, 1H, J=9.7, 1.8 Hz), 3.92 (dq, 1H, J=9.5, 7.1 Hz), 3.54 (dq, 1H, J=9.5, 7.1 Hz), 2.56 (dm, 1H, J=13.9 Hz), 2.30-2.20 (m, 1H), 2.10-1.96 (m, 4H), 1.94-1.87 (m, 2H), 1.84-1.76 (m, 1H), 1.72-1.63 (br.t, 1H, J=13.6 Hz), 1.52-1.43 (m, 1H), 1.40-1.21 (m, 5H), 1.22 (t, 3H, J=7.1 Hz), 1.10 (ddd, 1H, J=14.5, 12.4, 3.0 Hz); **^{13}C NMR**: 139.0 (d), 135.3 (s), 134.9 (d), 121.7 (d), 119.8 (s), 114.2 (t), 99.6 (d), 64.3 (t), 36.5 (t), 34.1 (d), 33.7 (t), 33.3 (t), 29.4 (t), 28.5 (t), 27.8 (t), 27.3 (t), 25.23 (t), 15.2 (q); **IR:** 3080 (w), 3060 (w), 3010 (ms), 1635 (s), 1625 (s). 1135 (s), 1120 (s), 1085 (ms), 1065 (s), 1050 (ms) cm^{-1}; **MS m/z** (relative intensity): 276 (M^+, 37), 230 (36), 186 (41), 161 (80), 147 (54), 135 (100), 132 (26), 122 (29); **HRMS** calcd for $C_{18}H_{28}O_2$: 276.2090, found: 276.2102.

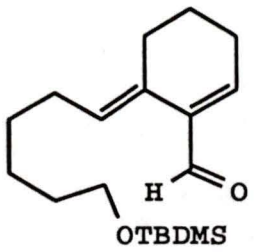
(E)-2-Bromo-1-(6-*t*-butyldimethylsilyloxyhexylidene)-2-cyclohexene (74)



To a mixture of 4-chlorobutyl *t*-butyldimethylsilyl ether **72** (3.38g, 15.2 mmol), magnesium (0.41 g, 16.7 mmol) and diethyl ether (15 mL) were added a small crystal of iodine and iodoethane (0.05 mL). The mixture was refluxed for 26 h and a solution of 4-(*t*-butyldimethylsilyloxy)butyl magnesium chloride was obtained. The solution was added to a suspension of dry copper iodide (1.45 g, 7.6 mmol) in diethyl ether (25 mL) at 0°C and the color changed to dark blue. Then, acetate **42** (0.93g, 3.8 mmol) in diethyl ether (25 mL) was added to the solution. The reaction mixture was stirred for 1 h at 0°C and quenched with saturated aqueous ammonium chloride (100 mL). The aqueous phase was separated and extracted with diethyl ether (2x50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent *in vacuo* followed by flash column chromatography eluting with hexanes-ethyl acetate (50:1) gave 2.5 g (>100%) of a mixture of compound **74** and *t*-butyldimethylsilyl butyl ether. The mixture was used directly in next reaction. **^{1}H NMR**: δ 6.18 (t, 1H, J=4.4 Hz), 5.85 (t, 1H, J=7.6 Hz), 3.58 (t, 2H, J=6.5, Hz), 2.41 (bt, 2H, J=6.2 Hz), 2.22-2.06 (m, 4H), 1.70 (qi, 2H, J=6.2 Hz), 1.62-1.12 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H); **^{13}C NMR**: 132.3 (s) 131.1 (d), 130.0 (d),124.4 (s), 63.2 (t), 32.7 (t), 29.2 (t), 27.7 (t), 26.9 (t), 26.0 (q), 25.8 (t), 25.6 (t), 22.2 (t), 18.4 (s), -5.3 (q); **IR:**3005 (w), 1600 (w), 1390 (w), 1258 (s), 1090 (s), 837 (s) cm^{-1}; **MS m/z** (relative intensity): 374 (M^+, ^{81}Br, 72), 372 (M^+, ^{79}Br, 67), 317

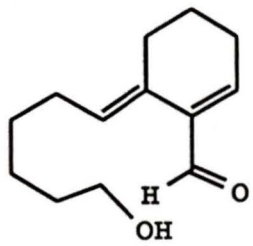
(82), 315 (79), 293 (35), 243 (25), 241 (20), 236 (47); **HRMS** calcd for $C_{18}H_{33}OSi^{81}Br$: 374.1465, found: 374.1471; calcd for $C_{18}H_{33}OSi^{79}Br$: 372.1485, found: 372.1484.

(E)-6-(6-*t*-butyldimethylsilyloxyhexylidene)-1-cyclohexene-1-carboxaldehyde (75)



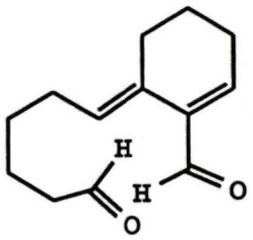
The same procedure as for compound **53** except that *n*-butyllithium (2.5 M in hexanes, 4.2 mL, 9.2 mmol)was added to bromide **74** (2.3 g, 6.2 mmol) in tetrahydrofuran (130 mL) and dimethylformamide (1.8 g, 24.8 mmol) was used. Flash column chromatography eluting with hexanes-ethyl acetate (15:1) gave a colorless oil (0.98 g, 80% from acetate **42**). **^{1}H NMR**: 9.46 (s, 1H), 6.63-6.57 (m, 2H), 3.56 (dt, 2H, J=6.4, 1.9 Hz), 2.39 (q, 2H, J=6.2 Hz), 2.31 (t, 2H, J=6.2 Hz), 2.11 (q, 2H, J=7.1 Hz), 1.69 (m, 2H), 1.54-1.42 (m, 2H), 1.39-1.21 (m, 4H), 0.85 (s, 9H), 0.01 (s, 6H); **^{13}C NMR**: 193.8 (d), 151.4 (d), 138.2 (s), 129.8 (d), 128.5 (s), 63.0 (t), 32.6 (t), 29.1 (t), 27.7 (t), 57.1 (t), 25.8 (q), 25.5 (t), 25.1 (t), 21.7 (t), 18.2 (s), -5.4 (q); **IR:**3030 (w), 3005 (ms), 2735 (w), 1734 (w), 1695 (s), 1597 (ms), 1390 (ms), 1256 (s) 1167 (ms), 1100 (s), 840 (s) cm^{-1}; **MS m/z** (relative intensity): 322 (M^+, 6), 304 (6), 265 (100), 247 (36), 193 (6), 131 (20); **HRMS** calcd for $C_{19}H_{34}O_2Si$: 322.2344, found: 322.2342;

(E)-6-(6-Hydroxyhexylidene)-1-cyclohexene-1-carboxaldehyde (76)



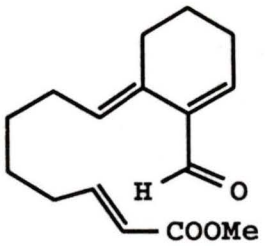
Aldehyde **75** (0.58 g, 1.8 mmol) was dissolved in a 16 mL solution of a 10:1 mixture of acetonitrile and 48% aqueous hydrofluoric acid. The resulting solution was stirred for 1.5 h at rt and then saturated aqueous sodium bicarbonate (10 mL) was added. The aqueous layer was separated and extracted with diethyl ether (2x10 mL). The combined organic portions were washed with brine (15 mL). Evaporation of solvent *in vacuo* followed by flash column chromatography eluting with hexanes-ethyl acetate (1:1) yielded **76** as a colorless oil (0.35 g, 92%). **^{1}H NMR**: δ 9.44 (s, 1H), 6.60-6.55 (m, 2H), 3.58 (dt, 2H, J=6.1, 1.2 Hz), 2.38 (q, 2H, J=6.1 Hz), 2.29 (bt, 2H, J=6.1 Hz), 2.10 (q, 2H, J=7.0 Hz), 1.83 (br.s, 1H), 1.68 (qi, 2H, J=6.1 Hz), 1.58-1.47 (m, 2H), 1.43-1.31 (m, 4H); **^{13}C NMR**: 194.1 (d), 151.9 (d), 138.1 (s), 129.7 (d), 128.5 (s), 62.6 (t), 32.5 (t), 29.0 (t), 27.6 (t), 27.1 (t), 25.4 (t), 25.1 (t), 21.7 (t); **IR:**3625 (w), 3660-3350 (b), 3030 (w), 3015 (ms), 2730 (w), 1695 (s), 1597 (ms), 1050 (ms) cm^{-1}; **MS m/z** (relative intensity): 208 (M^+, 56), 190 (66), 145 (50), 135 (73), 132 (65), 119 (100), 105 (36), 91 (90), 79 (89), 78 (39); **HRMS** calcd for $C_{13}H_{20}O_2$: 208.1464, found: 208.1466.

(E)-6-(5-Oxo-hexylidene)-1-cyclohexenecarbox-aldehyde (77)



A solution of dimethyl sulfoxide (222 mg, 2.84 mmol) in dichloromethane (2.8 mL) was added dropwise to a solution of oxalyl chloride (180 mg, 1.42 mmol) in dichloromethane (2.8 mL) at -60°C. The reaction mixture was stirred for 5 min and alcohol **76** (148 mg, 0.71 mmol) in dichloromethane (2 mL) was added at -60°C. The reaction was stirred for 15 min and then triethylamine (350 mg, 3.6 mmol) was added. After stirring for an additional 15 min the cooling bath was removed and the reaction was allowed to warm to rt. The reaction was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (2x10 mL). The combined organic phases were washed with brine (10 mL) and dried over magnesium sulfate. After removal of the solvent, the product was purified by flash column chromatography eluting with hexanes-ethyl acetate (3:1) to give **77** as an oil (124 mg, 85%). **^{1}H NMR**: 9.66 (t, 1H, J=1.8 Hz), 9.38 (s, 1H), 6.57-6.50 (m, 2H), 2.38-2.31 (m, 4H), 2.24 (bt, 2H, J=6.1 Hz), 2.07 (q, 2H, J=7.3), 1.68-1.49 (m, 4H), 1.42-1.30 (m, 2H); **^{13}C NMR**: 202.4 (d), 193.8 (d), 152.0 (d), 138.0 (s), 128.9 (d), 128.9 (s), 43.5 (t), 28.7 (t), 27.3 (t), 27.0 (t), 25.0 (t), 21.6 (t), 21.6 (t); **IR:**3030 (ms), 2730 (ms), 1725 (s), 1695 (s), 1640 (w), 1597 (ms) cm^{-1}; **MS m/z** (relative intensity): 206 (M^+, 39), 135 (36), 132 (100),119 (35), 91 (59); **HRMS** calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1313.

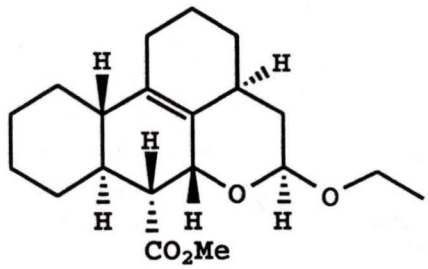
(E,E)-6-(7-Methoxycarbonyl-6-heptenylidene)-1-cyclohexene-1-carboxaldehyde (78)



Methyl diethylphosphonoacetate (89 mg, 0,41 mmol) was added slowly to a suspension of sodium hydride (17 mg, 0.43 mmol) in dry tetrahydrofuran (5 mL) at 0°C. The reaction mixture was stirred for 1 h and then added to a solution of dialdehyde **77** (80 mg, 0.39 mmol) in tetrahydrofuran (2 mL) via a cannula. After stirring for 2 h at 0°C the reaction was quenched with water (1 mL). Then, the mixture was washed with 1 N aqueous hydrochloric acid (1.5 mL) and saturated aqueous sodium bicarbonate (5 mL). The aqueous layers were separated and extracted with diethyl ether. The combined organic portions were washed with brine (5 mL) and dried over magnesium sulfate. Removal of solvent *in vacuo* followed by flash column chromatography eluting with hexanes-ethyl acetate (3:1) yielded product **78** (89 mg, 87%) as a colorless oil. **^{1}H NMR**: δ 9.43 (s, 1H), 6.90 (dt, 1H, J=15.7, 7.0 Hz), 6.59-6.54 (m, 2H), 5.75 (dt, 1H, J=15.7, 1.4 Hz), 3.66 (s, 3H), 2.38 (q, 2H, J=6.0 Hz), 2.27 (bt, 2H, J=6.1 Hz), 2.18-2.04 (m, 4H), 1.67 (qi, 2H, J=6.1 Hz), 1.45-1.38 (m, 4H); **^{13}C NMR**: 194.0 (d), 167.0 (s), 152.0 (d), 149.4 (d), 138.2 (s), 129.4 (d), 128.8 (s), 120.9 (d), 51.3 (q), 32.0 (t), 28.8 (t), 27.6 (t), 27.5 (t), 27.1 (t), 25.2 (t), 21.7 (t); **IR:** 3030 (ms), 3015 (ms), 2735 (w), 1725 (s), 1695 (s), 1660 (s), 1595 (ms), 1315 (s), 1270 (s), 1195 (s), 1175 (s) (ms) cm^{-1}; **MS m/z** (relative intensity): 262 (m^+, 2), 195 (11),

137 (35), 125 (67), 110 (71), 109 (14). **HRMS** calcd for $C_{16}H_{22}O_3$: 262.1570, found:262.1573.

Tetracyclic Compound 80a



The aldehyde **78** (35 mg, 0.13 mmol) and tris(6,6,7,7,8, 8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (21 mg, 0.02 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 5 days at rt. The excess ethyl vinyl ether was removed *in vacuo* and the residue was purified by flash column chromatography eluting with hexanes-ethyl acetate (9:1) to yield a 6:1 mixture of isomeric tetracyclic compound **80a** (39 mg, 87%) as a white solid. **mp:** 99-101°C; **^{1}H NMR**: δ 4.89 (t, 1H, J=7.2 Hz), 4.34 (dm, 1H, J=9.3 Hz), 3.72 (dq, 1H, J=9.7, 7.1 Hz), 3.64 (s, 3H), 3.40 (dq, 1H, J=9.7, 7.1 Hz), 2.68 (t, 1H, J=9.3 Hz), 2.19-2.17 (m, 1H), 2.14-2.12 (m, 1H), 1.99 (ddd, 1H, J=13.6, 6.7, 4.3 Hz), 1.96-1.87 (m, 2H), 1.83-1.76 (m, 2H), 1.76-1.62 (m, 3H), 1.61-1.51 (m, 1H), 1.43-1.34 (m, 1H), 1.28-1.13 (m, 4H), 1.16 (t, 3H, J=7.1 Hz), 1.11-0.96 (m, 2H); **^{13}C NMR**: 174.0 (s), 131.9 (s), 131.1 (s), 98.2 (d), 63.3 (d), 62.4 (t), 51.3 (q), 51.1 (d), 40.4 (d), 40.2 (d), 35.5 (t), 33.3 (t), 30.4 (d), 29.4 (t), 29.05 (t), 26.3 (t), 26.1 (t), 24.7 (t), 22.6 (t), 15.2 (q); **IR:** 1735 (s), 1620 (w), 1595 (w), 1375 (ms), 1235 (s), 1165 (s), 1150 (s), 1060 (s), 1010 (s) cm^{-1}; **MS m/z** (relative intensity): 334 (M^+, 13), 288 (70), 244 (12), 228 (22), 211 (24), 201 (31), 200 (30), 185 (52), 145 (53), 117 (51), 91 (100); **HRMS** calcd for $C_{20}H_{30}O_4$: 334.2145, found: 334.2139.

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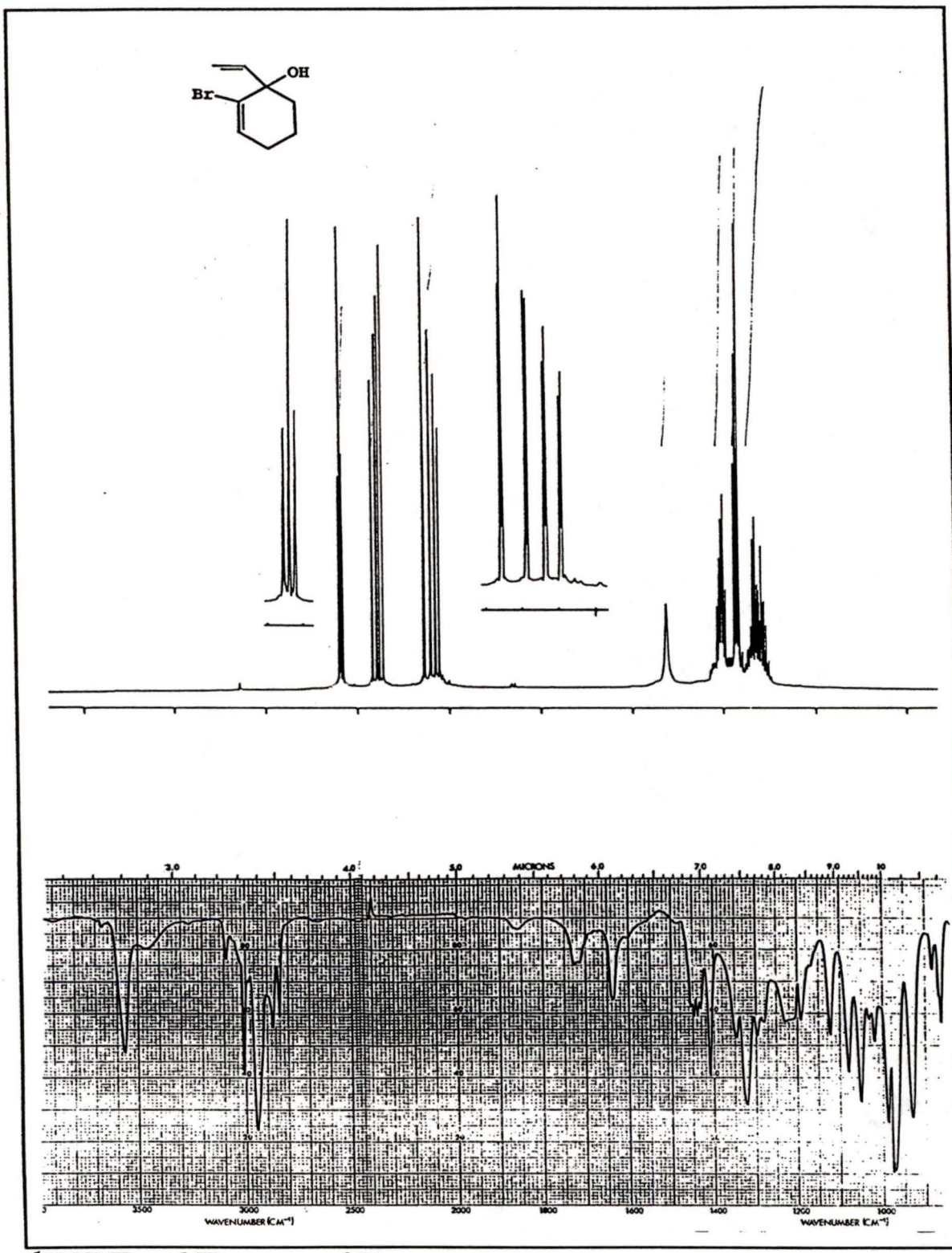
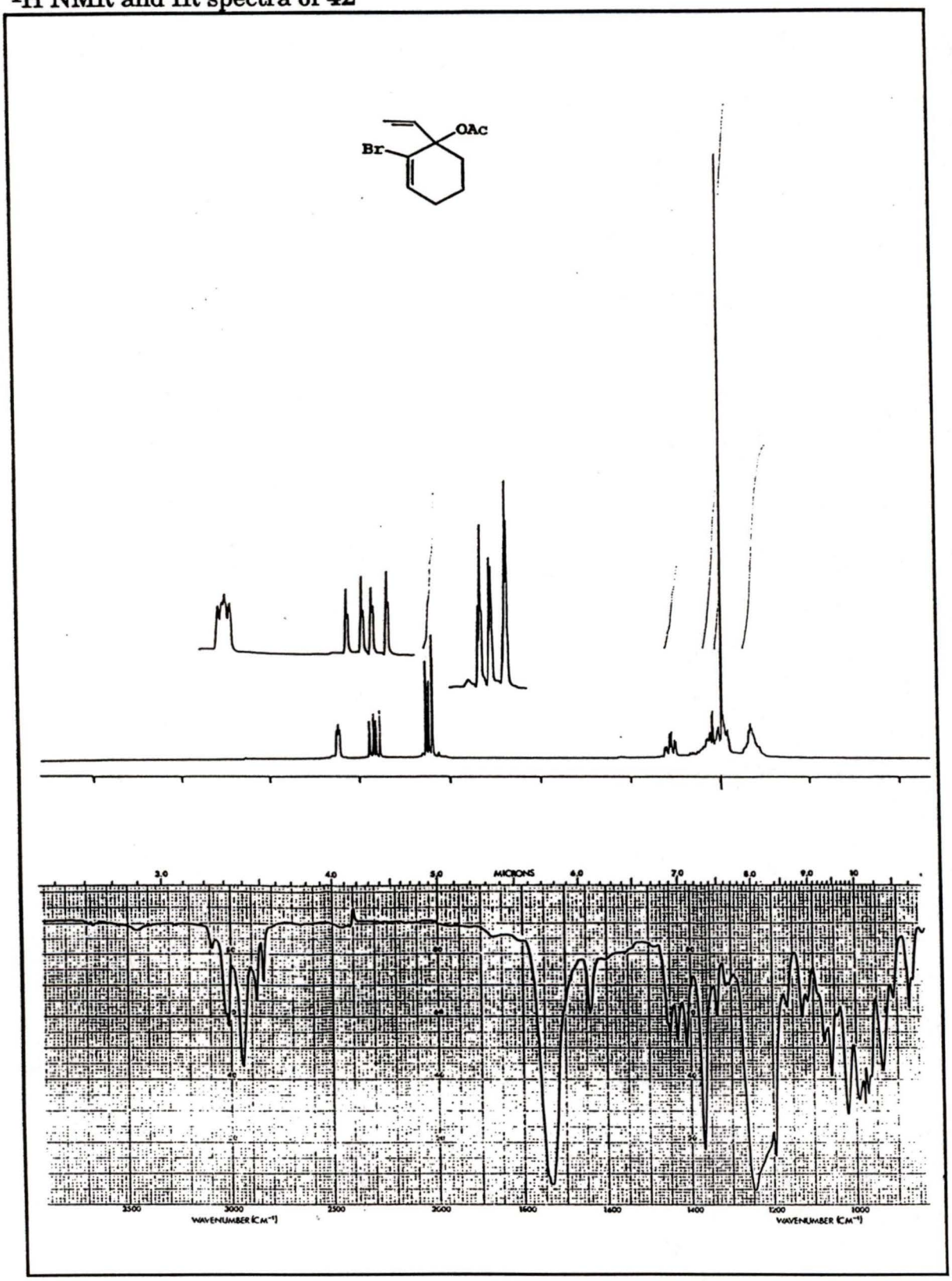
APPENDIX

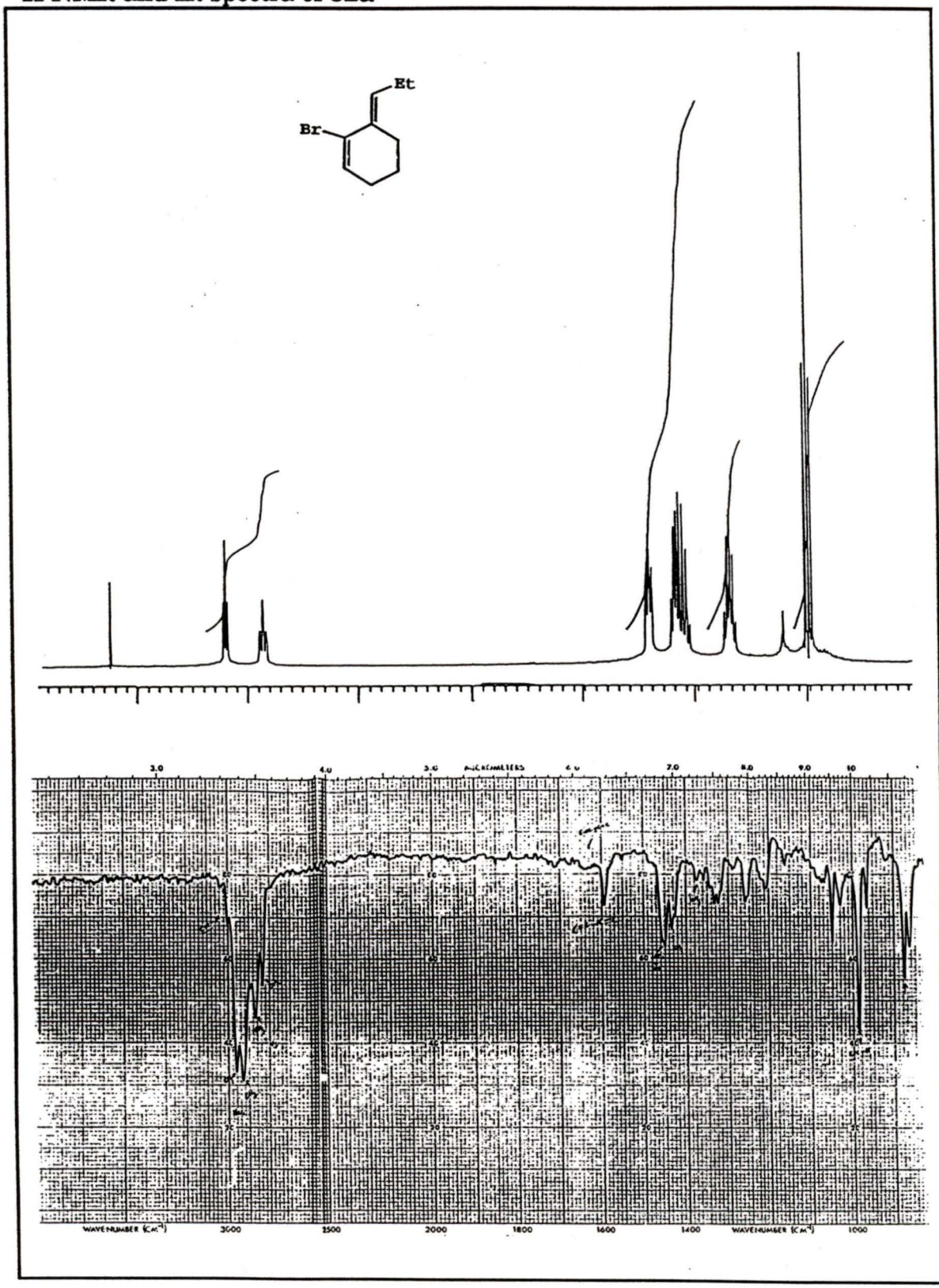


^{1}H NMR and IR spectra of **50a**

^{1}H NMR and IR spectra of 42



^{1}H NMR and IR spectra of 52a



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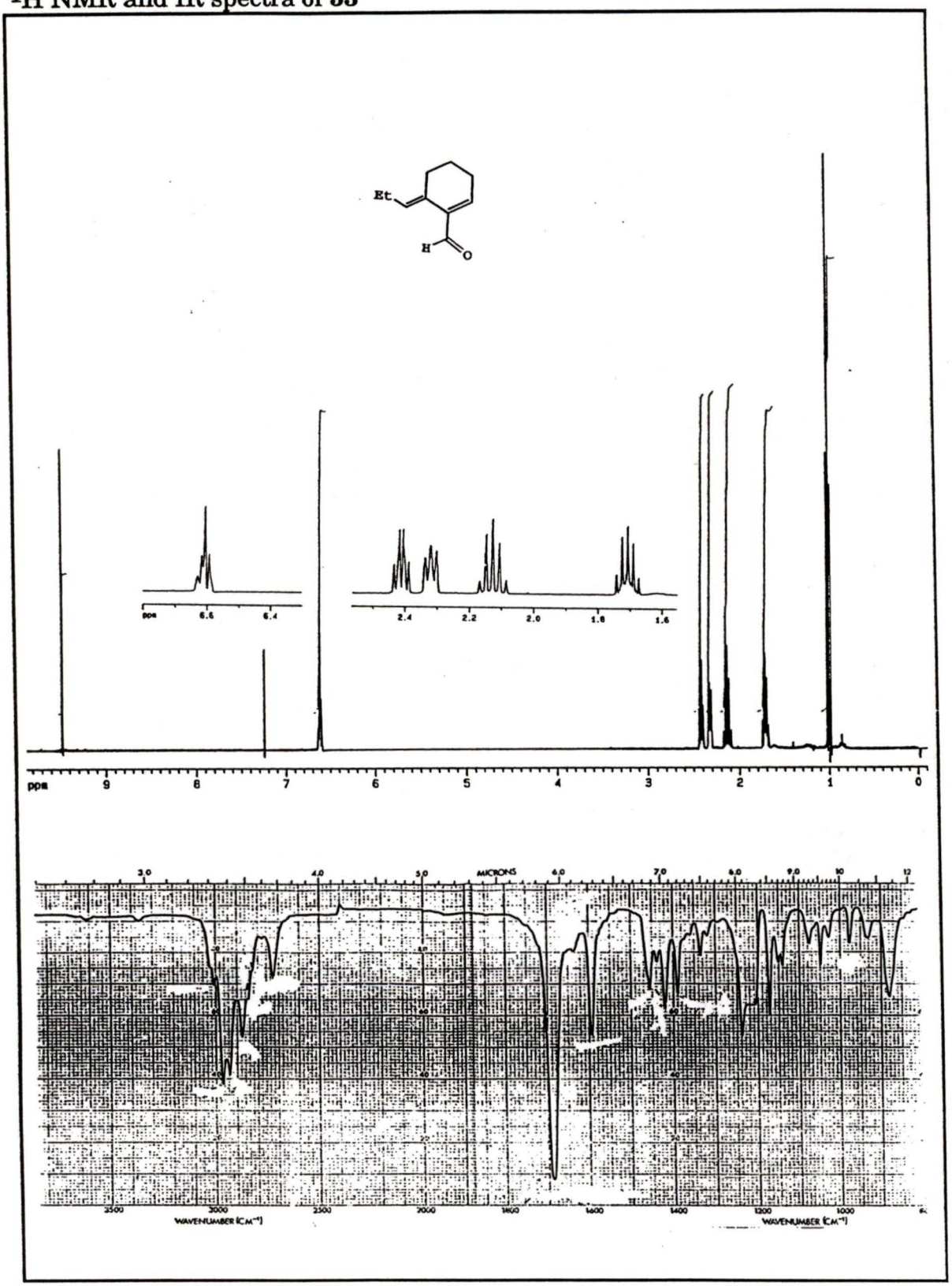

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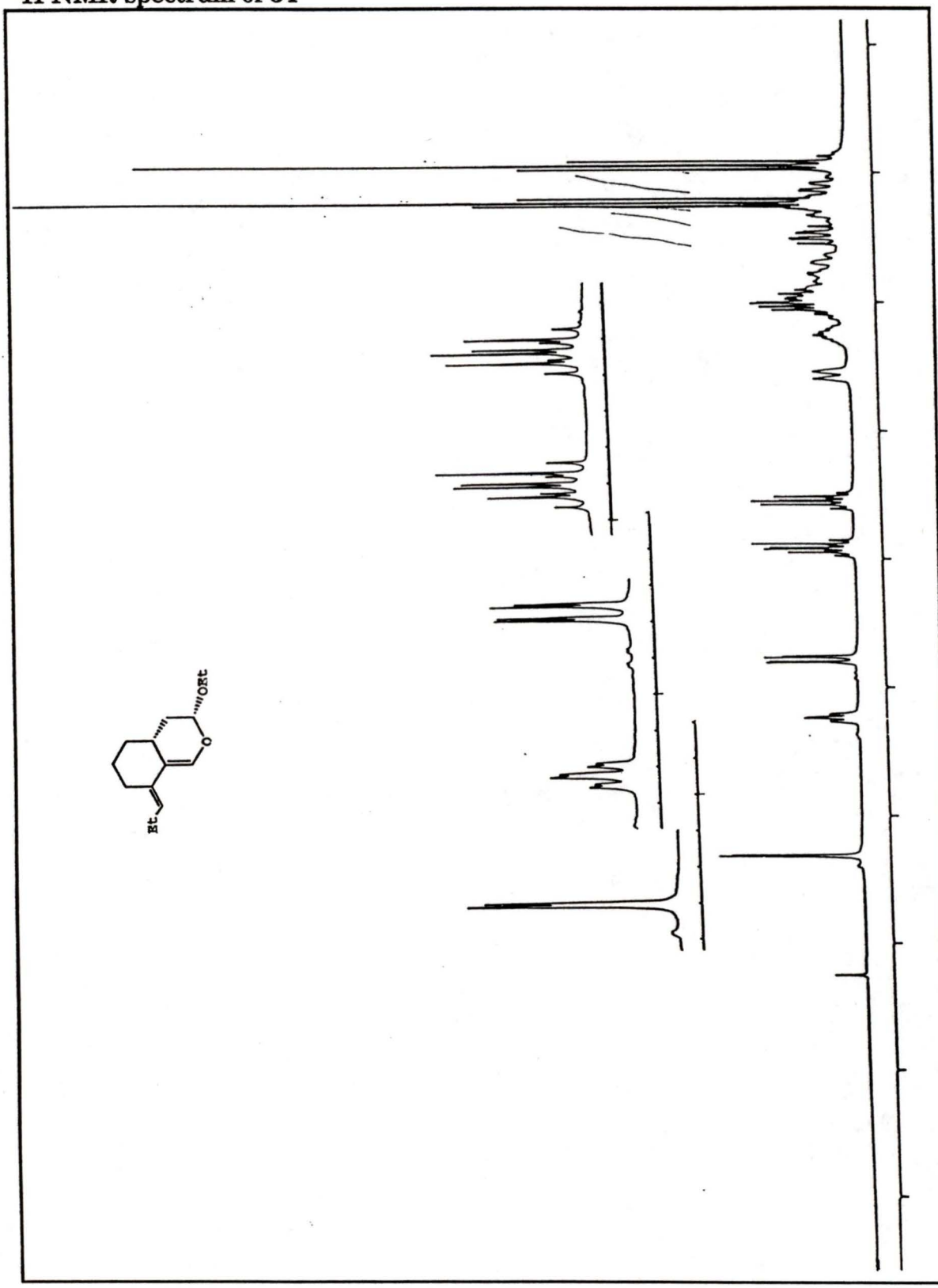
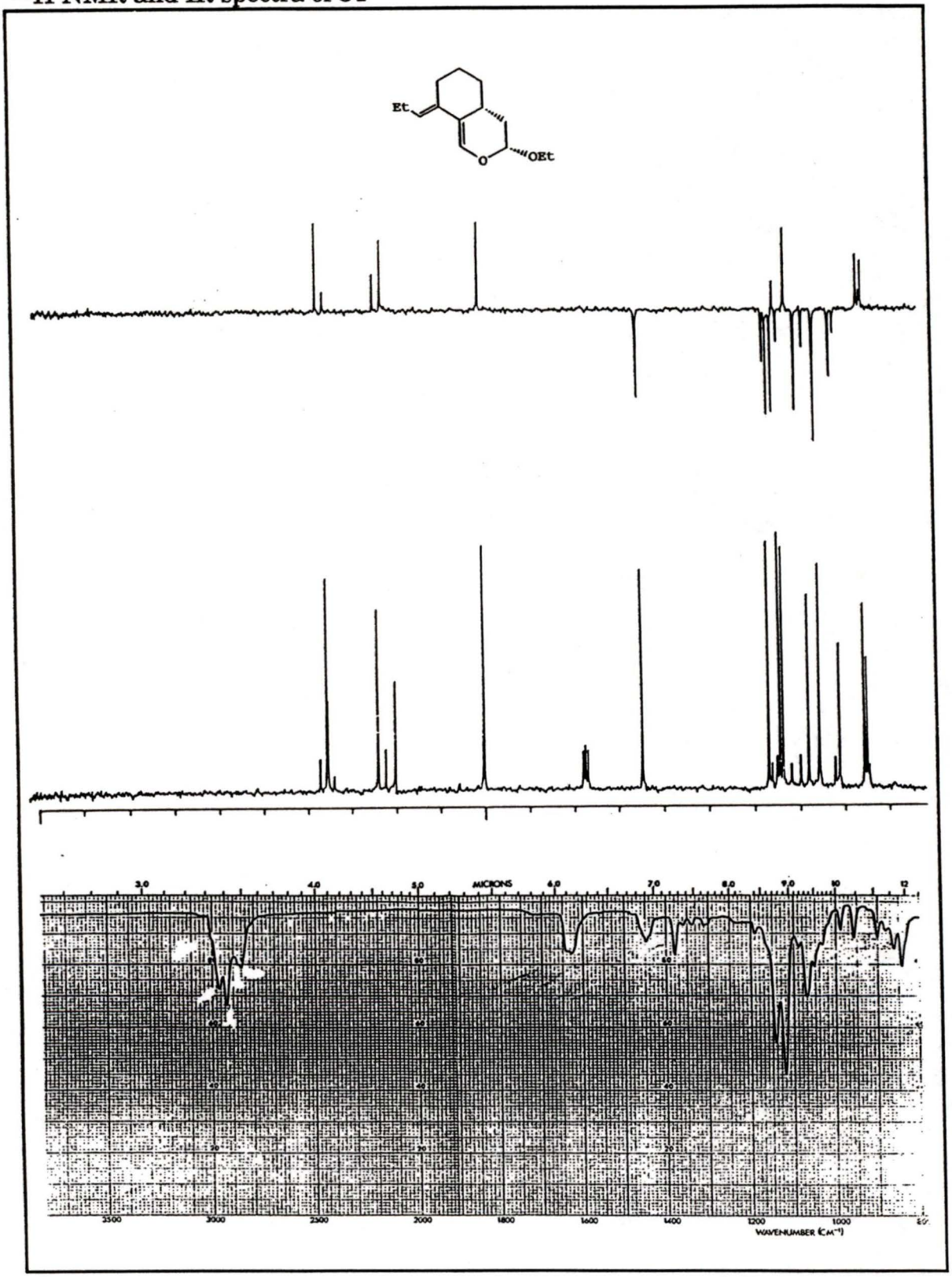
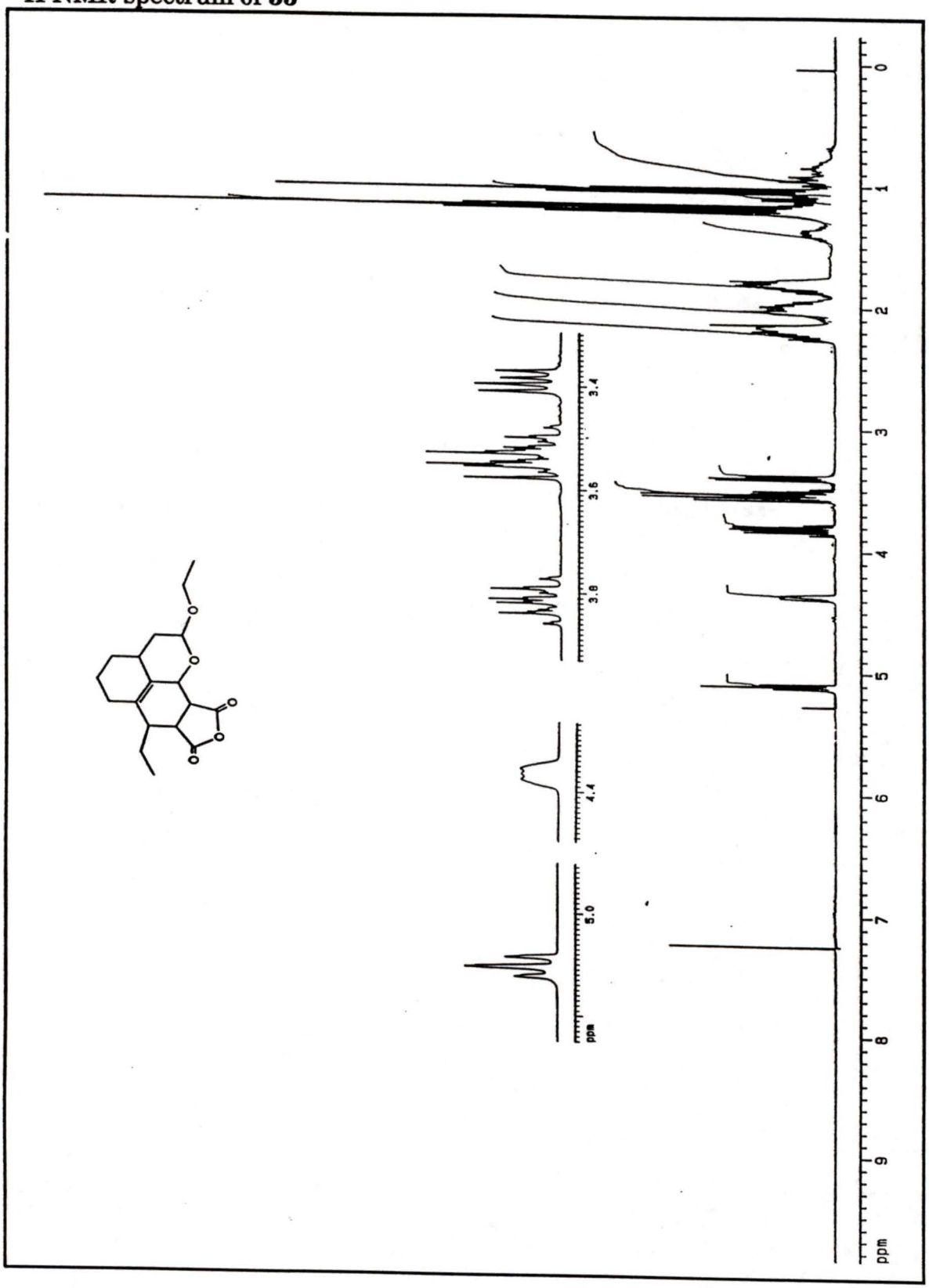


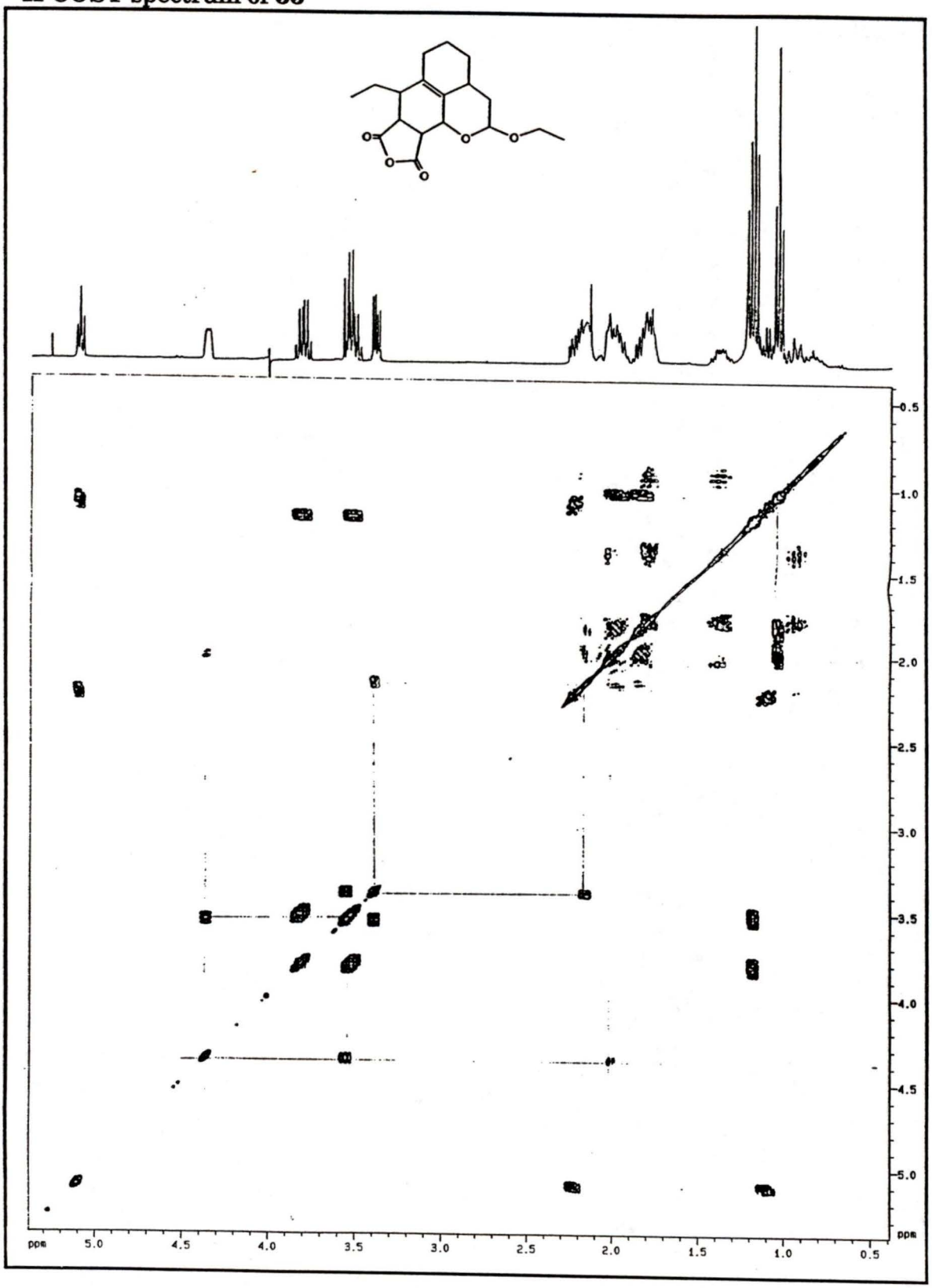
^{13}H NMR and IR spectra of **54**



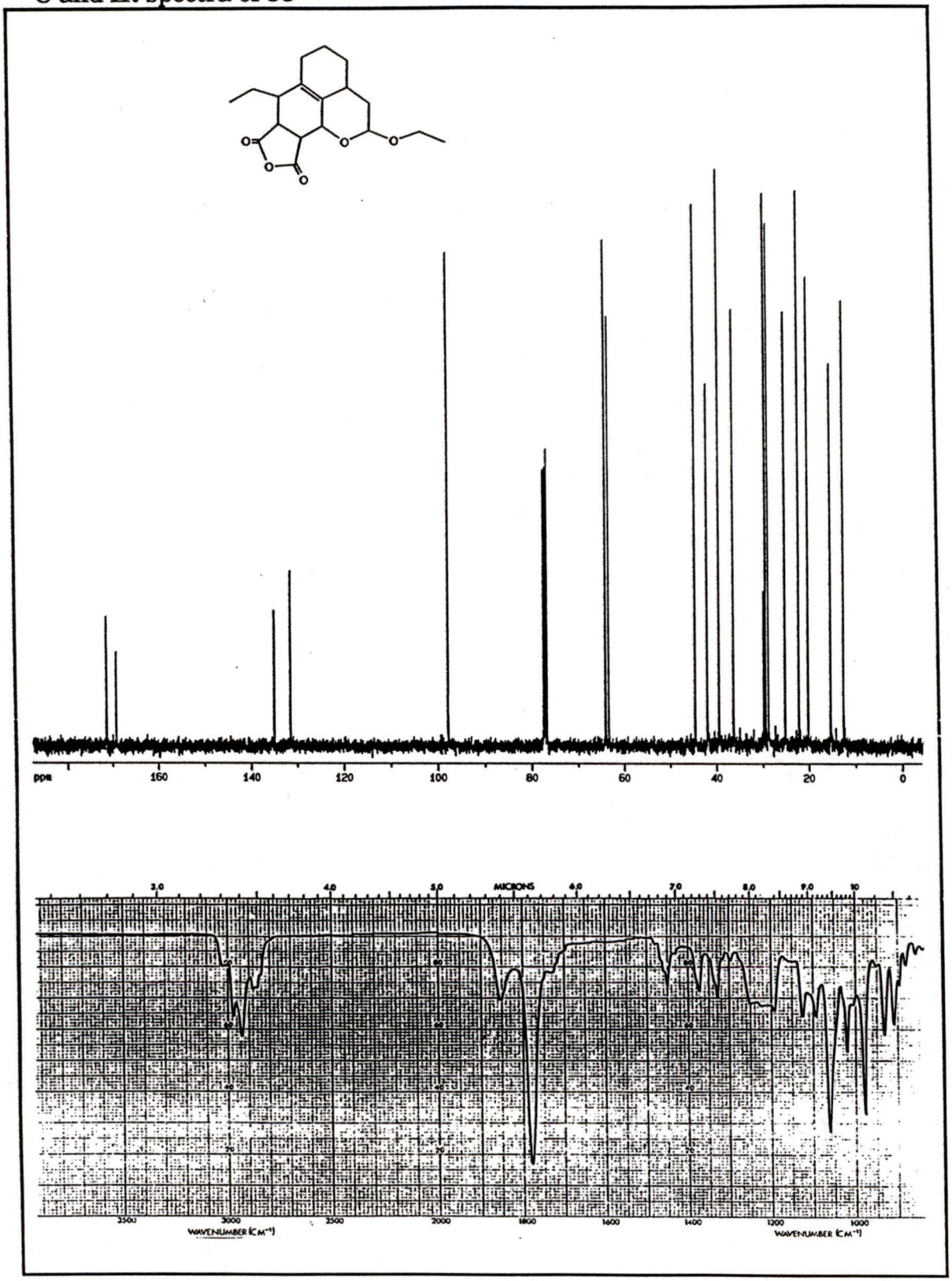
^{1}H NMR spectrum of 55



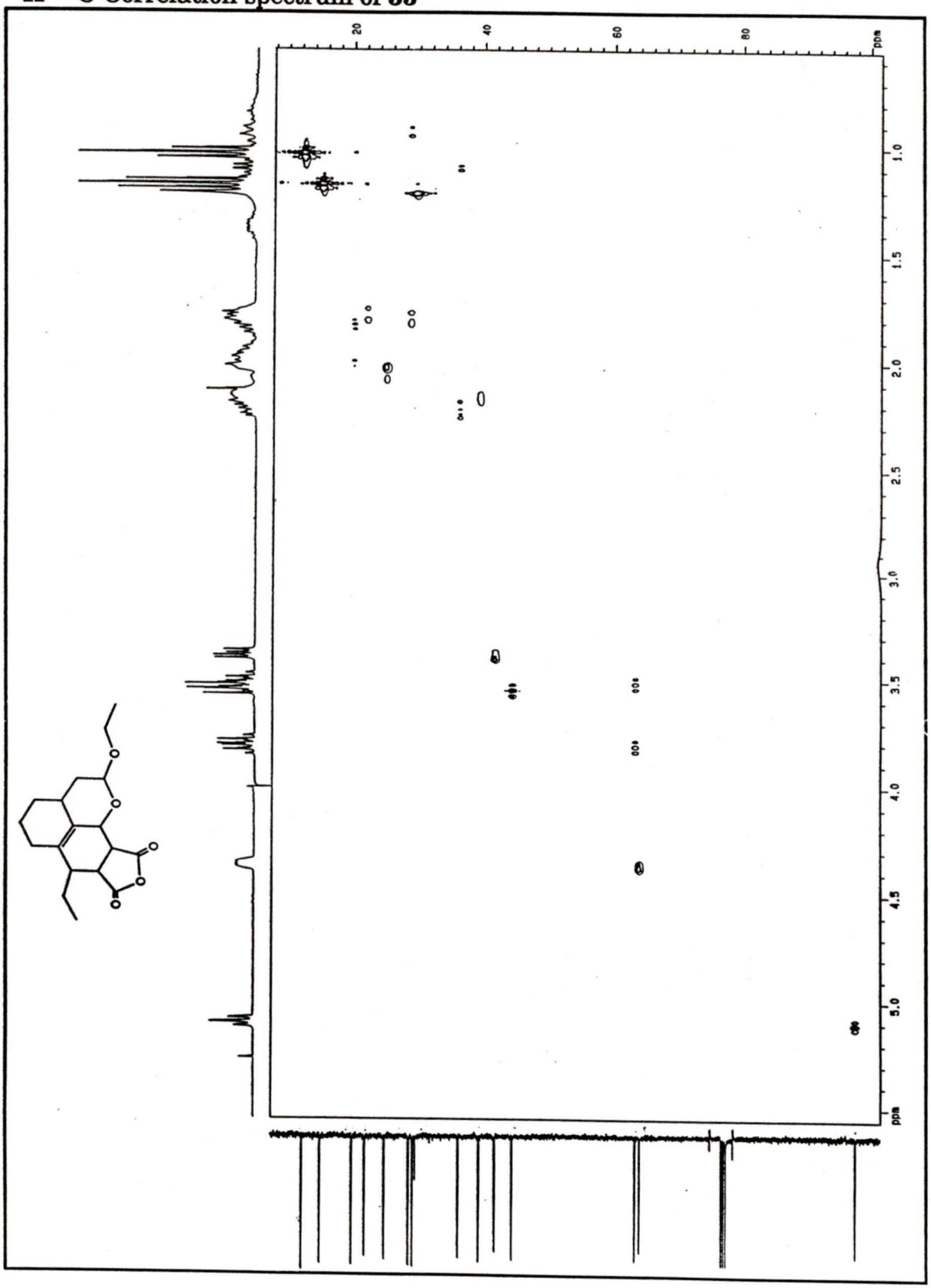
^{1}H COSY spectrum of 55



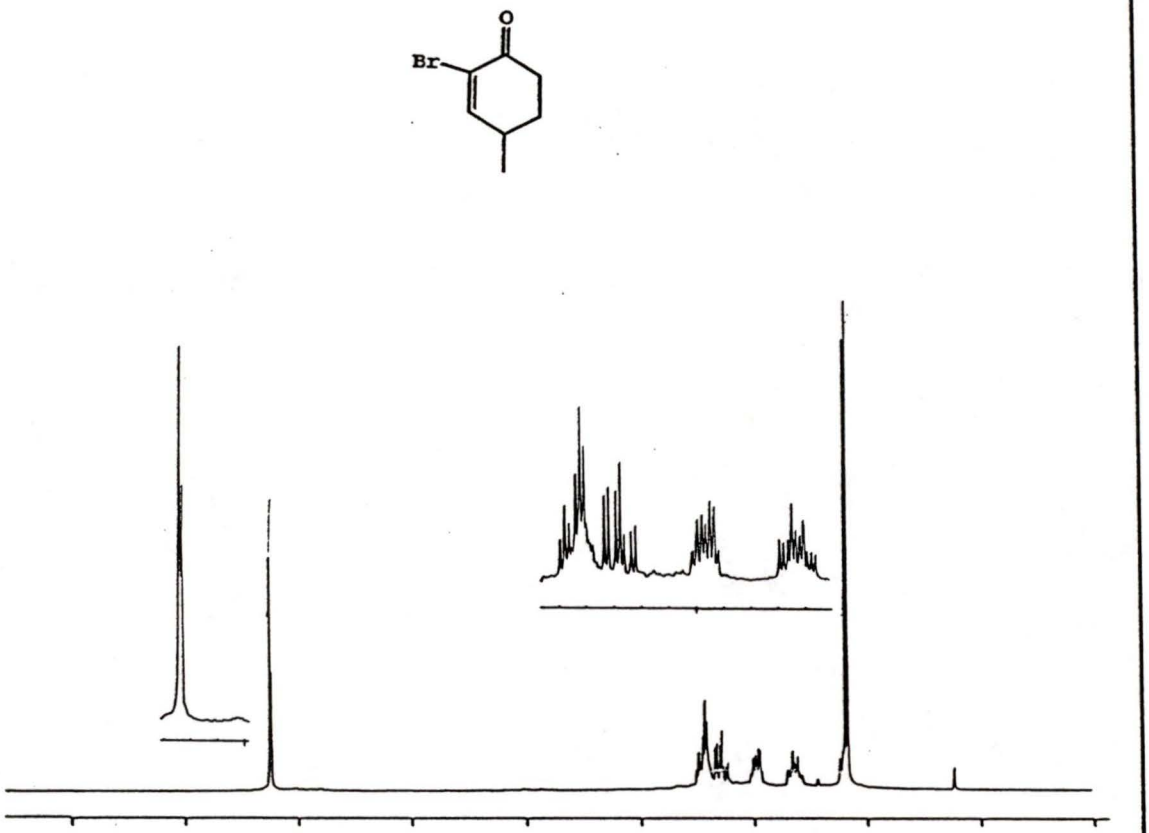
^{13}C and IR spectra of 55

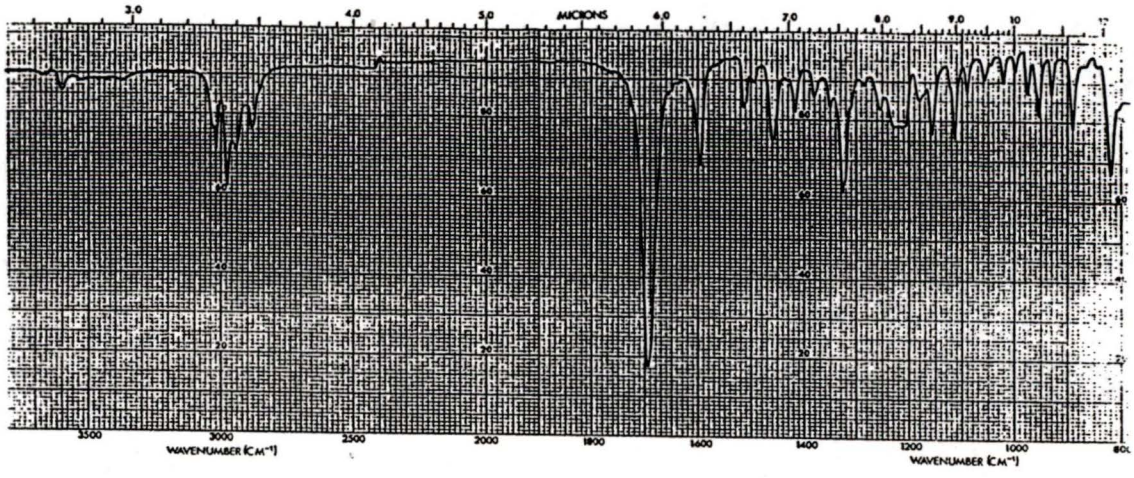


^{1}H-^{13}C Correlation spectrum of 55

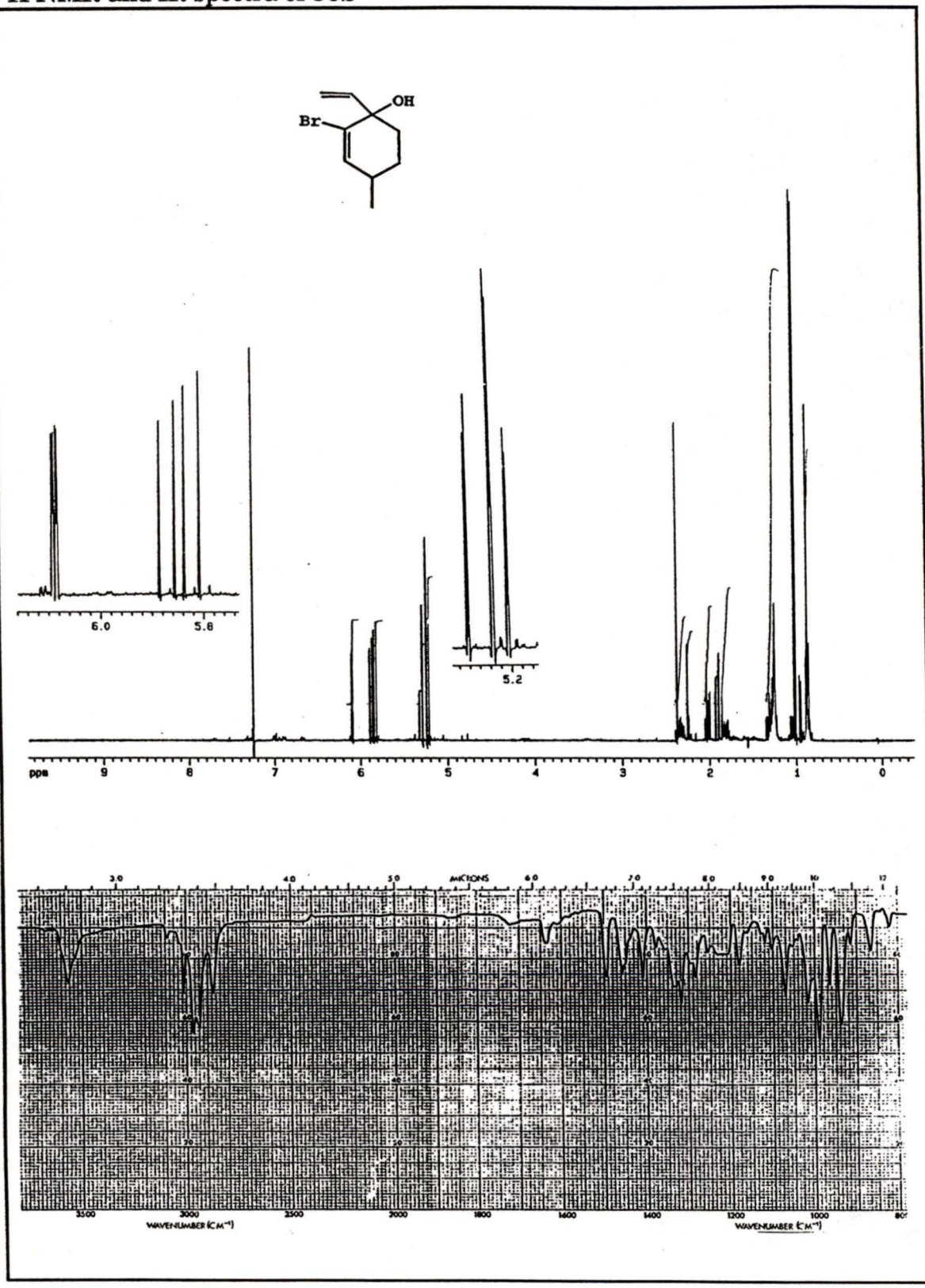


^{1}H NMR and IR spectra of 49b

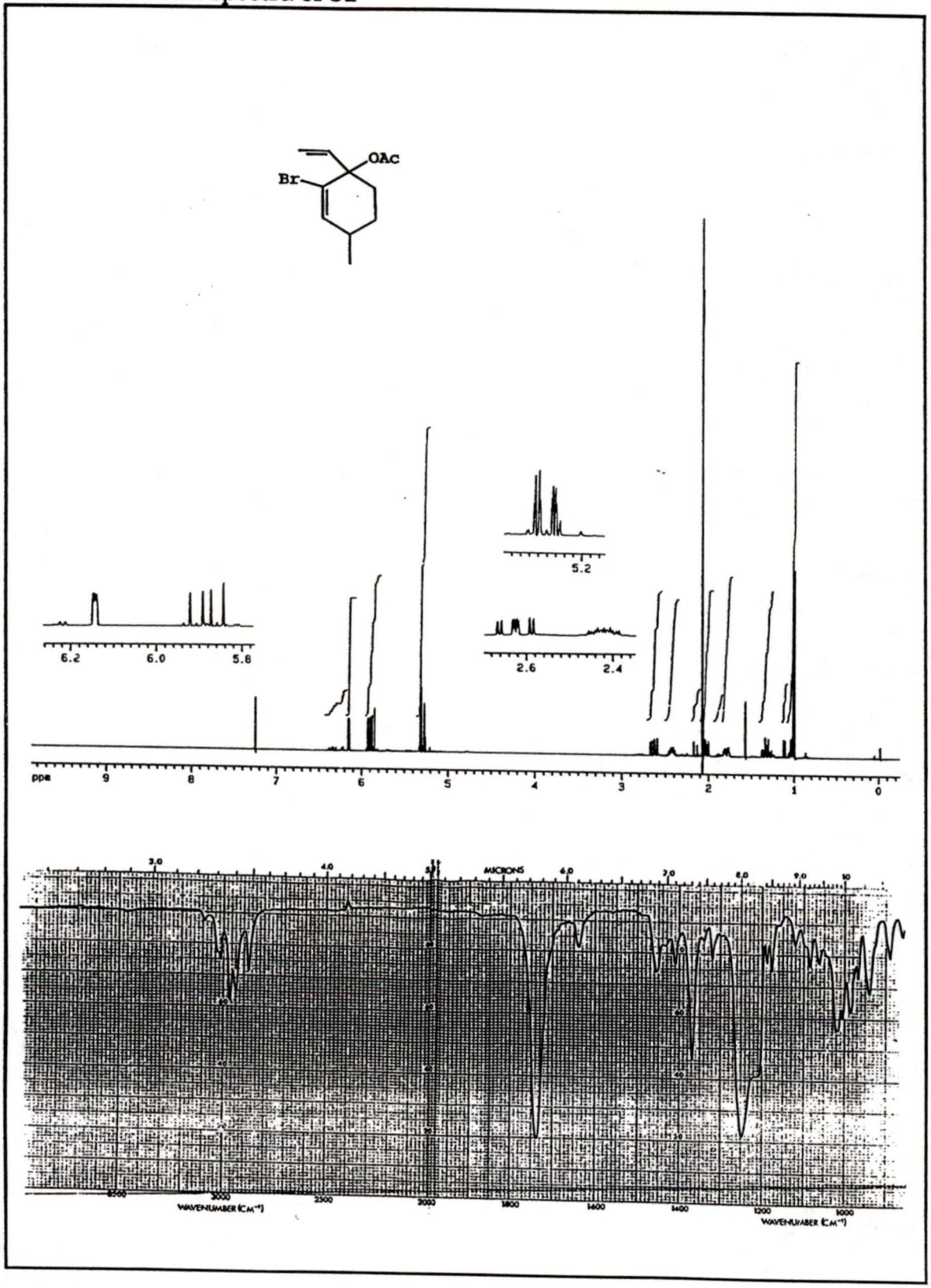




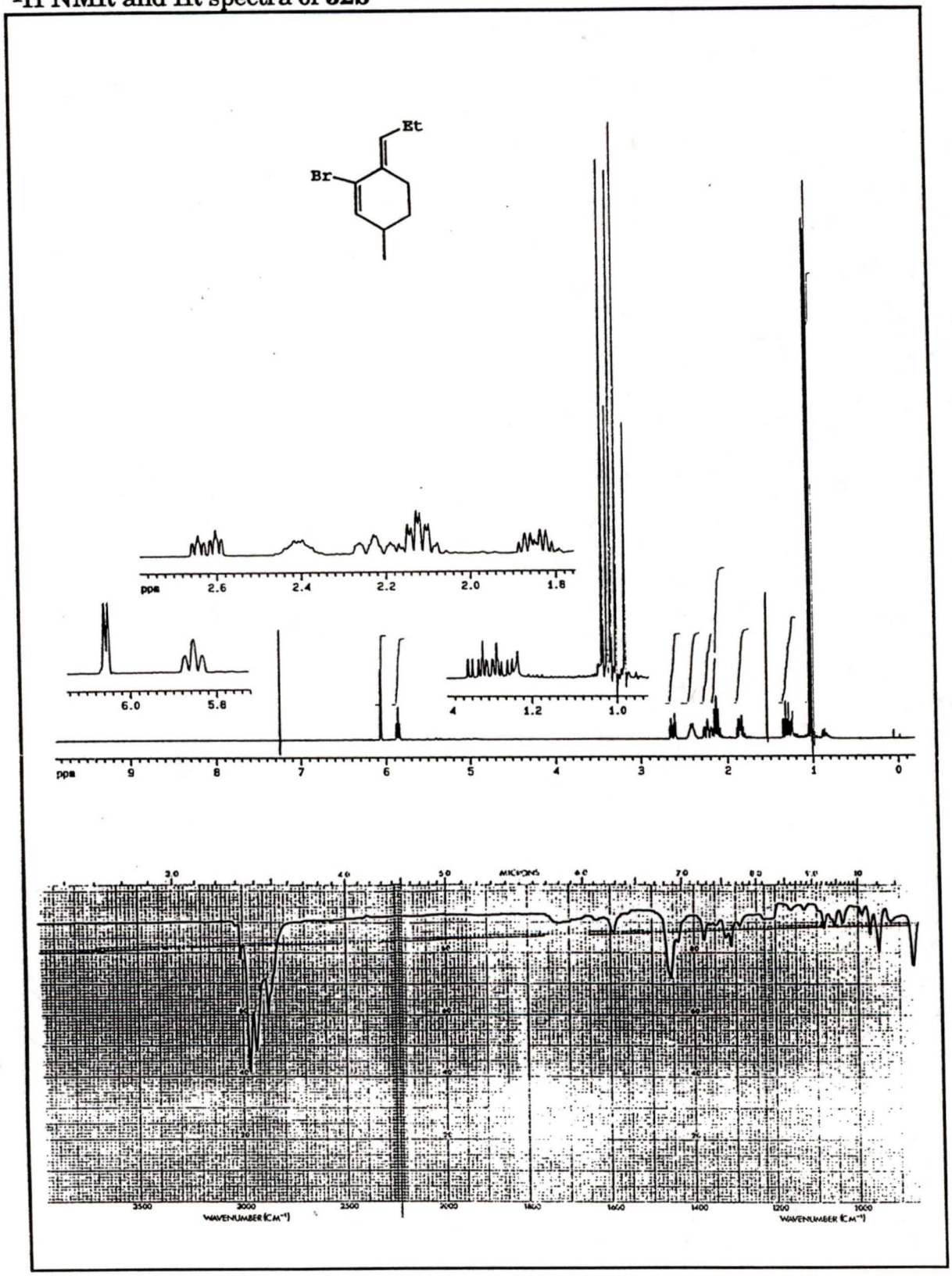
^{1}H NMR and IR spectra of **50b**



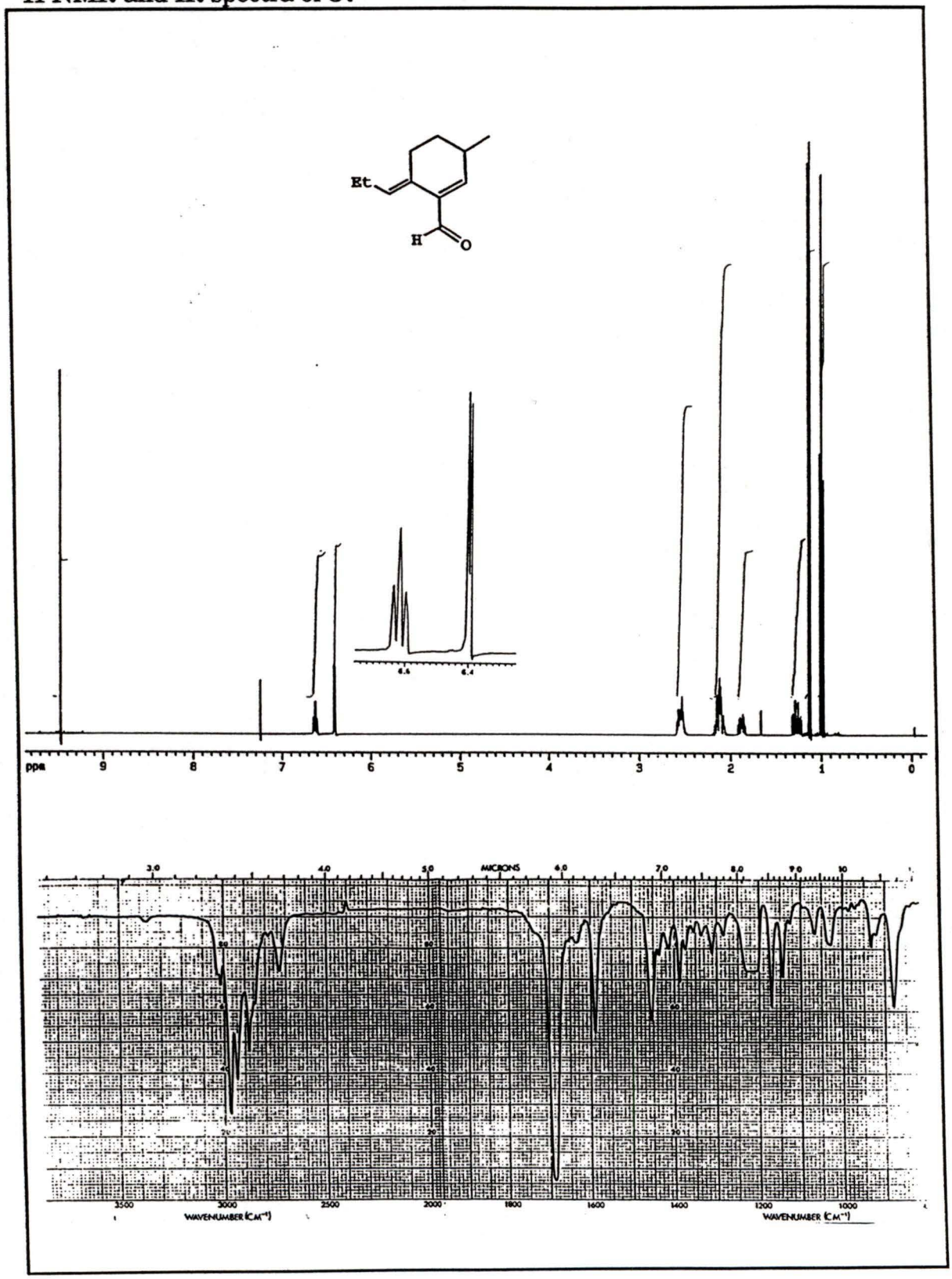
^{1}H NMR and IR spectra of **51**



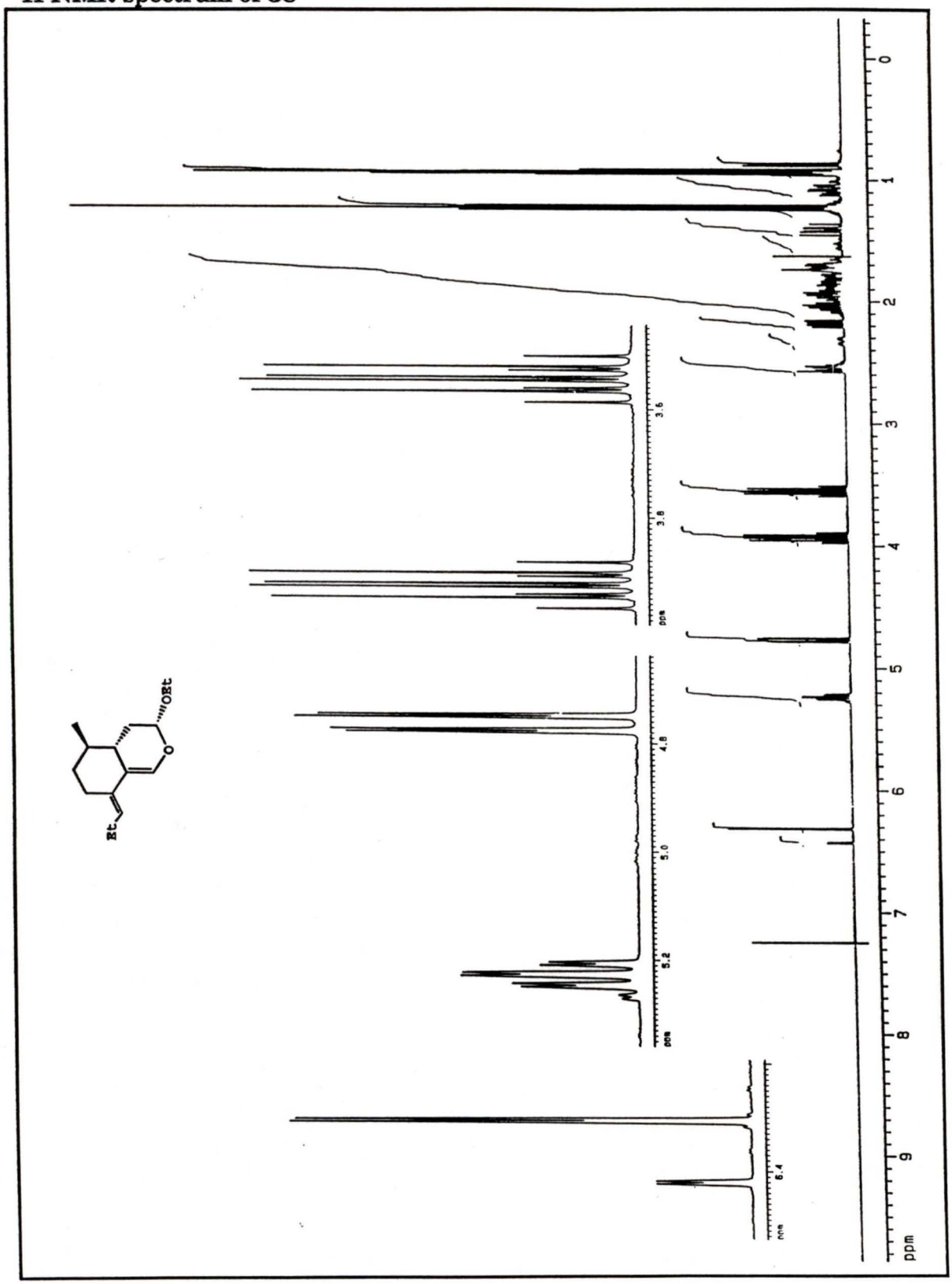
^{1}H NMR and IR spectra of **52b**



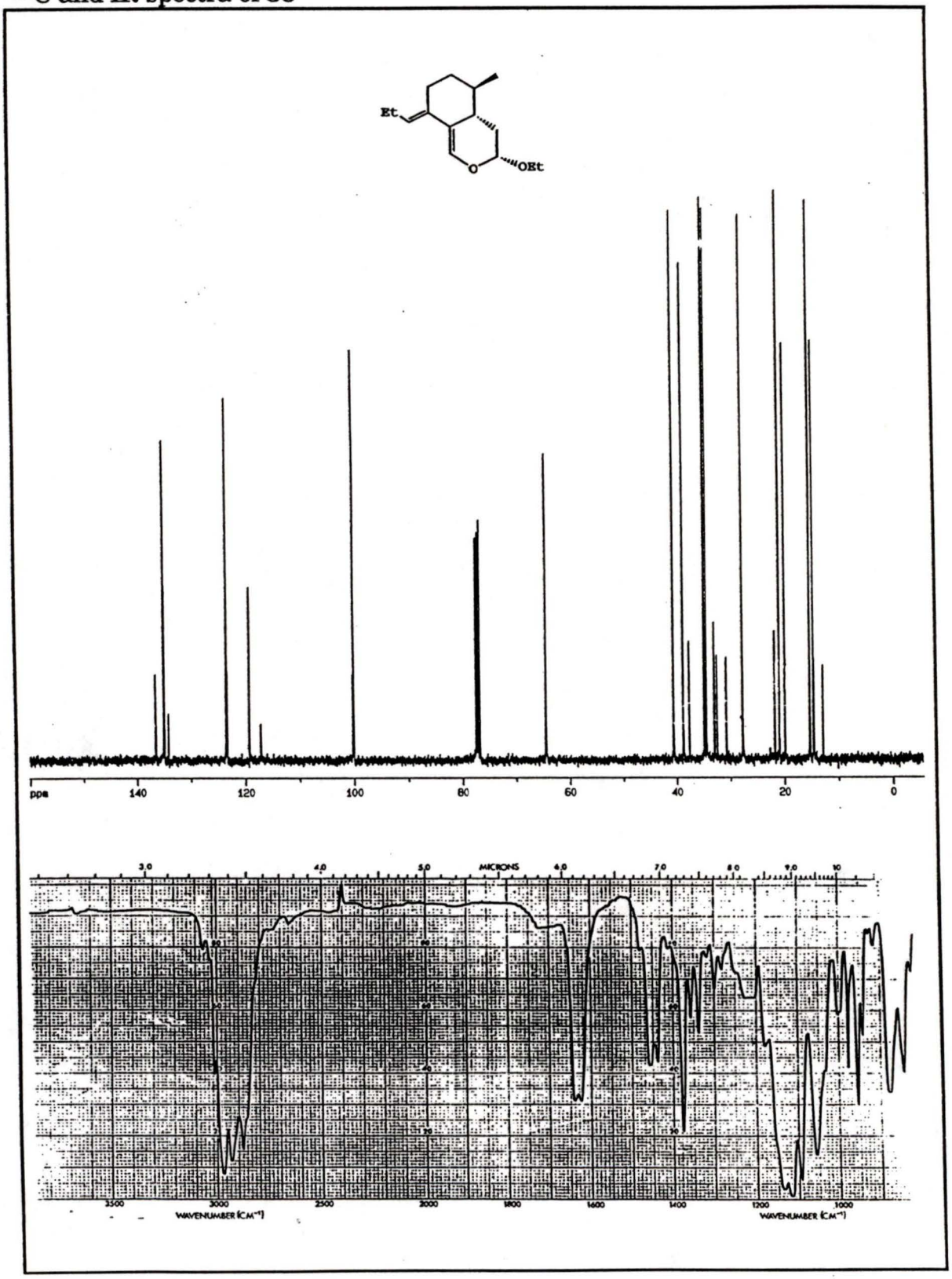
^{1}H NMR and IR spectra of 37



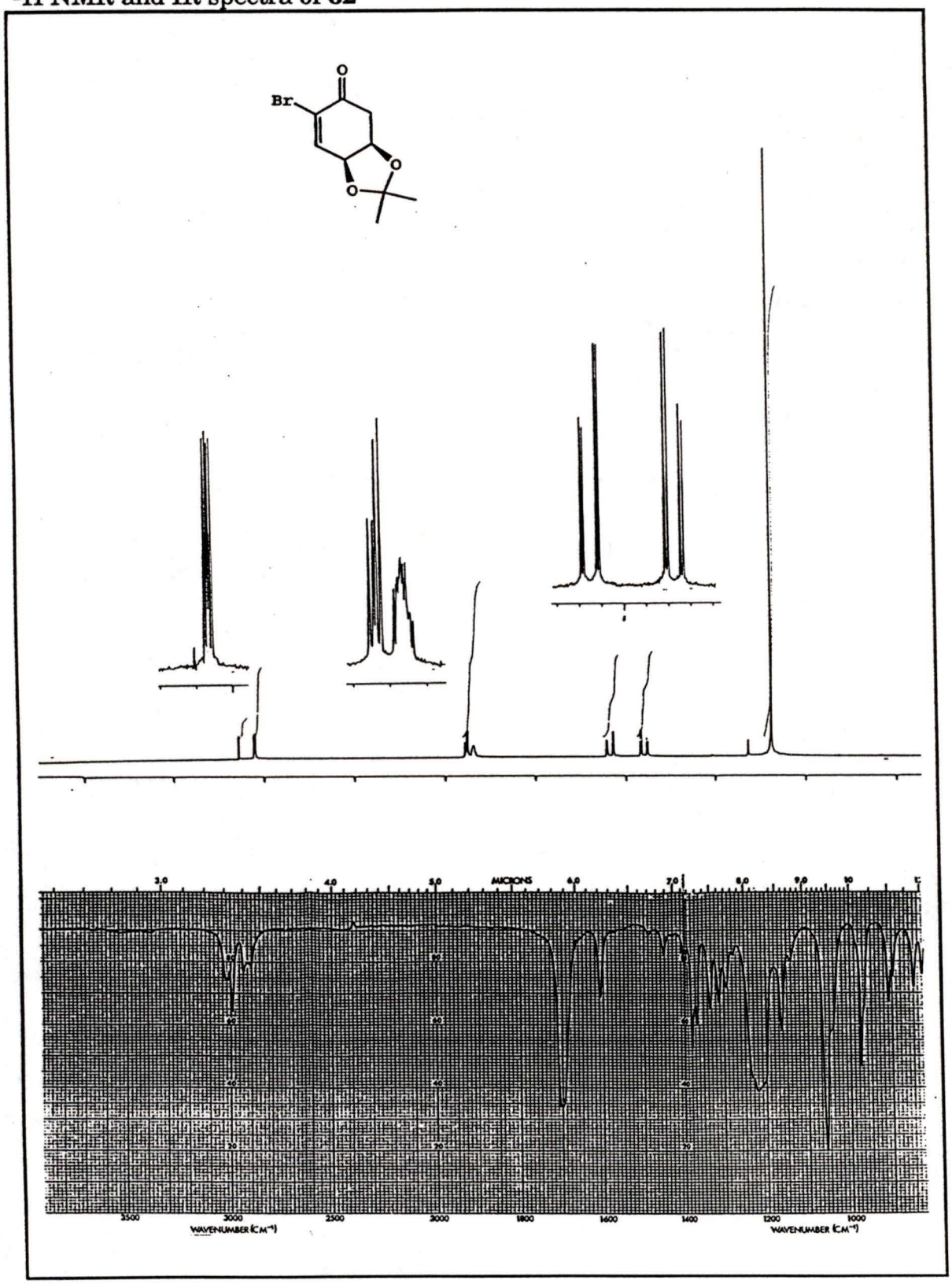
^{1}H NMR spectrum of 38



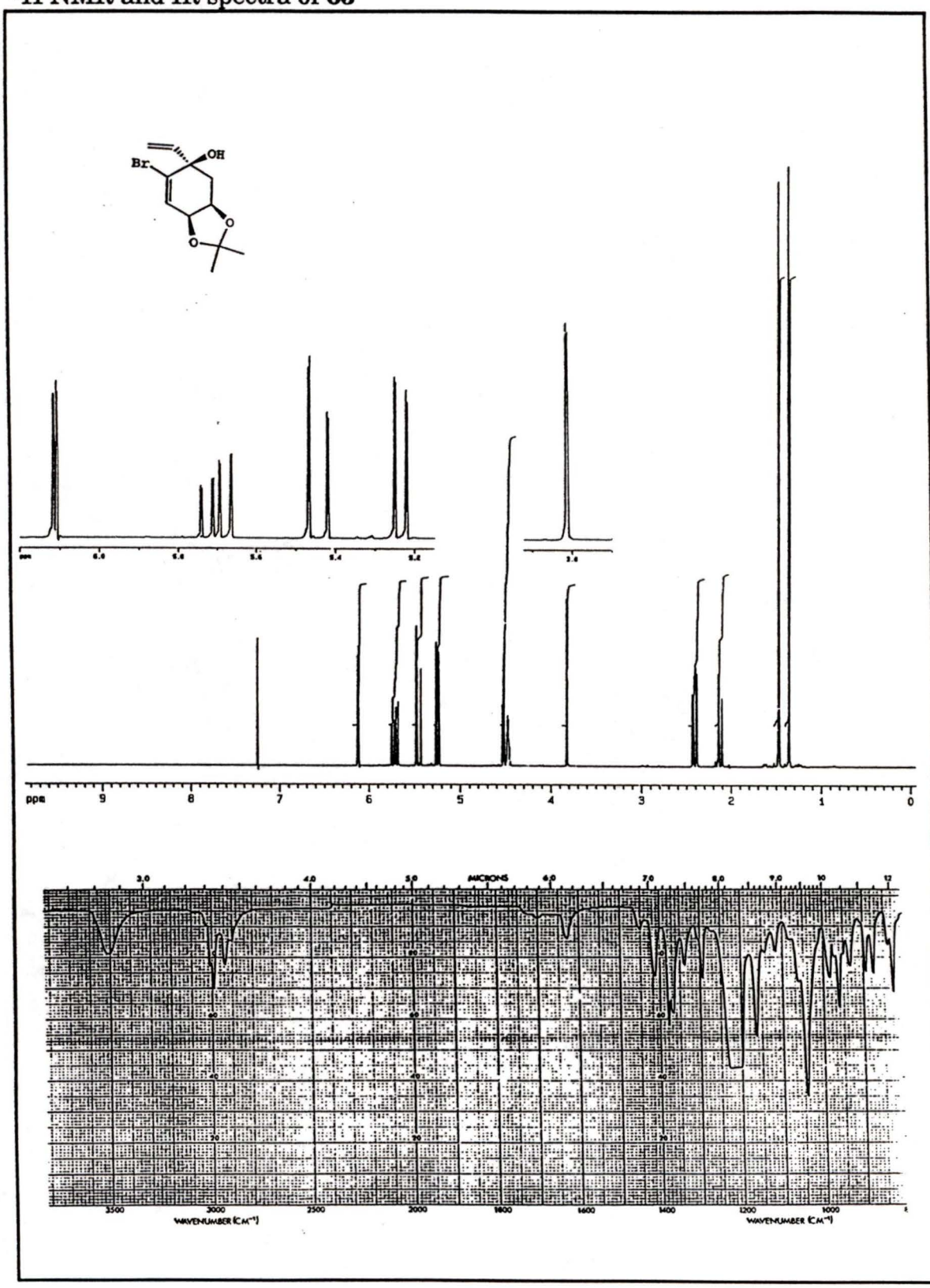
^{13}C and IR spectra of 38



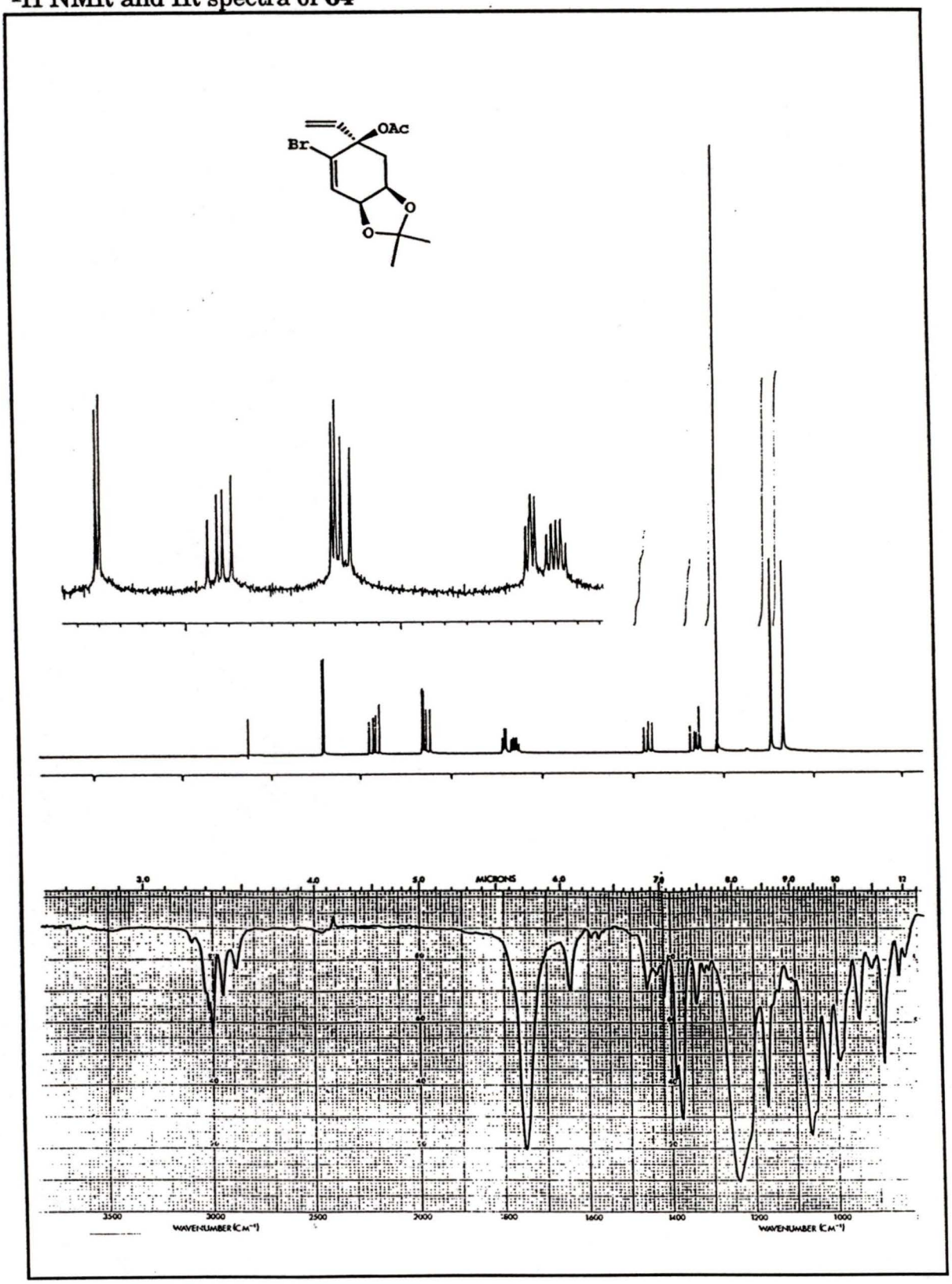
^{1}H NMR and IR spectra of 62



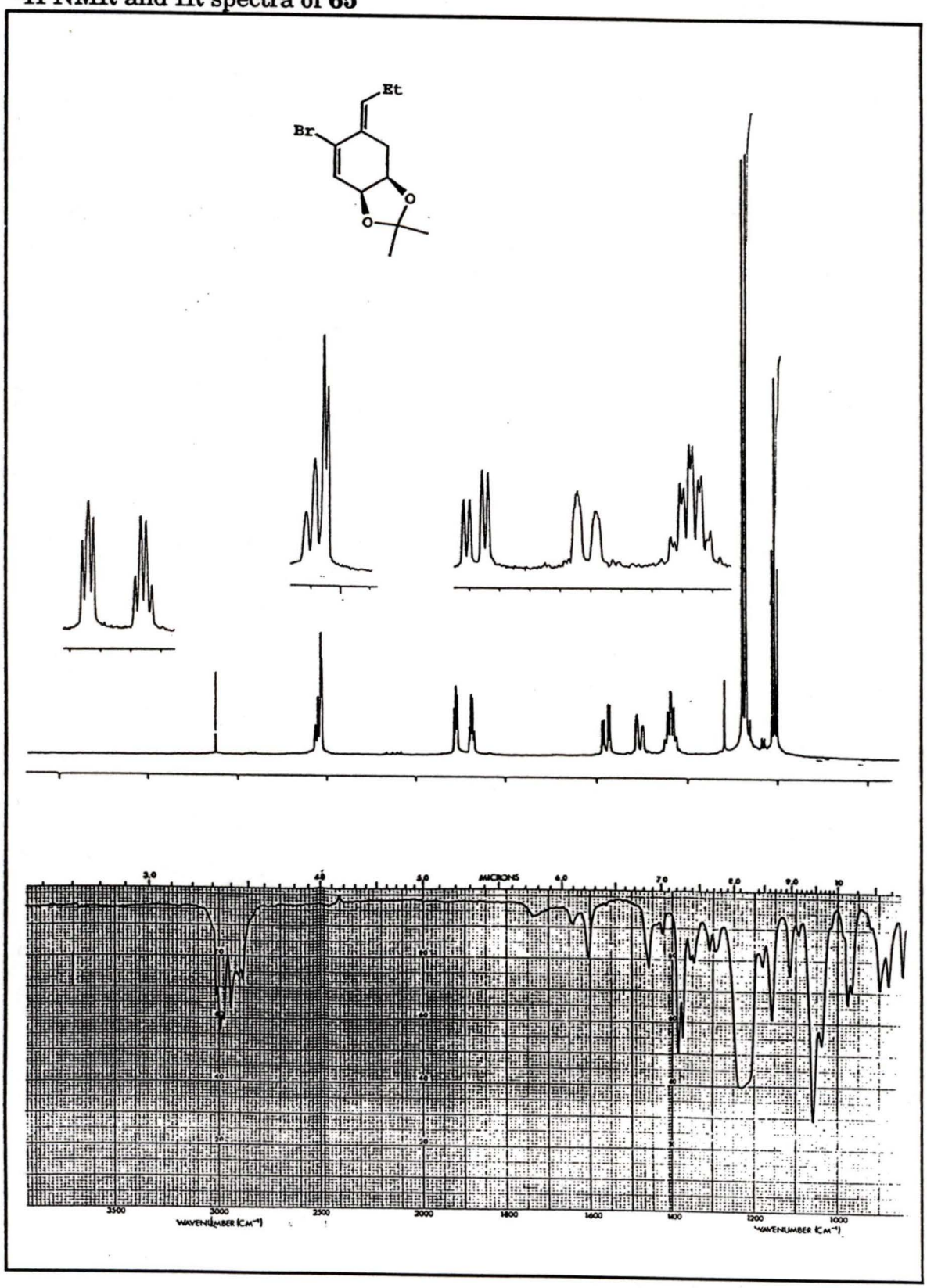
^{1}H NMR and IR spectra of 63



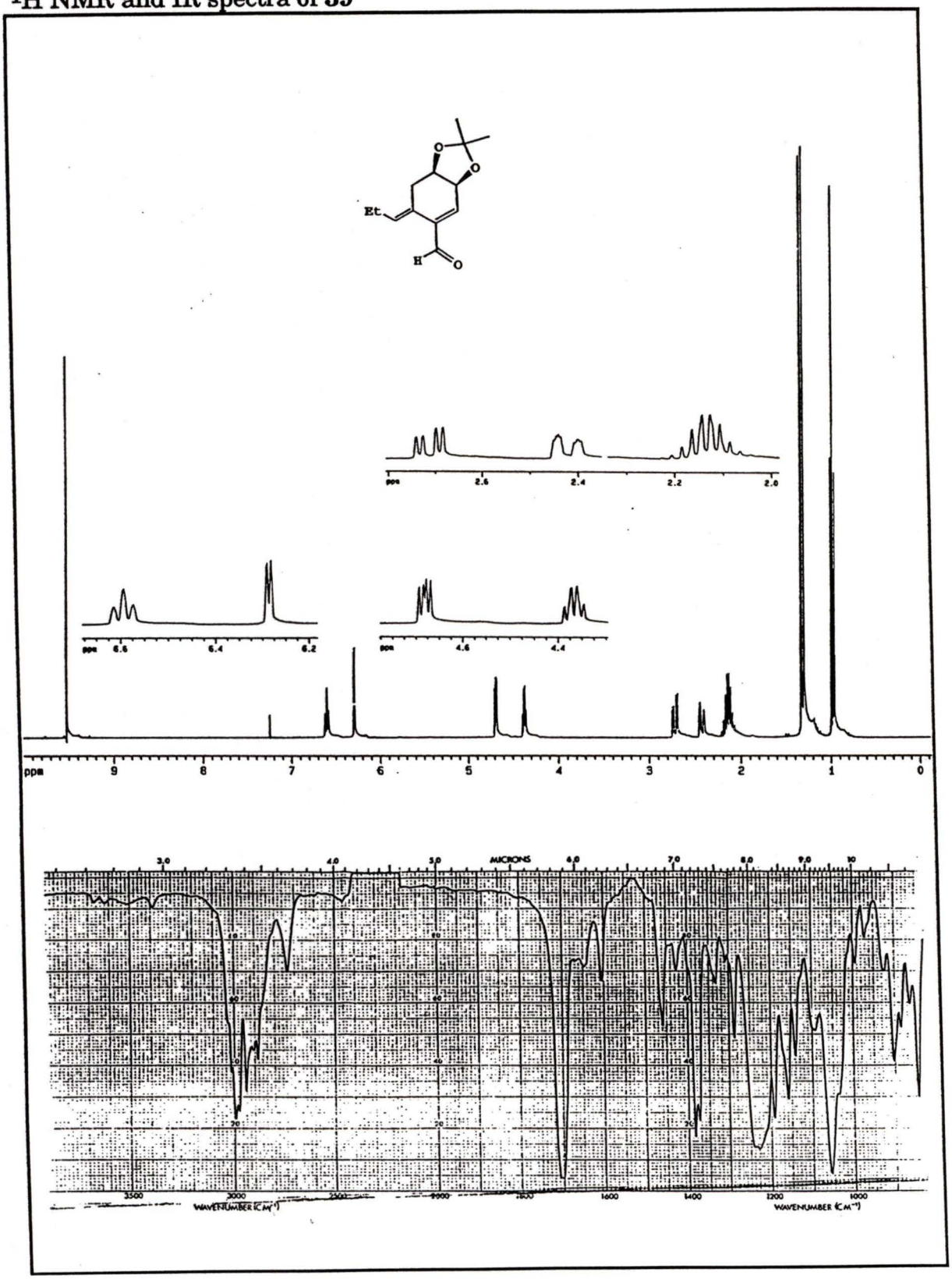
^{1}H NMR and IR spectra of 64



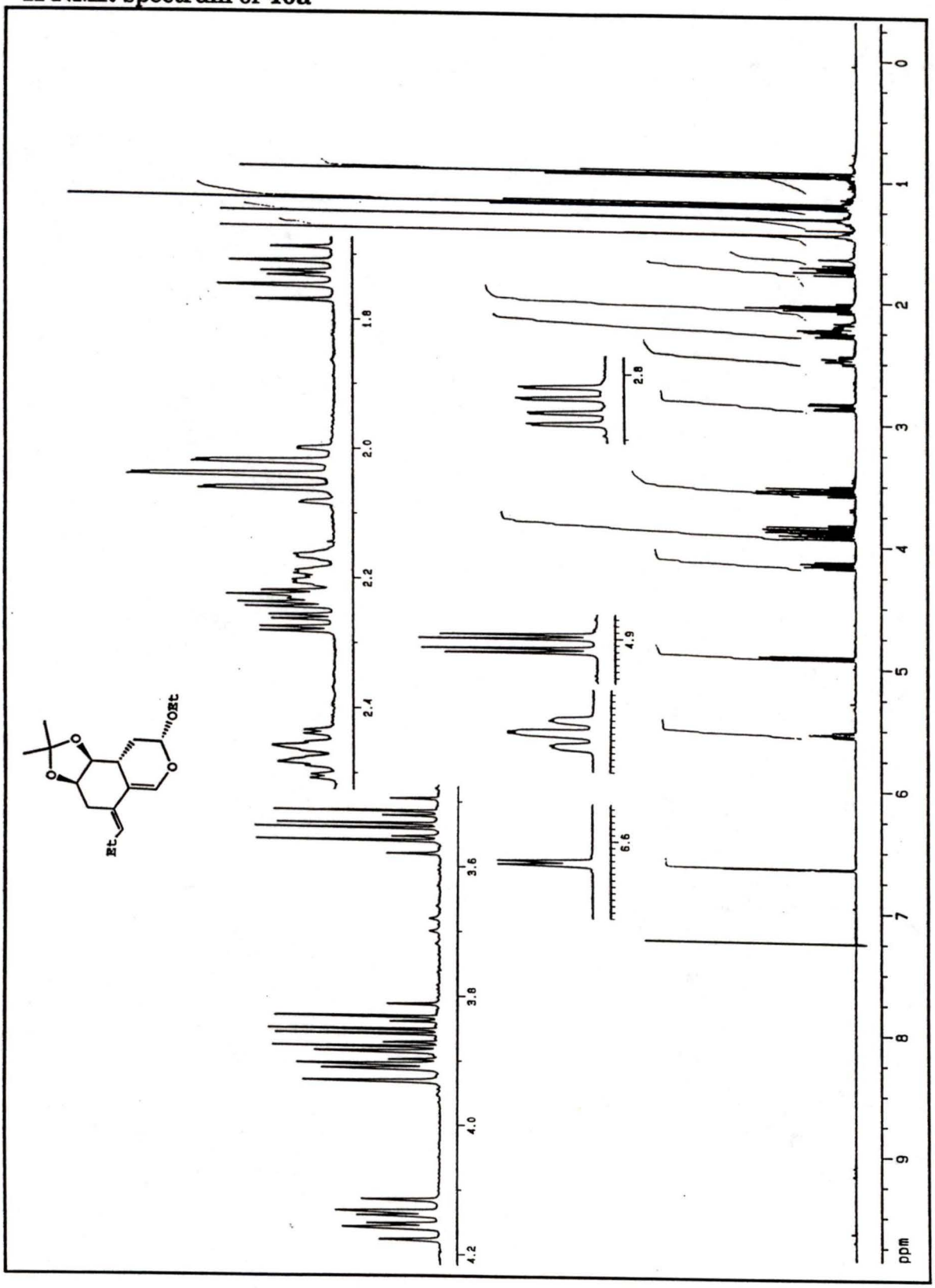
^{1}H NMR and IR spectra of 65



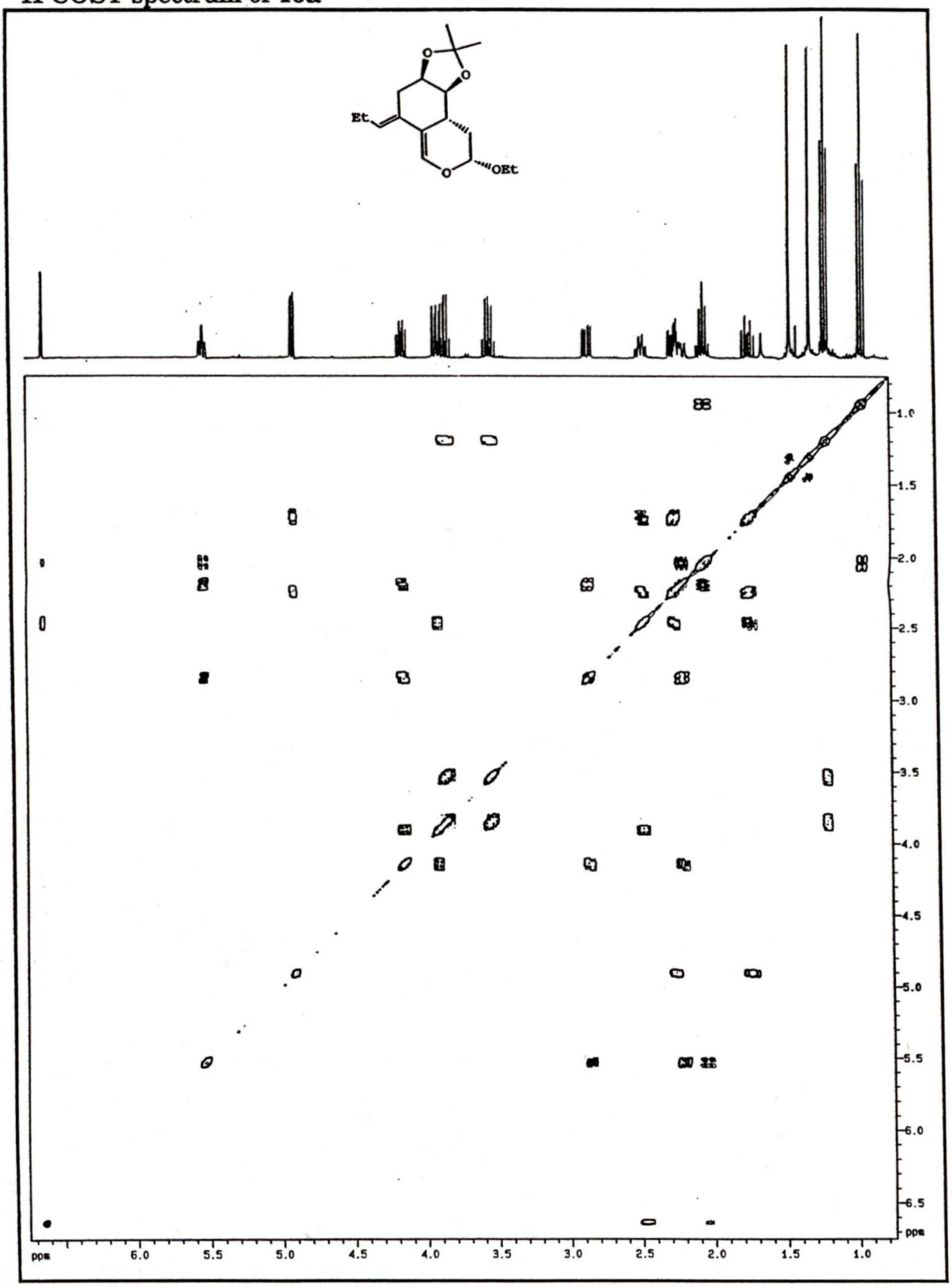
^{1}H NMR and IR spectra of 39



^{1}H NMR spectrum of 40a



^{1}H COSY spectrum of 40a



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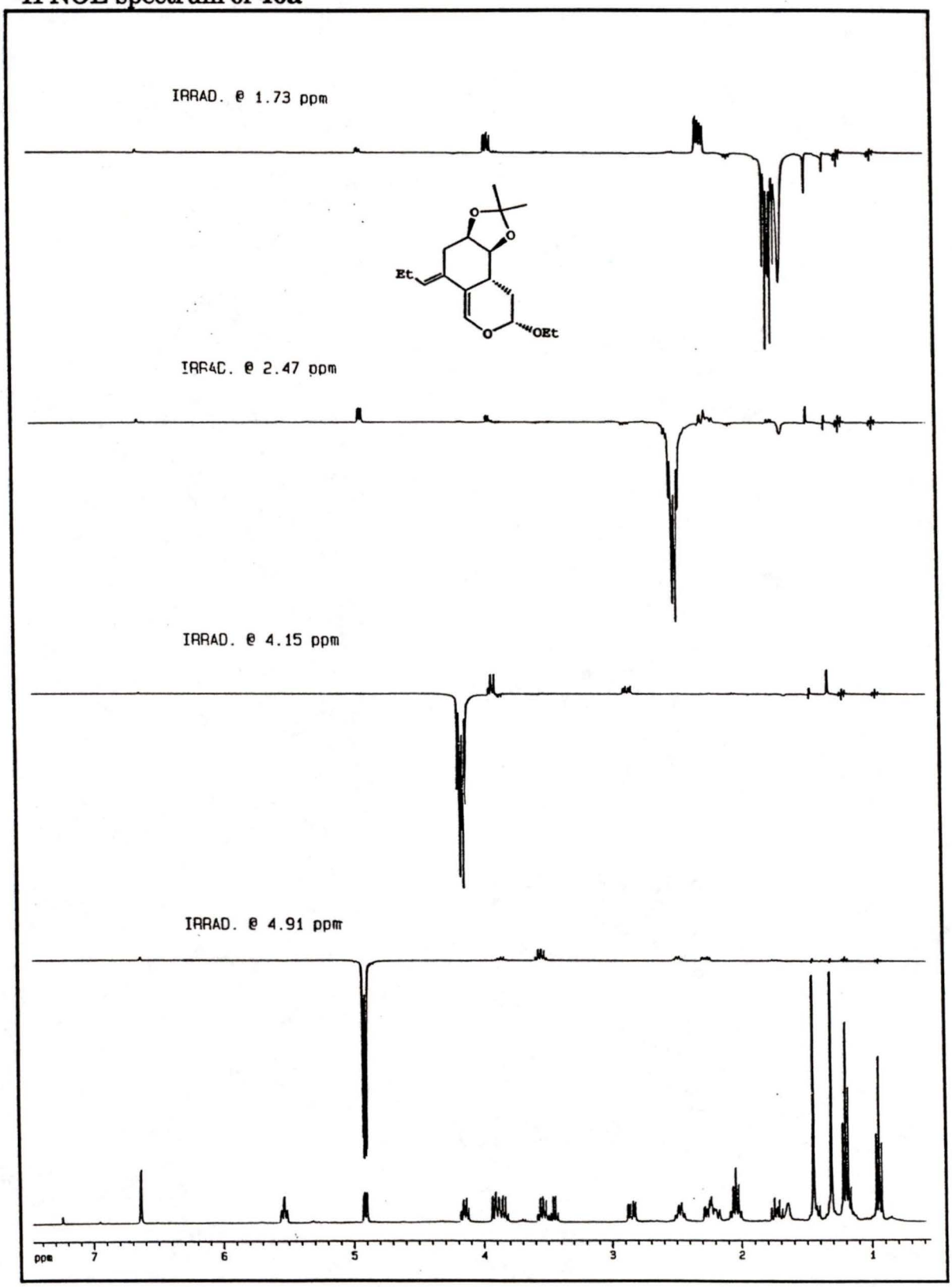
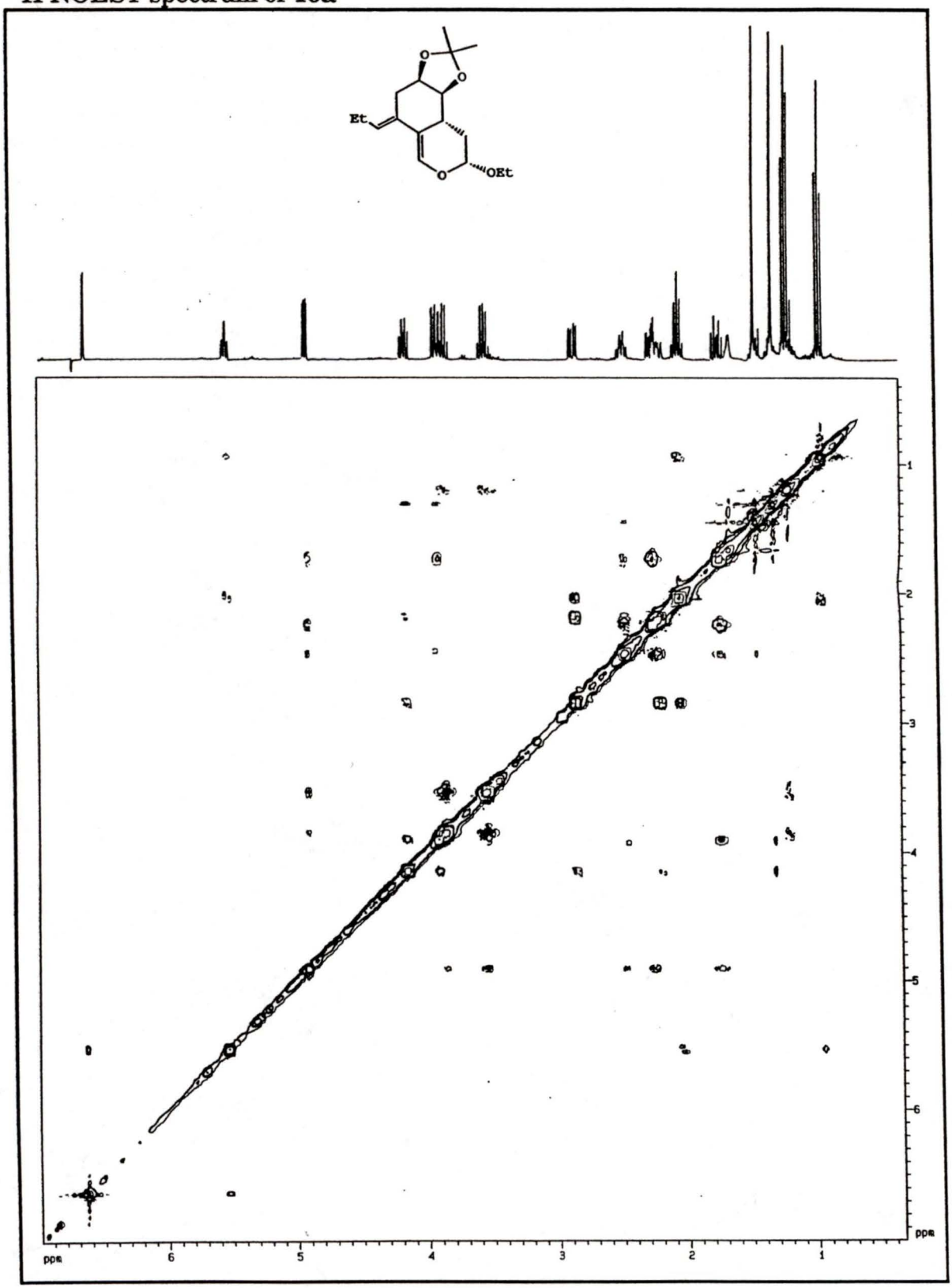
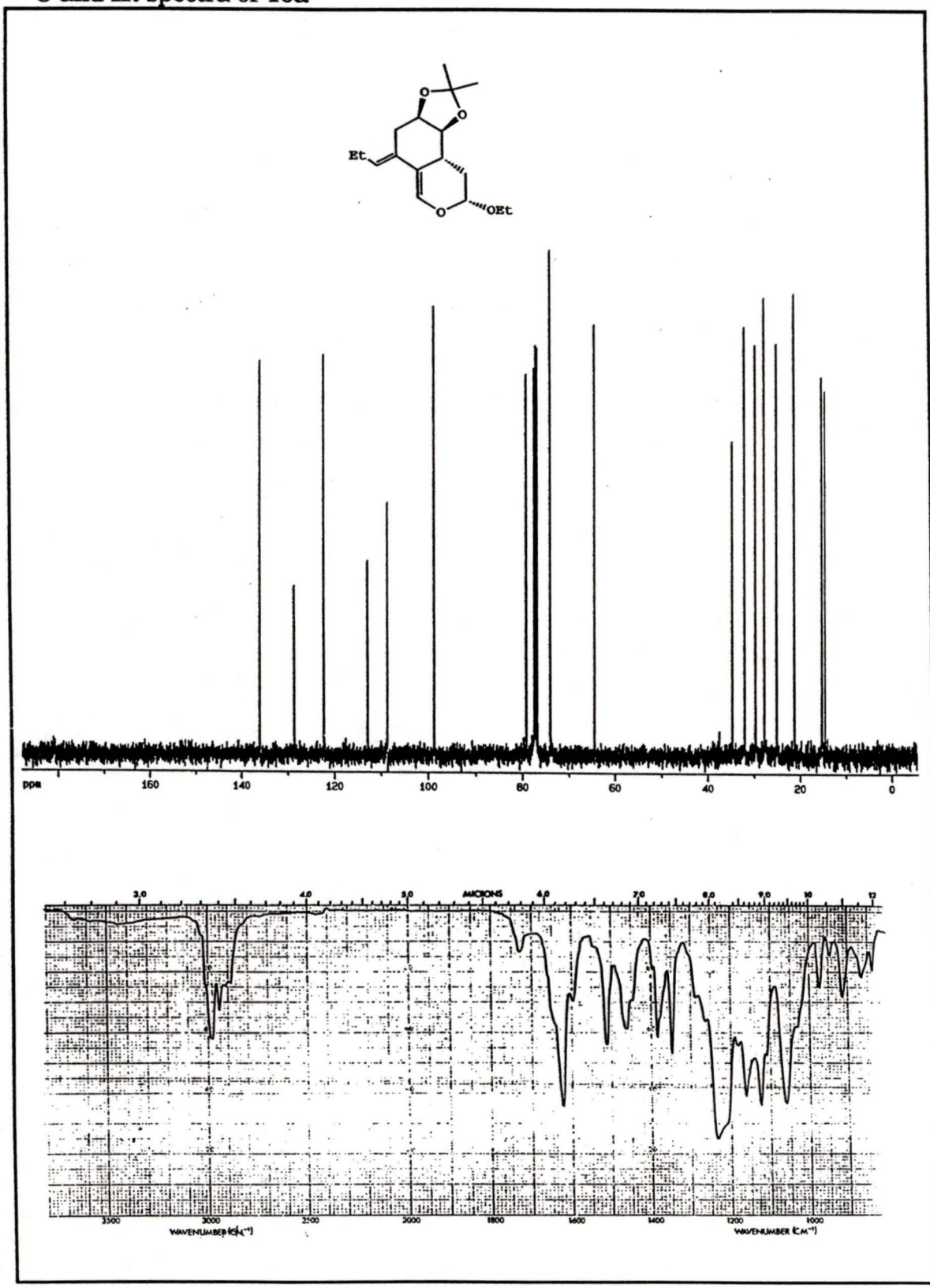


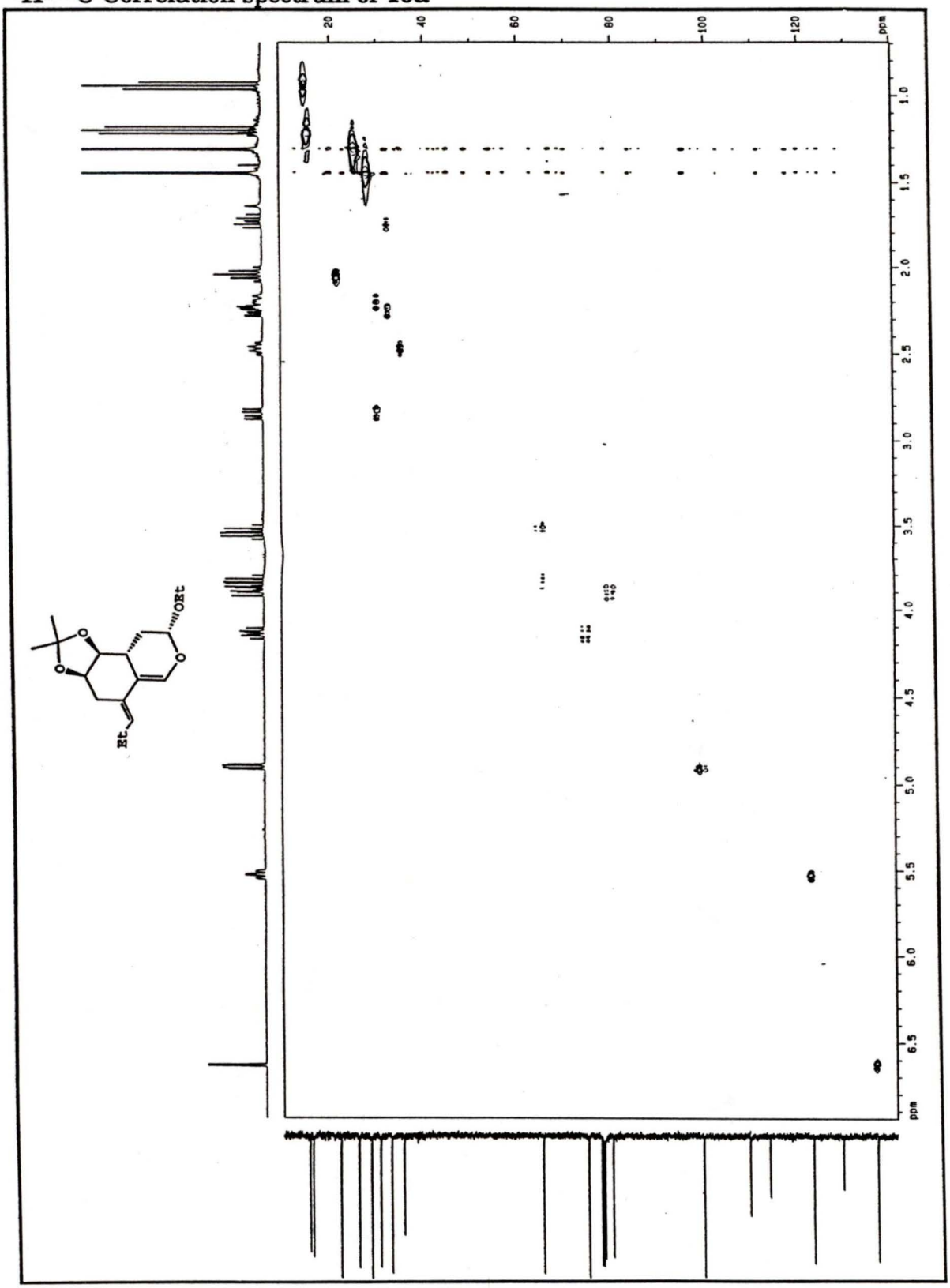
^{1}H NOESY spectrum of 40a



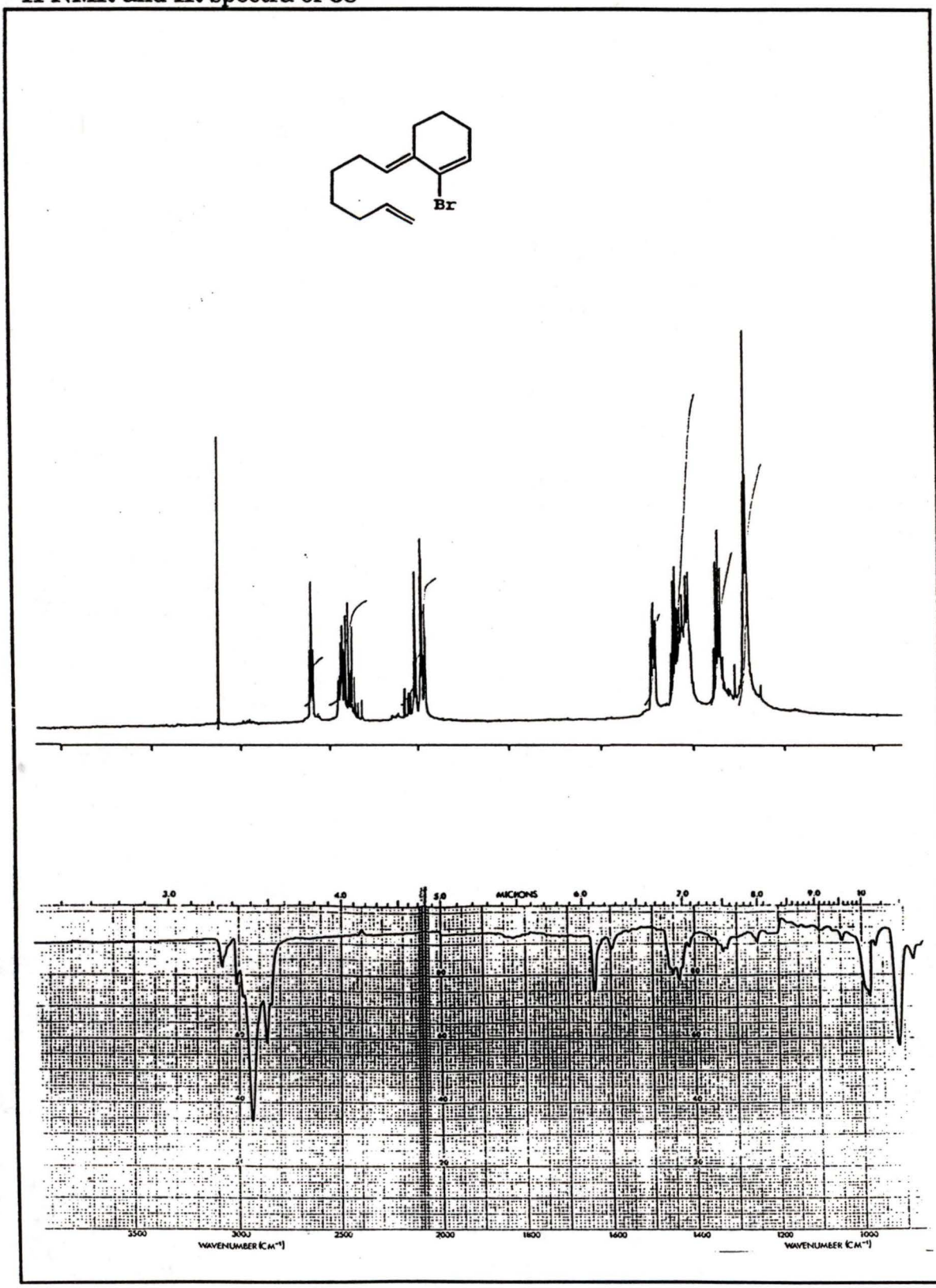
^{13}C and IR spectra of 40a



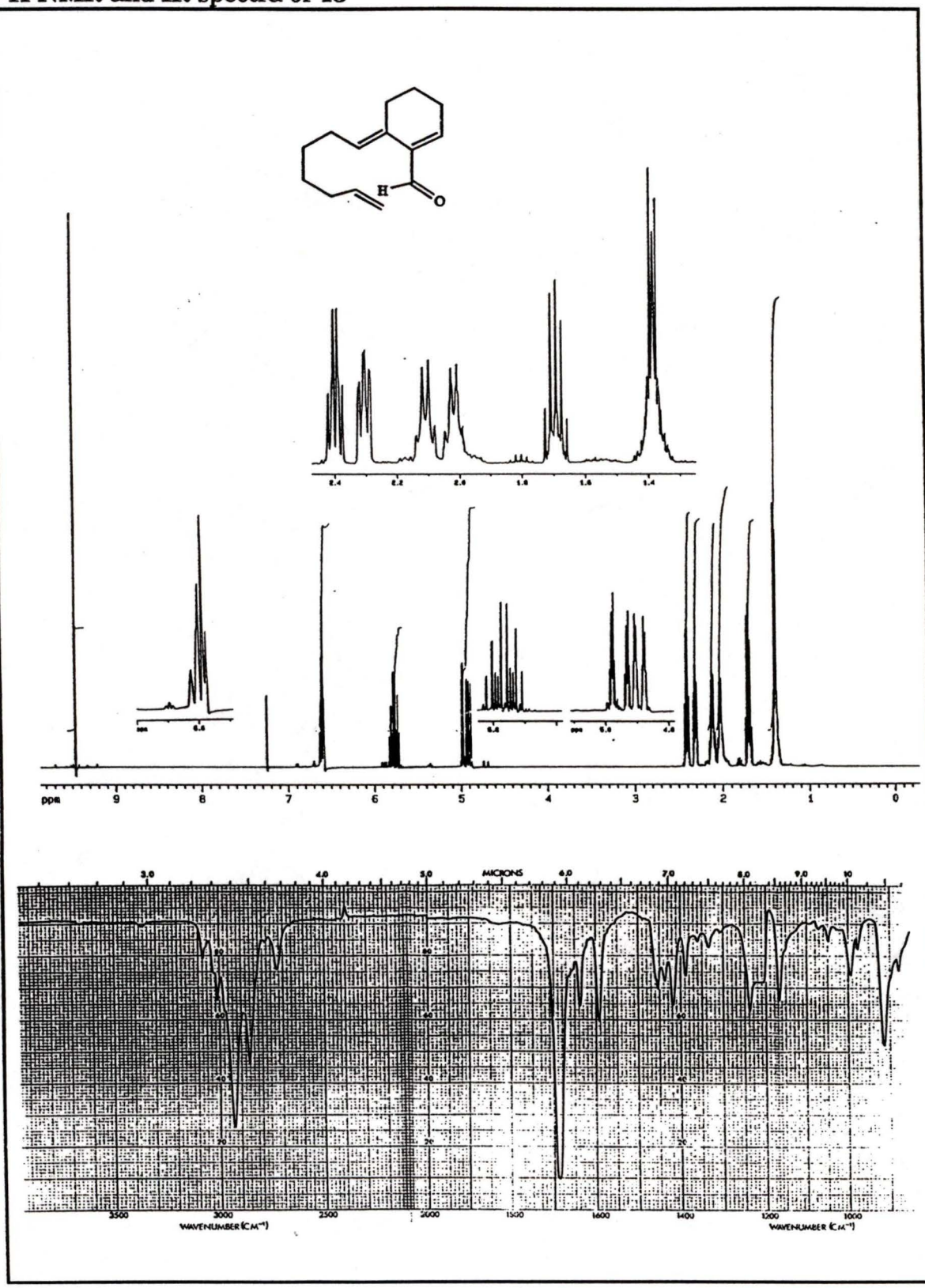
^{1}H-^{13}C Correlation spectrum of 40a



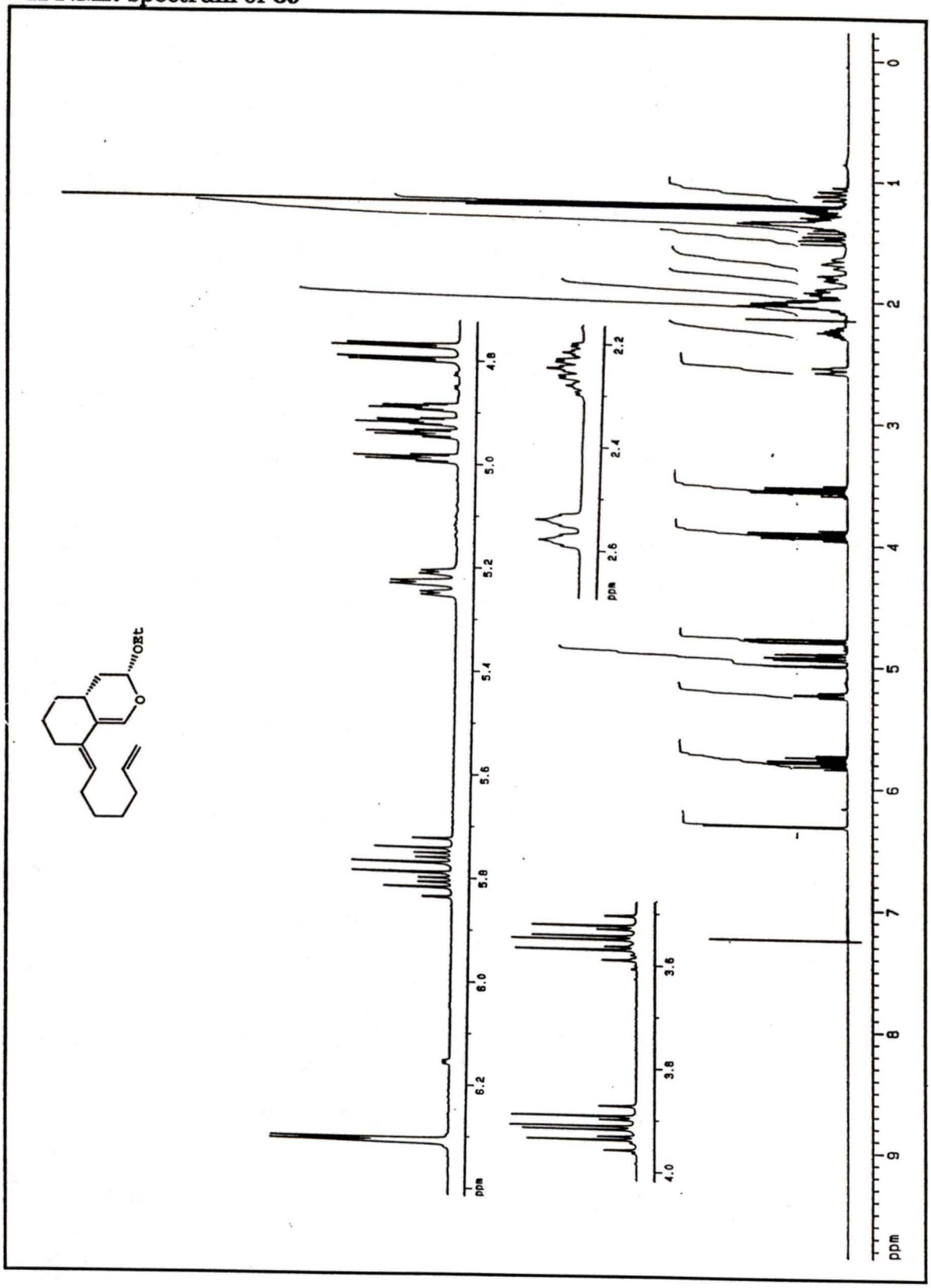
^{1}H NMR and IR spectra of 68



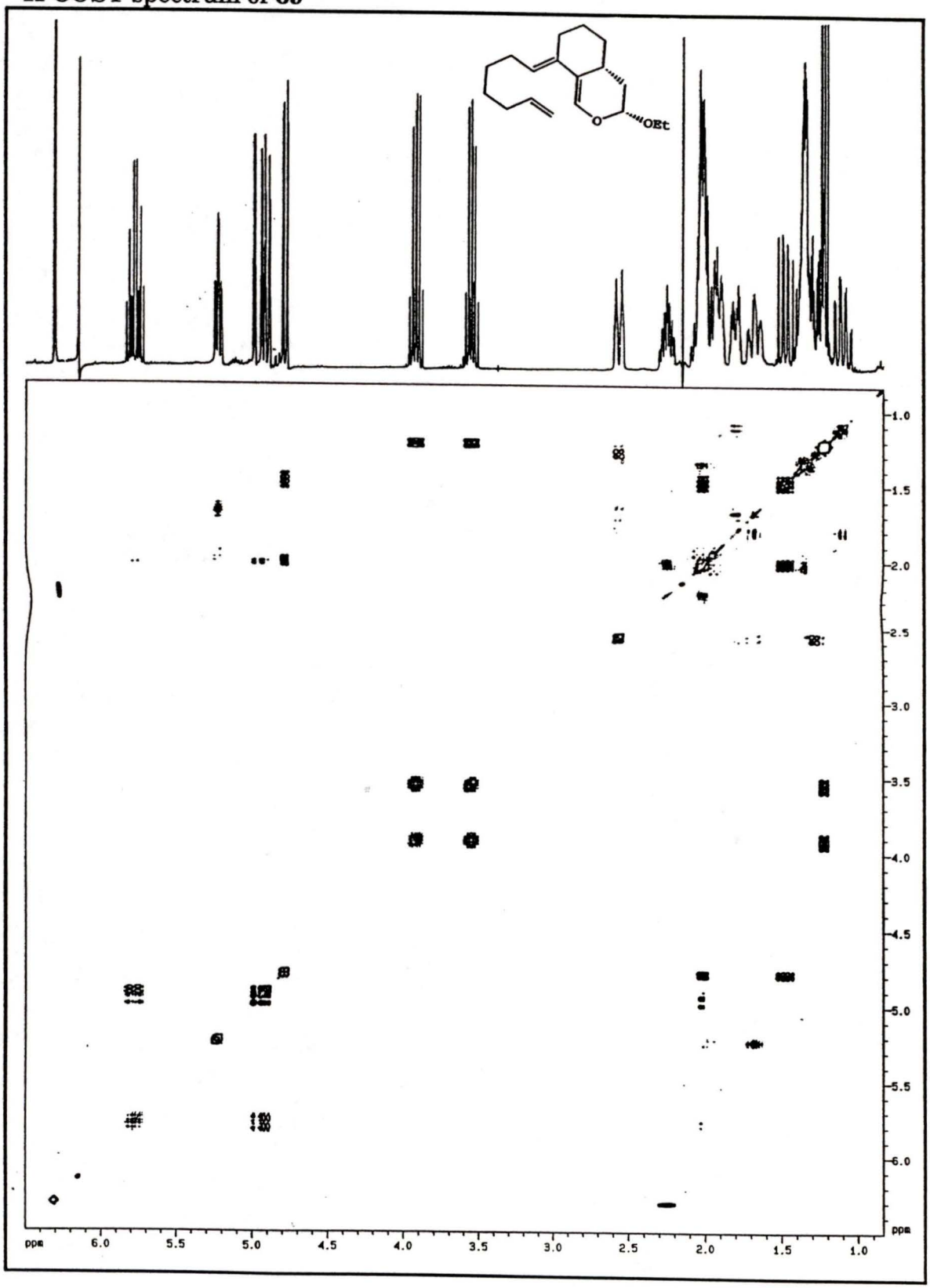
^{1}H NMR and IR spectra of 43



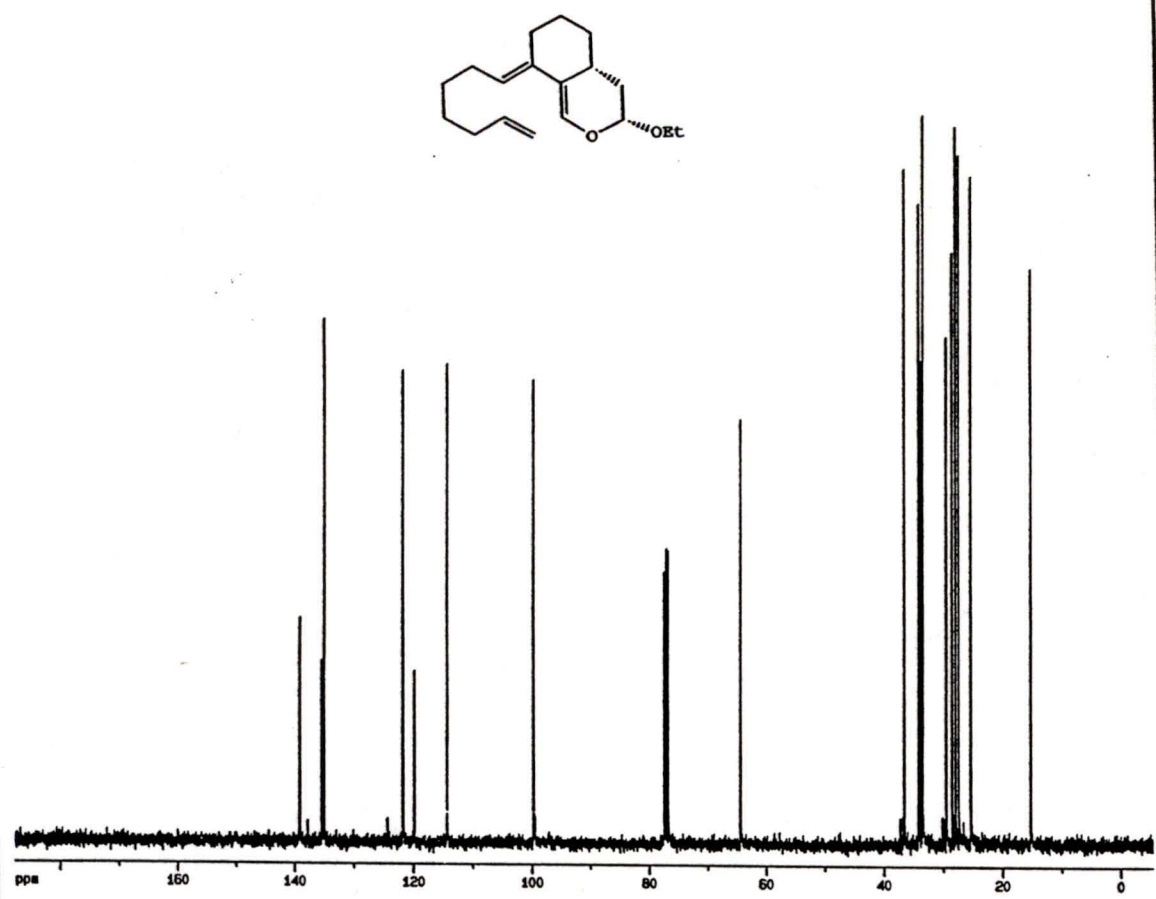
^{1}H NMR spectrum of 69

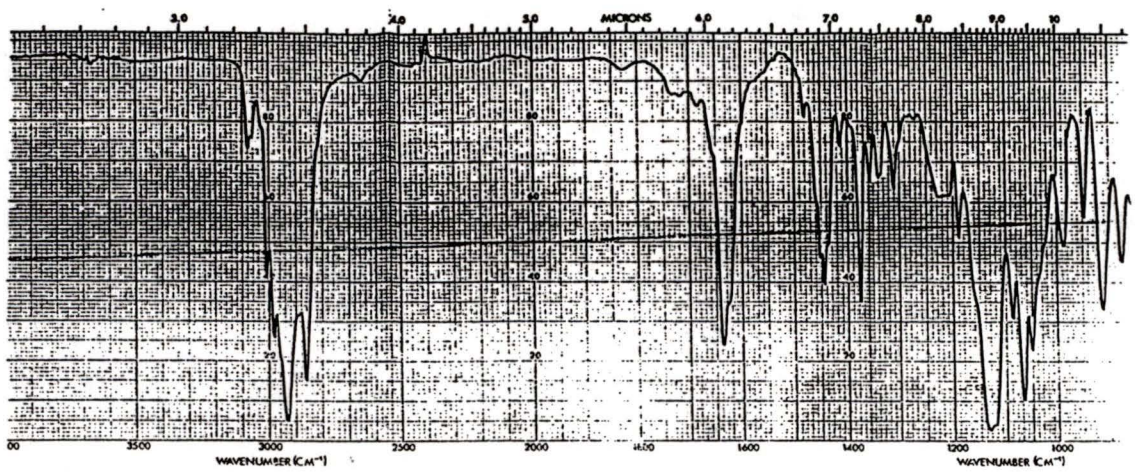


^{1}H COSY spectrum of **69**

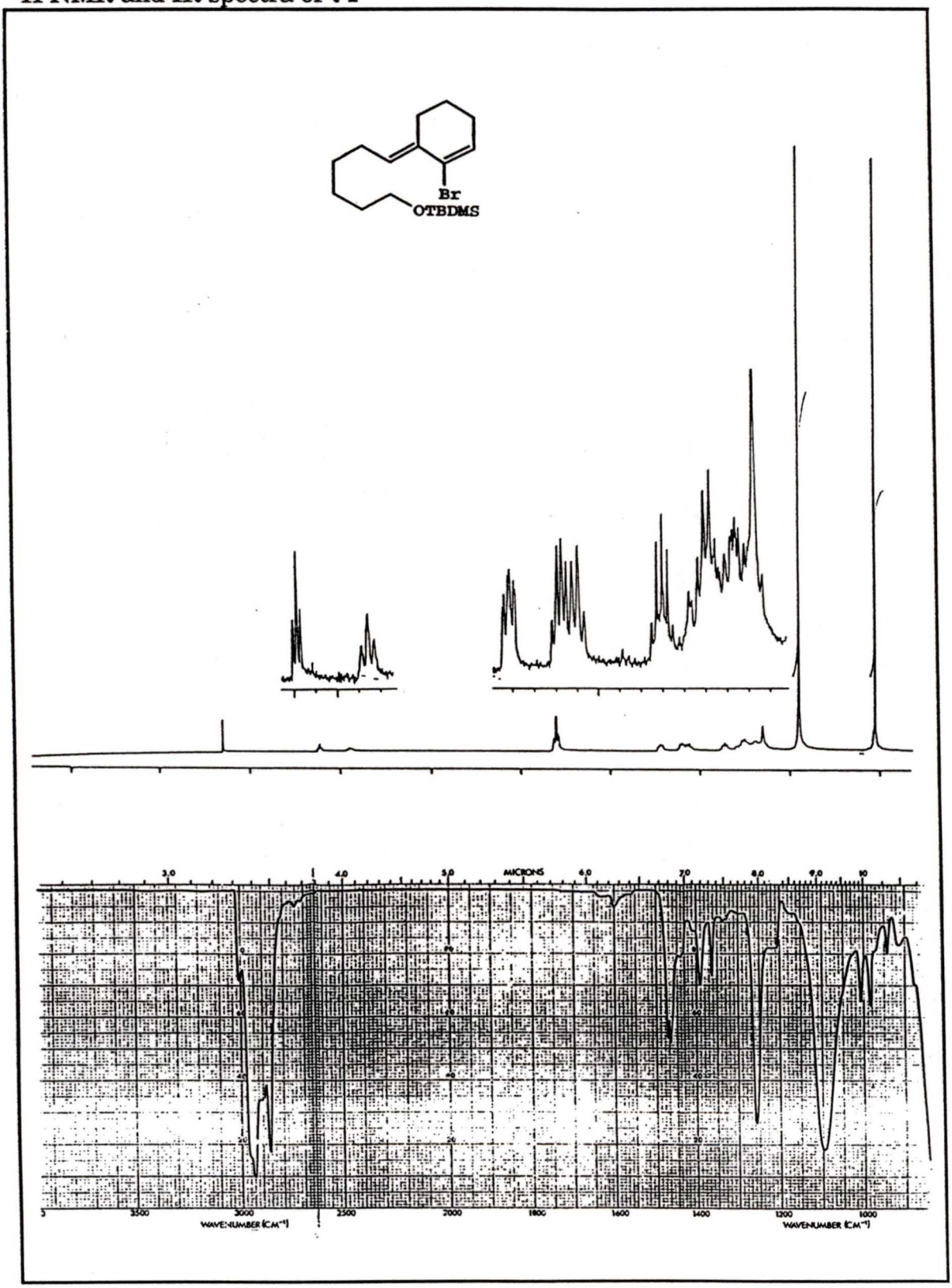


^{13}C and IR spectra of **69**

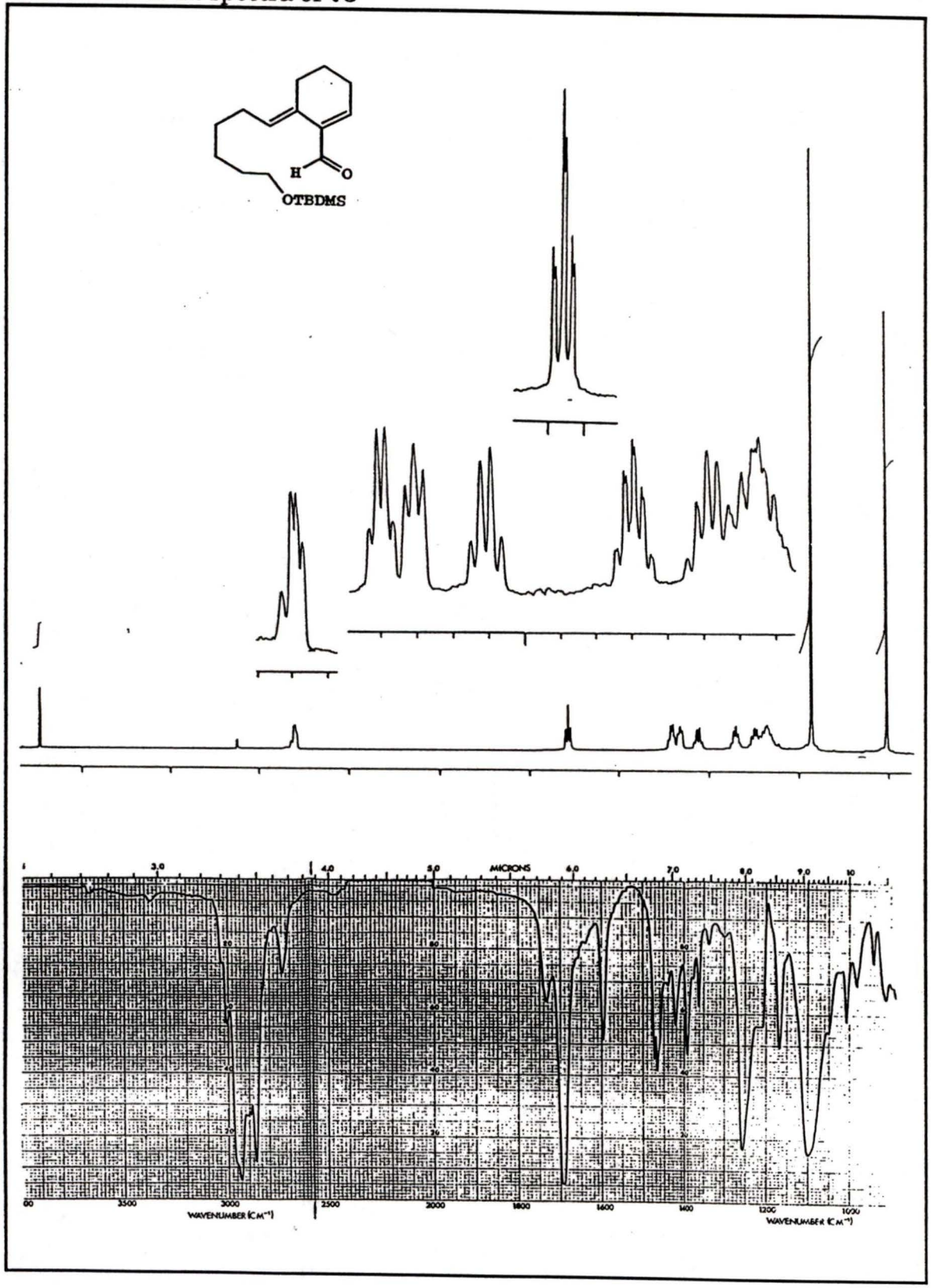




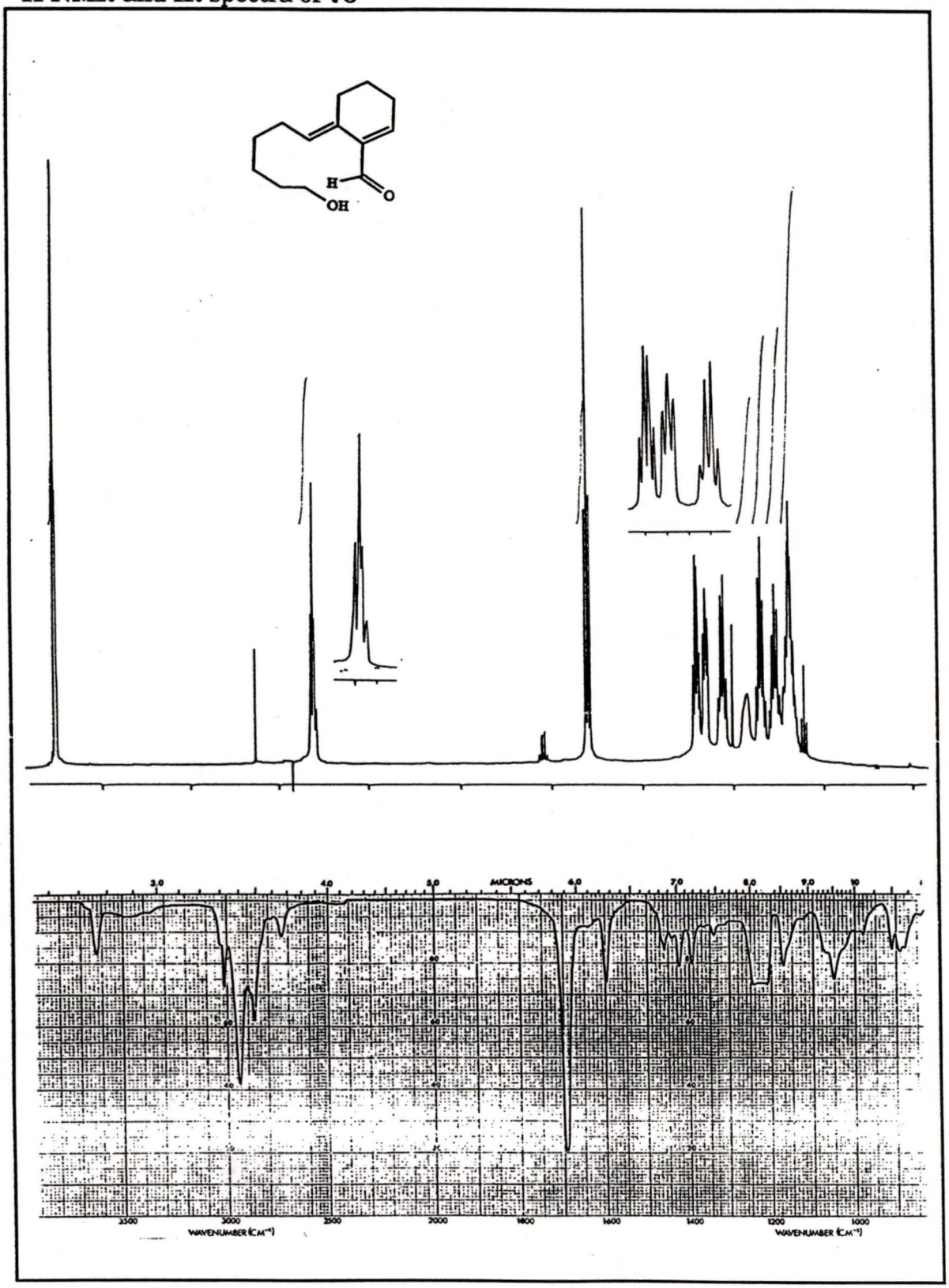
^{1}H NMR and IR spectra of 74



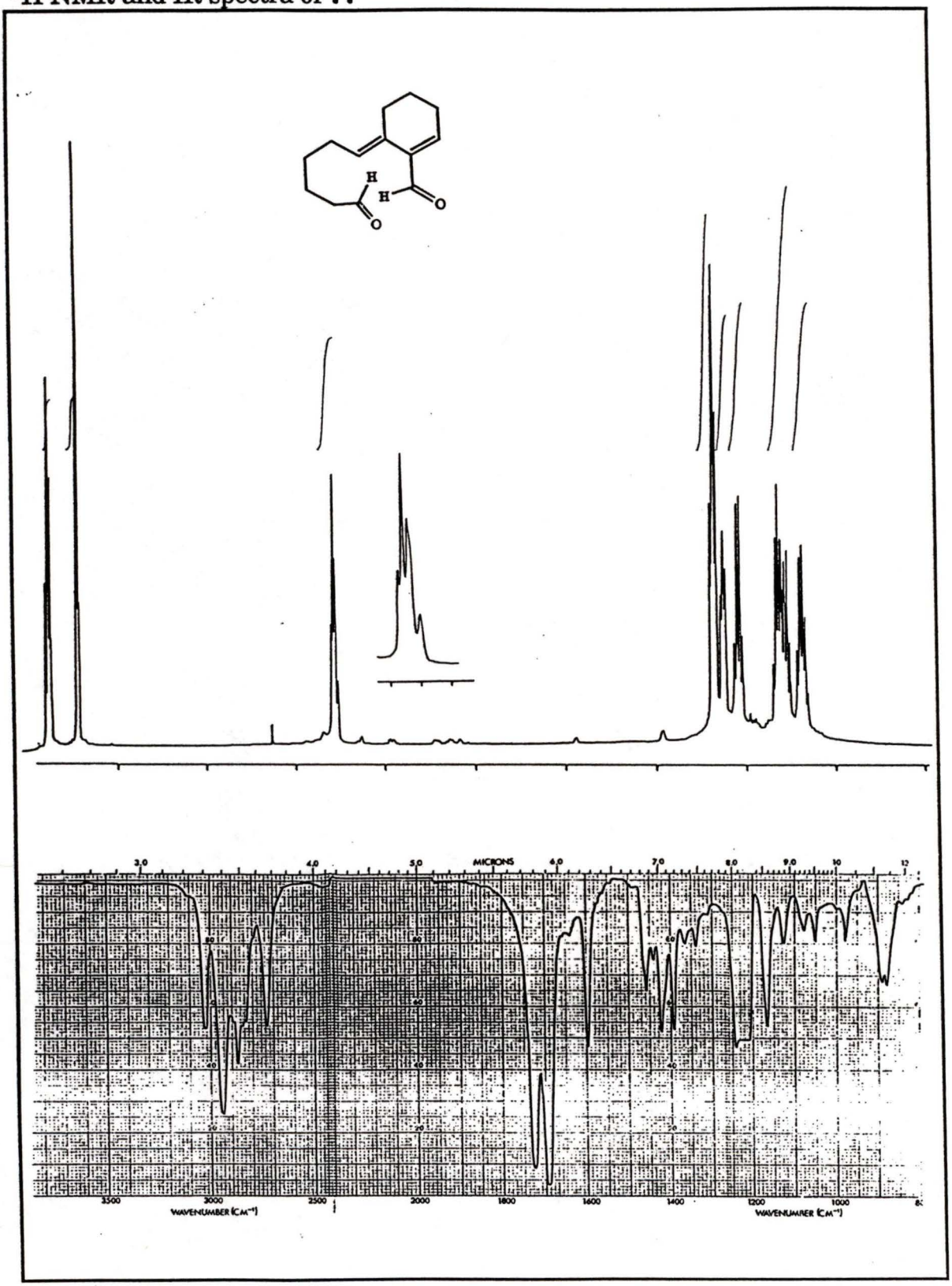
^{1}H NMR and IR spectra of **75**



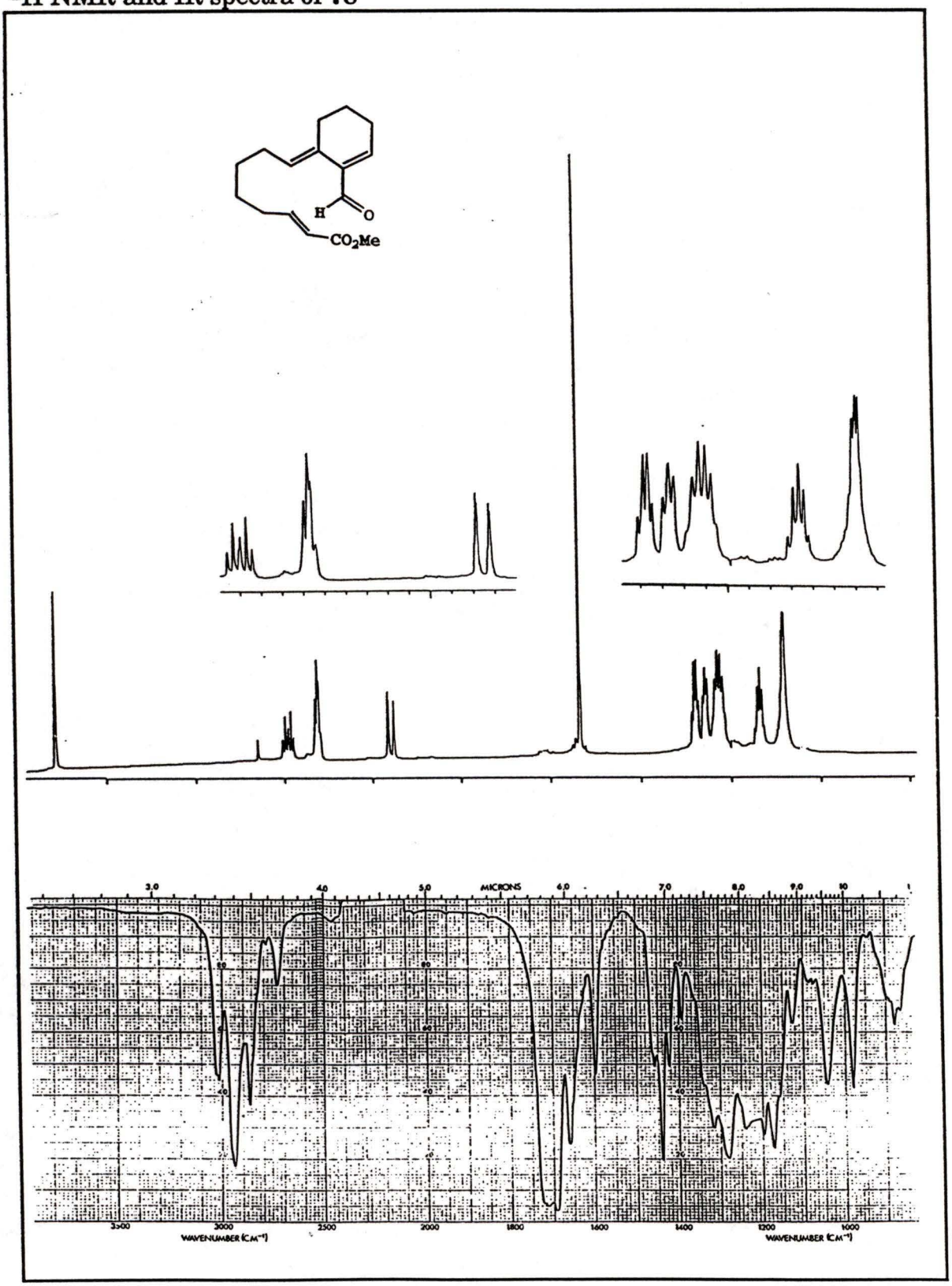
^{1}H NMR and IR spectra of 76



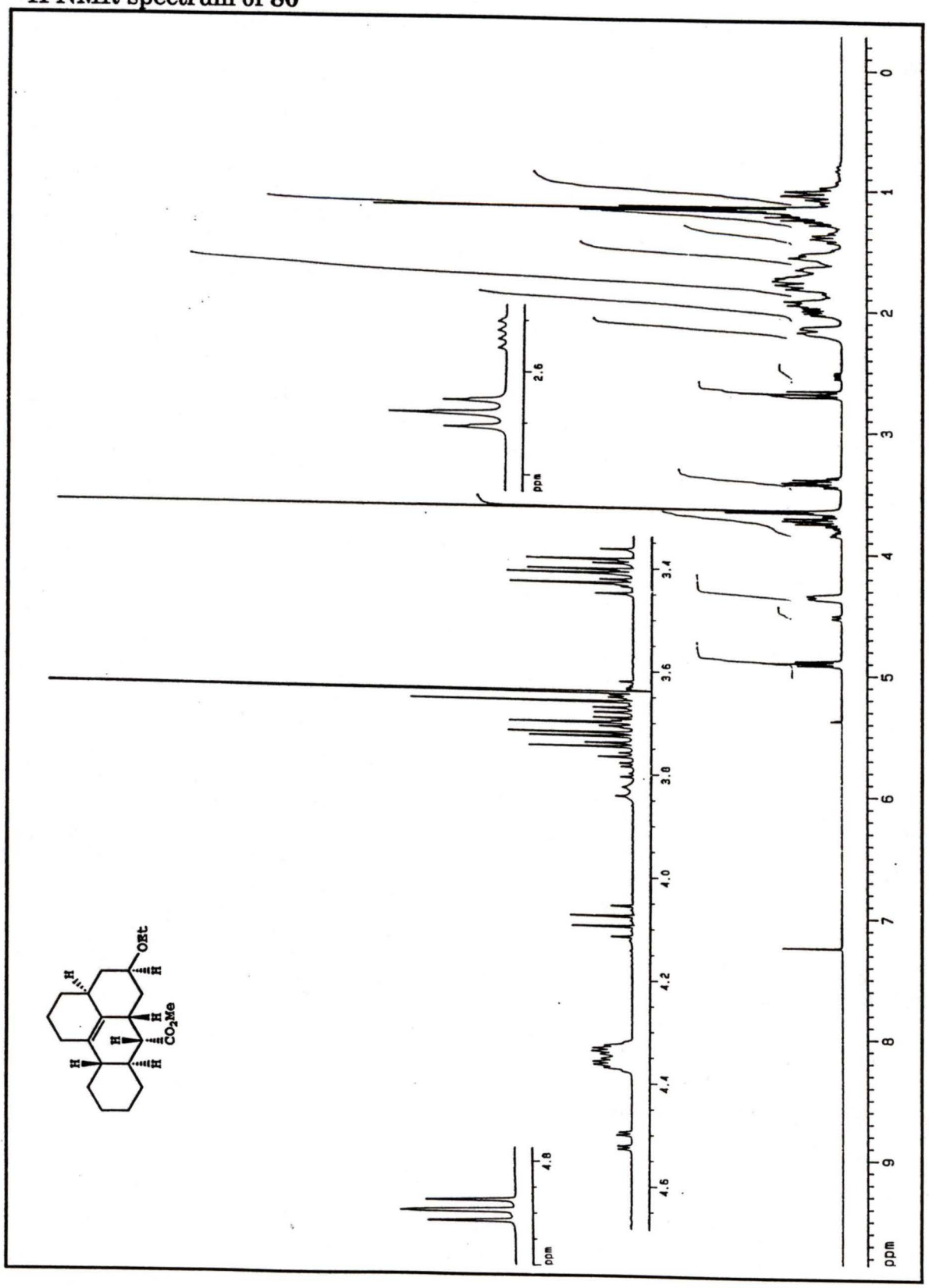
^{1}H NMR and IR spectra of 77



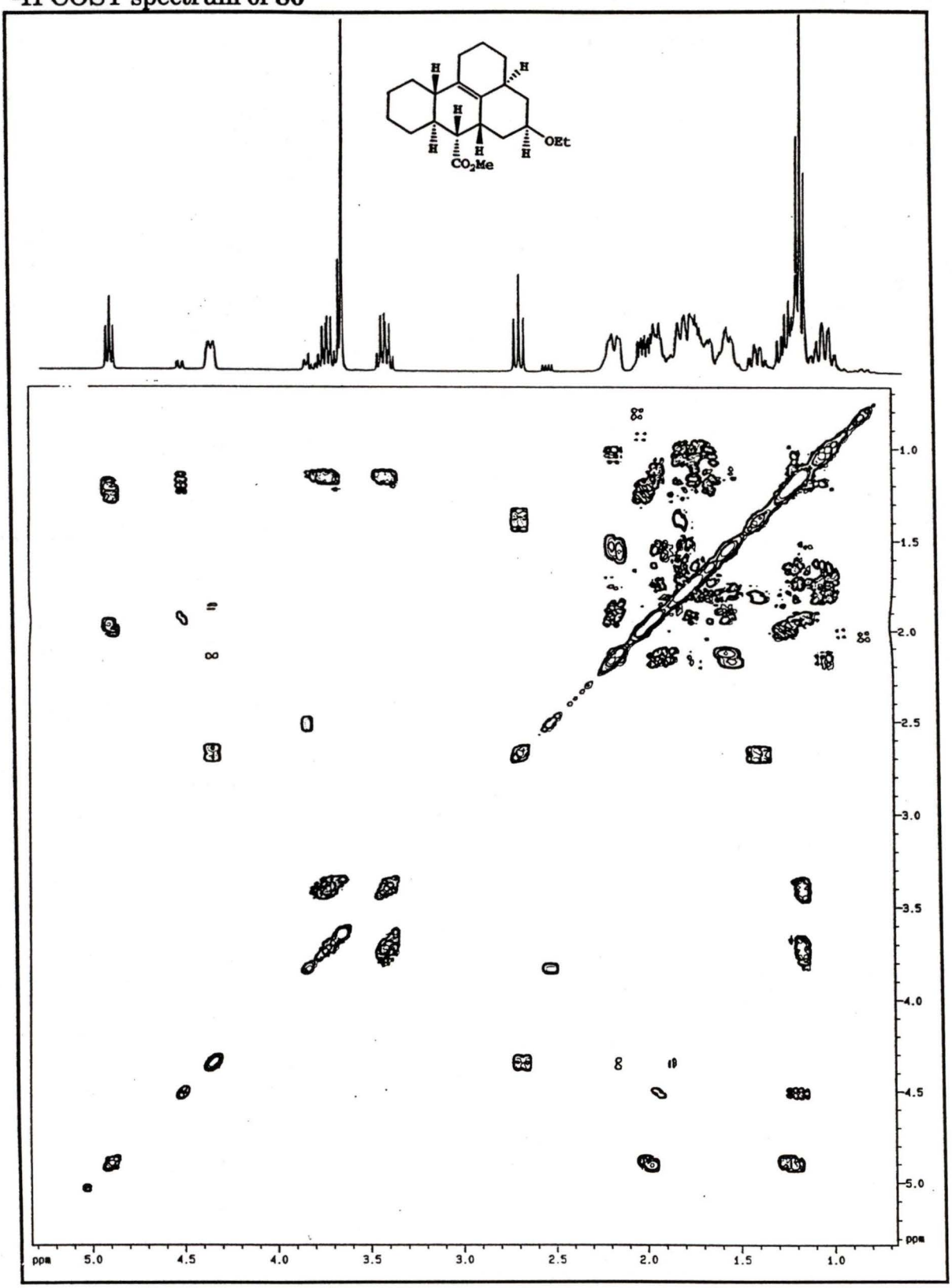
^{1}H NMR and IR spectra of 78



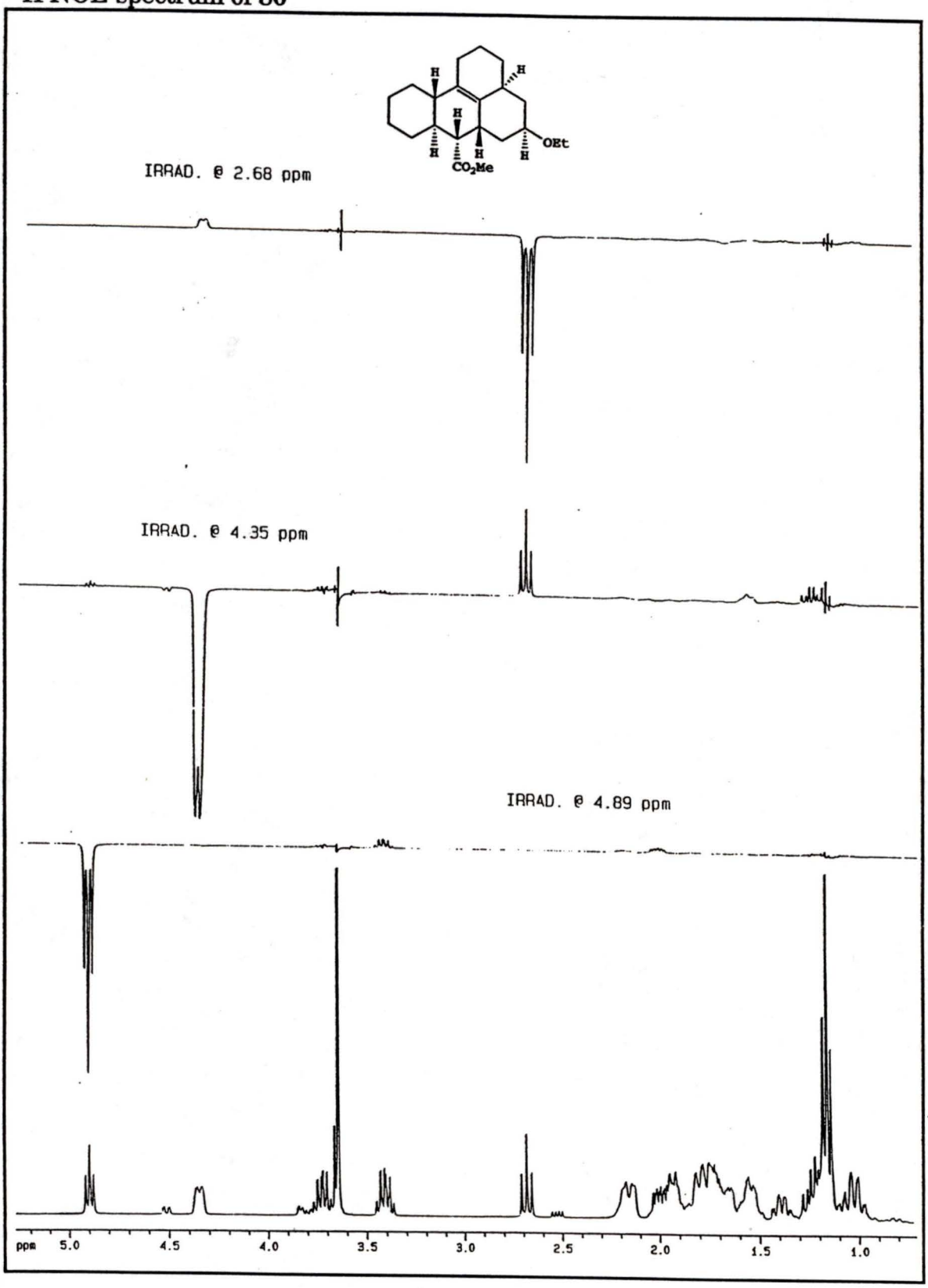
^{1}H NMR spectrum of 80



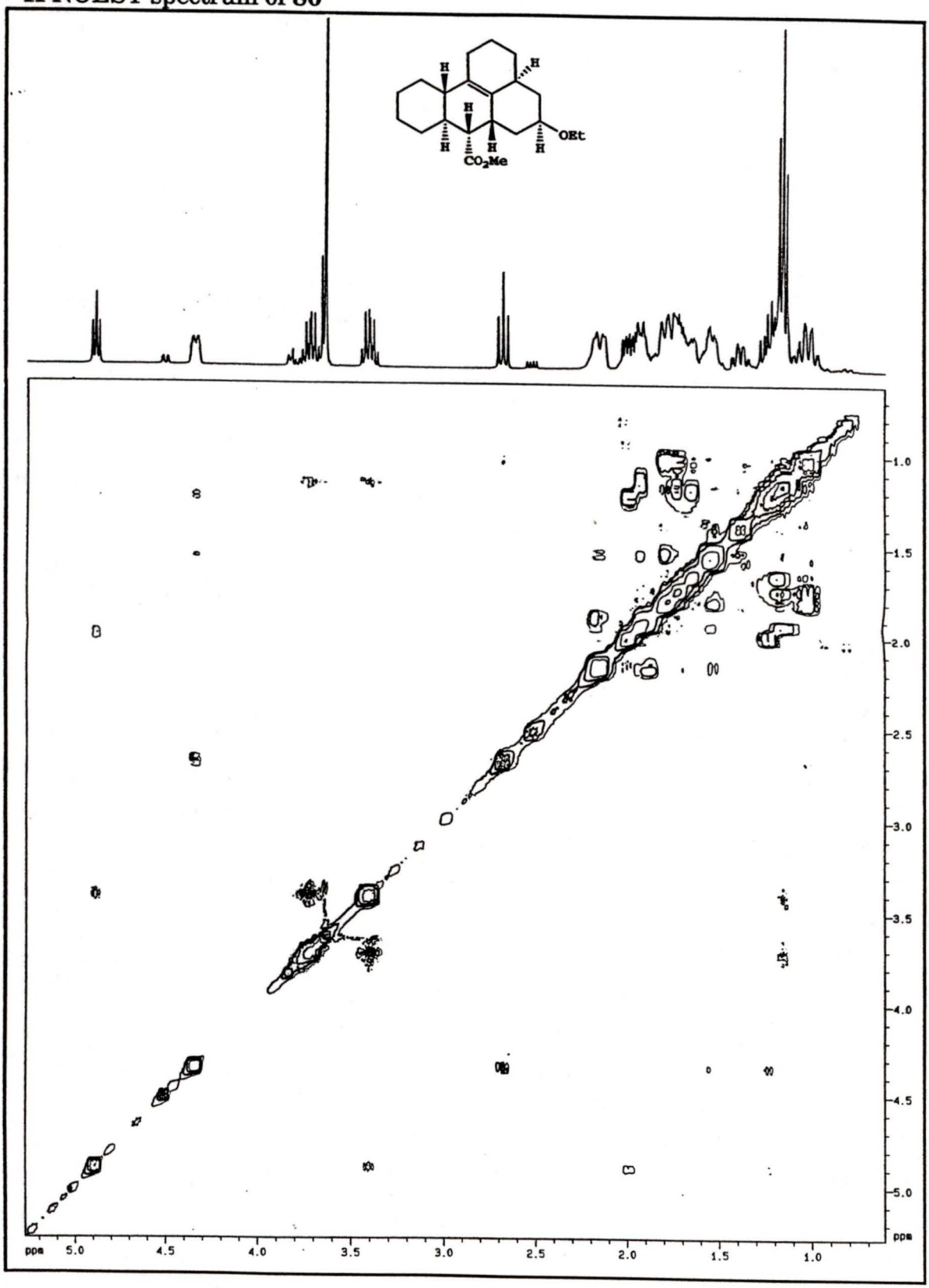
^{1}H COSY spectrum of **80**



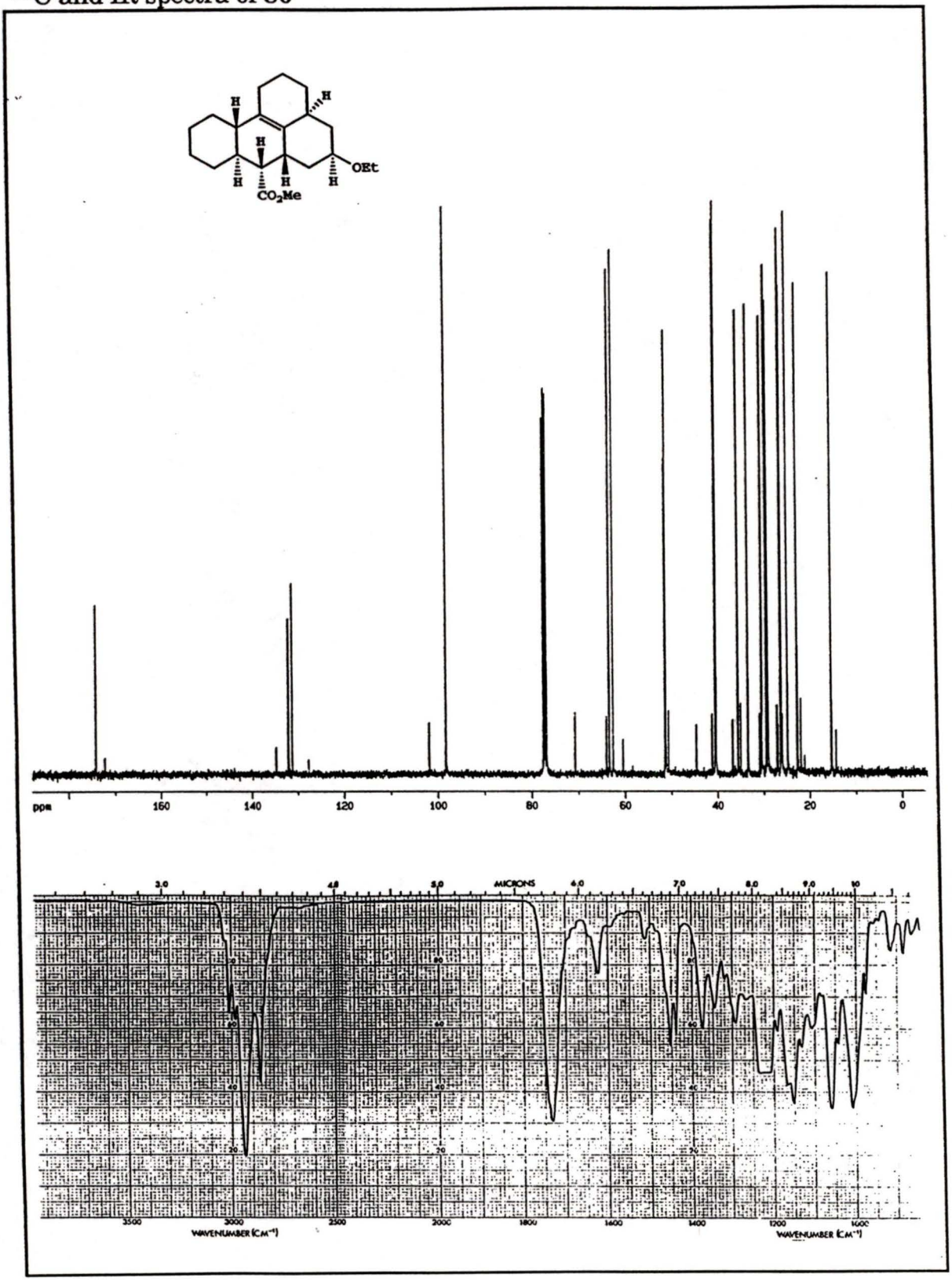
^{1}H NOE spectrum of 80



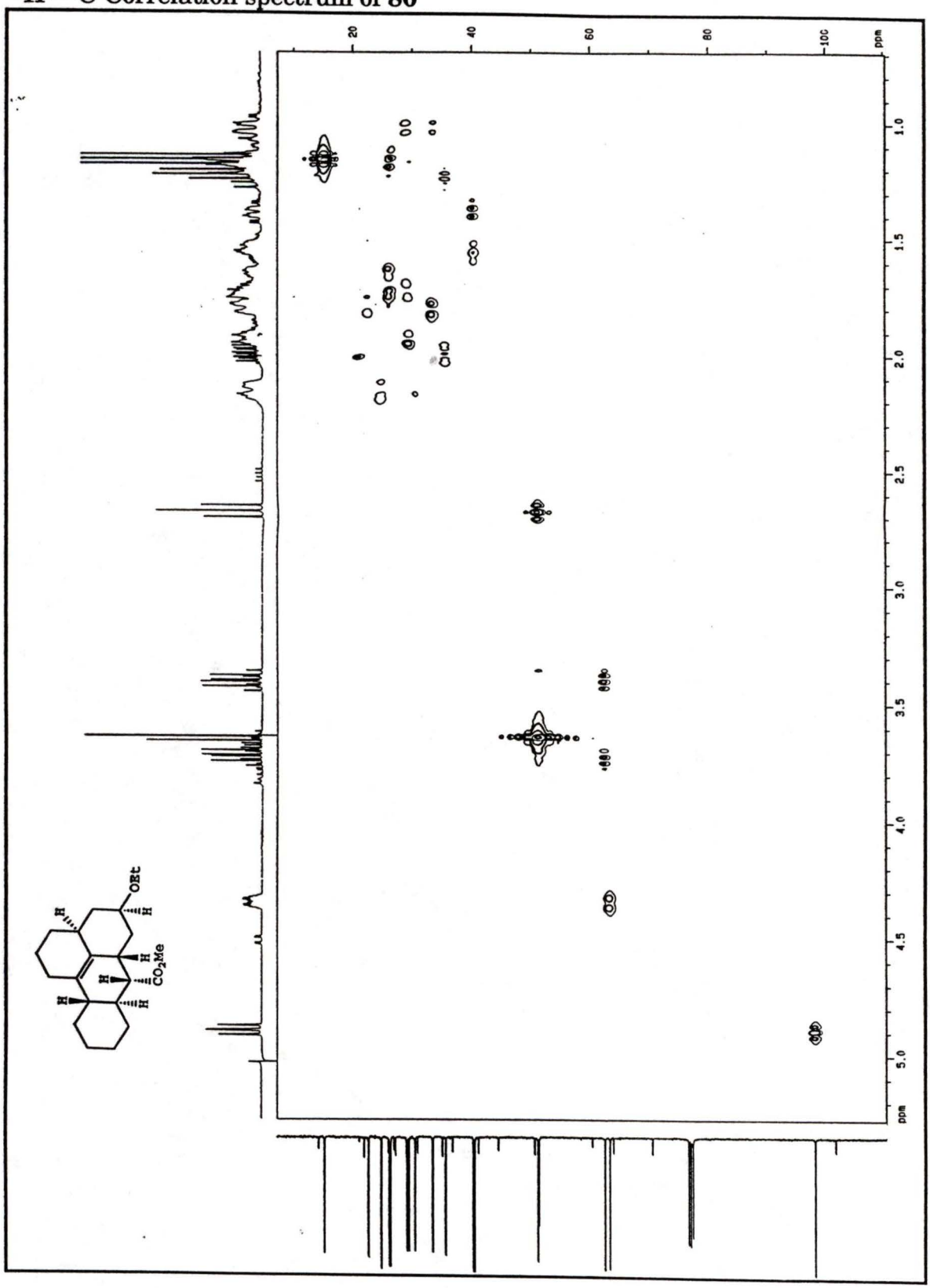
^{1}H NOESY spectrum of 80



^{13}C and IR spectra of **80**



^{1}H-^{13}C Correlation spectrum of 80



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Title of Thesis:

A Stereoselective Synthesis of the Tetracyclic Quassinoid Framework

Author: 
(signature)

GANG LIU
(Name)

March 11, 1993
(Date)