ENANTIOSELECTIVE SYNTHESIS OF TETRACYCLIC QUASSINOID INTERMEDIATES VIA A DIENE TRANSMISSIVE DIELS-ALDER STRATEGY

by

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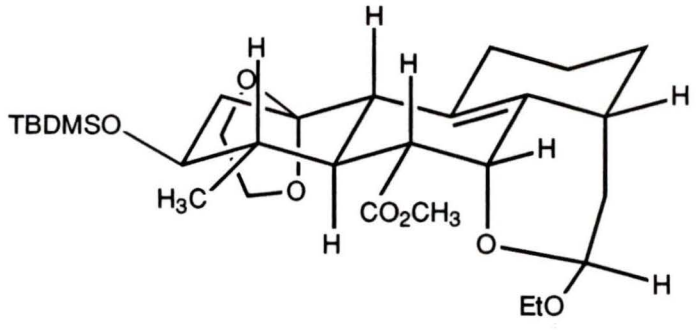

Supervisor: Dr. Claude Spino

ABSTRACT

Starting from 2-cyclohexene-1-one **62**, an enantioselective synthetic route to an optically pure tetracyclic quassinoids intermediate, compound **102**, was developed. Two bulky substituents (methyl at C_4 and *t*-butyldimethylsilyloxy at C_3) were introduced to affect the mode of the intramolecular Diels-Alder cycloaddition to the desired face which consequently controlled the absolute stereochemistry at C_5, C_6, C_7 and C_{10} of the tetracyclic compounds. This strategy, based on a diene-transmissive Diels-Alder cycloaddition, could be used for the enantioselective total synthesis of quassinoid bearing the same skeleton and stereochemistry at the ring junctions.

In addition, the added functionalities of the methyl at C_4 and *t*-butyldimethyl-silyloxy at C_3 set ring A in place for the totally synthesis of Bruceantin.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
n-BuLi	*n*-butyllithium
Bz	Benzo
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
DIBAL-H	diisobutylaluminum hydride
DMF	*N,N*-dimethylformamide
Et	ethyl
GC	gas chromatography
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
br	broad
d	doublet
dd	doublet of doublets
dt	double 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

LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MS	mass spectrum
PDC	pyridinium dichromate
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TFAA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TS	transition state
p-TsOH	*para*-toluenesulfonic acid

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I would like to express my gratitude to Dr. Claude Spino for his support and guidance throughout this project.

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Finally, I would like to thank my parents, my fiancée and all of the family members for their deep loving encouragement and patience.

Dedication

To mom

and

my wife-to-be: Lisa

CHAPTER ONE
INTRODUCTION

1.1 General Features of Quassinoids

"Quassinoids", sometimes called simaroubolides because of their origin in the plant family *Simaroubaceae*, is the generic name given to a large family of degraded triterpene natural products.[1] The Simaroubaceae family consists of six subfamilies with 32 genera and over 170 arboreous or shrubby species.[2] The largest genus is *Picramnia* with *ca* 40 species that are native to the New World tropics. The *Simaroubaceae* form a large botanical family of mostly pantropical distribution, with the exception of the genera *Picrasma* and *Ailanthus* which both extend into temperate Asia.[3] Many species of this family, for example *Quassia amara* , L. *Picraena excelsa* Lindt. and *Jamaica quassia*, have been known for many years to have a bitter taste due, in part, to substances collectively called "quassinoids". However, the isolation of individual constituents, and more importantly, the elucidation of their structures was not accomplished until modern physical techniques were available. Nuclear magnetic resonance spectroscopy, circular dichroism, mass spectroscopy and thin layer chromatography provided powerful tools for the investigation of complex natural products. During the intervening years since 1961, time at which the structure of the first quassinoid "quassin" was elucidated,[4] numerous quassinoids have been isolated and characterized. The dramatic increase in interest for the total synthesis of quassinoids in the last twenty years is a consequence of their wide range of biological activities, including antineoplastic, antiviral, antimalarial, and insect antifeeding.[1] The

complex array of stereocenters and the extent of oxygenation of the carbon skeleton make quassinoids challenging targets for the synthetic organic chemist.[5]

The naming of quassinoids are done according to the current rules of nomenclature for the picrasane nucleus. The classification can be divided into nine structural types (Type 1 to Type 9 in Figure 1.1).[6] Among the 174 quassinoids isolated up to 1991, 145 contained a Type 1 skeleton, nine are Type 2, two are Type 3, ten are Type 4, three are Type 5, two are Type 6 and one each is in the remaining three Types (Type 7 to Type 9).[6] The vast majority of the quassinoids displaying interesting biological activities belong to Type 1 and will be discussed in the following section.

1.2 Biological Activity of Quassinoids

1.2.1 Structure-Activity Relationship

Among the nine groups of quassinoids, compounds of Type 1 skeleton have demonstrated the most interesting and varied biological activities and therefore will be the only type discussed in this section. Type 1 quassinoids can be further divided into three groups (A, B, and C), where the division is made on the basis of the presence or absence of an additional ring in the form of a hemiketal (**Group A**), an ether (**Group B**), or no additional ring (**Group C**) (Figure 1.2).[7]

The quassinoids in Group A are all characterized structurally by the presence of an oxide linkage between C_8-C_{11}. The major structural differences within this group are related to the presence or absence of an ester substituent (either at C_6 or C_{15}), the presence of an α-methyl or a methylene group at C_{13}, and the oxidation state of C_1, C_2 and C_3. Those compounds which do not have an ester sidechain at C_{15} are all non-active against the P-388 leukemia system or show weak activity at high doses (>8 mg/Kg). However, compounds with C_{15} esters all show strong or

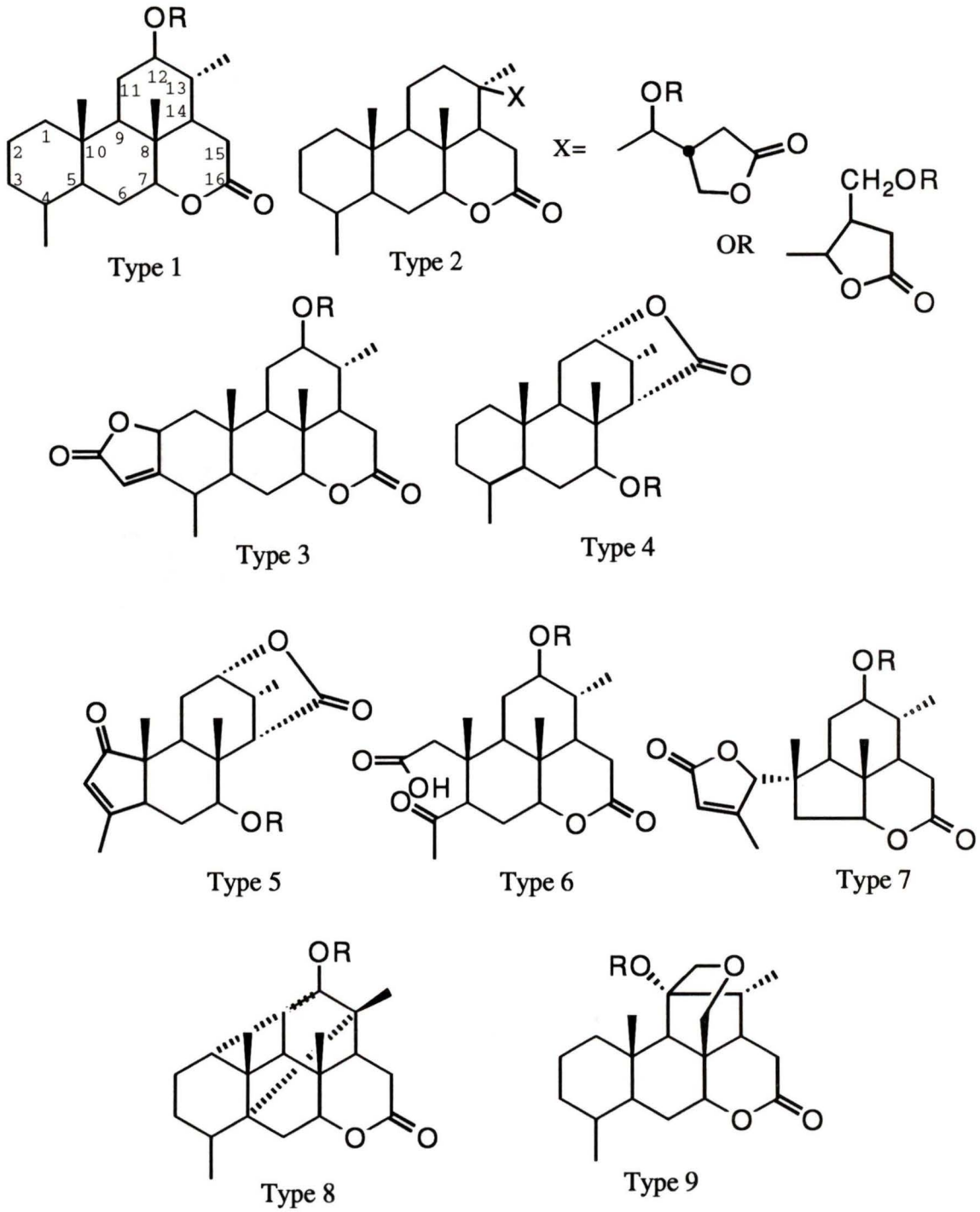
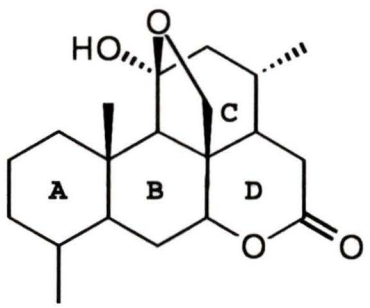
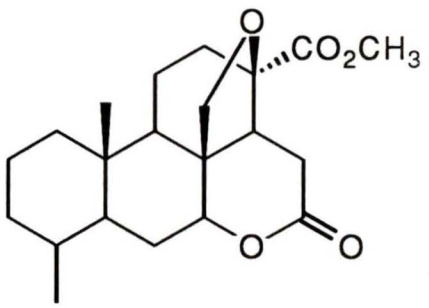


Figure 1.1 Structural Types of Quassinoids

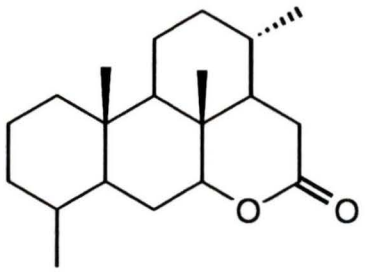
moderate activity (T/C ≥ 150) at doses in the 0.25-5 mg/Kg range (T/C is the ratio of test group survival to control group survival in tumored animals, expressed as a percentage). For example, chaparrinone **1** is only active towards P-388 leukemia at high dose range (5.0-40 mg/Kg) (T/C = 145) whereas holacanthone **2** operates in low dose range (0.13-13 mg/Kg) with high efficiency (T/C = 190) (Figure 1.3).[7] Also, it was found that the unsaturated ketone in ring A is required for optimal potency against P-388 leukemia as demonstrated by the inactivity of dihydroglaucarubolone-15-benzoate **3** at low dose range.[7]



Group A



Group B

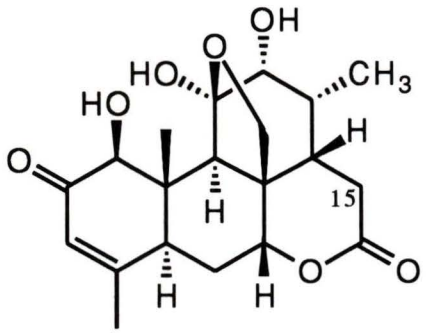


Group C

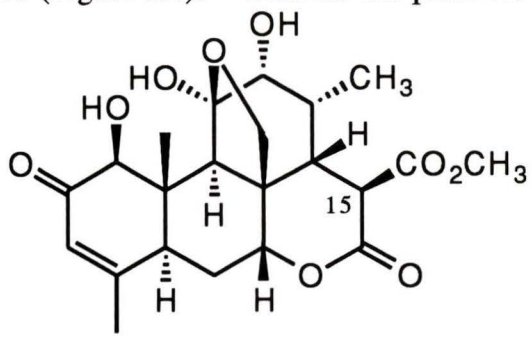
Figure 1.2 Structural group of Type 1 quassinoids

In Group B quassinoids, which possess a C_8-C_{13} oxide linkage, the nature of the ester side chain at C_{15} is much more critical to the antileukemic activity than it is

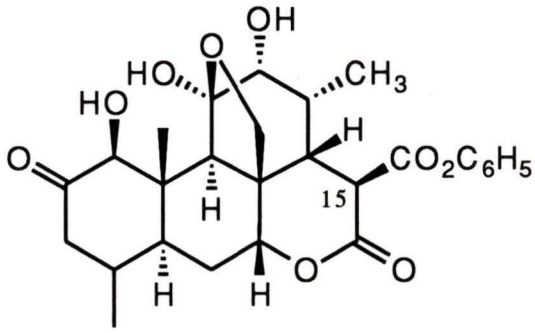
in the Group A quassinoids. For example, bruceantin **4** is highly active against P-388 leukemia but bruceine B **5** is much less active (Figure 1.4).[7] Whereas the presence of



Chaparrinone 1



Holacanthone 2



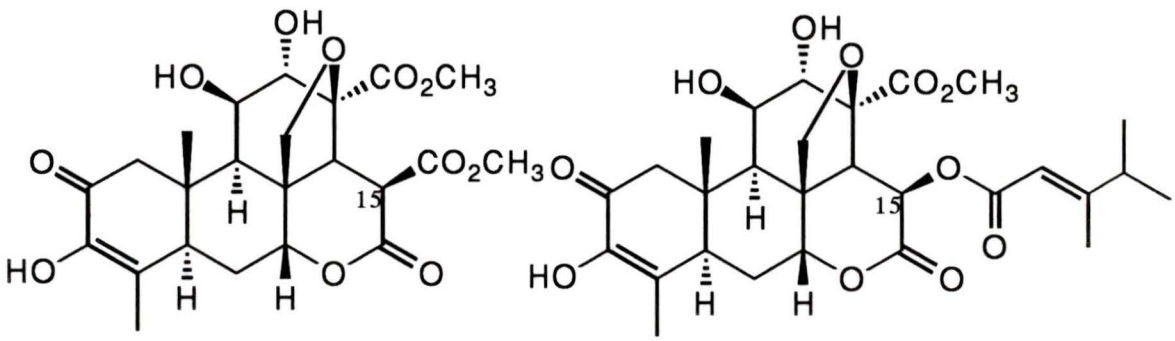
Dihydroglaucarubolone-15-benzoate 3

Figure 1.3

the oxide bridge is important, its orientation (C_8-C_{11} Vs C_8-C_{13}) is not critical for activity.[7] For example, ailanthinone **6** (Group A) and similikalactone D **7** (Group B) are of similar activity against P-388 leukemia (Figure 1.5). The structure of ring A is important in both group A and B and any deviation causes loss of activity. The most active Group A and B quassinoids possess a 1-hydroxy-2-oxo group or a diosphenol

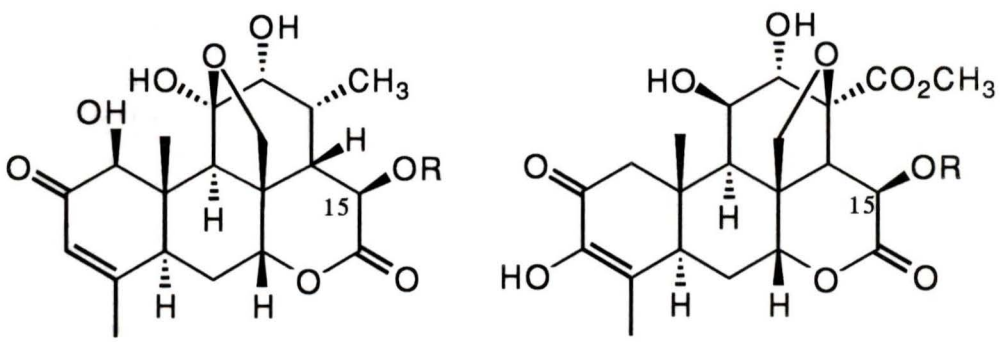
moiety as shown in Figure 1.6. Quassinoids of Group C, which do not possess an oxide bridge are all inactive biologically.

In addition, among those active quassinoids, bruceantin is by far the most potent and consistent over the broadest dose range. It has shown activity in the Colon 38, L-1210 leukemia, B16 melanoma system in mice in addition to P-388 leukemia.[7]



Bruceine B 5 **Bruceantin 4**

Figure 1.4



R=$COCH(CH_3)C_2H_5$

Ailanthinone 6 **Similikalactone D 7**

Figure 1.5

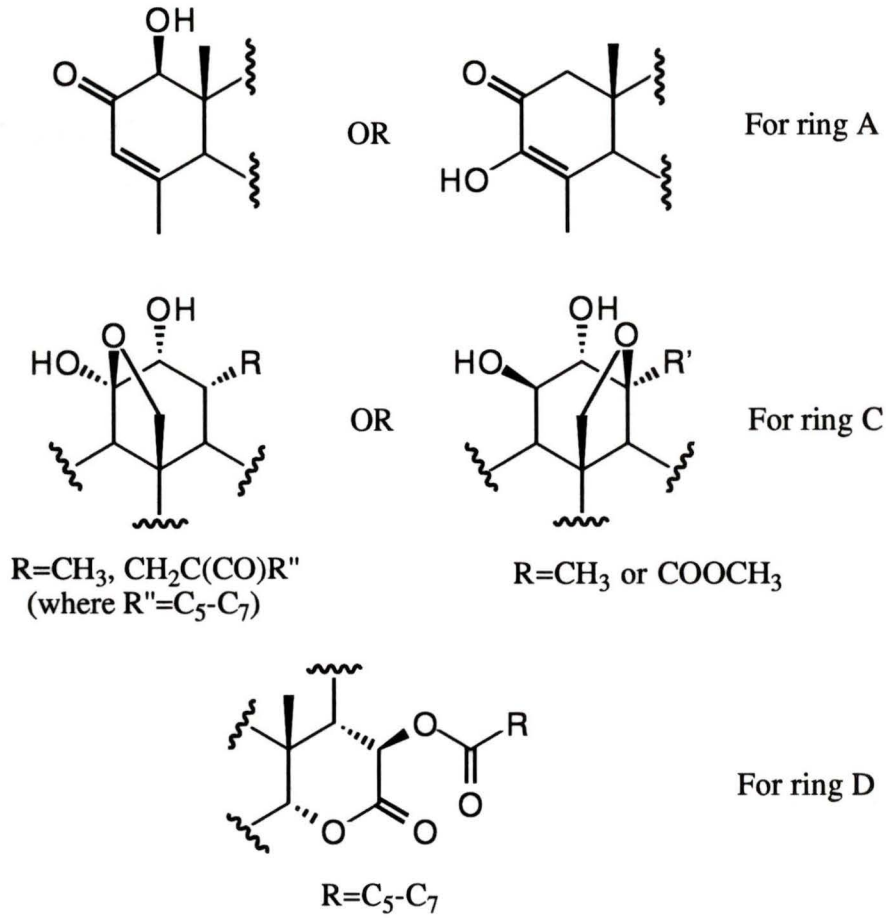


Figure 1.6 Essential features for antileukemic activity of quassinoids.

1.2.2 Clinical Studies with Bruceantin

Clinical studies of bruceantin were first conducted by Bedikian and coworkers. Sixty-six patients with various types of advanced solid tumors received 173 courses of bruceantin to evaluate its toxicity and efficiency.[8] It was found that hypotension, vomiting and fever were common at high doses. Other side effects including diarrhea, stomatitis, alopecia, paresthesia and rash. Myelosuppression was evidenced by the dramatic decrease in granulocyte and platelet counts. Out of the 58 evaluable patients, 15 showed no further growth of a previously rapidly growing tumor for at

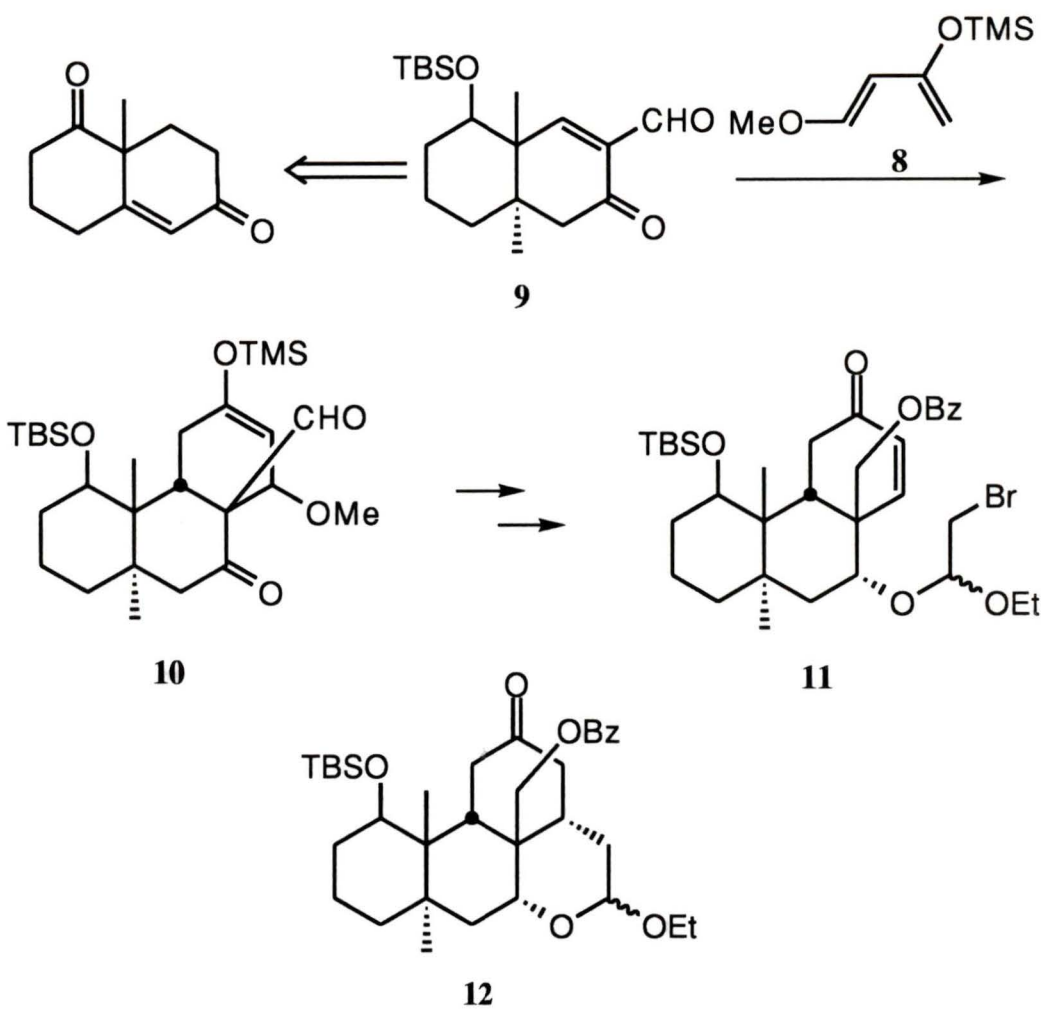
least 8 weeks. 24 showed no objective responses and 19 showed tumor progression. The results from the above study also showed that the maximum dose of bruceantin recommend in humans is 3.5 mg/m^2/day.

1.3 Synthetic Approaches to Quassinoids

As mentioned in the previous section, the many contiguous chiral centers and highly oxygenated carbon framework of the quassinoids make them very challenging target molecules for synthetic organic chemists. In 1980, almost two decades after its structure was elucidated, Grieco and coworkers first reported the synthesis of the parent quassinoid, quassin.[9] This was later followed by his total syntheses of castelanolide in 1982,[10] klaineanone in 1989,[11] shinjulactone D in 1991,[12] bruceantin,[13] chaparrinone, glaucarubolone and glaucarubinone in 1993.[14] Efforts from laboratories of Fuchs,[15] Watt,[16] Ganem,[17] Kraus,[18] Kametani,[19] Takahashi,[20] and Heathcock,[21] have also culminated in total syntheses of quassinoids. A brief outline of different approaches to the quassinoid skeleton is given below:

1.3.1 Watt's Approach

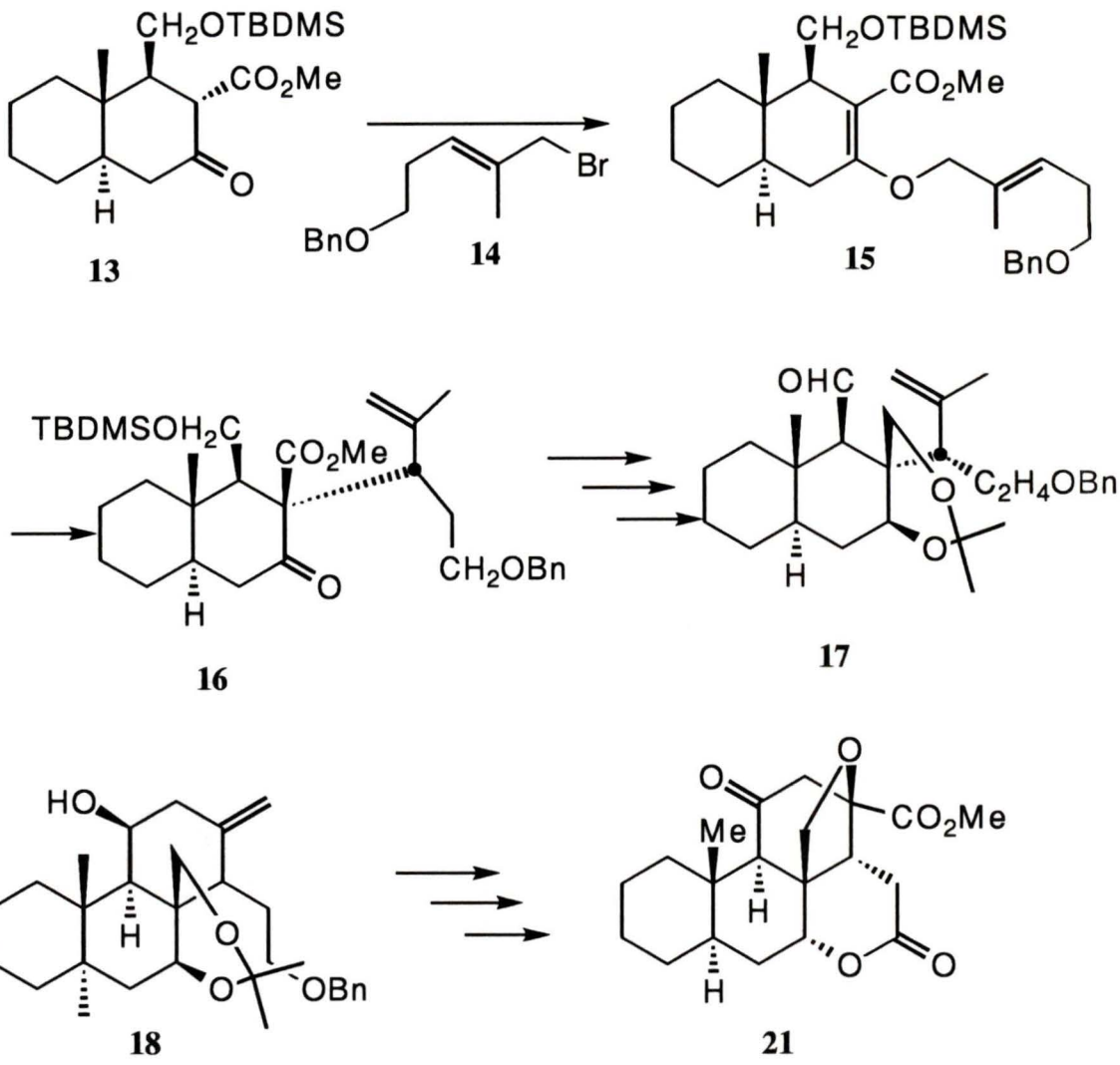
A synthesis of the ABCD rings skeleton of quassinoids **12** was developed by Watt and coworkers in 1988 (Scheme 1.1).[22] The key reaction of this approach is based on the Diels-Alder reaction of the highly electronically activated diene **8** (Danishefsky's diene) and the dienophile **9**. The resulting adduct **10** was then converted to the racemic compound **11** in two steps. When **11** was subjected to reductive tri-*n*-butyltin hydride condition, a free radical cyclization of the α-bromo acetyl resulted in the formation of tetracycle **12**.



Scheme 1.1

1.3.2 Ziegler's Approach

Ziegler and co-workers investigated a strategy for the synthesis of the pentacyclic ring system of bruceantin (Scheme 1.2).[23] Compound **15** was prepared by the O-alkylation of the β-keto ester **13** and the allylic bromide **14**. The key reaction



Scheme 1.2

involved heating compound **15** to give a single, diastereomeric Claisen rearrangement product **16**. Subsequent functional transformations on **16** gave aldehyde **17** which underwent a Lewis acid catalyzed ene reaction to give Compound **18**. Compound **18** was transformed in several steps to the pentacyclic bruceantin skeleton **21**.

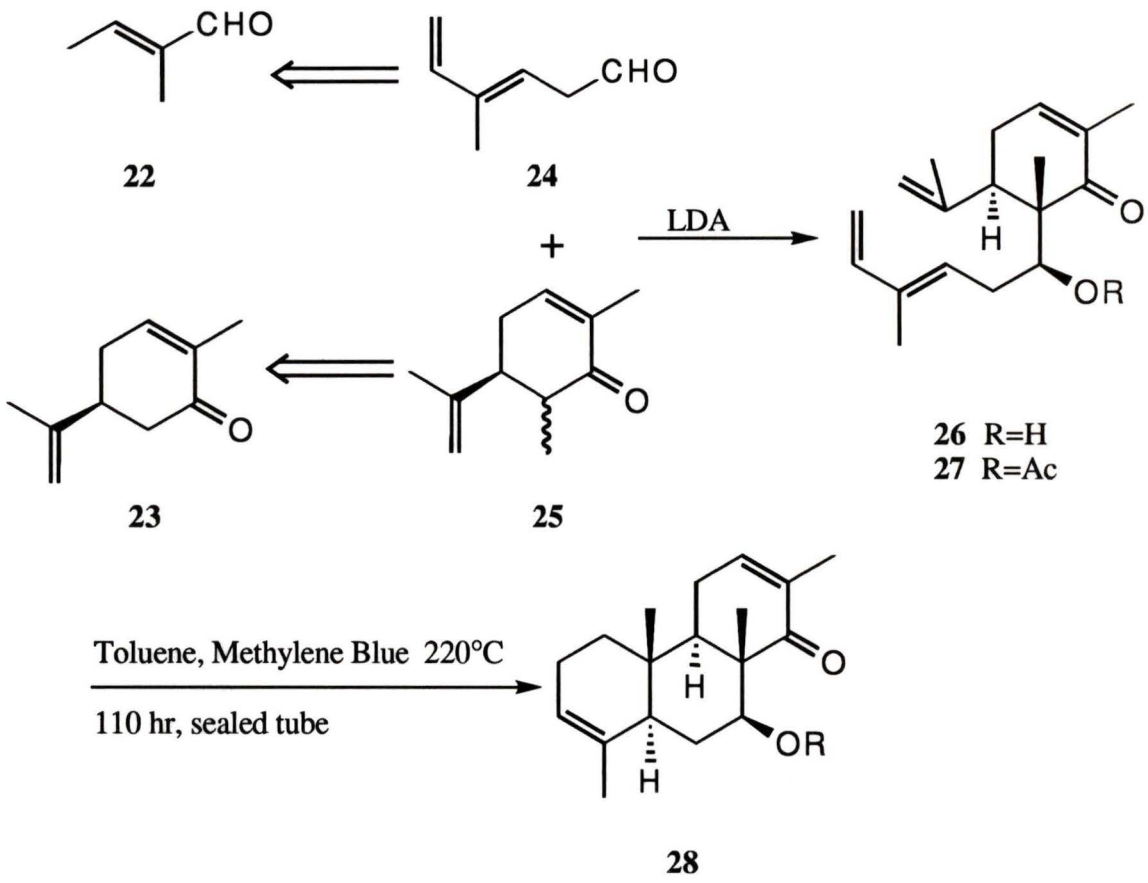
1.3.3 Aldol Condensation and Intramolecular Diels-Alder Reaction Approach

In 1989, Shing *et al* carried out an enantioselective synthesis of the ABC rings of the quassinoid skeleton based on a stereocontrolled aldol condensation and an endo-selective intramolecular Diels-Alder cycloaddition (IMDAC) (Scheme 1.3).[24]

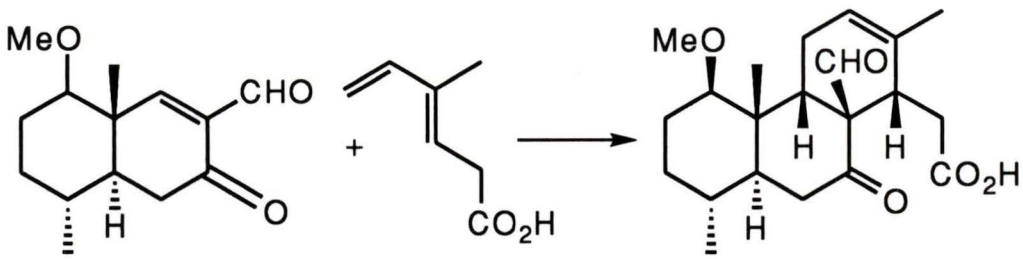
The aldol condensation between **24** and **25**, prepared from tiglic aldehyde **22** and (*S*)-carvone **23** respectively, occurred with the aldehyde approaching towards the less hindered α-face of the enolate. This secured the desired stereochemistry of the angular methyl group and of the hydroxyl group in **26**. The alcohol group was then protected as an acetate to yield triene **27** which then underwent an IMDAC to give **28** as the only product. The stereochemical outcome indicates that the reaction proceeded *via* an *endo*-chair-like transition state.

1.3.4 Grieco's Approach

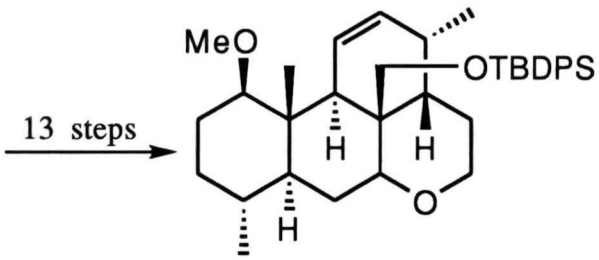
In 1993, Grieco *et al* synthesized three quassinoids, namely (-)-chaparrinone, (-)-glaucarubolone and (+)-glaucarubinone (Scheme 1.4).[13] Diels-Alder reaction of dienophile **29** and diene **30** gave the tricyclic ketone **31**. A stereoselective reduction of ketone **31** occurred exclusively from the β face permitted the construction, in a 12 step reaction sequence and a correction of the stereochemistry at C_9, of the Compound **33**. The latter was then used as the common building block for conversion to the following: (-)-chaparrinone **34** in 14 steps, (-)-glaucarubolone **35** in 20 steps and (+)-glaucarubinone **36** in 17 steps.[13]


CHO
CHO
22
24
+
LDA
H
O
OR
26 R=H
27 R=Ac
O
23
25
Toluene, Methylene Blue 220°C
110 hr, sealed tube
H
O
OR
H
28

Scheme 1.3



29 **30** **31**



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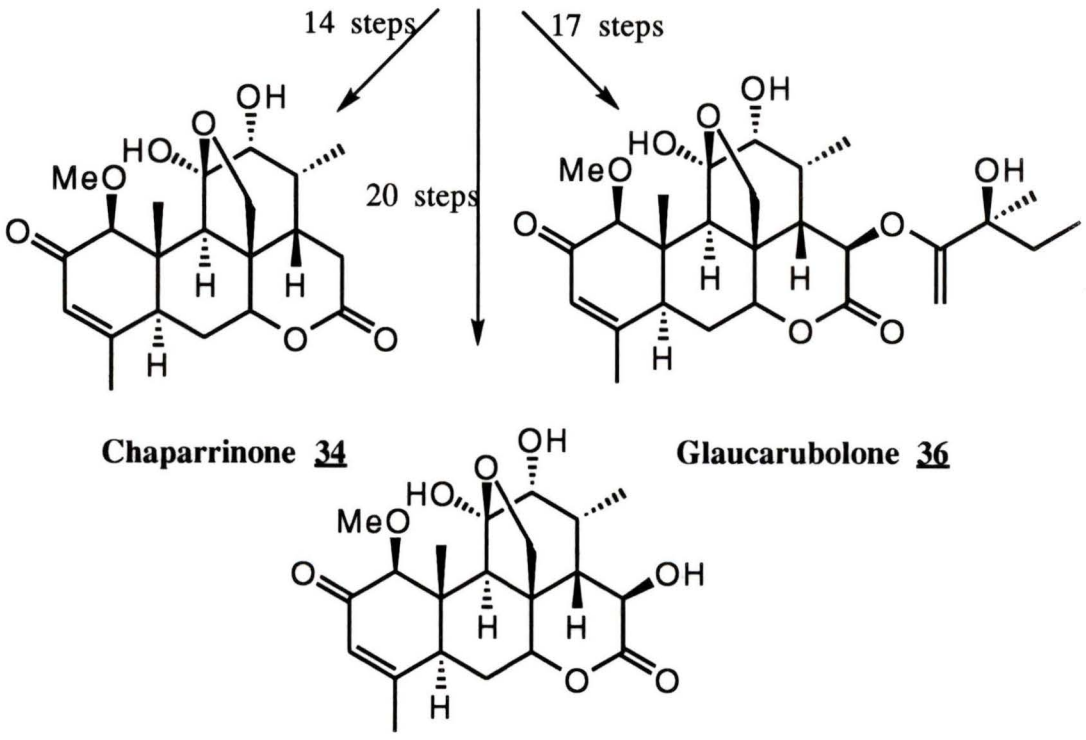


Chaparrinone 34 **Glaucarubolone 36**

Glaucarubinone 35

Scheme 1.4

1.4 The Diels-Alder Cycloaddition.

The Diels-Alder reaction, since its discovery more than 60 years ago by O. Diels and K. Alder, has become one of the most powerful tools in synthetic organic chemistry.[25] Its ability to simultaneously generate two carbon-carbon bonds (or carbon-hetero bonds) and four chiral centers with highly predictable stereoselectivity makes it applicable for numerous synthetic challenges which are often inaccessible by other means.

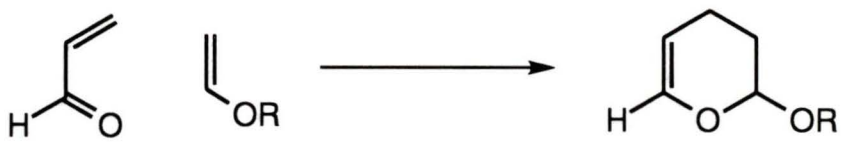
The Diels-Alder reaction can be of three general types; the intermolecular,[25] the intramolecular,[26] and the transannular types.[27] The intermolecular version involves a diene and a dienophile from two separate molecules (bimolecular reaction). On the other hand, the intramolecular and the transannular versions have the diene and dienophile contained within the same molecule (unimolecular reaction).

In our effort towards the synthesis of tetracyclic quassinoid structures, the role of the Diels-Alder reaction is inevitably important. The following paragraphs describe the type of Diels-Alder reactions that are pertinent to our synthesis.

1.4.1 The Intermolecular Hetero Diels-Alder Cycloaddition

Where one or more carbon atoms of the diene and/or dienophile have been replaced by hetero atoms, such as oxygen or nitrogen, the reaction is called a hetero Diels-Alder reaction.[28,29] One of the most widely used diene in the hetero Diels-Alder reaction involves α,β-unsaturated aldehydes **36** and electron rich vinyl ethers **37** (Scheme 1.5). This cycloaddition produces cyclic ethers regioselectively which can then be elaborated into several natural or unnatural products, including carbohydrates, polyether antibiotics and others.[29] The reaction is of the "inverse electron-demand" type controlled by a $HOMO_{dienophile}$-$LUMO_{diene}$ interaction in contrast to the normal

Diels-Alder reaction ($HOMO_{diene}$-$LUMO_{dienophile}$) (Figure 1.7). The uncatalyzed version of the inverse electron demand Diels-Alder cycloaddition usually proceeds only at elevated temperature and pressure.[30] However, it has been found that reaction of this type can be catalyzed by some Lewis acids.[31] One such a catalyst is the soluble lanthanide complex $Yb(Fod)_3$ (tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium).[32] The mild properties of this catalyst minimizes any side reaction with other fragile functional groups existing in the molecule. The catalyst chelates the carbonyl oxygen to form a complex, which lowers the LUMO energy (increase the frontier orbital coefficient) thus increasing the rate of reaction (Figure 1.8). In addition, *endo*-selectivity is increased due to an increase of the oxygen orbital coefficient (Figure 1.8). The regioselectively of this reaction is consistent with the FMO theory.[33] The use of only a few mole percent of catalyst is required for the reaction to proceed at a reasonable rate at room temperature.



36 **37**

Scheme 1.5

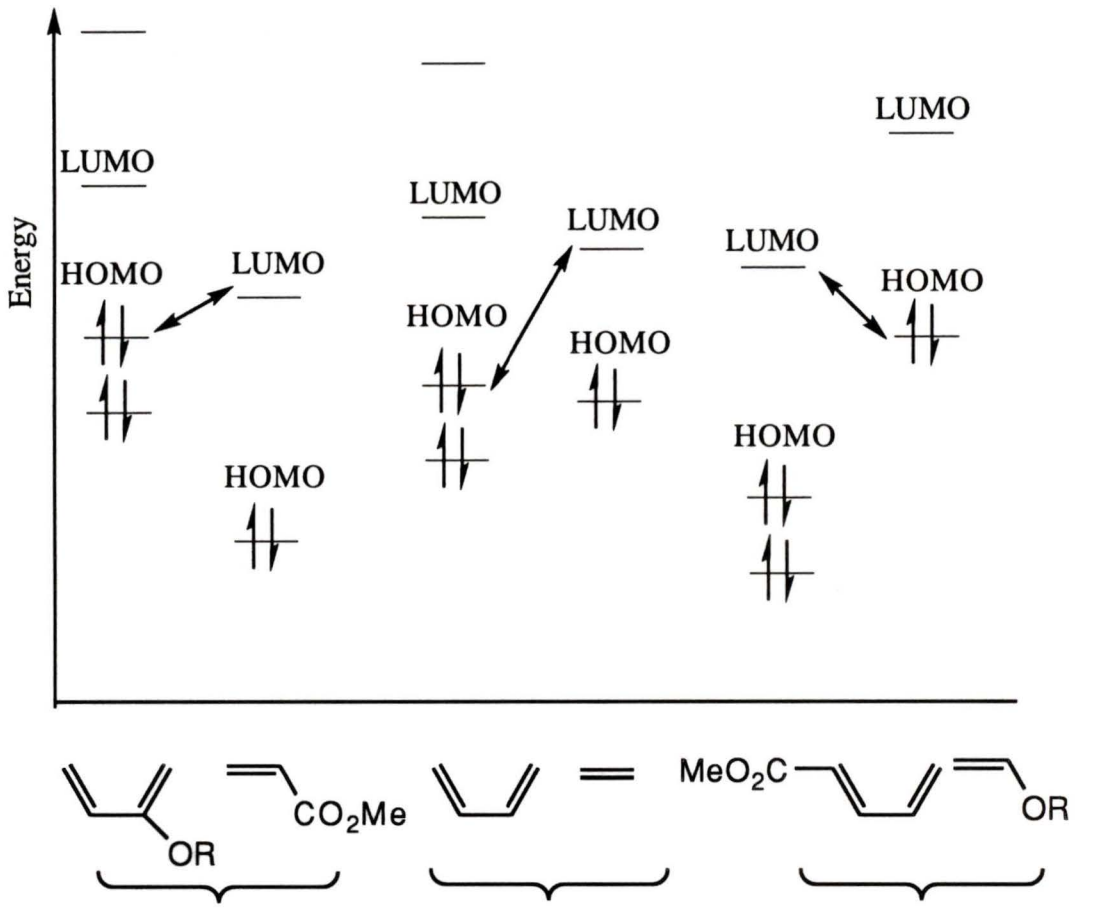


Figure 1.7 Relative positions of frontier orbitals in Diels-Alder reactions. (Double-headed arrows indicate main interaction)

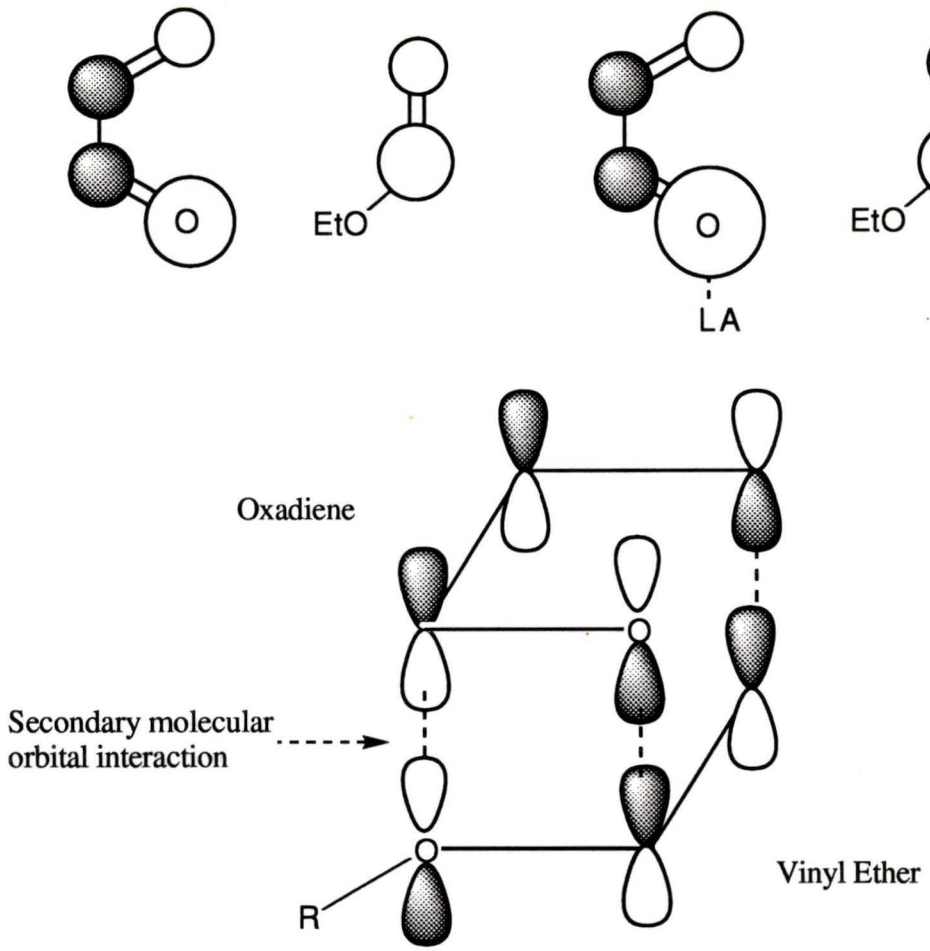


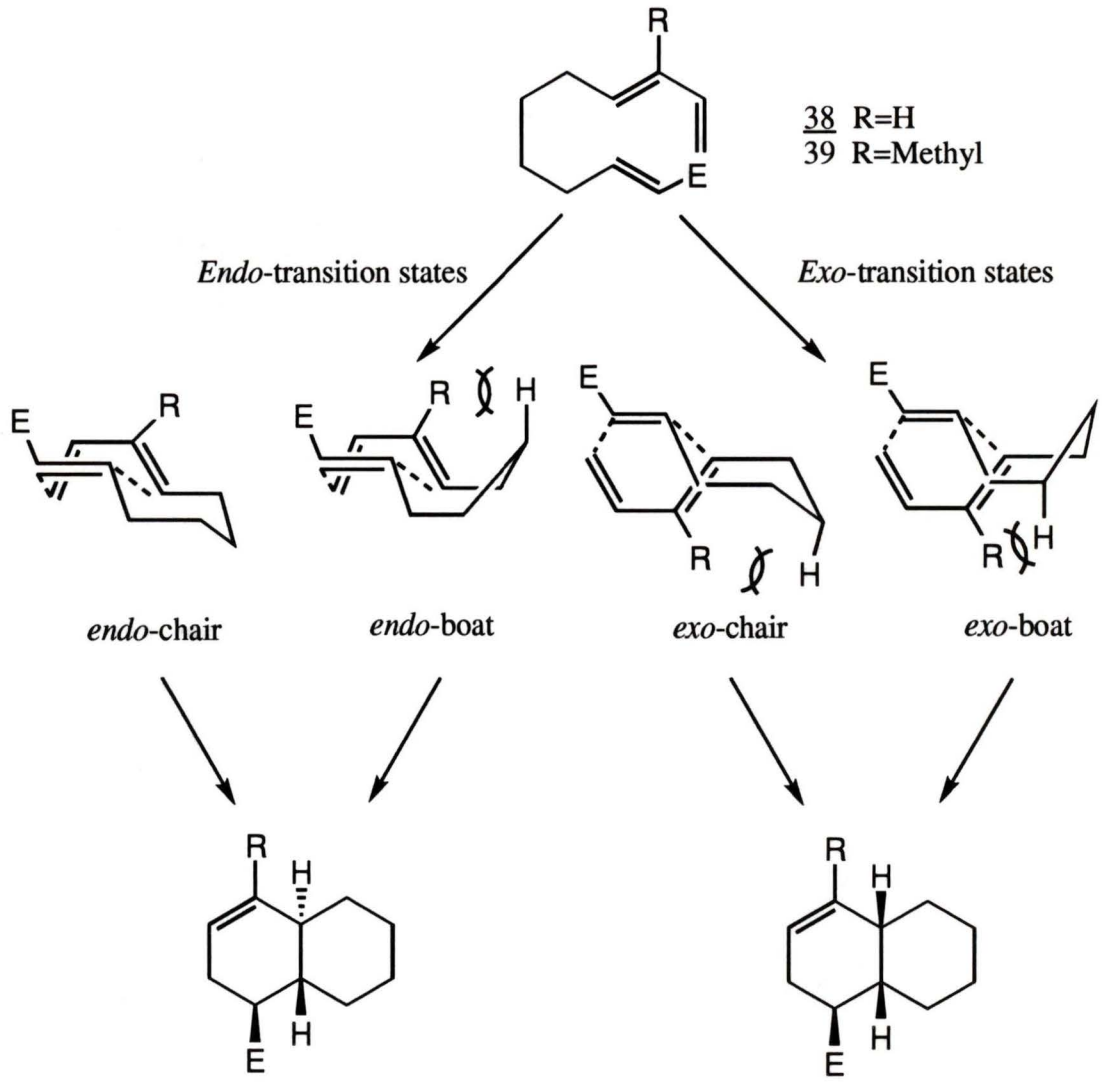
Figure 1.8 Effect of Lewis Acid (LA) catalyst on frontier orbital coefficients and *Endo*-Transition state between oxadiene and vinyl ether.

1.4.2 The Intramolecular Diels-Alder Cycloaddition Reaction (IMDAC)

Although over thirty years younger than its bimolecular counterpart, the intramolecular Diels-Alder reaction has gained a special status in modern organic synthesis.[34] It has been widely used in the construction of bicyclic [4.4.0] ring systems with high level of stereochemical control.[34] This type of ring system is common to a great number of natural products, including terpenoids, steroids, and others.[34]

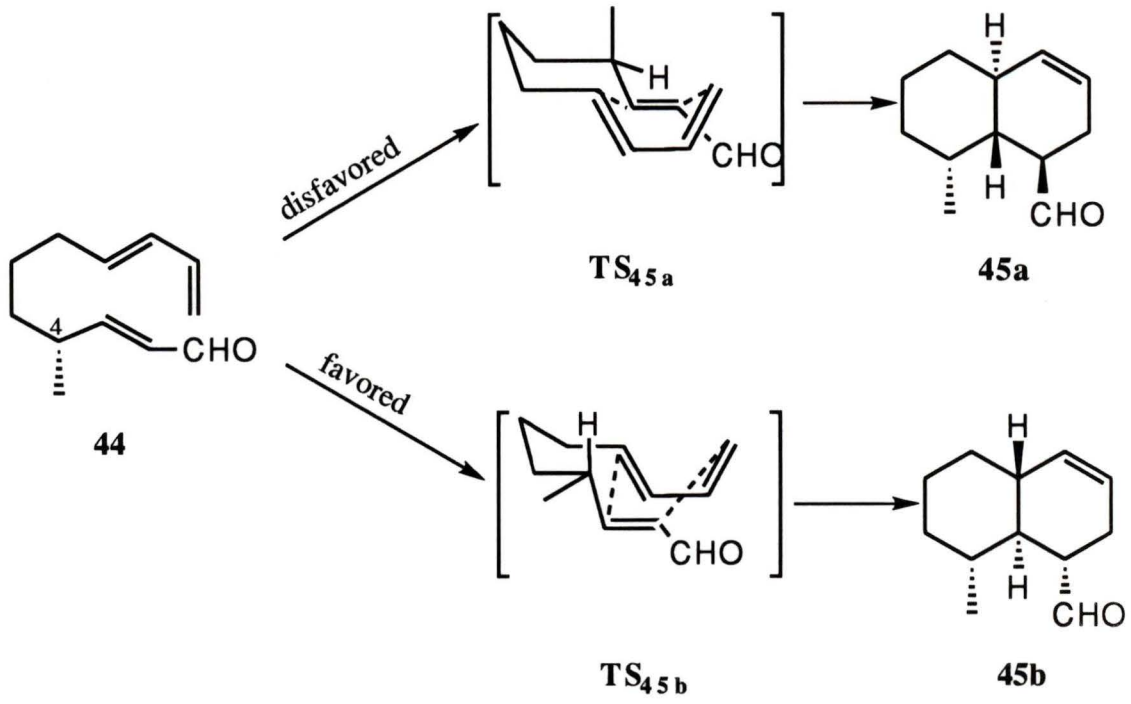
The IMDAC of *E,E*-1,3,9-decatriene **38** (R = H) may proceed *via* four distinct transition states which lead to two different products **40** and **42** (Scheme 1.6).[35] However, substituent can greatly affect the ratio of *trans*- and *cis*-fused products. For example, when R = Methyl (Compound **39**) (Scheme 1.6), a 1,4 diaxial interaction between the methyl and hydrogen will disfavor the formation of the two *boat*- and the *exo*- chair like transition states. This results in the exclusive formation of the *trans*-fused product.[36] Also, it is found that the formation of the *endo*-adduct is faster because of the possible secondary molecular orbital interaction (orbitals that are not directly involved in forming new bonds, cf. Figure 1.8) which lower the energy of the *endo* transition state relative to that of the *exo* transition state.[29]

In 1986, Marshill *et al* demonstrated that a methyl substituent at C_4 of enal **44** exerted a powerful directing effect on the mode of the IMDAC as shown in Scheme 1.7.[37] The tendency for the methyl to adopt an equatorial position in the transition state strongly favored the approach of the dienophile from the β face ($\mathbf{TS_{45b}}$) leading to the observed product **45b**. The effect of the substituents was applied in our synthesis to achieve stereochemical control in the IMDAC of compound **99** (vide infra).



E = Electron withdrawing group

Scheme 1.6



44 TS_{45a} 45a TS_{45b} 45b

Scheme 1.7

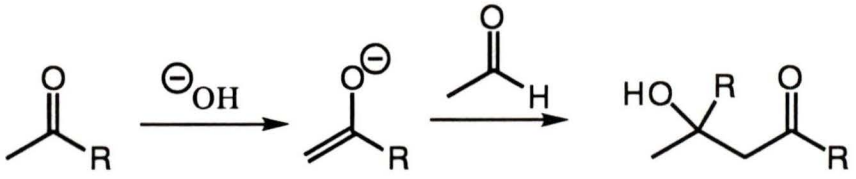
1.5 Using Aldol Condensation for C-C Bond Formation and Introducing Chiral Substituents

Aldol condensation, one of the oldest reactions in organic chemistry, has numerous applications in synthetic organic chemistry. It provides a method for linking two molecules with carbon-carbon bond formation. When the aldol condensation was first carried out, the product was usually an **ald**ehyde-alco**hol**, thus the common name **"aldol"**. The reactions of this general type have come to be known as aldol condensations (or aldol additions).

1.5.1 Self-Condensations of Carbonyl Compounds

Under the influence of dilute base or acid, two molecules of an aldehyde or a ketone may combine to form a β-hydroxy aldehyde or β-hydroxy ketone. In each

case, the product results from the addition of the enolate (or enol) of one molecule of aldehyde (or ketone) to the carbonyl of the second molecule in such a way that the α–carbon of the first becomes attached to the carbonyl carbon of the second.[38] An example of the self condensation reactions involving acetaldehyde 46 (R=H) and acetone 47 (R=Methyl) is given in Scheme 1.8.

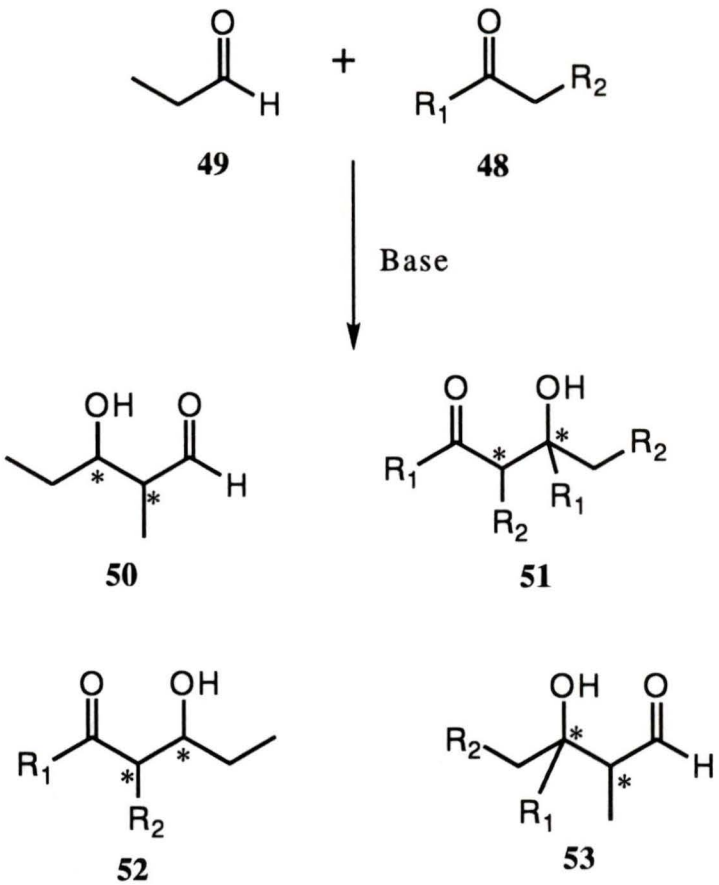


46 R=H
47 R=Methyl

Scheme 1.8

1.5.2 Crossed Aldol Condensation

An aldol condensation between two different carbonyl compounds, usually called a mixed or crossed aldol condensation, has the ability to create four different products. An example is given in Scheme 1.9 using ketone **48** and propanal **49**.[38] Two of the products, **50** and **51**, are the consequence of self-condensation whereas the remaining two products **52** and **53** arise from the enolate of one compound and the carbonyl of the other. Experimentally, it is difficult to avoid the formation of all four products in acid or base catalyzed reactions. In addition, each of these two products will have four possible stereoisomers because of the two newly formed chiral centers as shown in Scheme 1.9. As a result, the application of crossed aldol condensation was limited until the late 60's and 70's, when numerous methods of selective cross



Scheme1.9

aldol condensation appeared in the literature. Stable metal enolates could be formed and to the addition of the second carbonyl in conditions where equilibration was not occurring. Stereoselective reactions were discovered where it was demonstrated that the geometry of the enolate dictated the diastereoselectivity of the reaction (*syn* VS *anti* products, Figure 1.9).[39] The Zimmerman-Traxler model for the transition state (TS*anti* and TS*syn*) has been used to rationalized these results (Figure 1.9).[40] The 6-membered ring in a chair conformation, brought about by metal chelation of the

carbonyl and enolate oxygens, will have the larger R group from the aldehyde

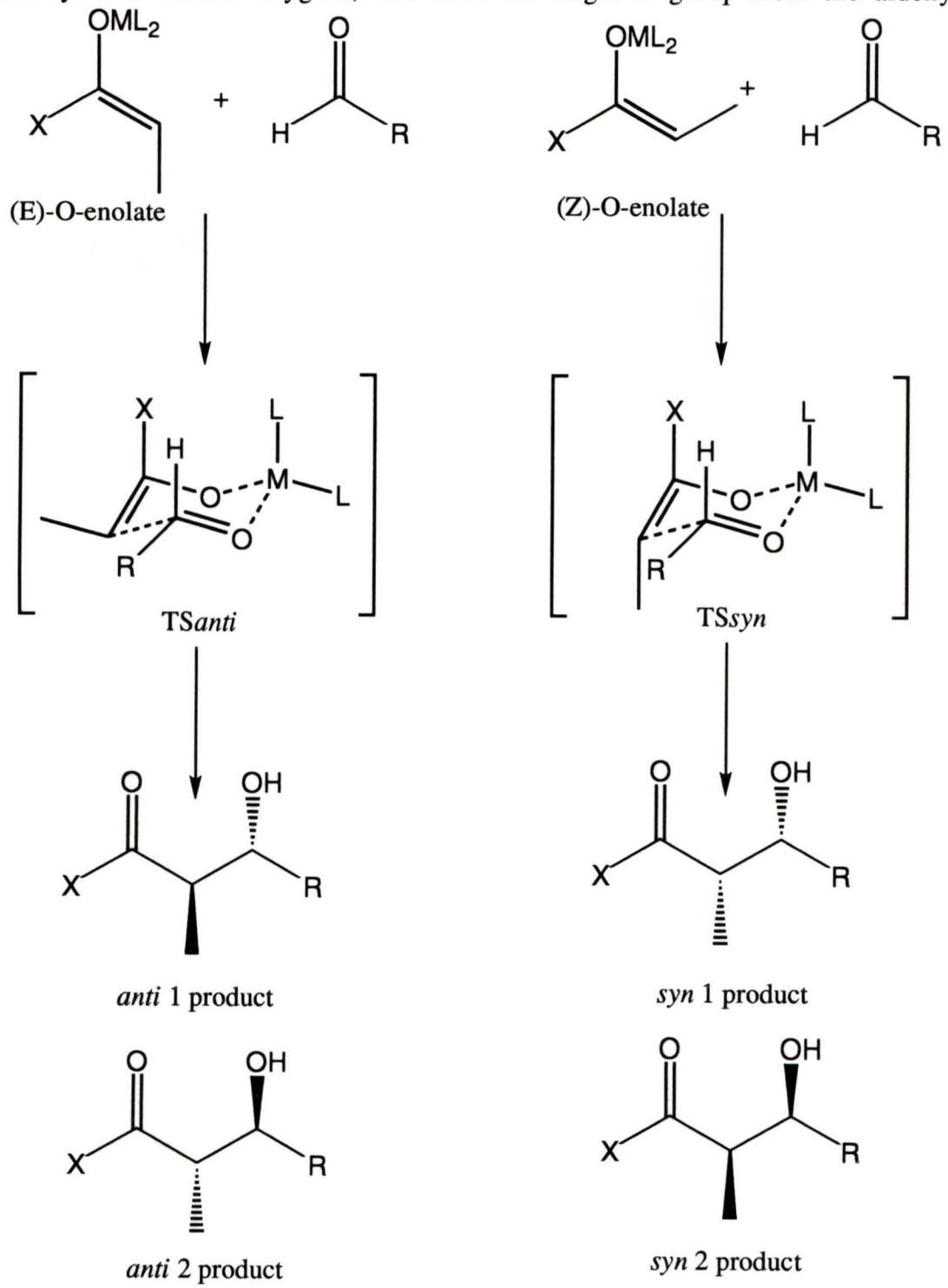


Figure 1.9

occupying the pseudo-equatorial position. The most selective reactions involved boron, zinc, and titanium metal enolates.

The aldol condensation can made much more useful if one can control the **absolute** stereochemistry of the products (*syn* 1 Vs *syn* 2 and *anti* 1 Vs *anti* 2) (Figure 1.9). There are many methods developed by different research groups which directly address this question.[41] Among the several methods, the Evans chiral oxazolidinone method has been particularly successful and is routinely used in many total syntheses today. It will be the subject of the next subsection.

1.5.3 Evans' Chiral Auxiliary

For control of the absolute stereochemistry of aldol adducts, Evans developed the oxazolidinone chiral auxiliaries **54** and **55** (Figure 1.10). The boron enolates generated are always in the *Z*-conformation because of the steric bulk of the oxazolidinone ring. In general, a variety of metals can be used for such purpose: lithium, magnesium, zinc, aluminum, titanium or zicornium. Boron is usually the metal of choice because of the short boron-oxygen bond length (Table 1).[41] Consequently, the two oxygens are chelated in close proximity in such a way that the steric interaction between the oxazolidinone ring and the ligands is greatly enhanced resulting in enhanced stereoselectivity (Figure 1.10).

Table 1: Oxygen-Metal Bond Lengths

Metal	Metal-Oxygen Bond length (Å)
Lithium	1.92-2.00
Magnesium	2.01-2.13
Zinc	1.92-2.16
Aluminum	1.92
Boron	1.36-1.47
Titanium	1.62-1.73
Zirconium	2.15

The substituents on the five-membered ring could be a methyl as in **54** or an isopropyl as in **55**. The purpose of these substituents is to create steric congestion as shown in $\mathbf{TS_{54a}}$ which in turn disfavors its formation. As a result, the absolute stereochemistry of the product can be fixed with the use of different chiral auxiliaries. Details of how this method was applied to our synthesis will be discussed in Chapter 2.

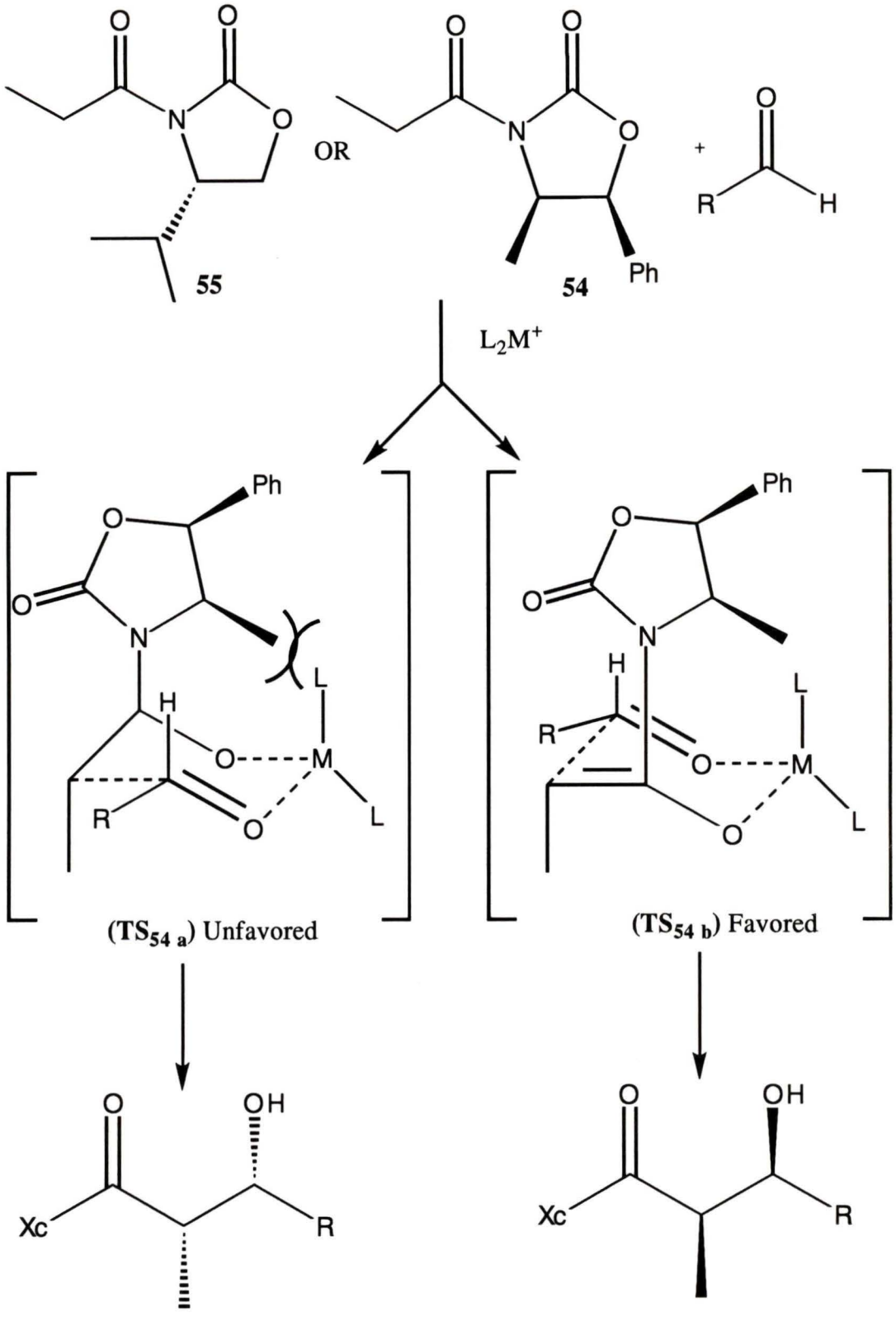

OR
55
54
Ph
+
R
H
L_2M^+
Ph
O
N
H
L
M
R
O
L
(TS54 a) Unfavored
(TS54 b) Favored
OH
Xc
R
Major Product

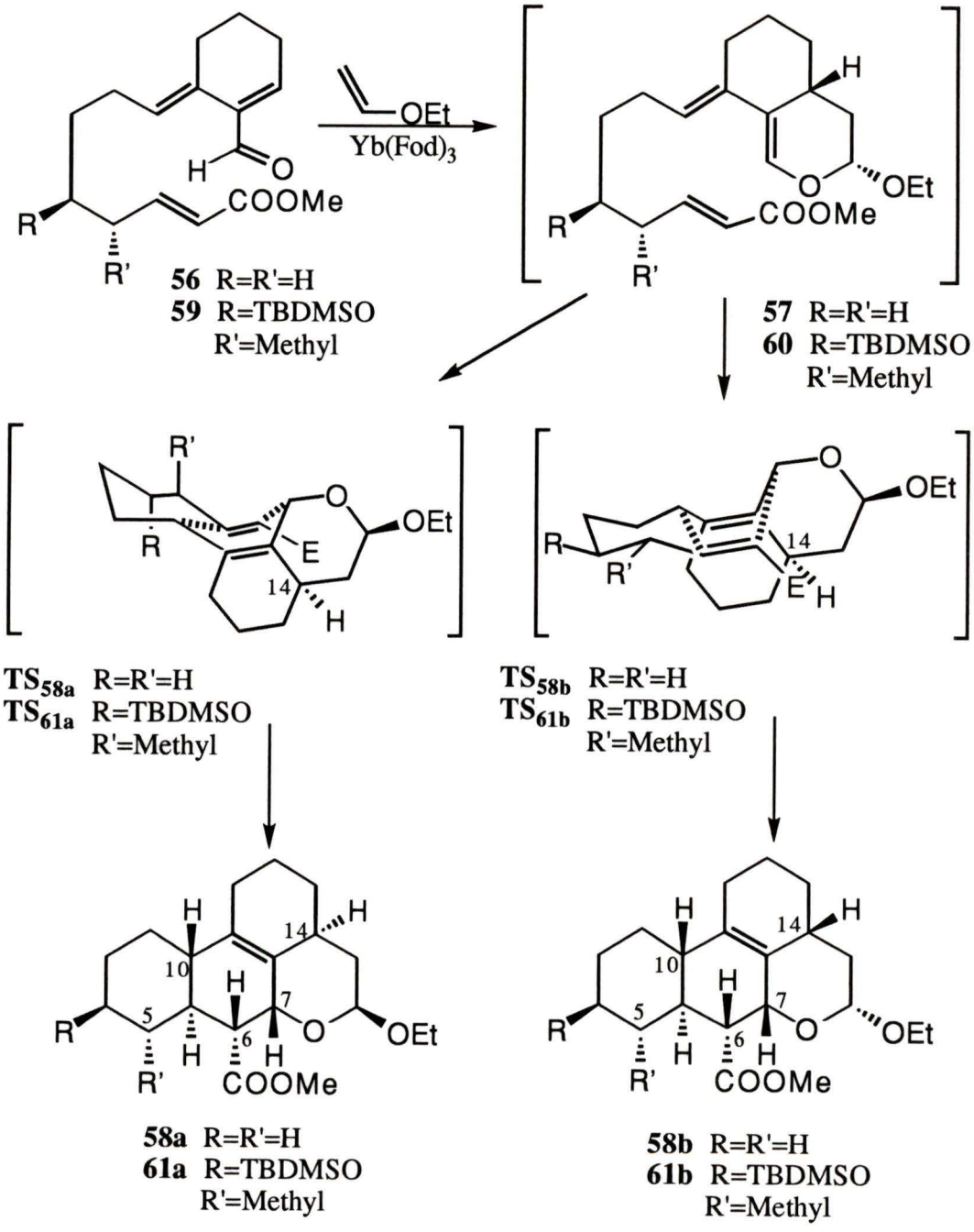
Figure 1.10

1.6 Background for the Proposed Synthetic Strategy

In 1993, Spino and Liu developed a method for the rapid construction of the tetracyclic ring skeleton in quassinoids based on a "diene-transmissive" Diels-Alder cycloaddition strategy (Scheme 1.10).[42] One advantage of this method is that it effectively and stereoselectively generates three rings and six chiral centers in a single operation. In addition, the key Diels-Alder reaction in this strategy should be compatible with many functional groups. This is important in the case of quassinoid total synthesis since they possess so many functional groups. The ytterbium-catalyzed, inverse-electron demand, Diels-Alder cycloaddition between **56** (R=R'=H) and ethyl vinyl ether at room temperature was immediately followed by a stereoselective intramolecular Diels-Alder cycloaddition to give the tetracyclic compounds **58a** and **58b** (R=R'=H) in a 6:1 ratio. The cyclization of the intermediate **57** proceeded via the more stable *endo* chair-like transition states $\mathbf{TS_{58a}}$ and $\mathbf{TS_{58b}}$. The 6:1 ratio in favor of **58a**, indicated that $\mathbf{TS_{58a}}$ is of lower energy than $\mathbf{TS_{58b}}$ which implies an attack of the dienophile from the same face as the C_{14} hydrogen. Unfortunately, the stereochemistry of the major isomer **58a** at C_{14} is opposite to that found in natural quassinoids. Nevertheless, the relative stereochemistry at C_5, C_6, C_7, and C_{10} was controlled via the preferred *endo* chair-like transition state.

It should be possible to force the attack of the dienophile on the desired α-face of the molecule by introducing one or more substituents (R and R') on the tether with a defined stereochemistry (Scheme 1.10, R=TBDMSO, R'=Methyl). With the stereochemistry of R and R' properly resolved, these substituents would adopt an axial position in the β-face attack ($\mathbf{TS_{61a}}$) but an equatorial orientation in the desired α-face attack ($\mathbf{TS_{61b}}$). This should strongly destabilize $\mathbf{TS_{61b}}$ and thus control the absolute stereochemistry of the adduct *regardless of the stereochemistry at* C_{14}. This

means that a prior introduction of C_{14} with the proper absolute stereochemistry is required to achieve control over all the stereogenic centers in the quassinoid intermediate. To test this hypothesis we set to prepare the model compounds **100a** and **100b** (p. 51). The control of the absolute stereochemistry at C_{14} will not be achieved in this model study to keep it at a manageable complexity and also because it will be interesting to observe the stereochemical outcome of the IMDAC on both C_{14}-stereochemistry.

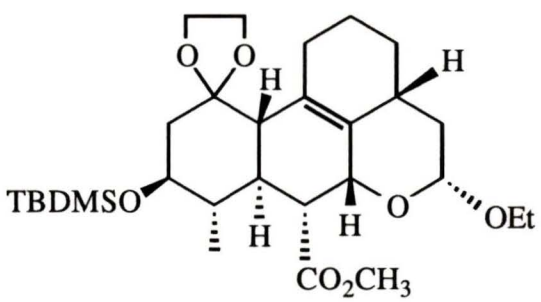


Enantiomers shown

Scheme 1.10

CHAPTER TWO
RESULTS AND DISCUSSION

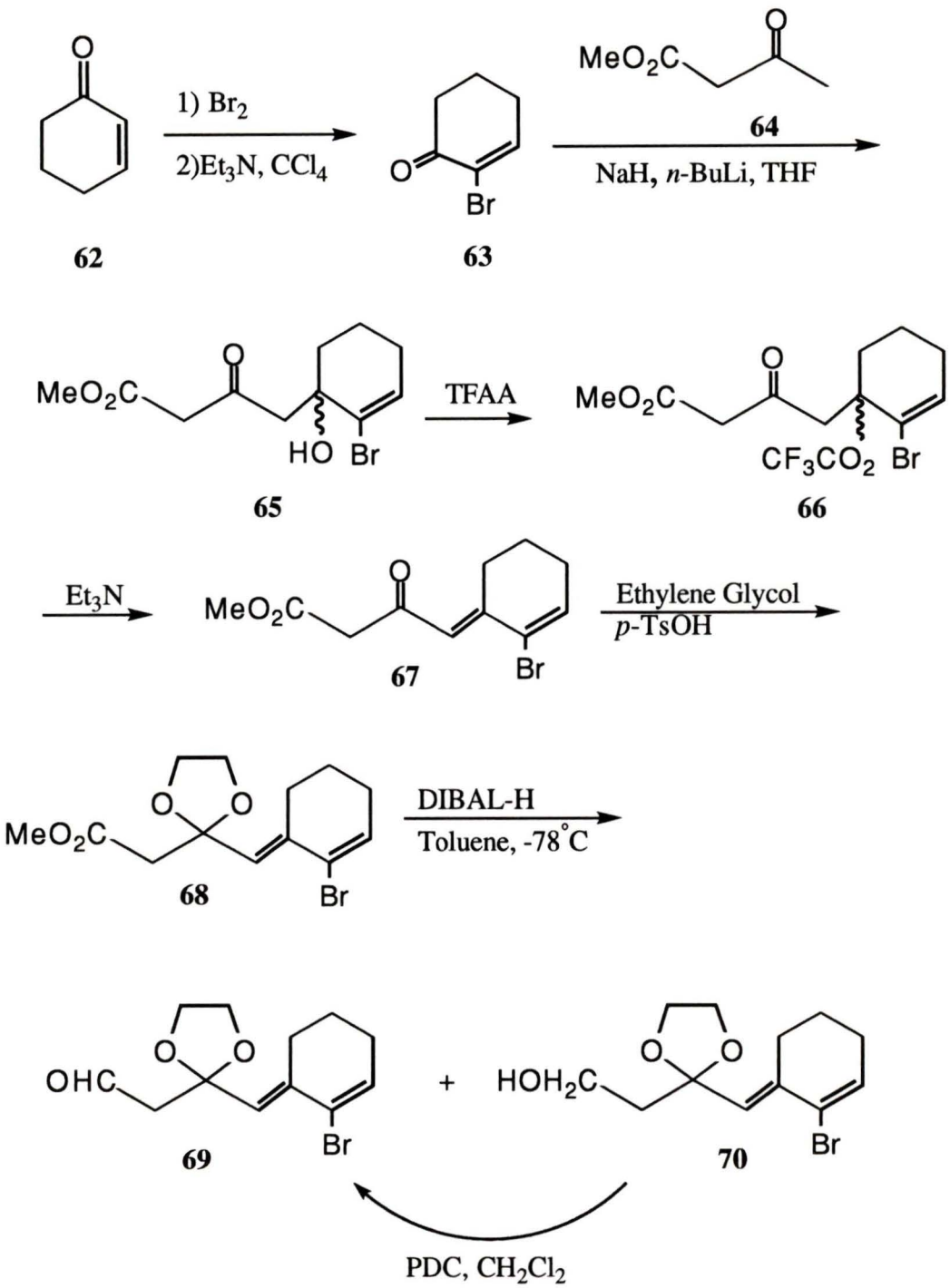
The synthetic route to the target compound **102** starts with the bromination-elimination reaction of the commercially available cyclohexene-2-one **62** to give the bromo-ketone **63** (Scheme 2.1).[43] The dianion of methyl acetoacetate **64**, generated with sodium hydride and *n*-butyllithium,[44] was allowed to react with ketone **63** at 0°C to produce alcohol **65** in 85% yield.



102

Treatment of **65** with *p*-toluenesulfonic acid with azeotropic removal of water in refluxing benzene led to recovery of starting material and the formation of only trace amounts of product. However, treatment of **65** with neat trifluoroacetic acid followed by triethylamine gave a 69% yield of the desired alkene **67**. We believe that **67** arises from the elimination of the trifluoroacetate intermediate **66** as it was possible to isolate **66** by withholding the addition of triethylamine. Moreover, addition of triethylamine to an etheral solution of the trifluoroacetate intermediate **66** afforded the alkene **67**. The ketone group in compound **67** was protected by treatment with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid to give ketal **68** in 87% yield.[43] The methyl ester in **68** was then reduced to the corresponding aldehyde **69** with diisobutylaluminum hydride in toluene at -78°C in 70% yield. A by-

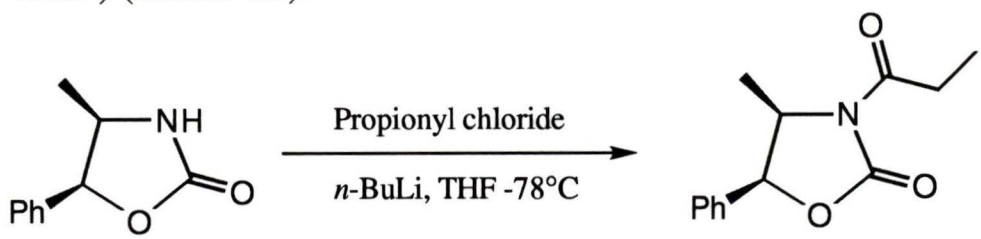
product in this reduction was the over-reduced alcohol **70** (25%) which could be separated and reoxidized in 80% yield to the desired aldehyde **69** with pyridium dichromate in dichloromethane.[45] The total yield of aldehyde **69** based on recycled alcohol was 90%.



Scheme 2.1

An asymmetric aldol condensation of aldehyde **69** with the boron enolate of optically pure oxazolidinone **71**, prepared from (4*R*, 5*S*)-4-Methyl-5-phenyl-2-

oxazolidinone (Scheme 2.2), selectively gave the desired optically pure alcohol **72** ($[\alpha]_D$ +11.0°) (Scheme 2.3).[46]



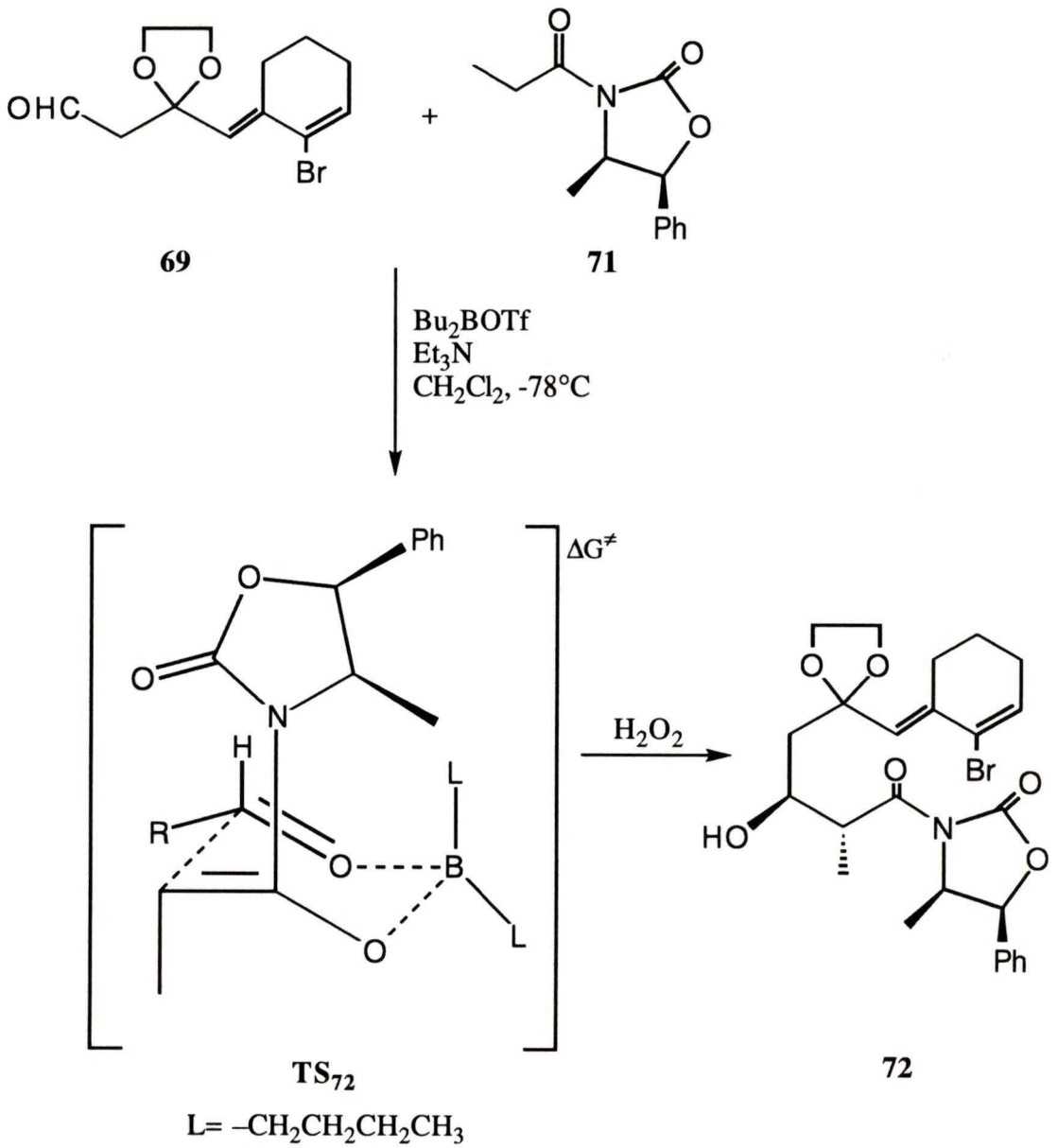
71

Scheme 2.2

The formation of **72** can be rationalized using the Zimmerman-Traxler model for the transition state structure $\mathbf{TS_{72}}$.[40] The short oxygen-boron bond makes for a tight chair-like transition state and the orientation of the oxazolidinone auxiliary forces the attack on the desired face of the enolate. The stereochemistry of the aldol adduct was assigned as shown based on the thorough studies by Evans and coworkers and on literature precedents.[46] We could confidently await until the formation of the rigid tetracyclic compound later in the synthesis to ascertain that fact.

The resulting secondary alcohol **72** was then protected with *t*-butyldimethylsilyl triflate in the presence of triethylamine to give **73** in 79% yield (Scheme 2.4). The ketal group in **72** was not very stable and underwent hydrolysis upon standing at room temperature. For example, about 10% (by NMR) of the ketone **74** was observed after 24 hours. The reported yields for the reductive removal of this oxazolidinone auxiliary are quite high using either lithium aluminum hydride or lithium borohydride at -20°C to 0°C (> 80%, less than 4 hours).[46] However, for the reduction of **73**, a variety of reducing agents and reaction conditions were used unsuccessfully (Table 2). Despite all these efforts, the maximum yield obtained for **75** was 40%. The unsatisfactory yields from these reaction conditions may be the result of several factors. The presence of a methyl group α to the amide carbonyl group on the acyclic

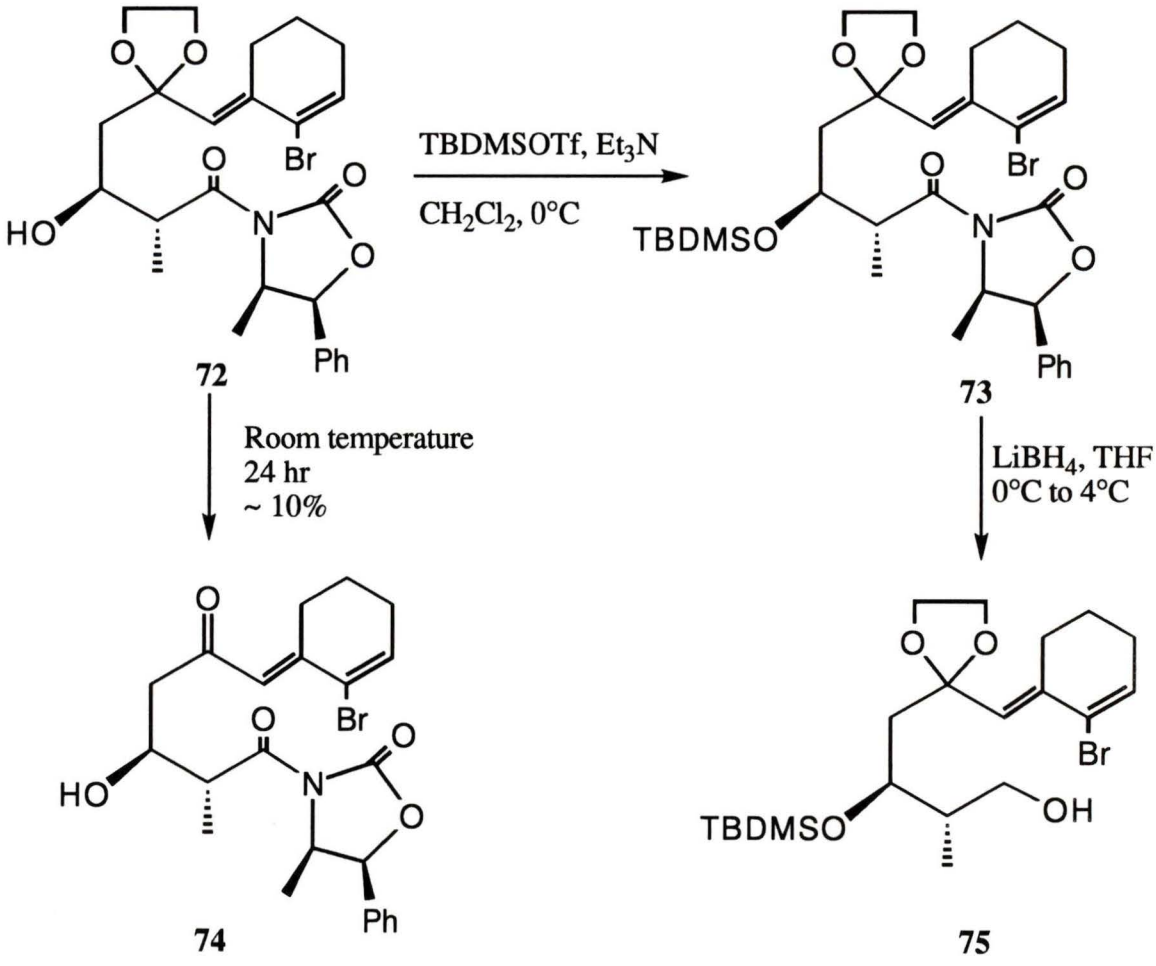
chain of **73** may sterically hindered its reduction and allow the carbonyl group in the oxazolidinone ring to be reduced at a comparable rate.



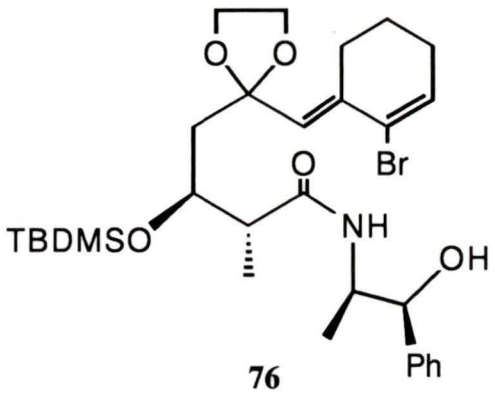
Scheme 2.3

This explanation was proven experimentally by the isolation of the amine **76**. A second reason may be that the product alcohol **75** is unstable and possibly

decomposed during work up and purification processes. The unstability of the product **75** towards heat generated during the addition of neat lithium aluminium hydride or



Scheme 2.4



76

Table 2: Summary of Reaction Conditions Used in the Reduction of Compound **73**.

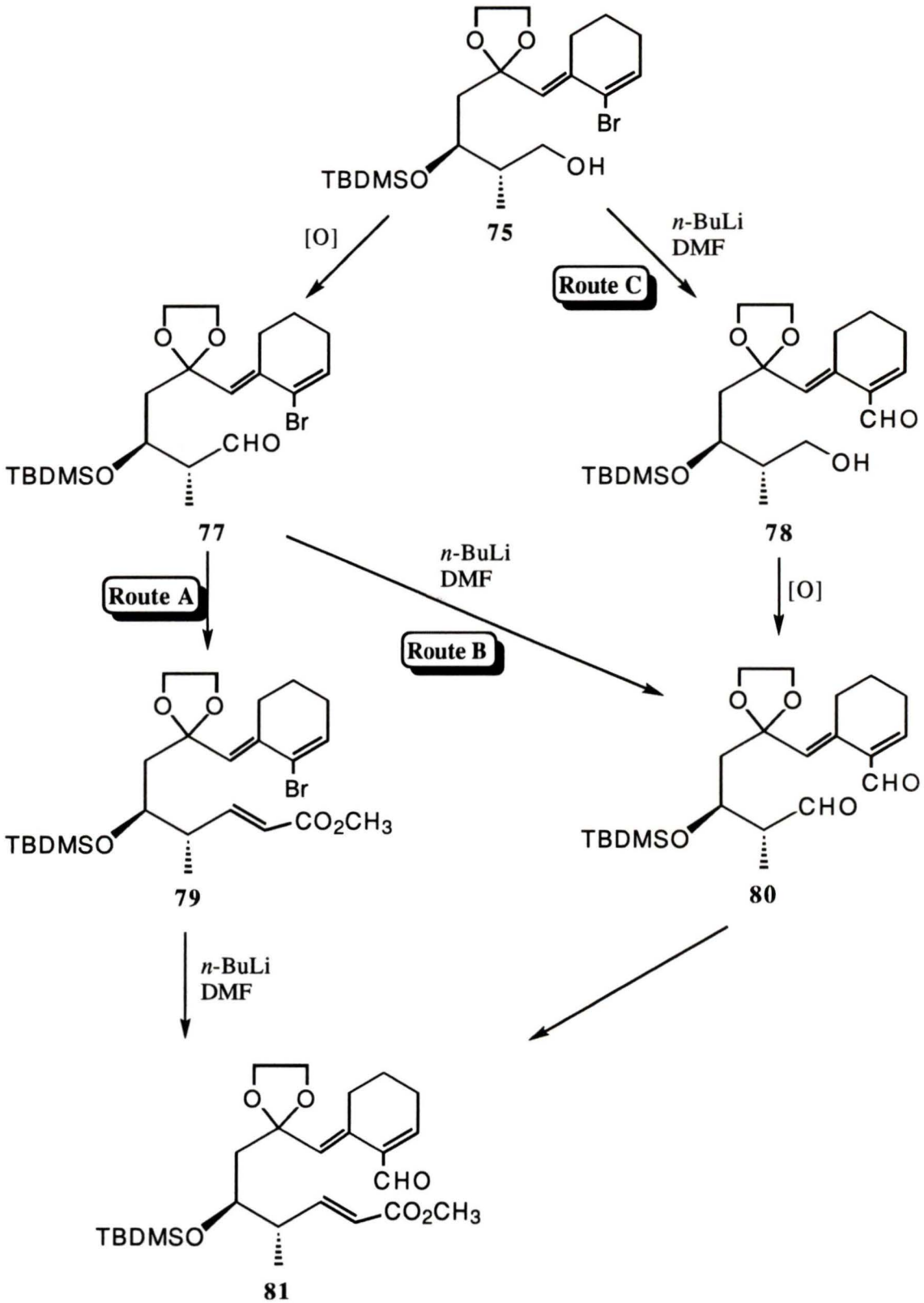
Reducing agent	**Molar equivalent**	**Temperature (°C)**	**Solvent**	**% Yield**
LAH	3	-78	THF/Et_2O	40
LAH	3	-78--> 0	THF/Et_2O	21
LAH	3	-30--> 0	THF/Et_2O	25
LAH	3	-10	THF/Et_2O	16
LAH	3	0	THF/Et_2O	20
LAH	3	10	THF/Et_2O	15
LAH	3	25	THF/Et_2O	0
LAH	1	0	THF/Et_2O	23
LAH	0.25	25	THF/Et_2O	19
DIBAL	3	-78	Et_2O	15
DIBAL	3	0	Et_2O	15
DIBAL	1	0	Et_2O	10
DIBAL	0.25	0	Et_2O	0
NaOMe//LAH	2	0	MeOH/THF	25
NaOMe/LAH	1	0	$MeOH/Et_2O$	20
NaOMe/ DIBAL-H	1	0	$MeOH/Et_2O$	30
$LiBH_4$	3	0--> 4	THF	83

lithium borohydride may also have contributed to the decomposition process. Successful reaction conditions were discovered fortuitously, involving a dropwise addition of a solution of lithium borohydride in THF to **73** (also dissolved in THF) at 0°C. Stirring was continued at 4°C for 10 days. Dissolving lithium borohydride in

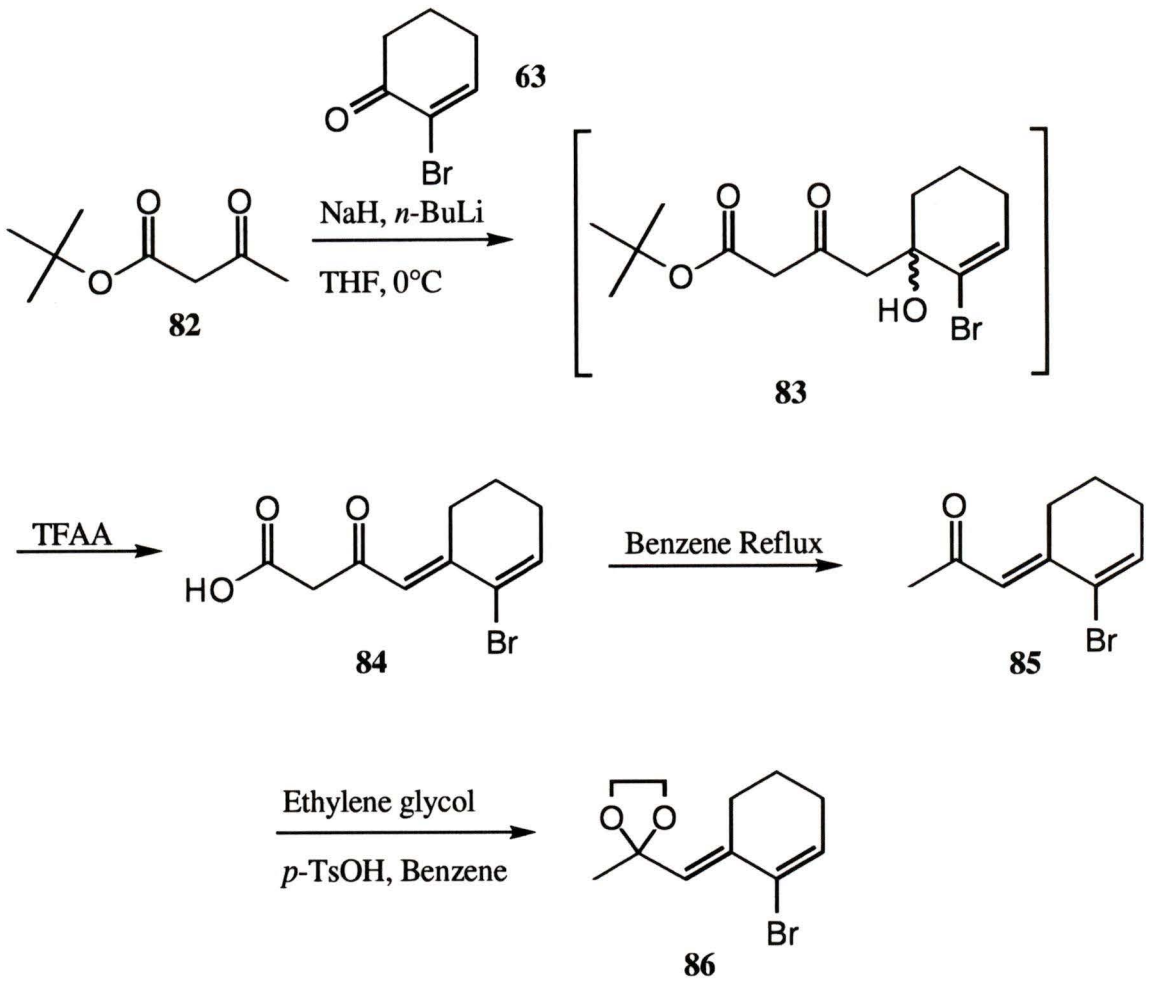
THF may have provided a greater control on the addition rate of the reducing agent and temperature of the reaction.

At this point of the synthesis, a decision had to be made as to when the conversion of the bromo functionality in **75** to the corresponding aldehyde would be best achieved. As illustrated in Scheme 2.5, several possibilities were considered (route A, B and C).

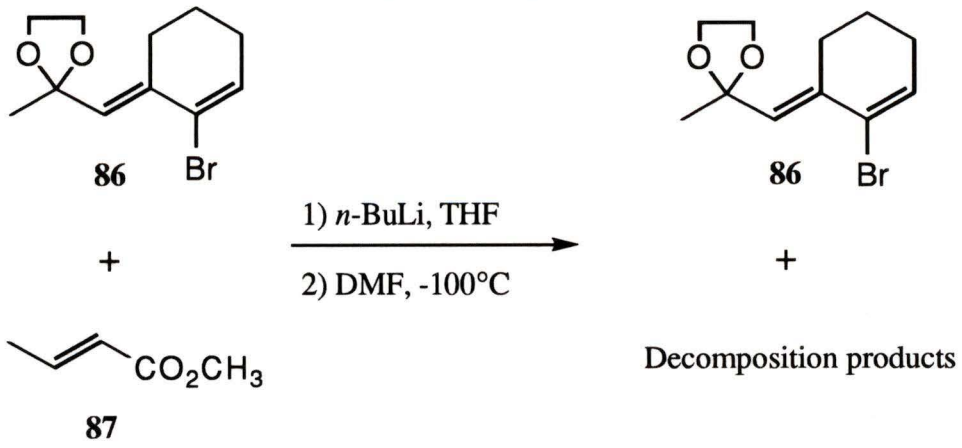
First we examined the possibility of carrying out a metal-halogen exchange reaction on compound **79** hopping the α,β–unsaturated ester group would not interfere (route A). To test the viability of this route, the model bromide **86** was prepared by a two-step synthesis from *t*-butylacetoacetate and bromo-ketone **63** (Scheme 2.6). The dianion of *t*-butylacetoacetate **82** was generated as previously described (vide supra) and was allowed to react with bromo-ketone **63**. The resulting alcohol **83** was not isolated but subjected to neat trifluoroacetic acid at 0°C which simultaneously eliminated the alcohol as water and hydrolyzed the *t*-butyl ester group to give the acid **84.** Without isolation, compound **84** was then decarboxylated in refluxing benzene to give **85** (55% yield). Protection of the ketone in **85** was carried out in the same fashion as for **67** (Scheme 2.1) and provided the required model bromide **86**. A 1:1 mixture of **86** and methyl crotonate **87**, which was chosen to mimic the α,β-unsaturated ester in **79**, was dissolved in THF and cooled to -100°C with a methanol-dry ice bath (Scheme 2.7). The reaction mixture was subjected to 2 molar equivalents of *n*-butyllithium and 2 molar equivalents of *N,N*-dimethylformamide and stirred for 2 hrs in between the two additions. According to the crude NMR spectrum on the resulting reaction mixture, all of the methyl crotonate **87** was consumed and upon purification, most of the starting bromide **86** was recovered.


TBDMSO
Br
OH
75
[O]
n-BuLi
DMF
Route C
CHO
77
78
Route A
Route B
CO2CH3
79
80
81

Scheme 2.5



Scheme 2.6

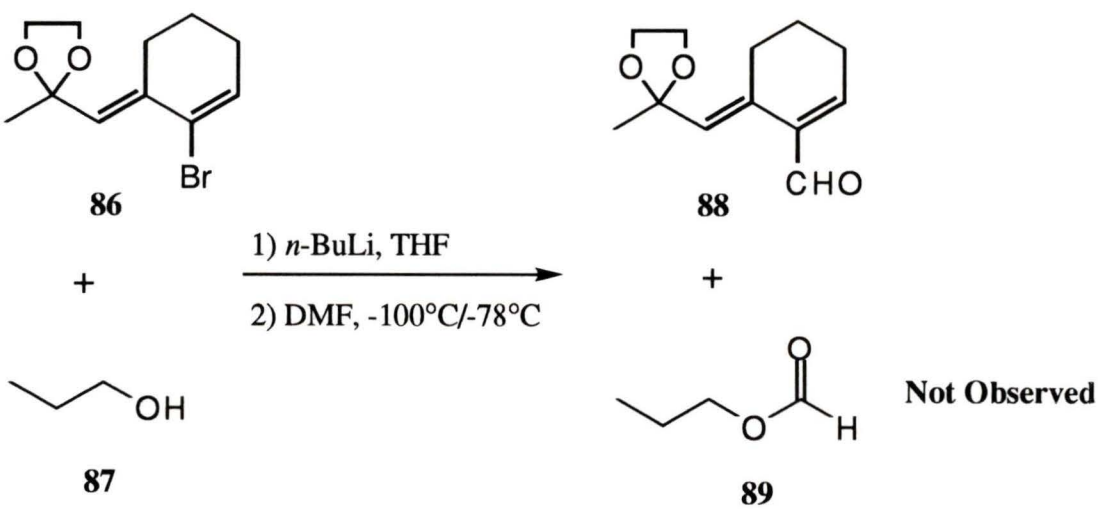


Scheme 2.7

Based on the results of this model study, it was clear that route A was not promising for our synthesis and the metal-halogen exchange reaction would have to be carried out prior to the introduction of the α,β-unsaturated ester.

Route B did not seem to be more viable than A based on the above model study since the saturated aldehyde in **77** is expected to be more reactive than the α,β-unsaturated ester in **79**. As a result, a model system mimicking route B was not investigated.

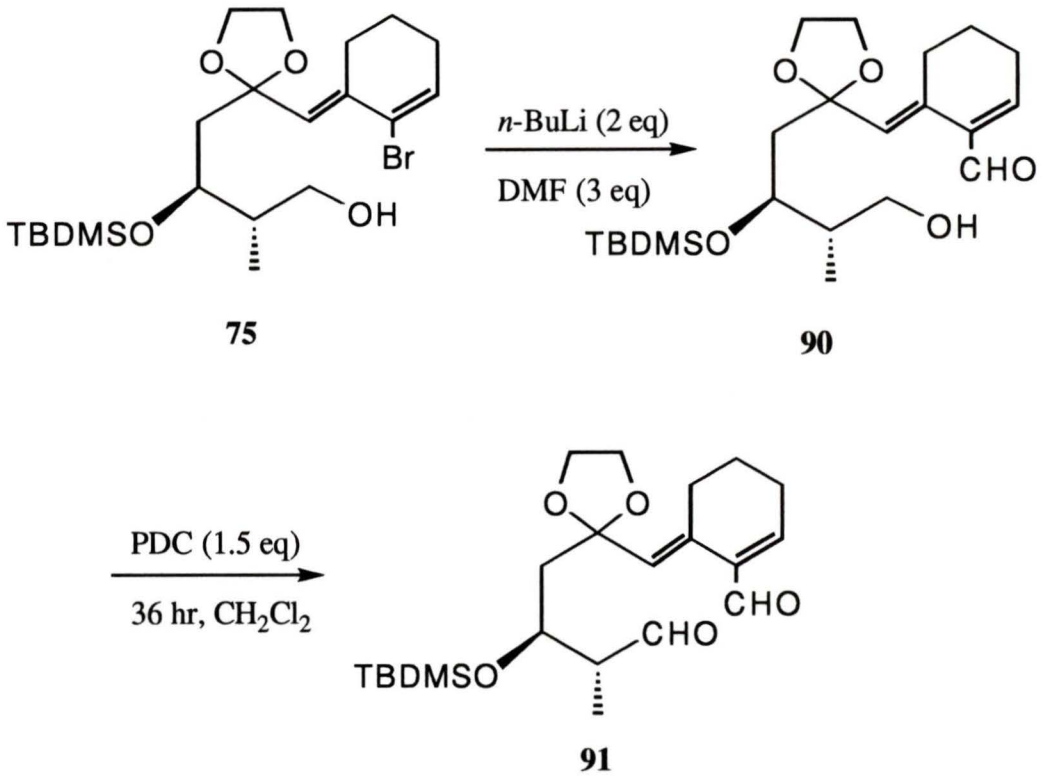
To test the feasibility of route C, a model study involving **86** and propanol **87** was carried out (Scheme 2.8). Two equivalents of *n*-butyllithium was added to a solution of **86** and propanol at -100°C or -78 °C followed by 3 equivalents of *N,N*-dimethylformamide. Upon purification, compound **88** was isolated in 75% yield. No propyl formate **89** was observed in the crude NMR. Compound **89** would display a singlet at δ=8.1 ppm, if formed. The results from this study provided evidence that route C should be viable for the synthesis of **81**.



Scheme 2.8

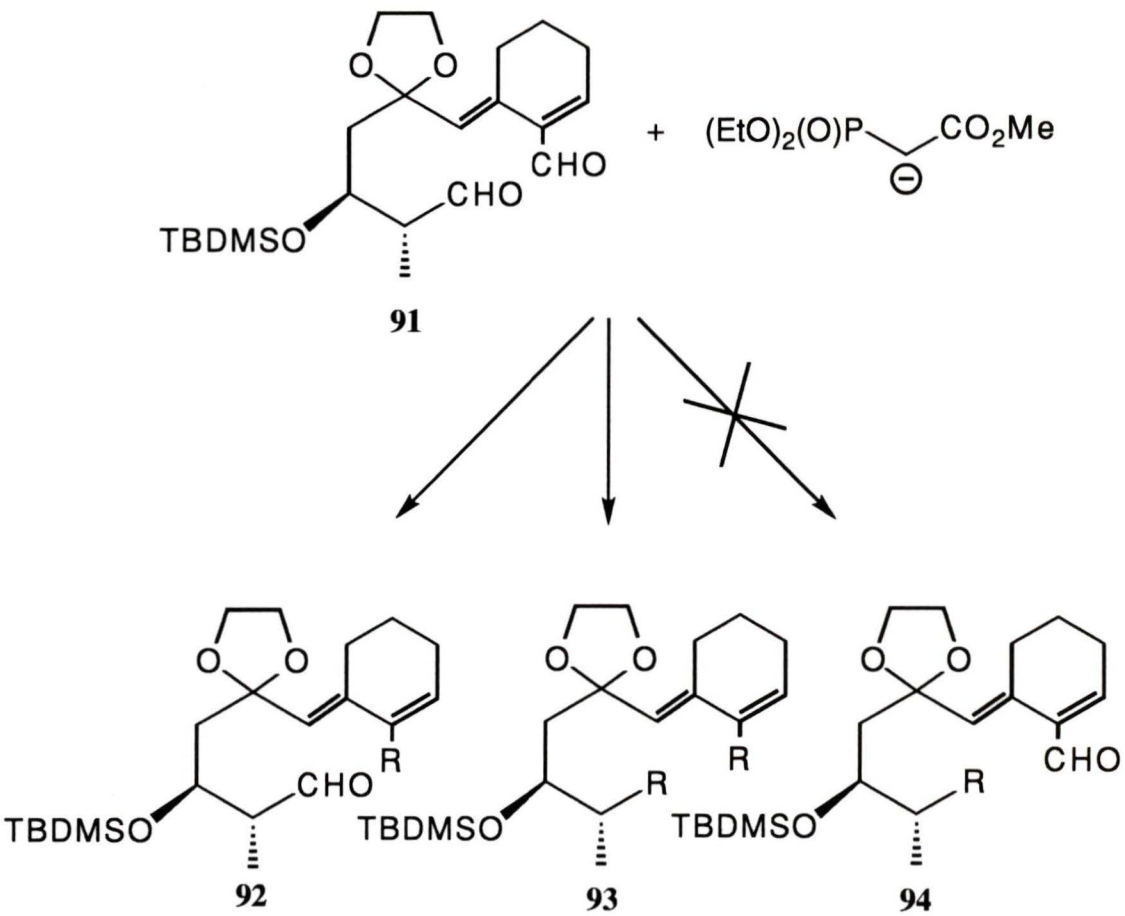
Accordingly, bromo-alcohol **75** was converted to the aldehyde-alcohol **90** in 60% yield with *n*-butyllithium and *N,N*-dimethylformamide at -78°C (Scheme 2.9). In this reaction, the primary alcohol was left unprotected since the above model studies indicated that the oxyanion generated was not reactive towards *N,N*-dimethylformamide under the reaction conditions. The resulting aldehyde-alcohol **90** was oxidized with pyridinium dichromate to give 70% yield of the dialdehyde **91**.[45] The structure of **91** was deduced from its ^{1}H NMR spectrum which gave a broad singlet at δ=9.63 ppm (for the saturated aldehyde) and a sharp singlet at δ=9.40 ppm (for unsaturated aldehyde).

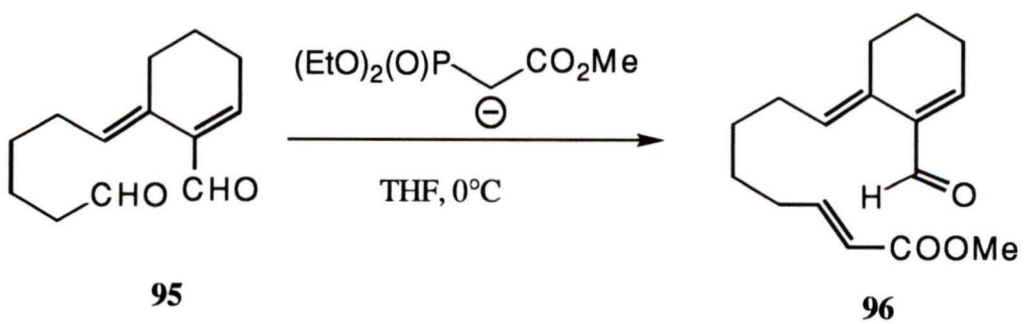
Unfortunately, when **91** was subjected to a Wadsworth-Emmons reaction (using 1.0 molar equivalent of the anion of methyl diethylphosphonoacetate), the reaction occurred preferentially with the unsaturated rather than the saturated aldehyde leading to the isolation of the monoester **92**, diester **93** and starting material (in a 2:1:1 ratio) (Scheme 2.10). A similar reaction carried out by Spino and Liu on dialdehyde **95**, an analog to dialdehyde **91**, gave the desired α,β-unsaturated ester **96** as the only observable product (Scheme 2.10).[42] In principle, the α,β-unsaturated aldehydes are less reactive than saturated aldehydes because of the stabilization energy gained from conjugation. It is possible that the methyl group α to the saturated aldehyde in **91** hinders the reaction site thus reducing the reactivity to such a degree that the unsaturated aldehyde reacted at a comparable rate.



75 **90** **91**

Scheme 2.9

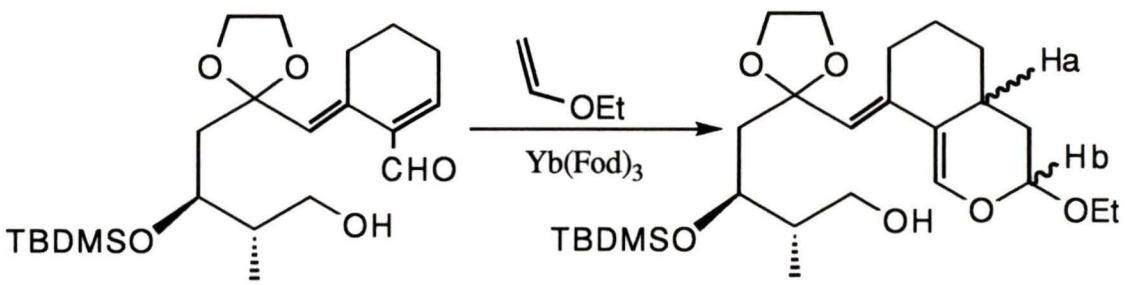

O
O
CHO
CHO
TBDMSO
+
(EtO)2(O)P
CO2Me
⊖
91
R
92
93
94
R=(-CH=CH-CO2CH3)


CHO CHO
(EtO)2(O)P
CO2Me
⊖
THF, 0°C
H
O
COOMe
95
96

Scheme 2.10

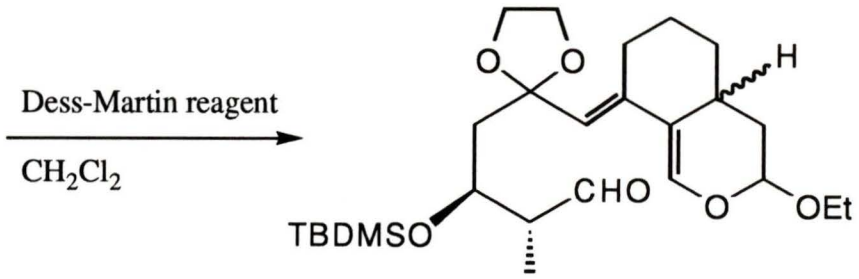
Because of the lack of chemoselectivity in the above reaction, the sequential Diels-Alder reactions of **81** and ethyl vinyl ether to give the final tetracyclic product could not be carried out without a significant increase in the number of synthetic steps. To circumvent this problem, the ytterbium-catalyzed,[47] inverse electron-demand, heterocyclic Diels-Alder cycloaddition reaction was carried out earlier in the synthetic scheme. Hydroxy-aldehyde **90** and ethyl vinyl ether (Scheme 2.11) reacted at room temperature in the presence of $Yb(Fod)_3$ for 10 days leading to the formation of a 1:1 mixture of bicyclic isomers **97a** and **97b** in 80% yield. The same reaction was also attempted between **91** and ethyl vinyl ether but the desired product was not observed and upon standing at room temperature for a longer period of time, decomposition resulted.

The 1:1 ratio of the two diastereomers was determined by GC and ^1H NMR. The isomers were purified by column chromatography but not separated. When compound **97** was subjected to the Swern oxidation[48] or pyridium dichromate oxidation conditions,[45] unexpectedly decomposition occurred. However, **97** was oxidized to the corresponding aldehyde **98** with the Dess-Martin periodinane in 82% yield. It was experimentally found that a pyridine buffer, as indicated in the literature, was required

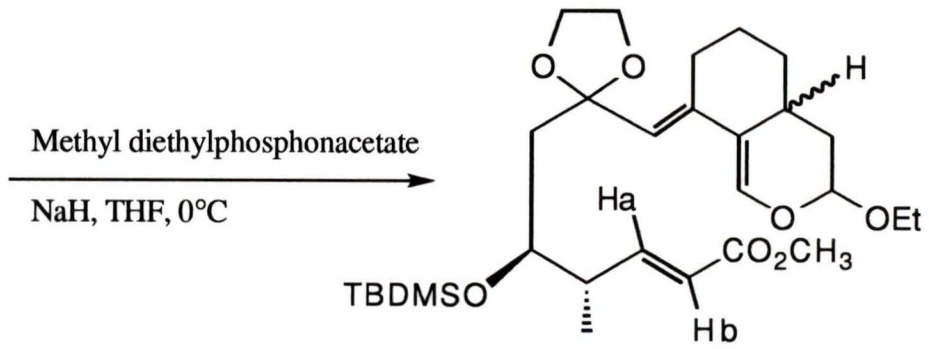


90

97a α-Ha, α-Hb
97b β-Ha, β-Hb



98

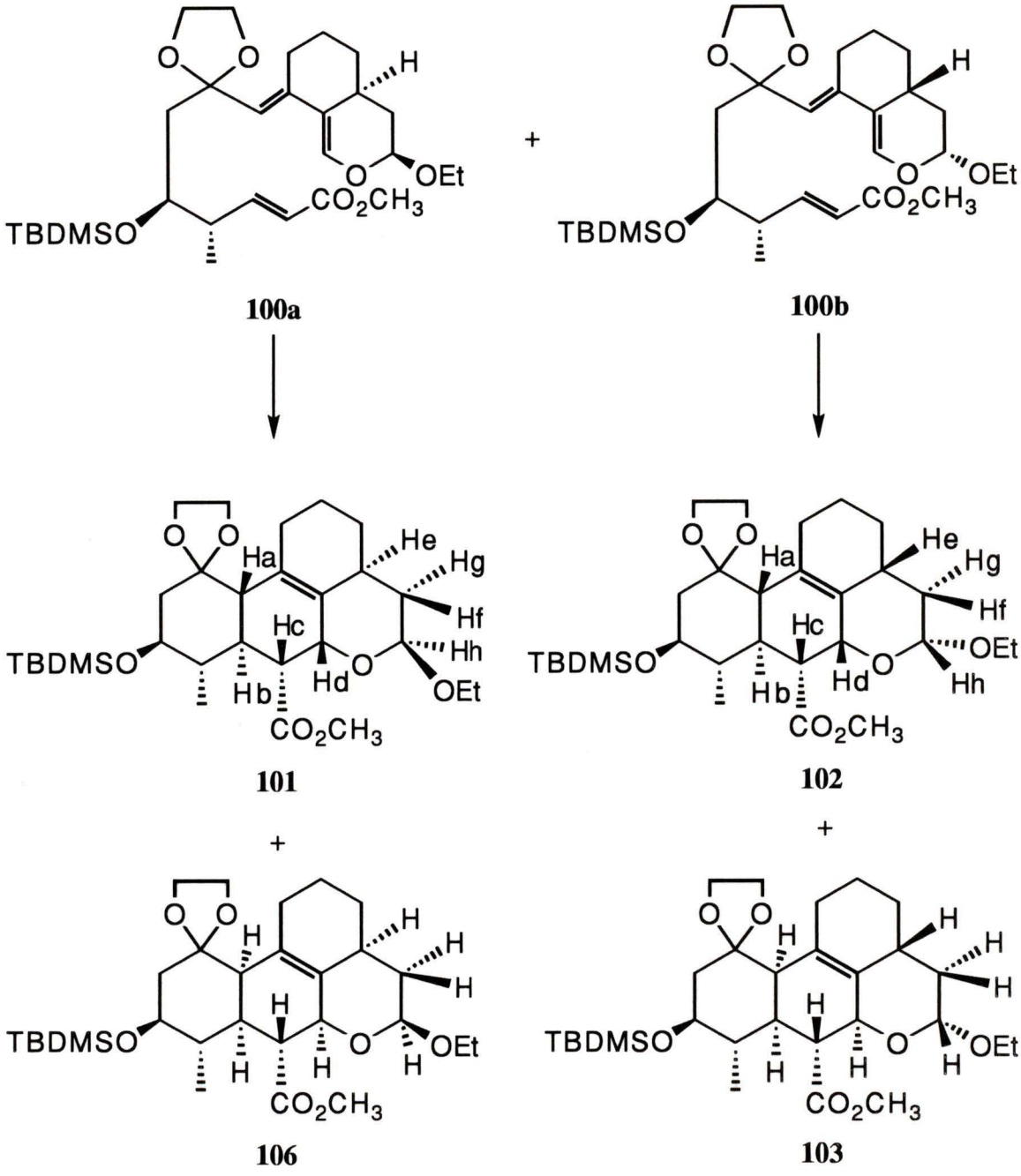


100

Scheme 2.11

for the oxidation of **97** to proceed.[49] Together with a thiosulfate work-up in a sodium bicarbonate buffer, nearly neutral conditions throughout the entire reaction and isolation sequence were maintained.[50] Based on the above evidence, the unsuccessful Swern or pyridium dichromate oxidation can be explain by the product instability towards acid or base. This was further proven by the decomposition of aldehyde **98** during the purification process using silica gel chromatography. Formation of **98** was proven by ^{1}H NMR spectroscopy (singlet at δ=9.62 ppm) but the product was best used directly without further purification. A Wadsworth-Emmons reaction between **98** and the anion of methyl diethylphosphonoacetate gave quantitatively the *E*-α,β-unsaturated ester **100**. Isolation of **100** was done within one hour after its formation and the double bond was shown to have the *E*-configuration by ^{1}H NMR spectroscopy (coupling constants of J=15.0 Hz for the two vinyl protons, Ha and Hb, Scheme 2.11).

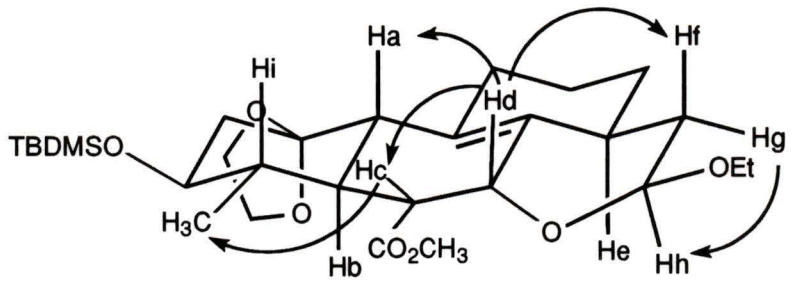
Upon standing at room temperature for 4 days, or at 39°C for 24 hours, compound **100** cyclized via an IMDAC reaction to afford a mixture of essentially three tetracyclic molecules **101**, **102** and **103**, and traces of what may be compound **106**, in 89% combined yield (Scheme 2.12).



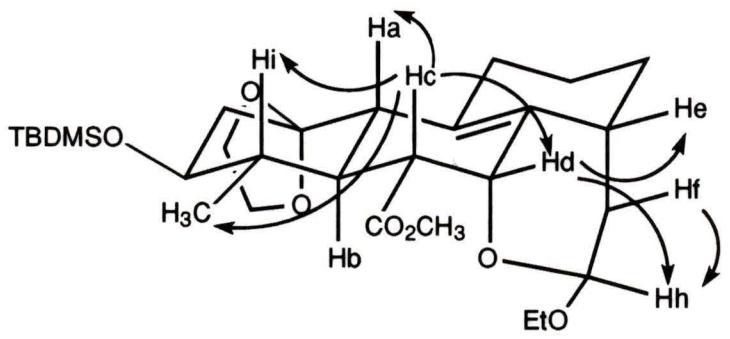
Scheme 2.12

The ratio of the three major isomers **101**, **102**, and **103** of the crude mixture was determined by GC to be roughly 2:2:1.5 respectively. However, partially

overlapping peaks on the G.C. trace made it impossible for us to be confident on this ratio. A more reliable ratio was obtained by NMR (by integration of the C_6 protons in the crude mixture) and isolated yields which both gave ratio of 2.4:1.4:1. The structures of **101** and **102** were confirmed by ^1H NMR, 2-D NMR and ^{13}C NMR (Figure 2.1). The NOESY spectrum of Compound **101** indicated positive enhancement between H_c-H_d; H_d-H_f; H_g-H_h and no enhancement between H_b-H_c. Compound **102** gave positive enhancement between H_c-H_d; H_h-H_f; H_h-H_d and no enhancement between H_b-H_c. Because of the fact that H_a-H_d must be *cis* and H_b-H_c must be *trans* for both **101** and **102**, their structures were confirmed (Figure 2.1). These compounds are thought to arise *via* two *endo*-chair-like transition states $\mathbf{TS_{101}}$ and $\mathbf{TS_{102}}$ which have the two bulky group (methyl and *t*-butyldimethylsilyl ether) adopting the equatorial positions (Scheme 2.14). In contrast, $\mathbf{TS_{104}}$ and $\mathbf{TS_{105}}$ will have the bulky groups trans-axial to each other which is highly unfavorable (Scheme 2.15). As a result, Compounds **104** and **105** are not observed.

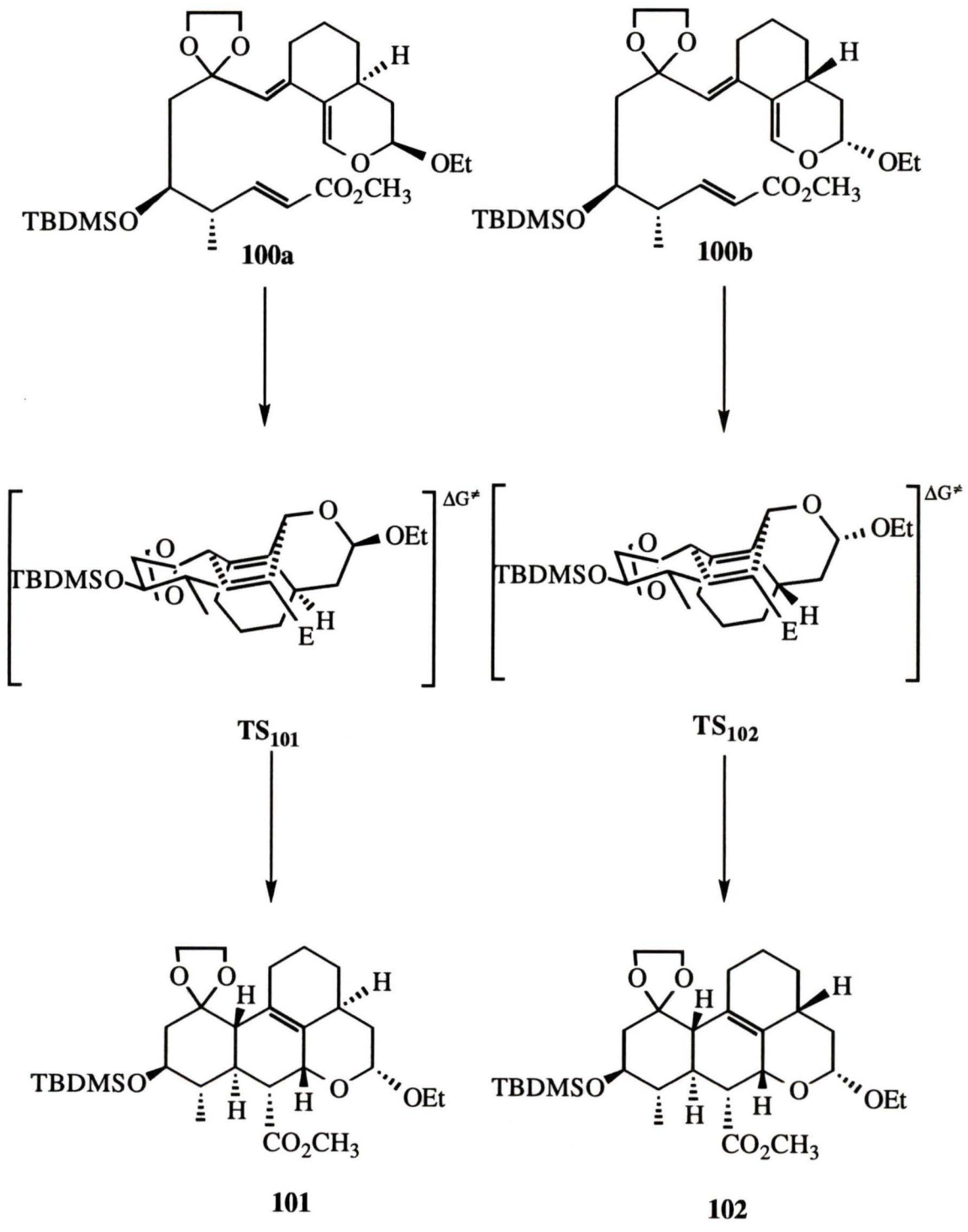


101

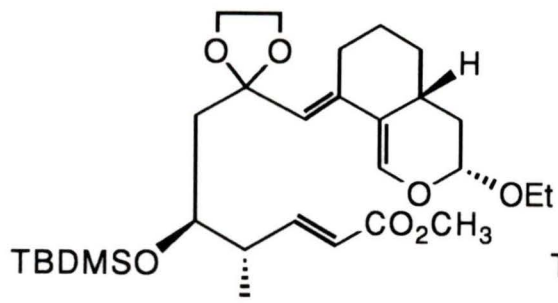


102

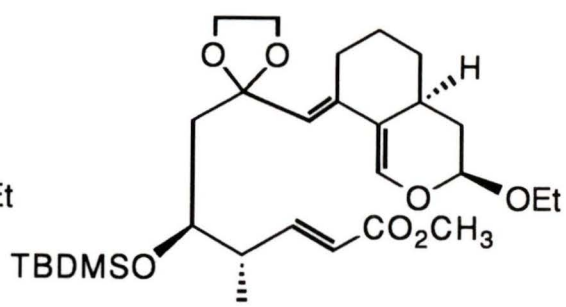
Figure 2.1: Conformations of **101** and **102**
Main nOe enhancements are indicated by arrows.


TBDMSO
OEt
CO_2CH_3
H
O
100a
100b
$\Delta G^{\neq}$
TS_{101}
TS_{102}
E
101
102

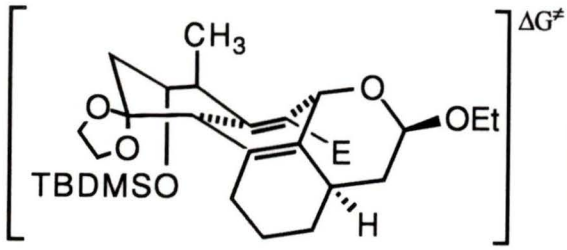
Scheme 2.14



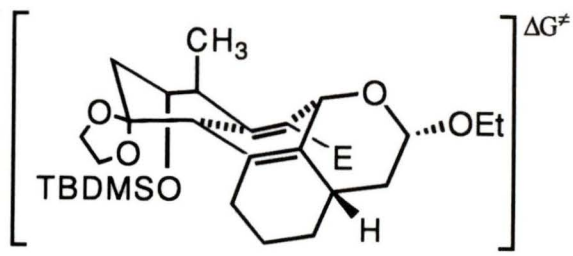
100a



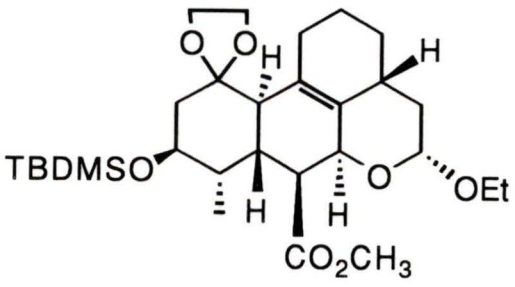
100b



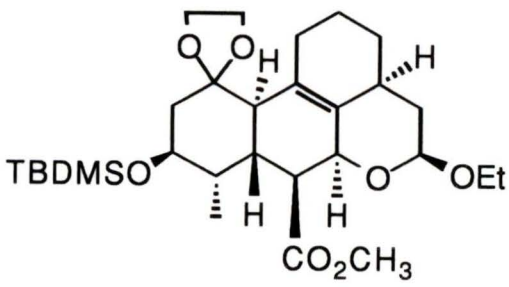
TS_{104}



TS_{105}



104

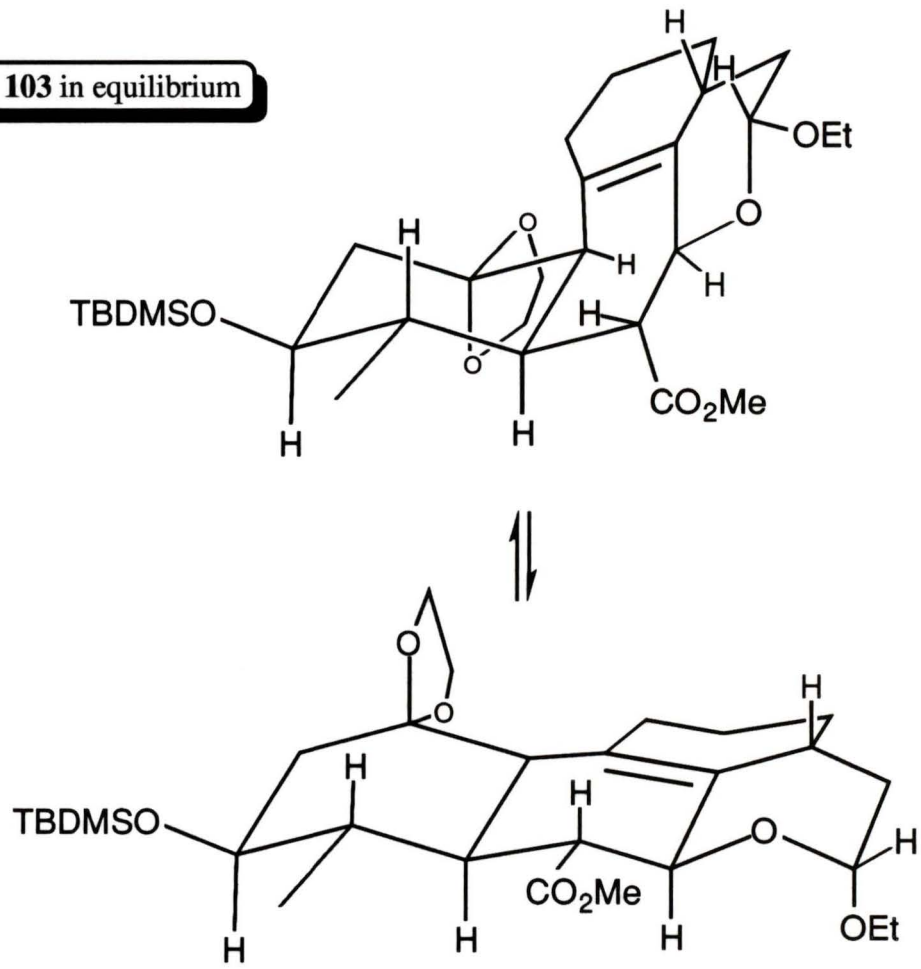


105

Scheme 2.15

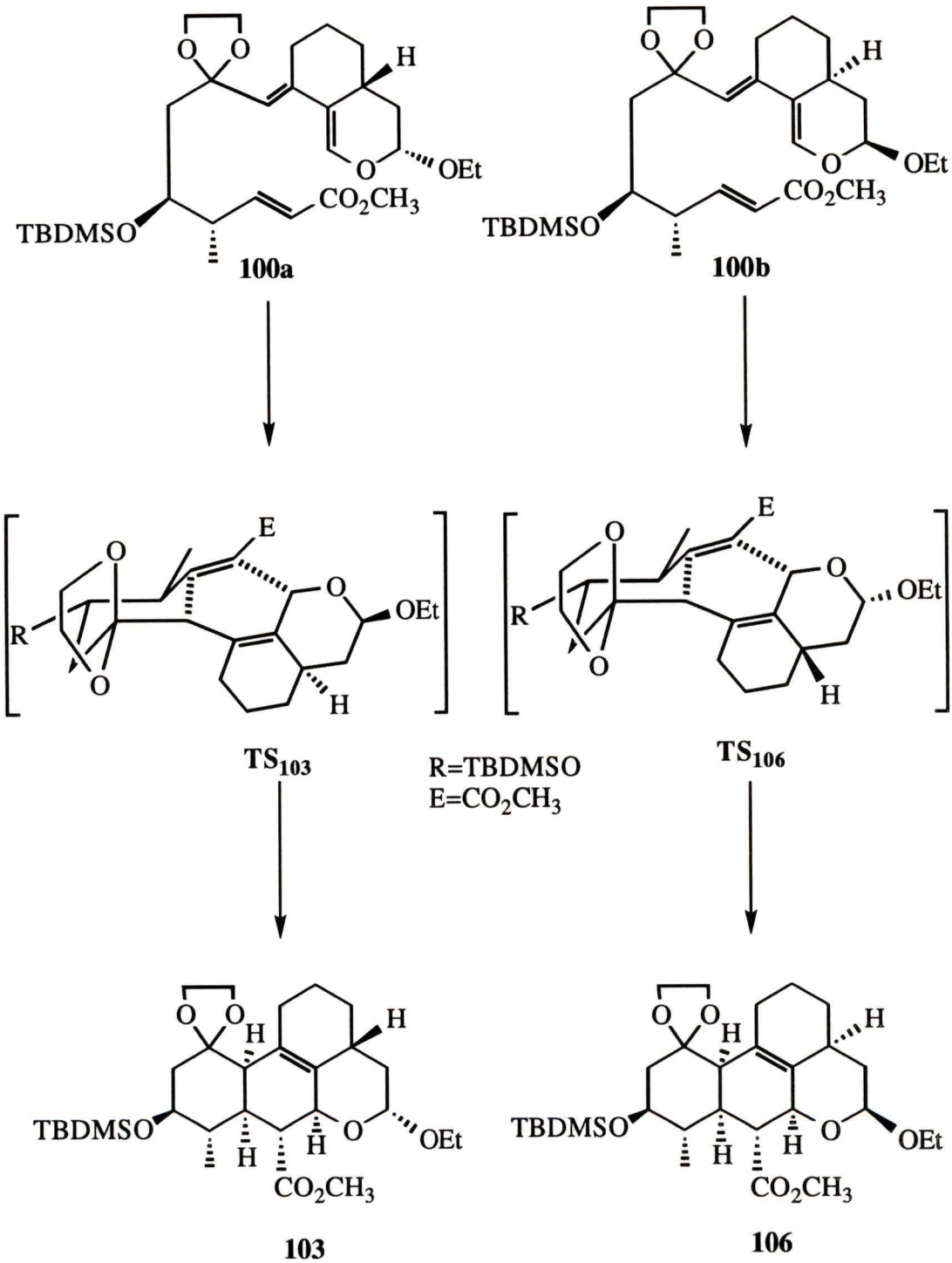
At first it was difficult to elucidate the structure of **103** based on its NMR spectra because of peak broadening. However, upon cooling to -30°C, peak sharpening was observed thoughout the entire ^{1}H and ^{13}C NMR spectra. Based on this observation and subsequent 2-D NMR experiments, we believe that **103** exists as an equilibrium between two conformations **103a** and **103b** (Figure 2.2). We also believe that **103** arose from an *exo* chair-like transition state $\mathbf{TS_{103}}$ (Scheme 2.16). The isolation of **103** indicated that despite the formation of the two major products **101** and **102** under the influences of the two bulky substituents, as expected, a second parameter was also inplayed in the IMDAC. Based on the structure of **103**, the second effect should come from the presence of a ketal group at C_1 which slightly raises the energy of the endo transition state $\mathbf{TS_{101}}$ and $\mathbf{TS_{102}}$. The result of this was the possibility for the IMDAC to go *via* a exo chair-like transition state ($\mathbf{TS_{103}}$). We also believe that there was a fourth isomer (**106**) formed in the same fashion as **103** since **100** is a mixture of two diastereomers. However, we did not observe any other product. This led us to speculate that the energy difference between $\mathbf{TS_{101}}$ and $\mathbf{TS_{106}}$ is greater than that of $\mathbf{TS_{102}}$ and $\mathbf{TS_{103}}$. As a result, Compound **106** was not formed or only in a very small quantity.

Conformers of **103** in equilibrium



103

Figure 2.2


TBDMSO
OEt
CO_2CH_3
100a
100b
TS_{103}
TS_{106}
R=TBDMSO
E=CO_2CH_3
103
106

Scheme 2.16

CHAPTER THREE
CONCLUSION

A new, enantioselective synthetic route to an advanced, optically pure tetracyclic quassinoid intermediate was developed. Several key reactions were involved in this methodology. A chiral aldol condensation reaction was employed to fix the absolute stereochemistry for the *t*-butyldimethylsilyloxy group at C_3 and the methyl at C_4 position. This was followed by an inverse electron demand hetero-nucleus Diels-Alder cycloaddition which generated the D ring in a complete *endo* selective fashion. Under the influence of the two bulky substituents at C_3 and C_4, the intramolecular Diels-Alder cycloaddition of compound **100** proceeded preferentially *via* the more stable *endo* chair-like transition states *regardless of the stereochemistry of* C_{14}. The ketal at C_1 may slightly raise the energy of the *endo* transition states leading to the formation of the observed *exo* adduct. In addition, ring A was fully functionalized as a result of the two substituents at C_3 and C_4, which can be conveniently transformed to the appropiate functionalities in natural quassinoids.

Base on the preferred formation of the tetracycles **101** and **102**, it is clear that the absolute stereochemistry of C_4, C_5, C_6, C_7 and C_{10} can be controlled As Spino and Liu have already demonstrated the method to control the stereochemistry at C_{14},[42] it should be possible to control the absolute stereochemistry of C_4, C_5, C_6, C_7, C_{10}, C_{14} which are common to all quassinoids.

CHAPTER FOUR
EXPERIMENTAL

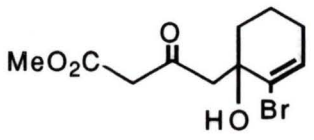
General Procedure

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; dichloromethane, 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) or florisil from Fisher Scientific (100-200 mesh).

Proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined at room temperature (except where otherwise stated), on a Brüker WM 250 (250 MHz) spectrometer or a Brüker AMX 360 (360 MHz) spectrometer with $CDCl_3$ as solvent (except where otherwise stated) 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 a Perkin-Elmer 1330 or on a Brüker IFS 25 FT-IR Spectro-photometer 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 was 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. Optical rotations were determined on a Autopol 3 automatic polarimeter using sodium *D* line (wavelength=589 nm) as the source of irradiation.

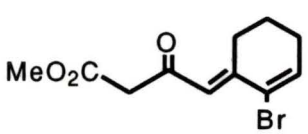
1-{1-Carbomethoxy-2-oxo-3-propyl}-1-hydroxy-2-bromo-2-cyclohexene 65.



Methyl acetoacetate (0.67 g, 5.7 mmol) was added dropwise to a suspension of NaH (0.16g, 6.7 mmol) in dried THF (10 mL) at 0°C. After effervescence had stopped, the reaction mixture was allowed to stir at that temperature for an additional 15 minutes followed by the dropwise addition of *n*-butyllithrium in hexane (2.2 M, 2.6 mL, 5.7 mmol). Stirring was continued for an additional 1 hour before the dropwise addition of 2-bromo-2-cyclohexen-1-one (1 g, 5.7 mmol) in dried THF (3 mL). The mixture was stirred at 0°C for 1 hr before quenching with a saturated solution of ammonium chloride (3 mL). The aqueous phase was separated and extracted with

diethyl ether (3x5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (1:1) gave 2-bromo-1-{1-carbomethoxy-2-oxo-3-propyl}-1-hydroxy-2-cyclohexene as a colorless oil (1.43 g, 85%). The β-keto ester product existed as an equilibrium between the keto and enol forms. **Keto form**: **^{1}H NMR** ($CDCl_3$): δ 6.21 (t, 1H, J=3.7 Hz), 3.72 (s, 3H), 3.53 (s, 2H), 3.35 (bs, 1H), 3.16 (d, 1H, J=16.4 Hz), 2.81 (d, 1H, J=16.4 Hz), 2.14-1.97 (m, 4H), 1.82-1.71 (m, 1H), 1.67-1.58 (m, 1H); **^{13}C NMR** ($CDCl_3$): δ 202.9 (s), 167.3 (s), 133.9 (d), 128.2 (s), 72.4 (s), 52.4 (q), 51.5 (t), 50.5 (t), 36.2 (t), 27.8(t), 18.5 (t); **Enol form**: **^{1}H NMR** ($CDCl_3$): δ 12.18 (s, 1H), 6.20 (t, 1H, J=3.7 Hz), 5.09 (s, 1H), 3.72 (s, 3H), 2.82 (d, 1H, J=14.5 Hz), 2.41 (d, 1H, J=14.5 Hz); **^{13}C NMR** ($CDCl_3$): δ 174.0 (s), 172.7 (s), 133.5 (d), 129.1 (s), 92.4 (d), 72.5 (s), 51.3 (q), 45.5 (t), 35.7 (t), 27.9 (t), 18.8 (t); **IR** ($CHCl_3$, cm^{-1}): 3600-3320 (br), 1748 (s), 1714 (s), 1646 (w); **MS** (*m/z*, relative intensity): 274 (M^+, 50), 272 (45), 262 (43), 261 (45), 259 (43), 232 (100), 230 (100); **Exact mass** calcd for $C_{11}H_{13}O_3{}^{79}Br$: 272.0048, found: 272.0073, (calcd for $C_{11}H_{13}O_3{}^{81}Br$): 274.0028, found: 274.0041; **Anal.** (calcd for $C_{11}H_{15}O_4Br$): C 45.38, H 5.19, Br 27.45, found: C 45.28, H 5.22, Br 27.43.

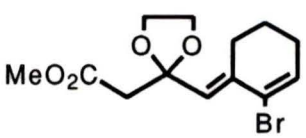
1-{1-Carbomethoxy-2-oxo-3-propylene}-2-bromo-2-cyclohexene 67.



To a 200 mL round-bottomed flask charged with bromide **65** (1g, 0.0034 mol) at 0°C was added trifluoroacetic acid (5 mL, 0.06 mol). The mixture was allowed to stir

at that temperature for 1 h before quenching with a mixture of water (50 mL) and ether (50 mL). The organic layer was separated, washed with water (3x30 mL), neutralized with sodium bicarbonate and stirred with triethylamine (5 mL) at room temperature for 30 min. It was then washed with brine (20 mL) and water (2x20 mL), dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave compound **67** as a colorless oil (0.65g, 69%). **Keto form:** ^{1}**H NMR** ($CDCl_3$): δ 6.72 (t, 1H, J=4.7 Hz), 6.51 (s, 1H), 3.67 (s, 3H), 3.50, (s, 2H), 3.00-2.96 (m, 2H), 2.24 (dt, 2H, J=6.3, 4.7 Hz), 1.67 (qi, 2H, J=6.3Hz); ^{13}**C NMR** ($CDCl_3$): δ 192.3 (s), 167.7 (s), 150.6 (s), 143.3 (d), 123.2 (d) 122.3 (s), 52.1 (q), 50.7 (t), 28.4 (t), 27.9 (t), 21.2 (t); **Enol form:** ^{1}**H NMR** ($CDCl_3$): δ 8.77 (s, 1H), 6.50 (t, 1H, J=4.7 Hz), 6.09 (s, 1H), 5.07 (s, 1H), 2.20 (dt, 2H, J=6.3, 4.7 Hz), 1.68 (qi, 2H, J=6.3Hz); ^{13}**C NMR** ($CDCl_3$): δ 173.1 (s), 171.0 (s), 143.2 (s), 138.7 (d), 123.1 (s), 122.4 (d), 93.3 (d), 51.1 (q), 28.21 (t), 28.0 (t), 21.7 (t); **IR** ($CHCl_3$, cm^{-1}): 1720 (s); **MS** (*m/z*, relative intensity): 275 (M^+, 7), 273 (M^+, 7), 241 (5), 225 (10), 193 (100); **Exact mass** calcd for $C_{11}H_{13}O_3{}^{79}Br$: 272.0048, found: 272.0038.

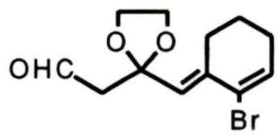
(*E*)-2-Bromo-1-{1-carbomethoxy-2-(1,3-dioxolan-2-yl)-3-propylidene}-2-cyclohexene 68.



A mixture of ester **67** (1.5g, 5.5mmol), dried benzene (60 mL), ethylene glycol (3 mL, 0.054 mol) and *p*-toluenesulfonic acid monohydrate (0.1g, 0.5 mmol) was heated at reflux with azeotropic removal of water (Dean-Stark trap) for 36 h. The

reaction was cooled to room temperature, triethylamine (2 mL) was added and the reaction was stirred for 30 min. The mixture was filtered through a cake of silica gel (15g) on anhydrous magnesium sulfate (5g) washing with dichloromethane (150 mL). Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave **68** as a colorless oil (1.52g, 87%). **^{1}H NMR** ($CDCl_3$): δ 6.32 (t, 1H, J=4.5 Hz), 5.91 (s, 1H), 3.96-3.83 (m, 4H), 3.64 (s, 3H), 2.82 (s, 2H), 2.69 (m, 2H), 2.18 (dt, 2H, J=6.2, 4.5 Hz), 1.67 (qi, 2H, J=6.2 Hz); **^{13}C NMR** ($CDCl_3$): δ 169.2 (s), 136.7 (s), 134.9 (d), 130.1 (d), 123.2 (s), 107.0 (s), 64.5 (t), 64.5 (t), 51.8 (q), 43.8 (t), 28.1 (t), 26.6 (t), 21.8 (t); **IR** ($CHCl_3$, cm^{-1}): 1736 (s), 1632 (w); **MS** (*m/z*, relative intensity): 318 (M^+, ^{81}Br, 53), 316 (M^+, ^{79}Br, 53), 245 (100), 243 (100); **Exact mass** calcd for $C_{13}H_{17}O_4{}^{81}Br$: 318.0290, found: 318.0293, (calcd for $C_{13}H_{17}O_4{}^{79}Br$): 316.0310, found 316.0309: **Anal.** (calcd for $C_{13}H_{17}O_4Br$): C 49.23, H 5.40, O 20.18, Br 25.19, found: C 49.27, H 5.42, Br 25.16.

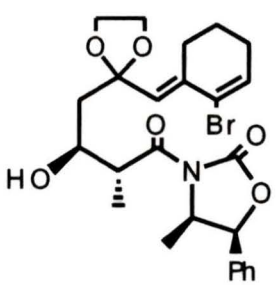
(*E*)-2-Bromo-1-{1-oxo-2-(1,3-dioxolan-2-yl)-3-butylidene}-2-cyclohexene 69.



To a solution of protected ester **68** (1.27g, 4.0 mmol) in dry toluene (30 mL) at -78°C was added dropwise diisobutylaluminum hydride (3.67 mL, 1.2M in hexane, 4.4 mmol). The reaction mixture was stirred for 30 min followed by quenching at -78°C with water (2 mL). The solution was allowed to warm up to room temperature after which time a sodium hydroxide solution (15% w/v, 4 mL) was added and the resulting mixture stirred for 15 min. The aqueous layer was separated and extracted with diethyl ether (3x10 mL), the organic layers combined, washed with brine (20 mL) and

water (20 mL), dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave **69** as a colorless oil (0.80g, 70%). **^{1}H NMR** ($CDCl_3$): δ 9.70 (t, 1H, J=2.9 Hz), 6.37 (t, 1H, J=4.5Hz), 5.89 (s, 1H), 4.02-3.90 (m, 4H), 2.80 (d, 2H, J=2.9 Hz), 2.73 (m, 2H), 2.19 (dt, 2H, J=6.1, 4.5 Hz), 1.69 (qi, 2H, J=6.1 Hz); **^{13}C NMR** ($CDCl_3$): δ 199.8 (s), 137.6 (s), 135.4 (d), 129.8 (d),122.9 (s), 104.9 (s), 64.5 (t), 64.5 (t), 50.9 (t),28.2 (t), 26.7 (t), 21.9 (t); **IR** ($CHCl_3$, cm^{-1}): 1740 (s), 1650 (w); **MS** (*m/z*, relative intensity): 288 (M^+, 5), 286 (M^+,4), 245 (100), 243 (97); **Exact mass** calcd for $C_{12}H_{15}O_3{}^{79}Br$: 286.0205, found: 286.0214 (calcd for $C_{10}H_{12}O_2{}^{81}Br$: 245.0000, found: 245.0003).

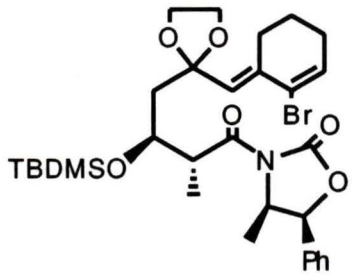
(+)-(4R, 5S)-{(2R, 3S)-(*E*)-6-(2-Bromo-1-cyclohexanylidene)-5-(1,3-dioxolan-2-yl)-3-hydroxy-2-methylhexanoyl}-4-methyl-5-phenyl-2-oxazolidinone 72.



A 200 mL, 2-neck round-bottom flask was charged with oxazolidinone **71** (1.68g, 7.2 mmol) in dried dichloromethane (20 mL). The solution was cooled to -78°C and stirred for 10 min. Then triethylamine (0.95g, 1.31 mL, 9.4 mmol) was added to the solution followed by di-*n*-butylboron triflate and the resulting solution was allowed to warm to 0°C over 1 h and stirred at 0°C for an additional 1 h. A solution of aldehyde **69** (2.07g, 7.2 mmol) in dry dichloromethane (20 mL) was added dropwise and stirring was continued for 1 hr. A pH 7.4 buffer (phosphate) (10 mL) was added

to the reaction mixture followed by an ice-cold mixture of 30% hydrogen peroxide (15 mL), methanol (30 mL) and the same buffer (15 mL) while stirring was continued for another hour. Then a solution of saturated aqueous sodium bicarbonate was added slowly to the cold mixture while stirring vigorously for 20 min. The aqueous phase was then separated, extracted with dichloromethane (3x30 mL). The organic phase combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (1:1) gave the aldol adduct **72** as a viscous oil (2.91g, 77%). **^{1}H NMR** ($CDCl_3$): δ 7.63-7.22 (m, 5H), 6.29 (t, 1H, J=4.6 Hz), 5.80 (s, 1H), 5.61 (d, 1H, J=7.2 Hz), 4.70 (dq, 1H, J=7.2, 6.6 Hz), 4.15 (m, 1H), 3.99-3.75 (m, 5H), 3.57 (bs, 1H, D_2O exchangeable), 2.67 (m, 2H), 2.15 (dt, 2H, J=5.8, 4.6 Hz), 2.01 (m, 2H), 1.64 (qi, 2H, J=5.8 Hz), 1.18 (d, 3H, J=7.0 Hz), 0.81 (d, 3H, J=6.6 Hz); **^{13}C NMR** ($CDCl_3$): δ 175.2 (s), 152.5 (s), 136.8 (s),134.7 (d), 133.1 (s), 130.5 (d), 128.4 (d), 125.4 (d), 124.4 (d), 123.0 (s), 109.4 (s), 78.6 (d), 68.5 (d), 64.0 (t), 63.7 (t), 54.7 (d), 42.4 (d), 40.5 (t), 28.0 (t), 26.3 (t), 21.7 (t), 14.1(q) 12.0 (q); **IR** ($CHCl_3$, cm^{-1}): 3500 (br), 1760 (s), 1670 (s); **MS** (*m/z*, relative intensity): 522 (M+1, 40), 520 (M+1, 40), 504 (80), 502 (100); **Anal.** (calcd for $C_{25}H_{30}O_6BrN$): H 5.82, C 57.79, N 2.70, O 18.49, Br 15.20, found: C 57.74; H 5.88; N 2.77; $[\alpha]^{25}_D$=+11.03° (c 0.68, $CHCl_3$).

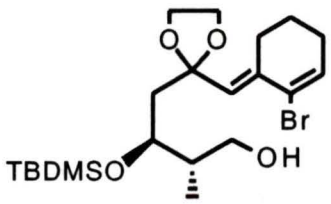
(-)-(4R, 5S)-{(2R, 3S)-(*E*)-6-(2-Bromo-1-cyclohexanylidene)-5-(1,3-dioxolan-2-yl)-3-*t*-butyldimethylsilyloxy-2-methylhexanoyl}-4-methyl-5-phenyl-2-oxazolidinone 73.



A solution of the alcohol **72** (3.40g, 6.5 mmol) in dichloromethane (30 mL) and *t*-butyldimethylsilyl triflate (1.72g, 6.5 mmol) was cooled to 0°C and stirred for 10 min before the dropwise addition of triethylamine (0.66g, 0.91 mL, 6.5 mmol). The resulting mixture was allowed to stir for 30 min and then it was quenched at the same temperature with a solution of saturated sodium bicarbonate (5 mL). The layers were separated, the aqueous layer extracted with dichloromethane (3x15 mL), the combined organic layers washed with brine (20 mL) and water (20 mL), dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave **73** as a viscous oil (3.25g, 79%). **^{1}H NMR** ($CDCl_3$): δ 7.42-7.24 (m, 5H), 6.33 (t, 1H, J=4.4 Hz), 5.88 (s, 1H), 5.58 (d, 1H, J=6.7 Hz), 4.67 (qi, 1H, J=6.7 Hz), 4.30 (m, 1H), 4.1 (m, 1H), 4.04-3.95 (m, 2H), 3.83-3.77 (m, 2H), 2.71 (m, 2H), 2.27 (dd, 1H, J=15.2, 8.1 Hz), 2.19 (dt, 2H, J=5.8, 4.4 Hz), 1.98 (dd, 1H, J=15.2, 3.2 Hz), 1.69 (qi, 2H, J=5.8 Hz), 1.18 (d, 3H, J=6.9 Hz), 0.87 (d, 3H, J=6.7 Hz), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** ($CDCl_3$): δ 175.0 (s), 152.1 (s), 136.3 (s), 134.3 (d), 133.4 (s), 132.1 (d), 128.6 (d), 125.6 (d), 123.6 (s), 108.2 (s), 78.7 (d), 68.6 (d), 63.9 (t), 63.8 (t), 55.4 (d), 43.8 (d), 42.5 (t), 28.3 (t), 26.5 (t), 25.8 (q), 22.0 (t), 18.0 (s), 14.2 (q), 11.1 (q), -4.3 (q), -5.1 (q); **IR** ($CHCl_3$, cm^{-1}): 1780 (s), 1706 (s), 1454 (ms); **MS** (*m/z*, relative

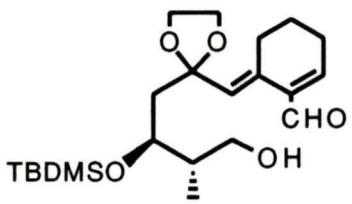
intensity): 636 (M^{+1}, 10), 634 (M^{+1}, 10), 620 (20), 618 (20), 578 (20), 576 (20), 504 (100), 502 (100); **Anal.** (calcd for $C_{31}H_{44}O_6BrNSi$): H 6.99, C 58.67, N 2.21, O 15.16, Si 4.42, Br 12.46, found: C 58.47; H 6.77; N 2.08; $[\alpha]^{25}_D$= –9.70° (c 1.34, $CHCl_3$).

(-)-(*E*)-2-Bromo-1-{(2R, 3S)-3-*t*-butyldimethylsilyloxy-5-(1,3-dioxolan-2-yl)-1-hydroxy-2-methyl-6-hexylidene}-2-cyclohexene 75.



To a solution of **73** (0.45g, 0.71 mmol) in THF (50 mL) at 0°C was added dropwise a solution of lithium borohydride (0.046g, 2.1 mmol) in THF (10 mL). The reaction mixture was allowed to warm up slowly to 4°C and was stirred at that temperature for 10 days. Saturated solution of ammonium chloride (5 mL) was added dropwise to the reaction mixture while stirring continued for another 20 minutes. The aqueous layer was separated and extracted three times with diethyl ether (15 mL each). The organic layers were combined, washed with brine (15 mL) and water (15 mL), dried over anhydrous magnesium sulfate, Evaporation of the solvent *in vacuo* followed by flash chromatography on florisil eluting with hexanes-ethyl acetate (3:1) gave **75** as a colorless oil (0.27 g, 83%). The product is unstable and decomposes slowly at room temperature. **^{1}H NMR** ($CDCl_3$): δ 6.35 (t, 1H, J=4.5 Hz), 5.88 (s, 1H), 4.10 (m, 1H), 4.0-3.8 (m, 4H), 3.52 (m, 2H), 2.75 (m, 2H), 2.3-2.2 (m, 2H), 2.1-2.0 (m, 2H), 1.8-1.7 (m, 2H), 0.99 (s, 9H), 0.82 (d, 3H, J=6.8 Hz), 0.15 (s, 3H), 0.10 (s, 3H); **IR** ($CHCl_3$, cm^{-1}): 3638 (w), 3500-3470 (bw), 1726 (s); $[\alpha]^{25}_D$= –13.0° (c 1.46, $CHCl_3$).

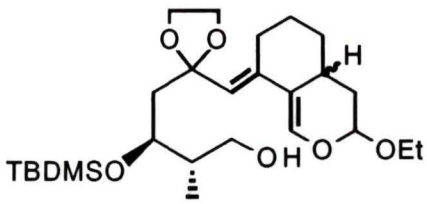
(-)-(*E*)-1-{(2R, 3S)-3-*t*-Butyldimethylsilyloxy-5-(1,3-dioxolan-2-yl)-1-hydroxy-2-methyl-6-hexylidene}-2-formyl-2-cyclohexene 90.



A 25 mL round-bottom flask was charged with a solution of compound **75** (0.116g, 0.25 mmol) in THF (5 mL). The mixture was cooled to -78°C (dry ice-acetone bath) and stirred for 10 min before the dropwise addition of *n*-butyllithium (2.5 M solution in hexane, 0.20 mL, 0.5 mmol). The mixture was stirred for 1 h and then *N,N*-dimethylformamide (0.056g, 0.77 mmol) was added in a dropwise fashion. The resulting mixture was stirred for an additional 2 h and then quenched with a solution of saturated ammonium chloride (2 mL) at -78°C. The reaction mixture was allowed to warm up to room temperature and was then acidified with hydrochloric acid (1N solution in water, 1 mL). The aqueous layer was separated and extracted with diethyl ether (3x5 mL), the organic layers were combined and washed with brine (5 mL) and water (5 mL). Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (2:1) to give **90** as a colorless oily product (0.062g 60% reacted yield) and starting material (0.029g). **^{1}H NMR** ($CDCl_3$): δ 9.45 (s, 1H), 6.73 (t, 1H, J=4.1 Hz), 6.54 (s, 1H), 4.09 (m, 1H), 3.9-3.8 (m, 4H), 3.52 (m, 2H), 2.58 (m, 2H), 2.45 (m, 2H), 2.15 (dd, 2H, J=14.7, 7.6 Hz), 1.99 (m, 1H), 1.94 (dd, 2H, J=14.7, 3.9 Hz), 1.72 (m, 2H), 0.84 (s, 9H), 0.80 (d, 1H, J=6.8 Hz), 0.0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** ($CDCl_3$): δ 193.4 (d), 154.6 (d), 137.9 (s), 132.3 (s), 130.4 (d), 108.8 (s), 69.7 (d), 66.20 (t), 64.0 (t), 63.7 (t), 42.2 (t), 40.3 (d), 27.2 (t), 25.8 (t), 25.5 (q), 21.9 (t), 18.0 (s), 10.4 (q), -4.2 (q), -4.8 (q); **IR** ($CHCl_3$, cm^{-1}): 3500

(bw), 1692 (ms), 1604 (w); **MS** (*m/z*, relative intensity): 410 (M^+, 5), 396 (40), 377 (20), 349 (100); **Exact mass** calcd for $C_{22}H_{38}O_5Si$: 410.2488, found: 410.2497. **Anal.** (calcd for $C_{22}H_{38}O_5Si$): C 64.35; H 9.34; O 19.49, Si 6.82, found: C 64.52; H 9.44; O 19.61; $[\alpha]^{25}_D$=-12.8° (c 1.33, $CHCl_3$).

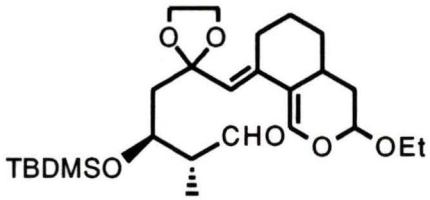
(*E*)-(4R,6R)-10- and (*E*)-(4S,6S)-10-{(2S, 3S)-3-*t*-Butyldimethylsilyloxy-5-(1,3-dioxolan-2-yl)-1-hydroxy-2-methyl-6-hexylidene}-4-ethoxy-3-oxabicyclo[4.4.0]non-1-ene 97a and 97b respectively.



To a mixture of **90** (0.334g, 8.14 mmol) in ethyl vinyl ether (5 mL) was added $Yb(FOD)_3$ (0.1g, 0.977 mmol). The reaction was allowed to stir under an argon atmosphere at room temperature for 10 days. Evaporation of the excess ethyl vinyl ether *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (3:1) gave a 1:1 mixture of two isomeric compounds **97a** and **97b** as a colorless oil (0.31g, 80%). Most signals of the two isomers in the NMR spectra are distinguishable. However, it was impossible to assign the resonances to a particular isomer. **^{1}H NMR** ($(CD_3)_2CO$): δ 6.44 (d, 1H, J=1.6 Hz), 6.39 (d, 1H, J=1.6 Hz), 5.24 (d, 1H, J= 1.9 Hz), 5.23 (d, 1H, J= 1.9 Hz), 4.82 (dd, 1H, J= 9.5, 2.1 Hz), 4.80 (dd, 1H, J= 9.5, 2.1 Hz), 4.20 (m, 1H), 4.18 (m, 1H), 3.9-3.1 (m, 18H), 2.4-1.1 (m, 24H), 1.15 (t, 6H, J=6.0 Hz), 0.862 (s, 9H), 0.860 (s, 9H), 0.804 (d, 3H, J=6.7 Hz), 0.802 (d, 3H, J=6.7 Hz), 0.10 (s, 3H), 0.07 (s, 3H), 0.060 (s, 3H), 0.055 (s, 3H); **^{13}C NMR** ($(CD_3)_2CO$): δ 140.6 (s), 140.4 (s), 136.8 (d), 136.7 (d), 123.9 (d), 123.7 (d), 120.1

(s), 119.9 (s), 109.1 (s), 108.9 (s), 100.4 (d), 100.4 (d), 68.8 (d), 68.5 (d), 65.6 (t), 65.4 (t), 65.3 (t), 64.8 (t), 64.7 (t), 64.6 (t), 64.3 (t), 64.1 (t), 44.5 (t), 44.5 (t), 41.4 (d), 40.8 (d), 37.2 (t), 37.2 (t), 34.8 (d), 34.8 (d), 33.9 (t), 33.8 (t), 28.9 (t), 28.8 (t), 26.3 (q), 26.3 (q), 25.8 (t), 25.7 (t), 18.7 (s), 18.7 (s), 15.5 (q), 15.5 (q), 9.8 (q), 9.6 (q), -3.9 (q), -4.0 (q), -4.7 (q); -4.7 (q); **IR** (CH_2Cl_2, cm^{-1}): 3460 (bm), 1735 (s), 1613 (w); **MS** (*m/z*, relative intensity): 483 (M+1, 4), 421 (15), 375 (11), 289 (21), 112(100); **Exact mass** calcd for $C_{26}H_{46}O_6Si$: 482.3064, found: 482.3051; **Anal.** (calcd for $C_{26}H_{46}O_6Si$): C 64.69, H 9.61, O 19.90, Si 5.80, found : C 64.32, H 9.70.

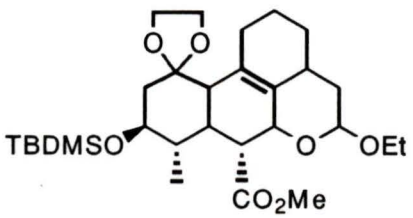
(*E*)-(4R,6R)-10- and (*E*)-(4S,6S)-10-{(2R,3S)-3-*t*-butyldimethylsilyloxy-5-(1,3-dioxolan-2-yl)-1-oxo-2-methyl-6-hexylidene}-4-ethoxy-3-oxabicyclo[4.4.0]non-1-ene 98.



To a mixture of the Dess-Martin periodinane (0.079g, 0.19 mmol) in dichloromethane (10 mL) at room temperature was added pyridine (0.15 mL, 1.9 mmol). The reaction mixture was allowed to stir for 10 minutes before the dropwise addition of alcohols **97** in dichloromethane (0.095g, 0.20 mmol). Stirring was continued for an extra 45 min. The reaction mixture was cooled to 0°C and a mixture of $Na_2S_2O_3$ (5% solution, 7 mL) and a saturated solution of sodium bicarbonate (12 mL) was added and stirring was continued for 1 hr. The solution was diluted with diethyl ether (5 mL), the aqueous layer was separated and extracted three times with diethyl ether (5 mL each). The organic layers were combined and washed with water (10 mL),

dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes-ethyl acetate (5:1) afforded a colorless oil (0.074 g, 82%). **^{1}H NMR** ($(CD_3)_2CO$): δ 9.62 (d, 2H, J=0.5 Hz), 6.40 (d, 1H, J=1.6 Hz), 6.39 (d, 1H, J=1.6 Hz), 5.27 (bs, 2H), 4.82 (d, 2H, J=9.4 Hz), 4.60 (m, 2H), 4.0-3.1 (m, 12H), 2.68 (qm, 2H, J= 6.9 Hz), 2.4-1.1 (m, 22H), 1.17 (t, 6H, J=6.0 Hz), 1.06 (d, 3H, J=7.2 Hz), 1.05 (d, 3H, J=7.2 Hz), 0.81 (s, 18H), 0.10 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); **IR** ($CHCl_3$, cm^{-1}):2840 (w), 1715 (w); **MS** (*m/z*, relative intensity): 482 (M^+, 17), 481 (58), 480 (11), 479 (13), 465 (30), 435 (100); **Exact mass** calcd for $C_{26}H_{44}O_6Si$: 480.2907, found: 480.2879; **Anal.** (calcd for $C_{26}H_{44}O_6Si$): C 64.96, H 9.23, O 19.98, Si 5.82, found : C 64.91, H 9.41.

(-)-$\Delta^{9,17}$-(1R,3S,5S,10S,13S,14S,15S,16R)- and
(-)-$\Delta^{9,17}$-(1R,3R,5R,10S,13S,14S,15S,16R)- and
(+)-$\Delta^{9,17}$-(1S,3R,5R,10R,13S,14S,15S,16R)-3-ethoxy-16-carbomethoxy-14-methyl-13-*t*-butyldimethylsilyloxy-11-{1,3-dioxolan-1-yl}-2-oxatetracyclo[7.7.1.$0^{5,17}$.$0^{10,15}$]hexadec-9-ene <u>101</u>, <u>102</u>, and <u>103</u> respectively.



Methyl diethylphosphonoacetate (0.51 mL, 0.47M solution in benzene, 0.24 mmol) was added slowly to a suspension of sodium hydride (5.6 mg, 0.24 mmol) in dried tetrahydrofuran (5 mL) at 0°C. The reaction mixture was stirred for 1 h and then added to a solution of aldehyde **98** (94 mg, 0.20 mmol) in tetrahydrofuran (4 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 a saturated aqueous solution of ammonium chloride (7 mL). The aqueous layer was separated and extracted with diethyl ether. The combined organic portions were washed with brine (5 mL) and dried over anhydrous magnesium sulfate. Removal of solvent *in vacuo* followed by flash column chromatography eluting with hexanes-ethyl acetate (6:1) yielded (*E*)-(4R,6R)-10- and (*E*)-(4S,6S)-10-{(*E*)-(3S,4S)-4-*t*-butyldimethylsilyloxy-6-(1,3-dioxolan-2-yl)-1-carbomethoxy-3-methylhept-2-en-7-ylidene}-4-ethoxy-3-oxabicyclo[4.4.0]non-1-ene **100** as a colorless oil (105 mg, 100%) which could be isolated for the purpose of identification. **^{1}H NMR** ($(CD_3)_2CO$): δ 7.0 (dd, 2H, J=15.0, 6.5 Hz), 6.40 (d, 2H, J=1.6 Hz), 5.80 (d, 2H, J= 15.0 Hz), 5.24 (bs, 2H), 4.82 (d, 2H, J=9.4 Hz), 4.0-3.1 (m, 14H), 3.82 (s, 6H), 2.75 (m, 2H), 2.4-1.1 (m, 22H), 1.17 (t, 6H, J=6.0 Hz), 1.06 (d, 3H, J=7.2 Hz), 1.05 (d, 3H, J=7.2 Hz), 0.81 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H).

This product was then dissolved in acetone-d_6 and transferred to an NMR tube. Immersing the NMR tube in a water bath at 39°C for 24 hr and monitoring by proton NMR revealed three new ester peaks. After the complete disappearance of the olefin signals of the α,β-unsaturated ester, careful integration of the new signals at 2.88 and 2.81 ppm (C_6) revealed a 1.7:1 ratio of **101** and **102**. The crude product was then purified by flash column chromatography eluting with hexanes-ethyl acetate (9:1) to yield three tetracyclic products **101**:**102**:**103** in a 1.6:1.5:1 isolated ratio. Thus the true ratio of **101**:**102**:**103** works out to be 2.4:1.5:1. The three products were identified as **101** (32 mg) **102** (30 mg), and **103** (20 mg) for a combined isolated yield of 89%. **Tetracycle 101: ^{1}H NMR** ($CDCl_3$): δ 4.90 (t, 1H, J=7.0 Hz), 4.27 (d, 1H, J=8.0 Hz), 4.10-4.07 (m, 1H), 4.04-3.92 (m, 4H), 3.81 (dd, 1H, J=7.1, 2.7 Hz), 3.60(s, 3H), 3.44 (dd, 1H, J=9.8, 7.1 Hz), 3.33-3.26 (m, 1H), 2.88, (dd, 1H, J=8.2, 5.5 Hz), 2.27 (br d, 1H), 2.14-1.99 (m, 5H), 1.75-1.65 (m, 2H), 1.63-1.57 (m, 1H), 1.53-1.47 (m, 1H),

1.37 (dd, 2H, J=12.8, 11.5 Hz), 1.17 (t, 3H, J=7.1 Hz), 1.08 (m, 1H), 1.00 (d, 3H, J=6.4 Hz), 0.86 (s, 9H), 0.01 (s, 6H); **^{13}C NMR** ($CDCl_3$): δ 175.2 (s), 134.8 (s), 127.8 (s), 109.7(s), 97.6 (d), 73.0 (d), 65.8 (d), 63.3 (t), 62.8 (t), 51.5 (d), 50.6 (d), 45.8 (d), 44.5 (d), 42.9 (d), 42.8 (t), 36.5 (t), 29.8 (q), 28.9 (t), 25.8 (q), 25.2 (t), 22.9 (t) 18.0 (s), 15.8 (q), -4.3 (q), -4.7 (q); **IR** ($CHCl_3$, cm^{-1}): 1730 (w), 1070 (s); **MS** (*m/z*, relative intensity): 537 (M^{+1}, 2.1), 535 (6), 521 (5), 491 (39), 126 (100); **$[\alpha]^{25}_D$**=-37° (c 0.5, $CHCl_3$). **Tetracycle 102: ^{1}H NMR** ($(CD_3)_2CO$): δ 4.53 (dd, 1H, J=1.8, 9.6 Hz), 3.99 (bs, 4H), 3.96 (dm, 1H, J=7.6 Hz), 3.75 (dq, 1H, J=7.5, 10.0 Hz), 3.61 (s, 3H), 3.39 (dq, 1H, J=7.5, 10.0 Hz), 3.38 (m, 1H), 2.81 (dd, 1H, J=2.2, 9.0 Hz), 2.38 (m, 1H), 2.27 (m, 2H), 2.16 (dd, 1H, J= 4.7, 17.8 Hz), 1.81 (ddd, 1H, J=2.0, 4.2, 12.1 Hz), 1.80-1.50 (m, 2H), 1.47 (dd, 1H, J= 10.7, 17.8 Hz), 1.4-1.0 (m, 4H), 1.10 (t, 3H, J=7.5 Hz), 0.90 (d, 3H, J=6.9 Hz), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** ($(CD_3)_2CO$): δ 173.6 (s), 131.5 (s), 131.0 (s), 111.6 (s), 101.7 (d), 73.7 (d), 70.9 (d), 64.5 (t), 63.8 (t), 63.6 (t), 51.2 (d), 50.0 (d), 49.0 (d), 47.5 (d), 45.6 (t), 40.7 (t), 38.2 (q), 36.3 (q), 31.0 (t), 29.2 (t), 26.2 (q), 23.6 (t), 18.5 (s), 16.0 (q), 15.5 (q), -4.1 (q), -4.6 (q); **IR** ($CHCl_3$, cm^{-1}): 1730 (w), 1070 (s); **MS** (*m/z*, relative intensity): 537 (M^{+1}, 2), 535 (6), 521 (5), 491 (38), 435 (16), 404 (13), 126 (100); **Exact mass** calcd for $C_{29}H_{48}O_7Si$: 536.3169, found: 536.3166; **Anal.** (calcd for $C_{29}H_{48}O_7Si$): C 64.89; H 9.02; O 20.88; Si 5.22, found: C65.01; H 9.12; **$[\alpha]^{25}_D$=-9.8°** (c 0.52, $CHCl_3$). **Tetracycle 103: ^{1}H NMR** ($CDCl_3$, -30°C): δ 4.96 (t, 1H, J=6.9 Hz), 2.55 (d, 1H, J=10 Hz), 3.96-3.86 (m, 4H), 3.69 (s, 3H), 3.64-3.57 (m, 1H), 3.5 (dd, 1H, J=14.0, 7.1 Hz), 3.38-3.30 (m, 1H), 2.23-2.13 (m, 5H), 1.96-1.87 (m, 3H), 1.77-1.71 (m, 5H), 1.40-1.36 (m, 1H), 1.20-1.16 (m, 1H), 1.14 (t, 3H, J=7.1 Hz), 0.96-0.91 (m, 3H), 0.82 (s, 9H), 0.01 (S, 6H); **^{13}C NMR** ($CDCl_3$): δ 176.5 (s), 135.1 (s), 126.0 (s), 97.3 (d), 73.2 (d), 68.3 (d), 64.6 (t), 63.3 (t), 62.5 (t), 52.2 (d), 50.6 (d), 43.7 (d), 42.7 (d), 42.6 (t), 40.6 (d), 36.0 (t), 28.6 (q), 28.5 (t), 26.5 (t), 25.9 (q), 25.7 (q), 22.3 (t), 19.1 (s),

15.1 (q), 14.8 (q), -4.4 (q), -4.9 (q); **IR** ($CHCl_3$, cm^{-1}): 1727 (w), 1060 (s); **MS** (*m/z*, relative intensity): 537 (M+1, 2), 535 (6), 521 (6), 126 (100); **$[\alpha]^{25}_D$=+8.4°** (c 0.37, $CHCl_3$).

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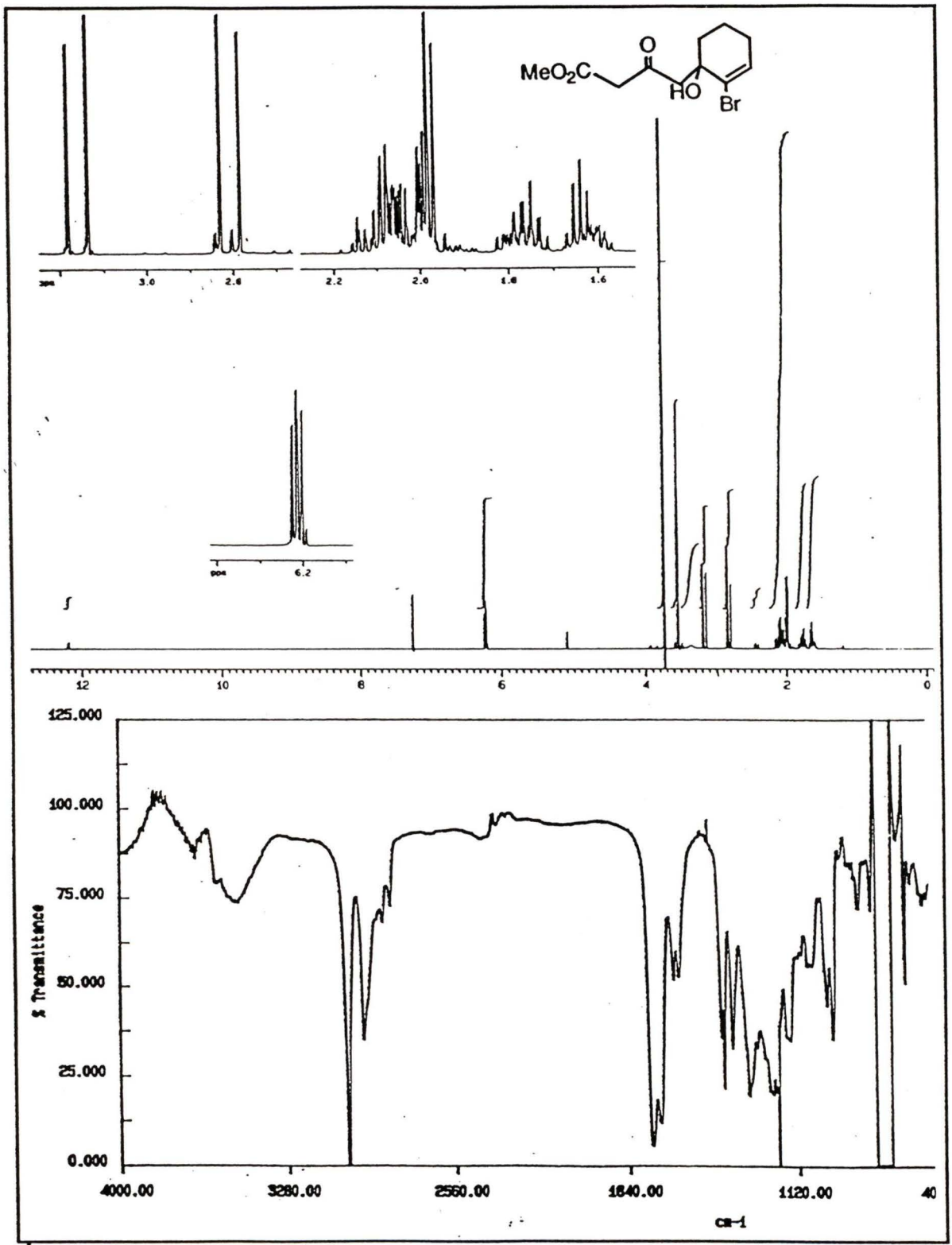
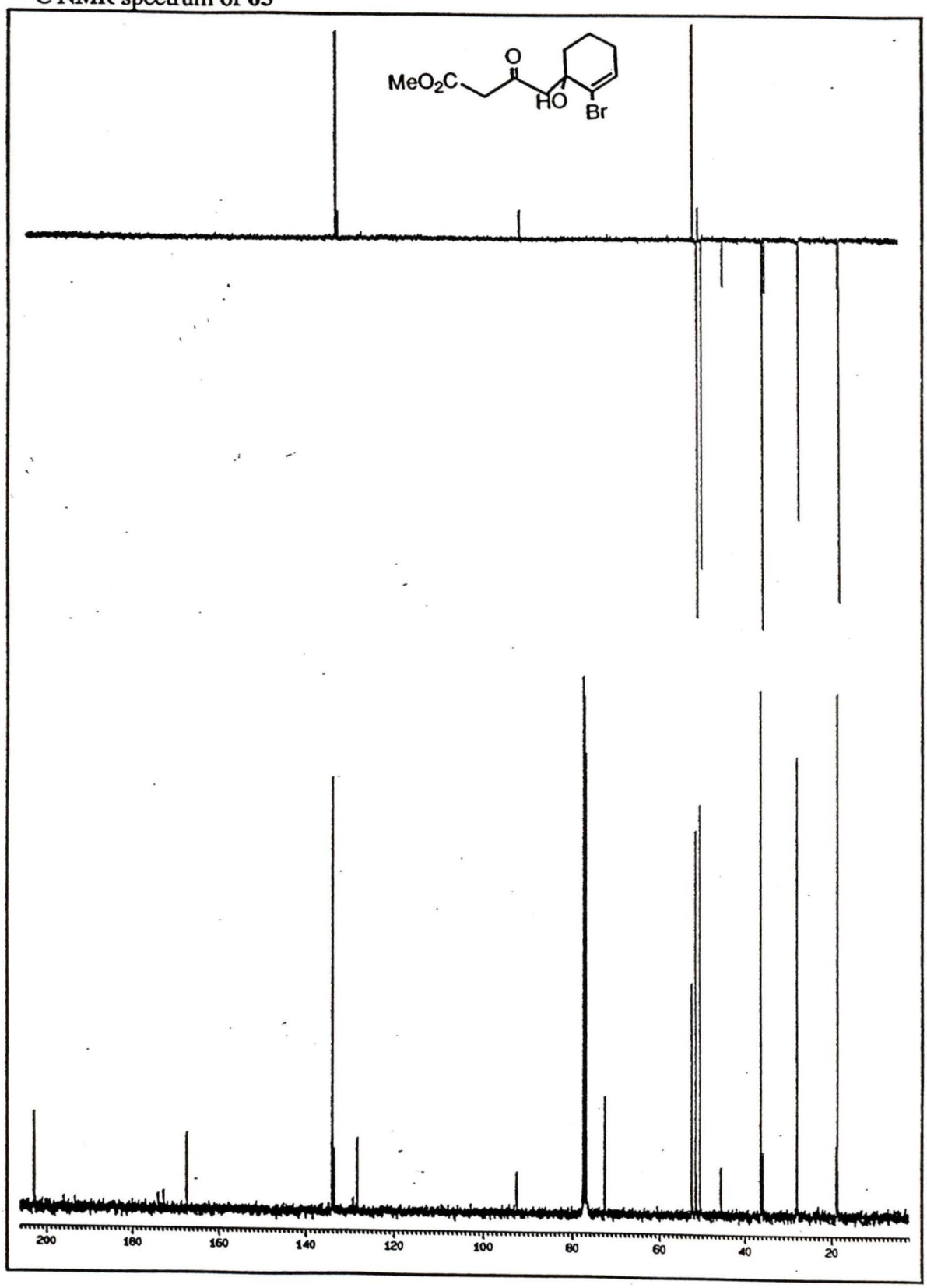
APPENDIX



^{1}H NMR and IR spectra of **65**

^{13}C NMR spectrum of **65**



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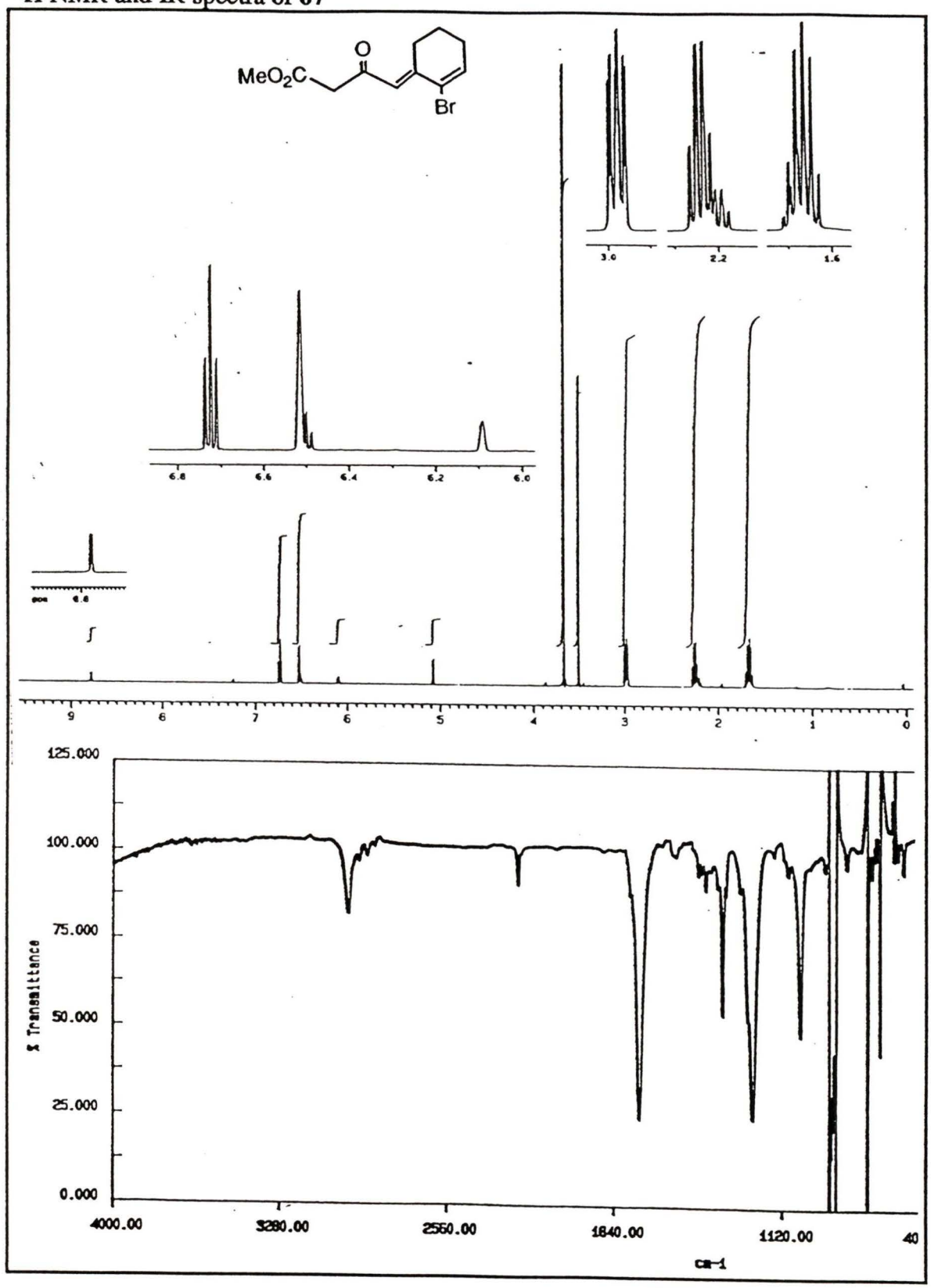

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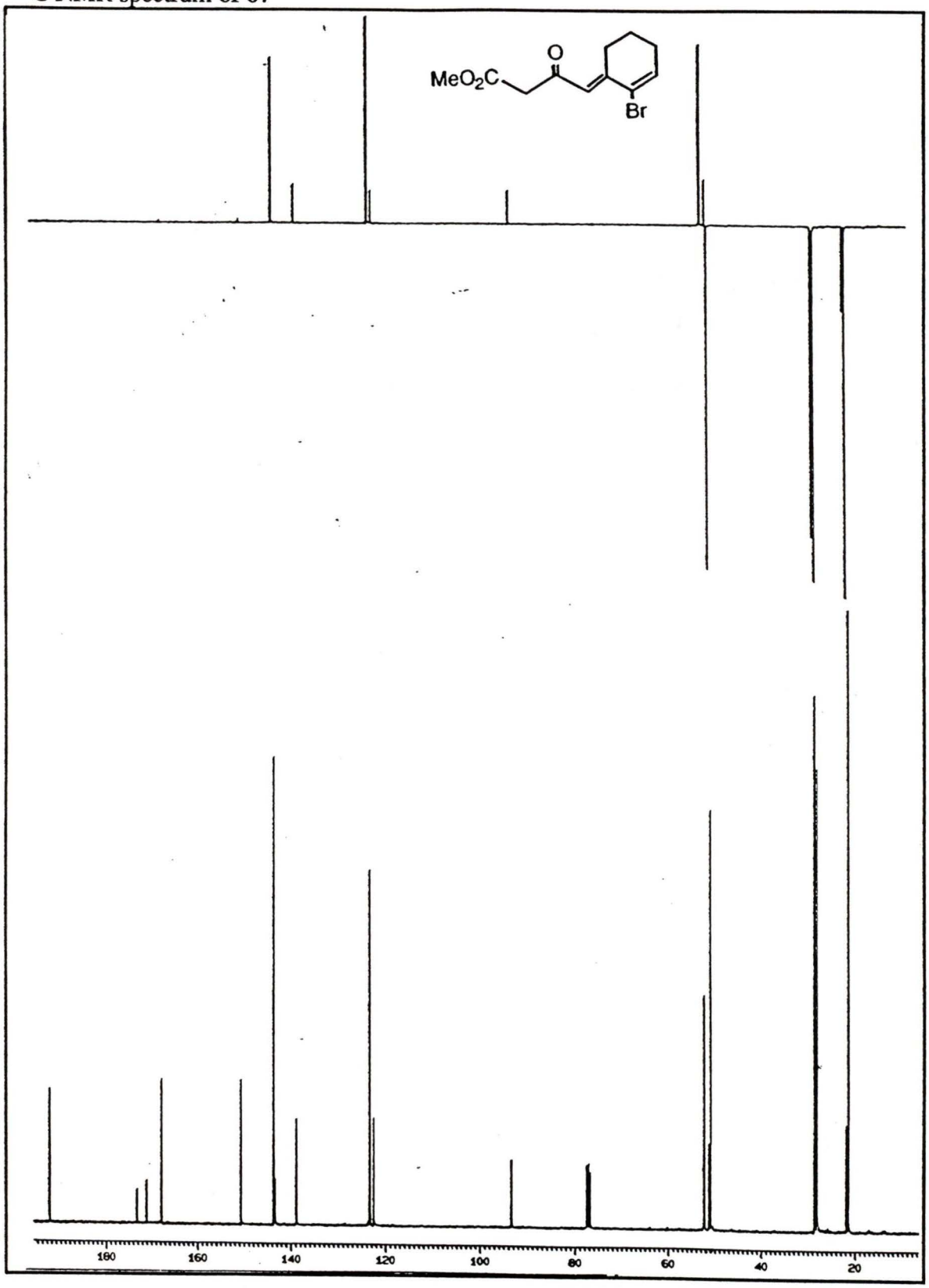

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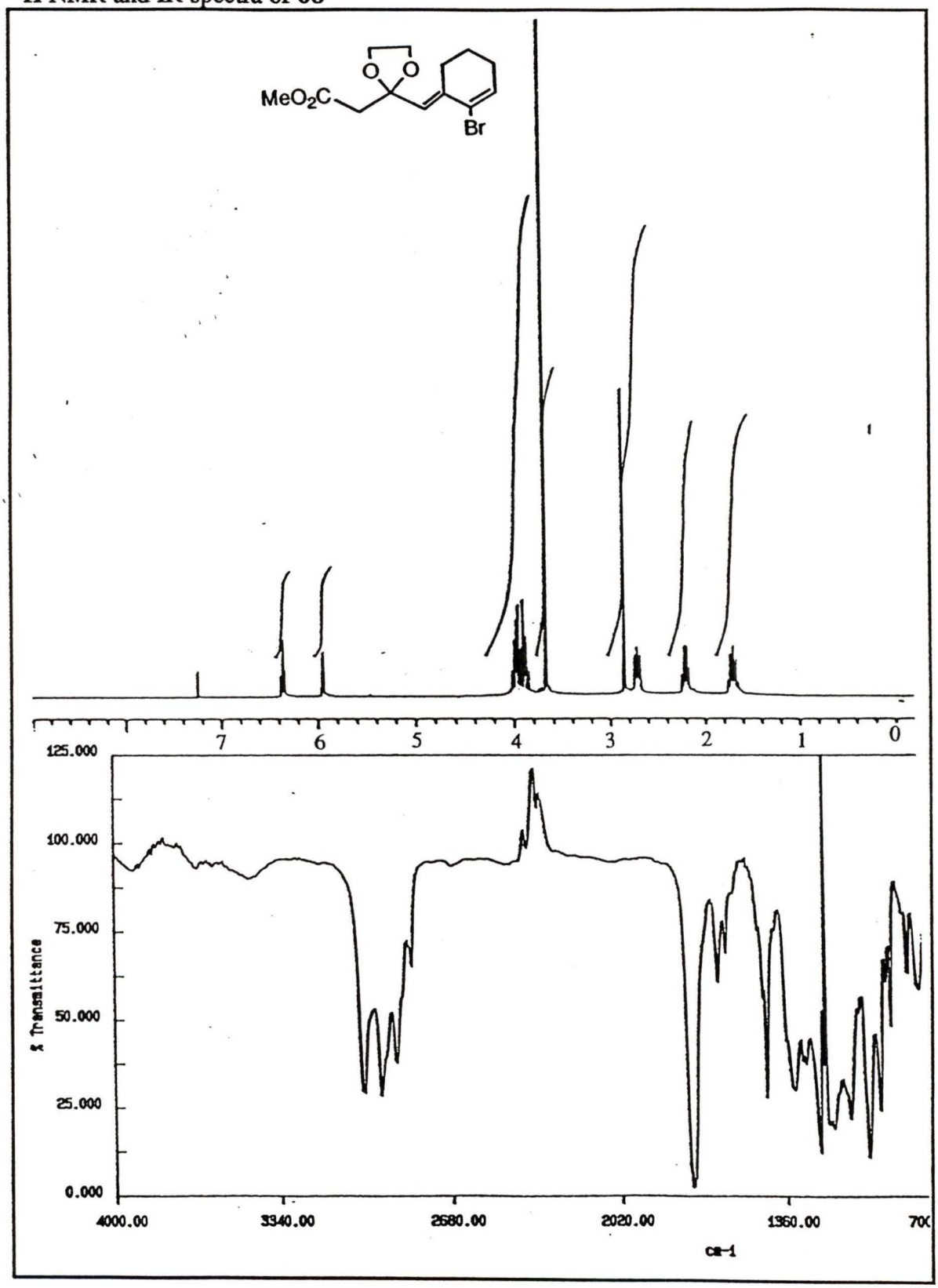

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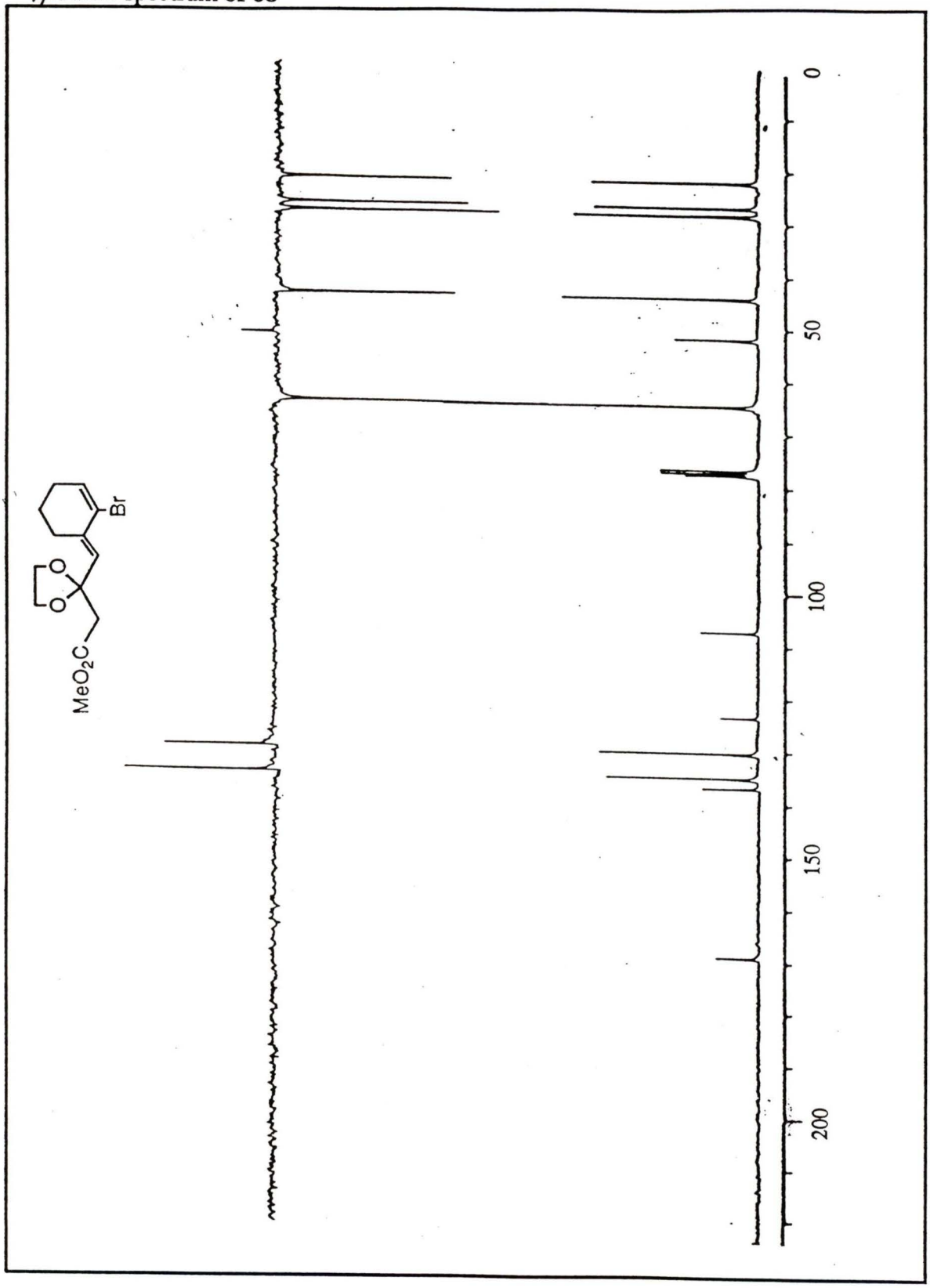
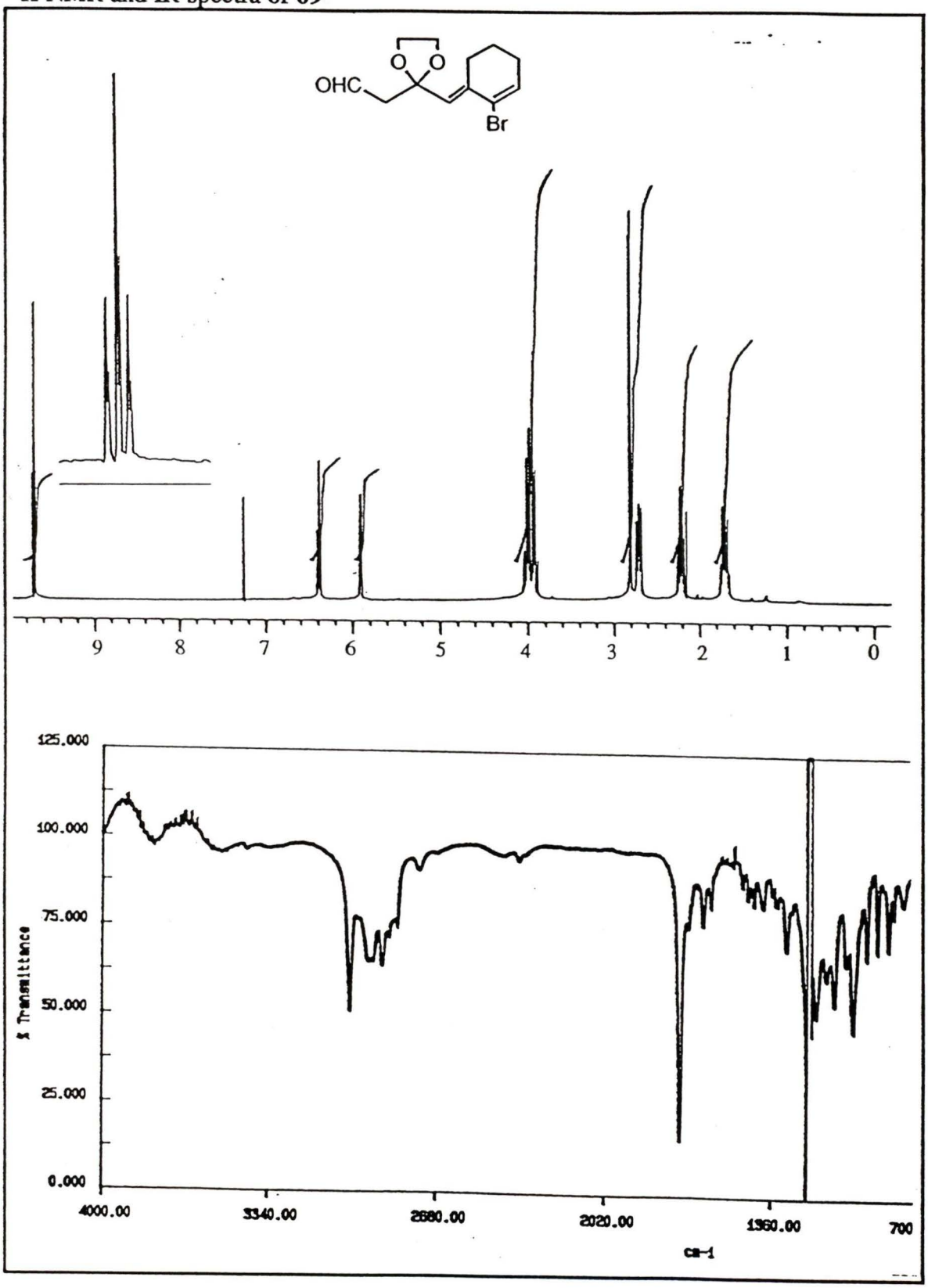


^{1}H NMR and IR spectra of **69**



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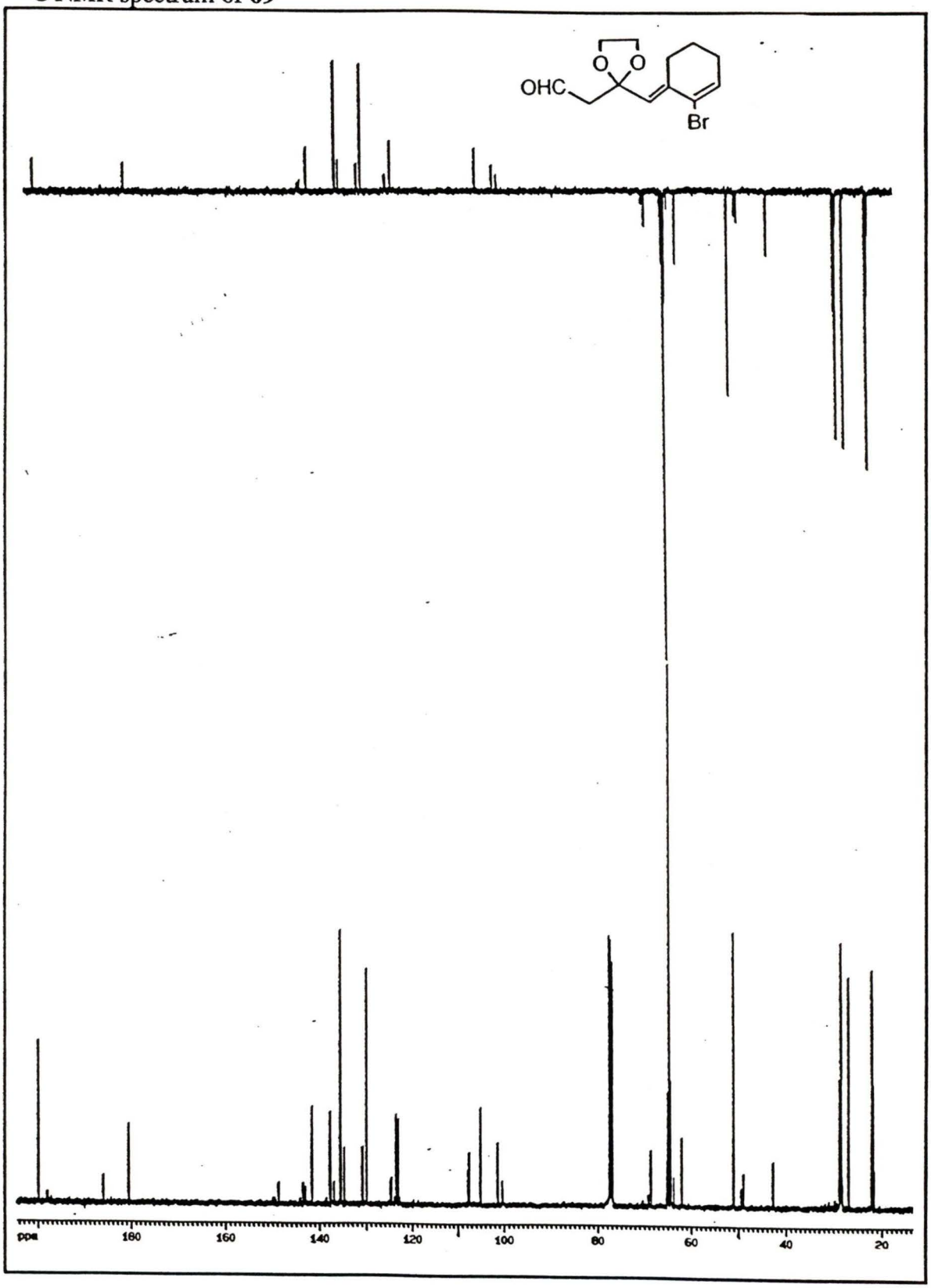
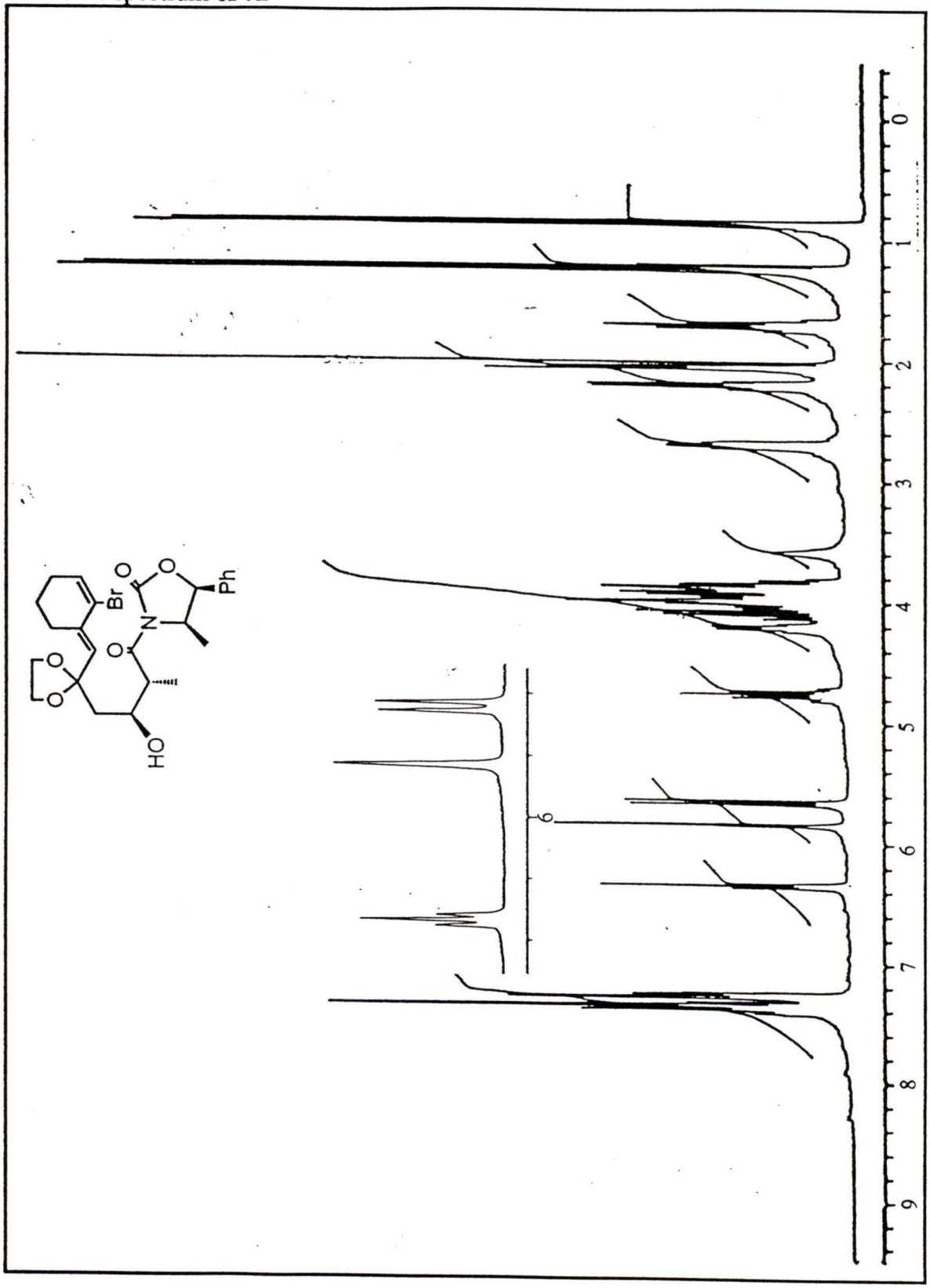
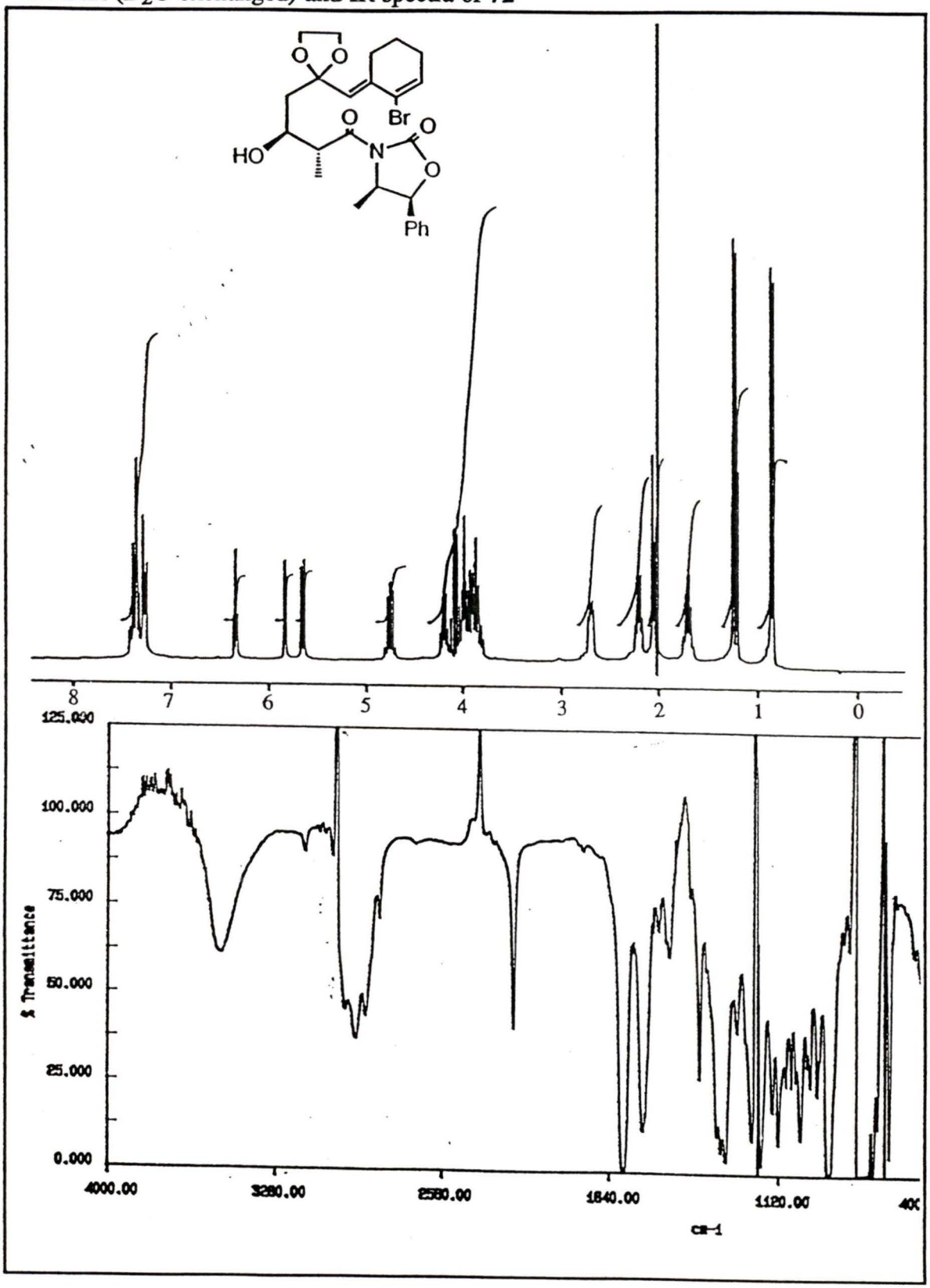


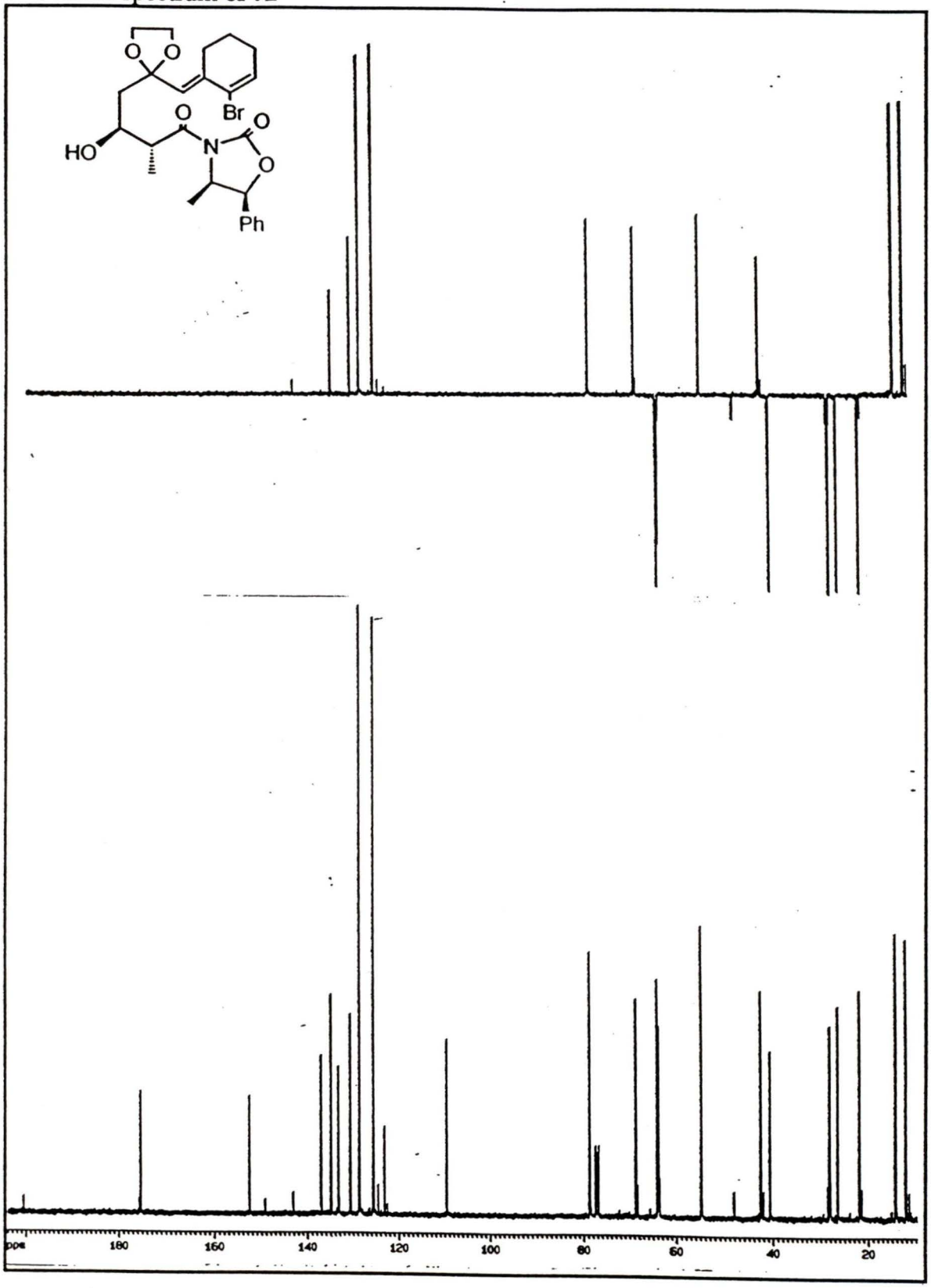
^{1}H NMR spectrum of 72



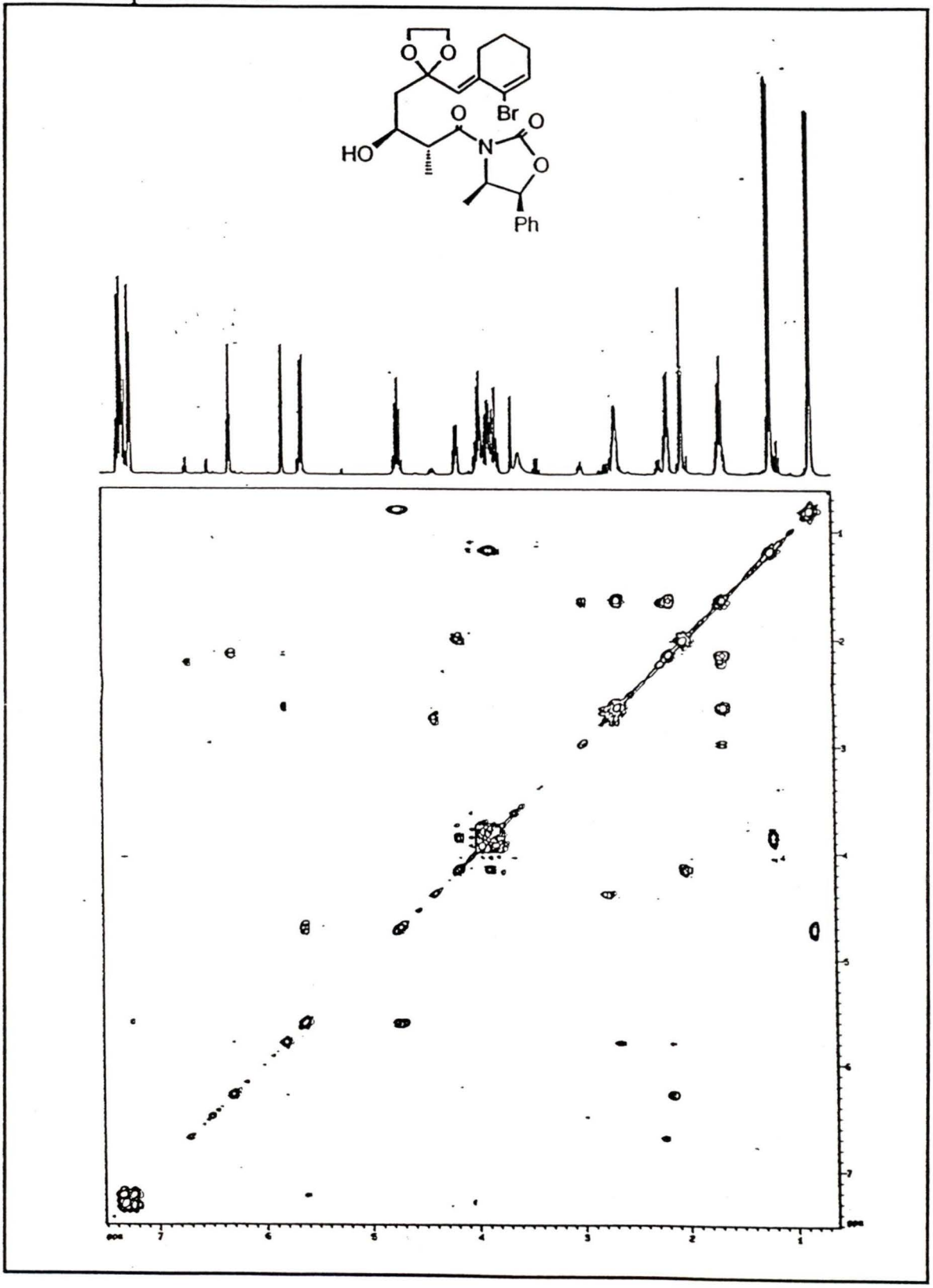
^{1}H NMR (D_2O exchanged) and IR spectra of **72**



^{13}C NMR spectrum of **72**



^{1}H COSY spectrum of 72



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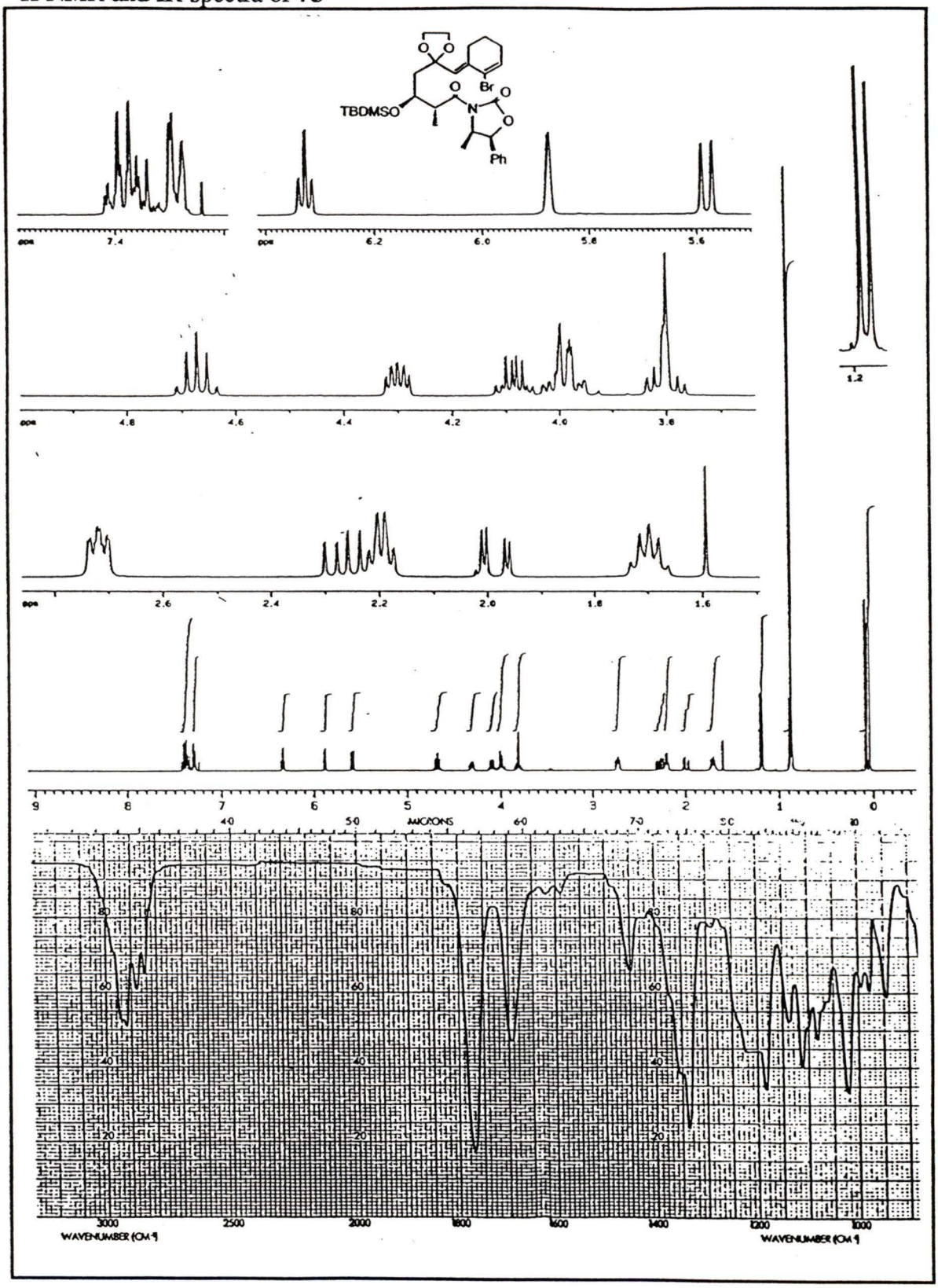

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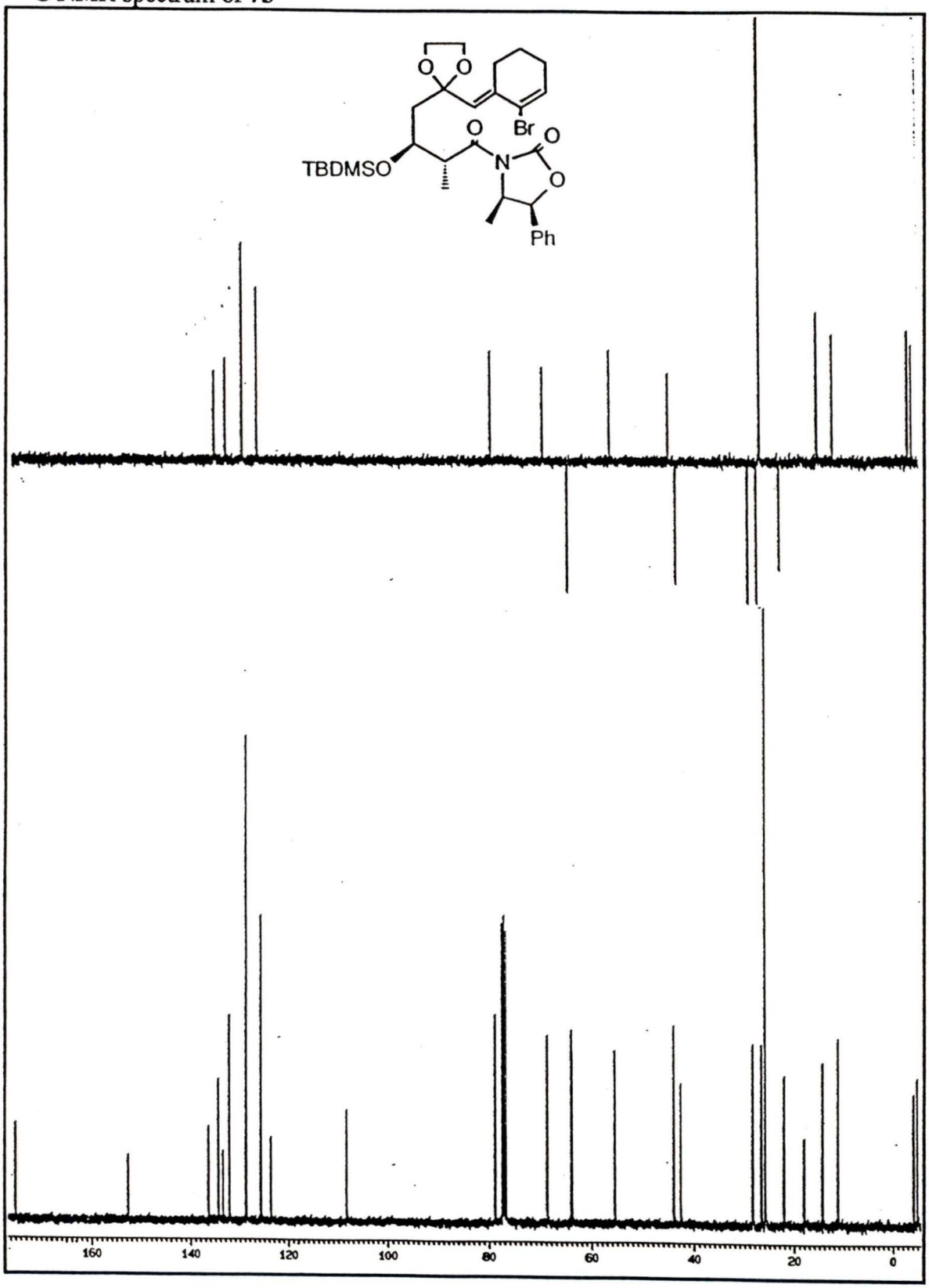

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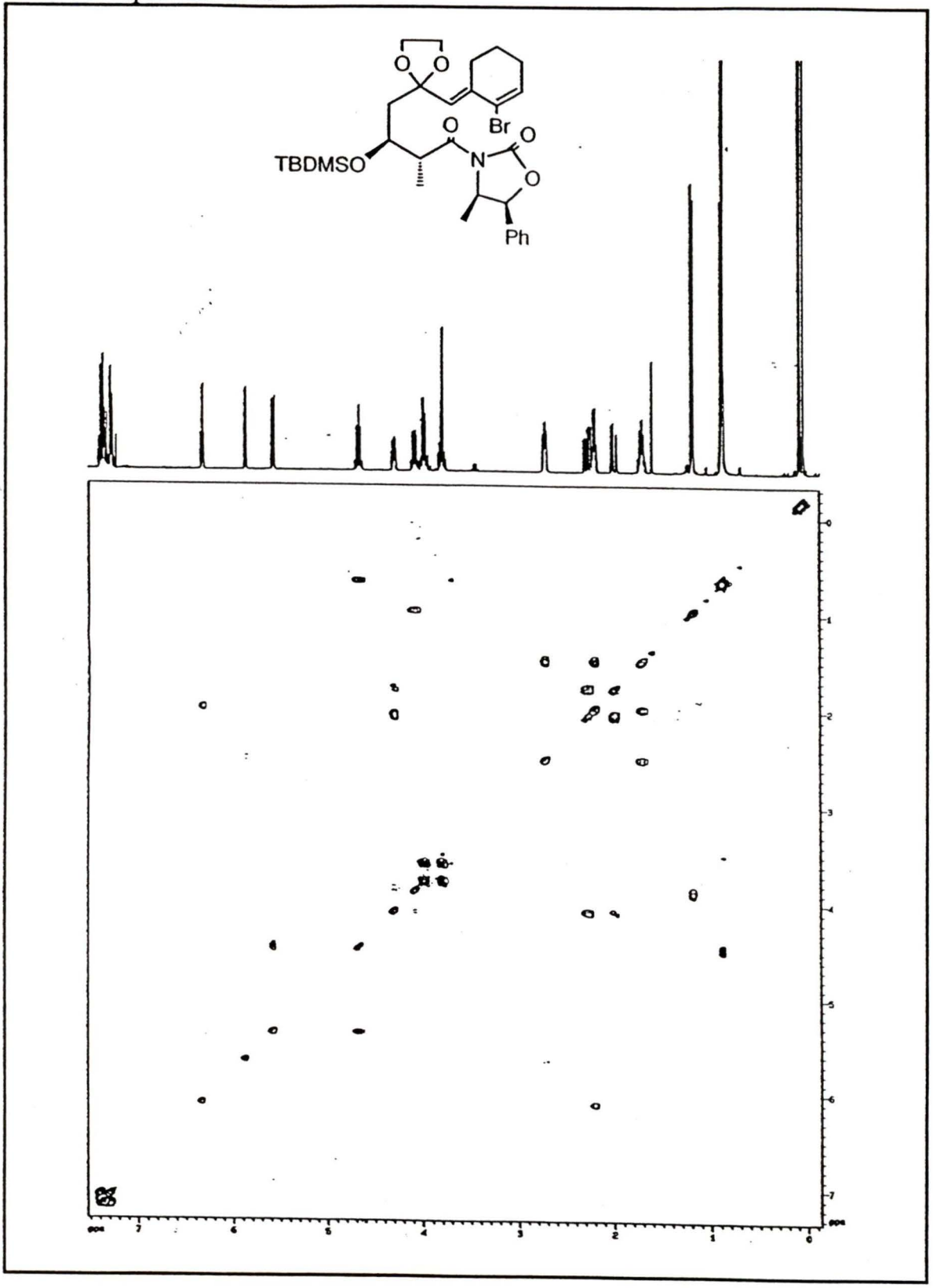
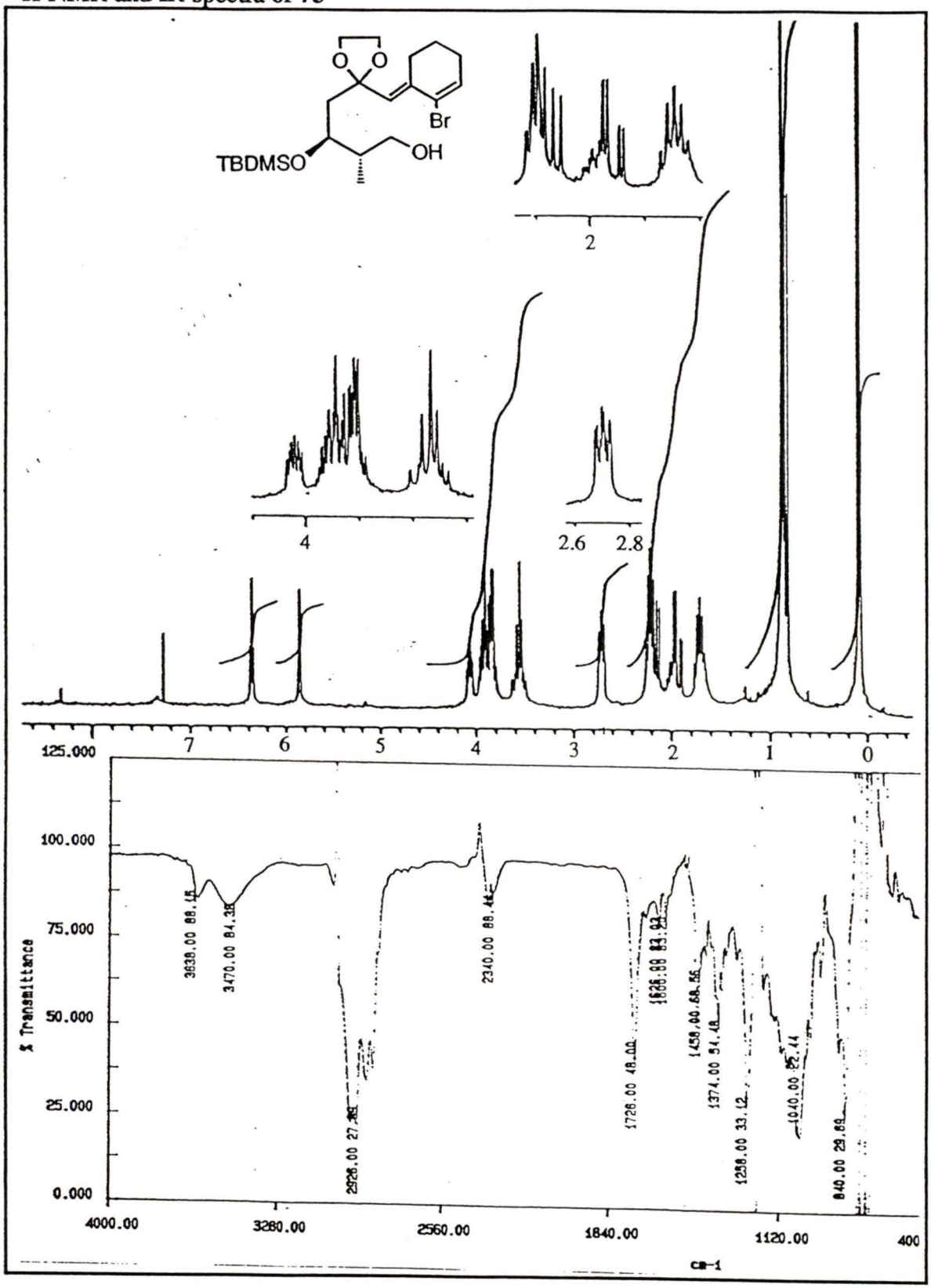
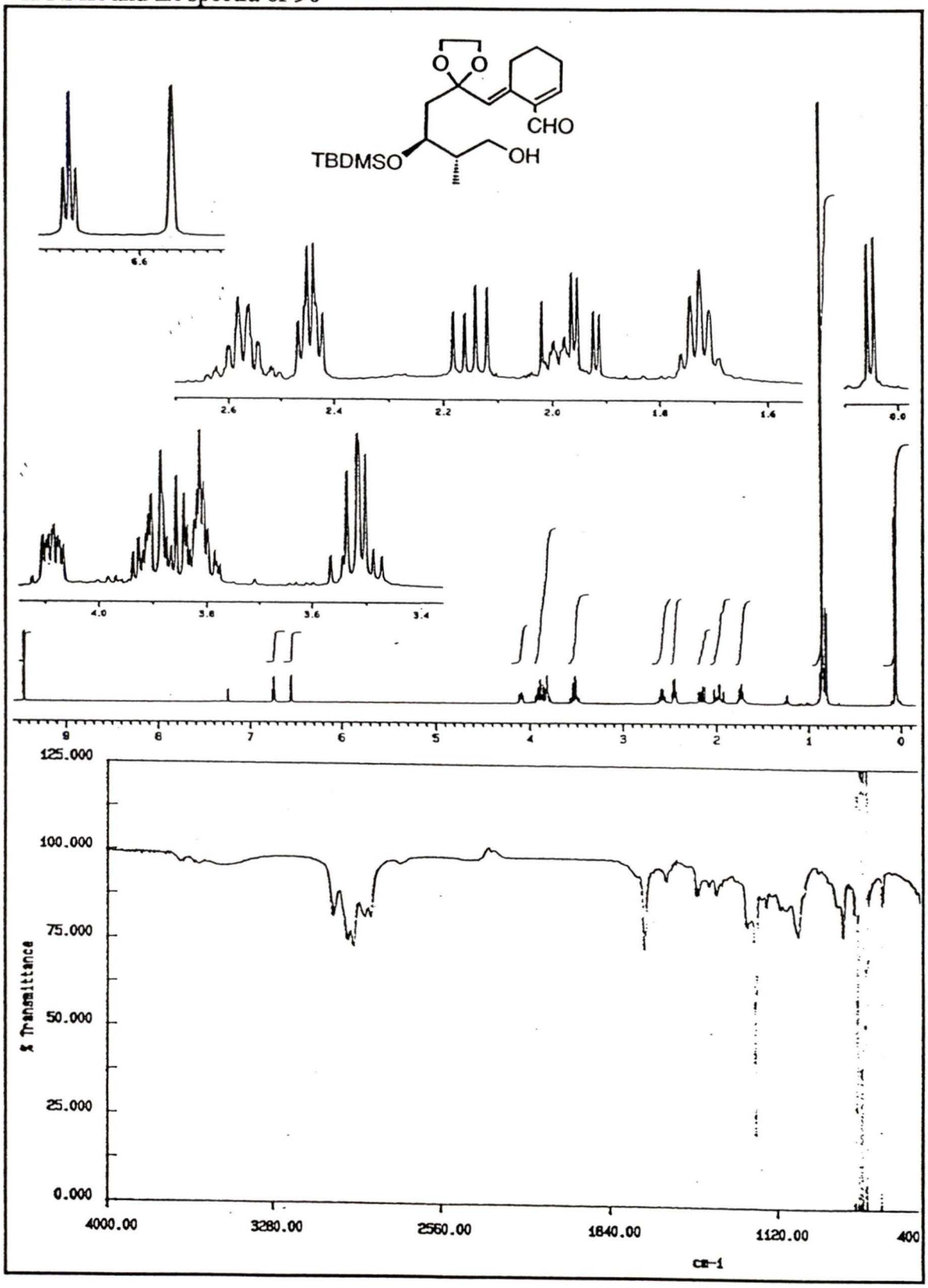


^{1}H NMR and IR spectra of **75**



^{1}H NMR and IR spectra of **90**



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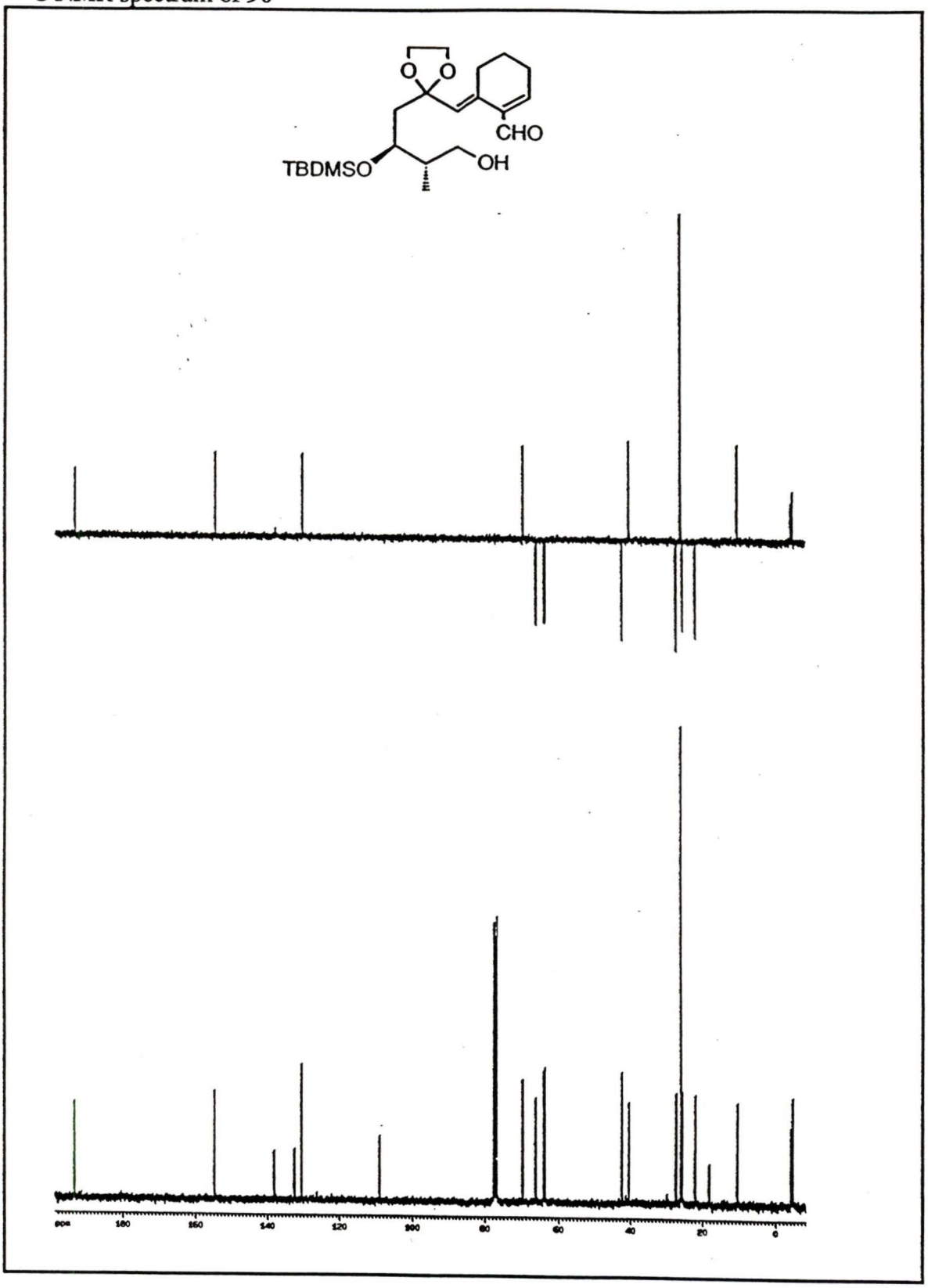

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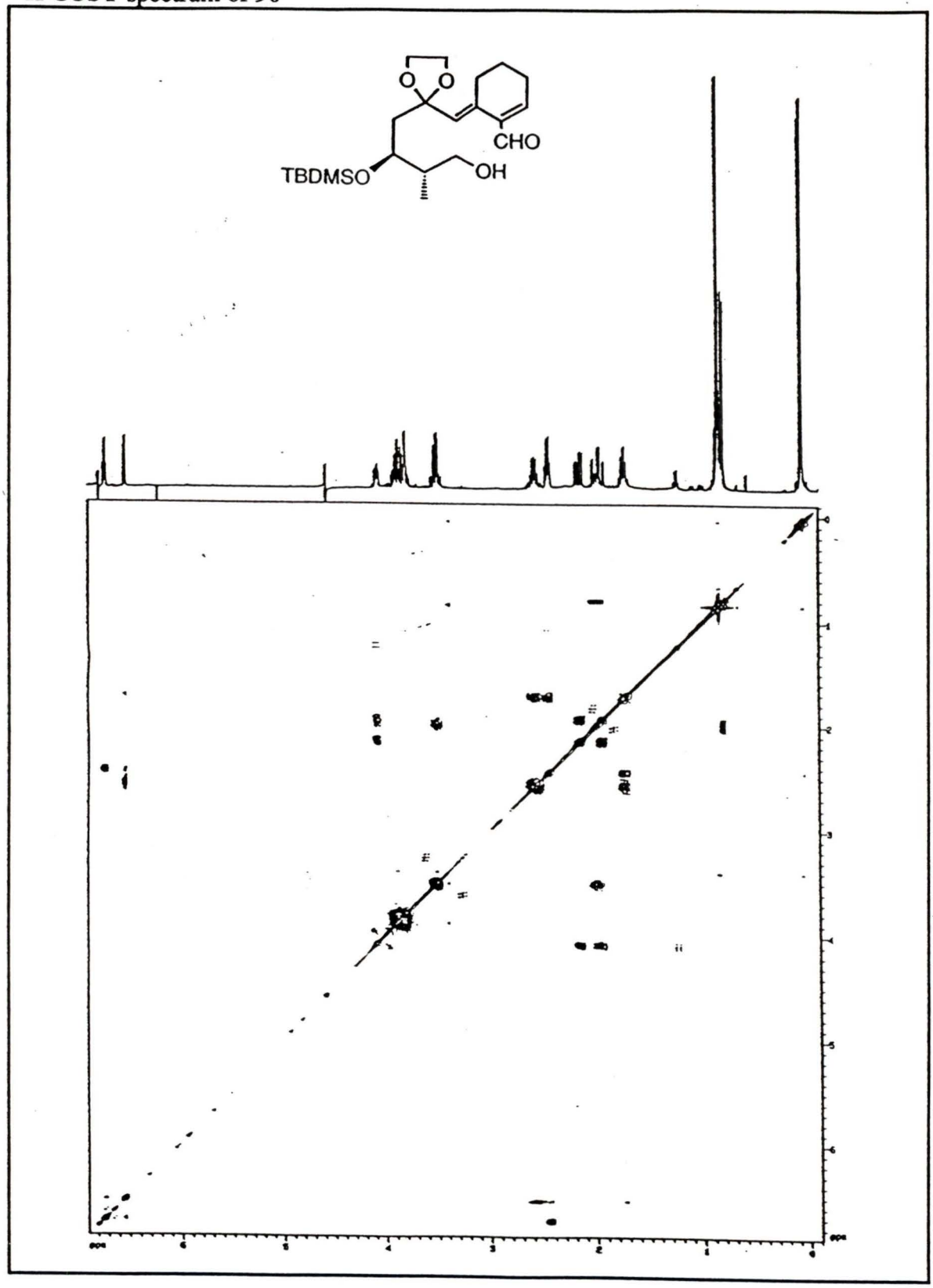
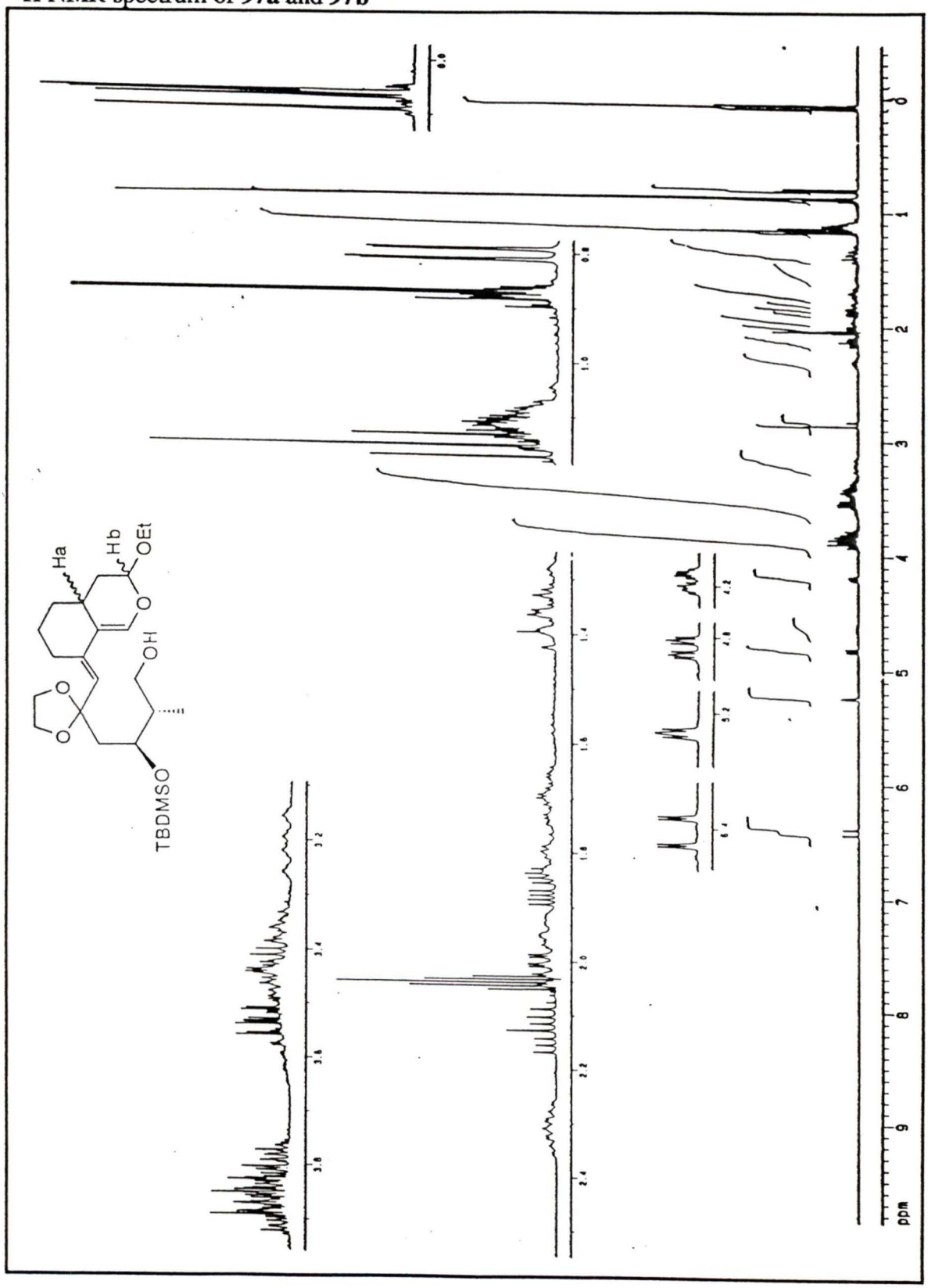


^{1}H NMR spectrum of **97a** and **97b**



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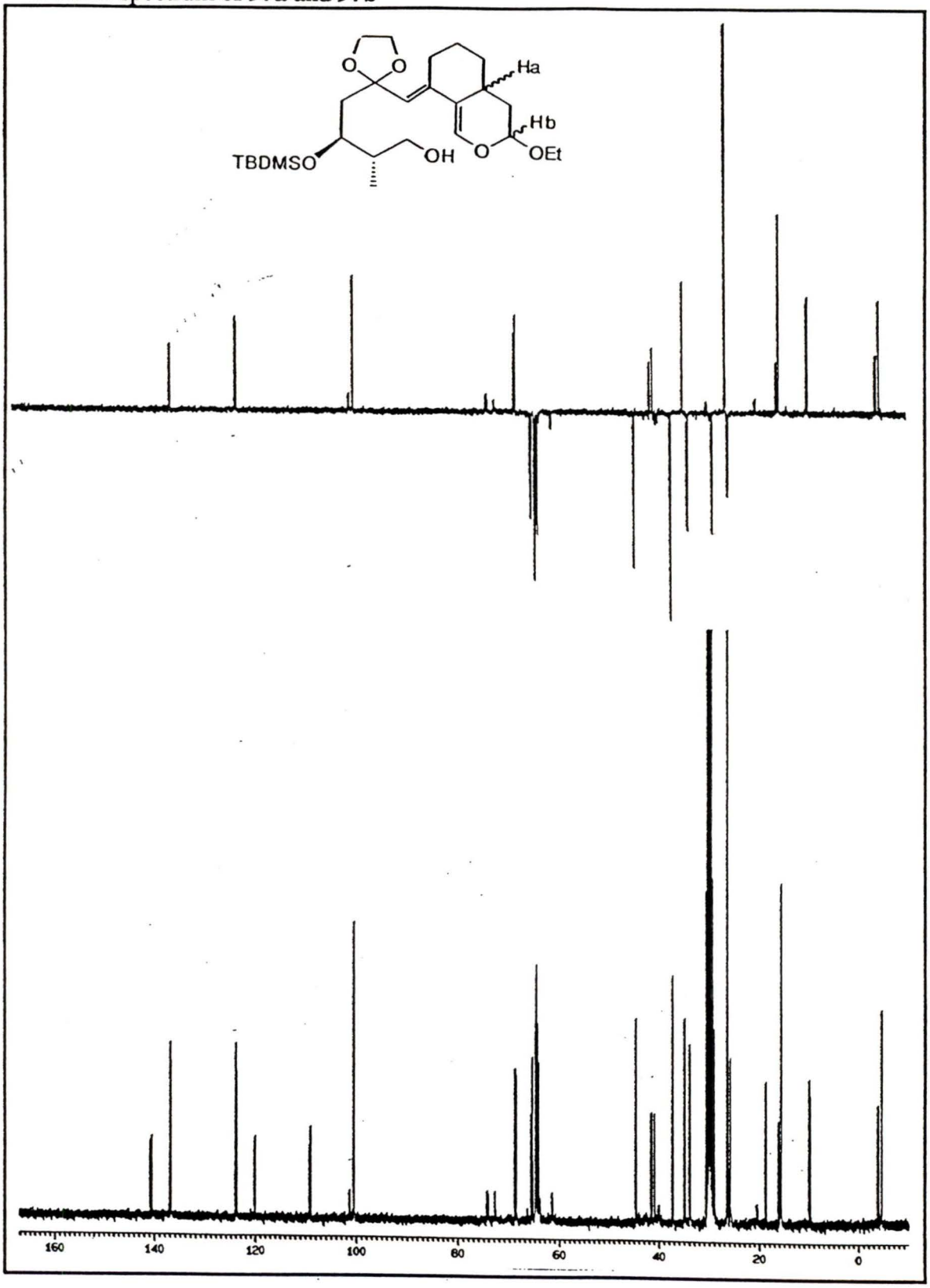
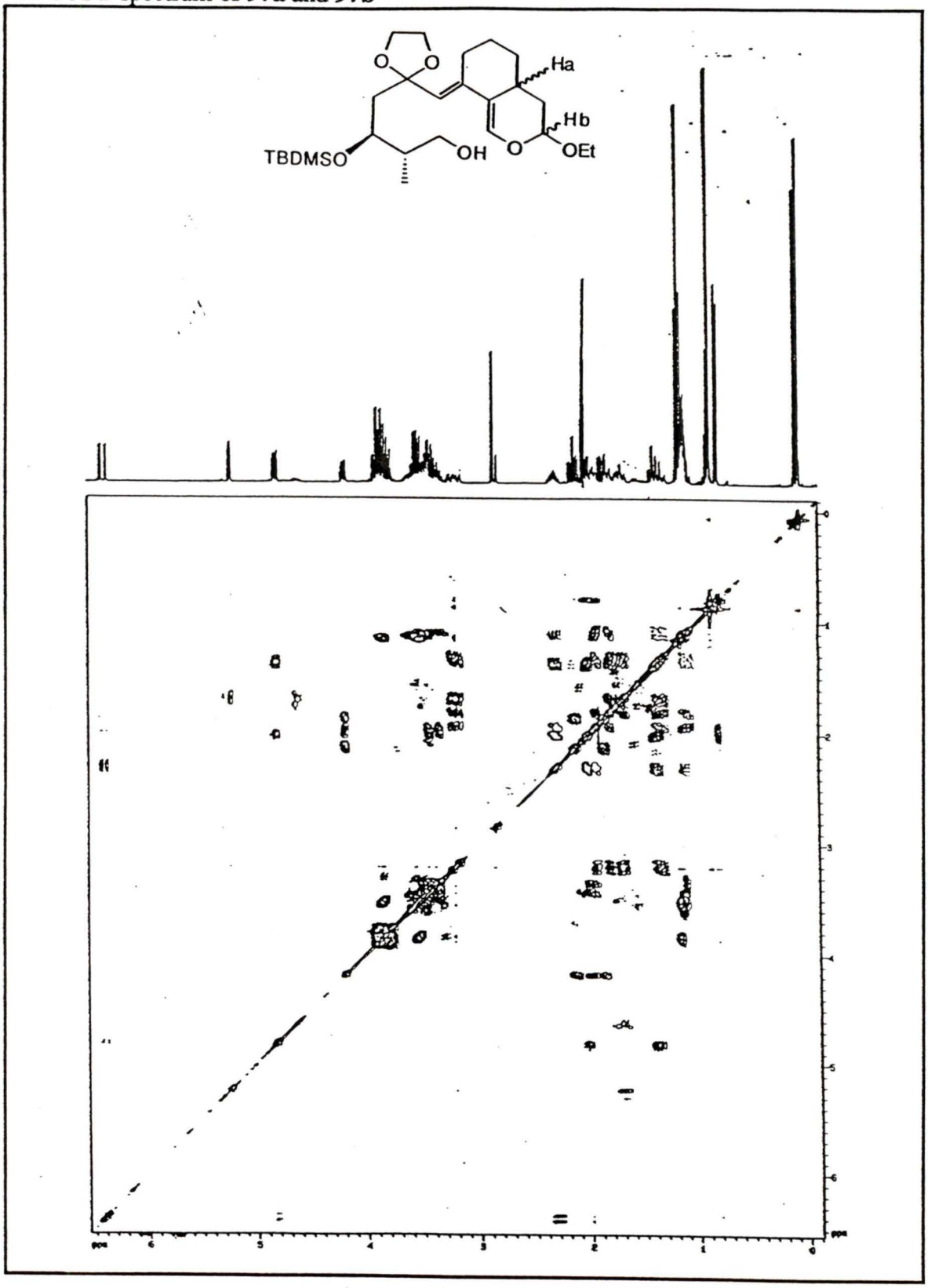
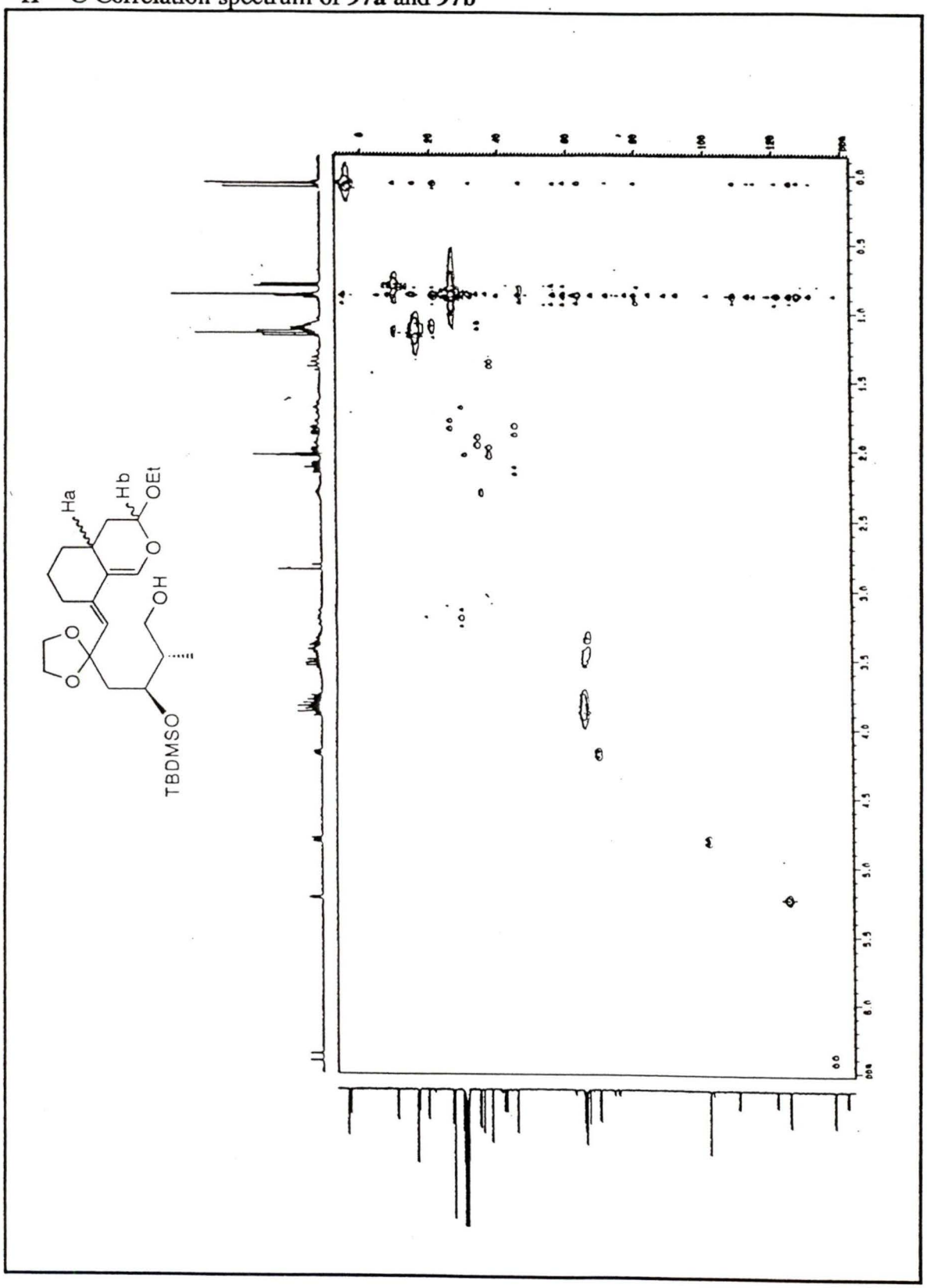


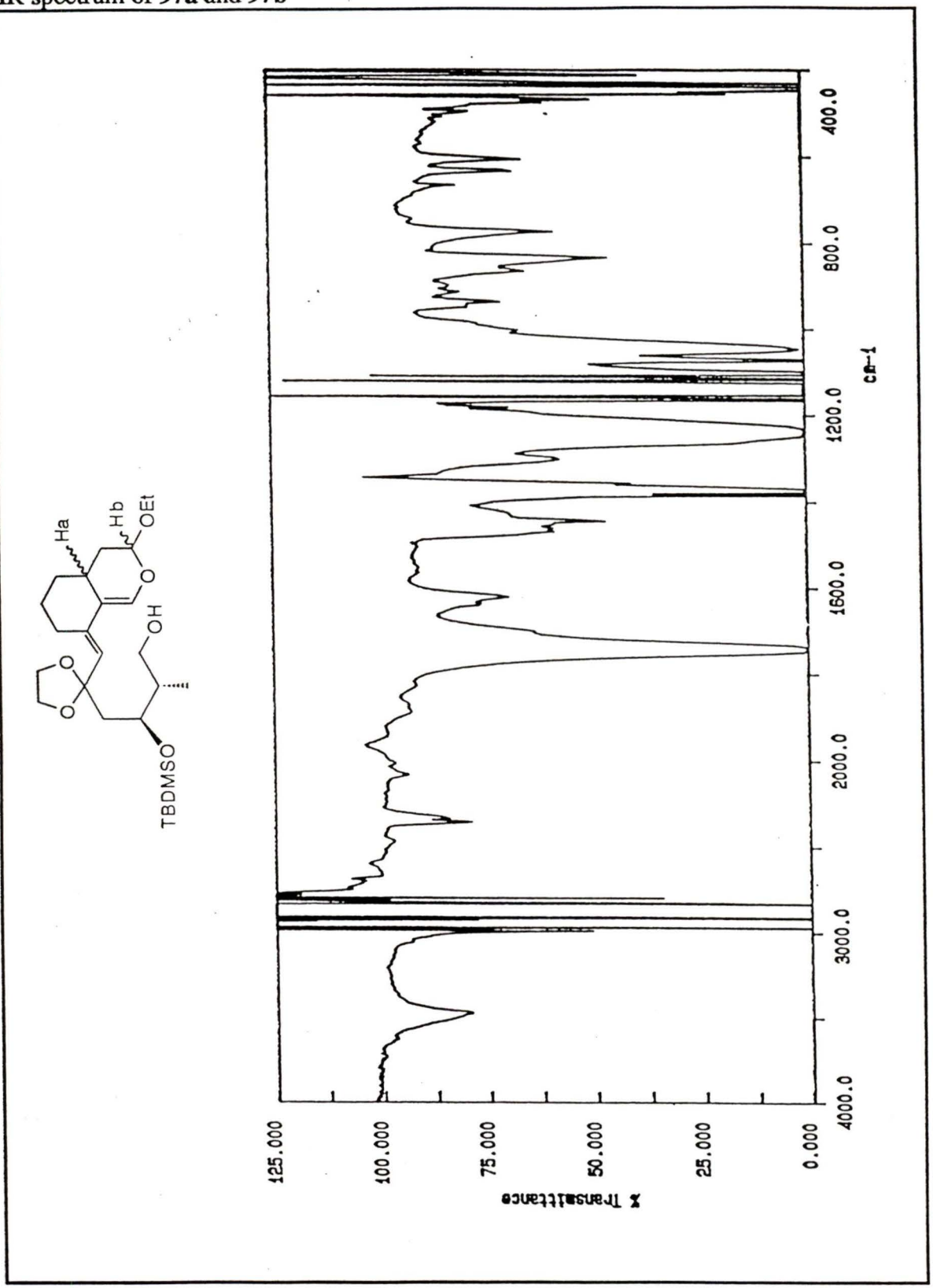
^{1}H COSY spectrum of **97a** and **97b**



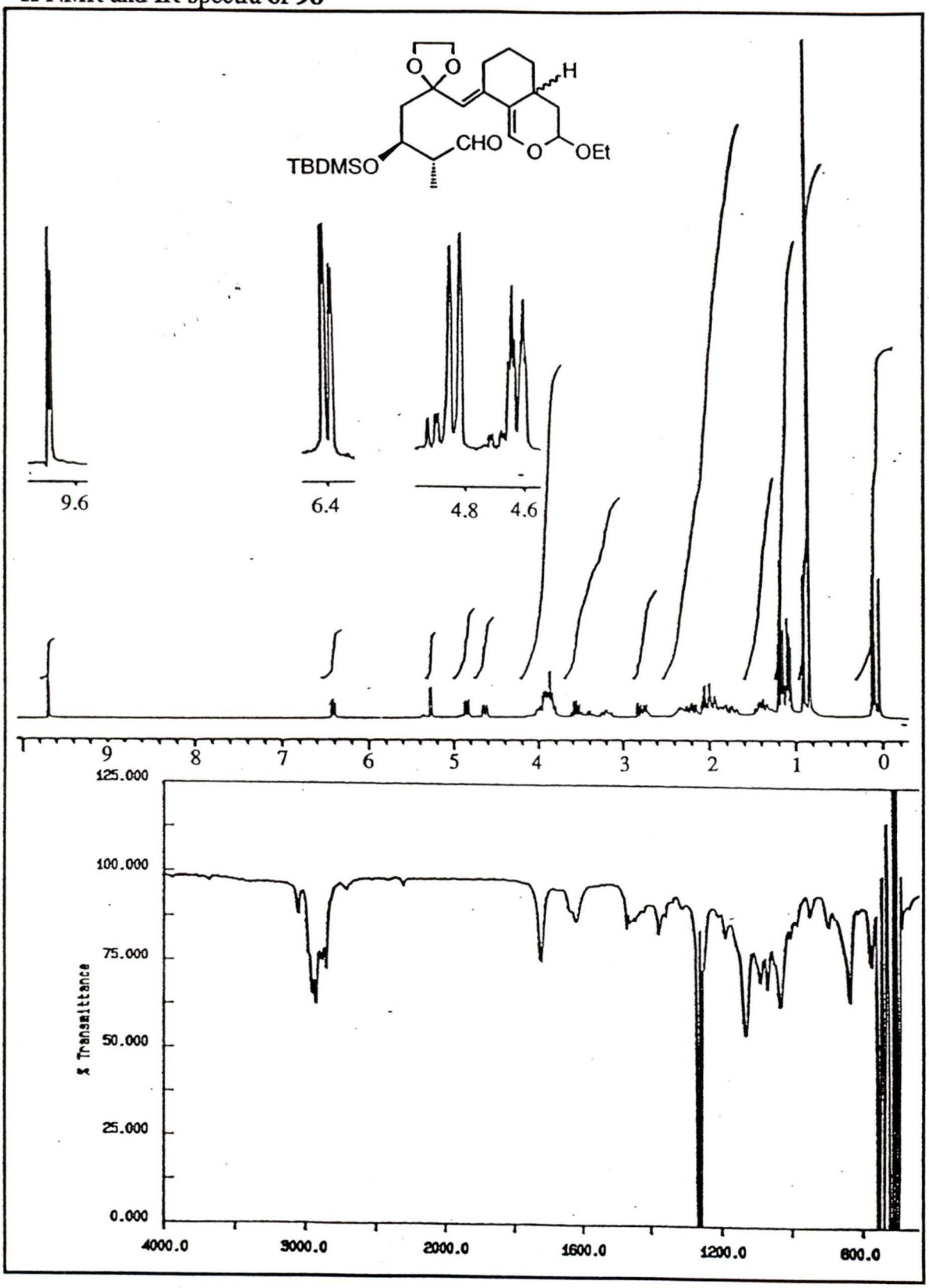
^{1}H-^{13}C Correlation spectrum of **97a** and **97b**



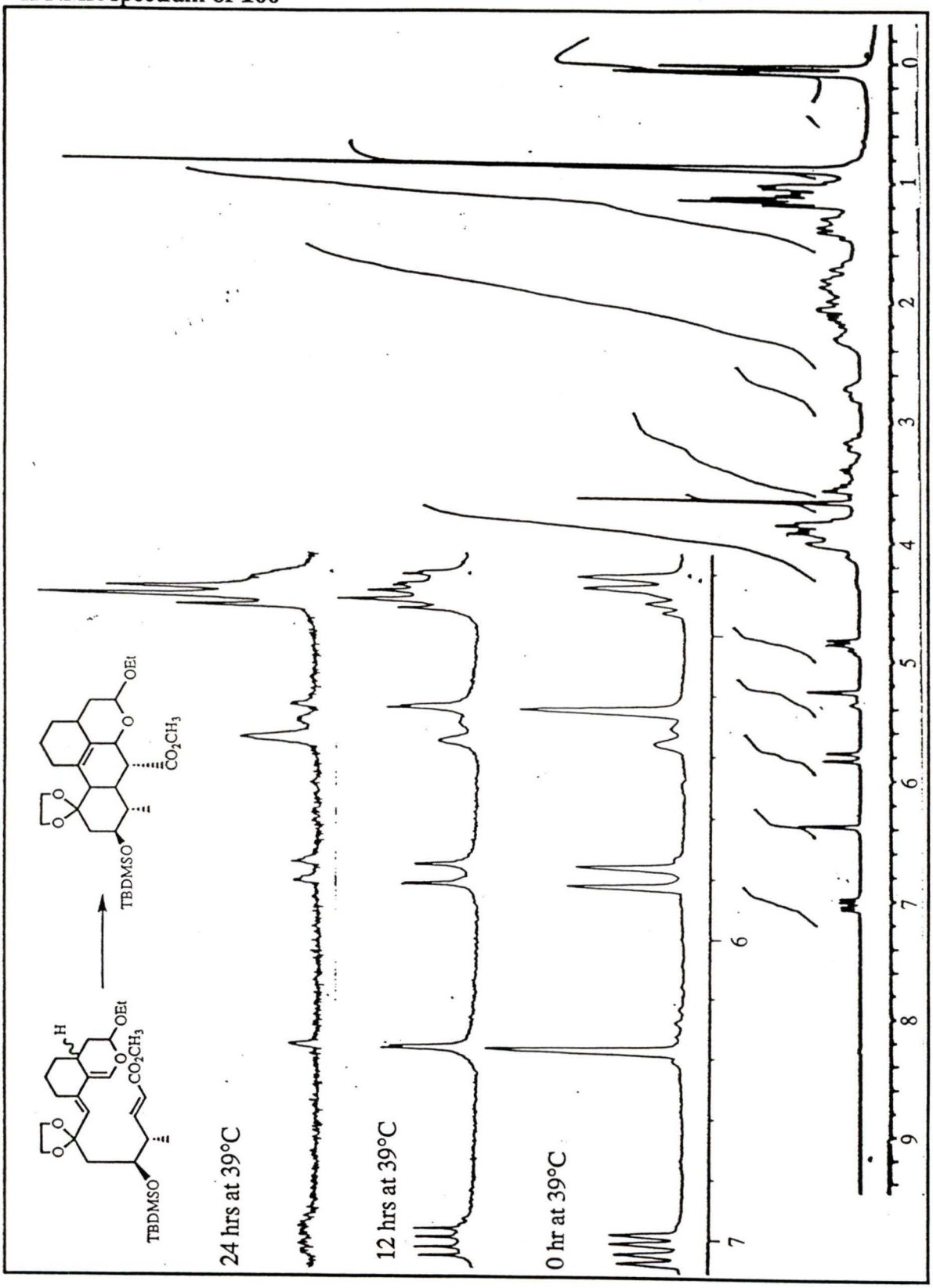
IR spectrum of **97a** and **97b**



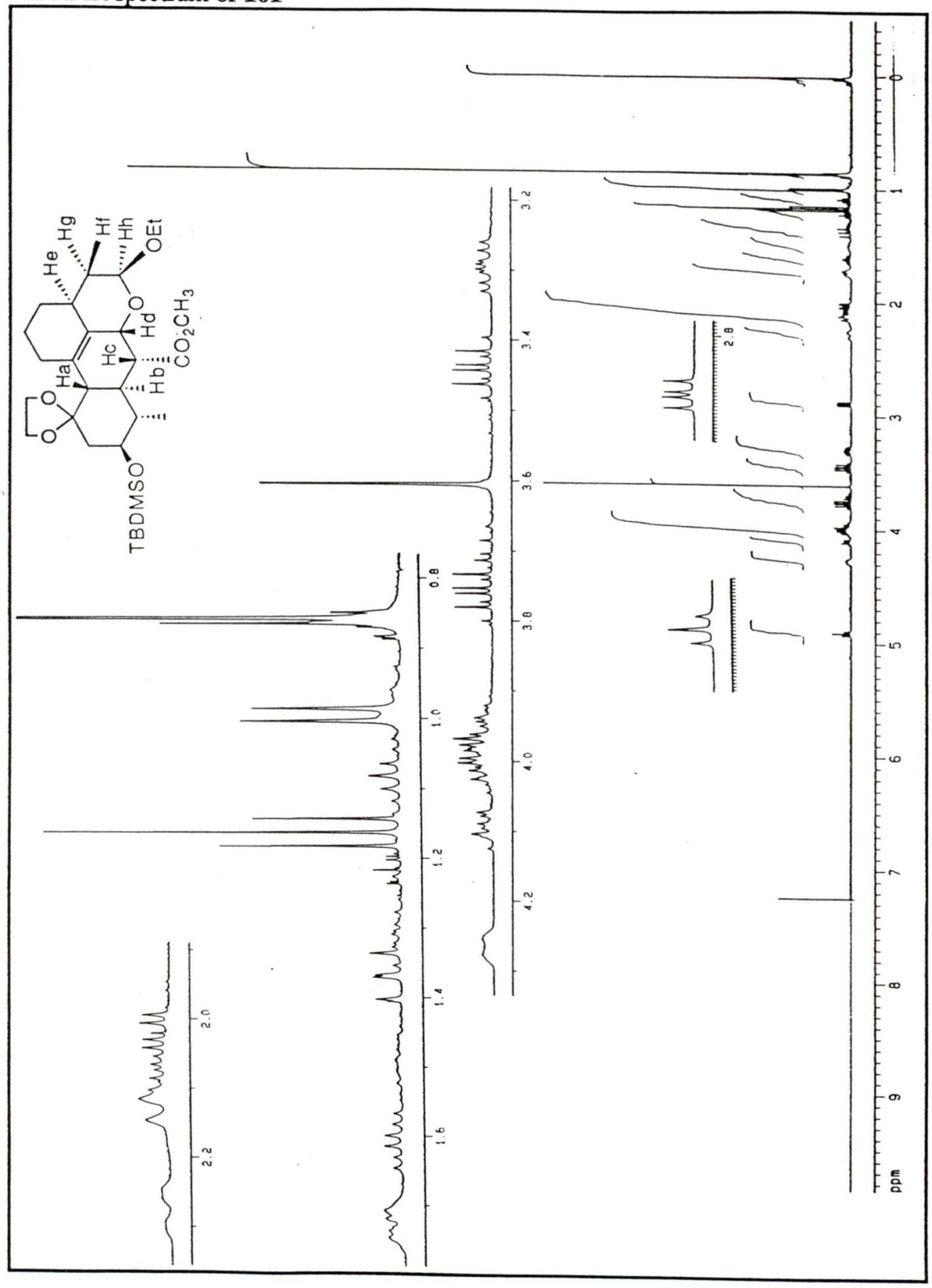
^{1}H NMR and IR spectra of **98**



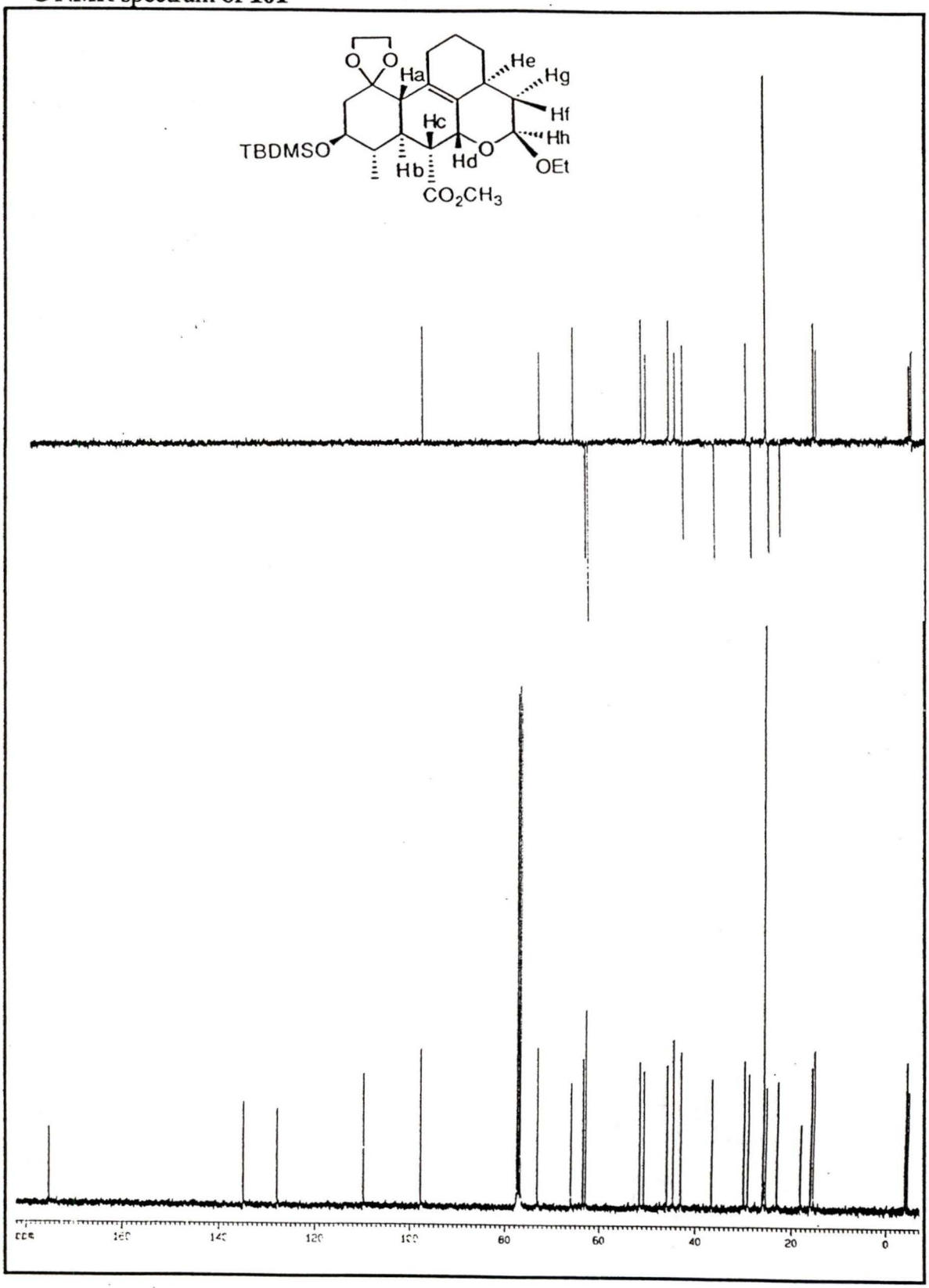
^{1}H NMR spectrum of **100**



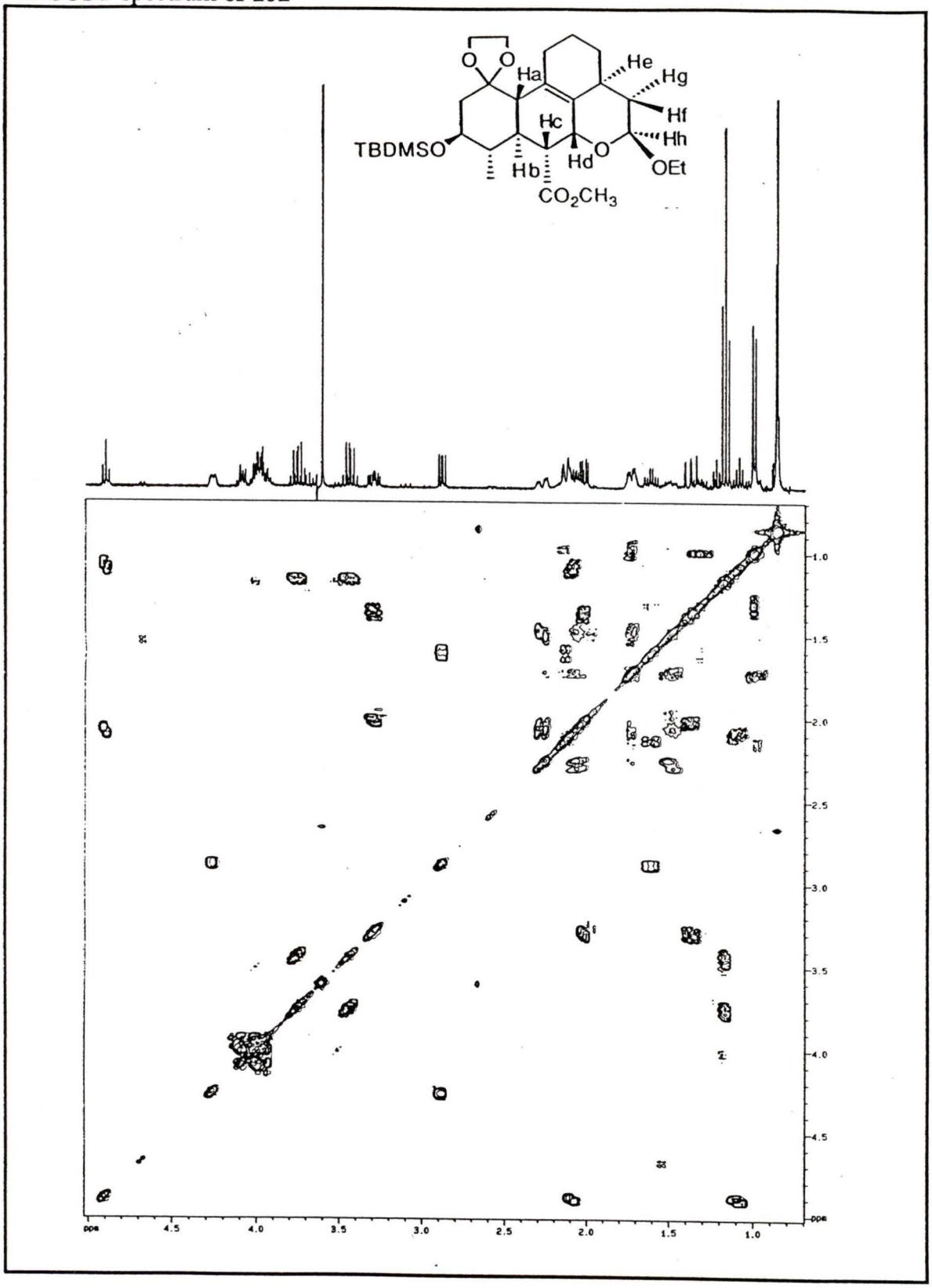
^{1}H NMR spectrum of 101



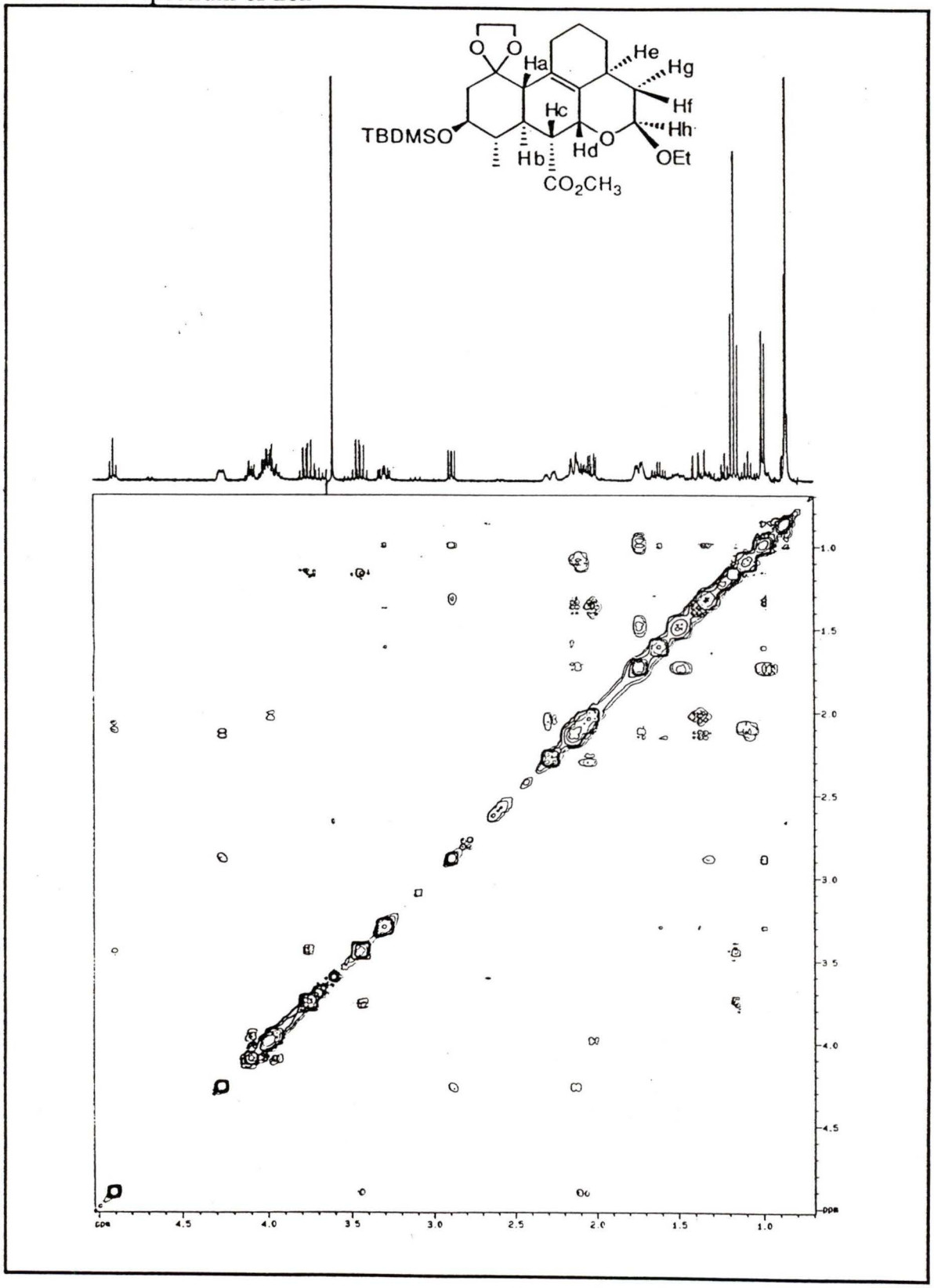
^{13}C NMR spectrum of **101**



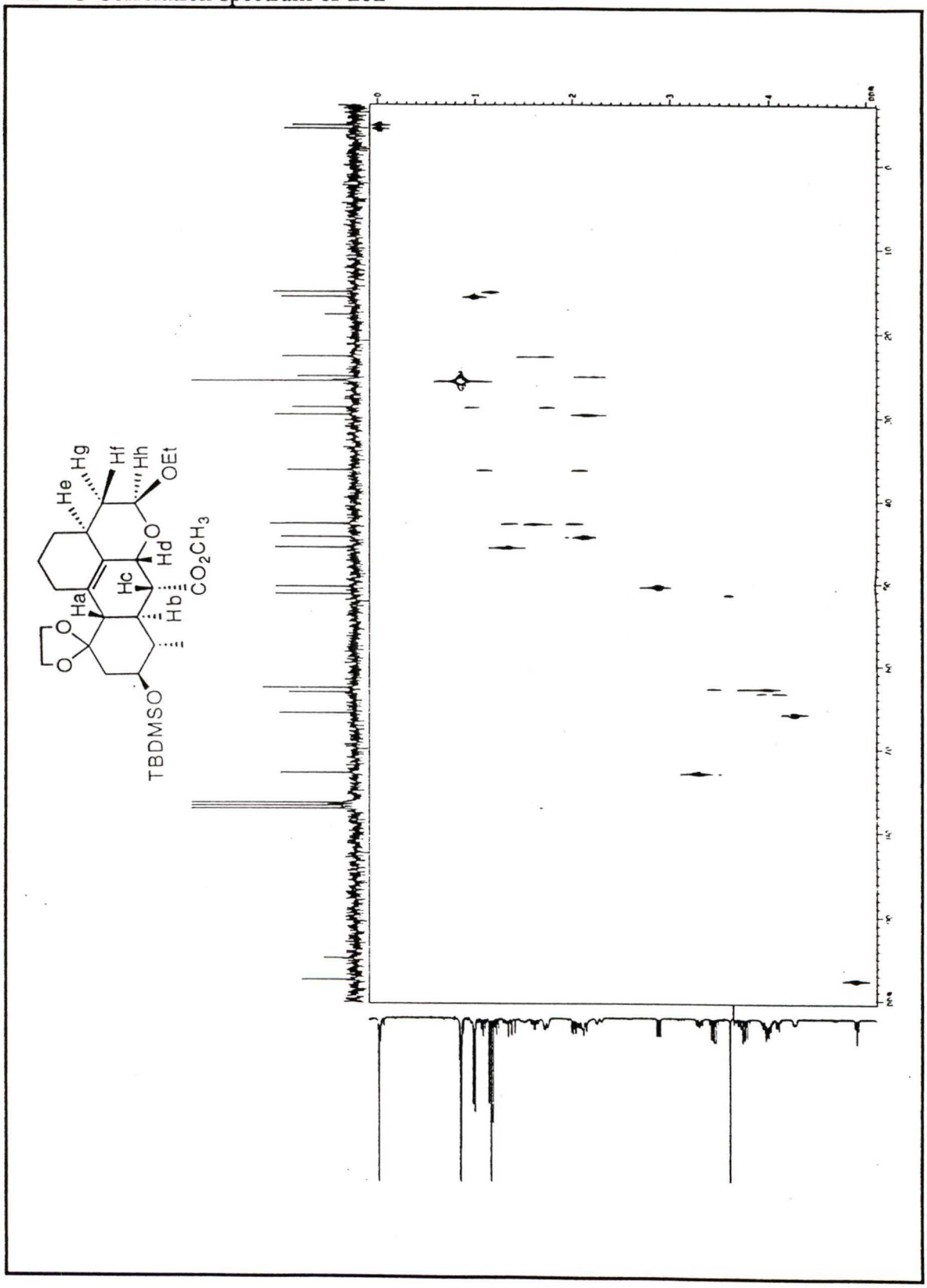
^{1}H COSY spectrum of **101**



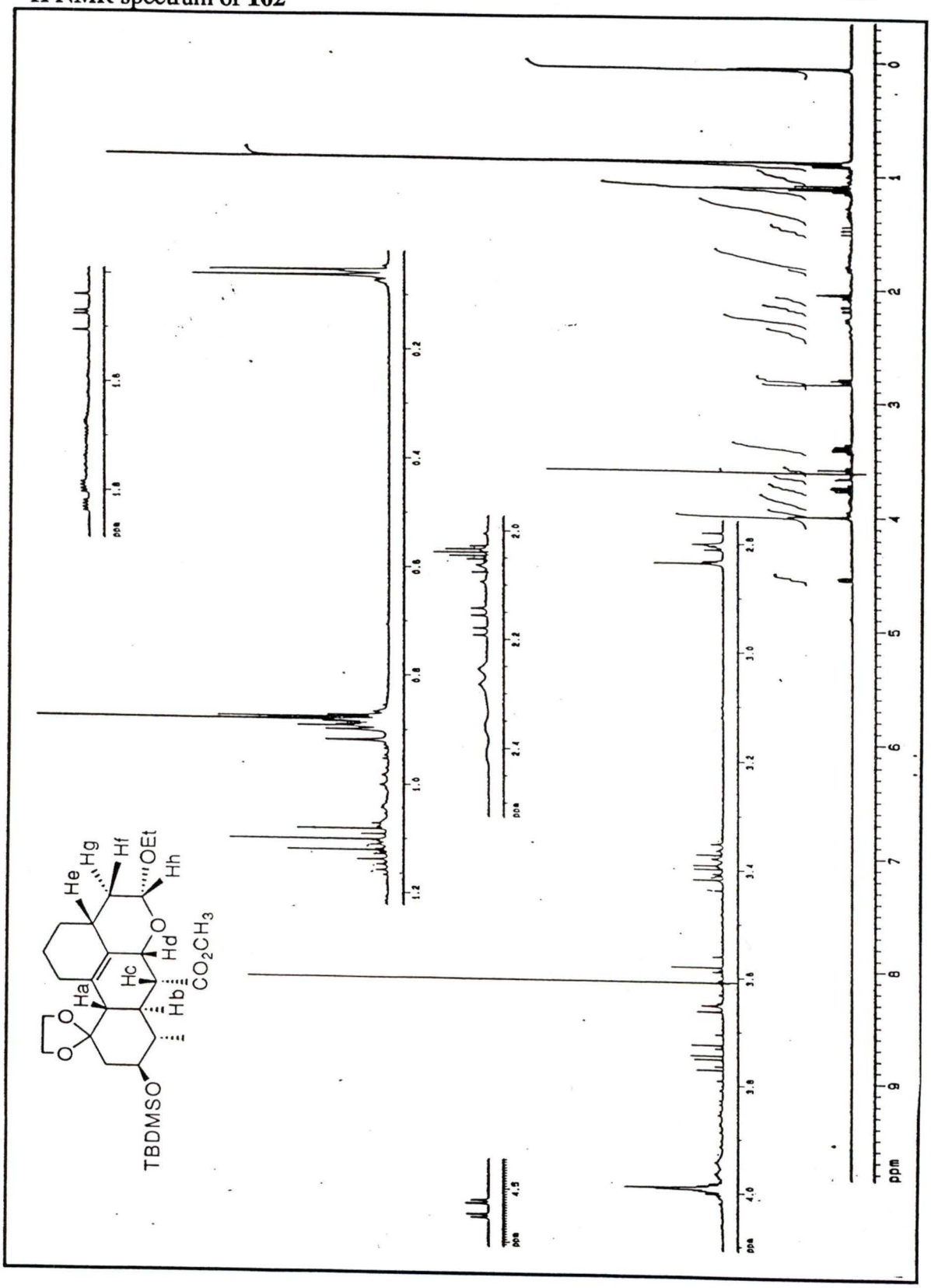
^{1}H NOESY spectrum of **101**



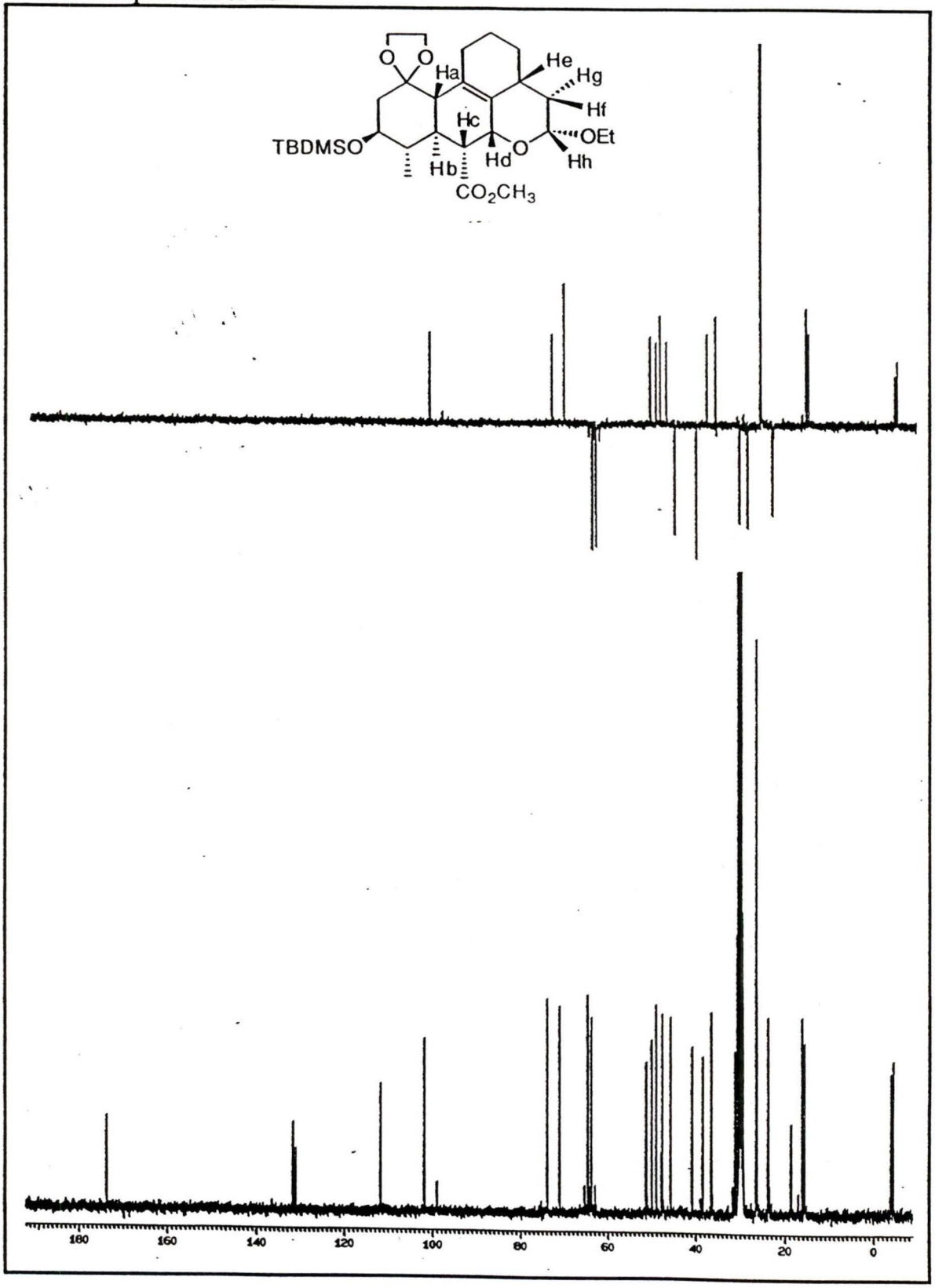
^{1}H-^{13}C Correlation spectrum of **101**



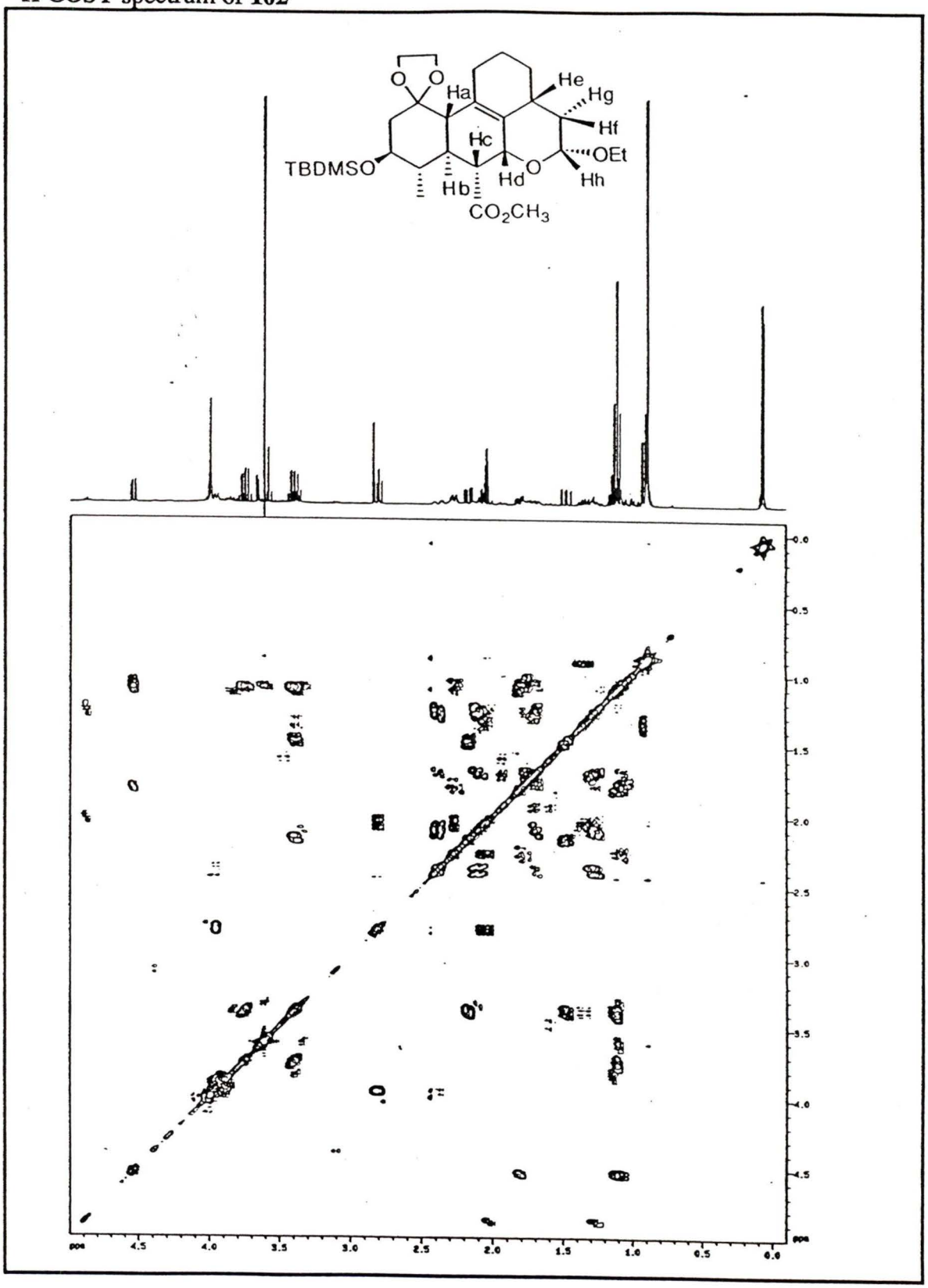
^{1}H NMR spectrum of **102**



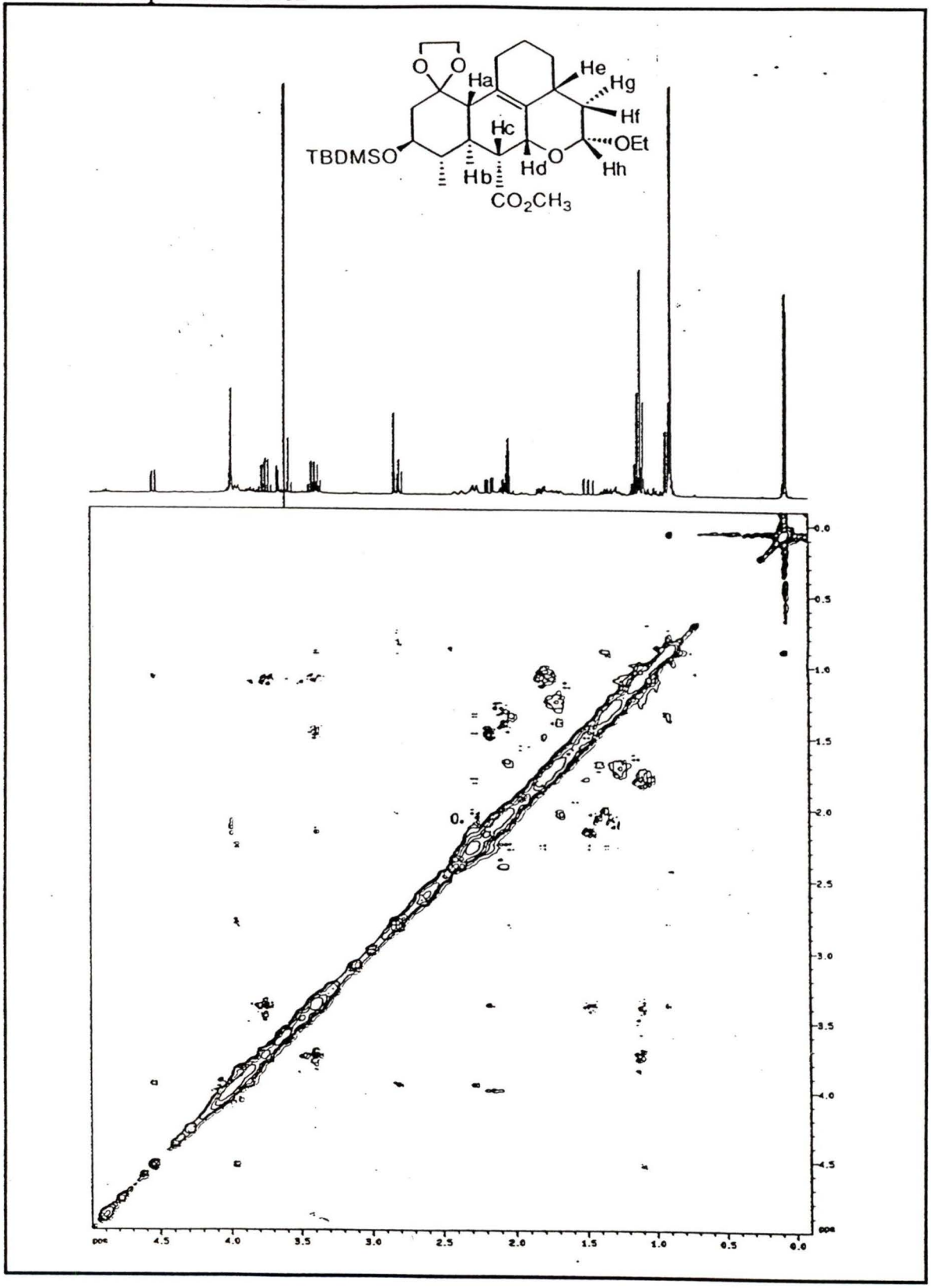
^{13}C NMR spectrum of **102**



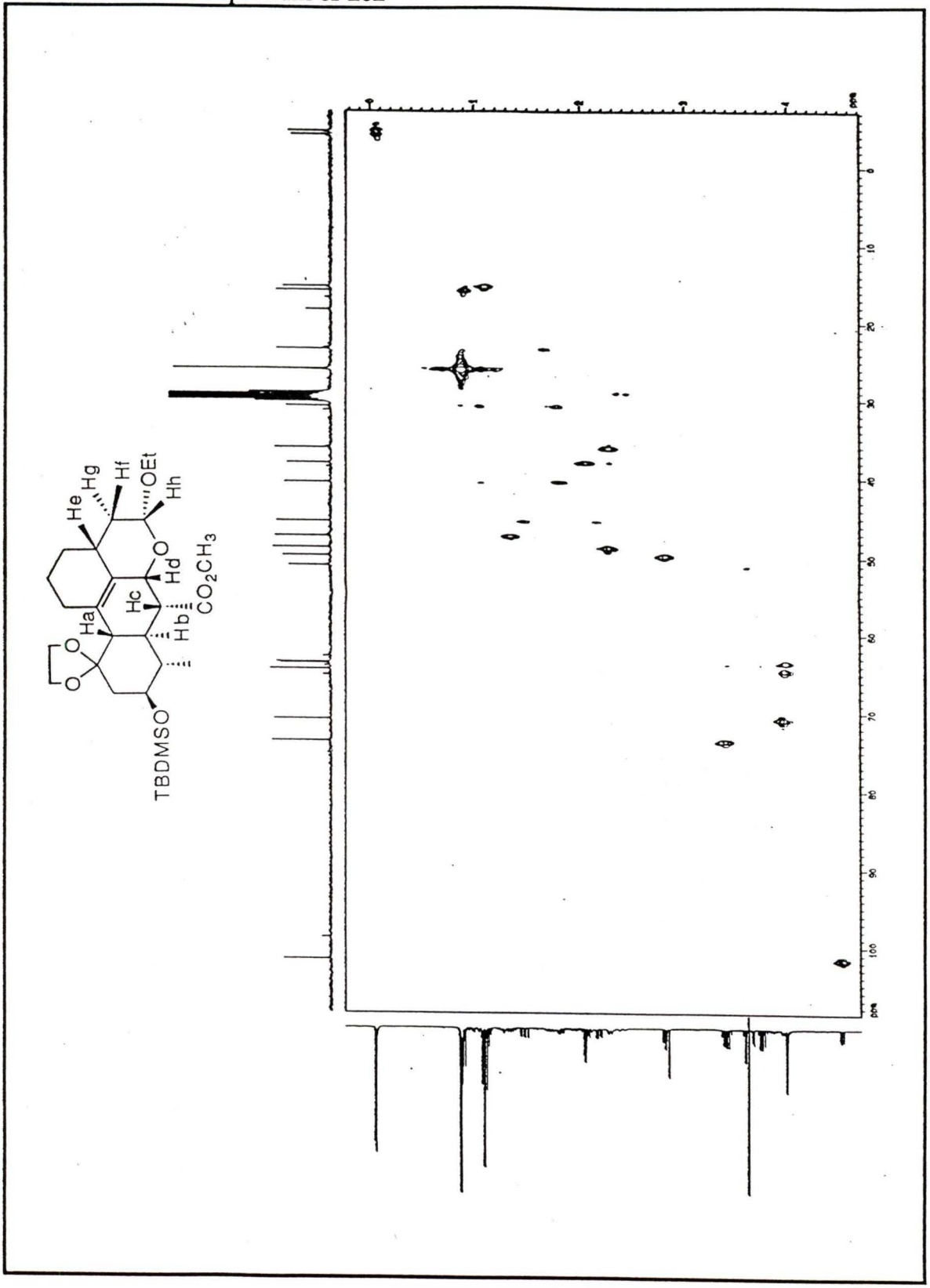
^{1}H COSY spectrum of **102**



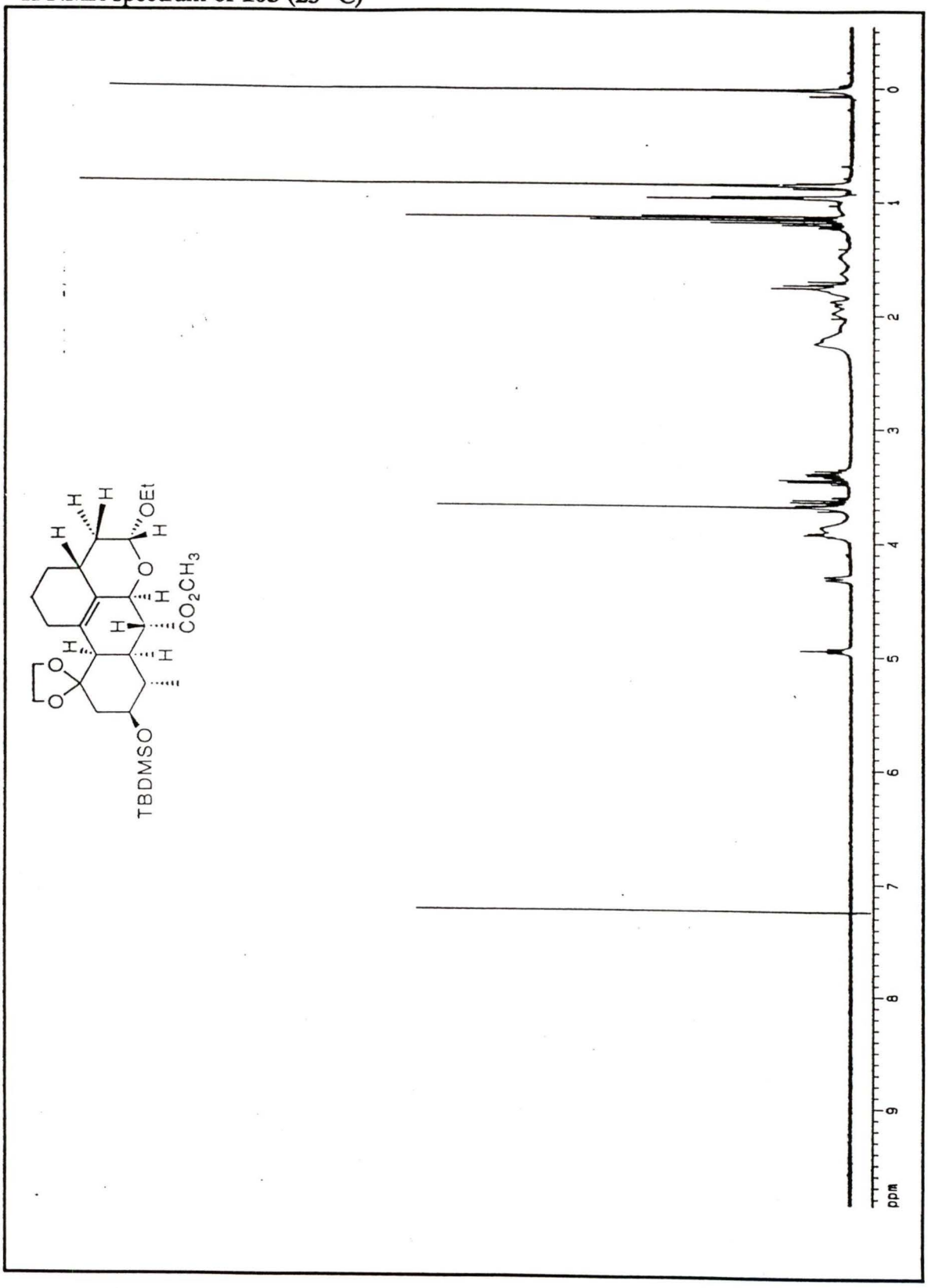
^{1}H NOESY spectrum of **102**



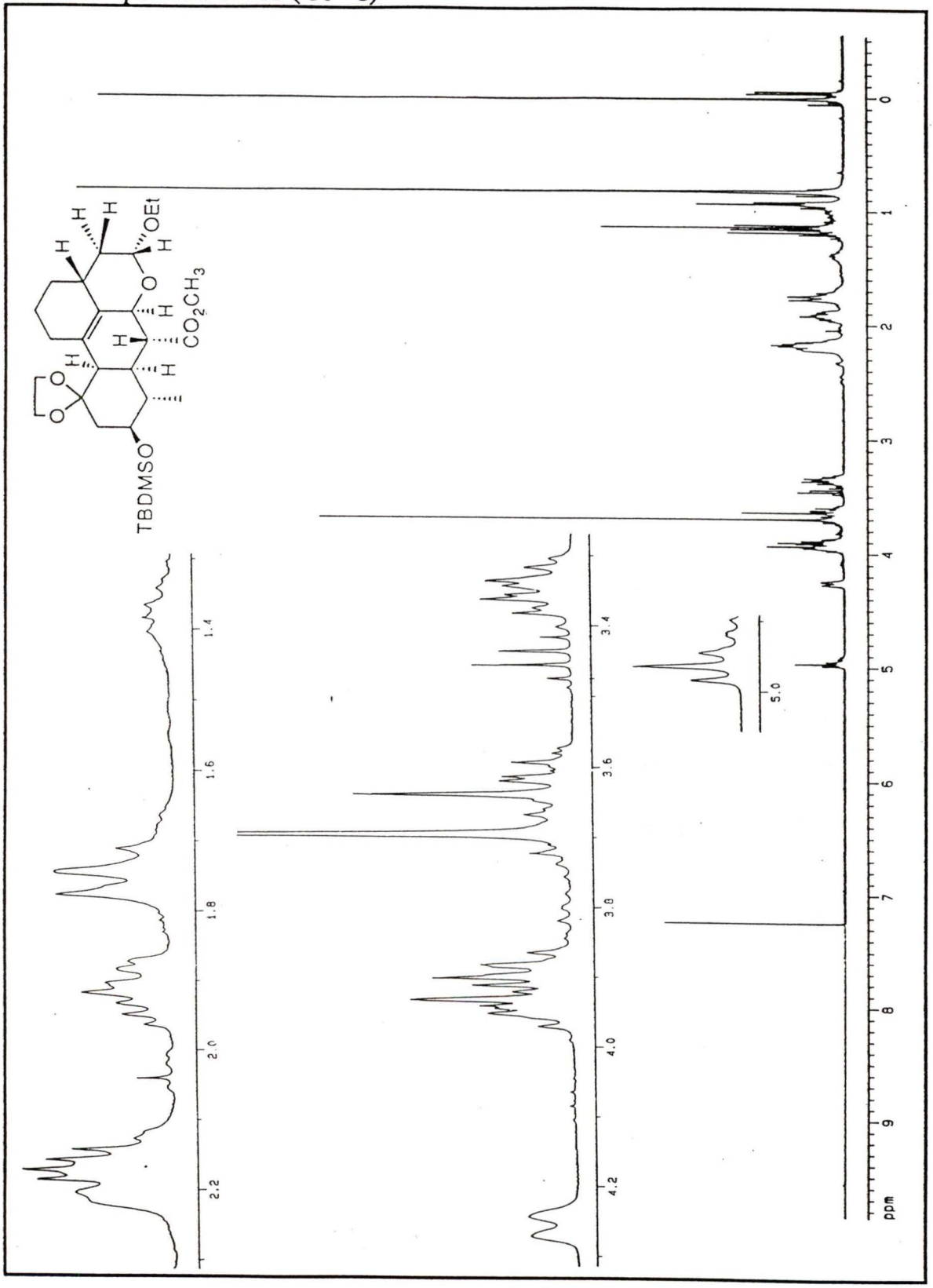
^{1}H-^{13}C Correlation spectrum of **102**



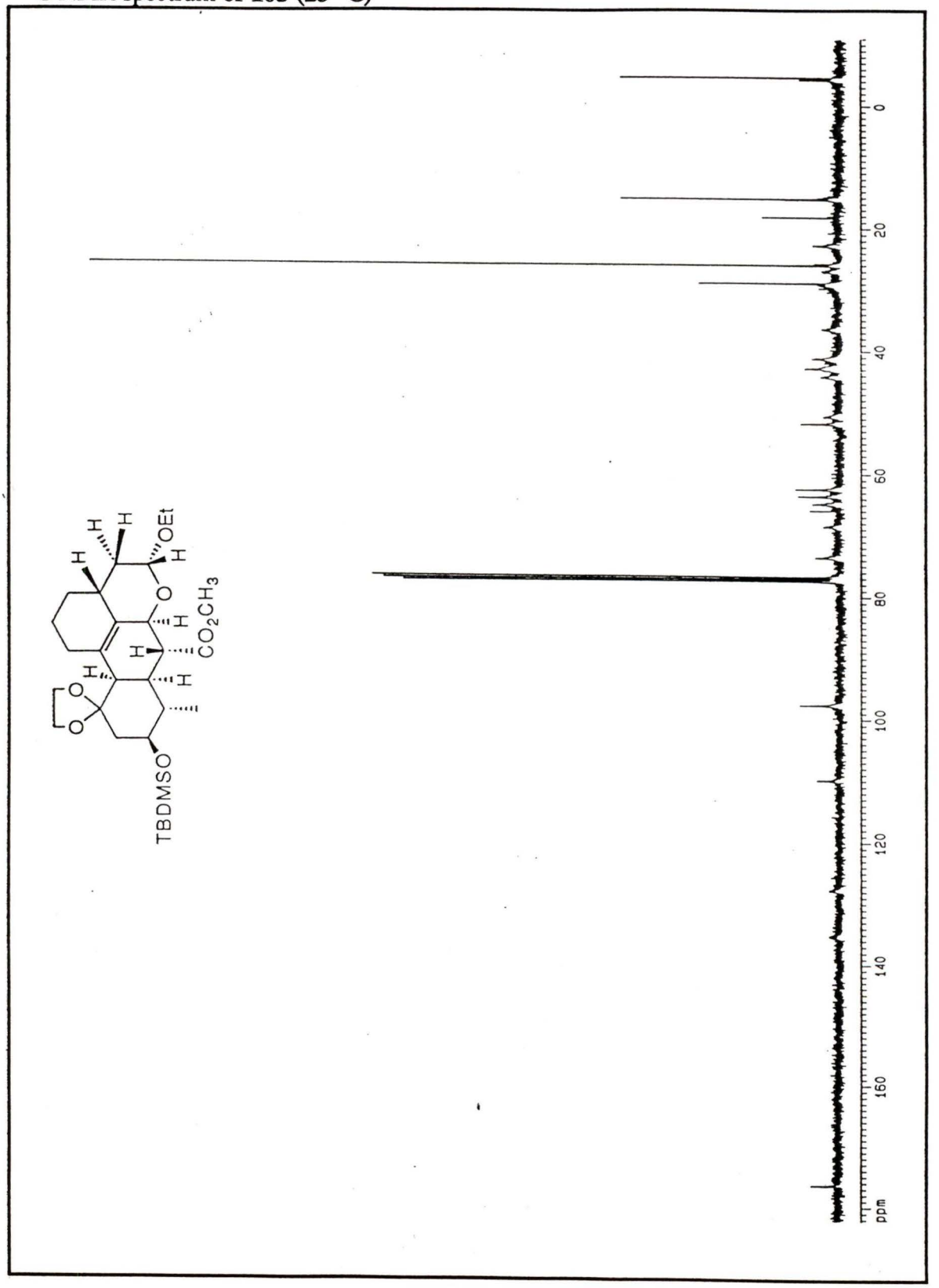
^{1}H NMR spectrum of **103** (25° C)



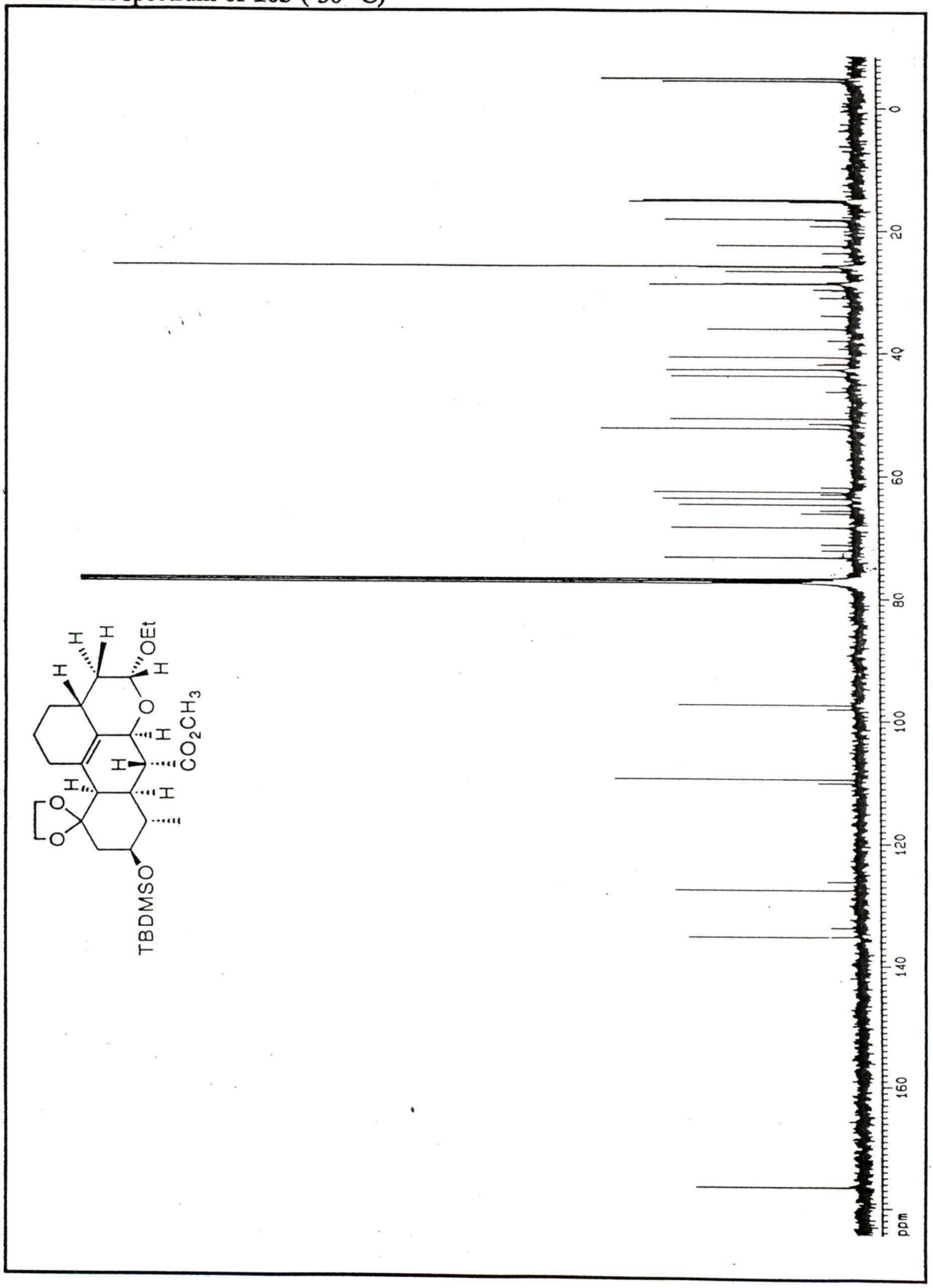
^{1}H NMR spectrum of **103** (-30° C)



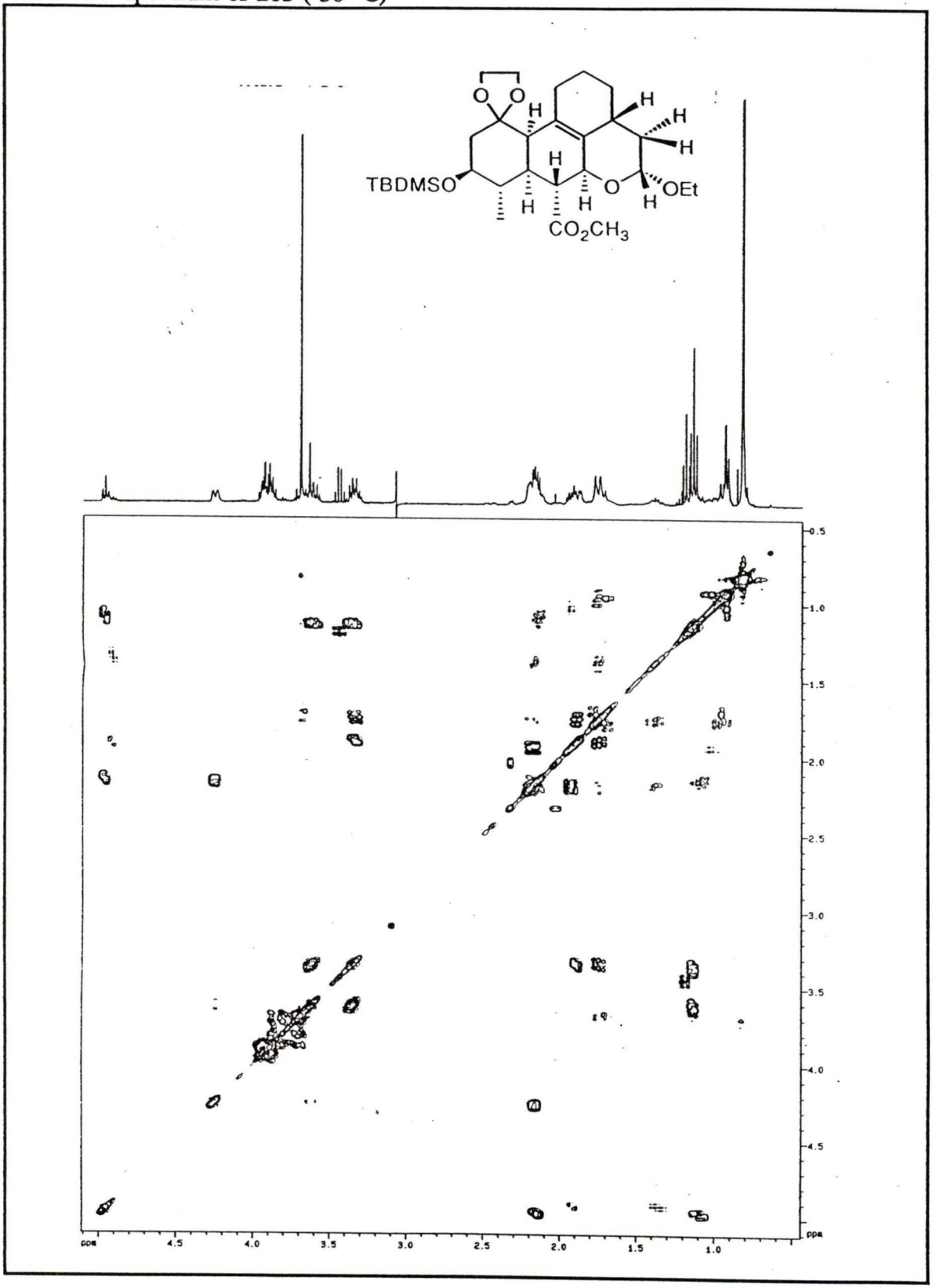
^{13}C NMR spectrum of **103** (25° C)



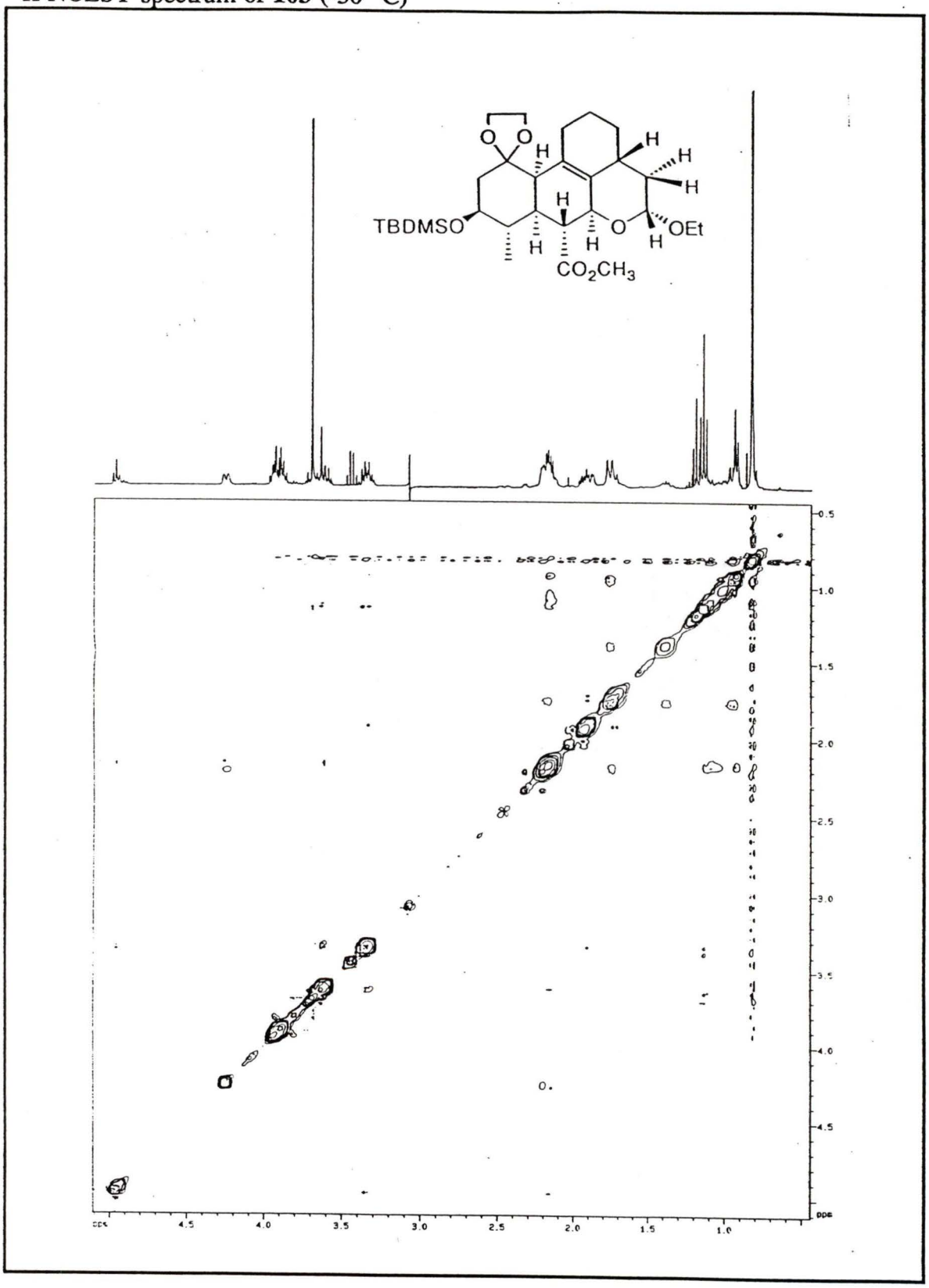
^{13}C NMR spectrum of **103** (-30° C)



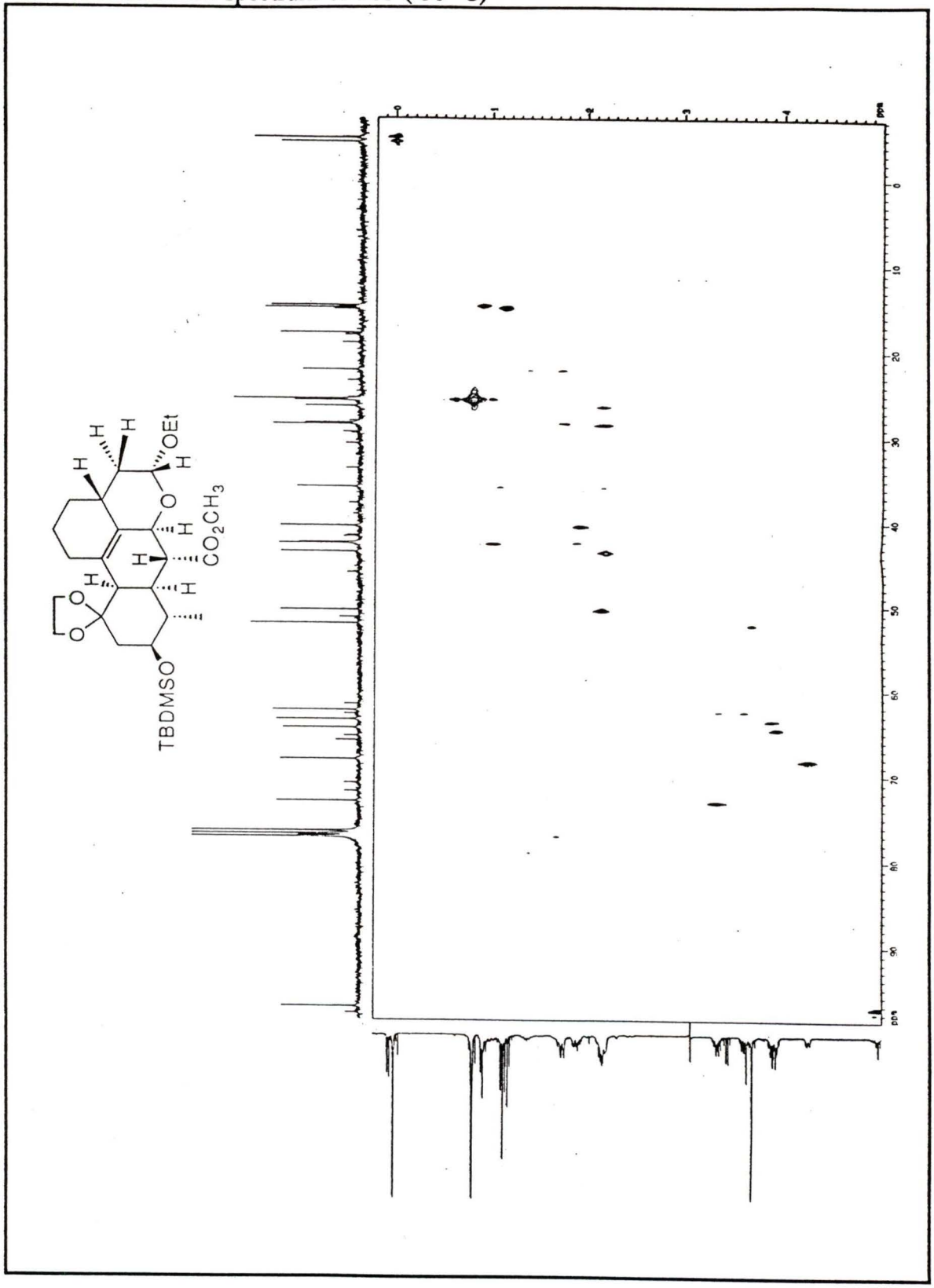
^{1}H COSY spectrum of **103** (-30° C)



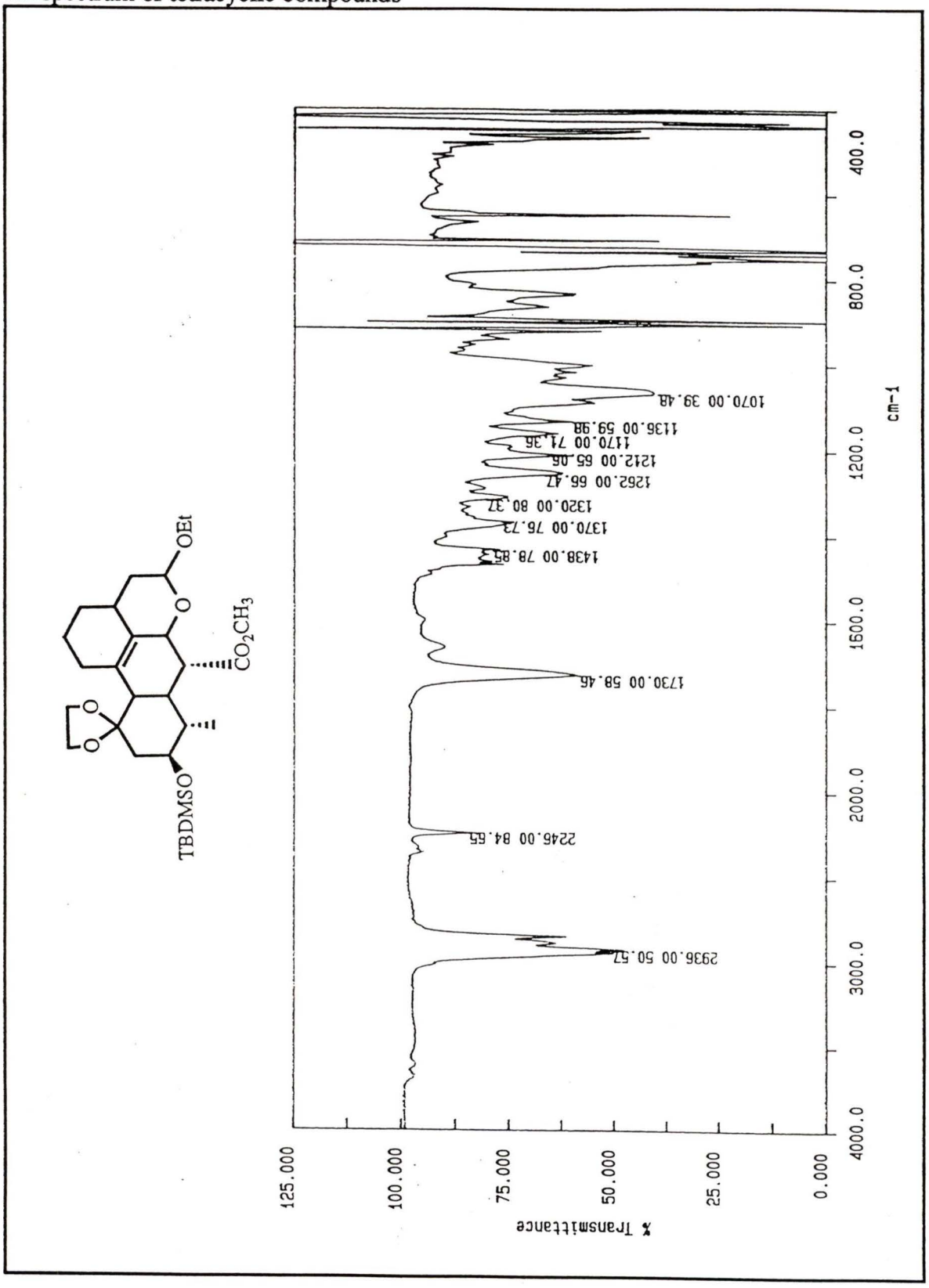
^{1}H NOESY spectrum of **103** (-30° C)



^{1}H-^{13}C Correlation spectrum of **103** (-30° C)



IR spectrum of tetracyclic compounds



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- "Photochemistry of 4-Cyano-2,3-benzobicyclo[4.2.0]octa-2,4,7-triene". *J. Org. Chem,* **1991**, *56*, 5015-5020

Presentations:

- "Stereoselective Synthesis of Tetracyclic Quassinoid via a Diene Transmissive Diels-Alder Strategy". 207th National Chemistry Conference of the American Chemical Society, San Diego, California. **1994**.
- "A Simple Method for the Homolagation of Polycyclic Aromatic Hydrocarbons". Fifth Annual Western Canada Student Conference of the Canadian Society for Chemistry. University of Manitoba, Winnipeg, Manitoba, Canada. **1991**.

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April 28, 94

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