

PALLADIUM ASSISTED RING CLOSURES

by

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This thesis is dedicated to my late father, _____,
whose wisdom, guidance, patience, and love have always guided me
through the years, and will continue to guide me through the future.

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Preface

The use of palladium in organic synthesis has been an area of intense research in recent years.¹ However, the use of palladium to form new cyclic systems has not been fully explored. The intent of this thesis is to investigate the utility of palladium as a mediator of carbocyclization reactions.

Part I of this thesis examines the possibility of utilizing carbopalladation²⁻⁶ to form carbocyclic systems.

Part II of this thesis explores the feasibility of employing insertion reactions to form macrocyclic ring systems.

PART I

PALLADIUM MEDIATED RING CLOSURES VIA CARBOPALLADATION

Chapter 1. Introduction

The utilization of palladium to create new bonds to carbon is among one of the most active areas of research in organic chemistry. The chemistry of palladium hinges upon the ability of palladium to coordinate to unsaturated systems and ultimately convert the unsaturated systems into mild, cationic-like alkylating or acylating agents. Thus, through activation by palladium, olefinic, acetylenic, allylic, benzylic, and aromatic systems have been used in a variety of ways to form new heteroatom-carbon and carbon-carbon bonds.¹ Of particular interest to us was the application of palladium to the construction of ring systems through the formation of new carbon-carbon bonds.

Although a large variety of heterocycles have been formed using palladium, the vast majority have been constructed by using the heteroatom as a nucleophile to create a new heteroatom-carbon bond. There are few examples of heterocyclic ring systems being created by carbon-carbon bond formation. With the exception of one lactonization method⁷, these have all been achieved either by an insertion reaction or an oxidative coupling. Most of these all carbon systems have resulted from dimerization and trimerization of acetylenes.

It is convenient to divide palladium mediated cyclizations into two categories: (a) those in which heterocyclic systems are formed, and (b) those which construct all carbon systems (carbocycles).

1. The Formation of Heterocyclic Ring Systems Via Palladium Mediation.

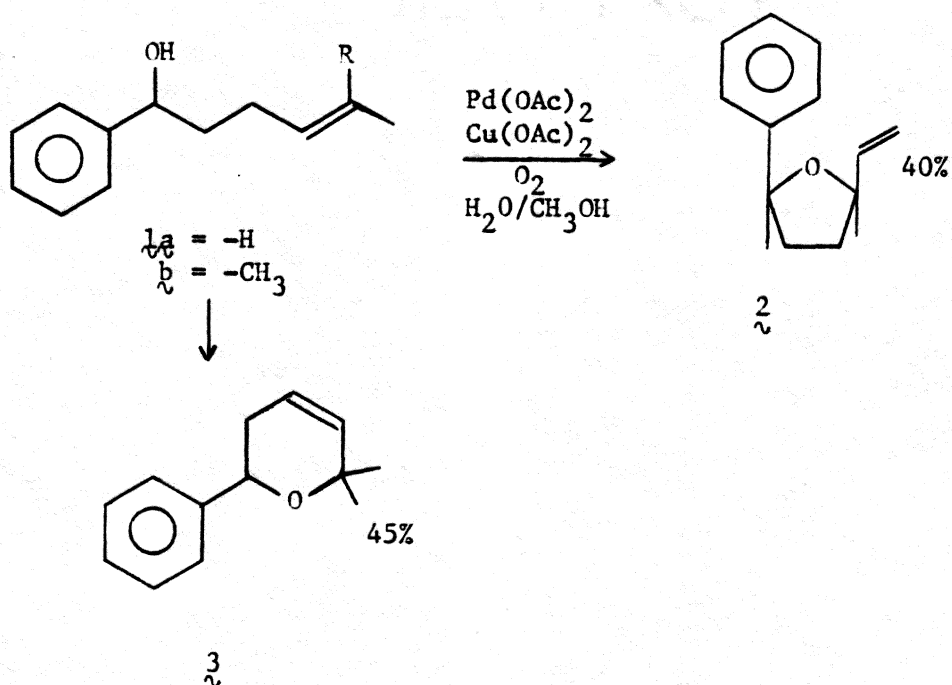
For the most part, heterocyclic ring systems have been formed either by attack of heteroatomic moieties on coordinated olefins, by insertion reactions, or by oxidative coupling.

1.1. Heterocycle Formation By Nucleophilic Attack Upon Palladium-Olefin Complexes.

Nucleophilic attack on olefin complexes to form heterocycles has been restricted to the use of oxygen and nitrogen as nucleophiles. Using palladium-olefin complexes, ring closures to form three-, five-, and six-membered rings have been achieved.⁸⁻²⁴

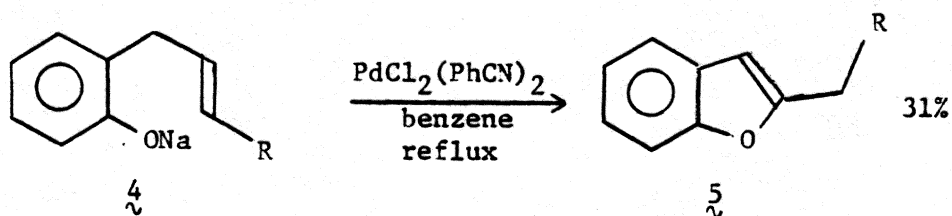
A variety of oxygen nucleophiles have been used to affect ring closures with olefins. These include alcohols, phenols, carboxylates, and oximes.⁸⁻¹⁵

Only one publication utilizes alcohol as the nucleophile.⁸ Benzyl alcohol 1a was converted to furan 2 stereospecifically with palladium catalysis, while benzyl alcohol 1b was converted to dihydropyran 3 under the same conditions.⁸ Several other similar examples are included; however, the yields are generally low.

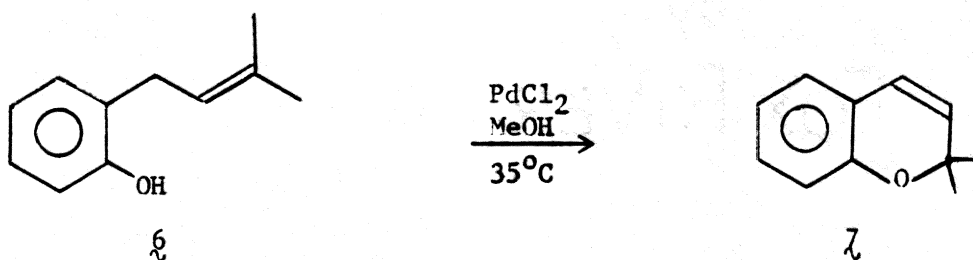


A larger number of cases have been reported in which phenol acts as nucleophile.^{9,10} Both 2-allyl phenols, such as **4**, and 2-hydroxy styrenes have been employed in ring closures. Unless elimination or migration into the ring are blocked, the products are benzofurans.⁹

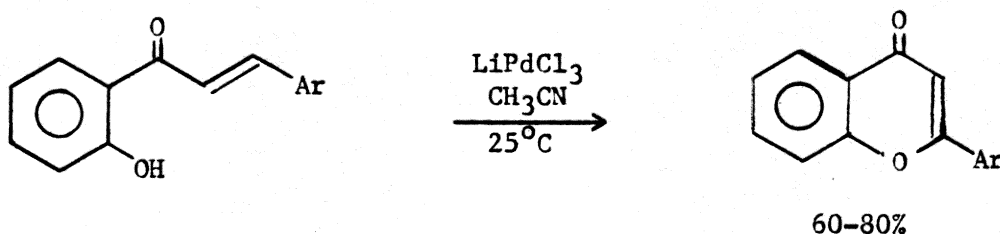
For example, phenoxide **4** was cyclized to benzofuran **5**. However, several



exceptions to the formation of benzofurans do appear. Although 2-allyl phenol **6** was converted to benzofurans as expected with palladium acetate, treatment with palladium chloride yielded benzopyran **7**, contaminated with only traces of benzofuran.

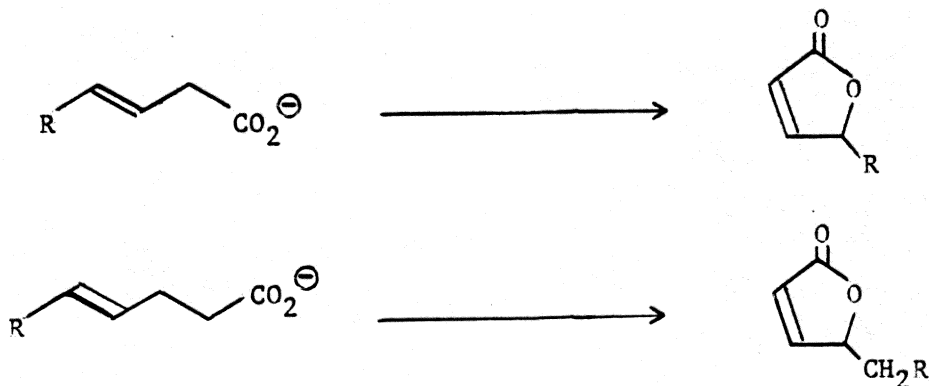


The last exception is the formation of flavones from 2-hydroxy catabols.¹⁰ This result may best be explained by the phenol acting

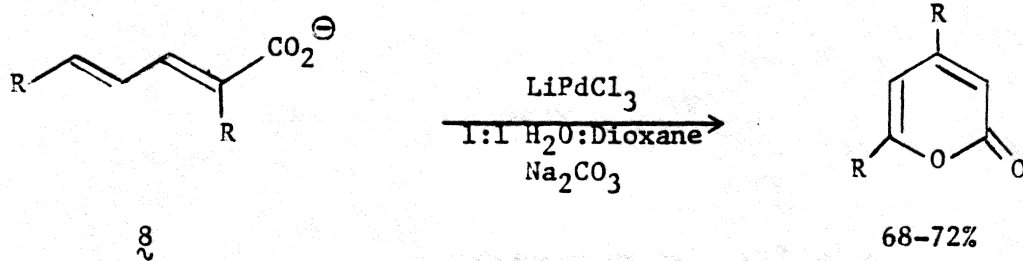


as a vinylogous acid. As will be shown later, the reaction of conjugated carboxylates is quite facile.

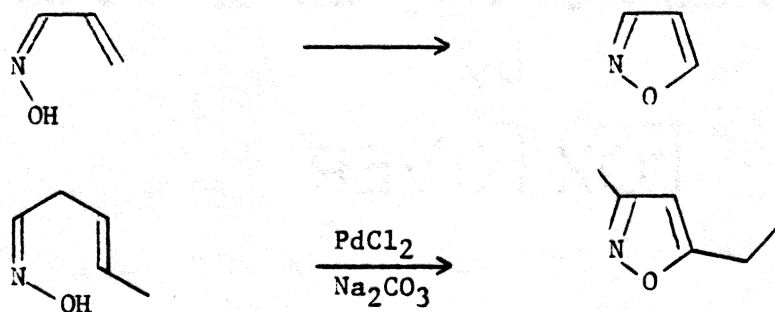
Carboxylate anions have also been utilized to form lactones.¹¹⁻¹³ Both allylic and homoallylic carboxylates yield α,β -unsaturated butyrolactones.¹¹ However, when the olefin is a conjugated diene,



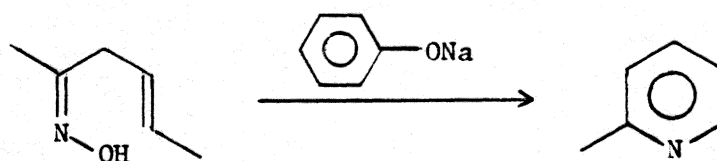
such as in **8**, the products are pyrones.^{12,13}



Oximes have also been used to form isoxazoles.^{14,15} For

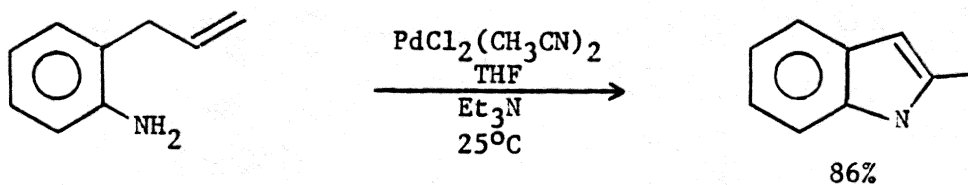


β,δ -unsaturated oximes, when the base is changed from carbonate to phenoxide, pyridines are formed.¹⁵

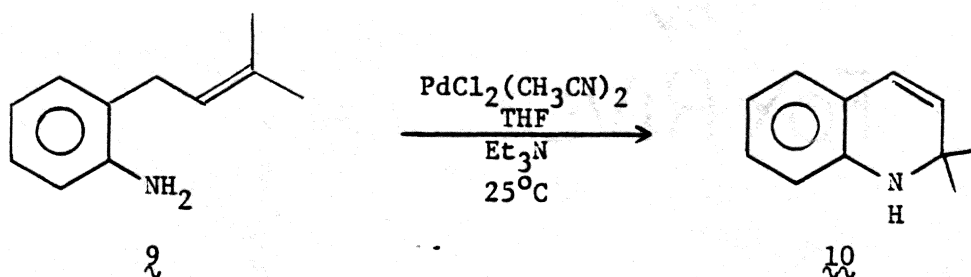


Amines, amides and hydrazides have been used as nitrogen nucleophiles to form heterocyclic systems.^{13,16-21}

Both 2-allyl anilines and 2-allyl benzylamines have been utilized as substrates for cyclization with amine as nucleophile.^{16,17} For example, 2-allyl aniline cyclizes readily to form methyl indole in high yield.¹⁷ The reaction is regioselective, giving exclusively

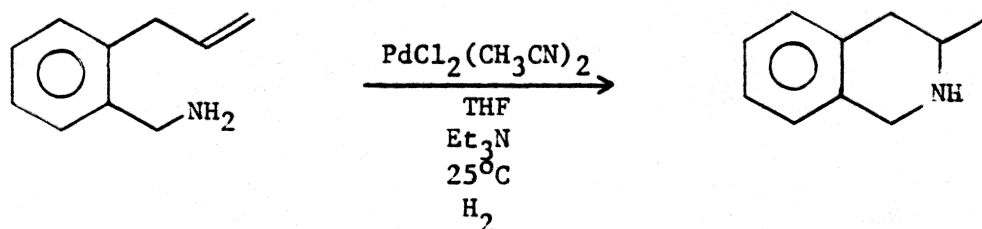


five-membered ring closure. However, the regiochemistry can be reversed with excess substitution at the terminus of the olefin. This is illustrated by the reaction of **9** to form dihydroquinoline **10**.¹⁶ This result is best explained by the fact that the ring closure closely



resembles a cationic process and the greater stability of the tertiary carbocation favors ring closure at the terminus of the olefin in **9**.

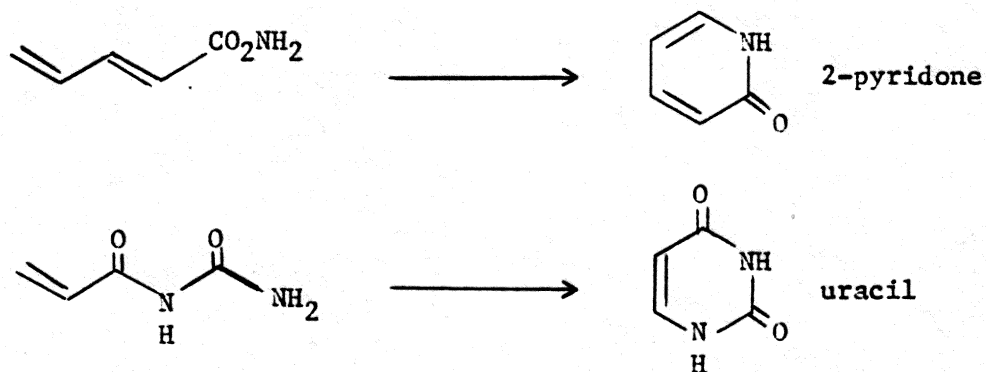
When 2-allyl benzylamines are the substrates, ring closure results in substituted tetrahydroisoquinolines after hydrogenation.¹⁶



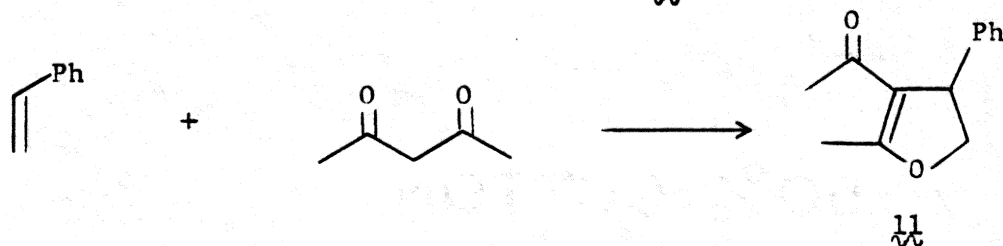
Amides act as nucleophiles in the same fashion as amines.^{13,18-21}

When *N*-acetyl-2-allylanilines are cyclized, *N*-acetyl indoles are

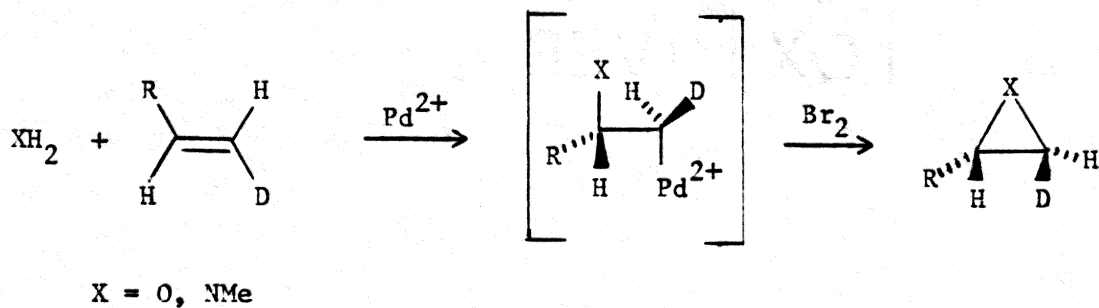
obtained.²¹ Extensions of this method have resulted in the construction of 2-pyridones and uracil.^{19,21}



One last example of this type of palladium mediated cyclization has been published. The intermolecular reaction of acetylacetone with styrene results in formation of dihydrofuran **11**.²²



Of all the cyclizations using heteroatoms, formation of aziridines²³ and epoxides²⁴ by palladium mediation may well be the most important.

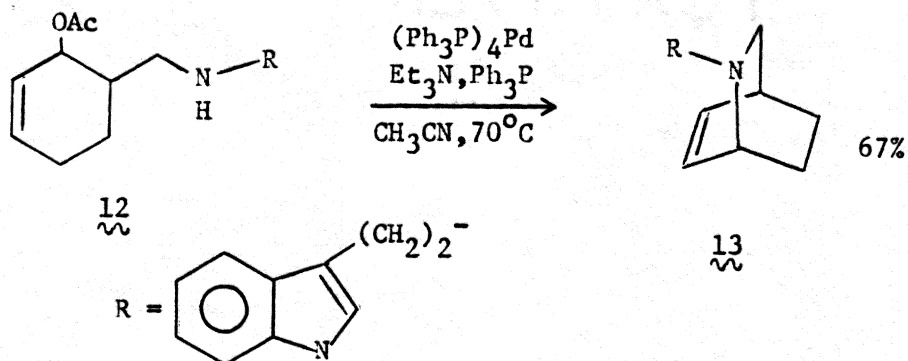


The significance of this reaction is that it demonstrates that nucleophilic attack by amines or water are indeed trans. The fact that the reaction of heteroatomic nucleophiles with olefins coordinated to palladium is stereospecific has not been utilized in more complex systems, and may prove to be very useful in the future.

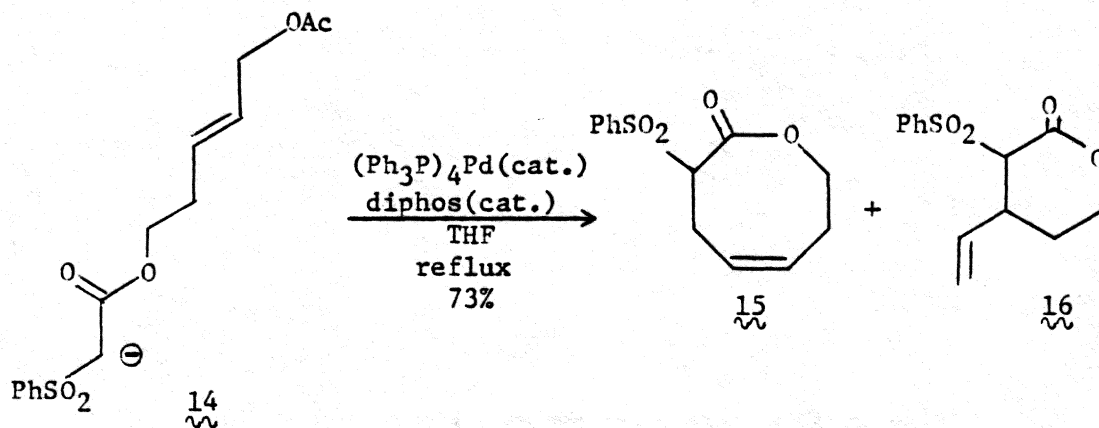
In summation, the intramolecular reaction of palladium coordinated olefins with heteroatomic nucleophiles appears to be regiospecific. The regiochemistry generally results in a five-membered ring closure. The regiospecificity, however, may be reversed by formation of better cations or conjugation with electron withdrawing groups. Whereas the yields with nitrogen nucleophiles are generally good, the yields with oxygen acting as nucleophile are only good where carboxylates and oximes are employed as nucleophiles.

1.2. Heterocycle Formation by Nucleophilic Attack on Allylic Systems

Several examples of palladium catalyzed nucleophilic attack upon allylic esters to form heterocycles have been published. Amines have been used as nucleophiles to form a variety of bicyclic azo compounds.²⁵ For example, indole amine 12 was cyclized with catalysis by tetrakis(triphenylphosphine) palladium to give the aza bicycle 13.



Of much greater significance to this thesis is the use of stabilized ester enolates to form lactones via palladium catalyzed displacement of allylic acetates.⁷ The utilization of stabilized enolates to form lactones constitutes one of the few examples of the use of a carbon nucleophile in a palladium assisted cyclization. Unlike the all-carbon cyclizations (to be discussed later), lactonizations appear to prefer the formation of larger ring systems. This is demonstrated by the ring closure of allylic acetate 14 to yield a mixture of lactones 15 and 16 in a 94:6 ratio, respectively. This reaction appears to reverse the normal order of reactivity. Thus,

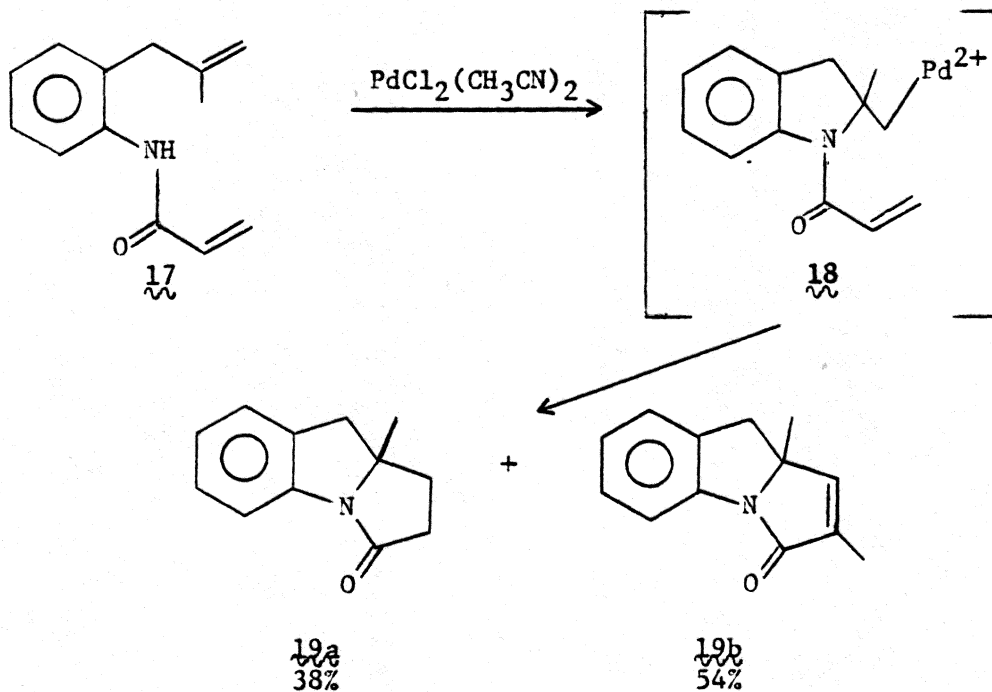


formation of 8-membered rings is favored over 6-membered rings; likewise, 9-membered rings are favored over 7-membered rings. As shall be illustrated later, this preference for larger rings isn't as strong for all carbon systems. This reaction has been utilized to form a number of macrocyclic lactones.²⁵

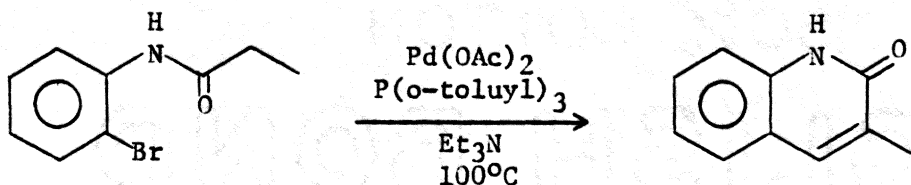
1.3. The Formation of Heterocycles Via Insertion Reactions

Insertion reactions constitute the largest number of documented cyclizations in which carbon-carbon bonds are formed.

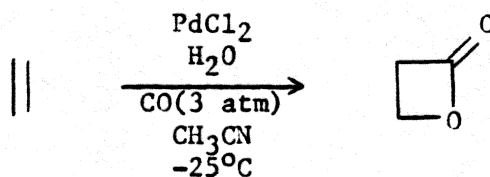
Olefin insertions have been used to form heterocycles in a limited number of cases.^{21,26-28} Apparently, the formation of five-membered rings is highly favored. For example, intramolecular trapping of the palladium intermediate 18 gave exclusively butyrolactams 19a and 19b.²¹ Therefore, intramolecular ring closures to form five-membered



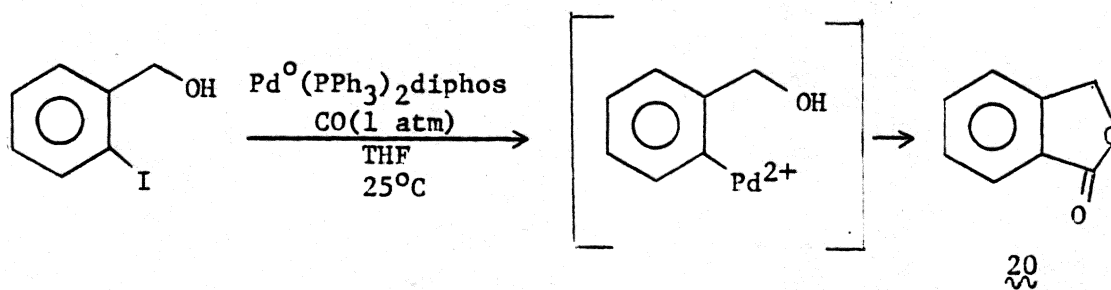
rings is so favored that the intramolecular version inverts the normal mode of reactivity. With palladium complexes, the normal mode of reactivity toward conjugated olefins is 1,4-addition not 1,3-addition.^{3,4,29} Normal 1,4-addition may again be attained by α -substitution of the olefin.²⁶



Carbon monoxide insertions have been used to form a variety of lactones³⁰⁻³⁵ and lactams.^{36,37} This type of insertion is interesting in that both a new carbon-carbon bond and a new carbon-heteroatom bond are formed simultaneously. The simplest example is the synthesis of propiolactone from ethylene.³³



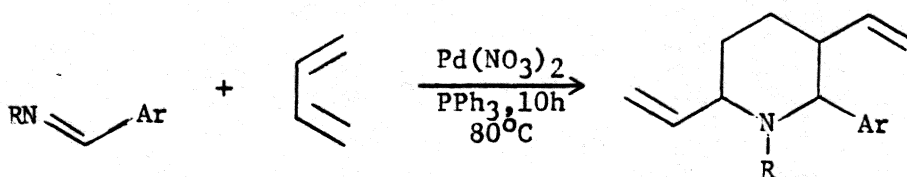
The carbon monoxide insertion may also be used to form lactones from haloalcohols. These reactions have been performed utilizing the oxidative addition of palladium with benzylic, allylic, vinyl and aryl halides to form the palladium complex, which subsequently undergoes the insertion reaction.³⁰ For example, 2-iodobenzyl alcohol readily lactonizes to form lactone 20. The reaction has been limited to the



formation of propio-, butyro-, and valerolactones.

In a similar fashion, lactams containing five through seven atoms have been constructed.^{36,37} Since these two types of insertions are the subject of Part II of this thesis, a much more detailed discussion of these types of insertions will appear in Part II, Chapter 1.

Of much less importance to this thesis are cyclizations via the trapping of intermediates obtained during the telomerization of butadiene. For example, Schiff bases can be trapped during dimerization of butadiene to form piperdines.³⁸ A variety of other multiply bonded

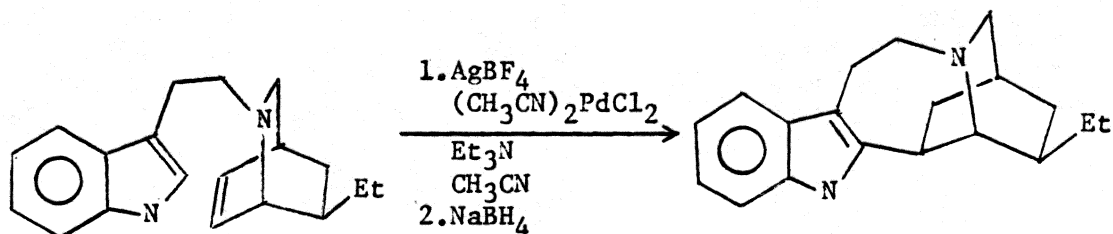


carbon-heteroatom bonds have been used as well.³⁸

1.4. Heterocycle Formation By Oxidative Coupling

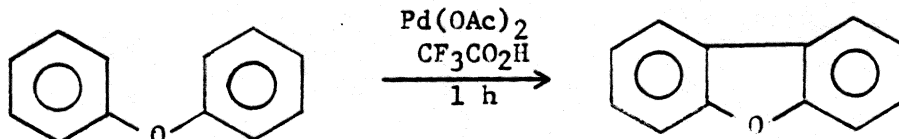
Olefins have been coupled to indoles to form new carbon-carbon

bonds. This method has been used to cyclize an assortment of



isoquinuclidines.²⁵ The yields are generally poor to moderate.

Biaryls have also been coupled to give heterocyclic systems.^{39,40} Unlike the aryl-olefin couplings illustrated above, the yields are generally good. For example, diphenyl ether was rapidly cyclized to dibenzofuran with a stoichiometric quantity of palladium acetate.

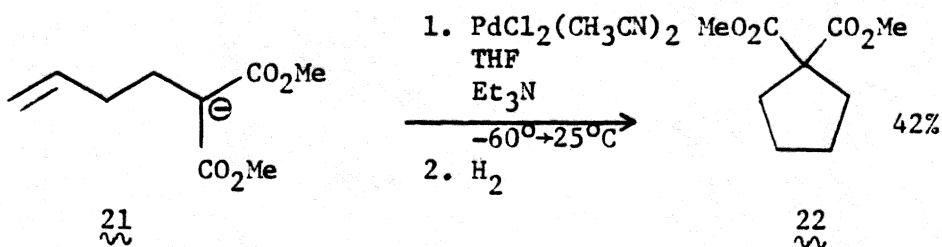


2. Formation of Carbocycles By Palladium Mediation

A large number of all carbon ring systems (carbocycles) have been formed through the mediation of palladium. By far, the majority of these have been accomplished using olefins to internally couple with intermediate palladium complexes, or through controlled polymerization of acetylene and olefins. Examples of carbanions being used as nucleophiles to effect carbocyclic ring closure are almost non-existent.

2.1. Formation of Carbocycles Via Nucleophilic Attack on Palladium-Olefin Complexes

Only one example of cyclization via nucleophilic attack by carbanions on olefins has been reported.^{2b} Homoallylic malonate 21 was cyclized to form cyclopentane 22 in moderate yield after hydrogenation.



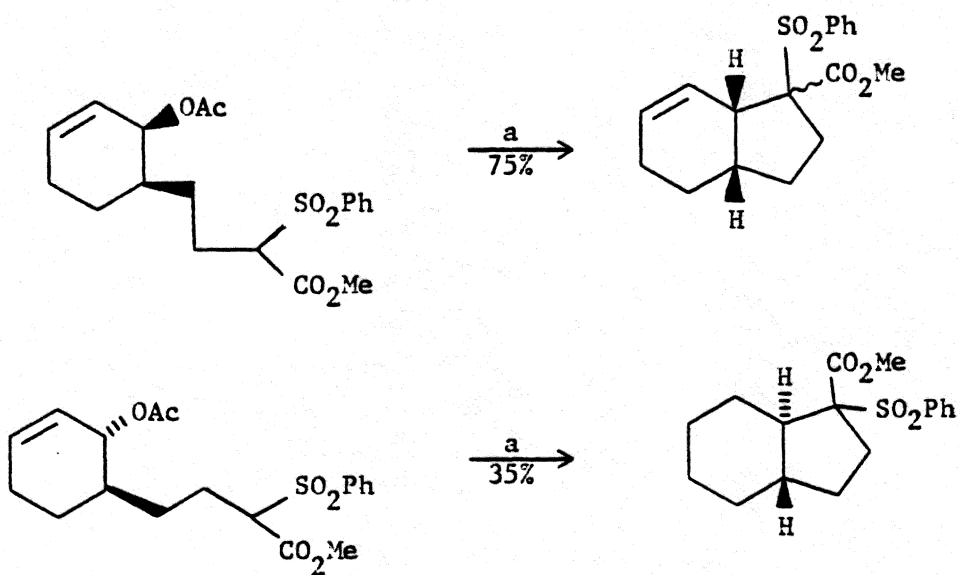
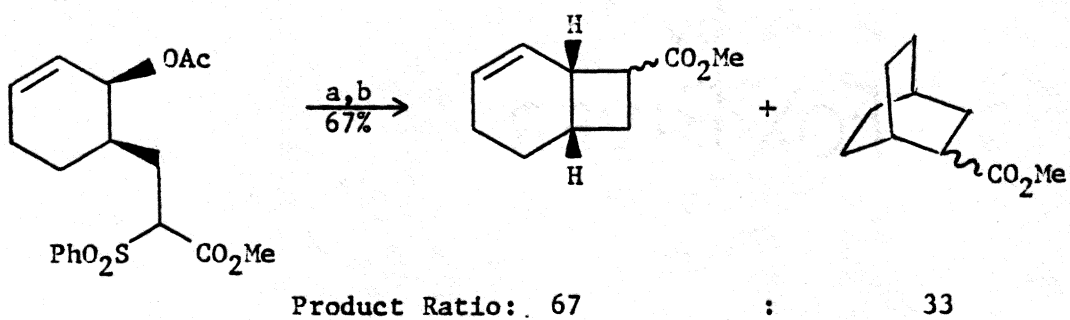
2.2. Carbocycles Formed From Allylic Acetates

All carbon rings have been constructed from allylic acetates utilizing palladium catalysts.^{7a,c,d} Unlike the lactonization procedure mentioned previously, the all carbon systems employing palladium catalysts don't appear to be nearly so regioselective. The examples shown in Scheme I demonstrate that the regiochemistry favors closure at the carbon bearing acetate. However, the regiochemistry is not always exclusive. This represents a distinct deficiency in this approach.

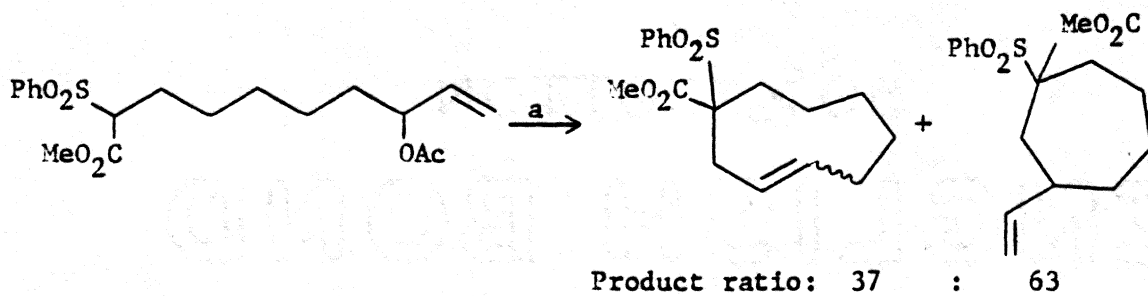
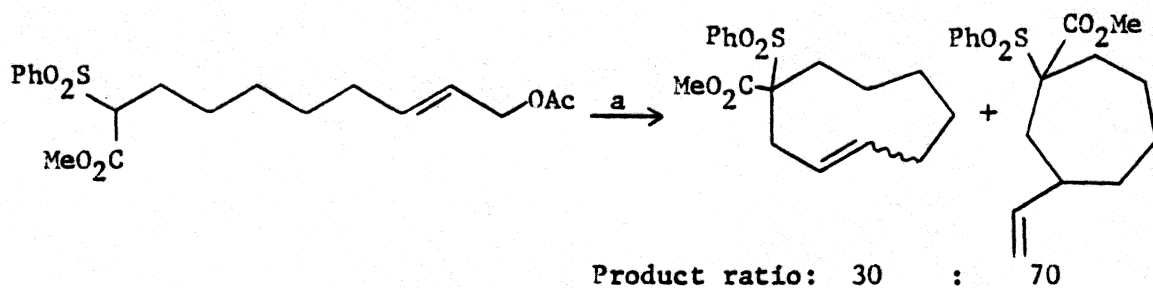
In addition, in all-carbon cases the formation of large rings is not as favorable as in the aforementioned lactonizations and mixtures are obtained.

Scheme I

Formation of Carbocyclic Rings by Palladium
Catalyzed Acetate Displacement



Scheme I (Cont'd.)



a) NaH , $(\text{Ph}_3\text{P})_4\text{Pd}$, THF, reflux

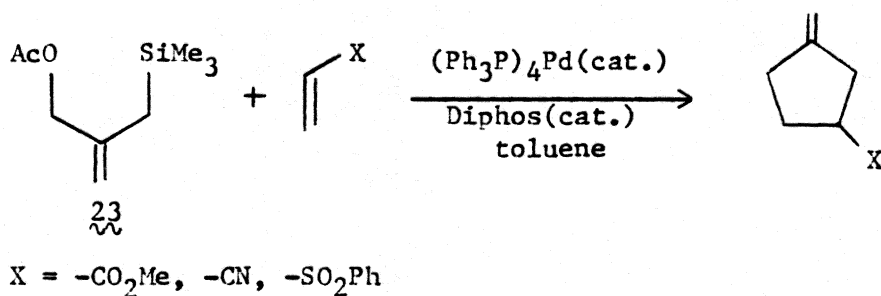
b) 6% Na/Hg , Na_2HPO_4 , CH_3OH , 0°C

The reaction does appear to be stereoselective. The stereochemistry about the acetate is retained. This observation has been explained by a double inversion mechanism.⁴¹

The only obvious difference between the all-carbon cases and the lactonization is the position of the enolate. In the all-carbon cases, the enolate is exo to the newly formed ring. On the other hand, in lactonizations, the enolate is endo to the newly formed rings. Although the geometric requirements for formation of large rings are ill-defined,^{7d} the distinct stereoelectronic differences between utilizing endo- and exo-enolates in ring closure have been elucidated in the construction of five-, six-, and seven-membered rings.⁴² The difference may be significant in these cases.^{7d}

Lacking a complete study of the distinctions between the carbocyclic ring closures and lactonizations, the regioselectivity of these processes must be regarded as more empirical than predictive.

One additional example of cyclizations via palladium-assisted ring closure of allylic acetates exists. Trimethylsilyl acetate 23 was heated in the presence of a variety of activated olefins, such as acrylates or acrylonitrile, to form exo-methylene cyclopentanoids.⁴³

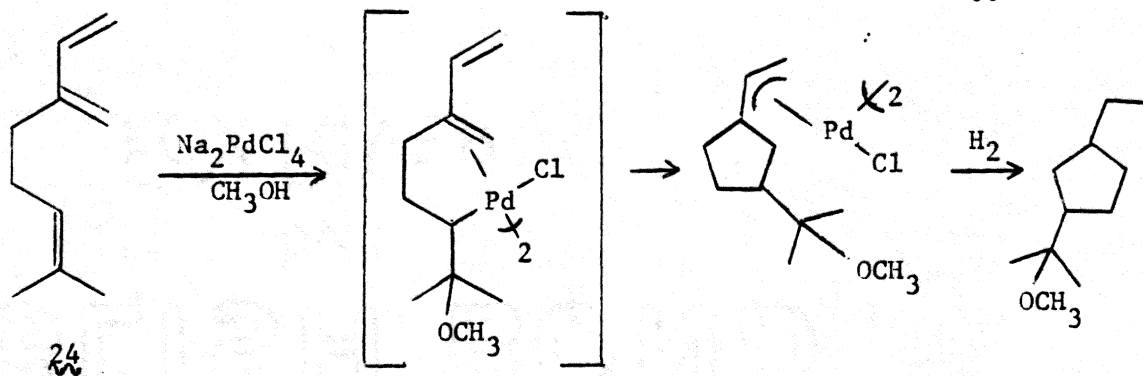


The conditions are fairly harsh, requiring refluxing solvent from 3 h - 10 days. Additionally, the yields are generally only poor to moderate.

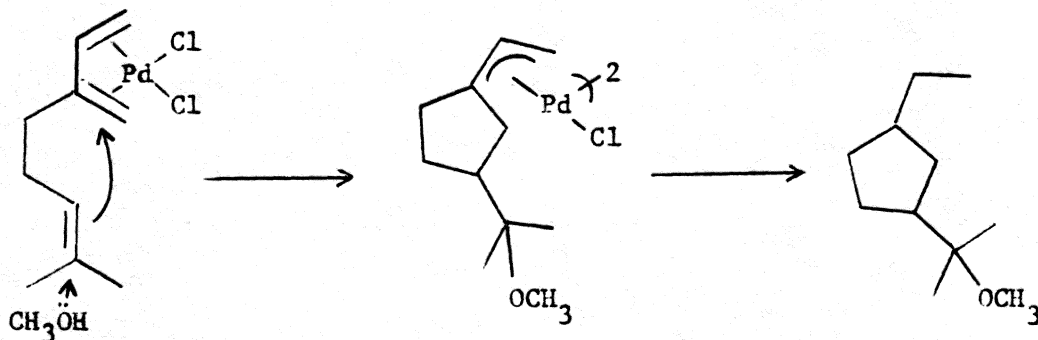
2.3. Carbocycles Via Insertion Reactions

The intramolecular insertion of olefins into palladium intermediates is, by far, the most common technique for forming non-aromatic carbocycles. The method has been used to trap a number of unstable aliphatic- and acyl-palladium complexes.⁴⁴⁻⁴⁸

The most common examples of σ -bonded aliphatic palladium complexes undergoing intramolecular olefin insertion are 1,5 dienes which have undergone initial external nucleophilic attack, followed by an insertion. One such example is the ring closure of myrcene ²⁴.^{44d}

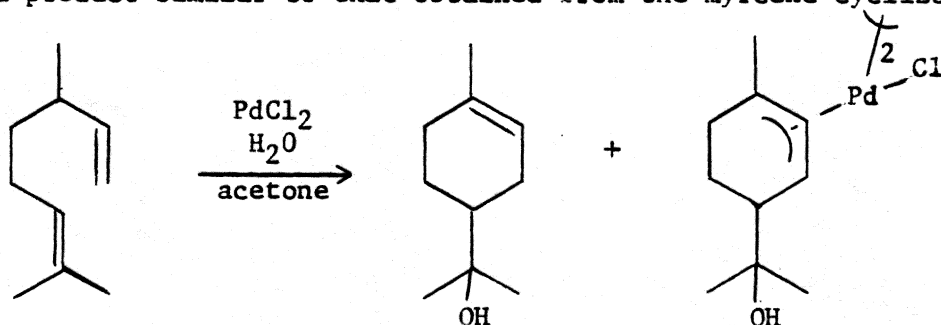


Although the ring closure of myrcene has been written as an insertion reaction, a second mechanism might be envisioned.

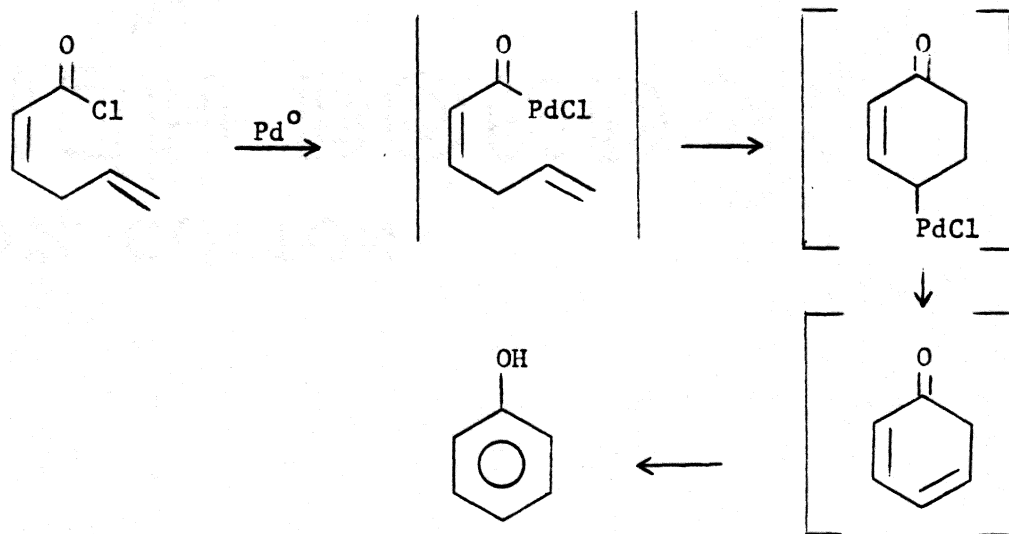


Several cases of cyclooctadiene undergoing a similar insertion to [3.3.0]-bicyclooctanes have also been documented.^{44b-e} The mechanism has been fairly well established as an intramolecular olefin insertion.^{44c}

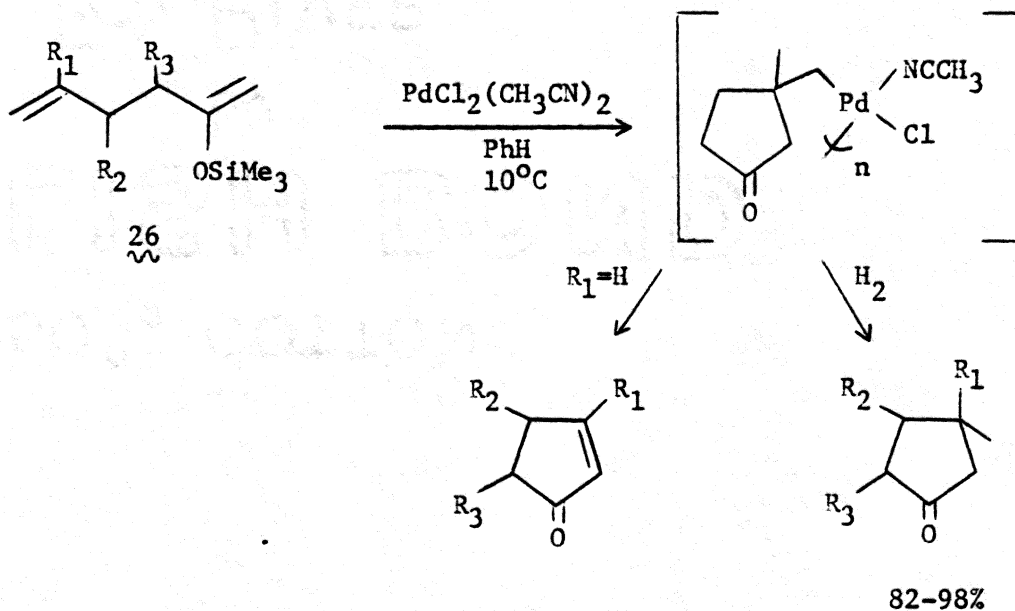
In one isolated example, a 1,6-diene has been found to cyclize to give a product similar to that obtained from the myrcene cyclization.⁴⁵



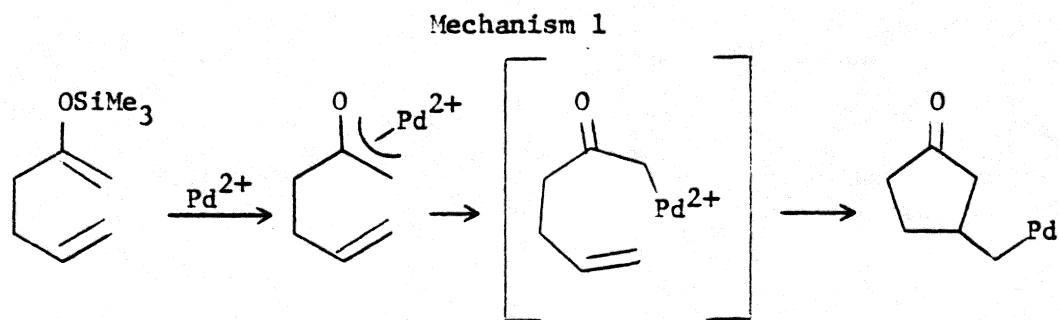
Olefins have also been used to trap acyl palladium intermediates. These are usually obtained from carbon monoxide insertions and yield cyclic ketones.^{46,47} Probably the simplest example is the attempted Rosenmund reduction of unsaturated acid chloride 25. Rather than reduction, oxidative addition takes place, followed by insertion to give phenol as the final product.⁴⁷



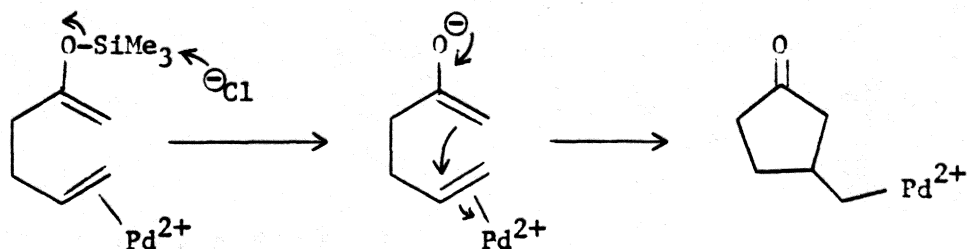
An extremely interesting example of an olefin insertion into palladium enolates has also appeared in the literature. Silylenol ethers, such as 26, readily cyclize to form cyclopentanones.⁴⁸



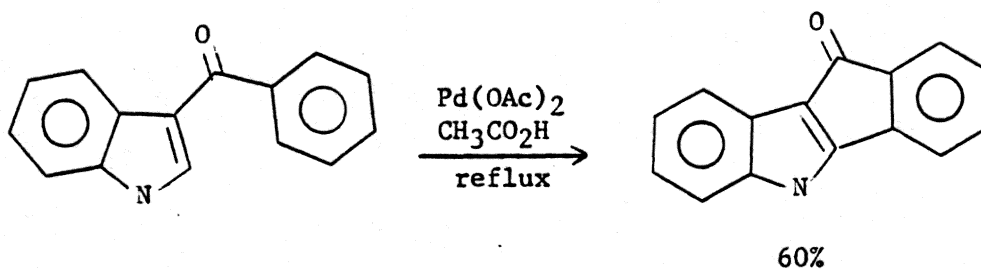
The authors claim this transformation is an insertion reaction into an oxo- π -allyl complex (Mechanism 1). However, the reaction may actually be an example of a nucleophilic attack by an enolate upon coordinated olefin (Mechanism 2).



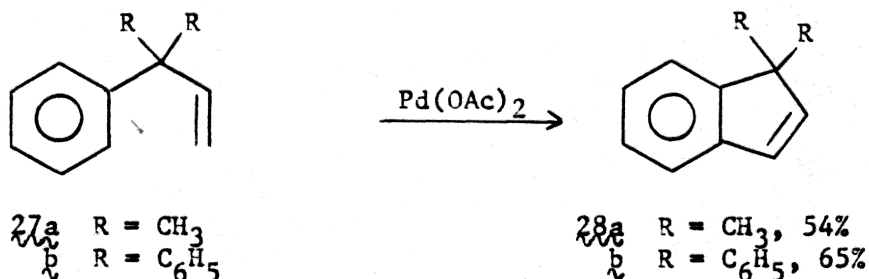
Mechanism 2

2.4. Formation of Carbocycles Via Oxidative Coupling

Two cases of the oxidative coupling of biaryls to form carbocycles have been documented.^{39,49} Benzophenone has been cyclized with palladium acetate to give 9-flourenone in 65% yield.³⁹ The second example is a simple extension in which a phenyl group has been replaced with indole. Methyl substitutions on either aromatic ring drastically

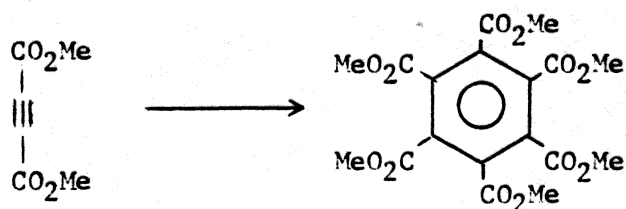


reduce the yields.⁴⁹ Allyl benzenes 27a and 27b have also been cyclized by oxidative coupling to form indenenes 28a and 28b.⁵⁰

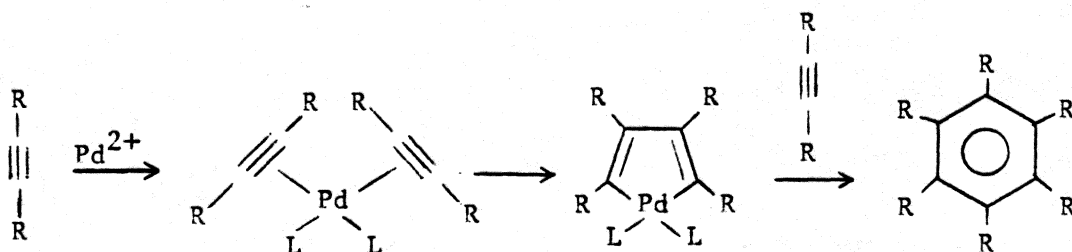


2.5. Aromatic Carbocycles Via Controlled Polymerization with Palladium

The largest number of carbocycles have been created by the controlled polymerization of acetylenes and olefins, resulting in aromatic systems.⁵¹ For example, dicarbomethoxy acetylene has been trimerized to give hexacarbomethoxy benzene.



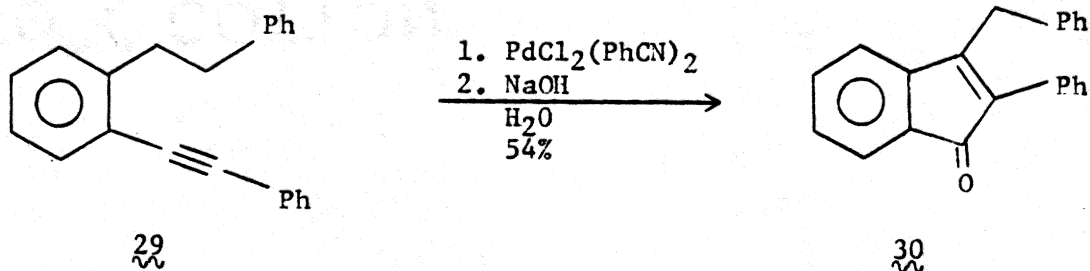
The reactions apparently involve a sequence of insertion reactions as shown below. These reactions have little relevance to this thesis



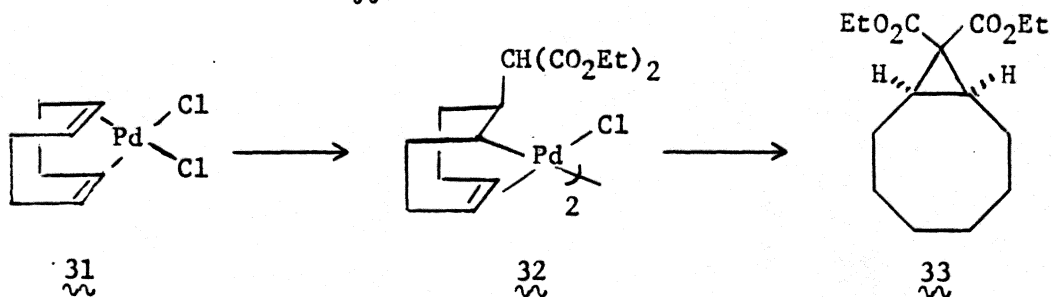
and, therefore, do not warrant further discussion.

2.6. Miscellaneous Methods of Forming Carbocycles with Palladium

Two cases of the coupling of acetylenic-olefins during palladium assisted hydrolysis have appeared in the literature.⁵² For example, acetylenic-olefin 29 was first complexed with palladium and, subsequently, hydrolyzed to give 30.^{52b}

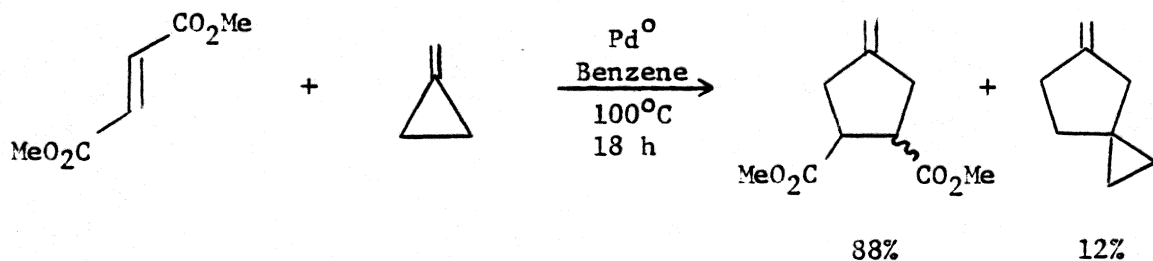


An example of an intramolecular back-side displacement of palladium has been published.⁶ The palladium complex 32, obtained by nucleophilic attack with sodio-diethylmalonate on the cyclooctadiene palladium complex 31, was treated with dimsyl anion to yield diethyl-[6.1.0.]nonane-9,9-dicarboxylate (33).



a) $(\text{EtO}_2\text{C})_2\text{CHNa}$; b) $\text{CH}_3\text{S}(\text{O})\text{CH}_2\text{Na}$

The last example of palladium assisted carbocycle formation is the reaction of vinyl cyclopropane with olefins. Vinyl cyclopropane reacts with dienophiles to give cyclopentanoids using palladium catalysis. The reaction is non-stereospecific. Mechanistically, this

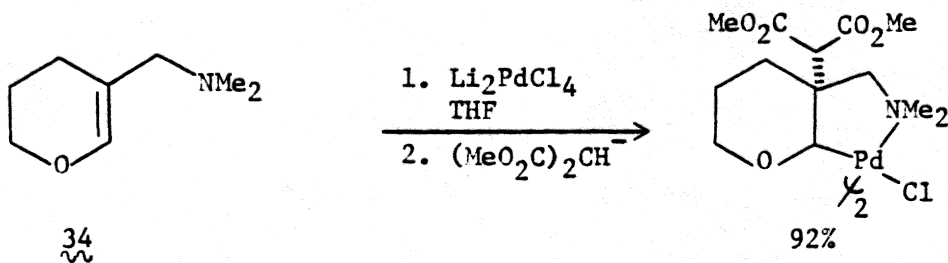


reaction is probably related to the cyclopentanoid formations from silyl acetate 23 (see section 2.2.).

The utilization of palladium-coordinated olefins in constructing carbocyclic systems has been sorely neglected. This is surprising, since the alkylation of stabilized enolates with olefins coordinated to palladium (termed "carbopalladation") might offer a number of distinct regio- and stereochemical advantages over conventional methods for ring closure.

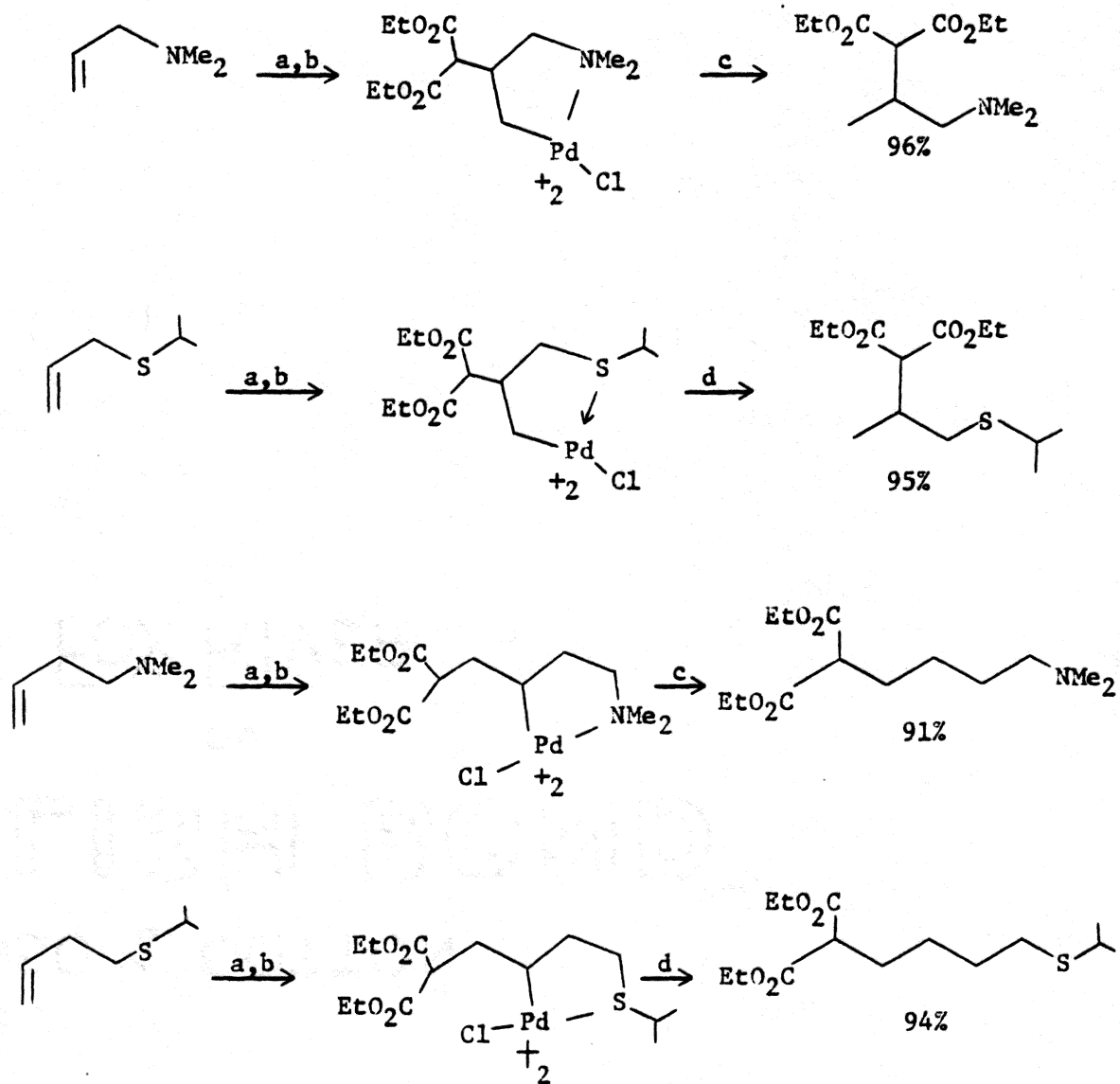
Intermolecular studies have shown the carbopalladation reaction is relatively non-regiospecific with isolated olefins.² However, in the presence of a second ligating group, such as sulfide or tertiary amine, the regiochemistry becomes extremely well defined.³⁻⁵ Allylic amines and sulfides alkylate utilizing the β carbon of an allylic system, whereas homoallylic amines and sulfides alkylate utilizing the γ -carbon (Scheme II).^{3,4} The regiochemistry is entirely guided by the formation of a stable five-membered metallocycle containing a σ -bonded alkyl group.

The strict adherence to this rule is best demonstrated in the carbopalladation of 34.⁵³ In this case, the nucleophilic attack occurs at the β -carbon despite a large steric barrier and a very unfavorable polarity about the olefin. This strict regiochemical control should



Scheme II

The Alkylation of Stabilized Enolates With
Palladium Complexes of Allylic and
Homo-Allylic Amines and Sulfides



- a) Li₂PdCl₄, THF, b) Na⁺, ⁻CH(CO₂Et)₂, THF, c) H₂, MeOH,
d) NaBH₄, MeOH

permit unambiguous regulation of the ring size during intramolecular carbopalladations.

Utilizing this regiochemical constraint, a variety of potential substitution patterns might be envisioned to arise. Tables 1 and 2 enumerate the possible patterns for simple cyclohexyl systems. Those systems shown in Tables 1 and 2 might easily be envisioned as possessing further substitution or as being extended to form five- and seven-membered rings.

The carbopalladation reaction is also stereospecific.^{3-6,54} Nucleophilic attack with stabilized enolates has been shown to proceed with net trans addition of the nucleophile and palladium to the olefinic linkage. For example, when cyclopentenyl amine **35** was carbopalladated and reduced, cyclopentyl amine **36** was obtained.⁴ Subsequent conversion to known lactone **37** established the stereochemical outcome as having been trans.

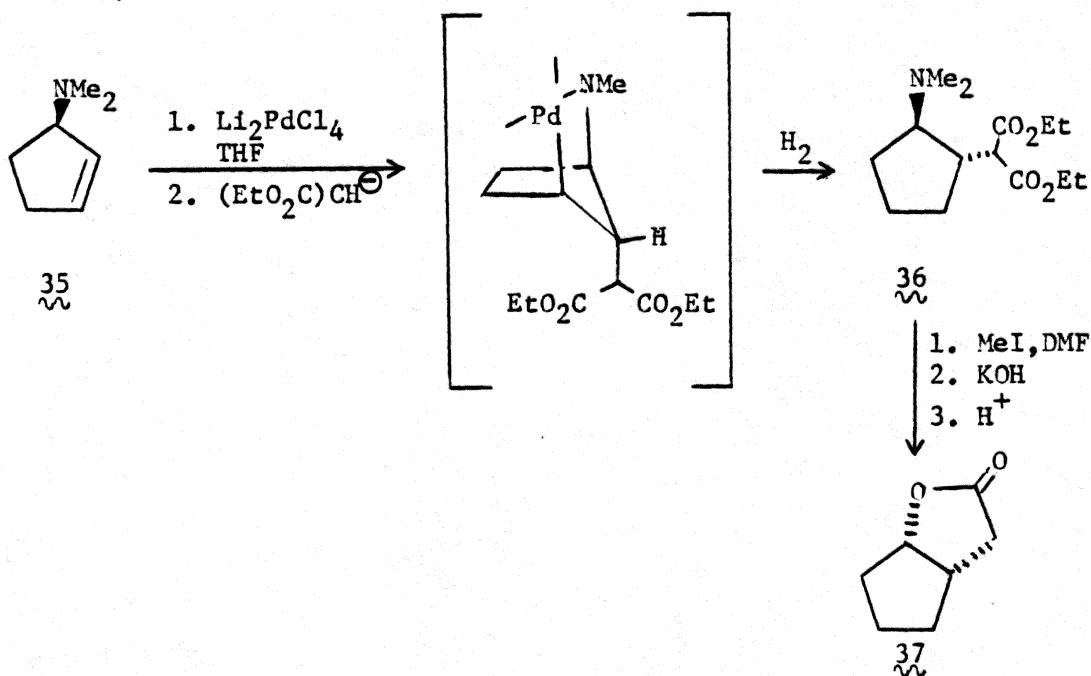
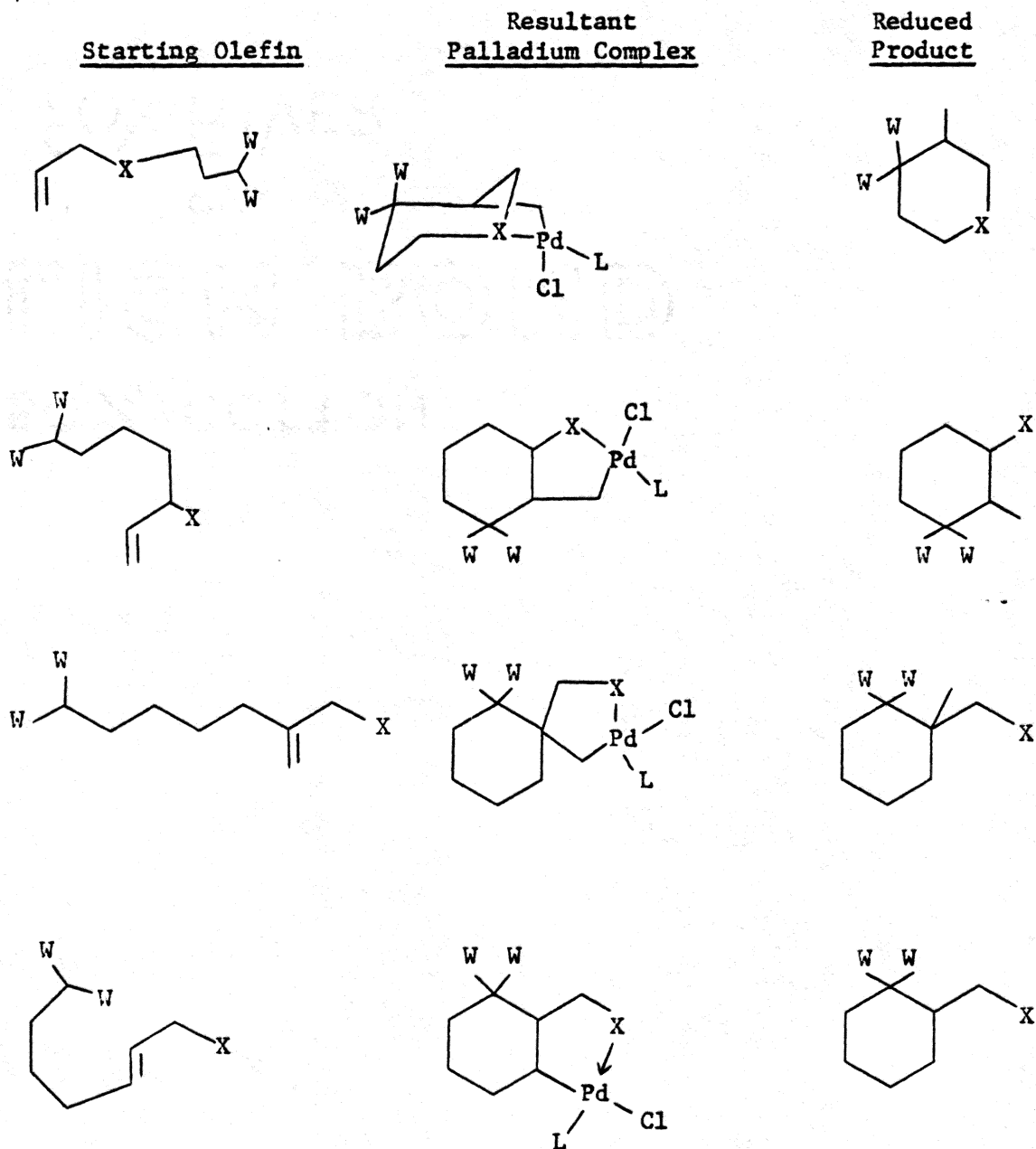


Table 1

Examples of Potential Cyclohexyl Systems
From Allylic Amines and Sulfides



X = -SR, -NR₂

W = electron withdrawing group

Table 2

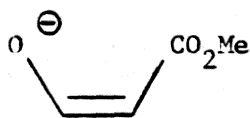
Examples of Potential Cyclohexyl Systems
From Homoallylic Amines and Sulfides

<u>Starting Olefin</u>	<u>Resultant Palladium Complex</u>	<u>Reduced Product</u>

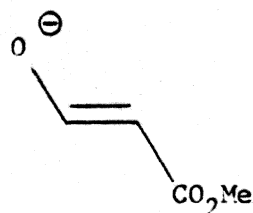
These results should permit prediction of the relative stereochemistry of the bicyclic palladocycles formed through cyclization. The ring closures of olefins possessing ligand and stabilized enolate at the termini of a chain might be considered illustrative (Scheme III).

An important point surfaces upon examining the potential closures shown in Scheme III. It should be possible to control the relative stereochemistry of two adjacent carbons in the bicyclic palladium complexes, simply by controlling the geometry of the olefin. For the "endocyclic" ring closures shown in Scheme III, this would result in control of the relative stereochemistry about the two carbons at ring fusion. On the other hand, for "exocyclic" ring closures this could potentially control the relative stereochemistry about the two carbons constituting the connection between the two cyclic systems.

It is likely that the stereochemistry about a third center might also be controlled. Recent investigations into the geometries of enolates have revealed that it is possible to dictate the geometry of a stabilized enolate by simply altering the cation.⁵⁵ For example, lithium enolates are apparently "cis" while potassium enolates appear to be "trans".

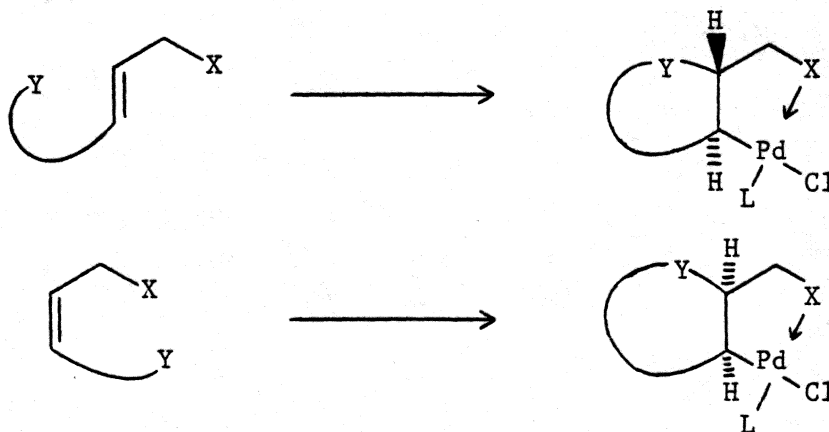
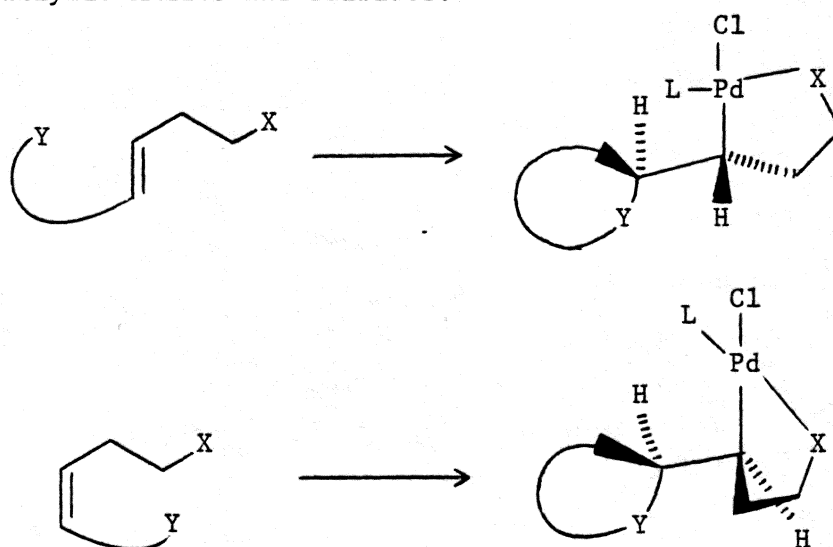


"cis" enolate



"trans" enolate

Scheme III

Predicted Stereochemical Outcomes For The Ring Closure
of Terminally Substituted Olefins1. Stereochemical Course of Endocyclic Ring Closures.
Allylic Amine and Sulfides2. Stereochemical Course of Exocyclic Ring Closures.
Homoallylic Amines and Sulfides.X = -SR, -NR₂

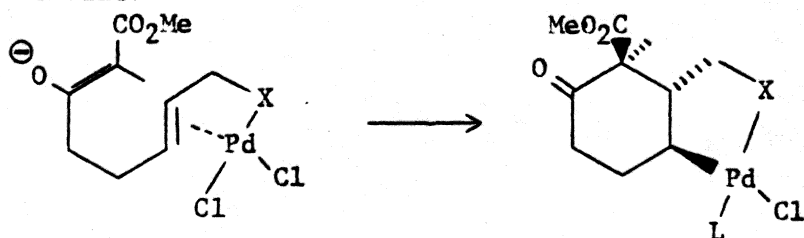
Y = stabilized enolate

Scheme IV

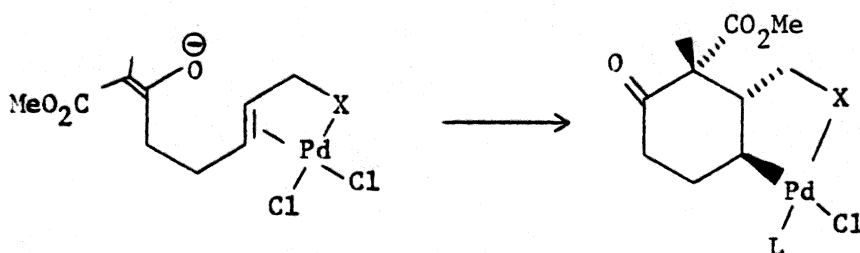
Potential Stereochemical Control Via Enolate Geometry.
Formation of Methyl Substituted Cyclohexanones

1. Endocyclic Ring Closures

"cis" enolate

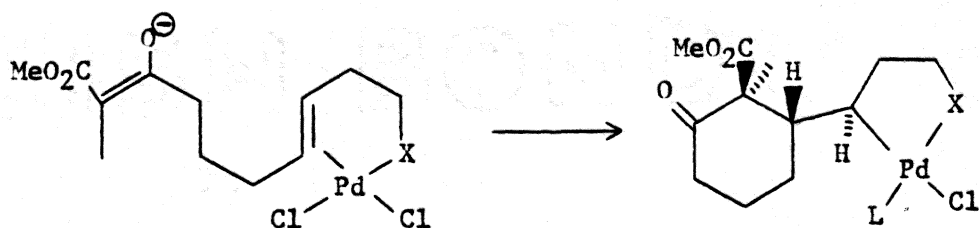


"trans" enolate

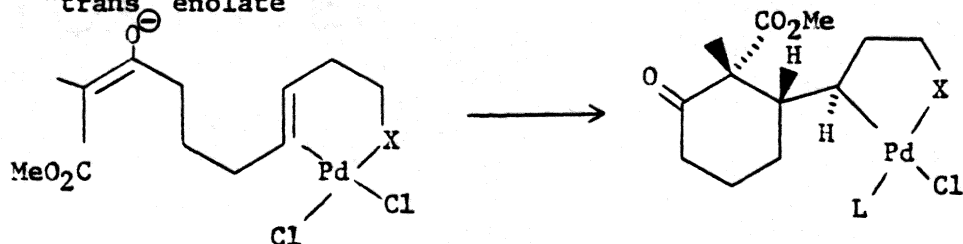


2. Endocyclic Ring Closures

"cis" enolate



"trans" enolate

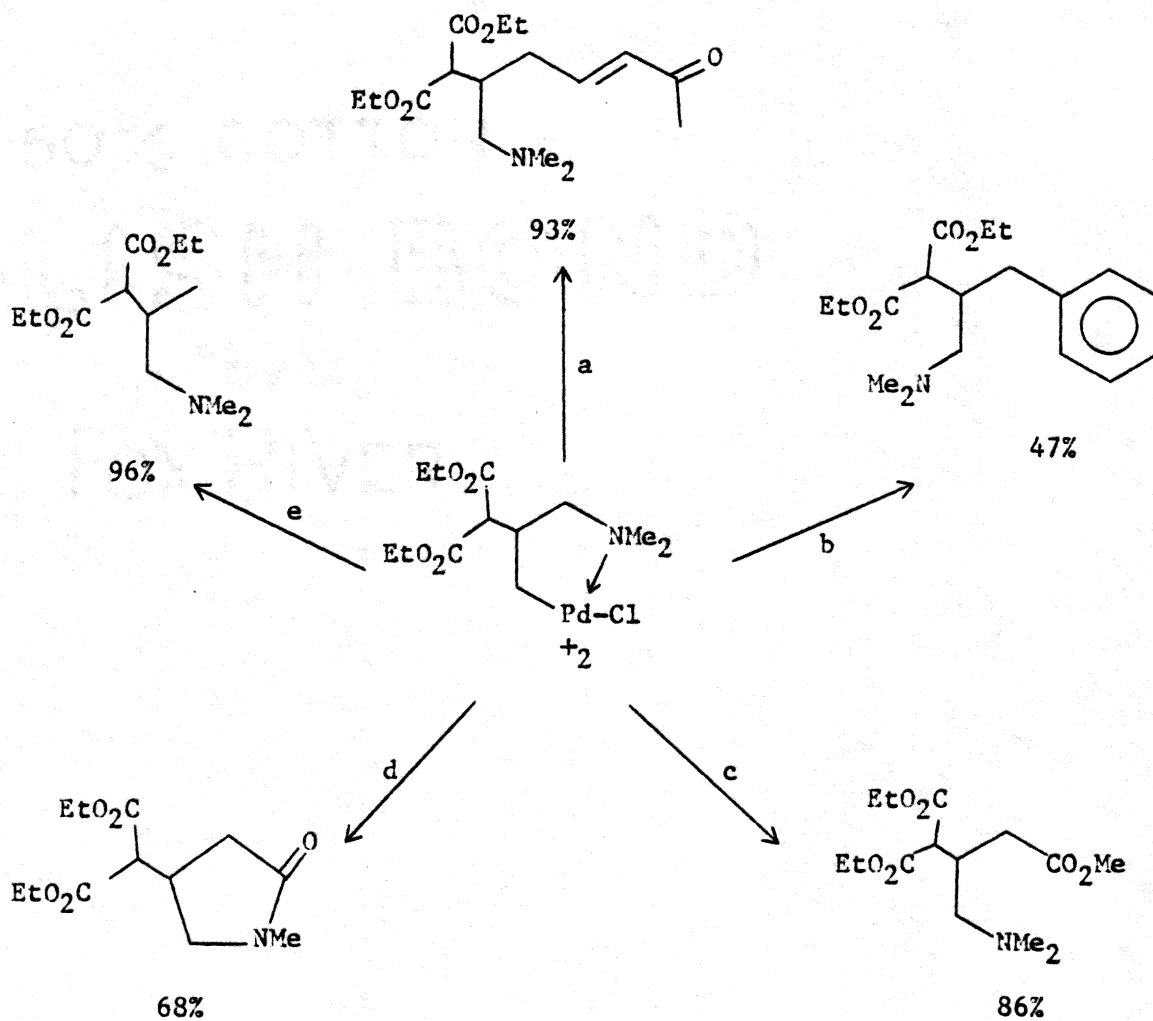
X = SR, NR₂

This would indicate the likelihood that, in the carbopalladation reaction, the stereochemistry about the central carbon of the enolate might be controlled as well. The implications of the enolate control approach are exemplified in Scheme IV through the synthesis of some methyl cyclohexanones.

Stabilized alkyl palladium complexes have been demonstrated to undergo a variety of reactions in which the palladium is replaced by a carbon moiety.^{3-5, 56,57} A brief sketch of the reactions accomplished to date appears in Scheme V.

The potential of these reaction sequences is probably best illustrated through a hypothetical example. Esterification via carbon monoxide insertion has been the most thoroughly studied of these reactions and, therefore, constitutes the best illustration. The stereochemistry of the carbon monoxide insertion has been shown to yield products with exclusive retention of the stereochemistry about the carbon-palladium bonds.^{5,56,57} Therefore, if the entire sequence was carried through for β -ketoester enolates 38 and 39, the resulting aminoketone should possess defined stereochemistry at three adjacent carbon atoms.

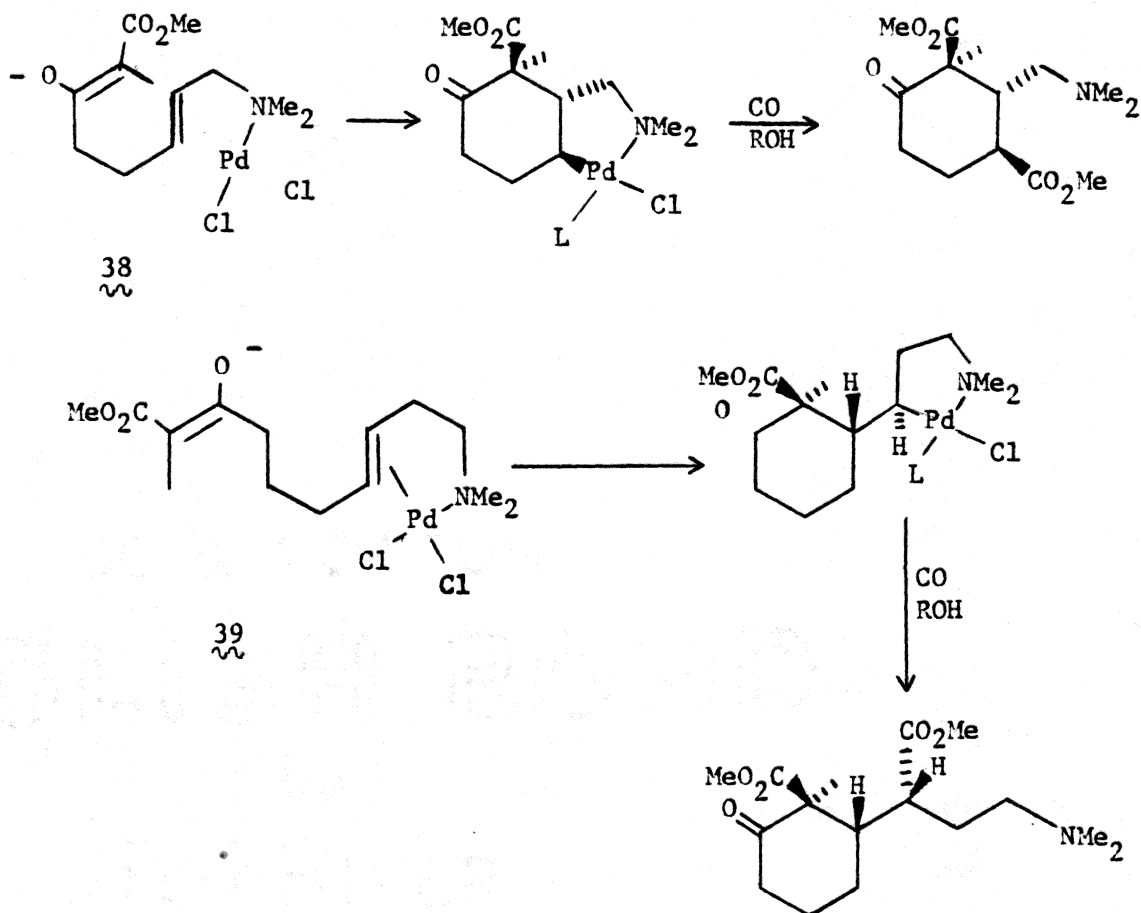
Scheme V

The Reactivity of Stabilized Alkyl Palladium Complexes^{3b}

a) MVK, Toluene reflux, b) $\text{Li}(\text{ZnPh}_3)$, THF, $-78^\circ \rightarrow \text{R.T.}$

c) CO, CH_3OH , Et_3N , Toluene, reflux, d) CO, Et_3N , Toluene, reflux

e) H_2 , MeOH, R.T.



The cyclization-substitution of 39 would be particularly interesting since methodology for controlling the stereochemistry of side-chains is quite rare in the literature.⁵⁸

Thus, the ultimate goals of this project are:

1. To utilize the carbopalladation reaction to regioselectively construct new ring systems from acyclic materials.

2. To employ the carbopalladation process to control the relative stereochemistry about two adjacent centers of a newly formed bicyclic palladium complex via control of the olefin geometry.

3. To use the present knowledge of enolate geometries to control the stereochemistry about a third contiguous carbon.

4. To ultimately replace the carbon-palladium bond with new carbon moieties.

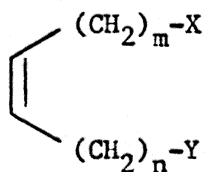
Part I of this thesis represents the realization of the first two of these objectives.

Chapter 2. Results and Discussion

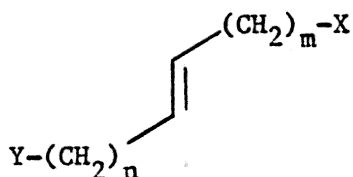
This chapter is divided into two sections. The first section of this chapter deals with the stereospecific synthesis of a series of olefinic substrates. The palladium mediated cyclization of the olefins generated in the first section will be discussed subsequently.

Synthesis of Starting Materials

In order to explore the utility of intramolecular carbopalladation reactions in the formation of carbocyclic systems, straight-chain disubstituted olefins, with the ligand and nucleophile at opposite termini of the chain (40a-i, 41a-h) were chosen as substrates. These types of olefins offered several advantages. They could be readily synthesized, and adequately demonstrate the feasibility of all the potential types of ring closure.

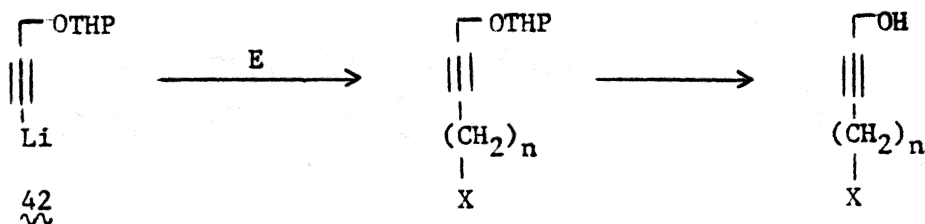


- 40a; X = NMe₂; Y = -CH(CO₂Me)₂; m = 1, n = 2
b; X = NMe₂; Y = -CH(CO₂Me)₂; m = 1, n = 3
c; X = NMe₂; Y = -CH(CO₂Me)₂; m = 1, n = 4
d; X = NMe₂; Y = -CH(CO₂Me)₂; m = 1, n = 6
e; X = NMe₂; Y = -COCH₂CO₂Me, m = 1, n = 5
f; X = SMe₂; Y = -CH(CO₂Me)₂, m = 1, n = 2
g; X = NMe₂; Y = -COCH₂CO₂Me, m = 1, n = 2
h; X = NMe₂; Y = -CH(CO₂Me), m = 2, n = 3
i; X = NMe₂; Y = -COCH₂CO₂Me, m = 2, n = 3



- 41a; X = SMe; Y = -COCH₂CO₂Me; m = 2, n = 2
 b; X = NMe₂; Y = -COCH₂CO₂Me; m = 2, n = 2
 c; X = SMe; Y = -CH(CO₂Me)₂; m = 1, n = 2
 d; X = SMe; Y = -COCH₂CO₂Me; m = 1, n = 3
 e; X = NMe₂; Y = -COCH₂CO₂Me; m = 1, n = 3
 f; X = NMe₂; Y = -CH(CO₂Me); m = 1, n = 2
 g; X = NMe₂; Y = -CH(CO₂Me); m = 1, n = 3
 h; X = NMe₂; Y = CH₃COCHCO₂tBu; m = 1, n = 2

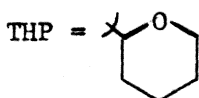
The synthesis of the allylic amino diesters 40a-d is outlined in Scheme VI. Alcohols 43a-c had been previously prepared⁵⁹⁻⁶¹ and were synthesized by the addition of the lithium salt of 1-oxytetrahydropyranyl-2-propyne (42)^{59,60} to an appropriate alkylating agent.^{59c,60} The protecting group was subsequently hydrolyzed with a catalytic amount of hydrochloric acid in methanol. These alcohols could easily



- E = a) ethylene oxide
 b) Br(CH₂)₃Cl
 c) Br(CH₂)₄Cl
 d) Cl(CH₂)₆OTHP

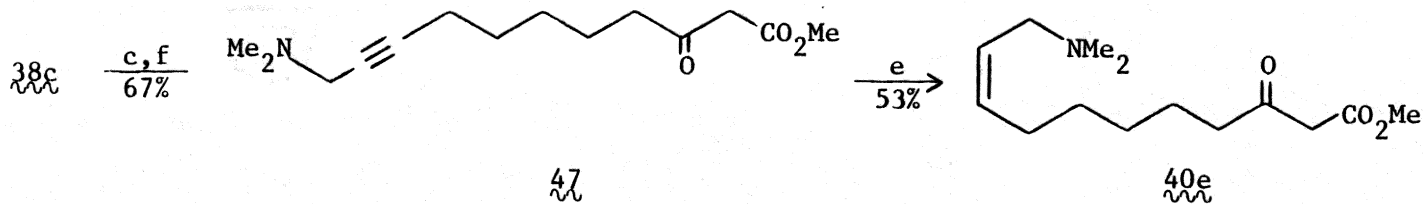
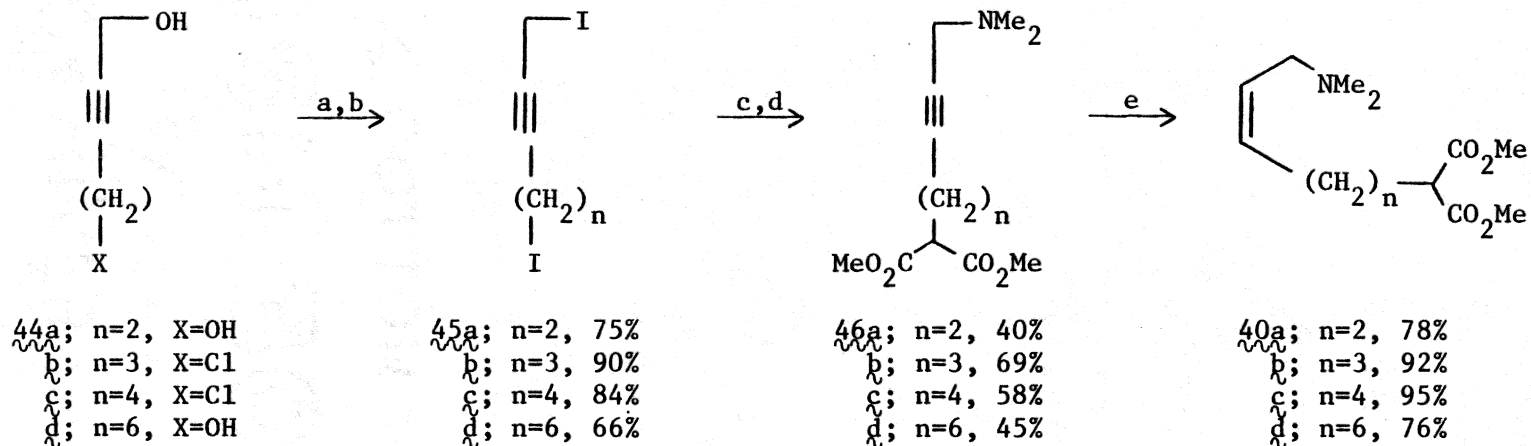
- 43a; n=2, X=OH
b; n=2, X=Cl
c; n=3, X=Cl
d; n=6, X=OTHP

- 44a; n=2, X=OH
b; n=3, X=Cl
c; n=4, X=Cl
d; n=6, X=OH



Scheme VI

Preparation of cis-Allylic Amines



- a) MsCl (1.0 equiv), Et_3N (1.05 equiv), THF, 0°C ; b) NaI (4 equiv), acetone, reflux; c) HNMe_2 (2.0 equiv), THF, 0°C ; d) $\text{NaCH}(\text{CO}_2\text{Me})_2$ (3 equiv), HMPA-THF, 25°C ; e) 5% Pd/ BaSO_4 , H_2 , MeOH; f) $\text{Na, Li}[\text{CH}_2\text{COCHCO}_2\text{Me}]$, THF, 0°C .

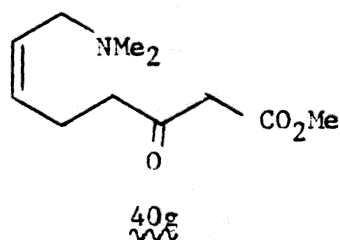
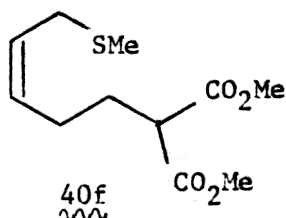
be converted to their corresponding acetylenic diiodides (See Scheme VI).

Regiocontrolled introduction of the functional groups relied upon the enhanced reactivity of propargyl iodides over isolated aliphatic iodides. Sequential addition of dimethyl amine, followed by either excess sodio dimethyl malonate or excess methyl acetoacetate dianion, gave acetylenic amines 46a-d and 47, respectively, in fair yields.

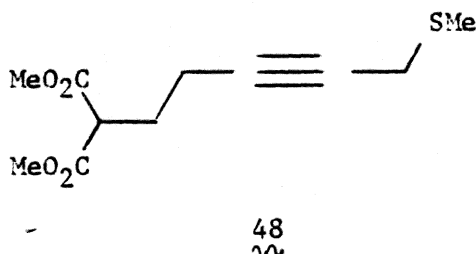
(See Scheme VI.)

The acetylenic amines 46a-d and 47 were readily reduced by careful hydrogenation over 5% palladium on barium sulfate⁶² to give allylic amines 40a-d and 40e (Scheme VI).

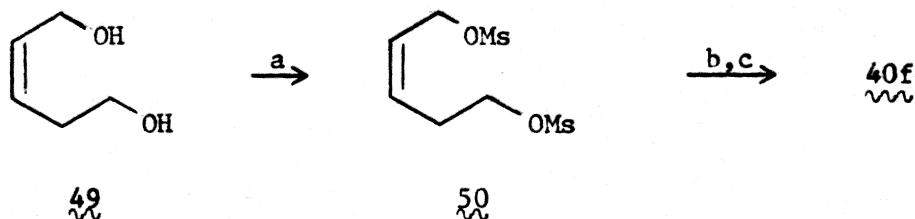
Empirically, this approach proved less successful for the syntheses of sulfide diester 40f and amino ketoester 40g.



Acetylenic sulfide 48 failed to undergo hydrogenation. Therefore,



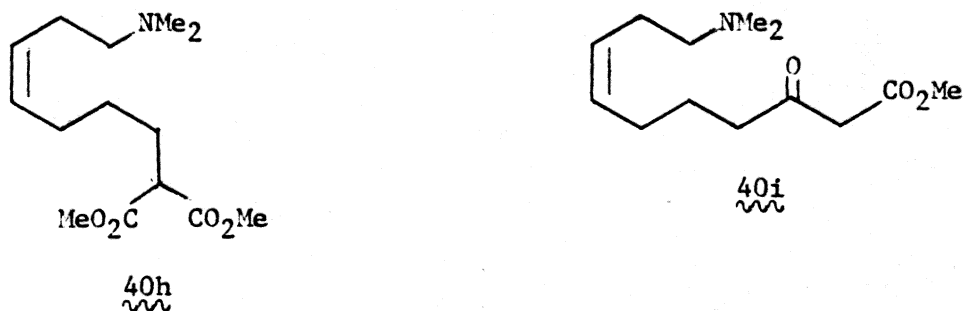
sulfide 40f was synthesized from Z-1,5-pentendiol⁵⁹ (49), via its dimesylate 50. Amino ketoester 40g was synthesized from



- a) MsCl (2.0 equiv.), Et₃N (2.1 equiv.), THF, 0°C
 b) NaSMe (1.0 equiv.), 10% HMPA-THF, -78°C - 0°C
 c) NaHC(CO₂Me)₂ (4 equiv.), NaI (0.1 equiv.), 10% HMPA-THF, 25°C, 3 days

Z-4-hydroxy-1-oxytetrahydropyranyl-2-butene (52).^{63,64} This synthesis is outlined in Scheme VII.

Cis-homoallylic amines 40h and 40i were synthesized from

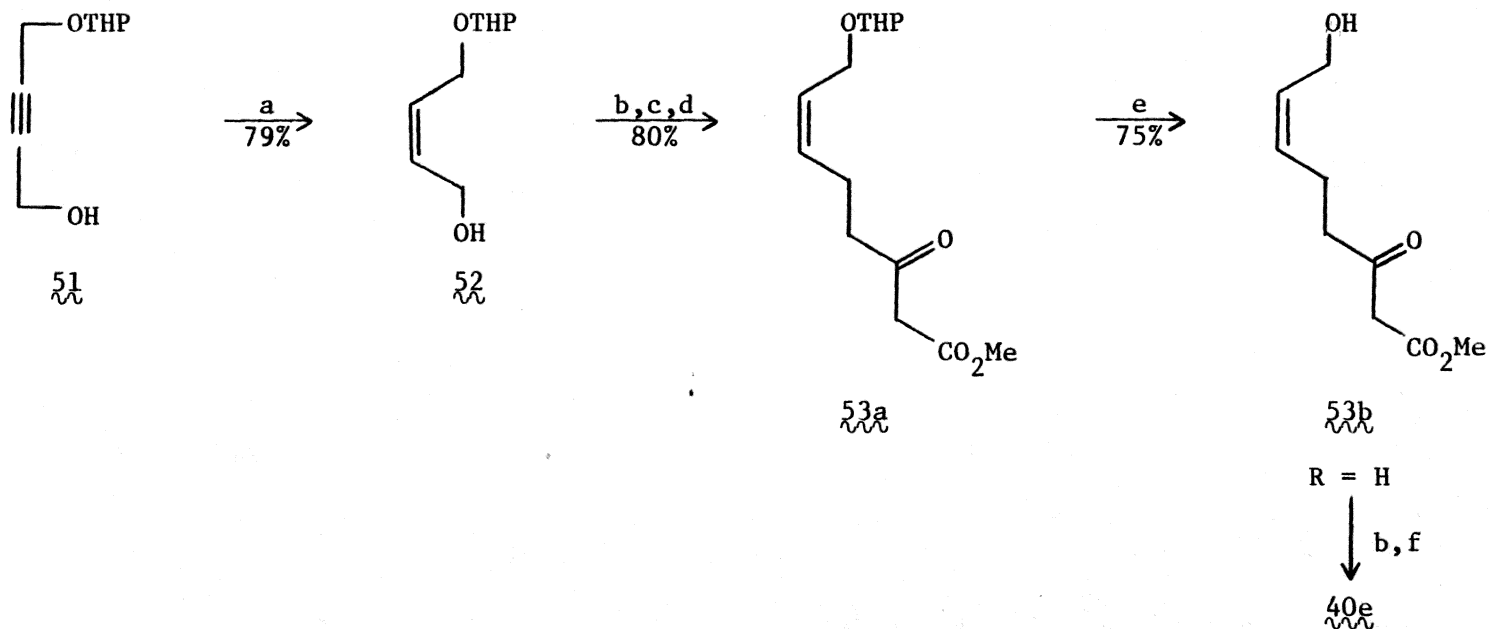


1-oxytetrahydropyranyl-3-butyne (55)⁶⁵ in a fashion directly analogous to the synthesis of tetrahydropyrans 43a-d.

If the tetrahydropyranyl protecting group is retained instead of cleaved, it may be utilized to mask one reactive site. Thus, the difunctional alkylating agent was used to alkylate the lithium salt of 1-oxytetrahydropyranyl-3-butyne (56).⁶⁵ The second functional group

Scheme VII

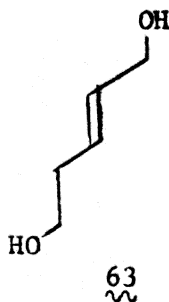
Preparation of Amino Ketoester 40e



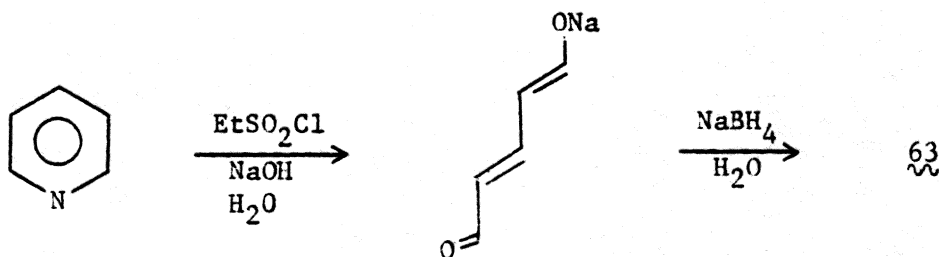
a) H₂, 5% Pd/BaSO₄, MeOH; b) MsCl (1.0 equiv), Et₃N (1.05 equiv), THF, 0°C; c) NaI (1.0 equiv), THF, 25°C, 20 min; d) NaLiCH₂COCHCO₂Me (1.5 equiv), THF, 0°C; e) HCl, MeOH; f) HNMe₂, THF, 0°C, 30 min.

of the alkylating agent was then used to alkylate carbon nucleophiles (Scheme VIII). Subsequent hydrolysis of the protecting group and amination gave the desired amines 40h and 40i (Scheme VIII).

The trans substrates were initially visualized as being derived from a trans diol system (63). However, the only reported synthesis of



63 involved the formation of the sodium salt of glutacondialdehyde from pyridine and subsequent reduction of this salt with sodium borohydride.^{59a} The procedure was tedious, requiring both

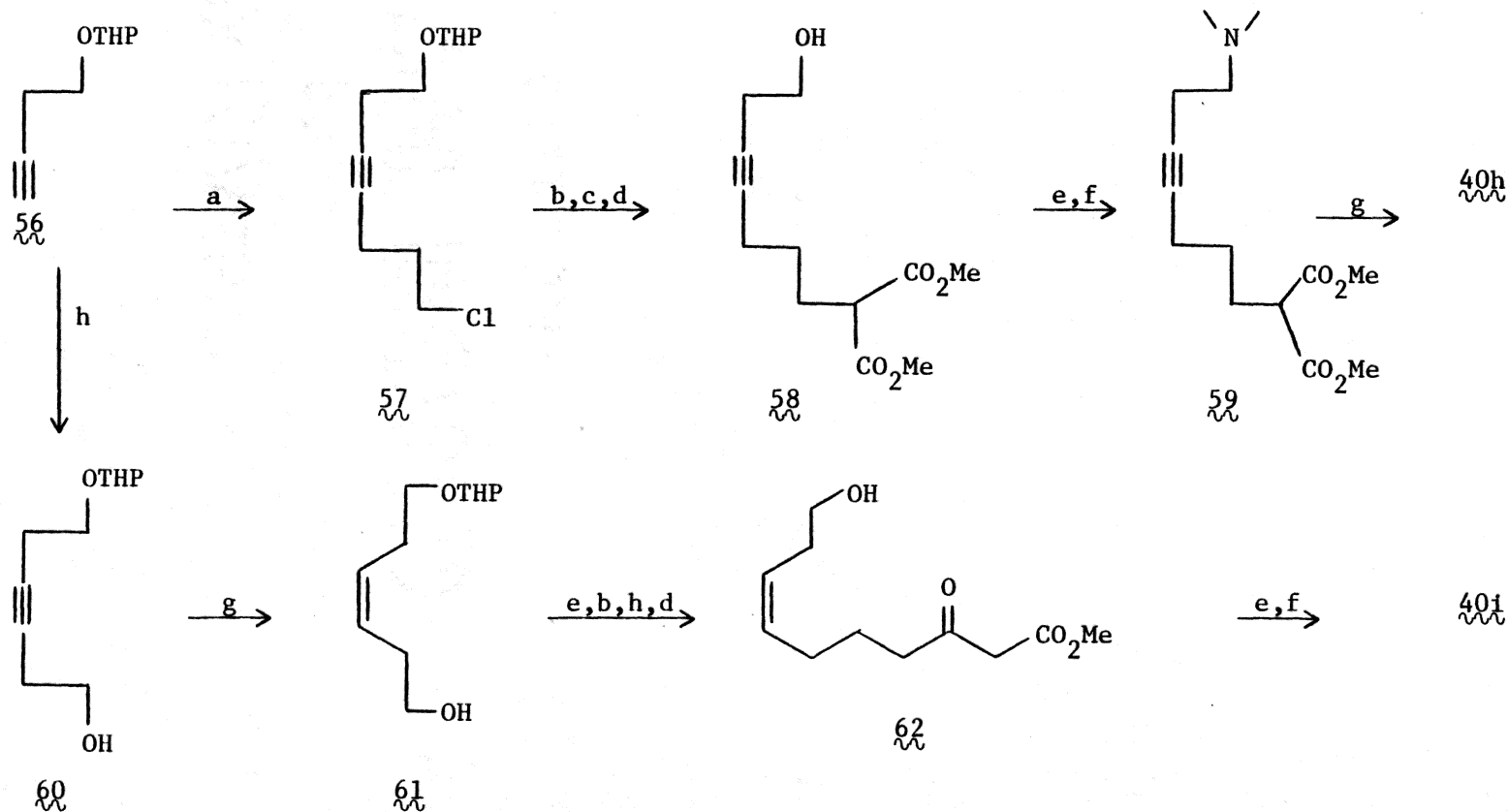


chromatography and subsequent distillation to afford a pure product in only 11% yield.

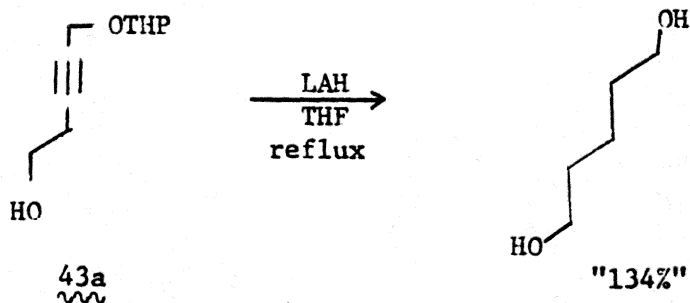
Alternative acetylene reduction routes, such as lithium-ethylamine⁶⁶ and lithium aluminum hydride reductions⁶⁷ led to overreduction. For example, lithium aluminum hydride reduction of alcohol 43a gave 1,5-pentane diol as the major product.

Scheme VIII

Synthesis of Cis-Homoallylic Amines



- a) 1. BuLi, 10% HMPA-THF, 0°C. 2. Br(CH₂)₃Cl, -78°C→25°C; b) NaI (3.0 equiv), acetone, reflux;
 c) NaCH(CO₂Me) (3 equiv), HMPA-THF; d) MeOH, H⁺; e) MsCl (1.0 equiv), Et₃N (1.05 equiv), THF, 0°C;
 f) HNMe₂ (20 equiv), NaI (1.0 equiv), THF, 45°C; g) 5% Pd/BaSO₄, H₂, MeOH; h) NaLi[CH₂COCHCO₂Me]
 (1.5 equiv), THF, 0°C.

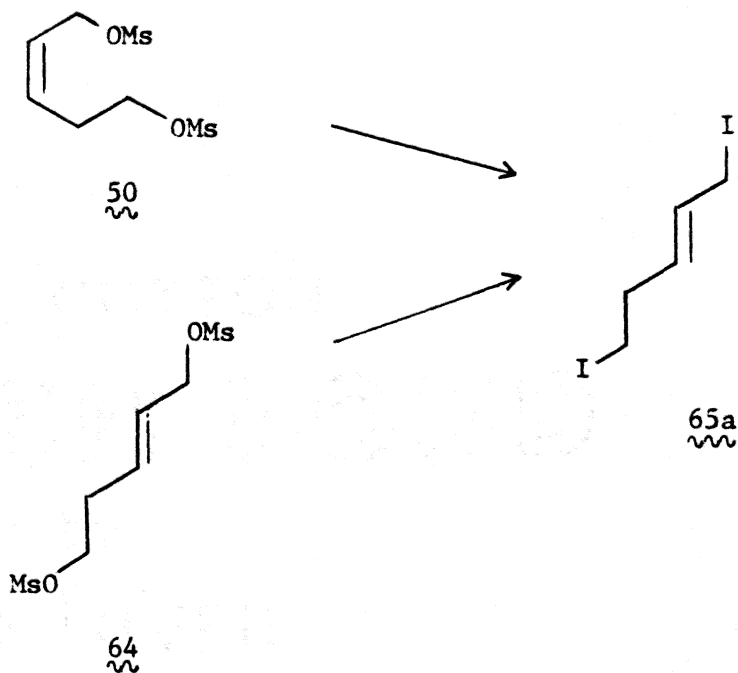


In this case, both the protecting group and the acetylene were reduced completely.

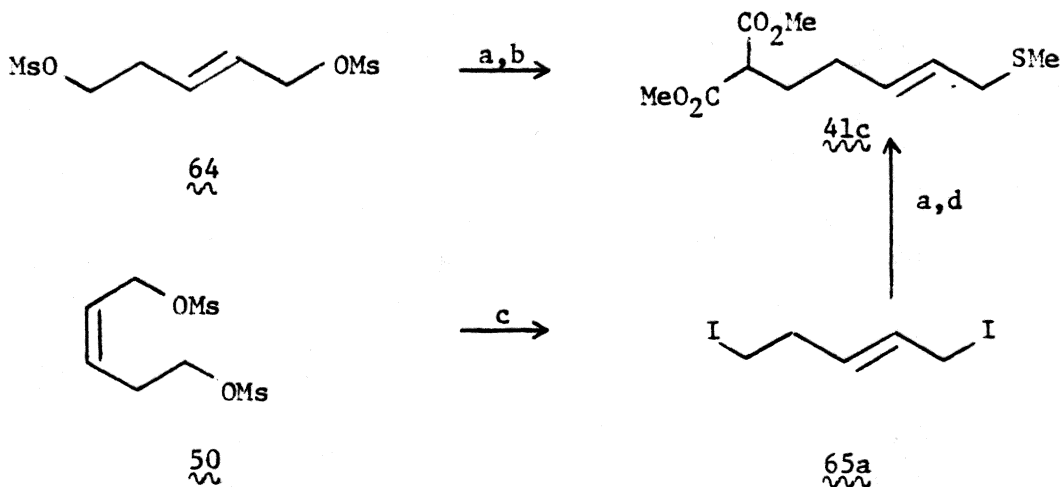
In attempts to synthesize both the cis- and trans-adducts of 41a and 41b, quantities of both cis- and trans- 1,5-penten-diol were prepared by the published procedures.⁵⁹ These were subsequently converted to their respective dimesylates.⁶⁸ These allylic mesylates failed to undergo displacement with the dianion of methyl acetoacetate.

It has been suggested that mesylates are poor leaving groups with dianions because the dianion may abstract a proton, rather than undergoing substitution. Therefore, the mesylate should be converted to a halide prior to displacement.⁶⁹ It was apparent that perhaps this might also be utilized to improve the yield of sulfide 40f as well.

Therefore, an attempt was made to synthesize the cis and trans isomers of 1,5-diiodo-2-pentene from their corresponding dimesylates 50 and 64. To our surprise, the NMR spectra of the diiodide obtained from the two dimesylates proved to be identical.

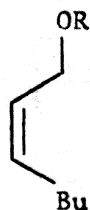


Further, when the dimesylate **64** was converted to sulfide diester **41c**, it proved to be identical to the sulfide **41c** obtained by similar conversion of the diiodide obtained from cis-dimesylate **50**.

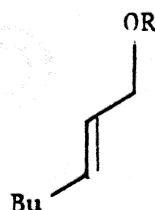


a) NaSMe, (1.0 equiv.), 10% HMPA-THF, -78° - 0° C; b) NaCH(CO₂Me)₂, (3.0 equiv.), NaI (cat.), THF, 3 days; c) NaI (4.0 equiv.), acetone, reflux, 12 h; d) NaCH(CO₂Me)₂, HMPA-THF, 2.5 h, 25° C

In an effort to selectively exchange the allylic mesylate of 50 for iodide (NaI, acetone or THF), an unexpected 3:1 mixture of trans and cis isomers was obtained.⁷¹ This result was unsatisfactory for stereospecific synthesis. Therefore, an adjunct study on the isomerization of olefins by displacement of allylic mesylates with iodide was initiated. The alcohols 66a and 67a were prepared as substrates for this investigation.^{62,67} These compounds could be readily converted to their mesylates⁶⁸ and acetates⁷⁰ by well precedented procedures.

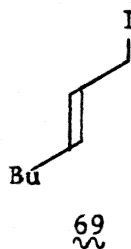
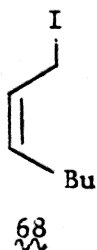


66a; R=H
66b; R=-SO₂CH₃
66c; R=-Ac



67a; R=H
67b; R=-SO₂CH₃
67c; R=-Ac

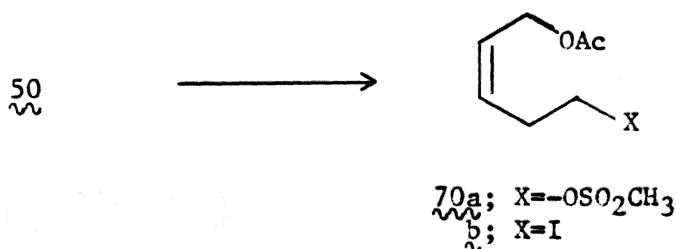
Iodide displacements of mesylates 66b or 67b could not be accomplished without some double bond isomerization with ordinary sodium iodide. However, when the sodium iodide was freshly recrystallized from methanol, the isomerization could be controlled. When mesylate 66b was treated with 1.1 equiv of freshly recrystallized sodium iodide in THF or acetone at room temperature for 20 minutes, a 94:6 mixture of 68:69 could be obtained.⁷¹



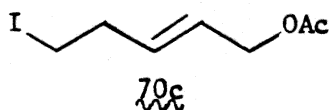
Both 68 and 69 could be readily converted to other materials via S_n2 displacement without isomerization. For example, 68 and 69 could be converted to their corresponding acetates 66c and 67c by treatment with sodium acetate (1.25 equiv) in dimethylformamide at room temperature for 3.5 h in 81 and 78% yields, respectively. The acetates obtained were compared with genuine samples obtained by acylation of the corresponding alcohols and found to be ca 95% isomerically pure by NMR analysis.

Longer reaction times with recrystallized sodium iodide led to increased isomerization until an equilibrium mixture consisting of a ca 3:1 ratio of 69:68 was attained after ca 24 h. Apparently, this equilibrium is attained much more rapidly with unrecrystallized sodium iodide.⁷²

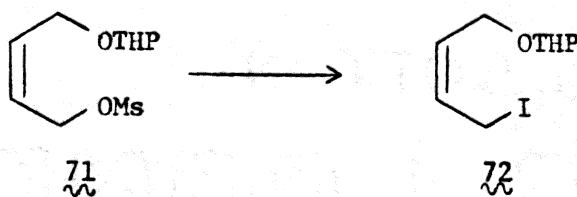
That double bond isomerization was more rapid than displacement of homoallyl mesylate was confirmed by the following experiments. When dimesylate 50 was treated with freshly recrystallized sodium iodide in acetone or THF for 20 min and the product subjected to 1.25 equiv of sodium acetate in dimethyl formamide at 25°C for 3.5 h, cis-acetate 53c was isolated as the sole product. The cis acetate 70a could be converted to its corresponding isomerically pure cis iodide 70b by treatment with excess iodide in acetone at reflux.



With these facts in hand, the conversion of cis-dimesylate 50 to diiodide 65a could now be examined. Treatment of the mixture obtained from the exchange of diiodide for dimesylate with sodium acetate (1.25 equiv) in dimethyl formamide revealed the diiodide 65a to be contaminated with ca 25% of its cis-isomer. However, trans diiodide 65a could conveniently be purified by low temperature crystallization from ether-hexane, giving pure trans diiodide 65a. Treatment of the crystallized trans diiodide 65a with sodium acetate (1.25 equiv) in dimethyl formamide afforded pure trans iodide 70c. The trans diiodide 65a allowed entry into a number of allylic and homoallylic substrates with exclusive trans stereochemistry (Scheme IX).



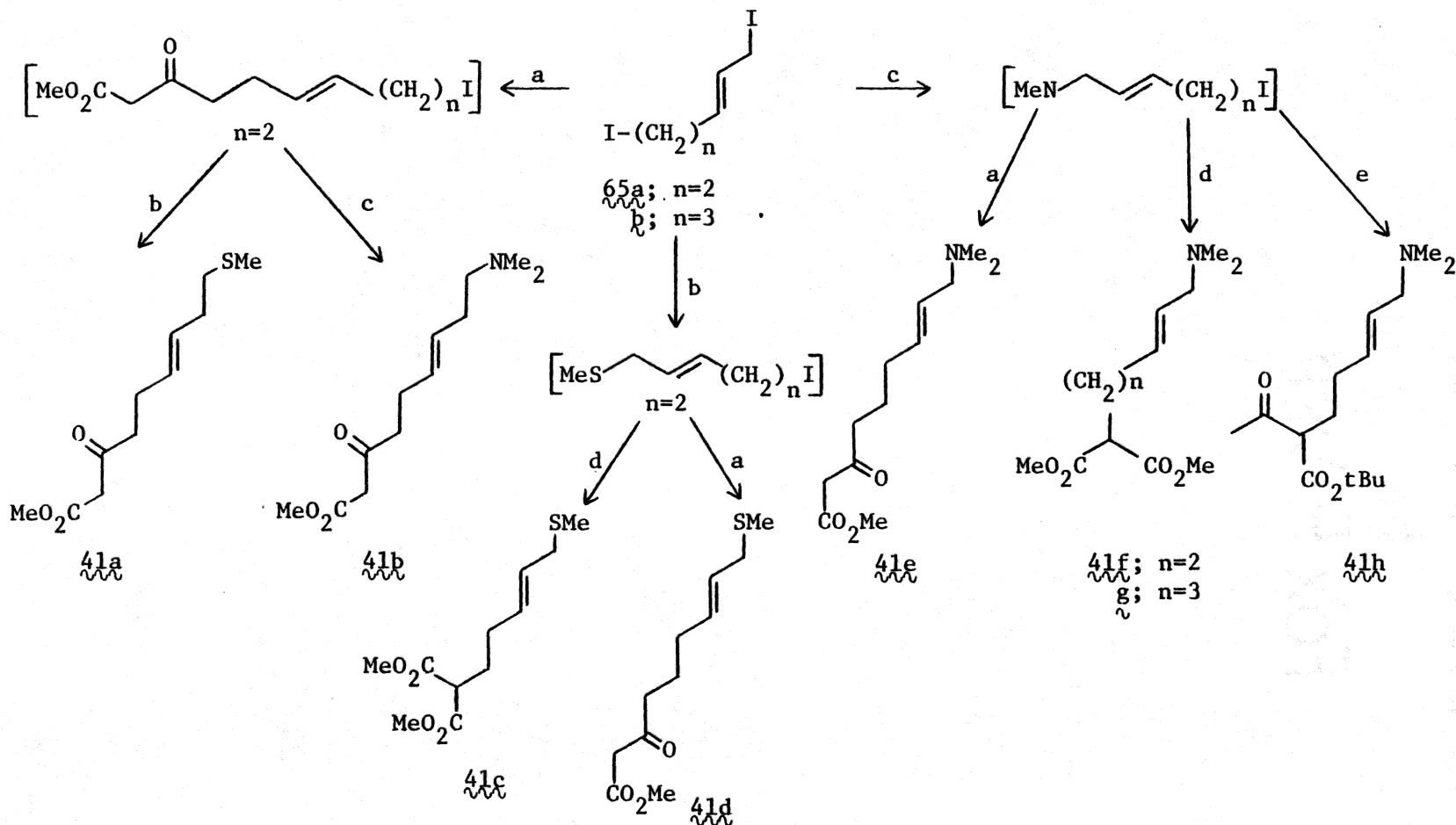
It was now possible to control the conversion of mesylate 71 to iodide 72 which was necessary for the synthesis of amino-keto-ester 40g (Scheme VII).



The methodology used to generate 65a was extended to generate 65b. Z-6-chloro-2-hexen-1-ol⁶⁰ was converted to its mesylate and subsequent displacement by excess sodium iodide in refluxing acetone gave isomerically pure diiodide 65b in 59% yield. Diiodide 65b is somewhat less stable than 65a and must be used immediately. Diiodide 65b was ultimately converted to 41g (Scheme IX).

Scheme IX

Preparation of Trans Olefinic Substrates

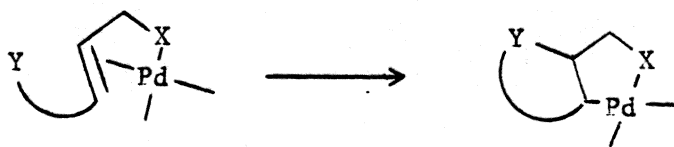


- a) methyl acetoacetate dianion, THF, -78°C ; b) NaSMe (1.0 equiv), 10% HMPA-THF, -78°C to 0°C ;
 c) HNMe₂ (2.0 equiv), THF, 0°C ; d) NaCH(CO₂Me)₂ (3 equiv), HMPA-THF, 25°C ; e) Na(CH₃COCHCO₂tBu)
 (3 equiv), HMPA-THF, 25°C .

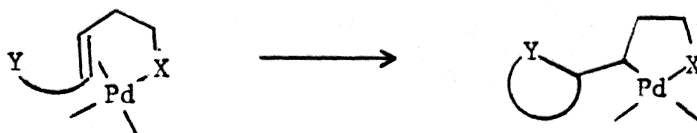
Ring Closures via Carbopalladation

Palladium assisted cyclizations have been subdivided into endo- and exocyclic ring closures. An endocyclic cyclization refers to a ring closure in which both carbons of the olefin are included in the newly formed ring. Exocyclic ring closures refer to closure in which only one carbon of the olefin is in the newly formed ring and the second carbon is α to the newly constructed ring system.

Endocyclic
cyclization

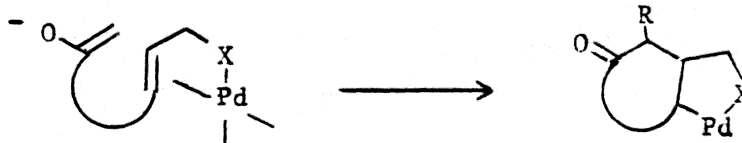


Exocyclic
cyclization

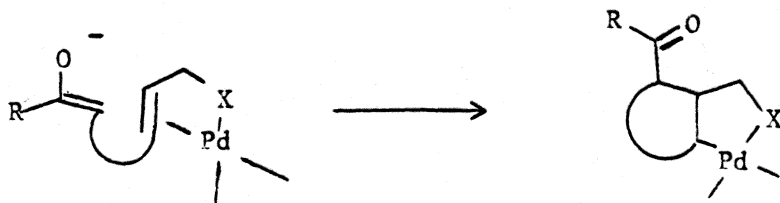


Endocyclic enolates refer to enolates in which the enolized functionality ultimately becomes part of the newly synthesized ring. Exocyclic enolates refer to enolized moieties which find their destination outside the newly constructed ring system.

Endocyclic
enolate



Exocyclic
enolate

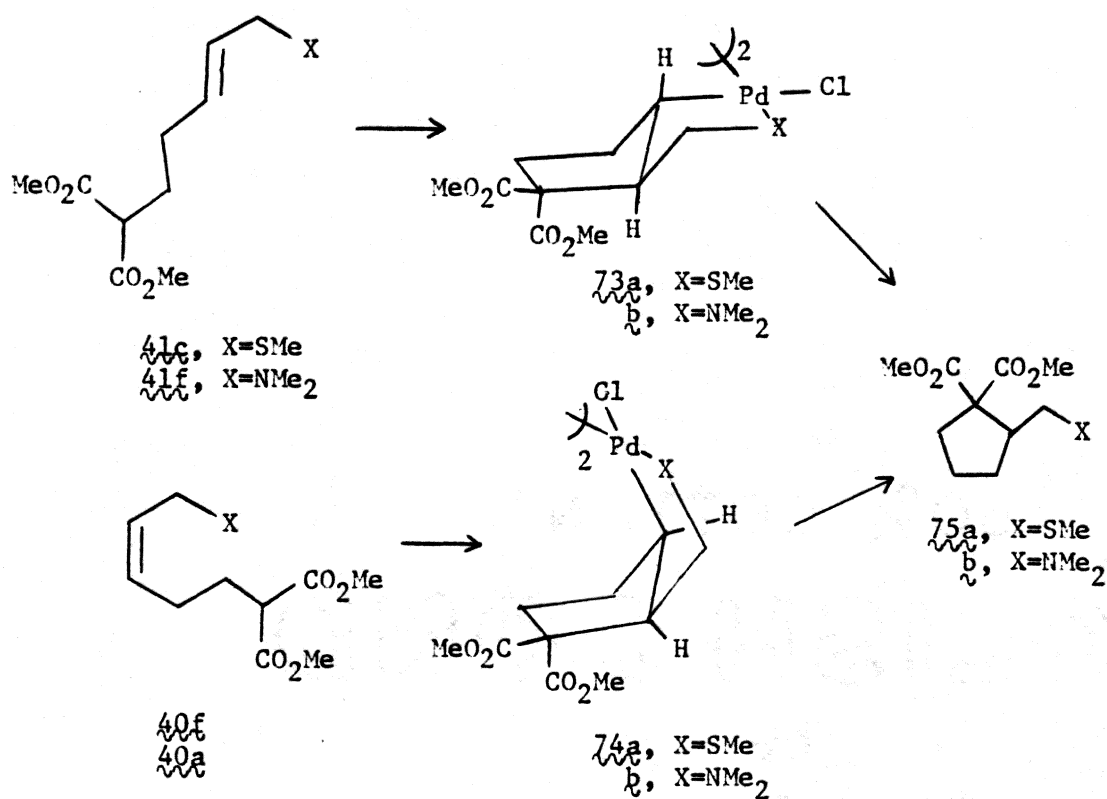


It is convenient to discuss the cyclizations with *exo*- and *endo*-cyclic enolates separately. The ring closures with exocyclic enolates shall be discussed first.

Cyclization of the trans sulfide diester 41c via treatment of the sulfide with 1.0 mol equiv of lithium tetrachloropalladate (LTP) and in situ generation of the enolate with 1.1 mol equiv of potassium *tert*-butoxide gave rise to palladium complex 73a (mp 76-78°C) after 15 h at room temperature. The stereochemically homogeneous complex was obtained in 53% yield after chromatography, and is presumed to contain a trans ring fusion. When the cis sulfide diester 40f was treated in a similar manner, a 65% yield of stereochemically pure palladocycle 74a (mp 78.5-81°C) was obtained. Complex 74a is believed to contain a cis ring fusion and exhibited spectral and chromatographic behavior different from that of complex 73a.

Direct reduction of palladocycles 73a and 74a with sodium borohydride in methanol gave cyclic sulfide 75a, as the sole product, in 71% yield from 41c and 68% yield from 40f. This is consistent with the structural assignments for stereoisomeric 73a and 74a.

The cyclizations of the amino diesters 41f and 40a proved to be considerably more facile. The palladocycles 73b (mp 96.5-98.5°C) and 74b (mp 151.5-153.5°C) were generated from 41f and 40a in 93% and 90% yields, respectively, by adding merely 1.0 mol equiv of LTP and 1.1 mol equiv of potassium tert-butoxide at 0°C for 0.5 h.

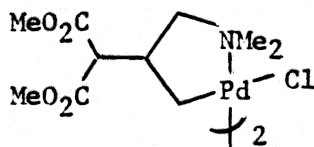


The kinetic difference between the cyclizations of sulfides and amines is noteworthy. Apparently, the sulfide, being a stronger electron donating ligand, reduces the charge on palladium, thus reducing the polarization of the olefin necessary to induce cyclization. This effect displays itself in both the rate enhancement when amine is used as ligand, and the much higher yields of aminopalladium complexes.

From the point of view of this study, the amines offered a series of other advantages. As with the sulfide diesters, direct reduction (hydrogenation) of complexes $73b$ or $74b$ yielded $75b$, as the sole product, in 95% and 93% yields, respectively. However, the physical differences between the two complexes were much more pronounced. Complexes $73b$ and $74b$ exhibited distinctly different melting points.

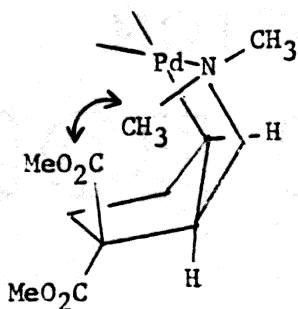
As with the sulfide complexes, palladocycles 73b and 74b showed different chromatographic behavior. Even more interesting was the pronounced differences in the NMR behaviors of complexes 73b and 74b.

Palladocycle 73b exhibits amino methyl resonances as singlets at 2.73 δ and 2.80 δ . Since palladocycle 76 exhibits resonances at



76

2.65 δ and 2.77 δ ^{3c}, these might be considered as normal. On the other hand, complex 74b exhibits amino methyl resonances at 2.39 δ and 2.88 δ . The dramatic upfield shift of one nitrogen methyl resonance can be attributed to exceedingly strong shielding of the "endo" methyl group in complex 66b by the "endo" carbomethoxy group. This interaction is depicted below. This difference is also reflected in the carbomethoxy



74b

proton resonances. The complex 73b exhibits resonances at 3.66 δ and 3.73 δ . However, the palladocycle 74b exhibits only a single methyl ester proton resonance at 3.80 δ .

NMR assignments of the protons in complexes 73b and 74b would depend upon comparison of the selectively decoupled carbon resonance spectra and proton NMR. The complexity of the carbon spectra of complexes 73b and 74b made absolute assignments of the protons in these complexes impossible. However, when complexes 73b and 74b were converted to their corresponding triphenylphosphine derivatives, 73c and 74c, the carbon spectra were considerably simplified. Thus, comparison of the selectively decoupled carbon-13 spectra (50 Hz) and the proton spectra (90 Hz, 200 Hz, 400 Hz and 600 Hz) allowed the absolute assignment of the protons in the spectra of complexes 73c and 74c (Tables 3 and 4). Once the proton spectrum was assigned, it was possible to ascertain a number of the coupling constants through decoupling experiments.

The 400 MHz ^1H NMR of palladocycle 73c exhibits an 11.5 Hz coupling constant for the bridgehead hydrogens (H_3 and H_4 in Table 3). Models indicate that these bridgehead hydrogens are nearly antiperiplanar and, therefore, the 11.5 Hz coupling constant is consistent with a trans ring juncture.

The 400 MHz ^1H NMR of palladocycle 74c exhibits a 6 Hz coupling constant for the bridgehead hydrogens (H_3 and H_4 in Table 4). This coupling constant is consistent with the ca 40 $^\circ$ dihedral angle estimated from models of palladocycle 74c. The ^1H NMR of palladocycle 74c also

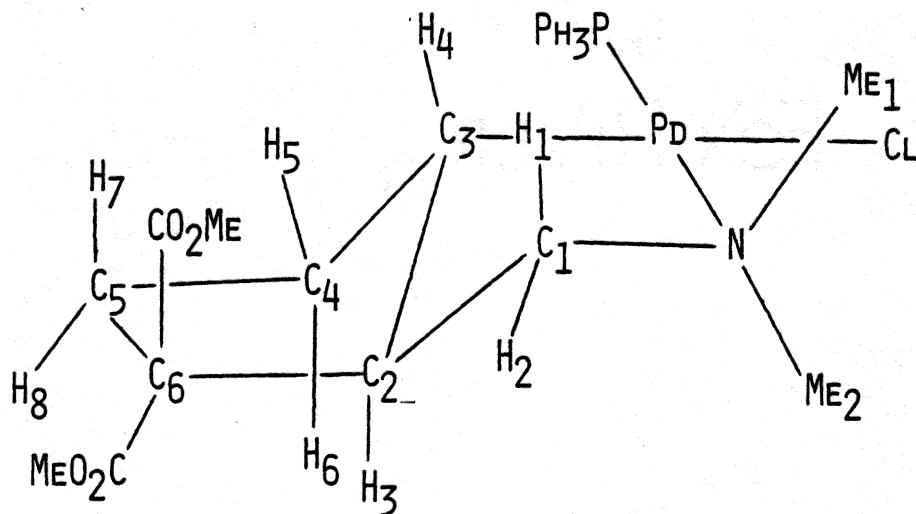


Table 3

NMR Data For Palladocycle 73cA. ^1H NMR Assignments for Palladocycle 73c (400 MHz)

Proton Number	Chemical Shift (δ)	Coupling Constants ($J_{x,y}$)	
		x,y	J(Hz)
H ₁	2.23	H ₁ ,H ₂	11.5
		H ₁ ,H ₃	11.5
H ₂	2.60	H ₂ ,H ₃	4
		H ₂ ,H _{NMe}	4
H ₃	2.55	H ₃ ,H ₄	11.5
H ₄	2.16	H ₄ ,H ₅	4
		H ₄ ,H ₆	11.5
H ₅	0.68	H ₅ ,H ₆	12
		H ₅ ,H ₇	8.5
		H ₅ ,H ₈	2.5

Proton Number	Chemical Shift(δ)	Coupling Constants($J_{x,y}$)	
		x,y	J(Hz)
H ₆	0.79	H ₆ ,H ₇	9.5
		H ₆ ,H ₈	10
H ₇	2.07	H ₇ ,H ₈	12.5
H ₈	1.72	---	---
NMe	2.89	---	---
	2.92	---	---
CO ₂ Me	3.67	---	---
	3.68	---	---

B. ¹³C NMR Assignments for Palladocycle 73c

Carbon	Chemical Shift (δ)
C ₁	63.1
C ₂	55.5
C ₃	46.0
C ₄	30.8
C ₅	33.7
C ₆	58.3
	51.9
NMe	47.8
	51.9
OMe	52.3
	52.6
CO	171.5
	172.7

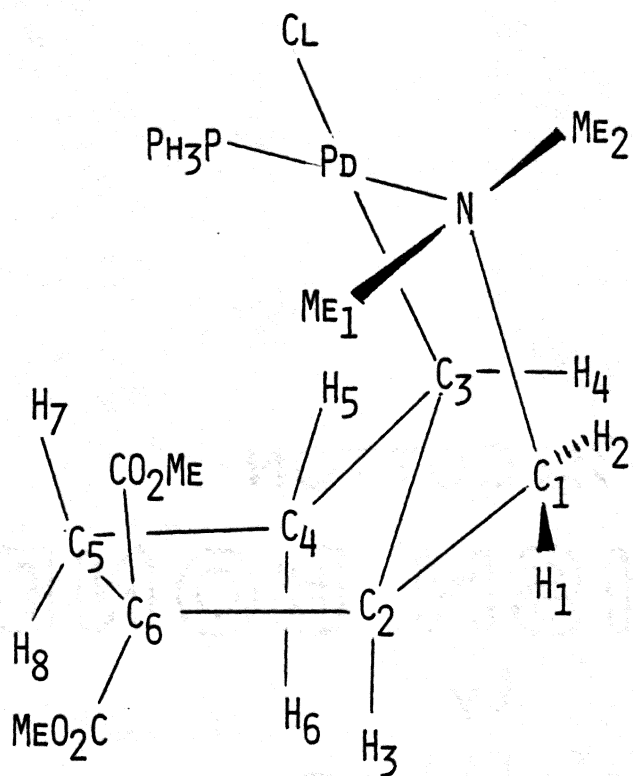


Table 4

NMR Data for Palladocycle 74cA. ^1H NMR Assignments for Palladocycle 74c (400 MHz)

Proton Number	Chemical Shift (δ)	Coupling Constants ($J_{x,y}$)	
		x,y	J(Hz)
H ₁	2.24	H ₁ ,H ₂	12
		H ₁ ,H ₃	14
H ₂	2.72	H ₂ ,H ₃	6
		H ₂ ,H ₄	2
		H ₂ ,H _{NMe}	2
H ₃	3.41	H ₃ ,H ₄	6
H ₄	1.90	H ₄ ,H ₅	10.5
		H ₄ ,H ₆	6

Proton Number	Chemical Shift(δ)	Coupling Constants($J_{x,y}$)	
		x,y	J(Hz)
H ₅	0.77	H ₅ ,H ₆	12
		H ₅ ,H ₇	8.5
		H ₅ ,H ₈	3.5
H ₆	1.72	H ₆ ,H ₇	8.5
		H ₆ ,H ₈	12
H ₇	2.07	H ₇ ,H ₈	12.5
H ₈	1.72	---	---
NMe	2.89	---	---
	2.92	---	---
CO ₂ Me	3.67	---	---
	3.68	---	---

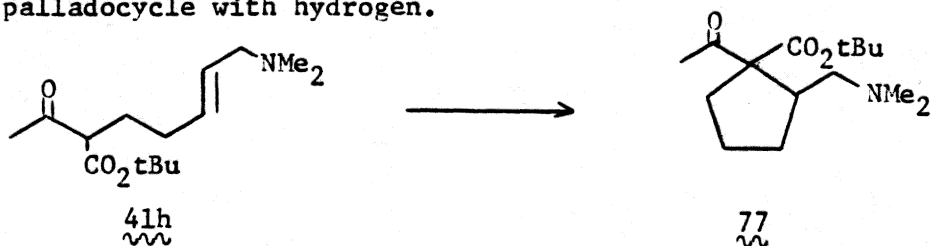
B. ¹³C NMR Assignments for Palladocycle 74c

<u>Carbon Number</u>	<u>Chemical Shift(δ)</u>
C ₁	65.3
C ₂	51.1
C ₃	48.6
C ₄	28.1
C ₅	31.9
C ₆	59.4
NMe	48.1
	52.2
OMe	52.6
CO	171.1
	172.6

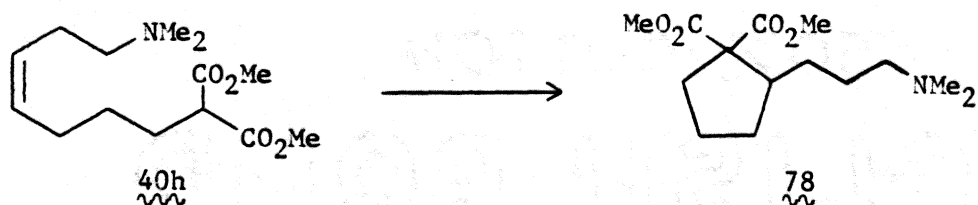
exhibits a 2 Hz coupling constant for the four-bond coupling between H_2 and H_4 (see Table 4). This four-bond coupling constant can only be consistent with a cis fused ring juncture.

These NMR studies firmly establish the stereoselectivity of these processes. The 1H NMR spectra of palladocycles 73c and 74c can only be consistent with a trans addition of palladium and the carbon nucleophile to the olefin.

In the same manner as ring closures with diesters, exocyclic enolates could also be used to generate exocyclic ketones. Amino ketoester 41h gave cyclopentane 77 in 85% yield after direct reduction of the palladocycle with hydrogen.



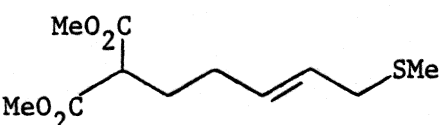
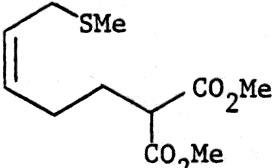
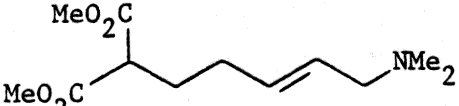
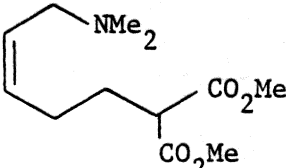
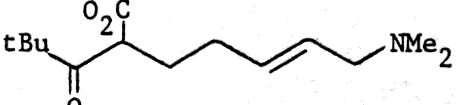
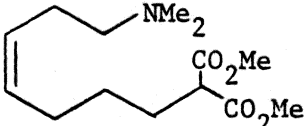
Likewise, the reaction proceeded readily when the amine was homoallylic. Amino diester 40h was converted to cyclopentane 78 in 30% yield after direct reduction of the metallocycle with hydrogen.



This reaction demonstrates the feasibility of extending this reaction to an exocyclic ring closure. However, unlike the previous cases in which the intermediate palladocycle was isolable, both the dimeric chloro complex and its triphenylphosphine adduct proved too unstable to

Table 5

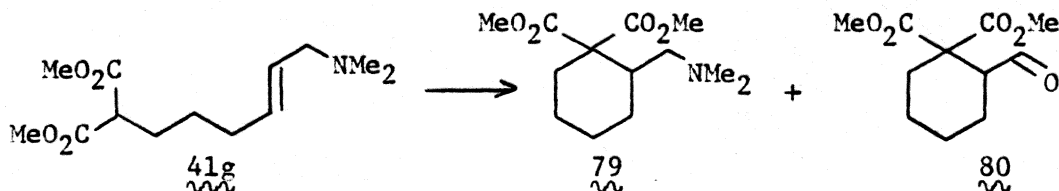
Cyclopentanoids Obtained From Exocyclic Enolates

<u>Starting Material</u>	<u>Palladium Complex^a</u> <u>(% yield)</u>	<u>Cyclopentane^b</u> <u>(% yield)</u>
 41c	73a (53) ~~~~	75a (71) ~~~~
 40f	74a (64) ~~~~	75a (68) ~~~~
 41f	73b (93) ~~~~	75b (95) ~~~~
 40a	74b (90) ~~~~	75b (93) ~~~~
 41h	c	77 (85) ~~~~
 40h	d	78 (80) ~~~~

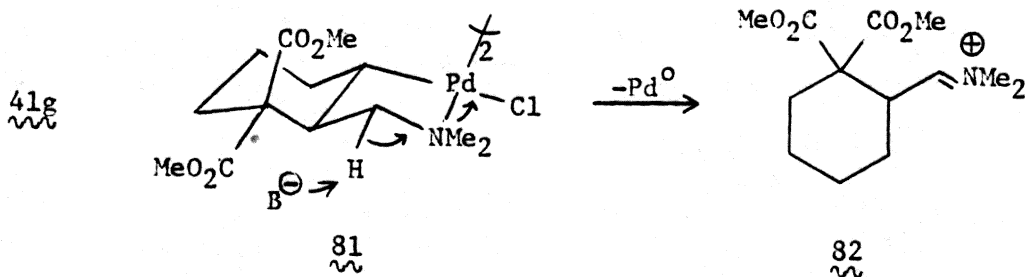
a) Isolated yield of pure chloride dimer; b) Yield of isolated pure cyclopentane via direct reduction; c) No attempt was made at isolation; d) Decomposes upon attempted isolation.

allow isolation and purification. For this reason, NMR confirmation of the stereochemical assignment of the bicyclic palladium complexes constructed via an exocyclic ring closure has not yet been obtained.

Cyclizations to produce larger ring systems also proceeded smoothly. However, the intermediate palladocycles proved too unstable to allow isolation. When trans amino diester 41g was treated under the same reaction conditions employed in the cyclopentane ring closures and directly reduced with hydrogen gas, a ca 3:1 mixture of cyclohexyl amine 79 and cyclohexyl aldehyde 80 was obtained.



Potentially, aldehyde 80 could arise from the imminium salt 82. Imminium salt 82 could be envisioned as arising from a decomposition of the intermediate palladium complex 81, in which β -elimination occurs through the amine as shown below. The imminium salt 82 could,

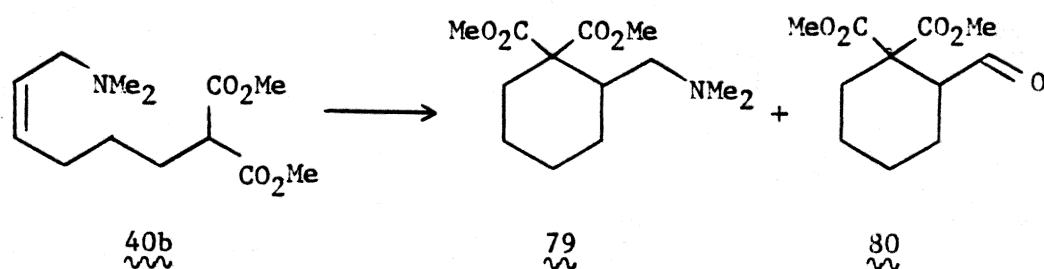


subsequently, undergo hydrogenation or hydrolysis by adventitious water. The amine might also be obtained by hydrogenation of complex 81.

This hypothesis led to the development of conditions which yielded either pure cyclohexylamine 79 or pure cyclohexylaldehyde 80. When Molecular Sieve 4\AA was added as a water scavenger prior to cyclization,

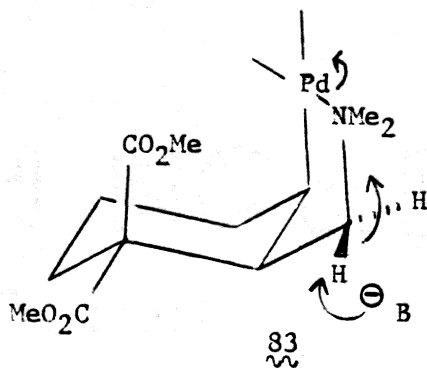
direct reduction yielded only cyclohexylamine 79 in 91% yield. When the reaction mixture was warmed to room temperature for six hours and subsequently hydrolyzed with water-acetic acid, cyclohexylaldehyde 80 was obtained in 93% yield.

The same sequence of events was repeated with the cis aminodiester 40b. Thus, cyclohexylamine 79 could be obtained from cis aminodiester

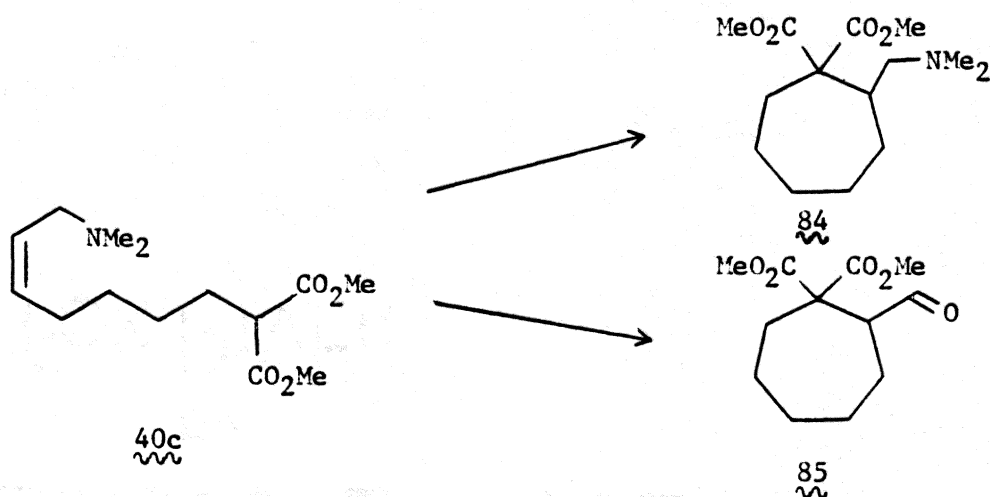


40b in 89% yield with molecular sieve, while cyclohexylaldehyde 80 could be obtained in 73% yield upon acetic acid hydrolysis.

The differing amounts of aldehyde obtained from the cis and trans isomers may reflect a difference in the conformations of the intermediate complexes. The hydrogen which is "antiperiplanar" to the palladium-nitrogen bond in complex 81 may be appropriately aligned for a trans elimination. The same bond in the cis complex 83 may not be as fortuitously aligned.



Seven-membered ring closures exhibited behavior which was analogous to the six-membered ring closures. In the absence of molecular sieves, a mixture of amine 84 and aldehyde 85 was obtained upon attempted cyclization of 40c. Inclusion of molecular sieves in the reaction mixture allowed isolation of cycloheptyl amine 84 in 71% yield, while acetic acid hydrolysis after 6 h at room temperature gave cycloheptyl aldehyde 85 in 70% yield.



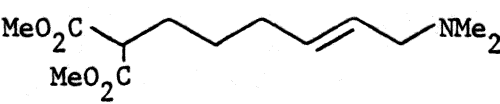
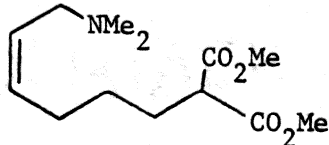
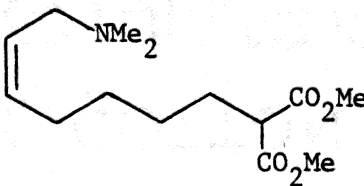
Although a rigorous kinetic study was not undertaken, the reactions to form five-, six-, and seven-membered rings with amine ligands were observed to proceed at distinctly different rates.

The ring closures to form five-membered rings are complete by gas chromatographic analysis in ca 20 min at 0°C , while the cyclohexyl rings were completely formed in ca 30 min at 0°C . The cycloheptyl systems were somewhat slower, requiring ca 45 min to 1 h to reach completion at the same temperature.

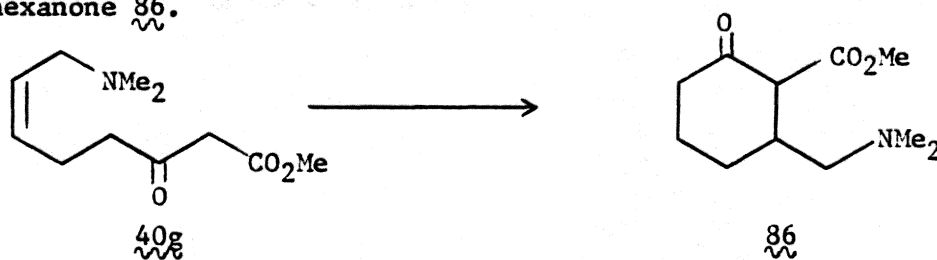
To this point, only reactions in which an exocyclic enolate was employed have been discussed. Whereas the exocyclic enolates all closed smoothly, the endocyclic enolates proved somewhat more difficult to close.

Table 6

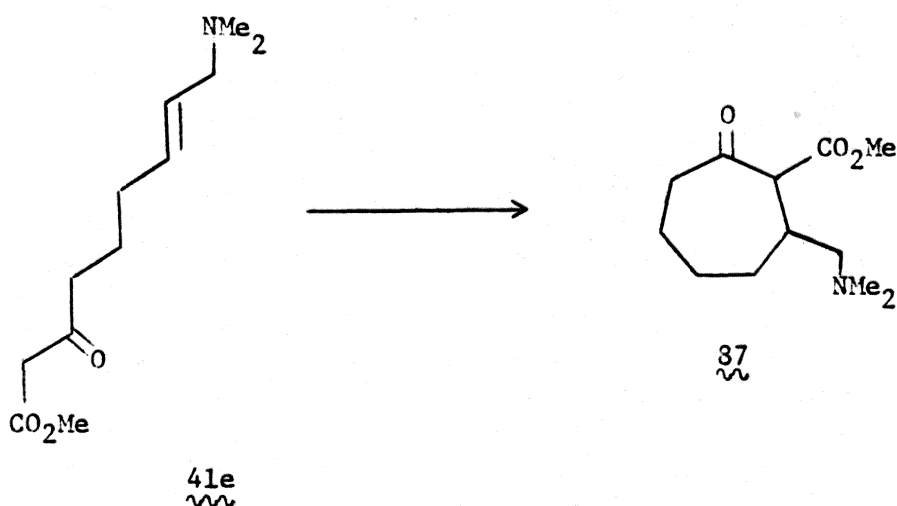
Summary of Ring Closures with Exocyclic Enolates
to Form Cyclohexyl and Cycloheptyl Systems

<u>Starting Material</u>	<u>Cyclic Amine (% Yield)</u>	<u>Cyclic Aldehyde (% Yield)</u>
 41g	79 (91)	80 (93)
 40b	79 (89)	80 (73)
 40c	84 (71)	85 (70)

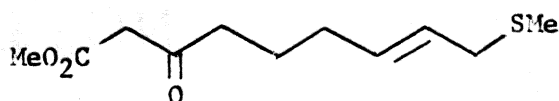
Allylic amines undergo intramolecular carbopalladation with endocyclic enolates. When aminoketoester 40g was added at room temperature to a 1:1 methylene chloride:THF solution containing 1.0 equiv of LTP and subsequent generation of the enolate with 1.1 equiv of potassium tert-butoxide, an intermediate palladium complex could be observed to completely form by TLC analysis over 1.5 h at room temperature. Reduction with hydrogen gas gave only a 35% yield of the desired cyclohexanone 86.



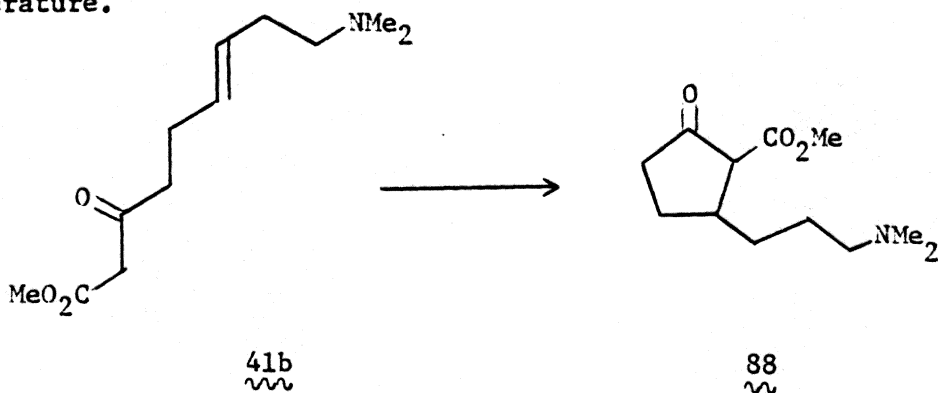
When aminoketoester 41c was cyclized under the same conditions, the reaction was cleaner (giving less side products), as fast, and gave a 65% yield of cycloheptanone 87.



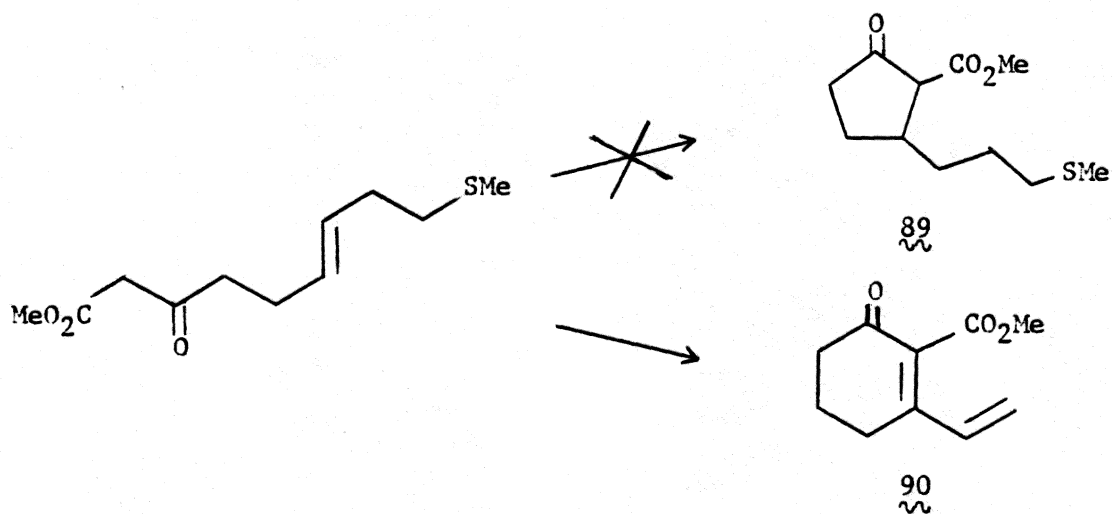
In view of the aforementioned sluggishness of sulfides in cyclizations and the reluctance with which endocyclic enolates undergo cyclization, it is not surprising that allylic sulfide 41d failed to undergo cyclization at all.

41d

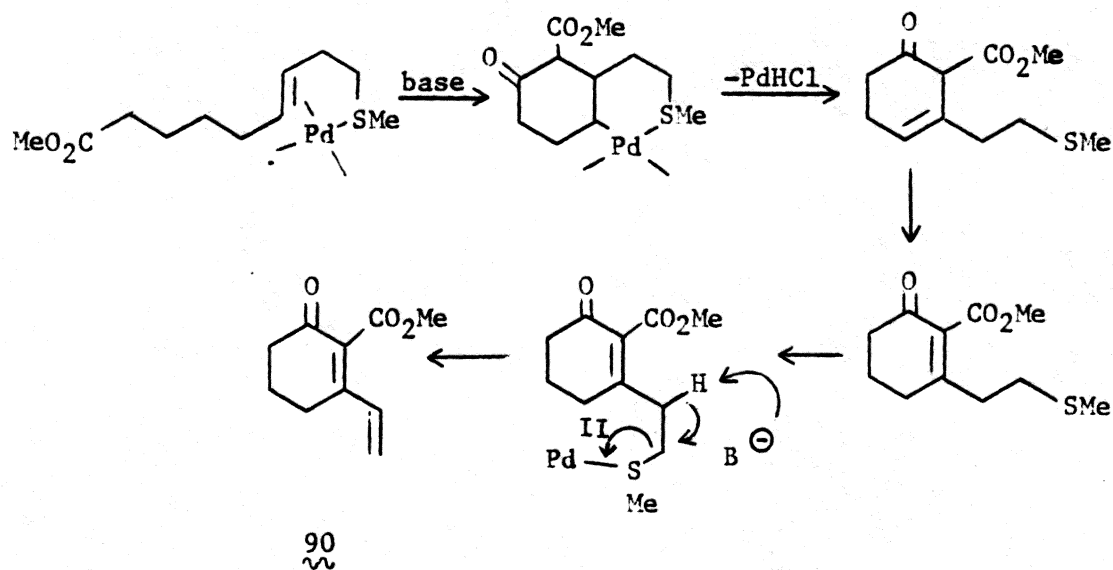
The reaction was readily extended to exocyclic ring closures. The amino ketoester 41b was cyclized under the same conditions as 40g and 41e to give a 64% yield of cyclopentanone 88 after 2.5 h at room temperature.

41b88

The sulfide 41a did not cyclize as anticipated. When sulfide 41a was treated with 1.0 mol equiv of LTP and 1.1 equiv potassium tert-butoxide over 36 h, diene 90 was isolated in 40% yield. None of the cyclopentanone 89 could be detected.



A proposed, but unsubstantiated, mechanism is shown below.



Unlike the cyclization of amino ketoester 41b, the cyclization of amino ketoester 40i proceeded very rapidly (less than 20 min) to give 91 in 98% yield.

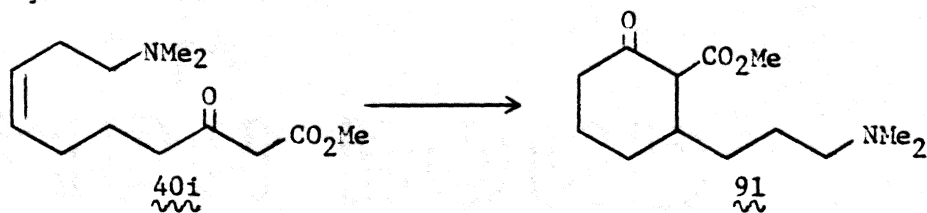
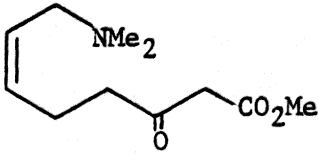
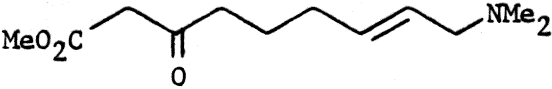

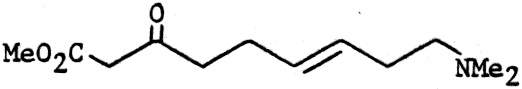
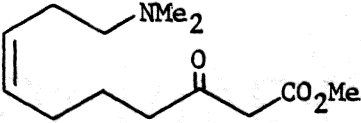
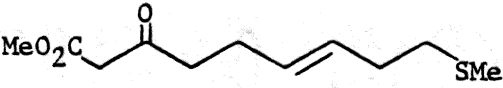


Table 7

Summary of Cyclizations with Endocyclic Enolates

<u>Starting Material</u>	<u>Cyclic Ketone (% Yield)</u>
 40g	86 (35)
 41e	37 (65)
 41d	0% yield
 41b	38 (64)
 40i	91 (98)
 41a	90 (40)

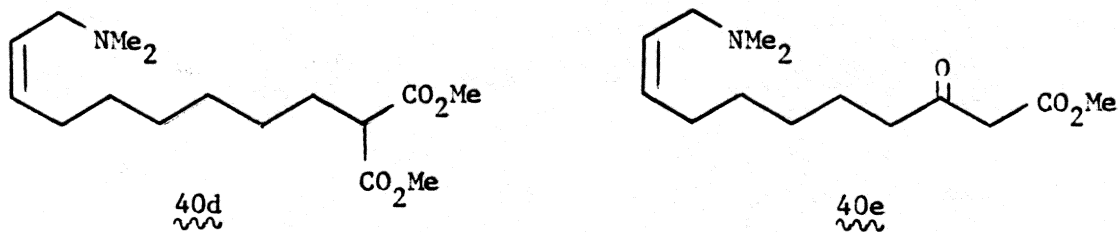
Cyclic ketoesters exhibit characteristic infrared spectra, and provide confirmation of the structural assignment of cyclic amino ketoesters 86-91. Due to the high degree of enolization, α -carboalkoxy-cyclohexanones, such as 86 and 91, usually exhibit weaker absorptions in the "normal" carbonyl region at 1700 cm^{-1} and 1735 cm^{-1} . Instead, they exhibit stronger carbonyl absorptions at 1600 cm^{-1} and 1645 cm^{-1} , corresponding to the enolic forms. α -Carboalkoxycyclopentanones, such as 88, exhibit similar behavior; however the "normal" carbonyl bands at 1700 cm^{-1} and 1745 cm^{-1} are stronger. The enolic carbonyl absorptions at 1615 cm^{-1} and 1660 cm^{-1} are somewhat weaker than the "normal" carbonyl bands. Both the pentacyclic and hexacyclic α -carboalkoxy ketones also exhibit weak enolic OH stretches at ca 3225 cm^{-1} and 3575 cm^{-1} . The cycloheptanone 87 also exhibited this dual carbonyl absorption behavior. Cycloheptanone 87 exhibited strong carbonyl stretches at 1705 cm^{-1} and 1735 cm^{-1} and weaker bands at 1605 cm^{-1} and 1640 cm^{-1} for the enolic form. These infrared bands are quite diagnostic, and present strong evidence that the regiochemistry of these processes was predicted properly.

The results obtained with the exocyclic ring closures of endocyclic enolates are important from a stereoelectronic viewpoint. Ring closures via carbopalladation might well be viewed as being somewhat analogous to the internal halide displacements used to establish Baldwin's rules for ring closure.⁴² Baldwin's rules for ring closure indicate that the stereoelectronic restrictions for five-membered ring closures with internal enolates highly disfavor carbon alkylation.⁴²

Instead, oxygen alkylation predominates. The formation of cyclopentanone 78a, therefore, constitutes a violation of Baldwin's rules for ring closure. On the other hand, Baldwin's rules would predict that the formation of cyclohexanones, such as 91, would proceed smoothly with exclusive carbon alkylation. This may explain why the ring closure of 41a gave the unpredicted regiochemistry. These stereo-electronic restrictions evidence themselves in the difference in product yields and in the stark rate differences exhibited for the ring closures of amino ketoesters 41b and 40i.

Unfortunately, the restrictions for endocyclic ring closures, in which an internal enolate and a polarized olefin must undergo closure, are not quite so clearly defined. These reactions would apparently be required to overcome the still larger steric barrier inherent in systems which contain four sp^2 hybridized centers. This is reflected in the rise in yield upon increasing the ring size from six to seven.

Attempts to extend these systems to medium sized rings failed to proceed cleanly. When either 40d or 40e were cyclized, the reactions



were exceedingly slow (1 to 2 weeks at room temperature) and gave at least nine major products by TLC analysis upon hydrogenation.

In summation, intramolecular carbopalladation allows facile entry

into a broad series of cyclopenta-, cyclohexa- and cycloheptanoids.

The further applications of these processes toward stereo- and regio-controlled organic synthesis is under active investigation.

Chapter 3. Experimental

All nuclear magnetic resonance spectra were recorded on a Varian EM 390 Spectrometer. The chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard.

All infrared spectra were recorded on a Perkin-Elmer 710B Infrared Spectrometer. All infrared data are reported in reciprocal centimeters.

Mass spectra were run either by the Virginia Polytechnic Institute and State University Chemistry Department on an Hitachi Perkin-Elmer RMU-7 Mass Spectrometer at 50 eV or by the Virginia Polytechnic Institute and State University Biochemistry and Nutrition Department on a Varian MAT 112 Mass Spectrometer at 70 eV.

Melting points were taken on a Bristol microscope equipped with a hot stage and are uncorrected.

Microanalyses were performed either by the Virginia Polytechnic Institute and State University Chemistry Department Analytical Services or Galbraith Laboratories, Knoxville, TN.

Solvents, Reagents, and Chromatography

Tetrahydrofuran (THF) (Fisher Reagents) was stored under nitrogen at constant reflux over lithium aluminum hydride (LAH) in a recycling still. THF which had been added to the still was considered dry when 10 mL consumed no more than 50 μ L of 1.6 M n-butyl lithium at about 0°C with triphenylmethane as an indicator. Hexamethylphosphoramide (HMPA) (Aldrich) was distilled at ca 1 mm Hg after being stirred at ca 100°C over calcium hydride overnight.

Dry acetone (Fisher) was obtained by freshly distilling acetone from anhydrous potassium carbonate under nitrogen. All other solvents were obtained from Fisher Scientific Products and distilled prior to use.

Sodium hydride was purchased from Alfa as a 50% oil dispersion and was washed with hexane in a fritted glass funnel immediately prior to use.

n-Butyl lithium was purchased from Aldrich and titrated by adding n-butyl lithium to 10 mL of 10% HMPA-THF containing a trace of triphenylmethane as an indicator and then cooling to -78°C . n-Butyl lithium was added until the solution turned red, and then ca 5 mmol of an alcohol was syringed in, and finally n-butyl lithium was added until the red color reappeared.^{3c}

Potassium tert-butoxide was obtained from Aldrich Chemicals and sublimed at ca 1 mm Hg prior to use. Molecular sieve 4\AA was obtained from Fisher Scientific Products and was predried at $170\text{--}200^{\circ}\text{C}$ at 1 mm Hg for 24 h.

The source and purification of other materials is given as they appear in the experimental.

Analytical TLC plates coated with silica gel GF (250 micron) were purchased from Analtech, Inc. Preparative TLC plates were made from silica gel PF-254 (EM Reagents) and dried in an oven at $110\text{--}120^{\circ}\text{C}$ for 2 h and then stored in a dessicator. Plug filtration was performed with Silica Gel 60 (70-230 mesh ASTM) (EM Reagents). Medium pressure liquid chromatography (MPLC or flash chromatography) was performed following the method of Still.⁷³

Apparatus

Reaction vessels, syringes, needles, and stirring bars were stored in an oven at greater than 110°C. Syringes were assembled hot and all glassware was assembled hot while being purged with a stream of dry nitrogen.

Experimental Procedures

Lithium Tetrachloropalladate

Lithium tetrachloropalladate was prepared by the method of Cope and Friedrich.⁷⁴

General Procedure A. Homopropargylic Alcohols From Acetylides.

Preparation of Tetrahydropyranyl Alcohol 43a.

The preparation of tetrahydropyranyl alcohol 43a follows a slight modification of the procedure of R. F. Borch, et. al.^{59c} and is typical for the synthesis of homopropargylic alcohols. To a solution of 21.2 g (0.151 mol) of 1-oxytetrahydropyranyl-2-propyne (42) in 200 mL of 10% hexamethylphosphoramide (HMPA)-THF, containing a trace of triphenylmethane as an indicator at 0°C, was added n-butyl lithium slowly. The color of the solution turns orange and then dark red at the endpoint. After the addition was complete 30 mL (0.604 mol) of cold ethylene oxide (Eastman) was added. The mixture was stirred at 0°C overnight and then partitioned between toluene and water. The toluene layer was dried over sodium sulfate and filtered. Concentration and distillation gave 24.8 g (89%) of known tetrahydropyranyl alcohol 43a.^{59c}

General Procedure B. The Preparation of Oxytetrahydropyranyl Alkynes
Via Halide Displacement. Preparation of Tetrahydropyranyl Chloride

43b.^{60b}
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The preparation of oxytetrahydropyranyl alkynes follows a slight modification of the procedure of A. I. Rachlin, et. al.<sup>60b</sup> The preparation of tetrahydropyranyl chloride 36b is typical. To a solution of 9.8 g (69.9 mmol) of 1-oxytetrahydropyranyl-2-propyne (42) in 100 mL of 10% HMPA-THF (containing a trace of triphenylmethane as indicator) chilled to 0°C was added n-butyl lithium slowly. The color of the solution turns orange and then dark red at the endpoint. After the addition was complete, the solution was chilled to -78°C and 10 mL (93 mmol) of 1,3-bromochloropropane (Aldrich) was added. The solution was allowed to slowly warm to room temperature overnight, and then partitioned between toluene and water. The toluene layer was dried over sodium sulfate and filtered. Concentration and distillation yielded 1.6 g of 1-oxytetrahydropyranyl-2-propyne (42) and 11.5 g (76%) of known tetrahydropyranyl chloride 43b<sup>60</sup>: nmr (CDCl<sub>3</sub>) δ 1.15-1.80 (m,6H), 1.85 (m,2H), 2.27 (d of t,2H,J=2,7 Hz), 3.21 (m,4H), 4.16 (d,2H,J=2 Hz), 4.67 (s,1H).

Tetrahydropyranyl Chloride 43c. Following procedure B, 69.3 g (0.474 mol) of 1-oxytetrahydropyranyl-2-propyne (42) and 100 g (0.585 mol) of 1,4-bromochlorobutane (Aldrich) was converted to 63.6 g (58%) of tetrahydropyranyl chloride 43c: bp 110-113°C (1 mm Hg); nmr (CDCl<sub>3</sub>) δ 1.20-2.11 (m,10H), 2.27 (d of t,2H,J=2,6 Hz), 3.30-3.67 (m,3H), 3.69-4.10 (m,1H), 4.27 (d,2H,J=2 Hz), 4.67 (s,1H); ir (CHCl<sub>3</sub>) 1020 cm<sup>-1</sup>,

1035  $\text{cm}^{-1}$ , 1115  $\text{cm}^{-1}$ , 1130  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e 57, 68, 86, 94, 102.

General Procedure C. Removal of Tetrahydropyranyl Protecting Groups.

Preparation of diol 44a.

The preparation of diol 44a<sup>59a,b</sup> is typical for the removal of tetrahydropyranyl protecting groups. To a solution of 27.4 g (0.195 mol) of tetrahydropyranyl alcohol 43a in 1.5 L of methanol was added 8 drops of concentrated hydrochloric acid at room temperature. The solution was stirred for 20 h and then excess (1.5–3.0 g) solid sodium bicarbonate was added. The mixture was stirred for 1 h and the methanol was removed in vacuo. The crude diol was dissolved in THF. The THF solution was filtered and concentrated to afford crude diol 44a. Distillation afforded 13.5 g (91%) of known diol 44a<sup>59a,b</sup> bp 90–93°C (1 mm Hg), nmr ( $\text{CDCl}_3$ )  $\delta$  2.31 (m, 2H), 3.4–4.2 (m, 8H); ir ( $\text{CHCl}_3$ ) 3370  $\text{cm}^{-1}$  (strong, broad), 3775  $\text{cm}^{-1}$ .

Chloroalcohol 44b: Following procedure C, 80.8 g (0.373 mol) tetrahydropyranyl chloride 43b was converted to 48.7 g (97%) of known chloroalcohol 44b<sup>60</sup> after distillation: bp 62–65°C (1 mm Hg); nmr ( $\text{CDCl}_3$ )  $\delta$  1.61–1.99 (m, 2H), 2.12–2.42 (d, t, 2H, J=2, 7 Hz), 2.60 (broad s, 1H), 3.52 (t, 6 Hz), 4.11 (broad s, 2H); ir ( $\text{CHCl}_3$ ) 1050  $\text{cm}^{-1}$ , 2125  $\text{cm}^{-1}$  (weak), 3400  $\text{cm}^{-1}$  (broad), 3780 (sharp); mass spectrum (70 eV) m/e 55, 70, 83, 85, 104, 106.

Chloroalcohol 44c: Following procedure C, 61.5 g (0.267 mol) of tetrahydropyranyl chloride 43c was converted to 39.3 g (99%) of known

chloroalcohol 44c<sup>61</sup>: bp 81–85°C (1 mm Hg); nmr (CDCl<sub>3</sub>) δ 1.33–2.02 (m, 4H), 2.08–2.29 (m, 2H), 2.92 (t, 1H, J=6 Hz, -OH), 3.46 (t, 2H, J=7 Hz), 4.17 (m, 2H); ir (CHCl<sub>3</sub>) 1050 cm<sup>-1</sup>, 2125 cm<sup>-1</sup> (weak), 3400 cm<sup>-1</sup> (broad), 3780 cm<sup>-1</sup> (sharp).

Diol 44d: Diol 44d was prepared by sequentially following procedures B and C without isolation of the intermediate ditetrahydropyran 43d with only a slight modification. Procedure B was followed with the exception that the reaction was refluxed for 3 days. In this way 14.67 g (0.105 mol) of 1-oxytetrahydropyran-2-propyne and 22.13 g (0.100 mol) of 1-oxytetrahydropyranyl-6-chlorohexane<sup>75</sup> afforded crude ditetrahydropyran 43d which was directly deprotected, without isolation, according to procedure C. Kugelrohr distillation (125–130°C at 1 mm Hg) afforded 8.15 g (52%) of diol 44d; nmr (CDCl<sub>3</sub>) δ 1.37 (s(broad), 8H), 2.07–2.27 (m, 2H), 2.83–3.7 (broad, 2H, -OH), 3.57 (t, 2H, J=6 Hz), 4.14 (t, 2H, J=2 Hz); ir (CHCl<sub>3</sub>) 3400 cm<sup>-1</sup> (broad), 3580 cm<sup>-1</sup> (sharp); mass spectrum (70 eV) m/e 57, 60, 79, 134.

General Procedure D. Conversion of Chloroalcohols and Diols to

Diiodides. Preparation of Diiodide 45a.

The preparation of diiodide 45a is typical of the formation of diiodides from diols and chloroalcohols. To a solution of 6.583 g (65.8 mmol) of diol 44a in 200 mL of THF at 0°C was added 19 mL (138 mmol) of triethylamine. To this mixture was added 10.2 mL (132 mmol) of methane sulfonyl chloride dropwise. The mixture was stirred 0.5 h, then filtered and the THF was removed in vacuo. The residue

was dissolved in 200 mL of dry acetone. To this solution was added 10 g (66.6 mmol) of sodium iodide in 100 mL of dry acetone. The mixture was swirled for 10 min and filtered through celite and washed with dry acetone. An additional 30 g (200 mmol) of sodium iodide in 300 mL of dry acetone was added and the mixture was refluxed for 16 h. The mixture was filtered through celite and the acetone was removed in vacuo. The crude diiodide was taken up in ethyl ether. Removal of the ether in vacuo and crystallization at  $-78^{\circ}\text{C}$  from 1:1 hexane:ethyl ether afforded 16.6 g (75%) of diiodide 45a: nmr ( $\text{CDCl}_3$ )  $\delta$  2.67 (m,2H), 3.20 (t,2H,  $J=7$  Hz), 3.70 (t,2H, $J=2$  Hz); ir ( $\text{CHCl}_3$ )  $1140\text{ cm}^{-1}$ ,  $1170\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 66, 67, 127, 193, 320.

Diiodide 45b: Following procedure D, with the exception that only half the quantities of triethylamine and methane sulfonyl chloride were necessary, 15.7 g (0.118 mol) of chloroalcohol 45b was converted to 35.57 g (90%) of 45b after trituration with hexane and subsequent crystallization at  $-78^{\circ}\text{C}$  from 1:2 ethyl ether:hexane: nmr ( $\text{CDCl}_3$ )  $\delta$  1.67-2.13 (m,2H), 2.17-2.43 (m,2H), 3.20 (t,2H, $J=7$  Hz), 4.63 (t,2H, $J=2$  Hz); ir ( $\text{CHCl}_3$ )  $1140\text{ cm}^{-1}$ ,  $1170\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 80, 207, 334.

Diiodide 45c: Following procedure D, with the exception that only half the quantities of triethylamine and methane sulfonyl chloride were necessary, 10.1 g (68.9 mmol) of chloroalcohol 44c was converted to 20.2 g (84%) of diiodide 45c after plug filtration with hexane: nmr ( $\text{CDCl}_3$ )  $\delta$  1.33-2.07 (m,4H), 2.09-2.44 (m,2H), 3.20 (t,2H, $J=7$  Hz), 4.63 (t,2H, $J=2$  Hz); ir ( $\text{CHCl}_3$ )  $1140\text{ cm}^{-1}$ ,  $1170\text{ cm}^{-1}$ ; mass spectrum (70 eV)

m/e 80, 94, 221, 348.

Diiodide 45d: Following procedure D, 7.90 g (50.6 mmol) of diol 44d was converted to 12.58 g (66%) of diiodide 45d after plug filtration with hexane: nmr (CDCl<sub>3</sub>)  $\delta$  1.37 (s(broad),6H), 1.57-1.97 (m,2H), 3.13 (t,2H,6 Hz), 3.63 (t,2H,J=2 Hz); ir (CHCl<sub>3</sub>) 1140 cm<sup>-1</sup>, 1170 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 69, 80, 82, 94, 121, 122, 249, 376.

General Procedure E. Formation of Amino Diesters From Diiodides.

Preparation of Amino Diester 46a.

The preparation of amino diester 46a is typical for the preparation of amino diesters from diiodides. To a solution of 14.42 g (45.1 mmol) of the diiodide 45a in 200 mL of THF at 0°C was added 5.7 mL (90.2 mmol) of chilled anhydrous dimethylamine via syringe. The mixture was stirred at 0°C for 20 min and then filtered into a solution of sodio dimethyl malonate (prepared by adding 17.0 mL (148.8 mmol) of dimethyl malonate dropwise into a suspension of 3.25 g (135.3 mmol) of sodium hydride in 500 mL of THF). The volume of the solution was reduced to ca 200 mL and 20 mL of HMPA was added. Stirring was continued for 4 h at room temperature and the mixture was then partitioned between toluene and saturated aqueous sodium bicarbonate. The toluene layer was exhaustively extracted with water. The toluene layer was dried over sodium sulfate and concentrated in vacuo to give a mixture of crude 46a and dimethyl malonate. The mixture was heated in a Kugelrohr oven to 50°C at 1 mm Hg and the distillate discarded. Kugelrohr distillation of the residue (95°C at 1 mm Hg) afforded 4.73 g (43%) pure amino diester 46a; nmr (CDCl<sub>3</sub>)  $\delta$



2.04–2.51 (m, 4H), 2.30 (s, 6H), 3.17 (t, 2H, J=2 Hz), 3.63 (t, 1H, J=5 Hz), 3.77 (s, 6H); ir (CHCl<sub>3</sub>) 1730 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (50 eV) m/e 58, 82, 97, 108, 110, 182, 210, 240, 241.

Anal. Calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.69; H, 8.01; N, 5.93.

Amino Diester 46b: Following procedure E, 17.06 g (51.1 mmol) of diiodide 45b was converted to 8.39 g (69%) of amino diester 46b after Kugelrohr distillation (110° at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.37–1.77 (m, 2H), 1.83–2.13 (m, 2H), 2.14–2.43 (m, 2H), 2.27 (s, 6H), 3.17 (t, 2H, J=2 Hz), 3.37 (t, 1H, J=7 Hz), 3.71 (s, 6H); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 119, 151, 254, 255.

Anal. Calcd for C<sub>13</sub>H<sub>21</sub>NO<sub>4</sub>: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.02; H, 8.20; N, 5.59.

Amino Diester 46c: Following procedure E, 14.778 g (42.5 mmol) of diiodide 45c was converted to 6.566 g (58%) of amino diester 46c after Kugelrohr distillation (110°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.27 (s(broad), 2H), 1.37–1.67 (m, 2H), 1.77–2.10 (m, 2H), 2.13–2.37 (m, 2H), 2.27 (s, 6H), 3.17 (t, 2H, J=2 Hz), 3.37 (t, 1H, J=7 Hz), 3.73 (s, 6H); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 82, 97, 110, 138, 145, 165, 210, 238, 254, 268, 269.162.

Calcd for C<sub>14</sub>H<sub>23</sub>NO<sub>4</sub>: 269.161.

Amino Diester 46d: Following procedure E, 12.58 g (33.5 mmol) of diiodide 45d was converted to 4.48 g (45%) of amino diester 46d after Kugelrohr distillation (150°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.15–1.58

(m,8H), 1.70-1.95 (m,2H), 2.03-2.31 (m,2H), 2.26 (s,6H), 3.13 (t,2H, J=2 Hz), 3.31 (t,1H,J=7 Hz), 3.73 (s,6H); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 82, 97, 110, 138, 238, 254, 268.

Anal. Calcd for C<sub>16</sub>H<sub>27</sub>NO<sub>4</sub>: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.98; H, 9.27; N, 4.72.

General Procedure F. Partial Hydrogenation of Acetylenes. Preparation of Amino Diester 40a. The preparation of olefinic amino diester 40a is typical of the partial hydrogenation of acetylenes to give olefins. Hydrogen was introduced into a solution of 4.34 g (18.0 mmol) of amino diester 46a in 75 mL of methanol containing 0.4 g of 5% palladium on barium sulfate. Hydrogen uptake was monitored via a buret. After 1.0 mol equivalent (405 mL) of hydrogen was consumed, increments of 0.1 mol equiv (40 mL) of hydrogen were allowed to enter the vessel until the reaction was complete by gas chromatographic analysis. The catalyst was filtered off by filtration through celite to give an orange solution. The methanol was removed in vacuo and the residue taken up in ethyl ether. Refiltration and solvent removal gave crude amino diester 40a. Kugelrohr distillation (95°C at 1 mm Hg) afforded 3.42 g (78%) of pure amino diester 40a: nmr (CDCl<sub>3</sub>) δ 1.79-2.39 (m,4H), 2.20 (s,6H), 2.87 (d,2H,J=6 Hz), 3.37 (t,1H,J=7 Hz), 3.75 (s,6H), 5.37-5.60 (m,2H); ir (CHCl<sub>3</sub>) 1730 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (50 eV) m/e 58, 85, 98, 110, 112, 212, 243.

Anal. Calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub>: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.15; H, 8.85; N, 5.82.

Amino Diester 40b: Following procedure F, 7.270 g (28.51 mmol) of amino diester 46b was converted to 6.724 g (92%) of amino diester 40b after Kugelrohr distillation (110°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.17-2.57 (m,8H), 2.23 (s,6H), 2.90 (d,2H,J=6 Hz), 3.37 (t,1H,J=7 Hz), 3.73 (s,6H), 5.50 (t,2H,J=5 Hz); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (50 eV) m/e 58, 85, 126, 226, 257.

Anal. Calcd for C<sub>13</sub>H<sub>23</sub>NO<sub>4</sub>: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.45; H, 9.33; N, 5.23.

Amino Diester 40c: Following procedure F, 4.743 g (17.63 mmol) of amino diester 46c was converted to 4.543 g (95%) of amino diester 40c after Kugelrohr distillation (110°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.25-1.45 (m,4H), 1.73-2.27 (m,4H), 2.23 (s,6H), 2.90 (d,2H,J=6 Hz), 3.34 (t,1H,J=7 Hz), 3.74 (s,6H), 5.40-5.47 (t,2H,J=6 Hz); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 85, 98, 134, 140, 240, 270, 271.

Anal. Calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.00; H, 9.34; N, 5.09.

Amino Diester 40d: Following procedure F, 3.928 g (13.23 mmol) of amino diester 46d was converted to 2.974 g (75%) of amino diester 40d after MPLC (0.5% NH<sub>3</sub>(aq)/4.5% MeOH/CHCl<sub>3</sub>) and subsequent Kugelrohr distillation (120°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.32 (s(broad),10H), 1.77-2.20 (m,4H), 2.23 (s,6H), 2.91 (d,2H,J=6 Hz), 3.33 (t,1H,J=7 Hz), 3.74 (s,6H), 5.40-5.60 (m,2H); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 85, 99, 168, 268, 298, 299.

Anal. Calcd for  $C_{16}H_{29}NO_4$ : C, 64.19; H, 9.76; N, 4.68. Found: C, 64.07; H, 10.02; N, 4.87.

General Procedure G. Allylic and Propargylic Amino Ketoesters via Dianion Displacements On Diiodides. Preparation of Amino Ketoester 47.

The preparation of amino ketoester 47 is typical of the preparation of amino ketoesters from diiodides. To a solution of 3.477 g (9.99 mmol) of diiodide 45c in 50 mL of THF at 0°C was added 1.32 mL (19.98 mmol) of chilled anhydrous dimethylamine via syringe. The solution was stirred for 20 min at 0°C and then filtered through a dry, coarse fritted glass funnel into a solution of 1.5 equiv of methyl acetoacetate dianion (prepared from 1.74 g (14.98 mmol) of methyl acetoacetate according to the procedure of Weiler<sup>76</sup>) by means of a double ended needle and a fritted glass funnel fitted with a serum cap. The solution was forced through the fritted glass funnel via a positive pressure of dry nitrogen. The reaction mixture was stirred at 0°C for 1 h and then partitioned between chloroform and saturated aqueous sodium bicarbonate. (If the aqueous layer was basic, 1 M acetic acid is added to adjust the pH to 7-8.) The chloroform layer was dried over sodium sulfate and filtered. Concentration afforded 1.693 g (67%) of spectroscopically homogeneous amino ketoester 41 which was used in the next step without further purification: nmr ( $CDCl_3$ )  $\delta$  1.27-1.87 (m, 6H), 2.10-2.40 (m, 2H), 2.24 (s, 6H), 2.53 (t, 2H, J=6 Hz), 3.13 (t, 2H, J=2 Hz), 3.41 (s, 2H), 3.69 (s, 3H); ir ( $CHCl_3$ )  $1710\text{ cm}^{-1}$ ,  $1740\text{ cm}^{-1}$ ,  $2770\text{ cm}^{-1}$ ,  $2810\text{ cm}^{-1}$ .

Amino Ketoester 40e: Following procedure F, 1.693 g (6.683 mmol) of

amino ketoester 47 was converted to 0.900 g (53%) of amino ketoester 40e after MPLC with 0.6% NH<sub>3</sub>(aq)/5.4% MeOH/CHCl<sub>3</sub>: nmr (CDCl<sub>3</sub>) δ 1.17-1.80 (m,6H), 1.90-2.13 (m,2H), 2.22 (s,6H), 3.46 (t,2H,J=7 Hz), 2.91 (d,2H,J=6 Hz), 3.40 (s,2H), 3.70 (s,3H), 5.39-5.53 (m,2H); ir (CHCl<sub>3</sub>) 1710 cm<sup>-1</sup>, 1745 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 84, 98, 222, 224, 255.185. Calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>3</sub>: 255.182.

cis-1,5-Pentene Diol (49): In a manner similar to R. F. Borch, et. al.<sup>59c</sup>, 52.3 g (0.281 mol) of alcohol 44a was hydrogenated according to procedure F to afford known Z-1-oxytetrahydropyranyl-5-hydroxy-2-pentene<sup>59c</sup> which was used without purification.

The tetrahydropyranyl protecting group of Z-1-oxytetrahydropyranyl-5-hydroxy-2-pentene was removed according to procedure C to afford an overall yield of 25.9 g (89%) of known Z-1,5-pentene diol 49<sup>59b</sup> after distillation.

Sulfide Diester 40f: To a solution of 4.058 g (39.7 mmol) of diol 49 in 200 mL of THF at 0°C was added 11.6 mL (83.4 mmol) of triethylamine. To this mixture was added 6.15 mL (79.4 mmol) of methane sulfonyl chloride dropwise. The mixture was stirred 0.5 h and then filtered. To the filtrate was added 20 mL of HMPA followed by 2.78 g (39.7 mmol) of powdered sodium methyl mercaptide. Stirring was continued for 30 h and the mixture was added to a solution of sodio dimethylmalonate in THF (prepared by adding 20 mL (175 mmol) of dimethyl malonate dropwise into a suspension of 3.81 g NaH (159 mmol) in 600 mL of THF). The volume of the solution was reduced to approximately 300 mL and 0.60 g

(4.0 mmol) of sodium iodide was added. The solution was stirred at room temperature for 3 days and partitioned between toluene and saturated sodium bicarbonate. The toluene layer was then exhaustively extracted with water. The toluene layer was dried over sodium sulfate and concentrated to give crude sulfide diester 40f. MPLC with 25% ethyl ether:hexane afforded 2.933 g (30%) of pure sulfide diester 40f: nmr ( $\text{CDCl}_3$ )  $\delta$  2.03 (s,7H), 3.10 (d,2H,J=7 Hz), 3.38 (t,1H,J=7 Hz), 3.76 (s,6H), 5.50 (m,2H); ir ( $\text{CHCl}_3$ )  $1725 \text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 56, 68, 80, 107, 138, 166, 198, 246.

Anal. Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{S}$ : C, 53.64; H, 7.37. Found: C, 53.59; H, 7.30.

Tetrahydropyranyl Alcohol 51: Tetrahydropyranyl alcohol 51 was prepared by the method of Eiter, et. al.<sup>63</sup>

Tetrahydropyranyl Alcohol 52: Following procedure F, 7.913 g (46.5 mmol) of tetrahydropyranyl alcohol 51 was converted to 6.162 g (77%) of known tetrahydropyranyl alcohol 52<sup>64</sup> after Kugelrohr distillation ( $125^\circ\text{C}$  at 1 mm): nmr ( $\text{CDCl}_3$ )  $\delta$  1.20-1.97 (m,6H), 2.87 (s,broad,1H), 3.33-4.10 (m,2H), 4.17 (d,4H,J=6 Hz), 4.63 (s,1H), 5.72 (d of t, J=6,10 Hz); ir ( $\text{CHCl}_3$ )  $3400 \text{ cm}^{-1}$  (broad),  $3575 \text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 56, 67, 71, 85, 101.

Anal. Calcd for  $\text{C}_9\text{H}_{16}\text{O}_3$ : C, 62.77; H, 9.36. Found: C, 62.51; H, 9.38.

Tetrahydropyranyl Ketoester 53a: To a solution of 4.563 g (26.5 mmol) of tetrahydropyranyl alcohol 52 in 100 mL of THF at 0°C was added 3.87 mL (27.8 mol) of triethylamine followed by dropwise addition of 2.05 mL (26.5 mmol) of methane sulfonyl chloride. Stirring was continued for 0.5 h and the mixture was then filtered. The filtrate was added to a solution of 4.37 g (29.1 mmol) of freshly recrystallized sodium iodide (from methanol) in 500 mL of THF and stirred for 20 min at room temperature. The mixture was filtered and concentrated to give a crude cis-allylic iodide intermediate which was used immediately.

The crude iodide was taken up in 50 mL of THF and added to a THF solution of 1.5 mol equiv of methyl acetoacetate dianion (prepared from 3.38 g (29.1 mmol) of methyl acetoacetate by the method of Weiler<sup>76</sup>). The solution was partitioned between ethyl ether and sodium bicarbonate.

The ether layer was dried over sodium sulfate and concentrated to afford crude ketoester 53a. MPLC with 1:1 ethyl ether:hexane afforded 5.763 g (80%) of pure tetrahydropyranyl ketoester 53a: nmr (CDCl<sub>3</sub>) δ 1.37-1.97 (m,6H), 2.20-2.51 (m,2H), 2.52-2.73 (m,2H), 3.37-4.00 (m,2H), 3.45 (s,2H), 3.83 (s,3H), 4.06-4.27 (m,2H), 4.60 (s,1H), 5.46-5.70 (m,2H); ir (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>, 1740 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 67, 70, 85, 95, 101, 104, 170.

Anal. Calcd for C<sub>14</sub>H<sub>22</sub>O<sub>5</sub>: C, 62.20; H, 8.20. Found: C, 62.09; H, 8.37.

Hydroxy Ketoester 53b: Following general procedure C, 4.274 g (15.81 mmol) of tetrahydropyranyl ketoester 53a was converted to 2.211 g (75%) after MPLC with ethyl ether: nmr (CDCl<sub>3</sub>) δ 2.10-2.70 (m,4H), 3.18

(s,1.33H), 3.27 (s,0.67H), 3.43 (s,1H), 3.67 (s,1H), 3.72 (s,2H), 4.17 (d,2H,J=6 Hz), 5.33-5.83 (m,2H); ir (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>, 1740 cm<sup>-1</sup>, 3450 cm<sup>-1</sup> (broad), 3600 cm<sup>-1</sup> (sharp); mass spectrum (70 eV) m/e 101, 150, 157, 168, 169, 186.090. Calcd. for C<sub>9</sub>H<sub>14</sub>O<sub>4</sub>: 186.088.

Amino Ketoester 40e: To a solution of 1.009 g (5.42 mmol) of hydroxy ketoester 53b in 50 mL of THF at 0°C was added 0.94 mL (6.7 mmol) of triethylamine followed by dropwise addition of 0.50 mL (6.5 mmol) of methane sulfonyl chloride. The mixture was stirred for 0.5 h and filtered. To the filtrate was added 7.2 mL (109 mmol) of chilled anhydrous dimethyl amine. The mixture was stirred overnight and filtered. Concentration gave 1.225 g of crude amino ketoester 40e. Preparative thin layer chromatography (0.7% NH<sub>3</sub>(aq)/6.3% MeOH/CHCl<sub>3</sub>) afforded 0.520 g (45%) of pure amino ketoester 40e: nmr (CDCl<sub>3</sub>) δ 2.10-2.70 (m,4H), 2.23 (s,6H), 2.93 (d,2H,J=6 Hz), 3.62 (s,2.25H), 3.73 (s,0.75H), 4.55 (s,0.75H), 5.45-5.67 (m,2H); ir (CHCl<sub>3</sub>) 1610 cm<sup>-1</sup> (strong), 1660 cm<sup>-1</sup> (strong), 1715 cm<sup>-1</sup> (weak), 1735 cm<sup>-1</sup> (weak), 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>, 3325 cm<sup>-1</sup>, 3580 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 82, 97, 136, 213.139. Calcd. for C<sub>11</sub>H<sub>19</sub>NO<sub>3</sub>: 213.139.

Tetrahydropyrany 56: Tetrahydropyran 56 was prepared by the method of Negishi and Chiu.<sup>65</sup>

Tetrahydropyrany Chloride 57: Following procedure B, 7.891 g (51.17 mmol) of tetrahydropyran 56 was converted to 5.191 g (44%) of tetrahydropyranyl chloride 57 after distillation: bp 110-113°C (1 mm Hg); nmr (CDCl<sub>3</sub>) δ 1.31-2.19 (m,8H), 2.22-2.65 (m,4H), 3.31-4.05 (m,6H),



4.61 (s,1H); ir ( $\text{CHCl}_3$ )  $1130\text{ cm}^{-1}$ ,  $1115\text{ cm}^{-1}$ ,  $1130\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 85, 91, 93, 101, 115.

Hydroxy Diester 58: To a solution of 4.793 (20.77 mmol) of tetrahydropyranyl chloride 57 in 150 mL of dry acetone was added 12.5 g (83.3 mmol) of granular sodium iodide. The mixture was refluxed for 2 days and then filtered. Concentration and trituration with ethyl ether afforded 6.371 g of an iodide intermediate which was used without further purification: nmr ( $\text{CDCl}_3$ )  $\delta$  1.31-2.19 (m,8H), 2.22-2.65 (m,4H), 3.31 (t,2H,J=7 Hz), 3.31-4.05 (m,4H), 4.63 (s,1H).

To a solution of sodio dimethyl malonate (prepared by adding 5.2 mL (45.8 mmol) of dimethyl malonate dropwise to a suspension of 1.0 g (41.7 mmol) sodium hydride in 250 mL of THF) was added 6.11 g (19.0 mmol) of the iodide intermediate in 50 mL of THF and 10 mL of HMPA. The volume of the mixture was reduced to ca 100 mL and stirred for 2 h. The mixture was partitioned between toluene and saturated aqueous bicarbonate, followed by exhaustive extraction of the toluene layer with water. Concentration and evacuation (1 mm Hg) at  $75^\circ\text{C}$  gave 5.907 g of a crude material which was immediately taken up in methanol.

Following procedure C, the tetrahydropyranyl protecting group was removed to afford 3.171 g of 58 (74% from tetrahydropyranyl chloride 49b) after MPLC with 4:1 chloroform:ethyl acetate: nmr ( $\text{CDCl}_3$ )  $\delta$  1.31-1.63 (m,4H), 1.83-2.50 (m,6H), 2.80 (t,1H,J=7 Hz), 2.40 (d of t, 1H, J=2,7 Hz), 3.60 (m,2H), 3.75 (s,3H); ir ( $\text{CHCl}_3$ )  $1725\text{ cm}^{-1}$ ,  $3525\text{ cm}^{-1}$  (broad); mass spectrum (70 eV) m/e 59, 60, 67, 69, 77, 79, 80, 84, 91, 93, 98, 110, 121, 132, 145, 152, 179, 227.

Anal. Calcd for  $C_{12}H_{18}O_5$ : C, 59.49; H, 7.49. Found: C, 59.20; H, 7.67.

General Procedure H. Amination of Homoallylic and Homopropargylic Alcohols. Preparation of Amino Diester 59.

The preparation of amino diester 59 is typical for the amination of homoallylic and homopropargylic alcohols. To a solution of 2.733 g (11.28 mmol) of hydroxy diester 58 in 50 mL of dry ethyl ether at 0°C was added 1.98 mL (14.2 mmol) of triethylamine followed by dropwise addition of 1.04 mL (13.4 mmol) of methane sulfonyl chloride. The solution was stirred at 0°C for 45 min and filtered. Concentration afforded a crude mesylate which was used without purification.

The crude mesylate was dissolved in 125 mL of THF and added to a 200 mL three-neck flask fitted with a thermometer and a dry ice condenser. To the mixture was added 15 mL (227 mmol) of cold, anhydrous dimethylamine and 0.169 g (1.13 mmol) of solid sodium iodide. The temperature of the reaction mixture was maintained at 44–45°C (reflux) for 10 h, filtered, and partitioned between ethyl ether and saturated aqueous sodium bicarbonate. The ethyl ether layer was dried over sodium sulfate and concentrated to afford crude amino diester 59. Kugelrohr distillation (125°C at 1 mm Hg) afforded 2.203 g (73%) of pure amino diester 59: nmr ( $CDCl_3$ )  $\delta$  1.37–1.77 (m, 2H), 1.90–2.60 (m, 8H), 2.25 (s, 6H), 3.38 (t, 1H, J=7 Hz), 3.77 (s, 6H); ir ( $CHCl_3$ ) 1730  $cm^{-1}$ ; mass spectrum (70 eV) m/e 58, 59, 77, 79, 81, 84, 86, 94, 108, 109, 110, 123, 145, 238, 240, 269.162. Calcd. for  $C_{14}H_{23}NO_4$ : 269.161.

Amino Diester 40h: Following procedure F, 1.342 g (4.98 mmol) of amino diester 59 was converted to 1.228 g (89%) of amino diester 40h after Kugelrohr distillation (120°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.23-1.57 (m,2H), 1.78-2.53 (m,8H), 2.23 (s,6H), 3.76 (t,1H,J=7 Hz), 3.73 (s,6H); ir (CHCl<sub>3</sub>) 1730 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 67, 79, 82, 84, 96, 109, 240, 241, 270, 271.

Anal. Calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.02; H, 9.37; N, 5.37.

Tetrahydropyranyl Alcohol 60: Following procedure A, 14.8 (96.0 mmol) of 1-oxytetrahydropyranyl-3-butyne (60) was converted to 9.45 g (50%) of tetrahydropyranyl alcohol 61 after distillation: bp 117-121°C (at 1 mm Hg); nmr (CDCl<sub>3</sub>) δ 1.33-2.07 (m,6H), 2.23-2.77 (m,4H), 2.97 (t,1H,J=7 Hz), 3.30-4.03 (m,6H), 4.61 (s,1H); ir (CHCl<sub>3</sub>) 3440 cm<sup>-1</sup> (broad), 3580 cm<sup>-1</sup> (sharp); mass spectrum (70 eV) m/e 67, 85, 101.

Anal. Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub>: C, 66.64; H, 9.15. Found: C, 66.77; H, 9.28.

Tetrahydropyranyl Alcohol 61: Following procedure F, 9.04 (45.6 mmol) of tetrahydropyranyl alcohol 60 was converted to 8.28 g (91%) of tetrahydropyranyl alcohol 61 after Kugelrohr distillation (125°C at 1 mm Hg): nmr (CDCl<sub>3</sub>) δ 1.19-2.00 (m,6H), 2.12-2.77 (m,4H), 3.22-4.02 (m,6H), 3.56 (s,1H), 5.47 (d of t,1H,J=6,10 Hz), 5.62 (d of t,1H,J=6,10 Hz); ir (CHCl<sub>3</sub>) 3450 cm<sup>-1</sup> (broad); mass spectrum (70 eV) 68, 81, 85, 101, 170.

Anal. Calcd for C<sub>11</sub>H<sub>20</sub>O<sub>3</sub>: C, 65.97; H, 10.07. Found: C, 65.83; H, 10.06.

Hydroxy Ketoester 62: To a solution of 5.687 g (28.40 mmol) of tetrahydropyranyl alcohol 61 in 150 mL of THF at 0°C was added 4.16 mL (29.8 mmol) of triethylamine, followed by dropwise addition of 2.20 mL (28.4 mmol) of methane sulfonyl chloride. The mixture was stirred for 30 min at 0°C, filtered, and concentrated. The concentrate was dissolved in 300 mL of dry acetone and 17.0 g (113 mmol) of solid sodium iodide was added. The mixture was refluxed for 16 h and filtered through celite. The filtrate was concentrated and triturated with ethyl ether. The ethyl ether solution was concentrated and solvent removed in vacuo. The residue was dissolved in 200 mL of THF and added via a double ended needle to a solution of 1.5 equiv of the dianion of methyl acetoacetate<sup>76</sup> at 0°C. The mixture was stirred for 1 h and then partitioned between ethyl ether and saturated aqueous sodium bicarbonate.

The ethyl ether layer was dried over sodium sulfate, filtered, and concentrated. The concentrate was dissolved in 1.5 L of methanol and 8 drops of concentrated hydrochloric acid added. After the mixture was stirred at room temperature for 4 h, 1.5 g of sodium bicarbonate was added and stirring continued for 1 h. The methanol was removed in vacuo and the residue triturated with chloroform. The chloroform was removed in vacuo to afford crude hydroxy ketoester 62. MPLC with 3:2 hexane:ether gave 3.468 g (57%) of pure hydroxy ketoester 62: nmr (CDCl<sub>3</sub>) δ 1.43-1.87 (m,2H), 1.92-2.45 (m,4H), 2.55 (t,2H,J=7 Hz), 3.17 (s,1H), 3.41 (s,2H), 3.57 (t,2H,J=7 Hz), 3.70 (s,3H), 5.37-5.57 (m,2H); ir (CHCl<sub>3</sub>) 1610 cm<sup>-1</sup> (weak), 1650 cm<sup>-1</sup> (weak), 1710 cm<sup>-1</sup>, 1740 cm<sup>-1</sup>,

3430  $\text{cm}^{-1}$  (broad); mass spectrum (70 eV) m/e 55, 56, 57, 59, 67, 68, 69, 74, 79, 80, 81, 84, 100, 115, 128, 166, 184, 196.

Anal. Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4$ : C, 61.66; H, 8.47. Found: C, 61.58; H, 8.56.

Amino Ketoester 40i: Procedure H was followed with the exception that chloroform was used to extract the product. In this way 1.005 g (4.69 mmol) of hydroxy ketoester 62 was converted to 0.426 g (35%) of amino ketoester 40i after MPLC with 0.7%  $\text{NH}_3(\text{aq})/6.3\%$  methanol/chloroform: nmr ( $\text{CDCl}_3$ )  $\delta$  1.51-1.88 (m,2H), 1.97-2.43 (m,8H), 2.23 (s,6H), 2.97 (d,1.2H,J=2 Hz), 3.61 (s,2.4H), 3.71 (s,0.6H), 4.53 (s,0.6H), 5.32-5.49 (m,2H); ir ( $\text{CHCl}_3$ ) 1610  $\text{cm}^{-1}$ , 1660  $\text{cm}^{-1}$ , 2770  $\text{cm}^{-1}$ , 2810  $\text{cm}^{-1}$ , 3325  $\text{cm}^{-1}$ , 3475  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e 58, 72, 66, 67, 125, 209, 240, 241.167. Calcd for  $\text{C}_{13}\text{H}_{23}\text{NO}_3$ : 241.165.

Trans-1,5-Pentene Diol (63): E-1,5-pentene diol (63) was prepared by the method of Becher.<sup>59a</sup>

Diiodide 65a: Following procedure D, 12.6 g (0.123 mol) of cis-1,5-pentene diol (49) was converted to 23.8 g (60%) of diiodide 65a after plug filtration with hexane and crystallization from 3:1 hexane:ethyl ether at  $-78^\circ\text{C}$ : nmr ( $\text{CDCl}_3$ )  $\delta$  2.61 (m,2H), 3.27 (t,2H,J=7 Hz), 3.91 (d,2H,J=7 Hz), 5.61 (d of t,1H,J=7,16 Hz), 5.89 (d of t,1H,J=7,16 Hz); ir ( $\text{CHCl}_3$ ) 1145  $\text{cm}^{-1}$ , 960  $\text{cm}^{-1}$ ; mass spectrum (50 eV) 195, 322.

Diiodide 65b: Following procedure F, 20.0 g (0.151 mol) of chloroalcohol 44b was converted to 12.1 g (60%) of known

Z-1-hydroxy-6-chloro-2-pentene<sup>60b</sup> after distillation: bp 54-58°C (1 mm Hg); nmr (CDCl<sub>3</sub>) δ 1.67-2.06 (m,2H), 2.13-2.47 (m,2H), 2.88 (s,1H), 3.56 (t,2H,J=7 Hz), 4.23 (d,2H,J=6 Hz), 5.47 (d of t,1H,J=6,10 Hz), 5.68 (d of t,1H,J=6,10 Hz); ir (CHCl<sub>3</sub>) 3400 cm<sup>-1</sup> (broad), 3580 cm<sup>-1</sup> (sharp); mass spectrum (70 eV) 44, 55, 57, 67, 81, 134.

Anal. Calcd for C<sub>6</sub>H<sub>11</sub>ClO: C, 53.54; H, 8.24. Found: C, 53.41; H, 8.26.

Following procedure D, with the exception that only half the quantities of triethylamine and methane sulfonyl chloride were required, 10.6 g (78.7 mmol) of Z-1-hydroxy-6-chloro-2-pentene was converted to 15.6 g (59%) of dioxide <sup>65b</sup> after plug filtration and crystallization from 10% ether hexane: nmr (CDCl<sub>3</sub>) δ 1.89-2.33 (m,4H), 3.19 (t,2H, J=7 Hz), 3.85 (d,2H,J=7 Hz), 5.60 (d of t,1H,J=7,16 Hz), 5.85 (d of t, 1H,J=7,16 Hz).

Alcohol <sup>66a</sup>: Following procedure B, 42.2 g (0.301 mol) of 1-oxytetrahydropyranyl-2-propyne and 41 g (0.301 mol) of n-butyl bromide was converted to 27.1 g (46%) of 1-oxytetrahydropyranyl-2-heptyne after distillation: bp 80-83°C (1 mm Hg); nmr (CDCl<sub>3</sub>) δ 0.90 (t,3H,J=7 Hz), 1.17-2.00 (m,10H), 2.13-2.37 (m,2H), 3.37-4.10 (m,2H), 4.17-4.33 (m,2H), 4.78 (s,1H).

Following procedure C, 19.3 g (98.3 mmol) of 1-oxytetrahydropyranyl-2-heptyne was converted to 10.4 g (95%) of known 1-hydroxy-2-heptyne<sup>77</sup> after distillation: bp 78-81°C (20 mm Hg); nmr (CDCl<sub>3</sub>) δ 0.90 (t,3H,6 Hz), 1.17-1.74 (m,4H), 2.07-2.37 (m,2H), 2.99 (t,1H, J=5 Hz), 4.23-4.33 (m,2H).

Following procedure F, 6.40 g (57.1 mmol) of 1-hydroxy-2-heptyne was converted to 5.12 g (79%) of known alcohol 66a<sup>77b</sup> after distillation: bp 73-75° (20 mm Hg); nmr (CDCl<sub>3</sub>) δ 0.89 (t,3H), 1.15-1.61 (m,4H), 1.85-2.25 (m,2H), 2.59 (s,1H), 4.09 (d,2H,J=6 Hz), 5.33 (d of t, 1H,J=6,10 Hz), 5.60 (d of t,1H,J=6,10 Hz).

Alcohol 67a: Using the procedure of Mori, et. al.<sup>78</sup> 5.34 g (47.6 mmol) of 1-hydroxy-2-heptyne was added to a suspension of 4.53 g (119 mmol) of lithium aluminum hydride in 500 mL of THF. The mixture was refluxed for 4 h and then allowed to cool to room temperature. The mixture was worked up by the addition of 400 mL ethyl ether followed by slow, sequential addition of 4.5 mL water, 4.5 mL of 15% aqueous sodium hydroxide, and 13.5 mL of water. The mixture was filtered and the filtrate concentrated to afford crude alcohol 67a. Distillation afforded 4.47 g (82%) of known trans-alcohol 67a<sup>78</sup>: nmr (CDCl<sub>3</sub>) δ 0.89 (t,3H,J=7 Hz), 1.19-1.56 (m,4H), 1.89-2.22 (m,2H), 3.07 (s,1H), 4.04 (d,2H,J=3 Hz), 5.56-5.76 (m,2H).

Acetate 66c: Using the method of Fieser,<sup>70</sup> 279 mg (2.44 mmol) of alcohol 66a was converted to 252 mg (78%) of acetate 66c: nmr (CDCl<sub>3</sub>) δ 0.90 (t,3H,J=7 Hz), 1.20-1.53 (m,2H), 2.05 (s,3H), 4.63 (d,2H,J=6 Hz), 5.47 (d of t,1H,J=6,10 Hz), 5.63 (d of t,1H,J=6,10 Hz).

Acetate 67c: Using the method of Fieser,<sup>70</sup> 277 mg (2.43 mmol) of alcohol 67a was converted to 280 mg (87%) of acetate 67c: nmr (CDCl<sub>3</sub>) δ 0.90 (t,3H,J=7 Hz), 1.19-1.51 (m,2H), 2.06 (s,3H), 4.50 (d,2H,J=5 Hz), 5.53 (d of t,1H,J=6,16 Hz), 5.83 (d of t,1H,J=5,16 Hz).

Allylic Mesylate 66b: Using the method of Crossland and Servis,<sup>68</sup>

713 mg (6.24 mmol) of alcohol 66a was converted to 1.20 g (100%) of crude mesylate 66b: nmr (CDCl<sub>3</sub>) δ 0.90 (t, 3H, J=7 Hz), 1.26-1.52 (m, 4H), 2.00-2.23 (m, 2H), 3.01 (s, 3H), 4.78 (d, J=6 Hz), 5.50 (d of t, 1H, J=6, 10 Hz), 5.83 (d of t, 1H, J=7, 10 Hz).

Allylic Mesylate 67b: Using the method of Crossland and Servis,<sup>68</sup>

710 mg (6.22 mmol) of allylic alcohol 67a was converted to 1.160 g (97%) of crude mesylate: nmr (CDCl<sub>3</sub>) δ 0.90 (t, 3H, J=6 Hz), 1.07-1.63 (m, 4H), 1.87-2.27 (m, 2H), 3.00 (s, 3H), 4.67 (d, 2H, J=6 Hz), 5.58 (d of t, 1H, J=7, 16 Hz), 5.95 (d of t, 1H, J=6, 16 Hz).

General Procedure I. Preparation and Analysis of Allylic Iodides. The Preparation and Analysis of Allylic Iodide 68.

The preparation and analysis of allylic iodide 68 is typical of preparation and analysis of allylic iodides. A freshly prepared solution of 351 mg (2.34 mmol) of freshly recrystallized sodium iodide (from methanol) in 30 mL of THF was added to 415 mg of mesylate 66b in a 50 mL round bottom flask. The mixture was stirred at room temperature for 20 min and then added to 200 mL of diethyl ether. The resultant precipitate was filtered and the filtrate concentrated in vacuo to give crude iodide 68. The concentrate was dissolved in 13 mL of dimethyl formamide and 235 mg (2.82 mmol) of powdered sodium acetate was added. The mixture was stirred at room temperature for 3.5 h and then partitioned between benzene and water. The benzene layer was dried over sodium sulfate and concentrated. The concentrate was dissolved in



deuterated chloroform and analyzed by nmr in the presence of tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium ( $\text{Eu}(\text{fod})_3$ ) to give a 94:6 mixture of acetates 66b and 67b, respectively.

Allylic Iodide 69: Following procedure I, with the exception that the reaction was run for 8 h, a 92:8 mixture of allylic acetates 66b and 67b was obtained.

Cis-Acetoxy Mesylate 70a: Following procedure I, in either THF or acetone as solvent, dimesylate 50 was converted to crude cis-acetoxy mesylate 70a which contained none of the trans isomer: nmr ( $\text{CDCl}_3$ )  $\delta$  2.03 (s,3H), 2.57 (q,2H,J=7 Hz), 2.99 (s,3H), 4.21 (t,2H,J=7 Hz), 4.60 (d,2H,J=6 Hz), 5.50-5.80 (m,2H); ir ( $\text{CHCl}_3$ )  $1725 \text{ cm}^{-1}$ .

Cis-Iodo Acetate 70b: To a solution of 367 mg (1.42 mmol) of dimesylate 50 in 7 mL of dimethyl formamide was added 147 mg (1.75 mmol) of powdered sodium acetate and 21 mg (0.14 mmol) of solid sodium iodide. The mixture was stirred for 4 h at room temperature and partitioned between benzene and water. The benzene layer was dried over sodium sulfate, filtered, and concentrated to afford crude acetoxy mesylate 70a. Crude mesylate 70a was dissolved in 30 mL of acetone and 640 mg (4.27 mmol) of solid sodium iodide was added. The mixture was stirred at reflux for 2.5 h and then added to 200 mL of ethyl ether. The mixture was filtered to afford crude iodo-acetate 70b. Preparative thin layer chromatography with 3:1 hexane:ethyl ether afforded 211 mg (59%) of pure iodo-acetate 70b: nmr ( $\text{CDCl}_3$ )  $\delta$  2.12 (s,3H), 2.57-2.87 (m,2H), 3.13 (q,2H,J=7 Hz), 4.61 (d,2H,J=6 Hz), 5.58 (d of t,1H,

$J=7,10$  Hz), 5.76 (d of t, 1H,  $J=6,10$  Hz); ir ( $\text{CHCl}_3$ )  $1730\text{ cm}^{-1}$ ; mass spectrum (50 eV)  $m/e$  52, 54, 56, 67, 68, 127, 212, 254.

Anal. Calcd for  $\text{C}_7\text{H}_{11}\text{IO}_2$ : C, 33.09; H, 4.36. Found: C, 32.98; H, 4.26.

Trans-Iodo Acetate 70c: To a solution of 368 mg (1.14 mmol) of diiodide 65a in 15 mL of dimethyl formamide at room temperature was added 120 mg (1.42 mmol) of powdered sodium acetate. The mixture was stirred at room temperature for 3.5 h and then partitioned between benzene and water. The benzene layer was dried over sodium sulfate, filtered, and concentrated to give crude iodo acetate 70c. Preparative thin layer chromatography with 1:1 ethyl ether:hexane to give 183 mg (63%) of pure iodo acetate 70c: nmr ( $\text{CDCl}_3$ )  $\delta$  2.07 (s, 3H), 2.47-2.80 (m, 2H), 3.12 (t, 2H,  $J=7$  Hz), 4.57 (d, 2H,  $J=6$  Hz), 5.60-5.83 (m, 2H); ir ( $\text{CHCl}_3$ )  $965\text{ cm}^{-1}$ ,  $1725\text{ cm}^{-1}$ ; mass spectrum (50 eV)  $m/e$  54, 56, 58, 67, 68, 113, 127, 212, 254.

Anal. Calcd for  $\text{C}_7\text{H}_{11}\text{IO}_2$ : C, 33.09; H, 4.36. Found: C, 32.78; H, 4.19.

Sulfide Ketoester 41a: To a solution of 19.71 g (61.2 mmol) of diiodide 65a in 200 mL of THF at  $-78^\circ\text{C}$  was added, via a double ended needle, to a 150 mL solution of the dianion of methyl acetoacetate in THF chilled to  $-78^\circ\text{C}$  (prepared from 7.11 g (61.2 mmol) of methyl acetoacetate by the method of Weiler<sup>76</sup>). The solution was allowed to slowly warm to  $0^\circ\text{C}$  at which time 4.72 g (67.3 mmol) of solid sodium methylmercaptide and 35 mL of HMPA was added. The solution was stirred

at room temperature overnight. The mixture was partitioned between toluene and 5% aqueous hydrochloric acid. The toluene layer was then partitioned between sodium bicarbonate and water. The toluene layer was dried over sodium sulfate, filtered, and concentrated. The concentrate was heated in a Kugelrohr oven at 65°C at 1 mm Hg. MPLC of the residue with 20% Et<sub>2</sub>O-hexane afforded 8.165 g (58%) of sulfide ketoester 41a: nmr (CDCl<sub>3</sub>) δ 2.13 (s,3H), 2.17-2.40 (m,4H), 2.43 (t,2H,J=6 Hz), 2.60 (t,2H,J=6 Hz), 3.44 (s,2H), 3.72 (s,3H), 5.40-5.53 (m,2H); ir (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>, 1740 cm<sup>-1</sup>; mass spectrum 62, 68, 81, 95, 101, 108, 109, 114, 129, 230.

Anal. Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub>S: C, 57.36; H, 7.88. Found: C, 57.31; H, 7.66.

Amino Ketoester 41b: To a solution of 6.001 g (18.6 mmol) of diiodide 65a in 150 mL of THF at -78°C was added, via a double ended needle, a 150 mL solution of methyl acetoacetate in THF chilled to -78°C (prepared from 2.16 g (18.6 mmol) of methyl acetoacetate by the method of Weiler<sup>76</sup>). The mixture was allowed to slowly warm to 0°C and then 13 mL (186 mmol) of chilled, anhydrous dimethylamine was added. The solution was stirred at 0°C overnight and partitioned between toluene and saturated aqueous sodium bicarbonate. The toluene layer was dried over sodium sulfate, filtered, and concentrated to give crude amino ketoester 41b. MPLC with 0.6% NH<sub>3</sub> (aqueous)/5.4% methanol/chloroform afforded 1.946 g (46%) of pure amino ketoester 41b: nmr (CDCl<sub>3</sub>) δ 2.09-2.41 (m,6H), 2.22 (s,6H), 2.49-2.72 (m,2H), 3.43 (s,2H), 3.71 (s,3H), 5.38-5.43 (m,2H); ir (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>, 1740 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>,

2810  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e 58, 67, 69, 110, 134, 154, 196, 227.

Anal. Calcd for  $\text{C}_{12}\text{H}_{21}\text{NO}_3$ : C, 63.41; H, 9.31; N, 6.16. Found: C, 63.34; H, 9.41; N, 6.19.

Sulfide Diester 4lc: To a solution of 3.428 g (10.65 mmol) of diiodide 65a in 100 mL of 10% HMPA-THF at  $-78^\circ\text{C}$  was added 0.7462 g (10.65 mmol) of solid sodium methyl mercaptide. The solution was slowly warmed to  $0$ – $10^\circ\text{C}$ . This solution was added to a solution of sodio dimethyl malonate in THF (prepared by dropwise addition of 4.0 mL (350 mmol) of dimethyl malonate to a suspension of 0.767 g (32.0 mmol) of sodium hydride in 200 mL of THF). The mixture was partitioned between toluene and saturated aqueous sodium bicarbonate. The toluene layer was subsequently partitioned with water. The toluene layer was dried over sodium sulfate, filtered, and concentrated. The concentrate was heated in a Kugelrohr oven at  $60^\circ\text{C}$  at 1 mm Hg. The distillate was discarded and the residue separated by MPLC (20% ethyl ether:hexane) to afford 0.7903 g (31%) of pure sulfide diester 4lc: nmr ( $\text{CDCl}_3$ )  $\delta$  2.00 (s, 3H), 2.07 (m, 4H), 3.03 (d, 2H,  $J=6$  Hz), 3.37 (t, 1H,  $J=7$  Hz), 3.74 (s, 6H), 5.39–5.50 (m, 2H); ir ( $\text{CHCl}_3$ )  $1730\text{ cm}^{-1}$ ; mass spectrum (70 eV) 67, 79, 107, 134, 135, 138, 167, 168, 184, 199, 200, 246.

Anal. Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{S}$ : C, 53.64; H, 7.37. Found: C, 53.59; H, 7.30.

Sulfide Ketoester 4ld: To a solution of 19.23 g (59.7 mmol) of diiodide 65a in 200 mL of 10% HMPA-THF chilled to  $-78^\circ\text{C}$  was added 4.187 g

(59.8 mmol) of solid sodium methyl mercaptide. The solution was allowed to slowly warm to room temperature and then rechilled to  $-78^{\circ}\text{C}$ . To this chilled mixture was added a solution of the dianion of methyl acetoacetate in THF (prepared from 7.63 g (65.7 mmol) of methyl acetoacetate by the method of Weiler<sup>76</sup>). The solution was allowed to slowly warm to room temperature. The mixture was partitioned between toluene and saturated aqueous sodium bicarbonate. The toluene layer was dried over sodium sulfate, filtered, and concentrated. The concentrate was heated in a Kugelrohr oven at  $60^{\circ}\text{C}$  at 1 mm Hg and any distillate was discarded. The residue was separated by MPLC (20% ether-hexane) to afford 6.202 g (45%) of pure sulfide ketoester 41d: nmr ( $\text{CDCl}_3$ )  $\delta$  1.56-1.90 (m, 2H), 2.02 (s, 3H), 2.00-2.23 (m, 2H), 2.56 (t, 2H,  $J=7$  Hz), 3.03 (d, 2H,  $J=6$  Hz), 3.43 (s, 2H), 3.73 (s, 3H), 5.36-5.57 (m, 2H); ir ( $\text{CHCl}_3$ )  $1710\text{ cm}^{-1}$ ,  $1740\text{ cm}^{-1}$ , mass spectrum (70 eV) m/e 56, 61, 63, 67, 68, 70, 80, 81, 82, 102, 105, 106, 109, 110, 132, 150, 151, 165, 183, 212.

Anal. Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_3\text{S}$ : C, 57.36; H, 7.88. Found: C, 57.29; H, 7.71.

Amino Ketoester 41e: Following procedure G, 6.033 g (18.74 mmol) of diiodide 65a was converted to 1.752 g (41%) of 41e after MPLC with 0.7%  $\text{NH}_3(\text{aq})/6.3\%$  methanol/chloroform: nmr ( $\text{CDCl}_3$ )  $\delta$  1.53-1.87 (m, 2H), 1.90-2.17 (m, 2H), 2.22 (s, 6H), 2.53 (t, 2H,  $J=7$  Hz), 2.83 (d, 2H,  $J=6$  Hz), 3.41 (s, 2H), 3.72 (s, 3H), 5.40-5.57 (m, 2H); ir ( $\text{CHCl}_3$ )  $1710\text{ cm}^{-1}$ ,  $1740\text{ cm}^{-1}$ ,  $2770\text{ cm}^{-1}$ ,  $2810\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 68, 72, 83, 110, 196, 227.

Anal. Calcd for  $C_{12}H_{21}NO_3$ : C, 63.41; H, 9.31; N, 6.16. Found: C, 63.82; H, 9.14; N, 6.09.

Amino Diester 4lf: Following procedure E, 19.972 g (62.04 mmol) of diiodide 65a was converted to 7.98 g (53%) of amino diester 4lf after Kugelrohr distillation (110°C at 1 mm Hg): nmr ( $CDCl_3$ )  $\delta$  1.9-2.1 (m,4H), 2.21 (s,6H), 2.89 (d,J=6 Hz), 3.38 (t,1H,J=7 Hz), 3.74 (s,6H), 5.44-5.60 (m,2H); ir ( $CHCl_3$ ) 1725  $cm^{-1}$ , 2770  $cm^{-1}$ , 2810  $cm^{-1}$ ; mass spectrum (70 eV) m/e 68, 83, 85, 98, 99, 110, 113, 212, 243.

Anal. Calcd for  $C_{12}H_{21}NO_4$ : C, 59.24; H, 8.70; N, 5.76. Found: C, 59.25; H, 8.74; N, 5.92.

Amino Diester 4lg: Following procedure E, 12.288 g (38.17 mmol) of diiodide 65b was converted to 5.561 g (59%) of amino diester 4lg after purification by Kugelrohr distillation (120°C at 1 mm Hg): nmr ( $CDCl_3$ )  $\delta$  1.16-1.53 (m,2H), 1.70-2.04 (m,4H), 2.14 (s,6H), 2.78 (d,2H,J=6 Hz), 3.28 (t,1H,J=7 Hz), 3.68 (s,6H), 5.38-5.53 (m,2H); ir ( $CHCl_3$ ) 1725  $cm^{-1}$ , 2770  $cm^{-1}$ , 2810  $cm^{-1}$ ; mass spectrum (70 eV) m/e 85, 99, 126, 226, 257.

Anal. Calcd for  $C_{13}H_{23}NO_4$ : C, 60.68; H, 9.01; N, 5.44. Found: C, 60.45; H, 9.03; N, 5.68.

Amino Ketoester 4lh: Following procedure E with the exception that tert-butyl acetoacetate was used in place of dimethyl malonate 8.426 g (26.17 mmol) of the diiodide 65a was converted to 3.566 g (51%) of amino diester 4lh after MPLC with 0.5%  $NH_3$ (aq)/4.5% methanol/chloroform: nmr ( $CDCl_3$ )  $\delta$  1.48 (s,9H), 1.80-2.10 (m,4H), 2.19 (s,9H), 2.33 (d,2H, J=6 Hz), 3.33 (t,1H,J=7 Hz), 5.43-5.60 (m,2H); ir ( $CHCl_3$ ) 1700  $cm^{-1}$ ,

1720  $\text{cm}^{-1}$ , 2770  $\text{cm}^{-1}$ , 2810  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e 60, 85, 99, 111, 113, 150, 168, 170, 196, 269.

Anal. Calcd for  $\text{C}_{15}\text{H}_{27}\text{NO}_3$ : C, 55.74; H, 5.46; N, 2.17. Found: C, 55.66; H, 5.59; N, 2.11.

General Procedure J. The Intramolecular Carbopalladation of Sulfides.

Palladocycle 73a.

The preparation of palladocycle 73a is typical for the intramolecular carbopalladation of sulfides. To a solution of 108 mg (0.412 mmol) LTP in 5 mL THF at room temperature was added a solution of 101 mg (0.410 mmol) of 41c in 2.5 mL of THF. The color of the initial solution lightened from dark red to light orange. After the addition was complete, stirring was continued for 10 min and 51 mg (0.454 mmol) of powdered potassium tert-butoxide was added. The mixture was stirred at room temperature for 15 h, then partitioned between water and chloroform. The chloroform layer was dried over sodium sulfate and filtered. Concentration gave crude complex 73a. Plug filtration with ethyl acetate gave 85 mg (54%) pure 73a as a yellow oil. The oil could be crystallized after MPLC with ethyl ether and recrystallization by precipitation from methylene chloride with hexane: mp 74–76°C; nmr ( $\text{CDCl}_3$ )  $\delta$  1.2–2.7 (m, 8H), 2.45 (s, 3H), 3.61 (s, 3H), 3.65 (s, 3H); ir ( $\text{CHCl}_3$ ) 1730  $\text{cm}^{-1}$ .

Anal. Calcd for  $(\text{C}_{11}\text{H}_{17}\text{O}_4\text{PdS})_2 \cdot 0.5 (\text{C}_2\text{H}_5)_2\text{O}$ : C, 35.52; H, 4.84. Found: C, 35.25; H, 4.90.

Palladocycle 74a: Following procedure J, cis-sulfide diester 40f (118 mg, 0.479 mmol) was converted to 125 mg (64%) of the etherate of palladocycle 74a after flash chromatography with ethyl ether: mp 78.5-81; nmr ( $\text{CDCl}_3$ )  $\delta$  1.73-3.73 (m, 8H), 2.70 (s), 2.73 (s), 3.85 (s, 6H); ir ( $\text{CHCl}_3$ )  $1725\text{ cm}^{-1}$ .

Anal. Calcd for  $(\text{C}_{11}\text{H}_{17}\text{O}_4\text{PdS})_2 \cdot 0.5(\text{C}_2\text{H}_5)_2\text{O}$ : C, 35.52, H, 4.84.

Found: C, 35.31; H, 4.87.

General Procedure K. Intramolecular Carbopalladation of Amines.

Palladocycle 73b.

The formation of palladocycle 73b is typical for the intramolecular carbopalladation of amines. To a solution of 125 mg (0.477 mmol) of LTP in 5 mL of THF at  $0^\circ\text{C}$  was added a solution of 115 mg (0.473 mmol) of trans-amino diester 41f in 2.5 mL of THF. The color of the initial solution immediately lightened from dark red to light orange. After the addition was complete, stirring was continued for 10 min at  $0^\circ\text{C}$  and 58 mg (0.52 mmol) of powdered potassium tert-butoxide was added. The mixture was stirred at  $0^\circ\text{C}$  for 30 min, then partitioned between water and chloroform. The chloroform layer was dried over sodium sulfate and concentrated to give crude complex 73b. Plug filtration with ethyl acetate, followed by crystallization from ethyl acetate, gave complex 73b poisoned with ethyl acetate. Slow concentration of an ether/hexane solution of these crystals, under a stream of nitrogen, afforded 193 mg (93%) of pure 73b: mp 96.5-98.5 d; nmr ( $\text{CDCl}_3$ )  $\delta$  1.1-1.3 (m, 1H), 1.8-2.7 (m, 7H), 2.73 (s, 3H), 2.80 (s, 3H), 3.66 (s, 3H), 3.73 (s, 3H); ir ( $\text{CHCl}_3$ )  $1725\text{ cm}^{-1}$ .



An analytical sample was prepared by flash chromatography with ethyl ether:

Anal. Calcd for  $(C_{12}H_{20}ClNO_4Pd)_2$ : C, 37.52; H, 5.25; N, 3.65.

Found: C, 37.54; H, 5.11; N, 3.52.

Palladocycle 73c: Following procedure K, with the exception that 319 mg (1.22 mmol) of powdered triphenylphosphine was added and stirred for 10 min prior to work-up, 270 mg (1.11 mmol) of trans-amino diester 41f was converted to 563 mg (79%) of palladocycle 73c after flash chromatography with ethyl ether: mp 147.5–148.5 d; nmr ( $CDCl_3$ )  $\delta$  0.50–0.87 (m, 2H), 1.50–3.0 (m, 6H), 2.87 (s, 6H), 3.57 (s, 6H), 7.20–7.49 (m, 9H), 7.49–7.80 (m, 6H); ir ( $CHCl_3$ )  $1725\text{ cm}^{-1}$ .

Anal. Calcd for  $C_{30}H_{35}ClNO_4PPd$ : C, 55.74; H, 5.46; N, 2.17.

Found: C, 55.66; H, 5.59; N, 2.11.

Palladocycle 74b: According to procedure K, 108 mg (0.444 mmol) of cis-amino diester 40a was converted to 141 mg (90%) of palladocycle 74b: mp 151.5–153.5 d; nmr ( $CDCl_3$ )  $\delta$  1.55–3.50 (m, 8H), 2.39 (s, 3H), 2.88 (s, 3H), 3.80 (s, 6H); ir ( $CHCl_3$ )  $1725\text{ cm}^{-1}$ .

An analytical sample was prepared by flash chromatography with ethyl ether.

Anal. Calcd for  $(C_{12}H_{20}ClNO_4Pd)_2$ : C, 37.52; H, 5.25; N, 3.65.

Found: C, 37.68; H, 5.32; N, 3.58.

Palladocycle 74c: Following procedure K, with the exception that 285 mg (1.09 mmol) of powdered triphenylphosphine was added and stirred for 10 minutes prior to work-up, 240 mg (0.986 mmol) of cis-amino diester

40a was converted to 516 mg (81%) of palladocycle 74c after flash chromatography with ethyl ether: mp 155.5–157 d; nmr (CDCl<sub>3</sub>) δ 0.61–0.88 (m, 1H), 1.48–2.03 (m, 3H), 2.80 (d, 3H, J=3 Hz), 2.93 (s, 3H), 3.63 (s, 3H), 3.71 (s, 3H), 7.20–7.49 (m, 9H), 7.49–7.80 (m, 6H); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>.

Anal. Calcd for C<sub>30</sub>H<sub>35</sub>ClNO<sub>4</sub>PPd: C, 55.74; H, 5.46; N, 2.17.

Found: C, 55.88; H, 5.59; N, 2.13.

General Procedure L. Formation of Carbocyclic Sulfides via Carbopalladation-Sodium Borohydride Reduction. Cyclopentane 75a from trans-Sulfide Diester 40f.

The preparation of cyclopentane 75a is typical for the formation of carbocyclic sulfides. Following procedure J, palladocycle 73a was prepared in situ from 100 mg (0.405 mmol) of trans-sulfide diester 40f. To this solution was added 153 mg (4.04 mmol) of powdered sodium borohydride, followed by 1 mL of methanol. After stirring 1 h, the mixture was partitioned between 1 N aqueous hydrochloric acid and ethyl ether. The ether layers were dried over sodium sulfate and concentrated to give crude cyclopentane 75a. Kugelrohr distillation (100°C at 1 mm Hg) afforded 71 mg (71%) of pure cyclopentane 75a: nmr (CDCl<sub>3</sub>) δ 1.00–3.73 (m, 9H), 1.93 (s, 3H), 3.51 (s, 3H), 3.53 (s, 3H); ir (CHCl<sub>3</sub>) 1720 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 67, 68, 69, 76, 78, 80, 84, 86, 99, 106, 112, 126, 131, 136, 137, 138, 144, 153, 166, 167, 198, 199, 215, 246.

Anal. Calcd for C<sub>11</sub>H<sub>8</sub>O<sub>4</sub>S: C, 53.64; H, 7.37. Found: C, 54.07; H, 7.68.

Cyclopentane 74a from cis-Sulfide Diester 40f: Following procedure L, 108 mg (0.438 mmol) of cis-sulfide diester 40f was converted to 73 mg (68%) of cyclopentane 75a after Kugelrohr distillation. The cyclopentane 75a obtained from cis-sulfide diester 40f was spectroscopically and chromatographically identical to that obtained from trans-sulfide diester 41c.

General Procedure M. Formation of Carbocyclic Amines via Carbopalladation-Hydrogenation. Cyclopentane 75b from trans-Amino Diester 41f.

The formation of cyclopentane 75b is typical for the formation of carbocyclic amines. Following procedure K, palladocycle 73b was prepared in situ from 106 mg (0.436 mmol) of trans amino diester 41f. Hydrogen was bubbled through the solution at 0°C for 1 h. The solution was partitioned between ether and saturated sodium bicarbonate. The combined ether layers were dried over sodium sulfate and concentrated to give crude cyclopentane 75b. Kugelrohr distillation of the crude material (100°C at 1 mm Hg) gave 101 mg (95%) pure 3b: nmr (CDCl<sub>3</sub>) δ 1.21-2.54 (m,8H), 2.20 (s,6H), 2.64-2.97 (m,1H), 3.64 (s,3H), 3.71 (s,3H); ir (CHCl<sub>3</sub>) 1720 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum 58, 84, 212, 243.

Anal. Calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub>: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.06; H, 8.77; N, 5.65.

Cyclopentane 75b from cis-Amino Diester 40a: With the exception of the addition of 1 mL of methanol prior to hydrogenation, procedure M was followed to convert 99 mg (0.407 mmol) of amino diester 40a to 92 mg

(93%) of cyclopentane 75b after Kugelrohr distillation. The product from 40a is spectroscopically and chromatographically identical to that obtained from 41f.

Cyclopentane 77: Following procedure M, 100 mg (0.371 mmol) of amino ketoester 41h was converted to 86 mg (86%) of cyclopentane 77 as a pair of diastereomers: nmr (CDCl<sub>3</sub>)  $\delta$  1.20–2.26 (m,8H), 1.48 (s,9H), 2.14 (s,6H), 2.23 (s,3H), 2.5–3.0 (m,1H); ir 1705 cm<sup>-1</sup>, 2760 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 84, 109, 169, 171, 197, 213, 269.

Anal. Calcd for C<sub>14</sub>H<sub>27</sub>NO<sub>3</sub>: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.94; H, 10.35; N, 5.10.

Cyclopentane 78: Following procedure M, 114 mg (0.420 mmol) of amino diester 40h was converted to 91 mg (80%) of cyclopentane 78 after Kugelrohr distillation (120°C at 1 mm Hg): nmr (CDCl<sub>3</sub>)  $\delta$  0.90–2.80 (m,12H), 2.20 (s,6H), 3.70 (s,3H), 3.75 (s,3H); ir (CHCl<sub>3</sub>) 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 132, 140, 212, 241, 271.174. Calcd for C<sub>14</sub>H<sub>25</sub>NO<sub>4</sub>. 271.177.

Cyclohexane 79 from trans-Amino Diester 41g: Procedure M was followed with the exception that 250 mg of Molecular Sieve 4Å was added prior to the addition of amino diester 41g. By this method, 104 mg (0.404 mmol) of trans-amino diester 41g was converted to 95 mg (91%) of cyclohexane 79 after Kugelrohr distillation (110°C at 1 mm Hg): nmr (CDCl<sub>3</sub>)  $\delta$  1.10–2.70 (m,11H), 2.22 (s,6H), 3.67 (s,3H), 3.70 (s,3H); ir 1725 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) 58, 61, 194, 198, 226, 257.

Anal. Calcd for  $C_{13}H_{23}NO_4$ : C, 60.68; H, 9.01; N, 5.44. Found: C, 60.53; H, 9.25; N, 5.36.

Cyclohexane 79 from cis-Amino Diester 40b: Procedure M was followed with the exception that 250 mg of Molecular Sieve  $4\text{\AA}$  was added, prior to the addition of the cis-amino diester 40b. In this way, 109 mg (0.424 mmol) of cis-amino diester 40b was converted to 97 mg (89%) of cyclohexane 79 after Kugelrohr distillation. The cyclohexane 79 obtained from cis-amino diester was chromatographically and spectroscopically identical to that obtained from trans-amino diester 41g.

General Procedure N. Formation of Carbocyclic Aldehydes via Carbopalladation-Hydrolysis. Cyclohexane 80 from trans-Amino Diester 41a.

The formation of cyclohexane 80 from trans-amino diester 41g is typical of the formation of carbocyclic aldehydes. The initial palladocycle 81 was formed from 103 mg (0.400 mmol) of the trans-amino diester 41g following procedure I. The mixture was then stirred at room temperature for 6 h. The solution rapidly blackens upon warming. The intermediate imminium salt was hydrolyzed by addition of 5 mL of 1 M aqueous acetic acid and stirring for 0.5 h.

The mixture was partitioned between ethyl ether and water. Exhaustive extraction of the aqueous layer, followed by drying over sodium sulfate, gave a crude yellow ether solution of cyclohexane 80.

Crude cyclohexane 80 was obtained by hydrogenating the crude ether solution to reduce any remaining soluble palladium salts, filtering through celite, and concentration. Kugelrohr distillation ( $110^\circ\text{C}$  at

1 mm Hg) afforded 85 mg (94%) of pure cyclohexane 80: nmr ( $\text{CDCl}_3$ )  $\delta$  1.2-3.2 (m,9H), 3.80 (s,6H), 9.77 (d,1H,J=2 Hz); ir ( $\text{CHCl}_3$ )  $1725\text{ cm}^{-1}$ ; mass spectrum (50 eV) 53, 59, 66, 79, 81, 113, 132, 145, 153, 169, 196.

Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}_5$ : C, 57.89; H, 7.07. Found: C, 58.23; H, 7.32.

Cyclohexane 80 from cis-Amino Diester 40b: Following procedure N, 103 mg (0.400 mmol) of cis-amino diester 40b was converted to 66 mg (72%) of cyclohexane 80. The cyclohexane 80 obtained from cis-amino diester 40b was chromatographically and spectroscopically identical to that obtained from trans-amino diester 41f.

Cycloheptane 84: Procedure M was followed with the exception that 250 mg Molecular Sieve  $4\text{\AA}$  was added prior to the addition of the amino diester 40c. The solution was stirred 1 h prior to hydrogenation. In this manner, 103 mg (0.382 mmol) of amino diester 40c was converted to 73 mg (71%) of cycloheptane 84 after Kugelrohr distillation ( $120^\circ\text{C}$  at 1 mm Hg): nmr ( $\text{CDCl}_3$ )  $\delta$  1.2-2.9 (m,13H), 2.20 (s,6H), 3.74 (s,6H); ir ( $\text{CHCl}_3$ )  $1730\text{ cm}^{-1}$ ;  $2770\text{ cm}^{-1}$ ,  $2810\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 58, 59, 212, 240, 271.

Anal. Calcd for  $\text{C}_{14}\text{H}_{25}\text{NO}_4$ : C, 61.97; H, 9.29; N, 5.16. Found: C, 61.92; H, 9.50; N, 5.05.

Cycloheptane 85: Procedure N was followed to convert 113 mg (0.420 mmol) of amino diester 40c to 71 mg (70%) of cycloheptane 85 after Kugelrohr distillation ( $120^\circ\text{C}$  at 1 mm Hg): nmr ( $\text{CDCl}_3$ )  $\delta$  1.20-3.0 (m,11H), 3.68 (s,3H), 3.70 (s,3H), 9.79 (d,1H,J=2 Hz); ir ( $\text{CHCl}_3$ )

1720  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e 79, 80, 81, 93, 95, 113, 122, 123, 132, 139, 145, 150, 151, 183, 200, 212, 215, 242.113. Calcd for  $\text{C}_{12}\text{H}_{18}\text{O}_5$ : 242.115.

General Procedure 0. Formation of Cyclic Ketoesters Via Carbopallada-  
tion-Hydrogenation. Preparation of Cyclohexanone 86.

To a solution of 129 mg (0.477 mmol) of LTP in 8 mL of 1:1 methylene chloride:THF was added 250 mg Molecular Sieve  $4\text{\AA}$  at room temperature. To this mixture was added 105 mg (0.492 mmol) of amino ketoester 40e in 2 mL of 1:1 methylene chloride:THF. After the addition was complete, stirring was continued for 10 min at room temperature and 61 mg of powdered potassium tert-butoxide was added. The mixture was stirred for 1.5 h at room temperature, at which time 1 mL of methane was added and hydrogen bubbled through the mixture for 1.5 h. The solution was immediately placed on an MPLC column and chromatographed with 0.7% aqueous ammonia/6.3% methanol/chloroform to afford 37 mg (35%) of pure cyclohexanone 86: nmr ( $\text{CDCl}_3$ )  $\delta$  1.20-1.87 (m,3H), 1.90-3.40 (m,6H), 2.27 (s,6H), 3.67 (s,3H), 6.20 (s,very broad, 1H); ir ( $\text{CHCl}_3$ ) 1600  $\text{cm}^{-1}$ , 1645  $\text{cm}^{-1}$ , 2770  $\text{cm}^{-1}$ , 2810  $\text{cm}^{-1}$ ; mass spectrum (70 eV) m/e 81, 84, 85, 93, 94, 97, 122, 152, 153, 154, 155, 213.139. Calcd for  $\text{C}_{11}\text{H}_{19}\text{NO}_3$ : 213.136.

Cycloheptanone 87: Following procedure 0, 108 mg (0.475 mmol) of amino ketoester 41e was converted to 70 mg (65%) of cycloheptanone 87: nmr

(CDCl<sub>3</sub>)  $\delta$  1.17–2.03 (m,5H), 2.07–3.00 (m,7H), 2.20 (s,5.4H), 2.25 (s,0.6H), 3.07–3.60 (m,1H), 3.69 (s,0.3H), 3.75 (s,2.7H); ir (CHCl<sub>3</sub>) 1600 cm<sup>-1</sup>, 1640 cm<sup>-1</sup>, 1705 cm<sup>-1</sup>, 1735 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 72, 122, 125, 151, 197, 200, 227.145. Calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>3</sub>: 227.151.

Attempted Intramolecular Carbopalladation of Sulfide Ketoester 4ld:

Following procedure A, 100 mg of sulfide ketoester failed to cyclize. TLC and <sup>1</sup>H NMR indicated the presence of starting olefin complex only, even after 1 month at room temperature.

Cyclopentanone 88: Following procedure O, with the exception that the reaction was stirred for 3 h, 145 mg (0.638 mmol) of amino ketoester 4lb was converted to 92 mg (64%) of cyclopentanone 88 after two passes through the chromatography column with 0.7% aqueous ammonia/6.3% methanol/chloroform: nmr (CDCl<sub>3</sub>)  $\delta$  1.20–1.87 (m,6H), 1.90–3.70 (m,5H), 2.23 (s,6H), 3.67 (s,3H), 6.07 (broad s,1H); ir (CHCl<sub>3</sub>) 1615 cm<sup>-1</sup>, 1660 cm<sup>-1</sup>, 1700 cm<sup>-1</sup>, 1745 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>, 3325 cm<sup>-1</sup>, 3475 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 83, 97, 114, 156, 196, 227.145. Calcd for C<sub>12</sub>H<sub>21</sub>NO<sub>3</sub>: 227.151.

Carbonalladation of Sulfide Ketoester 4la. Formation of Cyclohexanone

90: Following procedure A, with the exception that the reaction was run for 36 h, 159 mg (0.690 mmol) of sulfide ketoester was converted to 50 mg (40%) of cyclohexanone 90 after trituration with ethyl ether: <sup>1</sup>H nmr (CDCl<sub>3</sub>) 1.90–2.13 (m,2H), 2.40–2.70 (m,4H), 3.87 (s,3H), 5.59 (d,1H,J=10 Hz), 5.88 (d,1H,J=16 Hz), 6.63 (d of d,1H,J=10,16 Hz);



$^{13}\text{C}$  nmr ( $\text{CDCl}_3$ ) ppm 21.4, 24.4, 37.4, 52.4, 123.8, 133.0, 134.1, 153.1, 167.0, 195.9; ir ( $\text{CHCl}_3$ )  $1660\text{ cm}^{-1}$ ,  $1730\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 51, 53, 55, 59, 63, 65, 66, 77, 79, 91, 92, 93, 94, 118, 122, 124, 149, 180.073. Calcd for  $\text{C}_{10}\text{H}_{12}\text{O}_3$ : 180.078

Cyclohexanone 91: Following procedure O, with the exception that the reaction only required 20 min, 93 mg (0.385 mmol) of amino ketoester 40i was converted to 92 mg (98%) of cyclohexanone 90: nmr ( $\text{CDCl}_3$ )  $\delta$  1.11-1.90 (m,6H), 2.15-2.61 (m,4H), 2.22 (s,2.9H), 2.29(s,3.1H), 2.61-4.05 (m,2.6H), 3.65 (s,1.65H), 3.77 (s,1.45H), 6.10 (broad,0.4H); ir ( $\text{CHCl}_3$ )  $1600\text{ cm}^{-1}$ ,  $1645\text{ cm}^{-1}$ ,  $1710\text{ cm}^{-1}$ ,  $1735\text{ cm}^{-1}$ ,  $2770\text{ cm}^{-1}$ ,  $2810\text{ cm}^{-1}$ ,  $3325\text{ cm}^{-1}$ ,  $3475\text{ cm}^{-1}$ ; mass spectrum (70 eV) m/e 58, 73, 84, 122, 136, 155, 168, 169, 211, 214, 241.163. Calcd for  $\text{C}_{13}\text{H}_{23}\text{NO}_3$ : 241.167.

Attempted Carbopalladation of 40d: Procedure M was followed with the exception that the solution was diluted to 0.01 M in amino diester 40d and molecular sieve  $4\text{\AA}$  was added prior to the addition of the amino diester. In this way an attempt was made to cyclize 157 mg of amino diester 40d. Gas chromatographic analysis after reduction of a small aliquot of the reaction mixture failed to show even traces of a new product until the solution had been stirred for 48 h at room temperature. Within 2 wks at room temperature the starting material was completely consumed. TLC analysis of the reduced reaction mixture revealed a minimum of 9 major materials.

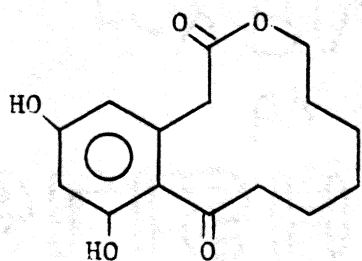
Attempted Carbopalladation of Amino Ketoester 40e: Procedure 0 was followed with the exception that the solution was diluted to 0.01 M in amino ketoester 40e. TLC analysis showed that the starting material was completely consumed in ca 1 wk. Reduction with hydrogen, as in procedure 0, revealed at least 9 major products.

PART II

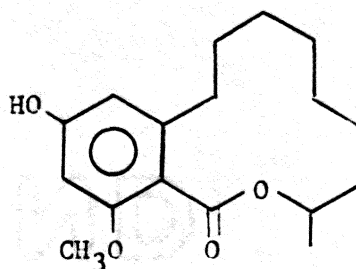
PALLADIUM MEDIATED FORMATION OF MACROCYCLIC  
SYSTEMS VIA INSERTION REACTIONS

## Chapter 1. Introduction

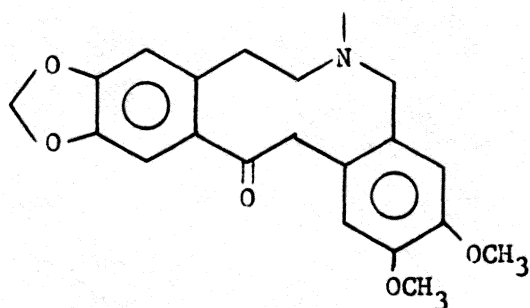
An assortment of natural products which possess useful pharmacological properties contain macrocyclic rings.<sup>79,80</sup> The synthesis of these large ring systems has presented an ongoing challenge to the organic chemist and has been the subject of recent reviews.<sup>81</sup> It was the pursuit of some of these macrocycles, in particular, curvularin (91),<sup>81</sup> lasiodiplodin (92),<sup>82</sup> fagarine (93),<sup>83</sup> and zearalanone (94)<sup>84</sup> which prompted our investigations into the possibility of utilizing either olefin insertions or carbon monoxide insertions into the carbon-palladium bond of aryl palladium complexes to construct macrocyclic ring systems.



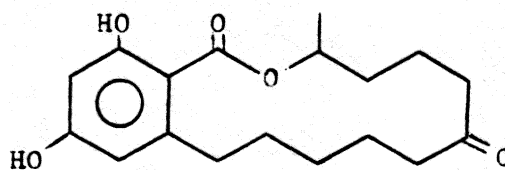
Curvularin (91)



Lasiodiplodin (92)



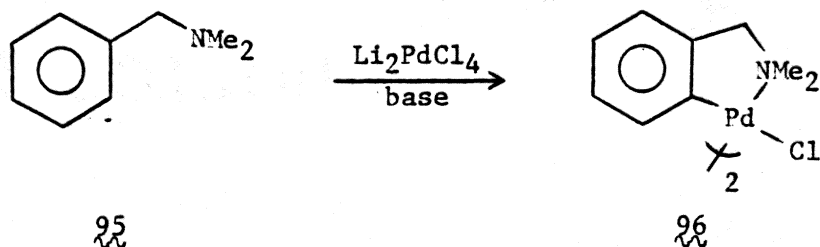
Fagarine (93)



Zearalanone (94)

Palladium mediated macrocyclizations have been reported in only one series of examples. These examples have used palladium(0) catalyzed allylic acetate displacements and have been discussed in detail in Part I, Chapter I, of this thesis.

Tertiary benzylic amine complexes have been used to control the regiochemistry of insertion reactions in a number of examples.<sup>29,37a,85,86</sup> Initially, a palladocycle is formed by the simple addition of salt of a palladium (II) and a tertiary amine base to a benzylic amine. The reaction, termed orthopalladation, yields air and room temperature stable palladium complexes. The formation of palladocycle **96** from *N,N*-dimethylbenzylamine (**95**) is an example.<sup>29a,74</sup>



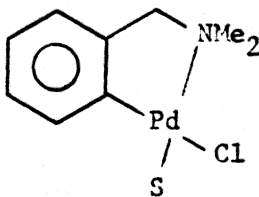
Once these palladocycles are formed, they can undergo insertion reactions with olefins<sup>29,86,81-90</sup> or carbon monoxide.<sup>37a</sup>

Olefin insertions on palladium complexes, referred to as Heck reactions, have been carried out catalytically using unstabilized palladium complexes. These unstabilized palladium complexes were formed in situ from organomercury, organolead, and organotin reagents.<sup>87,88</sup> Heck reactions have also been performed on aryl halides<sup>89</sup> and a variety of non-halogenated aromatic systems.<sup>89</sup>

Ligand stabilized complexes, such as **96**, have been shown to

undergo Heck reactions as well. However, the number of olefins successfully inserted into these complexes has been limited to styrene,<sup>90</sup>  $\alpha,\beta$ -unsaturated ketones,<sup>29a</sup> and acrylates.<sup>29b,e</sup> Prior to this work, only  $\alpha,\beta$ -unsaturated ketones had been shown to insert satisfactorily. As the next chapter will demonstrate, acrylates can also be coupled in high yield but only under rather stringent conditions.

The Heck reaction with ligand stabilized complexes, such as 96, might be envisioned as proceeding through two potential mechanisms (See Scheme X). The two mechanisms differ in the coordination number about palladium prior to the transfer of the aryl moiety to the coordinated olefin. The formation of intermediate complex 100 might proceed through either an intermediate resembling 97 or by initial solvent mediated dissociation of complex 96 to yield complex 101. Subsequent substitution of complex 101 by the olefin would yield intermediate 100.



S = solvent

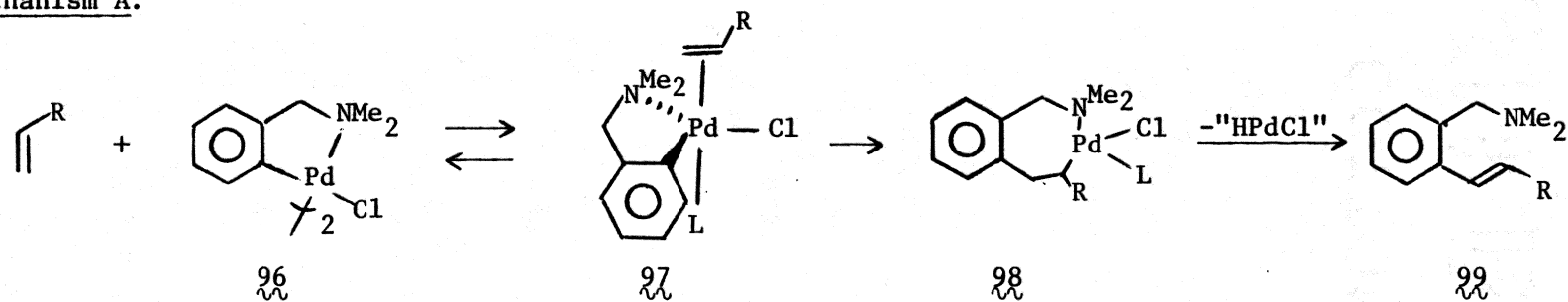
101

The literature holds only one hint as to which of these mechanisms is operative. When the triphenylphosphine complex 102 was treated with methyl vinyl ketone the reaction was observed to proceed at a rate similar to that observed with palladocycle 96. However, the addition of a second equivalent of triphenylphosphine significantly retarded

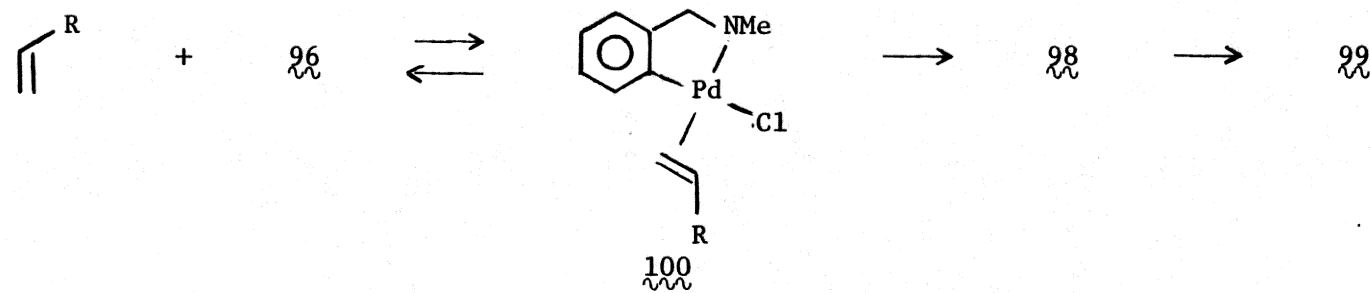
Scheme X

Potential Mechanistic Pathways of Olefin Insertion

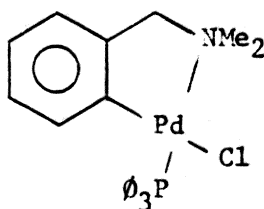
Mechanism A.



Mechanism B.



the reaction.<sup>29a,91</sup>



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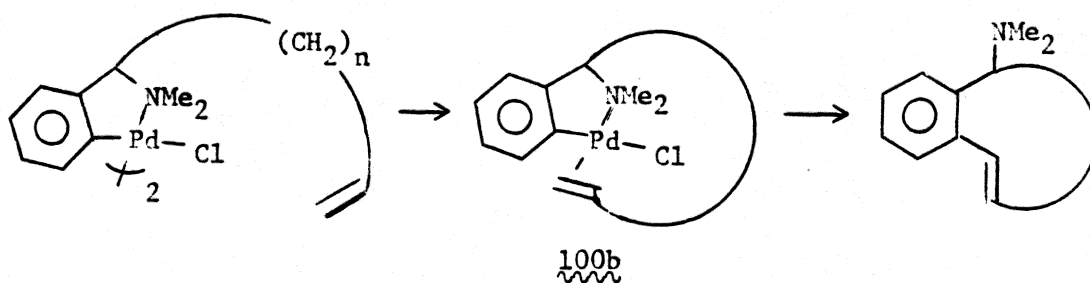
These findings might support Mechanism A. Since the reaction of methyl vinyl ketone is significantly retarded by the addition of triphenylphosphine, it would appear that methyl vinyl ketone is not particularly competitive with triphenylphosphine as a ligand. Thus, if Mechanism A is examined, it would appear that triphenylphosphine inhibits the reaction by occupying the apical site in preference to methyl vinyl ketone.

However, Mechanism B cannot be ruled out as a possibility. If methyl vinyl ketone is competitive with triphenylphosphine as a ligand, Mechanism B could still be consistent with these results. If the intermediate complex 100 is reached by initial solvent mediated dissociation of the complex to a solvated complex such as 101, the addition of extra triphenylphosphine would be expected to inhibit the reaction by competing with the olefin for the coordination site occupied by the solvent in complex 101. In the absence of any quantitative data, both mechanisms must be considered plausible.

These two mechanisms would have quite different implications for the synthesis of macrocyclic systems. Macrocycles might be formed by attachment of an appropriately functionalized side chain to the benzylic



position in tertiary benzylic amine complexes. If Mechanism B is operative, the side chain would have to be of sufficient length to traverse the  $180^\circ$  angle imposed by the square planar complex. Thus, if the macrocyclic olefin complex 100b were to undergo a subsequent insertion reaction, it would have to form a macrocycle. This hypothesis is demonstrated below. However, if Mechanism A is operative, the



formation of macrocycles would not be expected to be favored over intermolecular reactions. Instead, the reaction would be of greater utility in the formation of smaller rings.

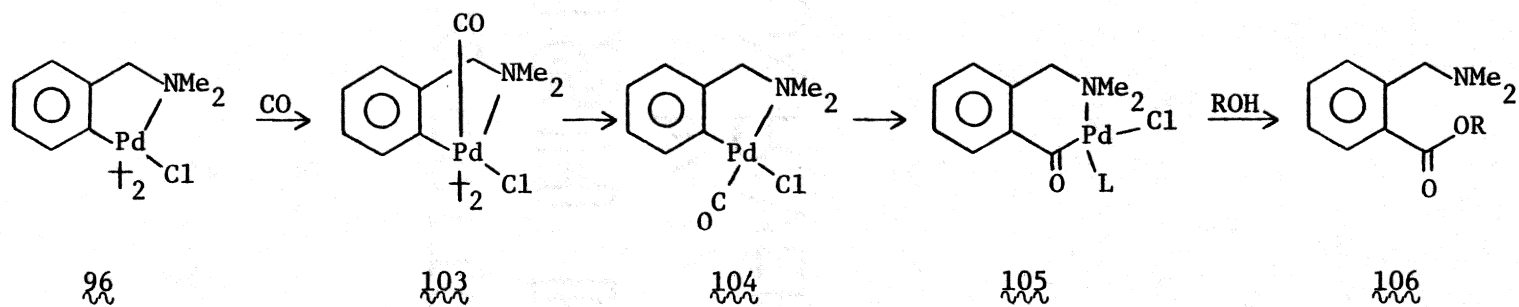
The previous examples of palladium mediated cyclizations employing olefin insertions are of little assistance in predicting the success of this approach. All the examples in Part I, Chapter I, of this thesis possess an olefin ligand which is cis to the organic moiety undergoing insertion.

The use of carbon monoxide insertion to form macrocycles rests on somewhat more precarious grounds. There are two possible mechanisms for the formation of esters and lactones via carbon monoxide insertions. Both have considerable corroboration in experiment.

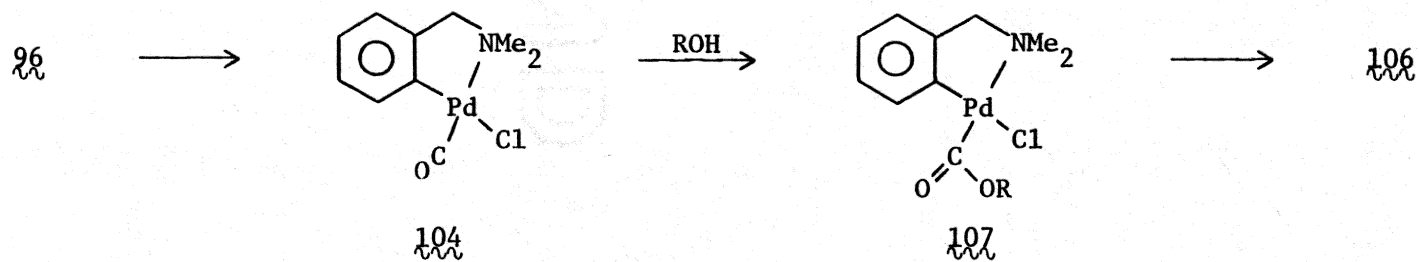
Scheme XI

Mechanisms For the Formation of Esters Via Carbonylation

Mechanism C.

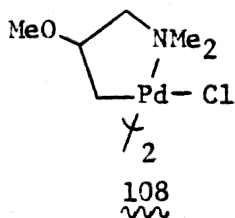


Mechanism D.



The first, and most probable mechanism, is Mechanism C.

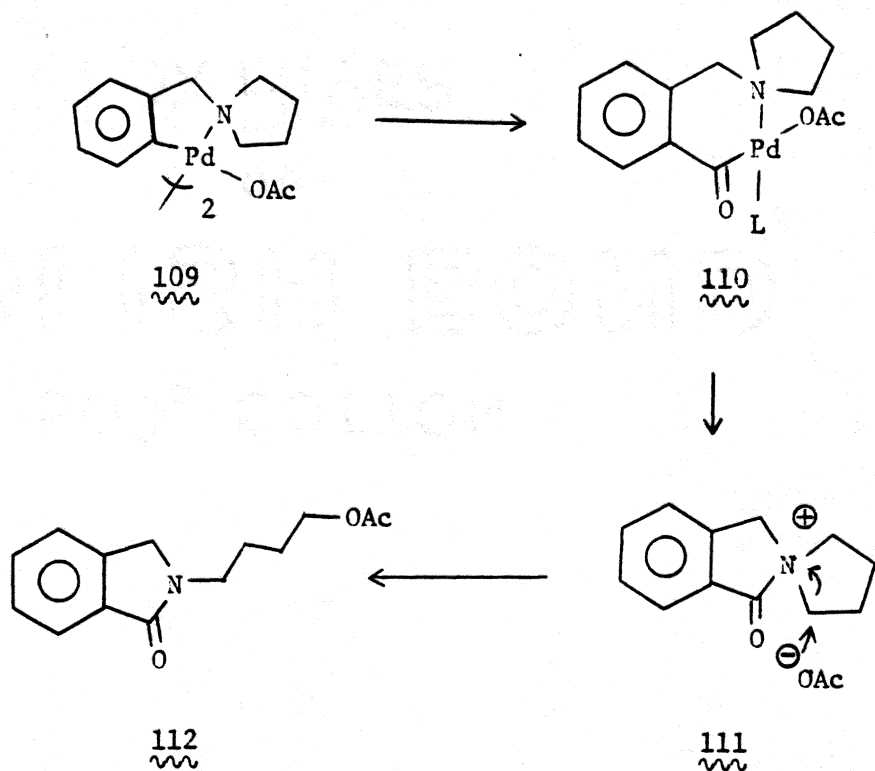
Medeema, et. al.<sup>56</sup> have proposed Mechanism C based on the observation of three distinct carbonyl frequencies in the carbonylation of 108.



They have assigned these frequencies to intermediates resembling 103, 104, and 106. In the same paper, Medeema, et. al. observed the uptake of a second equivalent of carbon monoxide. This observation implied that the ligand in intermediate 105 is carbon monoxide, and the transfer of the organic ligand to carbon monoxide is promoted by the coordination of a second carbon monoxide ligand in the apical position.

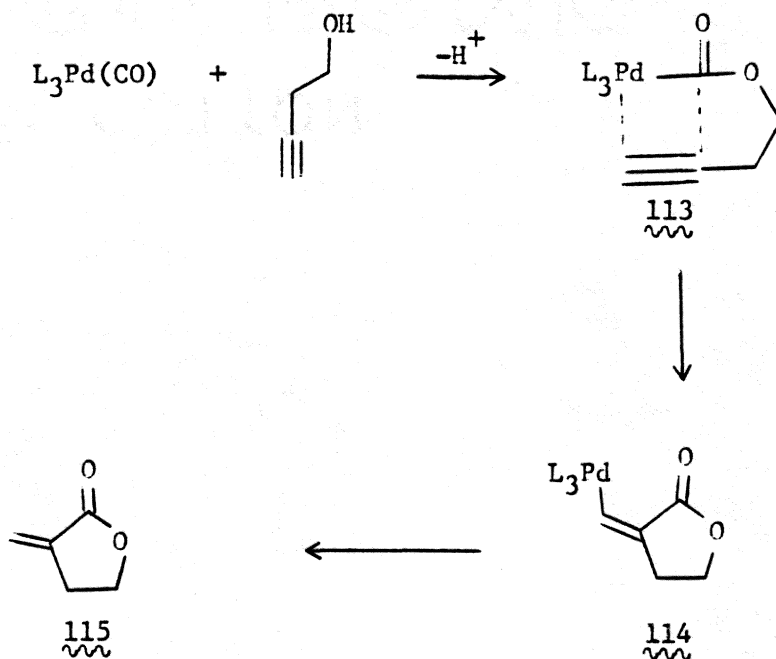
The reaction probably does not involve the transfer of the organic moiety to the apical carbon monoxide. The addition of one equivalent of a phosphine after one equivalent of carbon monoxide has been absorbed leads to the same products. This implies that a second strong ligand is all that is required to drive the insertion.

In further support of Mechanism C are carbonylations carried out in the absence of an alcohol.<sup>37</sup> Complex 109 was carbonylated in xylene to give lactam 112. Apparently, the formation of lactams from benzyl amine



complexes proceeds through an acyl-palladium complex such as 110. This would support Mechanism C.

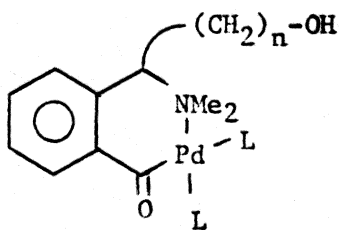
Several groups have proposed Mechanism D.<sup>92</sup> For example, the conversion of 3-buten-1-ol to  $\alpha$ -methylene lactone 115 has been extensively studied by Norton and co-workers.<sup>39e</sup> The mechanism appears to proceed as shown below. The mechanism proposed by Norton and co-workers is fairly well substantiated by experiment. Each of the intermediates 113 and 114 have been independently synthesized, isolated and demonstrated to yield  $\alpha$ -methylene lactone 115.



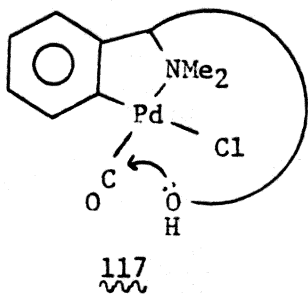
All the experiments supporting Mechanism D pertain to unstabilized complexes and are related to the  $\alpha$ -methylene lactone synthesis. It is possible that the mechanisms for carbonylation of ligand stabilized complexes and insertions into unstabilized complexes might be different.

The implications of Mechanisms C and D toward the prospects of successfully synthesizing macrocycles are quite different. If Mechanism C is operative, the prospects of forming a macrocyclic system via carbonylation are dim. The acylpalladium intermediate **116** could collapse to a lactam in a manner similar to the formation of lactam **112**. If the intermediate **116** is to favor lactonization, it would require the alcohol to coordinate to palladium and then transfer to the acyl moiety. Since neutral oxygen is generally a poor ligand to palladium,<sup>93</sup> this is highly unlikely. Instead, if intermediate **116** is formed, the

reaction should resemble lactonizations with acyl halides.



The prospects are somewhat better if Mechanism D is operative. As in the olefin insertion, if the alcohol is to act as a nucleophile with a carbon monoxide ligand coordinated cis to the aryl moiety, a long chain would be required in order to traverse the  $180^\circ$  angle imposed by the square planar complex. This would favor a macrolactonization.



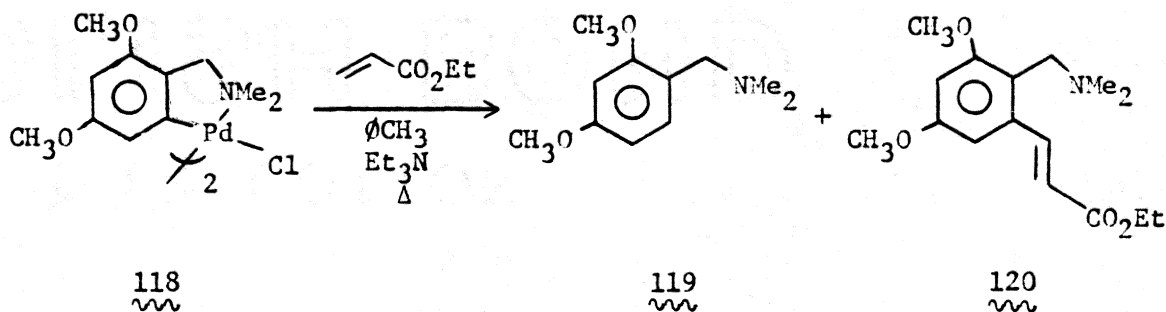
As in the olefin coupling, it is possible that an apically bound carbon monoxide ligand may be the reactive ligand. If this is true, the carbon monoxide insertion would favor smaller rings and intermolecular reactions over macrolactonizations.

In summary, the possibility of using insertion reactions to form macrocycles has a reasonably sound theoretical basis. However, a number of potential hazards exist.

## Chapter 2. Results and Discussion

The methodology involved in the coupling of olefins to ligand stabilized aryl palladium complexes was not satisfactory at the outset of this work. In order to maximize the chances of successfully performing macrocyclizations, it became apparent that some preliminary studies on this reaction would be required. These studies would be directed toward the optimization of yields by varying conditions for the coupling of olefinic moieties with aryl palladium complexes. This prompted an investigation into the coupling of ethyl acrylate with aryl palladium complexes.

Unlike the coupling with vinyl ketones, which proceeded smoothly and in high yield under a variety of conditions,<sup>29a</sup> the coupling with ethyl acrylate proved to be much more sluggish and considerably more sensitive to conditions. Whereas methyl vinyl ketone readily couples with benzylic amine complexes in refluxing benzene or toluene in the presence of triethylamine,<sup>29a</sup> ethyl acrylate gives a mixture of depalladated benzylic amine and cinnamates. For example, benzylic amine complex 118 gives amine 119 and cinnamate 120 in a 60:40 ratio.



The effects of solvent and base on the conversion of complex 118 to cinnamate 120 were studied. These efforts were directed toward maximizing the production of cinnamate 120 in preference to amine 119. The results of this study appear in Table 8.

The reaction is fairly insensitive to solvent polarity. The reaction is also insensitive to base concentration (entry 3). However, the effectiveness of certain bases is dependent on solvent. Whereas in toluene the addition of sodium carbonate holds no advantage over triethylamine (entries 2 and 5), in dimethylformamide (DMF) coupling is favored with sodium carbonate as base (entry 9). In DMF there is a notable cation effect with carbonate bases (entries 8-10).

The coupling in acetic acid (entry 16) is the most interesting reaction in Table 8. The reaction proceeded at a significantly increased rate at a somewhat lower temperature. The reaction gives cinnamate 120 in 90% isolated yield without any traces of amine 119. Entries 17 through 20 indicate the reaction is not catalytic in acetic acid, nor is it acid catalyzed. The acceleration cannot be attributed to a base change from amine to amino acetate. Sodium acetate in a mixture of DMF-dichloroethane (entry 14) fails to accelerate the reaction and leads completely to the production of benzylic amine 119 as the sole product by NMR analysis.

The observation of a rate enhancement for insertions in acetic acid was not unique to the acrylate system. The literature indicates that acetic acid is helpful in vinyl ketone couplings as well.<sup>29a</sup> Whereas methyl vinyl ketone readily couples with complex 96 over 4 h



Table 8

Coupling of Ethyl Acrylate With Complex  $85^{a,b}$ 

| <u>Entry No.</u> | <u>Solvent</u>                                                             | <u>Time</u> | <u>Temperature</u> | <u>Base(equiv.)</u>                           | <u>Ratio of</u><br><u>119:120</u><br><u>wt. wt.</u> |
|------------------|----------------------------------------------------------------------------|-------------|--------------------|-----------------------------------------------|-----------------------------------------------------|
| 1                | Benzene                                                                    | 5 days      | reflux             | Et <sub>3</sub> N(5)                          | c                                                   |
| 2                | Toluene                                                                    | 16 h        | reflux             | Et <sub>3</sub> N(5)                          | 60:40                                               |
| 3                | Toluene                                                                    | 22 h        | reflux             | Et <sub>3</sub> N(1.1)                        | 68:32                                               |
| 4                | Toluene                                                                    | 15 h        | reflux             | tBuOK(5)                                      | 100:0                                               |
| 5                | Toluene                                                                    | 15 h        | reflux             | Na <sub>2</sub> CO <sub>3</sub>               | 57:43                                               |
| 6                | Toluene                                                                    | 15 h        | reflux             | 2,4,6-tri-<br>t-butyl-pyridine(5)             | 83:17                                               |
| 7                | CH <sub>3</sub> CN                                                         | 38 h        | reflux             | Et <sub>3</sub> N(5)                          | 71:29                                               |
| 8                | DMF                                                                        | 17 h        | 109-111°C          | Li <sub>2</sub> CO <sub>3</sub> (5)           | 62:38                                               |
| 9                | DMF                                                                        | 17 h        | 109-111°C          | Na <sub>2</sub> CO <sub>3</sub> (5)           | 37:63                                               |
| 10               | DMF                                                                        | 17 h        | 109-111°C          | K <sub>2</sub> CO <sub>3</sub> (5)            | 71:29                                               |
| 11               | DMF                                                                        | 17 h        | 109-111°C          | Et <sub>3</sub> N(5)                          | 67:33                                               |
| 12               | DMF                                                                        | 15 h        | 109-111°C          | DABCO(5)                                      | 60:40                                               |
| 13               | DMF                                                                        | 3 days      | 25°C               | AgBF(1.1)/Na <sub>2</sub> CO <sub>3</sub> (5) | 100:0                                               |
| 14               | 3:1 DMF:<br>(C1CH <sub>2</sub> ) <sub>2</sub>                              | 16 h        | 110°C              | NaOAc                                         | 100:0                                               |
| 15               | 3:1 CH <sub>3</sub> CO <sub>2</sub> H<br>(C1CH <sub>2</sub> ) <sub>2</sub> | 20 min      | 111°C              | → <sub>2</sub> NEt(5)                         | 9:91                                                |
| 16               | CH <sub>3</sub> CO <sub>2</sub> H                                          | 4 h         | 70°C               | Et <sub>3</sub> N(5)                          | 0:100                                               |
| 17               | DMF                                                                        | 4 h         | 110°C              | AcOH(5)                                       | 69:31                                               |
| 18               | DMF                                                                        | 4 h         | 110°C              | AcOH(1)                                       | 67:33                                               |
| 19               | DMF                                                                        | 4 h         | 110°C              | AcOH(0.1)                                     | 79:21                                               |
| 20               | DMF/H <sub>3</sub> PO <sub>4</sub>                                         | 4 h         | 110°C              | ---                                           | 100:0                                               |

| <u>Entry No.</u> | <u>Solvent</u> | <u>Time</u> | <u>Temperature</u> | <u>Base(equiv.)</u>                      | <u>Ratio of</u><br><u>119:120</u><br><u>~~~~~</u> |
|------------------|----------------|-------------|--------------------|------------------------------------------|---------------------------------------------------|
| 21               | Toluene        | 24 h        | reflux             | Et <sub>3</sub> N(5)-<br>hydroquinone(1) | 60:40                                             |
| 22               | Toluene        | 11 h        | reflux             | none                                     | 60:40                                             |

- a) All reactions are carried out in the presence of 4.0 equiv of ethyl acrylate.
- b) All ratios were measured by NMR integration.
- c) The reaction was incomplete after even 5 days.

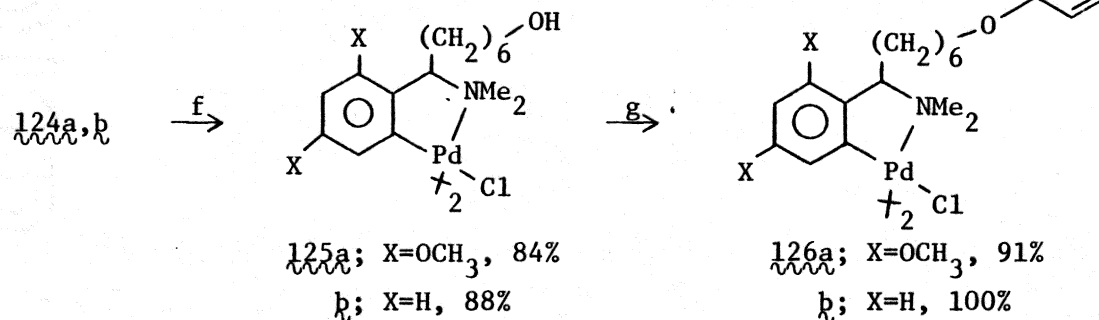
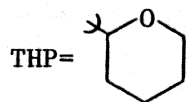
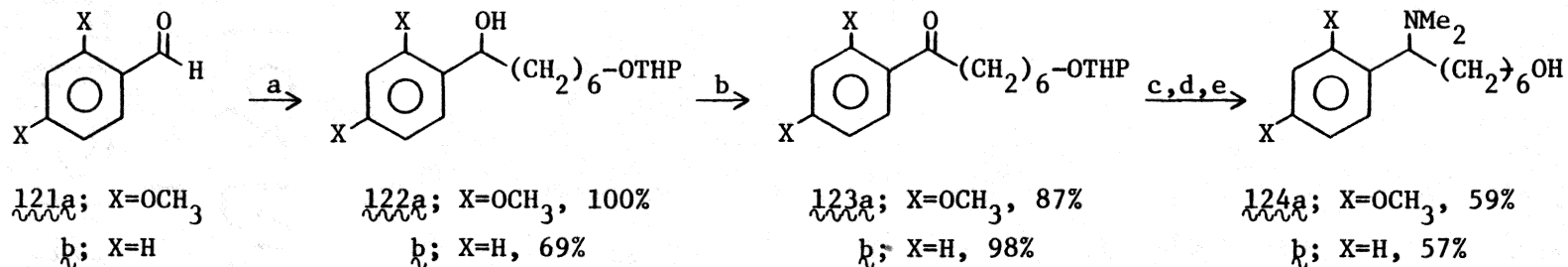
in refluxing benzene or toluene, the reaction takes about 3 h at 25°C in 3:1 acetic acid:dichloroethane.<sup>29a</sup>

The source of the reduction product 119 is also unclear. When there was no base present, a 60:40 ratio of 119:120 was obtained in refluxing toluene. The insensitivity to base concentration would indicate that triethylamine hydrochloride is not responsible for the production of amine 119.

It is also clear that the reduction is not due to radical dissociation of the carbon-palladium bond. No trace of dimeric benzylic amine, 1,2-diphenyl ethane or 4,4-dimethyl-biphenyl could be detected by TLC or NMR analysis. Additionally, inclusion of a free-radical scavenger (entry 22) failed to change the ratio of 119:120 obtained in refluxing toluene. When the acrylate was omitted, but triethylamine was present, no reaction occurs in refluxing toluene over 1 day. However, when the base was also omitted, the complex undergoes reduction to give benzylic amine 119 and traces of 2,4-dimethoxy benzaldehyde in refluxing toluene over 1 day.

In order to explore the possibility of extending this methodology toward macrocyclization, complexes 126a and 126b were synthesized as shown in Scheme XII. The synthesis of the ketones 123a and 123b was accomplished by addition of the magnesium salt of 1-oxytetrahydropyran-6-chlorohexane to a benzaldehyde and subsequent oxidation with Collins reagent. The reductive amination of ketone 123a and 123b was accomplished by the formation of an air and moisture sensitive enamine using dimethyl amine and titanium tetrachloride.<sup>94</sup> The enamine was

## Scheme XII

Synthesis of Complexes 90a and 90b

a) C1Mg(CH<sub>2</sub>)<sub>6</sub>OTHP, 1.1 eq, THF, 0°C→25°C; b) CrO<sub>3</sub>·py<sub>2</sub> (6 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25°C; c) HNMe<sub>2</sub> (1 equiv), TiCl<sub>4</sub> (1 equiv),  $\phi$ H, 0°C; d) H<sub>2</sub>, 10% Pd/C (1 atm for 92a, 50 psi for 92b); e) 10% HCl(aq); f) 1, LTP (1.0 equiv), (i-Pr)<sub>2</sub>EtN (2.2 equiv), MeOH or 2. (a) LTP (1.0 equiv), (i-Pr)<sub>2</sub>EtN (2.2 equiv), MeOH, (b) then AgBF<sub>4</sub> (3.0 equiv) (see text); g) acryloyl chloride (2.0 equiv), Et<sub>3</sub>N (2.0 equiv), ClCH<sub>2</sub>CH<sub>2</sub>Cl, 25°C.

reduced in situ with hydrogen and 10% palladium on charcoal. Acidic workup afforded the benzylic amines 124a and 124b.

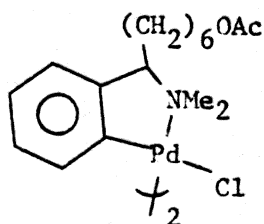
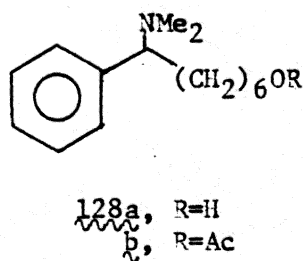
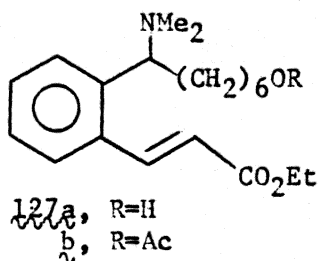
The formation of complex 125a required rather unique conditions. When benzylamine 125a was added to a solution of 1.0 equiv lithium tetrachloropalladate (LTP) and 2.2 equiv of diisopropylethylamine in methanol at 0°C, complex 125a was isolated in only 59% yield. When 3.0 equiv of silver tetrafluoroborate was added to the same reaction mixture, the yield of complex 125a was 84%. The formation of complex 125b was accomplished by adding 1.0 equiv of the benzylamine to 2.2 equiv of diisopropylethylamine and 1.0 equiv of LTP in methanol to afford a 93% yield of complex 125b.

The acrylate functionality was then introduced by adding an excess of triethylamine and 1.1 equiv of acryloyl chloride to a dichloroethane solution of complexes 125a and 125b at 0°C. This method afforded complexes 126a and 126b in 91% and 100% isolated yields.

Attempts were made to cyclize complex 126a in acetic acid and toluene. In both cases, comparison of the NMR of the crude reaction mixture with the NMR of cinnamate 120 indicated that there weren't any traces of coupled product. When complex 125a was treated with 4.0 equiv of ethyl acrylate and 5.0 equiv of triethylamine in either hot acetic acid (70-100°C) or refluxing toluene, NMR analysis indicated the complete absence of any coupled product. Only a small amount of coupled product (<10%) was detected by NMR analysis when complex 125a was treated with methyl vinyl ketone under the same conditions. The failure of complex 125a to undergo the Heck reaction in an intermolecular

sense left little hope of accomplishing an intramolecular version.

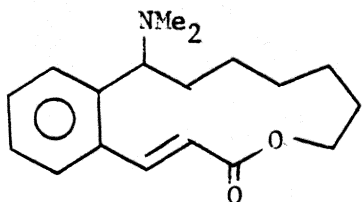
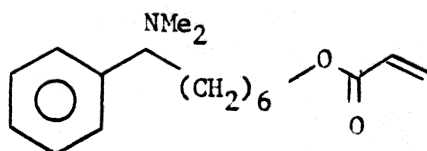
When complex 125b was treated with ethyl acrylate in acetic acid at 80°C for 14 h, NMR analysis indicated that coupled products constituted ca 45% of the product mixture. However, NMR analysis also indicated that a fair portion of the alcohol had been acetylated. Although the amino alcohols 127a and 128a weren't isolated from the product mixture in pure form, amino acetates 127b and 128b could be isolated by preparative thin layer chromatography in 27% and 32% yields, respectively. When the reaction was repeated using complex 129, the sole isolated product was 128b.



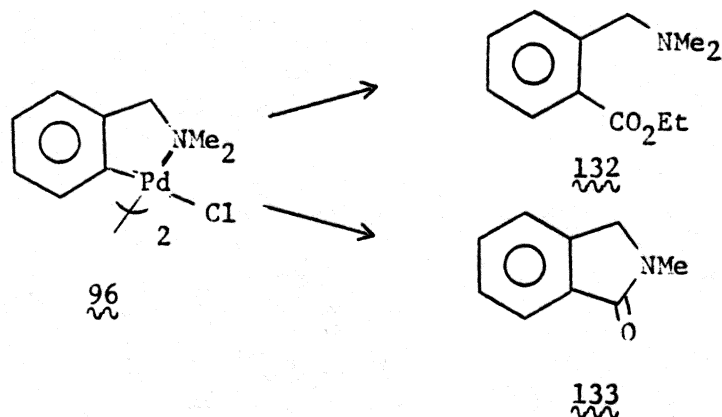
129

This poor intermolecular reactivity bodes poorly for the intramolecular reaction and may indicate a limitation regarding the olefin coupling reaction. It is possible that the reaction proceeds poorly with alkyl side chains. This limitation was not explored any further than has already been indicated.

Despite the poor intermolecular reactivity, complex 126b cyclized. When a 0.01 M acetic acid solution of complex 95b was heated to 70–75°C in the presence of 5 equiv of diisopropylethylamine for 30 h, a mixture of amines 130 (mp 42–44°C) (14%) and 131 (67%) was obtained. The remaining material was converted to a multitude of other products.

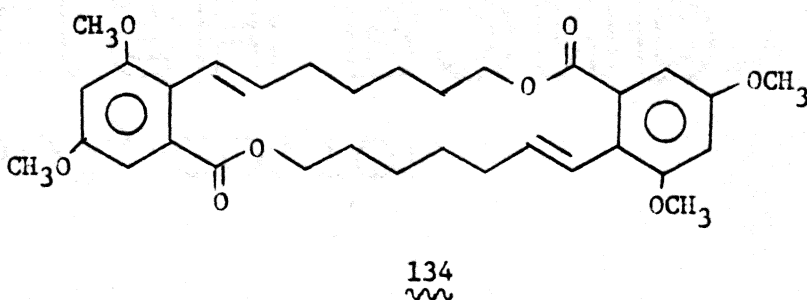
130131

Intermolecular carbonylation of complex 96 proceeded smoothly. When carbon monoxide was bubbled through a solution of toluene containing 4.0 equiv of ethanol and 5.0 equiv of triethylamine at reflux for 1 h, aminoester 132 was obtained in 83% yield. In the absence of an alcohol, the known lactam 133 (mp 112–114°C) was obtained in 82% yield, as reported by Heck.<sup>37a</sup>



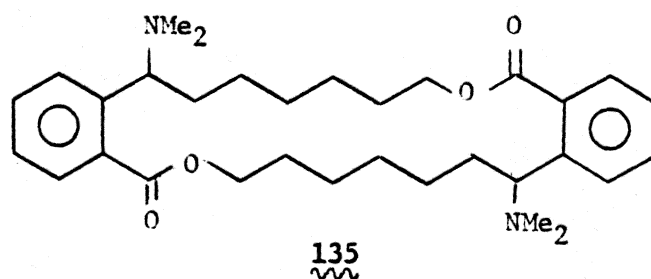
As in the olefin insertion, the presence of acetic acid produced a large accelerating effect. When carbon monoxide was bubbled through a mixture of complex 96 in acetic acid containing 4.0 equiv of ethanol and 5.0 equiv of diisopropylethylamine at room temperature for 20 min, amino ester 132 was obtained in 91% yield.

Attempted macrocyclizations via carbonylation failed to produce the desired products. Attempted cyclization of complex 125a in refluxing toluene containing 5.0 equiv of triethylamine gave a plethora of products. A small amount of lactone could be isolated after the crude reaction mixture was treated with one equivalent of meta-chloroperbenzoic acid and then refluxed in toluene.<sup>95</sup> Molecular weight determinations proved that the olefinic lactone 134, obtained in 5% yield, was dimeric.

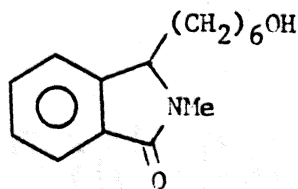




When carbon monoxide was introduced into a 0.01 M solution of complex 125b in refluxing toluene containing 5.0 equiv of diisopropylethylamine, a multitude of products was obtained, from which lactone 135 (mp 167.5–170°C) could be obtained in 9% yield after preparative thin layer chromatography. No monomeric lactone was detectable. Carbonylation in acetic acid at room temperature for 0.5 h produced lactone 135 in 13% yield. Again, no monomeric lactone was detectable.



When a syringe drive was used to slowly introduce complex 125b into the solution, the major products were different. When the reaction was run in toluene, the major product appeared to be lactam 136 (70% yield, as judged by comparison of the NMR and IR spectrum with lactam 133). Use of acetic acid as solvent led to a product which was too water soluble to permit isolation.



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In summary, the palladium mediated macrocyclizations of benzylic amine complexes via insertion reactions proceeded poorly, if at all.

## Chapter 3. Experimental

### Instrumentation

Nuclear magnetic resonance spectra were recorded on Perkin-Elmer R32 (90 MHz), Varian EM 390 (90 MHz), or Varian A-60 (60 MHz) nmr spectrometers. The chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard.

Infrared spectra were recorded on a Perkin-Elmer 137 Sodium Chloride Spectrometer or a Perkin-Elmer 710B Infrared Spectrometer. All ir data are reported in reciprocal centimeters.

Mass spectra were run by either the Purdue Chemistry Department Mass Spectroscopy Center, Virginia Polytechnic Institute and State University Analytical Services, or Virginia Polytechnic Institute and State University Biochemistry and Nutrition Department on either an Hitachi-Perkin-Elmer RMU-6A, a CEC-110, or Varian MAT 112 Spectrometer.

Melting points were taken on a Bristol microscope equipped with hot stage and are uncorrected.

Microanalyses were performed either by Dr. C. S. Yeh and C. M. Lam of Purdue University, Virginia Polytechnic Institute and State University Chemistry Department Analytical Services, or Galbraith Laboratories, Knoxville, TN.

### Solvents, Reagents, and Chromatography

Tetrahydrofuran (THF) (Fisher) was stored under nitrogen at constant reflux over lithium aluminum hydride (LAH) in a recycling still. THF which had been added to the still was considered dry when

10 mL consumed no more than 50  $\mu$ L of approximately 1.6 M n-butyllithium (Aldrich) at about  $-20^{\circ}\text{C}$  with triphenylmethane as an indicator.

Toluene and benzene were freshly distilled and stored over sodium ribbon. 1,2-Dichloroethane was distilled from phosphorus pentoxide and stored under nitrogen. Dimethyl formamide and acetonitrile were distilled from calcium oxide and stored under nitrogen. Glacial acetic acid was obtained from Mallinckrodt and used without further purification.

Triethylamine and diisopropylethylamine were distilled under nitrogen from sodium ribbon and stored under nitrogen. Silver tetrafluoroborate was purchased from Ozark-Mahoning and stored in a dessicator.

TLC plates coated with silica gel GF (250 microns) were purchased from Analtech Inc. Preparative TLC plates were made from silica gel 60 PF-254 (EM Reagents), dried in an oven at greater than  $110^{\circ}\text{C}$ , and stored in a dessicator. Plug filtration was performed with silica gel 60 (70-230 mesh ASTM) (EM Reagents).

#### Apparatus

Reaction vessels, syringes, needles, and stirring bars were stored in an oven at greater than  $110^{\circ}\text{C}$ . Syringes were assembled hot and glassware was assembled hot while being purged with a slow stream of nitrogen.

Experimental Procedures

Benzylic Amine 119: Known benzylic amine 119 was prepared by a sequence of reactions. Gaseous methylamine was bubbled through a solution of 29.36 g (0.177 mol) of 2,4-dimethoxybenzaldehyde in 200 mL of dry benzene for 10 min. The mixture was then brought to reflux and water was removed via a Dean-Stark trap. The mixture was refluxed until water ceased azeotropeing and the mixture was then cooled to room temperature. Gaseous methylamine was again introduced into the solution for 10 min and the mixture warmed to reflux until the evolution of water ceased. This process was repeated until water ceased azeotropeing. Concentration of the benzene solution afforded crude N-methyl-2,4-dimethoxy-benzylimine. Distillation afforded 30.8 g (97%) of pure N-methyl-2,4-dimethoxy-benzylimine: bp 66-68°C (1 mm Hg); nmr (CDCl<sub>3</sub>) (60 MHz) 3.45 (s,3H), 3.73 (s,6H), 6.33-6.63 (m,2H), 7.89 (d,1H,J=9 Hz), 8.57 (s,1H).

To a solution of 23.70 (0.132 mol) of N-methyl-2,4-dimethoxy-benzylimine in 100 mL of dry ethyl ether was added 50 mL of methyl iodide. The solution was stirred for 36 h at room temperature, and the precipitate was filtered off, washed with ethyl ether, and dried in vacuo to yield 42.05 g (99%) of N,N-dimethyl-2,4-dimethoxy-benzyliminium iodide which was used without further purification.

To a suspension of 42.05 g (0.131 mol) of N,N-dimethyl-2,4-dimethoxy-benzyliminium iodide in 300 mL of ethyl ether at 0°C was added 7.465 g (0.197 mol) of LAH in small portions. After the addition of LAH was complete the mixture was stirred for 0.5 h and the LAH was

quenched by careful dropwise addition of 7.5 mL of water followed by 7.5 mL of 15% NaOH (aqueous) and then 22.5 mL of water. The mixture was filtered and the filtrate concentrated to afford 23.7 g of crude benzylic amine 119. Distillation afforded 22.34 g (91%) of pure benzylic amine 119: bp 83–85°C (1 mm Hg); nmr (CDCl<sub>3</sub>) (60 MHz) δ 2.21 (s,6H), 3.37 (s,2H), 3.78 (s,6H), 6.31–6.54 (m,2H), 7.02 (d,1H, J=9 Hz); ir (CHCl<sub>3</sub>) 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 121, 151, 195.

Anal. Calcd for C<sub>11</sub>H<sub>17</sub>NO<sub>2</sub>: C, 67.66; H, 8.78. Found: C, 67.41; H, 8.65.

Palladocycle 118: To a solution of 337 mg of LTP (1.28 mmol) in 10 mL of methanol chilled in an ice bath was added a solution of 247 mg (1.27 mmol) benzyl amine 119 and 0.18 mL (1.3 mmol) of triethylamine in 5 mL of methanol. After addition was complete the ice bath was removed and the solution was stirred for 3 h at room temperature. The resultant green crystals were recovered by filtration and dissolved in methylene chloride. The dark green methylene chloride solution was filtered through celite and the filtrate plug filtered with ethyl acetate. The eluent was concentrated in vacuo to afford crude palladocycle 118 as a yellow oil. The yellow oil was dissolved in ca 20 mL of methylene chloride and ca 150 mL of hexane was added. Slow evaporation of the solvent to ca 50 mL afforded 375 mg (88%) of pure known complex 118:<sup>85</sup> mp 181.5–183.5 d; nmr (CDCl<sub>3</sub>) (90 MHz) δ 2.83 (s,6H), 3.70 (s,3H), 3.76 (s,3H), 3.92 (s,2H), 6.12–6.20 (m,1H), 6.36–6.44 (m,1H).

General Procedure A. The Intermolecular Coupling of Ethyl Acrylate

With Complex 118. Determination of Product Ratios in Table 8.

The product ratios of benzyl amine 119 and cinnamate 120 were determined by nmr analysis. The intermolecular coupling of ethyl acrylate with complex 118 in toluene (entry 1) is typical. To a mixture of 199 mg (0.361 mmol) of complex 118 in 5 mL of toluene was added 0.50 mL (2.9 mmol) of triethylamine followed by 0.32 mL (3.6 mmol) of ethyl acrylate. The mixture was then warmed to reflux for 16 h and partitioned between ethyl ether and saturated aqueous sodium bicarbonate. The ethyl ether layer was dried over sodium sulfate, filtered, and concentrated, and the solvent removed in vacuo. The residue was then dissolved in deuteriochloroform. The product ratio was determined by nmr analysis and comparison with isolated samples of benzyl amine 119 and cinnamate 120. The mixture was found to consist of a 60:40 ratio of benzylamine 119 and cinnamate 120, respectively.

Spectral and analytical data for cinnamate 120: nmr (CDCl<sub>3</sub>) (60 MHz)  $\delta$  1.40 (t, 3H, J=7 Hz), 2.24 (s, 6H), 3.50 (s, 2H), 3.80 (s, 6H), 4.38 (q, 2H, J=7 Hz), 6.37 (d, 1H, J=16 Hz), 6.51 (d, 1H, J=2 Hz), 6.75 (d, 1H, J=2 Hz), 8.01 (d, 1H, J=16 Hz); ir (CHCl<sub>3</sub>) 1700 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (50 eV) m/e 58, 121, 151, 176, 177, 195, 220, 247, 262, 291.

Anal. Calcd for C<sub>16</sub>H<sub>23</sub>NO<sub>4</sub>: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.90; H, 7.68; N, 4.94.

With the exception that benzene was used as the extraction solvent with dimethyl formamide (DMF) and acetonitrile (CH<sub>3</sub>CN), all the product

ratios in Table 8 were determined in this manner. Changes in solvent, temperature, base, and quantities of reagents are given in Table 8.

General Procedure B. Formation of Benzyl Alcohols From Benzaldehydes.

Preparation of Benzyl Alcohol 122a.

To a 500 mL three-neck round-bottom flask fitted with a condenser and a 100 mL addition funnel was added 3.130 g (0.129 mol) of magnesium turnings and 100 mL of THF. The addition funnel was filled with 24.34 g (0.110 mol) of 1-oxytetrahydropyranyl-6-chlorohexane<sup>75</sup> in 50 mL of THF and ca 20 mL of the solution was allowed to enter the flask. Several crystals of iodine and 0.1-0.2 mL of dibromoethane were added. When the reaction started, as indicated by a gentle bubbling of the THF solution, the remainder of the 1-oxytetrahydropyranyl-6-chlorohexane solution was added at a rate sufficient to maintain reflux. After addition was complete, the reaction was refluxed for 1.5 h and then cooled to 0°C. To the addition funnel was added a solution of 16.63 g (0.100 mol) of 2,4-dimethoxy-benzaldehyde in 50 mL of THF. The benzaldehyde solution was added dropwise to the flask and then allowed to warm to room temperature. To the mixture was added 150 mL of saturated aqueous sodium bicarbonate and the mixture was then filtered and the salts washed with ethyl ether. The filtrate was partitioned between ethyl ether and 10% aqueous potassium hydroxide. The ethyl ether layer was dried over sodium sulfate and concentrated to afford crude benzyl alcohol 122a. The crude benzyl alcohol was plug filtered with methylene chloride followed by ethyl ether to afford 35.25 g (100%) of slightly impure benzyl alcohol 122a which was used without further purification:

nmr ( $\text{CDCl}_3$ ) (60 MHz)  $\delta$  1.18–2.00 (m, 16H), 2.73 (s, 1H), 3.10–3.95 (m, 4H), 3.87 (s, 6H), 4.45–4.75 (m, 3H), 6.49 (m, 2H), 7.10 (d, 1H,  $J=9$  Hz).

Benzyl Alcohol 122b: Following procedure B, 7.88 g (35.7 mmol) of 1-oxytetrahydropyranyl-6-chlorohexane<sup>75</sup> and 3.64 g (3.43 mmol) of benzaldehyde was converted to 7.16 g (69%) of benzyl alcohol 122b after Kugelrohr distillation (130°C–140°C at 1 mm Hg): nmr ( $\text{CDCl}_3$ ) (90 MHz)  $\delta$  1.15–2.00 (m, 16H), 2.61 (s, 1H), 3.13–3.95 (m, 4H), 4.45–4.75 (m, 3H), 7.29 (s, 5H); ir ( $\text{CHCl}_3$ ) 3400  $\text{cm}^{-1}$  (broad), 3575  $\text{cm}^{-1}$  (sharp); mass spectrum (50 eV) m/e 85, 107, 191, 205, 206.

Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{O}_2$ : C, 73.93; H, 9.65. Found: C, 73.67; H, 9.64.

General Procedure C. Oxidation of Benzylic Alcohols. Preparation of Ketone 123a.

The oxidations of benzylic alcohols was accomplished using Collins reagent<sup>90a</sup> according to the procedure of Ratcliffe and Rodehorst.<sup>906</sup> The oxidation of benzylic alcohol 122a to ketone 123a is typical. To a solution of 350 mL (4.33 mol) of pyridine in 3400 mL of methylene chloride at 0°C was added 201.9 g (2.02 mol) of chromium trioxide. The mixture was stirred for 15 min and 118.6 g (0.336 mol) of benzyl alcohol 122a in 250 mL of methylene chloride was added in one portion. The ice bath was removed and the mixture stirred for 15 min. The mixture was filtered, reduced in volume to ca 750 mL and the residue dissolved in 2 L of ethyl ether. The ethyl ether layer was filtered and extracted with 10% KOH. The ethyl ether layer was dried over sodium sulfate,



filtered and solvent removed in vacuo to afford crude ketone 123a.

Crystallization from methanol at  $-25^{\circ}\text{C}$  afforded 102.7 g (87%) of pure ketone 123a: mp  $47-48.5^{\circ}\text{C}$ ; nmr ( $\text{CDCl}_3$ ) (90 MHz)  $\delta$  1.20-1.90 (m,14H), 2.91 (t,2H,J=7 Hz), 3.20-4.00 (m,4H), 3.86 (s,3H), 3.89 (s,3H), 4.57 (s,1H), 7.50-7.60 (m,2H), 7.77 (d,1H,J=9 Hz); ir ( $\text{CHCl}_3$ )  $1680\text{ cm}^{-1}$ ; mass spectrum (50 eV) m/e 85, 165, 180, 193, 256, 350.

Anal. Calcd for  $\text{C}_{20}\text{H}_{30}\text{O}_4$ : C, 68.55; H, 8.63. Found: C, 68.31; H, 8.80.

Ketone 123b: Following procedure C, 6.20 g (21.2 mmol) of benzyl alcohol 122b was converted to 6.01 g (98%) of ketone 123b after Kugelrohr distillation ( $130^{\circ}\text{C}$  at 1 mm Hg): nmr ( $\text{CDCl}_3$ ) (90 MHz)  $\delta$  1.20-2.00 (m,14H), 2.94 (t,2H,J=7 Hz), 3.33-4.03 (m,4H), 4.57 (s,1H), 7.30-7.70 (m,3H), 7.87-8.07 (m,2H); ir ( $\text{CHCl}_3$ )  $1680\text{ cm}^{-1}$ ; mass spectrum (50 eV) m/e 77, 85, 105, 121, 133, 205, 206.

Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{O}_2$ : C, 74.45; H, 9.02. Found: C, 74.70; H, 8.90.

#### General Procedure D. The Reductive Amination of Phenyl Ketones.

##### Preparation of Amino Alcohol 124a.

To a solution of 15.38 g (43.9 mmol) of ketone 123a in 150 mL of benzene was added 15 mL (227 mmol) of dimethylamine. This solution was chilled to  $0^{\circ}\text{C}$  and 2.8 mL (24 mmol) of titanium tetrachloride was added. The mixture immediately turned dark green. The mixture was warmed to room temperature for 2 h. The dark green color gradually turns to a beige suspension. To this mixture was added 1.5 g of 10% palladium on

charcoal and hydrogen was bubbled through the mixture for 18 h. The mixture was filtered and the solvent removed in vacuo. The residue was dissolved in 200 mL of 10% hydrochloric acid and allowed to stand for 0.5 h. The mixture was neutralized with 10% potassium hydroxide and partitioned with ethyl ether. The ethyl ether layer was dried over sodium sulfate, filtered, and concentrated to afford crude aminoalcohol 124a. Kugelrohr distillation at 160°C at 1 mm Hg afforded 7.65 g (59%) of pure aminoalcohol 124a: nmr (CDCl<sub>3</sub>) (90 MHz) δ 1.00-1.95 (m,10H), 2.29 (s,6H), 2.51 (s,1H), 3.55 (t,2H,J=7 Hz), 3.71-3.86 (m,7H), 6.49 (m,2H), 7.10 (d,1H,J=9 Hz); ir (CHCl<sub>3</sub>) 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (50 eV) m/e 151, 177, 250.

Anal. Calcd for C<sub>17</sub>H<sub>29</sub>NO<sub>3</sub>: C, 69.12; H, 9.89; N, 4.74. Found: C, 69.38; H, 9.64; N, 4.94.

Aminoalcohol 124b: Procedure D was followed with the exception that the material was hydrogenated at 50 psi in a Paar Apparatus and ethyl ether was used as solvent. Using this method, 11.34 g (3.90 mmol) of ketone 123b was converted to 5.24 g (57%) of aminoalcohol 124b after Kugelrohr distillation (140° at 1 mm Hg): nmr (CDCl<sub>3</sub>) (90 MHz) δ 0.90-1.59 (m, 8H), 1.70-1.93 (m,2H), 2.23 (s,6H), 3.11 (d of d,1H,J=5,9 Hz), 3.23 (s,1H), 3.50 (t,2H,J=7 Hz), 7.13-7.40 (m,5H); ir (CHCl<sub>3</sub>) 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>, 3600 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 151, 194, 195.

Anal. Calcd for C<sub>15</sub>H<sub>25</sub>NO: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.48; H, 10.72; N, 5.95.

Palladocycle 125a: To a solution of 269 mg (1.03 mmol) of LTP in 10 mL of methanol at 0°C was added a solution of 301 mg (1.03 mmol) of benzylic amine 124a and 0.20 mL (1.13 mmol) of diisopropylethylamine in 5 mL of methanol. To this mixture was added 601 mg (3.09 mmol) of silver tetrafluoroborate at 0°C. Stirring was continued for 15 min and the mixture was added to 50 mL of chloroform and filtered. The filtrate was plug filtered with 10% methanol in chloroform and the eluent concentrated to afford palladocycle 125a as a yellow oil. The yellow oil was dissolved in 5 mL of methylene chloride and ca 70 mL of hexane was added. Slow reduction of the volume of the solvent in vacuo afforded 374 mg (84%) of crystalline palladocycle 125a: mp 84–86°C d: nmr (CDCl<sub>3</sub>) (90 MHz) δ 1.20–1.73 (m,8H), 1.87–2.45 (m,3H), 2.60 (s,3H), 2.78 (s,3H), 3.40–3.87 (m,3H), 3.63 (s,3H), 3.70 (s,3H), 6.11 (d,1H, J=2 Hz), 6.35 (s,1H); ir (CHCl<sub>3</sub>) 3000 cm<sup>-1</sup>–3600 cm<sup>-1</sup> (v. broad).

Anal. Calcd for (C<sub>17</sub>H<sub>28</sub>ClNO<sub>3</sub>Pd)<sub>2</sub>: C, 46.80; H, 6.47. Found: C, 46.86; H, 6.52.

Palladocycle 125b: To a solution of 607 mg (2.32 mmol) of LTP in 10 mL of methanol at 0°C was added a solution of 533 mg (2.27 mmol) of benzyl amine 124b and 0.79 mL (4.5 mmol) of diisopropylethyl amine in 5 mL of methanol. Stirring was continued at 0°C for 25 min and the mixture partitioned between chloroform and saturated aqueous sodium bicarbonate. The chloroform layer was dried over sodium sulfate, filtered, and concentrated. Plug filtration with ethyl ether, then chloroform, afforded palladocycle 125b as a yellow oil after the chloroform fraction was concentrated. Crystallization from methylene chloride–hexane by

slow evaporation of the solvent afforded 751 mg (88%) of crystalline palladocycle 125b: mp 160–162°C d; nmr (CDCl<sub>3</sub>) (90 MHz) δ 1.00–1.80 (m, 8H), 1.90–2.37 (m, 3H), 2.67 (s, 3H), 2.87 (s, 3H), 3.15–3.54 (m, 2H), 3.54–3.77 (m, 2H), 6.63–7.49 (m, 4H); ir (CHCl<sub>3</sub>) 3400 cm<sup>-1</sup> (broad).

Anal. Calcd for (C<sub>15</sub>H<sub>24</sub>ClNOPd)<sub>2</sub>: C, 47.89; H, 6.43; N, 3.72.

Found: C, 47.64; H, 6.45; N, 3.59.

### General Procedure E. The Formation of Acrylate Palladium Complexes.

#### Preparation of Palladocycle 126a.

The formation of palladocycle 126a is typical of the formation of acrylate palladium complexes. To a solution of 1.027 g (1.18 mmol) of palladocycle 125a containing 1.48 mL (10.6 mmol) of triethylamine in 25 mL of 1,2-dichloroethane at 0°C was added 0.29 mL (3.5 mmol) of acryloyl chloride. Stirring was continued for 20 min at 0°C and the mixture partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The methylene chloride layer was dried over sodium sulfate, filtered, and concentrated to afford crude palladocycle 126a. Plug filtration with ethyl ether afforded 1.050 g (91%) of pure palladocycle 126a as a yellow-orange foam: nmr (CDCl<sub>3</sub>) (90 MHz) δ 1.10–1.90 (m, 8), 1.98–2.41 (m, 2H), 2.61 (s, 3H), 2.79 (s, 3H), 3.40–3.80 (m, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 4.10 (t, 2H, J=7 Hz), 5.75 (d of d, 1H, J=3, 10 Hz), 5.93–6.93 (m, 4H); ir (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>.

Palladocycle 126b: Following procedure E, 243 mg (0.323 mmol) of palladocycle 125b was converted to 276 mg (100%) of palladocycle 126b after crystallization from methylene chloride-hexane via slow solvent

evaporation in vacuo: mp 124-125.5, nmr ( $\text{CDCl}_3$ ) (90 MHz)  $\delta$  1.10-1.90 (m,6H), 1.97-2.50 (m,2H), 2.68 (s,3H), 2.88 (s,3H), 3.15-3.40 (m,1H), 4.11 (t,2H,J=7 Hz), 5.81 (d of d,1H,J=3,10 Hz), 5.80-6.60 (m,3H), 6.80-7.03 (m,2H), 7.10-7.33 (m,1H); ir ( $\text{CHCl}_3$ )  $1715\text{ cm}^{-1}$ .

An analytical sample was prepared by recrystallization from ethyl acetate. Anal. Calcd for  $(\text{C}_{18}\text{H}_{26}\text{ClNO}_2\text{Pd})_2$ : C, 50.25; H, 6.09; N, 3.26. Found: C, 50.24, H, 5.94; N, 3.10.

Insertion of Ethyl Acrylate With Palladocycle 125b. Amino Acetates

127b and 128b: To a mixture of 1.03 g (1.37 mmol) of palladocycle 125b in 25 mL of glacial acetic acid was added 2.4 mL (13.7 mmol) of diisopropylethylamine and 1.5 mL (13.7 mmol) of ethyl acrylate. The mixture was heated at  $80^\circ\text{C}$  for 14 h and partitioned between chloroform and 10% aqueous potassium hydroxide. The chloroform layer was dried over sodium sulfate, filtered, and concentrated in vacuo to afford 855 mg of a mixture containing four materials by TLC analysis. NMR analysis of the crude mixture indicated that coupled products constituted ca 45% of the mixture.

Preparative thin layer chromatography (0.5% aqueous  $\text{NH}_3$ /4.5 % methanol/chloroform) afforded 265 mg (27%) of pure amino diester 127b and 280 mg (32%) of amino ester 128b.

Spectral data for 127b: nmr ( $\text{CDCl}_3$ ) (90 MHz)  $\delta$  0.83-1.88 (m,10H), 1.31 (t,3H,J=7 Hz), 1.99 (s,3H), 2.20 (s,6H), 3.49 (d of d,1H,J=5,9 Hz), 3.99 (t,2H,J=7 Hz), 4.27 (t,2H,J=7 Hz), 6.30 (d,1H,J=16 Hz), 7.10-7.67 (m,4H), 8.33 (d,1H,J=16 Hz); ir ( $\text{CHCl}_3$ )  $1705\text{ cm}^{-1}$ ,  $1725\text{ cm}^{-1}$ ; mass spectrum (50 eV) m/e 73, 75, 119, 134, 232, 375.23. Calcd for

$C_{22}H_{33}NO_4$ : 375.24.

Spectral data for amino acetate 128b: nmr ( $CDCl_3$ ) (90 MHz)  $\delta$  0.99-1.98 (m,10H), 1.98 (s,3H), 2.19 (s,6H), 3.13 (d of d,1H,J=5,9 Hz), 3.99 (t,2H,J=7 Hz), 7.23 (s,5H); ir ( $CHCl_3$ )  $1725\text{ cm}^{-1}$ ; mass spectrum (50 eV) m/e 134, 277.18. Calcd for  $C_{17}H_{27}NO_2$ : 277.20.

Palladocycle 129: To a solution of 236 mg (0.313 mmol) of palladocycle 125b in 7 mL of methylene chloride (distilled from phosphorus pentoxide) at  $0^\circ\text{C}$  was added 2 mL of triethylamine and 1 mL of acetic anhydride. The mixture was warmed to room temperature and stirred for 3 h. The mixture was then partitioned between chloroform and saturated sodium bicarbonate. The chloroform layer was dried over sodium sulfate, filtered, and concentrated. Plug filtration with chloroform afforded 233 mg (89%) of spectroscopically and chromatographically homogeneous palladocycle 129 as a foam: mp  $136-136.5\text{ d}$ ; nmr ( $CDCl_3$ ) (90 MHz)  $\delta$  1.13-1.83 (m,8H), 1.89-2.30 (m,2H), 2.04 (s,3H), 2.68 (s,3H), 2.85 (s,3H), 3.15-3.41 (m,1H), 4.02 (t,2H,J=7 Hz), 6.67-6.97 (m,3H), 7.07-7.25 (m,1H); ir  $1725\text{ cm}^{-1}$ .

An analytical sample was prepared by crystallization from ethyl acetate. Anal. Calcd for  $C_{17}H_{26}NO_2$ : C, 48.82; H, 6.27; N, 3.35. Found: C, 48.49; H, 6.26; N, 3.16.

Attempted Coupling of Ethyl Acrylate With Palladocycle 129: Procedure A was followed using palladocycle 129 as substrate in acetic acid at  $70^\circ\text{C}$ . NMR and TLC analysis indicated that 128b was the sole product.

Cyclization of 126b. Preparation of Lactone 130: To a mixture of 754 mg (0.877 mmol) of palladocycle 126b in 88 mL of glacial acetic acid was added 1.5 mL (8.77 mmol) of diisopropylethylamine. The mixture was heated to 70-75°C for 30 h and then the volume of acetic acid was reduced in vacuo. The concentrate was partitioned between chloroform and saturated aqueous sodium bicarbonate. The chloroform layer was dried over sodium sulfate, filtered, and concentrated, and the concentrate was triturated with ethyl ether to afford a mixture of lactone 130 and benzylic amine 131. Crystallization from ethyl ether afforded 70 mg (14%) of lactone 130: mp 42-44°C; nmr (CDCl<sub>3</sub>) (90 MHz)  $\delta$  1.01-2.03 (m, 10H), 3.57 (m, 1H), 4.00-4.50 (m, 2H), 6.22 (d, 1H, J=16 Hz), 7.20-7.47 (m, 3H), 7.52-7.83 (m, 1H), 8.20 (d, 1H, J=16 Hz); ir (CHCl<sub>3</sub>) 1700 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 115, 144, 158, 159, 230, 272, 286, 287.180. Calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub>: 287.187.

Plug filtration of the mother liquor (0.5% aqueous NH<sub>3</sub>/4.5% methanol/chloroform) afforded 340 mg (67%) of pure benzylic amine 131: nmr (CDCl<sub>3</sub>) (90 MHz)  $\delta$  0.98-1.98 (m, 10H), 2.16 (s, 6H), 3.16 (d of d, 1H, J=5, 9 Hz), 4.10 (t, 2H, J=7 Hz), 5.69-6.63 (m, 3H), 7.13-7.42 (m, 5H); ir (CHCl<sub>3</sub>) 1715 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2820 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 91, 144, 145, 203, 289.195. Calcd for C<sub>18</sub>H<sub>27</sub>NO<sub>2</sub>: 289.203.

Esterification of Palladocycle 96 via Carbonylation in Toluene.

Preparation of Amino Ester 132: To a mixture of 240 mg (0.435 mmol) of palladocycle 96 in 8 mL of toluene was added 0.25 mL (4.3 mmol) of dry ethanol (distilled from magnesium turnings) and 0.76 mL (4.30 mmol) of diisopropylethylamine. The mixture was brought to reflux and

carbon monoxide bubbled through the mixture for 45 min. The mixture was filtered through celite and then partitioned between chloroform and saturated aqueous sodium bicarbonate. The chloroform layer was dried over sodium sulfate, filtered, and concentrated to afford crude amino ester 132. Kugelrohr distillation (100°C at 1 mm Hg) afforded 149 mg (83%) of pure amino ester 132: nmr (CDCl<sub>3</sub>) (90 MHz)  $\delta$  1.42 (t, 3H, J=7 Hz), 2.66 (s, 6H), 3.73 (s, 2H), 4.34 (q, 2H, J=7 Hz), 7.19–7.57 (m, 3H), 7.70 (d of d, 1H, J=2, 9 Hz); ir (CHCl<sub>3</sub>) 1705 cm<sup>-1</sup>, 2770 cm<sup>-1</sup>, 2810 cm<sup>-1</sup>; mass spectrum (50 eV) m/e 58, 91, 133, 146, 162, 178, 192, 207.

Anal. Calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub>: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.07; H, 5.92; N, 9.43.

Carbonylation of Palladocycle 96 in Toluene. Preparation of Lactam 133:

Palladocycle 96 was converted to lactam 133 by the method of Thompson and Heck<sup>37a</sup> with the exception that toluene was used as solvent. In this manner 275 mg (0.493 mmol) of palladocycle 96 was converted to 120 mg (82%) of lactam 133: mp 112–114°C; nmr (CDCl<sub>3</sub>) (90 MHz)  $\delta$  3.19 (s, 3H), 4.33 (s, 2H), 7.29–7.61 (m, 4H), 7.80 (d of d, 1H, J=2, 9 Hz); ir (CHCl<sub>3</sub>) 1675 cm<sup>-1</sup>.

Carbonylation of Palladocycle 96 in Acetic Acid. Amino Ester 132:

To a mixture of 206 mg (0.373 mmol) of palladocycle 96 and 7.0 mL of glacial acetic acid at room temperature was added 0.14 mL (2.28 mmol) of dry ethanol (distilled from magnesium turnings) and 0.65 mL (3.73 mmol) of diisopropylethylamine. Carbon monoxide was bubbled through



the solution for 20 min at room temperature and the mixture was partitioned between chloroform and 10% potassium hydroxide. The chloroform layer was dried over sodium sulfate, filtered, and concentrated to 140 mg (91%) of spectroscopically and chromatographically homogeneous amino ester 132. The amino ester 132 obtained in this manner was chromatographically and spectroscopically identical to that obtained in toluene.

Carbonylation-Elimination of Palladocycle 125a. Lactone 134: Carbon monoxide was bubbled through a mixture of 470 mg (0.539 mmol) of palladocycle 125a and 0.75 mL (5.39 mmol) in 100 mL of toluene at reflux for 2 h. The mixture was then partitioned between ethyl ether and saturated aqueous sodium bicarbonate. The ethyl ether layer was dried over sodium sulfate, filtered, and concentrated. The concentrate was dissolved in 25 mL of toluene and 207 mg (1.078 mmol) of 85% meta-chloroperbenzoic acid added (Aldrich). The mixture was stirred at room temperature for 1 h and was then refluxed for 2 h. This mixture was partitioned between ethyl ether and saturated aqueous sodium bicarbonate. The ethyl ether layer was dried over sodium sulfate, filtered, and concentrated. Preparative thin layer chromatography (ethyl acetate) afforded 15 mg (5%) of pure lactone 134: mp 161.5-163°C; nmr (CDCl<sub>3</sub>) (90 MHz)  $\delta$  1.10-1.95 (m,6H), 2.03-2.45 (m,2H), 3.80 (s,6H), 4.27 (t,2H, J=7 Hz), 5.91 (d of t,1H,J=7,16 Hz), 6.49 (d,1H,J=16 Hz), 6.51 (d,1H, J=2 Hz), 6.65 (d,1H,J=2 Hz); ir (CHCl<sub>3</sub>) 1710 cm<sup>-1</sup>.

Anal. Calcd for C<sub>32</sub>H<sub>40</sub>O<sub>8</sub>: C, 69.55; H, 7.24; Mol. Wt. 552.66.

Found: C, 69.81; H, 7.36; Mol. Wt. 540.36.

Carbonylation of Palladocycle 125b in Toluene. Formation of Lactone

135: A mixture of 257 mg (0.342 mmol) of palladocycle 125b and 0.59 mL (3.4 mmol) of diisopropylethylamine in 34 mL of toluene was brought to reflux and carbon monoxide was bubbled through the mixture for 1 h. The mixture was partitioned between chloroform and saturated aqueous sodium bicarbonate. The chloroform layer was dried over sodium sulfate, filtered, and concentrated. Preparative thin layer chromatography (0.5% aqueous ammonia/4.5% methanol/chloroform) afforded 16 mg (9%) of lactone 135: mp 167.5-170°C; nmr (CDCl<sub>3</sub>) (90 MHz)  $\delta$  0.80-2.10 (m, 8H), 2.20 (s, 6H), 3.88 (d of d, 1H, J=5, 10 Hz), 4.25 (q, 2H, J=6 Hz), 7.20-7.70 (m, 4H); ir (CHCl<sub>3</sub>) 1710 cm<sup>-1</sup>; mass spectrum (70 eV) m/e 58, 83, 85, 147, 179, 477, 505, 519, 520.

Carbonylation of Palladocycle 125b in Acetic Acid: Carbon monoxide was bubbled through a mixture of 210 mg (0.279 mmol) of palladocycle 125b and 0.49 mL (2.8 mmol) of diisopropylethylamine in 28 mL of glacial acetic acid at room temperature for 0.5 h. The reaction was filtered through celite and the filtrate reduced in volume. The residue was partitioned between chloroform and saturated aqueous sodium bicarbonate. The chloroform layer was dried over sodium sulfate, filtered, and concentrated. Preparative thin layer chromatography gave 19 mg (13%) of lactone 135 which was spectroscopically and chromatographically identical to that obtained in toluene.

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**Appendix**

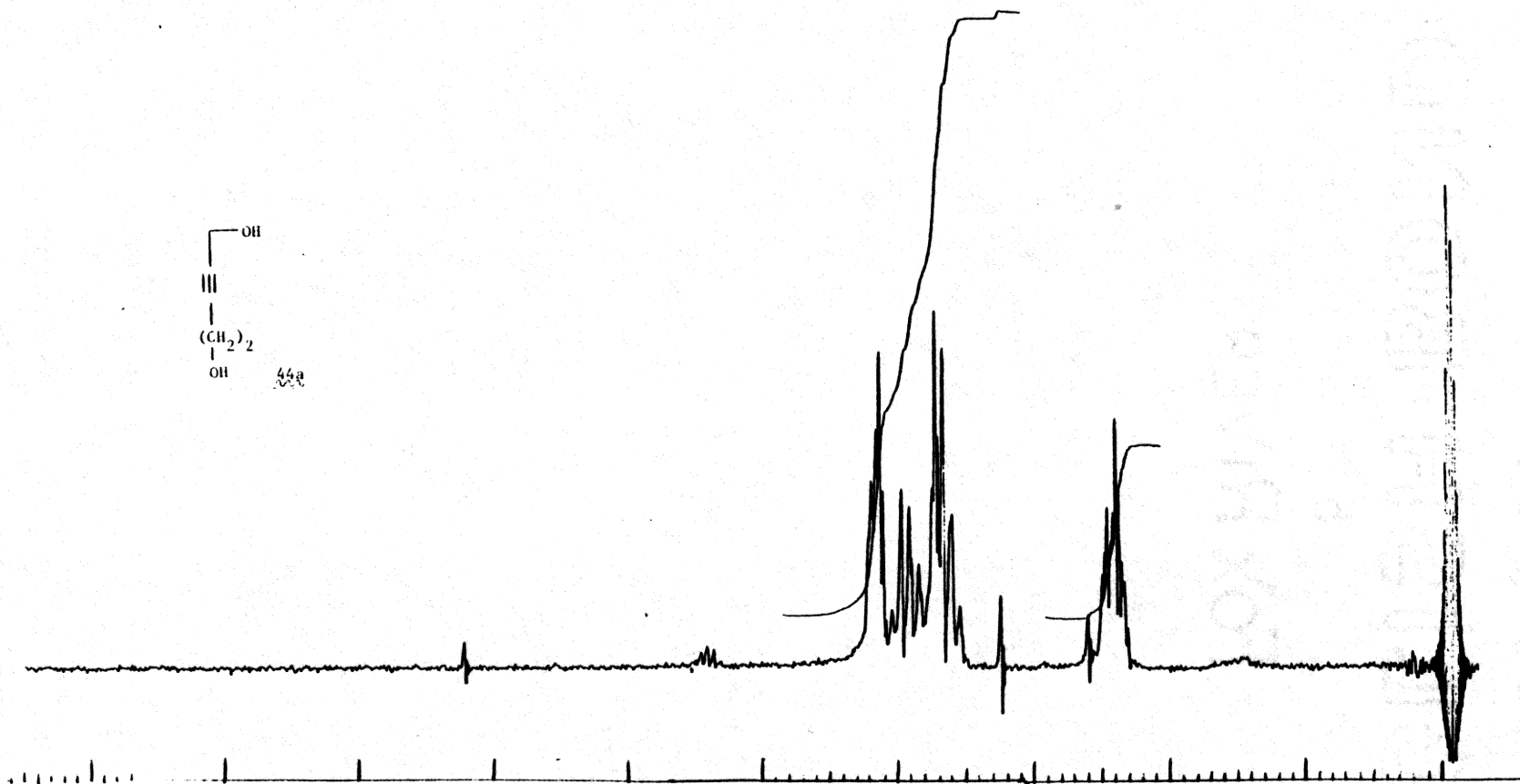


Figure 1a. 90 MHz NMR Spectrum of Diol 44a.

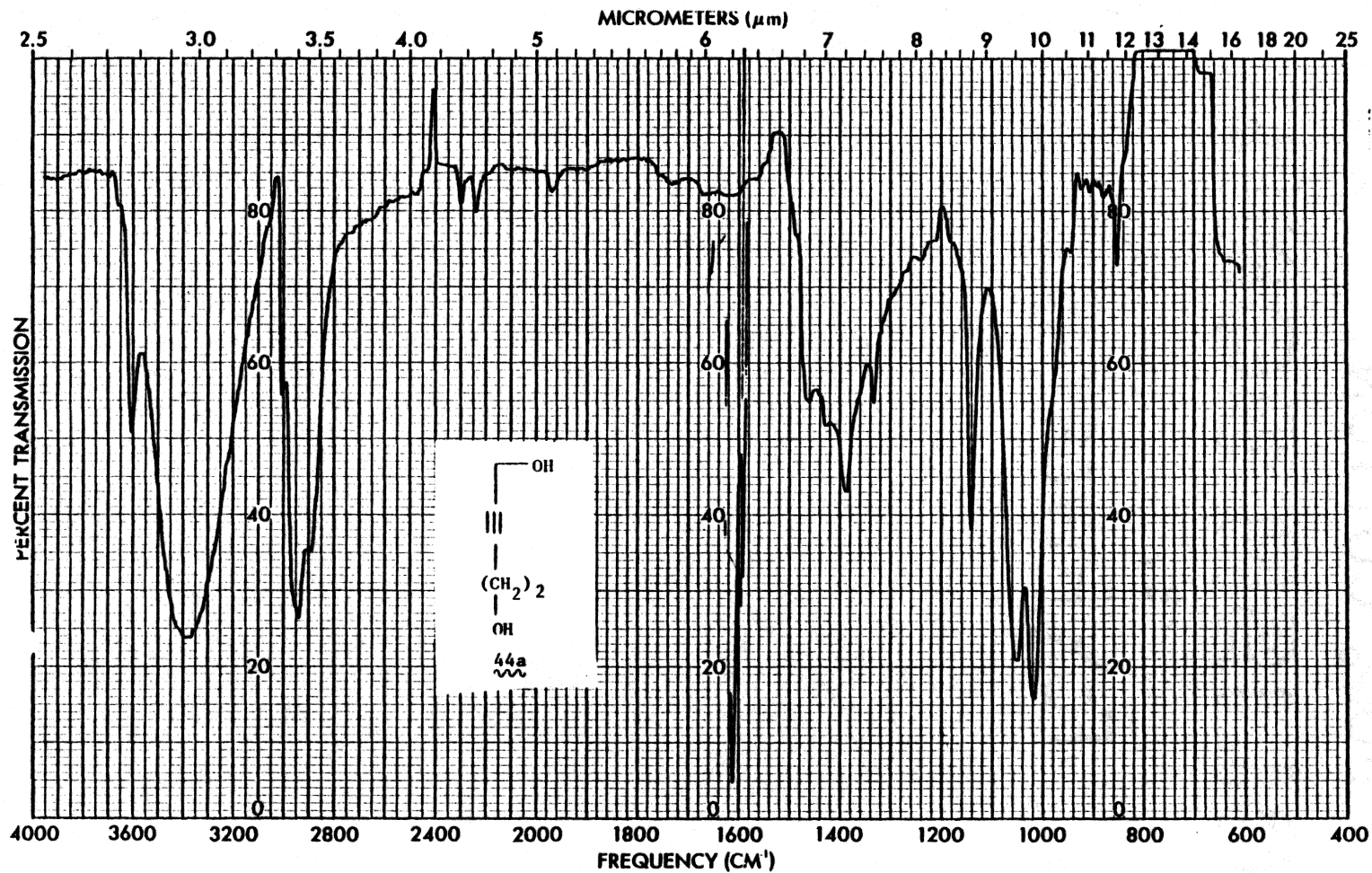


Figure 1b. IR Spectrum of Diol 44a.



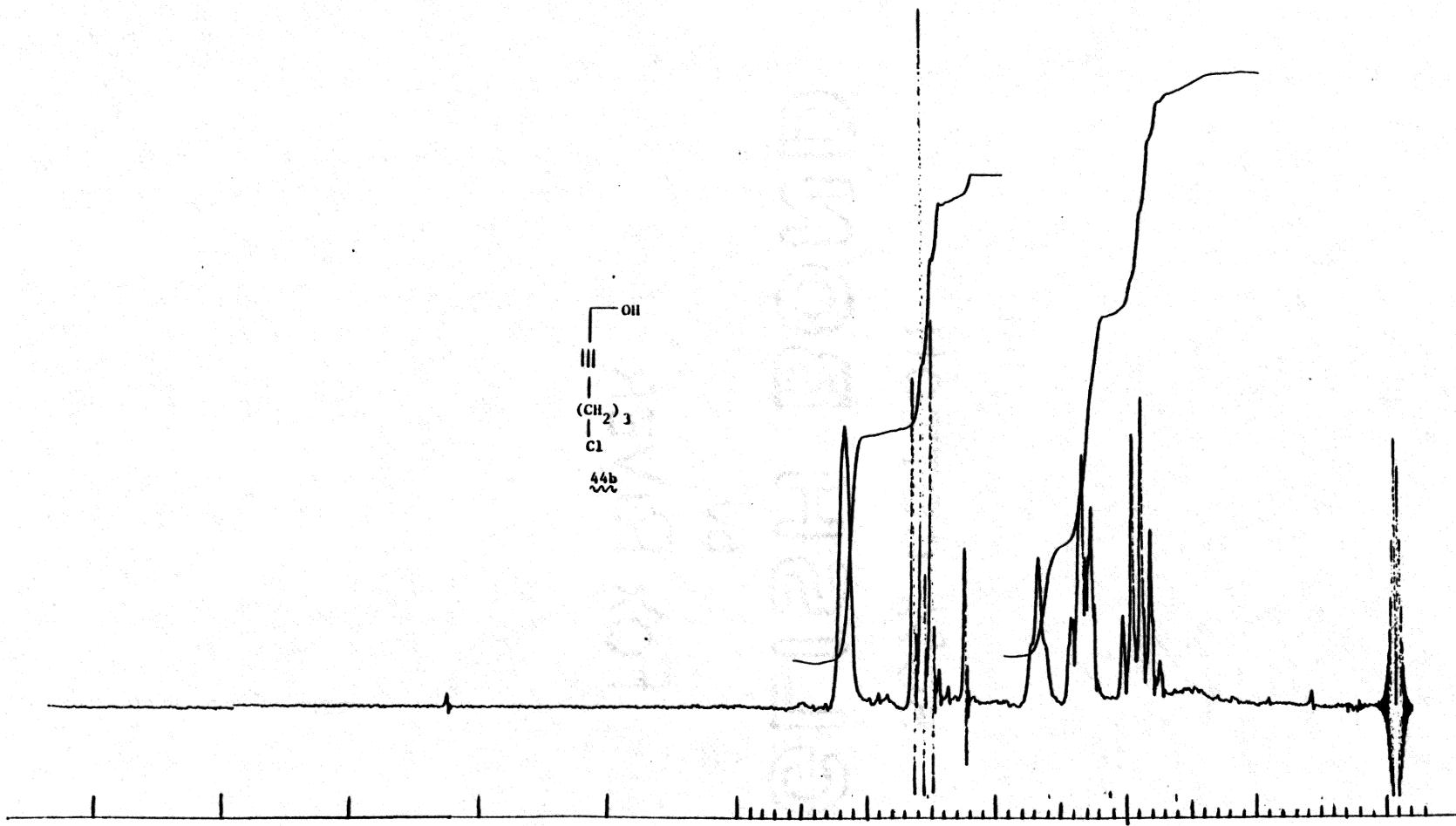


Figure 2a. 90 MHz NMR Spectrum of Chloroalcohol 44b.

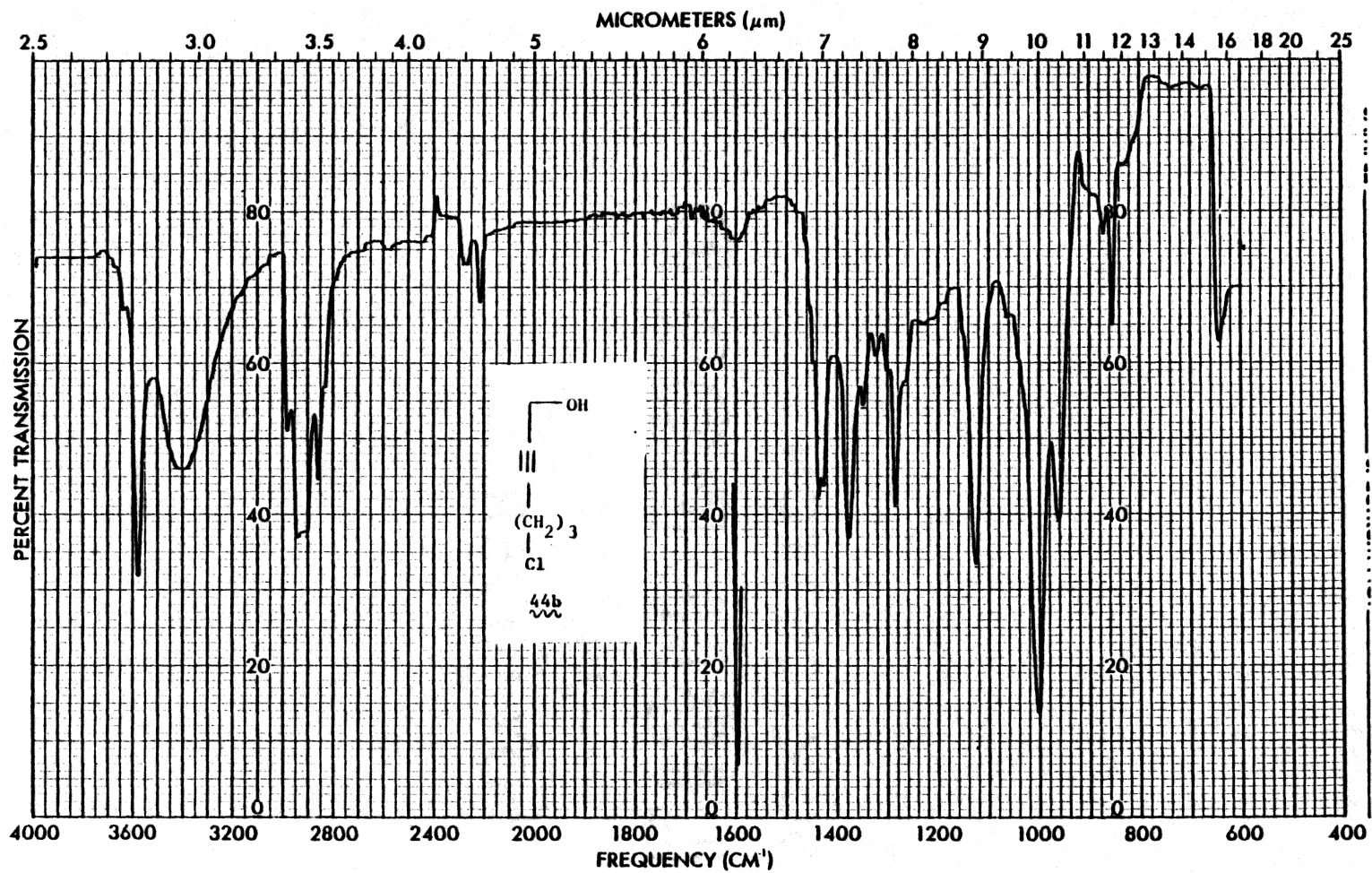


Figure 2b. IR Spectrum of Chloroalcohol 44b.

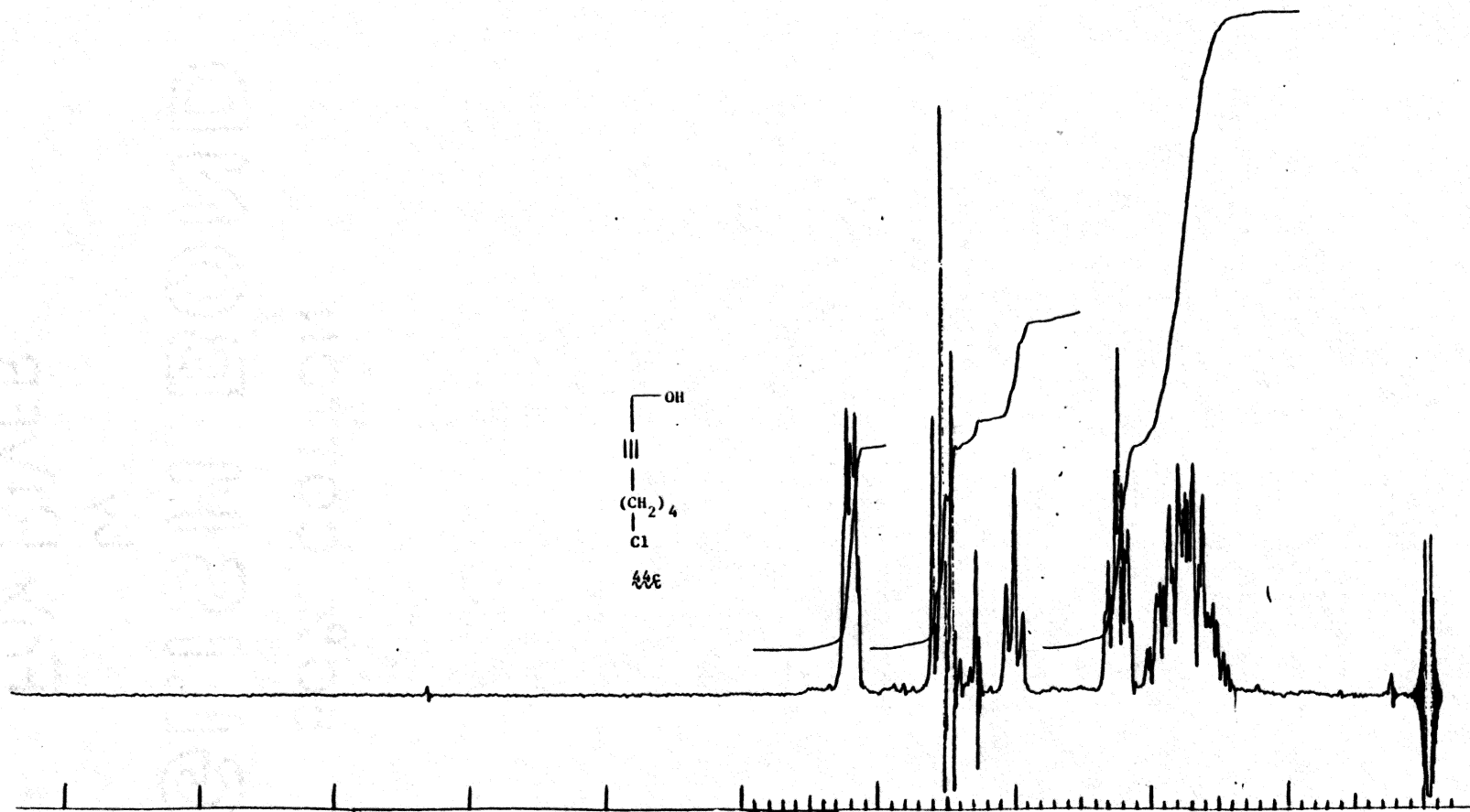


Figure 3a. 90 MHz NMR Spectrum of Chloroalcohol 44c.

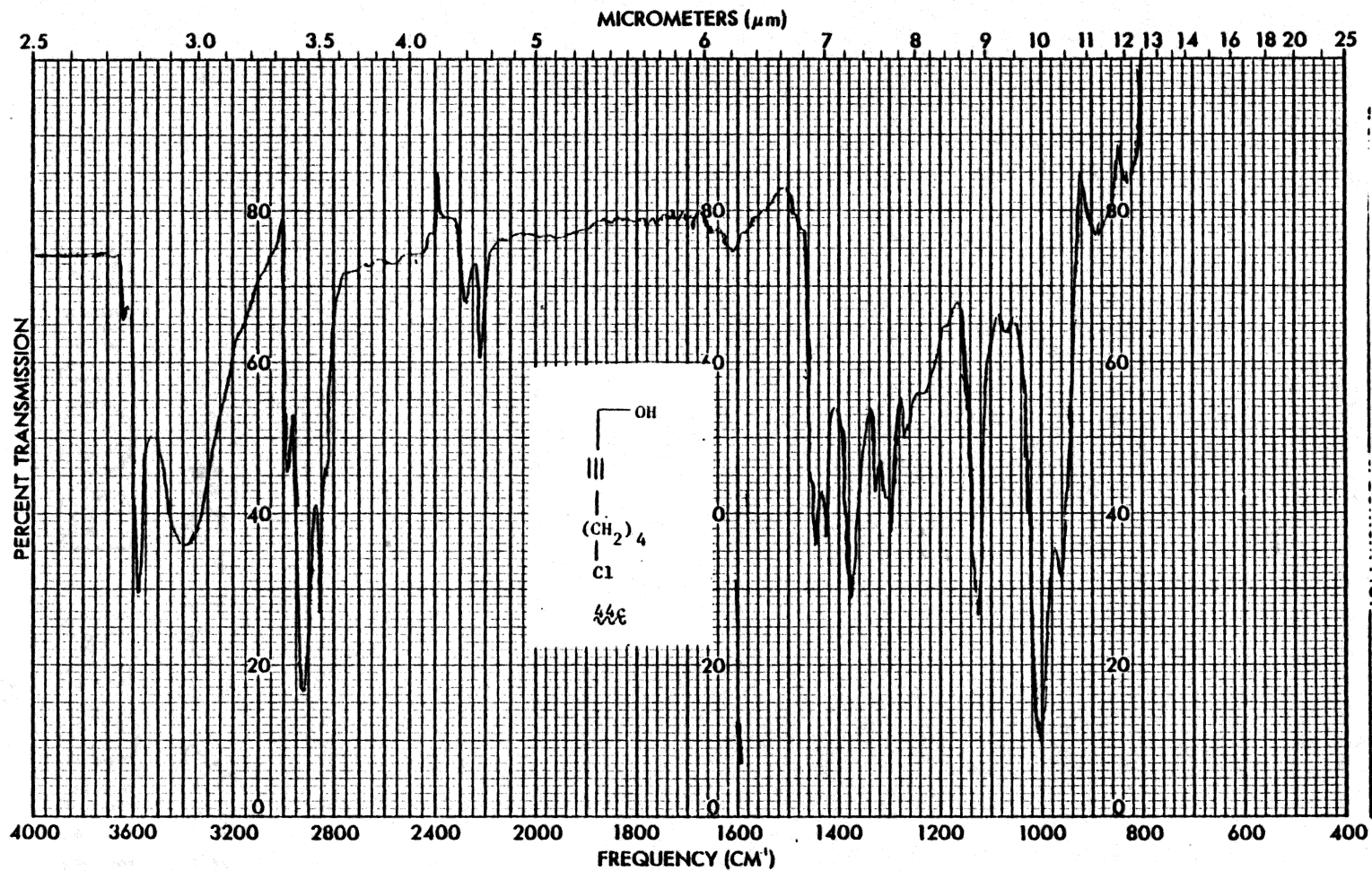


Figure 3b. IR Spectrum of Chloroalcohol 44c.

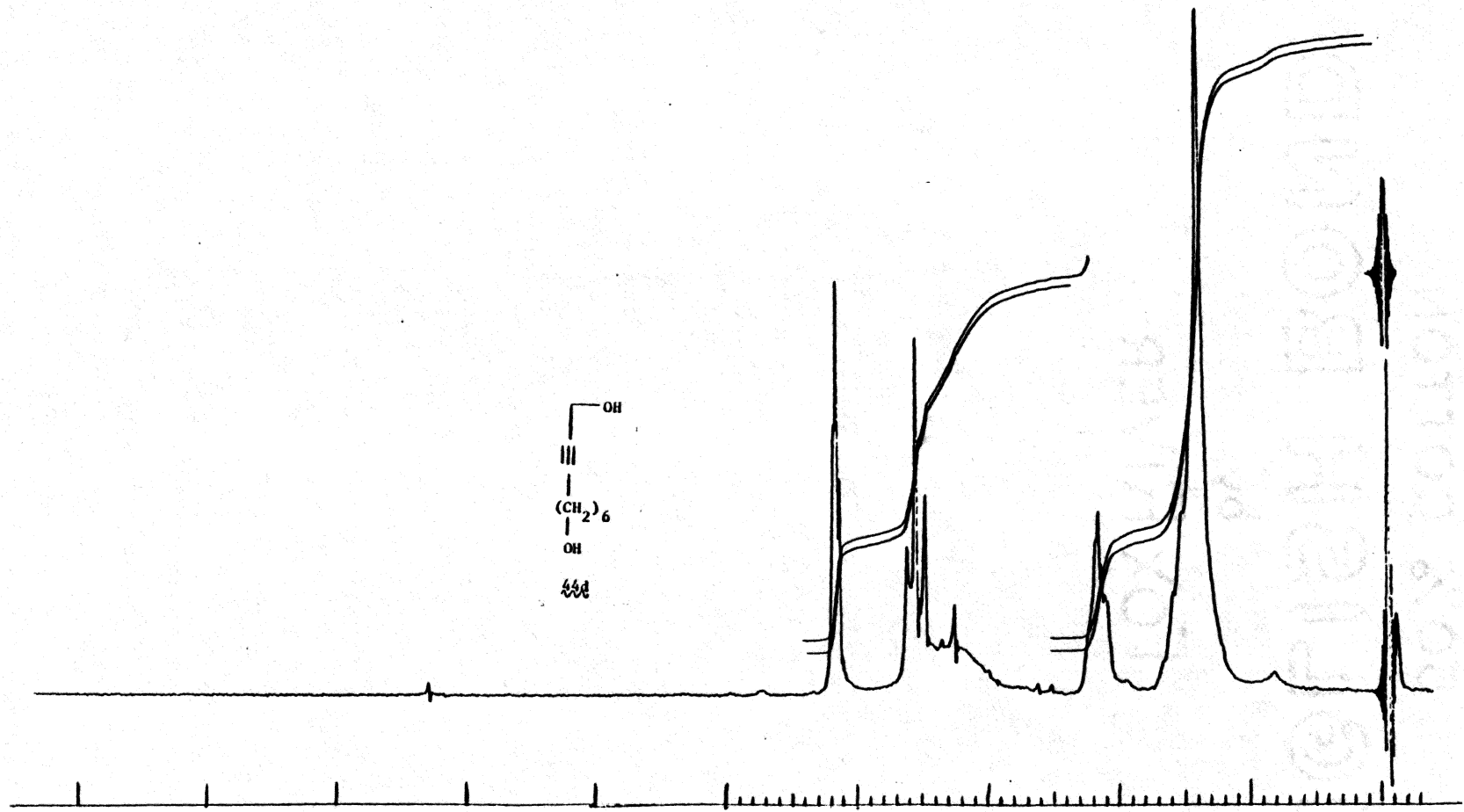


Figure 4a. 90 MHz NMR Spectrum of Diol 44d.

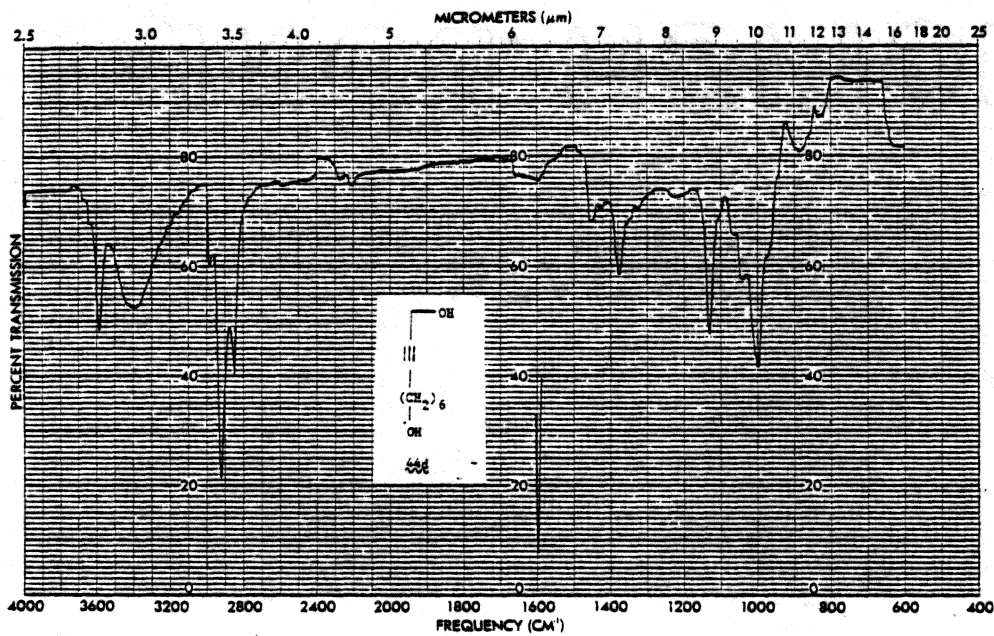


Figure 4b. IR Spectrum of Diol 44d.

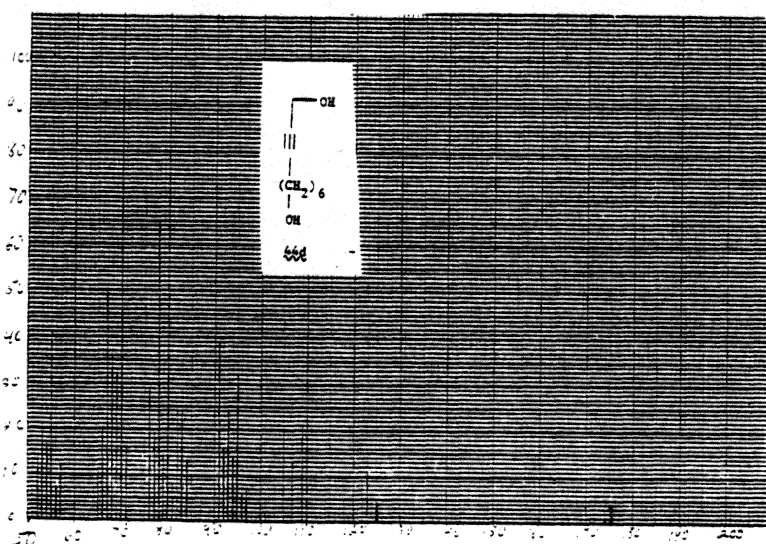


Figure 4c. Mass Spectrum of Diol 44d.

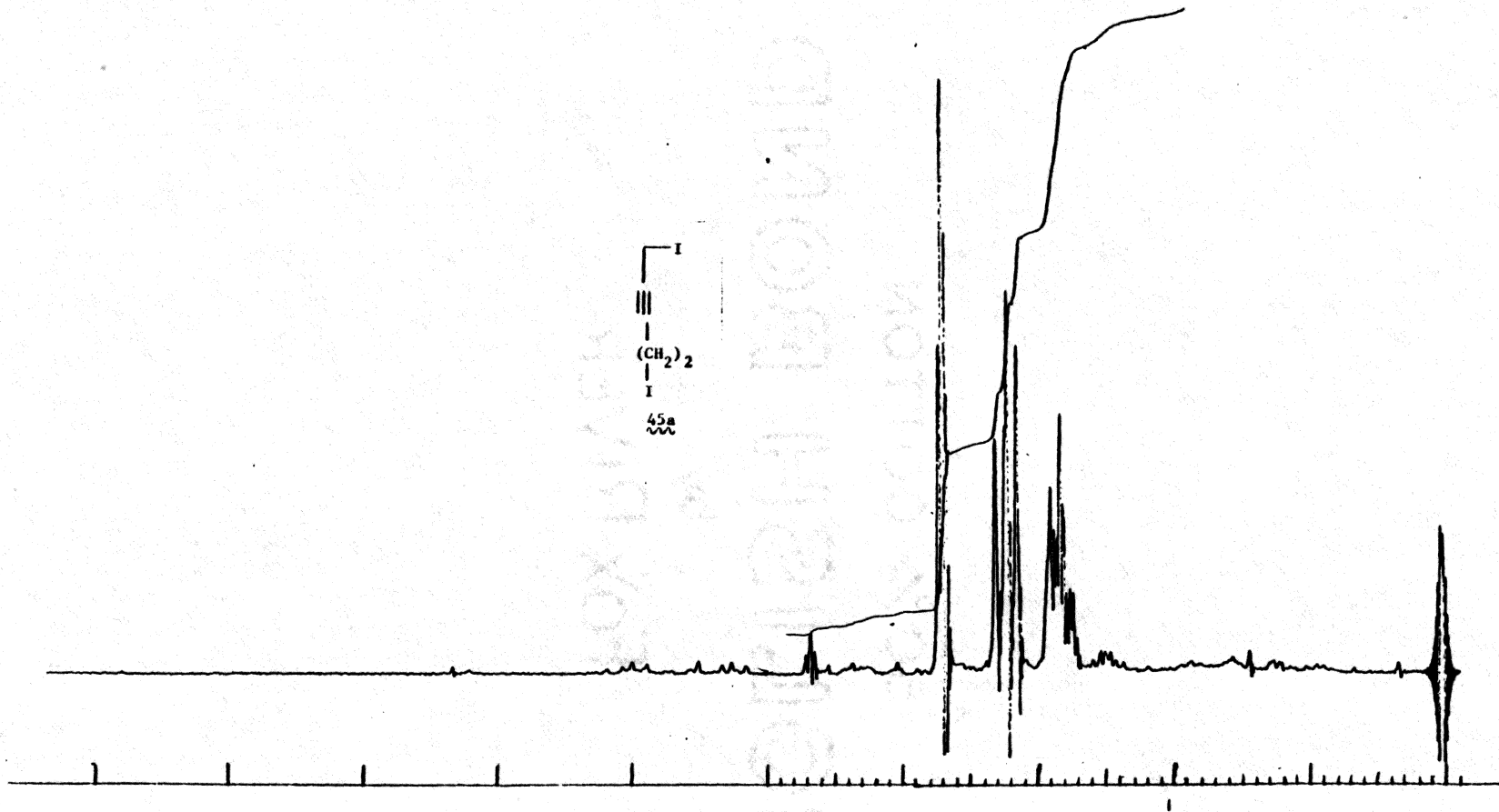


Figure 5a. 90 MHz NMR Spectrum of Diiodide 45a.

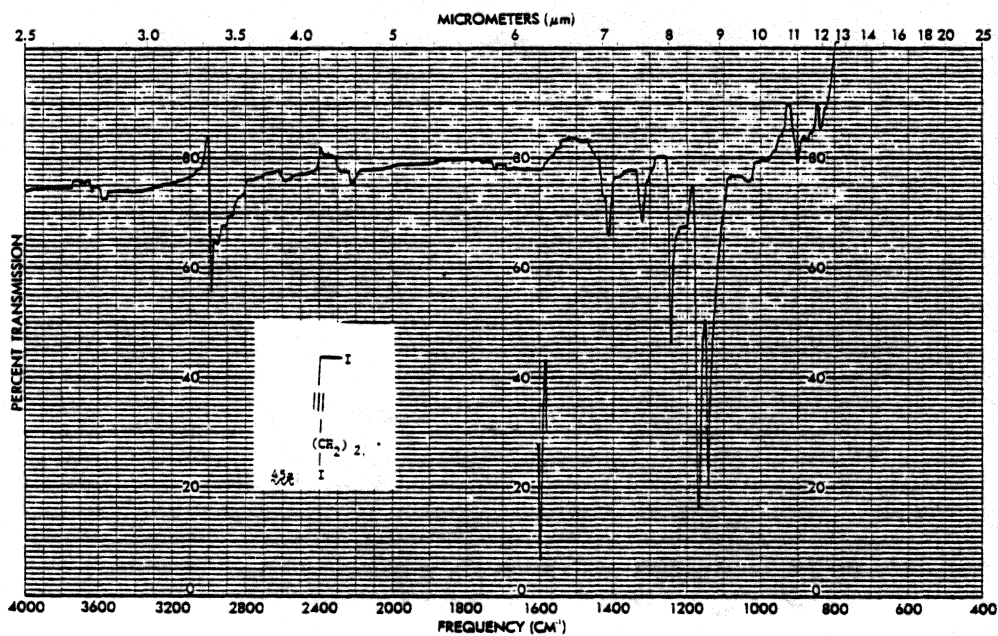


Figure 5b. IR Spectrum of Diiodide 45a.

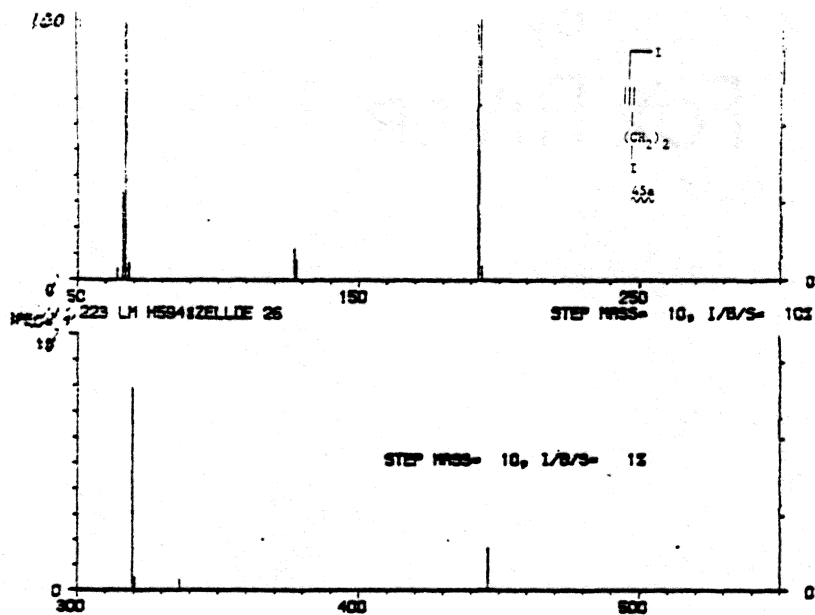


Figure 5c. Mass Spectrum of Diiodide 45a.



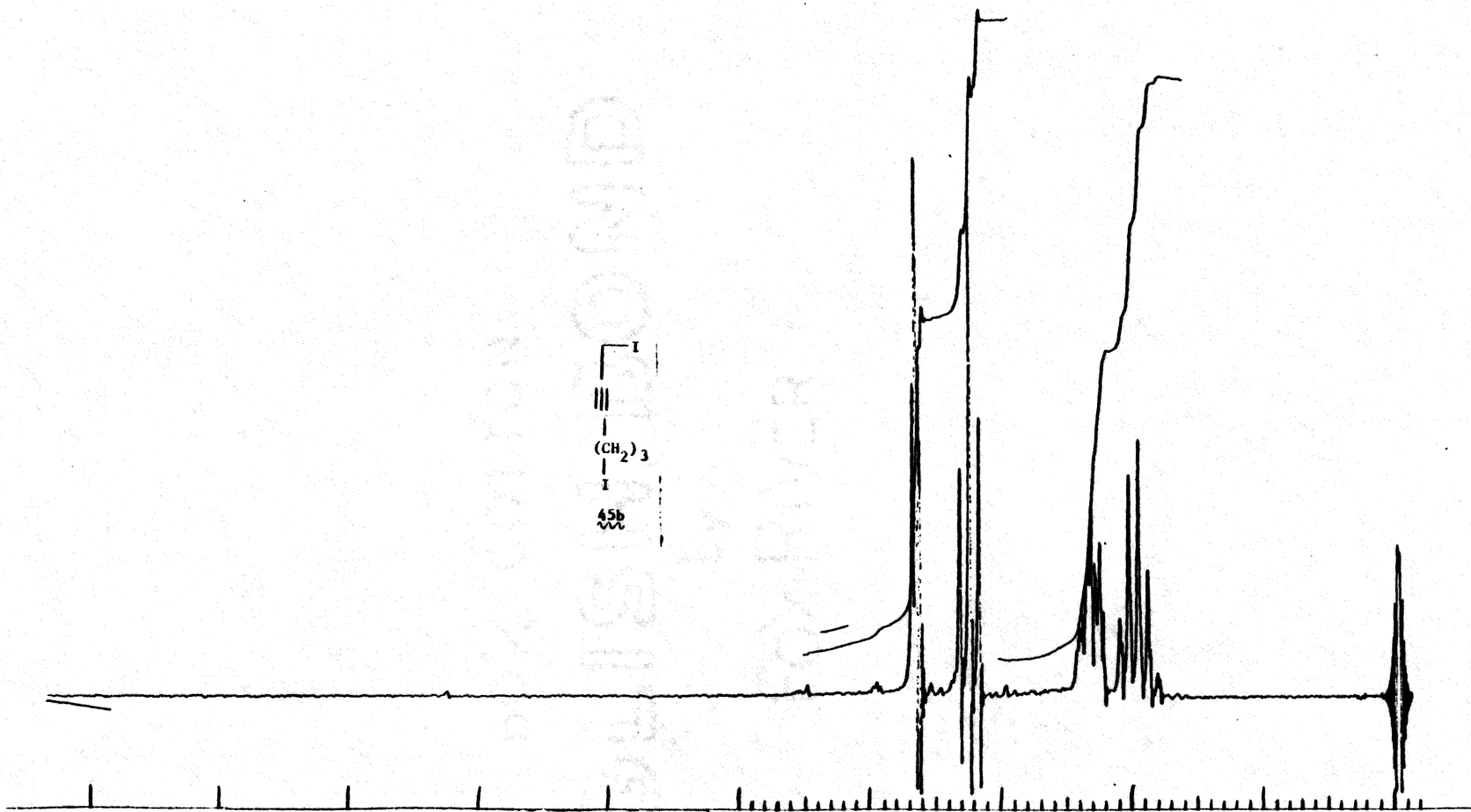


Figure 6a. 90 MHz NMR Spectrum of Diiodide 45b.

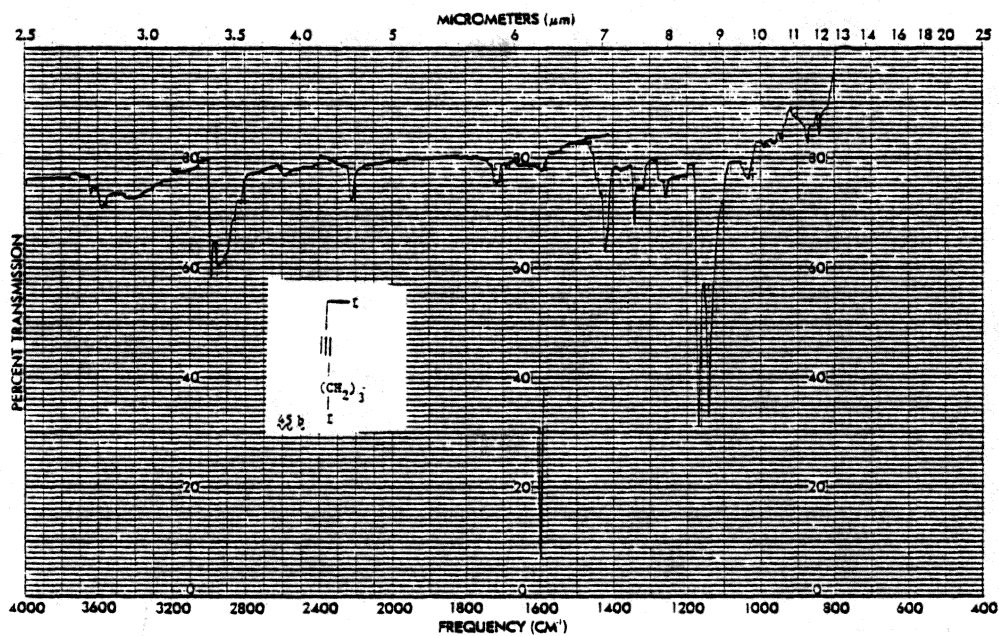


Figure 6b. IR Spectrum of Diiodide 45b.

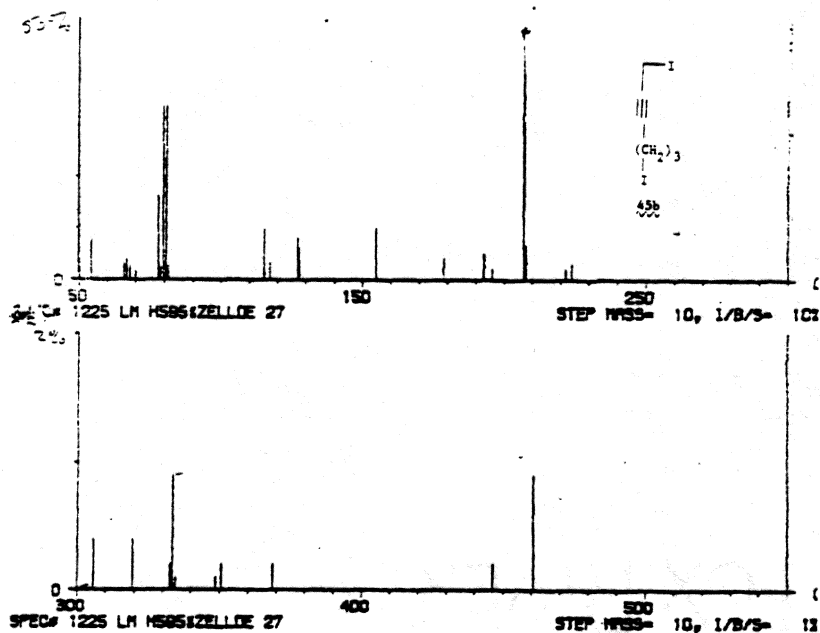


Figure 6c. Mass Spectrum of Diiodide 45b.

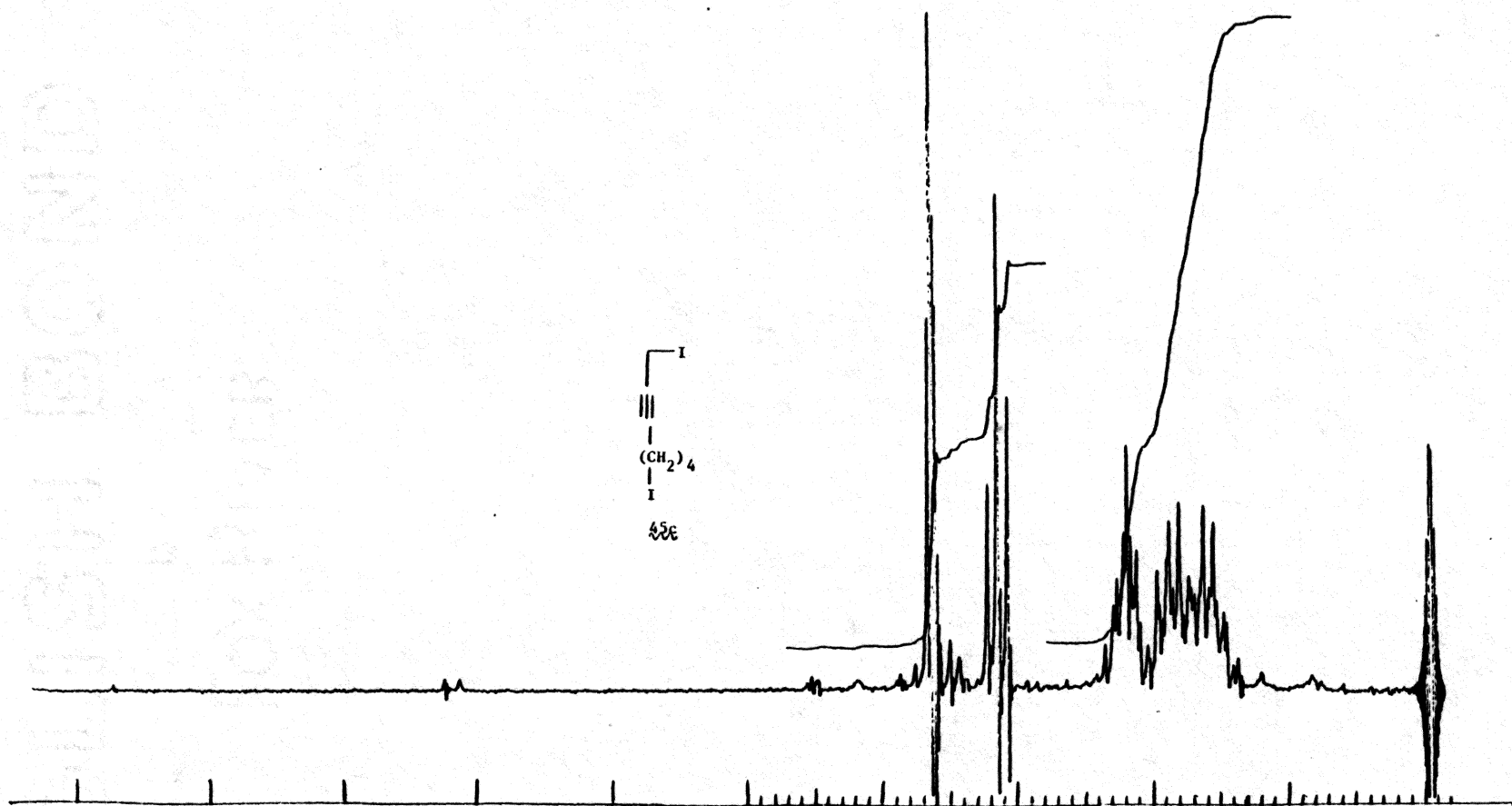


Figure 7a. 90 MHz NMR Spectrum of Diiodide 45c.

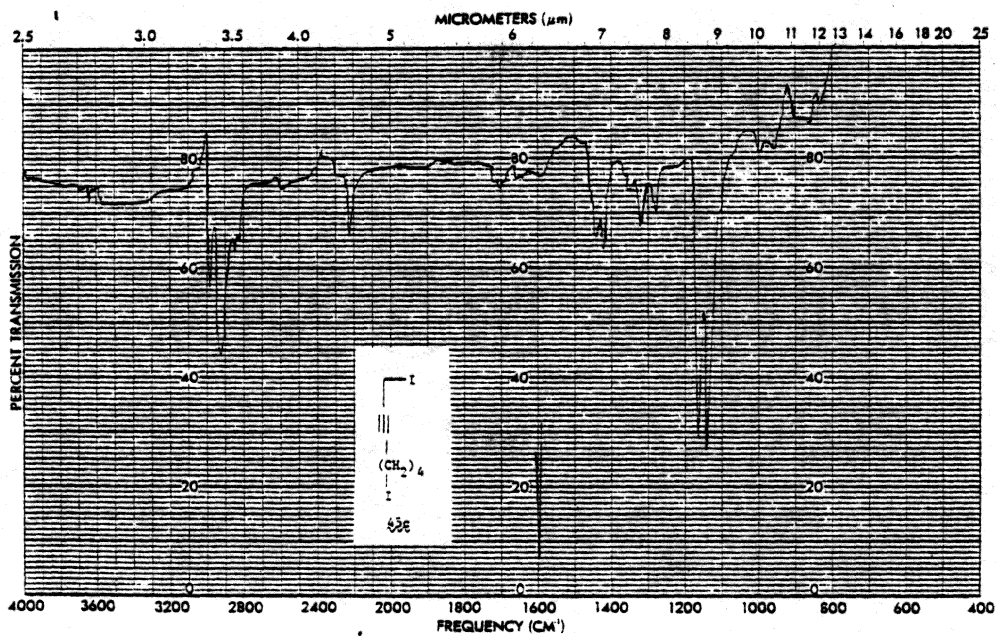


Figure 7b. IR Spectrum of Diiodide 45c.

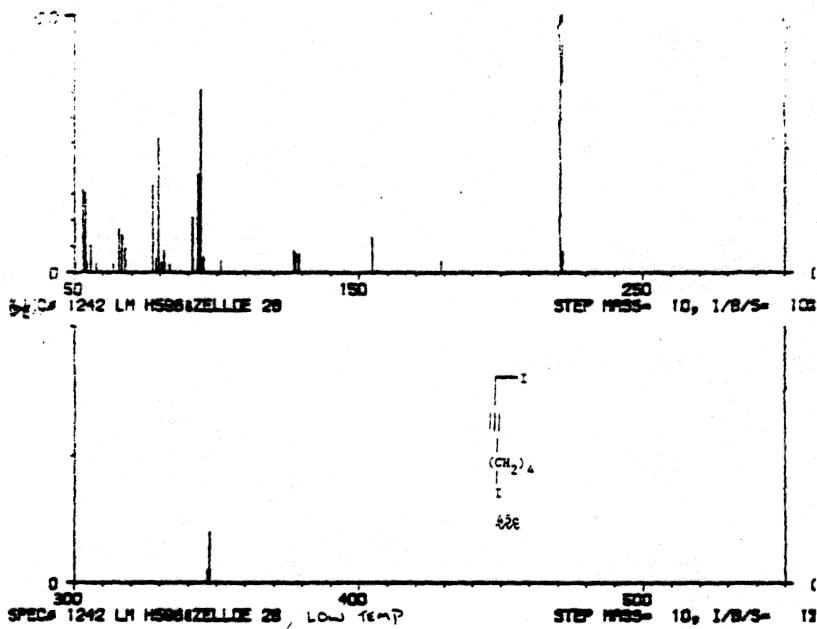


Figure 7c. Mass Spectrum of Diiodide 45c.

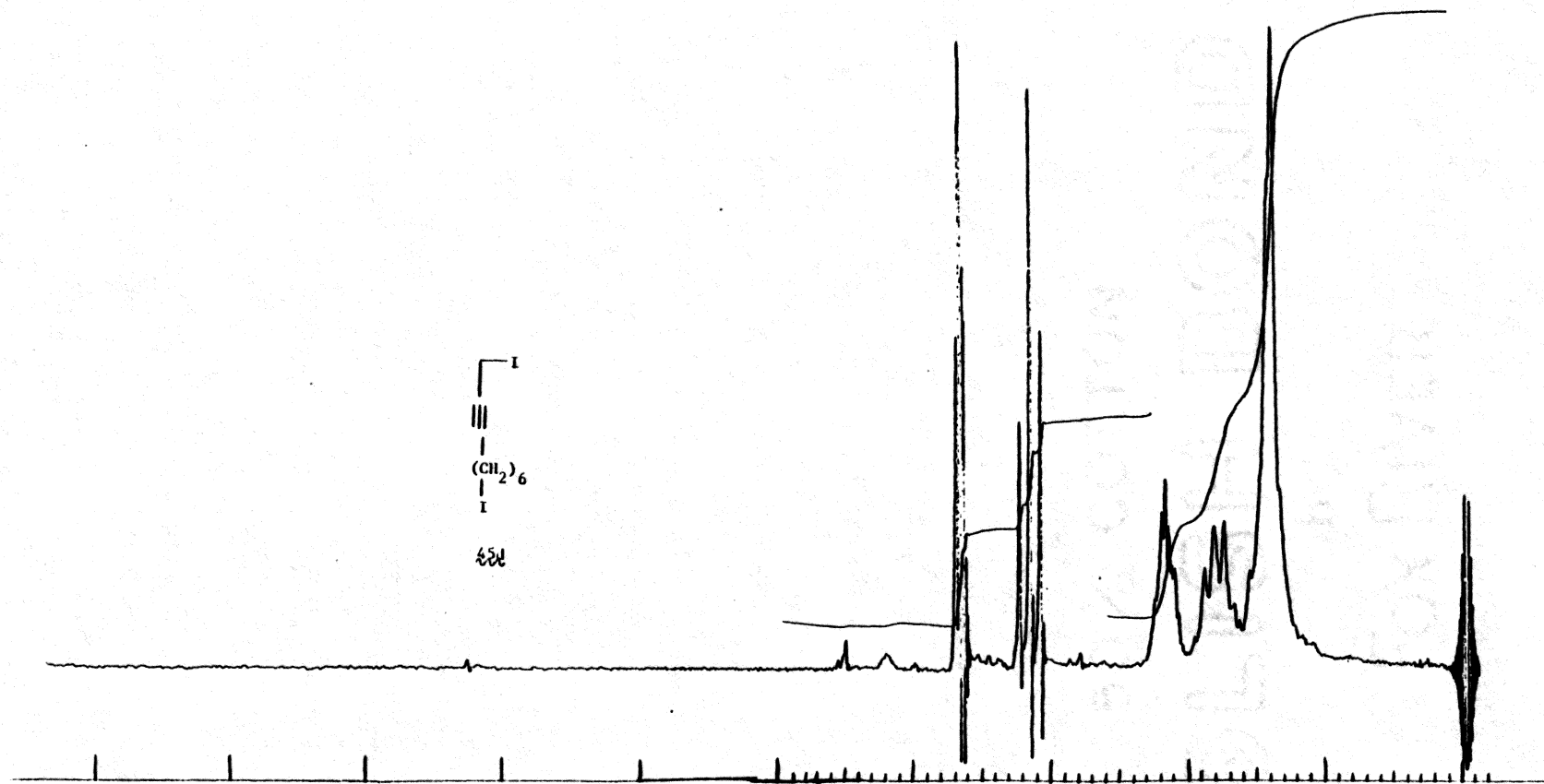


Figure 8a. 90 MHz NMR Spectrum of Diiodide 45d.

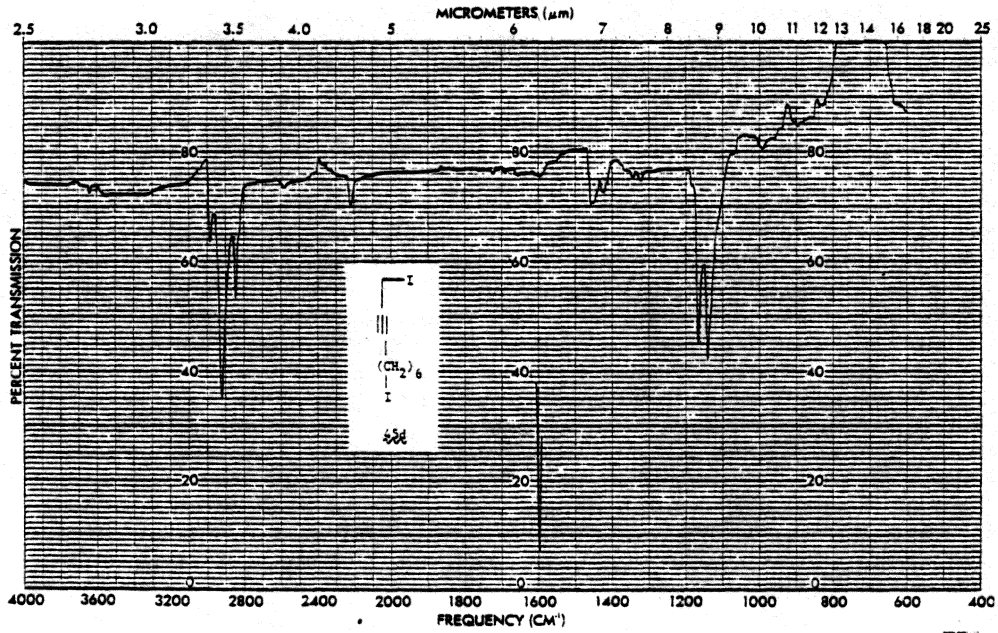


Figure 8b. IR Spectrum of Diiodide 45d.

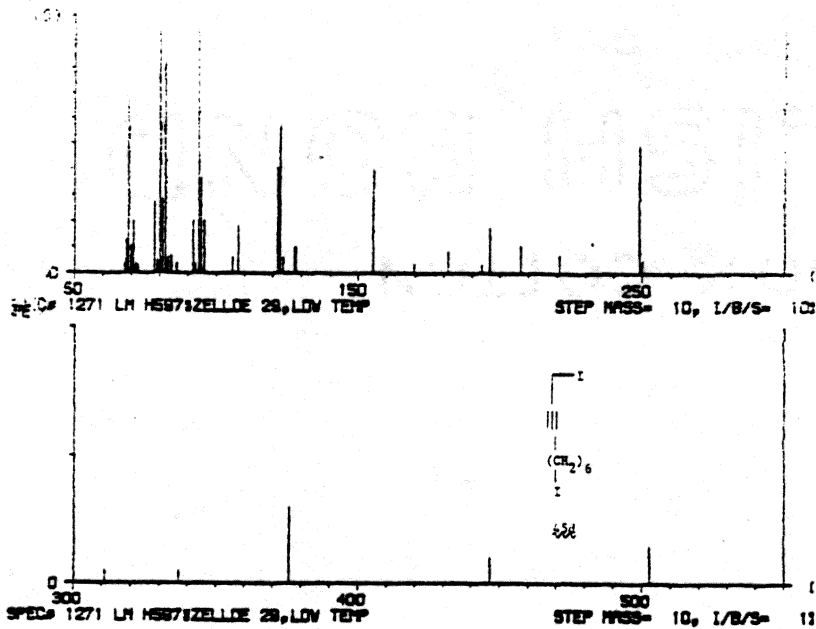


Figure 8c. Mass Spectrum of Diiodide 45d.

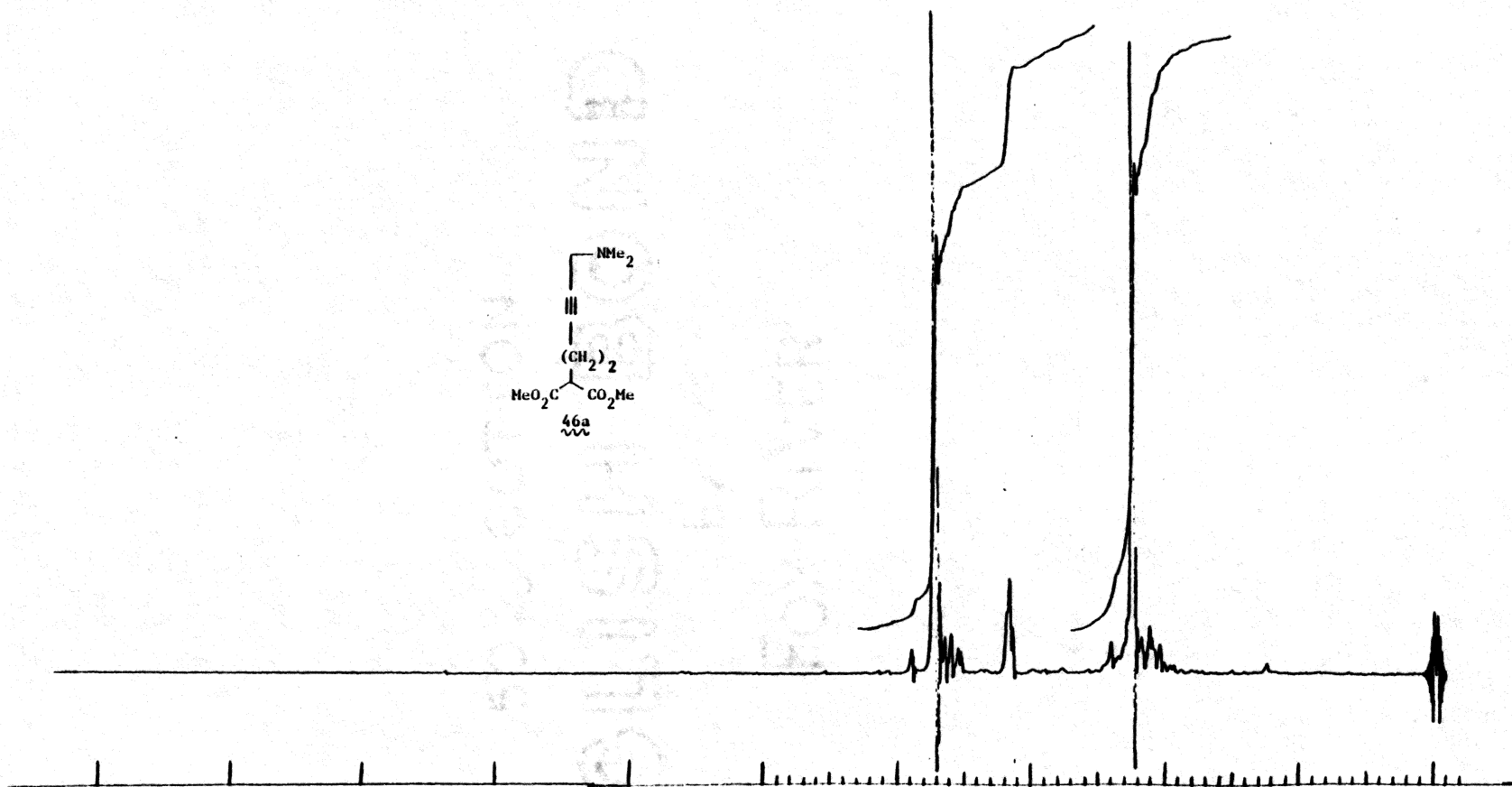


Figure 9a. 90 MHz NMR Spectrum of Aminodiester 46a.

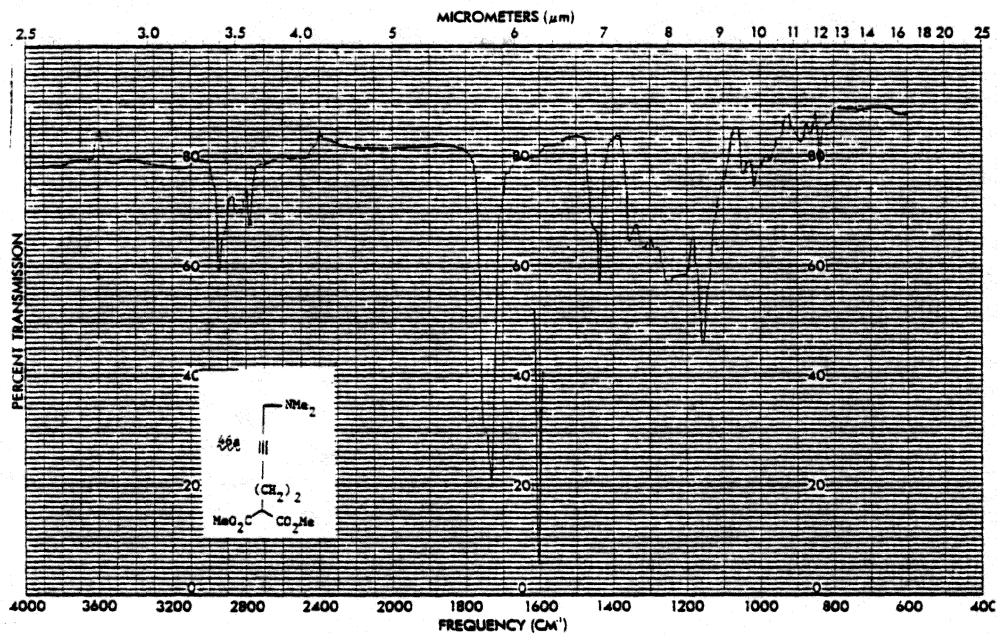


Figure 9b. IR Spectrum of Aminodiester 46a.

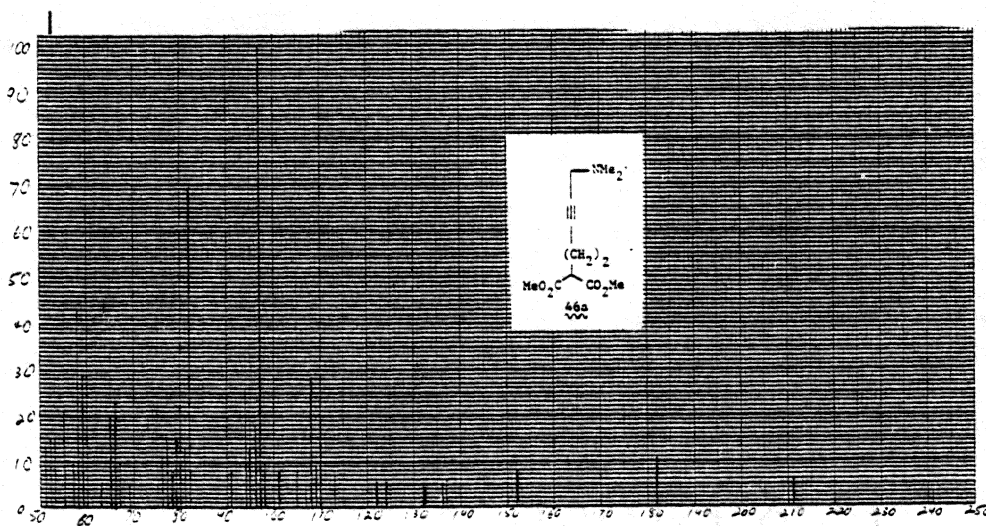


Figure 9c. Mass Spectrum of Aminodiester 46a.



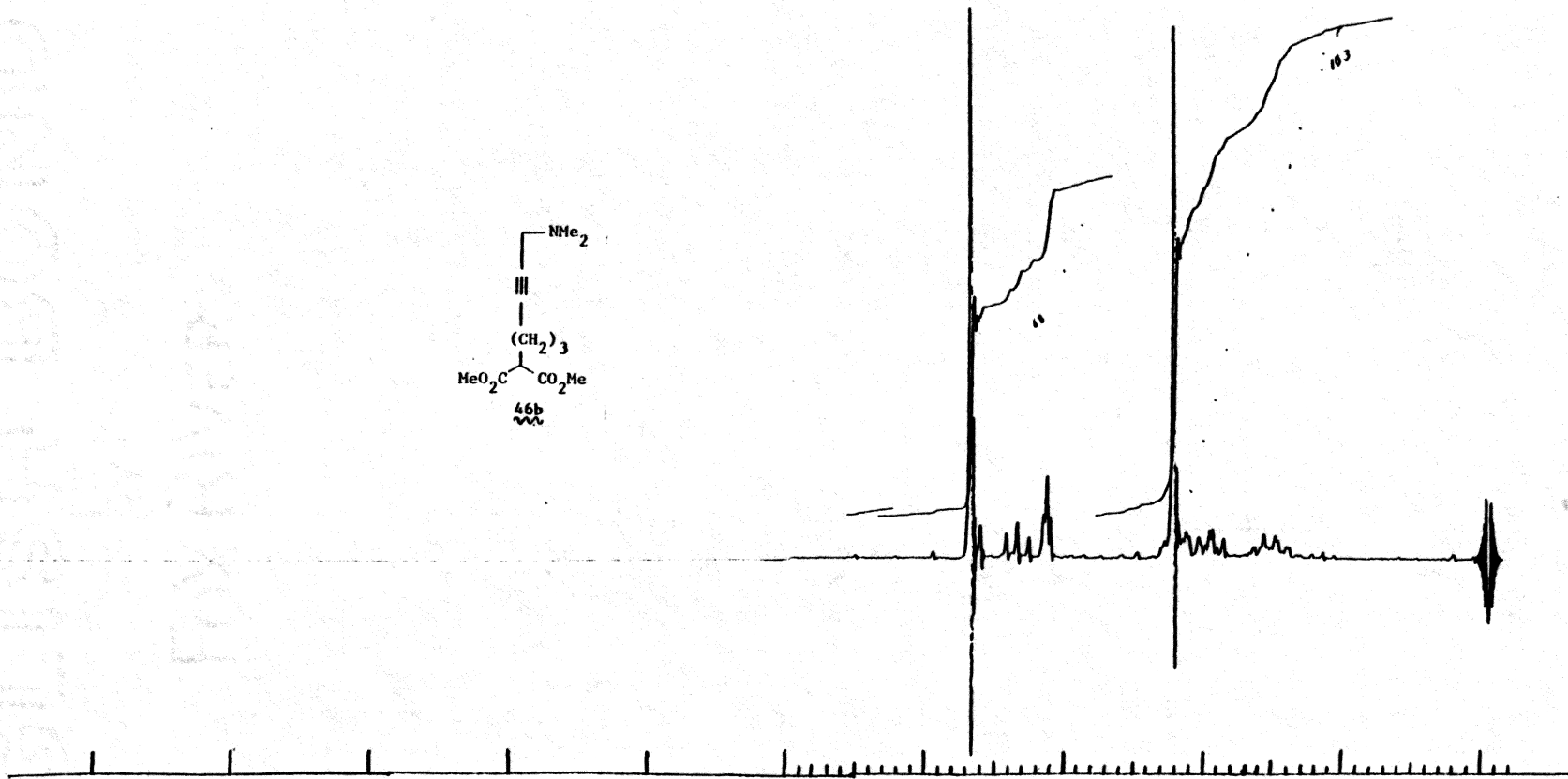
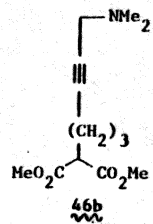
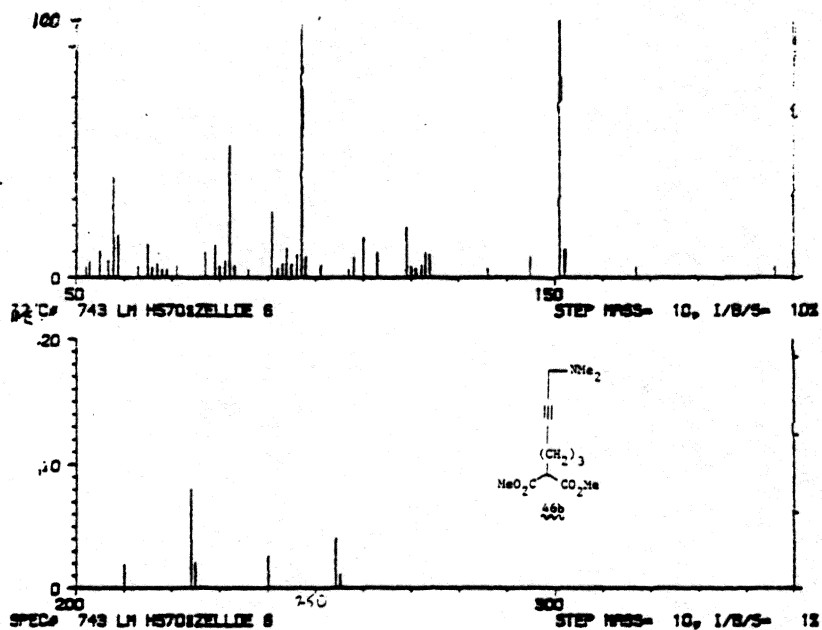
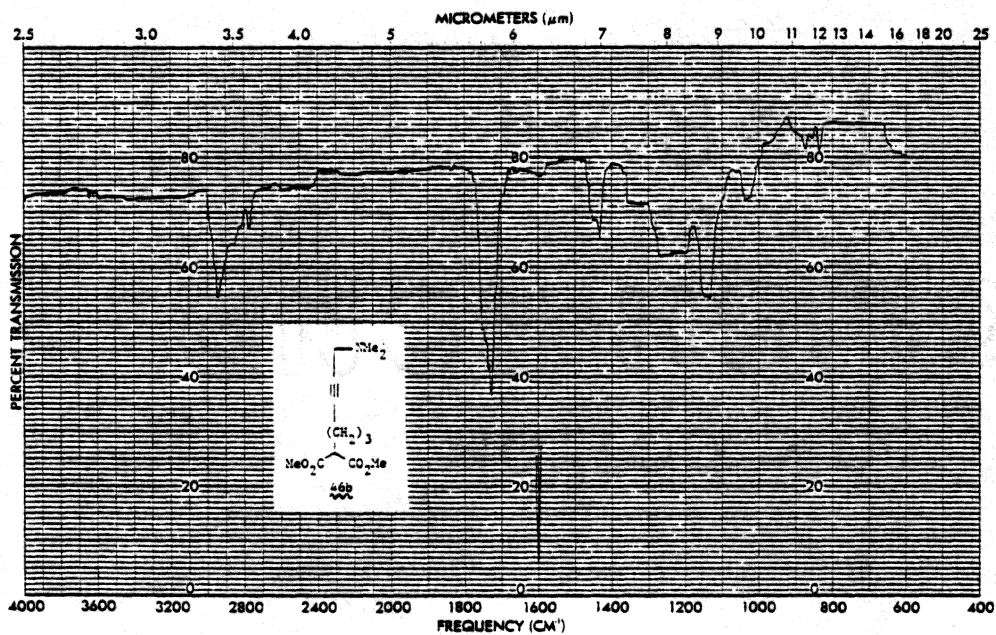


Figure 10a. 90 MHz NMR Spectrum of Aminodiester 46b.



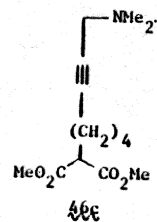
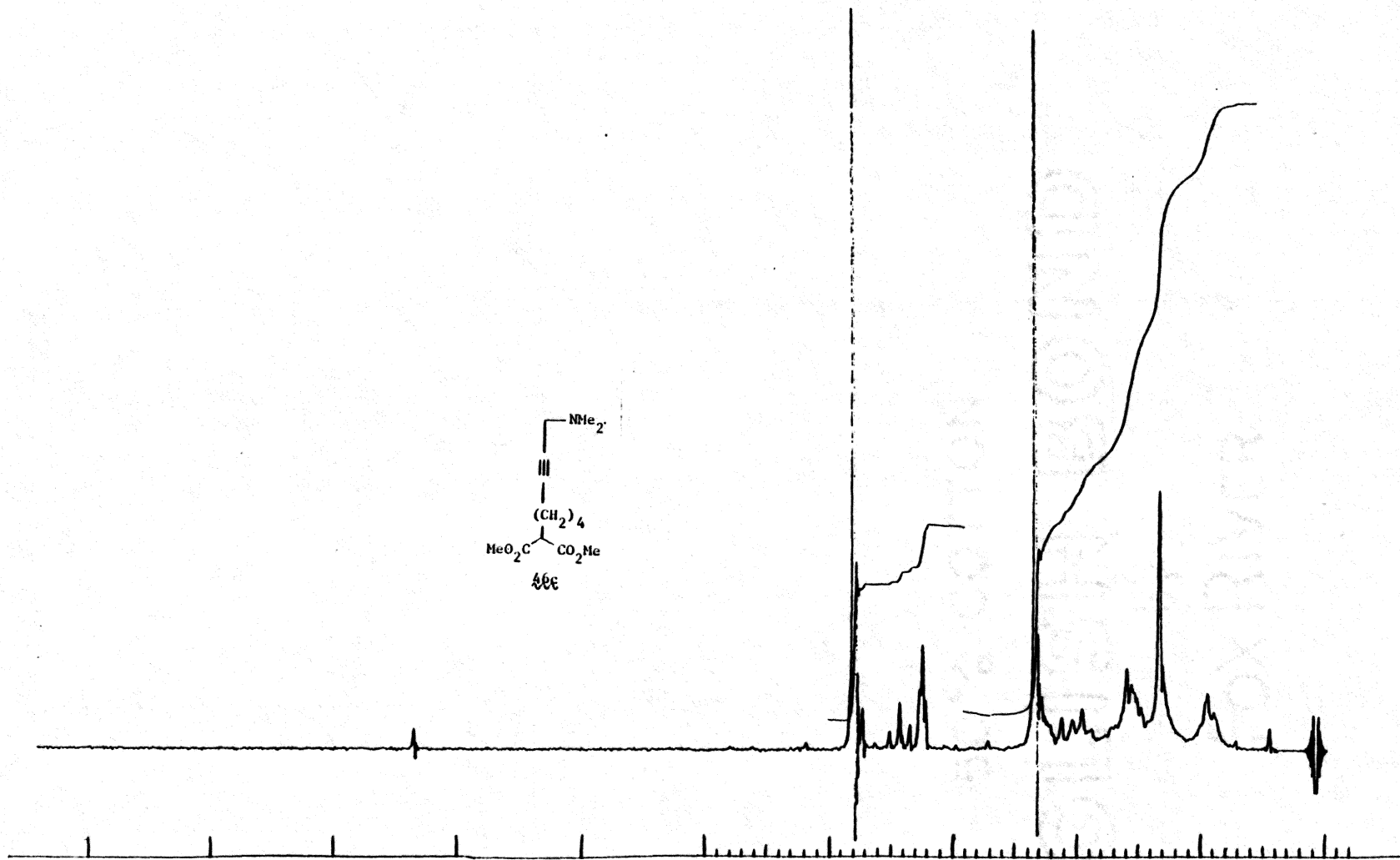


Figure 11a. 90 MHz NMR Spectrum of Aminodiester 46c.

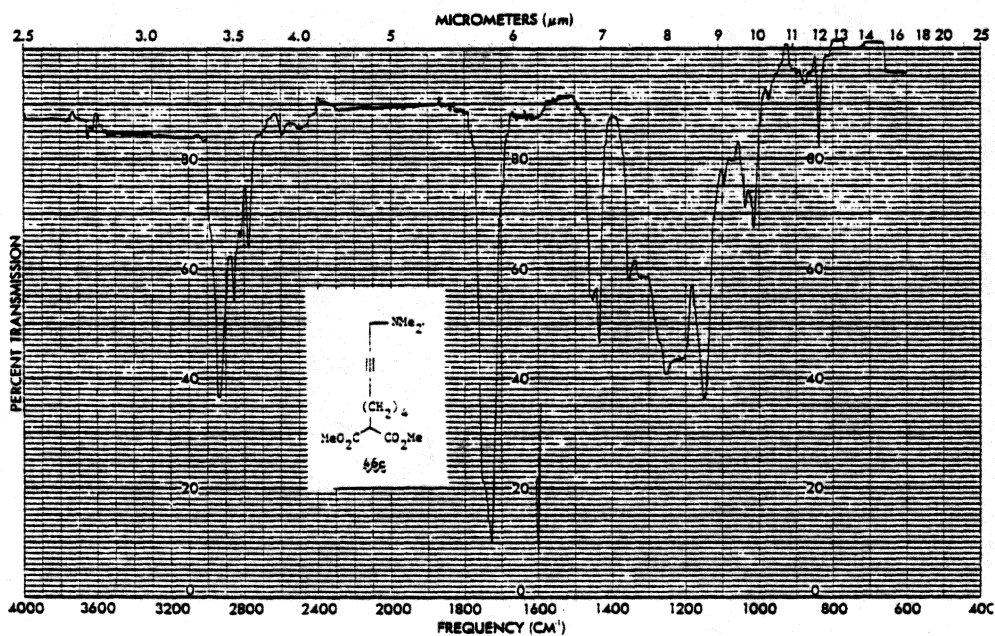


Figure 11b. IR Spectrum of Aminodiester 46c.

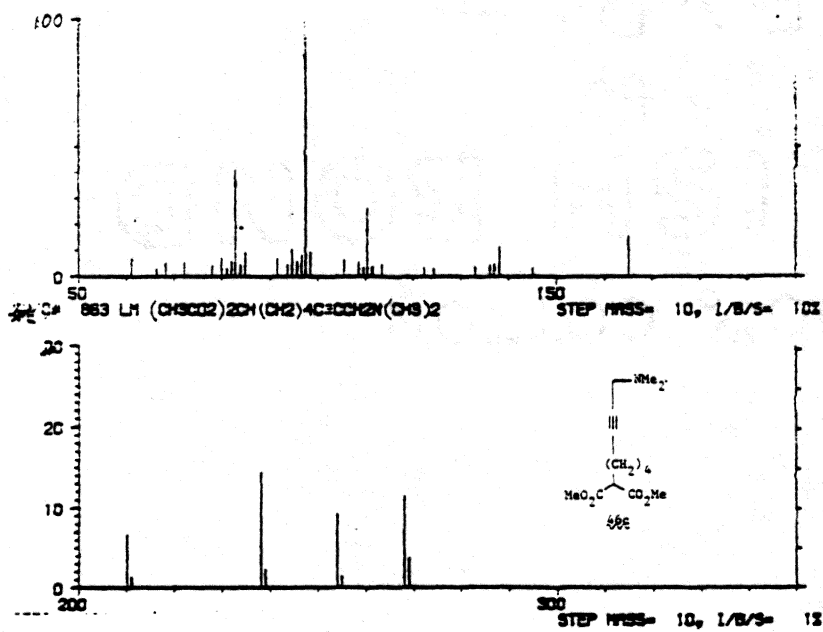


Figure 11c. Mass Spectrum of Aminodiester 46c.

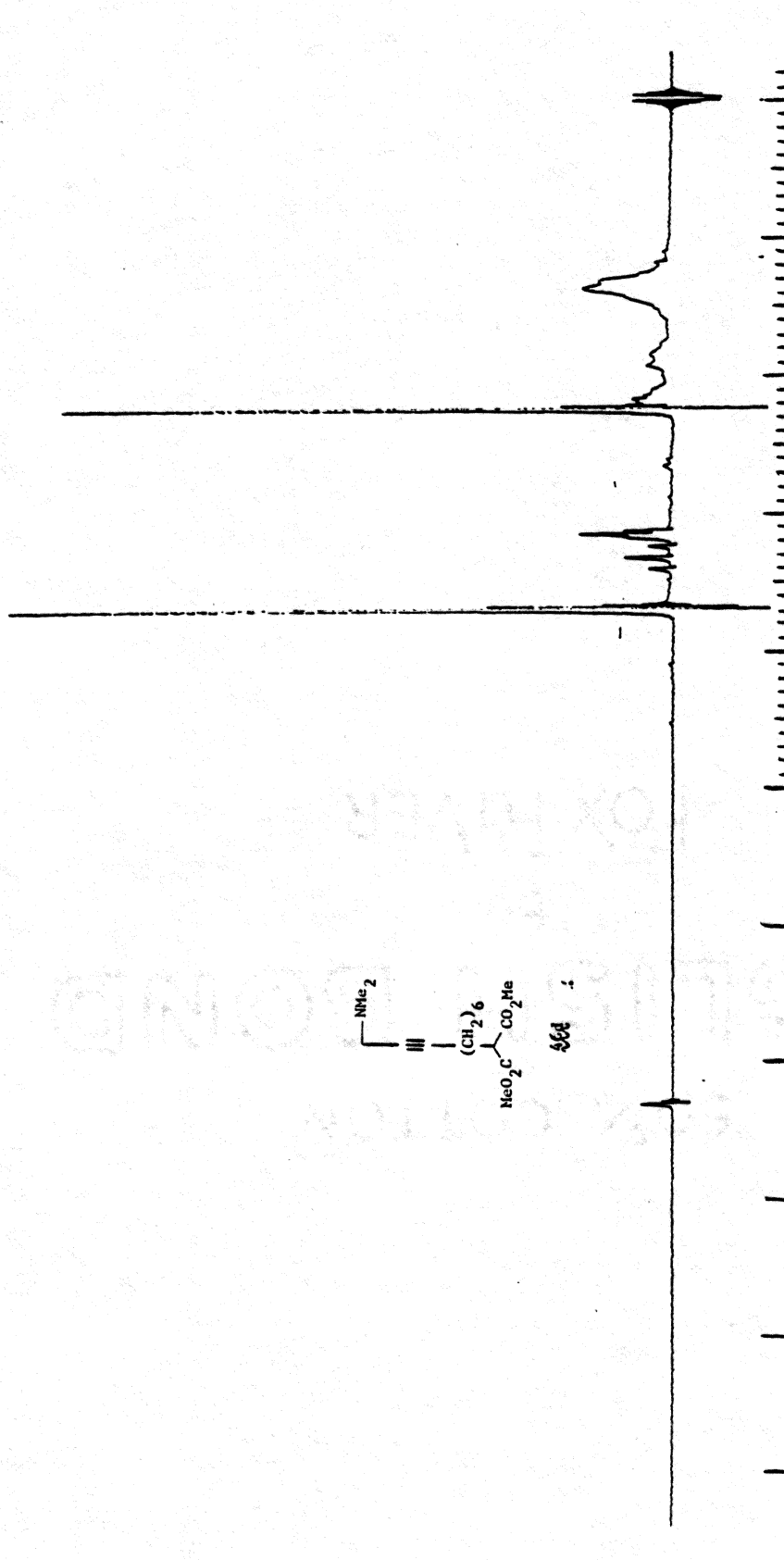


Figure 12a. 90 MHz NMR Spectrum of Aminodiester 46d.

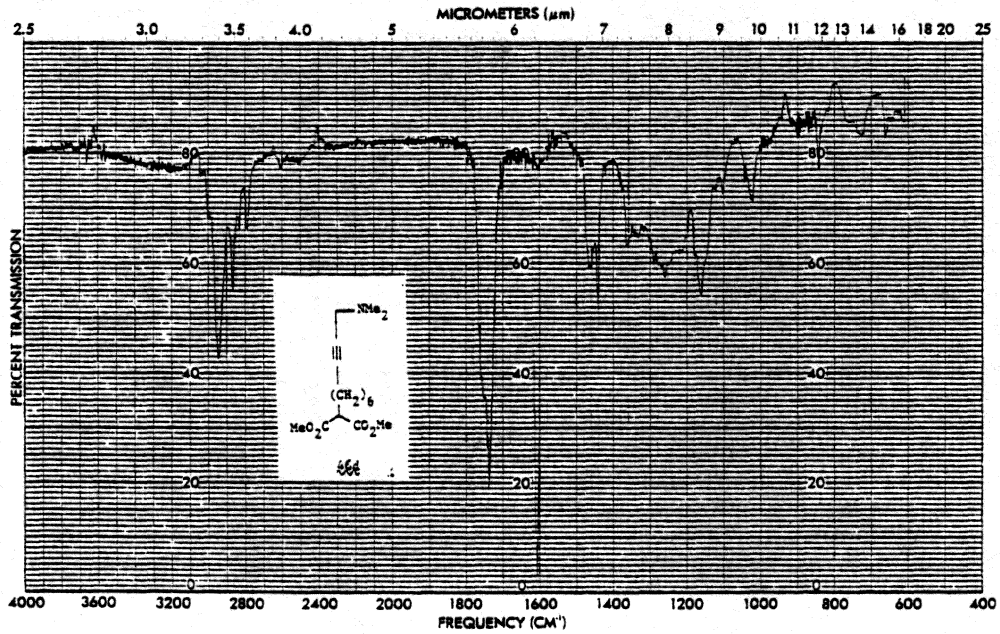


Figure 12b. IR Spectrum of Aminodiester 46d.

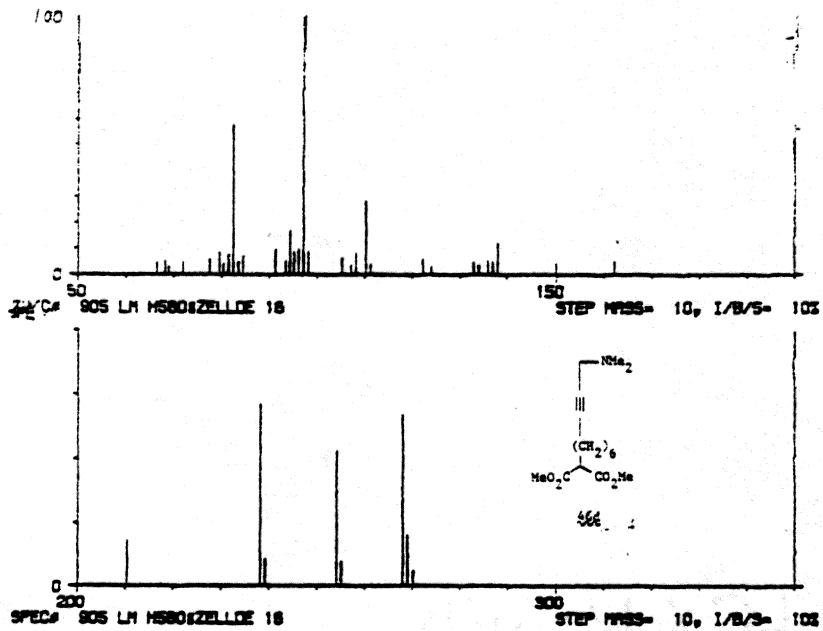


Figure 12c. Mass Spectrum of Aminodiester 46d.

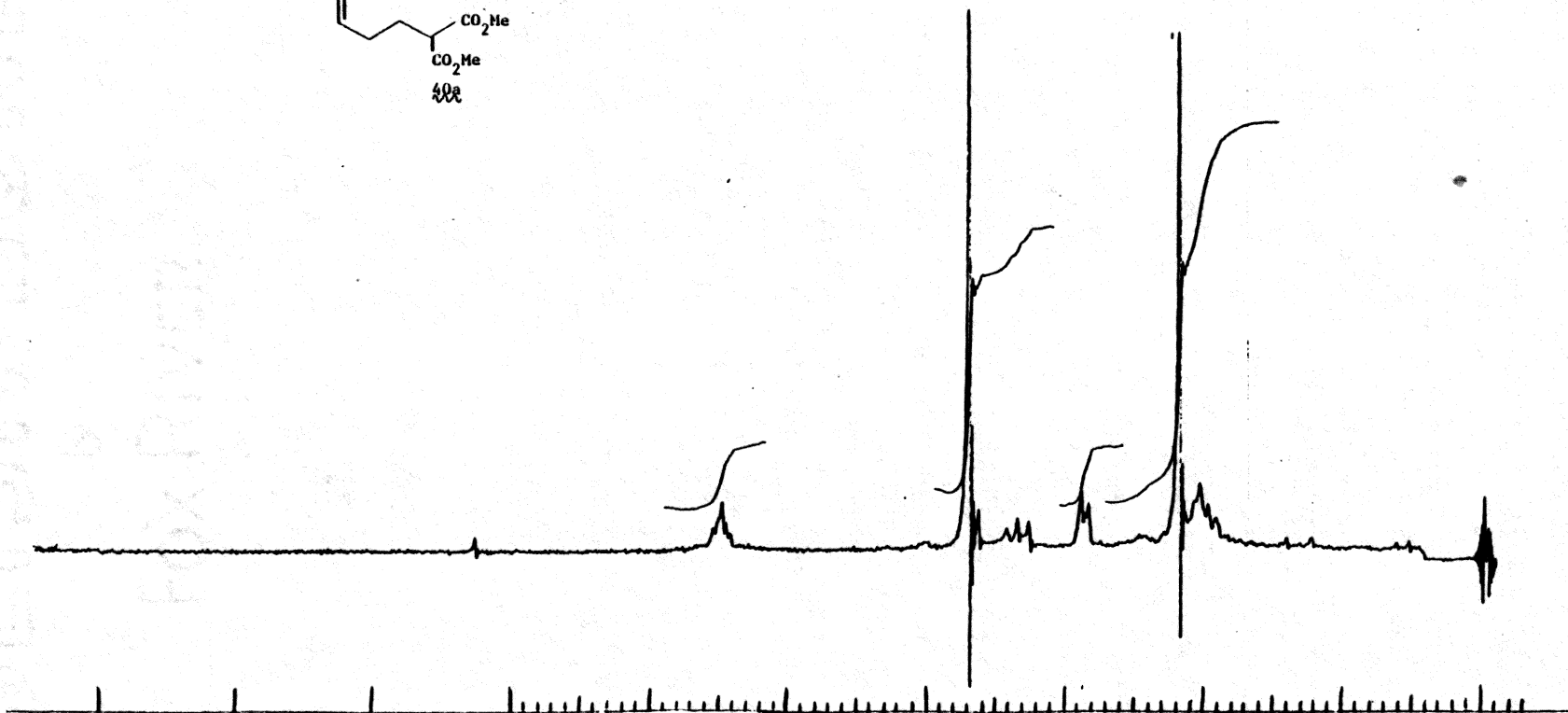
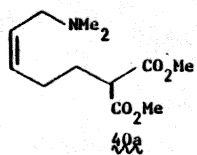


Figure 13a. 90 MHz NMR Spectrum of Aminodiester 40a.

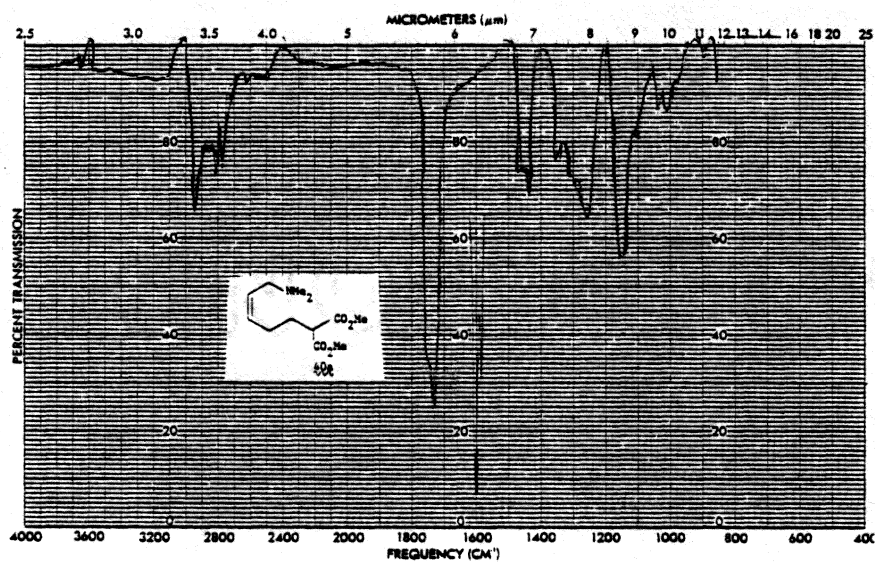


Figure 13b. IR Spectrum of Aminodiester 40a.

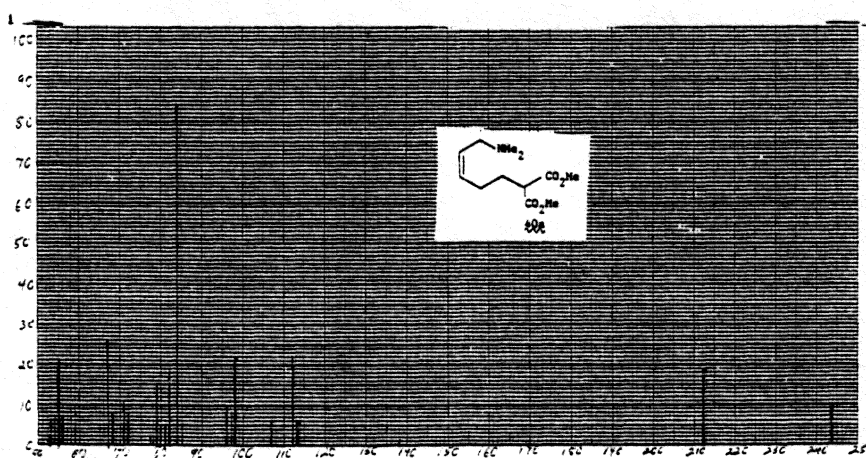


Figure 13c. Mass Spectrum of Aminodiester 40a.



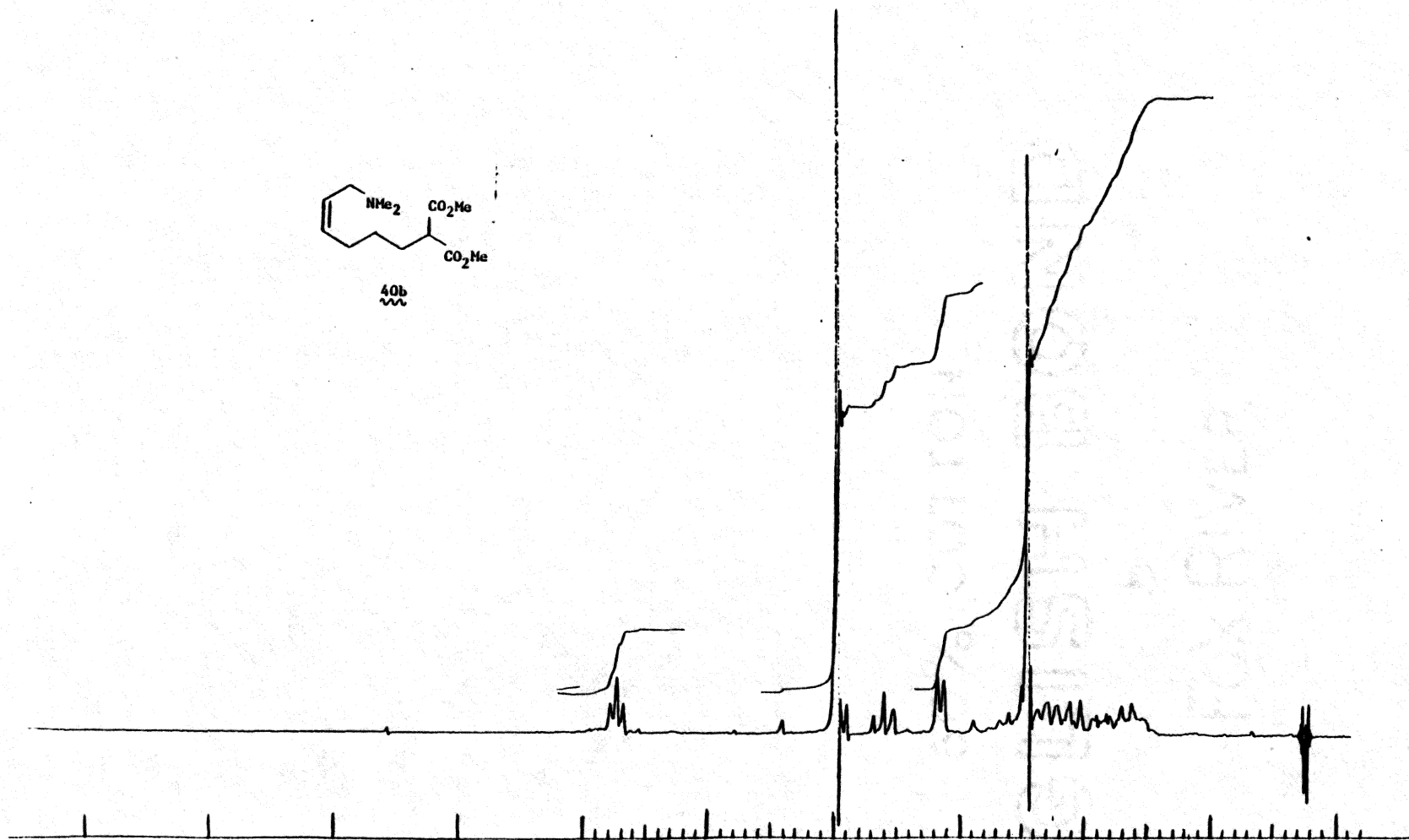
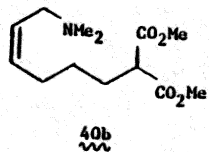


Figure 14a. 90 MHz NMR Spectrum of Aminodiester 40b.

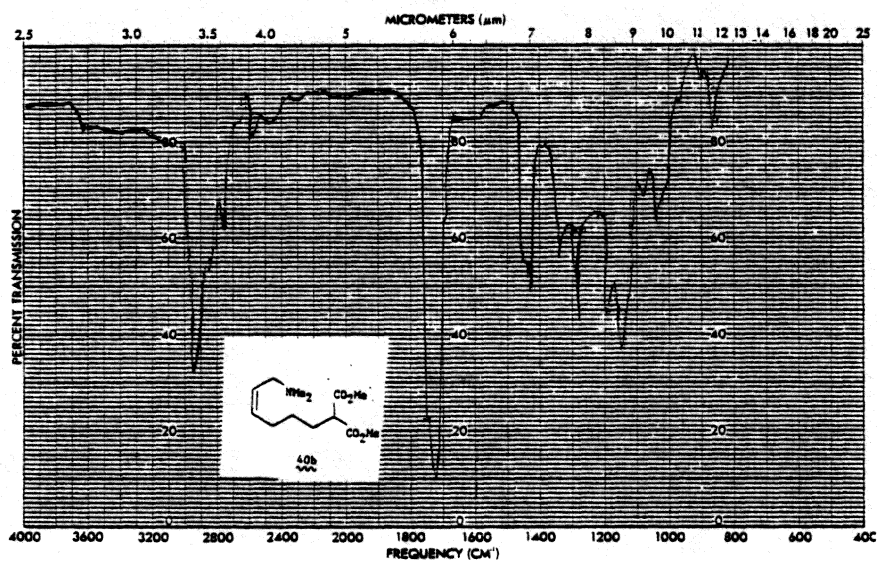


Figure 14b. IR Spectrum of Aminodiester 40b.

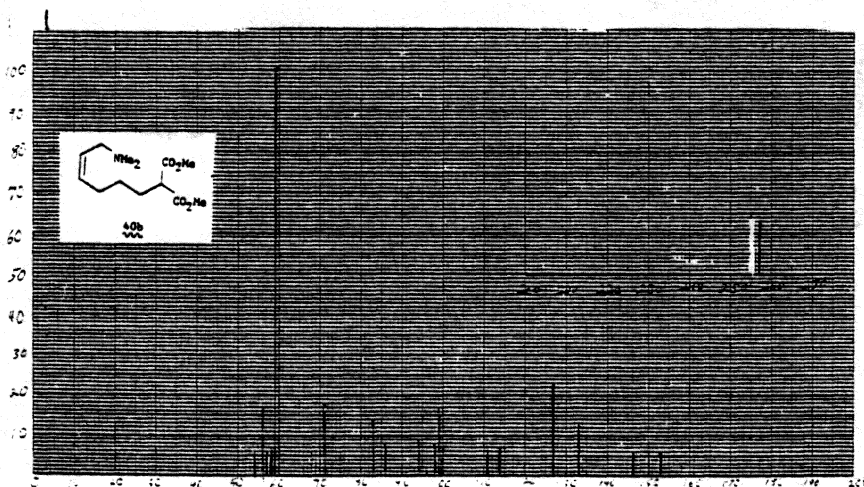


Figure 14c. Mass Spectrum of Aminodiester 40b.

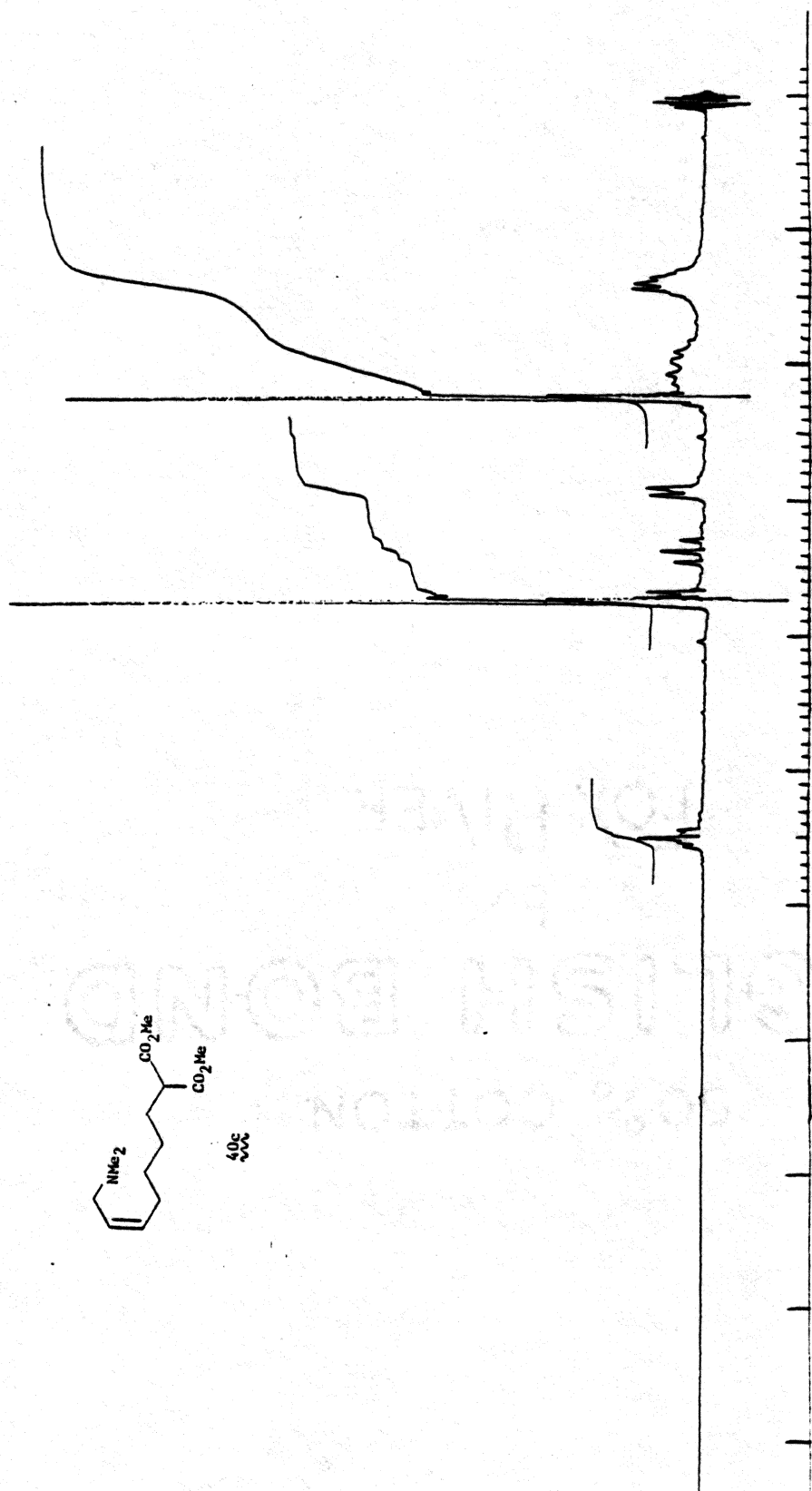


Figure 15a. 90 MHz NMR Spectrum of Aminodiester 40c.

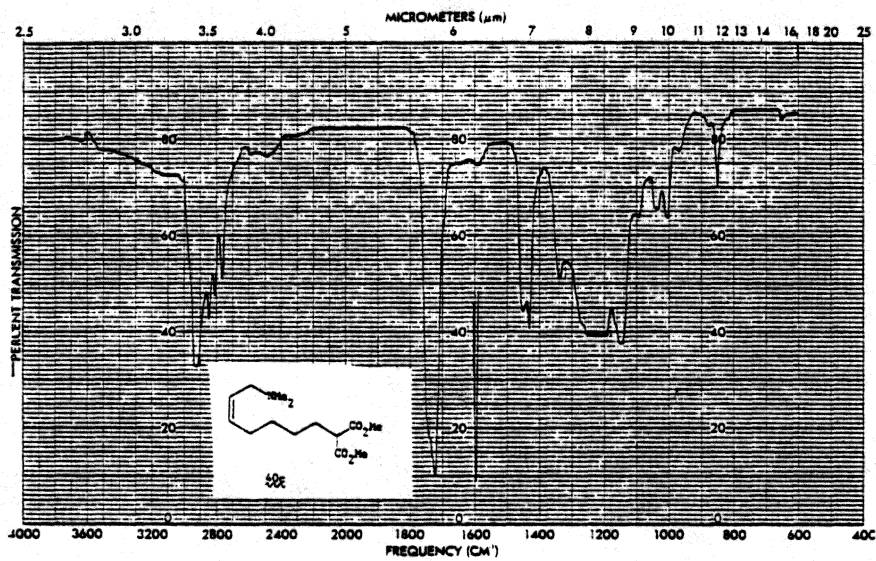


Figure 15b. IR Spectrum of Aminodiester 40c.

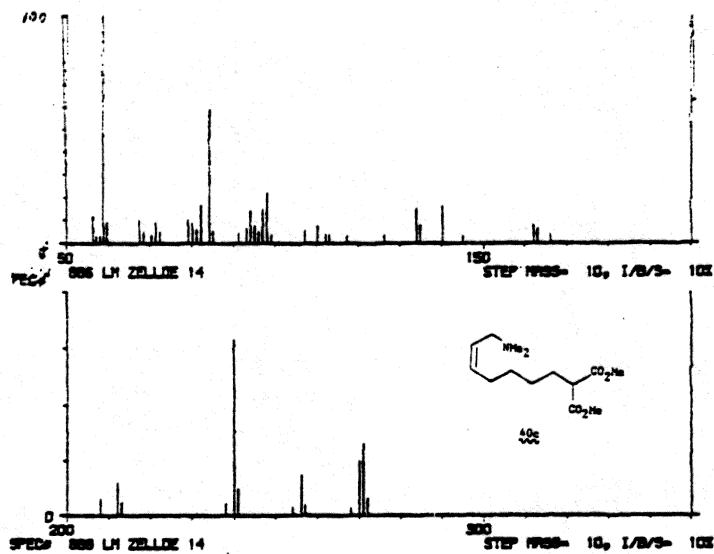


Figure 15c. Mass Spectrum of Aminodiester 40c.

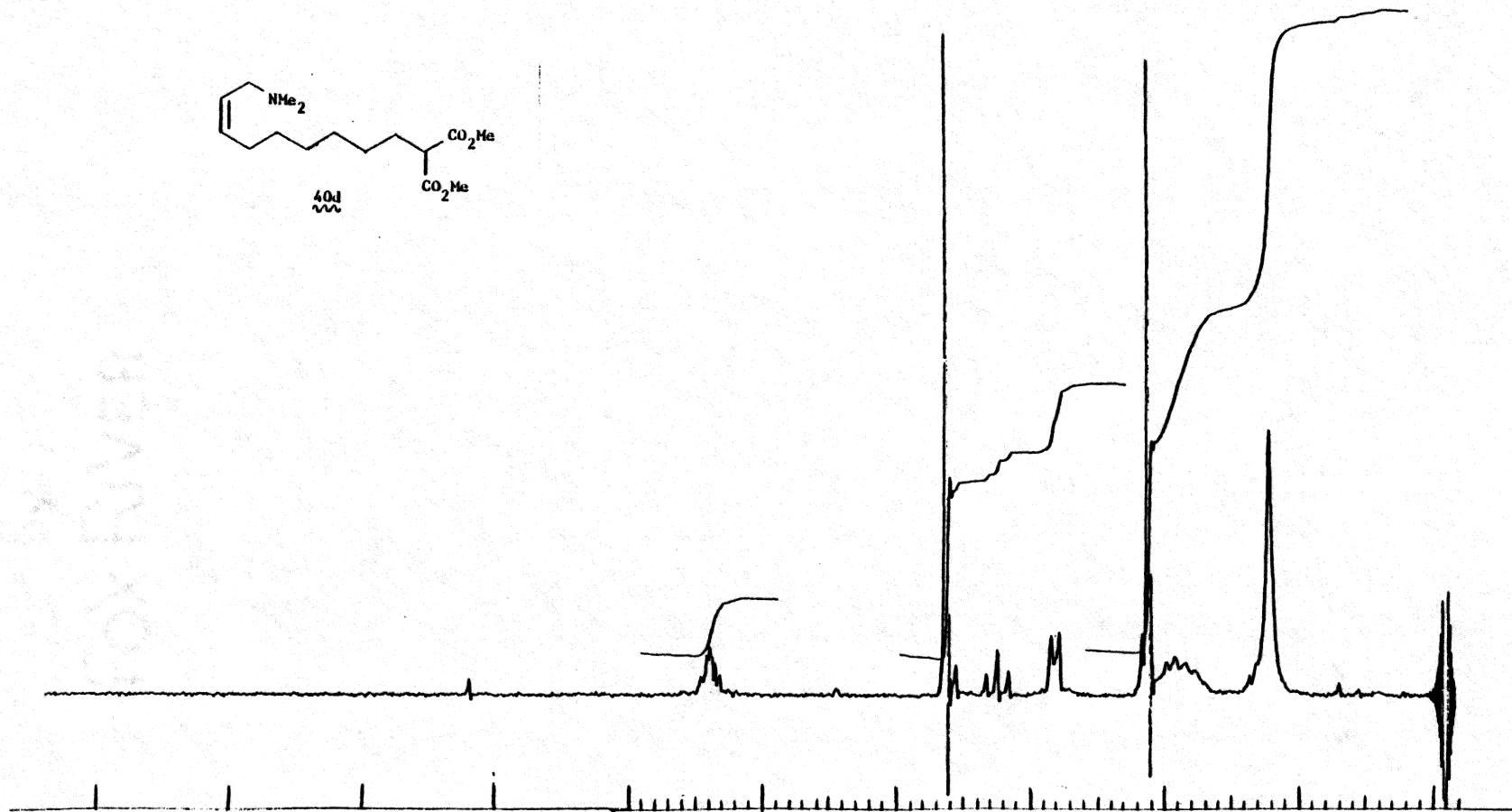
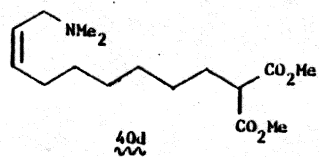


Figure 16a. 90 MHz NMR Spectrum of Aminodiester 40d.

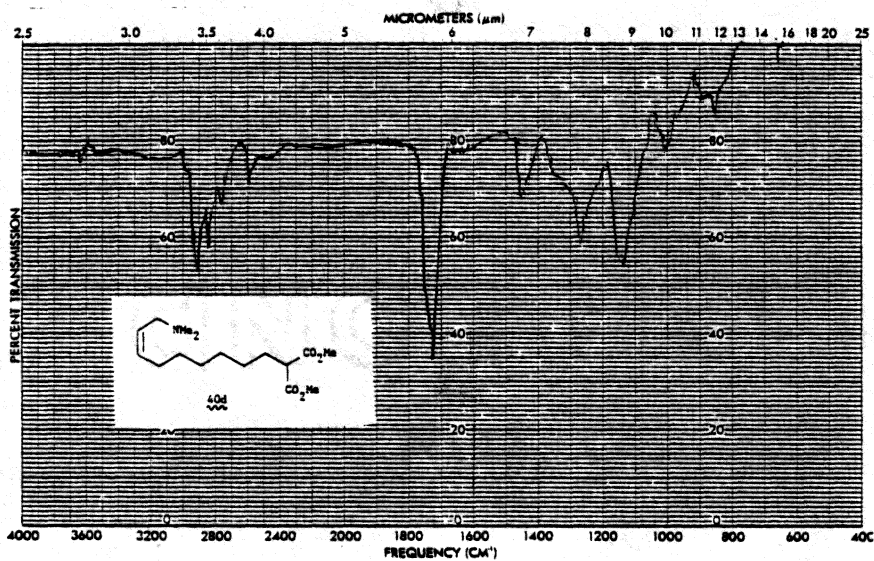


Figure 16b. IR Spectrum of Aminodiester 40d.

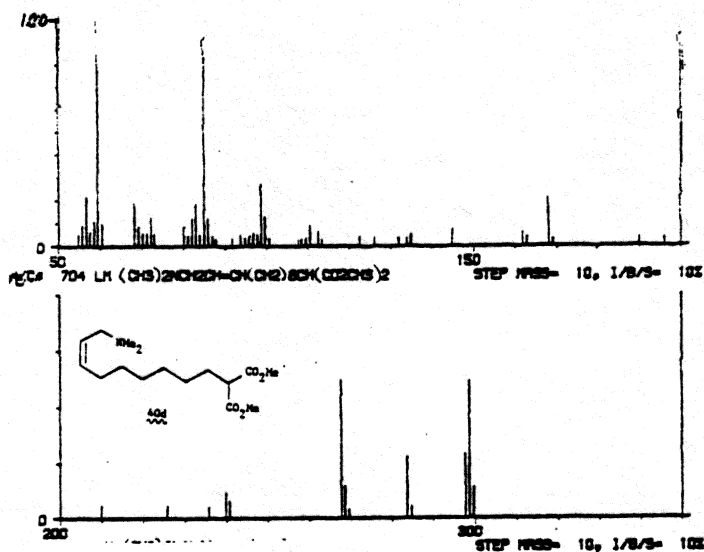
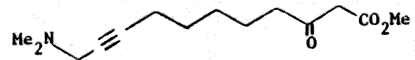


Figure 16c. Mass Spectrum of Aminodiester 40d.



47

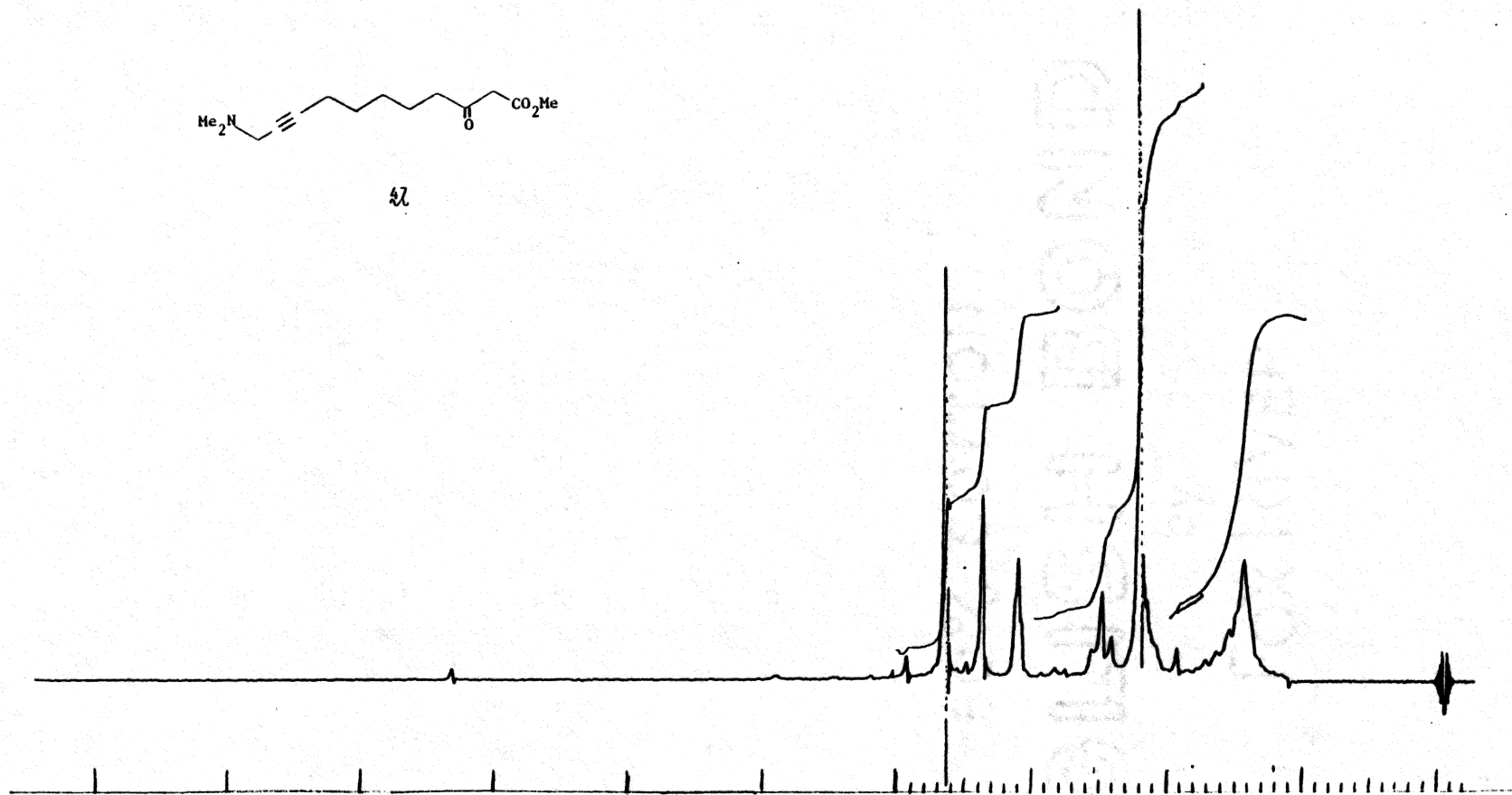


Figure 17a. 90 MHz NMR Spectrum of Amino Ketoester 47.

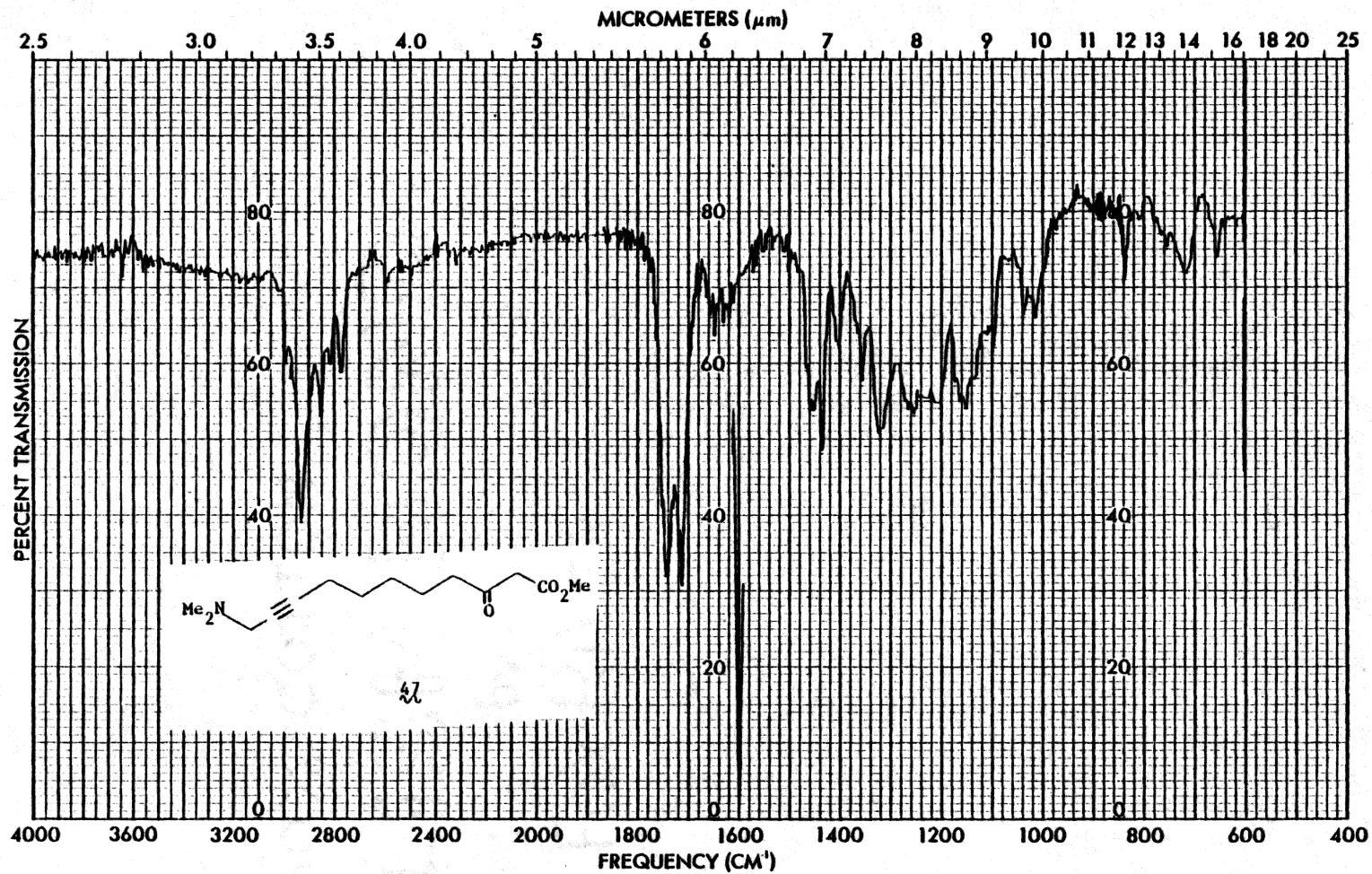
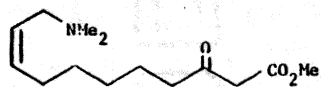


Figure 17b. IR Spectrum of Amino Ketoester 47.





40e  
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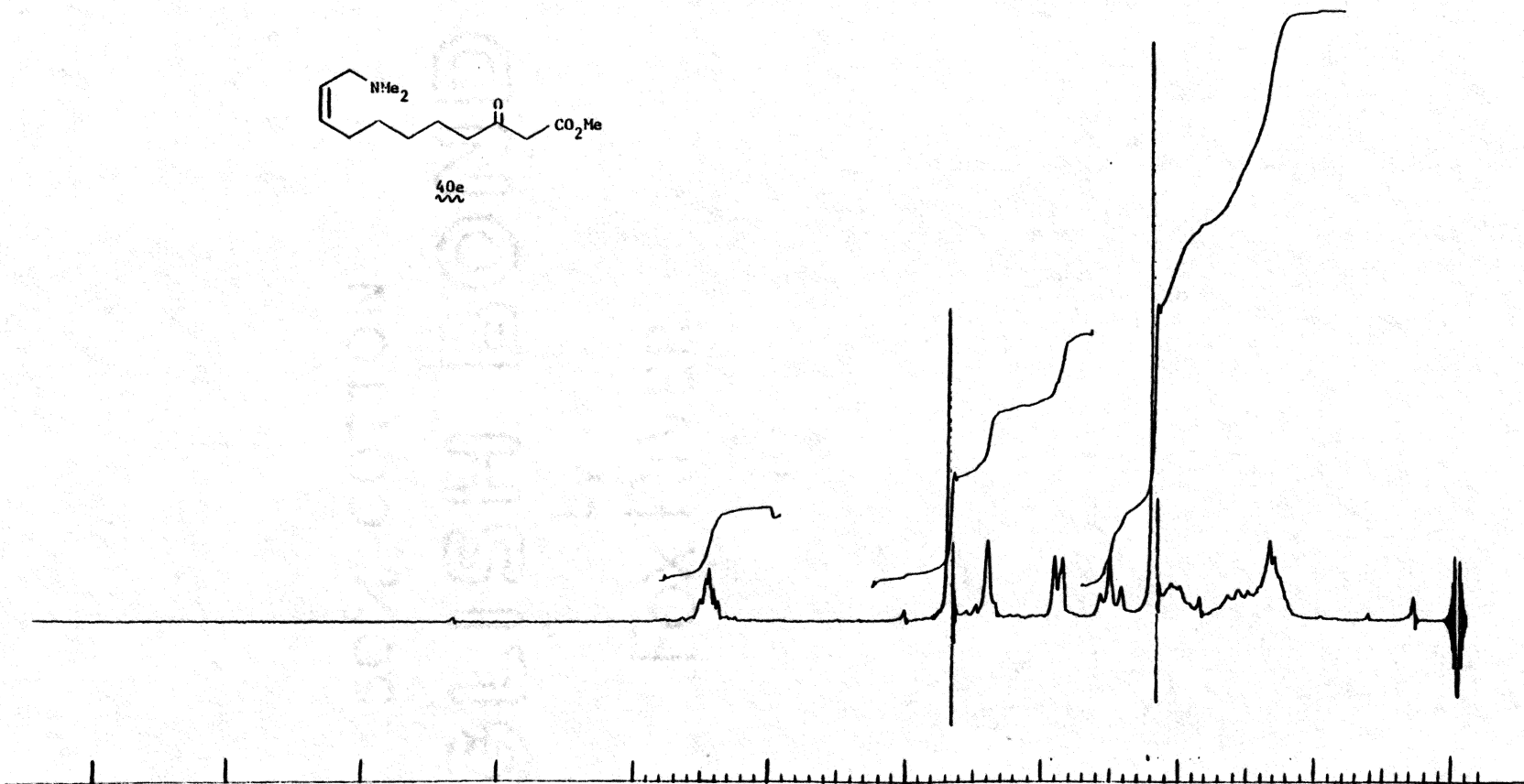


Figure 18a. 90 MHz NMR Spectrum of Amino Ketoester 40e.

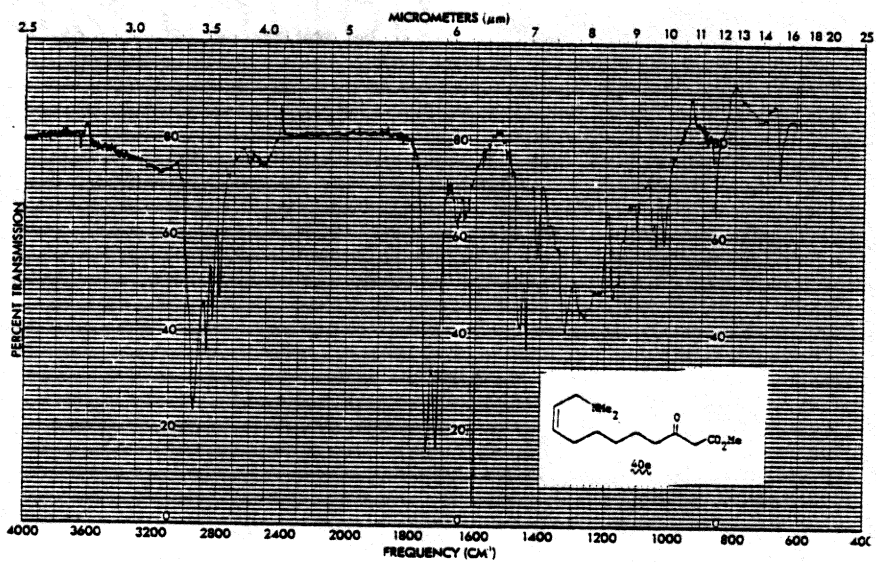


Figure 18b. IR Spectrum of Amino Ketoester 40e.

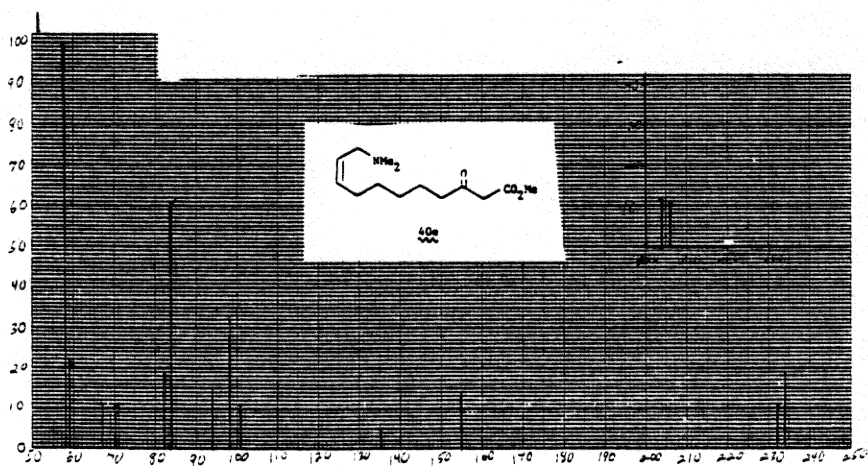


Figure 18c. Mass Spectrum of Amino Ketoester 40e.

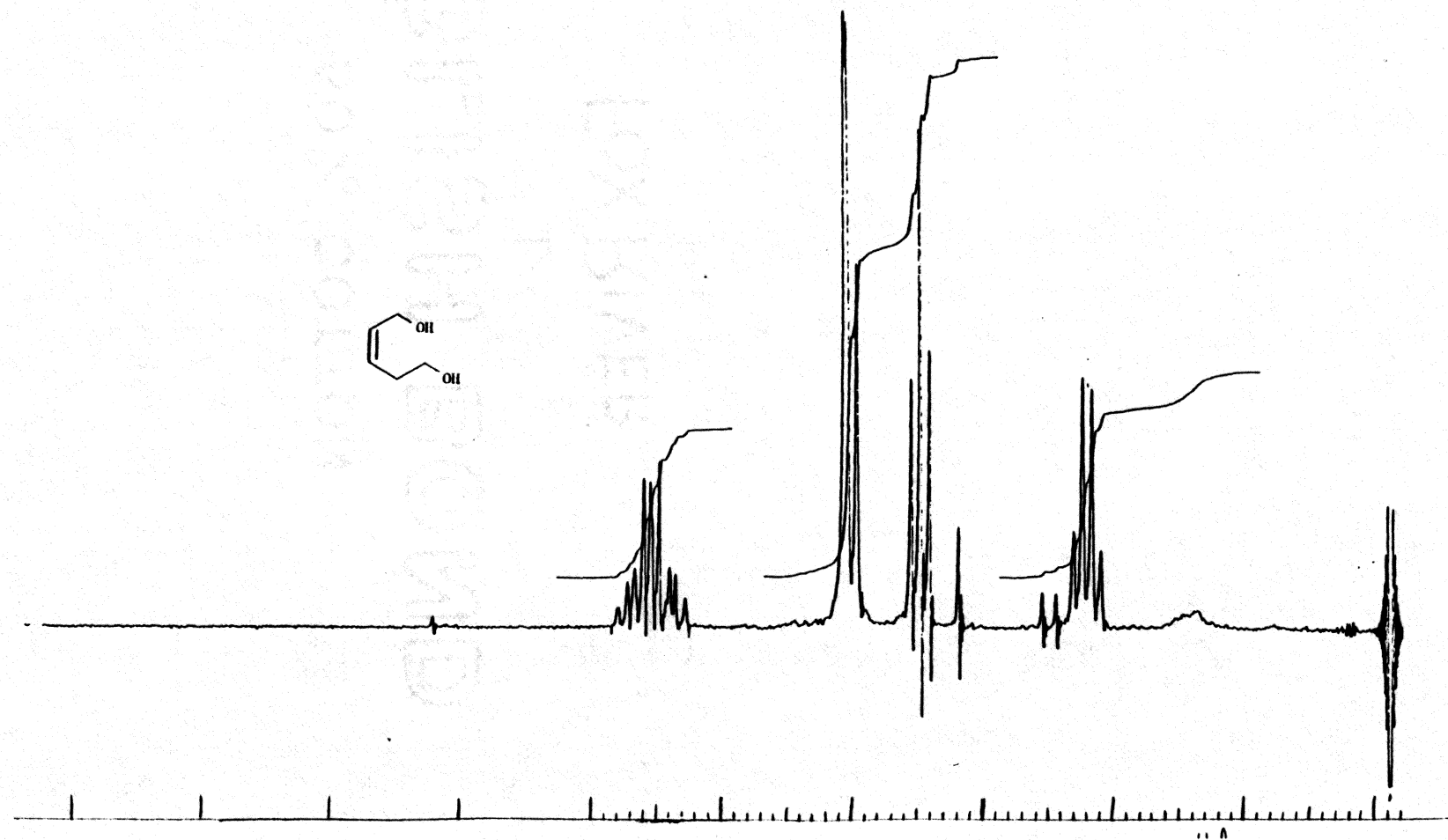


Figure 19a. 90 MHz NMR Spectrum of Diol 49.

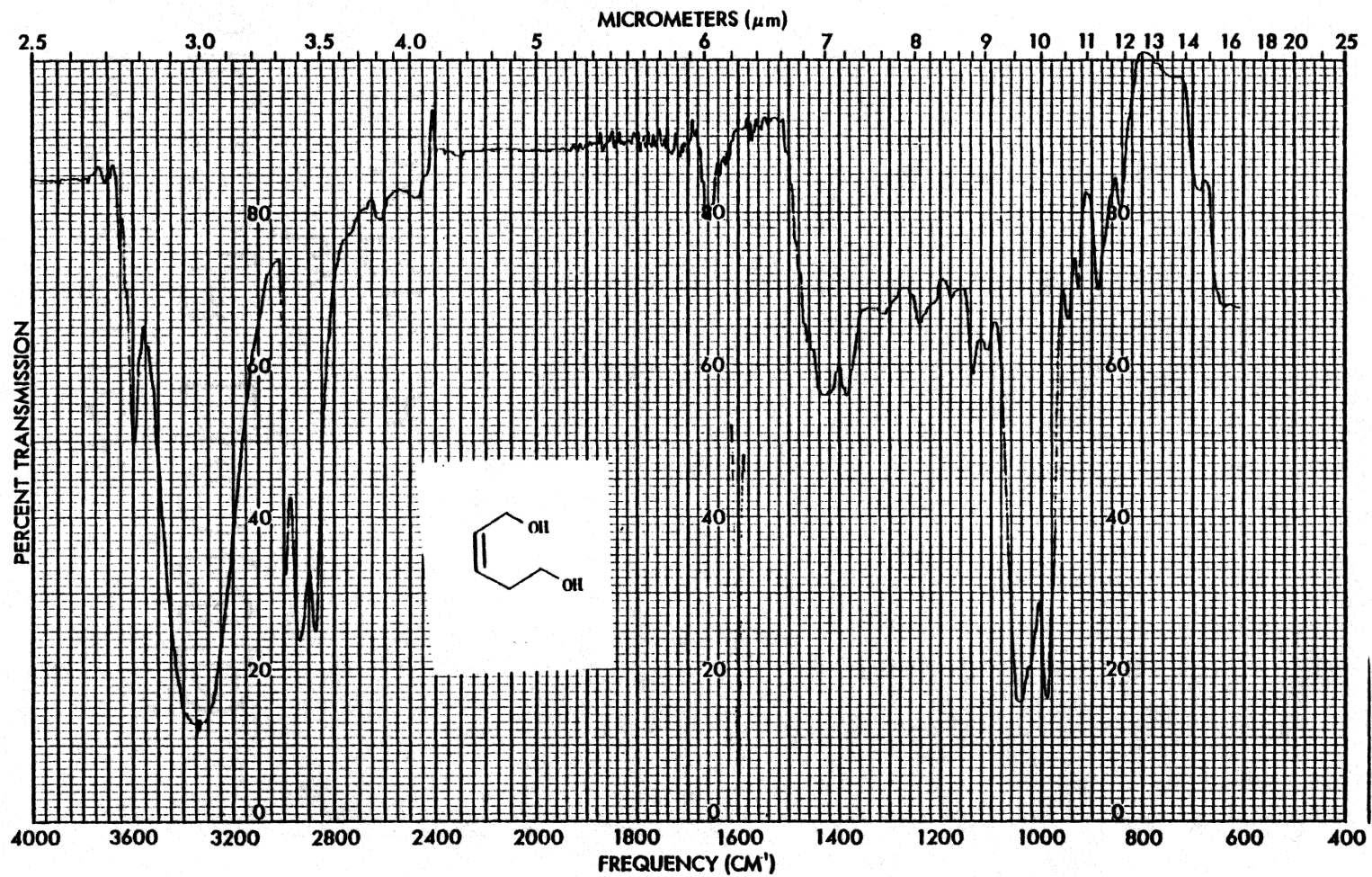


Figure 19b. IR Spectrum of Diol 49.

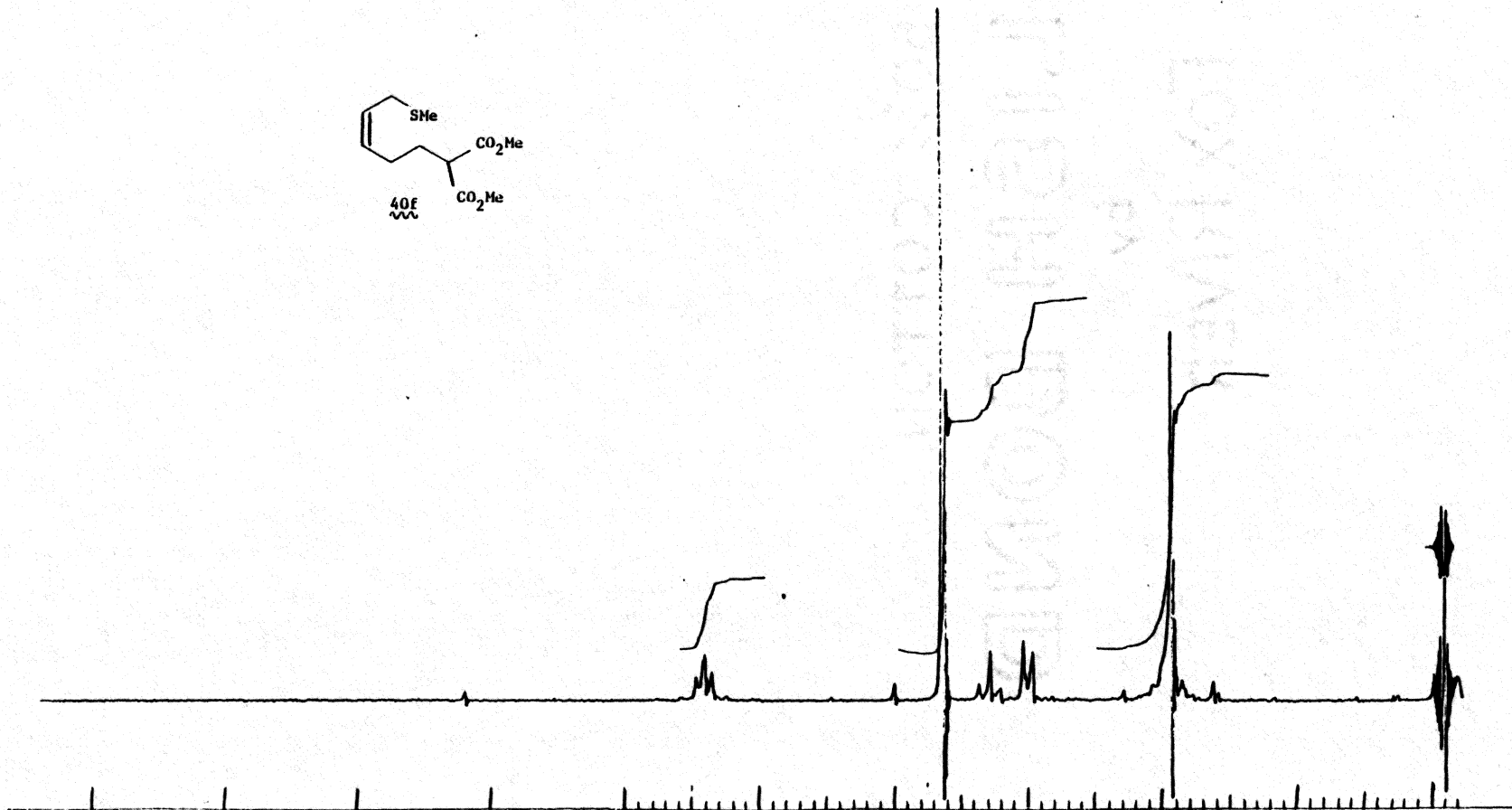
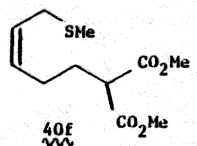


Figure 20a. 90 MHz NMR Spectrum of Sulfide Diester 40f.

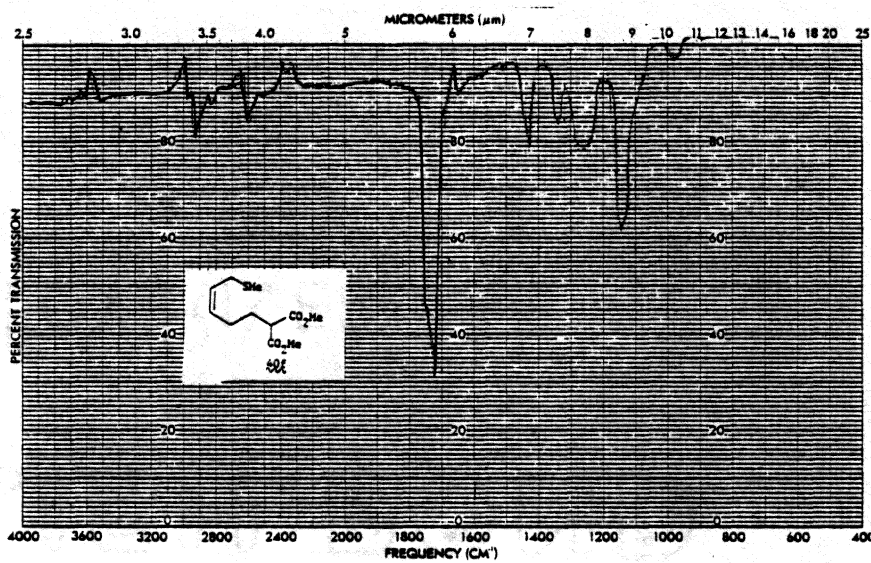


Figure 20b. IR Spectrum of Sulfide Diester 40f.

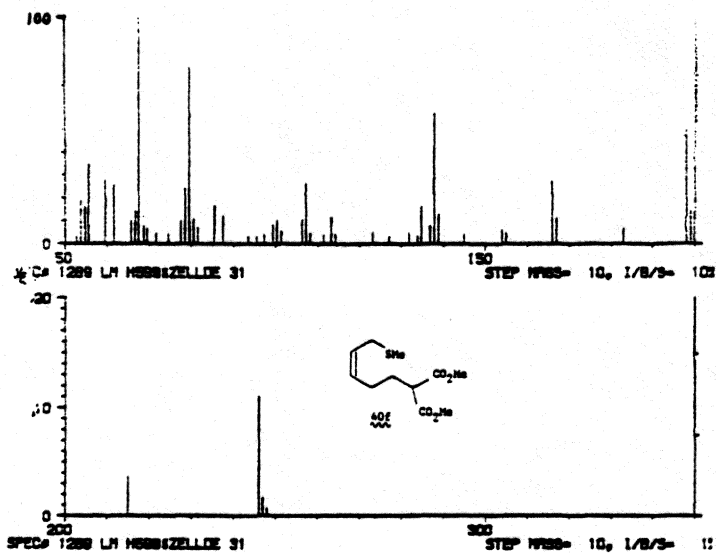


Figure 20c. Mass Spectrum of Sulfide Diester 40f.

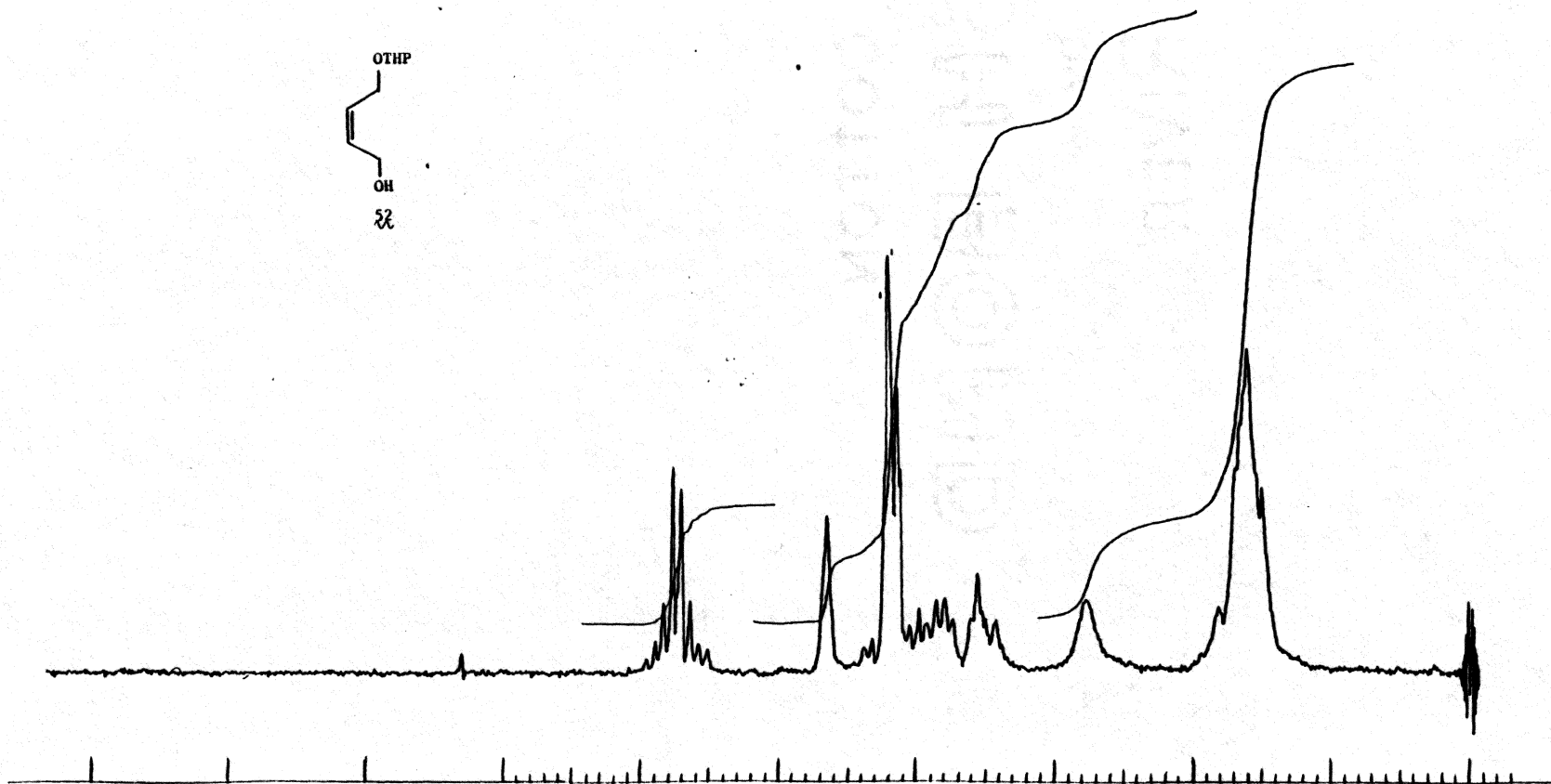
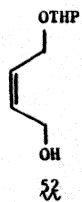


Figure 21a. 90 MHz NMR Spectrum of Tetrahydropyranyl Alcohol 52.

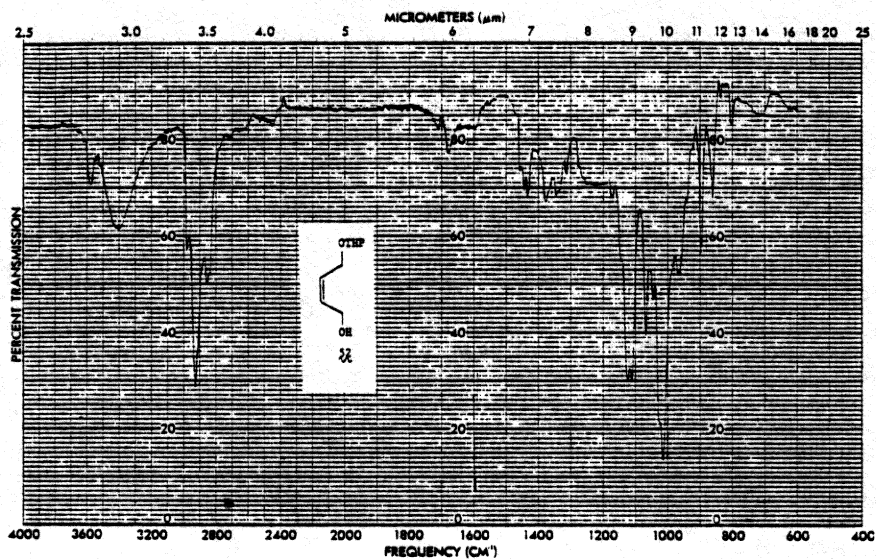


Figure 21b. IR Spectrum of Tetrahydropyranyl Alcohol 52.

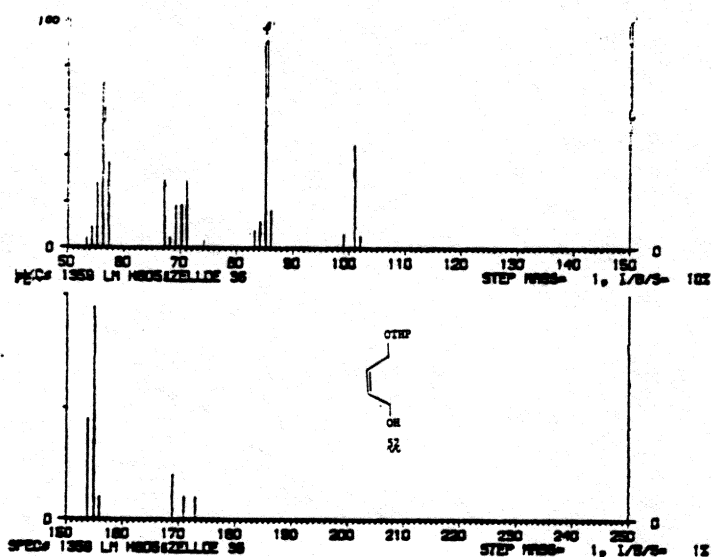


Figure 21c. Mass Spectrum of Tetrahydropyranyl Alcohol 52.

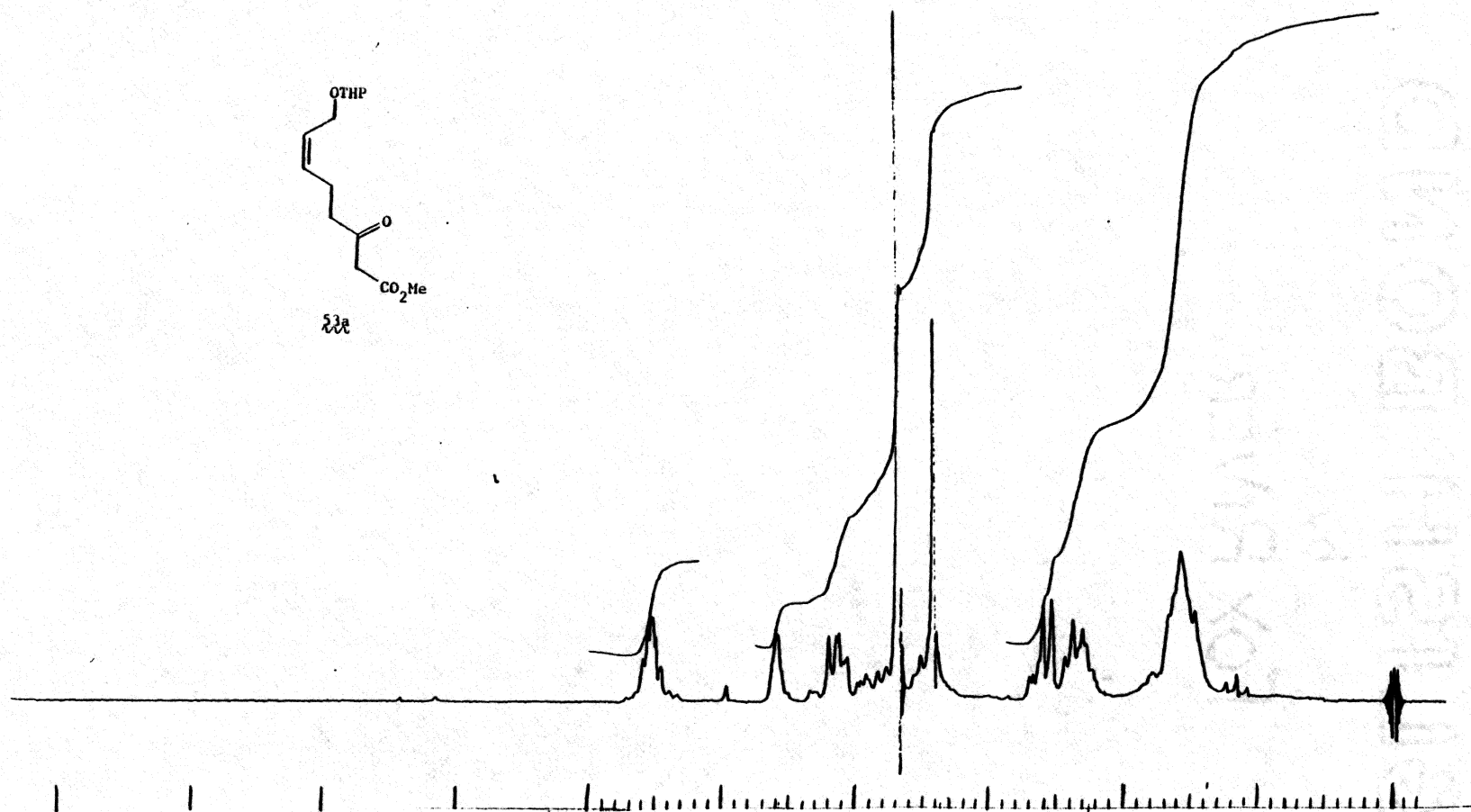


Figure 22a. 90 MHz NMR Spectrum of Ketoester 53a.

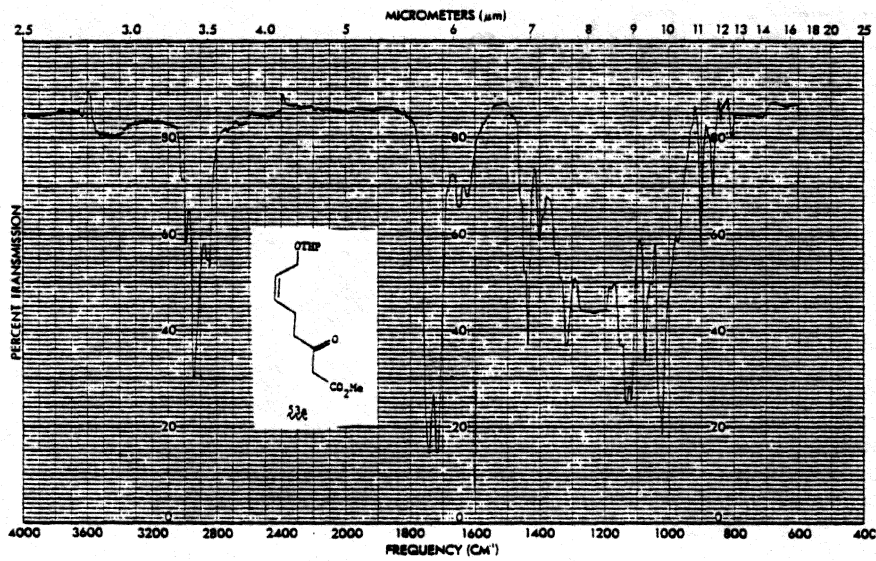


Figure 22b. IR Spectrum of Ketoester 53a.

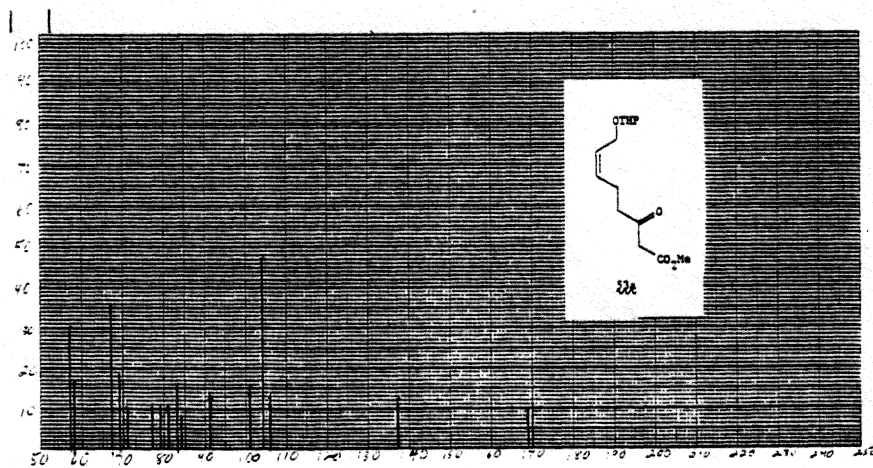


Figure 22c. Mass Spectrum of Ketoester 53a.

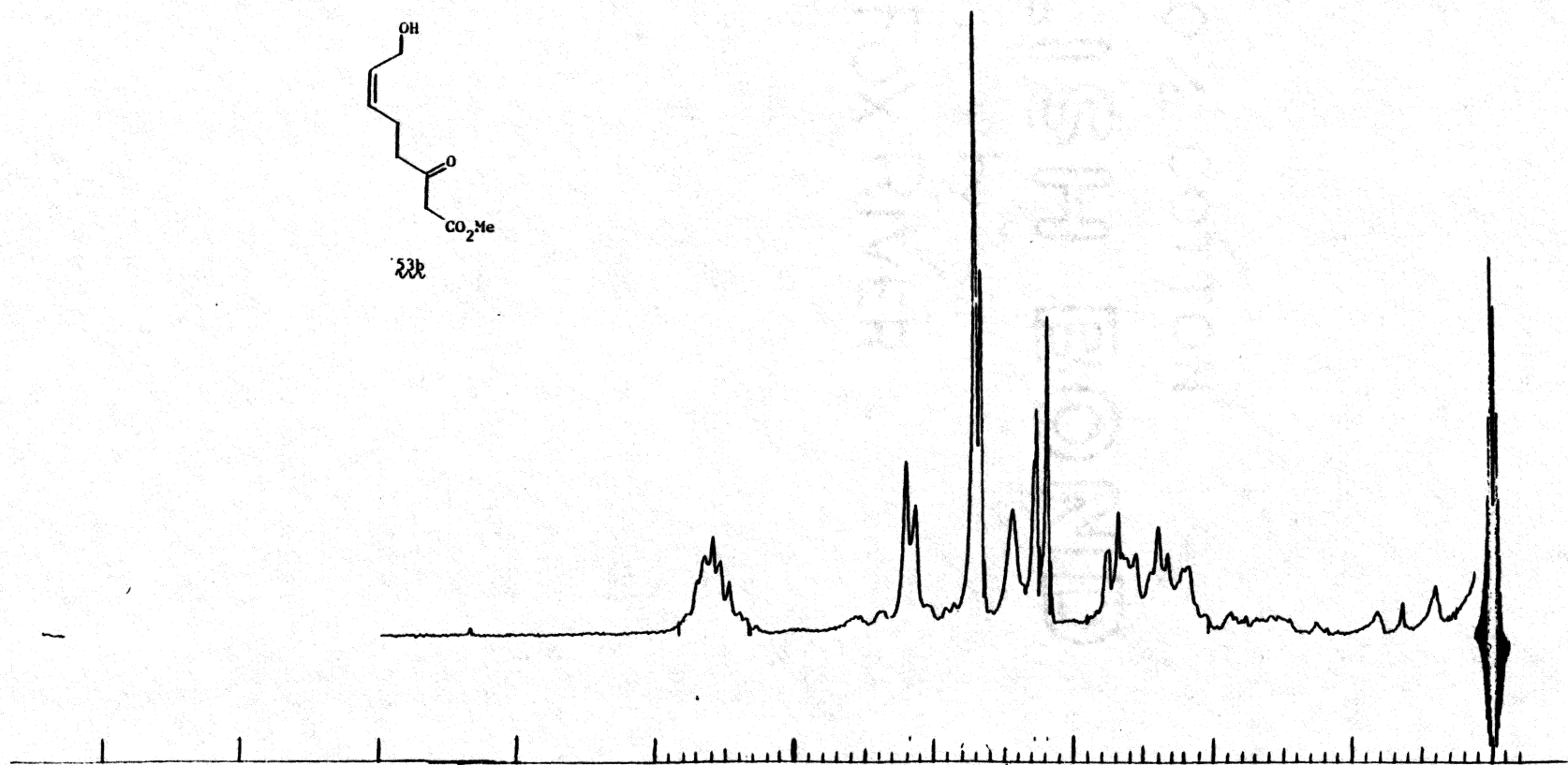
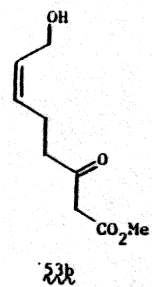


Figure 23a. 90 MHz NMR Spectrum of Hydroxy Ketoester 53b.

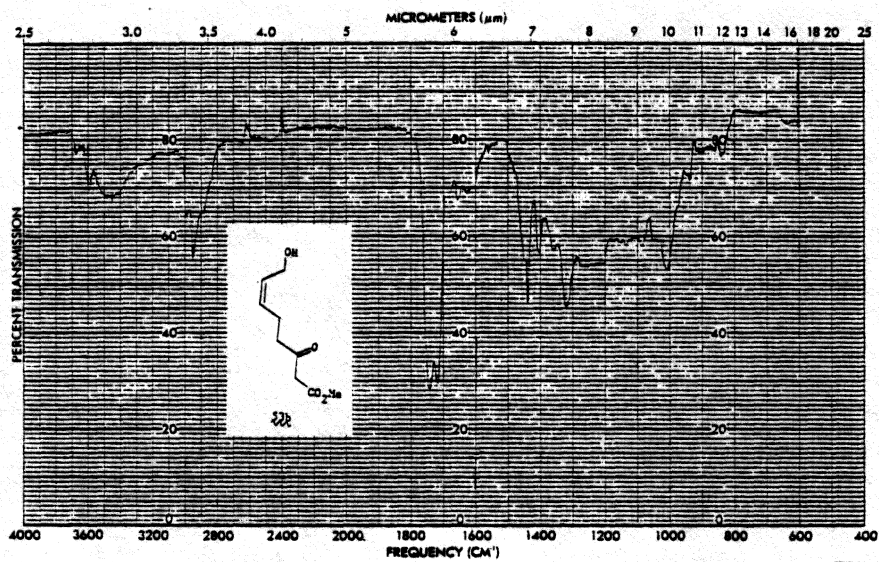


Figure 23b. IR Spectrum of Hydroxy Ketoester 53b.

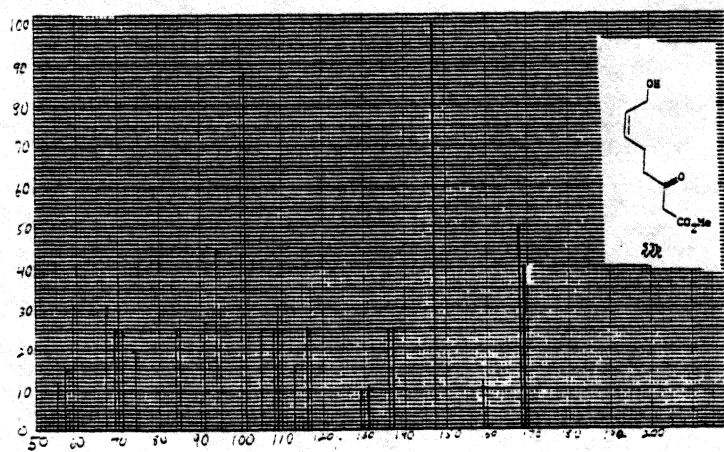


Figure 23c. Mass Spectrum of Hydroxy Ketoester 53b.

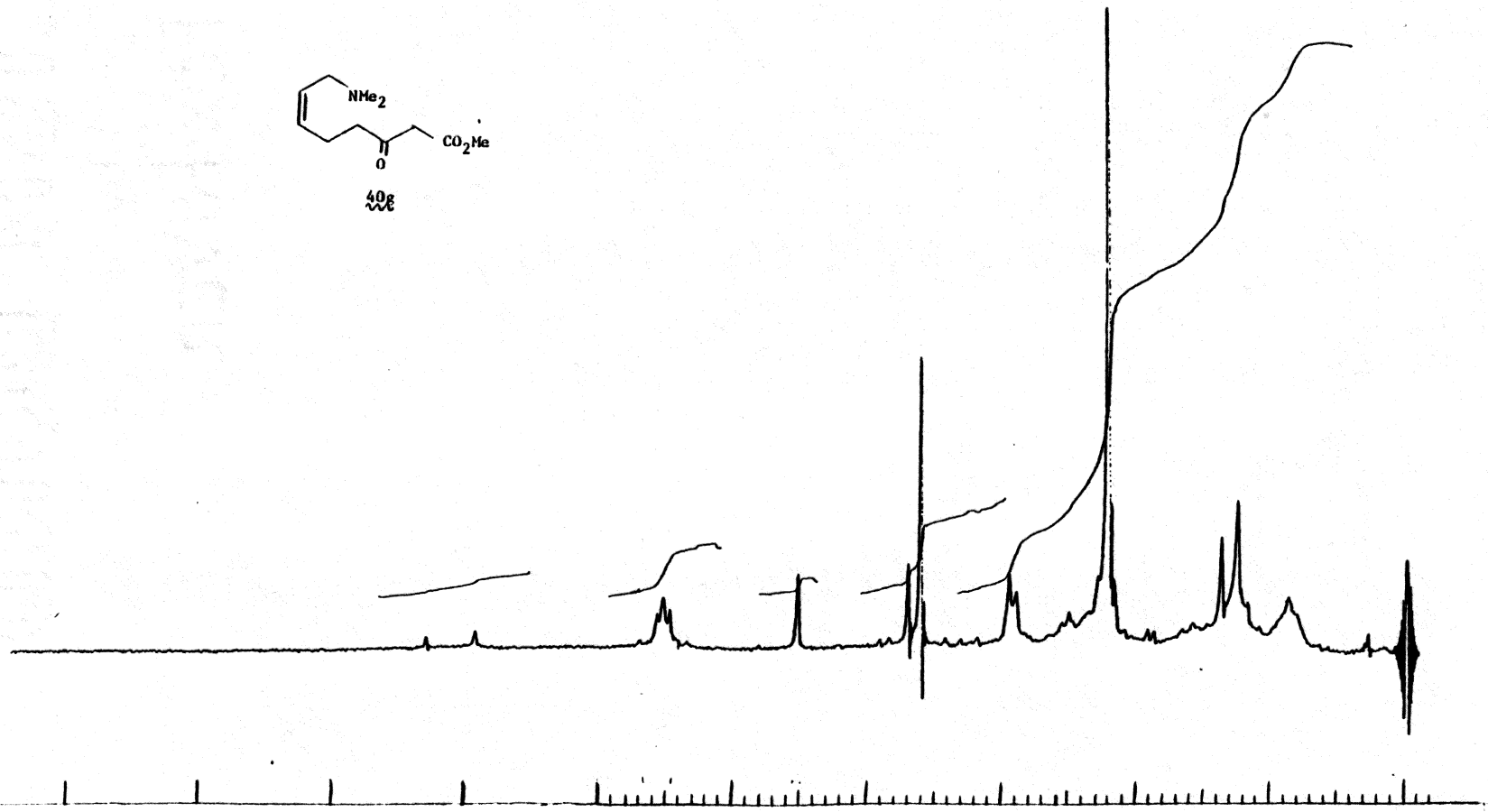
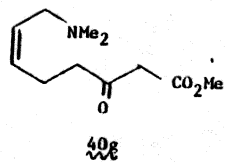


Figure 24a. 90 MHz NMR Spectrum of Amino Ketoester 40g.
mt

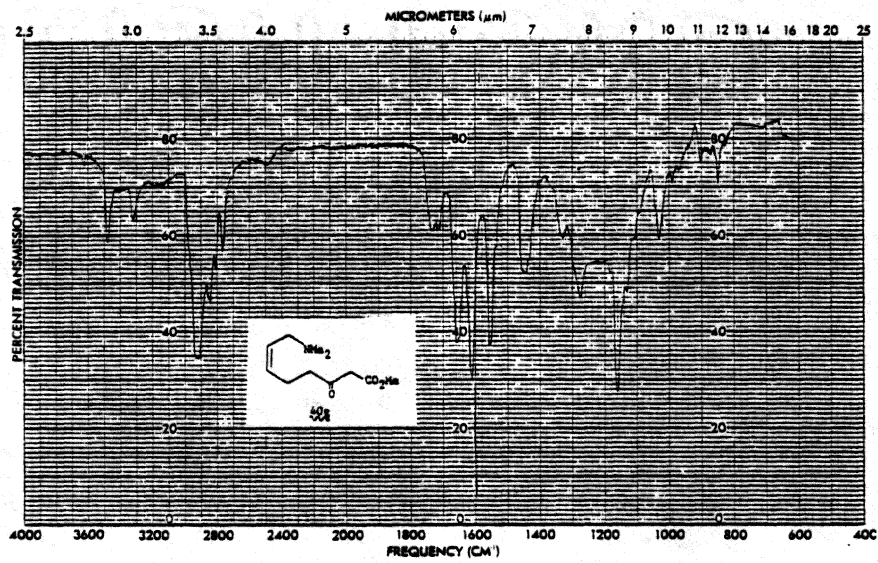


Figure 24b. IR Spectrum of Amino Ketoester 40g.

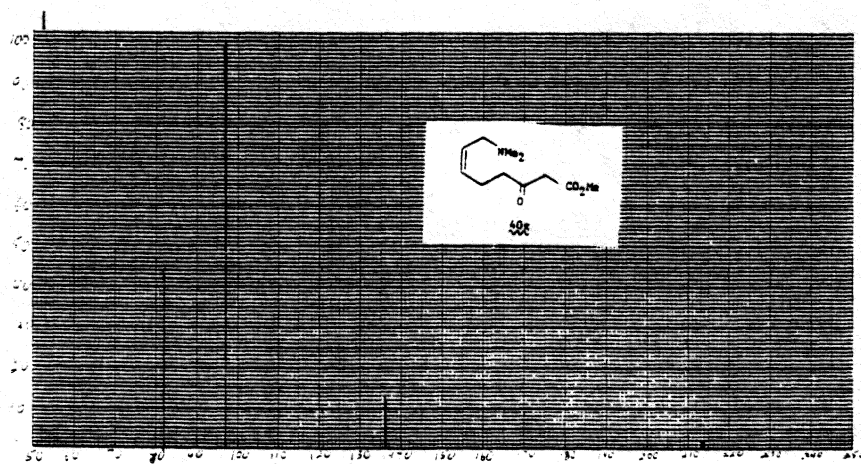


Figure 24c. Mass Spectrum of Amino Ketoester 40g.

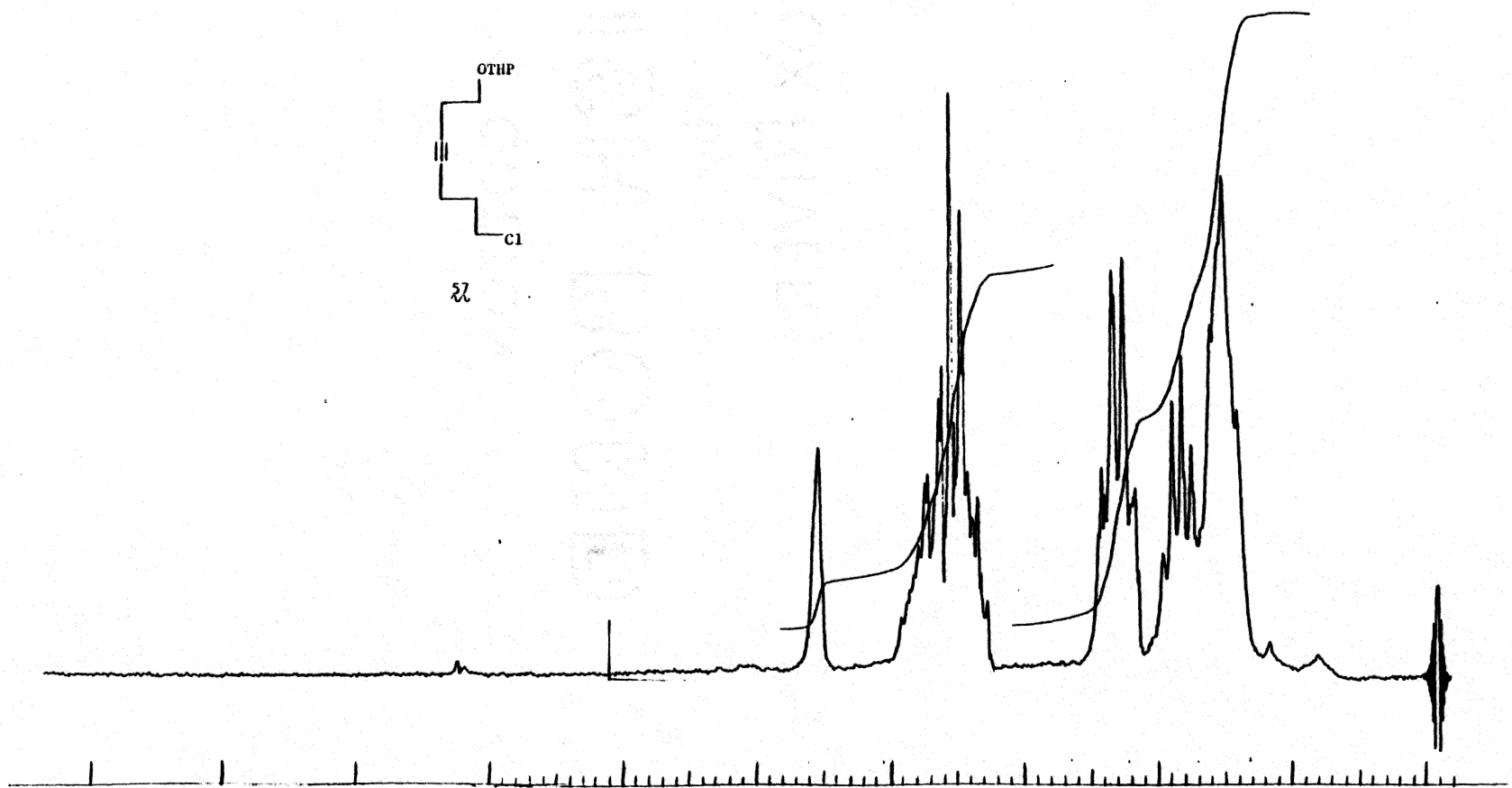


Figure 25a. 90 MHz NMR Spectrum of Tetrahydropyranyl Chloride 57.

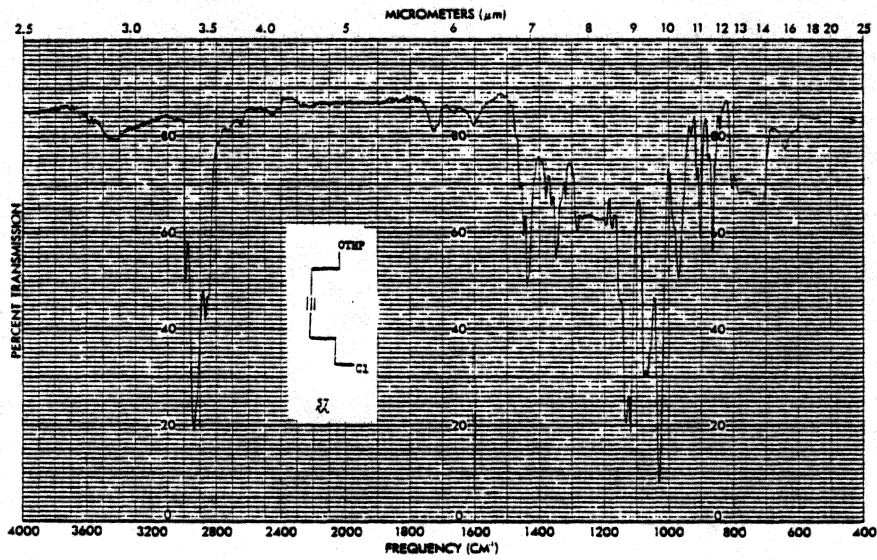


Figure 25b. IR Spectrum of Tetrahydropyranyl Chloride 57.

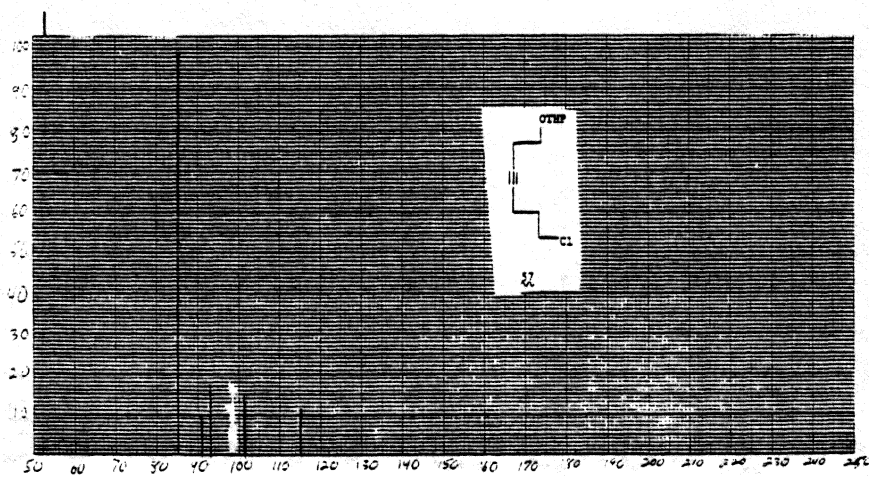


Figure 25c. Mass Spectrum of Tetrahydropyranyl Chloride 57.

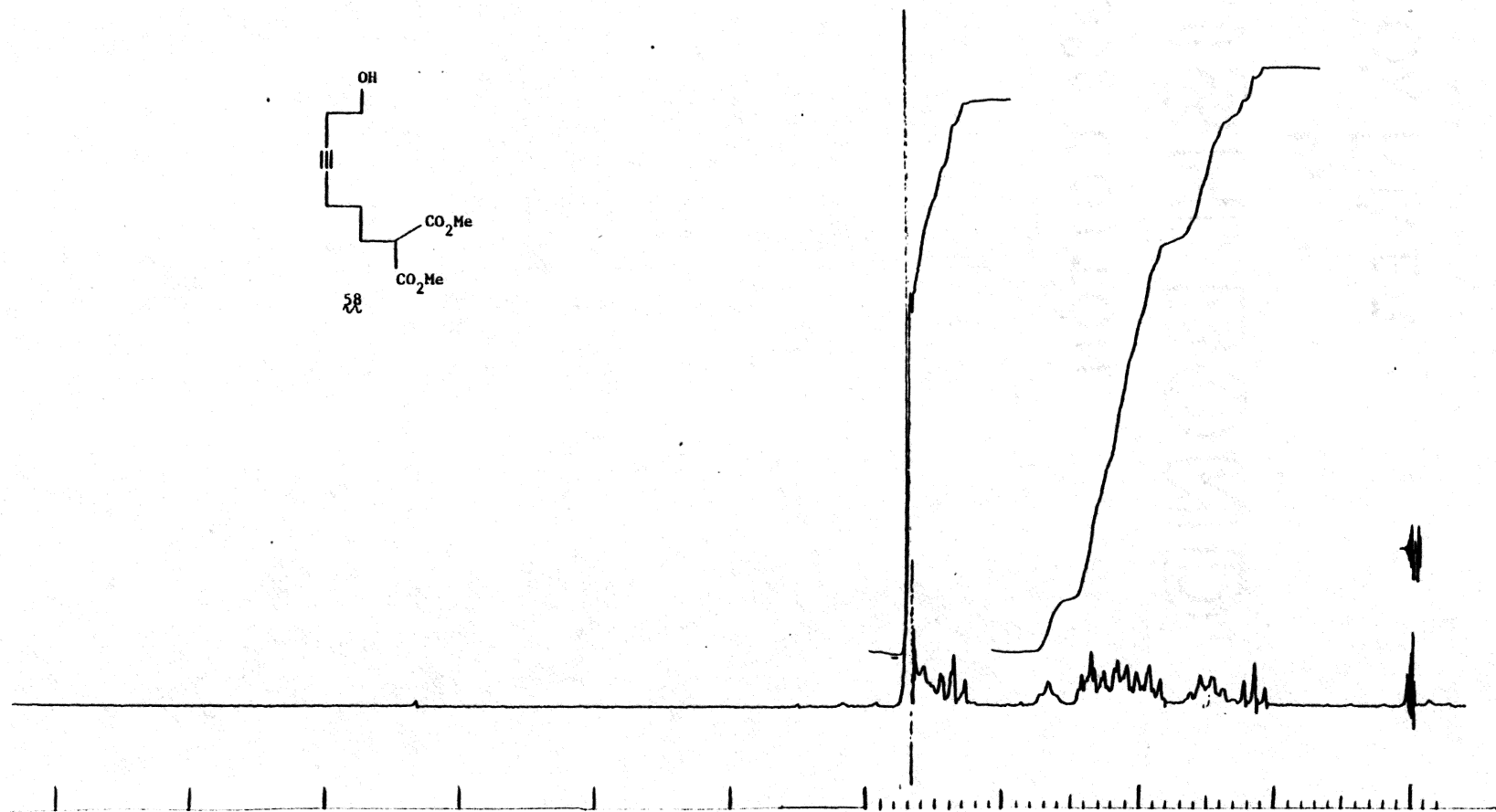


Figure 26a. 90 MHz NMR Spectrum of Hydroxy Diester 58.

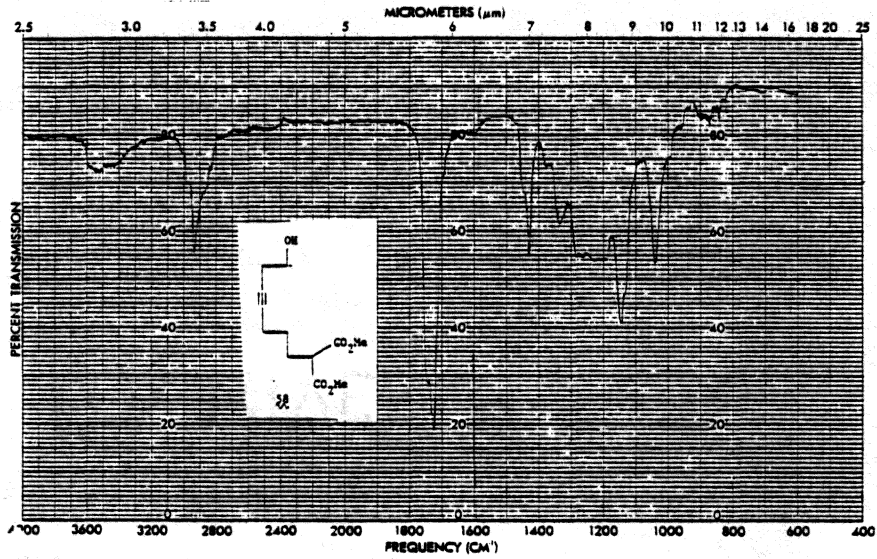


Figure 26b. IR Spectrum of Hydroxy Diester 58.

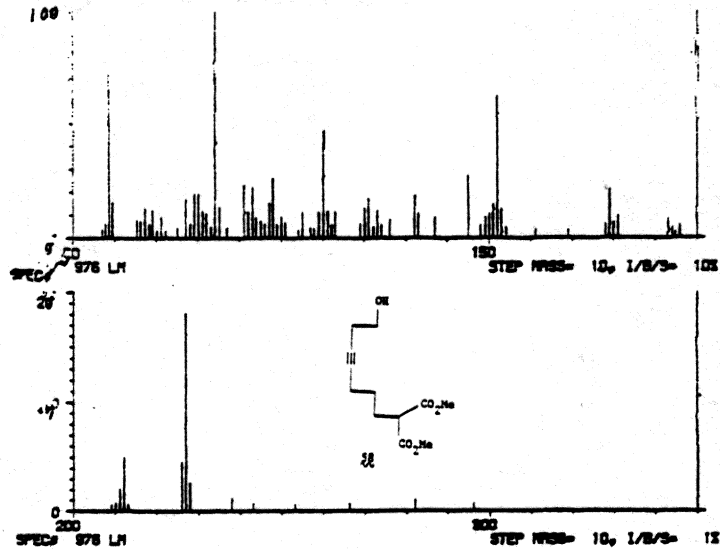


Figure 26c. Mass Spectrum of Hydroxy Diester 58.

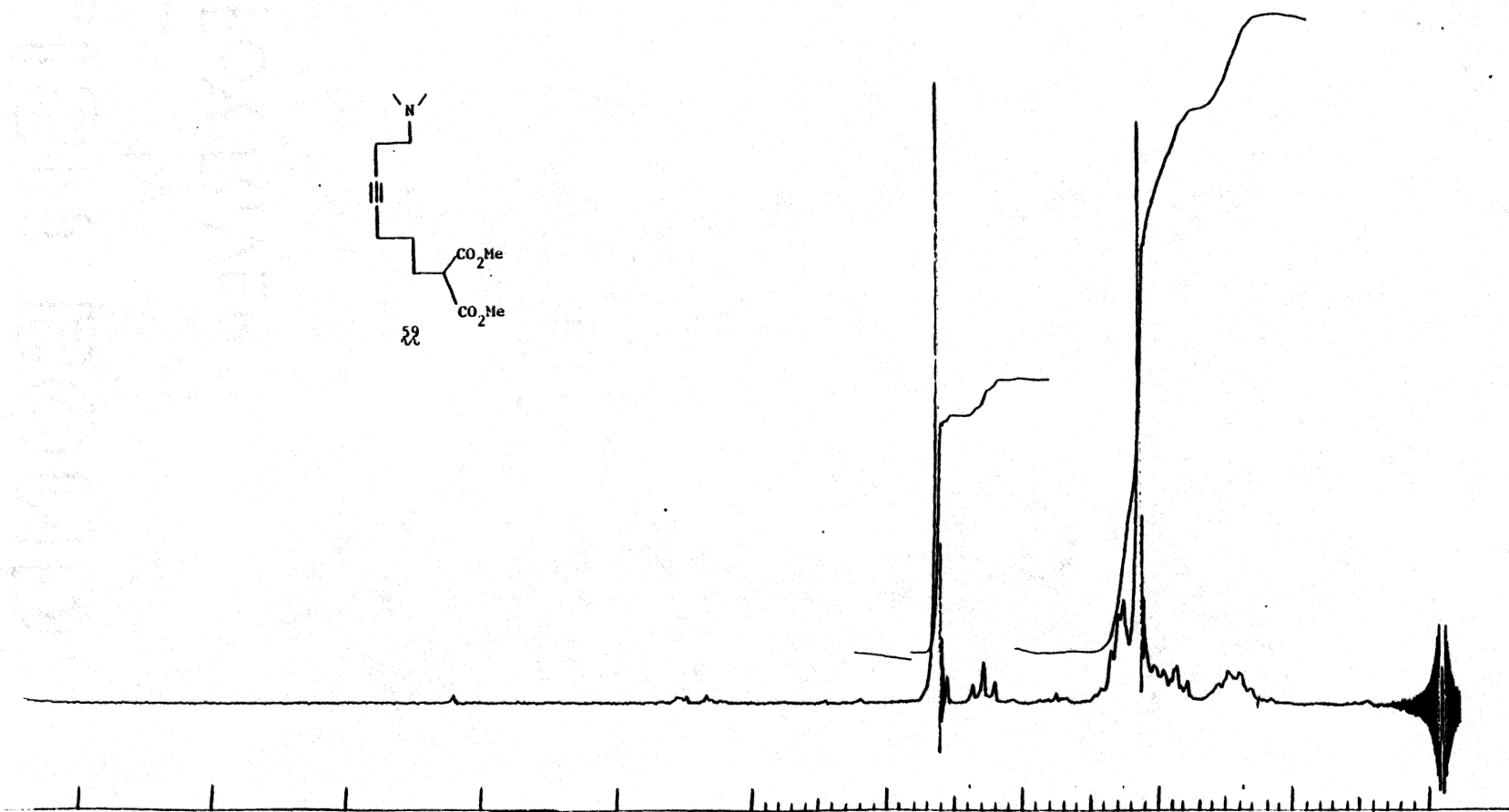


Figure 27a. 90 MHz NMR Spectrum of Amino Diester 59.

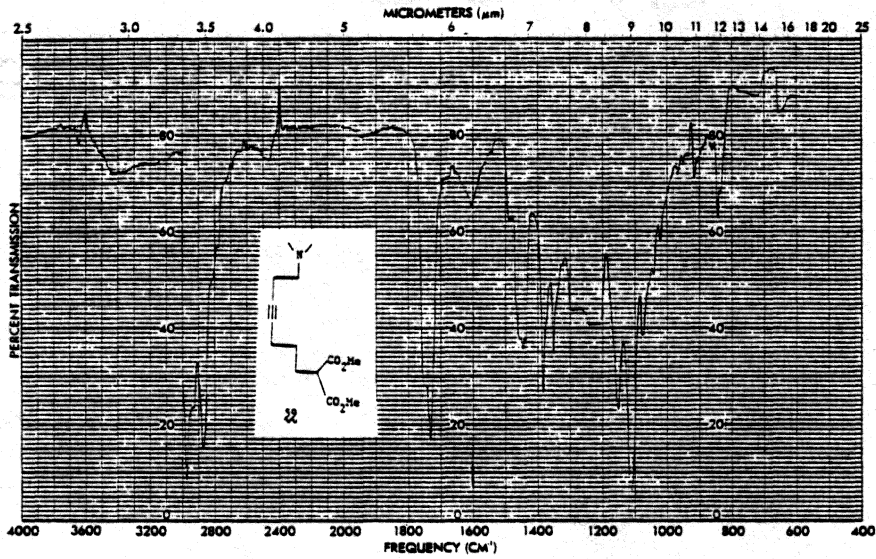


Figure 27b. IR Spectrum of Amino Diester 59.

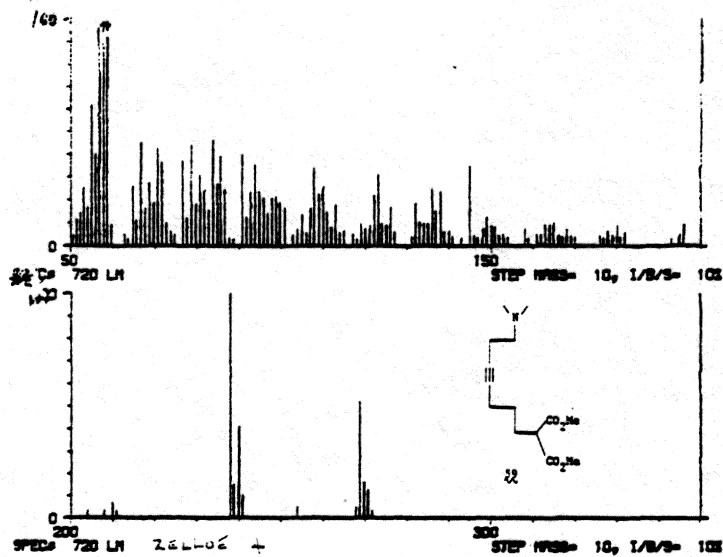


Figure 27c. Mass Spectrum of Amino Diester 59.

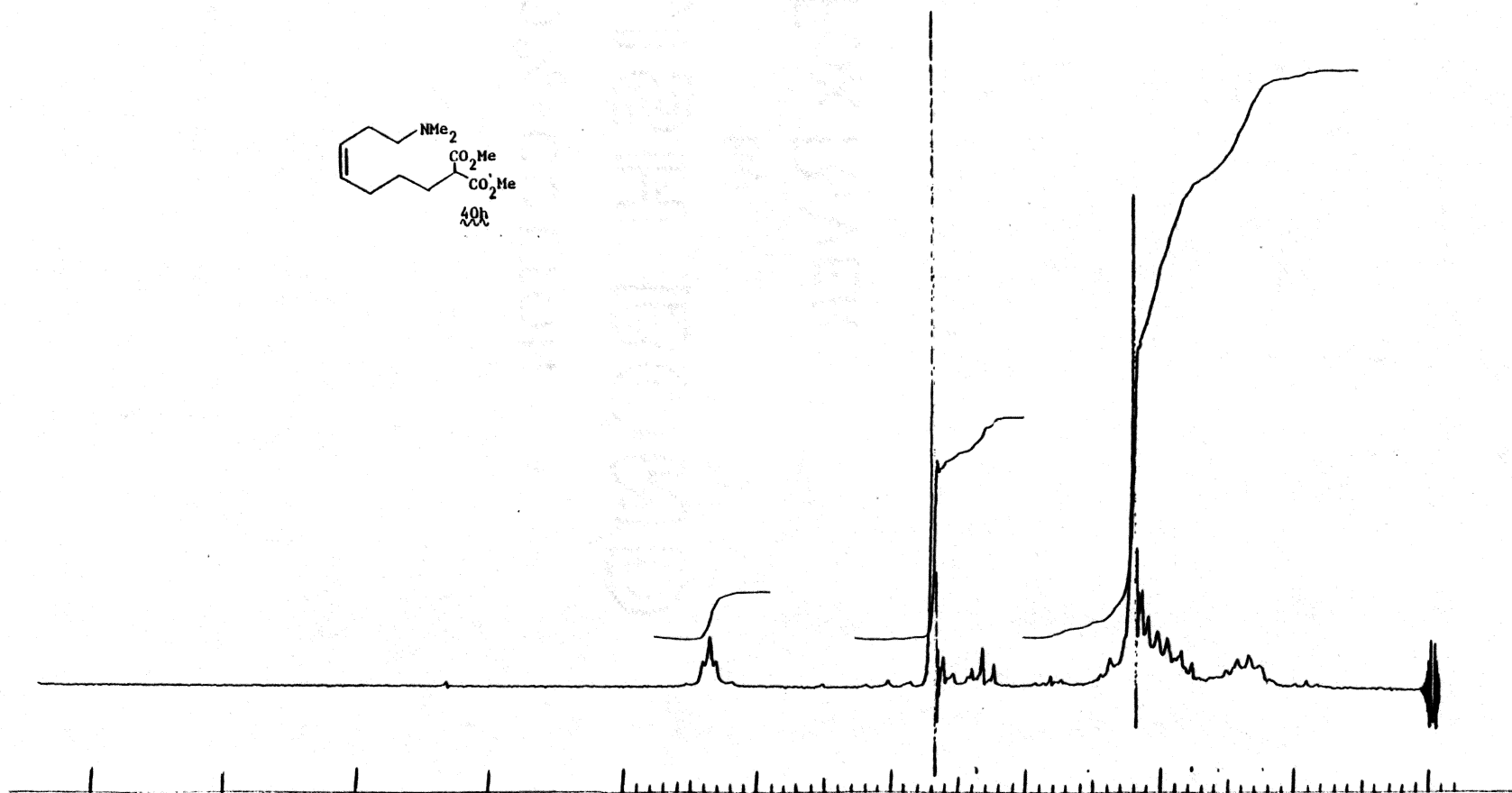
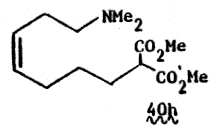


Figure 28a. 90 MHz NMR Spectrum of Amino Diester 40h.

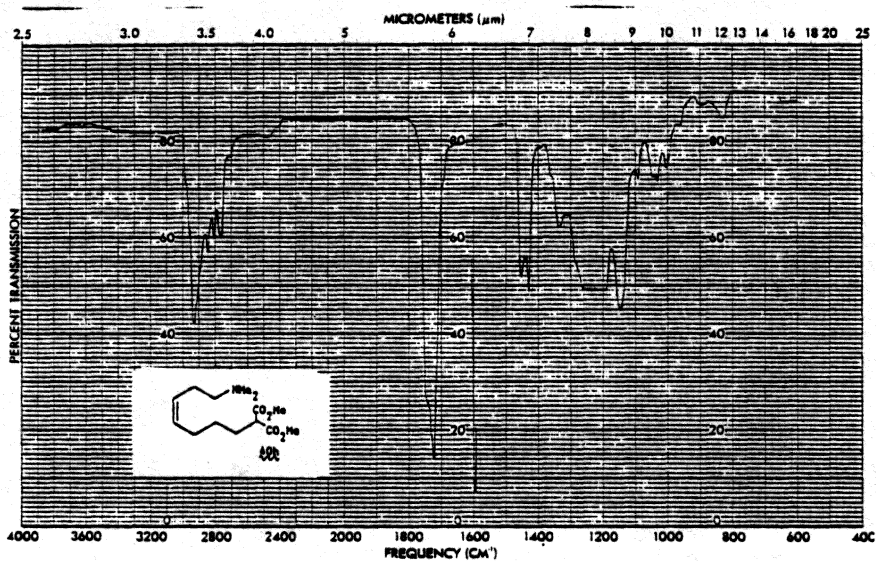


Figure 28b. IR Spectrum of Amino Diester 40h.

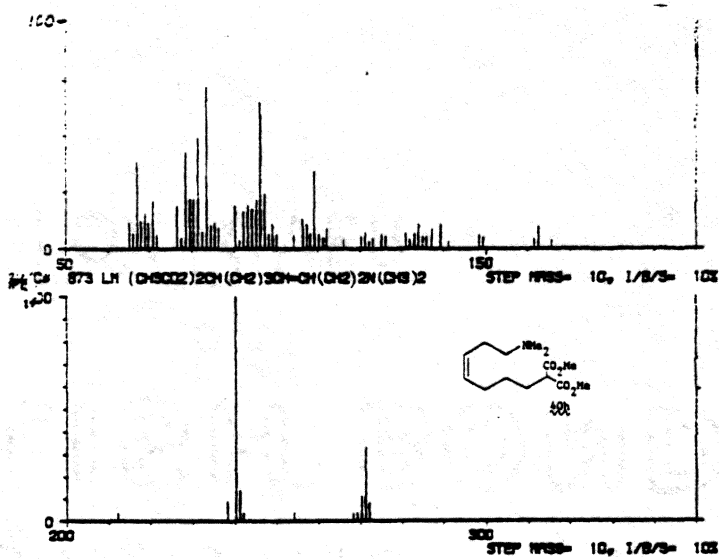


Figure 28c. Mass Spectrum of Amino Diester 40h.

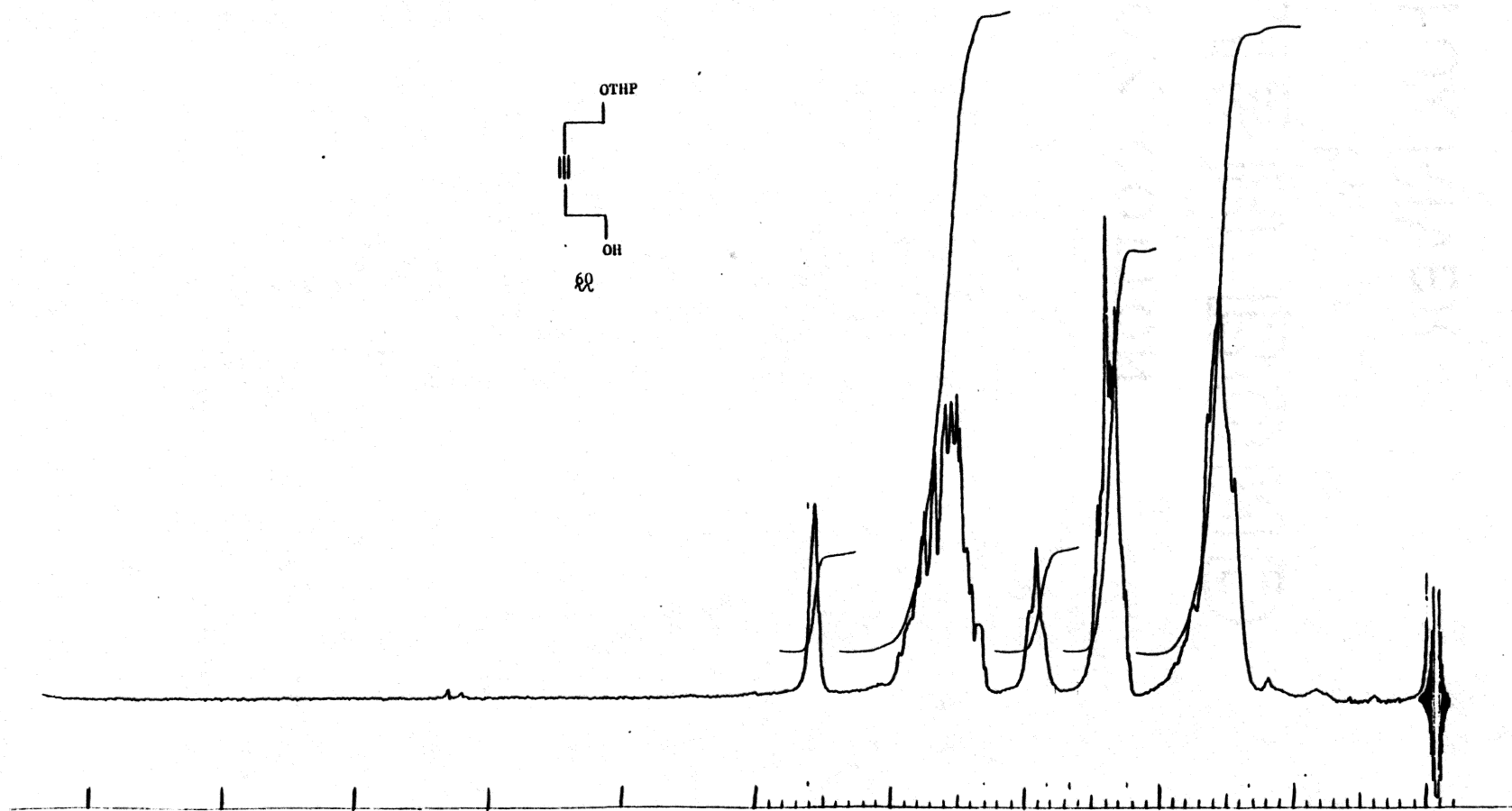


Figure 29a. 90 MHz NMR Spectrum of Tetrahydropyranyl Alcohol 60.

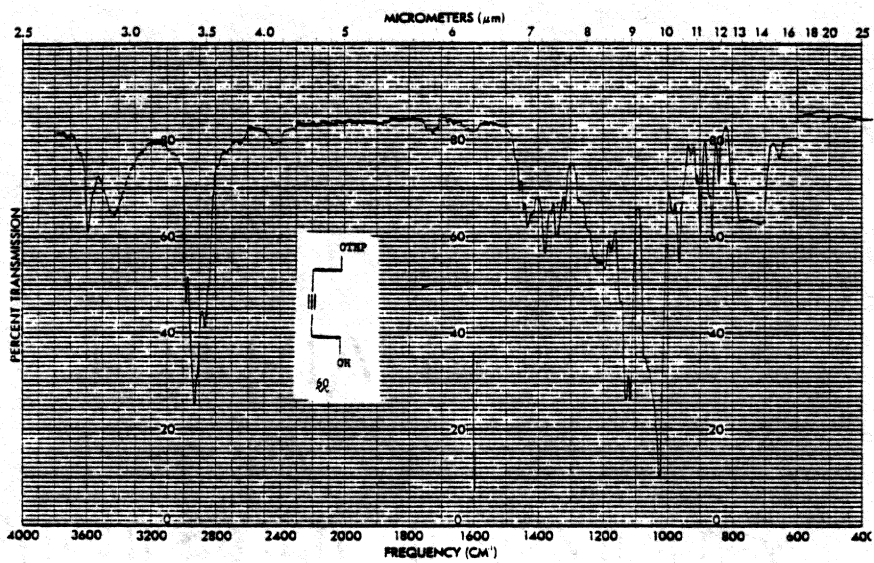


Figure 29b. IR Spectrum of Tetrahydropyranyl Alcohol 60.

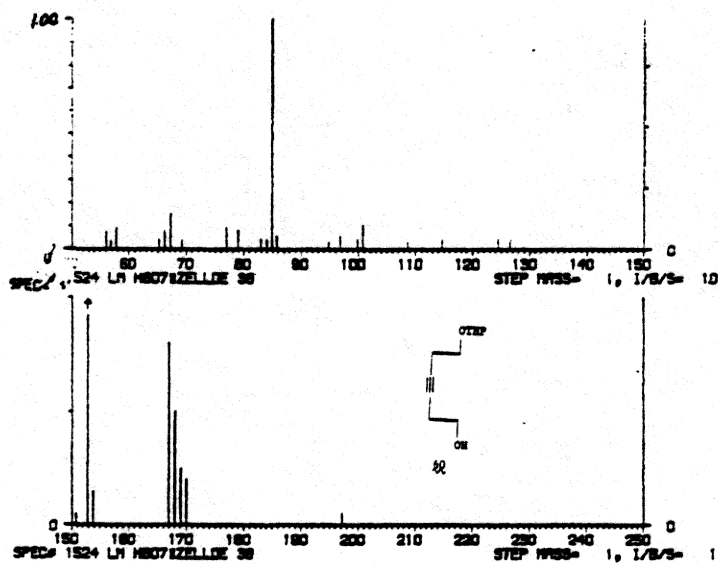


Figure 29c. Mass Spectrum of Tetrahydropyranyl Alcohol 60.

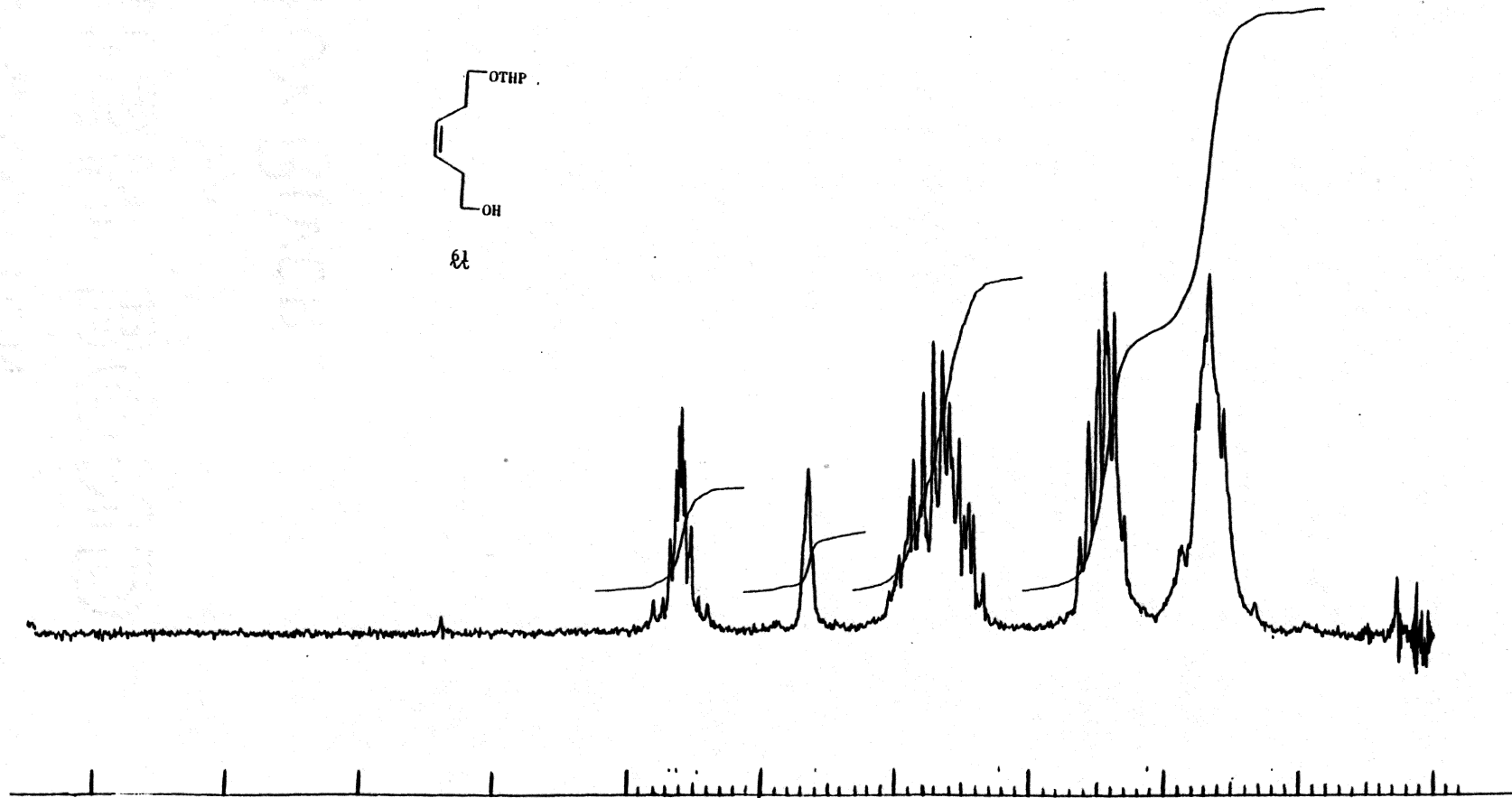
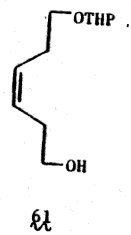


Figure 30a. 90 MHz NMR Spectrum of Tetrahydropyranyl Alcohol 61.

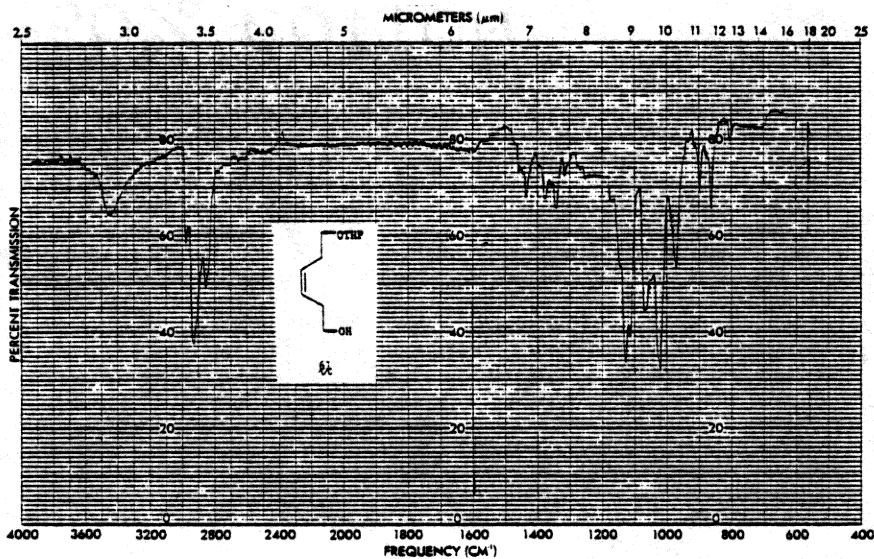


Figure 30b. IR Spectrum of Tetrahydropyranyl Alcohol 61.

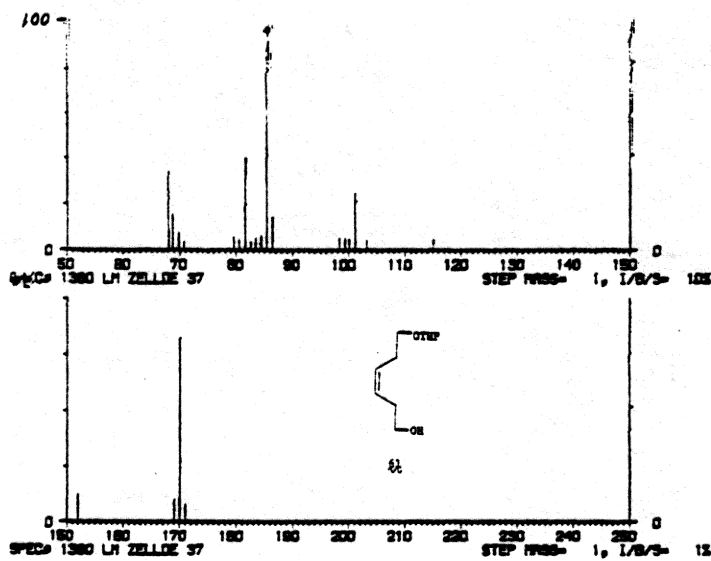


Figure 30c. Mass Spectrum of Tetrahydropyranyl Alcohol 61.

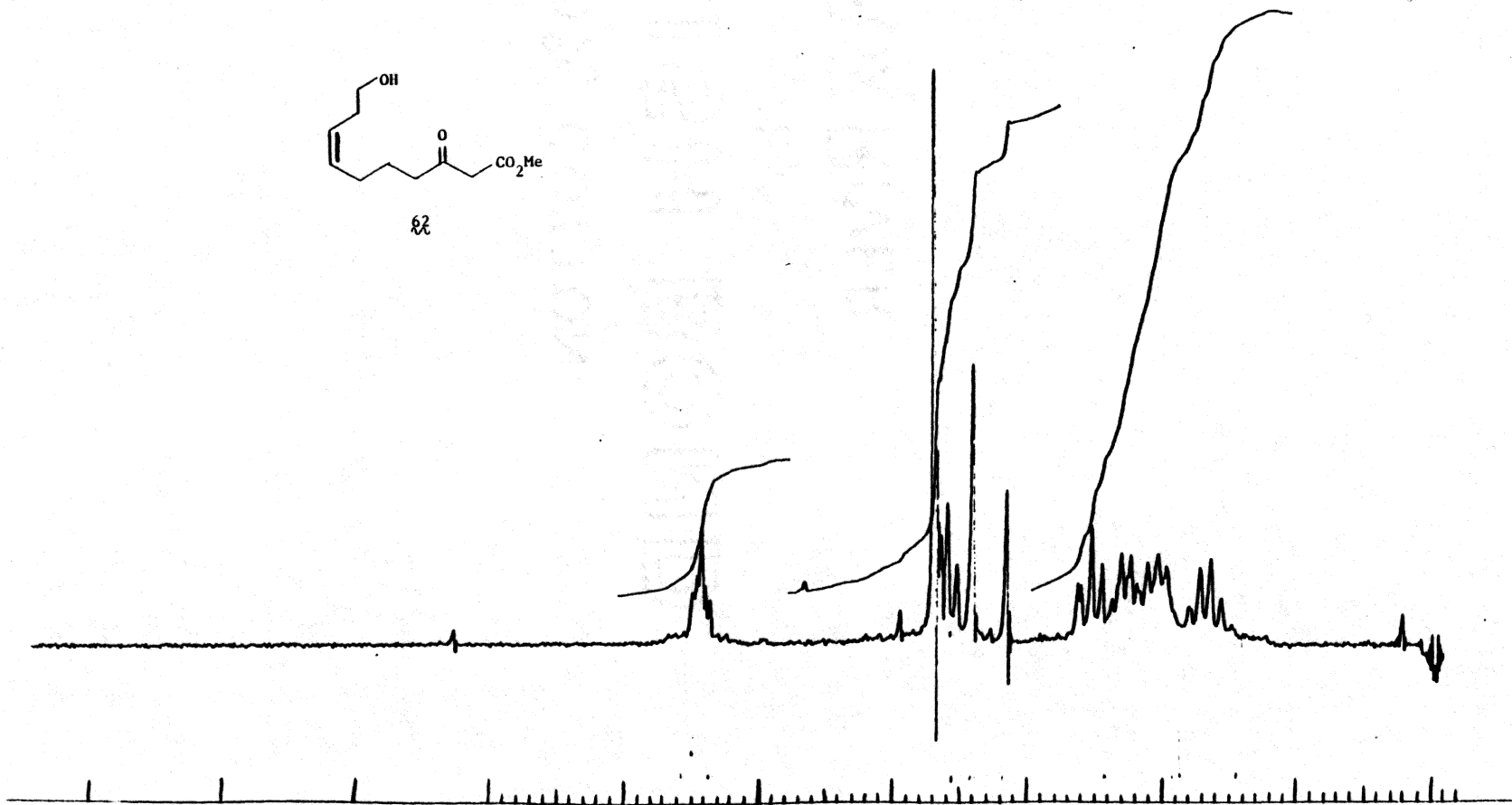
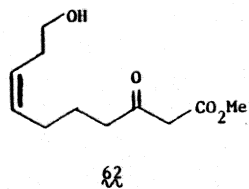


Figure 31a. 90 MHz NMR Spectrum of Hydroxy Ketoester 62.

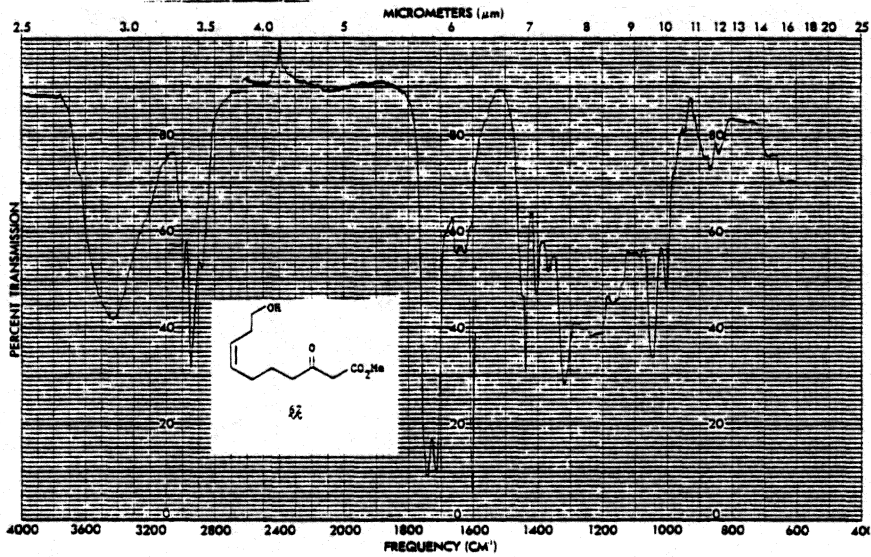


Figure 31b. IR Spectrum of Hydroxy Ketoester 62.

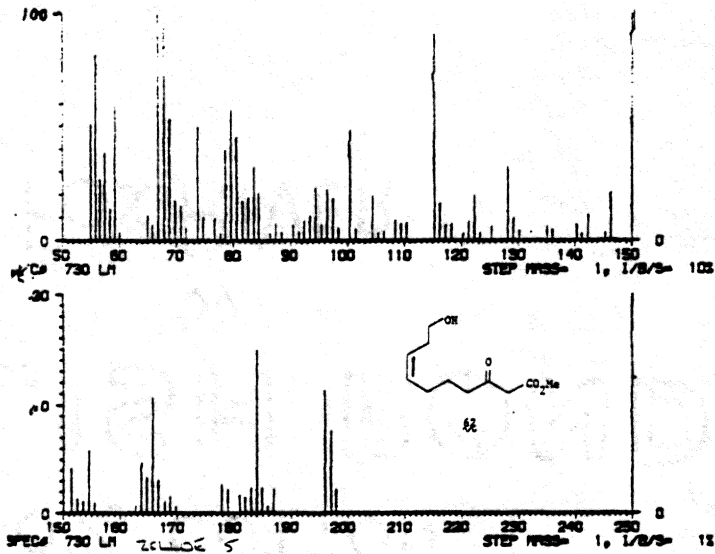


Figure 31c. Mass Spectrum of Hydroxy Ketoester 62.

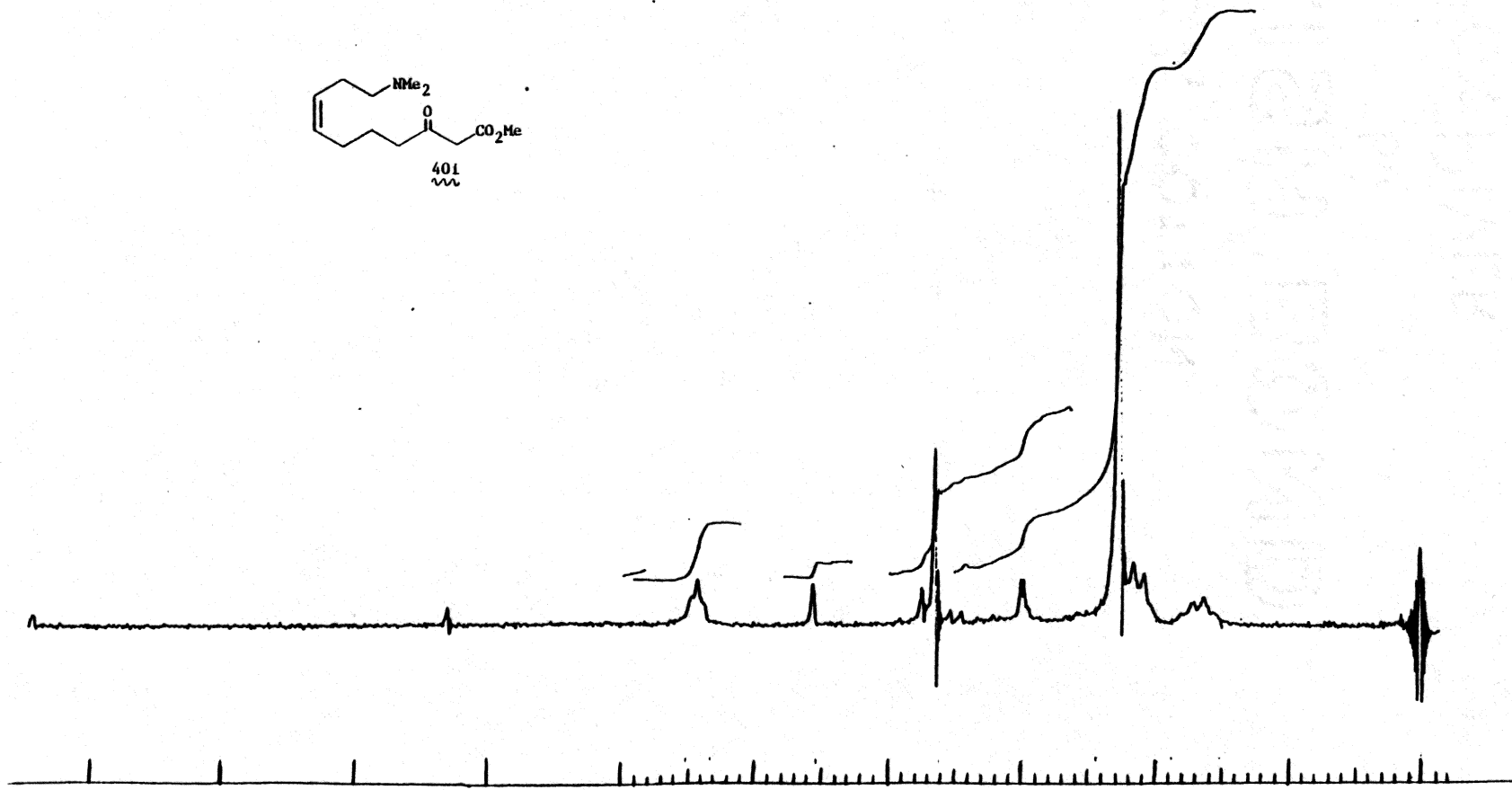
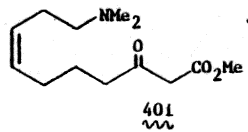


Figure 32a. 90 MHz NMR Spectrum of Amino Ketoester 401.

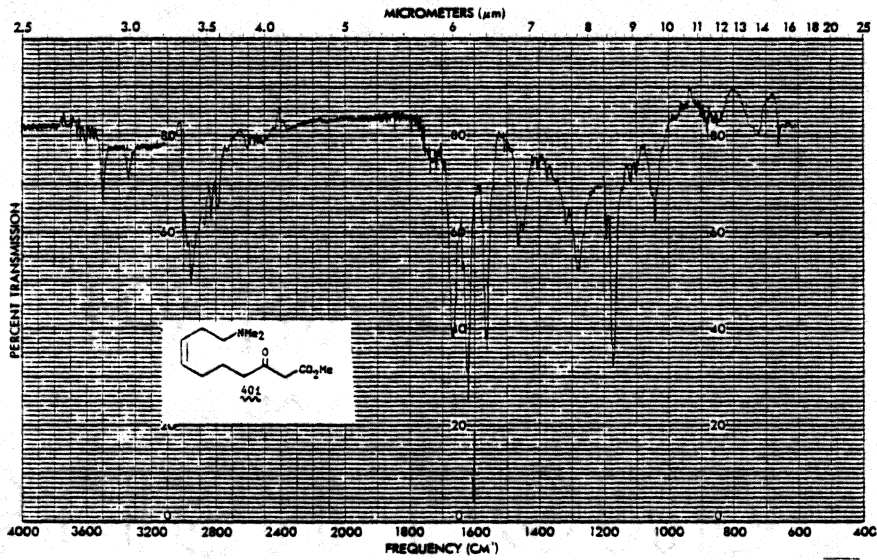


Figure 32b. IR Spectrum of Amino Ketoester 40i.

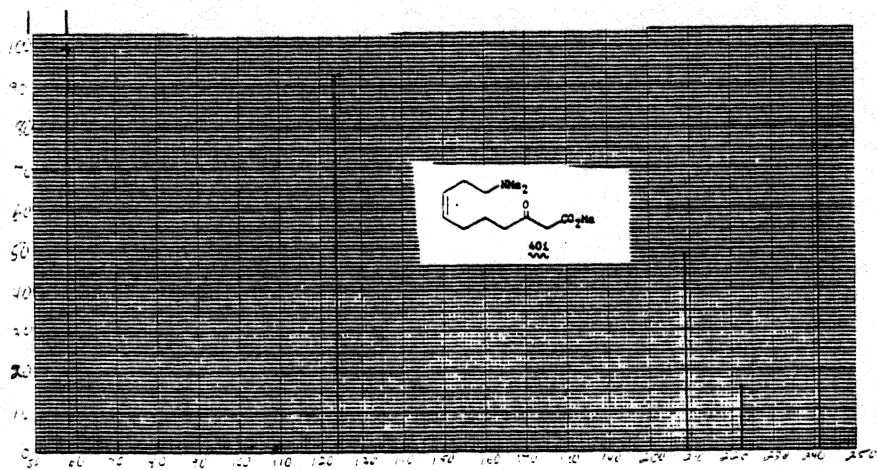


Figure 32c. Mass Spectrum of Amino Ketoester 40i.

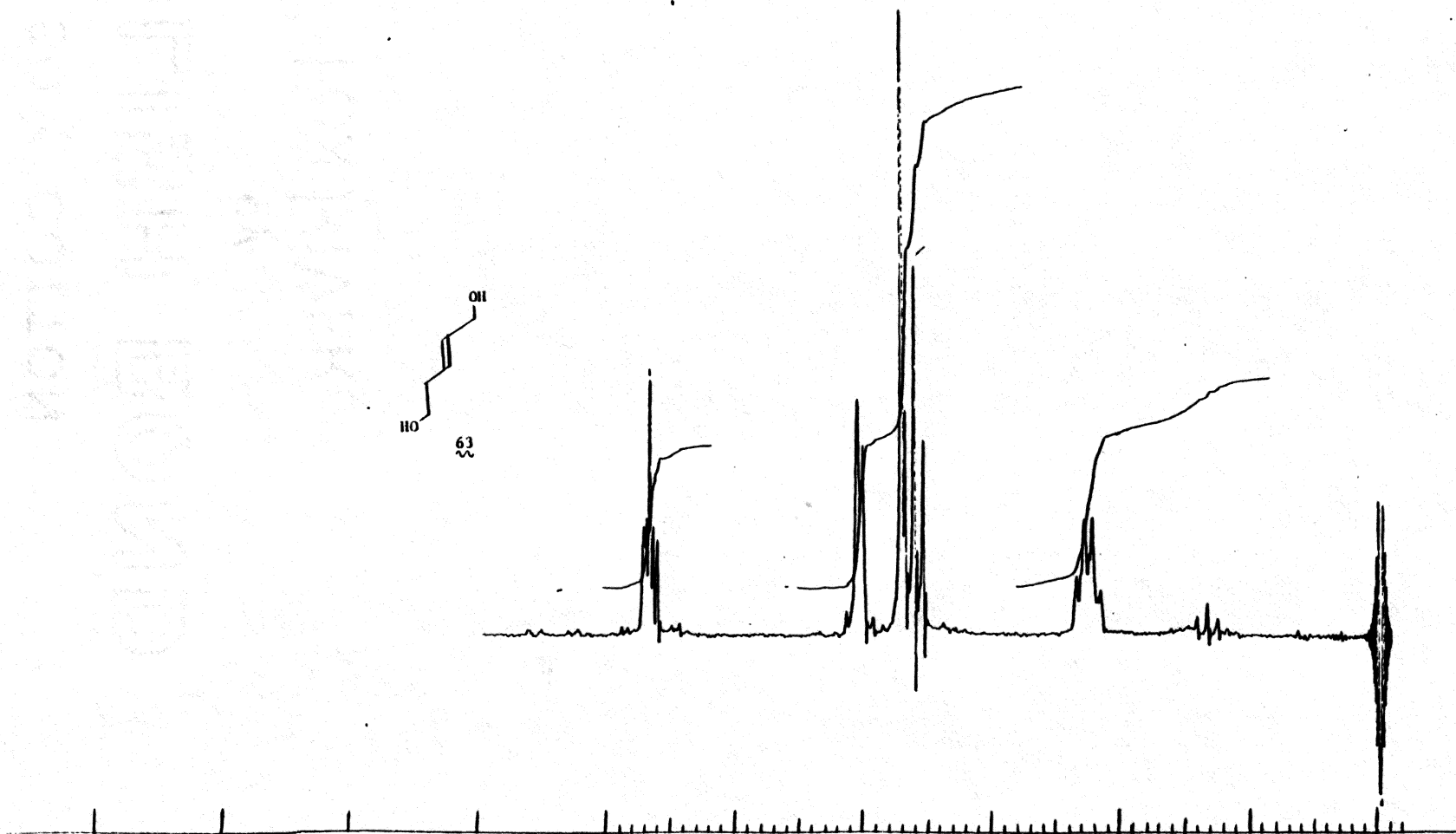
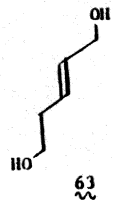


Figure 33a. 90 MHz NMR Spectrum of Diol 63.

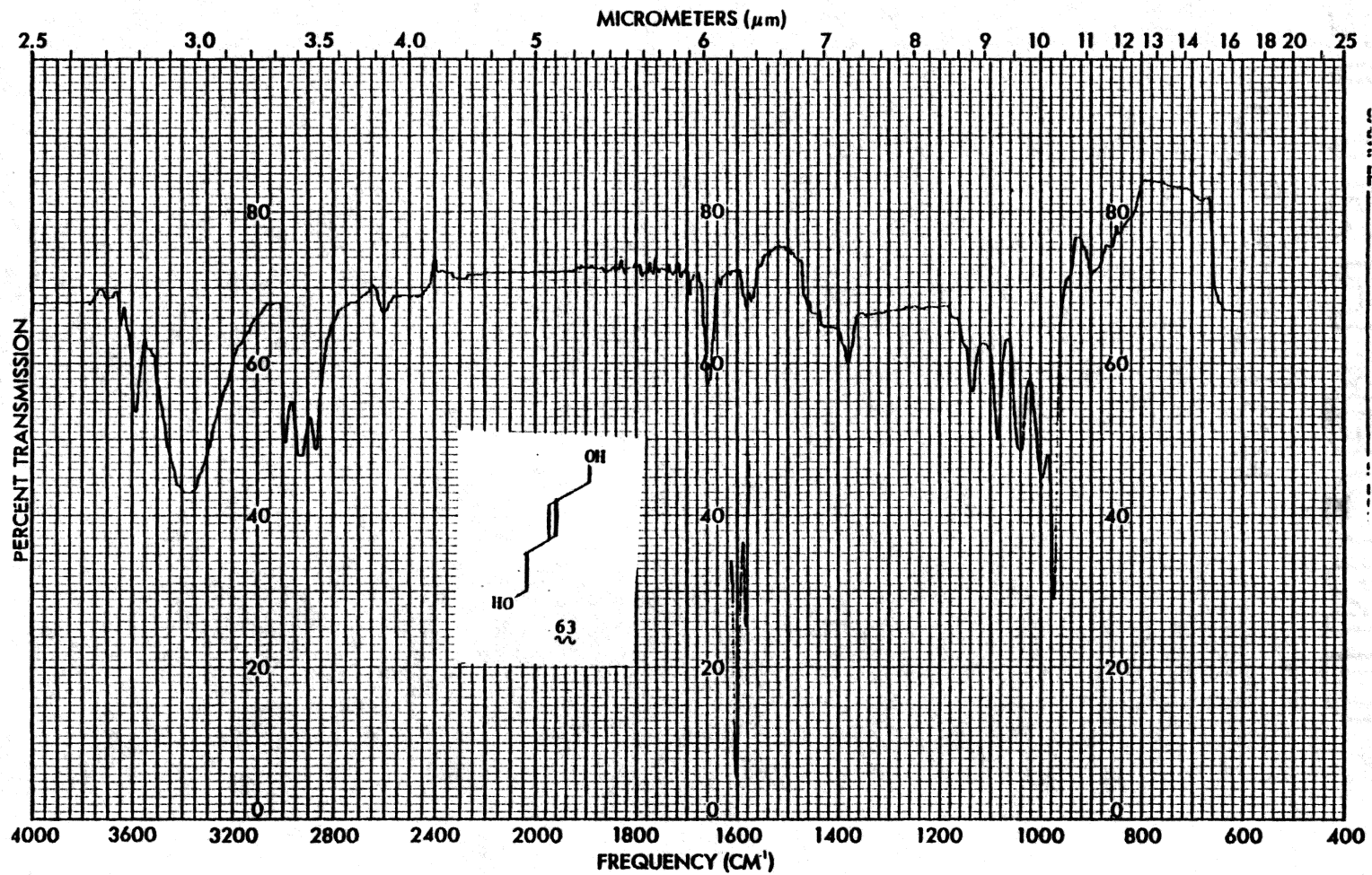


Figure 33b. IR Spectrum of Diol 63.

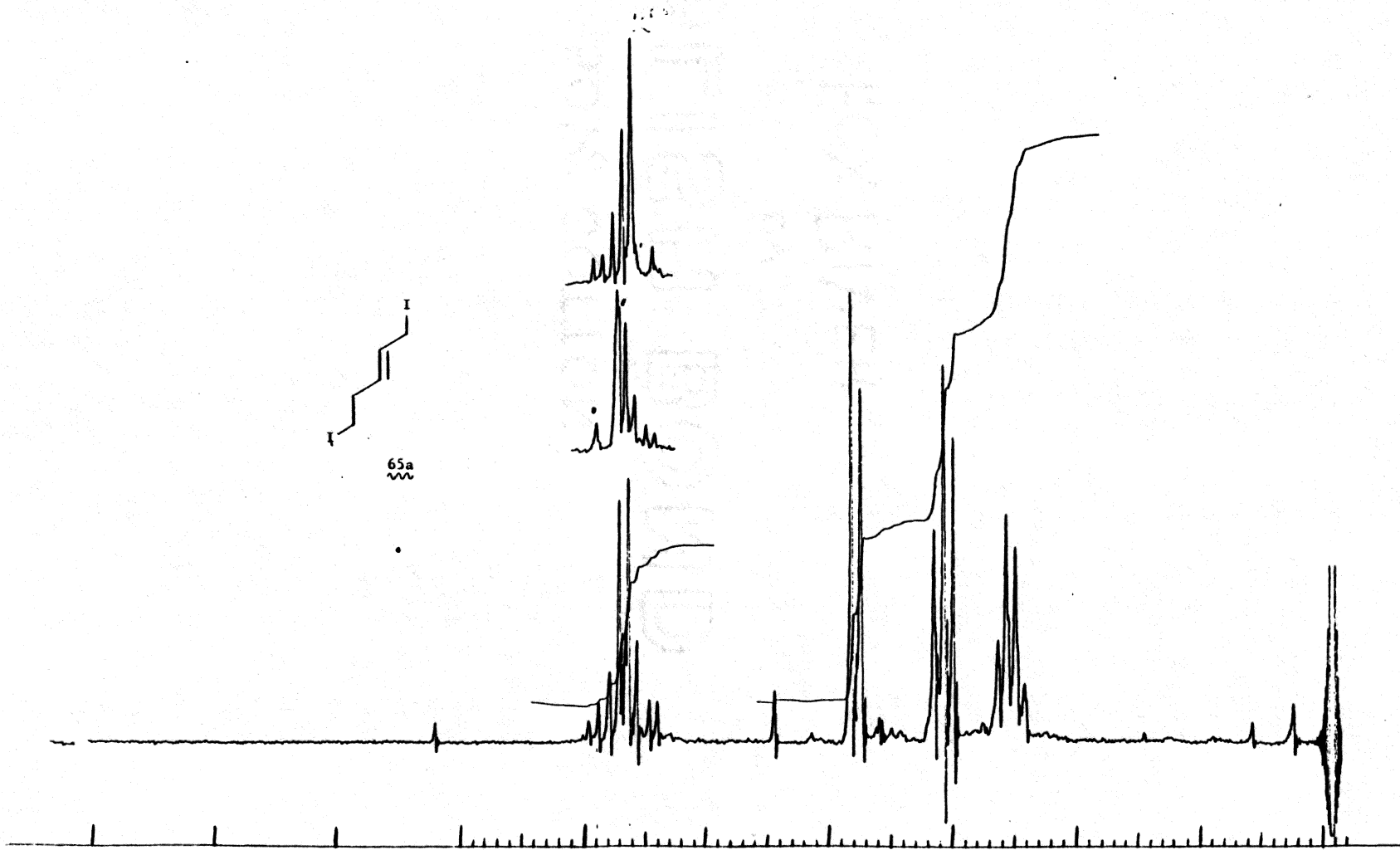


Figure 34a. 90 MHz NMR Spectrum of Diiodide 65a.

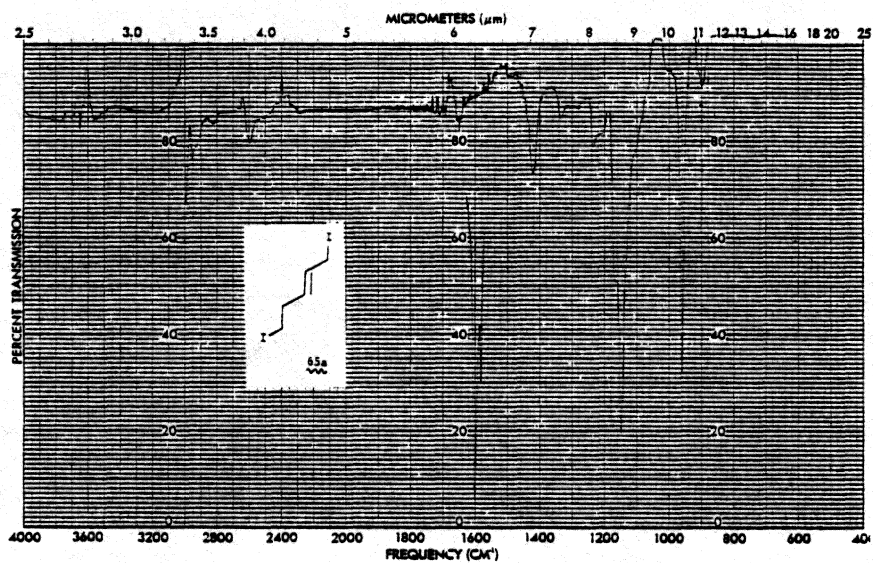


Figure 34b. IR Spectrum of Diiodide 65a.

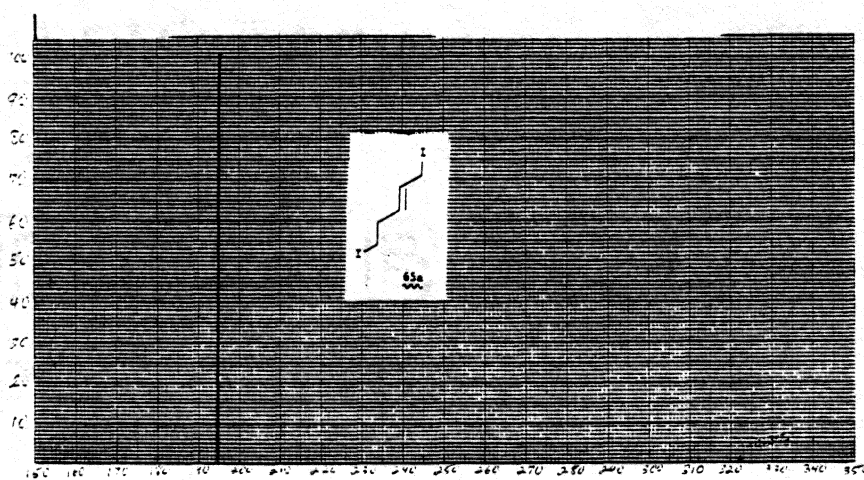


Figure 34c. Mass Spectrum of Diiodide 65a.

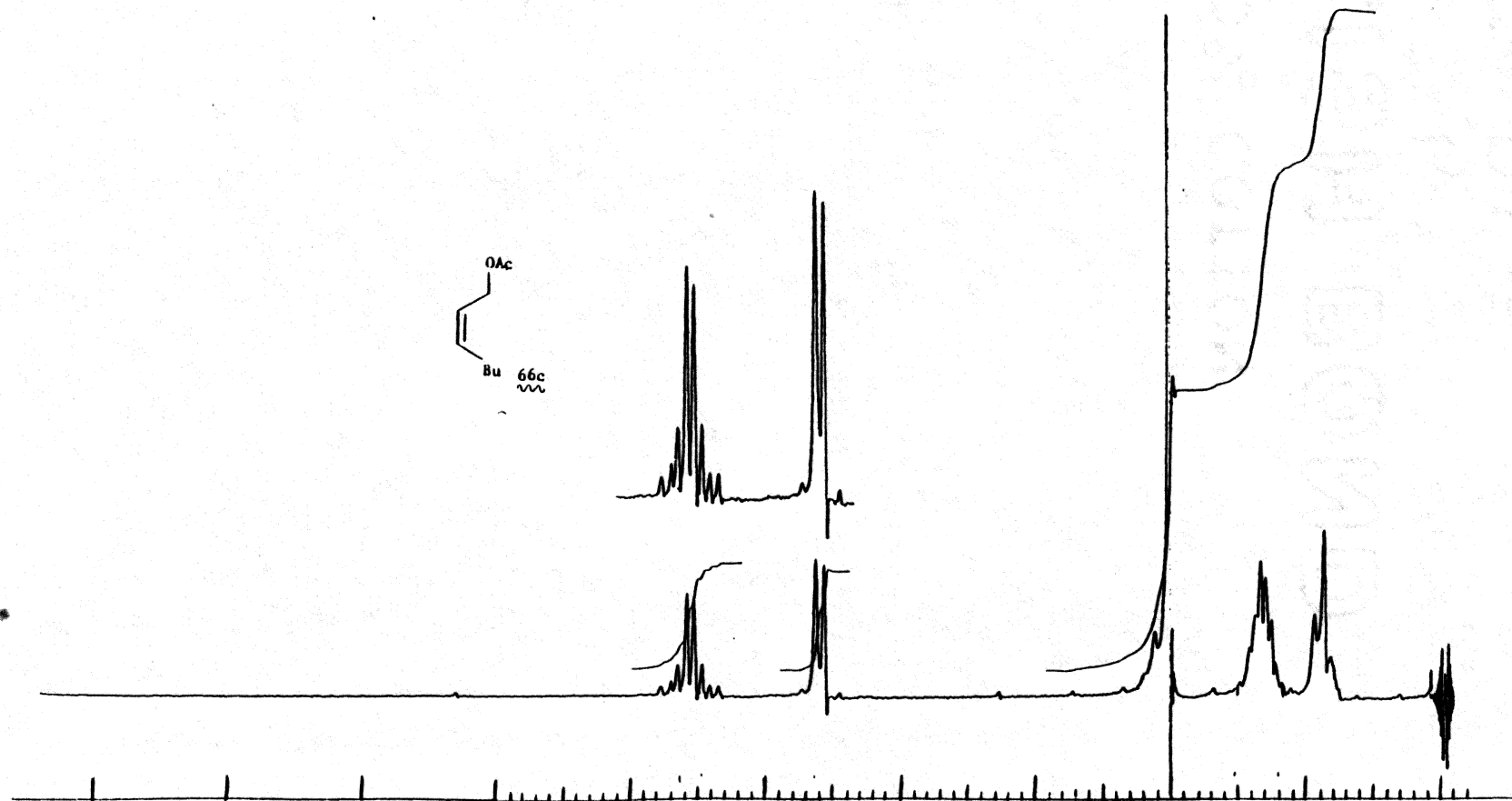


Figure 35a. 90 MHz NMR Spectrum of Allylic Acetate 66c.

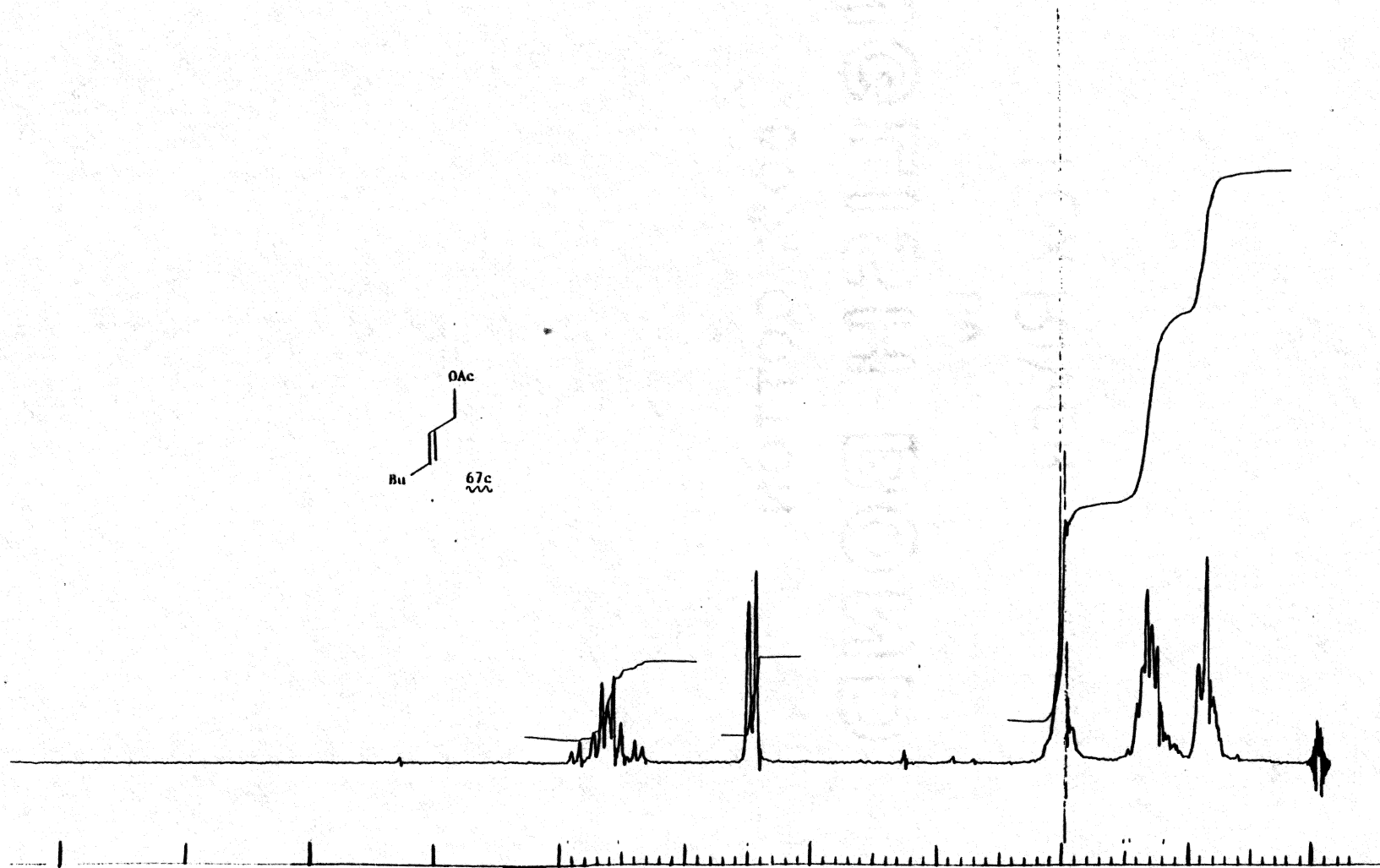


Figure 36a. 90 MHz NMR Spectrum of Allylic Acetate 67c.

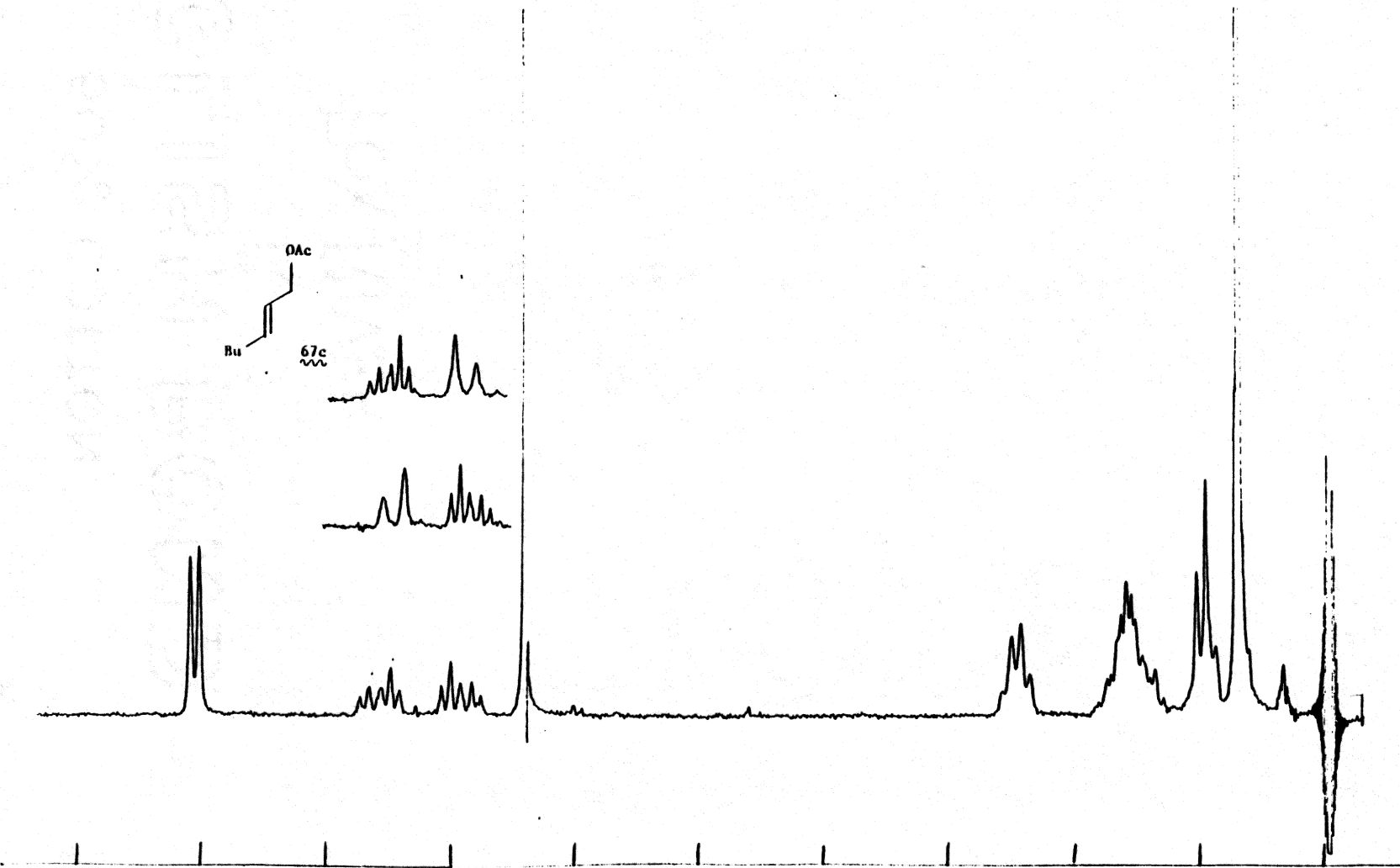


Figure 37a. 90 MHz NMR Spectrum of Allylic Acetate 67c plus $\text{Eu}(\text{fod})_3$.

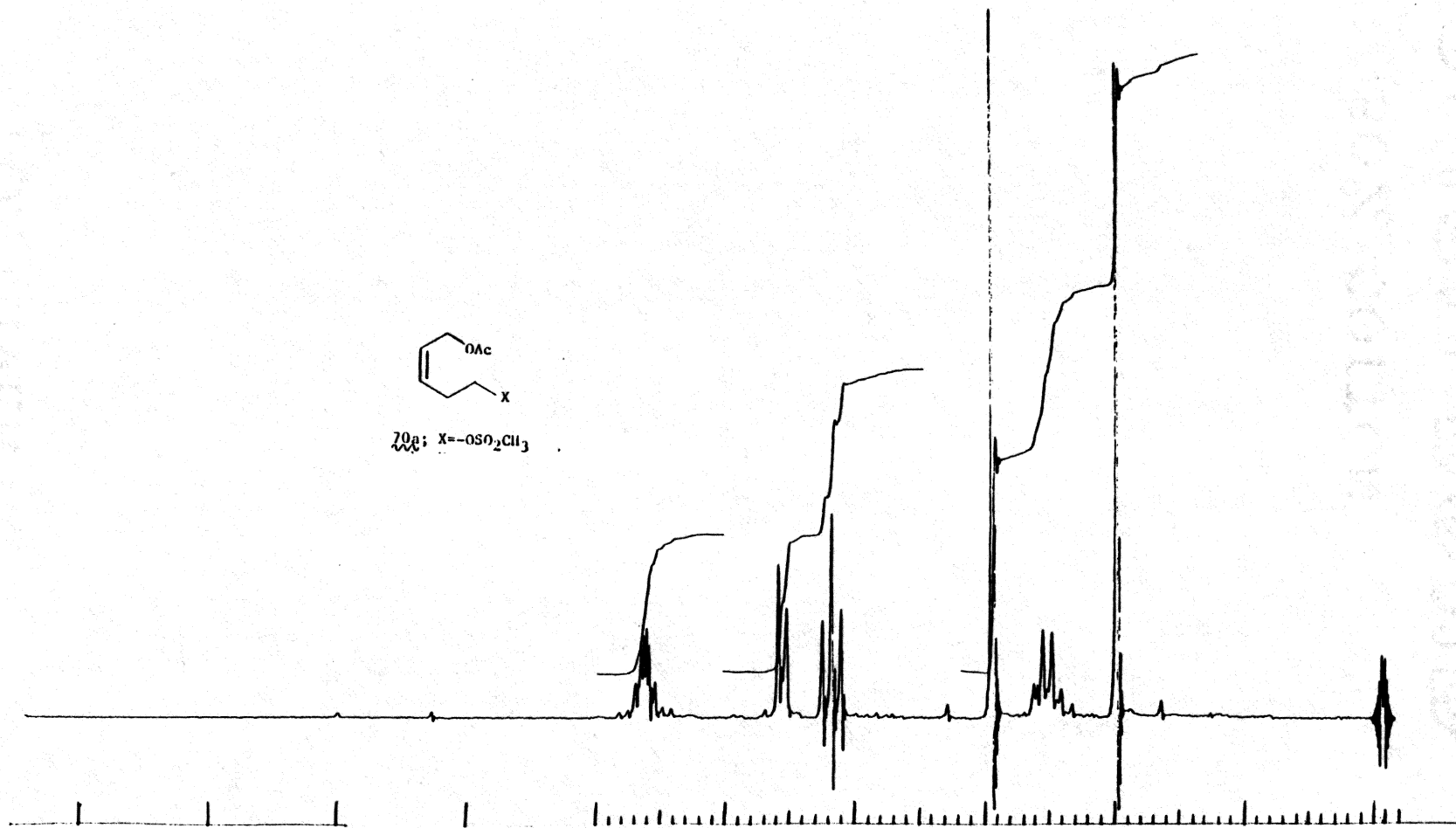


Figure 38a. 90 MHz NMR Spectrum of Allylic Acetate 70a.

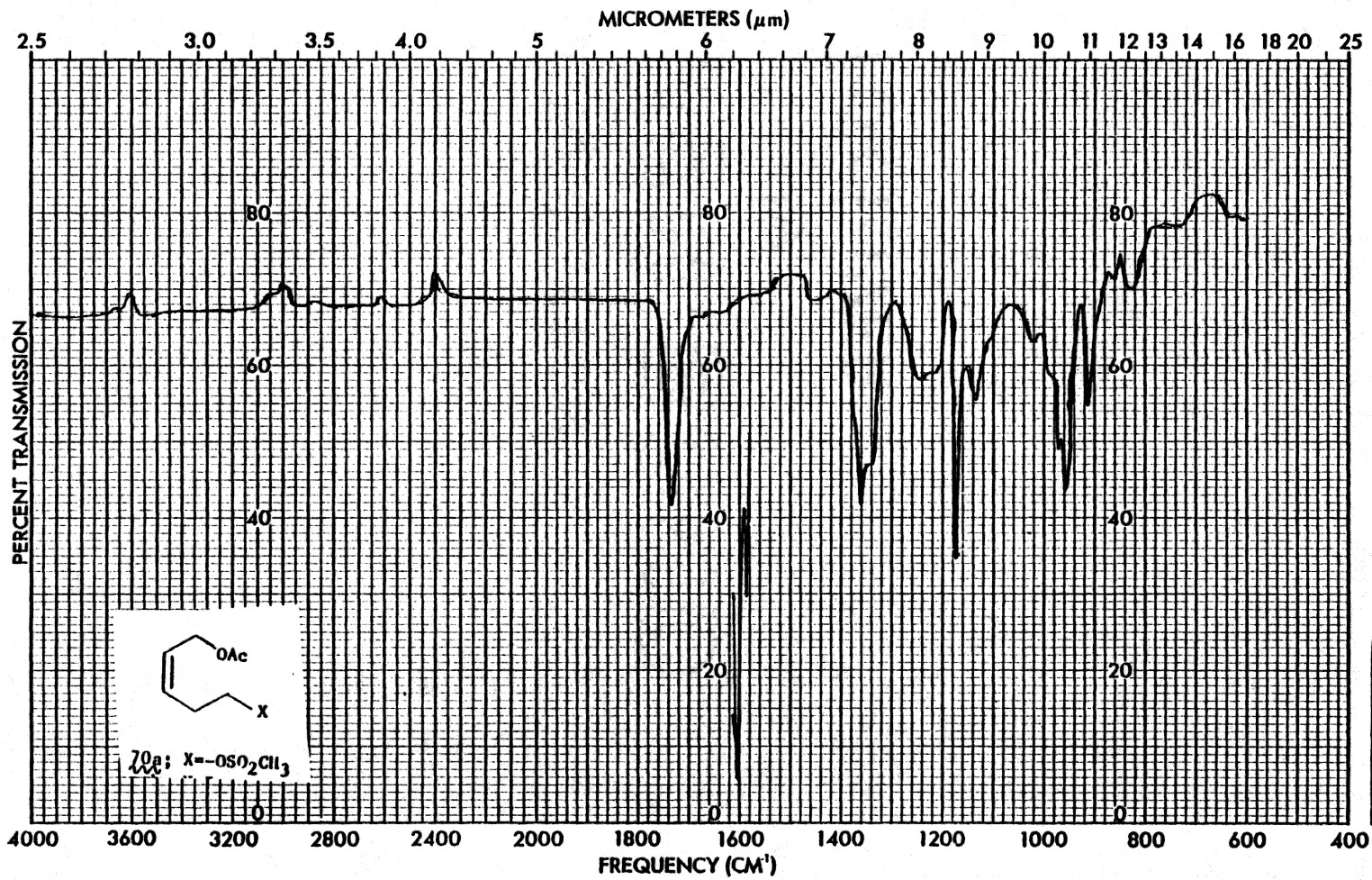


Figure 38b. IR Spectrum of Allylic Acetate 70a.

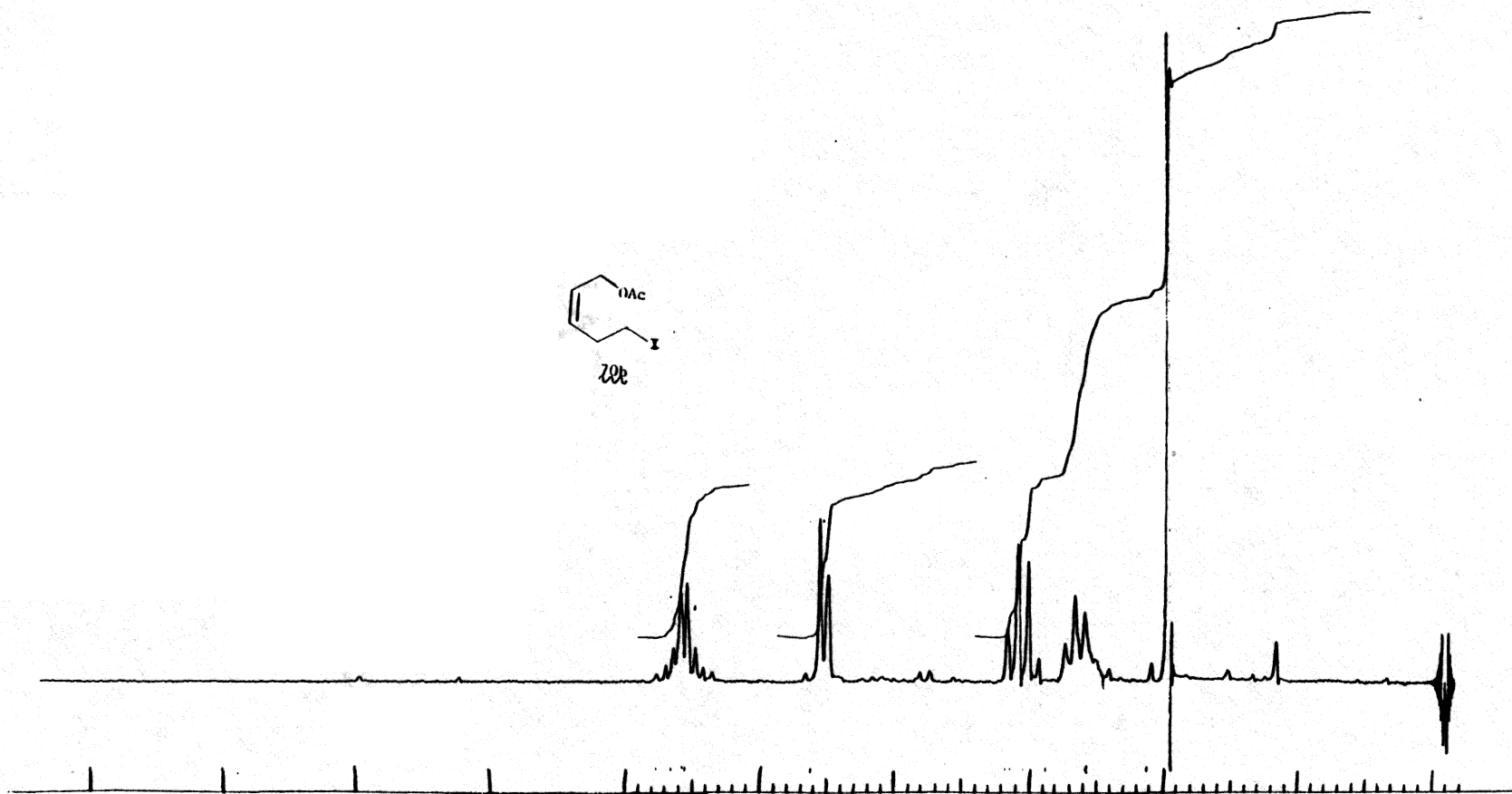


Figure 39a. 90 MHz NMR Spectrum of Acetoxy Iodide 70b.

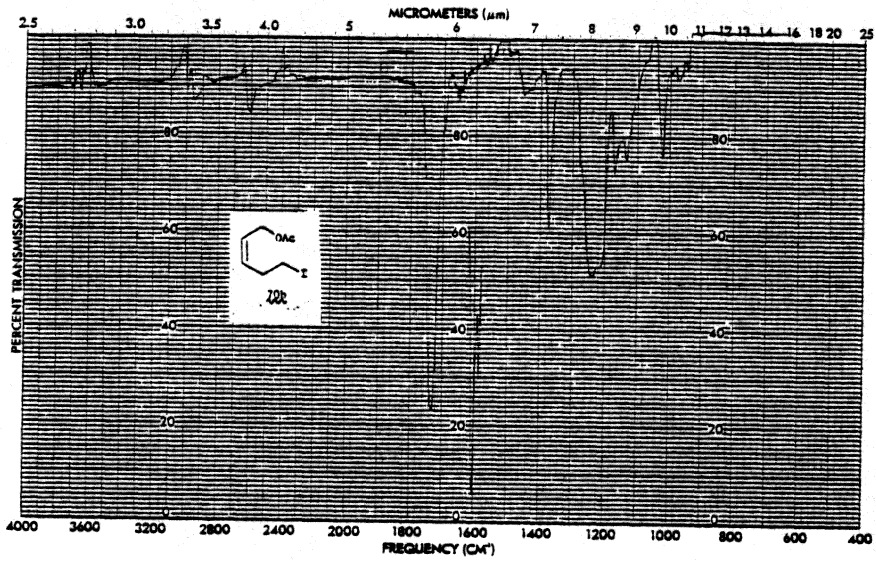


Figure 39b. IR Spectrum of Acetoxy Iodide 70b.

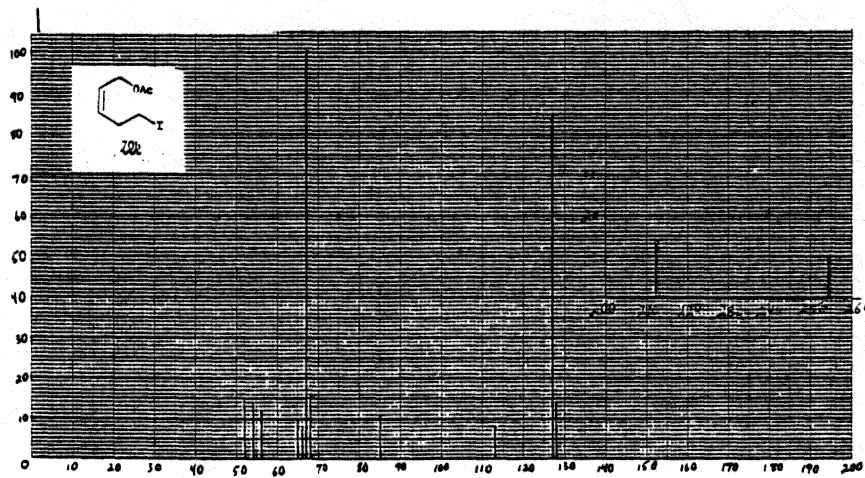


Figure 39c. Mass Spectrum of Acetoxy Iodide 70b.

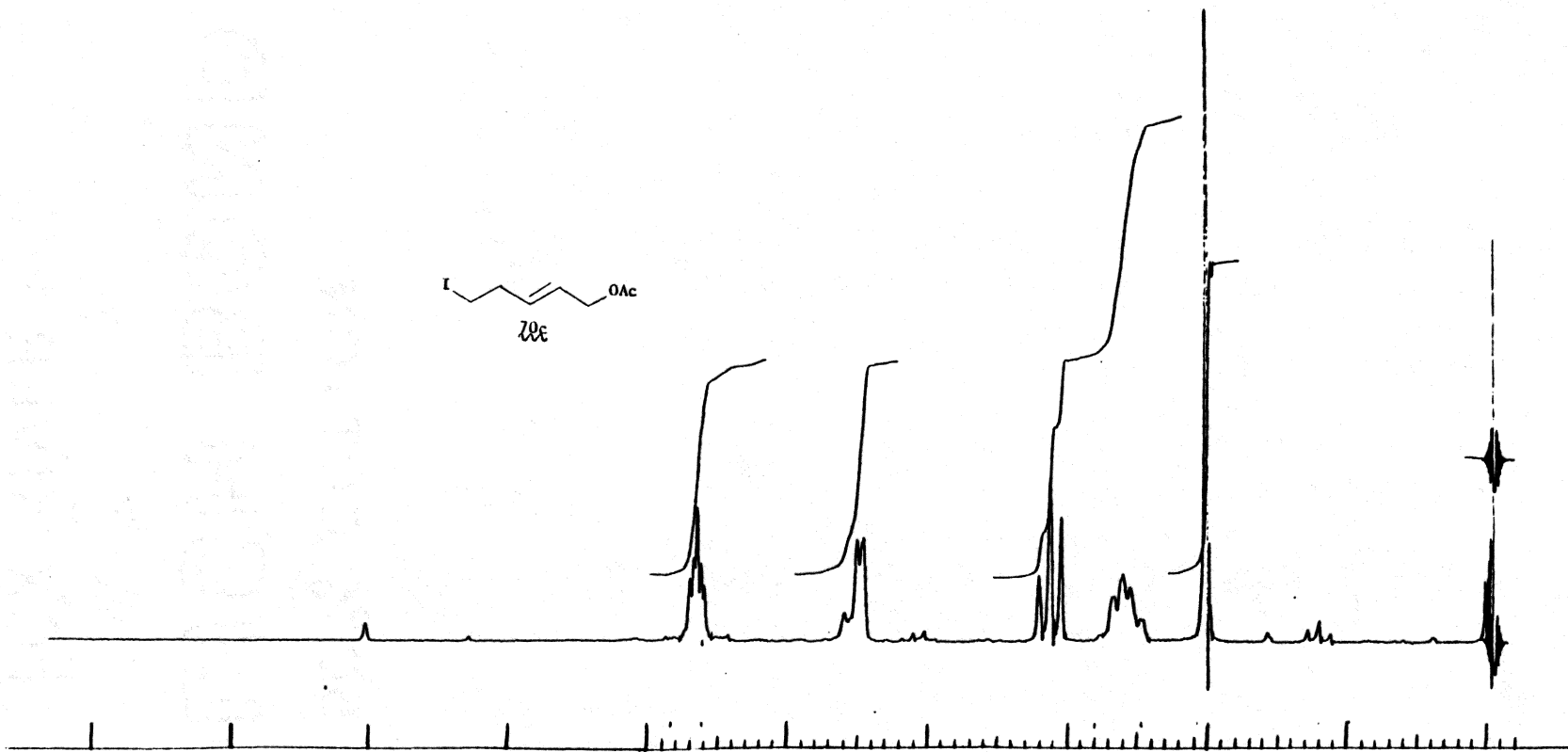


Figure 40a. 90 MHz NMR Spectrum of Acetoxy Iodide 70c.

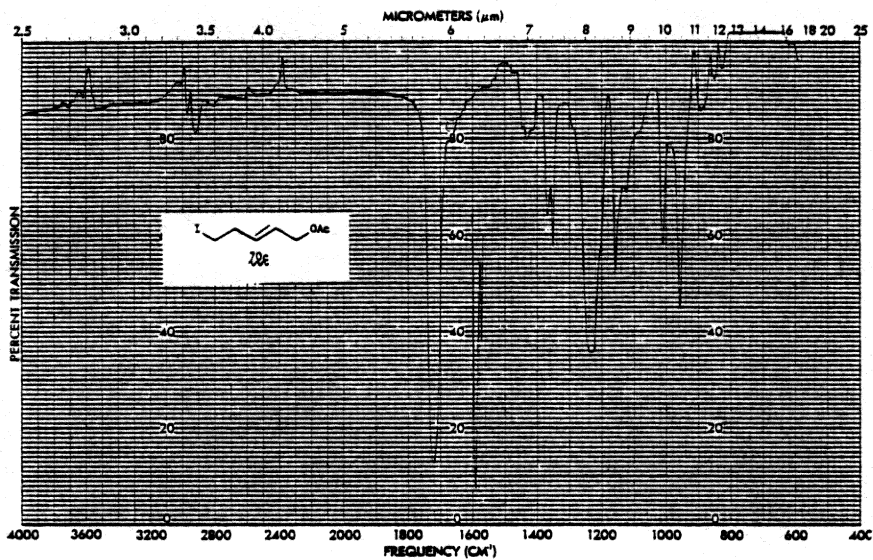


Figure 40b. IR Spectrum of Acetoxy Iodide 70c.

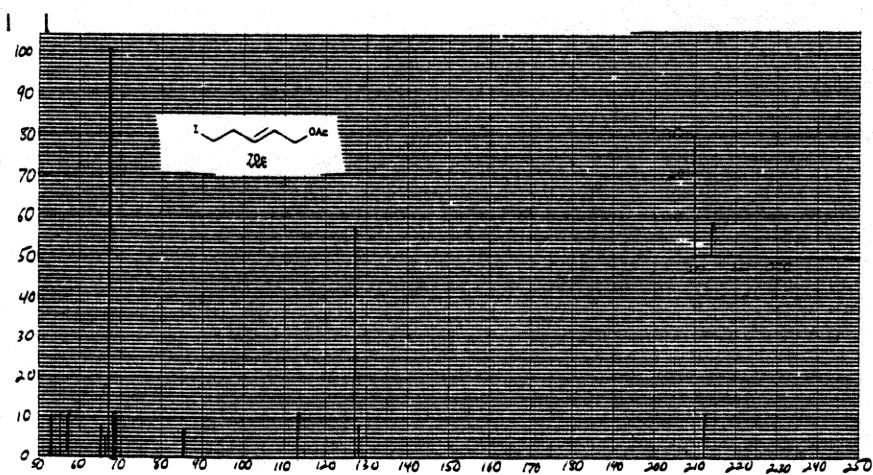


Figure 40c. Mass Spectrum of Acetoxy Iodide 70c.

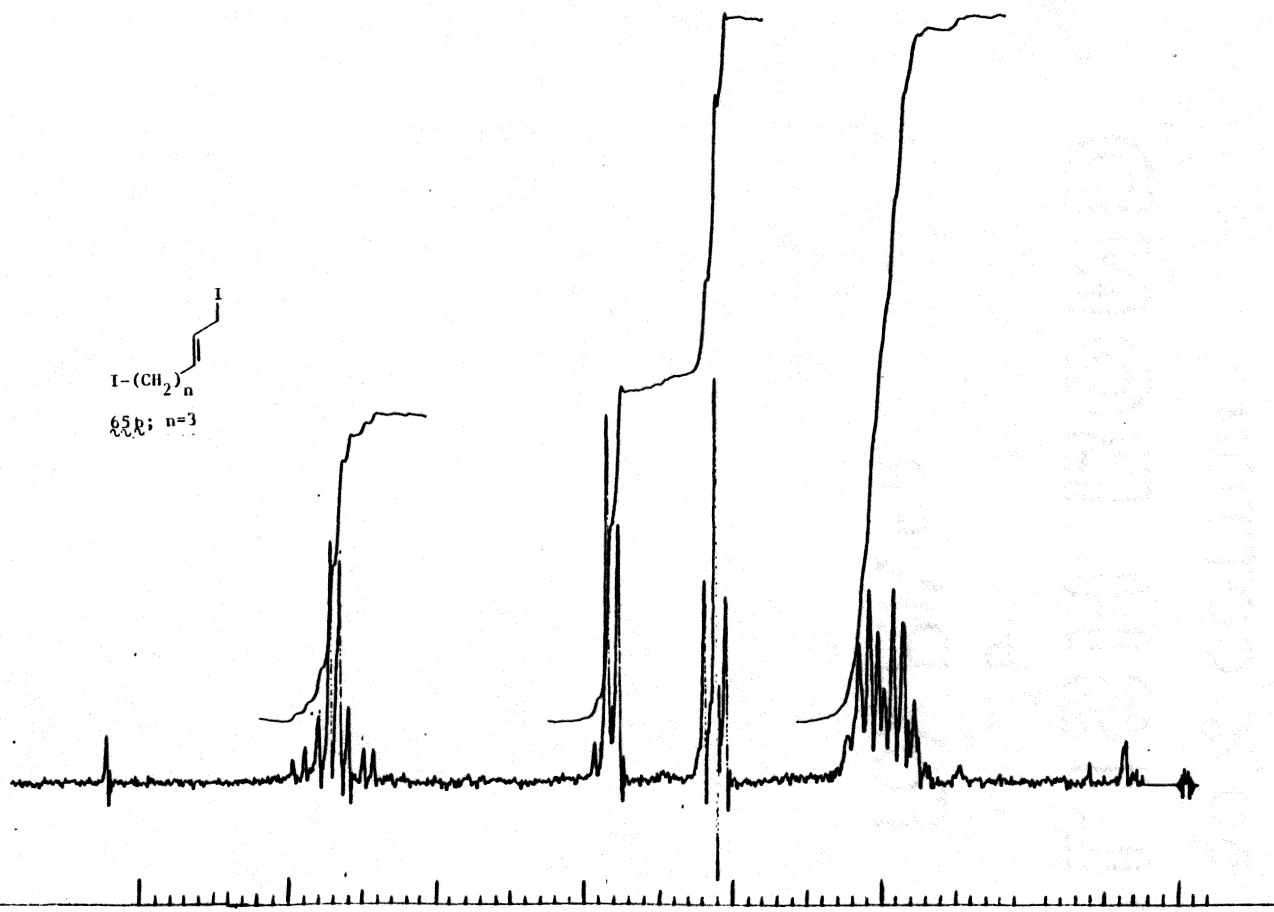


Figure 41a. 90 MHz NMR Spectrum of Diiodide 65b.

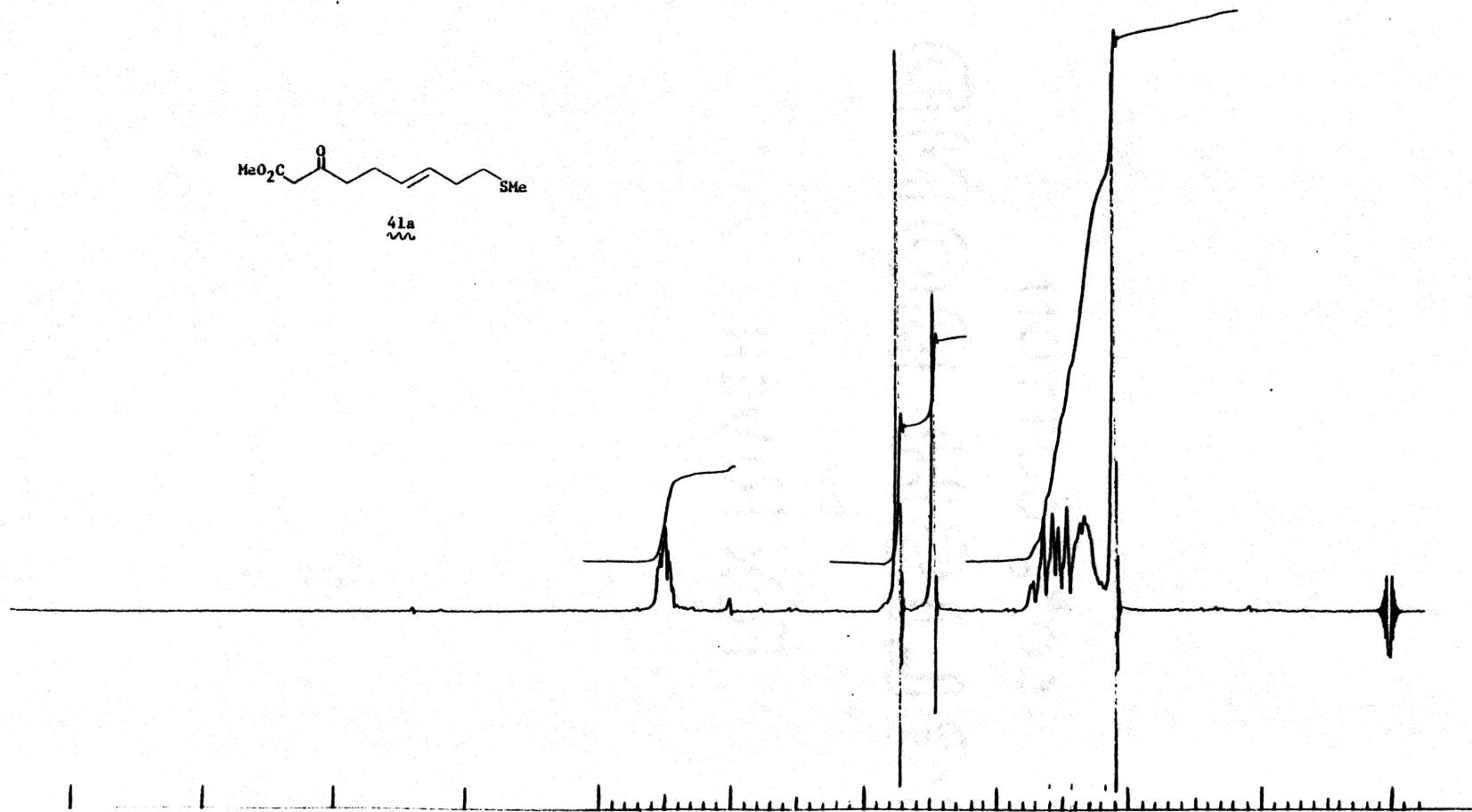
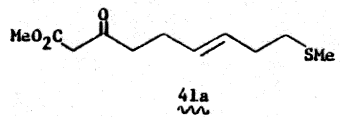


Figure 42a. 90 MHz NMR Spectrum of Sulfide Ketoester 41a.

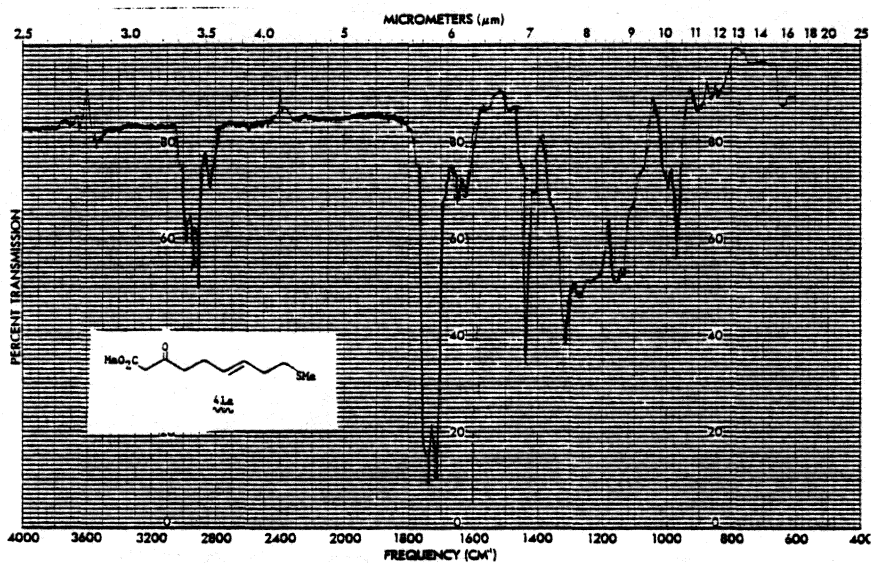


Figure 42b. IR Spectrum of Sulfide Ketoester 41a.

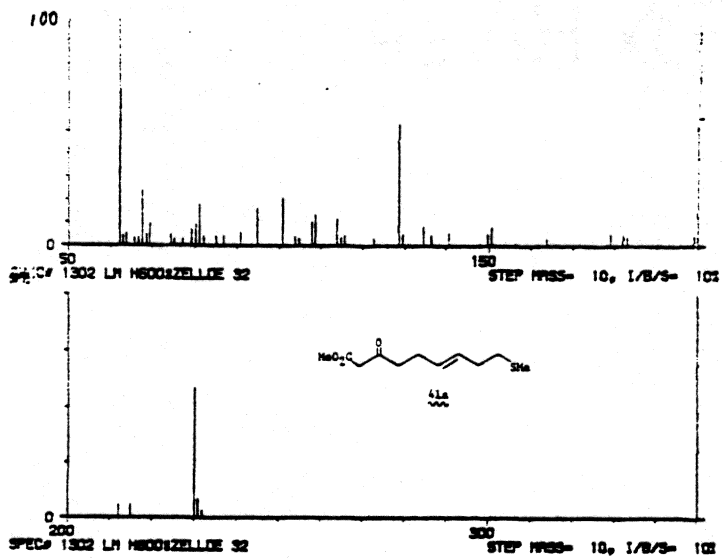


Figure 42c. Mass Spectrum of Sulfide Ketoester 41a.

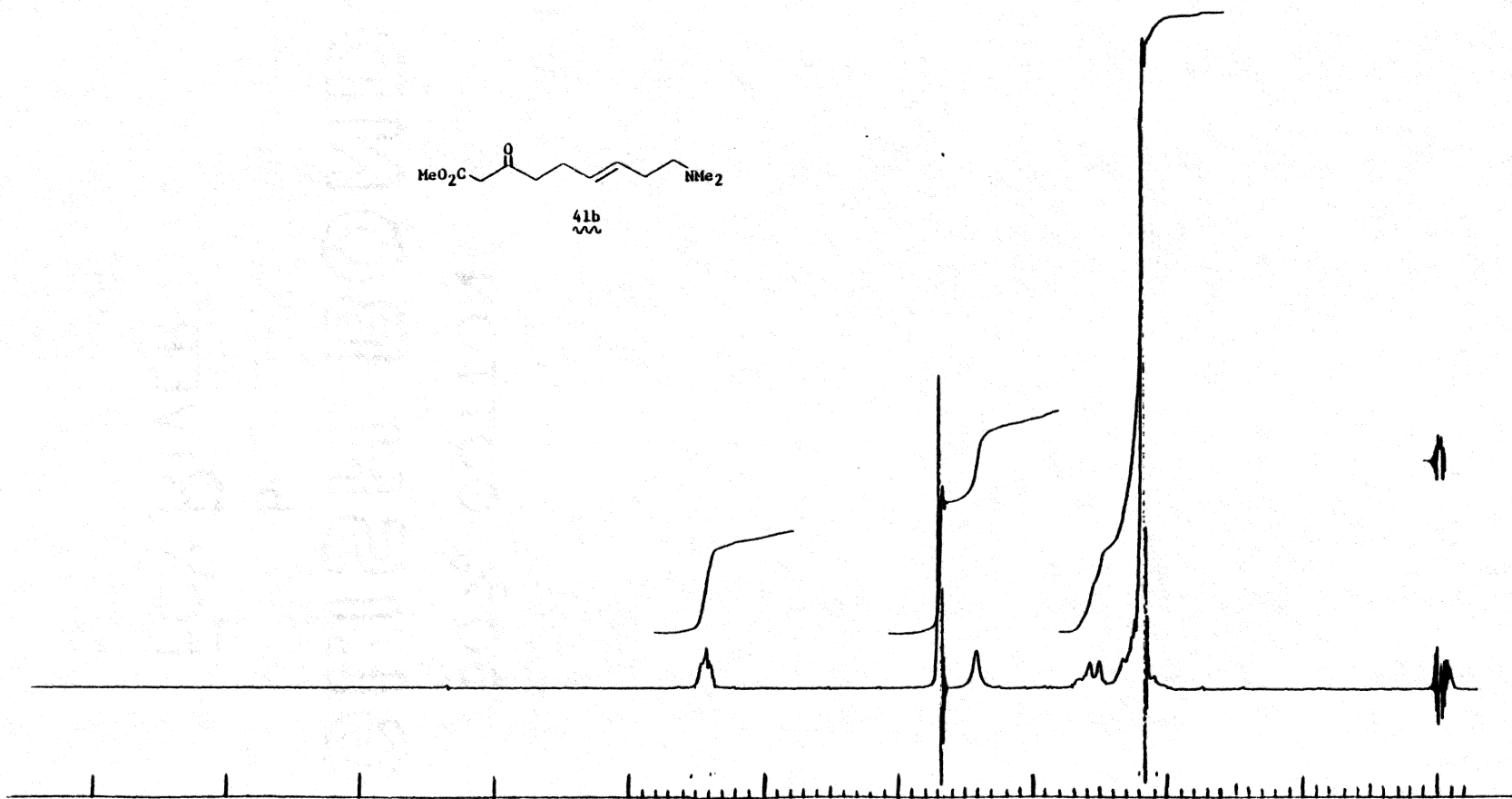
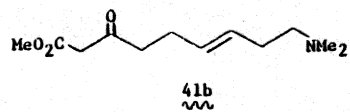


Figure 43a. 90 MHz NMR Spectrum of Amino Ketoester 41b.

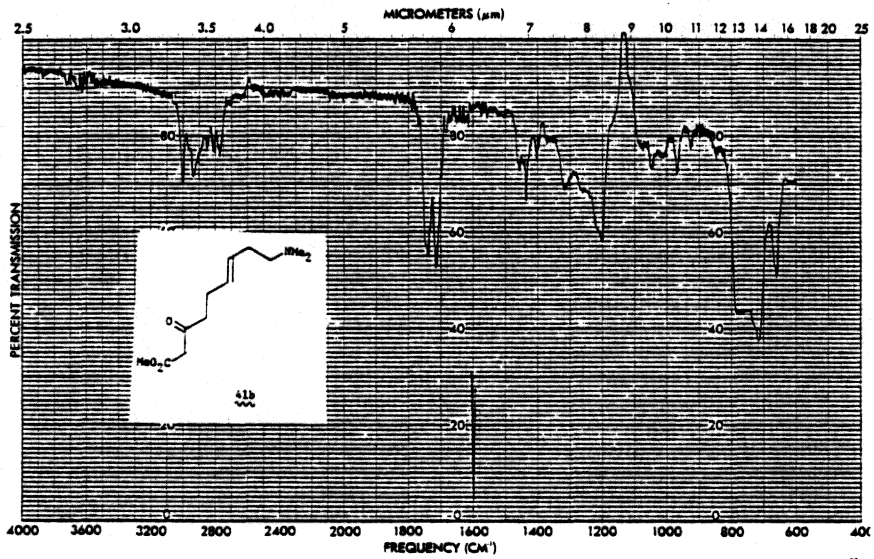


Figure 43b. IR Spectrum of Amino Ketoester 41b.

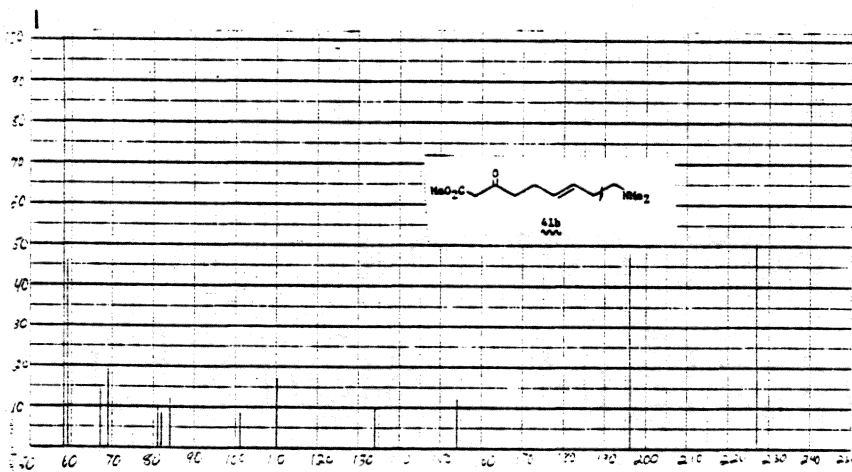


Figure 43c. Mass Spectrum of Amino Ketoester 41b.

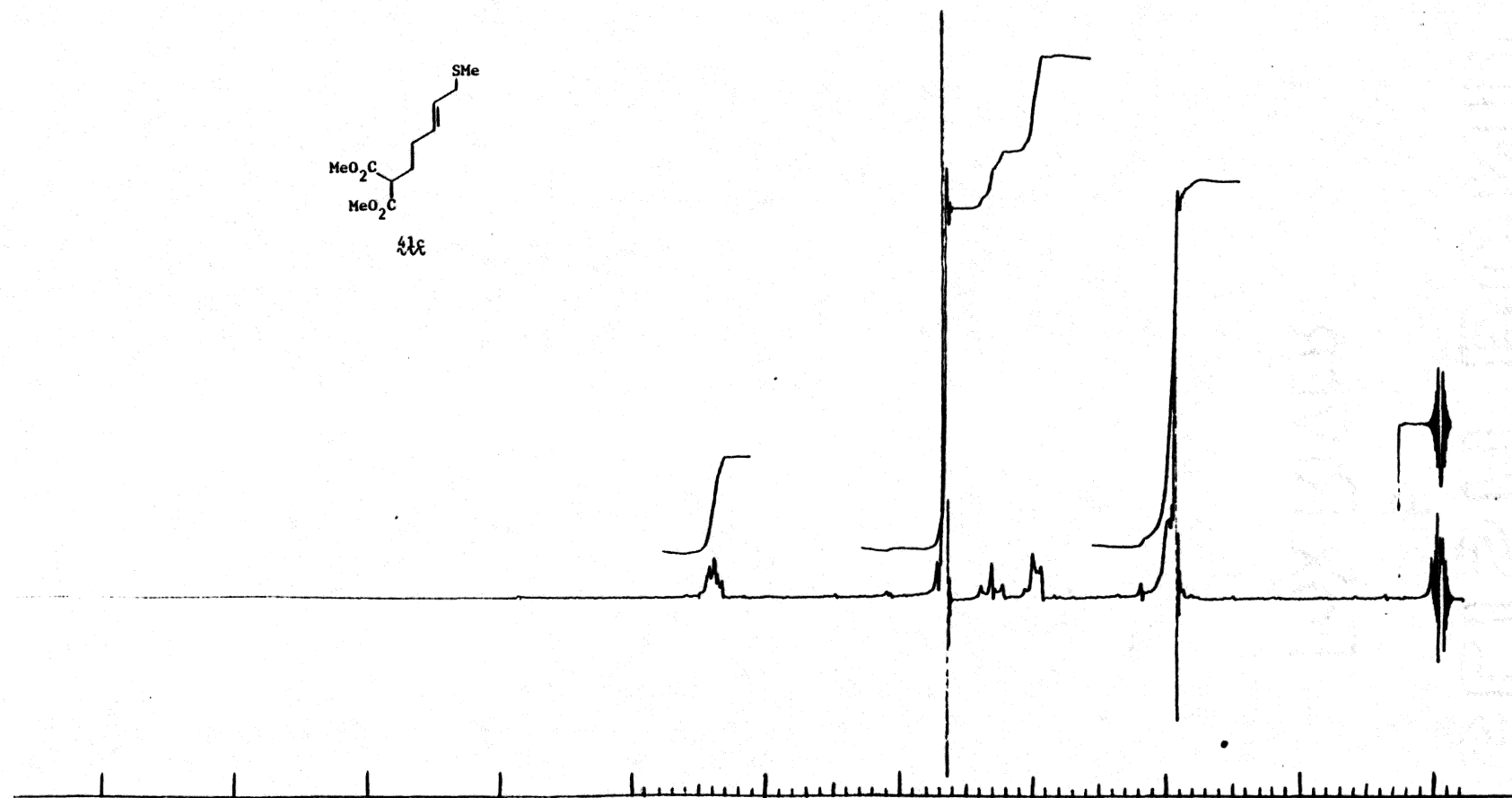


Figure 44a. NMR Spectrum of Sulfide Ketoester 41c.

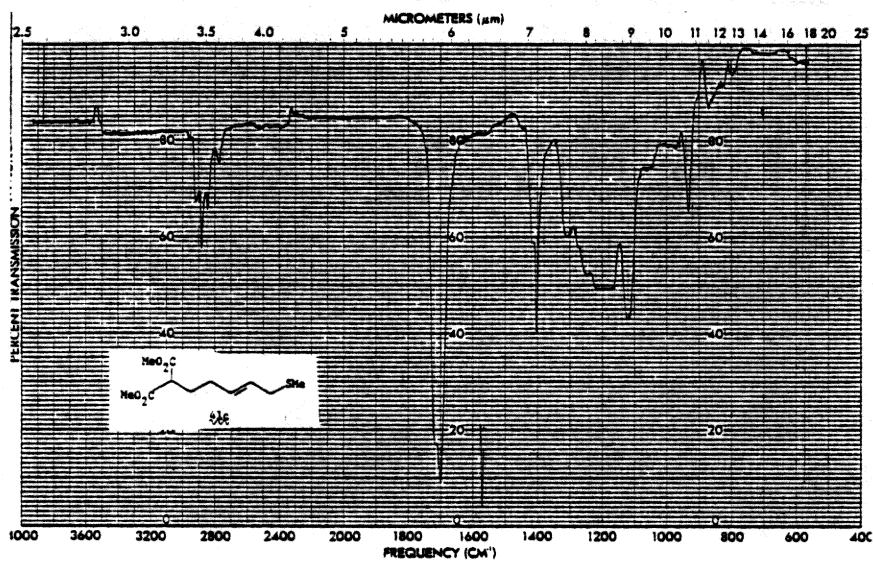


Figure 44b. IR Spectrum of Sulfide Ketoester 4lc.

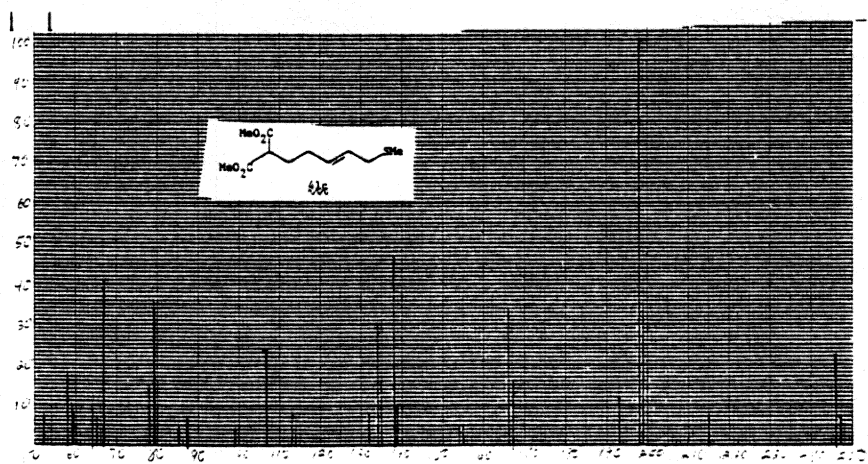


Figure 44c. Mass Spectrum of Sulfide Ketoester 4lc.

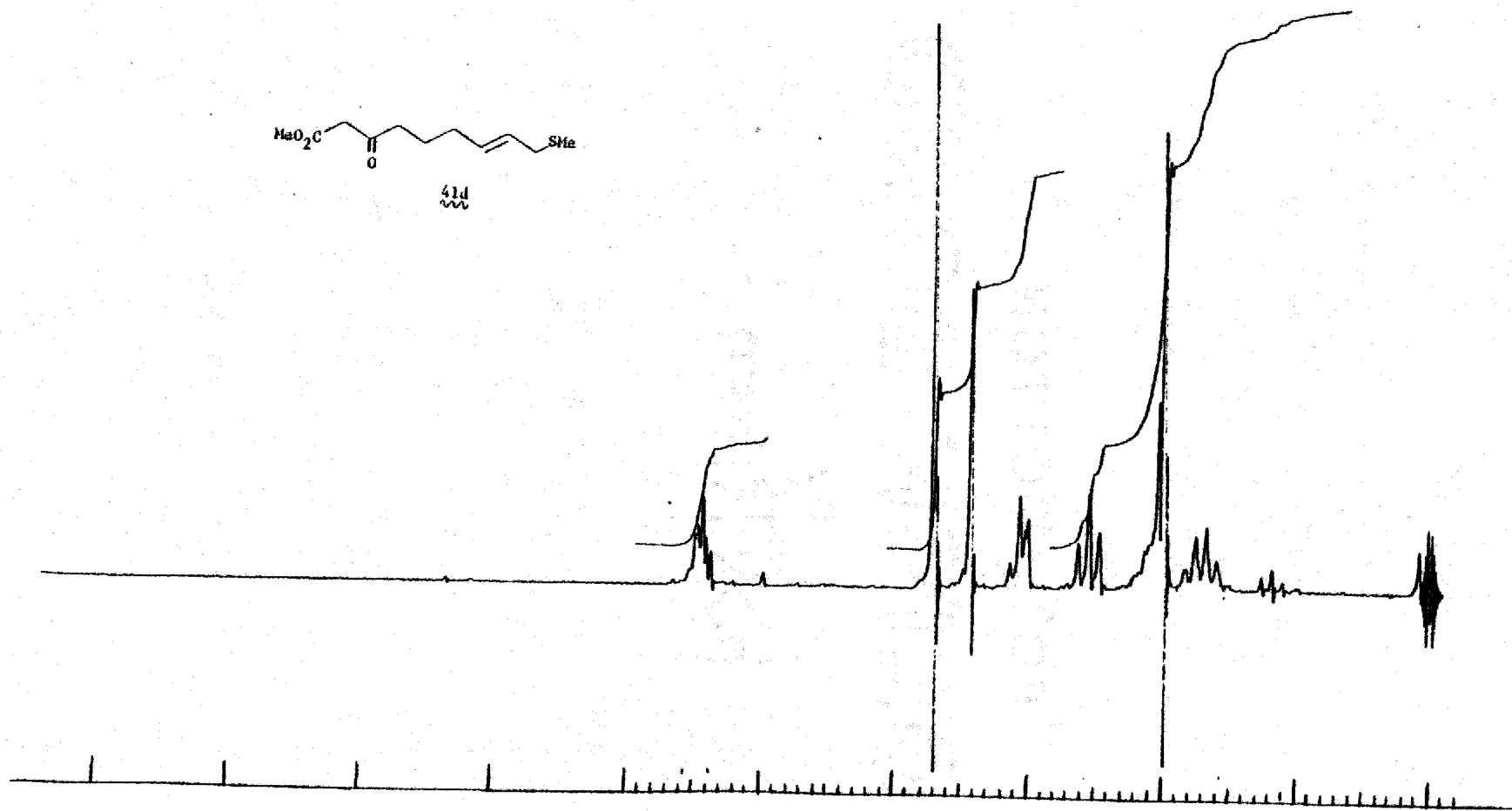


Figure 45a. 90 MHz NMR Spectrum of Sulfide Ketoester 4ld.

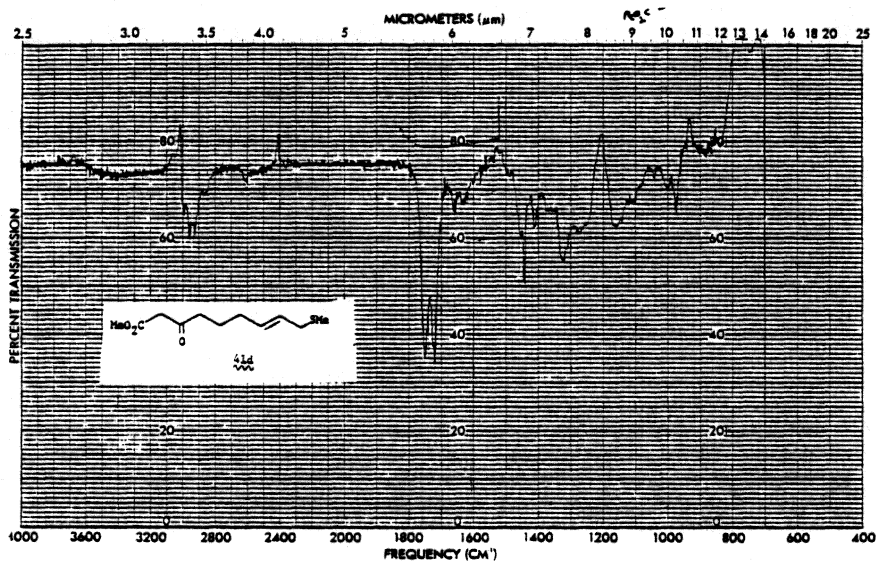


Figure 45b. IR Spectrum of Sulfide Ketoester 4ld.

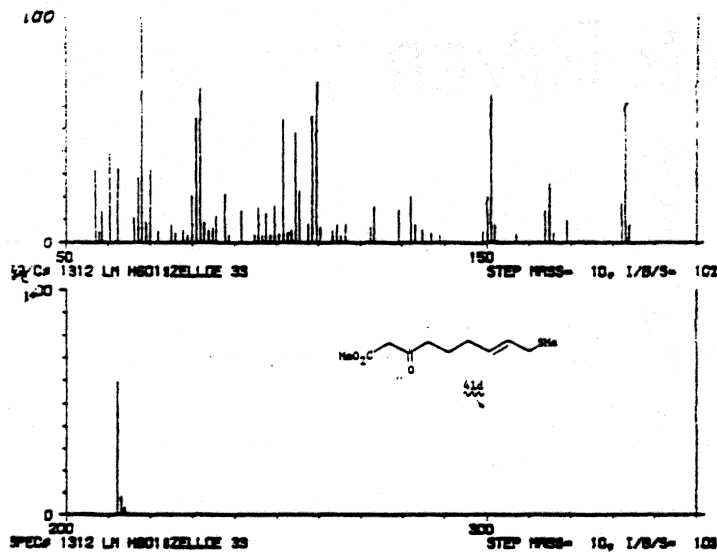


Figure 45c. Mass Spectrum of Sulfide Ketoester 4ld.

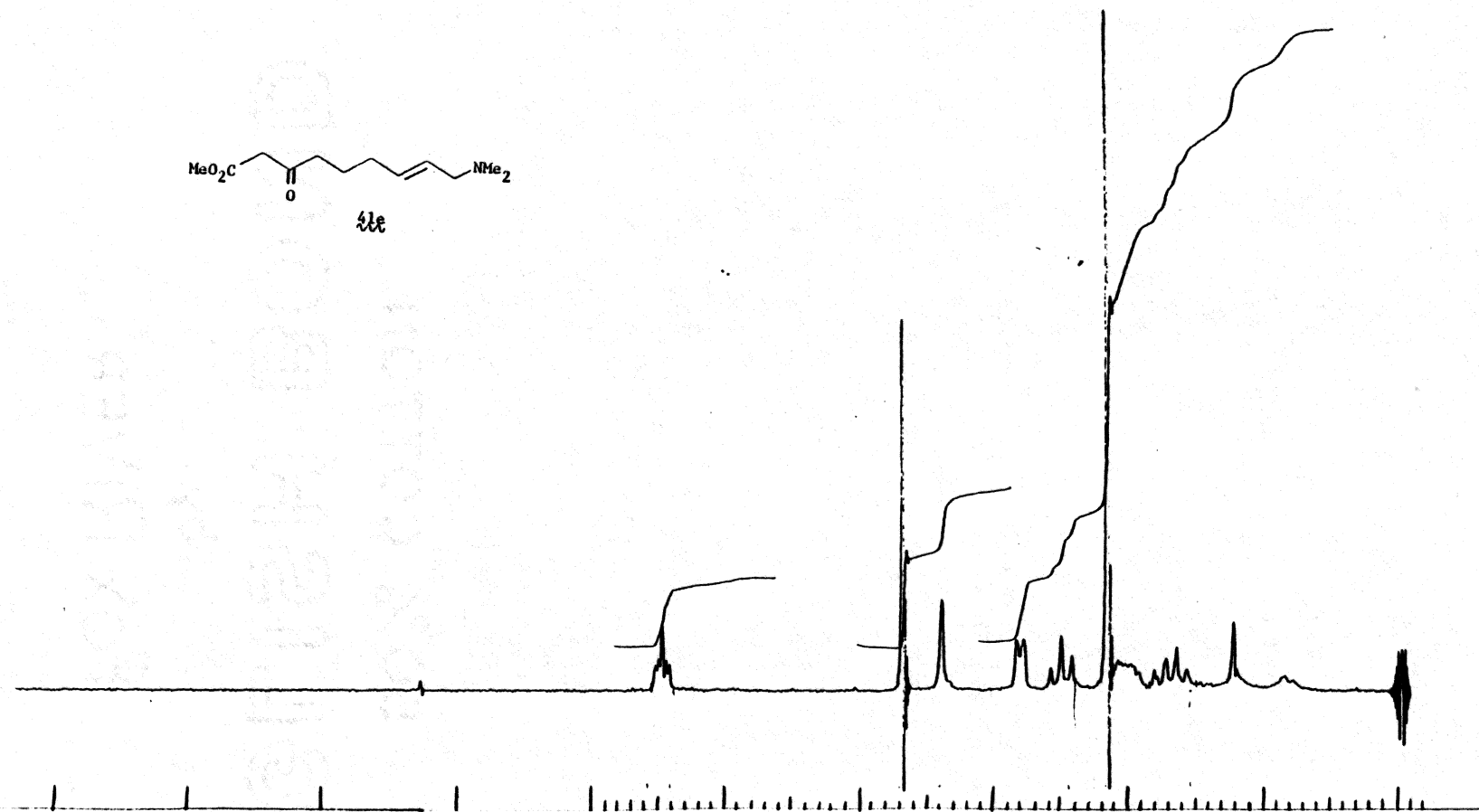


Figure 46a. 90 MHz NMR Spectrum of Amino Ketoester 4le.

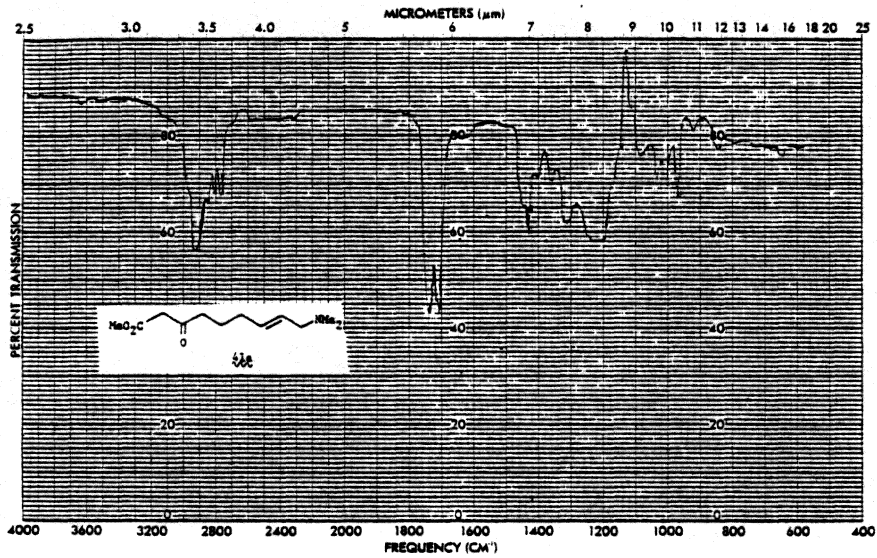


Figure 46b. IR Spectrum of Amino Ketoester 41e.

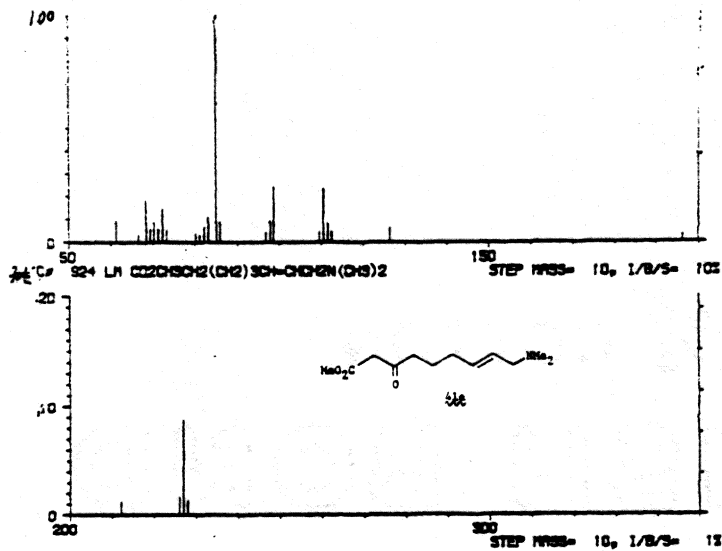


Figure 46c. Mass Spectrum of Amino Ketoester 41e.

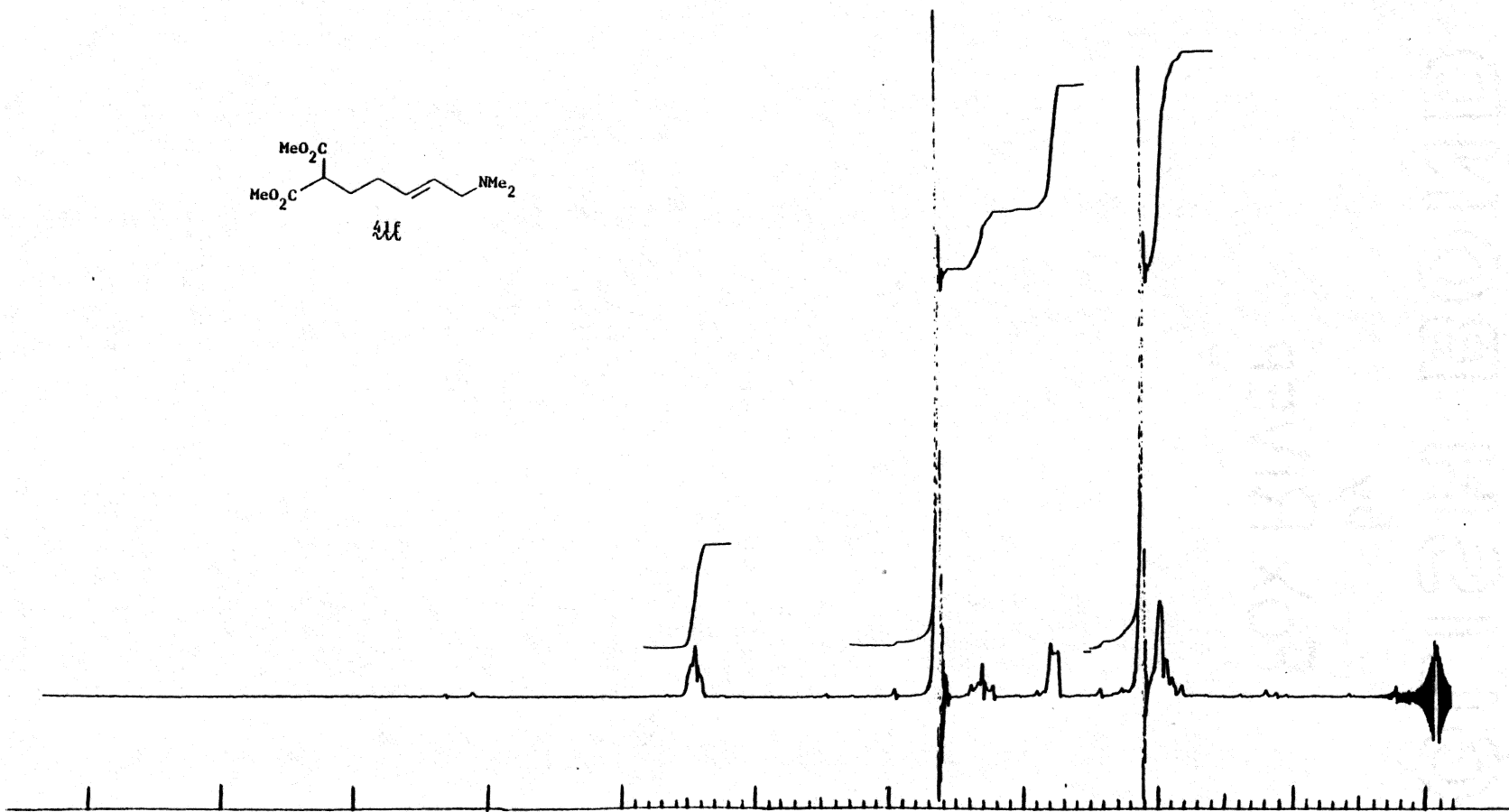


Figure 47a. 90 MHz NMR Spectrum of Aminodiester 41f.

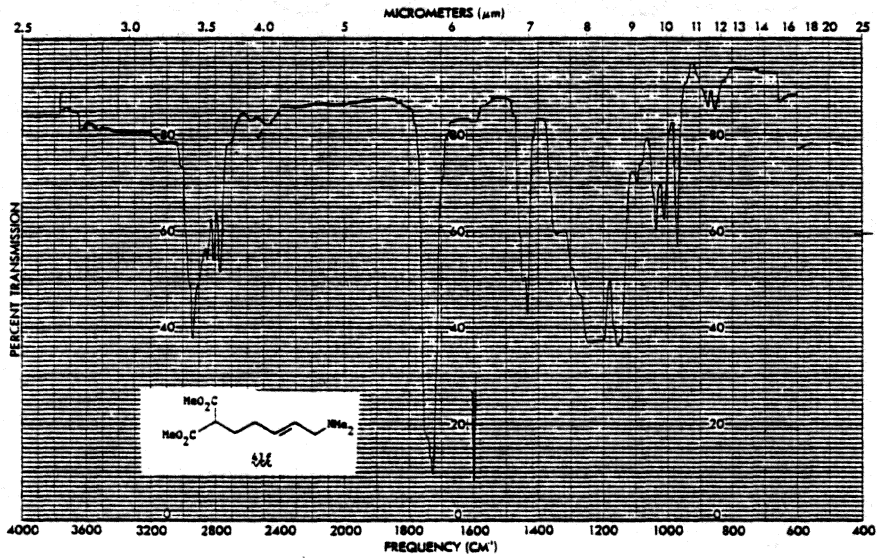


Figure 47b. IR Spectrum of Aminodiester 4lf.

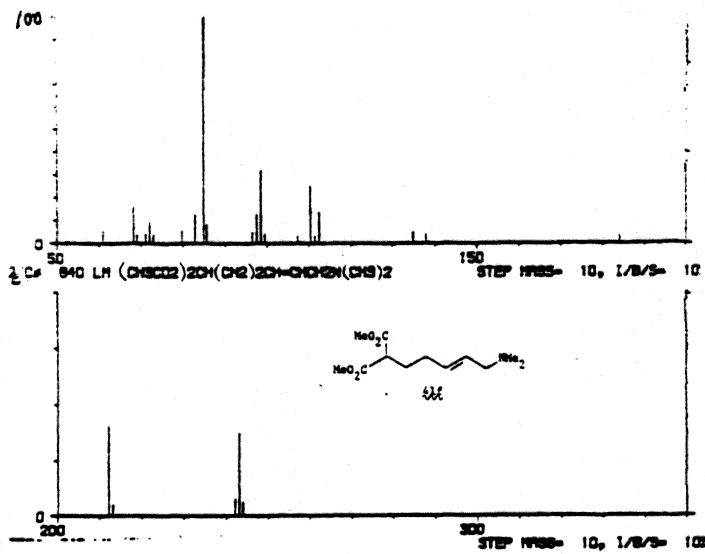


Figure 47c. Mass Spectrum of Aminodiester 4lf.

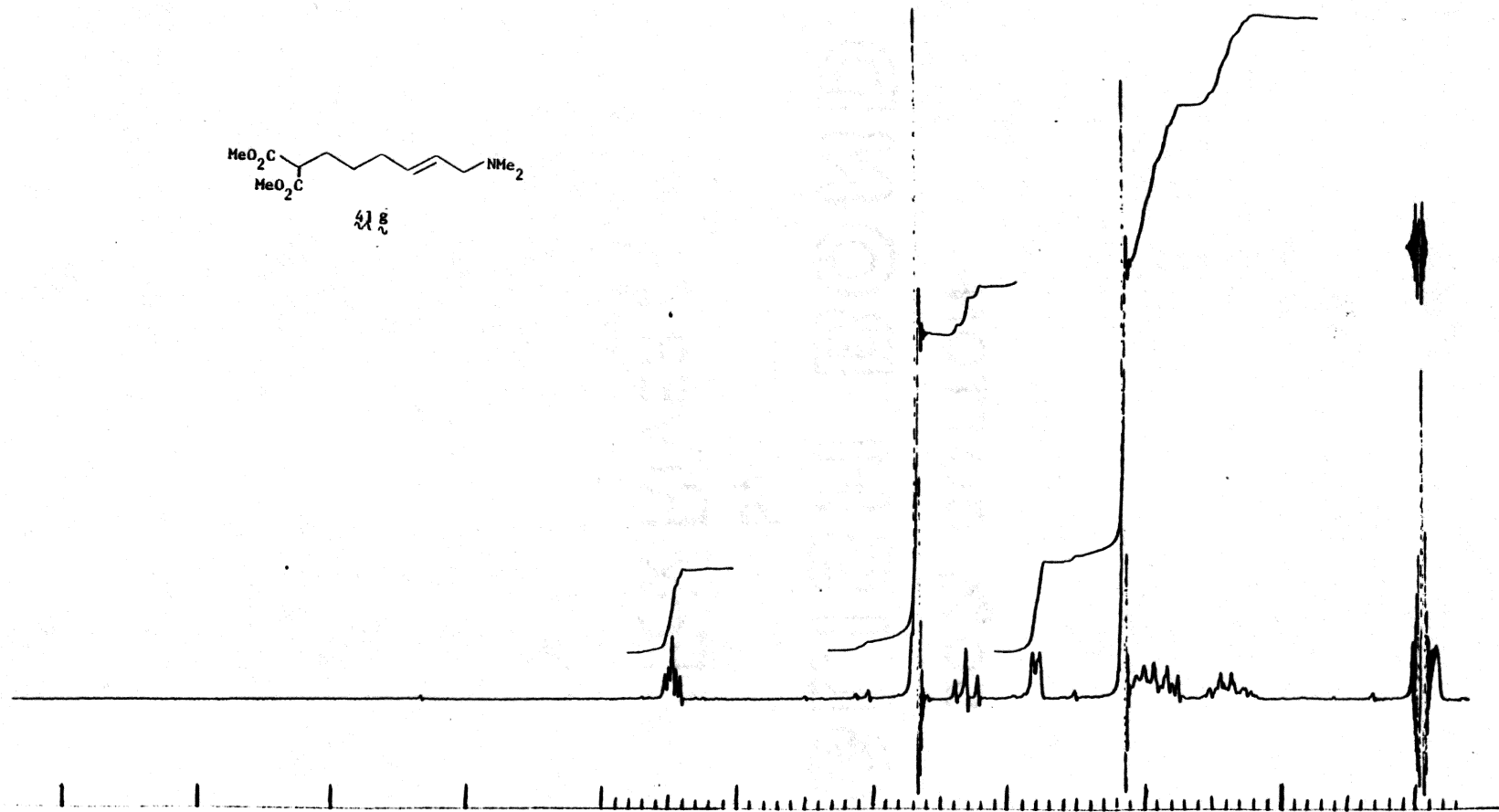


Figure 48a. 90 MHz NMR Spectrum of Aminodiester 4lg.

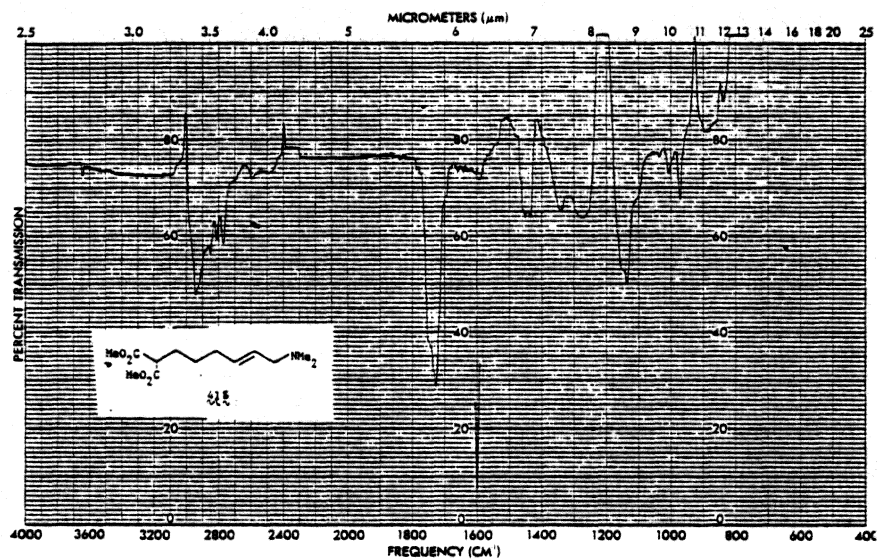


Figure 48b. IR Spectrum of Aminodiester 4lg.

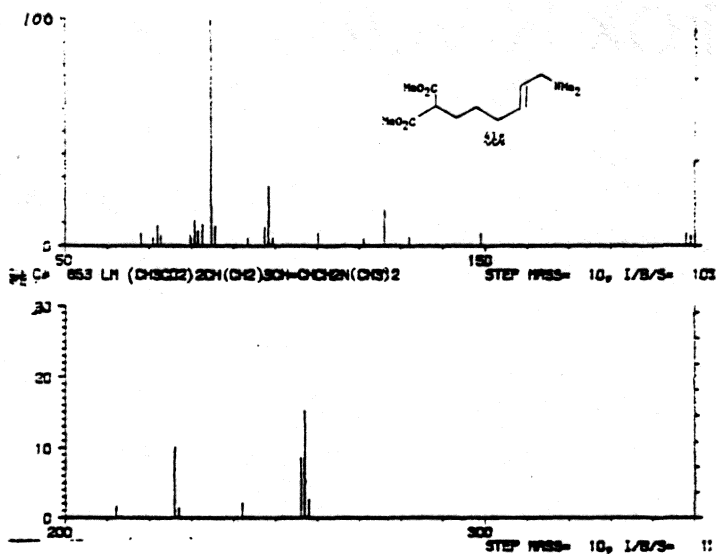


Figure 48c. Mass Spectrum of Aminodiester 4lg.

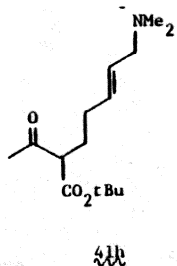
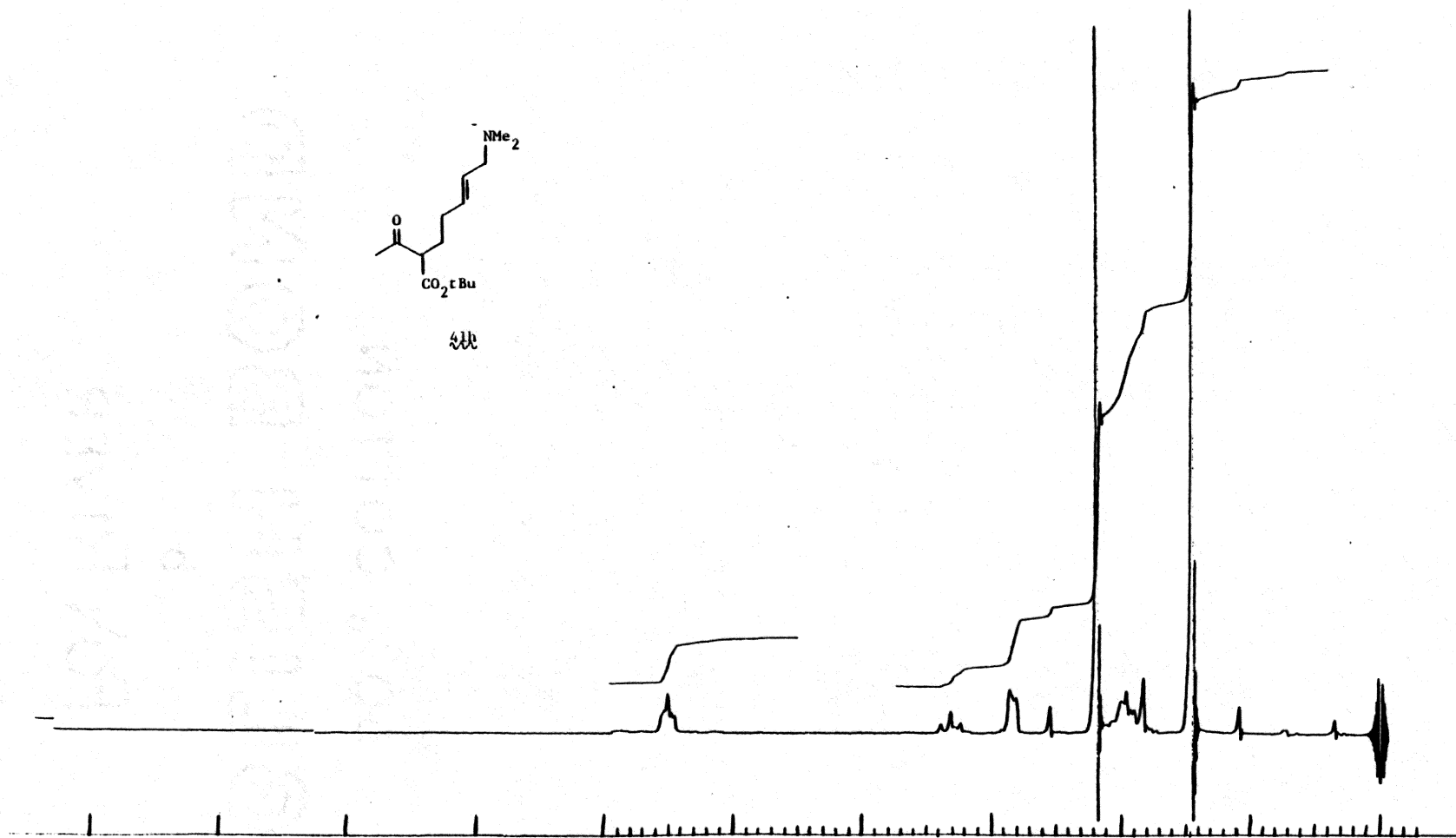
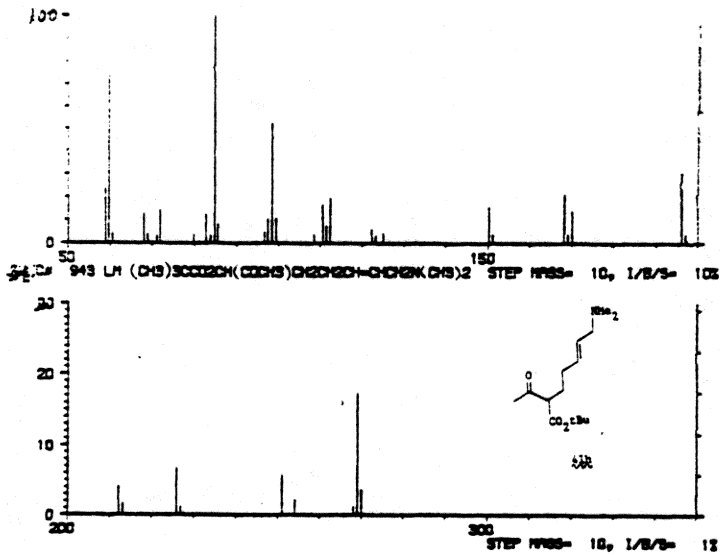
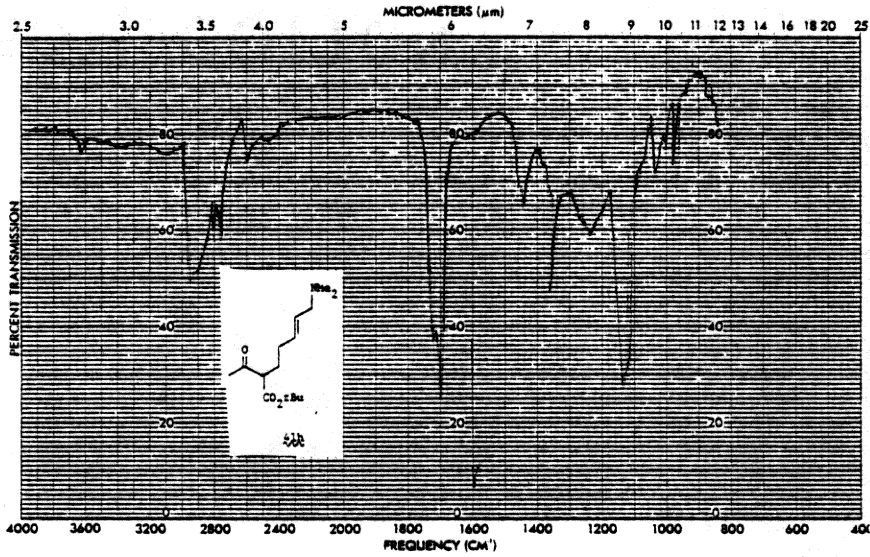


Figure 49a. 90 MHz NMR Spectrum of Amino Ketoester 41h.



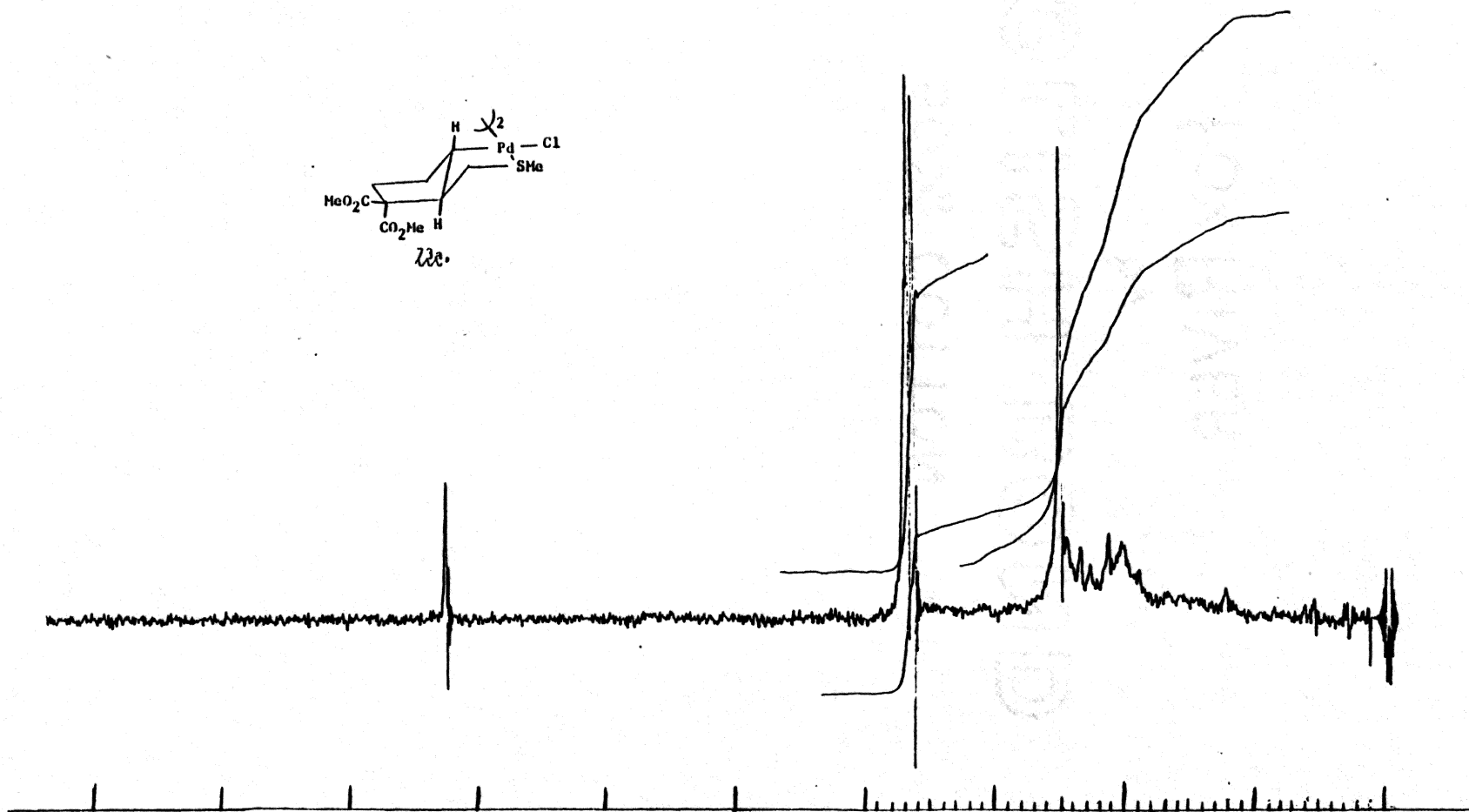


Figure 50a. 90 MHz NMR Spectrum of Palladocycle 73a.

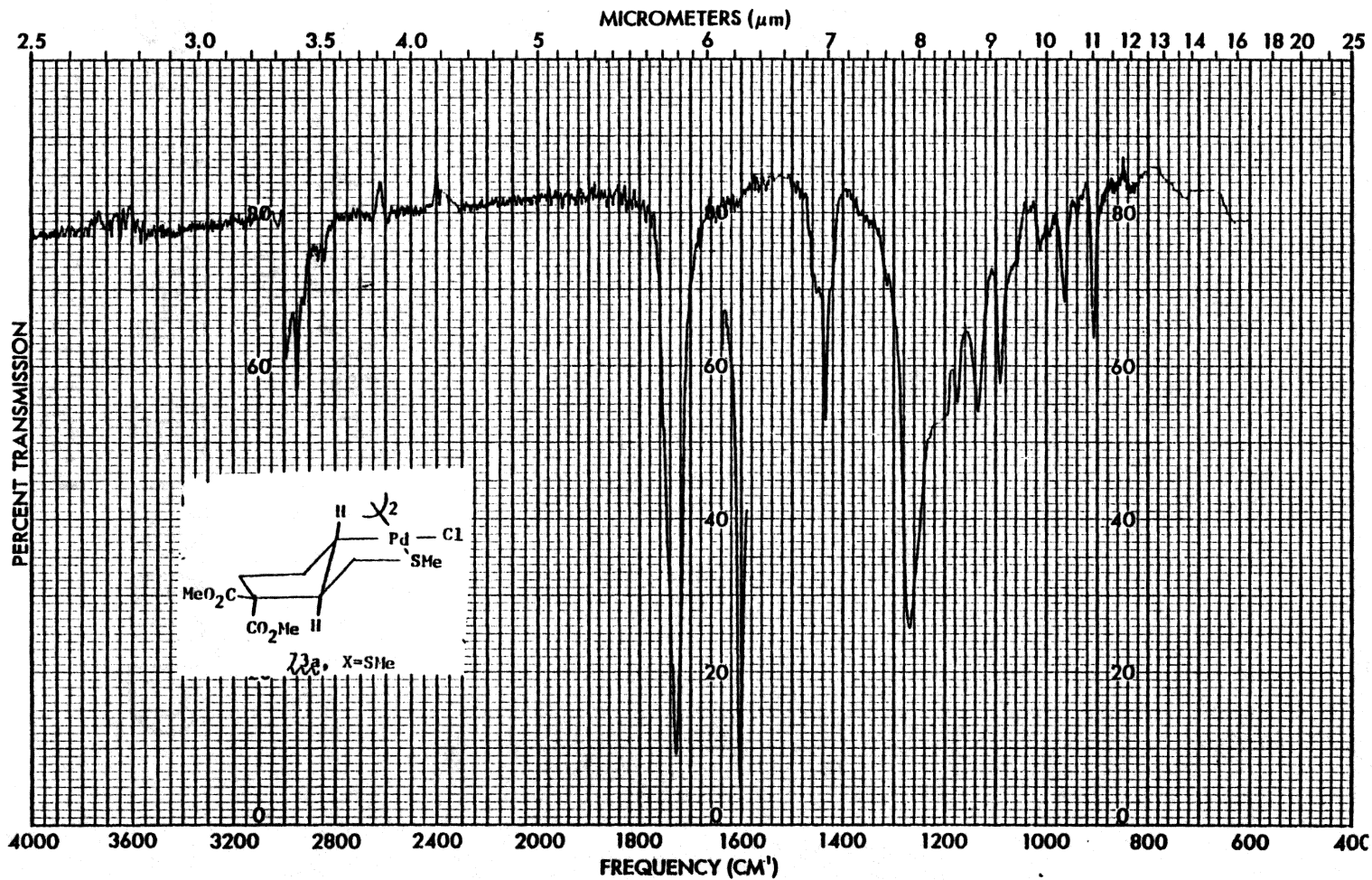


Figure 50b. IR Spectrum of Palladocycle 73a.

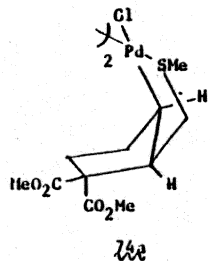
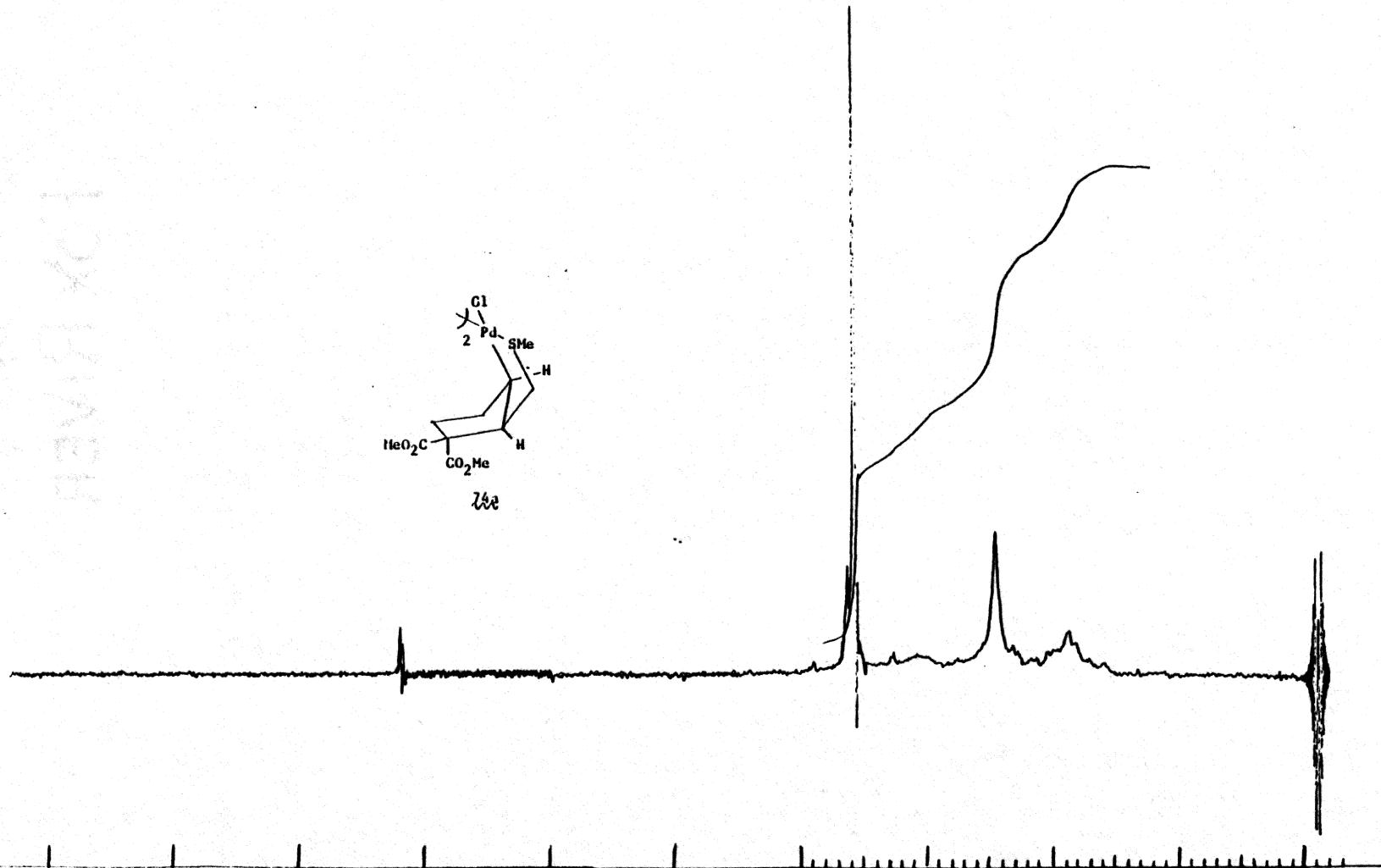


Figure 51a. 90 MHz NMR Spectrum of Palladocycle 74a.

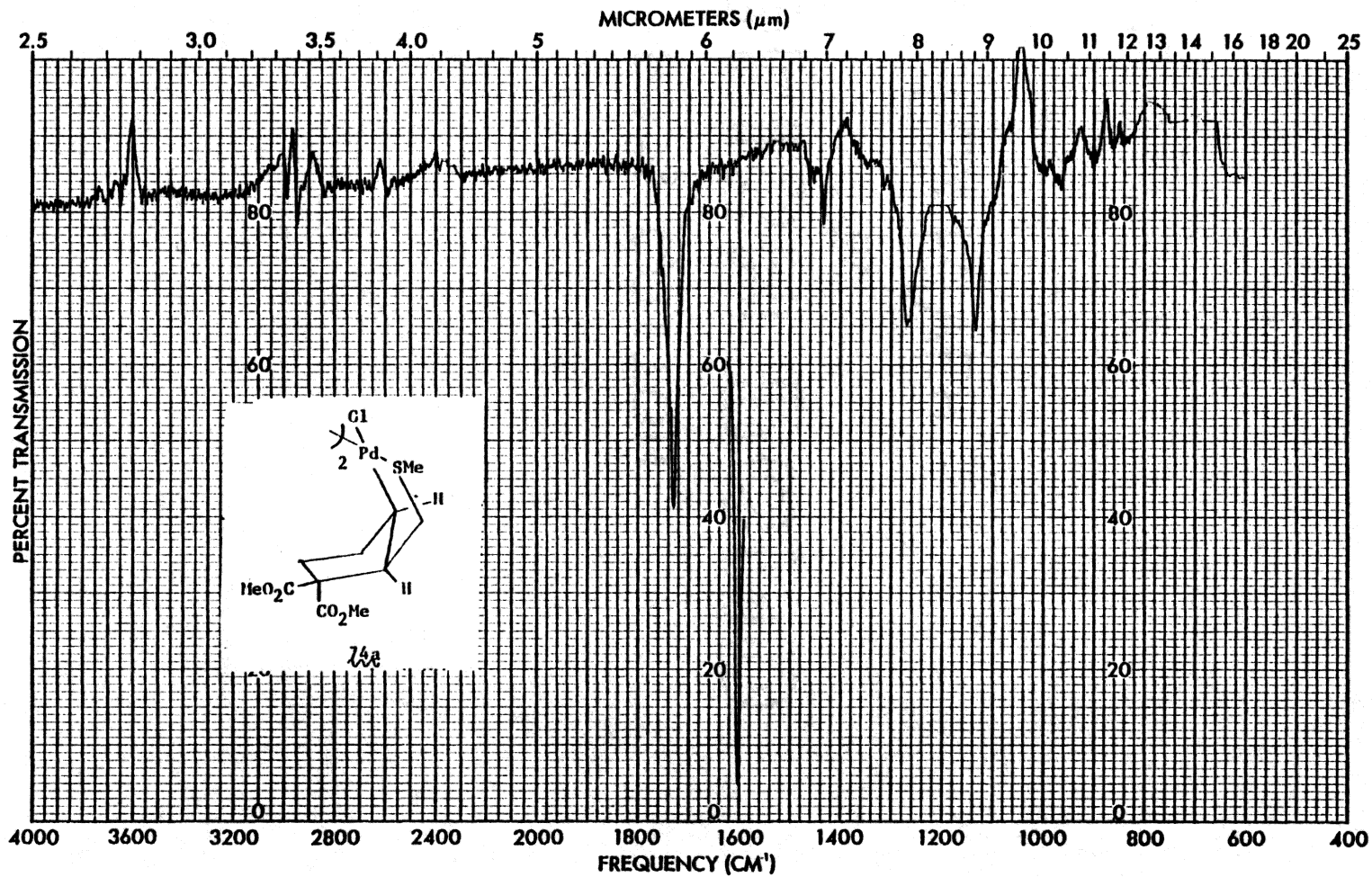


Figure 51b. IR Spectrum of Palladocycle 74a.

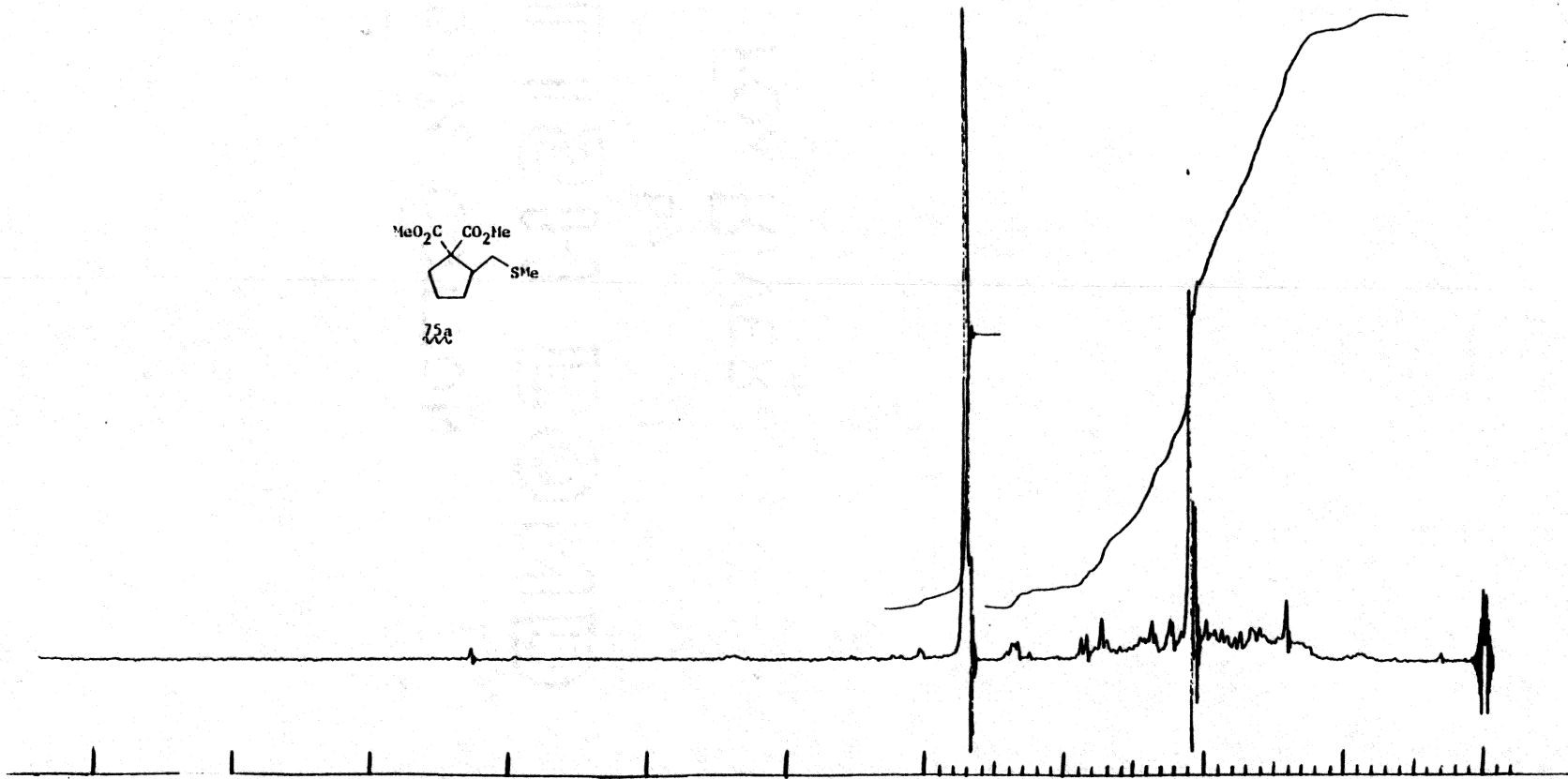
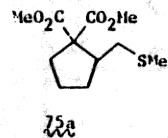


Figure 52a. 90 MHz NMR Spectrum of Cyclopentane 75a.

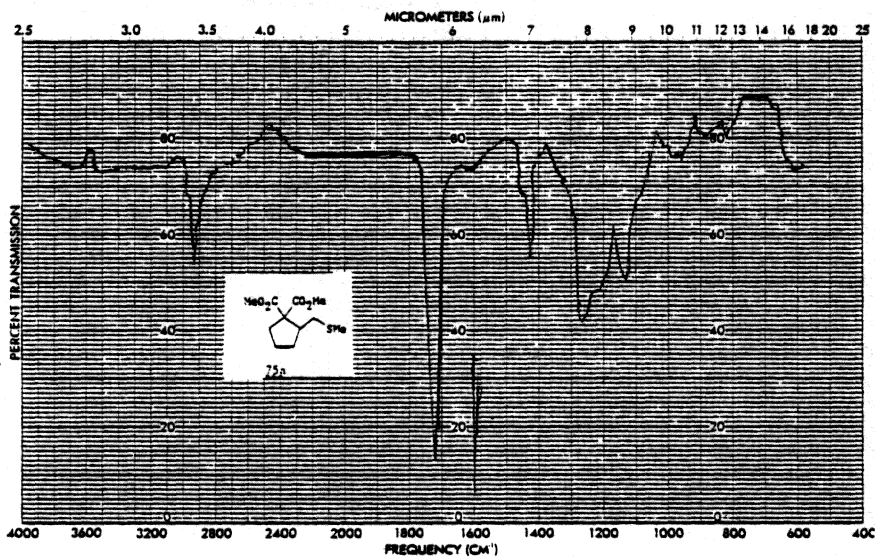


Figure 52b. IR Spectrum of Cyclopentane 75a.

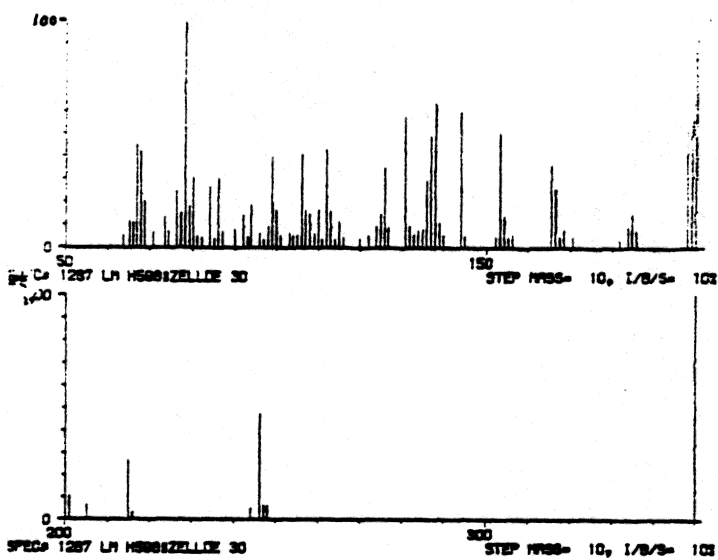


Figure 52c. Mass Spectrum of Cyclopentane 75a.

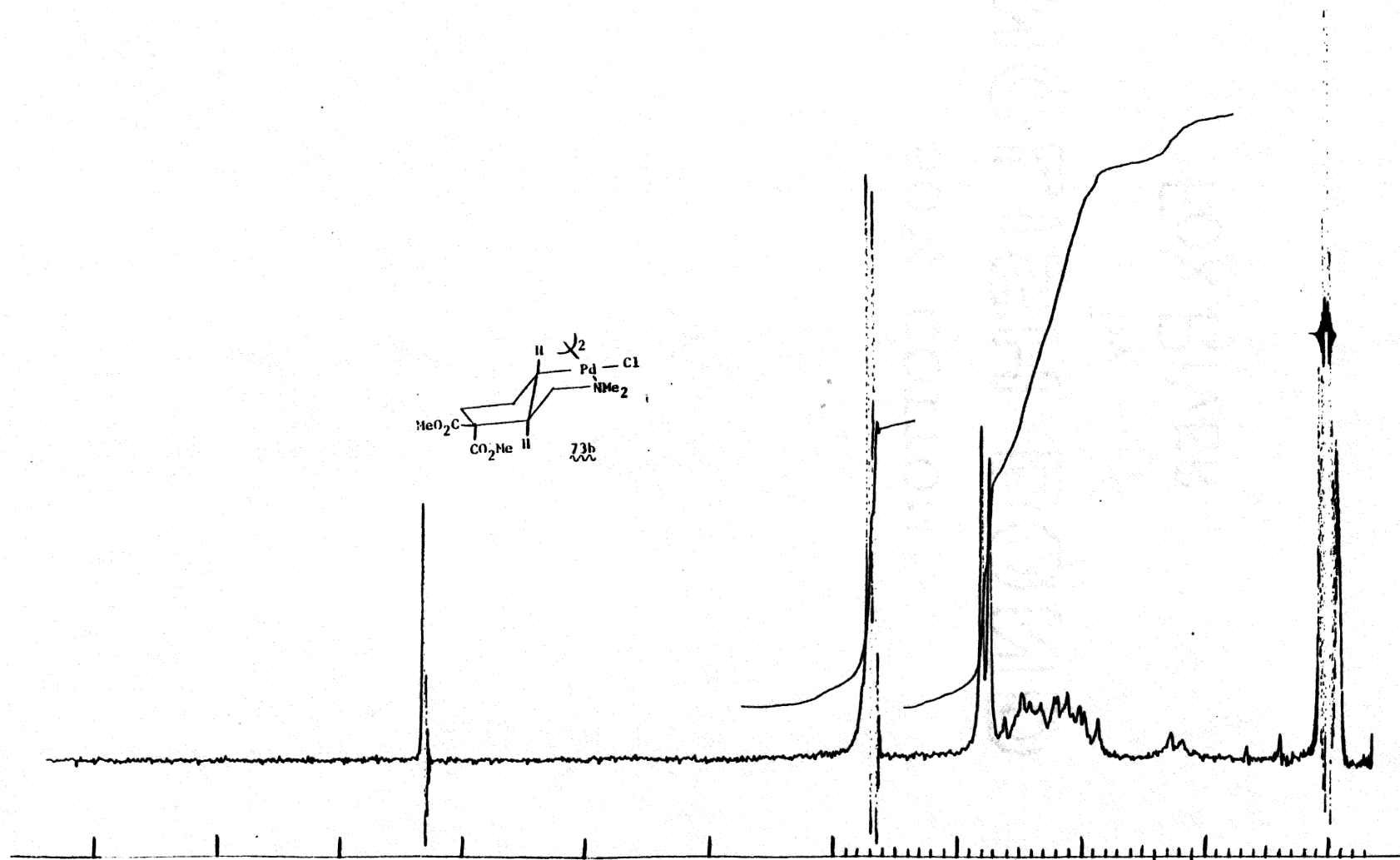


Figure 53a. 90 MHz NMR Spectrum of Palladocycle 73b.

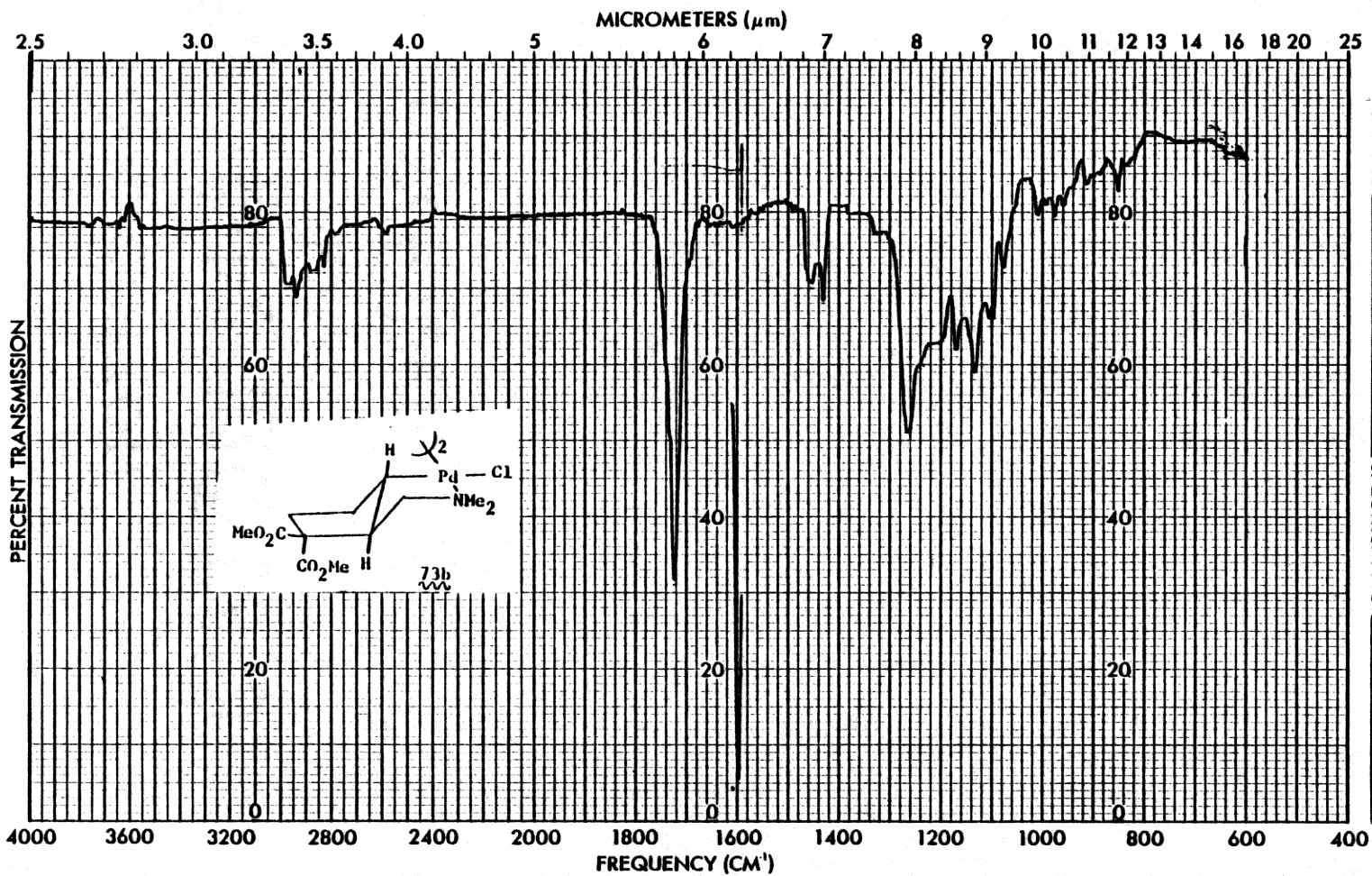


Figure 53b. IR Spectrum of Palladocycle 73b.

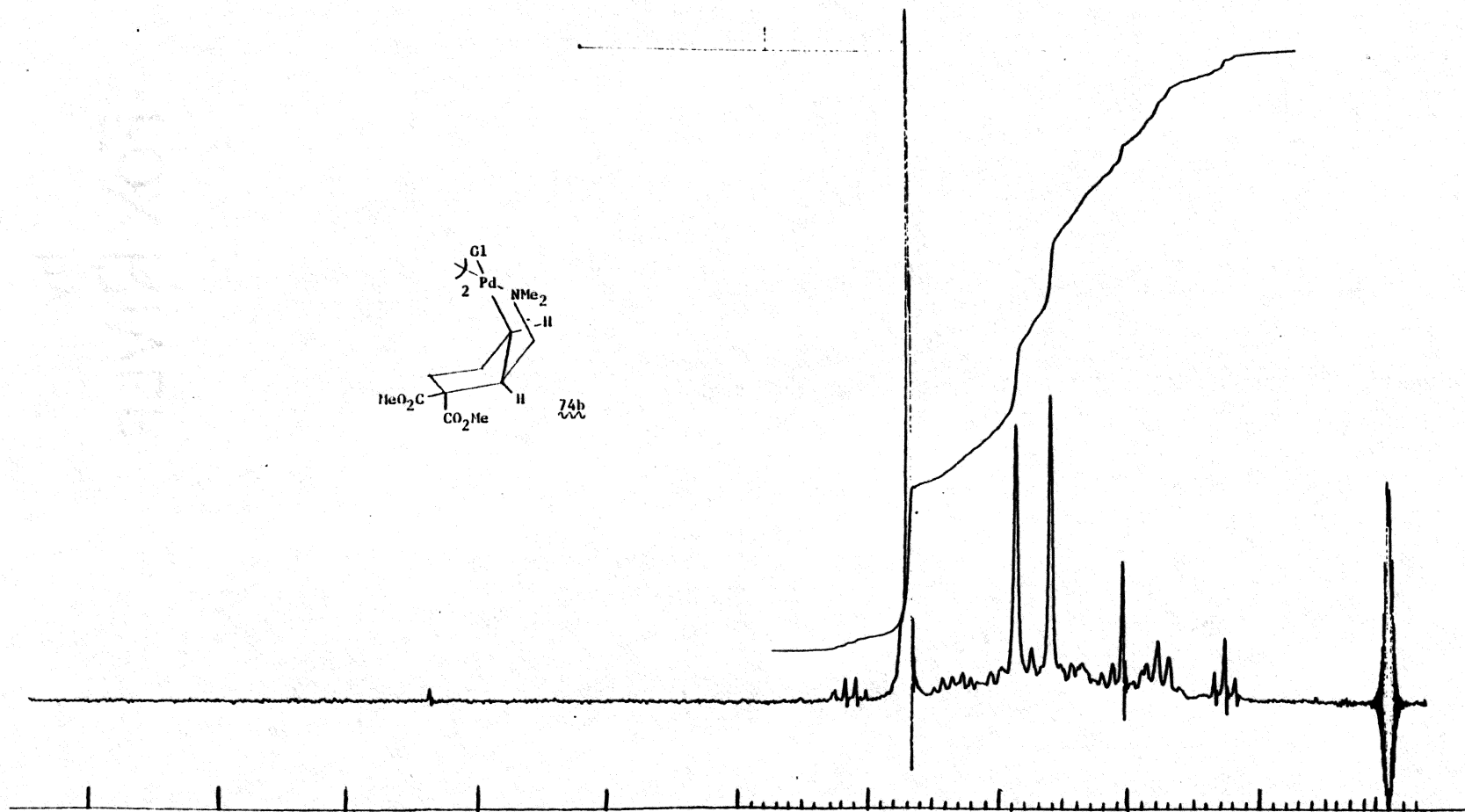


Figure 54a. 90 MHz NMR Spectrum of Palladocycle 74b.

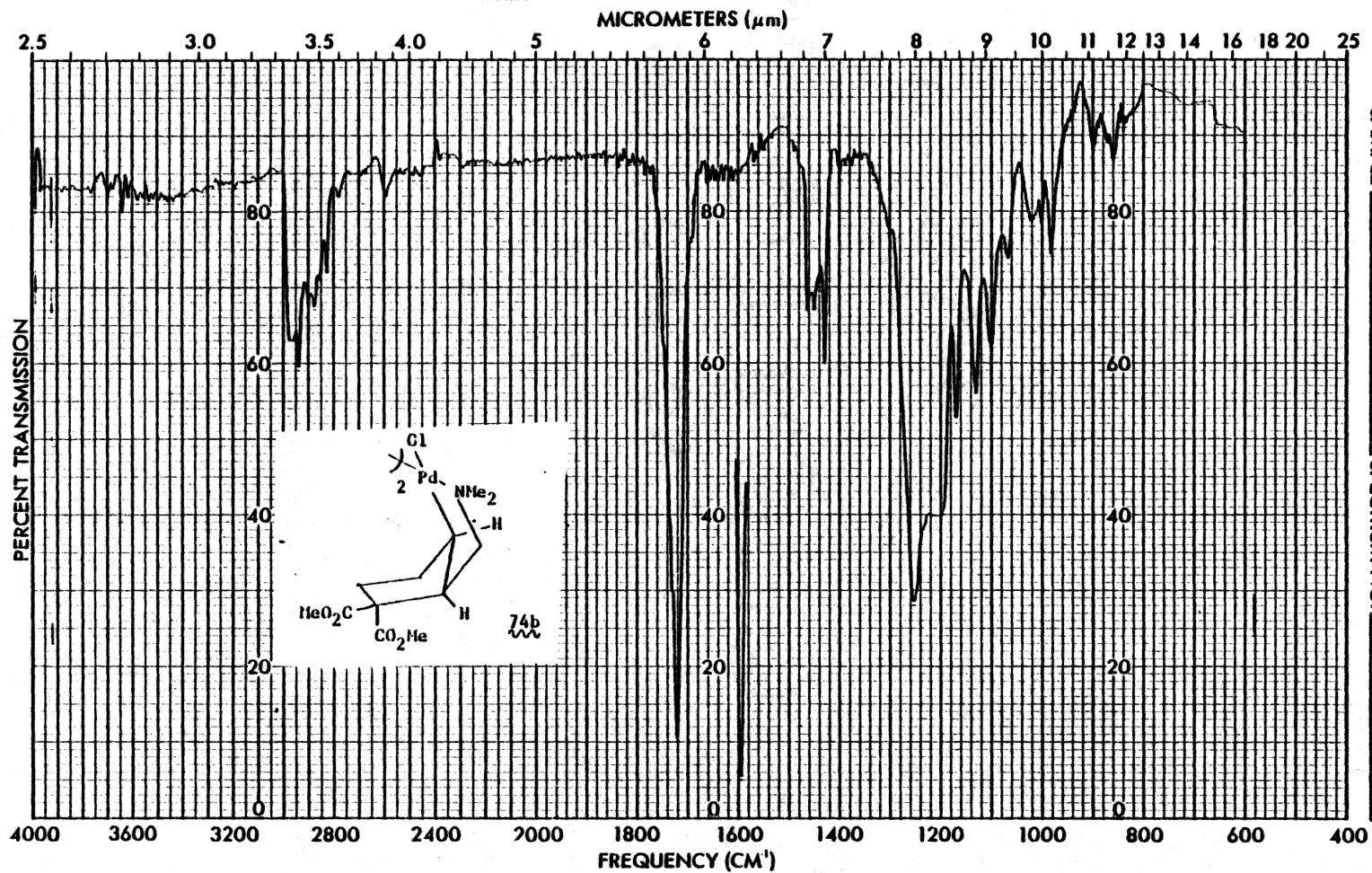


Figure 54b. IR Spectrum of Palladocycle 74b.

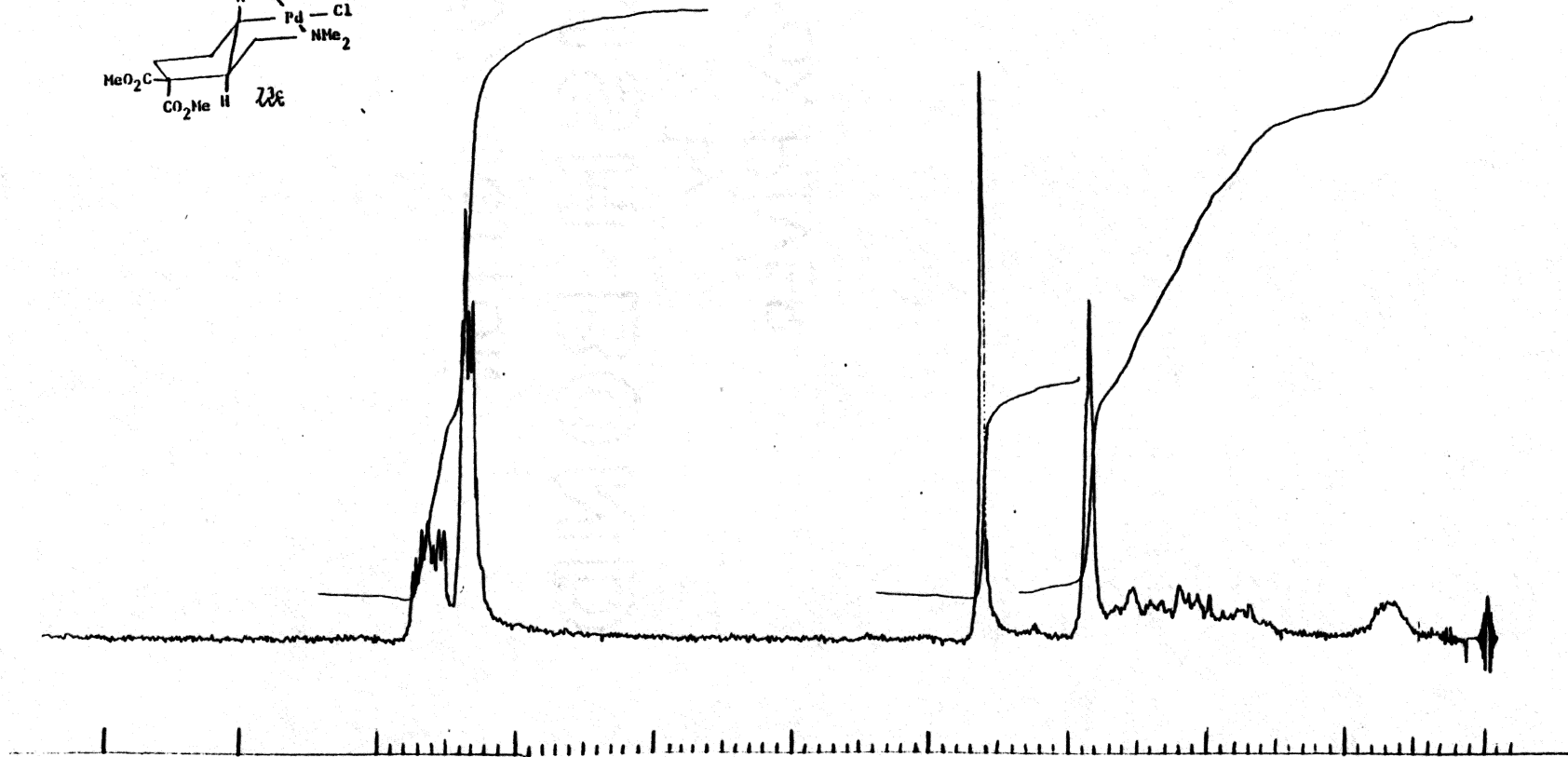
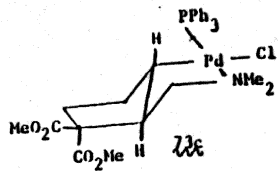


Figure 55a. 90 MHz NMR Spectrum of Palladocycle 73c.

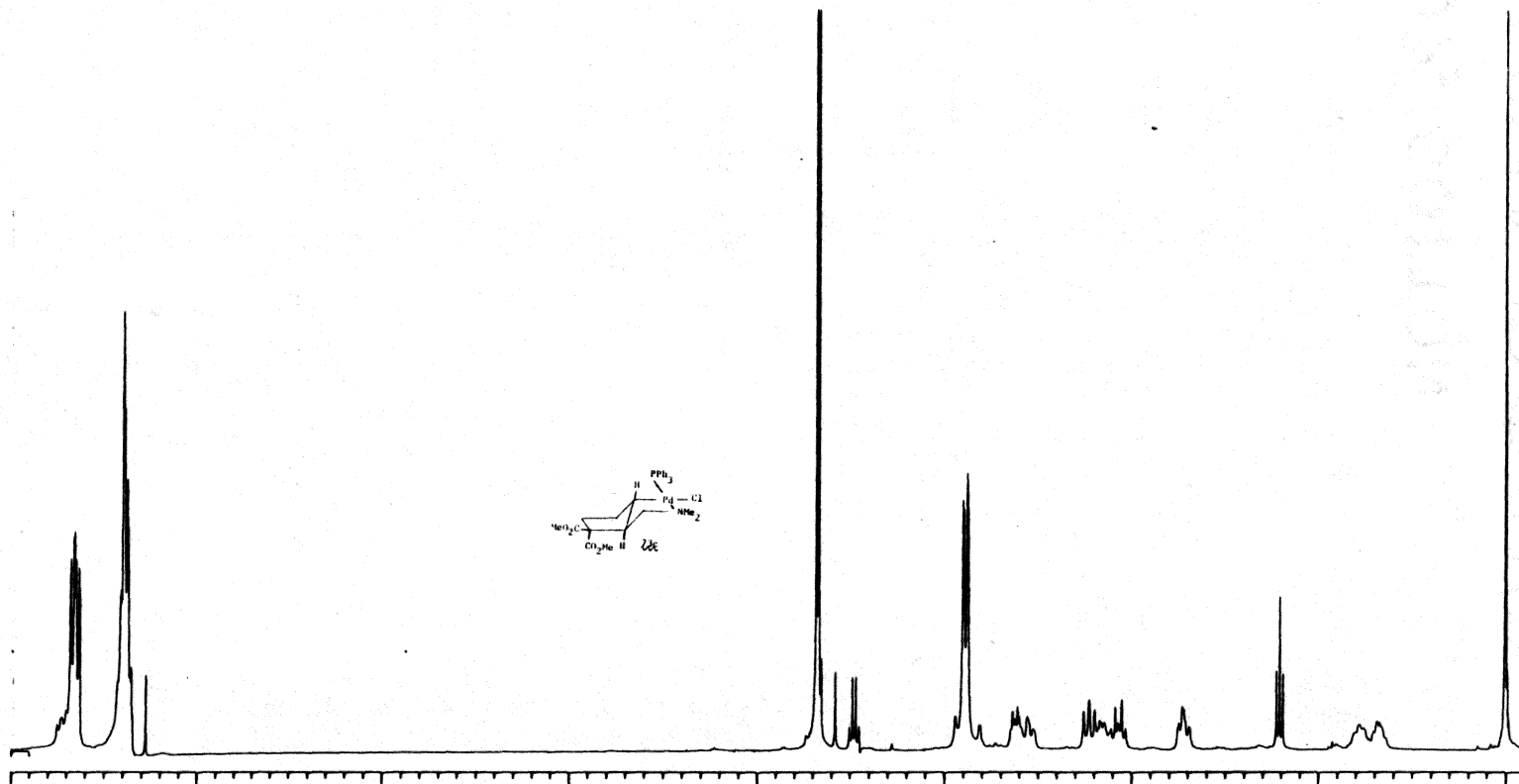


Figure 55b. 400 MHz NMR Spectrum of Palladocycle 73c.

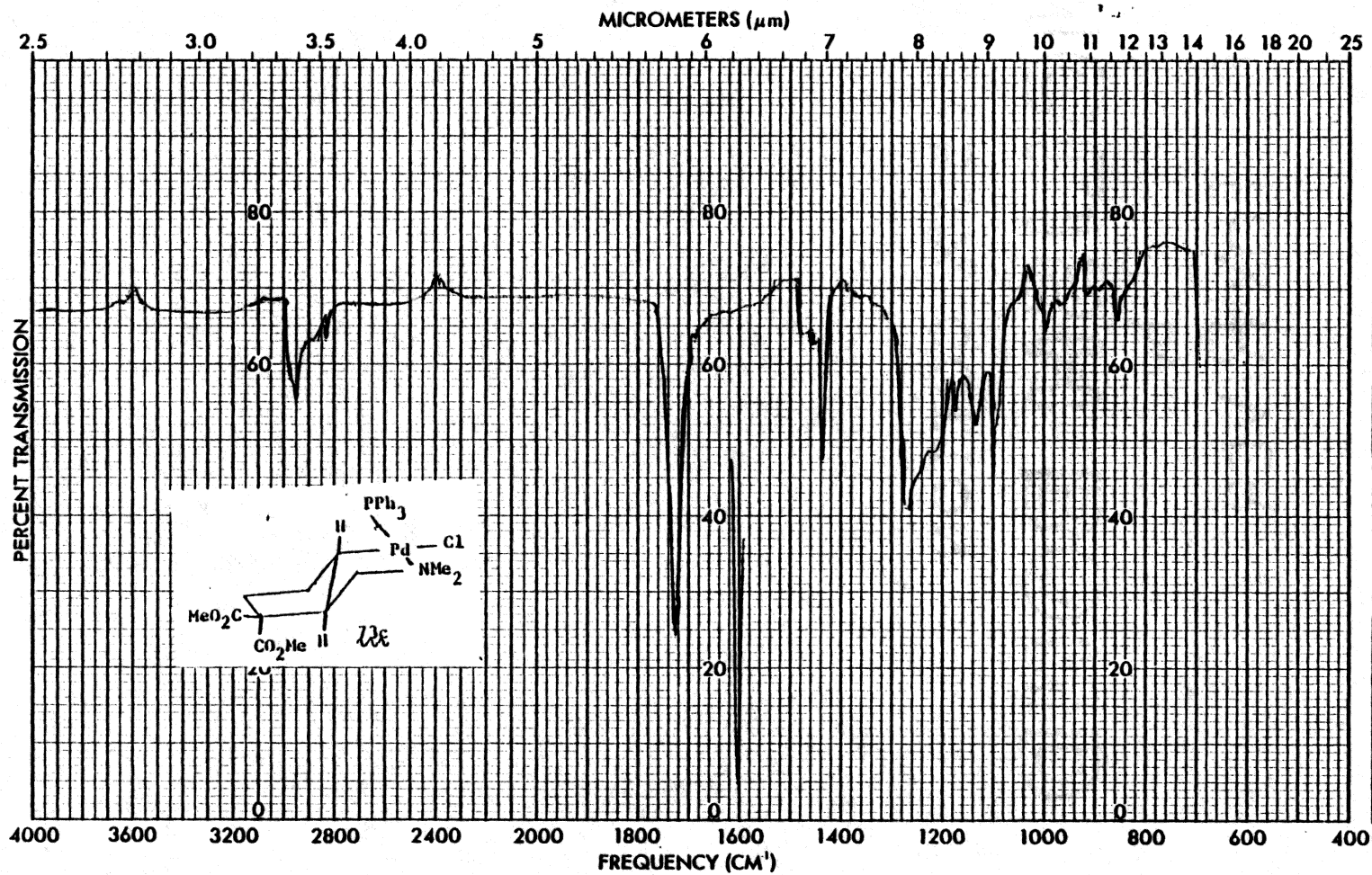


Figure 55c. IR Spectrum of Palladocycle 73c.

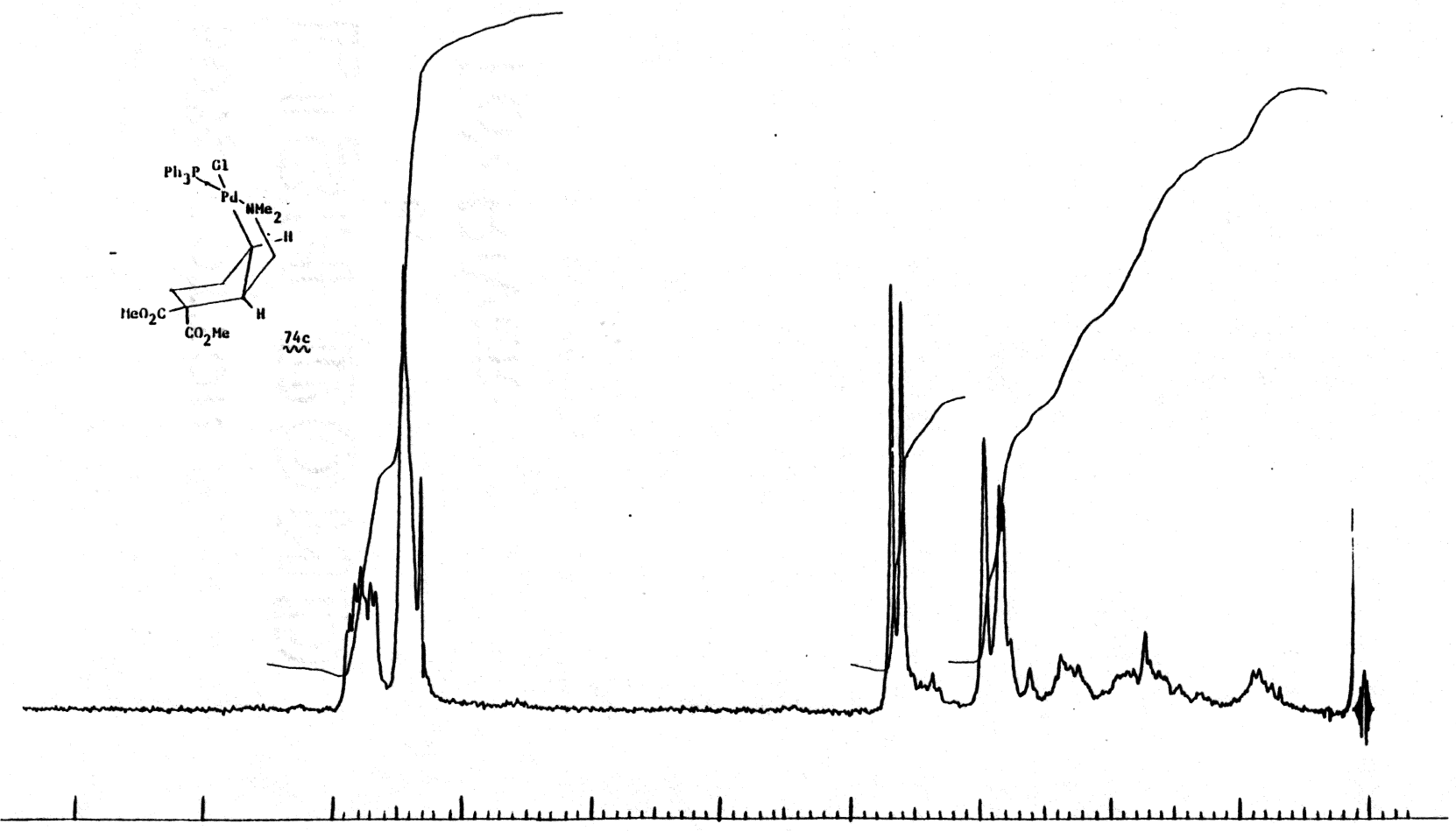


Figure 56a. 90 MHz NMR Spectrum of Palladocycle 74c.

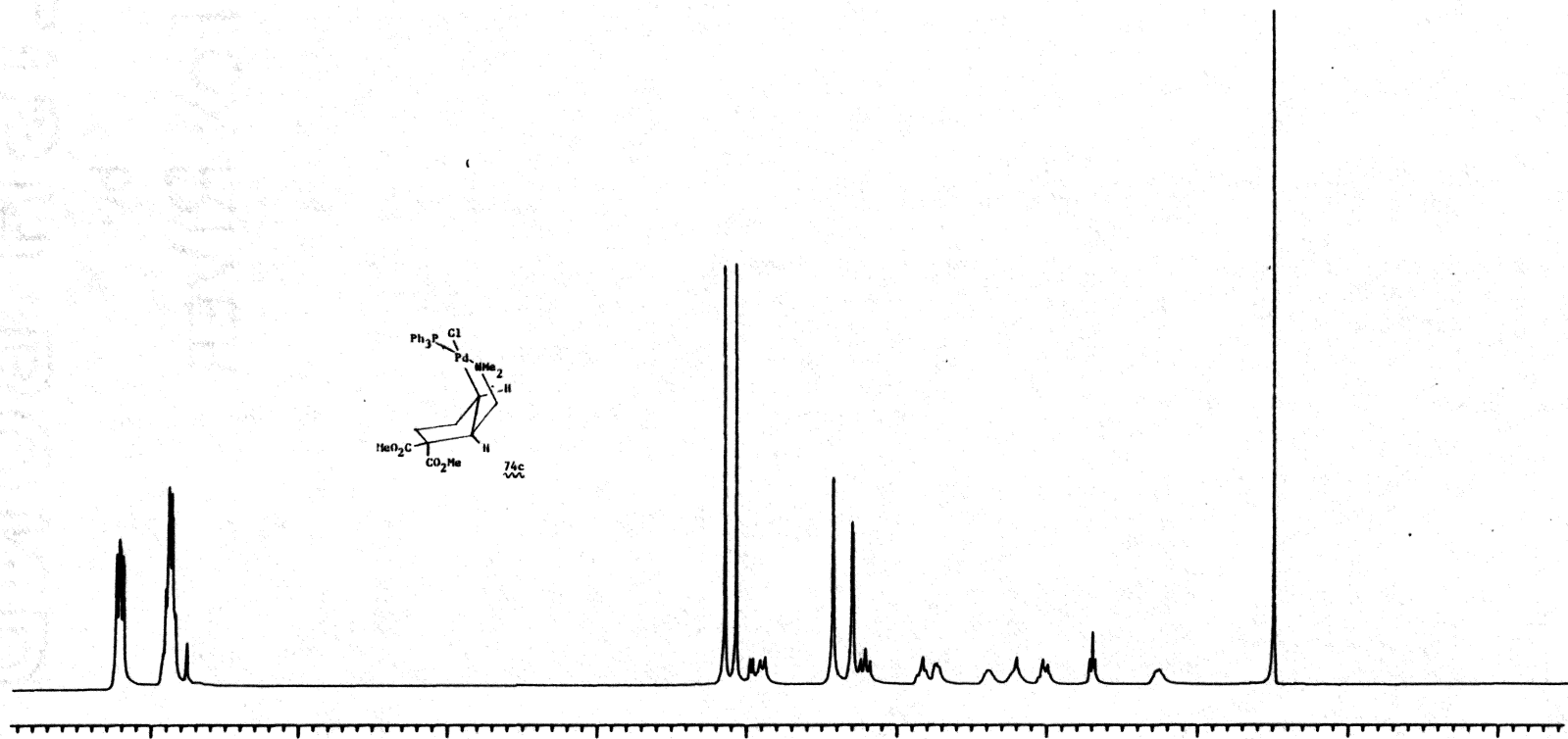


Figure 56b. 400 MHz NMR Spectrum of Palladocycle 74c.

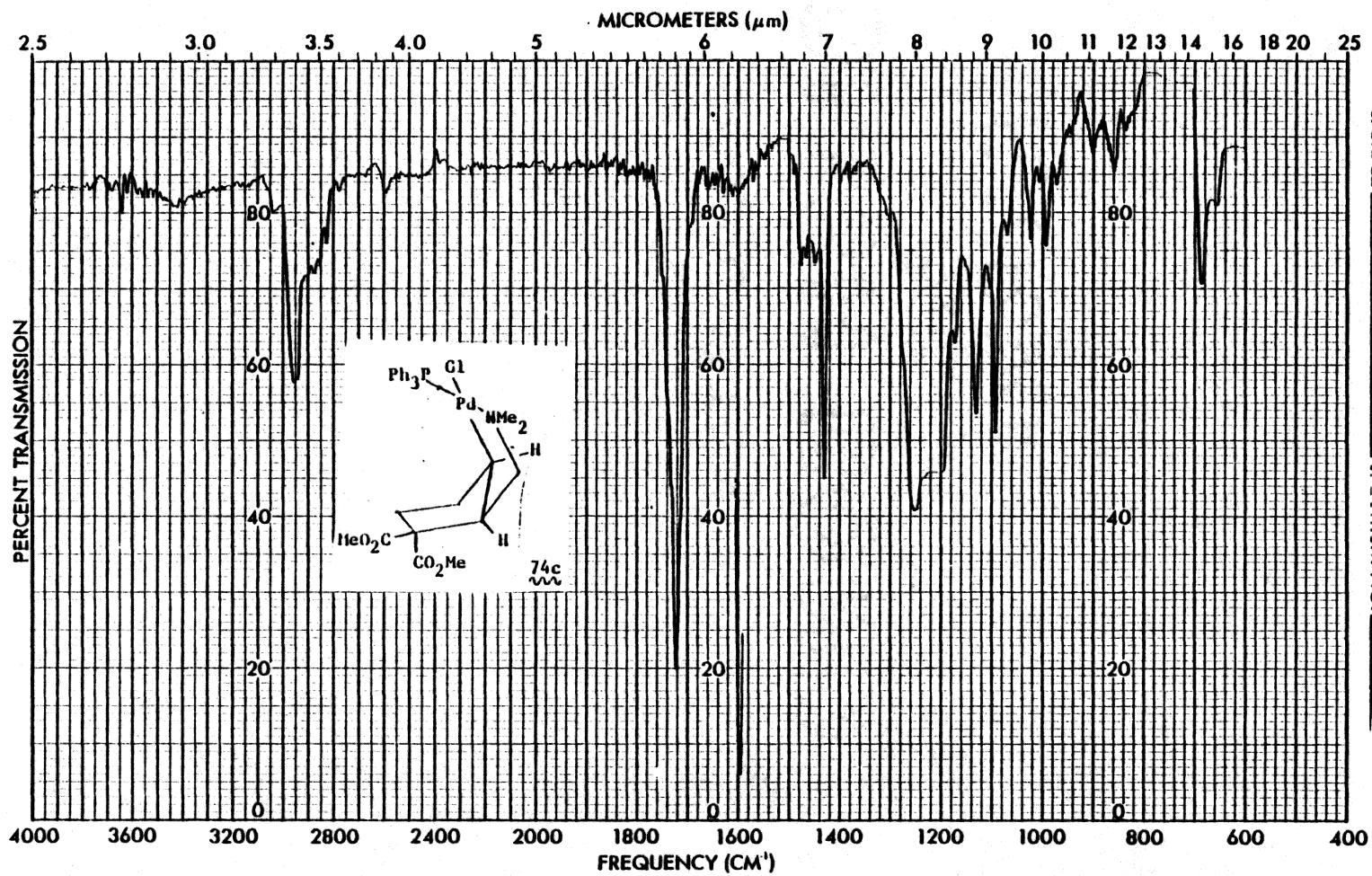
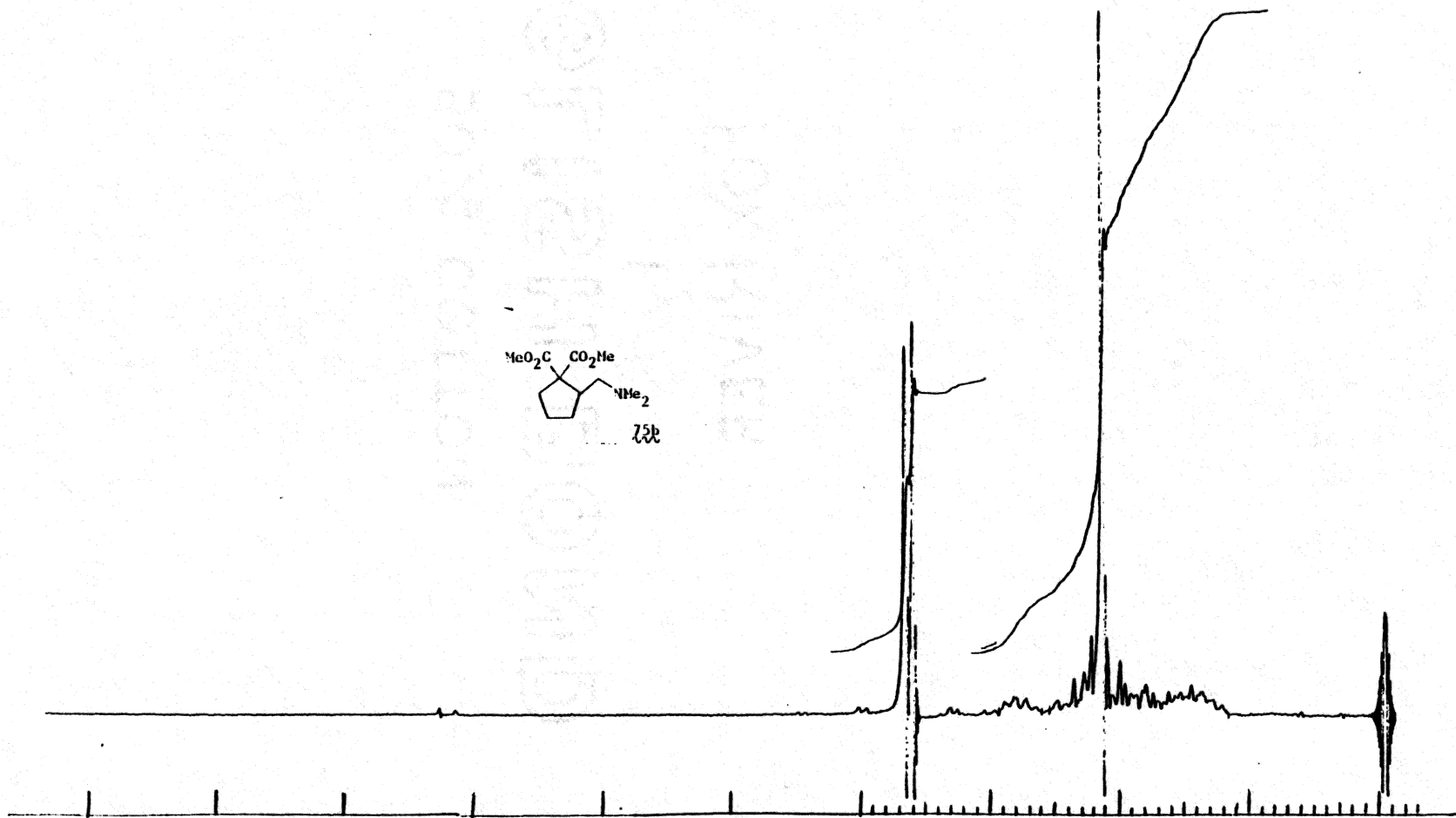


Figure 56c. IR Spectrum of Palladocycle 74c.



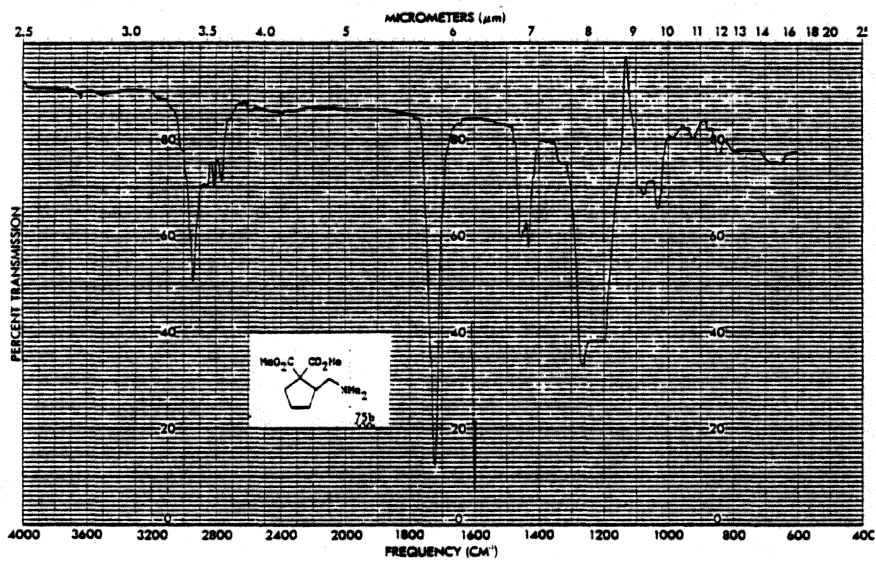


Figure 57b. IR Spectrum of Cyclopentane 75b.

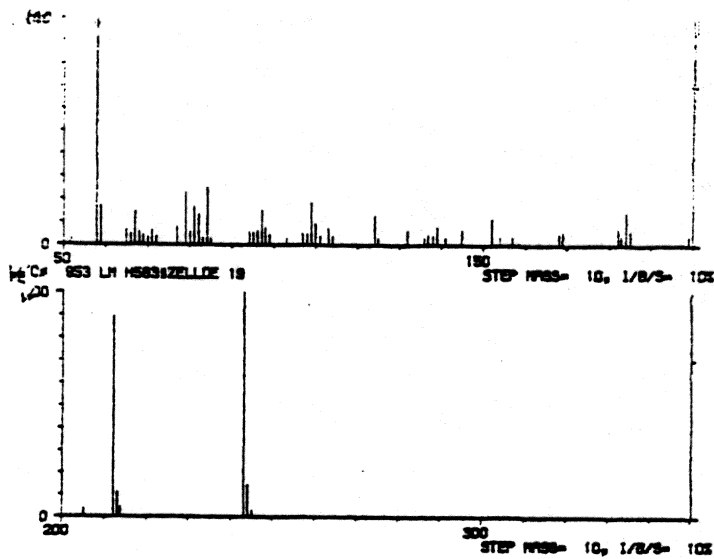
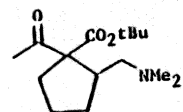


Figure 57c. Mass Spectrum of Cyclopentane 75b.



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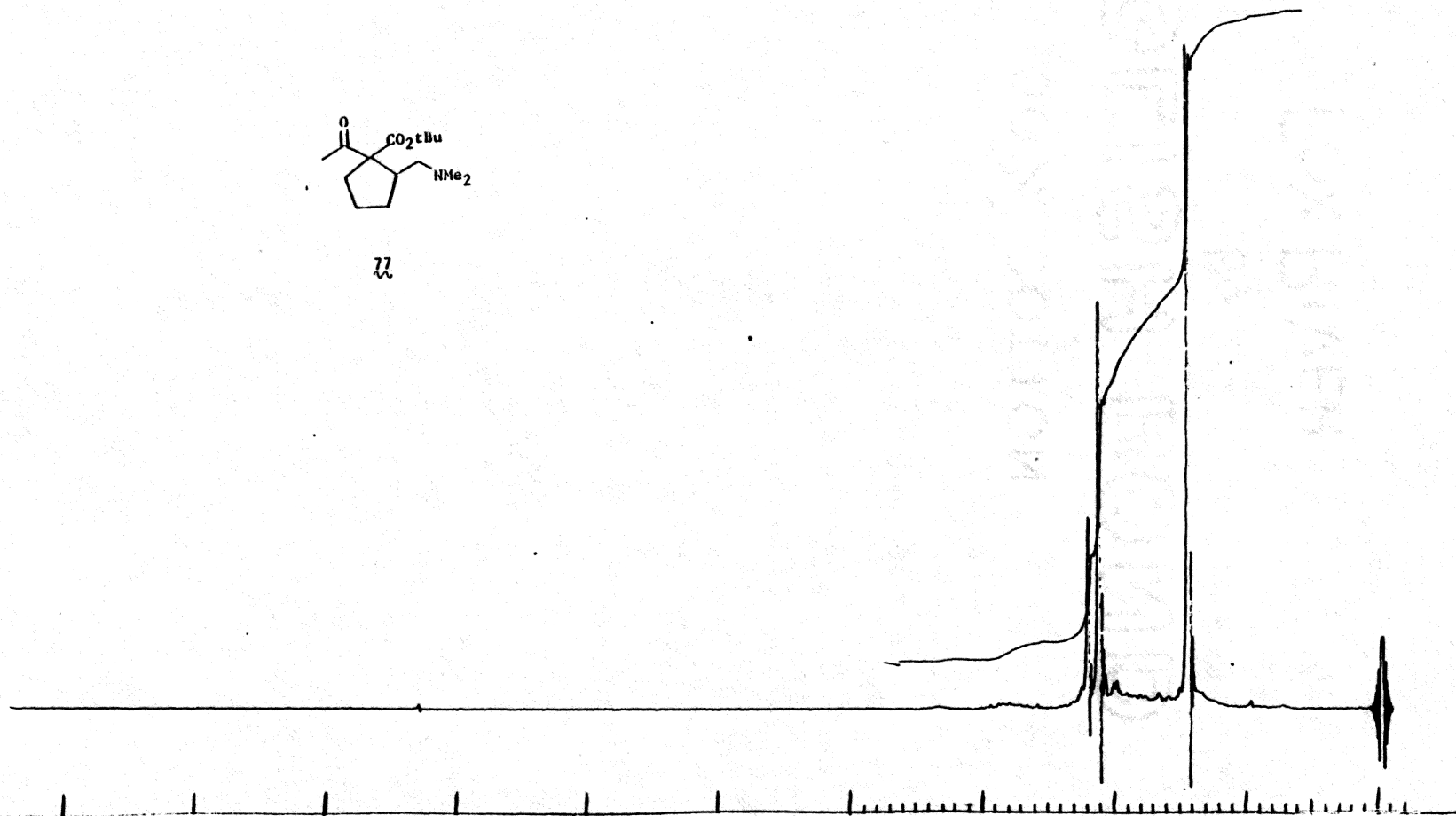


Figure 58a. 90 MHz NMR Spectrum of Cyclopentane 77.

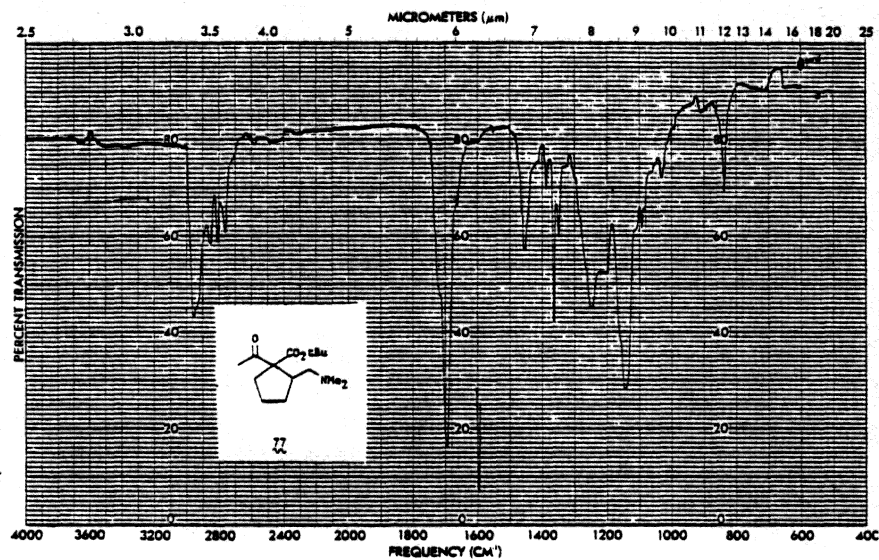


Figure 58b. IR Spectrum of Cyclopentane 77.

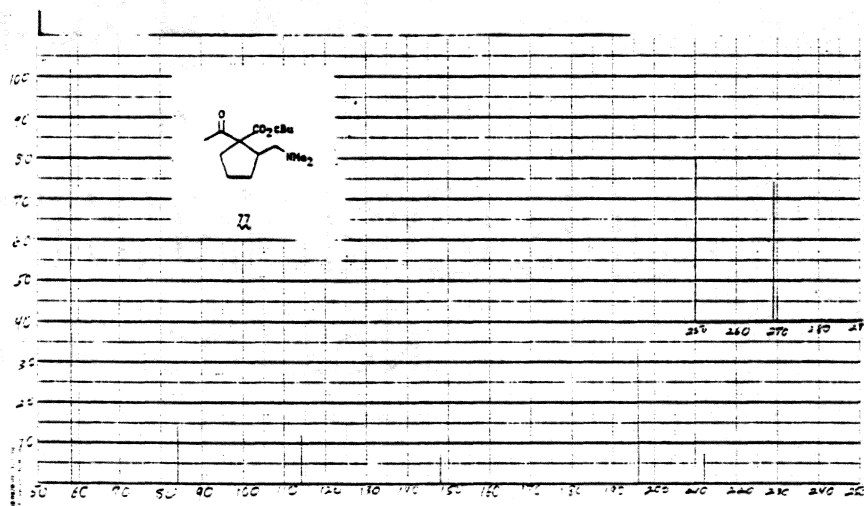


Figure 58c. Mass Spectrum of Cyclopentane 77.

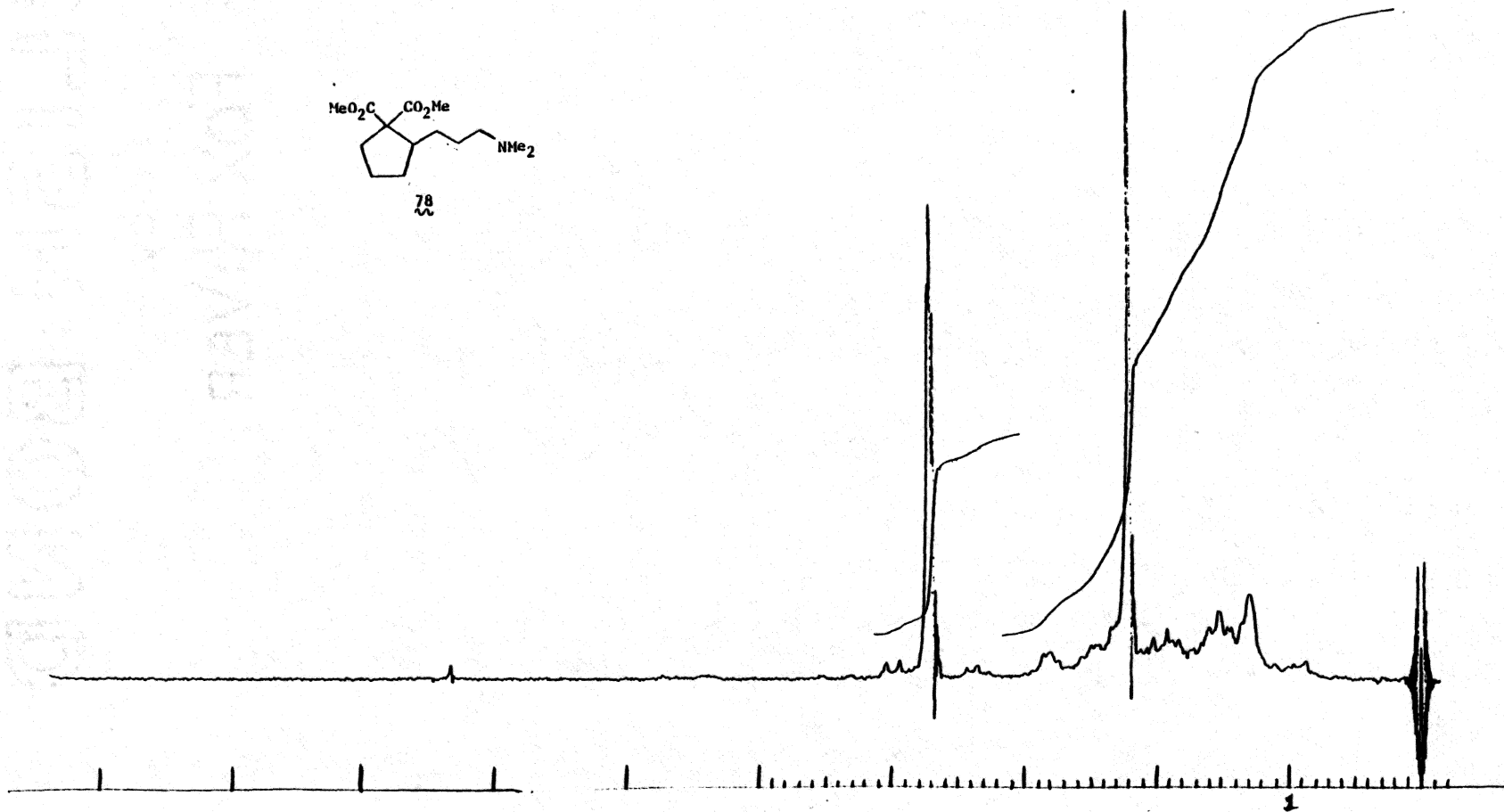
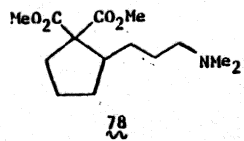


Figure 59a. 90 MHz NMR Spectrum of Cyclopentane 78.

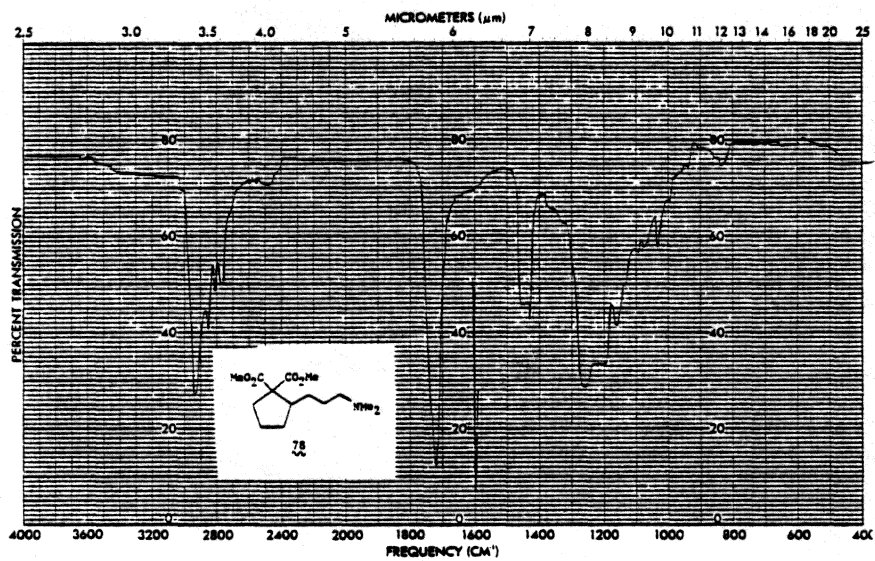


Figure 59b. IR Spectrum of Cyclopentane 78.

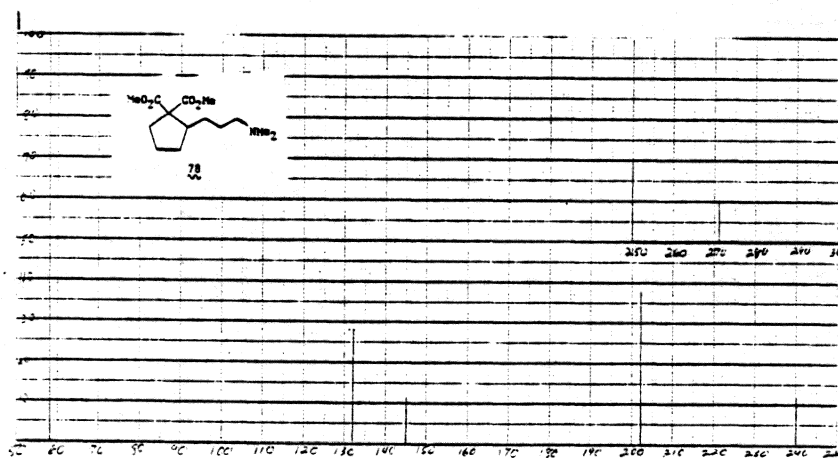
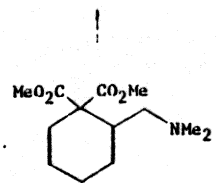


Figure 59c. Mass Spectrum of Cyclopentane 78.



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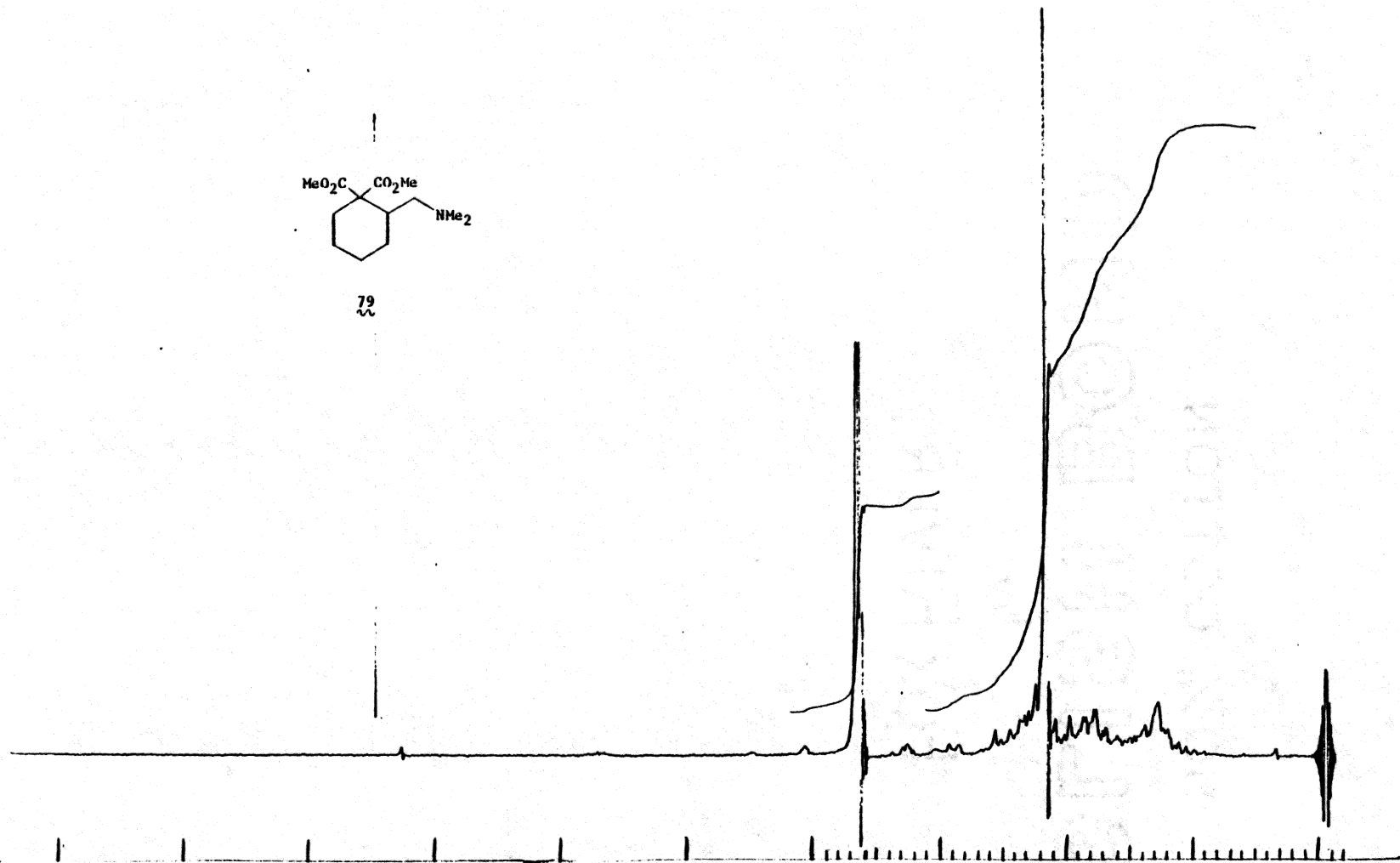


Figure 60a. 90 MHz NMR Spectrum of Cyclohexyl Amine 79.

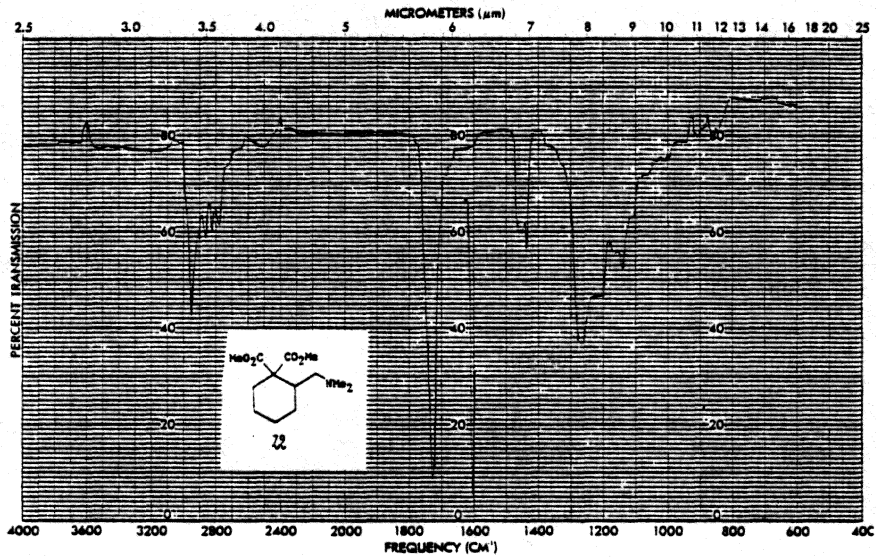


Figure 60b. IR Spectrum of Cyclohexyl Amine 79.

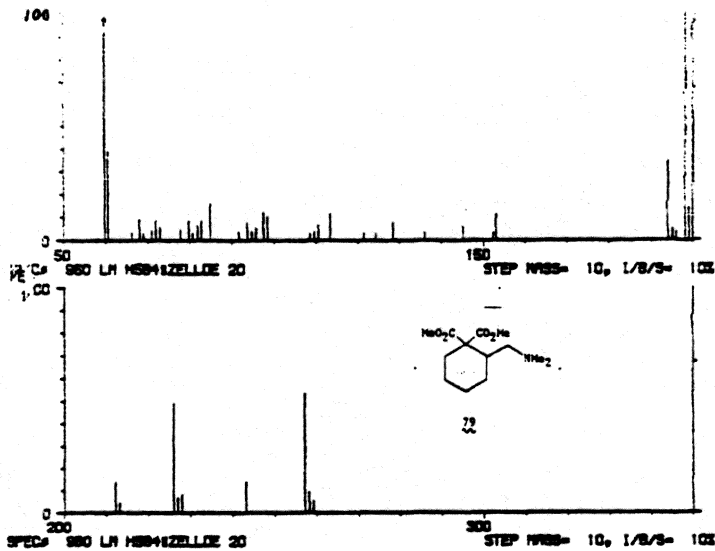


Figure 60c. Mass Spectrum of Cyclohexyl Amine 79.

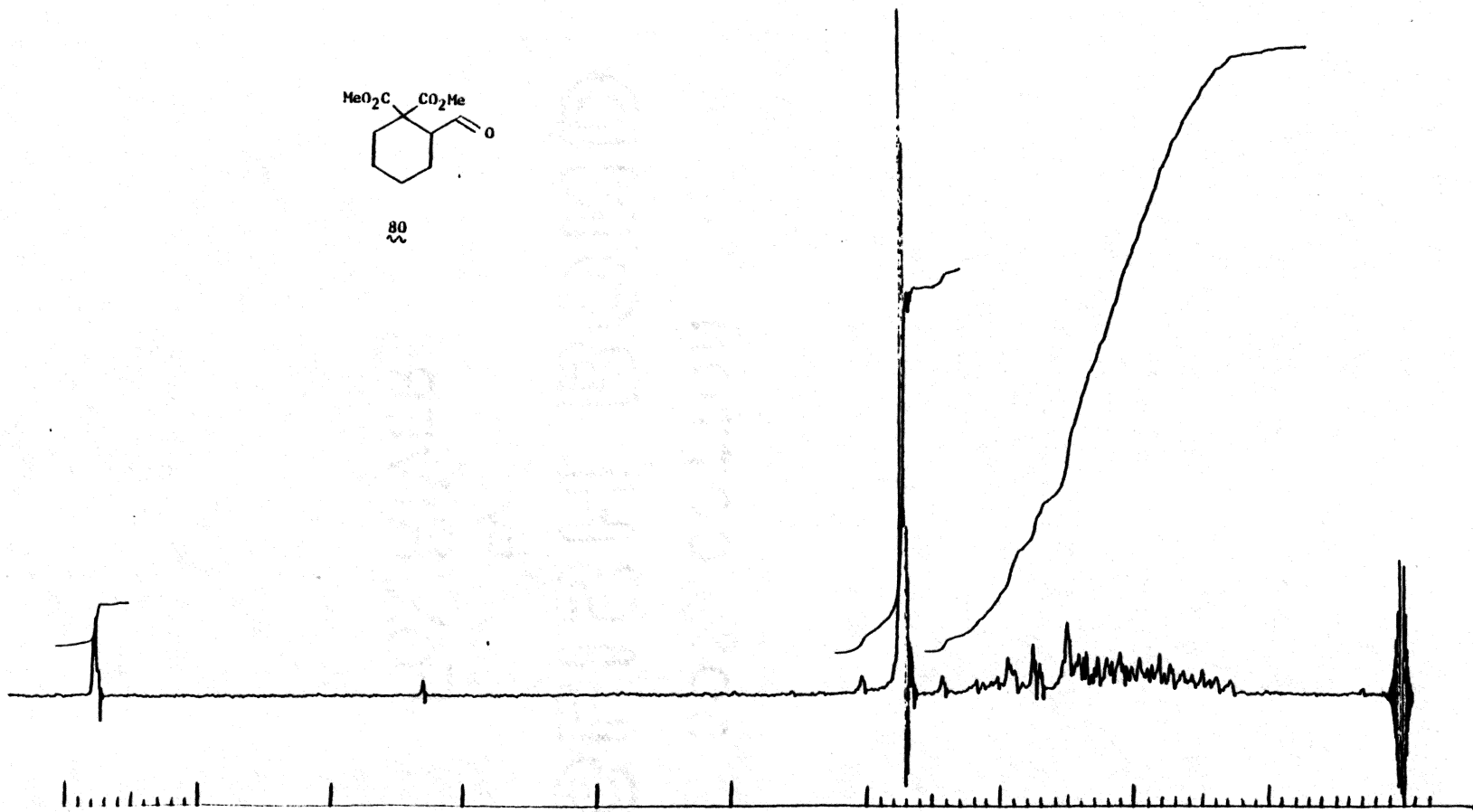
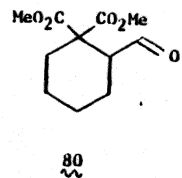


Figure 61a. 90 MHz NMR Spectrum of Cyclohexyl Aldehyde 80.

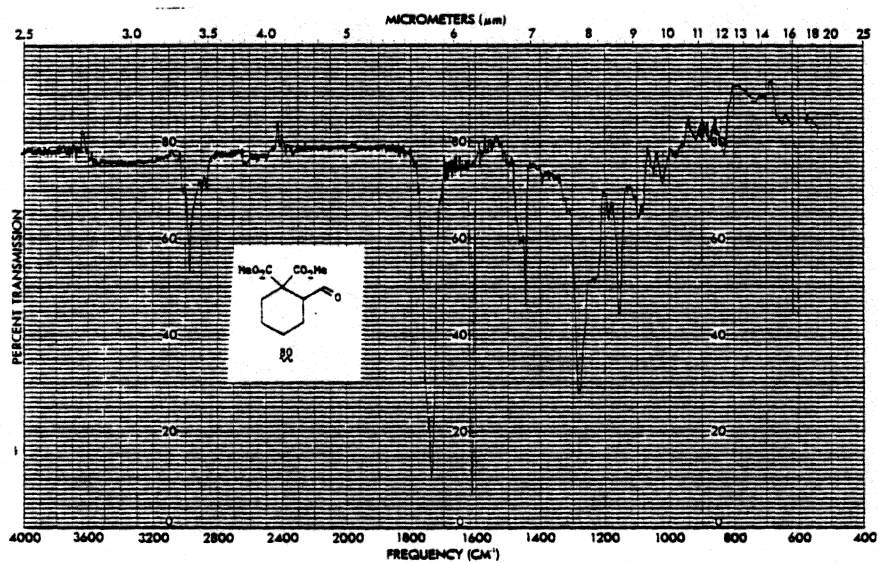


Figure 61b. IR Spectrum of Cyclohexyl Aldehyde 80.

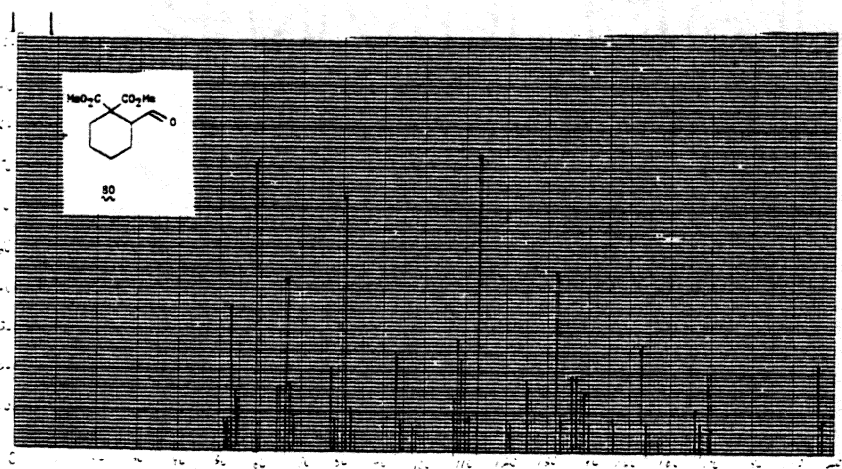


Figure 61c. Mass Spectrum of Cyclohexyl Aldehyde 80.

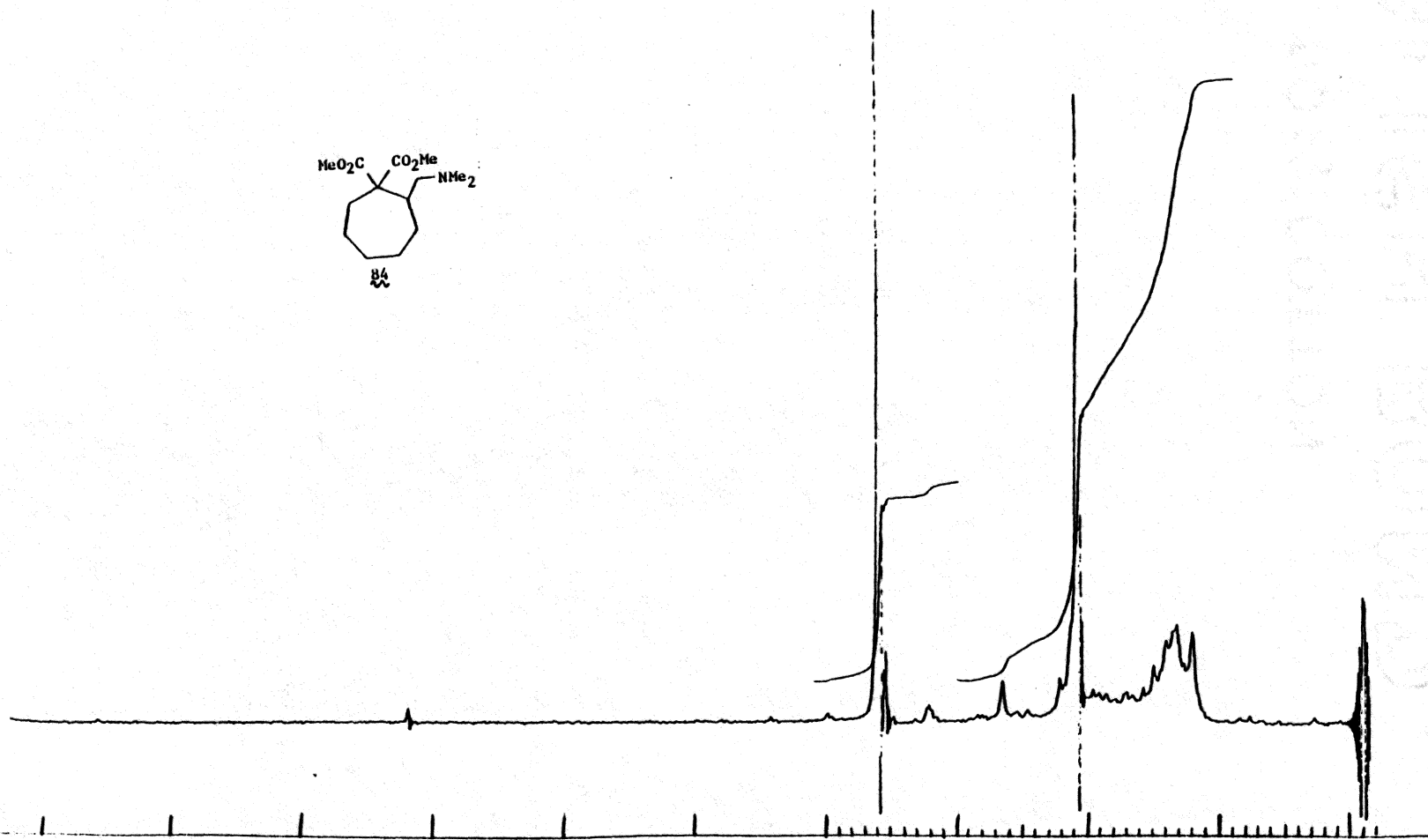
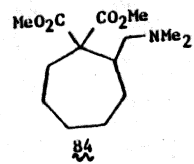


Figure 62a. 90 MHz NMR Spectrum of Cycloheptylamine 84.

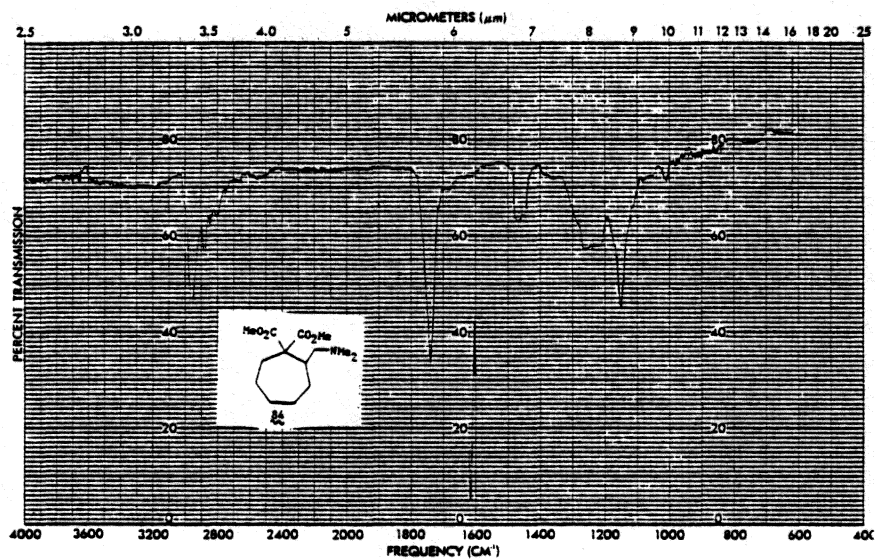


Figure 62b. IR Spectrum of Cycloheptylamine 84.

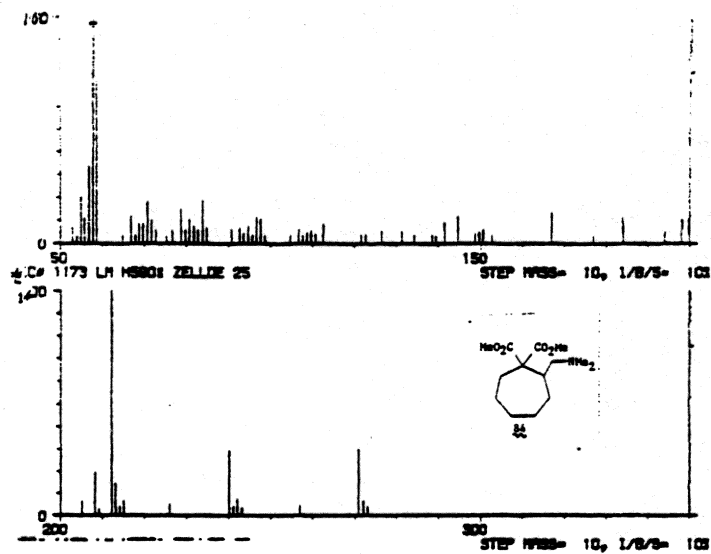


Figure 62c. Mass Spectrum of Cycloheptylamine 84.

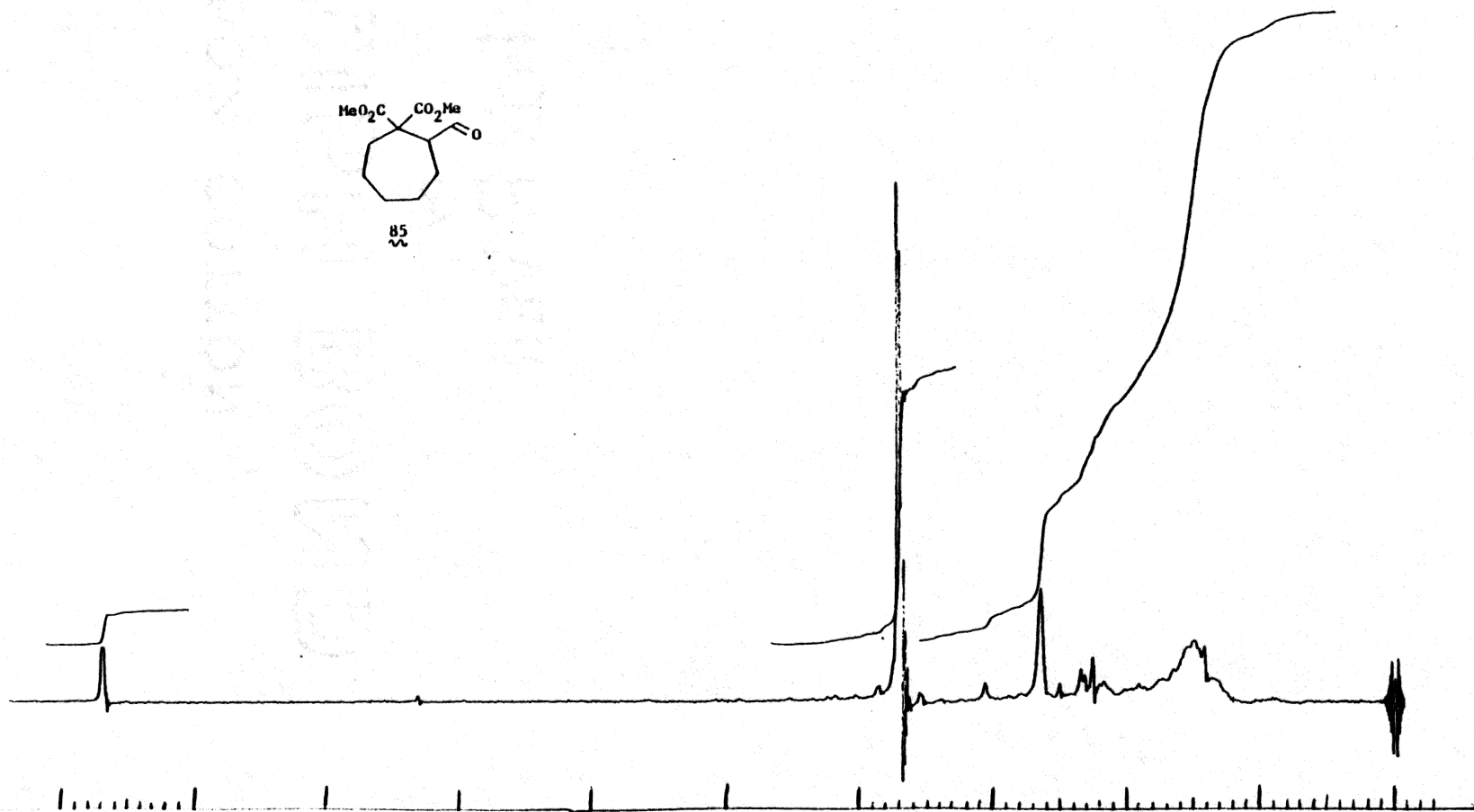


Figure 63a. 90 MHz NMR Spectrum of Cycloheptyl Aldehyde 85.

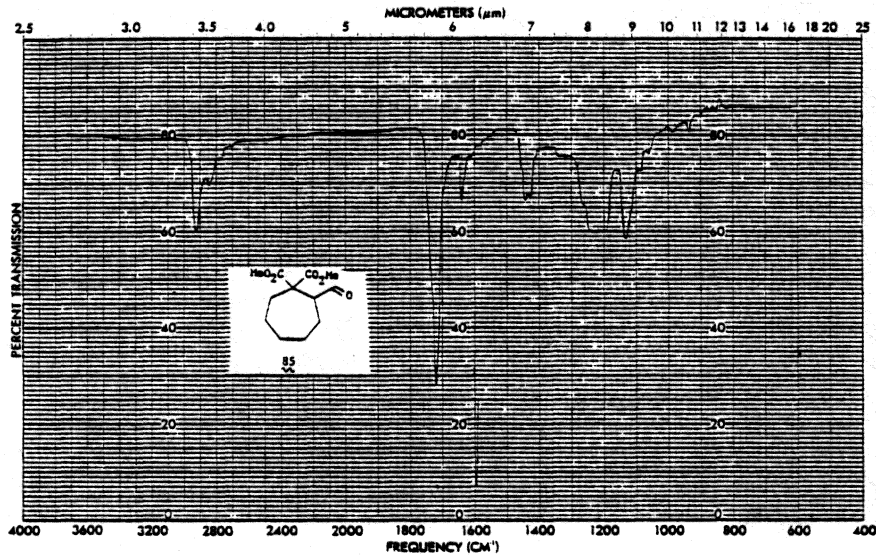


Figure 63b. IR Spectrum of Cycloheptyl Aldehyde 85.

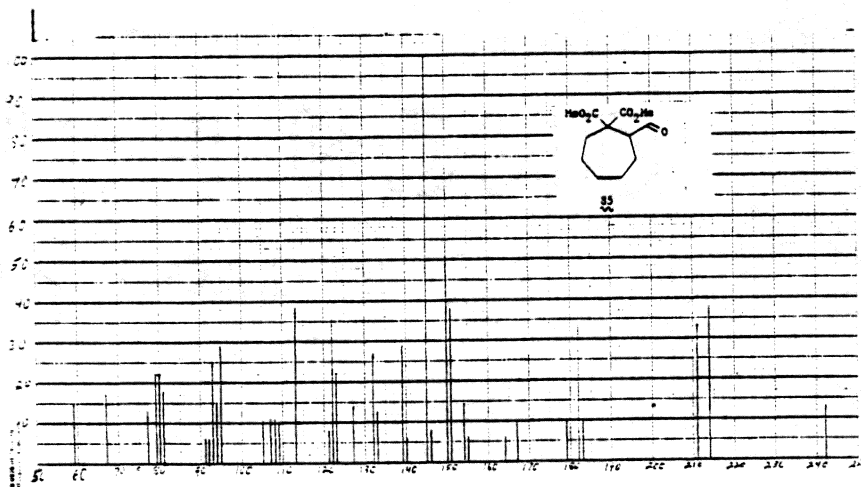


Figure 63c. Mass Spectrum of Cycloheptyl Aldehyde 85.

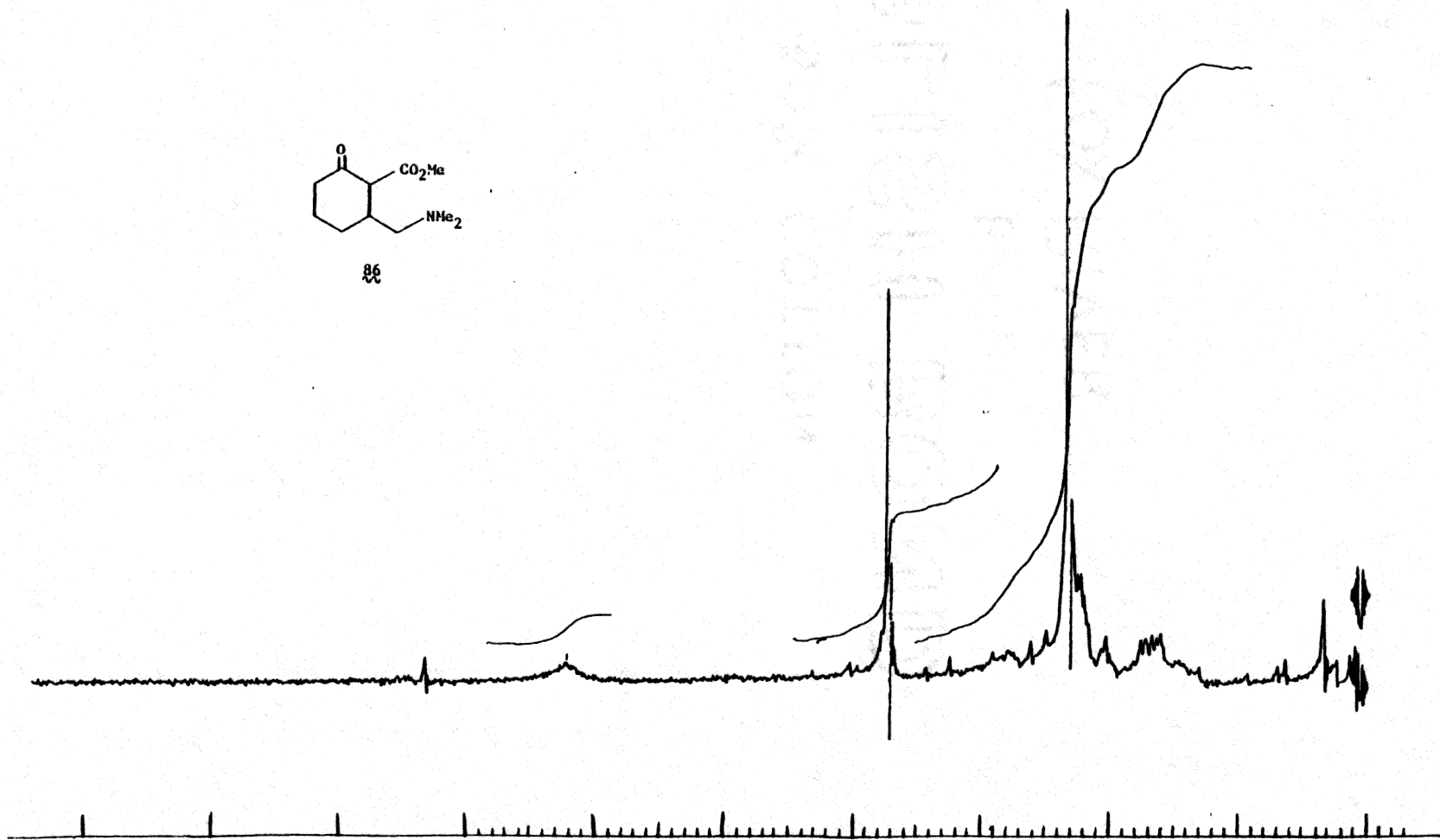
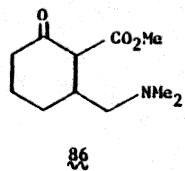


Figure 64a. 90 MHz NMR Spectrum of Cyclohexanone 86.

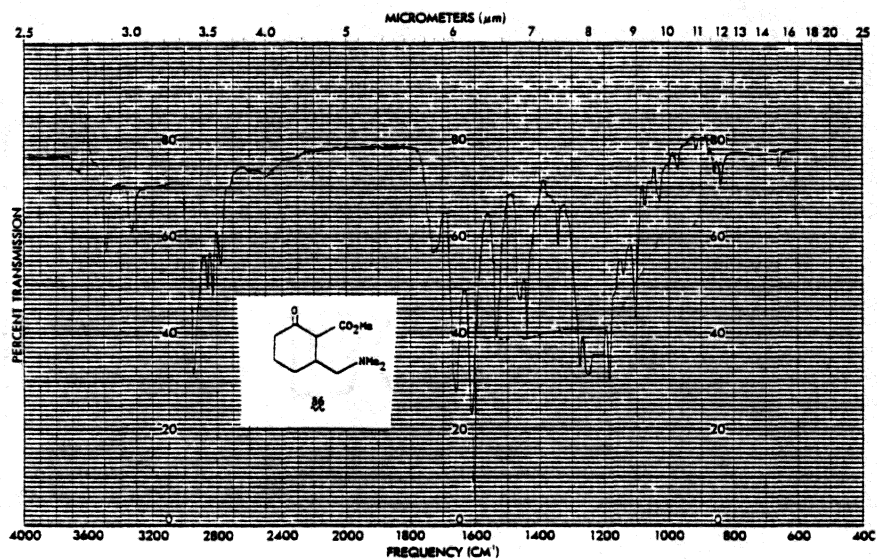


Figure 64b. IR Spectrum of Cyclohexanone 86.

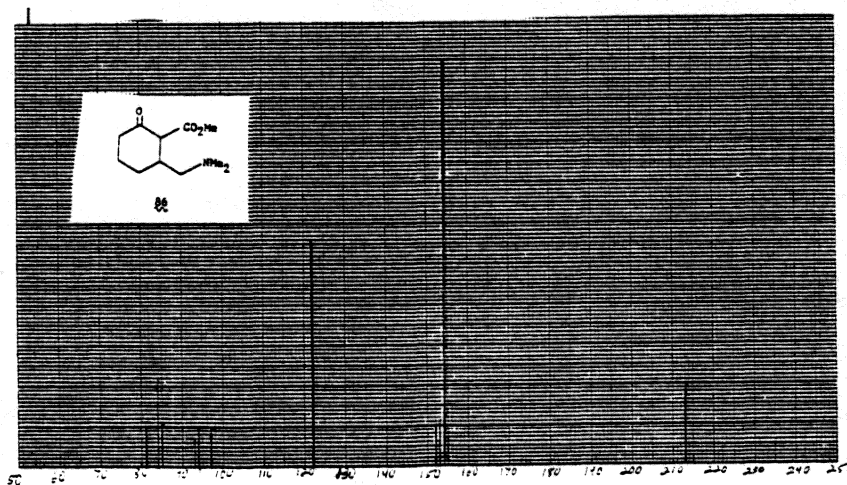


Figure 64c. Mass Spectrum of Cyclohexanone 86.

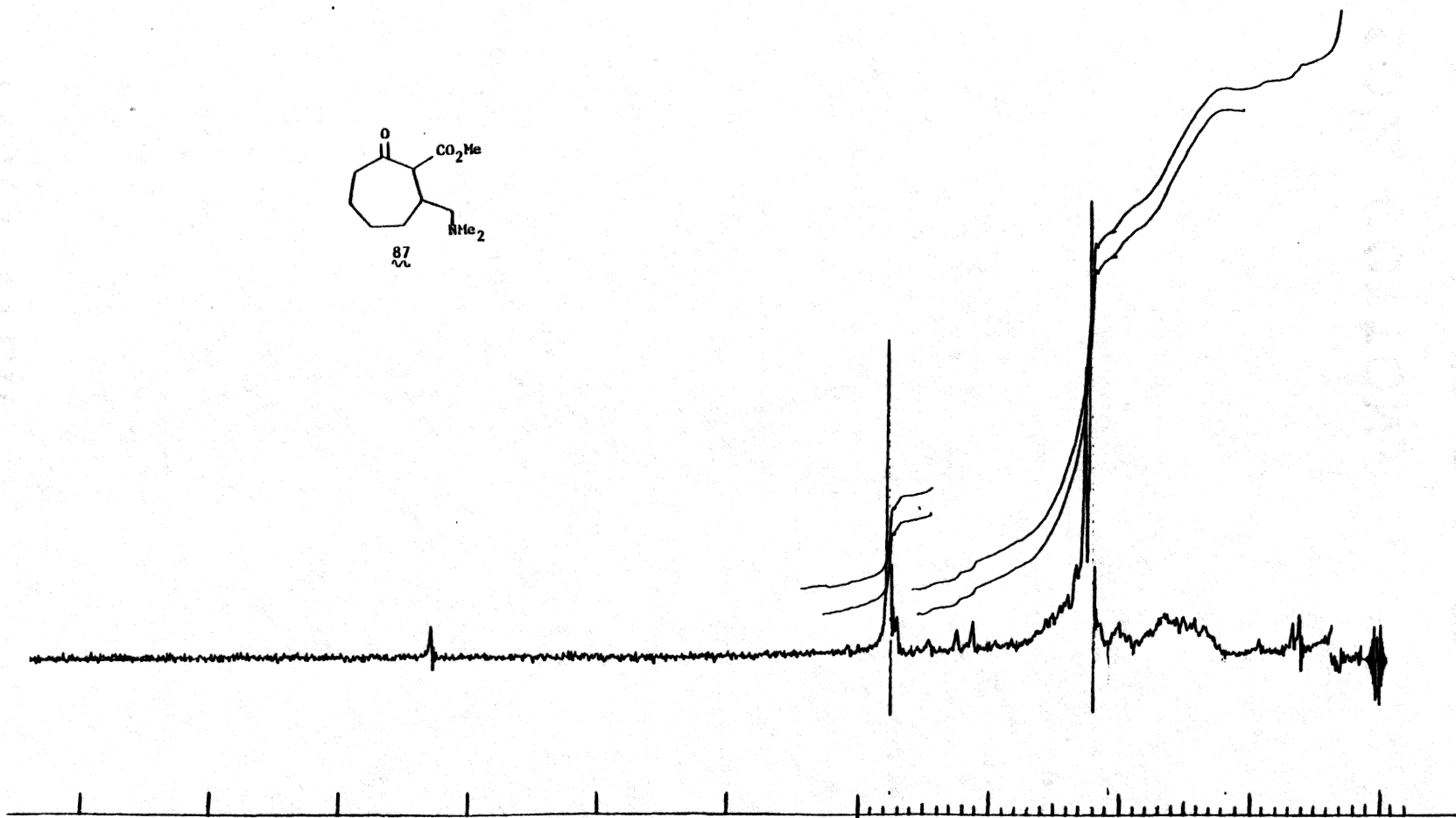
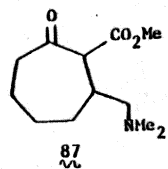


Figure 65a. 90 MHz NMR Spectrum of Cycloheptanone 87.

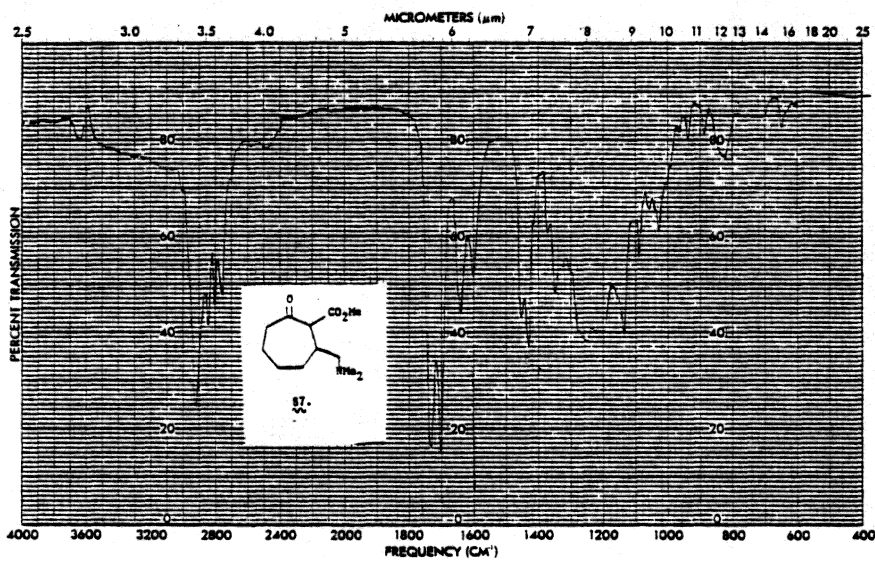


Figure 65b. IR Spectrum of Cycloheptanone 87.

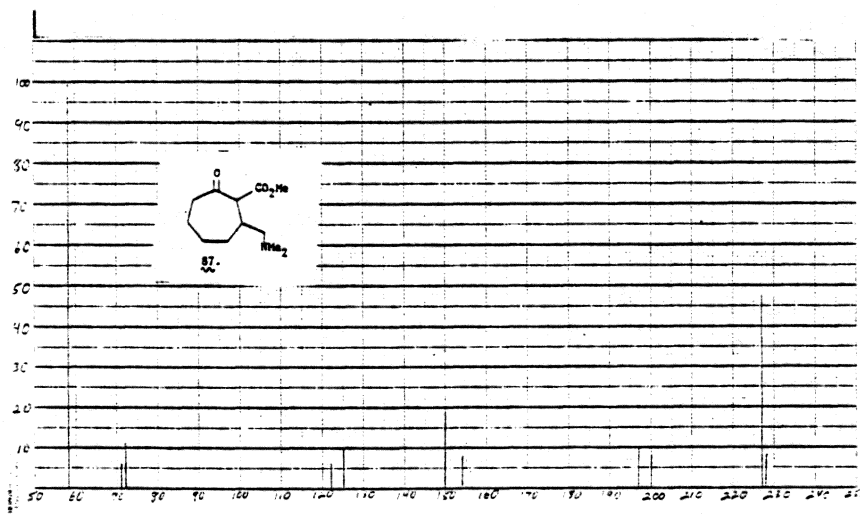
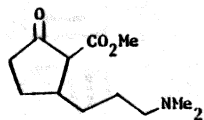


Figure 65c. Mass Spectrum of Cycloheptanone 87.



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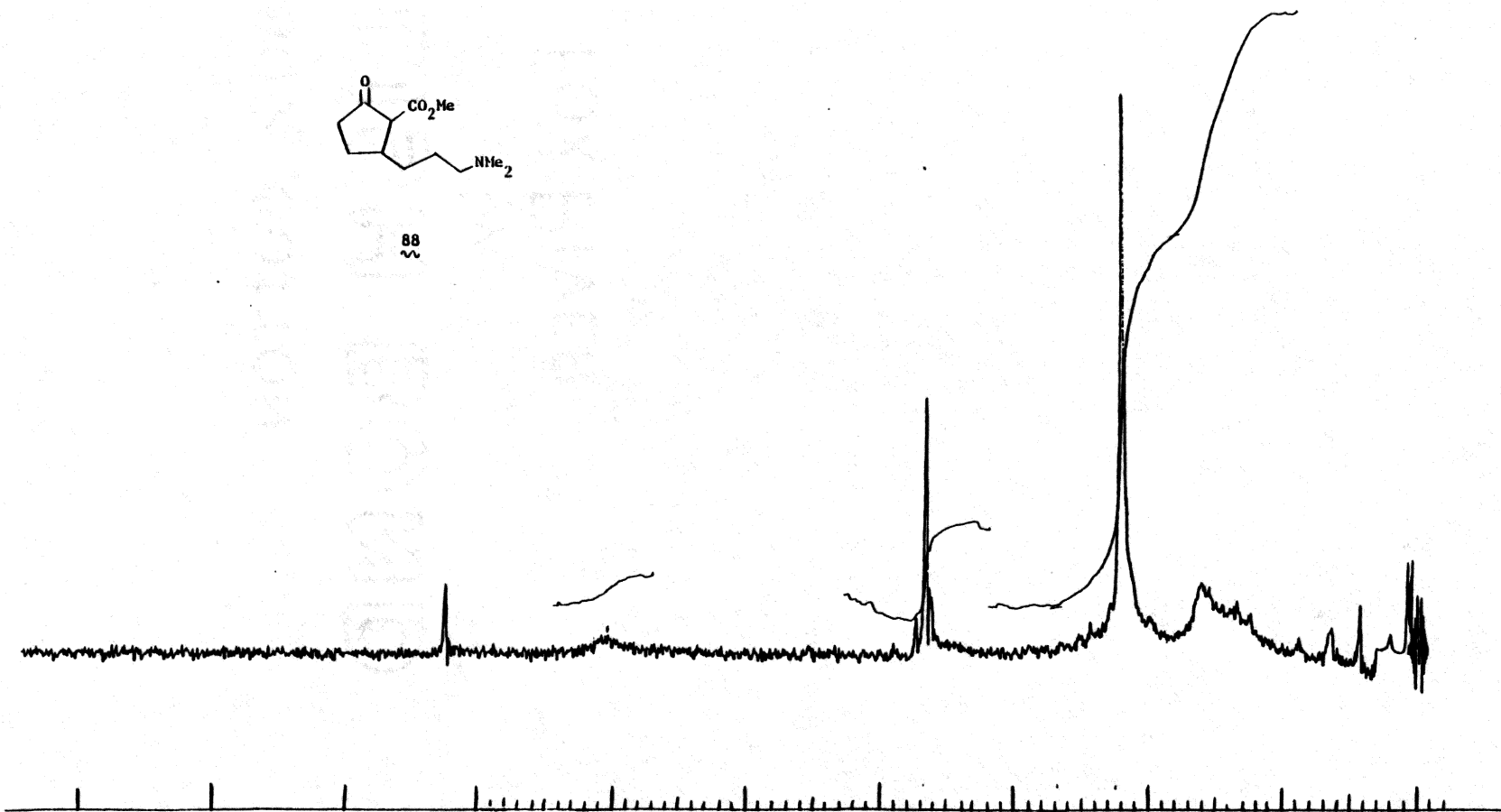


Figure 66a. 90 MHz NMR Spectrum of Cyclopentanone 88.

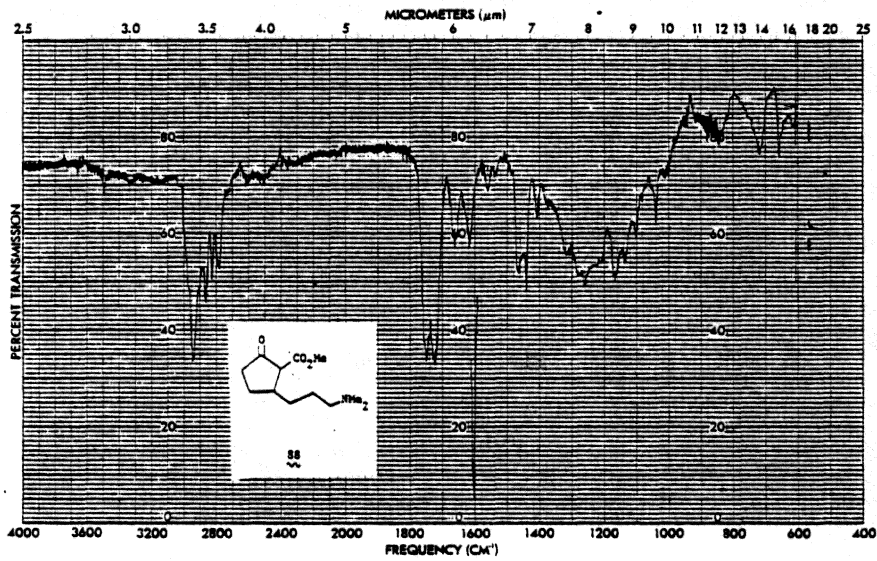


Figure 66b. IR Spectrum of Cyclopentanone 88.

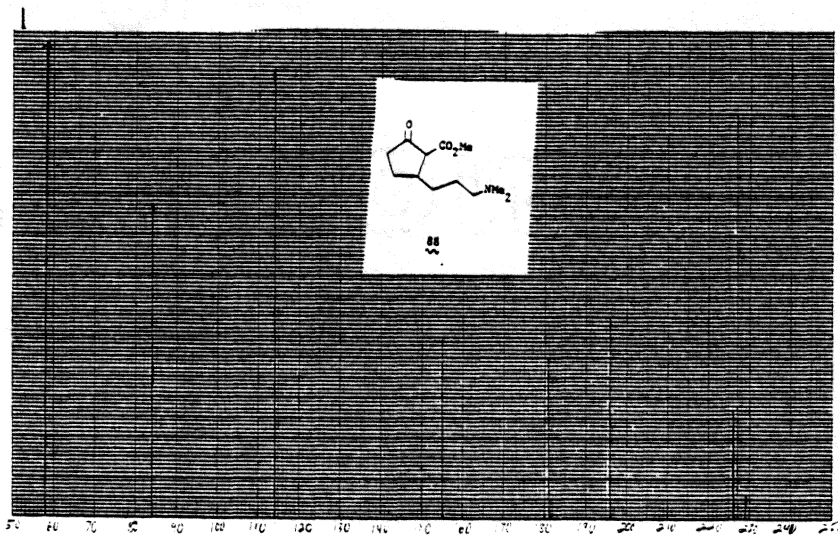


Figure 66c. Mass Spectrum of Cyclopentanone 88.

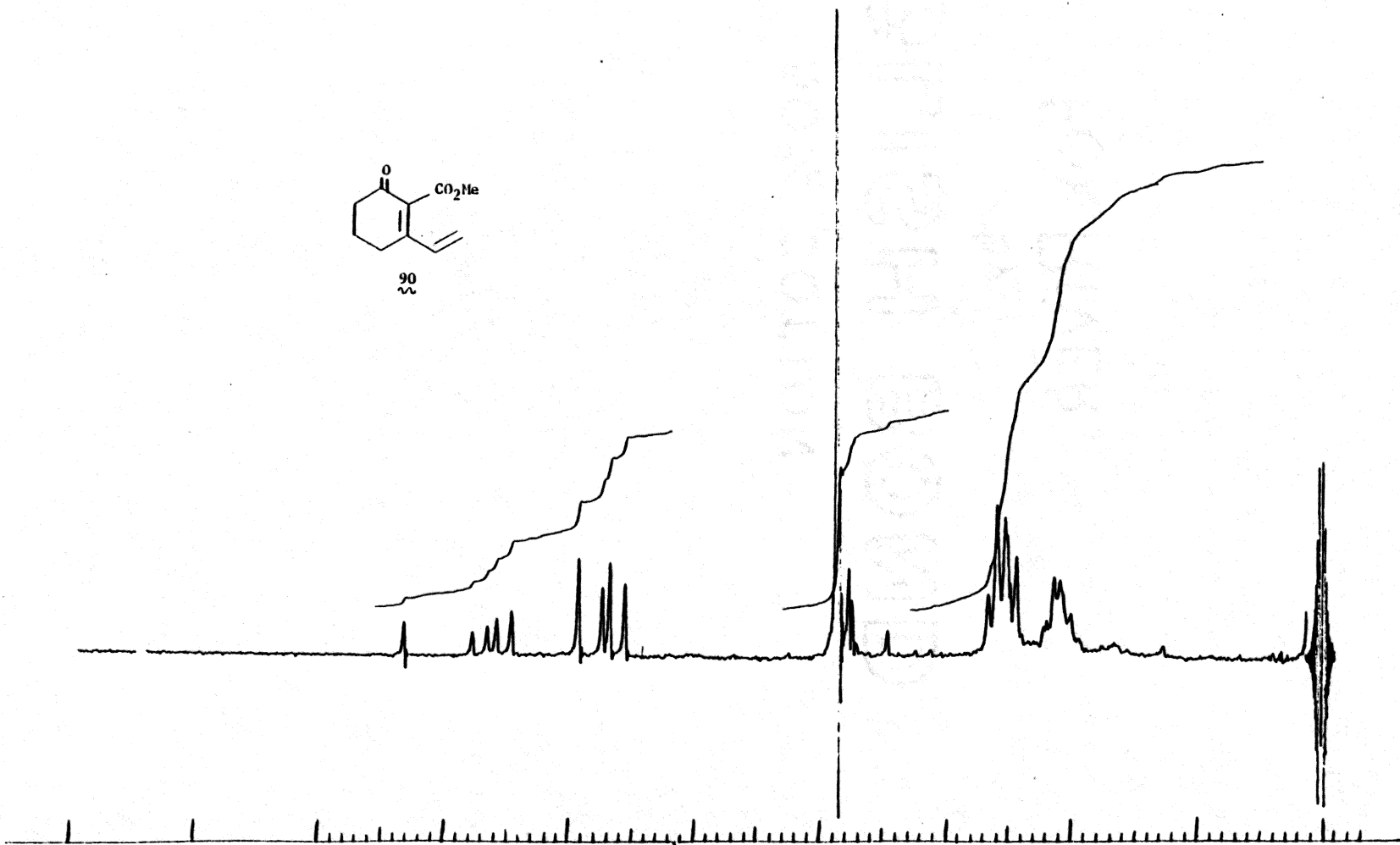


Figure 67a. 90 MHz NMR Spectrum of Cyclohexanone 90.

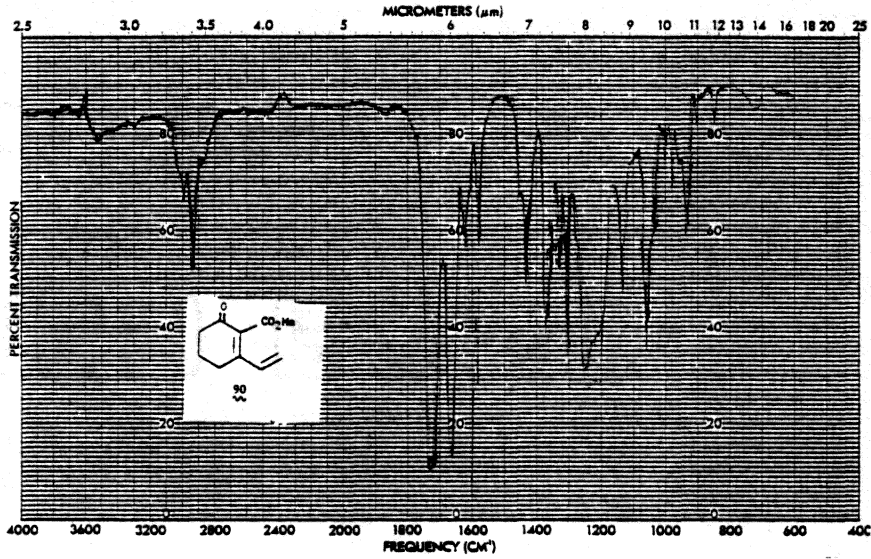


Figure 67b. IR Spectrum of Cyclohexanone 90.

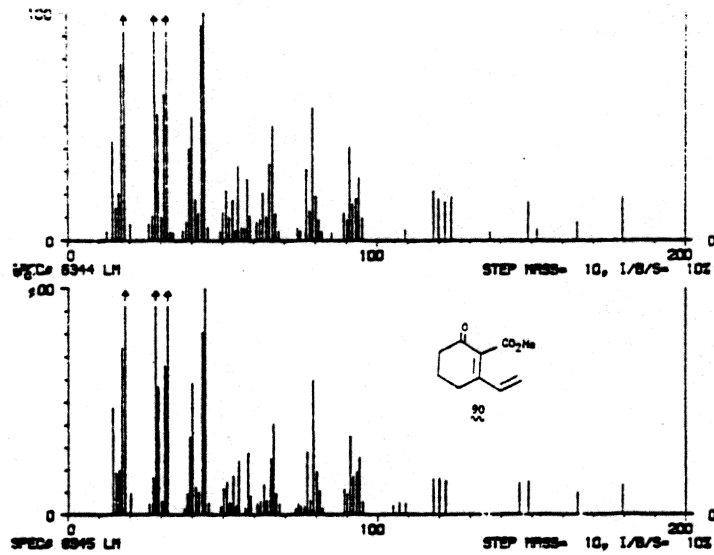


Figure 67c. Mass Spectrum of Cyclohexanone 90.

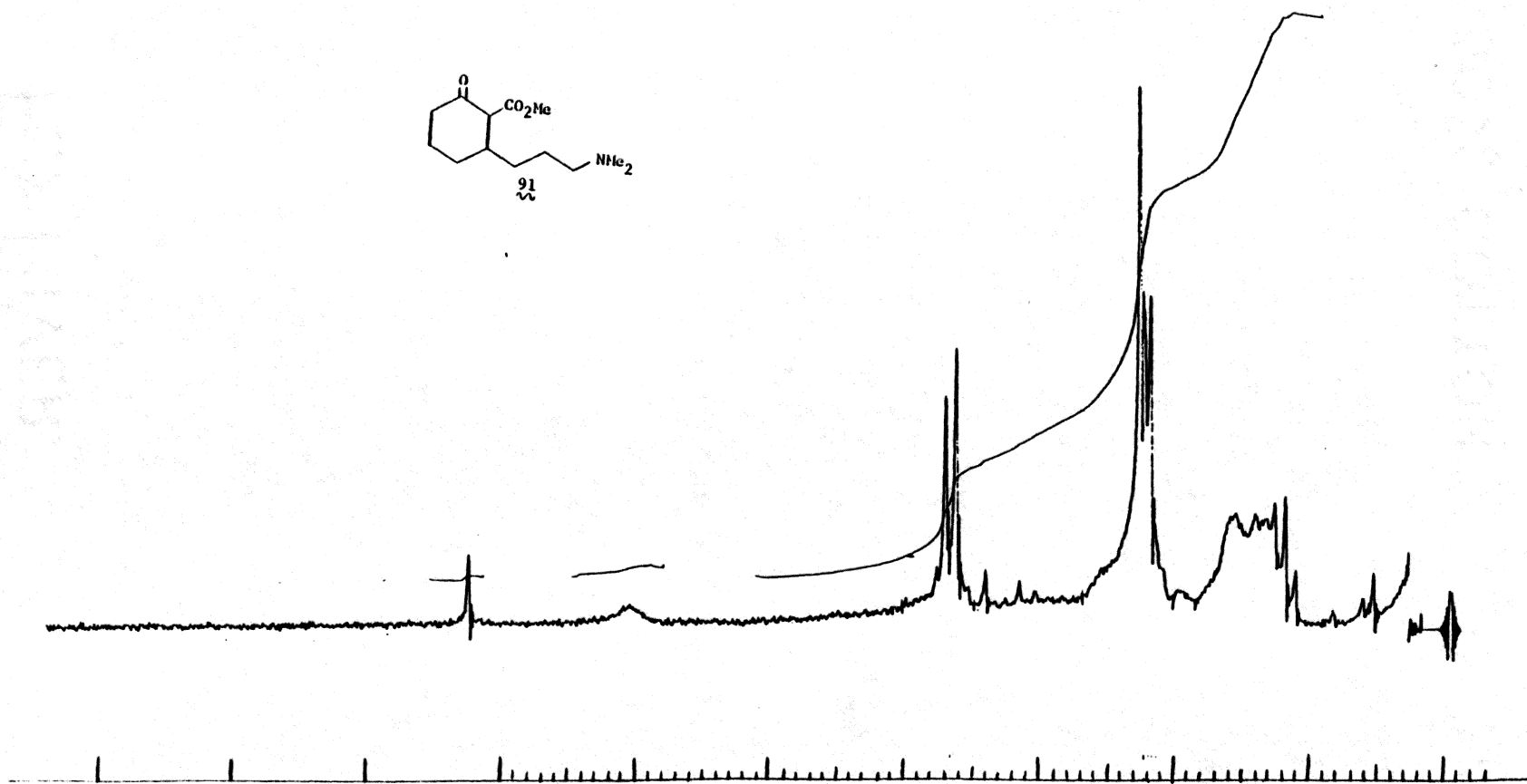


Figure 68a. 90 MHz NMR Spectrum of Cyclohexanone 91.

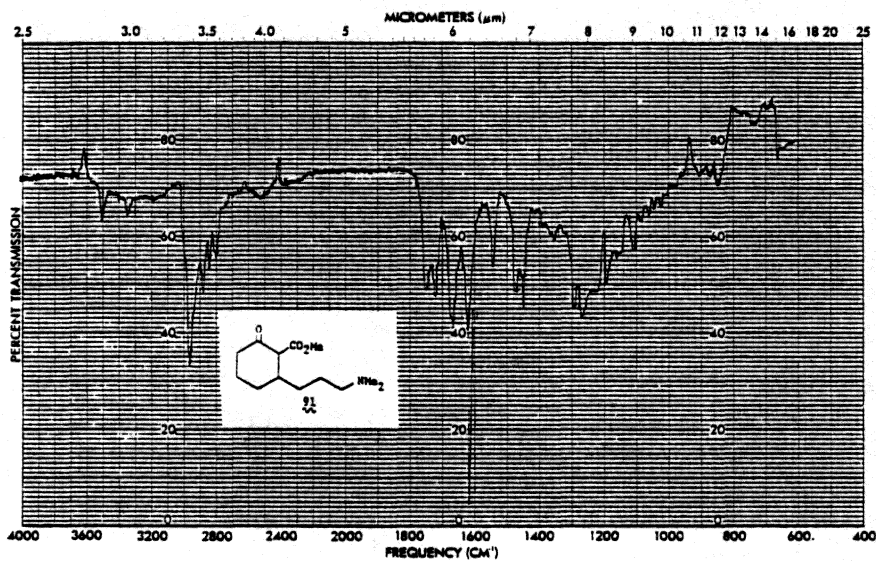


Figure 68b. IR Spectrum of Cyclohexanone 91.

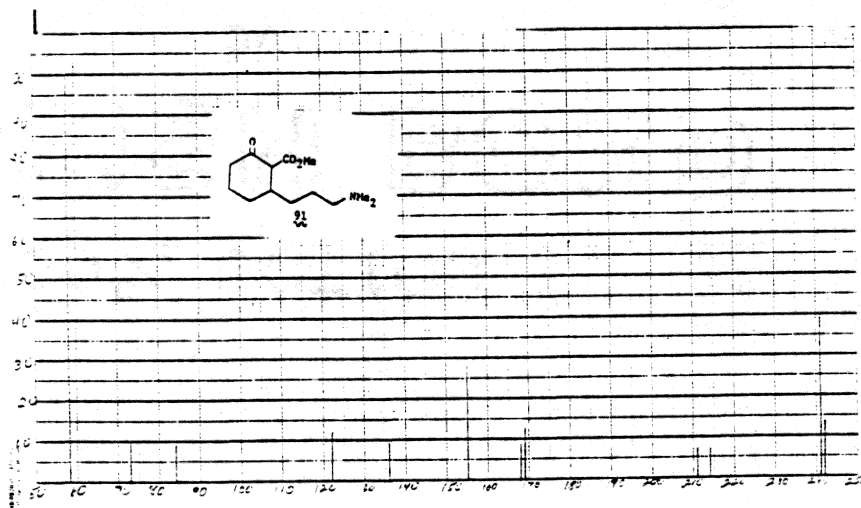
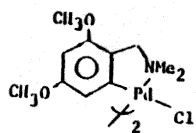


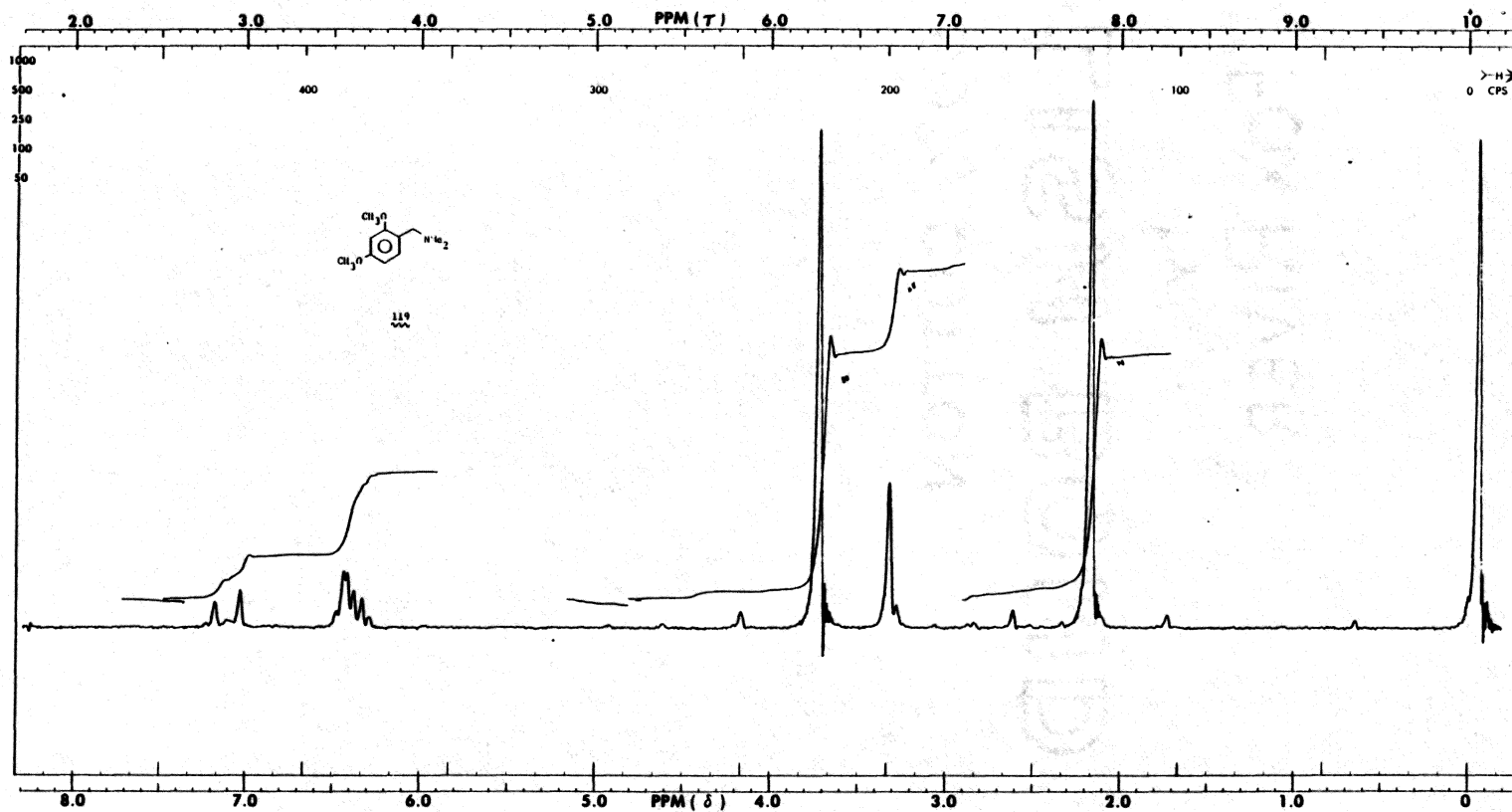
Figure 68c. Mass Spectrum of Cyclohexanone 91.



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Figure 69a. 90 MHz NMR Spectrum of Palladocycle 118.



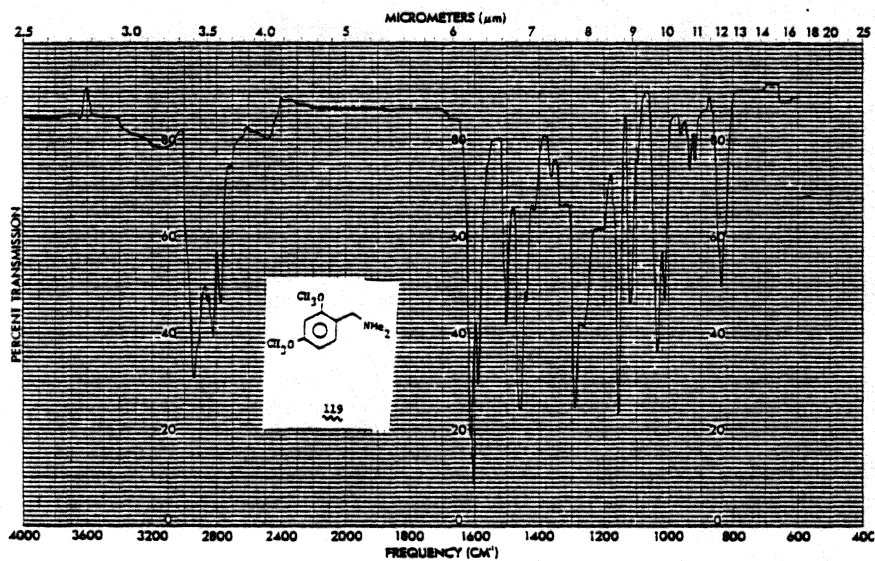


Figure 70b. IR Spectrum of Benzylic Amine 119.

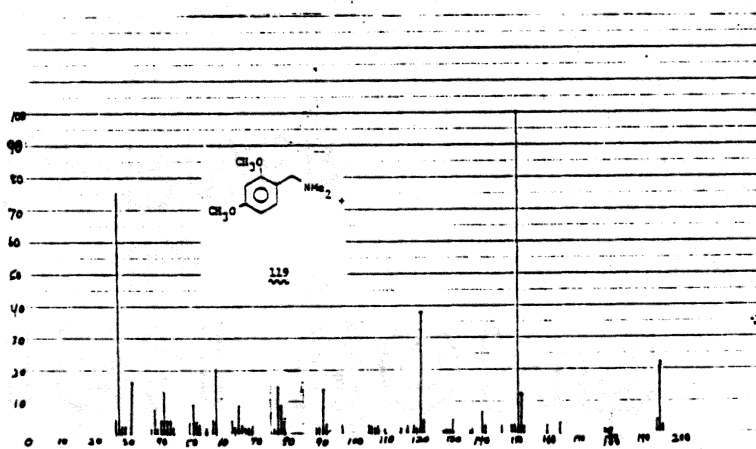


Figure 70c. Mass Spectrum of Benzylic Amine 119.

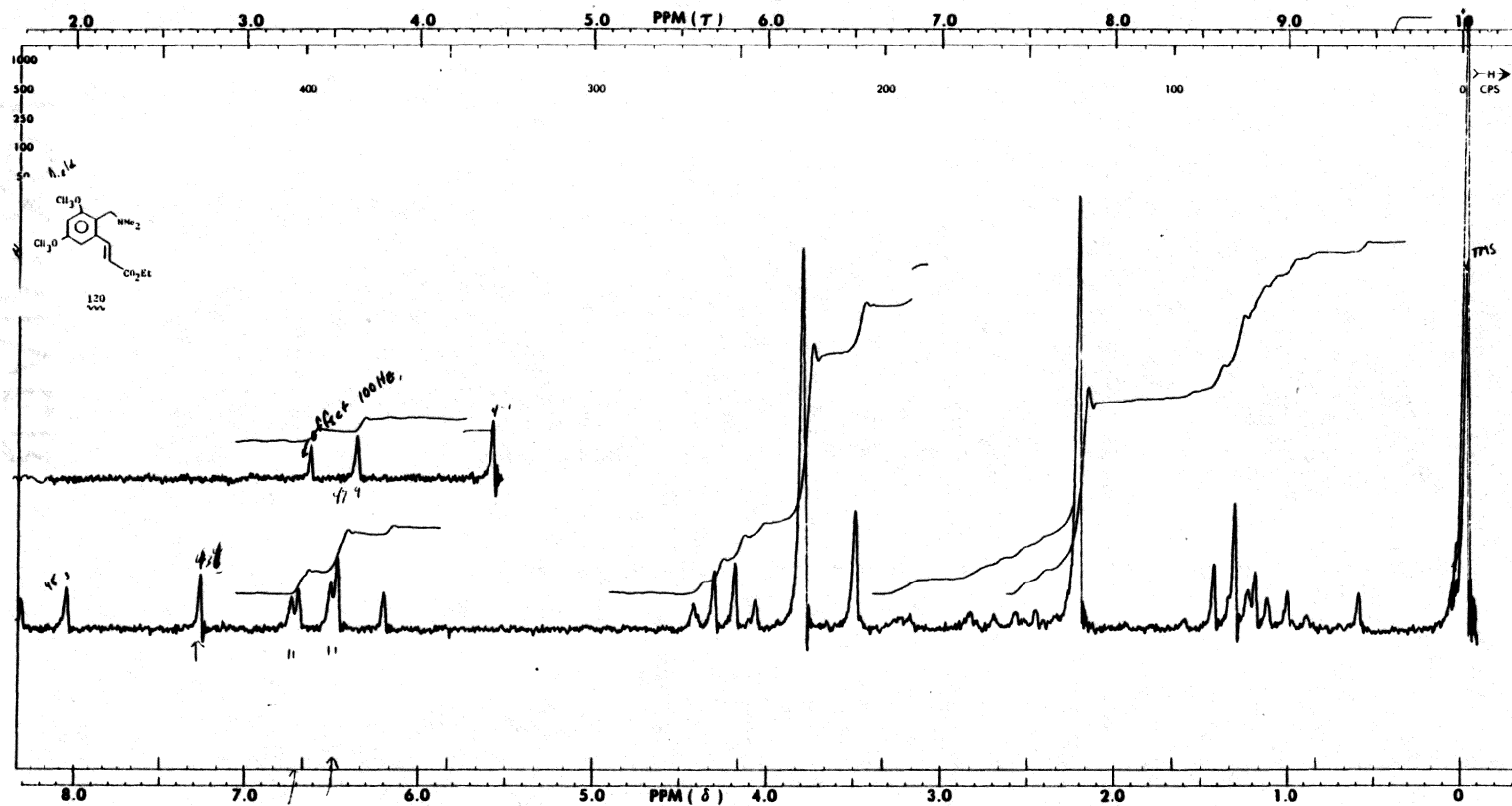
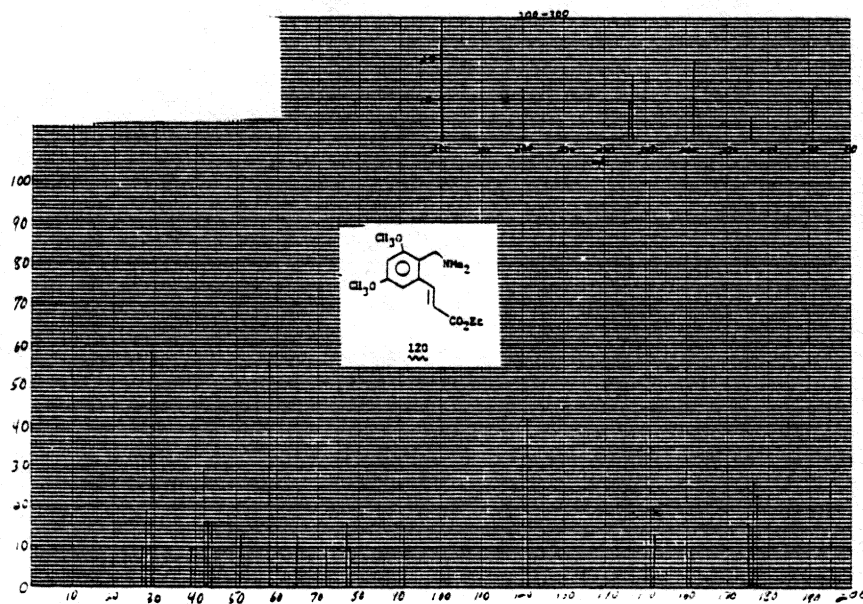
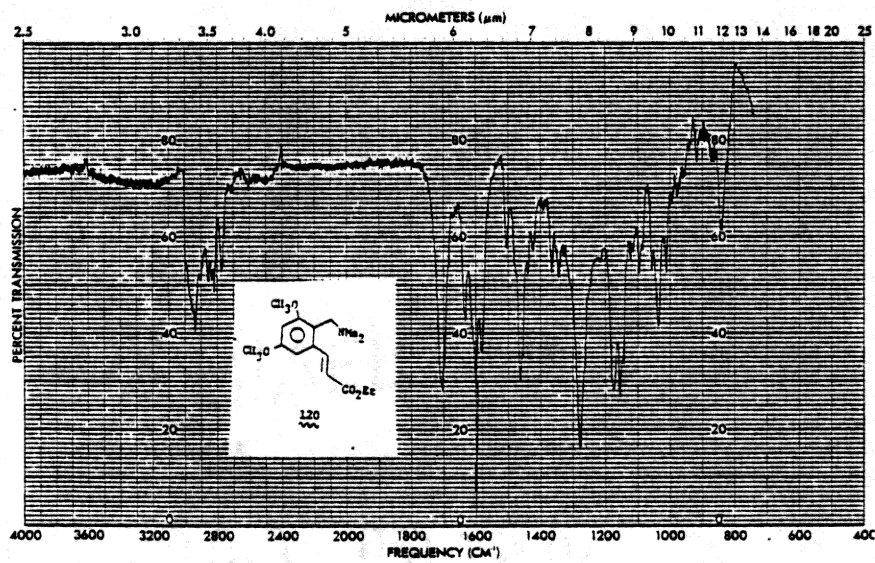


Figure 71a. 60 MHz NMR Spectrum of Cinnamate 120.



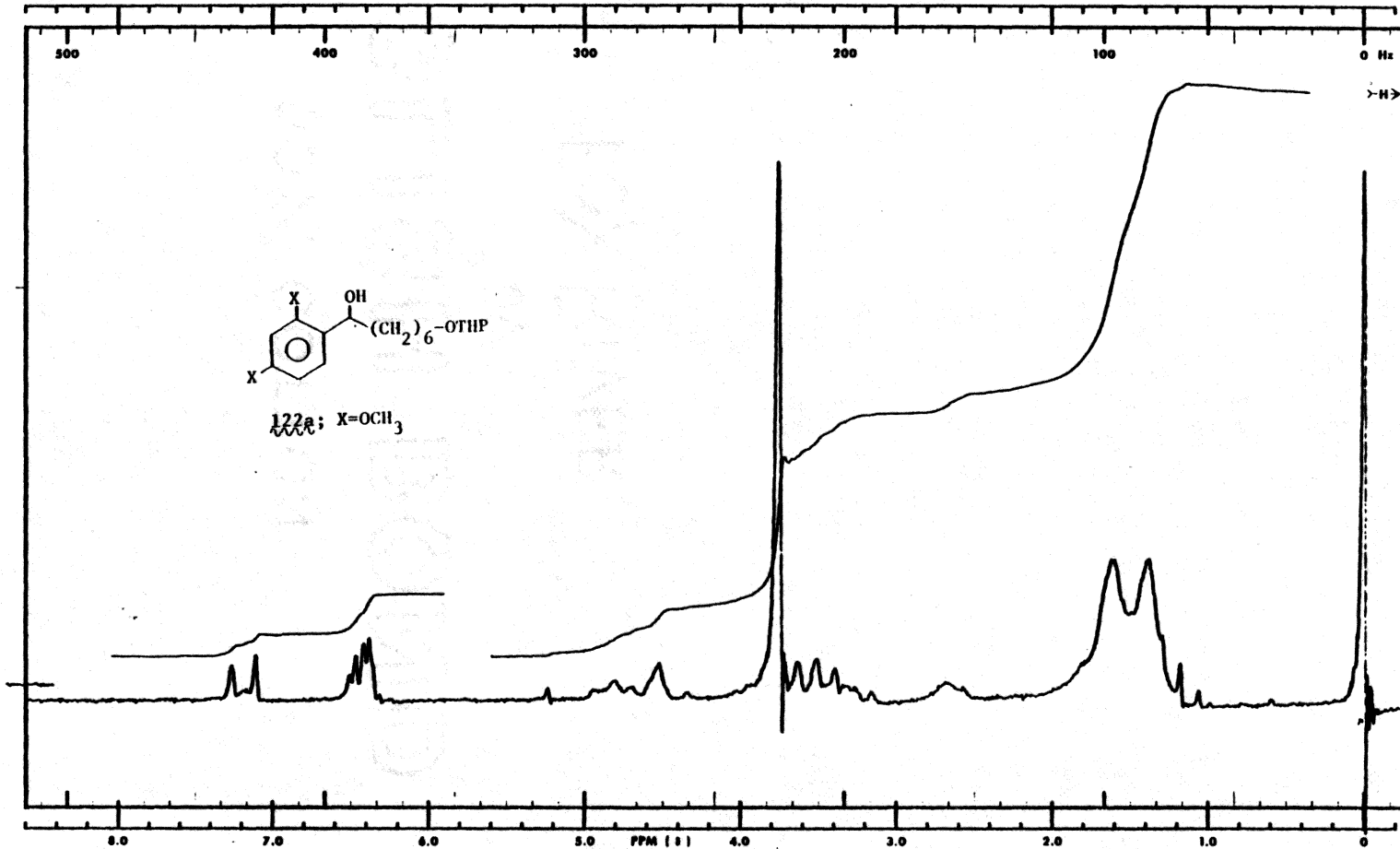


Figure 72a. 90 MHz NMR Spectrum of Benzylic Alcohol 122a.

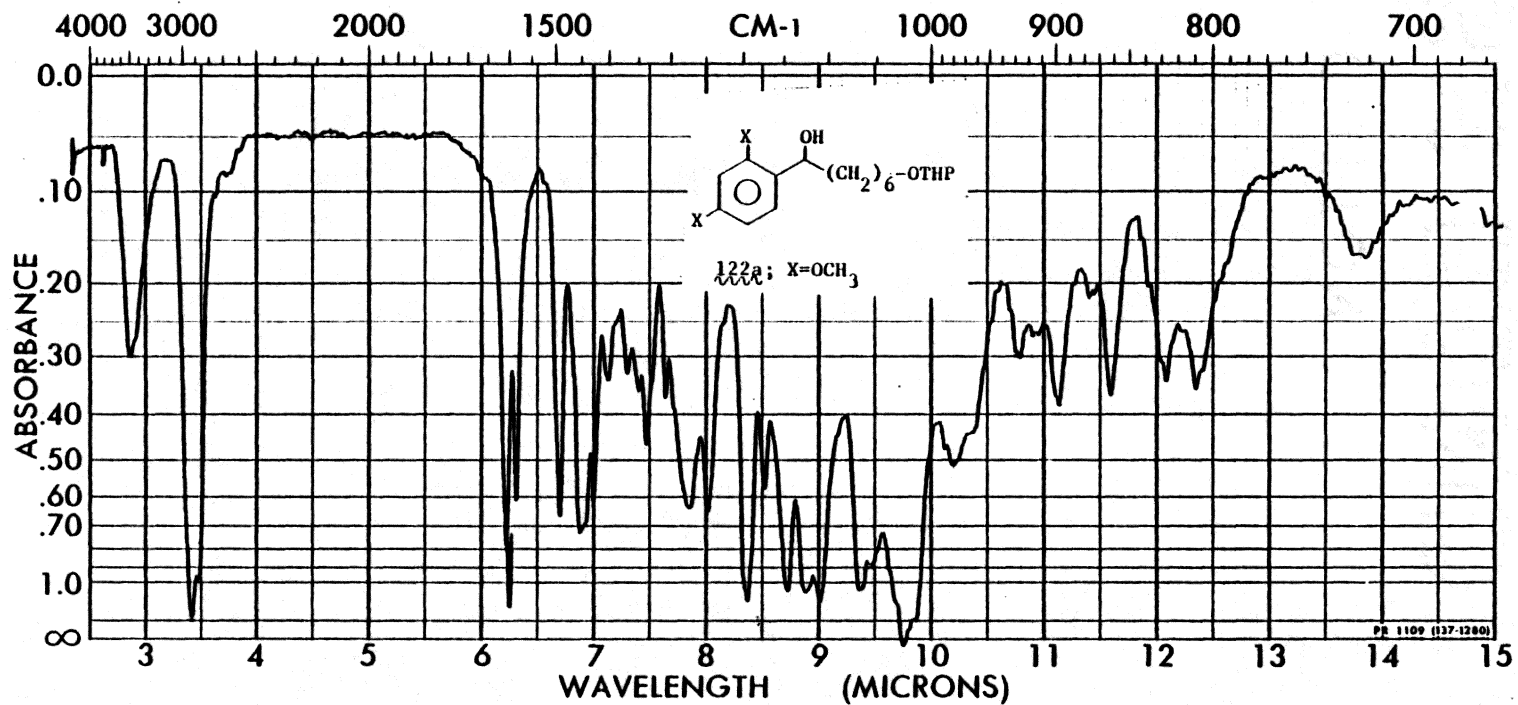


Figure 72b. IR Spectrum of Benzylic Alcohol 122a.

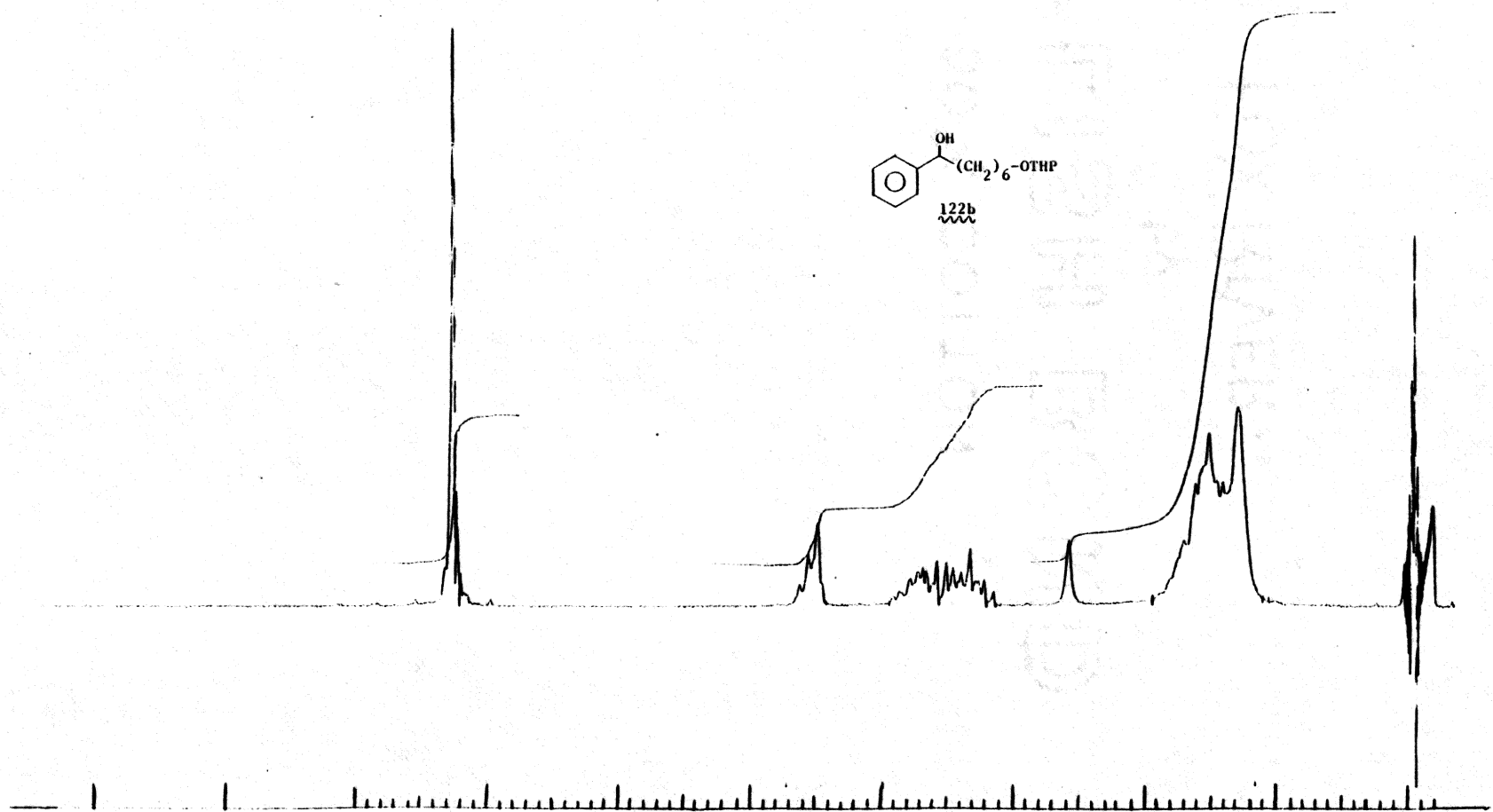


Figure 73a. 90 MHz NMR Spectrum of Benzylic Alcohol 122b.

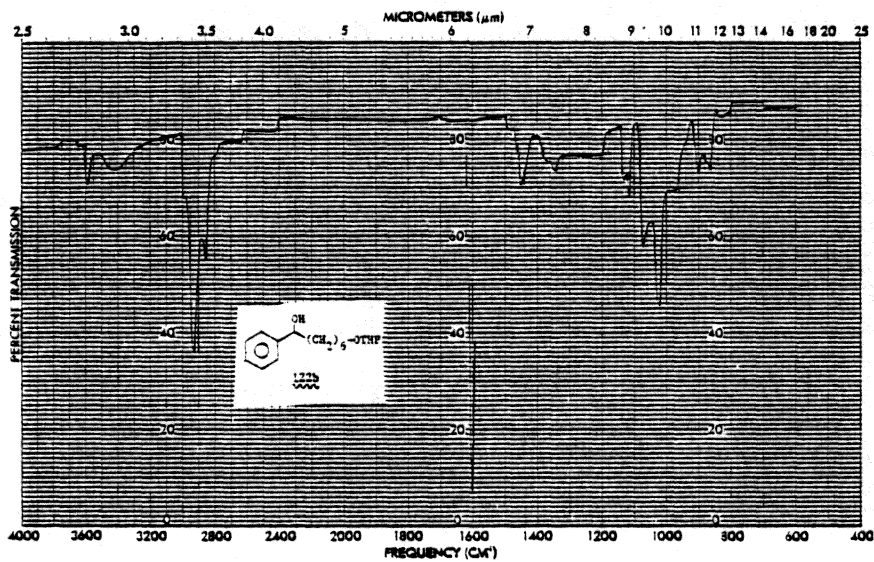


Figure 73b. IR Spectrum of Benzylic Alcohol 122b.

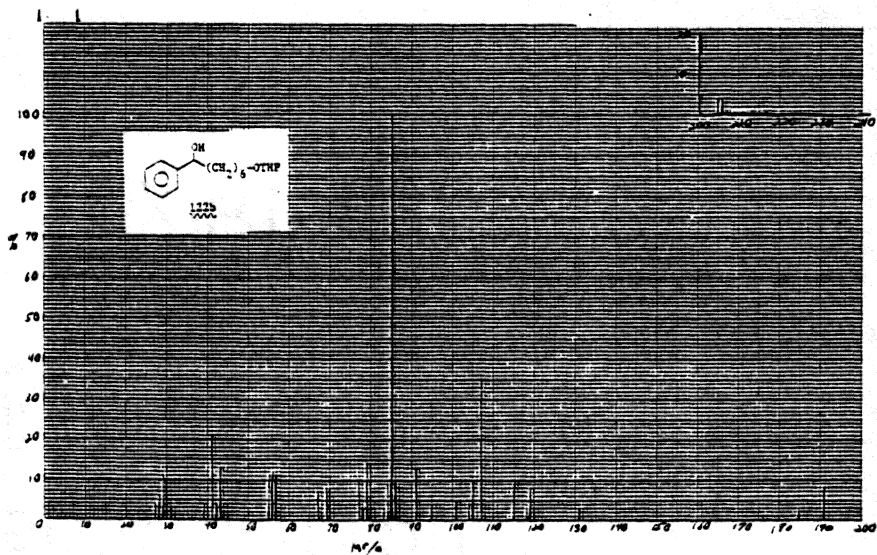


Figure 73c. Mass Spectrum of Benzylic Alcohol 122b.

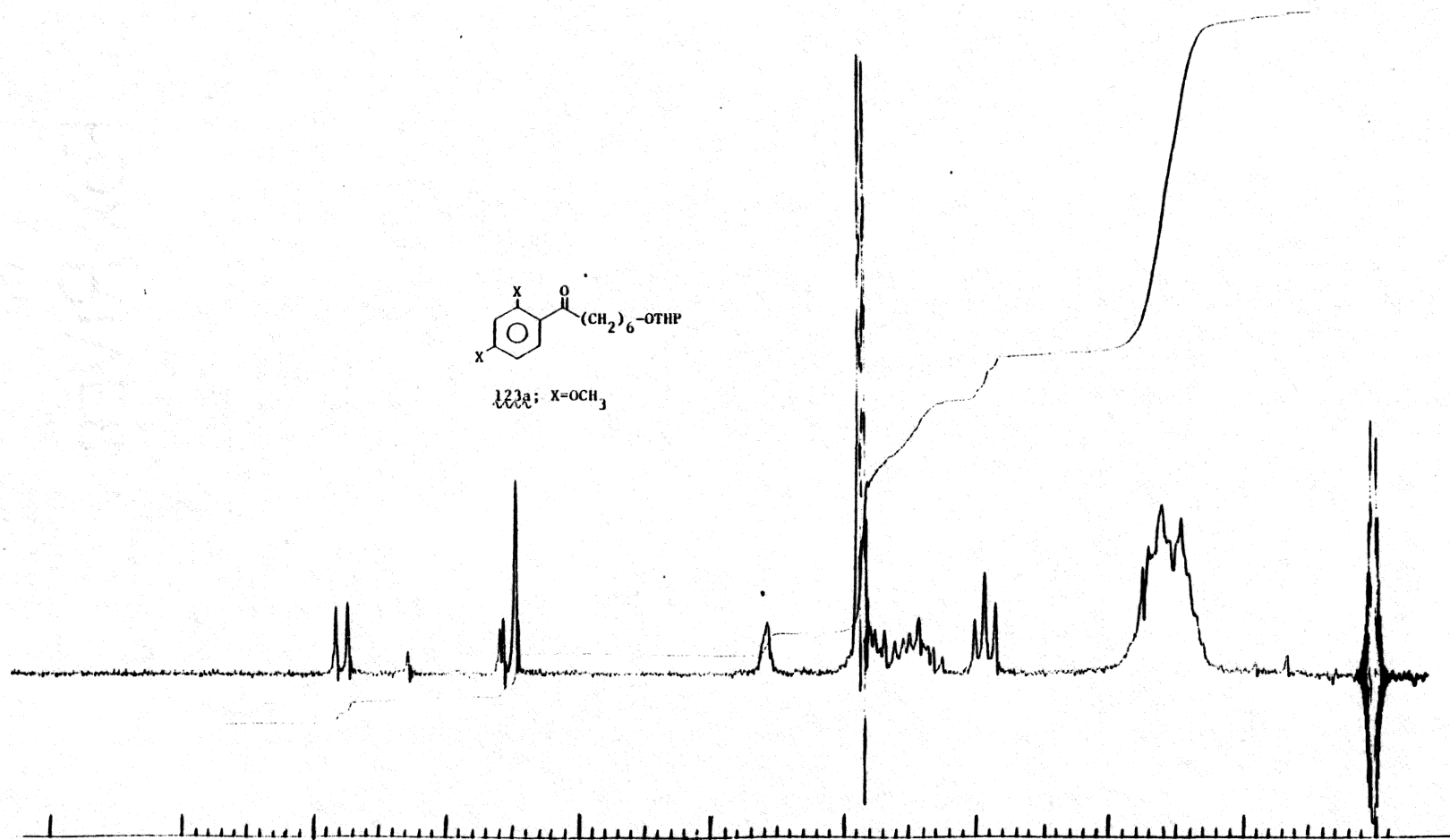


Figure 74a. 90 MHz NMR Spectrum of Ketone 123a.

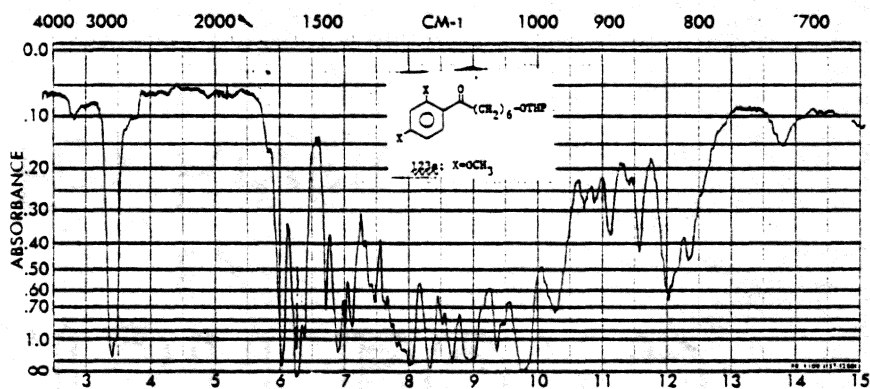


Figure 74b. IR Spectrum of Ketone 123a.

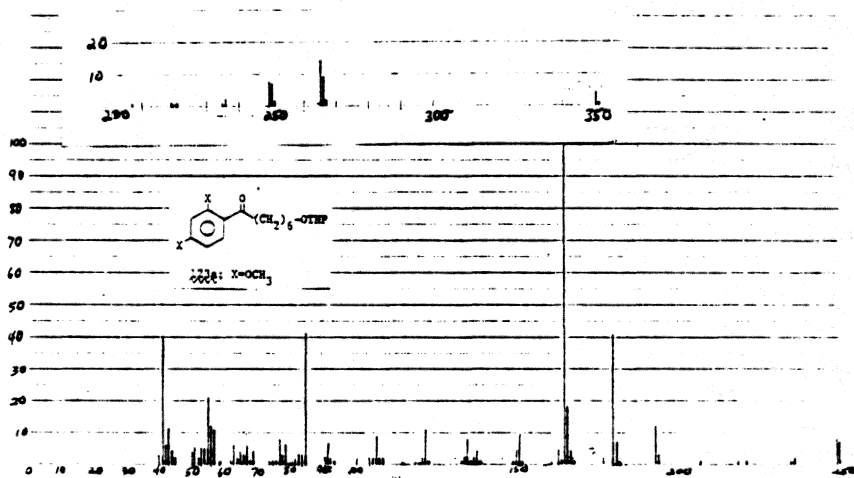


Figure 74c. Mass Spectrum of Ketone 123a.

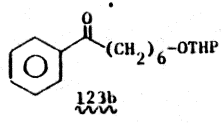
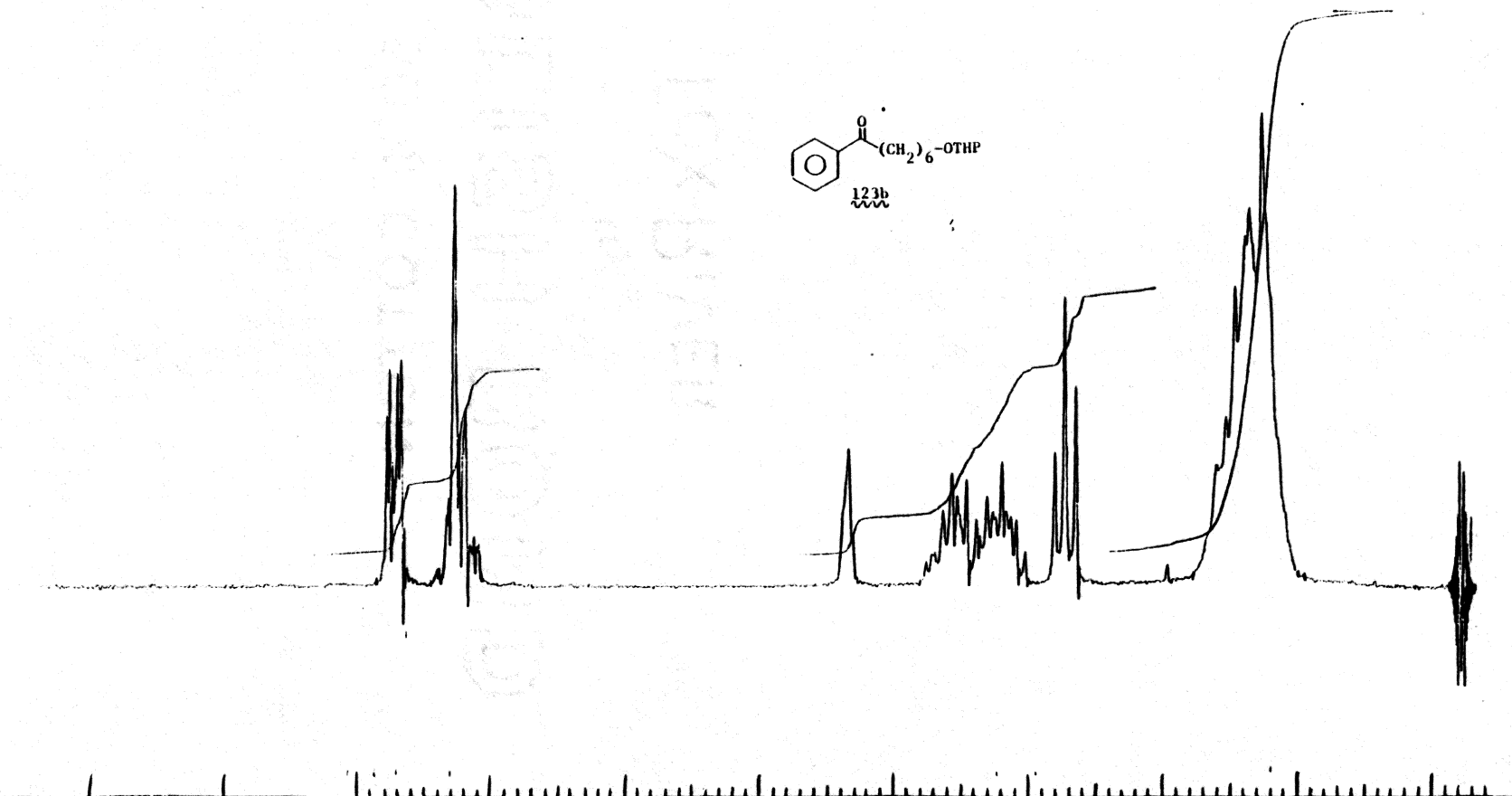


Figure 75a. 90 MHz NMR Spectrum of Ketone 123b.

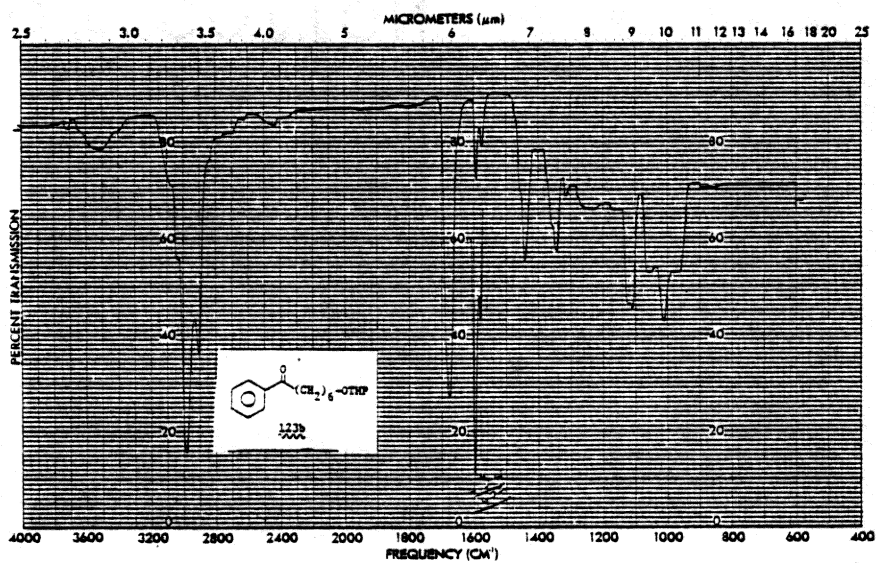


Figure 75b. IR Spectrum of Ketone 123b.

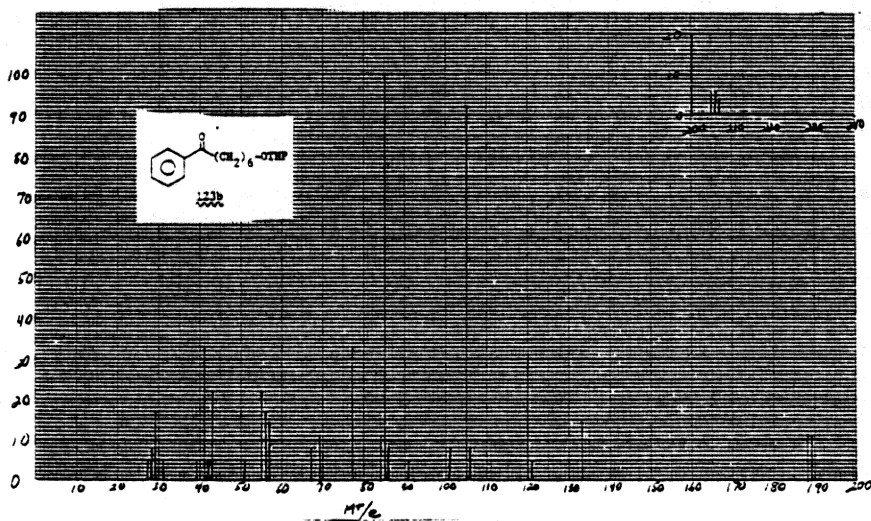
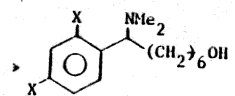


Figure 75c. Mass Spectrum of Ketone 123b.



124a; X=OCH₃

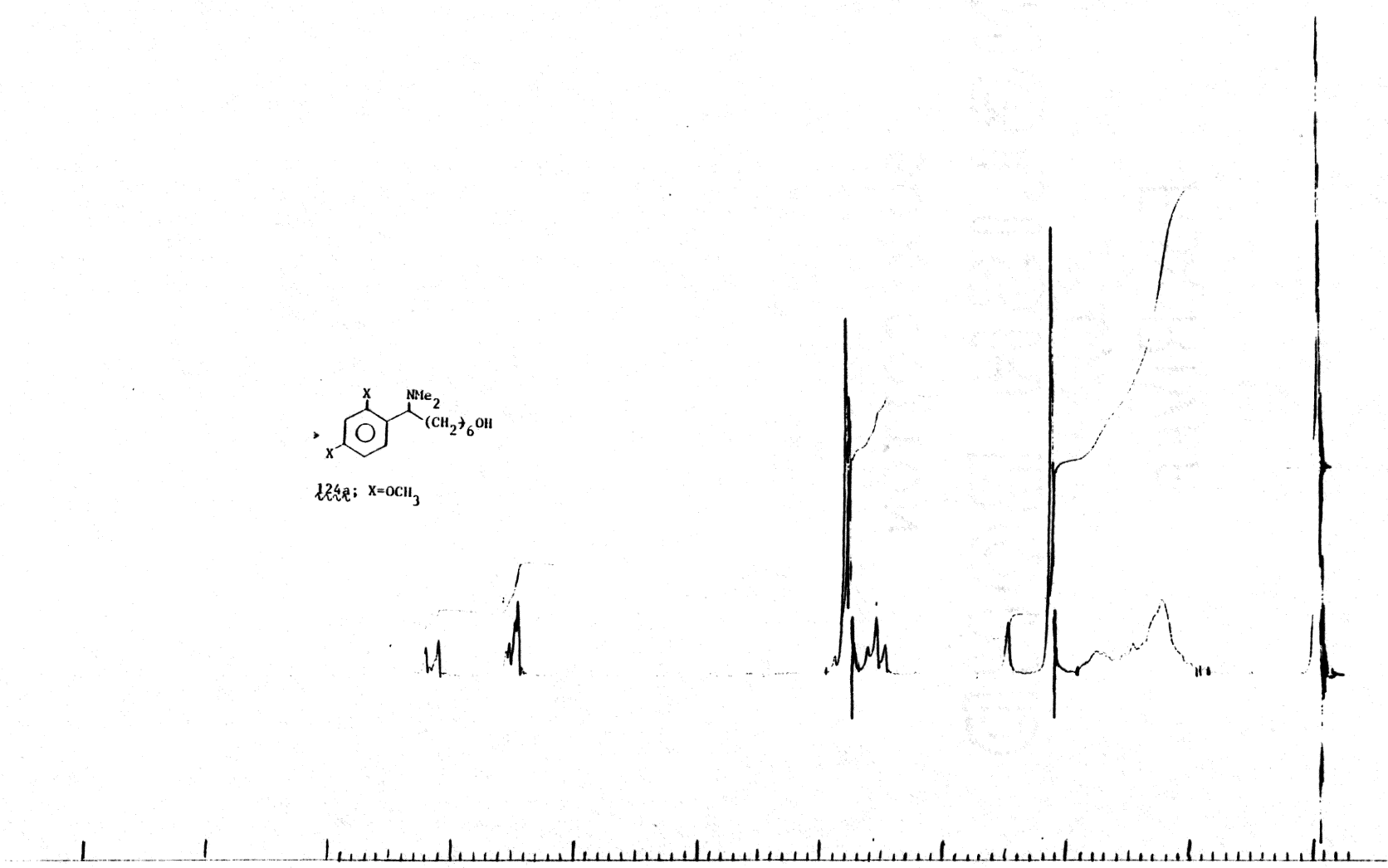


Figure 76a. 90 MHz NMR Spectrum of Amino Alcohol 124a.

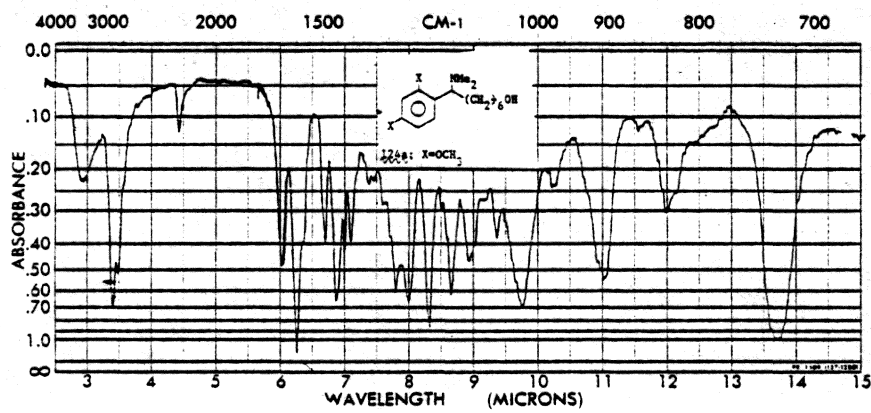


Figure 76b. IR Spectrum of Amino Alcohol 124a.

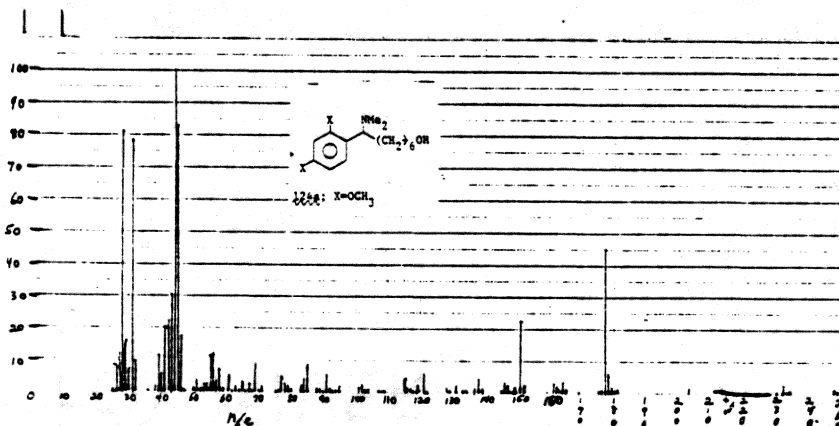


Figure 76c. Mass Spectrum of Amino Alcohol 124a.

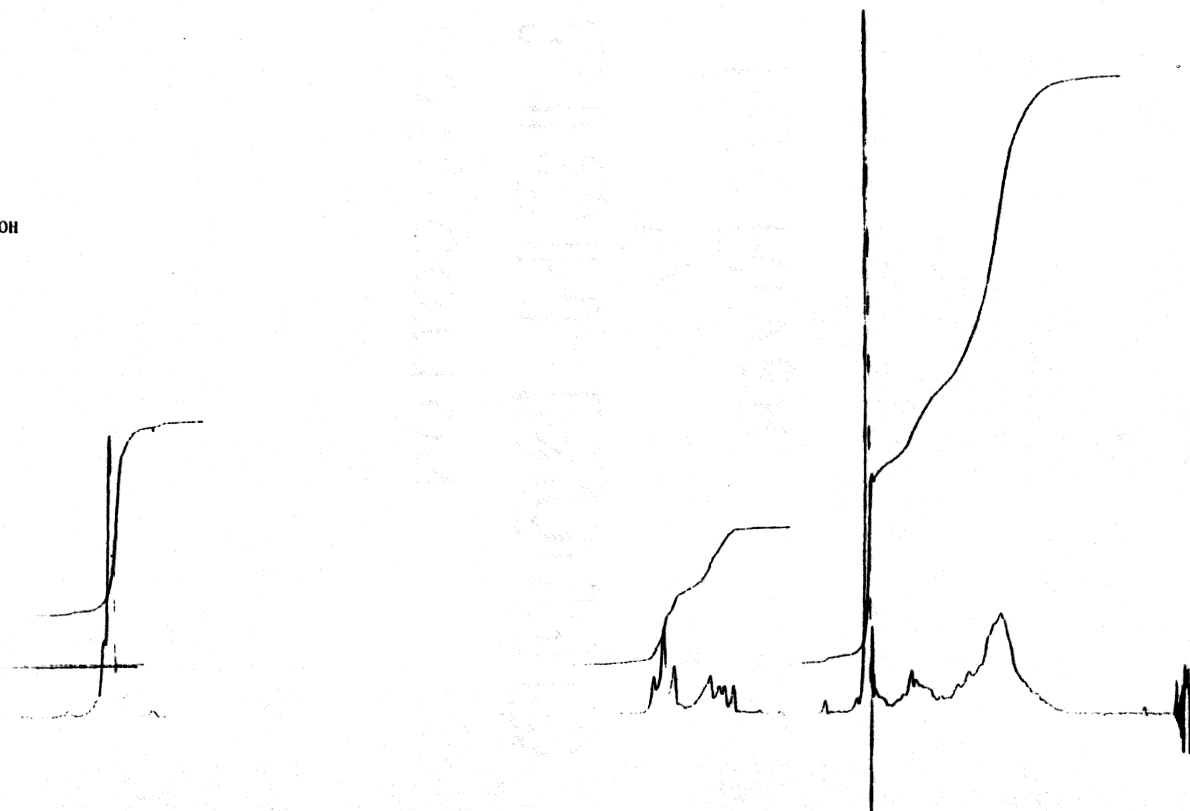
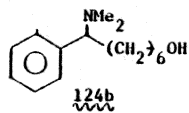


Figure 77a. 90 MHz NMR Spectrum of Amino Alcohol 124b.

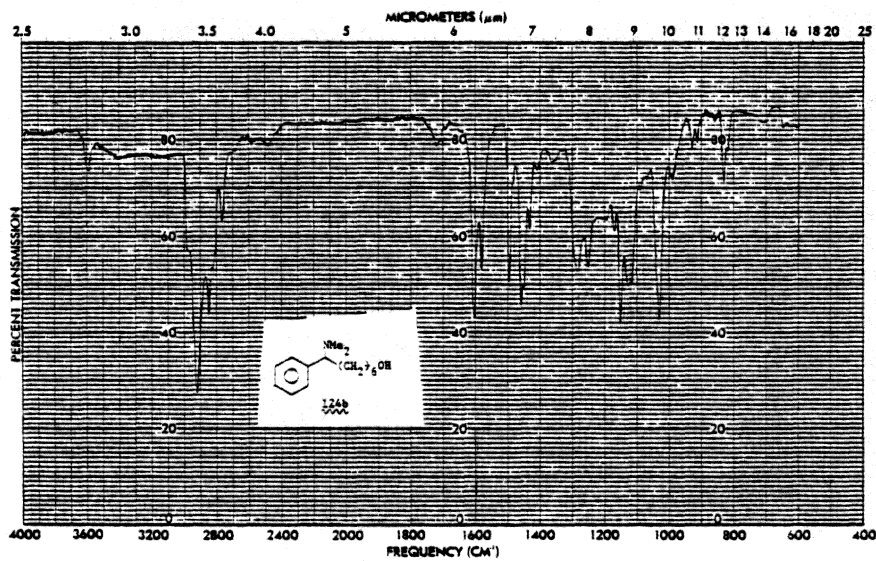


Figure 77b. IR Spectrum of Amino Alcohol 124b.

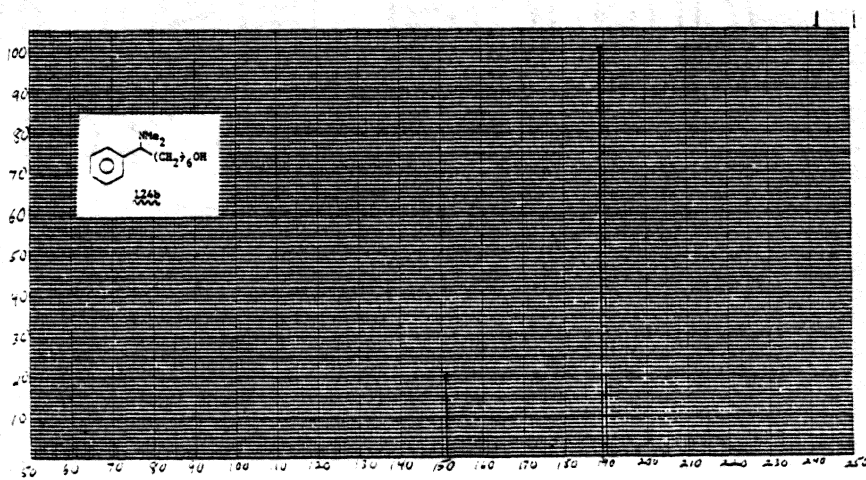


Figure 77c. Mass Spectrum of Amino Alcohol 124b.

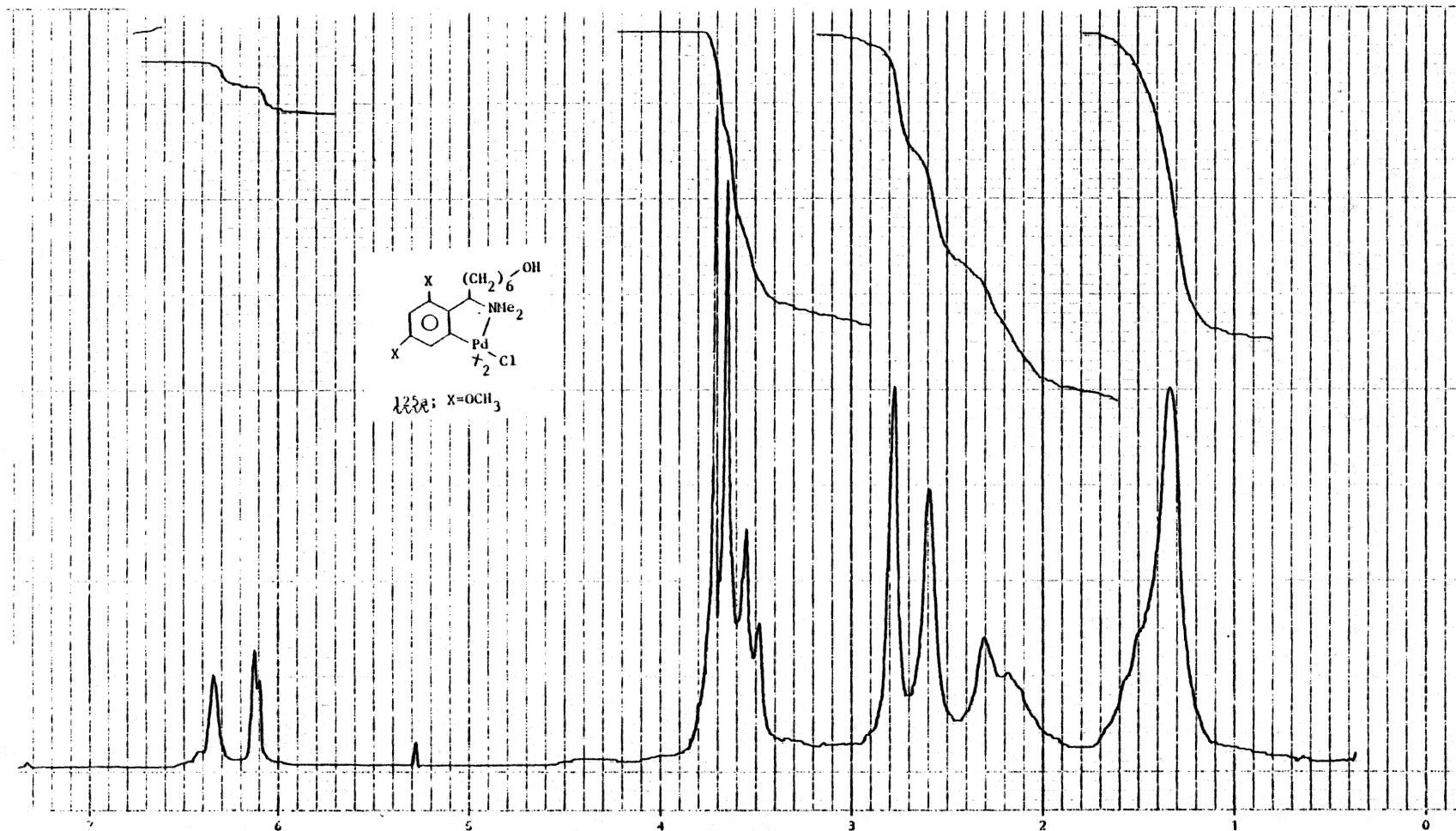


Figure 78a. 90 MHz NMR Spectrum of Palladocycle 125a.

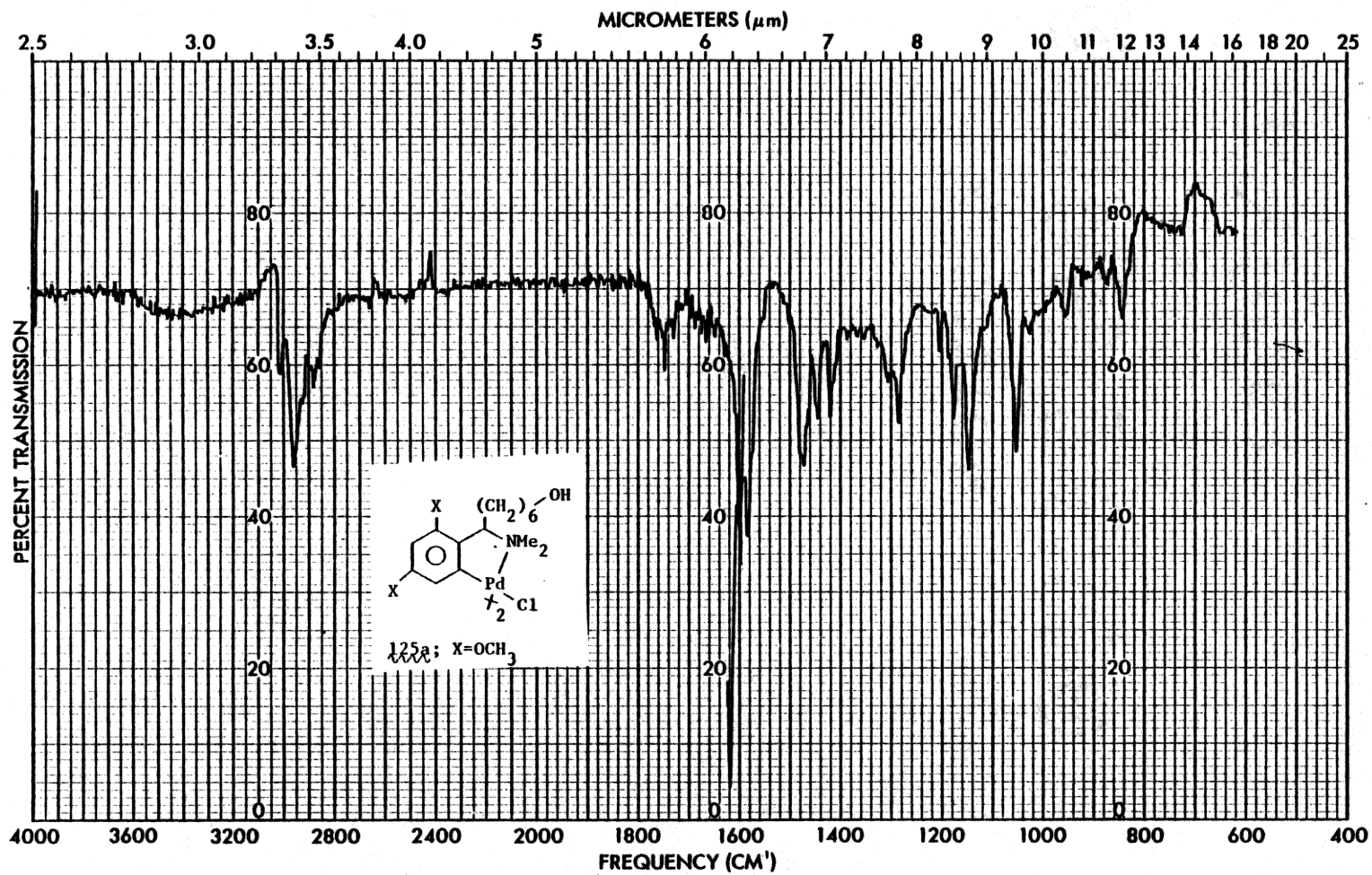


Figure 78b. IR Spectrum of Palladocycle 125a.

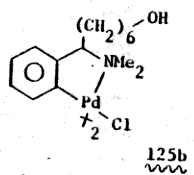
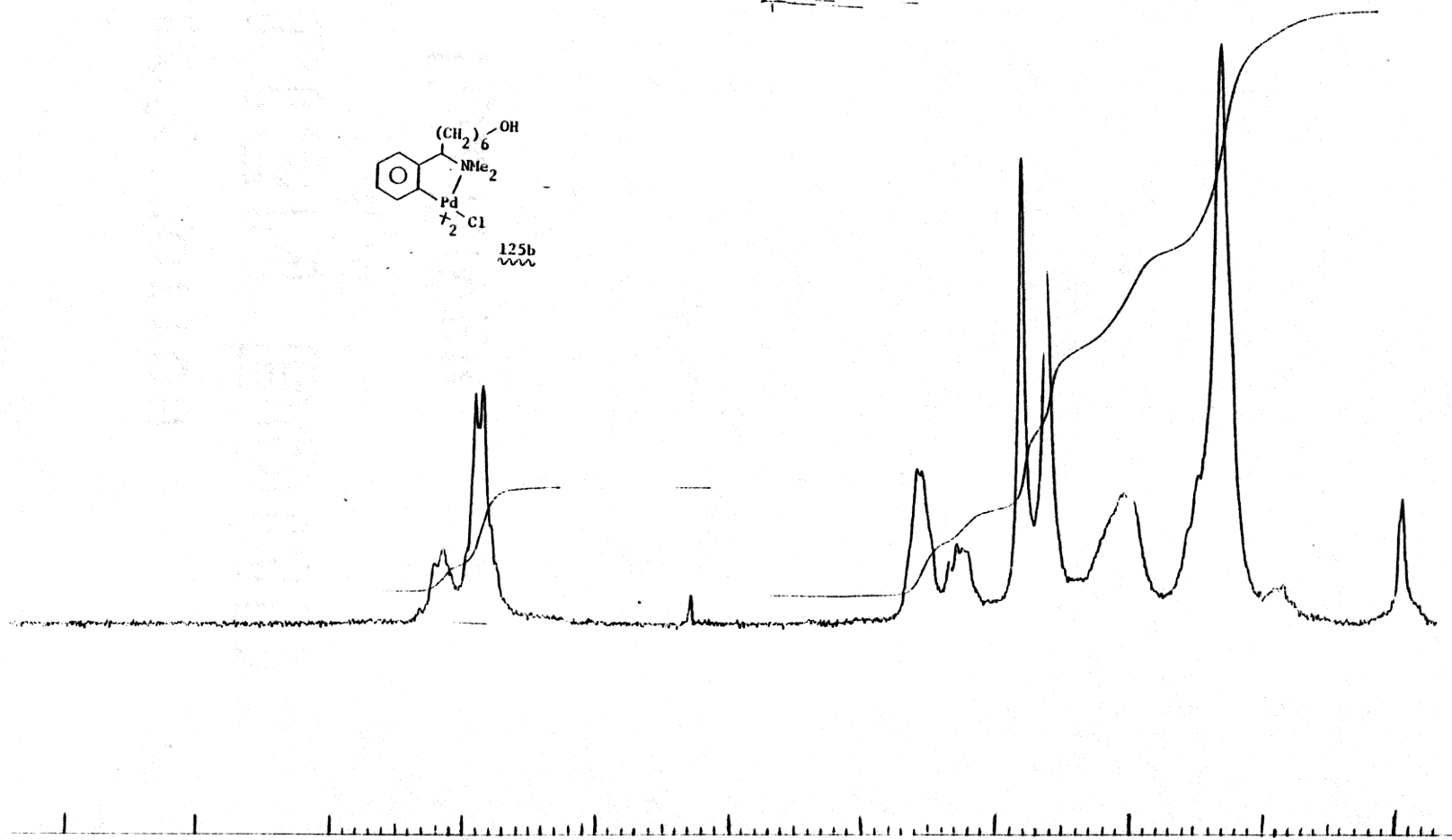


Figure 79a. 90 MHz NMR Spectrum of Palladocycle 125b.

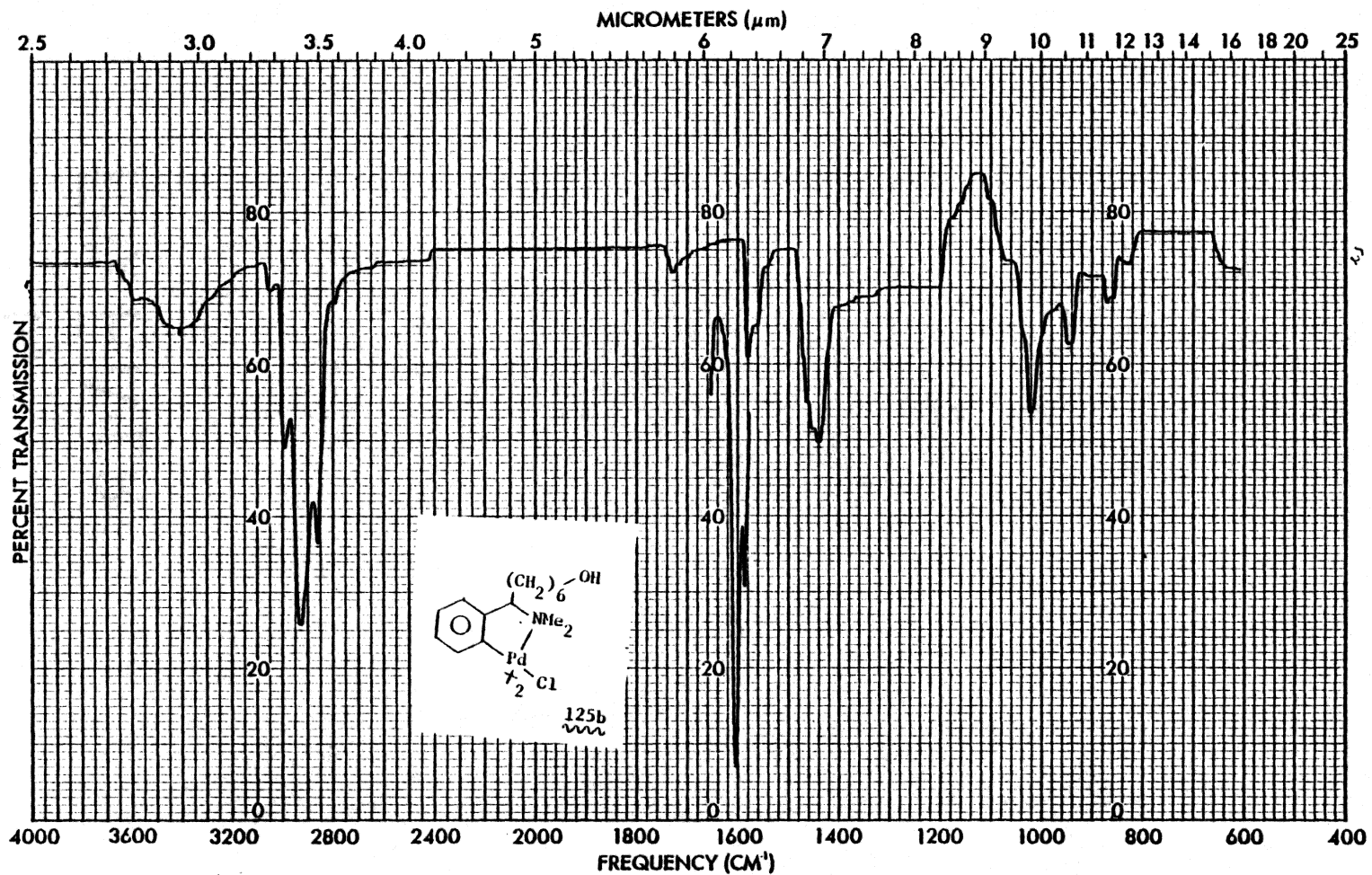


Figure 79b. IR Spectrum of Palladocycle 125b.

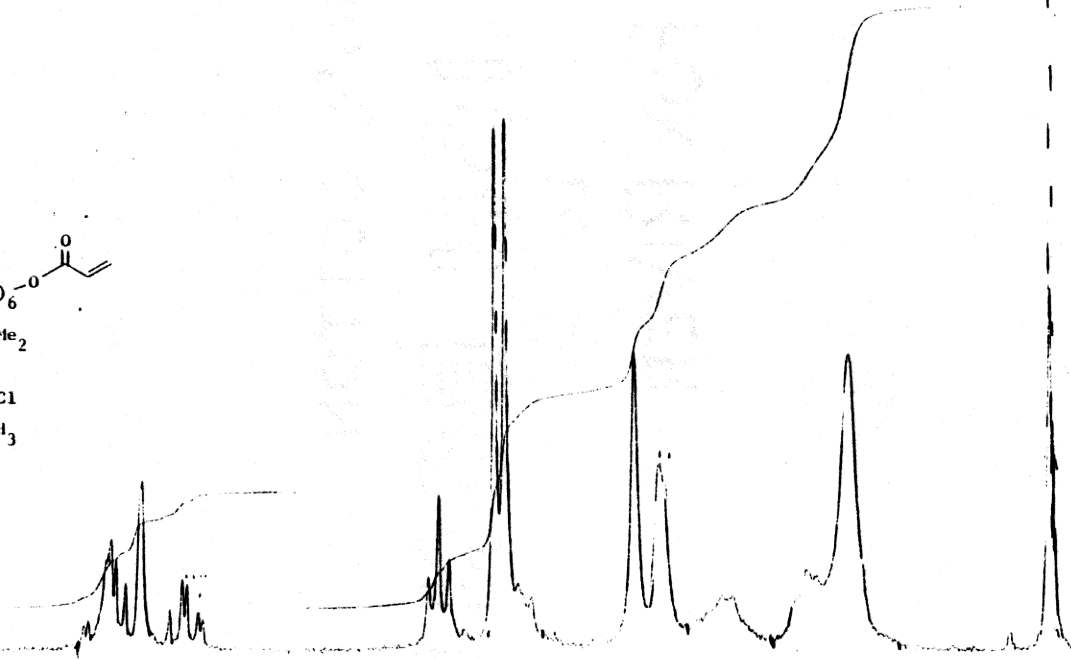
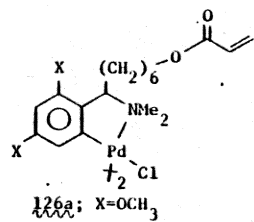


Figure 80a. 90 MHz NMR Spectrum of Palladocycle 126a.

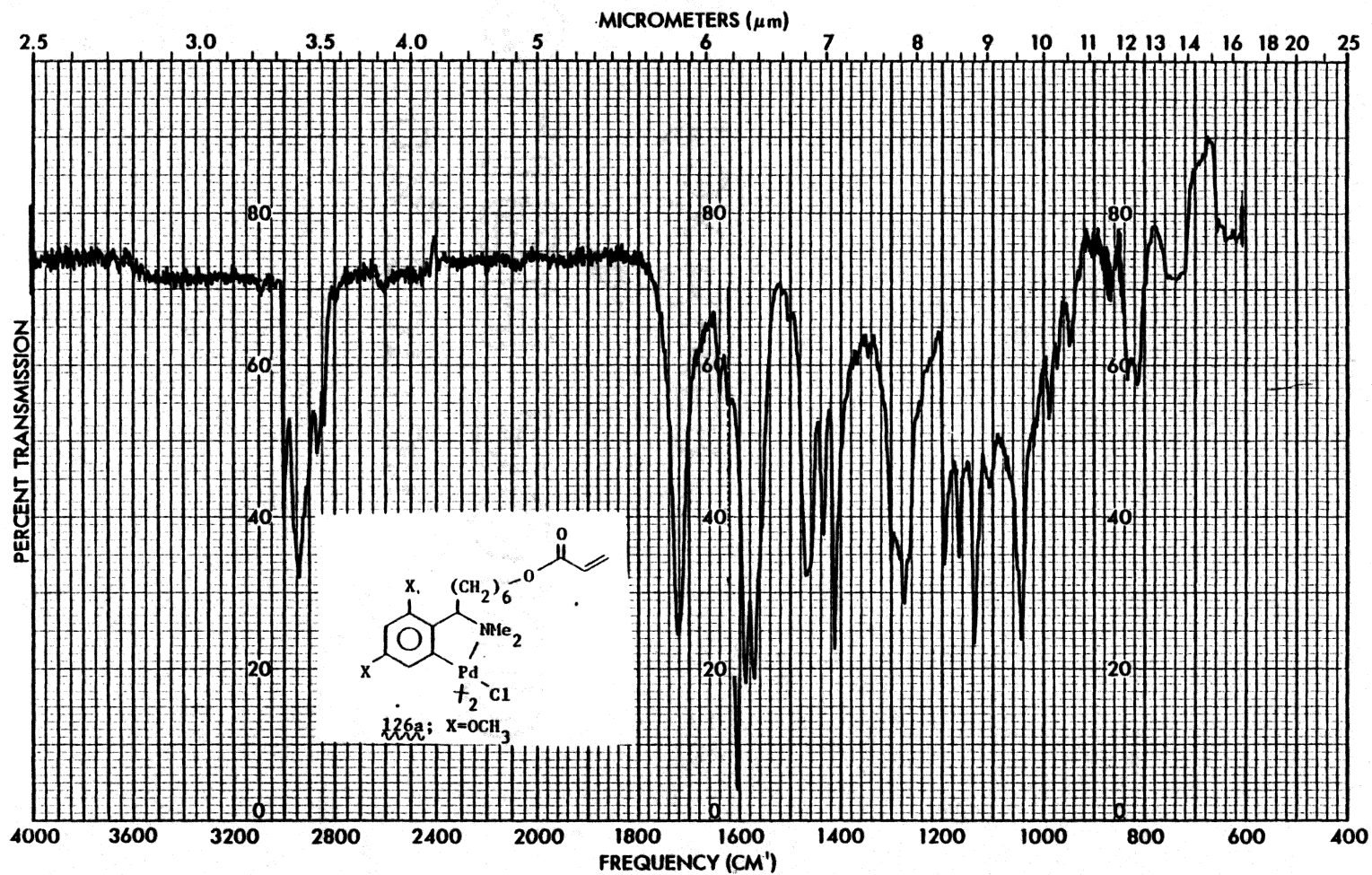


Figure 80b. IR Spectrum of Palladocycle 126a.

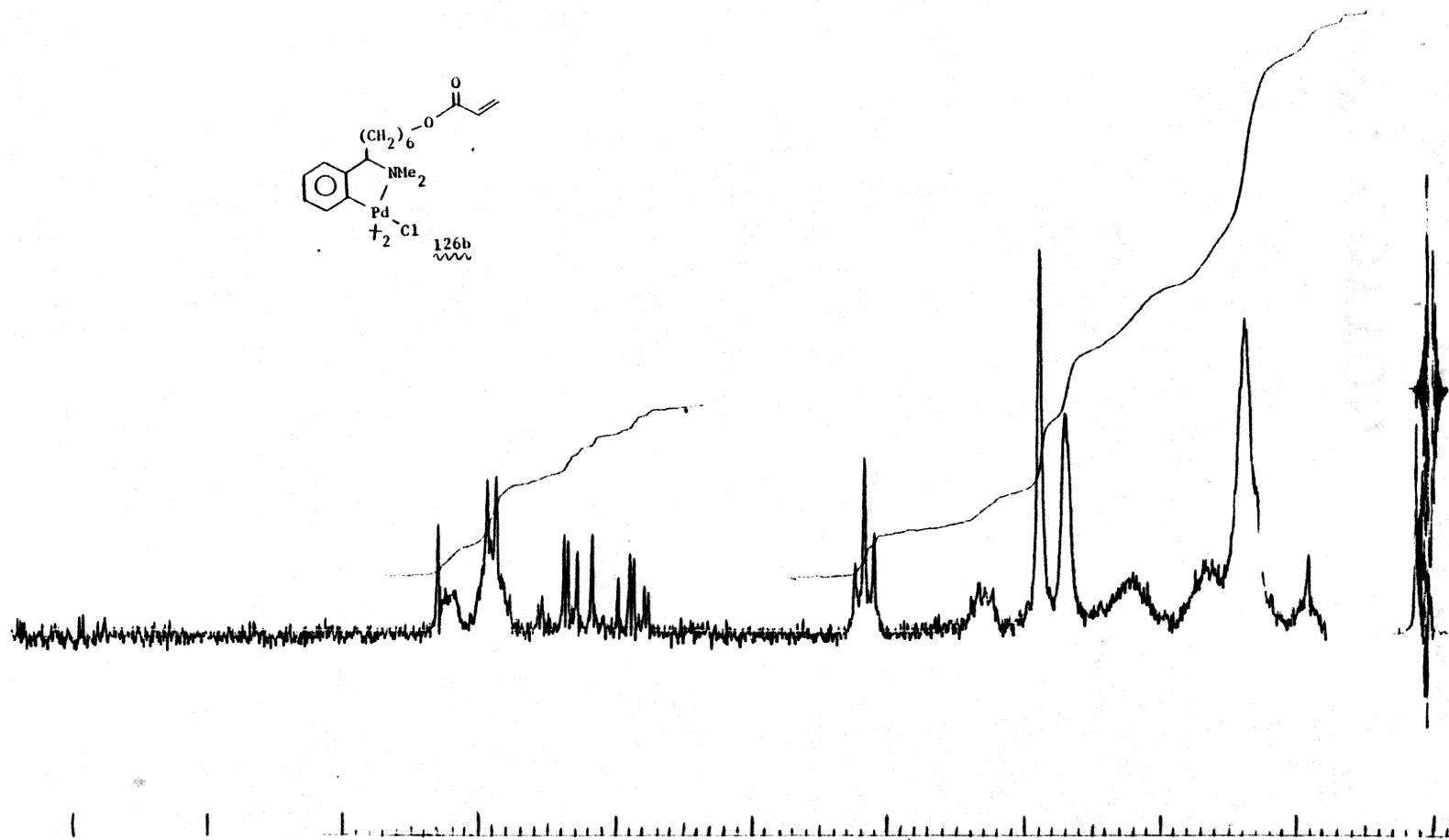


Figure 81a. 90 MHz NMR Spectrum of Palladocycle 126b.

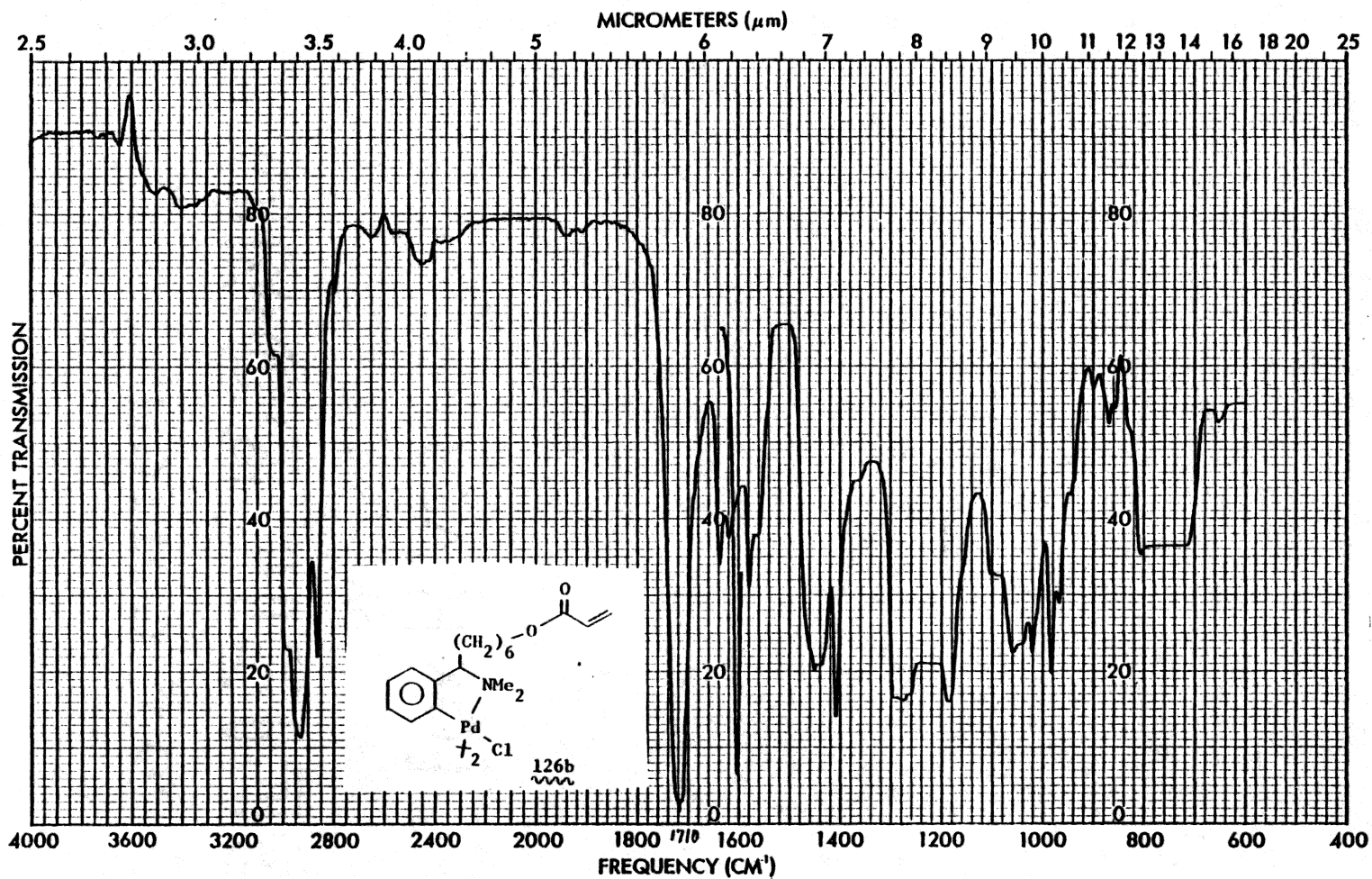


Figure 31b. IR Spectrum of Palladocycle 126b.

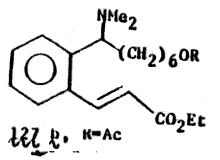
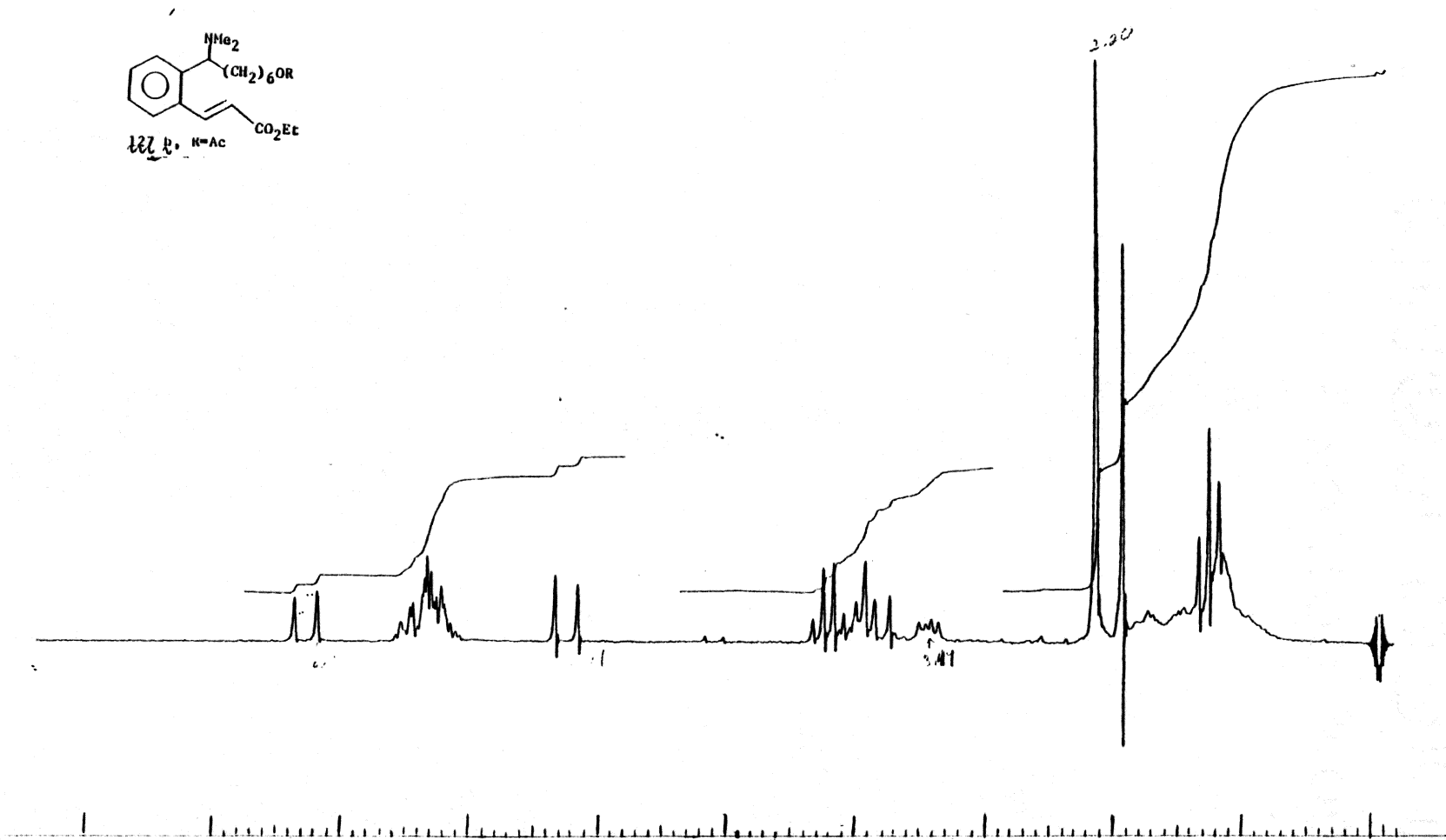


Figure 82a. 90 MHz NMR Spectrum of Cinnamate 127b.

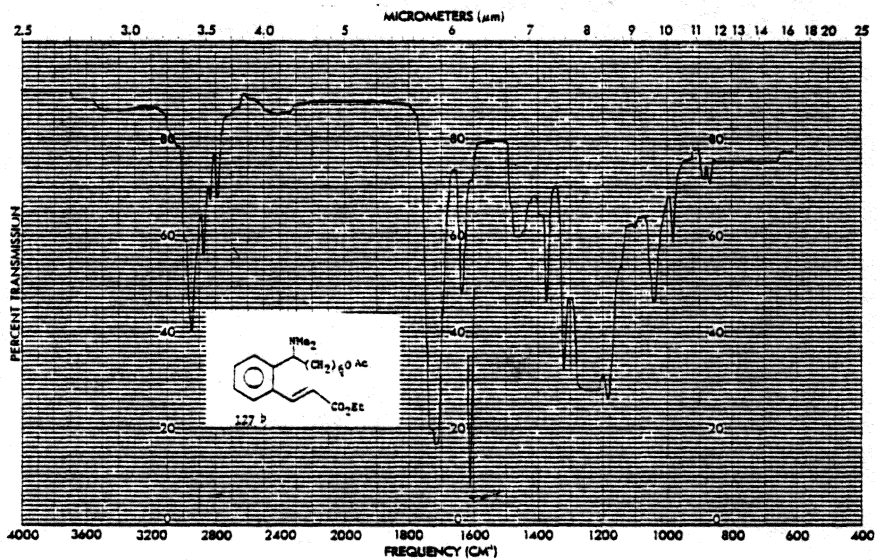


Figure 82b. IR Spectrum of Cinnamate 127b.

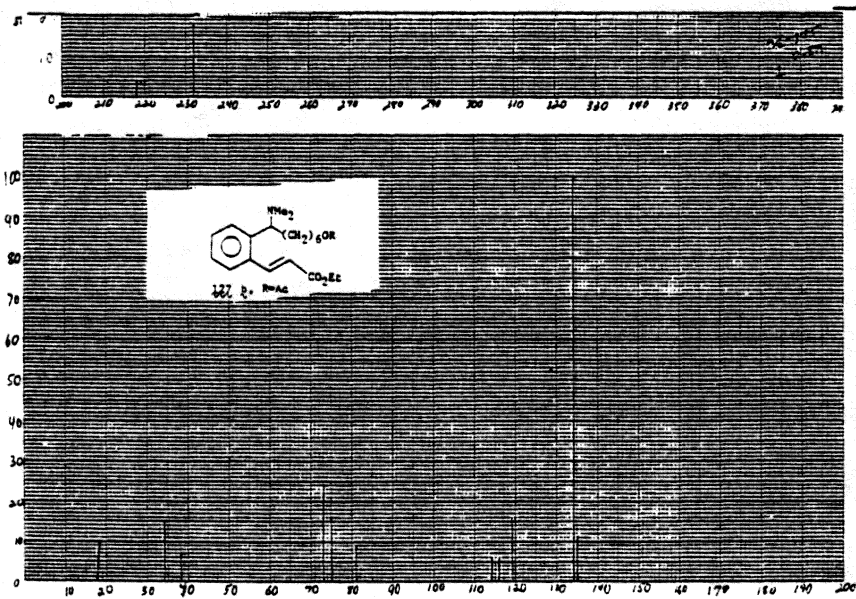
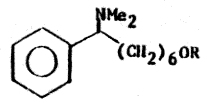


Figure 82c. Mass Spectrum of Cinnamate 127b.



128b, R=Ac

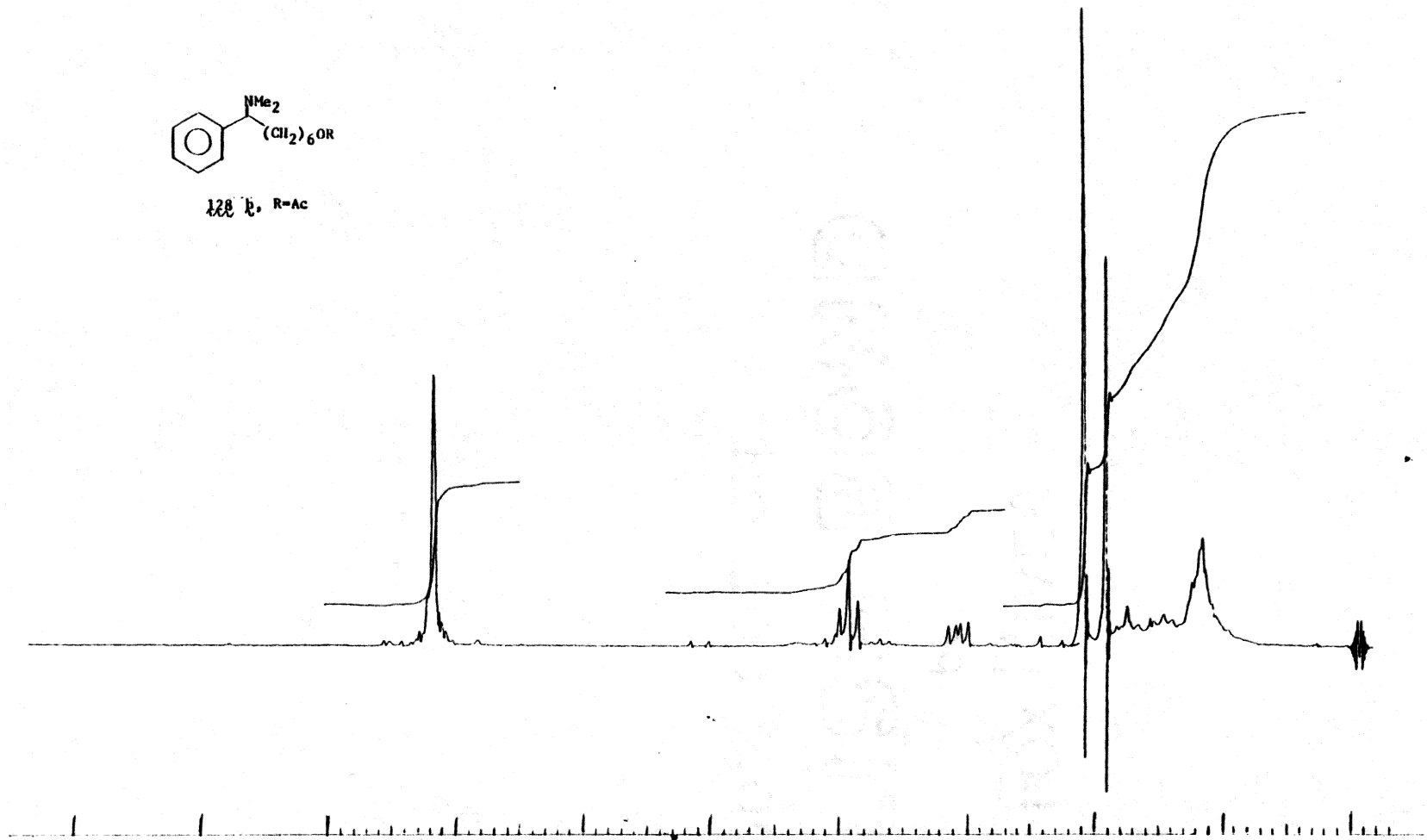


Figure 83a. 90 MHz NMR Spectrum of Amino Acetate 128b.

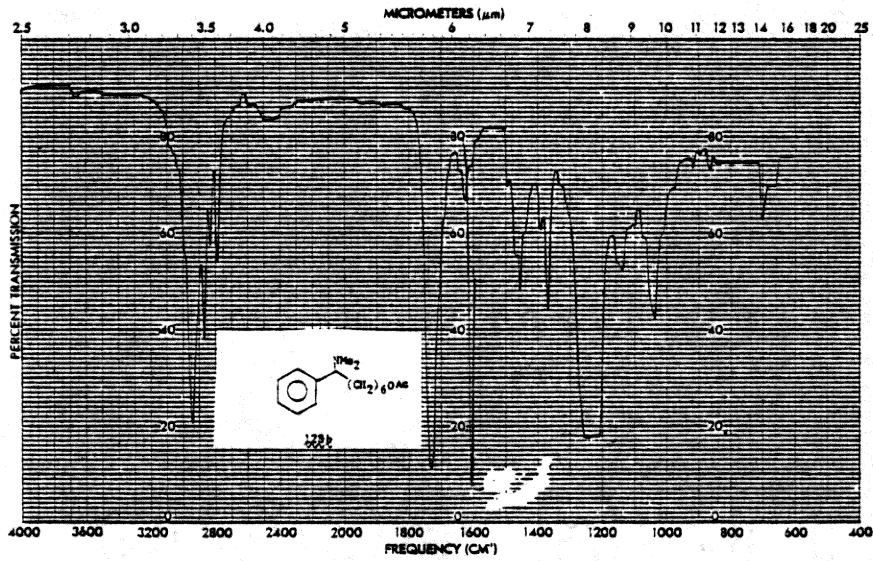


Figure 83b. IR Spectrum of Amino Acetate 128b.

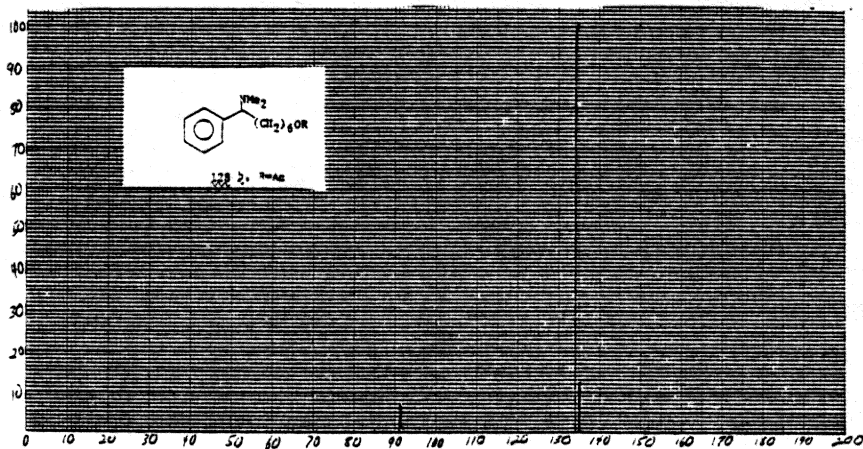
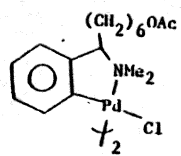


Figure 83c. Mass Spectrum of Amino Acetate 128b.



129

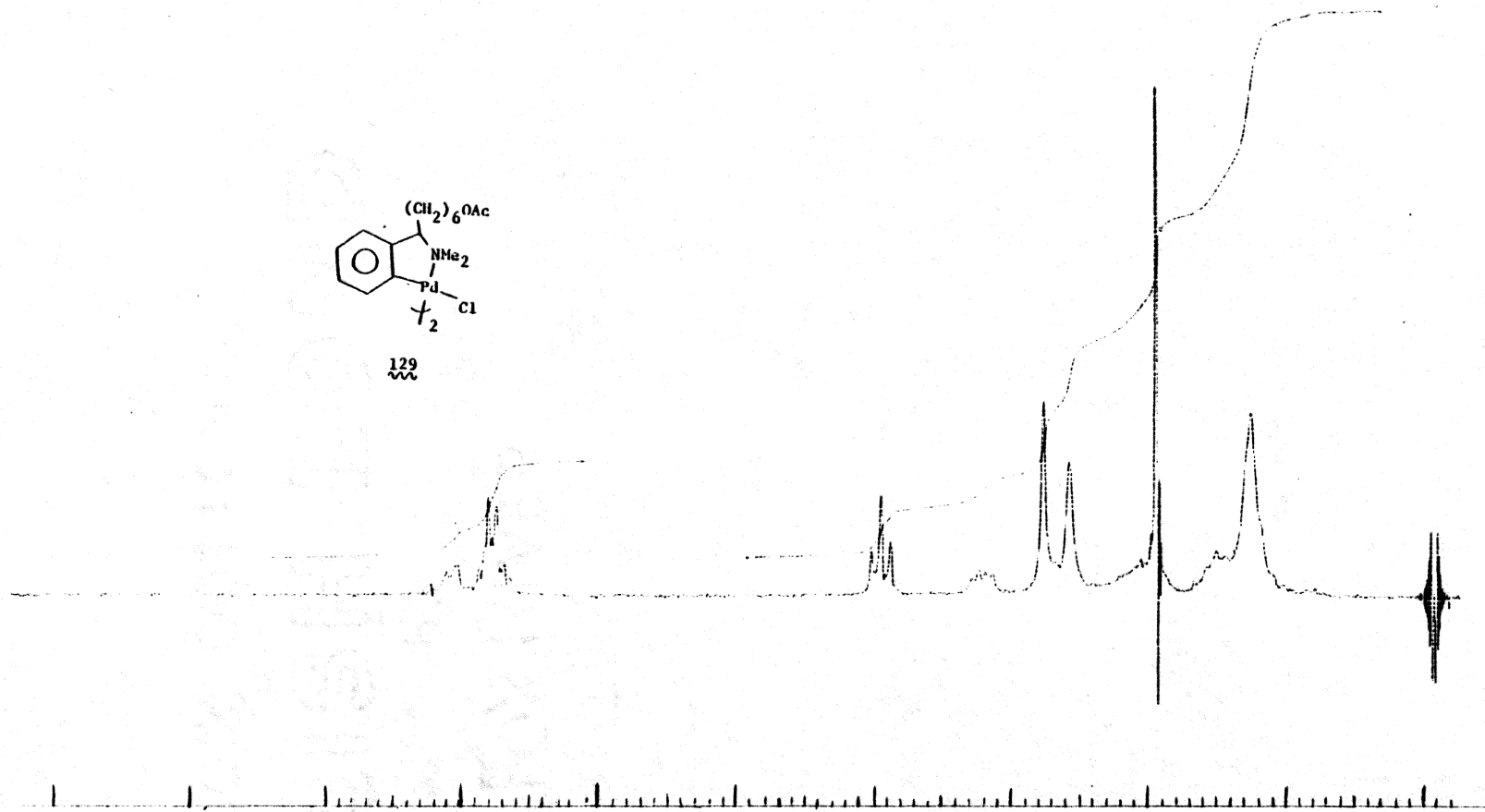


Figure 84a. 90 MHz NMR Spectrum of Palladocycle 129.

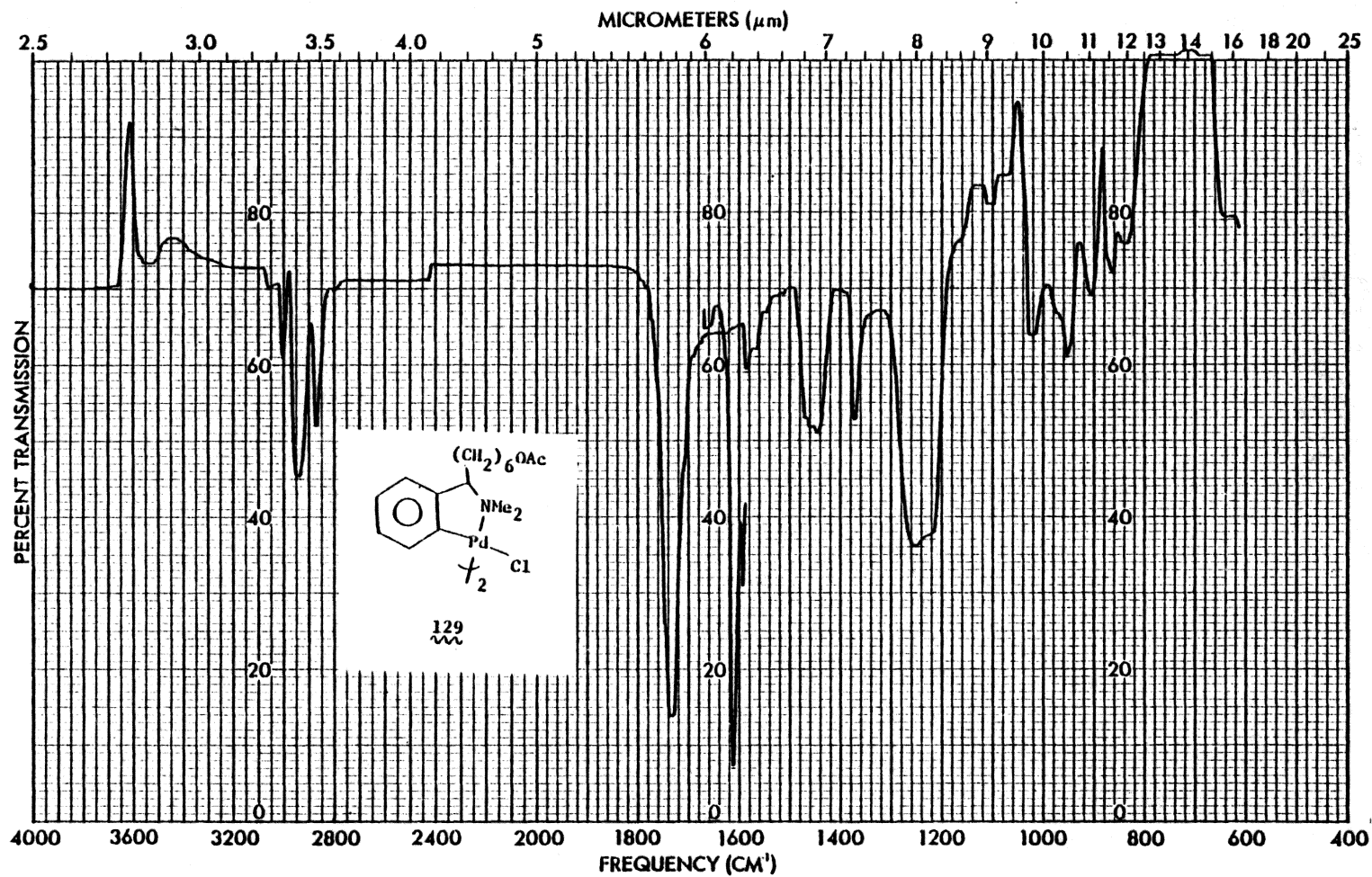


Figure 84b. IR Spectrum of Palladocycle 129.

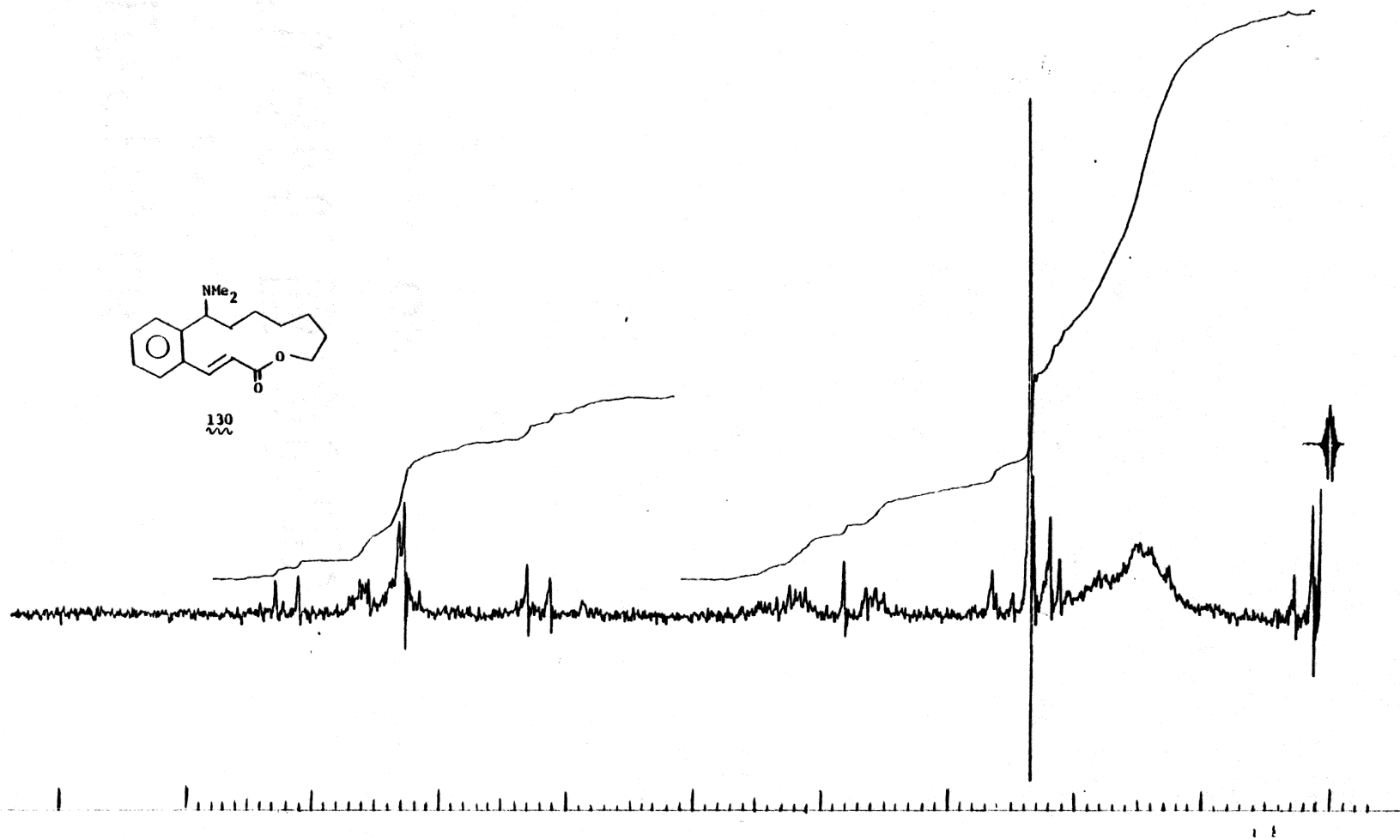


Figure 85a. 90 MHz NMR Spectrum of Lactone 130.

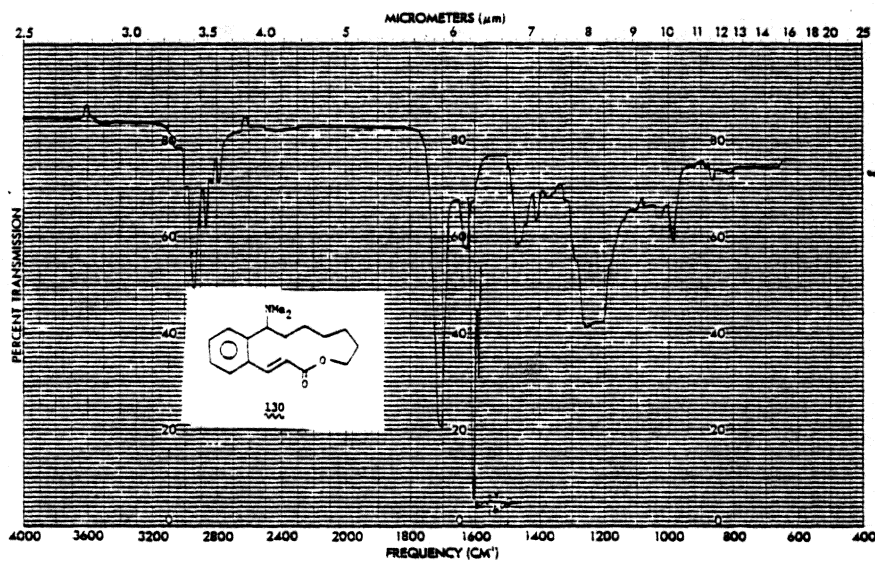


Figure 85b. IR Spectrum of Lactone 130.

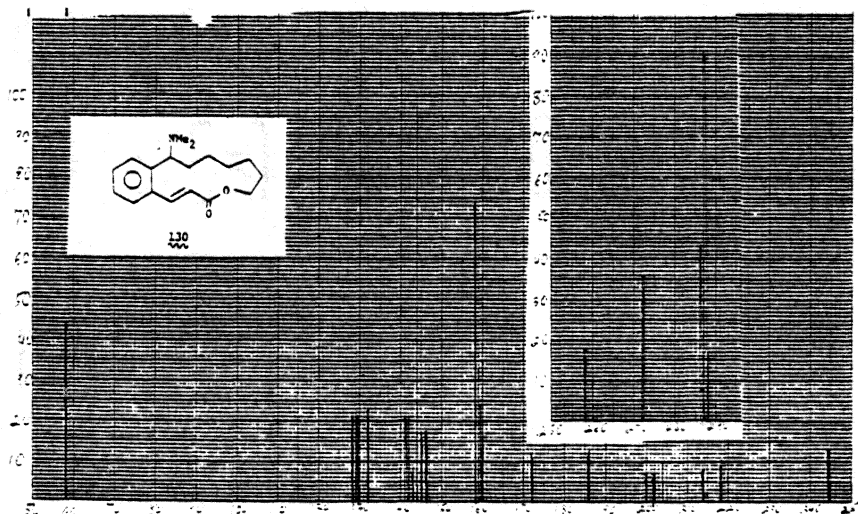
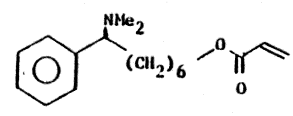


Figure 85c. Mass Spectrum of Lactone 130.



131
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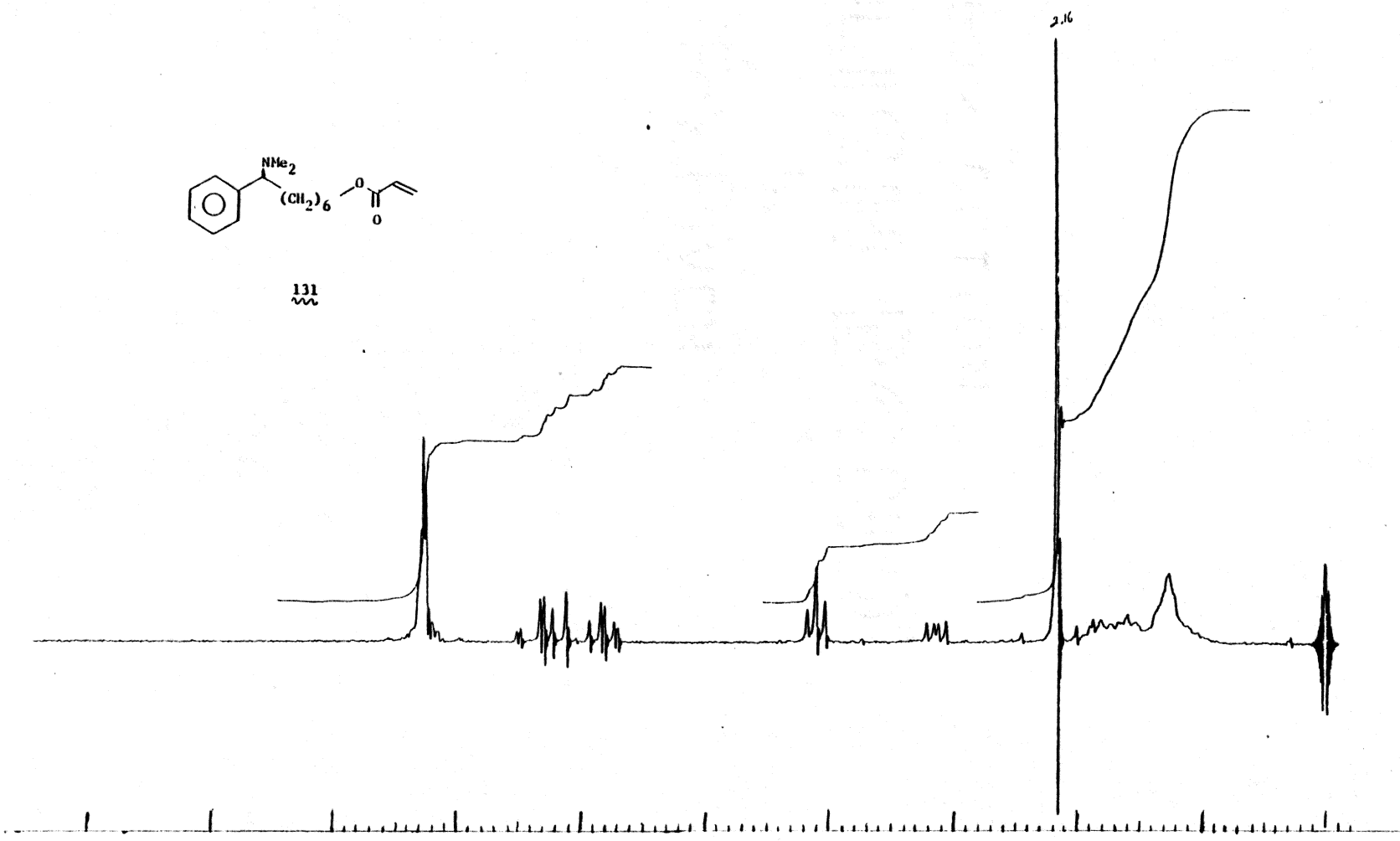


Figure 86a. 90 MHz NMR Spectrum of Amino Acrylate 131.
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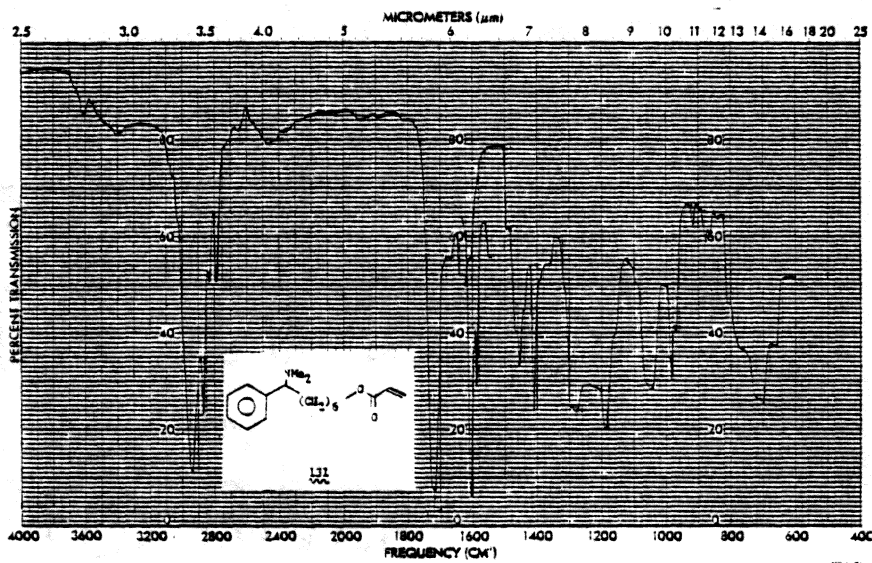


Figure 86b. IR Spectrum of Amino Acrylate 131.

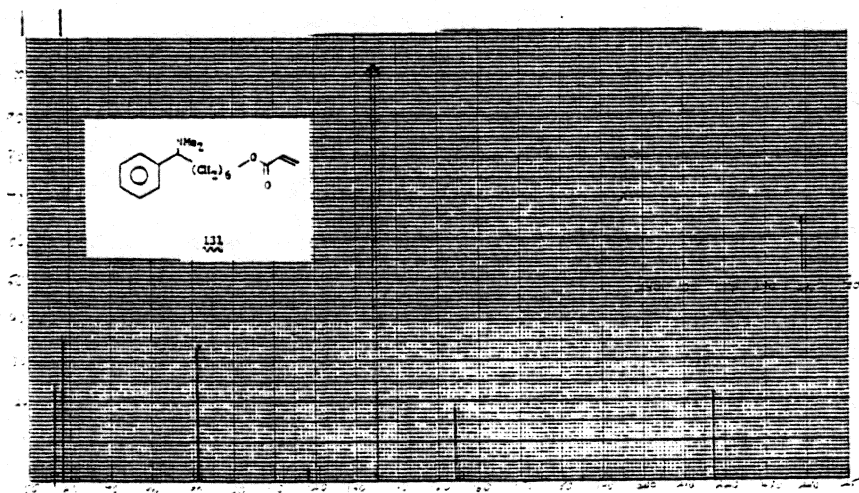


Figure 86c. Mass Spectrum of Amino Acrylate 131.

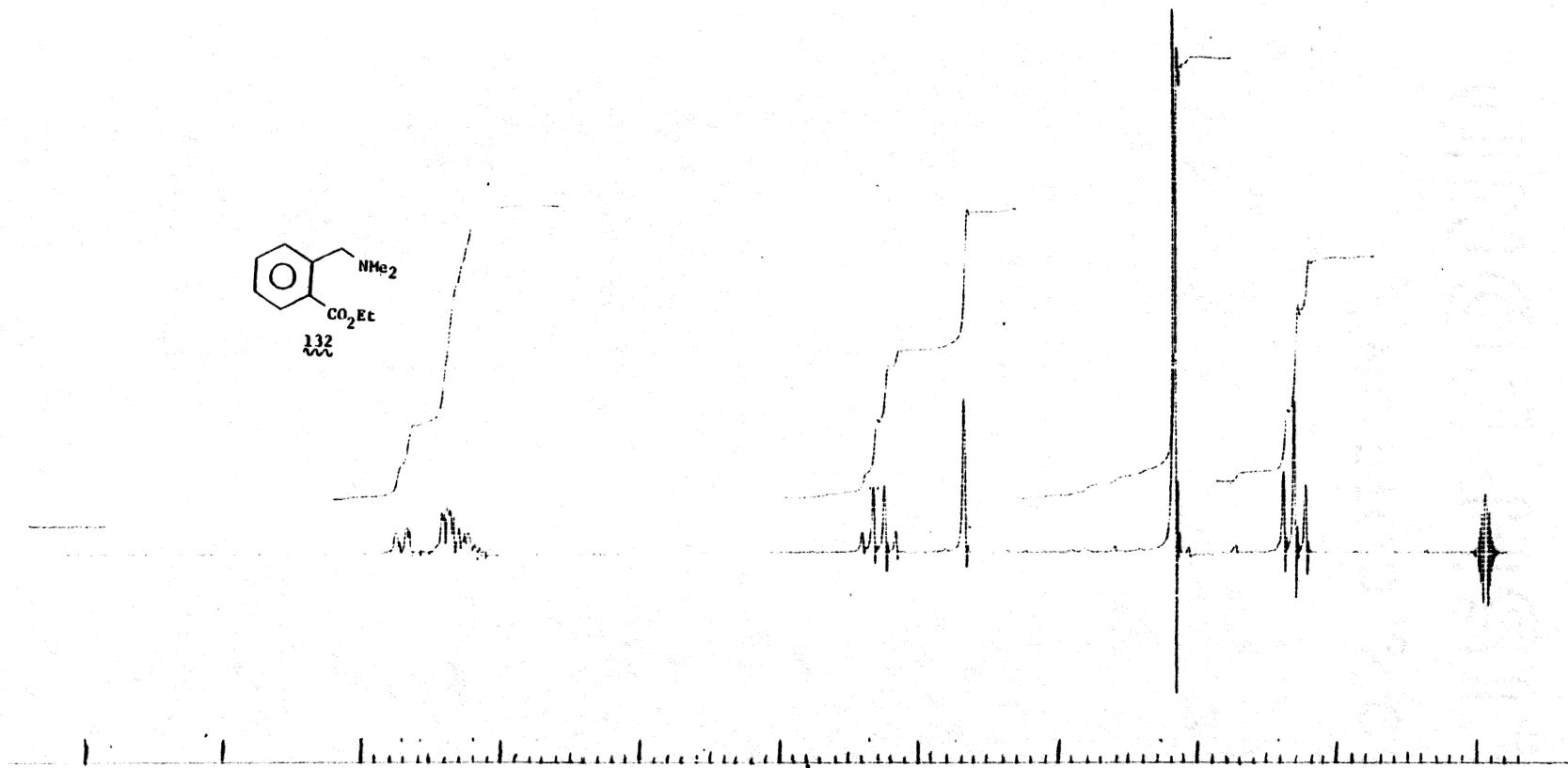


Figure 87a. 90 MHz NMR Spectrum of Amino Ester 132.

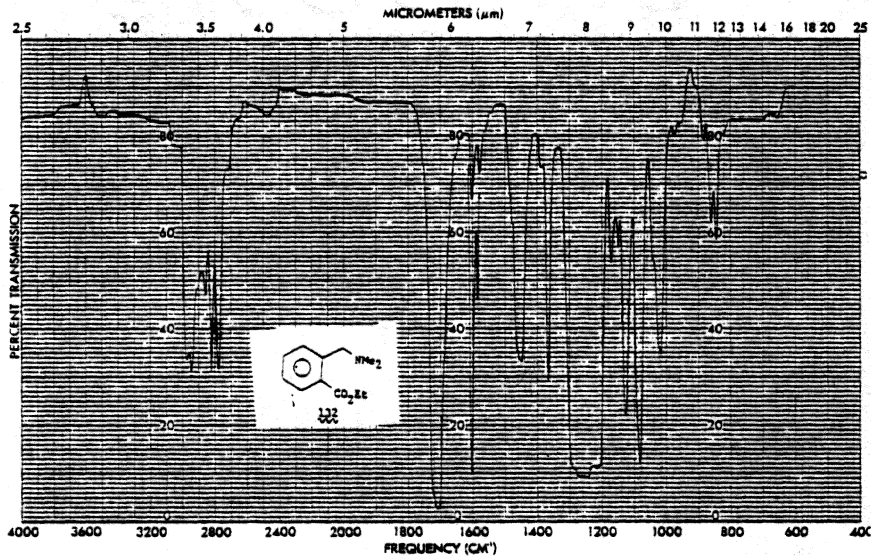


Figure 87b. IR Spectrum of Amino Ester 132.

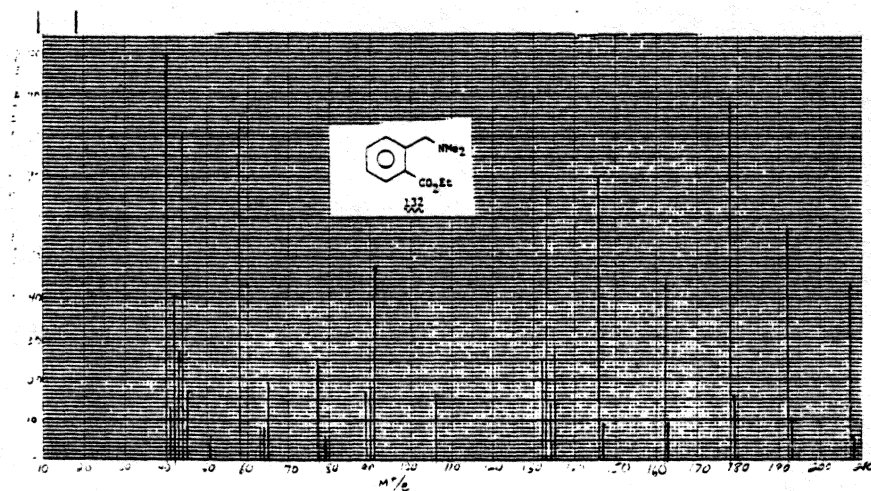


Figure 87c. Mass Spectrum of Amino Ester 132.

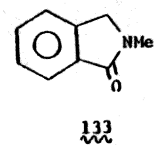
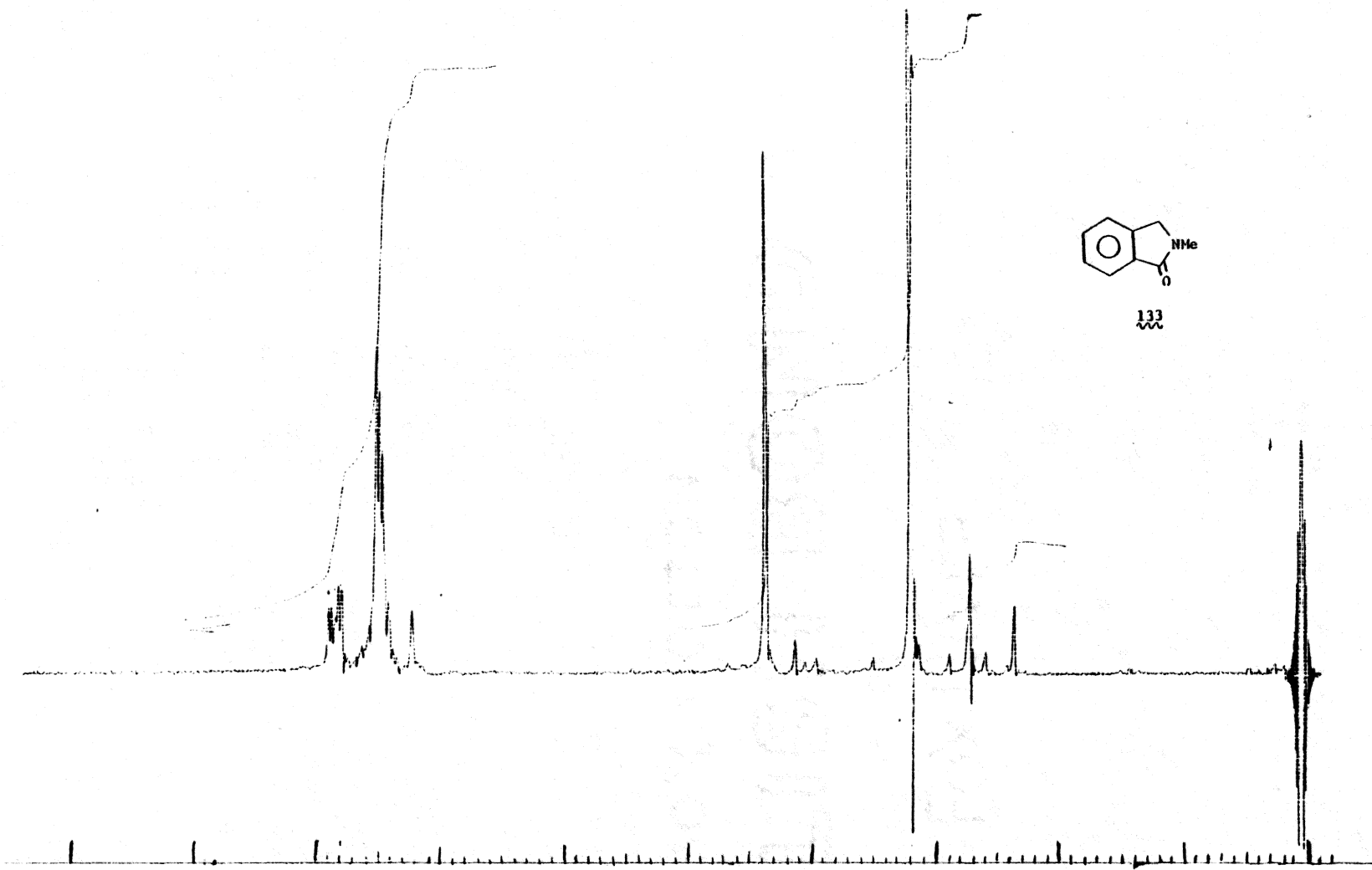


Figure 88a. 90 MHz NMR Spectrum of Lactam 133.

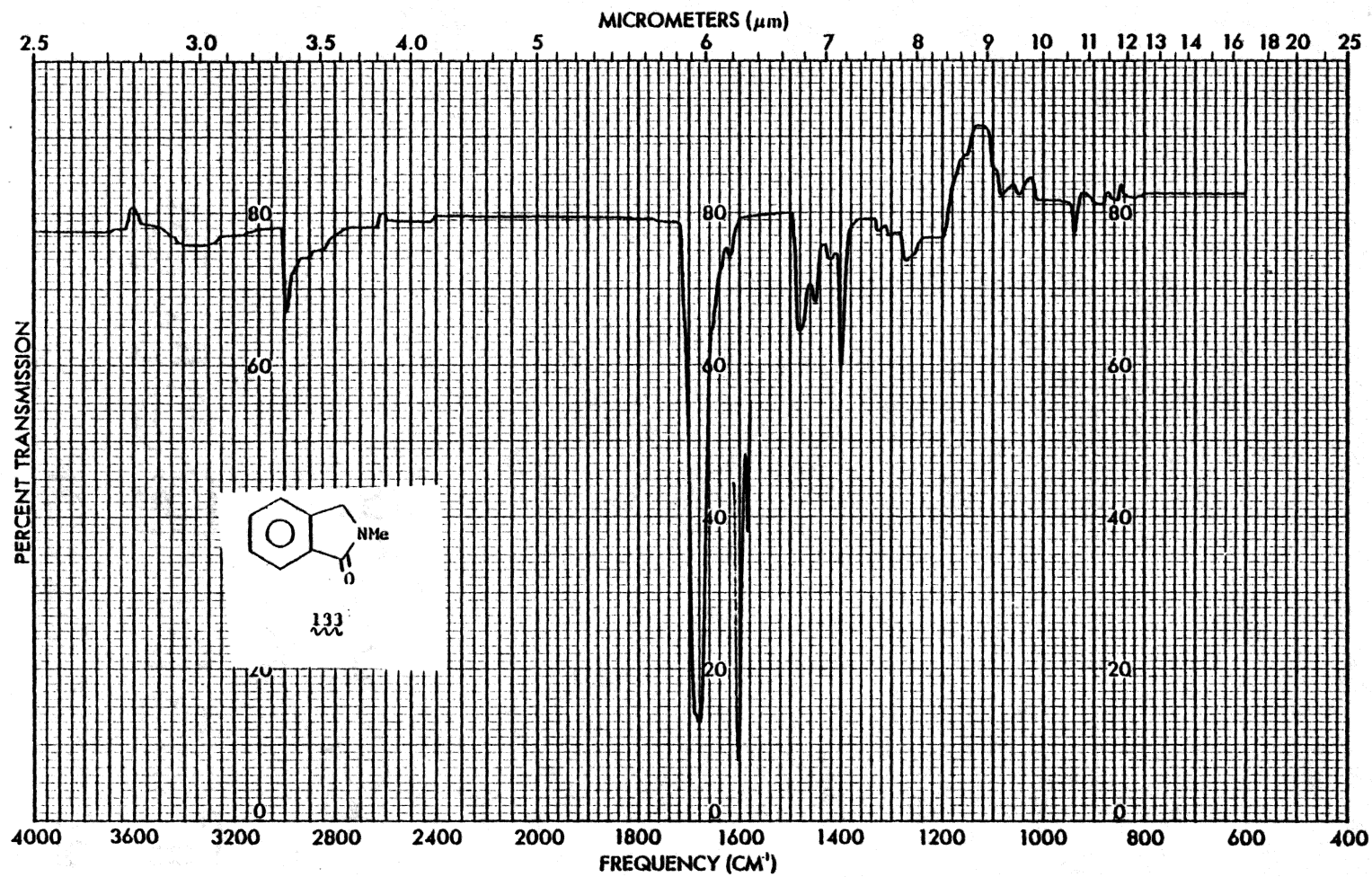


Figure 88b. IR Spectrum of Lactam 133.

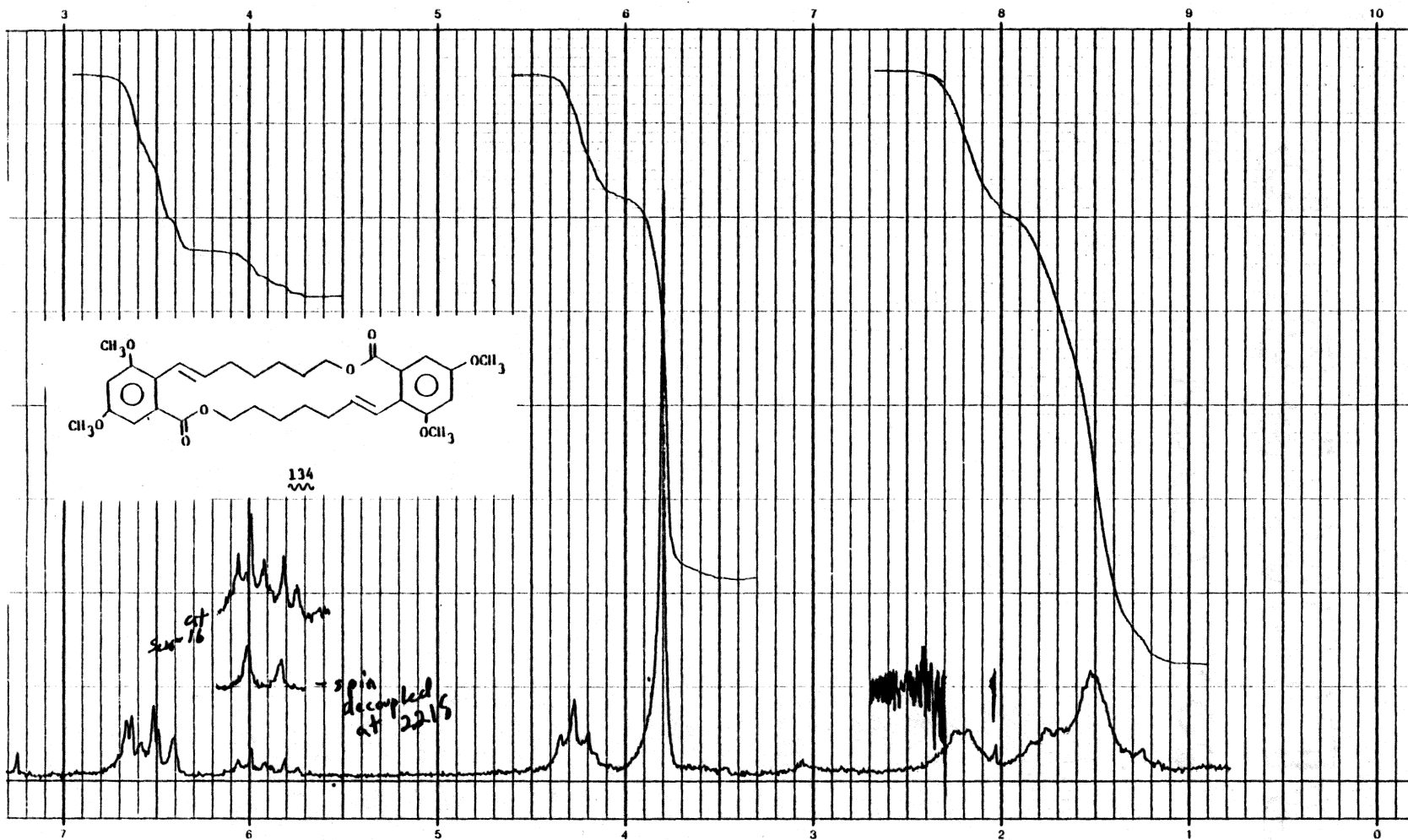


Figure 89a. 90 MHz NMR Spectrum of Lactone 134.

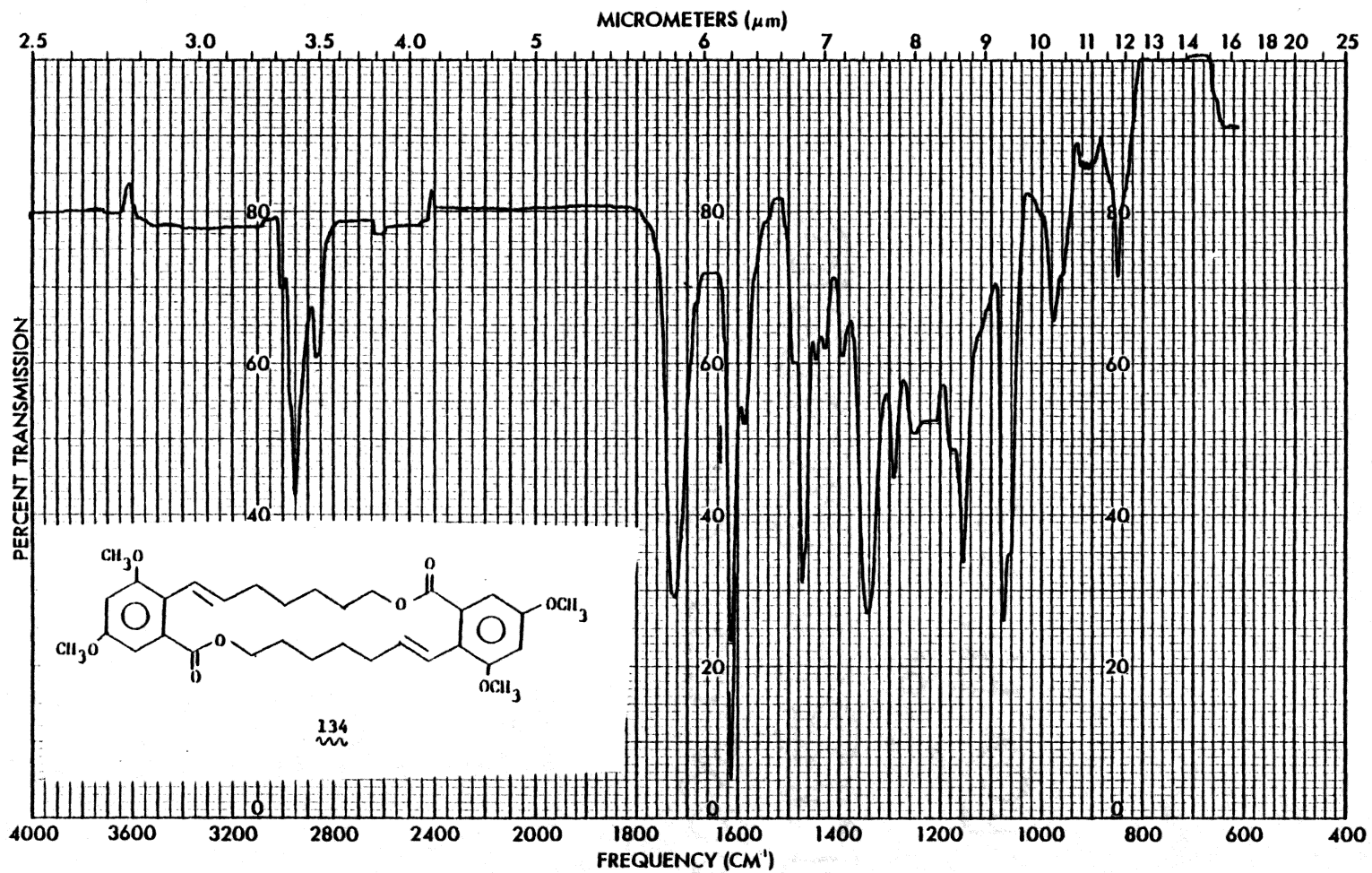


Figure 89b. IR Spectrum of Lactone 134.

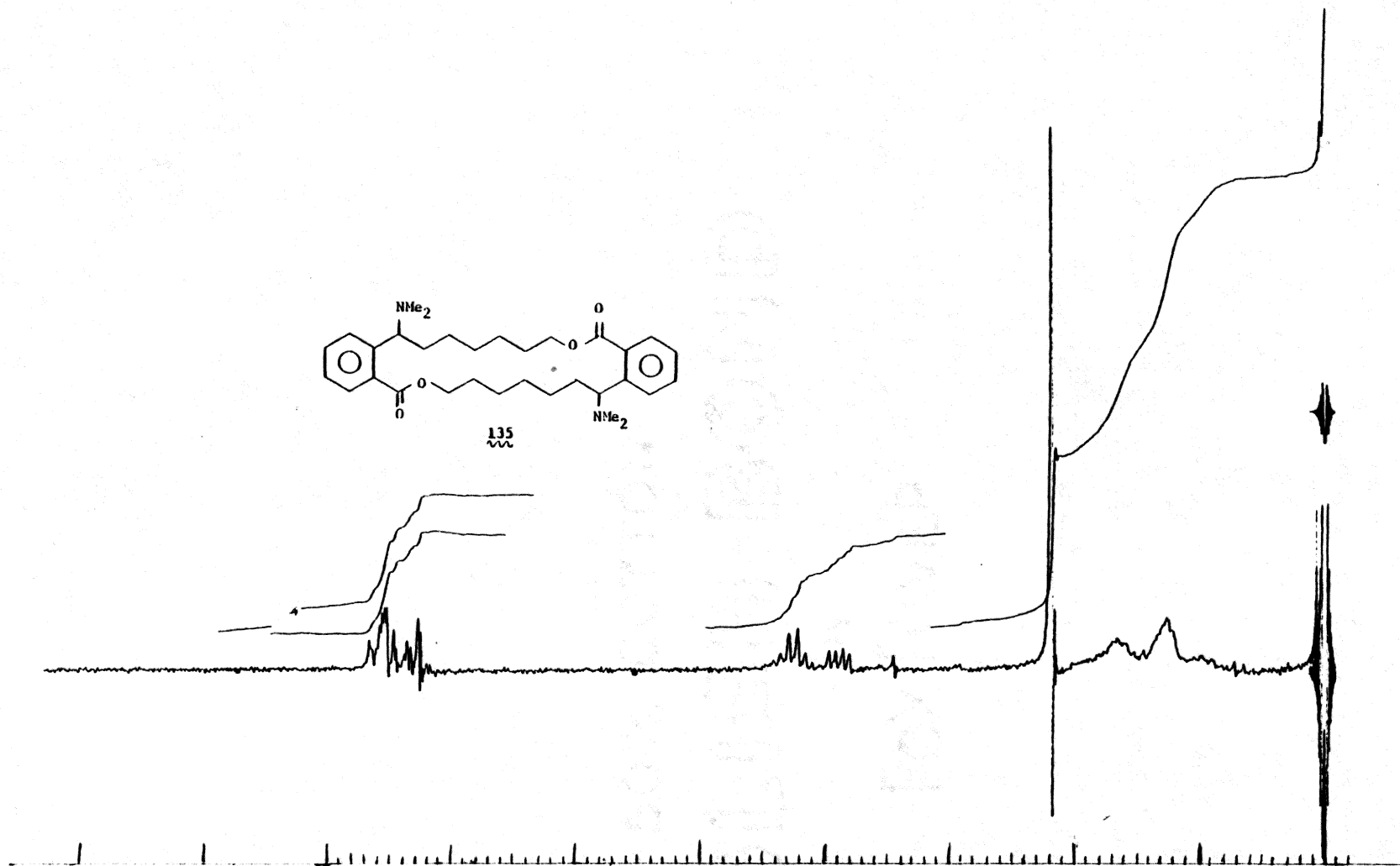


Figure 90a. 90 MHz NMR Spectrum of Lactone 135.

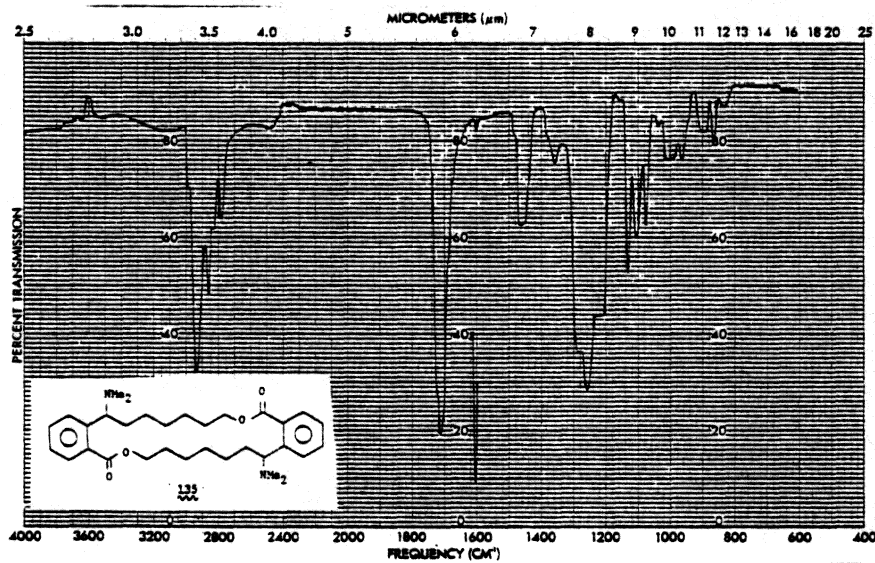


Figure 90b. IR Spectrum of Lactone 135.

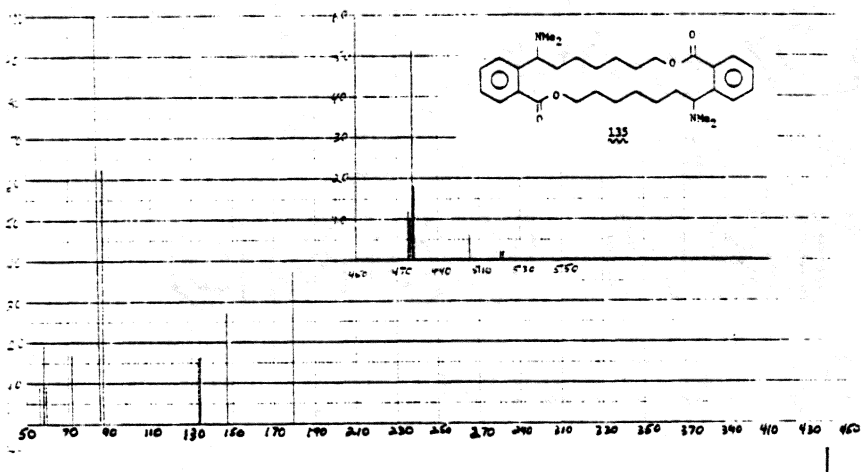


Figure 90c. Mass Spectrum of Lactone 135.

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PALLADIUM ASSISTED RING CLOSURES

by

Joseph Robert Zoeller

(ABSTRACT)

The carbopalladation process has been extended to form carbocyclic systems. The intramolecular version of the carbopalladation process stereospecifically generates fused bicyclic palladium complexes upon treatment of cis and trans methyl-S-methyl-2-carbomethoxy-7-thio-hept-5-en-1-oate with lithium tetrachloropalladate and potassium tert-butoxide in moderate yield. The cyclization of the corresponding amines, cis and trans methyl-N,N-dimethyl-2-carbomethoxy-7-amino-hept-5-en-1-oate, proceeded more rapidly and stereospecifically generate stable fused bicyclic palladium complexes in excellent yield. NMR studies revealed the bicyclic complexes generated in this manner resulted from a trans addition of palladium and the carbon nucleophile. Direct reduction with sodium borohydride (for sulfides) or hydrogen (for amines) resulted in cyclopentyl sulfides and amines in good to excellent yields. The reaction was extended to ketoesters and homoallylic amines to give a variety of cyclopentanoids.

Extensions to larger ring systems yielded unstable palladium complexes. These complexes underwent oxidation at the amine functionality upon warming. Hydrolysis of the intermediate complexes yielded cyclohexyl and cycloheptyl aldehydes whereas reduction with hydrogen in the presence of molecular sieves gave cyclohexyl and cycloheptyl amines

in excellent yields.

Attempts at utilizing olefin and carbon monoxide insertions to form macrocycles proceeded poorly, if at all.