This is to certify that the

dissertation entitled

Studies Toward the Stereoselective Construction of Steroidal Sidechains Using a Novel Reaction of Dichloroketene With Epoxy Olefins
Part II: Cyclobutanones as Precursors for Reactive Dienes

presented by

Usha V. Ramesh

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

William Reusch
Major professor

Date 11/19/87

PART I

STUDIES TOWARD THE STEREOSELECTIVE SYNTHESIS OF STEROIDAL SIDE CHAINS BY A NOVEL REACTION OF DICHLOROKETENE WITH EPOXY OLEFINS.

PART II

STUDIES OF CYCLOBUTANONES AS PRECURSORS FOR REACTIVE DIENES

By

USHA V. RAMESH

A DISSERTATION

Submitted to

Michigan State University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1988.

ABSTRACT

PART I

STUDIES TOWARD THE STEREOSELECTIVE SYNTHESIS OF STEROIDAL SIDE CHAINS BY A NOVEL REACTION OF DICHLOROKETENE WITH EPOXY OLEFINS.

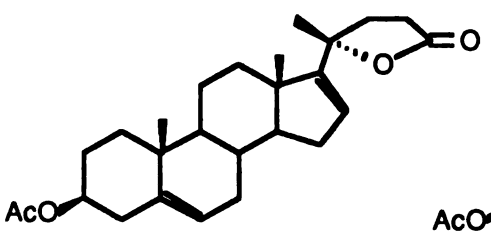
PART II

STUDIES OF CYCLOBUTANONES AS PRECURSORS FOR REACTIVE DIENES.

By

USHA V. RAMESH.

16α,17α - epoxypregnenolone acetate gave the corresponding methylene derivative **4** on Wittig reaction. Reaction of **4** with dichloroketene yielded (20R) - 23,23 - dichloro - 5- cholen - 24,20 - lactone - 3β - acetate **6**, via a novel and unprecedented rearrangement. Dechlorination of **6** with zinc gave (20R) - 5 - cholen - 24,20 - lactone - 3β - acetate, **8**. Selective dechlorination of **6** with tributyltin hydride gave (20R) - 23α - chloro - 5 - cholen - 24,20 - lactone - 3β - acetate.



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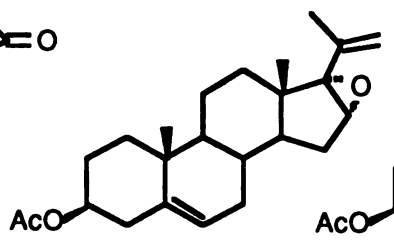

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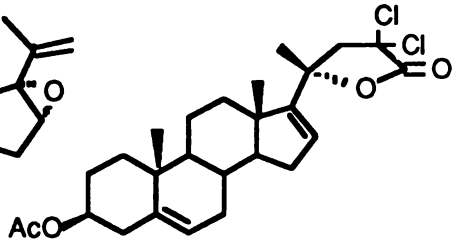

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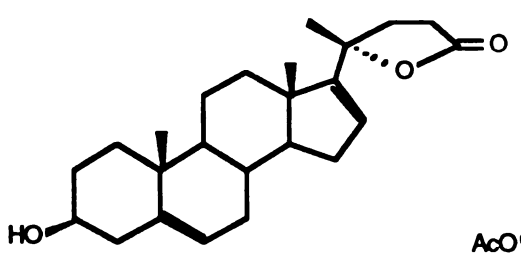
Reaction of **4** with dichloroketene gave the allyl chloride **12** as an early product. Further reaction of allyl chloride **12** with dichloroketene gave the

five membered lactone **6**. The mechanism of this rearrangement reaction was explored. There is strong evidence of the intermediacy of seven membered lactone **5** in the conversion of **4** to **6**. This unique 1,3 - oxygen shift of lactones such as **5** was confirmed by preparation of a similar compound **20** and study of its behaviour under conditions similar to the conversion of **4** to **6**. Compound **20** was prepared from the allyl chloride **12** by an alkylation with dimethyl malonate. The seven membered lactone of **20** underwent a rearrangement via a 1,3 - suprafacial oxygen shift on treatment with dichloroketene. On hydrolysis and decarboxylation of the product **26**, the lactone **28** was obtained. This compound was identical in every respect to the compound obtained by hydrolysis of **8.**



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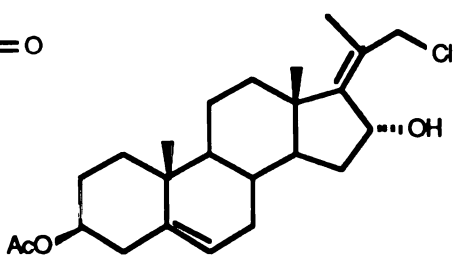

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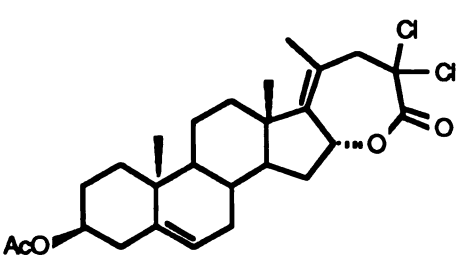

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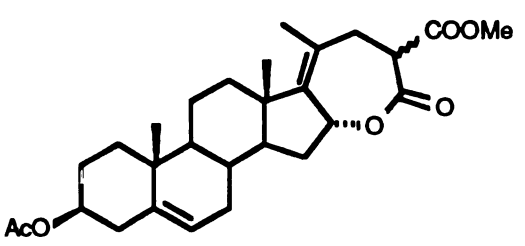

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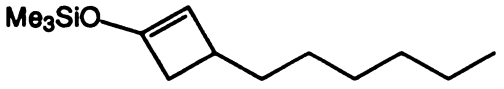
PART II

Cyclobutanones were prepared in high yield utilizing the $2\pi + 2\pi$ cycloaddition reaction of dichloroketene to olefins. These were converted to

the corresponding silylenol ethers in almost quantitative yields. The silylenol ethers were isolated and characterized. Thermolysis of silylenol ether **4** was accomplished and the diene thus generated, was trapped by benzophenone to yield a Diels Alder adduct. α,β - unsaturated ester **9**, was prepared in six steps from 3,3 - dimethyl glutaric acid.



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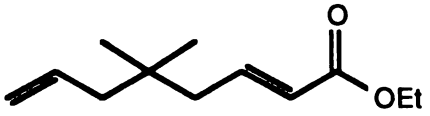

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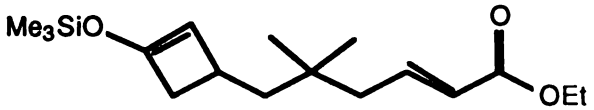

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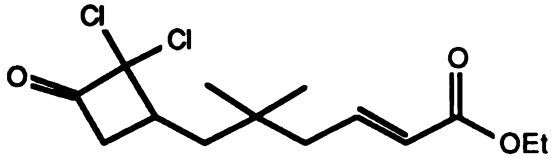

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Reaction of **9** with dichloroketene yielded the cycloadduct **18**. Cyclobutanone **19** was selectively converted to the silylenol ether **11**. Thermolysis of **11** failed to yield the expected Diels Alder adduct. Attempted Lewis acid catalyzed intramolecular Michael reaction of **11** also failed to yield the expected Michael adduct resulting instead in the recovery of cyclobutanone **19. 11** underwent intermolecular Michael reaction with benzylidene acetophenone (chalcone) when activated by Lewis acids.

DEDICATION

to

My father, whose love and support made this possible

and

My husband Ramesh, whose love and understanding makes it all worthwhile

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation to Professor William H. Reusch for his guidance and encouragement throughout the course of this work.

I am very grateful to my sister Shanta, brother-in-law Raja and nephew Prakash for their help, support and warm hospitality. They opened their home to me and made my stay in Lansing an extremely pleasant and happy one. I could not have made it without their help. I would also like to thank my parents Lakshmi and R.V. Iyer for being there .... all the time. They gave me the oppurtunities and freedom that they never had. Special thanks to the Reusch group, especially Balan and Ed for being good friends and great coworkers.

My warmest thanks and appreciation to Ramesh, for his endless patience and understanding over the last two years. Without his love, support and encouragement, this work would not have been possible. He was always there to cheer me up and motivate me when things got tough. Finally I would like to thank Michigan State University for financial assistance without which my stay in this country would have been impossible.

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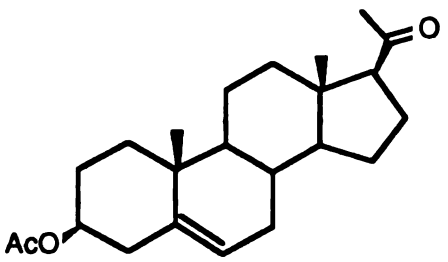
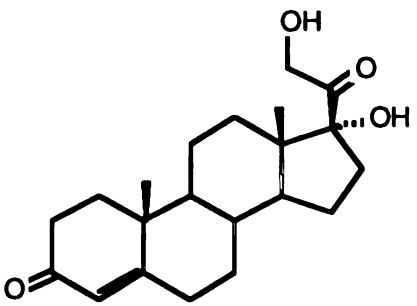
PART II

INTRODUCTION.

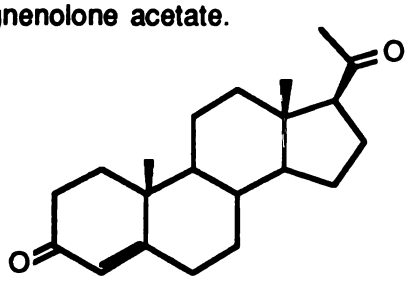
The total synthesis of steroids has long represented a major challenge to synthetic chemists, and they have responded with many elegant and practical approaches to this ring system[1]. The introduction of characteristic sidechains, however, has received much less attention in comparison. Early work on side chain construction focussed on simple ones, such as the two carbon side chains of the corticosteroids and pregnanes. (fig 1).



Pregnenolone acetate.



Cortisone



Progesterone

Figure 1

This was largely due to the remarkable therapeutic effects of these steroids. Furthermore, knowledge about the more elaborate side chains

present in other systems was increasing rapidly. With the isolation and characterization of metabolites of cholesterol and other sterols; insect hormones; Vitamin D metabolites; brain sterols; fungal sex hormones and marine sterols, an entirely new era opened up in the steroid chemistry. There was widespread interest and activity in the study of more elaborate side chains. (fig 2).

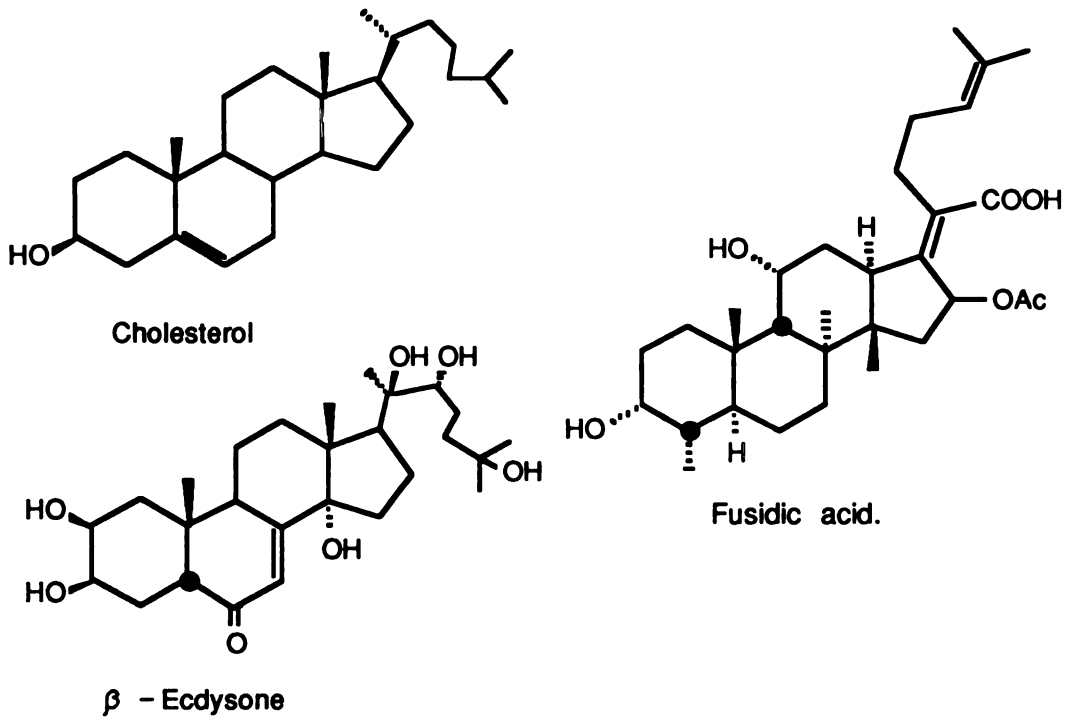


Figure 2.

In addition to these commonly found 8 carbon steroid side chains, several other interesting steroids with modified side chains have also been reported. (fig 3). Some examples are Withaferin A[2] and other Withanolides which have significant antitumor activity[3]; the plant growth promoters brassinolide[4] and castasterone[5]; the sex stimulating steroid antheridiol[6] of the water mold Achlya and all types of marine

sterols[7]. This has stimulated the search for stereoselective synthesis of steroid side chains.

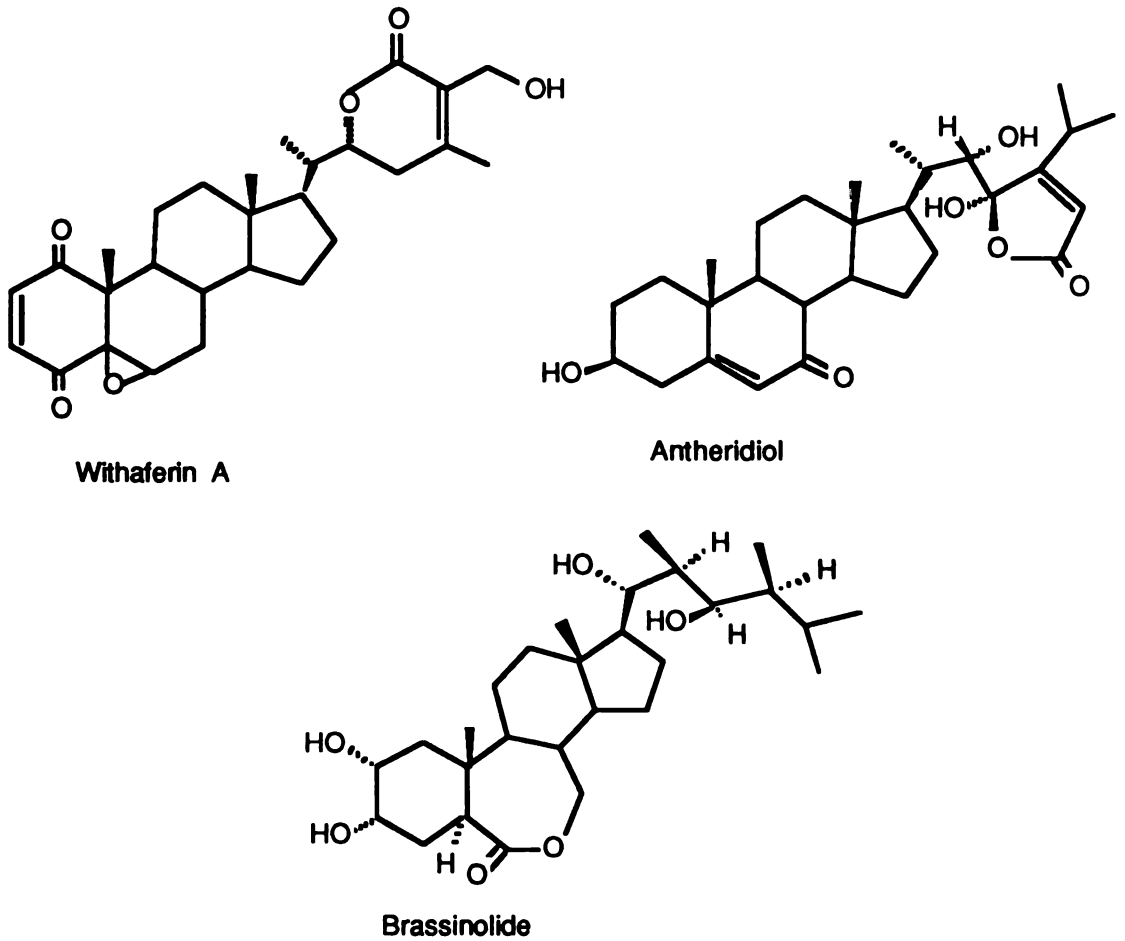
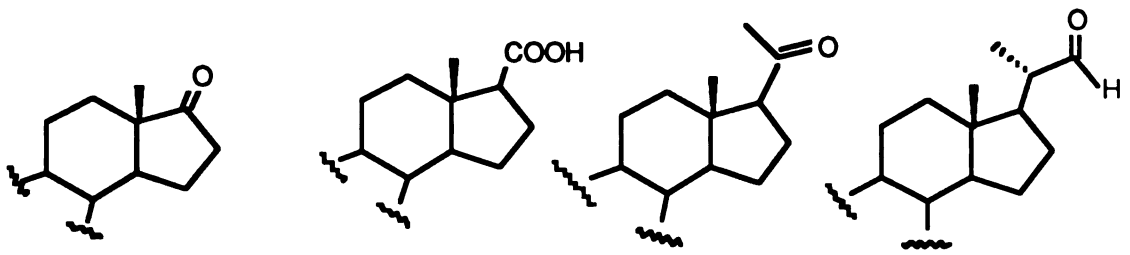


Figure 3.

An important aspect of side chain synthesis is control of stereochemistry, especially at C-17 and C-20. Most of the reported syntheses of steroid side chains start with one of the following substrates, (fig 4) due to their ready availability from naturally occuring compounds.



A B C D

Figure 4.

Compound **A** is prepared by efficient microbiological methods[8], **B** is the major product of chromic acid oxidation of cholesterol[9], **C** is derived from plant sapogenins such as diosgenin[10], and **D** by degradation of stigmasterol[11]. Earlier workers used **A** and **B** for the construction of the pregnane type side chain[12]. Common reactions at the C-17 carbonyl function included addition of HCN[13], acetylenes[14], Wittig reactions[15], and Reformatsky reaction[16]. (fig 5).

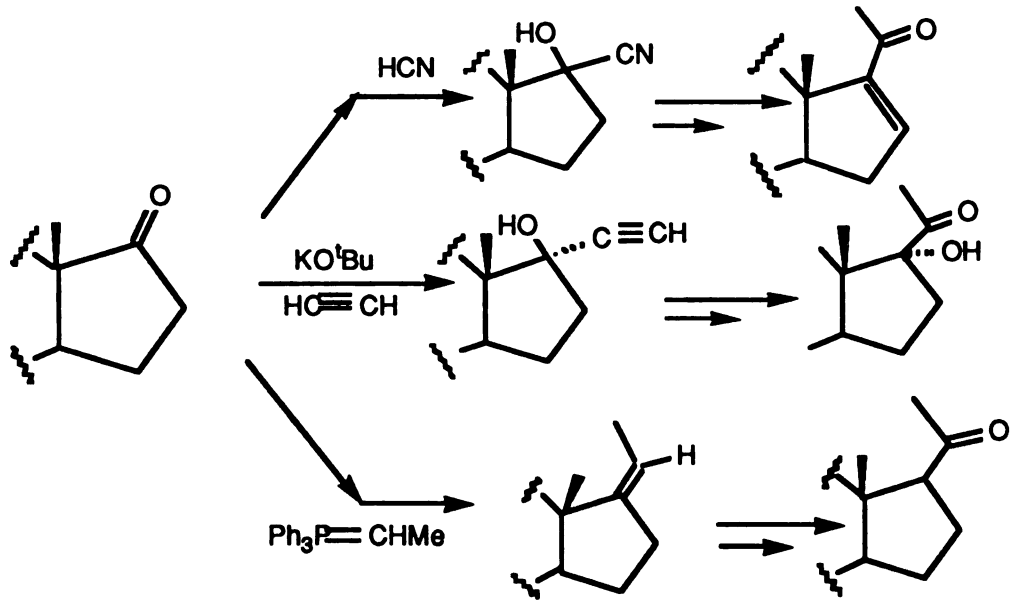


Figure 5.

The C-20 acid C may be transformed via its acid chloride[12] or by direct addition of Organolithium reagents[15a] as shown in fig 6.

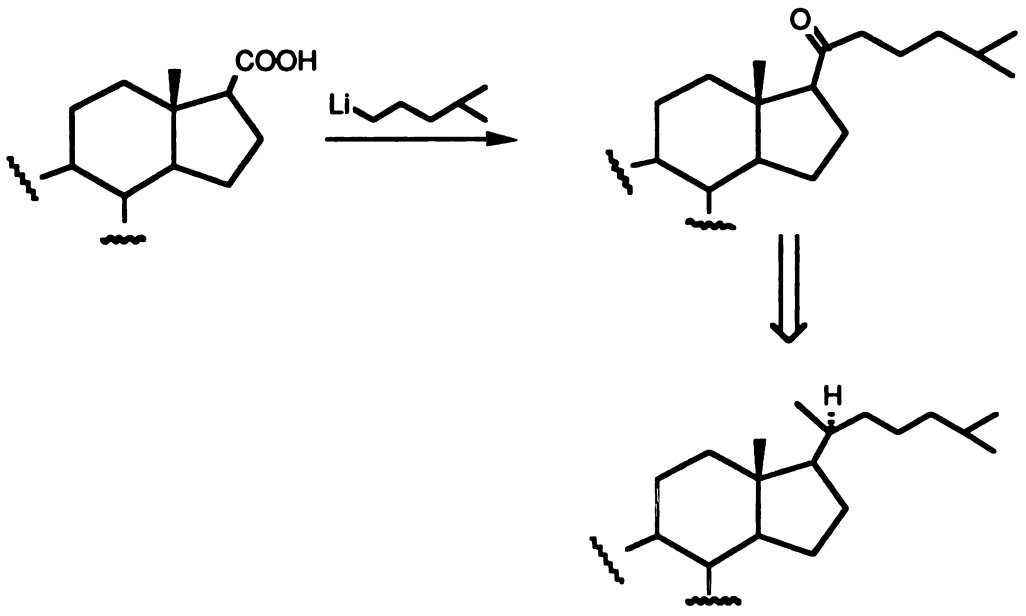


Figure 6.

Among the commonly used methods beginning with C-20 ketones were addition reactions of Grignard reagents and Wittig reactions. In the Grignard reactions, where a chiral center is created at C-20, a mixture of epimers usually resulted, the ratio depending on the structure of the steroid and the bulkiness of the reagent[17,18,19]. (fig 7).

In contrast to Grignard reagents, the addition of dimethyl Sulphoxoniummethylide, has been reported to proceed with a high degree of stereoselectivity, to give the 20-R epoxide[20]. Koreeda and coworkers[20], have used this selectivity in a synthesis of 20-iso cholesterol. (fig 8). The 20-R epoxide has also been synthesized by Krief et.al[21] via a stereoselective addition of methylselenomethyllithium. They have utilized this approach in the synthesis of the side chain of 20S isolanosterol (fig 9), obtaining an

80 : 20 mixture of the 20-S and 20-R stereoisomers.

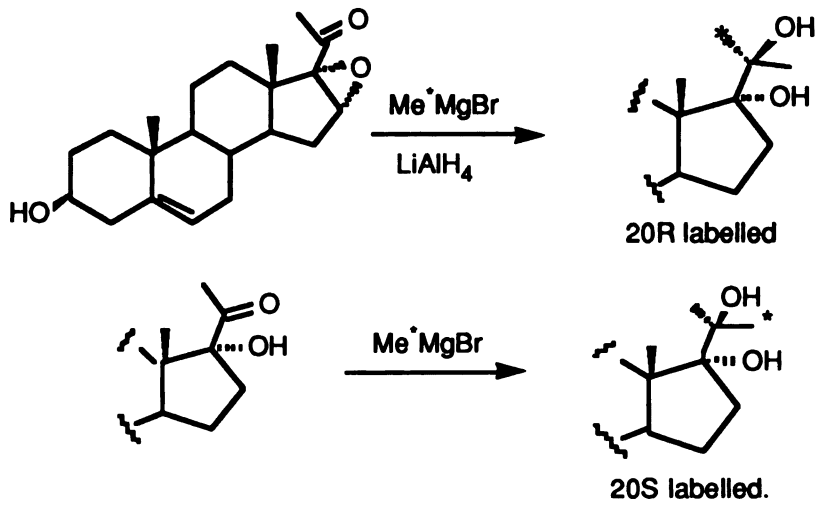


Figure 7.

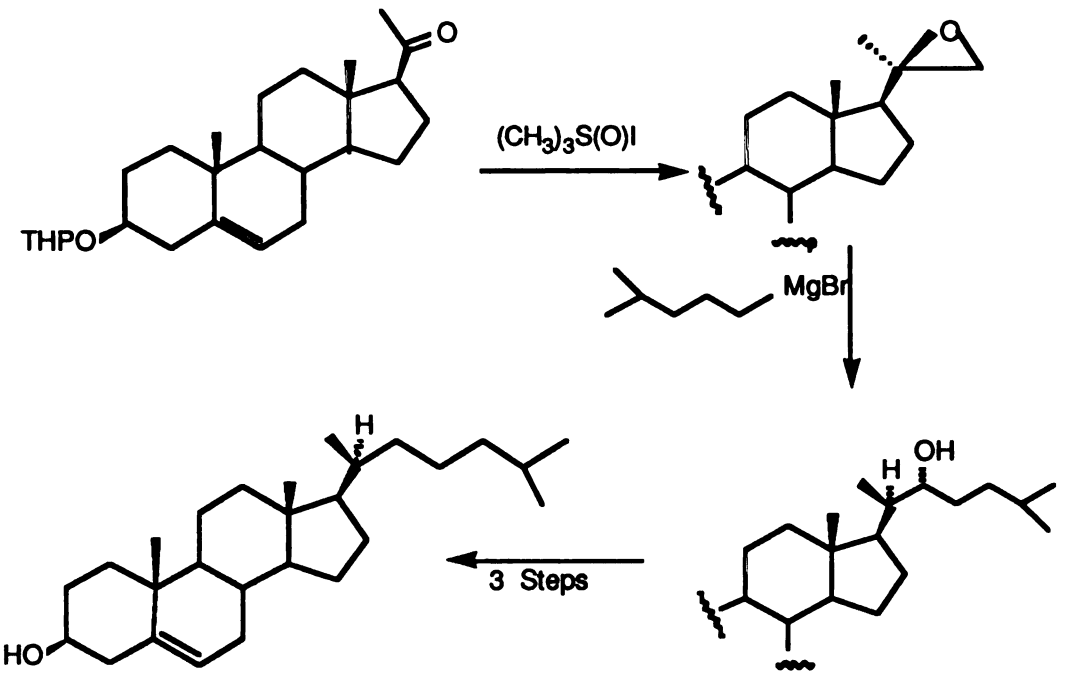


Figure 8.

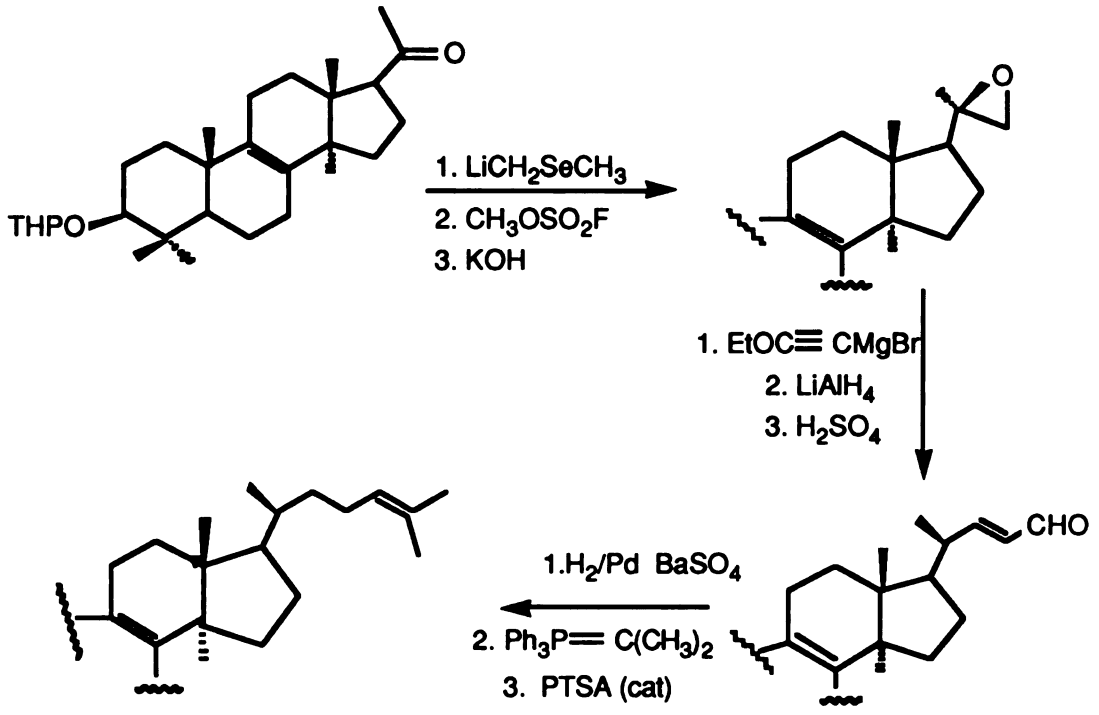


Figure 9.

The Grignard reaction is presumed to proceed via an initial Lewis - acid catalyzed, stereospecific isomerization of the epoxide into the 20-iso-21-aldehyde, followed by stereoselective addition of the Grignard reagent to the aldehyde.

Wittig reaction of C-20 methyl ketones with non - stabilized ylides, is noted to give solely the E-isomer[22]. Reaction with stabilized ylides such as diethylcyanomethylene phosphonate is also reported to give a high yield of the E-isomer[23]. An interesting example of an intramolecular Wittig cyclization was reported by Nickisch, Klose and Bohlman[24], using ketenyliden triphenyl phosphorane. (fig 10).

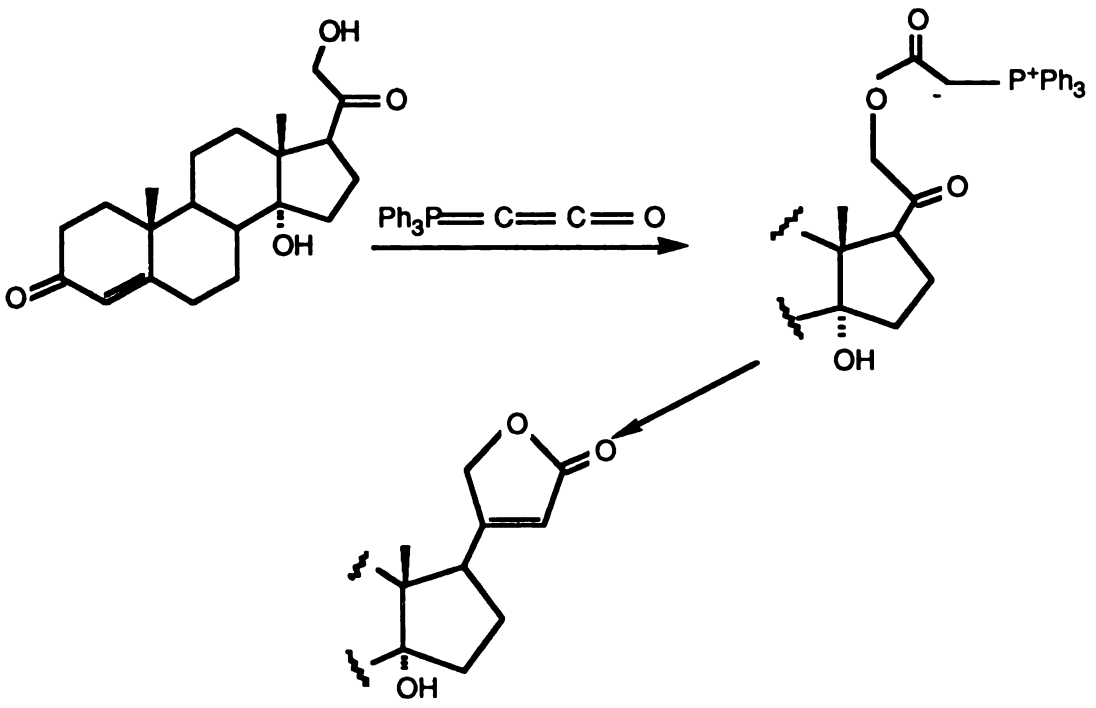


Figure 10.

The major disadvantage of the 20-carboxaldehydes (D) is the isomerization of C-20[25]. Reactions of 20-carboxaldehydes with Grignard reagents and other Organometallics usually give a mixture, the ratio depending on the type of reagent[26]. Wittig reaction with non stabilized ylides gives E or Z in varying ratios depending on the reaction conditions[27]. Reaction with stabilized ylides yield E-isomers[27a]. (fig 11).

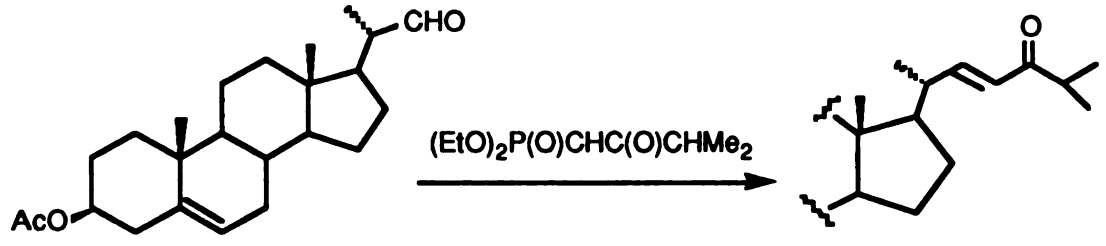
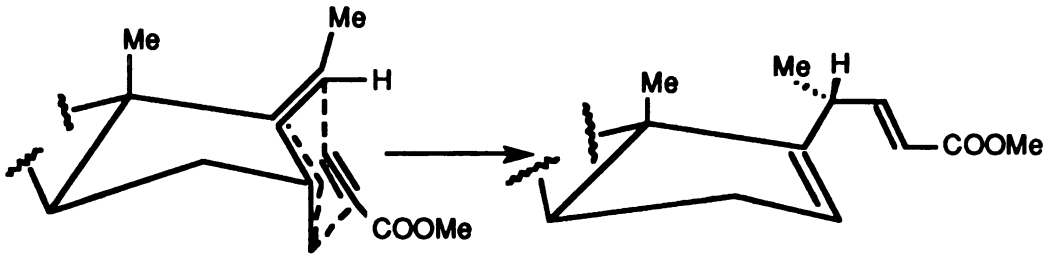


Figure 11.

It is well documented that the stereochemistry of the steroid sidechain is an important factor in determining its physiological activity[28]. Many of the methods mentioned earlier give imperfect stereoselectivity and need to be improved in this respect. In a flexible sidechain diastereoselectivity will be poor unless one uses reactions having highly - organized transition states which immobilizes key parts of the chain. This is the concept behind most recent work.

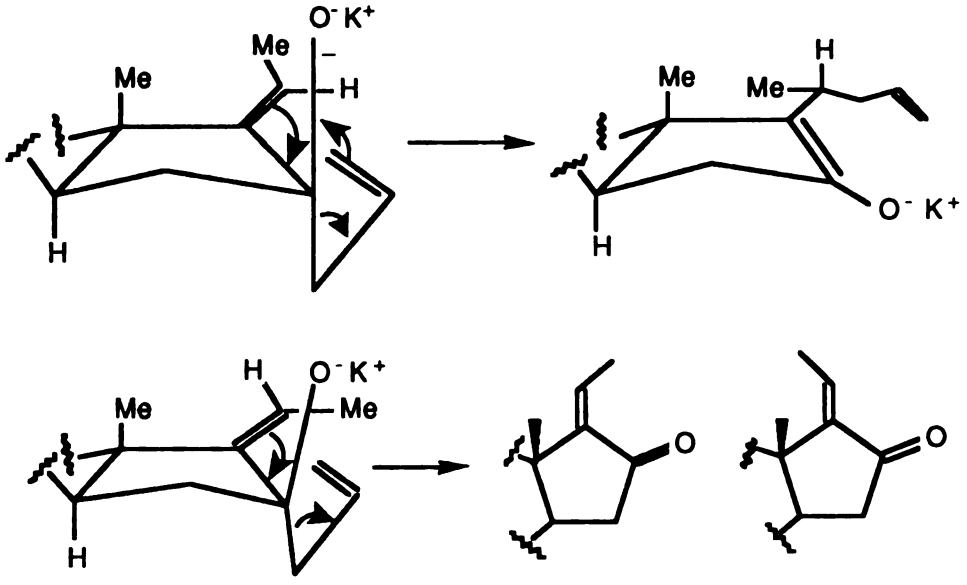
One of the simplest and most elegant approaches to sidechain construction was reported by Dauben et.al[29a,b] and later by Snider and coworkers[29c,d]. These workers used the known preference for α-attack on the C-17(20) double bond and the highly - ordered transition state of the ene reaction to set the stereochemistry at the C-20 carbon. The advantage of this methodology is that it permits stereospecific synthesis of both 20R and 20S steroidal sidechains. Starting with the (Z)-17(20)-steroid, reaction with methyl propiolate and diethylaluminumchloride gave excellent yields of the 20R steroid[29a]. On the other hand, under identical conditions, the E-17(20)-steroid gave exclusively, the 20S steroid[29b]. (Scheme 1).



Scheme 1.

An efficient synthesis of Desmosterol was reported by Koreeda, wherein he acheives stereochemical transmission via the Oxy Cope

rearrangement[30]. Only the 20R isomer derived from the (Z)-17(20) pregnene derivative could be prepared using this methodology. The related (E)-17(20)-pregnene derivative failed to undergo the rearrangement, presumably due to the quasi-1,3-diaxial interaction between the 16-$O^- K^+$ and the 20-CH_3 groups. (Scheme 2).



Scheme 2.

Several workers have used the Claisen rearrangement to control stereochemistry at C-20[31]. Both (E) and (Z)- Ethylidene sidechains smoothly undergo the Claisen - Carroll rearrangement to yield the 20R and 20S isomers respectively[31a]. (fig 12). This reaction succeeds however only with the 16 α isomer. The 16 β isomer fails to react, probably due to steric crowding of the β face[31b]. However, by employing the enol ether variant (the Saucy-Marbet variant[32]), it has been reported that the Claisen rearrangement is also feasible on the sterically crowded β face. Thus starting with a E-16 β alcohol, rearrangement proceeded smoothly, to yield the 20S epimer[31b]. (Fig

13). The success of this rearrangement is attributed to the lesser steric demand in the enol ether variant of the Claisen.

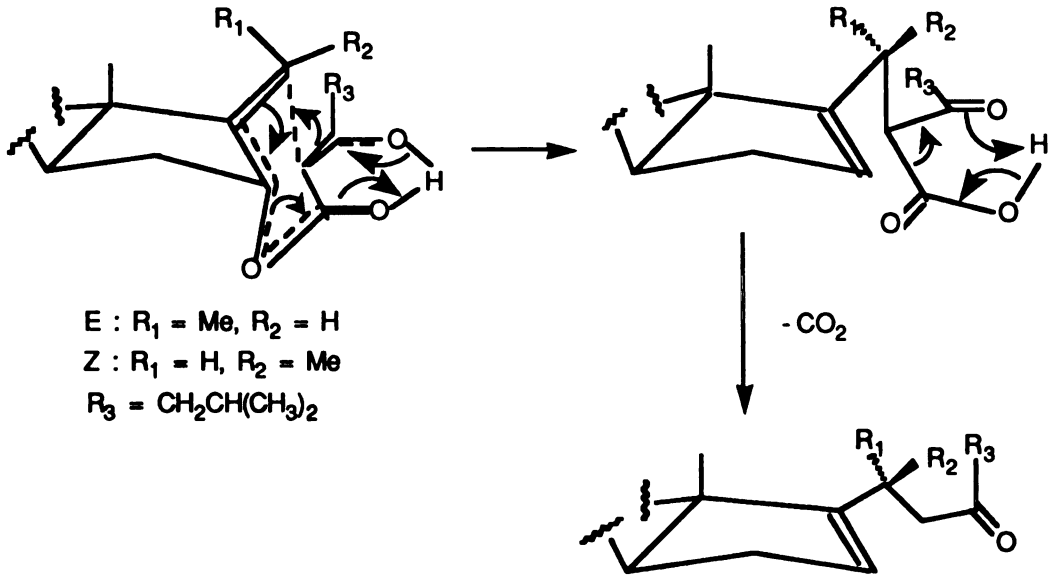


Figure 12.

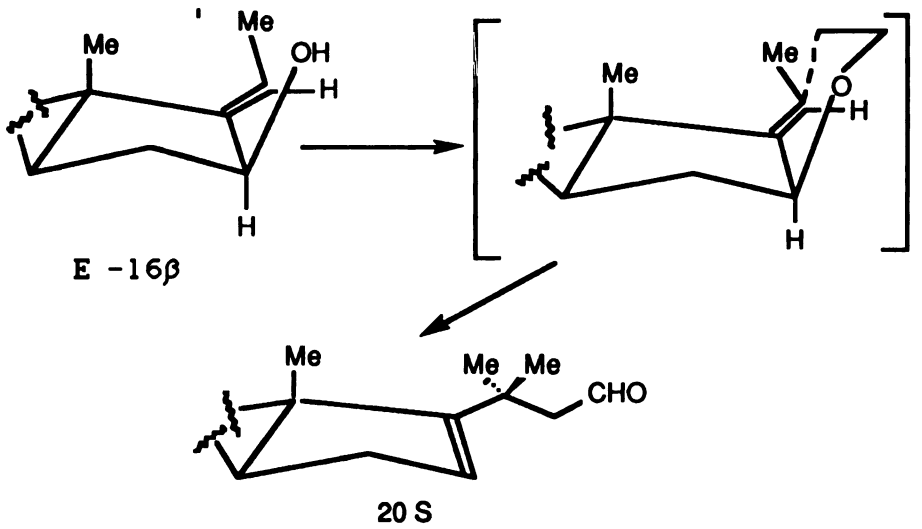


Figure 13.

In a distinctly different approach, steroid sidechains can be stereoselectively introduced by alkylation of a π-allyl Pd complex[33]. Trost used this approach to synthesize both the 20R and the 20S

epimers[33a]. Thus attack of a stabilized carbanion on the π-allyl Pd complex generated from the alkene **1**, gives the 20S epimer exclusively. On the other hand, generation of the π-allyl Pd complex from the allylic acetate **2**, using a catalytic amount of $(PPh_3)_4Pd$ yields the 20R epimer exclusively[33a]. (fig 14). Schwartz[33c], has reported that alkenyl Zirconium species couple with (π-allyl) palladium chloride complexes to give high yields of the resultant dienes. (fig 15).

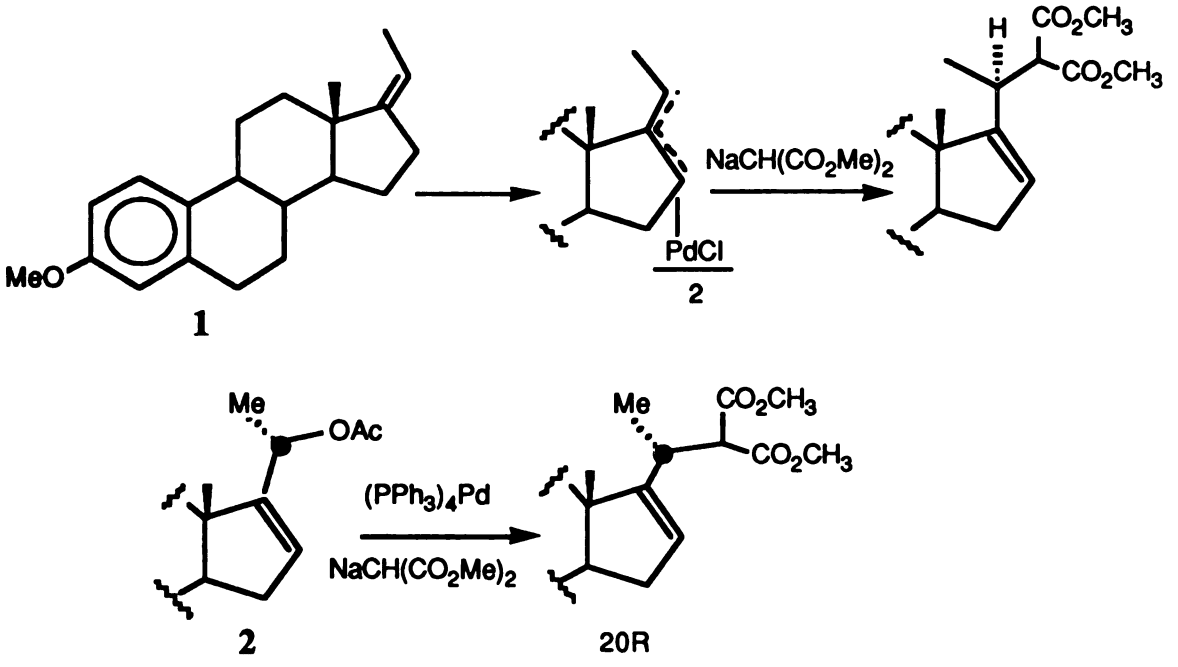


Figure 14.

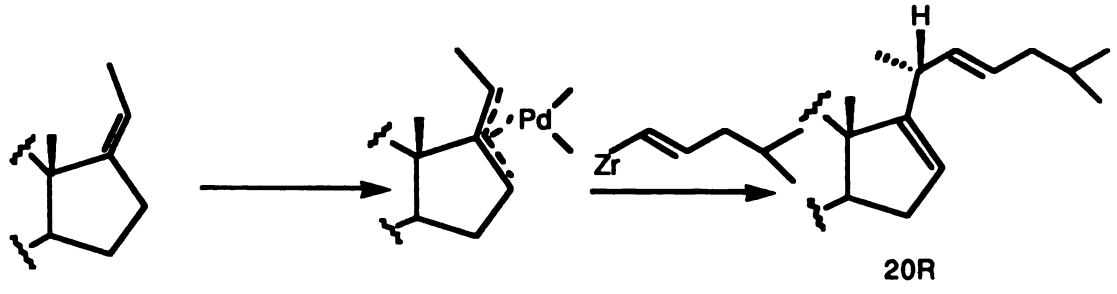


Figure 15.

Regio and stereospecific 1,4-addition of alkyl cyanocuprates to vinyl epoxides was the key step in a novel synthesis devised by Marino and coworkers[50]. (fig 16).

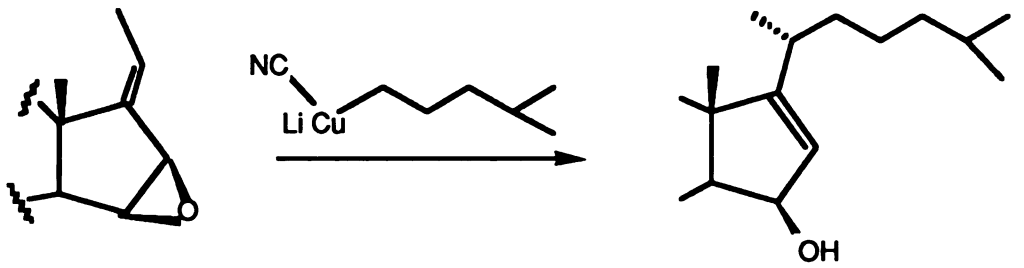
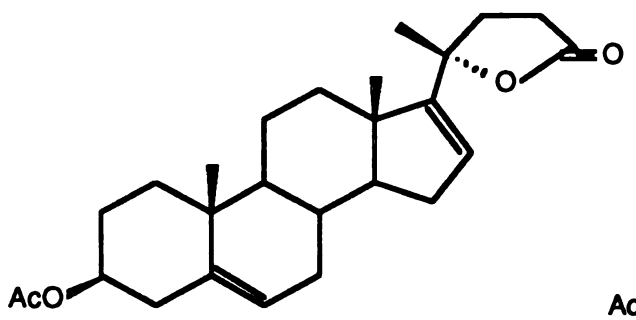


Figure 16.

This dissertation describes a new method for the construction of steroidal sidechains with control of stereochemistry at C-20. The synthesis of the steroidal lactone **8**, which is a potential precursor of steroid sidechain, has been accomplished. The lactone has been synthesized in a completely stereoselective manner from the epoxy olefin **4**. In the course of this study, we have observed a novel and unprecedented rearrangement of an epoxy olefin, when reacted with dichloroketene.



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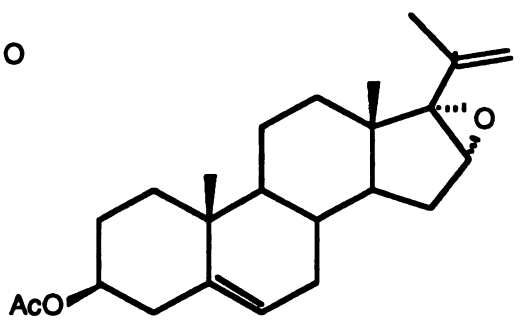
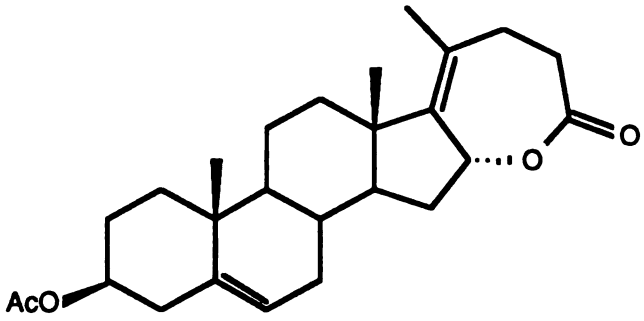


4.

Although there have been reports on the reaction of dichloroketene with allylic ethers and thioethers[34], there are no examples in the literature, concerning its reaction with epoxy olefins. The unexpected rearrangement observed here, should provide a fruitful area for further research in the future.

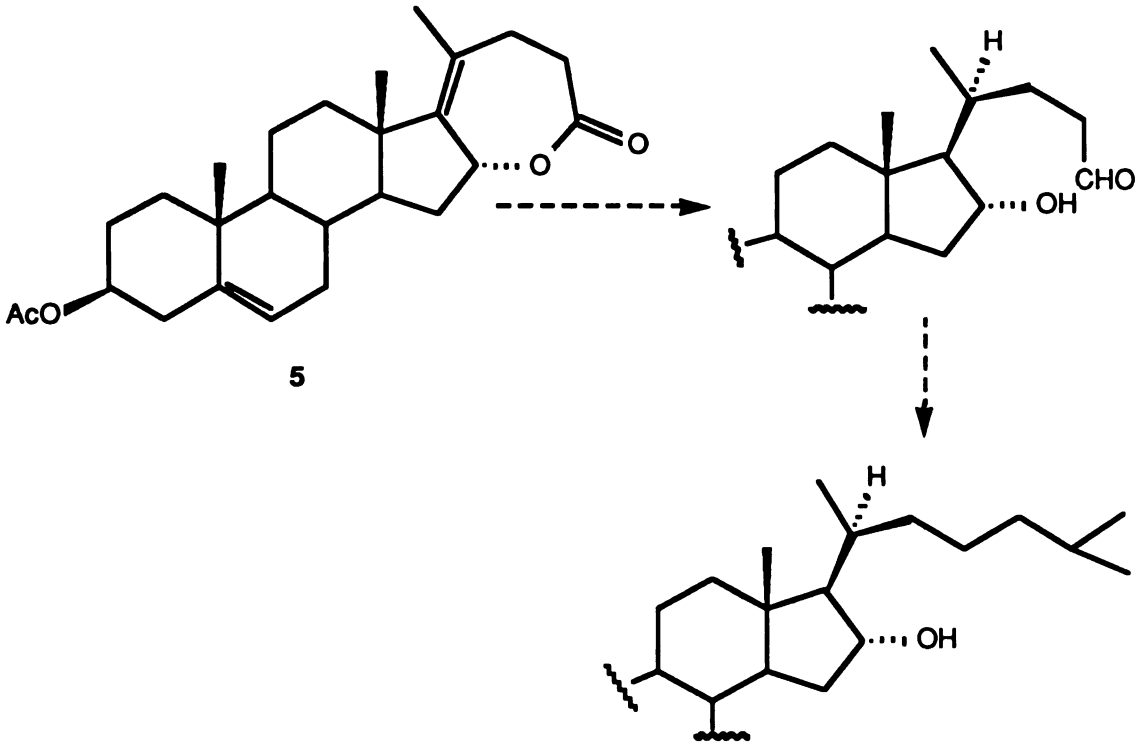
RESULTS & DISCUSSION.

At the outset, our aim was to synthesize seven membered lactones such as **5**, which we believed could be elaborated with good configurational control at C - 20. The lactone ring serves two major purposes. Firstly, due to its presence, the exocyclic double bond in **5** is constrained to assume the Z geometry. Secondly, the β face of this rigid ring is more sterically hindered than the α face. We believed these two factors enhanced considerably our chances of controlling the stereochemistry at C - 20. Furthermore, **5** would enable us to introduce a hydroxyl group at C - 16, a feature common in many steroids and tetracyclic triterpenes. Finally, a Wittig reaction using isopropyltriphenylphosphonium bromide would allow us to complete construction of the eight carbon side chain commonly found in most steroids. (fig 19).



5.

Figure 18



5

Figure 19.

Our strategy for the synthesis of **5**, was developed along the lines of a rearrangement observed when allyl ethers are reacted with dichloroketene[34]. A brief outline of this reaction and our reasoning behind its use are in order.

In recent years, reactions of dichloroketene have been the subject of extensive research. Several excellent reviews on this subject have appeared in the literature[35]. Undoubtedly, the reaction of dichloroketene that has attracted the most attention is the $2\pi + 2\pi$ cycloaddition with nucleophilic double bonds[36]. This reaction gives a dichloro cyclobutanone as the product and is probably the simplest way of constructing functionalized four membered rings (fig 20).

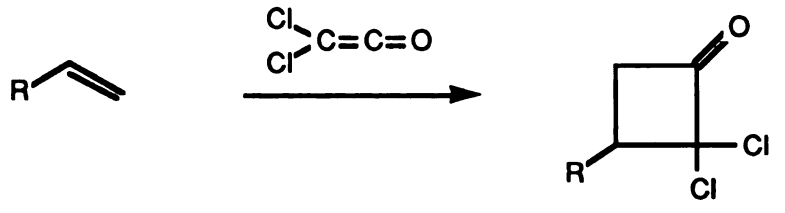


Figure 20.

The high yields and the ready availability of starting materials make this an especially attractive method. There have been several studies probing the mechanistic details of this reaction[37]. Recent modifications in reaction conditions have led to considerable improvement in the yield of the cycloadduct[38].

Normally the reaction proceeds with a high degree of chemoselectivity and regioselectivity, with no unwanted side reactions. However, when dichloroketene is reacted with allyl ethers or allyl sulfides, a competing rearrangement reaction is observed[34] (fig 21)

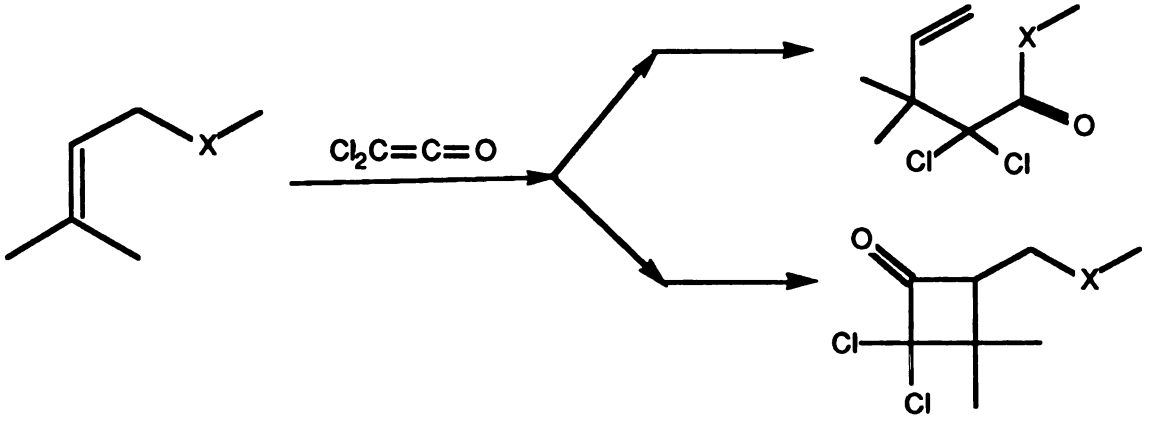
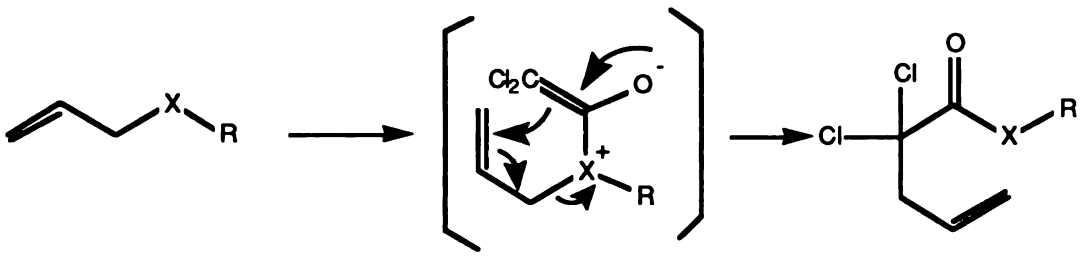


Figure 21

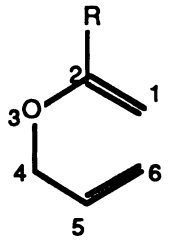


X = S or O. **22**

Figure 22

In this case the two nucleophilic sites; viz., the double bond and the oxygen (or sulfur), compete with each other for the electrophilic dichloroketene. In the case of allyl ethers (X = O), this competing reaction generally predominates and in most instances completely suppresses the $2\pi + 2\pi$ cycloaddition[34]. The reaction may proceed through formation of the 1, 3 - dipolar intermediate, **22**, which then undergoes a 3, 3 - sigmatropic rearrangement to yield the rearranged product. It is probable that nucleophilic attack at the carbonyl of dichloroketene leading to the 1, 3 - dipolar intermediate is facilitated by complexation of zinc chloride (which is formed in the reaction) at the carbonyl carbon.

An important feature of this "Claisen rearrangement" is that it occurs under very mild conditions. Claisen rearrangements have been studied quite extensively and have found several synthetic applications[39]. A major problem with this rearrangement has been the need to use rather high temparatures to achieve the desired transformation. This problem can be remedied by introducing suitable substituents on the Claisen substrate. It is well documented that the presence of π donor substituents at position C - 2 enhances the rate of the Claisen rearrangement significantly[40].



A second factor that facilitates this rearrangement is the presence of a positively charged hetero atom at position 3[41]. It is important to note that the 1, 3 - dipolar intermediate formed in the "ketene Claisen" incorporates both these activating factors. It is therefore not surprising that the rearrangement in this case is extremely facile.

Unlike the $2\pi + 2\pi$ cycloaddition reaction of haloketenes, this reaction has not been studied extensively, nor has it found many synthetic applications. In fact it is often considered an unwanted side reaction, competing with $2\pi + 2\pi$ cycloaddition reactions of allyl ethers and sulfides. In a recent synthesis of Lineatin, Oehschlager reported that side reactions arising due to participation of oxygen in these substrates could be minimized by using 1, 2 - dimethoxy ethane (glyme) as solvent[42]. He succeeded in obtaining significantly higher yields of the $2\pi + 2\pi$ cycloadduct under these conditions (fig 23), and proposed that under these conditions, glyme acts as a sequestering agent for zinc chloride. Consequently the 1, 3 - dipolar intermediate **22** is formed at a slower rate and the $2\pi + 2\pi$ adduct is obtained in a higher yield.

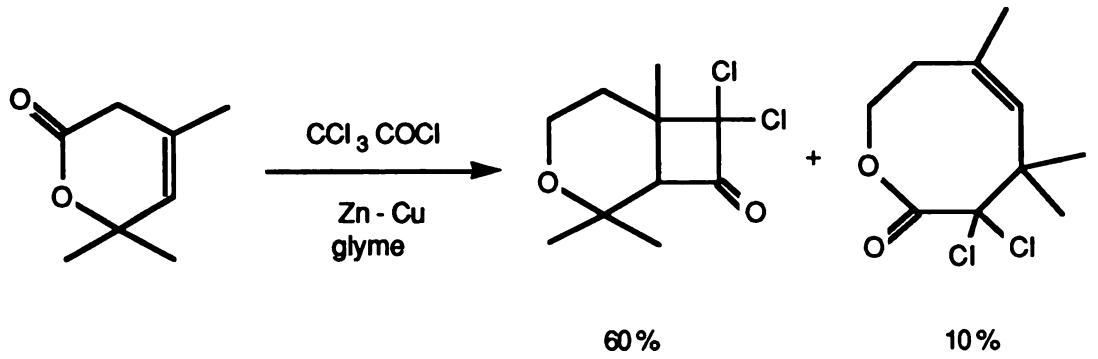
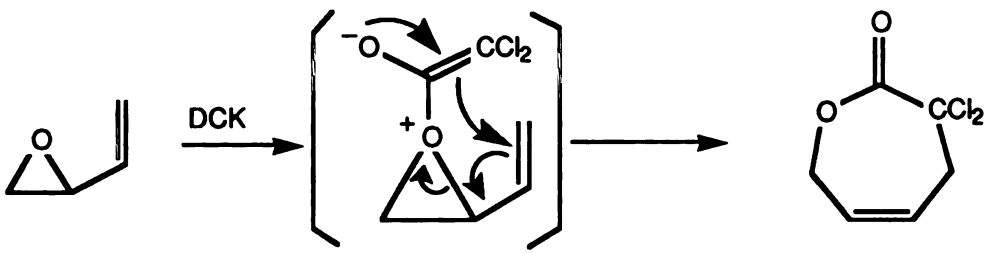


Figure 23

Our interest in this rearrangement was prompted by our expectation that epoxy olefins such as **23** would react with dichloroketene, yielding seven membered lactones as products. [Scheme 3].



23

Scheme 3

We also believed that this reaction would provide us with a simple and direct route to the steroidal seven membered lactone **5**, which we set out to synthesize. To this end, we chose the epoxy olefin **4**, as our substrate. This olefin was easily prepared from commercially available epoxy ketone **3** by a Wittig reaction with methyltriphenylphosphonium bromide[43] (fig 24).

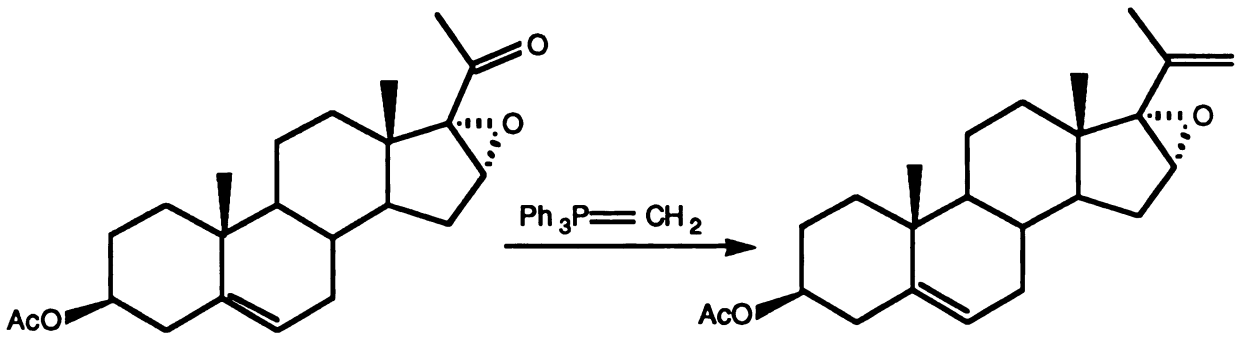
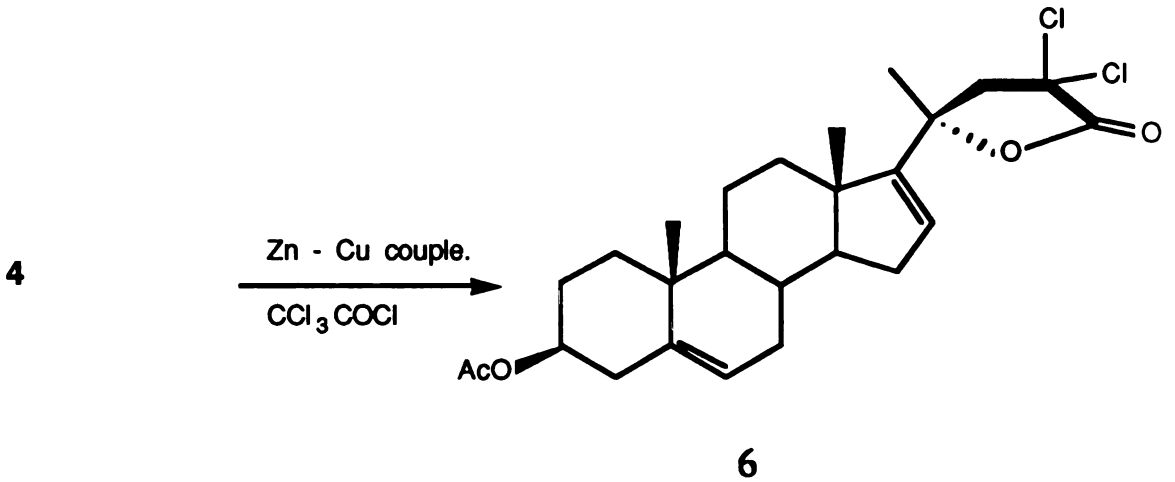


Figure 24.

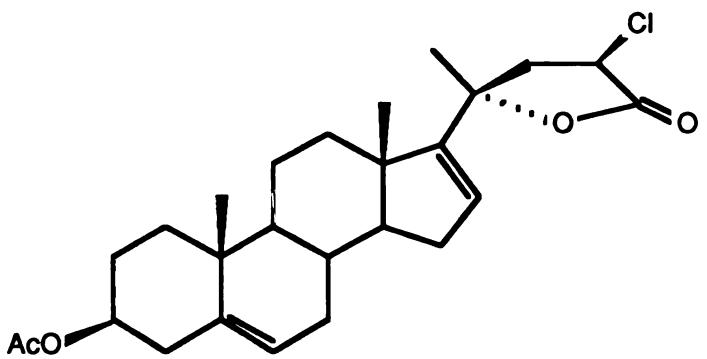
With the requisite epoxyolefin on hand, we proceeded to react it with dichloroketene, generated by zinc dehalogenation of trichloroacetyl chloride[38a]. Examination of the product obtained, indicated that addition of dichloroketene to **4** had indeed occured. However, spectral analysis of the product revealed it was not the anticipated seven membered lactone. The ^{13}C NMR spectrum of this compound revealed the presence of two ester like carbonyls and two trisubstituted olefins (off resonance decoupled ^{13}C NMR spectrum). A vinylic hydrogen signal at δ 5.68 ppm in the ^{1}H NMR spectrum also confirmed the presence of a second trisubstituted double bond. The infra - red spectrum of this compound showed two carbonyl absorptions at 1791 cm^{-1} and 1725 cm^{-1}. Since the ^{13}C NMR showed two ester carbonyl signals, we concluded that one of the carbonyl functions was a five membered lactone. Based on all the evidence, we concluded that the product from the reaction of **4** with dichloroketene was actually compound **6**. (fig 25)



6

Figure 25.

Final confirmation of structure **6** was eventually accomplished by X - ray analysis of monodechlorinated derivative **7** (vide infra). It must be added that **6** was the only product obtained whether the reaction was performed in ether solvent or conducted in glyme/ether as suggested by Oehschlager[42].



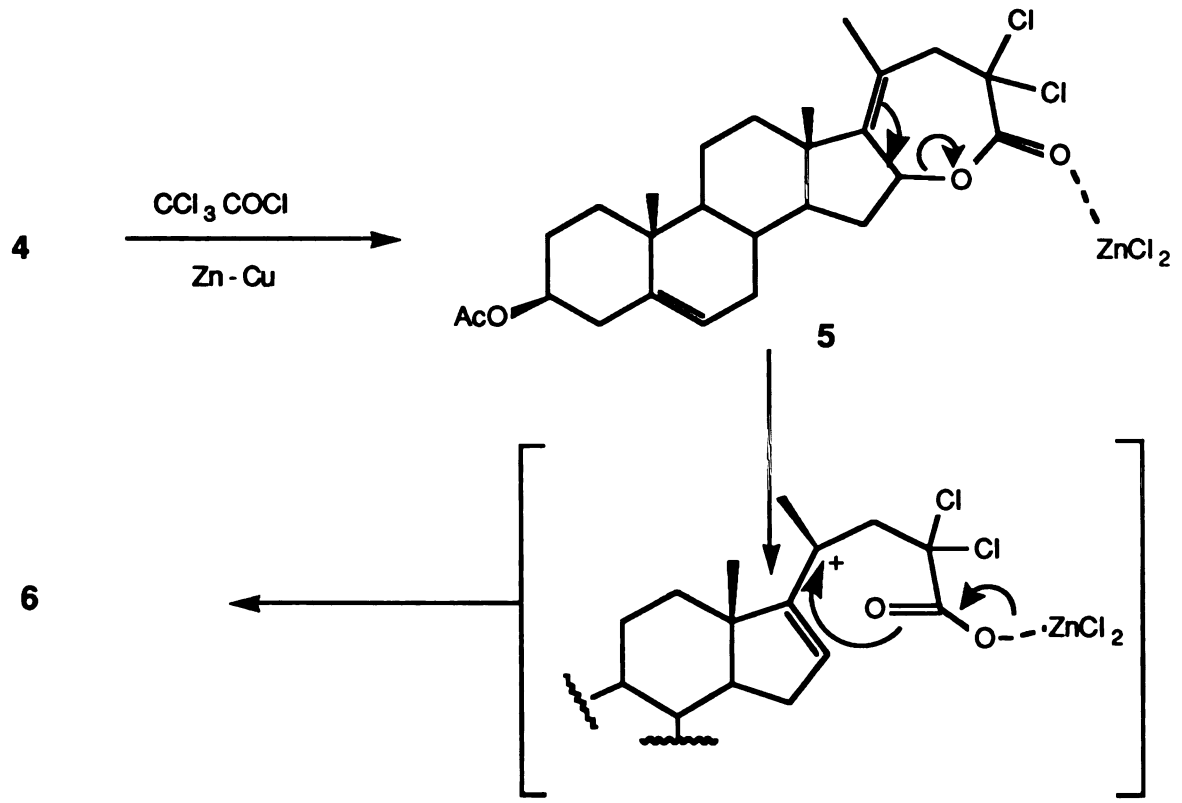
7.

Figure 26.

An interesting aspect of this reaction is that the oxygen atom of the 16a, 17a - epoxide in the starting material is no longer bonded to either of these

carbons (16 or 17) in the product. Furthermore, this oxygen shift is completely stereoselective, giving only one C - 20 epimer as the product.

Our initial speculation regarding the mechanism of the reaction of dichloroketene with epoxy olefin **4** centered around the possibility that the seven membered lactone **5** was formed as an intermediate. Under the reaction conditions an acid catalyzed suprafacial 1, 3 - shift of oxygen from C -16 to C -20 would then account for the stereoselective formation of five membered lactone **6.** (scheme 4)



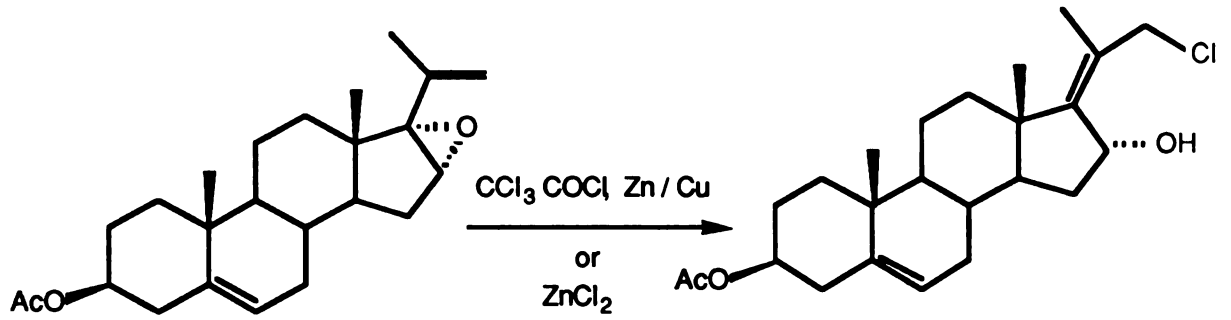
Scheme 4.

However, we were concerned about the fact that **5** was never observed or isolated during the course of this reaction. In our attempts to isolate **5** we repeated the key reaction while varying the number of equivalents of

dichloroketene, the reaction time and the concentration of the reactants. When **4** was reacted with one equivalent or less of dichloroketene, a new product was isolated after two to four hours of reaction. If the reaction was allowed to continue further, **6** was the only product isolated. The amount of new product isolated depended on the concentration of the reaction mixture. Under dilute conditions, significant quantities of this compound could be isolated even after four to five hours of reaction. On the other hand, in a more concentrated solution, We observed the formation of **6** (thin layer chromatography) after only 1.5 to 2 hours of reaction. In the course of identifying this new compound, we relied not only on spectroscopic evidence but also the chemical reactions it underwent with various reagents.

The new compound was assigned structure **12,** based on the following evidence. The ^{13}C NMR showed no carbonyl signal, other than the acetate (at C - 3). The off resonance decoupled ^{13}C NMR spectrum revealed the presence of one trisubstituted double bond and one tetrasubstituted double bond. The fact that **12** possesses one chlorine atom was evident from the mass spectrum. A signal at 3563 cm^{-1} in the infra red spectrum of **12** was indicative of a hydroxyl group.

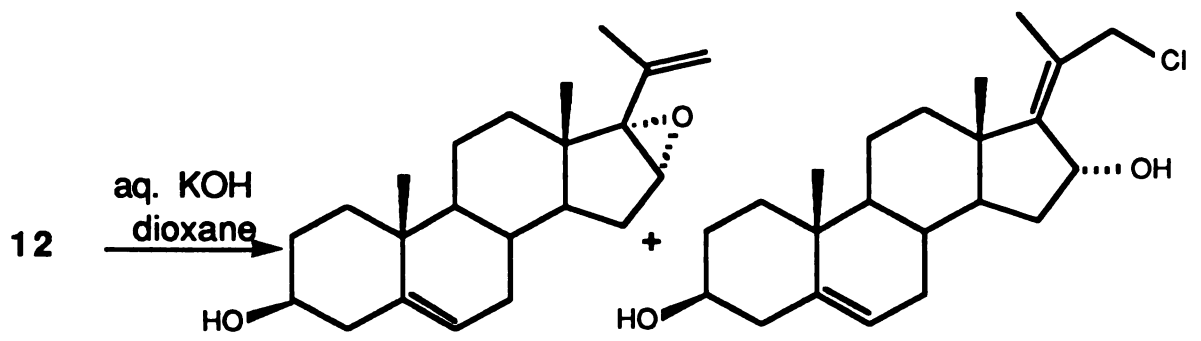
When epoxy olefin **4** was treated with zinc chloride in ether solution, **12** was obtained, albeit in rather poor yield. This indicated that there could be no increase in the number of carbons in the going from **4** to **12.** Reaction of **12** with dichloroketene, under the same conditions as with **4,** yielded **6** in good yield. Thus it was clear that **12** is an early product of the reaction of **4** with dichloroketene.



4 12

Figure 27

. The structure of **12** was later confirmed unambiguously, by studying its behavior in various chemical reactions. (figs 28 & 29). Thus, when **12** was reacted with methanolic potassium carbonate solution, hydroxy ether **13** was obtained. Reduction of **12** with lithium aluminum hydride gave diol **14,** and oxidation of **12** with pyridinium chlorochromate yielded enone **17**. Finally, on refluxing **12** with aqueous potassium hydroxide in dioxane, the original epoxy olefin, **15**, was isolated as the major product, along with a small amount of **16**.



15 16

Figure 28.

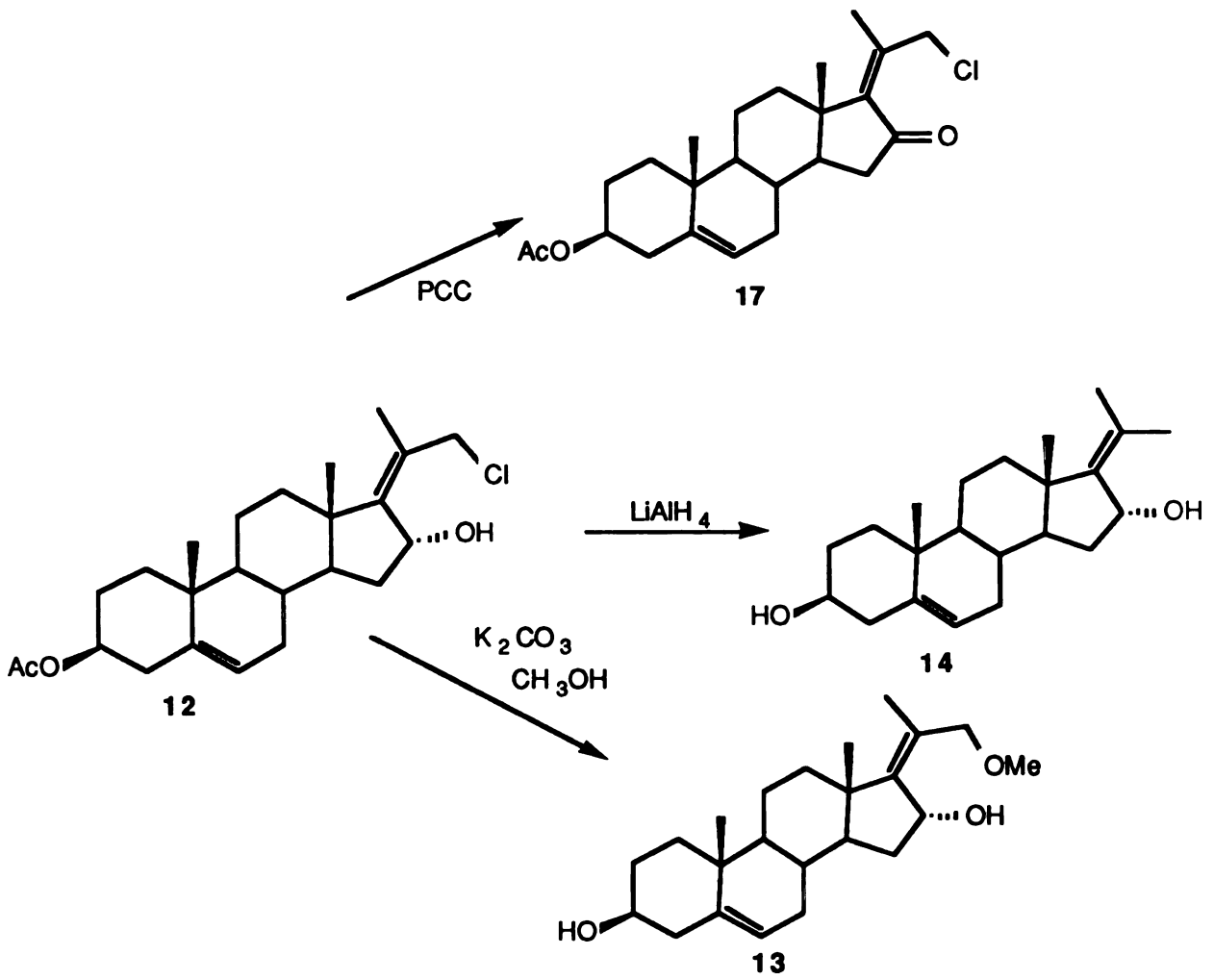
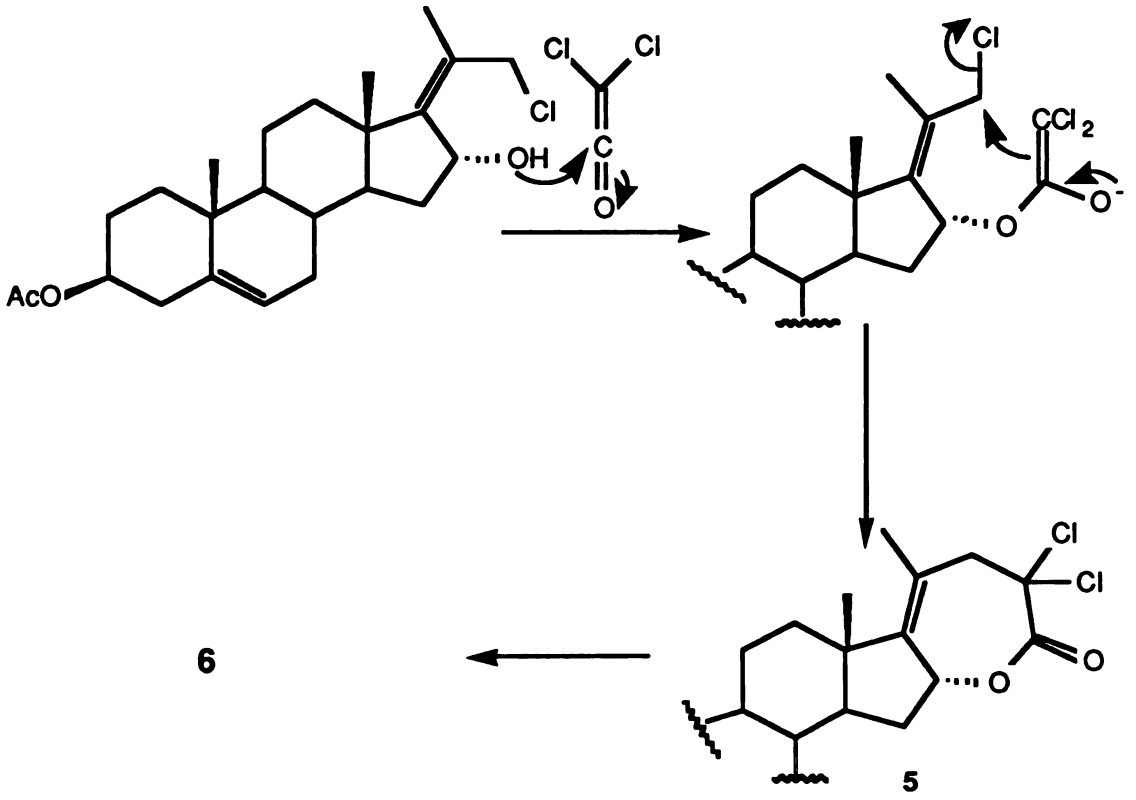


Figure 29

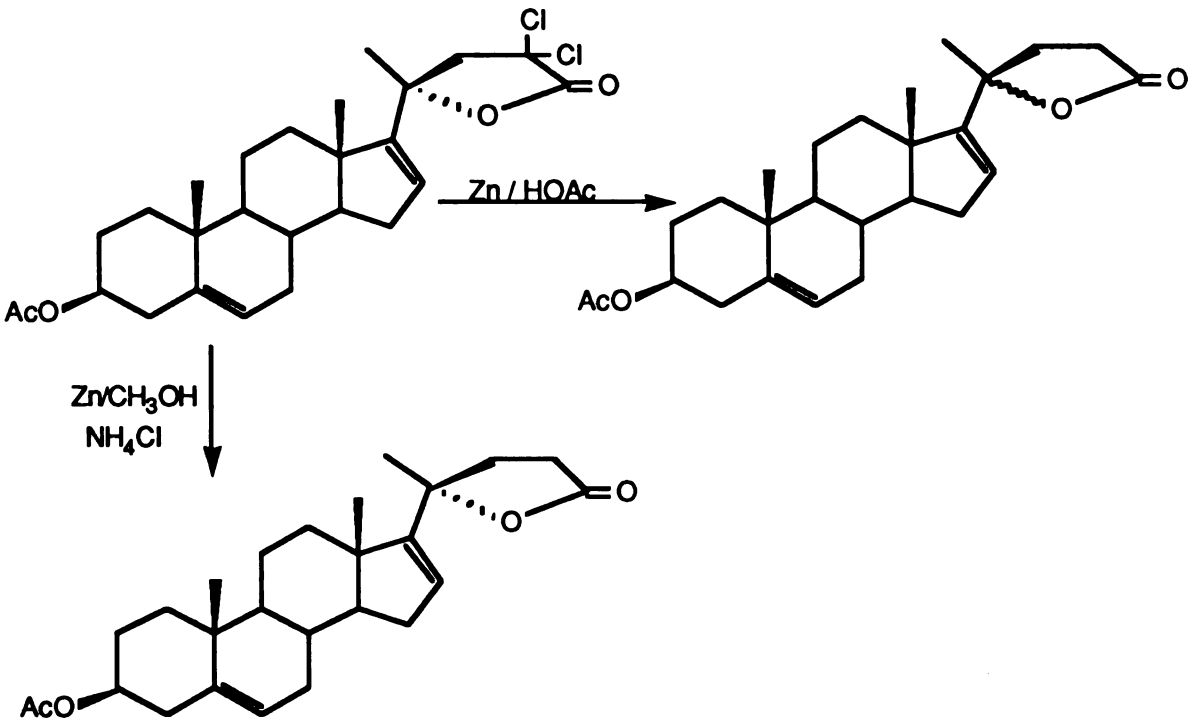
The results of these reactions leave no doubt as to the identity of **12**. The Z configuration of the double bond in **12** was established by chemical shift changes on converting **12** to **17**. Oxidation of the 16 - hydroxyl group causes the chemical shift of the 21 - methyl hydrogens to shift downfield by 0.1 ppm whereas the hydrogens of the chloromethylene group are shifted downfield by about 0.55 ppm. This compares well with the data obtained by Koreeda *et al* [52]. Although we did not isolate the seven membered lactone **5**, we continued to believe that it must be formed as an intermediate in the

conversion of **4** to **6.** There are two possible explanations for the observed result. The isolation of **12** as an early product may represent an unproductive detour in the ultimate conversion to **6,** or it may reflect a previously unsuspected path to **5.** In other words, one possibility is that **12** might be in equilibrium with **4,** which reacts with dichloroketene according to the mechanism oulined earlier (Schemes 3 and 4). A second possibility is that under the reaction conditions (viz., presence of Lewis acids), epoxy olefin **4** may first undergo a 1, 4 - addition to the allyl chloride **12**, which then may react with dichloroketene to give the seven membered lactone **5.** (Scheme 5). As shown in Scheme 5, the alcoholic oxygen may act as a nucleophile in the reaction with dichloroketene, similar to reactions of dichloroketene with allyl ethers. The chlorine atom of the allylic chloride serves as a nucleofugal leaving group, giving rise to the seven membered lactone **5**, which rearranges to **6** as suggested earlier (Scheme 4).. We believe the rearrangement of **5** is so fast under the reaction conditions as to preclude its isolation. This rearrangement is a curious and interesting one, and we know of no precedence for such a transformation. The most interesting aspect is, of course, the completely stereoselective nature of this 1, 3 - shift. The driving force for the rearrangement is presumably the increased stability associated with the relief of strain in going from a seven membered lactone to a five - membered lactone.



Scheme 5.

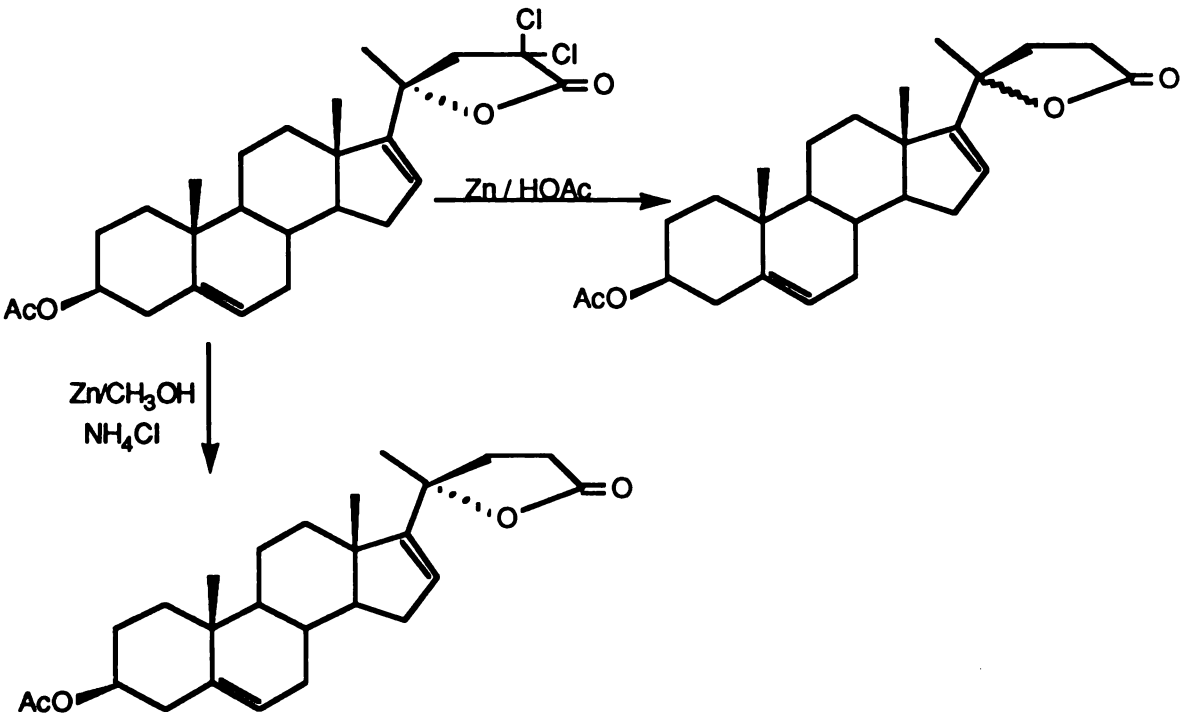
Dechlorination studies of **6** gave some interesting results. Dechlorination of **6** using zinc and acetic acid[44a], resulted in the isolation of **8** as a mixture of C - 20 epimers. The ratio of the two epimers were roughly 1 : 1. A doubling of ^{1}H NMR signals from protons on C - 16, C - 18 and C - 21, were indicative of this epimerization, which presumably is due to acid catalyzed ring opening and reclosure of lactone **6**. This undesirable epimerization can be avoided by conducting the dechlorination reaction in a methanol solution saturated with ammonium chloride[44b]. In this fashion lactone **8** was obtained in almost quantitative yield, from **6**. (fig 30.)



8

Figure 30.

The sensitivity of lactone **8** to acid catalyzed epimerization was demonstrated by brief exposure to zinc chloride in acetic acid solution, whereupon a 50 : 50 mixture of C - 20 epimers was obtained. This is in good agreement with the results obtained from a MM2[47] calculation, according to which both C - 20 epimers are of approximately equal energy. Lactones such as **8** are quite rare, the only previous synthesis, by Kocor et. al., being from 3b - methoxy - 5 - androsten - 17 - one in four steps with rather poor stereoselectivity[45] (fig 32). The key step in this strategy is the phenyl seleno lactonization of 17, 20 - unsaturated acids to the desired lactones. The poor yield of this reaction and the inability to control the stereochemistry of the 17 - 20 double bond are major drawbacks to this method. In another early report, Sarel et. al.,[46a] prepared similar lactones by oxidation of cholanol.



8

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However their strategy also lacked stereoselectivity (fig 31). Lactones of this kind were used in a synthesis of 14 a - Bufa - 20, 22 - dienolide[46b].

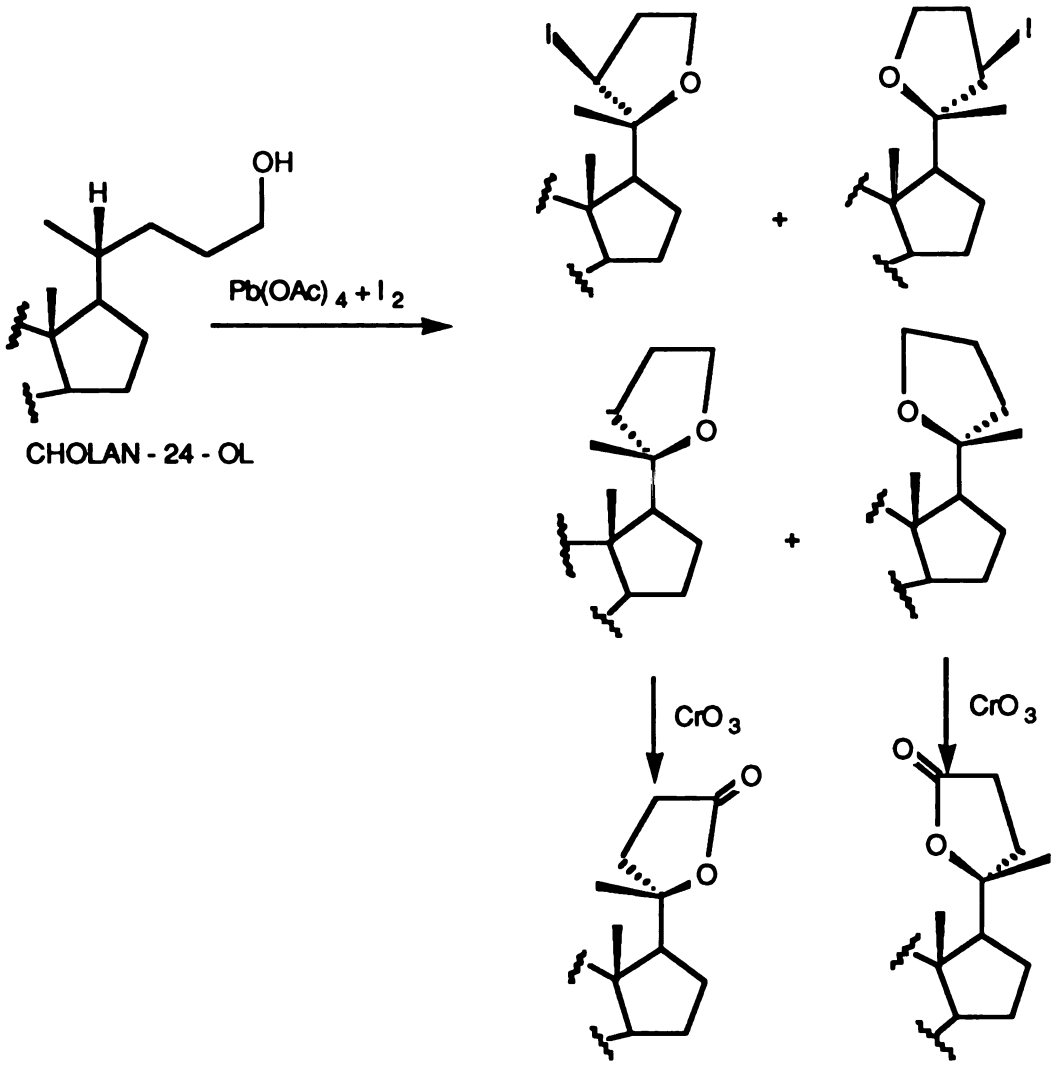
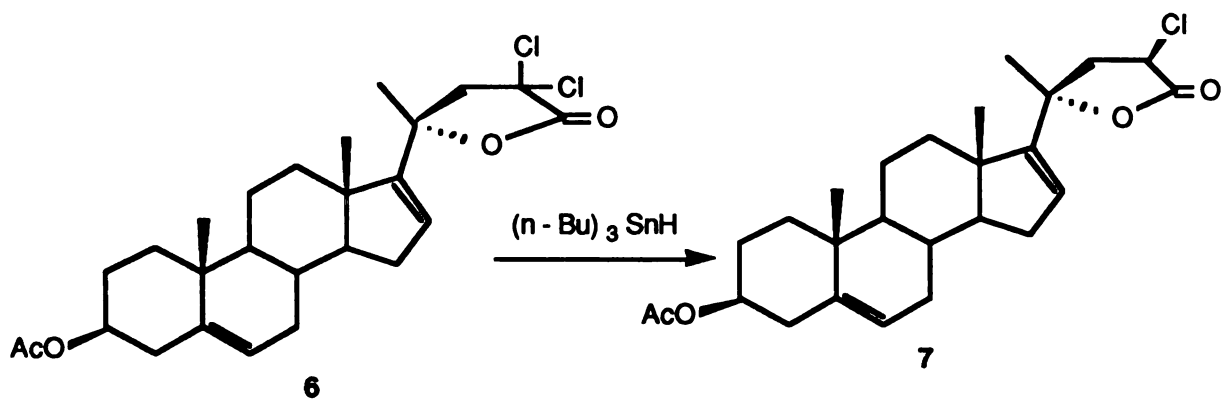


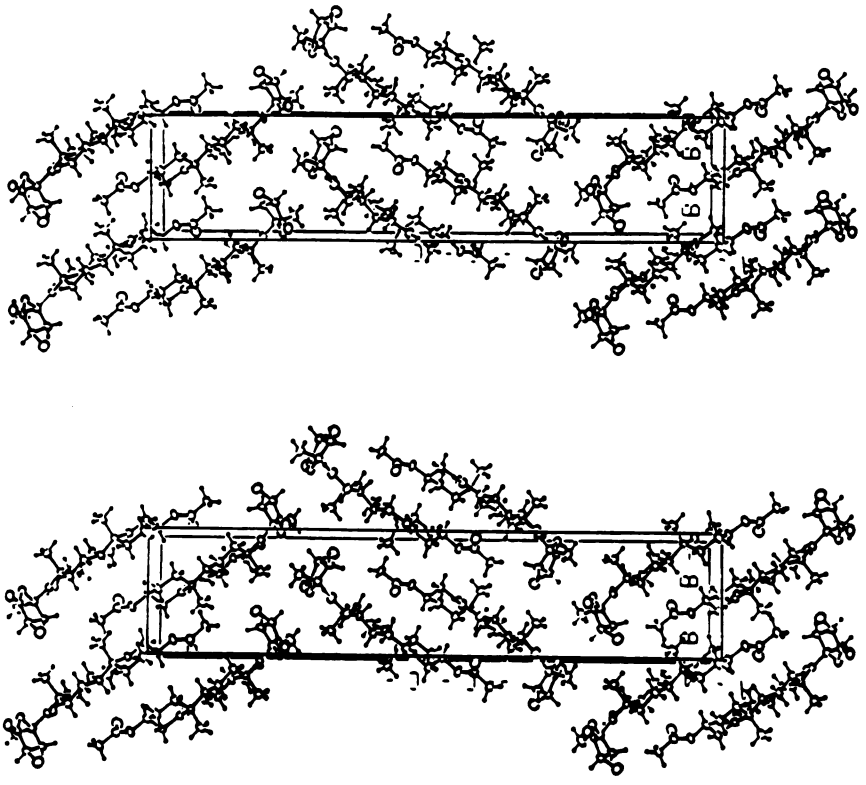
Figure 31.

During our study of the dechlorination reactions of **6**, we studied its reaction with tributyltin hydride[44c]. This reduction yielded a mono - dechlorinated product, **7**, (fig 33) as revealed by its mass spectrum and ^{1}H NMR studies. The reduction proceeds by selective dechlorination of the α - chlorine, indicating steric hindrance of the β - face. Neither treatment with excess tributyltin hydride nor longer reaction times or higher reaction temparatures caused further reduction of **7**. Compound **7** yielded crystals suitable for X - ray analysis. Figure 34 displays an ORTEP diagram of **7**, determined in the course of its structure elucidation and refinement. This diagram clearly discloses the 20 - **R** configuration in **7**, and consequently the corresponding configurations of **6** and **8**. Figure 34 also confirms that the stereoselective dechlorination of **6** proceeds with the loss of the less hindered chlorine atom. Interestingly, the structure displayed in figure 34 resembles closely the most stable C-17 : C-20 rotamer found by MM2[47] calculations on structure **7**.



6 7

Figure 33



Next we conducted some reactions of **8** with reducing agents. Reaction of **8** with diisobutylaluminum hydride at -20°C for four hours resulted in recovery of unchanged starting material. When the reduction was performed at 0°C using one equivalent of the reducing agent, reduction of the C - 3 acetate was observed. No reduction of the five membered lactone was detected. When excess reducing agent (5 equivalents) was used, and the reaction was performed at room temparature, the tetrahydrofuran **11** was isolated. (fig 35).

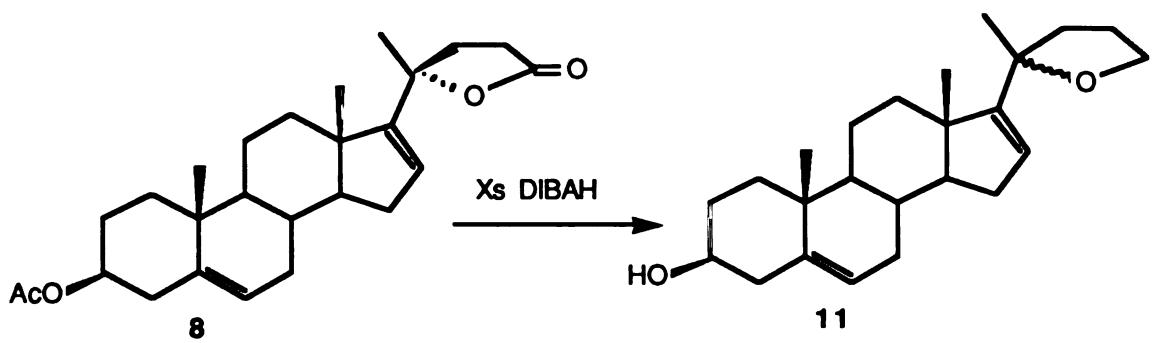


Figure 35

As can be seen from fig 35, **11** was isolated as a 1:1 mixture of C - 20 epimers. The reason for the slower reduction of the lactone function compared with the acetate is not entirely clear. It is possible that the Lewis acidic nature of DIBAL, causes the lactone ring to open up before it gets reduced. This would account for the epimerization at C - 20. The tetrahydrofuran itself is formed by dehydration of triol **9,** which is the initial reduction product. (fig 36) This dehydration is no doubt catalyzed by the Lewis acidic nature of the aluminum in this reducing agent.

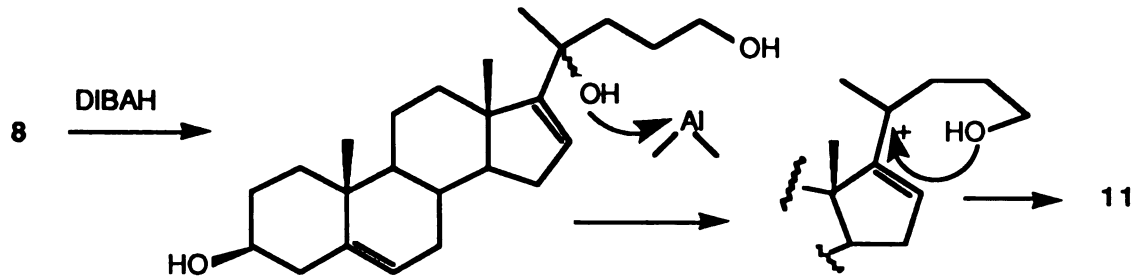


Figure 36

Triol **9** can be isolated by conducting the reduction of **8** with lithium aluminum hydride. In this manner the stereochemical integrity of C - 20 is preserved. The acid sensitive nature of triol **9** is demonstrated by the its facile dehydration to **11** in the presence of mild acids. In fact, a solution of **9** in $CDCl_3$ was completely converted to **11** over several hours. This dehydration could be avoided by adding a few drops of pyridine during the work up. In this fashion **9** remained stable over extended periods of time, even in solution. (fig 37).

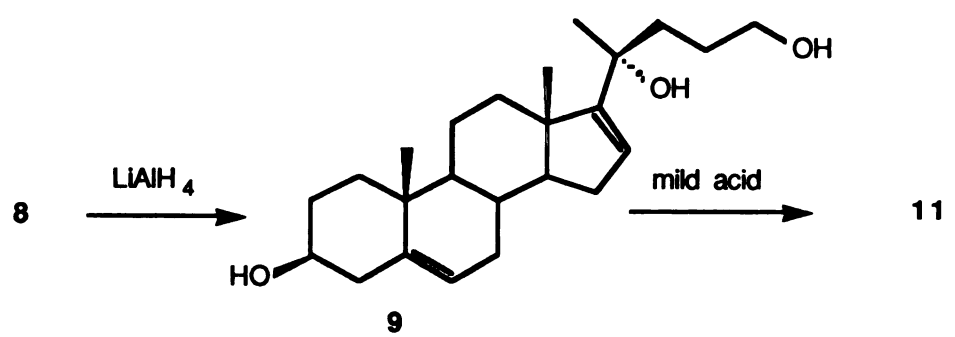


Figure 37.

Oxidation of triol **9** using pyridinium chlorochromate yielded enone **24.** Understandably, the acidic condition of this oxidizing reagent caused the

migration of the double bond from C - 5 to C - 4. Oxidation of **9** using pyridinium dichromate did not cause migration of the double bond and also enabled the isolation of the C - 24 aldehyde **25**. It also possible to protect selectively the two hydroxyl groups at C - 3 and C - 24 of **9** without affecting the stereochemistry of C - 20 in any way. Thus reaction of **9** with acetic anhydride in pyridine[48] yielded diacetate **10**. (fig 38).

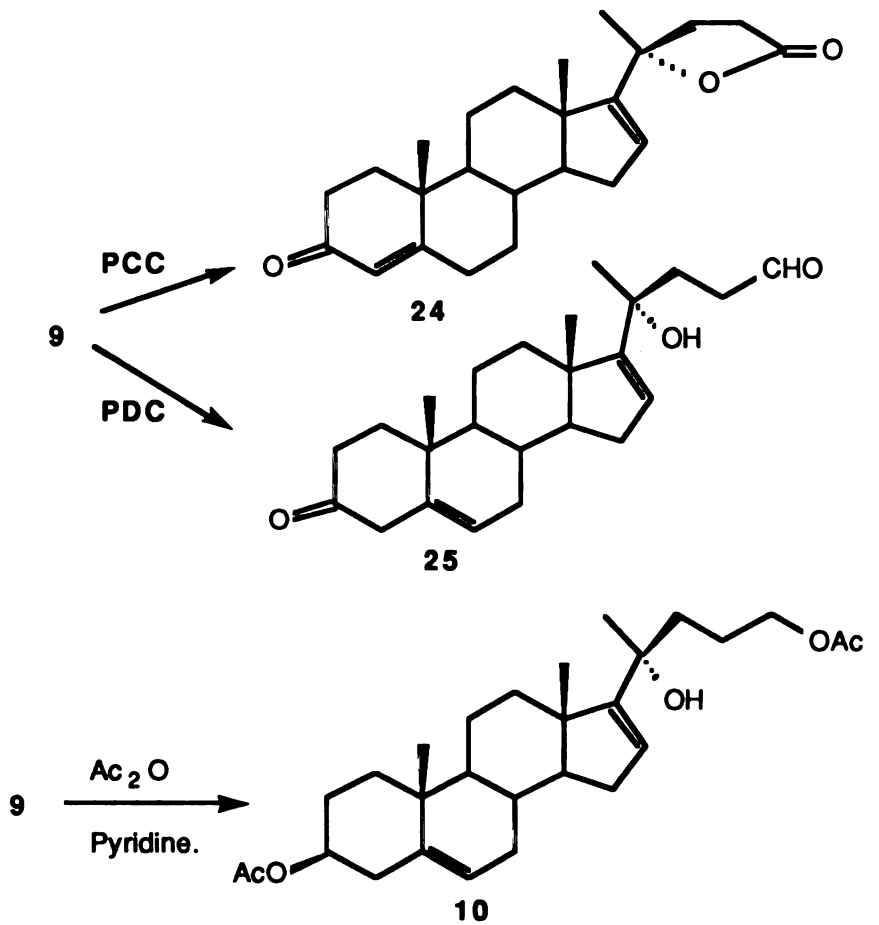
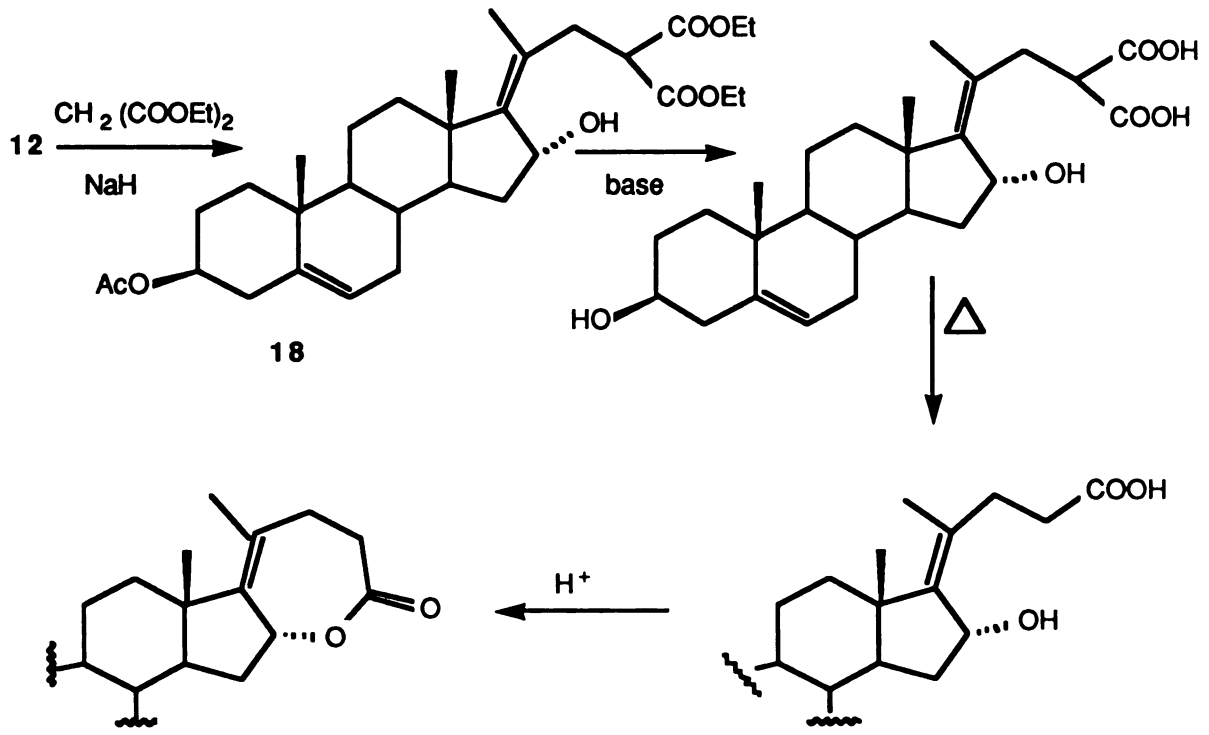


Figure 38.

As described earlier, we believe the conversion of epoxy olefin **4** to the five membered lactone **6** proceeds through the intermediacy of the seven membered lactone, **5**. We realized that this proposal would remain

speculative unless we were able to isolate the seven membered lactone **5** and study its rearrangement. However, all our efforts aimed at its isolation from the reaction of **4** with dichloroketene had been unsuccessful. Realizing that compound **5** is probably too unstable under these reaction conditions to allow its isolation, we turned our attention to other ways of constructing similar systems. We hoped that from our study of these related systems, we would be able to support our theories regarding the mechanism of the reaction of dichloroketene with epoxy olefin **4.** If we could prove that seven membered lactones similar to **5**, do indeed rearrange to five membered lactones as suggested earlier, it would give considerable credence to the proposed mechanism.

The isolation and characterization of the allyl chloride **12** provided us with a reasonable pathway for the synthesis of seven membered lactones similar to **5**. Alkylation of **12** with the anion of diethyl malonate, followed by hydrolysis of the ester and decarboxylation should lead us to the type of substrate we are interested in. (scheme **6**).



Scheme 6

The alkylation of **12** proceeded as anticipated[49] and **18** was isolated in near quantitative yield. However attempts to hydrolyze **18** failed to yield the expected diacid. The reaction generally resulted in the formation of a white solid, insoluble in most organic solvents and water. The ^{1}H NMR of this compound was not very helpful its identification. However there were indications of some decomposition.

At this point we decided to modify our approach slightly, by using the anion of dimethyl malonate to alkylate the allyl chloride **12,** since methyl esters can be converted to the corresponding acids by SN^2 type displacements[51]. Alkylation of **12** using the anion of dimethyl malonate was performed as described in the experimental section. The product isolated from this reaction was almost entirely the seven membered lactone **20**. Only a trace (6%) of the expected product **19**, was isolated. (fig 39).

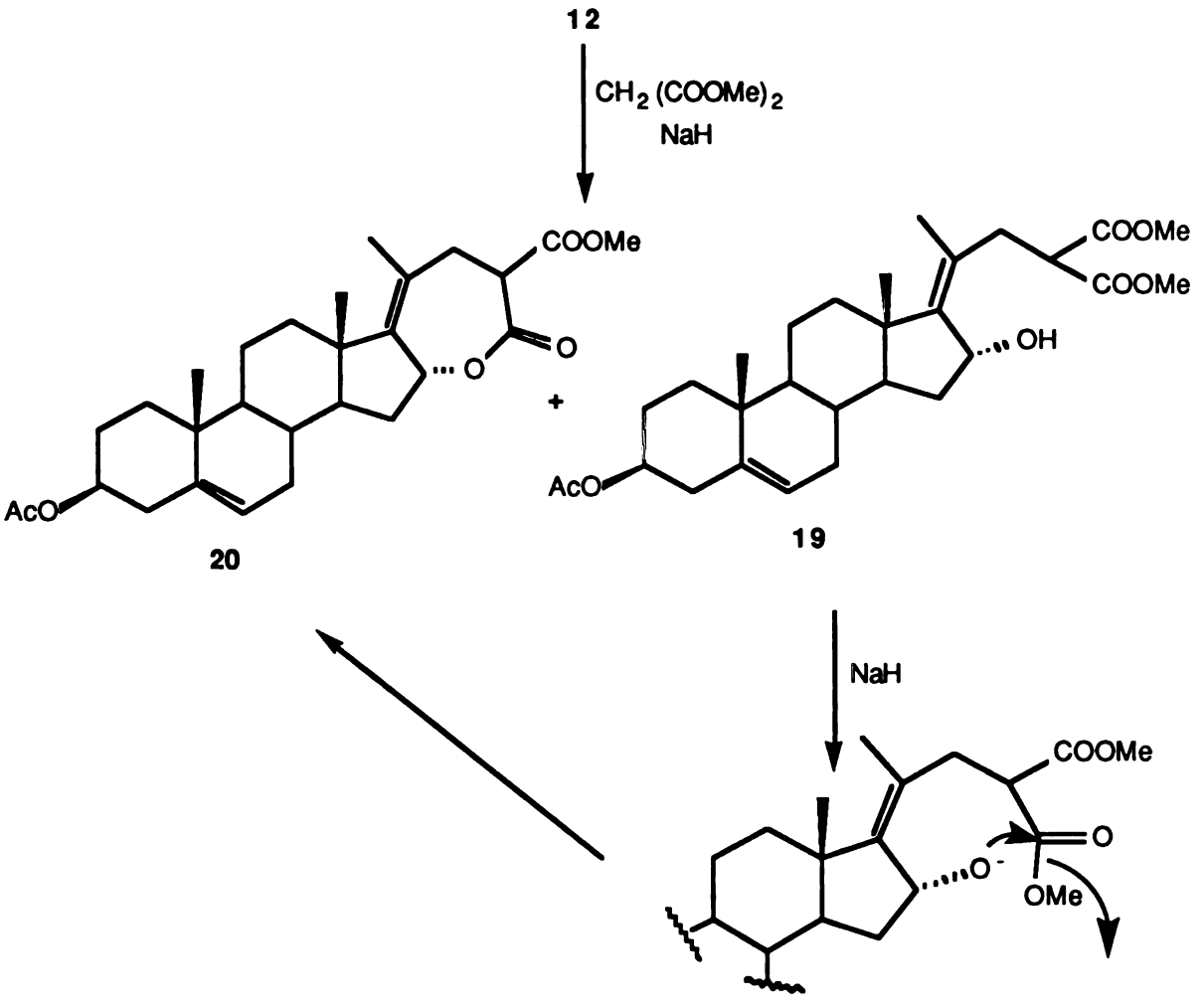


Figure 39.

The structure of **20** was confirmed beyond any doubt by spectroscopic evidence. The downfield shift of the proton at C - 16 by approximately 0.7 ppm (relative to the signal in **18** and **12**), and the presence of only one methoxy group in the ^{1}H NMR spectrum were indicative of the formation of **20**. The carbonyl absorption signal at 1752 cm^{-1} in the infrared spectrum of **20** also confirmed the presence of a seven membered lactone.

The isolation of **20** provided us with a substrate similar to **5,** and we decided to study its behaviour with Lewis acid catalysts. Thus **20** was reacted with trichloroacetyl chloride and zinc in ether solution, conditions similar to those under which **6** was formed from **4**. The ^{1}H NMR of the product revealed that the seven membered lactone of **20** had indeed undergone a rearrangement to the five membered lactone. The appearance of a new ^{1}H NMR signal at δ 5.68, due to the vinylic hydrogen at C - 16, was an indication of this fact. However this spectrum also revealed that the product was approximately a 5 : 1 mixture of two epimers. The infra red spectrum of this product showed a carbonyl absorption at 1775 cm^{-1}, confirming the presence of a five membered lactone.

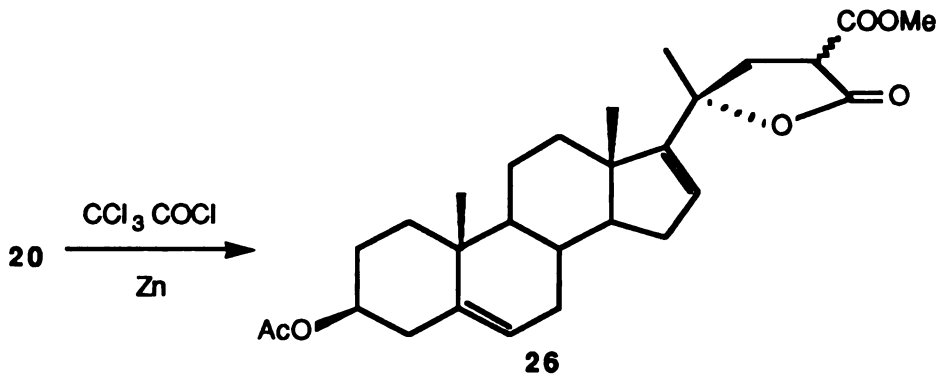


Figure 40

Hydrolysis of the methyl ester **26** using methanolic potassium hydroxide gave the acid **27.** On refluxing with benzene, 27 decarboxylated smoothly to yield the lactone **28.** The spectra of **28** are identical with those obtained from the compound produced by hydrolysis of **8** with methanolic potassium carbonate. (fig 41). The isolation of **28** as a single epimer by the hydrolysis and decarboxylation of **26** indicates that **26** must be epimeric at

C - 22. Thus the rearrangement of **20** to **26** is completely stereoselective, and we have demonstrated that seven membered lactones such as **5** undergo a novel and stereoselective 1, 3 - rearrangement.

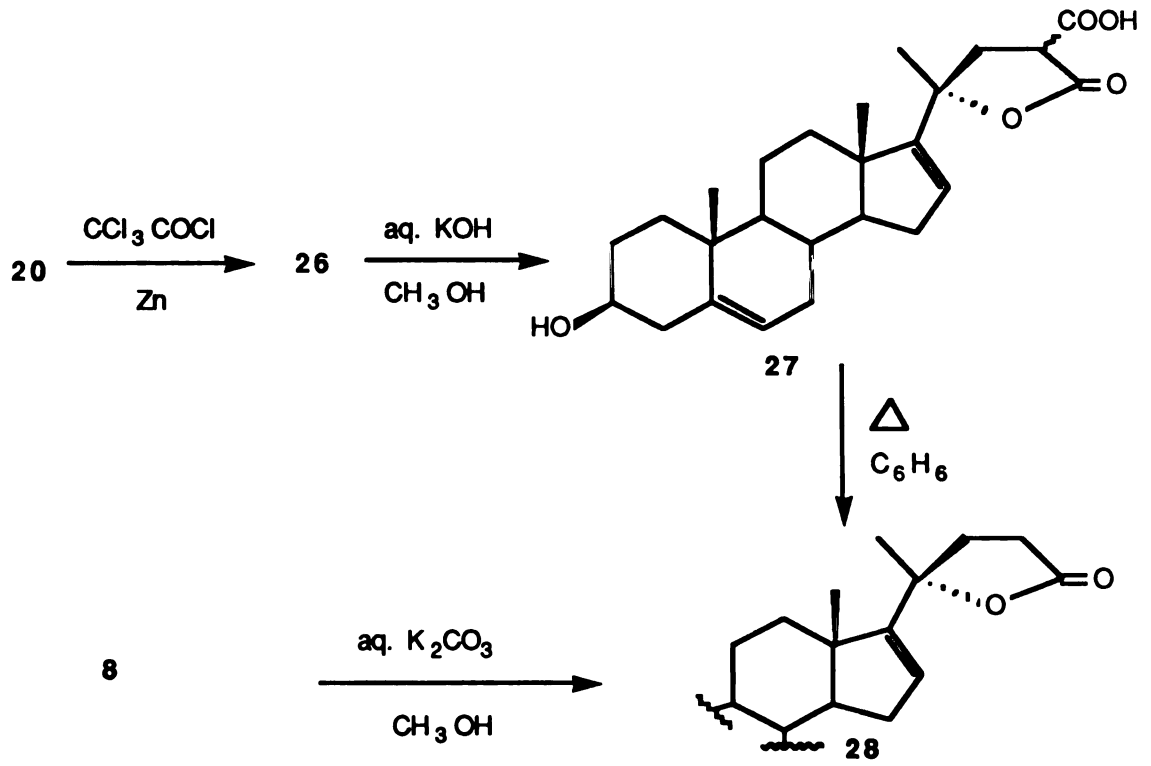


Figure 41

With the synthesis of lactone **20,** we have achieved one of the primary objectives of this work. We have also uncovered a new reaction of epoxy olefins with dichloroketene. This has led to ths synthesis of lactone **8** in a concise and stereoselective fashion. Compound **8** may be very useful for the elaboration of steroid side chains in a stereoselective manner.

EXPERIMENTAL

General.

Except where indicated, all reactions were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Magnetic stirrers were used for small scale reactions; large scale reactions were agitated using paddle stirrers. Organic extracts were always dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. The progress of most reactions were followed by thin layer chromatography and/or gas liquid chromatography. Visualization of the thin layer chromatograms was effected by 30% sulfuric acid with subsequent heating.

Analysis by GLPC was conducted with a Varian 1200 gas chromatograph. Flash chromatography was carried out on flash silica (37-53 mesh) as suggested by Still et al. Melting points were determined on a Hoover-Thomas apparatus (capillary tube) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were taken in deuterochloroform solutions with either a Varian T-60 or a Bruker 250 MHz spectrometer and are calibrated in most cases in parts per million (δ) downfield from tetramethylsilane as an internal standard. In some cases the chloroform peak (7.24 ppm) was used as a standard for ^{1}H NMR measurements. Carbon-13 NMR spectra were taken in deuterochloroform solutions with Bruker 250 MHz spectrometer and are calibrated in parts per million (δ) using

tetramethylsilane as an internal standard. Mass spectra were obtained with a Finnigan 4000 GC/MS spectrometer.

Microanlyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. High resolution mass spectroscopy were performed by Mass Spectroscopy Facility, Department of Biochemistry, Michigan State University, East Lansing, MI.

Wittig Reaction of 16 α, 17 α - Epoxypregnenolone Acetate

To a solution of 1.4 mL of diisopropylamine in 7 mL of THF held at 0° C was added 4 mL of 2.5 M n-Butyl lithium. The solution was stirred at this temparature for 20 min. The resulting lithium diisopropylamide solution was then transferred by a cannula to a suspension of 3.6 g (10 m.mol), of methyl triphenyl phosphonium bromide in 15 mL of THF (0°C). The yellow colored ylide was stirred at this temparature for a further 2 h, a solution of 2.97 g (8 m.mol) of 16 α, 17 α - epoxypregnenolone acetate (**3**) in 15 mL of tetrahydrofuran was then added and the resulting mixture was allowed to warm to room temparature. Following 4 to 5 h. of stirring, the reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with ether. The combined organic layers were evaporated and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane). In this manner pure **4** (2.53 g, 86% yield) was obtained together with 3 to 4 % of unreacted ketone. Characteristic properties of **4** :

M.P. : 129-131°C.

^{1}H NMR ($CDCl_3$). δ 5.34 (d, 1H, J = 4.9 Hz), 5.04 (t, 1H, J = 1.5 Hz),

4.98 (br. s, 1H), 4.55 (m, 1H), 3.38 (s, 1H), 2.00 (s, 3H), 1.798 (s, 3H), 1.01 (s, 3H), 0.799 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) δ: 170.89 (s), 140.37 (s), 122.70 (d), 116.37 (t), 74.29 (d), 73.06 (s), 61.44 (d), 50.79 (d), 46.21 (d), 42.50 (s), 38.56 (t), 37.38 (t), 37.24 (s), 32.91 (t), 31.97 (t), 30.96 (d), 28.18 (q), 27.89 (t), 21.83 (q), 21.42 (t), 21.19 (t), 19.71 (q), 16.24 (q) ppm.

IR ($CDCl_3$) : 2950, 2850, 1748 cm^{-1}

Mass spectrum (70eV), m/e (rel. intensity) : 370 (0.2); 310 (9.5); 242 (7.8); 198 (15); 43 (100).

Anal. Calcd. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25.

Found : C, 77.61; H, 9.26.

Reaction of dichloroketene with Epoxy Olefin 4 :

To 1.85 g (5 m.mol) of **4** was added 6 mL of anhydrous 1,2 - dimethoxyethane, 12 mL of diethyl ether and 500 mg of Zinc/copper couple. This mixture was stirred under nitrogen while 0.67 mL (6 m.mol) of trichloroacetyl chloride in 1 mL of ether was added dropwise. The resulting mixture was refluxed for 24 h, additional portions of the reagents (1 g of Zinc/copper couple, 5 mL of glyme and 5 mL of ether and 0.8 mL of trichloroacetyl chloride) were then added, the latter dropwise, and reflux was continued for an additional 24 h. The reaction mixture was filtered through celite, extracted with ether and the ether extracts were washed with saturated aqueous bicarbonate, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the solid residue then purified by column chromatography (silica gel, 15% ethyl acetate in hexane), giving 1.7 g (71%)

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of pure **6**. In ether solution alone, with excess dichloroketene, yields up to 85% have been obtained. Characteristic properties of **6** :

M.P. : 128-130°C.

^{1}H NMR ($CDCl_3$) : δ 5.675 (dd, 1H, J = 1.5 & 3 Hz), 5.36 (d, 1H, J = 4.4 Hz), 4.58 (m, 1H), 3.33 - 3.0 (AB quartet, 2H, J = 15 Hz), 2.0 (s, 3H), 1.7 (s, 3H), 1.02 (s, 3H) , 1.0 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) : δ 172 (s), 170.6 (s), 155.6 (s), 140.5 (s), 129 (d), 122.2 (d), 85.8 (s), 76.75 (s), 75.1 (d), 59 (d), 56.2 (t), 50.7 (d), 48.2 (s), 38.3 (t), 37.7 (t), 37.6 (s), 36.3 (t), 32.5 (t), 31 (d), 29.1 (q), 28.9 (t), 22 (q), 21.5 (t), 20 (q), 18.5 (q) ppm.

IR ($CDCl_3$) : 2900, 2830, 1791, 1728 cm^{-1}.

Mass spectrum (70eV): m/e (rel. intensity) 422 (2); 421 (0.7); 420 (3.3) [M-CH_3CO_2H]; 105 (10); 91 (13); 43 (100).

Anal. Calcd. for $C_{26}H_{34}O_4Cl_2$: C, 64.86; H, 7.12: Cl, 14.73.

Found : C, 64.76; H, 7.15; Cl, 14.70.

Dechlorination of 6 by Tributyltin Hydride :

A solution of 115 mg of **6** (0.24 m. mol) in 3 mL of toluene was cooled to 0°C and maintained under an argon atmosphere while 0.14 mL (0.53 m. mol) of tributyltin hydride was added. The reaction mixture was then allowed warm up to room temparature and stirred for 3 h. The reaction was quenched by the dropwise addition of water. The solution was extracted with ether, the organic layer dried over anhydrous sodium sulfate and the solvent evaporated. The solid residue was purified by flash chromatography (elution with hexane removes all the tin residues and further elution with methylene chloride gave a white solid). The product proved to be a single isomer, but one chlorine atom still remained (mass spectroscopy) and the final

identification was made by X-ray analysis. Purification gave 85 mg (80%) of **7**, which exhibited the following characteristics :

M.P. 210- 212°C.

^{1}H NMR ($CDCl_3$) δ 5.67 (dd, 1H, J = 1.4 & 3 Hz), 5.36 (d, 1H, J = 5.1 Hz), 4.58 (t overlapping m, 2H, J = 9 Hz), 2.72 (two overlapping doublets, 2H), 2.01 (s, 3H), 1.55 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) δ 171.92, 170.62, 155.88, 140.10, 127.23, 122.18, 84.82, 73.83, 57.91, 50.94, 50.11, 47.70, 44.61, 38.07, 36.81, 36.66, 35.54, 31.30, 31.19, 30.23, 27.65, 27.45, 21.38, 20.70, 19.14, 17.53.

IR (CH_2Cl_2) : 3060, 2950, 1785, 1730 cm^{-1}

Mass spectrum (70eV) : m/e (rel. intensity) : 388 (5); 387 (5); 386 (20) [M-CH_3CO_2H]; 371 (11); 253 (14); 159 (13);), 157 (13); 145 (24); 43 (100).

Dechlorination of 6 by Zinc in Methanolic Ammonium Chloride :

To a solution of 200 mg of **6** in 20 mL of methanol saturated with ammonium chloride was added 250 mg of zinc. This stirred mixture was refluxed under an argon atmosphere for 6 h. The reaction mixture was then cooled and filtered through a celite pad, followed by an ether wash. The white residue remaining after evaporation of the solvent was treated with dilute acid (0.5% sulfuric acid) and extracted with ether. The extracts were washed with brine, dried and the solvent evaporated, yielding 164 mg (95.5%) of **8**. This compound exhibited the following properties.

M.P. : 174-177°C.

^{1}H NMR ($CDCl_3$) δ 5.63 (dd, 1H, J = 1.5 & 3.2 Hz), 5.43 (d, 1H, J = 4.7 Hz), 4.58 (m, 1H), 2.55 (m, 2H), at 2.01 (s, 3H), 1.545 (s, 3H), 1.027 (s, 3H), 0.979 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) δ 176.92, 170.62, 156.58, 140.07, 126.24, 122.26, 87.02, 73.85, 58.00, 50.14, 47.28, 38.07, 36.83, 36.66, 35.63, 34.29, 31.33, 31.04, 30.27, 29.04, 27.86, 27.67, 21.35, 20.70, 19.14, 17.35 ppm.

IR ($CDCl_3$) : 2970, 1768, 1720 cm^{-1}.

Mass spectrum (70eV) : m/e (rel. intensity) : 352 (83) [M-CH_3CO_2H]; 337 (33); 253 (23); 99 (88); 43 (100).

$[\alpha]_D$ = -58.78° (4.1 mg/ml in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80.

Found : C, 74.96; H, 8.71.

Reduction of 8 by Diisobutylaluminum Hydride (DIBALH) :

A solution of 10 mg of the lactone **8** in 5 mL of ether was mixed with 5 equivalents of diisobutylaluminum hydride and the mixture was refluxed for 12 h. It was quenched by the addition of 3 mL of methanol. A 30% sodium - potassium tartarate solution was added and the mixture stirred for a further 2 h. It was then extracted with ether, the organic layer washed with sodium - potassium tartarate twice and the ether layers dried over anhydrous sodium sulfate. Evaporation of solvent yielded 7.1 mg (82%) of a white solid which proved to be **11**. From the ^1H NMR it is clear that the acetate group has been lost in the reduction. Efforts to reduce the lactone selectively without removing the acetate proved unsuccesful, even when the reduction was carried out at lower temparatures with one equivalent of diisobutylaluminum hydride. Furthermore, this reaction appears to cause some epimerization at C-20. Characteristic properties of **11** :

^1H NMR ($CDCl_3$) δ 5.61 (dd, 1H, J = 1.5 & 3.2 Hz), 5.4 (d, 1H, J = 4.92 Hz), 3.95-3.77 (m, 2H), 3.5 (m, 1H), 1.4 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 159.9, 141, 123.8, 121.7, 83.2, 71.6, 66.2, 58.1, 50.3, 46.6, 42.3, 37, 36.8, 36.2, 36, 31.9, 31.8, 31, 30.4, 27.8, 25.6, 21.2, 19, 17.3 ppm.

IR ($CDCl_3$) : 3610, 2940, 2860 cm^{-1}

Mass spectrum (70eV), m/e (rel. intensity) : 356 (8); 341 (38); 124 (43); 85 (100).

Reduction of 8 by Lithium Aluminum Hydride (LAH) :

A solution of 9 mg of lactone **8** in 7 mL of ether, was mixed 8 mg of lithium aluminum hydride and refluxed for 2 h. The reaction was quenched by the dropwise addition of aqueous sodium hydroxide and the resulting suspension was filtered. The residue was extracted with ether, the combined ether portions were dried and the solvent evaporated. The white solid thus obtained was purified by column chromatography yielding 7 mg (86%) of triol **9**. As expected, this compound was polar; furthermore, it slowly decomposed to tetrahydrofuran **11**, especially on exposure to acids (a chloroform solution of **7** was completely converted to **11** in a few hours). By adding a few drops of pyridine during workup, this dehydration could be prevented, even in solution. The triol **9** showed the following properties.

M.P. 129° to 132°C.

^1H NMR ($CDCl_3$) δ 5.54 (dd, 1H, J = 1.45 & 3.1 Hz), 5.34 (d, 1H, J = 5 Hz), 3.63 (t, 2H, J = 6 Hz), 3.52 (m, 1H), 1.36 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) δ 149.84, 141.125, 124.66, 121.55, 74.68, 71.68, 63.29, 58.17, 50.29, 47.19, 42.25, 38.95, 37.16, 36.65, 36.42, 31.58, 31.47, 30.95, 30.45, 29.09, 27.77, 20.94, 19.29, 17.82 ppm.

IR ($CDCl_3$) : 3610, 3420 (br), 2935, 2850 cm^{-1}.

Mass spectrum (70 eV): m/e (rel. intensity). 356 (1.7) [M-18], 341 (16), 315 (16), 124 (46), 91 (33), 85 (100).

Hydrolysis of the acetate group of 8 :

To 20 mg of the lactone **8**, in 2 mL of methanol, was added 6 mg of potassium carbonate, in 0.6 mL of water. The mixture was stirred for 3 h. The solvent was evaporated, the residue then extracted with ether. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and the solvent evaporated to yield a white solid. Purification by column chromatography, using 40% ethyl acetate in hexane as the eluent yielded 16.4 mg (93.8%) of the alcohol **23**. The compound exhibited the following properties :

M.P. : 159 - 162°C.

^{1}H NMR ($CDCl_3$) δ 5.65 (dd, 1H, J = 1.45 & 3.1), 5.33 (d, 1H, J = 5), 3.56 to 3.46 (m, 1H), methyl signals were at d 1.54, 1.01 and 0.97.

^{13}C NMR ($CDCl_3$) δ 176.80, 156.46, 141.10, 126.19, 121.23, 87.05, 71.68, 58.09, 50.24, 47.29, 42.24, 37.12, 36.62, 35.74, 34.30, 31.59, 31.38, 31.09, 30.36, 29.09, 27.89, 20.80, 19.26, 17.42.

Mass spectrum 70eV : m/e, (rel. intensity) : 370 (2.7); 355 (5.59); 337 (6.1); 271 (16.34); 99 (89.64); 55 (53.52); 43 (100).

IR ($CDCl_3$) cm^{-1} : 3600, 2940, 1770.

Preparation of the allyl chloride 12 :

To 2 g (5.4 m.mol) of epoxyolefin **4** in 100 mL of ether, was added 0.5 g (7.5 m.mol) of Zinc - Copper couple. This mixture was refluxed under an argon atmosphere, and to the refluxing mixture was added dropwise, a solution of 0.77 mL (7 m.mol) of trichloro acetylchloride in 50 mL of ether. Reflux was continued for 6 h; the mixture was then filtered through celite,

washed with saturated sodium bicarbonate solution and brine, dried and evaporated to yield 1.13 g (51.6%) of **7**, 0.68 g (34%) of unreacted starting material and a small amount of dichloroadduct **6**. Trace amounts (~ 1%) of 17 - chloro, 16 - hydroxy compound is also obtained. Compound **12** exhibited the following properties :

M.P. : 120 to 122°C.

^1H NMR ($CDCl_3$) δ 5.37 (d, 1H, J = 5 Hz), 4.72 (d, 1H, J = 4.7 Hz), 4.15 (AB quartet, 2H, J = 10.6 Hz), 2.01 (s, 3H), 1.86 (s, 3H), 1.01(s, 3H), 0.86 (s, 3H) ppm.

^{13}C NMR δ 170.5 (s), 153.2 (s), 139.8 (s), 129.4 (s), 122.3 (d), 73.8 (d), 71.9 (d), 52.5 (dd), 49.8 (d), 49.0 (t), 44.5 (s), 38.0 (t), 37.1, 36.9, 36.6, 35.4 (t), 31.6 (t), 30.5 (d), 27.7 (q), 21.4 (q), 21.1 (t), 19.2 (q), 16.5 (q) ppm.

IR (CCl_4) : 3563, 2935, 1721 cm^{-1}.

Mass spectrum (70eV) : m/e, (rel. intensity) : 348 (1.9), 346 (5.9) [M-CH_3COOH], 328 (1.1), 310 (13.14), 43 (100).

Preparation of hydroxy ether 13 :

To 40 mg of the compound **12** in 10 mL of methanol, was added, a solution of 50 mg of potassium carbonate in 0.5 mL of water. This mixture was stirred at room temparature for 3 h. The solvent was then evaporated, the residue dissolved in ether and washed twice with water. The combined organic layers were dried over anhydrous sodium sulfate and the solvent evaporated to yield 34 mg of a white solid which proved to be **13** (yield 96%). This compound exhibited the following characteristics :

M. P. : 69 to 71°C.

^{1}H NMR ($CDCl_3$) δ 5.34 (d, 1H, J = 5.1 Hz); 4.65 (d, 1H, J = 5.3 Hz); 4.18 to 3.67 (AB quartet, 2H, J = 10.4 Hz); 3.5 (m, 1H); 3.3 (s, 3H); 1.84 (s, 3H); 0.99 (s, 3H); 0.86 (s, 3H) ppm.

IR ($CDCl_3$) : 3610, 3450 (br), 2940, 2862 cm^{-1}.

Mass spectrum (70eV); m/e, (rel. intensity) : 342 (40.2) [M-18], 328 (8.9), 157 (30.3), 145 (40), 105 (81.7), 91 (100).

Preparation of the diacetate 10 :

To 10 mg of the triol **9** in 4 mL of benzene, was added 0.2 mL of pyridine and 0.1 mL of acetic anhydride. The mixture was maintained under an argon atmosphere and stirred overnight. It was then poured into water and extracted several times with ether. The combined organic layers were dried over anhydrous sodium sulfate and the solvent evaporated, to yield the diacetate **10**, as a white solid. Purification by column chromatography (silica gel / 25% ethyl acetate in hexane) yielded 13 mg (94% yield) of the diacetate **10,** which exhibited the following characteristics.

^{1}H NMR ($CDCl_3$) δ 5.52 (dd, 1H, J = 1.5 & 3 Hz); 5.36 (d, 1H, J = 4.5 Hz); 4.03 (t, 2H, J = 6 Hz); 2.02 (s, 3H); 2.01 (s, 3H); 1.35 (s, 3H); 1.03 (s, 3H); 0.96 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) δ 171.33, 170.71, 159.91, 140.07, 124.88, 122.47, 74.67, 73.96, 64.83, 58.06, 50.22, 47.23, 38.43, 38.14, 36.93, 36.75, 36.28, 31.46, 30.98, 30.41, 28.99, 27.75, 24.01, 21.42, 21, 20.89, 19.21, 17.82 ppm.

IR ($CDCl_3$) : 3600, 2975, 2940, 2860, 1728 cm^{-1}.

Mass spectrum (25 eV); m/e, (rel. intensity) : 398 (1.2) [M-CH_3COOH], 380 (13.83), 357 (37.03), 297 (90.3), 107 (34.75), 85 (100).

Reduction of 12 with Lithium Aluminum Hydride :

To 40 mg (0.098 m.mol) of **12** in 3 mL of ether, was added 11.34 mg (0.3 m.mol) of Lithium Aluminum Hydride. The mixture was stirred for 4 h. under an argon atmosphere. The reaction was quenched by the dropwise addition of 5% sodium hydroxide solution. The reaction mixture was filtered through a celite pad, the filtrate extracted with ether, and the combined ether extracts dried over anhydrous sodium sulfate. Evaporation of solvent yielded 30 mg (91.5% yield), of **14,** which exhibited the following properties :

M.P. : 154 to 155°C.

^{1}H NMR ($CDCl_3$) : δ 5.34 (d, 1H, J = 5 Hz), 4.6 (d, 1H, J = 4.76 Hz), 3.45 to 3.61 (m, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 0.99 (s, 3H), 0.84 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) : δ 147.3, 140.81, 129.63, 121.54, 72.65, 71.70, 53.07, 50.06, 43.95, 42.25, 37.83, 37.13, 36.57, 35.12, 31.68, 31.59, 30.57, 23, 21.31, 20.13, 19.31, 17.07 ppm.

IR ($CDCl_3$) : 3610, 2940, 2865 cm^{-1}.

Mass spectrum (70 eV); m/e, (rel. intensity) : 330 (7), 315 (18.8), 312 (33), 297 (37.6), 159 (50.87), 99 (88), 91 (100).

Hydrolysis of 12 with potassium hydroxide :

To 40 mg of **12** in 5 mL of dioxane, was added 1 mL of 5% aqueous potassium hydroxide solution. After refluxing for 2.5 h, the reaction mixture was cooled, the solvent evaporated and the residue extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent evaporated to yield a white solid. Purification by column chromatography (silica gel/20% ethyl acetate in hexane), yielded 22 mg (80%) of **15** and 1.8 mg (5%) of **16.**

Oxidation of 12 with pyridinium chlorochromate (PCC) :

To 18 mg of **12** in 3 mL of methylene chloride, was added 0.5 gm of celite and 40 mg (4 equivalents) of pyridinium chlorochromate added to it. After stirring for 6 h under an argon atmosphere, the reaction mixture was filtered through a celite pad, extracted several times with ether and the combined organic layers dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification of the residue by column chromatography (silica gel/ 30% ethyl acetate in hexane), gave 16 mg (89%), of **17**. **17** exhibited the following characteristics :

M.P. : 45 to 48°C.

^{1}H NMR ($CDCl_3$) : δ 5.35 (d, 1H, J = 5 Hz), 4.68 (s, 2H), 4.67 to 4.5 (m, 1H), 2.0 (s, 3H), 1.99 (s, 3H), 1.04 (s, 6H).

IR ($CDCl_3$) : 2951, 2863, 1725, 1714, 1625 cm^{-1}.

Mass spectrum (70eV) : m/e, (rel. intensity); 362, (3.85); 360, (10.94) [M - CH_3CHO]; 346, (11.77); 344, (33.81)[M - CH_3COOH]; 331, (31.53); 329 (100); 295, (15.43); 293, (40.31); 129, (54.75).

Preparation of compound 18 :

Sodium hydride (1.2 mg, 0.05 m.mol); was added to 2 mL of tetrahydrofuran, followed by the addition of 7.6 mL (0.05 m.mol) of diethyl malonate. After stirring for 45 mins under an argon atmosphere, a solution of 15 mg (0.04 m.mol) of **12** in 2 mL of tetrahydrofuran is added to it. The mixture was stirred at room temparature for 5 h. It was then quenched by the addition of saturated ammonium chloride and extracted with ether. The combined organic layers were dried and the solvent evaporated to give a

white solid. Purification by column chromatography yields 14 mg (71.5%) of **18**, and 3 mg (20%) of recovered **12**. Compound **18** exhibited the following properties :

M. P. : 168 to 169°C.

^{1}H NMR ($CDCl_3$) : δ 5.36 (d, 1H, J = 4 Hz), 4.66 (d, 1H, J = 5 Hz), 4.57 to 4.64 (m, 1H), 4.22 to 4.1 (two overlapping quartets, 4H, J = 7 Hz), 3.64 (dd, 1H, J = 6 & 10 Hz), 3.08 (br. s, 1H), 2.92 (dd, 1H, J = 10 & 14 Hz), 2.55 (dd, 1H, J = 6 & 14 Hz), 1.99 (s, 3H), 1.68 (s, 3H), 1.23 (t, 6H, J = 7 Hz), 0.99 (s, 3H), 0.84 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) : δ 170.51, 170.07, 169.19, 151.34, 127.11, 122.61, 73.88, 71.29, 61.83, 61.59, 52.53, 49.82, 49.78, 44.18, 38.07, 37.51, 36.87, 36.63, 35.59, 34.62, 31.58, 30.45, 27.72, 21.4, 21.22, 19.21, 16.81, 16.48, 14.06, 14.02 ppm.

IR ($CDCl_3$) : 3480 (br), 2970, 2945, 2910, 1738, 1725 cm^{-1}.

Mass spectrum (25eV) : m/e, (rel. intensity) : 515, (6.64) [M - 15]; 452 (23.86) [M- CH_3COOH & H_2O] ; 437, (22.77); 310, (30.61); 173, (75.27); 160, (100).

Alkylation of 12 with dimethyl malonate :

To a suspension of 12 mg (0.5 m.mol) of sodium hydride in 2 mL of tetrahydrofuran was added 0.06 mL (0.5 m.mol) of dimethyl malonate in 2 mL of tetrahydrofuran. After stirring for 1 h under an argon atmosphere, a solution of 81 mg (0.2 m.mol) of **12** in 1 mL of tetrahydrofuran was added. The mixture was stirred for a further 10 h. The reaction was then quenched by the addition of water. Extraction with ether and evaporation of solvent gave a white solid which was purified by column chromatography (silica-gel; 30% ethyl acetate in hexane) to yield 70.5 (75% yield) of **20** and 6 mg (6%) of **19**. The compound **20** exhibited the following properties.

M.P. : 185 to 187°C.

^{1}H NMR ($CDCl_3$) : δ 5.35 (two overlapping doublets, 2H); 4.6 (m, 1H); 4.29 (dd, 1H, J = 6.3 & 13 Hz); 3.76 (s, 3H); 2.75 (dd, 1H, J = 13 & 18 Hz); 2.49 (dd, 1H, J = 6.3 & 18 Hz); 1.99 (s, 3H); 1.74 (s, 3H); 0.99 (s, 3H); 0.86 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$) : δ 170.62, 170.41, 169.04, 143.19, 139.64, 128.96, 122.1, 78.53, 73.71, 52.62, 51.59, 49.4, 46.71, 45.95, 37.98, 37.42, 36.75, 34.69, 32.57, 31.24, 30.79, 27.63, 21.36, 21.07, 19.65, 19.19, 16.88 ppm.

IR ($CDCl_3$) : 2950, 1752, 1737, 1726, 1440 cm^{-1}.

Mass spectrum (70eV); m/e(rel. intensity) : 410 (75) [M-CH_3COOH] 395 (21), 370 (8.7), 355 (10.4), 295 (46), 157 (67.4), 135 (100).

Rearrangement of 20 to 21 :

To 50 mg (0.1 m.mole) of **20**, in 3 mL of diethyl ether, was added 9 mg of Zinc - Copper couple. The mixture was stirred under an argon atmosphere while a solution of 0.013 mL of trichloroacetyl chloride in 3 mL of ether, was added dropwise. After refluxing for 4 h. the reaction mixture was filtered through a celite pad and washed successively with saturated aqueous bicarbonate and brine solution. The combined organic layers were dried over anhydrous sodium sulfate and the solvent evaporated to yield 43.5 mg (87%) of **21.** The product appeared to be a mixture of epimers (4:1) from the ^{1}H NMR. The compound **21** exhibited the following characteristics.

^{1}H NMR ($CDCl_3$) : δ 5.68 (dd, 1H, J = 1.5 & 3 Hz); 5.34 (d, 1H, J = 4 Hz); 4.6 (m, 1H); 3.75 (s, 3H); 3.6 (dd, 1H, J = 6 & 18 Hz); 2.02 (s, 3H); 1.67 (s, 3H); 1.03 (s, 3H); 0.97 (s, 3H).

IR ($CDCl_3$) : 2950, 1775, 1735, 1720 cm^{-1}.

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hydrochlori

added to

upon atmo

ether extra

ether extra

evaporated

as compou

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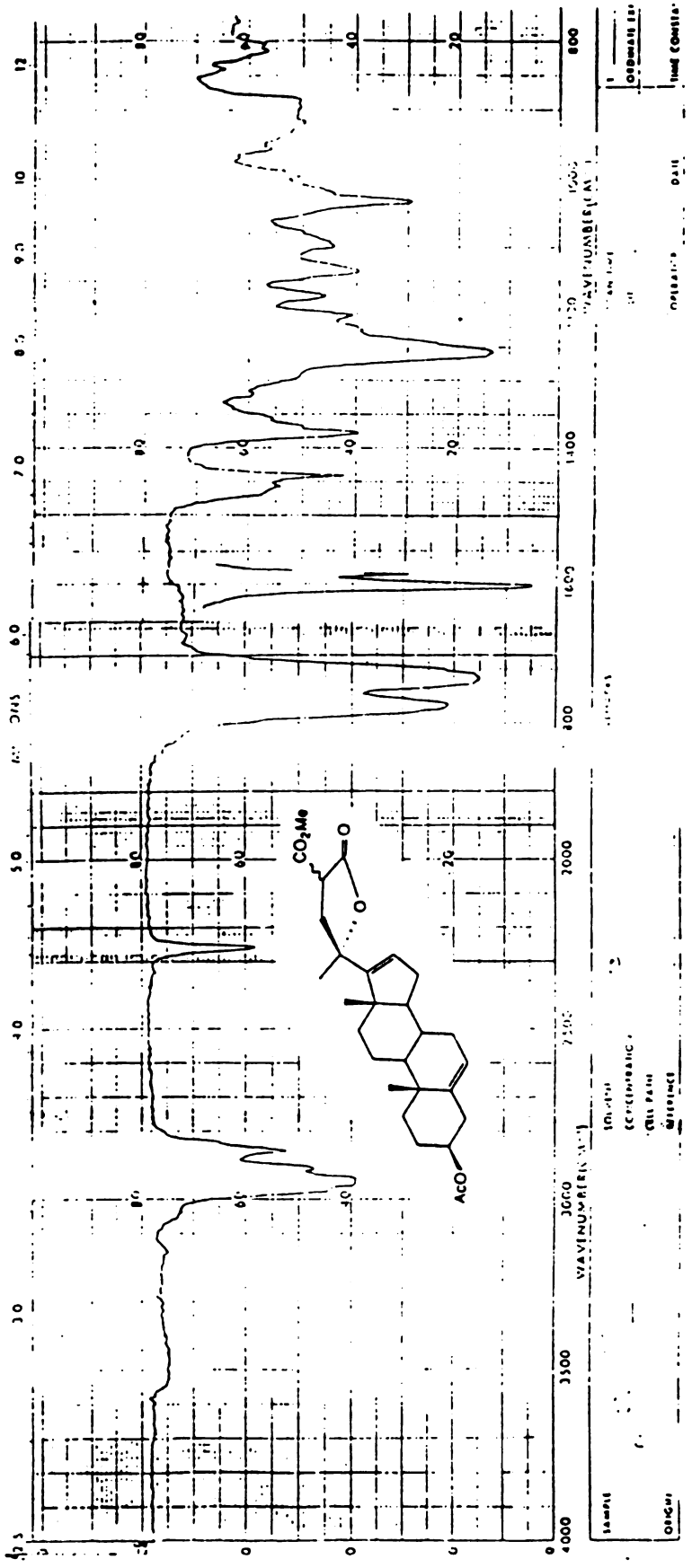
Hydrolysis and decarboxylation of 21 :

To 47 mg (0.1 m. mol.) of **21** in 3 mL of methanol, was added 3 mL of 0.1M of methanolic potassium hydroxide solution. This mixture was stirred and refluxed for 3 h. under an argon atmosphere. The mixture was then cooled and acidified to pH 5 by the dropwise addition of cold 0.1N hydrochloric acid. The solvent was then evaporated and 5 mL of benzene added to the white residue. The benzene solution was refluxed under an argon atmosphere, for 1 h. It was then cooled and extracted with ether. The ether extracts were washed successively with water and brine. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent evaporated to yield 32 mg of a white solid. Examination of the spectra of this compound revealed that it was identical to 23. This compound was obtained as a single isomer.

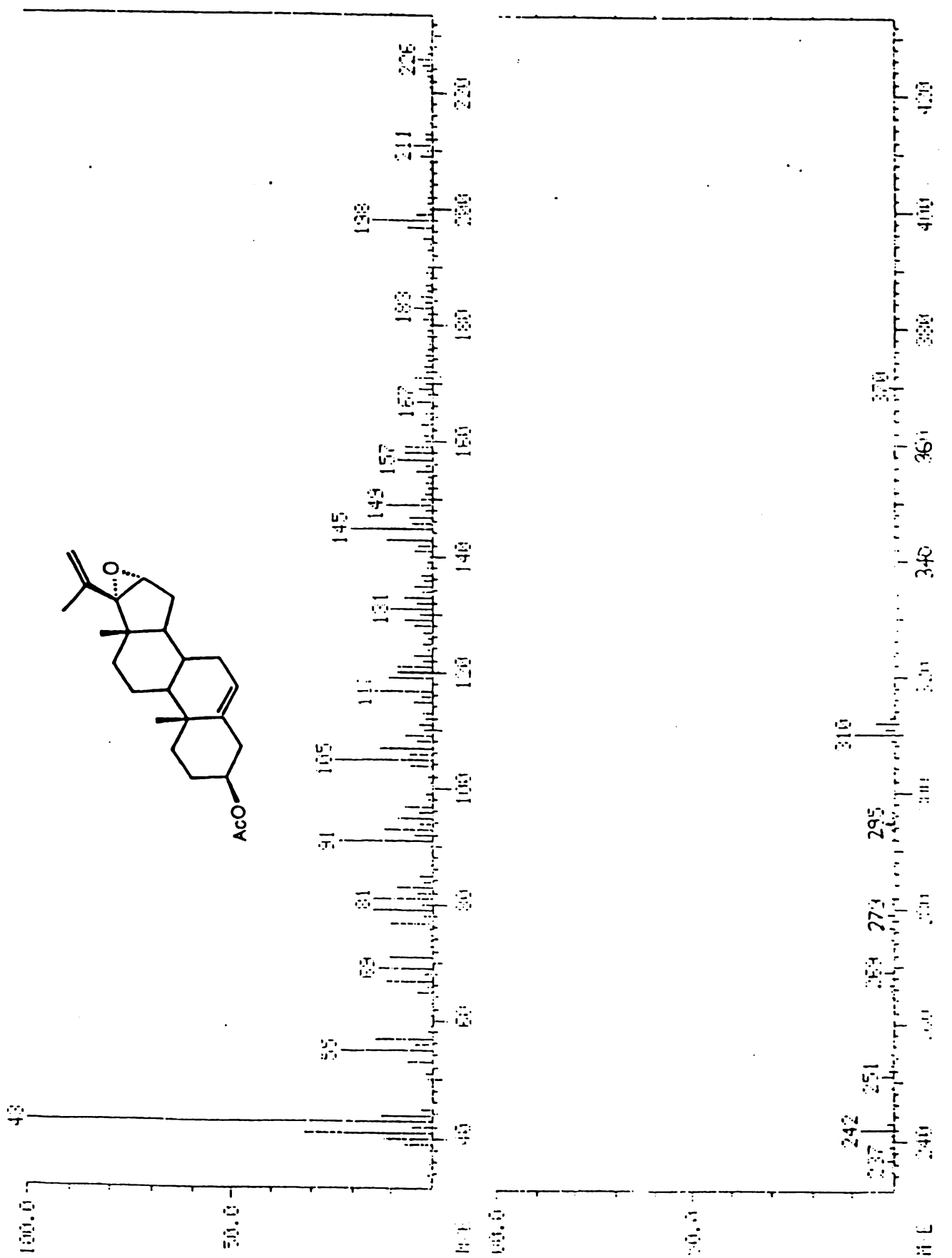
Hydrolysis and decarboxylation of 21 :

To 47 mg (0.1 m. mol.) of **21** in 3 mL of methanol, was added 3 mL of 0.1M of methanolic potassium hydroxide solution. This mixture was stirred and refluxed for 3 h. under an argon atmosphere. The mixture was then cooled and acidified to pH 5 by the dropwise addition of cold 0.1N hydrochloric acid. The solvent was then evaporated and 5 mL of benzene added to the white residue. The benzene solution was refluxed under an argon atmosphere, for 1 h. It was then cooled and extracted with ether. The ether extracts were washed successively with water and brine. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent evaporated to yield 32 mg of a white solid. Examination of the spectra of this compound revealed that it was identical to 23. This compound was obtained as a single isomer.

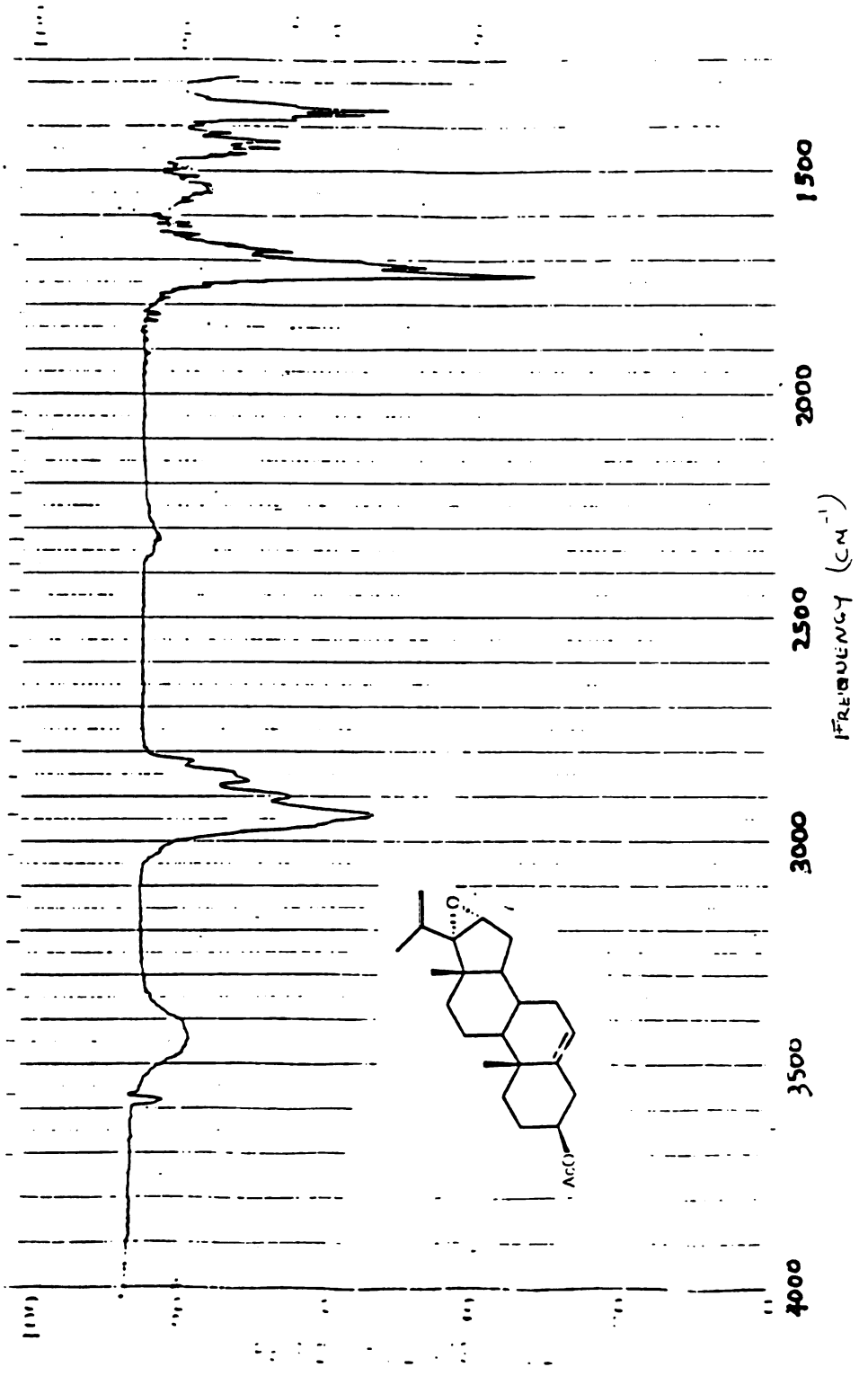
APPENDIX - I



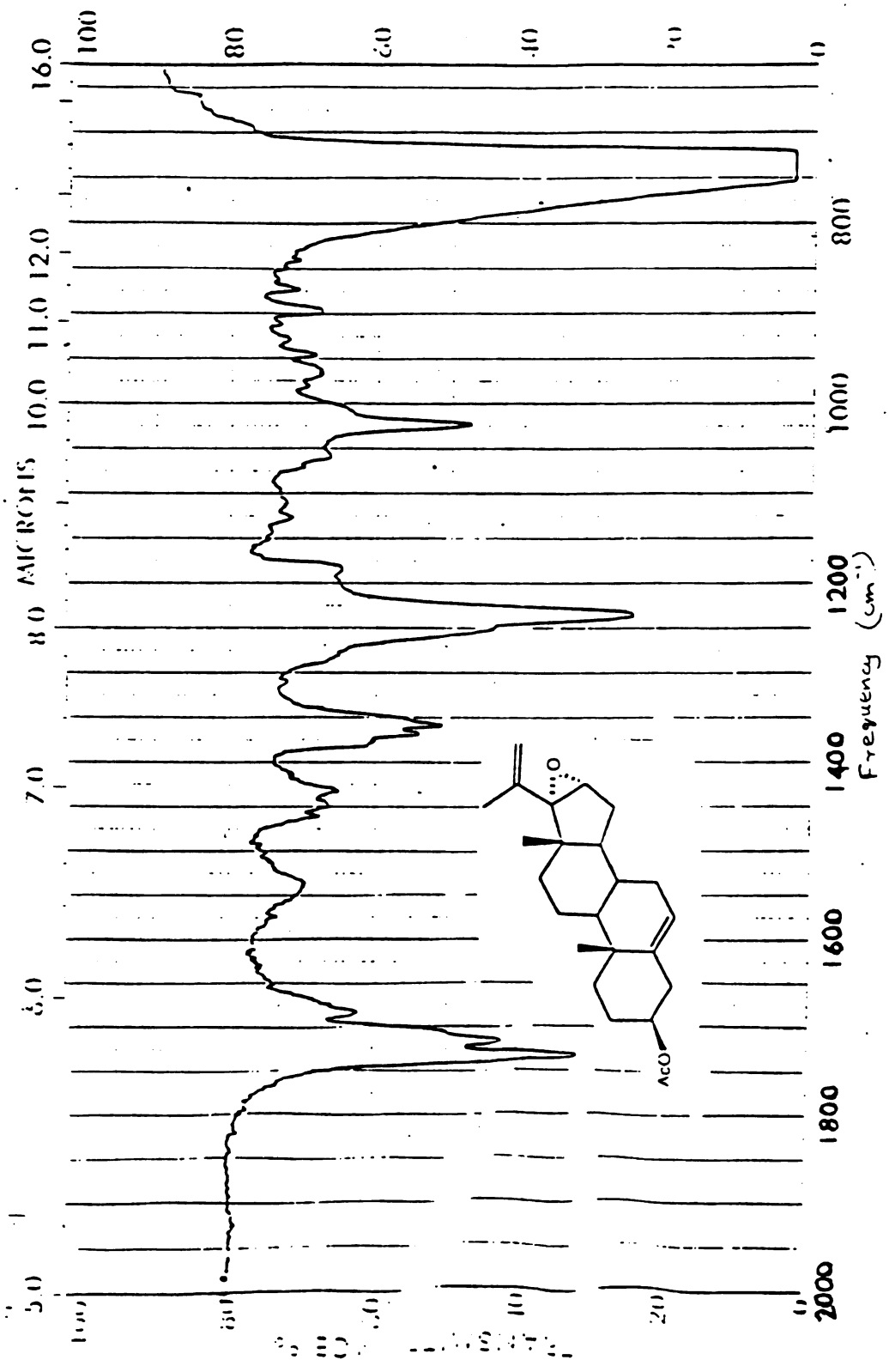
IR of 21



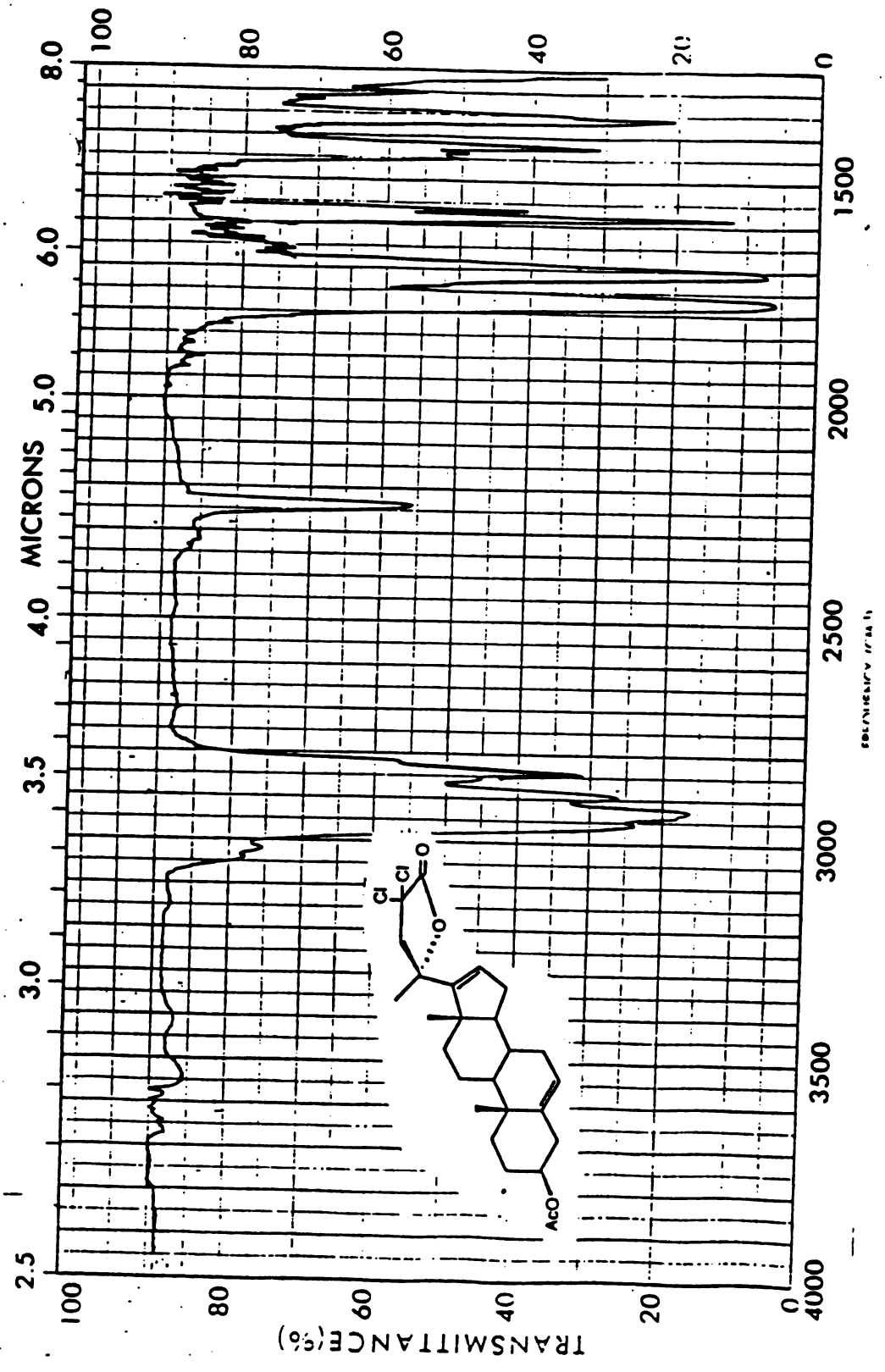
Mass spectrum of 4.



IR of 4.

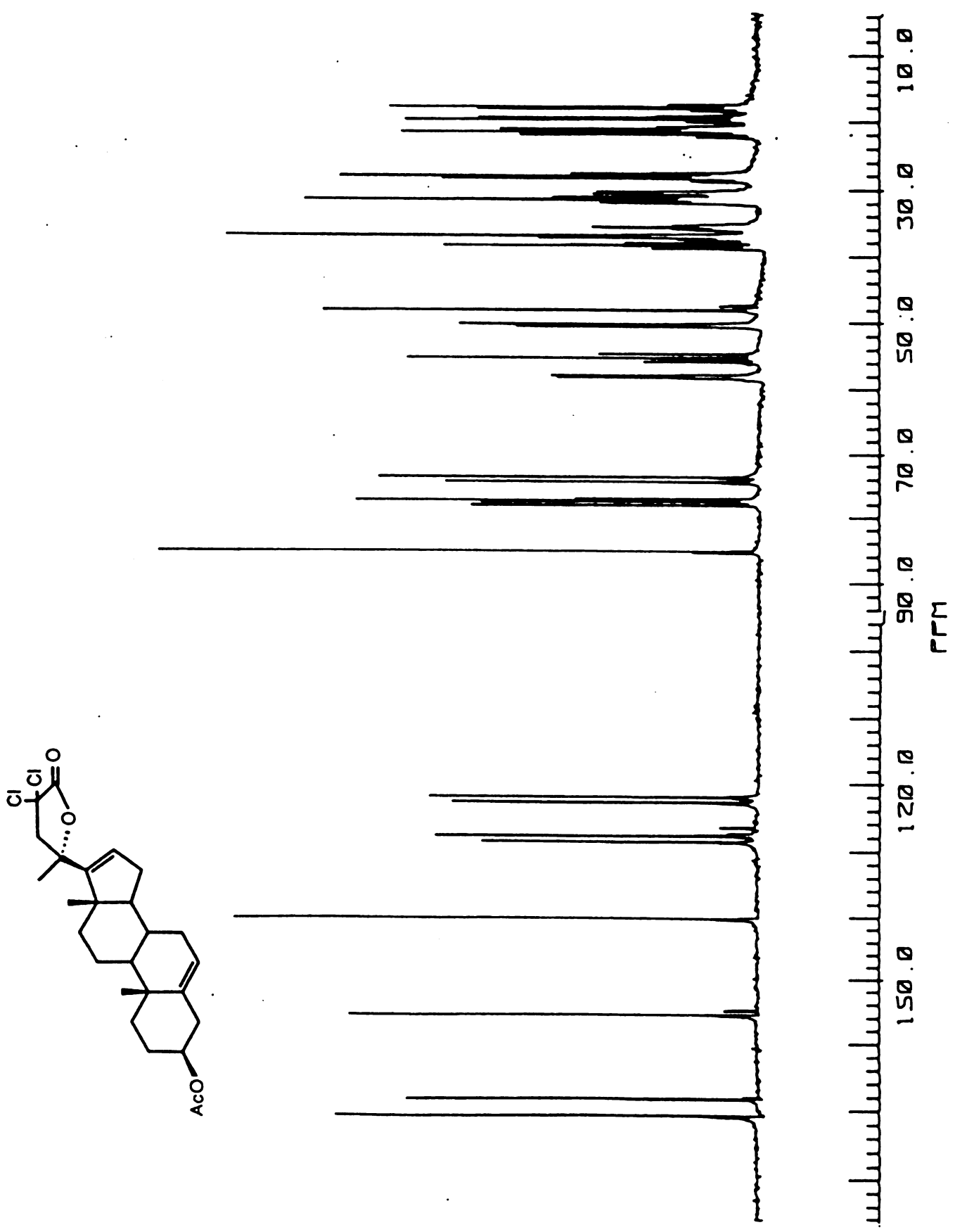


IR of 4

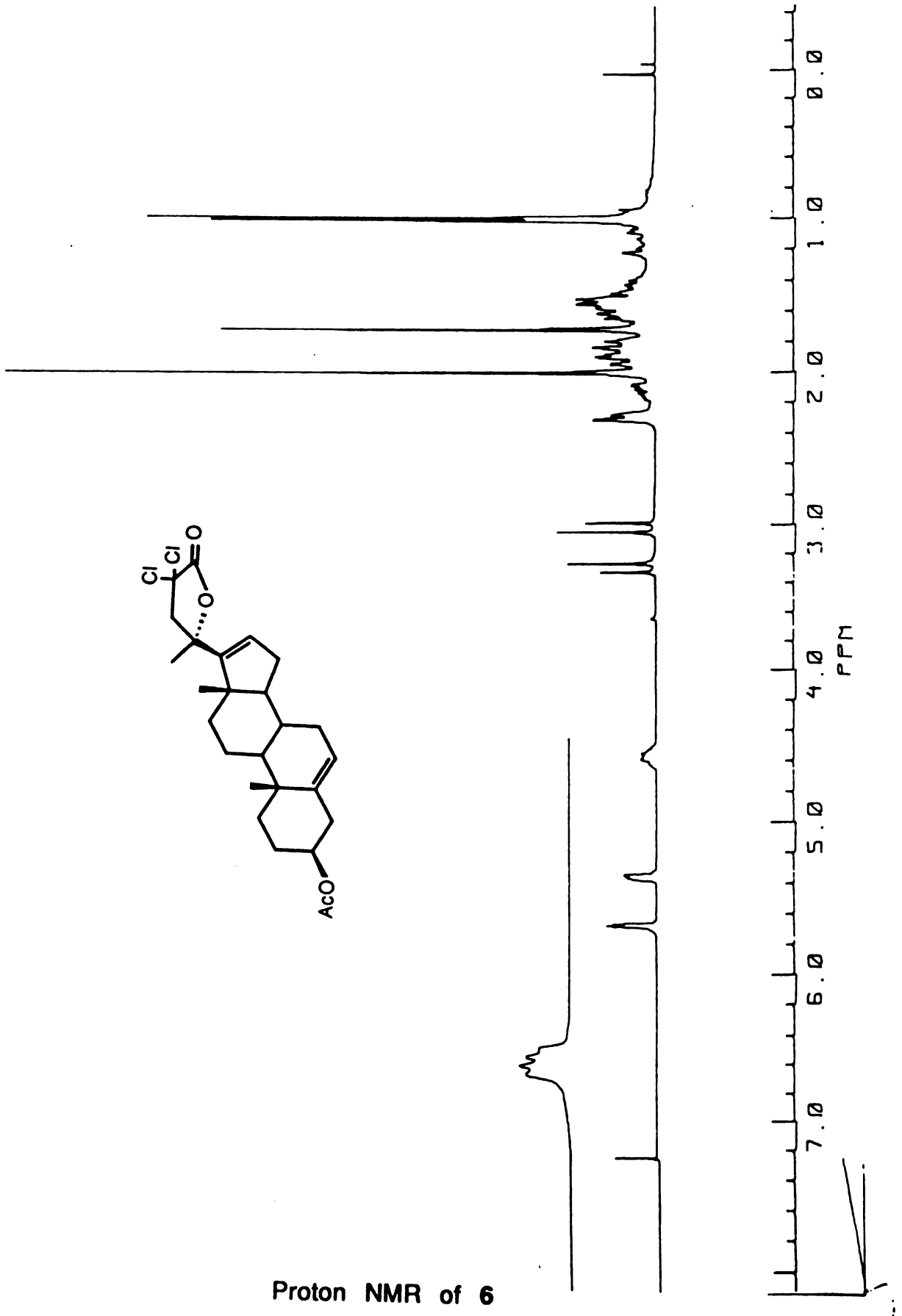

TRANSMITTANCE(%)
MICRONS
4000
3500
3000
2500
2000
1500
AcO
Cl
O

IR of **6**

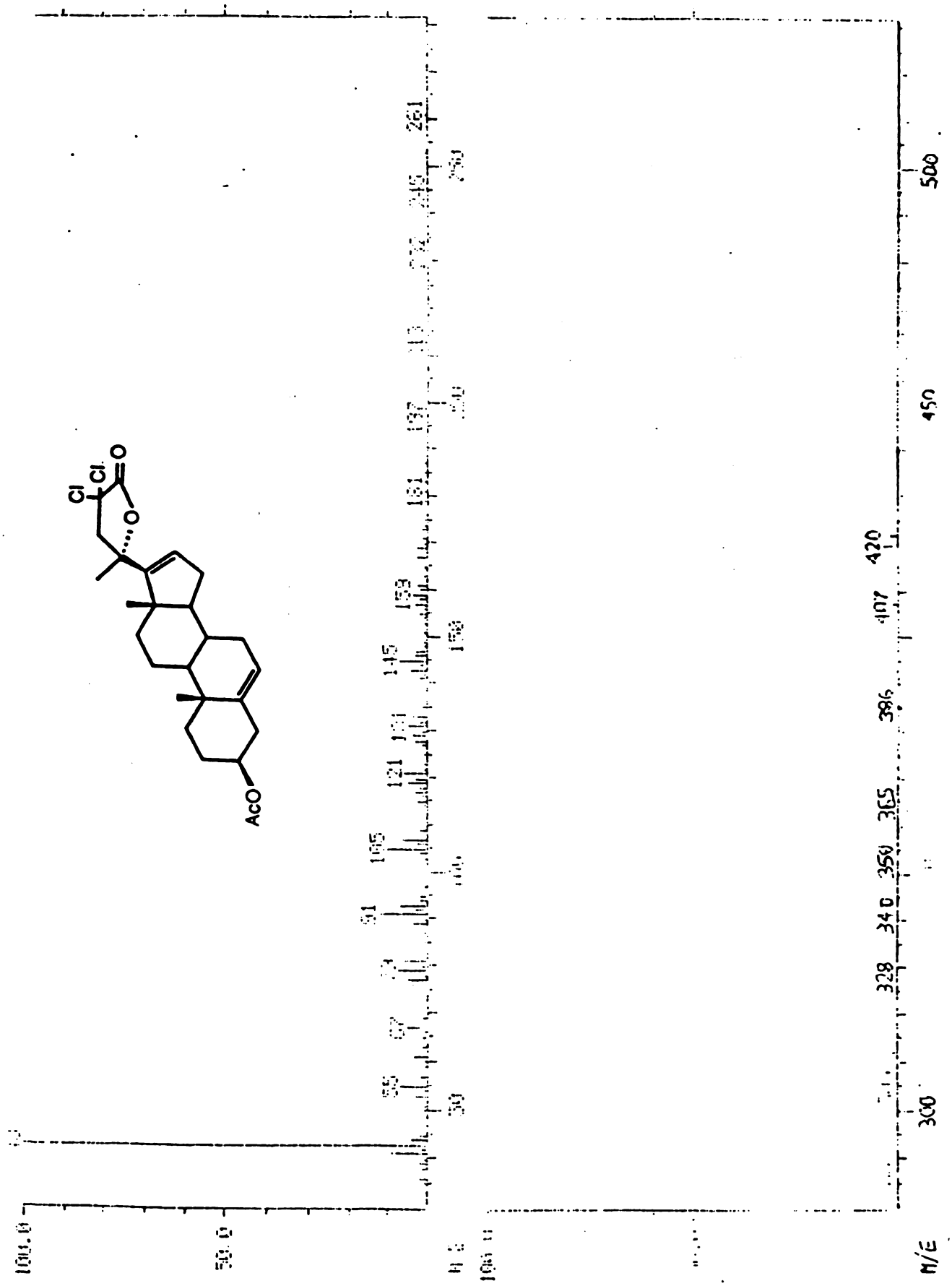
IR of **6**



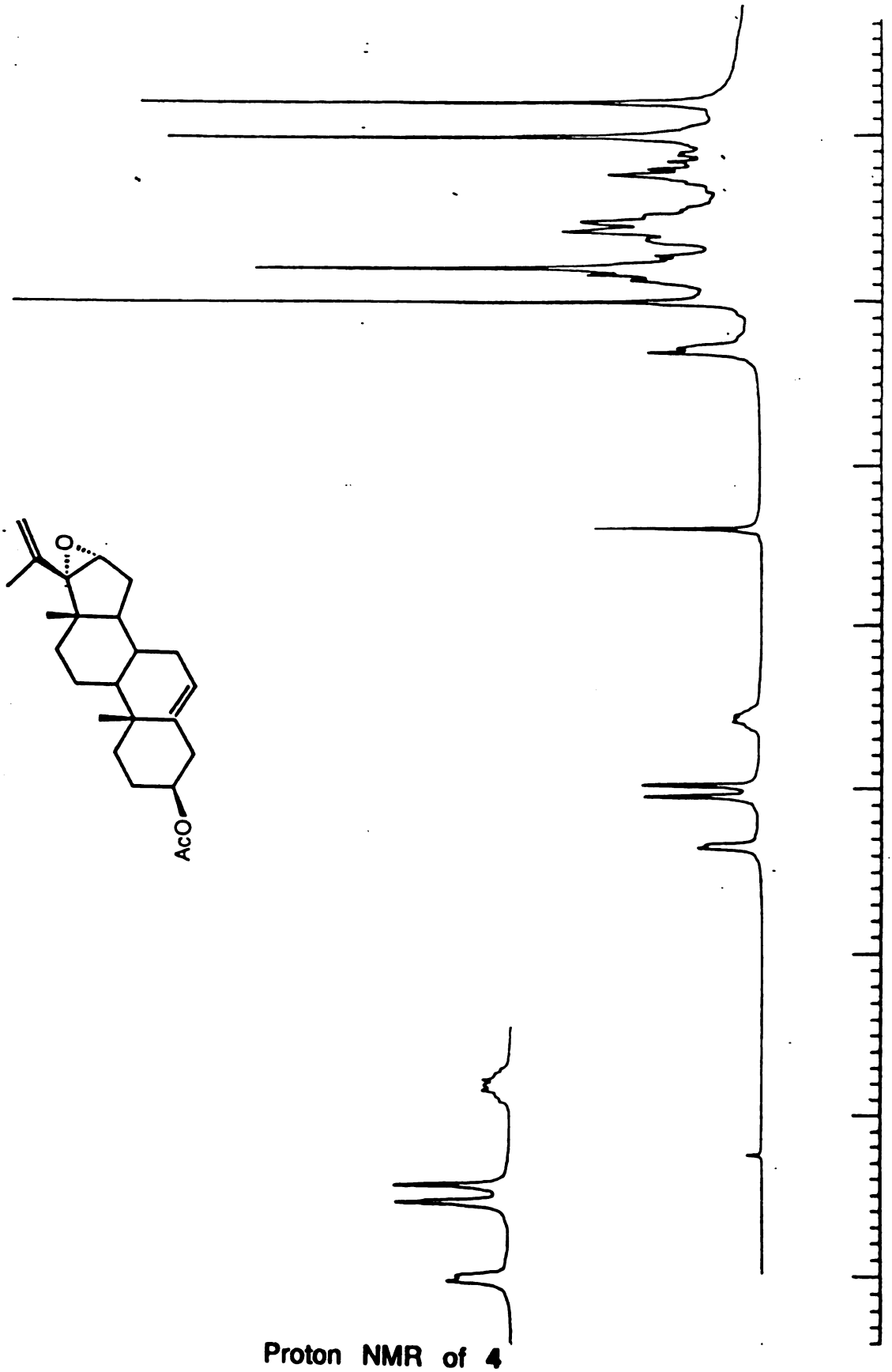
ORD C - 13 NMR of 6



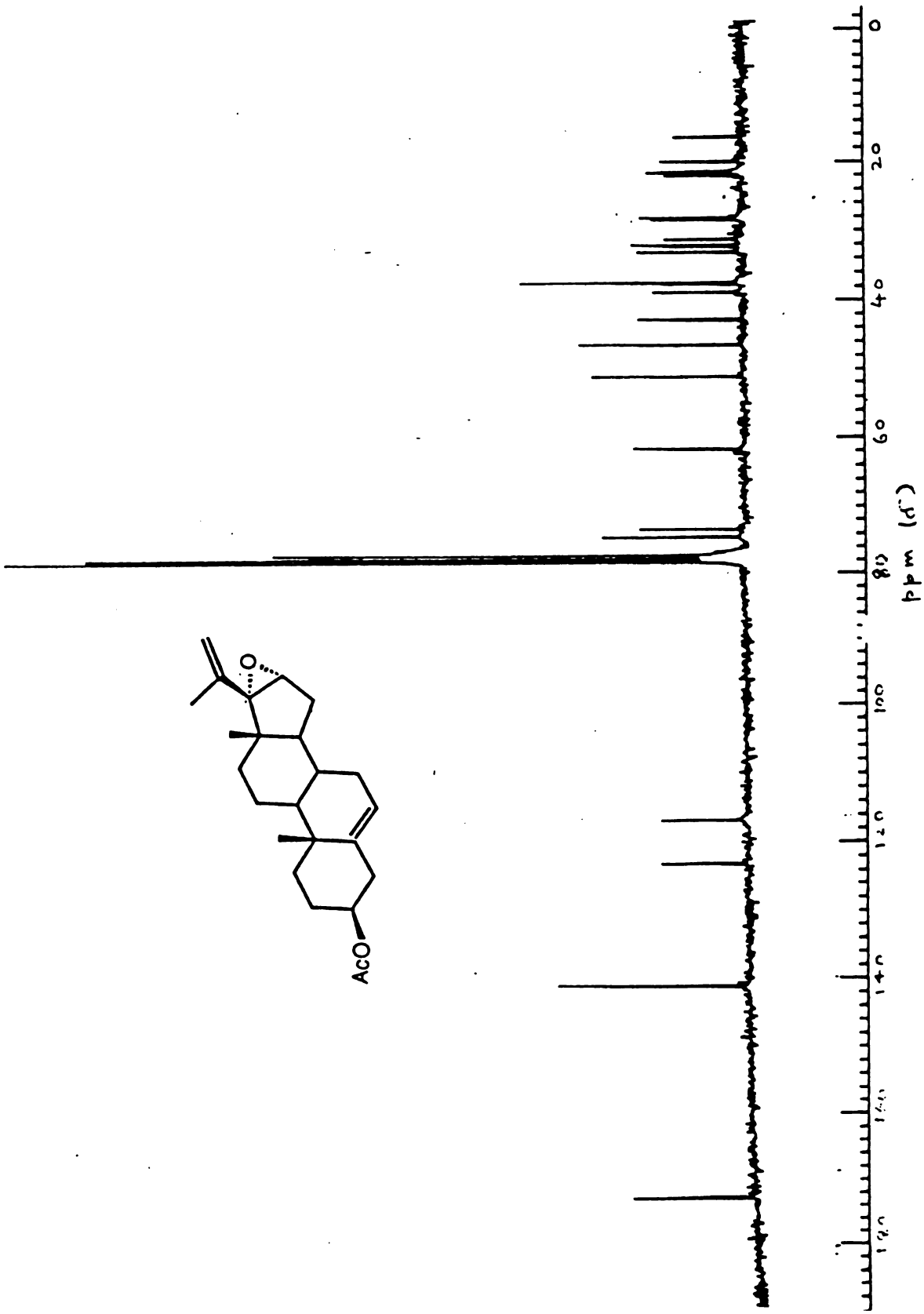
Proton NMR of **6**



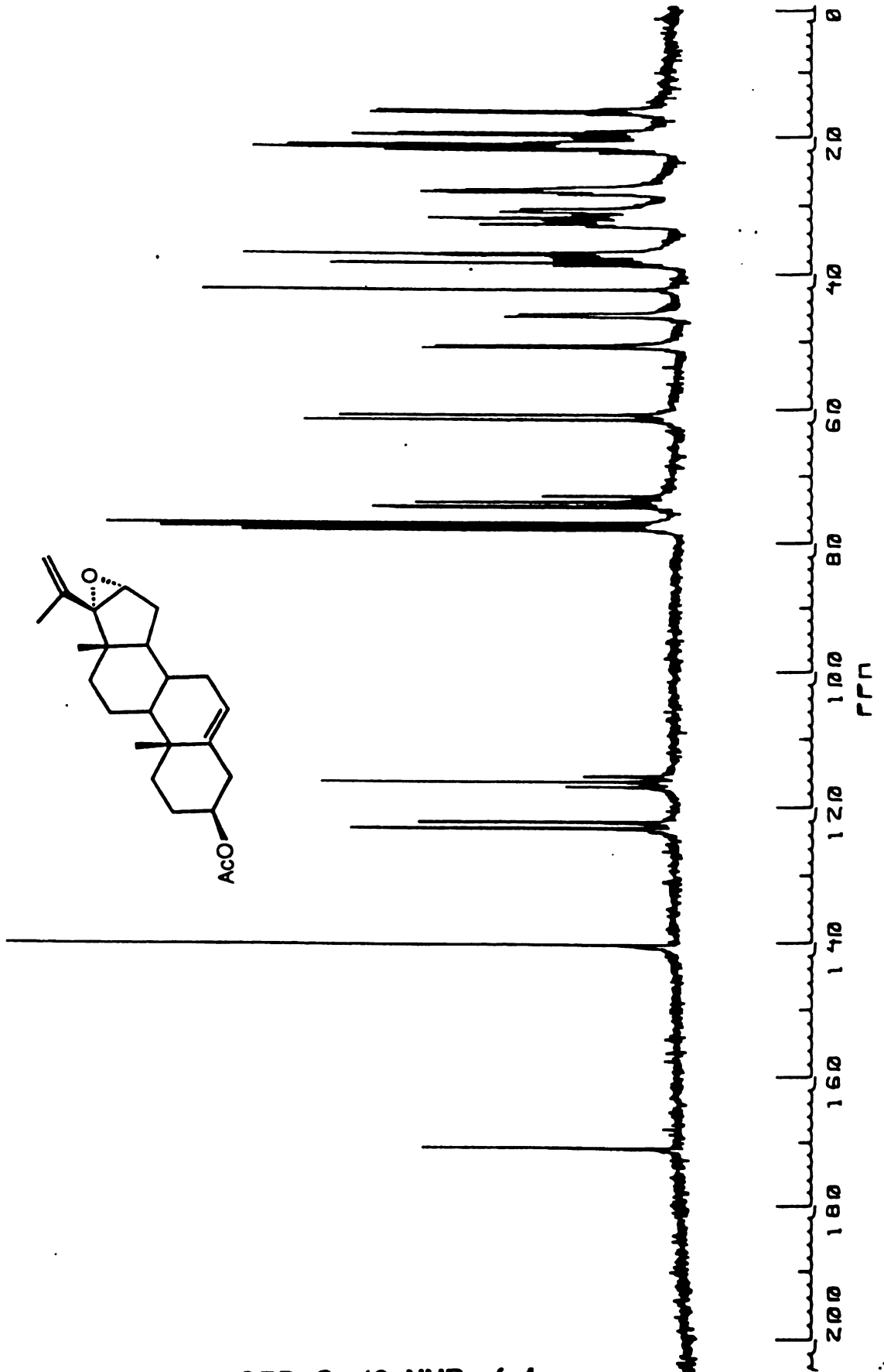
Mass spectrum of 6



Proton NMR of 4

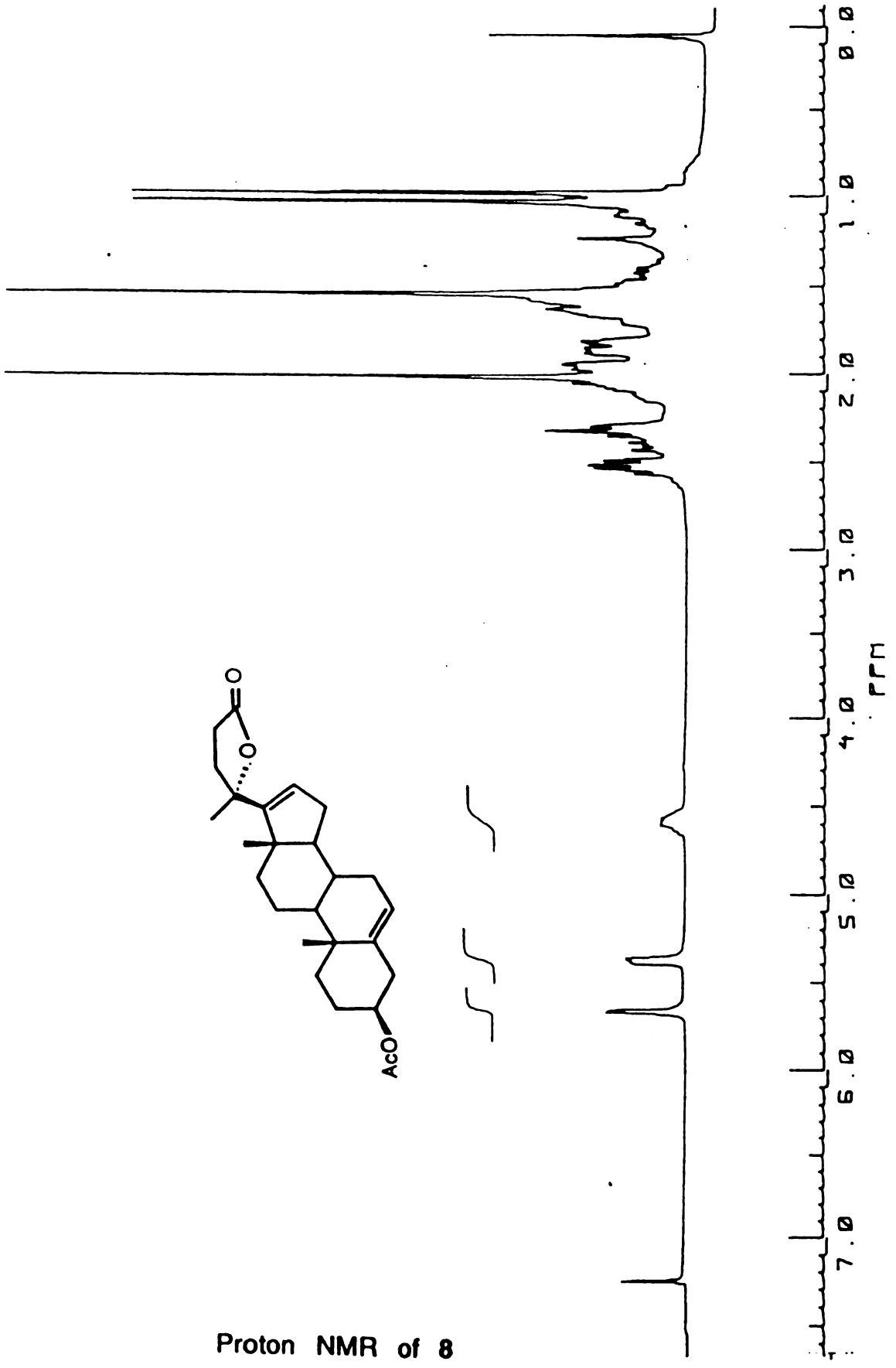


C - 13 NMR of 4

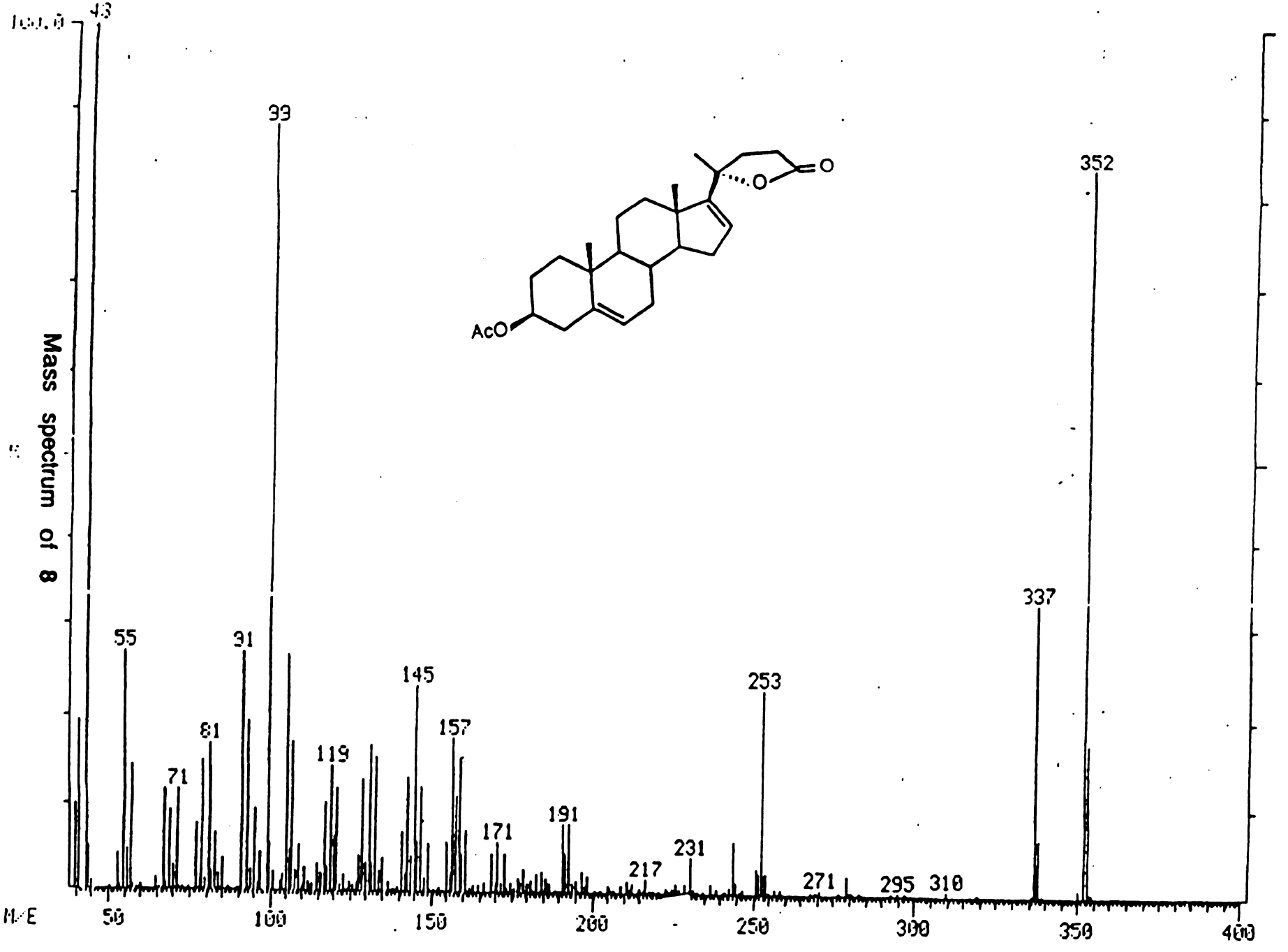


ORD C - 13 NMR of 4

C - 13 NMR of 8



Proton NMR of 8


Mass spectrum of 8
AcO
O
O
43
99
352
337
55
91
145
253
81
157
71
119
191
171
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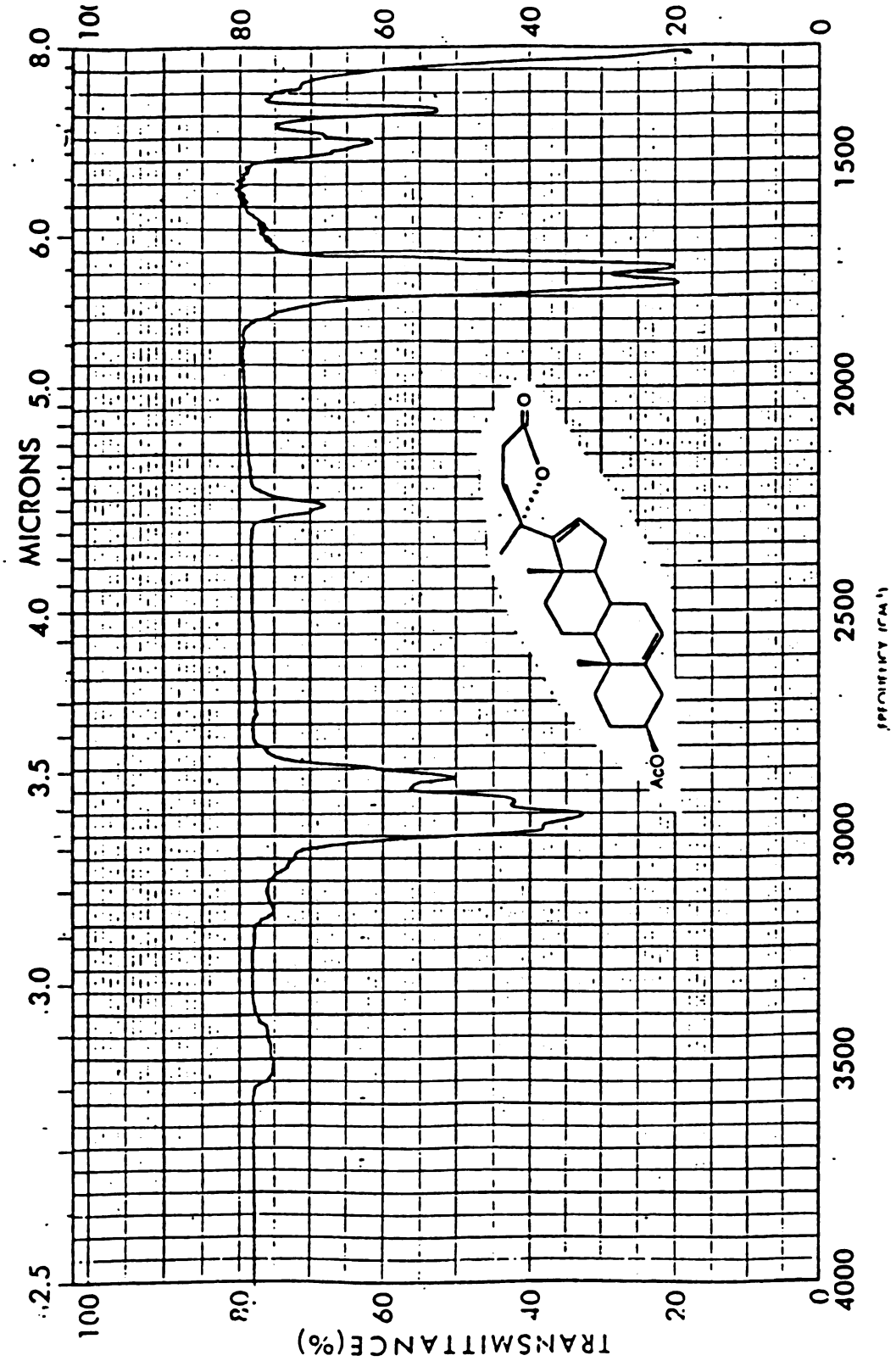
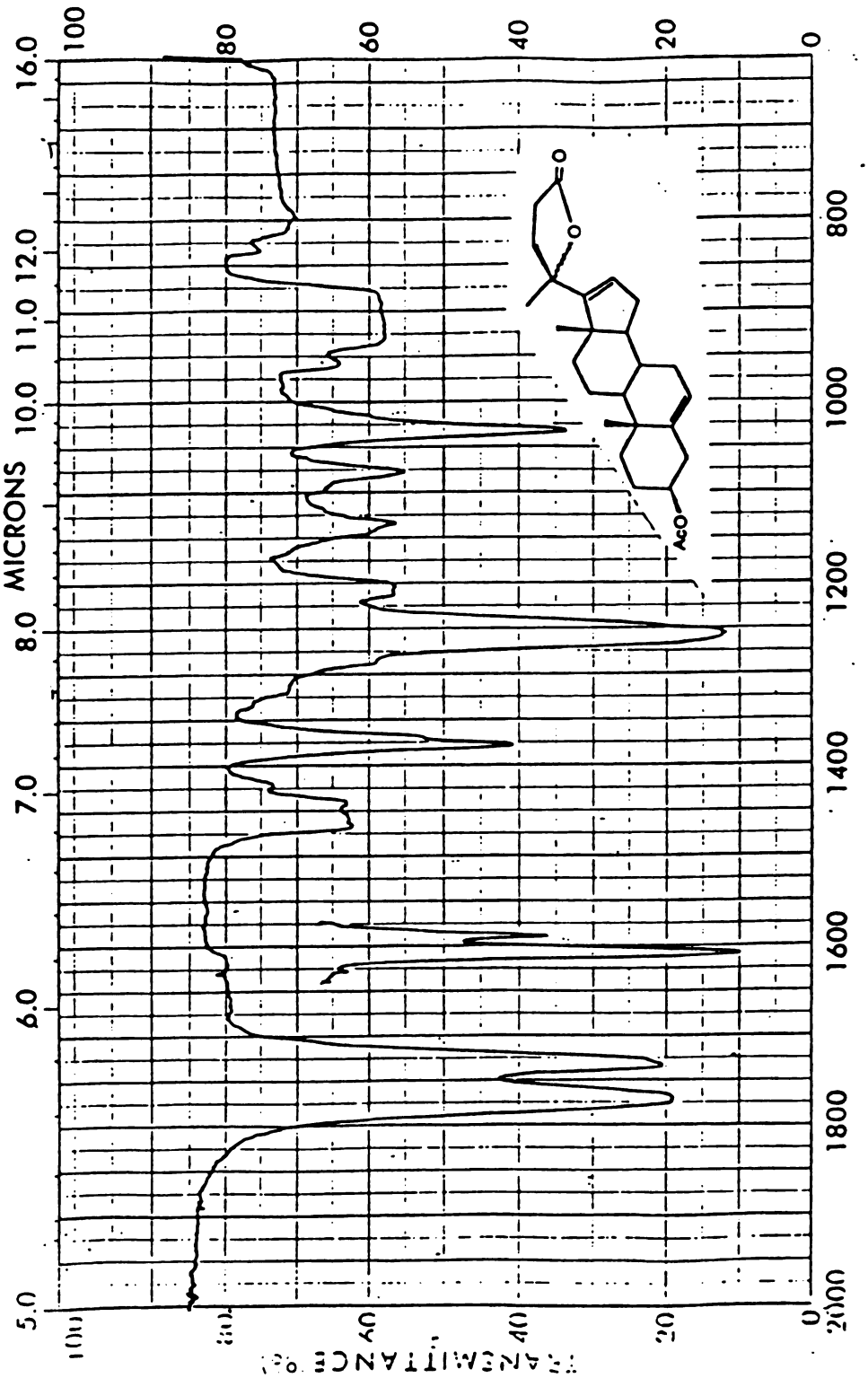
M/E
50
100
150
200
250
300
350
400



IR of **8**


MICRONS
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11.0
10.0
8.0
7.0
6.0
5.0
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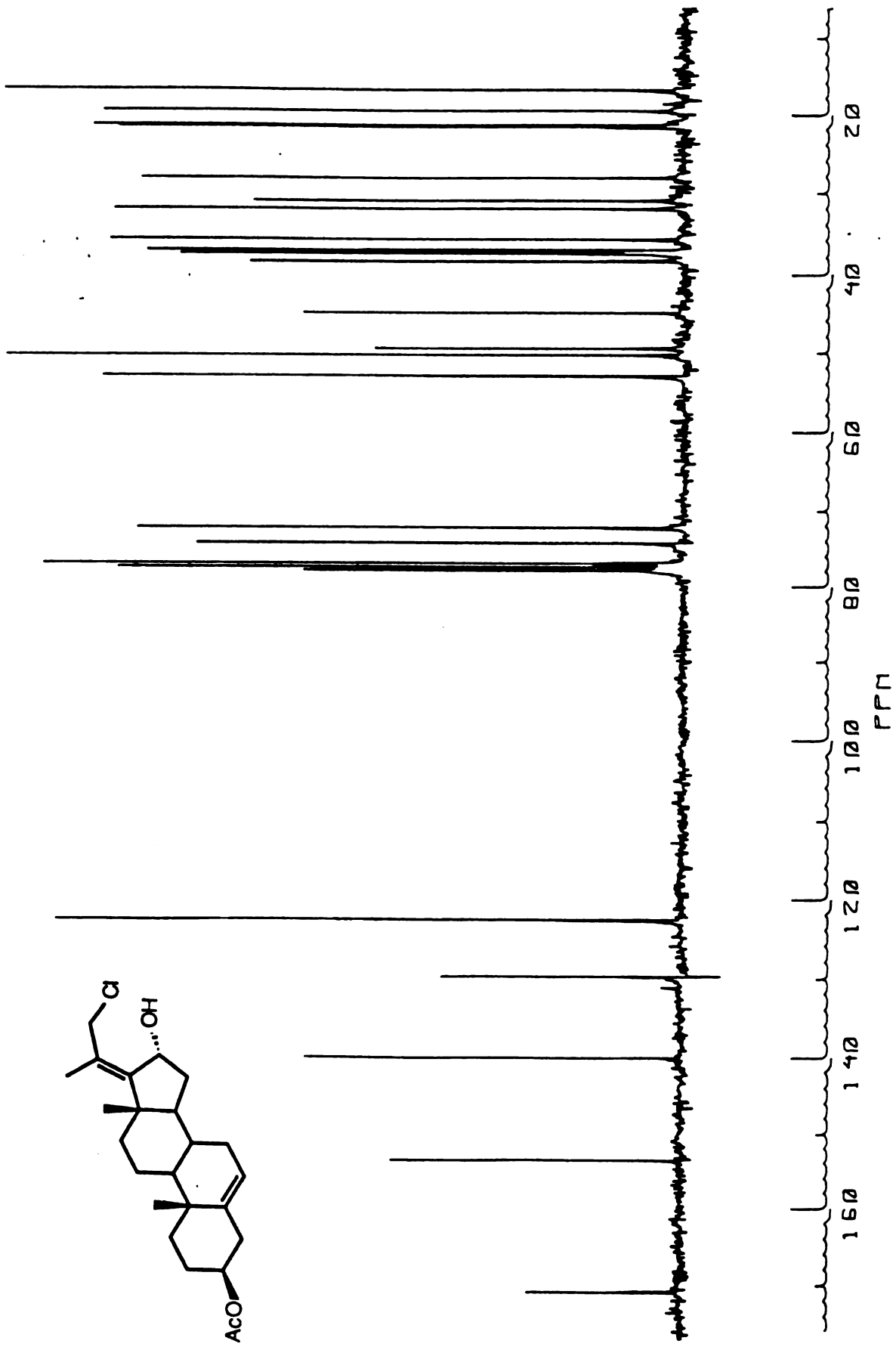
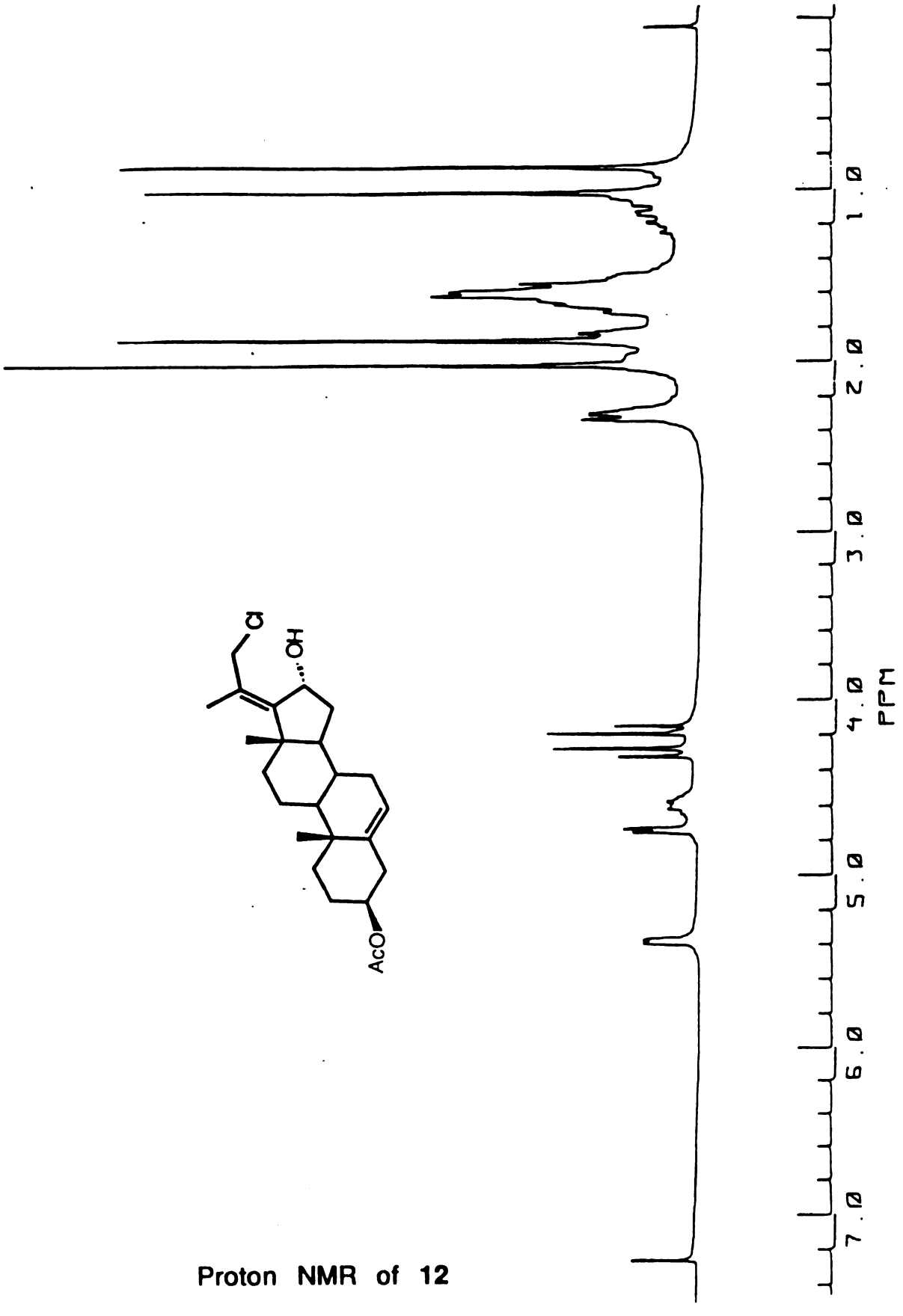
1800
1600
1400
1200
1000
800
0
20
40
60
80
100
AcO

IR of **8**

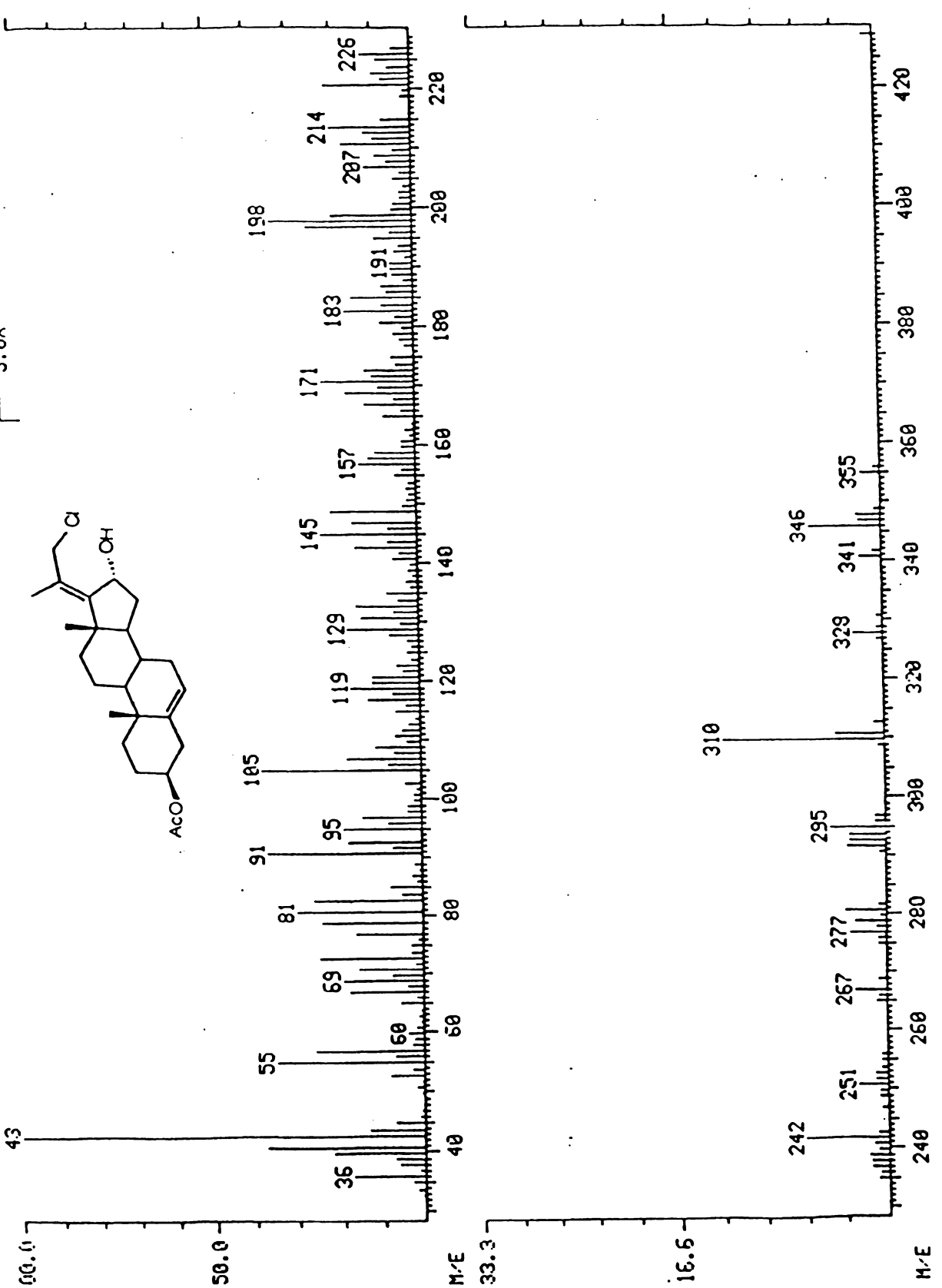


C - 13 NMR of **12**



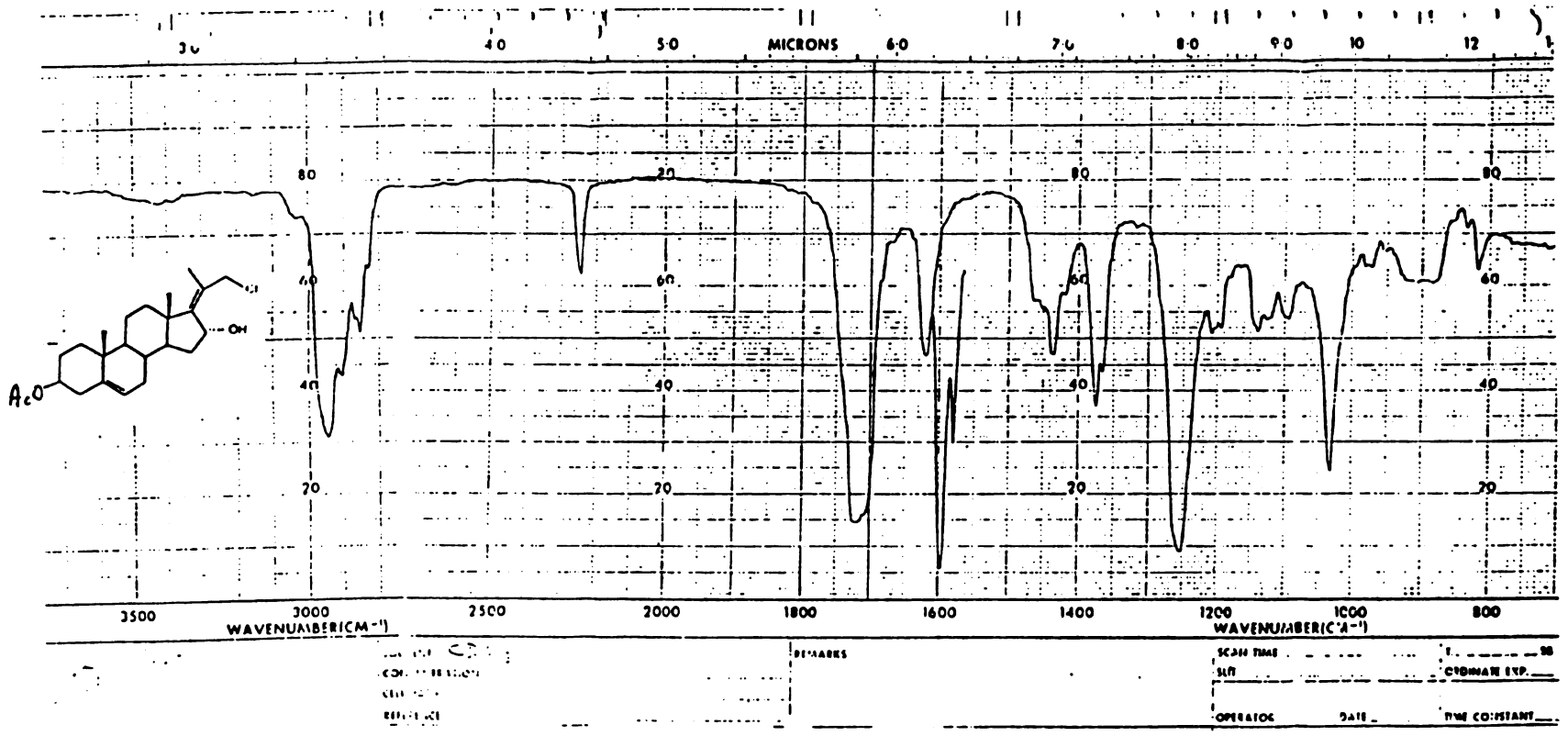
Proton NMR of 12

ORD C - 13 NMR of 12



Mass spectrum of 12

IR of 12


MICRONS
WAVENUMBER(CM⁻¹)
WAVENUMBER(CM⁻¹)
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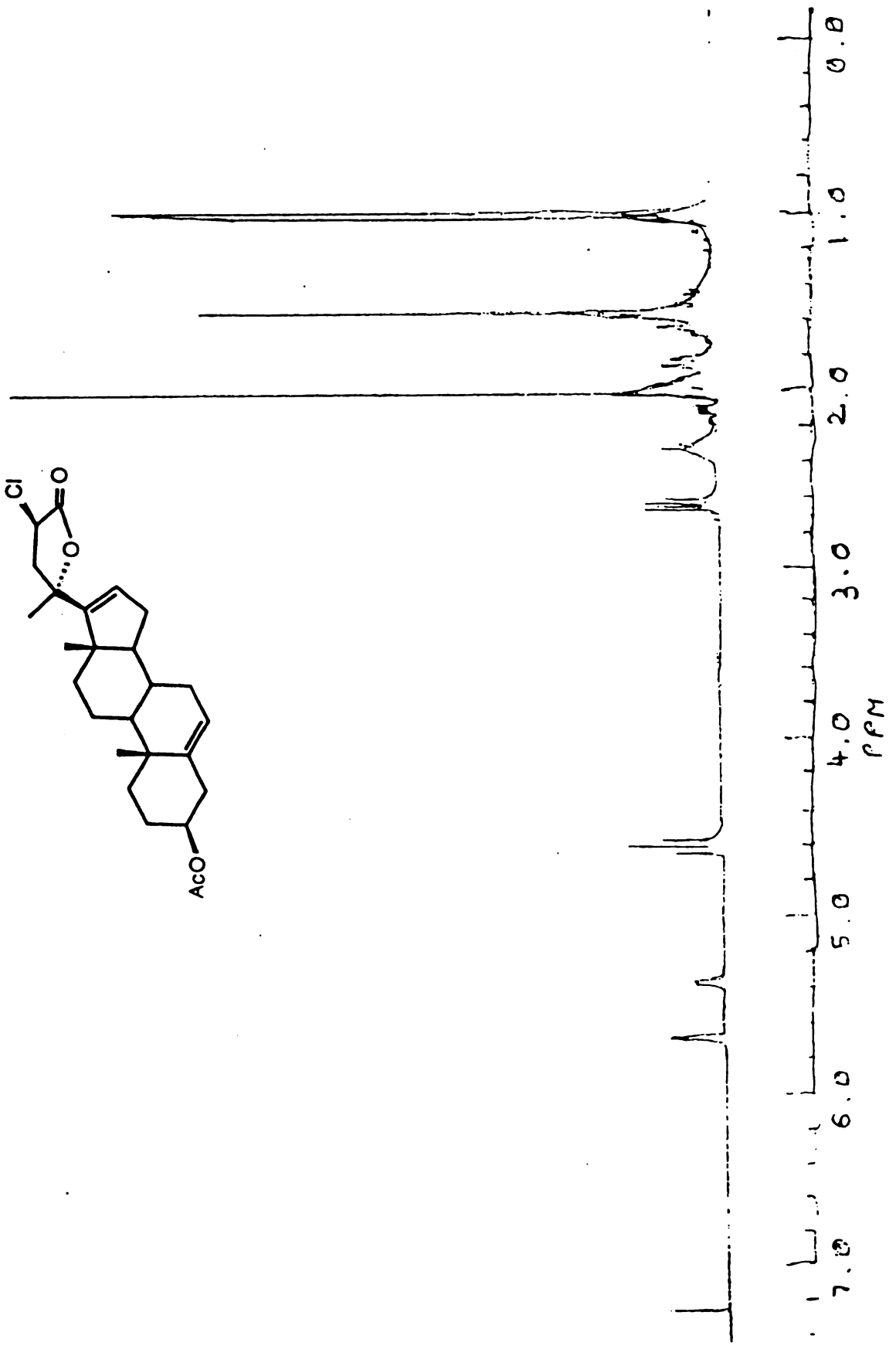
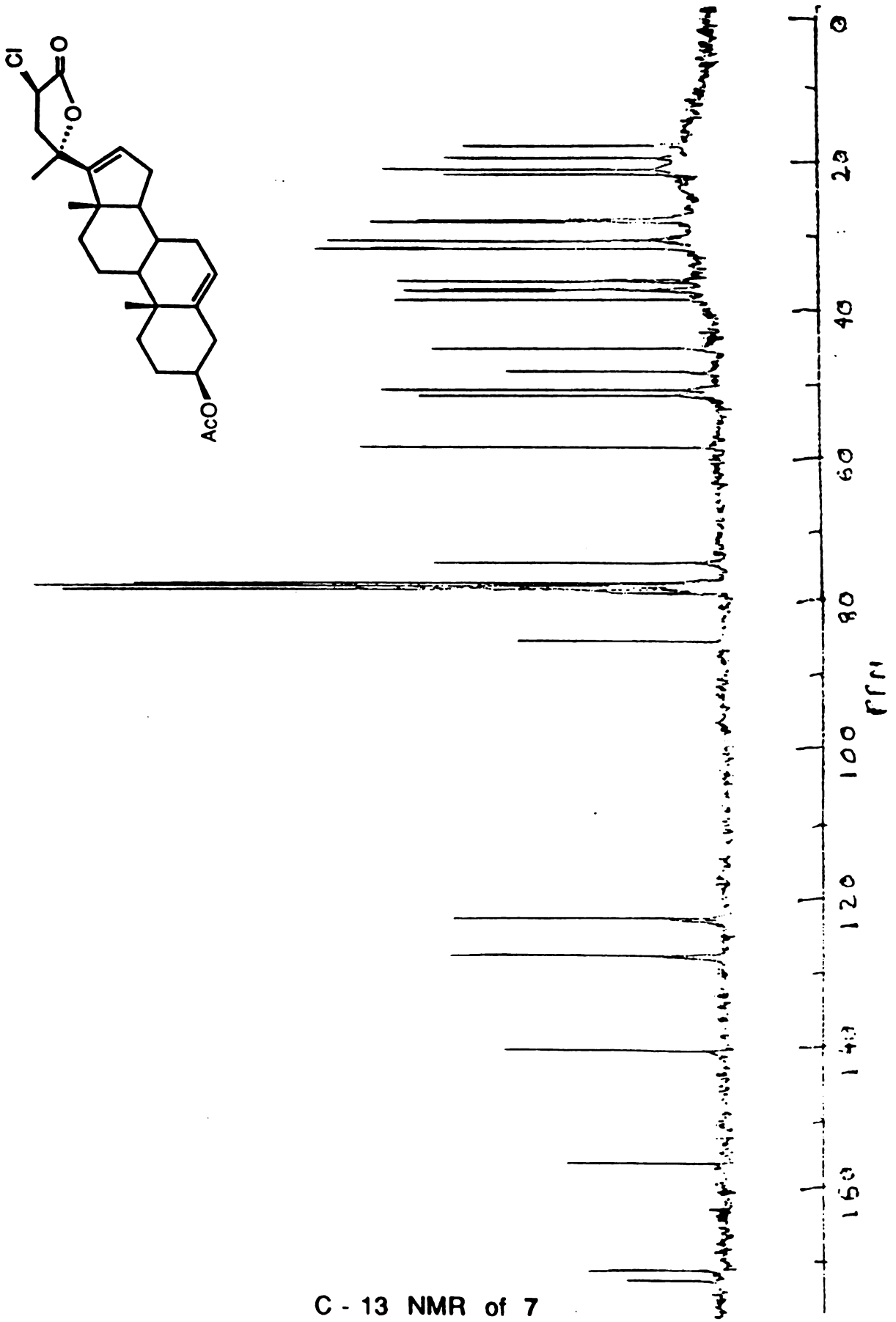
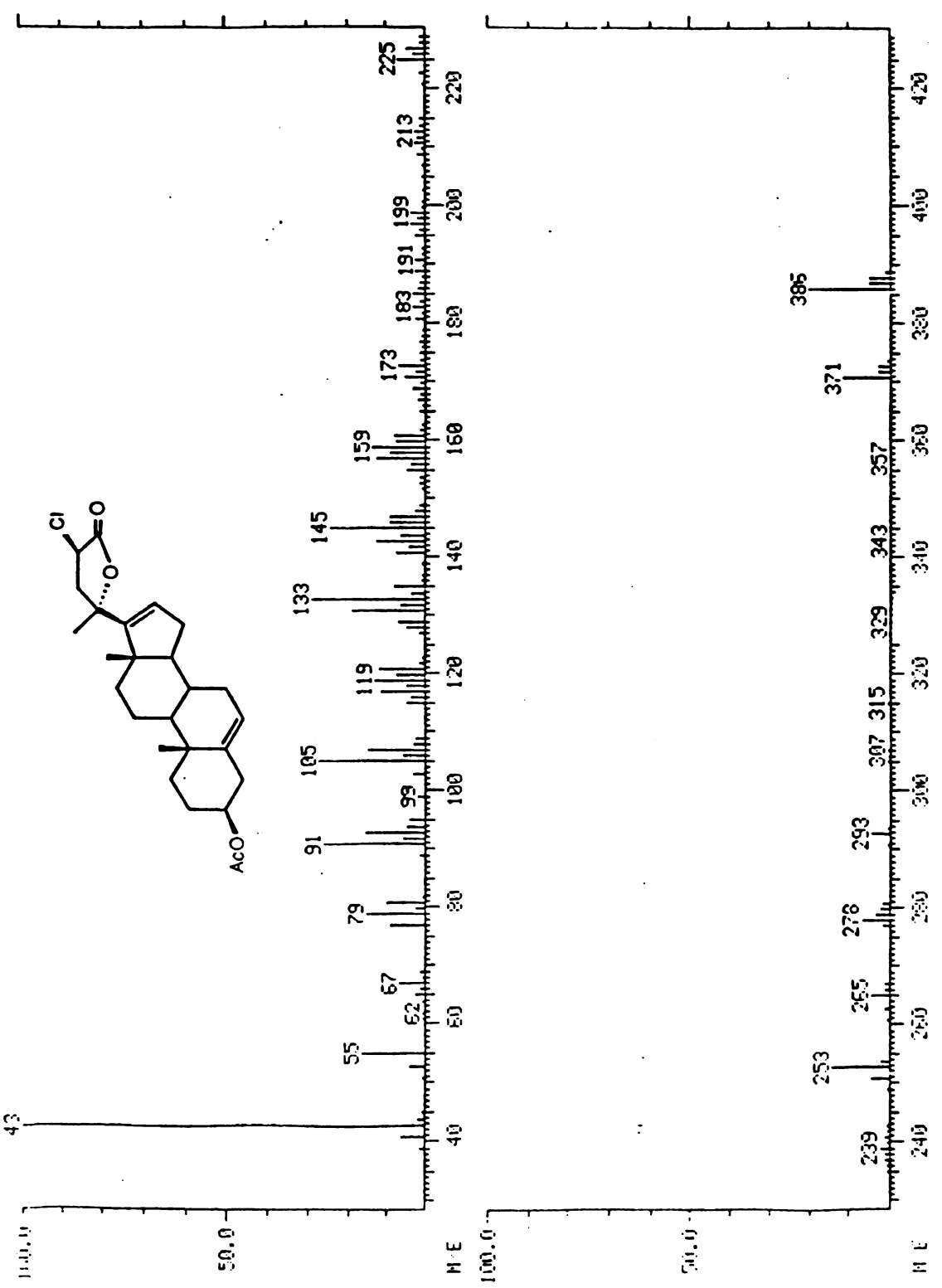
2500
2000
1800
1600
1400
1200
1000
800
OH
AcO



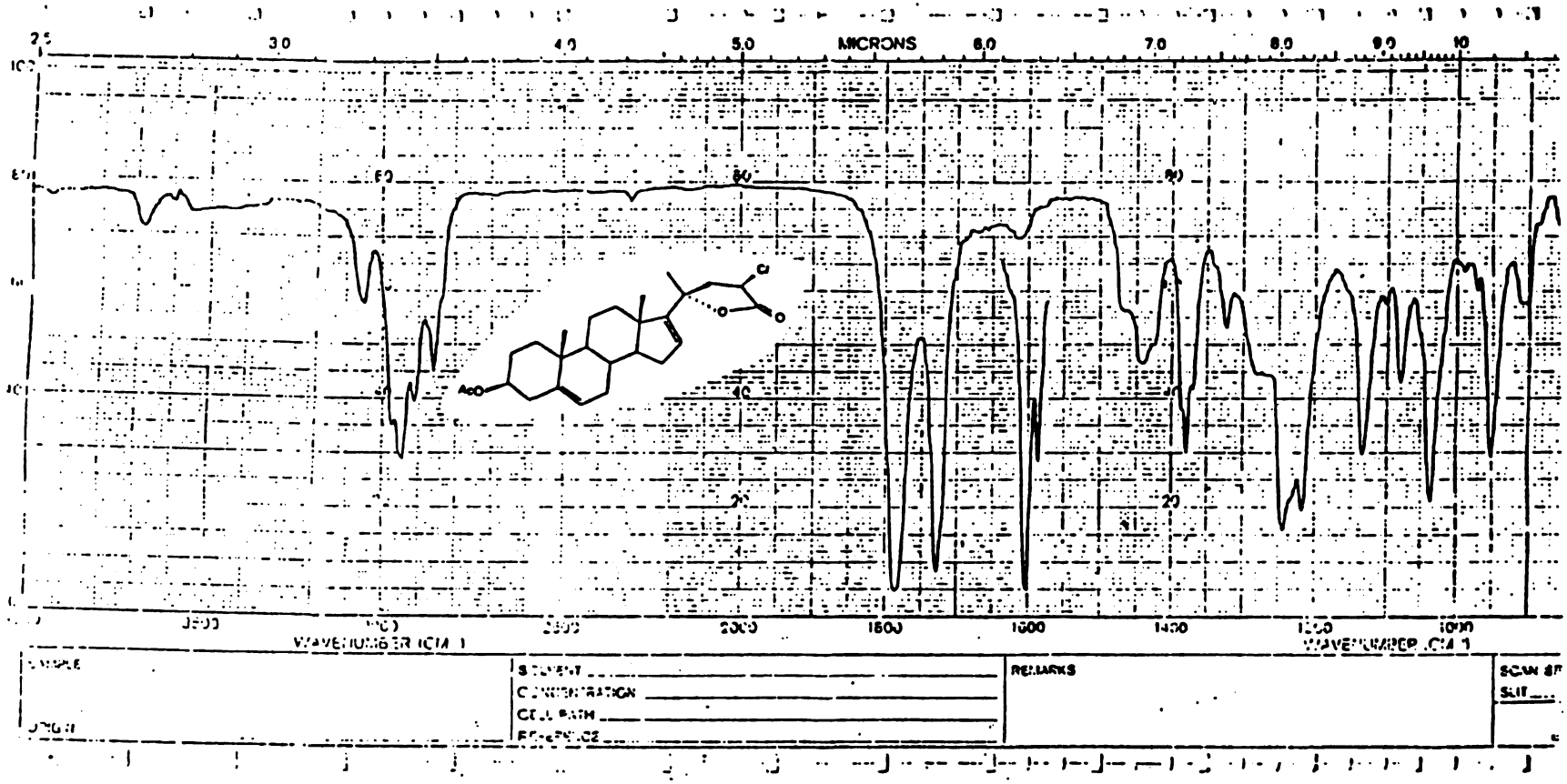
Proton NMR of 7

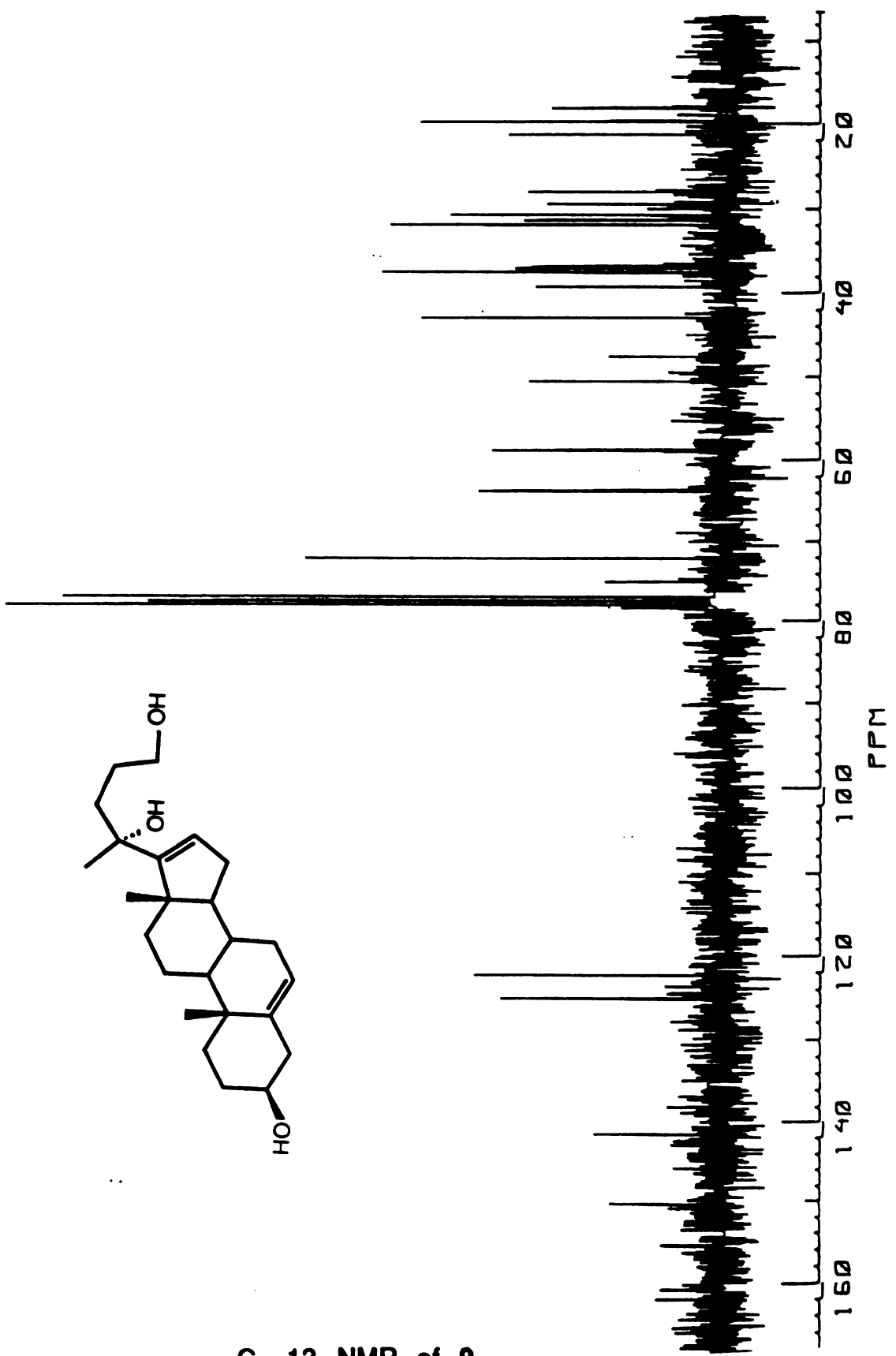


C - 13 NMR of 7

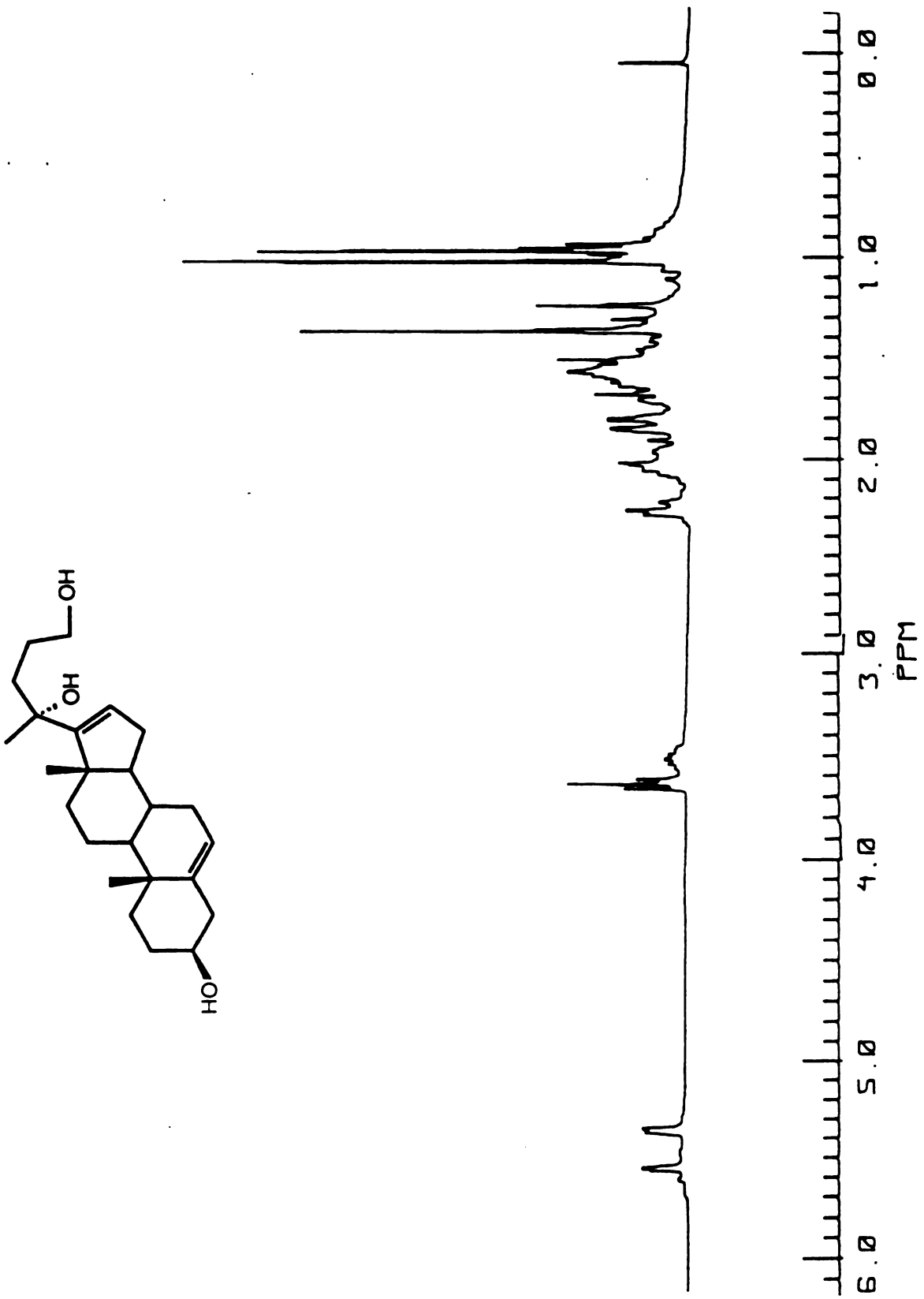


Mass spectrum of 7

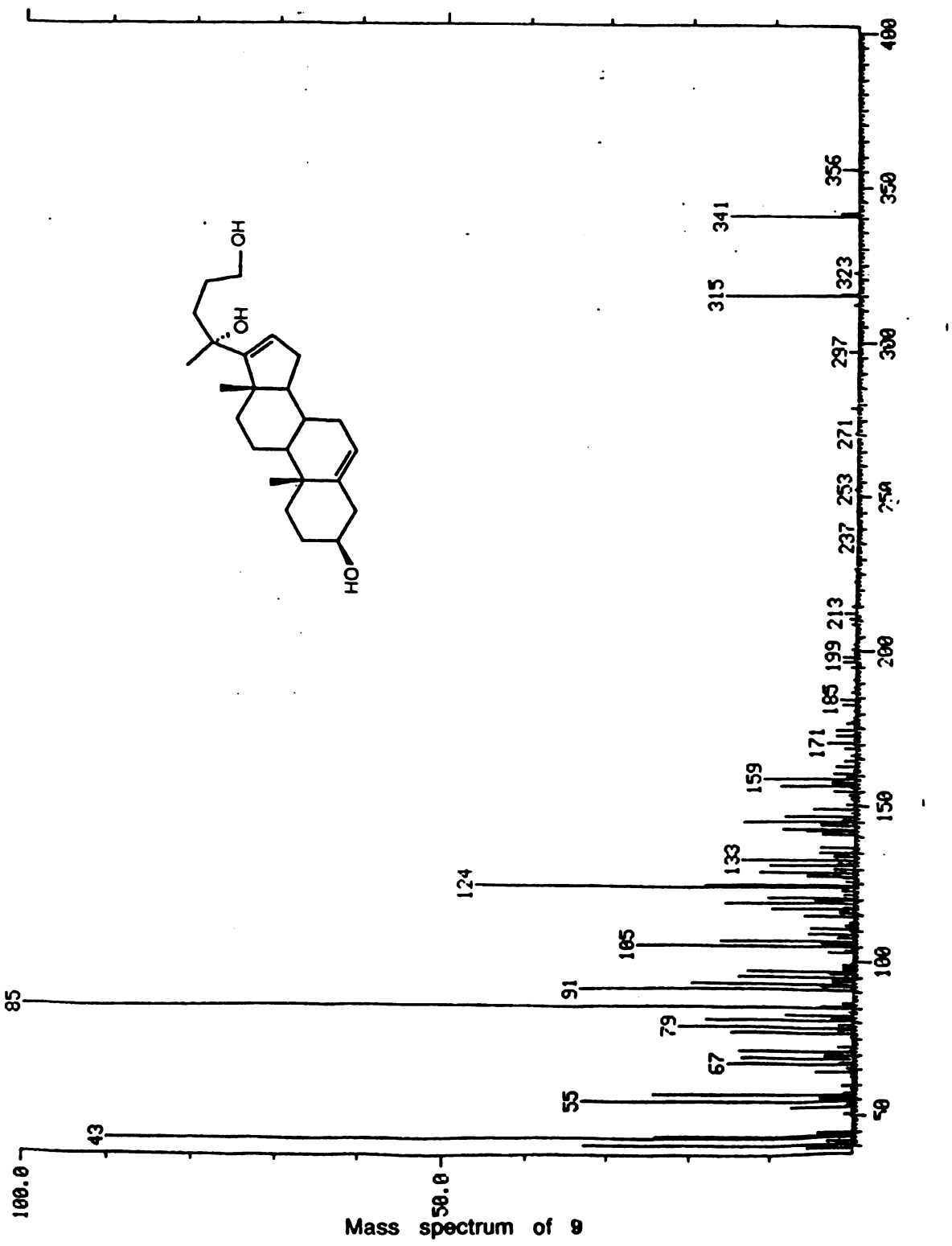

MICRONS
WAVENUMBER (CM-1)
WAVENUMBER (CM-1)
REMARKS
SOLVENT
CONCENTRATION
CELL PATH
SCAN SP
SLIT



C - 13 NMR of 9



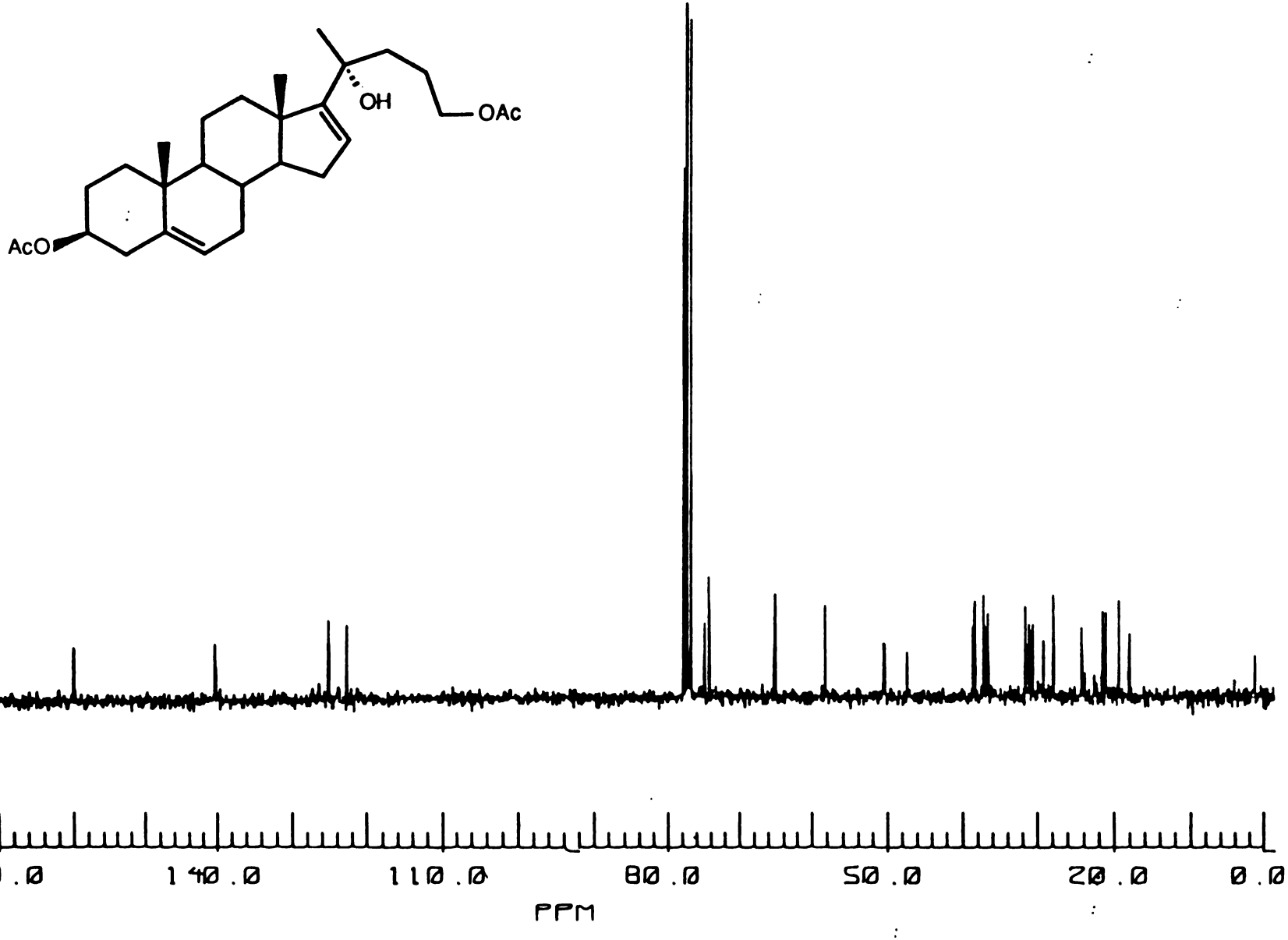
Proton NMR of **9**

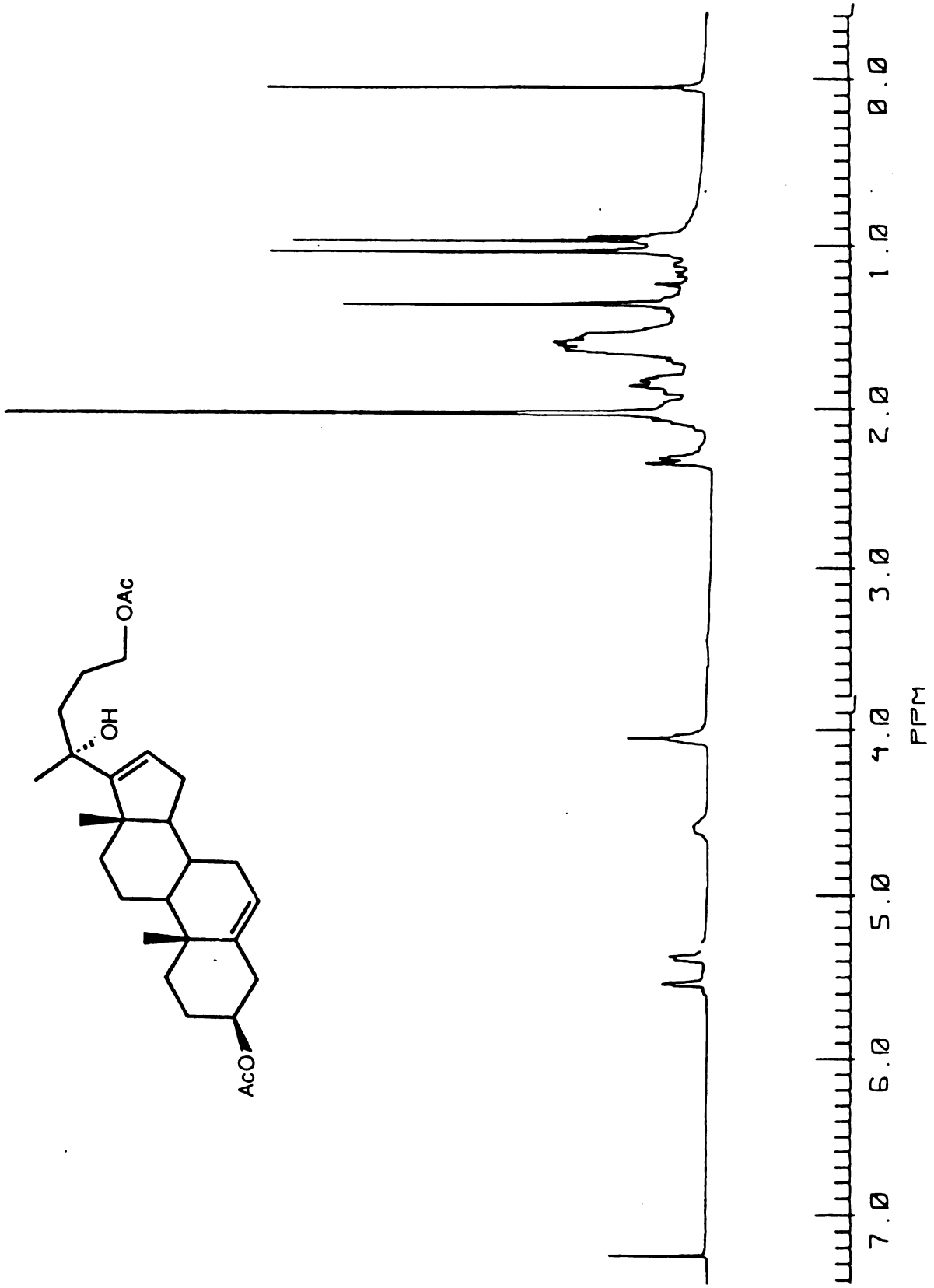


Mass spectrum of 9

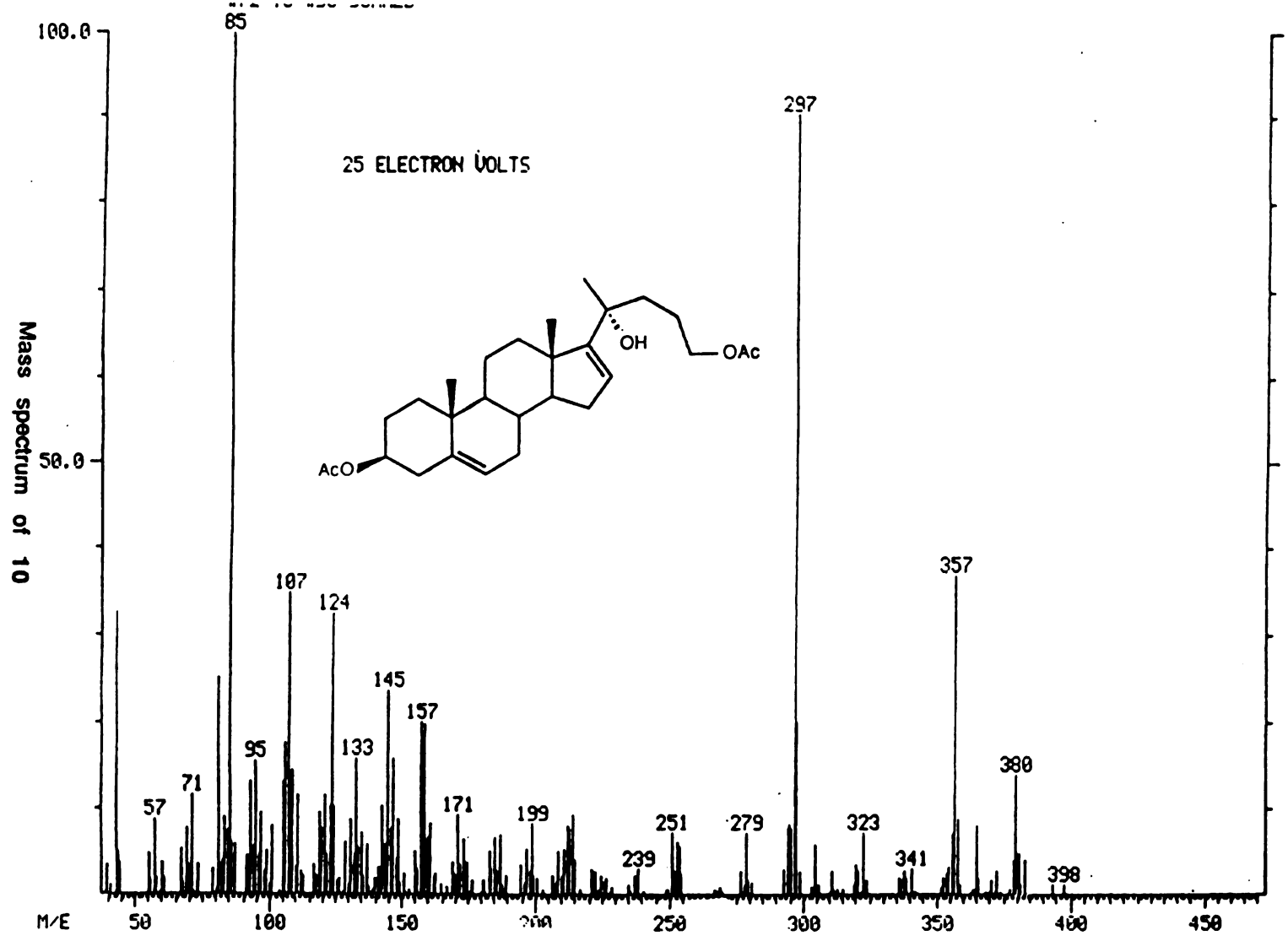
IR of 9

C - 13 NMR of 10





Proton NMR of **10**


100.0
50.0
Mass spectrum of 10
25 ELECTRON VOLTS
OH
OAc
AcO
M/E
50
100
150
250
300
350
400
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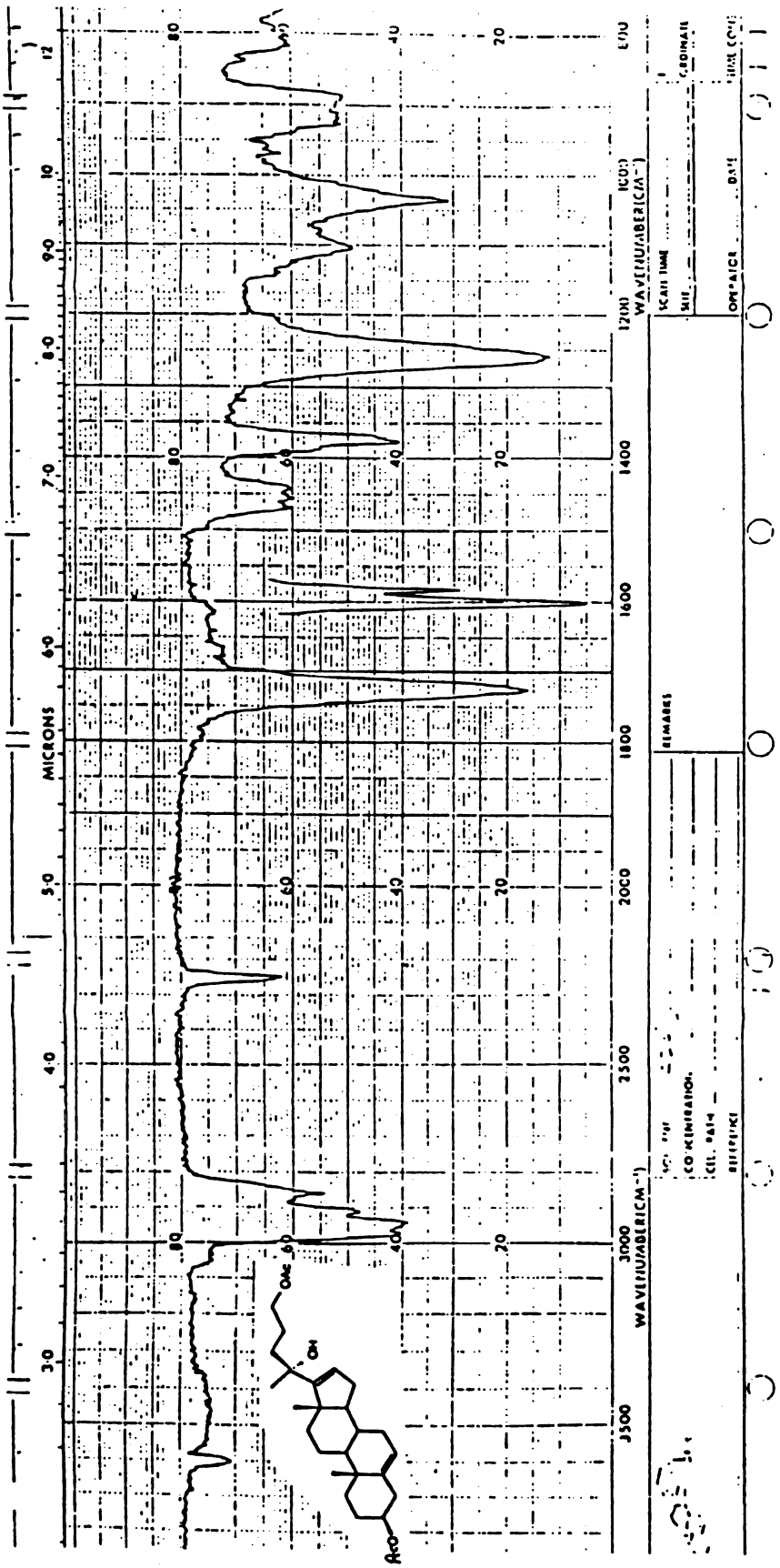
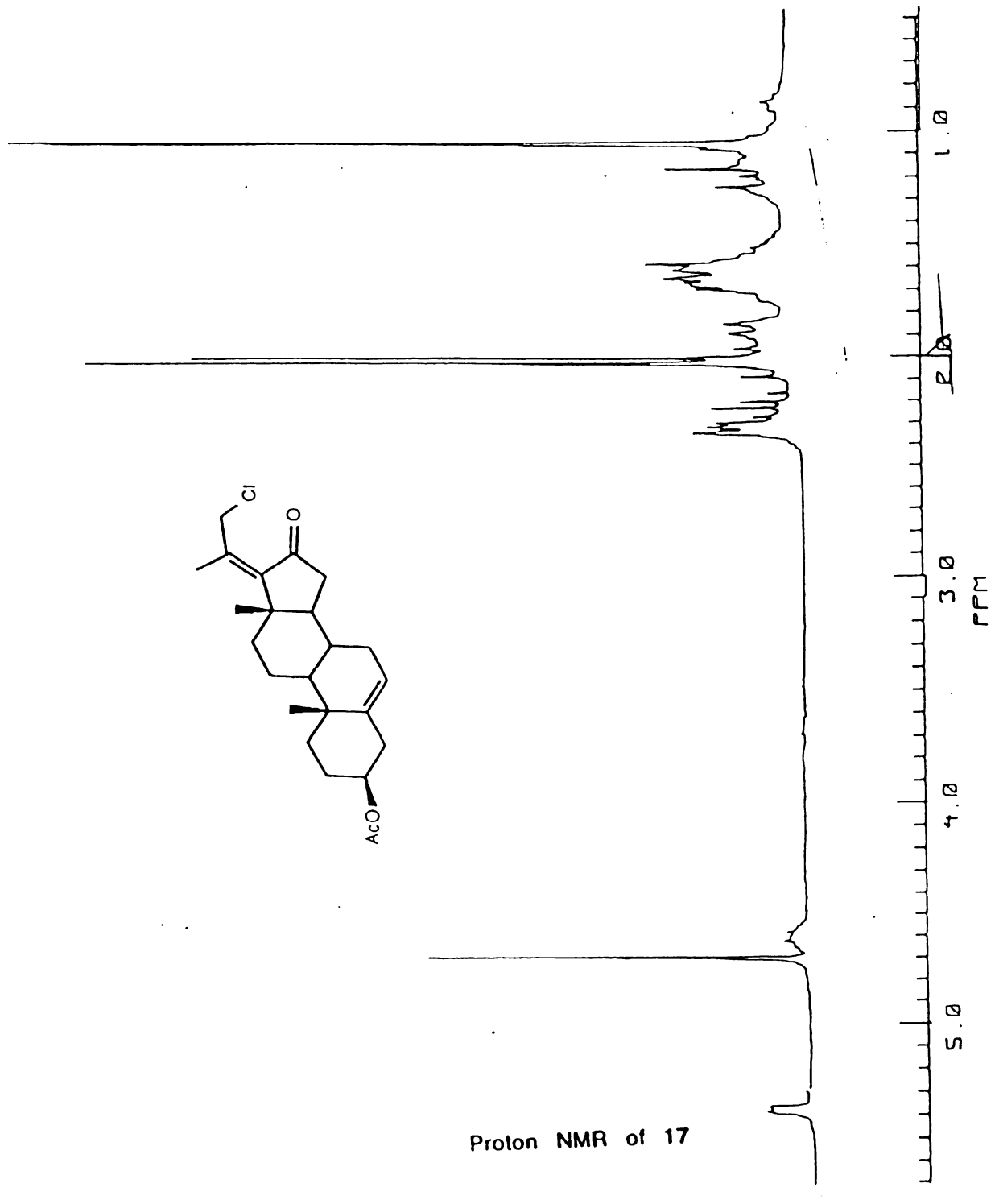
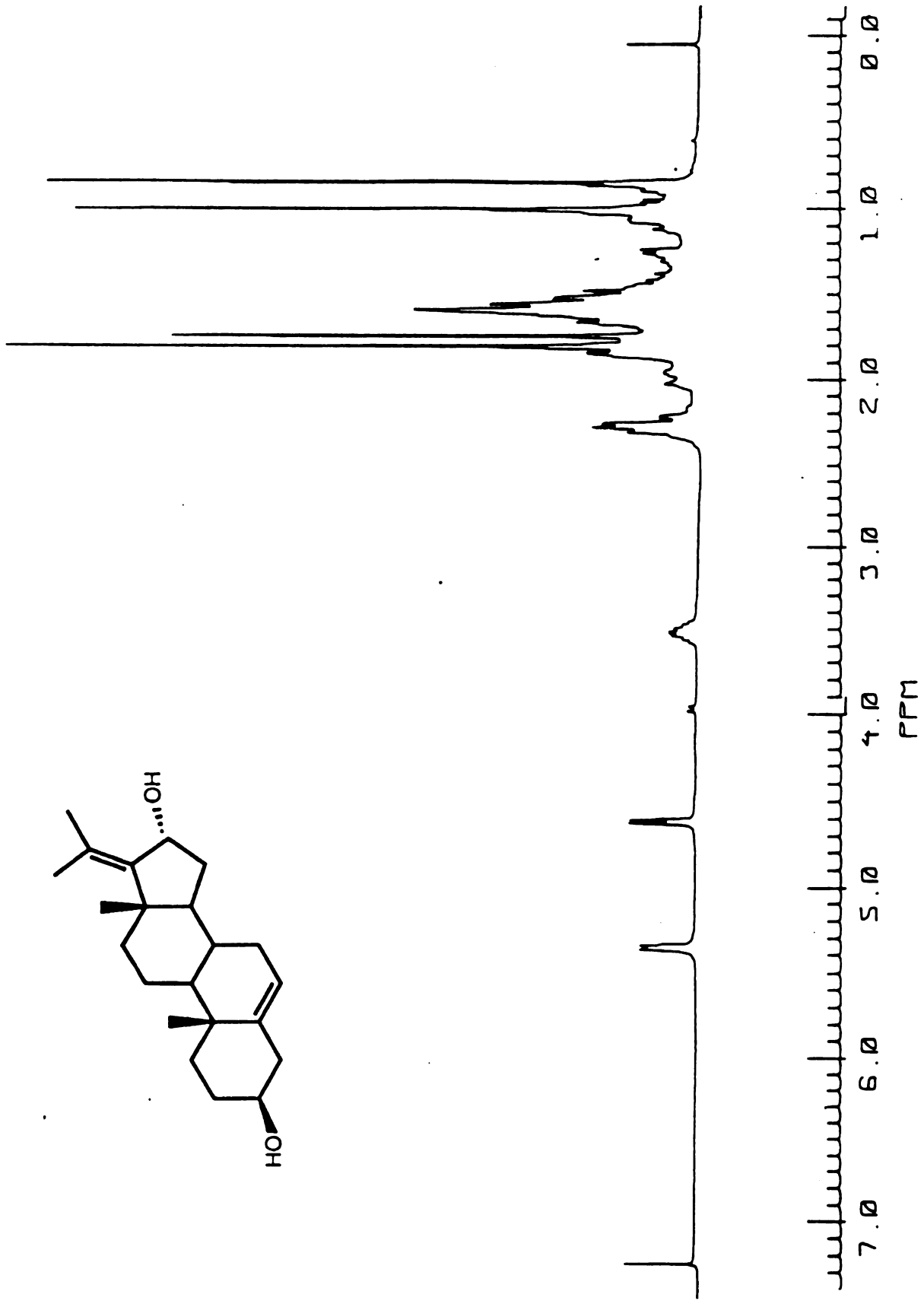
57
171
199
239
251
279
323
341
380
398



IR of 10

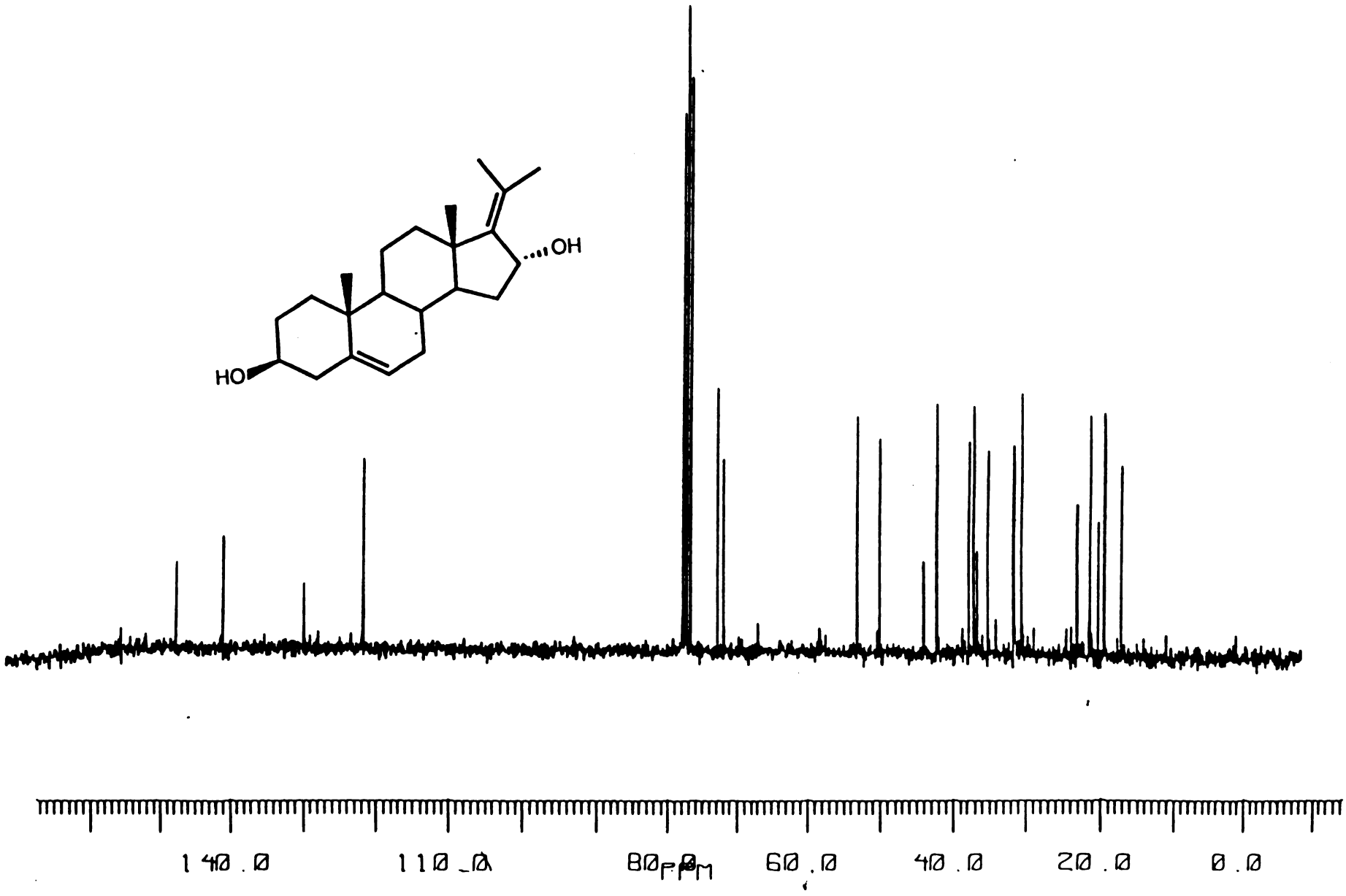


Proton NMR of 17



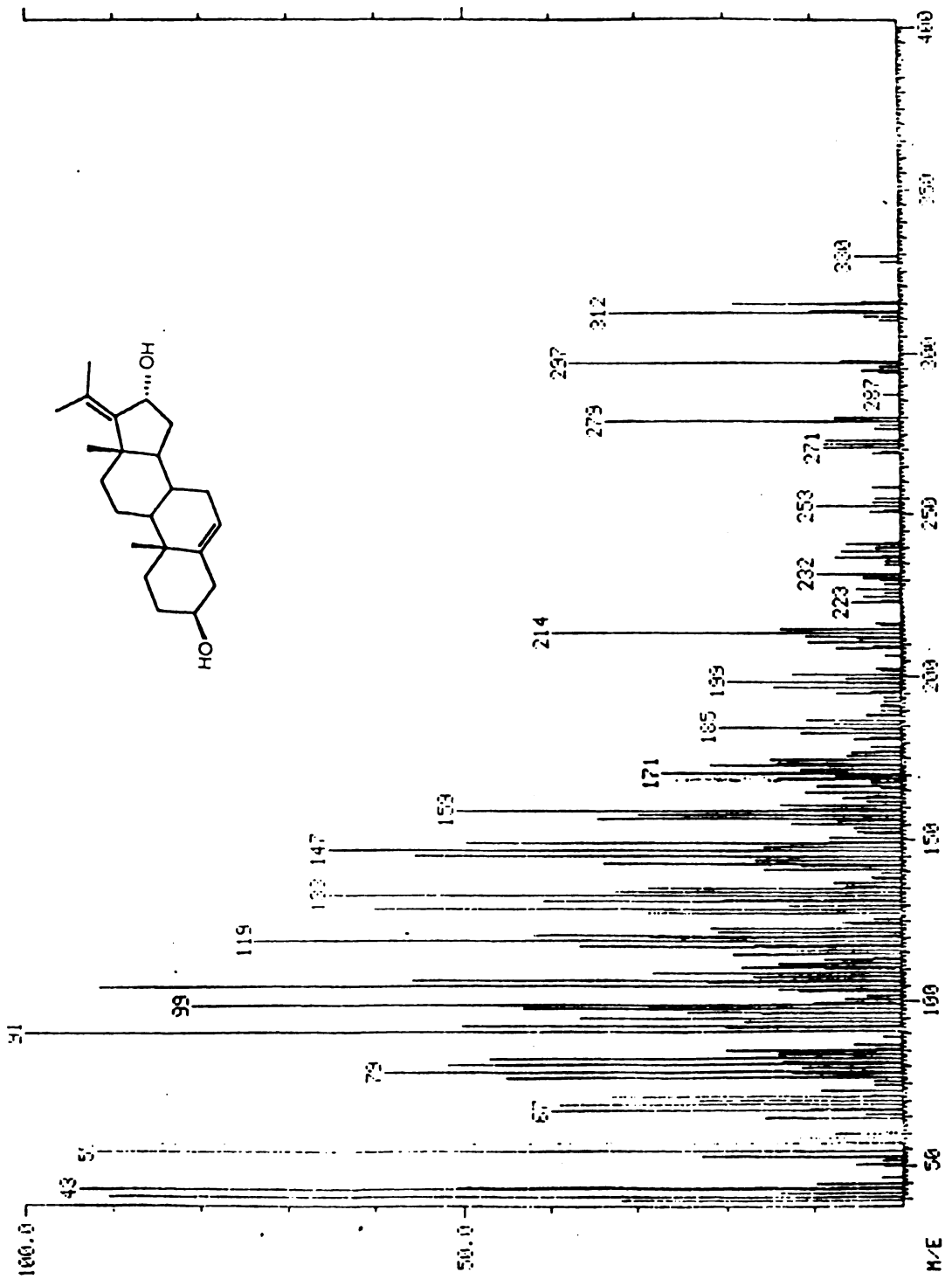
Proton NMR of 14

C - 13 NMR of 14

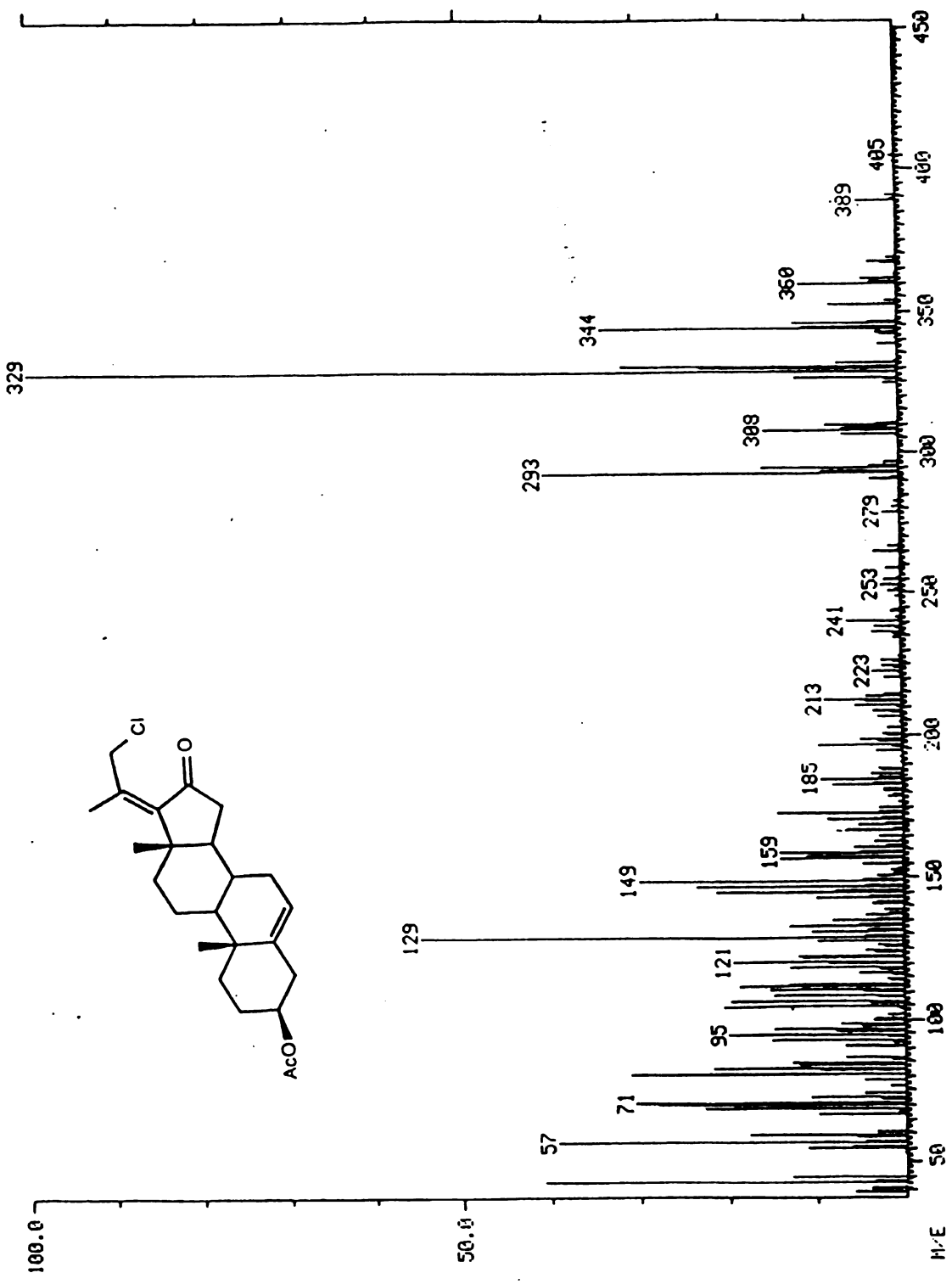


MICRONS
WAVENUMBER(CM⁻¹)
REMARKS
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
SCAN TIME
SLIT
OPERATOR
BASE
FILE COURSE
DMF

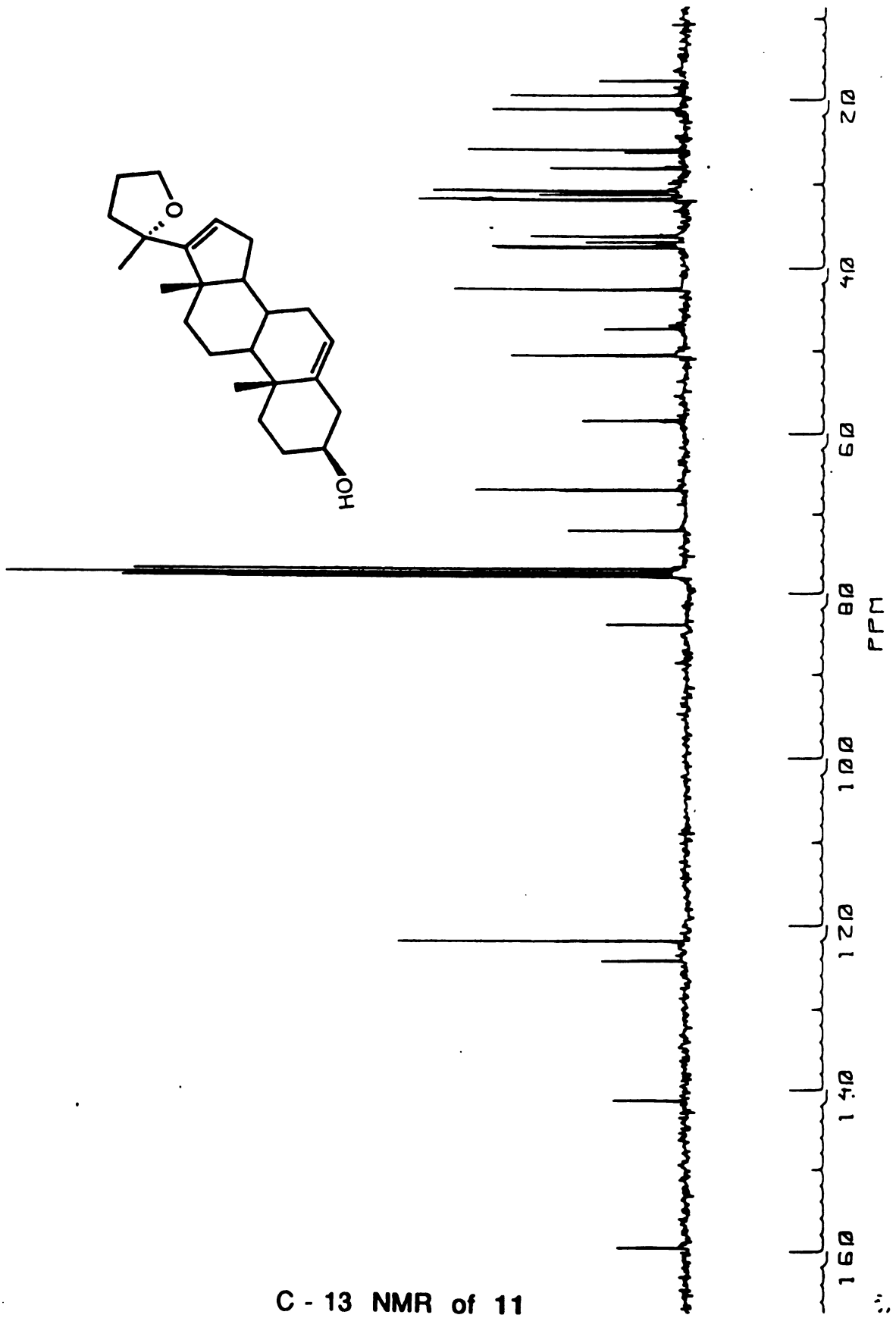
IR of **14**



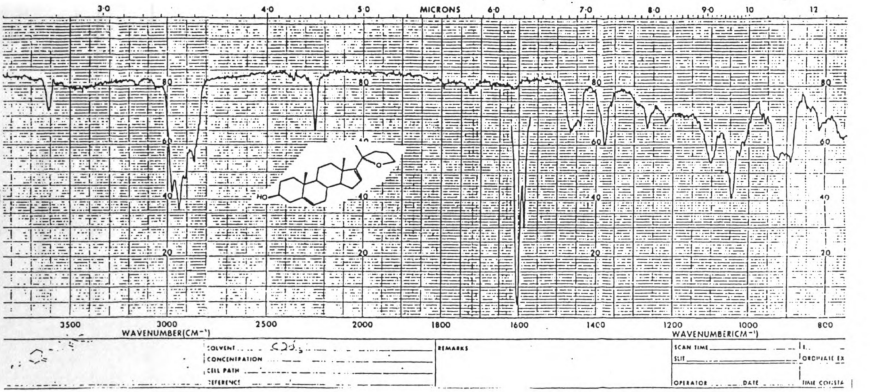
Mass spectrum of **14**

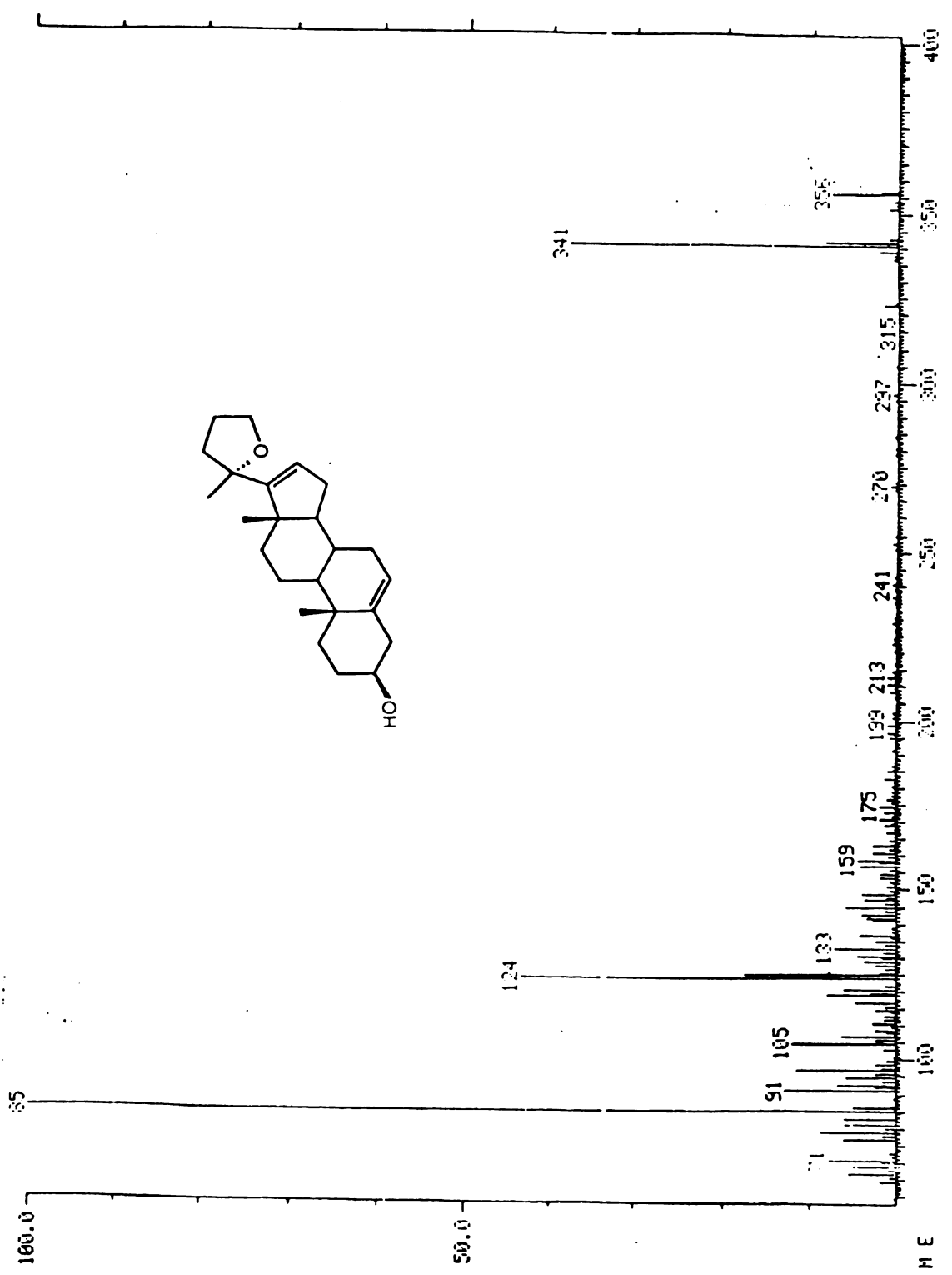


Mass spectrum of 17

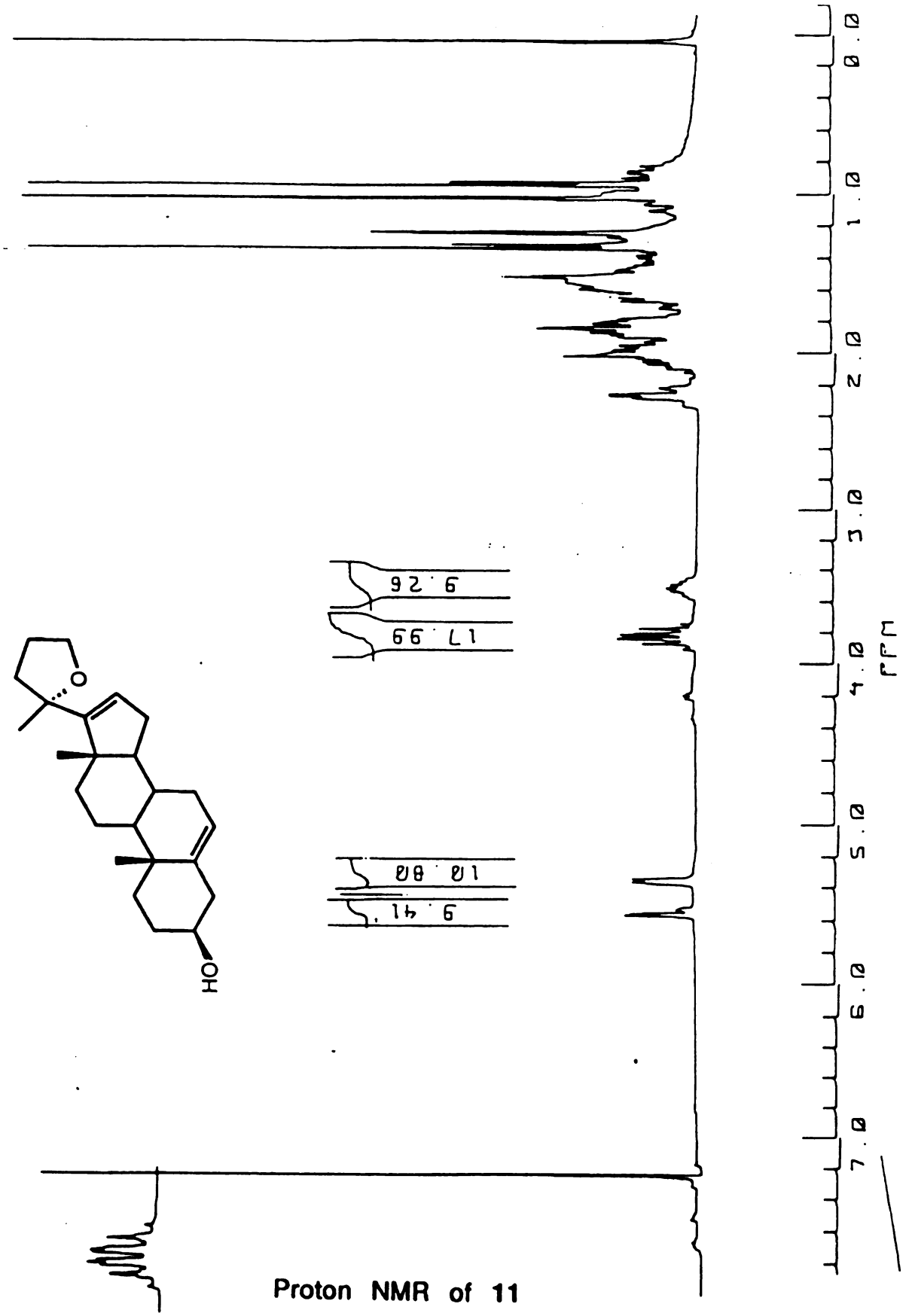


C - 13 NMR of 11

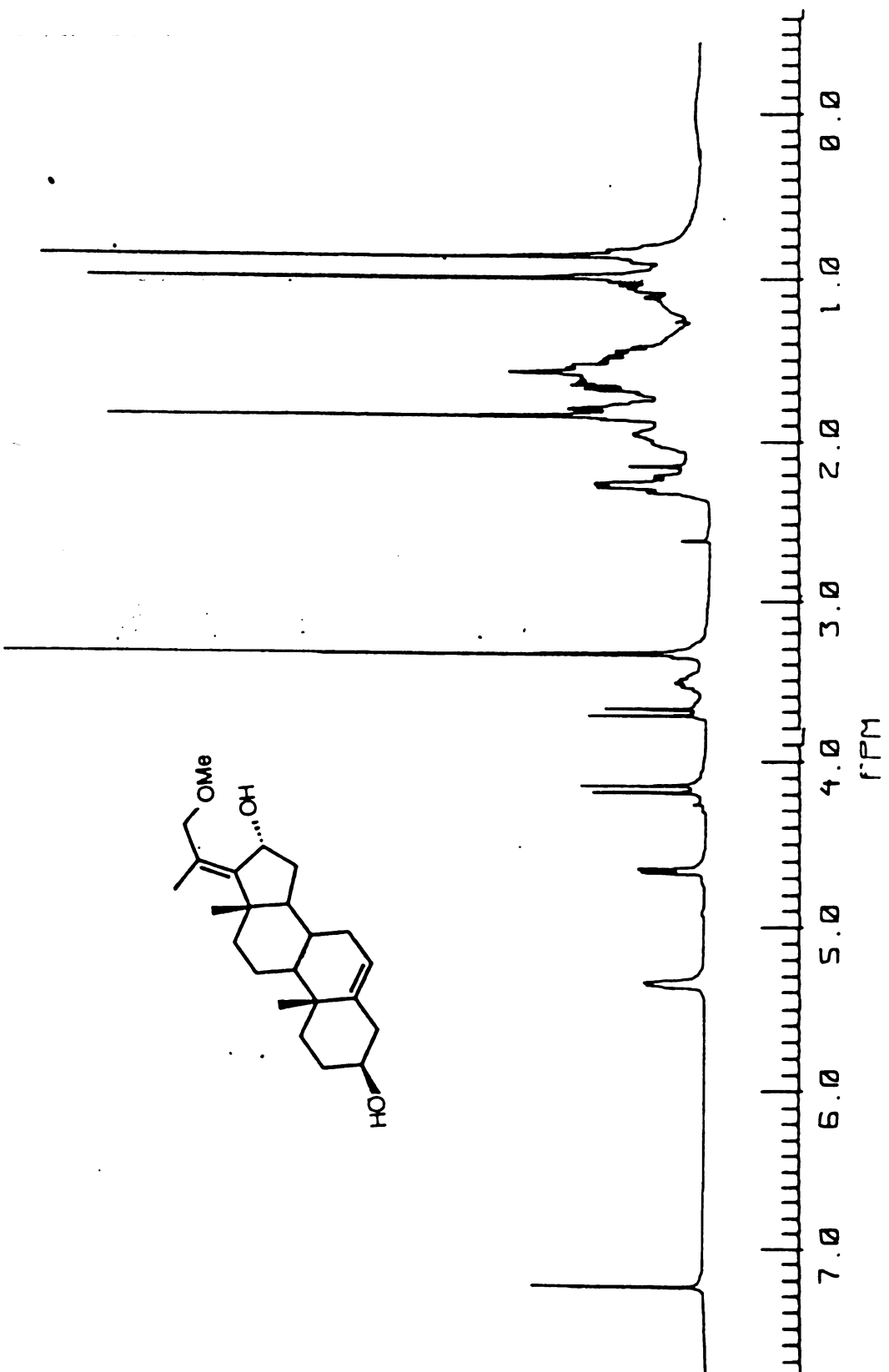

3·0
4·0
5·0
MICRONS
6·0
7·0
8·0
9·0
10
12
100
80
60
40
20
HO
O
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER(CM⁻¹)
WAVENUMBER(CM⁻¹)
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
SCAN TIME
SLIT
OPERATOR
DATE
TIME CONSTA



Mass spectrum of 11



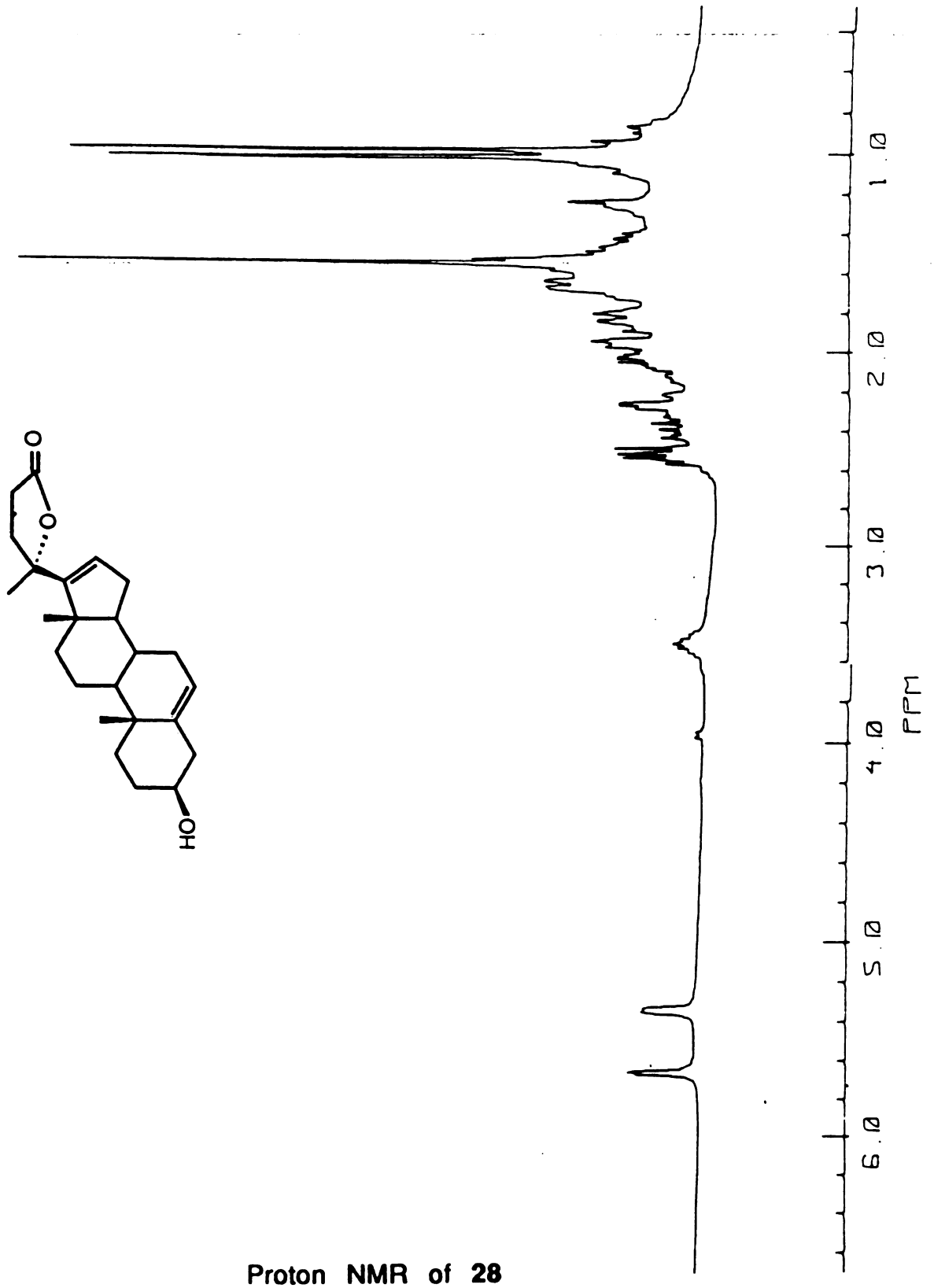
Proton NMR of 11



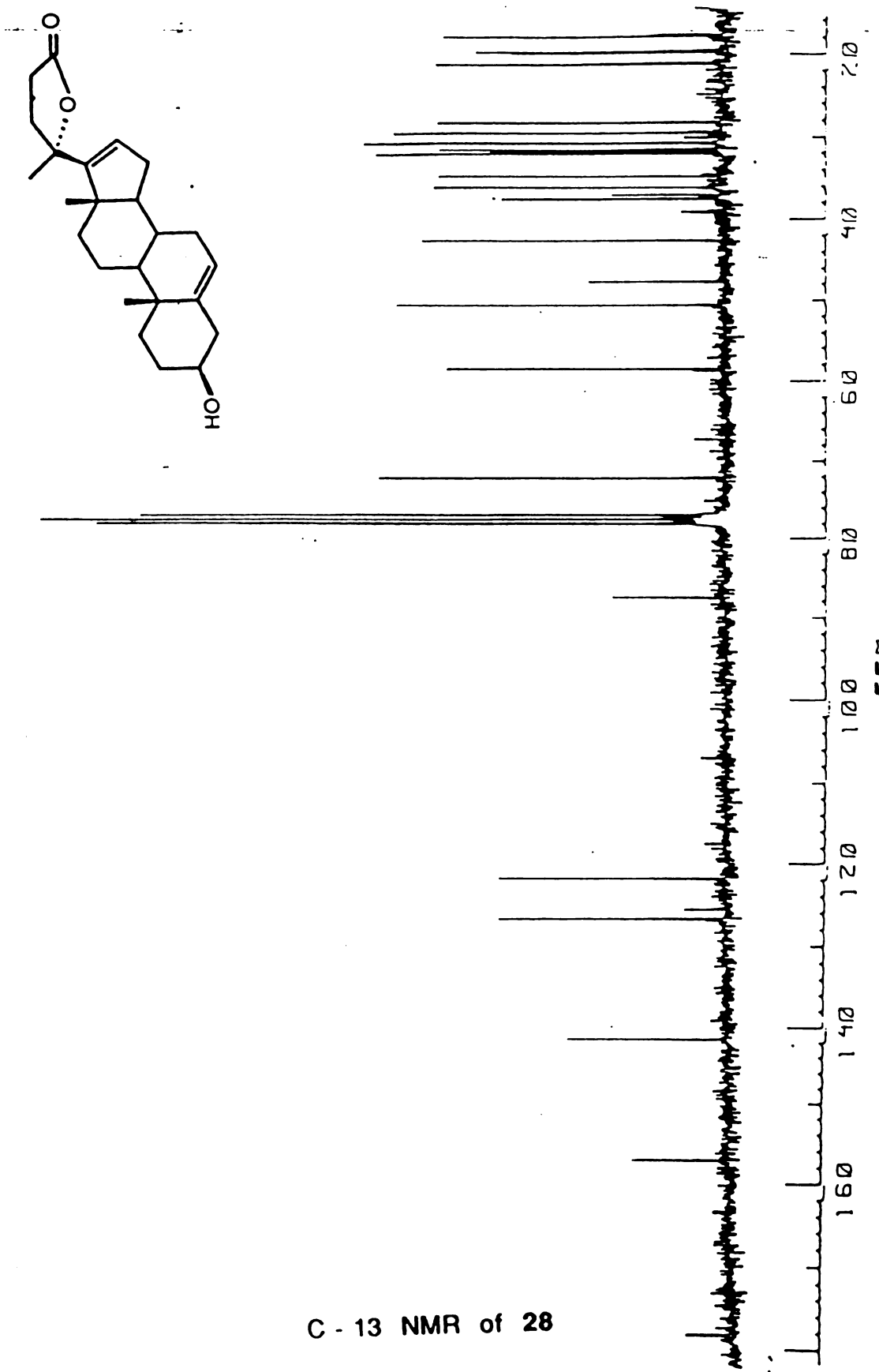
Proton NMR of 13

MICRONS
WAVENUMBERS(CM-1)
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
OPERATOR
DATE

IR of 13

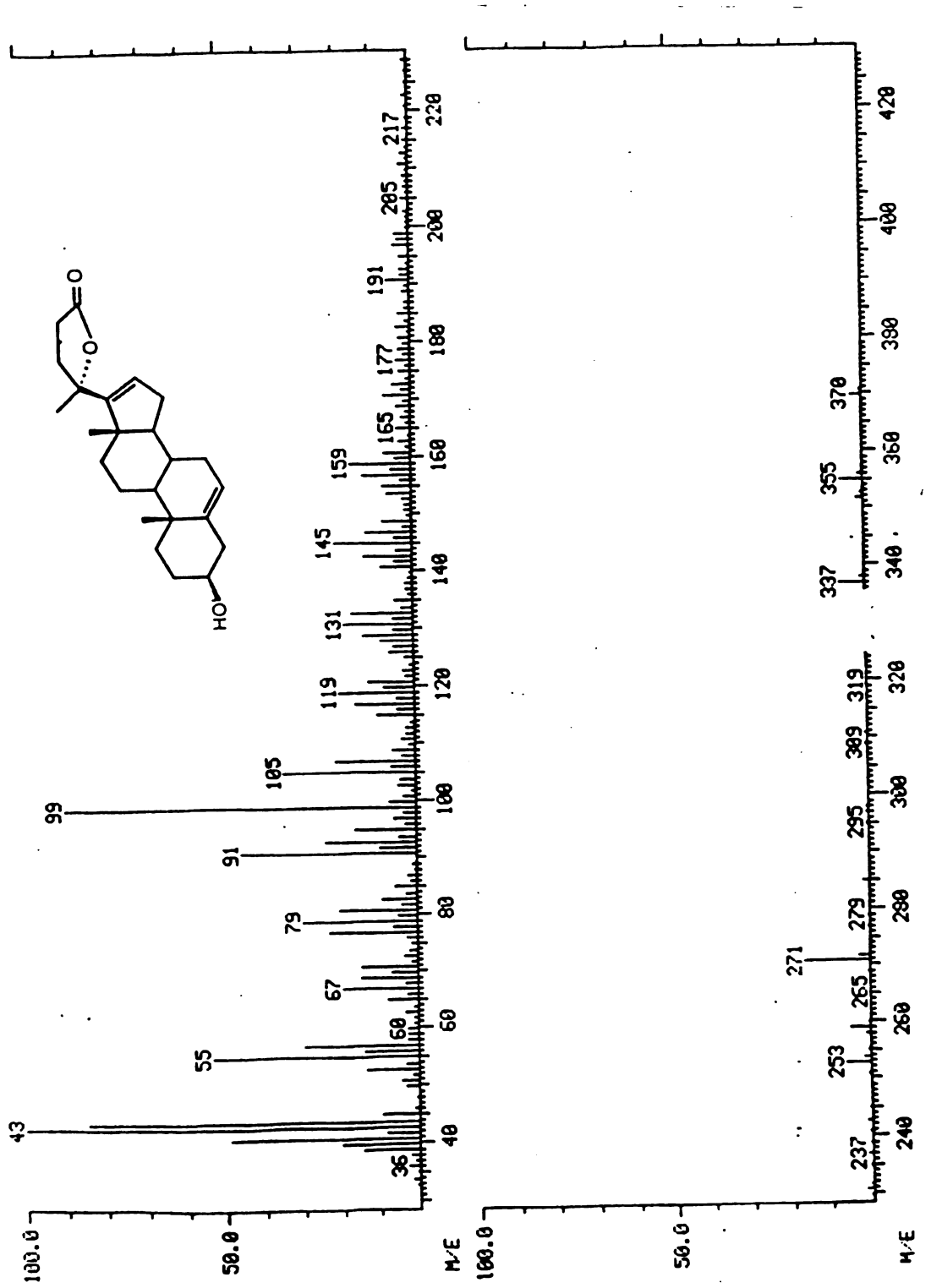


Proton NMR of **28**

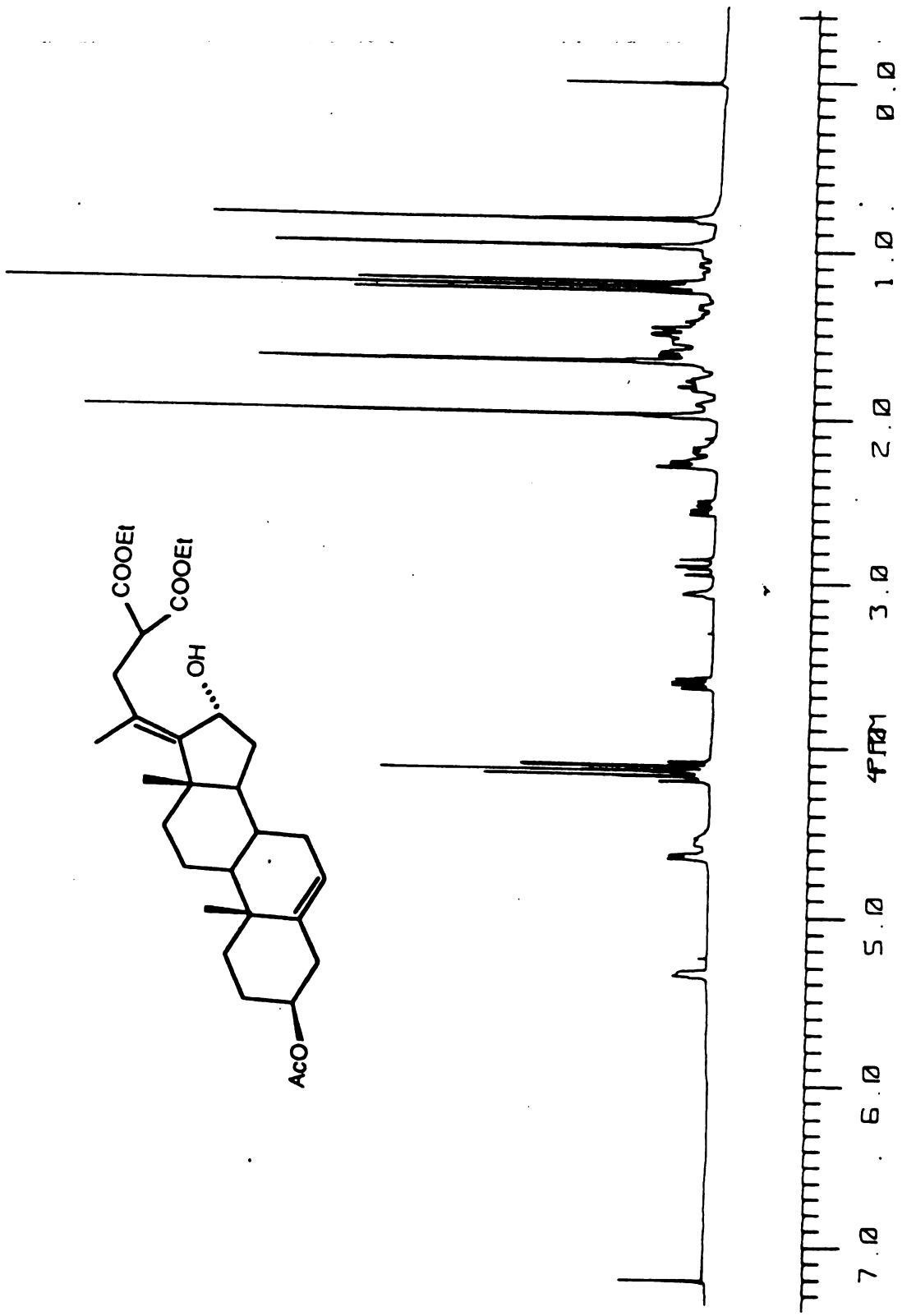


C - 13 NMR of **28**

IR of **28**

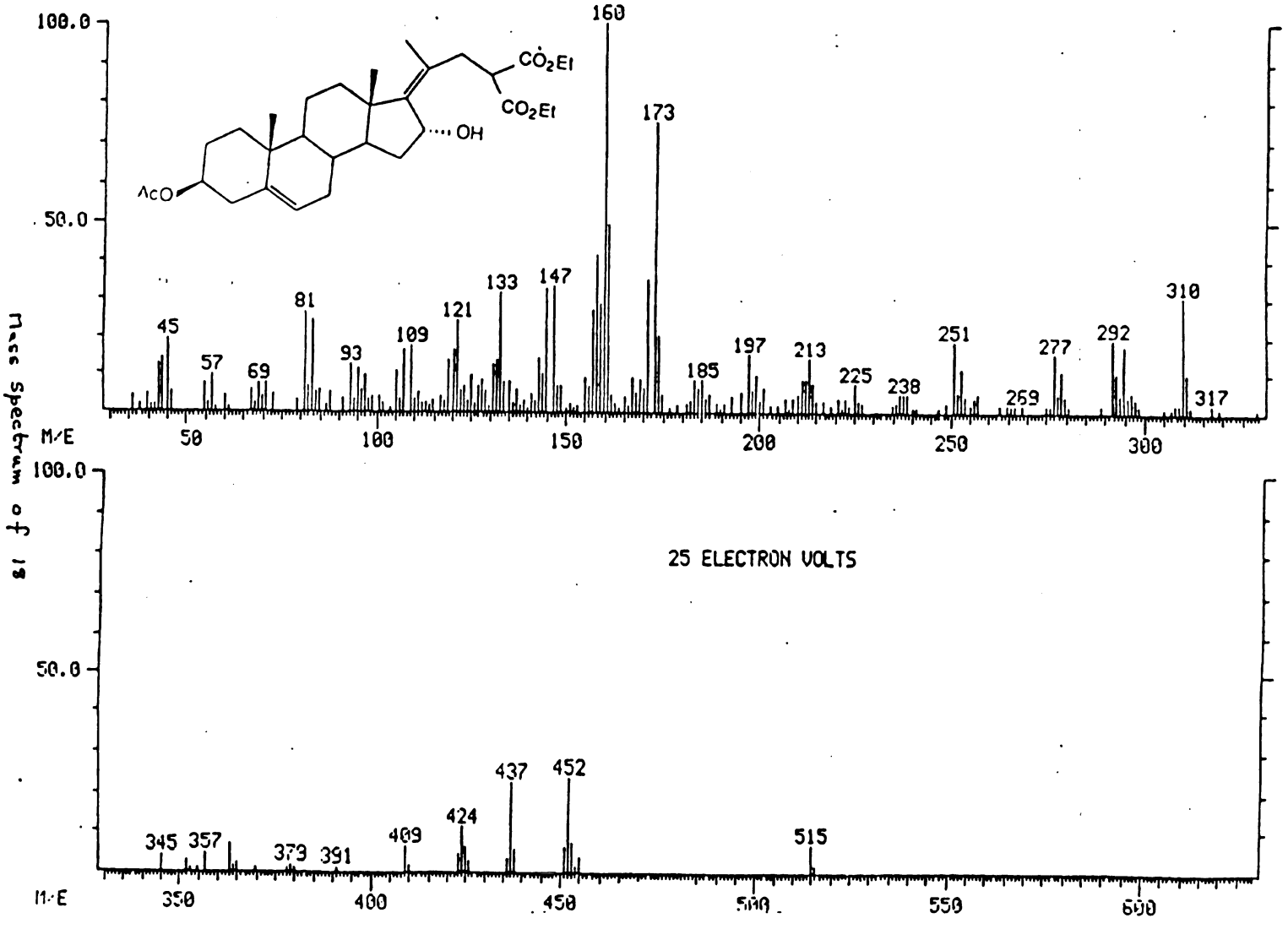


Mass spectrum of **28**



Proton NMR of 18

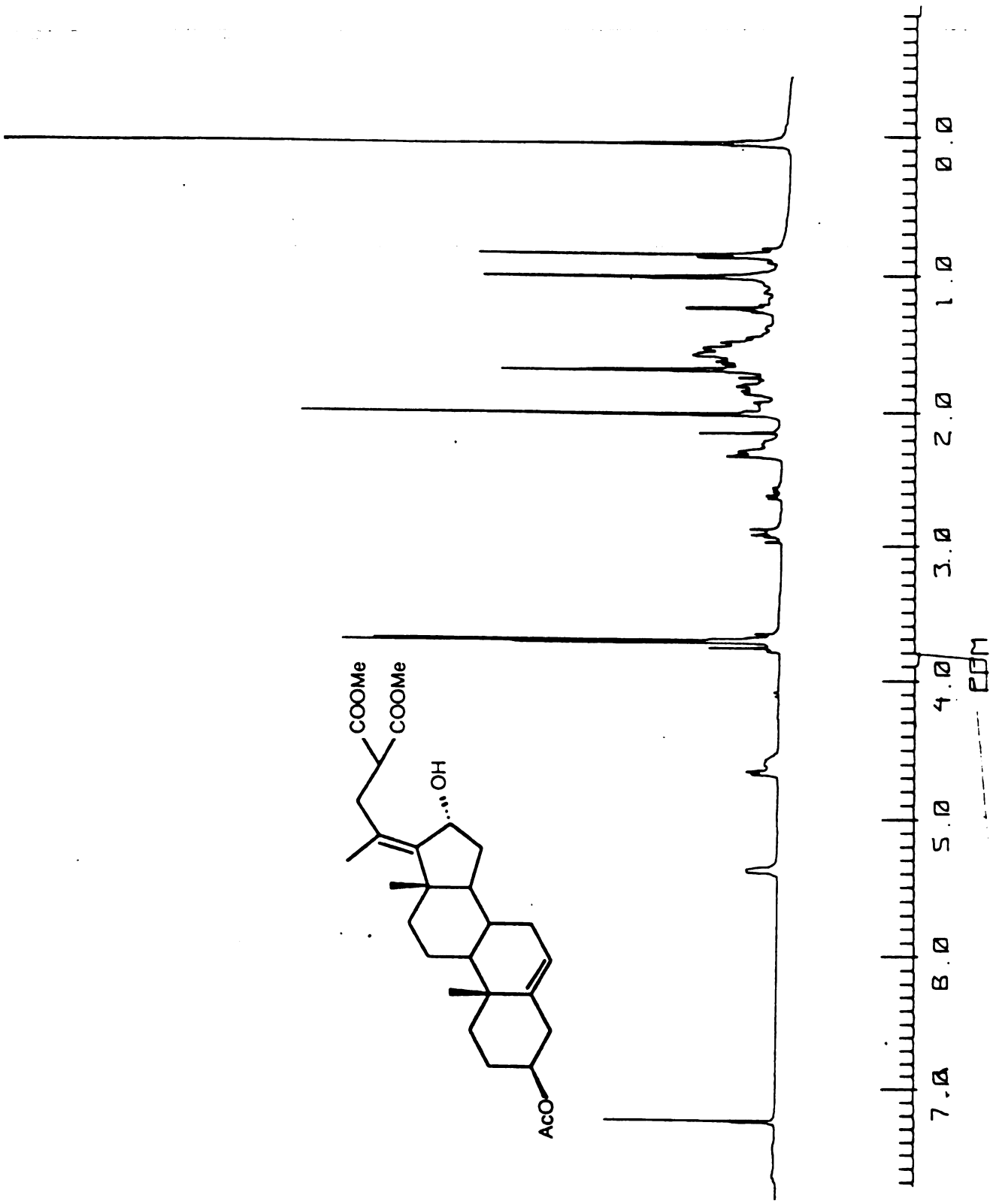
IR of **18**



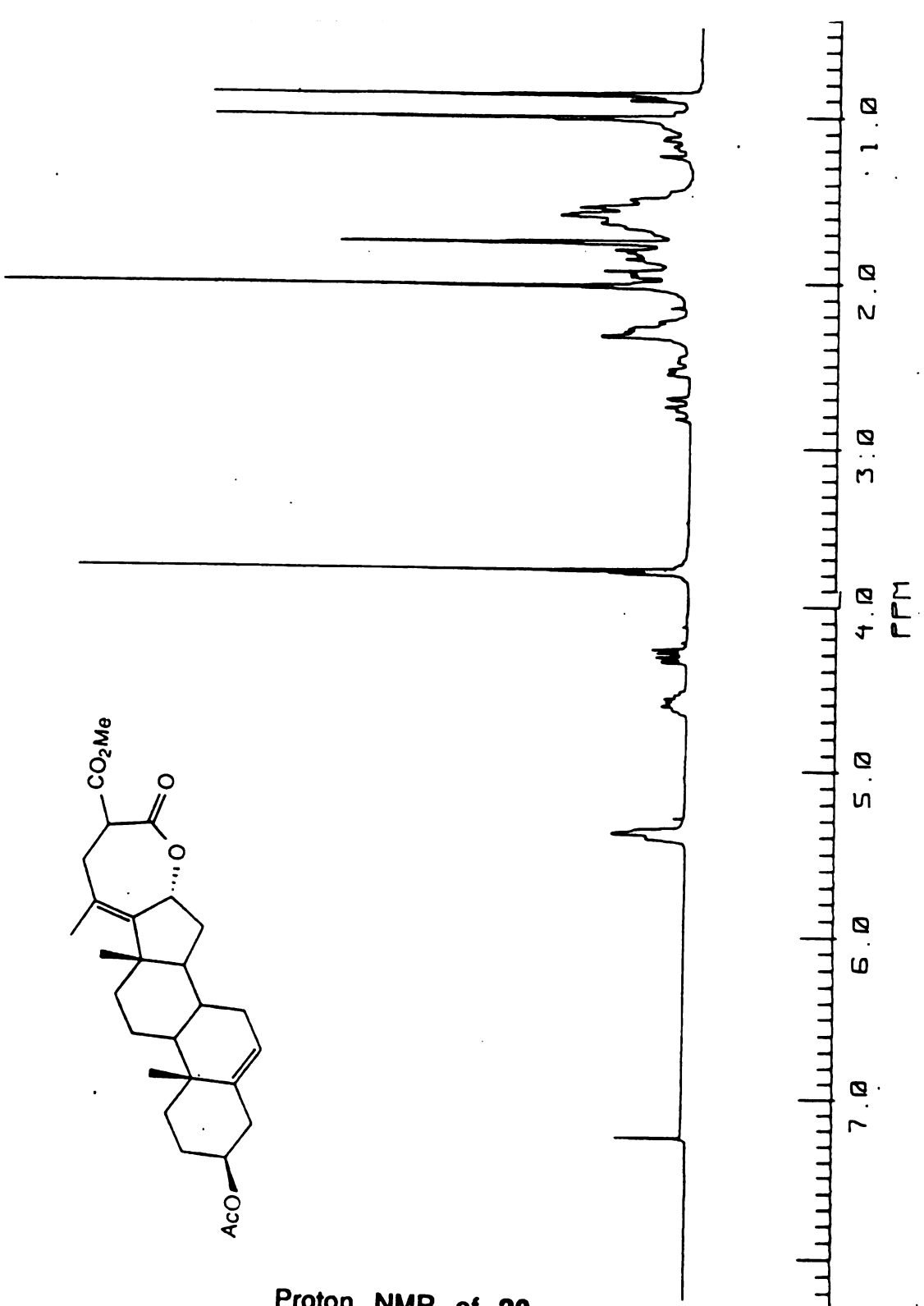
Mass spectrum of 18

CO2Et
CO2Et
OH
AcO
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
PPM

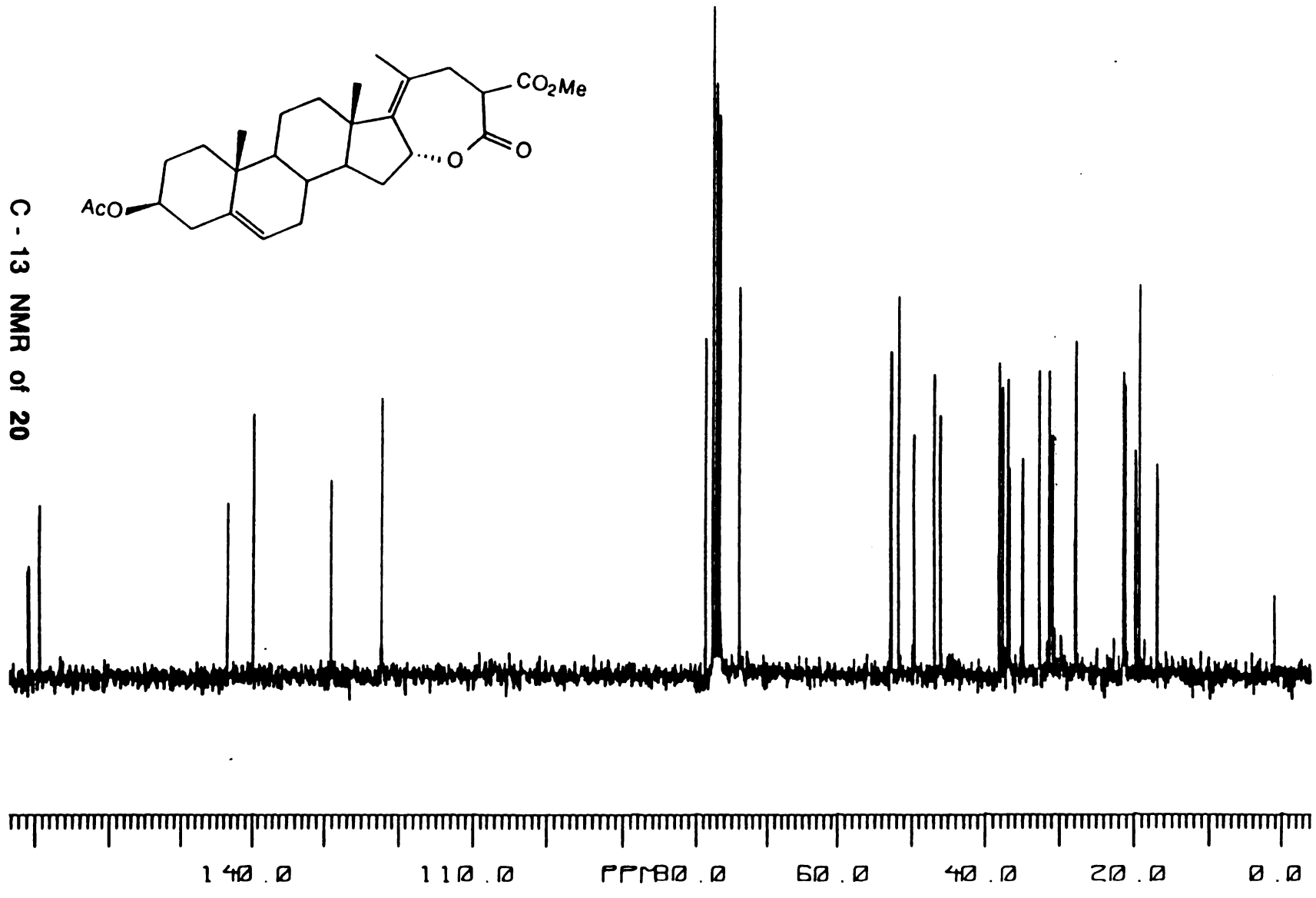
C - 13 NMR of 18



Proton NMR of 19

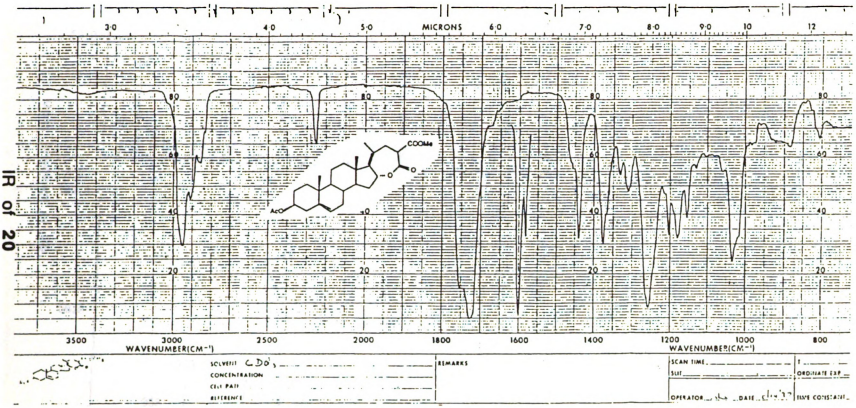


Proton NMR of **20**



C - 13 NMR of 20

IR of 20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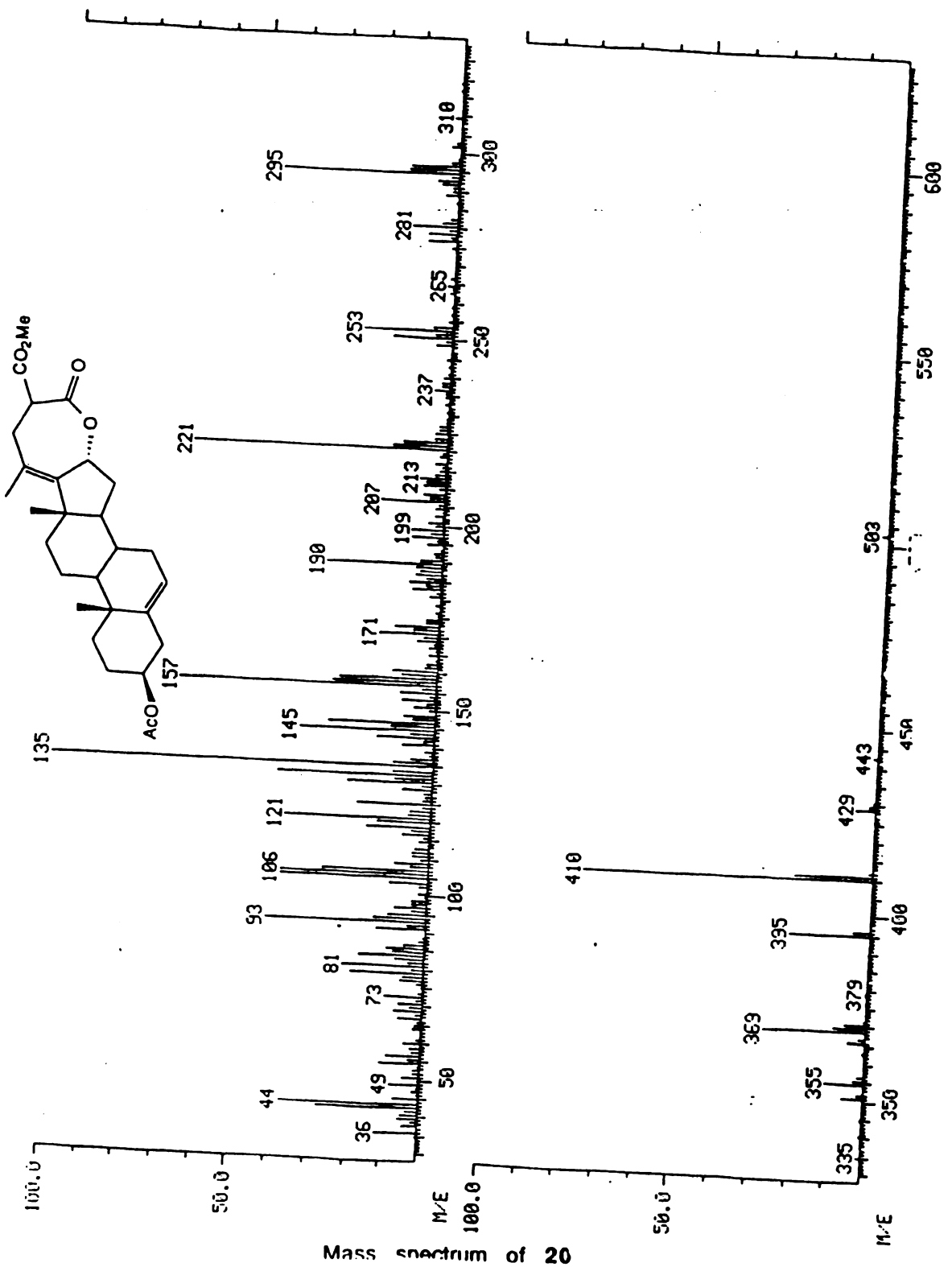
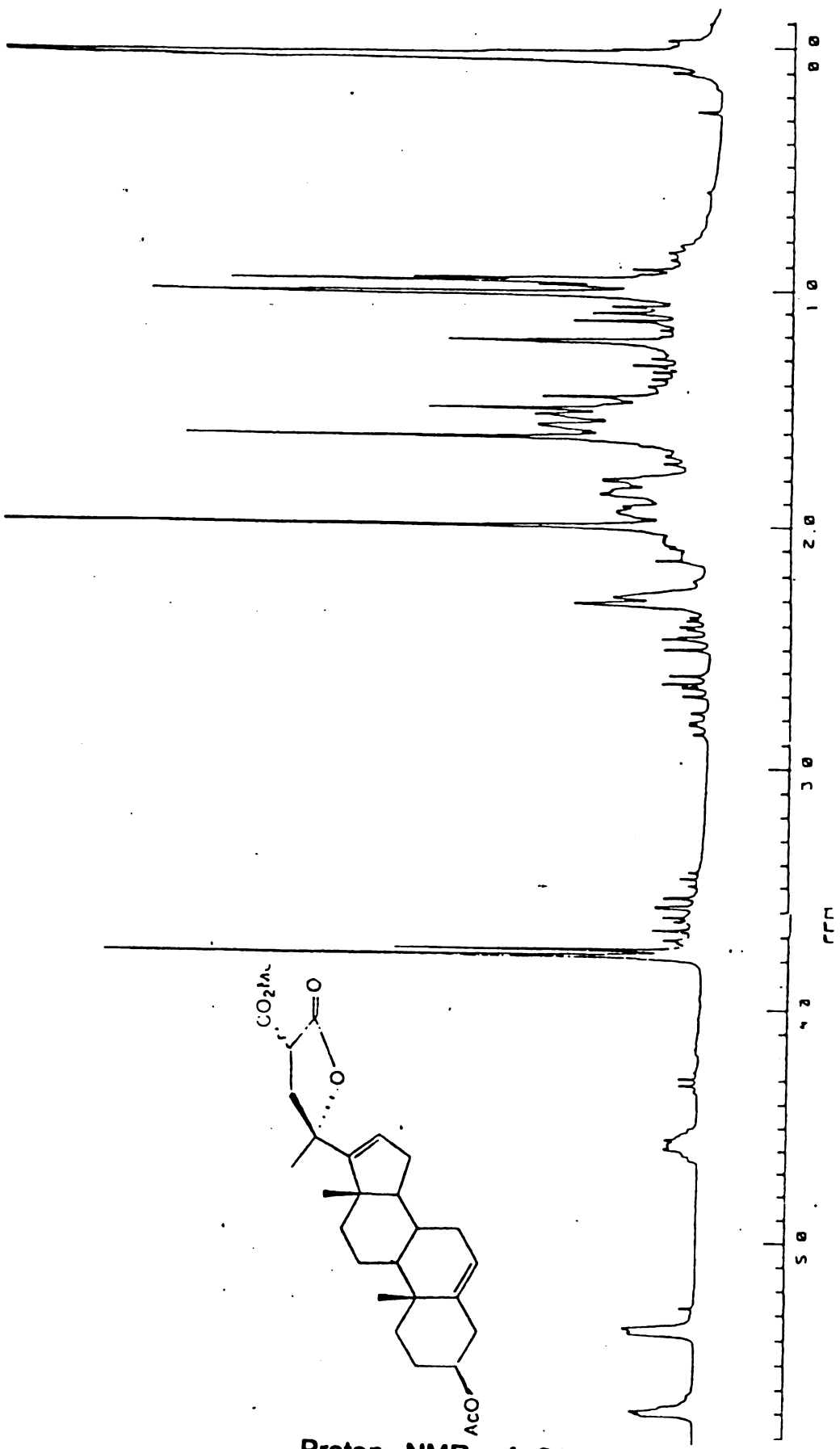
4·0
5·0
MICRONS
6·0
7·0
8·0
9·0
10
12
100
80
60
40
20
COOMe
AcO
O
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER(CM⁻¹)
WAVENUMBER(CM⁻¹)
SOLVENT CDCl3
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
SCAN TIME
SLIT
OPERATOR
DATE
ORDINATE EXP.
TIME CONSTANT

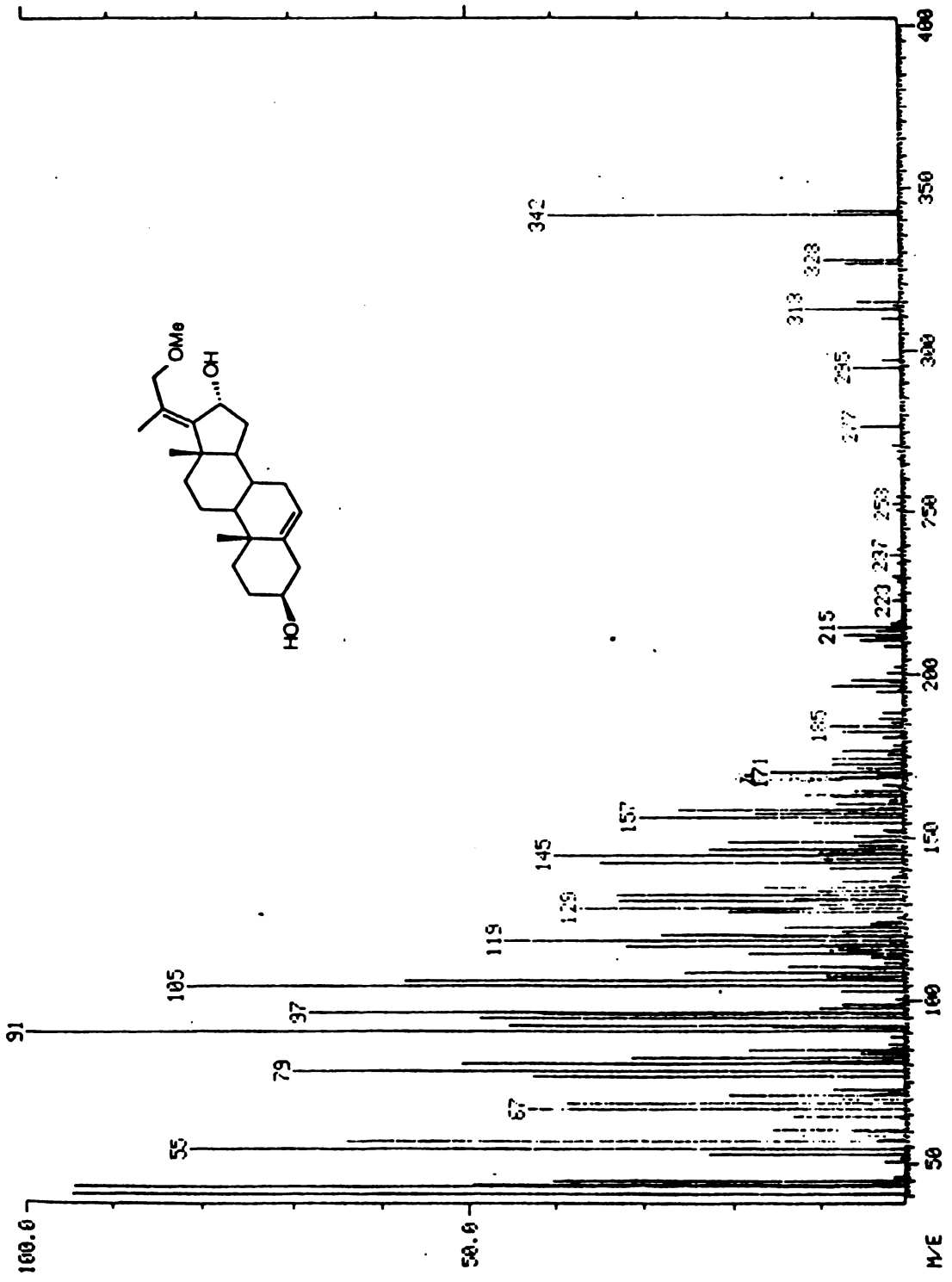


Mass spectrum of **20**

IR of **24**



Proton NMR of 21



Mass spectrum of 13.

C - 13 NMR of 6

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INTRODUCTION.

Among carbon - carbon bond forming reactions, cycloaddition reactions occupy a position of particular significance. An attractive feature of these reactions is the "simultaneous" formation of two bonds with the generation of up to four chiral centers[1]. The most prominent of the cycloaddition reactions is, undoubtedly the $4\pi + 2\pi$ cycloaddition reaction. Since its discovery nearly sixty years ago[2], the reaction has found extensive application in the synthesis of a wide array of complex organic molecules[3]. The high yields, mild reaction conditions, high stereoselectivity and regioselectivity of this reaction make it an invaluable tool to the synthetic organic chemist. Furthermore, the mechanism of the bimolecular Diels Alder reaction is sufficiently well understood, that the outcome of the reaction can be predicted with a high degree of accuracy[4].

The intramolecular version of the Diels Alder reaction has added an entirely new dimension to this already versatile synthetic method. This reaction has made it possible to create complex multicyclic arrays in a single step. Due to the entropic advantage of the intramolecular process, even relatively unreactive dienes and dienophiles undergo cycloaddition reactions in a facile manner. (fig 1). These factors have led to a tremendous growth in the field of intramolecular Diels Alder reaction, as evidenced by the number of reviews published on this topic in the recent past[5].

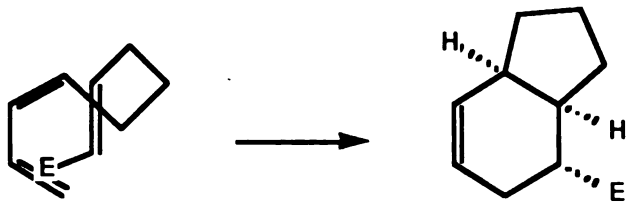


Figure 1

A major challenge in any synthetic strategy using the Diels Alder reaction is construction of the appropriate diene and dienophile moieties. The elegance of a synthetic strategy involving an intramolecular Diels Alder reaction depends to a great extent on facile construction of the requisite diene and dienophile moities. Furthermore, it is often difficult to carry a reactive diene or dienophile through various steps of a synthetic sequence. One way of overcoming this problem is to use latent dienes and dienophiles which may be unmasked at a convenient stage of the synthesis. This strategy has been used to advantage by many workers.

An interesting example of an intramolecular Diels Alder strategy using a latent diene and a latent dienophile is, Ichihara's synthesis of Coronafacic acid[6]. In this synthesis a single thermolysis unmasked the diene and dienophile and also accomplished an intramolecular Diels Alder reaction. (fig 2). A conrotatory ring opening of cyclobutene unmasked the diene, whereas a retro Diels Alder reaction with the elimination of fulvene, uncovered the dienophile. The intramolecular Diels Alder reaction between these two reactive species afforded a single product in 92% yield. This control of stereochemistry is an attractive feature of this strategy.

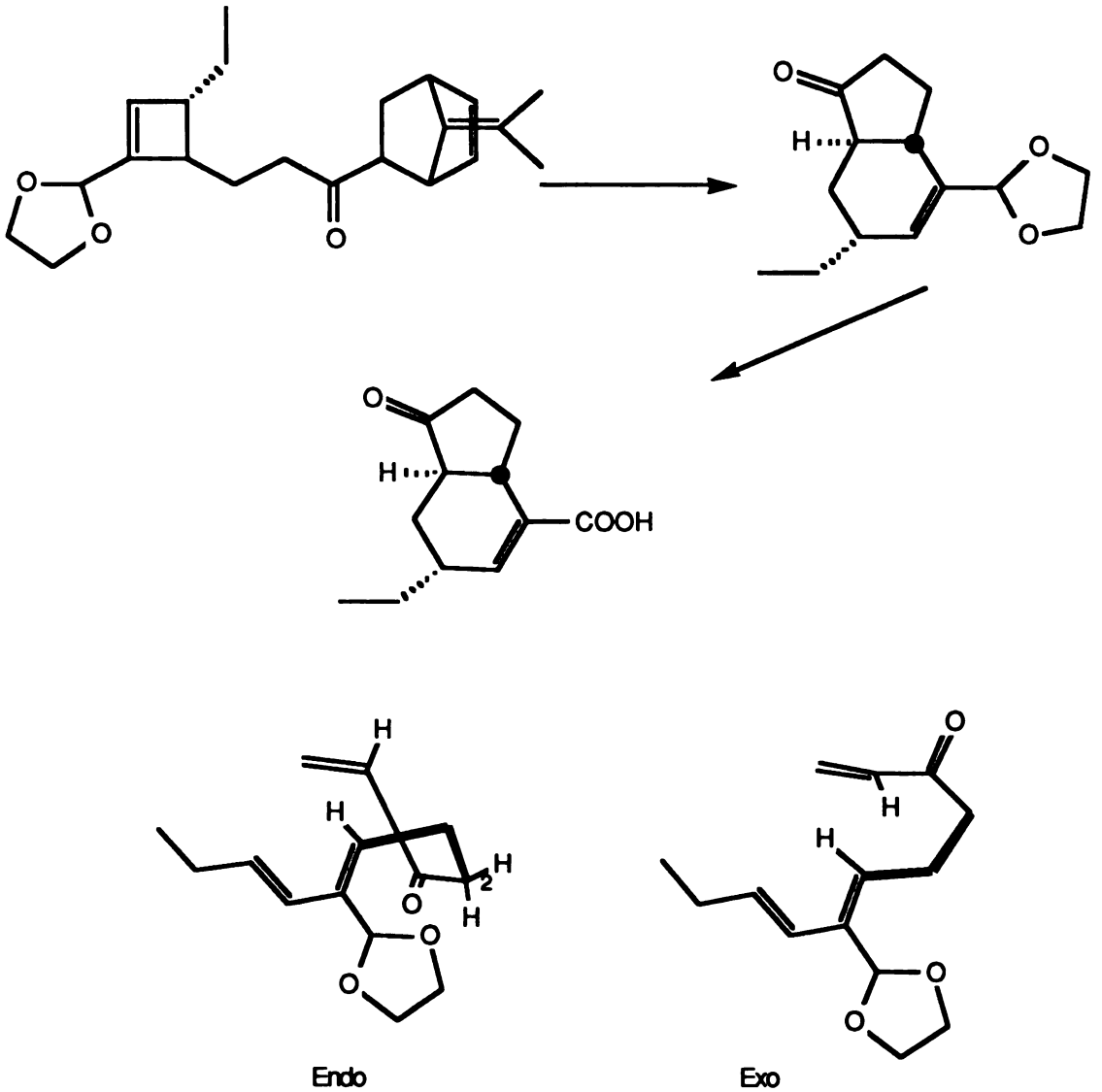


Figure 2.

As can be seen in fig 2, steric requirements in the transition state favor the exo arrangement more than the endo arrangement, which has a severe nonbonded interaction between 2 - H and the acetal oxygens.

Latent dienophiles have proven especially useful in alkaloid syntheses, due to the inherently unstable nature of many of the dienophiles used in hetero Diels Alder reactions. Acylimines, which are dienophiles in

imino Diels Alder reactions, are invariably generated in situ from the corresponding acetates and trapped by a suitable diene[7]. (fig 3). This technique has been used in the syntheses of several indolizidine alkaloids. An example is the synthesis of Elaeokanine A[7a], wherein Weinreb used an intramolecular imino Diels Alder reaction as the key step. The diene was generated from a dihydro thiophene dioxide, and the acyl imine dienophile was generated from the corresponding acetate. (fig 4).

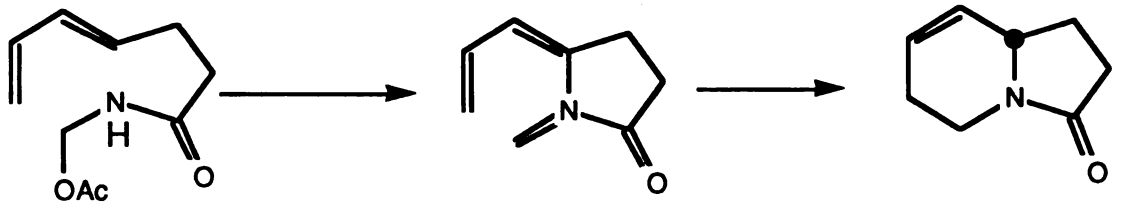


Figure 3.

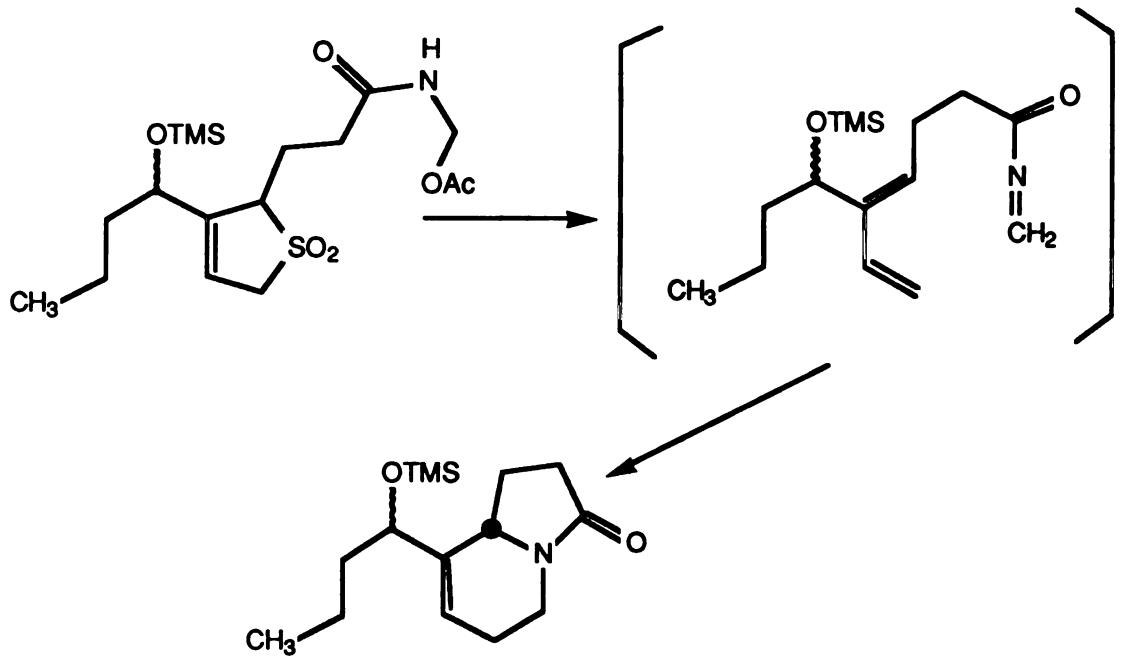
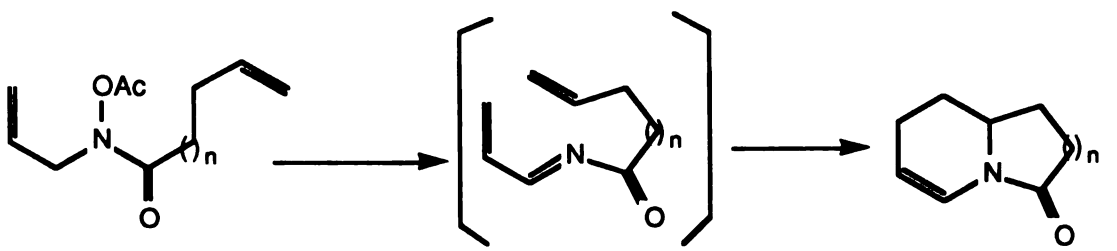


Figure 4

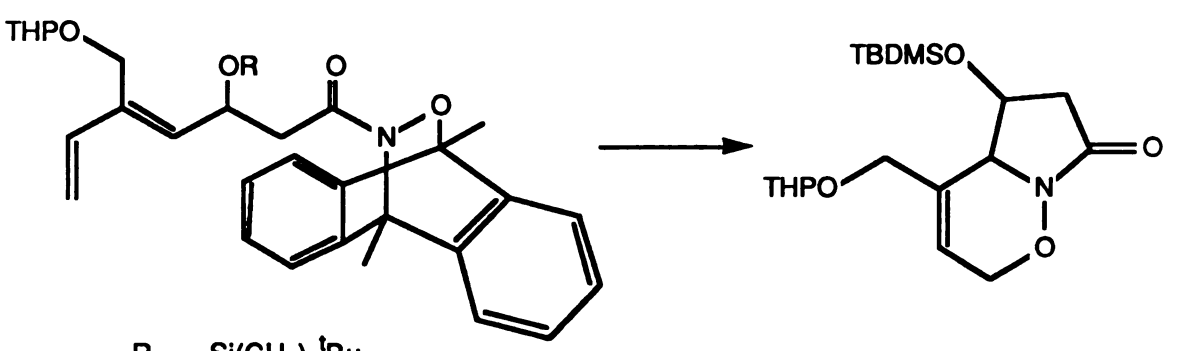
Complementing the work on the use of acyl imines as dienophiles, there have also been reports of reactions of N - acyl - 1 - aza - 1,3 - dienes in Diels Alder reactions[8].(fig 5). Although these species have not been directly observed, even when the N - acyl function does not contain a dienophile, there is strong evidence for their existence in these thermal reactions.



n = 1 or 2.

Figure 5.

The acyl nitroso group is another reactive but unstable dienophile. In the synthesis of Pyrrolizidine alkaloids, using an acyl nitroso group as the dienophile, Gary Keck[9] generated the dienophile <u>in situ</u> via a retro Diels Alder reaction with the elimination of 9, 10 - dimethylanthracene. (fig 6). Thus reactive species with only a brief lifetime may be efficiently employed in Diels Alder reactions by generation from a latent or protected precursor.



R = $Si(CH_3)_2{}^tBu$

Figure 6

Diene moities are commonly masked as dihydrothiophene dioxide. Its ease of preparation and thermolysis make it highly useful in synthesis of reactive dienes. Martin[10] has used this masked diene in several alkaloid syntheses for intramolecular 4 + 2 cycloadditions of enamides. (fig 7).

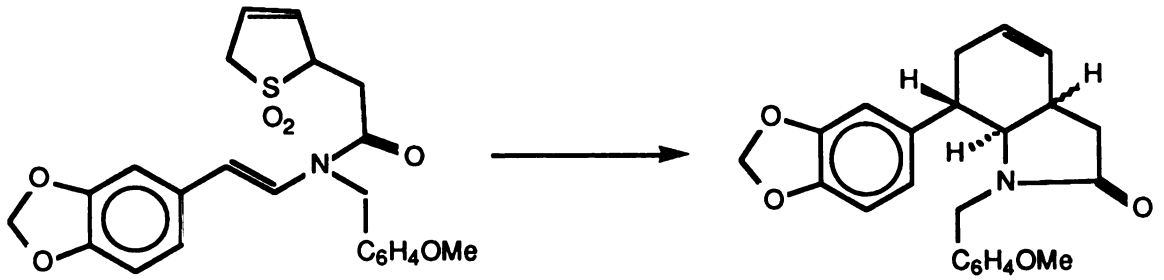


Figure 7.

Our work is aimed at using cyclobutanones as precursors for reactive dienes. We proposed to generate reactive dienes by thermolysis of cyclobutanone silyl enolethers and use these in Diels Alder reactions. (fig 8).

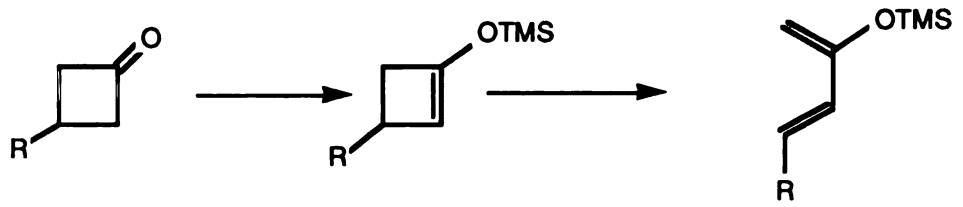


Figure 8.

The ring strain inherent in cyclobutane systems make appropriately derivatized cyclobutanones suitable candidates for further elaboration by thermal bond cleavage. Cyclobutene is known to undergo facile ring opening to butadiene. The thermolysis of benzocyclobutenes[11] and their use as

dienes in intramolecular Diels Alder reactions have been studied extensively. (fig 9)

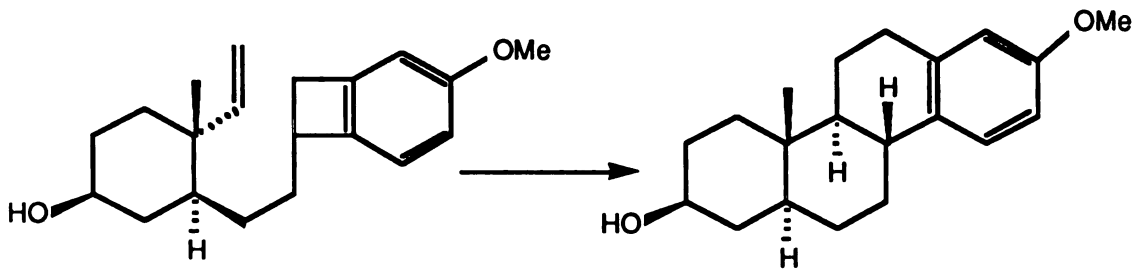


Figure 9

In contrast, however, thermolysis of cyclobutanone derivatives have not been examined in detail. One noteworthy example in this direction is Trost's use of 2 - methoxy - 3 - phenylthio buta - 1, 3 - diene as a latent diene[12]. (fig 10)

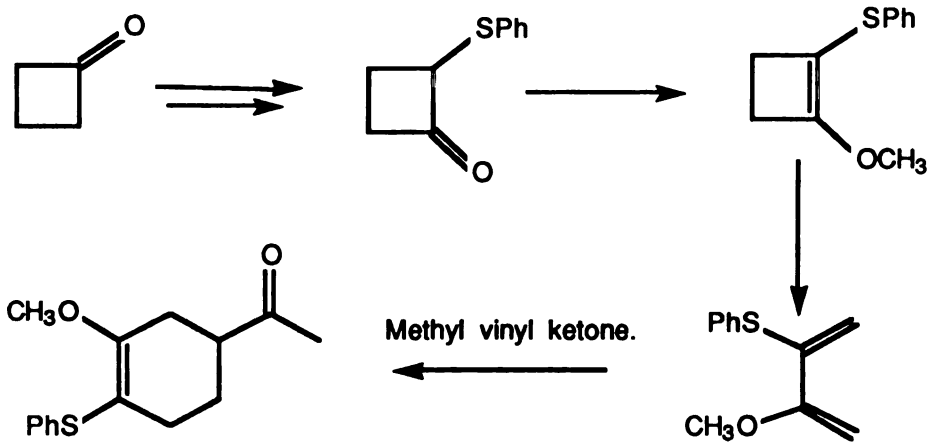


Figure 10

It is interesting to note here that phenyl thio rather than the methoxy group is controlling the regiochemistry in the thermal process where as methoxy

group plays a greater role in the catalyzed reaction. This approach permits the obtention of a regiochemistry that complements that obtained with usual dienes such as 2 - methoxy butadiene.

We proposed to study the synthesis and thermolysis of cyclobutanone silylenolethers, and their use in Diels Alder reactions. An attractive feature of this strategy is that the expected Diels Alder adducts incorporate potentially useful functional groups (fig 11).

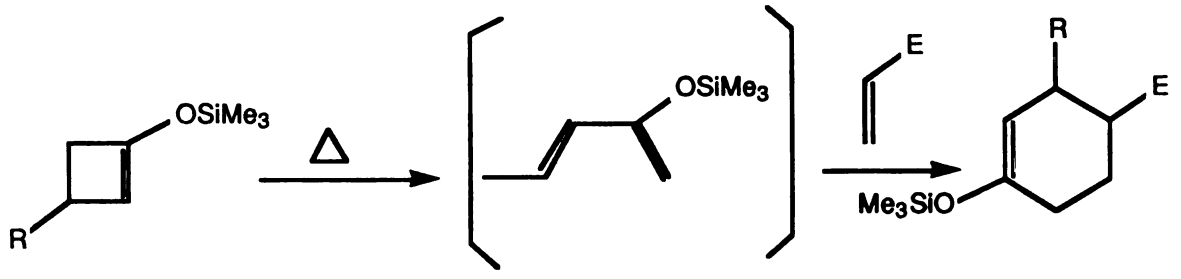


Figure 11 .

Although cyclobutanones are potentially very useful intermediates in organic synthesis, their application has been limited by the methods available for their construction. The $2\pi + 2\pi$ cycloaddition reaction provides a simple and direct route to this system. The ready availability and inexpensive nature of the reagents used, mild experimental conditions and good yields are some attractive features of this reaction[13a]. Furthermore the reaction is regiospecific. In the favored adducts, the most nucleophilic carbon of the olefin is always bonded to the sp-hybridized carbon atom of the ketene. The reaction is also chemoselective. Addition occurs preferentially to the most nucleophilic and the least hindered double bond[14].

Dichloroketene is an extremely reactive species and is commonly generated in situ and trapped by olefins. It is usually generated either by dehydrohalogenation of dichloacetyl chloride, using triethyl amine,[15a] or by zinc dehalogenation of trichloroacetyl chloride[15b-d]. Early researchers encountered several problems with both methods. Triethyl amine catalyzed the decomposition of dichloroketene. Zinc chloride, formed in the dehalogenation reaction, catalyzed polymerization of several olefins. Furthermore, dichloroketene itself was prone to polymerization under these conditions.

Recently, several methods have been developed to minimize side reactions catalyzed by the acidic zinc salts formed during dehalogenation of the acid chloride. Brady and Bak[15b] noted that high dilution conditions helped overcome the problem of ketene polymerization. Hassner reported that use of phosphorous oxy chloride improved the yield of cycloadducts and minimized unwanted side reactions[15c]. He proposed that phosphorous oxy chloride complexes the zinc cation formed in the reaction, thereby deactivating it. In the reaction of dichloroketene with allyl ethers, higher yields of cycloadducts were obtained by using glyme as a cosolvent with ether[15d].

The dehalogenation synthesis of dichloroketene initially called for the use of activated zinc. Mehta has reported that commercial zinc can be used for this reaction provided the reaction mixture was agitated by ultrasonic energy[16]. The yields compared favorably with those reported for other methods and the reaction times were considerably shorter.

Here we describe our attempts at synthesizing various cyclobutanone derivatives and converting them to their silylenolethers. We also describe the

results of our attempts at using these silylenolethers in Diels Alder reactions, both intramolecular and intermolecular.

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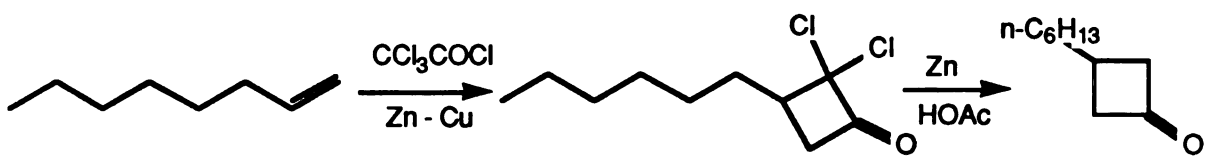
RESULTS AND DISCUSSION.

In our study of 3 - substituted cyclobutanones as precursors to 1 - alkyl - 3 - siloxy - substituted 1, 3 - butadienes, we chose n - octene (**1**) as our initial substrate. In our hands, the zinc dehalogenation method of generating dichloroketene gave the best results. Using Brady's high dilution procedure[15b], we isolated 2,2 - dichloro - 3 -hexyl cyclobutanone (**2**) in excellent yield (> 86%). All the spectroscopic evidence were in agreement with this structure. Dehalogenation of the α,α - dichloro cyclobutanone **2**, was accomplished by treatment with zinc and acetic acid[17]. The reduction proceeded smoothly to give 3 - hexyl - cyclobutanone (**3**), in near quantitative yield from **2** (fig 12).



1 2 3

Figure 12

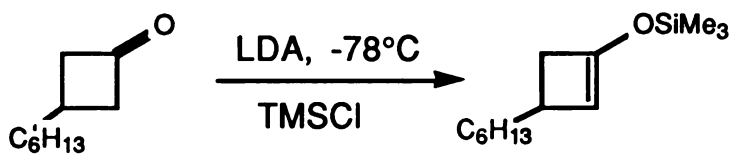
Having synthesized the requisite cyclobutanone precursor we proceeded to generate the corresponding silyl enol ether. This proved to be

a much tougher task than we had earlier anticipated. Treatment of **3** with triethyl amine in dimethyl formamide[18a] and trapping the enolate with chlorotrimethyl silane followed by the usual aqueous work up resulted in complete recovery of starting material. Use of lithium diisopropyl amide as a base gave identical results[18b]. Several other methods were also attempted but without any success[18]. Since it is known that tert-butyl dimethyl silyl enolethers are much more stable compared with trimethyl silyl enolethers, we modified our approach slightly and attempted the synthesis of tert-butyl dimethyl silyl enolether of **3**. The lithium enolate of **3,** generated by its reaction with lithium diisopropyl amide, was treated with hexamethyl phosphoramide and tert - butyl dimethyl silyl chloride[18c]. However after the usual aqueous work up only the starting material was recovered.

In all the above experiments, a GC trace of the reaction mixture before work up indicated probable formation of the desired silylenolether (GC - Mass spectrum). Hence we concluded that the enolether was sensitive to aqueous work up and was easily hydrolyzed to the ketone. We decided therefore to avoid the aqueous work up and attempted to isolate the enol ether by distillation. However, on evaporation of the solvent (tetrahydrofuran), substantial quantities of lithium chloride precipitated, making the distillation of product very difficult.

The problem of isolating the silyl enol ether was finally overcome in the following fashion. The enolate of **3** was generated using lithium diisopropyl amide and trapped with trimethyl silyl chloride. After the reaction was complete, an excess of dry pentane was added to the reaction mixture resulting in precipitation of lithium chloride. The mixture was allowed to stand until precipitation of lithium chloride was complete. The solution was then filtered under an argon atmosphere. The clear solution was evaporated under

vacuum to remove the solvent and the residue purified by bulb to bulb distillation. The colorless oil obtained possessed all the spectral features expected for silyl enolether **4**. Table 1 shows some important ^{1}H NMR, ^{13}C NMR and IR values of compound **4** and those reported in the literature[19] for cyclobutanone silyl enolether.



4

Figure 13.

	δ (^{13}C)			δ $^{1}H_{vinyl}$	IR: ν C=C cm^{-1}
	$C_{(1)}$	$C_{(2)}$	CH_3		
reported	148.48	102.15	0.10	4.52	1615 - 40
observed for **4**.	147.96	107.58	0.88	4.64	1617 - 40

Table 1.

A survey of the chemical literature reveals very little information regarding the preparation and isolation of cyclobutanone silyl enolethers. 1,2 - Bis (trimethylsiloxy) cyclobutene has been synthesized by an acyloin condensation[20]. Clark et.al have reported generation of the enolate of cyclobutanone by the reaction of the corresponding α-chloro compound with dimethyl copper lithium[21]. They have used these enolates in aldol condensations. Although they refer to the reaction of this enolate with

trimethyl silylchloride, it is not entirely clear whether they have isolated the silyl enolether (fig 14). They also report that reaction of **20** with lithium diisopropyl amide failed to generate the desired enolate.

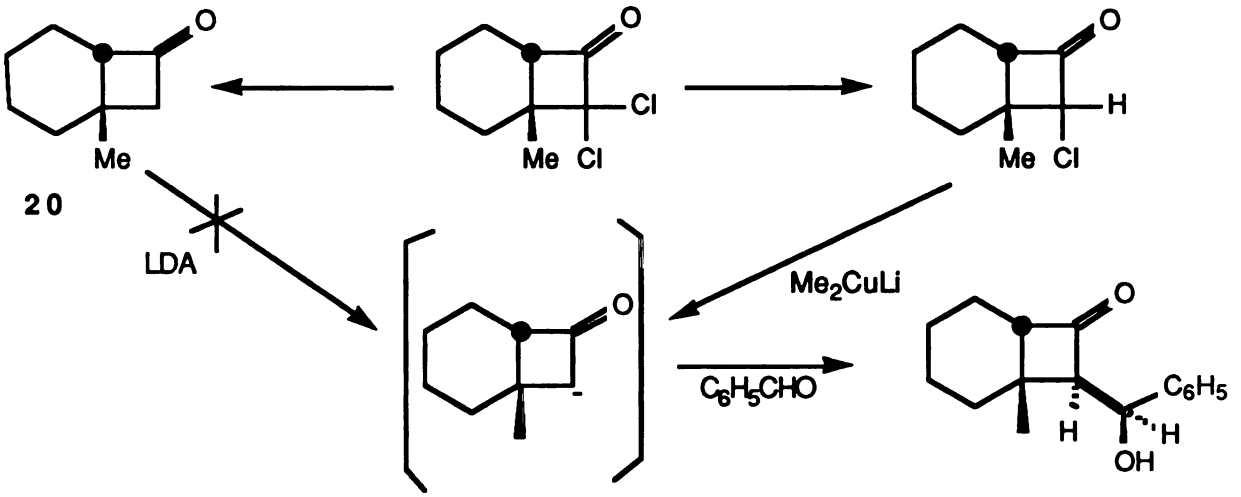


Figure 14.

The silyl enolether **4** was stored under an argon atmosphere, and in this fashion it could be used over extended periods of time. However, exposure to moisture causes rapid hydrolysis to the cyclobutanone **3**. Thermolysis of **4**, at 230°C generated the corresponding diene, which was trapped by benzoquinone to give the expected Diels Alder adduct. (fig 15). The thermolysis was conducted by passing a solution of the silyl enolether in tetrahydrofuran, through a pre - heated vertical column packed with glass beads. The hot vapors were collected in a receiver cooled with liquid nitrogen. This flask also contained a solution of the dienophile in tetrahydrofuran. The thermolysis was conducted under an argon atmosphere and the entire reaction was completed in less than five minutes.

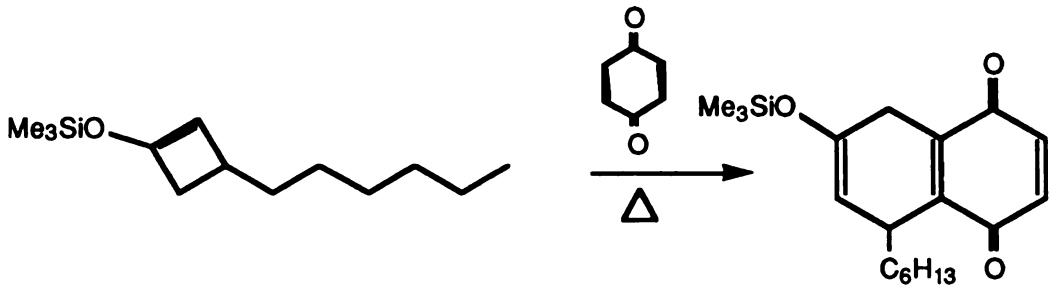


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Figure 15.

Encouraged by these results, we attempted to synthesize other reactive dienes by the same procedure. Our next substrate was the methylene derivative of β-cyclocitral (fig 16). This olefin **5** was prepared in good yield from β-ionone[22] (fig 16).

As expected, on reaction of **5** with dichloroketene addition occurred exclusively at the less hindered double bond to give **6**. Dehalogenation of **6** with zinc and acetic acid gave the cyclobutanone derivative **7**. Reaction of **7** with lithium diisopropyl amide followed by trapping of the enolate with trimethyl silyl chloride as described earlier, gave the expected silyl enolether **8**. Attempts to achieve a cleavage of the four membered ring of **8** followed by an electrocyclic ring closure did not succeed. This thermolysis was complicated by a methyl rearrangement, and resulted in a complex mixture of products (fig 17).

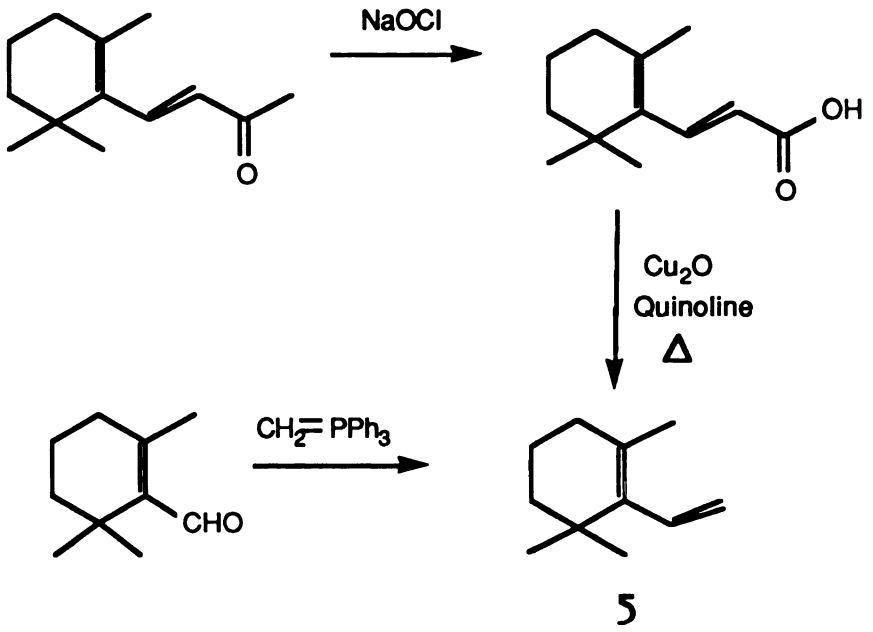


Figure 16

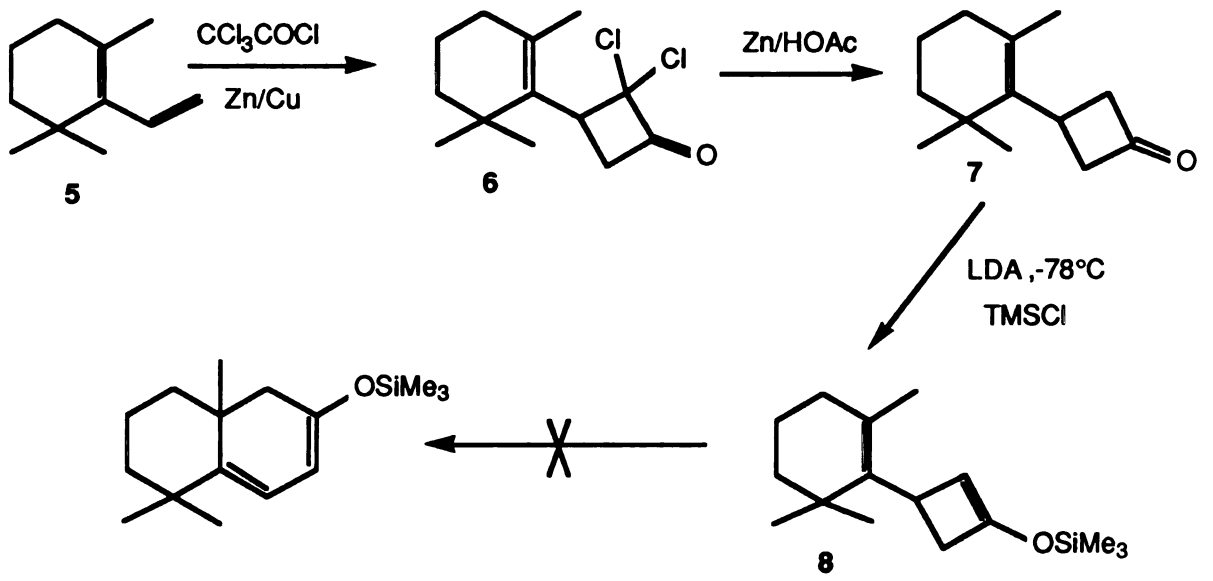
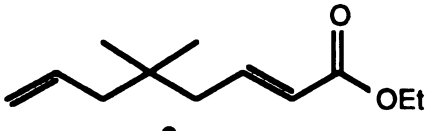


Figure 17.

Realizing that **8** was perhaps an anomalous case, we continued to explore this strategy further with other substrates. We decided to attempt an

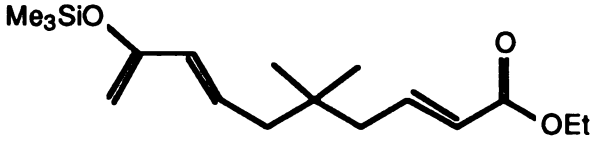
intramolecular Diels Alder reaction and chose the olefin **9** (fig 18) as our substrate.



9

Figure 18.

We anticipated that the $2\pi + 2\pi$ cycloaddition of **9** with dichloroketene would occur preferentially at the terminal double bond. Further elaboration of the cyclobutanone as described earlier would lead ultimately to diene **10** (fig 19). Compound **10** possesses both a reactive diene and a reactive dienophile, and is therefore a suitable substrate for an intramolecular Diels Alder reaction. The chain length connecting the diene and the dienophile in **10** is also appropriate for an intramolecular Diels Alder reaction.



10

Figure 19.

Another attractive feature of this study was the possibility that the cyclobutanone silylenol ether **11**, might undergo a Lewis acid - catalyzed intramolecular Michael reaction[23] (fig 20). The substituted bicyclo [4.2.0]

octanone expected from such a reaction would offer a number of subsequent transformations, having potential synthetic applications.

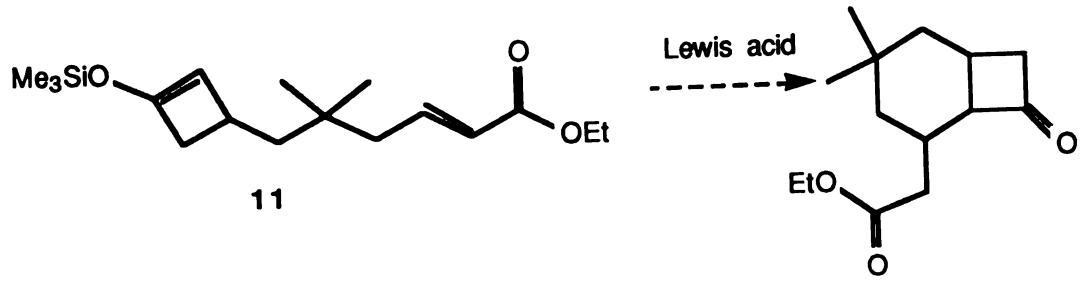


Figure 20.

Olefin **9** was synthesized, starting from 3, 3 - dimethyl glutaric acid, in six steps[24]. 3, 3 -dimethyl glutaric acid **12,** was converted to 3, 3 - dimethyl glutaric anhydride **13**, by refluxing in acetic anhydride. Reduction of anhydride **13**, using sodium borohydride gave the δ - lactone **14**, in near quantitative yield. Lactone **14**, was then reduced with diisobutyl aluminum hydride to the lactol **15** (fig 21).

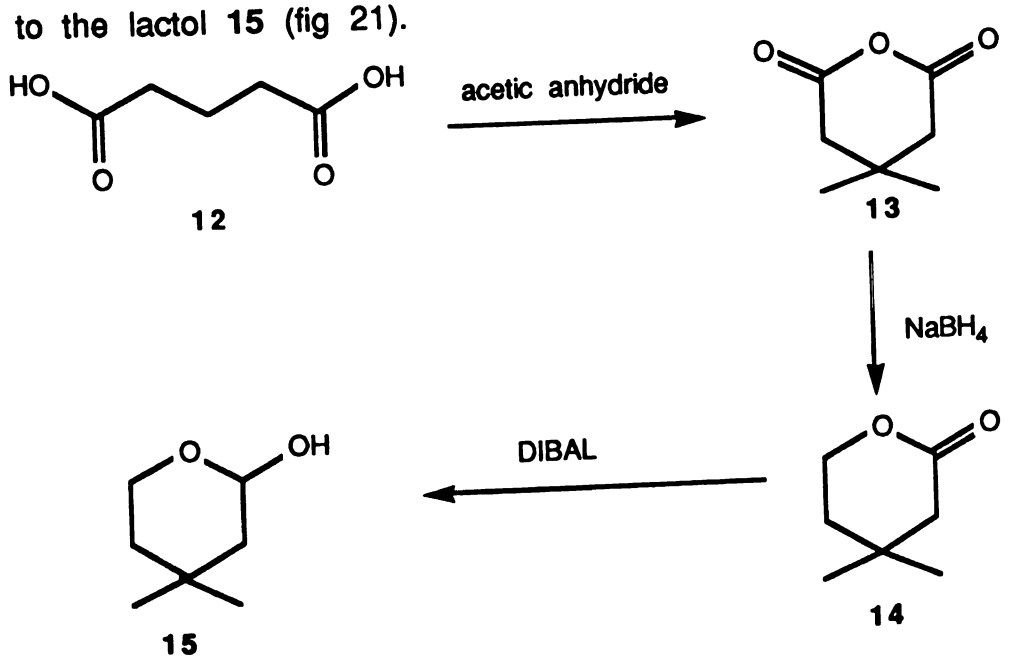


Figure 21.

Wittig reaction of lactol **15**, using carboethoxy methylene triphenyl phosphorane, yielded alcohol **16** as a 6 : 1 mixture of E and Z isomers (^{1}H NMR). This mixture was oxidized to the aldehyde **17** (E to Z ratio 6 : 1) by the action of pyridinium chlorochromate[25]. The isomeric aldehydes were easily separated by flash column chromatography; and the E isomer was converted to the corresponding methylene derivative, **9** by a Wittig reaction using methylene triphenyl phosphorane (fig 22).

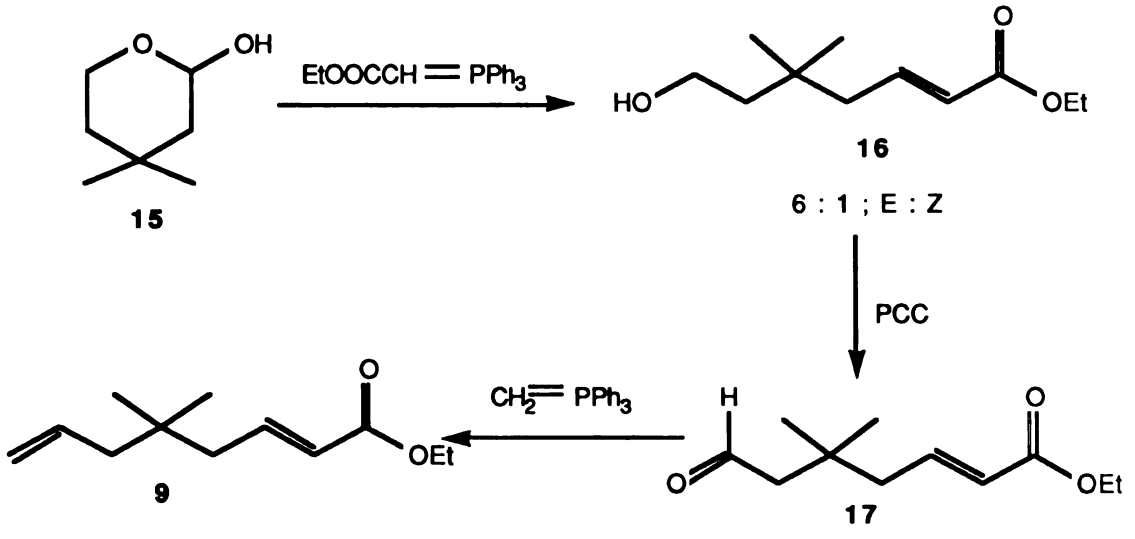


Figure 22.

On reaction with dichloroketene, olefin **9** yielded **18** via a $2\pi + 2\pi$ addition to the terminal double bond. The internal double bond in **9** is not only more sterically hindered but also less nucleophilic compared to the terminal double bond. The cycloadduct **18** on treatment with zinc and acetic acid was reduced to the dehalogenated compound **19** (fig 23).

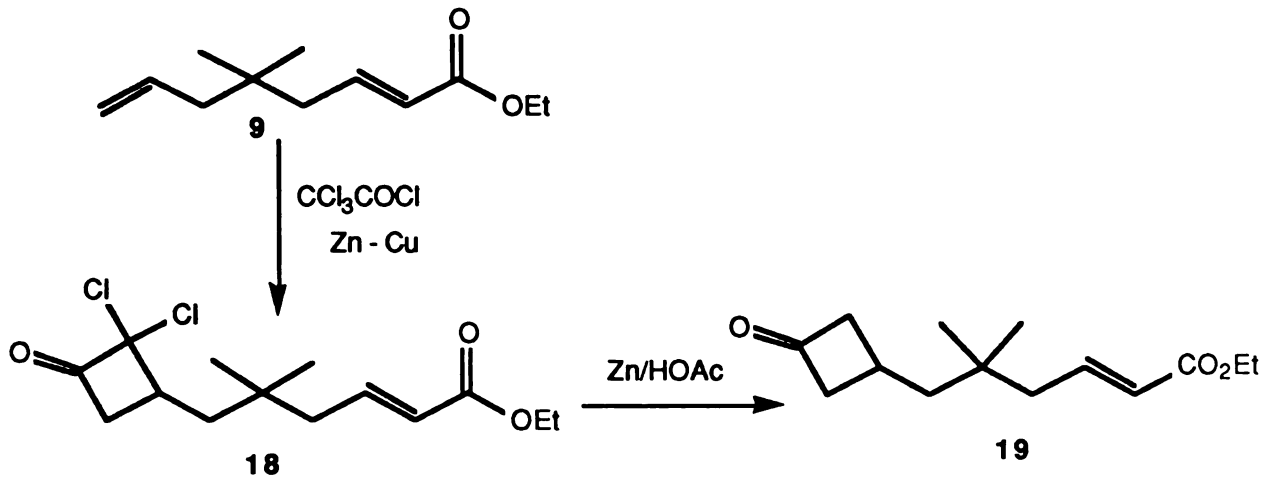


Figure 23.

Our next step was to generate the silyl enolether of **19**. We were aware of the presence of more than one acidic hydrogen in **19**. Since hydrogens α to a ketone are generally more acidic than hydrogens γ to the carbonyl of an α,β - unsaturated ester, we believed we could achieve selective deprotonation of the former. Furthermore, the γ - carbon atom of **19** is neopentyl in nature, and hence abstraction of a γ - hydrogen would be further disfavored. We were concerned however, that **19** might undergo an intramolecular Michael reaction on treatment with a strong base as shown in (fig 24).

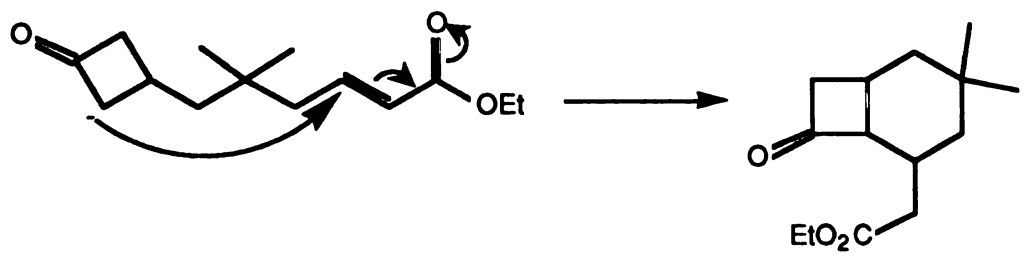
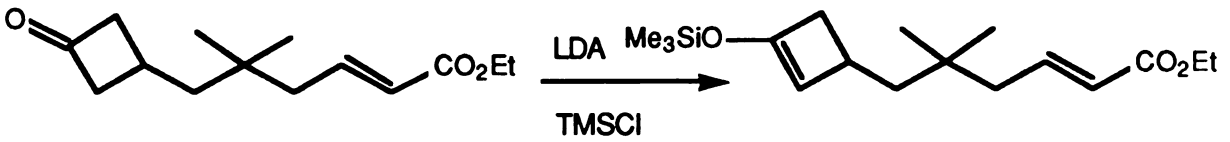


Figure 24.

When **19** was reacted with one equivalent of lithium diisopropylamide at -78°C, an orange red color ensued. The mixture was warmed up slowly to 0°C and quenched by the addition of trimethyl silyl chloride. The red coloration disappeared as soon as trimethyl silyl chloride was added to the reaction mixture. Addition of pentane to the reaction mixture caused precipitation of lithium chloride, which was filtered off under argon. Evaporation of the solvent yielded **11** as a colorless oil (fig 25).



11

Figure 25.

The structure of **11** was evident from its spectral features. A signal at δ 4.58 in the ^{1}H NMR of **11**, and an infrared absorption at 1618 cm^{-1} indicated the presence of the silyl enol ether moiety. The ^{13}C NMR showed no signal for the carbonyl of a cyclobutanone, instead signals at δ 147.95, 107.58 and 0.89 confirmed the presence of cyclobutanone silyl enolether. The NMR data of **11** also indicated that the unsaturated ester was unaffected in this transformation. The ^{1}H NMR of **11** showed signals at δ 6.95 (dt), 5.81 (dt), 4.05 (q) and 1.3 (t) ppm corresponding to the unsaturated ester. ^{13}C NMR showed signals at 166.49, 146.64 and 123.38 corresponding to the α,β-unsaturated ester. Compound **11** was highly sensitive to acidic conditions and was stored and handled under an argon atmosphere.

Thermolysis of **11** at 200°C yielded a single product (by thin layer chromatography). However the spectroscopic characteristic of this compound indicated that it was not the expected intra molecular Diels Alder product. We were unable to determine the actual structure of this new compound. The identity of this compound and also the course of the thermolysis of **11** are still under investigation in our laboratory.

We also explored the reaction of **11** with Lewis acids. We expected that **11** would undergo an intramolecular Michael reaction, as suggested earlier (fig 20). However, treatment of **11** with various Lewis acids resulted in the complete recovery of the corresponding cyclobutanone **19**. Presumably, Lewis acids cleave the silyl group first, causing regeneration of the cyclobutanone. Compound **11** undergoes intermolecular Michael reaction with other Michael acceptors when activated by titanium tetrachloride. Thus when a solution of benzylidine acetophenone (chalcone) in methylene chloride at -78°C, is treated with 0.3 equivalents of titanium tetrachloride and 0.2 equivalents of titanium tetraisopropoxide, followed by addition of a solution (1 equivalent) of the silyl enol ether **11** in methylene chloride, the Michael adduct **22** is isolated along with some cyclobutanone **19**. (fig 26).

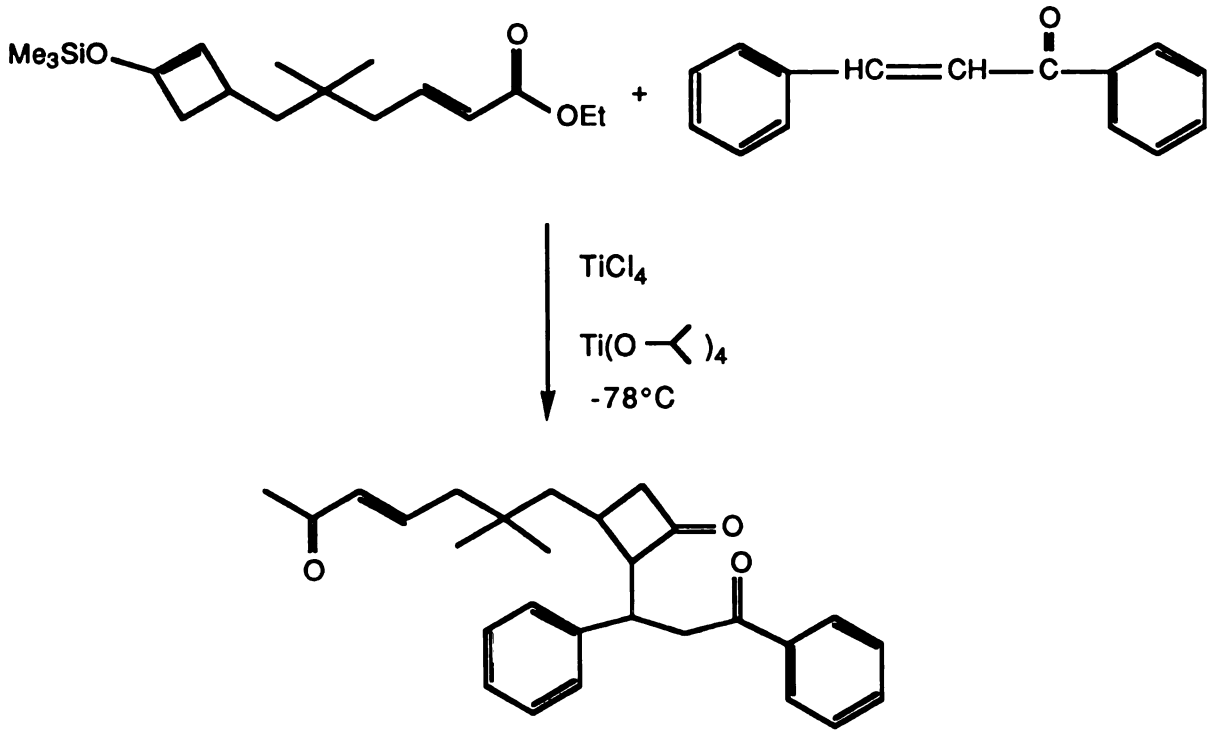


Figure 26

In summary it may be said that we have achieved some degree of success in our strategy of synthesizing reactive dienes from cyclobutanones. We can now synthesize and isolate cyclobutanone silyl enol ethers in good yields from the corresponding ketones. We also have learnt that these silyl enolethers can be converted to reactive dienes by thermolysis. However the thermolysis reaction needs to be studied in much greater detail and its reaction conditions optimized. This should make this approach a useful synthetic method.

EXPERIMENTAL

General.

Except where indicated, all reactions were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Magnetic stirrers were used for small scale reactions; large scale reactions were agitated using paddle stirrers. Organic extracts were always dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. The progress of most reactions were followed by thin layer chromatography and/or gas liquid chromatography. Visualization of the thin layer chromatograms was effected by 30% sulfuric acid with subsequent heating.

Analysis by GLPC was conducted with a Varian 1200 gas chromatograph. Flash chromatography was carried out on flash silica (37-53 mesh) as suggested by Still et al. Melting points were determined on a Hoover-Thomas apparatus (capillary tube) and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were taken in deuterochloroform solutions with either a Varian T-60 or a Bruker 250 MHz spectrometer and are calibrated in most cases in parts per million (δ) downfield from tetramethylsilane as an internal standard. In some cases the chloroform peak (7.24 ppm) was used as a standard for ^{1}H NMR measurements. Carbon-13 NMR spectra were taken in deuterochloroform solutions with Bruker 250 MHz spectrometer and are calibrated in parts per million (δ) using

tetramethylsilane as an internal standard. Mass spectra were obtained with a Finnigan 4000 GC/MS spectrometer.

Preparation of 2,2-dichloro-3-methyl cyclobutanone 2:

To a solution of 1.56 mL (10 m. mol.) of n-octene in 100 mL of ether, was added 920 mg (14 m. mol.) of zinc-copper couple. The mixture was refluxed under an argon atmosphere and a solution of 1.32 mL (12 m. mol.) of trichloroacetyl chloride in 100 mL of ether was added dropwise over a period of three hours. The mixture was refluxed for an additional 16 h, filtered through a celite pad and washed twice with saturated sodium bicarbonate solution. The organic layer was then washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by distillation of the residue (bulb to bulb distillation) gave 1.93 g. (86.9%) of **2** as a pale yellow oil. Compound **2** exhibited the following characteristics.
^{1}H NMR ($CDCl_3$). δ 3.4 to 3.2 (m, 1H), 3.0 to 2.77 (m, 1H), 1.97 to 1.82 (m, 1H) ppm.
^{13}C NMR ($CDCl_3$) δ: 195, 88, 47.5, 45, 32, 31.8, 29.5, 27.5, 22.5, 14 ppm.
IR ($CDCl_3$) : 2910, 2840, 1808 cm^{-1}
Mass spectrum (70eV), m/e (rel. intensity) : 222(1.8); 224(1.1); 182(15.4); 180(24.9); 109(55.3); 69(53.5); 56(78); 43(100).

Preparation of 3-hexyl cyclobutanone 3:

1.1 g. (5 m. mol.) of 1,1-dichloro-3-hexyl cyclobutanone **2**, was dissolved in 10 mL. of glacial acetic acid and 1.32 g. of zinc added to it. The mixture was refluxed at 90°C for five hours. The solution was cooled, filtered through a celite pad and 300 mL of ether added to it. The ether solution was

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washed with 10% aqueous sodium hydroxide solution, to a pH of 10. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded a pale yellow oil which was further purified by Kugel rohr distillation. The distillation yielded 730 mg. of **3**, (96% yield) as a colorless liquid with a strong odour. **3** exhibited the following characteristic properties:

^{1}H NMR ($CDCl_3$) : δ 3.2 to 3.07 (m, 2H); 2.72 to 2.6 (m, 2H); 2.45 to 2.27 (m, 1H) ppm.

IR ($CDCl_3$) : 2929, 1775 cm^{-1}.

Mass spectrum (70eV): m/e (rel. intensity) 154(1.7); 147(6.4); 126(13); 98(100).

Preparation of silyl enol ether 4:

To a solution of 3.1 mL. of diisopropyl amine in 20 mL. of tetrahydrofuran was added, 11 mL of 2.2M n-butyl lithium. The solution was maintained at 0°C and stirred for fifteen minutes under an argon atmosphere. The mixture was then cooled to -78°C, and a solution of 2.7 g. (18 m. mol.) of ketone **3** in 15 mL of tetrahydrofuran was added. The mixture was stirred for 30 minutes at this temparature and then warmed up to 0°C. A solution of 5.6 mL (44 m. mol.) of trimethyl silyl chloride in 3 mL of tetrahydrofuran was added to it. The mixture was stirred for 2 h. and 100 mL of dry pentane added to it. This caused the precipitation of lithium chloride. The mixture was allowed to stand for an additional 0.5 h. to allow precipitation to be complete. The solution was filtered under an argon atmosphere and the clear filtrate evaporated in a rotary evaporator to yield 3.85 g. (98% yield) of **4** as a colorless liquid. Compound **4** exhibited the following properties:

^{1}H NMR ($CDCl_3$) δ 4.66(s, 1H); 2.64(dd, 1H, J=4 & 14 Hz); 2.25(m, 1H); 2.0(d, 1H, J=14 Hz); 0.12(s, 9H) ppm.
^{13}C NMR ($CDCl_3$) δ 149, 107.6, 40, 35.8, 33, 32, 29.8, 28.3, 22.6, 14, 0.88 ppm.
IR ($CDCl_3$) : 2950, 2910, 1615 cm^{-1}
Mass spectrum (70eV) : m/e (rel. intensity) : 226(2.4); 211(2.0); 197(5.2); 141(100); 73(89.2).

Pyrolysis of 4 and its reaction with benzoquinone:

A vertical glass column was filled with glass beads and heated to 240°C using a heating jacket. The temparature was monitored using a thermocouple. A solution of silyl enol ether **4** (500 μL in 25 mL of THF) was added dropwise to the hot column. The system was continually flushed with argon and maintained under an argon atmosphere. The vapors emerging from the hot column were collected in a receiver containing a solution of benzoquinone in THF and cooled by liquid nitrogen. After the thermolysis was complete, the liquid in the receiver was refluxed for one hour and the compound purified by column chromatography. The cycloadduct **21** was obtained in 83% isolated yield. The adduct was the quinone rather than the enone presumably due to oxidation of the initial product by excess benzoquinone. The adduct **21** possessed the following properties.
^{1}H NMR ($CDCl_3$) δ 6.7(s, 2H); 4.9(d, 1H); 3.5(m, 1H); 3(m, 2H; 0.2(s, 9H) ppm.
IR ($CDCl_3$) : 2900, 2840, 1685 cm^{-1}.
Mass spectrum (70eV) : m/e (rel. intensity) : 332 (1.38); 247(60.9); 85(100); 73(39).[

Preparation of 5-Hydroxy-3,3-Dimethylpentanoic acid lactone 14:

To a suspension of sodium borohydride (1.42 g) in 7 mL of tetrahydrofuran at 0°C, was added over a half hour period, a solution of 3.7 g. of 3,3-dimethylglutaric anhydride, in 18 mL of tetrahydrofuran. The resulting solution was allowed to warm up to room temparature and stirred at this temparature for four hours. The solution was then cooled to 0°C and was quenched by careful addition of 12 mL of 1:1 hydrochloric acid solution. The addition of the acid caused considerable effervescence. The solution was then washed with brine and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and the solvent evaporated. The resulting oil was purified by column chromatography on 15 g ogf silica gel. Elution with 70% ether in pentane gave 2.95 g. (88%) of 5-hydroxy-3,3-dimethylpentanoic acid lactone **14**. Compound **14** exhibited the following characteristics :
^{1}H NMR ($CDCl_3$) δ 4.35(t, 2H, J=6), 2.30(s, 2H), 1.70(t, 2H, J=6), 1.10(s, 6H).
IR ($CDCl_3$) : 1740 cm^{-1}

Preparation of 2-hydroxy-4,4-dimethyltetrahydropyran 15:

To a stirred solution of 5-hydroxy-3,3-dimethylpentanoic acid lactone (2.6 g.) in 60 mL. of ether at 20°C was added dropwise, over one hour., a solution of diisobutyl aluminum hydride (22 mL of 1M solution in hexane). The resulting solution was stirred for an additional hour and then quenched by the addition of 17 mL of methanol. The solution was then allowed to warm up to room temparature and stirred overnight. The resulting suspension was diluted with 30 mL of 30% sodium potassium tartarate (3 x 30 mL). The combined aqueous layers were then extracted with ether and the combined

organic layers dried over anhydrous sodium sulfate. Evaporation of the solvent and purification of the resulting liquid by column chromatography (silica-gel; 70% ether in pentane) yielded 2.426 g. (92%) of **15**. Compond **15** exhibited the following properties:

^{1}H NMR ($CDCl_3$) δ 4.96(m, 1H0, 4.8(d, 1H, J=4), 4.18 to 3.37(m, 2H); 1.95 to 1.10(m, 4H), 1.05(s, 6H).

IR ($CDCl_3$) : 3575; 3300 (broad) cm^{-1}.

Preparation of Etyhl 7-Hydroxy-5,5-dimethylhept-2-enoate 16:

A stirred solution of 9.318 g (26.588 m.mol) of Carboethoxy methylene triphenylphosphorane and 22.3 g (17.8 m.mol) of the pyran in 70 mL of acetonitrile was refluxed for 34.5 h. Most of the solvent was removed in vacuo, 100 mL of ether added, and the mixture stirred for 2 h. The white solid formed was filtered off and washed thrice with cold ether. The solvent was again removed in vacuo and 50 mL of 70% ether in pentane was added. After half hour of stirring, the solid formed was once again filtered off and the filter cake washed with 70% ether in pentane. The solvents were removed in vacuo and the resulting material was purified by column chromatography. Elution with 70% ether in pentane gave 3.35 g. (95% yield) of cis and trans (1:6 respectively) unsaturated hydroxy ester **16**. The E-isomer exhibited the following properties.

^{1}H NMR ($CDCl_3$) δ 6.87(overlapping dt, 1H, J=16 & 8 Hz), 5.72(dt, 1H, J=16&1 Hz), 4.07(q, 2H, J=7 Hz), 3.56(t, 2H, J=8 Hz), 2.90(br s, 1H), 2.0(dd, 2H, J=8 &1 Hz), 1.42(t, 2H, J=8 Hz), 1.17(t, 3H, J=7 Hz), 0.98(br. s, 6H) ppm.

Preparation of Ethyl (Z) and (E) - 7 - Oxo - 5,5 - dimethylhept - 2 - enoate 17:

To a stirred suspension of 5.2 g. of pyridinium chlorochromate in 24.2 mL of methylene chloride and 5.2 g. of celite at room temparature was added 3 g. of the alcohol **16,** in 6 mL of methylene chloride. The solution turned dark brown and almost black. After stirring for 3.5 h. the suspension was diluted with ether andfiltered through flourosil. The filter cake was washed several times with ether and the solvent evaporated to yield a colorless oil. Purification of this oil by flash chromatography (15% ethyl acetate in hexane) gave 2.2 g. (74%0 of the (E) isomer and 0.37 g. (12.5%) of the (Z) isomer of **17.** The E - isomer of **17** exhibited the following characteristics.:

^{1}H NMR ($CDCl_3$) δ 9.89(t, 1H, J=3 Hz), 6.90(overlapping dt, 1H, J=16 & 8 Hz), 5.78(dt, 1H, J=16&1 Hz), 4.05(q, 2H, J=7 Hz), 2.27(d, 2H, J=3 Hz), 2.30(dd, 2H, J=8 & 1 Hz), 1.17(t, 3H, J=7 Hz), 1.15(s, 6H) ppm.

^{13}C NMR δ 203, 166, 145, 125, 60.1, 55, 46, 36, 28, 14 ppm.

IR ($CDCl_3$) : 2788, 1784, 1723 cm^{-1}.

Mass spectrum (70eV) : m/e, (rel. intensity) : 198(1.35), 183(0.52), 168(3.97), 153(17.24), 139(8.14), 114(55.82), 86(66.38), 81(36.58), 68(35.61), 57(52.42), 41(100).

Preparation of Ethyl - (E) - 5,5 - dimethyl oct - 2,7 - dien - oate 9:

Asolution of potassium tert-butoxide (294 mg. 2.6 m. mol) and methyl triphenyl phosphonium bromide (937 mg. 2.6 m. mol), in 10 mL of toluene was stirred for 20 minutes at -20°C. To the yellow ylide formed, was added a solution of 400 mg. (2 m. mol) of the aldehyde **17** in 5 mL. of toluene. The solution was stirred at -20°C for an additional 1.5 h., allowed to warm

up to room temparature and stirred for further 3 h. The mixture was then poured into cold water, and extracted several times with ether. The ether extracts were dried over anhydrous sodium sulfate and the solvent evaporated to yield an oil. Purification by chromatography using 20% ether in hexane as eluent, gave 331 mg. (83.6%) of the compound **9**. Compound **9** exhibited the following properties :.

^{1}H NMR ($CDCl_3$) δ 7.02(overlapping dt, 1H, J=16 & 8 Hz), 5.75(dt & m, 2H), 5.05(m, 2H0, 4.07(q, 2H, J=7 Hz), 1.17(t, 3H, J=7 Hz), 2.1(dd, 2H, J=1 & 8 Hz), 1.96(d, 2H, J=7 Hz), 1.17(t, 3H, J=7 Hz), 0.9(s, 6H) ppm.

IR ($CDCl_3$) : 1710, 1650 cm^{-1}.

Mass spectrum (70eV); m/e, (rel. intensity) : 196(0.52), 181(1.0), 167(20.99), 149(58.32), 114(17.79), 83(21.66), 71(28.77), 55(77.99), 41 (100).

Addition of dichloroketene to olefin 9:

A 200 mL three necked flask equipped with a condenser, addition funnel, magnetic stirrer and nitrogen inlet was flame dried while purged with nitrogen. When cool, it was charged with 210 mg. of olefin **9**, 100 mg. of zinc-copper couple and 50 mL of dry ether. The mixture was heated to reflux and to this refluxing mixture was added dropwise over a period of 2 hours, a solution of 0.2 mL trichloro acetyl chloride in 30 mL of ether. The mixture was refluxed for 16 h. It was cooled, filtered through a celite pad, extracted with ether and the ether extracts were washed with saturated aqueous sodium bicarbonate solution. The combined organic layers were dried over anhydrous sodium sulfate and the solvent evaporated to yield a pale yellow oil. Purification by chromatography (20% ethyl acetate in hexane) gave

215 mg. (66% yield) of compound **18. 18** exhibited the following characteristics:

^{1}H NMR ($CDCl_3$) δ 6.95(overlapping dt, 1H, J=16 & 8 Hz), 5.85(dt, 1H, J=16 &1 Hz), 4.18(q, 2H, J=7 Hz), 3.2 to 2.8(m, 2H), 2.18(dd, 2H, J=8 & 1 Hz), 1.9(dd, 2H, J=4 & 14 Hz), 1.26(t, 3H, J=7 Hz), 0.98(s, 3H), 0.95(s, 3H) ppm.

^{13}C NMR ($CDCl_3$) δ 192.41, 166, 144.82, 124.1, 89.86, 59.98, 49.28, 44.91, 42.87, 42.29, 33.52, 26.88, 26.8, 13.91 ppm.

IR ($CDCl_3$) : 1708, 1799 cm^{-1}.

Preparation of compound 19:

A mixture of 153 mg of **18**, 2 mL of glacial acetic acid and 352 mg of zinc was stirred under nitrogen for 5 h. The mixture was cooled, filtered through celite and extracted with ether. The ether extracts were washed with 10% sodium hydroxide solution to a pH of 10. The ether layer was washed with brine, dried over anhydrous sodium sulfate and the solvent evaporated to yield a pale yellow oil. Purification by chromatography (20% ethyl acetate in hexane) gave 106 mg. (88.5% yield) of **19. 19** exhibited the following characteristics:

^{1}H NMR ($CDCl_3$) : δ 6.92(overlapping dt, 1H, J=16 & 8 Hz), 5.78(dt, 1H, J=16 & 1 Hz), 4.02(q, 2H, J=7 Hz), 3.25 to 2.6(m, 4H0, 2.2(m, 1H0, 2.08(dd, 2H, J=1 & 8 Hz), 1.58(d, 2H, J=7 Hz), 0.98(s, 6H) ppm.

^{13}C NMR ($CDCl_3$) : δ 208.07, 166.34, 145.69, 123.79, 60.23, 54.21, 48.75, 45.32, 34.67, 29.64, 26.99, 20.25, 14.21 ppm.

IR ($CDCl_3$) : 1775, 1710 cm^{-1}.

Mass spectrum (70 eV); m/e, (rel. intensity) : 238(1.0), 155(14.17), 114(34.63), 83(40.74), 69(42.5), 55(100), 41(81.94).

Preparation of silyl enol ether 11:

0.92 m. mol of lithium diisopropylamide was generated by the reaction of 0.13 mL of diisopropyl amine in 7 mL of tetrahydrofuran, with 0.42 mL of n-butyl lithium (2.2M in hexane) at 0°C. The solution was cooled to -78°C and 200 mg of **19** (0.84 m.mol) in 5 mL of tetrahydrofuran was added to it. The solution instantly acqquired an orange -red color. It was stirred at -78°C for another 40 minutes. The mixture was warmed up to 0°C and 0.43 mL (3.36 m.mol) of chlorotrimethyl silane was added to it. The red color disappeared on the addition of trimethyl chloro silane. The mixture was allowed to warm up to room temparature and stirred for four hours. It was then transferred using a cannula to a 250 mL. round bottomed flask containing 150 mL of dry pentane. The mixture was allowed to stand under nitrogen for fifteen minutes. The white precipitate formed was filtered under nitrogen. The clear filtrate was evaporated in vacuo, to remove the solvent. Nitrogen was introduced into the system when the vacuum was broken. Extreme precautions were taken at all stages of the reaction, to not expose the compound to air and moisture. The yield of silyl enol ether **11,** was nearly quantitative. Compound **11** exhibited the following characteristic spectral features :

^{1}H NMR ($CDCl_3$) : δ 6.95(overlapping dt, 1H, J=16 &8 Hz), 5.81(dt, 1H, J=16 & 1 Hz), 4.58(s, 1H0, 4.05(q, 2H, J=7 Hz), 2.65(dd, 1H, J=4 & 13 Hz), 2.3(q, 1H, J=4 Hz), 2.05(m, 3H), 1.4(dd, 2H, J= Hz), 1.3(t, 3H, J=7 Hz), 0.98(s, 3H0, 0.97(s, 3H), 0.3(s, 9H) ppm

^{13}C NMR ($CDCl_3$) : δ 166.49, 147.95, 146.64, 123.38, 107.58, 60.01, 47.39, 45.35, 41.65, 34.60, 28.96, 27.12, 14.17, 0.89 ppm.

IR ($CDCl_3$) : 1618, 1703 cm^{-1}.

Mass spectrum (70eV) : m/e, (rel. intensity) : 310(1.94), 295(3.36), 265(2.36), 237(2.94), 73(100).

IR of 2

16.0

12.0

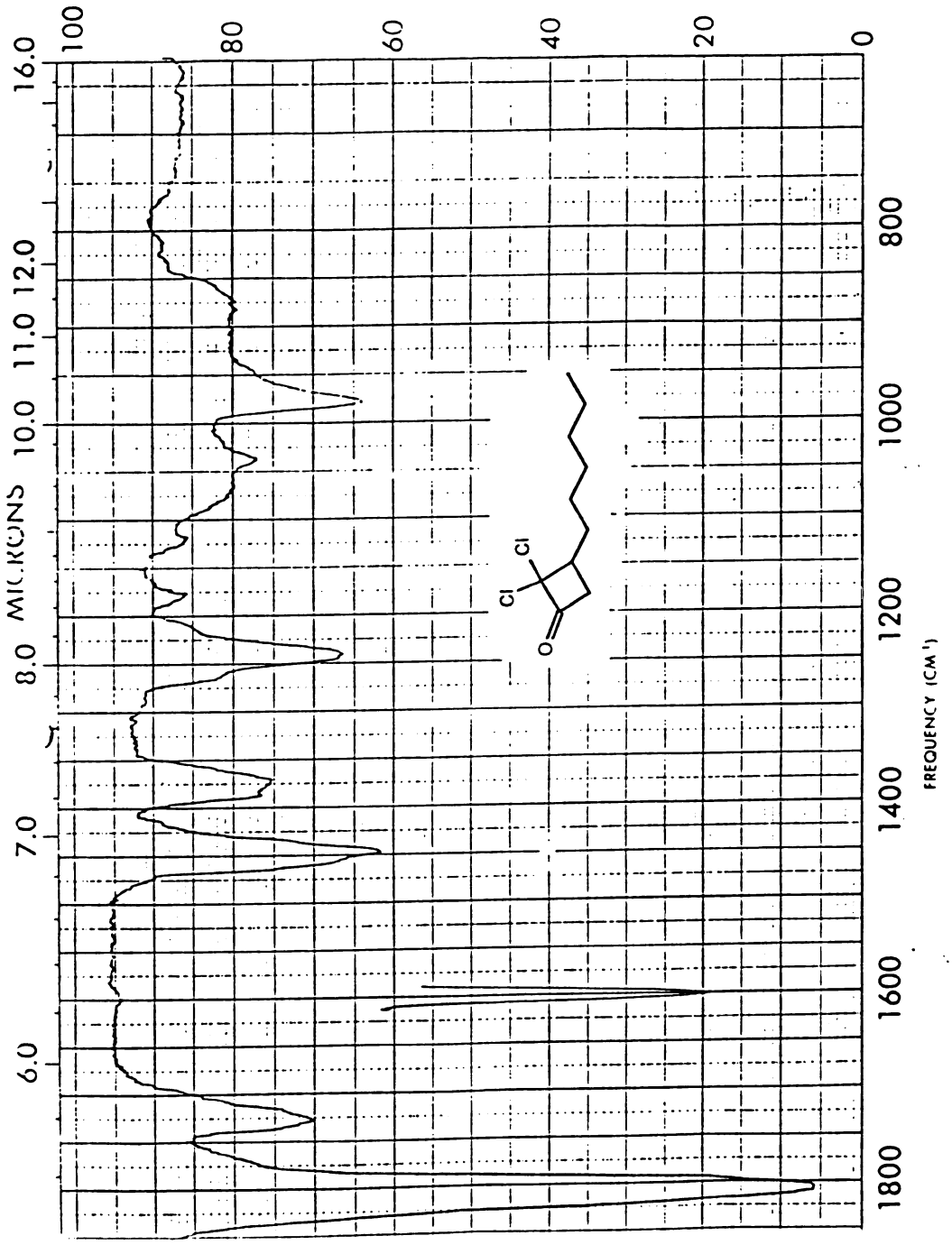
11.0

10.0

8.0

4.0

2.0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11.0
10.0
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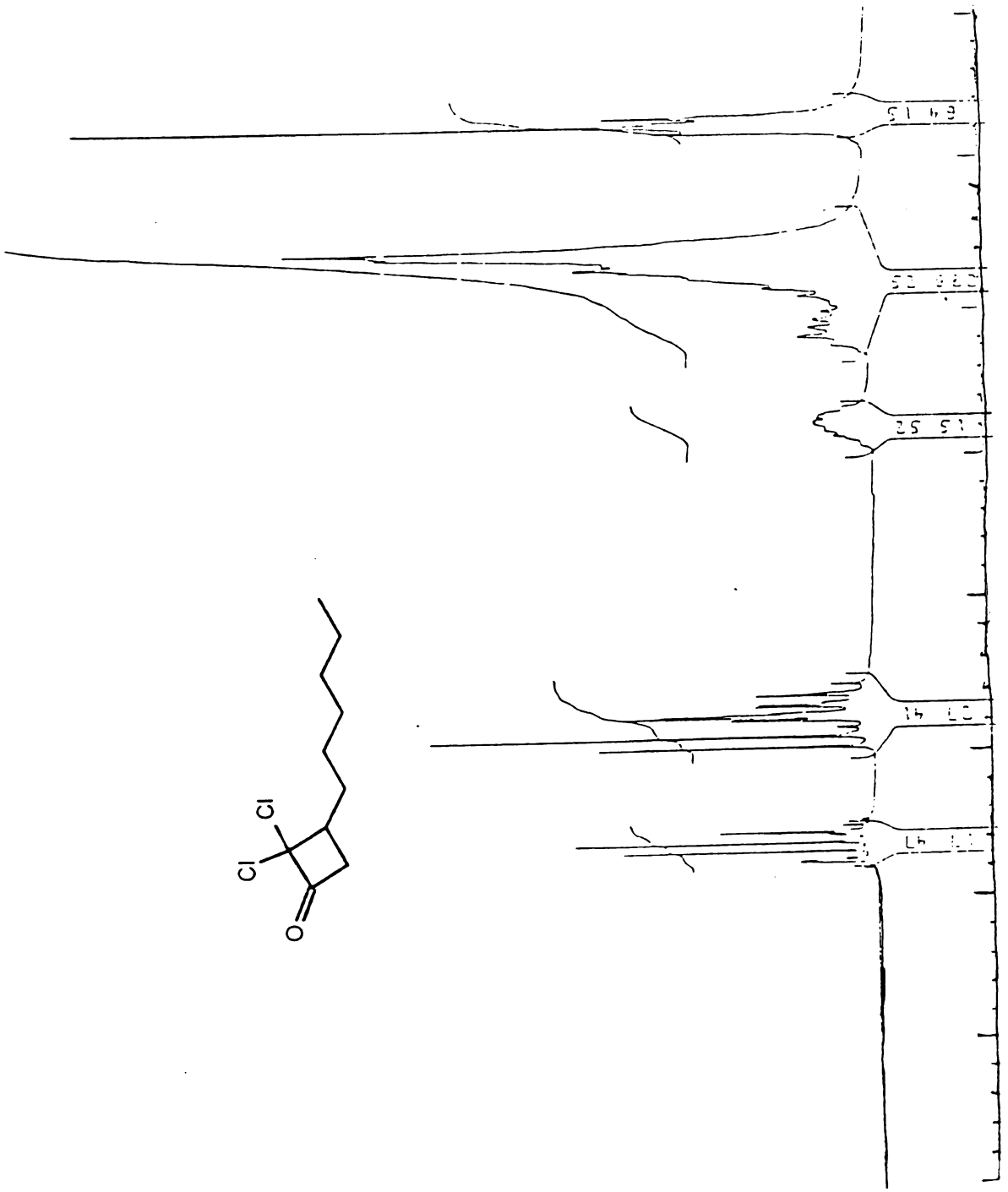
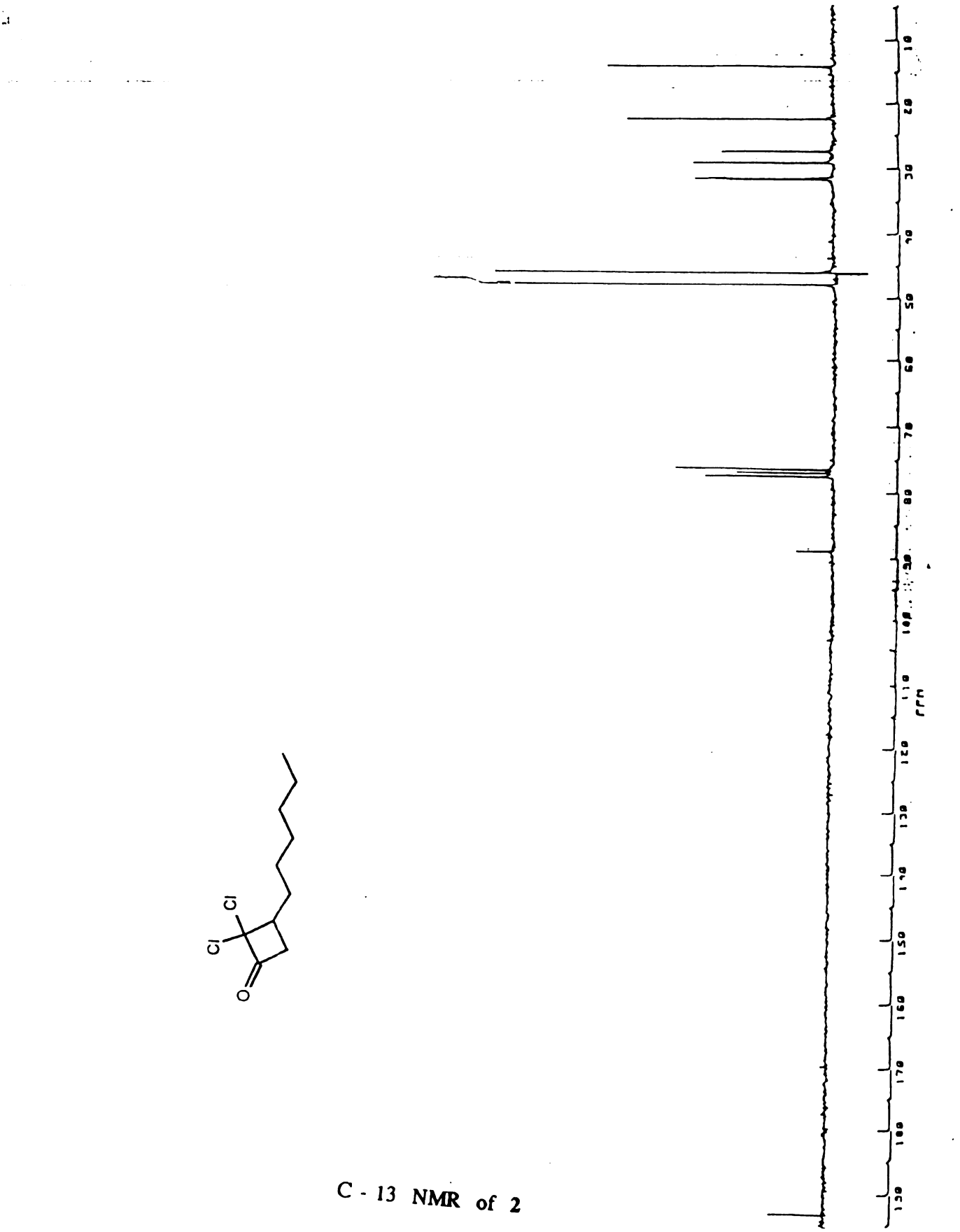
1000
1200
1400
1600
1800
FREQUENCY (CM⁻¹)
Cl
Cl
O

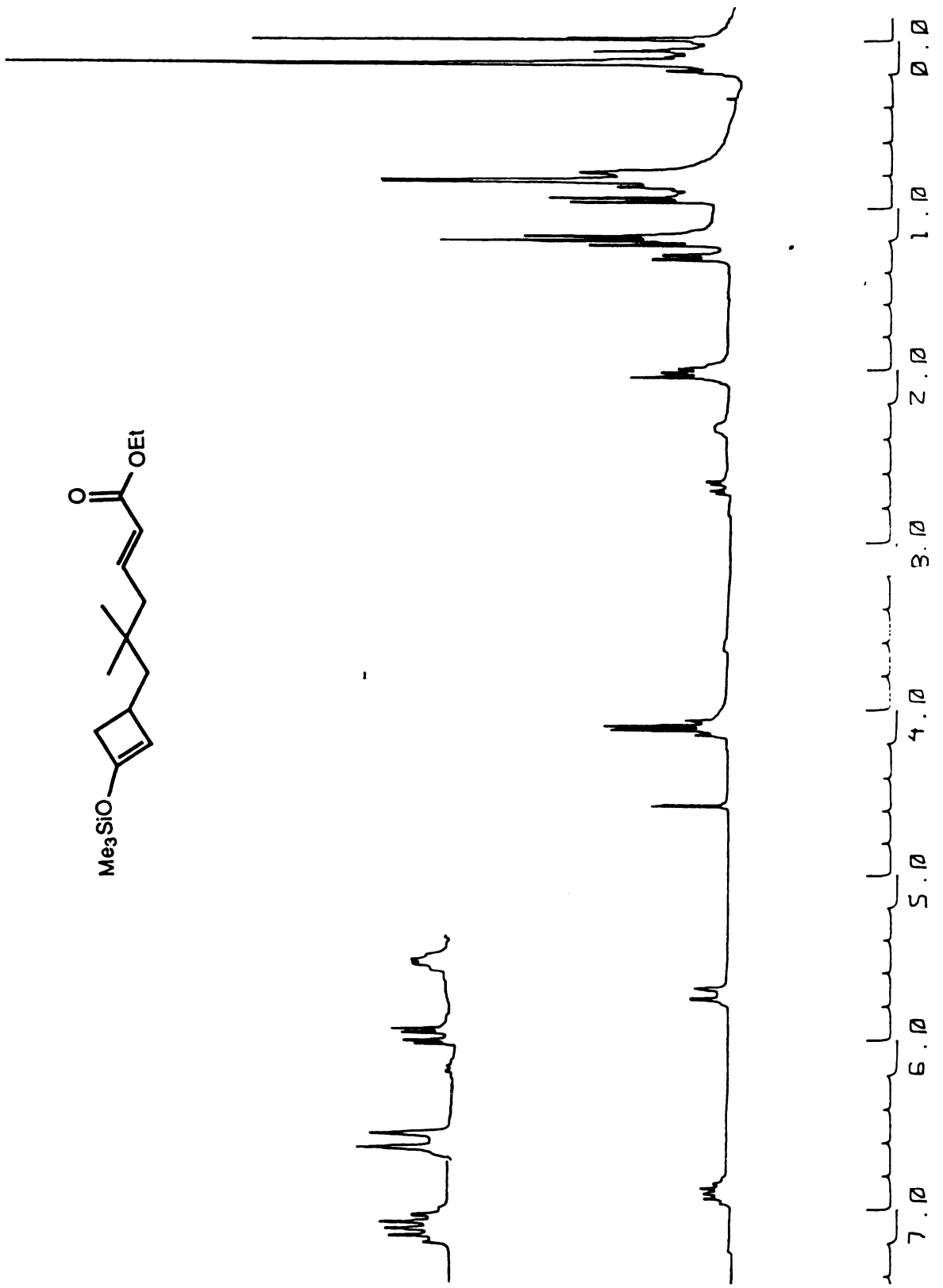
IR of 2



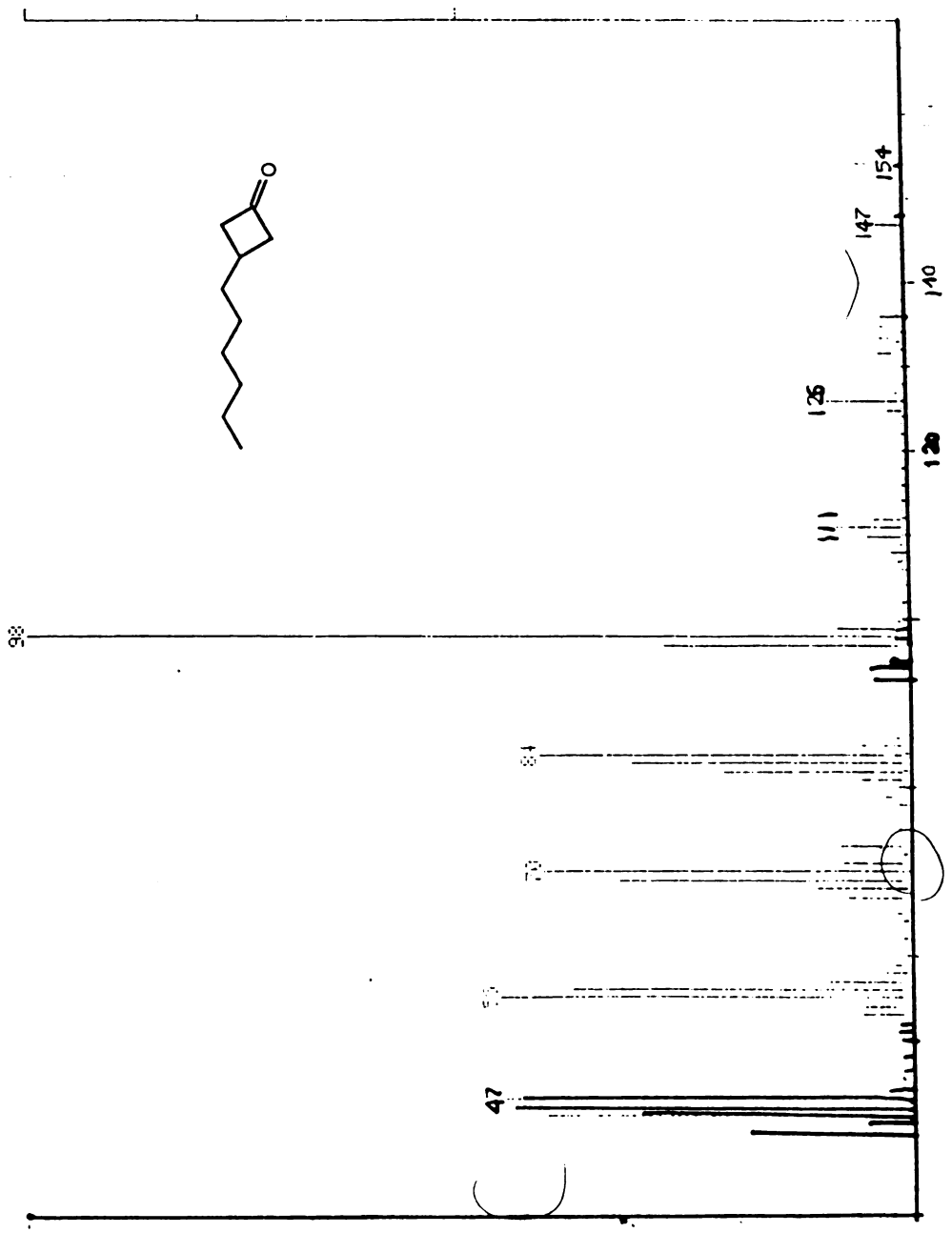
Proton NMR of 2



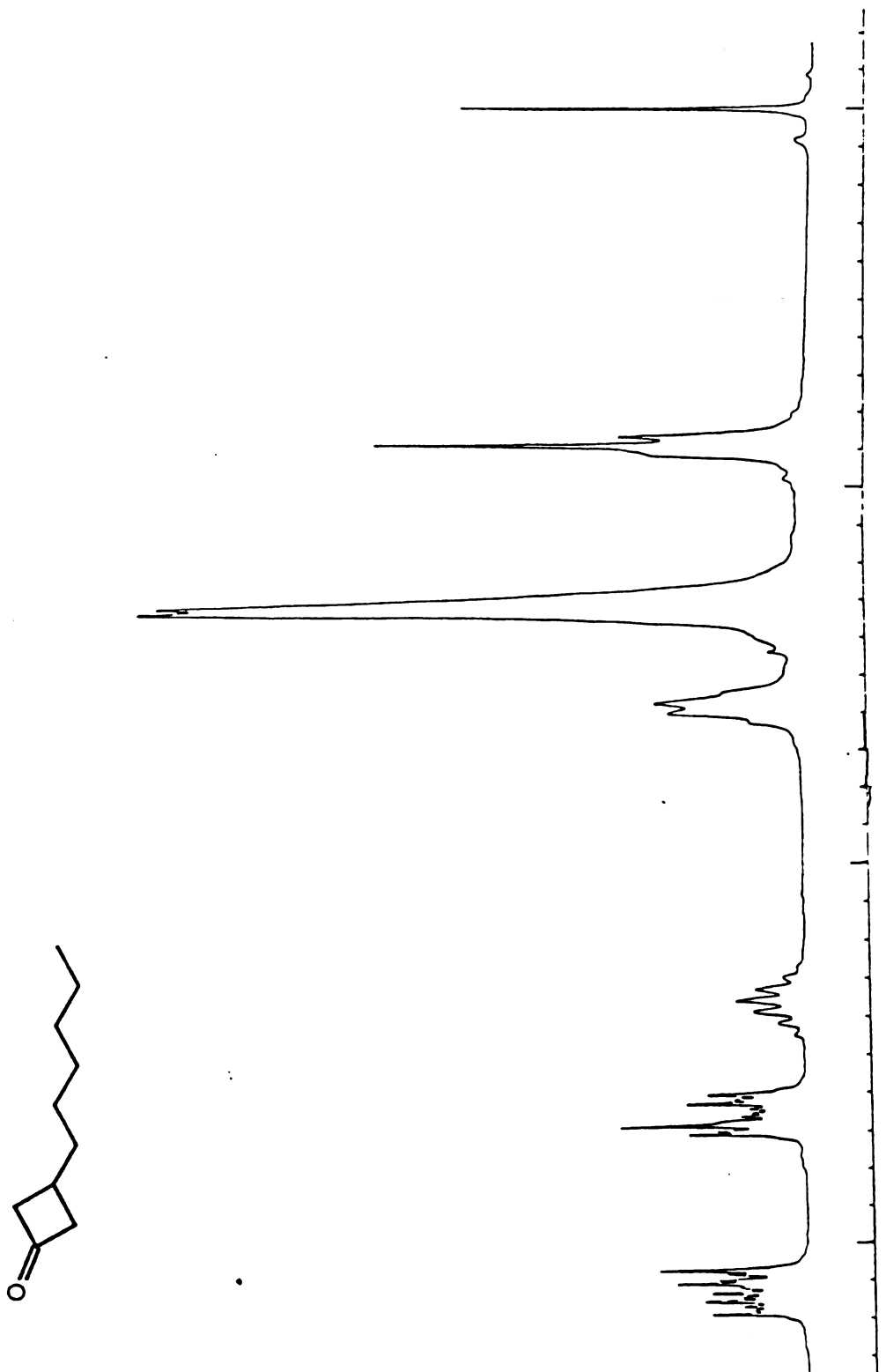
C - 13 NMR of 2



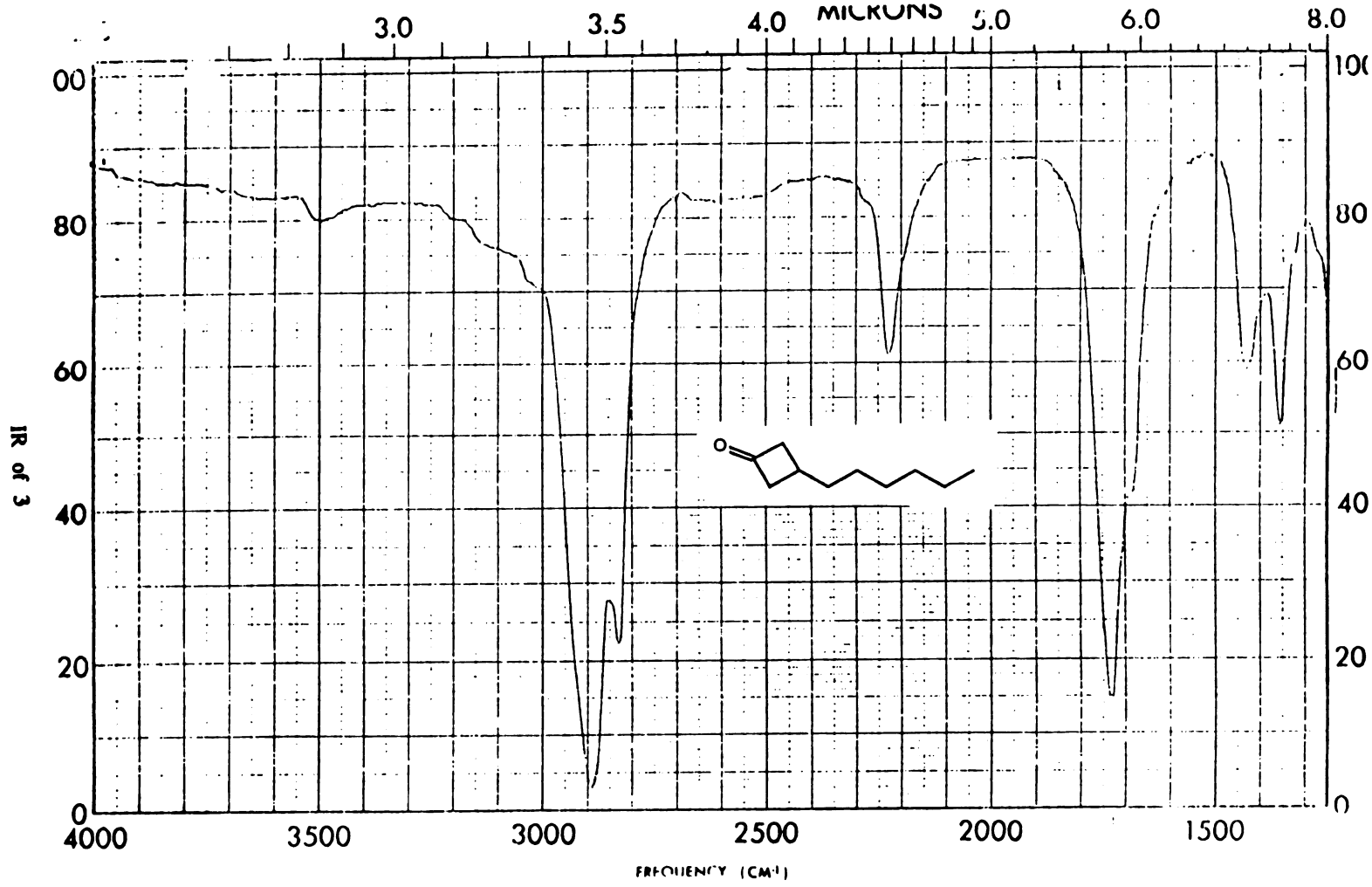
Proton NMR of 11



Mass spectum of



Proton NMR of 3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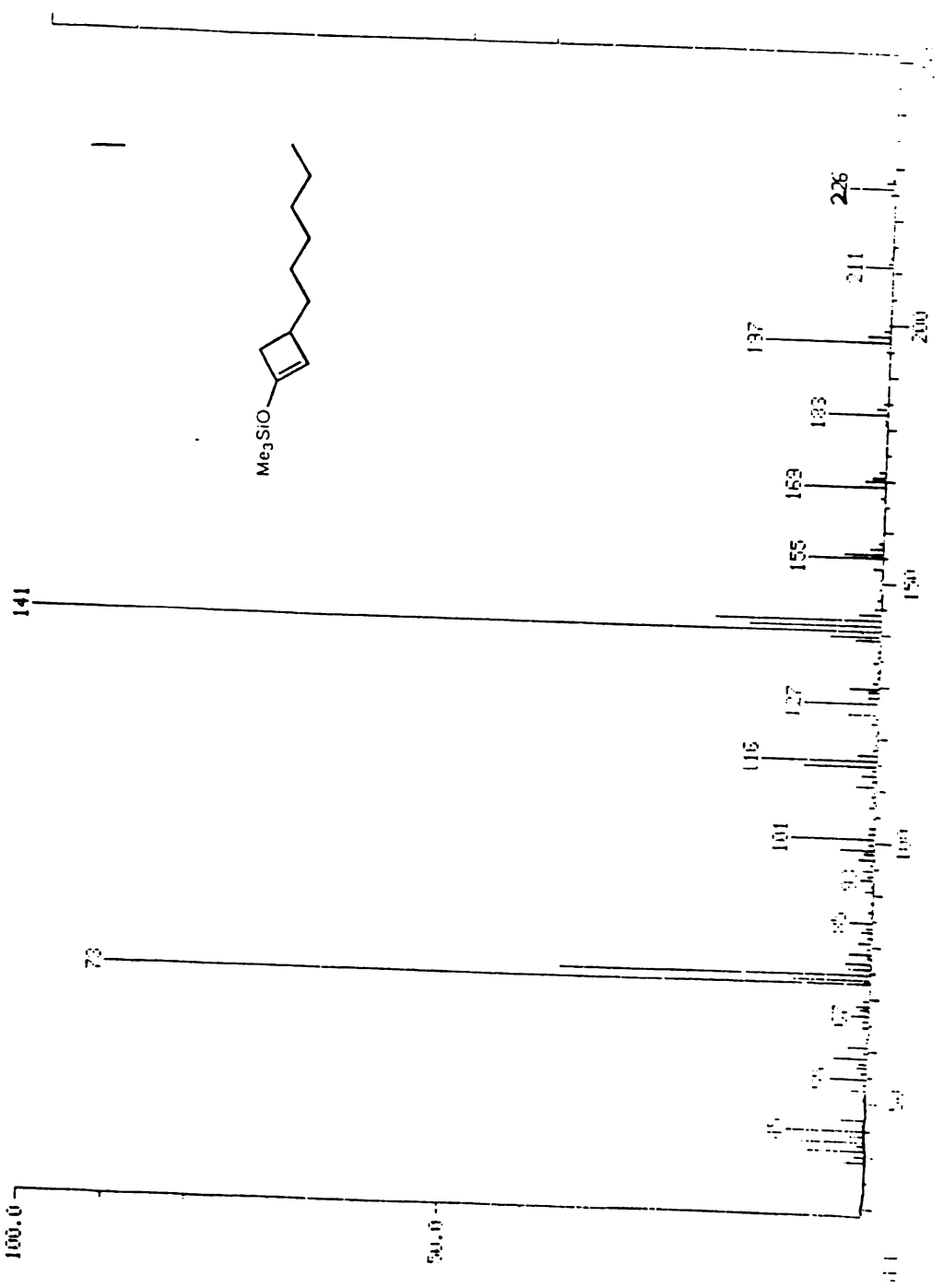
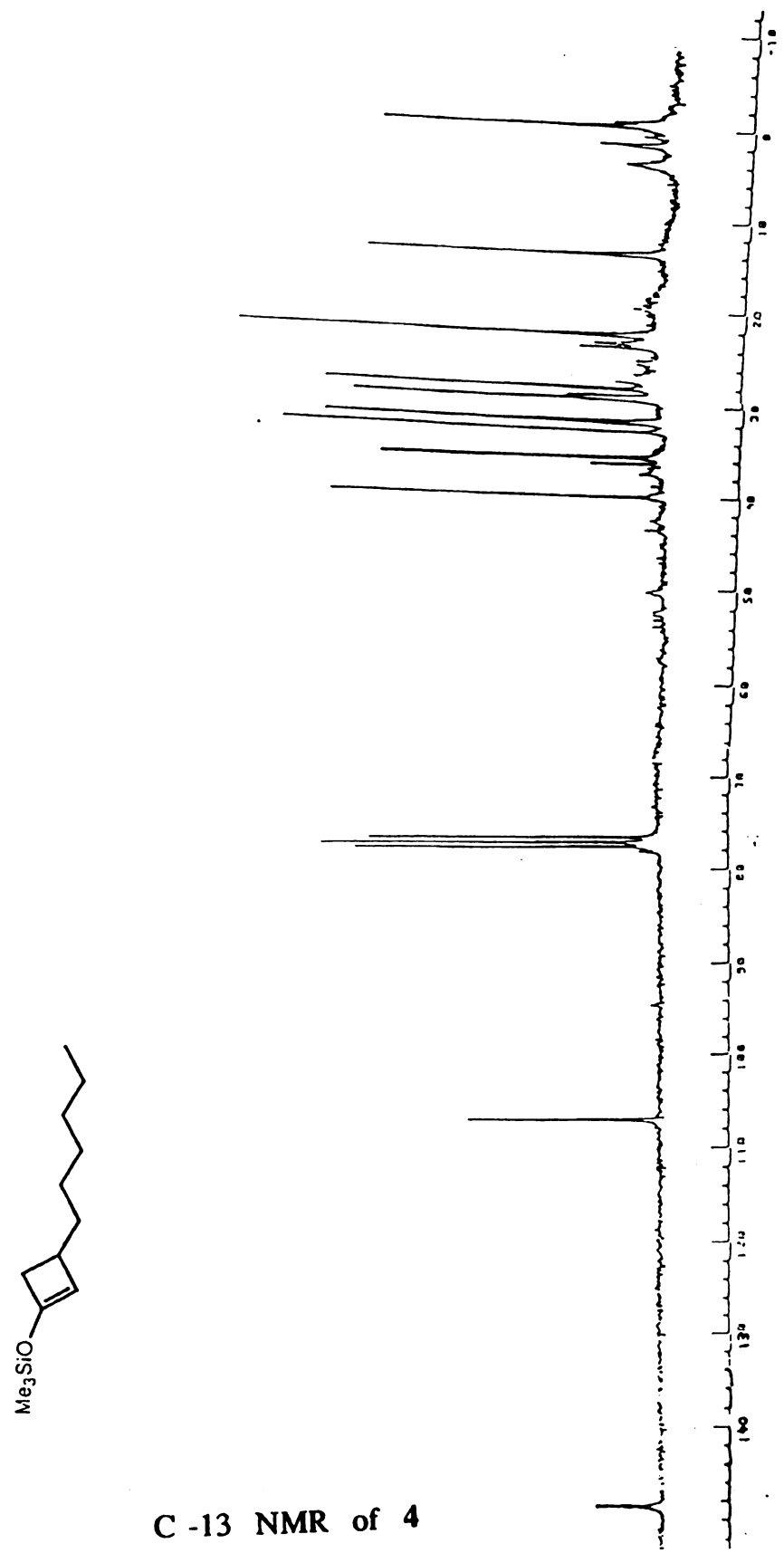
FREQUENCY (CM-1)
IR of 3
O

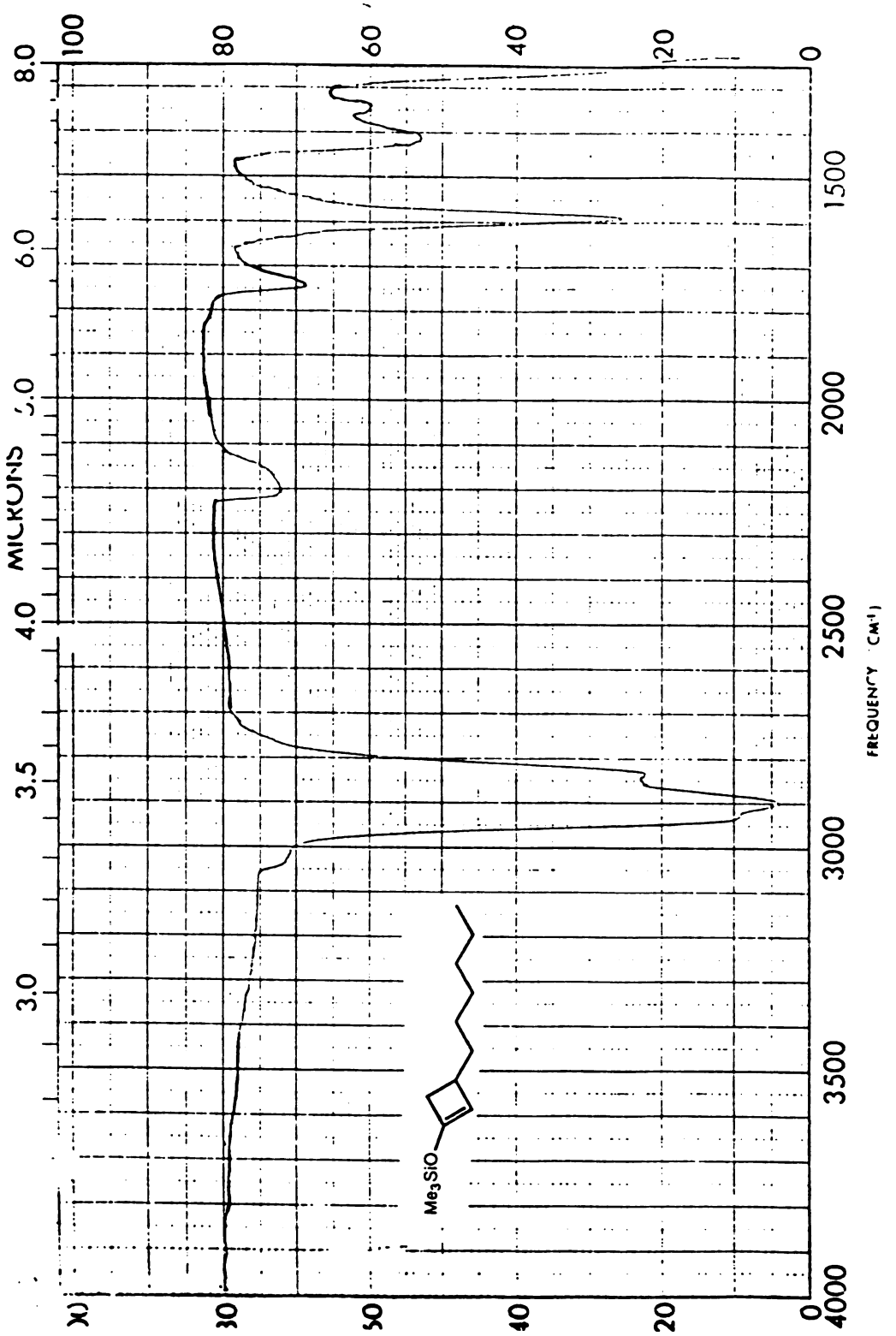
IR of 3



Mass spectrum of 3



C -13 NMR of 4



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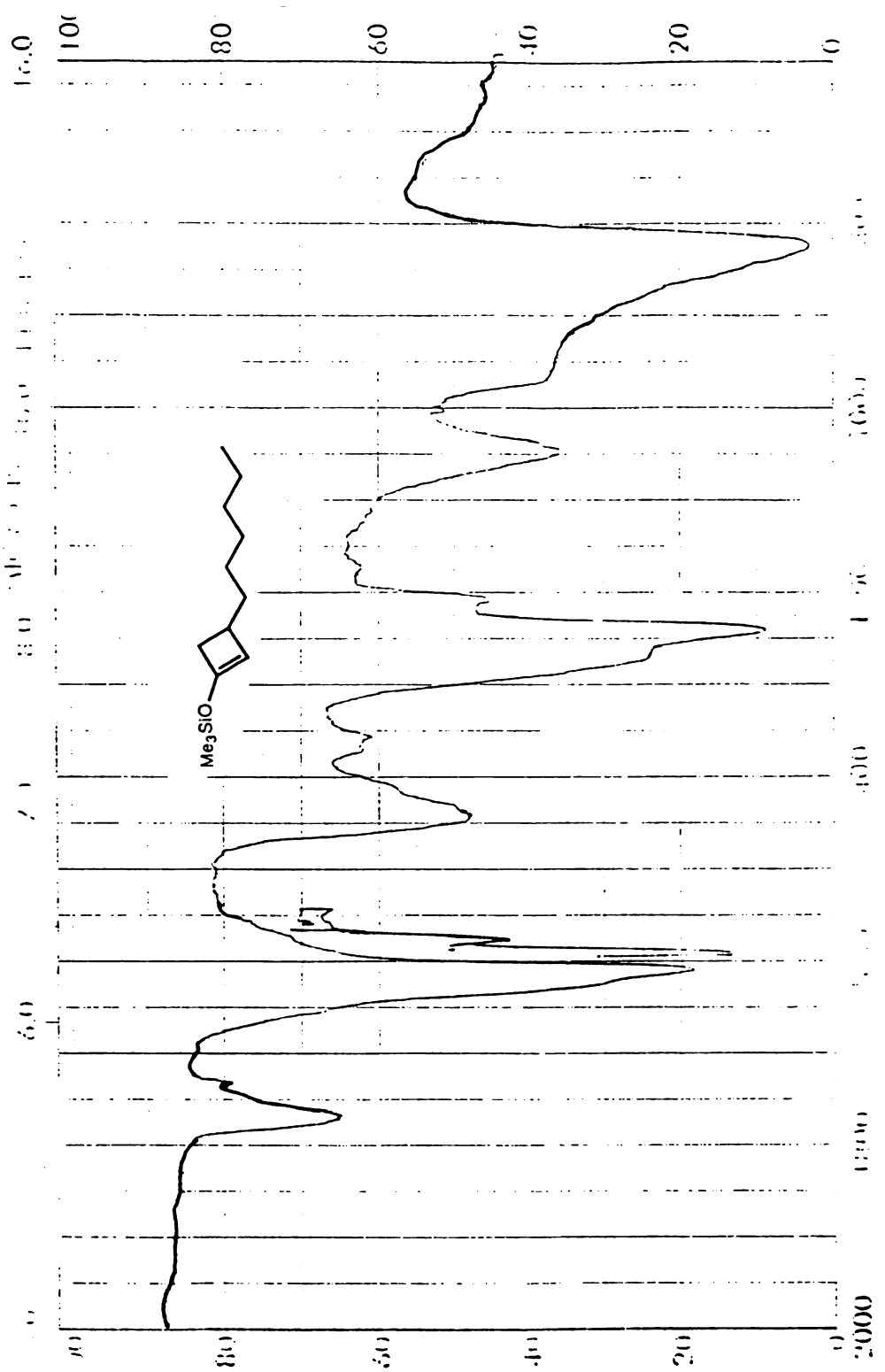

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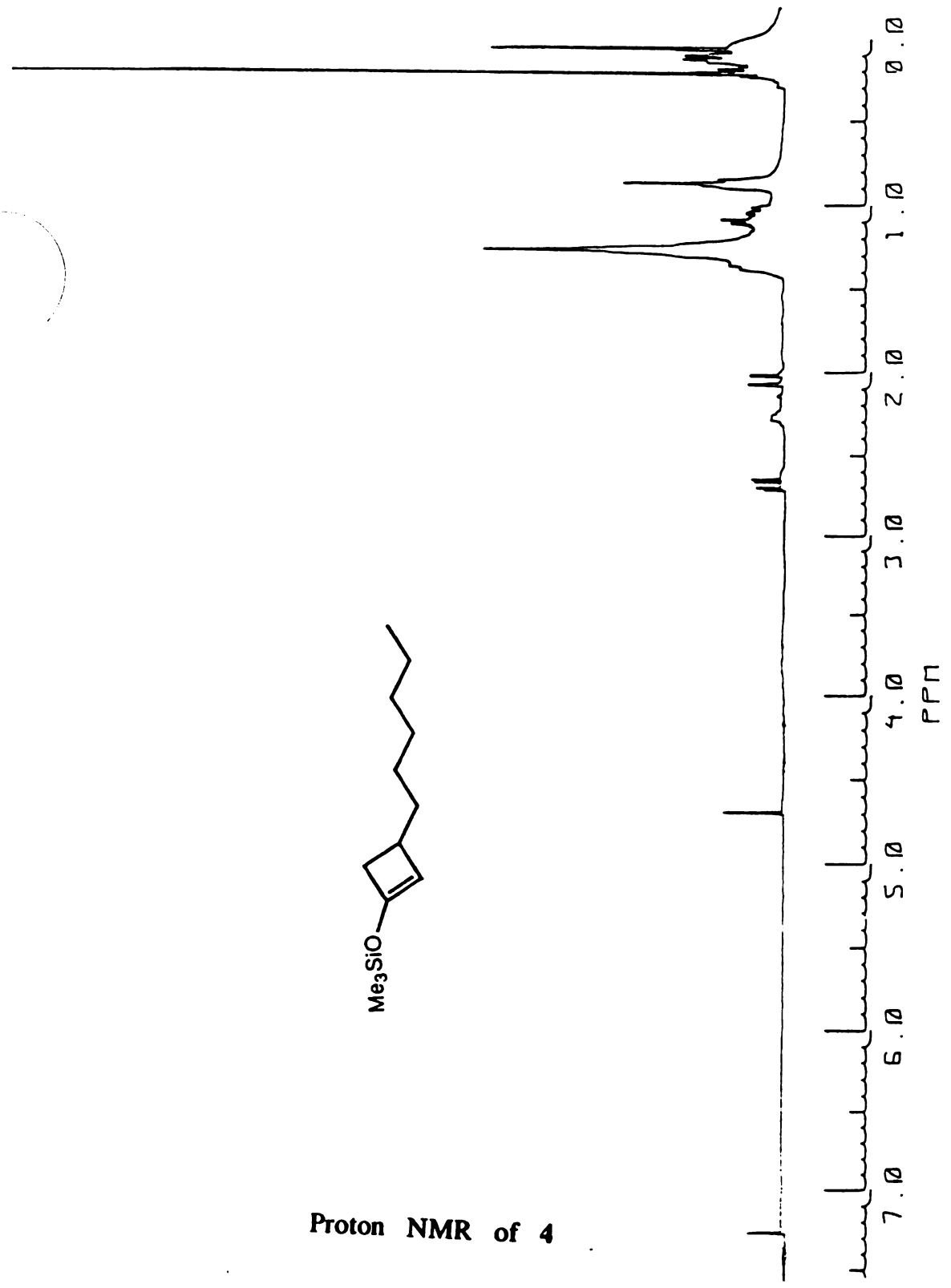
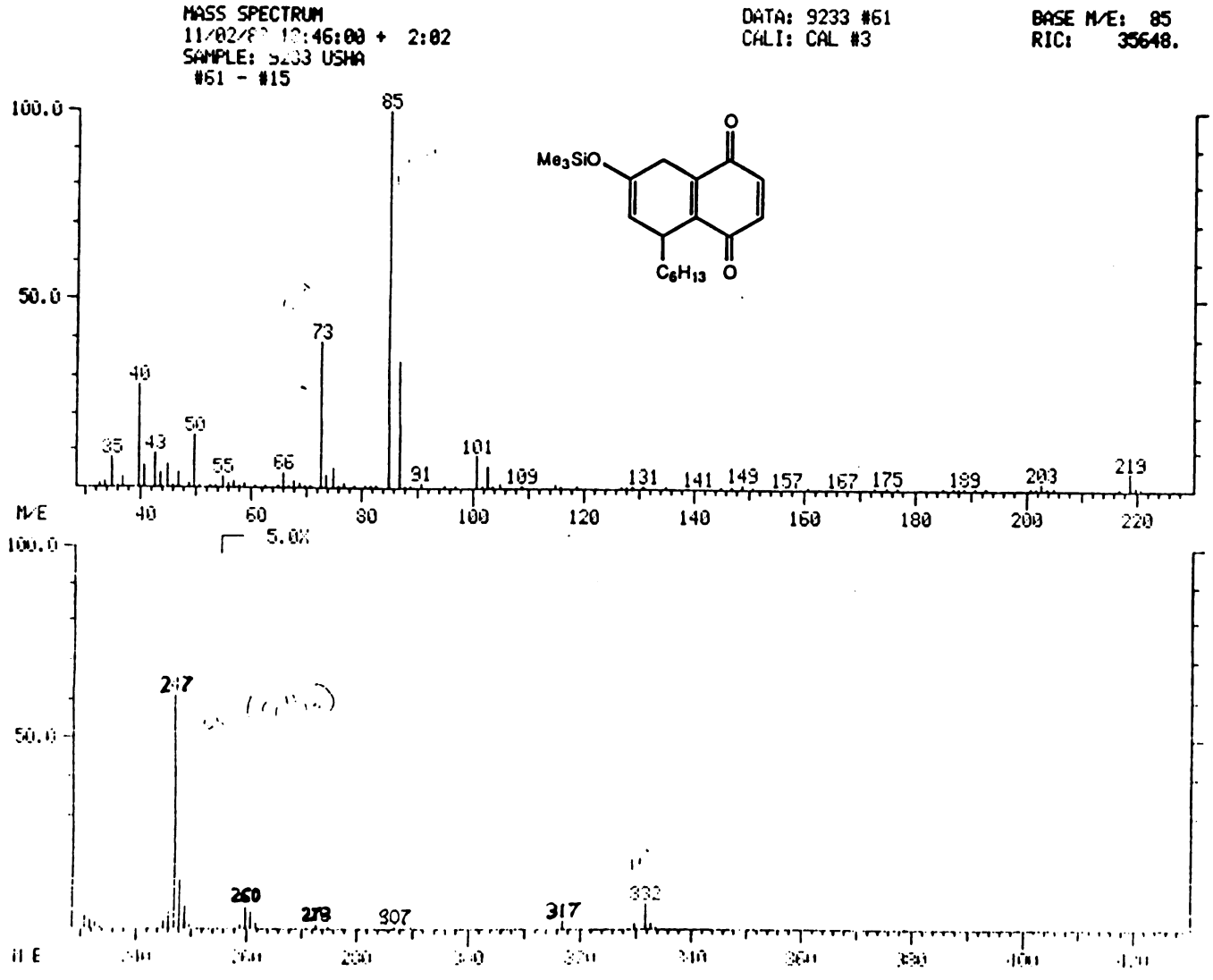
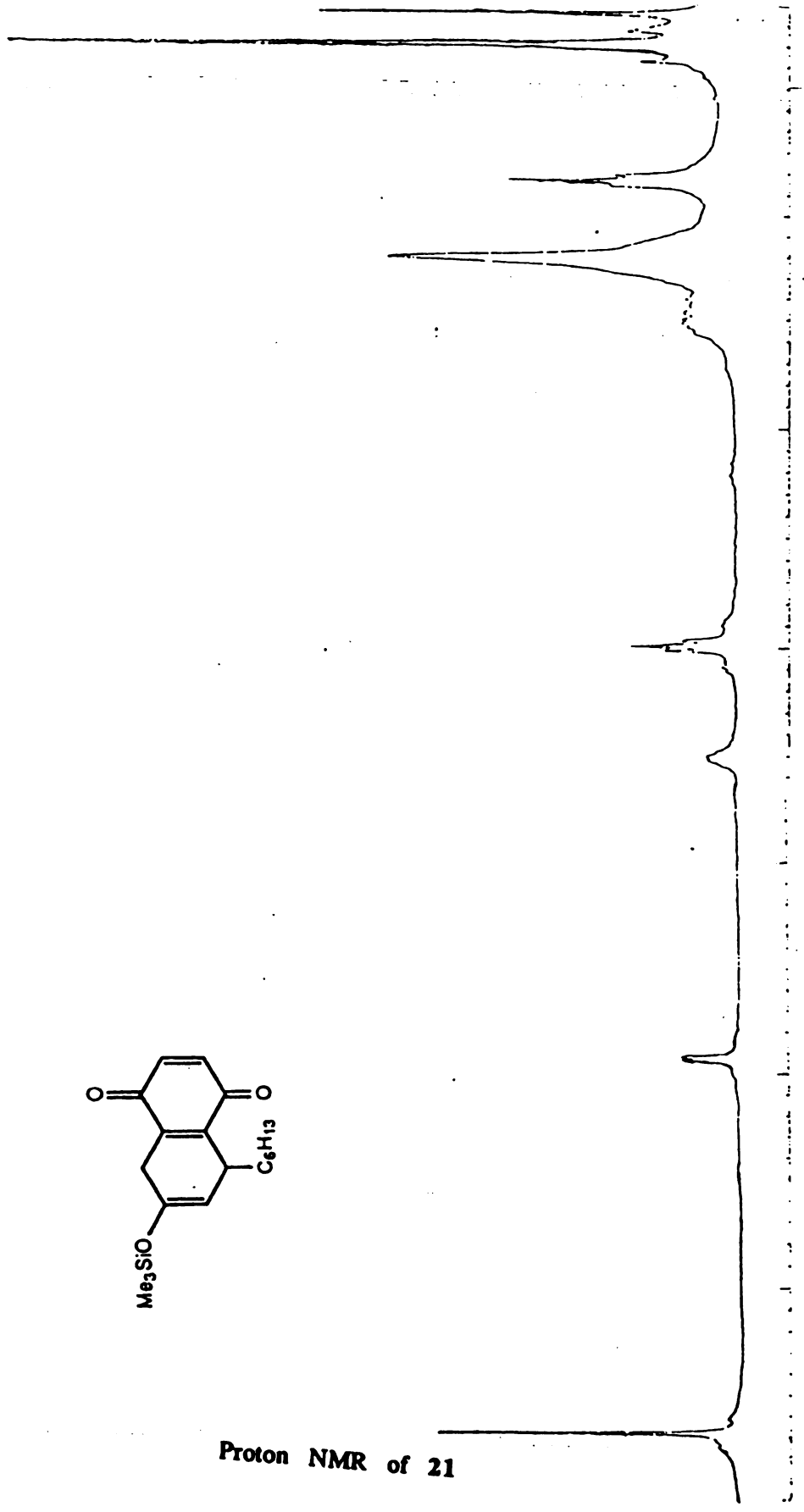


Proton NMR of 4



Mass spectrum of 21



Proton NMR of 21

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3500
3000
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3.5
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MICRONS
5.0
8.
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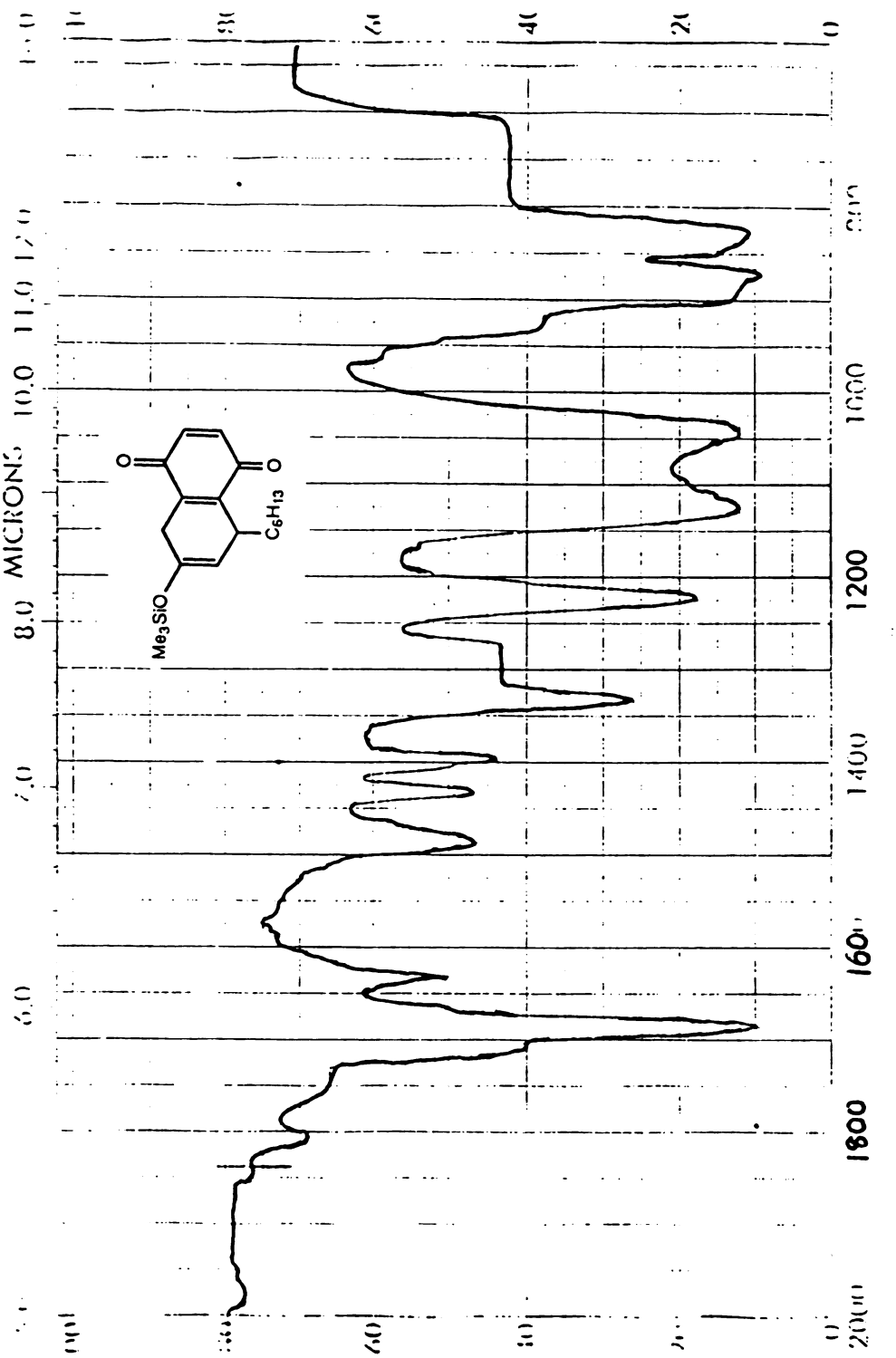
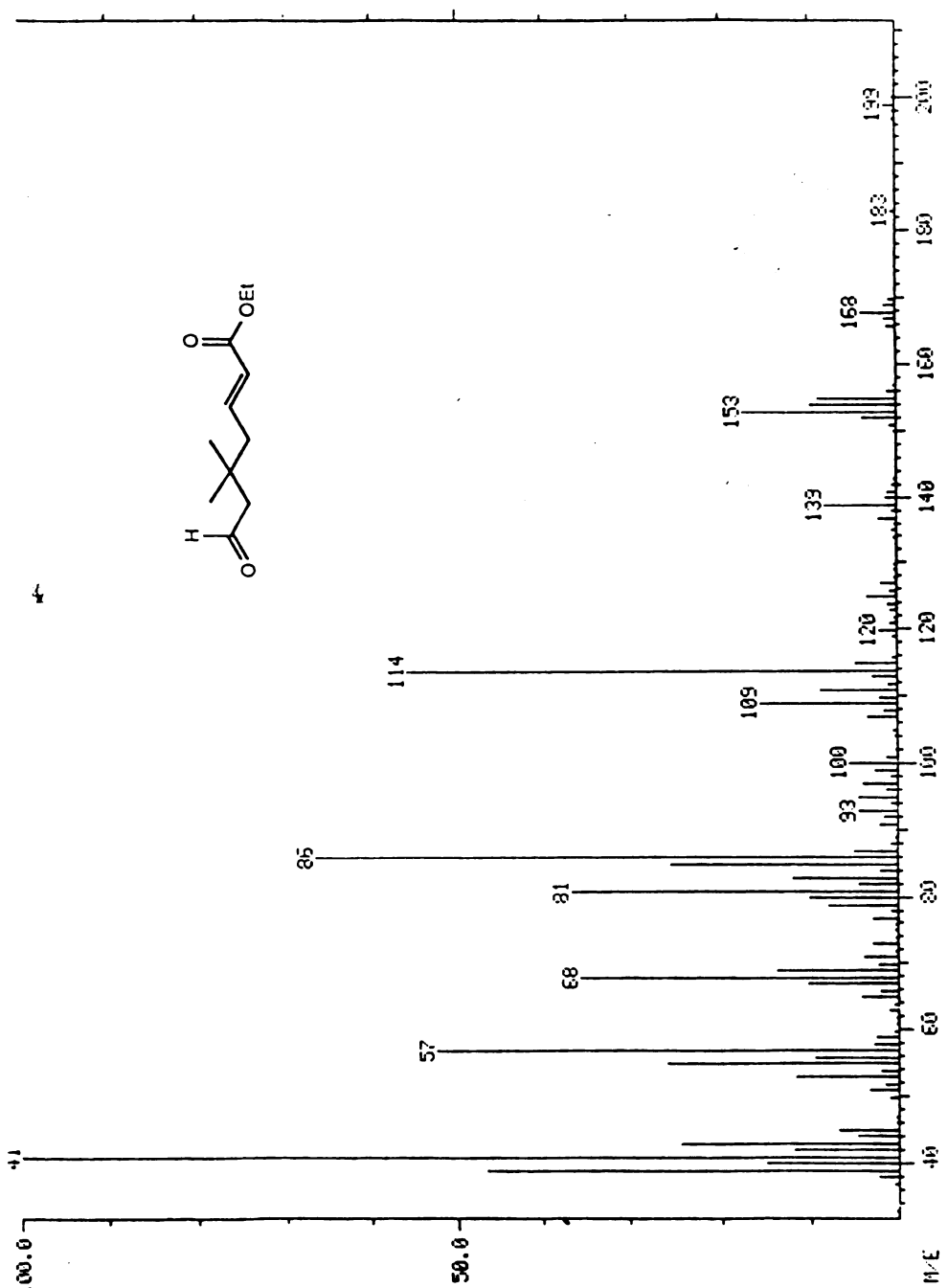
C6H13
O
O

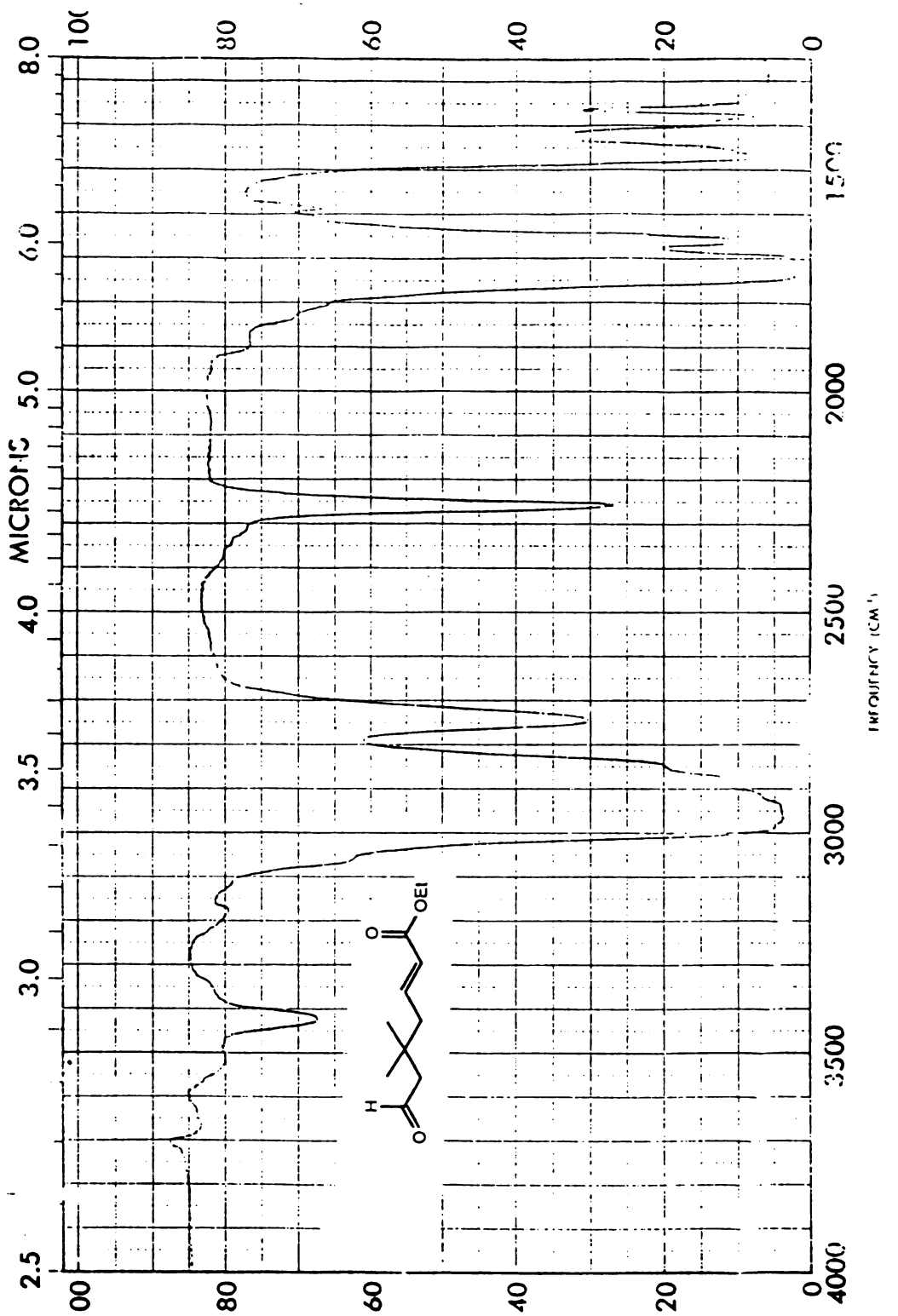
IR of 21



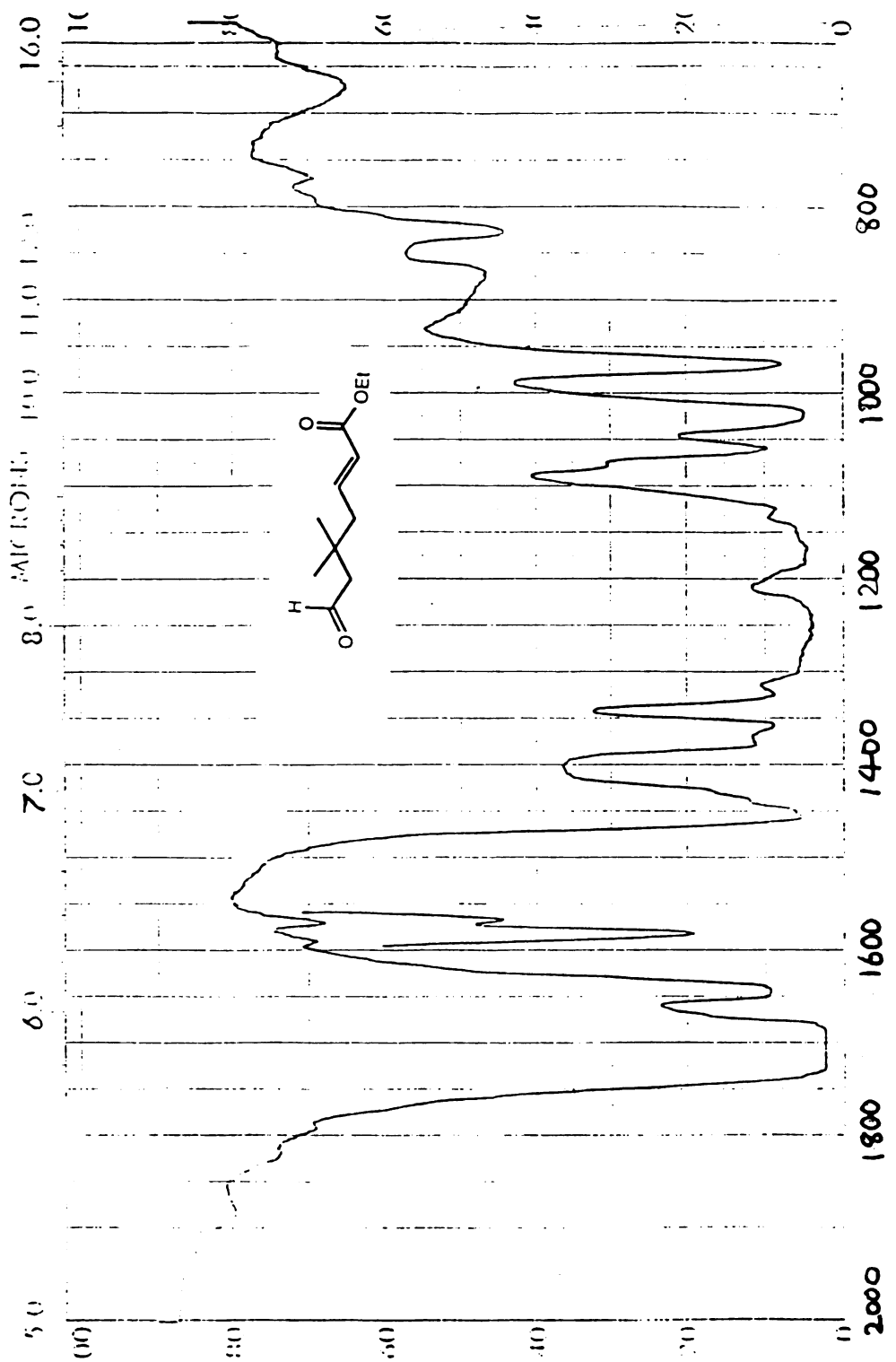
IR of 21



Mass spectum of 17



IR of 17



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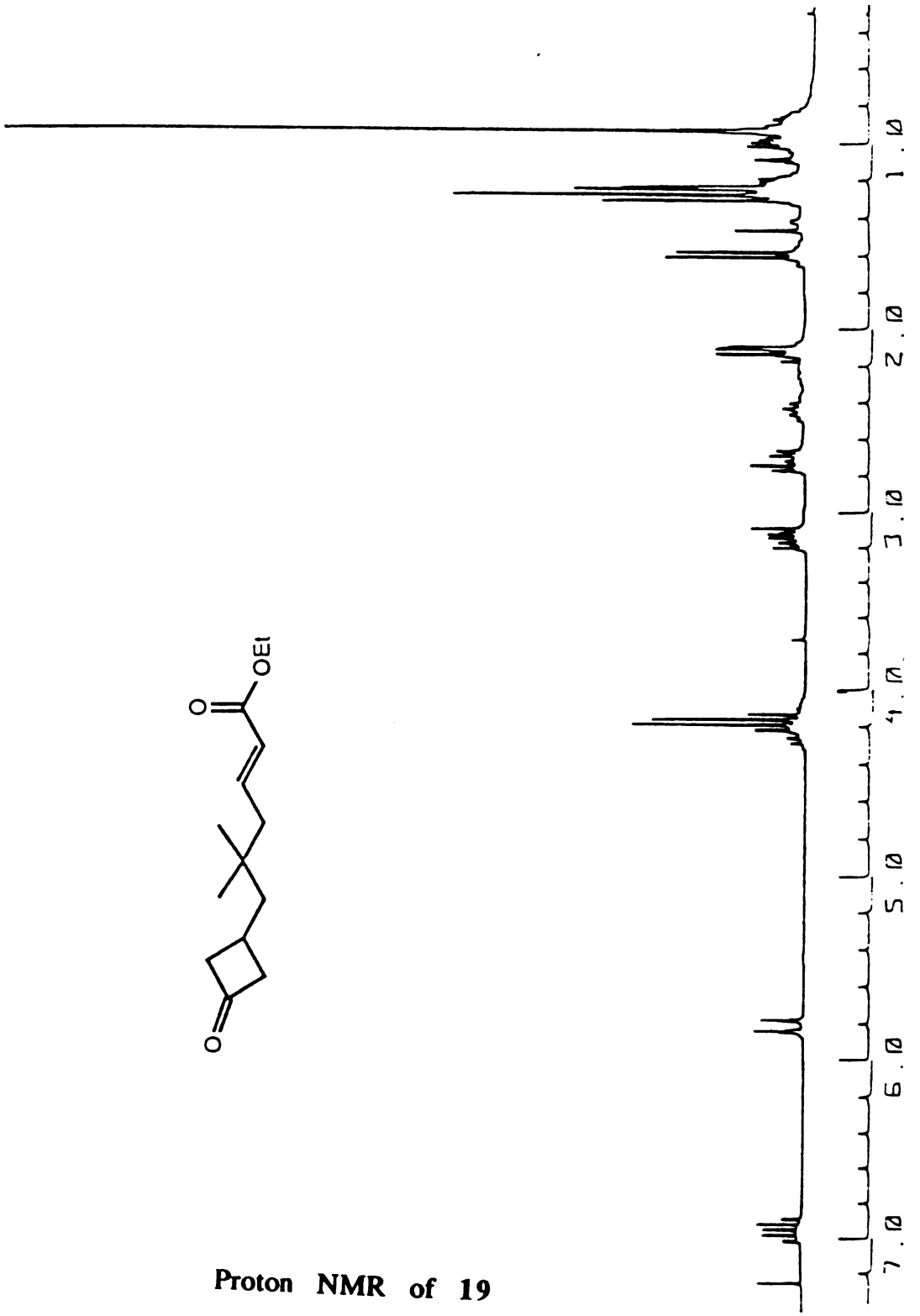
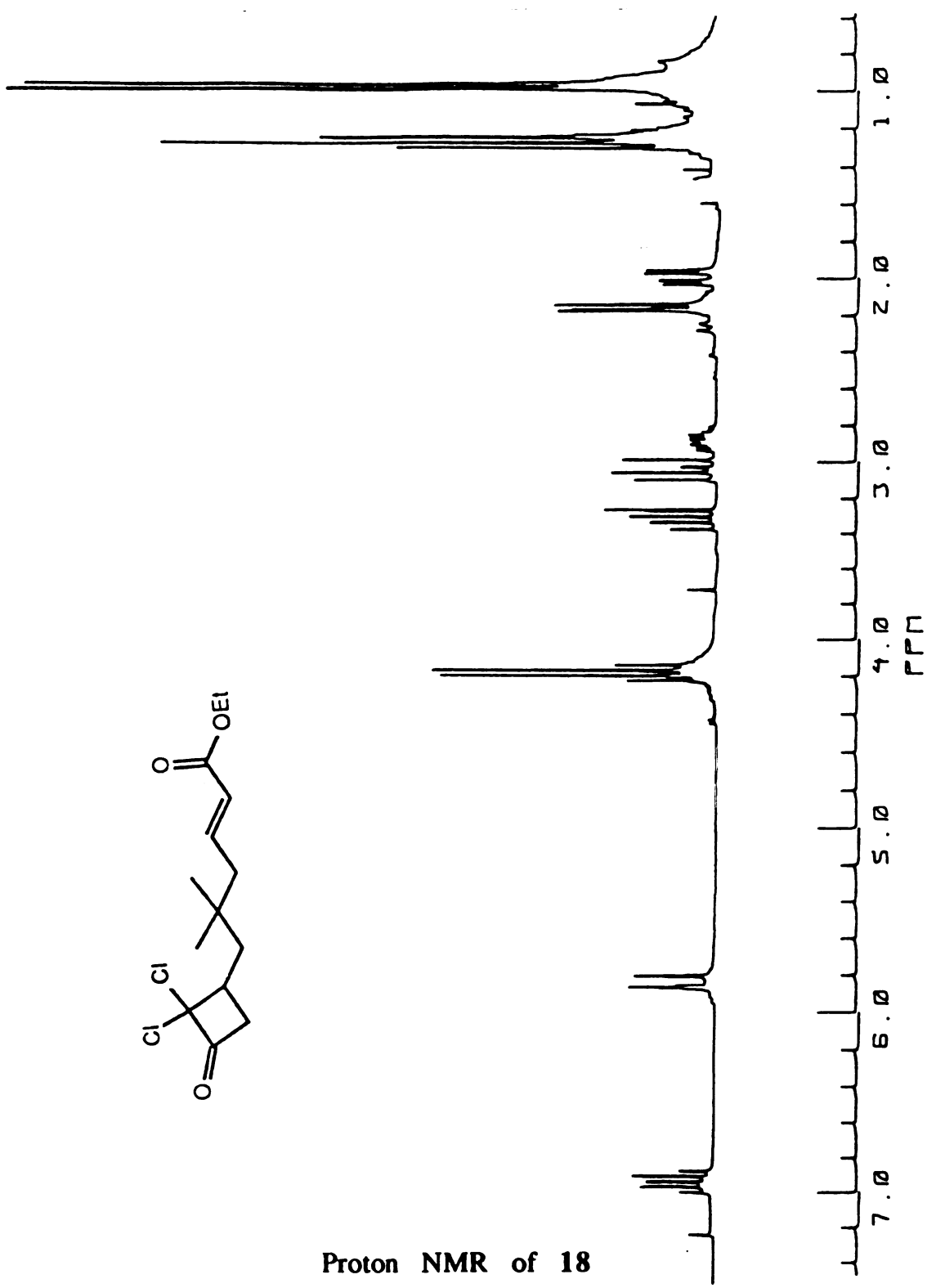
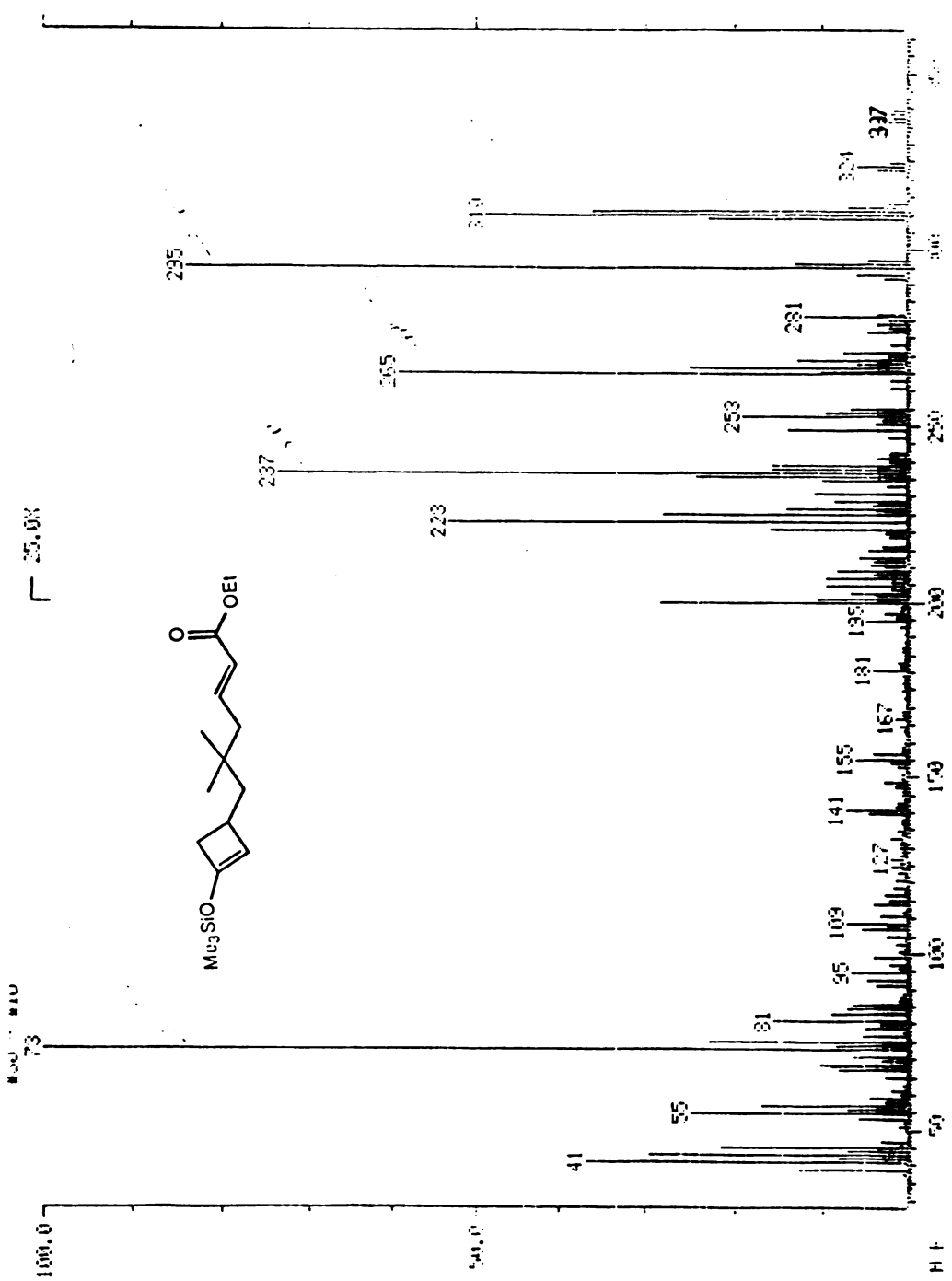


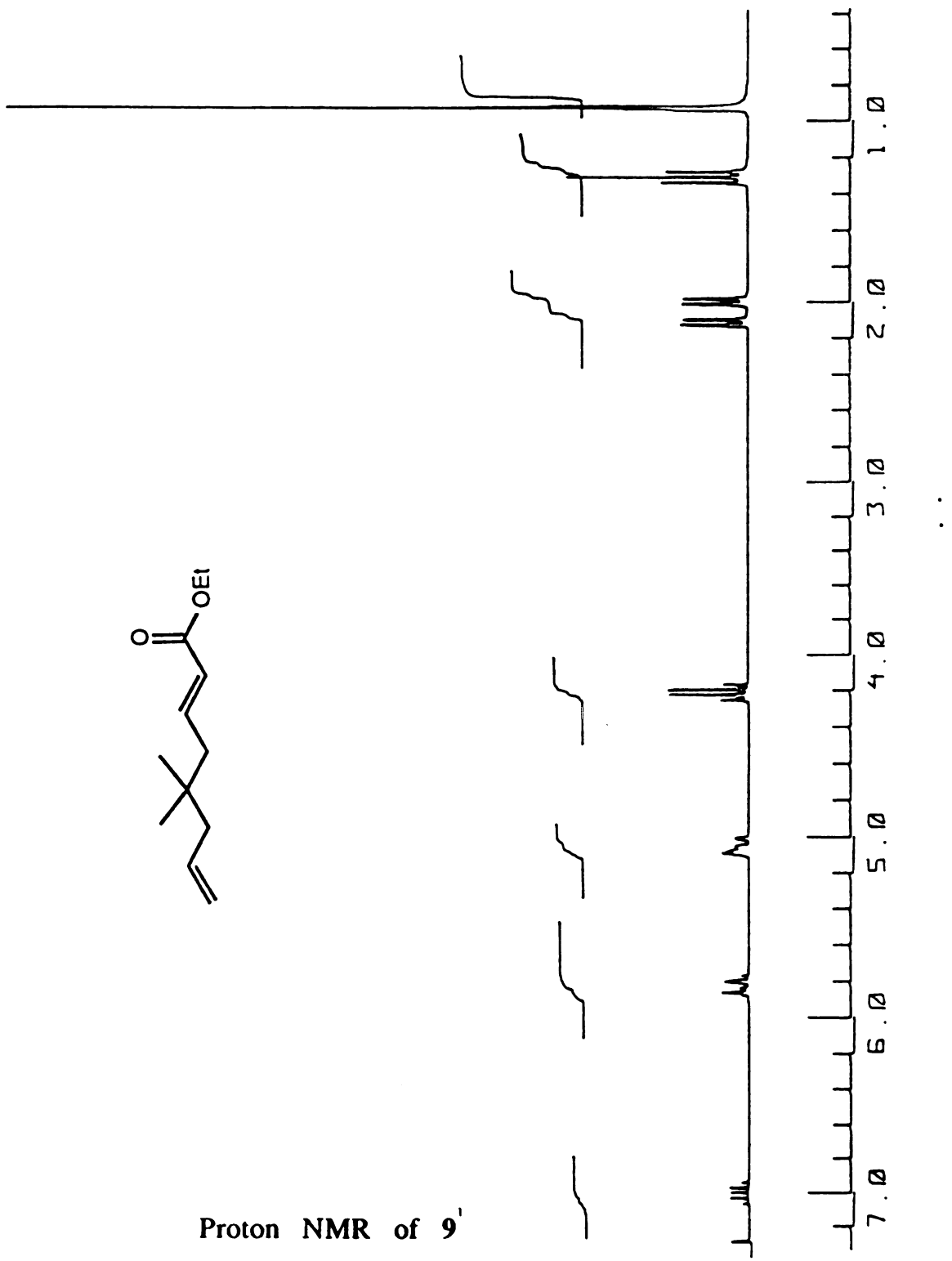
Proton NMR of 19



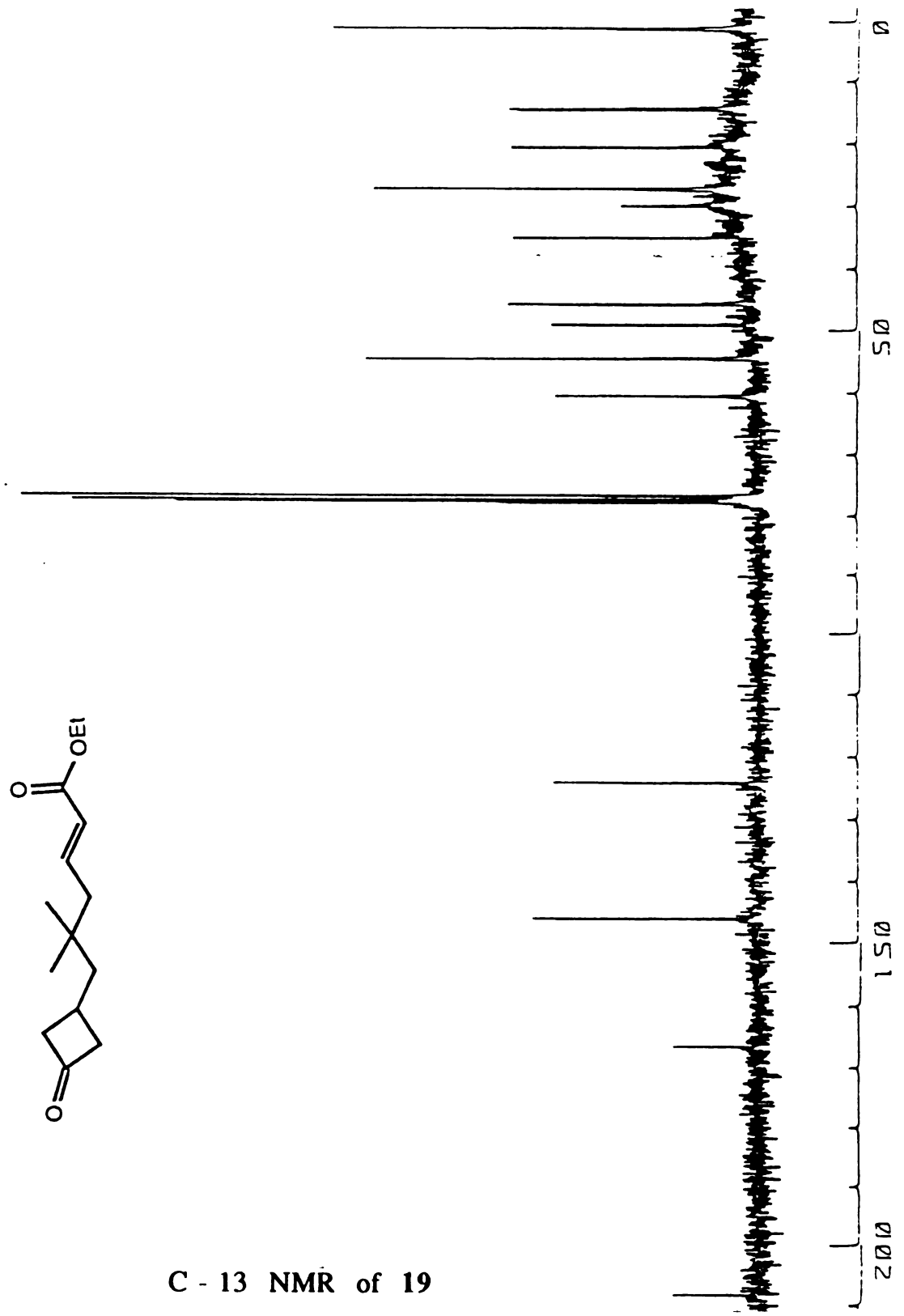
Proton NMR of 18



Mass spectrum of 11

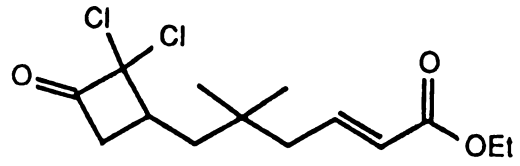


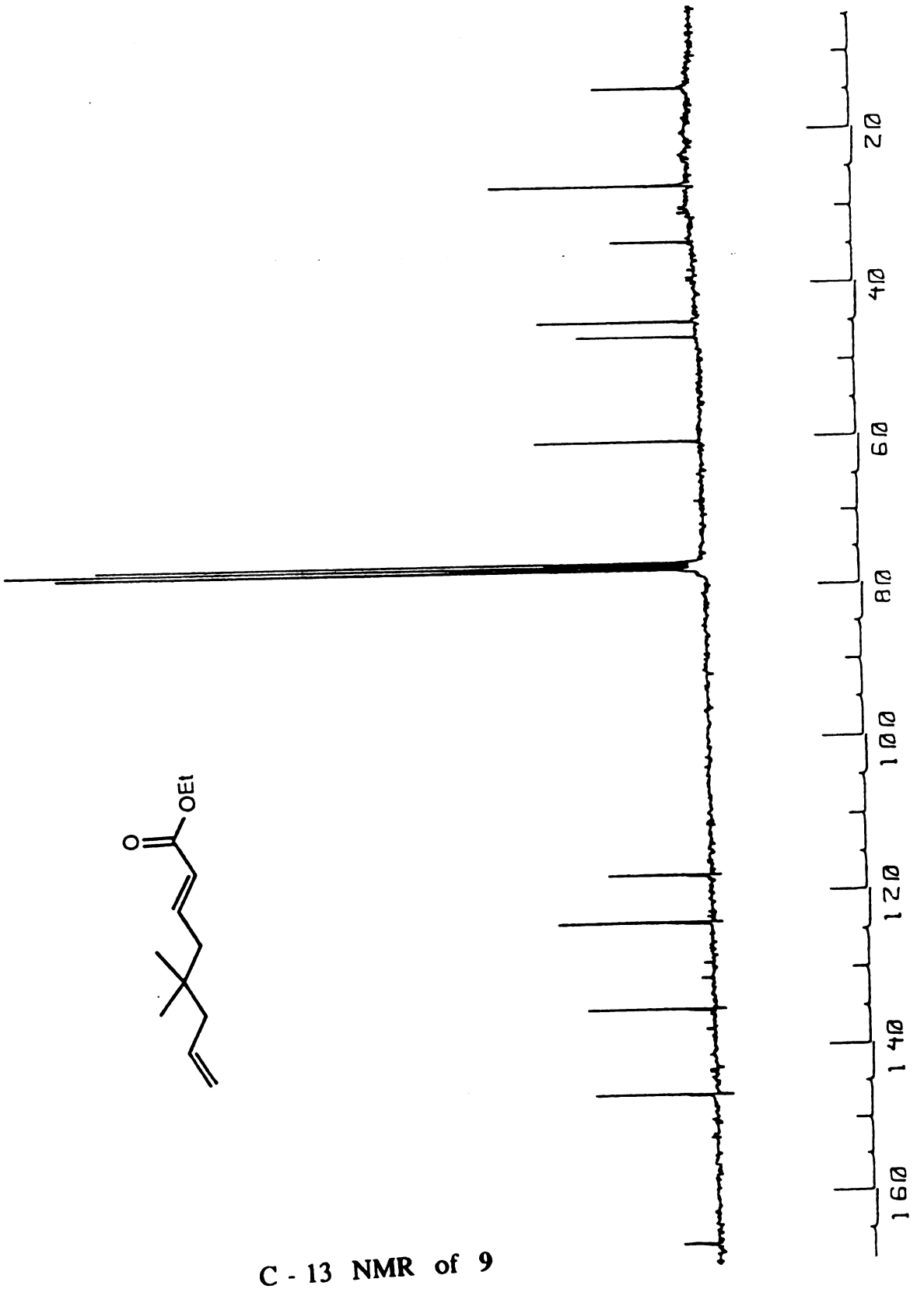
Proton NMR of 9'



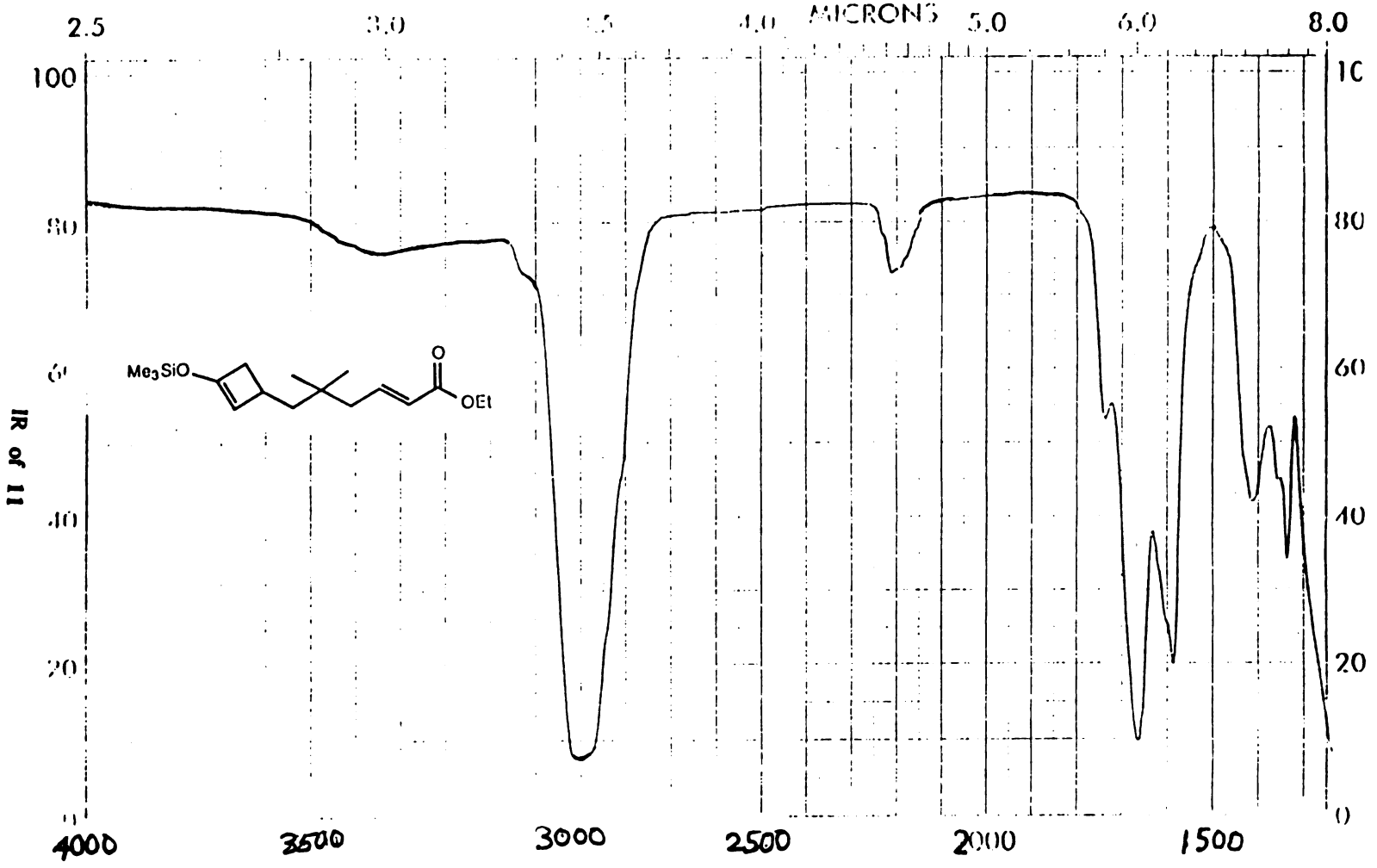
C - 13 NMR of 19

C - 13 NMR of 18





C - 13 NMR of 9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2000
1500
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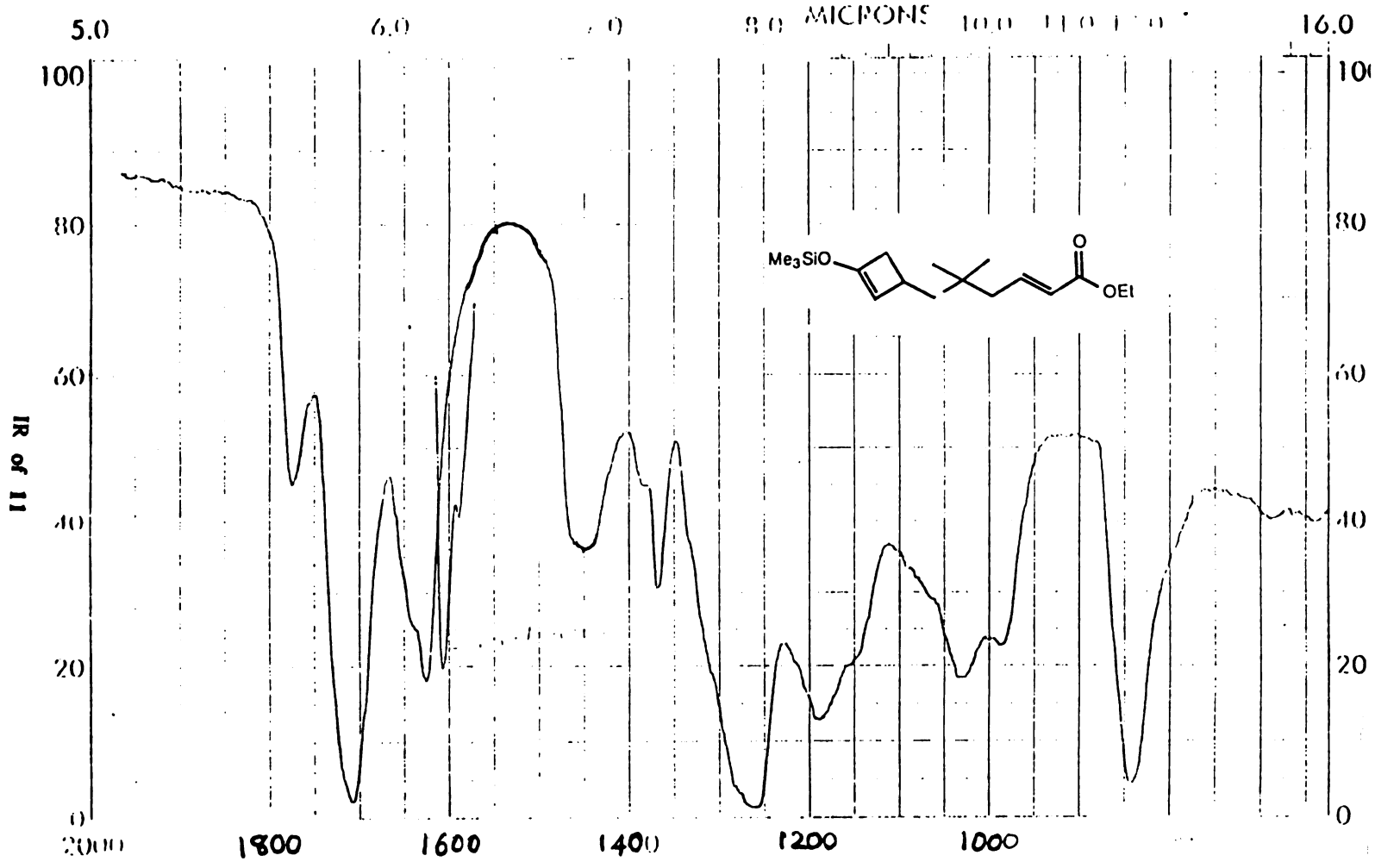
O
OEt

IR of 11

190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MICRONS
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1000
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Me3SiO
O
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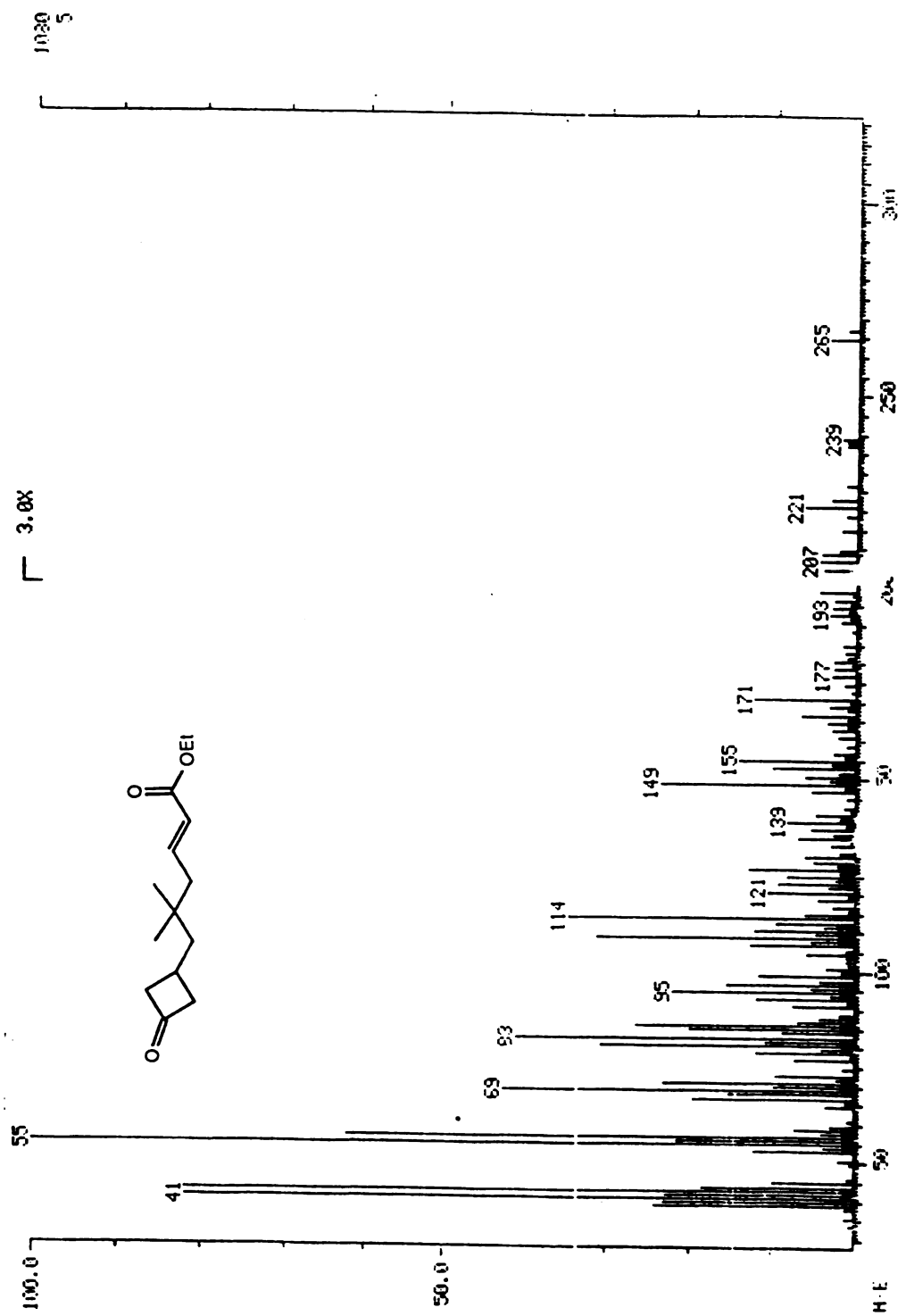
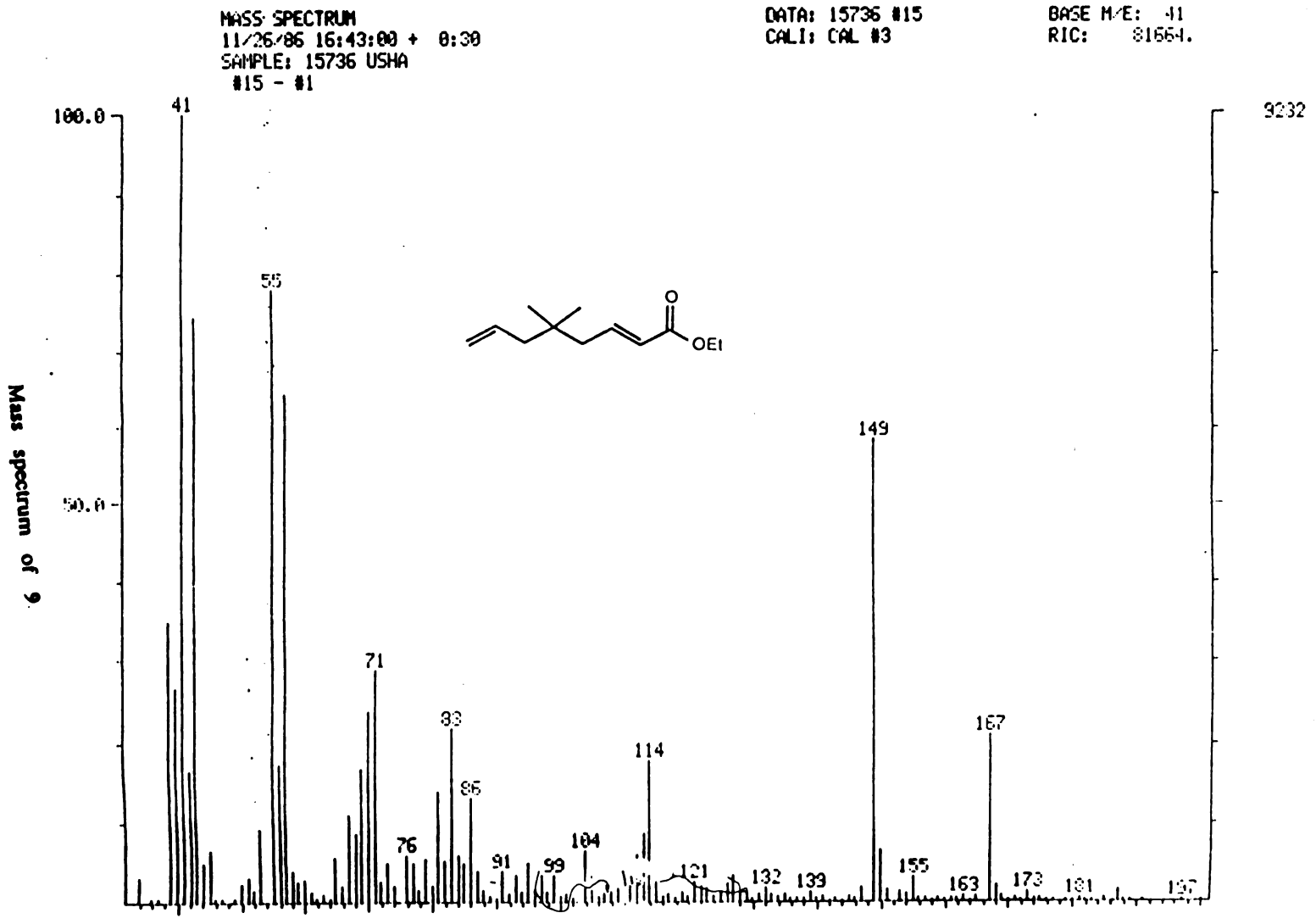
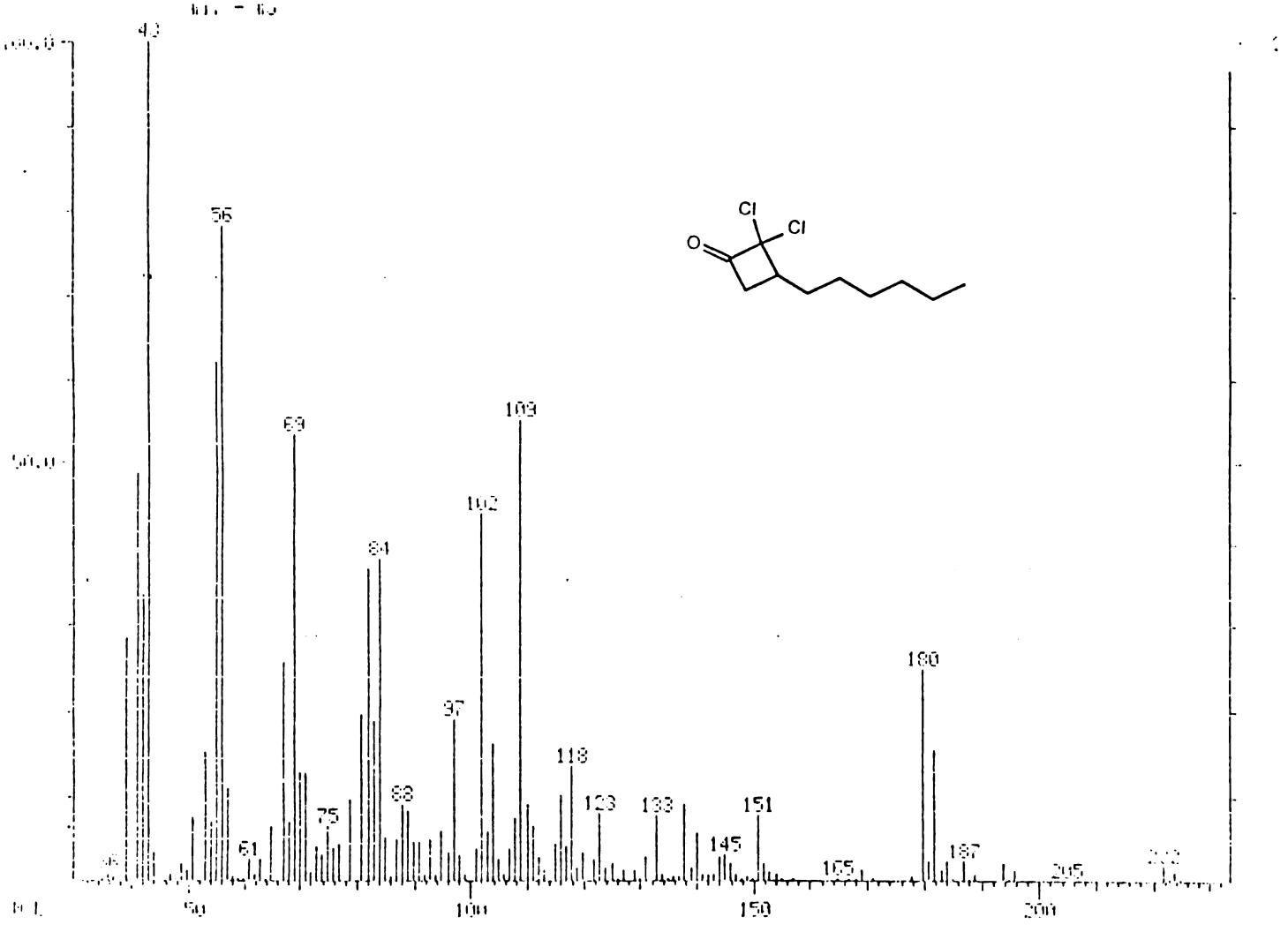
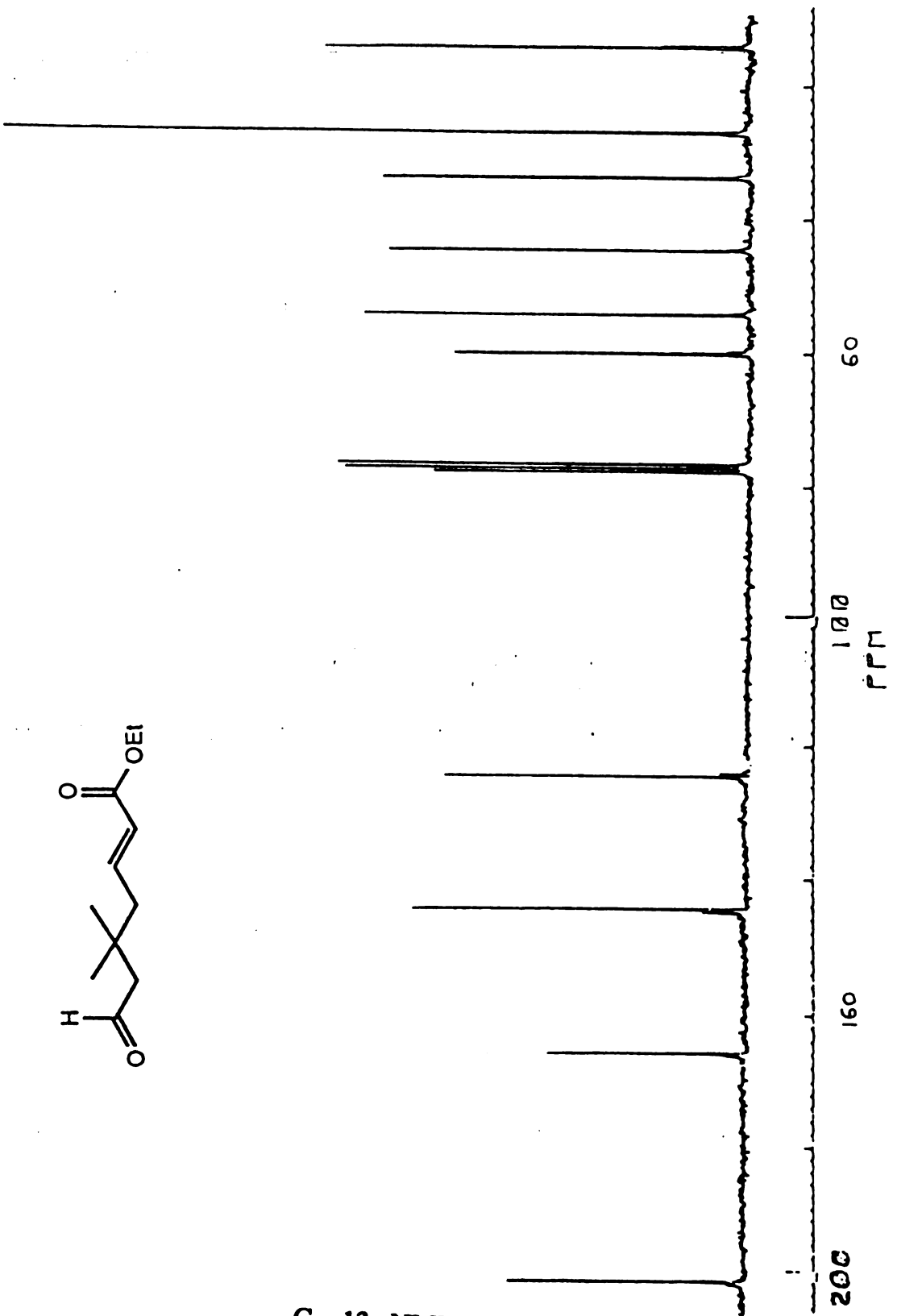


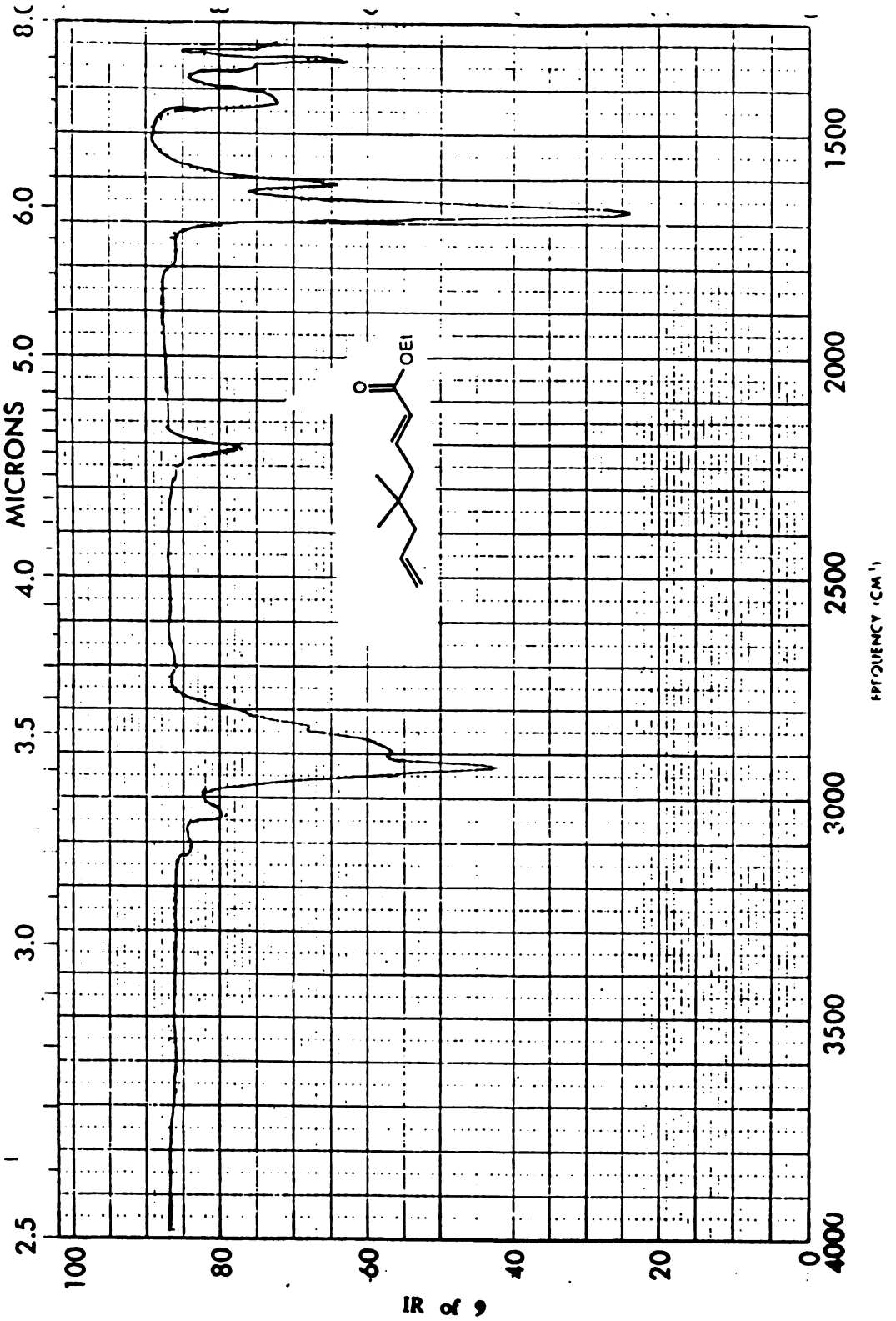
Mass spectrum of 19


MASS SPECTRUM
11/26/86 16:43:00 + 0:30
SAMPLE: 15736 USHA
#15 - #1
DATA: 15736 #15
CALI: CAL #3
BASE M/E: 41
RIC: 81664.
100.0
50.0
41
55
71
83
86
76
91
99
104
114
121
132
139
149
155
163
167
173
181
197
9232
Mass spectrum of 9

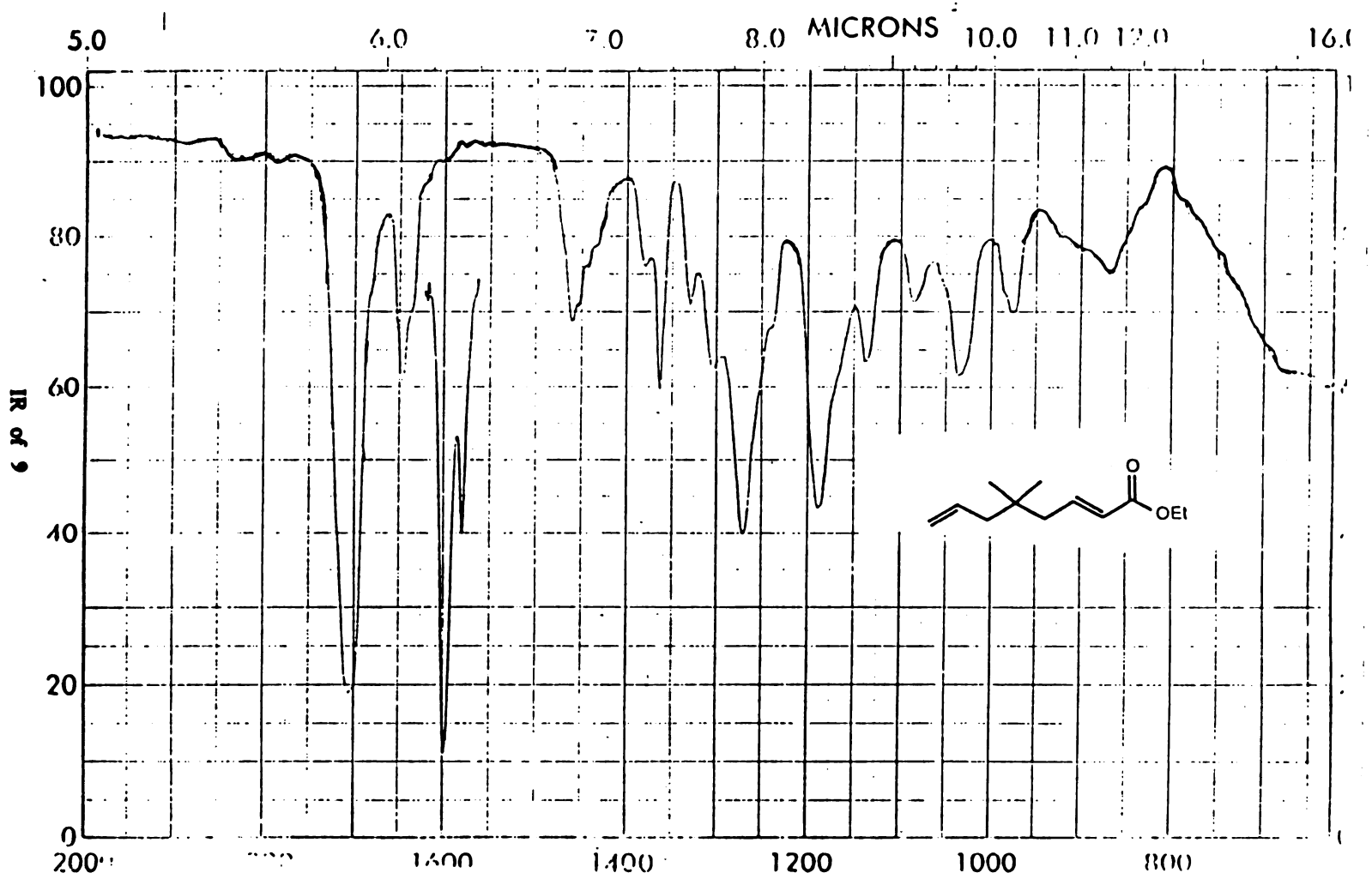

43
56
69
84
97
102
109
118
123
133
145
151
180
187
205
Cl
Cl
O
50
100
150
200

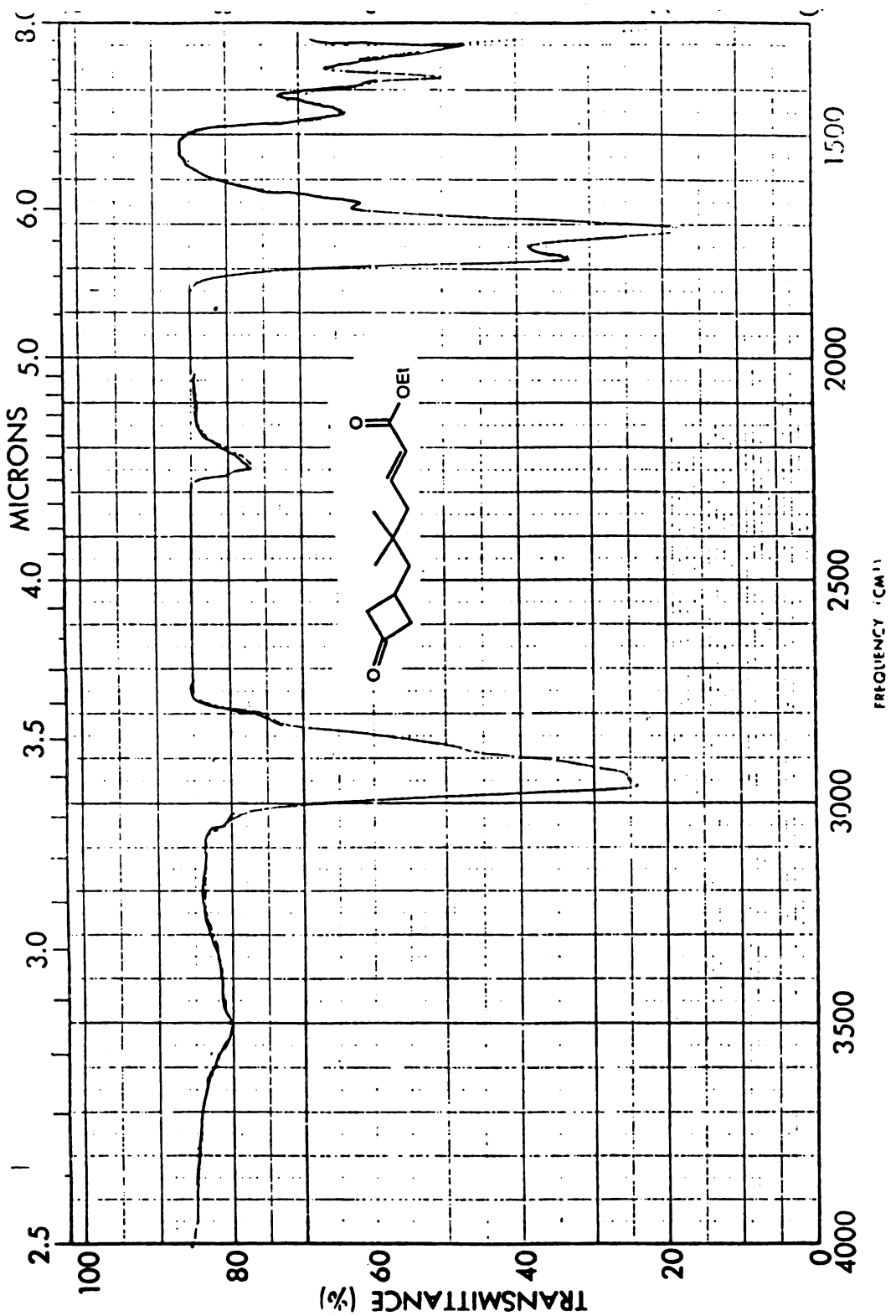


C - 13 NMR of 17

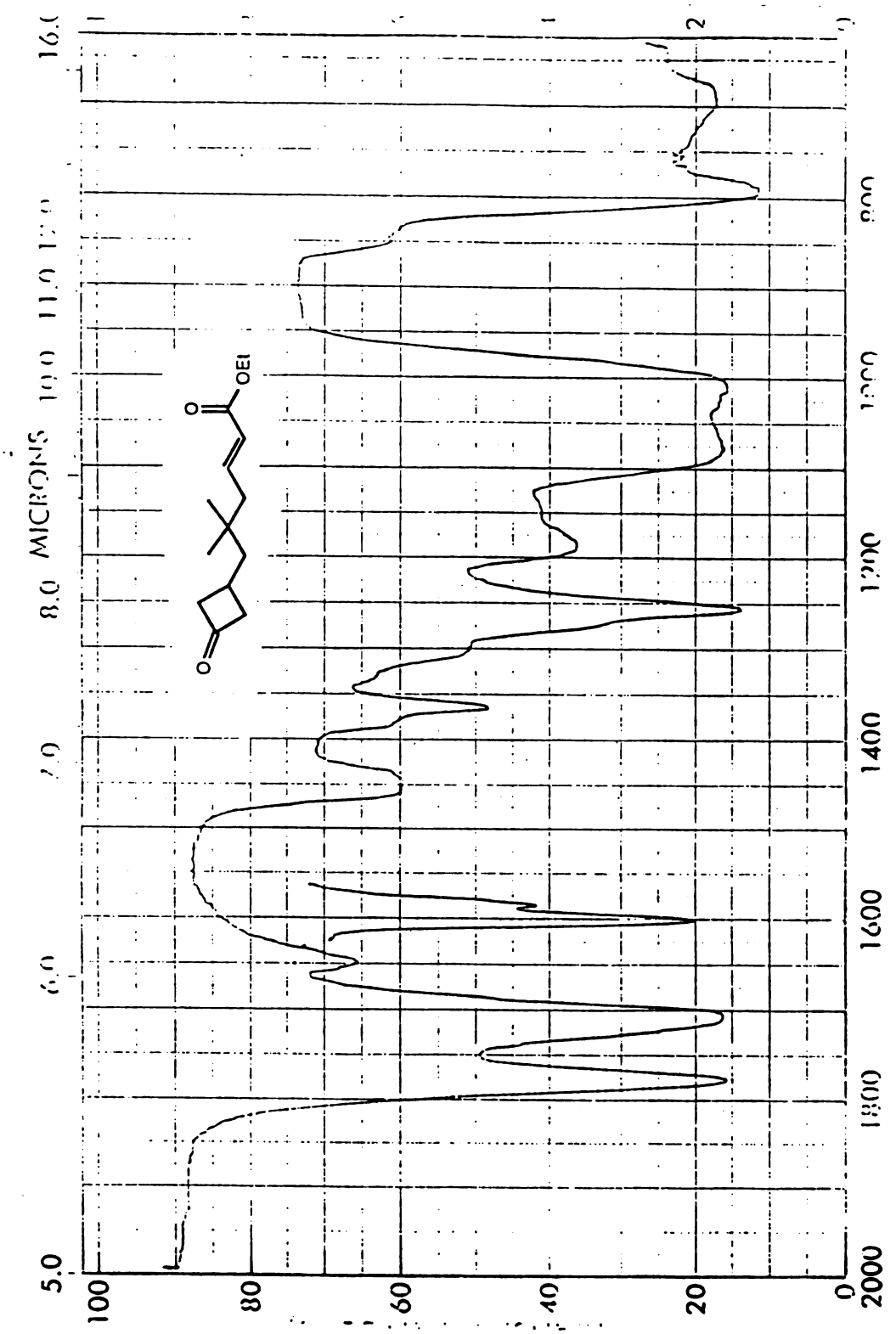

MICRONS
2.5
3.0
3.5
4.0
5.0
6.0
8.0
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
OEt
O

IR of 9

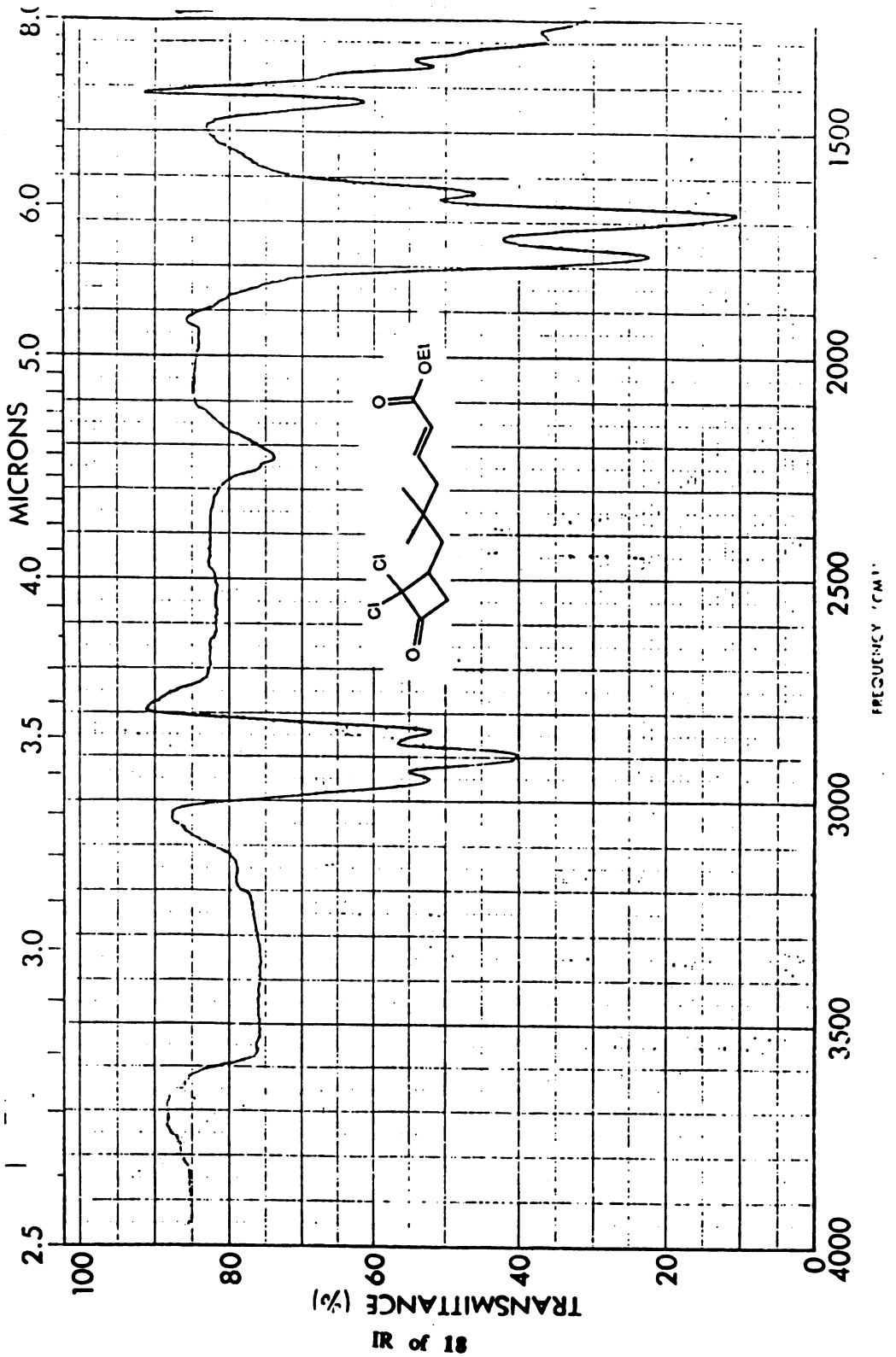

5.0
6.0
7.0
8.0
MICRONS
10.0
11.0
16.0
100
80
60
40
20
0
IR of 9
1400
1200
1000
800
O
OEt


TRANSMITTANCE (%)
100
80
60
40
20
0
2.5
3.0
3.5
4.0
5.0
6.0
MICRONS
4000
3500
3000
2500
2000
1500
FREQUENCY (CM⁻¹)
OEt
O
O

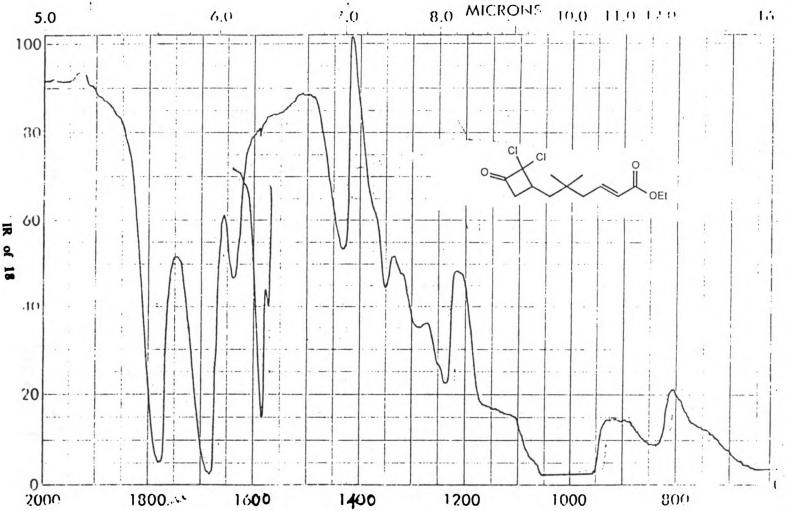
IR of 19

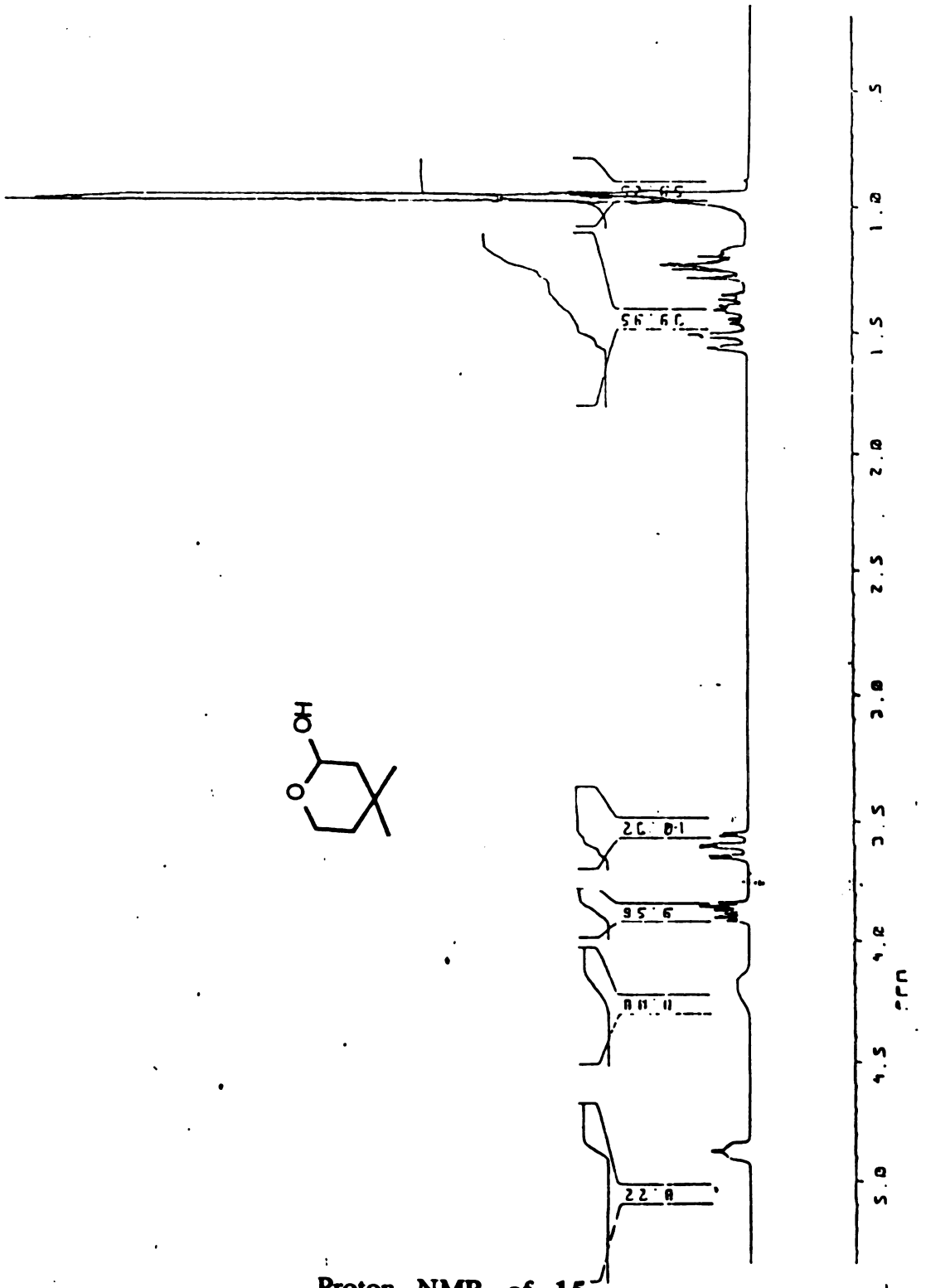


IR of 19

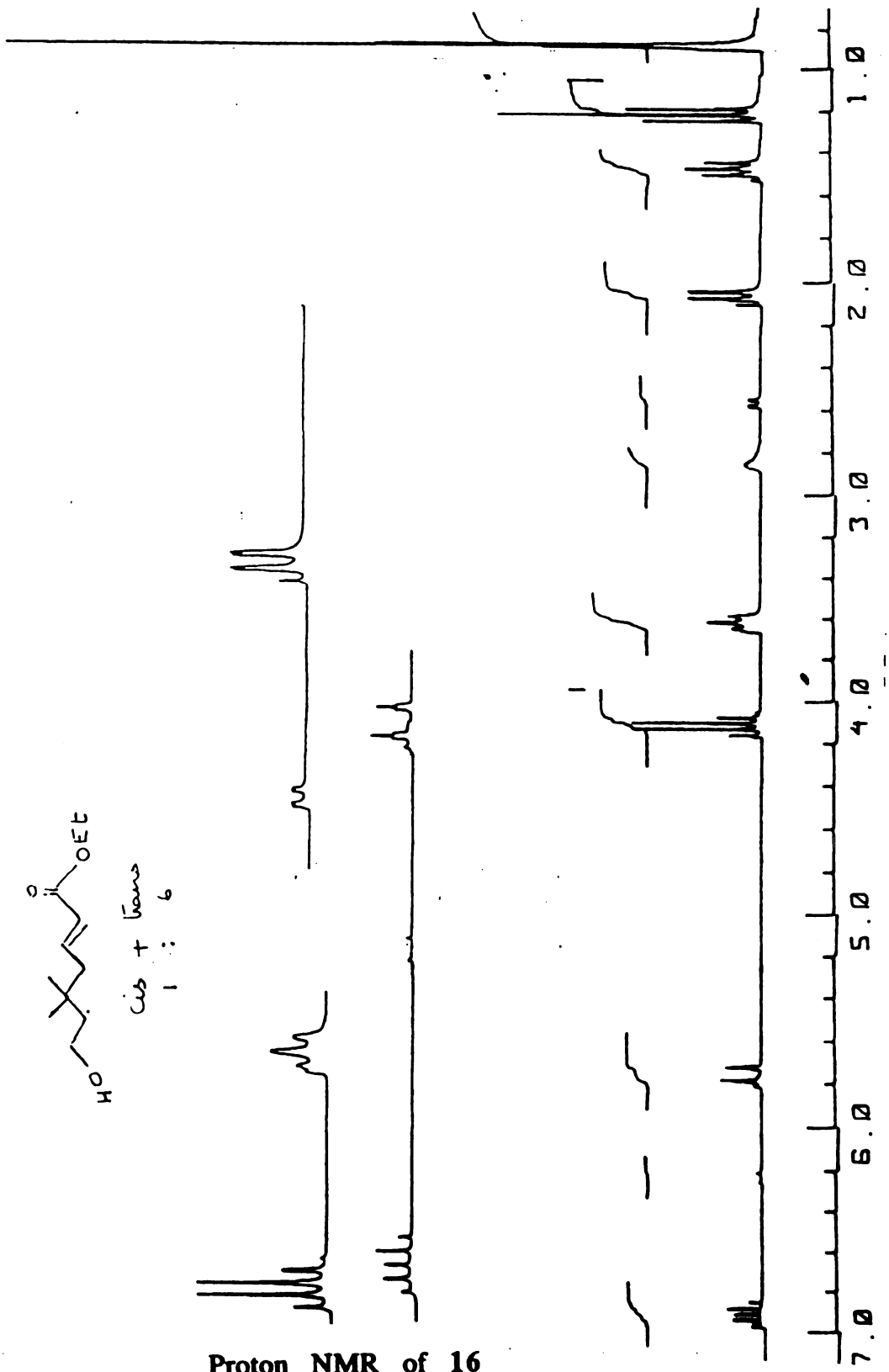

TRANSMITTANCE (%)
100
80
60
40
20
0
MICRONS
2.5
3.0
3.5
4.0
5.0
6.0
8.(
4000
3500
3000
2500
2000
1500
FREQUENCY (CM⁻¹)
OEt
O
Cl
Cl
O

IR of 18

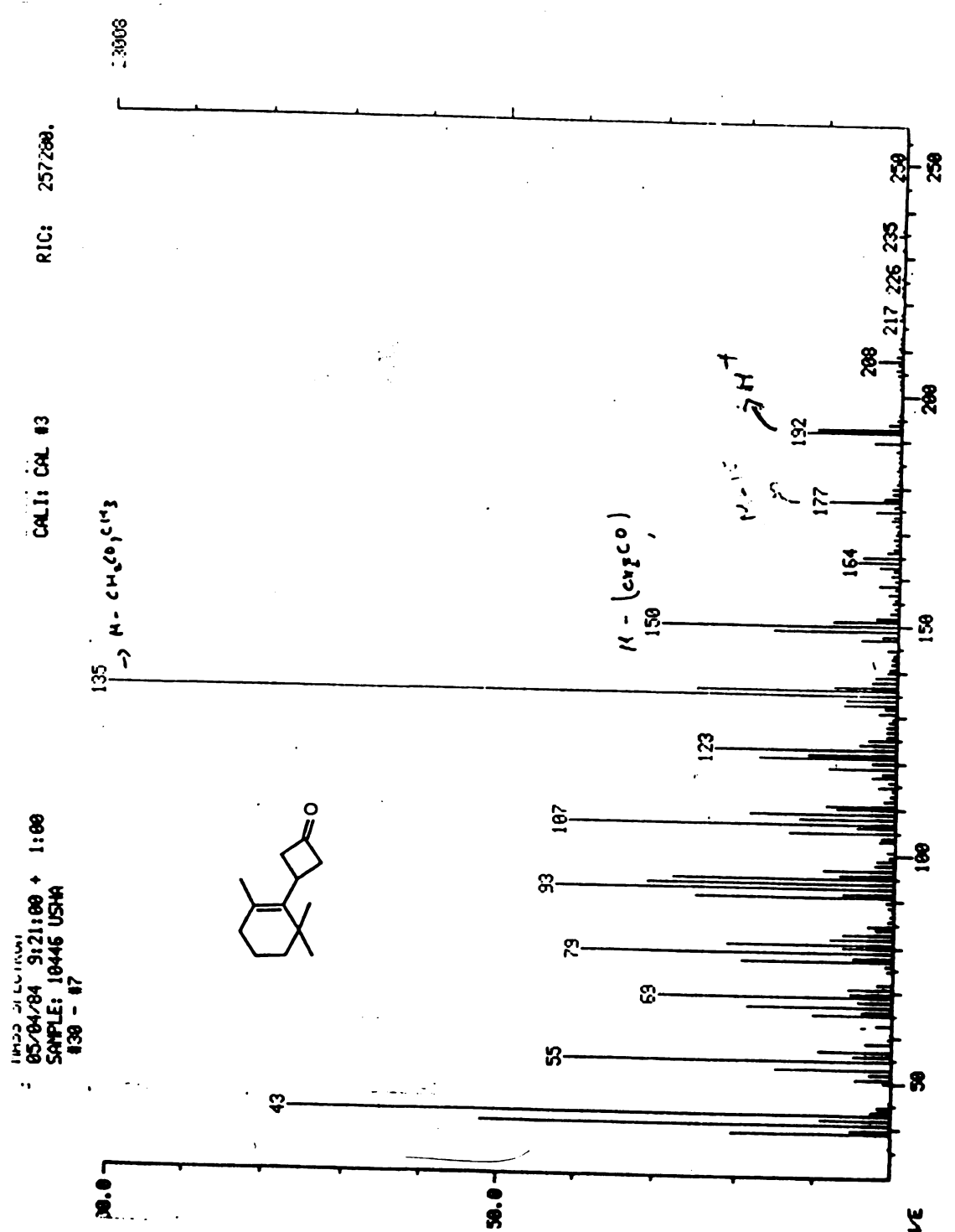

5.0
6.0
7.0
8.0
MICRONS
10.0
11.0
15
100
80
60
40
20
0
IR of 18
2000
1800
1600
1400
1200
1000
800
Cl
Cl
O
O
O
OEt



Proton NMR of 15



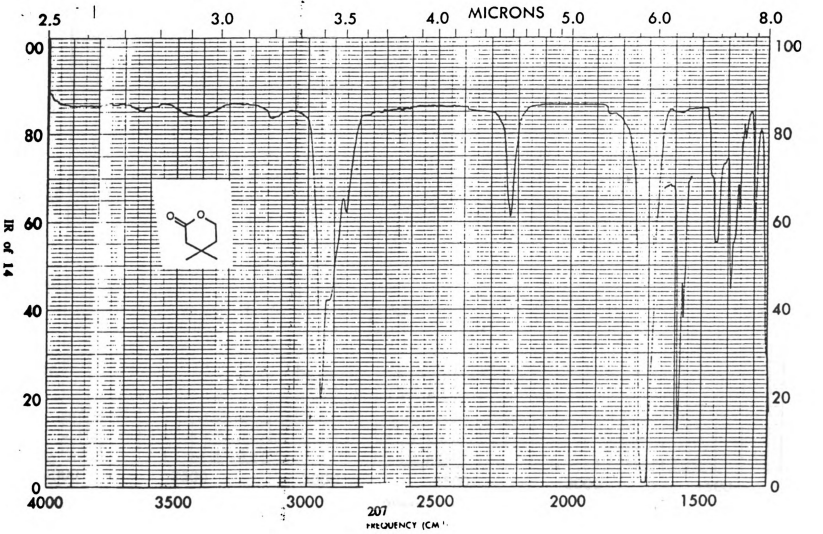
Proton NMR of 16

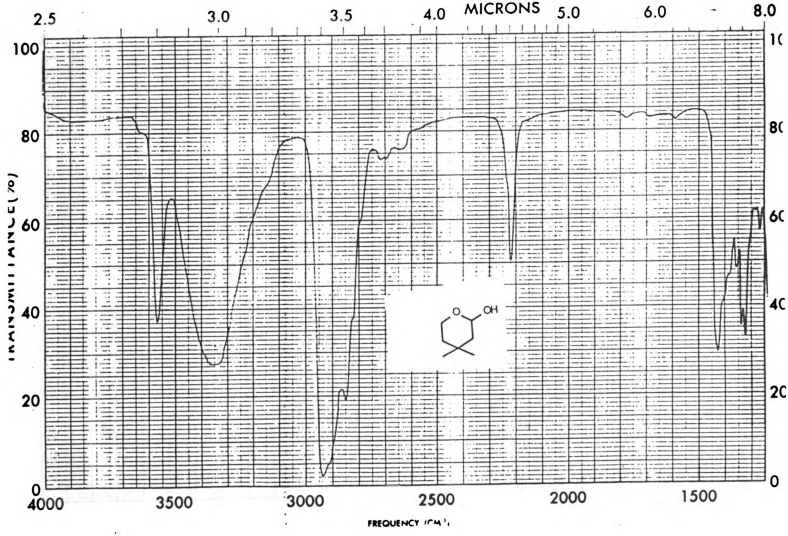


Mass spectrum of 7

TRANSMITTANCE(%)
100
80
60
40
20
0
5.0
6.0
7.0
8.0
MICRONS
10.0
11.0
12.0
16.
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM
O
O
O

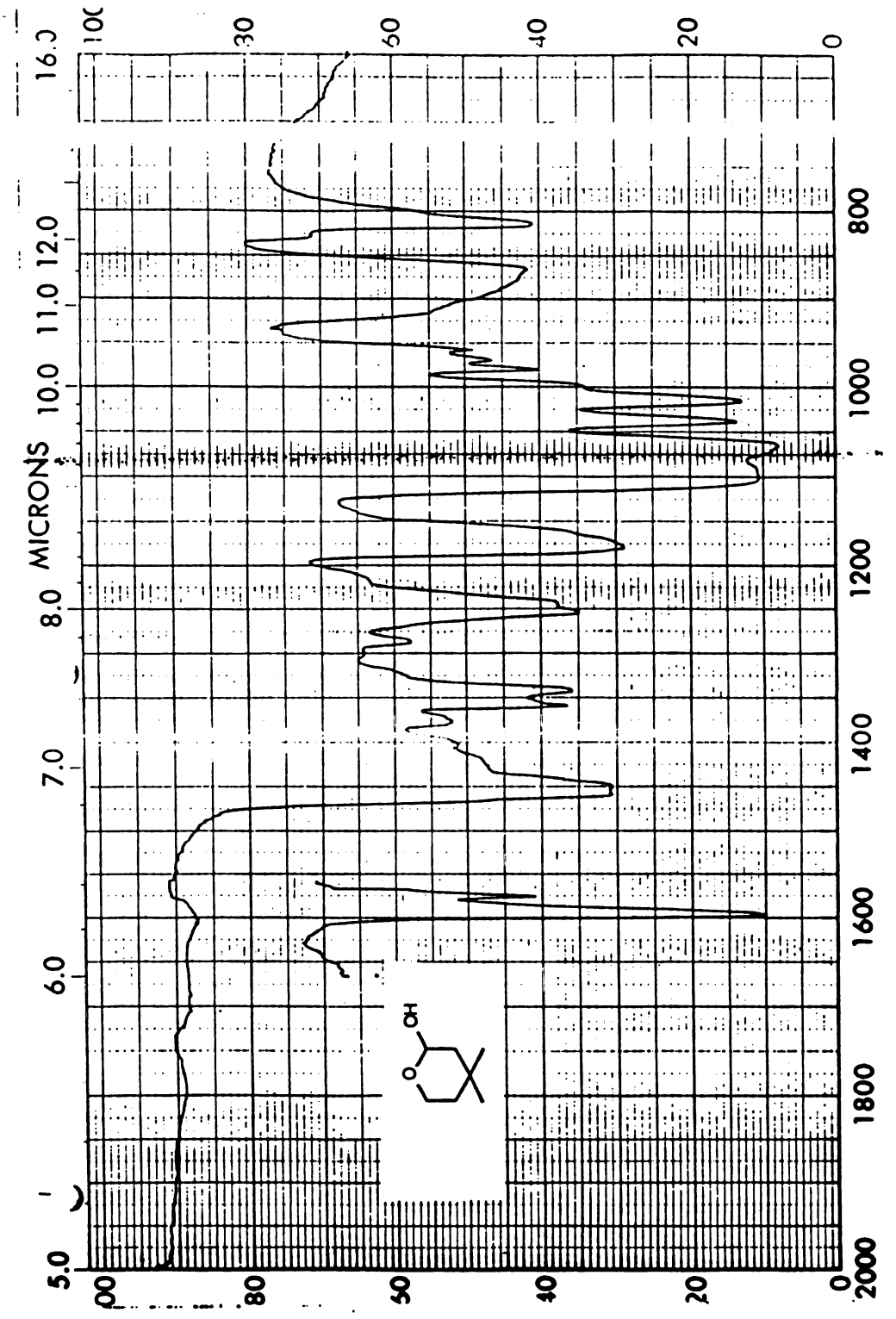
IR of 14


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
IR of 14
4000
3500
3000
2500
2000
1500
207
FREQUENCY (CM⁻¹)

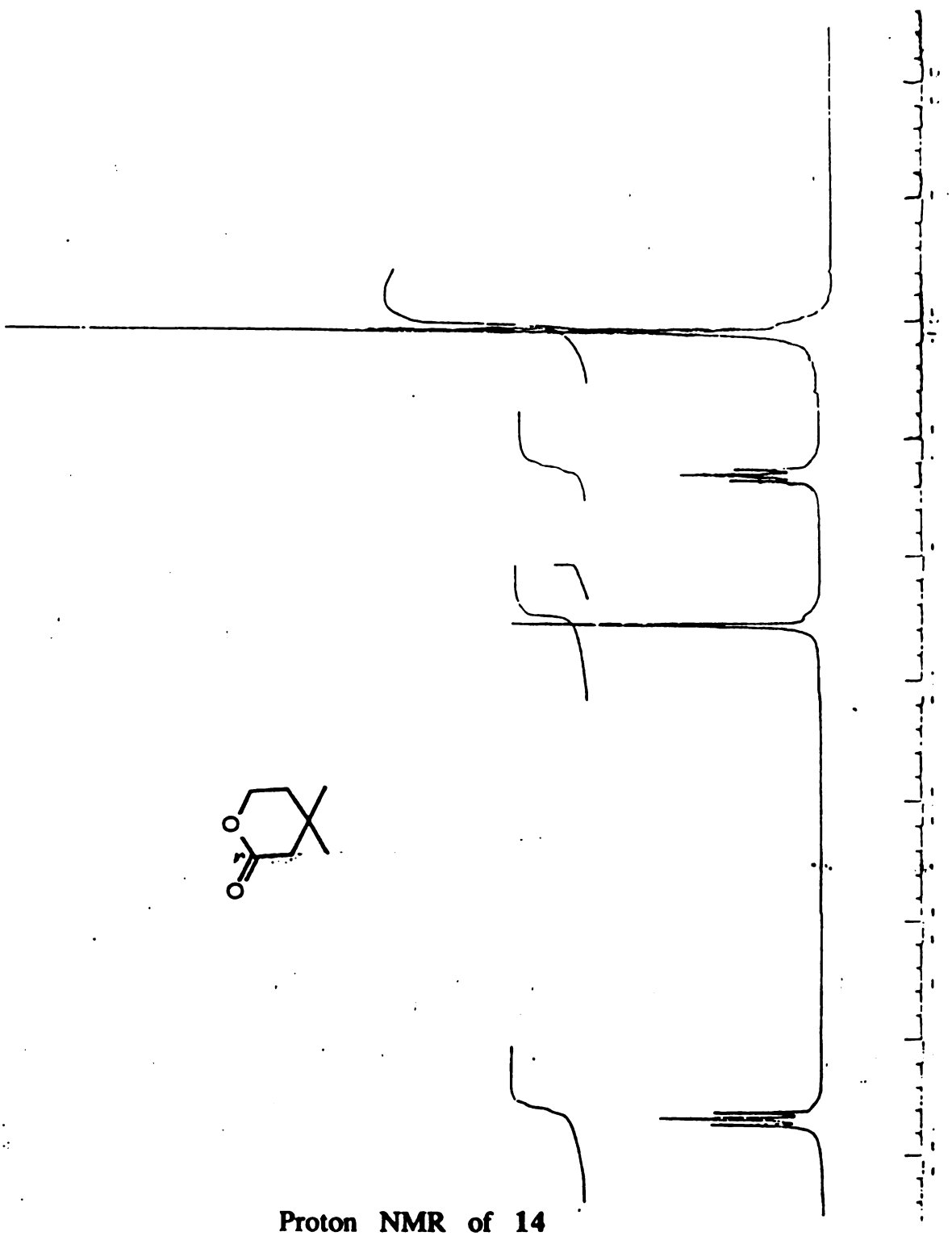

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
100
80
60
40
20
0
4000
3500
3000
2500
2000
1500
OH
O

IR of 15

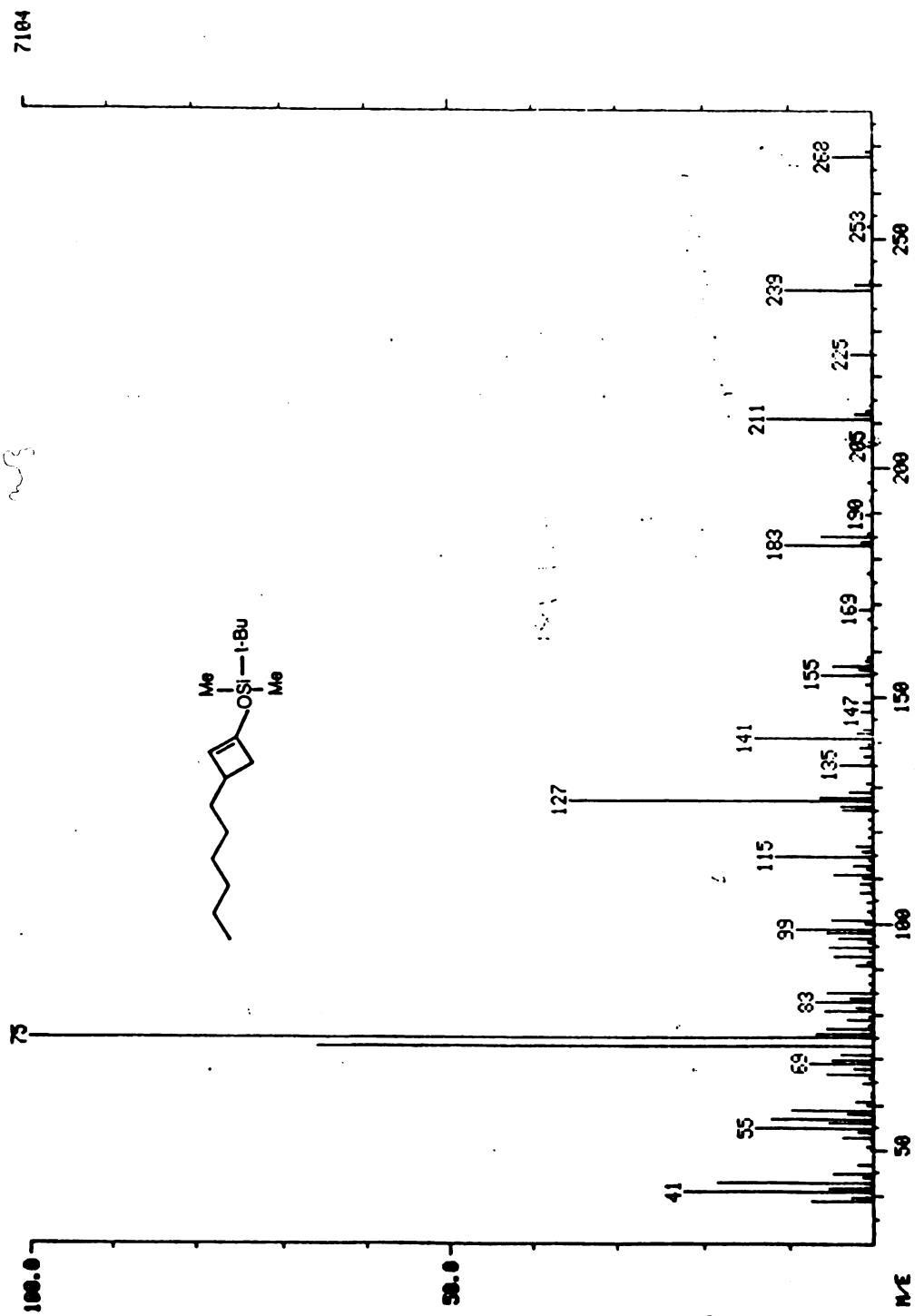
208


MICRONS
5.0
6.0
7.0
8.0
10.0
11.0
12.0
16.0
2000
1800
1600
1400
1200
1000
800
0
20
40
60
80
100
OH
O

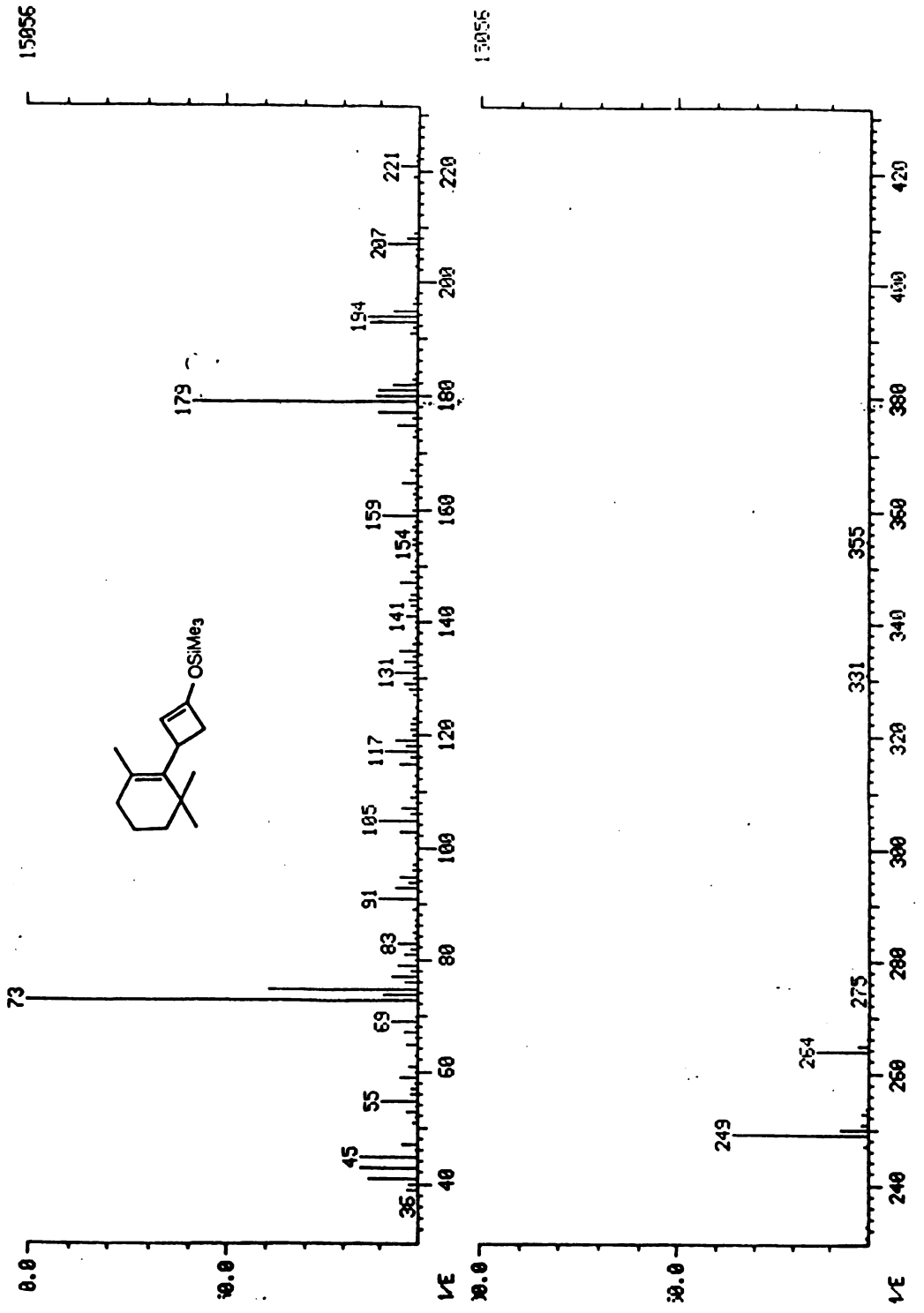
IR of 15



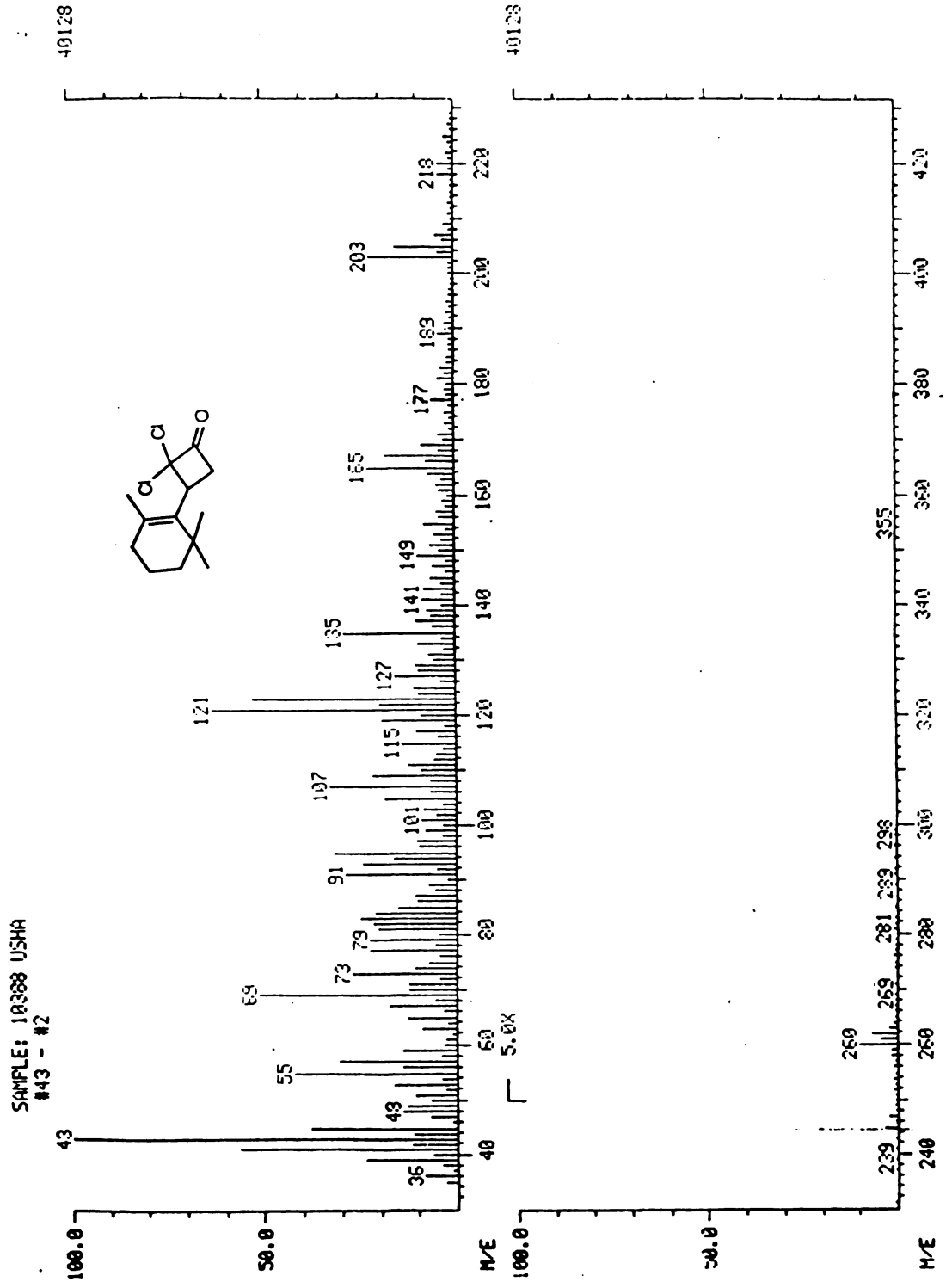
Proton NMR of 14



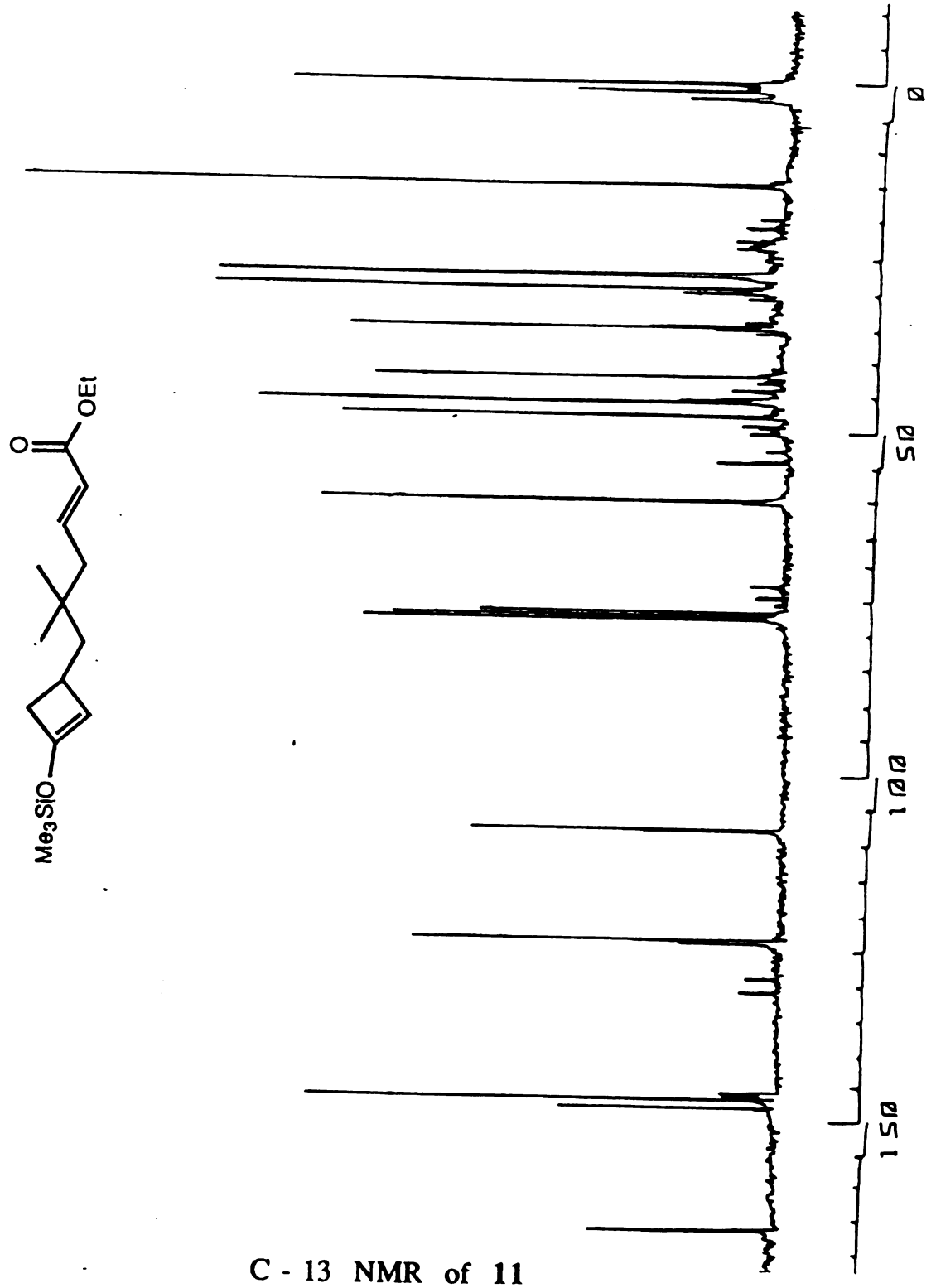
Mass spectrum of TBDMS enol ether of 3



Mass spectrum of 8



Mass spectrum of 6



C - 13 NMR of 11

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