STUDIES TOWARD THE TOTAL SYNTHESIS OF TETRACYCLIC TRITERPENES

By

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ABSTRACT

STUDIES TOWARD THE TOTAL SYSNTHESIS OF TETRACYCLIC TRITERPENES

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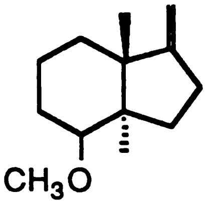
Studies of triterpene side chain synthesis, employing the model compounds **12** and **13**, and lanostane skeleton transformation from compound **18** are presented in two separate parts.



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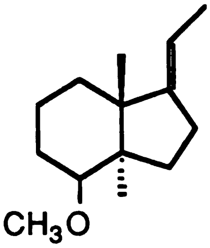

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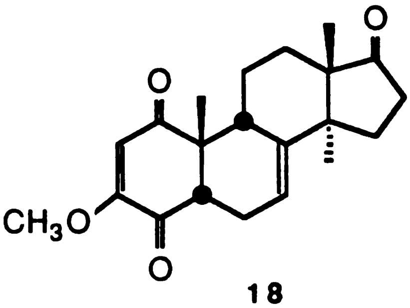
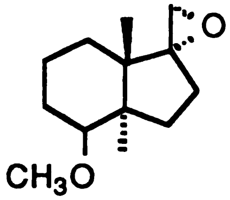


18

Part 1: Oxidation of **12** with m-chloroperbenzoic acid gave epoxides **36a** and **36b**. These compounds proved acid-sensitive, and facile rearrangement to **39** even occurred on treatment with 1-diethylalumino-2,2,6,6-tetramethyl piperidine.[57] Smaller amide bases, such as lithium diethylamide, transformed **36a** to the allylic alcohol **37**, which was subsequently oxidized to enal **38**. Isomeric **36b** was inert toward all the bases tested.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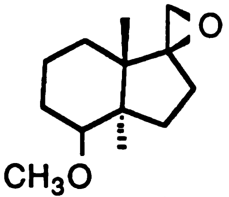
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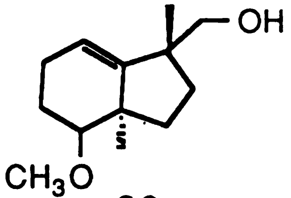
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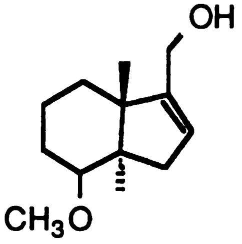
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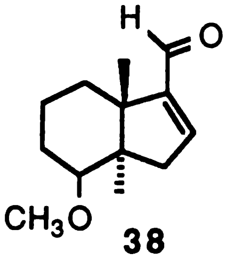
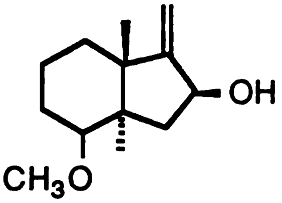

38

Oxidation of **12** with selenium dioxide gave β-alcohol **46**. Borohydride reduction of the corresponding ketone **48** led to the α-epimer **47**. Each allylic alcohol (**46** and **47**) reacted stereospecifically with phenylsulfenyl chloride to give, respectively, diastereoisomeric sulfoxides **53** and **55**. The latter yielded a conjugate base that was methylated selectively to give sulfoxide **56**. Desulfuration of **56** with trimethylphosphite generated the ethylidene α-alcohol **57**, and following PDC oxidation, *E*-enone **66**.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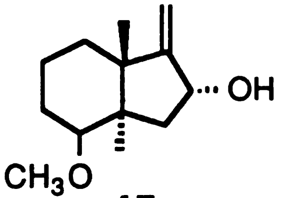
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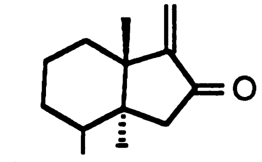
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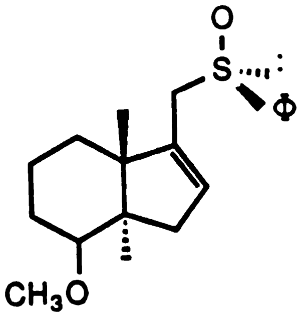
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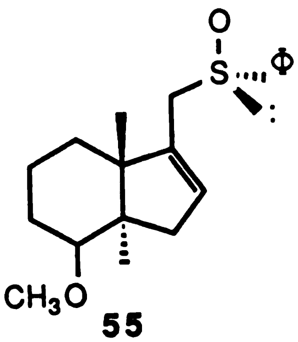
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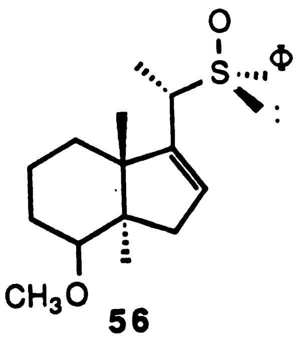
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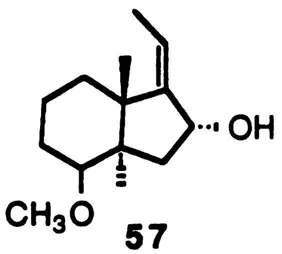
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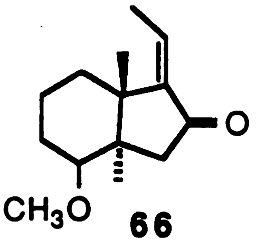
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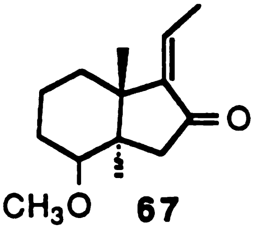
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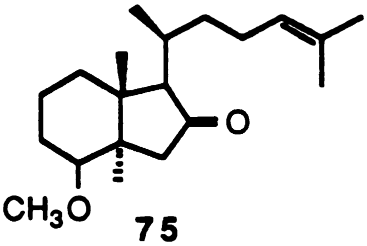
An alternative synthesis, beginning with ethylidene derivative **13**, yielded enone **66** as a minor product. Treatment of **13** with selenium dioxide followed by PDC gave the isomeric *Z*-enone **67** as the major product. Reaction of **67** with lithium bis-4-methyl-3-pentenylcuprate proceeded by facial-selective conjugate addition to give ketone **75**, which on Wolf-Kishner reduction gave the euphane CD-model **17**. The E-isomer **66**, under similar conditions gave only an unresolved mixture.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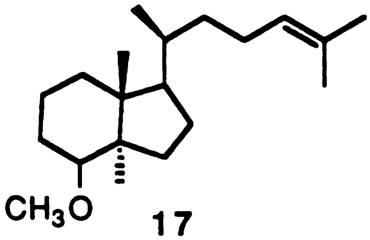
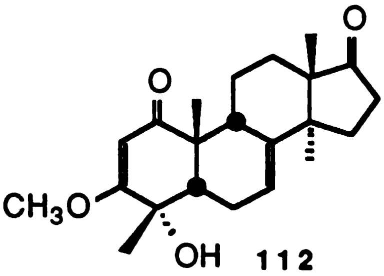

17

Part 2: Methylation of **18** with methyl lithium or the corresponding Grignard reagent yielded adducts **112** and **113**. These alcohols were reduced with DIBAL, followed by hydrolysis, to give **114**, **115**, **116** and **117** which were then oxidized to **118** and **119**.



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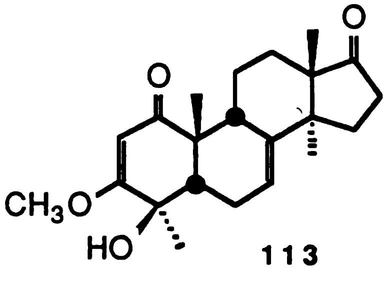

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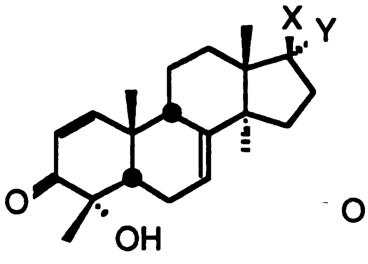
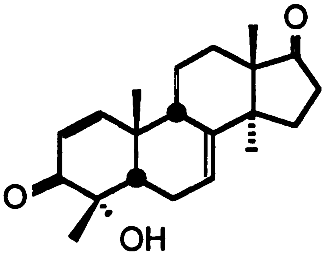


114, x= H , y= OH
115, y= H , x= OH



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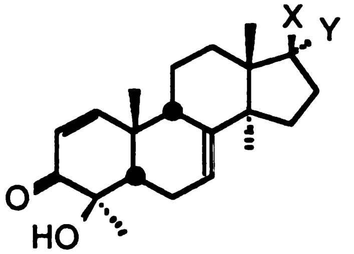
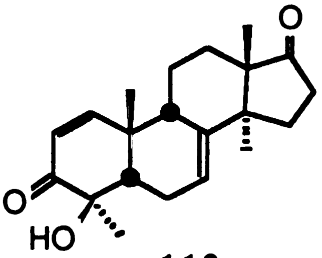
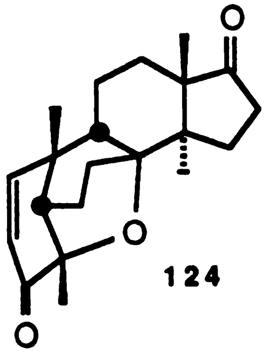


116 , x= H , y= OH
117 , y= H , x= OH



119

Acid-catalyzed dehydration of **118** gave cyclic ether **124**, which was then reduced by lithium in ammonia to **125**. The C-4 epimer **119** gave complex mixtures on dehydration; however, **119** was deoxygenated cleanly with zinc, giving **120** and subsequently **121**. Finally, addition of trimethylsilyl methyl lithium to **18** generated epimers **128** and **129**, which were subsequently transformed to **130**.



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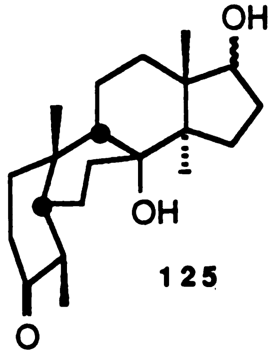

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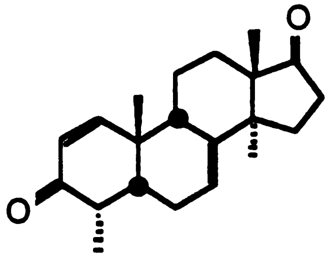

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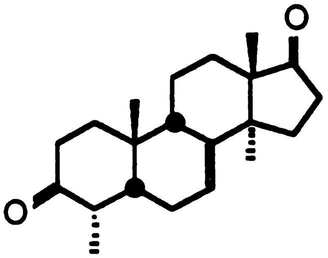

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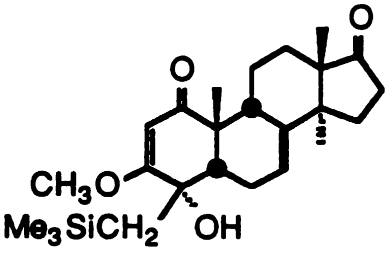

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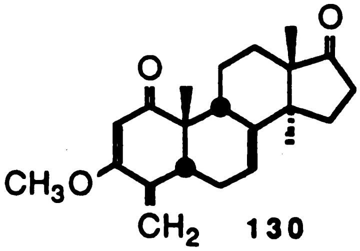

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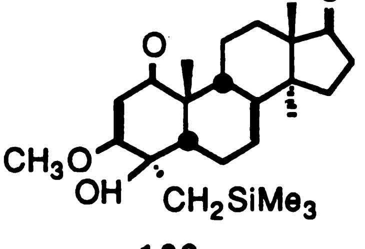

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DEDICATION

This Dissertation Is Dedicated To My Parents

ACKNOWLEDGEMENTS

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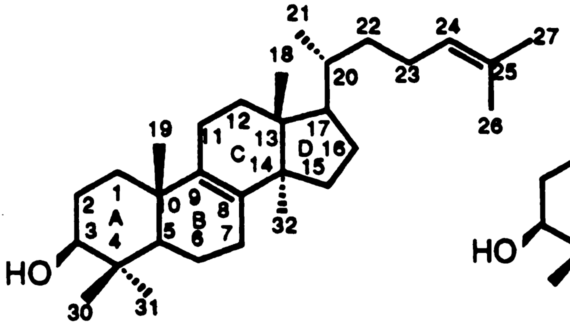
INTRODUCTION

The tetracyclic triterpenes containing 30 carbons and having a common perhydro-cyclopentenphenanthrene skeleton are found widely in nature.[1]



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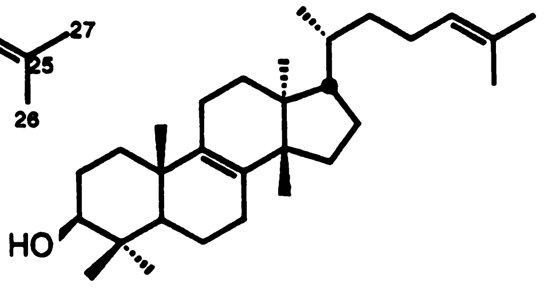
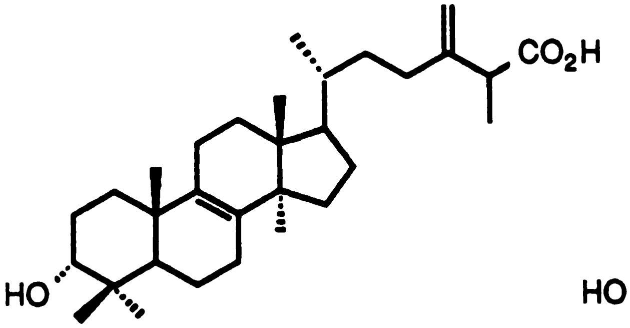
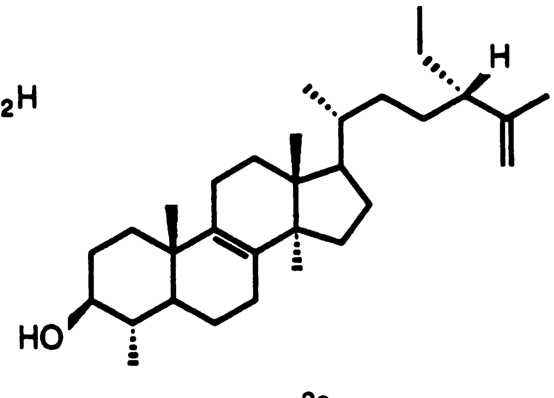


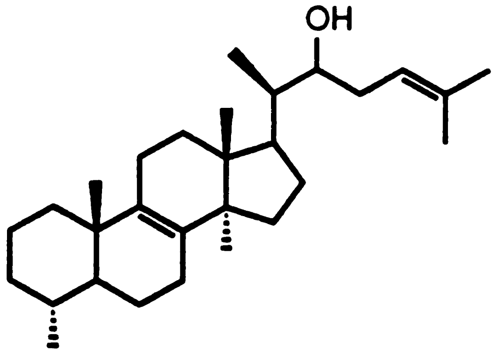
2 , Euphol



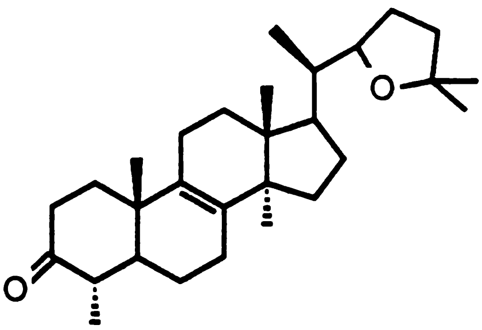
3 ,Polyporenic Acid D[2b]



4a[2a]



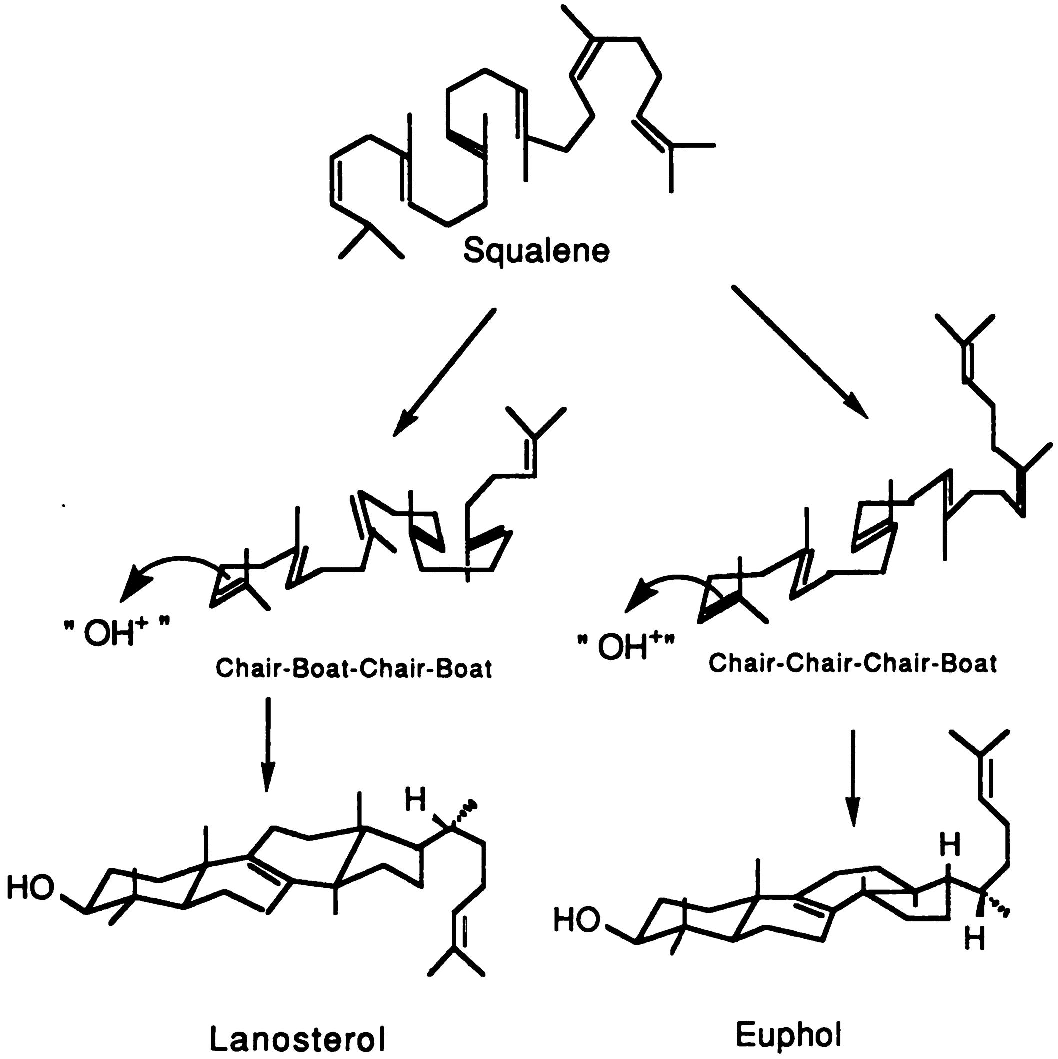
4b ,3-Deoxosenexonol[45a]



4c ,Oxidosenexone[45a]

Two important members of this group are lanosterol and euphol. Lanosterol was isolated from wool wax[3] and euphol from euphorbium resin and several other *Euphoribia* species.[4] More recently, cucurbitacins,[5] an important structurally related group, have been identified.

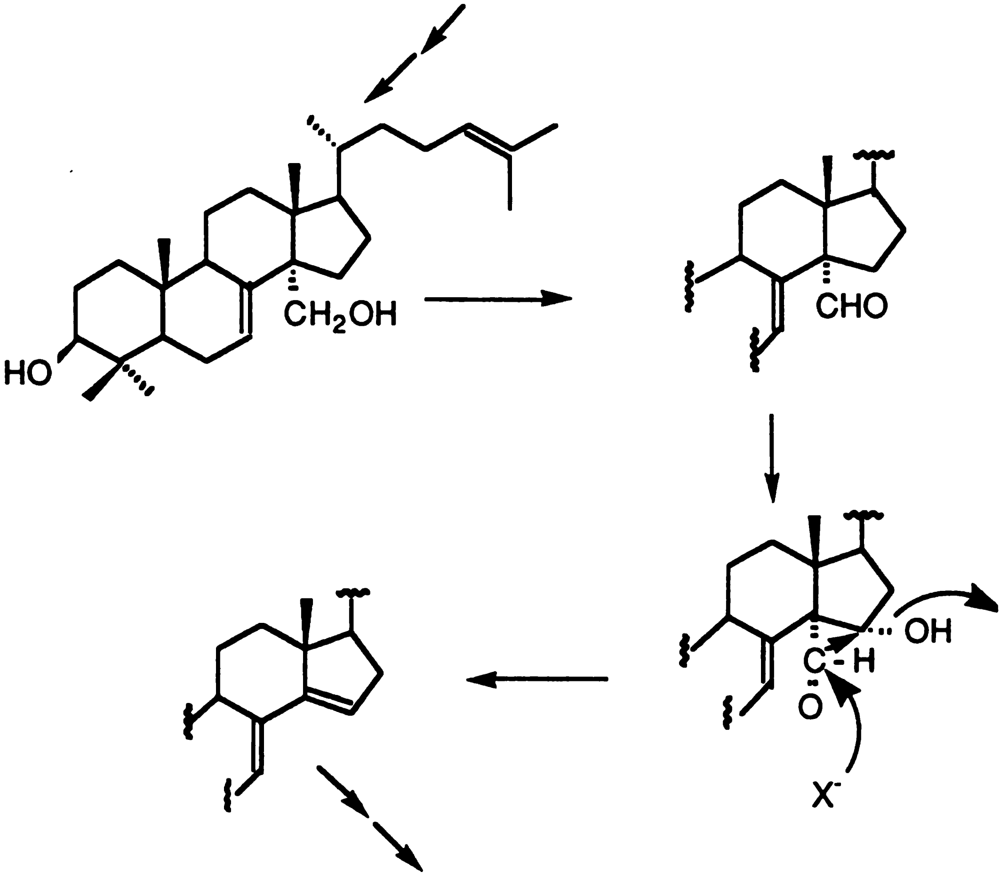
Different tetracyclic triterpenes show cytotoxic, cytostatic, antimicrobial, and herbicidal activity. Numerous lanostane type compounds from *Neamatoloma fasciculare* and *N. membranacea*[6] have demonstrated growth inhibitory properties on young plants. Lanostane bitter principles from mushroom *Ganoderma lucidum*[7] have been used as folk medicine in Asia. Euphane-like compound meliantriol[8] has demonstrated antifeedant properties. Both isocucurbitacin D and 3-epi-isocucurbitacin D, from *Phormium tenax*, show tumor inhibitory properties against KB cell culture.[9] Cucurbitacins from African *Euphorbiaceae*[10] killed HeLa cells, inhibited mitosis in *Allium sativum* meristems and its root growth. Cucurbitacin D and I, isolated from *Purshiatridenta,*[11] inhibited seed germination.



Scheme 1

In living organisms the tetracyclic triterpenes are enzymatically synthesized from squalene. Under physiological conditions, squalene may assume chair-boat-chair folding to give lanosterol or all chair folding to give euphol[12] (Scheme 1). Lanosterol has been shown to lose three methyls to give chlolesterol in biological systems[13,14] (Scheme 2):

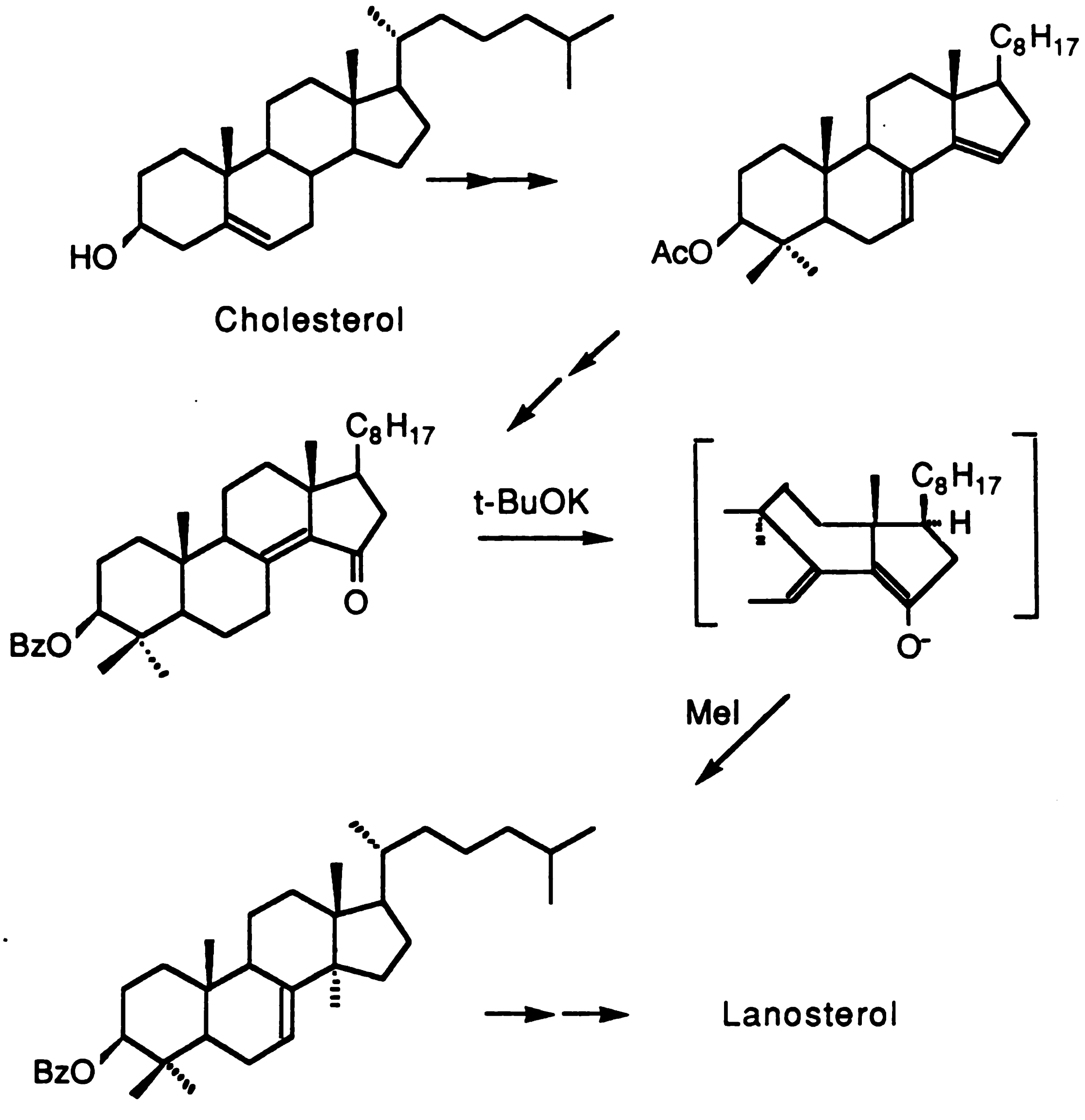
Lanosterol



Cholesterol

Scheme 2

Compared to the vast work in the field of steroid syntheses, few total syntheses of tetracyclic triterpenes have ever been reported. The first total synthesis of a tetracyclic triterpene, specifically lanostenol, was accomplished starting from cholesterol in 1953 by R. B. Woodward *et al.* (Scheme 3).[15]



Scheme 3

A key step in this synthesis is the stereoselective introduction of a methyl group at C-14. This result may be rationalized by considering transition states for electrophilic attack on the enolate. The β-face of ring D is blocked chiefly by the 13β angular methyl group and the side chain. Steric approach control therefore favors approach of the methyl group from the α-face.

A biomimetic acid induced polyene cyclization, work of van Tamelen *et al.*, led to syntheses of lanostenol as well as many other natural products, demonstrating alternative efficient methods for organic synthesis.[16,17]

Over the past 30 years, many new triterpenes have been isolated. About 400 new triterpenes were identified during the period 1977-1981.[18] However, new total syntheses of tetracyclic triterpenes are surprisingly few. For example, J.ApSimon's recent review[19] on progress in triterpene synthesis covering the past 12 years reported no total synthesis of a tetracyclic triterpene! It is possible that the well developed field of steroid chemistry has obscured the necessity of looking at the tetracyclic triterpenes as independent targets.

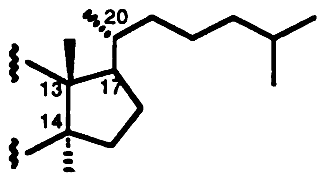
Although existing syntheses such as Woodward's and van Tamelen's serve as good examples, the relatively well known methods and reagents used therein are unlikely to lead to improved new approaches. In particular, van Tamelen's approach is unlikely to be useful for the synthesis of euphanes because of their facile rearrangement to corresponding isoeuphane systems.[20] New general synthetic strategies and reagents are therefore needed to achieve efficient total syntheses of these compounds.

SYNTHETIC STRATEGIES

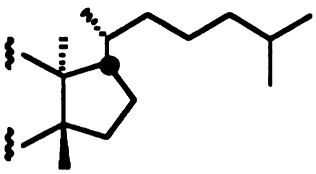
We propose to approach the total synthesis of tetracyclic triterpenes in two stages: 1. Side chain attachment. 2. Construction of the tetracyclic nucleus.

Methods of steroid side chain synthesis have been the subject of study since the 1930's. As more and more biologically active compounds such as ecdysones,[21] various active metabolites of vitamin D,[22] and marine sterols[23] were isolated and characterized, research revealing the relationship between biological activities and side chain structures increased. Therefore, new approaches to side chain synthesis were developed as well. Recent progress in this field has witnessed numerous ingenious designs and novel reagents. Examples included applications of: ene reaction;[24] oxy-Cope,[25] Claisen[26] and Wittig[27] rearrangments; nucleophilic attack at p-allylpalladium complexes;[28] 1,4 additions of organocuprates to conjugated epoxides[29] or conjugated ketones;[30] nucleophilic displacement of tosyl group;[31] Birch reduction of unsaturated ketones[32] and addition of Grignard reagent to side chain epoxides.[33]

It is necessary that any successful side chain synthesis have selective control of configurations at C-17 and C-20. The configurations of C-13, C-14 and C-17 of lanostane have a mirror image relationship with those of euphane. The only difference lies at C-20. Therefore, controlled syntheses of C-20 epimers will give either lanostane side chains or euphane side chains.

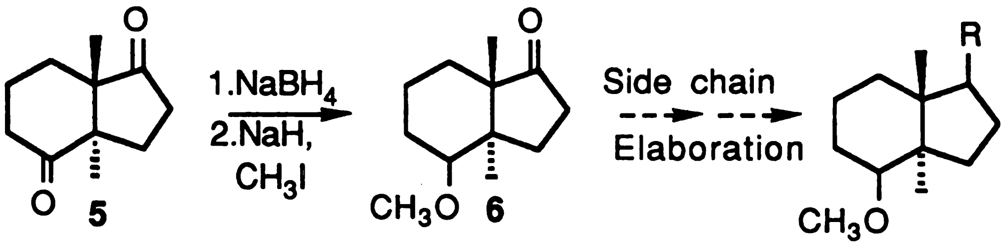


Lanostane system



Euphane system

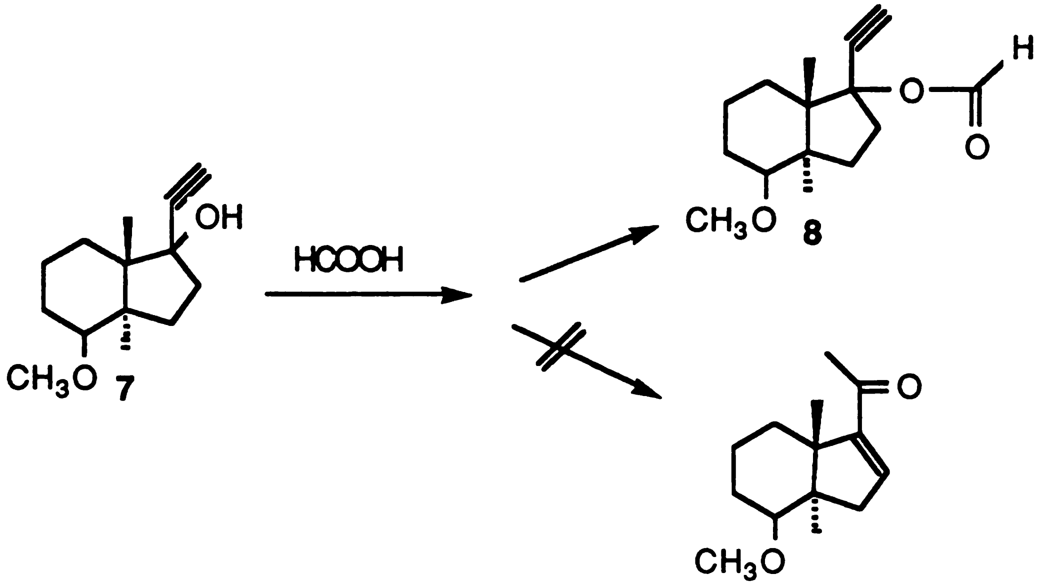
Since side chain synthesis involves reactions on ring D, at sites relatively remote to rings A and B, it is reasonable to assume that the influences to these rings (A and B) is quite small. In other words, it should be possible to use a bicyclic C,D ring model as a substrate to test new methods of the side chain synthesis. In practice, our studies were carried out on compound **6** which was made from compound **5** (as shown in Scheme 4).[34]



Scheme 4

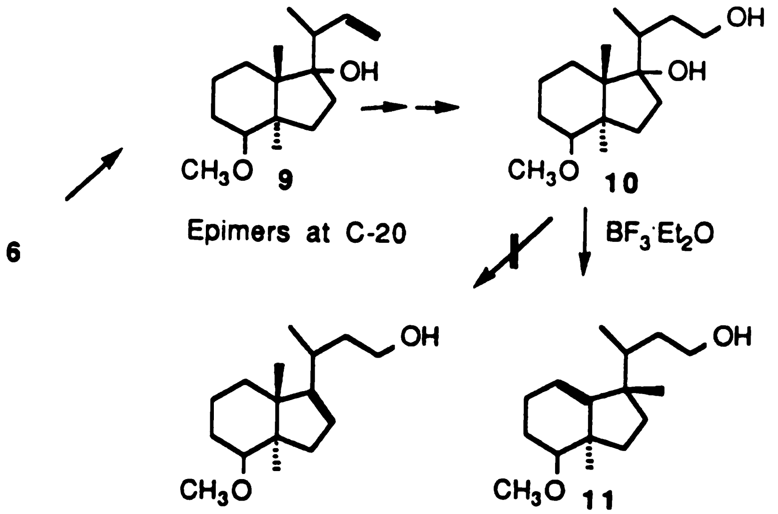
As a model compound, **6** has obvious advantages. Both angular methyl groups are in place and a ketone group at C-17 (triterpene numbering system)[35] is available for side chain development. Though steroidal 17-ketones have been favorite starting materials for many side chain constructions, the use of triterpene counterparts (with a 14α angular methyl group in place) has been explored little. The presence of 14-angular methyl group blocks the α-face of ring D; as a result, methods for the syntheses of steroid side chains become less predictable when applied to our model system.

A preliminary examination of model **6** for side chain synthesis was first conducted by Dr. J. L. Martin[34]. The five membered ketone function was found to be unreactive toward a variety of nucleophiles, such as stabilized ylides, enolates and common organometallic reagents. This behavior was in part due to facile enolization of the ketone by strong bases. Sodium acetylide reacted with **6** to give the acetylide adduct **7**, but treatment of **7** with formic acid failed to effect a Rupe rearrangement[36] as expected from a recorded steroid side chain synthesis.[37] Alkynyl ester **8** was obtained instead (Scheme 5):



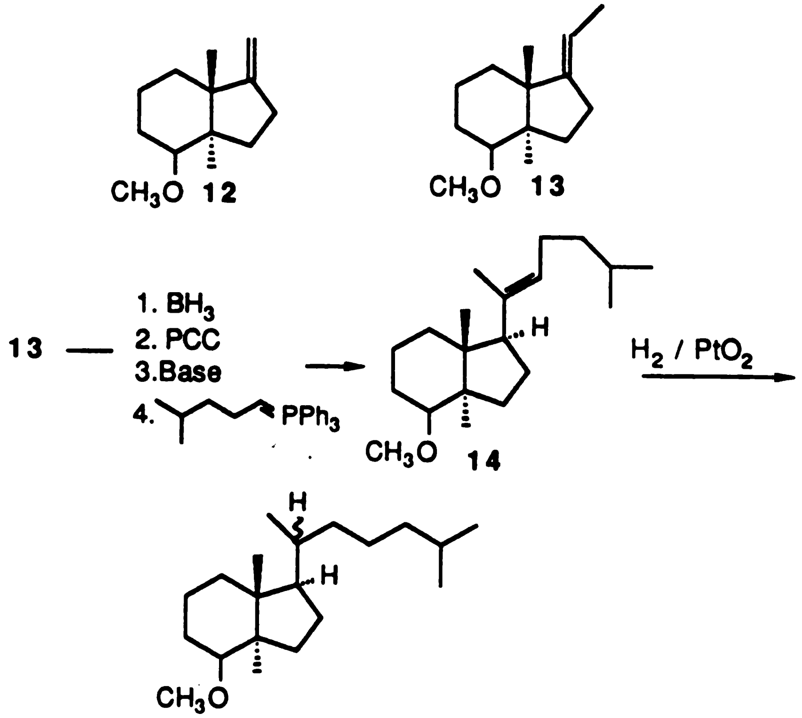
Scheme 5

Another useful reaction was the addition of crotyl magnesium bromide to methoxy ketone **6**. A cyclic transition state involving metal-oxygen coordination is known[38] to facilitate allylic additions. Unfortunately, Lewis acid induced dehydration of **10**, derived from **9**, caused rearrangement to the undesired compound **11** (Scheme 6):[39]



Scheme 6

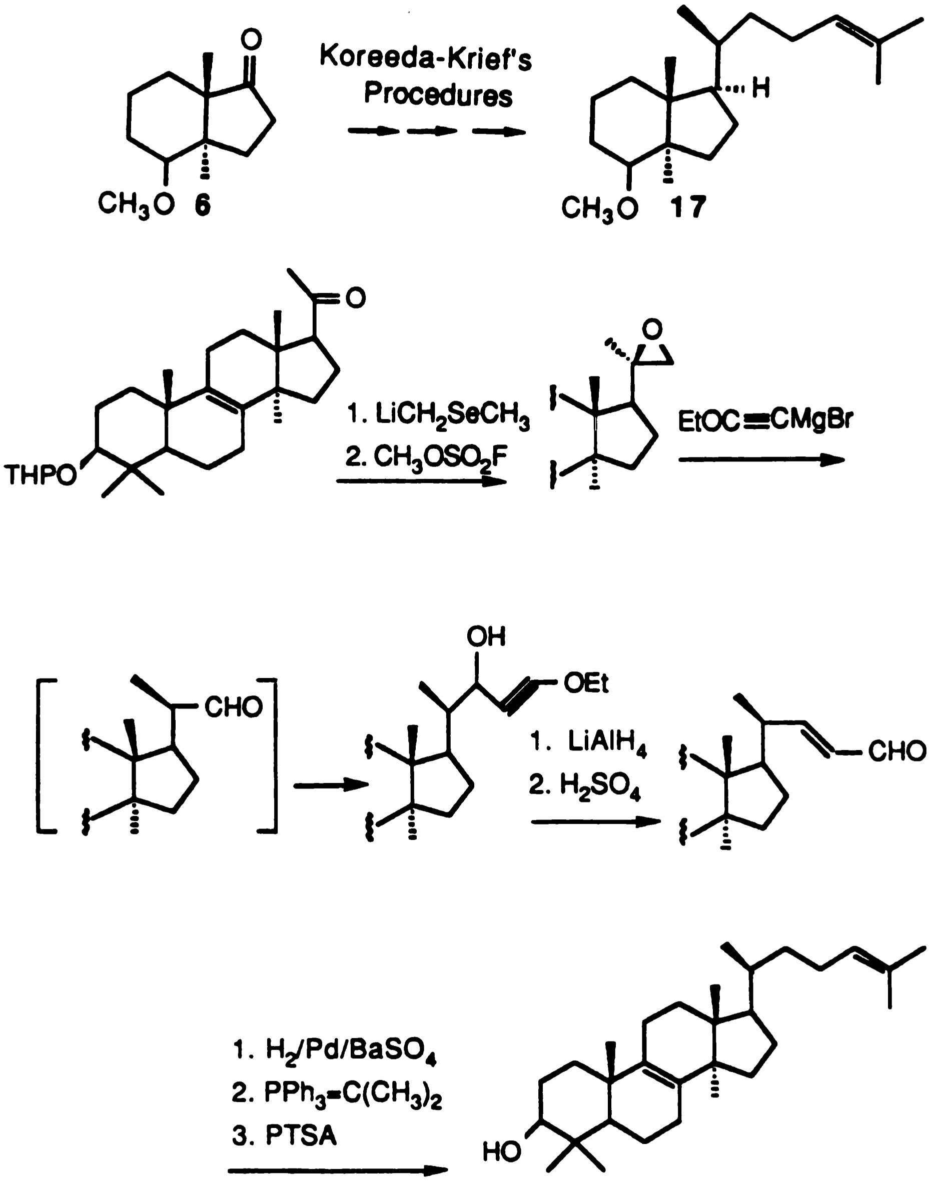
Further studies were carried out by Dr. J. R. Gibson.[39] Reaction of **6** with unstabilized phosphorylidene ylides gave olefins **12** and **13**. Starting from **13**, compound **14** was obtained through a four step sequence (Scheme 7). When **14** was catalytically hydrogenated, a mixture of C-20 epimers (**15** and **16**) was formed, in agreement with examples in steroid side chain synthesis.[40]



15 and **16** Epimers (1:1) at C-20

Scheme 7

More recently, Krief *et al.*[33] used 17-keto steroids and lanostanes as starting materials to demonstrate stereoselective side chain synthesis in which reaction of Grignard reagents with the 20, 22-epoxides of a 17β-isopropenyl derivative was a key step. When the same sequence was carried out on the model compound **6** by Dr. H. Ok[41] in our laboratory, the euphane like side chain substituted derivative **17** was obtained in good yield (Scheme 8).

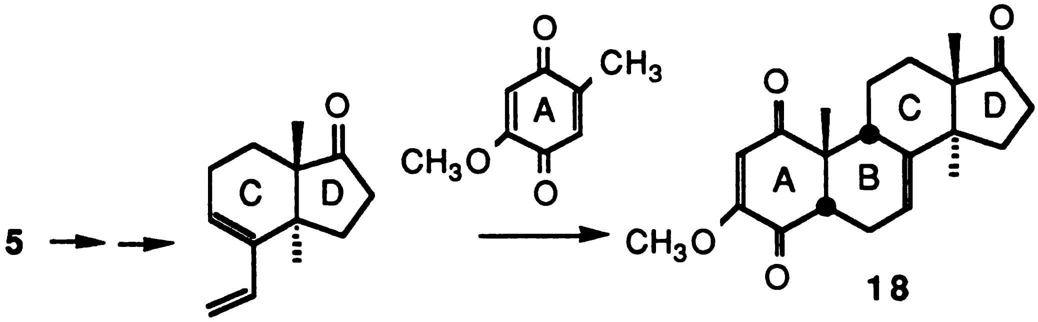


Scheme 8

In our approach to side chain synthesis, we proposed to introduce functionality at C-16 concurrent with side chain construction. Many naturally occurring triterpenes, such as tumulosic acid, echinodol, kulinone, and holotoxin, have hydroxyl or carbonyl groups at this site.[42] Birch reduction of 16-keto-17-ethylidene derivative by Djerassi *et al.*,[32] and oxy-Cope rearrangement conducted by Koreeda *et al.*[29] provided examples of such syntheses. Recent work[30] by Trost and Schmuff has established the usefulness of C-16 functionality in facilitating steroid side chain synthesis.

In this dissertation, our exploration of sulfenate-sulfoxide rearrangements in side chain synthesis will be highlighted. Base induced epoxide ring opening and 1, 4-addition of organocuprates[26a] to an *exo* enone derived from **13** will also be discussed.

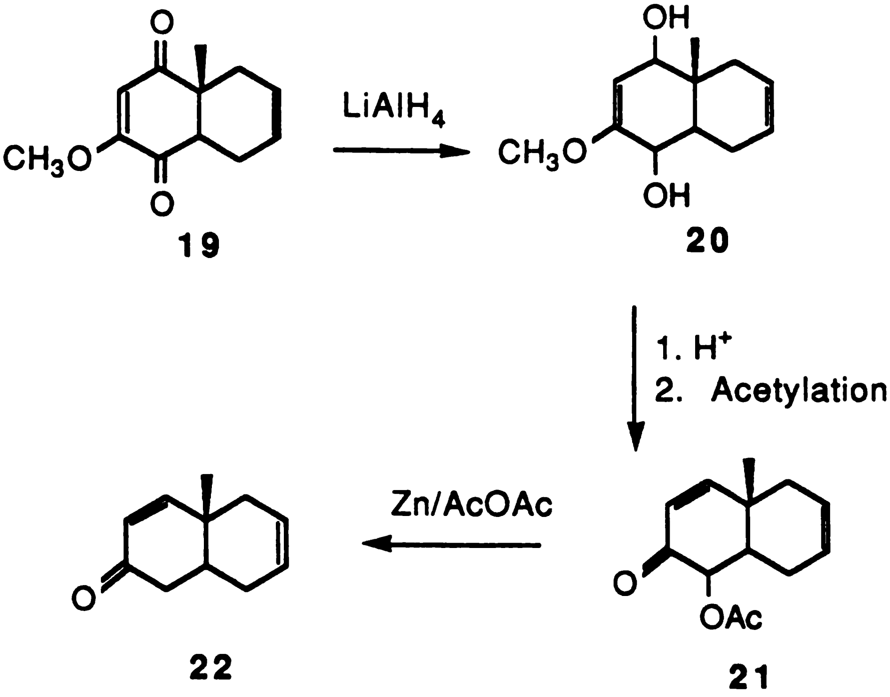
A second concern of this research program is construction of the tetracyclic framework. A large number of such examples can be found in the field of steroid synthesis. More than a dozen approaches[43] are available. A synthesis[43] of tetracyclic compound **18** from bicyclic compound **6**, using Diels-Alder cycloaddition (CD--ABCD, Scheme 9), provided an attractive intermediate for lanostane total synthesis.



Scheme 9

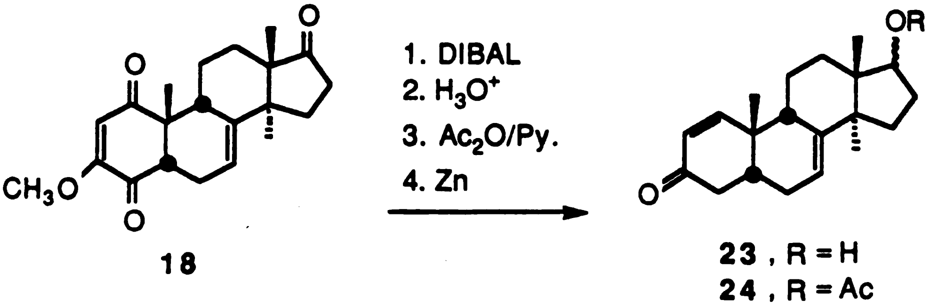
A comparison of compound **18** with possible target molecules, such as senexonol[45] and lanosterol, identifies the tasks remaining in such syntheses. These are outlined below: 1. Functional group in ring A should be reduced and altered; 2. Methyl group (s) should be introduced to C-4; and 3. Configurations at C-5 and C-9 should be adjusted. With strong reducing agents such as lithium aluminum hydride (LAH) or diisobutyl aluminum hydride (DIBAL), all the ketone groups in **18** (two ketones in ring A and one ketone in ring D) will be reduced. Selective reduction at C-4 can also be achieved, since the 4-ketone group is more reactive than the 1- and 17-ketone groups (ester like ketone and five membered ketone[46] respectively).

The reduction with strong reducing agent, lithium aluminum hydride, of a bicyclic compound, equivalent to rings A and B of model compound **18**, was precedent. In their cholesterol synthesis,[47] R. B. Woodward *et al.* exhaustively reduced the bicyclic enedione system **19** to a diol, which on acidic hydrolysis yielded the 4-acetoxyl enone **21**. Cleavage of the acetoxyl group in **21** by zinc in acetic anhydride, led to formation of enone **22** (Scheme 10). Woodward's method efficiently reduced ring A functionality, yet still reserved some important functional group such as 3-ketone for further synthetic development in ring A.



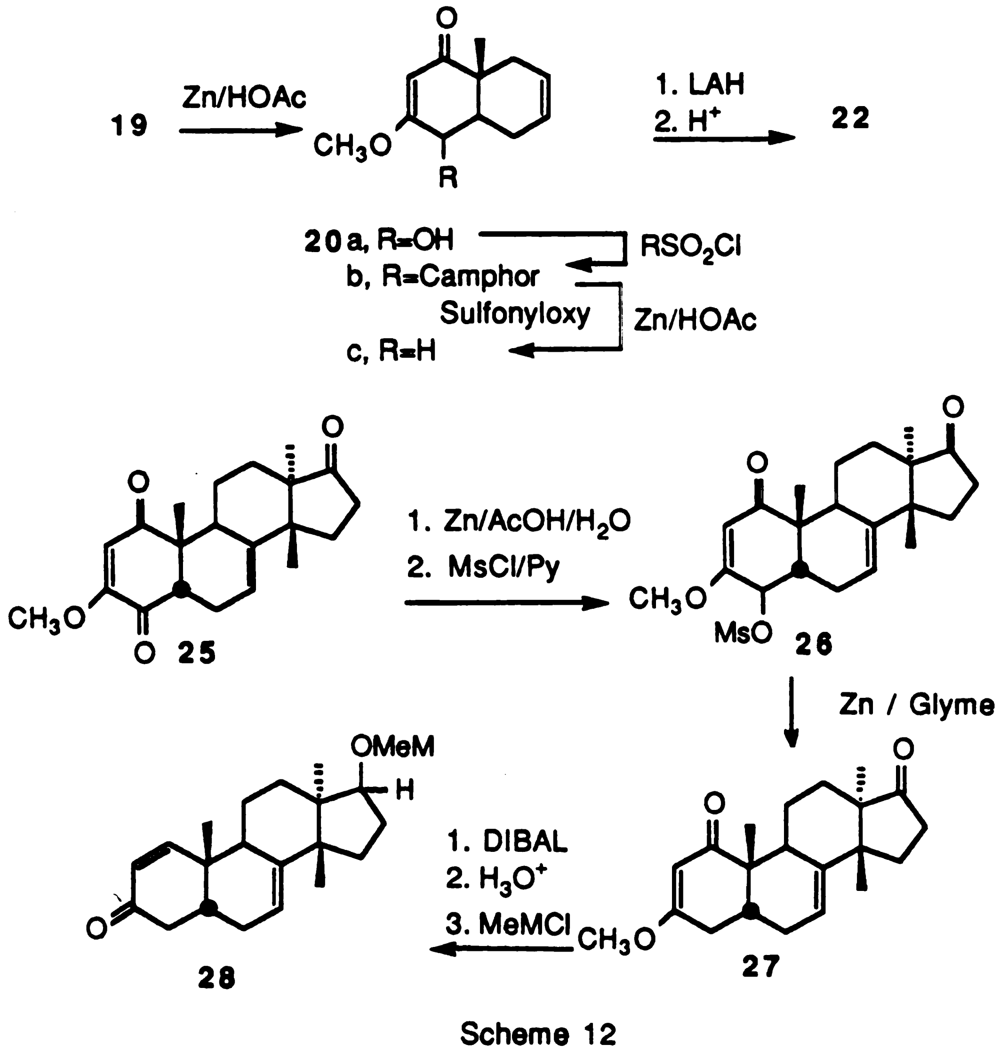
Scheme 10

On the basis of their structural resemblance, Dr. W. Munslow[48] carried out the same sequence of reactions on **18**, using similar reagents. As expected, compound **23** and **24** were obtained, but in a low overall yield (Scheme 11).



Scheme 11

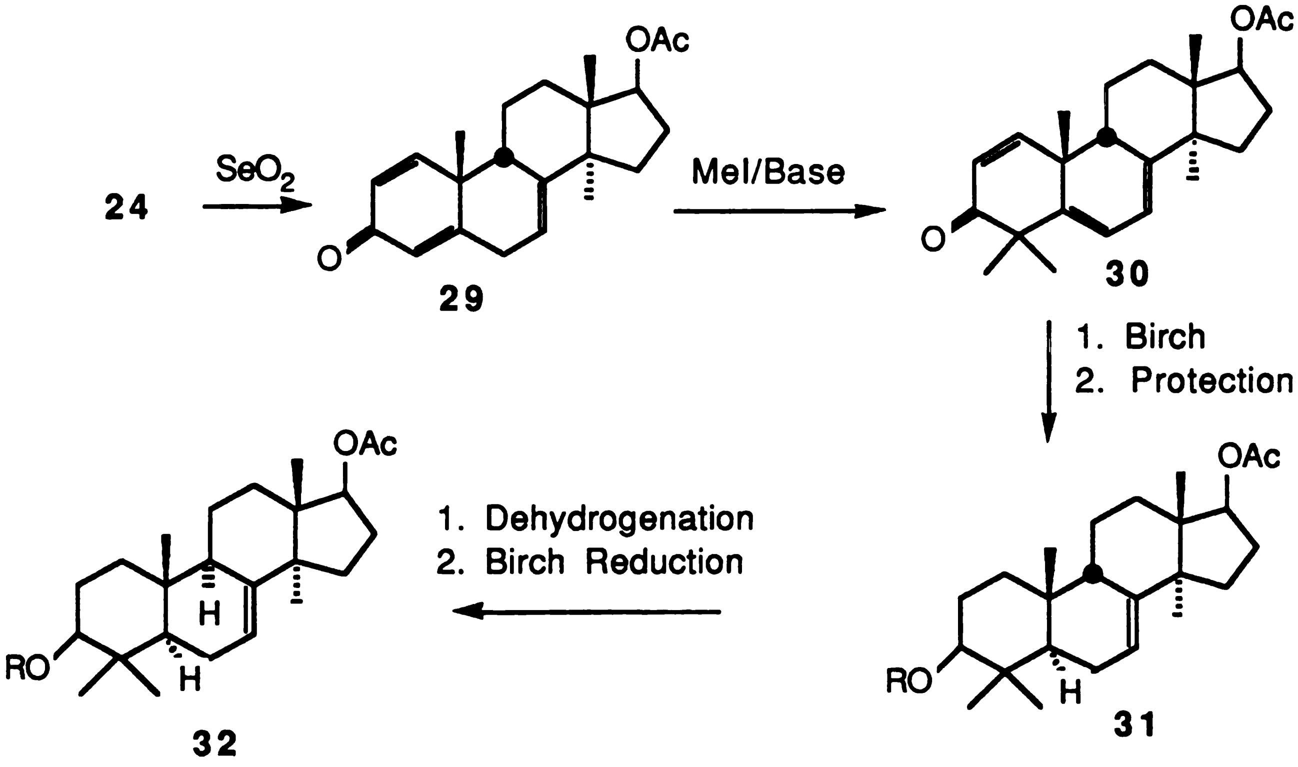
Related to the work of Woodward *et al.* was a modification reported by Speziale *et al.*,[49]in which a 1-hydroxy-4-keto-2-methoxy-10-methyl-Δ2,6-hexahydronaphthalene **20a** was prepared first, by zinc reduction of the same starting bicyclic compound **19** in acetic acid. From alcohol **20a**, a camphor-10-sulfonyl derivative **20b** was made, which, after cleavage of the camphor sulfonyloxy group with zinc and subsequent LAH reduction gave **22** in 55-60 % overall yield. Indeed, Dr. L. Kolaczkowski's 5-epi-euphol synthesis[44] demonstrated a successful application of this method to system **25** (different from **18** only in the relative configurations of the A, B and C, D ring fusions) to give **28** in good yield (Scheme 12):



Scheme 12

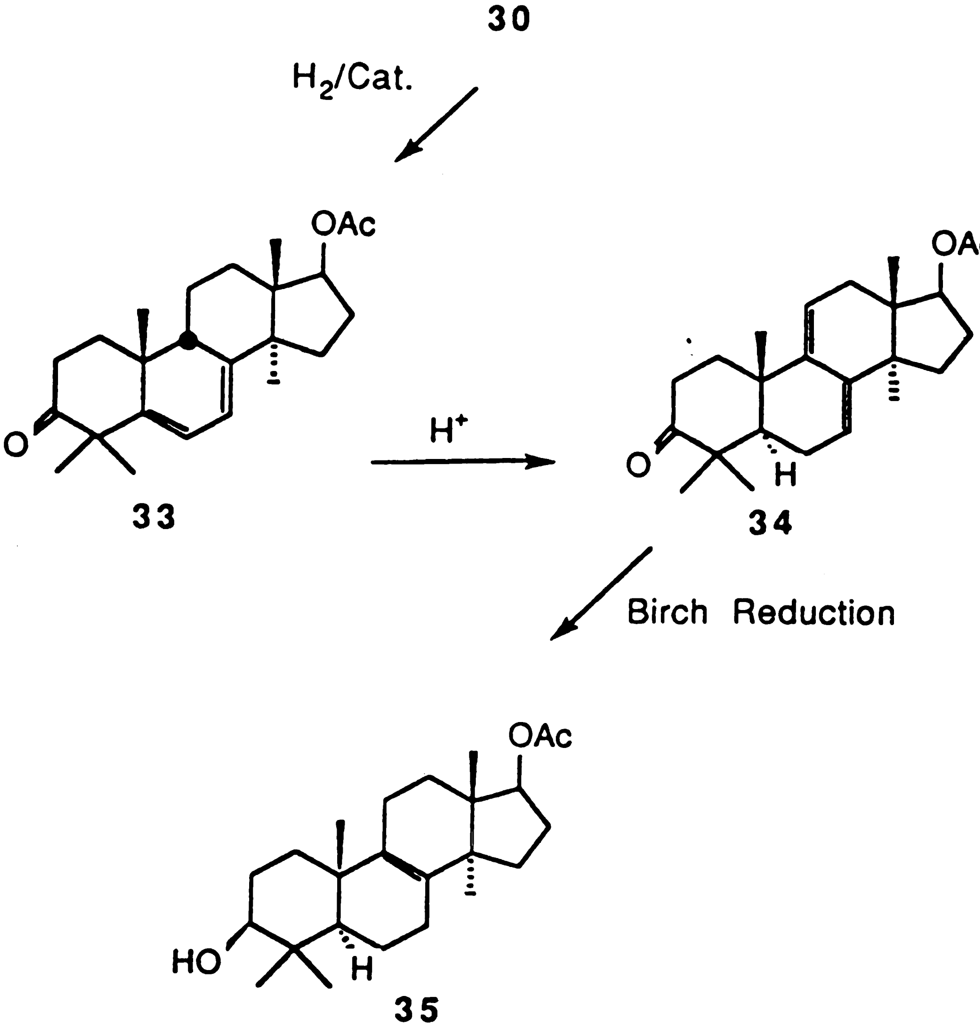
This result suggests that Speziale's stepwise reduction procedure may provide a cure for the poor yield encountered when **23** was prepared previously. We predicted that the difference between compounds **18** and **25** in ring junctions should not seriously alter the chemistry at ring A.

If **24** could be obtained in good yield, Woodward's[15] and Klyne's[50] C-4 methylation methods, illustrated for lanosterol in the former work, should give the homoannular diene **30**. The derivative **31**, after mercury salt catalyzed dehydrogenation and Birch reduction, would give compound **32** (see Scheme 13).



Scheme 13

Alternatively after catalytic hydrogenation of **30**,[51] acid induced double bond migration[52] of **33** would give **34** (with proton at C-5 presumably being α), which after Birch reduction, should generate **35** as final product (Scheme 14).



Scheme 14

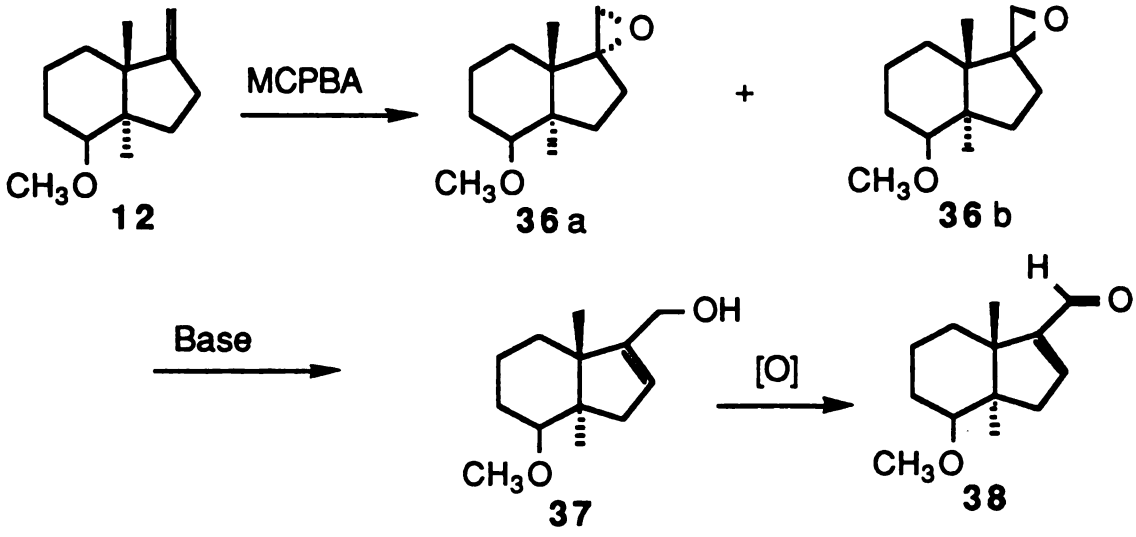
In the second part of the dissertation, the tests of the available methods to reduce ring A functionality of compound **18** will be described. In fact, selective methyl group introduction at C-4 may be achieved[53] prior to the reduction of compound **18**. Our study of methylation at C-4, featuring addition of organometallic reagents or Peterson olefination will also be discussed.

RESULTS AND DISCUSSION

PART 1. STUDIES AND SYNTHESIS OF TRITERPENE SIDE CHAINS ON A MODEL SYSTEM

1.1 Base-Induced Epoxide Ring Opening as an Approach to Side Chain Synthesis

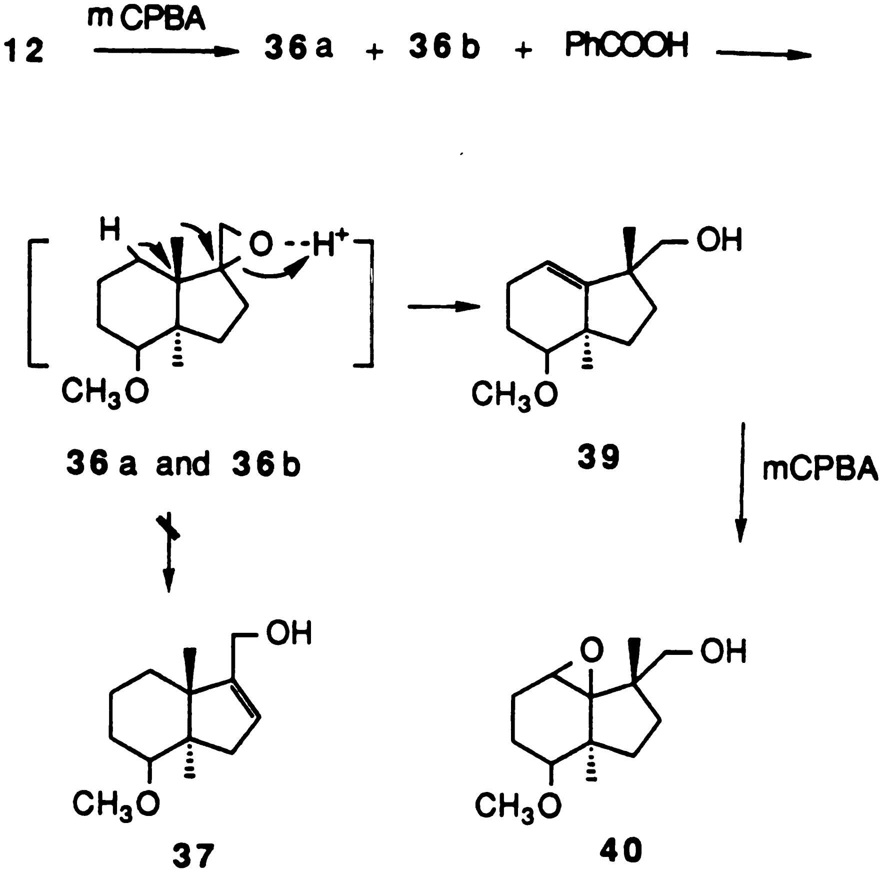
The first goal in our investigation was the preparation of compound **38**, a potentially useful intermediate for side chain attachment. An efficient plan for the synthesis of **37** and its derived aldehyde is shown in Scheme 15 :



Scheme 15

Since the angular methyl groups in compound **12** block both sides of ring D,[35] we anticipate that a mixture of two epoxides, **36a** and **36b**, would be obtained in epoxidation. This lack of facial discrimination contrasts with steroid analogues, which react chiefly at the α-face. The subsequent base treatment should convert both epoxides to alcohol **37**. Finally, controlled oxidation of this alcohol with pyridinium dichromate (PDC)[54] would generate the desired aldehyde **38.**

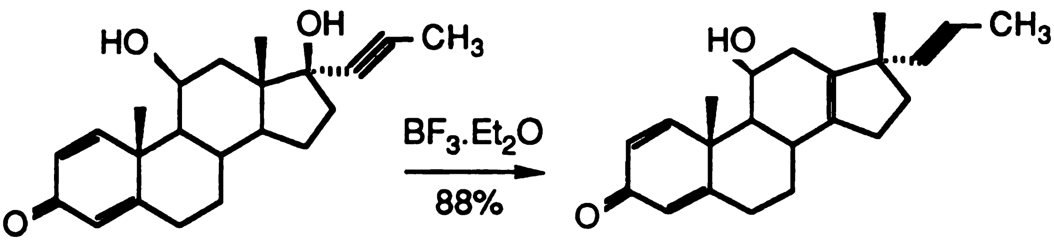
In the event, epoxidation of **12** was first attempted with m-chloroperbenzoic acid (*m*CPBA) in methylene chloride solution. The resulting white crystalline product **40** displayed only one epoxide proton signal in its proton NMR spectrum, in contradiction to **36** for which two epoxy protons should be observed. Furthermore, the mass spectrum gave a molecular ion at 226, suggesting that the initially formed epoxide might have rearranged into an alcohol which was further oxidized. A possible mechanism is shown in Scheme 16 to account for the formation of compound **40**:



Scheme 16

Accordingly, epoxidation of **12** generated the expected epoxide, **36**, as the initial product, and the latter on exposure to m-chlorobenzoic acid (released from *m*CPBA) underwent ring opening. During the ring opening step, a positive charge gradually developed at C-17,[35] inducing the angular methyl group at C-13 to migrate. The rearranged compound **39** was then oxidized by excess peracid to give compound **40**. This rationale was supported by a control experiment in which an authentic sample of **36** (its synthesis will be described latter) was treated with boron trifluoride etherate ($BF_3 \cdot Et_2O$) or p-toluene sulfonic acid (*p*TSA) to yield **39**, which was subsequently epoxidized into **40**. The possibility that compound **37** was also formed in these reactions was eliminated by examination of the crude proton NMR spectrum.

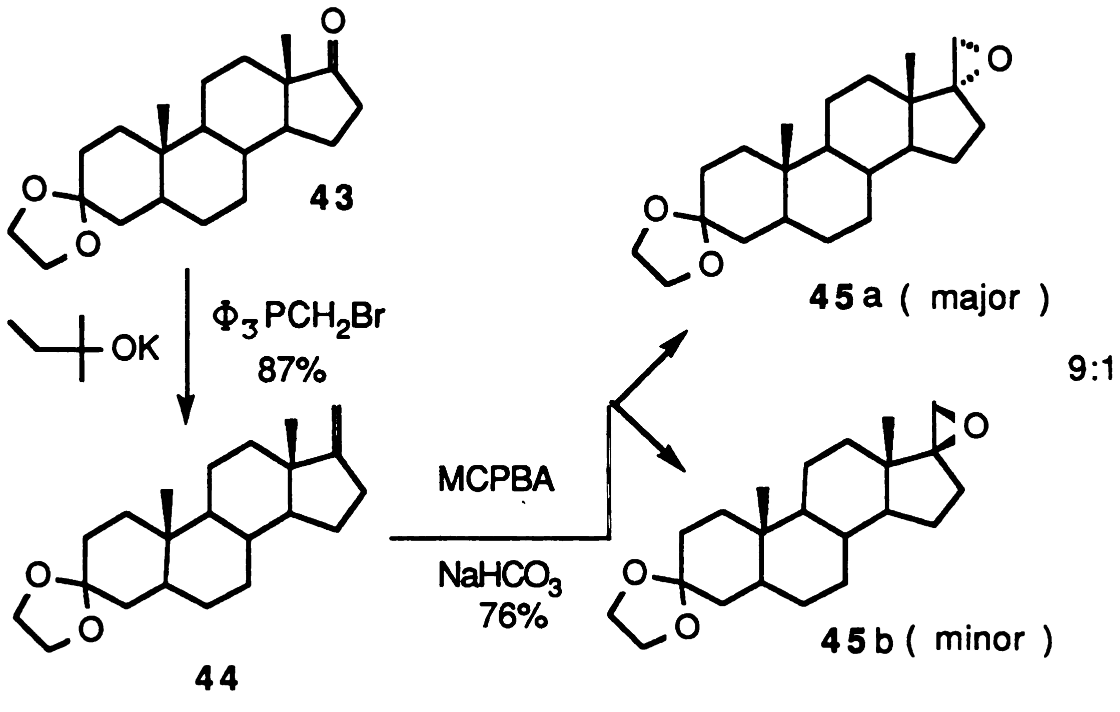
Such acid-induced angular methyl group migration has been also reported by others.[39,55] Thus treatment of alcohol **10** with BF_3 etherate gave **11** (see page 10), and similar treatment of 11β,17β-dihydroxy-17α-propynyl-androstan-1,4-dien-3-one (**41**) with a Lewis acid gave the rearranged compound **42** (Eq. 1).



41 **42**

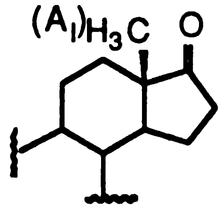
Eq. 1

More suitable epoxidation conditions were then sought. Concurrent use of a buffer during the reaction seemed advisable in order to keep the reaction system slightly basic. The two-phase system (methylene chloride / aqueous sodium bicarbonate) reported by Anderson and Veygeslu^{56} was employed, since this procedure had been successful in preparing epoxides which would otherwise decompose. Indeed, when this procedure was carried out on **12**, epoxides **36a** and **36b** were obtained in 85% yield without contamination with rearranged products. As expected, the ratio of **36a** and **36b** was 1:1. As a comparison, the same epoxidation reaction with steroid **44** gave epoxide **45a** in eight-fold excess over its isomer **45b** (Scheme 17):

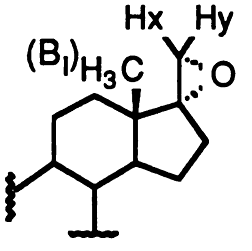


Scheme 17

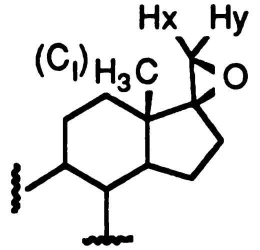
The structural assignments of epoxides **36a** and **36b** were made from their proton NMR spectra by comparisons with known compounds such as **43** and **6**. Angular methyl groups (A_I and A_{II}) in the model system (**6**) and steroid analog (**43**) provided reference NMR signals against which signals from methyls B_I and B_{II} (in **45a** and **36a** respectively) and methyls C_I and C_{II} (in **45b** and **36b**) could be measured.



43

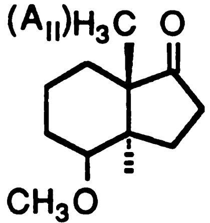


45a

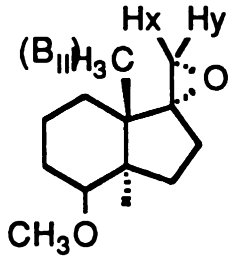


45b

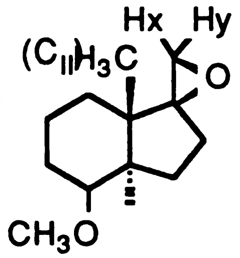
Series I



6



36a



36b

Series II

The molecules in series I and II, with equivalent configurations at C-17 and C-20 (e.g.α-epoxides **45a** and **36a**), should display a similar difference in the chemical shifts of their angular methyl groups relative to those of the reference molecules (**43** and **6**). In other words, the chemical shift difference between **45a** and **43** ($\delta_{BI}-\delta_{AI}$) should be similar to that between **36a** and **6** ($\delta_{BII}-\delta_{AII}$). This correlation should also hold for $\delta_{CI}-\delta_{AI}$ and $\delta_{CII}-\delta_{AII}$.

Furthermore, the chemical shift differences of the epoxide ring protons (i.e., the C-20 protons) can also be used to identified the configurations (α or β) of these epoxides. Since the structures and corresponding NMR spectra of compounds **43**, **45a**, **45b** and **6** are known, we can therefore assign structures for **36a** and **36b** (see Tables 1a and 1b).

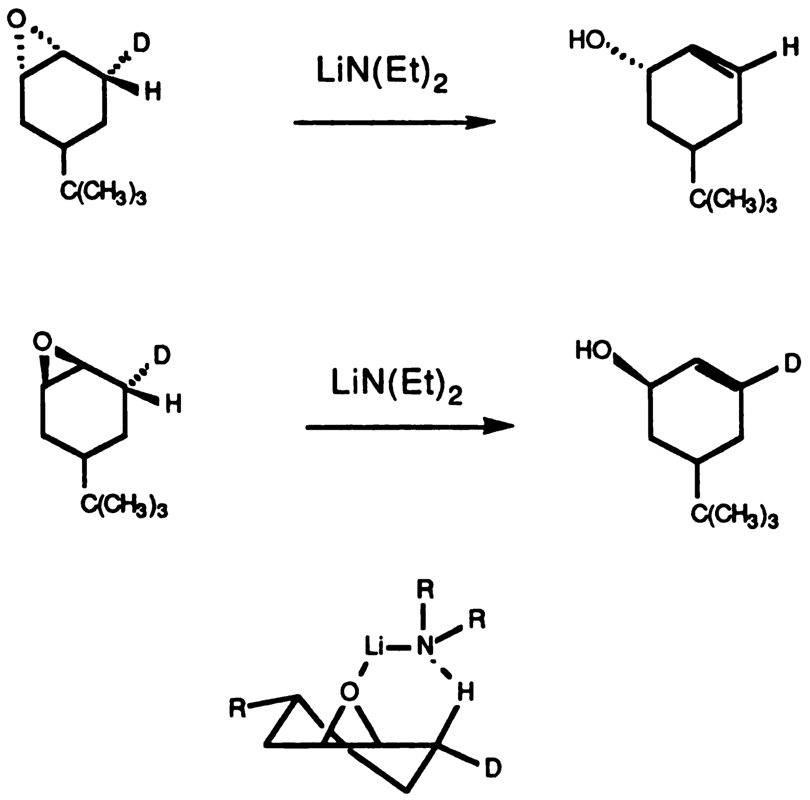
Table 1a Chemical Shifts of Angular Methyl Groups in Selected Steroids and Model Compounds

	δ_A	δ_B	δ_C	$\delta_A - \delta_B$	$\delta_A - \delta_C$
Steroids (Series 1)	0.855	0.815	0.880	0.040	-0.025
Triterpene Models (Series 2)	1.150	1.113	1.200	0.037	-0.050

Table 1b Chemical Shifts of Epoxide Protons in Selected Steroids and Model Compounds

	α Epoxide			β Epoxide		
	δx	δy	δ (x-y)	δx	δy	δ (x-y)
Steroids (Series 1)	2.731 (d,j=5)	2.659 (d,j=5)	0.072	2.895 (d,j=5)	2.595 (d,j=5)	0.300
Triterpene Models (Series 2)	2.635 (d,j=5)	2.560 (d,j=5)	0.073	2.870 (d,j=5)	2.650 (d,j=5)	0.220

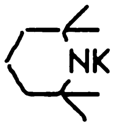
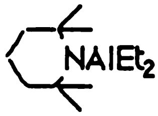
Having obtained the desired epoxides **36a** and **36b** in good yield, we next examined their base induced rearrangement. Such reactions have been widely studied in recent years. A mechanistic study,[57] using an isotope labeled substrate, showed that the proton *syn* to the epoxy ring was selectively removed by base through a cyclic transition state (Scheme 18). This so-called *syn* mechanism is also followed, to some degree, by other reactions such as base eliminations of 4-butyl hexyl trimethyl ammonium chloride and 1-butyl hexyl toluene-p-sulfonate.[58]



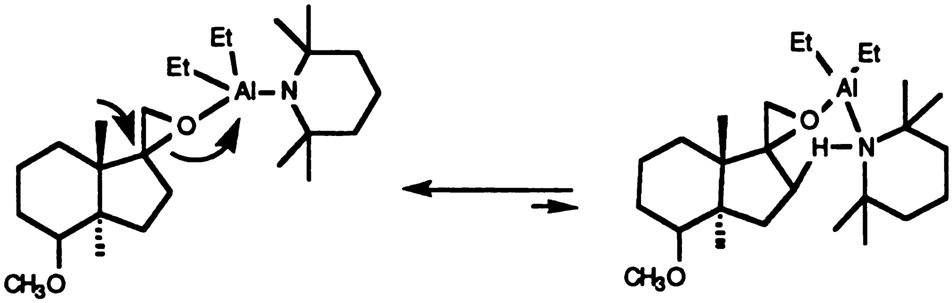
Scheme 18

In the present study, the epoxide mixture (**36a** and **36b**) was used directly, since further chromatographic purification of this mixture caused extensive rearrangement. A number of conditions were tested to effect these rearrangements, and the results are listed in Table 2:

Table2 Base Induced Epoxide Ring Opening

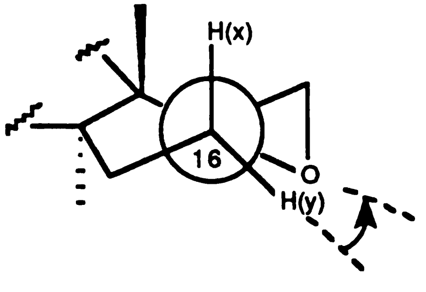
Run	Base	C°	h	Result		
1	LDA/Ether	40	31	Starting Materials		
2	LDA/Dioxane	45	38			
3	LDA/THF	-75	8			
4	LDA/HMPA	45	38			
5	t-BuOK/t-BuOH	83	96			
6	t-BuLi/THF	-78	20			
7	$^{-}CH_2SOCH_3$ DMSO	43	41	Unknown Mixtures		
8		—	—	Starting Materials		
9		0	6.5	**39** + Other Compounds		
				36a	**36b**	**37**
10	Et_2NLi/Et_2O	40	10	10%	50%	40%
11	Me_2NLi Et_2O	0	13	0%	50%	50%
12	Me_2NLi/Et_2O /MeI	40	25	0%	50%	50%

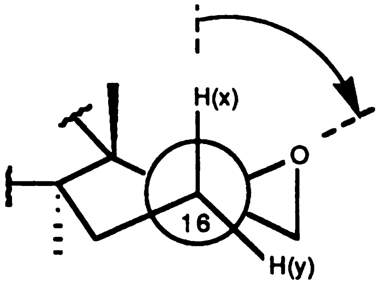
Most bases failed to open the epoxide ring of either **36a** or **36b** under various conditions (elevated temperature, extended reaction time, coordinating or non-coordinating solvents), and the starting materials were fully recovered. Entry 9 is an interesting case. It was originally thought that Yamamoto's reagent[59] might be the reagent of choice because of its dual function. The aluminum would coordinate with the oxygen atom of the epoxide ring, thus weakening the O-C bond. At the same time, the piperidide base would serve to abstract an α-proton.

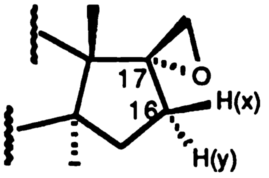


The formation of compound **39** from reactions with Yamamoto reagent indicated that this reagent was indeed a Lewis acid. The cyclic mechanism suggested above for the direct elimination might be destabilized by steric hindrance involving the bulky piperidide group. Consequently, rearrangement dominated.

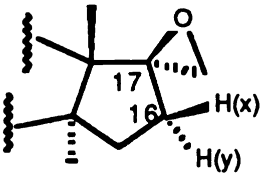
Having realized that steric hindrance was a major problem, we began to search for smaller bases. When **36a** and **36b** were treated with lithium diethylamide in refluxing ether, some of the expected allylic alcohol **37** was formed. Encouraged by this result, we then examined a smaller base--lithium dimethylamide. Unfortunately, only a slight improvement was realized. Added lithium salts did not change the product ratio (run 12). It was interesting that only **36a** rearranged, **36b** remained unchanged.







36a



36b

According to previous discussions, the base induced epoxide eliminative opening follows a *syn* mechanism. In compound **36a**, H (y) is *syn* to the epoxide oxygen, and the dihedral angle < H (y)-C(16)-C(17)-O is rather small (about 0° by a Molecular Mechanics calculation[58]). On the other hand, in compound **36b**, H (x) is *syn* to the epoxide, and the dihedral angle < H (x)-C(16)-C(17)-O is much larger (about 30°, by the Molecular Mechanics Calculation). As a result, epoxide **36a** opens more readily than does its epimer epoxide **36b**, since the smaller the dihedral angle the better the overlap of the orbitals and the faster the reaction.

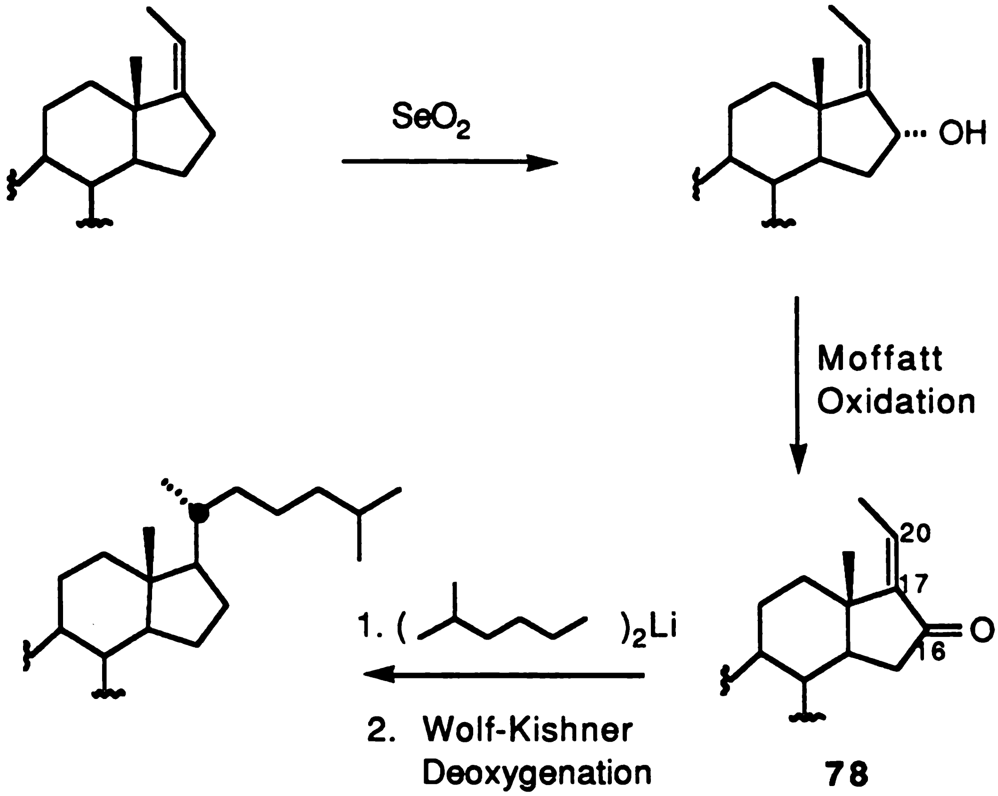
1.2 Studies of Sulfoxide-Sulfenate Rearrangements as a Tool in Side Chain Synthesis

Continuing the studies of side chain synthesis, we began to look for new, alternative approaches which would functionalize C-16[35] as well as introduce side chain segments selectively. Of particular interest was the possibility that C-16 functionality could be used to control developing stereochemistry at C-20. Beginning with compounds **12** or **13**, we first looked for methods that would functionalize allylic carbons.

Common reactions of this kind include bromination with N-bromosuccinimide (NBS)[61] and oxidation with selenium dioxide (SeO_2).[62] The former reagent selectively brominates positions allylic to a C-C double bond. In cases having more than one allylic site, the dominant product is usually derived from the most stable allylic radical out of many competing radicals. As precusors for side chain synthesis, bromides resulting from NBS reaction with **13** could be further converted into the corresponding alcohols, from which other chemical transformations could be carried out. As an alternative, the corresponding Grignard reagents might also be used in alkyl halide coupling reactions. Unfortunately, the conventional procedures failed to generate the derived allylic bromides from **13**. Therefore, the bromination method was ultimately abandoned, and selenium oxide reactions were studied in their stead.

Selenium dioxide is a reliable and predictable reagent for allylic oxidation reactions. Furthermore, Sharpless[62] has developed a modification of this reaction which uses a catalytic quantity of selenium dioxide together with a stoichiometric amount of t-butylhydroperoxide. This procedure greatly reduced the formation of undesired by-products and facilitated applications in organic synthesis.

Reactions of 17-alkylidene steroids with SeO_2 have been studied recently. Following allylic oxidation, N. R. Schmuff and B. M. Trost reported a steroidal side chain synthesis,[30] featuring 1,4-addition of an organocuprate reagent to a 17, 20-unsaturated-16-ketone derivative (Scheme 19):

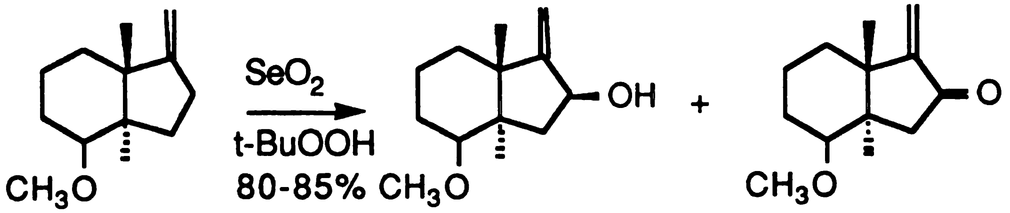


Scheme 19

The initial product from SeO_2 treatment was the α alcohol which was transformed to the unsaturated ketone **78** by Moffatt oxidation;[63] and the synthesis was finished by conjugate addition of an appropriate organometallic reagent, followed by deoxygenation. The product was a steroid having the "natural" R configuration at C-20.

The Schmuff and Trost' study of steroids serves as a good guide for our work. In model compound **12**, there is an extra methyl group at C-14, and the selenium dioxide oxidation should reflect this structural difference. From an inspection of Dreiding models, we anticipated that reactions at C-16 in compound **12** should occur from the less hindered β-side of the five membered ring. Of course, lack of a substituent at C-20 assured that the allylic reaction occurred only at C-16. The homologous compound **13** is in fact a better choice to reveal differences between steroids and our model systems. Reactions of this compound will be discussed in the next section.

Accordingly, compound **12** was treated with 0.5 eq selenium dioxide and 4 eq t-butylperoxide in methylene chloride. As expected, the reaction occurred only at C-16, and the product consisted of a single alcohol **46** and the derived enone **48** (shown in Eq. 2):

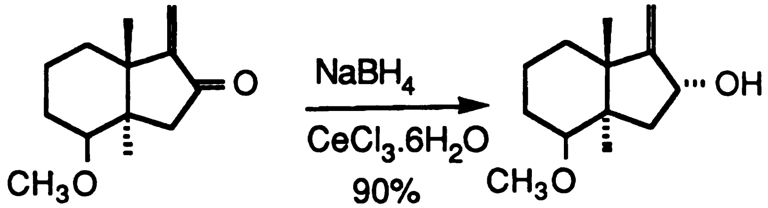


12 **46** **48**

(4:1)

Eq. 2

The ^{1}H NMR spectrum of ketone **48** was characteristic. Two proton singlets could be seen at δ 4.87 ppm and δ 5.75 ppm respectively, and the C-15 methylation displayed an AB pattern centered at δ 2.23 ppm. The assignment of compound **46** was not made until isomeric alcohol **47** was obtained by sodium borohydride reduction[64] of **48** (Eq. 3), and these epimers were compared by NMR.

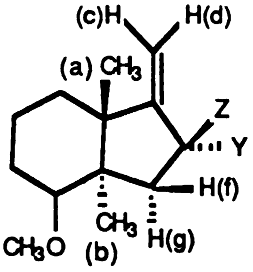


48 **47**

Only Product

Eq. 3

With the help of molecular models, double resonance experiments, and shift reagent experiments,[65] structural assignments for alcohols **46** and **47** were made.



46 , Z=OH, Y=H

47 , Z=H, Y=OH

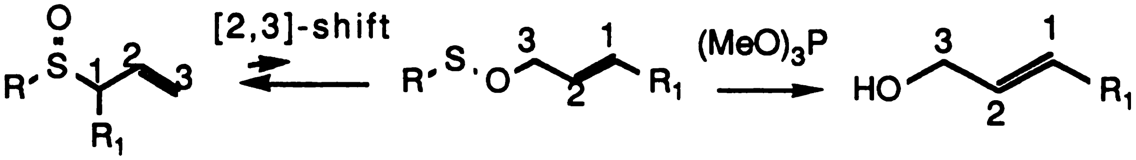
A key to assigning structures of **46** and **47** was the ^{1}H NMR signal of the C-16 carbinol proton. For example, alcohol **47** displayed a broad doublet at δ 4.78 ppm, characteristic of coupling with the adjacent protons H (f) and H (g). Molecular models indicated that the dihedral angle between H (g) and Z was near 90 degrees, while that between H (f) and Z was less than 30 degrees. Therefore Z should appear as a doublet, in accordance with the observed data. Long range coupling was also clearly demonstrated in the proton NMR spectrum. Thus the H (f) signal appeared as a doublet of doublet of quartets, due to a vicinal coupling with Z, a geminal coupling with H (g) and a long range coupling with methyl group (b). When CH_3 (b) was irradiated, H (f) collapsed to a sharp doublet of doublets, confirming the long range coupling between H (b) and H (f). Shift reagent experiments were also conducted with **47**, and the results supported the structural assignment (Figure 1 and Figure 2). Thus, CH_3 (b) shifted downfield to a greater extent than CH_3 (a), and H (g) shifted to a greater extent than H (f). In the same manner, the structure of **46** was assigned. Detailed chemical shift data are listed in Table 3.

Table 3. Selected ^1H NMR Data

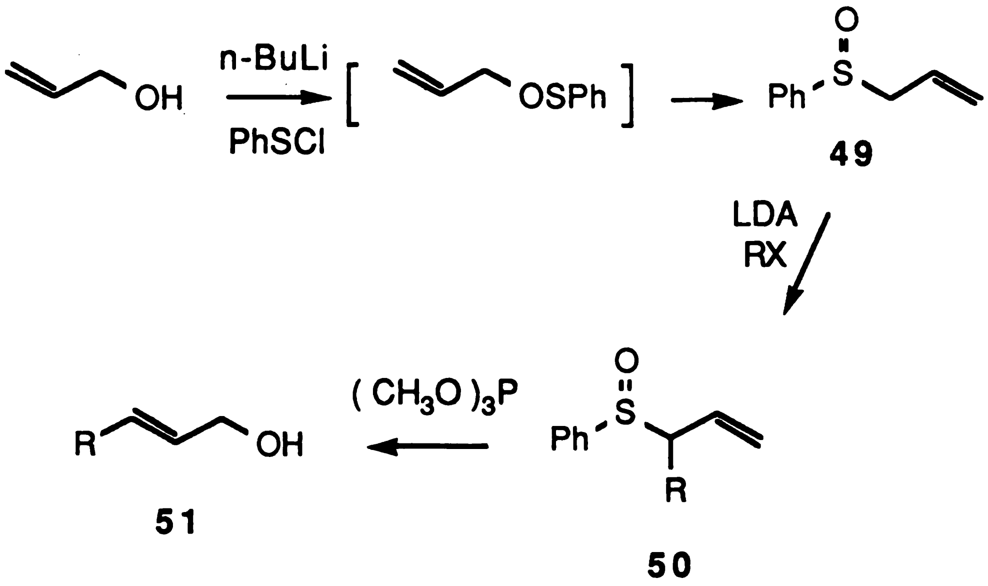
Compound	Proton (s)	Chemical Shift	Multiplicity (J)
48 Y=Z=O	a (3)	1.25 ppm	s
	b (3)	0.92	d (J^{bf} =1Hz)
	c (1)	4.87	s
	d (1)	5.75	s
	f (1)	2.88	d,q (J^{fg} =17, J^{bf} =1)
	g (1)	1.77	d (J^{fg} =17)
46 Y= $H^{(e)}$, Z=OH	a (3)	1.28	s
	b (3)	0.75	d (J^{bf} =1Hz)
	c (1)	4.78	d (J^{ce} =2)
	d (1)	5.03	d (J^{de} =1)
	e (1)	4.59	t,t ($J^{ef,eg}$ =7, $J^{ce,de}$ =1.5)
	f (1)	2.12	d,d,q (J^{fg} =12, J^{ef} =7, J^{bf} =1)
	g (1)	1.6 - 1.9	Hidden
47 Y= OH, Z= $H^{(e)}$	a (3)	1.08	s
	b (3)	0.92	d (J^{bf} =1Hz)
	c (1)	4.74	d (J^{ce} =2)
	d (1)	4.95	d (J^{de} =2)
	e (1)	4.78	d,t (J^{ef} =8, $J^{ce,de}$ = 2)
	f (1)	2.65	d,t,q (J^{fg} =13, J^{ef} = 8, J^{bf} =1)
	g (1)	1.20	d (J^{fg} =13)

This convenient preparation of intermediates **46**, **47** and **48** next prompted a study of possible applications of these compounds to side chain synthesis. To this end we wanted to develop a synthesis in which the stereochemistry at C-20 would be directed by the functional group at C-16. After attachment of an appropriate side chain, the functionality at C-16 could be retained (many natural triterpenes have a carbonyl or a hydroxyl group at C-16) or readily removed.

We first turned our attention to sulfoxide and sulfenate rearrangements[66] because these [2,3]-sigmatropic shifts usually proceeded stereoselectively via a suprafacial reaction path.[67] Normally the rearrangement of a sulfenate ester, prepared from the corresponding allylic alcohol, would give an equilibrium strongly favoring the sulfoxide product. It is known, however, that steric hindrance, electronegativity of substituent groups, and polarity of solvents can influence this equilibrium. In the presence of a thiophile, such as trimethyl phosphite, the sulfenate component may be trapped by desulfuration so that the allylic alcohol is obtained:



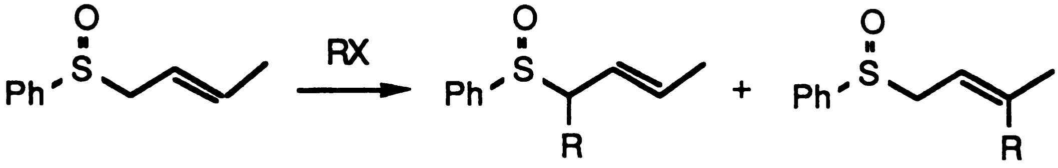
Evans and Andrews first demonstrated synthetic applications[64] of this rearrangement to the preparation of substituted allylic alcohols (Scheme 20):



Scheme 20

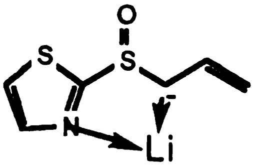
The starting alcohol was treated with n-butyl lithium, followed by addition of phenyl sulfenyl chloride to give an allyl sulfenate ester which quickly rearranged to the isomeric sulfoxide. On treatment with strong base, the sulfoxide (**49**) was deprotonated at the α-carbon and reacted with an alkyl bromide to yield sulfoxide **50**. Desulfuration of **50** with trimethyl phosphite then produced the alkylated allylic alcohol **51**. This reaction sequence proceeded in the high overall yield.

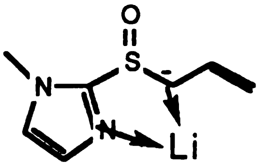
Despite the potential importance of this method in organic synthesis, it has limitations such as the formation of undesired γ-substituted products (Eq. 4).



Eq. 4

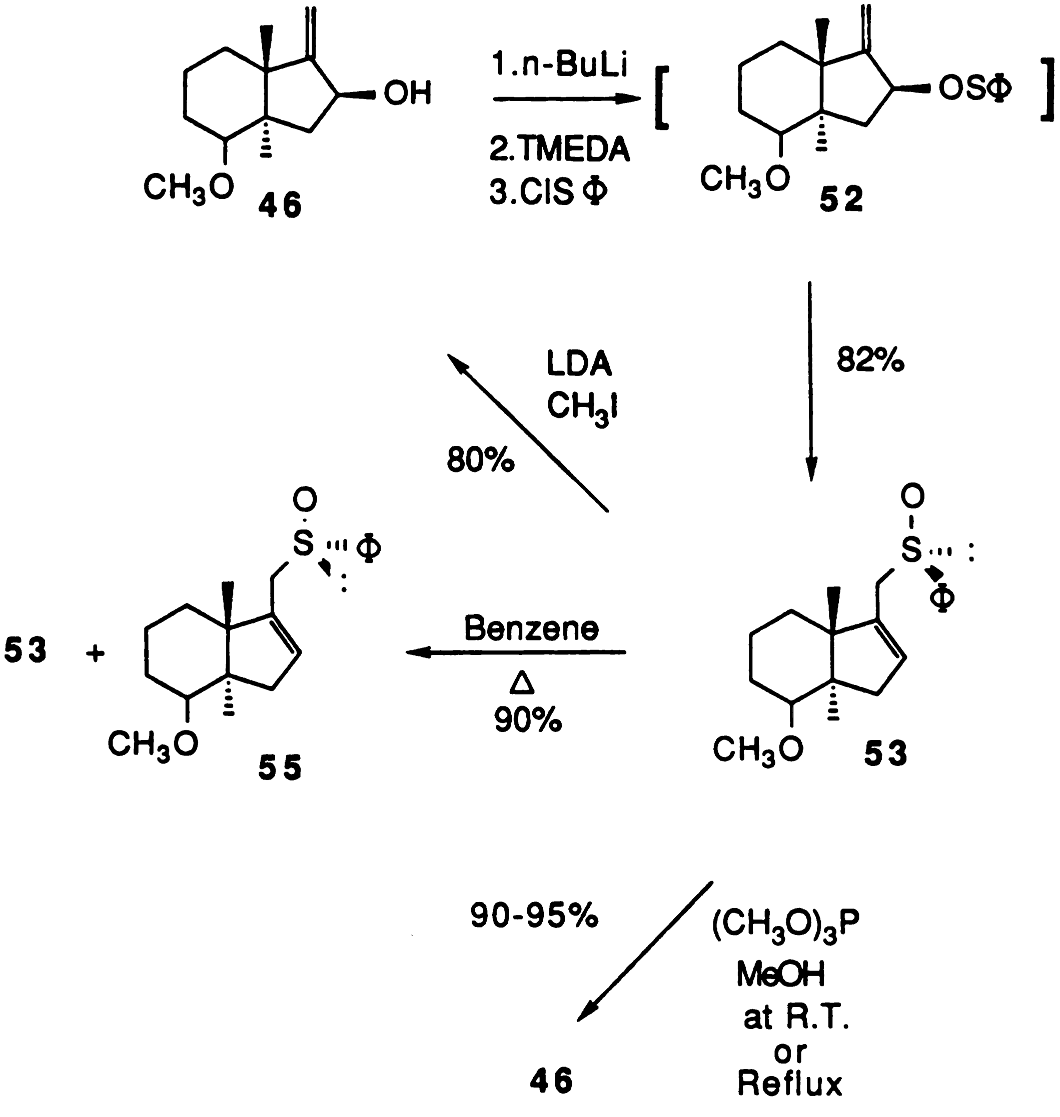
Evans has noted that the use of thiozoline and imidazol derivatives[68] greatly enhanced the regioselectivity for α-alkylation. The chelated lithium ion served to localize the negative charge at the α-position of the sulfoxide.





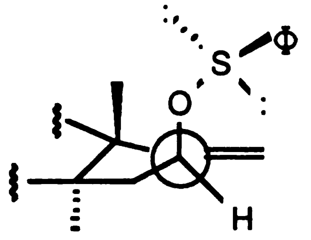
It was also noted that only methyl iodide and allyl bromide gave facile alkylation, the reaction with other halides being sluggish. Desulfuration of the resulting sulfoxides, using phosphorous-containing thiophiles, such as trimethyl phosphite and hexamethyl phosphorous triamide (HMPT), proved to be most effective.

To incorporate this method in our synthetic plan, the allylic alcohols **46** and **47** need to be converted to corresponding sulfoxides, and then selectively alkylated at the α-position (i.e., at C-20). In practice, both **46** and **47** were individually studied in the Evans/Mislow rearrangement. Our work with **46** is undertaken first, and the results are summarized in Scheme 21:

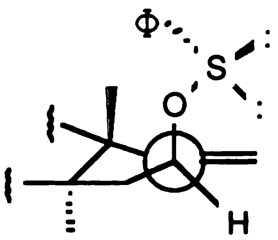


Scheme 21

The alkoxide anion prepared from **46** by low temperature reaction with n-butyl lithium was treated with phenyl sulfenyl chloride, directly producing sulfoxide **53** in excellent yield. Addition of tetramethylethylenediamine (TMEDA) proved necessary to achieve best results. This sulfoxide was stable at room temperature, but decomposed slowly to alcohol **46** on exposure to air. The proton NMR of pure **53** showed a characteristic AB system at δ 3.68 ppm for the methylene protons adjacent to the sulfoxide group. Presumably the sulfoxide **46** was formed from the intermediate sulfenate **52**. Of two possible transition state conformations for the conversion of **52** to **53**, conformation **A** should have lower energy (*exo*-transition state) than conformation **B** (*endo*-transition state); the latter would be destabilized by steric hindrance between the 14-angular methyl group and the phenyl group. Transition state **A** would lead to a sulfoxide having an R configuration at the chiral sulfur.



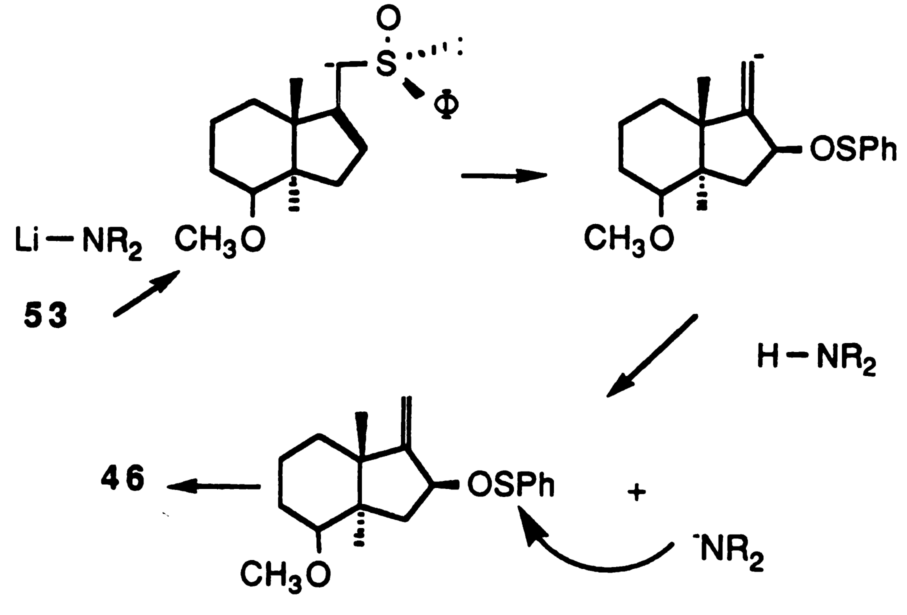
A
Lower energy
conformation



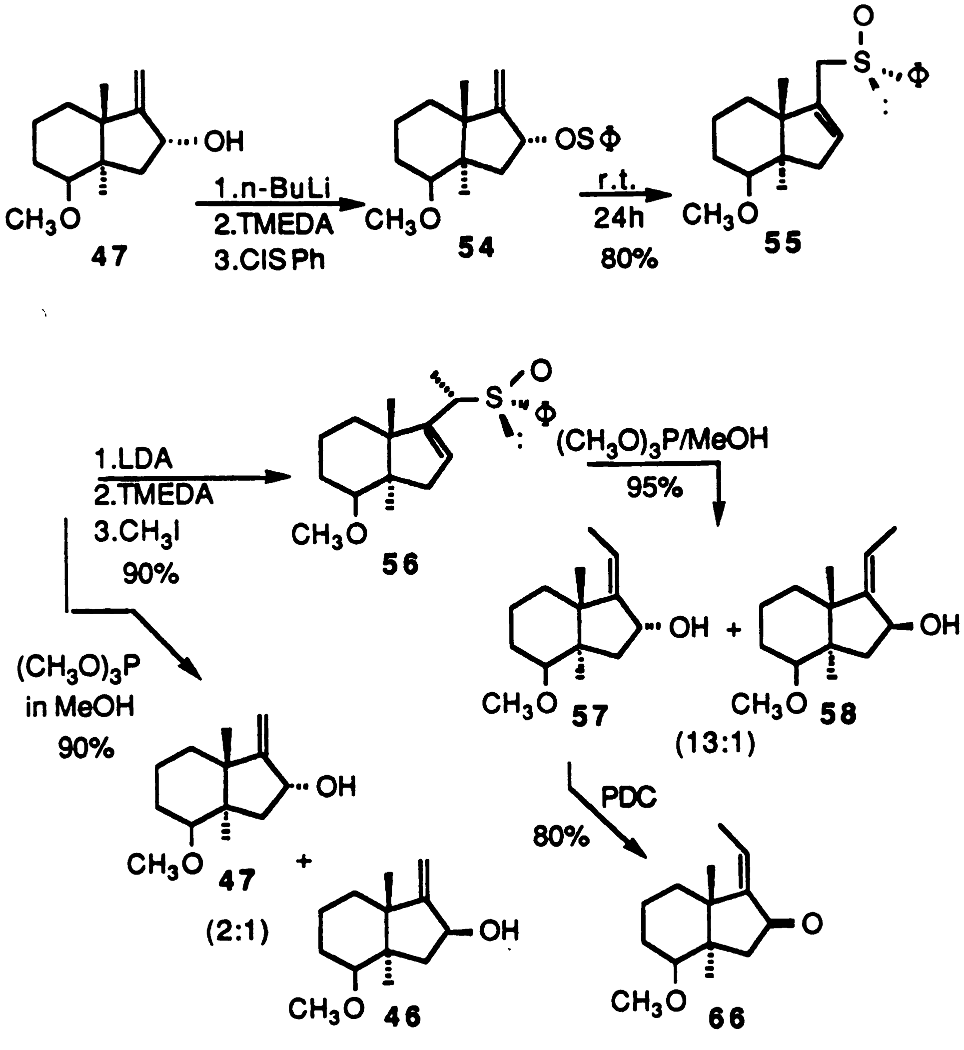
B
Higher energy
conformation

With the sulfoxide **53** in hand, we proceeded to study the following reactions. 1. Desulfuration: conversion of β,γ-unsaturated sulfoxides to allylic alcohols; 2. Epimerization: interconversion of sulfoxide isomers by a crossover involving diastereomeric transition state, and 3. Alkylation: introduction of an alkyl group α to the sulfoxide.

When compound **53** was treated with trimethyl phosphite either at room temperature or in refluxing methanol, only alcohol **46** was recovered. This result confirmed that in the interconversion of sulfoxide **53** and sulfenate ester **52**, the favored *exo*-transition state has a lower energy than the *endo*-transition state (see conformations **A** and **B**). Sulfoxide **53** was equilibrated to a 1:1 mixture of two isomeric sulfoxides (**53** and **57**) in refluxing benzene. Finally, methylation of sulfoxide **53** with methyl iodide resulted in the recovery of allylic alcohol **46**. No methyl sulfoxide was isolated (Scheme 21). The intermediate sulfoxide anion may have rearranged to a vinyl anion (Scheme 22), which then abstracted a proton from diisopropyl amine to regenerate lithium diisopropyl amide (LDA). The attack of the latter at sulfur would give lithium alkoxide, which after work-up produced **46**.



Although the methylation of sulfoxide **53** failed to work, this study provided a useful basis for further investigation of isomeric alcohol **47**, its derived sulfoxide and related reactions. As it turned out, the reactions of **47** included several highly selective transformations as outlined in Scheme 23.

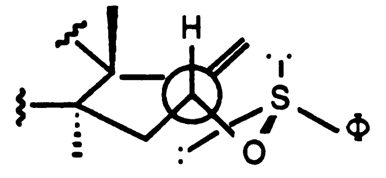


Scheme 23

As in the case of alcohol **46**, epimer **47** yielded an isomeric sulfoxide, **55**, under the reaction conditions previously described. Of particular interest, however, was the isolation of sulfenate **54**. This intermediate was stable enough to survive a rapid chromatographic separation and was characterized by ^{1}H NMR. Thus **54** exhibited two vinyl singlets at δ 4.79 ppm and δ 5.17 ppm, compared with equivalent proton signals at δ 4.74 ppm and δ 4.95 ppm in starting alcohol **47**. The proton at C-16 in **54**, displayed a well resolved doublet at δ 4.70 ppm (J=8 Hz); whereas in **47**, it appeared as a doublet at δ 4.78 ppm (J=8 Hz), partially overlapping with the peak at δ 4.74 ppm.

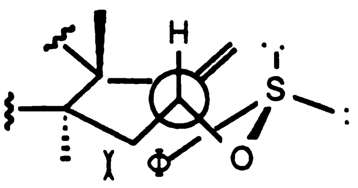
The striking difference in stability between the sulfenate esters **52** and **54** can be explained in terms of steric hindrance. It has been noted that the five-membered rings of our model compounds have a more hindered α-side, in contrast to steroid. A sulfenoxyl group located on the more relaxed β-side, as in intermediate **52**, is able to achieve the rearrangement transition state with little steric distortion. Consequently, rearrangement to **53** may take place rapidly. In contrast, the α-sulfenate **54** is inhibited by steric distortion of the corresponding transition state, and the rearrangement to **55** is slower.

Sulfenate **54** is transformed to sulfoxide **55** over 24 hours of period at room temperature. Of two possible transition states for the rearrangement to a sulfoxide, **C** is clearly lower in energy than is **D**. If sulfoxide **55** is formed from the lower energy conformation (**C**) it will necessarily have an S configuration at the sulfur atom:



C

Lower energy

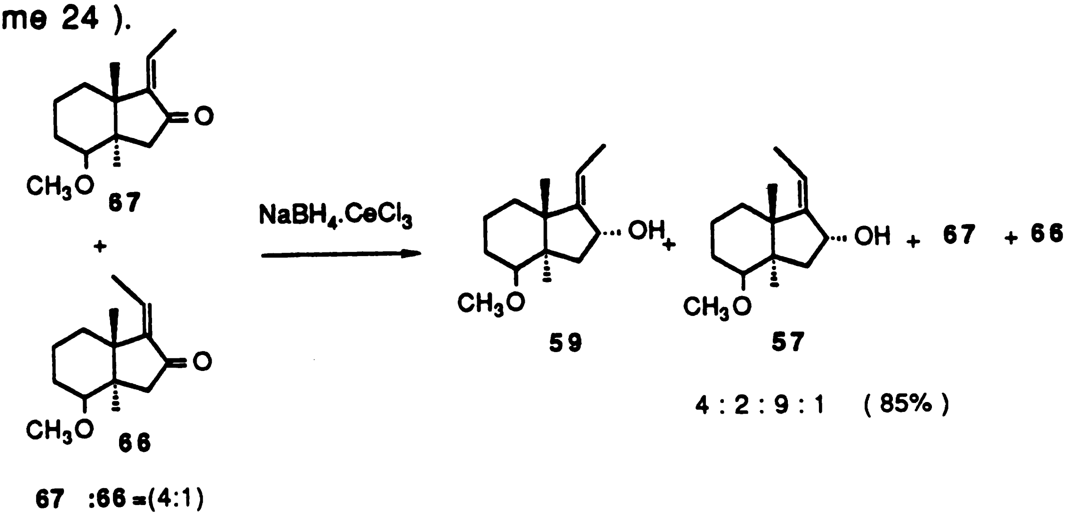


D

Higher energy

Sulfoxide **55** gradually equilibrated to a 1:1 mixture of sulfoxides **55** and **53** on standing for several days. Desulfuration of **55** with trimethyl phosphite in refluxing methyl alcohol (at room temperature the reaction did not occur) yielded alcohols **47** and **46** in ratio of a 3:1. This suggested that the reaction path leading to these alcohols had quite high activation energies, but a relatively small difference in energy.

Unlike isomer **53**, the conjugate base of sulfoxide **55** cleanly reacted with methyl iodide to give methyl sulfoxide **56** in high yield. The configuration of the newly formed chiral center at C-20 was tentatively assigned as S, on the assumption that attack from α-face was favored. When sulfoxide **56** was treated with methanolic trimethyl phosphite under reflux it was converted to alcohols **57** (major product) and **58** (minor product) in a high ratio. These compounds were easily separated, and on oxidation with pyridinium dichromate, yielded the corresponding enone **66**, with a little double bond isomerization to the *Z* isomer **67** (5%). When the mixture of enones **66** and **67** was reduced by sodium borohydride, β-facial attack ocurred and alcohols **57** and **59** were obtained. However, recovery of a substantial amount of starting material (**66** and **67**) prevented this reaction from being of synthetic value (Scheme 24).



Scheme 24

To summarize, an energy diagram encompassing sulfoxides **53** and **55**, sulfenates **52** and **54**, and various transition state conformations is presented in Figure 3.

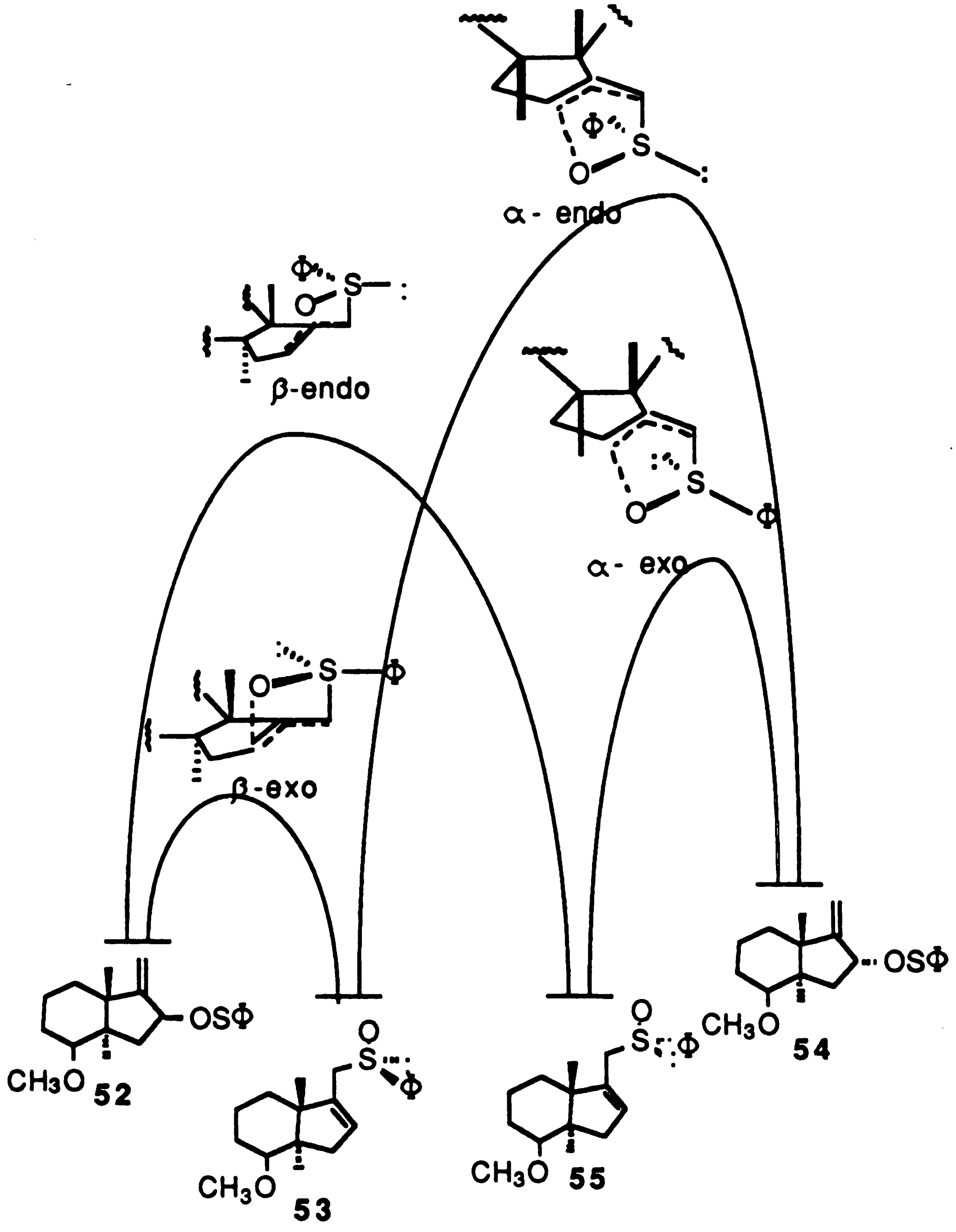
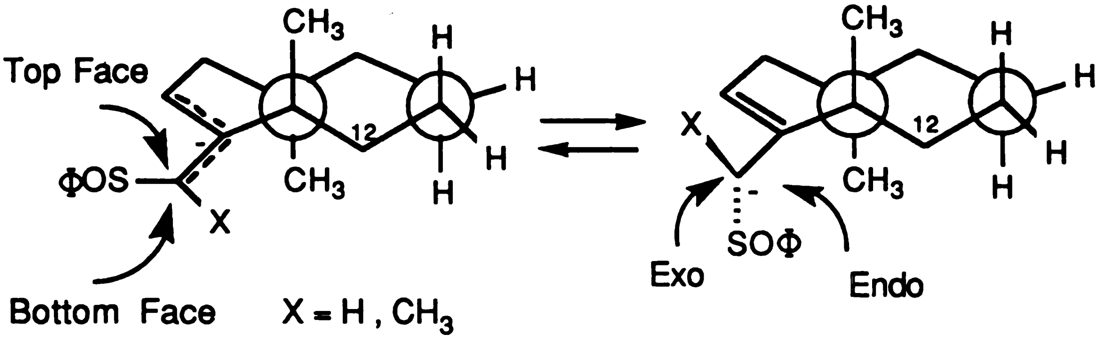


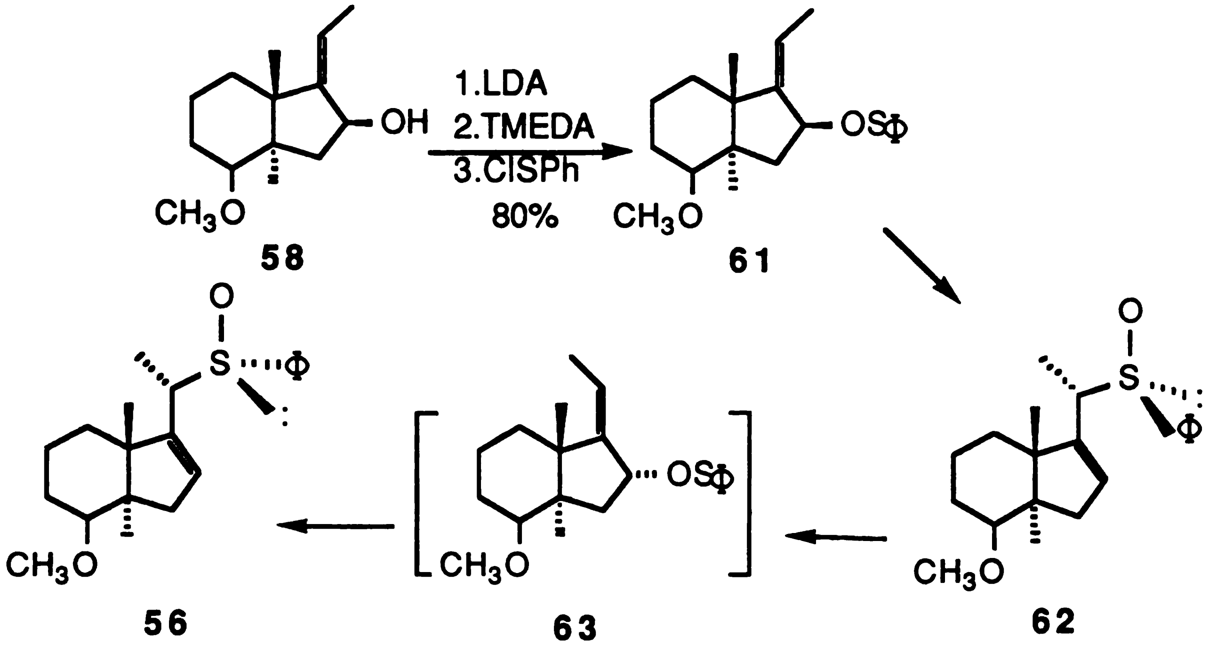
Figure 3

Energy Diagram for Various Sulfoxides and Sulfenates

Further studies of methylated sulfoxide **56** were then conducted. The conjugate base of **56** (generated by reaction with LDA) was quenched in turn with ammonium chloride, acetic acid, and deuterium oxide (D_2O). The first two quenchings gave back the original sulfoxide **56** and suggested that protonation occurred from the top face of the anion. To explain these results conveniently, the following equation was depicted. When X=H (i.e., methylation experiment), the left planar conformation is more favored and in this case, methyl iodide approaches the molecule from the bottom face to give sulfoxide **56**.



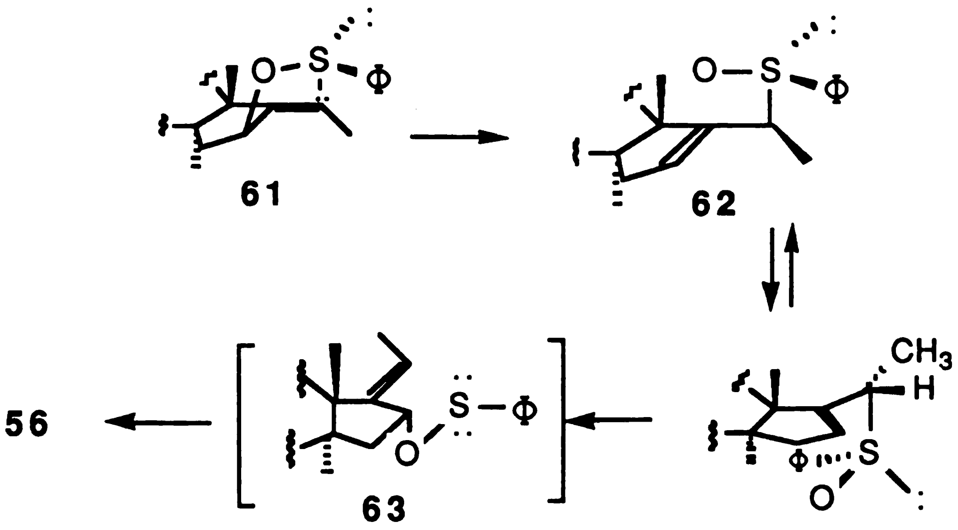
On the other hand, when X=CH3 (i.e., proton quenching experiments), the left conformer is destabilized by repulsion between X and C-12. By rotating the methyl group upward, the methyl group moved farther away from C-12 to assume the more favored conformation on the right. The loss of π-conjugation with the double bond is not serious for α-sulfonyl or α-sulfoxide anions. The alternative conformation in which the larger sulfoxide and methyl groups are switched is destabilized by crowding of the sulfoxide group with the angular methyl at C-13. Protonation (or deuteration) from the more accessible *exo*-face regenerated **56**.



62 : **63** : **56** = 3:1:1

Scheme 25

Additional studies of the sulfenate ester-sulfoxide rearrangement were also conducted with methylated substrates related to **56** (Scheme 25). From alcohol **58** (its preparation will be described later) the sulfenate derivative **61** was prepared, and at room temperature this slowly isomerized to a mixture of two sulfoxides (**56** and **62**) in the ratio indicated. Sulfoxide **62** was easily distinguished by chemical shift difference in the proton signal at C-20: **62** exhibited a quartet at δ 3.09 ppm, whereas **56** gave a quartet at δ 3.47 ppm. The formation of **56** may be the result of epimerization through a higher energy α-*endo* transition state (Scheme 26):



Scheme 26

A summarizing energy diagram of these methylsulfoxides, their analogues sulfenates and the corresponding alcohols is shown in Figure 4. Unlike the parent β-sulfenate ester **52**, sulfenate ester **61** is isolable, implying a higher energy transition state for the sigmatropic rearrangement. Absence of sulfenate **63** suggested a lower activation energy for its rearrangement to sulfoxide **56**. The sulfenate **61** and the sulfoxide **56** are plotted at the same energy based on their equal thermodynamic distribution.

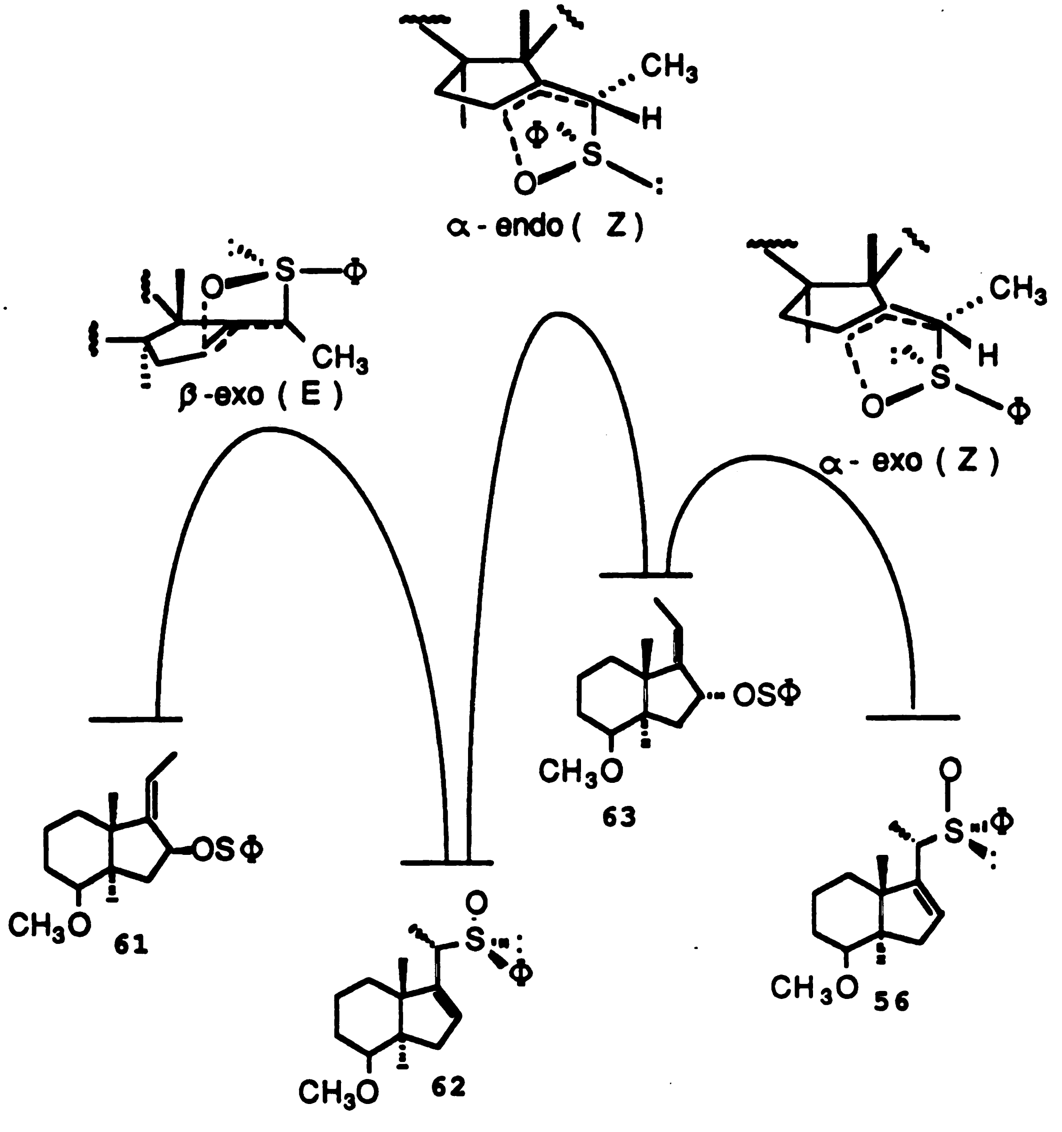


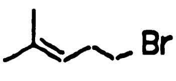
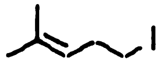
Figure 4

Energy Diagram for Methyl Sulfoxides and Sulfenates

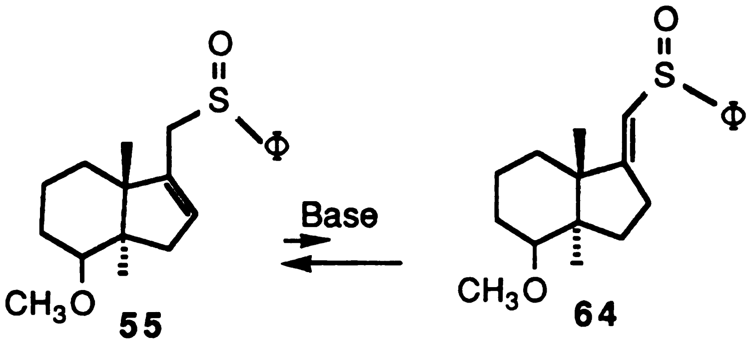
A brief investigation of additional alkylation of methyl sulfoxide **56** and sulfoxide **55** is described in Table **4**.

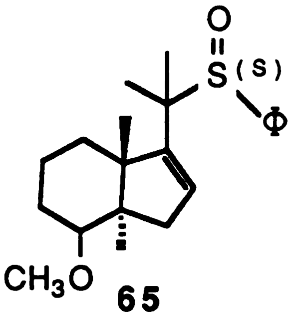
Table 4 Alkylation of Sulfoxides

Run	Sulfoxide	Condition	RX	Result
1	**56**	45' at -45°;3h at 0°; 4h at 25°.	**73**	**56 + 57**
2	**55**	1h at -78°; 2h at 0-20°.	**73**	**55 + 64**
3	**55**	**74**, 10', at -45° MeI,1.5h, at -45°.	**74** MeI	**65+55+56**
4	**55**	20',-45°;30',-10°; 30',30°.	**74**	Unknown Mix.
5	**55**	1h,-45°.		**55**
6	**55**	1.5h,-45°.	MeI	**64+65+56**

73 =  **74** = 

We first examined the reactivity of **56** toward alkylation with 4-methylpentenyl bromide. When **56** was treated with lithium diisopropyl amide and then the alkyl bromide for several hours at various temperatures, only **56** and some decomposed alcohol **57** were recovered (run 1). Even sulfoxide **55** failed to be alkylated with **73**. The starting sulfoxide **55** and a rearranged isomer **64** (shown below) were recovered (run 2). The results with reactive halides such as 4-methyl pentenyl iodide, and allyl bromide were also disappointing. Finally, product **65**, the only dialkylation product, was obtained (run 6) in a moderate yield.



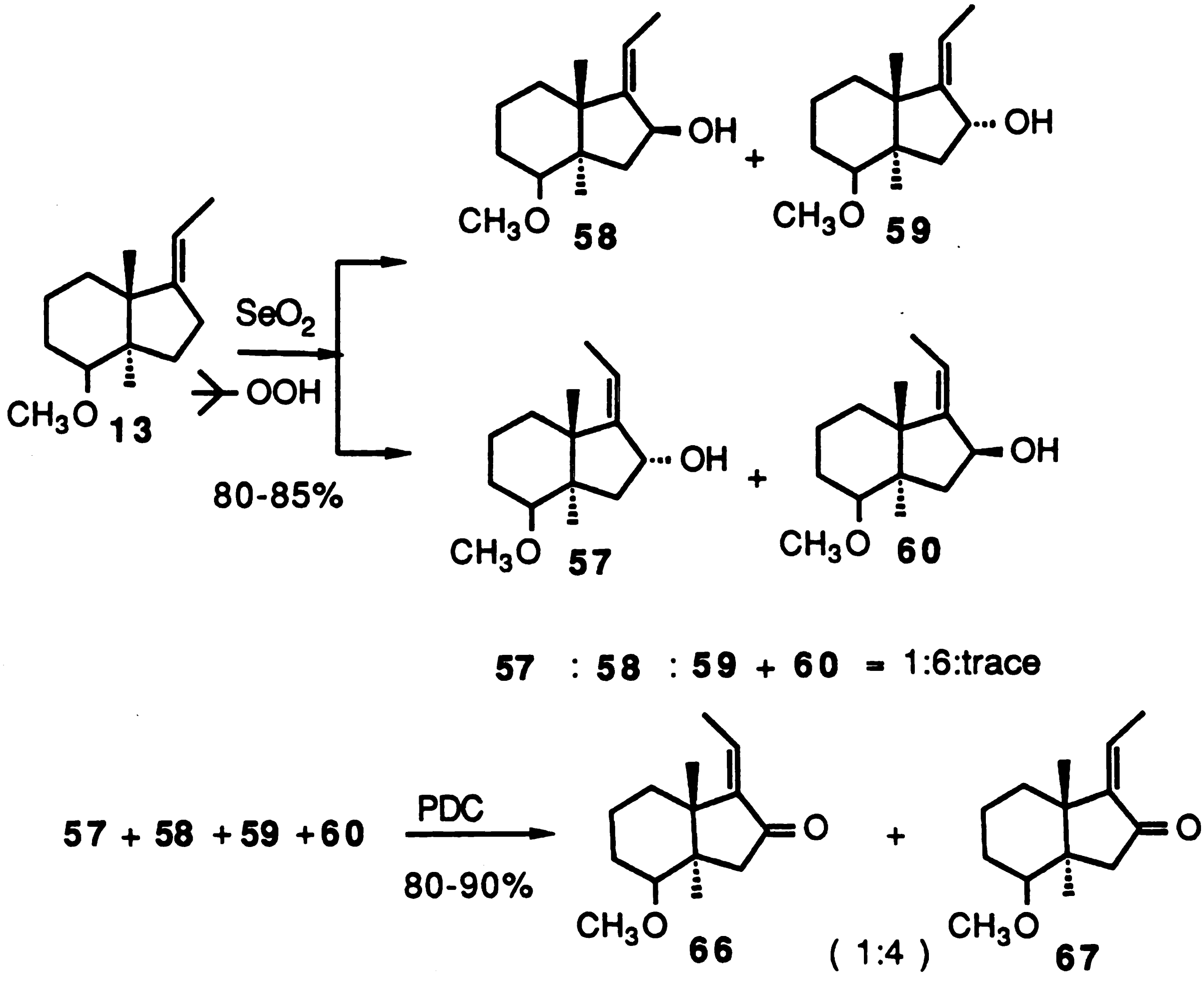


65

In conclusion, we have explored the feasibility of using sulfoxide-sulfenate rearrangement in triterpene side chain synthesis, and observed some interesting results. In the next section, a study of conjugate addition of organometallic reagents to enones **66** and **67** will be presented.

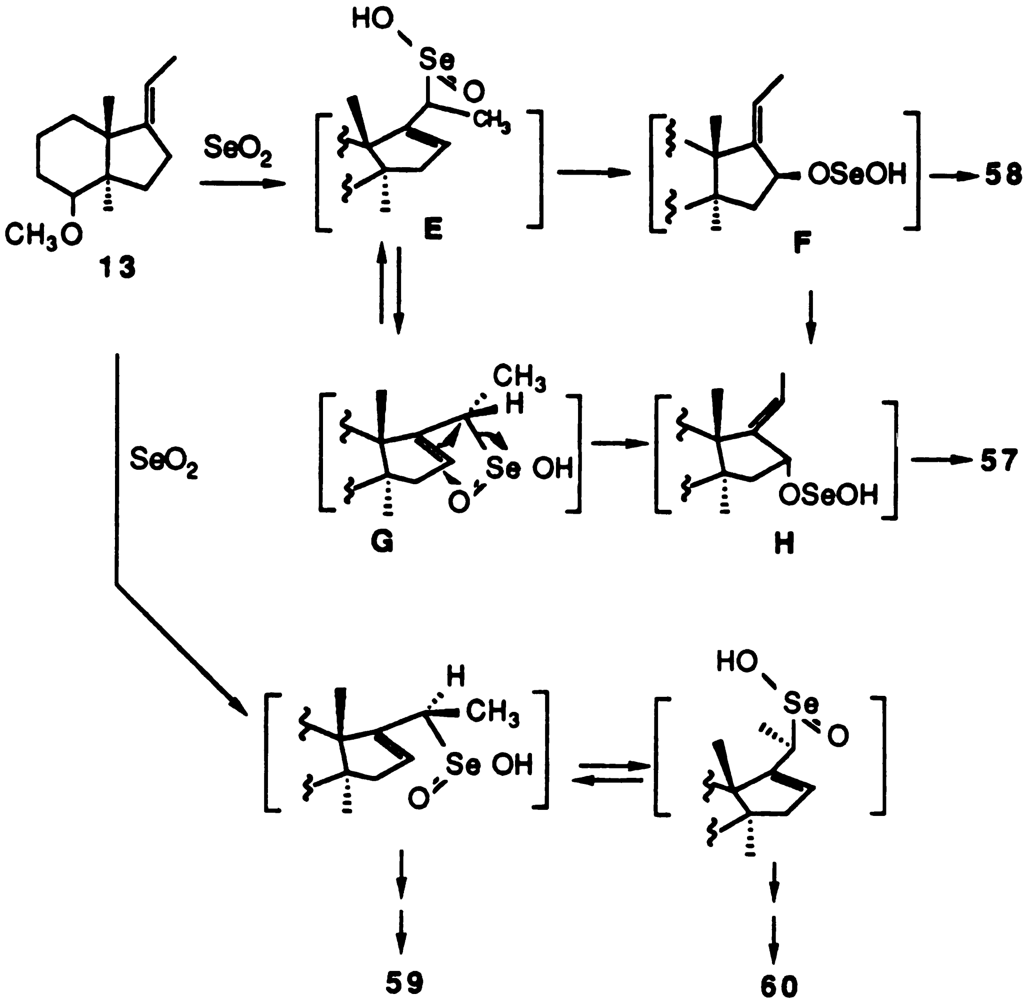
1.3 Conjugate Addition of Organocuprates to 17-Ethylidene-16-Ketones **66** and **67** as a Key Step for Side Chain Synthesis

Enone **67** was prepared from olefin **13** by a two-step sequence similar to that we used to prepare **48** from **12**. Thus, treatment of **13** with selenium dioxide gave alcohols **57** and **58** as a 1:6 mixture in good yield. Large scale reactions also produced a small amount (5 - 8 %) of **59** and **60**. The alcohol mixture was then oxidized to enones **66** and **67** by the action of pyridinium dichromate (Scheme 27):



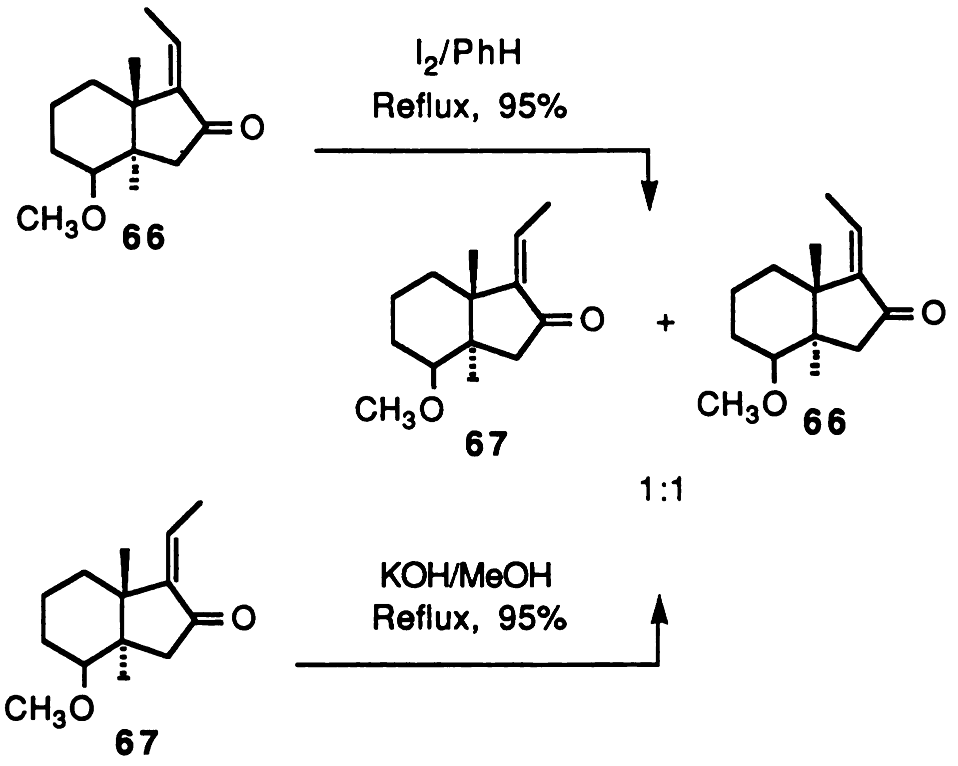
Sccheme 27

As expected, attack of the selenium reagent occurred mainly at the less hindered β-face of the olefin substrate. The initial intermediate **E** either rearranged directly to the major product (**58**) via intermediate **F** or, prior to the rearrangement, assumed a less stable conformation **G**, which yielded the minor product **57**. The detection of trace amounts of alcohols **59** and **60** suggested the possibility that some selenium dioxide also reacted at the α-face of olefin **13** in the initial step (Scheme 28).



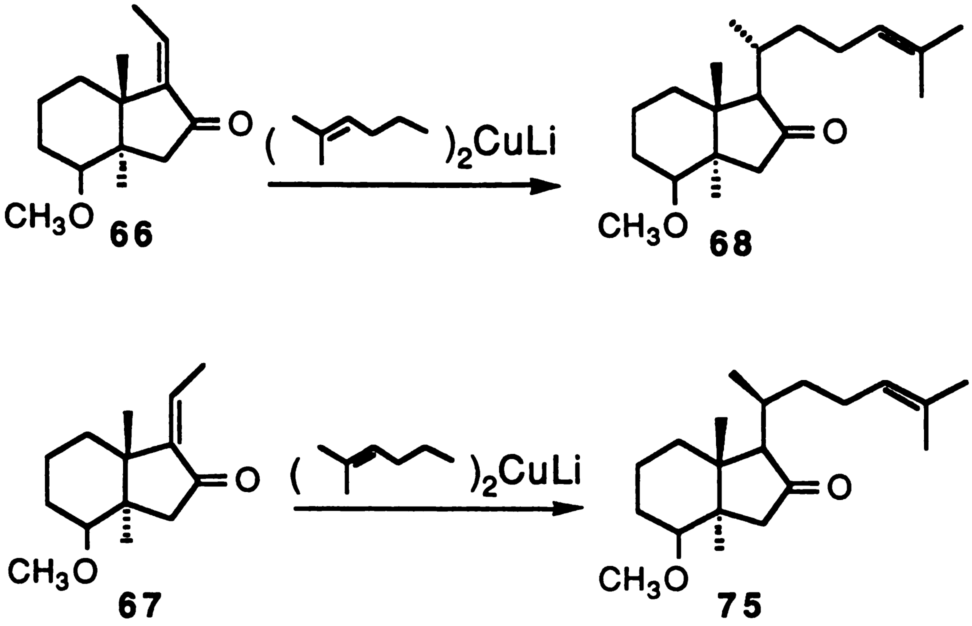
Scheme 28

In the course of developing methods for enone preparation, we found[30] that **66** slowly isomerized to **67** on exposure to air. Under reflux in benzene with a trace of iodine, **66** equilibrated to a 1:1 mixture with **67**. Curiously, **67** did not rearrange to **66** under the same conditions; however, on base-treatment in refluxing methanol it was converted to the same 1:1 mixture. These findings enabled the yield of **67** to be raised to over 90% (Scheme 29).



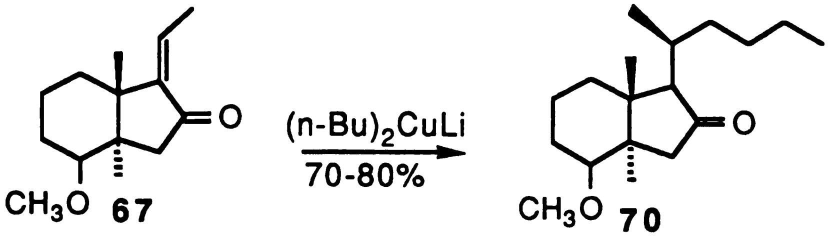
Scheme 29

We anticipated that the stereoselectivity for nucleophile attack at C-20 would be mainly controlled by the methyl group at C-13. Consequently, conjugate addition of organometallic reagents to these enones (**66** and **67**) should occur from the less hindered α-face to give **68** and **75**, respectively (Scheme 30):



Scheme 30

To confirm this prediction, a cuprate reagent was prepared from n-butyl lithium and cuprous bromide (dimethyl sulfide complex) and first reacted with a solution of **67** (chosen because of its convenient preparation). A single isomer **70** was obtained after work-up. The product was believed to be the thermodynamically favored 17β-isomer, because base treatment of it did not cause any change (Eq. 4).



Eq. 4

In order to apply this reaction to triterpene side chain syntheses we needed to prepare lithium bis-(4-methylpentenyl) cuprate. The 4-methyl pentenyl lithium, needed for making the cuprate, was eventually prepared from the corresponding alkyl halides. Generally, organolithium compounds can be generated by the reaction of alkylhalides with lithium metal,[69] by homogeneous metal-halogen exchange[70] by homogeneous metal-metal exchange[71] (Eqs. 5, 6 and 7, respectively).

$$2\ Li + RX \longrightarrow RLi + LiX \qquad \text{Eq. 5}$$

$$RX + R'Li \longrightarrow RLi + R'X \qquad \text{Eq. 6}$$

$$Ph_3SnR + PhLi \longrightarrow RLi + Ph_4Sn \qquad \text{Eq. 7}$$

The first method is used most frequently and seems particularly suited to our needs. For best result, a small amount of sodium metal is usually added to initiate the reaction. Applications of the second method are often for the preparation of primary alkyl lithium reagents from a tertiary alkyl lithium and a primary halide. Although metal-metal exchange is less commonly used, this method finds unique value in preparing organolithiums from very active halides such as allyl bromide and benzylbromide by preventing potential polymerizations. Recently, Luche *et al.*[72] reported that ultrasonic irradiation[73] improved the reaction of alkyl halides with metals. No initiators, such as I_2 or dibromoethane, were needed, and the yields of alkyllithium were greatly improved with reduced reaction time periods. Nonetheless, opposite examples also exist. For example, Boudjouk[74] showed that ultrasound promoted coupling of alkyl halides in presence of lithium.

We examined all three methods with different halides (**72**, **73**, and **74**) for the preparation of organolithium reagents. In some cases ultrasonic technique was used.

$$(CH_3)_2C{=}CHCH_2CH_2X \; + \; Li \longrightarrow (CH_3)_2C{=}CHCH_2CH_2Li$$

72 , X=Cl
73 , X=Br
74 , X=I

Table 5 Reaction of Halides with Metals

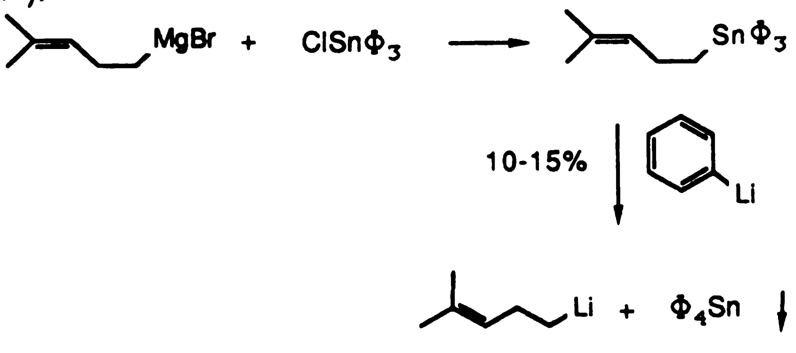
Run	RX	Metal	T (C°)	t (h)	Ultra-Sound	Result
1	**72**	Li	-15	12	No	No Reaction (N.R.)
2	**72**	Li	-15	5	Yes	N.R.
3	**73**	Li	-15	15	No	17% Pdt + **73**
4	**73**	Li	r.t.	12	No	N.R.
5	**73**	Li	r.t.	7	Yes	Coupling
6	**74**	Li	-15	15	No	N.R.
7	**73**	Li with 1% Na	-20	12	No	40% Pdt + **73**
8	**73**	Mg	r.t.	4-5	No	90%
9	**74**	Mg	r.t.	4-5	No	90%

The halides **72, 73** and **74** were prepared from 2-cyclopropyl isopropanol by the procedure of McCormick[75] and Balme.[76] It was found that lithium wire (even with sodium present) did not efficiently react with these halides. A large quantity of unreacted lithium metal was usually recovered and the ultrasound technique did not improve the yield of the desired product. In some instances coupling products were formed (runs 1-6, Table 5).

Table 6 Metal Halogen Exchange

Run	RX	RLi	T (C^{o})	t (h)	Result
1	**73**	t-BuLi	- 78	4-5	N.R.
2	**73**		- 45	4-5	N.R.
3	**74**		- 78	4-5	N.R.
4	**74**		- 55	4-5	N.R.

Attempts to effect metal halogen exchange with these halides[77] were unsuccessful (Table 6). As shown in the following scheme, transmetallation reactions were also ineffective. The metal exchange did not go to completion (Scheme 31).

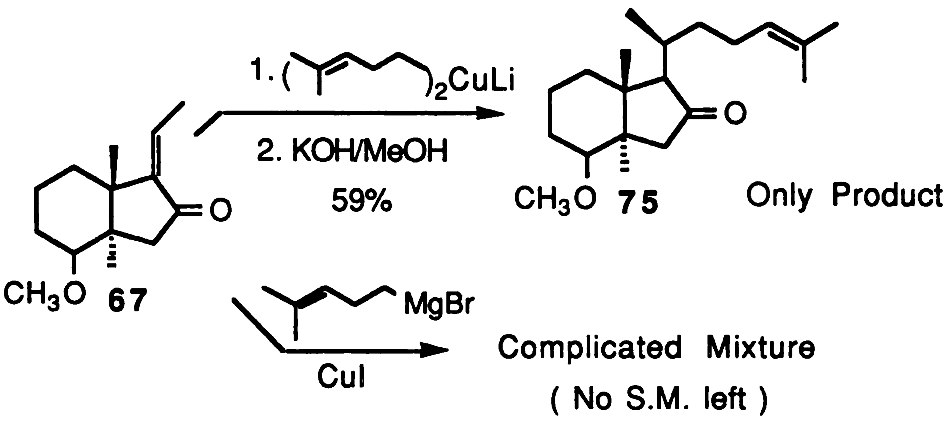


(Poor Yield)

Scheme 31

Finally, when a dispersion of lithium-sodium alloy (sodium content, 1 %) was used, the desired 4-methyl-3-pentenyl lithium was generated in good yield[78] (run 7, Table 5). The freshly made methylpentenyllithium was titrated by a standard method.[79] Alkylhalides **73** and **74** were also shown to give the Grignard reagent in high yield (runs 8,9).

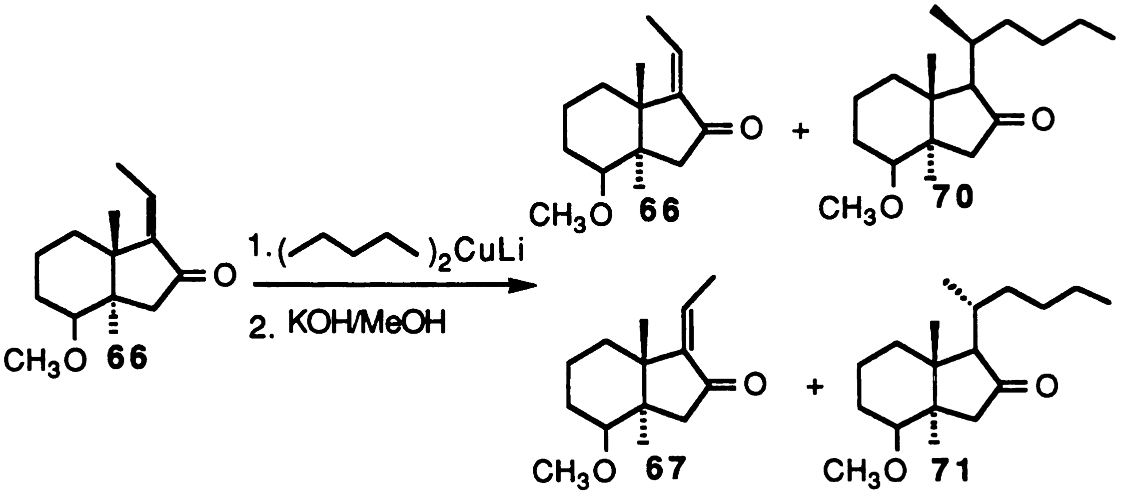
When enone **67** was treated with freshly prepared alkylcuprate derived from **73**, a mixture of two compounds was obtained. Base treatment of this mixture in refluxing methanol produced a single isomer as shown below (Scheme 32).



Scheme 32

Addition of the corresponding Grignard reagent to **67** was also studied, but this reaction gave a complicated mixture of products. This mixture was not simplified by base treatment. The similar poor selectivity with Grignard reagents in conjugate additions has also been reported by others.[32,80]

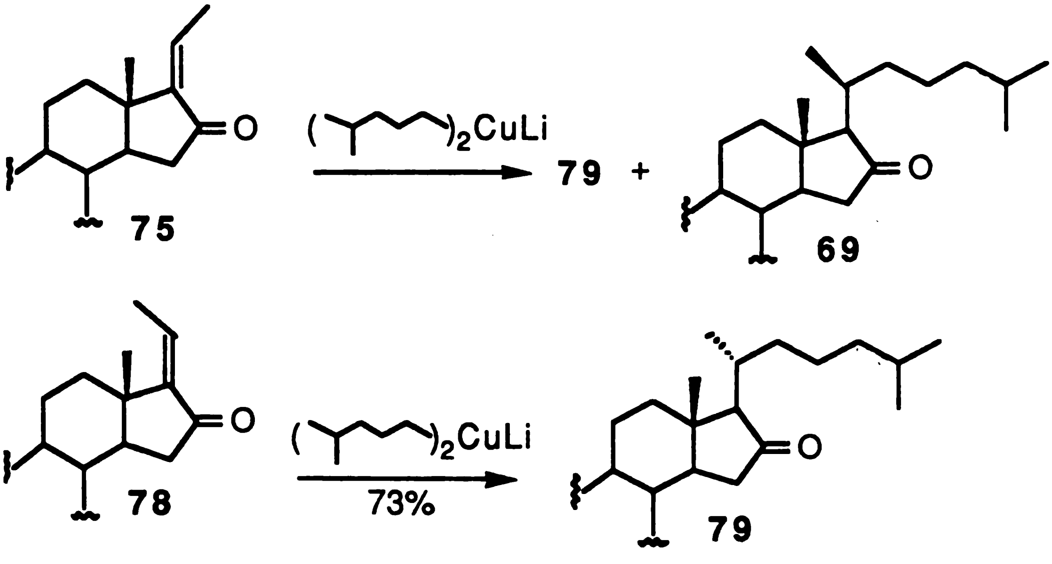
We hoped that addition of organocuprates to **66** could be equally selective, giving the C-20 epimer of compound **70** or **75**. However, when this enone was treated with lithium bisbutylcuprate, a mixture of products was obtained. and base treatment of this mixture yielded four products as shown below (Scheme 33):



66 : **67** : **70** : **71** = 1 : 1 : 2 : 1

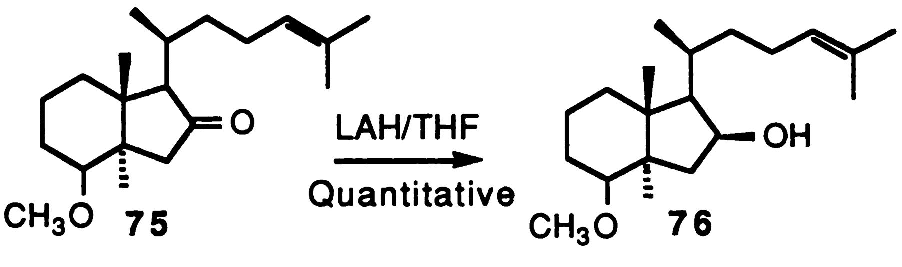
Scheme 33

Our results revealed an interesting difference in the behavior of **66** and **67** in conjugate addition reactions. These findings contrasted with those[30] reported by Trost *et al.* for the addition of lithium isohexylcuprate to a similar steroidal enone. Thus, compound **75** (corresponding to our enone **67**) gave a mixture of C-20 isomers, whereas the same addition to steroidal enone **78** (corresponding to our enone **66**) yielded only the single isomer **79**, with a R configuration at C-20 (Scheme 34).



Scheme 34

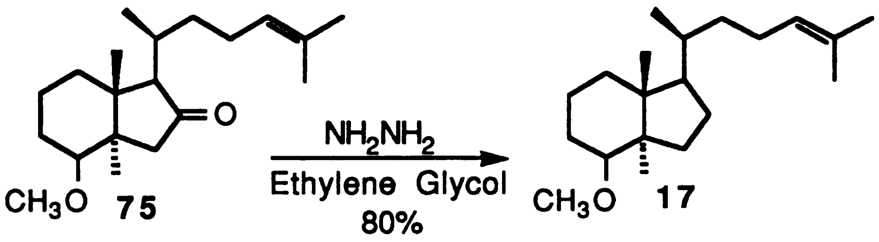
Compound **75** was cleanly reduced by lithium aluminum hydride to a single alcohol **76**, which we assigned as the β-epimer **76** by comparison of its proton NMR spectrum with that of a steroidal analogue[81] (Eq. 8).



Eq. 8

The preparation of **75** and **76** has provided a useful synthesis of triterpene side chains with concurrent functionality at C-16.

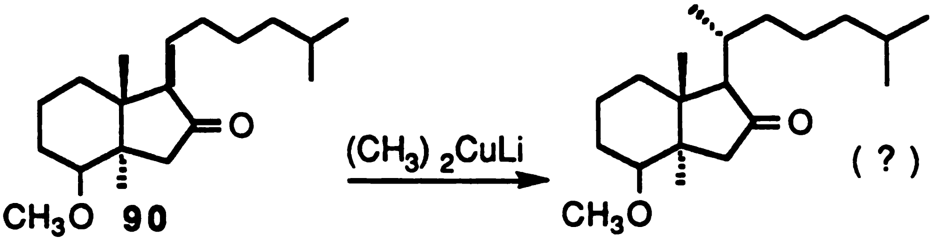
The carbonyl group at C-16 in compound **75** was finally removed by a Wolf-Kishner reductive deoxygenation[82] to give **17** in good yield (Eq. 9):



Eq. 9

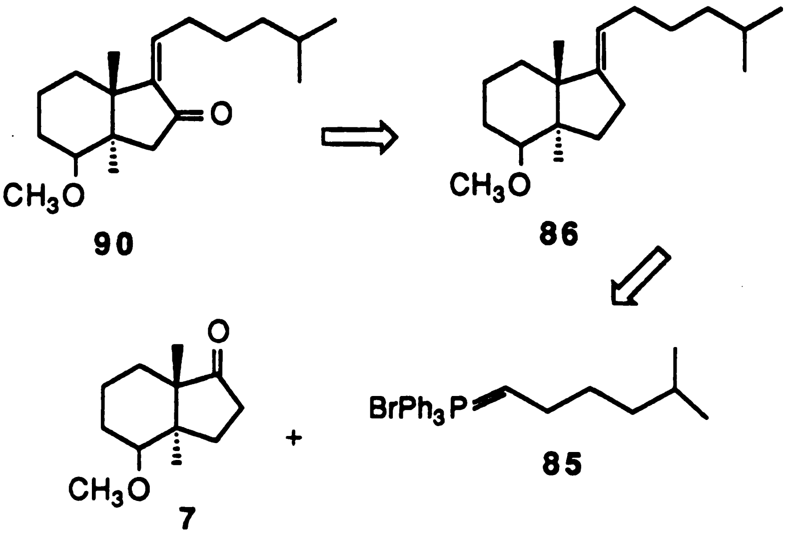
The configuration at C-20 of product **17** was established. From previous studies of triterpene ^{13}C NMR spectra[83], it is clear that significant chemical shift differences are observed between equivalent lanostanes and euphanes, especially for carbons 12, 16, 17, 20 and 22 ($\Delta\delta \geq 0.5$ ppm). Since compound **17** constitutes a racemic model of the euphane side-chain, we expected to find a correlation of appropriate ^{13}C NMR signals *vis-a-vis* those of the lanostanes. The data in Table 7[84] show this to be the case (a comparative value for C-12 is omitted, since the methoxy group in **17** causes a large perturbation at this site). Finally, **17** proved to be identical with the product from Koreeda/Krief[33] side chain synthesis, as applied to **6**.

The stereochemistry observed in the conjugation addition of dialkylcuprate reagents to *Z* enone **68** suggested a means for achieving opposite selectivity at C-20. If a compound like **90** could be prepared in good yield, a corresponding conjugate addition with lithium dimethyl cuprate would give a product having an R configuration at C-20. This would provide a complementary method for construction of side chains (Eq. 10).



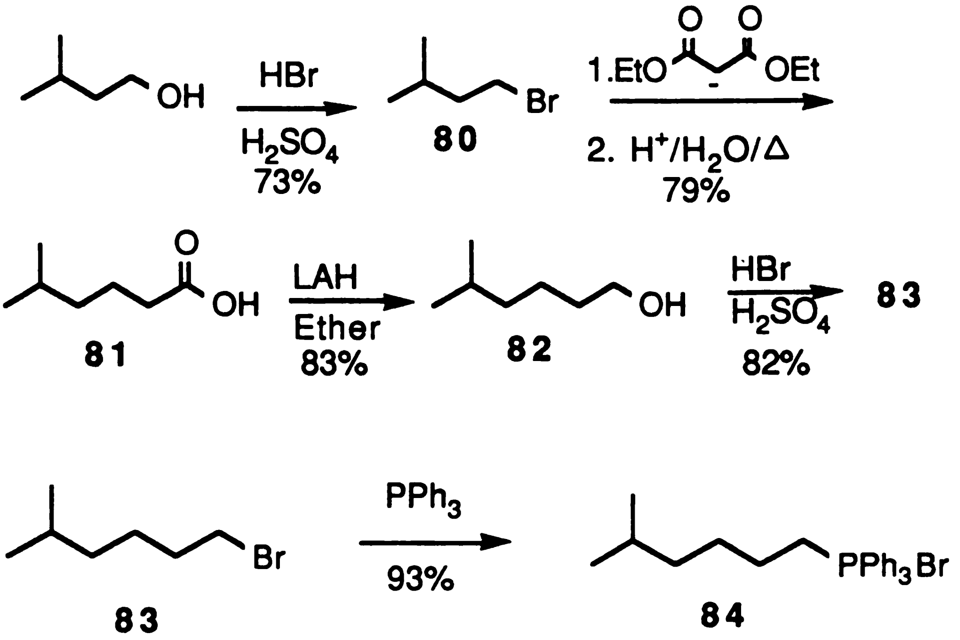
Eq. 10

In the retro-synthetic strategy shown in Scheme 35, it is clear that a method for preparing the *E* olefin **86** must be developed. In this case, the use of a bulkier ylide, would require the Wittig reaction to be undertaken at a higher temperature. Selenium dioxide oxidation of this olefin should be routine and is expected to give the β-alcohol, which would be oxidized to enone **90** (Scheme 35).



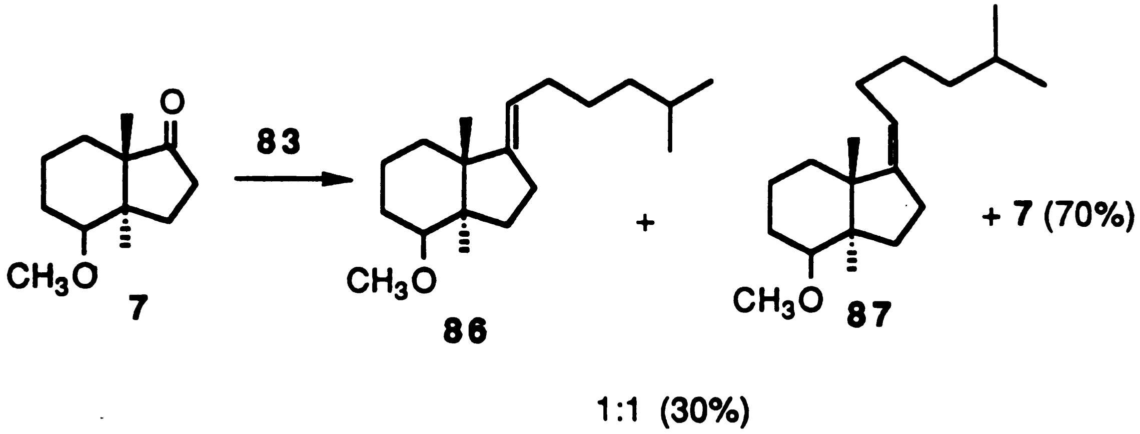
Scheme 35

The preparation of the phosphonium precursor to ylide **85** is described in Scheme 36. Treatment of 3-methyl butanol with HBr gave bromide **80** in good yield[85] Condensation of **80** with malonic ester[86] followed by acidic hydrolysis produced acid **81**, which was reduced by lithium aluminium hydride[87] to alcohol **82**. Bromination of **82** yielded the desired bromide **83**, which gave the phosphonium salt **84** in 93% yield.



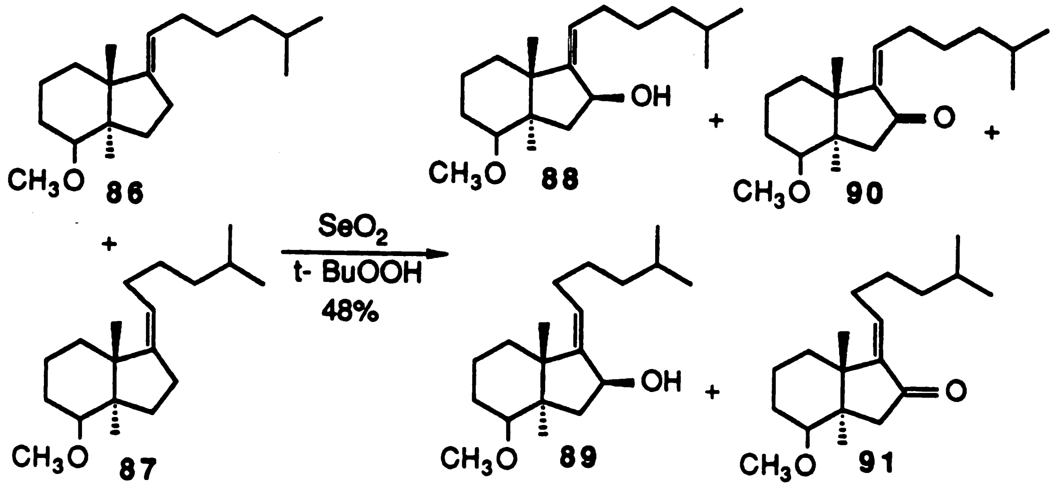
Scheme 36

Unfortunately, the reaction of ylide **85** with ketone was very sluggish. Even after four days in refluxing toluene, only a 23% conversion to a mixture of olefins **86** and **87** was realized. A substantial amount of the starting material was recovered (Eq. 11).



Eq. 11

To test the facial selectivity of the selenium oxidation, we treated the olefin mixture with selenium dioxide and t-butylperoxyl alcohol. A mixture of four compounds was obtained. These products were separated, and were identified as **88**, **89**, **90** and **91** on the basis of their NMR spectra (Scheme 37).



88 : **90** : **89** : **91** = 8 : 1 : 5 : 2

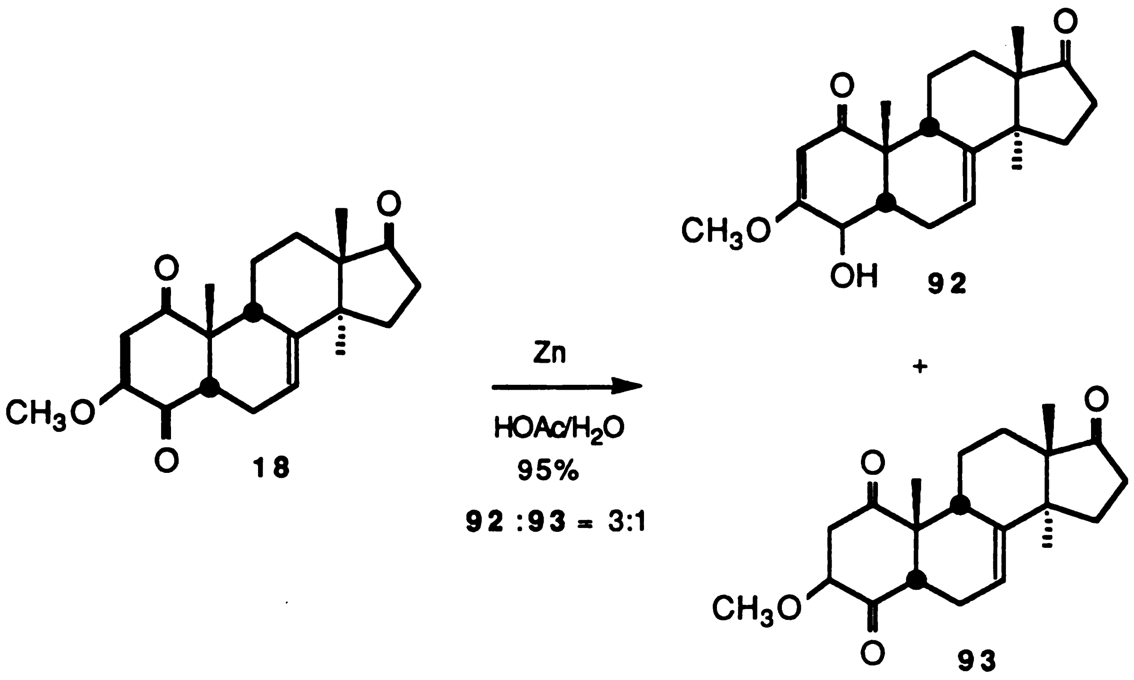
Scheme 37

Finally, compound **90** was treated with lithium methyl cuprate and proved to be unreactive. None of the desired adduct was detected and the starting enone was fully recovered.

PART 2. CONSTRUCTION OF THE TETRACYCLIC FRAMEWORK OF SENEXONOL AND LANOSTEROL

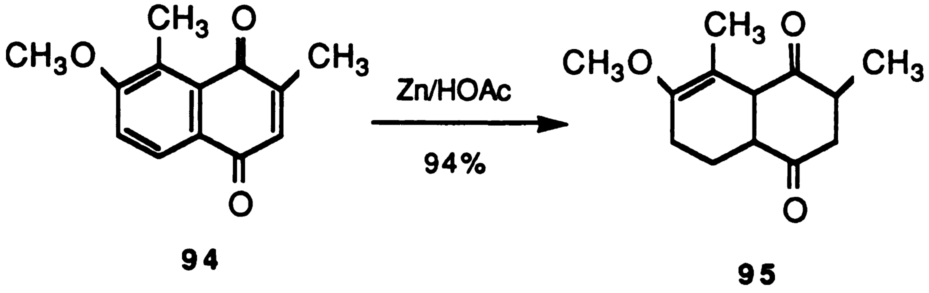
2.1 Reduction of Ring-A Functionalities of 18

In the synthesis of senexonol or lanosterol from **18**, the removal of excess functionality from ring A must be effected at some stage. Speziale's reduction procedure[49] gave good results when applied to the structurally related compound **25**. Treatment of **18** with zinc powder in acetic acid-water gave two isomeric products, **92** and **93** (Scheme 38), in a ratio that depended upon the acetic acid concentration. Glacial acetic acid gave a 1:1 mixture, whereas in dilute acid the formation of desired alcohol **92** was favored (3:1 ratio in 1:1 acetic acid-water).



Scheme 38

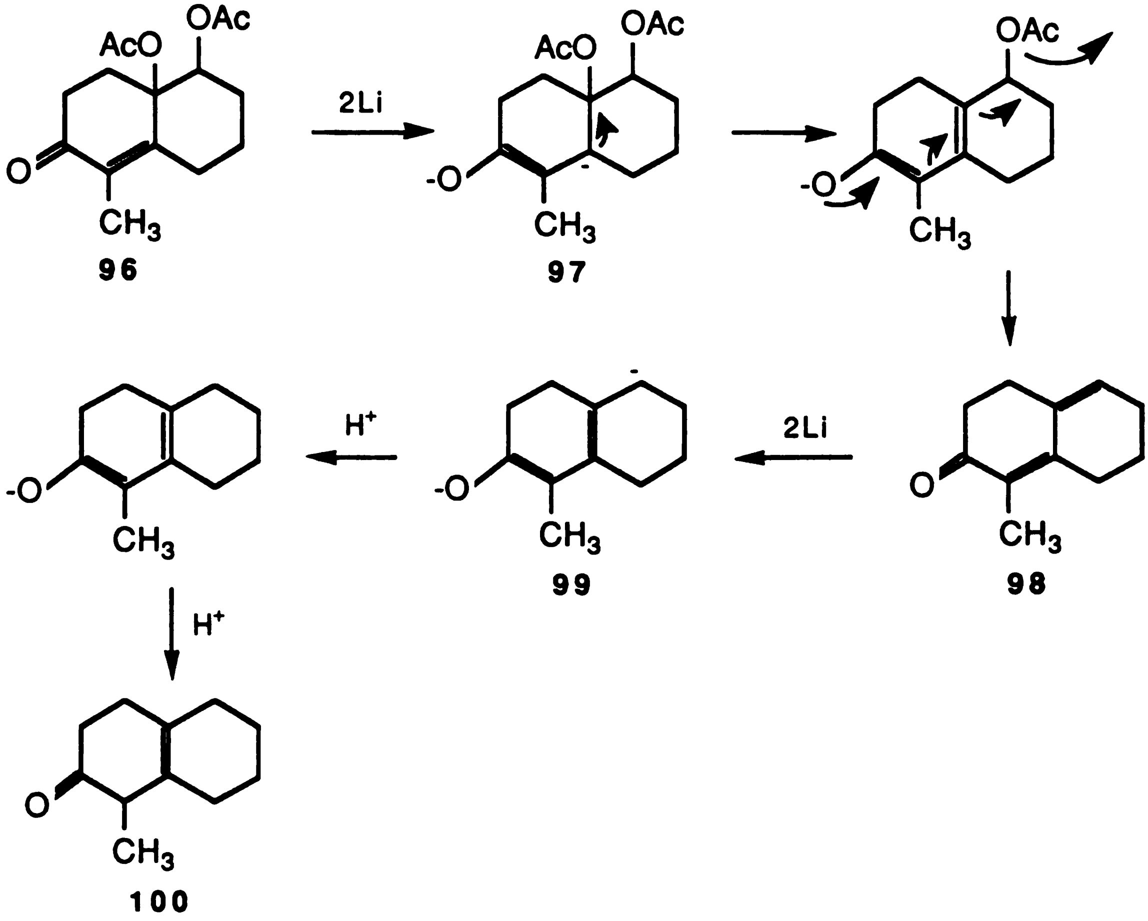
Reduction of the double bond of a conjugated enedione is not unprecedented. L. Sarett *et al.* observed[88] that compound **94** was reduced to give **95** as the only product (Scheme 39).



Scheme 39

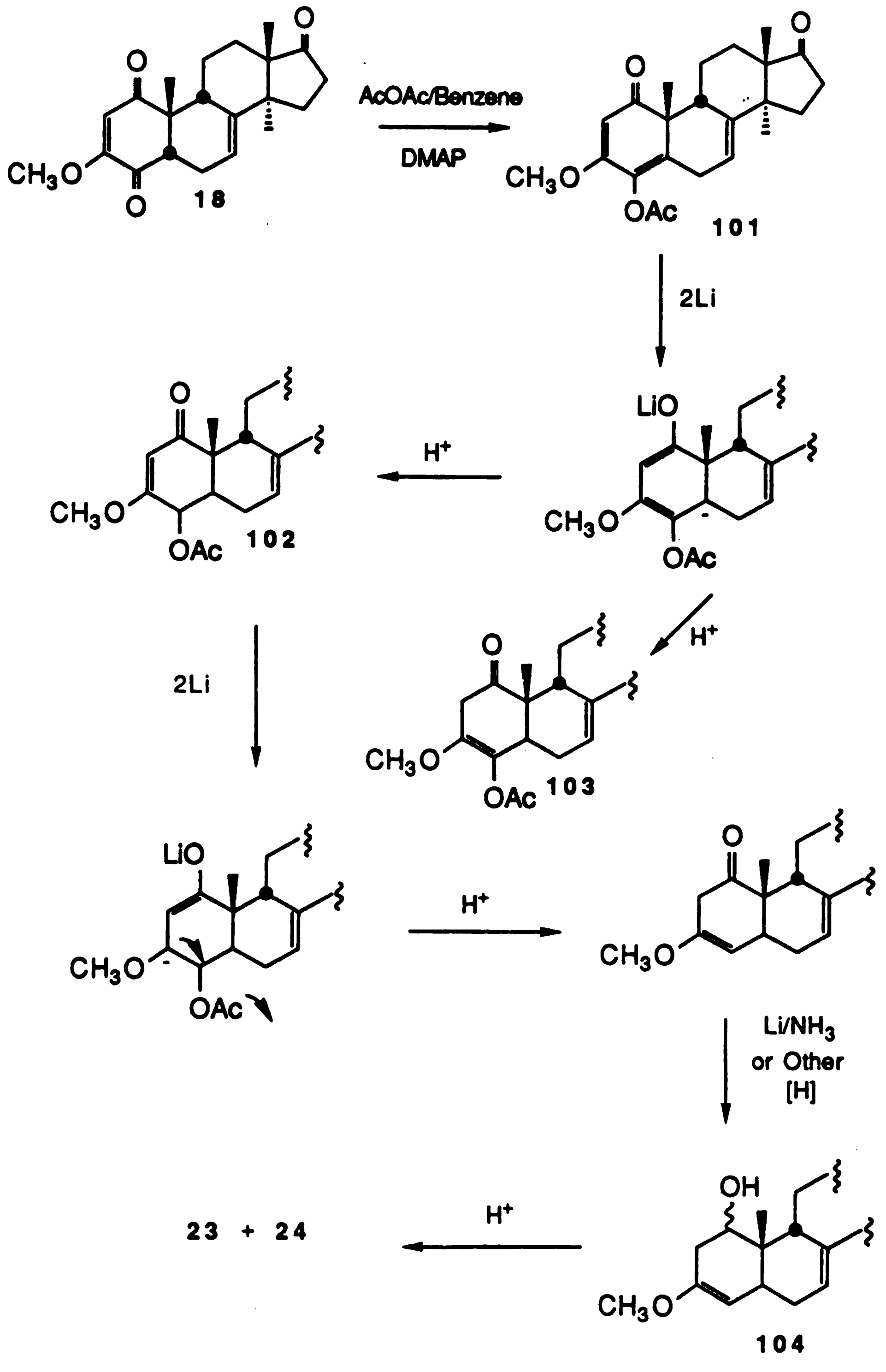
Other reducing agents such as sodium borohydride and sodium acetylborohydride[89] were also examined. Reduction of sodium borohydride with **18** gave a mixture of three products, **92** and two other unidentified compounds. On the other hand, only starting material was recovered, when sodium acetyl borohydride was used.

Another method for reducing ring A functionality is the dissolving-metal reaction, using alkali metal in liquid ammonia. Spencer *et al.* [90] have reported a sequential Birch reduction of a diacetoxy enone system **96** (Scheme 40).



Scheme 40

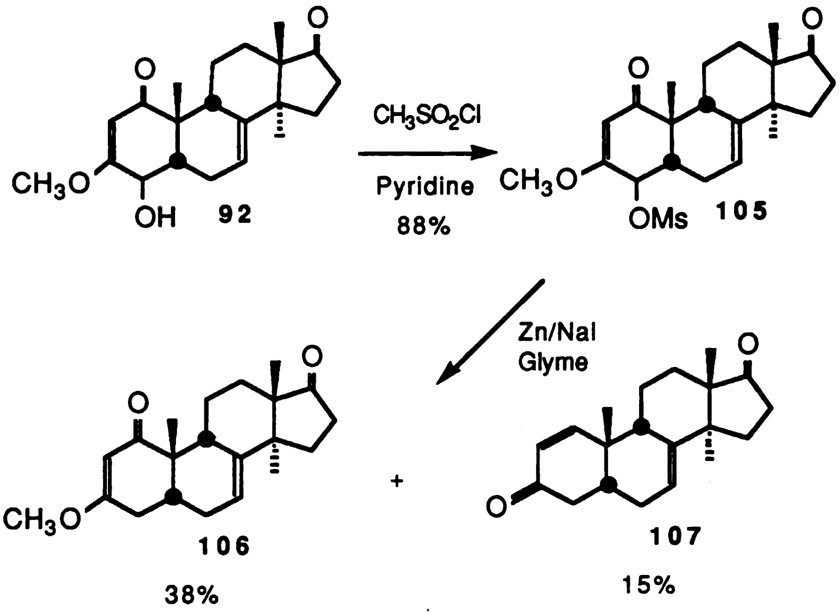
Direct Birch reduction of compound **18** is not feasible, because it would likely cause the loss of the useful 3-methoxyl group. The derived enol ester **101** is a better candidate for this reduction.[44b,c] If the initial protonation gives **102**, instead of **103**, further reduction eventually should yield alcohol **104**. Acid-catalyzed hydrolysis of this alcohol would give desired products **23** or **24** (Scheme 41).


18
AcOAc/Benzene
DMAP
101
2Li
H+
102
H+
103
2Li
H+
Li/NH3
or Other
[H]
104
H+
23 + 24

Scheme 41

Compound **101** was treated with lithium in liquid ammonia under various conditions. In all cases either the starting material **18** or a complex mixture of products was obtained.

At the same time that we were looking for better conditions to effect reduction of ring A, we also investigated subsequent transformations with alcohol **92**. A previously developed sequence is shown in Scheme 42.

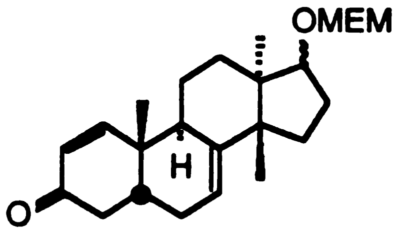


Scheme 42

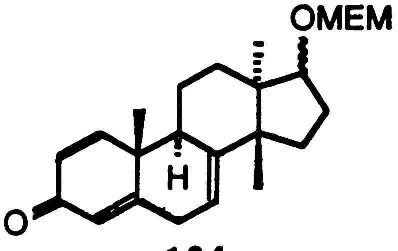
Alcohol **92** was first converted to a mesylate derivative **105** in high yield. Reduction of **105** with zinc in glyme gave two products in low yield, **106** (38%) and enone **107** (15%). This result contrasted with earlier work reported by our group. Thus, the 10-epimer of **105** (i.e., **26**) was reductively removed by zinc in glyme to give only enone **27** in high yield (p. 15).

2.2 Methylations at C-4 and Subsequent Transformations

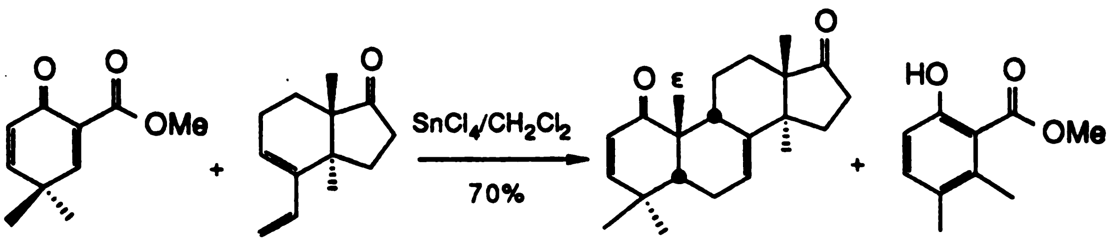
Eventually, one or two methyl groups must be introduced at C-4, depending on whether the ultimate synthetic target is senexanol or lanosterol. Previous work in our research group has probed the possibility of incorporating these methyl groups in a dienophile capable of reacting with diene **109**. Dienophile **108**[91] reacted slowly with **109** under stannic chloride catalysis; however, the yield of the desired product (Eq. 9) was low, and substantial aromatization occurred on heating. Direct methylation of enolate intermediates was successful using tetracyclic substrates **133** and **134**.[41,44b]



133



134

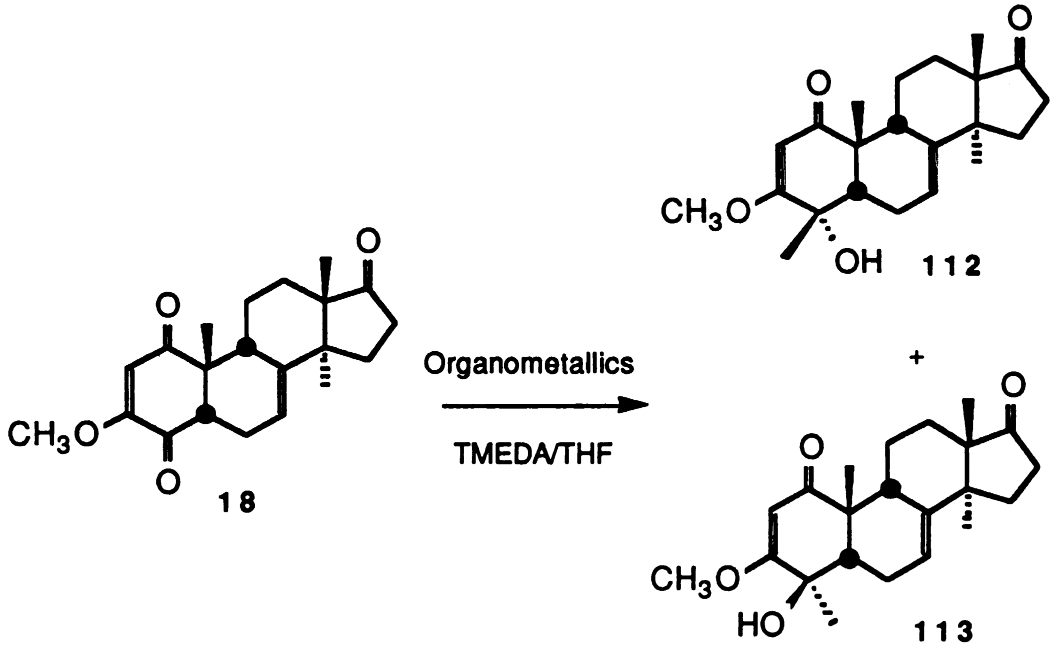


108 **109** **110** **111**

1:9

Eq. 9

We began our investigation with a study of the addition of methyl magnesium iodide to compound **18**. Although it was reported[44] that methyl lithium did not give good results in this reaction, the addition of the corresponding Grignard reagents was not investigated. We found that reaction of methyl magnesium iodide with **18** proceeded to give the 4-methyl derivatives **112** and **113** (10:1) in good overall yield. Unexpectedly, we also found that the addition with methyl lithium generated these derivatives in even better yield but lower ratio (Scheme 43):



MeMgI, 85%, **112** : **113** = 10:1
MeLi, 95%, **112** : **113** = 1:1

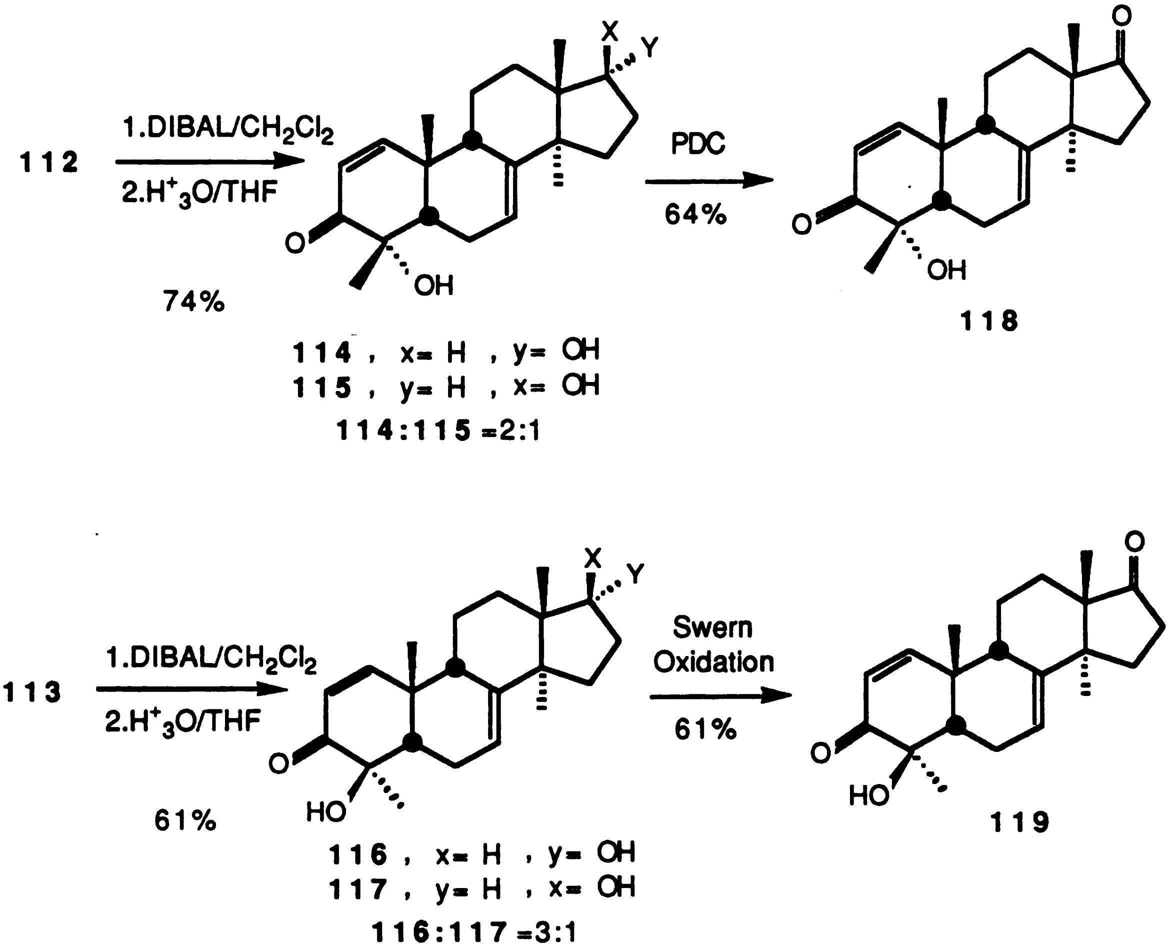
Scheme 43

The different selectivity observed here can be rationalized. Since the A-B ring junction is *cis*, the β-face of ring A should be more accessible than the α-face. Therefore a moderately reactive nucleophile such as methyl magnesium attacks preferentially from the β-side. Methyl lithium, being more reactive, attacks at both faces of ring A with little discrimination.

Following the preparation of **112** and **113**, we proceeded to study methods for removing the hydroxyl group from C-4. A simple approach to this deoxygenation is treatment with refluxing acetic acid and zinc, as described by Barton *et al.*[92] in their steroid synthesis. Birch reduction is another possibility. Derivatization of the C-4 hydroxyl in **112** and **113** with electron withdrawing groups may be necessary to facilitate cleavage of the oxygen function.

Zinc dust reduction of **112** was attempted but proved to be ineffective. Derivatization of both **112** and **113** with a number of reagents, such as acetyl anhydride, acetyl chloride, and methyl sulfonyl chloride was also largely unsuccessful. Furthermore, electrophile reagents such as methyl iodide and acetic anhydride failed to quench the initially formed anion (from addition of methyl lithium to **18**) to give the corresponding derivatives. In all cases, the starting materials were recovered. Finally, lithium-ammonia reduction of compounds **92, 112,** and **113** were also conducted, and complex mixtures were found in each case.

We next considered an alternative procedure, which involved initial conversion of **112** and **113** to four products: **114, 115, 116** and **117**.[93] Oxidation of **114** and **115**, or **116** and **117**, gave **118** or **119** in good yields. These results are shown in Scheme 44.



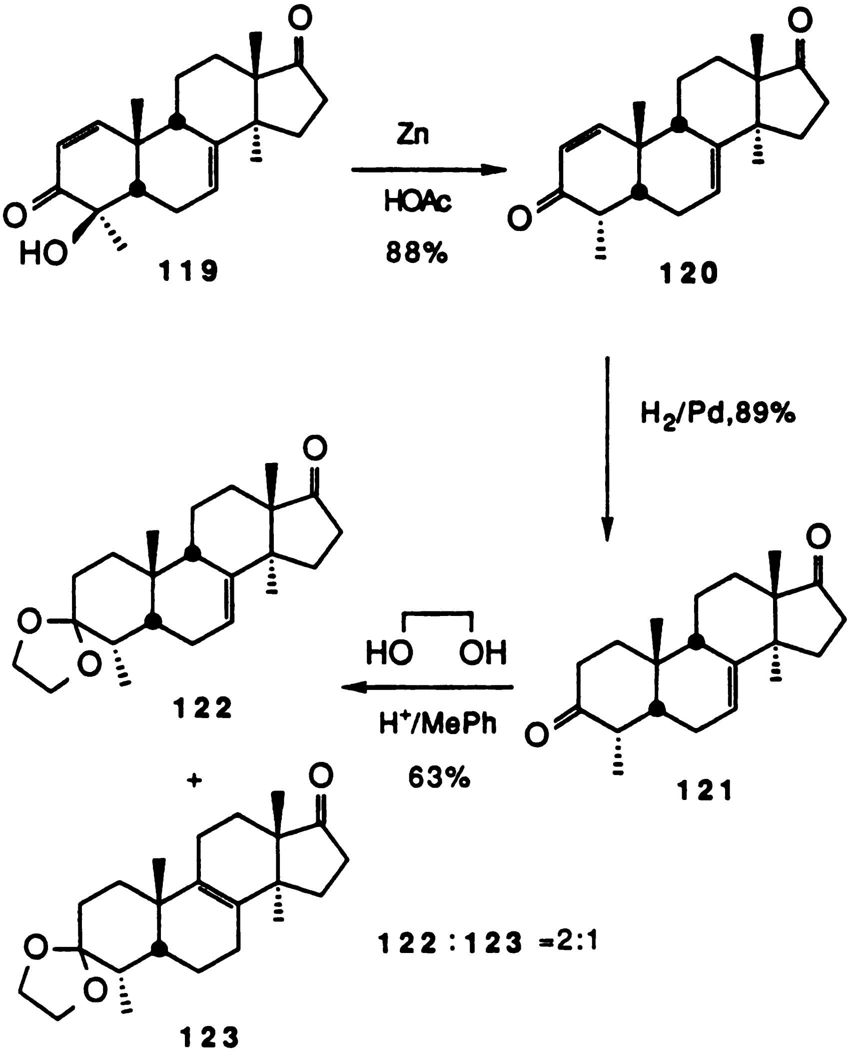
114 , x= H , y= OH
115 , y= H , x= OH
114:**115** =2:1

116 , x= H , y= OH
117 , y= H , x= OH
116:**117** =3:1

Scheme 44

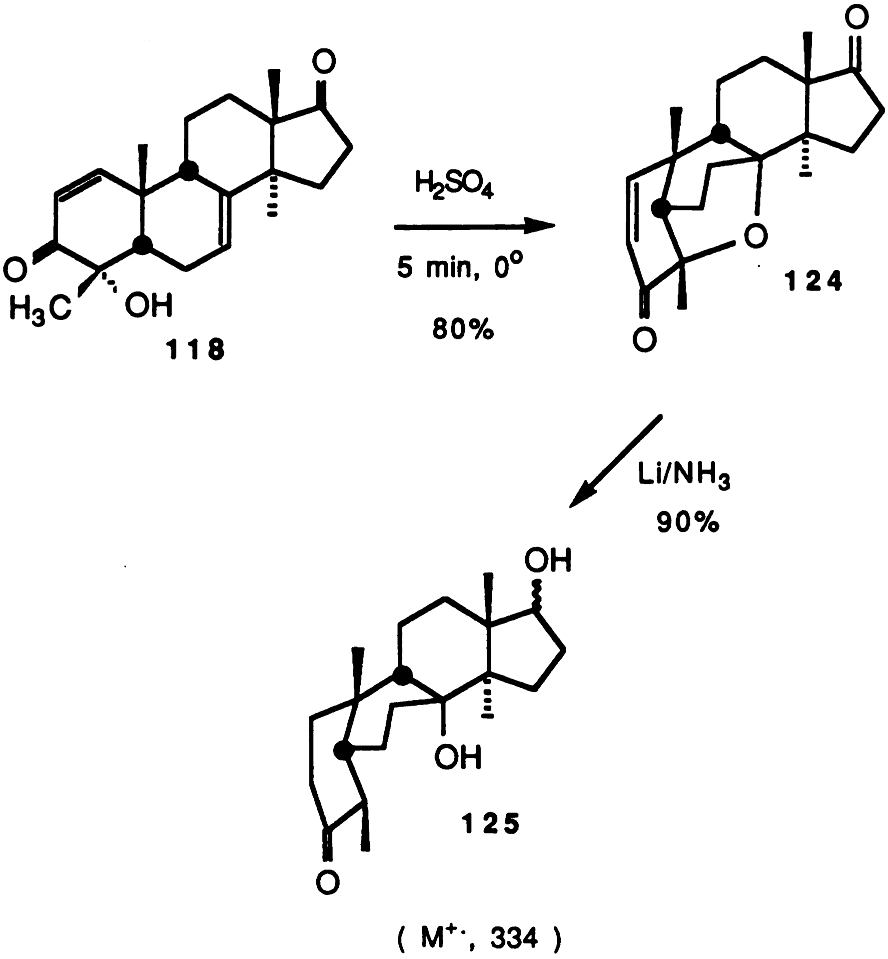
The configurations of C-17 for all four diols were determined by ^{1}H NMR. For example, C-14 angular methyl in **114** is *syn* to the 17α-hydroxyl group and therefore shifted downfield to a greater degree than the 13-angular methyl. On the contrary, the 13-angular methyl in **115**, being *syn* to the 17β-hydroxy group, should have greater downfield shift. As a result, compound **114** (4α, 17α-dihydroxyl derivative) would display two methyl singlets (in the proton NMR) with a larger $\Delta\delta_{CH_3(13)}$-$\delta_{CH_3(14)}$ than that of epimer **115**.

Once compounds **118** and **119** were prepared, they were treated with zinc in refluxing acetic acid. Although **118** did not react, **119** gave the reduced dienone **120** in high yield. By catalytic hydrogenation, **120** was converted cleanly to **121** which was then protected by ketalization at C-3 to give the potentially useful isomers **122** and **123** (Scheme 45).



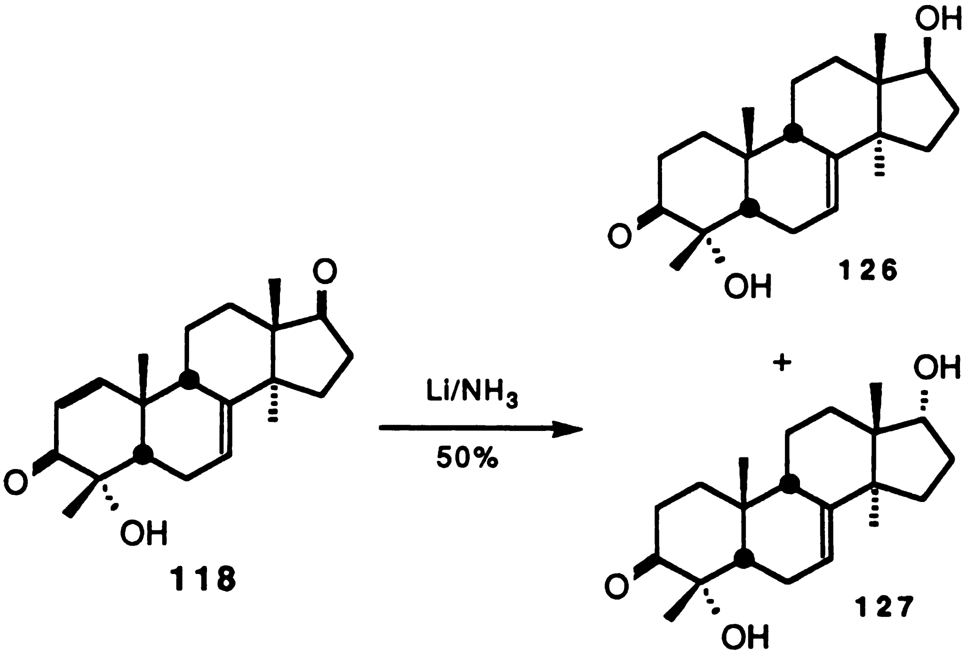
Scheme 45

Another approach, involving deoxygenation with concurrent formation of a carbon double bond, was also considered. It has been reported[94] that α-hydroxy ketones are dehydrated by strong acid to give a α,β-unstaturated ketones. If compounds **118** and/or **119** could be transformed to the corresponding enone in this way, we should be able to control the configuration of C-5 by Birch reduction, thus moving closer toward the synthesis of senexonol skeleton.[45] Alternatively, a second methyl group might be attached at C-4 (using Woodward's method[15]) to generate the lanosterol skeleton. Care must be taken in applying this method to compounds **118** or **119**, because these compounds may undergo acid-catalyzed rearrangements.[95] Indeed, compound **119** was found to give involved products, possibly from the rearrangement, on treatment with conc. H_2SO_4 at 0 °C, whereas under the same conditions, **118** gave a single product **124**. This newly obtained product exhibited no C-7 olefinic signal in its proton NMR and showed a molecular ion at 328 (m/e) in mass spectrum. These facts suggested that either the Δ-7,8 had migrated to the 8,9 position, or that intramolecular addition of the C-4 hydroxyl to 7,8-double bond had occurred. Birch reduction of **124** gave only **125**, which exhibited a methyl doublet in its proton NMR (suggesting hydrogenolysis of the C-O bond at C-4) and a molecular ion at mass 334. Considering this information, we have proposed the following scheme.



Scheme 46

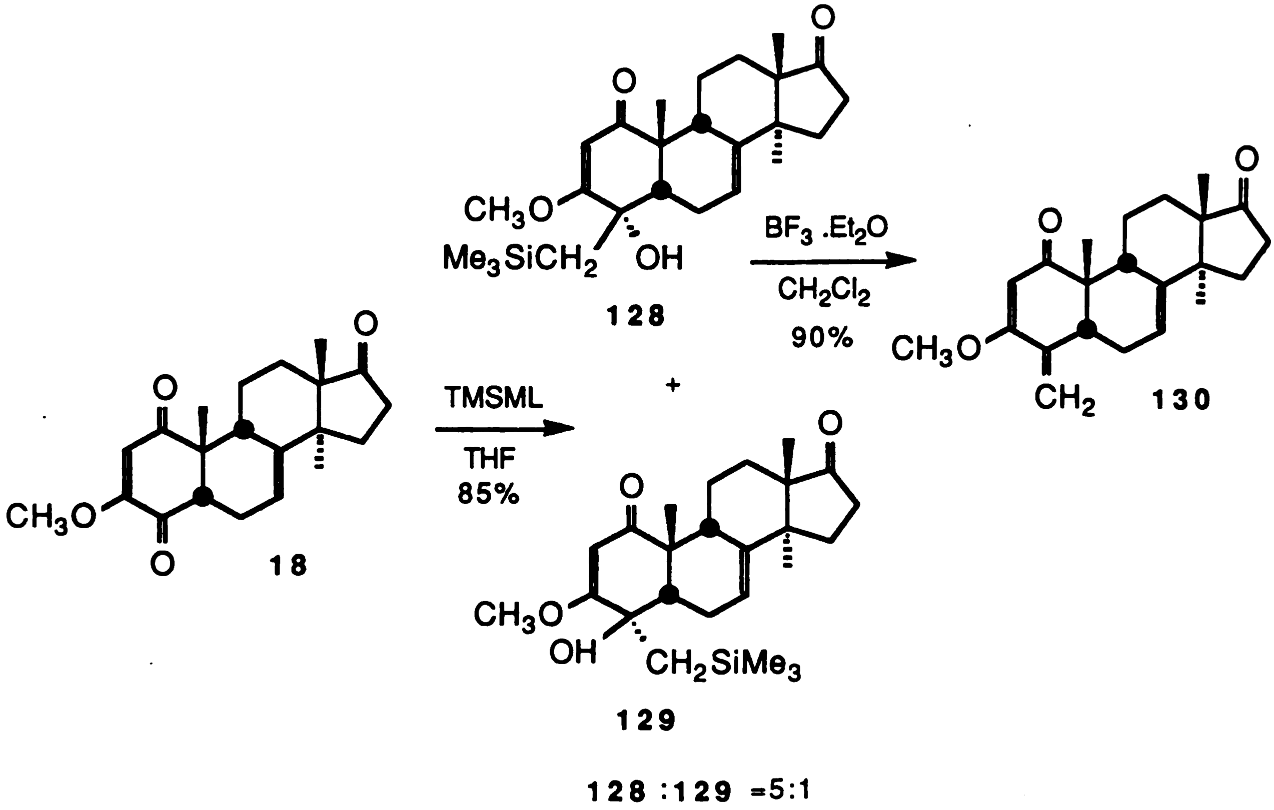
Molecular models of **118** indicate that the hydroxy group at C-4 has an ideal orientation for addition to the 7,8-double bond. The Birch reduction of the resulting cyclic ether (**124**) cleaved the C-O bond at C-4, leaving a hydroxyl group at C-7. Interestingly, this C-O bond in **118** was not cleaved in the Birch reduction, giving only the saturated diols **126** and **127** (Scheme 47).



126:**127** =6:1

Scheme 47

Finally, methylation for converting intermediate **18** to its 4-methylene derivative was studied. Reactions of **18** with methylene triphenylphosphorane did not proceed well.[44b] We found, however, that addition of trimethylsilylmethyl lithium[96] efficiently converted **18** to **128** and **129** (5:1) in excellent yield. Furthermore, the silyl group in both **128** and **129** was readily removed by the action of boron trifluoride, to yield **130** as the only product (Scheme 48):



Scheme 48

Selective methylene addition to the exocyclic methylene group in **130** should give a cyclopropyl derivative, which might then be cleaved to a 4,4-dimethyl compound by catalytic hydrogenation.[97]

EXPERIMENTAL SECTION

Unless otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere, using solvents distilled from appropriate drying agents. Reactions were generally monitored by thin layer chromatography (silica gel 60 F_{254}, E. Merck), and analytical samples were prepared by Flash Chromatography using 230-400 mesh silica gel. UV spectra were obtained on a Perkin-Elmer spectrophotometer-HITACHI 200. IR spectra (with sample in $CDCl_3$) were obtained on Perkin-Elmer 237 B or on Perkin-Elmer 599 Infrared spectrophotometers. ^1H NMR spectra were taken in $CDCl_3$ solution using either a Varian T-60 (60 MHz) or a Bruker Cryospec WM 250 (250 MHz) spectrometer, and were calibrated in parts per million (δ) from tetramethyl silane. ^{13}C NMR spectra were determined in deuterated chloroform with Bruker Cryospec WM 250 (250 MHz) instruments and calibrated in parts per million from $CDCl_3$. Double resonance experiments were made on the same Bruker instruments using a directional coupler. Shifting reagent studies were conducted with 2,2,6,6-tetramethyl heptanedionate europium. Mass spectra were obtained with a Finnigan model 4000 gas chromatography / mass spectrometer system, and recorded as m/e vs relative intensity. High resolution mass measurements were determined on a JEOL HX 100 spectrometer. Ultrasound assisted experiments used a Branson 2200 laboratory cleaner, or the High Intensity Ultrasonic Processor (frequency 20 K Hz) made by Sonic and Materials Inc.. Elemental analyses were conducted by Spang Microanalytical Laboratory. Melting points (°C, uncorrected) were measured on a Thomas Hoover Capillary Melting Point Apparatus or on a Reichert hot stage.

Epoxidation of methoxy olefin 12 with unbuffered peracid. A 0.140 g (0.72 mmol) sample of **12** dissolved in 5 mL CH_2Cl_2 at 0 °C, was treated with a solution of 100 mg MCPBA (85%) in 5 mL CH_2Cl_2 for 30 h. To this, was added 10 mL Na_2SO_3 (5%) to reduce unreacted peracid. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave a light brown oil, which was passed through a column of silica gel (Ether-Pet.Ether/ 2:1) to give 85 mg of white crystalline **40**.

Characteristic properties of **40**: mp, 70.5-71.5 °C; ^{1}HNMR, 3.39 (1H, B of AB, J=11), 3.28 (3H, s), 3.26 (1H, A of AB, J=11), 3.17 (1H, s), 2.92 (1H, d, J=4), 0.99 (3H, s), 0.91 (3H, s); MS, 226 (M+.).

Epoxidation of 12 to give epoxides 36a and 36b. To a flask containing 15 mL $NaHCO_3$ solution (0.5 M), was added 194 mg (0.1 mmol) of methoxy olefin **12** in 15 mL methylene chloride. This was followed by addition of 0.22 g MCPBA (85%) in 10 mL methylene chloride through a dropping funnel. After the bi-layer mixture was stirred one day at r.t., 5 mL Na_2SO_3 solution (5%) was added to reduce excess peracid. The two layers were separated. The aqueous layer was extracted with 10 mL CH_2Cl_2. The combined organic layer was washed three times with 0.5 M $NaHCO_3$ solution, and dried with K_2CO_3 (one drop pyridine was added to maintain slightly basic condition). A 155 mg mixture of **36a** and **36b**, as a yellow oil, was obtained after removal of the solvent. Flash chromatography of the mixture gave pure samples in 85% recovery.

Characteristic properties of **36a** (α epoxide): ^{1}H NMR, 3.31 (3H, s), 2.63 (1H, d, J=5), 2.56 (1H, s), 1.13 (3H, s),1.04 (3H, s).

Characteristic properties of **36b** (β epoxide): ^{1}H NMR, 3.31 (3H, s), 2.88 (1H, d, J=5), 2.66 (1H, d, J=5), 1.19 (3H, s), 0.97 (3H, s). Since the two epoxides were acid sensitive, they were directly used for next reaction without further purification.

Reaction of epoxides 36a and 36b with diethyl aluminum-2,2,6,6-tetramethyl piperidide to give 39. To 1.48 mL n-BuLi (1.6 M in hexane) was added 0.84 mL (2.4 mmol) 2,2,6,6-tetramethyl piperidine followed 20 min. later by addition of 1.55 mL Et_2AlCl (1.48 M in benzene). A solution of epoxides **36a** and **36b** (0.115 g, 0.55 mmol) in 5 mL of benzene was added to this stirred mixture, and after a 4 h period, the reaction was quenched by addition of 2 mL aqueous methanol (1:1). The resulting mixture was neutralized carefully and extracted with ether. The ether layer was dried over K_2CO_3, and after evaporation of the solvent gave a 0.113 g of a yellow oil. Chromatographic separation yielded 38 mg of **39**, and 46 mg of an unidentified product. An acetate derivative, **132**, of **39** was prepared by treatment with acetic anhydride in pyridine (70 % yield).

Characteristic properties of **39**: IR, 3610, 1600, 1090, 1025, 827. ^{1}H NMR, 5.37 (1H, tr, J=3), 3.44 (1H, B of AB, J=13), 3.37 (1H, A of AB, J=13), 3.35 (3H, s), 3.24 (1H, tr, J=3), 1.40 (1H, d, d, J_1=8, J_2=12), 1.25 (1H, d, d, J_1=7, J_2=12), 1.05 (3H,s), 1.00 (3H, s).

Characteristic properties of **132**: IR, 1720, 1600, 1452, 1370, 1250, 1083, 1025, 815. ^{1}H NMR, 5.38 (1H, tr, J=4), 3.96 (1H, B of AB, J=11), 3.90 (1H, A of AB, J=11), 3.35 (3H, s), 3.24 (1H, tr, J=3), 2.06 (3H, s), 1.00 (3H, s), 1.43 (1H, d of d, J_1=7, J^2=14), 1.24 (1H, d, d, J_1=6, J_2=11), 1.06 (3H, s). As expected, **39** gave **40** upon epoxidation with MCPBA.

Lithium dimethyl amide induced epoxide ring opening of 36. Liquid Me_2NH (0.15 ml) was treated with 3.0 mL n-BuLi (1.6 M in hexane) at -78 °C for five min. This mixture was then warmed to -5 °C and allowed to react with a 159 mg (0.76 mmol) sample of epoxides (**36a** and **36b**) dissolved in 6 mL of ether. The colorless solution turned slightly yellow and some precipitates was observed. After the reaction mixture was stirred overnight at 0 °C, it was quenched with water and extracted with ether. The ether extracts were washed, dried over K_2CO_3 and evaporated to give a yellow oil (140 mg), which was shown to be a mixture of **37** and **36b** (1:1) by ^1H NMR. When this reaction was conducted in refluxing ether, a similar ratio of **37** to **36b** was observed. Characteristic properties of **37**: IR, 3600, 1630, 1460, 1375, 1200,1100, 1085, 880. ^1H NMR: 5.50 (1H, s), 4.17 (2H, s), 3.34 (1H, s), 3.33 (3H, s), 2.70 (1H, d, J=16), 1.17 (3H, s), 1.01 (3H, s). ^{13}C NMR: 152.6, 122.6, 83.2, 60.1, 57.7, 50.4, 48.3, 37.7, 30.9, 26.8, 24.7, 23.3, 22.6,17.5.

Olefination of 43 to give 44. To 4.0 mmol orange colored triphenyl phosphonium methylide (generated from methyl triphenylphosphonium bromide by treatment with potassium t-amylate in refluxing benzene solution) was added 117 mg (0.35 mmol) of ketone **43** in 5 mL hot benzene. This mixture was refluxed for 22 h, then cooled and quenched with ice. The crude product was mixed with water and extracted with ether. The ether extract was dried over $MgSO_4$, and after evaporation of the solvent gave 550 mg of a solid residue. Chromatographic purification produced 101 mg of olefin **44**. Characteristic properties of **44**: mp, 105-107 °C; ^1H NMR, 4.70 (2H, br. s), 3.99 (4H, s), 2.51-1.00 (22H, m), 0.89 (3H, s), 0.81 (3H, s).

Epoxidation of 44 to epoxides 45a and 45b. Two phase methylene chloride-aqueous sodium bicarbonate solvent mixture (10 mL each) was mixed with 90 mg (0.5 mmol) of MCPBA, followed after 10 min by addition of 100 mg (0.30 mmol) of olefin **44** in 4 mL methylene chloride. After being stirred for 8 h, the reaction mixture was treated with Na_2SO_3 solution and extracted with methylene chloride. Evaporation of the solvent gave 80 mg of a mixture of **45a** and **45b** in ratio of 9:1.

Characteristic properties of **45a**: ^{1}H NMR, 3.94 (4H, s), 2.73 (1H, d, J=5), 2.66 (1H, d, J=5), 1.90-1.10 (22H, m), 0.84 (3H, s), 0.82 (3H, s).

Characteristic properties of **45b**: ^{1}H NMR, 3.94 (4H, s), 2.90 (1H, d, J=5), 2.60 (1H, s, J=5), 1.90-1.10 (22H, m), 0.98 (3H, s), 0.88 (3H, s).

Oxidation of allylic alcohol 37 to unsaturated aldehyde 38. To 0.160 g (0.43 mmol) of PDC in 5 mL DMF at 0 °C , was added 74 mg (0.35 mmol) of allylic alcohol **37** in 4 mL DMF. This mixture was stirred for 12 h at 0 °C then filtered. The filtrate was diluted with ether, which was then washed with water. The ether solution was dried over $MgSO_4$. Removal of the solvent under vacuum yielded 90% of unsaturated aldehyde **38**.

Characteristic properties of **38**: ^{1}H NMR, 9.71 (1H, s), 6.67 (1H, d, d, J_1=2, J_2=4), 3.33 (1H, s), 3.31 (3H, s), 2.91 (1H, d, J=18),1.22 (3H, s), 0.99 (3H, d, J=1).

Selenium dioxide oxidation of 12 to allylic alcohol 46 and unsaturated ketone 48. A mixture of 0.23 mL (4 eq) 90% t-butylhydroperoxide and 28.6 mg (0.5 eq) SeO_2 in 10 mL methylene chloride was agitated for 30 min, before addition of a 100 mg (0.52 mmol) sample of methoxy olefin **12** in 5 mL CH_2Cl_2. The reaction mixture was stirred at r.t. for 22 h, then washed with NaOH (10%, 3x25 mL), and brine (25 mL). Evaporation of the solvent yielded a lightly colored oil (118 mg). ^{1}H NMR (250 MHz) indicated that the oil contained **46** (80%) and **48** (20%). Separation of the mixture was carried out by means of chromatography.

Characteristic properties of **46**: IR, 3602, 1470, 1375, 1315, 1200, 1135, 1085, 1020, 880; ^{1}H NMR, 5.03 (1H, d, J= 1), 4.78 (1H, d, J=2), 4.59 (1H, d, d, tr, J_1=8, J_2=7, J_3=1), 3.31 (3H, s), 3.20 (1H, tr, J=3), 2.12 (1H, d, d, qua, J_1=9, J_2=7, J_3=1), 2.00 (1H, s, br),1.82-1.42 (7H, m), 0.75 (3H, d, J=1); ^{13}C NMR, 163.8, 104.9, 83.1, 73.7, 57.8, 46.3, 45.6, 40.4, 29.1, 24.6, 24.2, 23.2,17.3; MS, 210 (0.6), 192 (0.6), 177 (3), 160 (12), 145 (36), 71 (80), 41 (100). Elemental analysis, Cal., C, 74.24; H, 10.54. Found, C,74.33; H, 10.50.

Characteristic properties of **48**: IR, 2830, 1725, 1650, 1270, 1130, 1085, 890; ^{1}H NMR, 5.75 (1H, s), 4.87 (1H, s), 3.31 (3H, s), 3.28 (1H, s), 2.88 (1H, d, q, J_1=17, J_2=1), 1.77 (1H, d, J=17), 1.60-1.95 (7H, m), 1.25 (3H, s), 0.92 (3H, d, J=1); ^{13}C NMR, 207.8, 155.9, 110.0, 81.7, 57.5, 45.6, 44.8, 42.5, 28.2, 24.4, 22.8,17.3; MS, 208 (8), 193 (2), 176 (9.4), 165 (3), 161 (15), 148 (17), 135 (44), 107 (19), 71 (78), 55 (54), 41 (100). Elemental analysis, Cal., C, 74.96, H, 9.68. Found, C, 74.74; H, 9.72.

The unsaturated ketone **48** could be also obtained by the following one-pot reaction procedures: a 98 mg (0.51 mmol) sample **12** in 10 mL methylene chloride was treated, in the same manner, with SeO_2 and peroxy t-butanol. After 24 h, 0.291 g (1.5 eq) PDC was added. The heterogeneous mixture was stirred for six h, and filtered through a short column of silica gel which was then rinsed, for a few times, with ether. The filtrate was washed with Na_2SO_3 (10%), NaOH (10%), water, and brine, and dried over $MgSO_4$. A 100 mg product (lightly colored oil) was obtained. ^{1}H NMR spectrum showed the desired product **48** to be 90% pure.

Reduction of unsaturated ketone 48 to alcohol 47. To a 82 mg (0.39 mmol) sample of enone **48**, was added 146.9 mg (1 eq.) $CeCl_3 \cdot 7\ H_2O$ in 1 mL CH_3OH, followed by slow addition of $NaBH_4$ (12 mg, 1 eq). Hydrogen gas evolved immediately. After 5 min, the mixture was poured into water and extracted with ether. The organic layer was washed with water, brine and dried over $MgSO_4$. Removal of the solvent yielded a colorless oil (90%) which, on standing, solidified. ^1H NMR showed it to be pure alcohol **47**.

Characteristic properties of **47**: mp, 71.0-72.5 °C; IR, 3605, 3070, 1450, 1370, 1250, 1195, 1075, 875; ^1H NMR, 4.95 (1H, d, J=2), 4.78 (1H, d, J=8), 4.74 (1H, d, J=2), 3.29 (3H, s), 3.23 (1H, s), 2.65 (1H, d, d, qua, J_1=13, J_2=8, J_3=1), 1.27 (6H, m), 1.20 (1H, d, J=13), 1.08 (3H, s), 0.92 (3H, d, J=1); ^{13}C NMR, 165.0, 101.3, 83.1, 72.2, 57.6, 47.4, 45.5, 40.6, 28.9, 24.6, 24.1, 23.2, 16.9; MS, 210 (1), 178 (12), 163 (31), 145 (29), 121 (50), 107 (39), 93 (35), 79 (36), 71 (100), 55 (57); Elemental analysis, Cal., C, 74.24; H, 10.54. Found, C, 74.27; H, 10.59.

Preparation of R-sulfoxide 53. To1.5 eq n-BuLi (in hexane) diluted with 5 mL THF at -78 °C was added a 77 mg (0.37 mmol) sample of alcohol **46** in 5 mL THF, followed, 15 min later, by slow addition of 0.1 mL TMEDA. The mixture was stirred for another 5 min. then treated with 107 mg (0.74 mmol) phenyl sulfenyl chloride in 5 mL THF. White particles (LiCl) deposited within a few seconds. Temperature was raised to -45 °C at which the milky reaction mixture was stirred for another 30 min. The reaction was quenched by addition of NH_4Cl saturated solution, and extracted with ether. The ether extract was dried over $MgSO_4$. Removal of the solvent under vacuum gave 332 mg orange oil which upon the flash chromatography (eluent, ether-hexane) yielded 84 mg (82 %) R-sulfoxide **53** as a colorless oil.

Characteristic properties of 15: ^{1}H NMR, 7.52-7.68 (5H, m), 5.48 (1H, s), 3.59 (1H, d, B of AB, J=13), 3.52 (1H, d, A of AB, J=13), 3.29 (3H, s), 3.29 (1H, s), 2.68 (1H, d, J=15), 1.15-1.81 (7H, m), 1.09 (3H, s), 0.93 (3H, s); ^{13}C NMR, 142.0, 131.1, 120.4, 129.0, 124.6, 124.2, 83.1, 57.7, 57.8, 49.3, 38.4, 26.4, 24.7, 23.1, 22.3, 17.5; MS, a weak molecular ion (318) was observed. Strong fragment ions were found at 161, 149, 119, 105, 91, 77, 71 and 55.

Desulfuration of R-sulfoxide 53 under various conditions. *Condition A*: The R-sulfoxide was stirred at r. t. with trimethyl phosphite in methanol for 12 h. 95% R-sulfoxide and 3% alcohol **46** were recovered.

Condition B : The R-sulfoxide was stirred at r. t. with trimethyl phosphite in methanol for 2 days. Alcohol **46** was the only product (> 95%) recovered.

Condition C : The R-sulfoxide was refluxed in methanol for one day in presence of trimethyl phosphite, and found to be transformed quantitatively to alcohol **46**, free of alcohol **47**.

Preparation of sulfenate ester 54 and S-sulfoxide 55. To 0.5 mL n-BuLi (1.3 M, in hexane) diluted with 5 mL THF at -78 °C, was added a 92 mg (0.44 mmol) sample of alcohol **47** in 5 mL THF, and after 20 min, 0.1 mL TMEDA. This was followed by addition of 107 mg (0.74 mmol) phenyl sulfenyl chloride in 5 mL THF. White particles (LiCl) formed shortly. Temperature was warmed up-to -45 °C, at which the reaction mixture was stirred for another h. Saturated NH_4Cl solution was poured to quenched the reaction. The reaction mixture was extracted with ether. The organic layer, without being washed with water, was dried over $MgSO_4$. A 322 mg orange colored oil was yielded. ^{1}H NMR spectrum showed it to be sulfenate ester **54**. On standing at r.t. for 24 h, **54** transformed entirely into a crude product of **55** (free of R isomer, as judged by ^{1}H NMR). Flash chromatography (eluent, ether-hexane) gave a 88 mg analytical sample of S-sulfoxide **55** as an oil .

Characteristic properties of **54**: ^{1}H NMR, 7.40-7.64 (5H, m), 5.17 (1H, s) , 4.79 (1H, s), 4.70 (1H, d, J=8), 3.23 (3H, s), 3.18 (1H, s), 2.57 (1H, d, d, J_1=14, J_2=9), 1.13-1.79 (7H, m), 1.01 (3H, s), 0.91 (3H, s).

Characteristic properties of **55**: IR, 1460, 1445, 1375, 1265, 1200, 1180, 1080, 1030, 880, 690; ^{1}H NMR,7.50-7.70 (5H, m), 5.57 (1H, s), 3.54 (1H, d, B of AB, J=15), 3.40 (1H, d, A of AB, J=15), 3.31 (3H, s), 2.70 (1H, d J=15), 1.60-1.90 (7H, m), 1.16 (3H, s), 1.03 (3H, s); ^{13}C NMR, 145.0, 142.3, 131.8, 131.2, 129.5, 124.7, 83.3, 59.2, 58.0, 50.5, 49.4, 38.5, 26.8, 24.9, 23.1, 22.4, 17.6; MS, a molecular ion was not observed. Strong fragment ions were found at 161 ($C_{10}H_9S$), 119, 105, 91, 77, 71 and 55.

Preparation of methyl sulfoxide 56. A solution of 0.08 mL Et_2NH (in 3 mL THF) was treated with 1.2 eq n-BuLi. To this base was added, 15 min later, a 85 mg (0.27 mmol) sample of S-sulfoxide **55** in 5 mL THF. The originally light yellow solution turned orange immediately. The reaction mixture was stirred at -78 °C for 10 min, warmed up to - 45 °C for 5 min, then re-cooled to -78 °C. To this bright orange solution, was added 0.1 mL TMEDA, followed,10 min late, by addition of 0.1 mL MeI (6 eq) in 3 mL THF. The solution was stirred for 5 min then warmed to -45 °C, and white particles were observed within 20 min. The reaction was continued for another 1.5 h, then quenched by addition of NH_4Cl saturated solution. The mixture was extracted with ether. Removal of the solvent yielded 80 mg light yellow oil. ^{1}H NMR spectrum of the reaction mixture showed **56** as the only product, free of other isomers.

Characteristic properties of **56**: IR, 1460, 1448, 1375, 1265, 1200, 1090, 1035, 1025, 880, 790; ^{1}H NMR, 7.46-7.57 (5H, m), 5.36 (1H, s). 3.47 (1H, qua, J=8), 3.34 (1H, s), 3.32 (3H, s), 2.75 (1H, d, J=15), 1.42-1.82 (7H, m), 1.21 (3H, s), 1.12 (3H, d, J=8), 0.95 (3H, s).

Proton and deuterium quenching of conjugated base of 56. A 68 mg (0.20 mmol) sample of methyl sulfoxide **56** in 10 mL THF was treated with 1.2 eq Et_2NLi at -78 °C for 20 min. One part of this freshly made methyl sulfoxide anion solution was poured through side arm of a flask to an ice-cold saturated NH_4Cl solution (kinetic quenching). To the remaining anion solution warmed to 0 °C was added slowly acetic acid (thermodynamic quenching). Products from both ways of quenching proved to be the same as starting methyl sulfoxide **56**.

A 20 mg (0.06 mmol) sample of methyl sulfoxide **56** was treated with 1.2 eq Et_2NLi at -78 °C, warmed to 0 °C, then quenched with D_2O. Deuterated methyl sulfoxide (22 mg) was recovered after workup ^1H NMR showed that the original methyl doublet (1.12 ppm, J=8) became a singlet.

Desulfuration of S-sulfoxide 55 under various conditions. *Condition A*: To a 30 mg (0.09 mmol) sample of sulfoxide **55** in 8 mL methanol was added via syringe 0.07 mL of distilled trimethyl phosphite. The resulted solution was stirred for 11 h at room temperature. TLC showed that a considerable amount of sulfoxide still existed. The temperature was raised up to the b.p. of methanol, and the reaction stirred for 24 h. Removal of the solvent gave a product residue (30 mg) which was shown to be a mixture of two alcohols **46** and **47** in ratio of 1 : 2.

Condition B: The S-sulfoxide was stirred at r.t. for 2 days. No desulfuration was observed. Starting sulfoxide **55** was fully recovered.

Desulfuration of phenyl sulfenate 54. The phenyl sulfenate **54** was stirred in MeOH at r.t. with trimethyl phosphite (3 fold) for 31 h. Alcohol **47** (70%) was obtained as only isomer.

Treatment of alcohol 46 and alcohol 47 respectively with trimethyl phosphite. Alcohol **46** was stirred in refluxing methanol with trimethyl phosphite (1.5 eq) for 14 h and same alcohol (**46**) was recovered; Alcohol **47** was treated with trimethyl phosphite (2.5 fold) in refluxing methanol for one day. Only **47** was recovered.

Desulfuration of methyl sulfoxide 56. A 80 mg (0.24 mmol) sample of methyl sulfoxide **56** in 10 mL MeOH was stirred with 0.1 mL $P(OMe)_3$ at r.t. for 16 h, and the reaction progress was checked by NMR: about 50% sulfoxide **56** still remained. So the sulfoxide mixture was refluxed with 0.1 mL $P(OMe)_3$ in 10 mL MeOH for 12 h and compounds **57** and **58** (13:1) were the only products recovered. In another run the methyl sulfoxide **57** was directly refluxed in methanol with trimethyl phosphite for 12 h, high transformation (100 %) and equally good selectivity was achieved.

Preparation of dimethyl sulfoxide 65 and rearranged sulfoxide 64. In ether at -78 °C the sulfoxide **55** was treated with 2.5 eq LDA for 15 min. and 0.19 mL of TMEDA for 10 min. To this mixture was added 15 eq methyl iodide. The temperature was raised to -45 °C and the mixture was stirred for 1 h. After work-up procedures, a mixture (173 mg), containing **56, 65** and **64** in ratio of 2:2:1, was recovered.

Characteristic properties of **64**: ^{1}H NMR, 7.63-7.48 (5H, m), 5.85 (1H, tr, J=2), 3.31 (3H, s), 2.93 (1H, m), 2.31 (1H, qua, J=9), 1.21 (3H, s), 0.74 (3H, d, J=1).

Characteristic properties of **65**: ^{1}H NMR, 7.65-7.45 (5H, m), 4.73 (1H, tr, J=7), 3.30 (3H, s), 3.17 (1H, s), 2.13 (1H, d, d, J_1=12, J_2=7), 1.78 (3H, s), 1.71 (3H, s), 1.31 (3H, s), 0.77 (3H, s).

Preparation of methyl sulfoxide 62 from alcohol 58. Alcohol **58** (66 mg, 0.29 mmol), was treated with 3 eq LDA, 3 eq TMEDA and 4 eq phenyl sulfenyl chloride (see experimental part for preparation of sulfoxide **53** or **55**). After work-up procedures, a crude sulfenate ester **61** (96 mg) was obtained. At r.t. on standing, **61** slowly reached an equilibrium with **62** and **56** in a ratio of 1:3:1.

Characteristic properties of **61**: ^{1}H NMR, 7.20-7.70 (5H, m), 5.23 (1H, d, qua, J_1=8, J_2=2), 3.29 (3H, s), 2.26 (1H, d, d, d, J_1=13, J_2=8, J_3=1), 1.65 (3H, d, J=8), 1.25 (3H, s), 0.65 (3H, d, J=1).

Characteristic properties of **62**: ^{1}H NMR, 7.20-7.70 (5H, m), 5.83 (1H, s), 3.29 (3H, s), 3.15 (1H, s), 3.09 (1H, qua, J=8), 2.74 (1H, d, d, J_1=14, J_2=8), 1.32 (3H, d, J=8), 0.97 (3H, s), 0.84 (3H, s).

Oxidation of 13 with SeO_2. A mixture of 0.21 mL t-butylhydroperoxide (90 %) and 26.4 mg (0.5 eq) SeO_2 in 10 mL methylene chloride was slowly dripped to a 100 mg (0.45 mmol) sample of **13** in 10 mL CH_2Cl_2. After being stirred for 44 h at r.t., the resulting mixture was diluted with 20 mL CH_2Cl_2 and washed with NaOH (10 % 3x25 mL), H_20 (25 mL), brine (25 mL) and dried with $MgSO_4$. A 0.110 g colorless oil was obtained. ^{1}H NMR showed that **57**

and **58** (1:5) were the major products (6-8% **59** and **60** were isolated in another run).

Characteristic properties of **57**: ^{1}H NMR, 5.44 (1H, qua, d, J_1=7, J_2=2), 4.59 (1H, d, qua, J_1=9, J_2=2), 3.27 (3H, s), 3.20 (1H, tr, J=3), 2.56 (1H, d, d, qua, J_1=14, J_2=9, J_3= 1), 1.71 (3H, d, d, J_1=7, J_2=2), 1.50-2.10 (7H, m), 1.14 (3H, s), 0.99 (3H, d, J=1).

Characteristic properties of **58**: ^{1}H NMR, 5.16 (1H, qua, d, J_1=7, J_2=2); 4.80 (1H, tr, J=7), 3.31 (3H, s), 3.19 (1H, tr, J=2), 2.12 (1H, d, d, J_1=12, J_2=7), 1.74 (3H, d, J=6), 1.24 (3H, s), 0.71 (3H, d, J=1).

Characteristic properties of **59**: ^{1}H NMR, 5.14 (1H, qua, d, J_1=7, J_2=2), 4.96 (1H, d, J=9), 3.30 (3H, s), 2.60 (1H, m), 1.82 (3H, d, d, J_1=7, J_2=2), 1.02 (3H, s), 1.00 (3H, d, J=1).

Characteristic properties of **60**: ^{1}H NMR, 5.51 (1H, qua, d, J_1=7, J_2=1), 4.45 (1, tr, qua, J_1=8, J_2=1), 3.30 (3H, s), 1.74 (3H, d, J=6), 1.35 (3H, s), 0.80 (3H, d, J=1).

Oxidation of 57 and 58 to 66 and 67. A 110 mg (0.5 mmol) crude sample of allylic alcohols (mainly **57** and **58**, 1:6) in 15 mL methylene chloride was treated with 290 mg PDC at r.t. for 5 h. The reaction mixture was filtered through a column of silica gel. A mixture of **66** and **67** (86 mg) was obtained in a ratio of 1:4.

Characteristic properties of **66**: IR,1740-1720 (d), 1650, 1450, 1375, 1200, 1123, 1080, 875; ^{1}H NMR, 6.39 (1H, qua, J=7), 3.27 (3H, s), 3.24 (1H, tr, J=3), 2.80 (1H, d, qua, J_1=17, J_2=2), 1.72 (1H, d, J=17), 1.75 (3H, d, J=8), 1.60-2.10 (6H, m), 1.28 (3H, s), 0.92 (3H, d, J=1); ^{13}C NMR, 207.8, 147.5, 126.2, 82.0, 57.6, 46.5, 44.7, 42.9, 30.0, 25.0, 23.6, 22.4, 17.5; MS, 222 (3), 207 (1), 175 (3), 163 (2), 149 (13), 135 (4), 121 (7), 107 (19), 85 (19), 71 (100), 55 (39). High resolution MS, Cal. 222.1697 for $C_{14}H_{22}O_2$; Found, 222.1618.

Characteristic properties of **67**: mp, 67-69 °C; IR,1708, 1640, 1435, 1190, 1075, 870; ^1H NMR, 5.52 (1H, qua, J=7), 3.30 (3H, s), 3.24 (1H, tr, J=2), 2.84 (1H, d, J=18), 2.07 (3H, d, J=7), 1.72 (1H, d, J=17), 1.45-1.95 (6H, m), 1.21 (3H, s), 0.92 (3H, d, J=1); ^{13}C NMR, 210.2, 148.0, 127.8, 82.1, 57.6, 46.6, 42.7, 28.6, 25.3, 24.4, 22.7; MS, 222 (5), 207 (6), 190 (1), 175 (11), 162 (2), 149 (21), 119 (10), 105 (15), 71 (100), 55 (27); High resolution MS, Cal. 222.161971 for $C_{14}H_{22}O_2$; Found, 222.1636.

Isomerization of 66 and 67 mixture under various conditions.

Treatment with iodine: A 25 mg sample of **66** was heated in refluxing benzene in presence of I_2 (one piece) for one day. The product was shown to be a mixture of **66** and **67** in ratio of 1:1.

Treatment with base: A 25 mg sample of **67** was treated with KOH in refluxing methanol over night to transform to a mixture of **66** and **67** in ratio of 1:1.

Reduction of enones 66 and 67. To 1.0 mL methanol solution of $CeCl_3.H_2O$ (149 mg) was added a 86 mg (0.39 mmol) sample of unsaturated ketones **66** and **67** (1 : 4) and followed, after 5 min, addition of 12 mg of $NaBH_4$. H_2 was evolved rapidly. The reaction mixture was stirred at r.t. for 10 min., then poured into water which was extracted with ether. A product mixture (71 mg) was obtained after work-up. The mixture was judged by ^1H NMR to be : **67** (45 %), **66** (5 %), **59** (20 %), **57** (10 %).

Preparation of 70. To 256 mg $CuBr{\cdot}Me_2S$ (4 eq) in 3 mL ether at -78 °C, was added slowly 1.03 mL (2.2 M, in hexane) of n-BuLi to give a light yellow

precipitate. The reaction was warmed to -45 °C (chlorobenzene/CO_2 cooling bath) and stirred for a few seconds when the initial yellow solid turned snow white. This mixture turned brown then grayish within a period of 5 min. At this point, a 62 mg (0.28 mmol) sample of enone **67** in 3 mL THF was slowly added. The mixture, turning dark quickly, was stirred at -45 °C for 30 min., then warmed to -15 °C and stirred for another 30 min. The reaction was quenched and the resulting mixture was extracted with ether. The organic layer was diluted with ether and filtered through silica gel. Evaporation of the solvent gave 85 mg **70** as an oil. Base treatment of **70** with NaOMe/HOMe did not result in new isomer. Flash chromatography gave 50 mg analytical sample.
Characteristic properties of **70**: ^{1}H NMR, 3.22 (3H, s), 3.15 (1H, s), 2.60 (1H, d, J=18), 1.09 (3H, s), 1.01 (3H, d, J=6), 1.00 (3H, s);

Preparation of 4-methyl-3-pentenyl lithium. A 2.0 mL mineral oil slurry of lithium powder (25 % v/v; sodium content, 1%) was washed three times with pentane and blown to dryness by argon. To this, was added 7 mL ether and followed by addition of 20 drop of 5-bromo-2-methyl pentene **73** ether solution (prepared by mixing 7.0 g bromide with 35 mL ether). The material was stirred for 10 min. and cooled to -20 °C, and rest of the bromide solution was dripped slowly over 2 h. The cloudy, light yellow mixture was warmed to -15 °C and stirred for another 2 h. Up to 20 mL ether was added and the resulting mixture was stirred for an additional hour at 0 °C. The aliquot was taken to be titrated, and found 0.22 M.

Preparation of 75. To 206 mg snow white CuBr·Me_2S in 3 mL ether at -78 °C, was added 4.9 mL 4-methyl-3-pentenyl lithium. This mixture was stirred for 5 min. and then warmed to -45°C (controlled by amount of dry ice in the acetone cooling bath). The slight pink solution, turning slowly to light brown, was re-cooled to -78 °C and treated with 50 mg (0.23 mmol) enone **12** in 3 mL ether. This was again stirred, at -45 °C for 1.5 h and at -20 °C for 1 h, and quenched by addition of saturated NH_4Cl solution. The resulting mixture was extracted with ether. The ether extracts were dried over $MgSO_4$. The solvent was removed to give 90 mg oil as a mixture of isomers. Base treatment (KOH/HOMe) of the mixture resulted in a single isomer **75**. Analytical sample (38) mg was chromatographically prepared.

Characteristic properties of **75**: IR, 1725, 1449, 1370, 1080, 860; ^1H NMR, 5.09 (1H, tr, J=5), 3.30 (3H, s), 3.22 (1H, s), 2.67 (1H, d, J=21), 2.20-2.33 (2H, m), 2.10 (1H, d, J=5), 1.25-1.90 (10H, m), 1.69 (3H, s), 1.61 (3H, s), 1.15 (3H, s), 1.09 (3H, d, J=6), 1.07 (3H, d, J=1); ^{13}C NMR, 219.9, 130.8, 124.6, 83.2, 61.1, 57.7, 46.3, 44.3, 43.0. 37.1, 30.9, 30.1, 25.7, 25.5, 24.0, 22.6, 18.7, 18.2, 17.4.

Reduction of 75 to 76. A 16 mg (0.05 mmol) sample of ketone **25** in 3 mL THF was stirred with 0.5 mL (0.1 M) $LiAlH_4$ (in THF) at 0 °C for 40 min and then the reaction was quenched with water. The mixture was diluted with both water and ether. The ether extracts were combined, which were washed with H_2O, brine, and dried over $MgSO_4$. Evaporation of ether yielded 20 mg **76** as the only product. Analytical sample (13 mg) was obtained by chromatographic purification (eluent, ether/hexane).

Characteristic properties of **76**: ^1H NMR: 5.09 (1H, s), 4.43 (1H, d, d, J_1=12, J_2=7), 3.30 (3H, s), 3.14 (1H, s), 1.68 (3H, s), 1.60 (3H, s), 1.17 (3H, s), 1.01 (3H, d, J=7), 0.83 (3H, s); MS: 293 (9), 276 (1), 259 (1), 181 (23), 149 (100).

Deoxygenation 75 to 17. To 2.2 mL triethylene glycol solution of ketone **75** (33 mg, 0.11 mmol), was added 0.232 mL $H_2N_4 \cdot H_2O$ (80 %), followed by addition of 232 mg K_2CO_3. The mixture was heated to 165 °C for 1.5 h. Then water condenser was replaced by a distillation head. The mixture was heated to 220 °C for 10 min. At this time, water beads were formed on the inside of distillation head which, after being cooled, was rinsed with hexane into the reaction vessel to reduce possible loss of compound **17**. The remaining moisture (hexane didn't remove the water beads) on the distillation head was rinsed out with MeOH. The one-piece distillation apparatus was put back to the flask and the reaction mixture was heated to 220 °C for another 10 min. When the water beads appeared on the inside of distillation head again, the reaction mixture was cooled, and the apparatus rinsed with hexane and methanol in the same way as described above. This process was repeated four or five times till no water beads condensed upon heating to 220 °C. The water condenser, used previously, was re-installed. The reaction mixture was stirred for 10 h at 220-230 °C. The originally colorless solution turned dark brown. The cooled mixture was partitioned between 15 mL hexane and 35 mL 4N HCl. The organic layer was washed with water, $NaHCO_3$ (0.5 M) and brine. The solvent was removed to yield 38 mg light yellow oil. Analytical sample of **17** (25 mg) was prepared by passing the crude oil through silica gel with hexane as an eluent. Characteristic properties of **17**: ^1H NMR, 5.09 (1H, tr, J=6), 3.28 (3H, s), 3.17 (1H, s), 1.67 (3H, s), 1.60 (3H, s), 1.00 (3H, s), 0.86 (3H, s), 0.85 (3H, d, J=5); ^{13}C NMR, 130.8, 125.3, 85.5, 57.7, 51.0, 48.9, 43.9, 35.4, 34.8, 33.4, 30.0, 29.2, 26.9, 25.7, 24.8, 23.6, 23.2, 18.9, 17.8, 16.6; MS (25 ev), 292 (1), 277 (4), 260 (20), 179 (23), 147 (58), 122 (100), 107 (52), 71 (80), 55 (11); High resolution MS, Calculated for $C_{20}H_{36}O$, 292.27660. Found, 292.2759.

Preparation of 3-methyl butyl bromide **80**, 4-methyl pentyl bromide and 5-methyl hexyl bromide **83** from the corresponding alcohols: see *Org. Syn.*, Col. II, P.246 and Laboratory Notebook IV, p.22, p.18, and p.26; **Condensation of 80** with diethyl molanate: see *Org. Syn.*, Col. II, P.474 and Laboratory Notebook IV, P.23; **Reduction of** acid **81** to alcohol: see R. F. Nystrom and W. G. Brown, *J. AM. Chem. Soc.*, 1947, 69, 2548

Preparation of iso-heptyl triphenyl phosphonium bromide 84. A mixture of 44.0 g (0.168 mol) triphenyl phosphine and 28.5 g (0.16 mol) isoheptyl bromide **83** was refluxed in 50 mL benzene for 12-15 h, then cooled slowly to 0 °C. The thick liquid solidified on standing over a period of 1 h. The crude product was triturated in 265 mL ether-ethanol system (17:1) at r.t., and filtered, to give 65.8 g (93.4%) white crystal.

Characteristic properties of **84**: mp, 226-227 °C; ^{1}H NMR, 7.7-7.9 (15H, m), 3.73 (2H, br. s), 1.45 (1H, m, J=6), 0.80 (6H, d, J=6).

Olefination of 6 with isoheptyl triphenyl-phosphonium bromide. A 31.5 g (0.072 mol) sample of isoheptyl triphenylphosphonium bromide **84** was treated with 68 mL 0.94 M potassium t-amylate in toluene at 80 °C for 40 min. and at 110 °C for 30 min. To this red-colored mixture was added a 2.4 g (0.012 mol) sample of methoxy ketone **6** in 20 mL solvent. The reaction mixture was stirred for four days, then cooled and checked by TLC. A large amount of starting ketone **6** was still found. The dark solution was neutralized with 48% HBr to recover some Wittig salt. The solid salt was separated out by suction filtration and rinsed with ether. The filtrate was distilled under vacuum till all toluene was removed. Chromatographic separation yielded 1.55 g sample which was shown to be a mixture of triphenyl phosphine oxide and the olefins **86** and **87** (4:1:1). A 1.26 g starting ketone was also recovered.

Oxidation of olefins 86 and 87 with SeO_2. The crude sample of the olefins (1.55 g, 3.58 mmol) was treated with SeO_2 (see preparation of **46**) for 3 days. Flash chromatography gave **88** (11 mg), **89** (74 mg), **90** (14 mg), and **91**(74 mg). 147 mg starting ketone was also recovered. The total yield of the ketones and alcohols was calculated to be 48%, based on starting olefin content in the crude starting material.

Characteristic properties of **88**, IR, 3595, 1450, 1370, 1175, 1000, 875; ^{1}H NMR, 5.06 (1H, tr, J=7), 4.47 (1H, tr, J=8), 3.31 (3H, s), 3.20 (3H, s), 2.30-1.15 (17H, m), 1.26 (3H, s), 0.87 (6H, d, J=7), 0.72 (3H, s); MS, 294, 276 (2), 262 (1), 245 (1), 177 (21), 159 (38), 71 (100).

Characteristic properties of **89**, IR, 3600, 1460, 1375, 1080, 875; ^{1}H NMR, 5.91 (1H, tr, J=8), 4.46 (1H, tr, J=8), 3.30 (3H, s), 3.18 (1H, br. s), 2.30-1.20 (17H, m), 1.35 (3H, s), 0.86 (6H, d, J=7), 0.79 (3H, s); MS, 294, 276 (5), 262 (2) 245 (8), 229 (8), 187 (10), 177 (20), 159 (38), 135 (17), 121 (23), 71 (100).

Characteristic properties of **90**, IR, 1715, 1649, 1460, 1120, 1075, 875; ^{1}H NMR, 5.4 (1H, tr, J=8), 3.30 (3H, s), 3.25 (1H, br. s), 2.84 (1H, d, d, J_1=18, J_2=1), 2.60 (2H, m), 1.72 (1H, d, J=18), 1.21 (3H, s), 0.94 (3H, d, J=1), 0.86 (6H, d, J=7); MS, 292 (18), 277 (100), 261 (2), 245 (13), 227 (3), 217 (8), 203 (5), 175 (12), 161 (14), 147 (15), 91 (20), 70 (70), 55 (36), 43 (70).

Characteristic properties of **91**, IR, 1708, 1640, 1445, 1360, 1075, 870; ^{1}H NMR, 6.35 (1H, tr, J=8), 3.30 (3H, s), 3.26 (1H, br. s), 2.85 (1H, d, J=17), 1.73 (1H, d, J=17), 1.30 (3H, s), 0.95 (3H, s), 0.86 (6H, d, J=6); MS, 292

(12), 277 (23), 261, 245 (5), 235 (1), 219 (6), 207 (10), 175 (25), 161 (9), 147 (16), 105 (15), 91 (21), 79 (20), 71 (100), 55 (31), 43 (58).

Reduction of 18 with Zn. A 400 mg (1.17 mmol) sample of the off-white solid **18** was stirred in a HOAc-H_2O (2:1) system with 200 mg Zn powder (3.13 mmol). The trione **18** did not dissolve at beginning, but slowly went into solution after 30 min. Following a period of two hours, t.l.c. test was done, showing that the starting material was totally consumed. The solution was filtered and the filtrate was extracted with ether. The organic solution was washed, in turn, with water, saturated $NaHCO_3$ solution, brine, and dried over $MgSO_4$. A white solid (375 mg) was obtained after evaporation of solvent. Flash chromatography gave 214 mg **92** and **93** (3:1).

Characteristic properties of **92**: mp, 289-290 °C; IR, 3600, 1735, 1668, 1620, 1462, 1438, 1225; ^1H NMR, 5.28 (1H, m), 5.13 (1H, s), 4.98 (1H, d, J=4), 3.73 (3H, s), 1.32 (3H, s), 1.30 (3H, s), 1.03 (3H, s); ^{13}C NMR, 218.2, 202.1, 170.5, 144.0, 117.4, 100.6, 77.2, 68.7, 56.1, 50.9, 48.6, 46.8, 46.4, 43.2, 34.3, 30.9, 25.4, 24.8, 24.5, 23.4, 21.8, 18.5; MS, 344 (27), 329 (6), 314 (21), 299 (11), 284 (11), 257 (15), 215 (60), 190 (43), 43 (100).

Characteristic properties of **93**: mp, 162-165 °C; IR, 1735-1725, 1605, 1250-1200, 910; ^1H NMR, 5.29 (1H, s), 4.28 (1H, d, d, J_1=8, J_2=10), 3.52 (3H, s), 1.32 (3H, s), 1.23 (3H, s), 1.02 (3H, s); ^{13}C NMR, 219.5, 208.0, 206.0, 144.8, 114.0, 77.7, 58.9, 56.5, 50.6, 50.5, 46.9, 44.5, 42.0, 34.2, 31.2, 26.9, 24.9, 24.1, 23.7, 17.8.

Preparation of mesyl derivative 105 from 92. To a solution of 150 mg (0.44 mmol) alcohol **92** in 10 mL pyridine at 0 °C, was added 0.1 mL (1.3 mmol) methanesulfonyl chloride. The mixture was stirred at 0 °C for 3.5 h, then solvent was pumped out. The residue was diluted with methylene chloride, which was washed three times with water and once with brine. The organic layer was dried over Na_2SO_4. Evaporation of the solvent left 152 mg (89%) light yellow solid. Analytical sample was prepared by recrystalization from ethyl acetate.

Characteristic properties of **105**: mp, 147-150 °C; IR, 2900-3000, 1750, 1680, 1640, 1325-1400, 1225, 1180, 750; ^1H NMR, 5.75 (1H, d, J=5), 5.22 (1H, m), 5.15 (1H, s), 3.69 (3H, s), 3.09 (3H, s), 1.30 (3H, s), 0.94 (3H, s); ^{13}C NMR, 219.3, 200.5, 165.8, 144.3, 116.8, 102.6, 78.0, 56.6, 50.8, 49.3, 46.8, 42.9, 38.9, 34.4, 31.0, 25.6, 25.0, 24.8, 23.4, 22.0, 18.3; MS, 423 (2), 422 (4), 343, 326, 311, 233 (46), 154 (100), 119 (16), 105 (19).

Preparation of enediones 106 and 107. To a 190 mg (0.45 mmol) sample of mesylate **105** in 12 mL glyme were added 450 mg NaI and 500 mg Zn. This mixture was refluxed for 8 h. TLC showed three new spots but no starting material. This mixture was cooled and filtered through a short column of silica gel. The filtrate was diluted with ether, then washed with water and brine. The organic layer was dried with magnesium sulfate. Removal of the solvent yielded 110 mg oil which slowly solidified on standing. Crystalization brought about 54 mg (38 %) pure product **106** and 20 mg **107**.

Characteristic properties of **106**: mp, 172-174 °C; IR, 3000-2850, 1750, 1670, 1625, 1375, 1210, 1190, 1175, 900, 800-700; ^1H NMR, 5.20 (1H, s), 5.10 (1H, s), 3.66 (3H, s), 1.28 (3H, s), 1.44 (3H, s), 1.01 (3H, s); ^{13}C NMR, 220.2, 202.9, 172.7, 144.5, 117.0, 100.6, 55.5, 50.8, 46.7, 46.6, 42.9, 39.9, 34.3, 33.0, 30.8, 30.1, 25.4, 24.8, 23.3, 22.0, 18.7; MS, 329 (3), 328 (2), 311 (6), 295, 284, 267, 253, 215 (10), 139 (100).

Characteristic properties of **107**: mp, 165-167 °C; IR, 1748, 1670, 1625, 1375 (doublet), 1203, 1195, 1175, 903, 725; ^{1}H NMR, 7.33 (1H, qua, J=3), 6.11 (1H, d, J=5), 5.42 (1H, br. s), 2.88 (1H, s), 2.75-1.5 (14H), 1.24 (3H, s), 0.81 (3H, s), 0.79 (3H, s); MS, 284 (28), 269 (5), 189 (56), 171 (12), 145 (52), 133 (38), 119 (40), 105 (54), 91 (78), 77 (55), 65 (33), 55 (100), 41 (90).

Stannic chloride catalyzed Diels-Alder reaction of enone 108 with diene 109 to give adduct 110. To a sample of 94 mg (0.52 mmol) methyl carboxylate enone **108** in 3 mL deuterated chloroform, was added 0.061 mL freshly distilled stannic chloride, followed by addition of 100 mg (0.53 mmol) diene **109**. The resulting mixture was stirred at r.t. for 4 h. TLC indicated that most diene **109** still remained. The mixture was warmed to 50 °C and stirred for overnight. The reaction was quenched with water and 1.5 g product mixture was recovered. Chromatographic separation of this mixture gave **110** (10 mg) and **111** (90 mg).

Characteristic properties of **108**: ^{1}H NMR, 7.6 (1H, d, J=3), 6.85 (1H, d, d, J_1=10, J_2=3), 6.21 (1H, d, J=10), 3.88 (3H, s), 1.37 (6H, s).

Characteristic properties of **110**: ^{1}H NMR, 6.22 (1H, d, J=10), 5.9 (1H, d, J=10), 5.23 (1H, s), 3.74 (3H, s), 2.95 (1H, br.s), 2.65-1.5 (11H), 1.20 (3H, s), 1.15 (3H, s), 1.10 (3H, s), 1.00 (3H, s); MS, 370 (5), 310 (13), 241 (3), 181 (85), 149 (100), 139 (40), 96 (53).

Characteristic properties of **111**: ^{1}H NMR, 7.13 (1H, d, J=8), 6.70 (1H, d, J=8), 3.90 (3H, s), 2.38 (3H, s), 2.01 (3H, s),

Preparation of alcohols 112 and 113. To a 50 mg (0.146 mmol) sample of trione **18** in 10 mL THF solution at -78 °C was added 3 eq methyl magnesium bromide (in ether). This mixture was stirred and slowly warmed to r.t. through a period of 7 h, then poured into 10 mL sat. ammonium chloride. The organic layer was diluted with methylene chloride, washed with water and brine, and dried. Evaporation of the solvent yielded 55 mg crude product as a light yellow solid. The mixture was shown by NMR to be **112** and **113** in ratio of 10:1. Flash column chromatography gave 40 mg of **112** and **113** and an unknown (non u.v. sensitive) product (8 mg). The methylation of **18** with methyl lithium (-78 °C, 1 day, 3 eq MeLi, 3 eq TMEDA, THF) gave a 1:1 mixture of **112** and **113** in 90%-95% yield.

Characteristic properties of **112**: mp, 210 °C; IR, 3585, 1735, 1660, 1620, 1450, 1223, 1160, 1100, 900; ^{1}H NMR, 5.32 (1H, s), 5.17 (1H, s), 3.75 (3H, s), 1.74 (3H, s), 1.41 (3H, s), 1.17 (3H, s), 1.00 (3H, s); ^{13}C NMR, 220.2, 202.4, 172.5, 143.0, 117.8, 99.9, 73.1, 55.0, 51.3, 50.6, 46.6, 42.6, 34.3, 30.7, 29.6, 26.7, 25.8, 24.8, 23.3, 19.0; MS, 297, 215, 187, 169 (60), 137 (100).

Characteristic properties of **113**: mp, 235-237 °C; IR, 3583, 1735, 1660, 1618, 1460, 1225, 1170, 1050, 875; ^{1}H NMR, 5.22 (1H, br. s), 5.10 (1H, s), 3.72 (3H, s), 1.59 (3H, s), 1.45 (3H, s), 1.18 (3H, s), 1.05 (3H, s); ^{13}C NMR, 220.3, 170.9, 144.1, 116.4, 99,9, 74.2, 56.0, 50.1, 48.9, 46.6, 42.9, 34.3, 30.8, 28.6, 26.0, 25.8, 25.6, 24.8, 23.3, 18.6; MS, 213, 187, 169 (57), 153 (15), 137 (100), 123 (11), 105 (11.5), 91 (6.8).

Preparation of diol 131. To 10 mg (0.26 mmol) lithium aluminium hydride in 5 mL THE at 0 °C was added a 33 mg (0.092 mmol) sample of alcohol **18** in 5 mL THF. The mixture was reacted for 4 h, then quenched with 3 mL water. The water solution was extracted with ether. The ether extract was washed with brine and dried with magnesium sulfate. Crude product **131** (29 mg, 87%) was obtained.

Characteristic properties of **131**: mp, 190-192 °C; IR, 3600, 3000-2850, 1670, 1620, 1460, 1230, 1220, 1100, 900; ^{1}H NMR, 5.20 (1H, br. s), 5.10 (1H, s), 3.76 (1H, d, J=9), 3.70 (3H, s), 1.69 (3H, s), 1.39 (3H, s), 1.27 (3H, s), 0.78 (3H, s); ^{13}C NMR, 202.6, 172.6, 146.5, 116.5, 100.3, 79.8, 73.1, 56.0, 51.2, 49.6, 48.9, 46.5, 43.0, 35.1, 33.4, 29.8, 27.8, 26.6, 25.5, 25.4, 19.7; MS, 361, 343, 327, 299, 215, 169 (69), 137 (100), 105 (21), 43 (93).

Preparation of epimeric diols 114 and 115 from 112. A 422 mg (1.2 mmol) sample of dione **112** in 10 mL methylene chloride was treated with 12 mL solution (1.0 M) of diisobutyl aluminium hydride (DIBAL) for 14 h. at 0-25 °C, then the mixture was poured to aqeous potassium sodium tartrate. The colloidal residue was filtered. The filtrate was extracted with methylene chloride. The filtering funnel was rinsed with 20 mL hot methanol which was combined with the methylene chloride extract. The organic layer was washed with water, brine and dried over magnesium sulfate. A 545 mg mixture (sticky solid) was recovered after evaporation of the solvent. This solid was dissolved in a 50 mL THF-H_2O (4:1) system to which was added 6-8 drops conc. hydrochloric acid. The solution was stirred overnight at r.t., then diluted with water and extracted with methylene chloride. The organic layer was washed with water, brine and dried over magnesium sulfate. Evaporation of the solvent yielded 424 mg crude product (solid foam) which was subjected to chromatographic separation (ether-hexane as an eluent), giving 286 mg of both **114** and **115** in ratio of 2:1.

Characteristic properties of **114**: mp, 134-135 °C; IR, 3605, 3510-3490, 3000-2870, 1675, 1450, 1375, 1240, 1150-1100, 1040, 880, 820; ^{1}H NMR, 6.99 (1H, d, J=10), 5.94 (1H, d, J=10), 5.18 (1H, m), 3.79 (1H, d, J=7), 1.47 (3H, s), 1.35 (3H, s), 1.17 (3H, s), 0.78 (3H, s); ^{13}C NMR, 203.1, 153.8, 147.2, 125.6, 118.3, 79.6, 75.9, 50.2, 48.6, 47.1, 45.1, 42.1, 34.2, 33.4, 31.8, 26.5, 25.4, 25.1, 24.6, 23.3, 18.0; MS, 330, 312, 297, 287 (1), 269 (3), 241, 225, 209, 192, 174 (6), 159 (18), 105 (23), 43 (100).

Characteristic properties of **115**: mp, 119-122 °C; IR, 3605, 3580-3460, 2900-2880, 1680, 1450, 1375, 1080; ^{1}H NMR, 6.61 (1H, d, d, J_1=10, J_2=1), 5.97 (1H, d, J=10), 5.27 (1H, m), 4.10 (1H, d, d, J_1=9, J_2=7), 3.76 (1H, m), 1.52 (3H, s), 1.41 (3H, s), 0.86 (3H, s), 0.74 (3H, s), ^{13}C NMR, 203.1, 153.7, 146.4, 125.7, 118.9, 80.1, 75.9, 50.1, 47.9, 44.8, 42.2, 32.4, 31.8, 30.8, 29.4, 25.2, 24.7, 23.4, 19.0, 17.7; MS, 330, 287, 269 (1), 215, 192 (10), 117 (9), 149 (10), 133 (11), 121 (16), 105 (20), 91 (17), 69 (11), 55 (28), 43 (100).

Oxidation of 114 and 115. To a 219 mg (0.66 mmol) sample of diol (**114** and **115**) in 20 mL methylene chloride was added 214 mg (1.5 eq.) pyridinium chlorochromate (PCC). The brown mixture was stirred at r.t. for 5 h. then filtered through a short column of silica gel. Removal of the solvent of the filtrate gave a brown oil (188 mg). Chromatographic separation gave 150 mg (69%) pure **118**.

Characteristic properties of **118**: mp, 141-143 °C; UV, λmax=234, ε=9.3x10^3; IR, 3500-3480, 1735, 1680, 1115, 1085; ^{1}H NMR, 6.45 (1H, d, J=10), 6.03, (1H, d, J=10), 5.45 (1H, m), 3.75 (1H, s), 1.58 (3H, s), 1.45 (3H, s), 0.92 (3H, s), 0.87 (3H, s); ^{13}C NMR, 220.0, 202.8, 152.9, 143.8, 125.8, 120.6, 75.9, 51.0, 50.0, 45.9, 44.7, 41.9, 34.2, 31.6, 29.8, 25.1, 24.6, 24.2, 23.5, 22.5, 17.4; MS, 328 (1.5), 313, 395, 285 (5), 267 (1), 227, 190 (16), 175 (18), 139 (24), 121 (30), 105 (19), 43 (100).

Preparation of epimeric diols 116 and 117 from 113. A 317 mg (0.885 mmol) sample of **113** in 10 mL methylene chloride was treated with 9 mL

DIBAL (1.0 M) at 0 °C for 12 h. The mixture was then poured to saturated potassium sodium tartrate solution. The resulted colloidal mixture was filtered by suction. The filtering funnel (containing the colloidal solid) was rinsed with hot methanol to same filtering flask. The filtrate was diluted with water and extracted with methylene chloride. Removal of the solvent gave a 467 mg sticky solid. Acid hydrolysis of this product (stirring in 25 mL THF-H_2O system [4:1] with 6 drops conc. HCl) gave, after work-up procedures, a 317 mg solid product. Chromatographic separation of the product yielded 135 mg **116** and 59 mg **117**.

Characteristic properties of **116**: mp, 198-199.5 °C; IR, 3600, 3500-3470, 3020-2830, 1670, 1665, 1600, 1450, 1380, 1240, 1200, 1100, 1040, 1000, 850, 830; ^1H NMR, 7.00 (1H, d, J=10), 5.97 (1H, d, J=10), 5.21 (1H, m), 4.19 (1H, d, J=8), 1.48 (3H, s), 1.37 (3H, s), 1.18 (3H, s), 0.80 (3H, s); ^{13}C NMR, 200.5, 154.8, 147.3, 126.6, 117.8, 79.5, 76.6, 49.2, 48.2, 46.5, 42.6, 40.5, 34.7, 33.3, 27.6, 27.5, 27.4, 27.1, 25.1, 24.8, 18.5; MS, 330, 315, 297, 287, 269 (1), 218, 192 (6), 159 (18), 145 (6), 121 (10), 105 (20), 43 (100).

Characteristic properties of **117**: mp, 191.5-192.5 °C; IR, 3600, 3500-3450, 1670, 1655, 1450, 1380, 1080, 1040, 880; ^1H NMR, 6.96 (1H, d, d, J_1=10, J_2=2), 5.94 (1H, d, J=10), 5.15 (1H, m), 4.12 (1H, d, d, J_1=7, J_2=6), 1.46 (3H, s), 1.36 (3H, s), 1.00 (3H, s), 0.88 (3H, s); ^{13}C NMR, 200.4, 154.6, 146.5, 126.7, 118.1, 80.4, 76.6, 48.5, 48.1, 44.1, 42.3, 40.5, 33.1, 30.7, 29.7, 27.7, 27.1, 26.8, 25.1, 19.9, 18.2; MS, 330, 287, 259, 241, 192 (9), 177 (4), 159 (6), 149 (9), 105 (16), 55 (28), 43 (100).

Swern oxidation of 116 and 117 to 119. To a 10.3 mL methylene chloride solution of oxalyl chloride (0.44 M) cooled at -78 °C, was added a methylene chloride solution of dimethyl sulfoxide. The reaction mixture was stirred for 20 min. and turned cloudy. At this point, a 416 mg (1.26 mmol) sample of diols in 20 mL methylene chloride was slowly added. The reaction was quenched after 30 min. by addition of 2.0 mL triethyl amine (TEA). A 470 mg crude product was recovered. Flash chromatography gave 300 mg (73 %) pure product **119**.

Characteristic properties of **119**: mp, 199-201 °C; IR, 3580, 3460, 2980-2890, 1730, 1670-1650, 1450, 1410, 1380, 1110, 1080, 1030, 1000, 830; ^{1}H NMR, 6.97 (1H, d, d, J_1=10, J_2=2), 5.97 (1H, d, J=10), 5.34 (1H, m), 1.48 (3H, s), 1.38 (3H, s), 1.03 (3H, s), 1.00 (3H, s); ^{13}C NMR, 219.3, 199.9, 153.6, 143.5, 126.7, 119.2, 76.2, 50.3, 47.9, 46.0, 42.3, 40.2, 34.0, 30.2, 27.4, 26.7, 26.4, 24.6, 24.2, 22.9, 17.6; MS, 328 (1), 313, 295, 285 (2), 267, 257, 227, 203, 175 (12.7), 121 (16), 105 (16), 91 (20), 55 (22), 43 (100).

Zinc reduction of 119 to 120. A mixture of 93 mg (0.28 mmol) sample of **119**, 294 mg (4.6 mmol) zinc and 25 mL galcial acetic acid was refluxed for 12 h when white particles (ZnO) was formed. The mixture was then chilled and filtered, and the filtrate was diluted with water. The aqueous solution was extracted with methylene chloride. The organic layer was washed with water, sodium bicarbonate solution and brine, and dried over magnesium sulfate. Evaporation of the solvent gave 108 mg white solid. Flash chromatography yielded 78 mg (88%) **120**.

Characteristic properties of **120**: mp, 149.5-150.5 °C; IR, 3020-2850, 1735, 1665, 1470, 1415, 1400, 1380, 820; ^{1}H NMR, 6.88 (1H, d, d, J_1=10, J_2=2), 5,86 (1H, d, J=2), 5.38 (1H, m), 3.10 (1H, d, q, J_1=4, J_2=7), 1.30 (3H, s), 1.14 (3H, d, J=7), 1.04 (3H, s), 1.00 (3H, s); ^{13}C NMR, 219.3, 201.6, 150.7, 143.2, 129.0, 120.6, 50.5, 46.2, 45.9, 42.5, 42.1, 39.7, 34.1, 30.4, 26.7, 25.7, 24.3, 23.6, 23.1, 17.9, 12.1; MS, 314 (1), 297 (2), 255 (2), 241 (2), 213 (2), 190 (33), 175 (38), 157 (23), 133 (40), 123 (100), 105 (323), 91 (49), 79 (43).

Hydrogenation of 120 to 121. To a 37 mg (0.12 mmol) sample of enedione **120** in 10 mL ethanol (95%) was added 16 mg powder of Pd/C (5%). The black mixture was purged with H_2 three times, and stirred under hydrogen (1 atm) for 2.8 h. The reaction mixture was filtered, and the filtrate was evaporated to give white 33 mg (89%) product of **121**.

Characteristic properties of **121**: mp, 160-163 °C; IR, 2980-2880, 1730, 1700, 1460, 1380, 890; ^{1}H NMR, 5.36 (1H, m), 3.02 (1H, m), 1.35 (3H, s), 1.08 (3H, s), 1.00 (3H, d, J=7), 0.85 (3H, s); ^{13}C NMR, 219.5, 213.6, 142.2, 117.8, 50.5,47.8, 56.5, 44.5, 37.7, 35.5, 34.2, 30.7, 27.0, 26.2, 25.3, 24.7, 23.6, 23.2, 28.3, 11.7; MS, 315 (7), 314 (31), 299 (7), 281 (8), 257 (4), 230 (6), 211 (14), 190 (11), 175(20), 171 (13), 145 (12), 156 (55), 119 (100), 105 (57), 91 (36), 79 (23), 67 (24), 55 (64).

Preparation of ketal derivatives 122 and 123 from dione 121. A mixture of 31 mg (0.1 mmol) of dione **20**, 30 mL toluene, 3 mg of *p*-toluene sulfonic acid (*p*TSA), and 0.61 mL (8.8 mmol) ethylene glycol was refluxed for 8 h, then chilled and diluted with methylene chloride. The organic layer was washed with sodium bicarbonate, brine and dried with magnesium sulfate. Evaporation of the solvent gave 39 mg product from which 19 mg ketal derivative **122** and 10 mg **123** were isolated.

Characteristic properties of **122**: IR, 2985-2850, 1735, 1480-1430, 1380, 1180, 1050, 930; ^{1}H NMR, 5.39 (1H, s), 4.05-3.73 (4H, br.s), 1.08 (3H, s), 1.05 (3H, s), 0.95 (3H, s), 0.87 (3H, d, J=7); ^{13}C NMR, 220.2, 140.4, 119.2, 111.2, 65.5, 63.7, 50.7, 46.4, 44.5, 44.4, 37.3, 35.2, 34.3, 31.6, 30.7, 26.7, 24.8, 23.6, 23.5, 23.0, 18.0.

Characteristic properties of **123**: ^{1}H NMR, 3.96 (4H, br. s), 2.50-1.20 (18H), 0.98 (3H, s), 0.94 (3H, s), 0.91 (3H, d, J=9).

Acid-induced conversion of 118 to 124. To a 11 mg (0.03 mmol) sample of **118** at -5 °C was added 15 drops of conc. sulfuric acid. The original light yellow compound turned brown quickly. This mixture was stirred at same temperature for 7 min. then quenched with a piece of ice. The diluted aqueous layer was extracted with methylene chloride. The organic extract was washed with H_2O, brine and dried with magnesium sulfate. A 8.5 mg product (77%) of **124** was obtained. Analytical sample was prepared by Flash chromatography. Characteristic properties of **124**: mp, 138 °C; UV, λmax = 234, ε=2.3x10^3; ^{1}H NMR, 6.83 (1H, d, J=9), 6.08 (1H, d, J=9), 1.50 (3H, s), 1.40 (3H, s), 1.05 (3H, s), 1.00 (3H, s); MS, 329(1), 328 (10), 233 (5), 207 (25), 193 (19), 148 (92), 136 (100).

Birch reduction of 118 and 124. To a dry flask containing 45 mg Li (6.4 mmol) at -78 °C, was condensed 15 mL ammonia (dried by refluxed with sodium for 30 min.). The blue solution was stirred for 15 min. to allow Li fully dissolved. This blue solution was splitted into two portions. To one of these portions (7 mL), was added a 15 mg (0.07 mmol) sample of **118** in 10 mL THF. To the remaining ammonia solution (5 mL) was added a 9 mg (0.042 mmol) sample of **124** in 5 mL THF. In these two flasks, the reactions were carried out for 30 min. and then quenched with solid ammonium chloride. After evaporation of ammonia, the residues in both flasks were treated separately, with the same procedure shown below:

The residue was diluted with water. The aqueous mixture was extracted with methylene chloride. The organic layer was washed with water, brine and dried with magnesium sulfate. Removal of the solvent, a 9 mg mixture of **126** and **127** (6:1) was obtained from **118** and 9 mg product **125** from **124**. Chromatographic separation gave analytical samples of **125** (6 mg), **126** (6 mg) and **127** (1 mg).

Characteristic properties of **125**: ^{1}H NMR, 4.17 (1H, d, d, J_1=9, J_2=6), 2.23 (3H, m), 2.0-1.1 (17H, m), 1.04 (3H, d, J=8), 0.98 (3H, s), 0.95 (3H, s), 0.83 (3H, s); MS, 334 (2), 319 (30), 274, 262 (12.3), 247 (18), 233, 215 (8), 165 (41), 147 (15), 95 (29), 55 (72.0), 43 (100).

Characteristic properties of **126**: ^{1}H NMR, 5.22 (1H, m), 4.09 (1H, d, d, J_1=9, J_2=7), 1.64 (3H, s), 1.39 (3H, s), 0.98 (3H, s), 0.94 (3H, s); MS, 332, 317, 299, 281, 271, 159 (12), 149 (16), 133 (8), 119 (12), 105 (21.5), 91 (16.1), 69 (10.3), 55 (32.6), 43 (100).

Characteristic properties of **127**: ^{1}H NMR, 5.26 (1H, m), 3.81 (1H, d, J=8), 1.65 (3H, s), 1.41 (3H, s), 1.14 (3H, s), 0.83 (3H, s); MS, 332, 317, 299 (2.0), 289 (5), 271 (10), 153 (3), 213 (2), 105 (21), 55 (30), 43 (100).

Preparation of trimethylsilylmethyl dervatives 128 and 129. To a 331 mg (0.97 mmol) sample of **18** in 30 mL THF at -35 °C was added 4.5 mL (1.0 M) trimethylsilylmethyl lithium. The resulting yellow thick mixture was stirred for 5 h, then warmed to 0 °C, at which the reaction was carried out for another 5 h. The reaction mixture was poured into ammonium chloride solution, and extracted with methylene chloride. The organic extraction was washed with water, brine and dried with magnesium sulfate. Evaporation of the solvent gave 519 mg light yellow oil which, on standing, solidified and was shown to be a mixture of **128** and **129** in ratio of 5:1. Flash chromatography gave 353 mg (85 %) both silyl derivative.

Characteristic properties of **128**: mp, 178.5-181 °C; IR, 3600, 2980, 1730, 1650, 1610, 1400, 1415, 1370, 1330, 1250, 1220, 1180, 1010, 990, 840; ^{1}H NMR, 5.23 (1H, m), 5.00 (1H, s), 3.63 (3H, s), 2.50-1.70 (12H, m), 1.46 (3H, s), 1.34 (2H, s), 1.05 (3H, s), 0.95 (3H, s), 0.06 (9H, s); ^{13}C NMR, 220.0, 202.0, 173.0, 143.0, 117.8, 99.4, 75.3, 55.8, 50.6, 50.1, 48.9, 46.5, 42.8, 34.2, 30.9, 30.6, 26.4, 25.9, 25.8, 24.7, 23.3, 19.0, 0.67; MS, 431 (8), 430 (13), 413, 241 (99), 225, 209 (83), 193 (16), 151 (77), 137 (28), 121 (16), 119 (17), 105 (23), 91 (21), 77 (10), 75 (50),73 (100).

Characteristic properties of **129**: ^{1}H NMR, 5.13 (1H, s), 4.96 (1H, s), other peaks overlap with the corresponding peaks of **128**.

Eliminative desilylation of 128 (or 129) to 130. A 12 mg (0.028 mmol) sample of silyl derivative **128** in 5 mL methylene chloride was treated with 0.1 mL boron triflouride etherate for 2 h. The mixture, diluted with methylene chloride, was poured into water. The organic layer was washed with 0.5 M sodium bicarbonate, brine, and dried with magnesium sulfate. Evaporation of the solvent gave a 9 mg (94%) product of **130**.

Characteristic properties of **130**: mp, 176-178 °C; ^{1}H NMR, 5.75 (1H, s), 5.36 (1H, s), 5.21 (1H, m), 5.12 (1H, s), 3.75 (3H, s), 2.90-1.50 (12 H, m), 1.27 (3H, s), 1.18 (3H, s), 1.03 (3H, s); MS, 341, 340 (3), 325 (7), 297 (4), 281, 253, 151 (100), 121 (8), 105 (6), 91 (7), 69 (5), 55.

APPENDIX

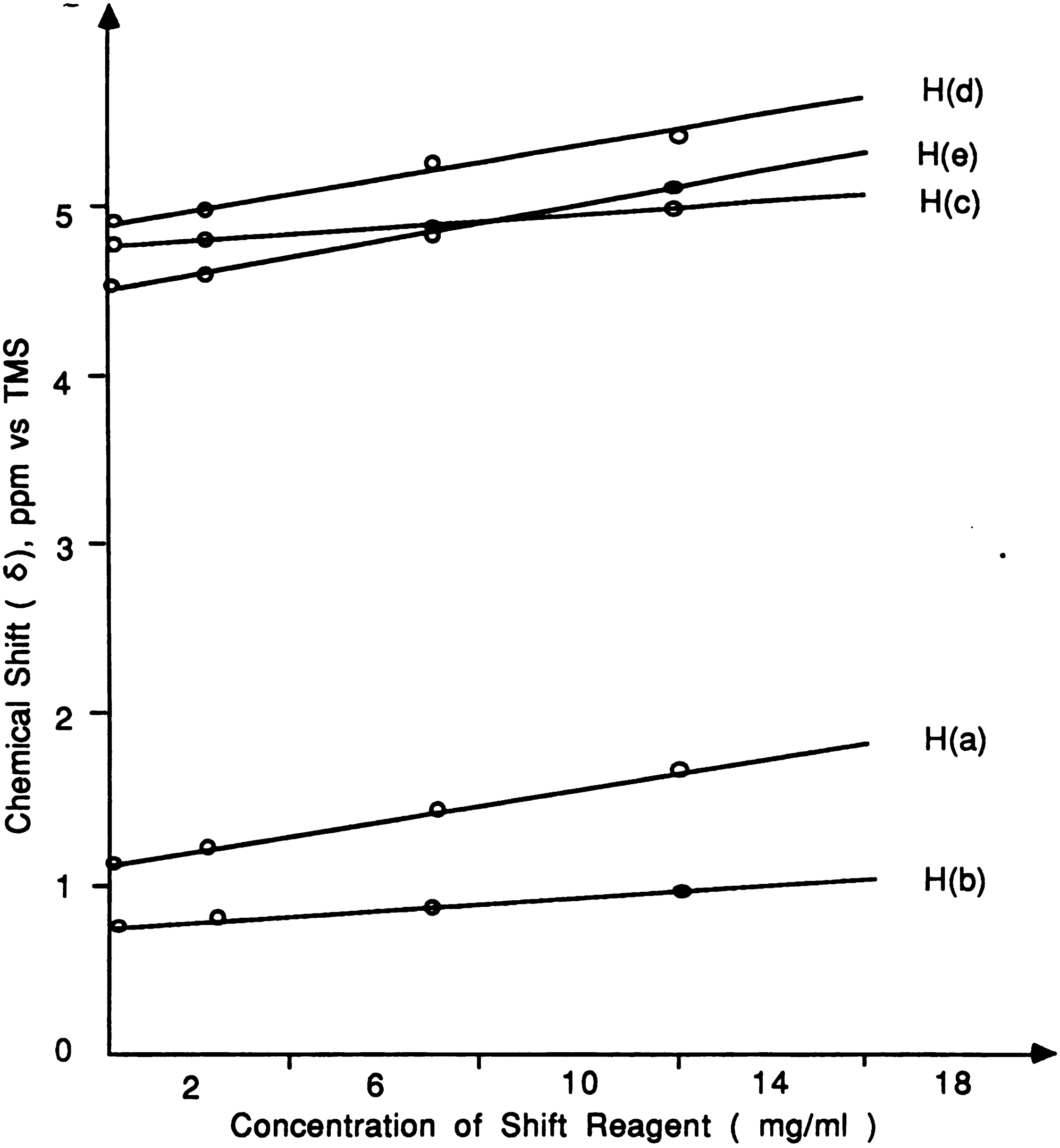


Figure 1. Variation in Chemical Shift for Protons in Alcohol **46**

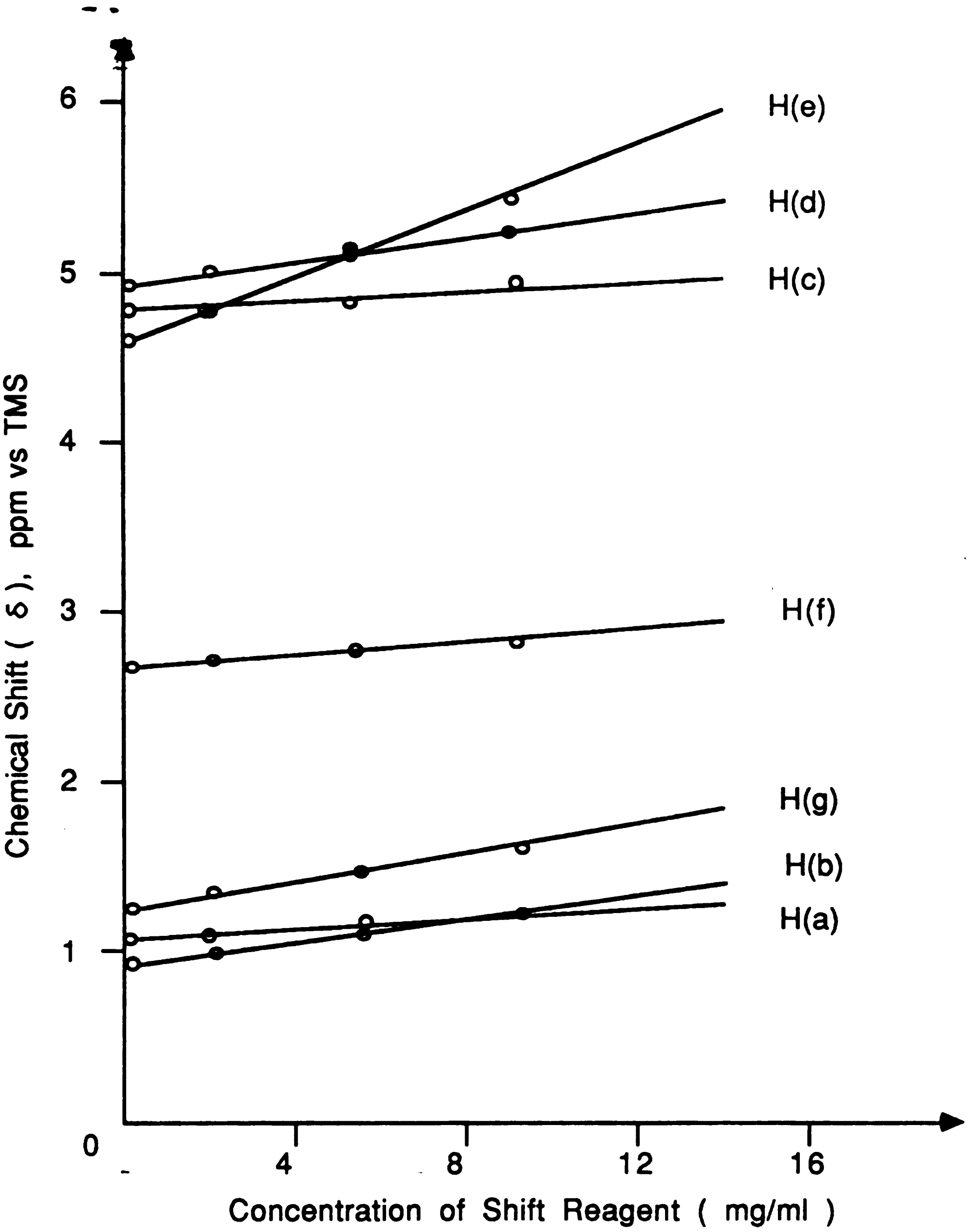


Figure 2. Variation in Chemical Shfit for Protons in Alcohol **47**

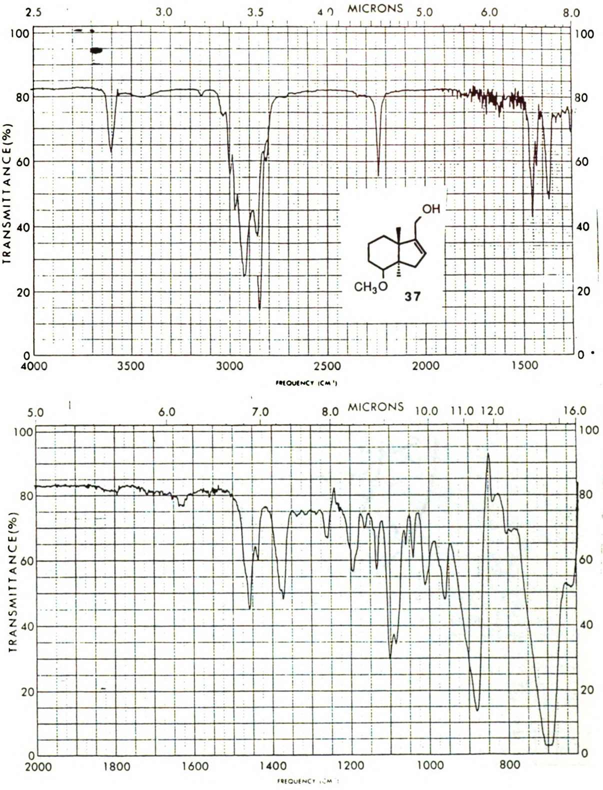


Figure 5. Infrared spectrum of **37**

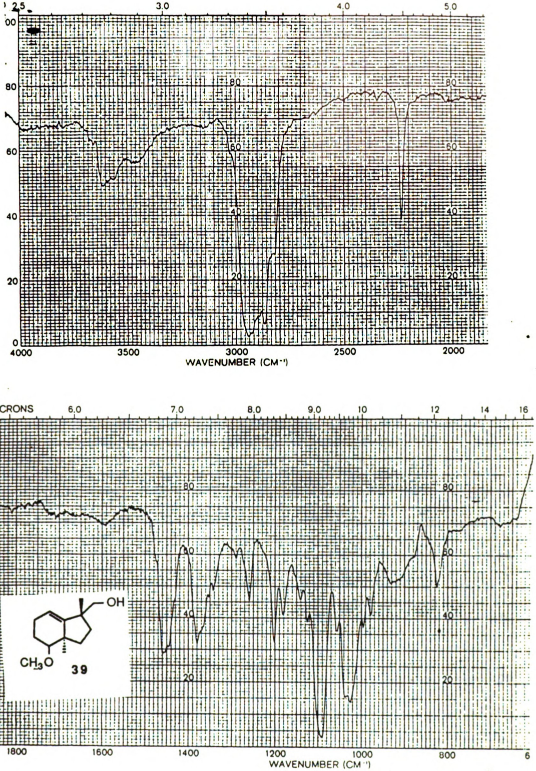


Figure 6. Infrared spectrum of 39

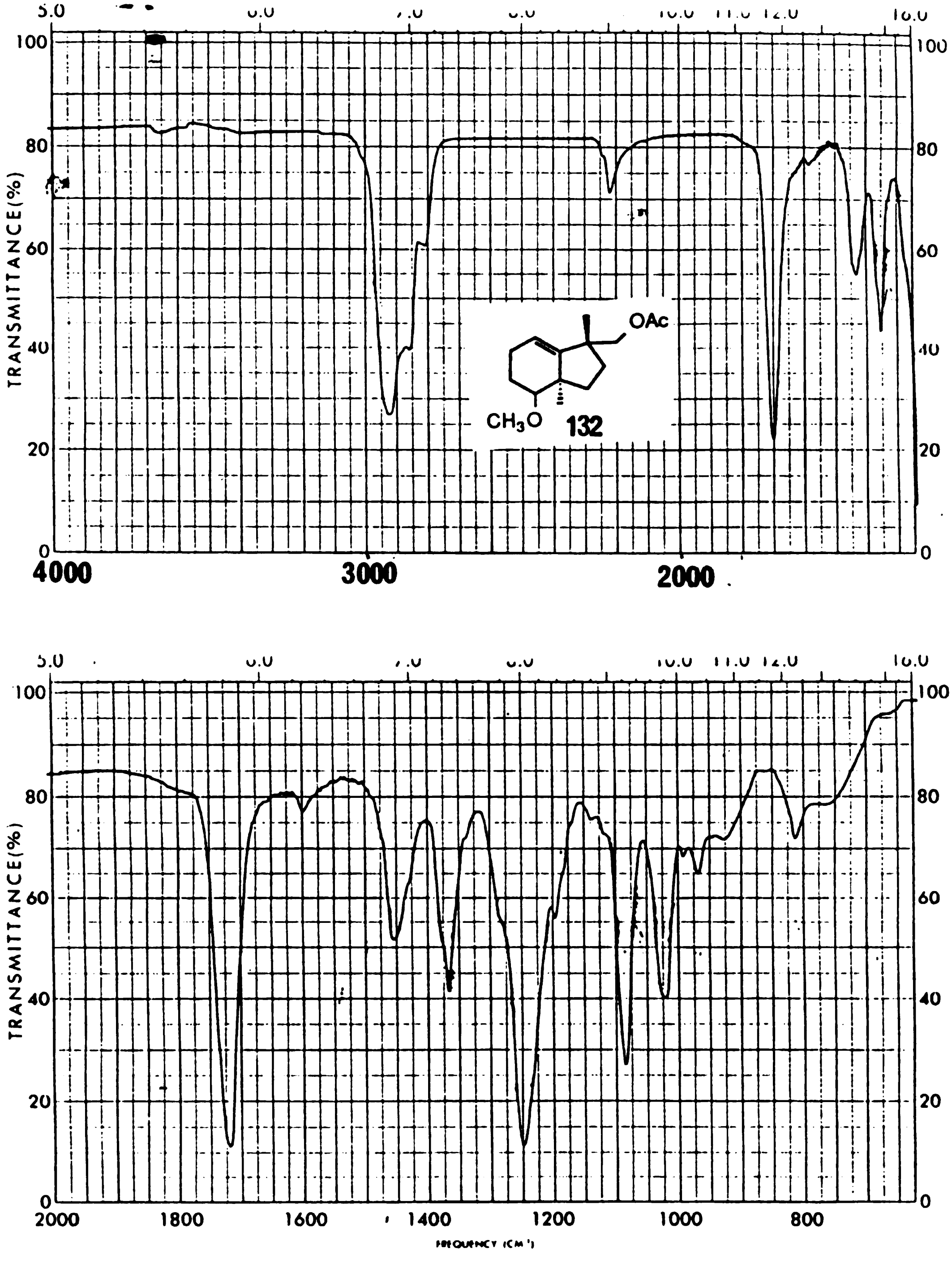


Figure 7. Infrared spectrum of **132**

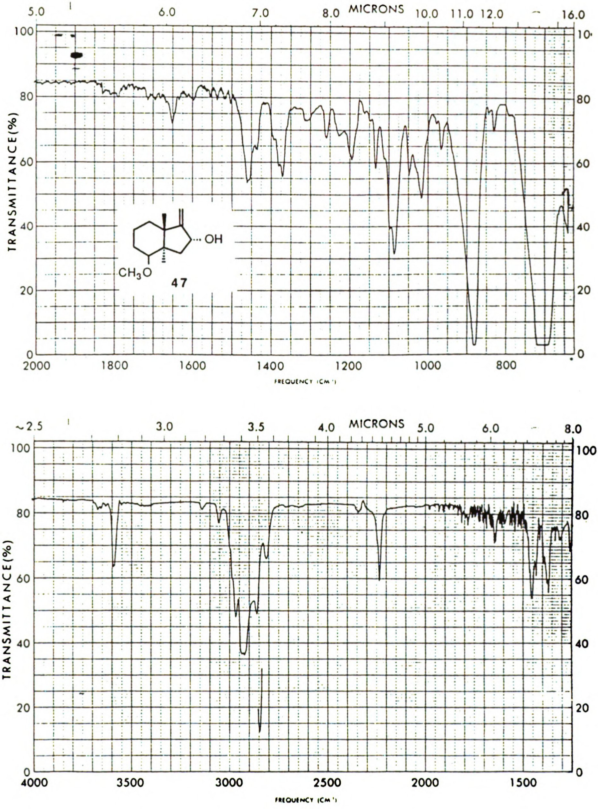


Figure 8. Infrared spectrum of **47**

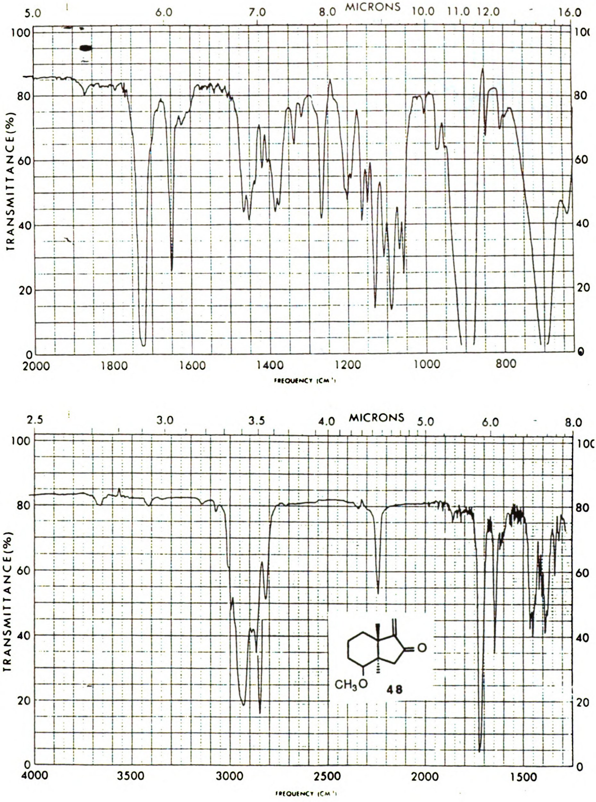


Figure 9. Infrared spectrum of **48**

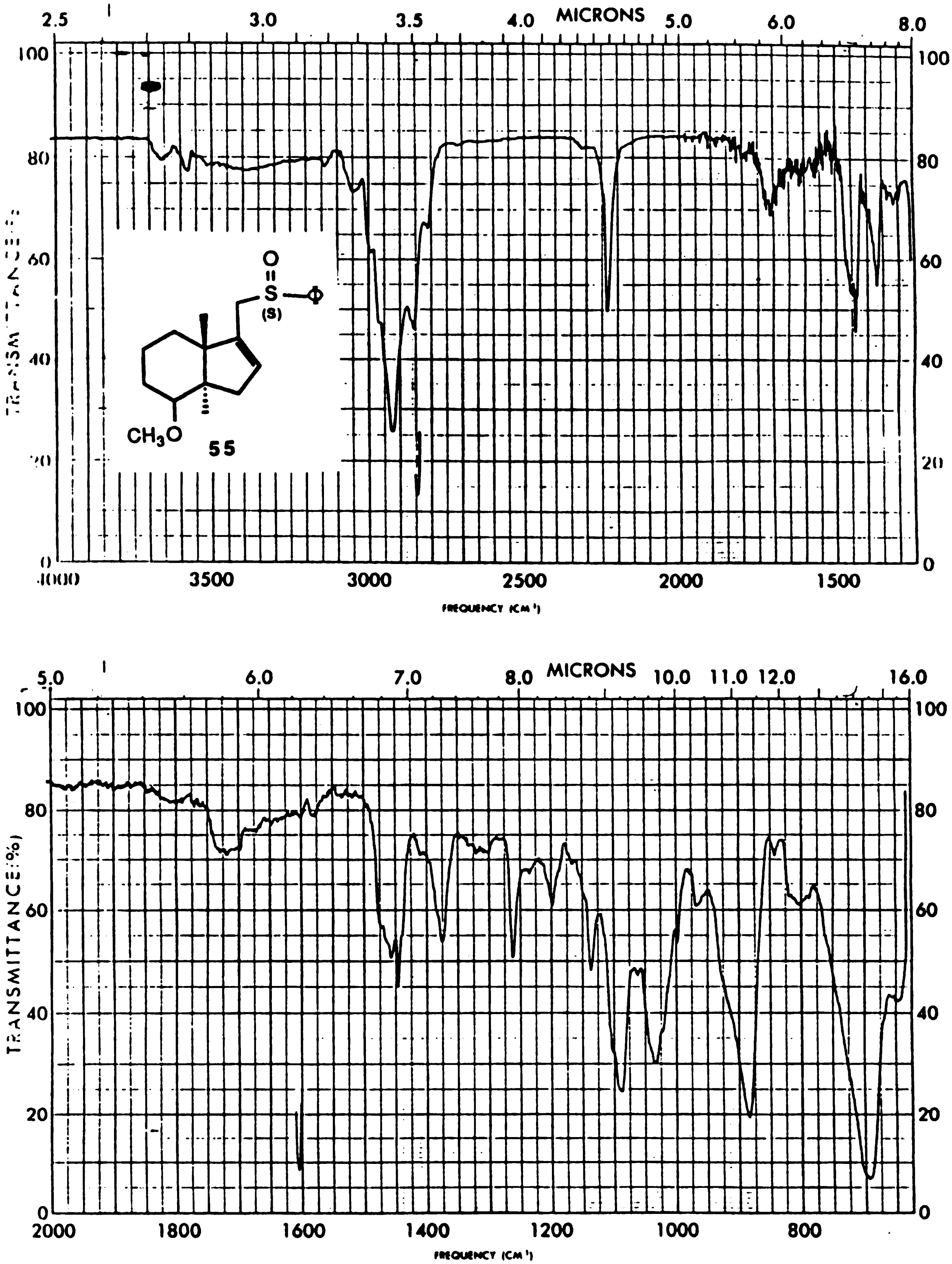


Figure 10. Infrared spectrum of 55

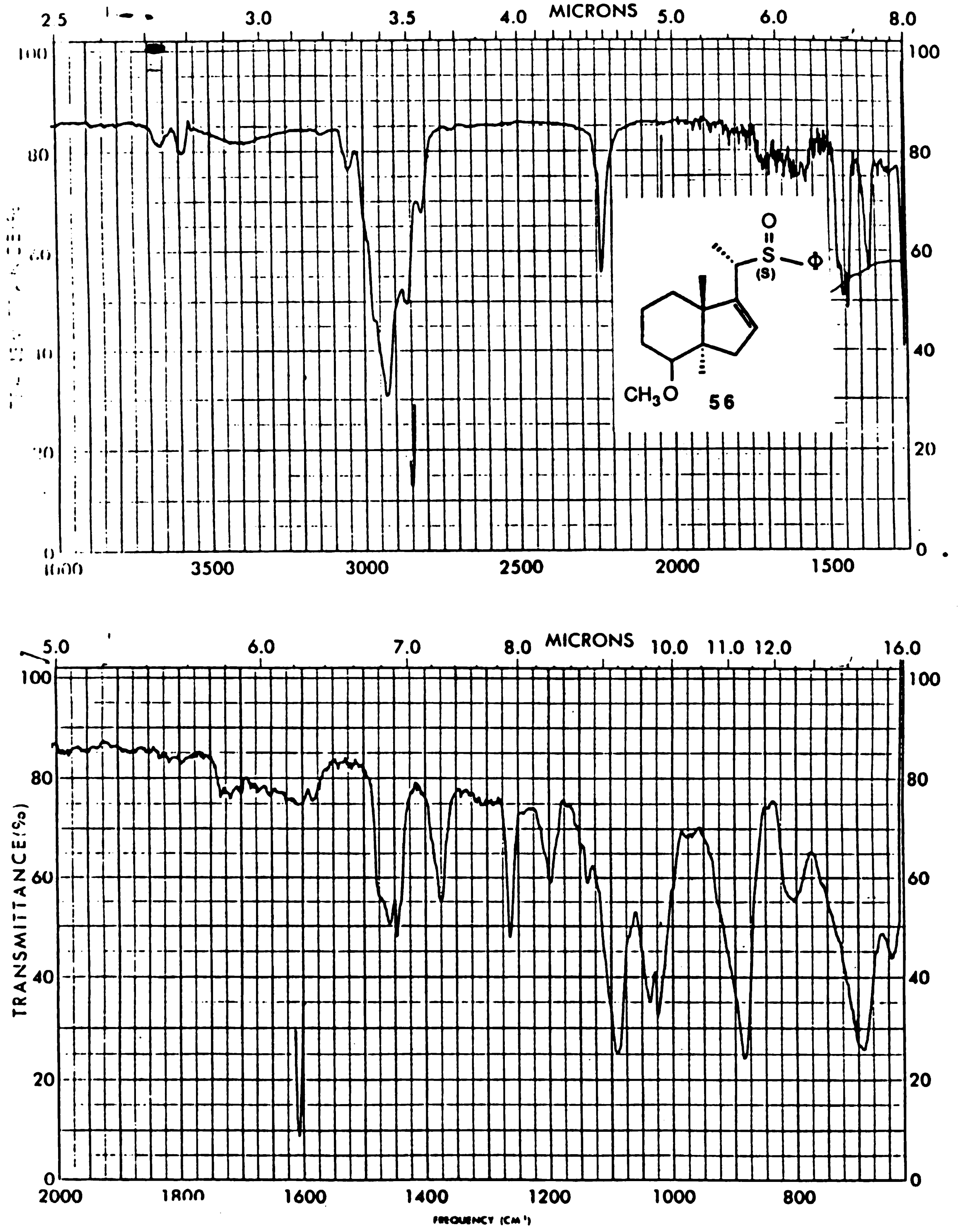


Figure 11. Infrared spectrum of **56**

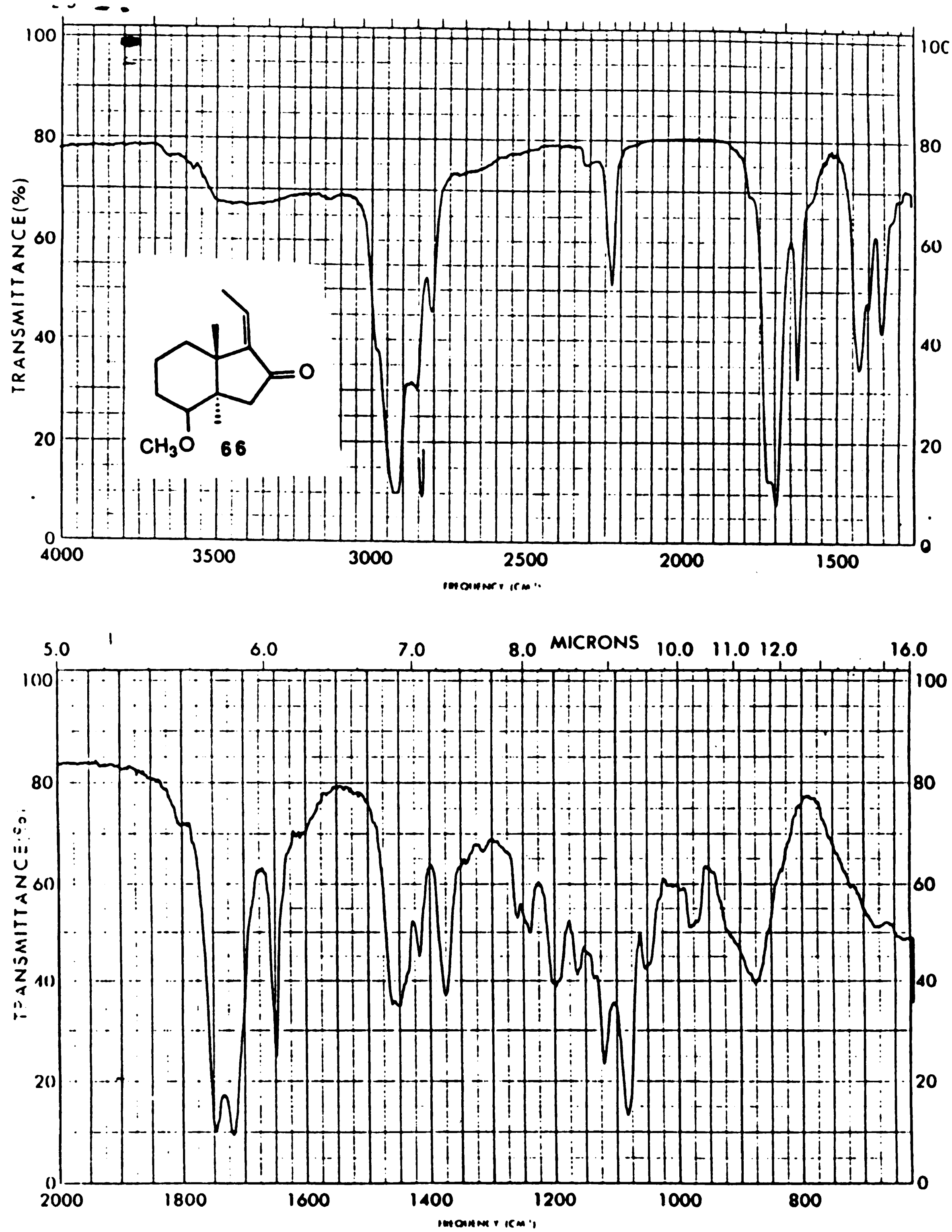


Figure 12. Infrared spectrum of **66**

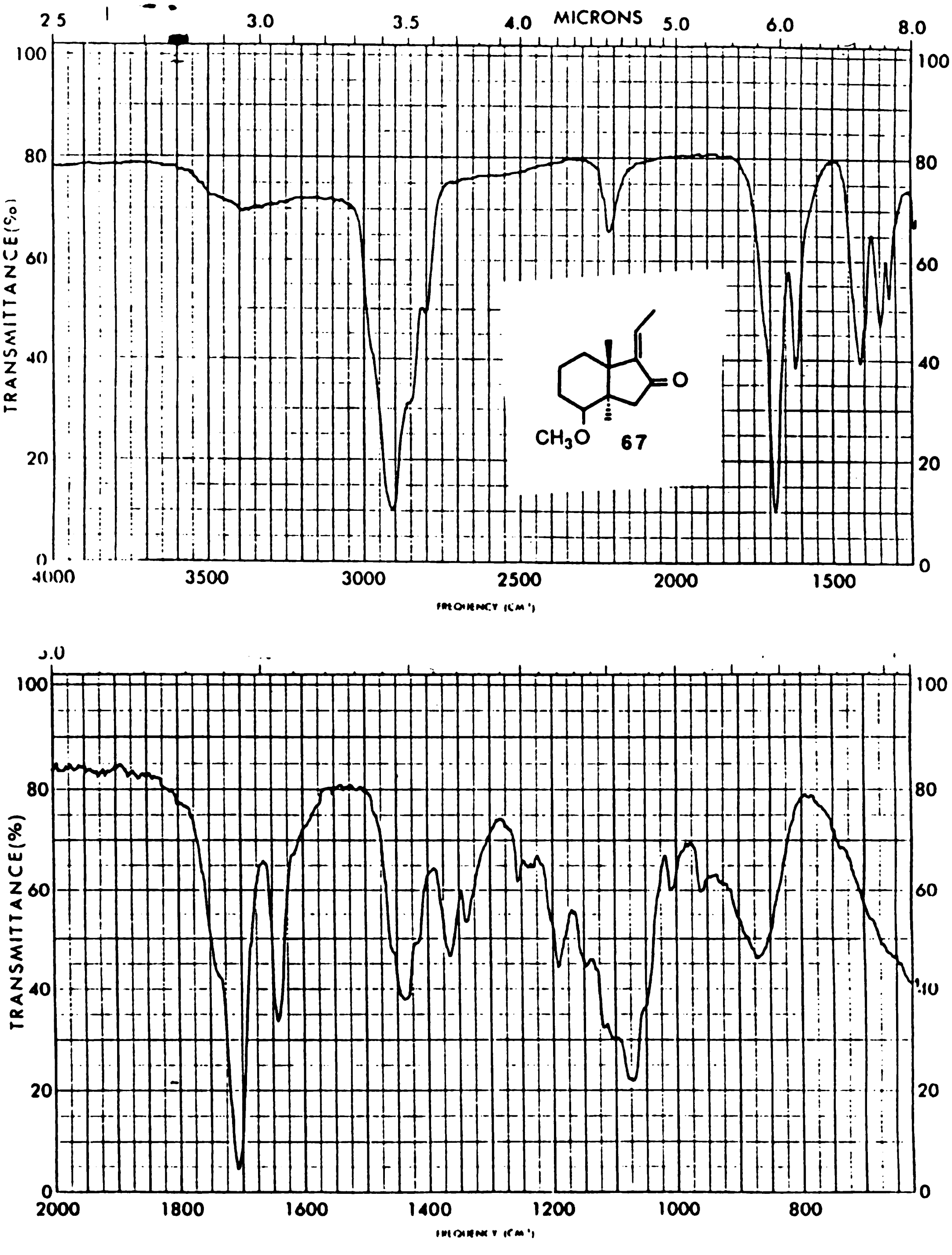


Figure 13. Infrared spectrum of **67**

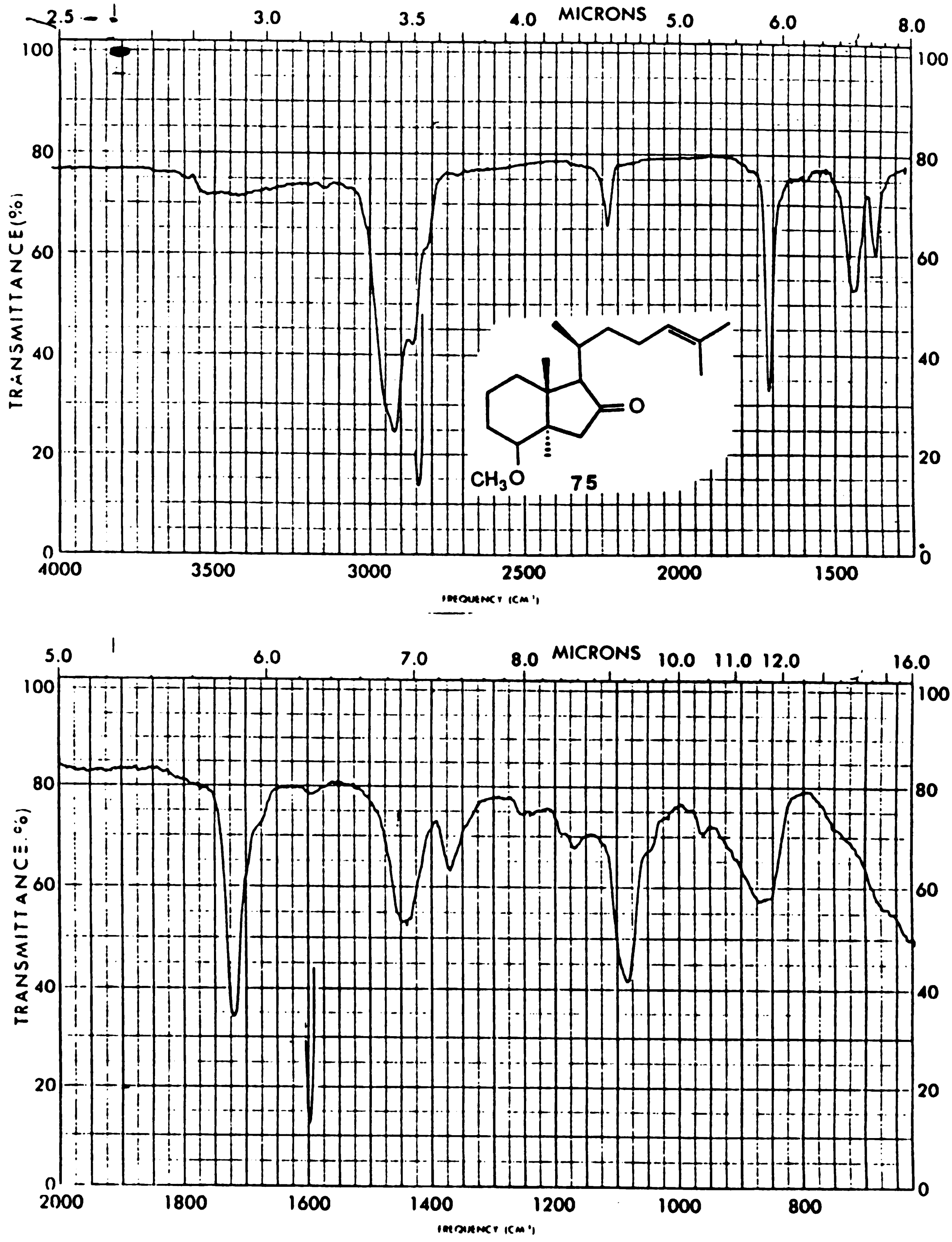


Figure 14. Infrared spectrum of 75

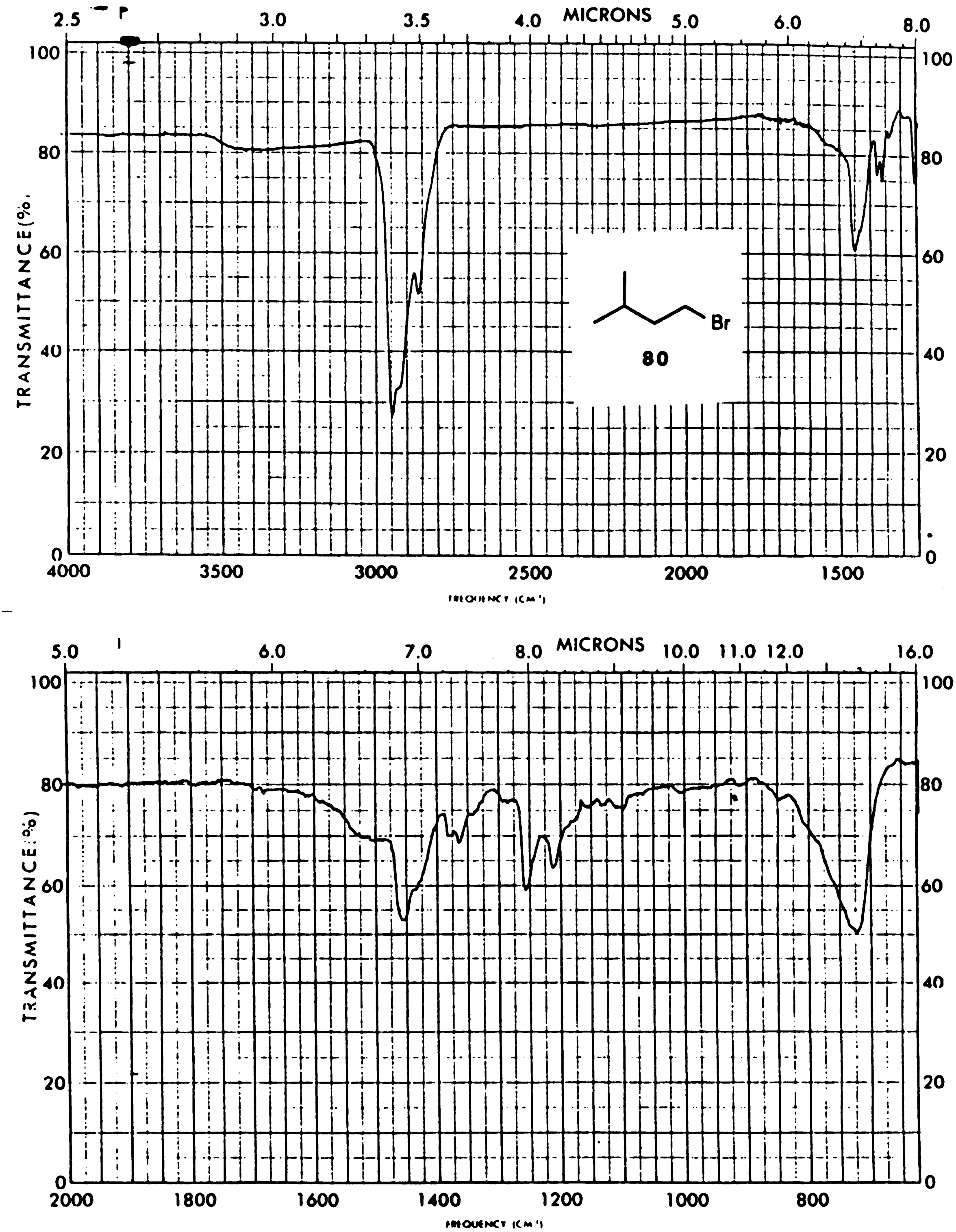


Figure 15. Infrared spectrum of **80**

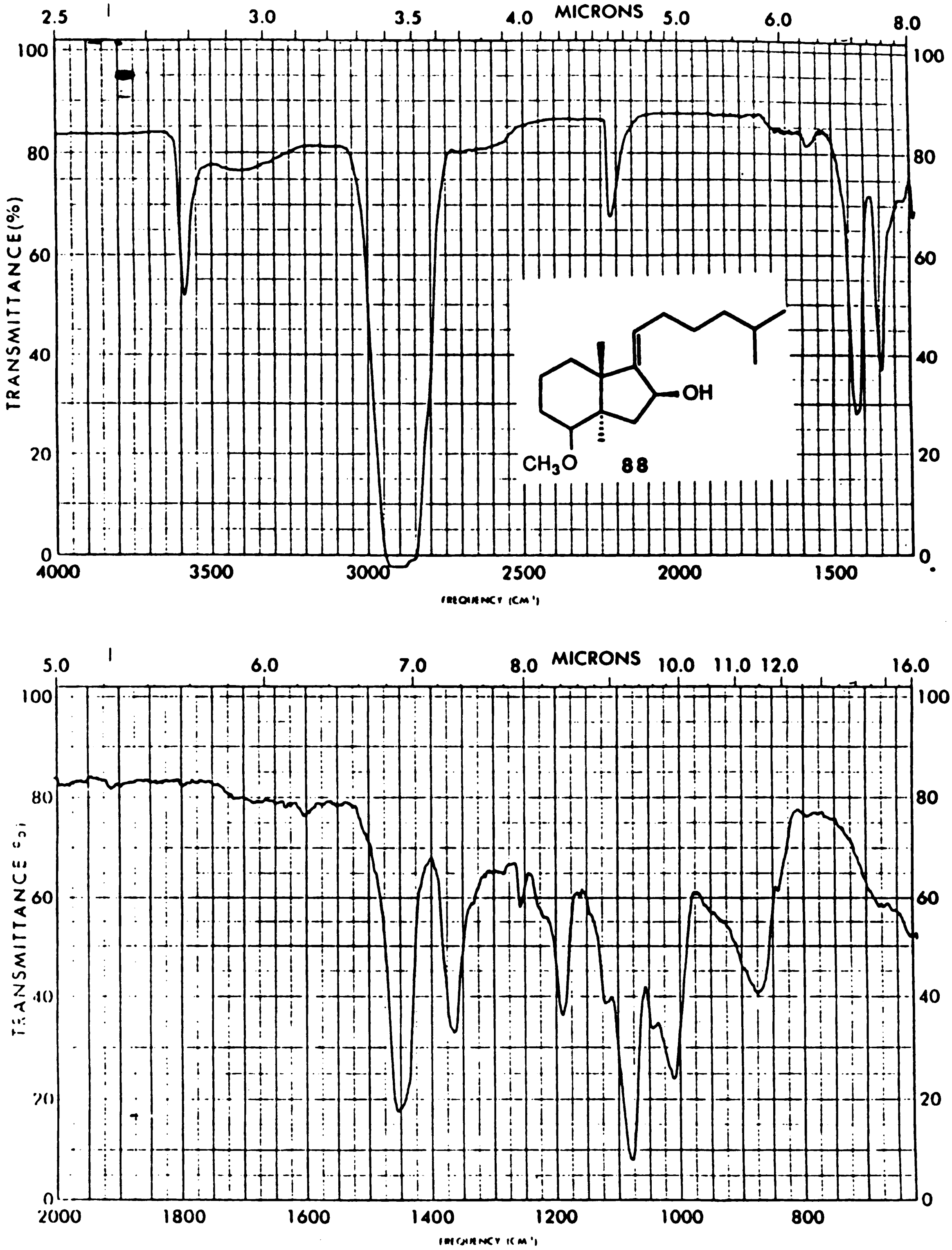


Figure 16. Infrared spectrum of 88

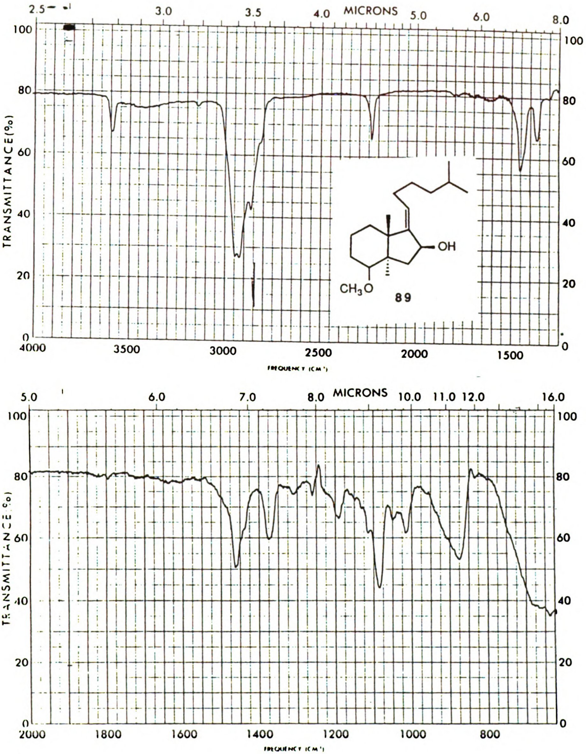


Figure 17. Infrared spectrum of **89**

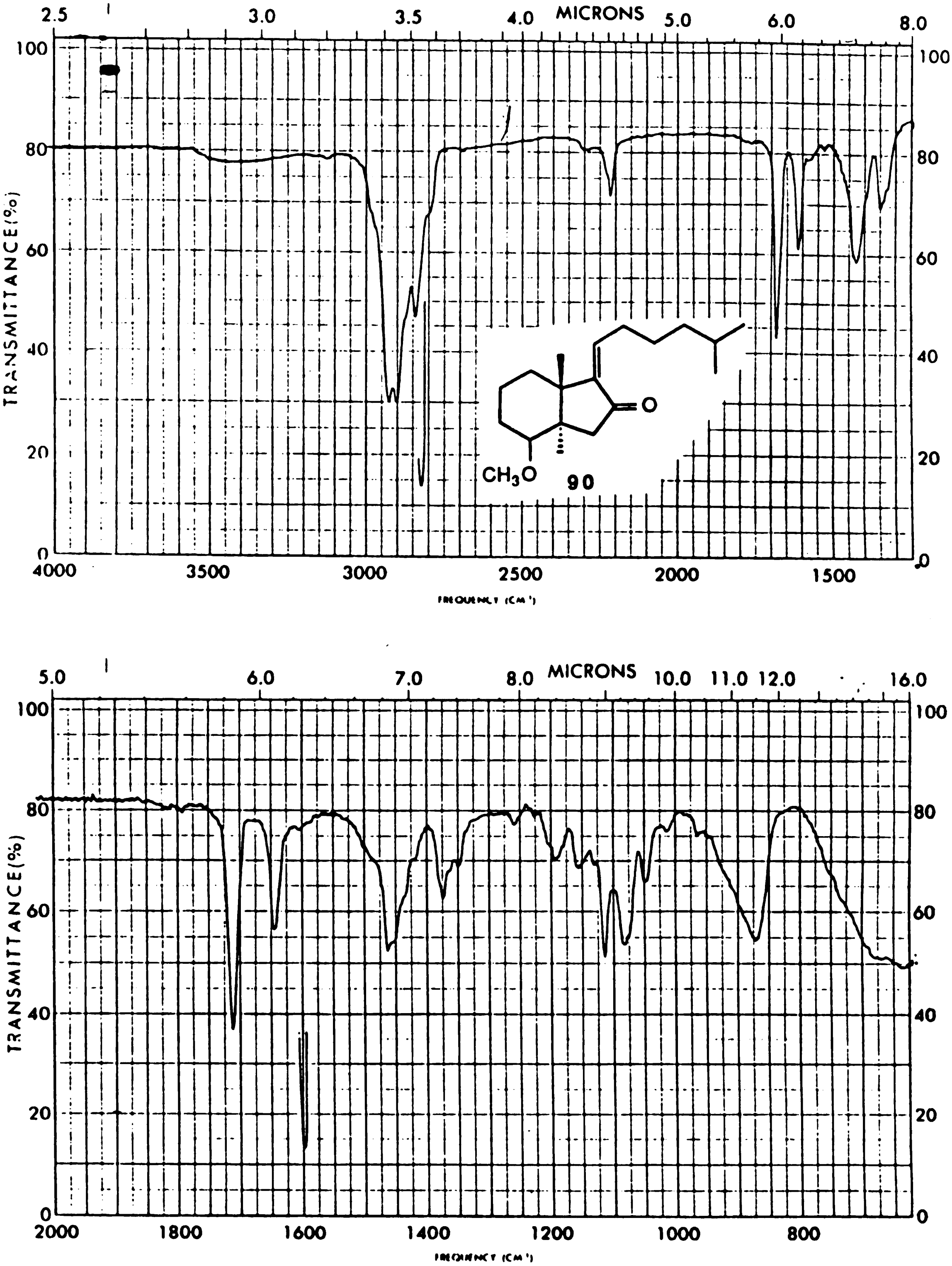


Figure 18. Infrared spectrum of **90**

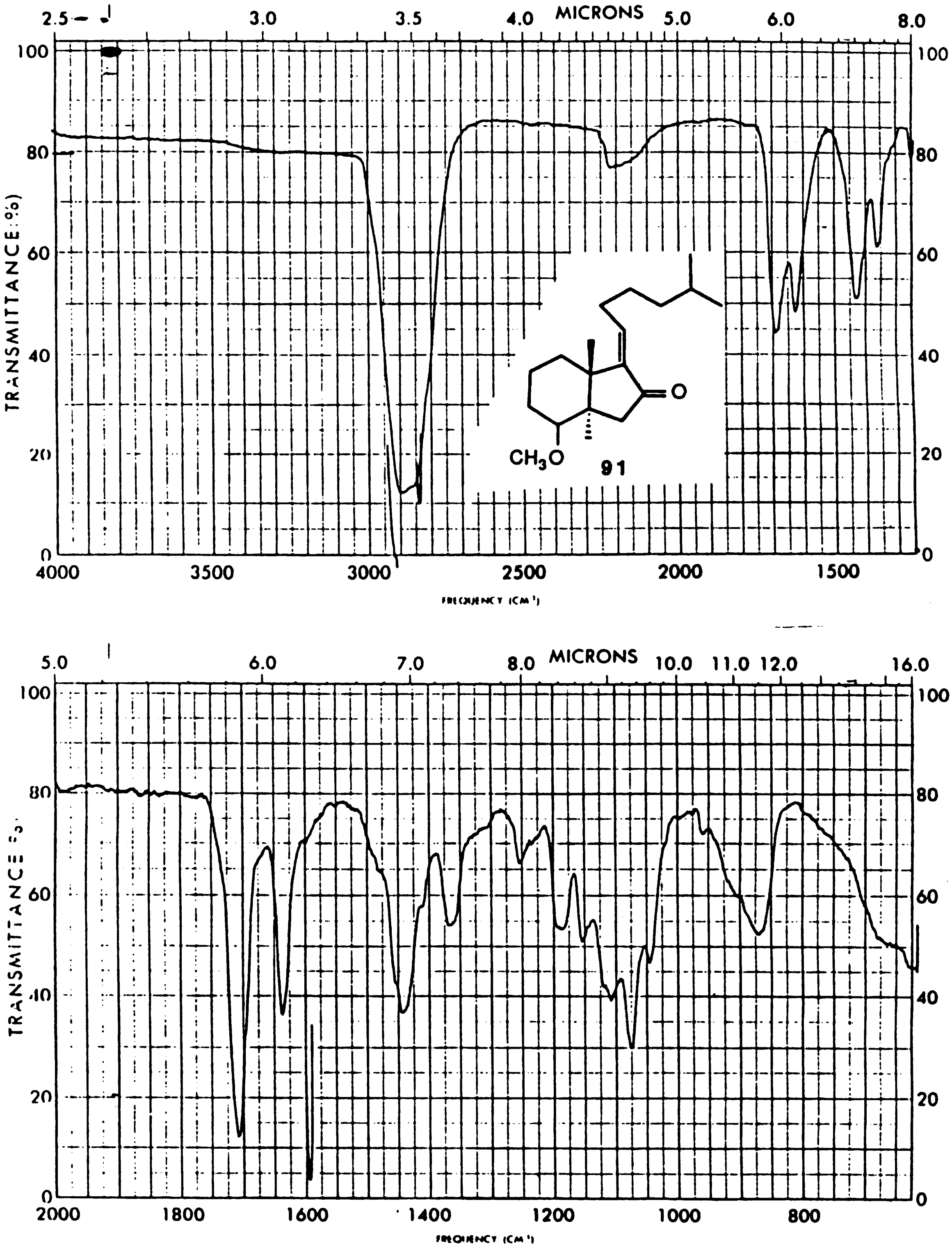


Figure 19. Infrared spectrum of 91

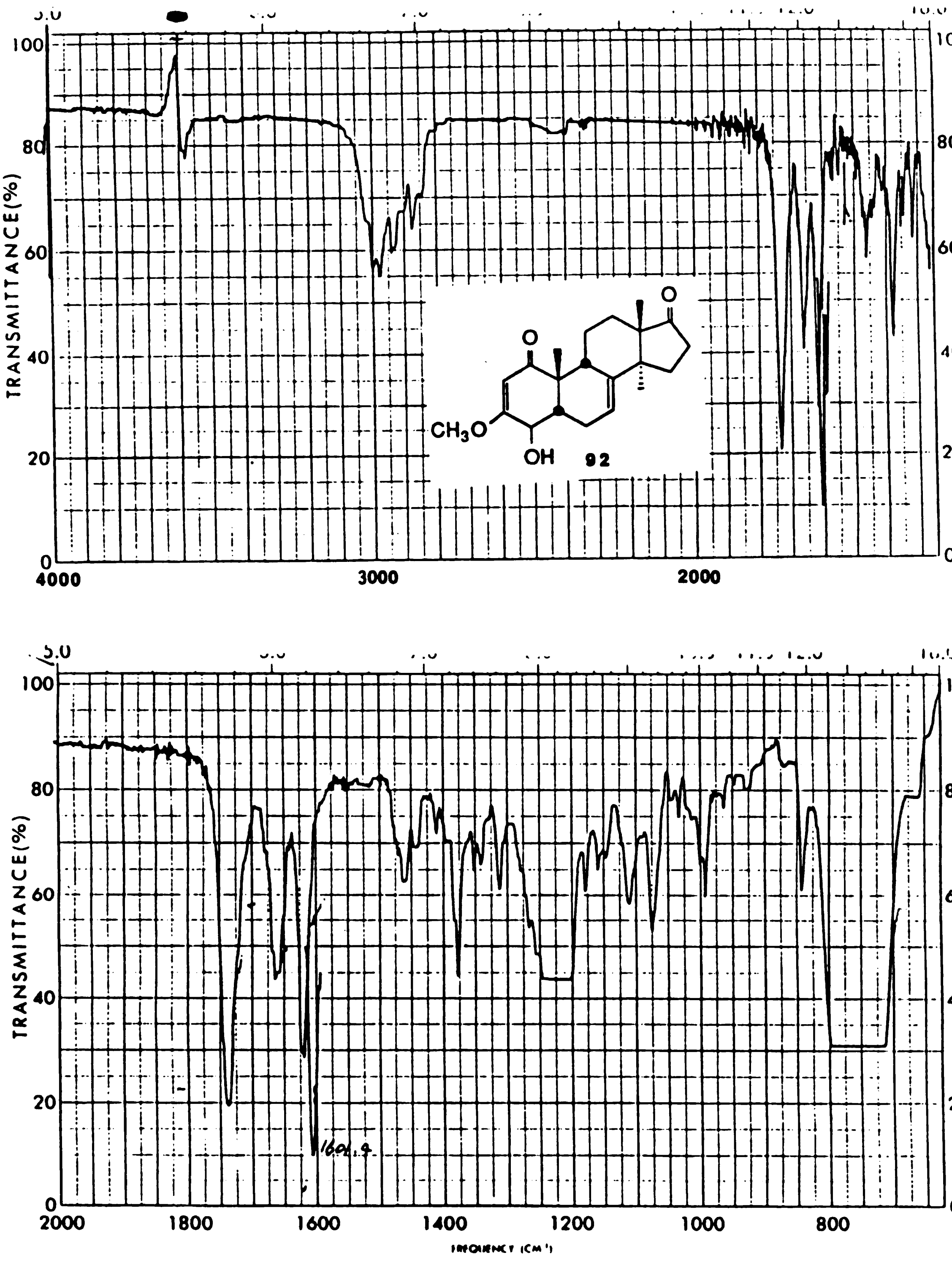


Figure 20. Infrared spectrum of 92

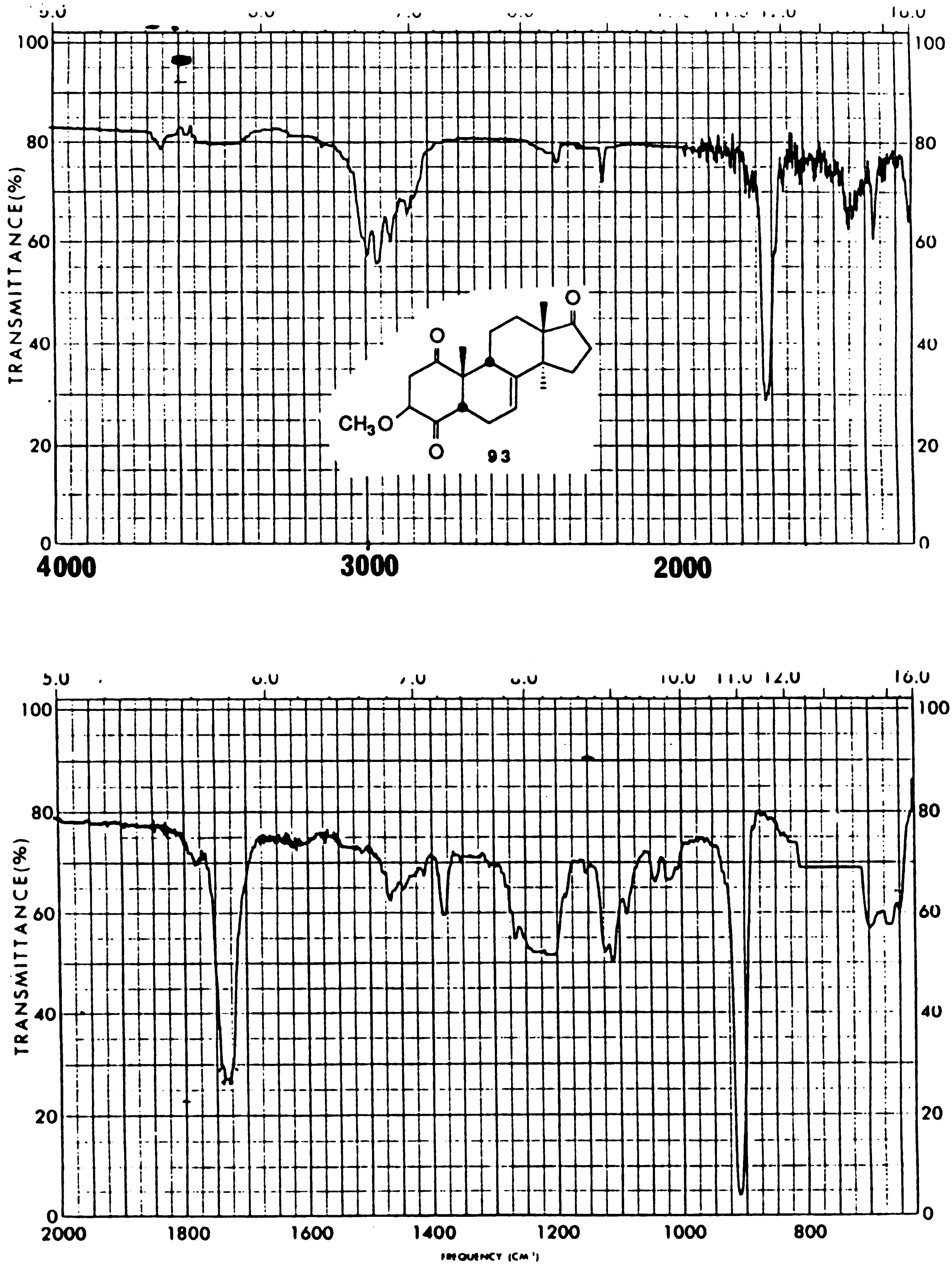


Figure 21. Infrared spectrum of 93

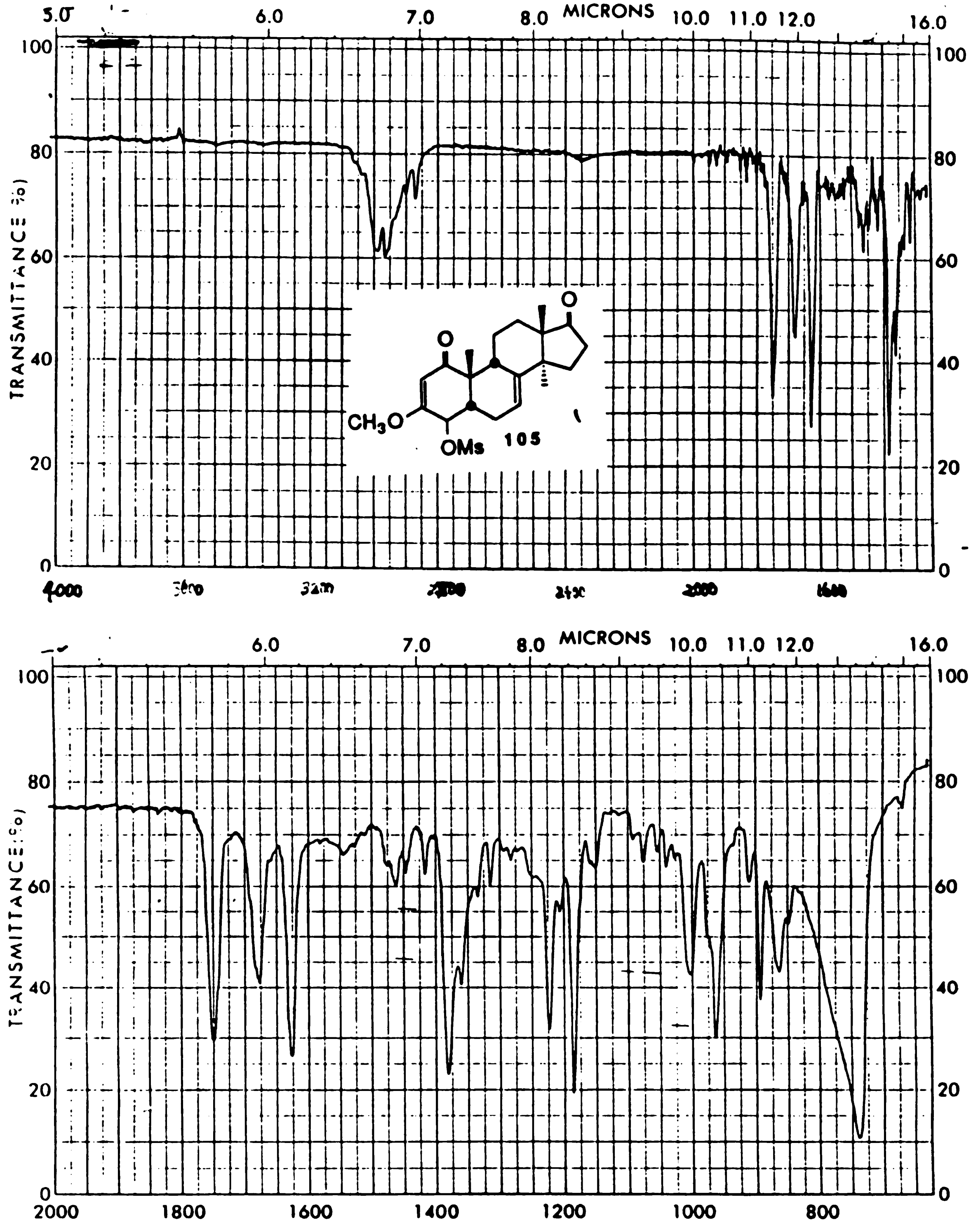


Figure 22. Infrared spectrum of **105**

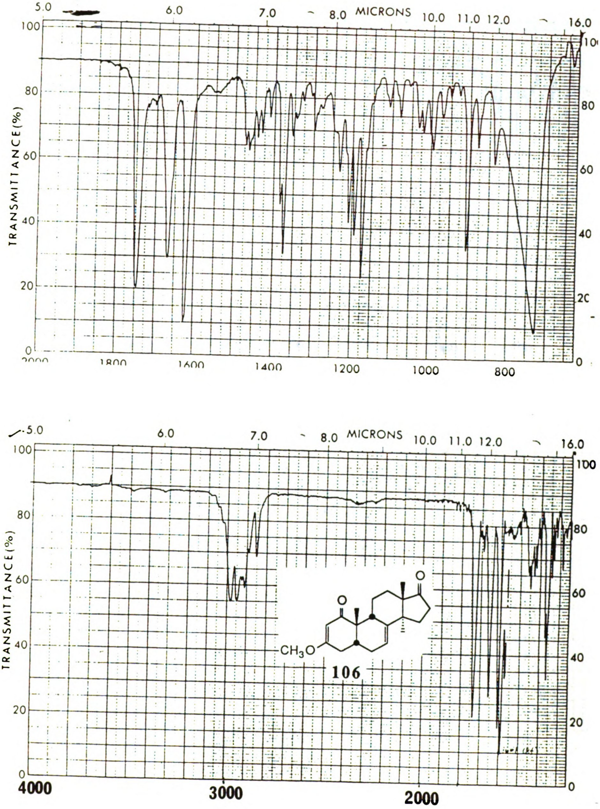


Figure 23. Infrared spectrum of **106**

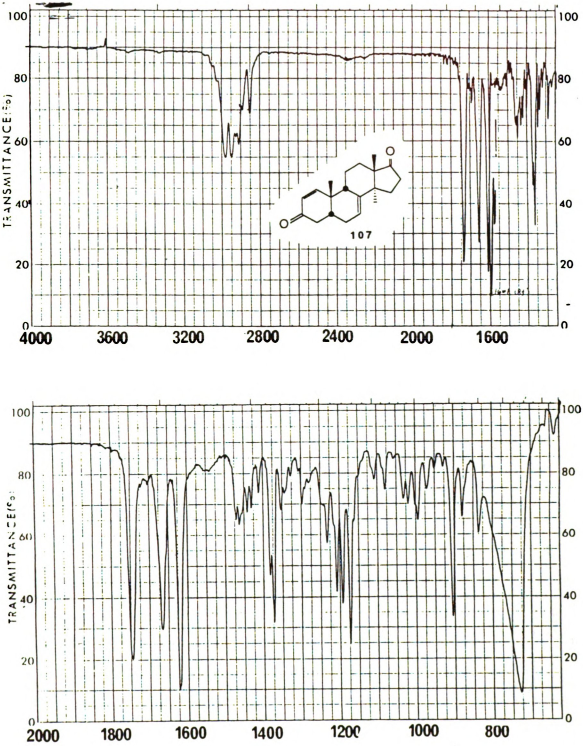


Figure 24. Infrared spectrum of **107**

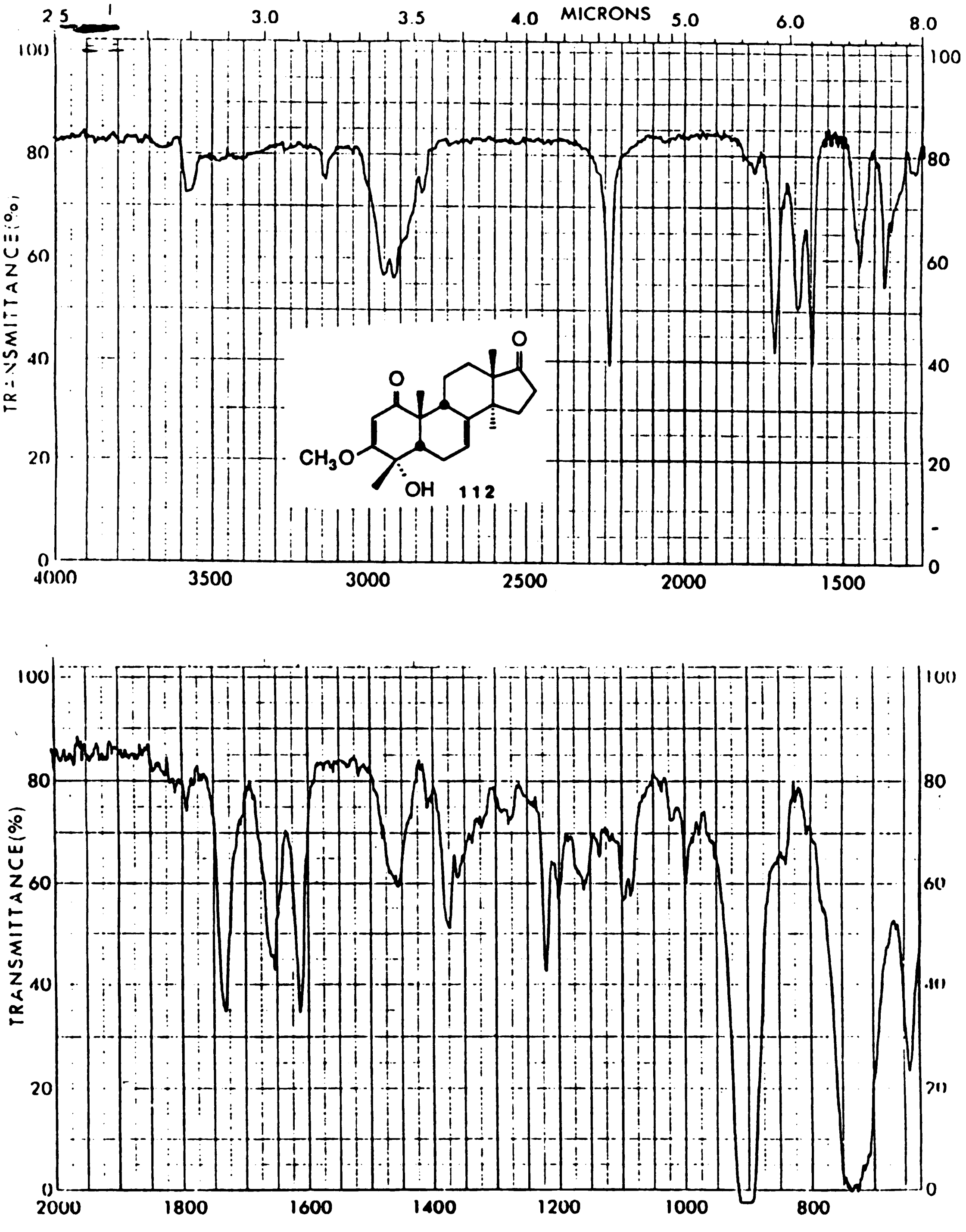


Figure 25. Infrared spectrum of **112**

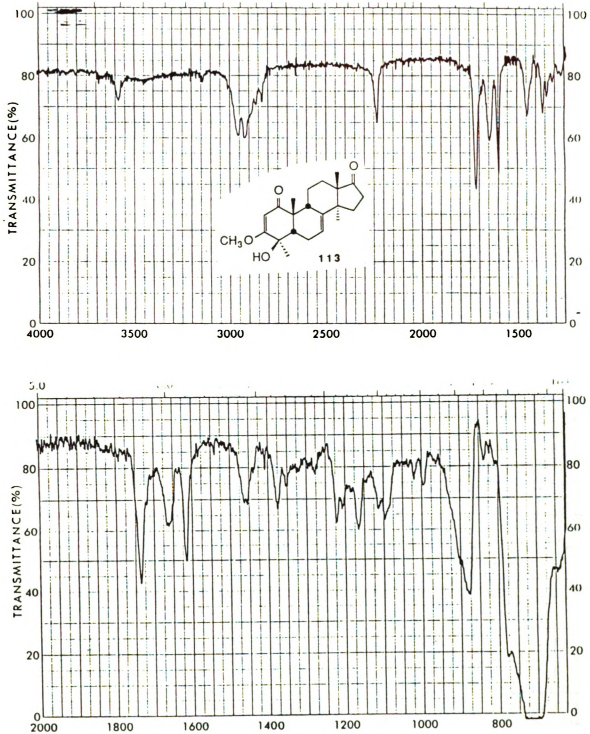


Figure 26. Infrared spectrum of **113**

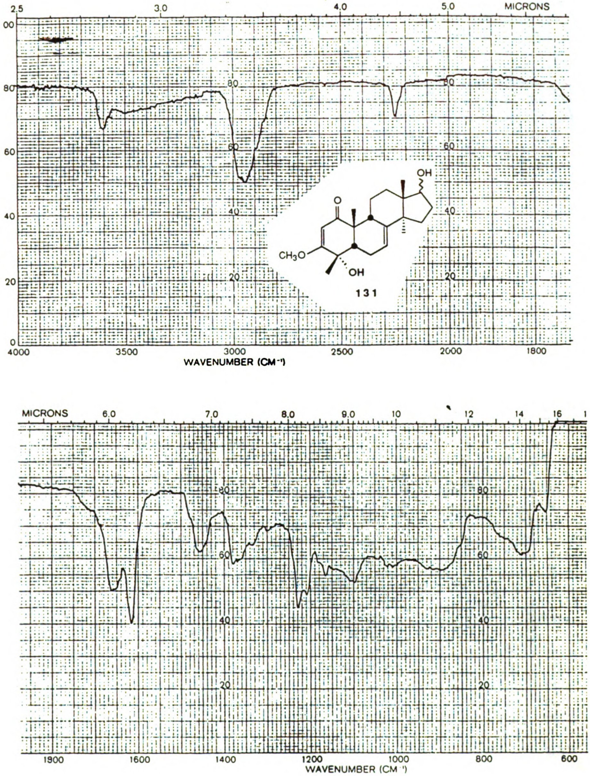


Figure 27. Infrared spectrum of **131**

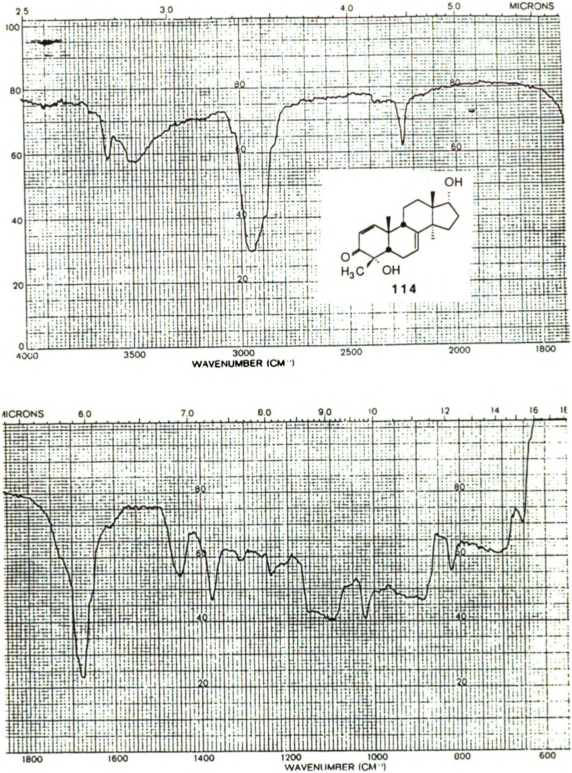


Figure 28. Infrared spectrum of **114**

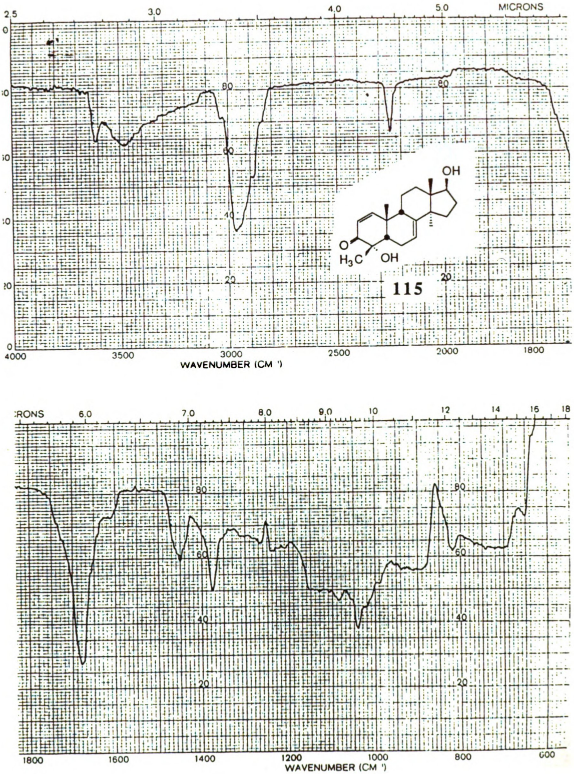


Figure 29. Infrared spectrum of **115**

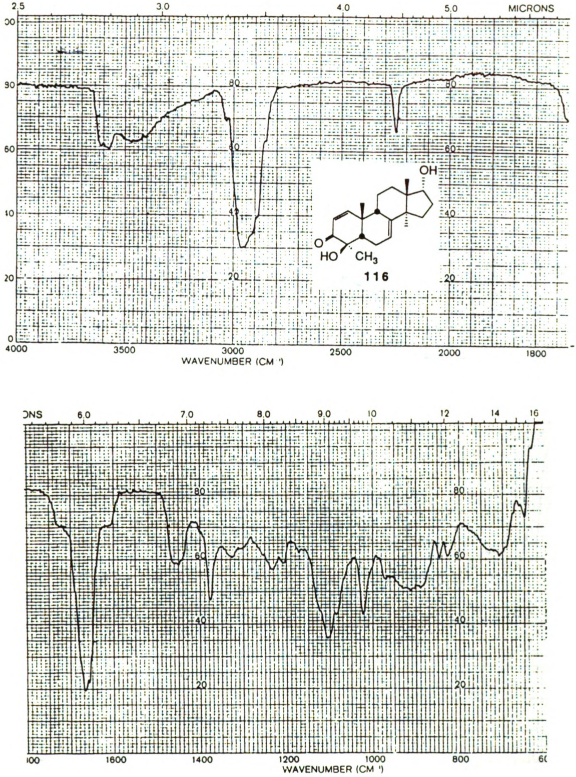


Figure 30. Infrared spectrum of **116**

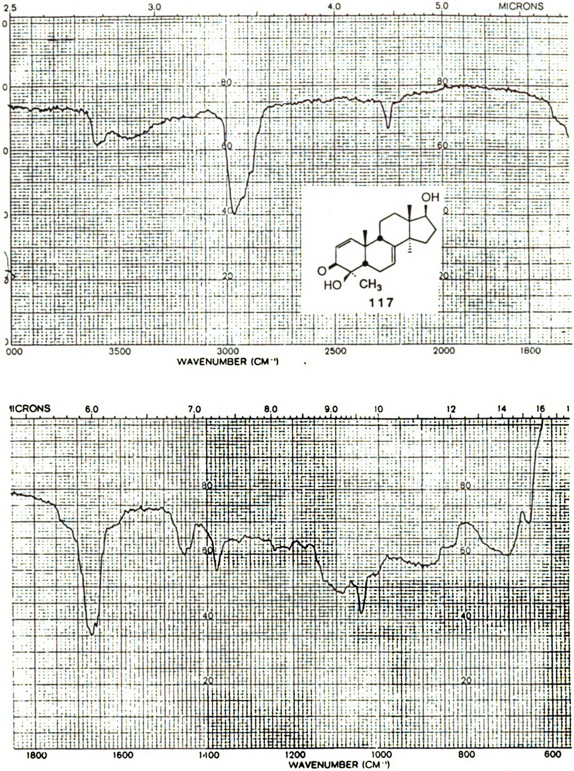


Figure 31. Infrared spectrum of **117**

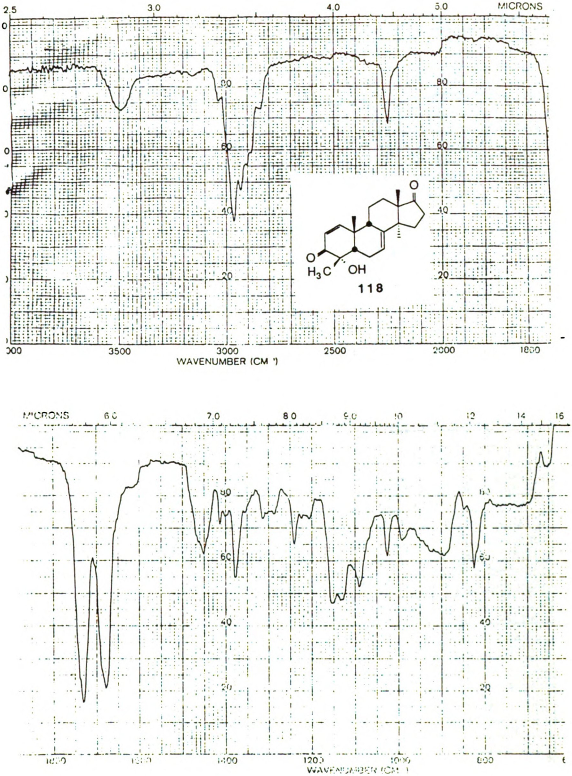


Figure 32. Infrared spectrum of **118**

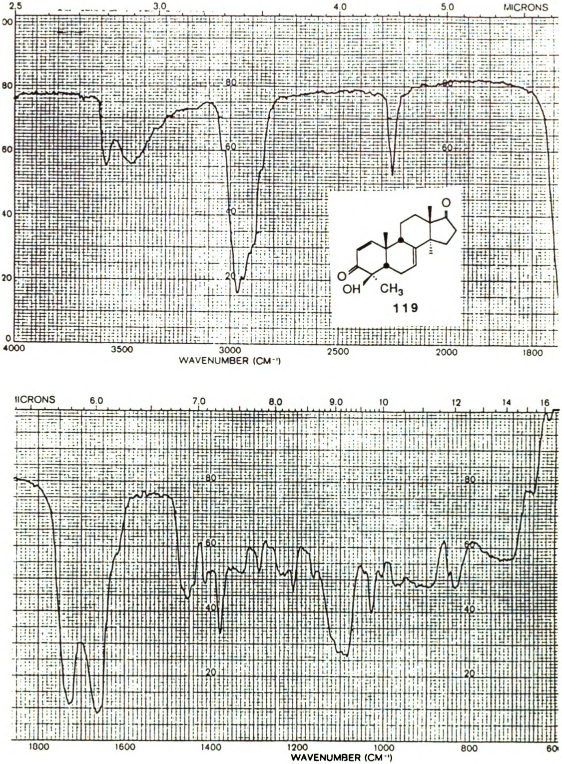


Figure 33. Infrared spectrum of **119**

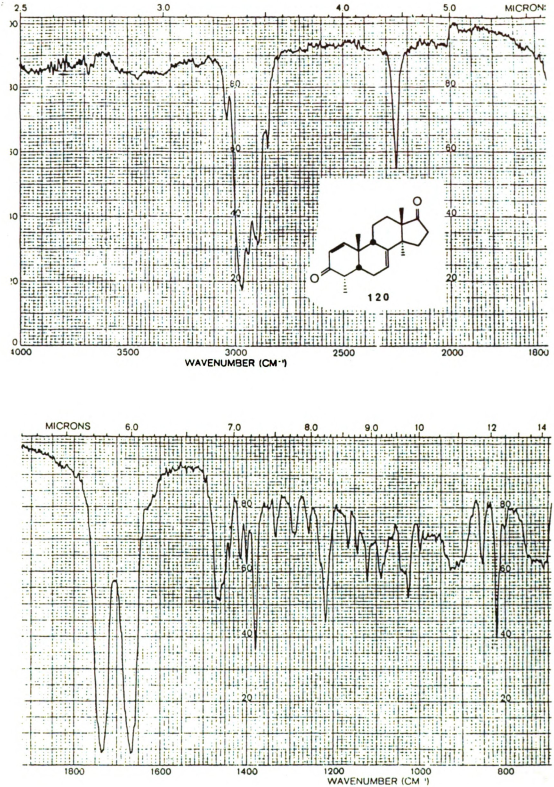


Figure 34. Infrared spectrum of **120**

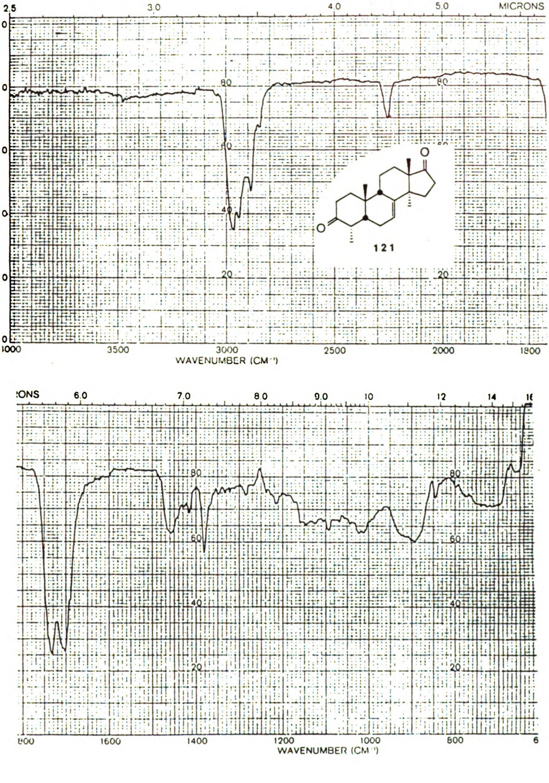


Figure 35. Infrared spectrum of **121**

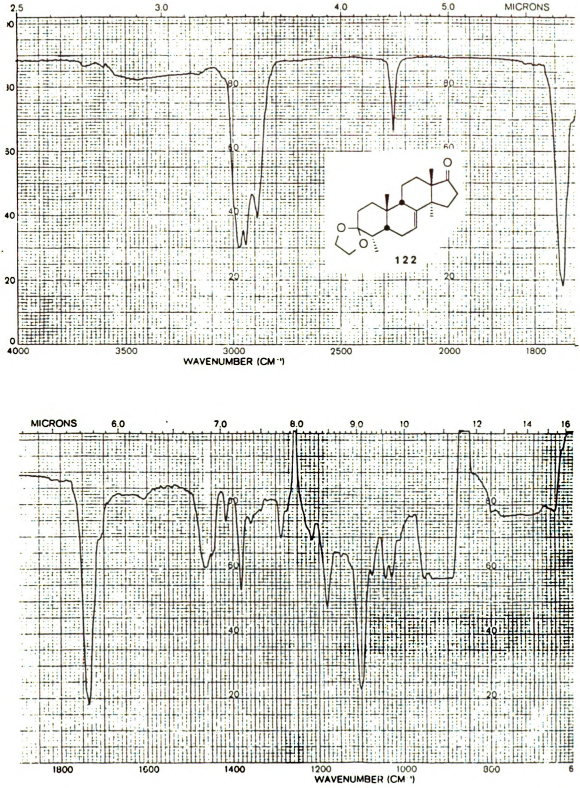


Figure 36. Infrared spectrum of **122**

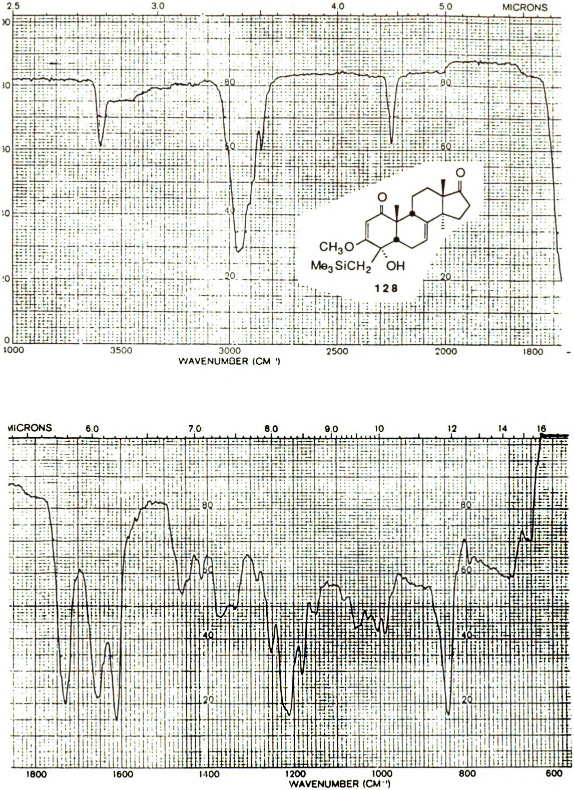


Figure 37. Infrared spectrum of **128**

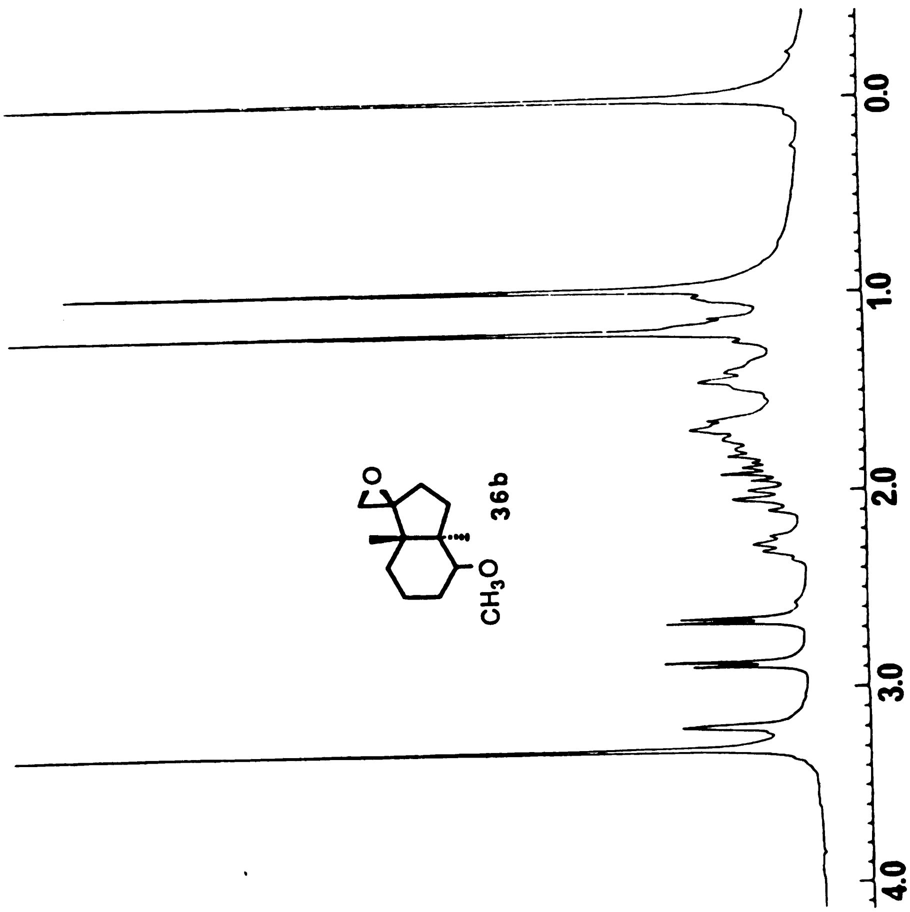


Figure 38. PMR spectrum of 36b

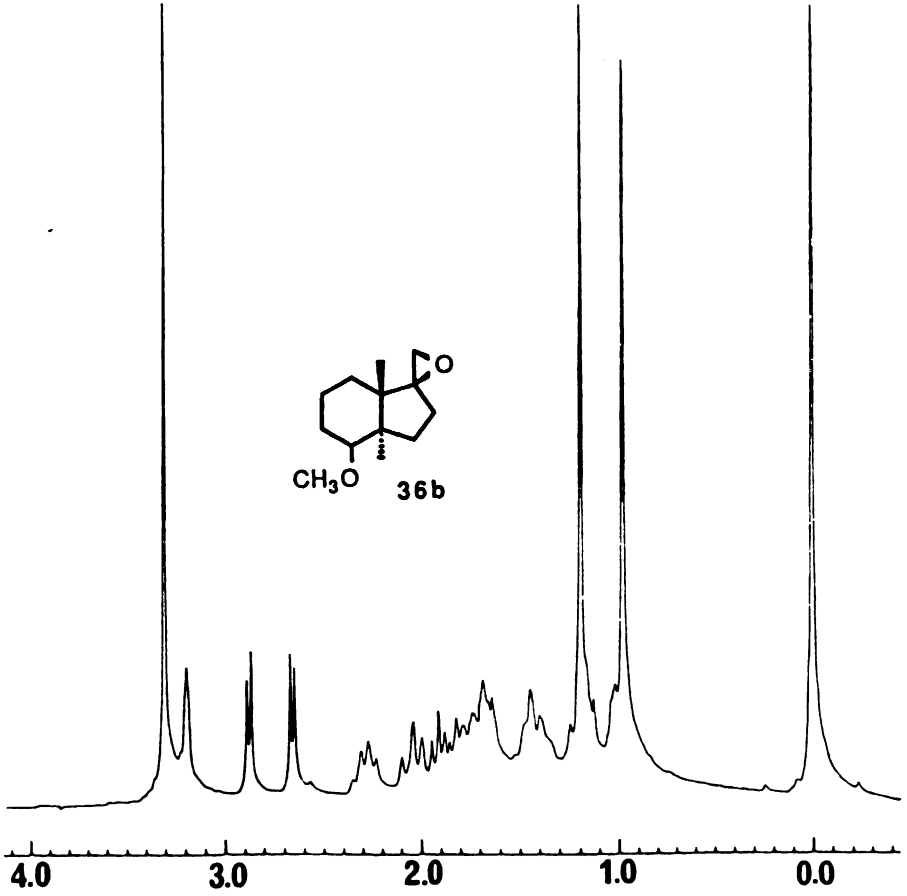


Figure 38. PMR spectrum of 36b

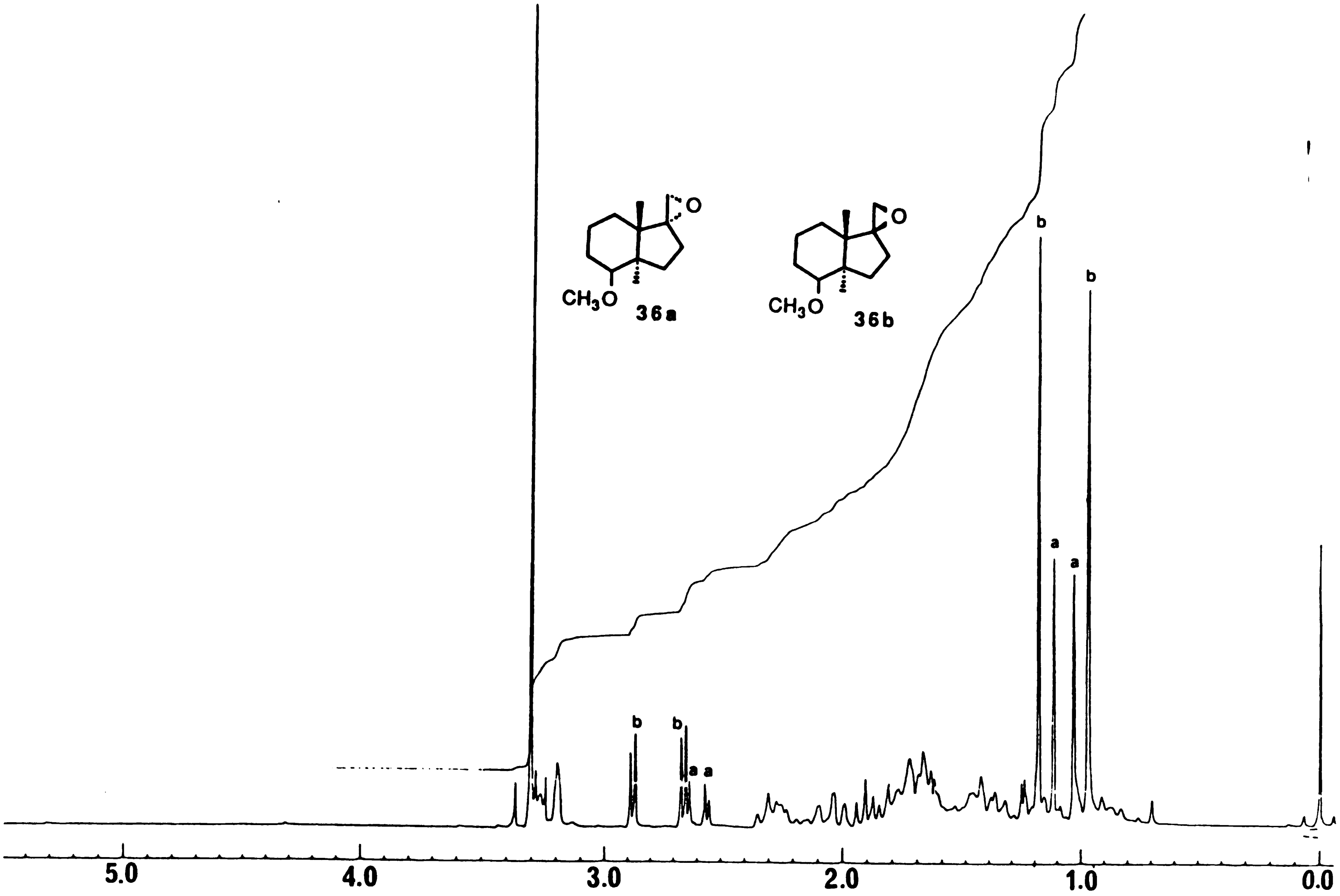


Figure 39. PMR spectrum of '36a and 36b

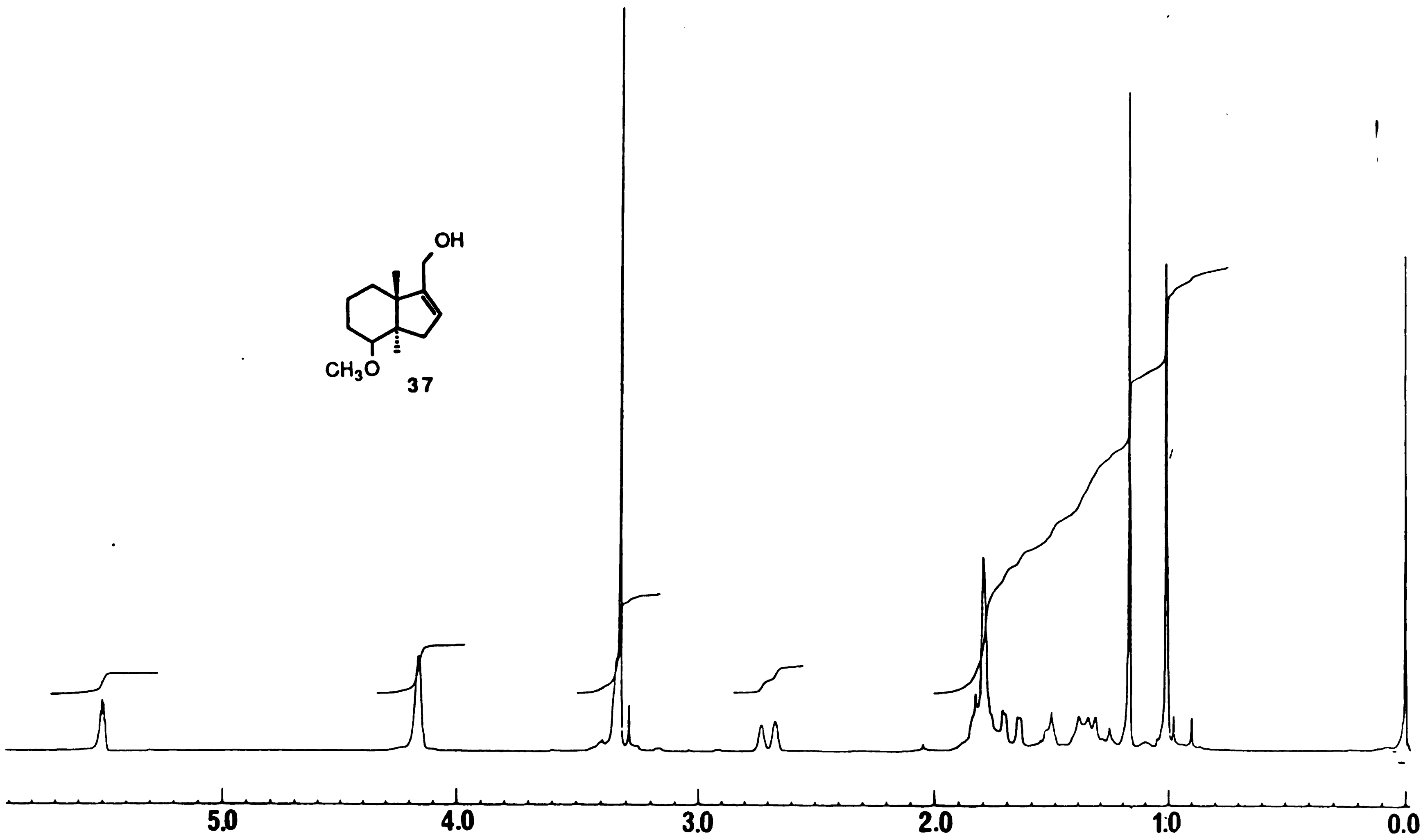


Figure 40. PMR spectrum of 37

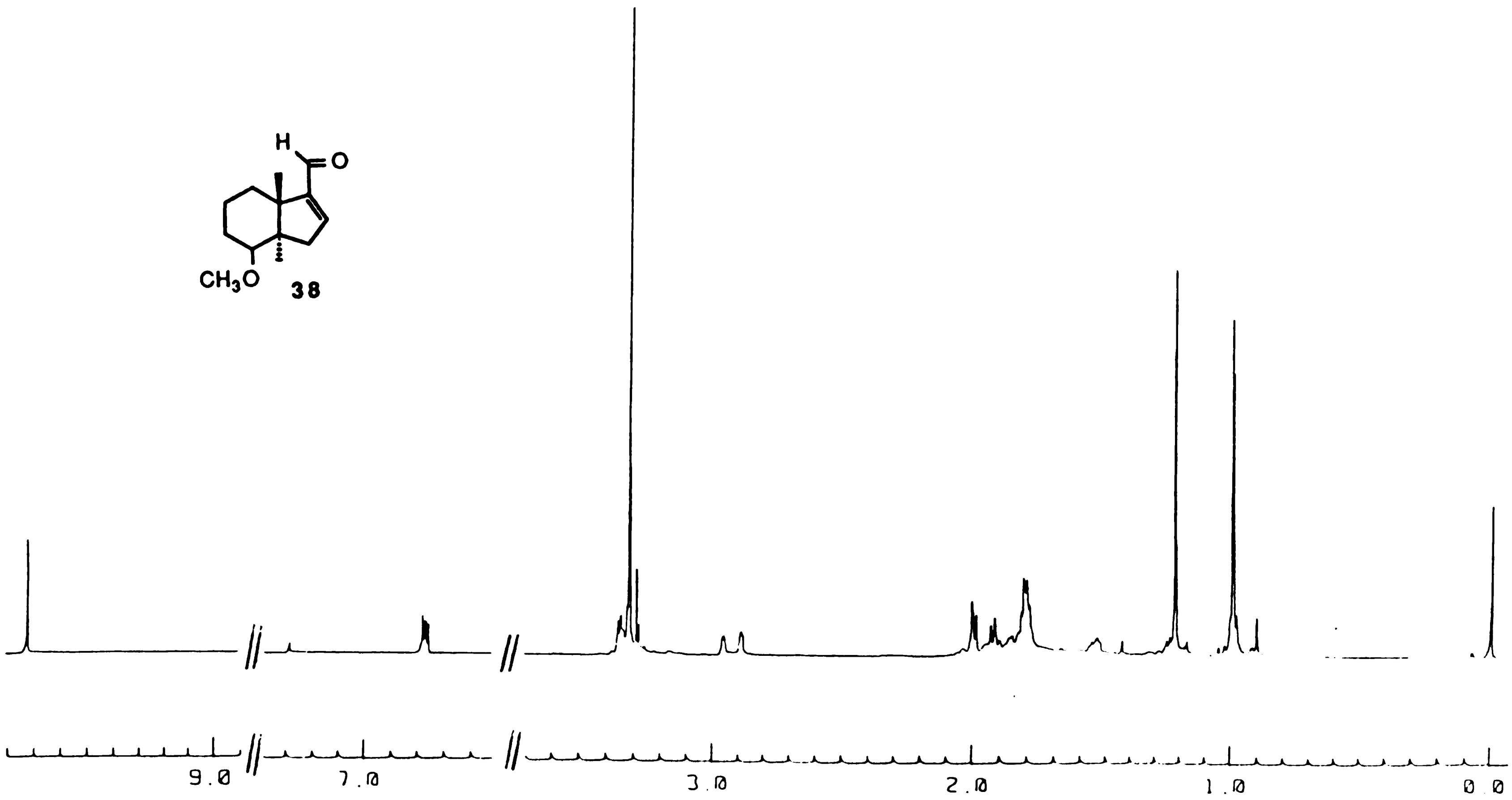


Figure 41. PMR spectrum of **38**

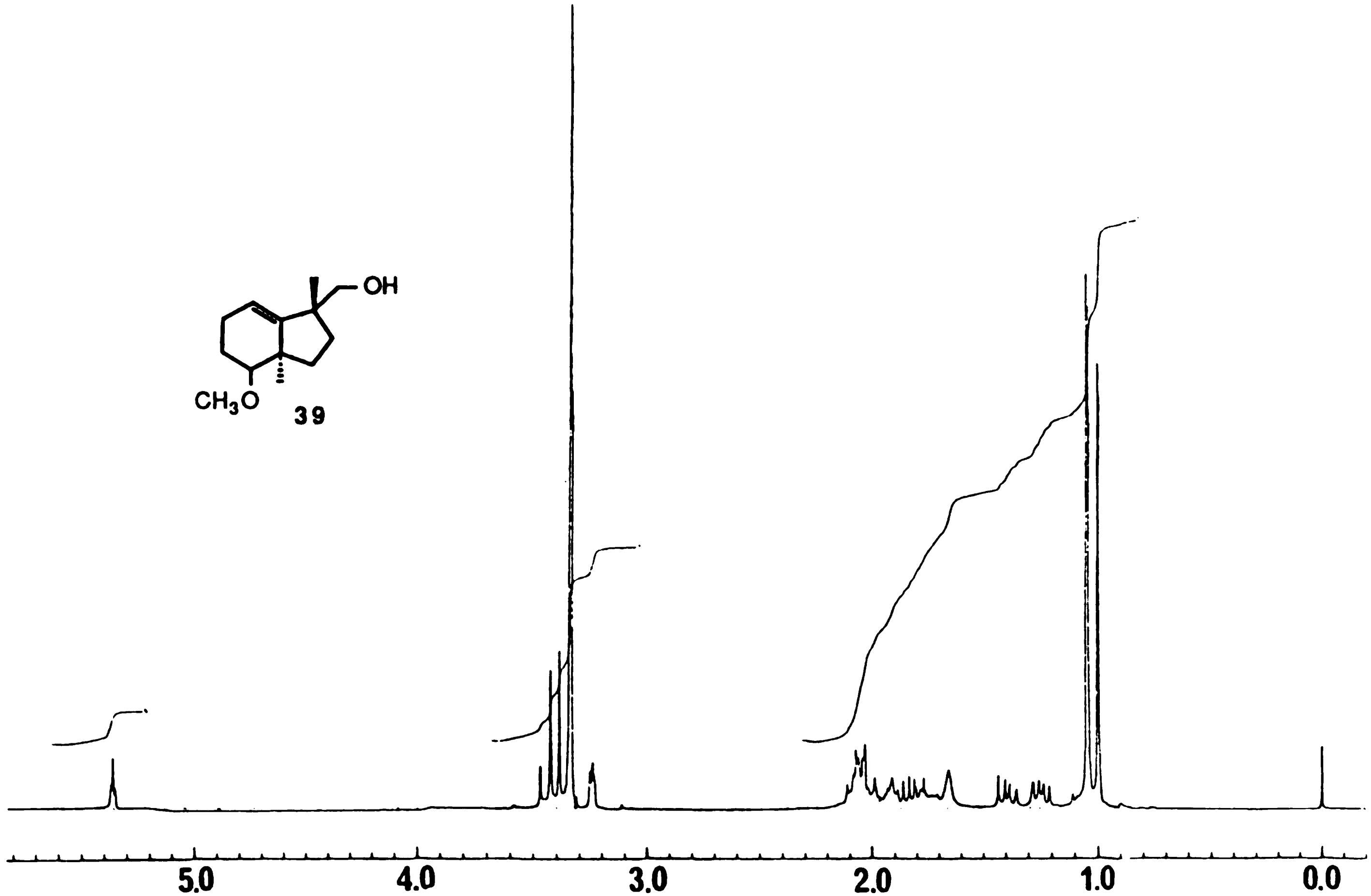


Figure 42. PMR spectrum of 39

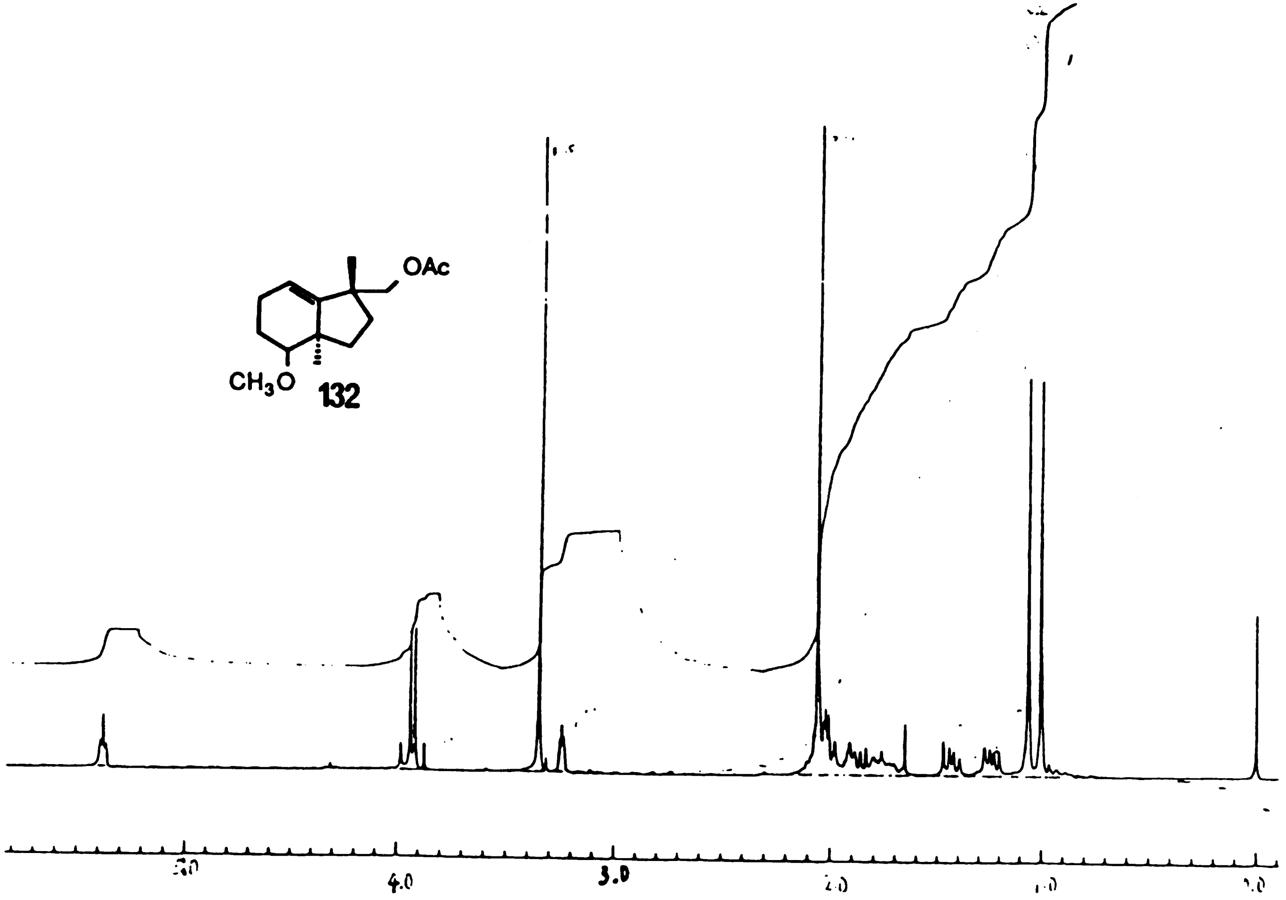


Figure 43. PMR spectrum of 132

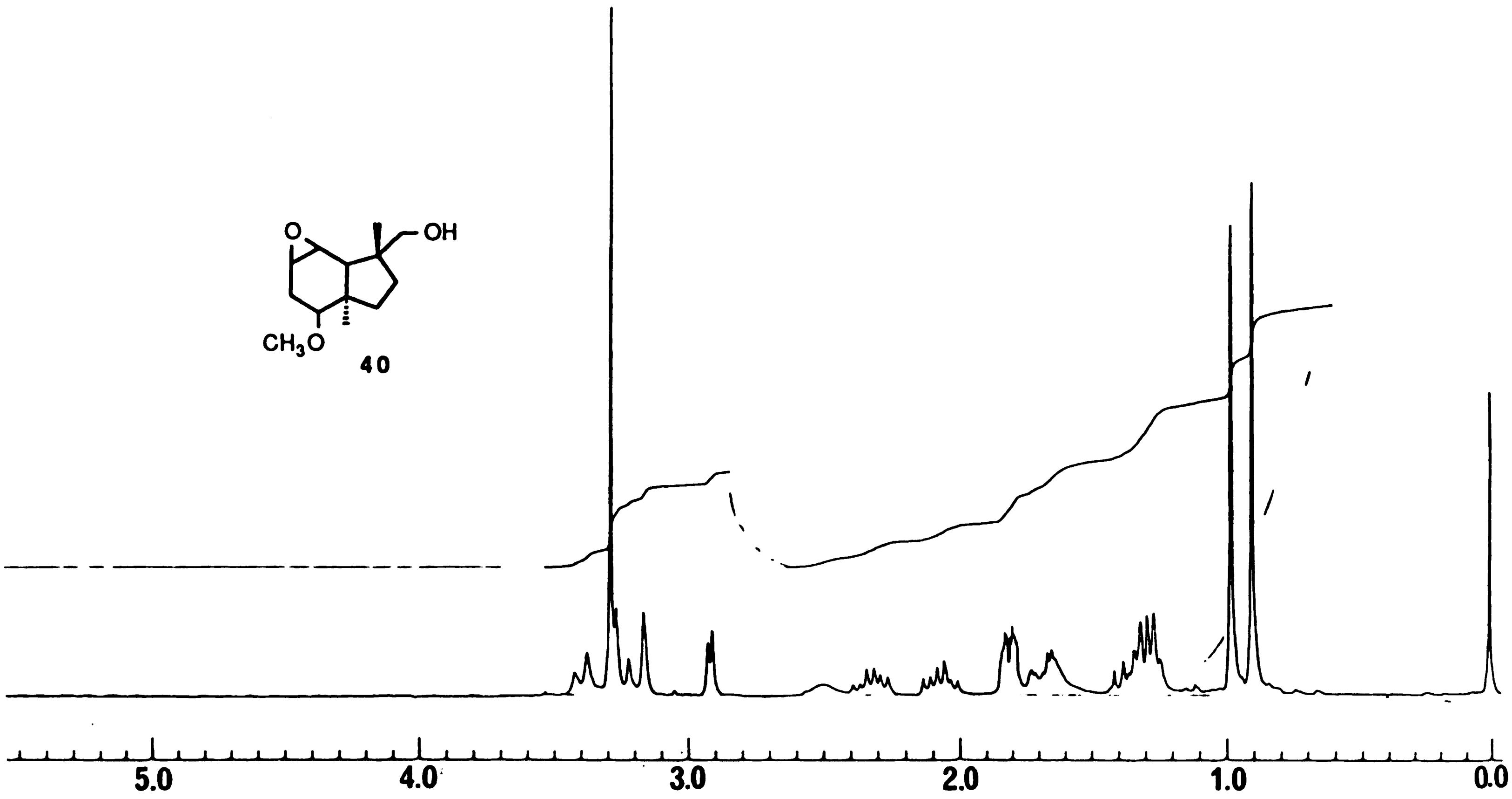


Figure 44. PMR spectrum of **40**

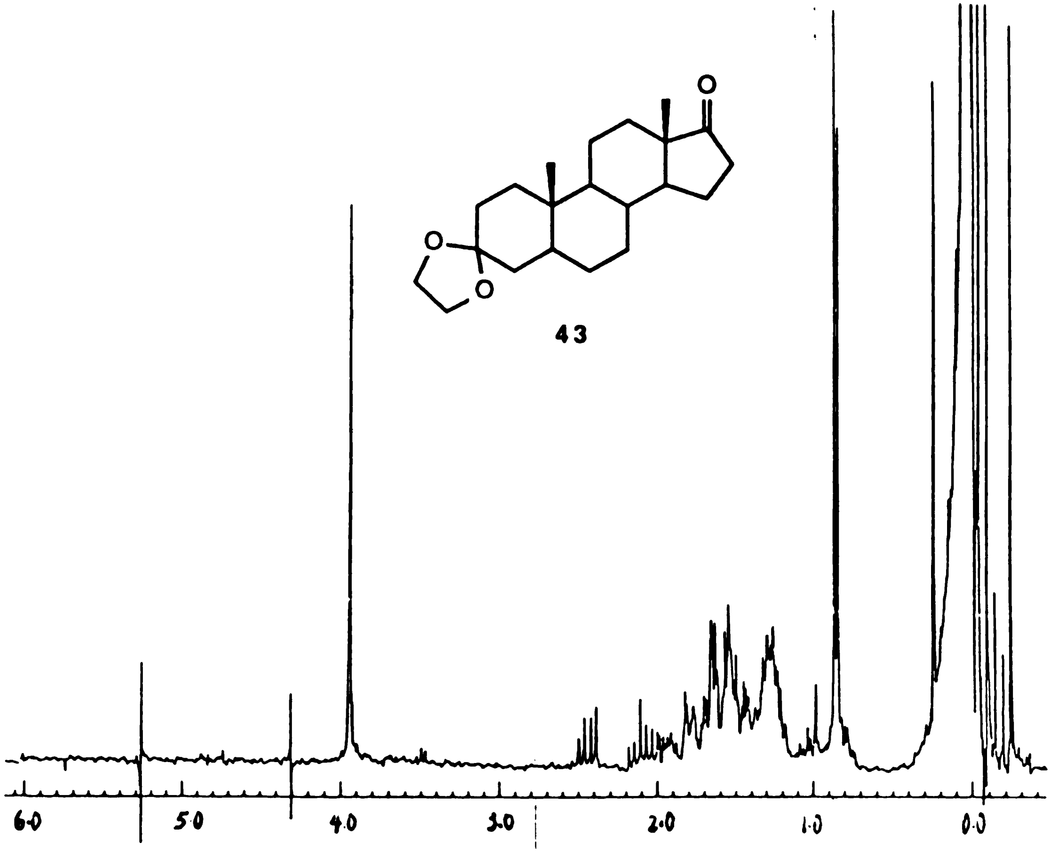


Figure 45. PMR spectrum of **43**

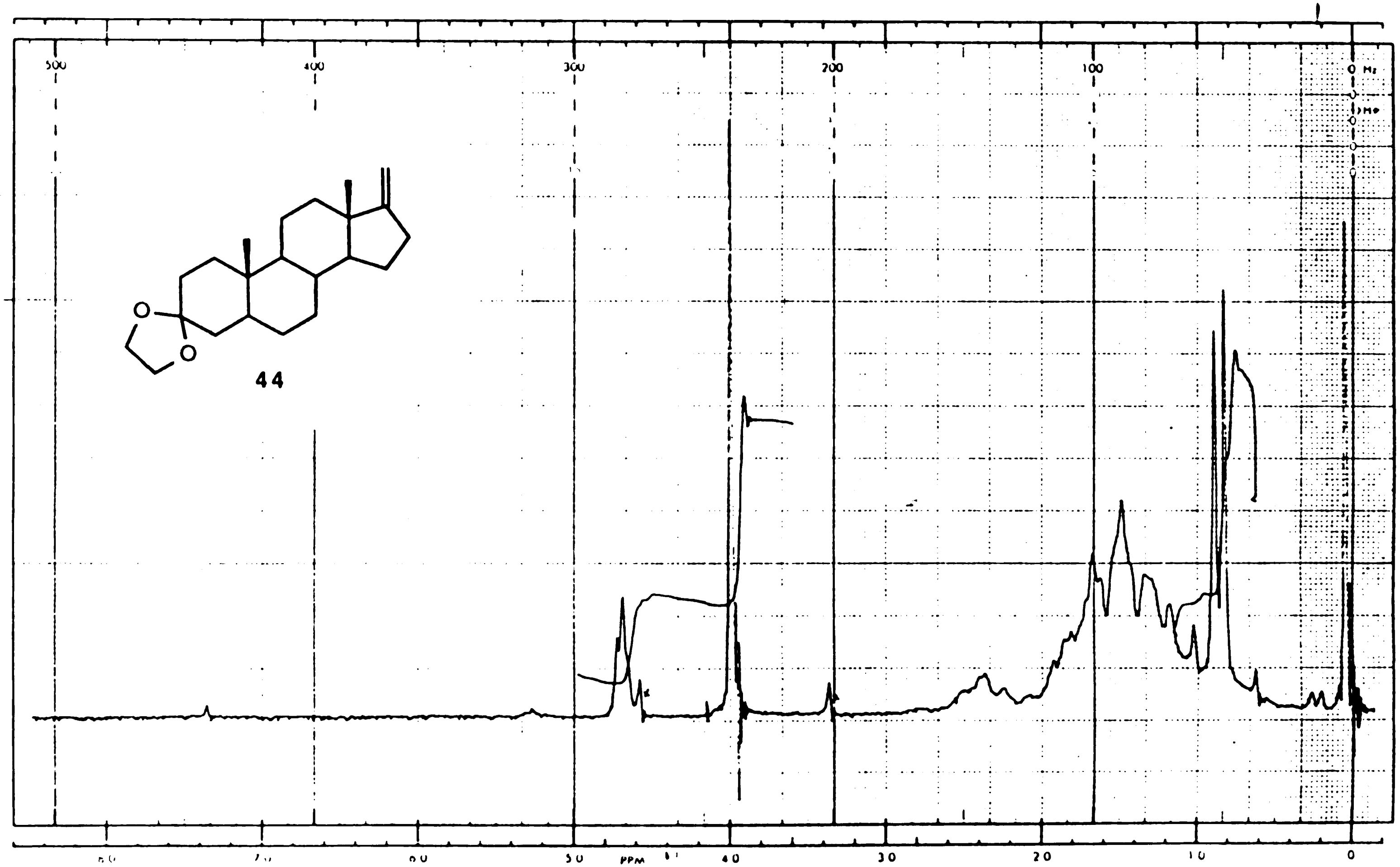


Figure 46. PMR spectrum of 44

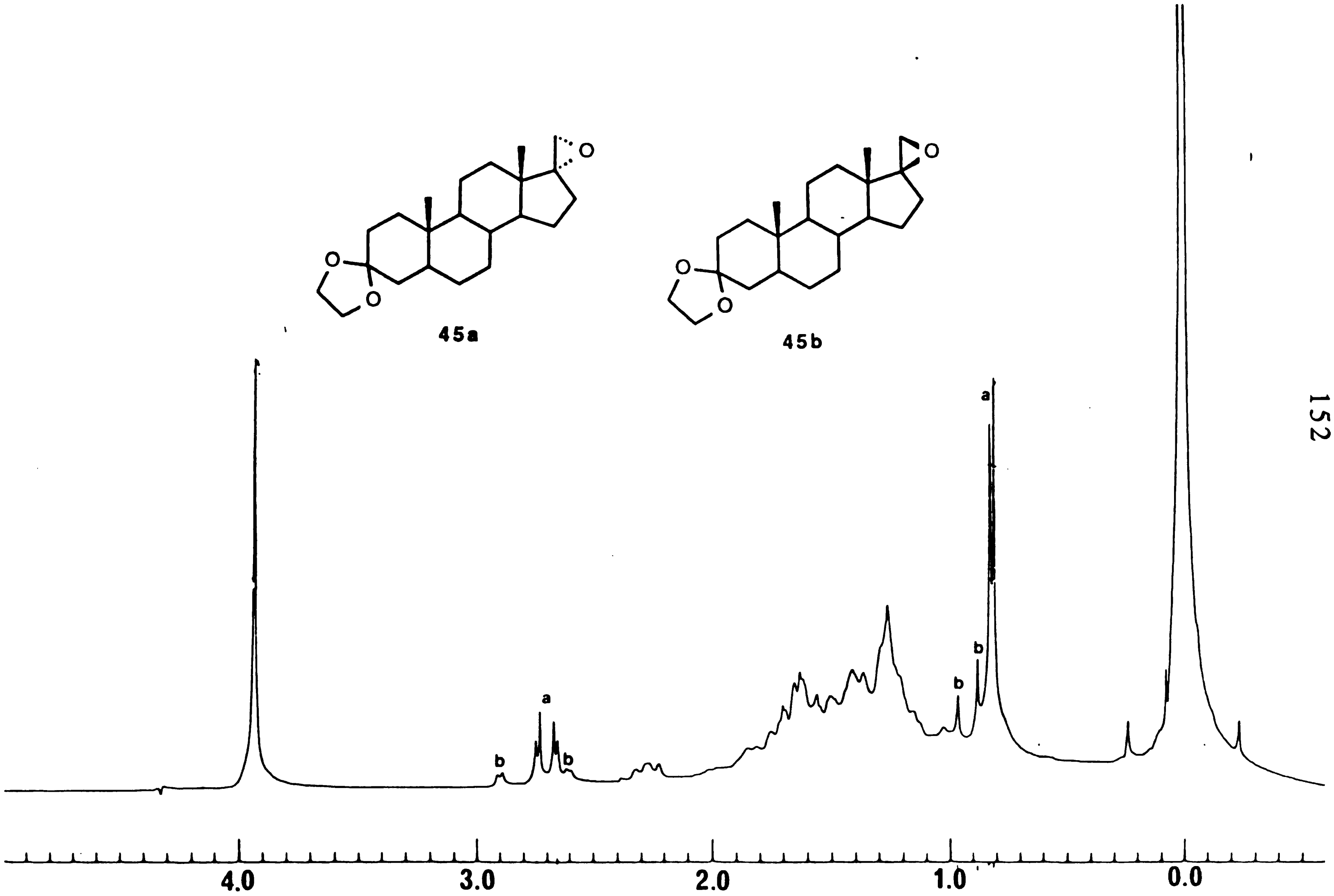
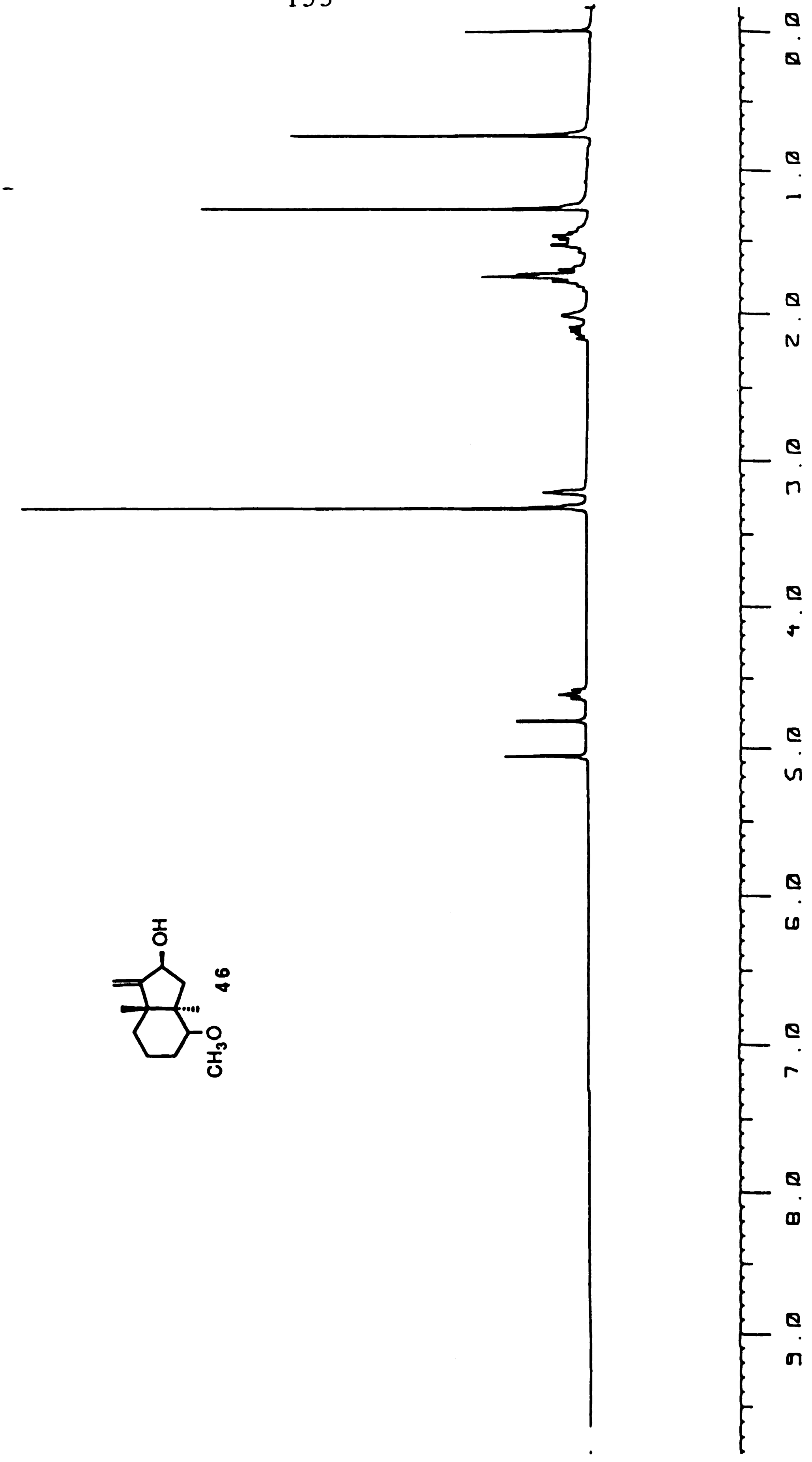


Figure 47. PMR spectrum of 45a and 45b



46

Figure 48 PMR spectrum of **46**

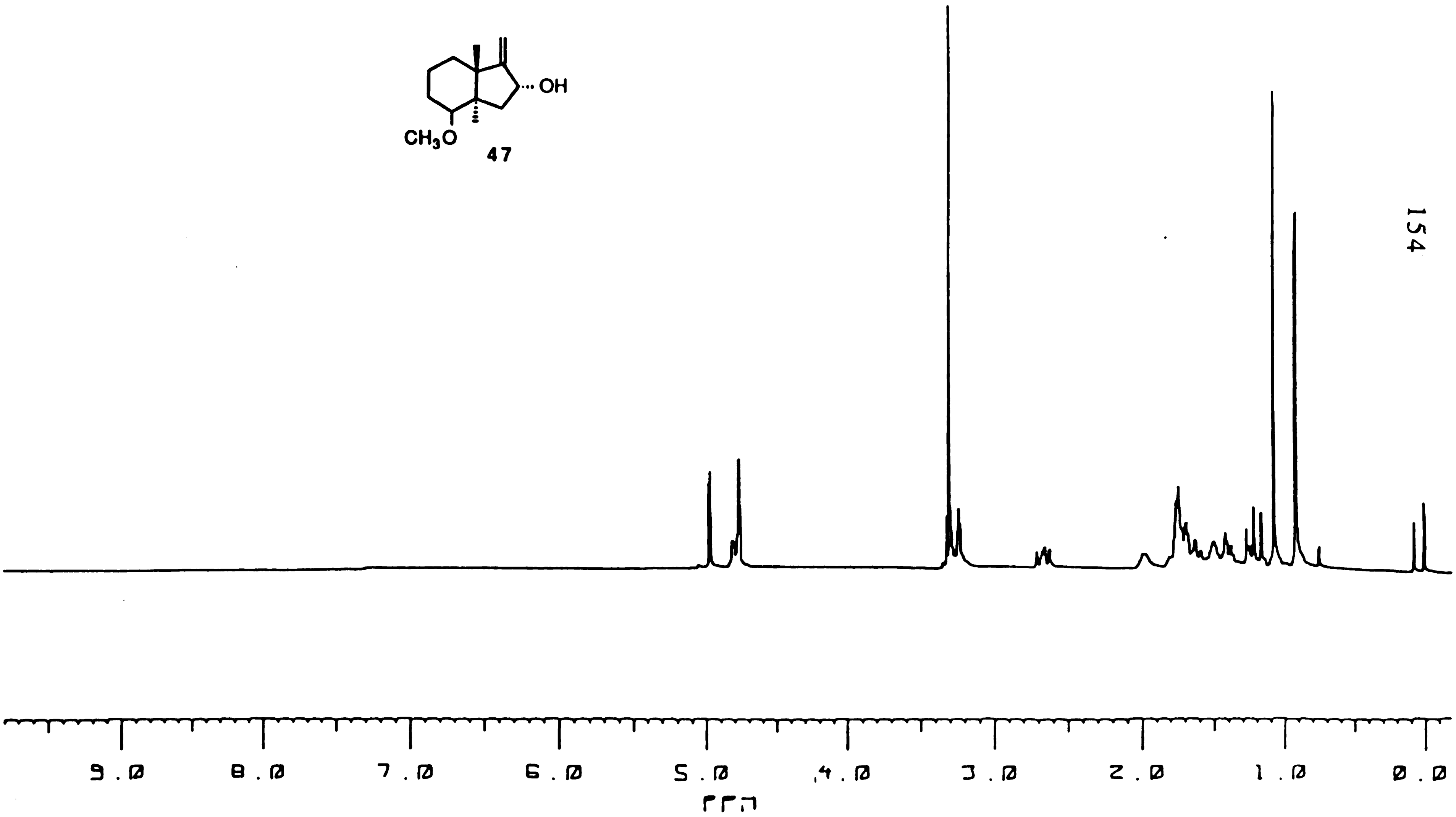


Figure 49. PMR spectrum of 47

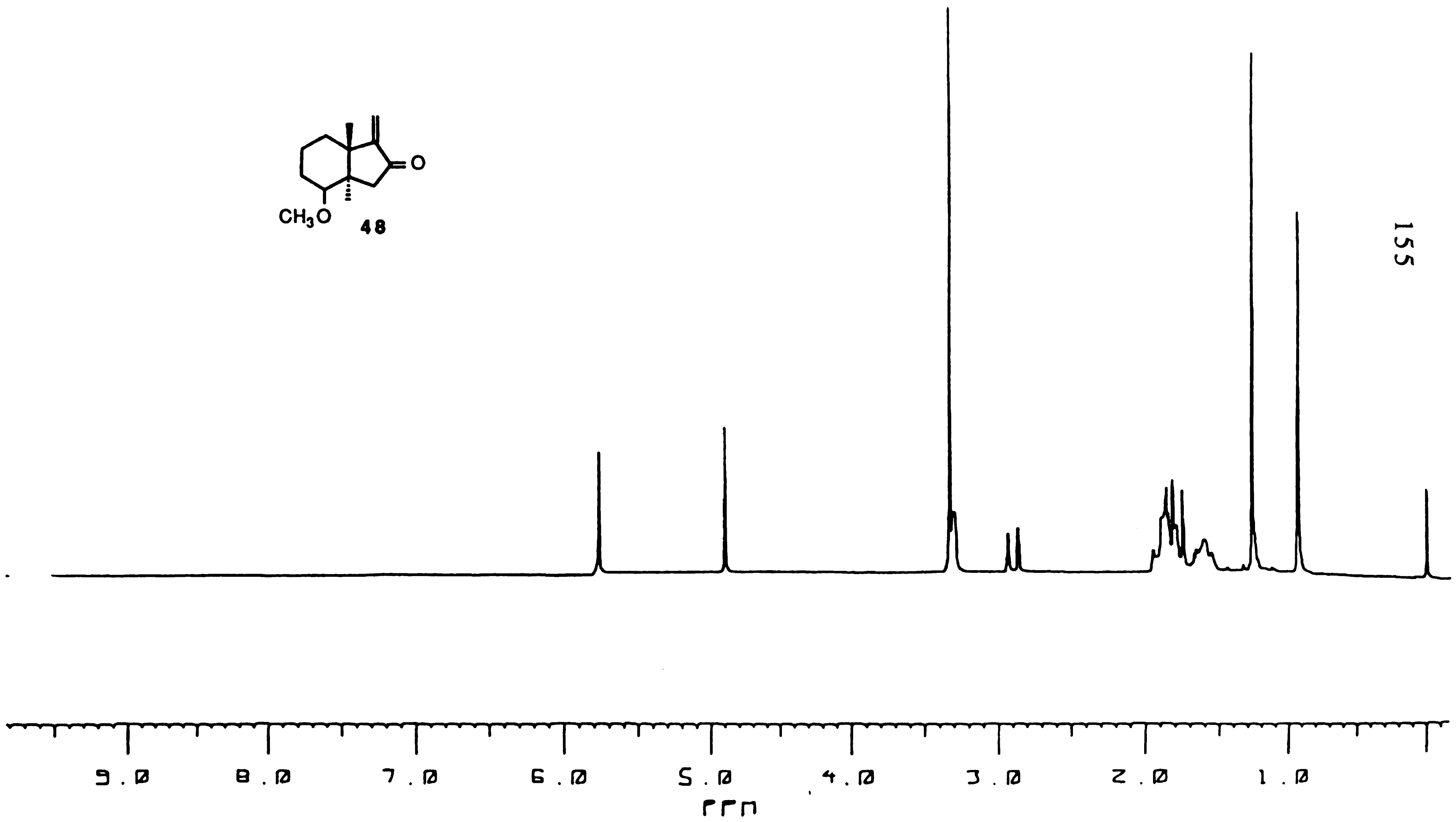


Figure 50. PMR spectrum of **48**

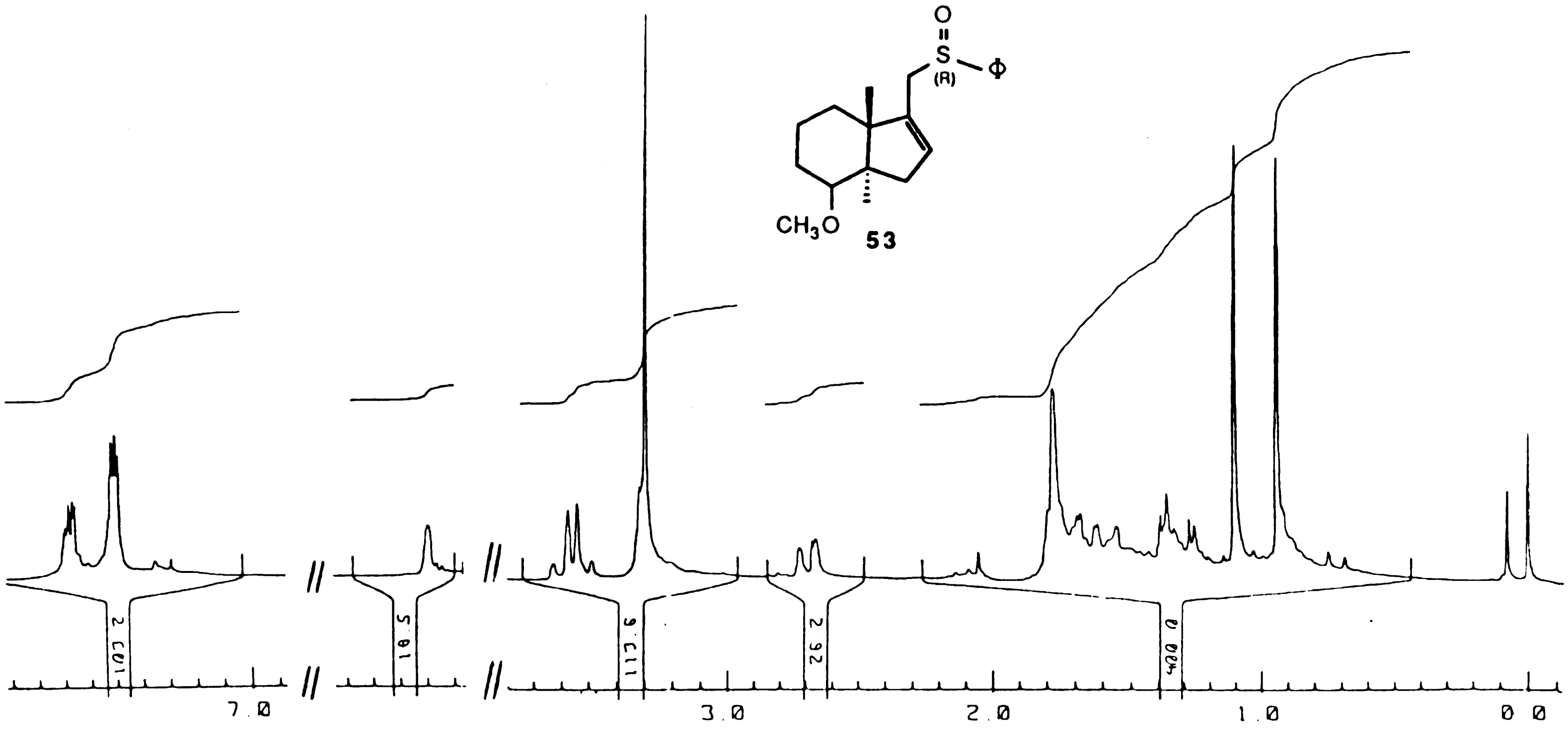


Figure 51. PMR spectrum of 53

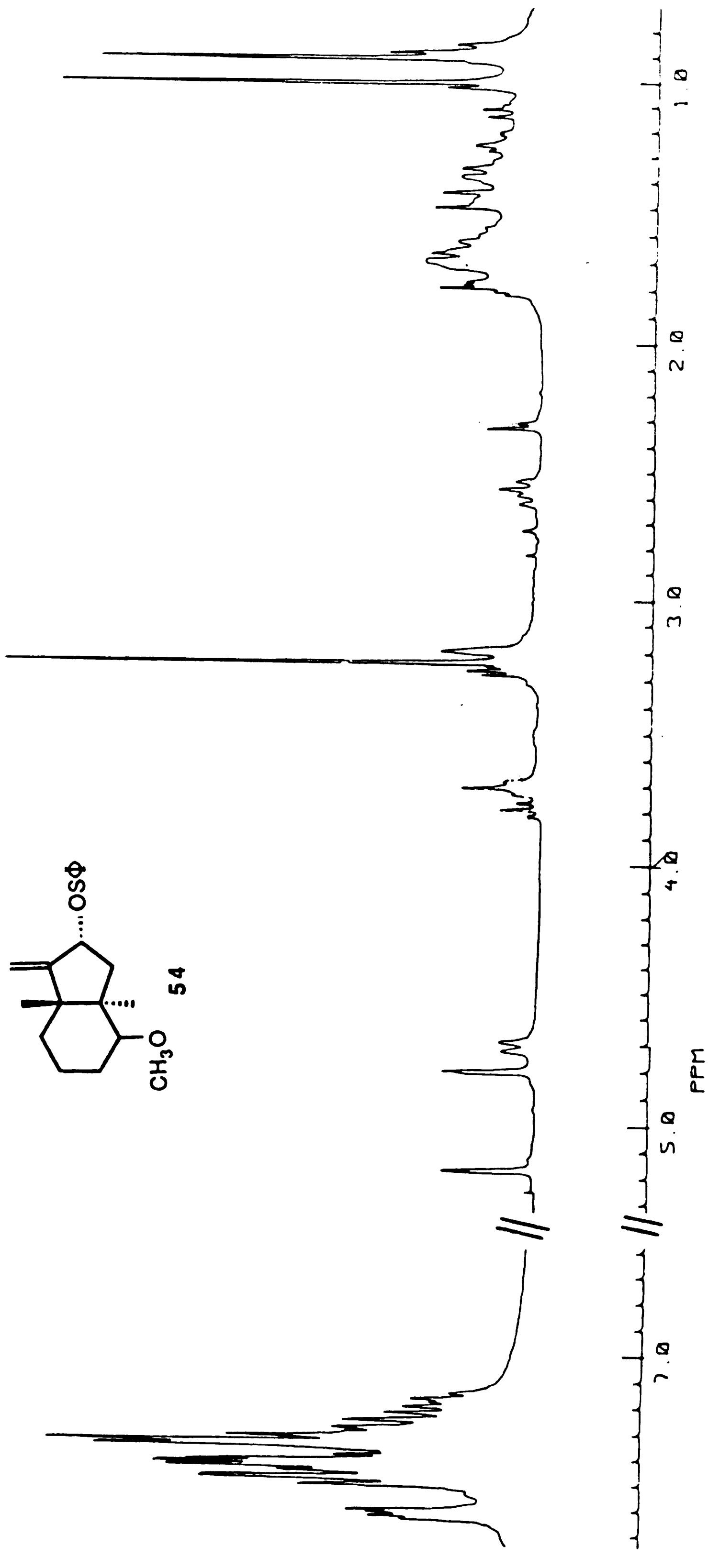


Figure 52. PMR spectrum of 54

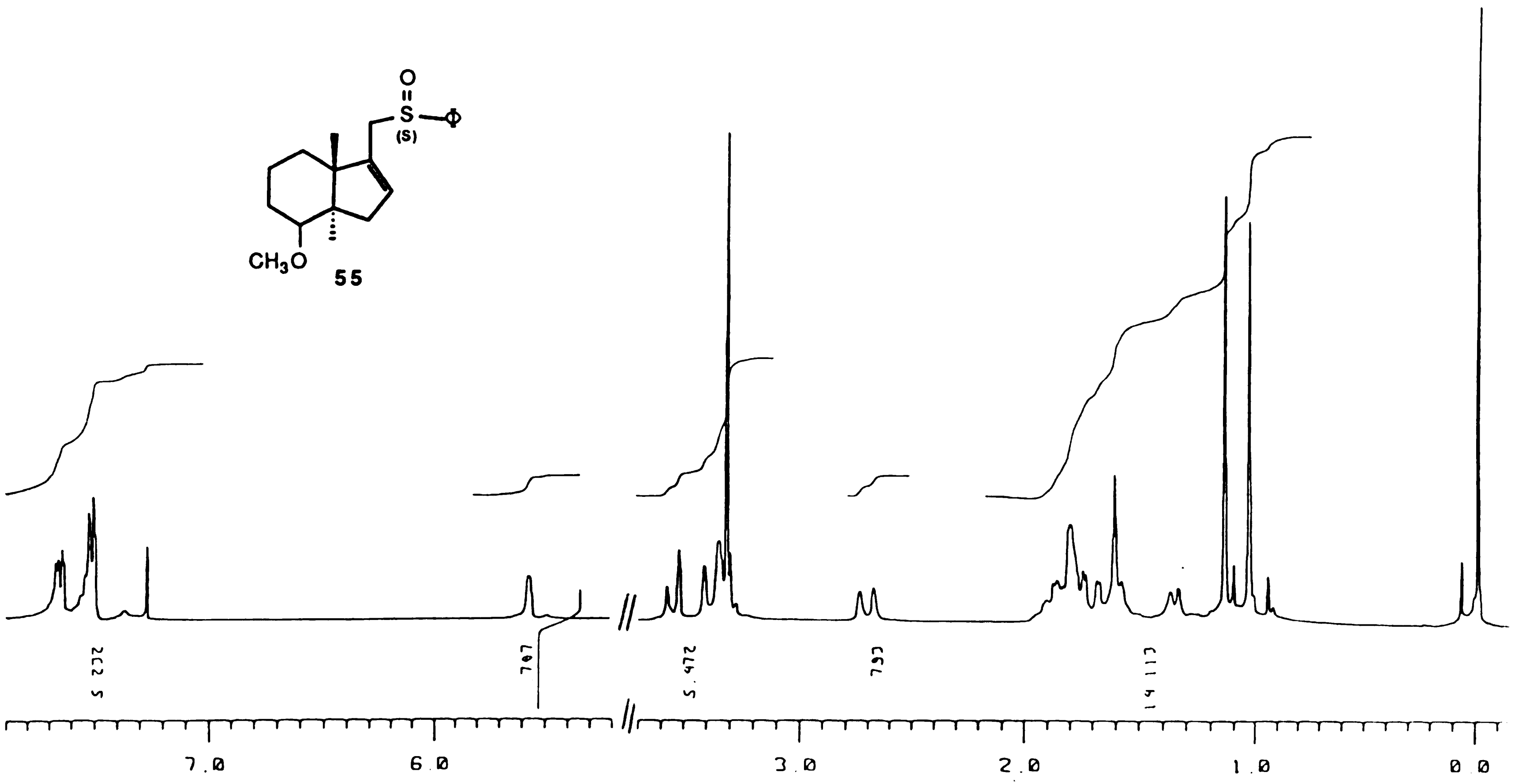


Figure 53. PMR spectrum of 55

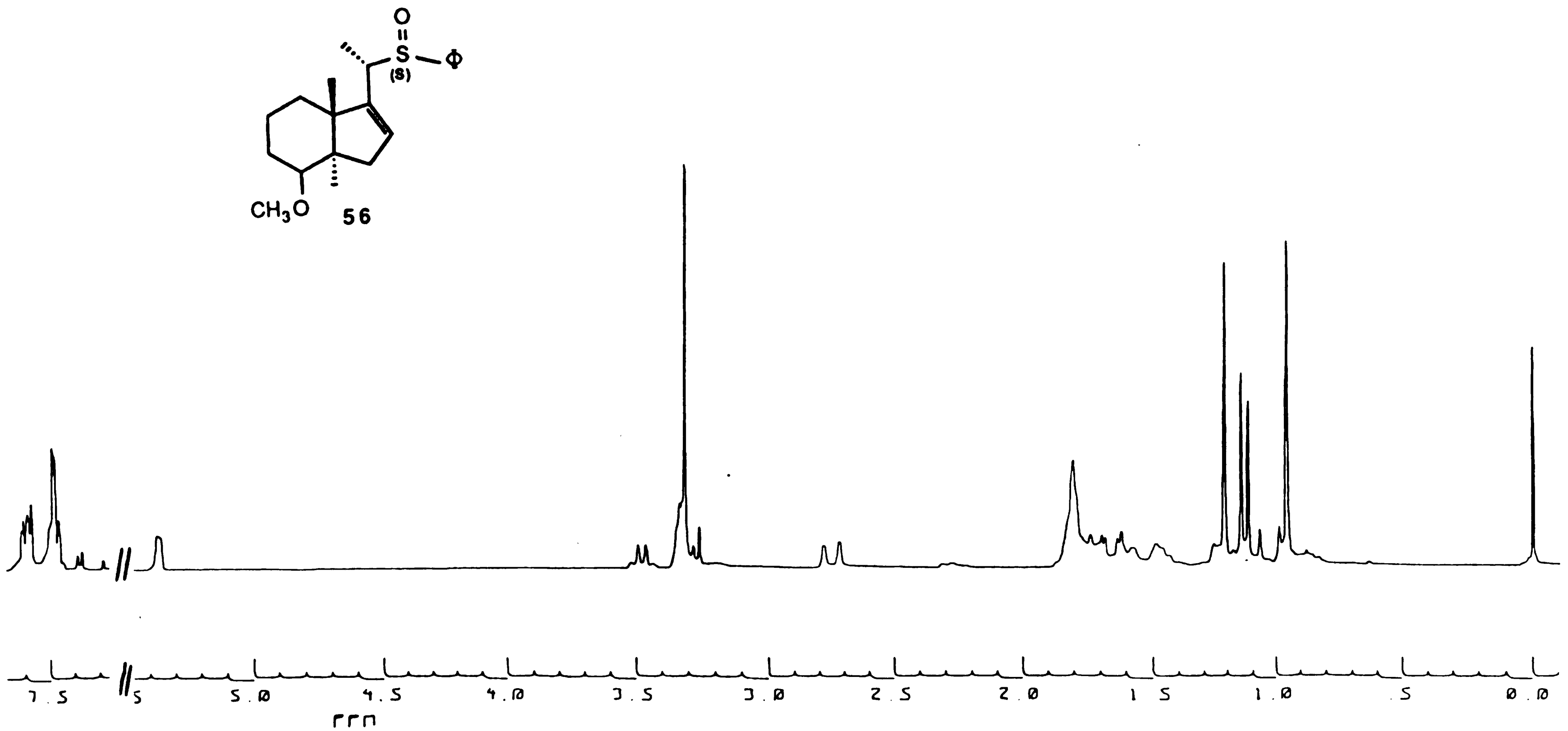


Figure 54. PMR spectrum of **56**

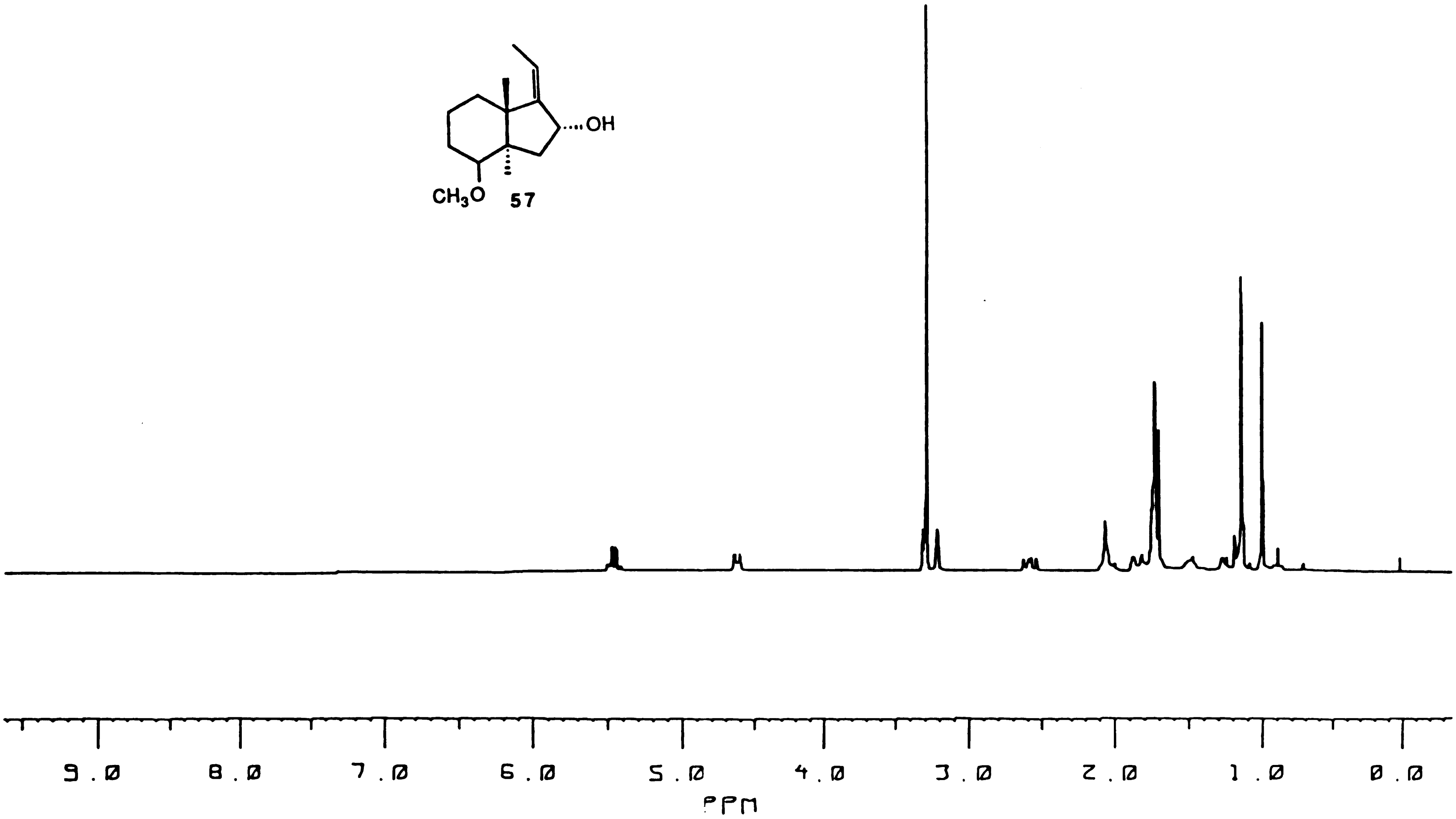


Figure 55. PMR spectrum of 57

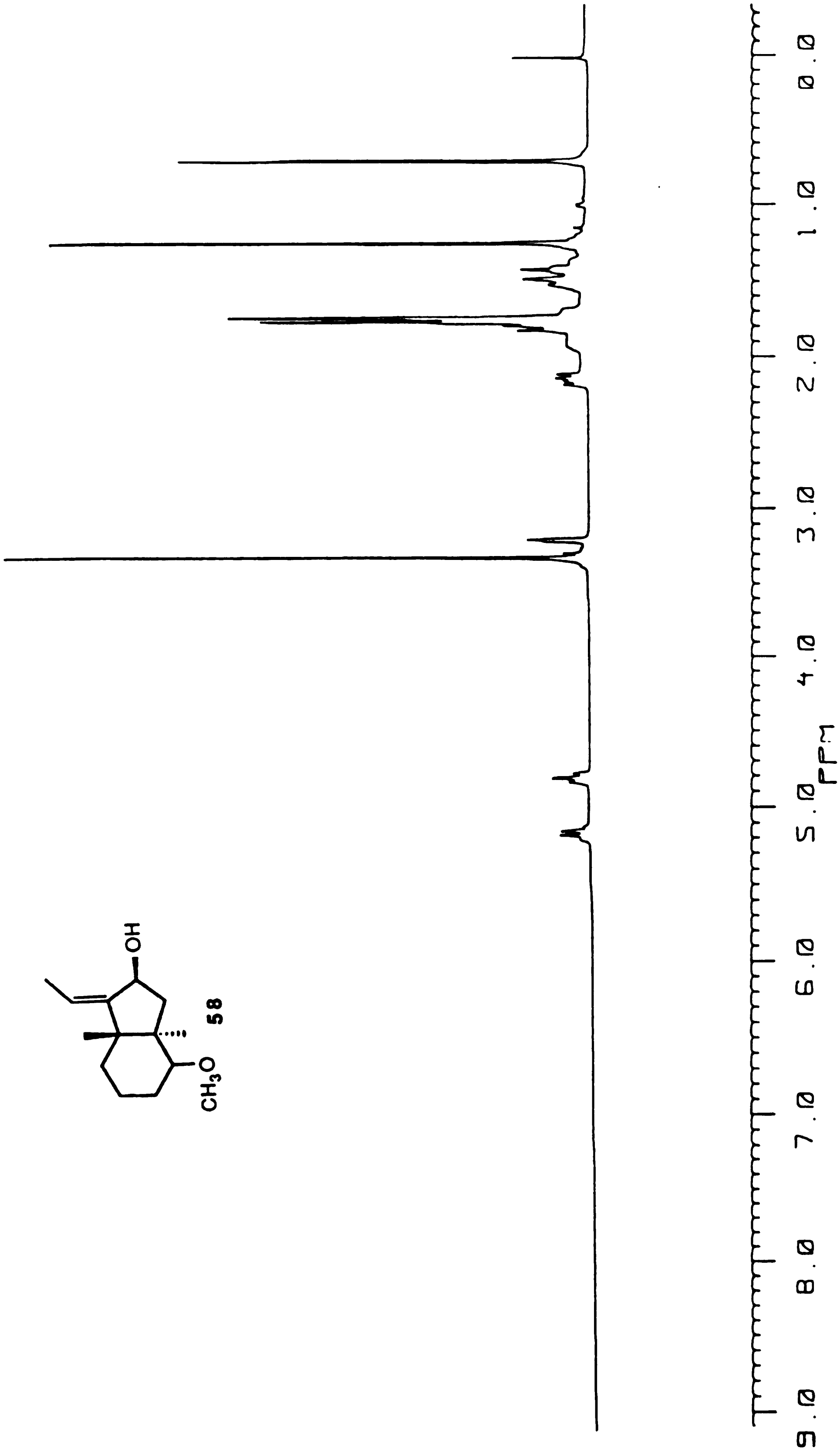


Figure 56. PMR spectrum of 58

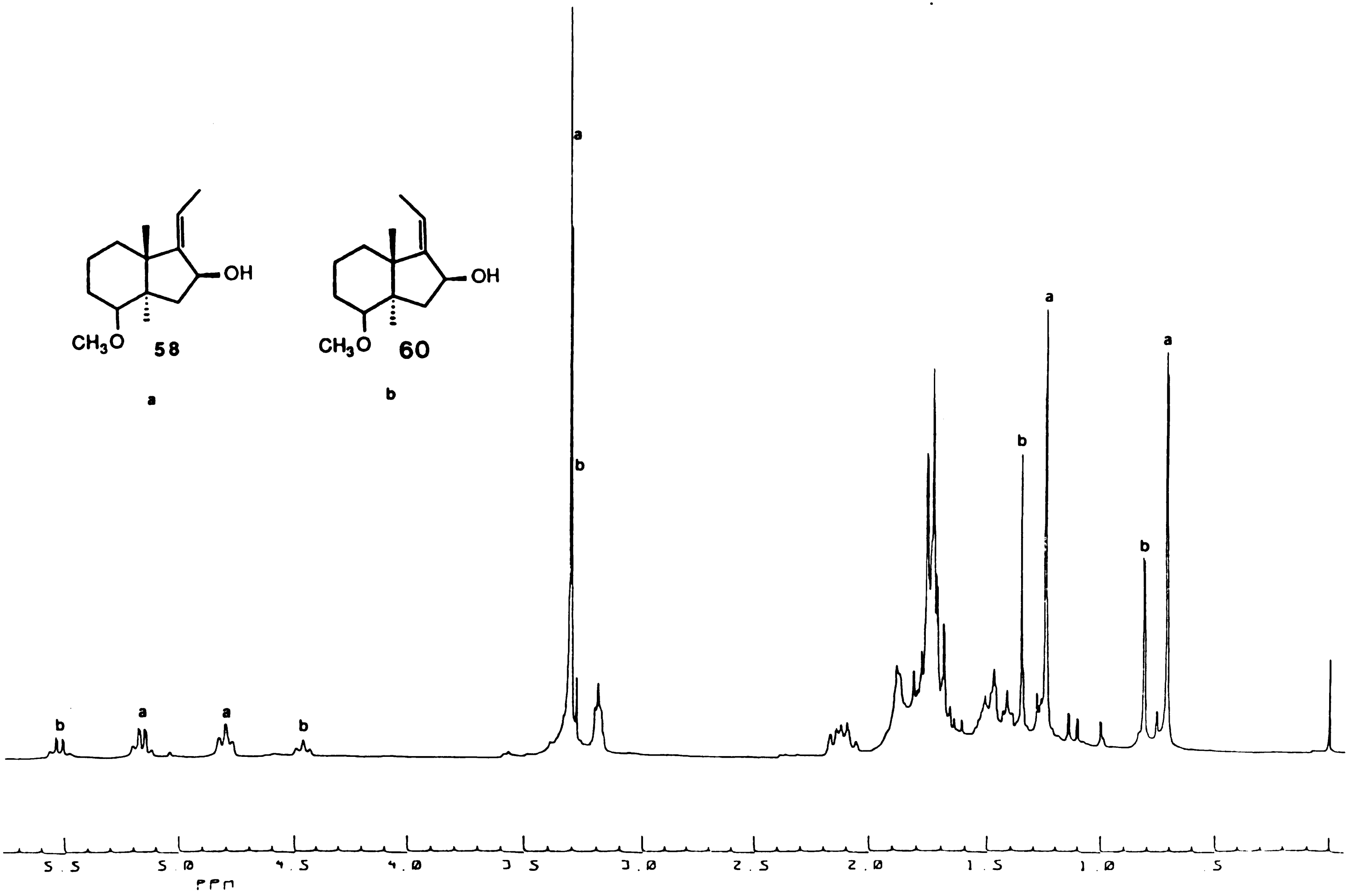


Figure 57. PMR spectrum of **58** and **60**

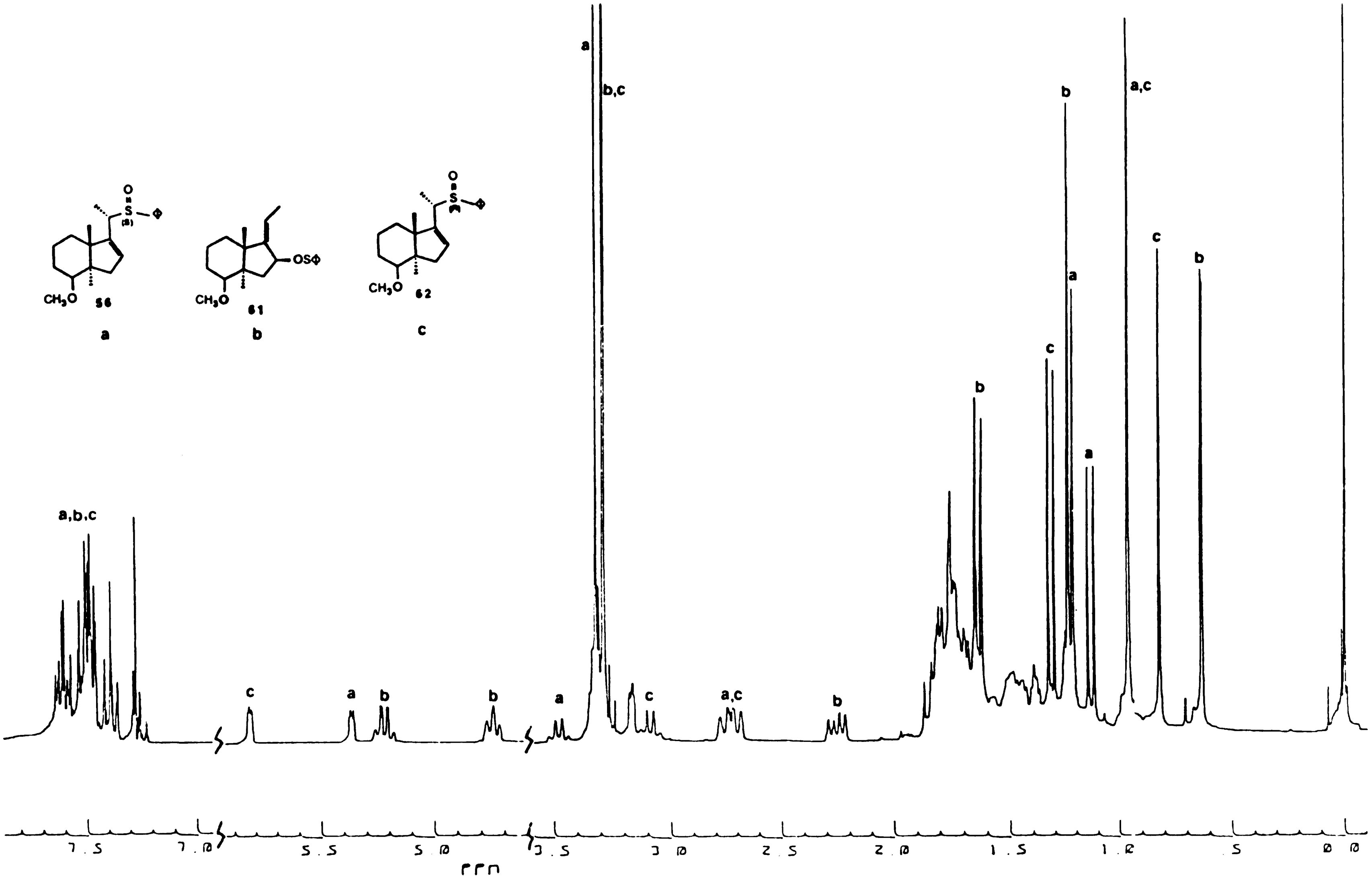


Figure 58. PMR spectrum of **56**, **61** and **62**

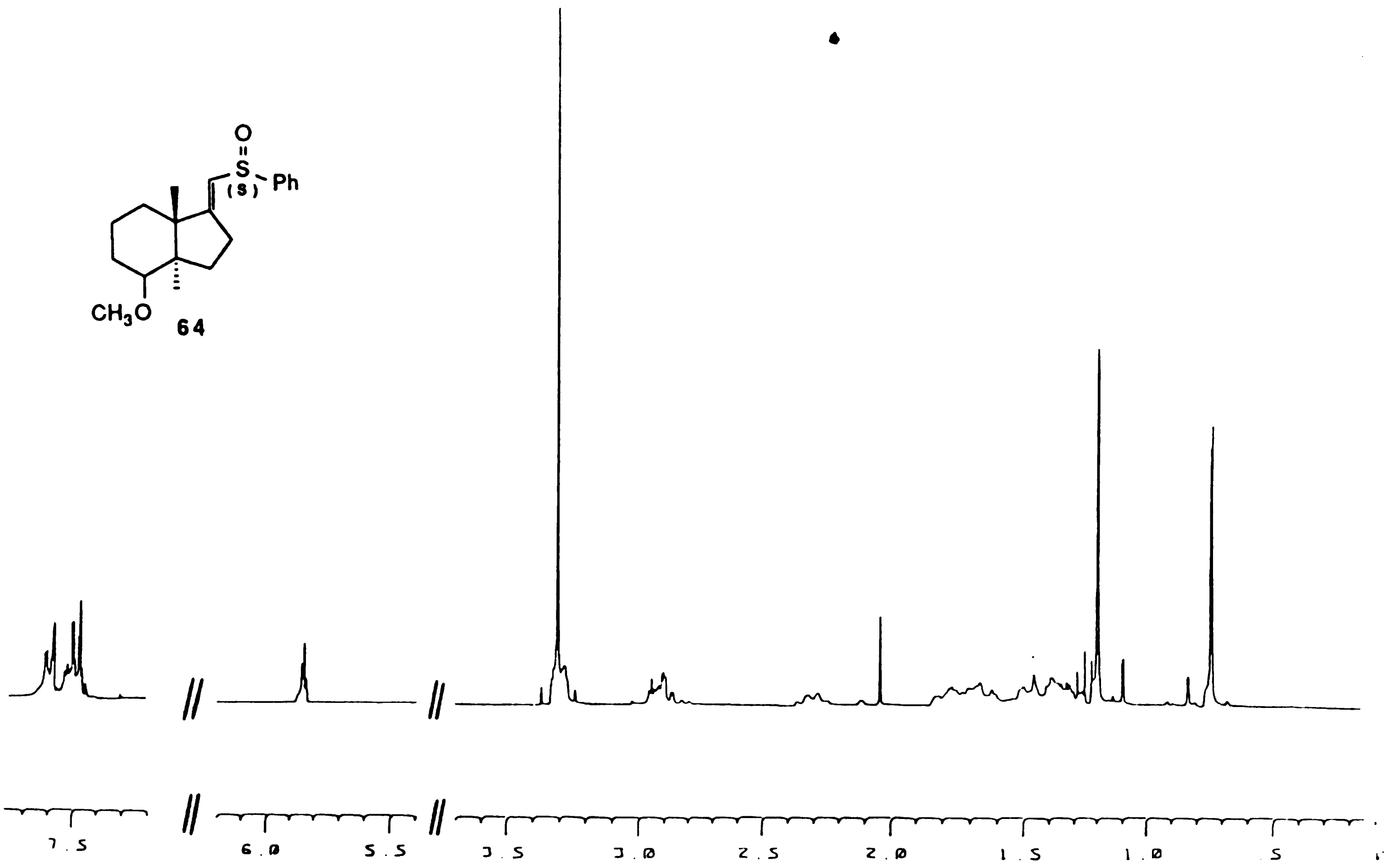


Figure 59. PMR spectrum of **64**

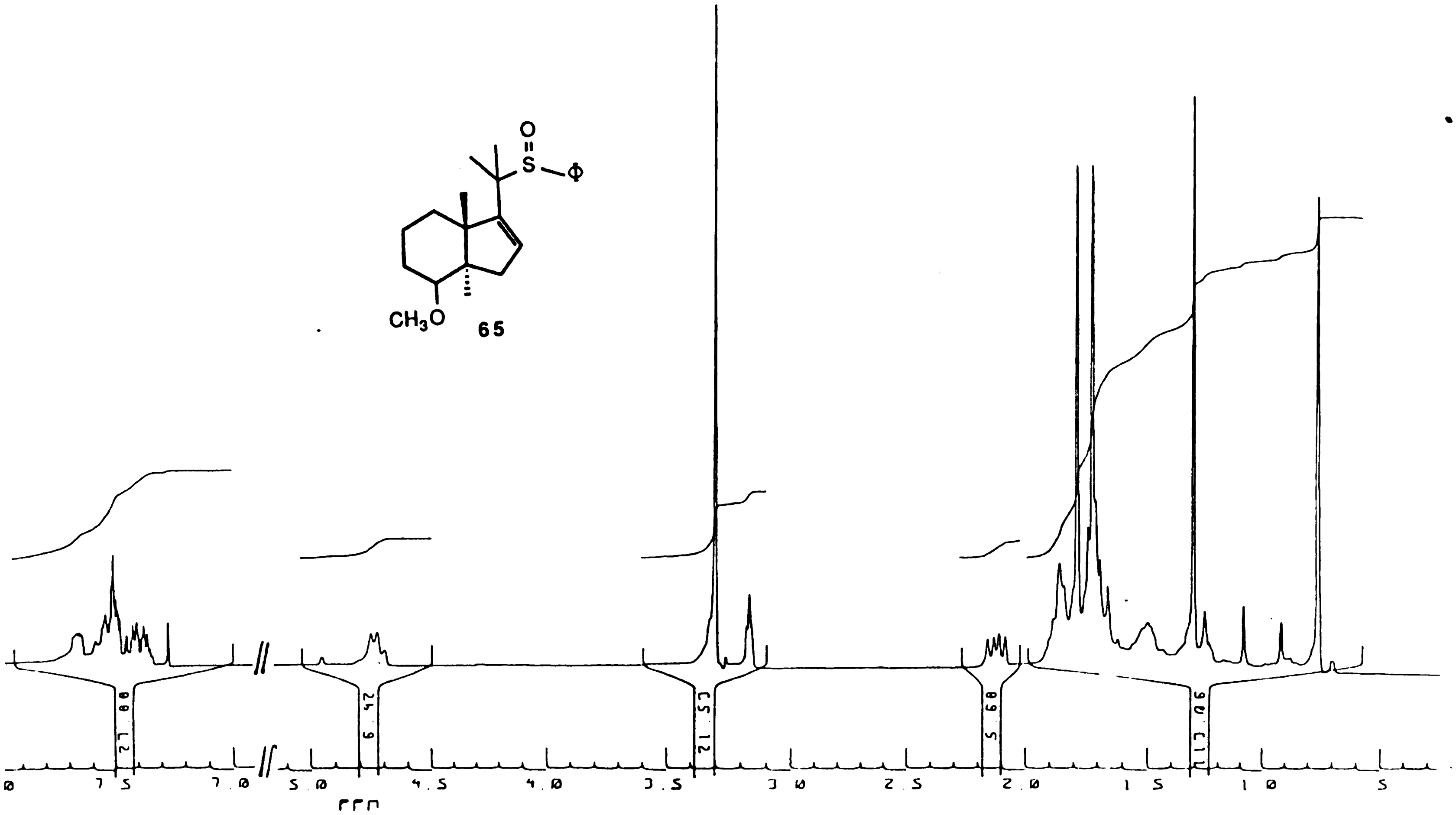


Figure 60. PMR spectrum of 65

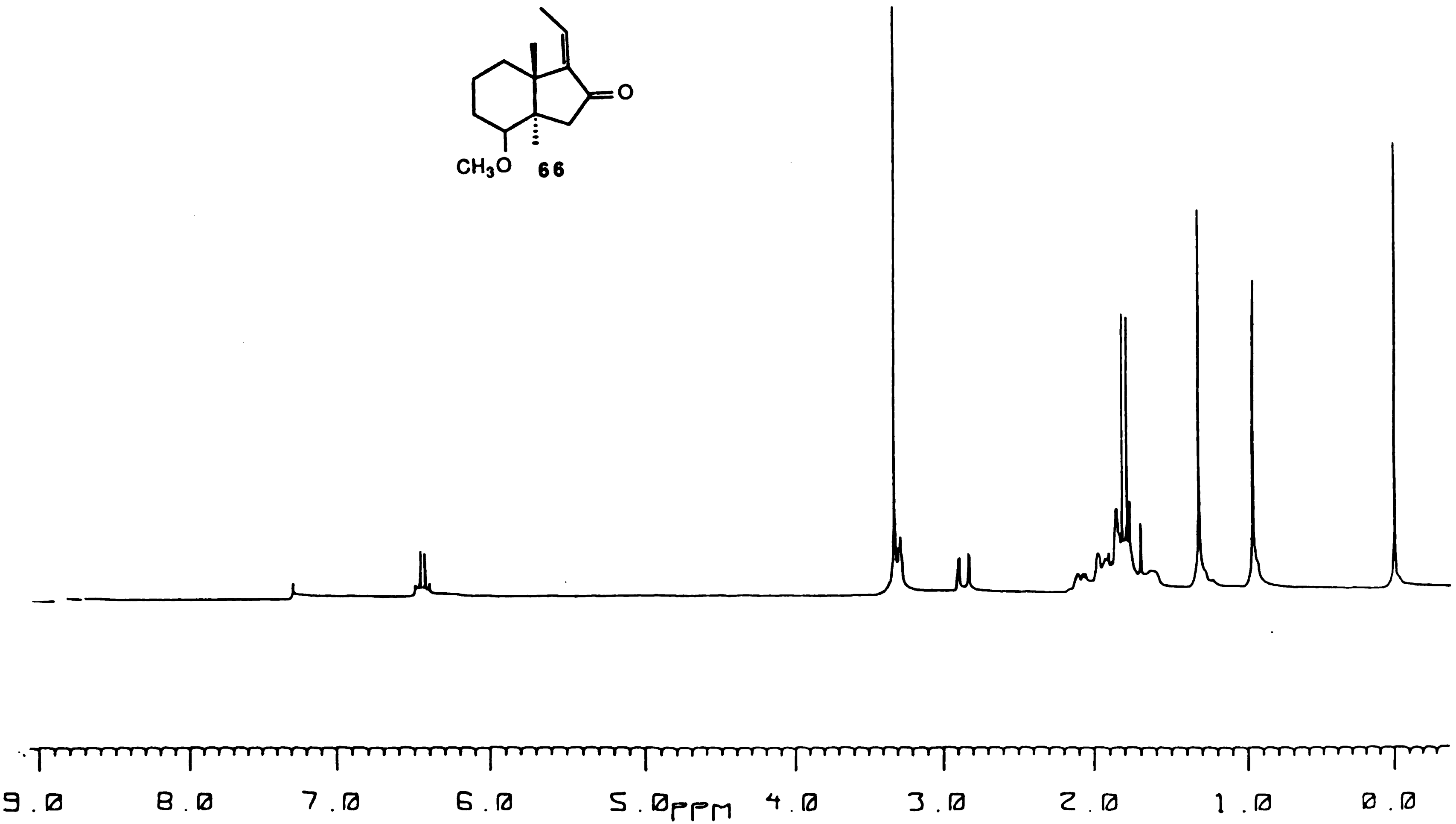


Figure 61. PMR spectrum of **66**

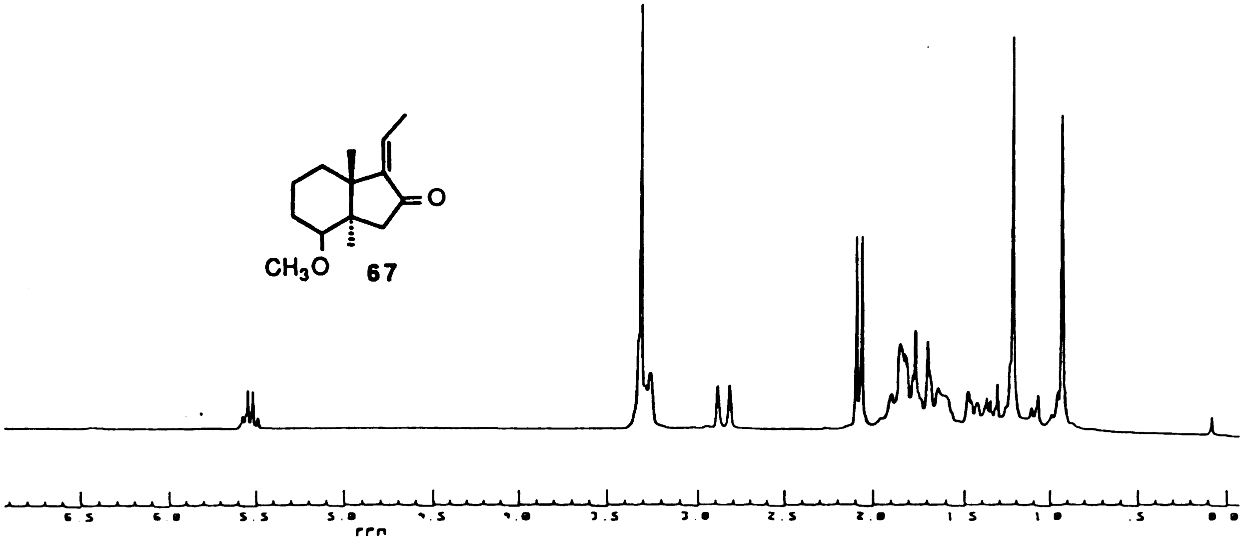


Figure 62. PMR spectrum of 67

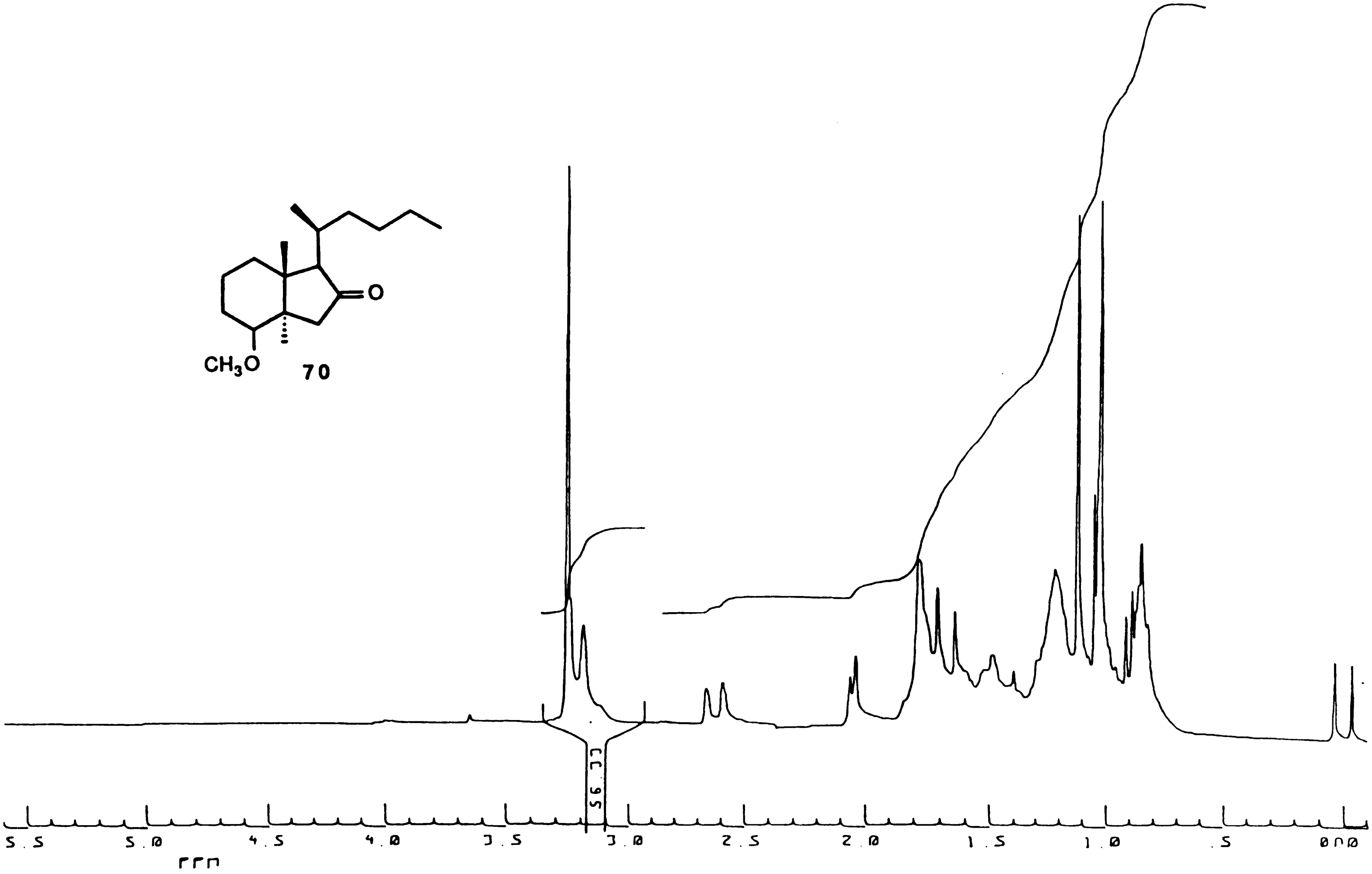


Figure 63. PMR spectrum of 70

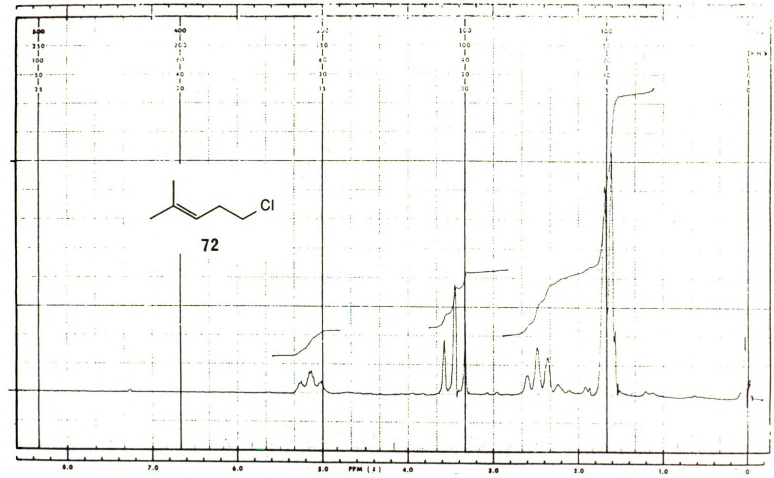


Figure 64. PMR spectrum of 72

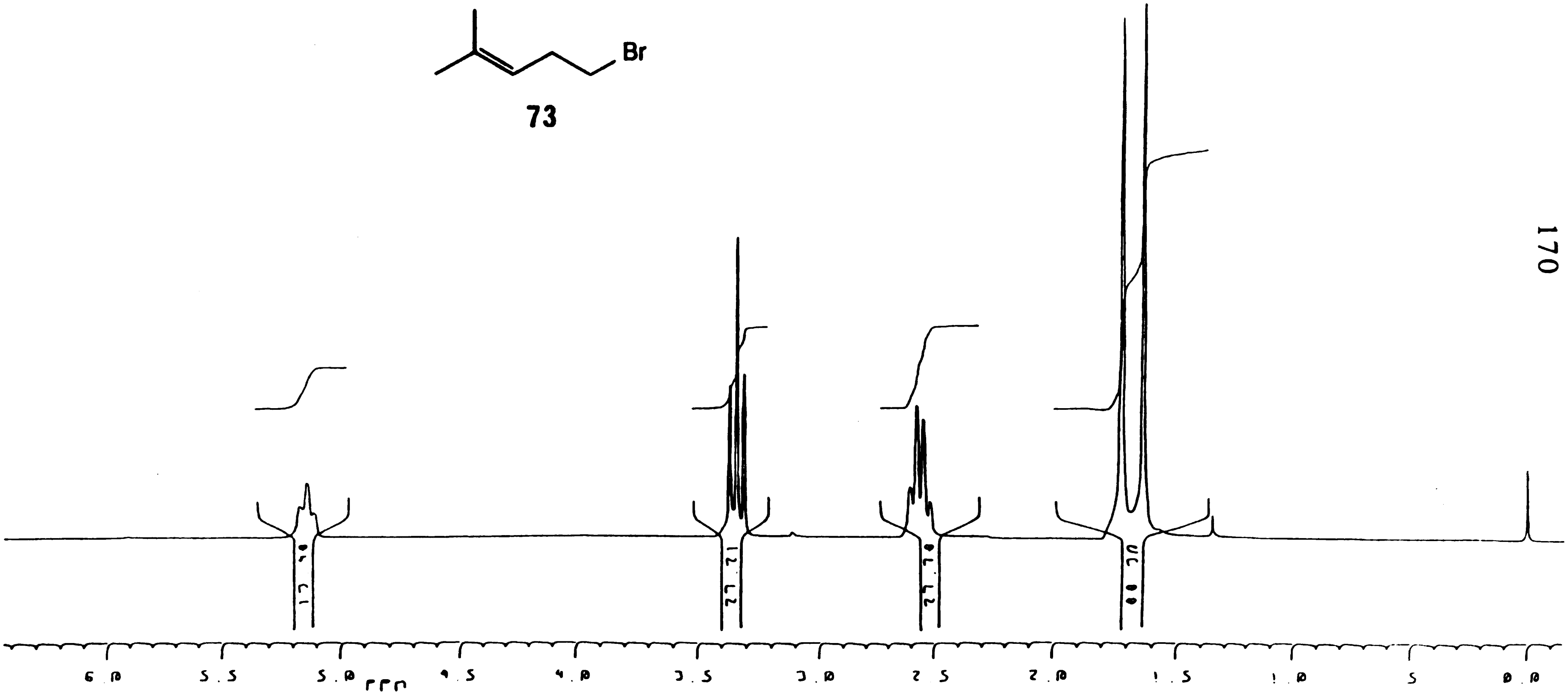


Figure 65. PMR spectrum of 73

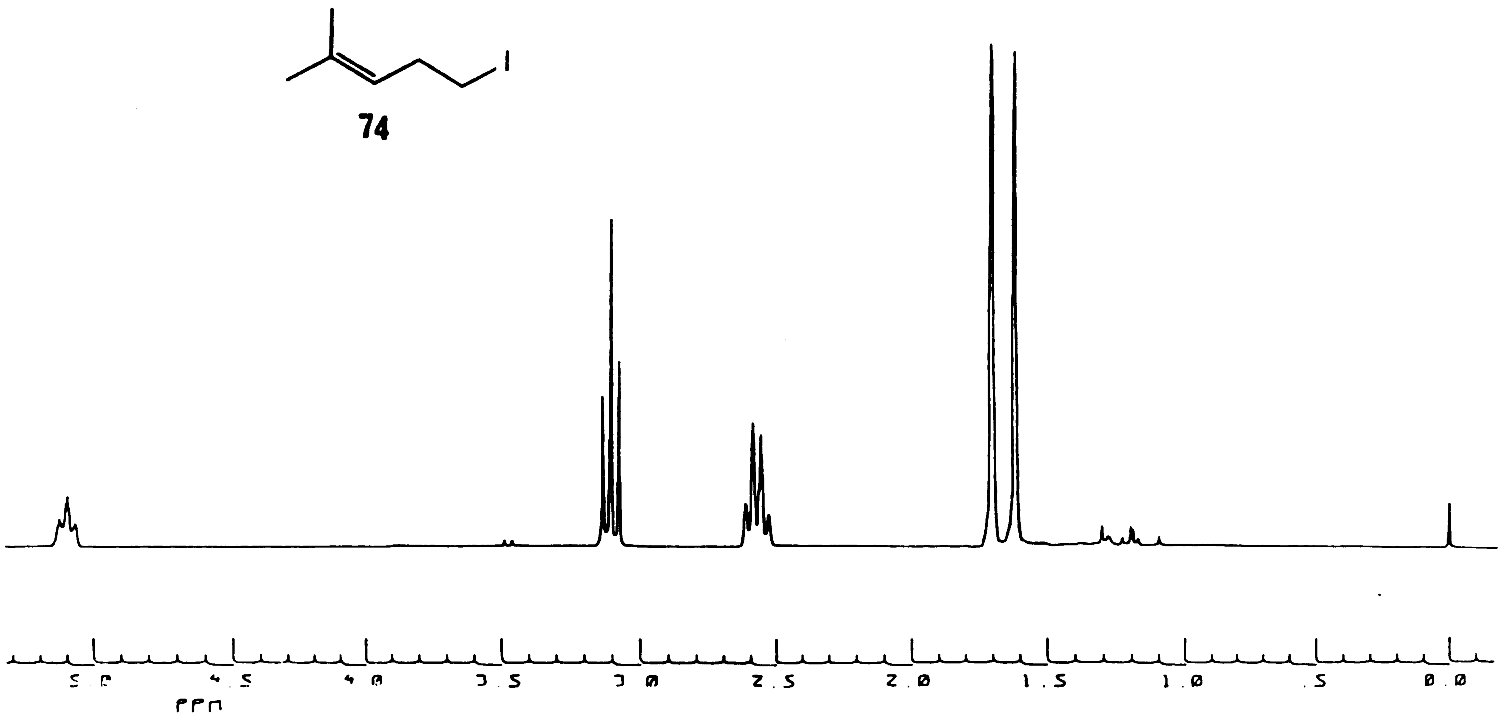


Figure 66. PMR spectrum of 74

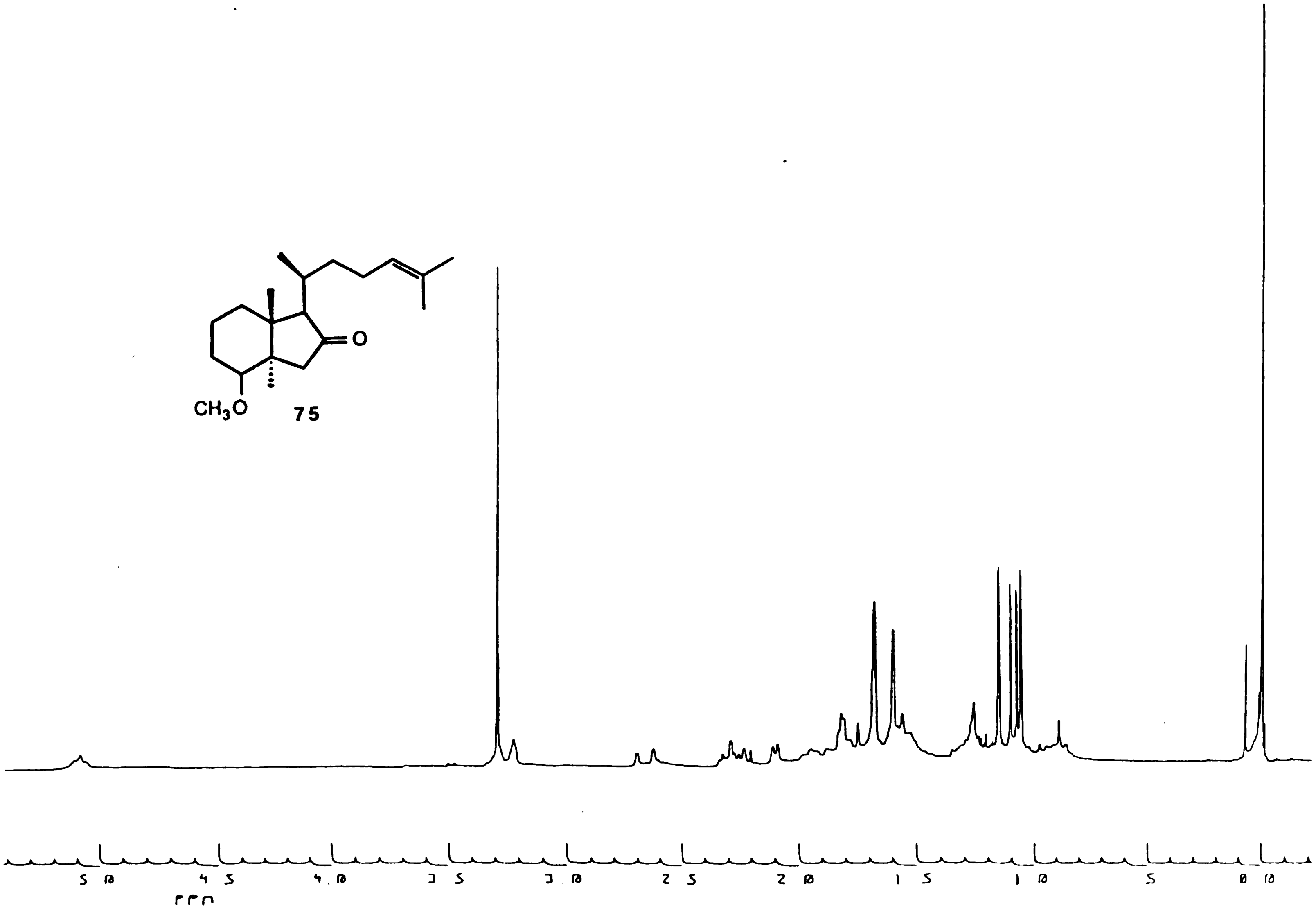


Figure 67. PMR spectrum of 75

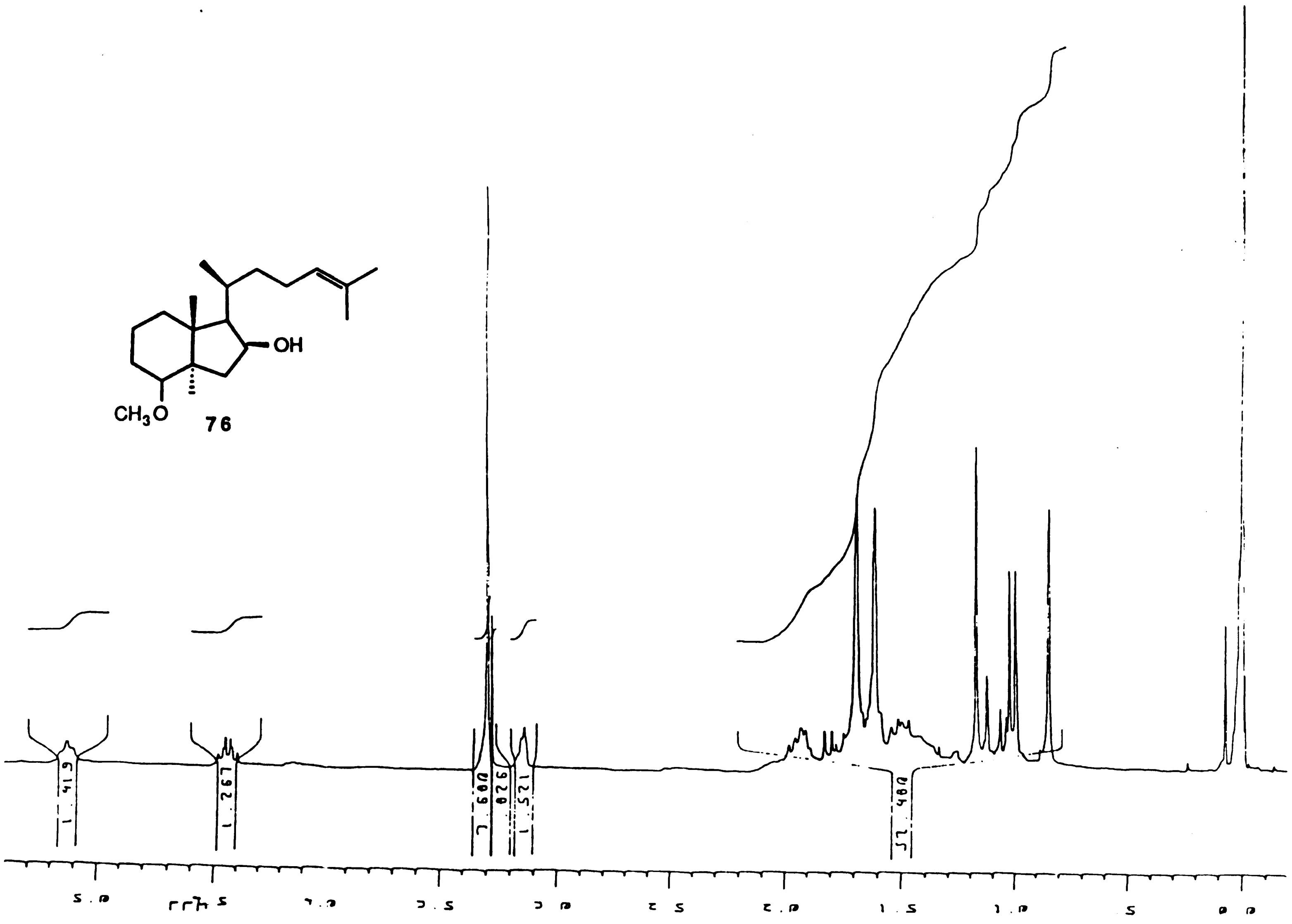


Figure 68. PMR spectrum of 76

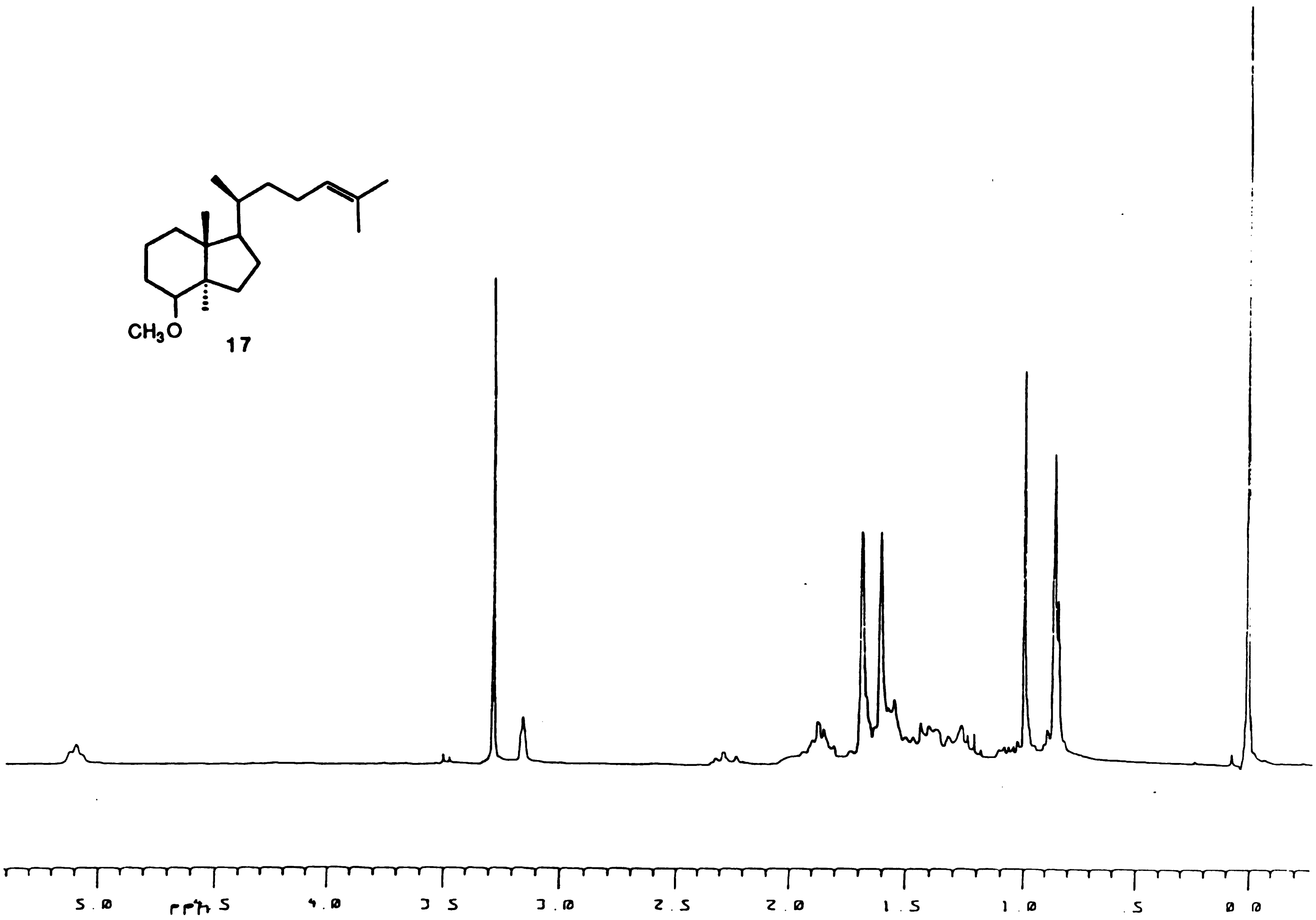


Figure 69. PMR spectrum of 17

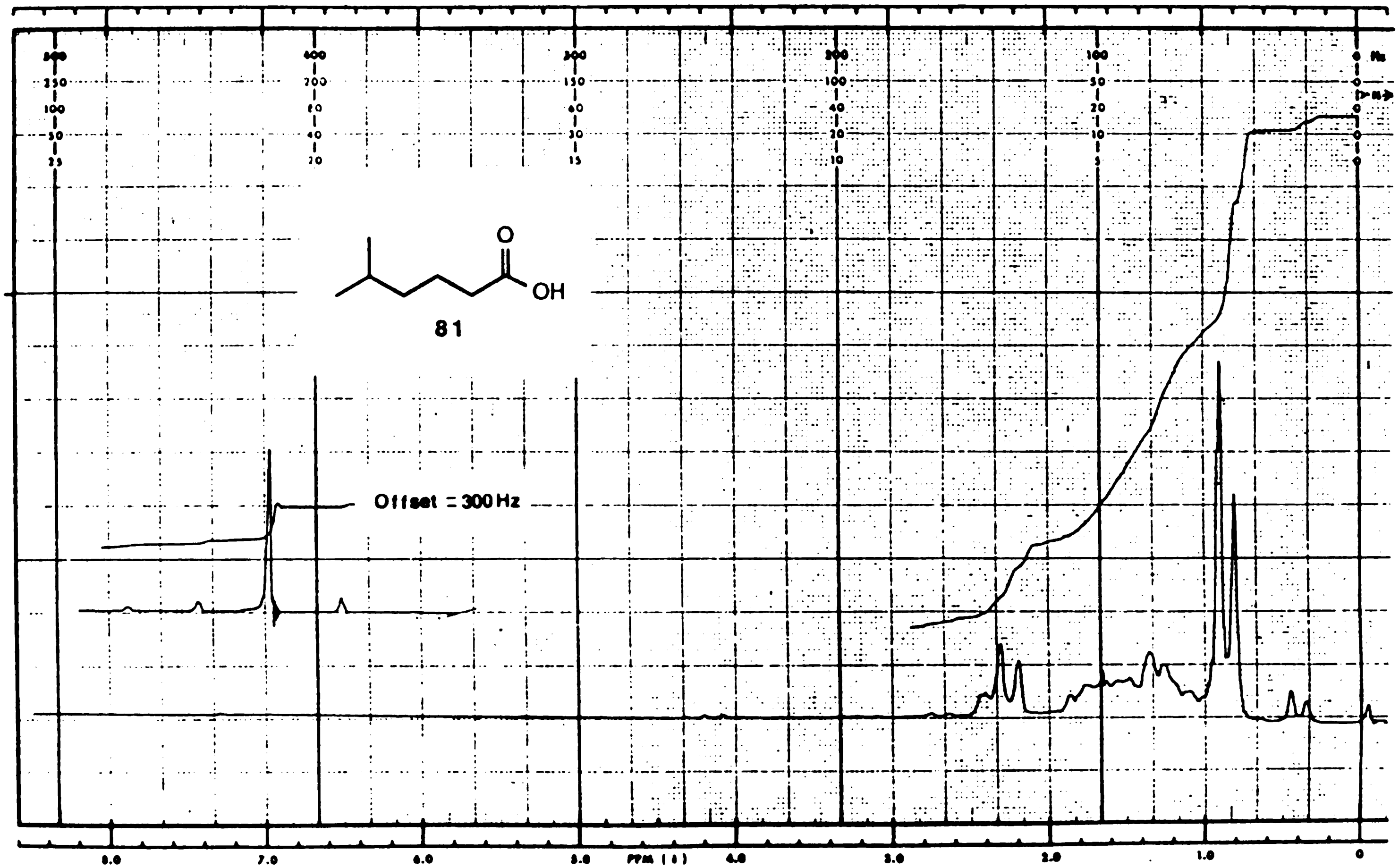


Figure 70. PMR spectrum of 81

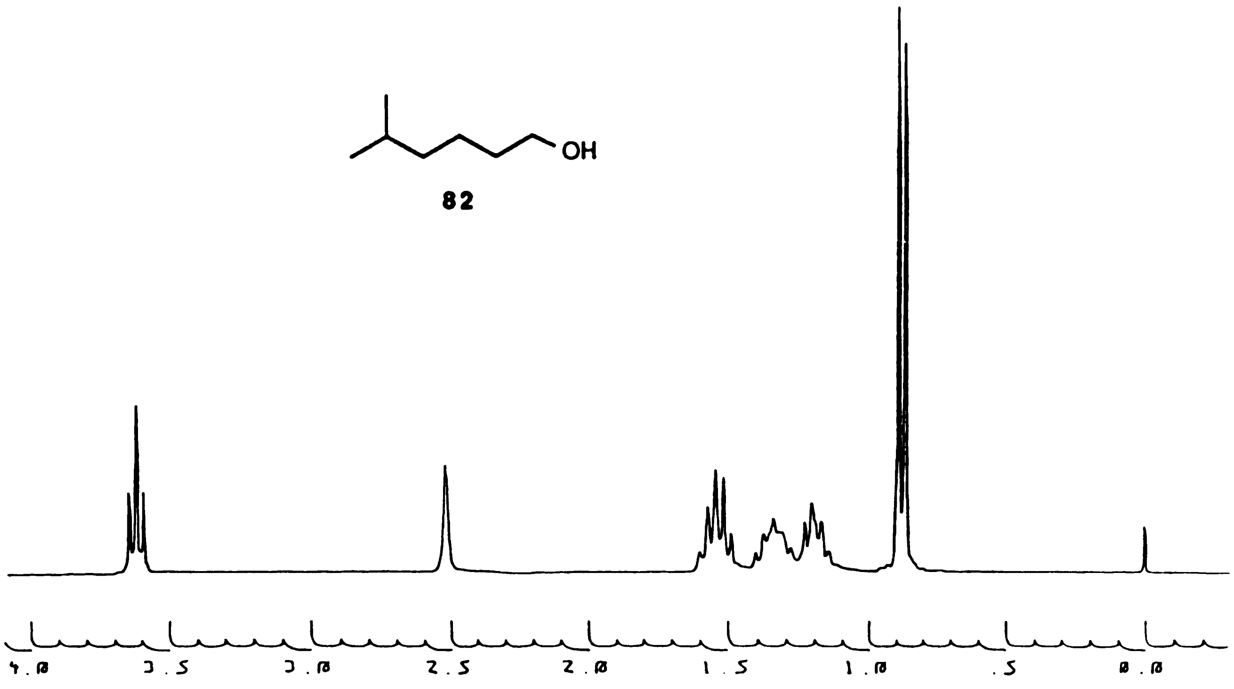


Figure 71. PMR spectrum of **82**

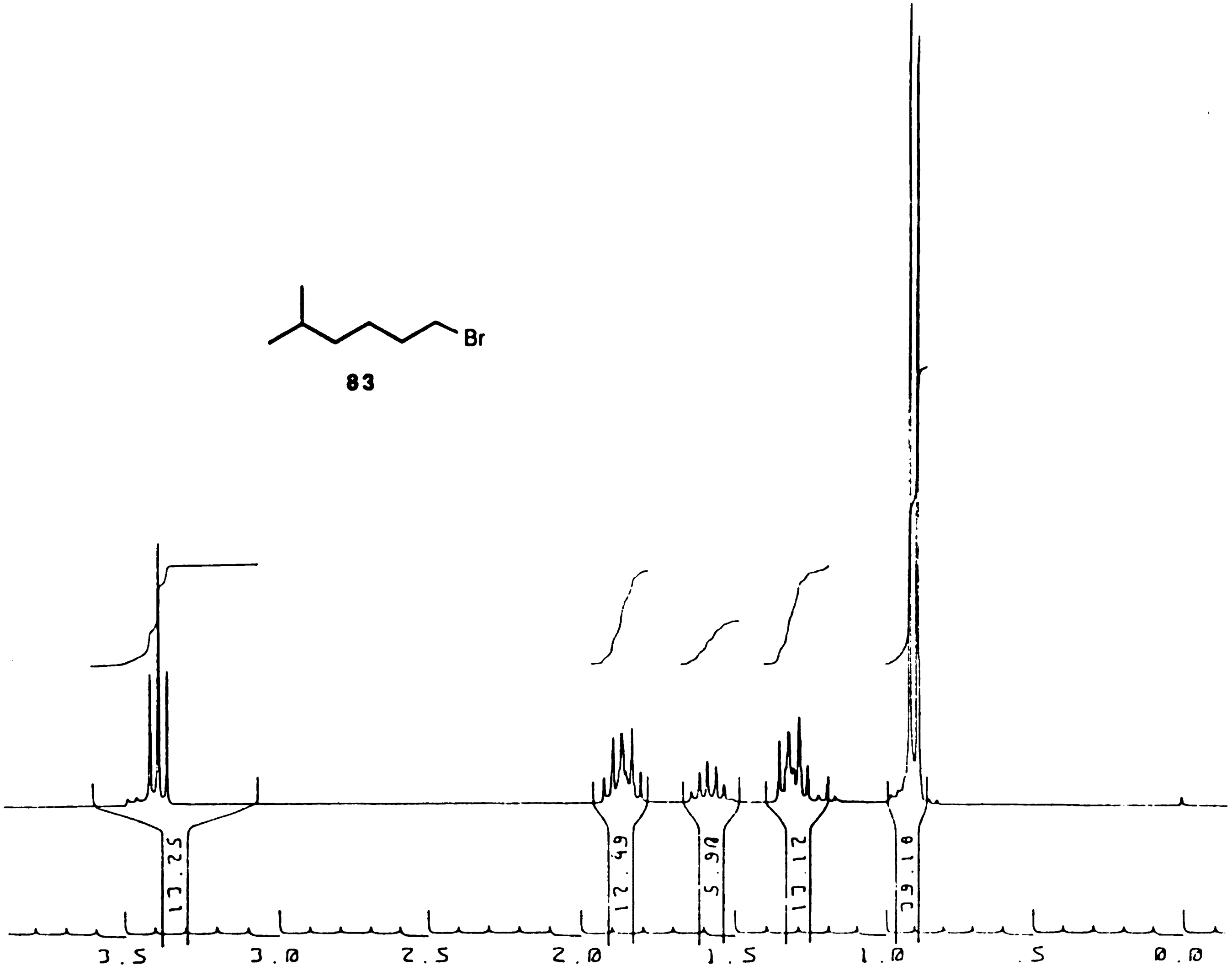
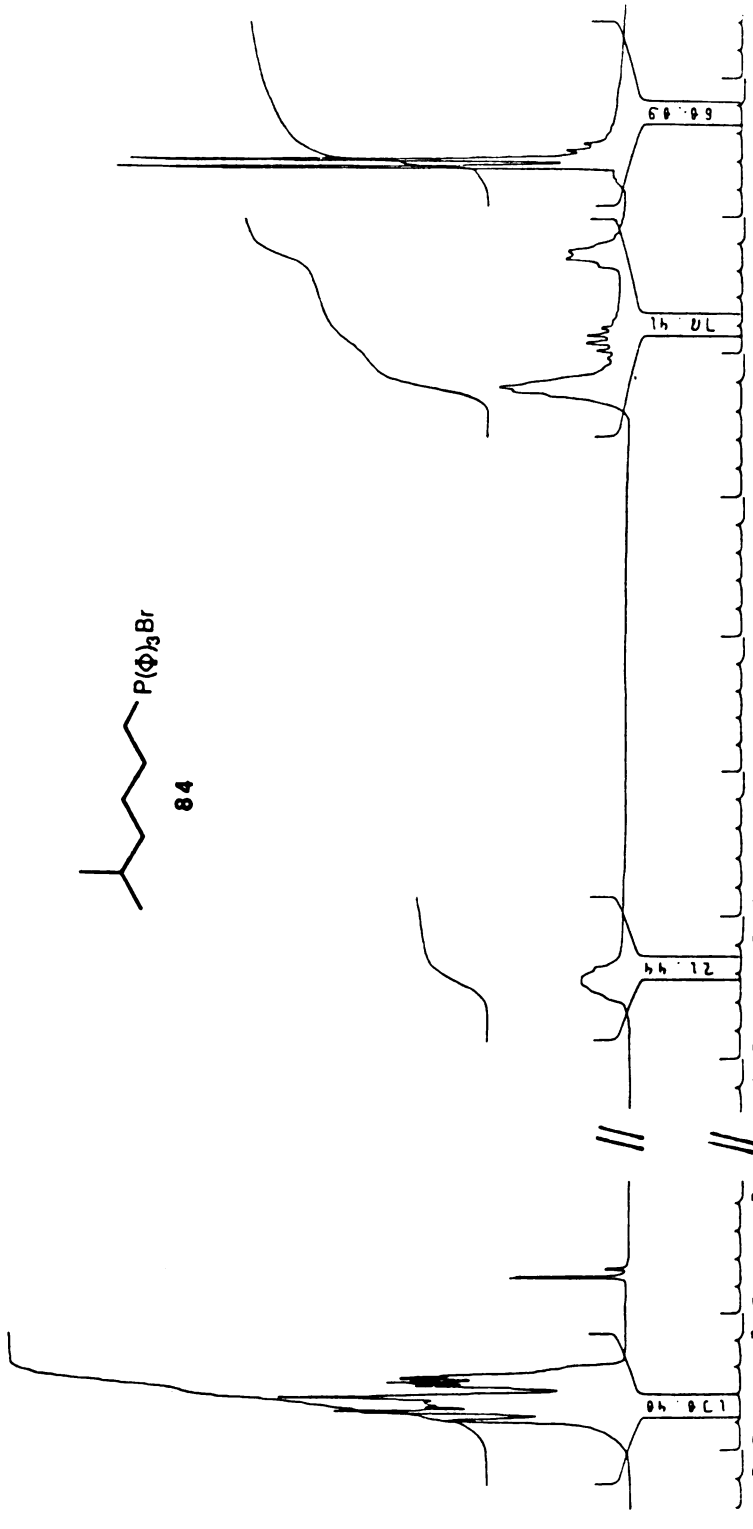


Figure 72. PMR spectrum of 83



84

Figure 73. PMR spectrum of 84

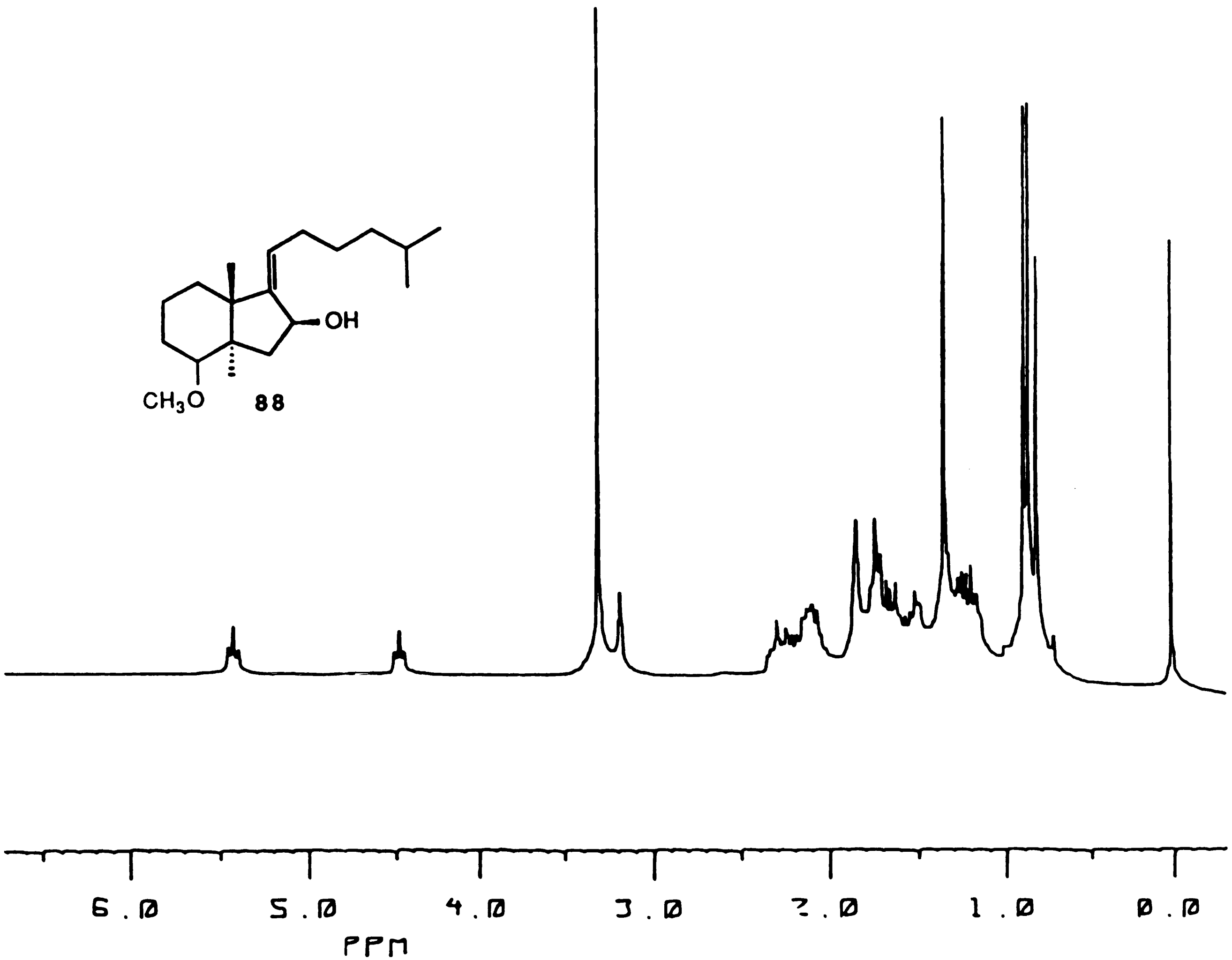


Figure 74. PMR spectrum of 88

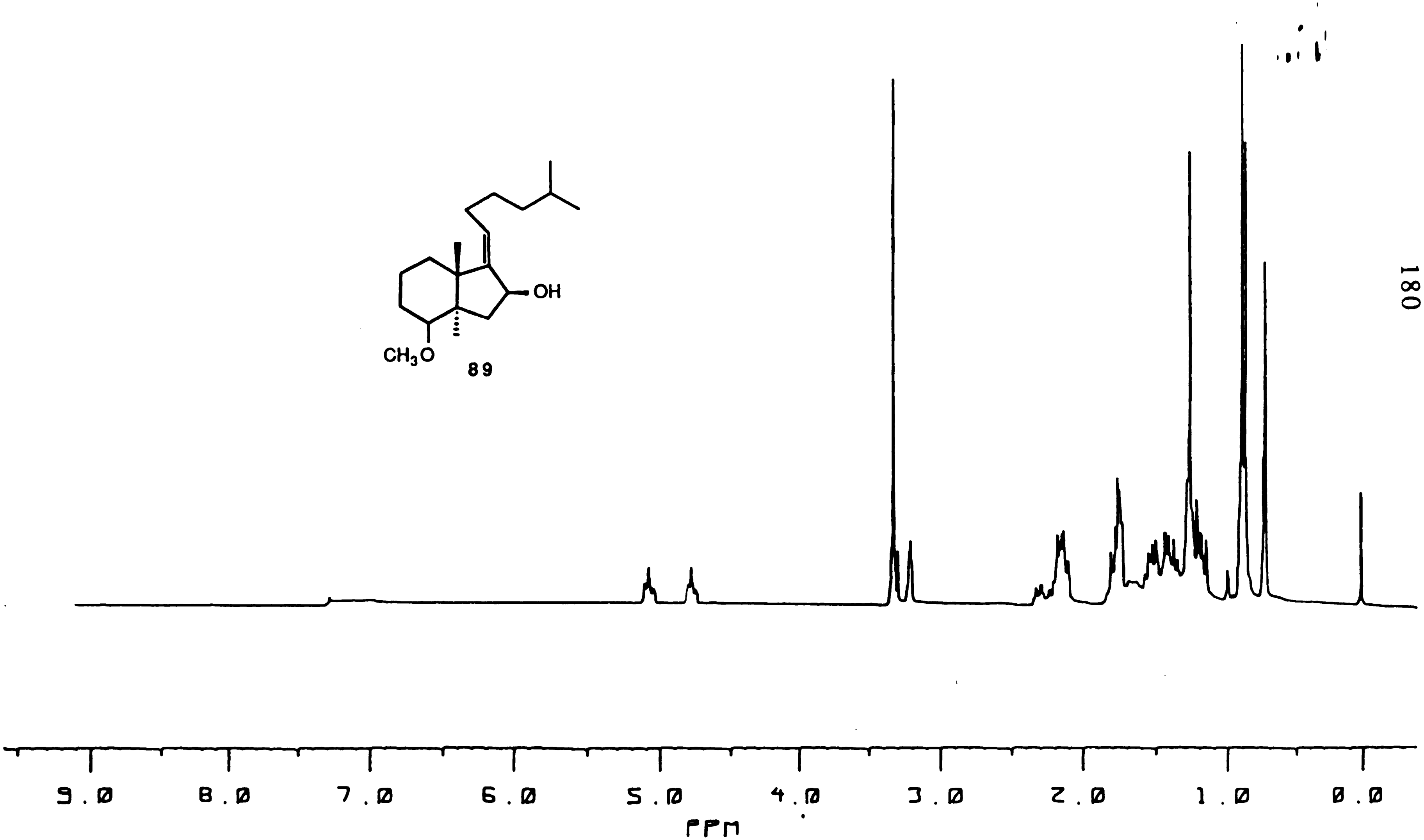


Figure 75. PMR spectrum of **89**

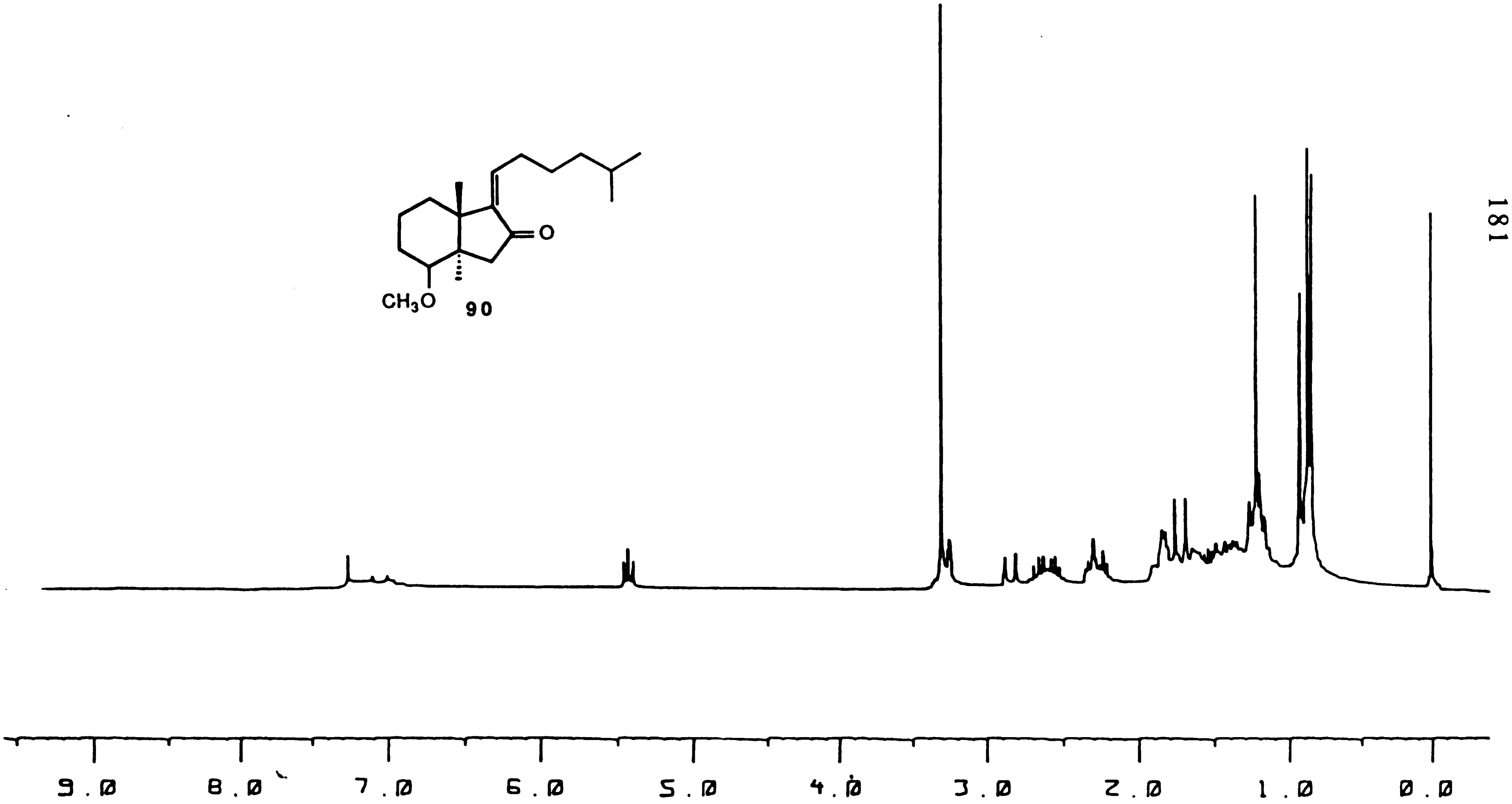


Figure 76. PMR spectrum of 90

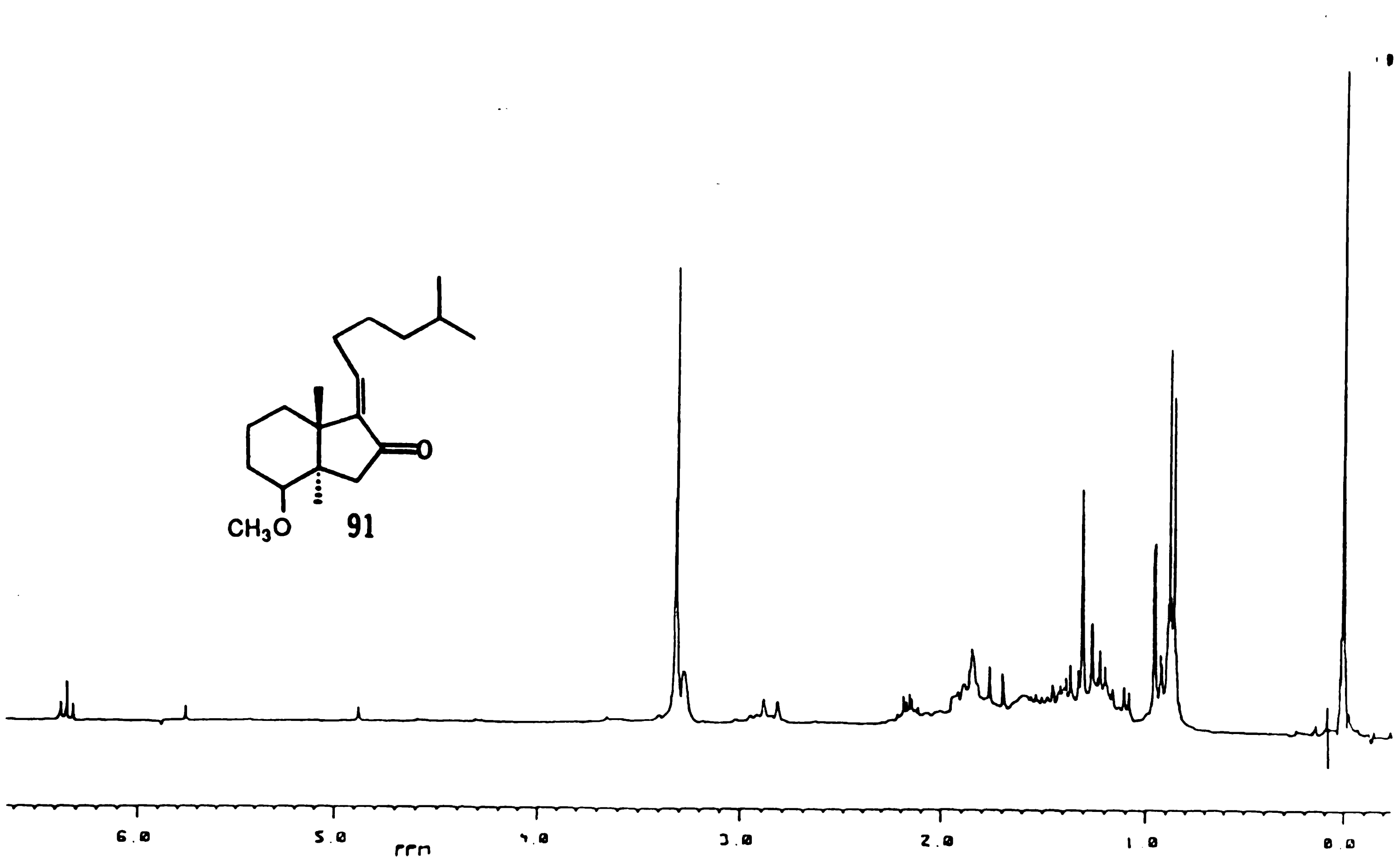


Figure 77. PMR spectrum of 91

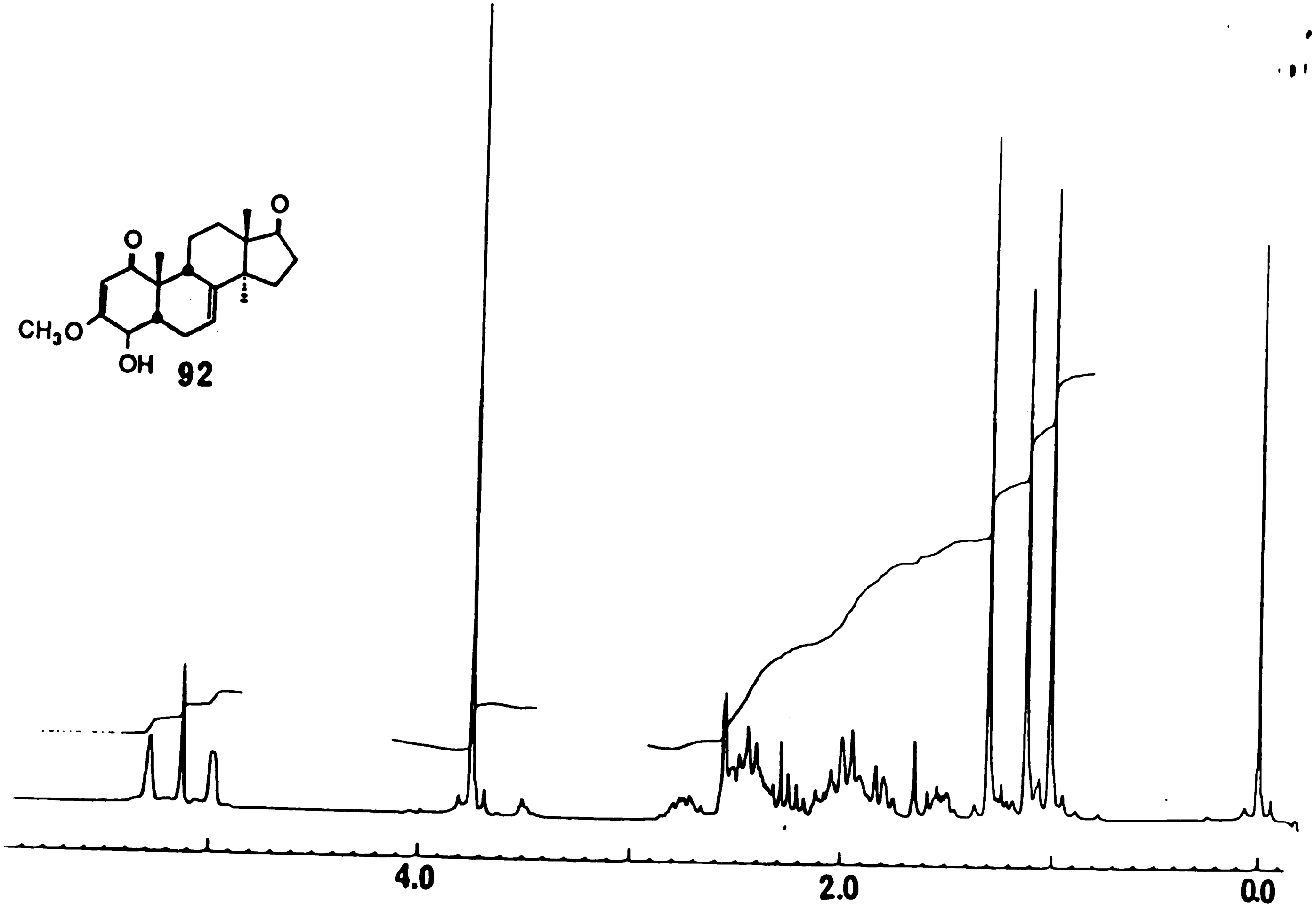


Figure 78. PMR spectrum of 92

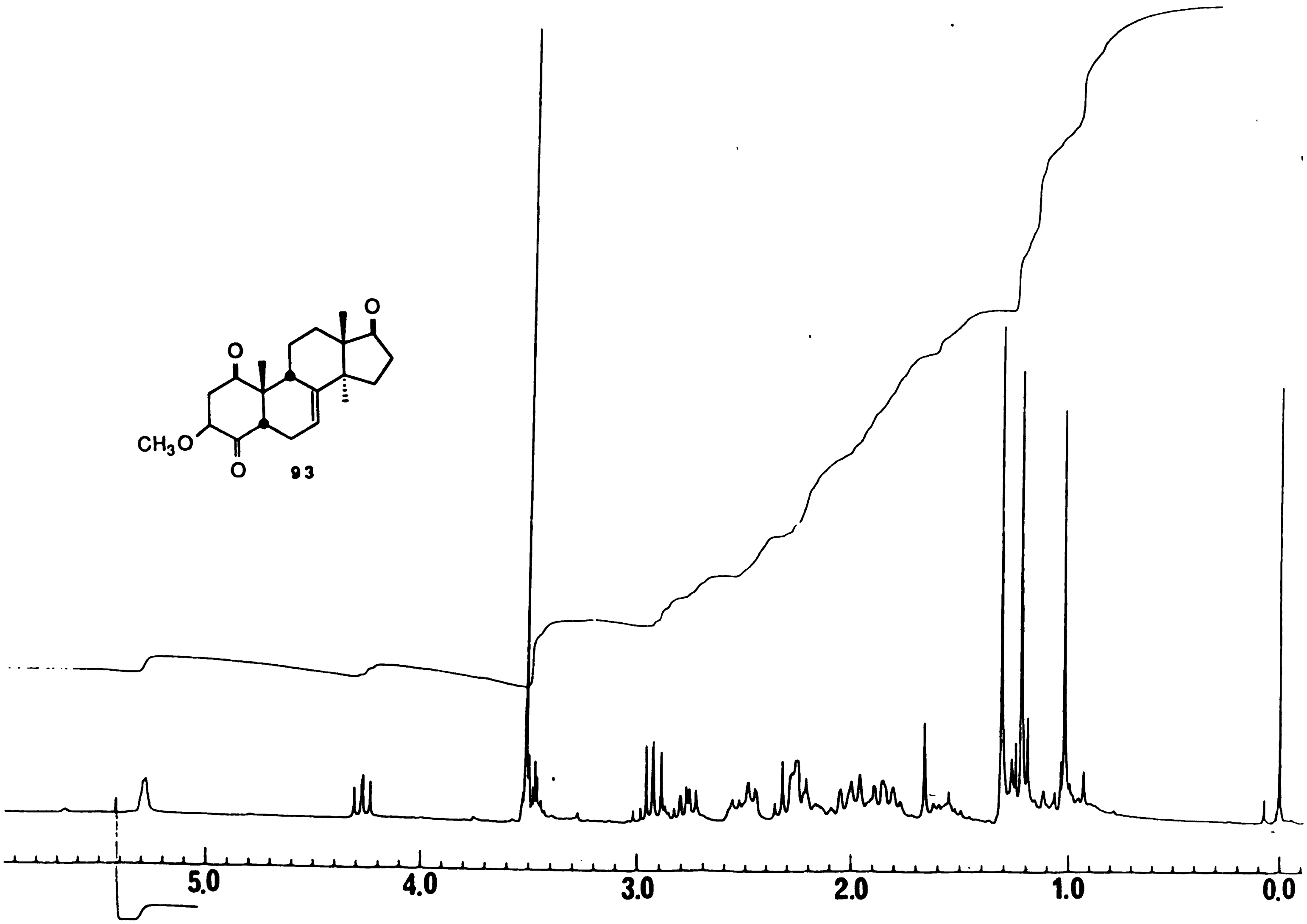


Figure 79. PMR spectrum of 93

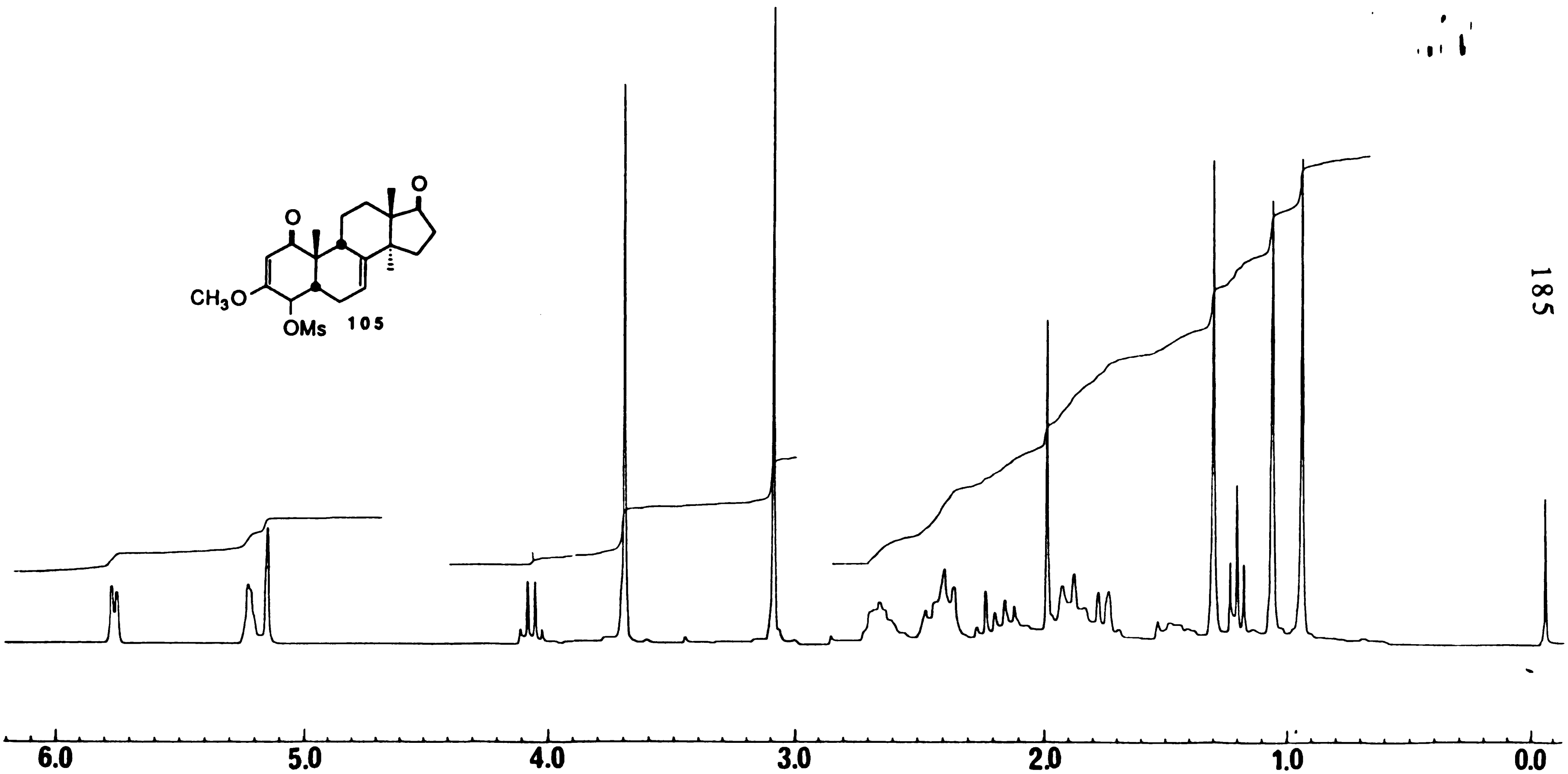


Figure 80. PMR spectrum of **105**

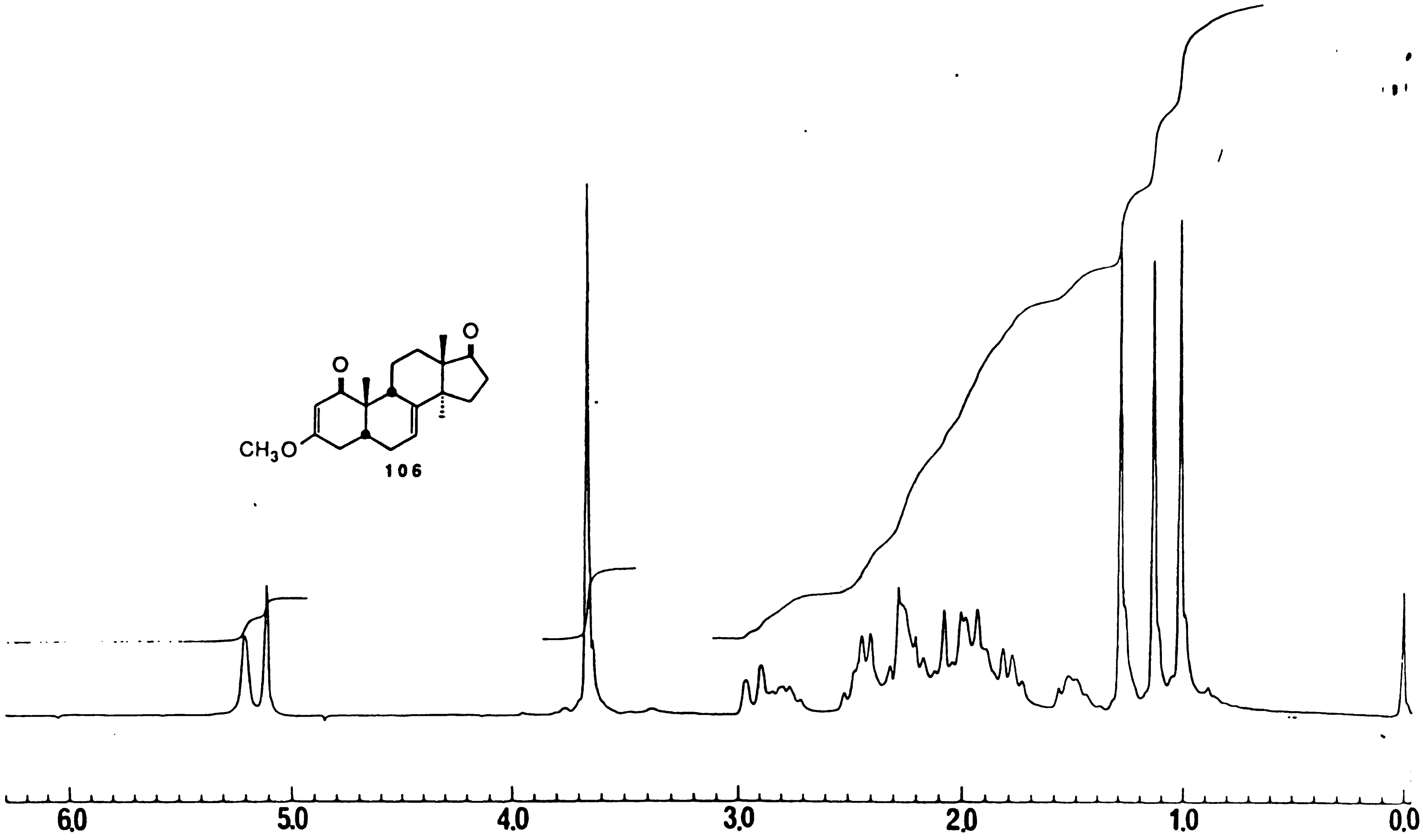


Figure 81. PMR spectrum of 106

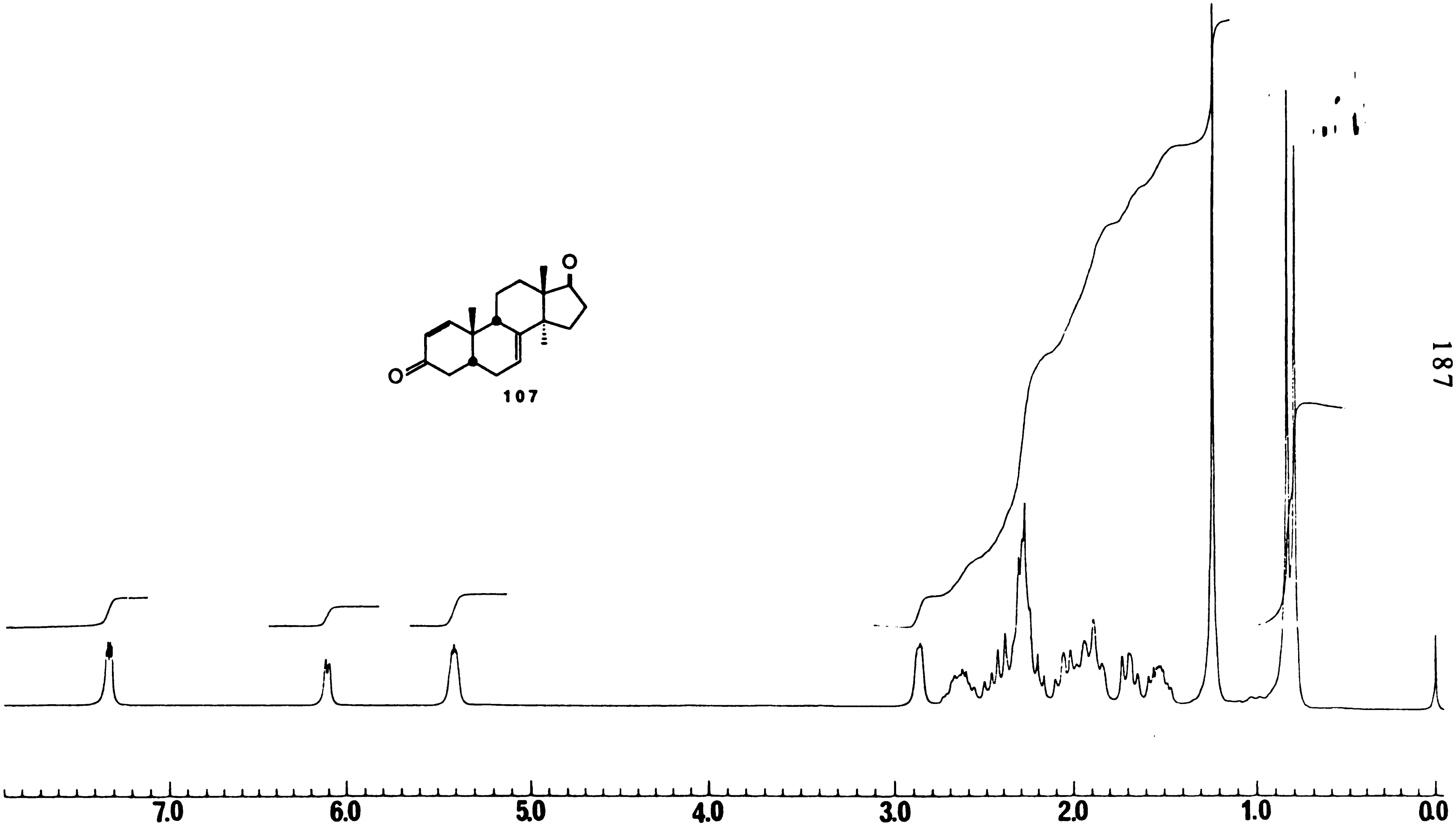


Figure 82. PMR spectrum of **107**

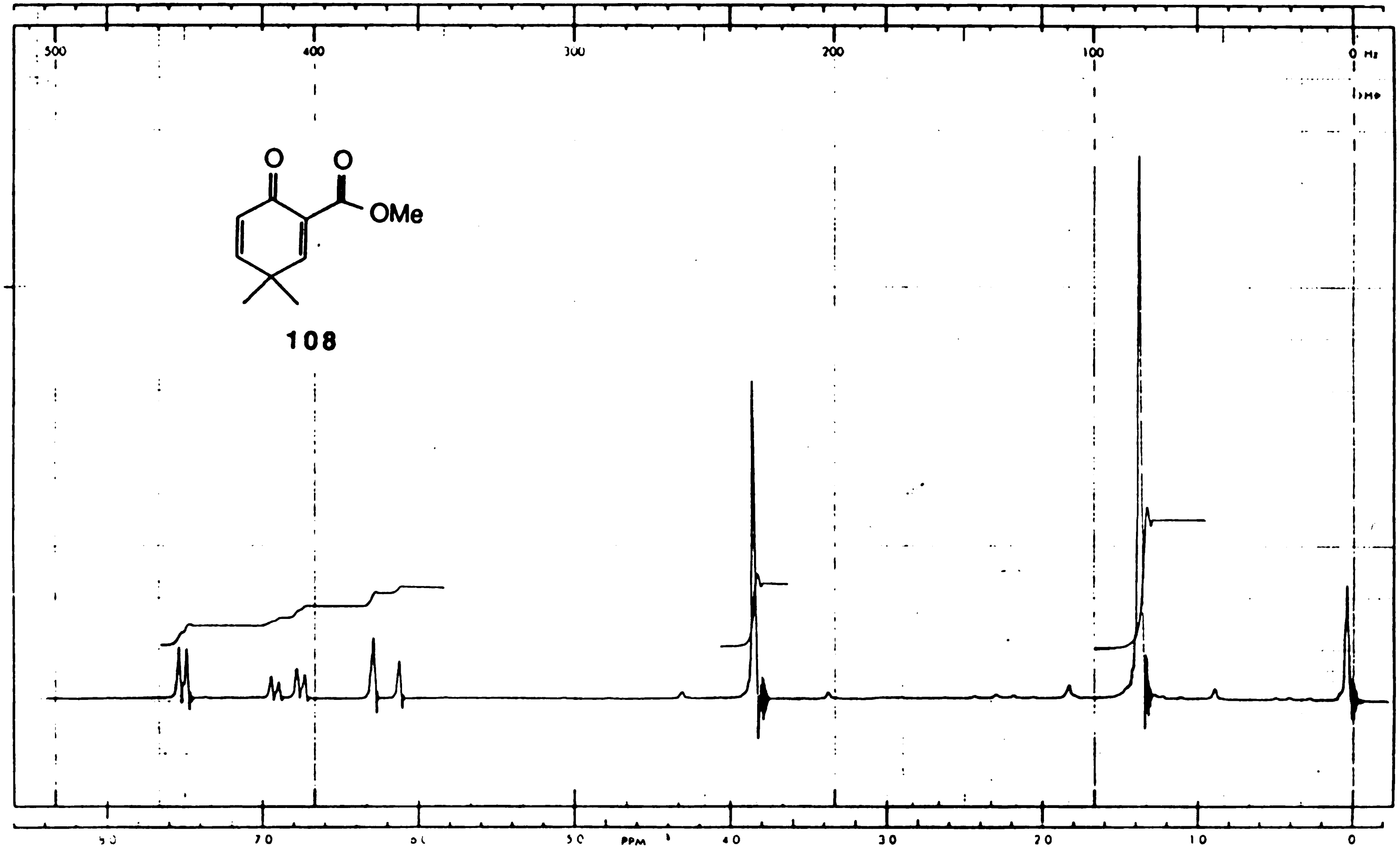
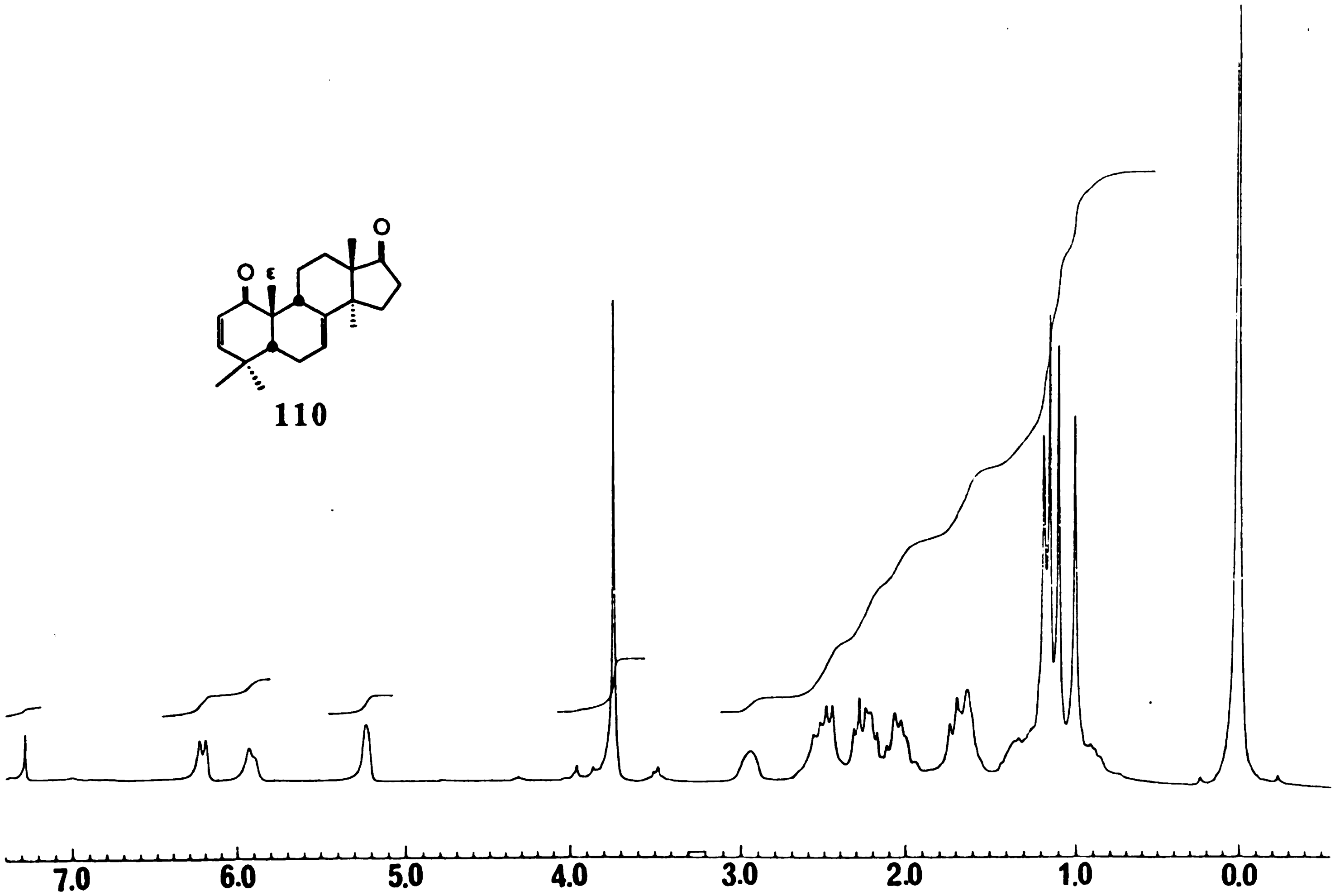


Figure 83. PMR spectrum of **108**



110

Figure 84. PMR spectrum of 110

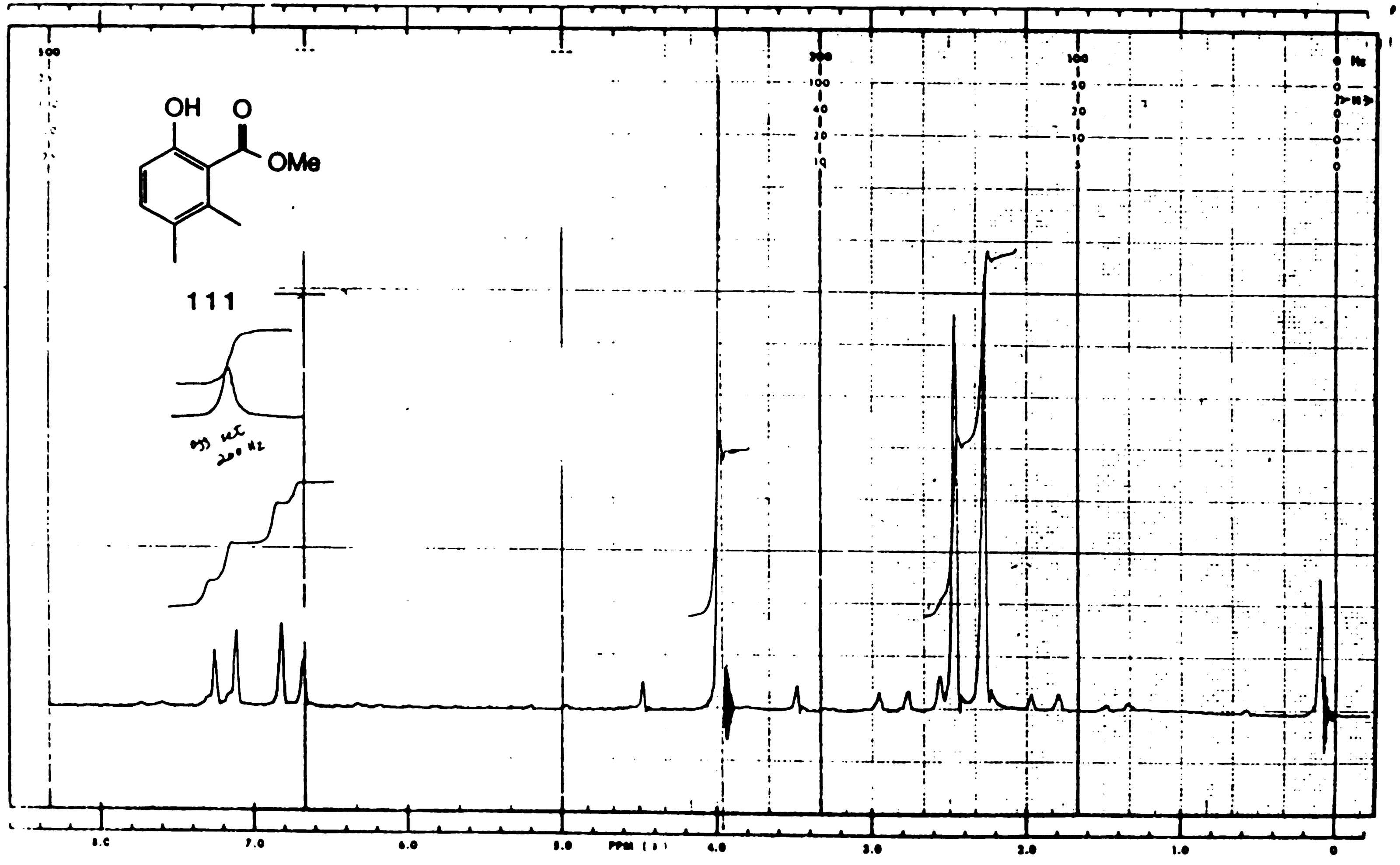


Figure 85. PMR spectrum of 111

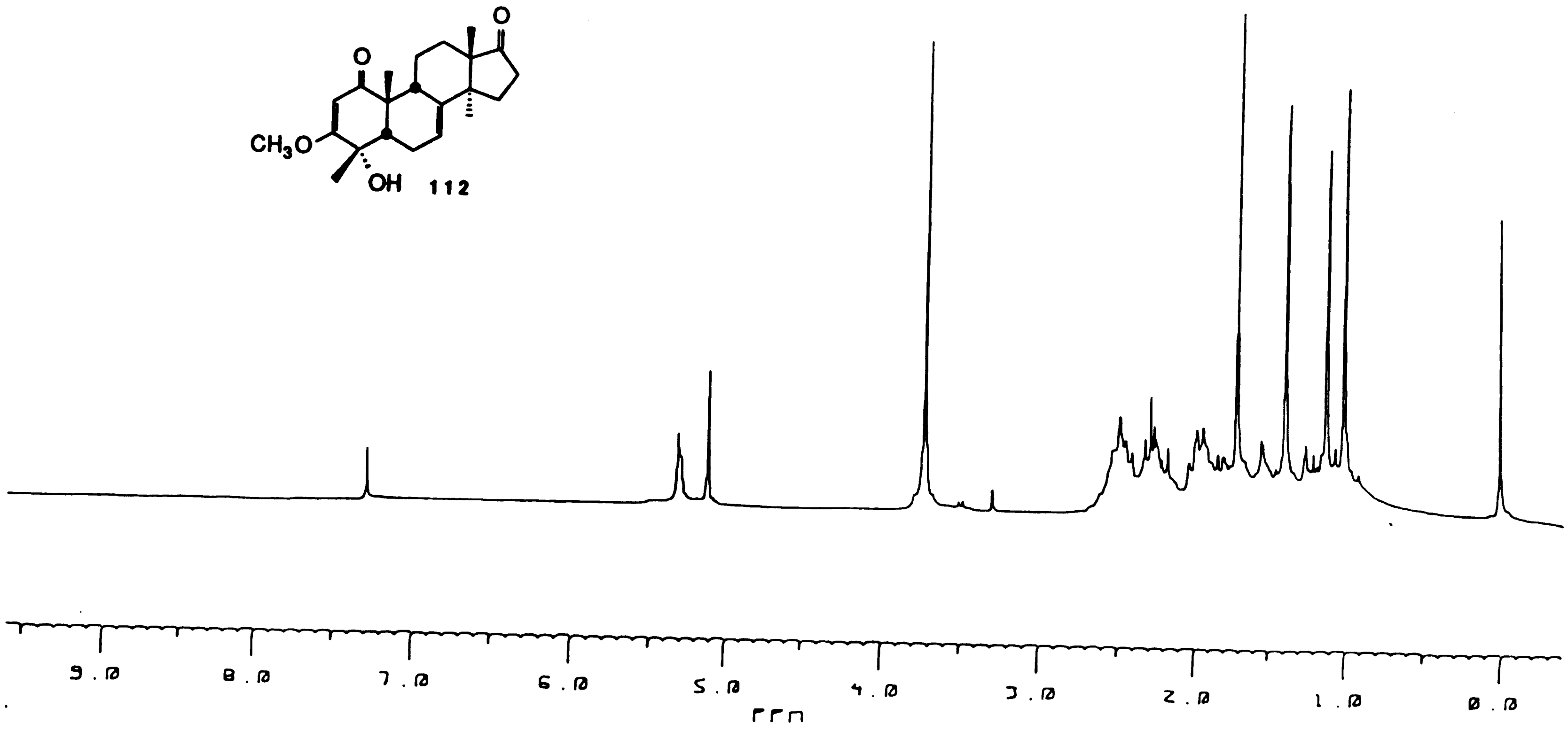


Figure 86. PMR spectrum of **112**

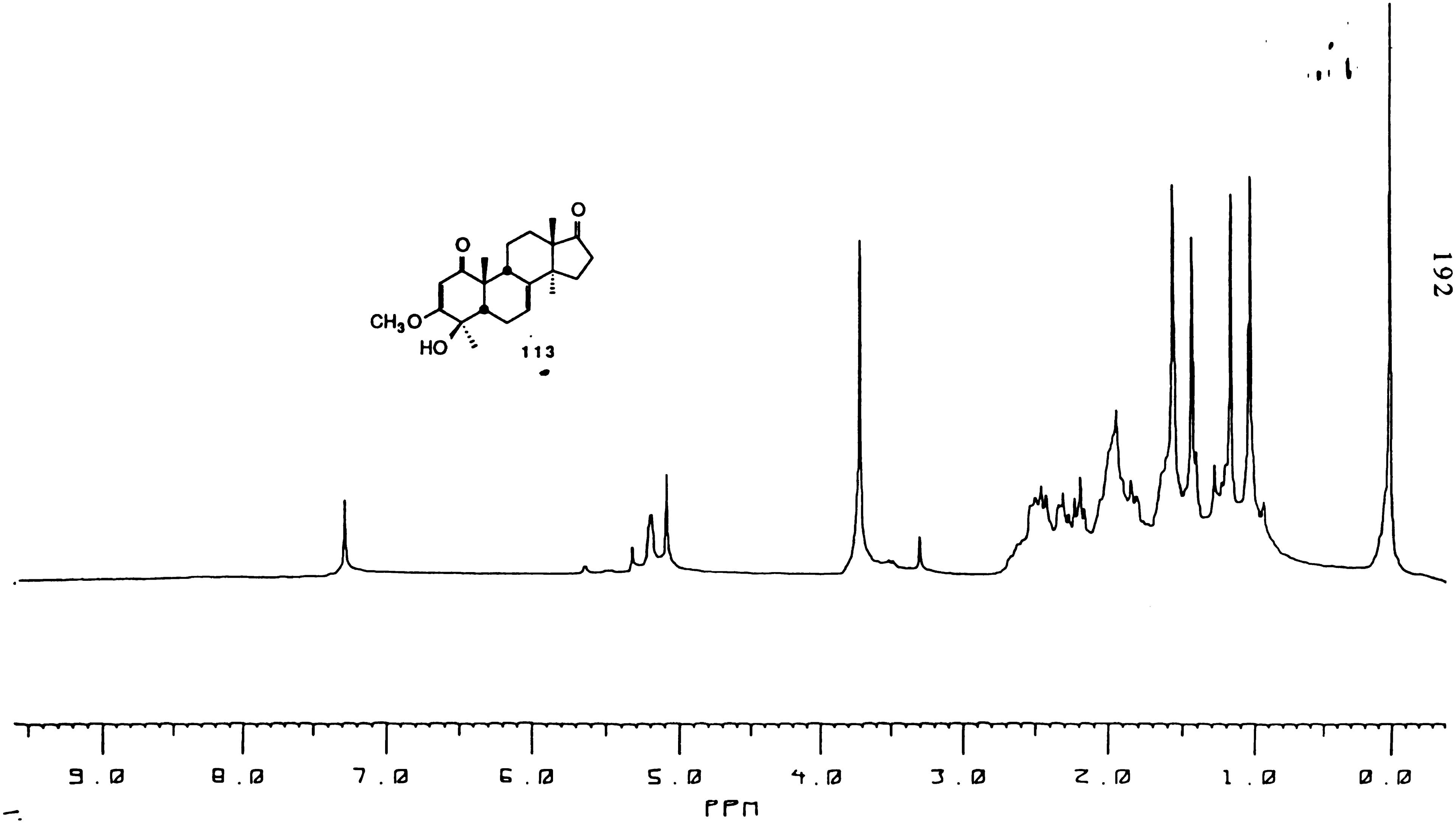


Figure 87. PMR spectrum of **113**

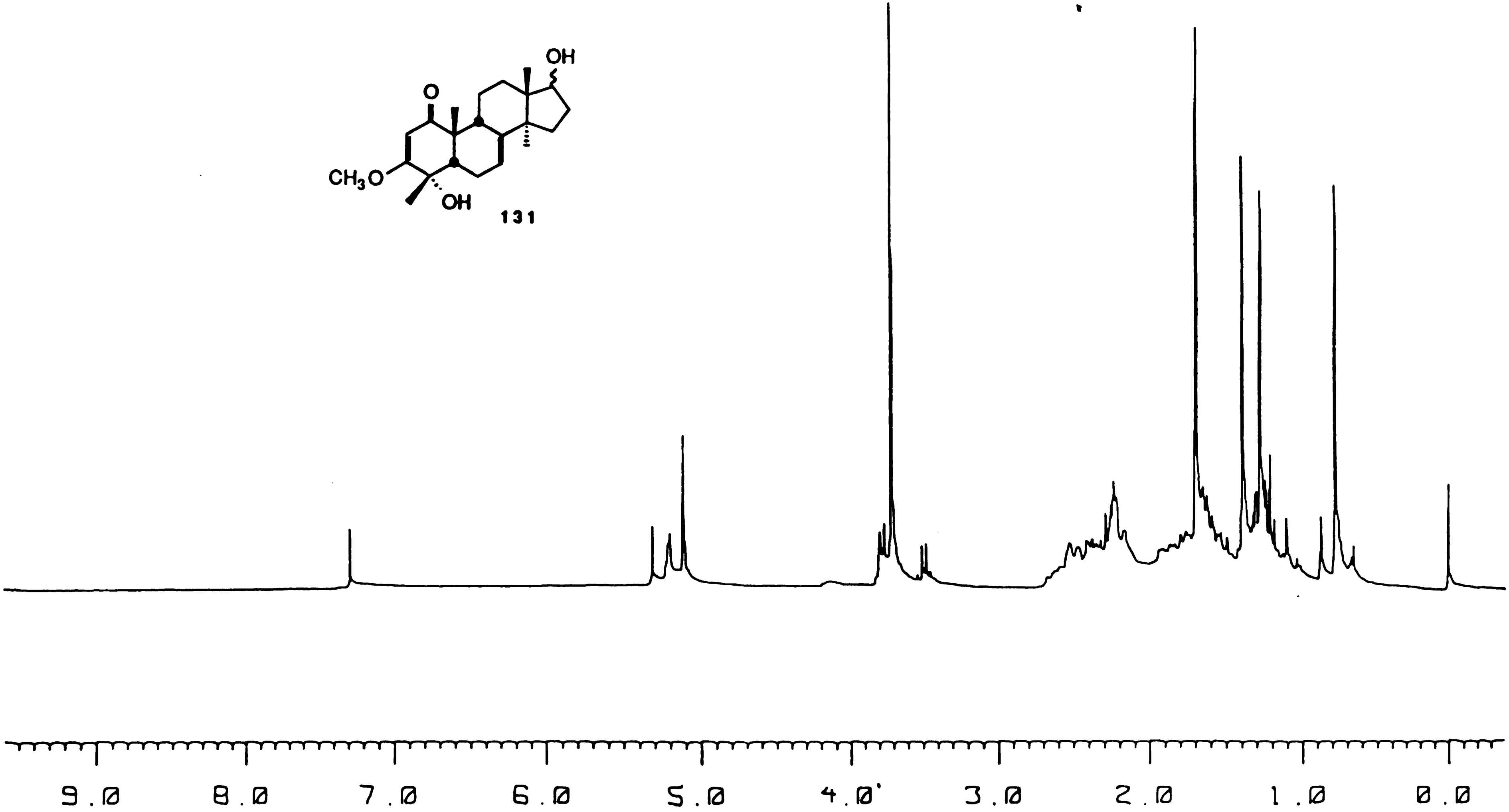


Figure 88. PMR spectrum of **131**

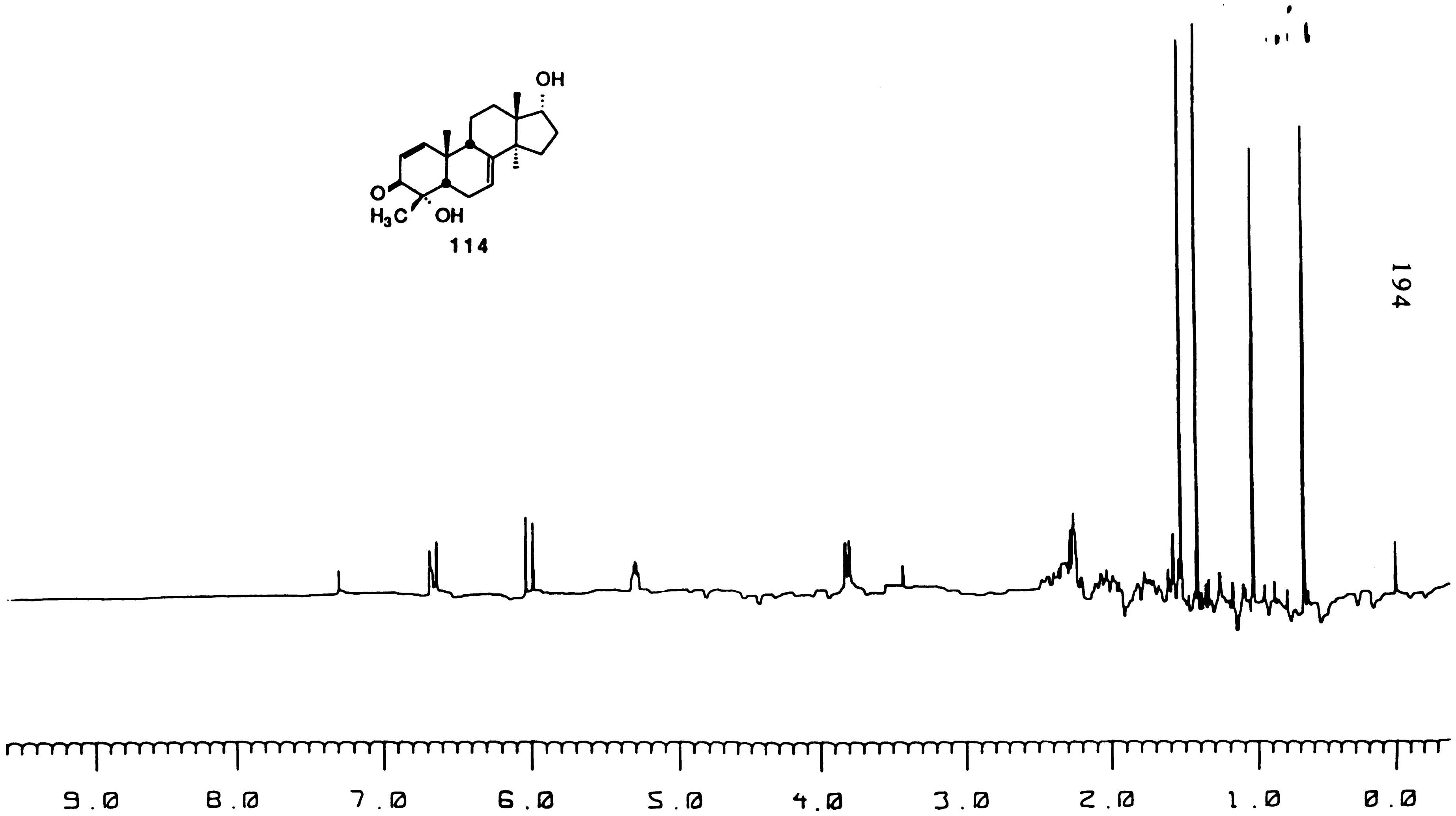
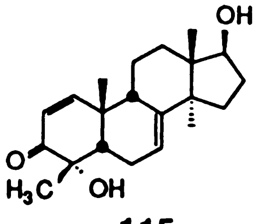


Figure 89. PMR spectrum of **114**



115

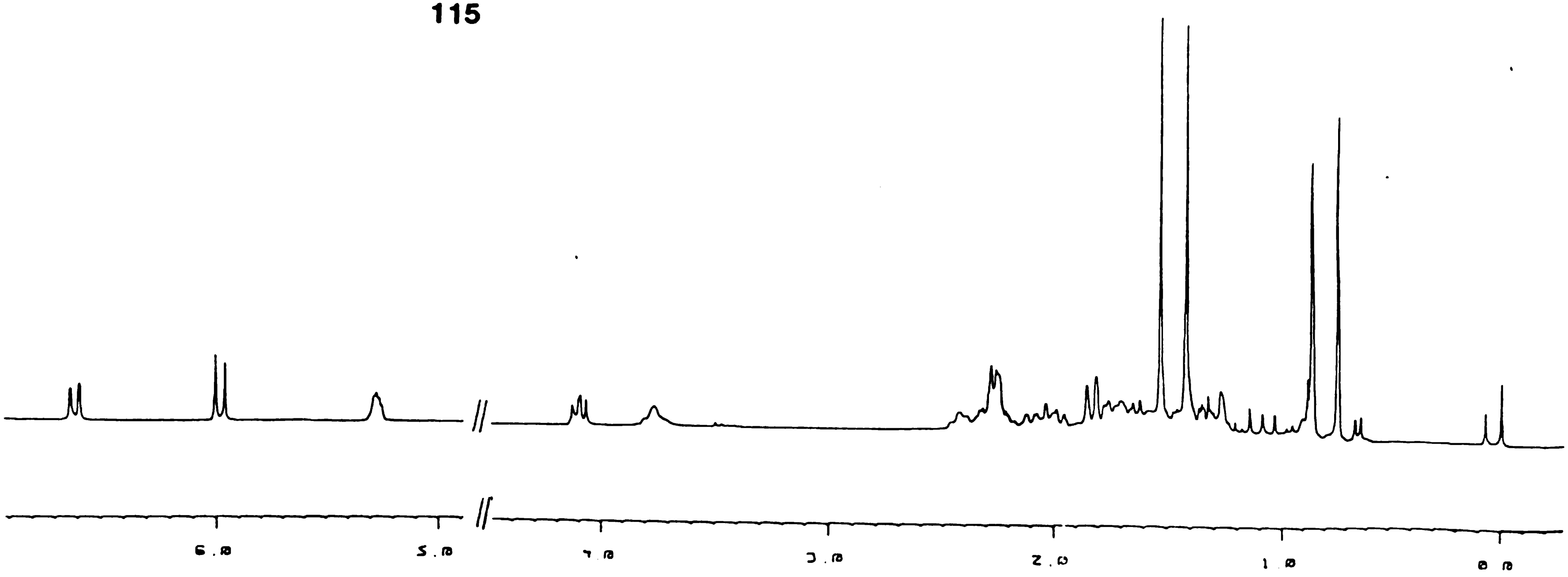


Figure 90. PMR spectrum of 115

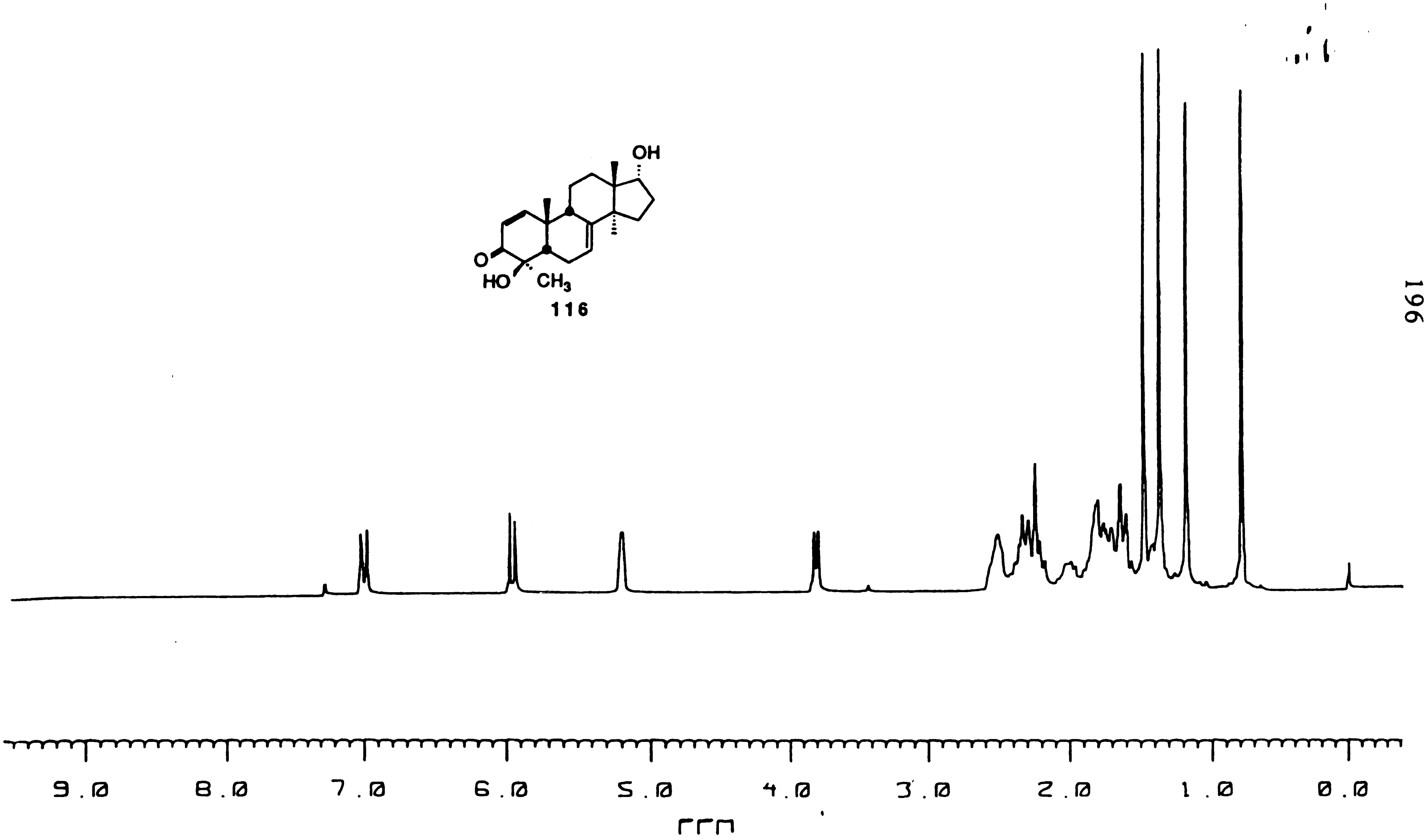


Figure 91. PMR spectrum of **116**

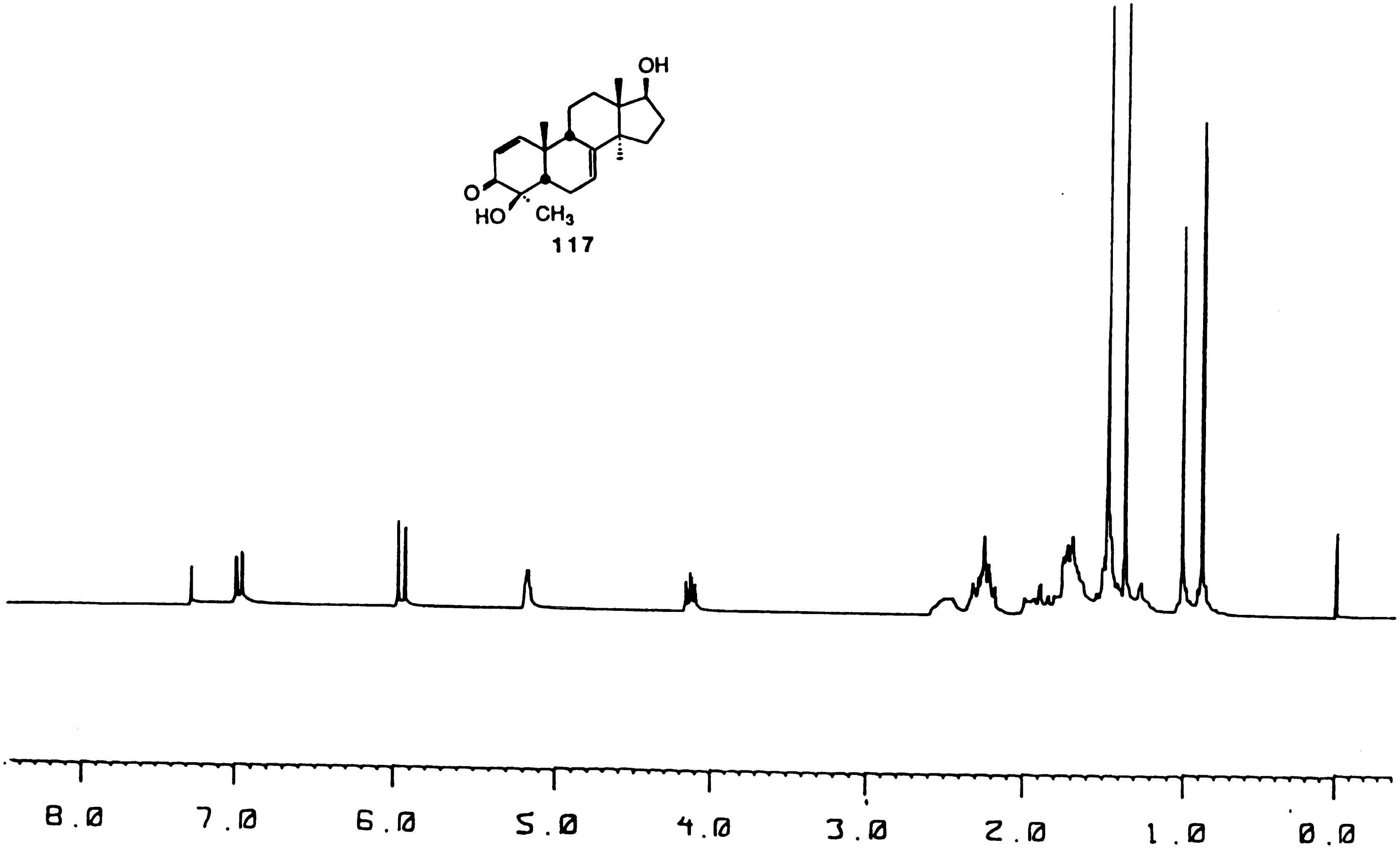


Figure 92. PMR spectrum of **117**

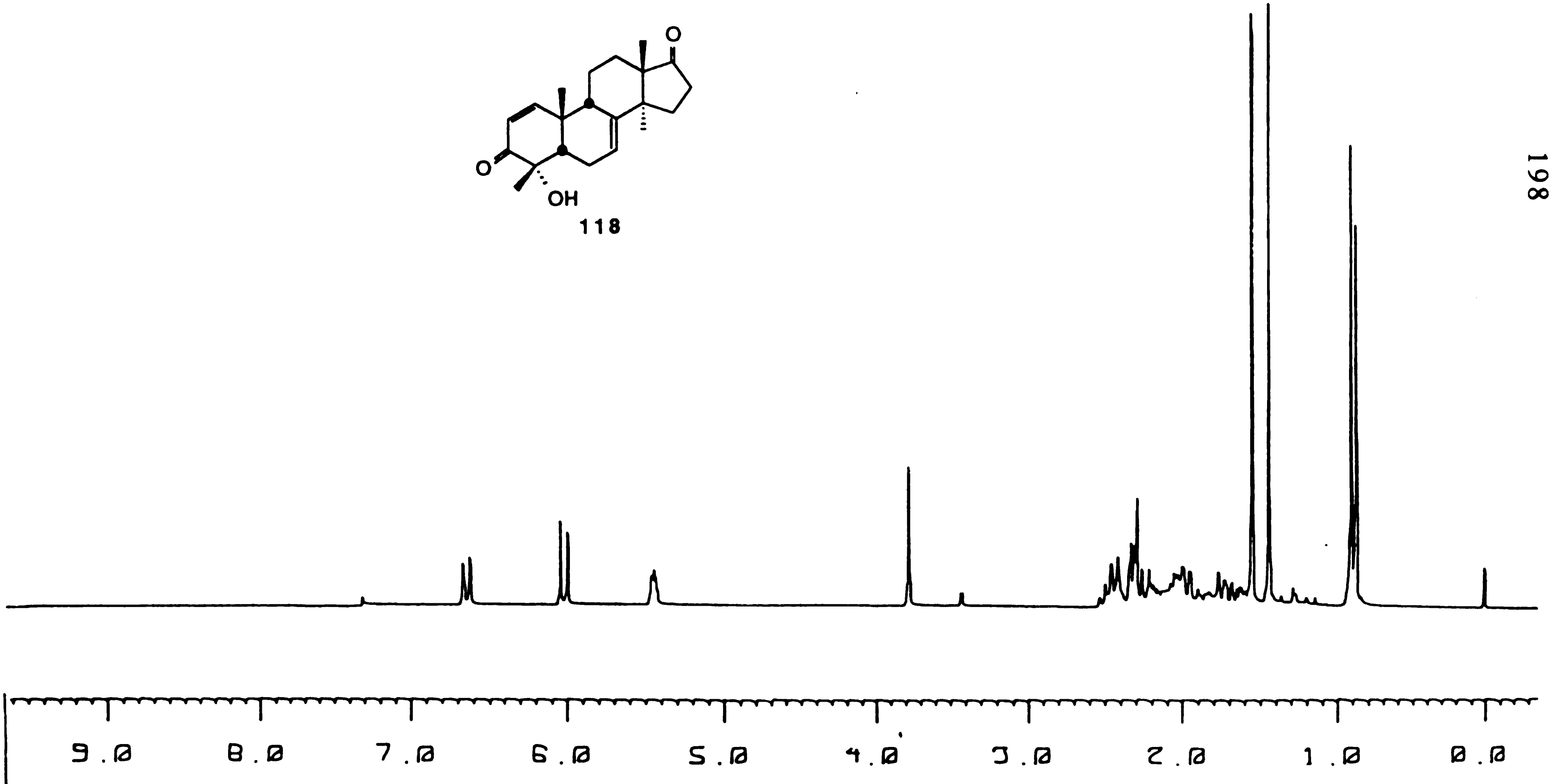


Figure 93. PMR spectrum of **118**

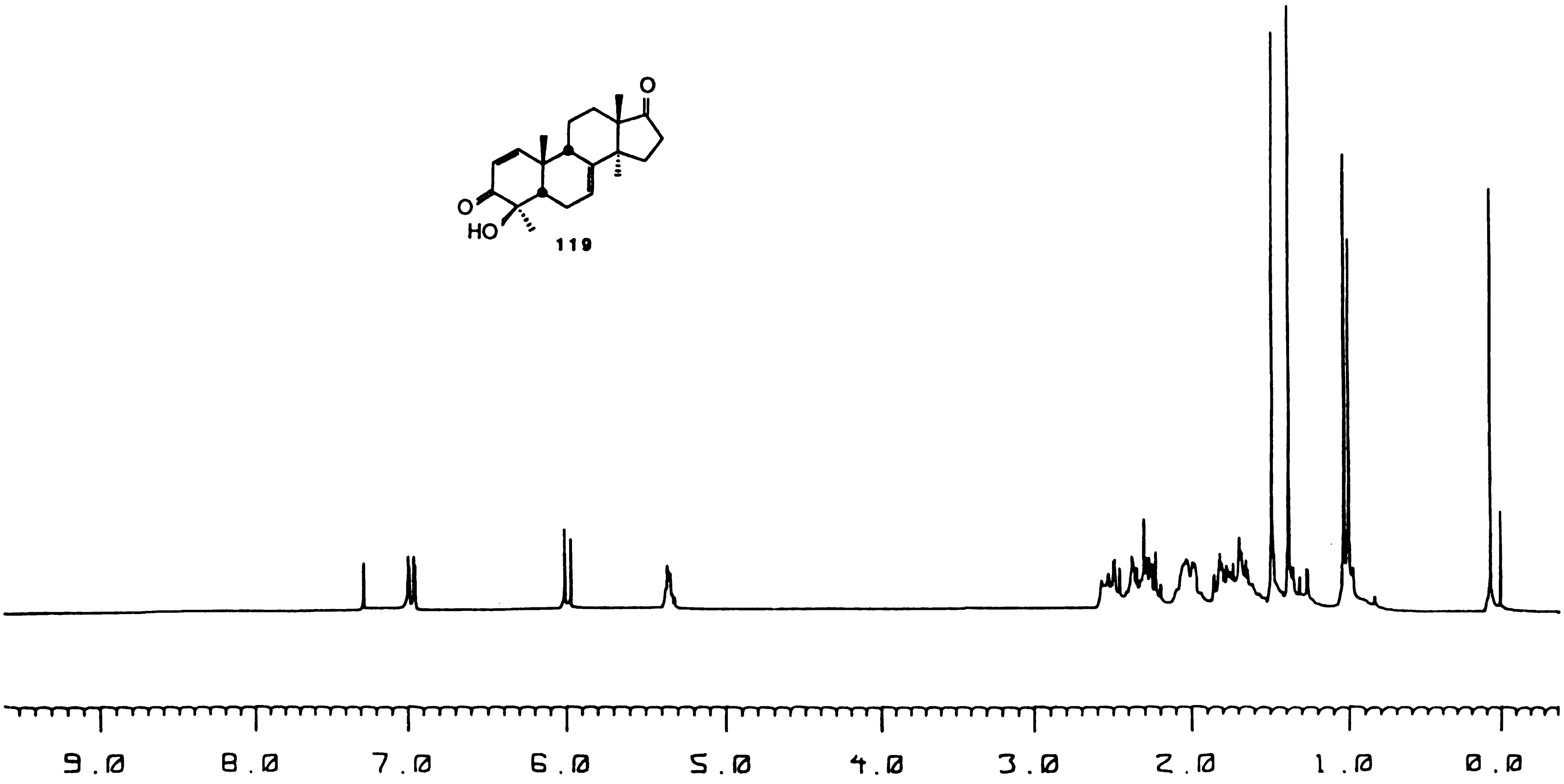
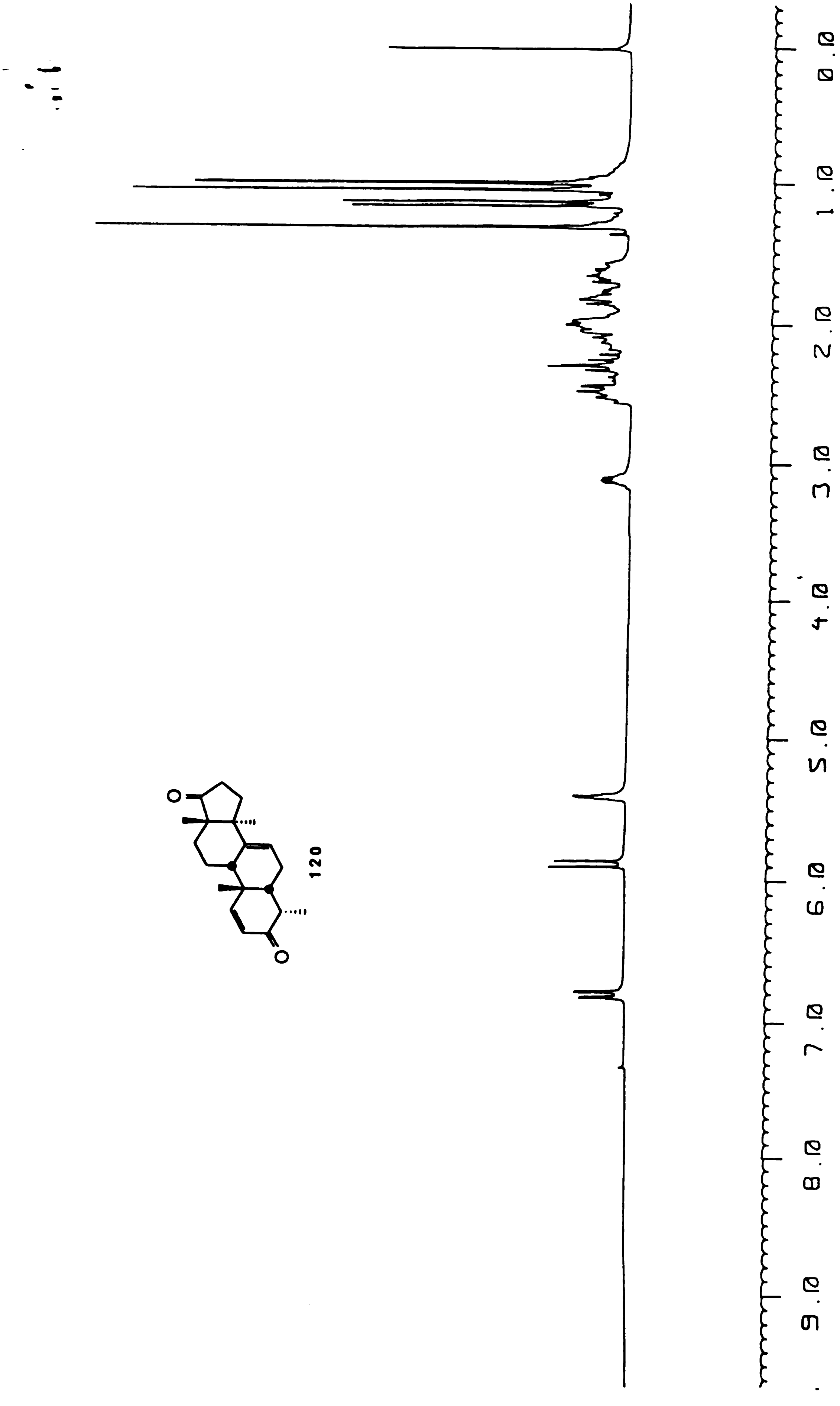


Figure 94. PMR spectrum of 119



120

Figure 95. PMR spectrum of 120

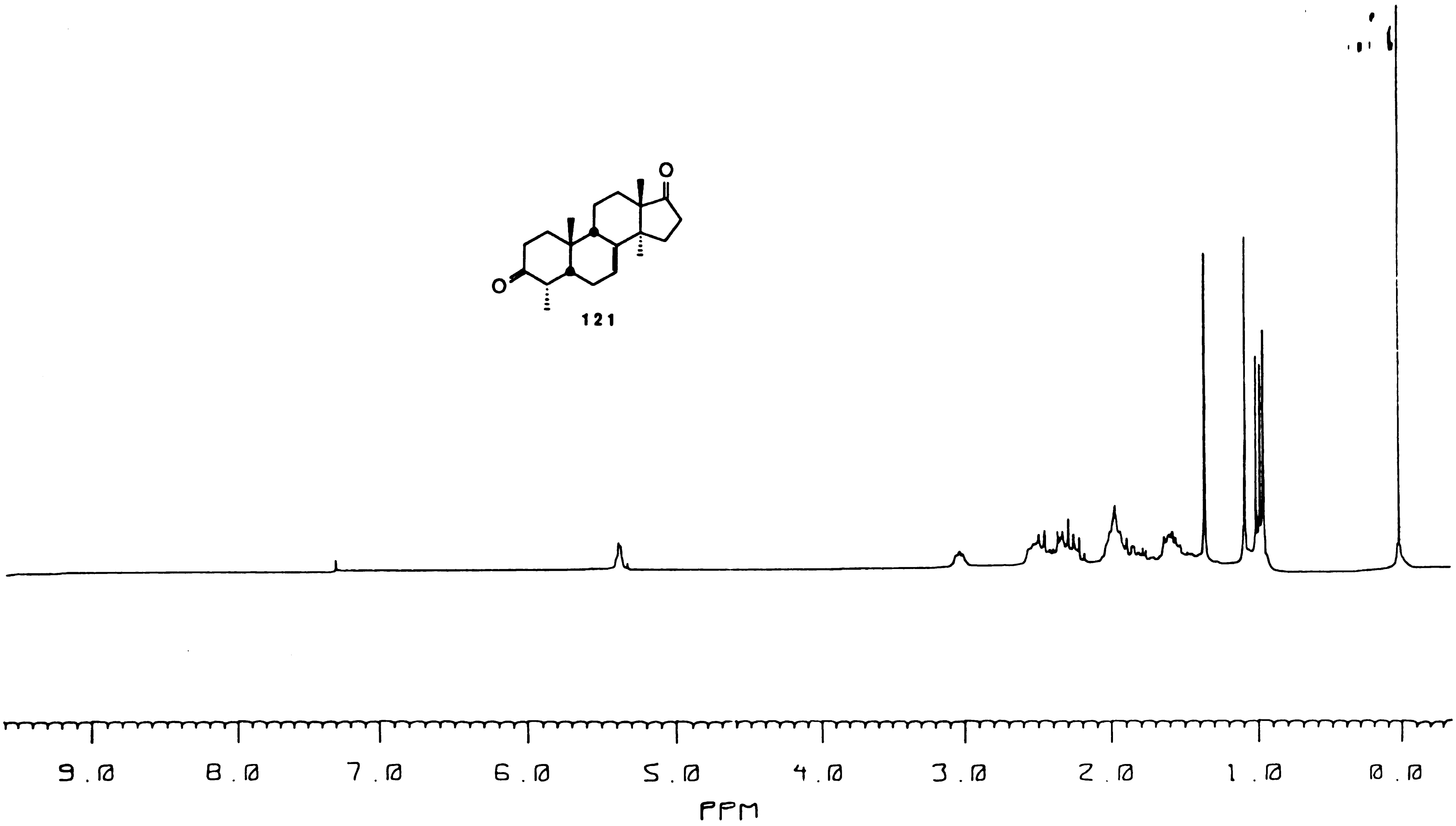
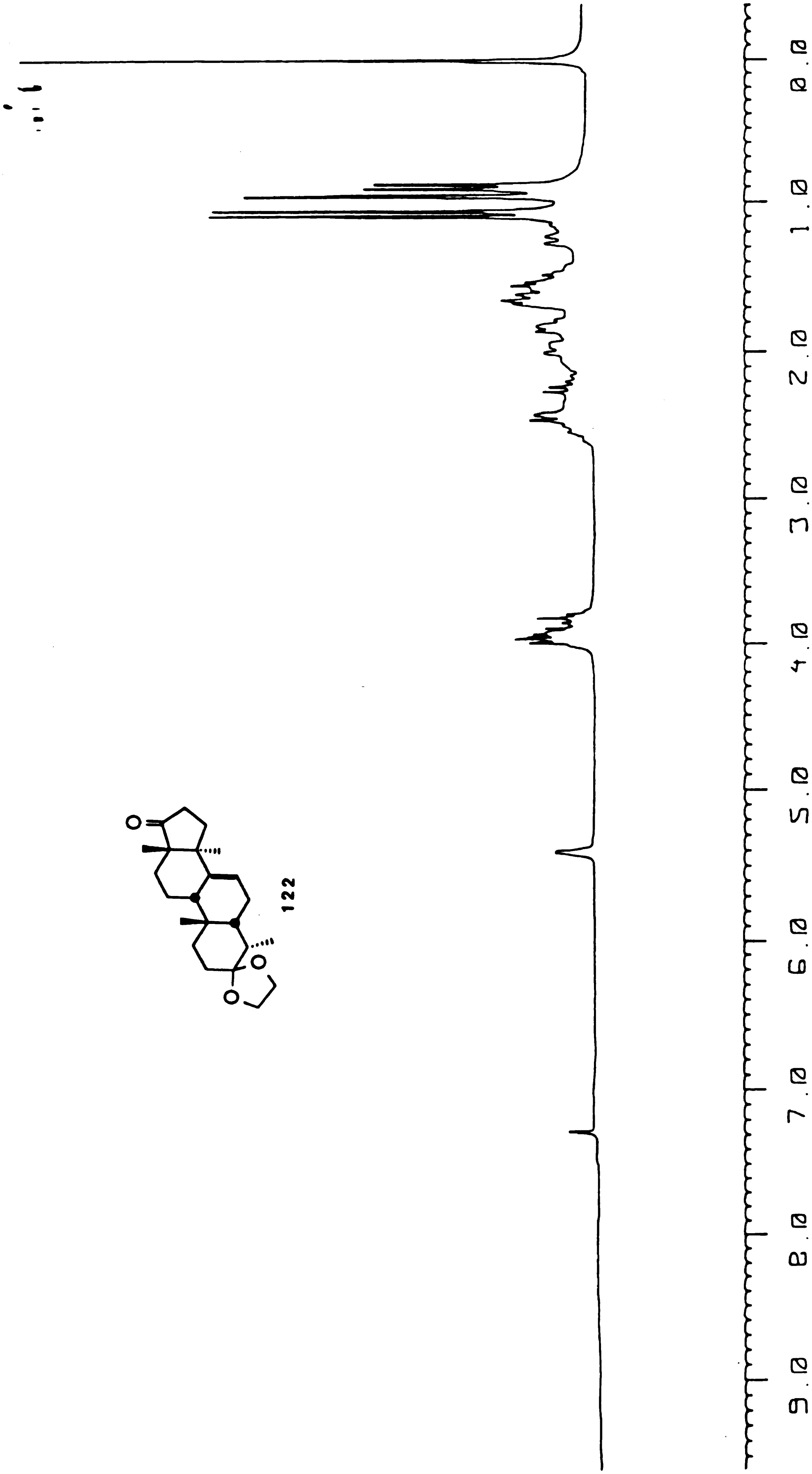


Figure 96. PMR spectrum of **121**



122

Figure 97. PMR spectrum of 122

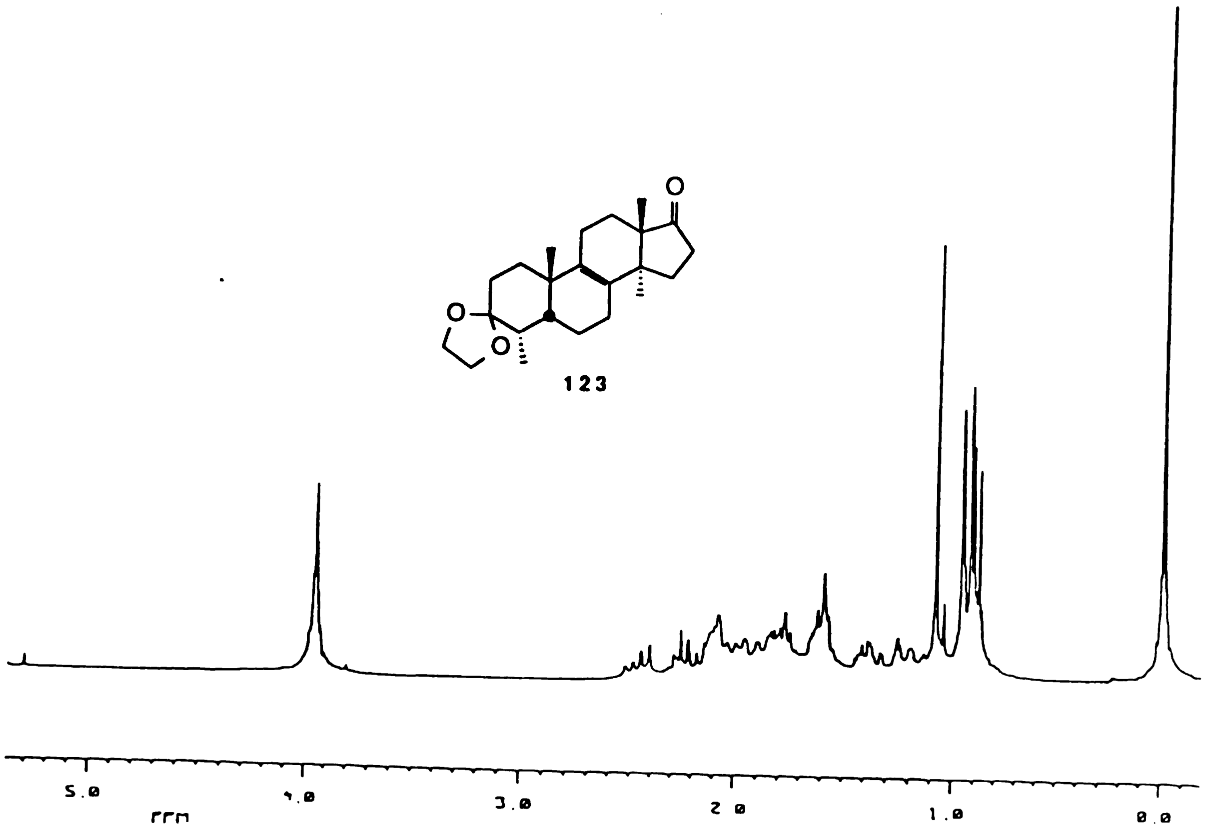


Figure 98. PMR spectrum of **123**

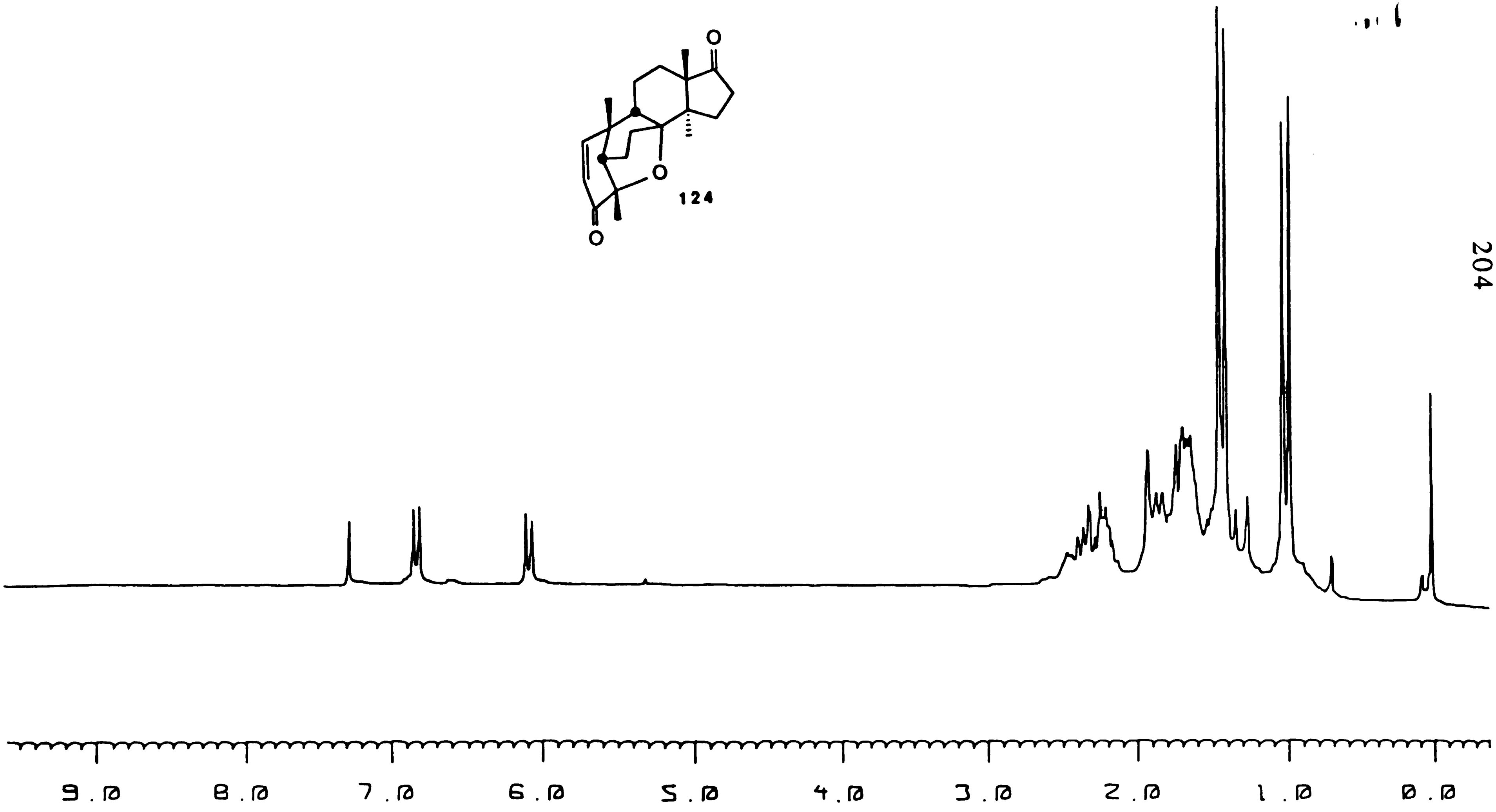


Figure 99. PMR spectrum of **124**

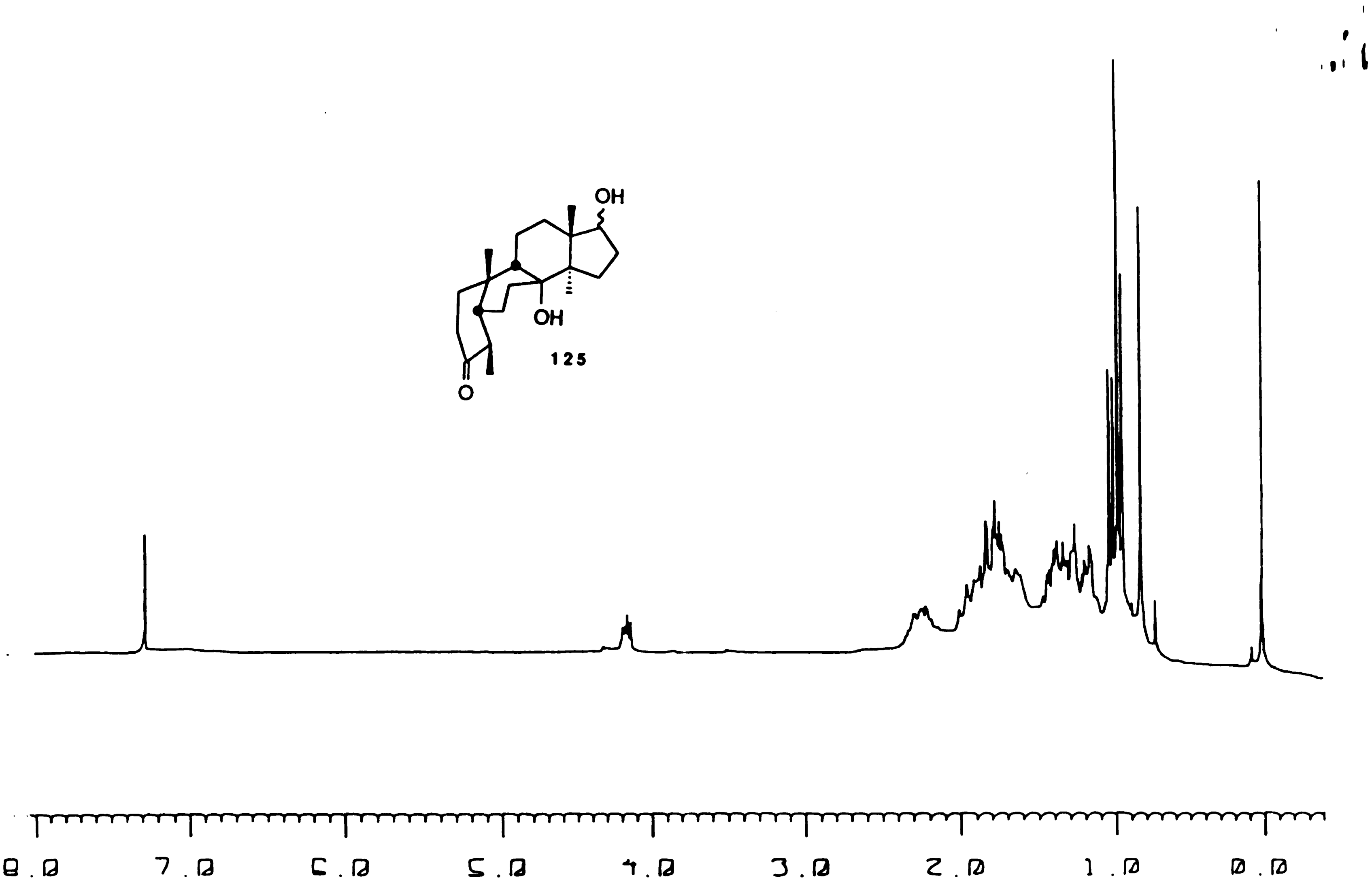


Figure 100. PMR spectrum of **125**

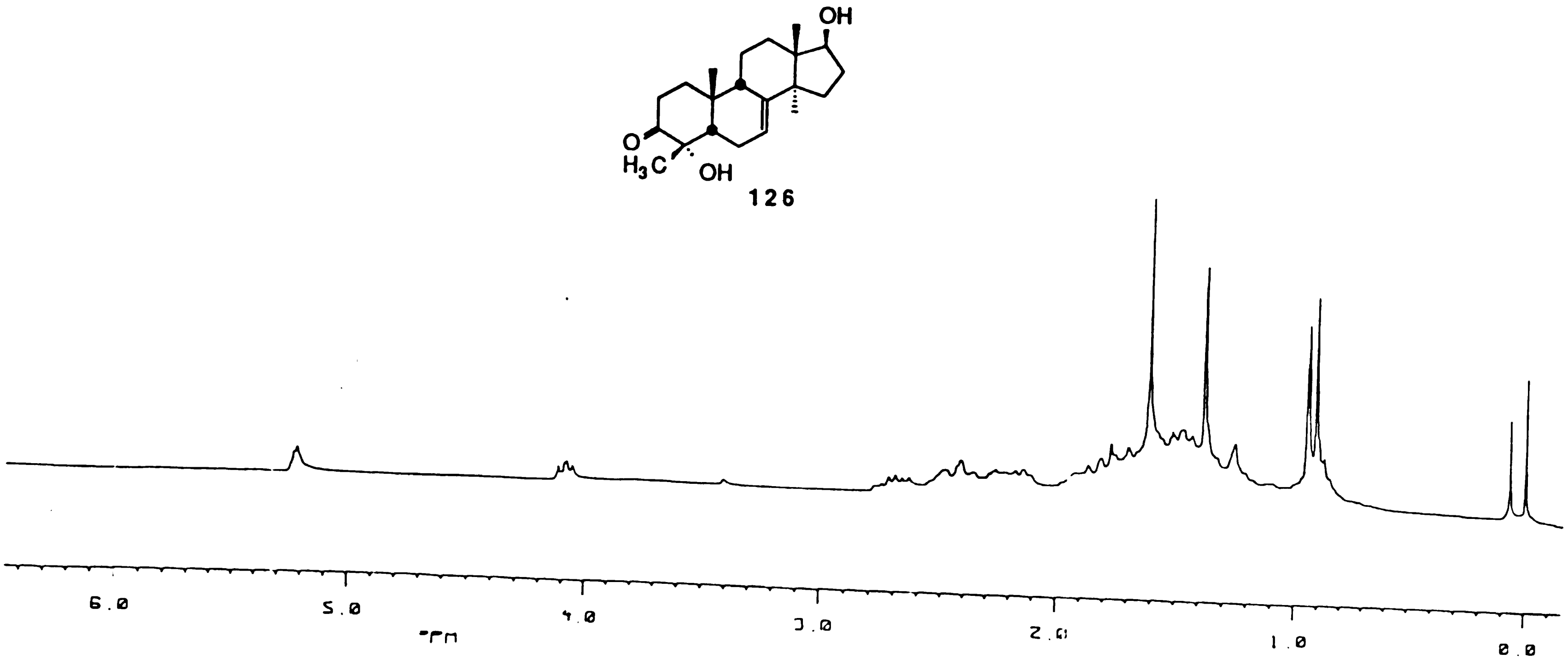
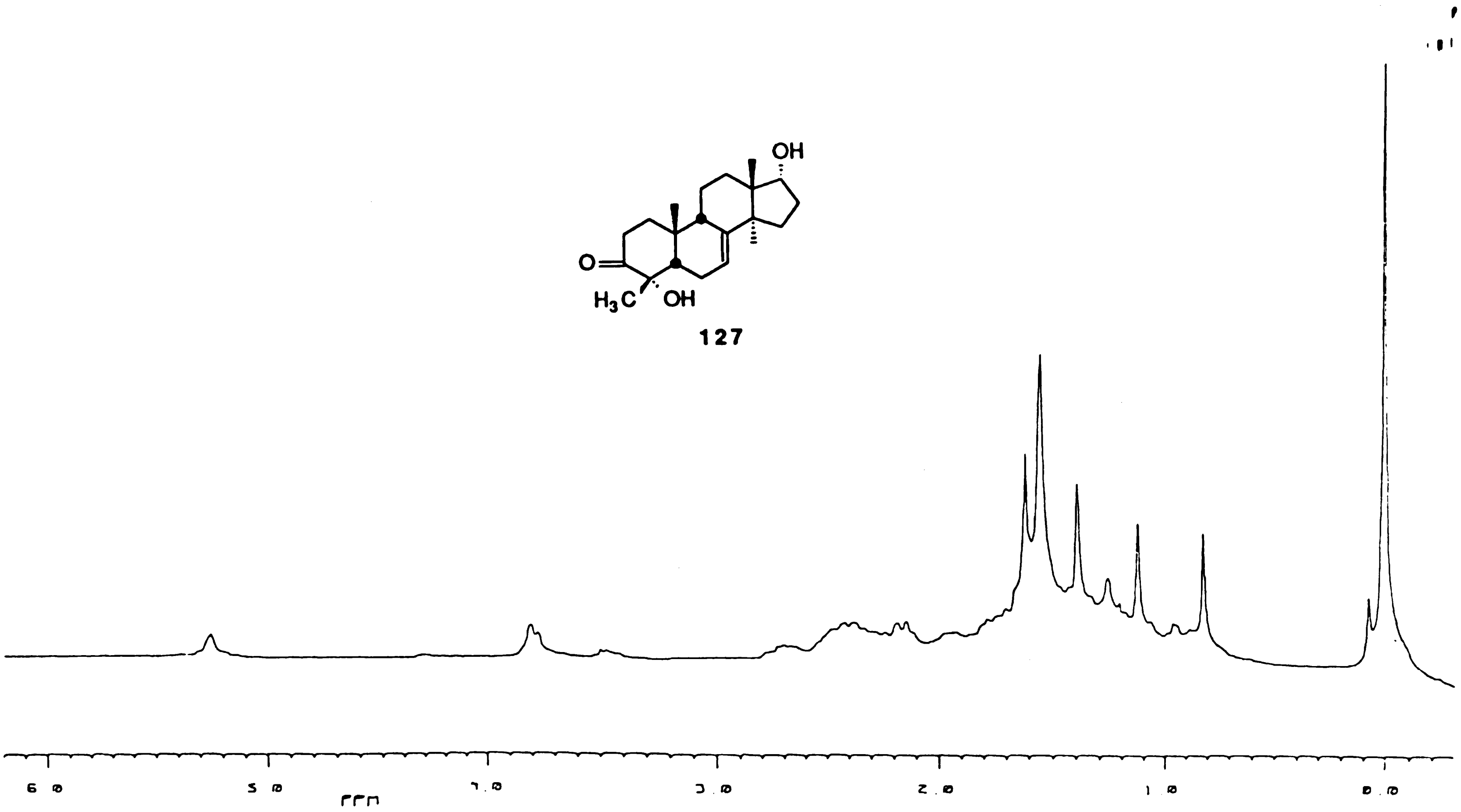


Figure 101. PMR spectrum of **126**



127

Figure 102. PMR spectrum of 127

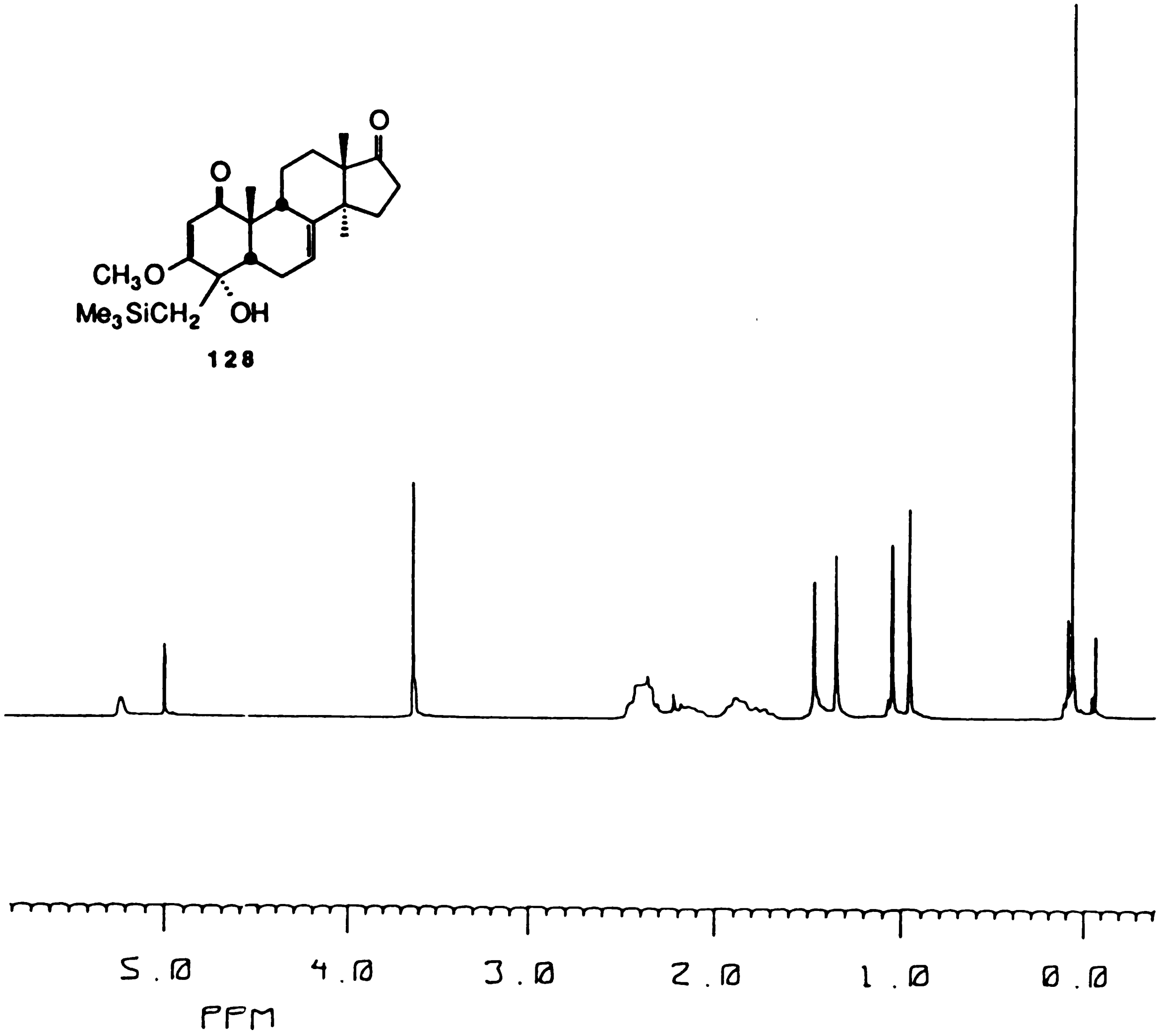


Figure 103. PMR spectrum of **128**

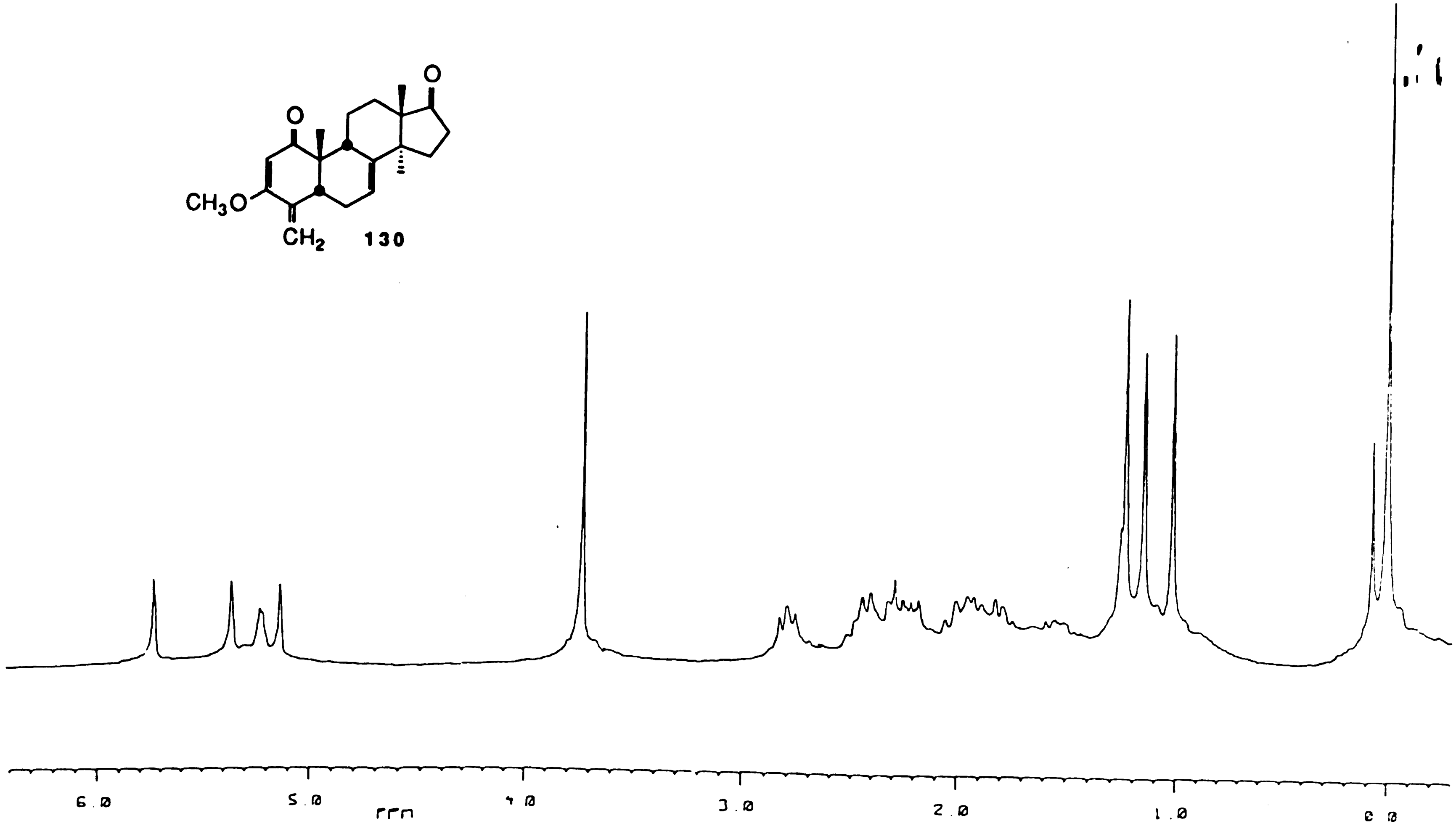


Figure 104. PMR spectrum of 130

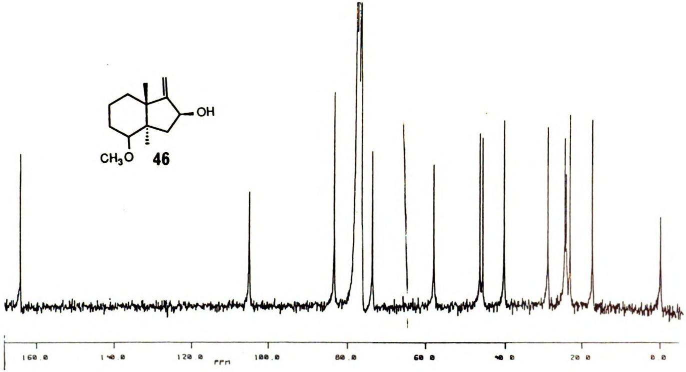


Figure 105. CMR spectrum of **46**

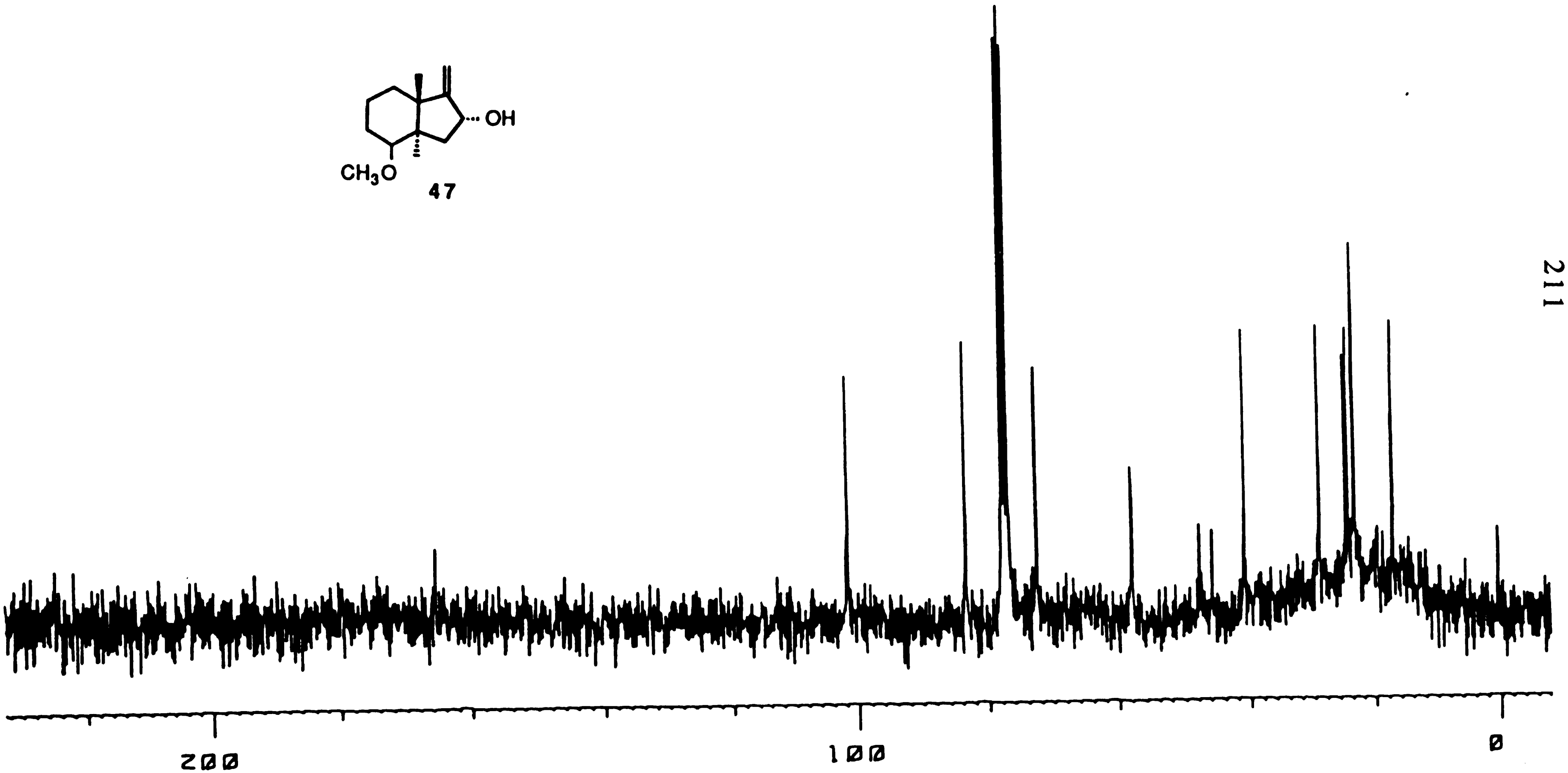
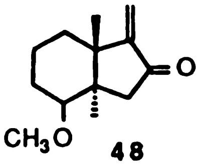


Figure 106. CMR spectrum of 47



48

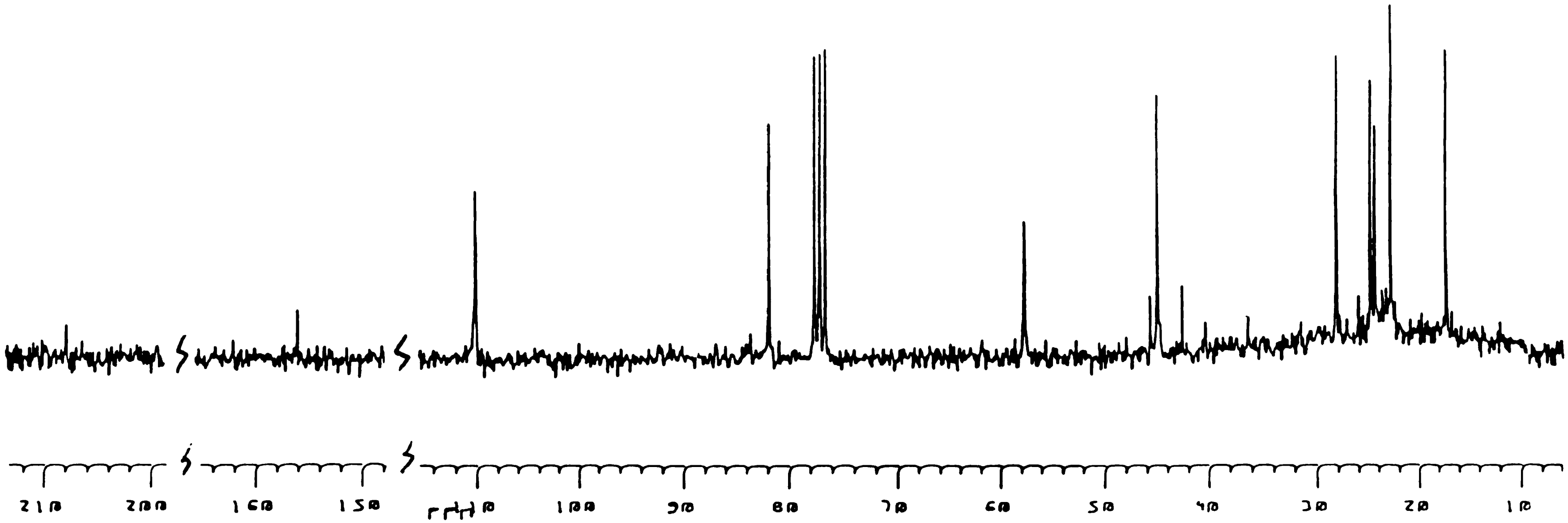


Figure 107. CMR spectrum of 48

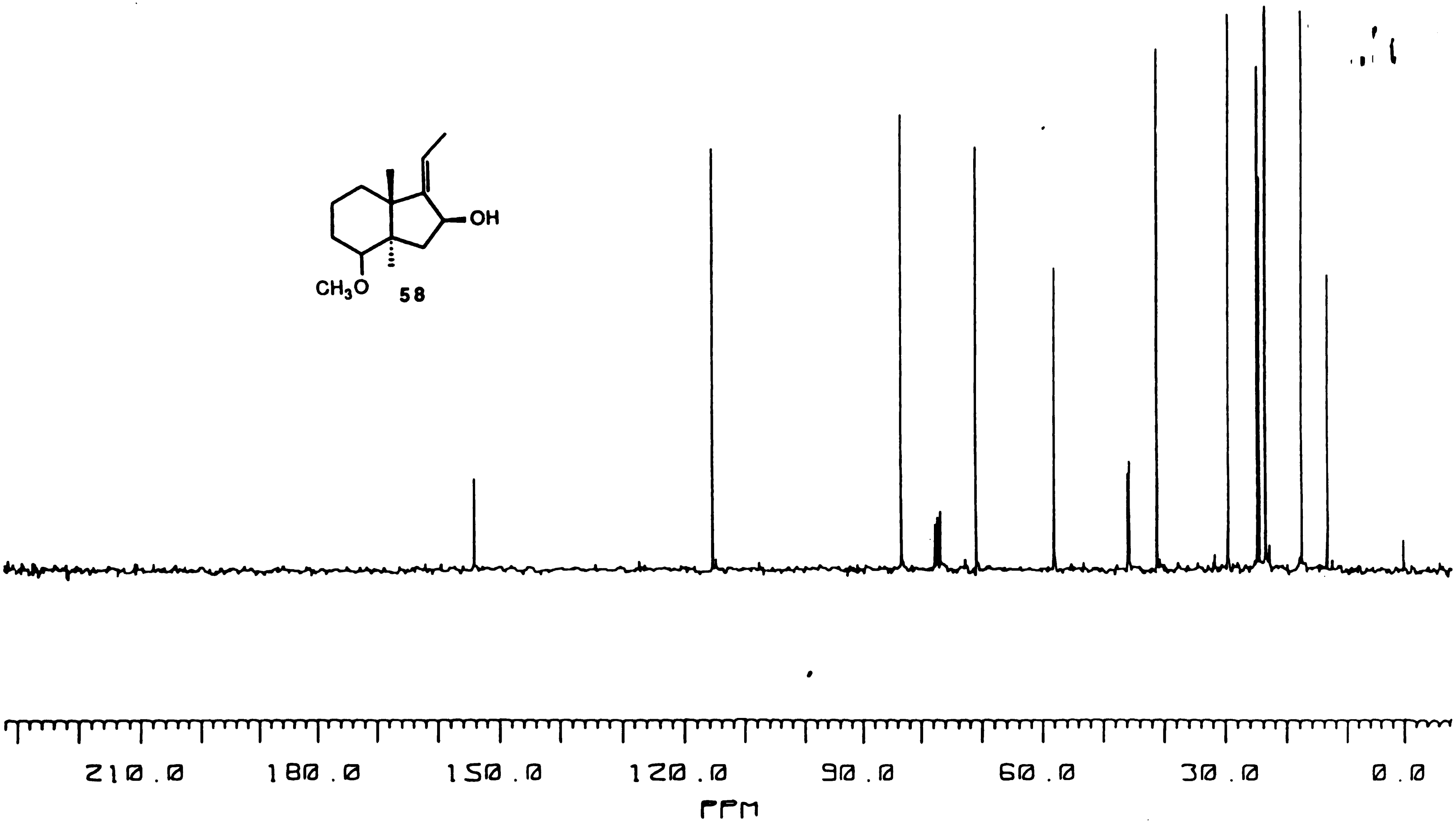


Figure 109. CMR spectrum of 58

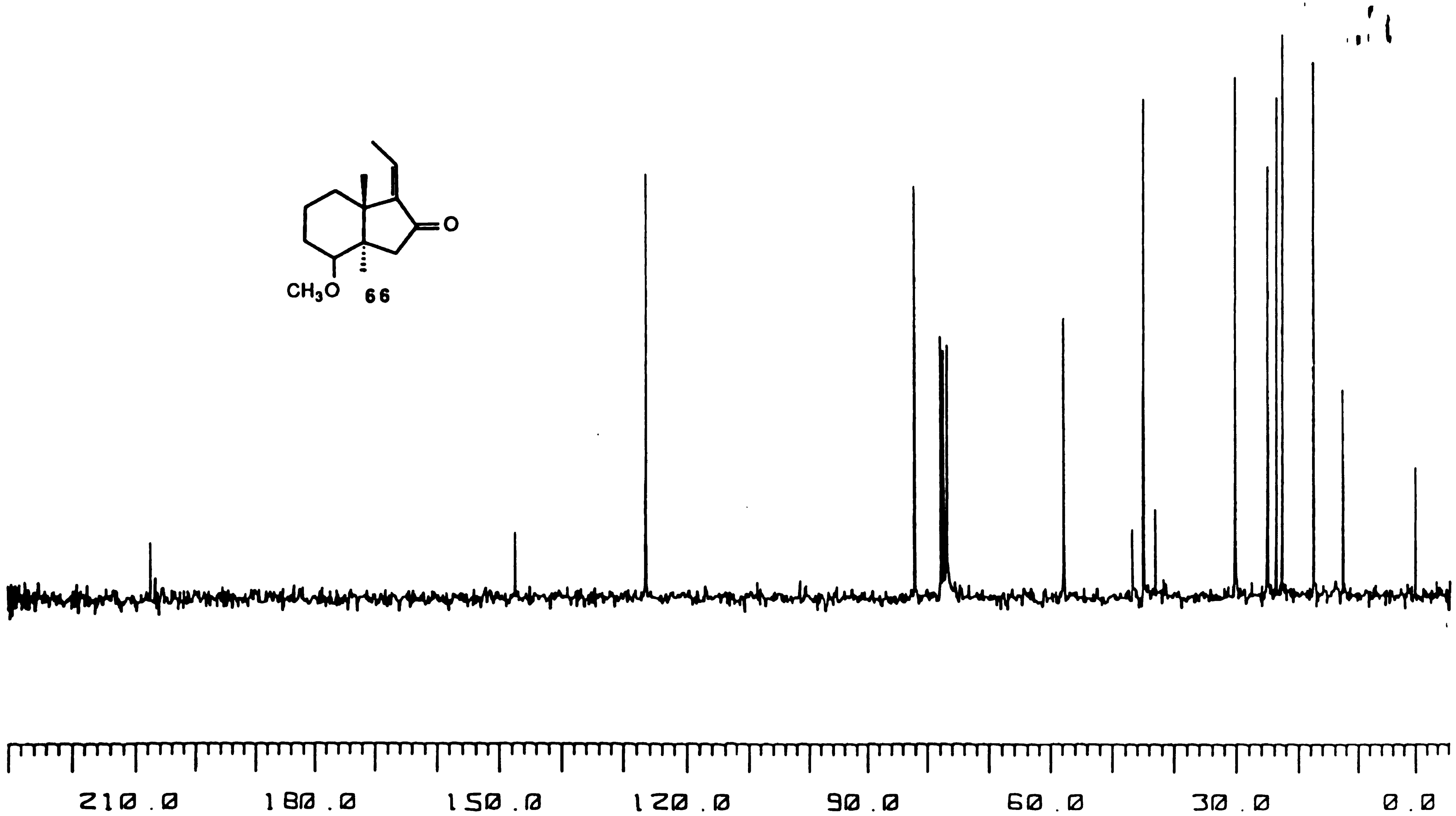


Figure 110. CMR spectrum of **66**

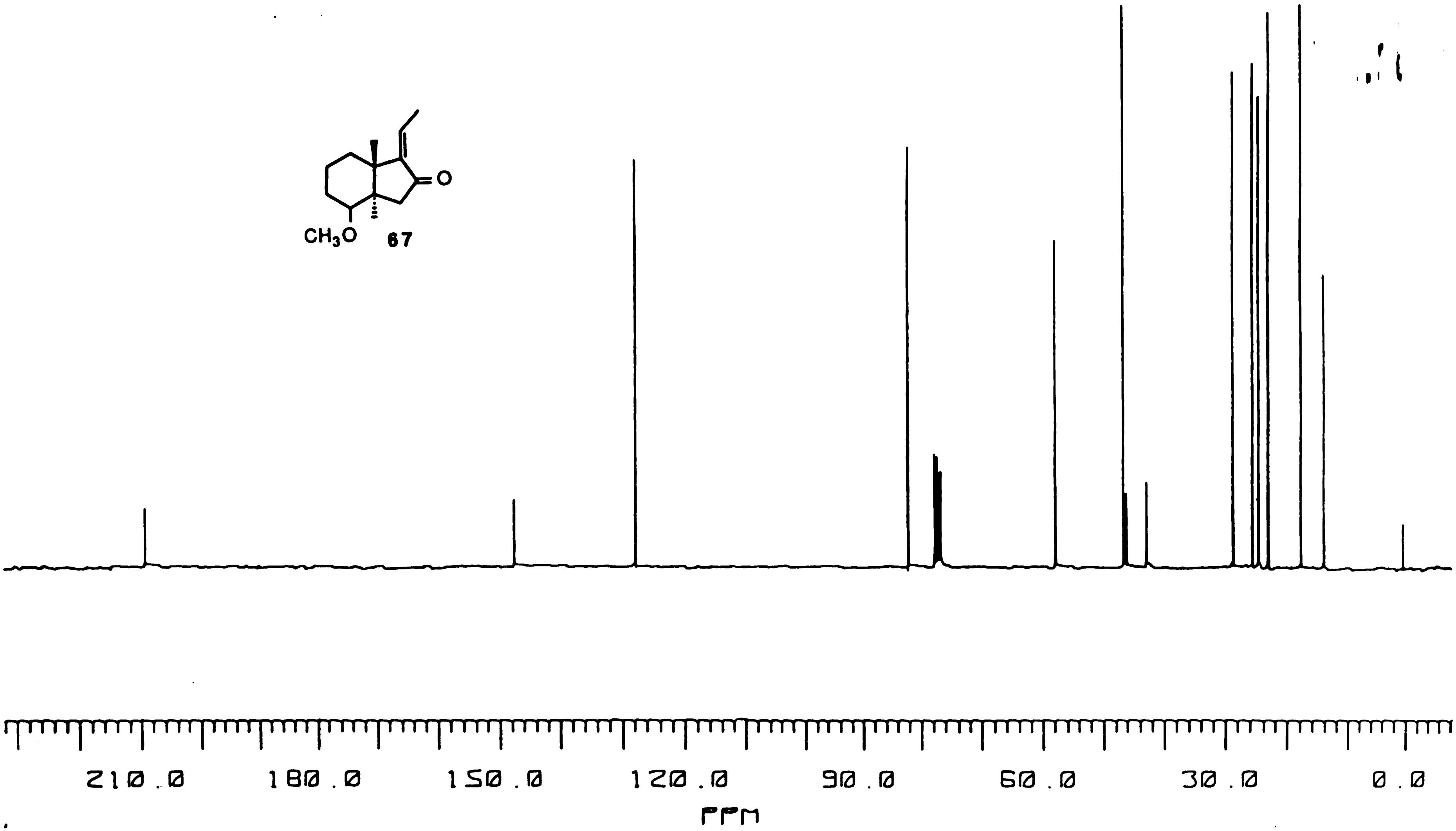


Figure 111. CMR spectrum of 67

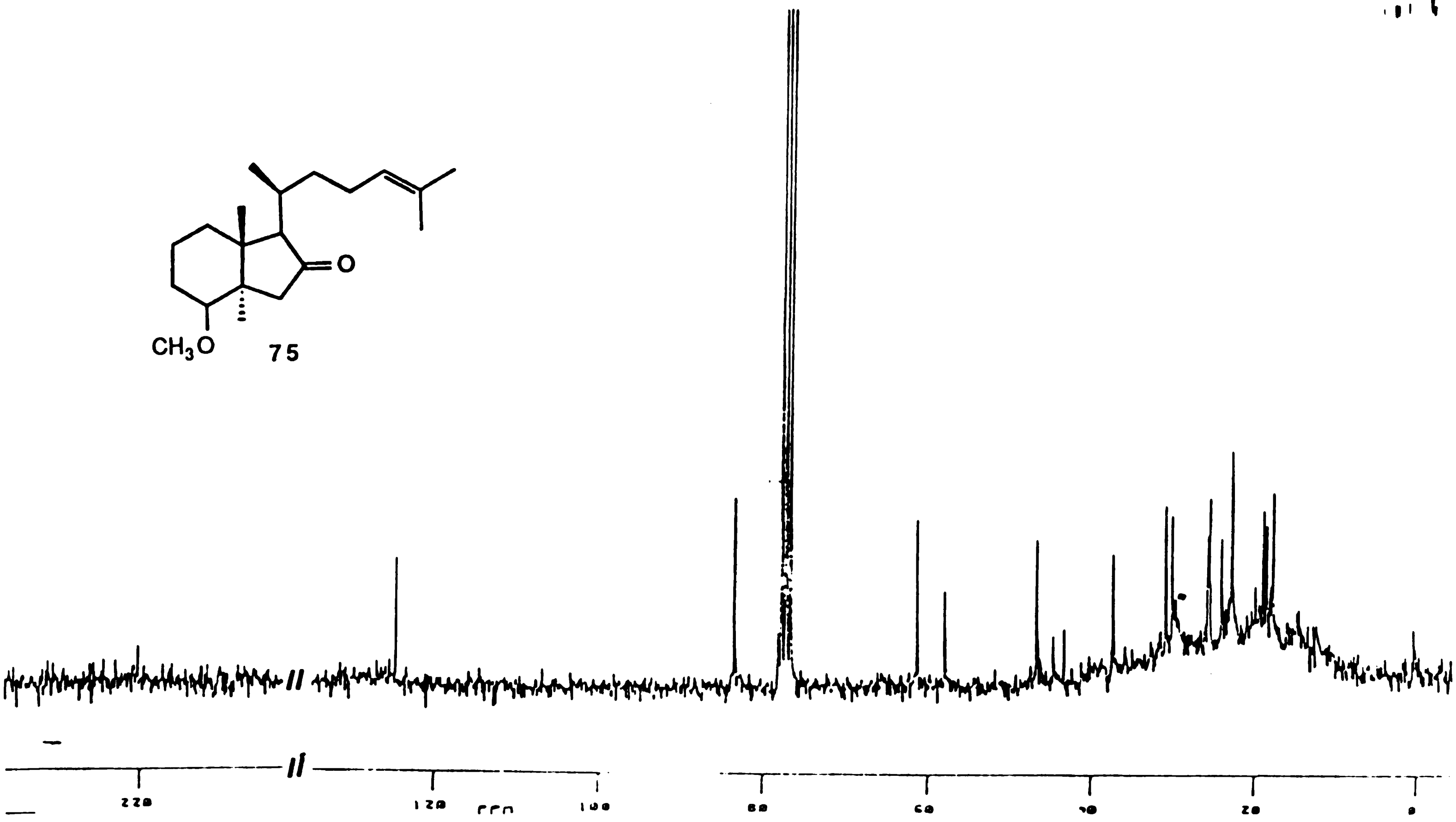


Figure 112. CMR spectrum of 75

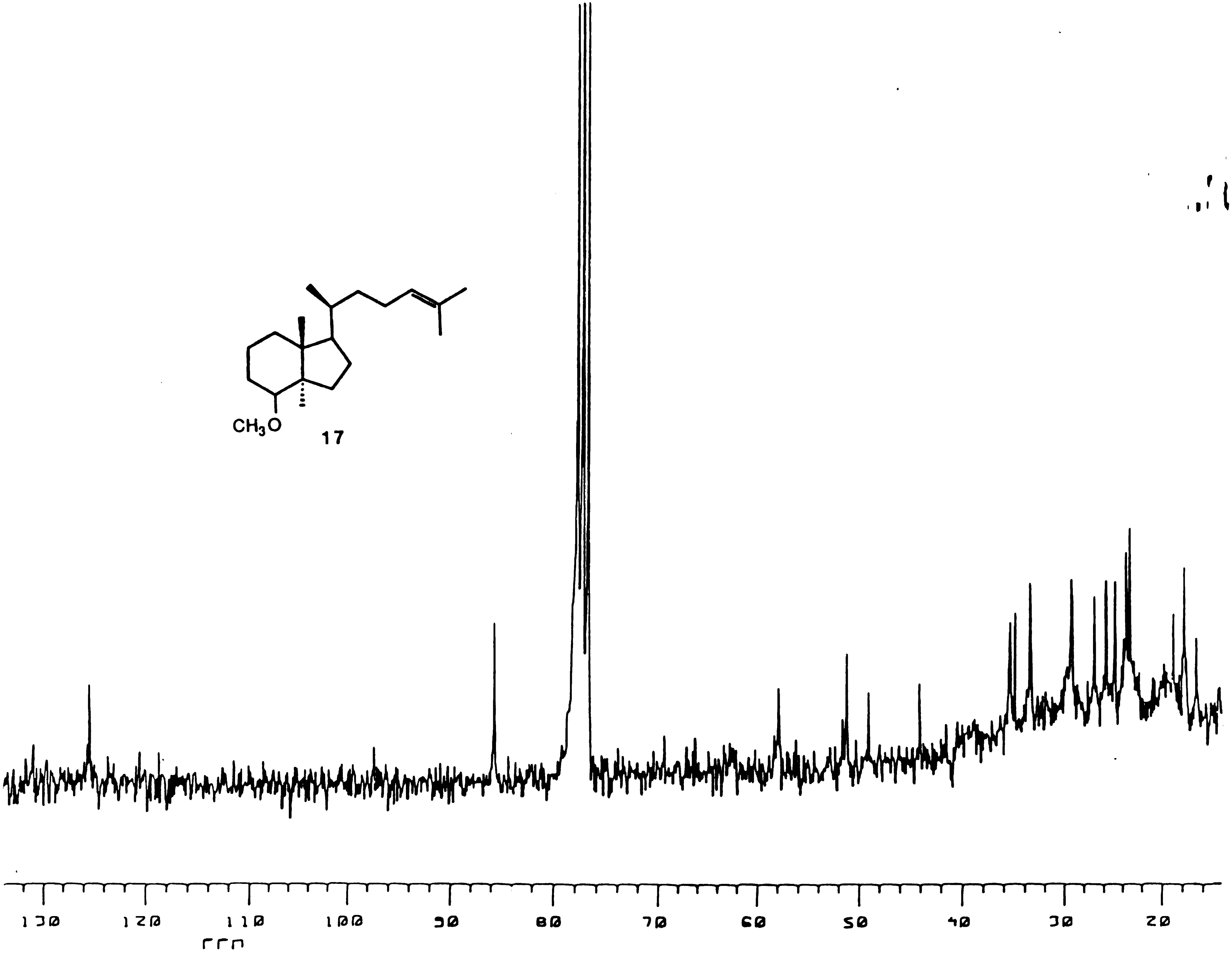


Figure 113. CMR spectrum of 17

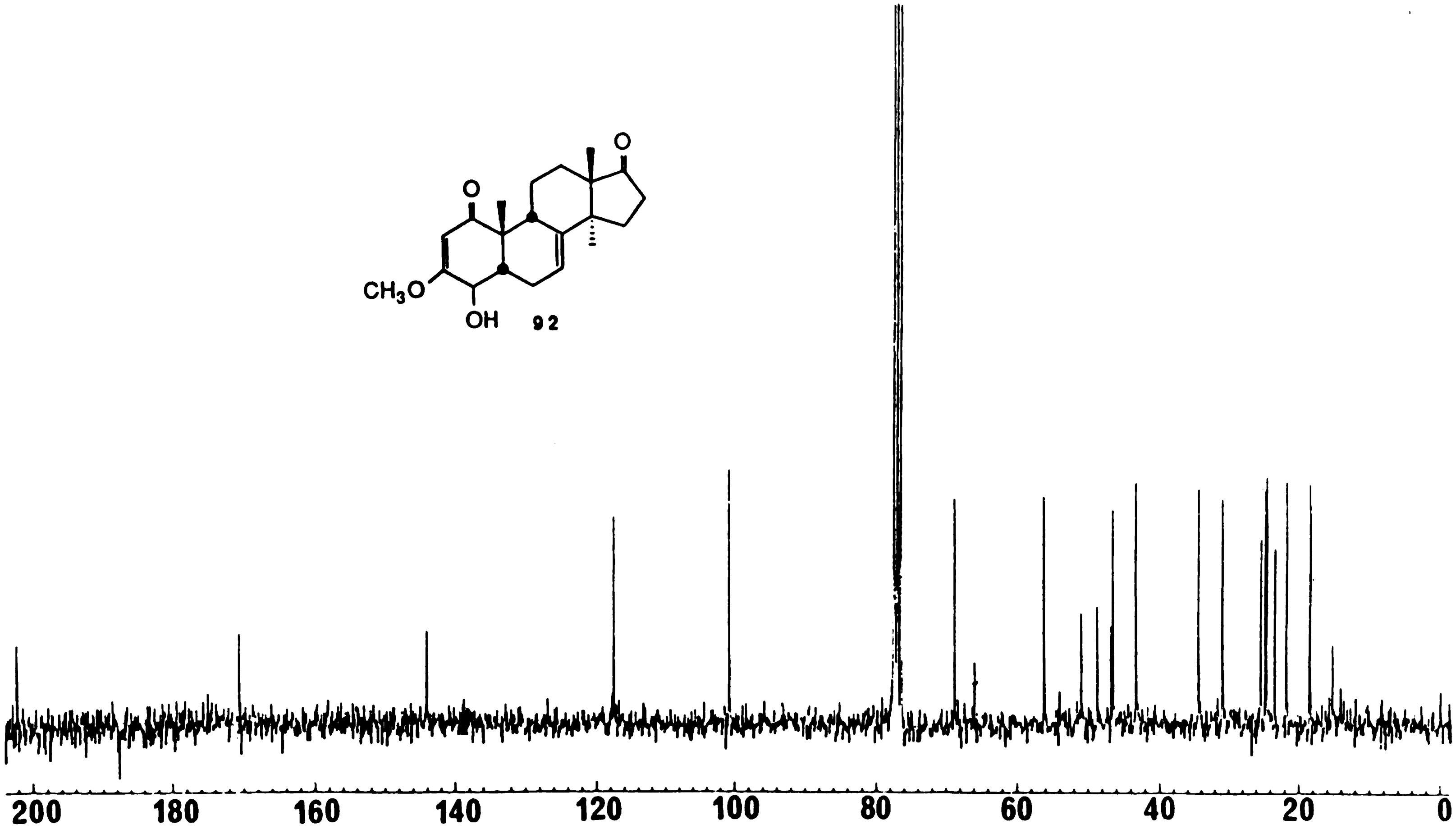


Figure 114. CMR spectrum of 92

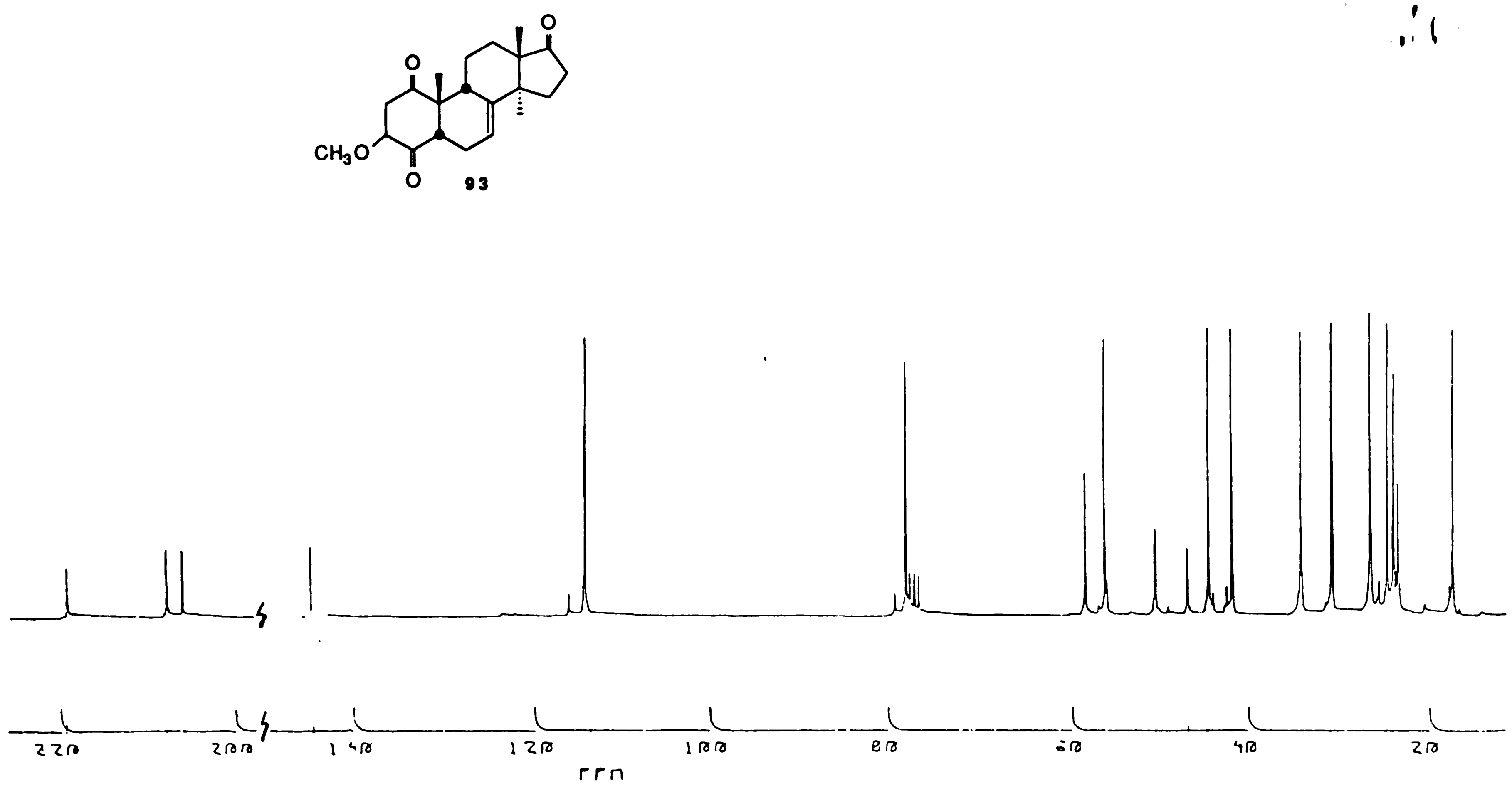


Figure 115. CMR spectrum of 93

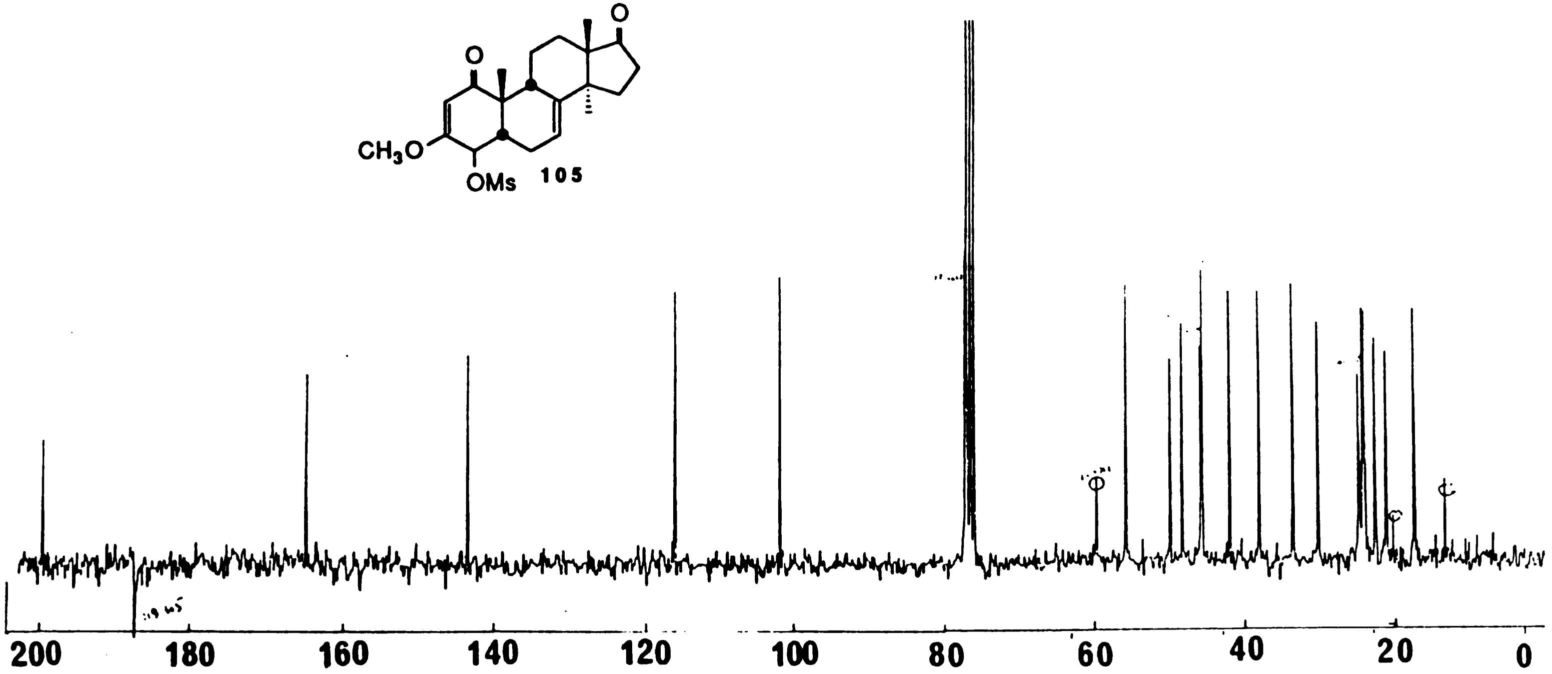


Figure 116. CMR spectrum of **105**

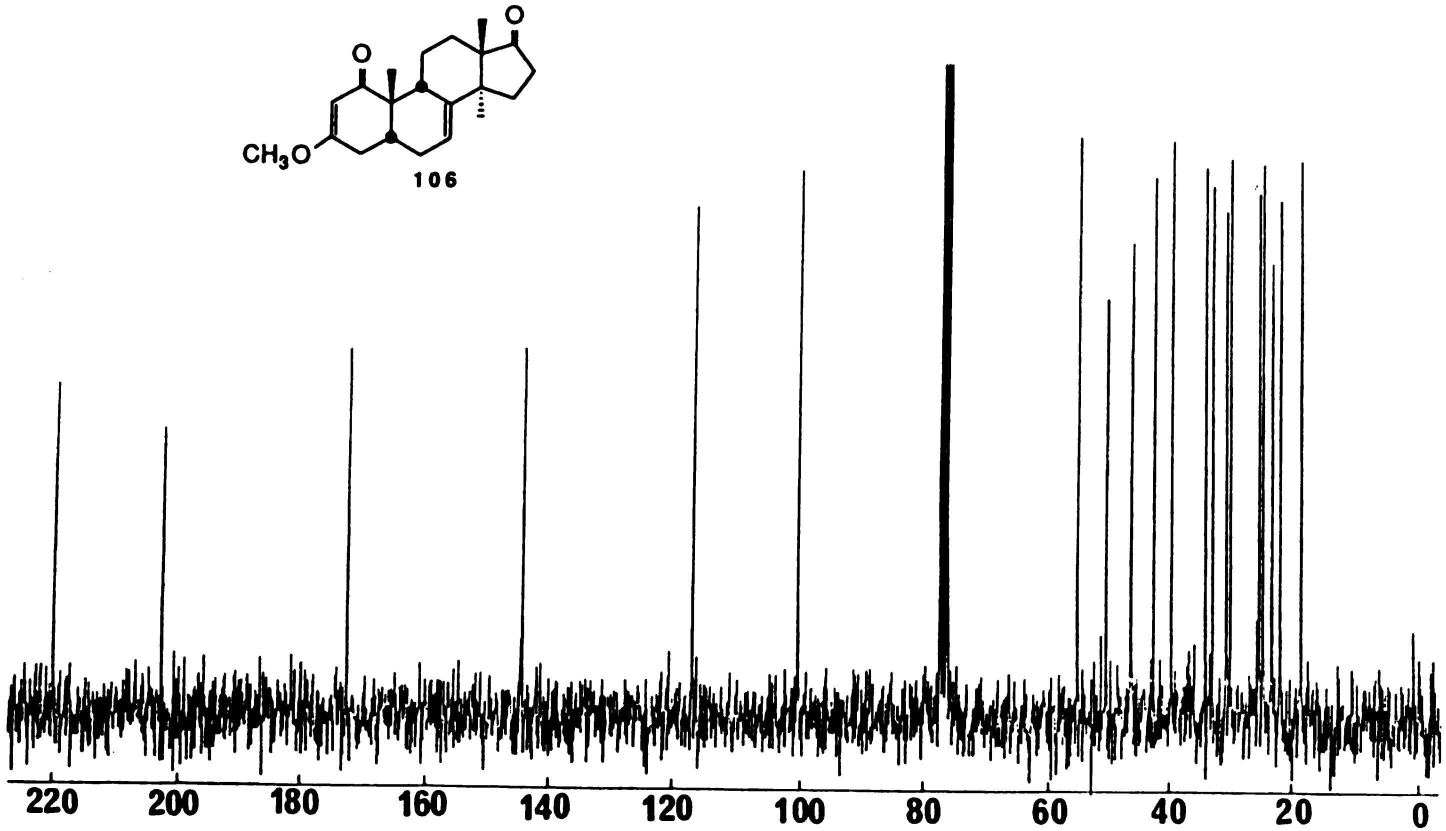


Figure 117. CMR spectrum of 106

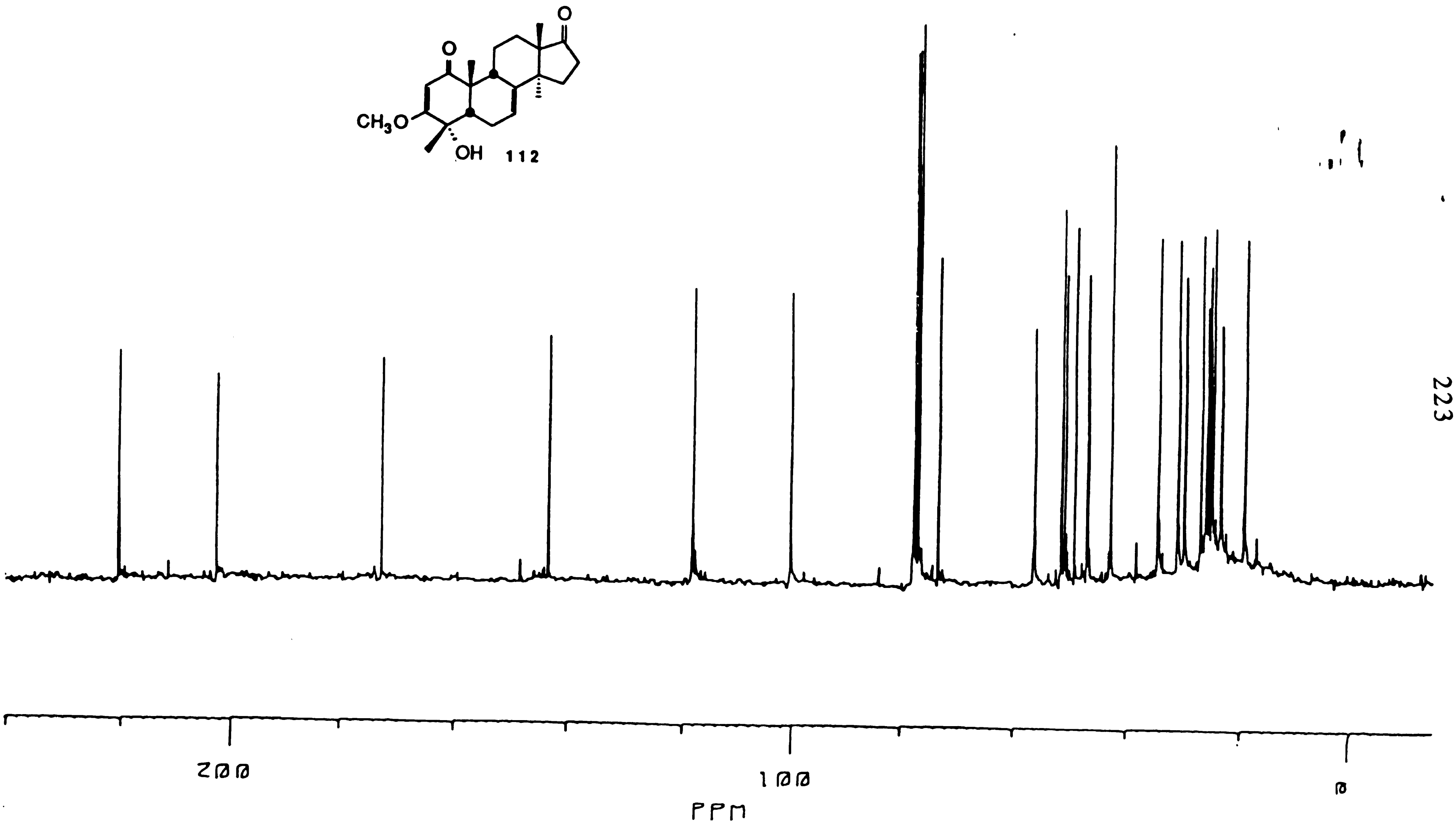


Figure 118. CMR spectrum of 112

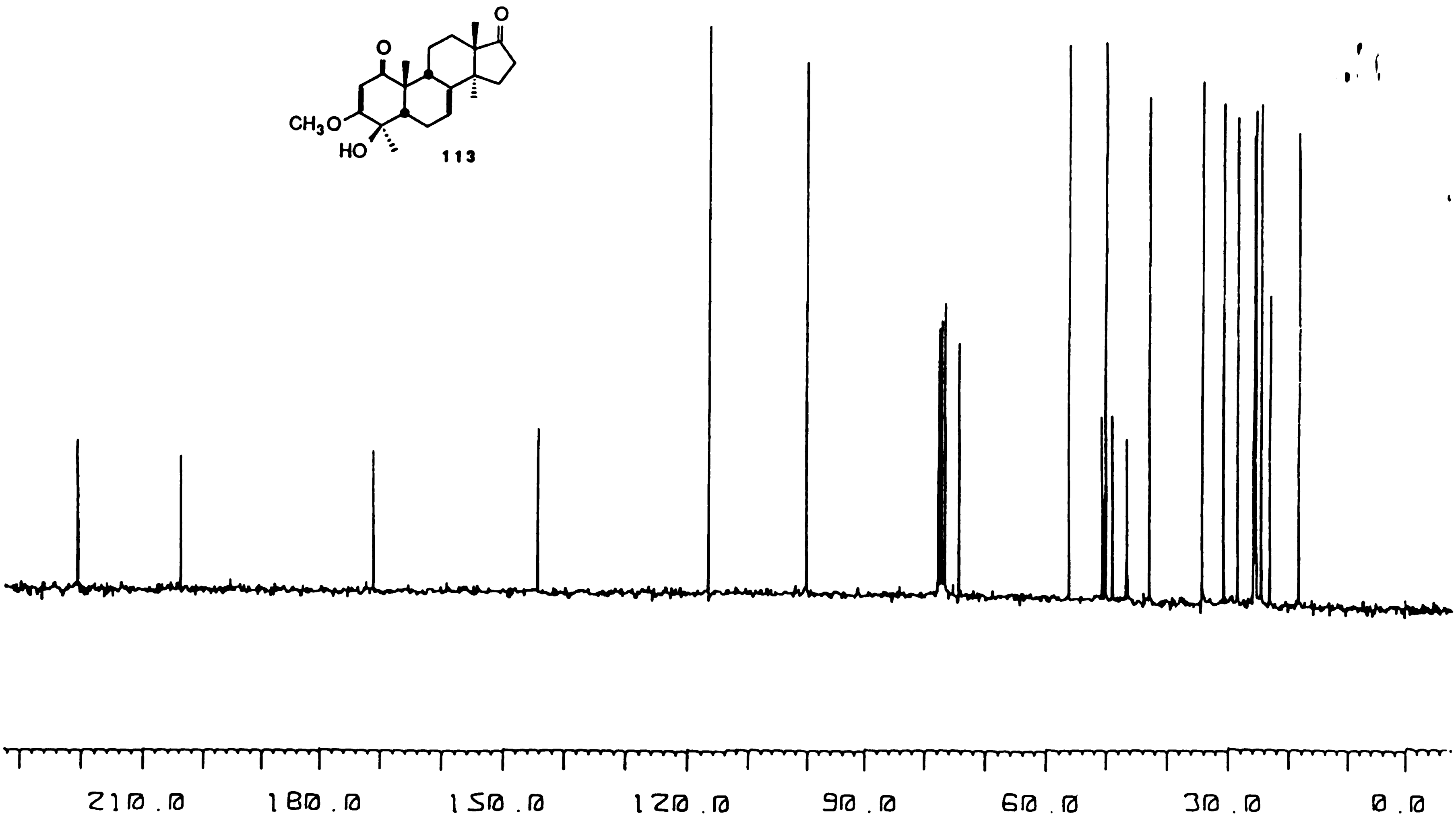


Figure 119. CMR spectrum of 113

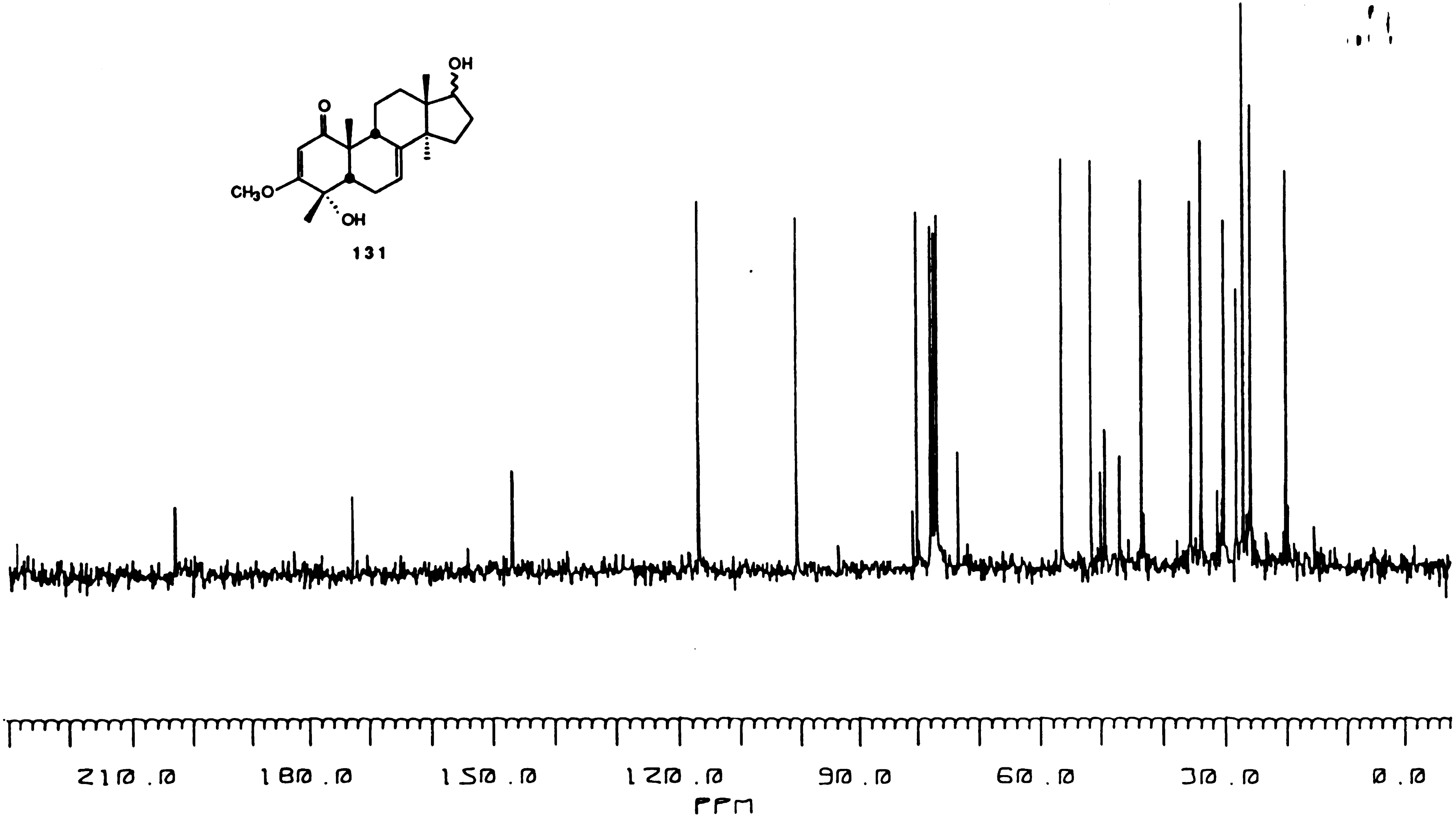


Figure 120. CMR spectrum of 131

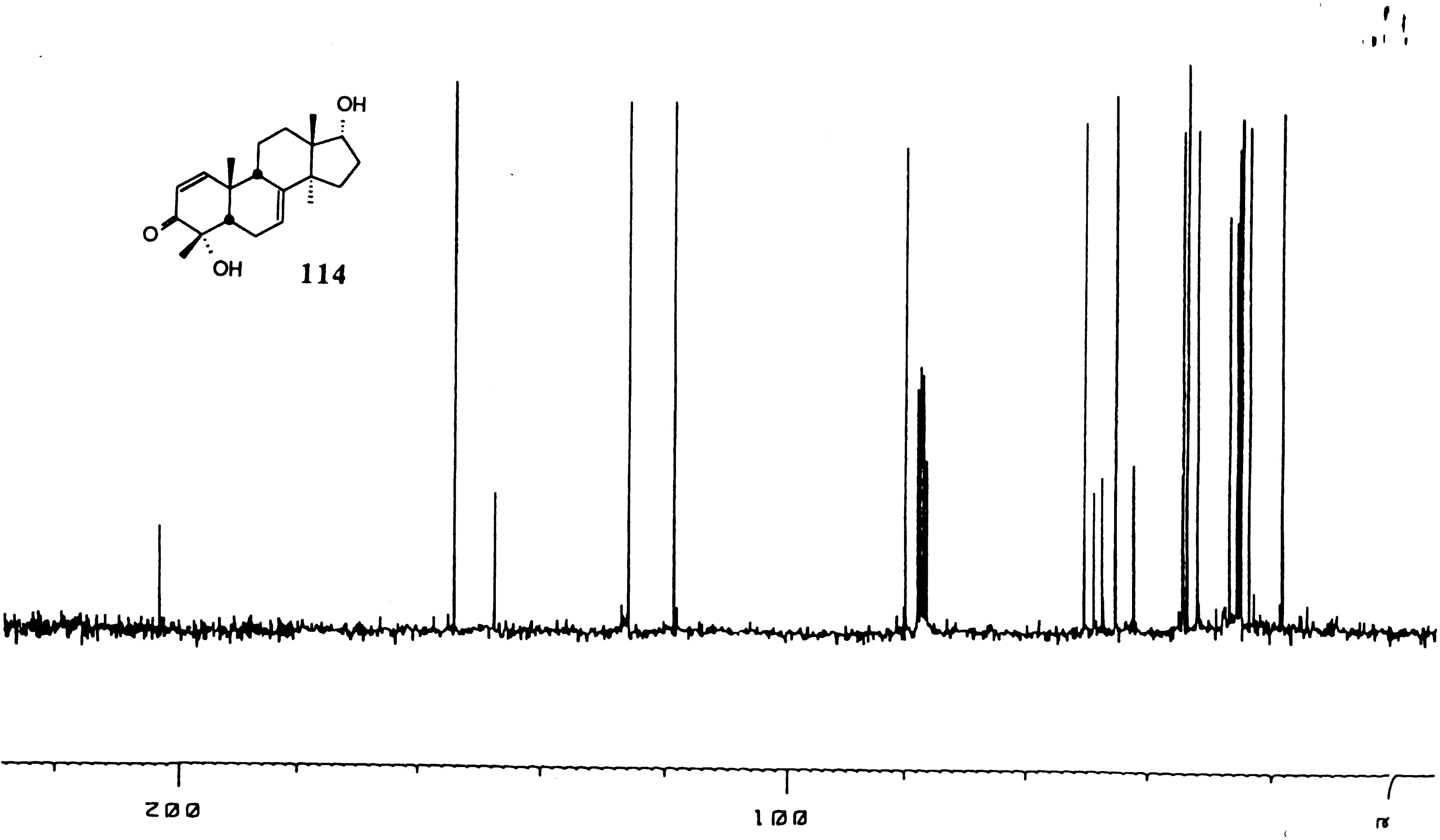


Figure 121. CMR spectrum of 114

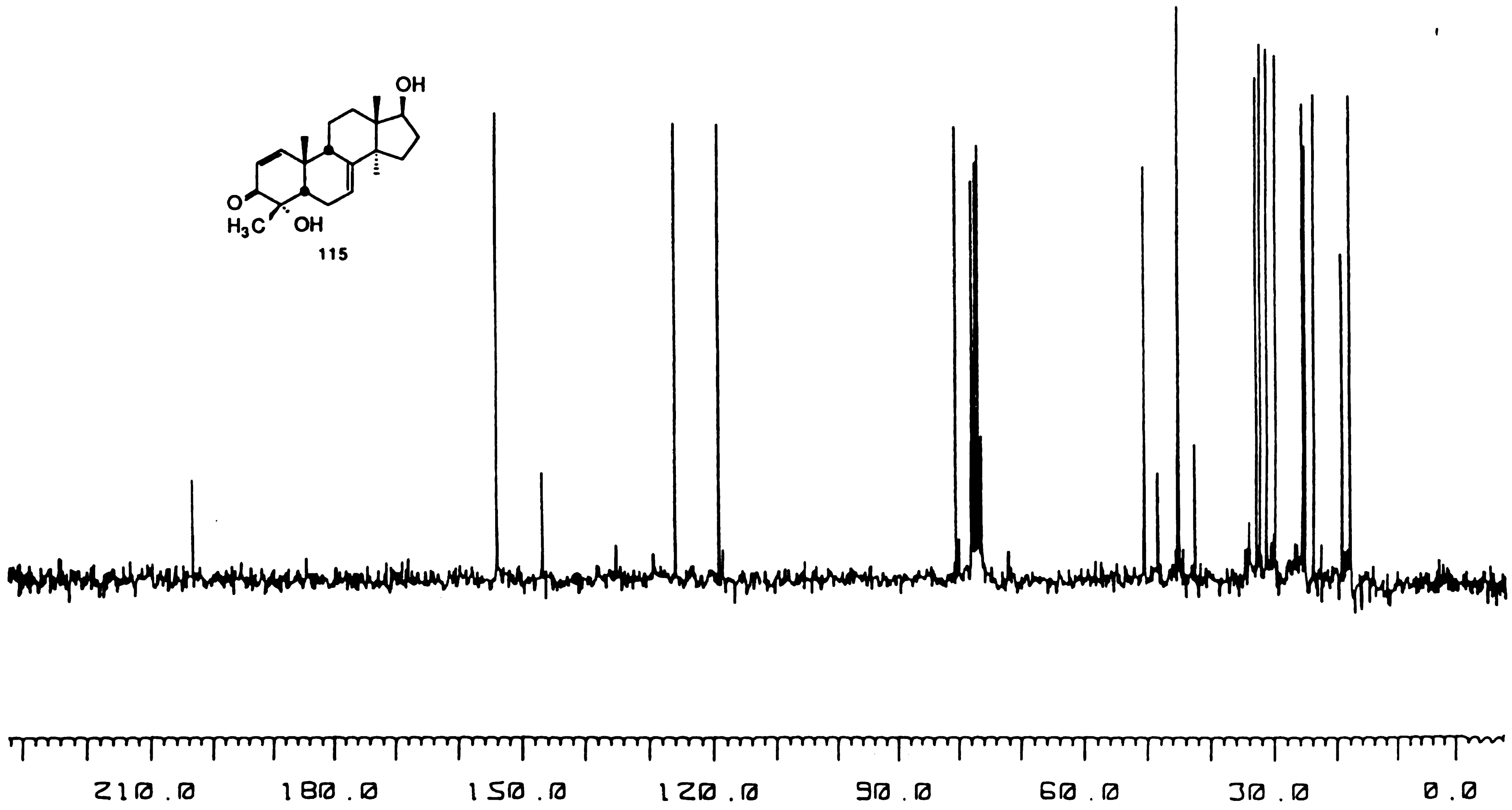


Figure 122. CMR spectrum of **115**

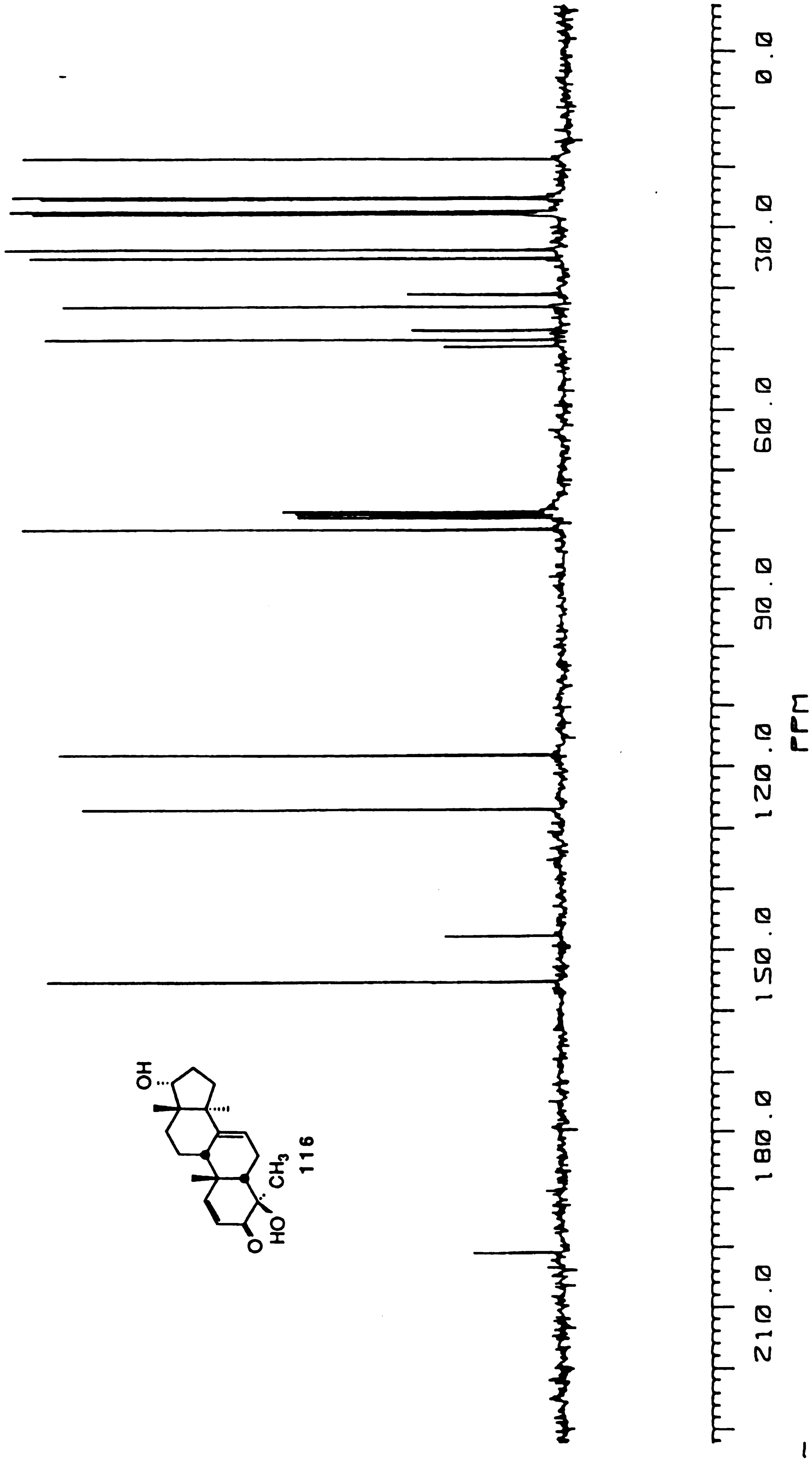
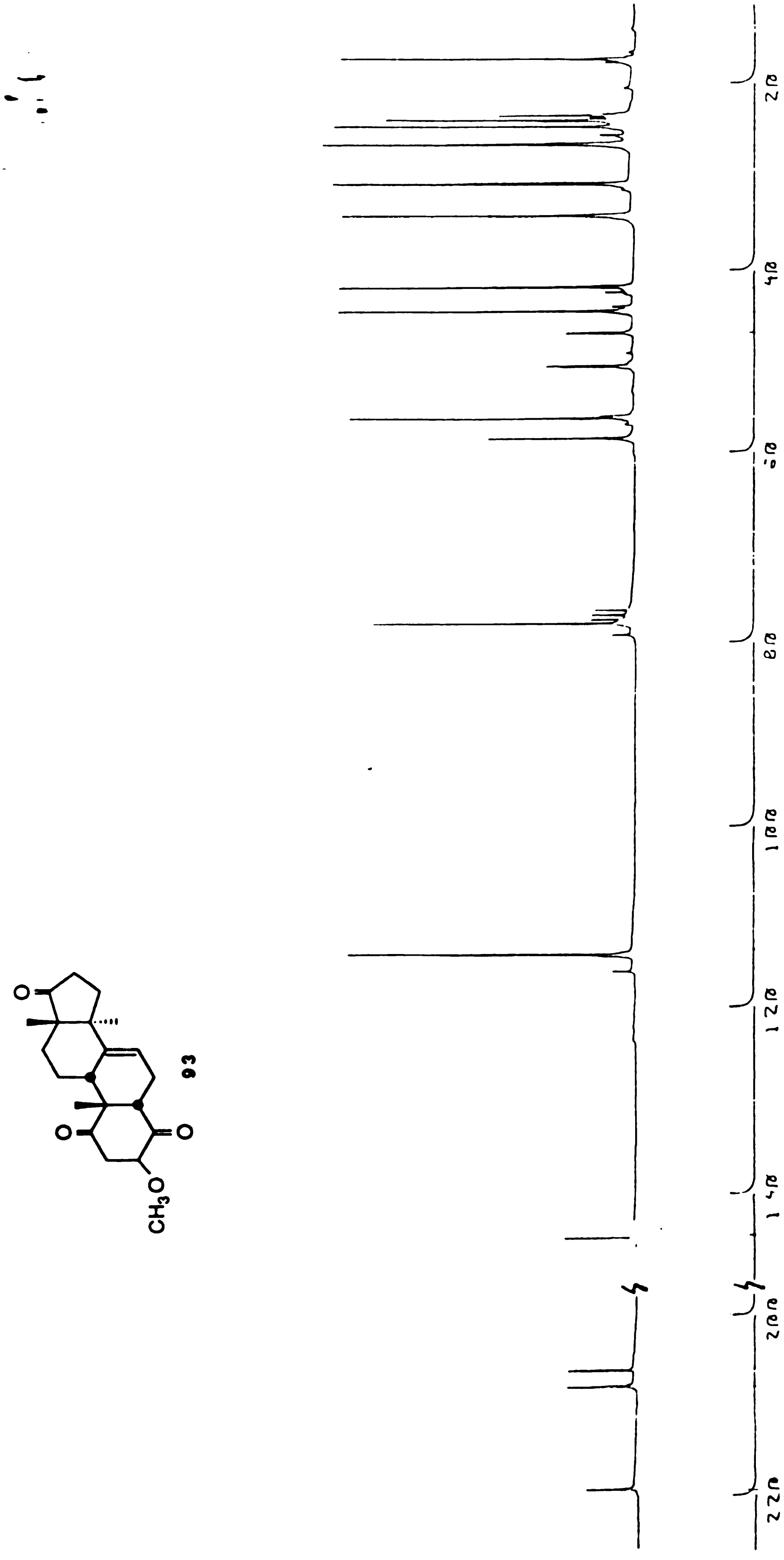


Figure 123. CMR spectrum of 116



93

Figure 115. CMR spectrum of 93

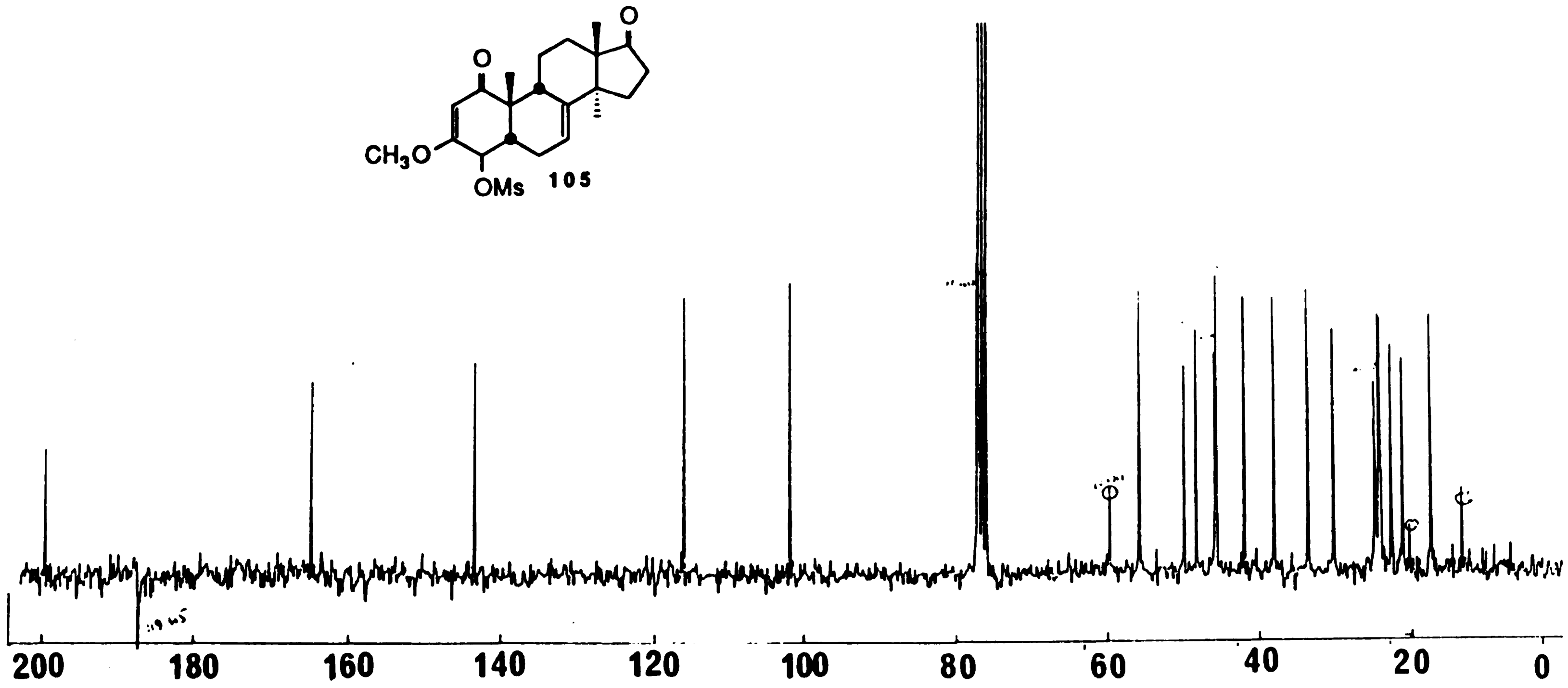


Figure 116. CMR spectrum of 105

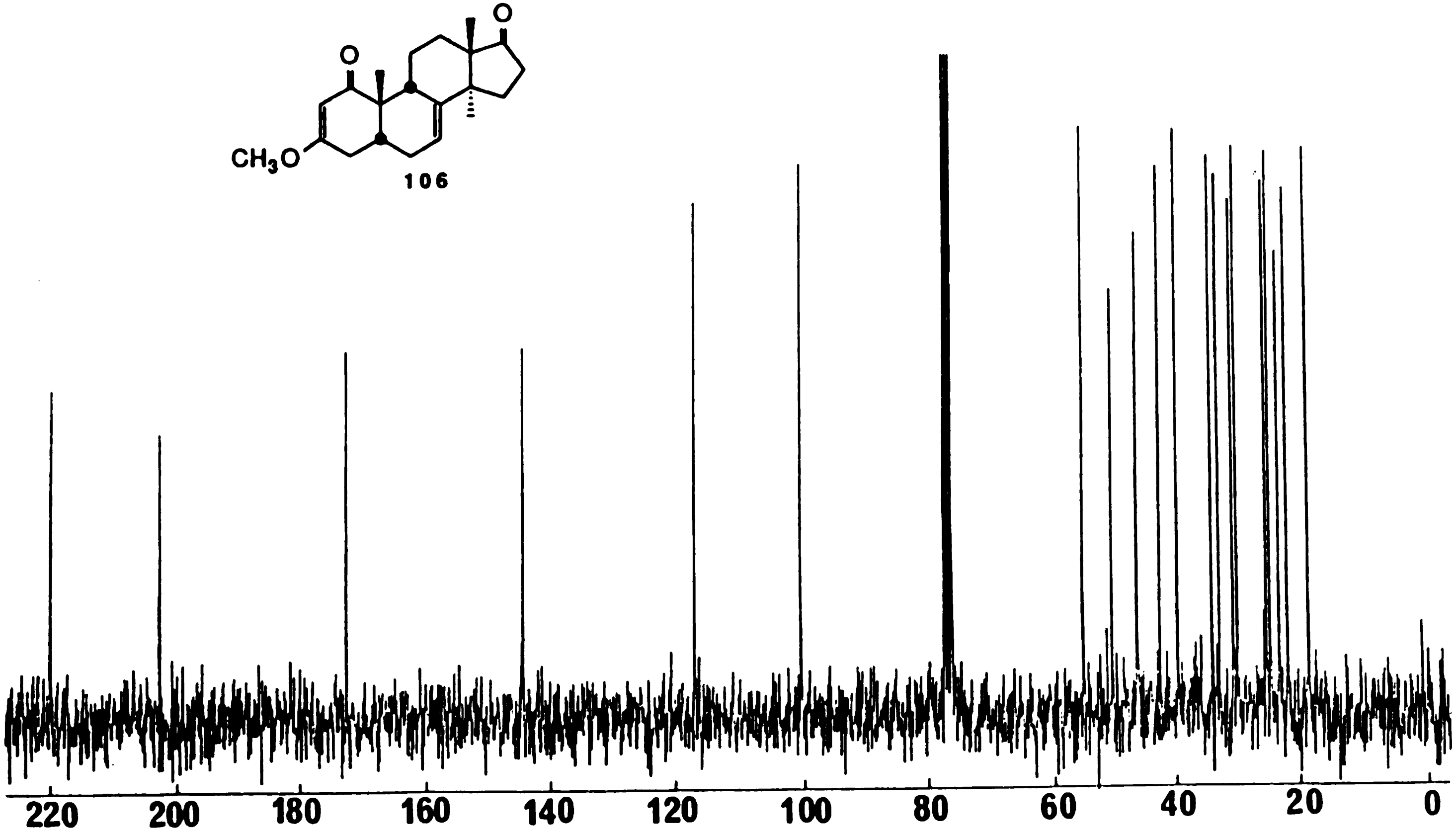


Figure 117. CMR spectrum of **106**

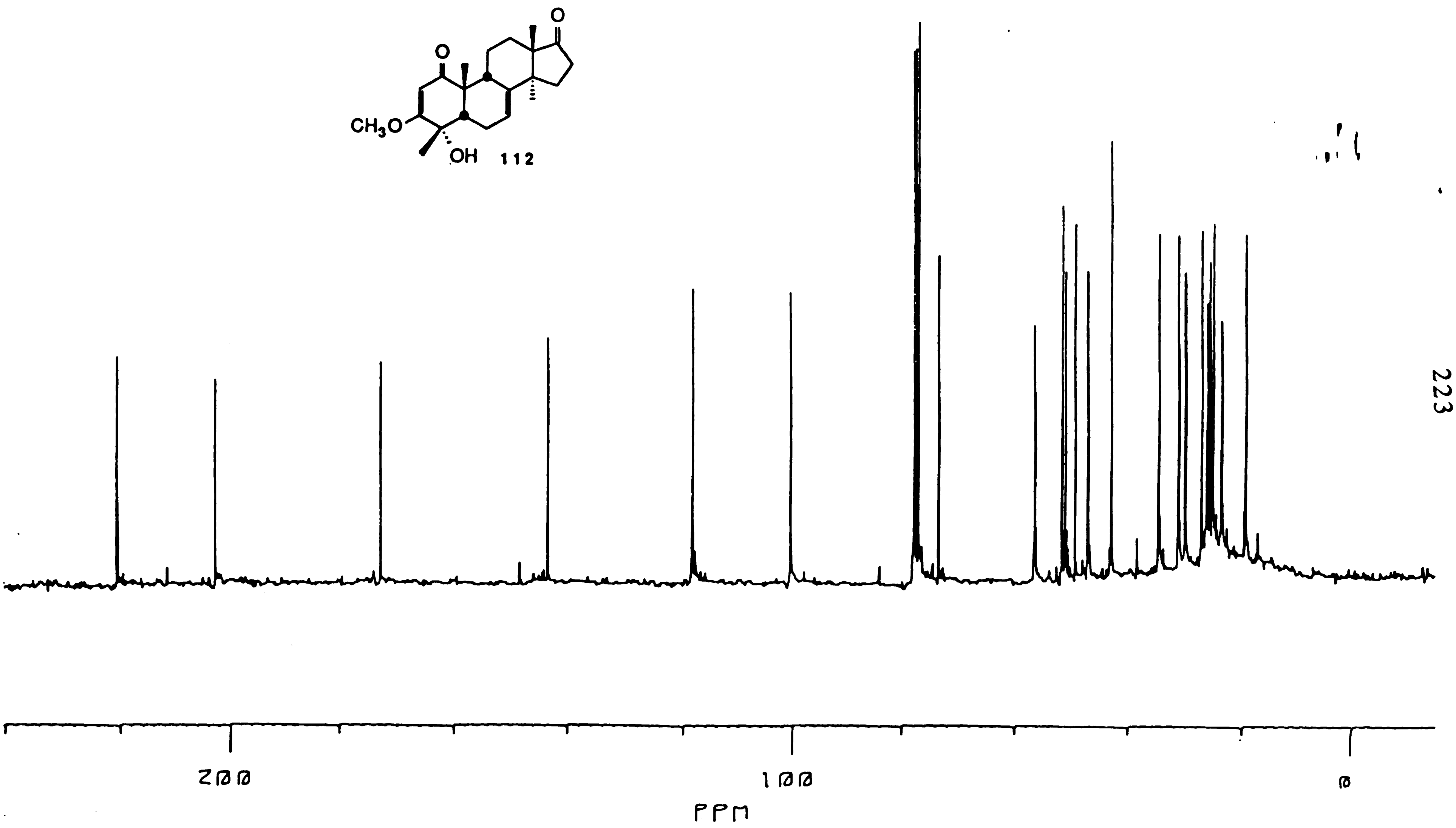


Figure 118. CMR spectrum of 112

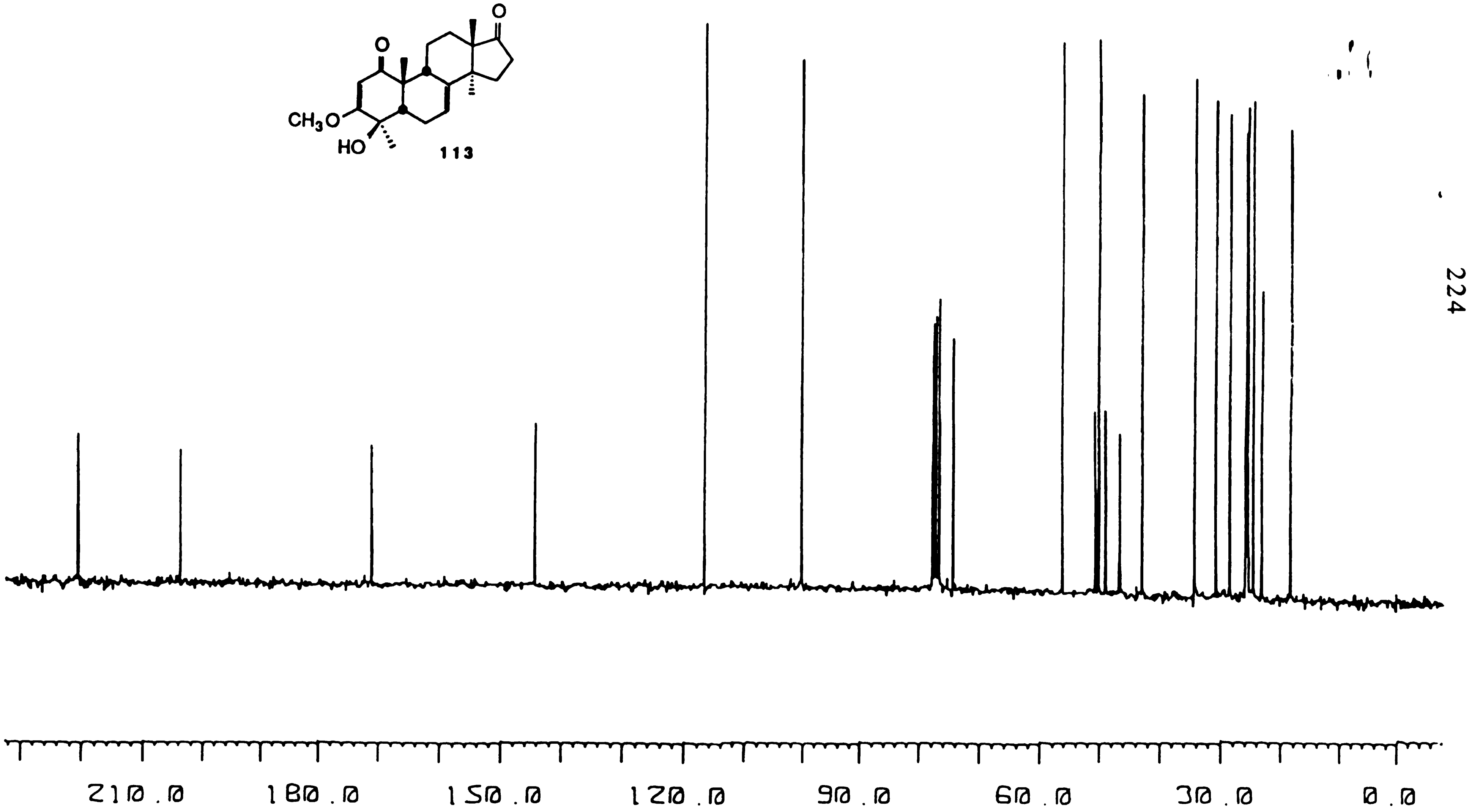


Figure 119. CMR spectrum of 113

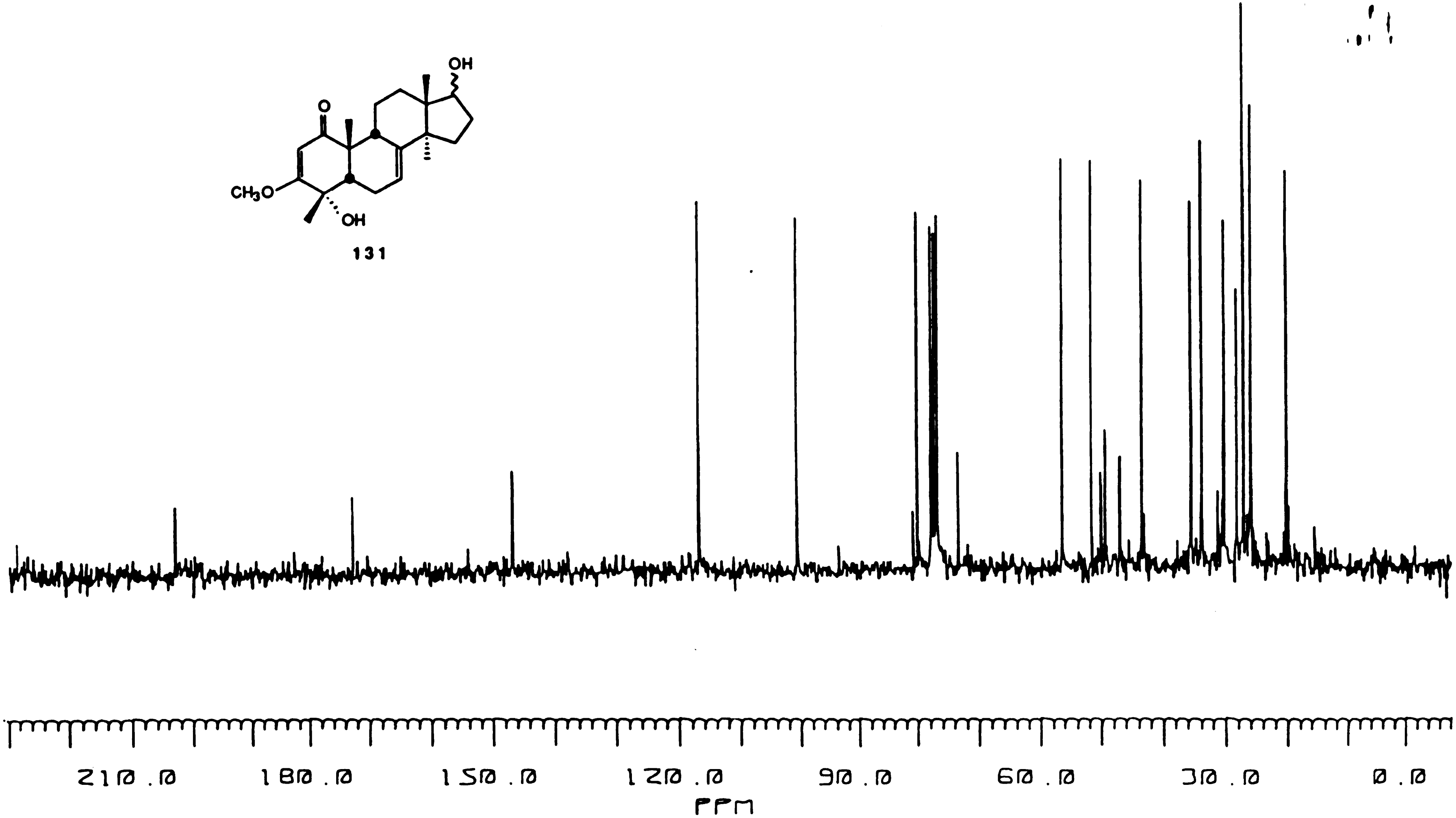


Figure 120. CMR spectrum of 131

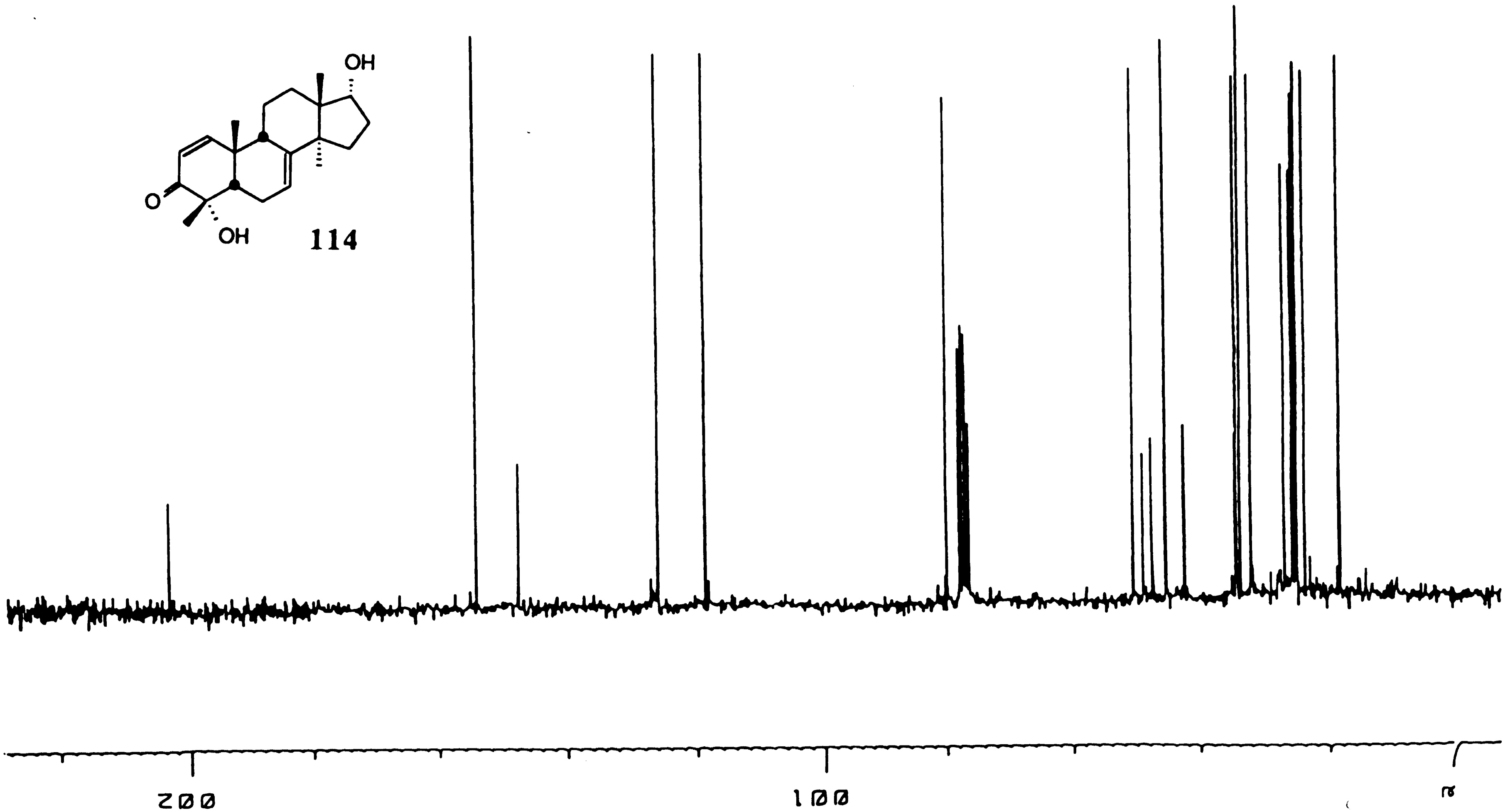


Figure 121. CMR spectrum of 114

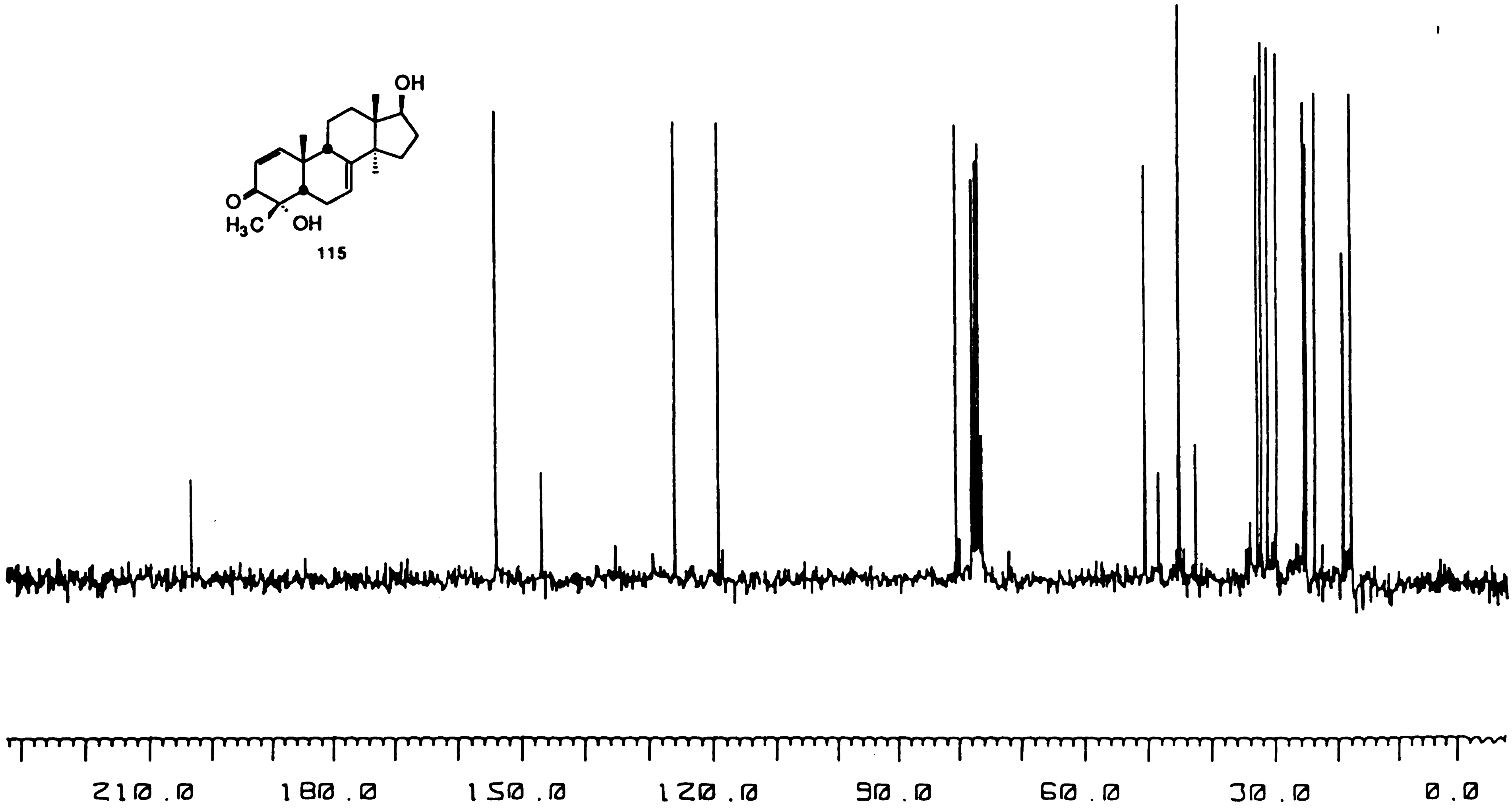


Figure 122. CMR spectrum of 115

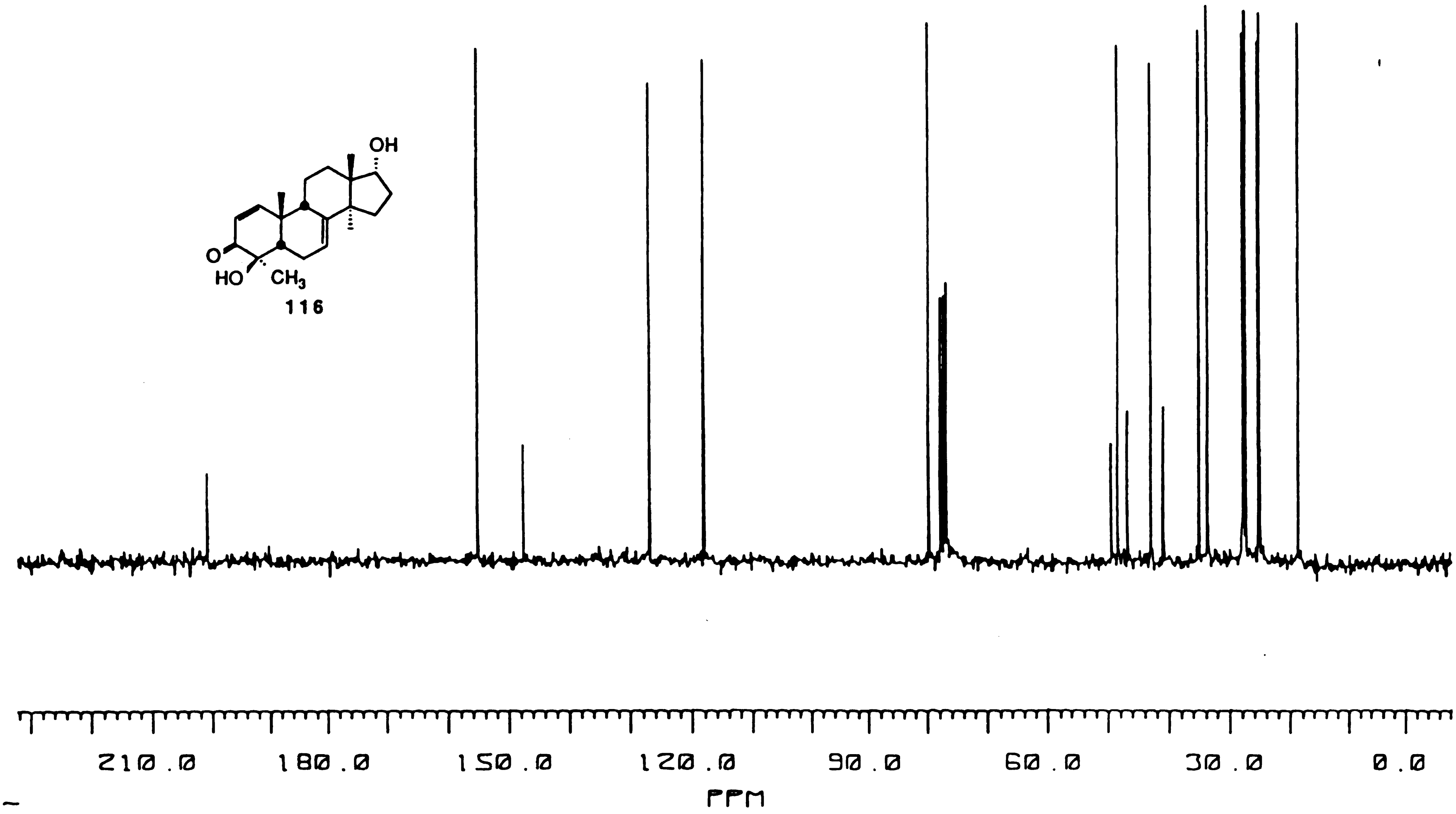


Figure 123. CMR spectrum of **116**

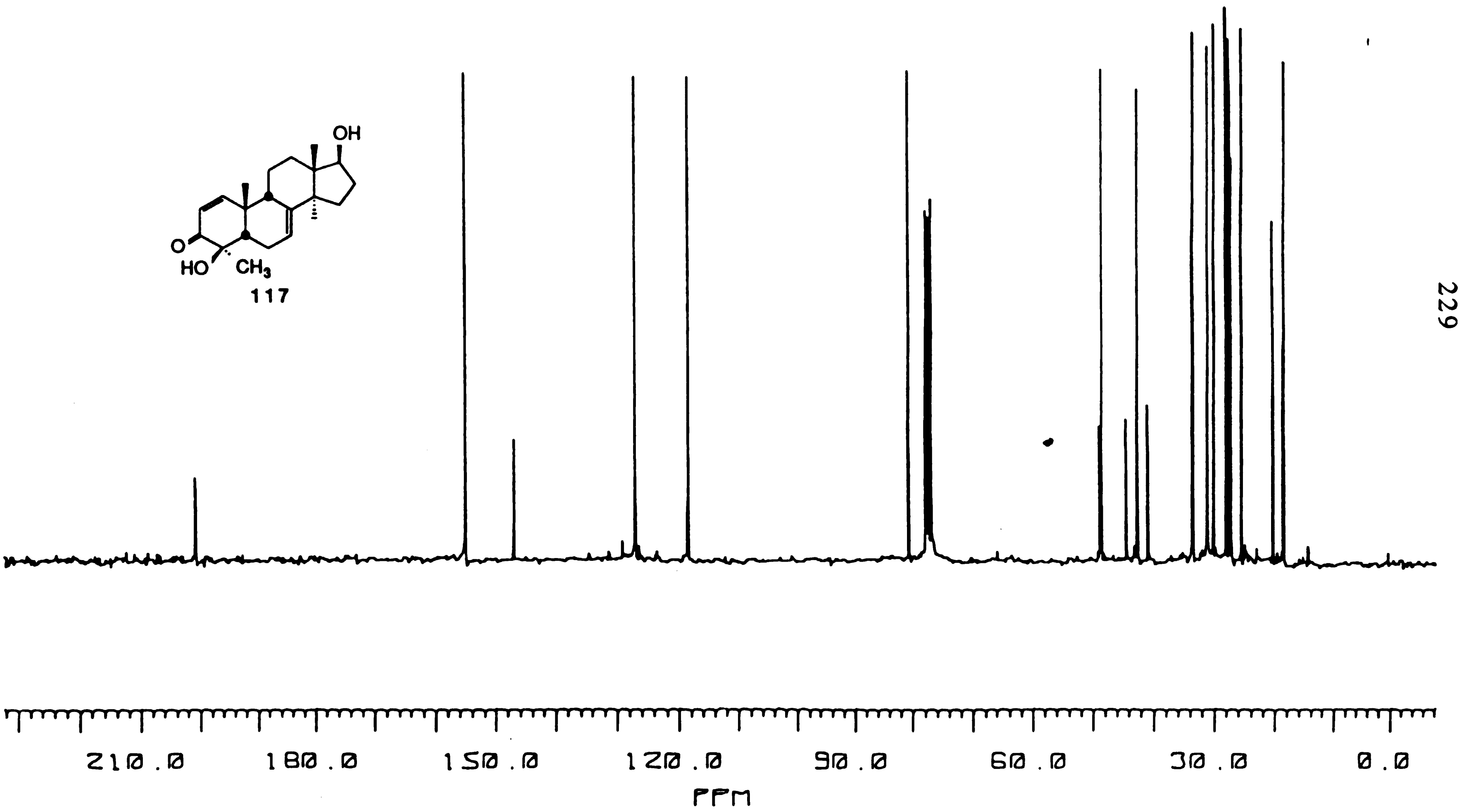
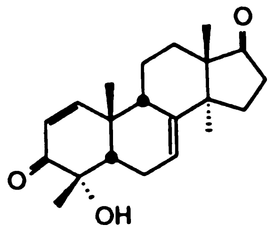


Figure 124. CMR spectrum of **117**



118

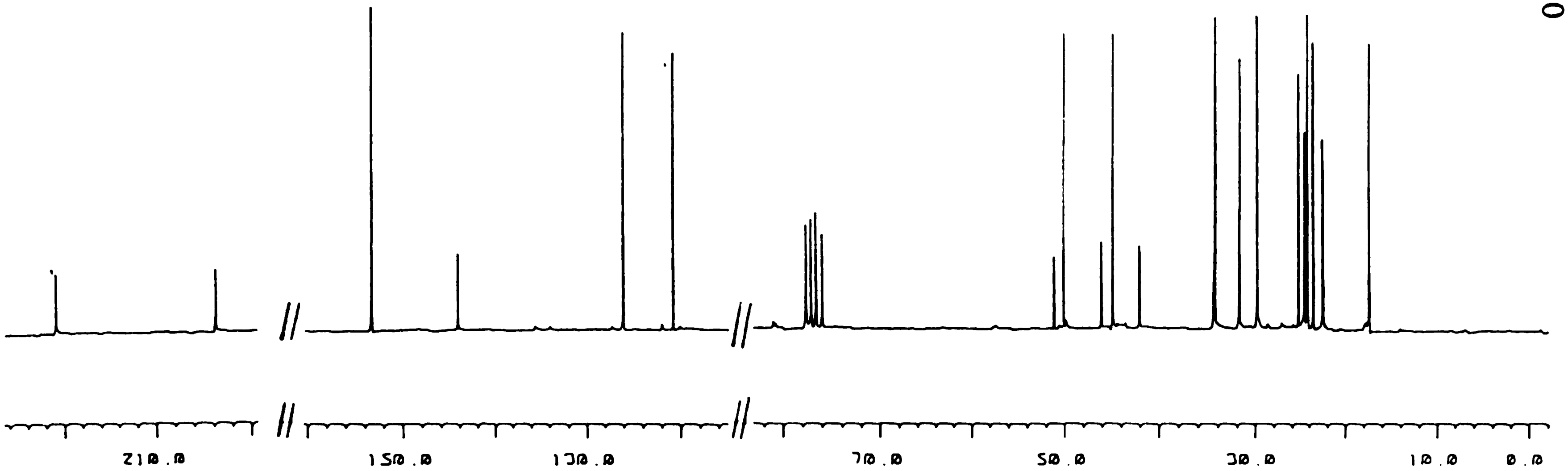


Figure 125. CMR spectrum of 118

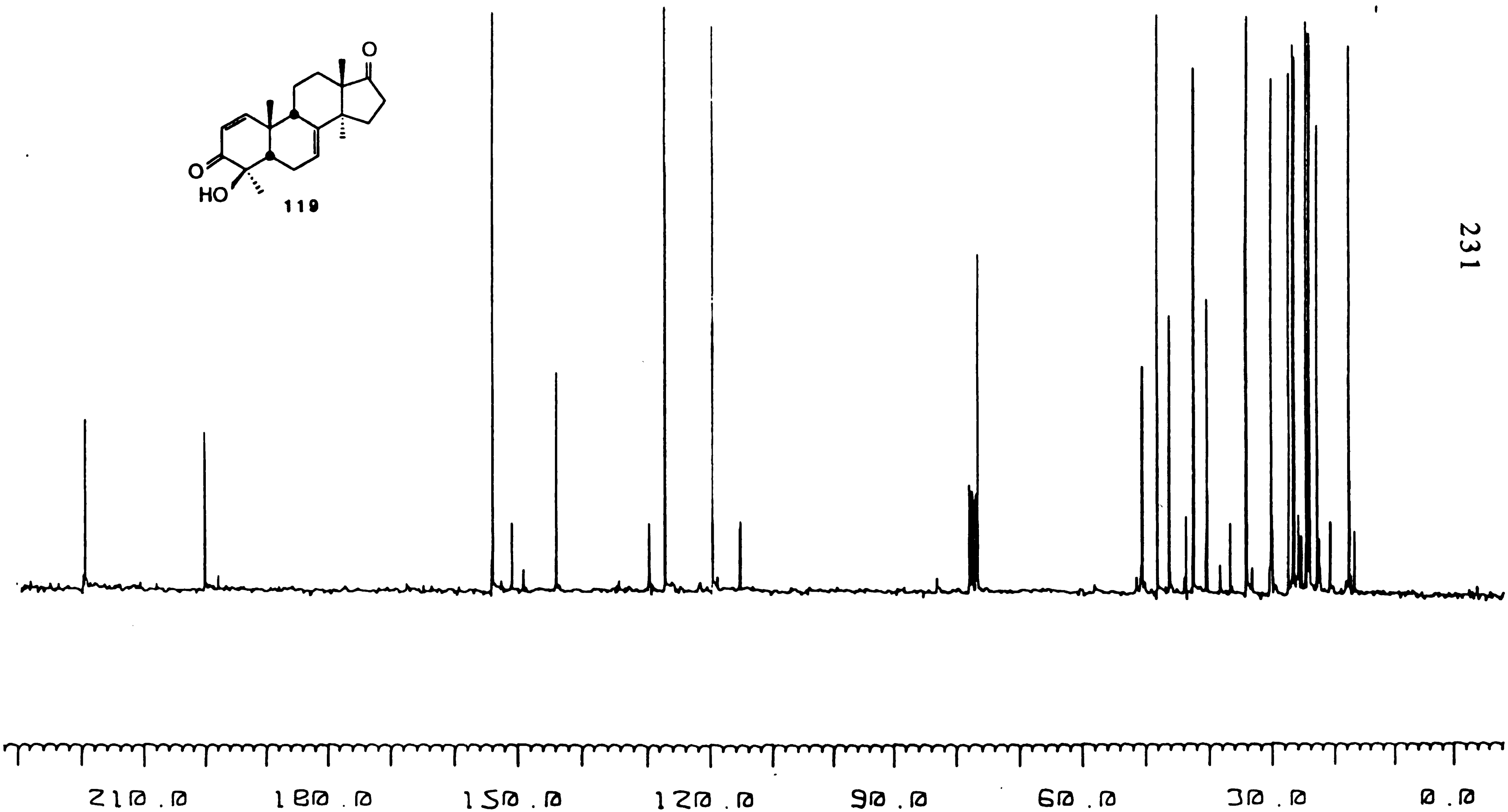


Figure 126. CMR spectrum of 119

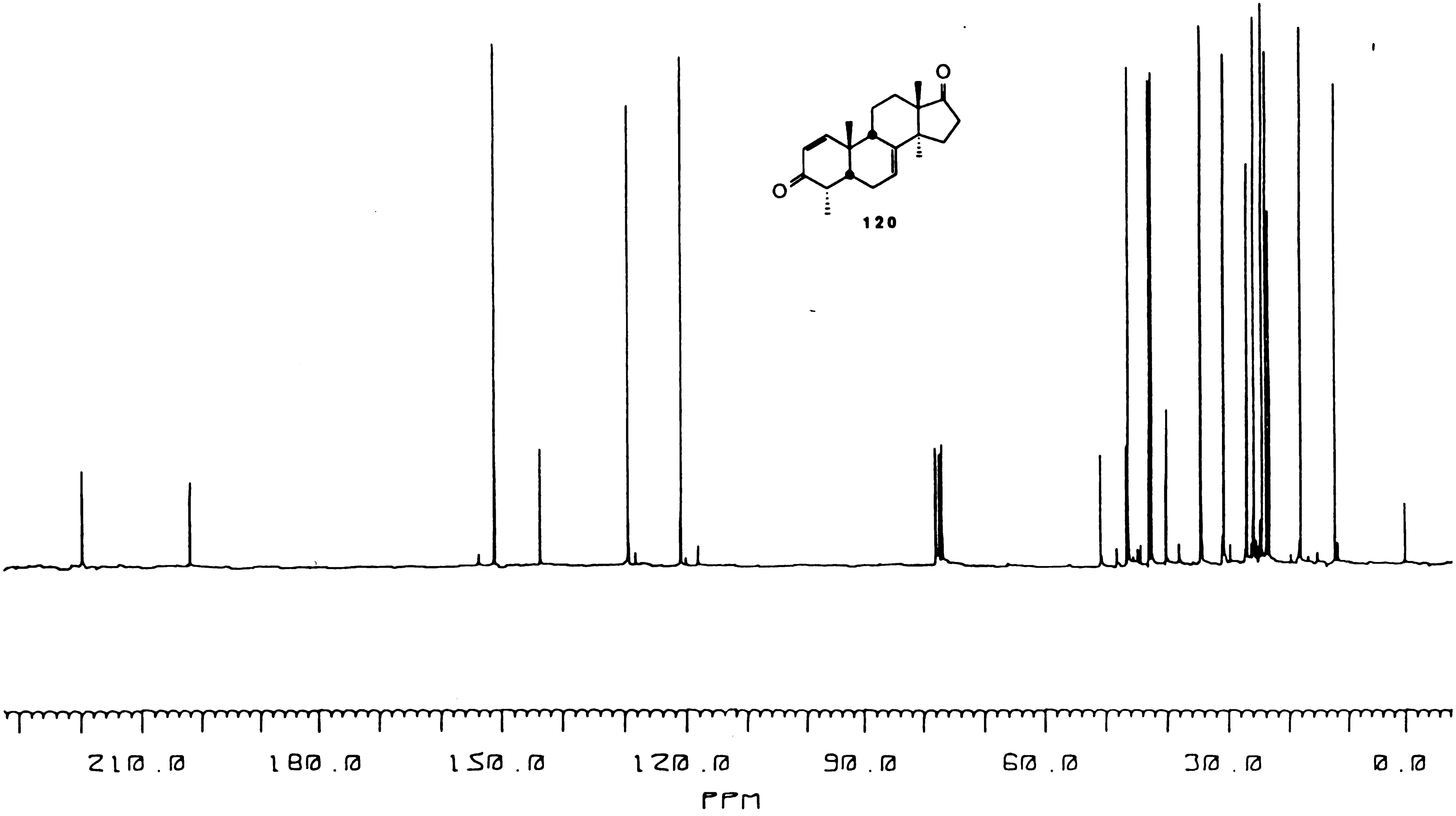


Figure 127. CMR spectrum of **120**

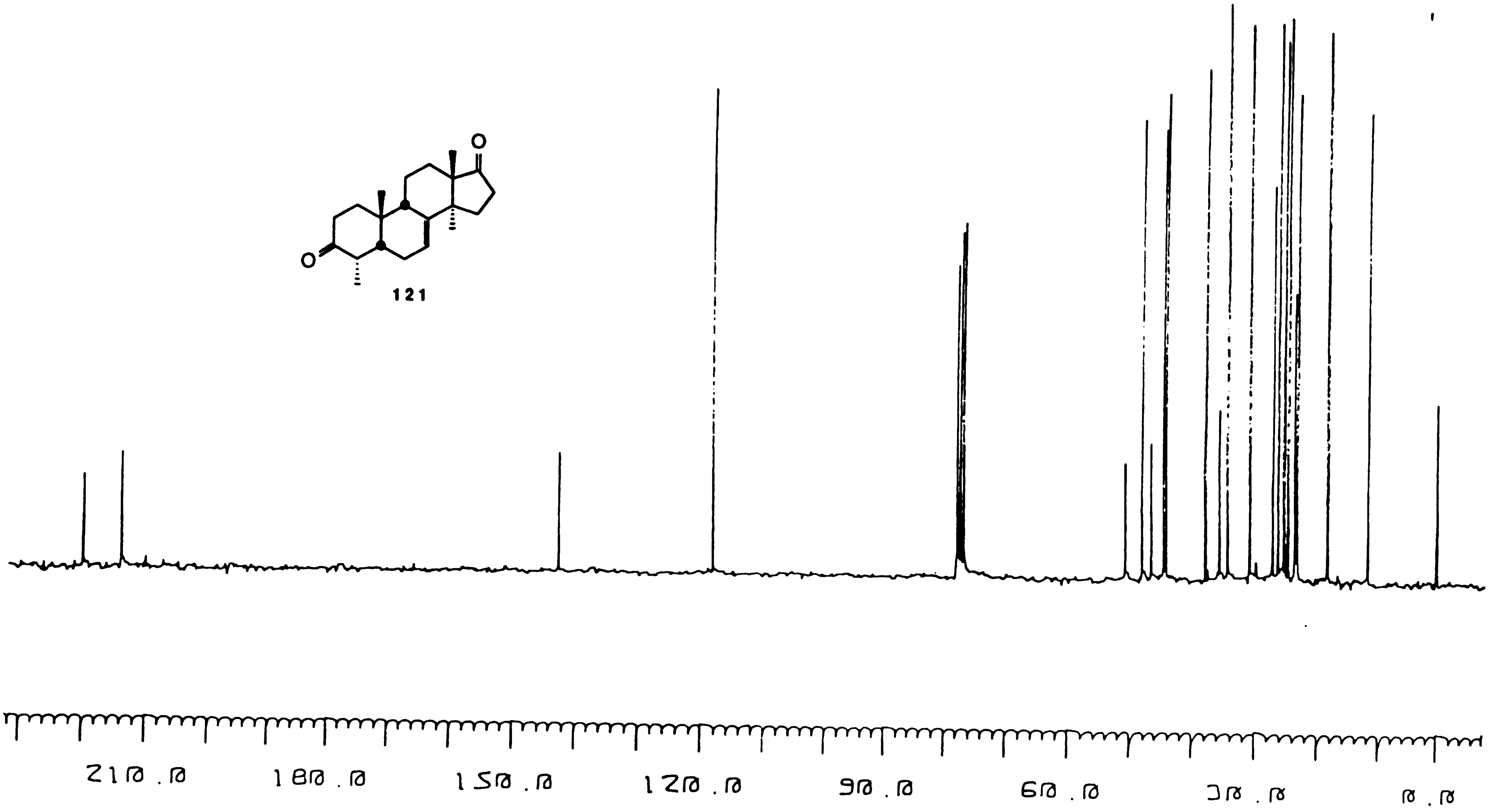


Figure 128. CMR spectrum of 121

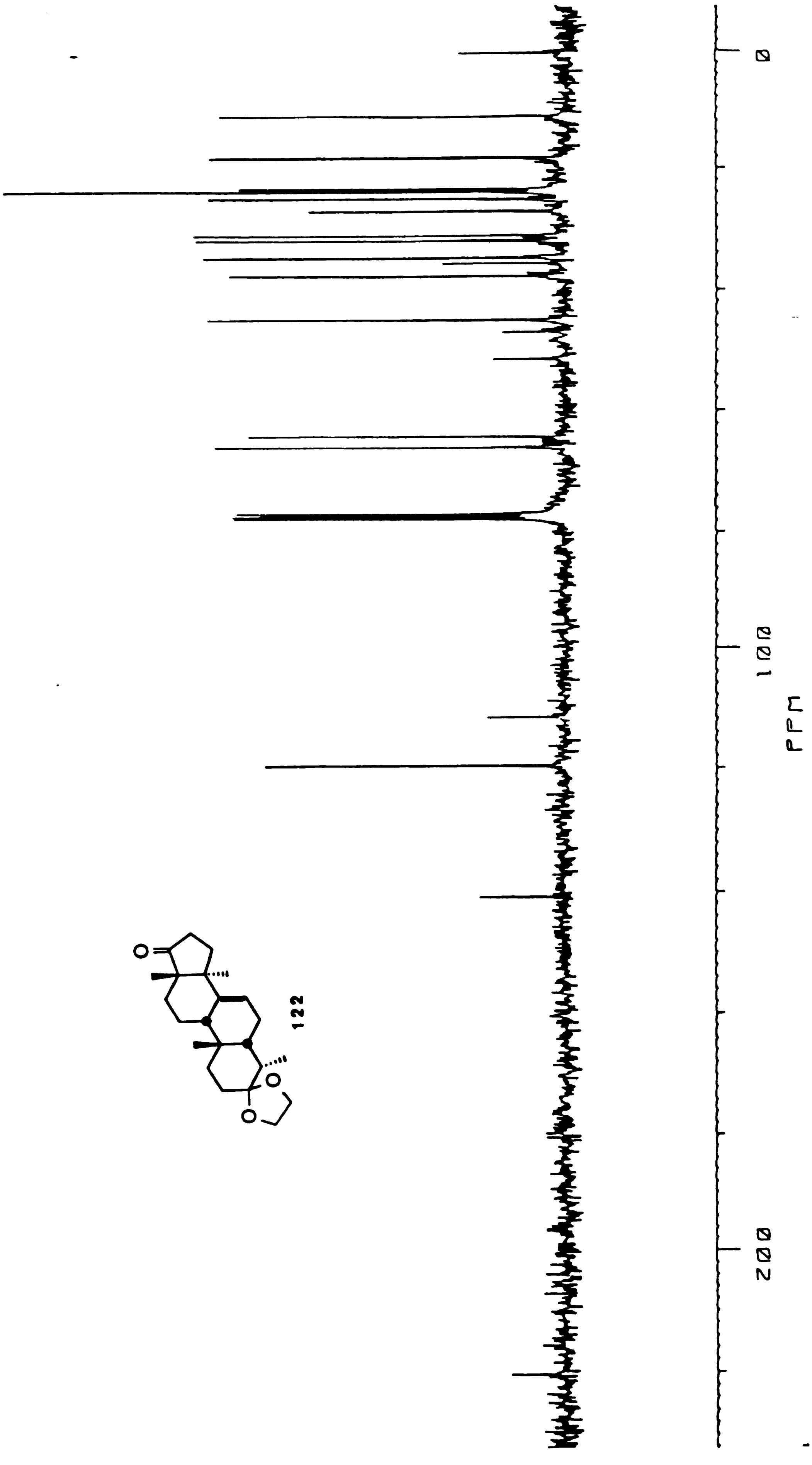


Figure 129. CMR spectrum of 122

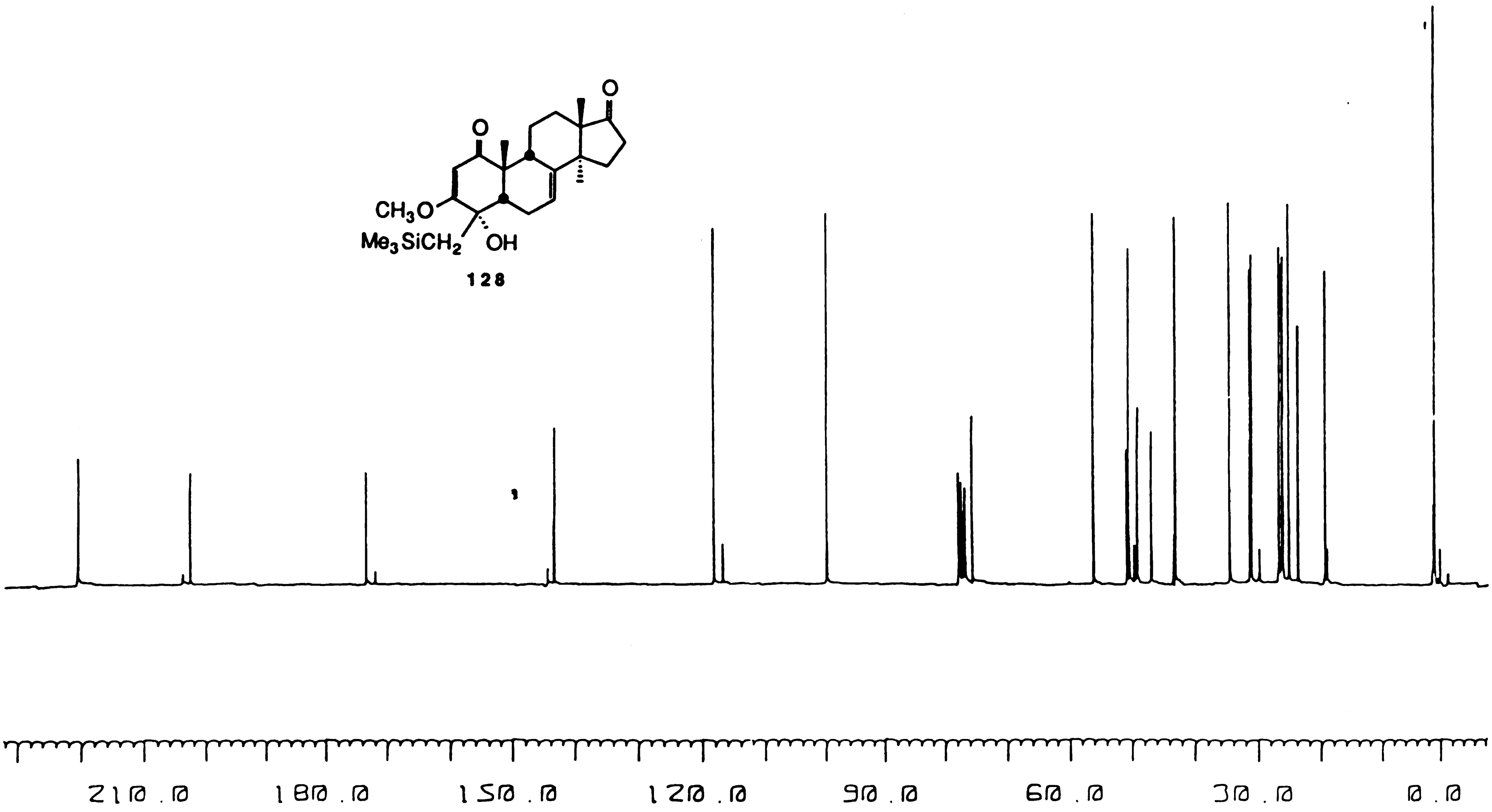


Figure 130. CMR spectrum of **128**

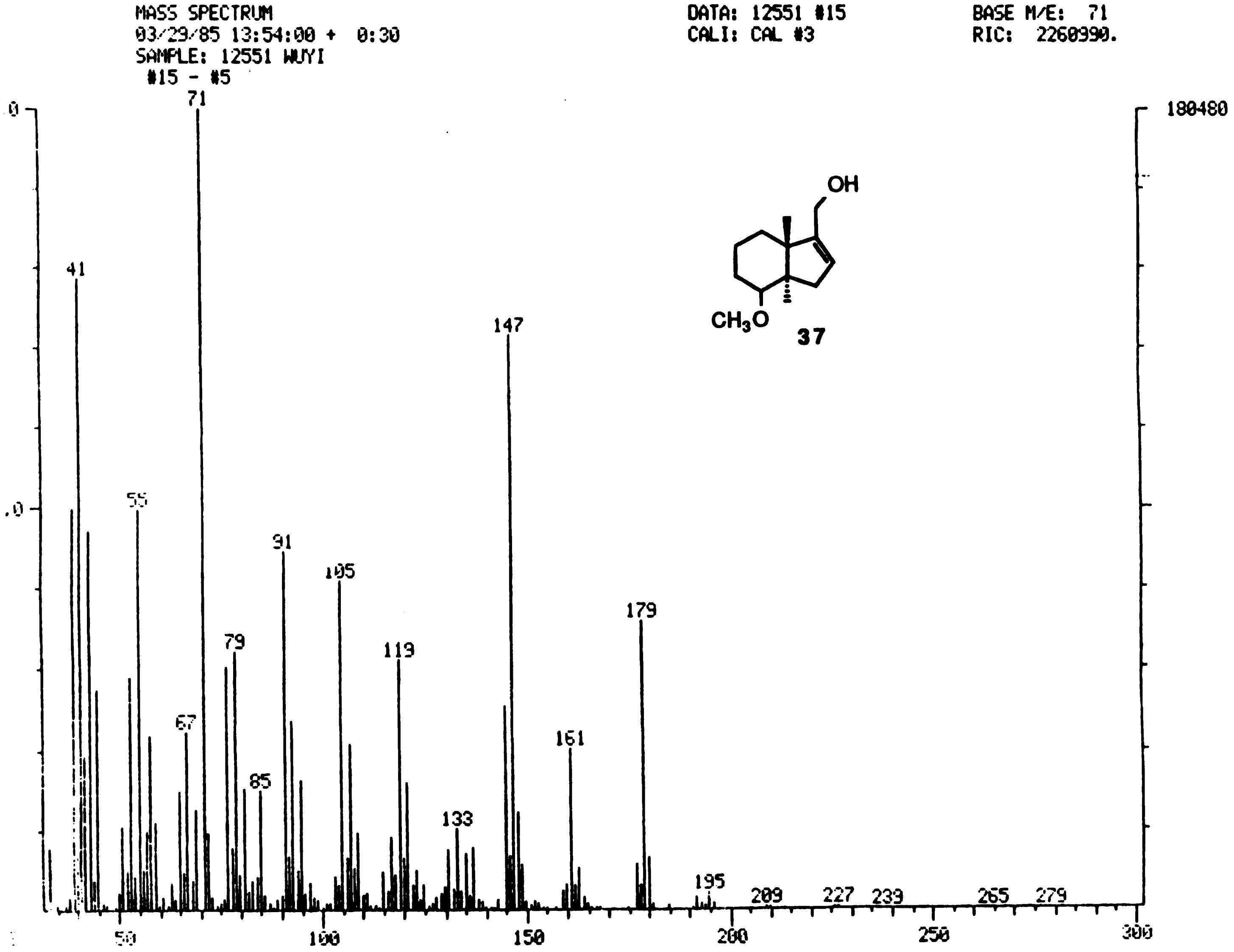


Figure 131. Mass spectrum of 37

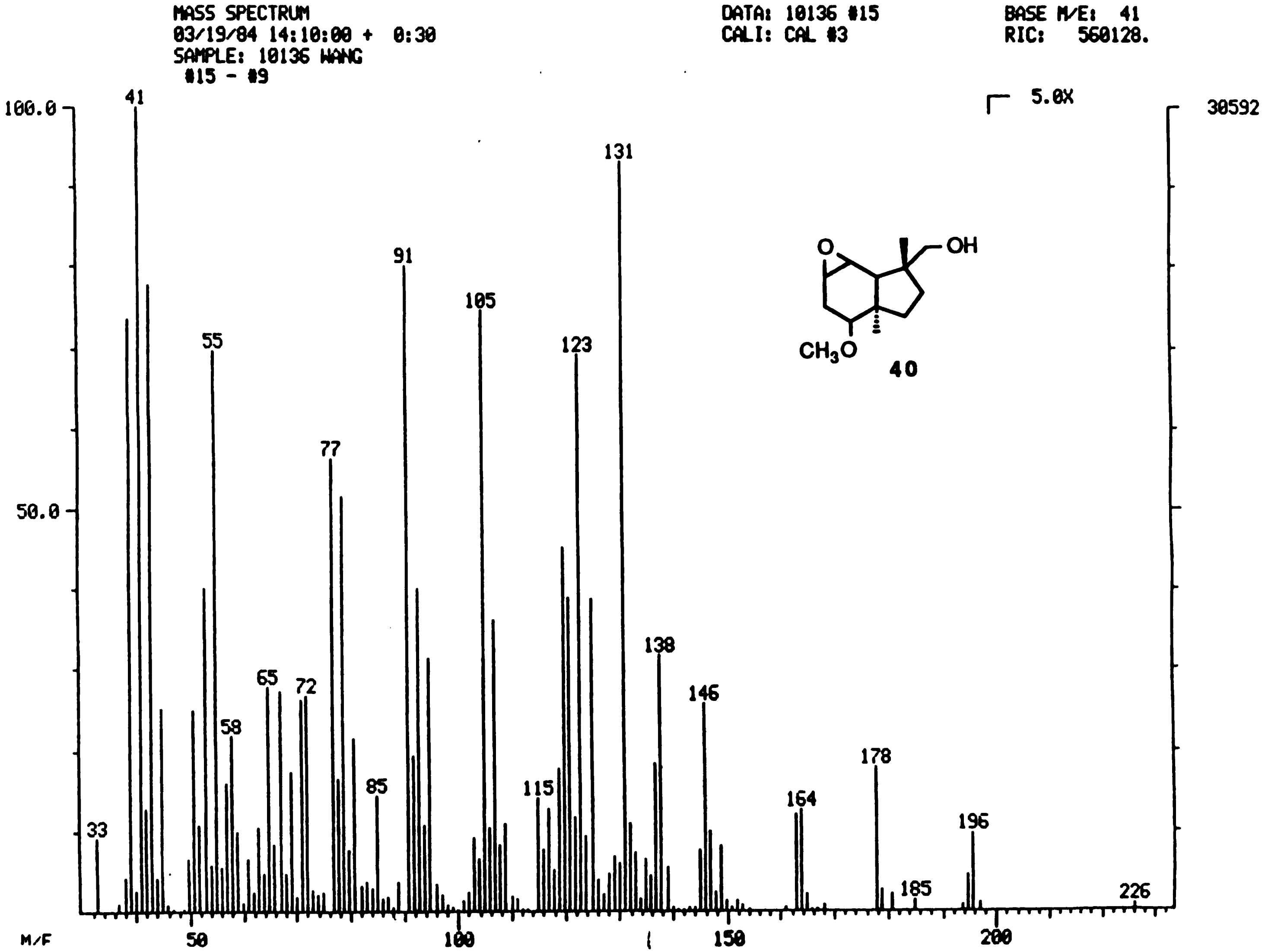


Figure 132. Mass spectrum of **40**

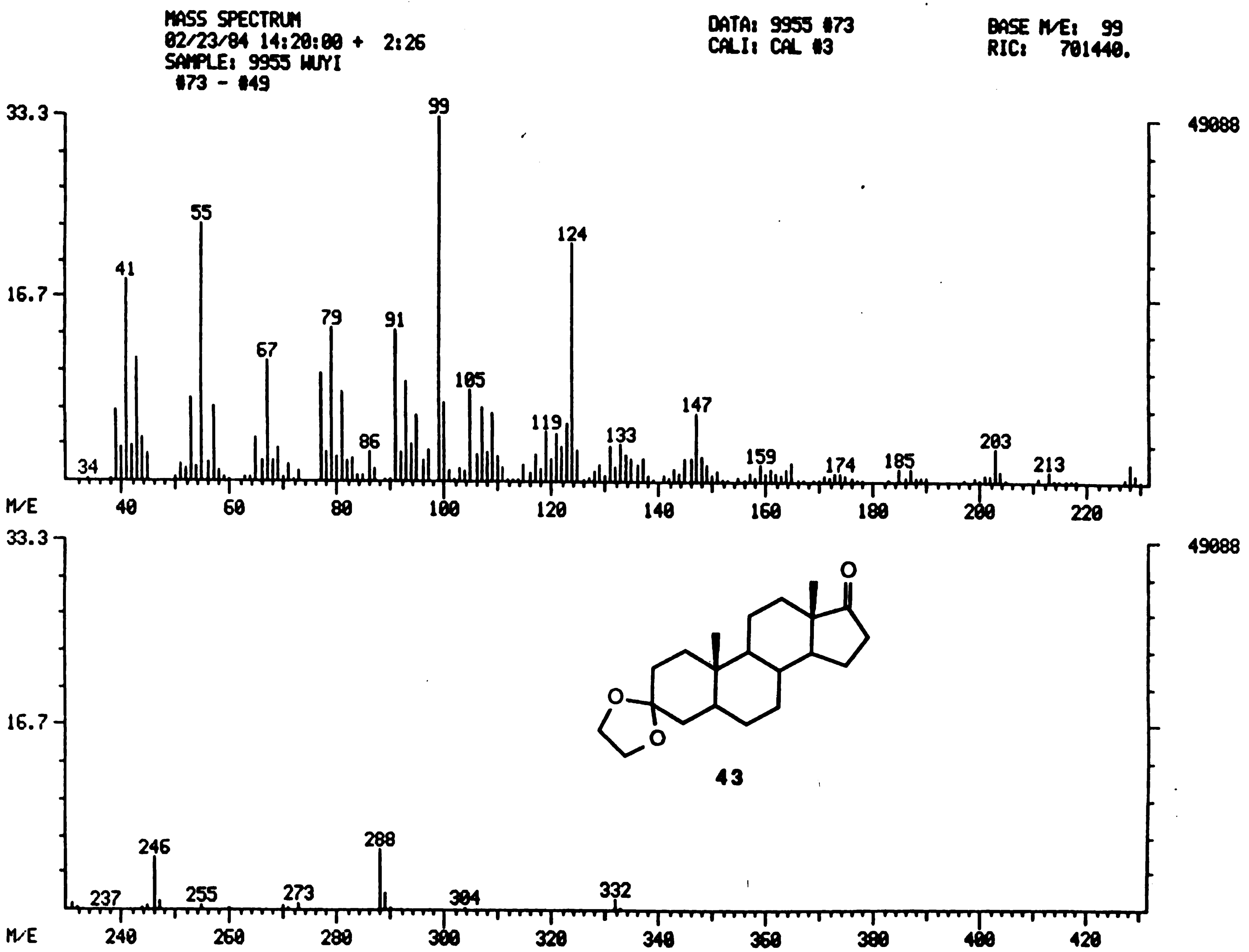


Figure 133. Mass spectrum of 43

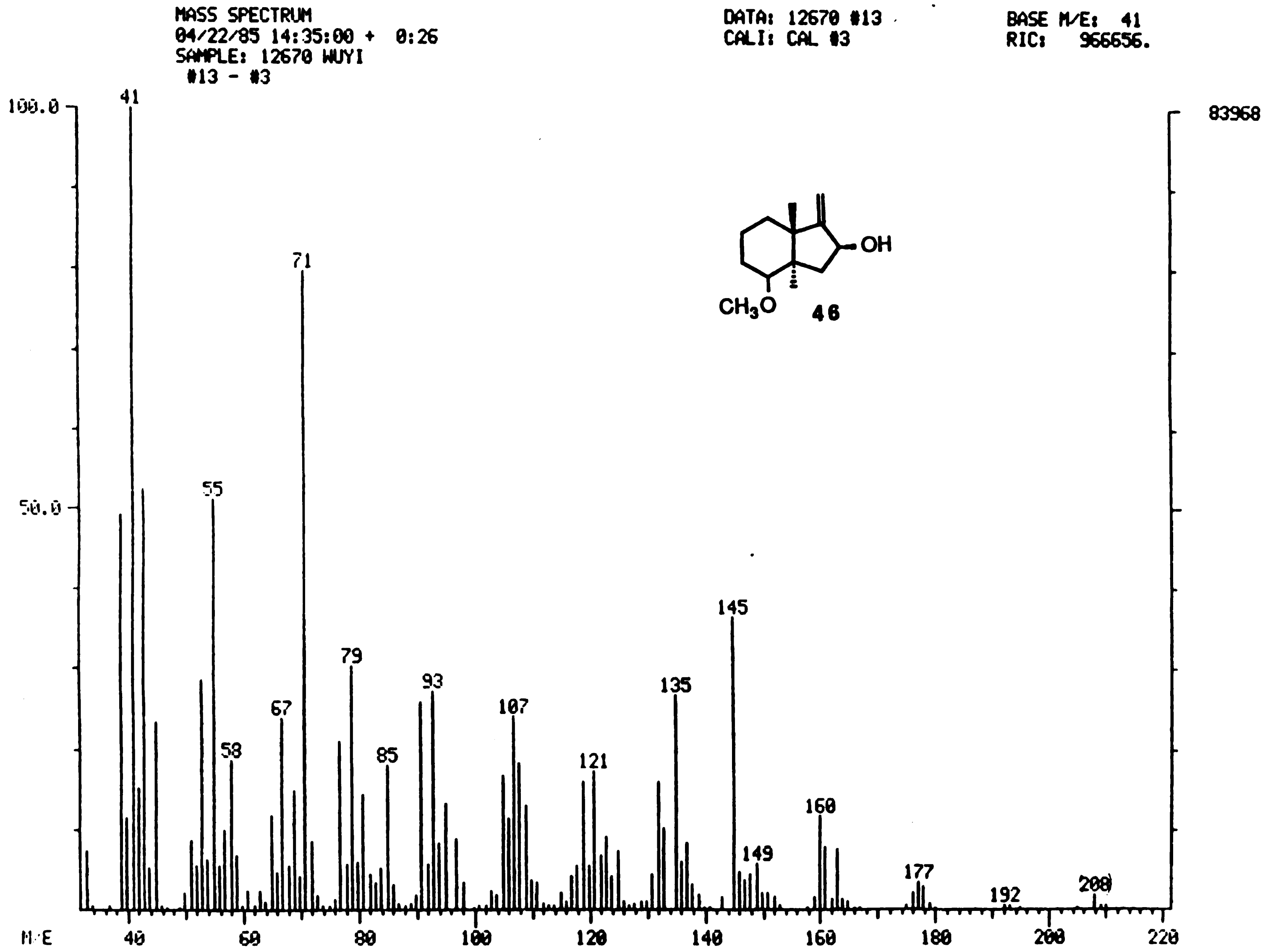


Figure 134. Mass spectrum of 46

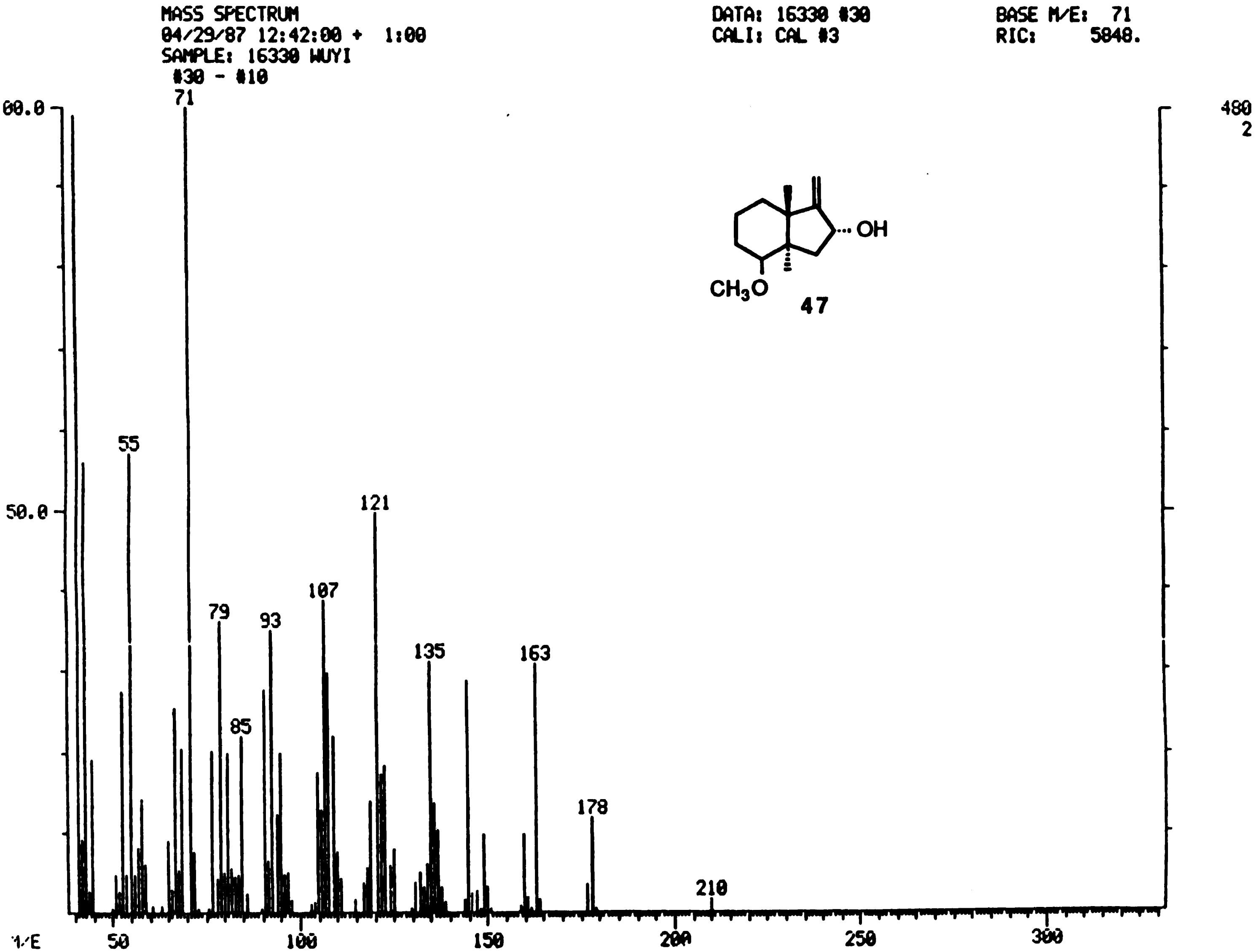


Figure 135. Mass spectrum of **47**

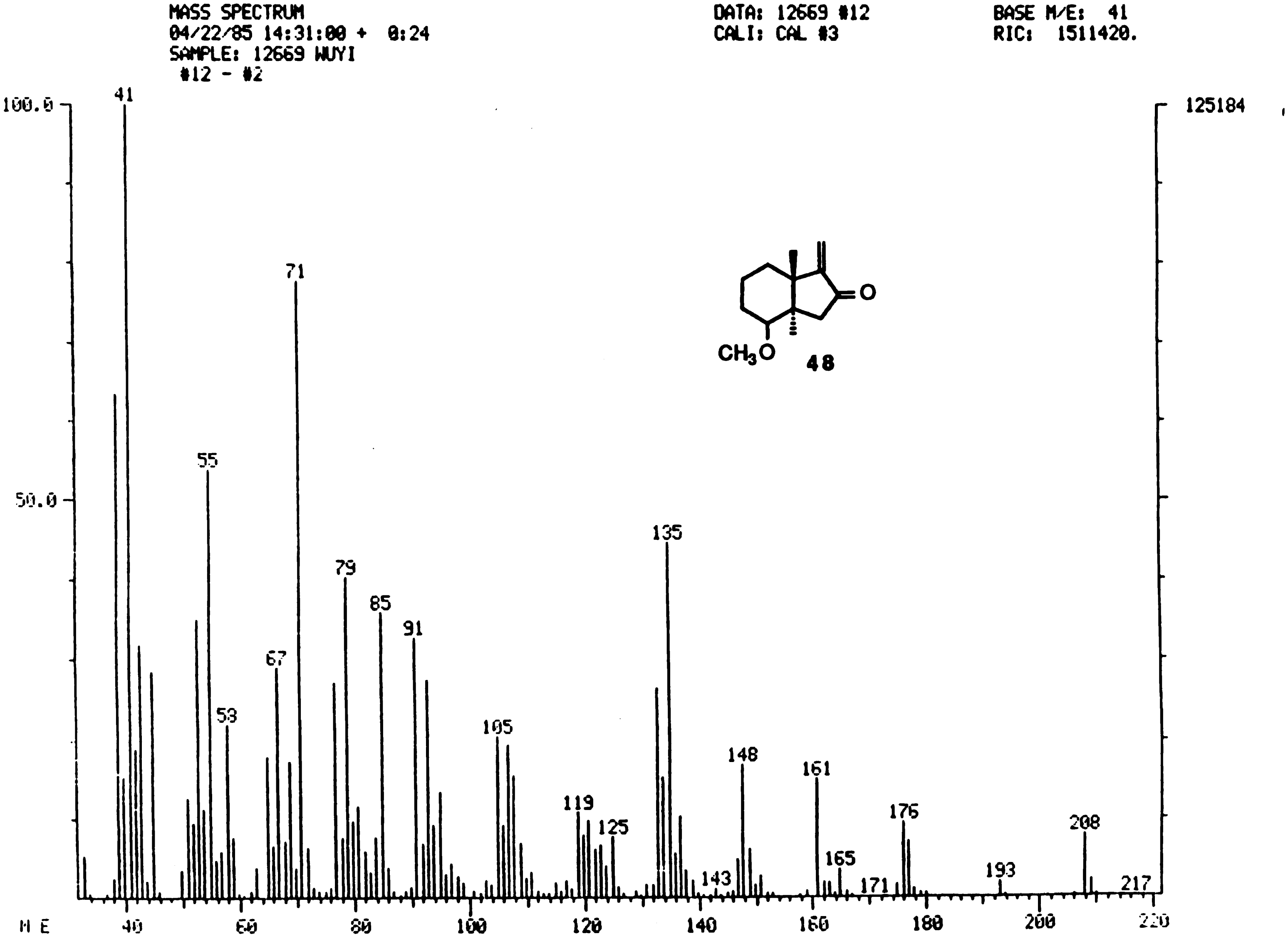


Figure 136. Mass spectrum of **48**

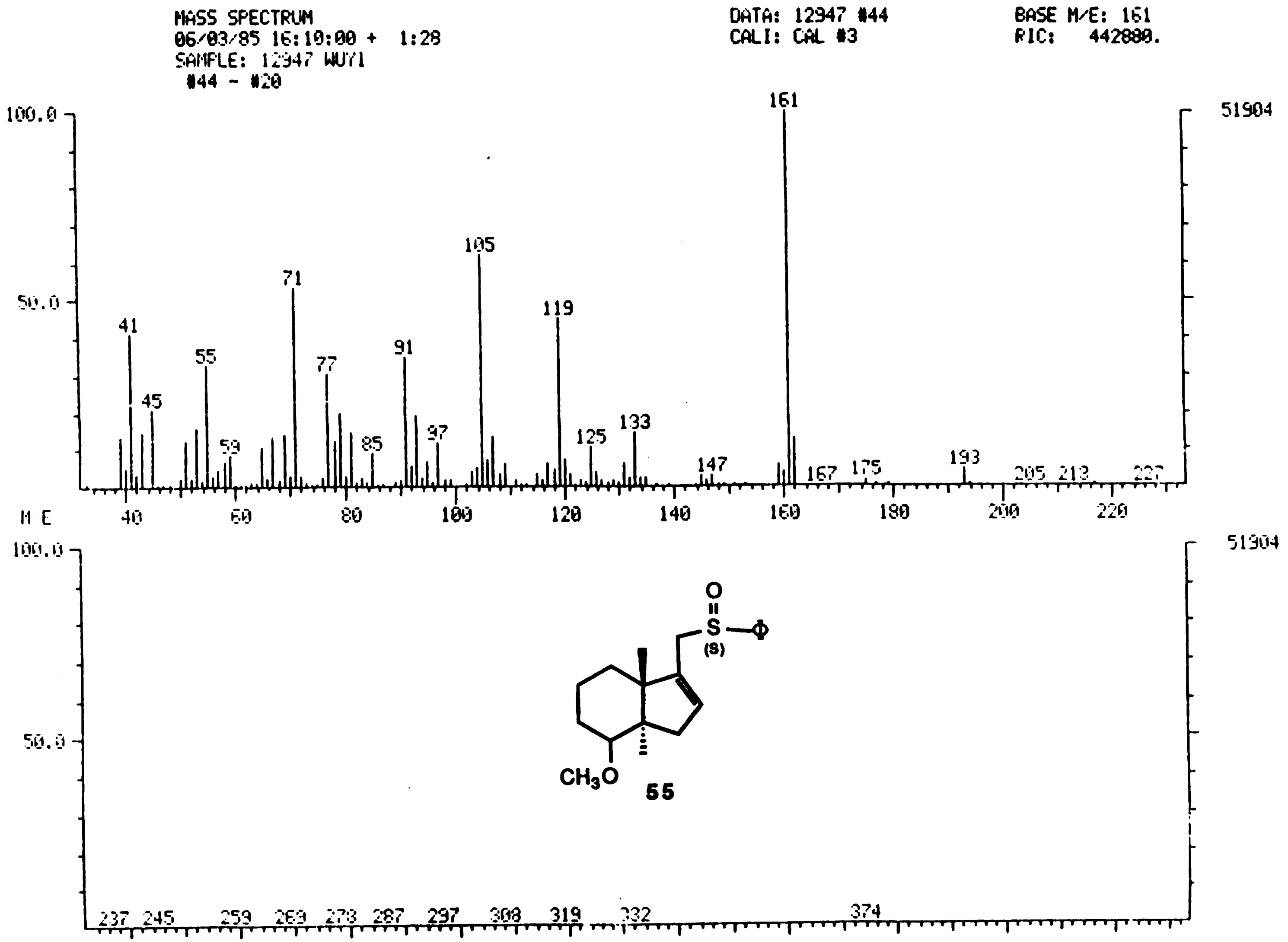


Figure 137. Mass spectrum of 55

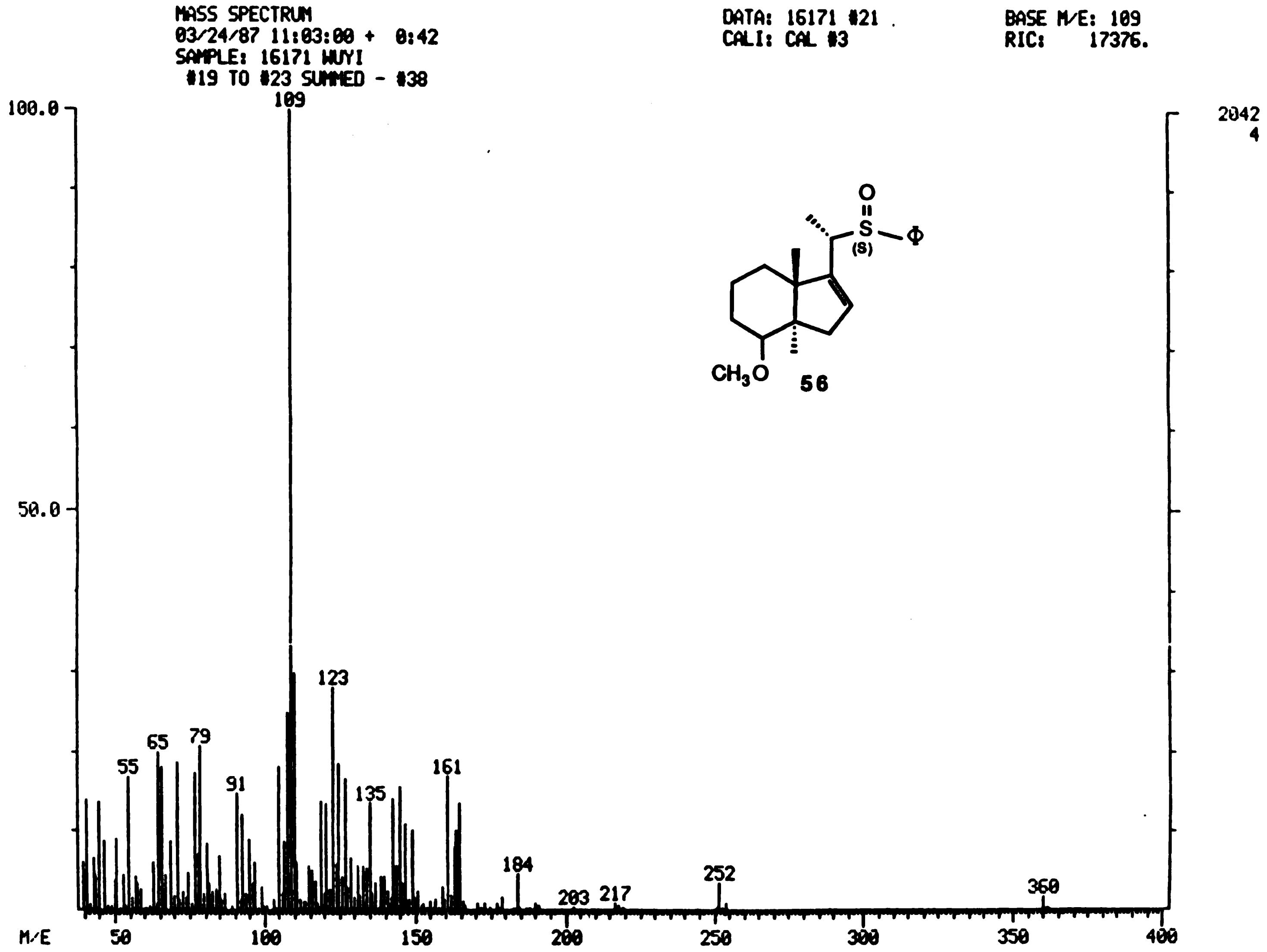


Figure 138. Mass spectrum of **56**

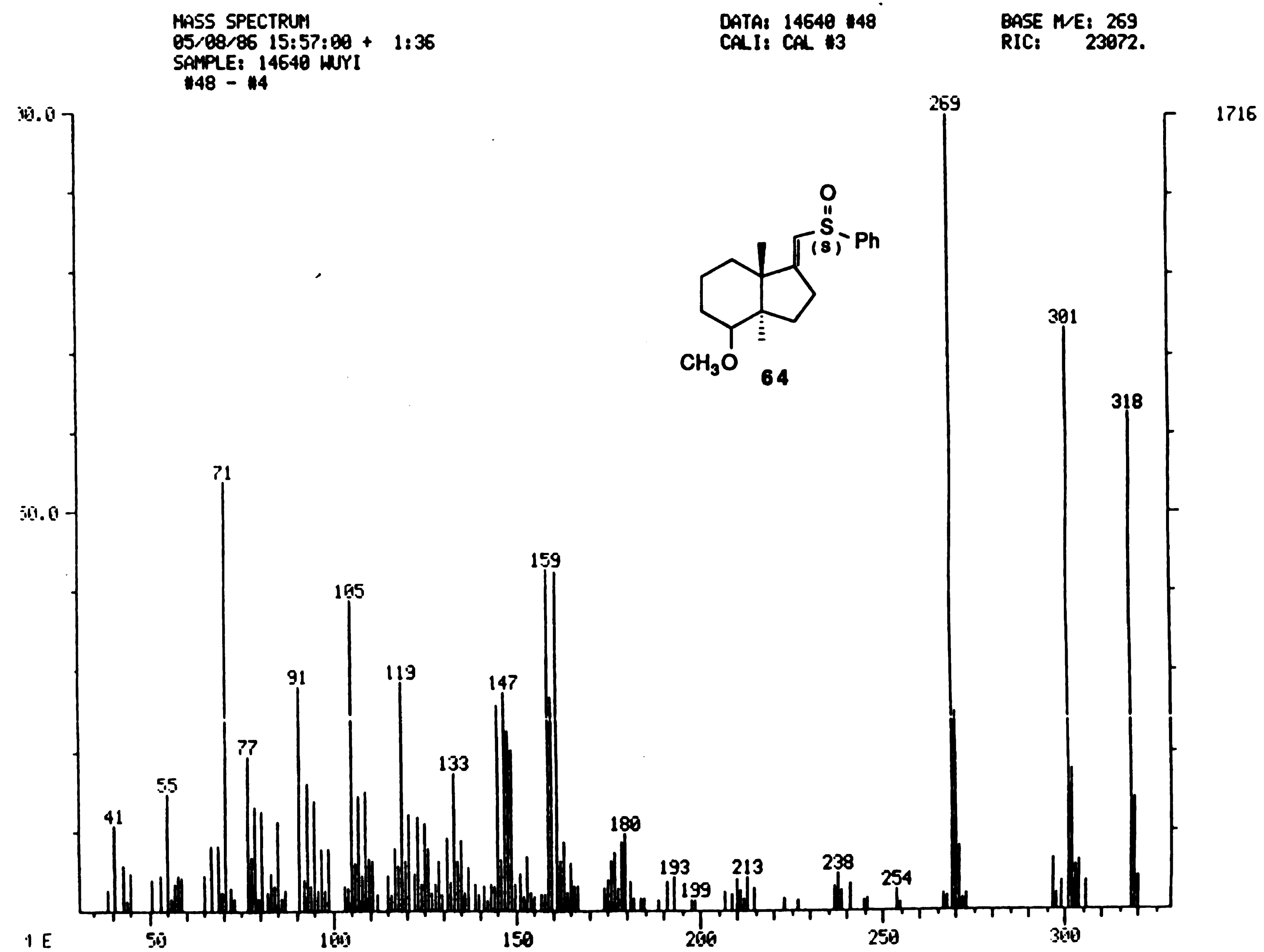


Figure 139. Mass spectrum of 64

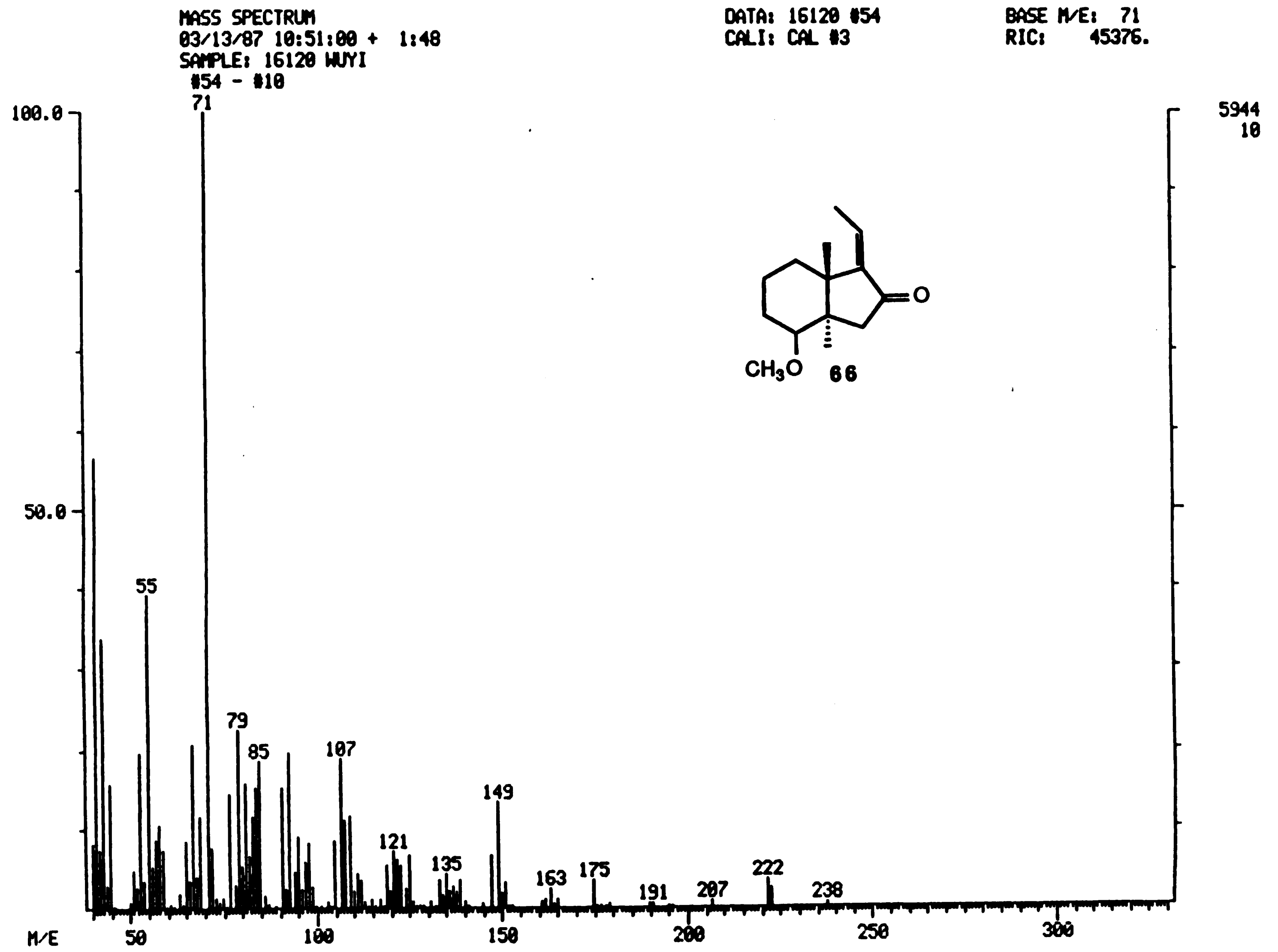


Figure 140. Mass spectrum of **66**

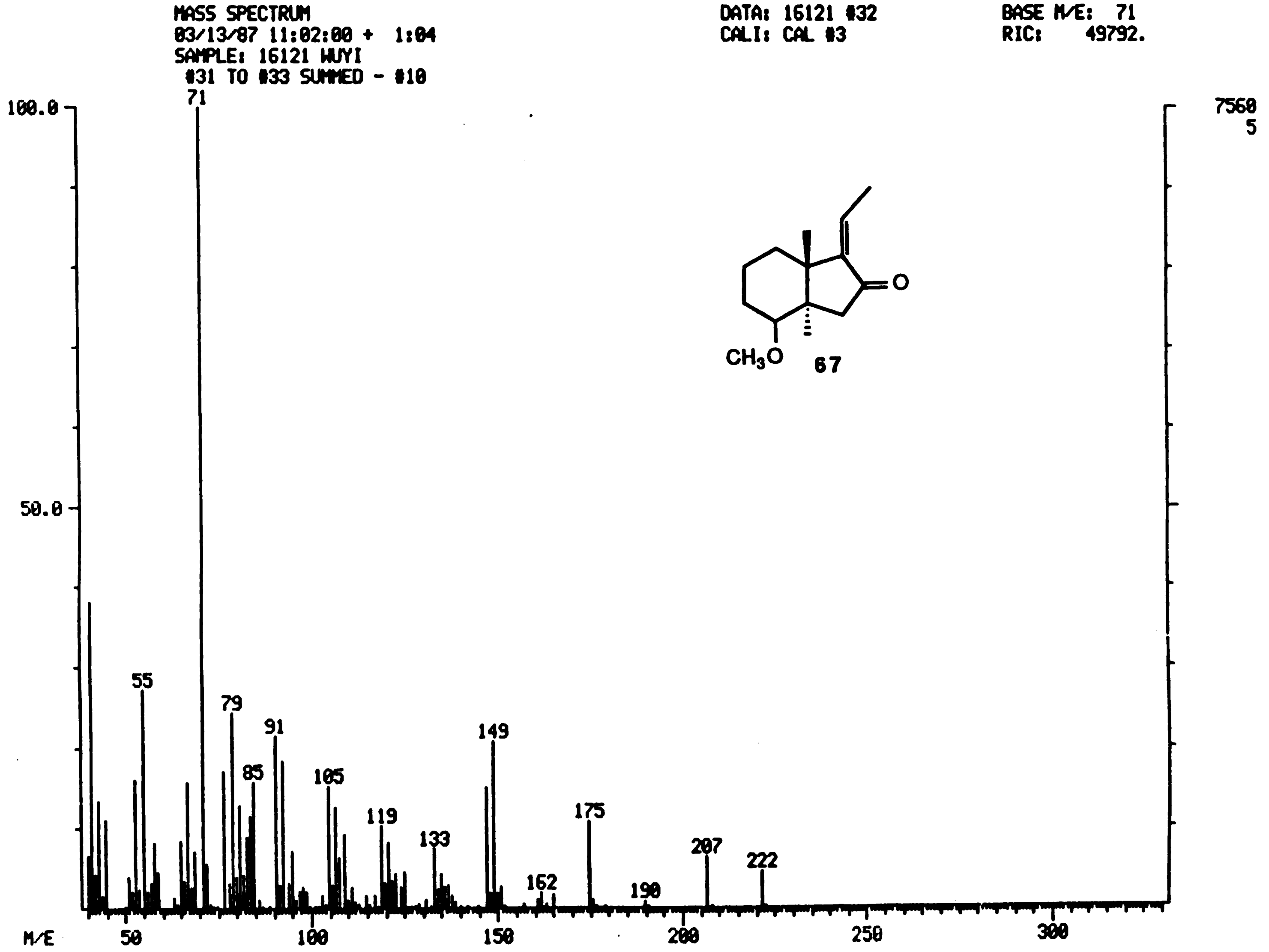


Figure 141. Mass spectrum of 67

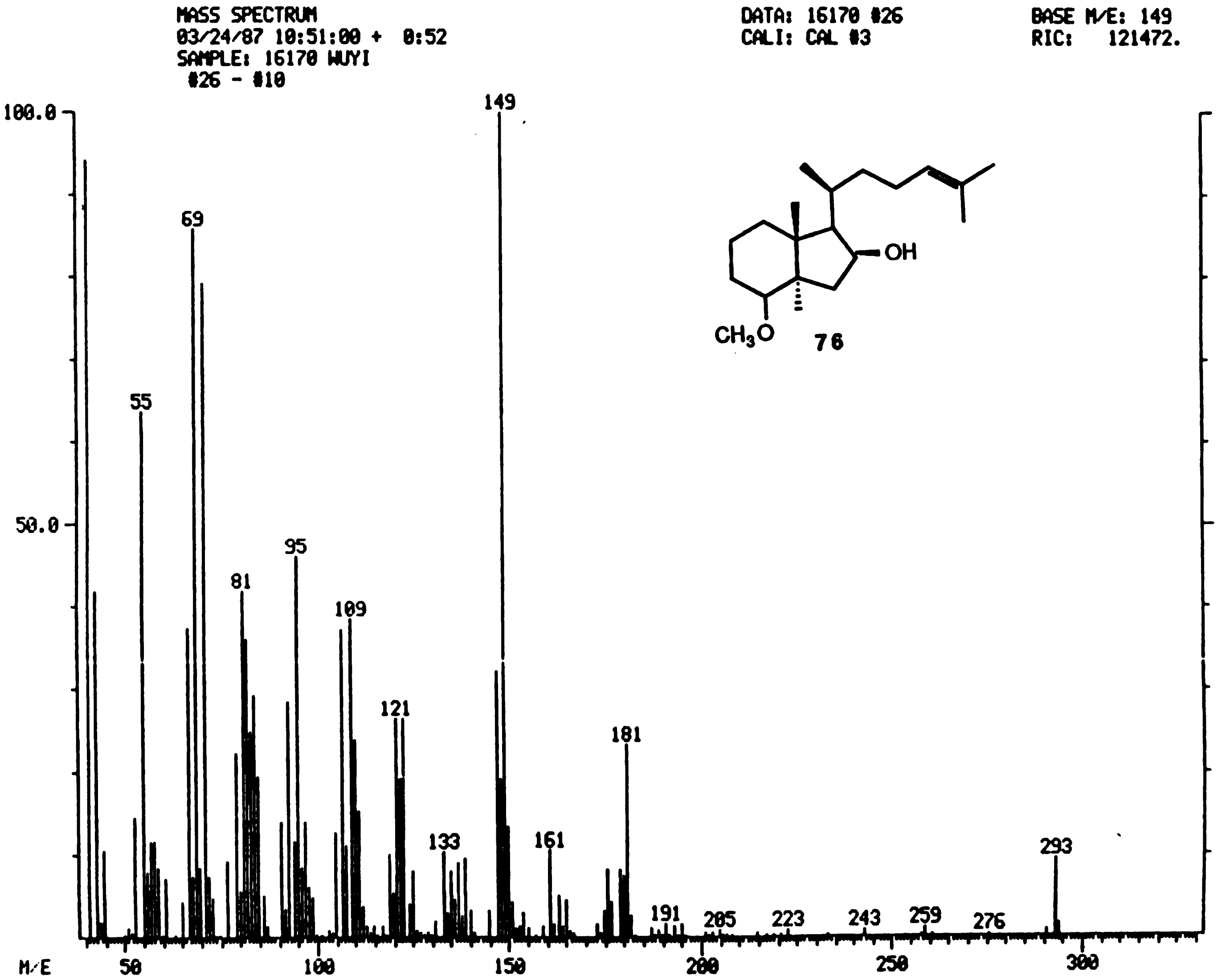


Figure 142. Mass spectrum of 76

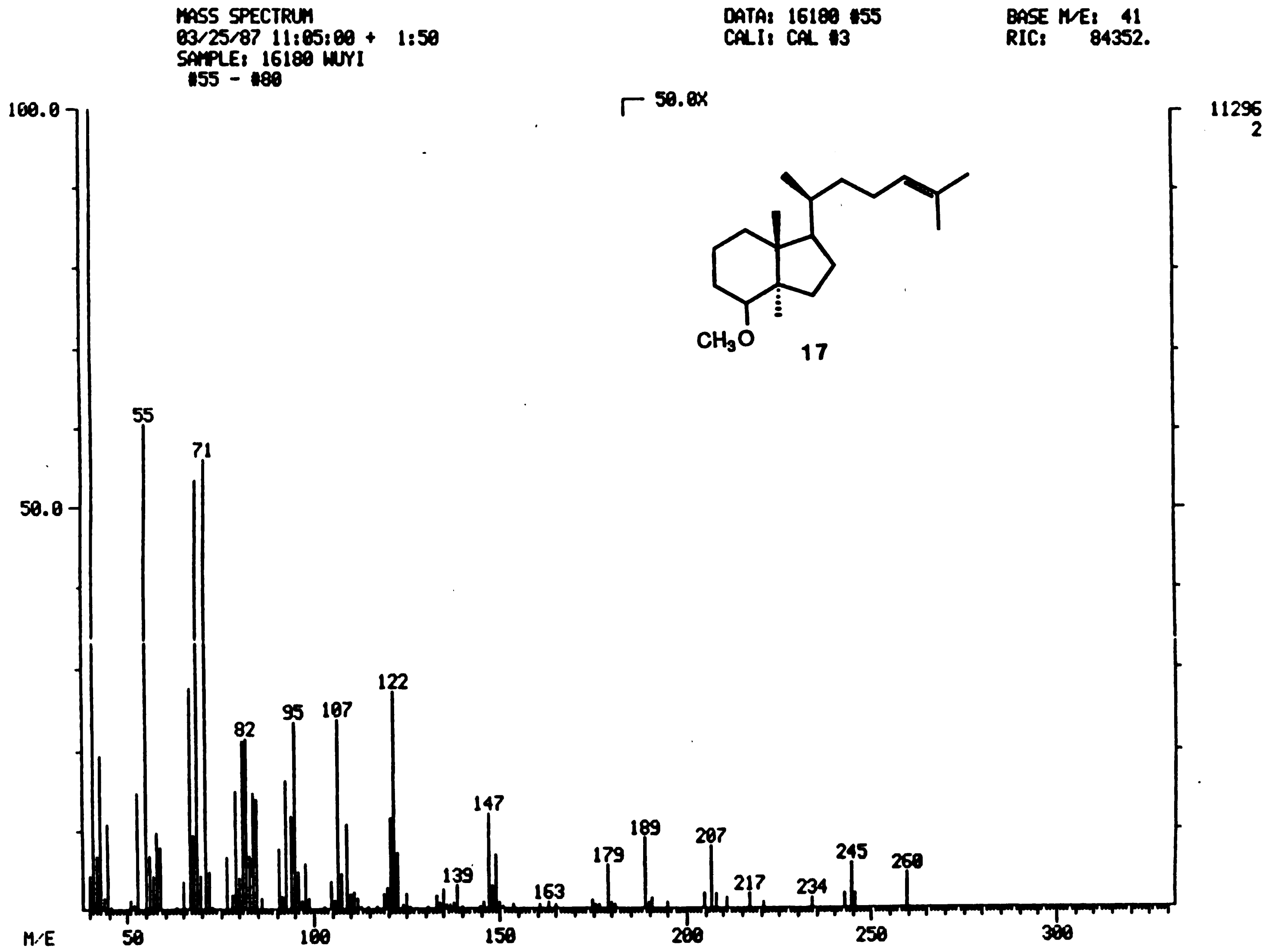


Figure 143. Mass spectrum of 17

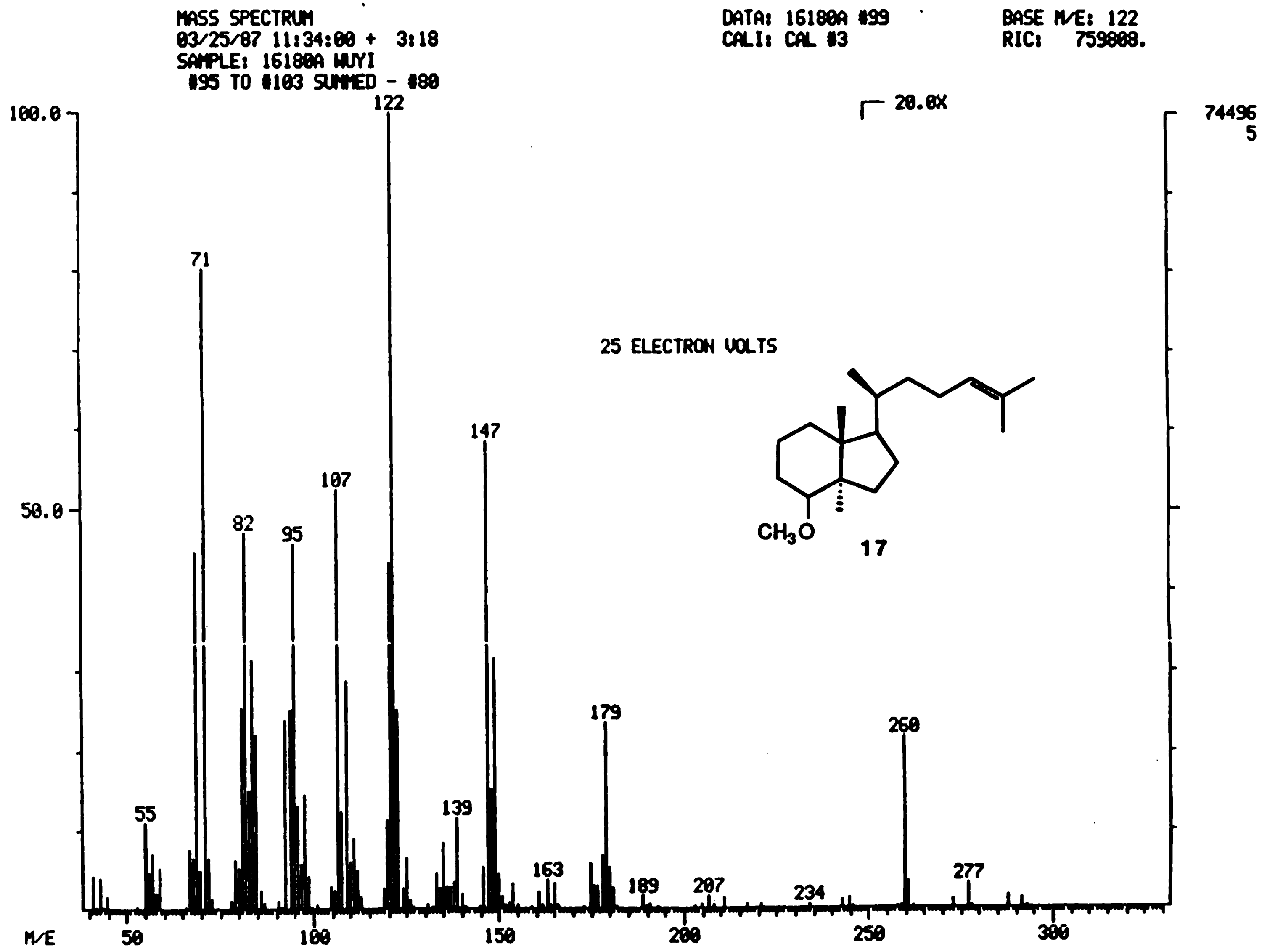


Figure 144. Mass spectrum of **17** (25 e.v.)

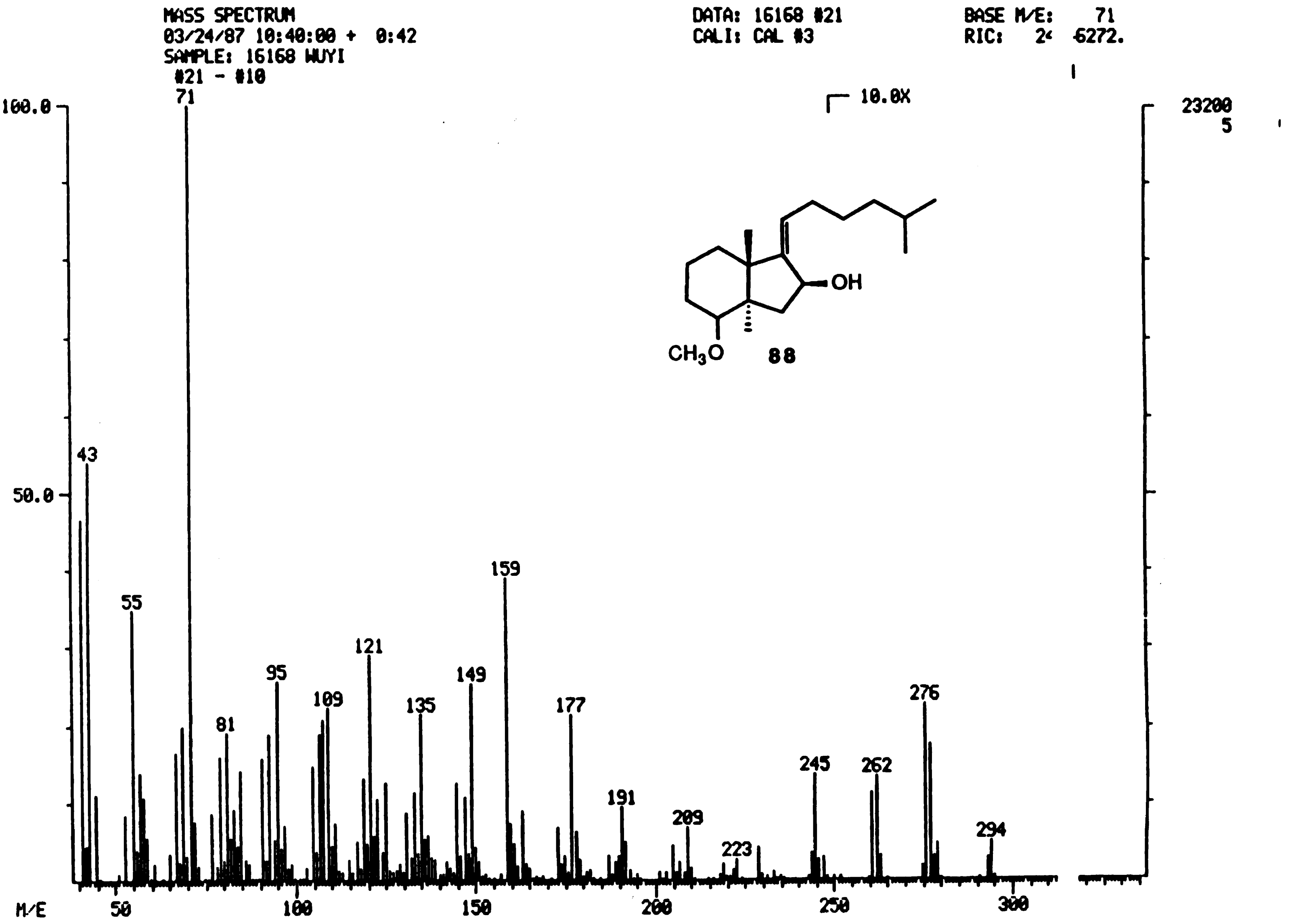


Figure 145. Mass spectrum of **88**

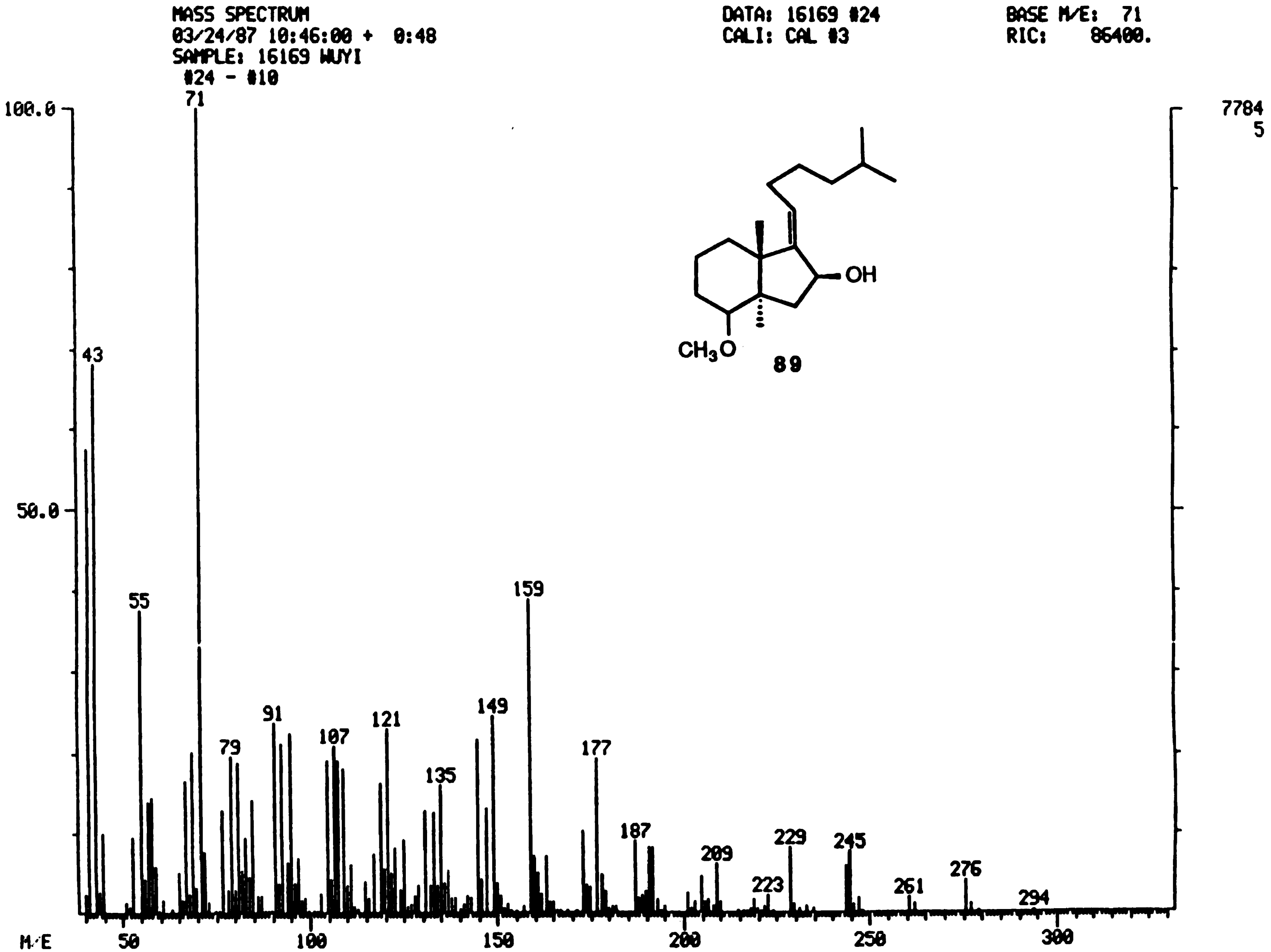


Figure 146. Mass spectrum of **89**

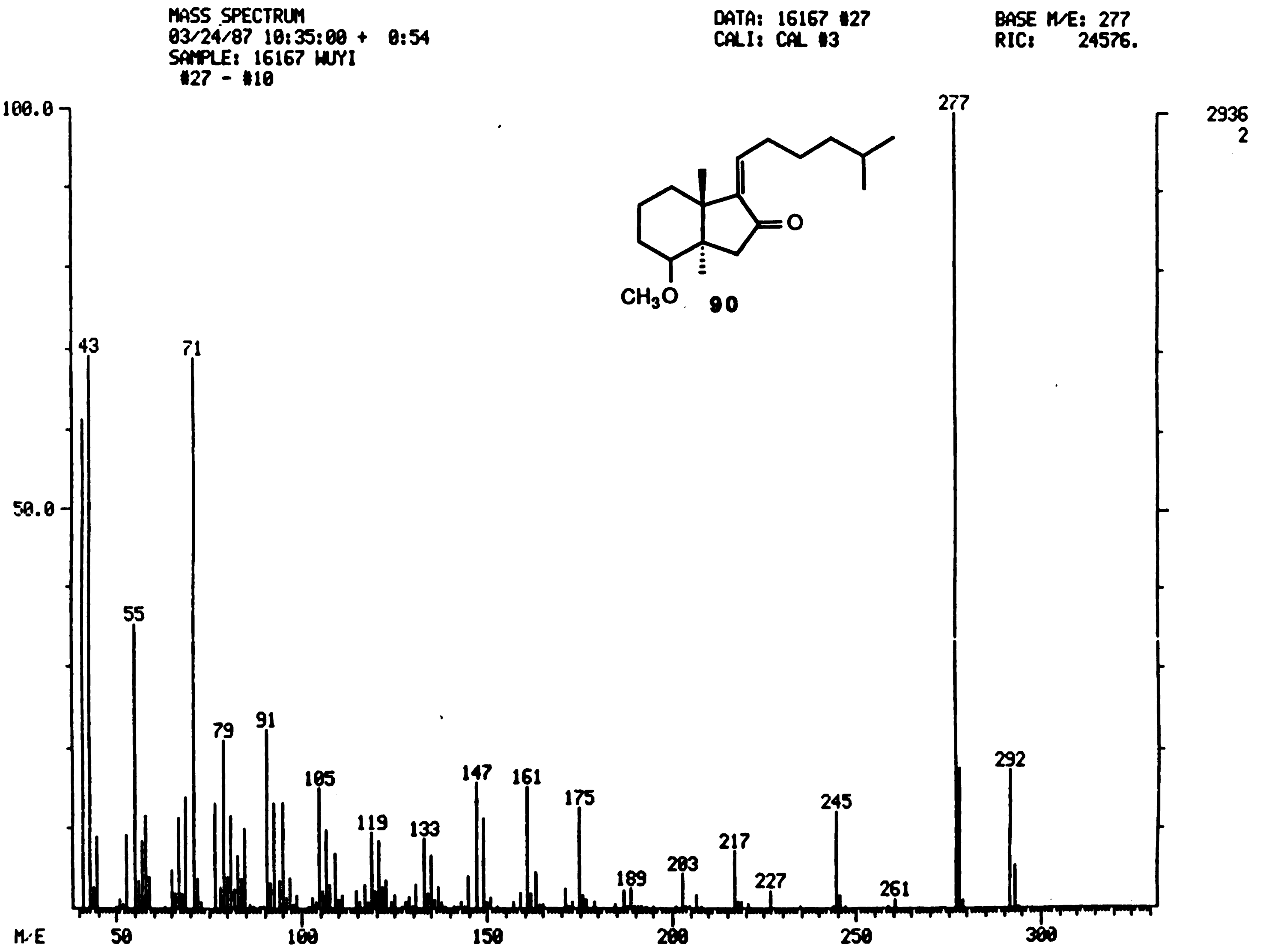


Figure 147. Mass spectrum of **90**

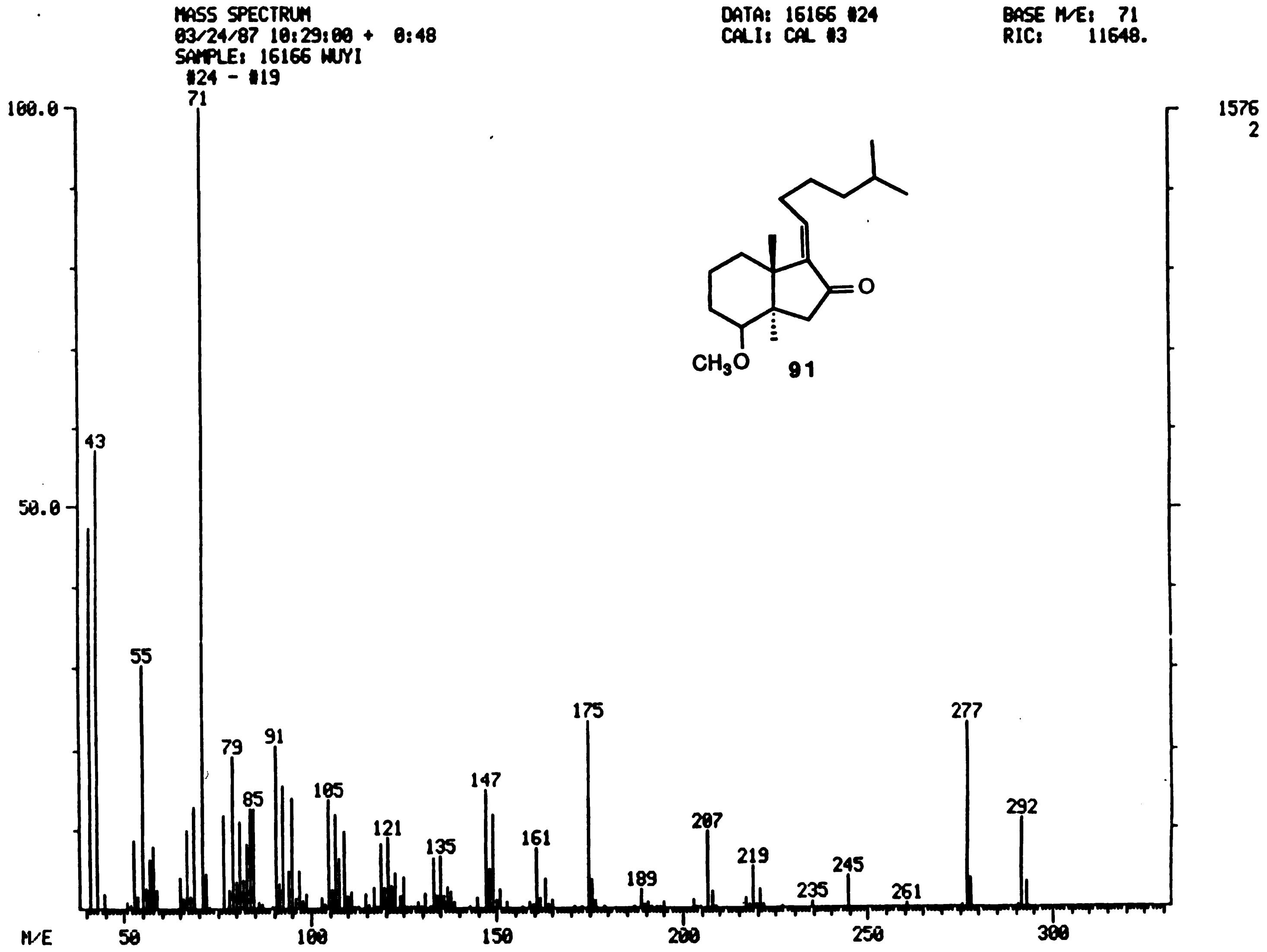


Figure 148. Mass spectrum of 91

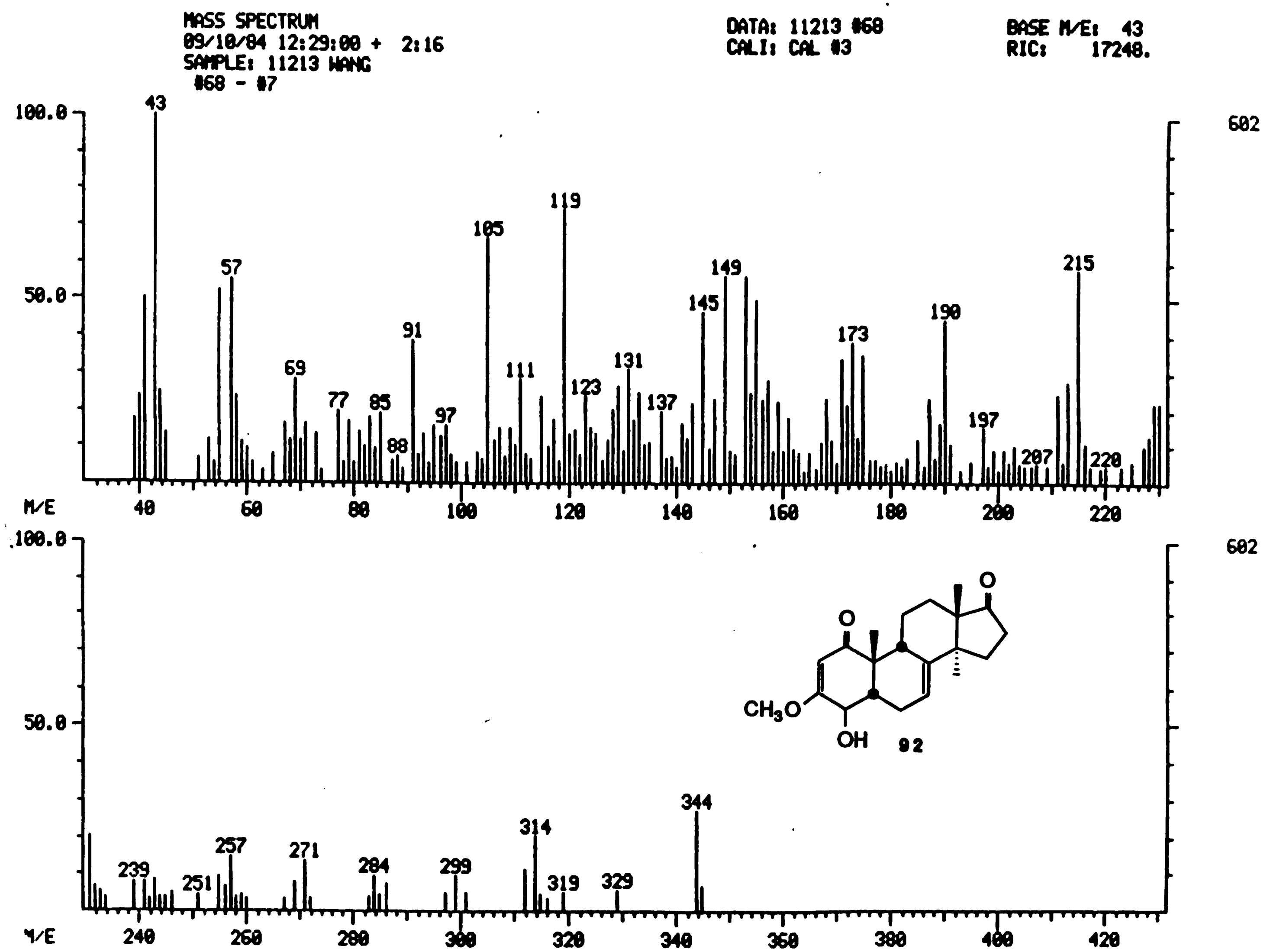


Figure 149. Mass spectrum of 92

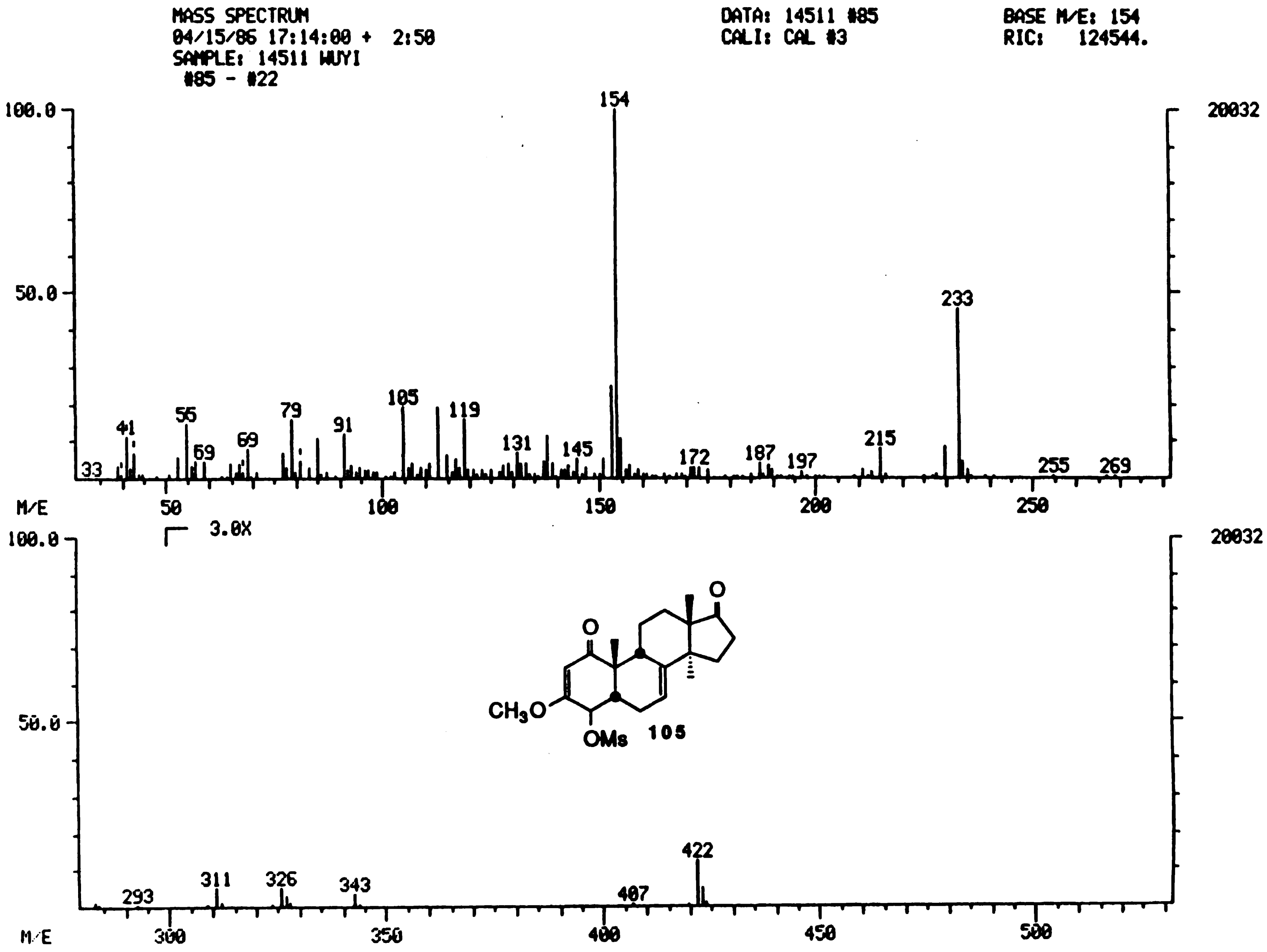


Figure 150. Mass spectrum of 105

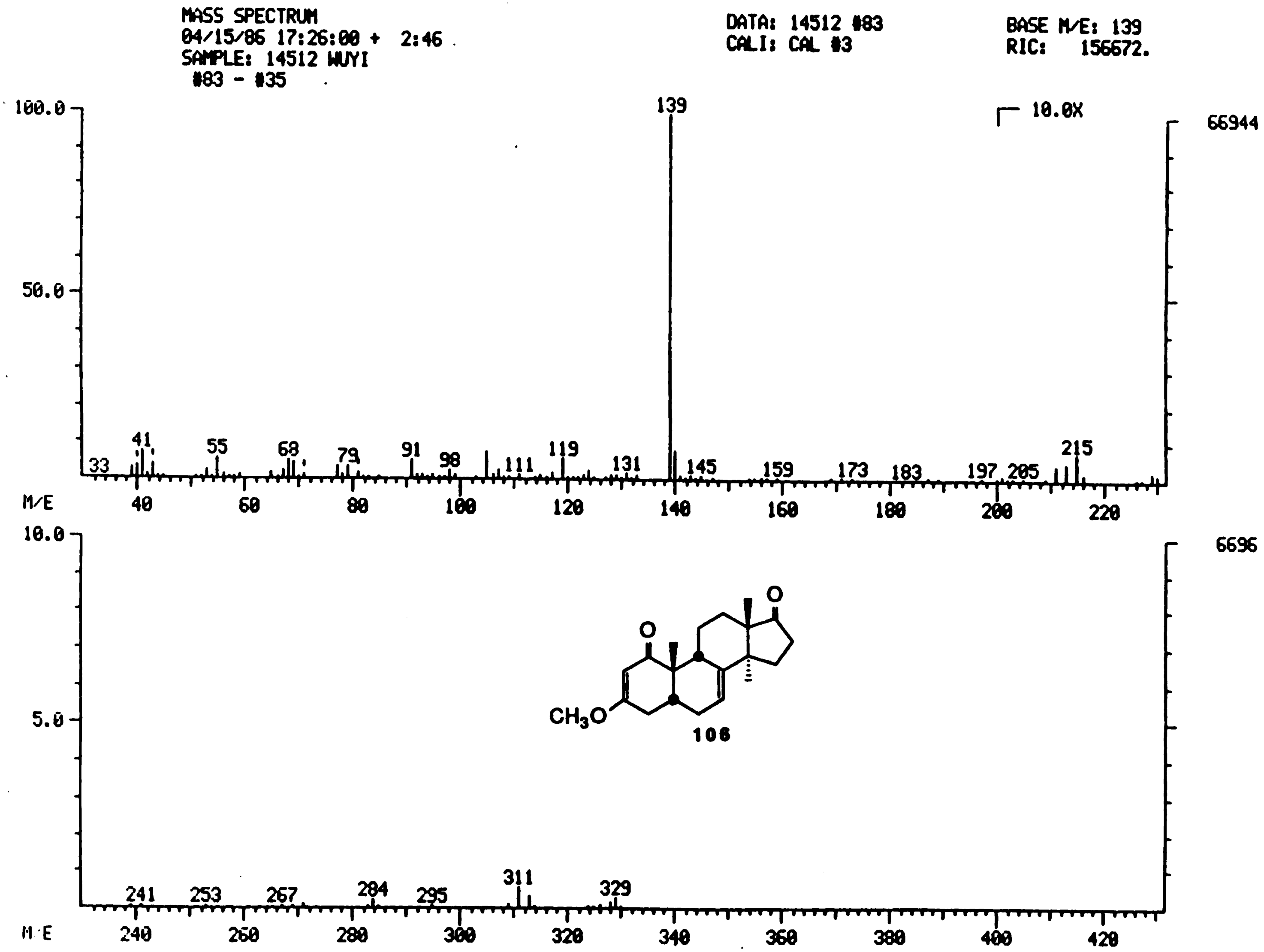


Figure 151. Mass spectrum of 106

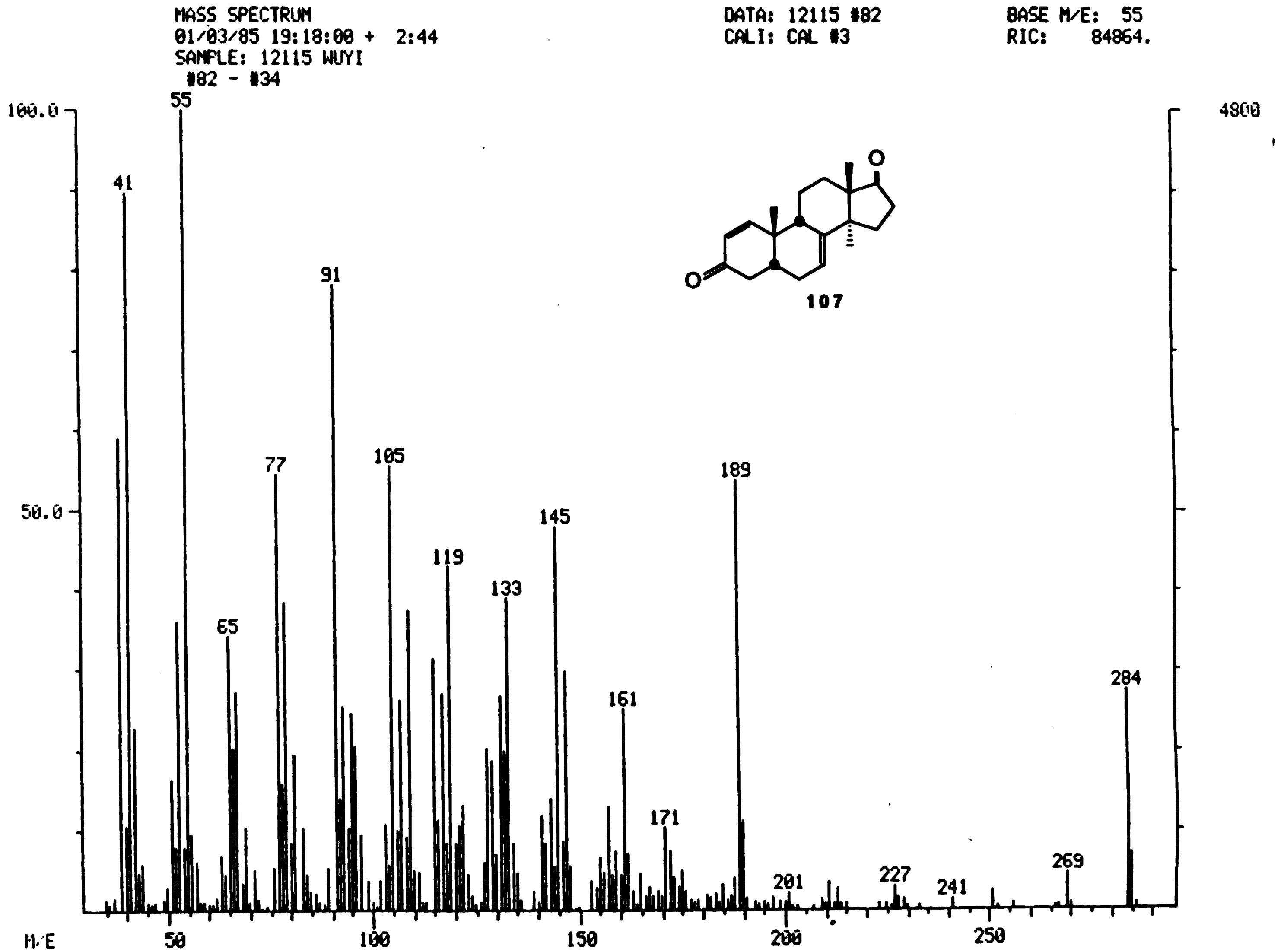


Figure 152. Mass spectrum of 107

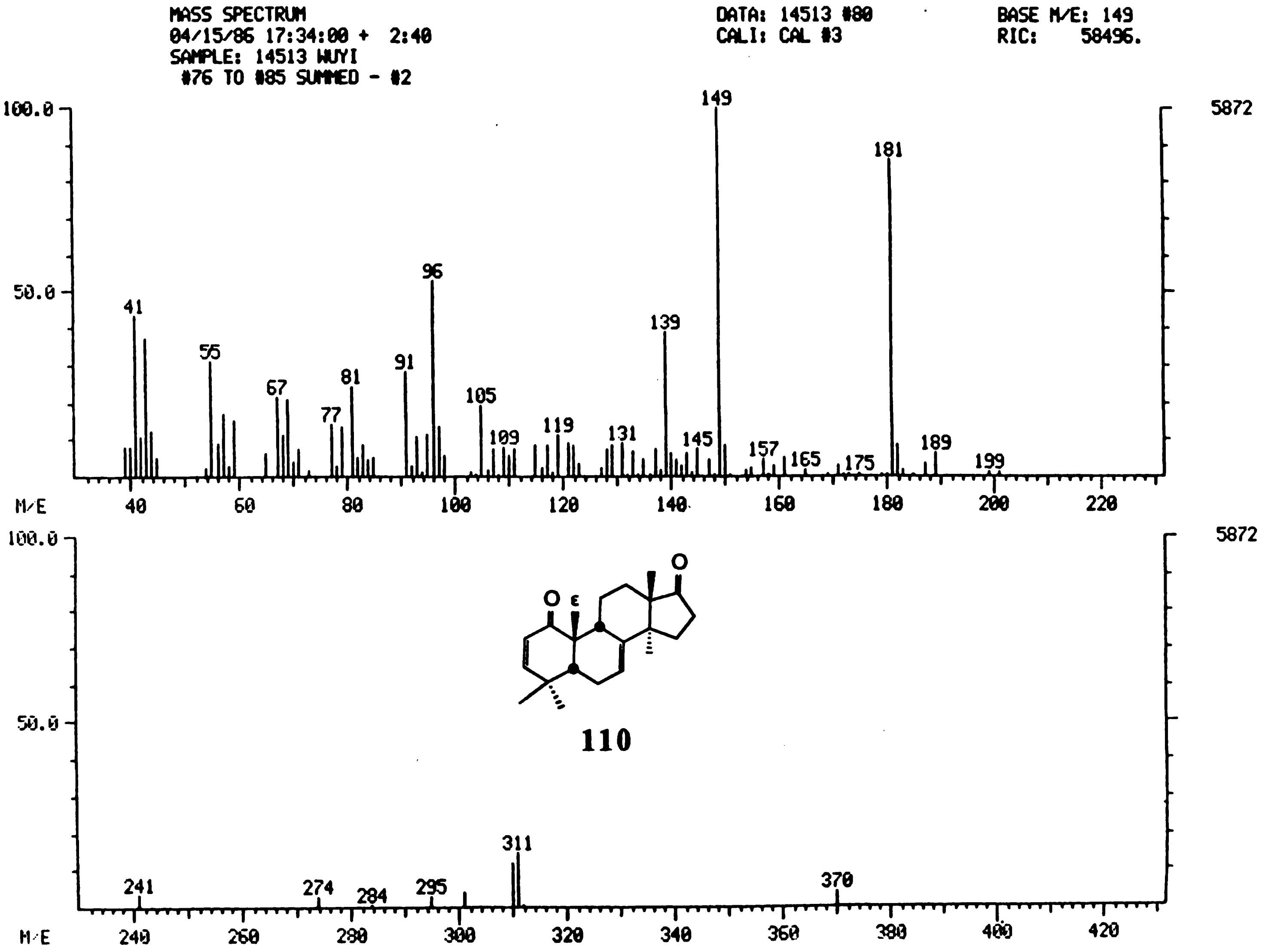


Figure 153. Mass spectrum of 110

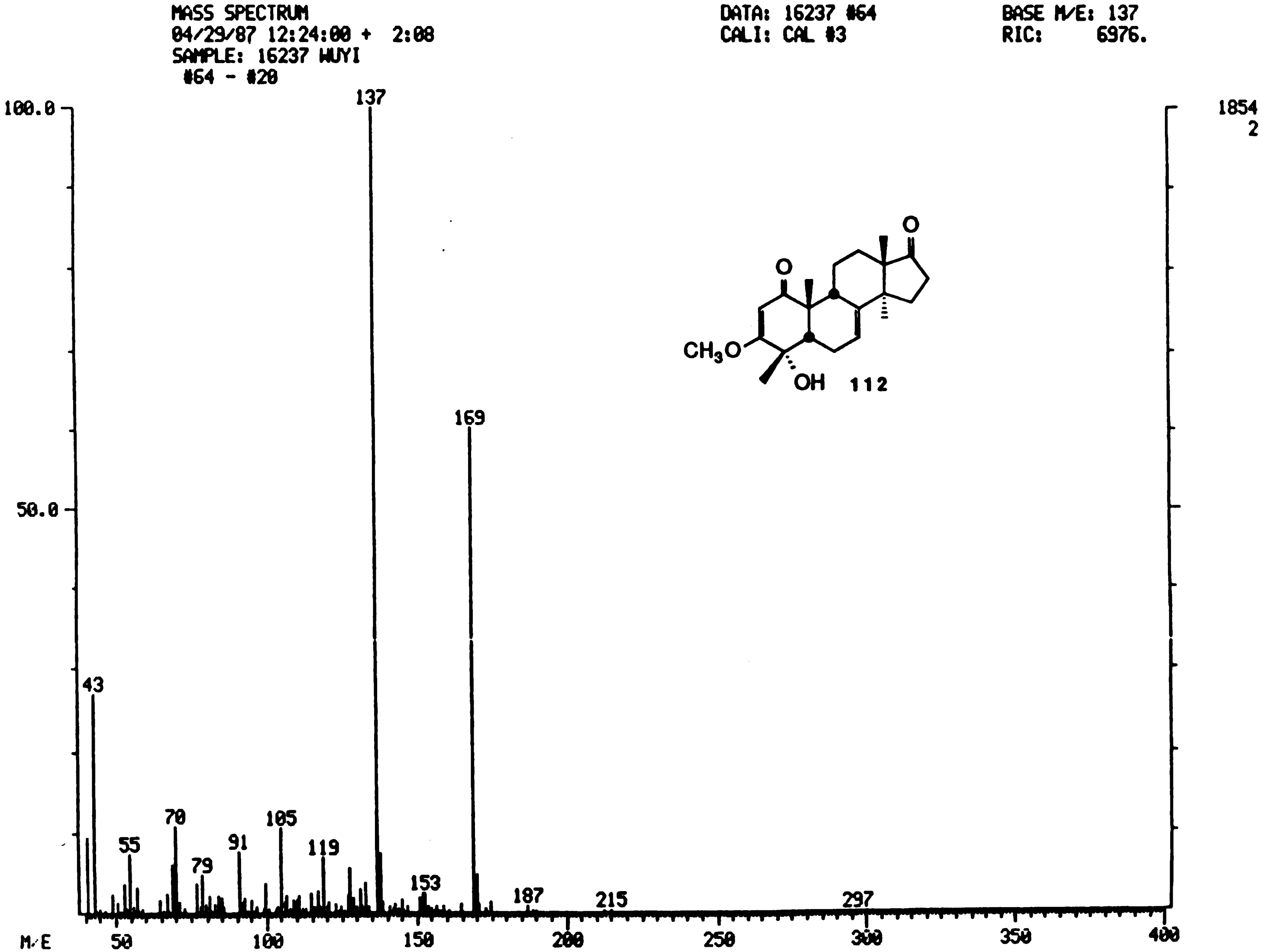


Figure 154. Mass spectrum of 112

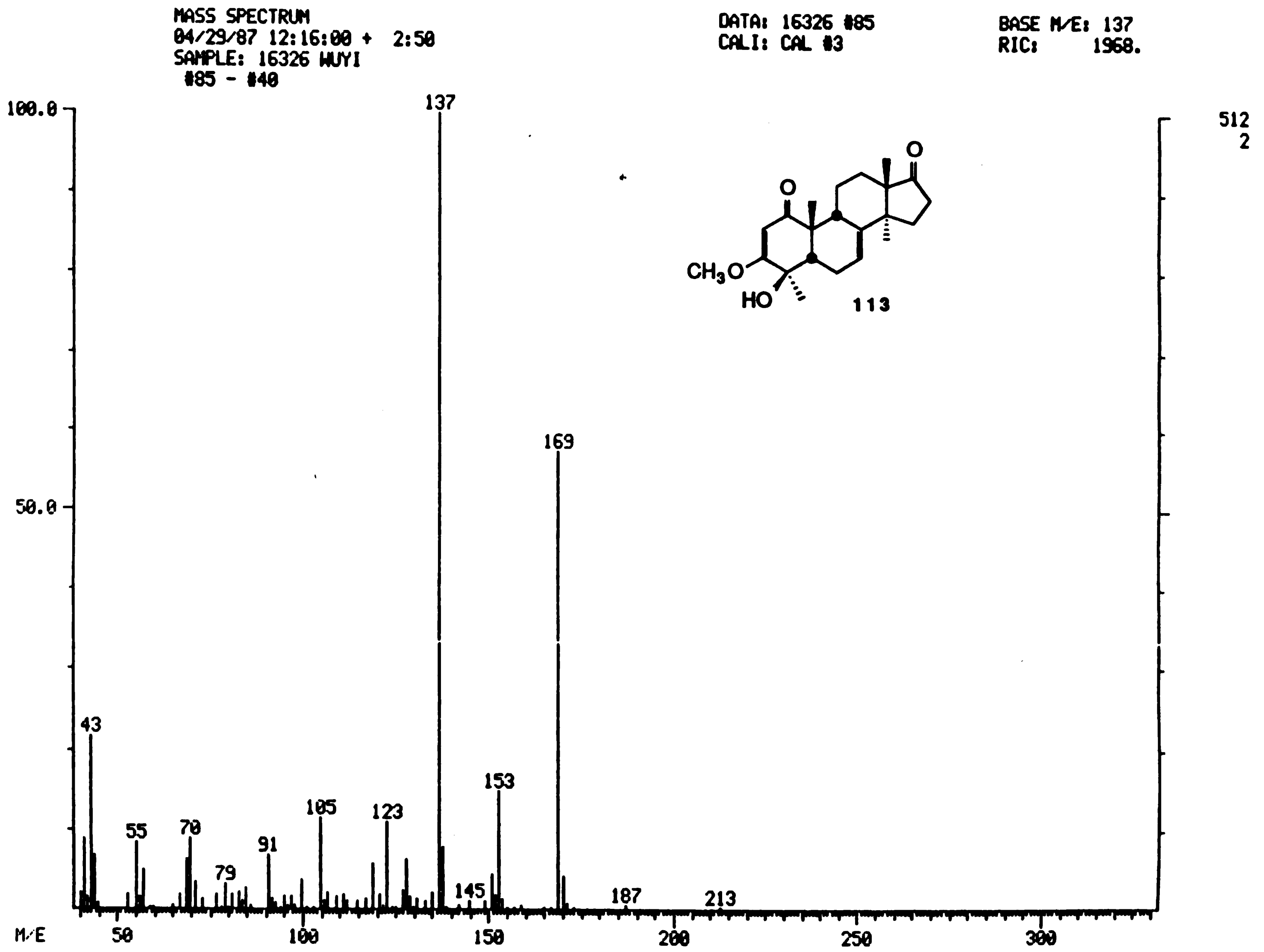


Figure 155. Mass spectrum of 113

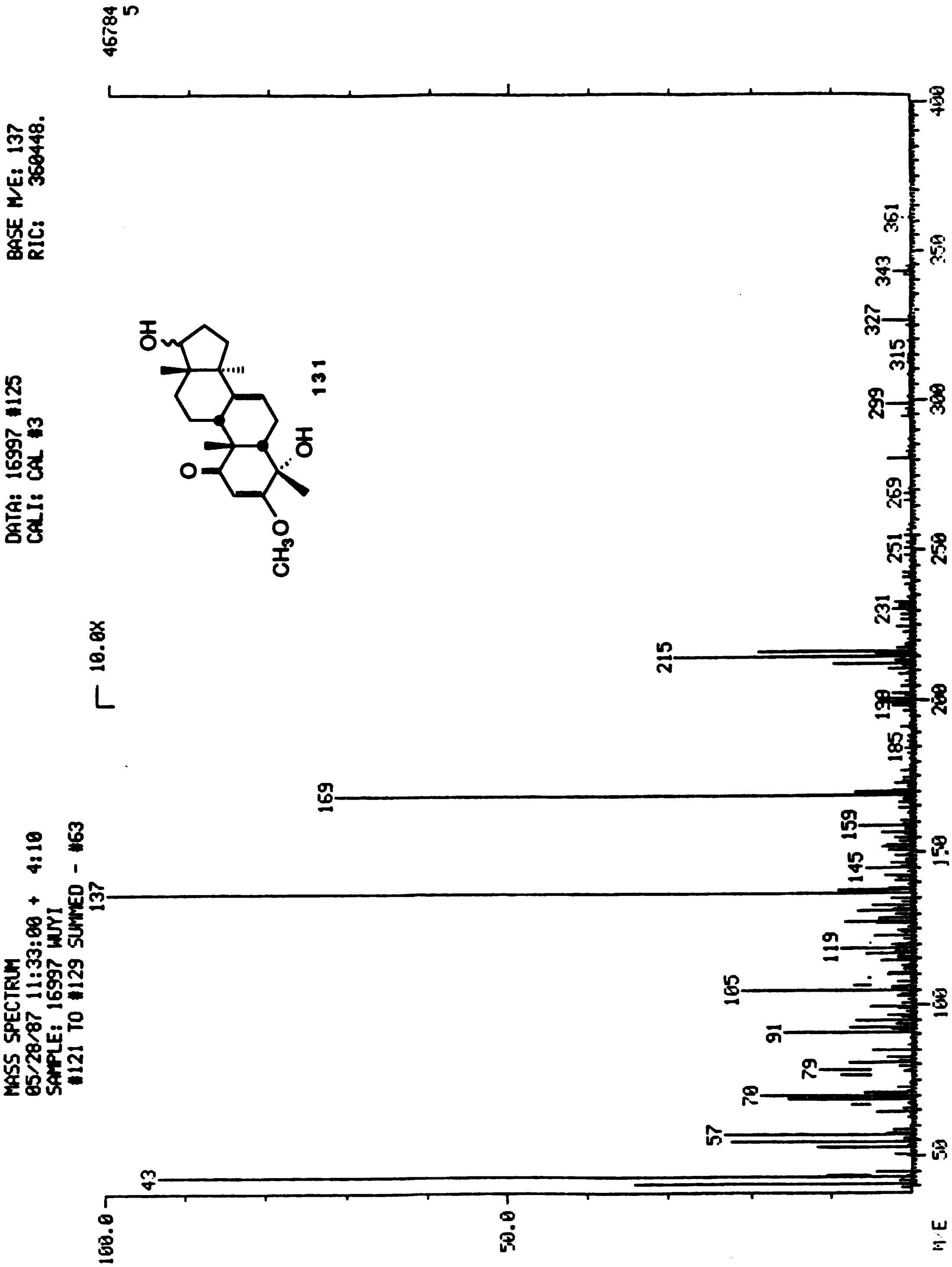


Figure 156. Mass spectrum of 131

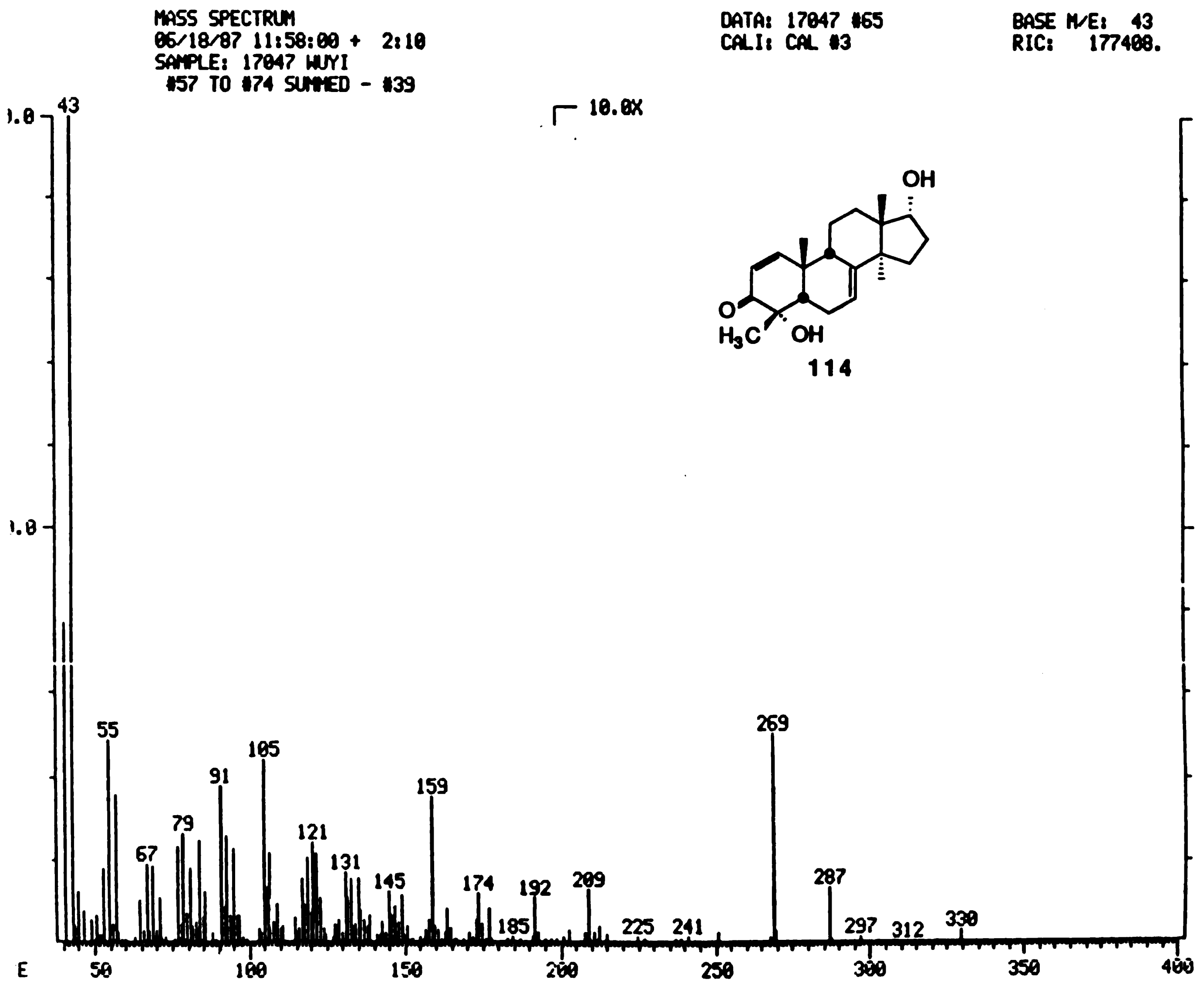


Figure 157. Mass spectrum of **114**

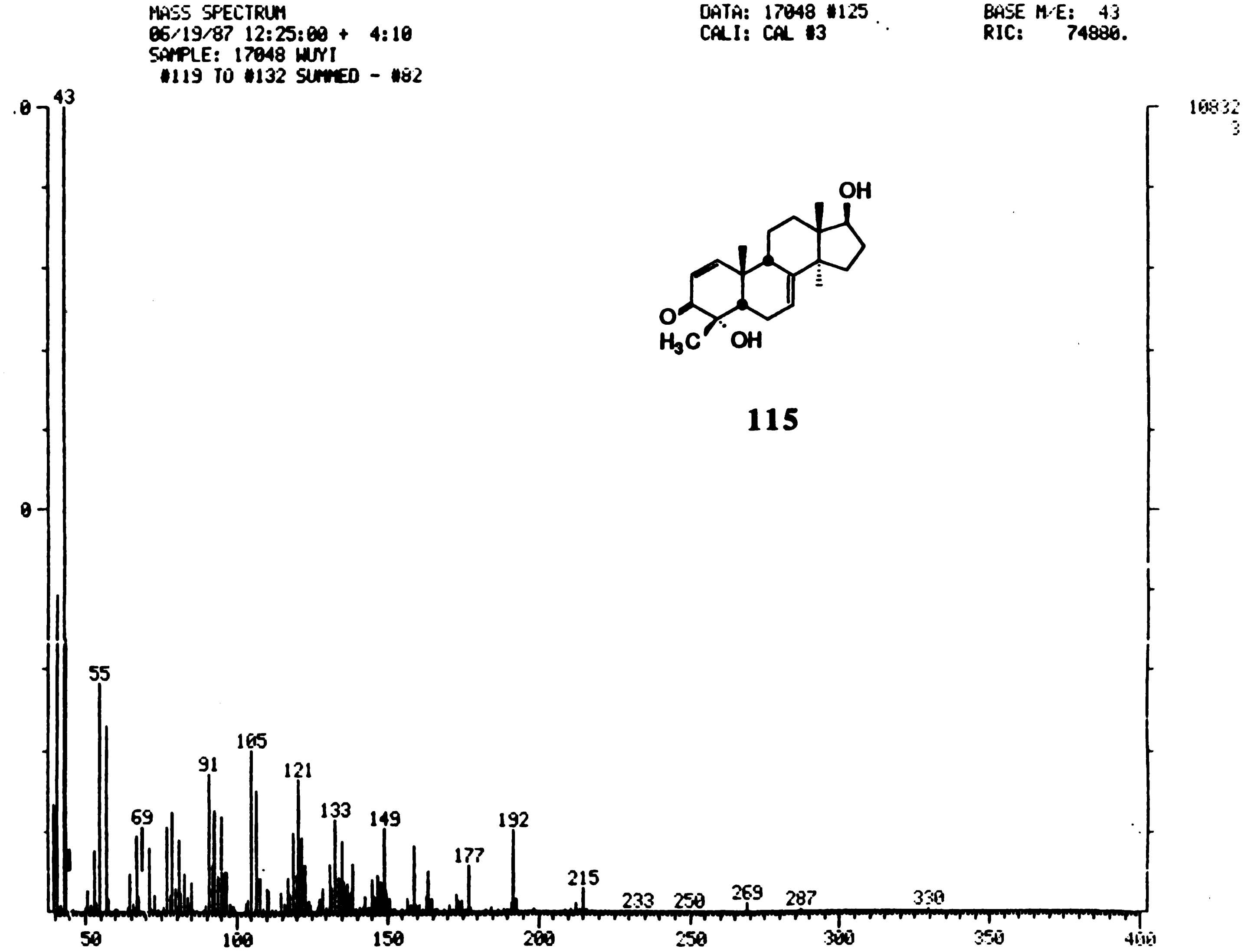


Figure 158. Mass spectrum of 115

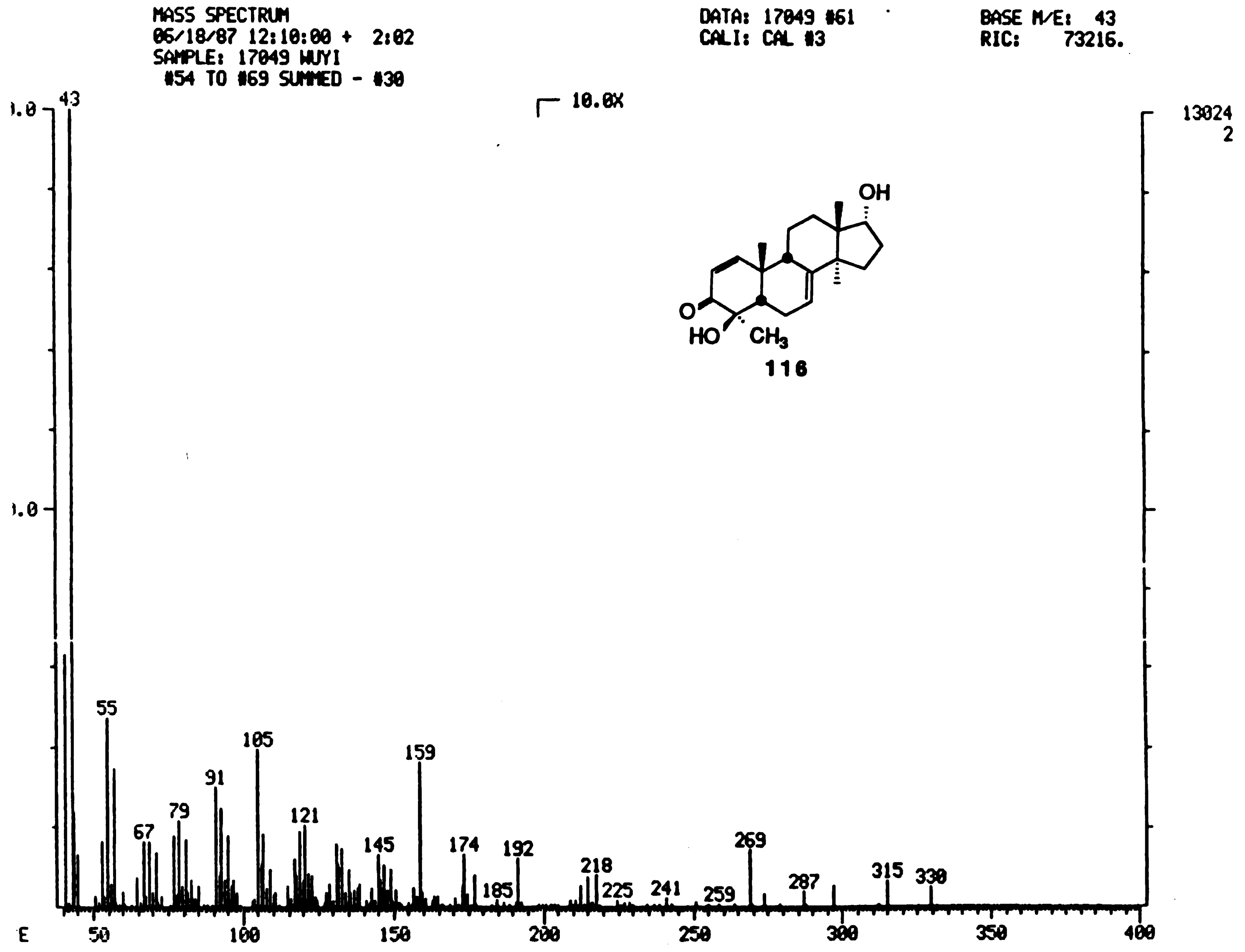


Figure 159. Mass spectrum of 116

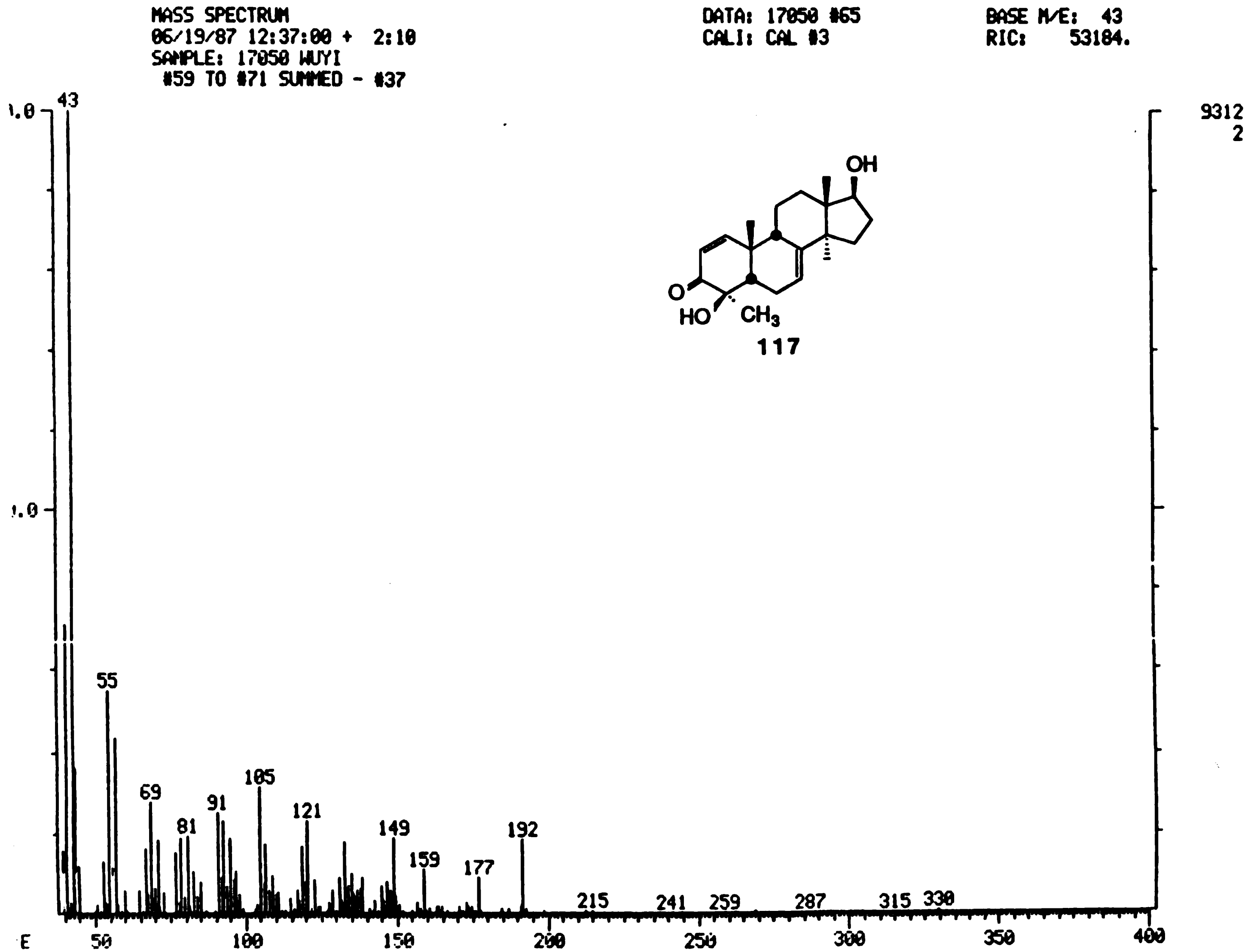


Figure 160. Mass spectrum of 117

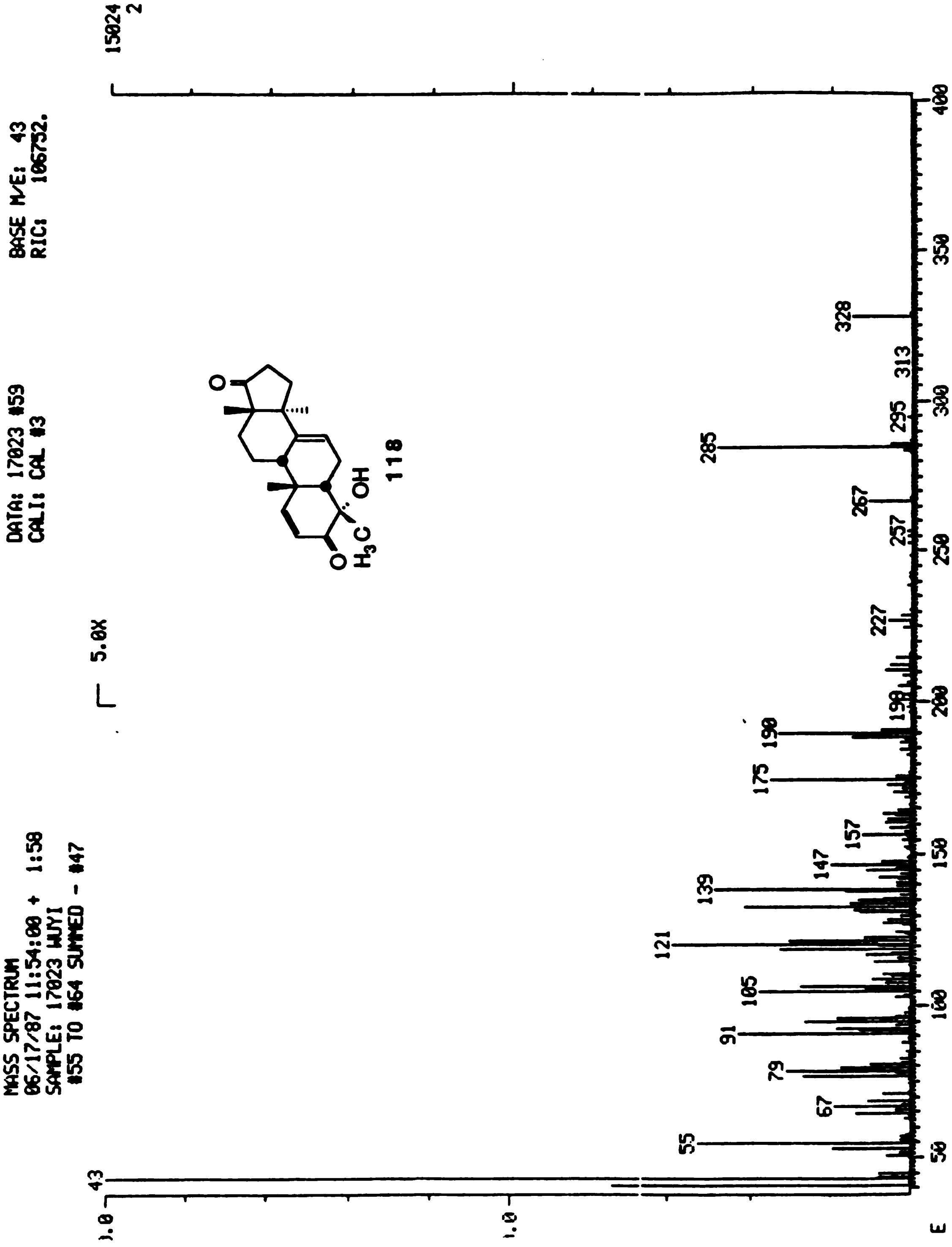


Figure 161. Mass spectrum of 118

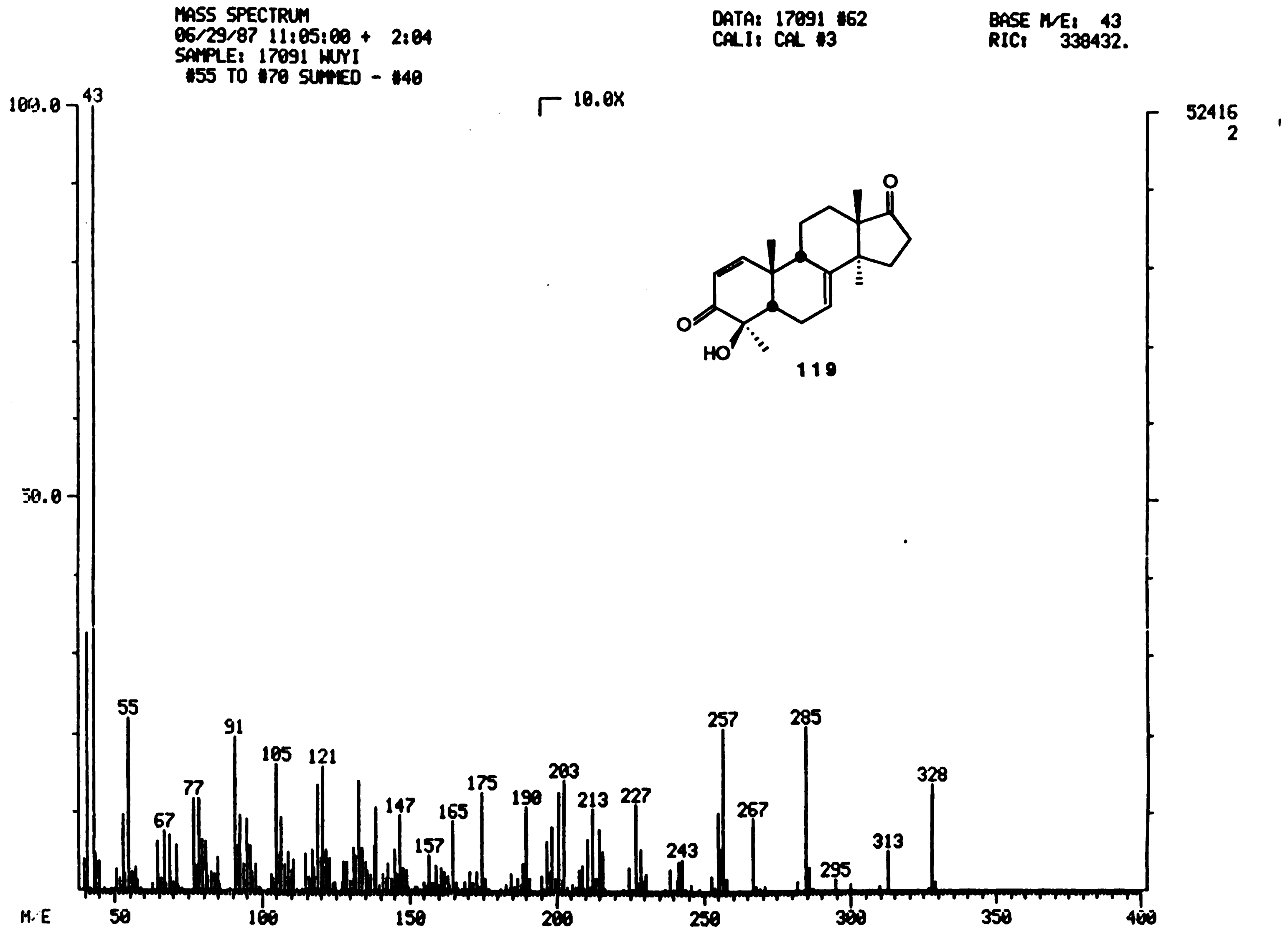


Figure 162. Mass spectrum of 119

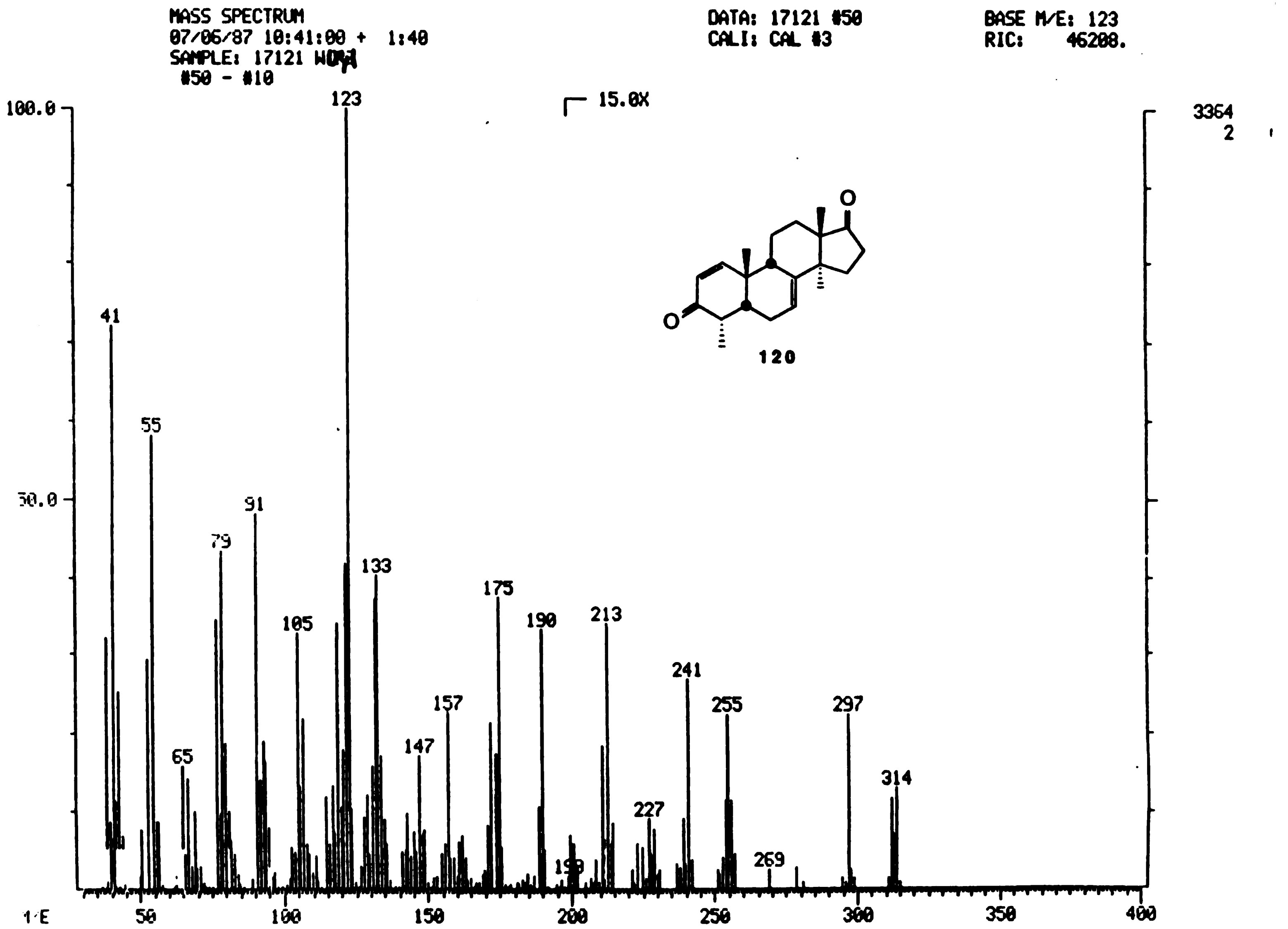


Figure 163. Mass spectrum of **120**

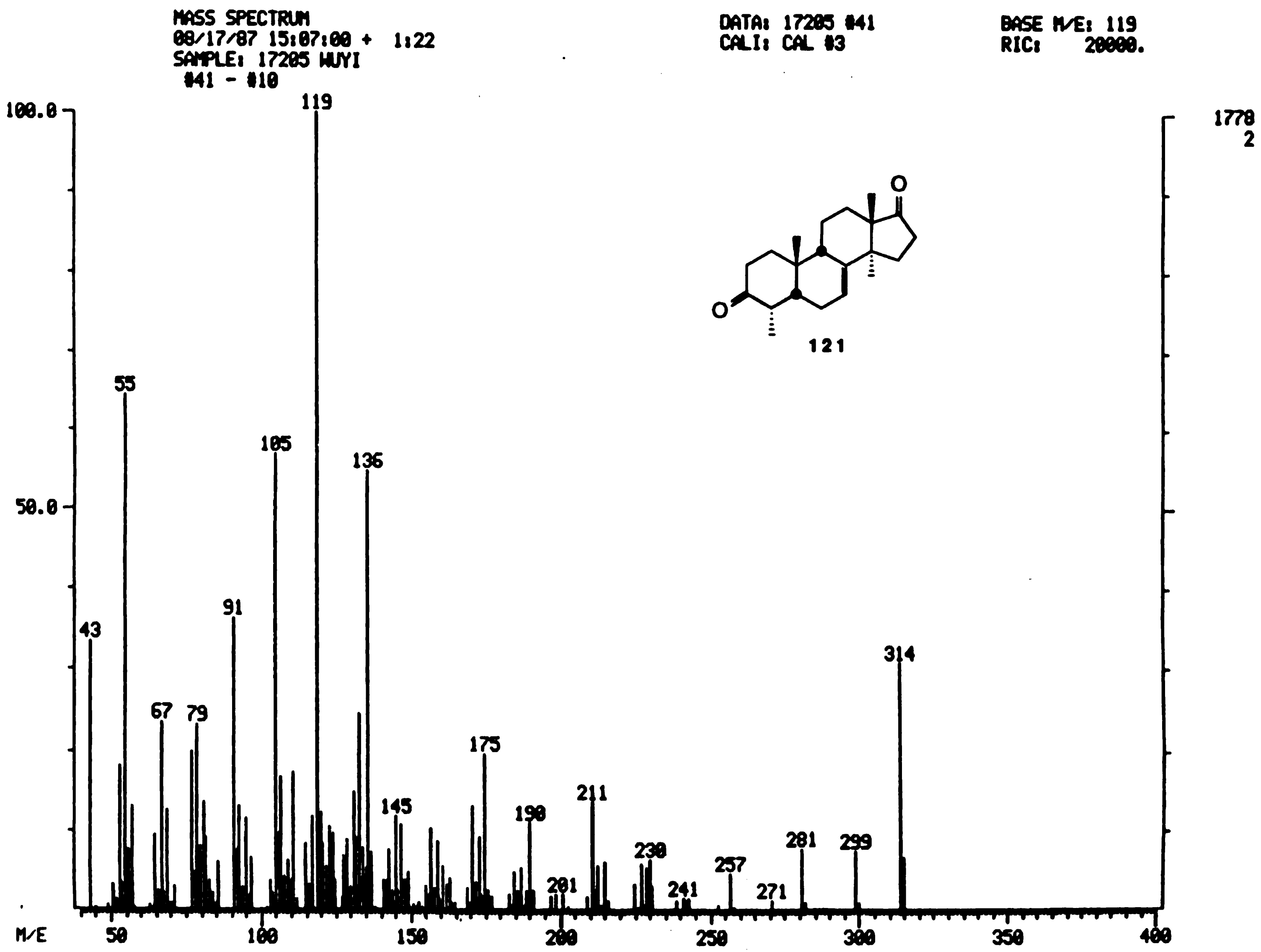


Figure 164. Mass spectrum of 121

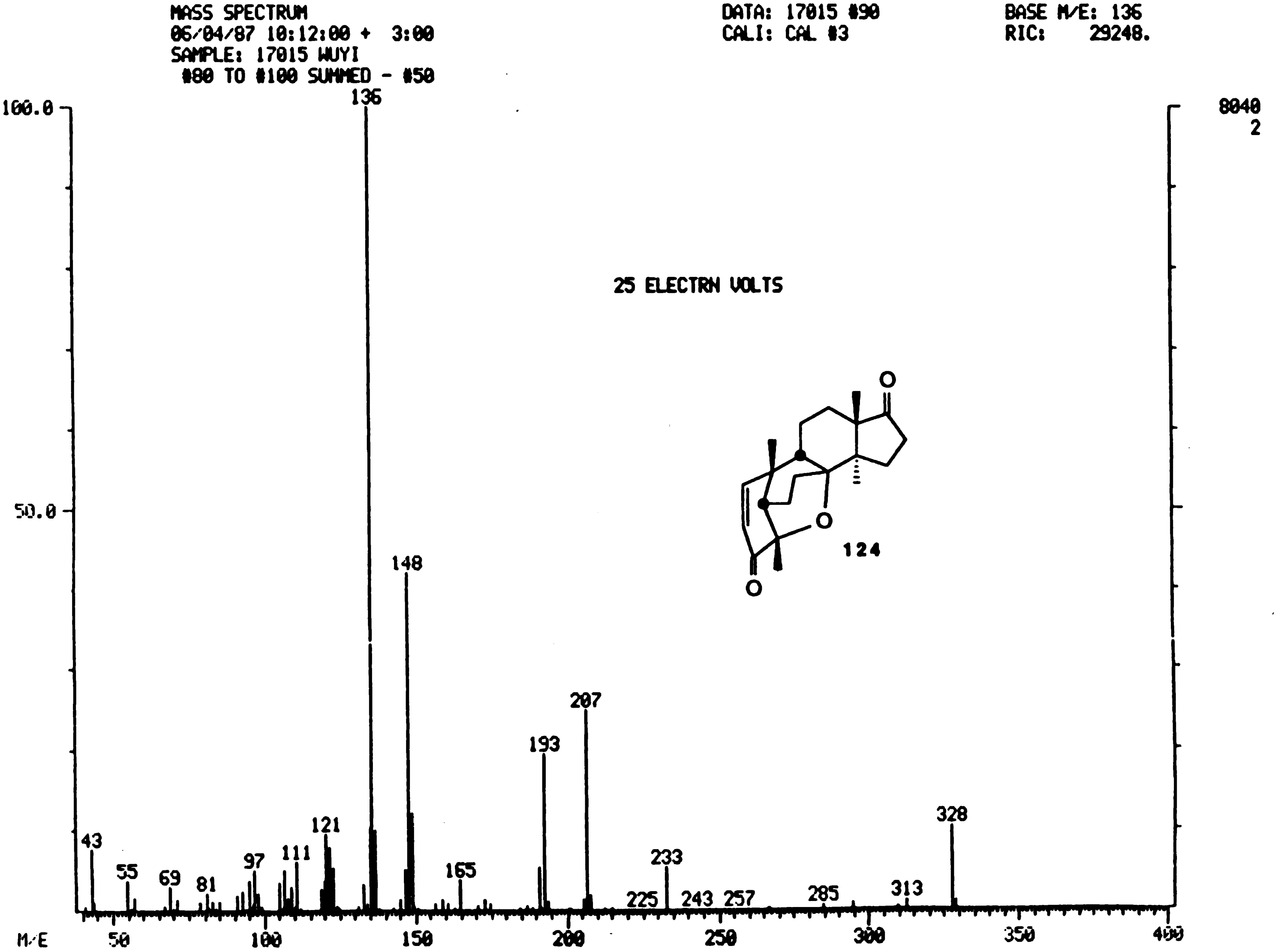


Figure 165. Mass spectrum of **124**

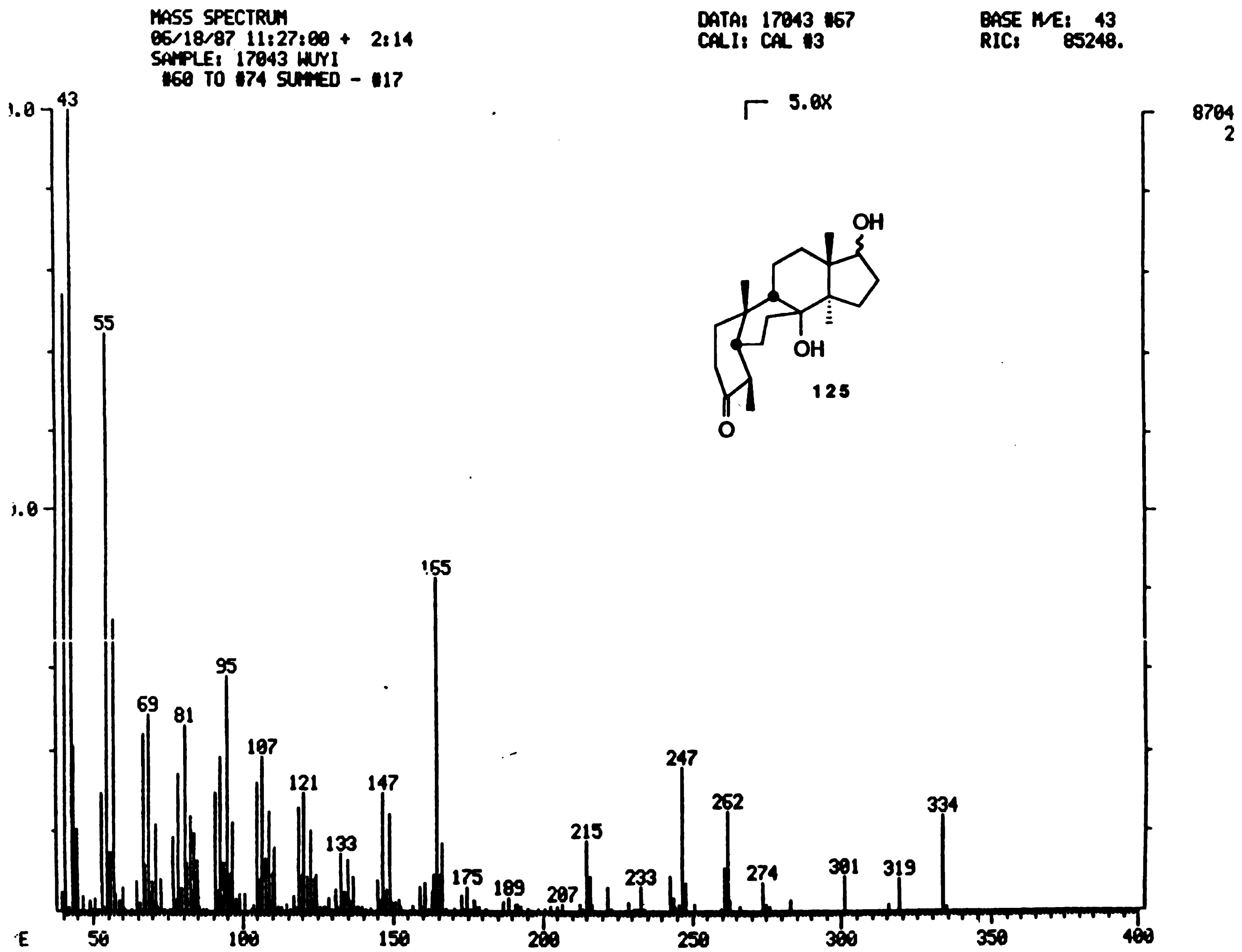


Figure 166. Mass spectrum of 125

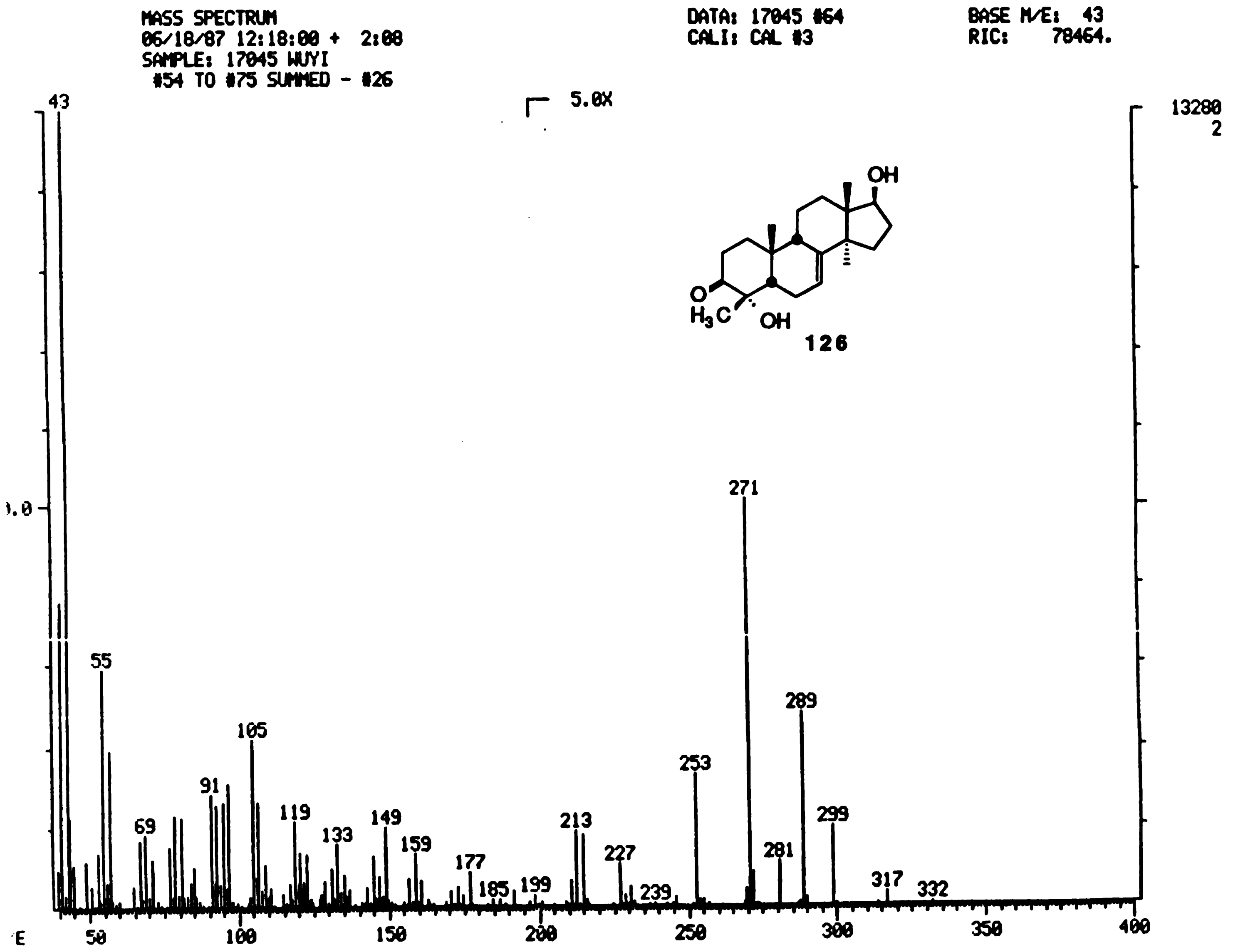


Figure 167. Mass spectrum of **126**

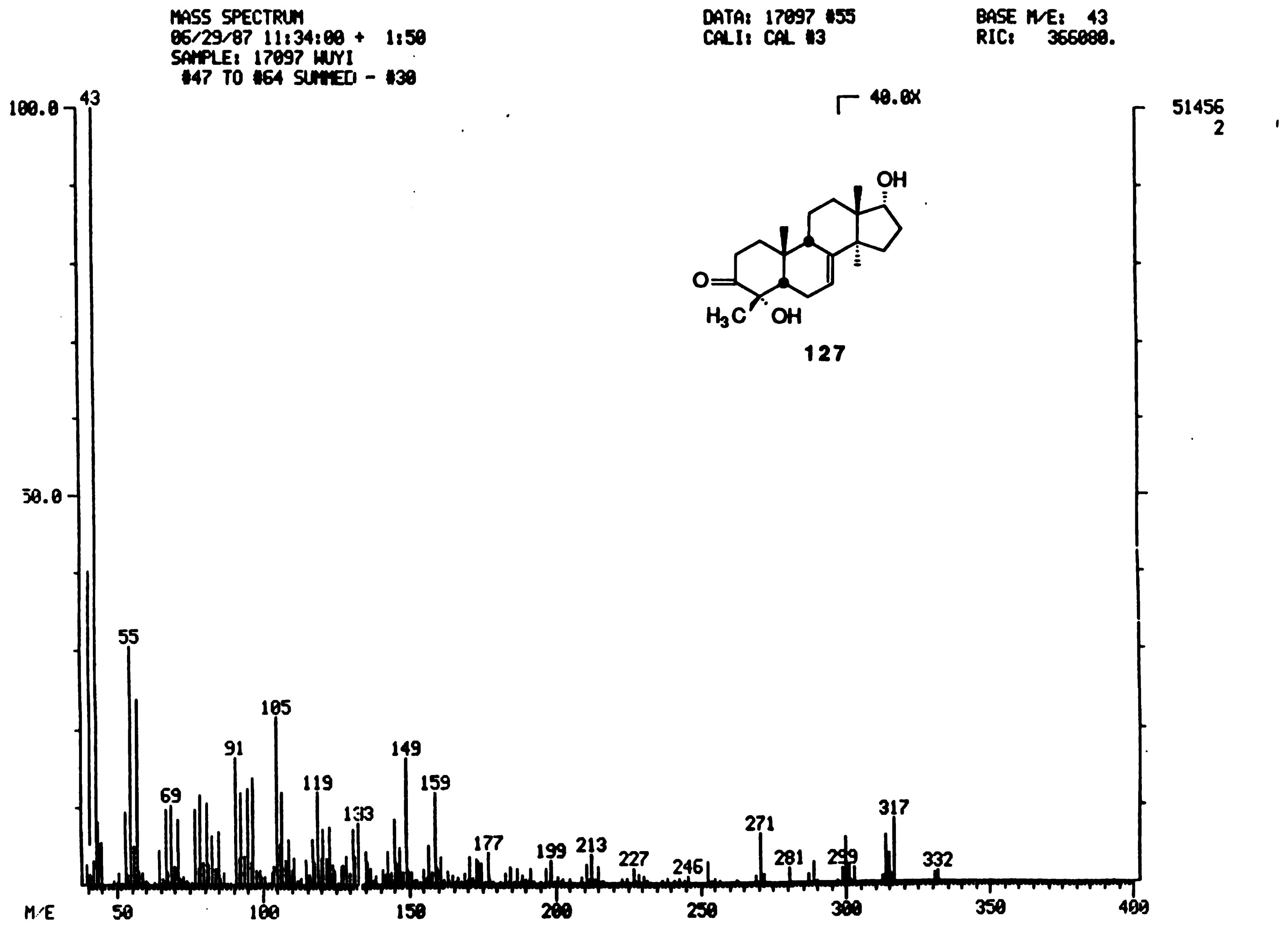


Figure 168. Mass spectrum of 127

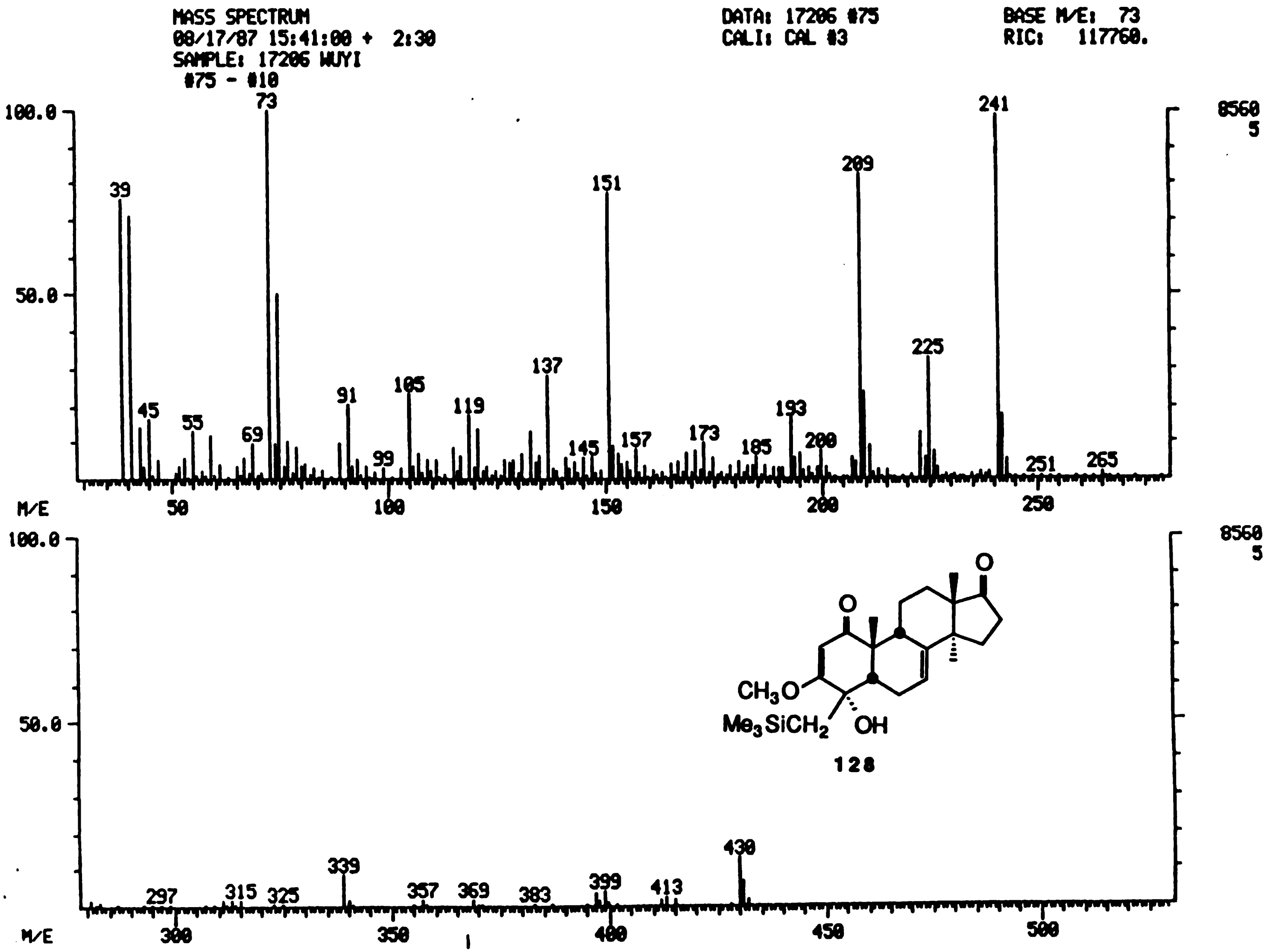


Figure 169. Mass spectrum of 128

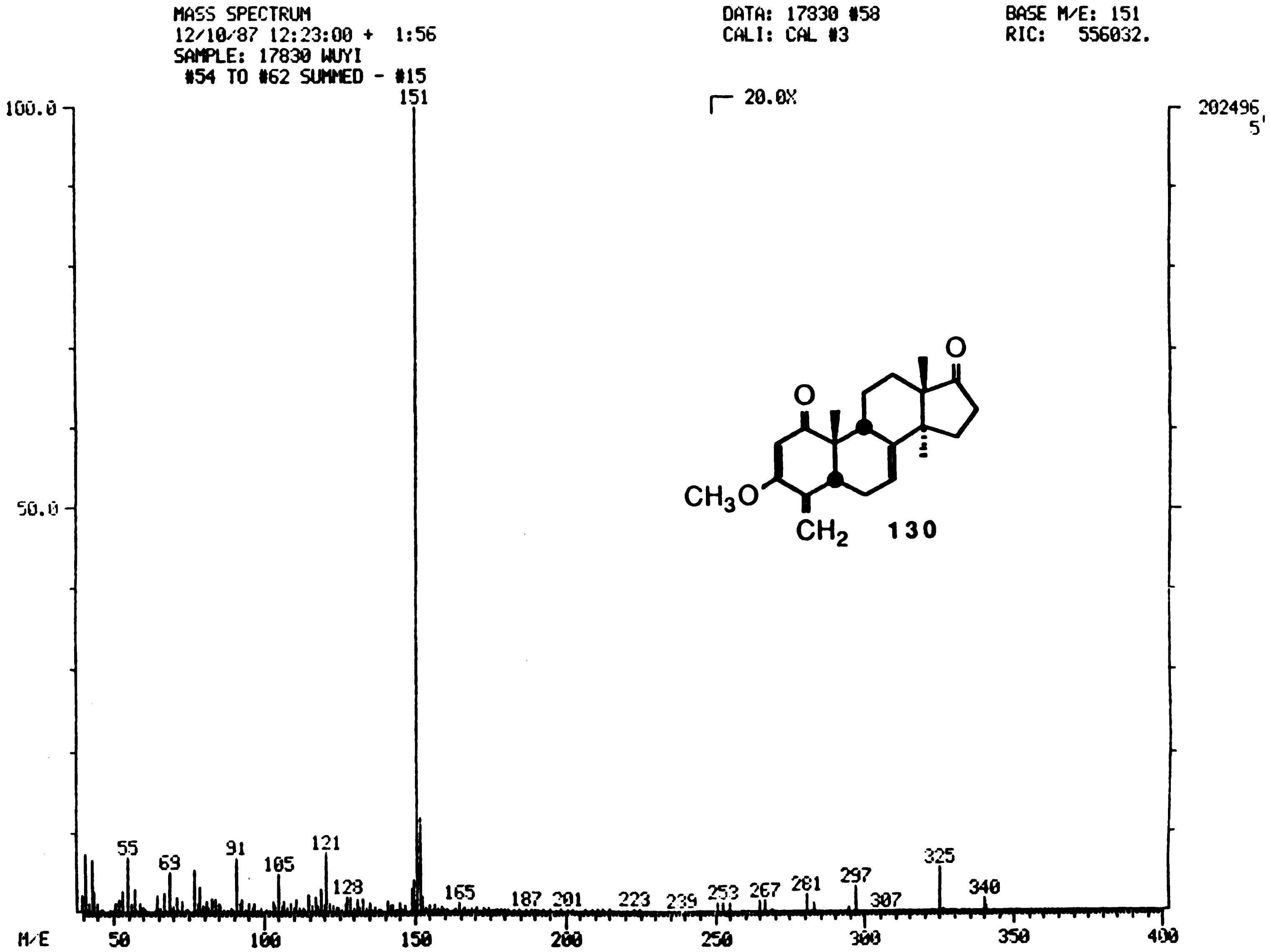


Figure 170. Mass spectrum of 130

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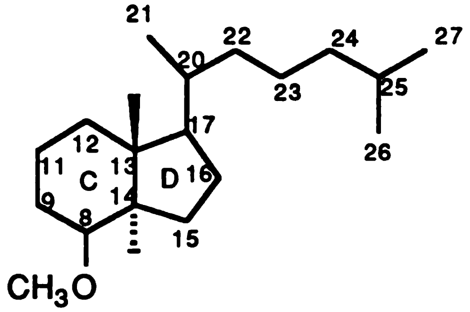
35. For convenience, in this dissertation we use a numbering system equivalent to that of triterpenes. Likewise we use C and D to designate the six-and -five membered rings in the bicyclic model (as shown below).



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84. **TABLE 7:**

Selected ^{13}C NMR Chemical Shifts for Lanosterol, Euphol and 17

Carbon Atoms[a,b]	Chemical Shift[c] in: Lanosterol	Euphol	17
16	30.7	29.7	29.2
17	50.3	49.6	48.9
20	36.7	35.3	34.9
22	36.2	35.7	35.4

a. Triterpene numbering; b. A comparative value for C-12 is omitted, since the methoxy group in 17 causes a large perturbation at this site; c. Parts per million from internal tetramethylsilane.

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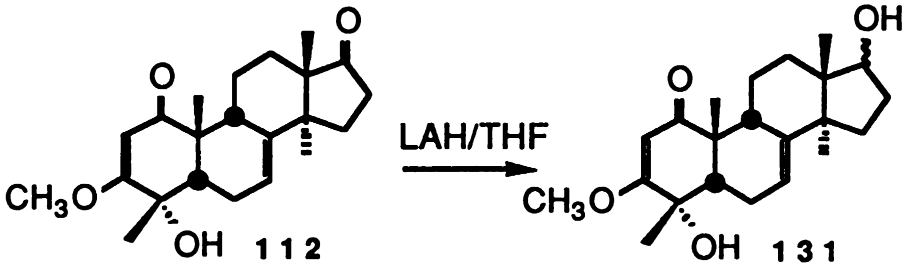
93. Compound **112** was reduced by LAH to **131** in excellent yield:



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