This is to certify that the

dissertation entitled

Studies Directed Toward the Synthesis
of Euphane Triterpenes

presented by

Lawrence Kolaczkowski

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

William H. Reusch
Major professor

Date 12-8-85

Studies Directed Toward the Synthesis of Euphane Triterpenes

By

Lawrence Kolaczkowski

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1984

DEDICATION

Dedications are, by nature, usually rather short. However in the journey leading to this degree, several people have had a profound influence on my life, and I dedicate this work to them.

To my parents, Eugene and Esther Kolaczkowski, who gave me a warm and loving environment to grow up in. The only advice they gave was to do the best I could. Their only wish for me was to be happy.

To my brothers and sisters, Gene, Marcia, Jim, Sandy, Dan, and Chris, who along with mom and dad have made my family one of life's true treasures.

To Susan Kauzlarich, whose love and encouragement has made the difference in my life.

To Dave Odelson, a special friend and colleague, whose help and companionship made the ups and downs of life in graduate school a lot easier to take.

To Brian Sumner, one of my oldest and dearest friends, for always being there.

To Dr. Robert M. Coates, who gave me my first opportunity to do research.

To Dr. Caetan Vaz, who taught me the art of chemistry on a millimole scale.

To Dr. William Reusch, who taught me never to speculate until all of the data is in.

And last, but certainly not least, to Al and Fran Price, Dave and Emily Johnson and all the Johnson Scholars, who reminded me that there is a world outside of chemistry.

ACKNOWLEDGEMENTS

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Finally, the author wishes to thank Michigan State University for a Teaching Assistantship, and also the Amway Corporation and Union Carbide, for a Summer term Research Fellowship.

DIBAL, followed by mild acid treatment gave the desired ring A enone as a mixture of C-17 hydroxyl epimers 8$\underset{\sim}{1}$ and 8$\underset{\sim}{2}$. Protection of these alcohols as MEM-ethers, followed by methylation with excess potassium t-butoxide and methyl iodide produced the C-4 gem-dimethyl compounds 9$\underset{\sim}{1}$ and 9$\underset{\sim}{2}$. Deprotection with $TiCl_4$ followed by PDC oxidation gave diketone 9$\underset{\sim}{5}$. Finally catalytic reduction of the Δ^1 double bond, followed by selective reduction of the C-3 carbonyl function with $NaBH_4$ yielded 7$\underset{\sim}{3}$. The structure of 7$\underset{\sim}{3}$ has been confirmed by X-ray crystallography.

Preliminary work on a modification of this synthesis to give the AB-trans product 7$\underset{\sim}{1}$ is also presented.

ABSTRACT

STUDIES DIRECTED TOWARD THE SYNTHESIS OF EUPHANE TRITERPENES

By

Lawrence Kolaczkowski

Studies directed toward the synthesis of the euphane triterpenes are presented. The key steps in the synthesis are a regiocontrolled, Lewis acid-catalyzed Diels-Alder reaction, and a selective photochemical epimerization at a quaternary carbon center. Thus, the Diels-Alder reaction between quinone 28 and diene 24 in the presence of $BF_3 \cdot OEt_2$ gave the tetracyclic adduct 29 in good yield. Irradiation of a mono-enol acetate derivative of 29 (61) with light filtered to block wavelengths less than 365 nm yielded a 5.5:1 mixture of the C-10 methyl epimer 62 and recovered 61 respectively. In this manner our key tetracyclic intermediate was converted from a lanostane configuration to a euphane configuration in one step.

Surprisingly, solvolysis of enol acetate 62 in basic methanol yielded the AB-cis fused enedione 70 rather than the expected AB-trans isomer 65.

The C-4 carbonyl oxygen in 70 was removed by selective reduction with zinc and acetic acid, conversion of the resultant alcohol 79 to mesylate 80, followed by reduction with zinc and sodium iodide. Reduction of dienone 83 with

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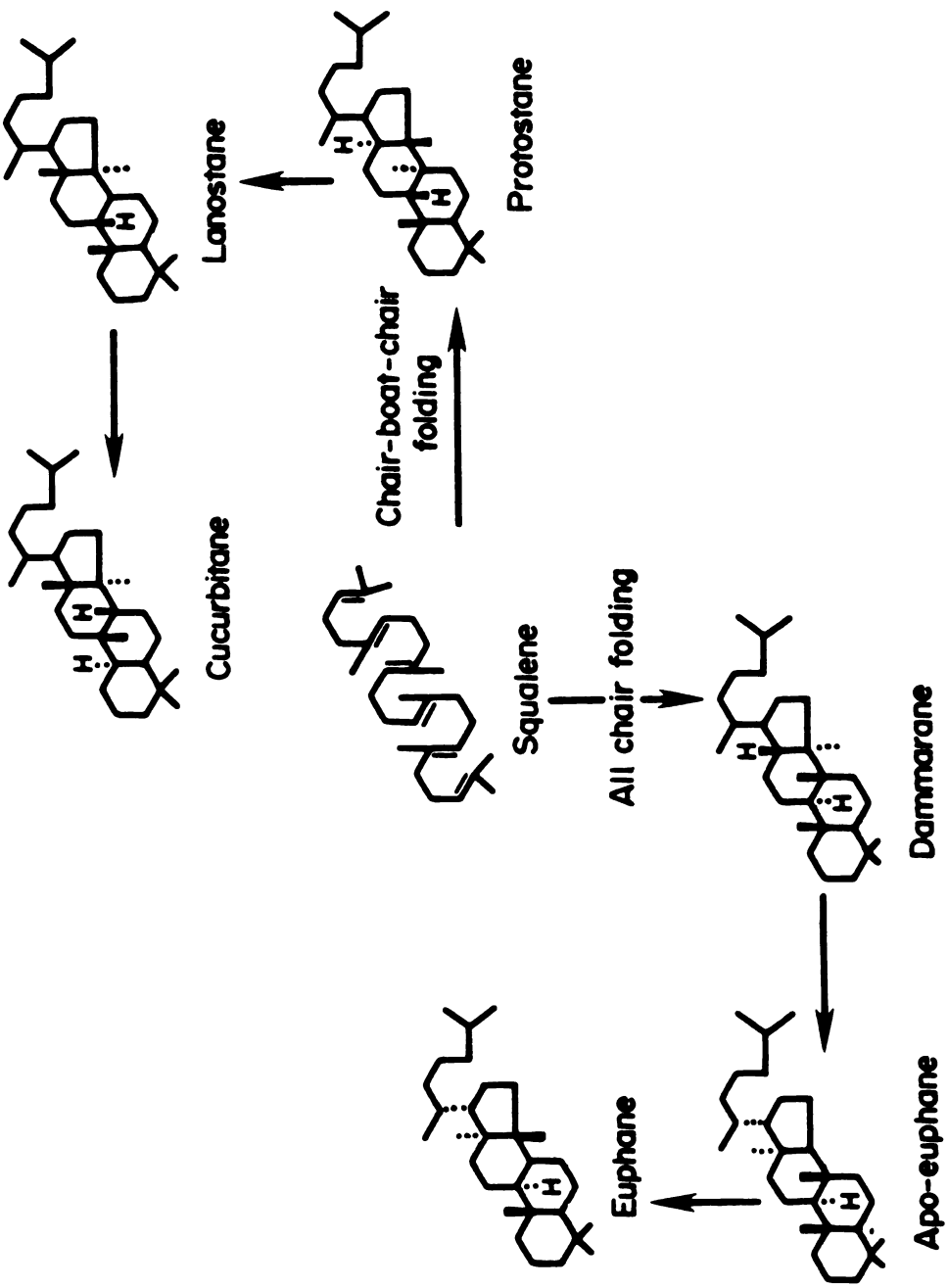
INTRODUCTION

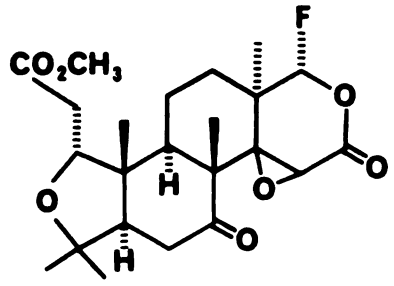
Terpenoid compounds are ubiquitous in the plant kingdom. Their presence in plants in such great numbers and structural diversity is enigmatic. Whereas many terpenoid compounds accumulate in concentrations greater than those normally associated with active metabolism, their exact function in plants is largely unknown.

Triterpenes represent the largest class of terpenoid compounds. Many triterpenes, especially the more highly functionalized members, exhibit a wide variety of physiological activity. Tetracyclic triterpenes, a small yet structurally diverse sub-group, are composed primarily of two families, the euphanes and the lanostanes. Constitutionally both the euphanes and lanostanes are very similar to the steroids. All have a common origin; enzyme mediated cyclization of squalene.[1] The conformational constraints imposed by interaction with a specific enzyme determine into which manifold the cyclizations fall. As demonstrated in Scheme I, an all chair folding prior to cyclization leads to the euphanes, whereas a chair-boat-chair folding leads to the lanostanes and eventually the steroids.

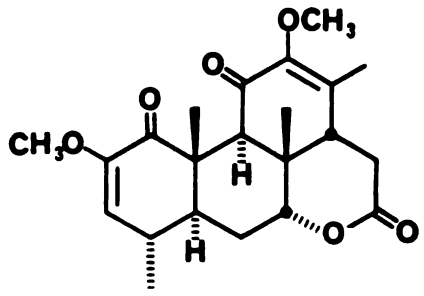

Lanostane
Protostane
Cucurbitane
Chair-boat-chair folding
Squalene
All chair folding
Dammarane
Euphane
Apo-euphane

SCHEME I

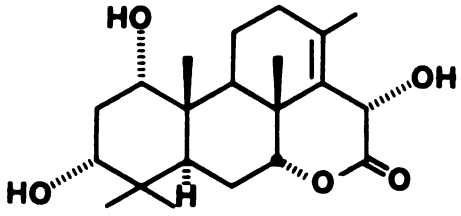
The euphanes are important compounds, not only in their own right, but as precursors to a variety of oxidized and rearranged natural products such as the limonoids, meliacins, and simaroubalides.



veprisone
a limonoid



quassin
a simaroubalide

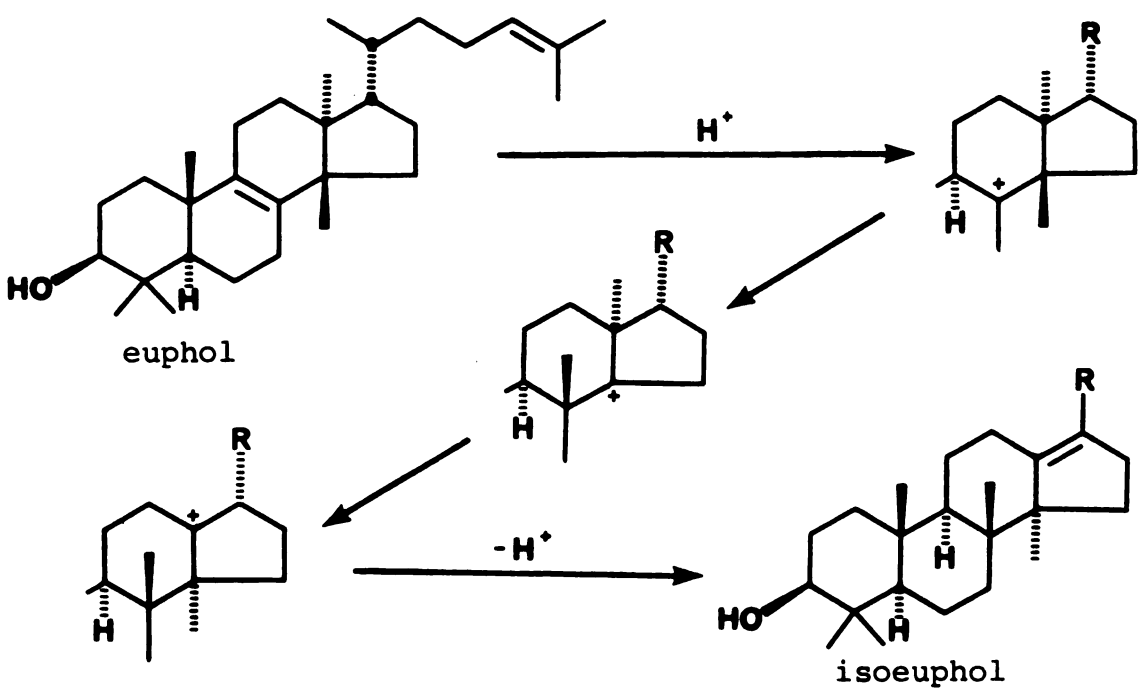


kivol
a meliacin

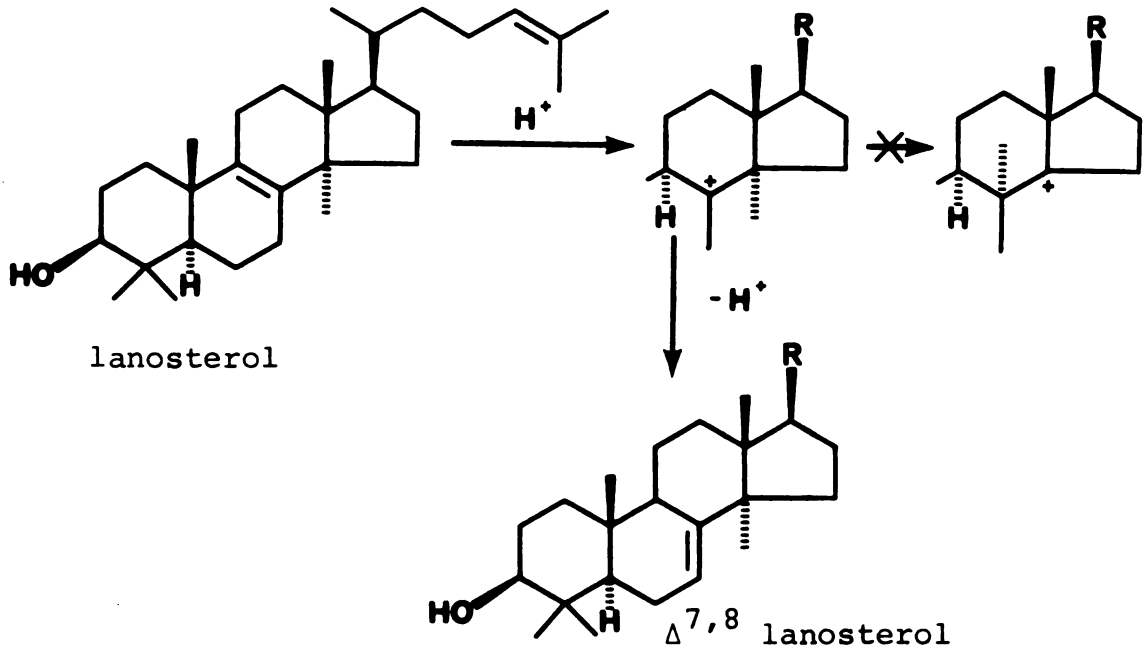
Euphol, one of the best known euphane triterpenes was first isolated by Newbold and Spring in 1944[2] from several plants of the genus *Euphorbia*. The correct structural assignment however, was not reported until 1955. Many chemical and physical tests suggested a structure for euphol which was identical to the previously identified lanosterol. There were, nonetheless, subtle differences in the reactivity of the two compounds, the most conspicuous being their behavior under acidic conditions.

Treatment of lanosterol with protic acid results in isomerization of the $\Delta^{8,9}$ double bond to the $\Delta^{7,8}$ position.

However, when euphol is treated under identical conditions, it undergoes rearrangement to yield the isoeuphane ring system. The structural and/or stereochemical differences responsible for such drastically different reactivity were unclear. Finally in 1955 Barton et al.[3] determined conclusively the structure of euphol and isoeuphol. Barton reasoned that the structural relationship of the C and D rings in euphol and lanosterol was enantiomeric (although this initial report did not fix the stereochemistry at C-17). This configuration forces the B and C rings of euphol into strained "half-boat" conformations. Protonation and subsequent sigmatropic 1,2 methyl shifts establish a BC trans-ring fusion, which allows both rings to assume more stable chair conformations. Barton termed this relief of steric strain a "conformational driving force."



In the lanostanes, where the B and C rings are already in the chair-chair conformation, the rearrangement does not occur, as this would lead to the higher energy cis fused system.

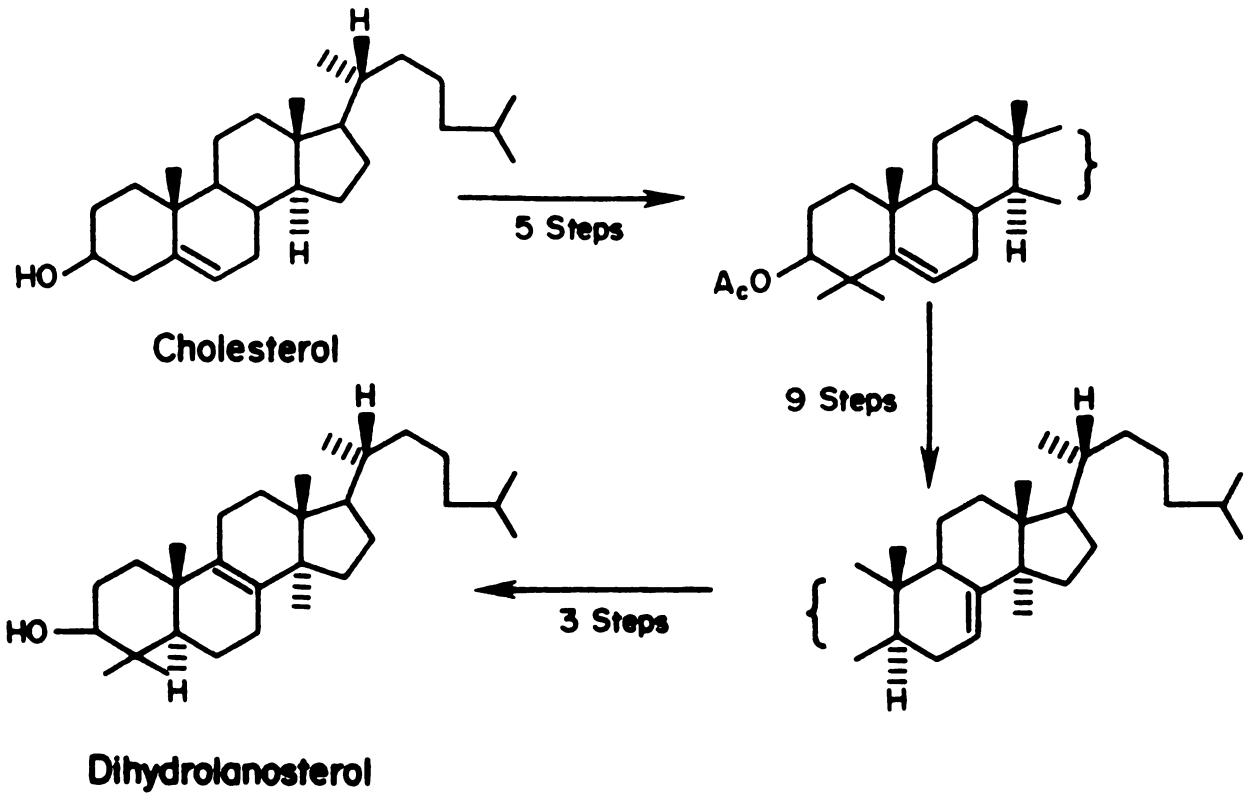


lanosterol

$\Delta^{7,8}$ lanosterol

Despite the structural similarity between tetracyclic triterpenes and steroids there is a a great disparity in the amount of work published in each area. While over 100 steroid syntheses have been reported, to date only two tetracyclic triterpene syntheses have appeared in the literature. The great structural similarities belie the significantly greater synthetic challenge of the tetracyclic triterpenes. Both tetracyclic triterpene syntheses reported have been in the lanostane family, and this work represents our efforts toward the first euphane triterpene synthesis.

The two lanostane syntheses reported represent substantially different strategic approaches. The first was reported by Woodward and co-workers in 1954.[4] In it they take advantage of the constitutionally and configurationally steroid-like character of lanosterol. Starting with cholesterol, the conversion to lanosterol was accomplished in 17 steps, as outlined in Scheme II.

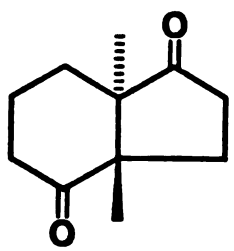


This approach emphasizes one of the most challenging problems in tetracyclic triterpene synthesis; construction of the bis-angular methyl CD ring fusion. Most of the steps in the Woodward synthesis addressed this problem.

The synthesis reported by the van Tamelen group[5] used a biomimetic strategy. The polyene precursor was synthesized in 23 steps from (-) limonene. Lewis acid-initiated cyclization of the epoxide gave a 30% yield of tetracyclic adducts (see Scheme III).

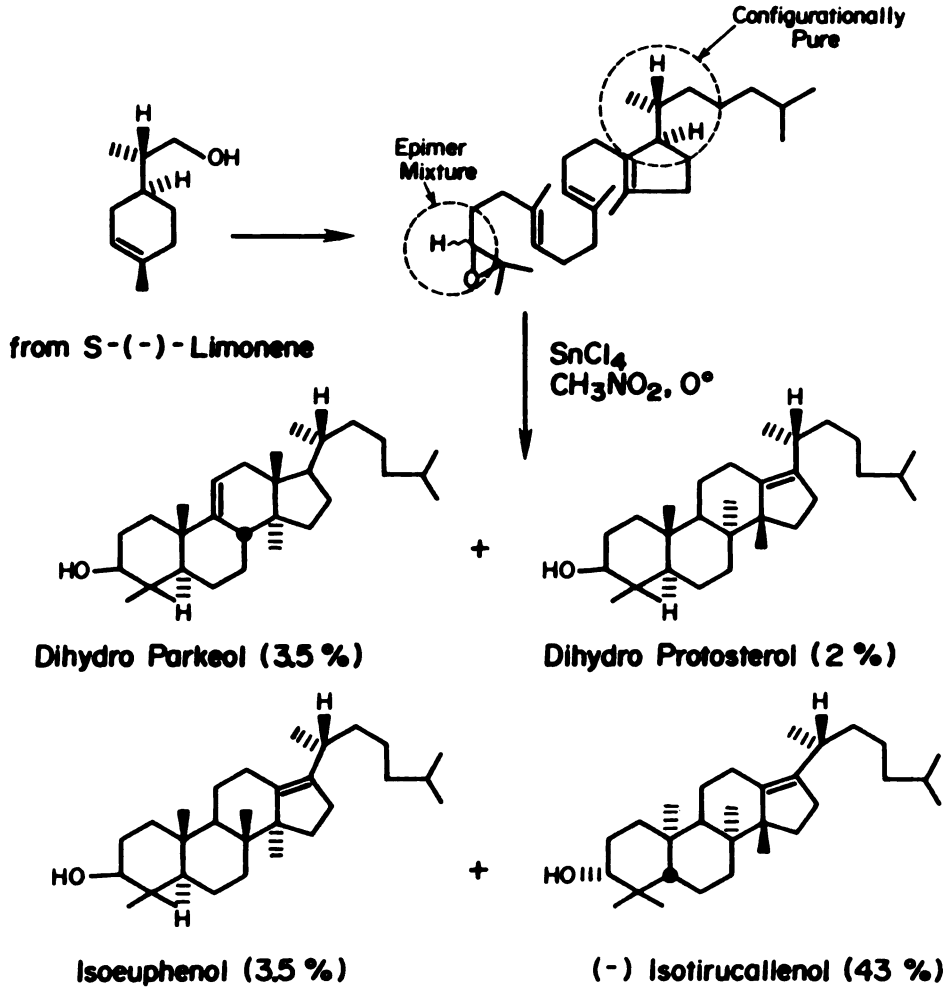
It is of interest to note that all the isomers formed from a chair-boat-chair folding are isoeuphane in nature (presumably resulting from the initially-formed euphane ring system). This demonstrates not only the sensitivity of these molecules to rearrangement, but also the inappropriate nature of this approach to the synthesis of the euphane triterpenes.

Previous work in our research group[6] has provided a simple means of preparing multigram quantities of diketone 1. This diketone contains the requisite trans dimethyl functionality found in the CD rings of many



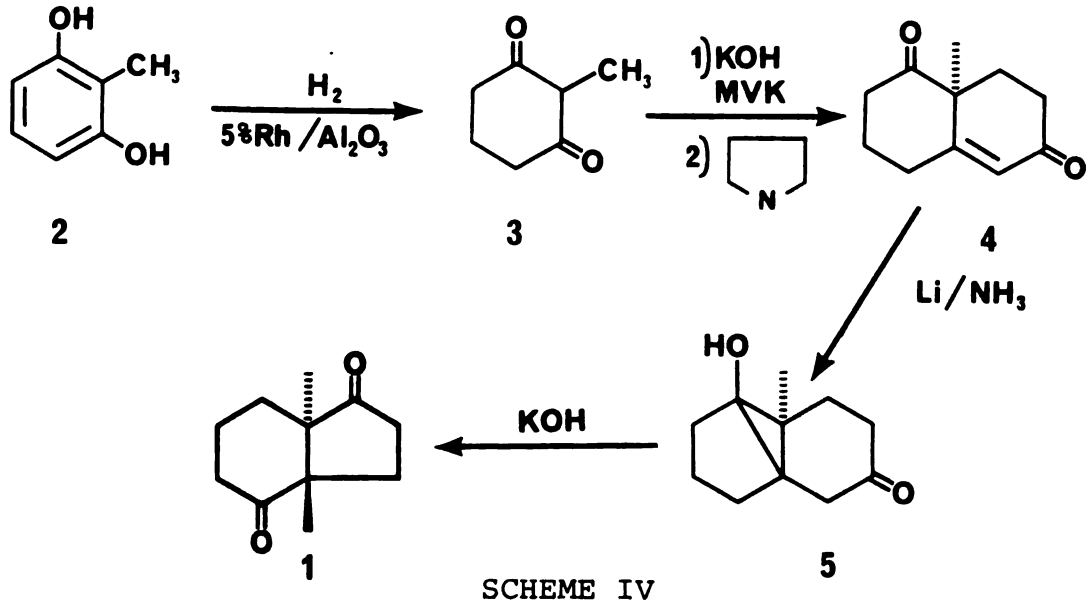
1

tetracyclic triterpenes. Use of 1 as a starting material for the synthesis of such compounds handily avoids the problem of angular methyl group introduction encountered by the Woodward group in their synthesis of lanosterol.


Configurationally Pure
Epimer Mixture
from S-(-)-Limonene
SnCl4
CH3NO2, 0°
Dihydro Parkeol (3.5 %)
Dihydro Protosterol (2 %)
Isoeuphenol (3.5 %)
(-) Isotirucallenol (43 %)

SCHEME III

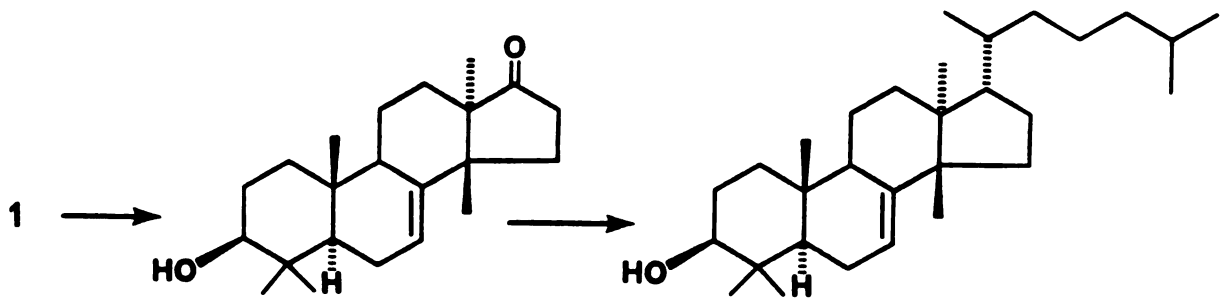
The synthesis of 1 is outlined in Scheme IV. If the



SCHEME IV

aldol cyclization is effected with enantiomerically-pure proline as the catalyst, good yields of optically active Wieland-Miescher ketone 4 can be obtained.[7] This enables us to synthesize either optical antipode of 1, one enantiomer for euphane synthesis, and the other for the lanostanes. Since 1 is the only chiral component in our strategy, this provides an easy access to an optically active synthesis of the euphanes.

Our approach to the synthesis of the euphane triterpenes was envisioned as two steps: fusing of the AB ring system to the six-membered ring and attaching the side chain to the five-membered ring.



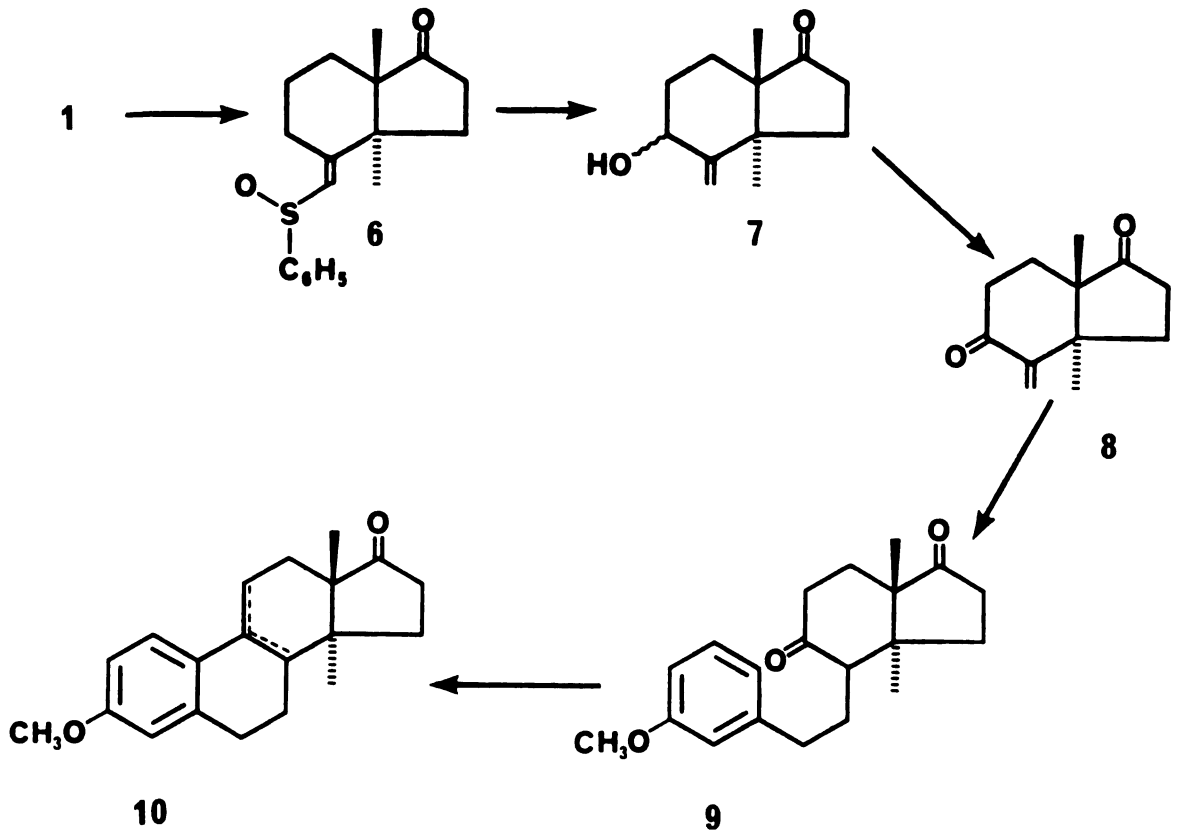
Several strategies are possible for construction of the carbocyclic framework from diketone 1. Using terminology borrowed from steroid chemistry, they fall into three categories, each which will be discussed in turn.

I. A + CD ⟶ ACD ⟶ ABCD

In this approach an A-ring component is added to the CD ring system, and then the B-ring is closed to complete the tetracyclic system. Several examples of this strategy, where an A-ring anion is added to a C-ring carbonyl have been accomplished by W.S. Johnson et al.[8] A direct application of this strategy using diketone 1 has been reported recently by Bull and Bischofberger[9] in their 14α-methyl-19-norsteroid synthesis (see Scheme V).

Addition of the diethyl(phenylsulfinyl)methylphosphonate anion to 1 gave the expected unsaturated sulfinate 6. Double bond isomerization followed by sulfinate-sulfoxide rearrangement yielded allylic alcohol 7. Oxidation followed by conjugate addition

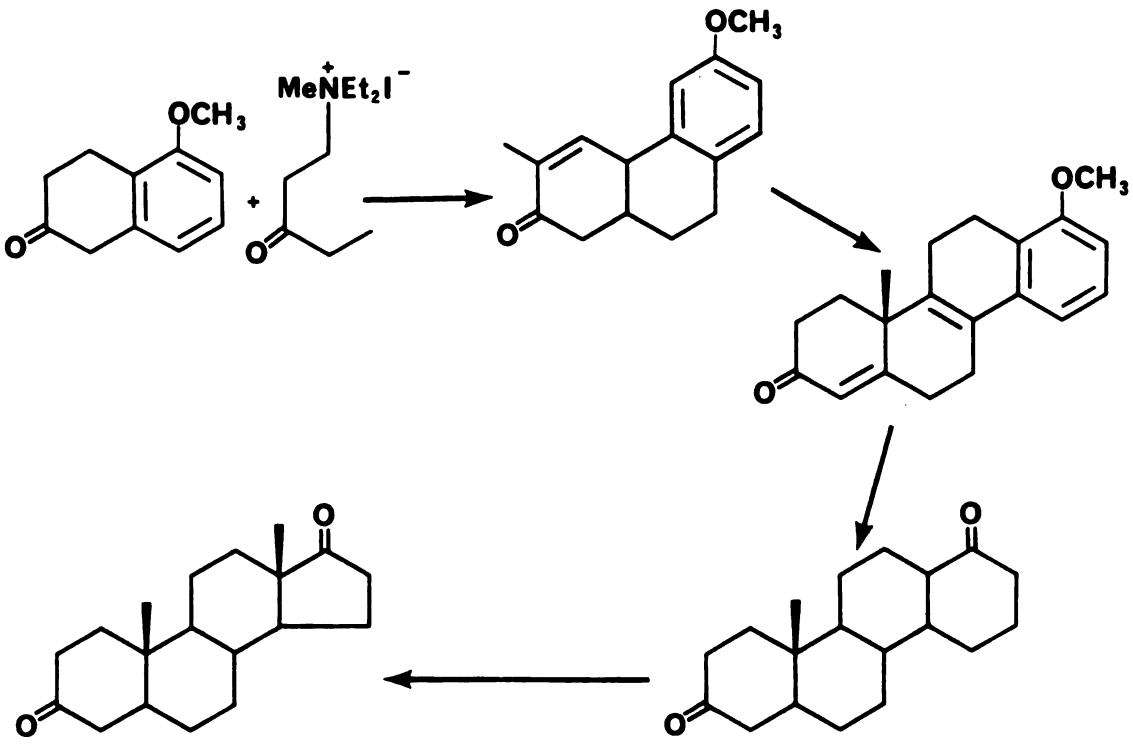
SCHEME V



of 3-methoxybenzylmagnesium chloride to 8 joins the A and CD rings in compound 9. Treatment of 9 with para-toluene sulfonic acid closes the B-ring to give 10 as a mixture of $\Delta^{8,9}$ and $\Delta^{9,11}$ isomers.

II. B + CD ⟶ BCD ⟶ ABCD

A majority of the applications of this strategy are again found in the work of W.S. Johnson. The hydrochrysene approach[10] has been used in the synthesis of several steroids, as outlined in Scheme VI.



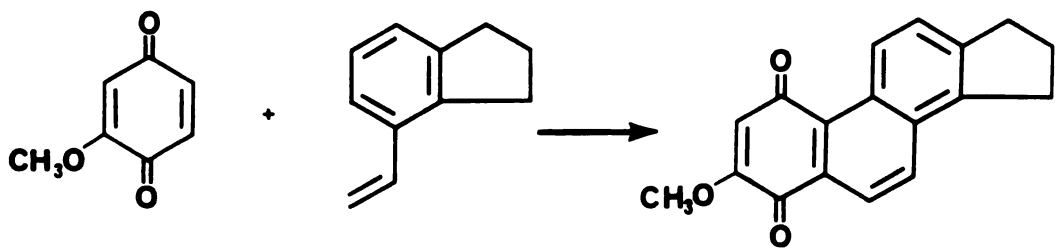
SCHEME VI

III. A + CD —> ABCD

Of the three approaches, the A + CD cycloaddition is by far the most efficient for construction of the tetracyclic framework. Because of the high degree of stereoselectivity in the Diels-Alder reaction, the stereochemistry at the newly generated centers should be cleanly fixed. Despite these advantages, very little attention has been given to this approach.

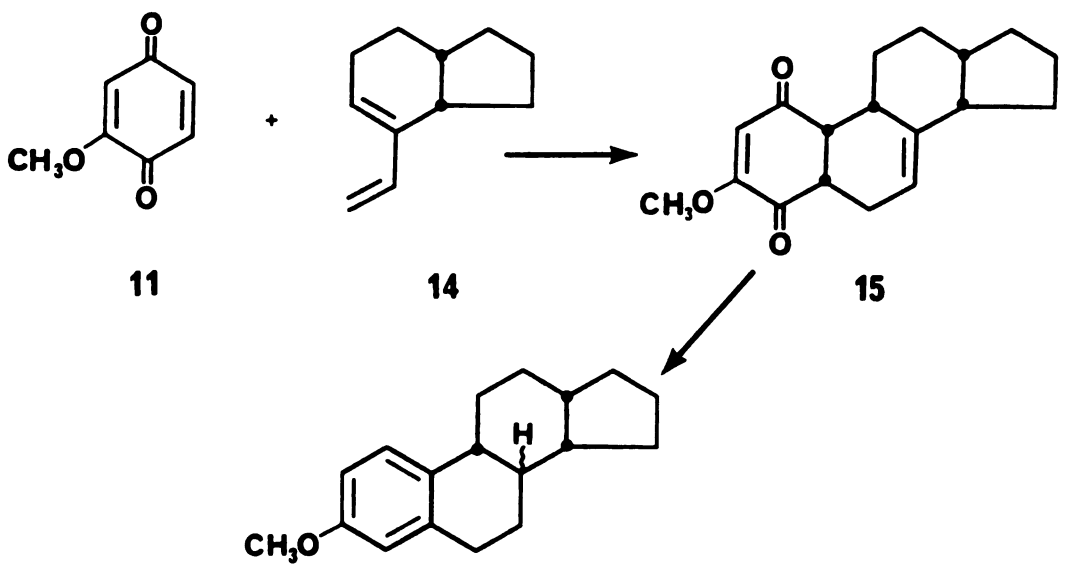
Lora-Tomayo et al.[11] have reported the thermal cycloaddition of quinone 11 to diene 12 to yield tetracyclic adduct 13 as the only product. Reaction of

methoxy-p-benzoquinone 11 with diene 14 reportedly yields



11 12 13

cycloadduct 15,[12] again as a single regioisomer. Compound 15

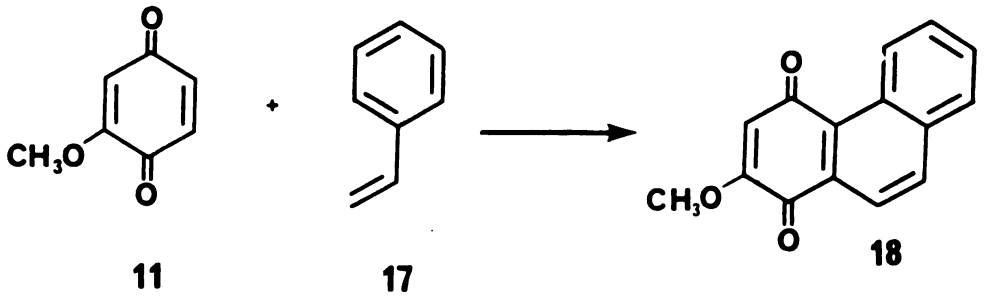


11 14 15 16

was then converted in several steps to the steroid-like 16.

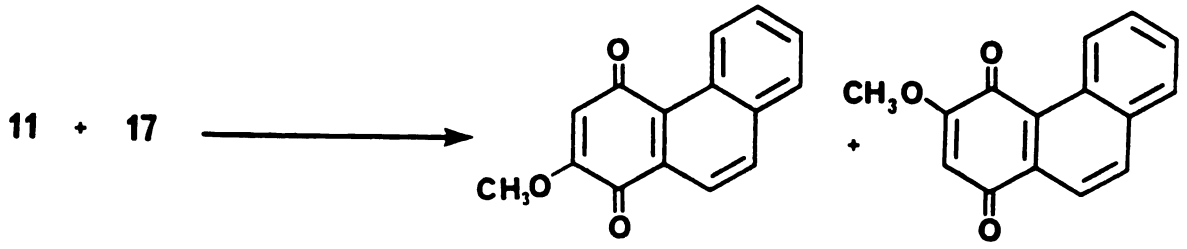
Both of these reports, however, are suspect. The regiochemistry of the cycloadditions is contrary to that expected, based on results obtained both in our laboratory[13] and elsewhere.[14] A study undertaken by Inouye and Kakisawa[15] confirms the questionable nature of these reports.

Lora-Tomayo and co-workers have reported[16] the cyclo-addition of quinone 11 and styrene 17 to yield 18 as a



11 17

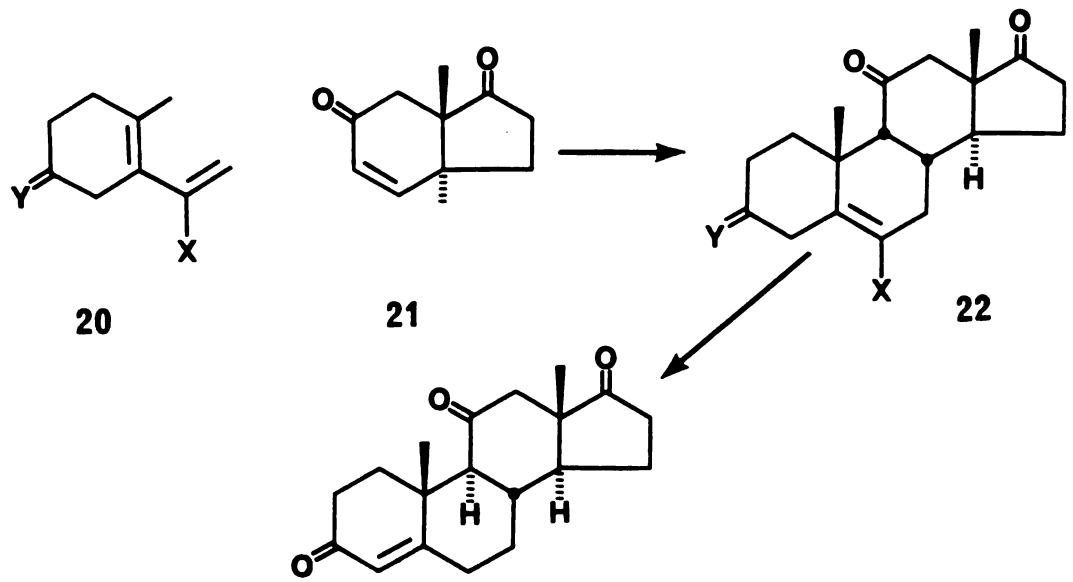
single isomer. Inouye and Kakisawa report a completely different result for this same reaction. Careful chromatographic analysis of the product shows it to



18 19

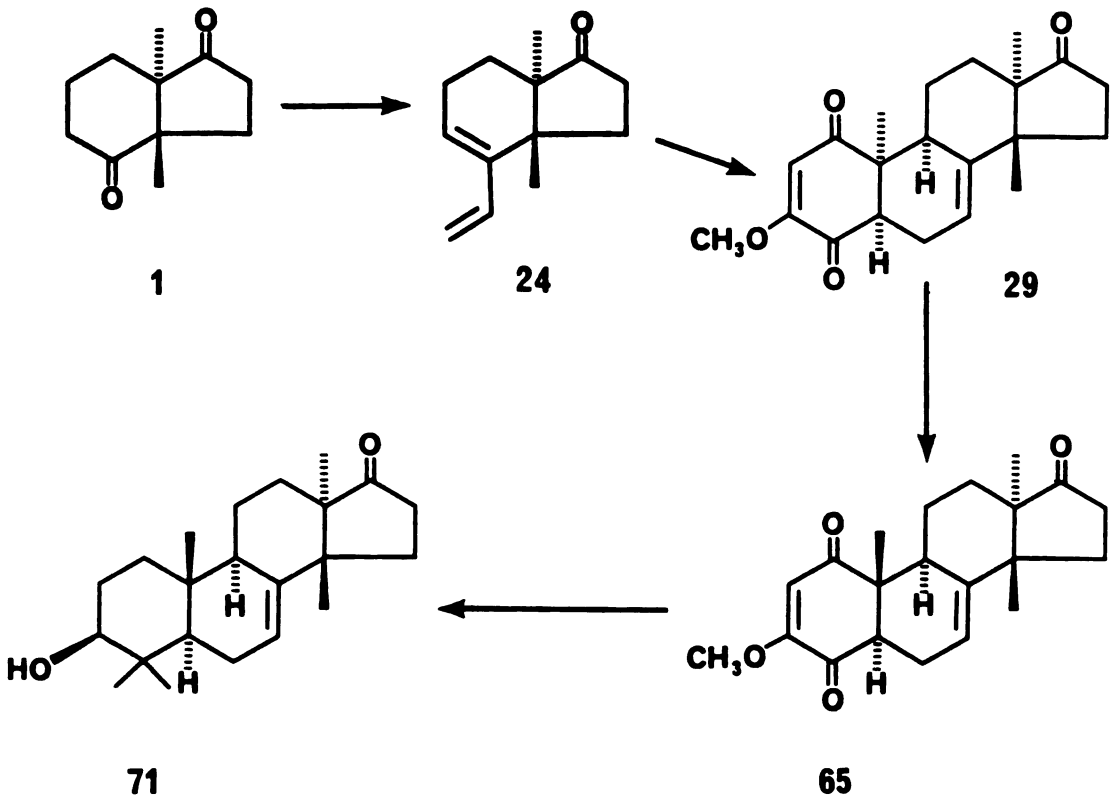
be a mixture of two adducts 18 and 19, the latter predominating by a 12:1 margin.

Denmark[17] has proposed an A + CD Diels-Alder approach to steroid synthesis as outlined in Scheme VII, but to date the only report in this area has been on the synthesis of the trans-hydrindenone 21.



20 21 22 23 SCHEME VII

In this dissertation we present our efforts toward the first synthesis of a euphane triterpene ring system. Our strategy is based on the two key reactions, a Lewis acid-catalyzed regiocontrolled Diels-Alder reaction, and a unique photochemical epimerization at a quaternary carbon center. A summary of our approach is outlined in Scheme VIII. In the course of this synthesis a study of the effect of various Lewis acids on the regioselectivity of Diels-Alder reactions with 2-methoxy-5-methyl-p-benzoquinone was conducted, and will be discussed.

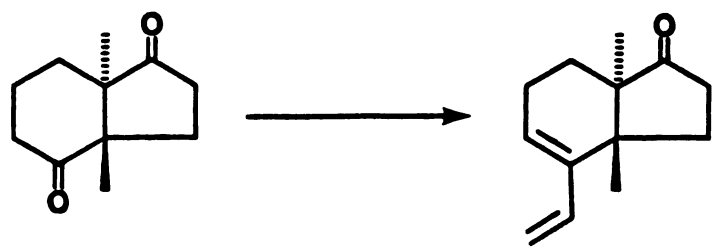


SCHEME VIII

RESULTS AND DISCUSSION

Preparation of Diene 24

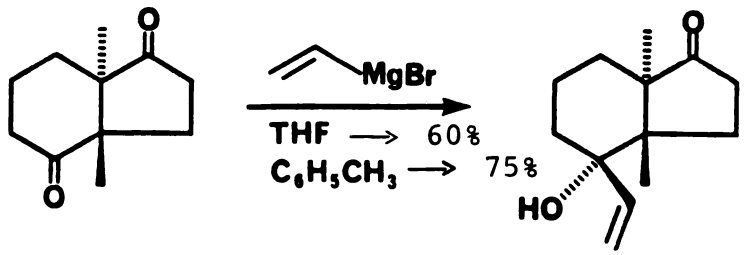
Synthesis of the carbocyclic framework of the euphane triterpenes by an A + CD ⟶ ABCD Diels-Alder strategy requires an efficient route to cisoid diene 24 from diketone 1. A straightforward approach to 24 involves addition of a vinyl anion to the six-membered ring carbonyl, followed by dehydration of the resultant tertiary allylic carbinol.



1 24

Of central importance to this approach is the ability to carry out reactions selectively at the cyclohexanone carbonyl. A greater rate of nucleophilic addition reactions for cyclohexanones versus cyclopentanones has been documented.[18,19] This selectivity is reflected in many reactions of diketone 1. Thus Martin, Tou, and Reusch[20] have reported selective addition of a series of nucleophiles to the six-membered ring carbonyl of 1. For example, the reaction of excess vinyl magnesium bromide

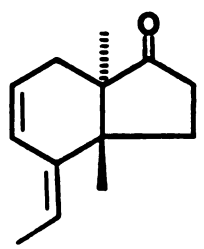
with 1 gives a good yield of alcohol 25. Changing the solvent from tetrahydrofuran (THF) to toluene enhances



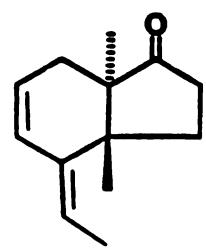
1 25

the 1,2 addition of Grignard reagents to easily enolizable ketones, and improves the yield of 25 from 60% to 75%.

Care must be exercised in the dehydration of alcohol 25 to diene 24. In the presence of strong Bronsted acids the only products obtained are the transoid dienes 26 and 27, resulting presumably from isomerization of the initially



26



27

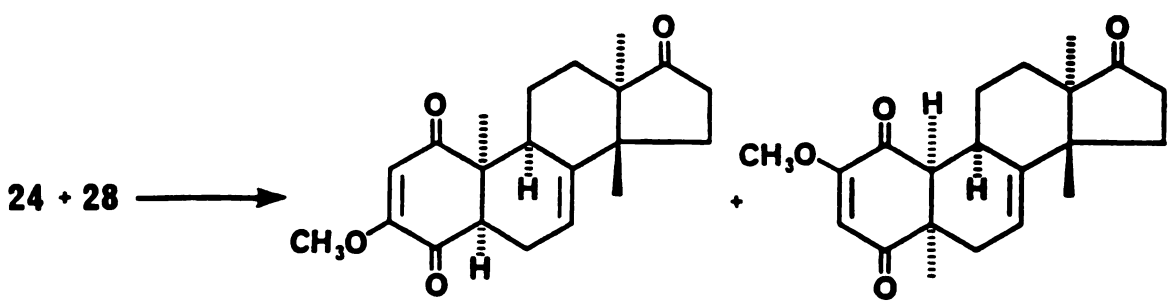
formed diene 24. Since the transoid dienes 26 and 27 do not react with dienophiles, and isomerization to 24 is sluggish, formation of these transoid dienes must be avoided.

Earlier work has shown that a solution of boron trifluoride etherate ($BF_3 \cdot OEt_2$), in benzene/THF[21] serves to dehydrate 25 to 24 without subsequent isomerization. Furthermore, recent studies have shown that copper(II)

sulfate induced dehydration[22] of 25 on a small scale gives a near quantitative yield of 24. Further studies on the use of this method are currently underway.

Diels-Alder Reactions of 24

Tou and Reusch[23] have demonstrated the feasibility of using an A+CD Diels-Alder approach for synthesis of the lanostane ring system. Under thermal conditions diene 24 reacted with 2-methoxy-5-methyl-p-benzoquinone 28 to give a poor yield of tetracyclic adducts 29 and 30. Clearly this is not a suitable reaction for synthetic applications; however it is possible to improve both the yield and the selectivity of this Diels-Alder reaction by Lewis acid catalysis. The effect of two of the most selective catalysts ($BF_3 \cdot OEt_2$ and $SnCl_4$) is shown in Table 1. In



29 30

Table 1

CATALYST	RATIO (29:30)	YIELD
Heat	2:1	34%
$SnCl_4$	1:99	74%
$BF_3 \cdot OEt_2$	10:1	55%

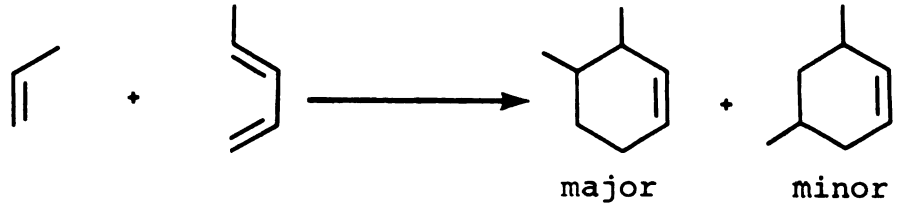
each case examined, the products exhibited an α-endo configuration (i.e. had the same relative configuration at C-10, C-13, and C-14 found in the lanostanes).

In planning a synthesis of the euphane skeleton there were two fundamental questions about this Diels-Alder reaction we wanted to answer. First, was it possible to increase the regioselectivity favoring isomer 29? While in principle both isomer 29 and isomer 30 could be converted to the A-ring system found in many tetracyclic triterpenes, conversion of isomer 29 would clearly be more straightforward. Secondly, could the stereochemical course of the reaction be altered to provide products having a euphane-like configuration at the C-10, C-13, and C-14 centers? (α-exo transition state geometry in the Diels-Alder reaction).

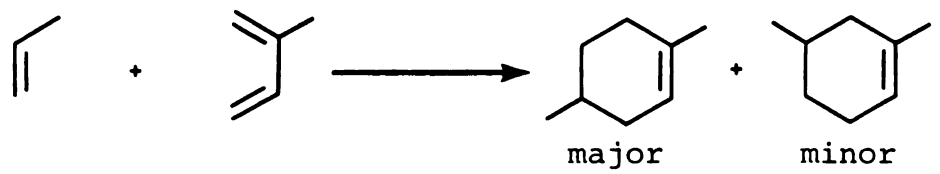
From a study of the vast body of data on Diels-Alder reactions several conclusions concerning regiochemistry and stereochemistry have been made.[23-25]

1) Reactions between simple dienes and simple dienophiles.

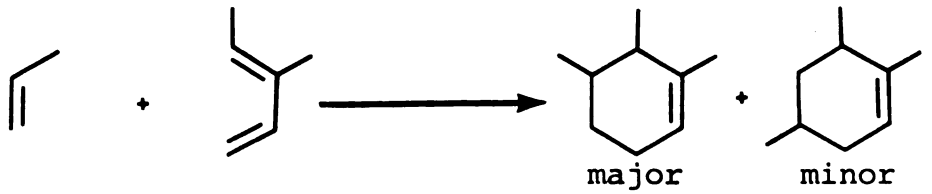
   A) 1-substituted dienes favor products in which alkyl substituents are on adjacent sites (ortho alkyl effect).



B) 2-substituted dienes favor para products.

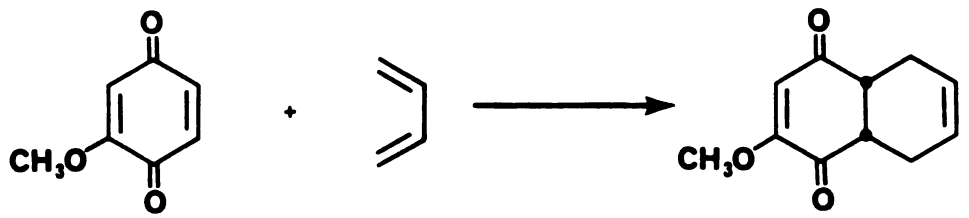


C) With 1,2 disubstituted dienes, the 1-substituent influences regiochemistry more than the 2-substituent.

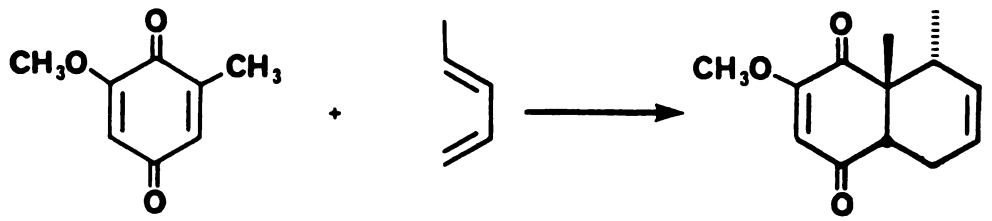


2) Quinone dienophiles:

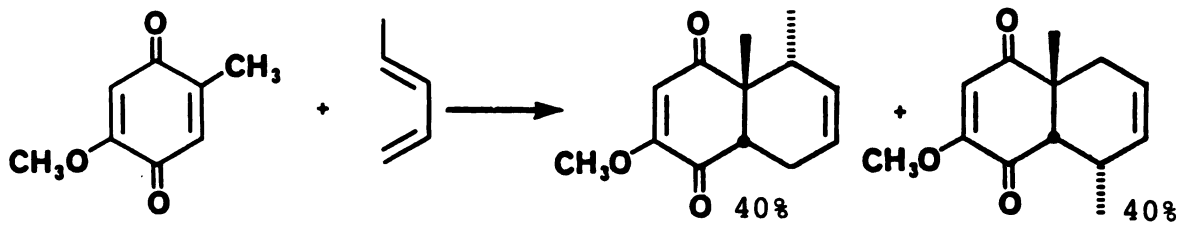
A) Electron donating groups on a quinone deactivate the double bond to which they are bound towards reaction.



B) In monoalkoxyquinones the alkoxy group is able to donate electron density to one of the two carbonyl groups, making it ester-like. In the Diels-Alder reaction between monoalkoxyquinones and 1-substituted dienes, the alkoxy group directs the regiochemistry in such a way that the substituent on the diene is proximal to the ketone-like carbonyl in the product.

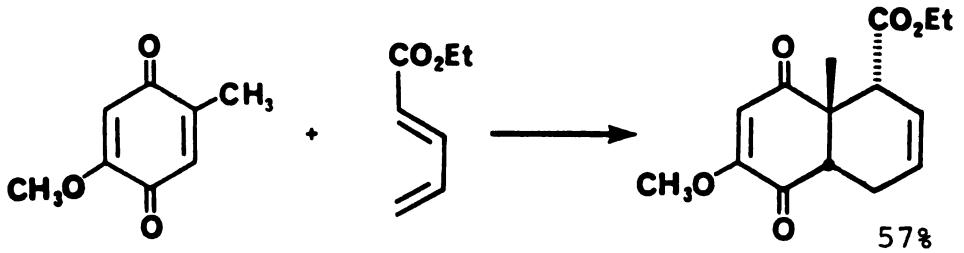


Note that in the last example the directing effects observed in 1A) and 2B) complement each other. However when these influences oppose one another as they do for quinone 21 mixtures of products are observed with 1-substituted dienes.[26] In order to achieve good

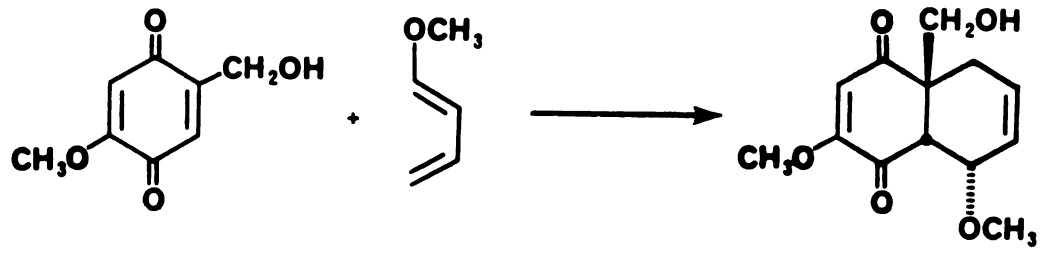


regioselectivity in Diels-Alder reactions of quinone 28 one or the other of these effects must be enhanced or moderated *vis-a-vis* the other.

One means of enhancing the ortho alkyl effect is to place an electron withdrawing group on C-1 of the diene.[14]



In a similar way, an electron donating substituent in this



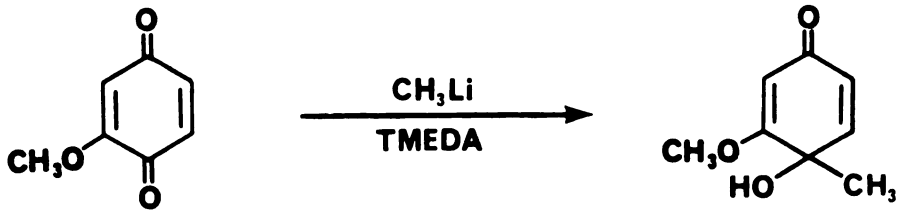
93%

position favors the other adduct.[27]

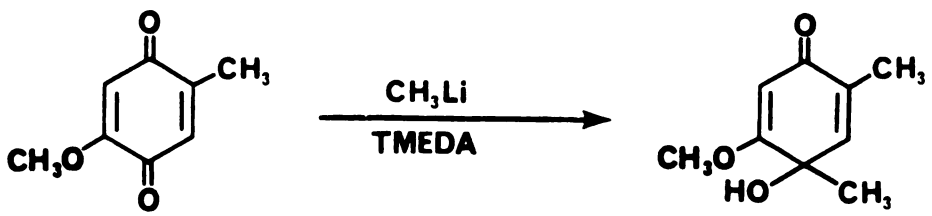
An alternative means of achieving greater selectivity in the Diels-Alder reaction of quinones is to alter the electrophilic character of one of the two carbonyl groups by selective activation or deactivation.

By deactivating one of the carbonyl functions of a quinone we obtain a cross-conjugated dienone system which should resemble a cyclohexenone in its function as a dienophile. Although cycloalkenones are generally reluctant dienophiles, their reactivity may be enhanced by Lewis acid catalysis. (A discussion of the Lewis acid-catalyzed Diels-Alder reaction appears in the following section). For the present, we will focus on deactivation by selective addition to one quinone carbonyl group.

Liotta and co-workers[28,29] have achieved selective addition of nucleophiles to substituted quinones to give good yields of mono-addition products. We have obtained similar results in the reaction of methyllithium with

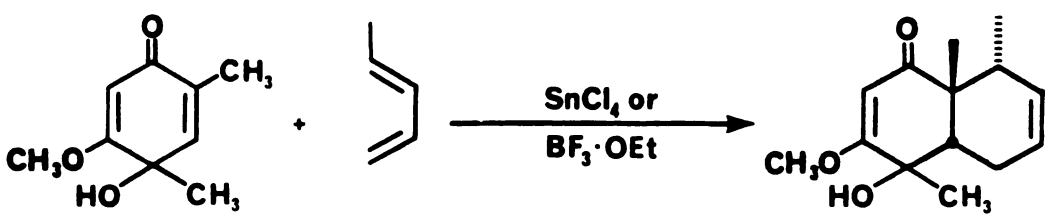


quinone 28. This addition took place at the more reactive ketone-like carbonyl function, giving quinol 36 in 57% yield.



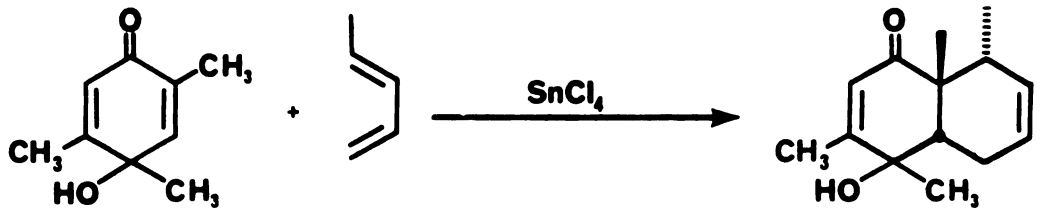
28 36

We reasoned that if quinol 36 served as a dienophile, the regioselectivity with or without Lewis acid catalysis would be improved and would lead to the desired product. As anticipated, both $SnCl_4$ and $BF_3 \cdot OEt_2$ catalysis in the reaction of 36 with piperylene led exclusively to adduct 37.



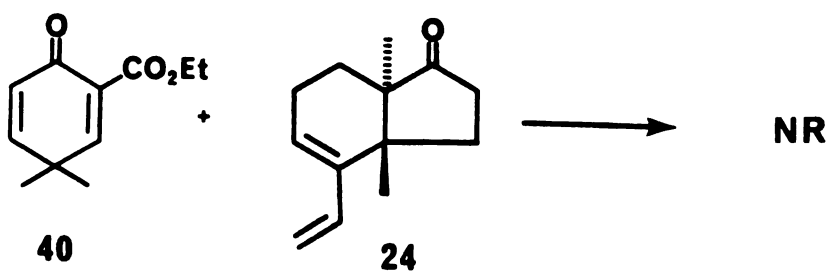
36 32 38

A similar result has been reported for the related quinol 38. Unfortunately, when we attempted a Diels-Alder



38 32 39

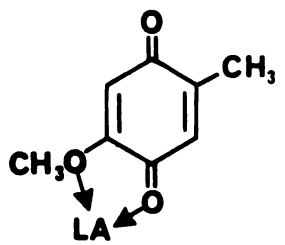
reaction between quinol 36 and diene 24, no cycloaddition products were obtained. Apparently the reduced activation and increased steric hinderence of dienophile 36 combined with the bulkiness of diene 24 prohibit this cycloaddition. A similar lack of reactivity had been observed earlier for dienone 40 and 24.[26]



40 24

Selective activation of one quinone carbonyl group presents an alternative means for controlling regiochemistry in the Diels-Alder reaction. This can be accomplished with the use of Lewis acid catalysis, as was demonstrated in the Diels-Alder reaction between quinone 28 and diene 24 (see Table 1). The influence of $SnCl_4$ and $BF_3 \cdot OEt_2$ on the distribution of products may be explained in terms of the complexes they form with the quinone dienophile. It is proposed that tin, which is able to expand its

coordination sphere to hexacoordinate, is stabilized by chelation as in 41. Such coordination increases the electrophilic character of the more substituted position on the quinone double bond. Boron, which is normally



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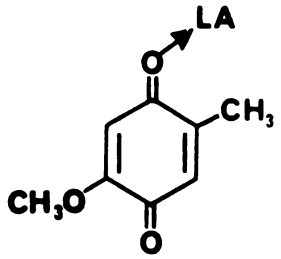


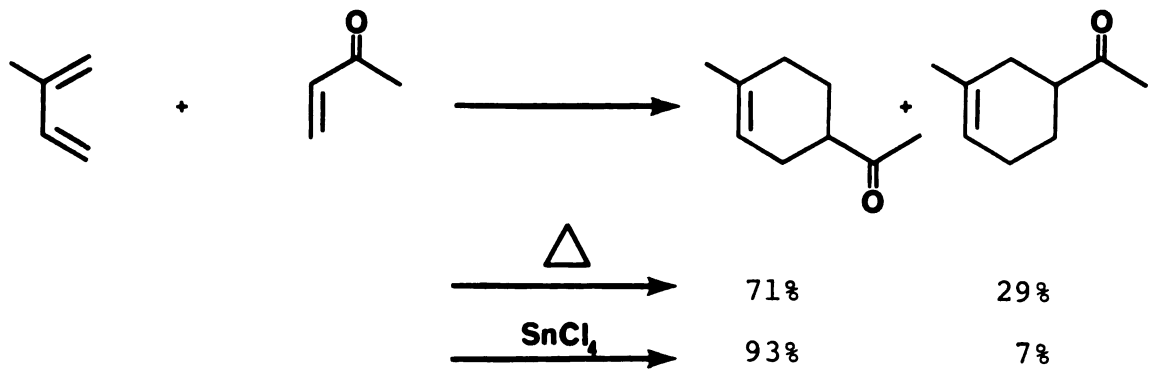
42

tetracoordinate, prefers complexation at the more basic ester-like carbonyl group as in 42. This activates the less-substituted position on the dienophilic double bond. A wide variety of Lewis acids are available as potential electrophilic complexing agents and should provide a large degree of flexibility in control of the Diels-Alder reaction.

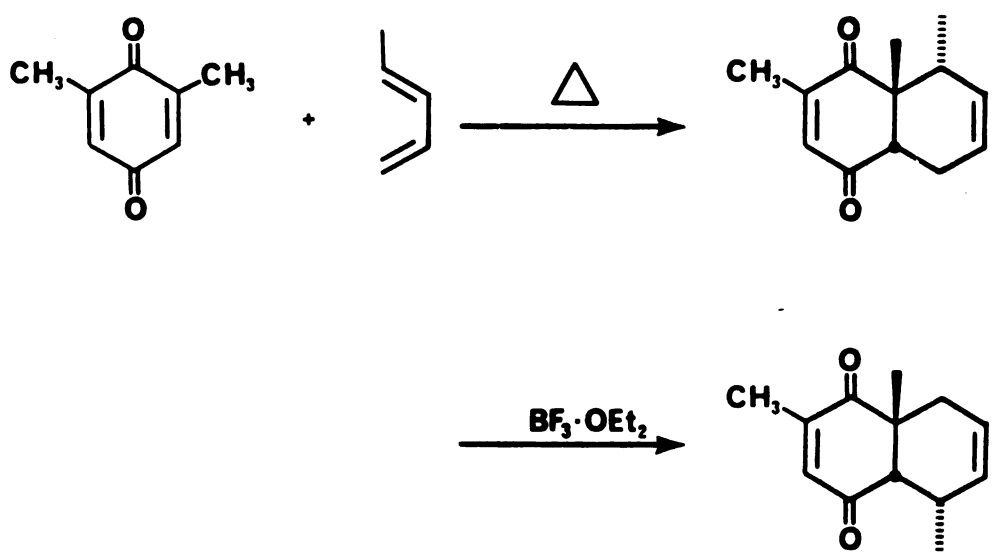
Lewis Acid Catalysis of Enone-like Dienophiles in Diels-Alder Reactions

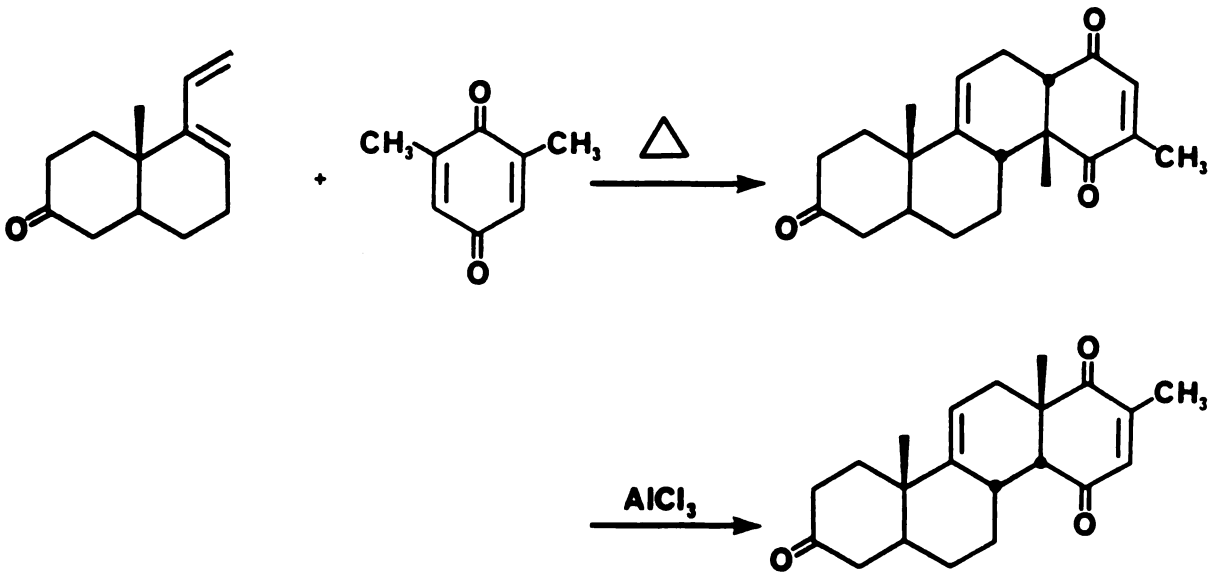
In 1960[31] Eaton and Yates reported a dramatic rate acceleration for the Diels-Alder reaction between anthracene and maleic anhydride in the presence of $AlCl_3$. Subsequent reports by other groups have shown that Lewis acids can markedly effect the regiochemistry of the cycloaddition as well.

As first reported by Lutz and Bailey in 1964,[33] the



presence of a Lewis acid catalyst tends to enhance formation of the isomer favored in the thermal reaction. In more complex systems (most notably with quinone dienophiles) the regiochemistry of the catalyzed reaction may be completely reversed from that of the thermal reaction. Such examples were first reported by Valenta and co-workers in 1972,[33] followed by a more elaborate report in 1975.[34] The following examples are from the latter work.





In their study of the regioselectivity of Diels-Alder reactions involving quinone 28 Tou and Reusch[13] were the first to suggest that differences in complexation are important in determining product structure. To gain further understanding of this subject, a study of different Lewis acid complexes with 28 was undertaken. We hoped that one result of this study would be improved regioselectivity and yield in the preparation of adduct 29.

Although the list of possible Lewis acids is extensive, aluminum chloride ($AlCl_3$), tin(IV) chloride ($SnCl_4$), and boron trifluoride etherate ($BF_3 \cdot OEt_2$) are by far the most widely used catalysts. The effectiveness of these catalysts in improving the yield and controlling

regiochemistry in the reaction of quinone 28 with diene 24 is well documented.[13] We therefore chose to study the effect of altering the electronic environment on the acceptor atoms of these three catalysts by varying the ligands. The results of these experiments are summarized in Table 2. (Standard reaction conditions may be found in the Experimental section.) In place of diene 24 (expensive), we used piperylene as a reference diene. This simple 1-substituted diene has been shown to exhibit the same regiochemistry in these Diels-Alder reactions as does 24.[26]

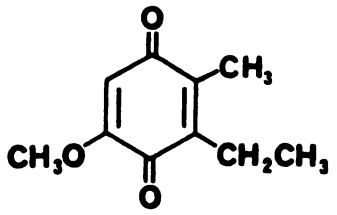
Because previous studies have shown $BF_3 \cdot OEt_2$ to be the most effective catalyst for synthesis of 29, the boron based catalysts were the first investigated. Boron trifluoride, when introduced as the diethyl etherate, must undergo exchange and recomplexation with a basic oxygen to be effective. To determine the effect of slowing down this exchange, the more basic ether THF was substituted for diethyl ether in this reaction system. Although the reaction with $BF_3 \cdot THF$ was noticably slower than with $BF_3 \cdot OEt_2$, the distribution of products proved to be the same. Alternatively, the use of BF_3 gas would provide a more active catalyst, but measurement and addition of exact quantities of BF_3 gas is difficult. Thus, when piperylene was added to a methylene chloride solution of quinone 28 saturated with BF_3 gas, only adduct 34 was

Table 2 Diels-Alder reaction of 28 and 32. (The ratio of catalyst to 28 is 1:1 unless otherwise indicated.)

Catalyst		Ratio(33:34)	Yield of cyclo-adducts
Heat		1:1	80%
$SnCl_4$		1:20	85%
$BF_3 \cdot OEt_2$		4:1	85%
$BF_3 \cdot THF$		4:1	70%
BF_3 gas		34 only	43%
$B(Et)_3$			0%
$B(Ph)_3$			0%
$SbCl_5$			0%
$AlCl_3$	(0.5 eq)	3:2	64%
	(1.0 eq)	7:6	76%
	(2.0 eq)	1:2	
$AlCl_3/Al(i\text{-}PrO)_3$	(0.5 eq/0.5 eq)	2.5:1	35%
	(1.0 eq/0.5 eq)	1:1	50%
$Al(i\text{-}PrO)_3$			0%
$AlCl_2Et$			10%
$AlClEt_2$			0%
$AlEt_3$			0%
$TiCl_4$		34 only	87%
$TiCl_4/Ti(OEt)_4$	(1.0 eq/1.0 eq)	34 only	40%
$Ti(OEt)_4$			0%
$n\text{-}BuSnCl_3$			0%
$(n\text{-}Bu)_2SnCl_2$			0%
$(n\text{-}Bu)_4Sn$			0%

formed. The ambiguity in measuring the amount of BF_3 gas introduced in such reactions makes it difficult to draw any conclusions about this result.

If the electron withdrawing halogen substituents on boron are replaced with electron donating alkoxy groups the catalytic activity of the resulting borate esters vanishes. Based on their Lewis acidity, trialkyl boranes should exhibit intermediate catalytic activity. However, they undergo facile addition reactions with quinone 28. Thus, reaction of 28 with piperylene and BEt_3 did not give cycloaddition products. The only product isolated and identified from this reaction was 43, which presumably results from initial 1,4 addition to 28, followed by



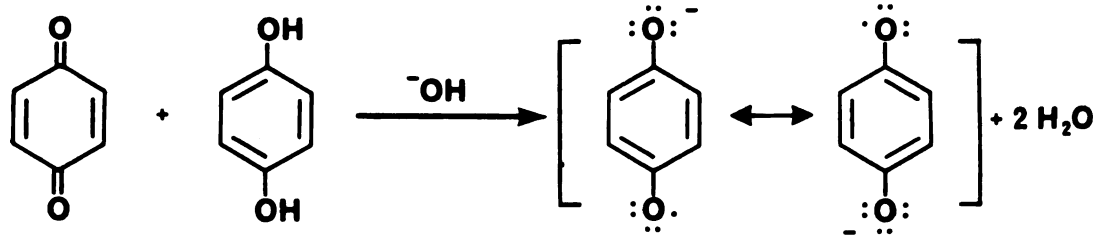
43

oxidation back to the quinone state. Similar addition reactions of several alkyl boranes with p-benzoquinone 44 giving the corresponding 2-alkyl-hydroquinones were reported by Hawthorne and Reinte[35] in 1965. Interestingly, these authors also noted that quinones other than 44 were relatively unreactive towards alkyl boranes. Furthermore, when the alkyl groups attached to boron were replaced with phenyl substituents (BPh_3), only starting materials were recovered.

We have observed a similar pattern of behavior for aluminum catalysts. Thus, aluminum chloride was an effective catalyst, but aluminum isopropoxide was ineffective in promoting the Diels-Alder reaction between quinone 28 and piperylene. The use of mixed aluminum chloride/aluminum isopropoxide catalysts did not improve either the yield of cycloaddition products, or the regioselectivity compared with $AlCl_3$ alone.

When the halogen atoms on $AlCl_3$ were replaced with alkyl groups, the yield of cycloaddition products dropped dramatically. For example, when added to a solution of 28 and piperylene, ethyl aluminum dichloride ($AlEtCl_2$) yielded less than 10% of the expected cycloaddition product after 6 hr. Diethyl aluminum chloride ($AlEt_2Cl$) and triethylaluminum ($AlEt_3$) did not catalyze this reaction at all.

An unusual observation was made during the $AlEtCl_2$ and $AlEt_2Cl$ experiments. While, in general, addition of Lewis acids to a solution of quinone 28 produced orange-yellow solutions, the two alkyl aluminum chlorides gave a deep blue color. This behavior is reminiscent of the classical quinhydrone reaction. Thus, mixing equimolar amounts of p-benzoquinone 44 and hydroquinone 45 in basic solution gives a dark green (almost black) solid called quinhydrone. This reaction proceeds by an electron transfer from the hydroquinone ion to the quinone molecule, giving resonance-stabilized semiquinone ions 46.



44 45 46

Solutions of this complex have an intense green coloration. Although direct physical evidence is lacking in this case, a similar charge transfer complex, involving hydroquinone species generated by 1,4 alkyl addition to 28 may be responsible for the blue coloration observed in the ethyl aluminum chloride reactions.

Similar studies were conducted with tin based reagents. While $SnCl_4$ gave good yields of Diels-Alder adducts, n-butyl substituted tin chlorides as catalysts were ineffective.

Ironically, the most effective catalyst found in our survey proved to be selective not for 33 but rather for 34. Titanium(IV) chloride ($TiCl_4$) gave cycloaddition yields and regioselectivity which surpassed even $SnCl_4$ in the synthesis of 34. Interestingly, this result conflicts with the report of Henderickson and Singh[36] that $TiCl_4$ catalyzed Diels-Alder reactions with a series of quinones and dienes gave regioselectivity identical to that of the corresponding thermal reaction.

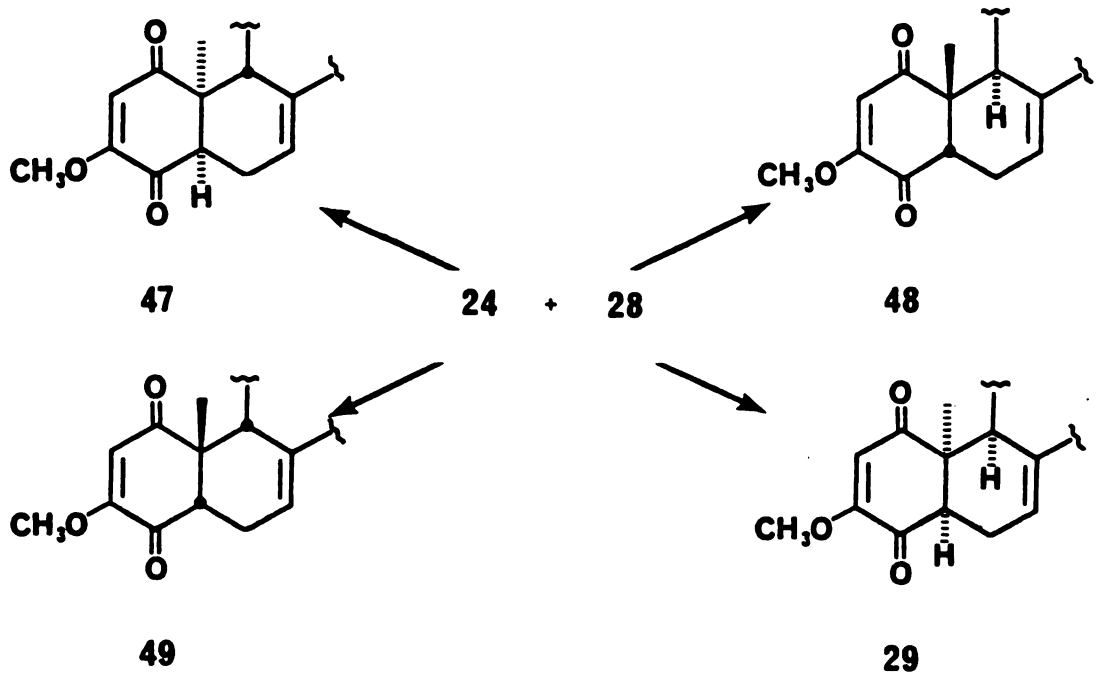
It was hoped that a catalyst-regioselectivity relationship might emerge from our study of Diels-Alder

reactions of quinone 28. Unfortunately, this did not happen. Furthermore, no such relationship has appeared in the literature. Consequently catalyst selection has been in many respects a trial and error process. Childs, Mulholland, and Nixon[37] have published a scale of relative Lewis acid strengths based on induced proton NMR chemical shifts for various Lewis acid-carbonyl compound complexes. These values vary by less than an order of magnitude from the strongest acid (BBr_3) to the weakest ($AlEt_3$), and do not correlate well with the observed effectiveness of these catalysts in the Diels-Alder reactions of quinone 28. Some catalysts such as BBr_3 and $SbCl_5$ which are listed as "stronger" Lewis acids than $BF_3 \cdot OEt_2$ and $SnCl_4$ do not catalyze the Diels-Alder reaction of quinone 28 with piperylene. It is not clear, however, whether this is due to reactions of the catalyst with the quinone (as was clearly the case with BEt_3) of just a failure of the catalyst to form the type of complex necessary to activate the quinone towards reaction.

It is apparent from this brief study that much more work needs to be done before any conclusions can be drawn concerning the catalyst regioselectivity question for quinone 28. It remains to be seen whether a more effective catalyst than $BF_3 \cdot OEt_2$ exists for the synthesis of 29.

Stereochemical Considerations

Control of stereochemistry in our key Diels-Alder reaction was the second problem posed by a euphane synthesis. Four stereoisomers are possible from the reaction of diene 24 with quinone 28. Dienophile 28 can approach from the α or β face of diene 24 and in each case in an endo or exo orientation to lead to adducts 47, 48, 49 and 29. Two of these stereoisomers, 48 and 49, would be useful for a euphane triterpene synthesis, as they have the required relative stereochemistry at C-10, C-13 and C-14. The stereochemistry at the two other newly-generated centers should be amenable to change at a later stage. Thus the C-5 configuration may be changed if necessary by



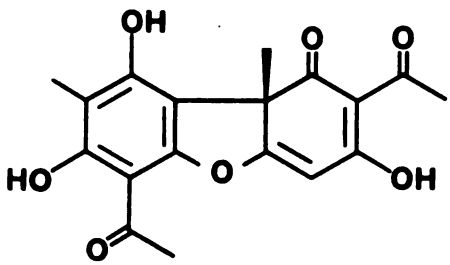
epimerization, and the C-9 stereocenter will eventually be lost by migration of the $\Delta^{7,8}$ double bond to the $\Delta^{8,9}$ position.

In practice the only stereoisomer obtained from Diels-Alder reactions between diene 24 and quinone 28 is the β-endo adduct 29. A Dreiding model of diene 24 shows that the C-13 methyl group is oriented over the endocyclic double bond of the diene, effectively blocking the bottom face of the diene from attack. Dienophile approach is therefore favored at the β face of the diene, in spite of the fact that this yields a product in which the C-ring is forced into a twist boat conformation.

An effort was next made to alter the stereochemical course of the Diels-Alder reaction. In the transition state leading to isomer 29 the methoxy group of the dienophile lies above the plane of the CD ring system, very close to the C-14 methyl group. By changing the methoxy group to a bulkier group (e.g. trityl), we hoped to increase the steric congestion enough to favor a β-exo transition state. However, initial attempts to convert quinone 28 to a bulkier ether by simple exchange were unsuccessful. The prospect of a multi-step quinone synthesis, coupled with early success in an alternative approach to the stereochemical control problem led us to curtail our studies in this area.

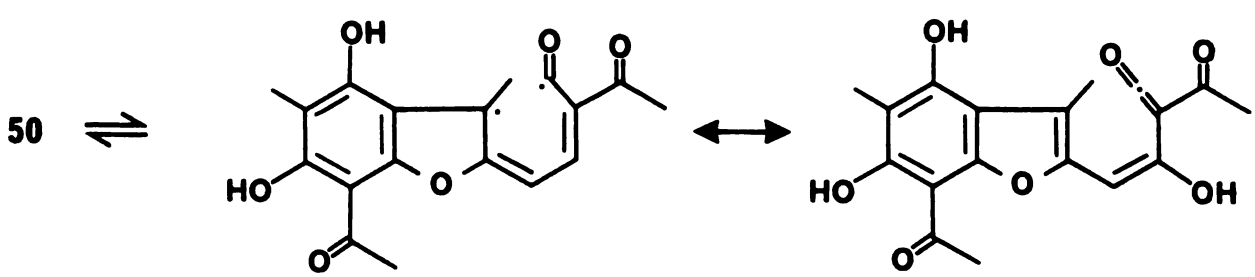
A solution to the problem of stereochemical control at C-10 was finally achieved by a photochemical

isomerization following the Diels-Alder reaction. The desired transformation is, in fact, similar to the classical example of usnic acid racemization. The structure of usnic acid 50, a constituent in several genera of



50

lichens, was the subject of debate for over 100 years following its isolation by Rochleder and Heldt in 1843.[38] Although optically active, usnic acid racemized when heated in acetic acid, or on acetylation with acetic anhydride in the presence of strong acids. This racemization represented a rare example of an isomerization at a quaternary carbon center. In 1955 Stork[39] proposed a diradical/ketene pathway for this racemization (see Scheme IX). Bond cleavage gives diradical 51, and

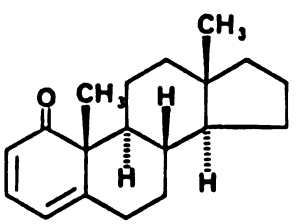


51 52

SCHEME IX

one resonance form which can be drawn is the conjugated diene ketene 52. Ring closure then leads to racemic usnic acid.

Beginning in 1957, Barton and co-workers published a series of papers under the unassuming title "Photochemical Transformations". In the sixth paper of the series Barton and Quinkert[40] reported their investigations into the photochemistry of cyclohexadienones, including the photochemical racemization of usnic acid. Quinkert and co-workers have since continued an extensive study of fully conjugated cyclohexadienone systems.[41a-e] In 1979 Quinkert et al.[41e] reported a detailed study of solvent effects and excitation wavelength effects on the isomerization of 2,4 androstadien-1-one 53. Irradiation of 53 in the absence of external nucleophiles gave a mixture of 53 and 54. Irradiation of 54 gave the same relative



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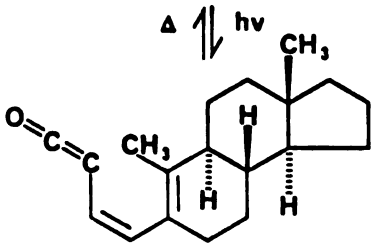

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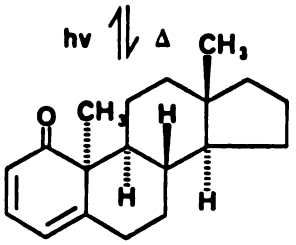


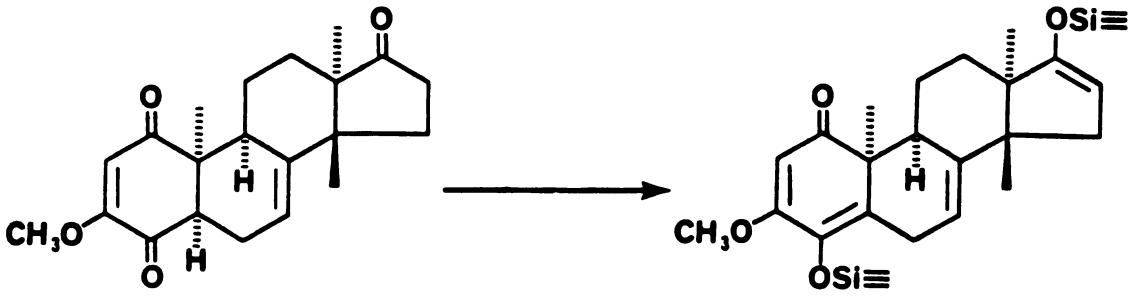
54

ratio of 53 and 54, indicating a true photoequilibrium established between the two tetracyclic compounds. Photostationary ratios of 53 and 54 varied from 6.5:1 to 3.7:1, depending on the reaction conditions. A ketene intermediate, 55, was supported by spectroscopic studies,[42] and by trapping experiments with cyclohexylamine.

That the naturally occurring C-10 β-methyl isomer 53 predominates at equilibrium is not surprising. The anti relationship of the C-10 methyl and the C-9 proton allows the B-ring to assume a stable chair conformation. The C-9, C-10 cis relationship in isomer 54 forces the B-ring into an energetically less favorable boat conformation.

These results suggest a solution to our problem of configurational control at C-10 for purposes of affecting a euphane synthesis. By introducing a $\Delta^{4,5}$ double bond into the Diels-Alder adduct 29 we generate a fully conjugated cyclohexadienone system analogous to the minor isomer 54 in the Quinkert study. If the substituents at C-3 and C-4 and the $\Delta^{7,8}$ double bond do not seriously perturb the photochemical reaction, it should be possible to use this same transformation to convert 29 to the desired C-10 epimer. Relief of steric interactions in the B-ring twist boat conformation, resulting from the β-endo transition state in the Diels-Alder, provides the driving force for this conversion.

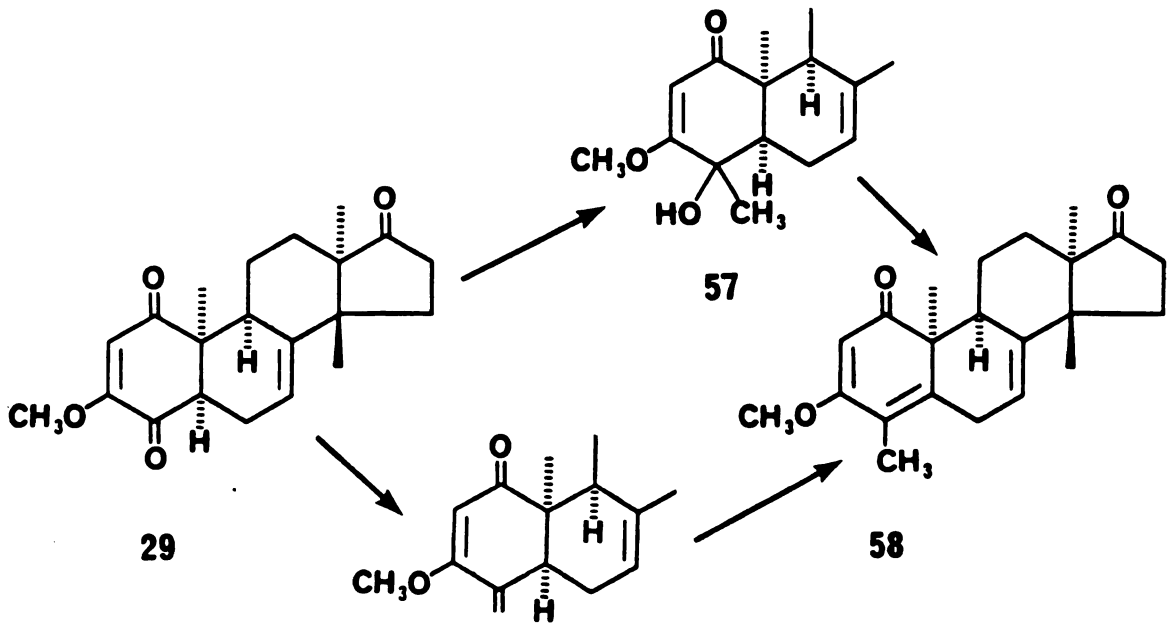
Several methods are available for converting enediones such as 29 to a 2,4 cyclohexadienone system. Treatment of triketone 29 with two equivalents of lithium diisopropylamide (LDA) followed by quenching the resultant bis-enolate with two equivalents of trimethylsilyl chloride (TMSCl) should give the bis-silyl enol ether 56. Not surprisingly the bis-enolate was insoluble in THF



29 56

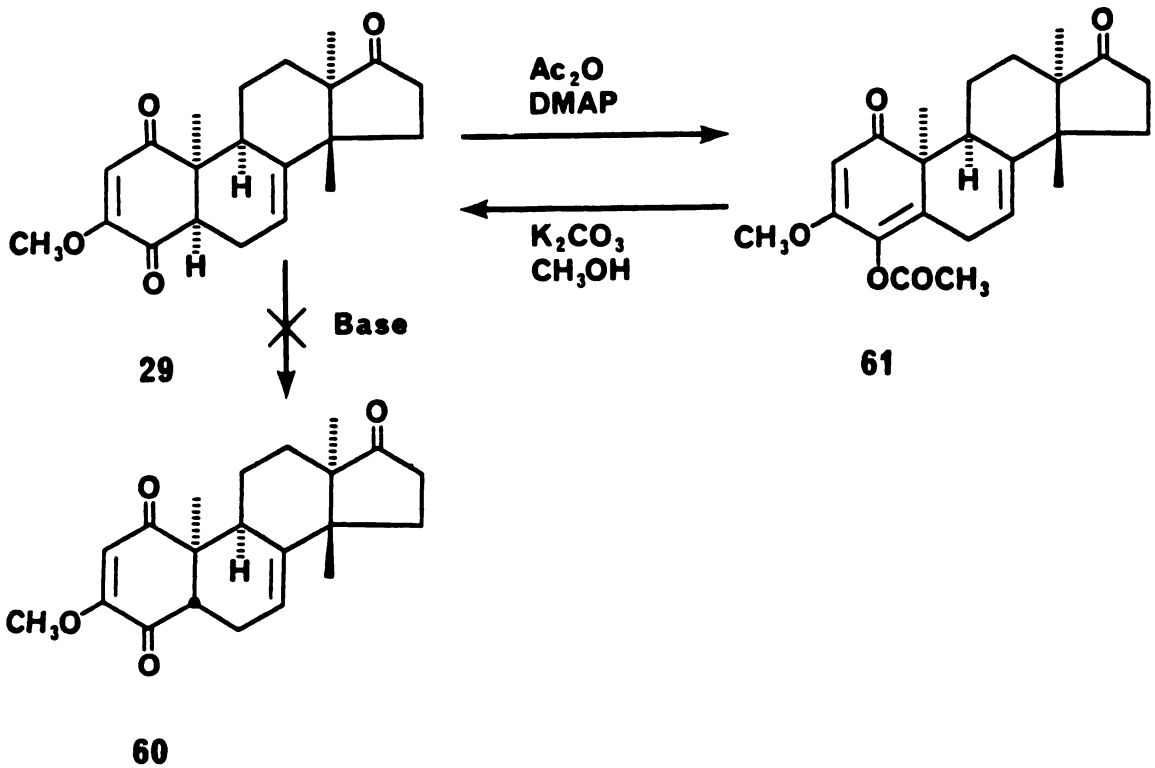
at -78°C and quenching the enolate without use of a co-solvent gave poor yields of 56. Large amounts of hexamethylphosphoric triamide (HMPA) achieved solution of the bis-enolate, but this procedure was undesirable on a large scale. Furthermore, 56 proved to be moisture sensitive, which made subsequent manipulations unnecessarily cumbersome.

An alternative route to the A-ring dienone involved addition of a methyl group to the more reactive C-4 carbonyl function. This was attempted by addition of a methyl organometallic reagent, followed by a dehydration to give 58. Wittig olefination to give 59 followed by isomerization to 58 was another possibility.



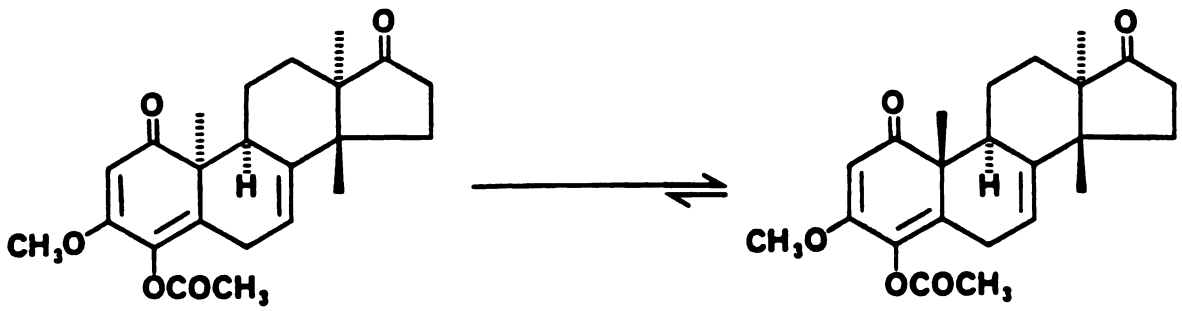
The same procedure which had been applied successfully to the synthesis of quinol 36 failed to give selective addition to the C-4 carbonyl of 29 in reasonable yield. Furthermore dehydration of 57 under a variety of conditions failed to yield dienone 58. Similarly, Wittig olefination suffered from poor yields, and these approaches to the 2,4 cyclohexadienone system were ultimately abandoned. It was from seemingly unrelated work in the lanostane synthesis that a source of an appropriate linearly conjugated dienone system was found.

During the course of studies on the lanostane system, attempts were made to isomerize the C-5 position in 29 with base to give the AB-trans ring fusion product 60.



Under a variety of conditions only starting material was recovered. That enolization had in fact occurred was demonstrated by trapping with acetic anhydride to give enol acetate 61. Treatment of 61 with mild base (K_2CO_3 in methanol) gave back triketone 29, indicating that the AB-cis configuration was more stable. Clearly enol acetate 61 fulfills all requirements as a substrate in the photochemical reaction. It is an easily made, stable, non-hygroscopic crystalline solid, and the acetate group is easily hydrolyzed by treatment with mild base. Of concern, however, was the possible effect of the oxygen functionality at C-3 and C-4 on the course of the photoisomerization.

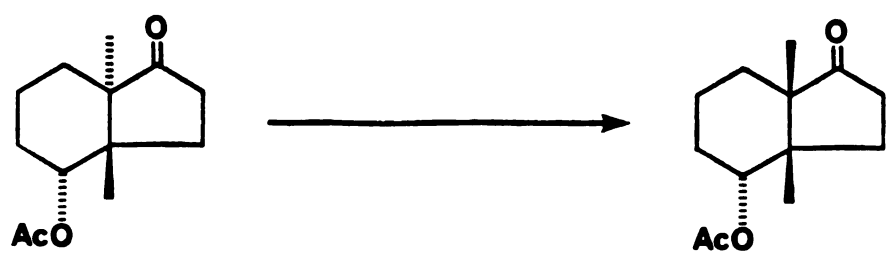
In the event, irradiation of a solution of enol-acetate 61 in dry acetonitrile with a 400 watt medium-pressure Hanovia lamp gave a 5.5:1 mixture of photoenol acetate isomer 62 and starting material 61 respectively. The structure of 62 has been confirmed by X-ray



61 62

crystallography[43] (see Figure 1).

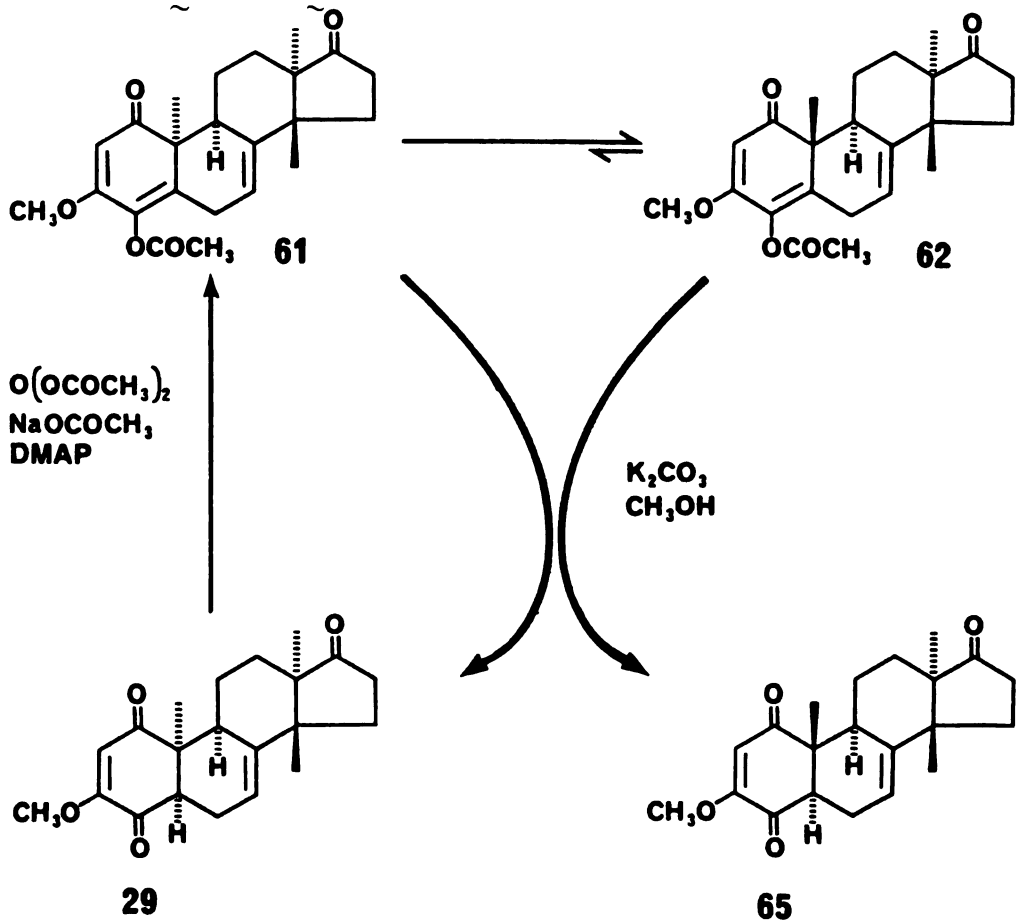
Conditions for the reaction of 61 are more critical than those in the Quinkert work, because of the presence of a C-17 carbonyl function. Previous work in our laboratories[45] has demonstrated that irradiation of keto-acetate 63 in ether solution with a pyrex filter causes isomerization to the cis-fused keto-acetate 64. Since this Norrish type I cleavage-recombination reaction



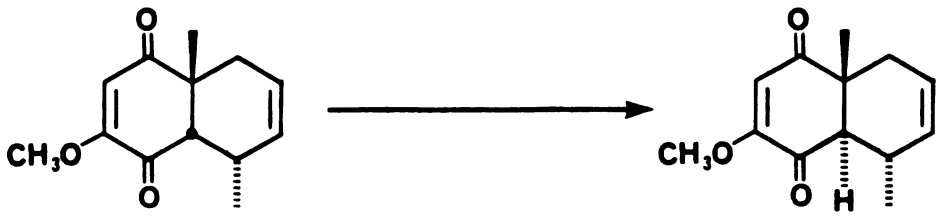
63 64

requires higher energy light than the photoepimerization of 61, this undesired epimerization is avoided by using a saturated copper(II) sulfate filter solution, which blocks wavelengths below 365 nm.

Although 61 and 62 have very different molecular shapes, a mixture of these two epimers was not easily separable by routine chromatographic techniques. Small amounts of pure 62 were obtained by thick layer chromatography using a repeated development technique (silica, 2000 microns, 50% ether/hexanes). Fortunately, the two C-10 isomers may be separated by flash chromatography[45] after solvolysis. Treatment of the photoequilibrium mixture with potassium carbonate (K_2CO_3) in methanol gave isomeric enediones 29 and 65.

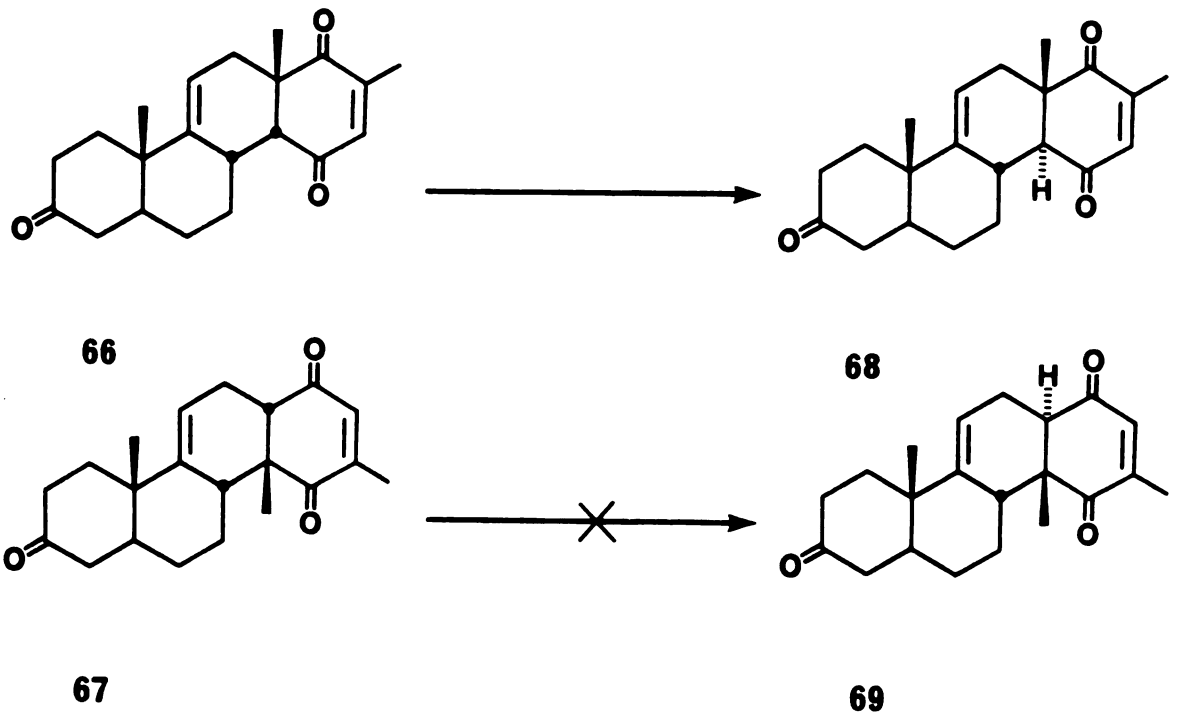


Our assignment of the AB-trans ring fusion to isomer 65 was based on an overwhelming body of evidence for a number of related systems. Bohlmann, Mathar, and Schwarz[14] have studied the Diels-Alder reactions of several quinones, including 28, with a number of simple dienes. In each case the initially formed cis-fused bicyclic adducts were readily converted to the corresponding trans-fused products on mild base treatment. In fact, we have observed that solid samples of 34 on standing will eventually isomerize to the trans compound 35.

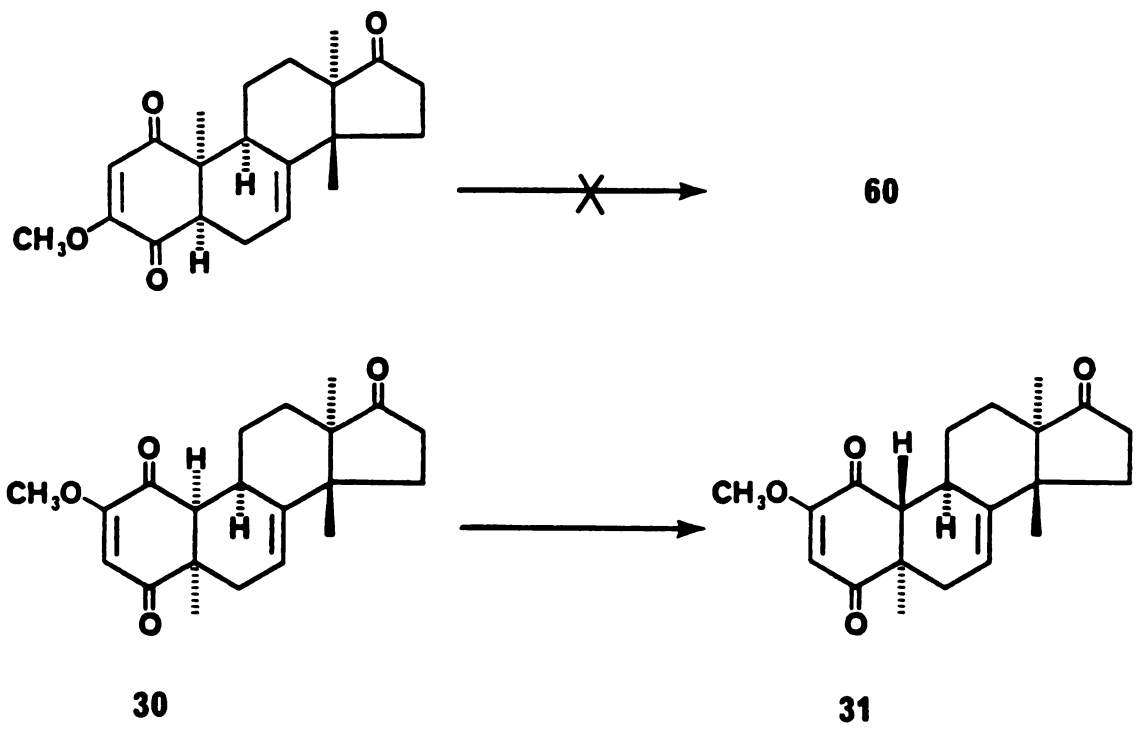


34 35

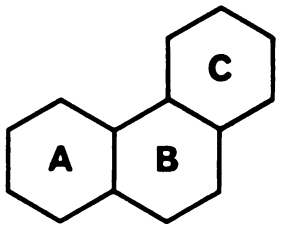
With a more complex system Valenta et al.[34] reported the synthesis of Diels-Alder products 66 and 67. Although 66 was converted smoothly to 68, under a variety of conditions 67 failed to give 69. As noted earlier, the anti-trans relationship at C-8, C-13 and C-14 in 68 is a particularly stable configuration, whereas the cis relationship in 67 is more stable than the related syn-anti configuration 69. A similar observation was made for



the regioisomeric Diels-Alder adducts 29 and 30.[26]



From these results, since an anti-relationship at C-9 and C-10 exists in 62, it followed that the trans ring fusion should result after hydrolysis. This conclusion also agreed with the work of W.S. Johnson[46] on the relative stability of perhydrophenanthrene isomers. Johnson's analysis uses the B-ring of the tricyclic system

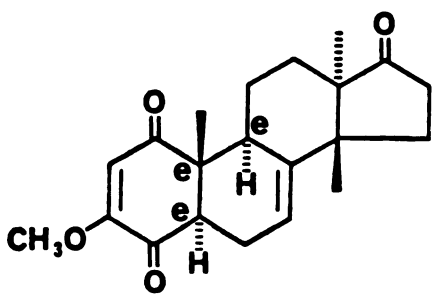


The Penanthrene Ring System

as a reference, and counts the number of eclipsing and skew interactions between the fused rings. After assigning a numerical value to each interaction (3.6 kcals/eclipsing interaction and .8 kcal/skew interaction) the relative stability of each isomer may be predicted. A simple mneumonic for this analysis is "the greater number of equitorial ring bonds to the B-ring, the more stable the configuration."

While the B-ring in 65 and 70 is not a true chair because of the presence of the $\Delta^{7,8}$ double bond, the distortion is not a serious one. Dreiding models show that the three ring bonds in 65 are equitorial, while in 70 two ring bonds are equitorial and one is axial. This

analysis also predicts the formation of 65 from 62.



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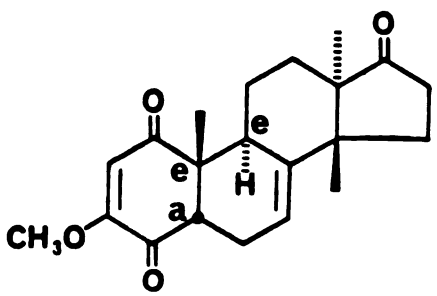
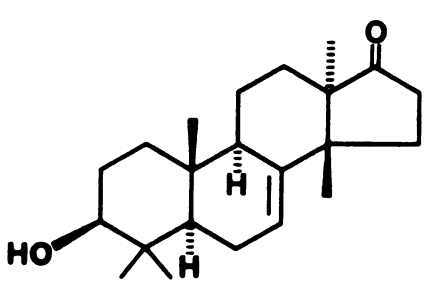


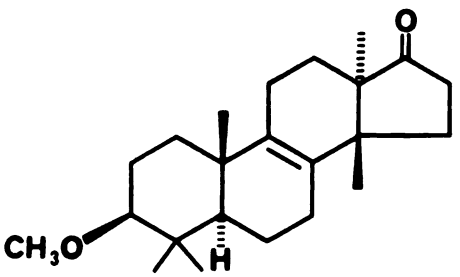
70

At this stage of our synthesis, the critical task of fixing the relative configuration of the angular methyl groups was completed. The remaining task, modification of the A-ring, required the introduction of geminal methyl groups at C-4, introduction of an equitorial hydroxyl at C-3, and removal of the C-1 carbonyl to give 71.



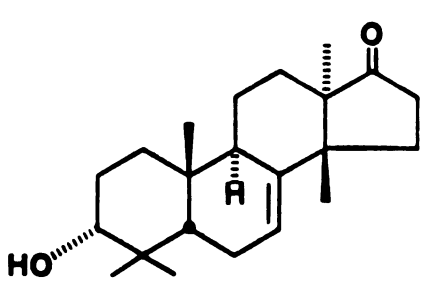
71

As a definitive structure proof of 71 it was our intent to convert it to 72, a compound recently obtained by Levisalles and Audouin[47] by chemical degradation of the side chain of euphol.



72

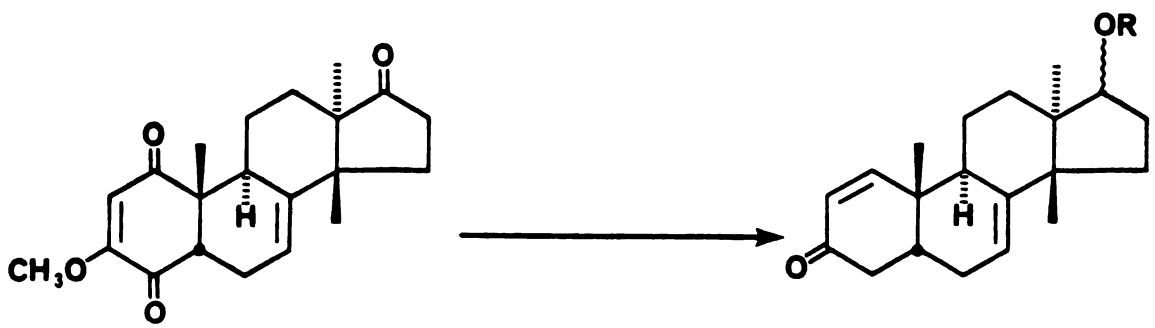
For this comparison we needed to effect isomerization of the $\Delta^{7,8}$ double bond to the $\Delta^{8,9}$ position, and methylation of the C-3 hydroxyl. Compound 71 proved to be resistant to all attempts at migration of the double bond. Since this is a well known reaction in the euphane ring system we sought to confirm our structural assignment on 71 by X-ray crystallography.[44] It was at this point we discovered the actual structure of our product was not the trans-fused 71 but rather the cis-fused 73.



73

Functional Group Transformations Leading to the C-5 epi-Butyrospermol Ring System

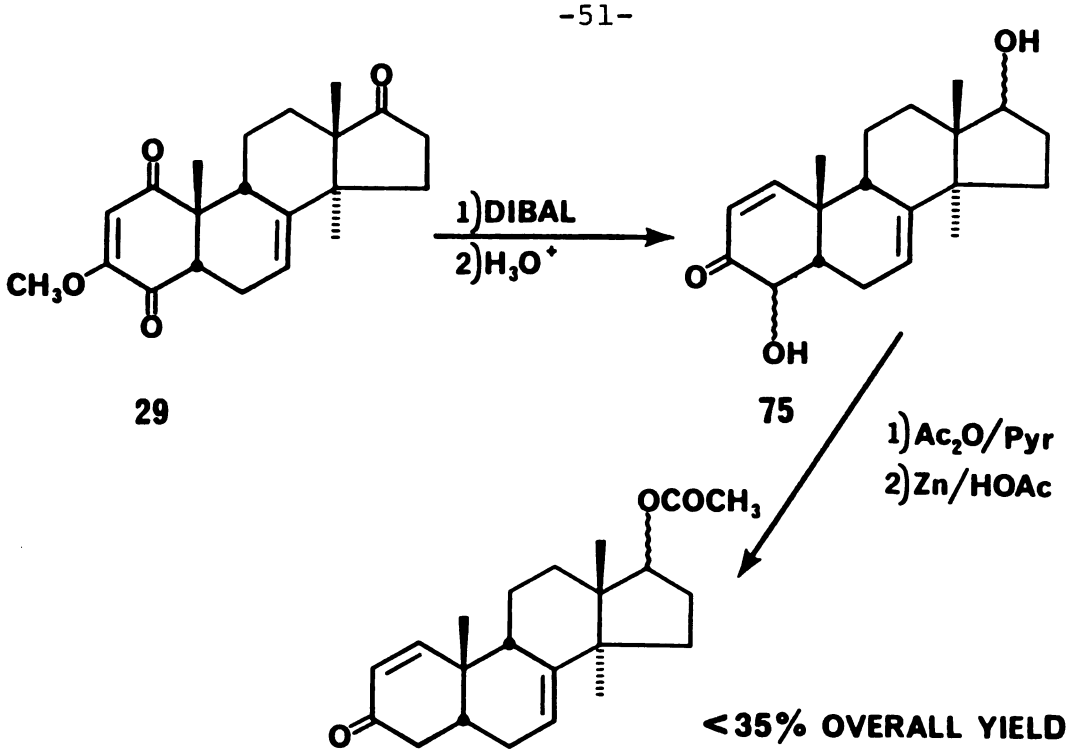
Our plans for converting the A-ring of 70 to the A-ring structure found in triterpenes centered on intermediate enone 74. Thus the A-ring system in 74 appeared ideally



70 74

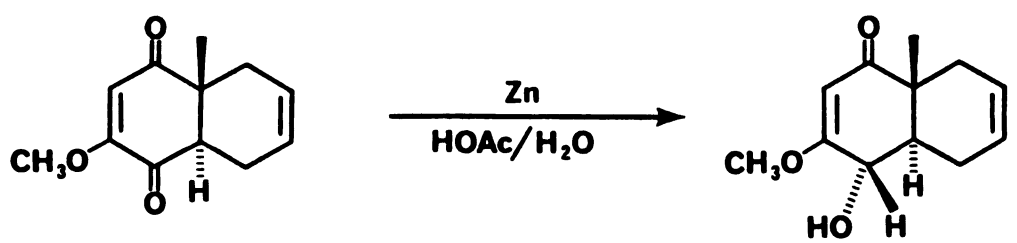
suited for introduction of the geminal methyl groups at C-4. Alkylation at C-16 is prevented by reduction of the C-17 carbonyl, and alkylation at C-2 is blocked by the Δ^1 double bond.

Our initial approach to 74 was based on a reaction sequence developed by Woodward and co-workers for their synthesis of cholesterol.[4] This conversion has been studied by a member of our research group working with lanosterol intermediate 29. Yields for the reactions in this sequence were generally good to excellent, with the exception of the final reductive deacetoxylation.



29 75 76

Since a low yield sequence such as this was deemed unacceptable, an alterative procedure was sought. One such alternative was found in the work of Speziale, Stevens, and Thompson, involving a modification of the Woodward cholesterol synthesis.[48] Thus, treatment of Diels-Alder adduct 77 with zinc dust and aqueous acetic



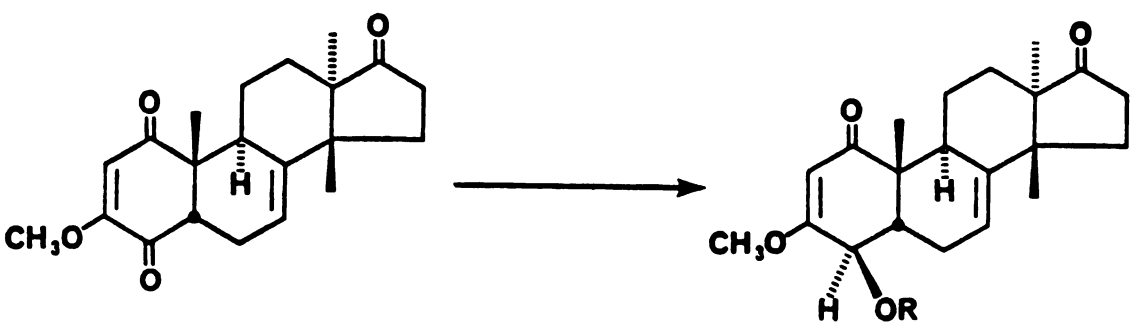
77 78

acid gave an excellent yield of the C-4 alcohol 78 as a single isomer. Selective reduction of one carbonyl function in this case is not surprising, since the C-1

carbonyl is ester-like in character, due to donation of electron density from the C-3 methoxy group, and is consequently less reactive than the C-4 carbonyl.

We anticipated that this reaction could be applied to the euphane synthesis without significant modification, and that it would reduce only the C-4 carbonyl. The presence of an additional ketone function at C-17 was not a concern, as experience has demonstrated this to be the least reactive of the three carbonyl groups.

In the event, treatment of 70 with zinc dust in aqueous acetic acid for 1.5 hr gave an excellent yield of alcohol 79 as a colorless crystalline solid. In order to complete the conversion of 70 to enone 74 in a concise fashion, we planned to transform the hydroxy function at C-4 to a good leaving group, and then effect simultaneous



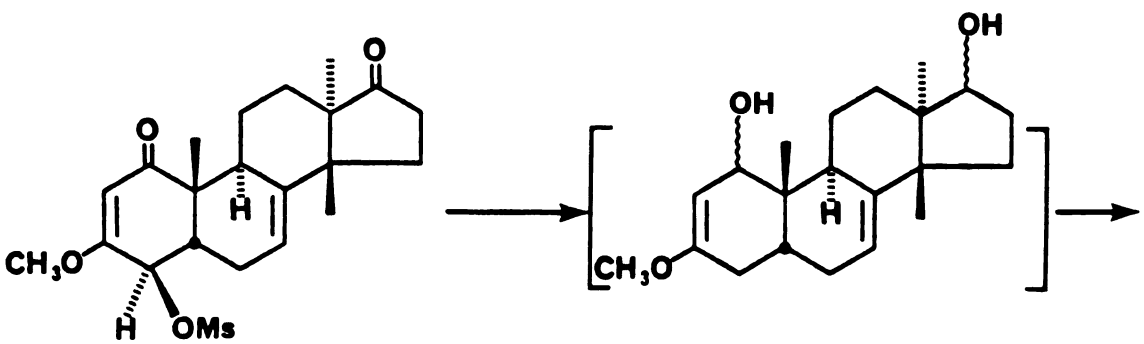
70

79 R=H
80 R=Ms

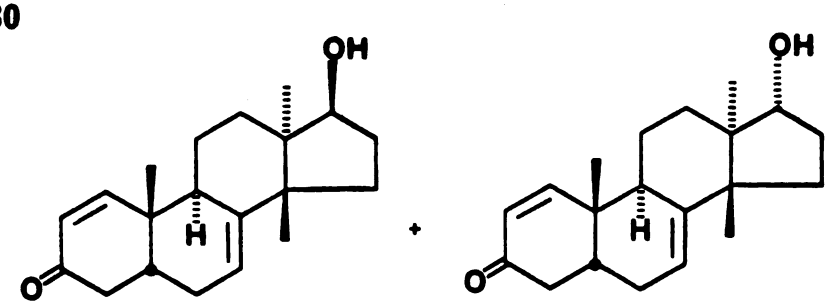
displacement and reduction of the two remaining carbonyl groups with an appropriate hydride reducing agent. Work by Holder and Matturro[49] suggested that lithium triethylborohydride (Super-Hydride), which is a source of

exceptionally nucleophilic hydride, was the reagent of choice for this transformation.

To this end alcohol 79 was smoothly converted to the corresponding mesylate 80 in 94% yield. Attempts to prepare the corresponding tosylate gave less than 50% conversion after 24 hours. Unfortunately reduction of 80 with three equivalents of Super-Hydride produced a complicated mixture of products. The problem with this



80



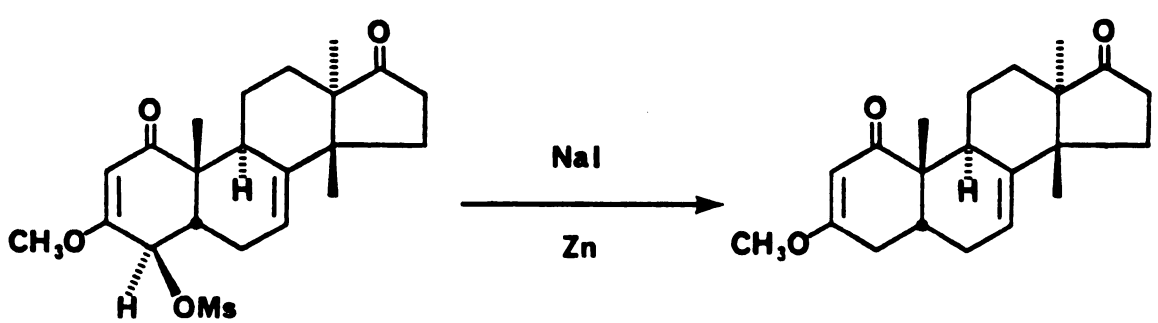
81 82

reaction may lie in the work-up. Triethyl boron (a pyrophoric liquid) is a product in the reaction and must be destroyed before it is exposed to the atmosphere. How well the reduction product survives the basic hydrogen peroxide treatment normally used to destroy the

triethyl boron is not known. The crude reduction product obtained from subsequent extraction followed by a mild acid wash yielded small amounts of the desired enones 81 and 82.

Attempts to effect the same reductions using solubilized lithium aluminum hydride (LAH) in THF, which Brown claims[50] is superior to an LAH/THF slurry for the reductive removal of tosylates and mesylates, gave similar results.

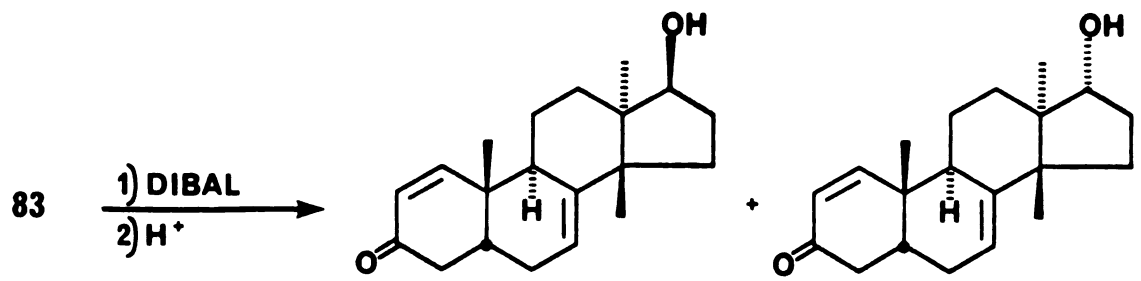
In light of these observations, a stepwise removal of the mesylate followed by reduction of the remaining carbonyl functions was explored as an alternative route to 81 and 82. Several methods for the selective removal of mesylates in the presence of other sensitive functionality have been reported.[51a-c] One of the mildest, the method of Fujimoto and Tsatsuno,[51c] involves treatment of mesylate 80 with sodium iodide and zinc dust in refluxing glyme. This gave a very good yield of enedione 83 as a crystalline solid. Subsequent reduction



80 83

of diketone 83 with two equivalents of diisobutylaluminum hydride (DIBAL) in methylene chloride, followed by

treatment with dilute HCl in 4:1 THF/water, then gave an 86% yield of 81 and 82 in a 2:1 ratio.



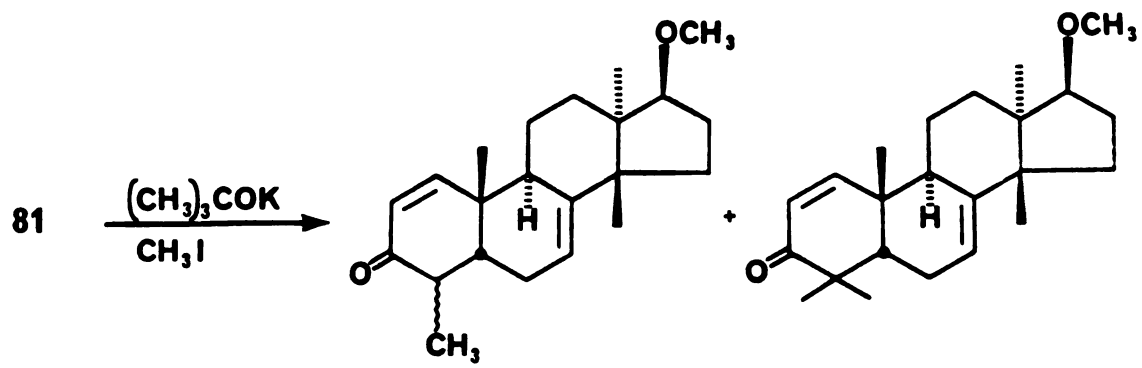
81 82

The overall yield for our four step conversion of 70 to a mixture of 81 and 82 was greater than 69%, which more than doubles the yield from the Woodward procedure.

Introduction of the geminal dimethyl substituents at C-4 presented many unexpected problems. Initial alkylation studies were conducted using lithium diisopropylamide (LDA) as a base. It was hoped that the oxaphilic character of lithium, coupled with the hindered nature of the C-17 oxygen would serve to minimize O-alkylation at that site. However, the alkoxyenolate generated by treatment of 81 with two equivalents of LDA proved to be insoluble in THF. Addition of HMPA as a co-solvent was necessary to achieve a homogeneous system. Reaction of this solution with one equivalent of methyl iodide followed by one equivalent of a proton source gave a mixture of C-4 methylated, and O-methylated products, together with recovered starting material.

O-methylation at C-17 was not viewed as a serious problem at this stage, due to the variety of reagents available for the cleavage of methyl ethers. The most reasonable course at this point seemed to be exhaustive methylation, followed by cleavage of the C-17 O-methyl ether. Unfortunately attempts at exhaustive methylation using LDA as the base gave mixtures, and the yield of the tri-methylated product was never maximized to a satisfactory level.

Remarkably, treatment of 81 with a large excess of potassium t-butoxide in THF followed by excess methyl iodide gave only two products, 84 and 85. Extended reactions times led to 85 as the sole identifiable product; however the yield of 85 was only fair (45%).



Although the sensitivity of the euphane triterpenes to protic acids limited the choice of reagents for ether cleavage,[52] several well-studied methods seemed attractive. The most promising of these were boron tribromide (BBr_3)[53a,b] and trimethylsilyl iodide (TMSI).[54a-c]

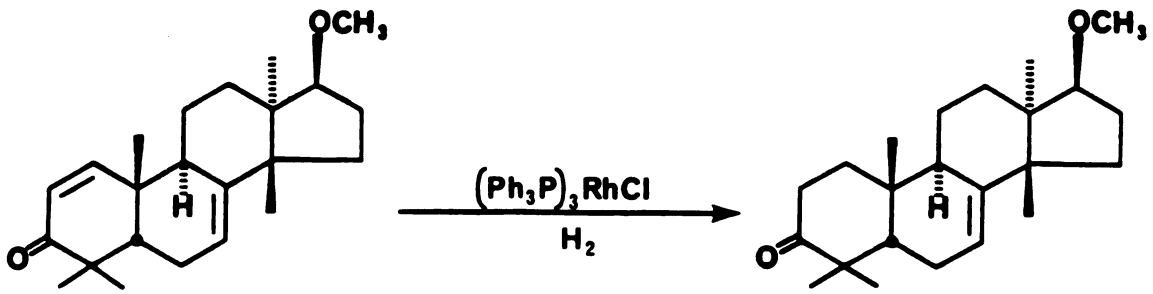
Table 3 Attempted cleavage of 85 and 86.

Substrate	Reagent	Solvent	Time	Temperature	Product	Reference
85	TMSCl/NaI	CH_3CN	24 h	RT	nr	54c
85	TMSCl/NaI	CH_3CN	25 h	82°	nr	54c
85	TMSI	$CHCl_3$	12 h	RT	nr	54a
85	TMSI	$CHCl_3$	12 h	62°	nr	54a
85	BBr_3	CH_2Cl_2	16 h	0 → RT	multiple products	53a
85	BBr_3, KI 18-crown-6	CH_2Cl_2	12 h	-46°	tar	53b
86	TMSCl/NaI	CH_3CN	16 h	82°	87	54c
86	TMSI	$CHCl_3$	12 h	62°	87	54a

Unfortunately, under a variety of conditions, these reagents failed to yield any products which could be identified as the C-17 hydroxyl compound. The results of these experiments are summarized in Table 3.

Dreiding models show that the C-17 methyl ether is extremely hindered by surrounding groups, making approach of these relatively large demethylating reagents difficult. Comparative studies with the steriod derivative 17-methoxy-androst-4-en-3-one 86 bear out this argument. Although BBr_3 failed to give cleavage products, the silicon reagents gave variable yields of testosterone 87 as seen in Table 3.

To ensure that the Δ^1 double bond in 85 was not causing unwanted side reactions in the experiments with BBr_3, it was removed by catalytic hydrogenation with Wilkinson's catalyst.[55] However reaction of 88 with BBr_3 under a variety of conditions still gave only complex



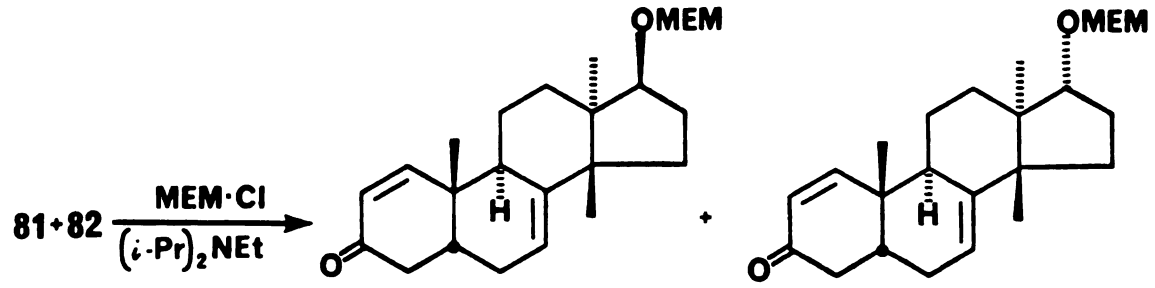
85 88

product mixtures.

A different approach to ether cleavage was reported recently by Olah et al.[56] Treatment of simple secondary methyl ethers with cerric ammonium nitrate and sodium bromate in aqueous acetonitrile gave the corresponding ketone as the chief cleavage product. However, in our hands, this method failed to give any of the desired methyl cleavage product.

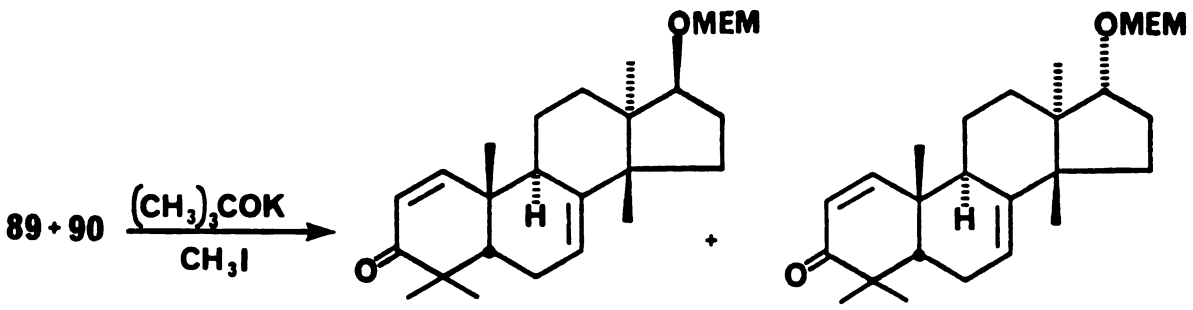
The resistance of our C-17 methyl ether derivatives to a variety of ether cleavage reactions required that a different protective group be used for the C-17 hydroxyl function. The hindered nature of this group was once again evident in the protection step. Common reagents for the introduction of trimethylsilyl (TMS), t-butyldimethylsilyl (TBDMS), benzyl, benzoyl, and

pivaloyl protecting groups all failed to react, or did so in poor yield. Fortunately, β-methoxyethoxymethyl chloride (MEM-Cl), a reagent developed by E.J. Corey et al.,[57] reacted smoothly with a mixture of 81 and 82 to give the corresponding MEM ethers in 87% yield. Dimethylation of



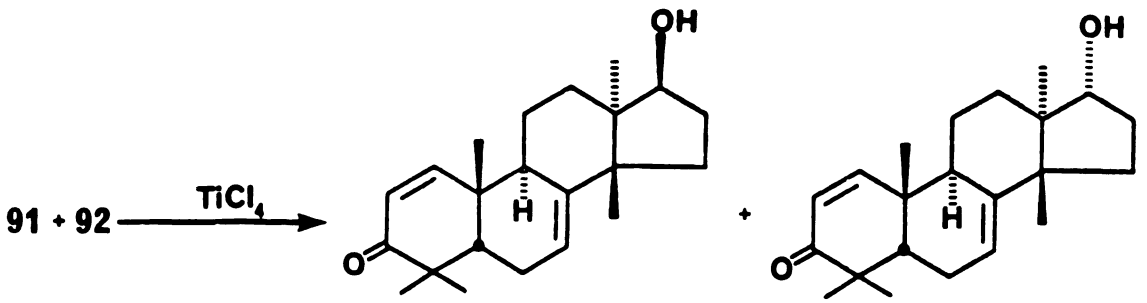
89 90

the protected alcohols with potassium t-butoxide and methyl iodide in THF as previously described gave a 57% yield of the gem-dimethyl compounds 94 and 95. As



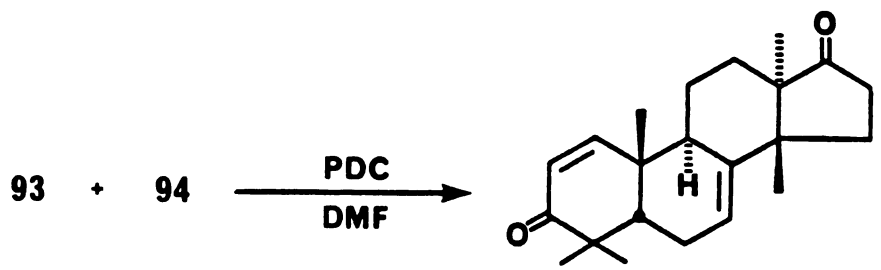
91 92

expected, the MEM protecting groups proved to be easily removed by treatment with $TiCl_4$ in methylene chloride. It should be noted, however, that zinc bromide, which is effective for deprotection in most instances, failed in this case to give cleavage products cleanly.



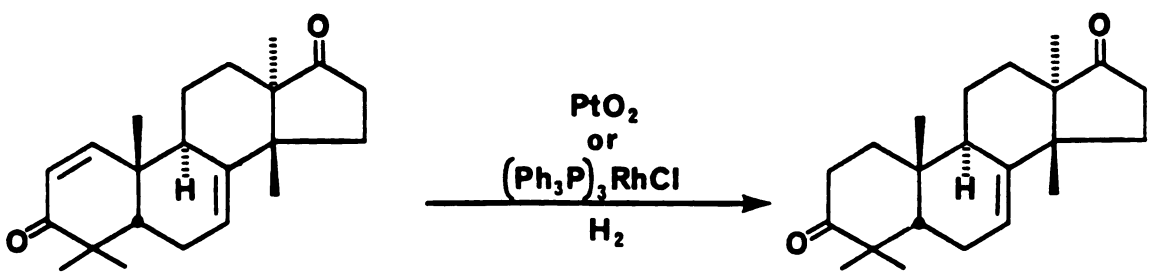
93 94

Finally, oxidation of the resulting epimeric alcohol mixture with pyridinium dichromate (PDC)[58] in dimethylformamide gave diketone 95.



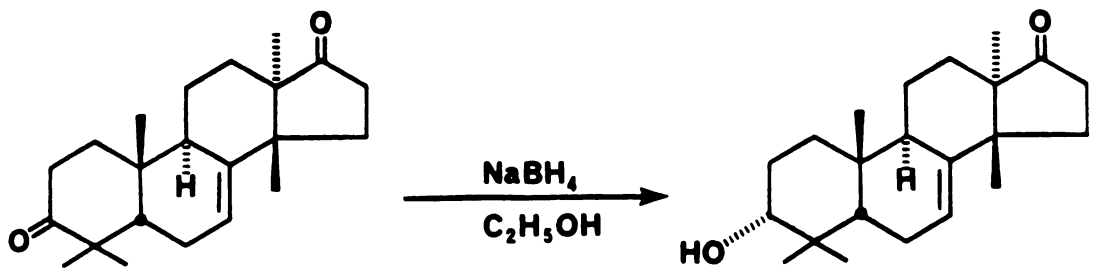
95

The last two steps of this synthesis were straightforward. Catalytic hydrogenation of the Δ^1 double bond with Adam's or Wilkinson's catalyst[55] gave the saturated ketone 96 in near quantitative yield.



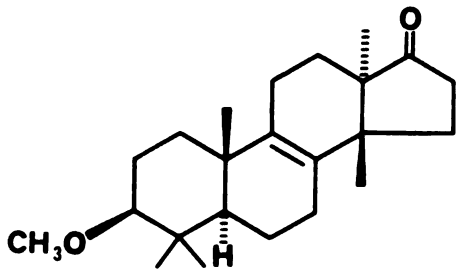
95 96

Finally, taking advantage of the low reactivity of the C-17 carbonyl function, treatment of 96 with sodium borohydride gave selective reduction of the C-3 carbonyl, yielding the axial alcohol 73 in 91% yield.



96 73

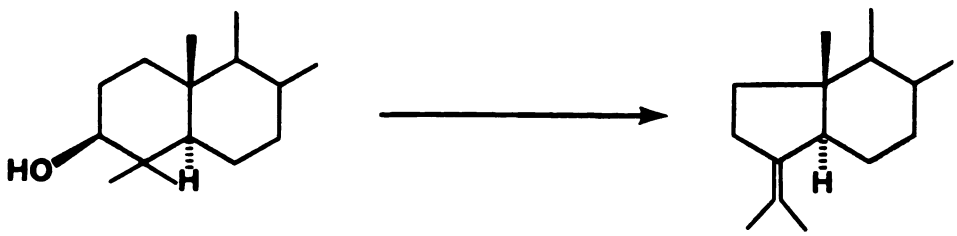
At this stage we were unaware of the AB-cis nature of the ring fusion in 73. It was our intention to convert the final product (which we believed to be 71) into 72 in order to achieve a final structure proof. An optically active antipode of 72 was obtained recently by



72

Levisalles and Audouin[47] through a side chain degradation of euphol. A direct comparison of our synthetic product with this degradation compound would require an isomerization of the $\Delta^{7,8}$ double bond, followed by methylation of the C-3 hydroxyl group in 71.

Butyrospermol has been converted to euphol by two different methods,[59,60] and these served as a basis for the double bond isomerization experiments. The first method involves an acid-catalyzed double bond shift. Although treatment of butyrospermol with strong acid leads to isoeuphane products, a simple $\Delta^{7,8}$ to $\Delta^{8,9}$ double bond migration results from mild acid treatment (HCl gas in chloroform). In the second method, treatment of butyrospermol with a hydrogen saturated Adam's catalyst (PtO_2) induces olefin isomerization to give euphol. Since 4,4-dimethyl steroids containing an equitorial hydroxyl at C-3 undergo a ring contraction rearrangement on treatment with strong acid, our acid catalyzed isomerization reactions were carried out on the 3-keto derivative.



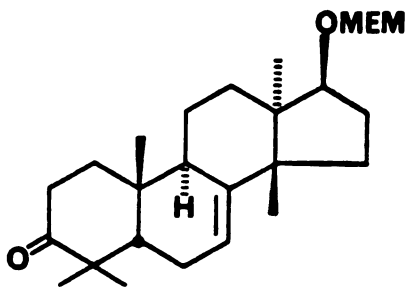
Diketone 96 was treated with a series of acid and transition metal catalysts in an attempt to isomerize the $\Delta^{7,8}$ double bond. The results of these experiments are summarized in Table 4. Much to our surprise in all cases

Table 4 Attempted olefin isomerization of 96.

Catalyst	Solvent	Temperature	Time	Result
collidine·HCl	CH_2Cl_2	40°	4 hr	nr
HCl	$CHCl_3$	0°	2 hr	nr
HCl	$CHCl_3$	25°	1.5 hr	nr
HCl	$CHCl_3$	25°	8 hr	nr
PtO_2/H_2	$HOAc/C_6H_{12}$	25°	1 hr	nr
$RhCl_3 \cdot 3H_2O$	$EtOH/CHCl_3$	70°	24 hr	formation of 95
p-TSA·H_2O	THF	67°	12 hr	nr
	C_6H_6	25°	1 week	nr
	C_6H_6	80°	4 hr	nr
70% $HClO_4$	CH_3CN	25°	10 hr	nr

but one starting material was recovered unchanged. Even treatment with perchloric acid yielded only starting material, which seemed remarkable in light of the euphanes proclivity toward rearrangement under these conditions.

Isomerization was next tried with 97. The results of



97

these experiments are summarized in Table 5. Once again no

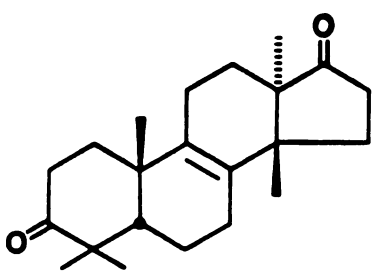
Table 5 Attempted olefin isomerization of 97.

Catalyst	Solvent	Temperature	Time	Result
HCl gas	$CHCl_3$	25°	2 hr	cleavage of MEM ether
PPTS	C_6H_6	25°	24 hr	nr
PPTS	C_6H_6	48°	24 hr	nr
PPTS	C_6H_6	80°	24 hr	nr
P·TSA	C_6H_5	80°	24 hr	several products
$PdCl_2 \cdot 2C_6H_5CH_2CN$	C_6H_5	80°	12 hr	several products
$PdCl_2 \cdot HCl$	$HOAc/H_2O$	reflux	24 hr	several products

products corresponding to the $\Delta^{8,9}$ double bond isomer were identified.

The failure of these efforts to effect double bond isomerization was disturbing. Consequently, a sample of keto-alcohol 73 was submitted for X-ray crystallographic analysis. The results of this analysis was that 73 proved to be the unexpected AB-cis isomer (see Figure II).

We can now rationalize the reluctance of the $\Delta^{7,8}$ double bond to migrate to the $\Delta^{8,9}$ position. Models of 98 show severe interactions between either the C-4 α-methyl

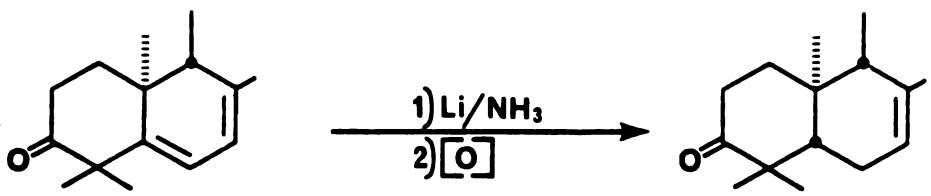


98

and the C-13 angular methyl, or the C-4 β-methyl and the C-10 angular methyl. Only in 96 can these methyl interactions be avoided without invoking non-chair forms in the A and B rings.

Once we discovered that the previous synthesis had produced a 5-epi-butyrospermol derivative (AB-cis), modifications were sought that would redirect it to the desired AB-trans ring fusion. The most attractive of these modifications was based on work by Pike, Summers and Klyne.[61] Thus lithium-ammonia reduction of the

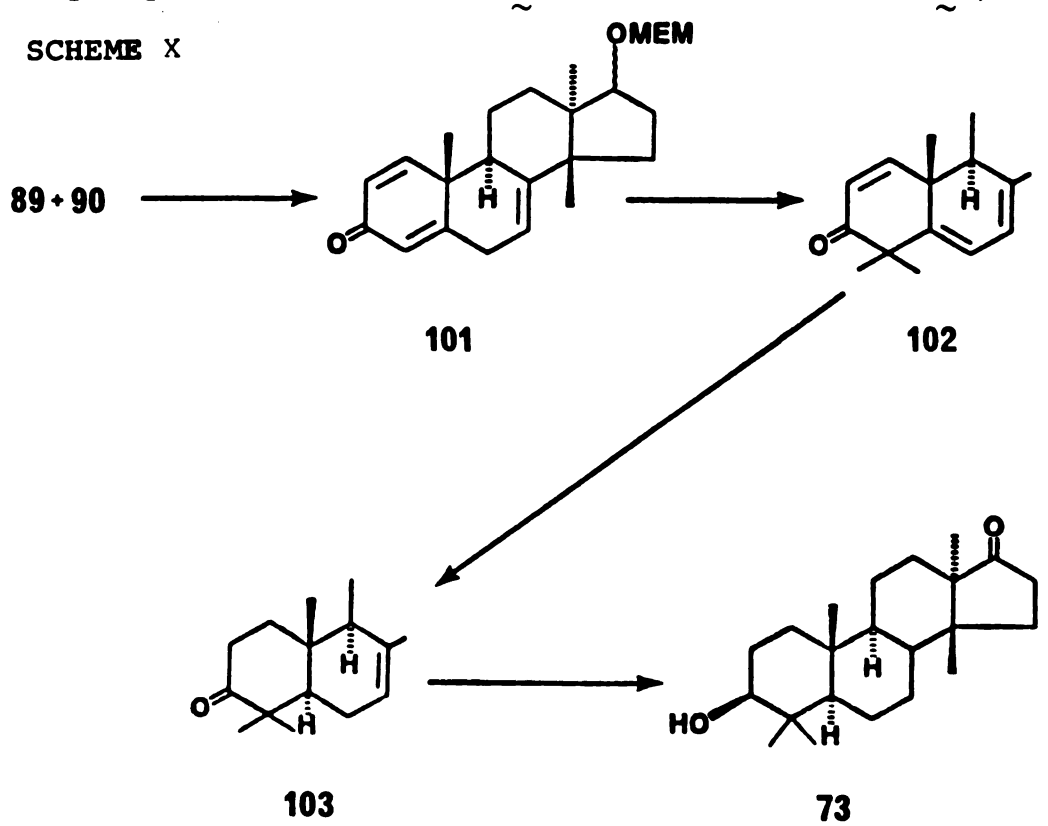
4,4-dimethyl-lumista-5,7-diene-3-one derivative 99 was reported to give the 4,4-dimethyl-5β-lumistan-3-one 100 in good yield. In our system an analogous B-ring homoannular diene may be generated first by introduction



99 100

of a $\Delta^{4,5}$ double bond in 89 and 90, followed by bis-methylation at C-4 as previously described (Scheme X). Lithium-ammonia reduction of 102 should then lead to the butyrospermol derivative 103. Modification of 103, using

SCHEME X



methodology developed in the synthesis of 73, would lead to 71.

Preliminary work in this area is encouraging. Indeed, initial results indicate that the alkylation step (to form 102) proceeds in higher yield than that observed for the formation of the cis-fused 4,4-dimethyl adducts 91 and 92.

EXPERIMENTAL

General

Except where otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere, using solvents distilled from appropriate drying agents. All glassware was oven dried at 180-200°C for four hours previous to use, or flame dried (three times) under a continuous stream of dry argon or nitrogen. Reactions were monitored by thin layer chromatography (Merck Silica Gel-60, F-254, .2 mm) with visualization by ultraviolet fluorescence, or spray reagent (30% H_2SO_4 or 5% p-anisaldehyde in ethanol) with subsequent heating.

Small scale chromatographic separations were accomplished with the use of 2 mm silica plates (Merck F-254, 20 × 20 cm). Larger scale separations were effected by flash chromatography (40-63 millimicron silica gel, Merck 9385). Melting points were determined on either a Thomas-Hoover capillary melting point apparatus, or a Reichert hot-stage microscopic, and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Mass spectra (MS) were obtained with a Finnigan 4000 GC/MS spectrometer. Proton magnetic resonance spectra (PMR)

were taken in deuterochloroform and recorded on either a Varian T-60 or a Bruker WM 250 spectrometer at 250 MHz, and are calibrated in parts per million (δ) downfield from tetramethylsilane (TMS) as an internal standard. Carbon magnetic resonance spectra (CMR) were recorded on a Bruker WM 250 spectometer at 69.8 MHz using deuterochloroform as solvent and are calibrated in parts per million (δ) downfield from TMS as internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Eagle Harbor, MI.

General Procedure for the Evaluation of Lewis Acids in the Diels-Alder Reaction of Quinone 28 and Piperylene 32

To a solution of quinone 28 (152 mg, 1 mmol) in 5 mL of methylene chloride, which has been cooled to 0°C, is added 1 mL of a 1 M solution of Lewis acid in methylene chloride. After stirring for .5 hr, the solution is cooled to -15°C and 1 mL (681 mg = 10 mmol of a 1:1 cis/trans mixture) of piperylene 32 in 4 mL of methylene chloride is added slowly over .5 hr. Reaction progress is monitored by GLC. The reaction is quenched by addition of 1:1 methanol/water and warming to room temperature. The mixture is diluted with methylene chloride, washed with saturated sodium bicarbonate, water, and brine, and dried over sodium sulfate. Removal of solvent yields the crude product as an orange oil.

Preparation of quinol 36

Quinone 28 (152 mg, 1.0 mmol) was dissolved in 50 mL of dry THF in a 100 mL, three-neck flask. To this solution is added 0.9 mL (696 mg, 6.0 mmol) of tetramethylethylenediamine (TMEDA) and this mixture was cooled to -78°C. Following slow addition of .72 mL of 1.4 M methyllithium (1.01 mmol) in ether, the reaction mixture was stirred for 7 hr, quenched with methanol, and warmed to room temperature. Removal of solvents under vacuum gave a brown oil, which was dissolved in methylene chloride, and washed with water, brine, and dried over sodium sulfate. Evaporation of this solution yielded crude 36 as a brown oil. Further purification was effected by passage through a short column of silica gel, followed by crystallization from chloroform/hexanes to give 95 mg (57%) of 36 as a white powder.

Characteristic properties of 36 are:

M.P. 103-103.5°C

Mass spectra (70 eV) m/e (rel. intens.) 168(40), 153(100), 125(34), 108(14), 69(33), 53(18), 43(42), 39(20).

Infrared ($CDCl_3$) 3560(s), 3400(br), 2970, 2230, 1750, 1675, and 1640 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 1.49 (d, 3H, J = 5.8 Hz), 1.86 (d, 3H, J = 1.5 Hz), 3.04 (s, 1H), 3.77 (d, 3H, 6.1 Hz), 5.44 (s, 1 H), 6.45 (br s, 1H).

Diels-Alder reaction of quinol 36 and piperylene 32

Quinol 36, (76 mg, .45 mmol) was dissolved in 7 mL of methylene chloride and cooled to -46°C (CO_2/cyclohexanone). To this solution was added 0.5 mL of a 1.0 M solution of tin (IV) chloride in methylene chloride (0.5 mmol). After stirring for 15 min, a solution of 0.5 mL of piperylene (50% cis-trans isomers, 0.34 g, 5.0 mmol) in 5 mL methylene chloride was added slowly over 1 hr. After stirring for 4 hr at -46°C, there was no evidence of adduct formation by GLG analysis so the temperature was increased to 0°C. After stirring for 6 hr at 0°C, the reaction mixture was quenched with water. The organic phase was diluted with methylene chloride, washed with saturated sodium bicarbonate, water, brine, and then dried over sodium sulfate. Analysis by GLC showed formation of a single adduct, plus a small amount of unreacted quinol. Column chromatography (silica-ether) yielded 50 mg (47%) of 37 as a white solid. An analytical sample was prepared by recrystallization from ether/hexanes. When this Diels-Alder reaction was conducted using boron trifluoride etherate as the catalyst, an adduct which proved identical to 37 by mixed melting point and 250 MHz PMR was isolated in 41% yield. Characteristic properties of 37 are:

M.P. 130.5-132°C

Mass spectra (70 eV) m/e (rel. intens.) 236(12), 203(14), 175(13), 169(63), 152(27), 137(98), 128(67), 127(30),

109(44), 100(58), 91(30), 70(100), 68(54), 43(80).
Infrared ($CDCl_3$) 3550(br), 2960, 2240, 1710, 1670, 1640, 1610, and 1260 cm^{-1}.
PMR ($CDCl_3$) 250 MHz, δ 0.99 (d, 3H, J = 7.5 Hz), 1.35 (s, 3H), 1.46 (s, 3H), 2.32 (s, 1H), 1.10-2.50 (m, 4H), 3.75 (s, 3H), 5.43 (s, 1H), 5.68 (d, 1H, J = 9.6 Hz), 5.79 (m, 1H).

Diels-Alder reaction of quinone 28 and diene 24

Quinone 28 (15.2 g, .10 mol) was dissolved in 500 mL of methylene chloride in a two-liter, three-neck, round bottomed flask equipped with a mechanical stirrer, and a pressure equalizing addition funnel. After cooling this solution to 0°C, 14.7 mL (16.96 g, .12 mol) of boron trifluoride etherate was added in one portion. The resulting orange solution was stirred for 15 min., cooled to -15°C (CO_2/ethylene glycol) and a solution of diene 24 (11.8 g, .062 mol) in 250 mL of methylene chloride was added slowly over a 2 hr period. The temperature of the now dark green solution was maintained at -15°C for 24 hours. After addition of 100 mL of 50% methanol/water, the reaction mixture was warmed to room temperature. The organic phase was separated and concentrated to ca. 150 mL. Unreacted quinone was removed by reduction with 200 mL of 10% sodium bisulfite. The disappearance of quinone was monitored by TLC (silica-ether). When the quinone was no longer present the

organic phase was separated, washed with water, brine, and dried over sodium sulfate. Evaporation of the solvent gave an orange oil, which when triturated with ether yielded a creme colored solid. Recrystallization from methylene chloride/cyclohexane gave 10.9 g of 29 as an off-white solid. The mother liquor proved to be a 1:1 mixture of 29 and regioisomer 30. This mixture was easily separated according to the following procedure.

Separation of 29 and 30

A mixture of regioisomers 29 and 30 (1.9 g, 5.6 mmol) was added to a solution of sodium bicarbonate (.48 g, 5.71 mmol) in 150 mL of methanol and heated under reflux for 6 hr. After chilling in ice, the mixture was filtered and the collected solid was dissolved in methylene chloride, washed with water, brine, and dried over sodium sulfate. Removal of the solvent gave 1.0 g of an off-white solid, which by TLC and 250 MHz PMR proved to be pure 29. Regioisomer 31, contaminated with a small amount of 29, may be recovered from the mother liquor by removing the solvent under vacuum, and repeating the previous process on the resulting solid. The combined yield of 29 from the initial crystallization and subsequent treatment of the mother liquor is 12.47 g (59% based on starting diene).

Characteristic properties of 29 are:

M.P. 260-261°C

Mass spectrum (70 eV) m/e (rel. intens.) 342(1), 314(15), 299(9), 189(11), 155(10), 154(100), 145(12), 119(15), 105(17), 69(10).

Infrared ($CDCl_3$) 2960, 2150, 1720, 1700, 1660, 1605, 1150 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 1.01 (s, 3H), 1.15 (d, 3H, J = 0.9 Hz), 1.39 (s, 3H), 1.40-2.80 (m, 11H), 2.99 (dd, 1H, J = 7.9 and 10.1 Hz), 3.78 (s, 3H), 5.29 (dd, 1H, J = 3.1 and 6.4 Hz), 5.67 (s, 1H).

CMR ($CDCl_3$) 69.8 MHz, δ 219.54, 201.54, 196.02, 159.11, 145.15, 115.74, 109.54, 56.31, 56.10, 50.90, 50.66, 46.75, 42.31, 34.20, 30.76, 27.58, 25.94, 25.35, 24.55, 23.38, 17.58.

Characteristic properties of 31 are:

M.P. 218-220°C

Mass spectrum (70 eV) m/e (rel. intens.) 342(1), 327(1), 314(33), 299(27), 145(23), 131(31), 126(22), 125(26), 119(25), 105(46), 91(48), 79(22), 77(27), 69(100), 55(36), 41(41).

Infrared ($CDCl_3$) 2920, 2240, 1760, 1725, 1665, and 1610 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 1.06 (s, 3H), 1.24 (d, 3H, J = 0.9 Hz), 1.39 (s, 3H), 1.49-2.95 (m, 11H), 2.51 (ddd, 1H, J = 1.8, 9.8 and 19.2 Hz), 3.77 (s, 3H), 5.27 (dd, 1H, J = 2.7 and 7.0 Hz), 5.78 (s, 1H).

Preparation of enol-acetate 61

A mixture of the triketone 29 (8.4 g, 24.6 mmol), anhydrous sodium acetate (4.03 g, 49.2 mmol), and 4-(dimethylamino)pyridine (DMAP) (20 mg, .16 mmol) was added to 300 mL of 2:1 (v/v) benzene and acetic anhydride. After heating under reflux for four days, the mixture was cooled to room temperature and filtered to remove sodium acetate. The solvent was removed under vacuum, and the resulting solid dissolved in methylene chloride, washed with water and brine, and dried over sodium sulfate. Removal of solvent yielded a solid for which TLC (silica-ether) showed two spots $R_f = .34$, and $R_f = .21$. Separation by flash chromatography (silica-40% methylene chloride/ether) yielded 8.7 g (92%) of 61 as the lower R_f component, and .4 g (5%) of unreacted 29 as the higher R_f component. An analytical sample of enol-acetate was prepared by recrystallization from ethyl acetate/petroleum ether.

Characteristic properties of 61 are:

M.P. 195-197°C

Mass spectrum (70 eV) m/e (rel. intens.) 384(3), 342(24), 327(15), 324(22), 299(11), 129(11), 128(10), 119(11), 115(11), 105(18), 91(16), 69(20), 55(13), 43(100), 41(13).

Infrared ($CDCl_3$) 2950, 1760, 1740, 1675, and 1605 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.97 (s, 3H), 1.26 (s, 3H), 1.50 (s, 3H), 2.26 (s, 3H), 1.60-3.10 (m, 11H), 3.75 (s, 3H), 5.43 (s, 1H), 5.56 (q, 1H).

Photoenol-acetate 62

A solution of 61 (1.5 g, 3.9 mmol) in one liter of dry acetonitrile was deoxygenated by bubbling a stream of dry argon through the solution for 15 min. The solution was then irradiated for 1.5 hr using a Hanovia medium-pressure mercury lamp filtered by pyrex and a saturated copper(II) sulfate solution. The filter solution was cooled by an ice-calcium chloride bath, and circulated through a jacketed vessel surrounding the lamp. Removal of the solvent yielded 1.5 g of a gummy yellow solid. Separation of products was difficult, but was accomplished on a small scale. Thus 150 mg of crude product was subjected to preparative TLC (silica-ether, 4 passes). Three bands were noted: $R_f = .58$ (8.4 mg, not identified), $R_f = .50$ (109 mg) 62, and $R_f = .44$ (19 mg) 61.
Characteristic properties of 62 are:
M.P. 176-177.5°C
Mass spectrum (70 eV) m/e (rel. intens.) 384(8), 342(42), 207(16), 204(14), 181(20), 167(35), 166(83), 161(18), 119(20), 105(17), 69(21), 43(100).
Infrared ($CDCl_3$) 2990, 1785, 1755, 1645, and 1600 cm^{-1}.
PMR ($CDCl_3$) 250 MHz, δ 0.97 (s, 3H), 1.06 (s, 3H), 1.27 (s, 3H), 2.27 (s, 3H), 0.80-3.30 (m, 11H), 3.77 (s, 3H), 5.43 (d, 1H, $J = 3.9$ Hz), 5.49 (s, 1H).
CMR ($CDCl_3$) 69.8 MHz, δ 218.87, 200.72, 199.10, 168.67, 164.85, 143.50, 142.41, 117.59, 99.92, 56.25, 51.14,

50.25, 46.73, 43.11, 34.14, 31.08, 26.88, 26.23, 24.17, 23.25, 20.23, 17.35, 15.09.

Preparation of triketone 70

The mixture of enol-acetates 61 and 62 (2.0 g, 5.2 mmol) was dissolved in 100 mL of dry methanol. Potassium carbonate (0.5 g, 3.6 mmol) was then added in one portion and the mixture was stirred for 10 min. Filtration followed by solvent removal yielded a brown solid which was dissolved in methylene chloride, and washed with 10% aqueous acetic acid, water, and brine. The aqueous phase was back-extracted with methylene chloride. The combined organic phases were dried over sodium sulfate. Evaporation of the solvent yielded a brown solid, which after trituration with ether, gave 1.5 g of a light yellow solid. Flash chromatography (silica gel-5% methylene chloride/ether) yielded two products, 29 (R_f = .39, .25 g), and 70 (R_f = .28, 1.25 g).

Characteristic properties of 70 are:

M.P. 229-232°C

Mass spectrum (70 eV) m/e (rel. intens.) 342(19), 299(10), 211(15), 171(16), 138(12), 119(16), 114(100), 105(29), 91(19), 86(32), 69(28), 55(12), 44(15).

Infrared (CH_2Cl_2) 2990, 1750, 1725, 1680, and 1625 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.91 (s, 3H), 0.97 (s, 3H), 1.34 (s, 3H), 1.30-3.15 (m, 12H), 3.81 (s, 3H), 5.46 (q, 1H), 5.87 (s, 1H).

CMR ($CDCl_3$) 69.8 MHz, δ 218.5, 201.5, 193.3, 162.1, 141.8, 117.9, 109.5, 56.3, 53.5, 52.1, 50.5, 46.6, 40.1, 34.1, 30.7, 26.9, 24.5, 23.7, 21.1, 19.2, 14.3.

Preparation of alcohol 79

Triketone 70 (1.5 g, 4.39 mmol) and zinc dust (.5 g, 7.65 mmol) were added to 60 mL of 2:1 (v/v) acetic acid/water. After stirring at room temperature for 1.5 hr the unreacted zinc was removed by filtration, washed several times with hot methanol, and discarded. The combined organic and aqueous phases were washed with ether (5 times), and the combined ether phases were washed with saturated sodium bicarbonate, water, and brine. After drying over sodium sulfate removal of solvent by rotary evaporation yielded 1.43 g (95%) of 79 as a white solid. An analytical sample was prepared by recrystallization from methanol (colorless plates).

Characteristic properties of 79 are:

M.P. 256.5-257°C

Mass spectrum (70 eV) m/e (rel. intens.) 344(10), 155(17), 154(100), 123(13), 56(8).

Infrared ($CDCl_3$) 3585(s), 3545(br), 2240, 1724, and 1613 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 1.00 (s, 3H), 1.02 (s, 3H), 1.08 (s, 3H), 1.20-2.75 (m, 12H), 2.99 (d, 1H, J = 2.8 Hz), 3.78 (s, 3H), 4.34 (dd, 1H, J = 2.4 and 10.0 Hz), 5.31 (s, 1H), 5.49 (q, 1H, J = 3.1 Hz).

CMR ($CDCl_3$) 69.8 MHz, δ 202.0, 189.0, 173.7, 143.4, 118.3, 100.2, 68.1, 56.1, 50.5, 47.6, 46.8, 46.2, 36.5, 34.2, 30.9, 27.2, 24.6, 24.1, 24.0, 18.6, 14.3.

Analysis: Calculated for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19
Found: 73.39 8.16

Preparation of mesylate 80

The alcohol 79 (1.36 g, 3.95 mmol) was dissolved in 50 mL dry pyridine and cooled to 0°C. Mesyl chloride (0.62 mL, 0.91 g, 6.3 mmol) was added via syringe, and the mixture was placed in the freezer overnight. Pyridine hydrochloride was removed by filtration and discarded. After removal of the solvent under vacuum, the residue was dissolved in methylene chloride, and washed with water, brine, and dried over sodium sulfate. Removal of solvent by rotary evaporation yielded 1.56 g (94%) of 80 as a yellowish solid. Recrystallization from methylene chloride/heptane gave pure 80 as a white crystalline solid.

Characteristic properties of 80 are:

M.P. 196-198°C

Mass spectrum (70 eV) m/e (rel. intens.) 422(8), 343(48), 326(19), 187(27), 154(57), 153(81), 150(56), 119(59), 113(100), 105(62), 98(60), 69(28), 55(35), 41(34).

Infrared ($CDCl_3$) 2950, 1725, 1650, 1620, 1350, and 1175 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 1.01 (s, 3H), 1.05 (s, 3H), 1.12 (s, 3H), 1.25-2.65 (m, 12H), 3.17 (s, 3H), 3.82 (s, 3H), 5.34 (d, 1H, J = 9.5 Hz), 5.41 (d, 1H, J = 1.2 Hz), 5.52 (m, 1H).

CMR ($CDCl_3$) 69.8 MHz, δ 200.3, 189.4, 168.8, 143.5, 117.6, 102.3, 78.1, 56.4, 50.4, 48.4, 44.8, 39.1, 36.6, 34.1, 30.9, 27.2, 24.6, 24.1, 18.6, 14.0.

Analysis: Calculated for $C_{22}H_{30}O_6S$: C, 62.54; H, 7.16; S, 7.59; Found: C, 62.71; H, 7.14; S, 7.51.

Preparation of enedione 83

The mesylate 80 (1.0 g, 2.37 mmol), sodium iodide (1.78 g, 11.8 mmol), and zinc dust (1.54 g, 23.6 mmol) were added to 20 mL of dry glyme and heated under reflux for 3 hr. After cooling to room temperature and filtering, the solution was diluted with water and extracted with ether. The combined ether extracts were washed with brine and dried over sodium sulfate. Evaporation of the solvent yielded 0.698 g (89%) of 83 as a white powdery solid. An analytical sample of 83 was prepared by recrystallization from ether (white needles).

Characteristic properties of 83 are:

M.P. 215-217°C

Mass spectrum (70 eV) m/e (rel. intens.) 328(47), 313(14), 230(17), 215(19), 213(23), 139(95), 138(100), 119(37), 105(38), 99(19), 91(19), 40(20).

Infrared ($CDCl_3$) 2975, 1740, 1620, 1390, and 900 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 1.01 (s, 3H), 1.05 (s, 3H), 1.06 (s, 3H), 1.35-2.80 (m, 14H), 3.70 (s, 3H), 5.28 (d, 1H, J = 1.4 Hz), 5.44 (dd, 1H, J = 2.8, and 6.5 Hz).

CMR ($CDCl_3$) 69.8 MHz, δ 202.94, 189.26, 175.42, 143.87, 117.50, 100.41, 55.53, 50.57, 46.84, 46.13, 38.25, 34.67, 34.14, 32.99, 30.87, 28.70, 27.11, 24.64, 23.94, 18.41, 14.20.

Analysis: Calculated for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59
Found: 76.89 8.44

Preparation of enones 81 and 82

Diketone 83 (1.10 g, 3.35 mmol) was dissolved in 20 mL of dry methylene chloride, and cooled to 0°C. To this solution was added 10 mL of 1 M diisobutylaluminum hydride (DIBAL) in hexane (10 mmol). After stirring for 1.25 hr excess hydride was destroyed by the addition of 10 mL of saturated sodium potassium tartrate. The reaction mixture was then extracted with ether. A solid which appeared in the aqueous phase was collected, boiled with methanol, and filtered. The filtrate was combined with the ether extracts, and the solvent was removed to yield 1.10 g (99%) of a white solid, which showed a single spot on TLC (silica-ether). This product was dissolved in 100 mL of 4:1 (v/v) THF/water along with four drops of concentrated HCl. The resulting solution was stirred at room temperature overnight, diluted with water, and then extracted with ether. The combined

ether extracts were washed with saturated sodium bicarbonate, water, brine, and dried over sodium sulfate. Evaporation of solvent yielded a light yellow solid which by TLC (silica-ether) proved to be a mixture of three products. Flash chromatography (silica-ether) gave 8$\underset{\sim}{1}$ (R_f = .43, 578 mg, 58%), 8$\underset{\sim}{2}$ (R_f = .35, 278 mg, 28%), and a small amount of material which was not identified (not UV-active on silica TLC). The total yield for 8$\underset{\sim}{1}$ and 8$\underset{\sim}{2}$ was 86%.

Characteristic properties of 8$\underset{\sim}{1}$ are:

M.P. 181-183°C

Mass spectra (70 eV) m/e (rel. intens.) 300(1), 285(7), 267(4), 192(67), 174(49), 159(96), 109(100), 105(58), 91(49), 79(39), 41(46).

Infrared (CH_2Cl_2) 3625(sh), 3490(br), 2975, 2910, 1700, and 1325 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.77 (s, 3H), 1.06 (s, 3H), 1.22 (s, 3H), 1.20-2.80 (m, 15H), 3.78 (dd, 1H, J = 1.7 and 7.5 Hz), 5.31 (q, 1H, J = 3.1 Hz), 5.96 (d, 1H, J = 10.1 Hz), 6.97 (d, 1H, J = 10.1 Hz).

CMR ($CDCl_3$) 69.8 MHz, δ 200.42, 162.72, 146.08, 128.15, 116.57, 79.44, 49.74, 46.64, 41.81, 39.93, 39.75, 37.76, 35.22, 33.22, 29.22, 28.34, 27.99, 25.24, 19.64, 18.99.

Analysis: Calculated for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39

Found: 79.95 9.31

Characteristic properties of 82 are:

M.P. 168-169°C

Mass spectrum (70 eV) m/e (rel. intens.) 301(3), 285(9), 192(56), 177(18), 159(25), 133(32), 119(37), 109(100), 91(58), 79(52), 41(48).

Infrared (CH_2Cl_2) 3610(s), 3465(br), 2965, 2890, 1680, 1665, and 1480 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.88 (s, 3H), 1.04 (s, 6H), 1.40-2.80 (m, 15H), 4.10 (dd, 1H, J = 6.9 and 8.7 Hz), 5.28 (q, 1H, J = 3.1 Hz), 5.96 (d, 1H, J = 10.1 Hz), 6.96 (d, 1H, J = 10.1 Hz).

CMR ($CDCl_3$) 69.8 MHz, δ 201.12, 162.38, 145.20, 127.91, 116.40, 80.20, 48.54, 43.92, 41.49, 39.40, 39.31, 37.43, 33.30, 30.16, 29.81, 28.87, 27.05, 20.67, 19.40, 18.37.

Analysis: Calculated for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39

Found: 79.92 9.29

Preparation of MEM-ether derivative 89

This procedure will be illustrated for the single C-17 epimer 81. Normally mixtures of 81 and 82 are protected.

Alcohol 81 (700 mg, 2.33 mmol) was dissolved in 3 mL of methylene chloride in a dry 10 mL pear shaped flask with a side arm. To this solution was added β-methoxyethoxymethyl chloride (MEM-Cl) (400 microliters, 435 mg, 3.5 mmol), followed by diisopropylethylamine (610 microliters, 452 mg, 3.5 mmol). After stirring at

room temperature for 3 hr the starting material was no longer evident by TLC analysis (silica-ether) and the reaction was halted. After addition of 5 mL of water, the organic phase was separated, and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were washed with brine, and dried over sodium sulfate. Removal of the solvent by rotary evaporation yielded 783 mg of 89 (87%) as a yellow oil.

Characteristic properties of 89 are:

Mass spectrum (70 eV) m/e (rel. intens.) 389(2), 283(28), 175(25), 137(9), 109(17), and 89(100).

Infrared ($CDCl_3$) 2900, 2240, 1660, and 1050 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.80 (s, 3H), 1.05 (s, 3H), 1.16 (s, 3H), 0.80-2.80 (m, 15H), 3.39 (s, 3H), 3.56 (m, 2H), 3.67 (m, 2H), 4.61 (d, 1H, J = 6.7 Hz), 4.72 (d, 1H, J = 6.7 Hz), 5.30 (dd, 1H, J = 3.1 and 6.4 Hz), 5.95 (d, 1H, J = 10.1 Hz), 6.95 (d, 1H, J = 10.1 Hz).

Preparation of 91 and 92

To a 100 mL pear shaped flask containing 1.22 g (10 mmol) of potassium t-butoxide (Aldrich) was added a mixture of 89 and 90 (905 mg, 2.33 mmol) as a solution in 50 mL of THF. The yellow-orange solution turned brown on contact with the base. After stirring this mixture for 10 min, methyl iodide (.62 mL, 1.42 g, 10 mmol) was added in one portion. The solution immediately turned a milky white, and the flask became warm to the touch. Stirring

was continued at room temperature for two days. An additional portion of methyl iodide was added, and following an additional two days, the reaction mixture was diluted with 100 mL of water and 100 mL of ether. The aqueous phase was separated, extracted twice with ether, and the combined ether extracts were washed with water (twice), brine, and dried over sodium sulfate. Removal of the solvent yielded 946 mg of product as a dark yellow oil. Preparative TLC (silica-50% ether/hexanes) yielded two products, 91 (R_f = .62, 362 mg), and 92 (R_f = .53, 180 mg). The total yield for 91 and 92 was 56%.

Characteristic properties of 91 are:

Mass spectrum (70 eV) m/e (rel. intens.) 416(4), 372(4), 340(4), 320(4), 311(1), 174(7), 159(7), 145(4), 137(15), 89(77), 59(100).

Infrared (neat) 2932, 2880, 1660, 1460, 1370, 1111, and 1035 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.76 (s, 3H), 1.06 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.17 (s, 3H), 0.80-2.80 (m, 13H), 3.39 (s, 3H), 3.56 (m, 2H), 3.67 (m, 2H), 4.62 (d, 1H, J = 6.7 Hz), 4.73 (d, 1H, J = 6.7 Hz), 5.38 (q, 1H, J = 3.1 Hz), 5.93 (d, 1H, J = 10.1 Hz), 6.89 (d, 1H, J = 10.1 Hz).

Characteristic properties of 92 are:

Mass spectrum (70 eV) m/e (rel. intens.) 372(1), 340(1), 311(1), 280(1), 174(7), 159(7), 137(15), 89(77), and 59(100).

Infrared (neat) 2946, 2884, 1664, 1457, 1350, 1105, and 1057 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.84 (s, 3H), 1.04 (s, 3H), 1.05 (s, 3H), 1.10 (s, 3H), 1.15 (s, 3H), 0.75-2.80 (m, 13H), 3.40 (2, 3H), 3.55 (m, 2H), 3.68 (m, 2H), 3.99 (dd, 1H, J = 6.4 and 9.2 Hz), 4.70 (s, 2H), 5.35 (q, 1H, J = 3.1 Hz), 5.94 (d, 1H, J = 10.1 Hz), 6.88 (d, 1H, J = 10.1 Hz).

Preparation of alcohol 93

This procedure will be illustrated for the single C-17 epimer 91. Normally mixtures of 91 and 92 are deprotected. A solution of 91 (271 mg, .65 mmol) in 3 mL methylene chloride was cooled to 0°C. Pyridine (40 microliters, 39.5 mg, .5 mmol) was added, followed by titanium (IV) chloride (215 microliters, 371 mg, 1.95 mmol). The solution turned dark brown. After 30 min the starting material was no longer evident by TLC analysis (silica-ether). The reaction was quenched by the addition of 2 mL concentrated ammonium hydroxide solution and then diluted with 5 mL of water. After separation of the organic phase, the aqueous phase was extracted twice with methylene chloride. The combined organic phases were washed with water until the aqueous phase was neutral, then with brine, and finally dried over sodium sulfate. Removal of the solvent gave a brown oil. Passage through a short silica column yielded 171 mg (80%) of 93 as a yellowish solid, which was recrystallized from methylene chloride/ hexanes.

Characteristic properties of 93 are:

M.P. 221-224°C

Mass spectra (70 eV) m/e (rel. intens.) 328(1), 313(1), 192(29), 159(34), 137(100), 105(24), 93(18), 91(17), 43(19), 41(21).

Infrared ($CDCl_3$) 3600, 2950, and 1660 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.73 (s, 3H), 1.06 (s, 3H), 1.09 (s, 3H), 1.16 (s, 3H), 1.21 (d, 3H, J = 0.7 Hz), 0.80-2.80 (m, 13H), 3.77 (dd, 1H, J = 1.5 and 7.6 Hz), 5.39 (q, 1H, J = 3.1 Hz), 5.94 (d, 1H, J = 10.1 Hz), 6.90 (d, 1H, J = 10.1 Hz).

Preparation of diketone 95

A mixture of epimeric alcohols 93 and 94 (40 mg, .12 mmol) was added to a stirred solution of pyridinium dichromate (PDC) in 2 mL of dimethylformamide (DMF). The initial bright orange solution turned brown as the reaction proceeded. After stirring overnight (16 hr) at room temperature, the solution was diluted with water and extracted (three times) with ether. The combined ether extracts were washed with water, brine, and dried over sodium sulfate. Evaporation of the solvent yielded 32 mg (81%) of 95 as a brown oil. Passage through a short silica column gave pure 95 as a colorless oil.

Characteristic properties of 95 are:

Mass spectrum (70 eV) m/e (rel. intens.) 327(1), 311(1), 190(1), 175(14), 137(97), 133(24), 44(43), 40(100).

Infrared (neat) 2960, 2880, 1735, 1665, 1455, and 1370 cm^{-1}. PMR ($CDCl_3$) 250 MHz, δ 0.98 (s, 3H), 1.03 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.17 (s, 3H), 0.70-2.40 (m, 10H), 2.42-2.56 (ddd, 1H, J = 1.8, 9.5 and 19.2 Hz), 2.66-2.80 (m, 1H), 5.53 (q, 1H, J = 3.1 Hz), 5.96 (d, 1H, J = 10.1 Hz), 6.88 (d, 1H, J = 10.1 Hz).

Preparation of saturated diketone 96

A 25 mL pear shaped flask containing 10 mg (.044 mmol) of platinum oxide (Adam's catalyst) suspended in 2 mL of benzene was connected to an atmospheric pressure hydrogenation apparatus. After three cycles of evacuating the system under aspirator vacuum then filling with hydrogen gas, a solution of 95 (105 mg, .32 mmol) dissolved in absolute ethanol was added with a syringe, and the hydrogen gas uptake was monitored. After 6 hr hydrogen uptake ceased and the reaction was stopped. The catalyst was removed by filtration, and the remaining solution was concentrated to yield 102 mg (97%) of 96 as a colorless oil. Characteristic properties of 96 are:
Mass spectra (70 eV) m/e (rel. intens.)

Infrared (neat) 2960, 1745, 1700, 1465, 1375, and 730 cm^{-1}. PMR ($CDCl_3$) 250 MHz δ 0.92 (s, 3H), 1.02 (d, 3H, J = 0.85 Hz), 1.06 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 0.80-2.40 (m, 13H), 2.43-2.58 (ddd, 1H, J = 1.8, 9.5 and 19.2 Hz),

2.59-2.75 (ddd, 1H, J = 5.2, 14.8 and 9.6 Hz), 2.93-3.08 (m, 1H, 5.51 (dd, 1H, J = 3.4 and 6.7 Hz).

Preparation of 73

Ketone 96 (35 mg, .11 mmol) was dissolved in 3 mL of 95% aqueous ethanol, and cooled to 0°C. To this pale yellow solution was added 1 mL of .1 M sodium borohydride in 3 N aqueous sodium hydroxide. This mixture was stirred at 0°C, and the reaction progress was monitored by TLC (silica-ether). After 3 hr the starting material was no longer present, and the solution was diluted with 5 mL of water and extracted three times with ether. The combined ether extracts were washed with water, brine, and dried over sodium sulfate. Removal of the solvent by rotary evaporation produced 32 mg (91%) of 73 as an oil which crystallized on standing. An analytical sample was prepared by recrystallization (methylene chloride/petroleum ether) to yield 73 as a colorless crystalline solid.

Characteristic properties of 73 are:

M.P. 192.5-194.5°C

Mass spectra (70 eV) m/e (rel. intens.) 330(4), 297(29), 230(21), 133(22), 119(37), 107(24), 105(39), 91(41), 79(26), 57(36), 55(62), 43(92), 41(100).

Infrared ($CDCl_3$) 3670, 3600, 2920, 2220, and 1725 cm^{-1}.

PMR ($CDCl_3$) 250 MHz, δ 0.82 (s, 3H), 0.89 (s, 3H), 0.97 (d, 3H, J = 0.92 Hz), 1.04 (s, 3H), 1.05 (s, 3H),

0.80-2.40 (m, 15H), 2.41-2.55 (ddd, 1H, J = 1.8, 9.5 and 19.2 Hz), 2.74-2.87 (m, 1H), 3.31 (dd, 1H, J = 6.4 and 9.5 Hz), 5.43 (q, 1H, 3.2 Hz).

CMR ($CDCl_3$) 69.8 MHz, δ 219.82, 143.28, 119.70, 79.33, 50.65, 50.24, 46.63, 39.86, 35.63, 34.65, 34.60, 34.37, 30.95, 29.51, 27.21, 27.08, 24.99, 24.70, 23.75, 23.52, 17.59, 14.81.

Preparation of 85

A mixture of 81 (100 mg, 0.33 mmol), potassium t-butoxide (244 mg, 2.0 mmol), and 5 mL dry THF was stirred at room temperature for 10 min. To this opaque orange mixture was added methyl iodide (200 microliters, 3.2 mmol) in one portion. The reaction mixture immediately turned milky white. After stirring for 93 hr the reaction was halted by diluting with 50 mL of water, and extracting the resulting clear solution three times with ether. The combined ether phases were washed with water, brine, and dried over sodium sulfate. Removal of the solvent yielded a yellow oil, which when subjected to preparative TLC (silica-ether) gave 53 mg (46%) of 85 as a yellow oil, plus unidentified polymeric material.

Characteristics of 85 are:

Mass spectra (70 eV) m/e (rel. intens.) 342(1), 327(29), 312(15), 284(15), 269(17), 257(18), 256(38), 160(29), 129(21), 128(42), 105(82), 73(100), 55(63), 43(57), 41(72).

Infrared ($CDCl_3$) 2950, 2250, 1680, 1125, and 910 cm^{-1}. PMR ($CDCl_3$) 250 MHz δ 0.75 (s, 3H), 1.05 (s, 3H), 1.09 (s, 3H), 1.15 (br s, 6H), 0.60-2.80 (m, 12H), 3.18 (dd, 1H, J = 1.8 and 7.3 Hz), 3.25 (s, 3H), 5.37 (q, 1H, J = 3.3 Hz), 5.94 (d, 1H, J = 10.4 Hz), 6.89 (d, 1H, J = 10.4 Hz).

Preparation of 88

A 25 mL pear shaped flask equipped with a side arm containing 5.0 mg (0.02 mmol) of platinum oxide (Adam's catalyst) and 2 mL of benzene was connected to an atmospheric pressure hydrogenation apparatus. After three cycles of evacuation under aspirator vacuum, followed by filling with hydrogen gas, a solution of 35 mg (0.10 mmol) of 85 in 3 mL absolute ethanol was added to the flask with a syringe. After approximately 6 hr hydrogen uptake ceased, and the reaction was stopped. The catalyst was removed by filtration, and the remaining solution was concentrated to yield 35 mg (100%) of 88 as a brown oil. Characteristics of 88 are:
Mass spectra (70 eV) m/e (rel. intens.)

Infrared (neat) 2950, 1725, 1480, 1390, and 1140 cm^{-1}
PMR ($CDCl_3$) 250 MHz, δ 0.83 (s, 3H), 0.89 (s, 3H), 1.06 (s, 3H), 1.08 (s, 3H), 1.14 (s, 3H), 0.80-2.40 (m, 14H), 2.69 (ddd, 1H, J = 5.2, 15.0 and 14.7 Hz),

2.87-3.04 (m, 1H), 3.21 (dd, 1H, J = 1.8 and 7.3 Hz), 3.26 (s, 3H), 5.34 (q, 1H, J = 3.4 Hz).

APPENDIX

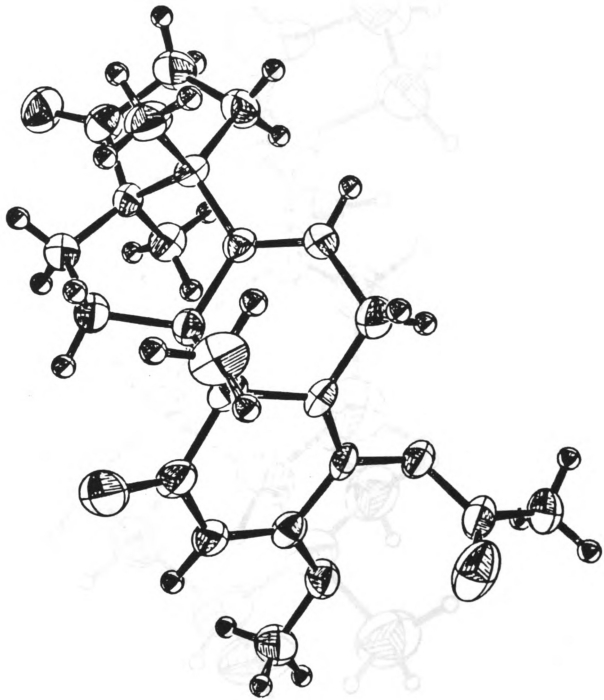


Figure 1. ORTEP drawing of 62.

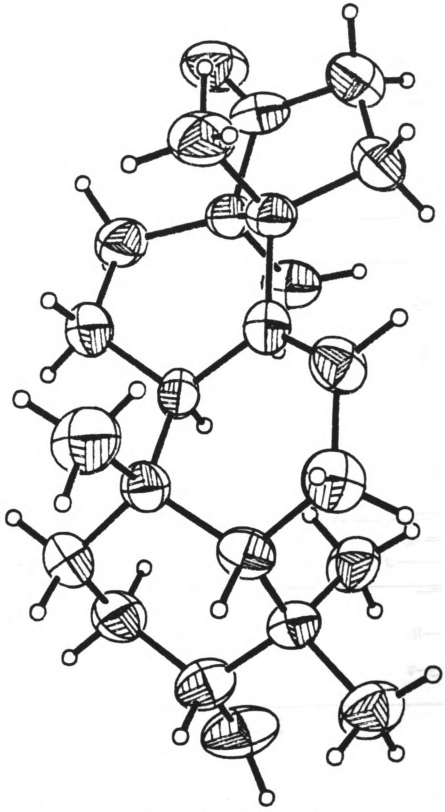


Figure 2. ORTEP drawing of 73.

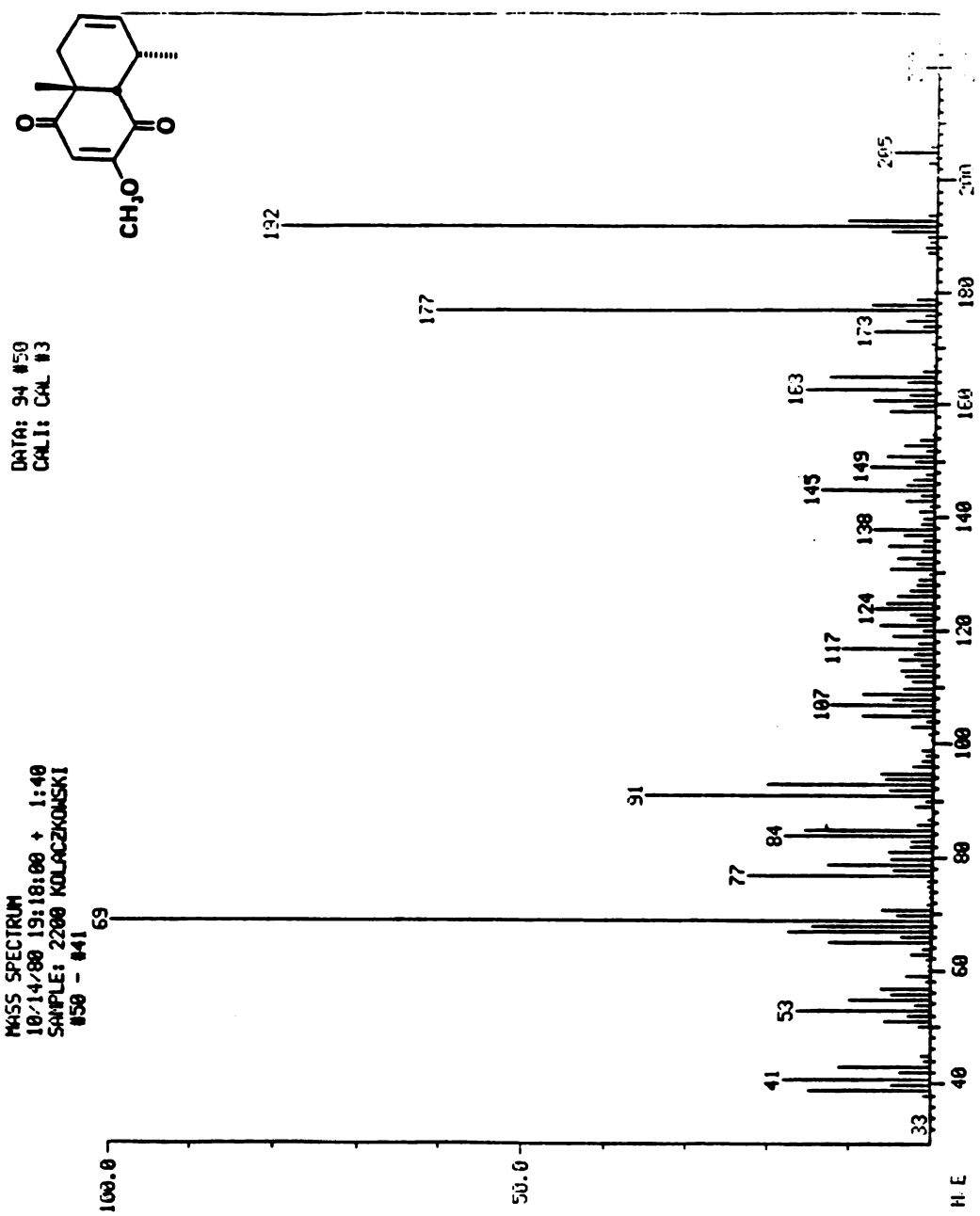


Figure 3. Mass spectrum of 34.

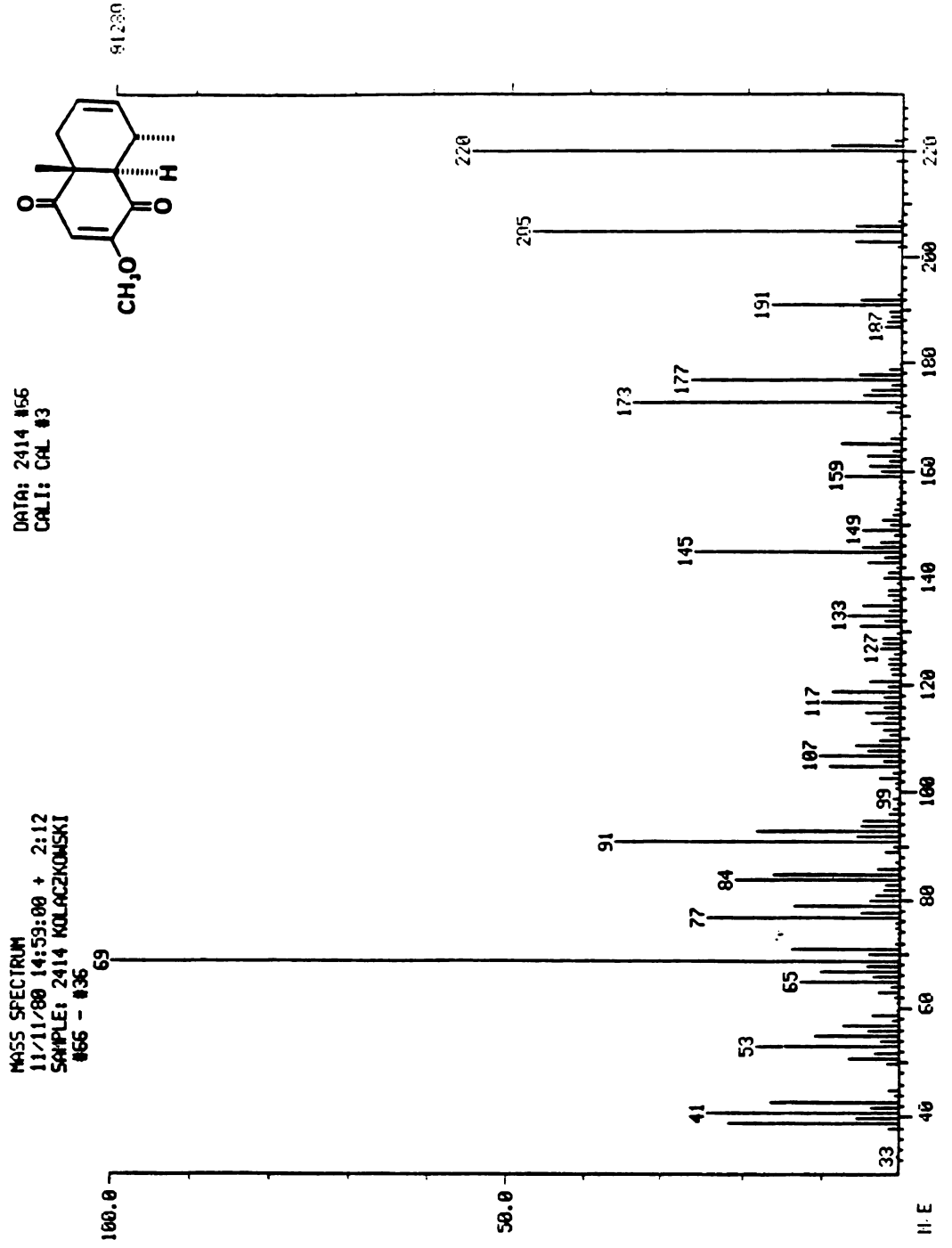


Figure 4. Mass spectrum of 35.

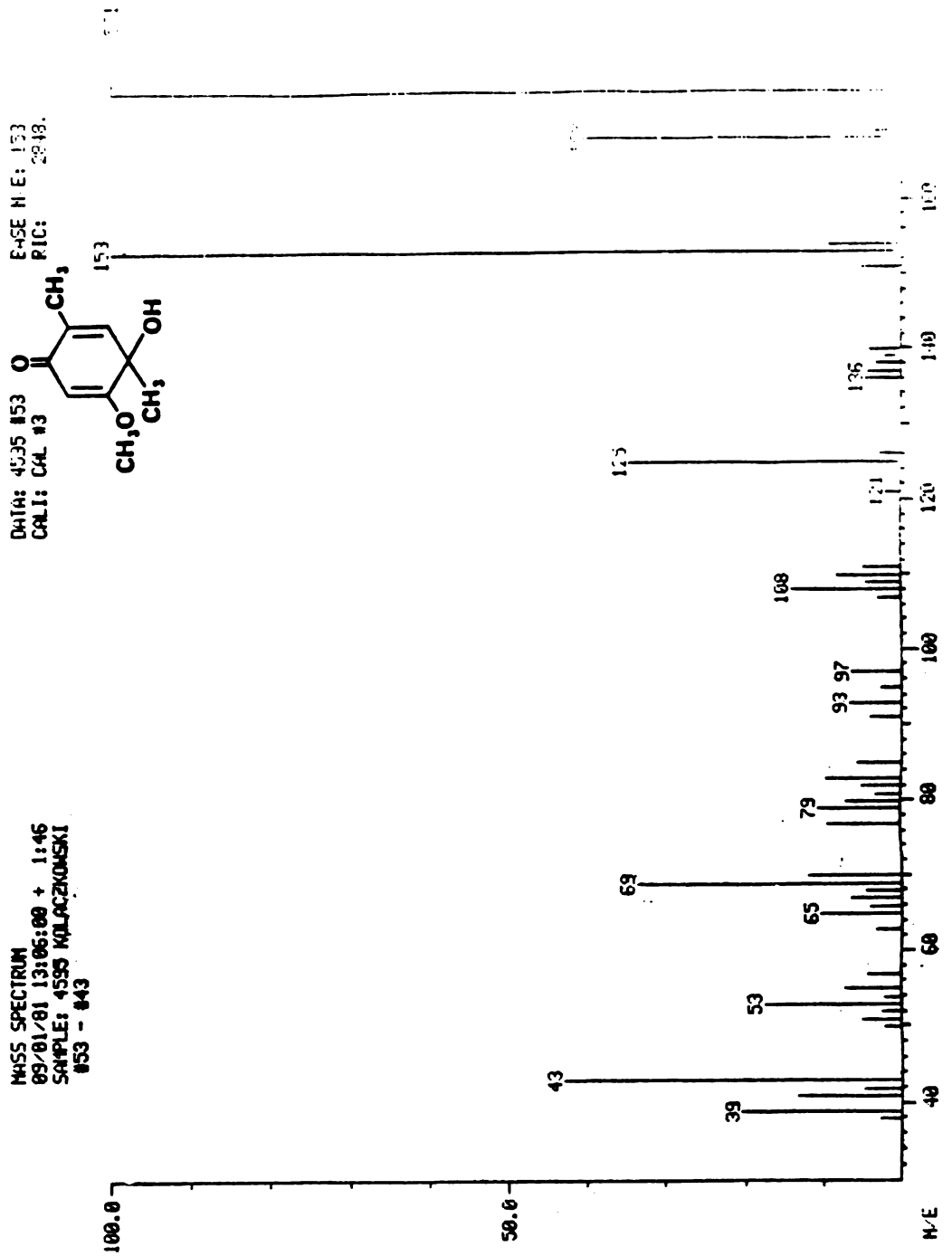


Figure 5. Mass spectrum of 36.

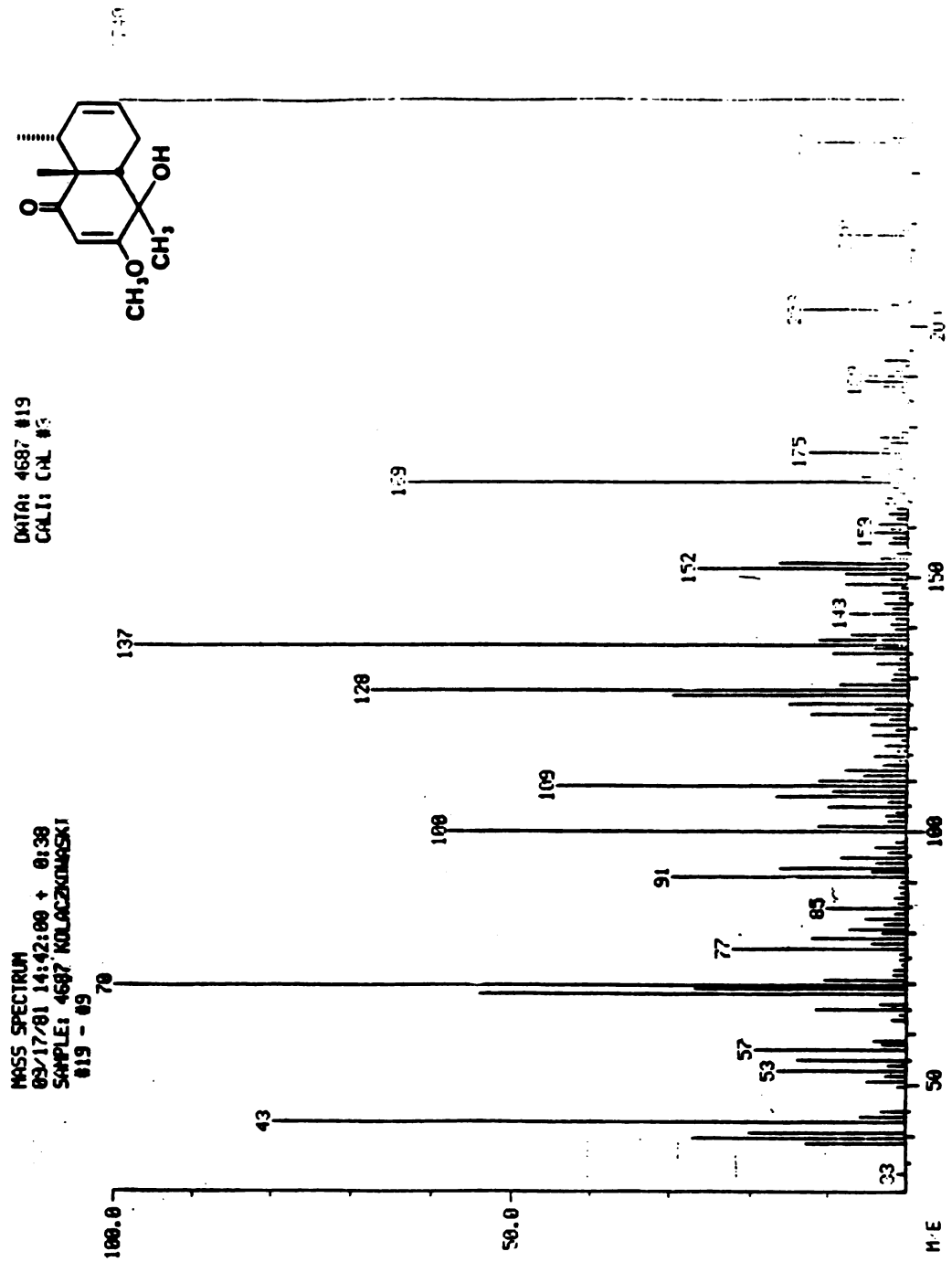


Figure 6. Mass spectrum of 37.

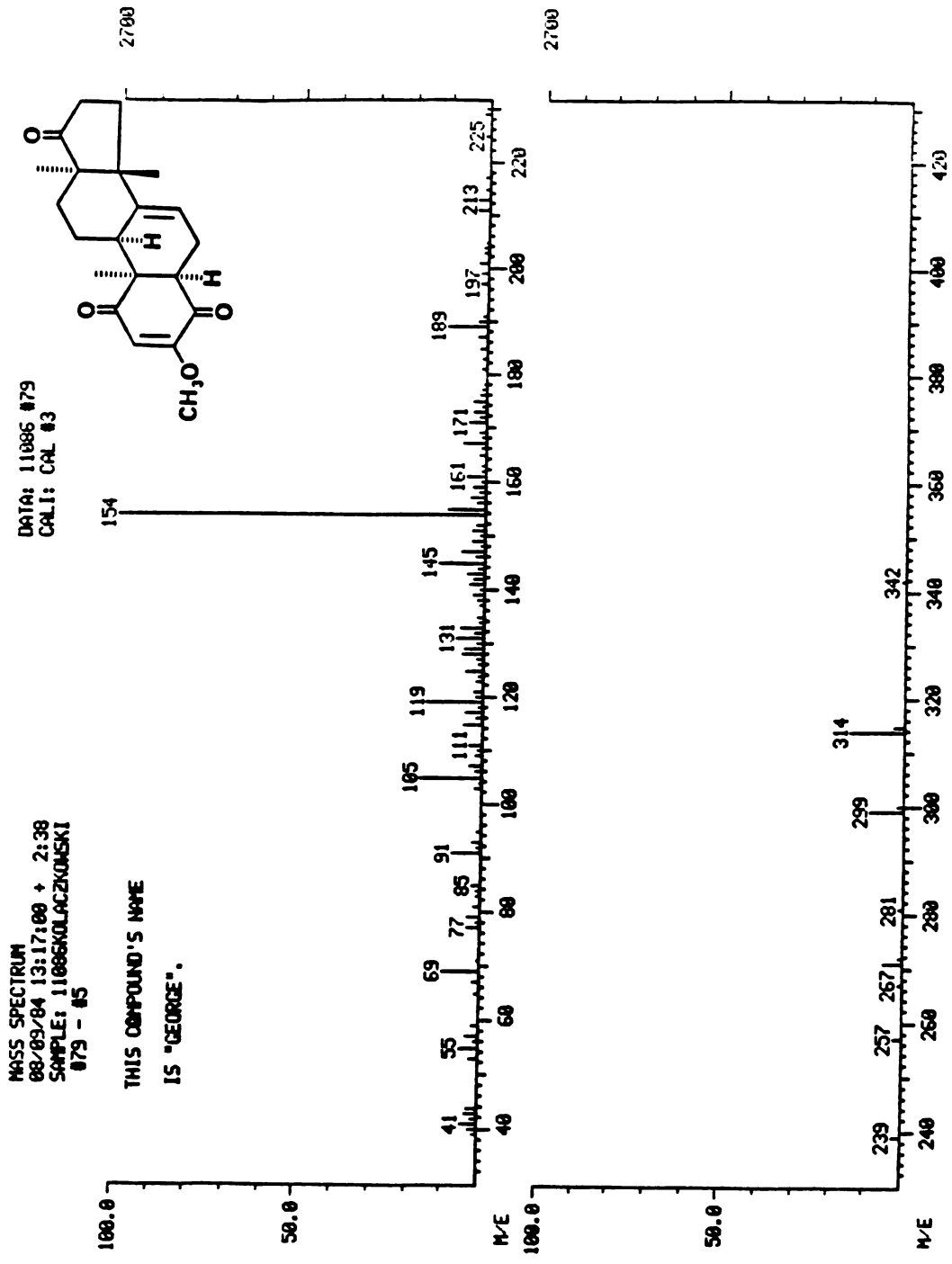


Figure 7. Mass spectrum of 29.

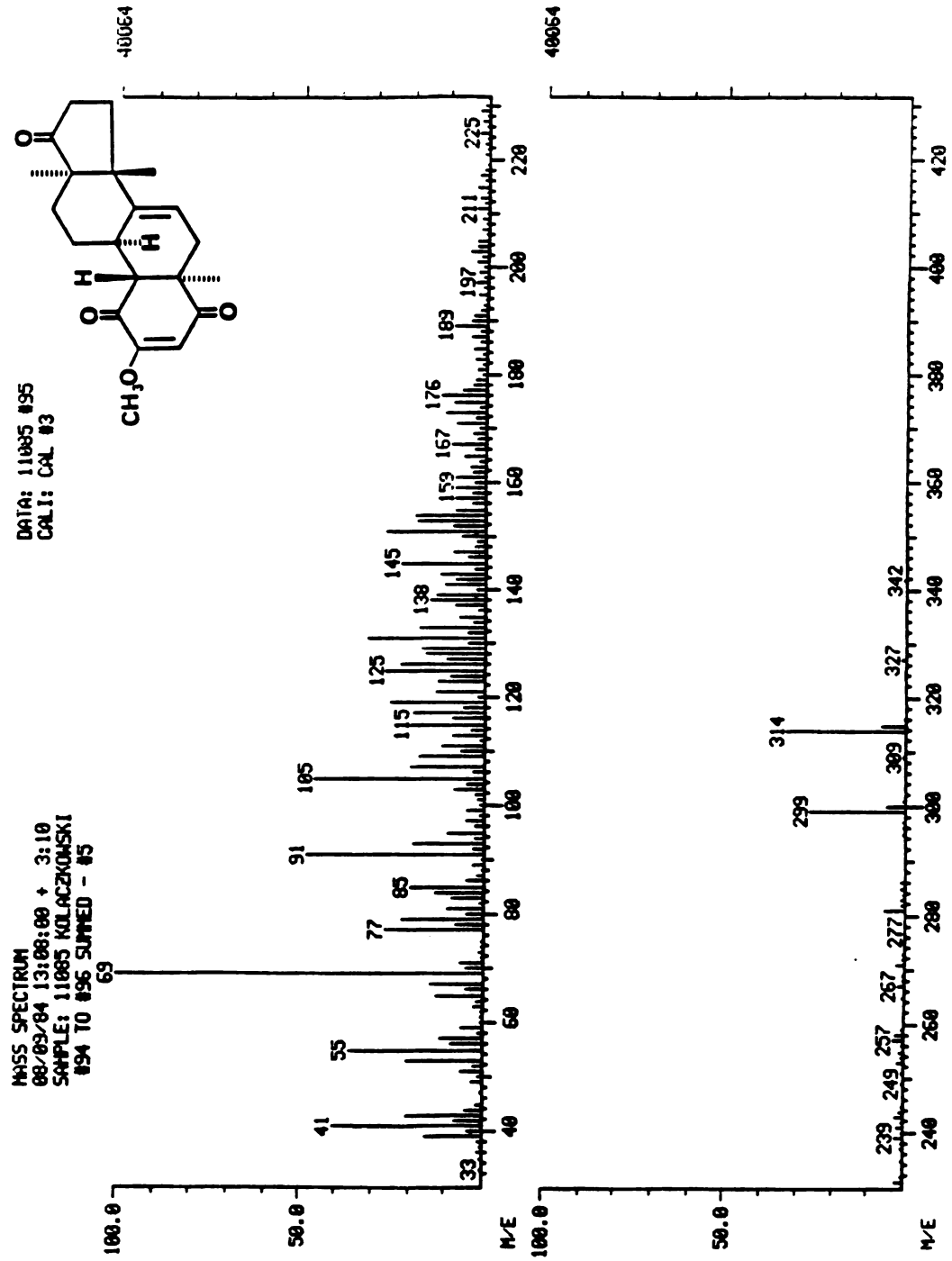


Figure 8. Mass spectrum of 31.

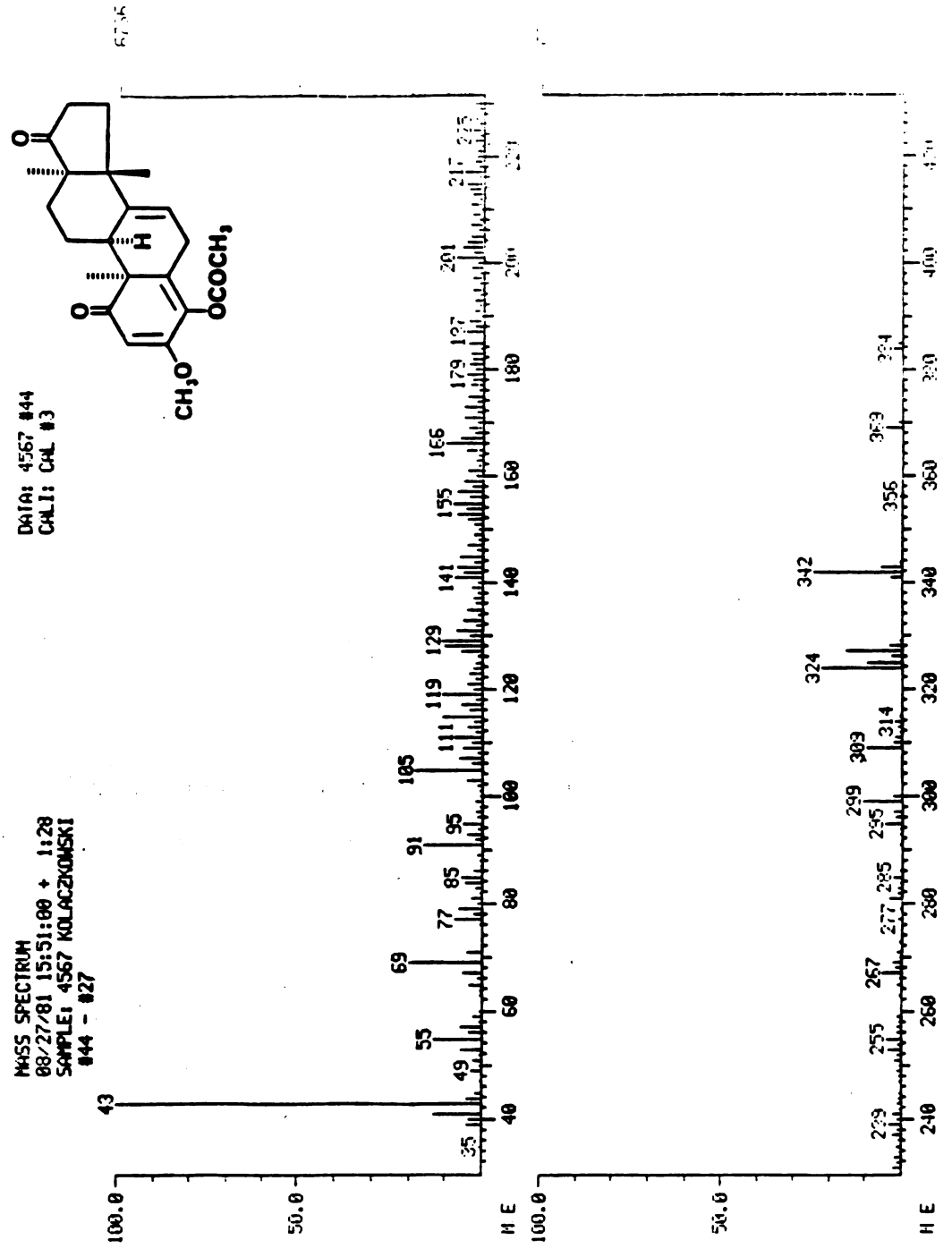


Figure 9. Mass spectrum of 61.

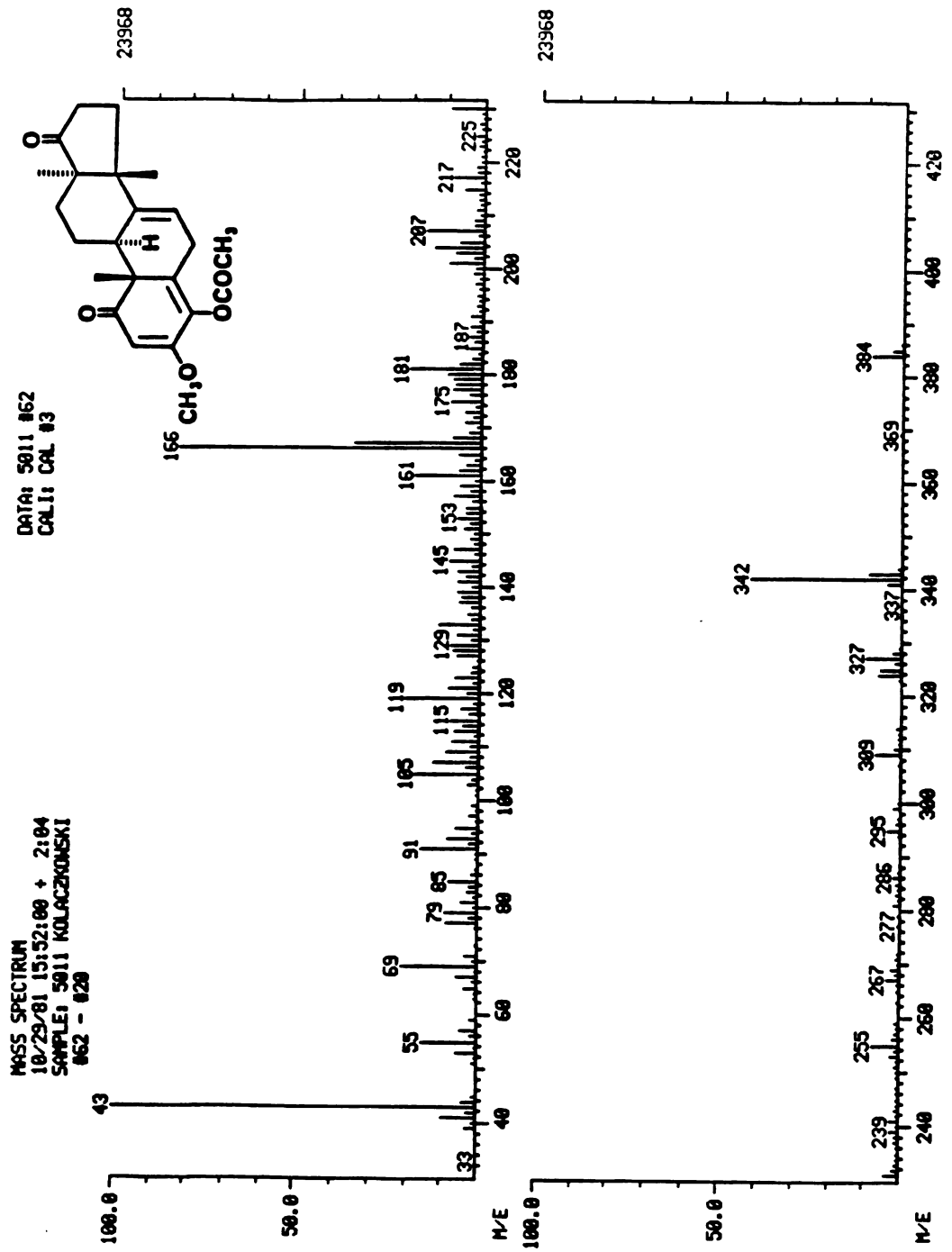


Figure 10. Mass spectrum of 62.

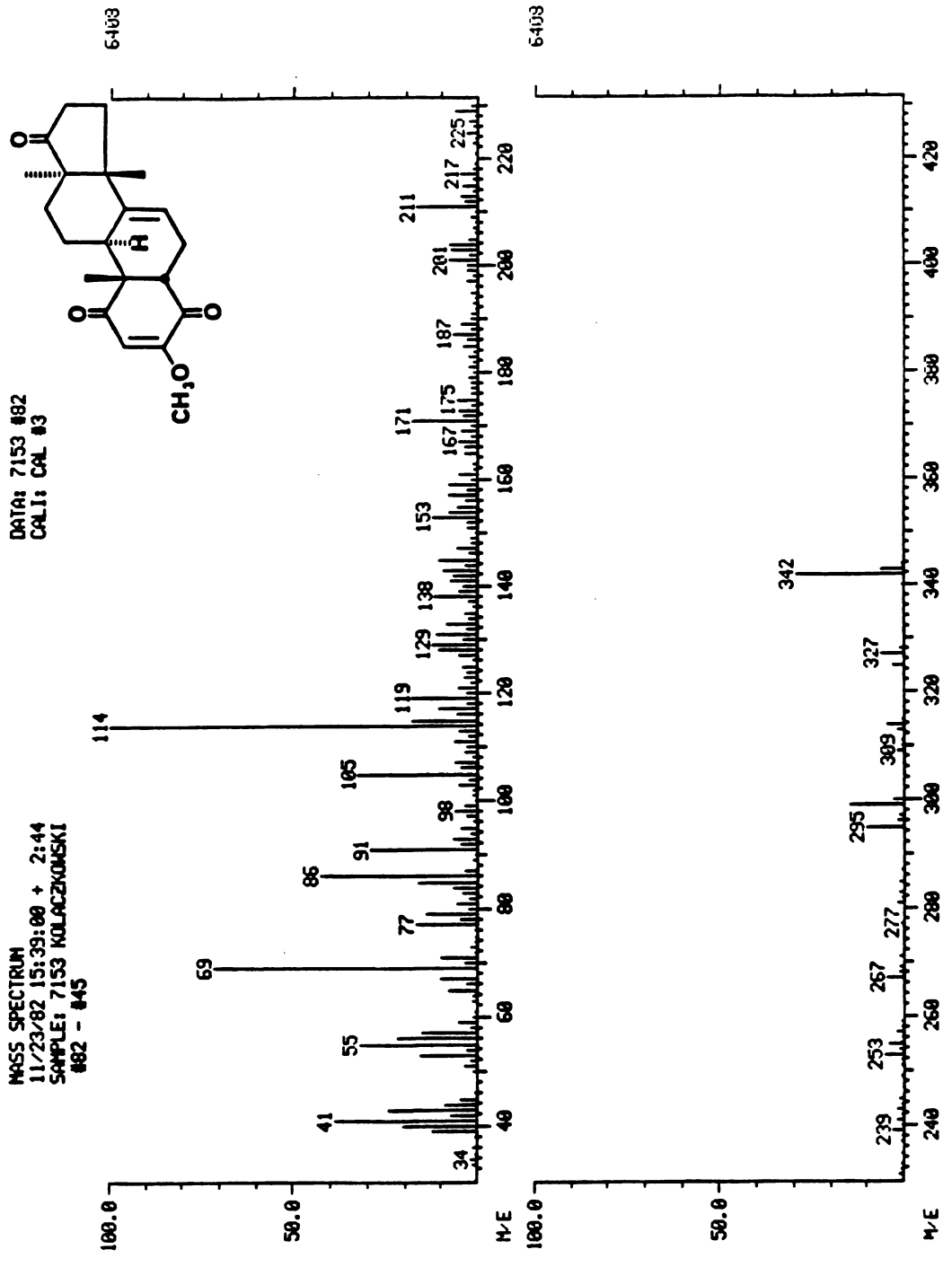


Figure 11. Mass spectrum of 70.

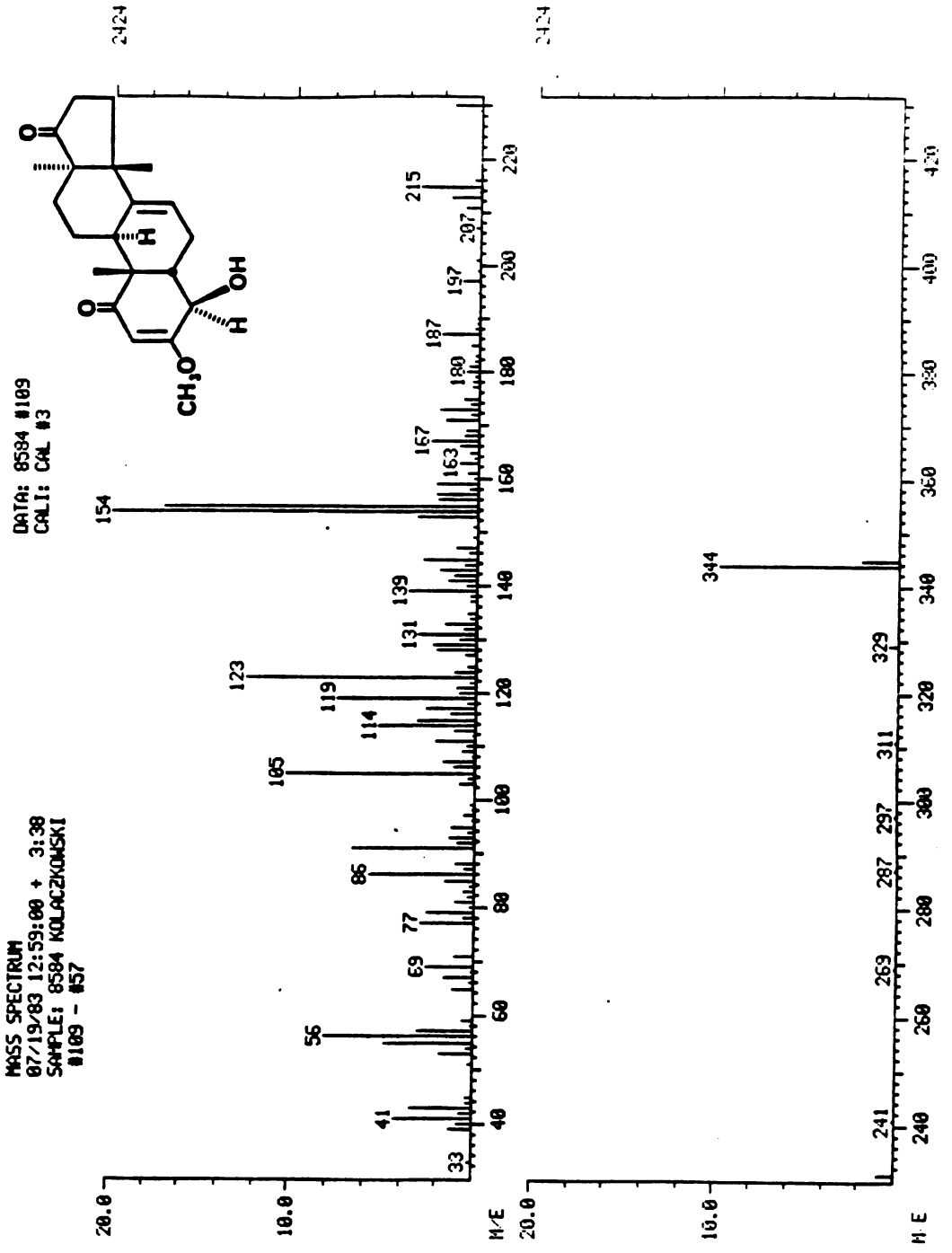


Figure 12. Mass spectrum of 79.

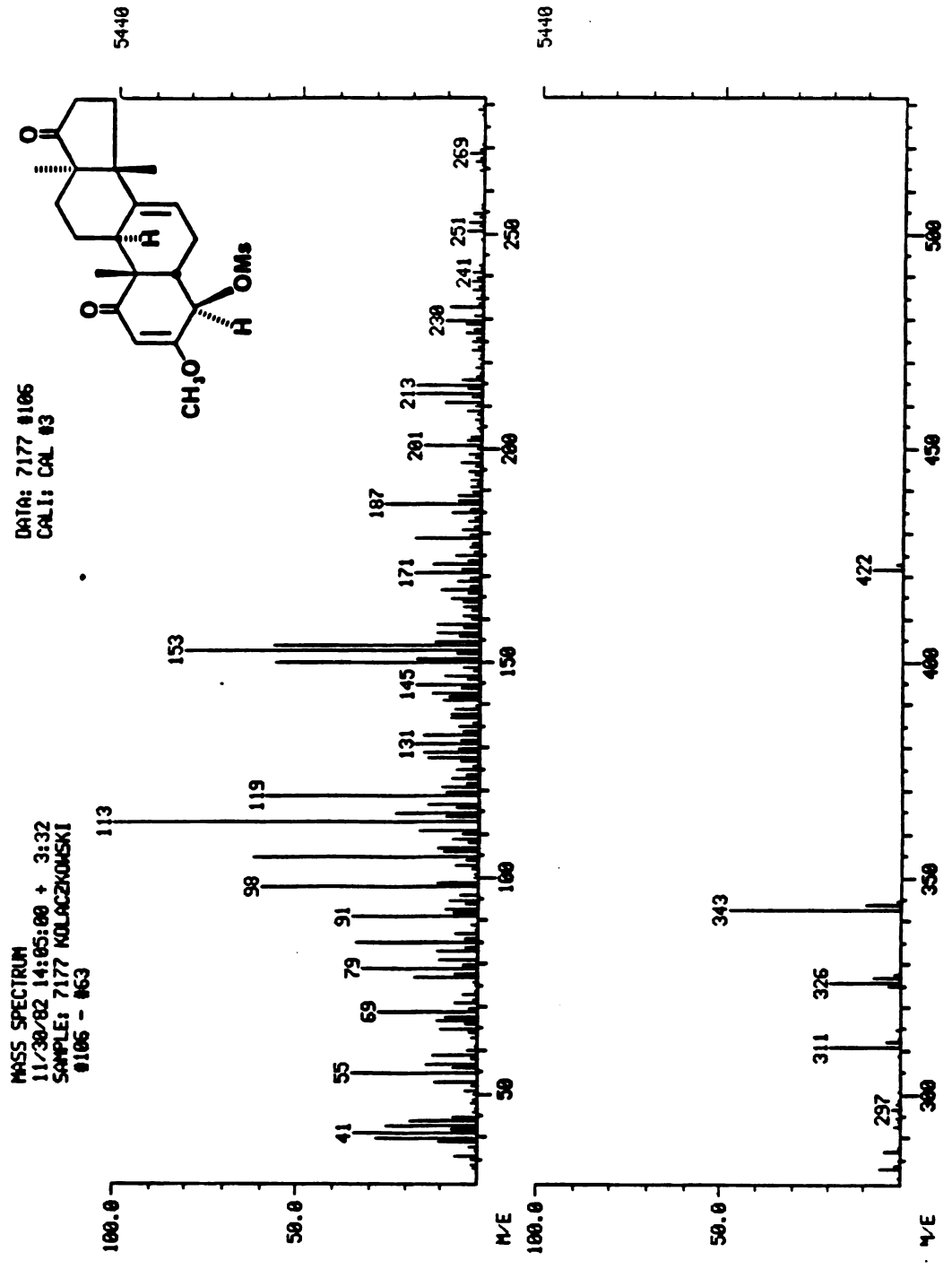


Figure 13. Mass spectrum of 80.

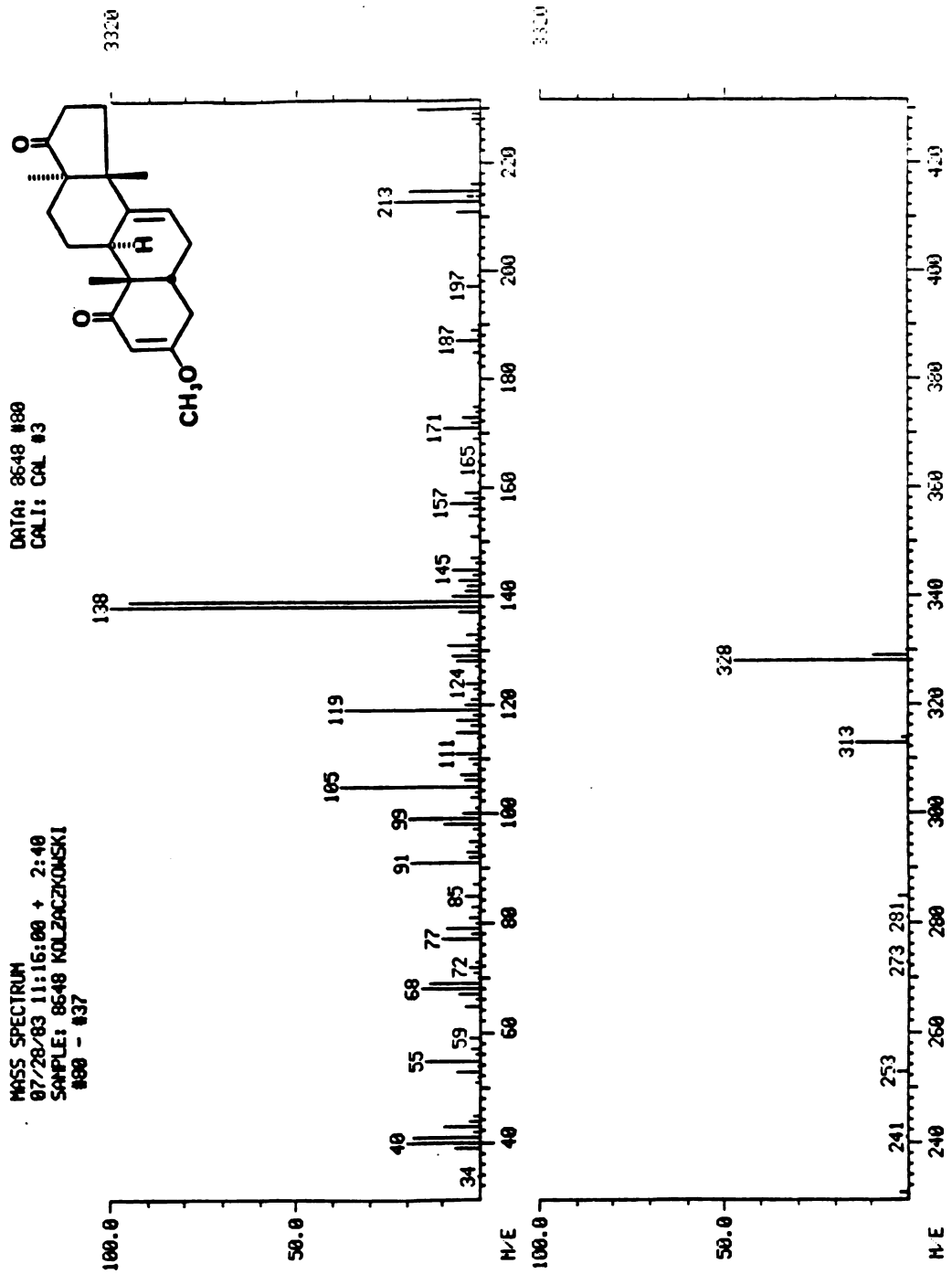


Figure 14. Mass spectrum of 83.

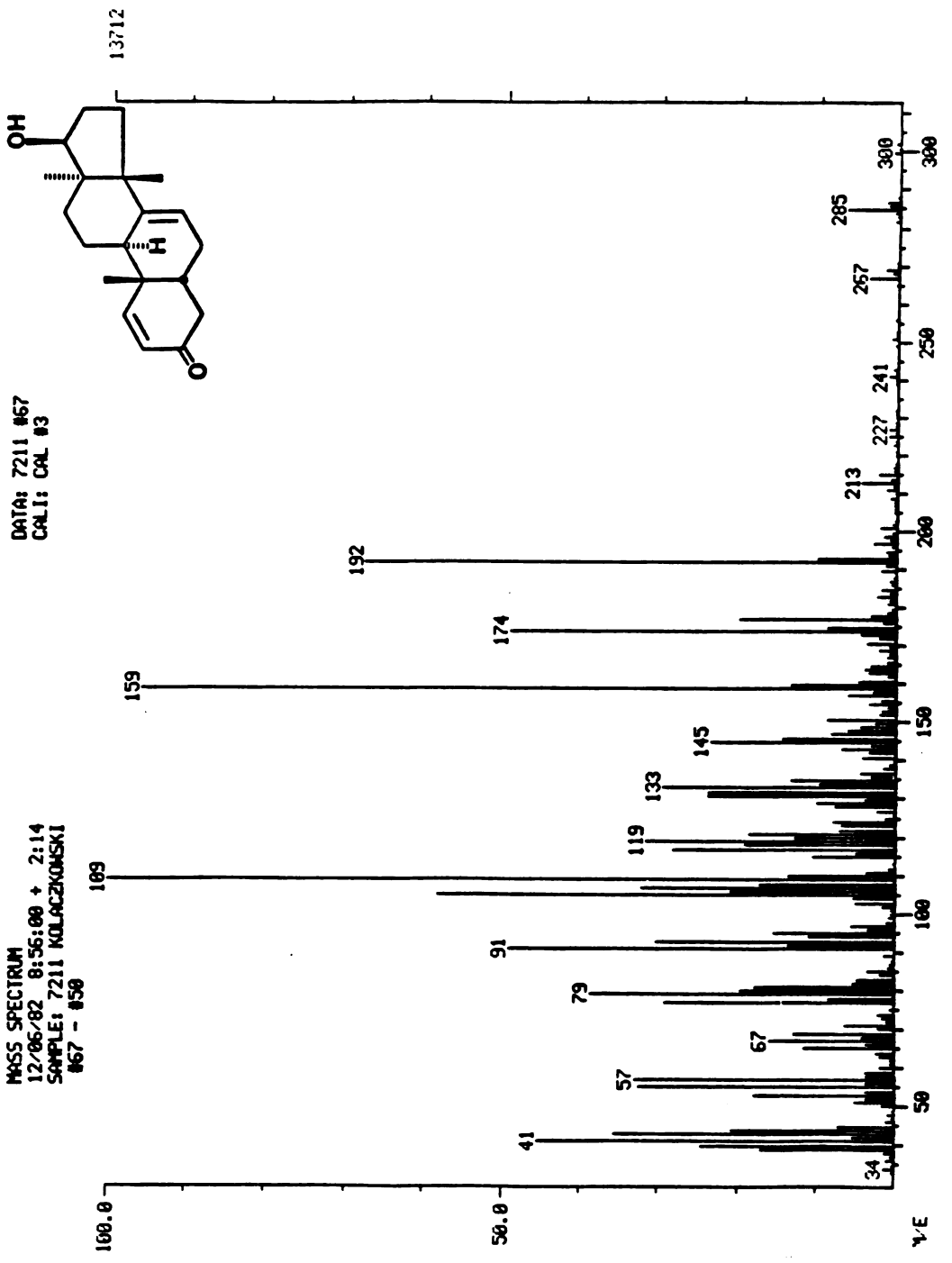


Figure 15. Mass spectrum of 81.

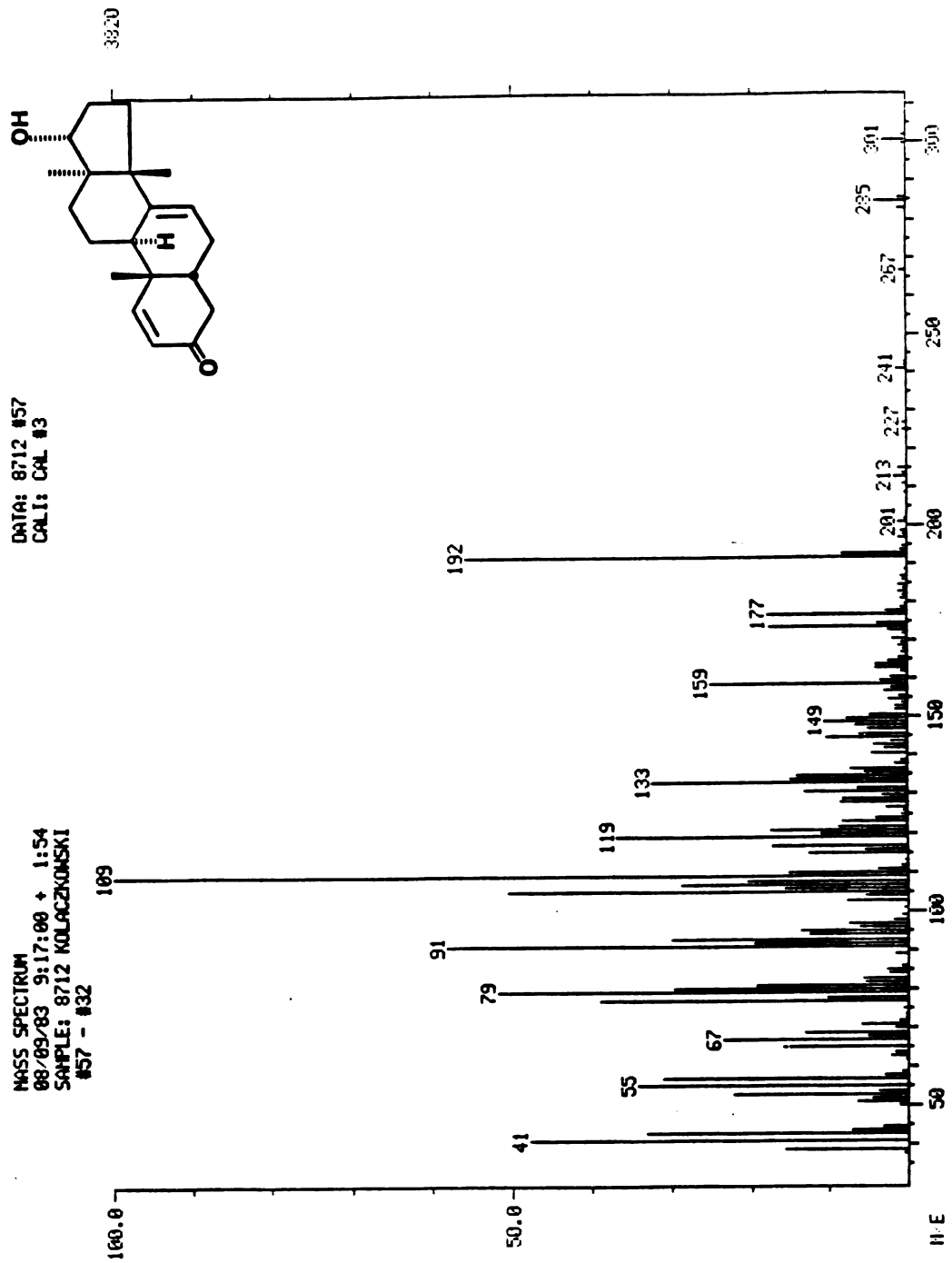


Figure 16. Mass spectrum of 82.

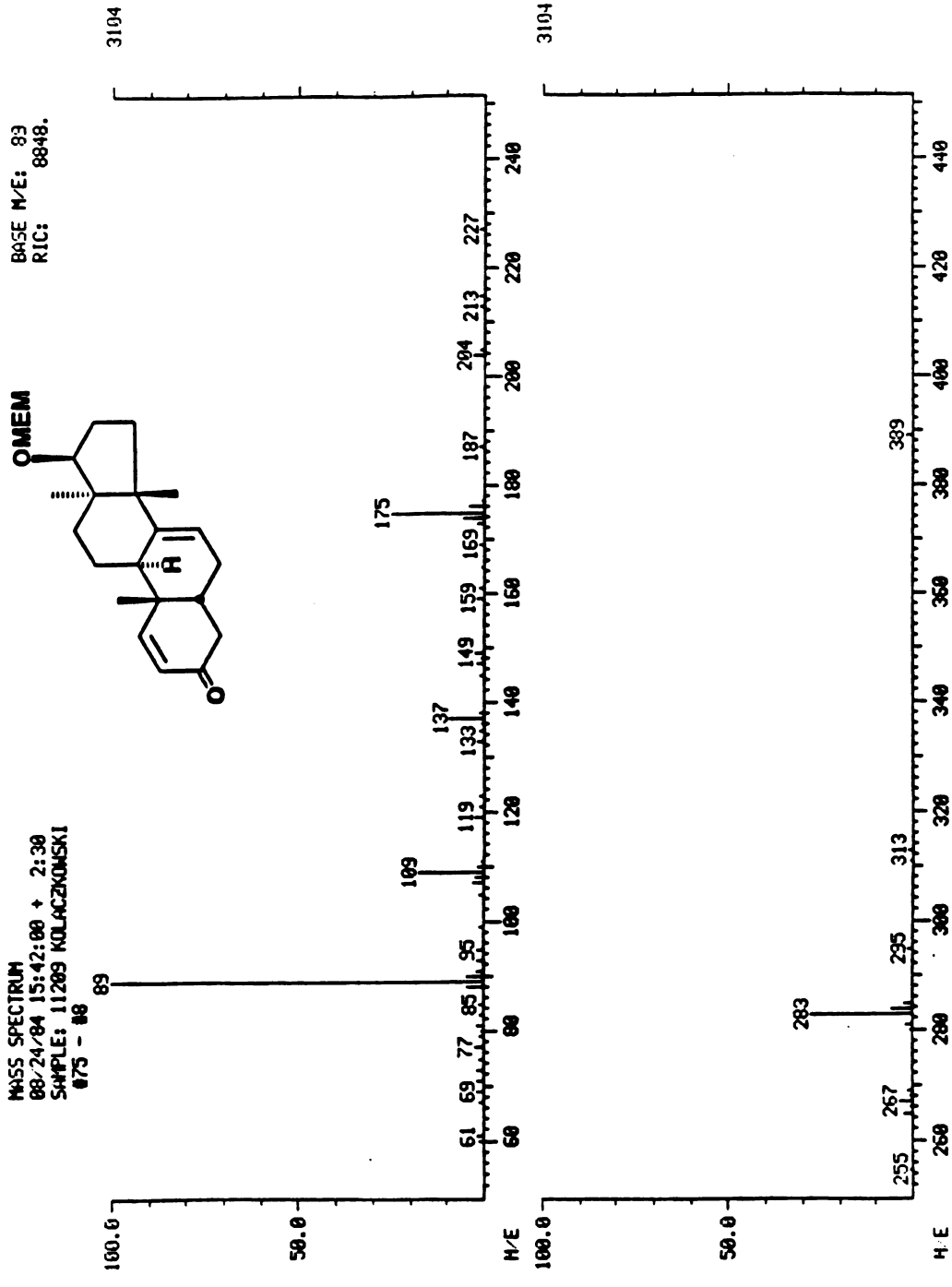


Figure 17. Mass spectrum of 89.

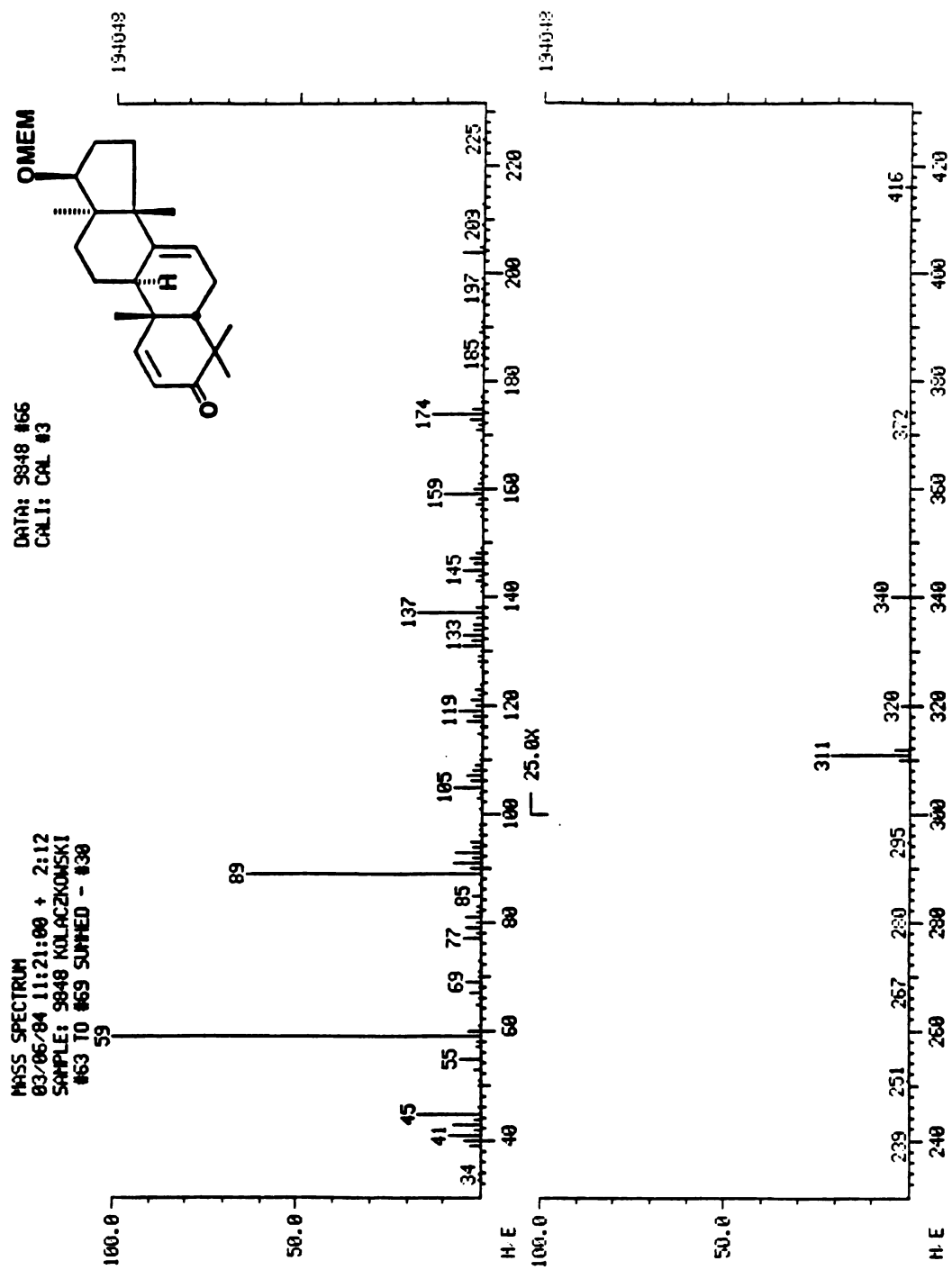


Figure 18. Mass spectrum of 91.

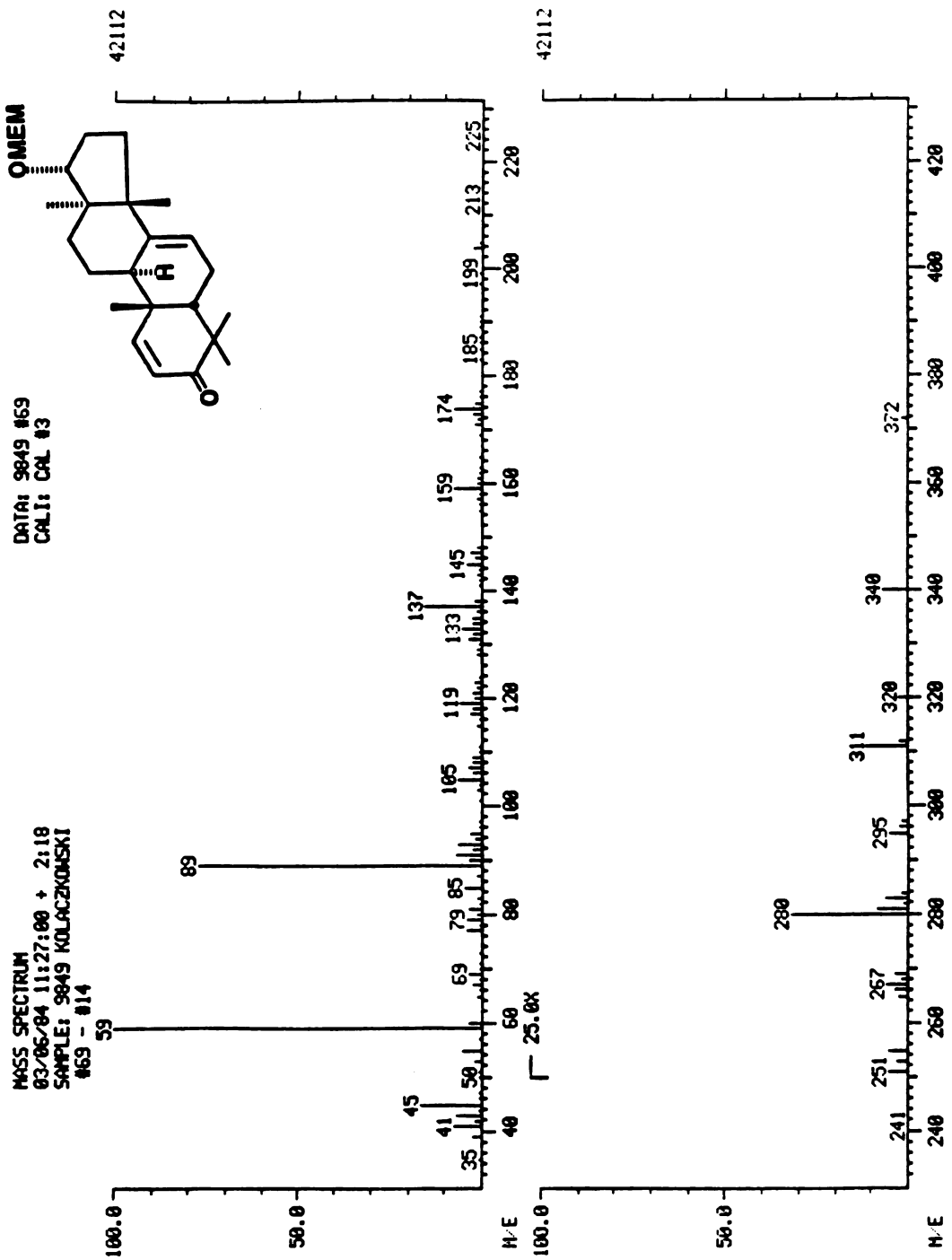


Figure 19. Mass spectrum of 92.

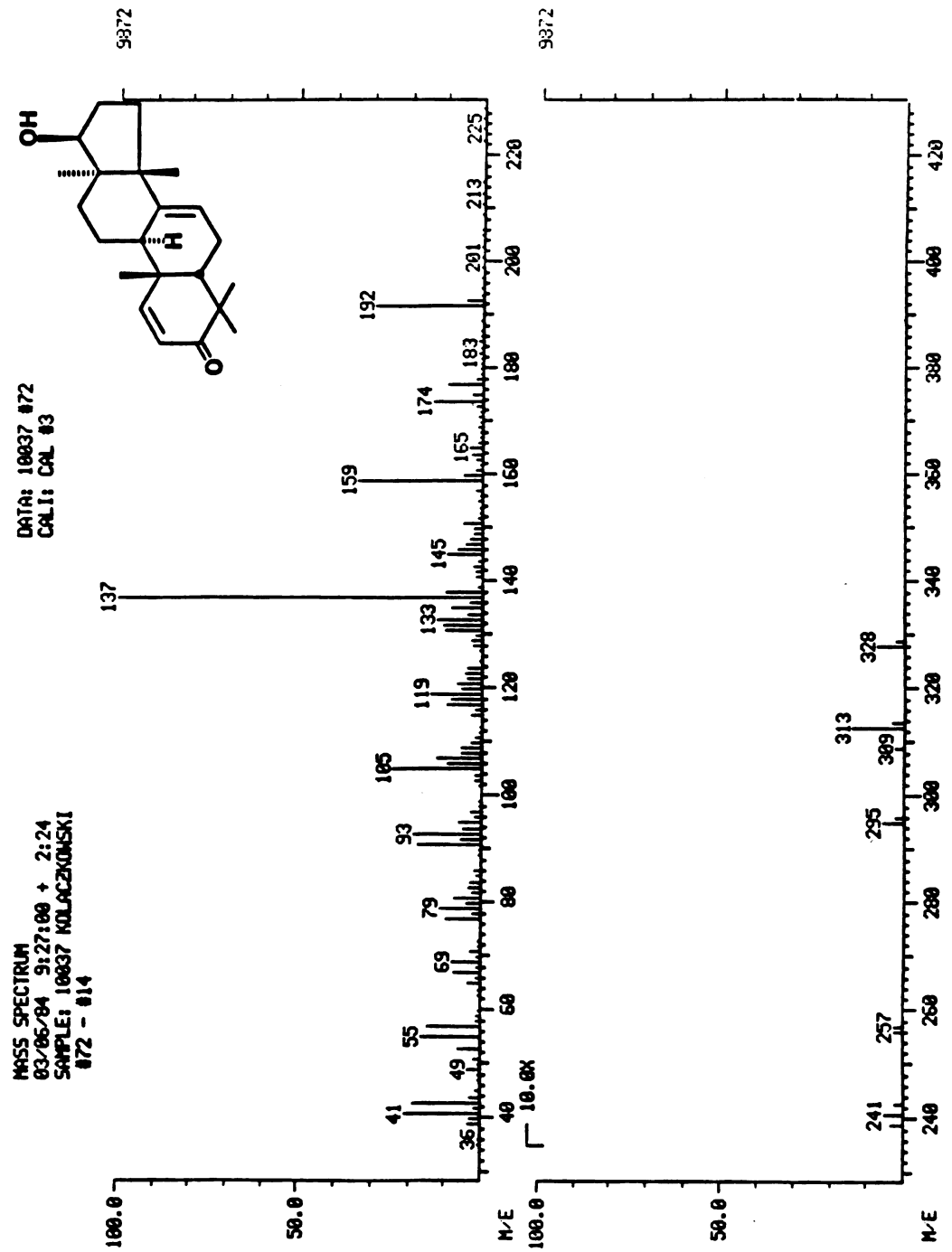


Figure 20. Mass spectrum of 93.

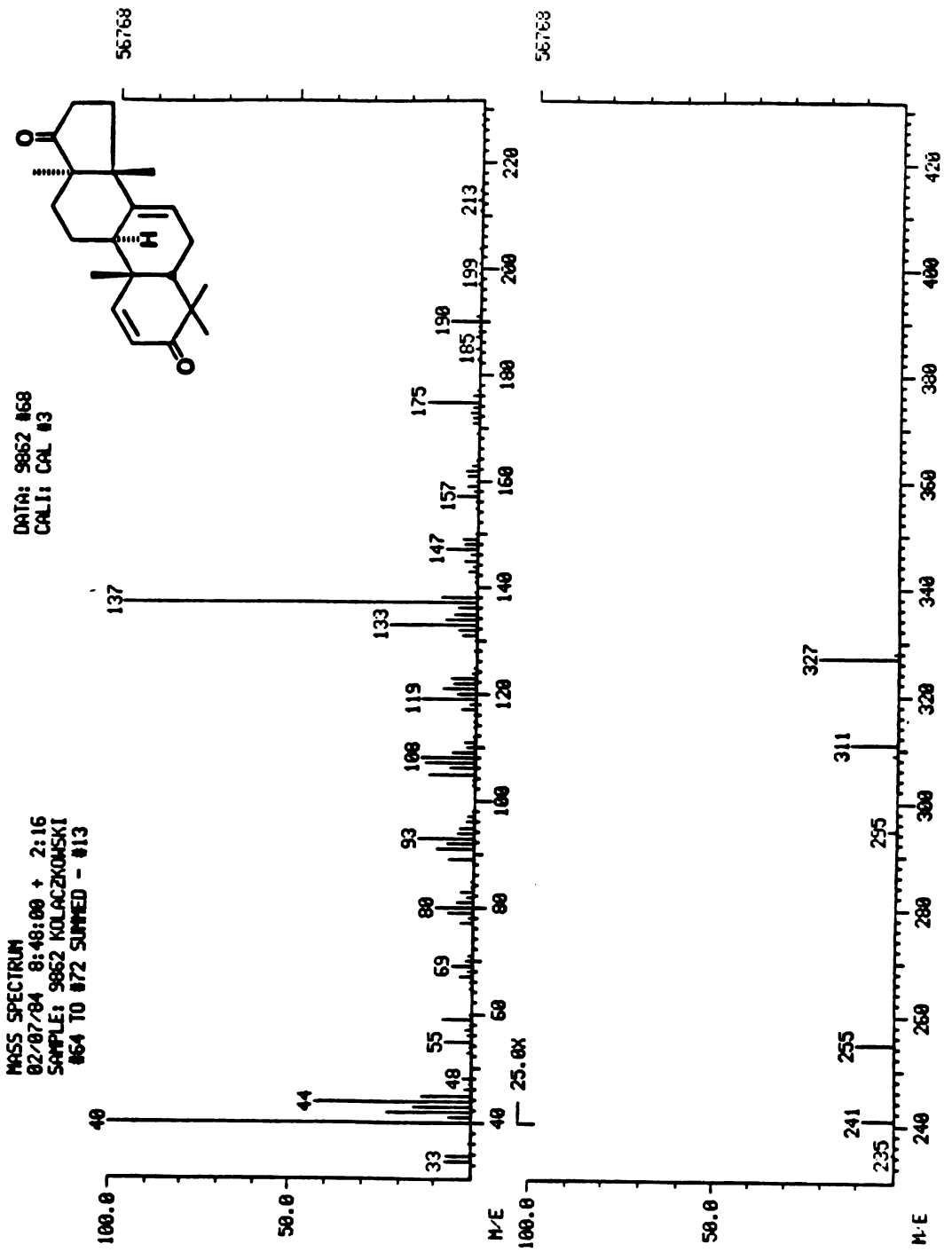


Figure 21. Mass spectrum of 95.

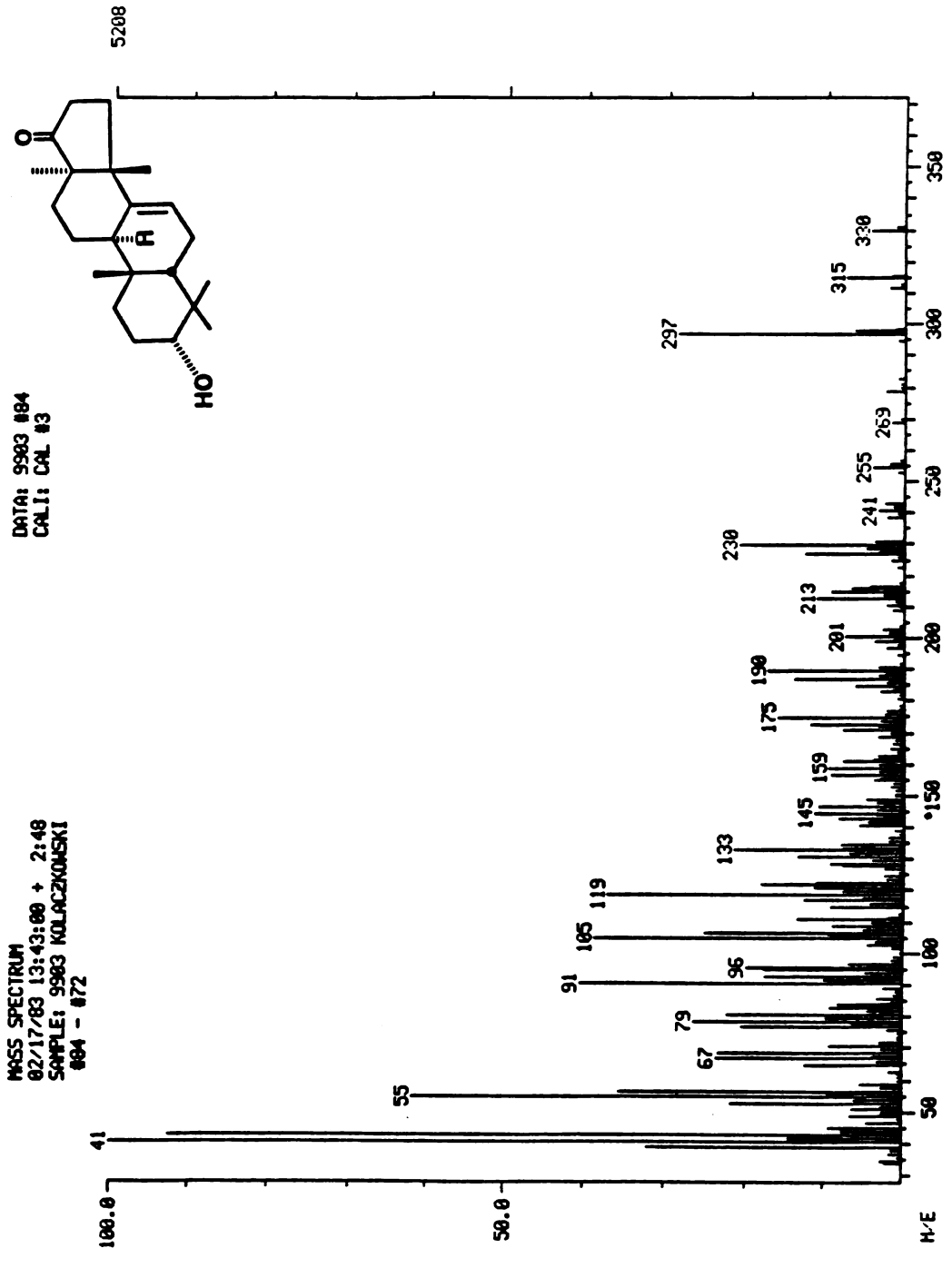


Figure 22. Mass spectrum of 73.

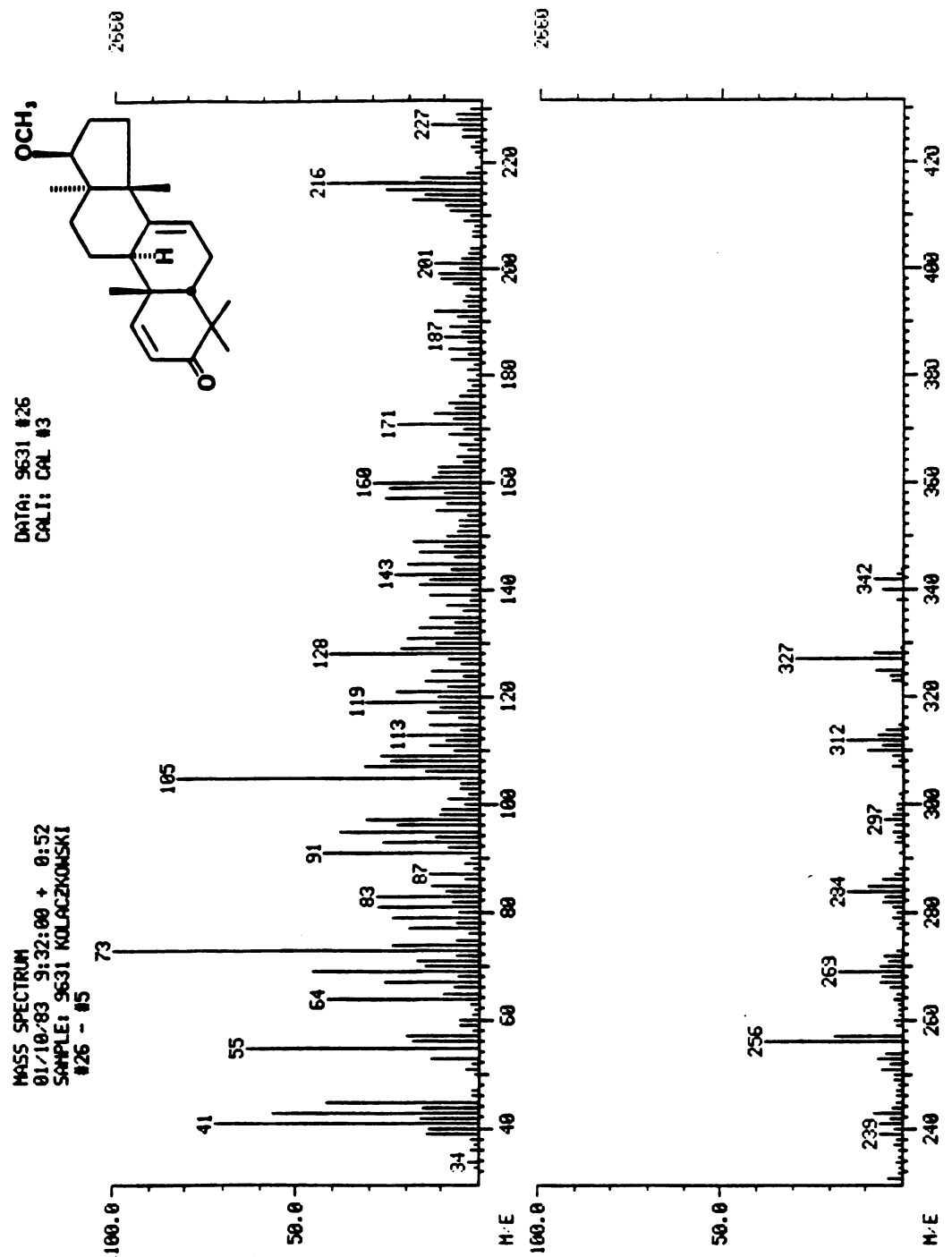


Figure 23. Mass spectrum of 85.

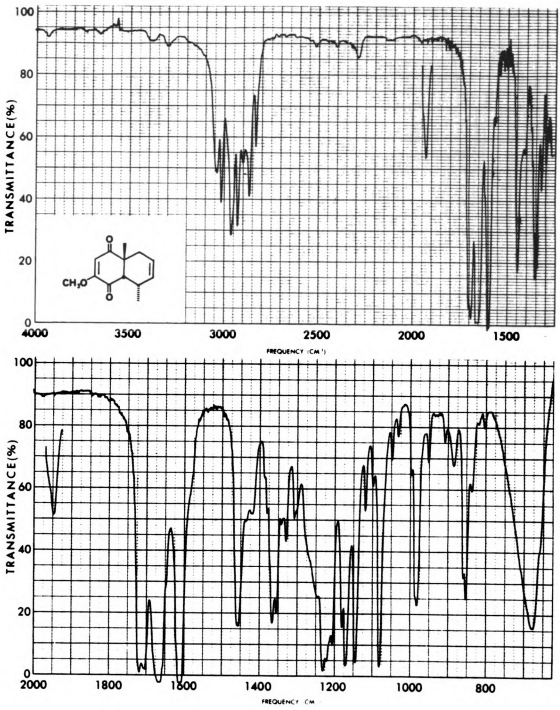


Figure 24. Infrared spectrum of 34.

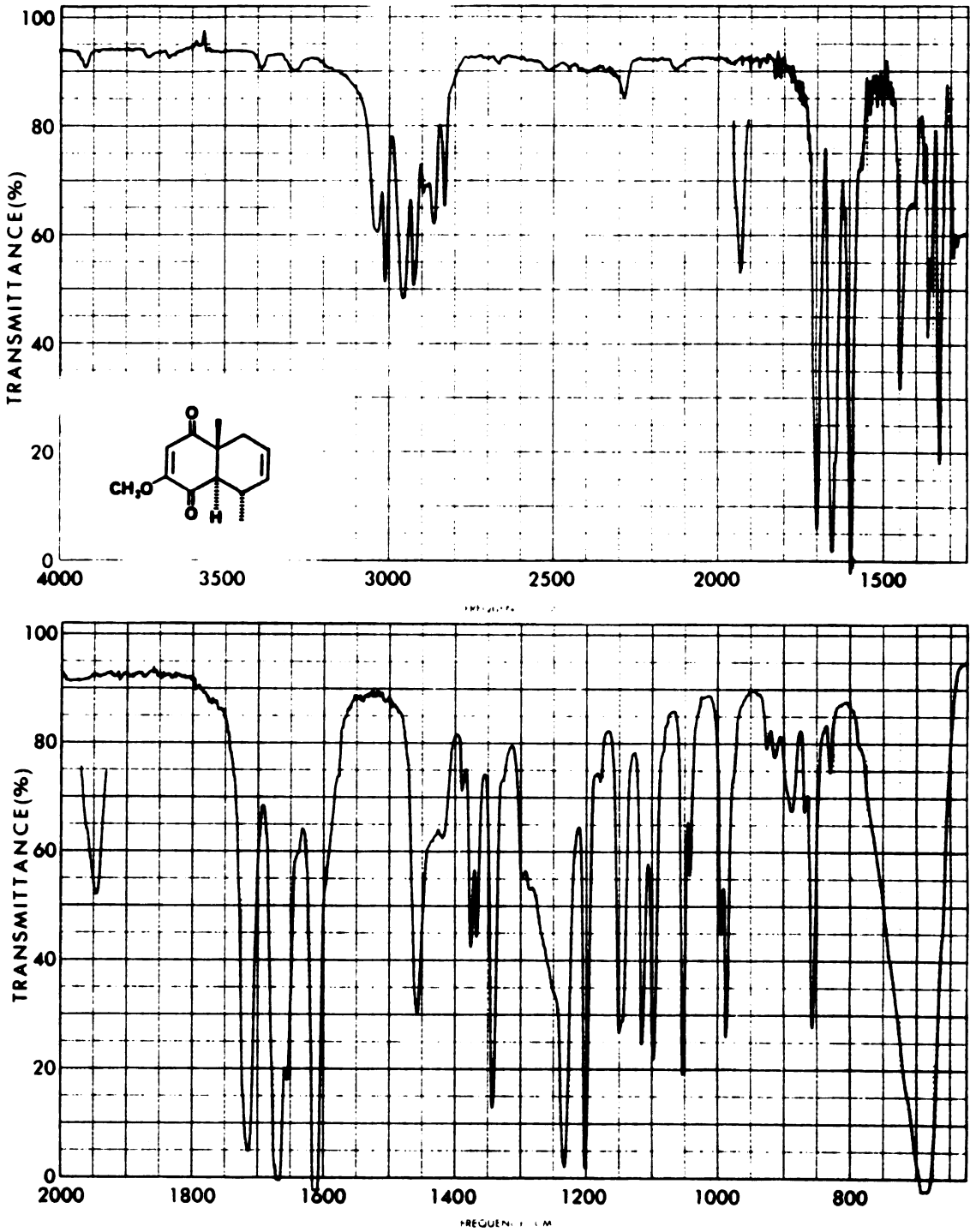


Figure 25. Infrared spectrum of 35.

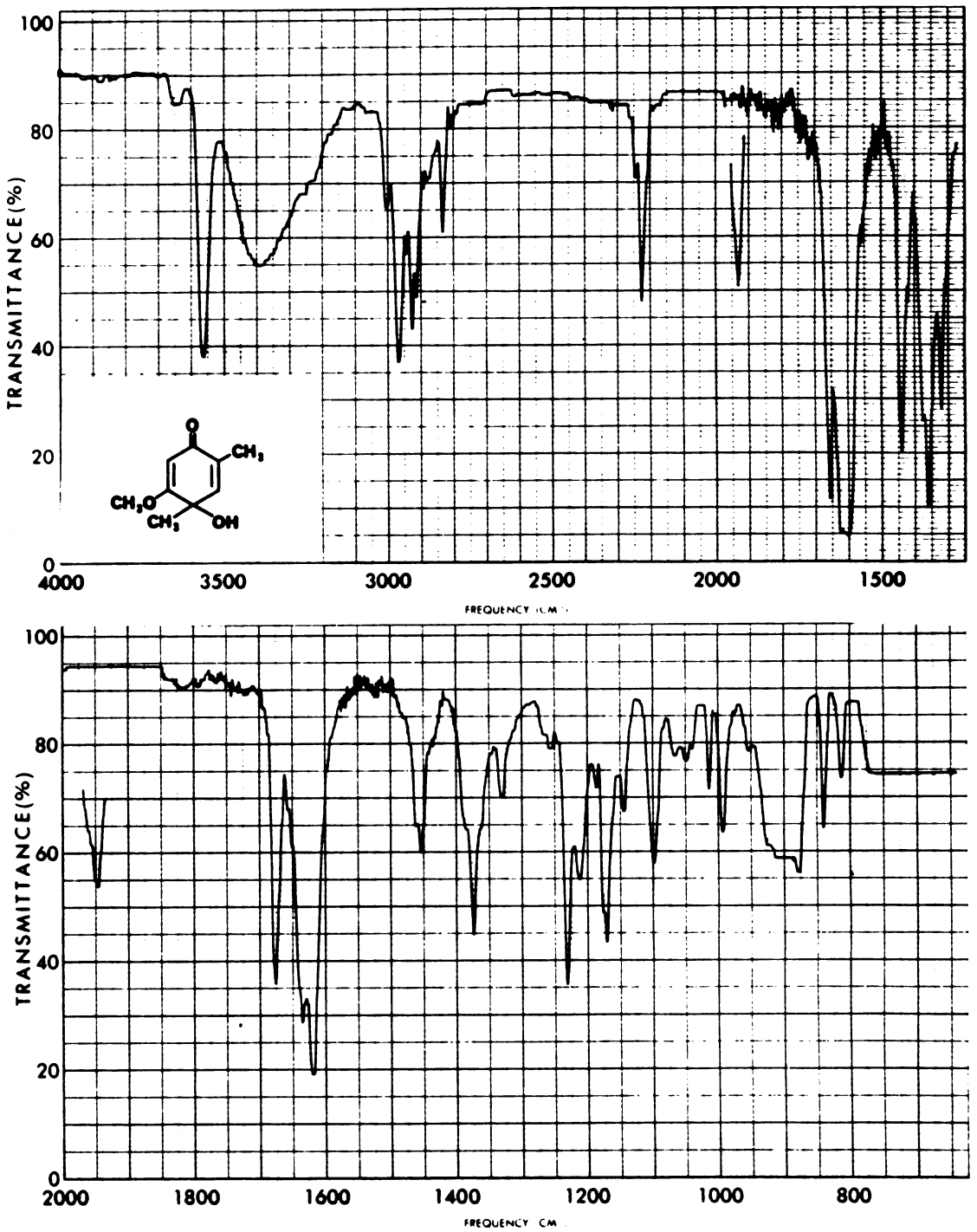


Figure 26. Infrared spectrum of 36.

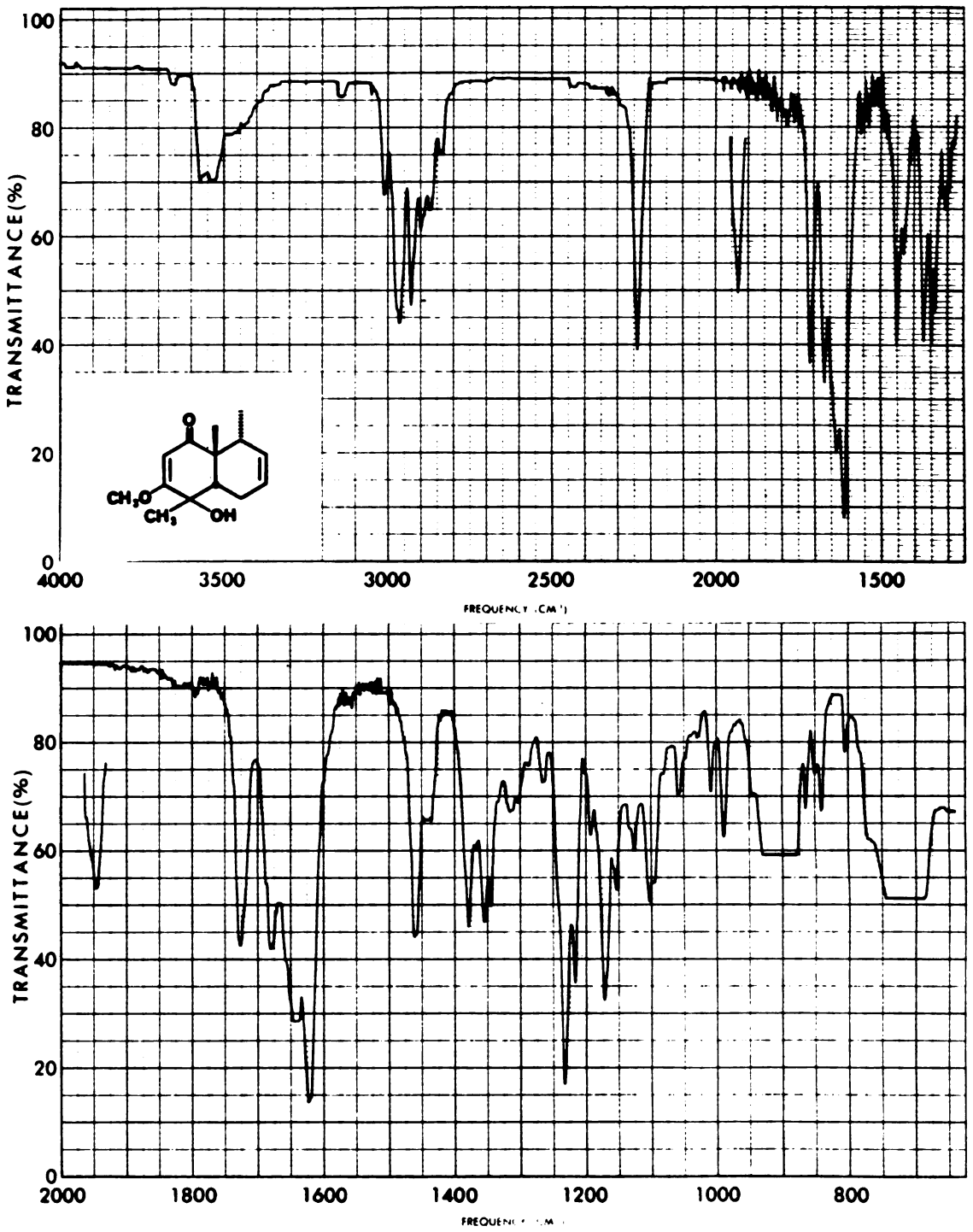


Figure 27. Infrared spectrum of 37.

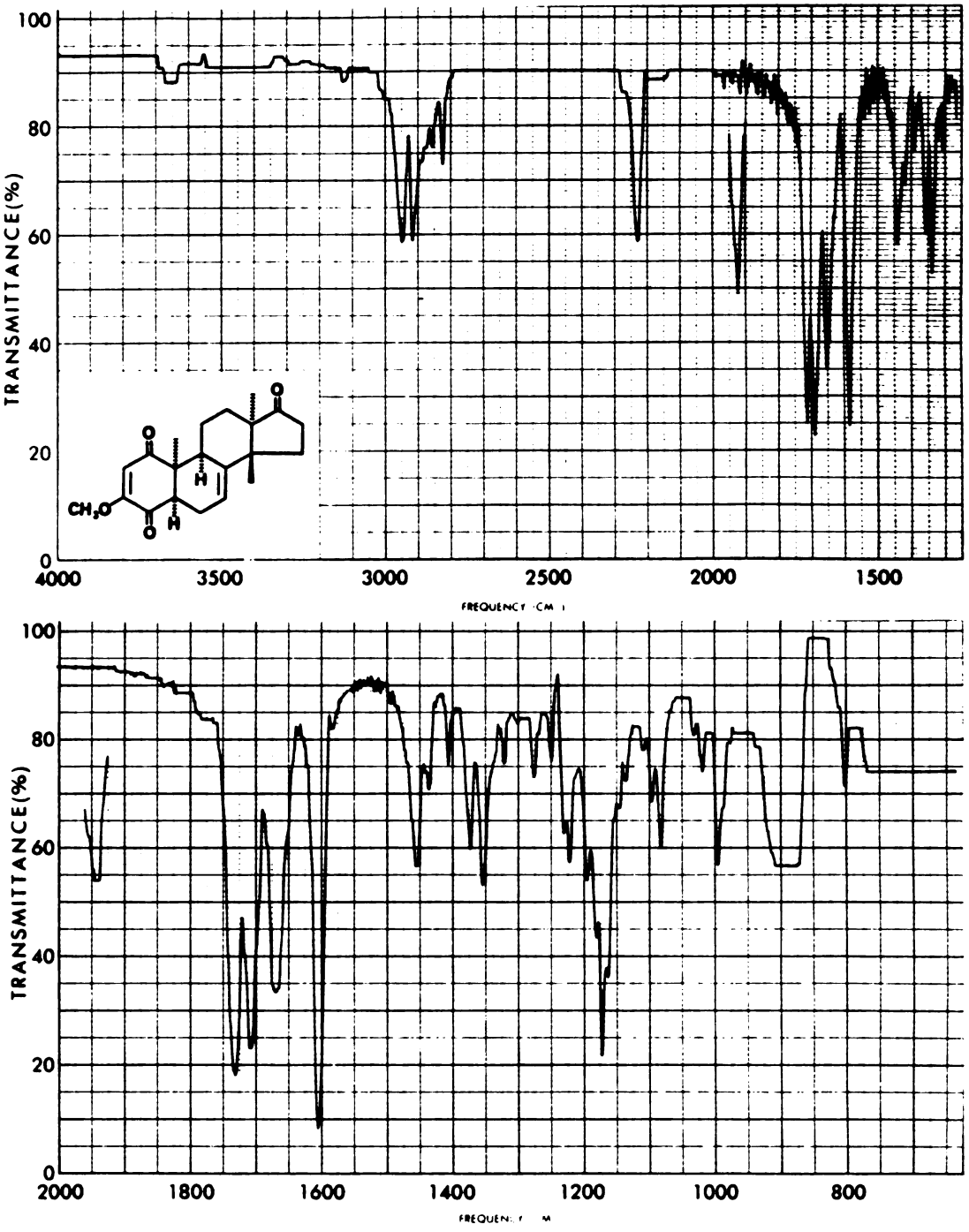


Figure 28. Infrared spectrum of 29.

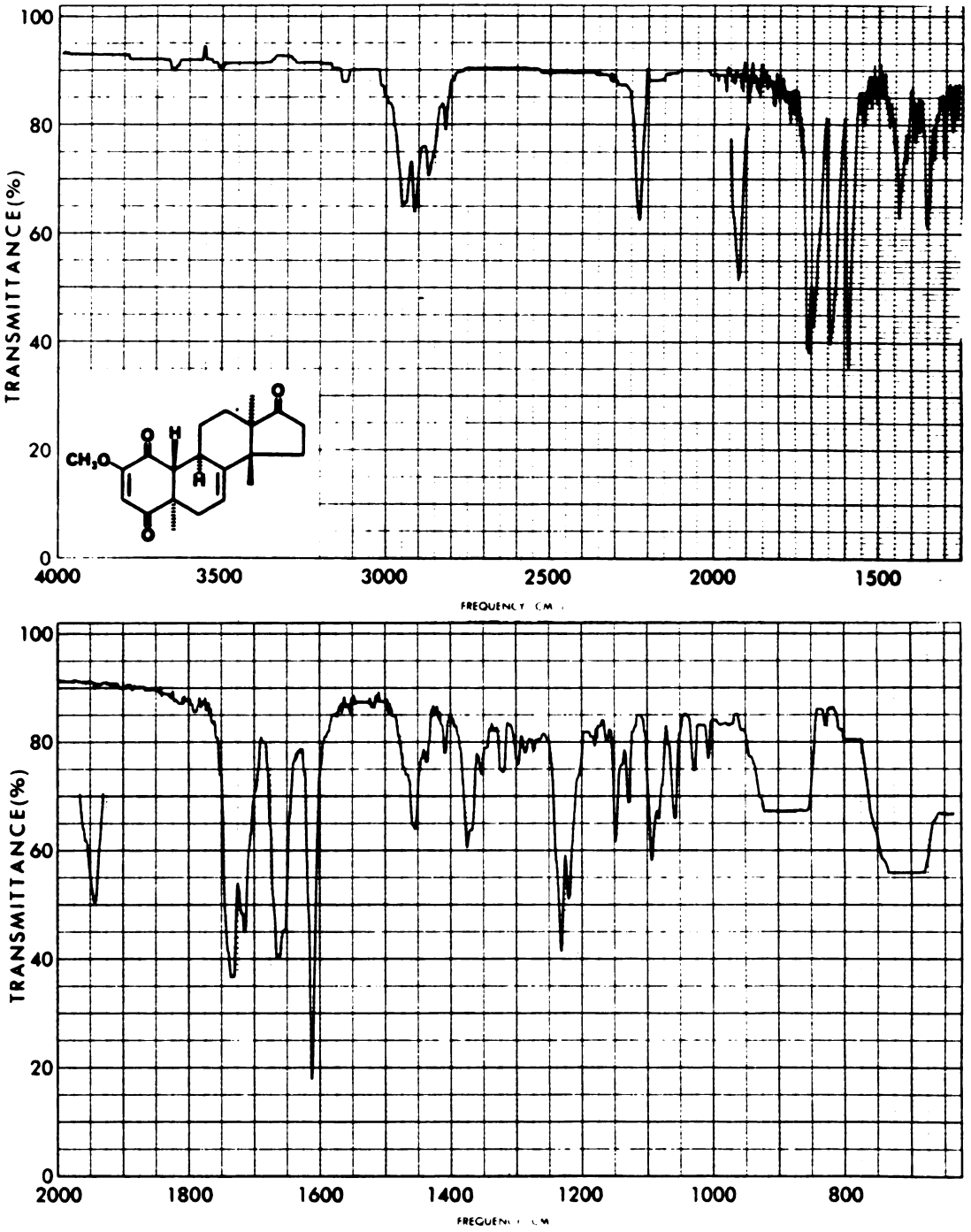


Figure 29. Infrared spectrum of 31.

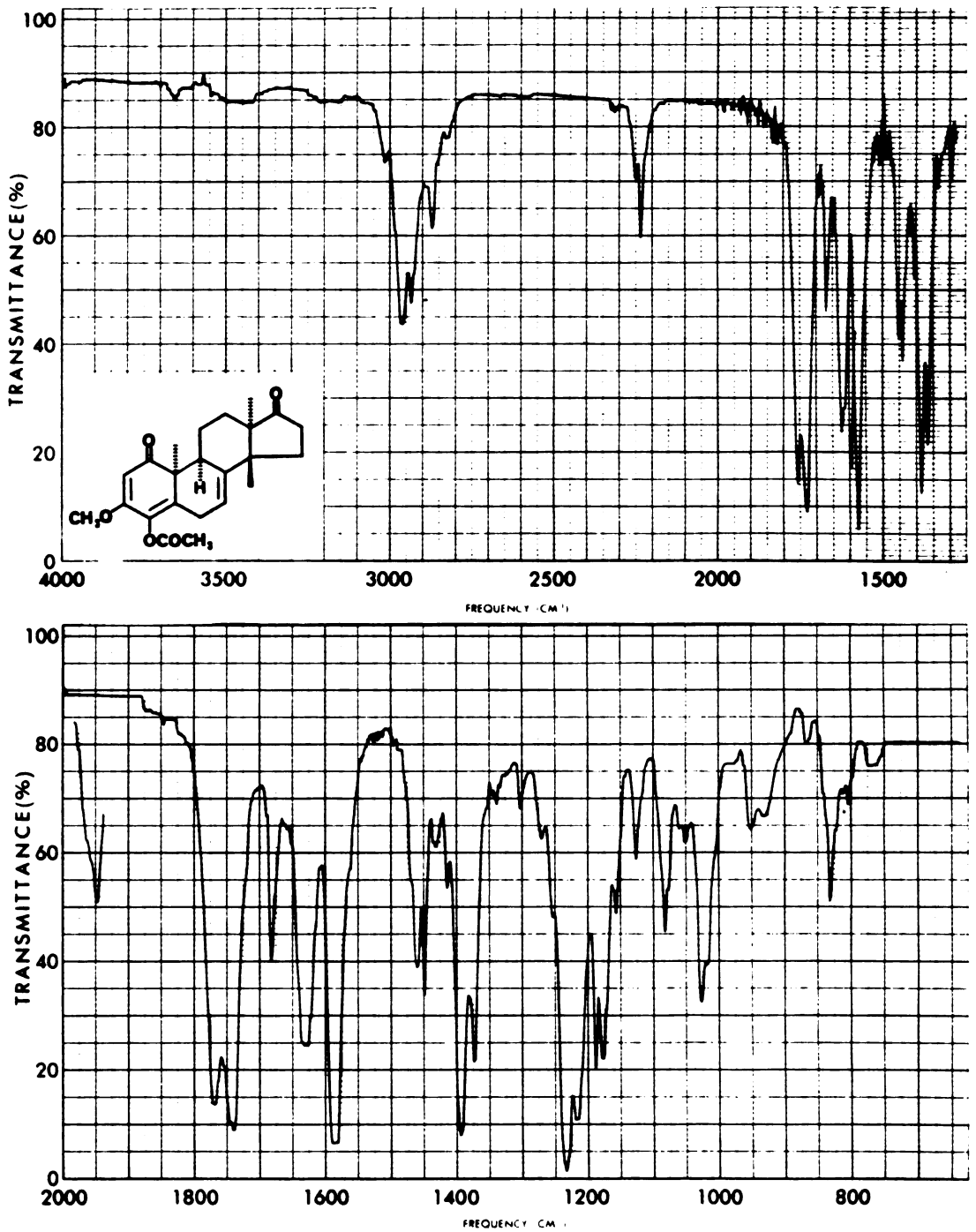


Figure 30. Infrared spectrum of 61.

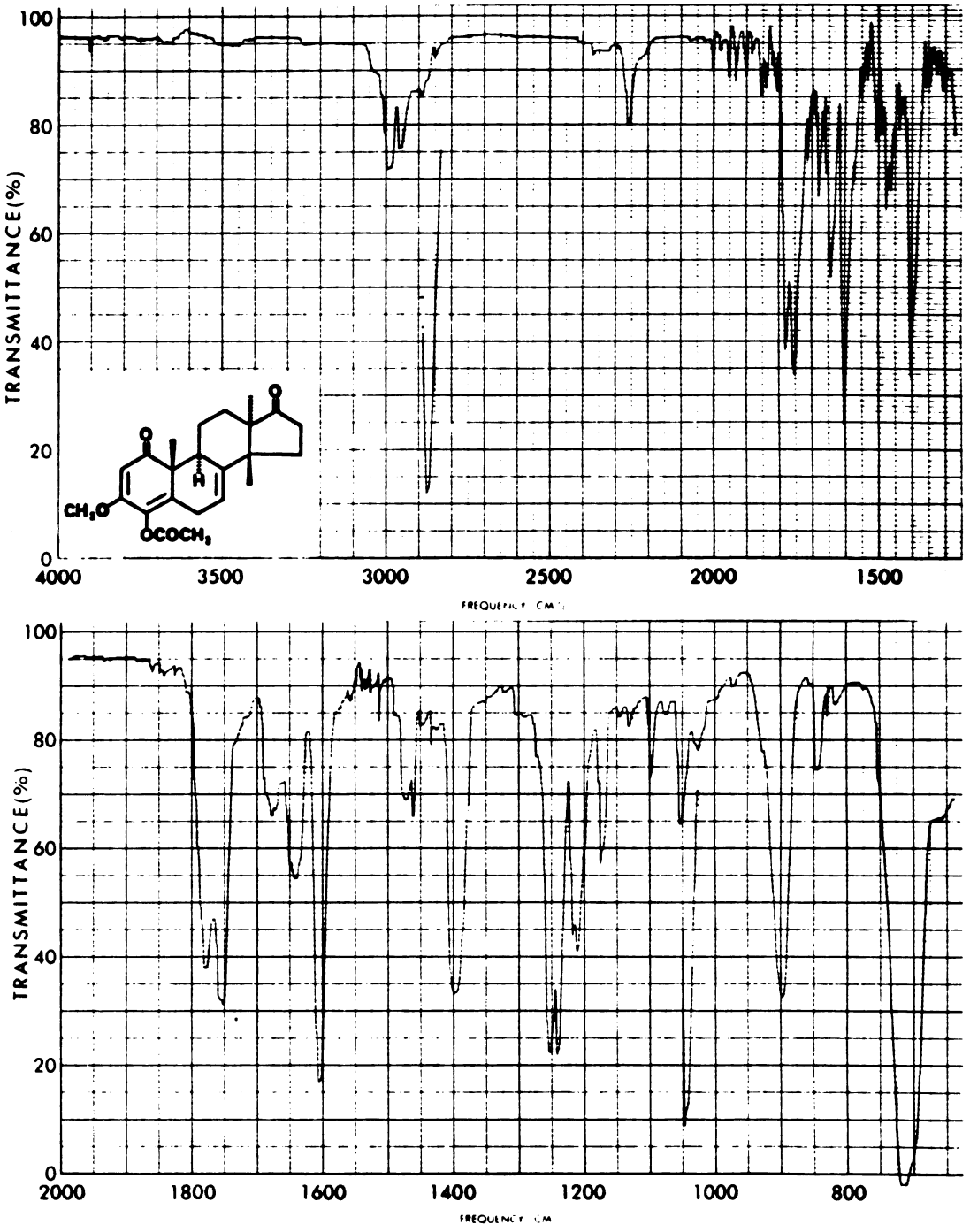


Figure 31. Infrared spectrum of 62.

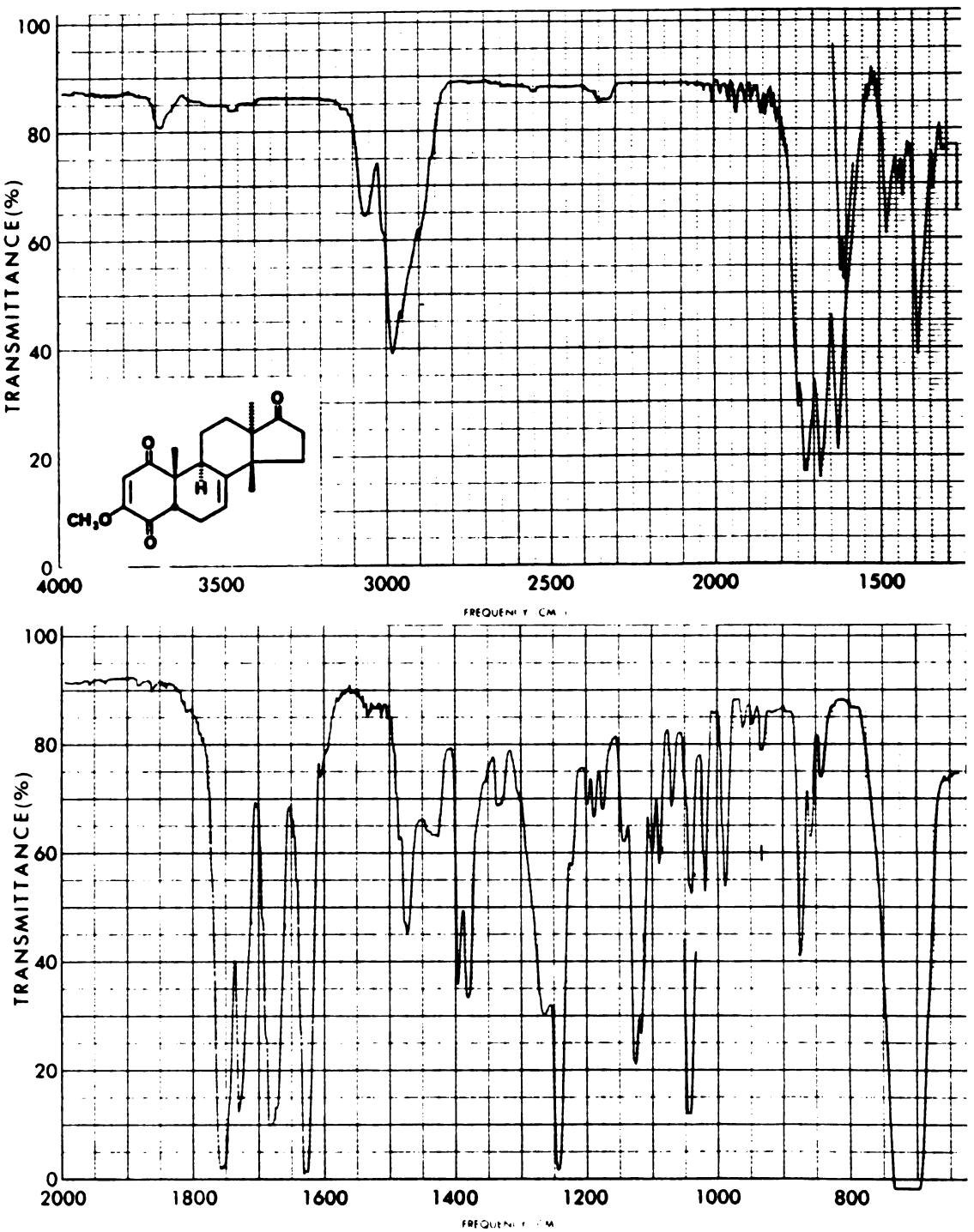


Figure 32. Infrared spectrum of 70.

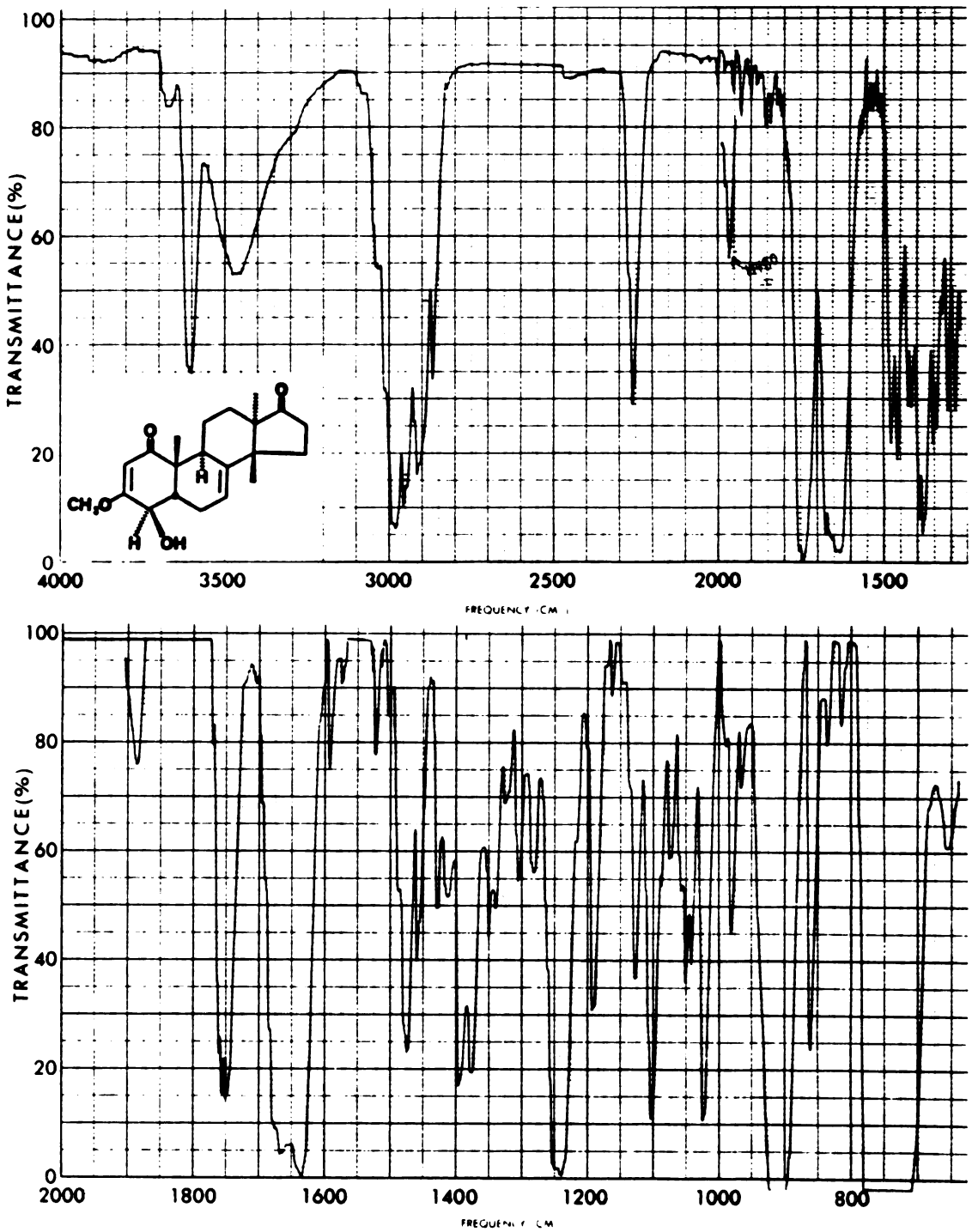


Figure 33. Infrared spectrum of 79.

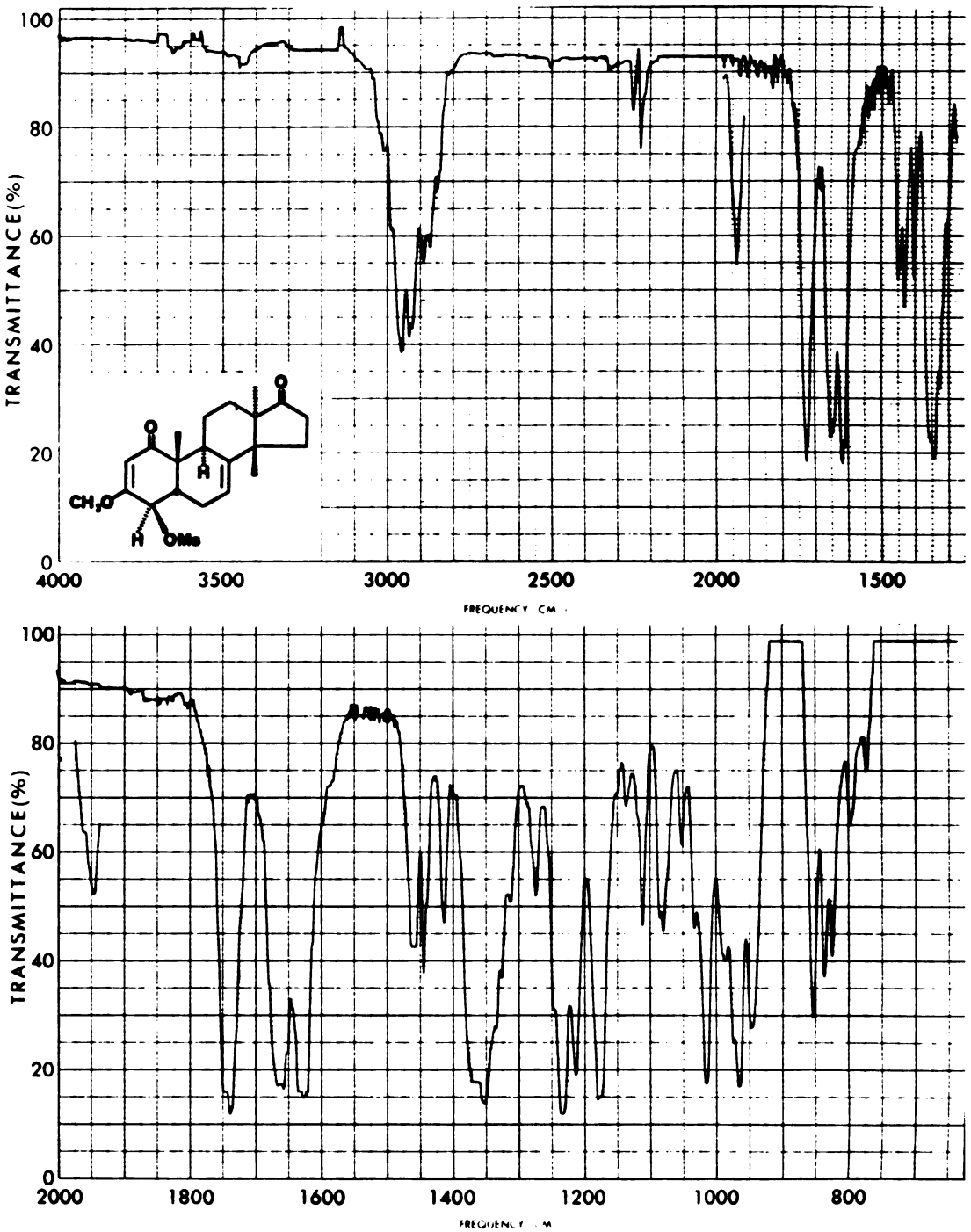


Figure 34. Infrared spectrum of 80.
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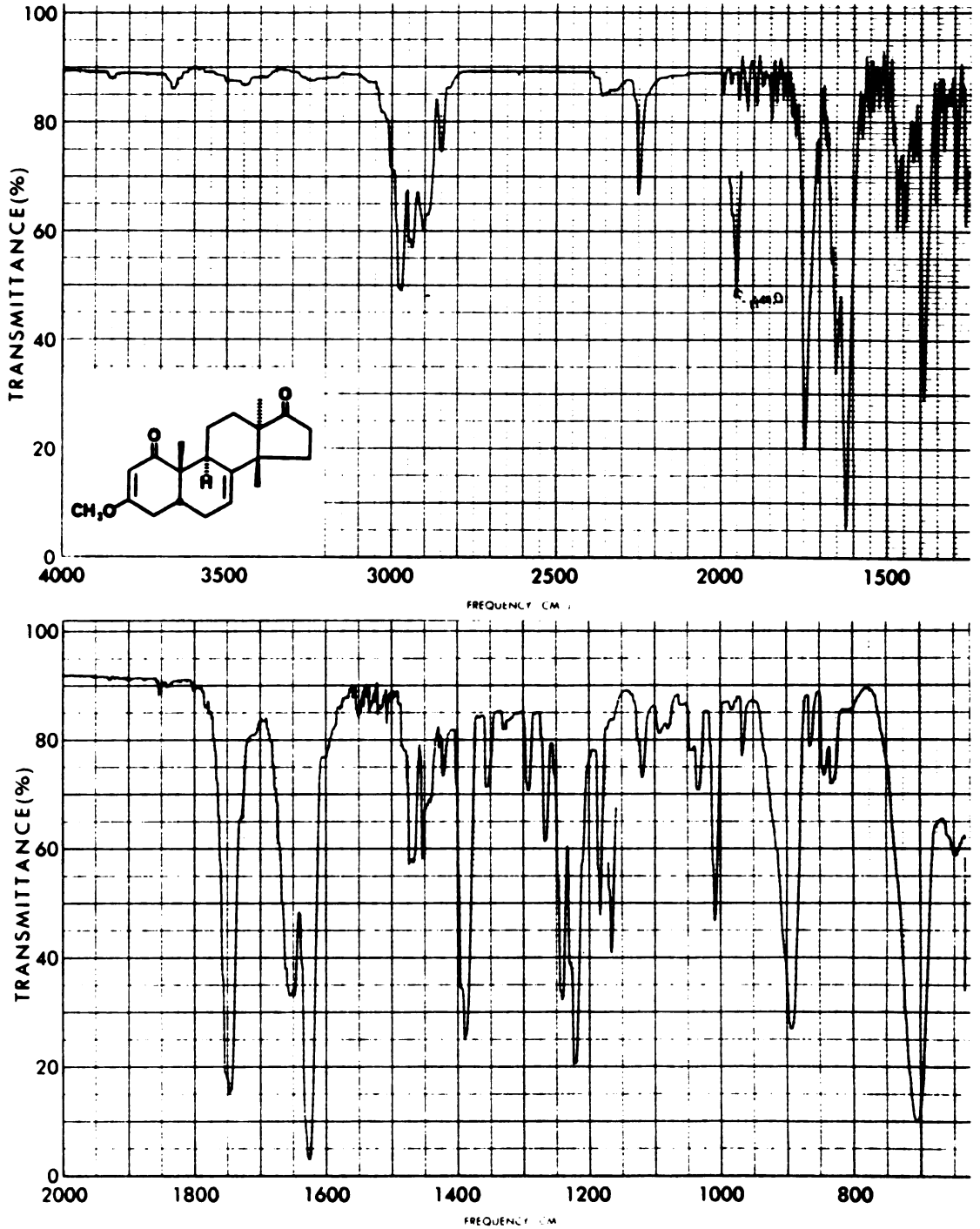

Figure 35. Infrared spectrum of 83.

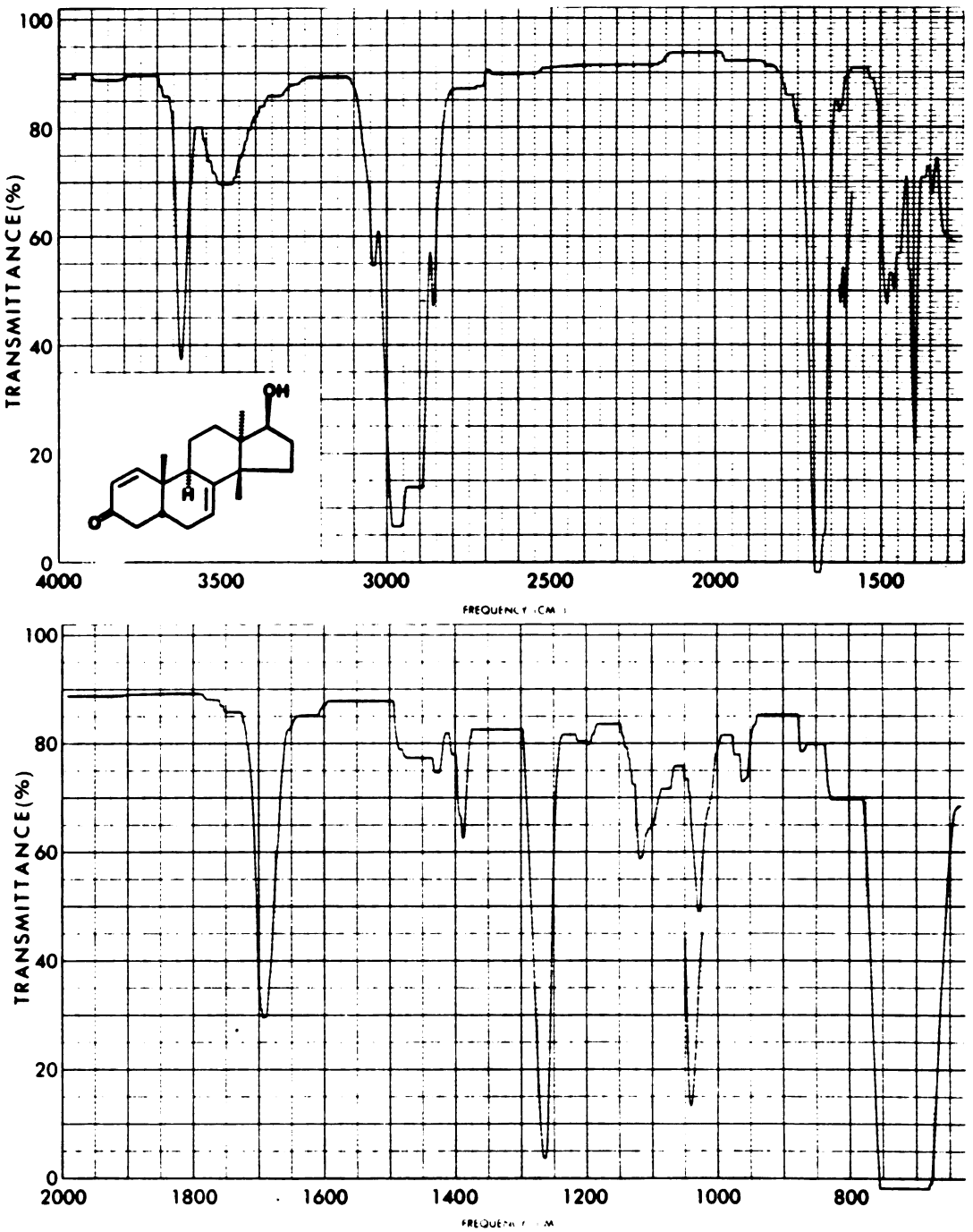

Figure 36. Infrared spectrum of 81.

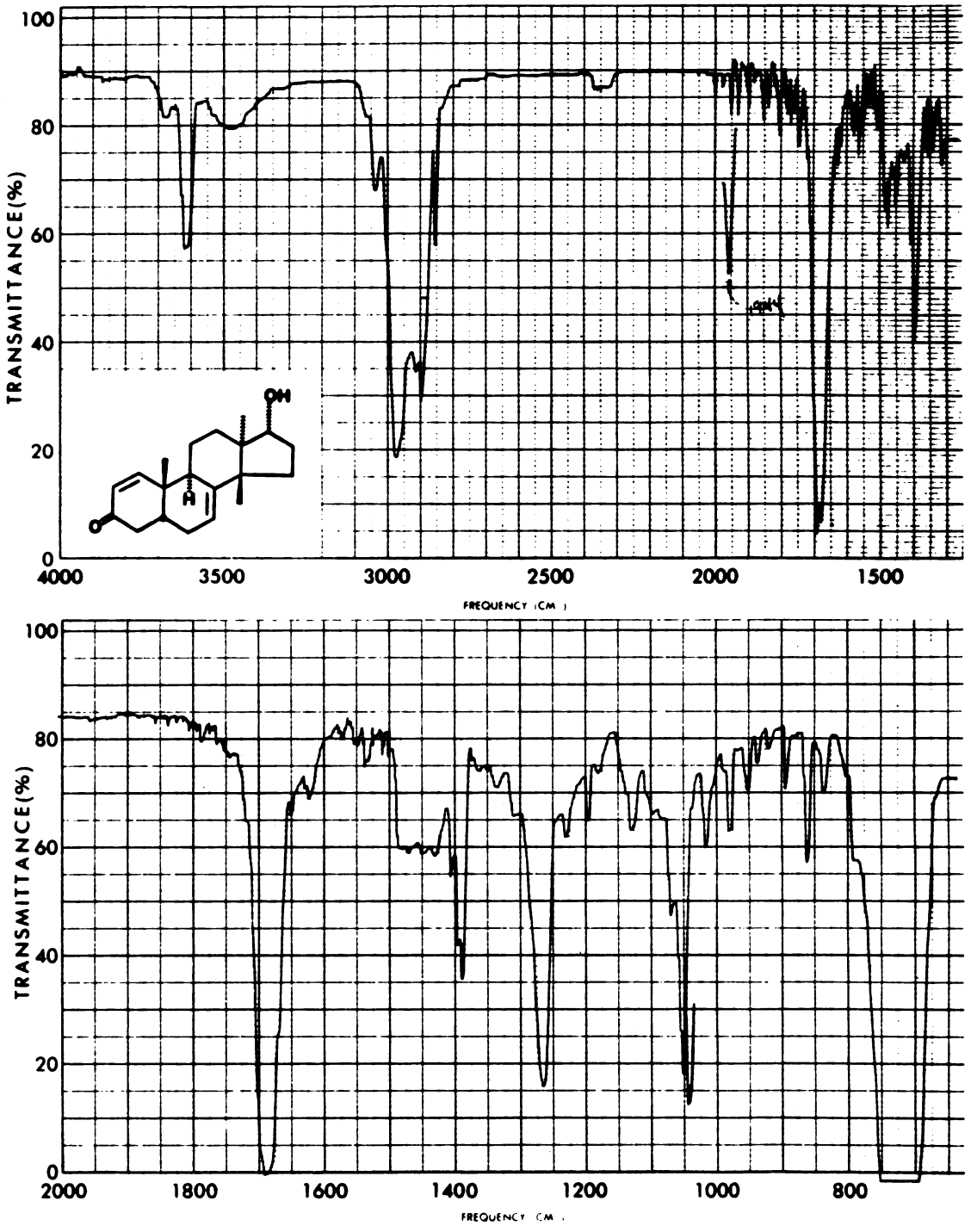

Figure 37. Infrared spectrum of 82.

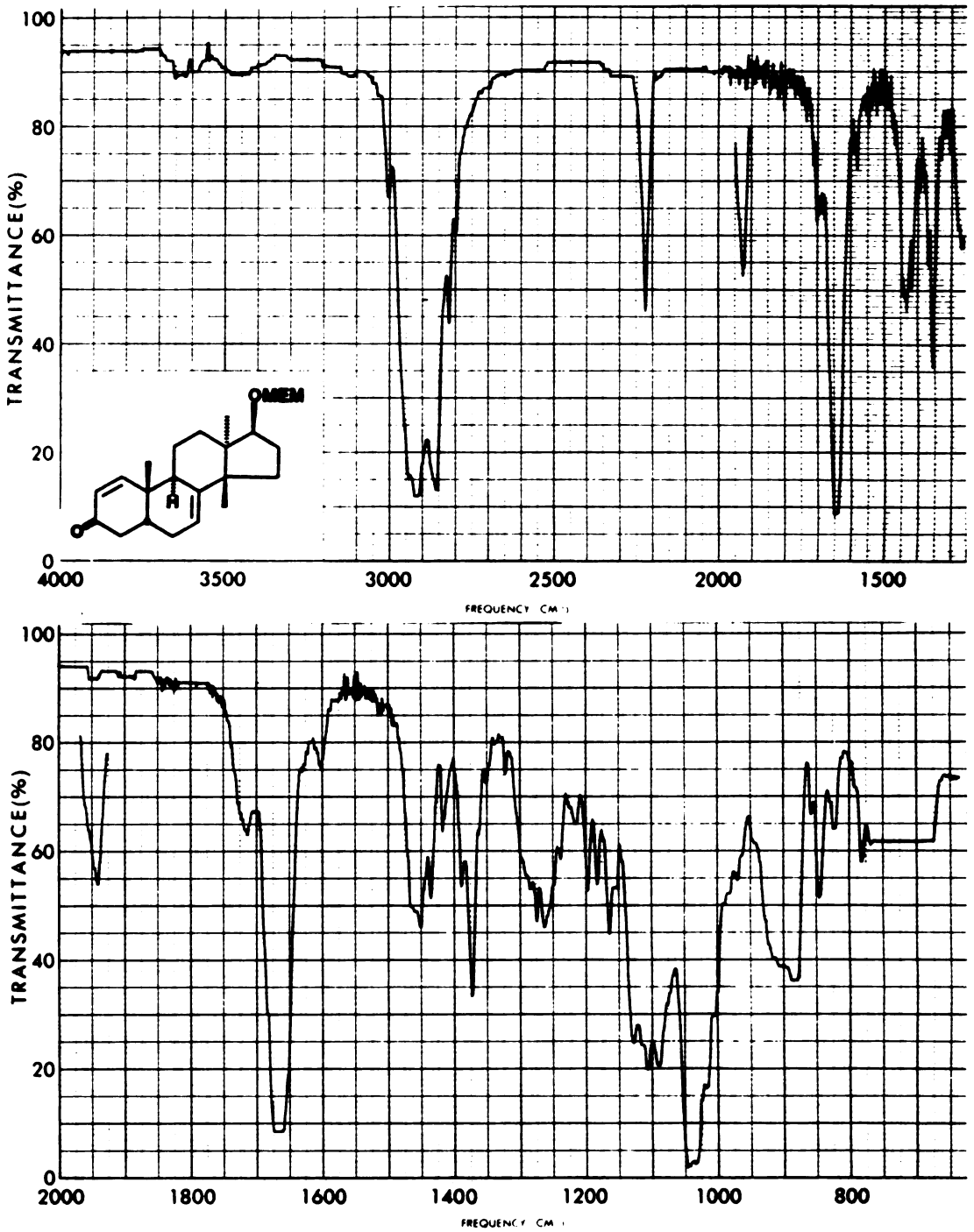

Figure 38. Infrared spectrum of 89.

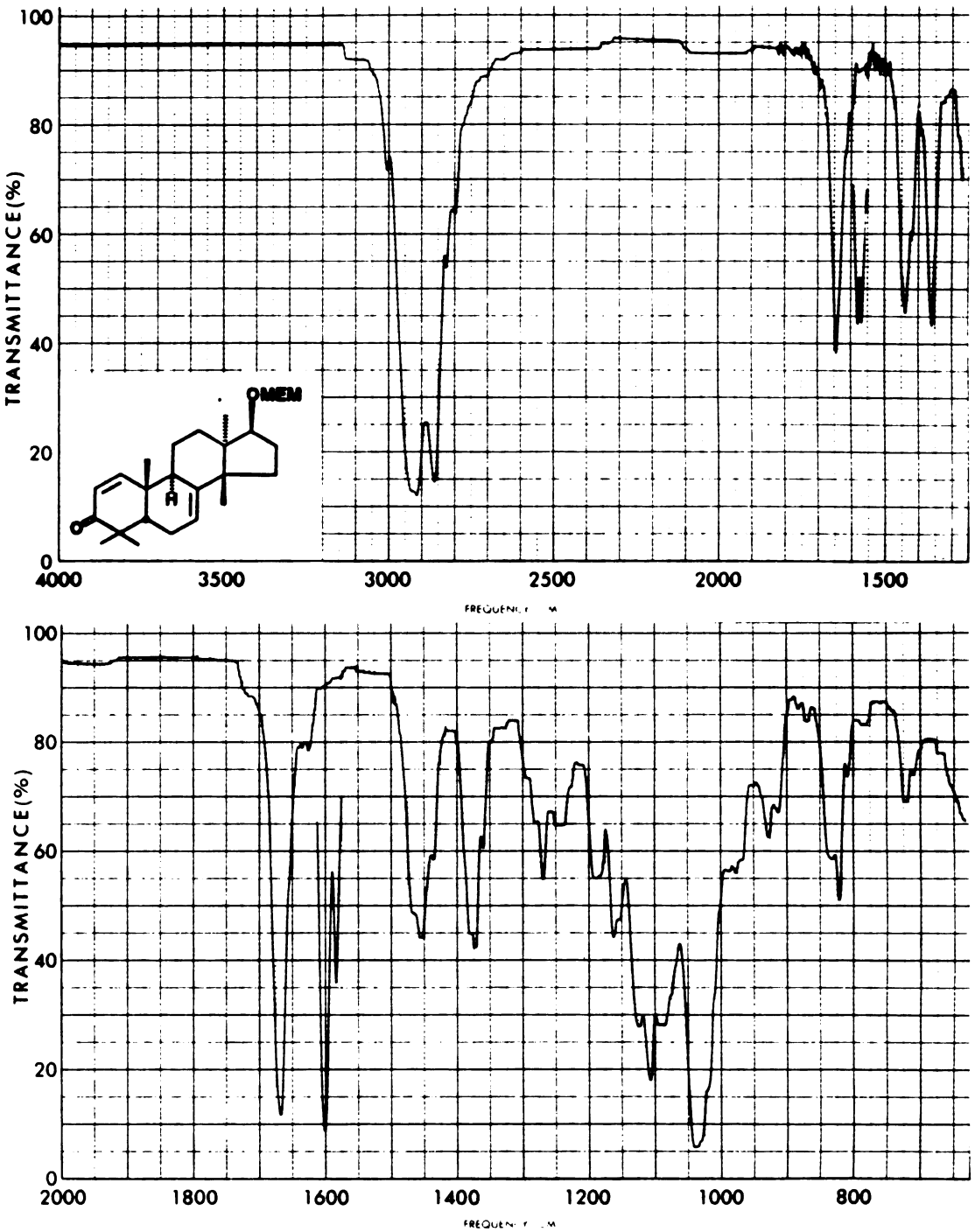

Figure 39. Infrared spectrum of 91.

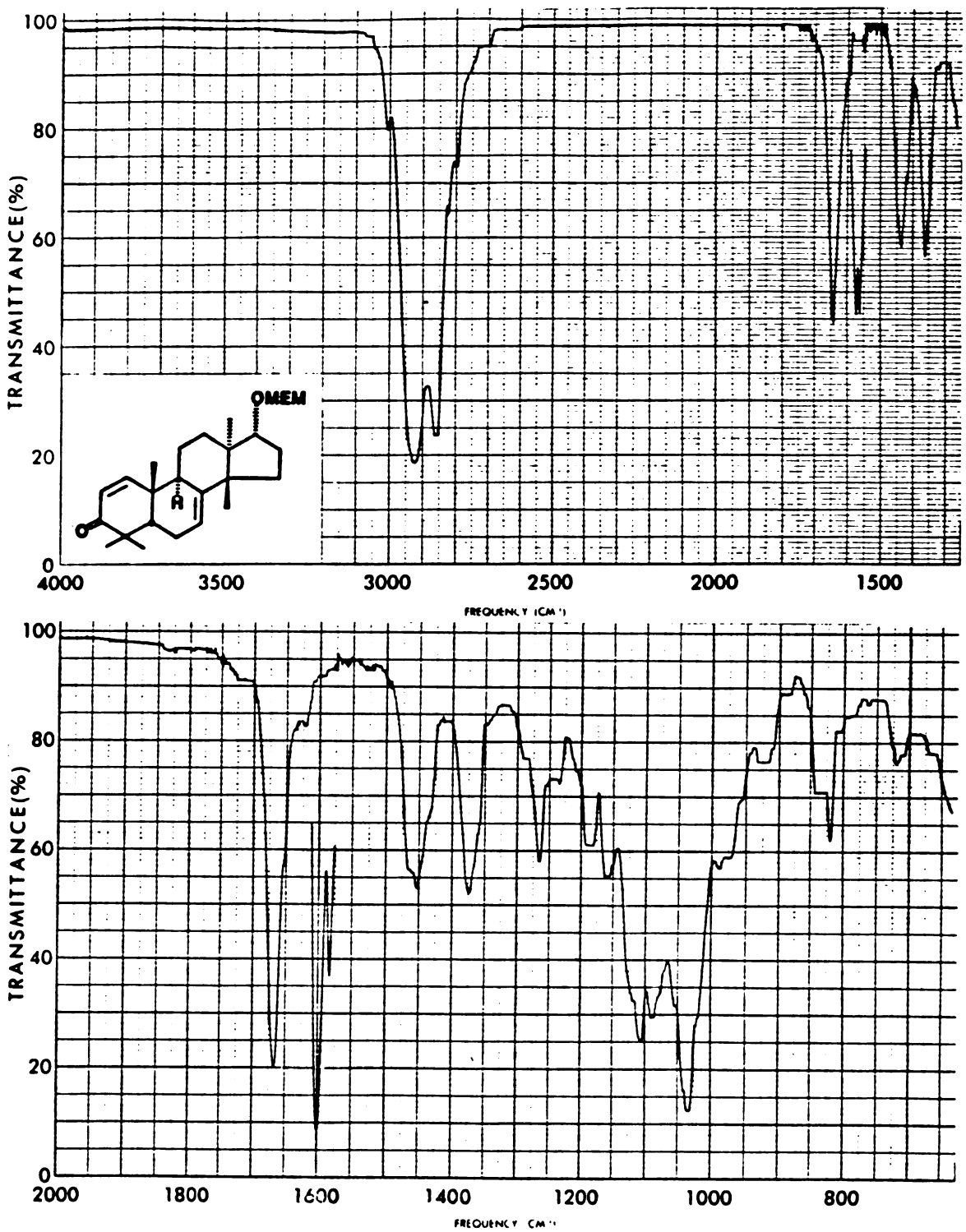

Figure 40. Infrared spectrum of 92.

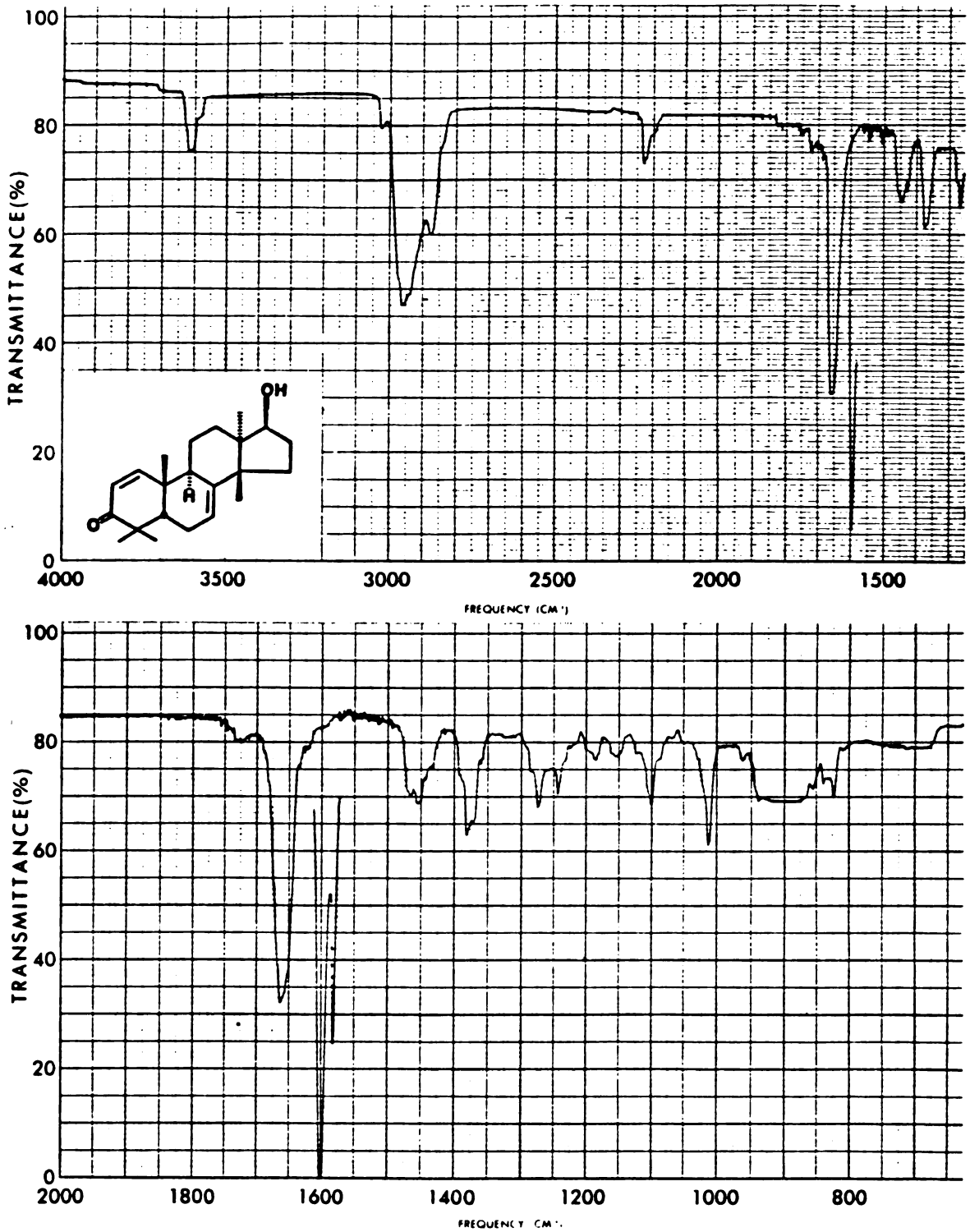

Figure 41. Infrared spectrum of 93.

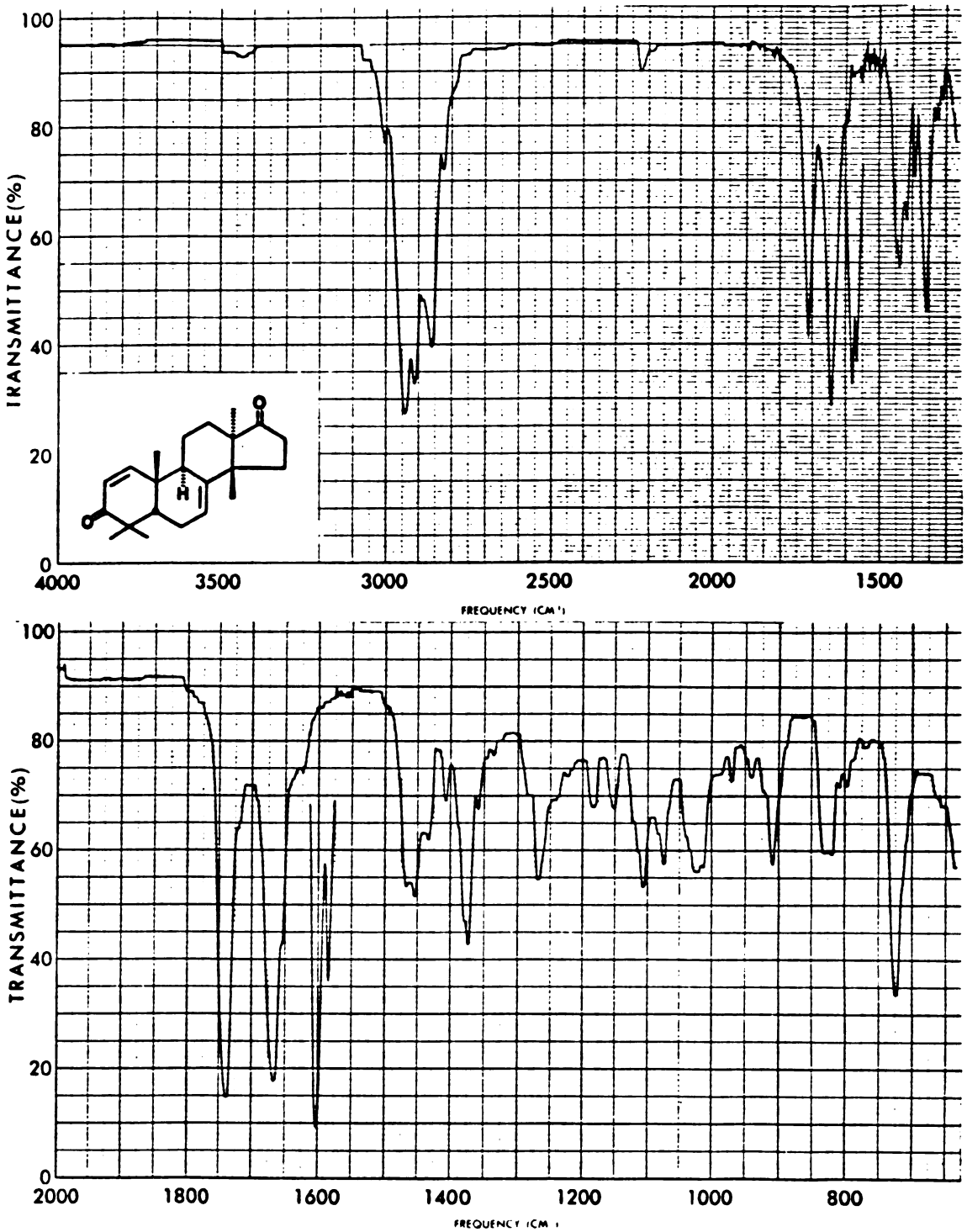

Figure 42. Infrared spectrum of 95.

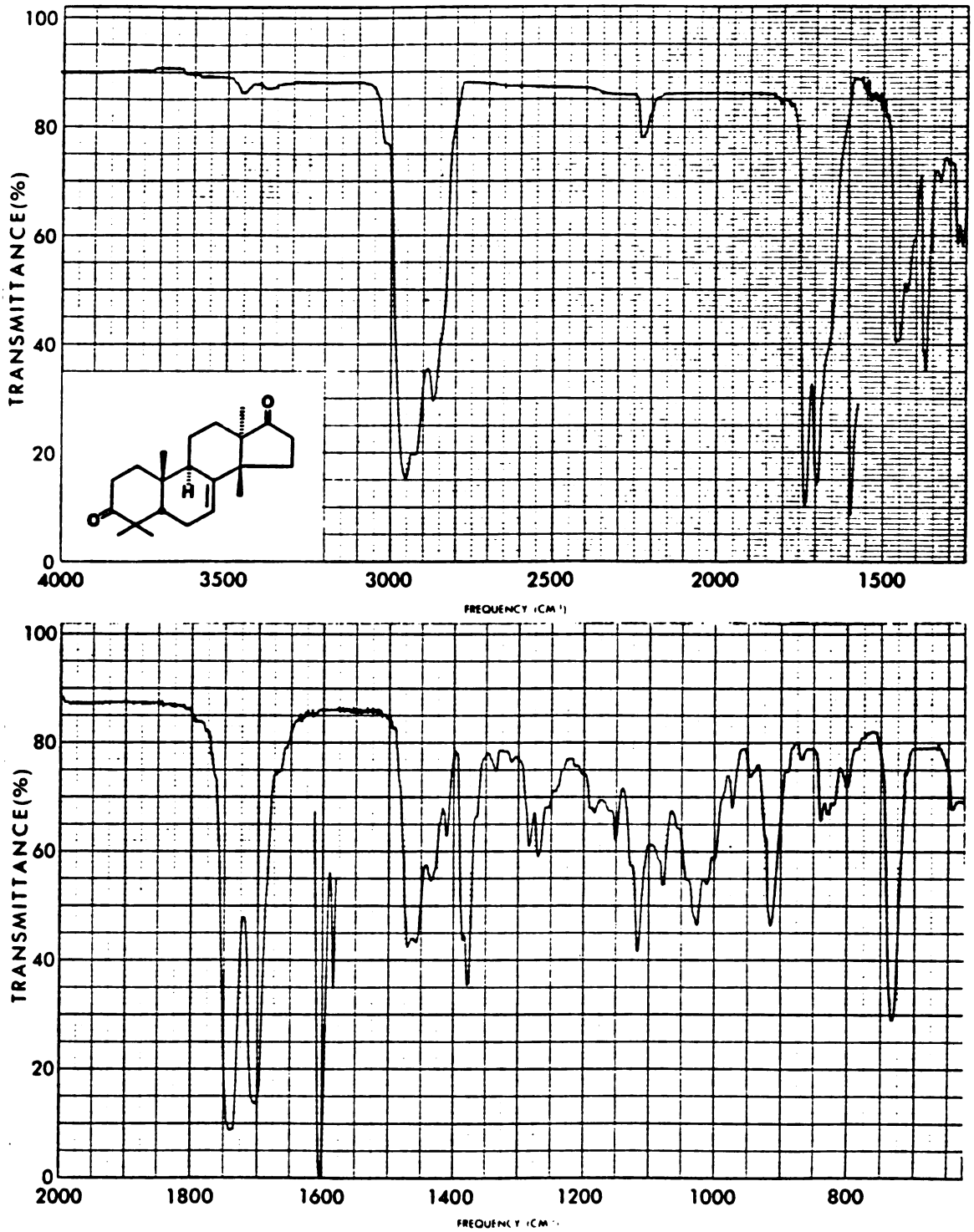

Figure 43. Infrared spectrum of 96.

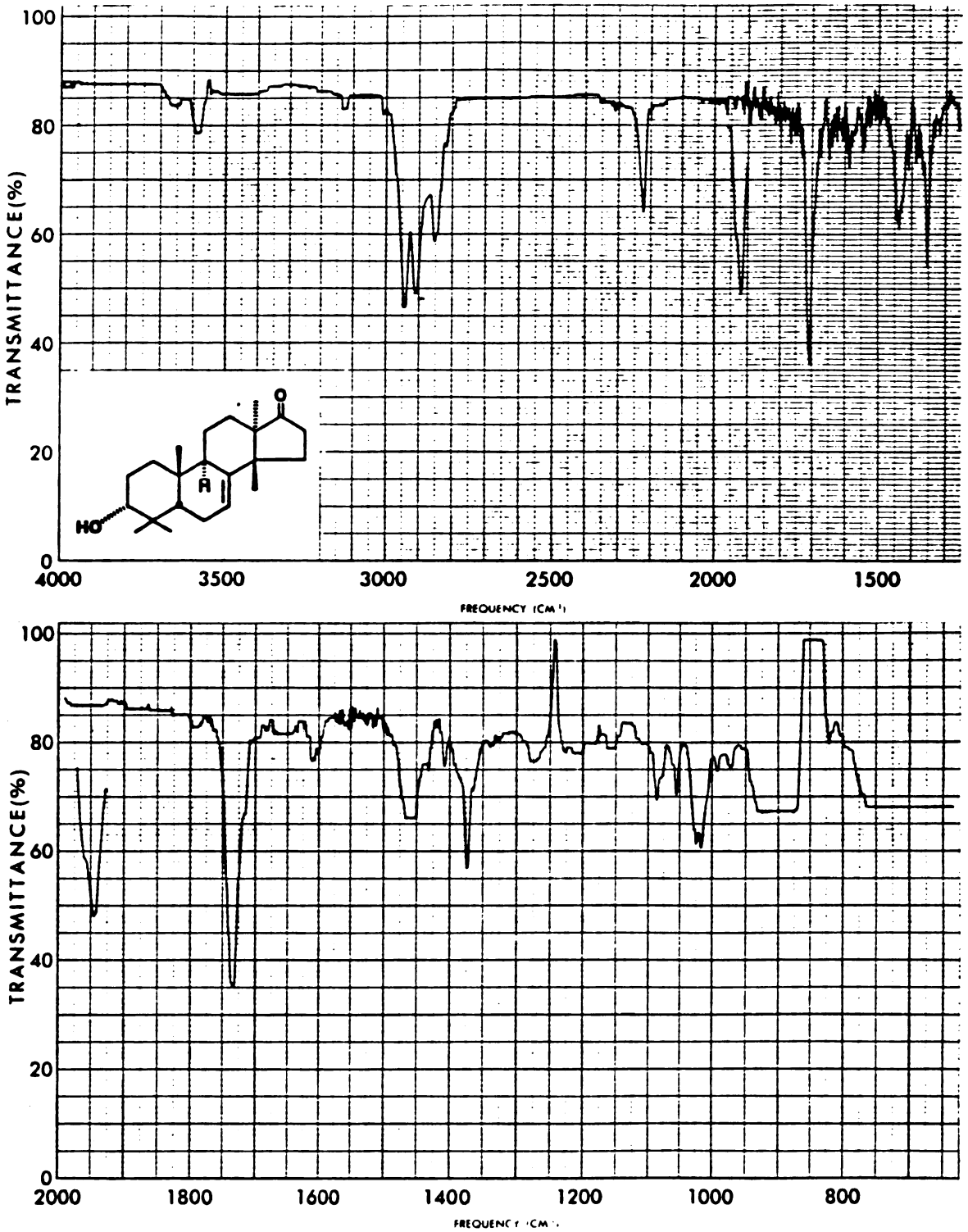

Figure 44. Infrared spectrum of 73.

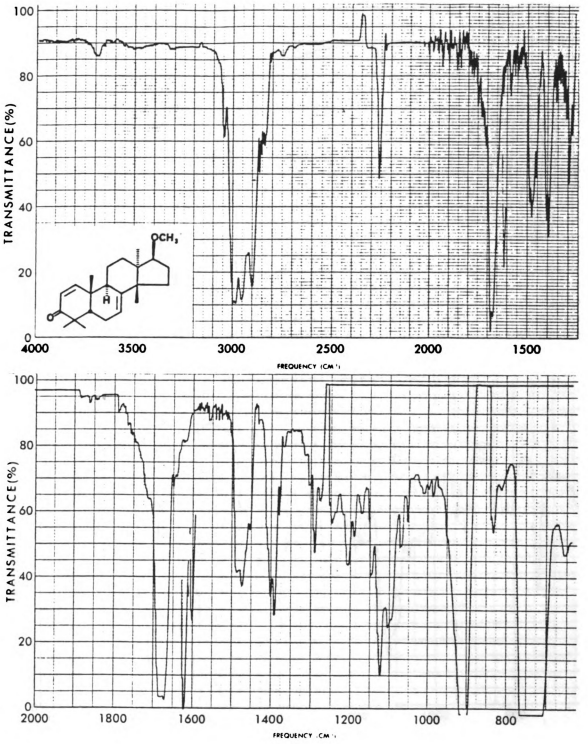

Figure 45. Infrared spectrum of 85.

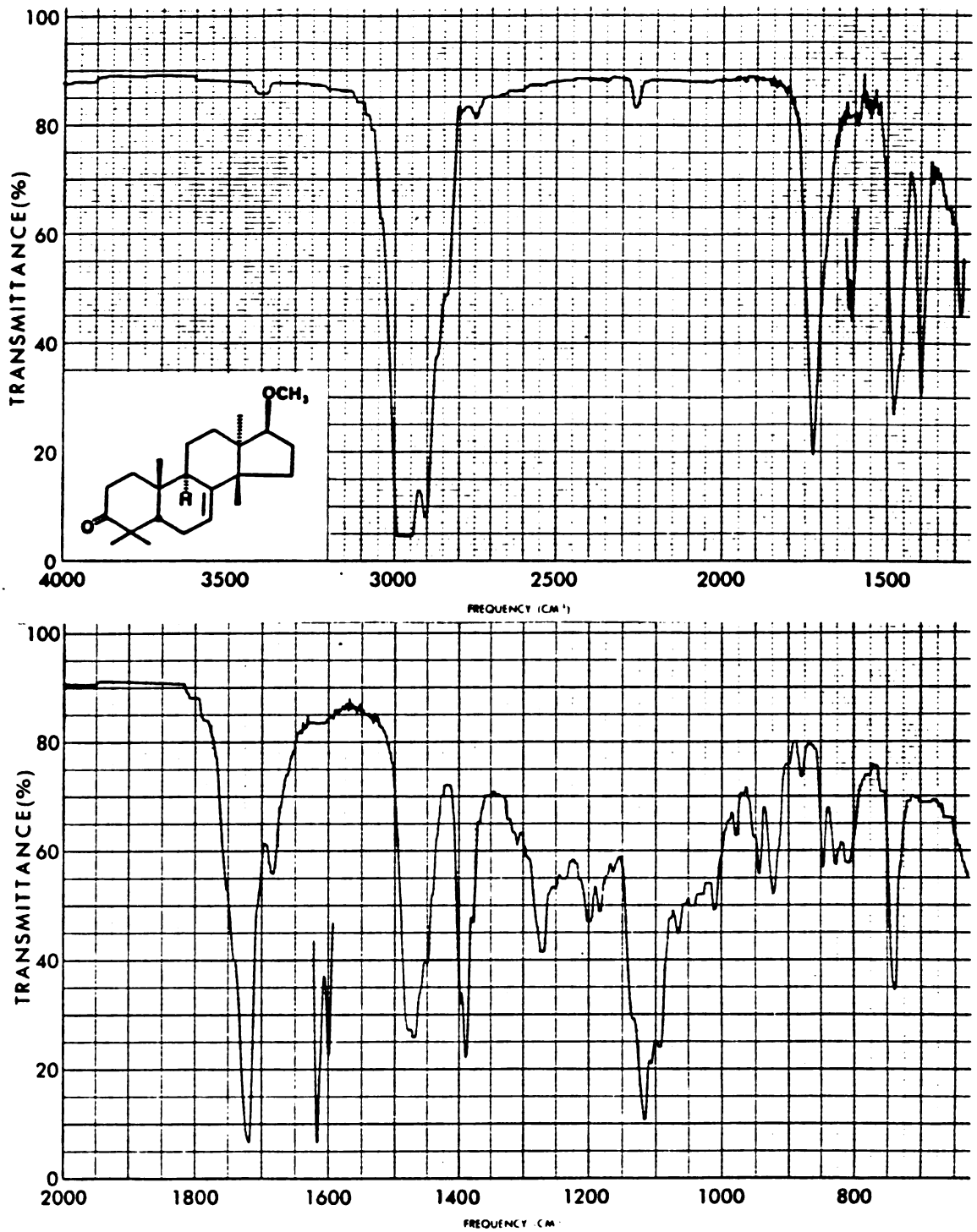

Figure 46. Infrared spectrum of 88.

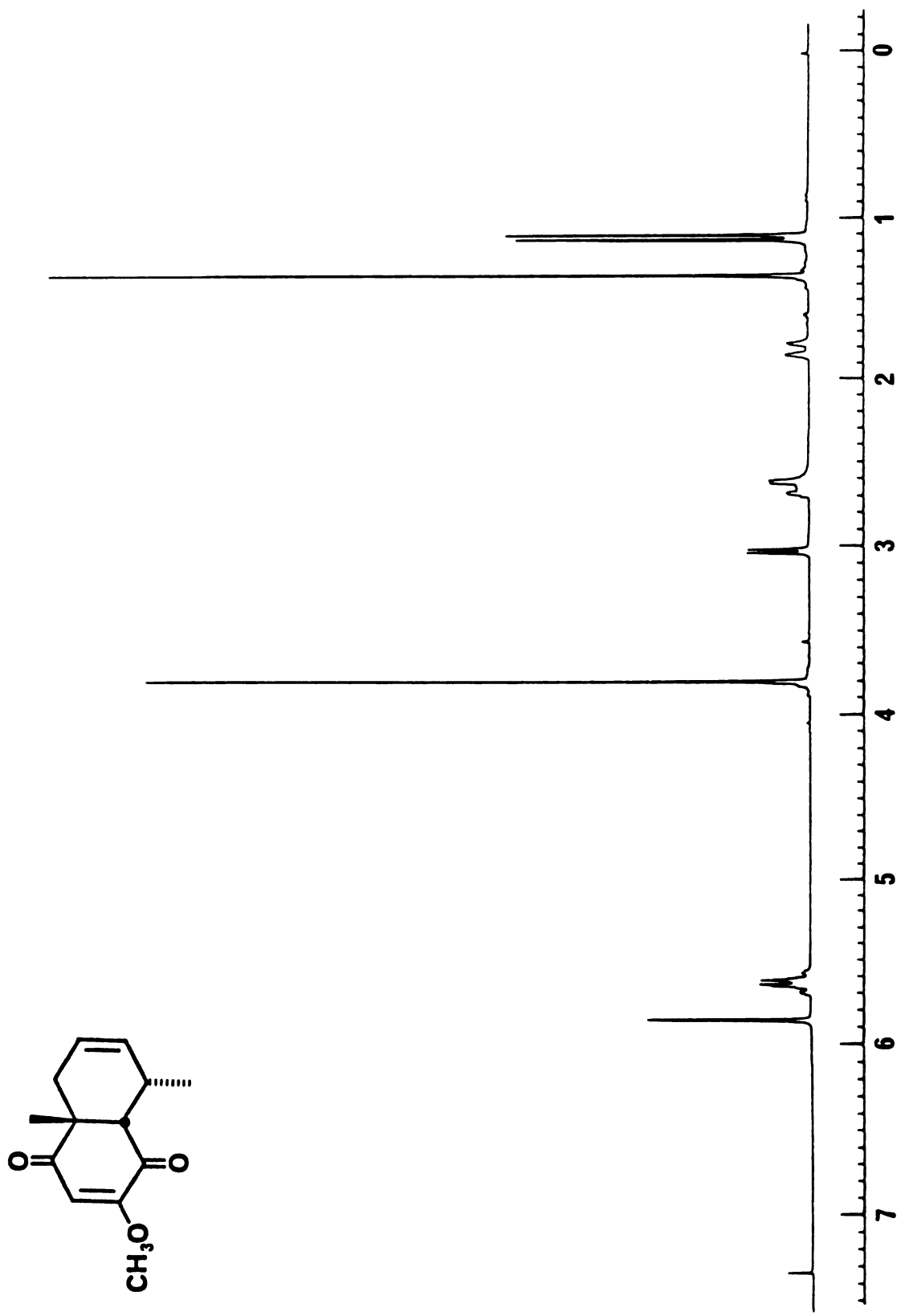

Figure 47. PMR spectrum of 34.

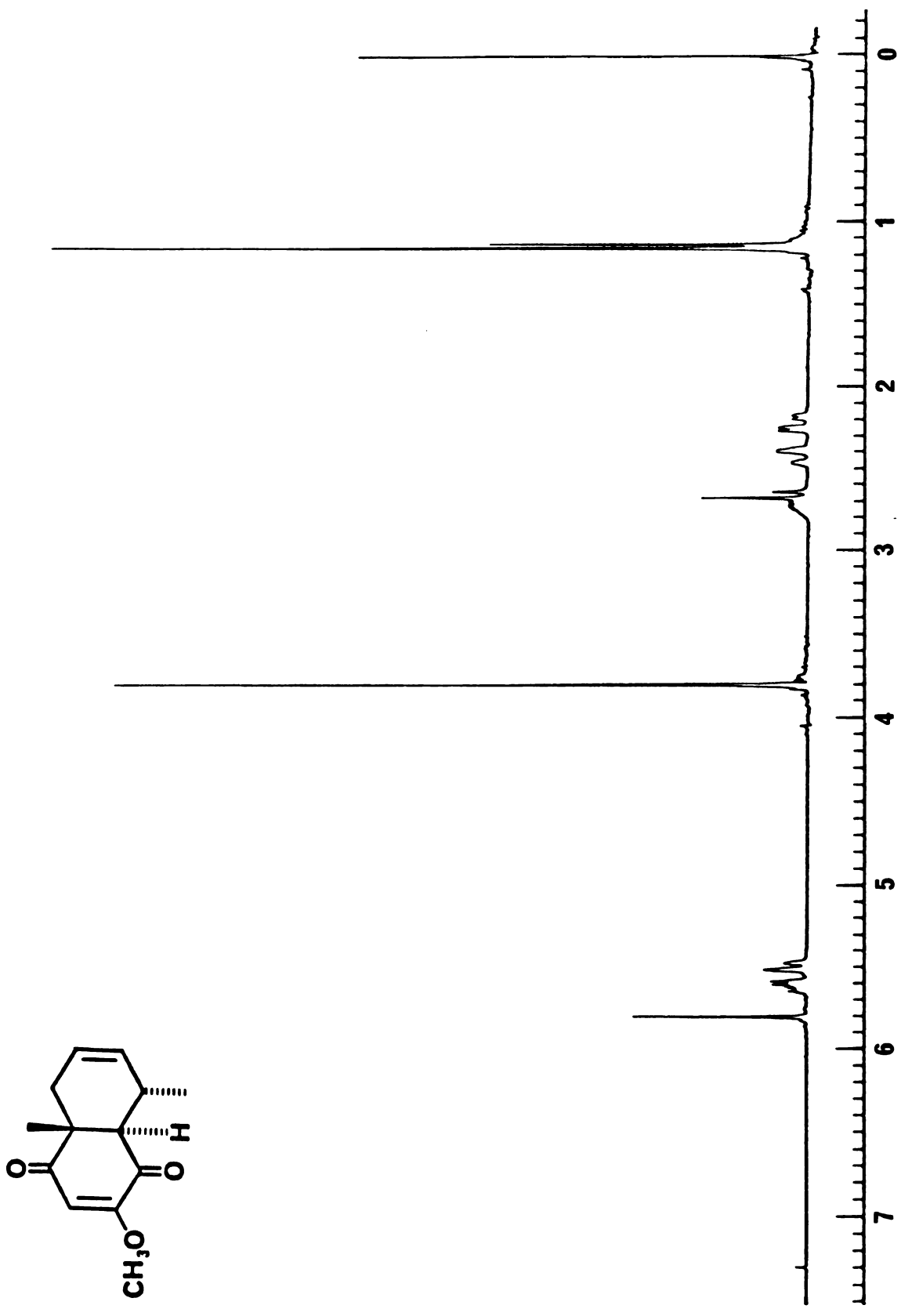

Figure 48. PMR spectrum of 35.

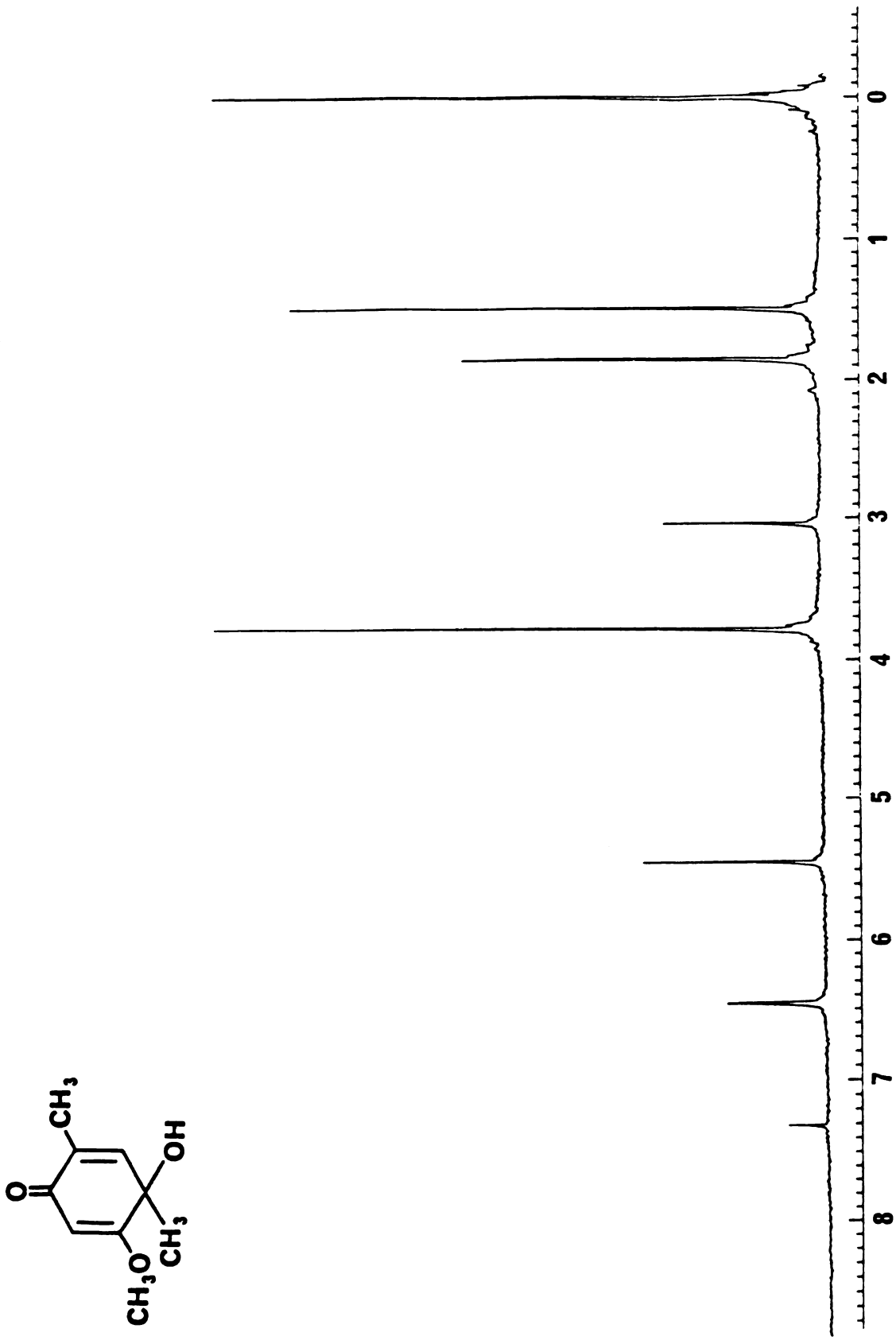

Figure 49. PMR spectrum of 36.

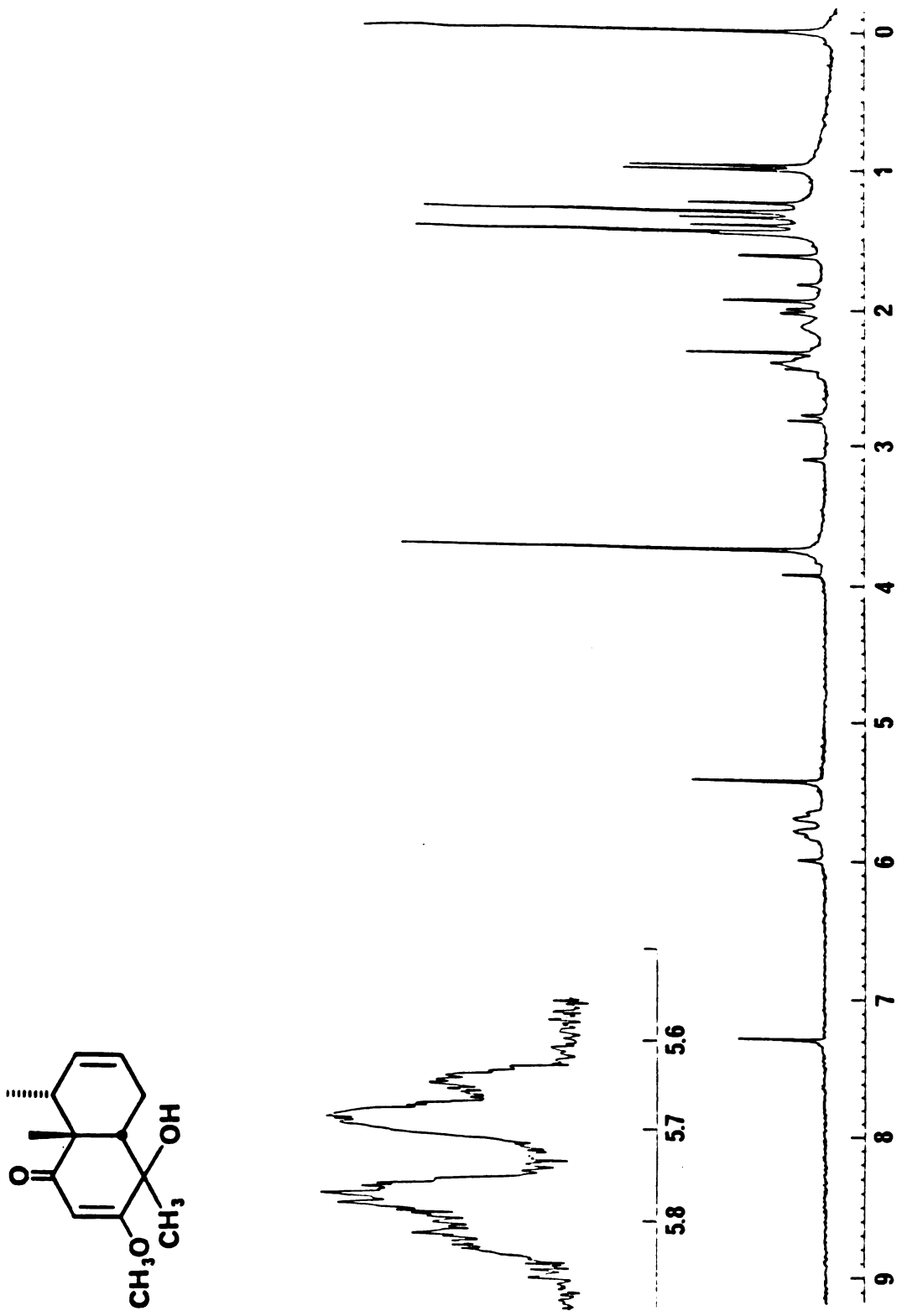

Figure 50. PMR spectrum of 37.

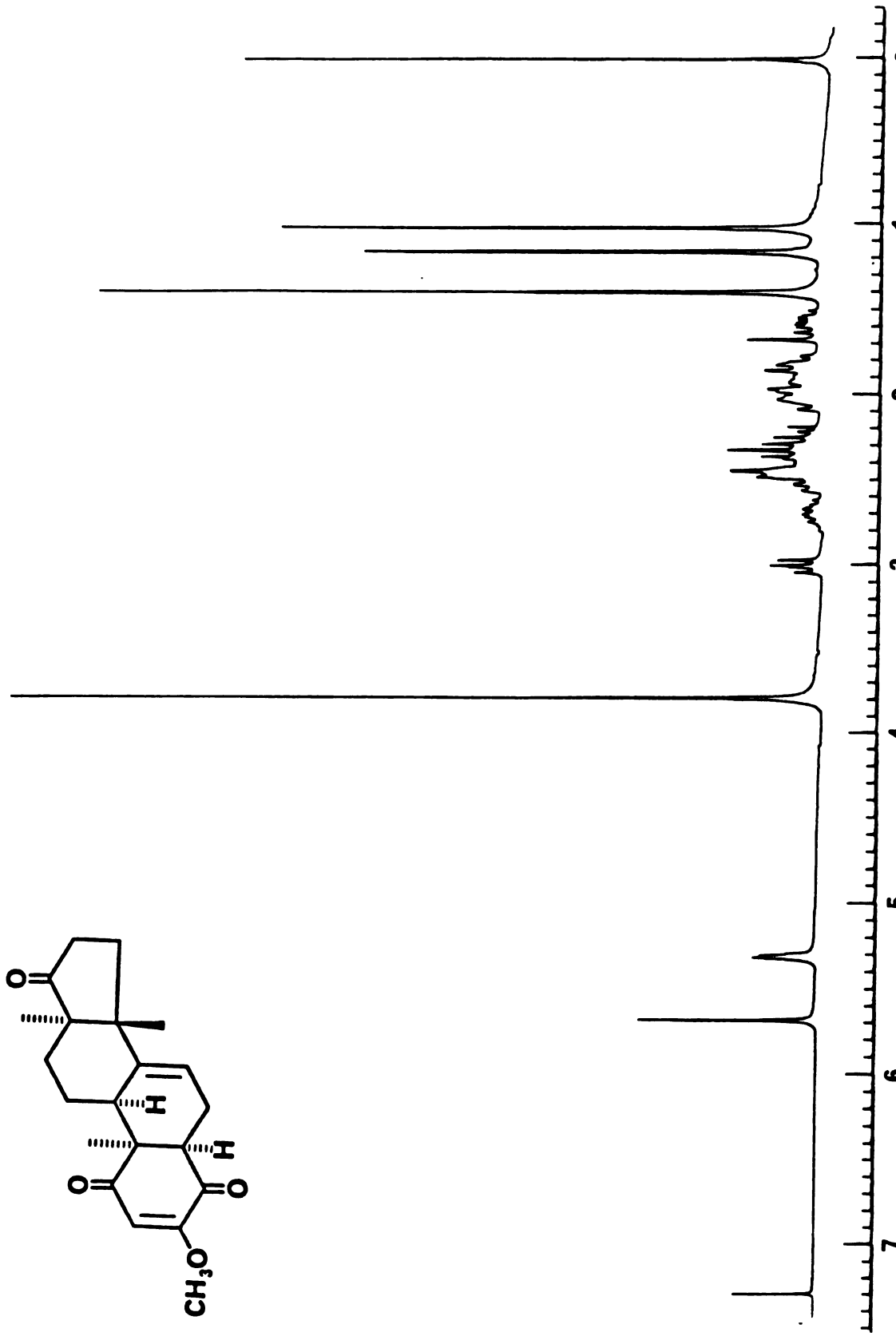

Figure 51. PMR spectrum of 29.

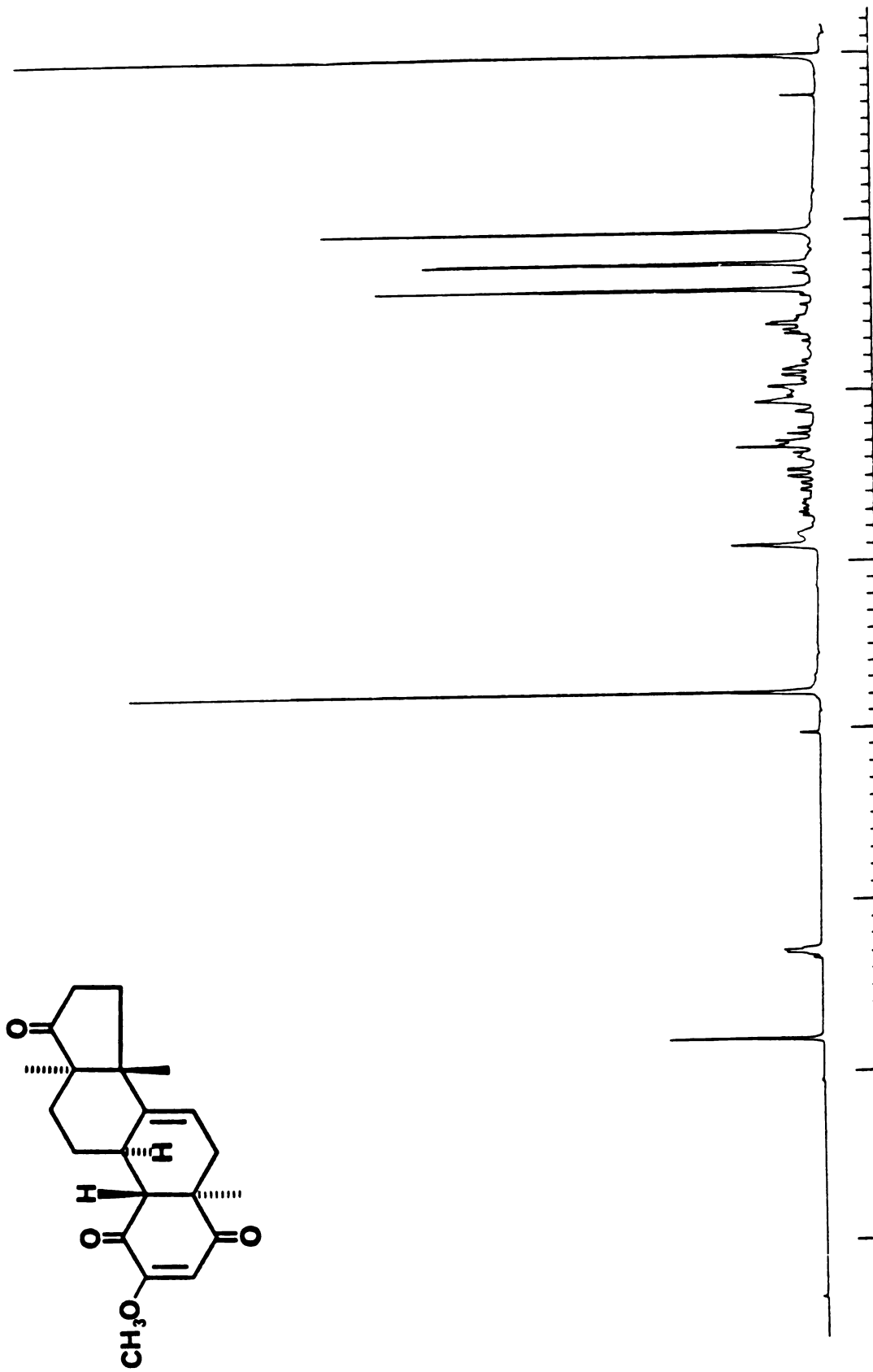

Figure 52. PMR spectrum of 31.

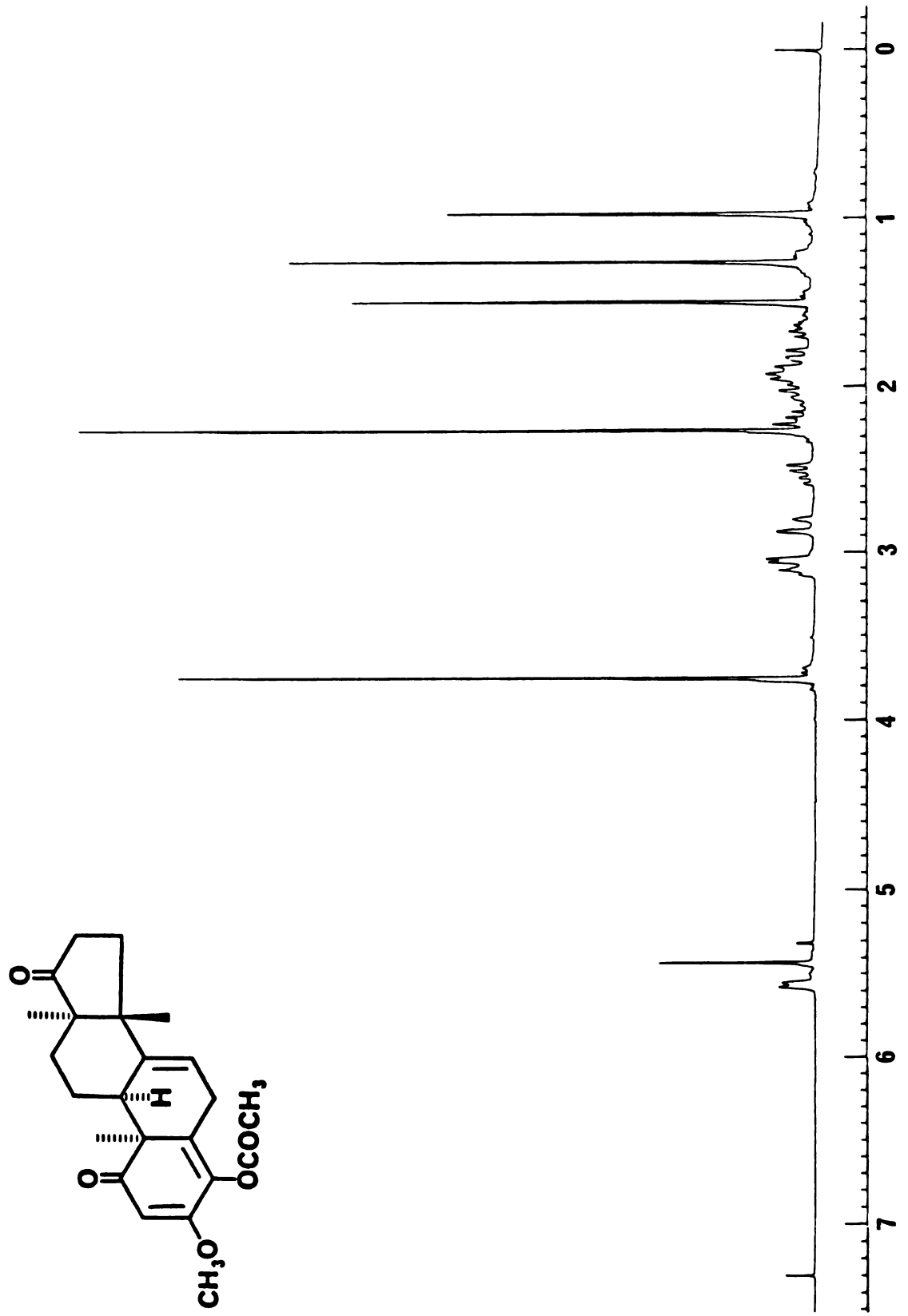

Figure 53. PMR spectrum of 61.

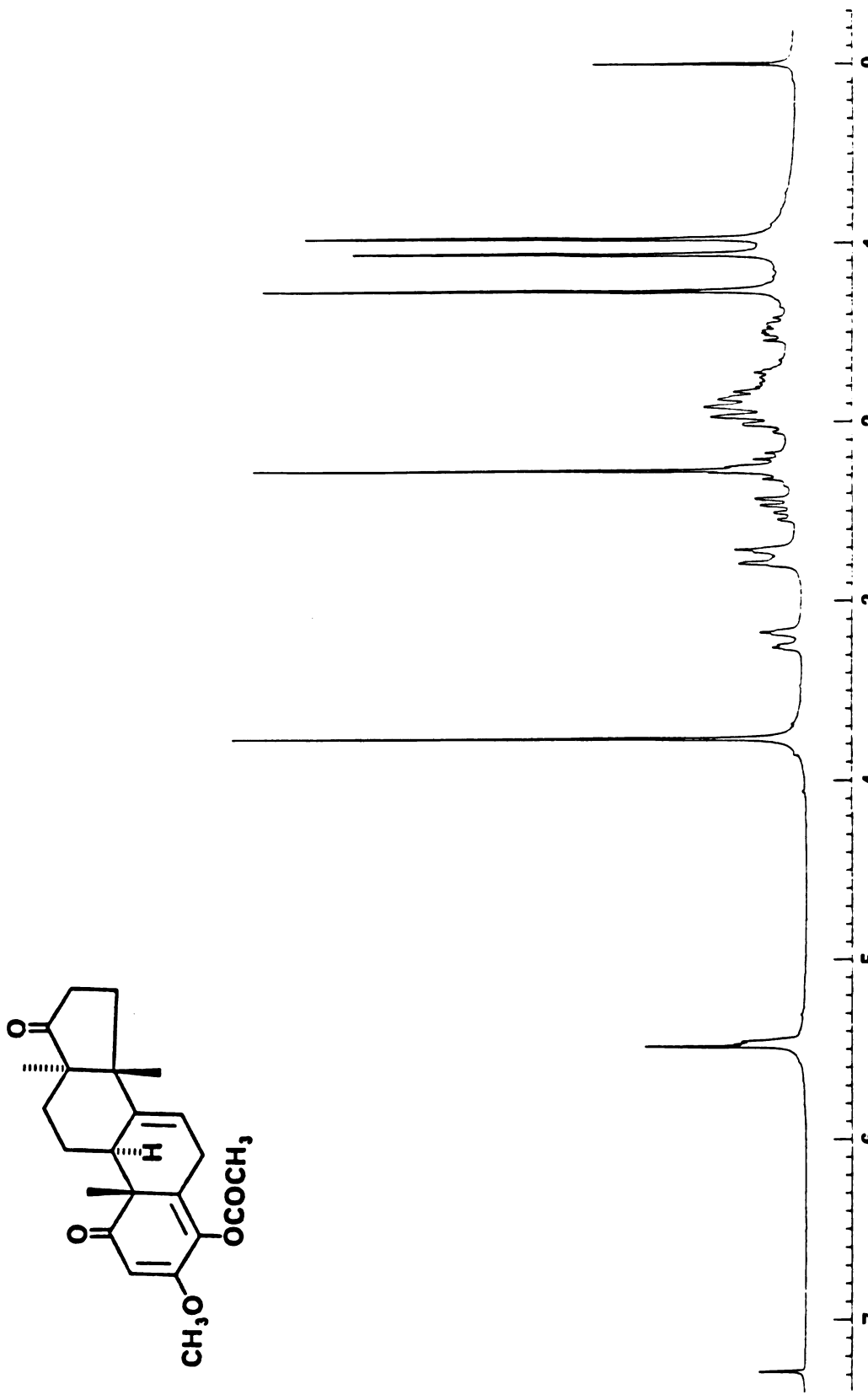

Figure 54. PMR spectrum of 62.

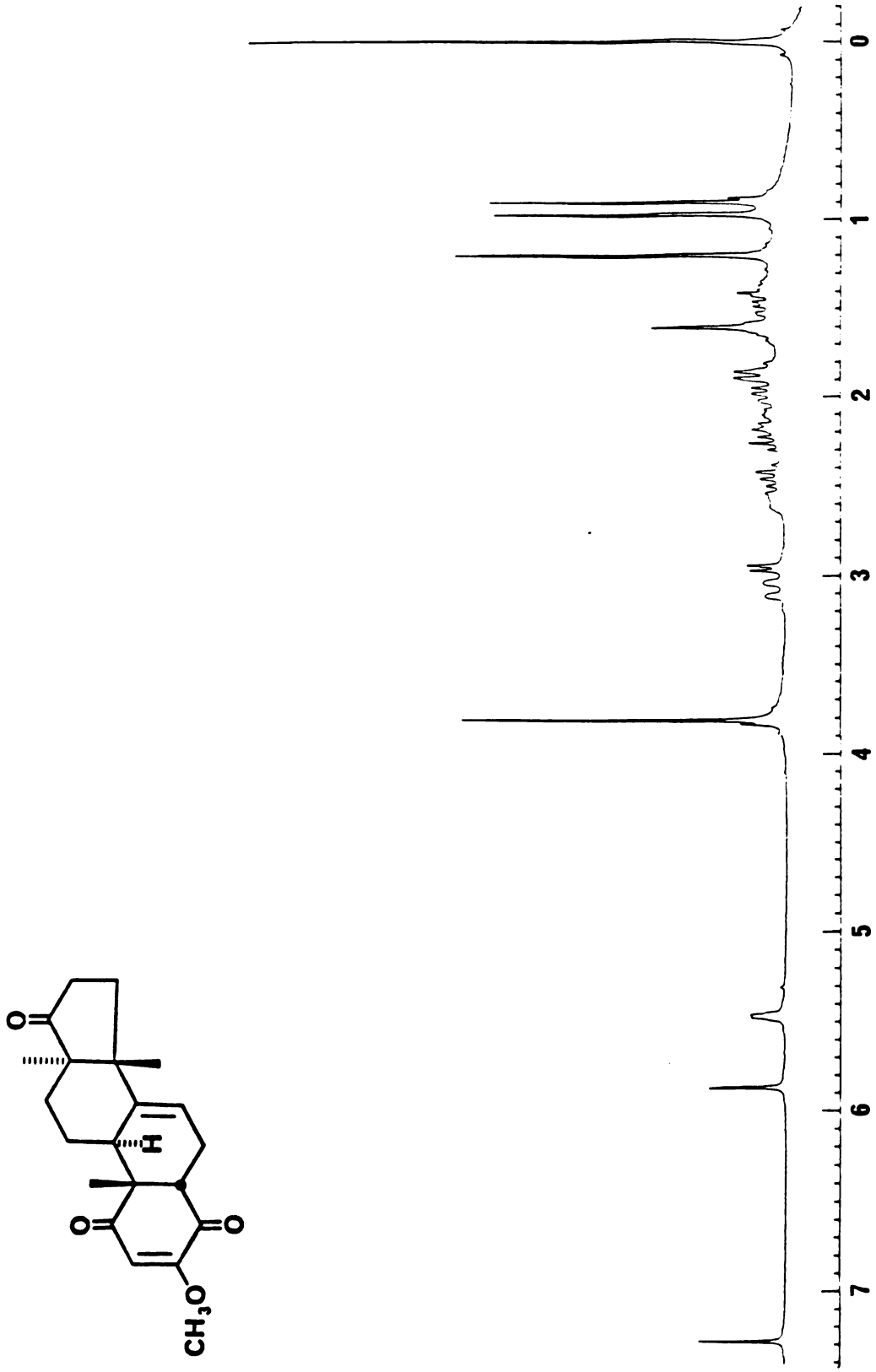

Figure 55. PMR spectrum of 70.

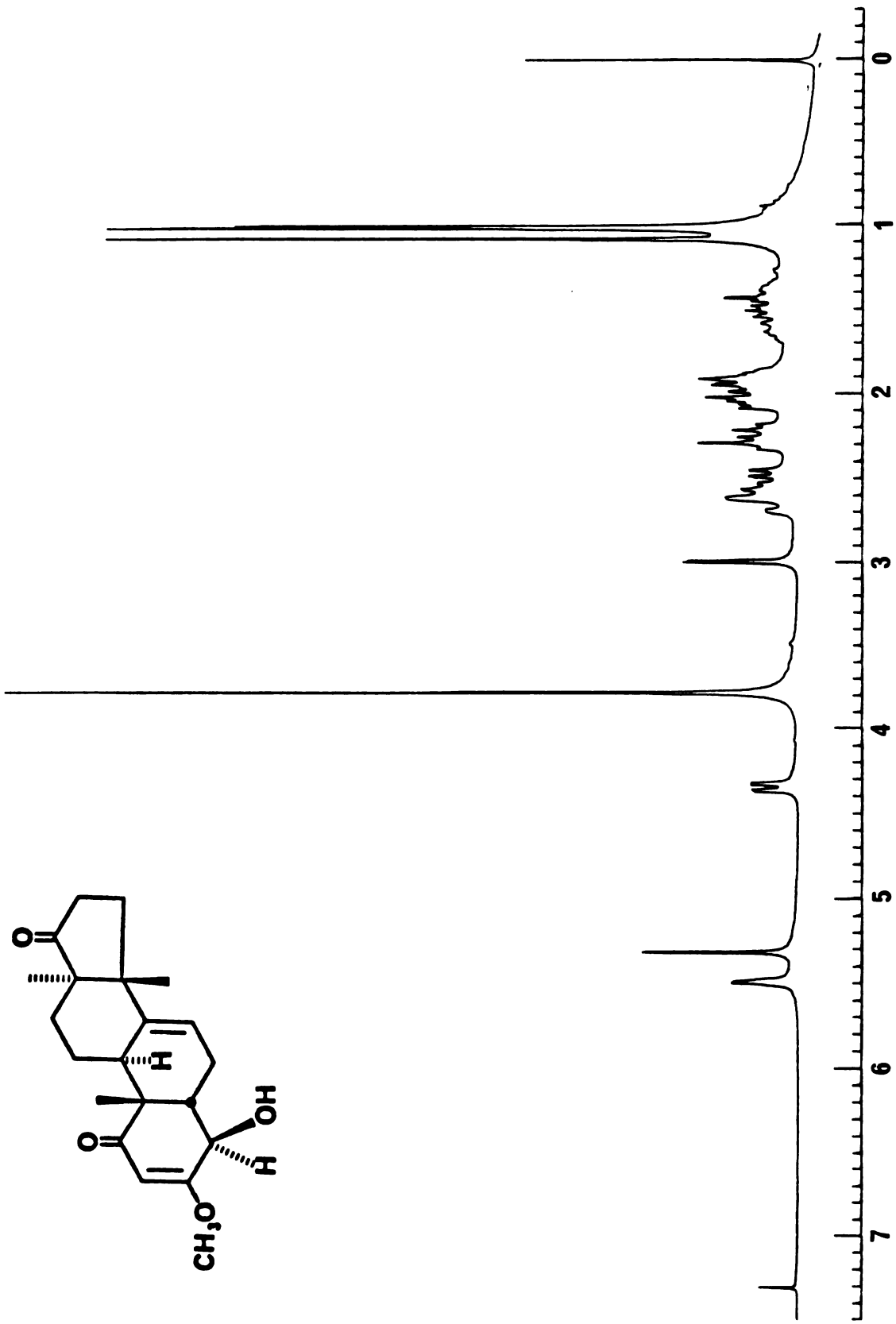

Figure 56. PMR spectrum of 79.

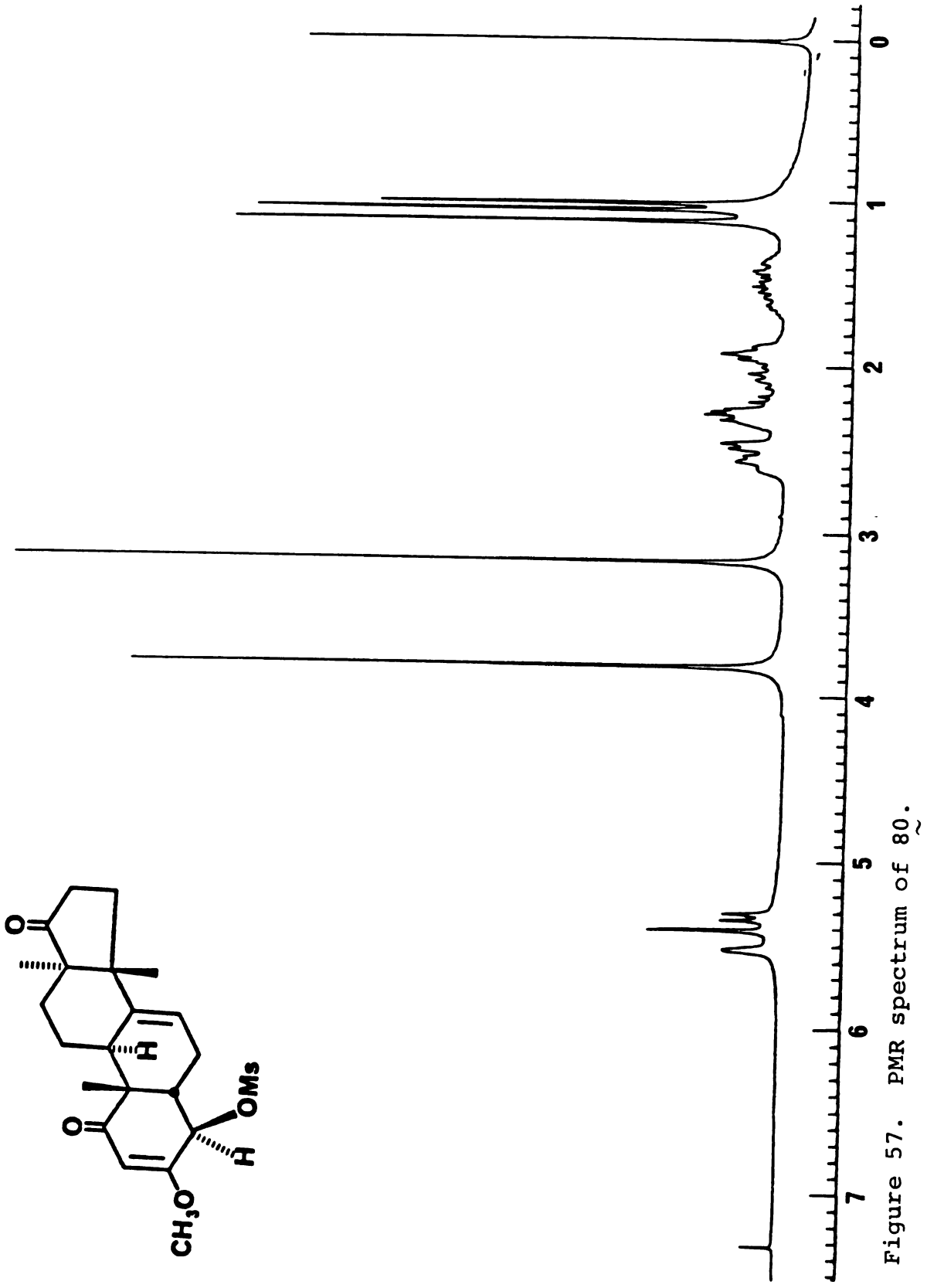

Figure 57. PMR spectrum of 80.

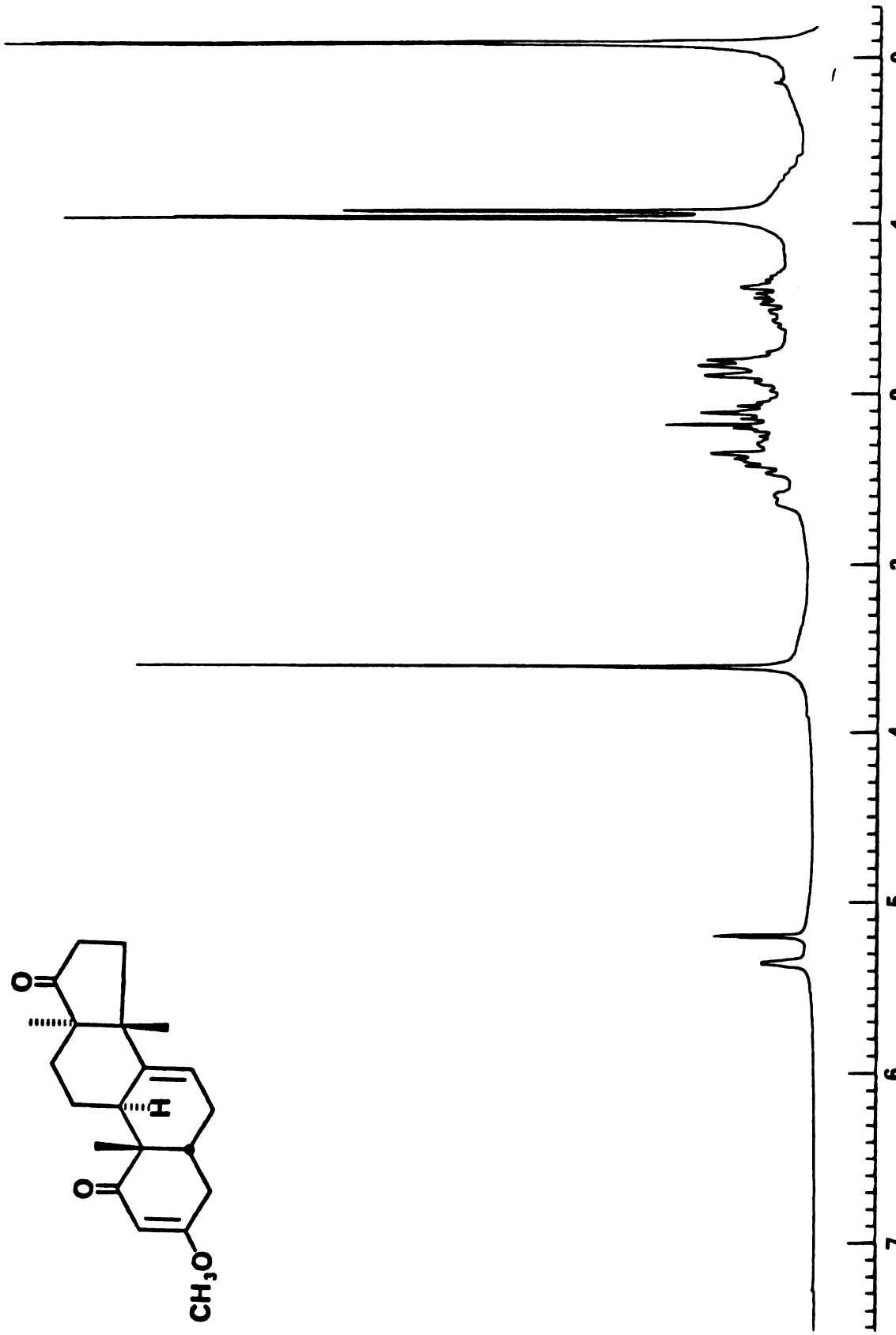

Figure 58. PMR spectrum of 83.

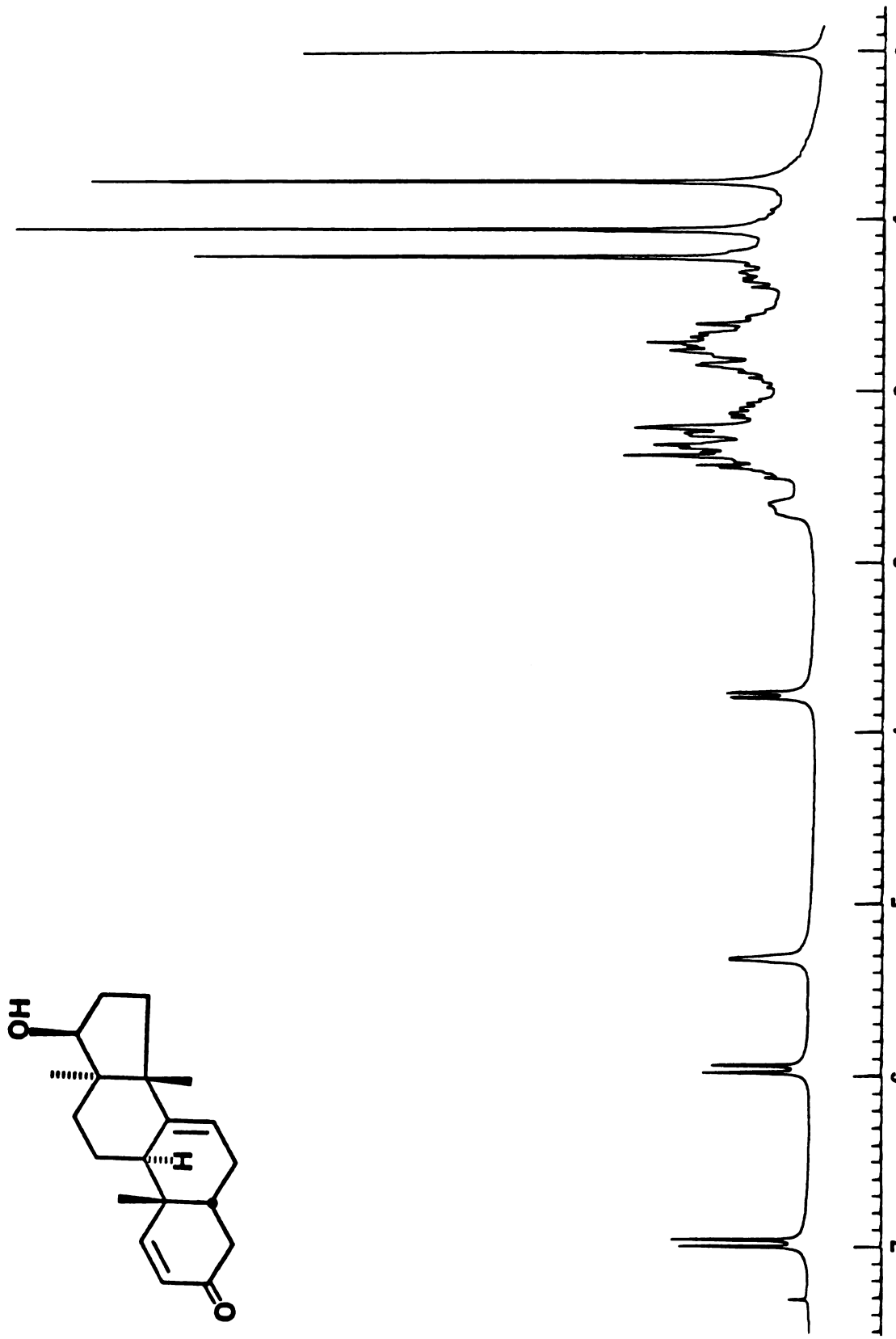

Figure 59. PMR spectrum of 81.

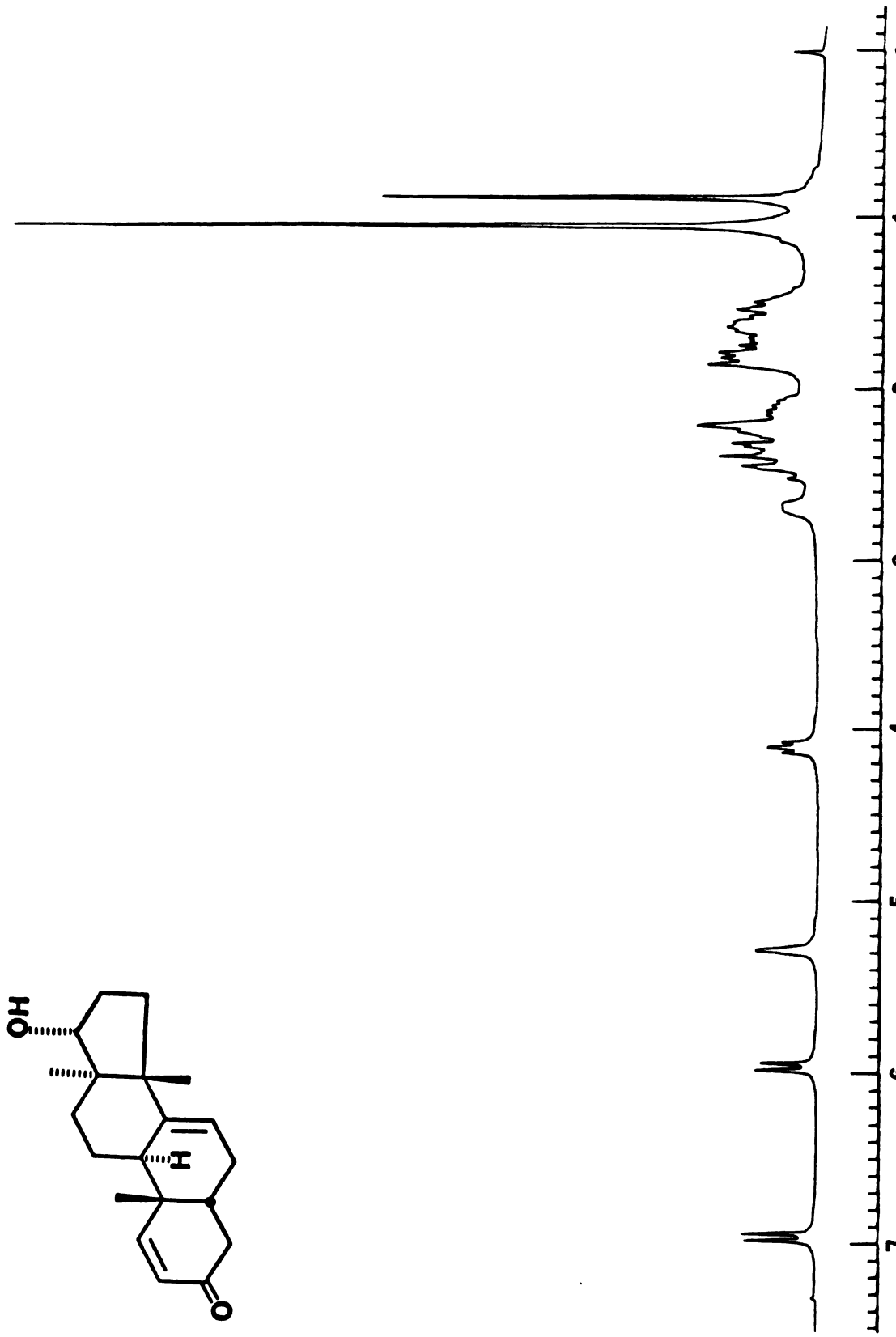

Figure 60. PMR spectrum of 82.

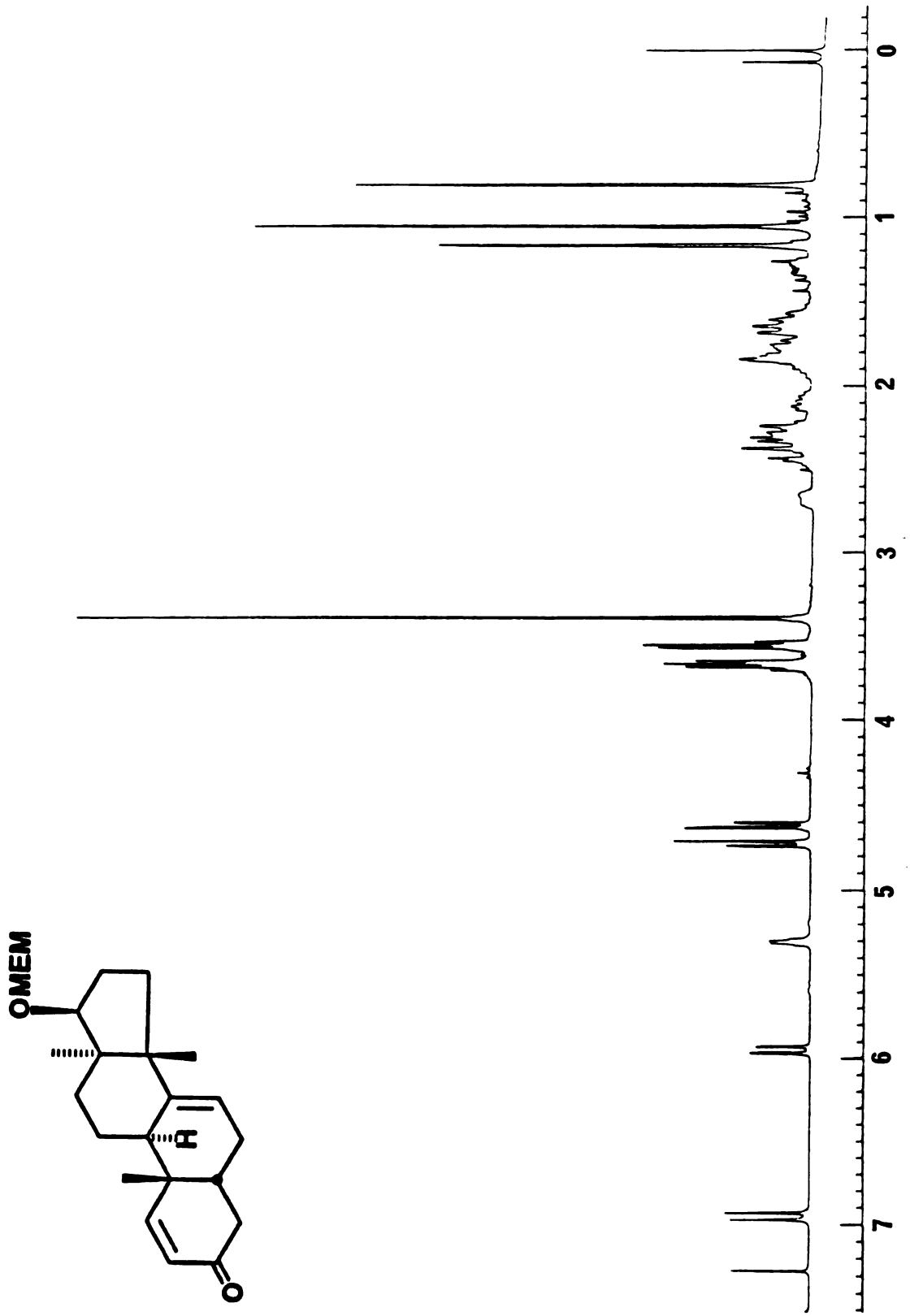

Figure 61. PMR spectrum of 89.

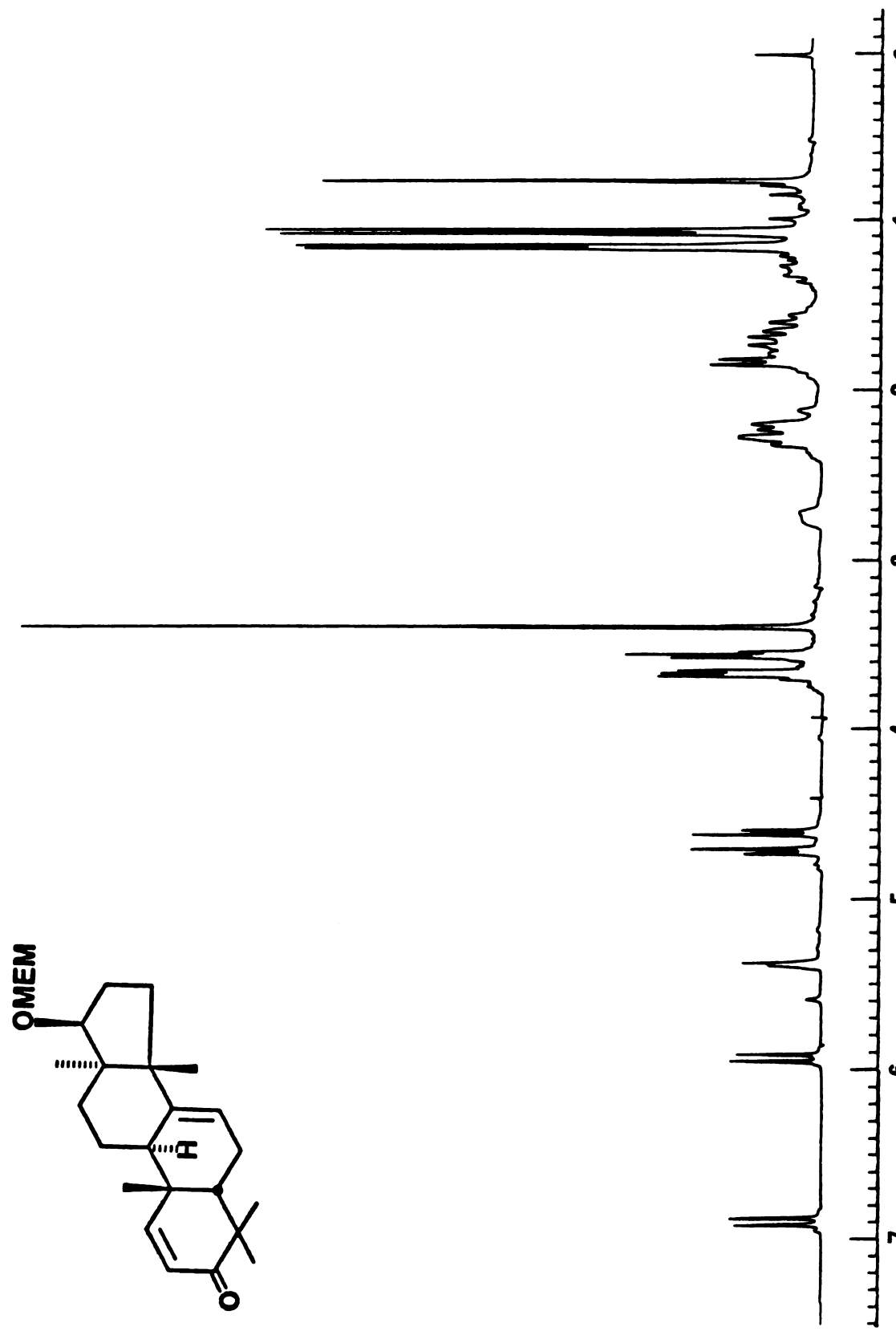

Figure 62. PMR spectrum of 91.

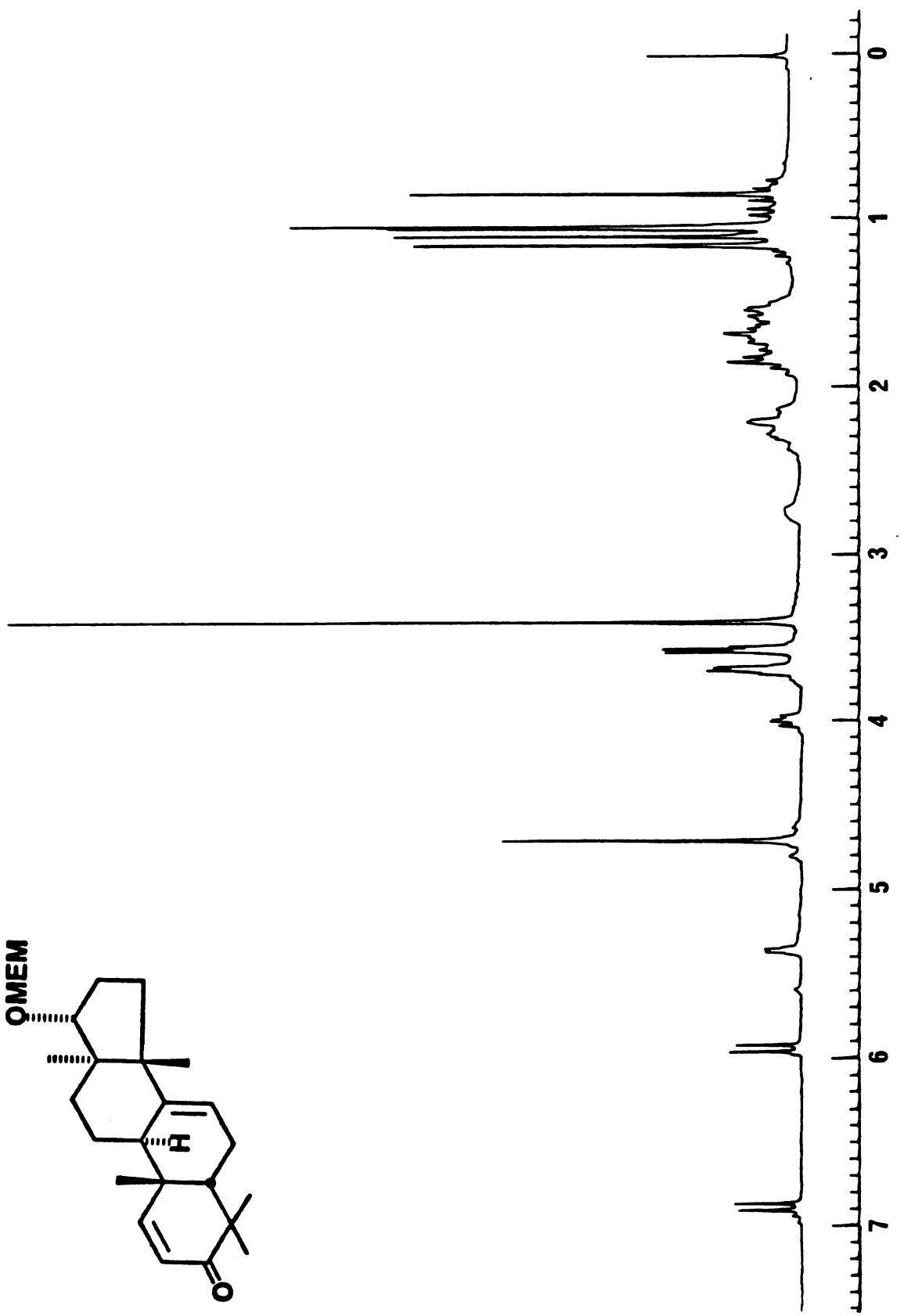

Figure 63. PMR spectrum of 92.

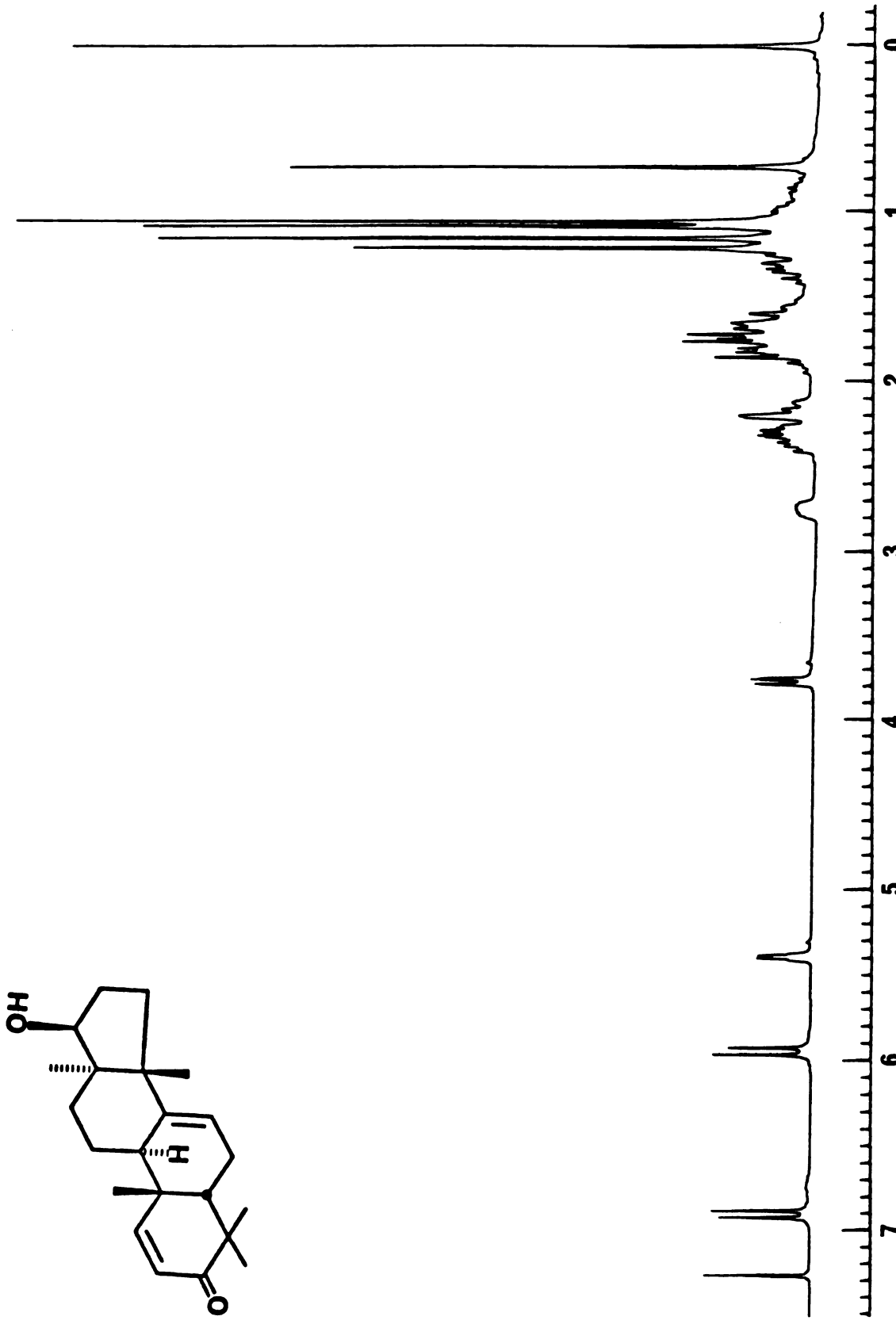

Figure 64. PMR spectrum of 93.

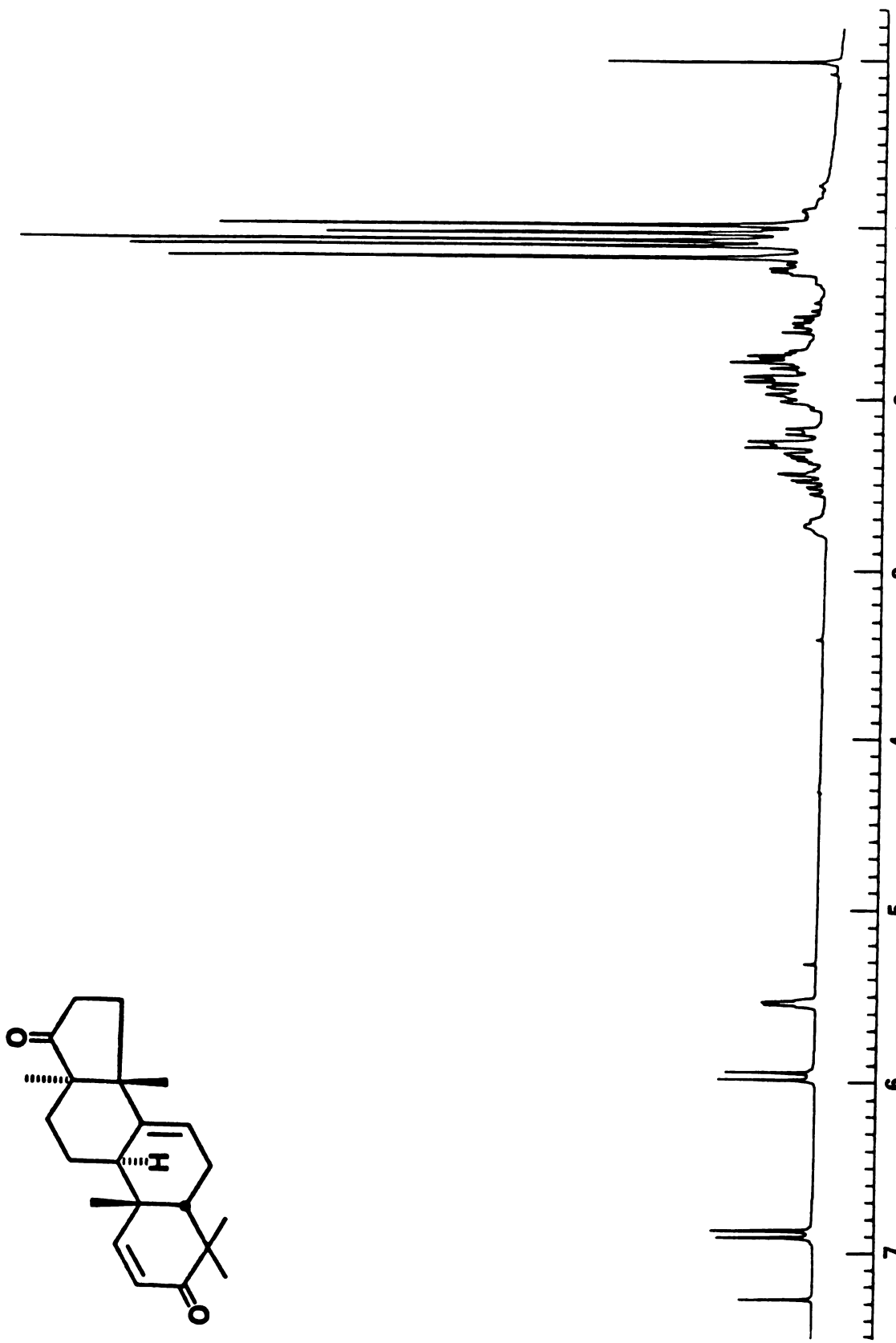

Figure 65. PMR spectrum of 95.

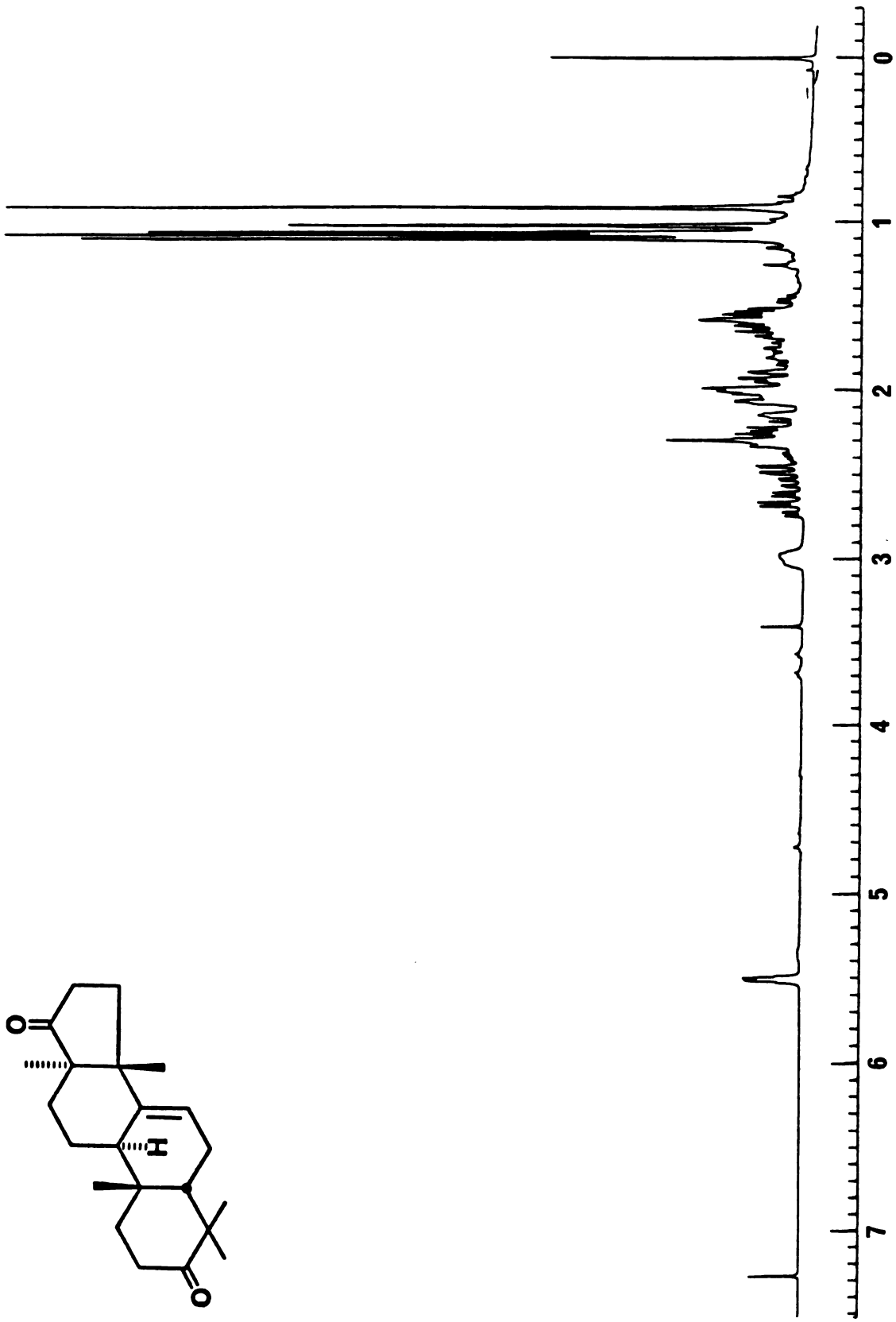

Figure 66. PMR spectrum of 96.

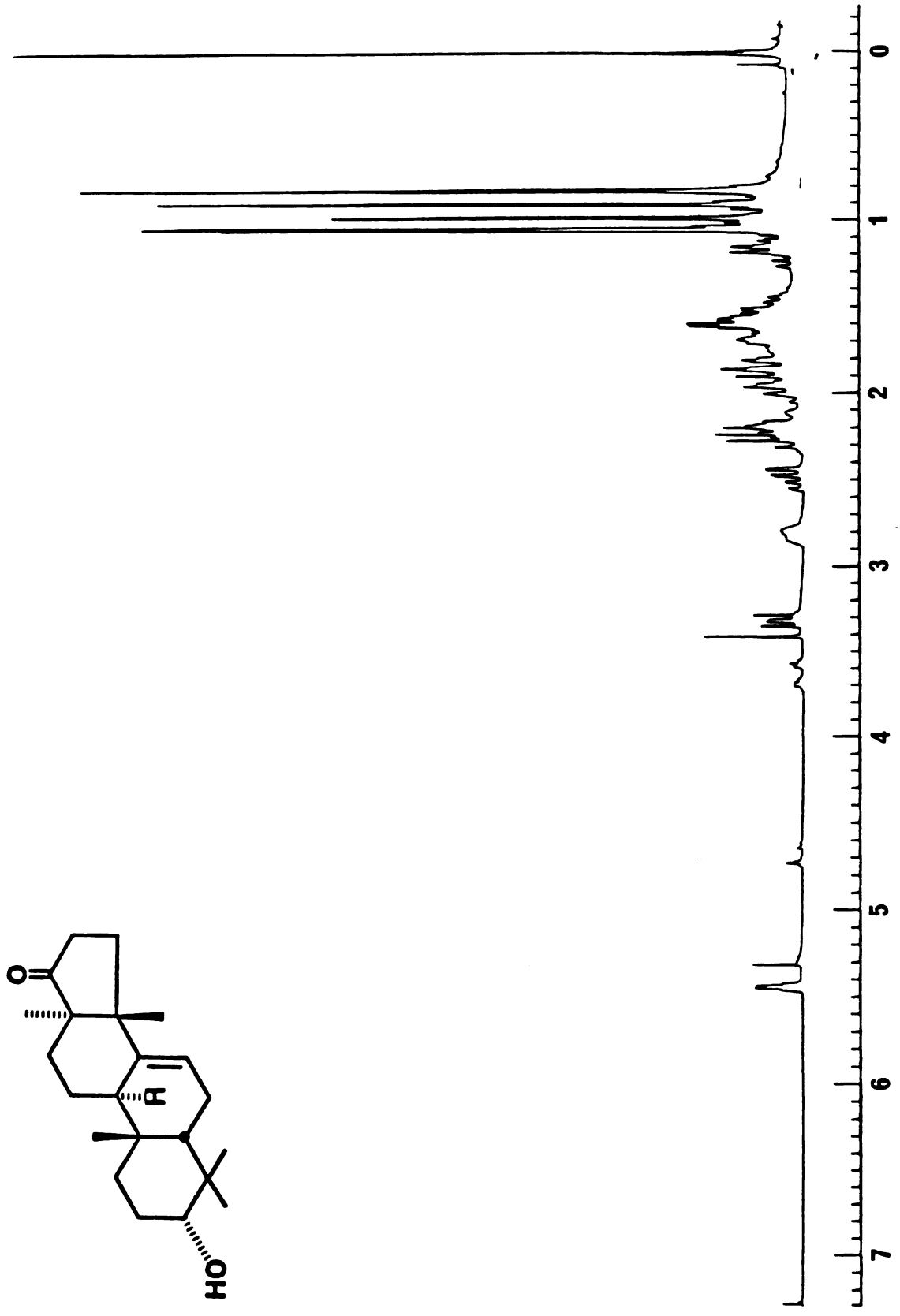

Figure 67. PMR spectrum of 73.

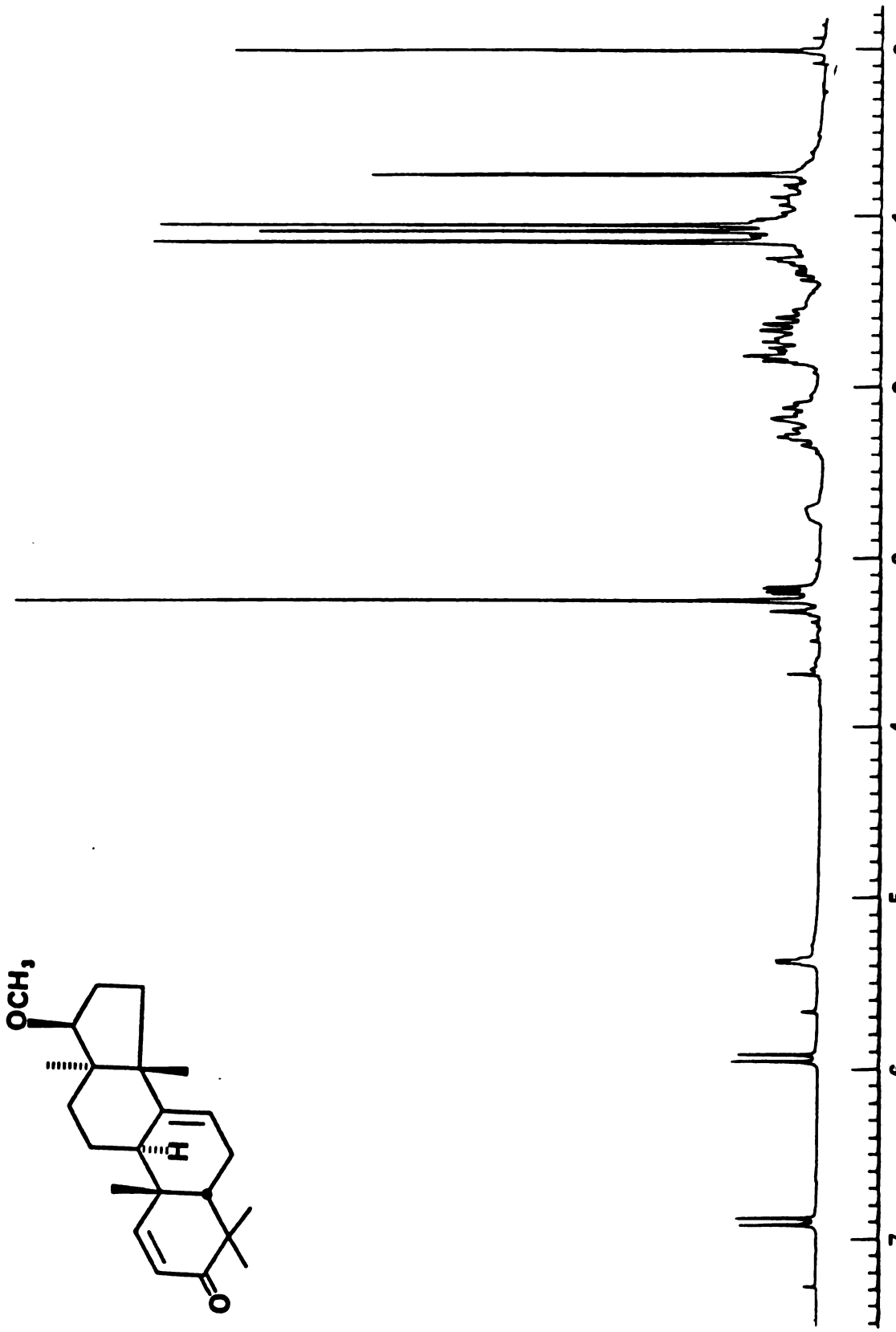

Figure 68. PMR spectrum of 85.

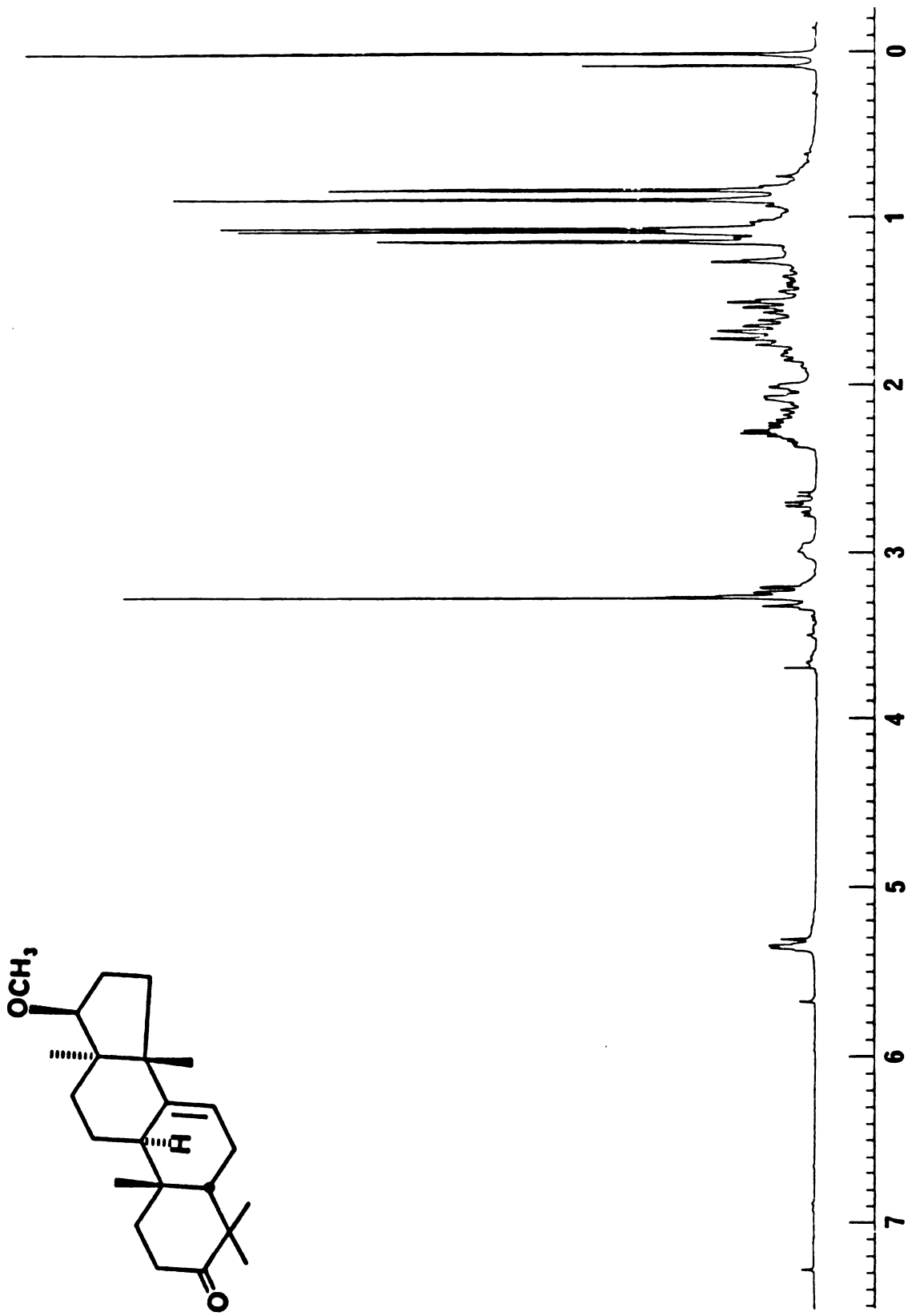

Figure 69. PMR spectrum of 88.

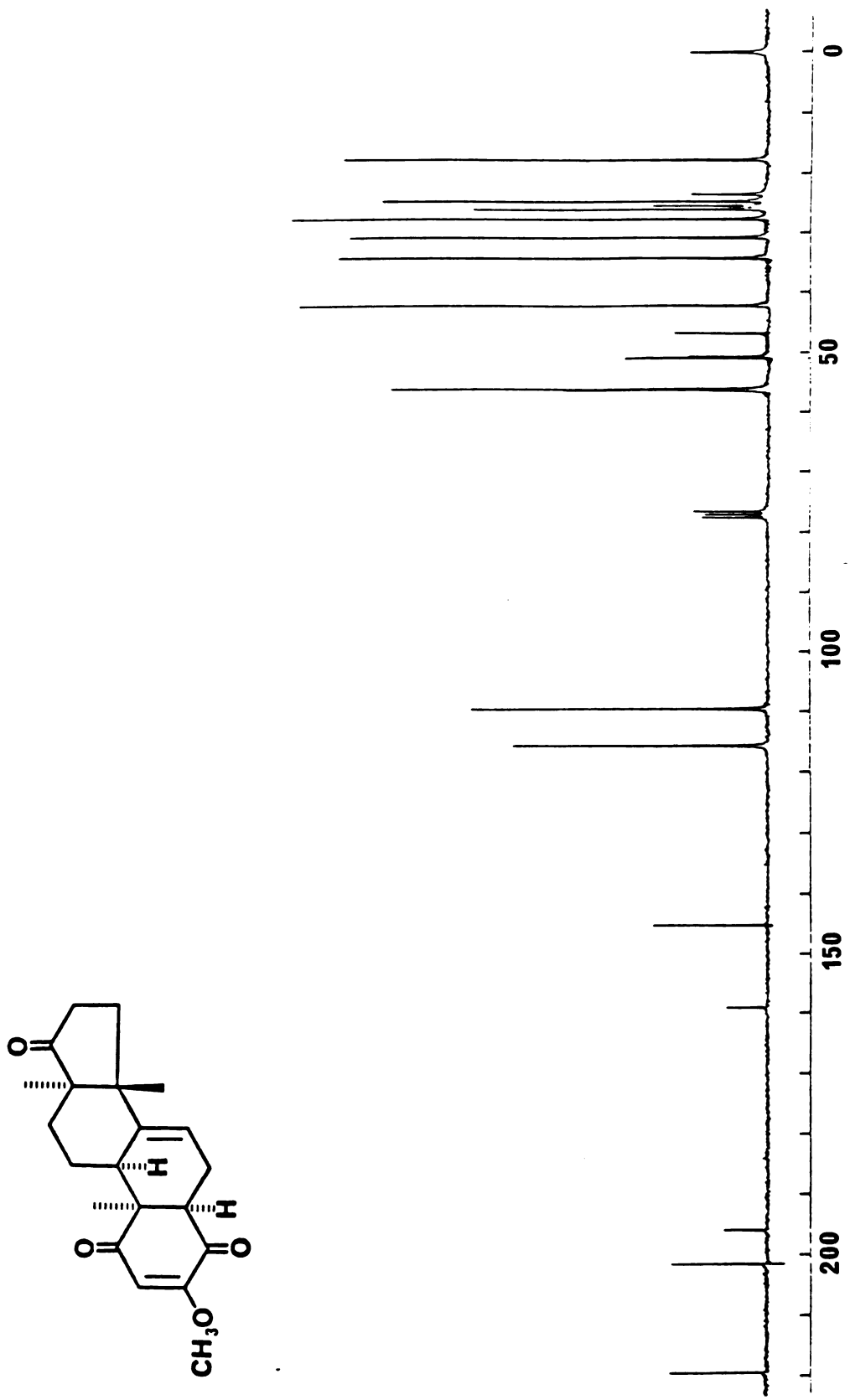

Figure 70. CMR spectrum of 29.

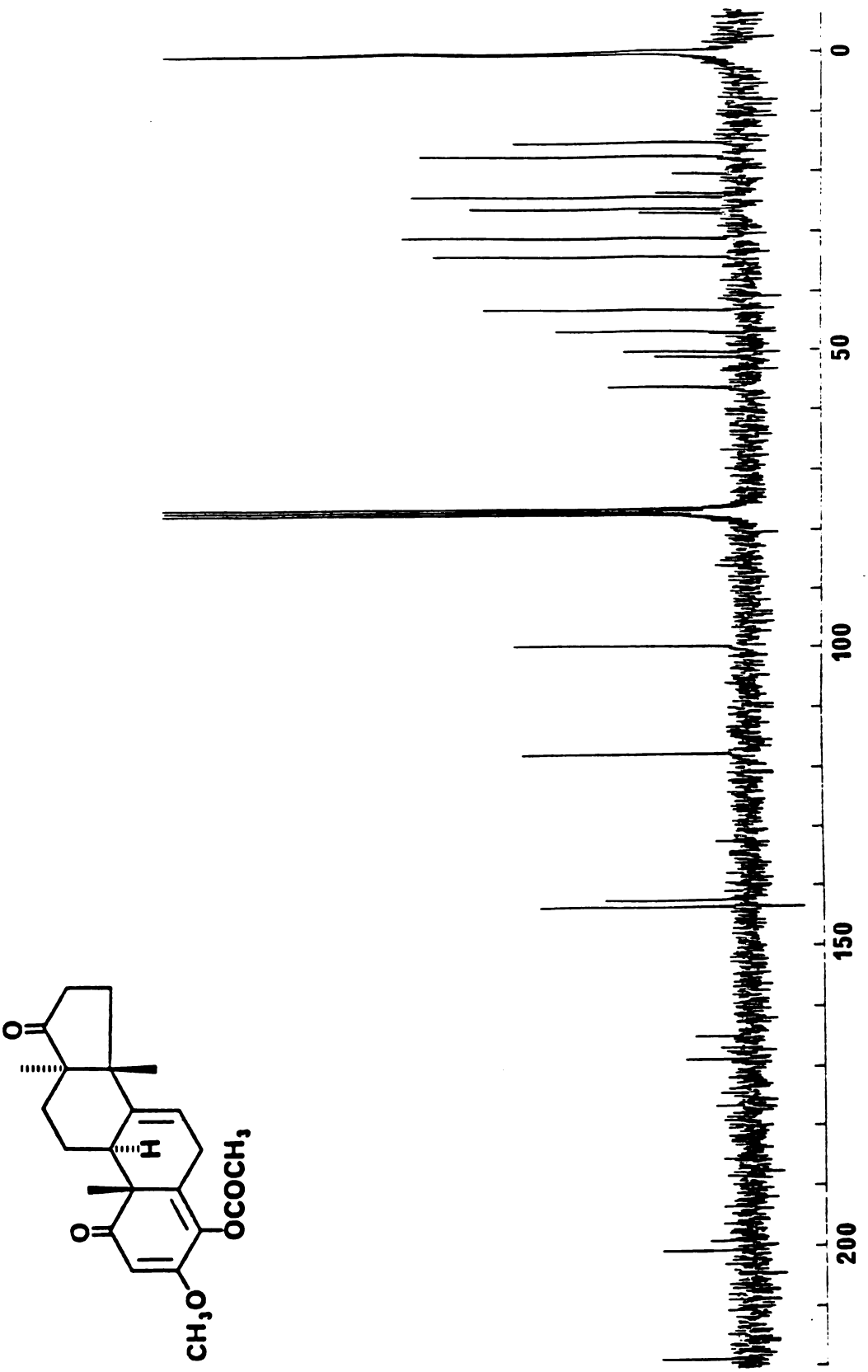

Figure 71. CMR spectrum of 62.

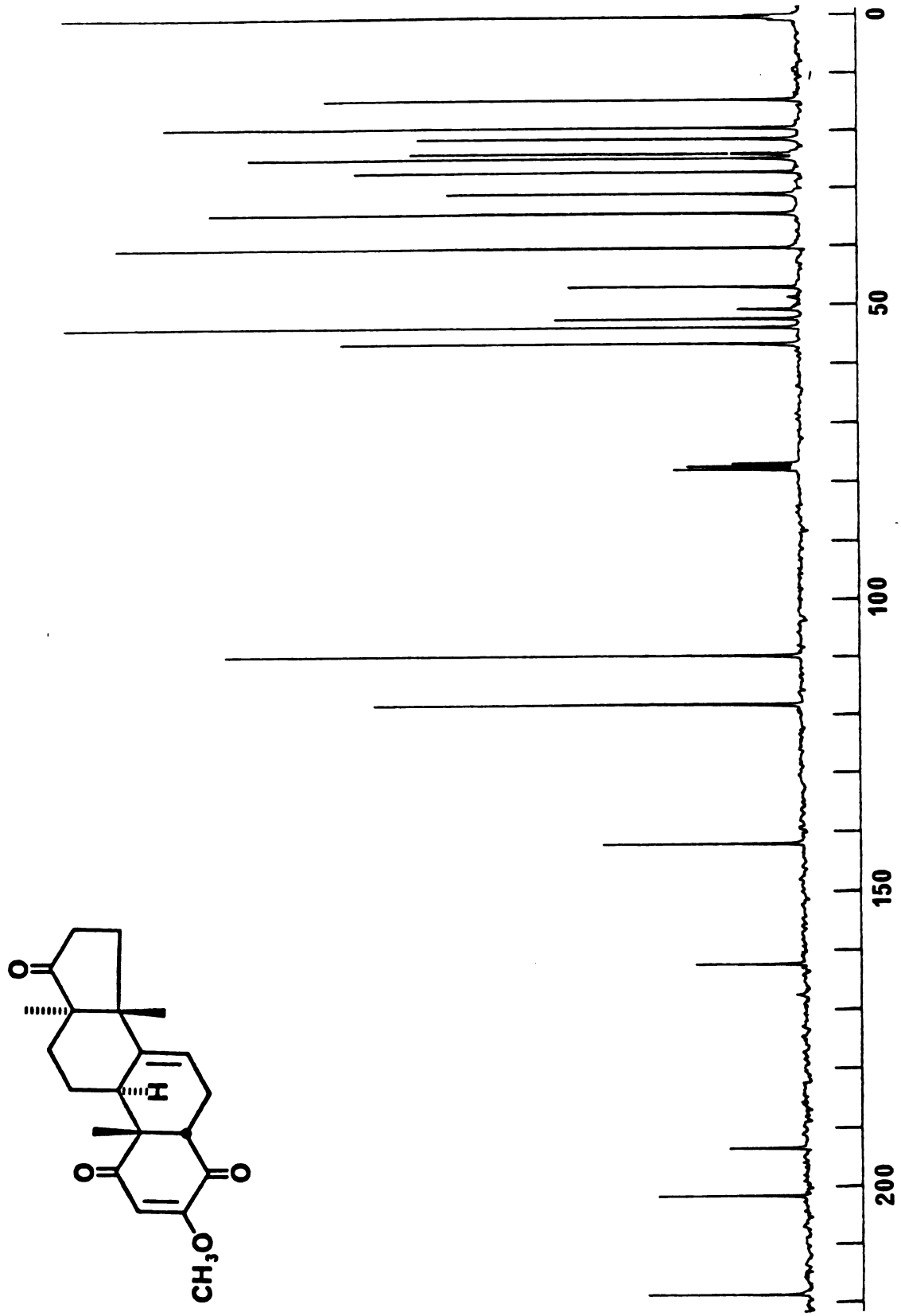

Figure 72. CMR spectrum of 70.

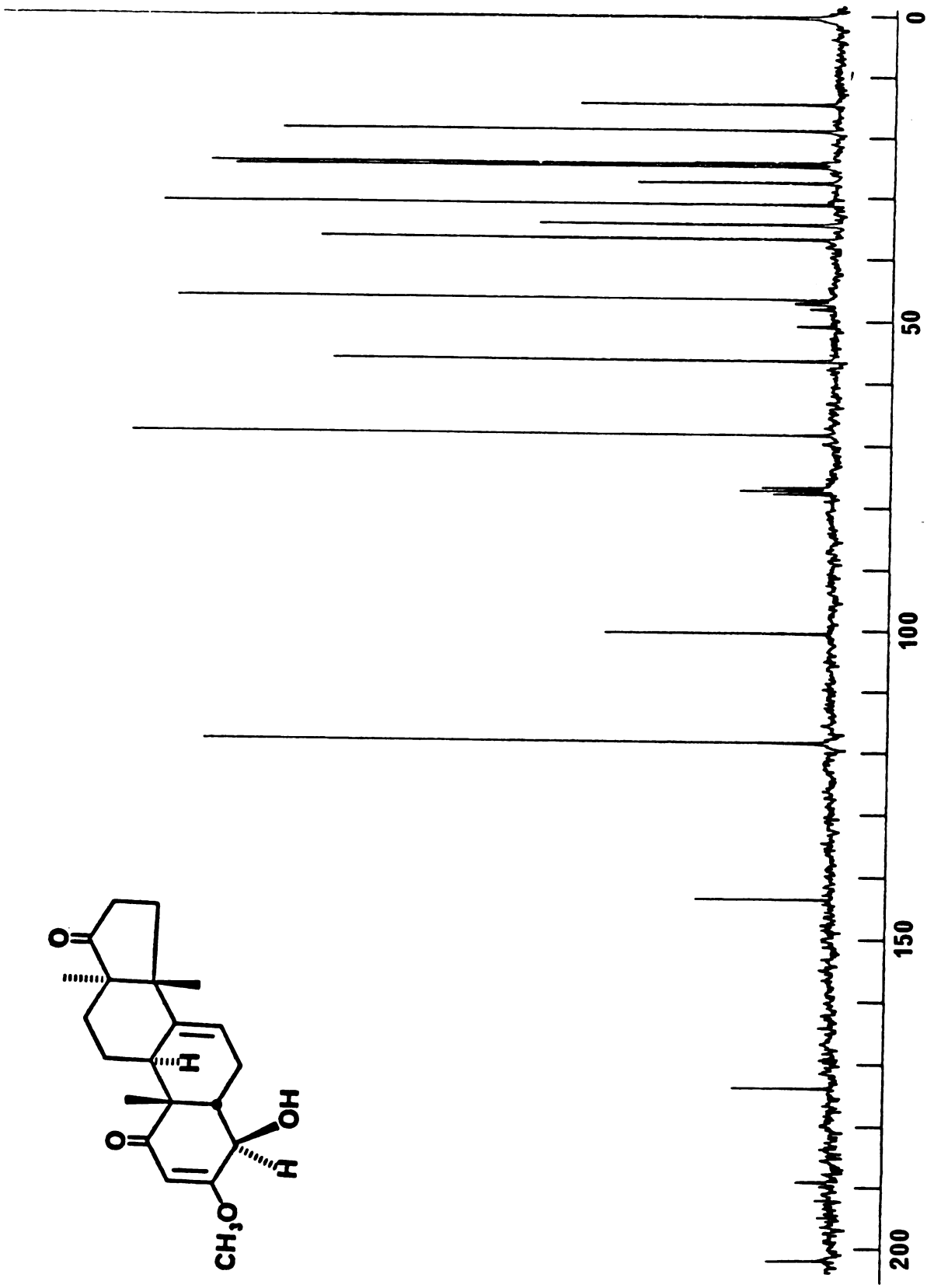

Figure 73. CMR spectrum of 79.

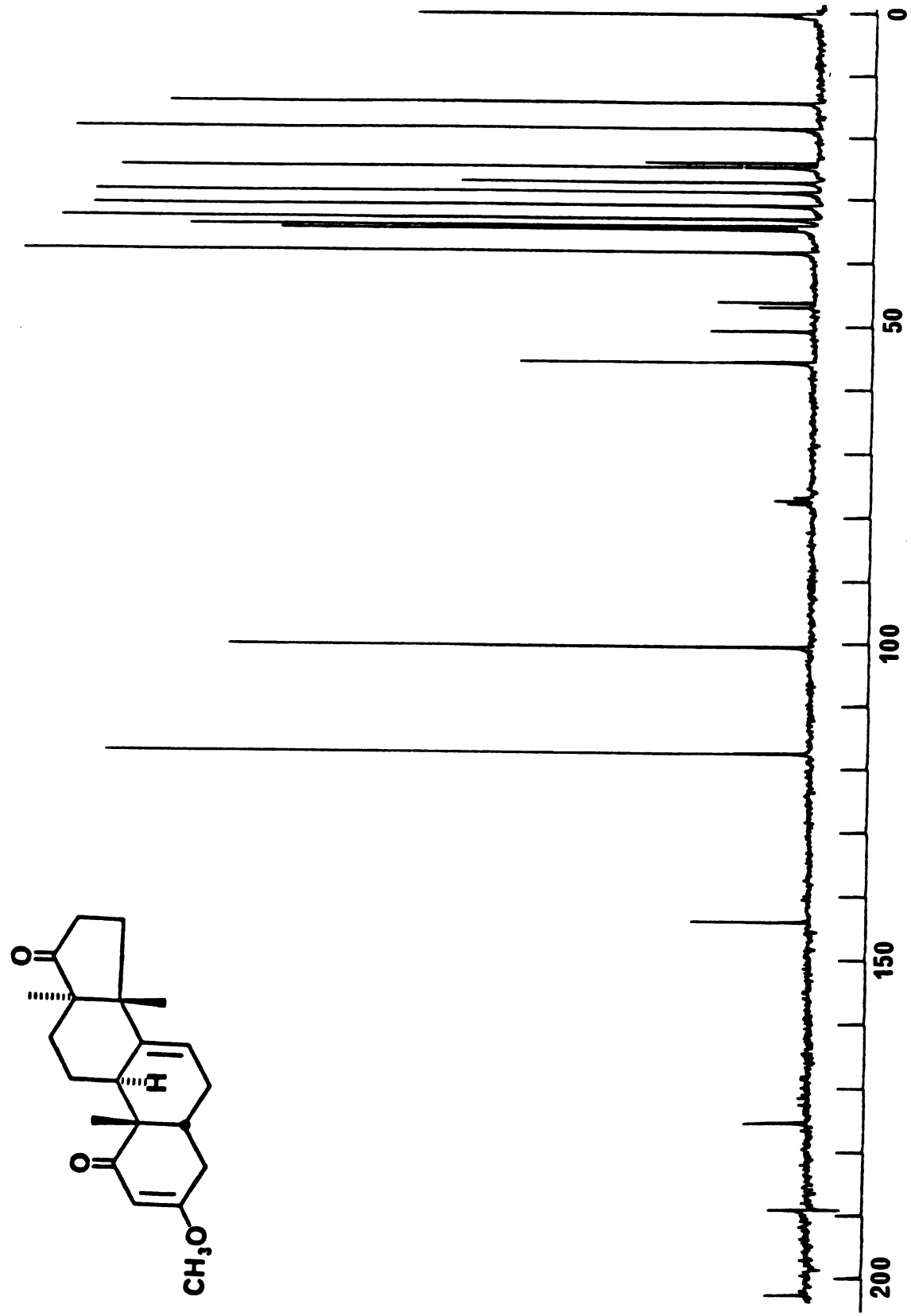

Figure 74. CMR spectrum of 83.

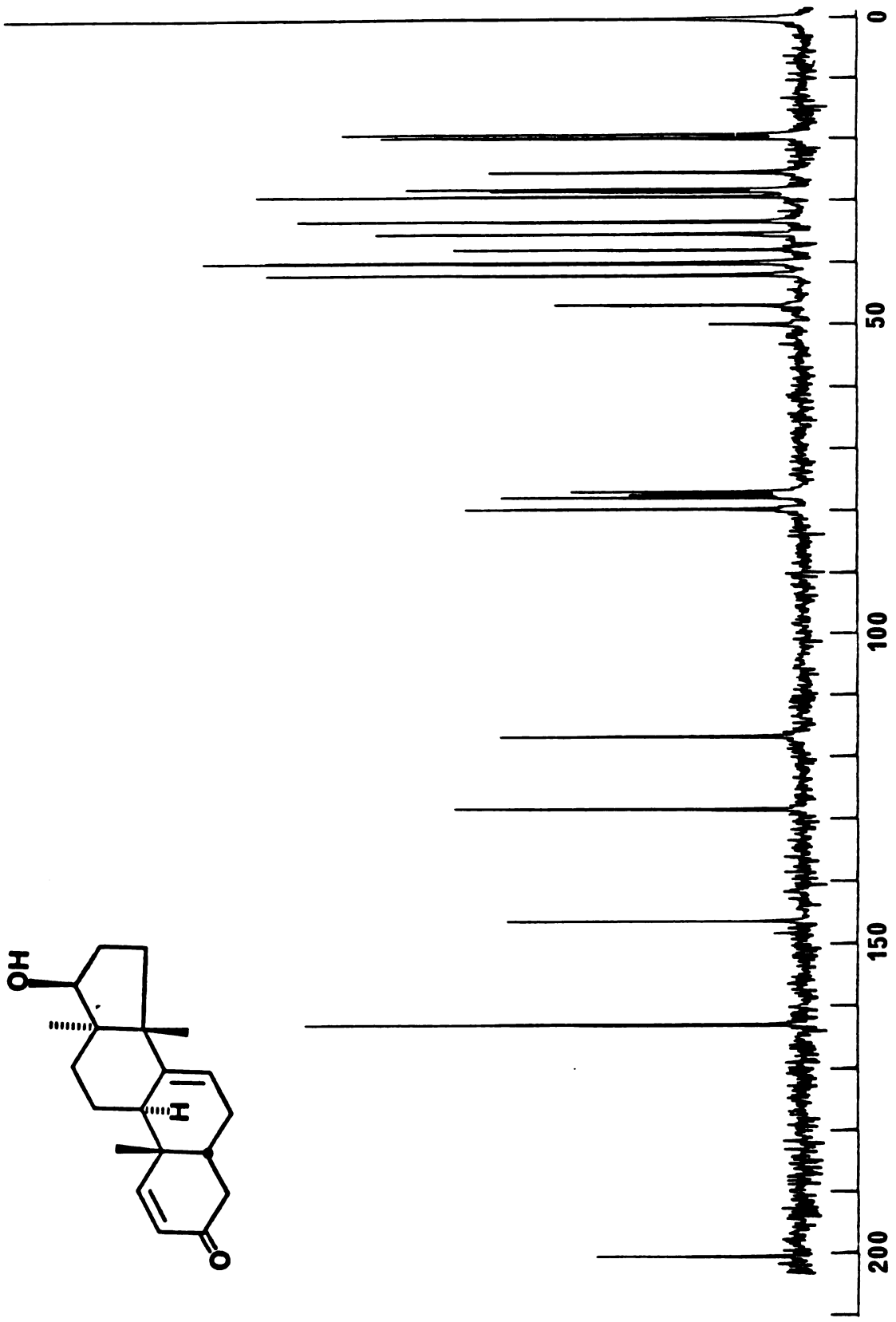

Figure 75. CMR spectrum of 81.

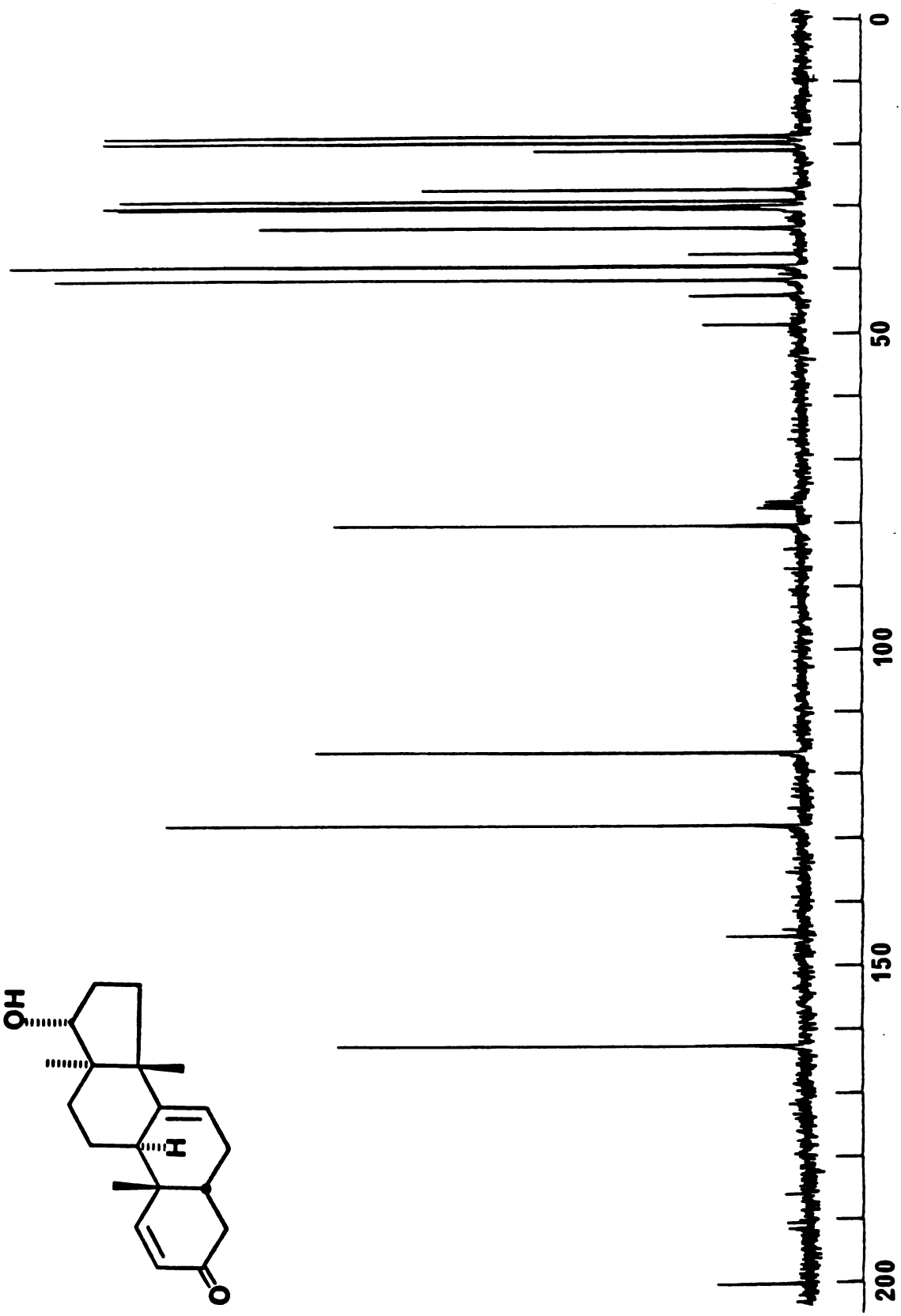

Figure 76. CMR spectrum of 82.

BIBLIOGRAPHY

We have all drunk from wells we did not dig, warmed ourselves by fires we did not build.

-Author unknown-

BIBLIOGRAPHY

1. (a) Geissman, T.A.; and Crout, D.H.G.; "Organic Chemistry of Secondary Plant Metabolism", Freeman, Cooper & Company, San Francisco, 1969; (b) Ourisson, G.; Crabbé, P.; and Rodig, O.R.; "Tetracyclic Triterpenes", Holden-Day, Inc., San Francisco, 1964; (c) de Nayo, P.; "The Higher Terpenoids", Interscience Publishers, Inc., New York, 1959.

2. Newbold, G.T.; and Spring, F.S.; J. Chem. Soc. 1944, 249.

3. Barton, D.H.R.; McGhie, J.F.; Pradhan, M.K.; and Knight, S.A.; J. Chem. Soc., 1955, 876.

4. Woodward, R.B.; Patchett, A.A.; Barton, D.H.B.; Ives, D.A.J.; and Kelly, R.B.; J. Chem. Soc., 1956, 1131.

5. van Tamelen, E.E.; and Anderson, R.J.; J. Amer. Chem. Soc., 1972, 94, 8225. See also van Tamelen, E.E.; and Murphy, J.W.; J. Amer. Chem. Soc., 1970, 92, 7204.

6. Grimm, K.; Venkataramani, S.; and Reusch, W.; J. Amer. Chem. Soc., 1971, 95, 270.

7. Eder, U.; Sauer, G.; and Wiechert, R.; Angew. Chem.: Internat. Edit., 1971, 10, 496.

8. (a) Johnson, W.S.; Banerjee, D.K.; Schneider, W.P., and Gutsche, C.D.; J. Amer. Chem. Soc., 1950, 72, 1426; (b) Johnson, W.S.; and Chinn, L.J.; J. Amer. Chem. Soc., 1951, 73, 4987; (c) Johnson, W.S.; Banerjee, D.K.; Schneider, W.P.; Gutsche, C.D.; Shelberg, W.E.; and Chinn, L.J.; J. Amer. Chem. Soc., 1952, 74, 2832.

9. Bischofberger, K.; and Bull, J.R.; J. Chem. Soc., Chem. Commun., 1982, 1051.

10. Johnson, W.S.; Marshall, J.A.; Keana, J.F.W.; Franck, R.S.; Martin, D.G.; and Baeur, V.J.; Tetrahedron, 1966, 22, Suppl. 8, 541.

11. Lora-Tomayo, M.; and Corrall, C.; An. Real. Soc. Espan. Fis. Quim., 1952, Ser. B 48, 693.

12. Alberola, A.; Lora-Tomayo, M.; Delkey, A.; Soto, J.L.; and Soto, M.; An. Real. Soc. Espan. Fis. Quim. 1963, Ser B 59, 151.

13. Tou, J.S.; and Reusch, W.; J. Org. Chem., 1980, 45, 5012.

14. Bohlmann, F.; Mathar, W.; and Schwarz, H.; Chem. Ber., 1977, 110, 2028.

15. Inouye, Y.; and Kakisawa, H.; Bull. Chem. Soc. Japan, 1971, 44, 563.

16. Lora-Tomayo, M.; Tetrahedron, 1958, 4, 17.

17. Denmark, S.E.; and Germanias, J.P.; Tetrahedron Lett., 1984, 25, 1231.

18. Brown, H.C.; Brewster, J.H.; and Shechter, H.; J. Amer. Chem. Soc., 1954, 76, 467.

19. Brown, H.C.; Ihikawa, K.; Tetrahedron, 1957, 1, 221.

20. Martin, J.L.; Tou, J.S.; and Reusch, W.; J. Org. Chem., 1979, 44, 3666.

21. Cohen, N.; Banner, B.L.; Eichel, W.F.; Valenta, Z.; and Dickinson, R.A.; Synth. Comm., 1978, 8, 427.

22. Hollingshead, D.M.; Howell, S.C.; Ley, S.V.; Mohan, M.; Ratcliffe, N.M.; and Worthington, P.A.; J. Chem. Soc., Perkin I, 1983, 1579.

23. Sauer, J.; Angew Chem. Internat. Edit., 1966, 5, 211.

24. Sauer, J.; Angew Chem. Internat. Edit., 1967, 6, 16.

25. Andreev, V.M.; and Andreeva, L.K.; in "Organic Compounds: Reactions and Methods", Kazanskii, B.A.; Knunyants, I.L.; Shgmyakin, M.M.; and Mel'Nikov, N.N.; editors, volume 21, Plenum Press, New York, 1973.

26. Tou, J.; Ph.D. Dissertation, Michigan State University, 1979.

27. Danishefsky, S.; Schuda, P.; and Kato, K.; J. Org. Chem., 1976, 41, 1081.

28. Liotta, D.; Saindane, M.; and Barnum, C.; J. Org. Chem., 1981, 46, 3370.

29. Liotta, D.; Saindane, M.; and Waykole, L.; J. Amer. Chem. Soc., 1983, 105, 2922.

30. Liotta, D.; Saindane, M.; and Barnum, C.; J. Amer. Chem. Soc., 1981, 103, 3224.

31. Eaton, P.; and Yates, P.; J. Amer. Chem. Soc., 1960, 82, 4436.

32. Lutz, E.F.; and Bailey, G.M.; J. Amer. Chem. Soc., 1964, 86, 3899.

33. Stojanac, Z.; Dickinson, R.A.; Stojanak, N.; Woznow, R.J.; and Valenta, Z.; Can. J. Chem., 1975, 53, 616.

34. (a) Dickinson, R.A.; Kubela, R.; MacAlpine, G.A.; Stojanac, Z.; and Valenta, Z.; Can. J. Chem., 1972, 50, 2377; (b) Das, J.; Kubela, R.; MacAlpine, G.A.; Stojaniac, Z.; and Valenta, Z.; Can. J. Chem., 1979, 57, 3308.

35. Hawthorne, M.F.; and Reintjes, M.; J. Amer. Chem. Soc., 1965, 87, 4585.

36. Hendrickson, J.B.; and Singh, V.; J. Chem. Soc., Chem. Comm., 1983, 837.

37. Childs, R.F.; Mulholland, D.L.; and Nixon, A.; Can. J. Chem., 1982, 60, 801.

38. Rochleder and Heldt; Annalen, 1843, 48, 11.

39. Stork, G.; Chem. and Ind., 1955, 915.

40. Barton, D.H.R.; and Quinkert, G.; J. Chem. Soc., 1960, 1.

41. (a) Quinkert, G.; Angew. Chem. Internat. Ed., 1965, 4, 211; (b) Quinkert, G.; Angew. Chem. Internat. Ed., 1972, 11, 637; (c) Quinkert, G.; Angew. Chem. Internat. Ed., 1972, 11, 1072; (d) Quinkert, G.; Bronstert, B.; Egert, D.; Michaelis, P.; Jurges, P.; Prescher, G.; Syldatk, A.; and Perkampus, A.; Chem. Ber., 1976, 109, 1332; (e) Quinkert, G.; Engert, H.; Ceckh, F.; Stegk, A.; Haupt, E.; Leibfritz, D.; and Rehm, D.; Chem. Ber., 1979, 112, 310.

42. Quinkert, G.; Photochem. Photobiol., 1968, 7, 783.

43. X-ray crystallographic structure determinations on 62 and 73 were graciously performed by Dr. Paul Williard, Brown University, Providence, Rhode Island.

44. Shau, J; Ph.D. Dissertation, Michigan State University, 1979.

45. Still, W.C.; Kahn, M.; and Mitra, A.; J. Org. Chem., 1978, 43, 2923.

46. Johnson, W.S.; J. Amer. Chem. Soc., 1953, 75, 1498.

47. Audouin, M.; and Cevisalles, J.; Tetrahedron, 1983, 39, 2799.

48. Speziale, J.A.; Stephens, J.A.; and Thompson, Q.E.; J. Amer. Chem. Soc., 1954, 76, 5011.

49. Holder, R.W.; and Matturro, M.G.; J. Org. Chem., 1977, 42, 2166.

50. Krishnamurthy, S.; and Brown, H.C.; J. Org. Chem., 1982, 47, 276.

51. (a) Masemune, S.; Rossy, P.A.; Bates, G.S.; J. Amer. Chem. Soc., 1973, 95, 6152; (b) Hutchins, R.O.; Maryanoff, B.E.; and Milewski, C.A.; J. Chem. Soc., Chem. Comm., 1971, 1097; (c) Fujimoto, Y.; and Tatsuno, T.; Tetrahedron Lett., 1976, 3325.

52. Bhatt, M.J.; and Kulkarni, S.U.; Synthesis, 1983, 249.

53. (a) McOmie, J.F.W.; Watts, M.L.; and West, D.W.; Tetrahedron, 1968, 24, 2289; (b) Niwa, H.; Hida, T.; and Yamada, K.; Tetrahedron Lett., 1981, 22, 4239.

54. (a) Jung, M.E.; and Lyster, M.A.; J. Org. Chem., 1977, 42, 3761; (b) Jung, M.E.; and Lyster, M.A.; Org. Syn., 19 , 59, 35; (c) Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R.; J. Org. Chem., 1979, 44, 1247.

55. (a) Osborn, J.A.; Jardine, J.F.; and Wilkinson, G.; J. Chem. Soc. (A), 1966, 1711; (b) Djerassi, C.; and Gutzwiller, J.; J. Amer. Chem. Soc., 1966, 88, 4537.

56. Olah, G.A.; Gupta, B.G.B.; and Fung, A.P.; Synthesis, 1980, 897.

57. Corey, E.J.; Gras, J.; and Ulrich, P.; Tetrahedron Lett., 1976, 809.

58. Corey, E.J.; and Schmidt, G.; Tetrahedron Lett., 1979, 399.

59. Danson, M.C.; Halsall, T.G.; Jones, E.R.H.; and Robins, P.A.; J. Chem. Soc., 1953, 586.

60. Dawson, M.C.; Halsall, T.G.; Jones, E.R.H.; Meakins, G.D.; and Phillips, P.C.; J. Chem. Soc., 1956, 3172.

61. Pike, W.T.; Summers, G.H.R.; and Klyne, W.; J. Chem. Soc., 1965, 7199.