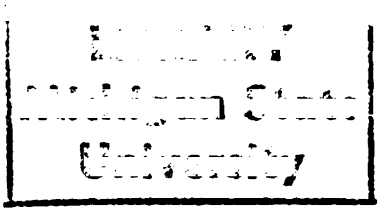

This is to certify that the

dissertation entitled

STUDIES TOWARD THE TOTAL SYNTHESIS OF TETRACYCLIC TERPENES: (+)BUTYROSPERMOL AND (+)EUPHOL

presented by

Hyun Ok Ok

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

William Reusch
Major professor

Date May 28, 1986



O-12771

# STUDIES TOWARD THE TOTAL SYNTHESIS OF TETRACYCLIC TRITERPENES: (±)BUTYROSPERMOL AND (±)EUPHOL

By

Hyun Ok Ok

A DISSERTATION

Submitted to

Michigan State University

in partial fulfillment of the requirements

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DOCTOR OF PHILOSOPHY

Department of Chemistry

1986

## ABSTRACT

### STUDIES TOWARD THE TOTAL SYNTHESIS OF TETRACYCLIC TERPENES: (±)BUTYROSPERMOL AND (±)EUPHOL

By

Hyun Ok Ok

Studies toward the total synthesis of tetracyclic terpenes (±)butyrospermol and its double bond isomer (±)euphol from the (±)5-epibutyrospermol ring system are presented.

Conversion of **9** to **47** followed the procedures for (±)5-epibutyrospermol. The introduction of a double bond at C-4(5) and the subsequent gem-di-methylation generated β-ring homodiene system **63**, and then the dissolving metal reduction of homodiene provided the trans-AB-ring fused tetracyclic core **64**. The conformation of this trans-AB-ring fusion came after deprotection and functional group manipulation to give **69**. Comparison of **69** with its C-5 epimer **49**, prepared and characterized in an earlier study, provided unequivical evidence for these assignments.

With the tetracyclic core of butyrospermol **69** in hand, the attachment of the $C_8H_{15}$ side-chain with control of the configuration at C-17 and C-20 was examined with model ketone **12**.

Stereoselective addition of methylthiomethyl lithium led to the epoxide **80**, and treatment with ethoxyethynyl magnesium bromide, followed by reduction and then acid-catalyzed rearrangement, produced the $\alpha,\beta$-unsaturated aldehyde **83**. Subsequent reduction and Wittig olefination provided the final model side-chain system. Configuration at C-17 and C-20 was studied by comparing carbon-13 chemical shifts of equivalent natural products.

**For my family, for their love,**

**support and understanding.**

## ACKNOWLEDGEMENTS

The author wishes to express her deepest appreciation to Professor William Reusch for his guidance and encouragement throughout this study. Appreciation is extended to Professor Steven P. Tanis for his helpful suggestions and informative discussions.

Thanks are extended to my colleagues for their friendship and many helpful discussions during the past years. Many thanks also goes to Miss Tonya Acre for her help in preparing this manuscript.

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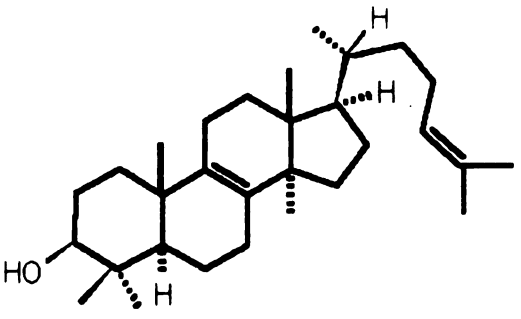
# INTRODUCTION

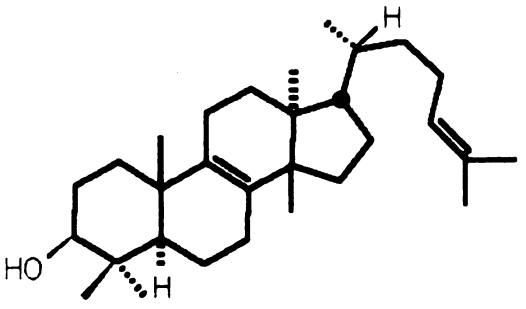
The triterpenoids form the largest group among the terpenoids. They are widely distributed in the plant kingdom, either in the free state or as esters or glycosides, although a few important members have been found in the animal kingdom. These include squalene, first isolated from shark liver oil, and a number of tetracyclic compounds, including lanosterol (obtained from wool fat).

Among the tetracyclic terpenes having a penhydrocyclopentanophenanthrene skeleton, the lanostanes, the euphanes and the cucurbitanes all bear trans-oriented methyl groups at C-13 and C-14. Representative structures of each group are shown below.

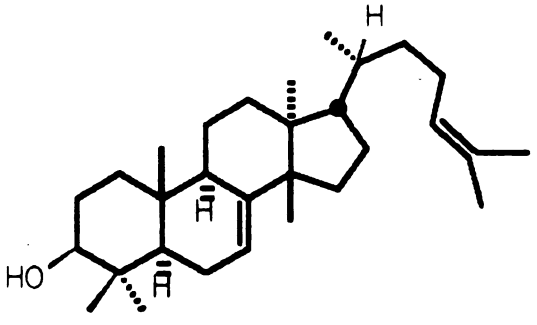
In nature, the tetracyclic triterpenes are formed by enzymatic cyclization of squalene followed by rearrangement.[1] Steroids are generated by subsequent loss of methyl groups from lanostanes. A chair-boat-chair-boat folding of squalene leads to the lanostane system, whereas a chair-chair-chair-boat conformation leads to euphol and/or tirucallol derivatives. Non-enzymatic, acid-catalyzed cyclization of appropriate polyene intermediates has also



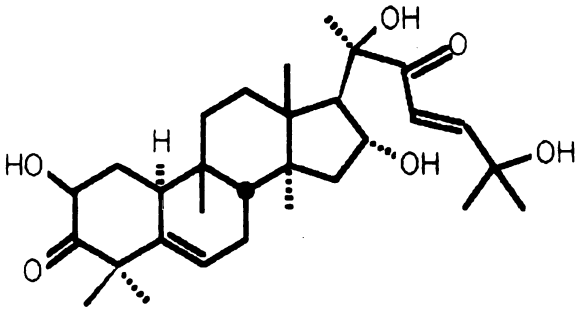

Lanosterol




Euphol

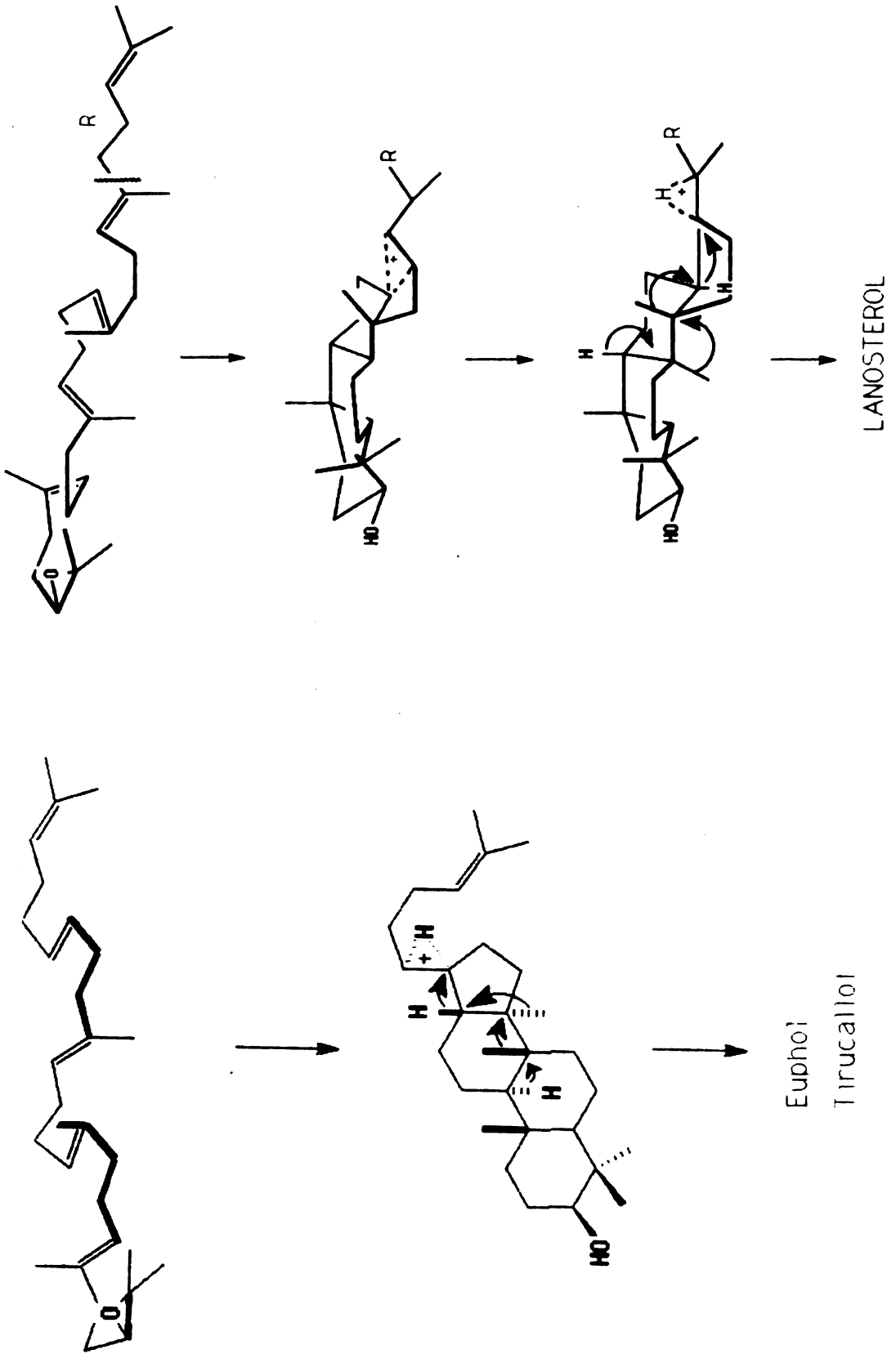


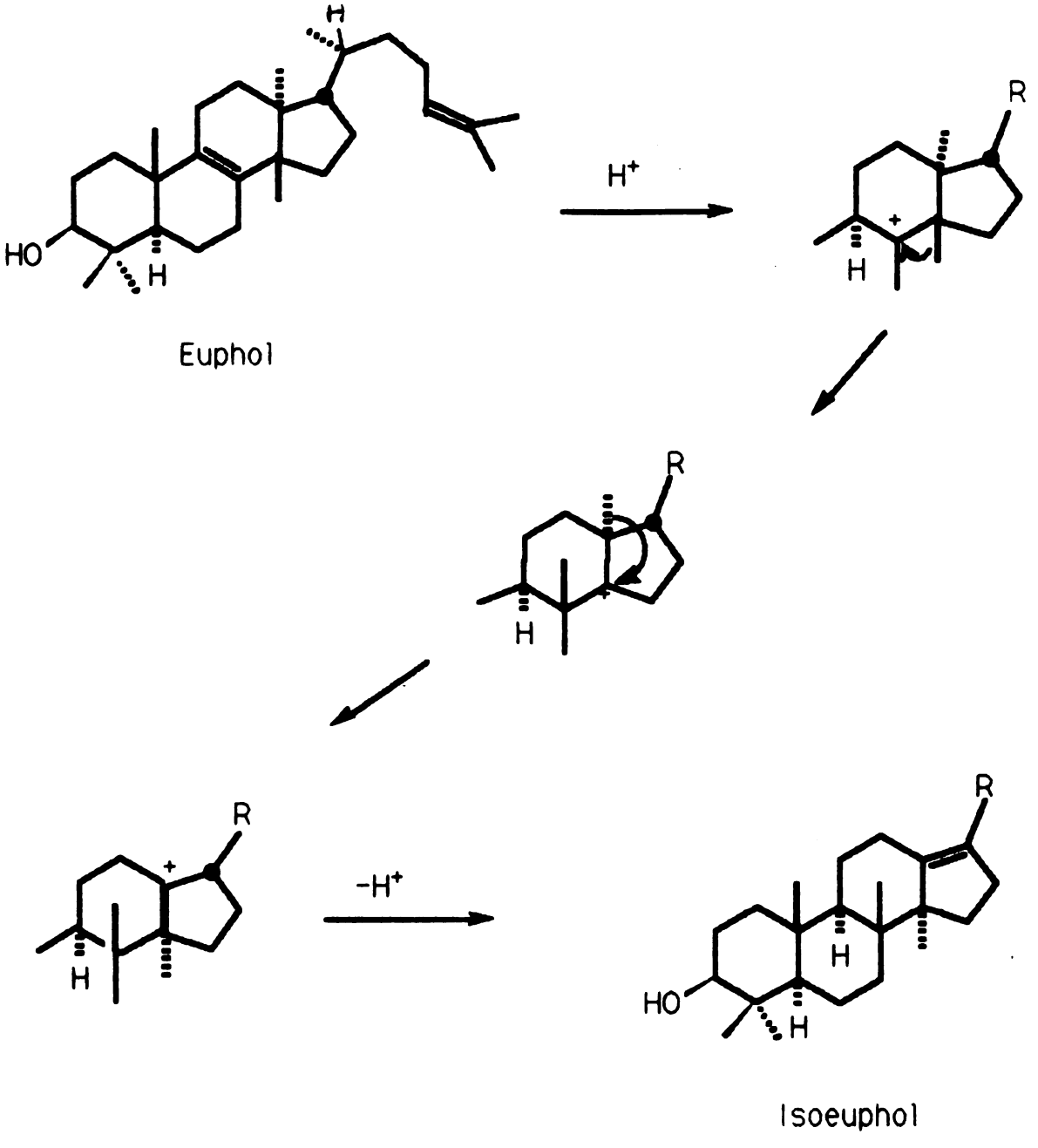

Butyropermol




Cucurbitacin I

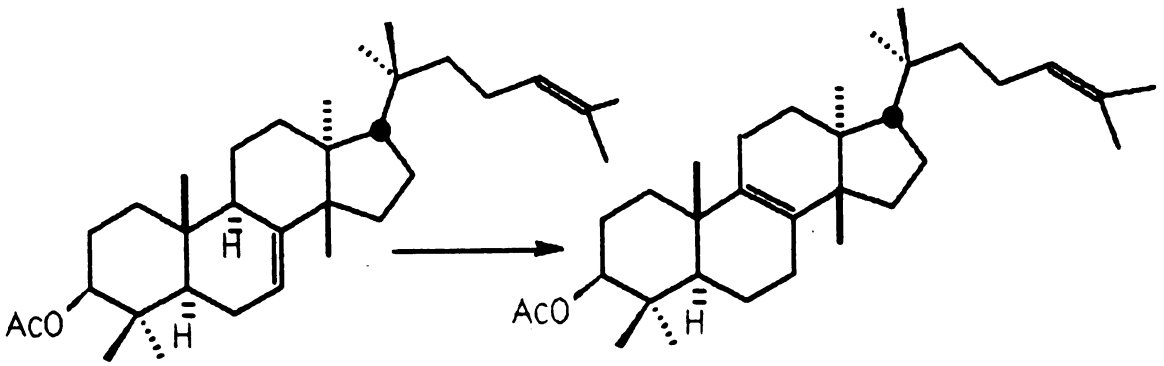
**generated the lanostane skeleton. However, the euphane skeleton cannot be obtained by such cation-induced polyene cyclization due to its facile rearrangement to the isoeuphane structure.**


R
HO
LANOSTEROL
Euphol
Tirucallol




Butyrospermol, isolated from the non-saponifiable fraction of shea-nut oil from *Butyrospermum Parkii*, was first characterized in pure form by Heibron, Jones and Robins in 1949.[2] Like so many other members of the Euphane group, it is a secondary alcohol with one easily reduced

double bond, present in the side chain, and a second double bond resistant to hydrogenation. Addition of bromine to the side chain double bond of butyrospermol acetate, followed by careful treatment with hydrogen chloride at 0°, and regeneration of the side chain ethylenic linkage by reaction with zinc gave euphenyl acetate. The acidic conditions

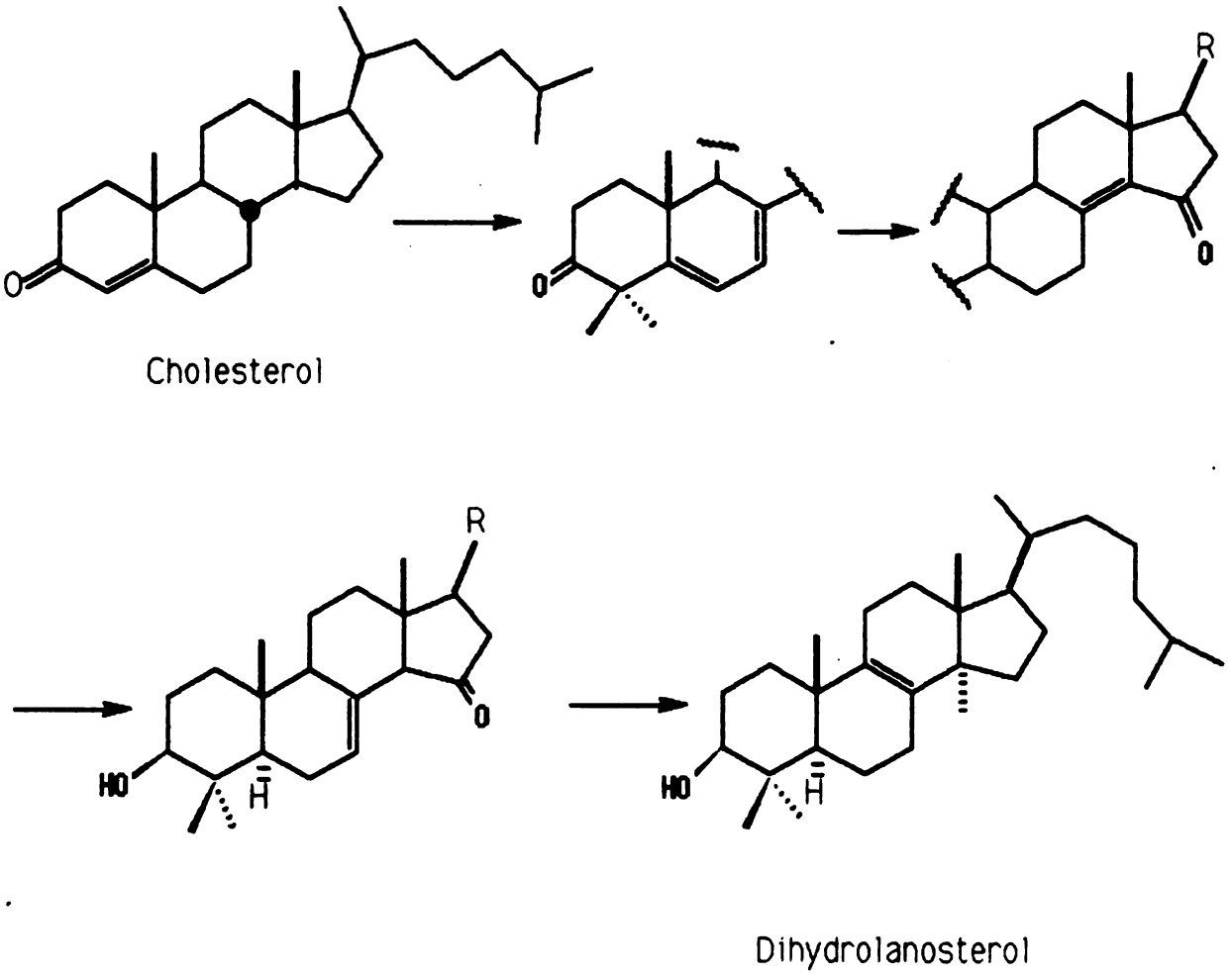



Butyrospermol acetate Euphenyl acetate

required to convert dihydrobutyrospermol to euphol are milder than those required to isomerize euphol to isoeuphol.[3]

Chemical studies of the triterpenoids started in the late nineteenth century, and 50 years have passed since the initial structural work was reported by Ruzika, *et. al.*[4] The main structural difference between steroids and tetracyclic triterpenes is the presence of three extra methyl groups, two at C-4 and one at C-14, in the latter. Despite their overall similarities, very little work has been accomplished on the total synthesis of tetracyclic triterpenes, whereas

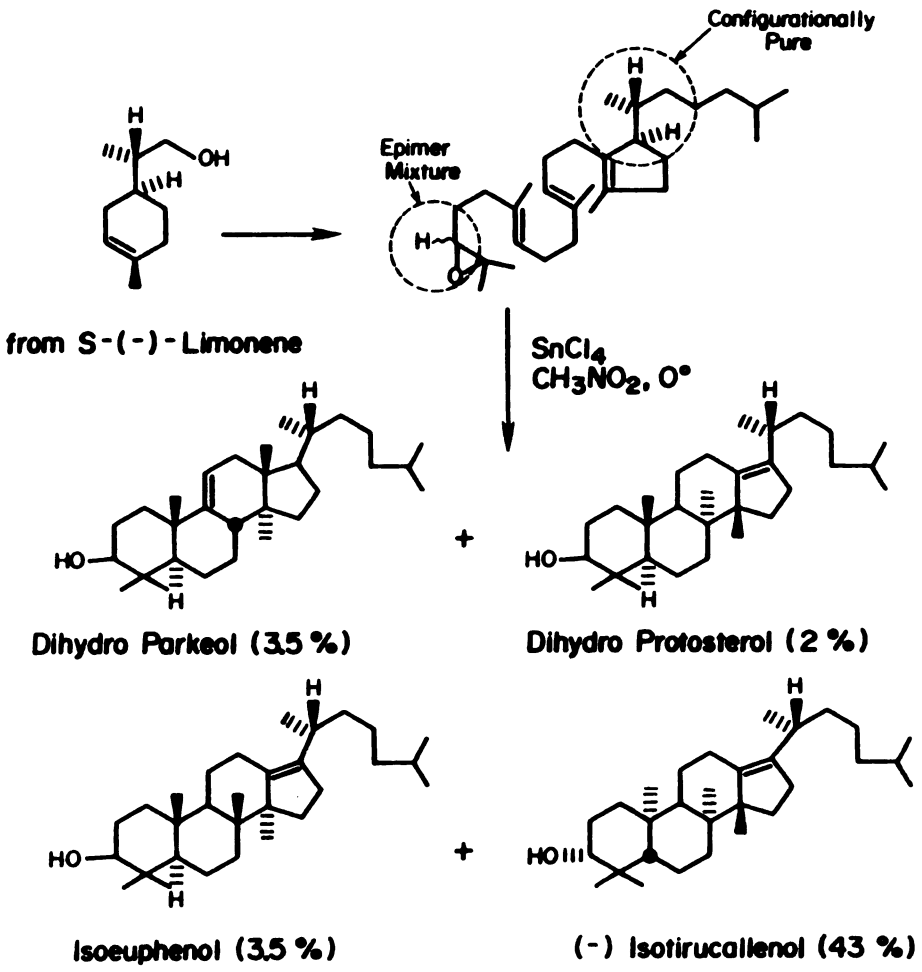
more than 100 steroid syntheses have been reported.[5] To date, two total syntheses of lanostane triterpenes have been reported, one by R. B. Woodward's group in 1954[6] and the other by E. E. van Tamelen's group in 1972.[7] These two syntheses show significantly different strategic approaches. In the Woodward approach, cholesterol served as the starting material, and the introduction of three additional methyl groups was accomplished as shown in Scheme 1. On the other




Cholesterol

Dihydrolanosterol

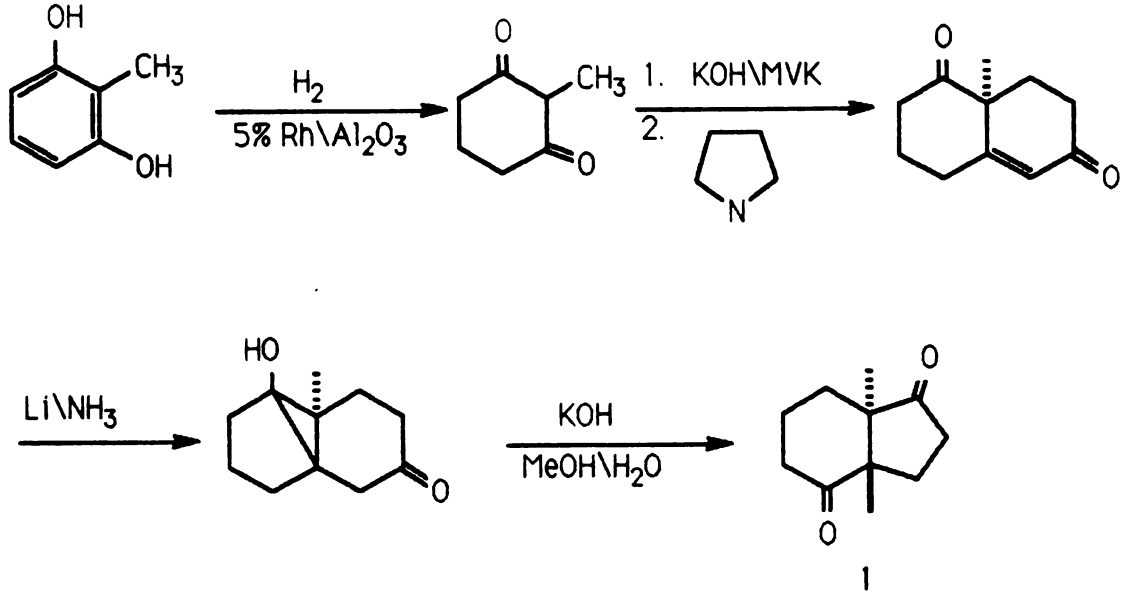
Scheme I


Configurationally Pure
Epimer Mixture
from S-(-)-Limonene
$SnCl_4$
$CH_3NO_2$, 0°
Dihydro Parkeol (3.5 %)
Dihydro Protosterol (2 %)
Isoeuphenol (3.5 %)
(-) Isotirucallenol (43 %)

Scheme II

hand, van Tamelen's synthesis applied a biomimetic strategy. A polyene precursor was synthesized from (-)-limonene, and the Lewis acid-induced cyclization of a derived epoxide gave either parkeal or isotrucallol depending on the configuration at C-3, as outlined in Scheme II. There are no reported syntheses of the euphane ring system, and due to its facile acid-induced rearrangement to the isoeuphane system[8], a polyene cyclization approach is unlikely to be effective.

Recently, the 5-epi-Euphane ring system was synthesized in this laboratory[9] starting from the well-known Wieland-Mieshler ketone, which was converted in two steps to bicyclic diketone 1.[10] The synthesis of 1 is outlined in




1

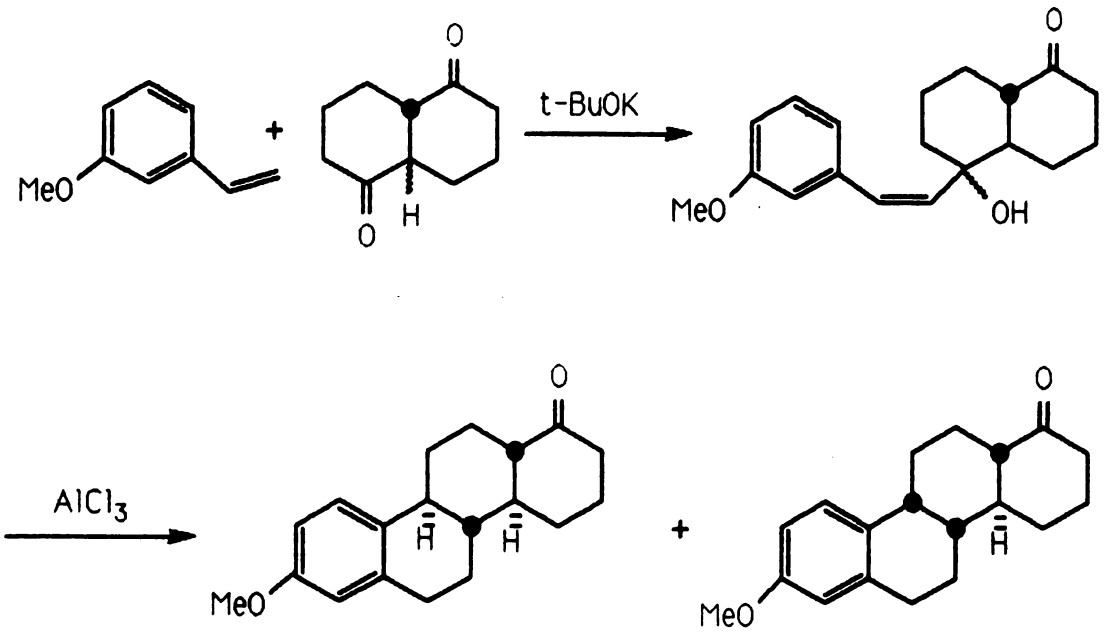
Scheme III

Scheme III. Using 1 as a starting material for the tetracyclic triterpene synthesis offers certain advantages since this compound contains the required trans dimethyl functionality found in the CD rings of these natural products. Furthermore, by using enantiomerically-pure proline in the Aldol condensation step, either antipode of the Wieland-Mieshler ketone can be obtained[11], permitting the synthesis of enantiomerically pure, as well as racemic, products.

There are several possible ways to prepare tetracyclic compounds from CD intermediates. In the total syntheses of steroids, bicyclic intermediates incorporating the C and D rings have been used to prepare both aromatic and nonaromatic steroids.[5] The assembly strategies fall into three fundamentally different categories. The first of these comprises syntheses in which ring A is first added to the initial CD fragment, followed by closure of ring B (A + CD ⟶ ACD ⟶ ABCD). In the second, the sequence of ring formation is reversed: first ring B and then ring A (CD ---> BCD ⟶ ABCD). Finally, the third method involves the formation of ring B by Diels-Alder diene condensation with the simultaneous introduction of ring A as a component part of the dienophile (CD + A ⟶ ABCD).

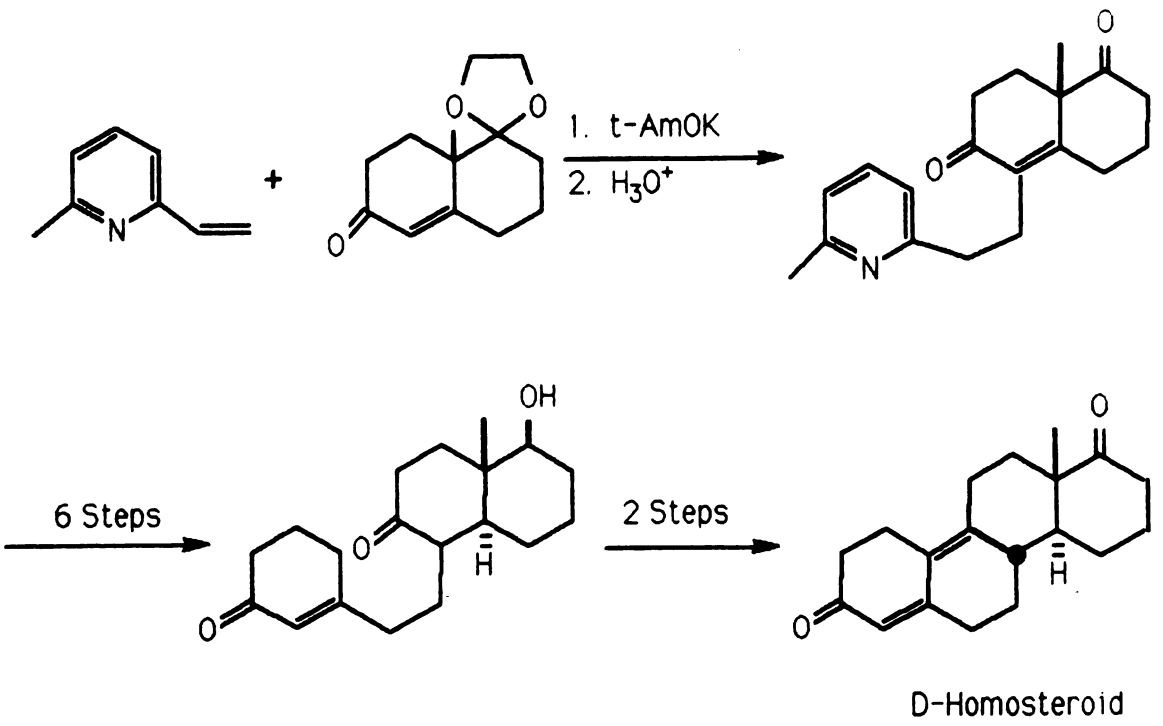
**I. A + CD ⟶ ACD ⟶ ABCD.**

**This strategy can be divided into many parts according to the type of reaction used in the condensation of the A fragment with the CD portion. The representative approaches are first, reaction of an anionic ring A with a keto function in the CD portion, as developed by Johnson in his first estrone synthesis (Scheme IV).[12] A second approach**




Scheme IV

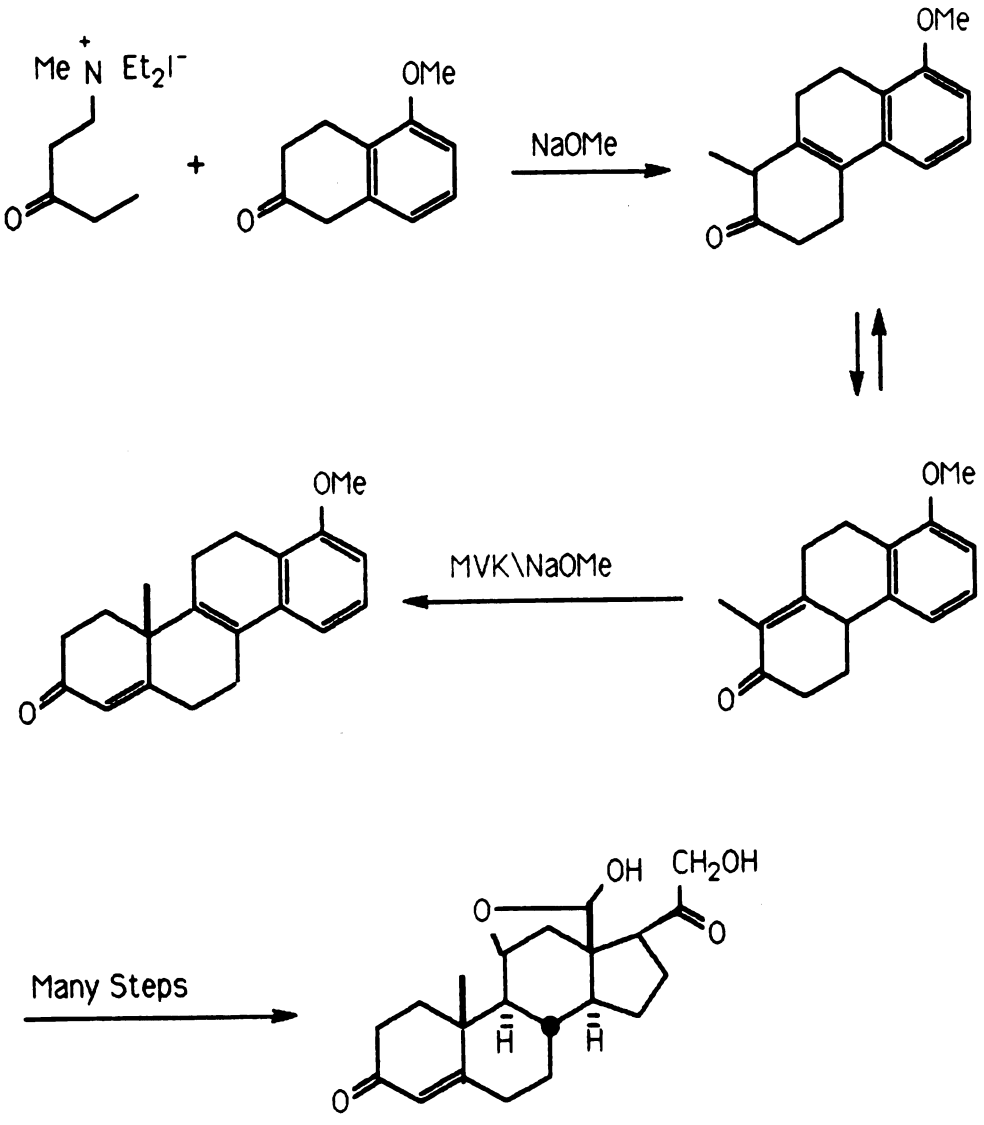
**uses an anionic derivative of the CD portion to react with A. Danishefsky, *et. al.*, were able to prepare D-homosteroids by this route, which is outlined in Scheme V.[13]**




Scheme V

II. CD ⟶ BCD ⟶ ABCD.

**Many examples of the CD ⟶ BCD ⟶ ABCD route are found in the work of W. S. Johnson and his co-workers on the synthesis of *dl*-Aldosterone derivatives.[14]**



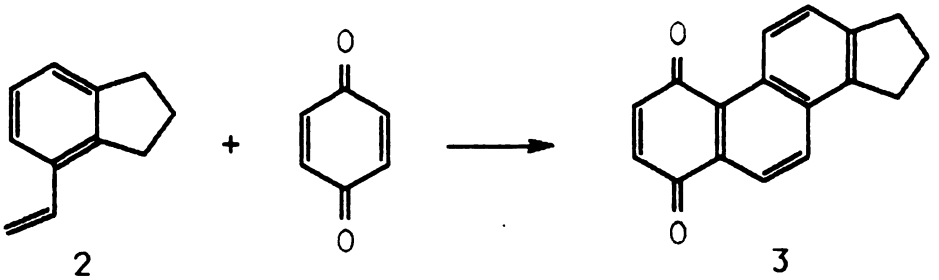

dl-Aldosterone

III. CD + A ⟶ ABCD.

**The key step in this method is a Diels-Alder diene condensation of 4-vinylindan with appropriate dienophiles; this leads simultaneously to the formation of ring B and the**

introduction of ring A. Of the three approaches, this cycloaddition is the most efficient way to form a tetracyclic system due to the generally high regio- and stereoselectivity of Diels-Alder reactions.

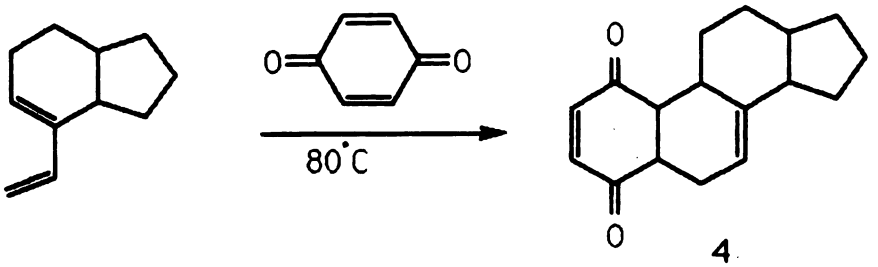
The reaction of 4-vinylindan 2 with benzoquinones lead to moderate yields of adduct 3, and an equivalent reaction

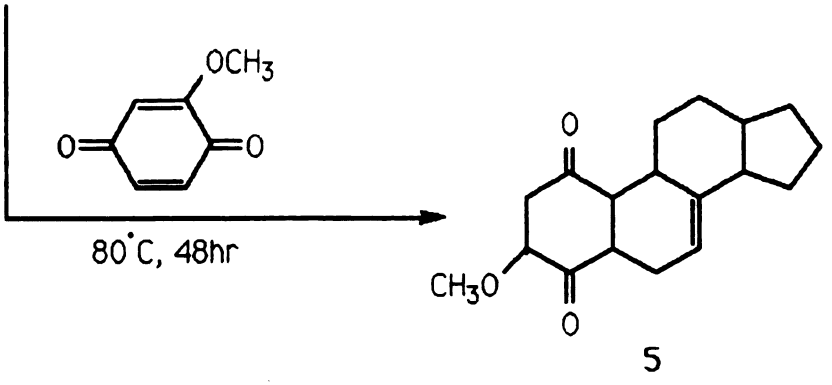



2 3

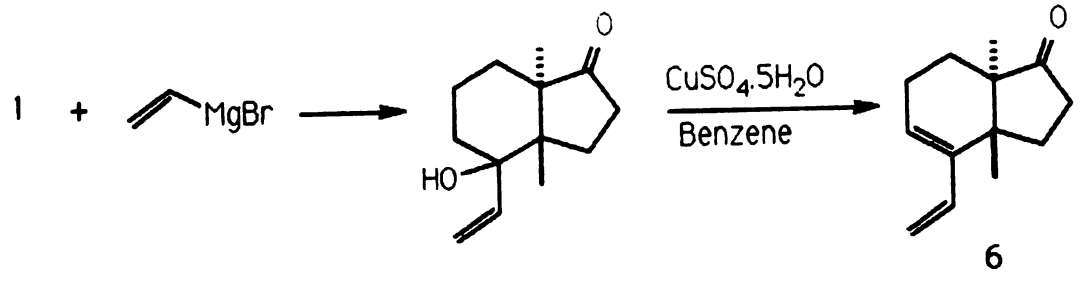
with toluquinone and methoxyquinone led to similar adducts with a substituent at C-3.[15] Similar reactions of saturated analogs of diene 2 with benzoquinone and its methoxy derivatives gave yields of about 20% of the cis-syn adducts 4 and 5, respectively.[16]

Recently, a common tetracyclic precursor for both euphane and lanostane triterpenes has been synthesized in this laboratory by a Diels-Alder cycloaddition reaction of diene 6.[17] This diene was prepared in 70% yield from diketone 1 in two steps. It has been demonstrated that cycloaddition reactions of 6, with a number of dienophiles under both thermal and acid-catalyzed conditions, gave excellent stereoselectivity. The reactions yielded β-endo adducts exclusively, despite the steric congestion of the



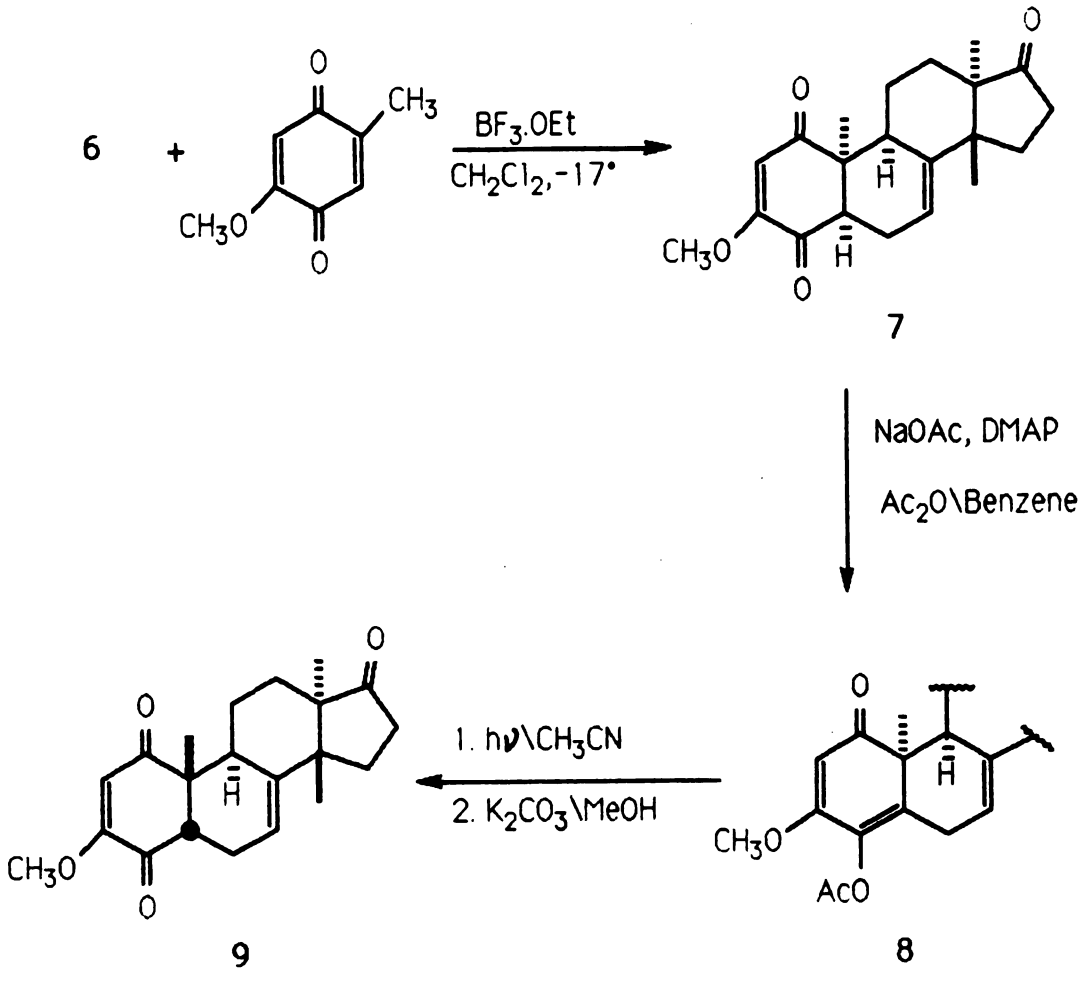




endo transition state. The regioselectivity of the cycloaddition of 6 with 2-methyl-5-methoxybenzoquinone can be controlled by selective Lewis-acid catalysis. Thus, an efficient synthesis of the lanostane-like tetracyclic




intermediate 7 was achieved as shown in Scheme VI. Subsequent conversion of 7 to a euphane-like intermediate

was accomplished by photoisomerization of enolacetate 8, followed by hydrolysis.

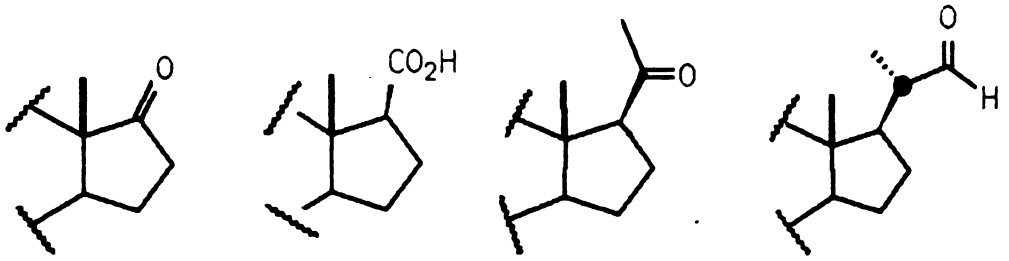



Scheme VI

All the triterpenes mentioned earlier have a $C_8$ side chain at C-17. These side chains are often alkyl in nature but may incorporate a variety of functional groups, as in the cases of cucurbitacins. There are many reported side-

chain syntheses for steroids[18], and they have been documented in two excellent reviews.[19,20] However, it must be noted that almost all of the studies referred to above have been conducted in the absence of a $C_{14}$-$\alpha$ methyl substituent.

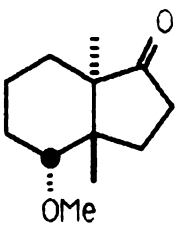
A crucial aspect of side-chain synthesis is the control of stereochemistry, especially at C-17 and C-20. A large number of steroid side-chain syntheses use one of the following substrates due to their availability from naturally occuring compounds. Common reactions of the C-17




carbonyl group include addition of hydrogen cyanides[21], acetylides[22] and Wittig reagents.[23] The C-20 carboxylic acid intermediate is usually transformed into an acid chloride[21] or is transformed by direct addition of alkyl lithium reagents.[24] In reactions of the C-17 acetyl group, the stereochemical outcome is dependent on conformational preferences and will vary with different substituents. For example, Grignard-reagent additions to 20-ketones[25,26] and 20-aldehydes[27] yield mixtures of isomers, whereas addition of dimethyl sulfoxonium methylide is highly stereoselective

and gives the 20-R epoxide.[28] A 20-R epoxide was also obtained by stereoselective addition of methyl selenomethyl lithium.[29]

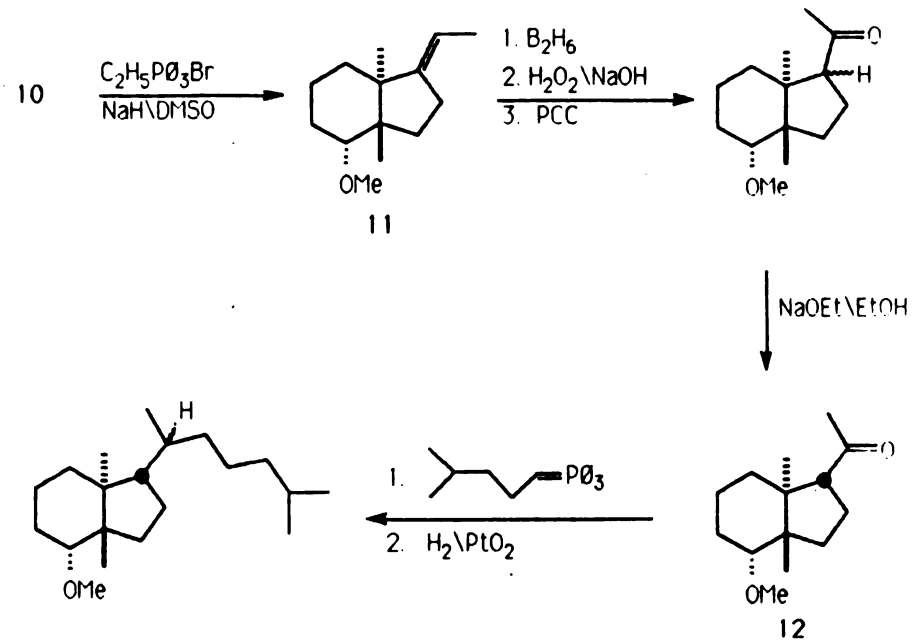
Reusch and Gibson reported that Wittig ethylidenation of a bicyclic (C/D) triterpenoid model, **10**, gave the E olefin **11**.[30] In contrast, the equivalent reaction of 17-keto




**10**

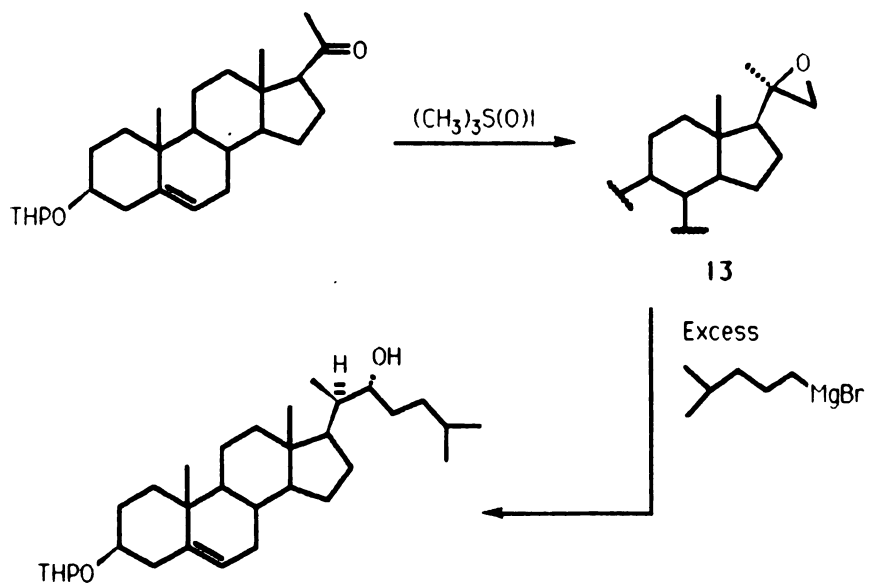
steroids gave predominantly the Z isomer. Hydroboration of **11**, followed by oxidation, led to an epimeric mixture of 20-ketones, which could be epimerized cleanly to the α-epimer **12**. However, chain extension by Wittig olefination followed by catalytic hydrogenation gave only fair configurational control at C-20. The overall synthetic approach is outlined in Scheme VII.

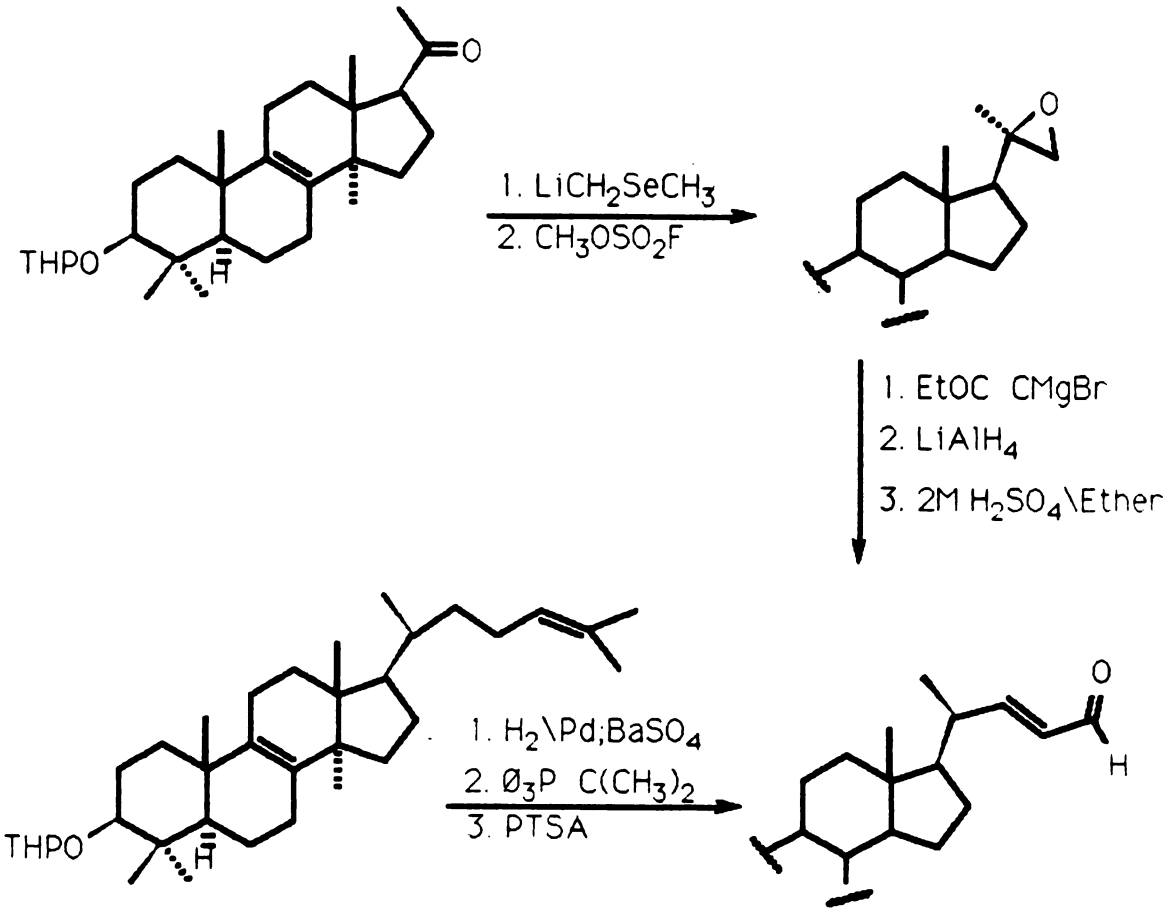
Recently, Koreda has described[28] a 20-isocholesterol side-chain synthesis involving reaction of isoamyl magnesium bromide with epoxide **13**. Rearrangement of the epoxide proceeded by a completely stereoselective hydride shift to an intermediate aldehyde. Krief also applied a similar




Scheme VII

**epoxide-rearrangement-addition reaction sequence for the side-chain synthesis of 20-S isolanosterol.[29] He obtained an 80/20 mixture of the 20S/20R stereoisomers, as illustrated in Scheme VIII.**






Scheme VIII

**This dissertation describes an efficient means of converting the 5-epi-euphane (cis A/B ring fusion) tetracyclic ring skeleton to the correct A/B trans configuration and stereoselective side-chain construction of a bicyclic (C/D) triterpenoid model.**

## RESULTS AND DISCUSSION

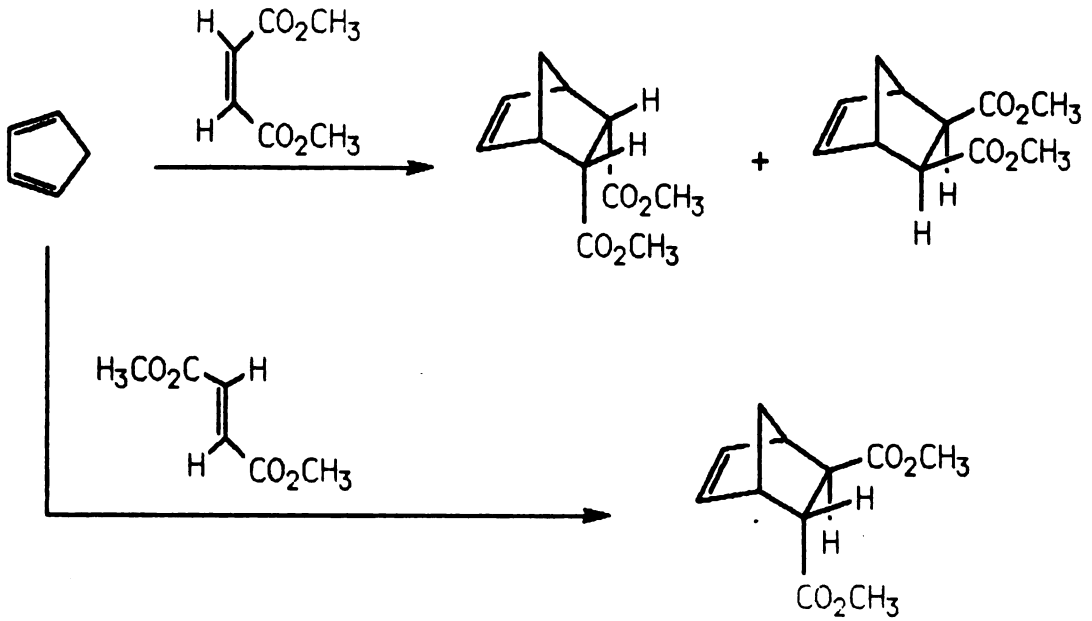
A total synthesis of butyrospermol can be divided into two sections: first, construction of the euphane-like tetracyclic system and, second, the subsequent attachment of the C8 side chain.

### I. Construction of the Tetracyclic Core.

Fused six-membered carbocyclic ring systems may be assembled in a number of different ways, but the most efficient of these is undoubtedly the Diels-Alder reaction. Since its discovery in 1928[31], the Diels-Alder [4+2] cycloaddition has been widely studied and is valued as a synthetic tool because of its normally high regio- and stereoselectivity.

The stereochemistry of the adduct obtained in many Diels-Alder reactions can be predicted on the basis of two imperical rules[32]: the cis-principle and the endo-addition rule. According to the cis-principle, the relative configuration of substituents in both the dienophile and diene is retained in the adducts. Thus, a dienophile with trans substituents will give an adduct in which their

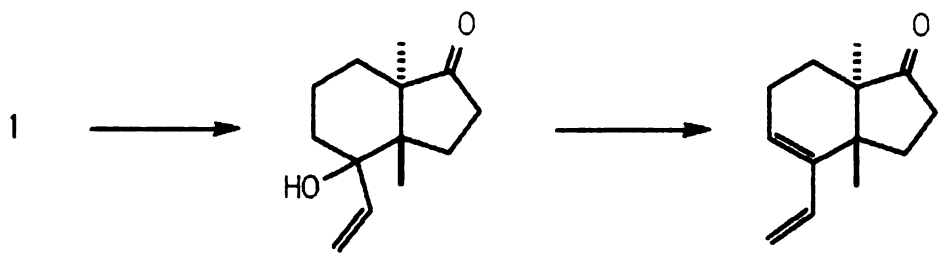
configuration is retained; likewise, a cis substituted dienophile will yield an adduct in which the substituents are cis to each other. According to Alder's endo-addition rule, a dienophile and a diene approach each other in parallel planes, and the most stable transition state arises




from that orientation in which there is a maximum overlap of double bonds, including those of the activating groups of the dienophile. The endo rule is not always obeyed and the exo/endo composition in such cases often varies with the structure of the dienophile and the reaction conditions.[33]

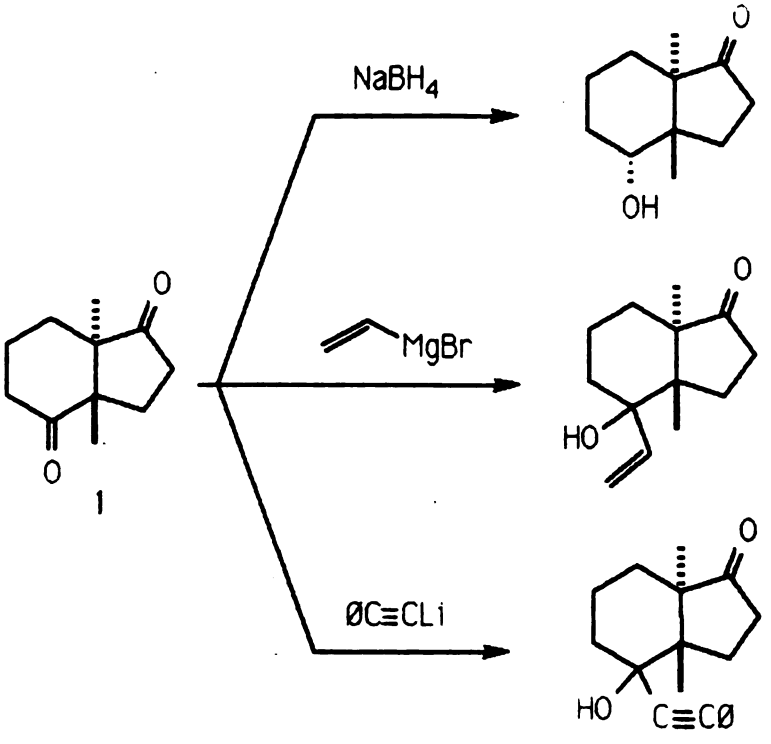
Construction of the Butyrospermol ring system by an A + CD ⟶ ABCD Diels-Alder strategy requires an appropriate cisoide diene (CD ring portion), incorporating the trans C-13 and C-14 methyl groups.

Diene 6 can be obtained from diketone 1 in two steps: nucleophilic addition of a vinyl anion to the six-membered ring carbonyl followed by dehydration of the resulting tertiary allylic alcohol 14. It has been known[34] that the

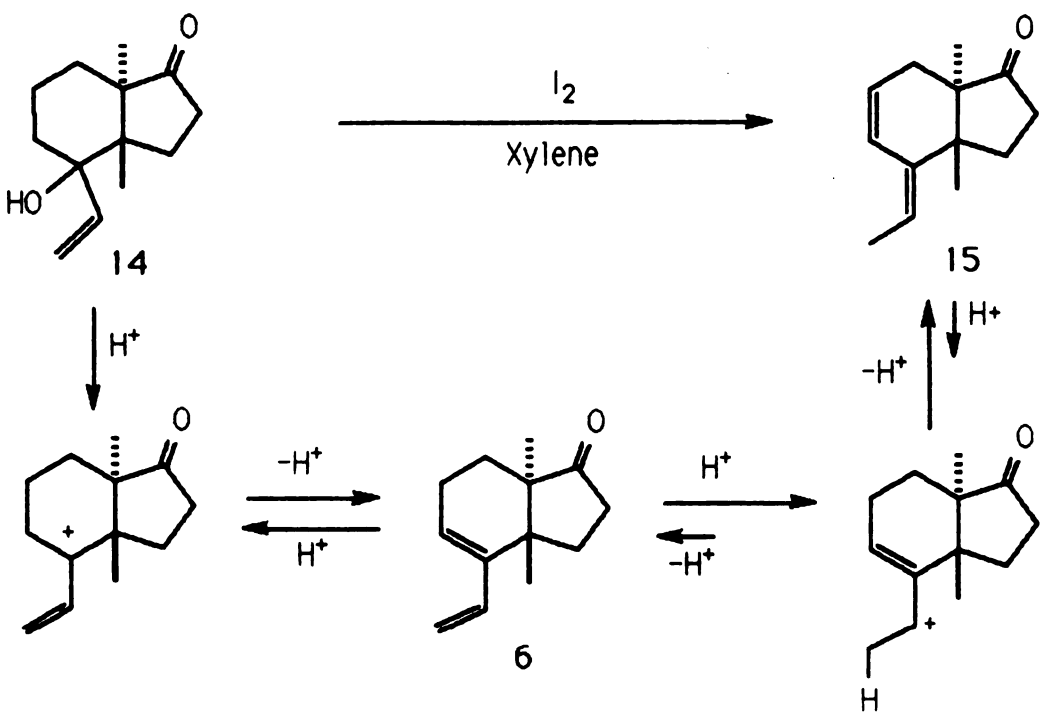



14 6

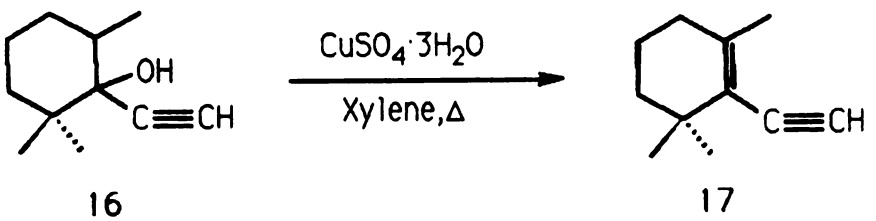
reactivity of cyclohexanones in a nucleophilic addition reaction is greater than that of cyclopentanones; and Martin, Tou and Reusch have reported[35] the selective addition of a series of nucleophile to the six-membered ring carbonyl of 1 without protecting the five-membered ring carbonyl group. For example, sodium borohydride ($NaBH_4$) reduction, lithium phenylacetylide addition and vinyl magnesium bromide addition all favored reaction at the six-membered ring carbonyl site. For this synthesis, the addition reaction of vinyl magnesium bromide with diketone 1 is best effected by using excess Grignard reagent in toluene.[36] This improves the yield of 14 from 60% (in THF) to 75% since the change of the solvent enhances the 1,2 addition of Grignard reagents to easily enolizable ketones.




Dehydration of the vinyl alcohol **14** in refluxing xylene containing a trace of iodine was troublesome due to the acid-catalyzed rearrangement[37] of the initially formed cisoid diene **6** to the transoid isomer **15** under this condition. Based on an initial report by N. Cohen, *et. al.*[38], Tou and Reusch found that boron trifluoride etherate ($BF_3 \cdot OEt_2$) in refluxing benzene-THF solution serves to dehydrate **14** to **6** without subsequent isomerization in 75~80%.[39] Recently, Ley and co-workers dehydrated the

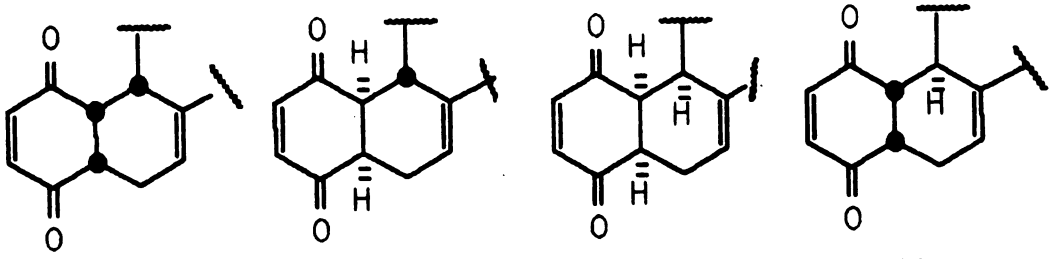



carbinol **16** in the presence of copper sulfate trihydrate in refluxing xylene to give enyne **17** in very good yield.[40]




**Dehydration of vinyl alcohol 14 with copper sulfate pentahydrate in refluxing benzene followed by Kugelrohr distillation of the crude product gave essentially pure diene 6 in over 90% yield on a multi-gram scale.**

The Diels-Alder reaction of diene **6** with various dienophiles has been studied intensively in this laboratory. Tou and Reusch reported[41] that, among four possible diastereomeric structures for the cycloaddition adducts derived from the symmetrical dienophiles p-benzoquinone and maleic anhydride α-endo **18**, d-exo **19**, β-endo **20**, and β-exo **20**, where α and β refer to the bottom and top sides of the diene as drawn here, the β-endo adducts were formed

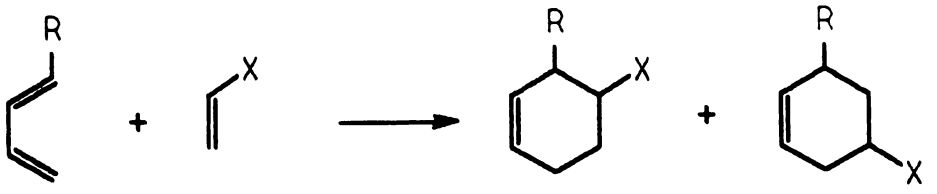


18 19 20 21

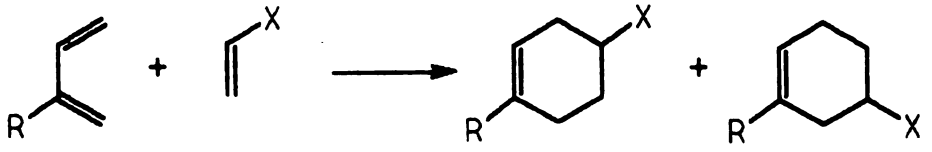
exclusively in both cases. The configurations of the adducts were confirmed by pmr studies and x-ray diffraction analysis of substituted quinone adducts.

An examination of molecular models of diene **6** shows that the C-13 methyl group is tilted over the endocyclic double bond whereas the C-14 methyl group is tilted back away from it. The overall effect of this distortion is that the top side (or β-face) of the diene is more accessable than the bottom side (or α-face). Thus, β-addition should be favored in the transition state of the Diels-Alder reaction (steric approach control).

Diels-Alder cycloaddition of an unsymmetrical diene with an unsymmetrical dienophile may take place in two orientations, which give two regioisomeric adducts. However, in practice, formation of one of these isomers is usually favored[42], as shown below. This regioselectivity in



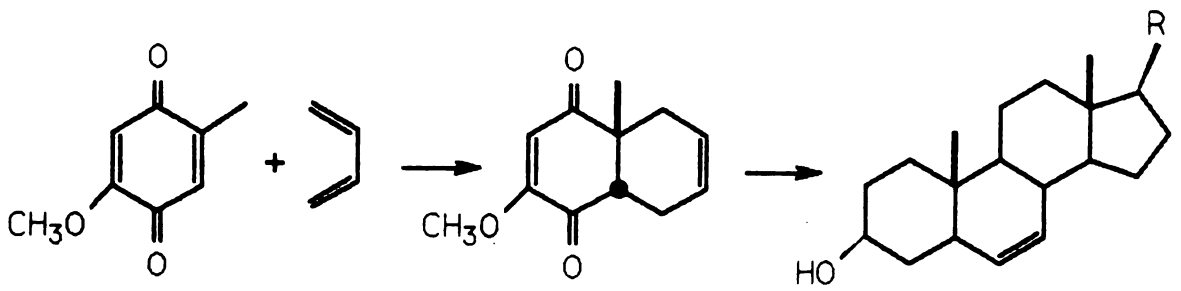

Major



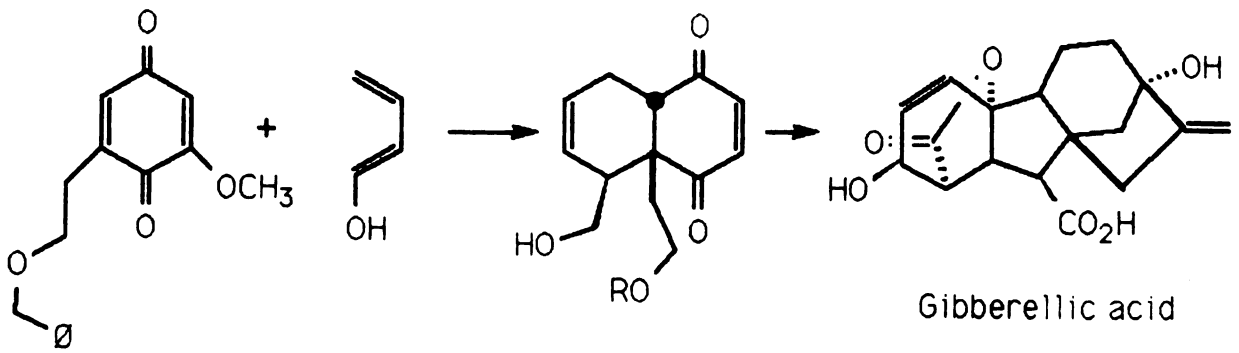

Major

which the "ortho" or "para" product is favored over the "meta" has been rationalized by molecular-orbital calculations.[43]

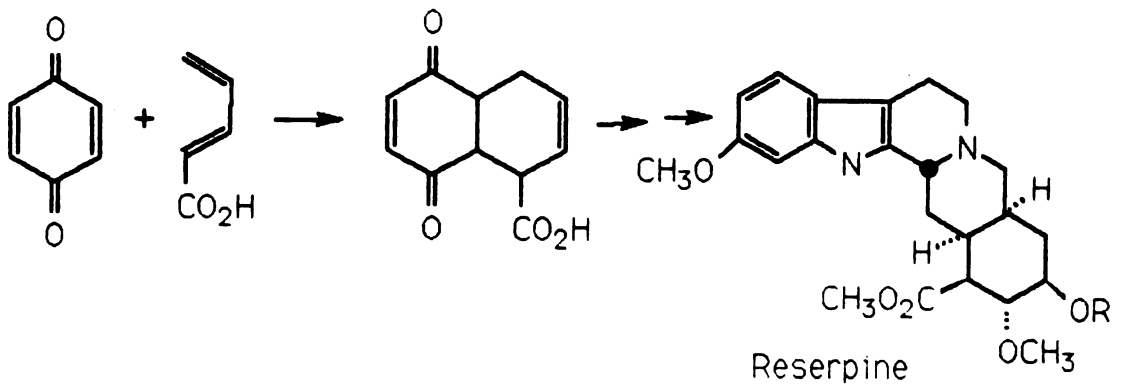
Derivatives of p-benzoquinone have been used as dienophiles to construct the fused six-membered ring systems found in many natural products. Their high degree of functionality offers special interest and advantages in subsequent transformations. Examples include the syntheses of steroids[38,44], gibberellic acid[45], reserpine[46] and trichodermol[47], as outlined on the following page.



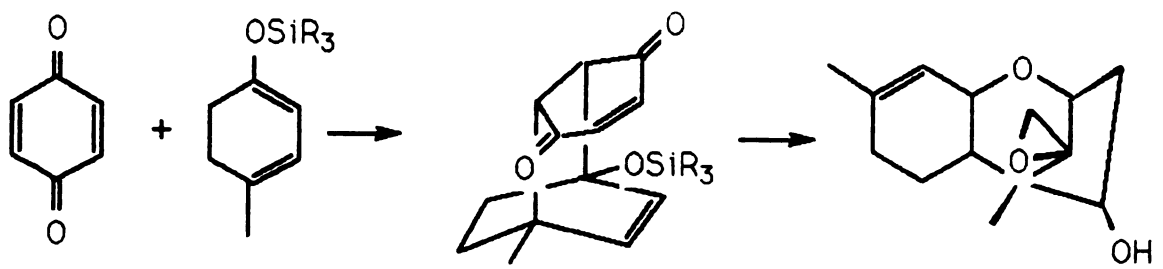

Cholesterol




Gibberellic acid

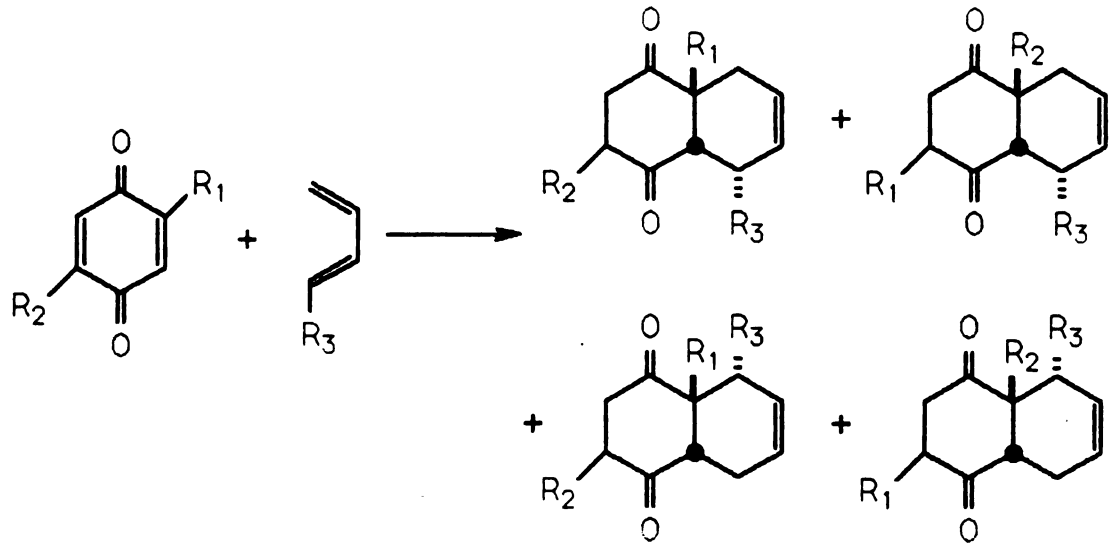



Reserpine




Trichodermol

When an unsymmetrically substituted p-benzoquinone is used as a dienophile in reactions with unsymmetrical dienes, four possible regioisomers may be obtained as shown in Scheme IX.

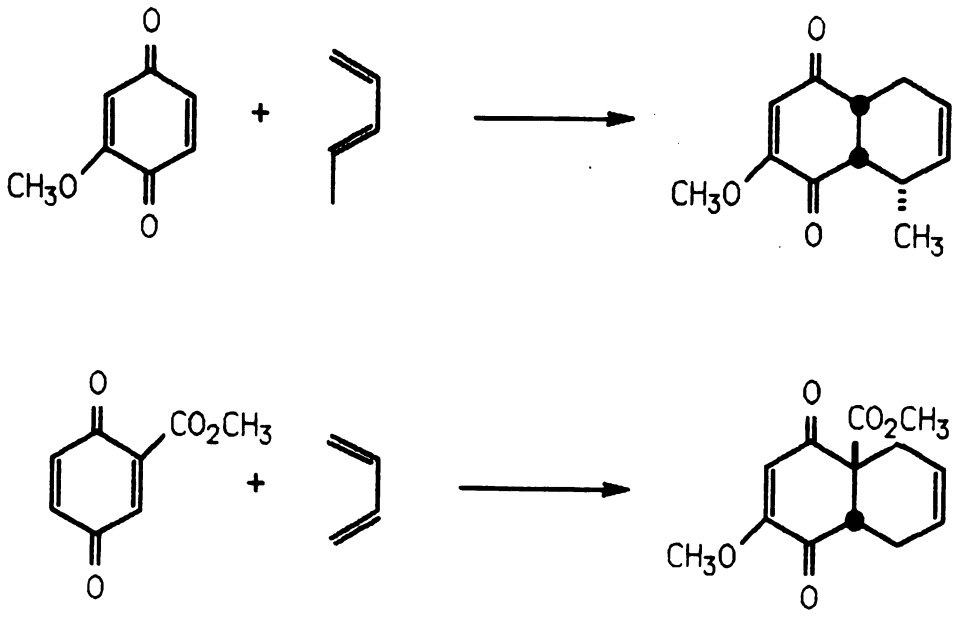


Scheme IX

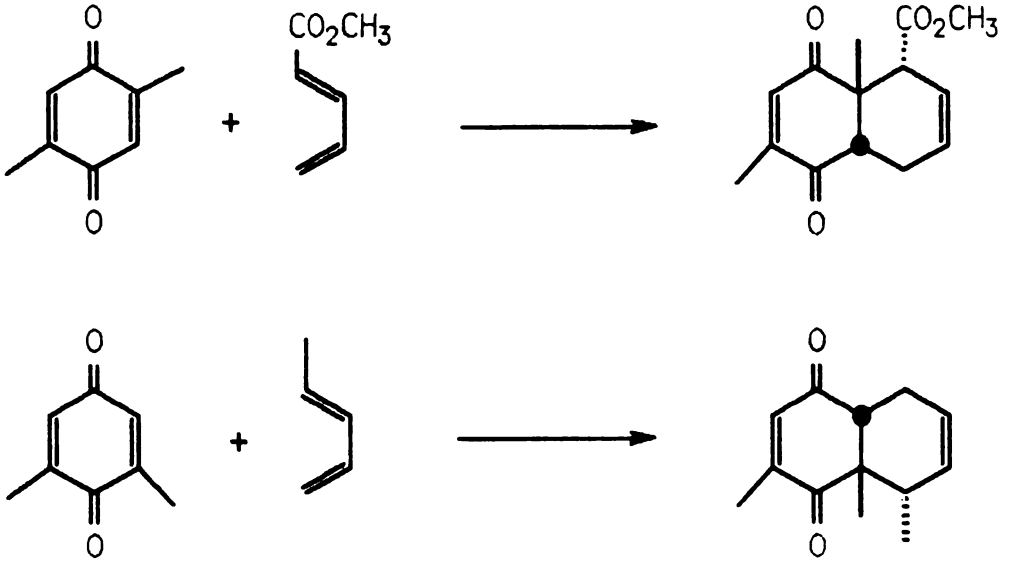
Several important observations have been made concerning the directing effects of substituents on p-benzoquinone.

They are:

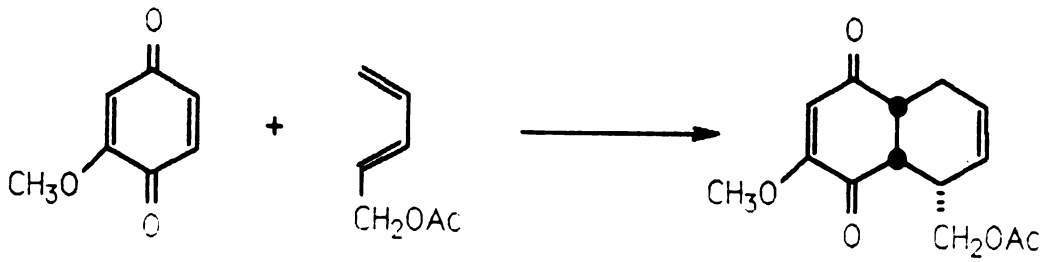
(1) Electron-donating substituents on the quinone deactivate the double bond to which they are attached.[48] In contrast, electron-withdrawing substituents further activate quinone double bonds as dienophiles.[49]



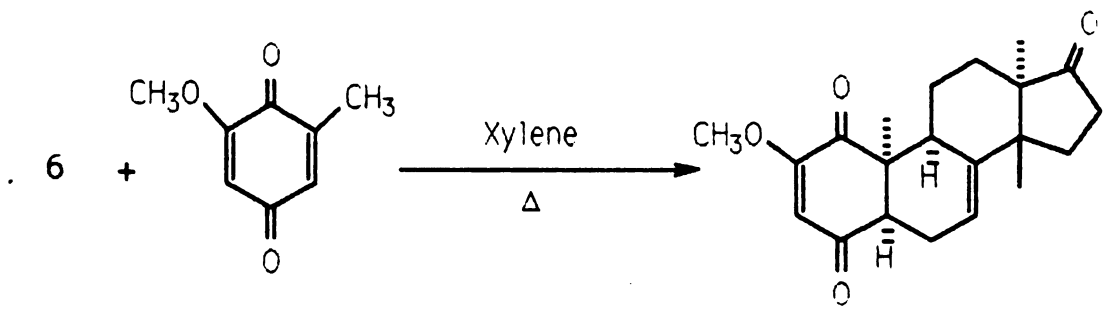
**(2) Substituents on quinone dienophile usually direct the cycloaddition reaction to give <u>ortho</u>-adducts with 1-substituted dienes[48,50] and <u>para</u>-products with 2-substituted dienes.**



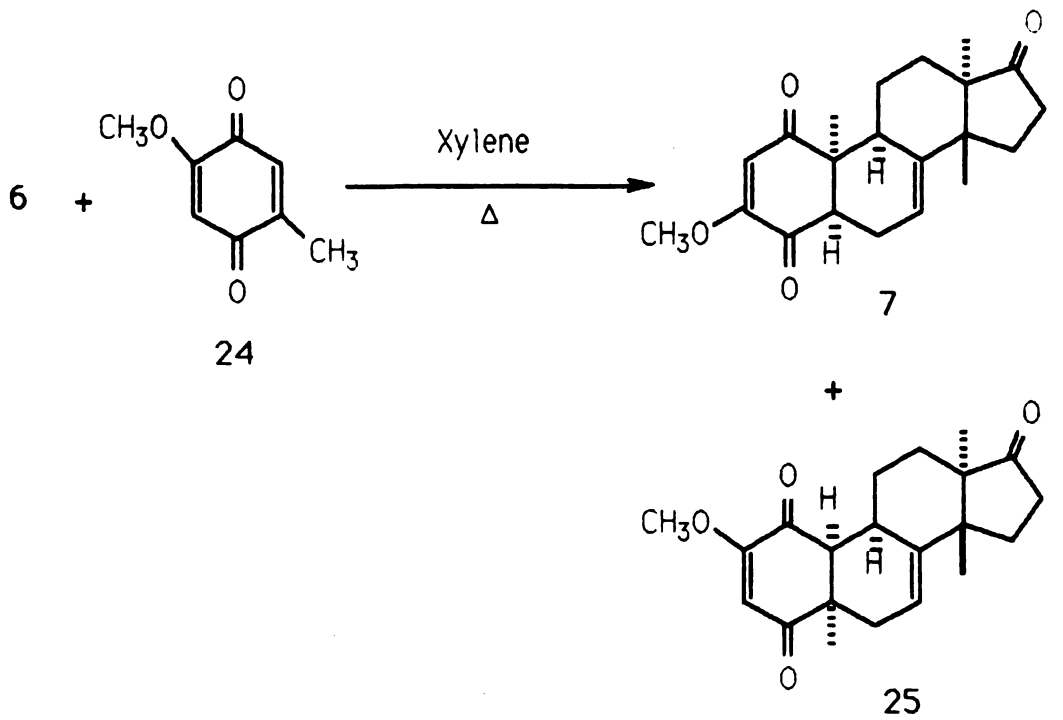
(3) A methoxy substituent exerts a strong influence on one of the two carbonyl groups of a quinone through a vinylogous ester-like relationship. This interaction results in a substantial perturbation of the double bond on the other side of the substituted quinone, leading to strong regioselectivity in the Diels-Alder reaction.[48]



The regioselectivity of Diels-Alder reactions of diene **6** and unsymmetrically substituted p-benzoquinones has been examined.[41] For example, the reactions of 2-methoxy-5-methyl-p-benzoquinone **22** with **6** in refluxing xylene solution gave adduct **23** exclusively. However, the reaction of 2-methoxy-4-methyl-*p*-benzoquinone **24** with **6** under thermal conditions gave poor regioselectivity and a poor yield of

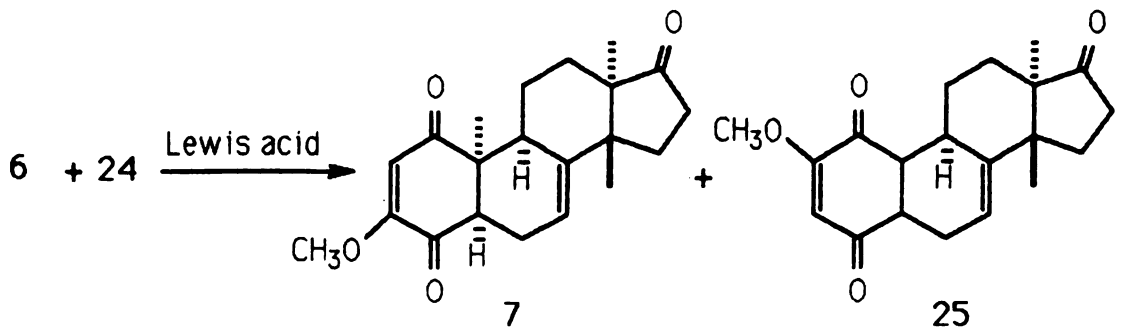


22 23



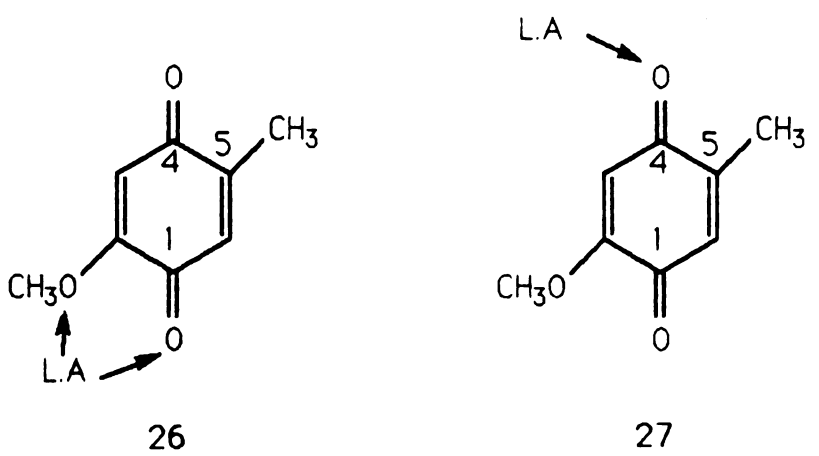

tetracyclic adducts **7** and **25**. Both the yield and the regioselectivity of this Diels-Alder reaction were greatly improved by Lewis acid catalysis.[51] The effect of two of the most selective catalysts, $BF_3 \cdot OEt_2$ and stannic chloride ($SnCl_4$), is shown below.

This regioselectivity may be explained by a site-specific coordination of the Lewis acid with one of the carbonyl groups of **24** to give a reactive quinone:Lewis acid complex. When a 1:1 ratio of quinone **24** to Lewis acid is used, two types of mono-complexation may occur; and the preferred complexation will depend on the nature of Lewis acid. First, the Lewis acid may be stabilized by chelation with the methoxy substituent, as in **26**. Second, the Lewis




| Catalyst used | ratio ( 7:25 ) | yield (%) |
|---|---|---|
| Heat | 2 : 1 | 34 |
| $SnCl_4$ | <1 : >99 | 74 |
| $BF_3 \cdot OEt_2$ | 10 : 1 | 55 |

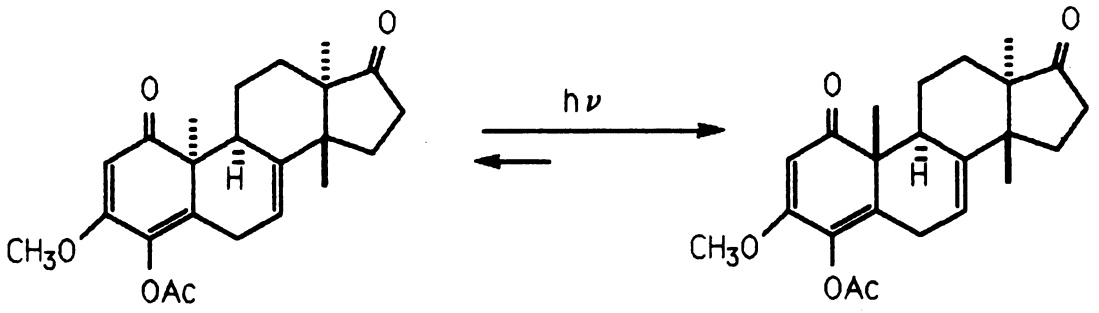
**acid may coordinate to the more basic ester-like C-4 carbonyl group as in 27. Boron trifluoride etherate, which**




**is normally tetracoordinate, prefers complex 27, and this leads to activation at C-6 to yield the <u>ortho</u>- or <u>para</u>-cycloadduct in the Diels-Alder reaction. On the other hand,**

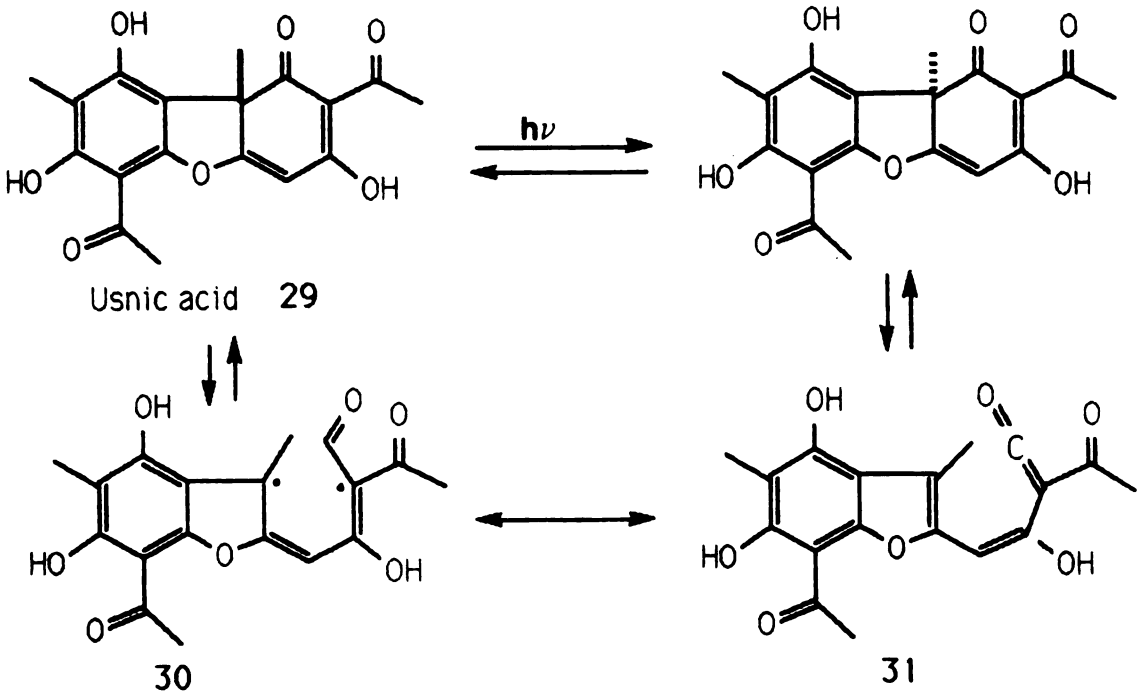
tin tetrachloride, which is able to expand its ligand shell to hexacoordinate, prefers complex **26**. The resultant activation at C-5 gives the meta-oriented cycloadducts.

No synthesis of a euphane triterpene or of the characteristic tetracyclic core of this large family of natural products has yet been achieved. Recently, Kolaczkowski and Reusch reported[9] an efficient means of converting the lanostane-like configuration of **8** to a euphane configuration **28** via photoisomerization.



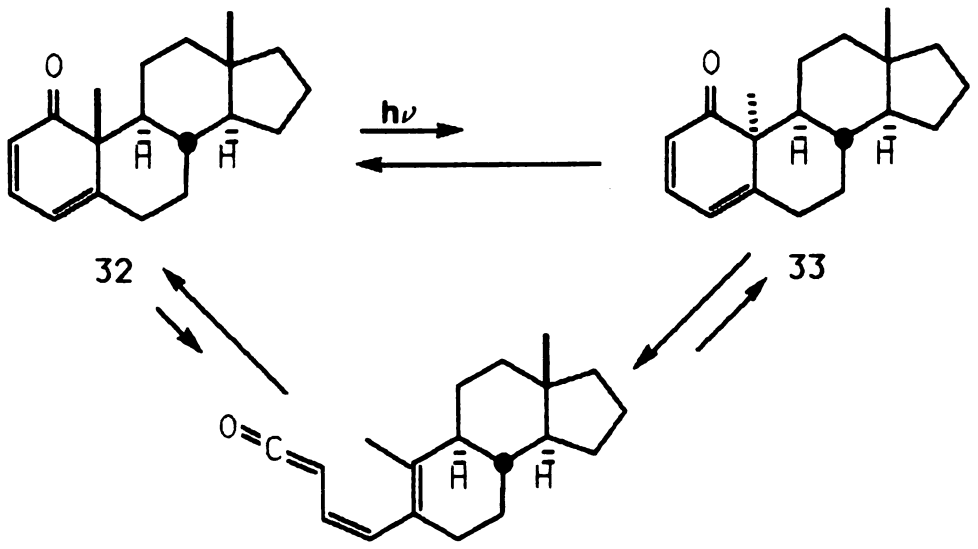

8 28

It has been known[52] that Usnic acid **29**, a constituent in several genera of licheues, racemized when heated in acetic acid or on acetylation with acetic anhydride in the presence of strong acid. This rare isomerization at a quarternary center was explained by Stork in 1955 (see Scheme X).[53] Initial bond cleavage of **29** gives a diradical **30** and one of the resonance forms which can be drawn is the conjugated diene ketene **31**. Subsequent ring closure of **31** leads to racemic usnic acid.




Scheme X

Intramolecular photochemical reactions of saturated and unsaturated ketones have been studied for decades. In 1960, Barton and Quinkert reported[54] their investigations into the photochemistry of cyclohexadienones, including the photochemical racemization of usnic acid. Nineteen years later, Quinkert and co-workers reported[55] a detailed study of solvent and excitation wavelength effects on the isomerization of 2,4-androstadiene-1-one **32**. They found that irradiation of either **32** or **33** in the absence of external nucleophiles gave a mixture of isomers **32** and **33**. The relative ratio of **32** and **33** in the photostationary state



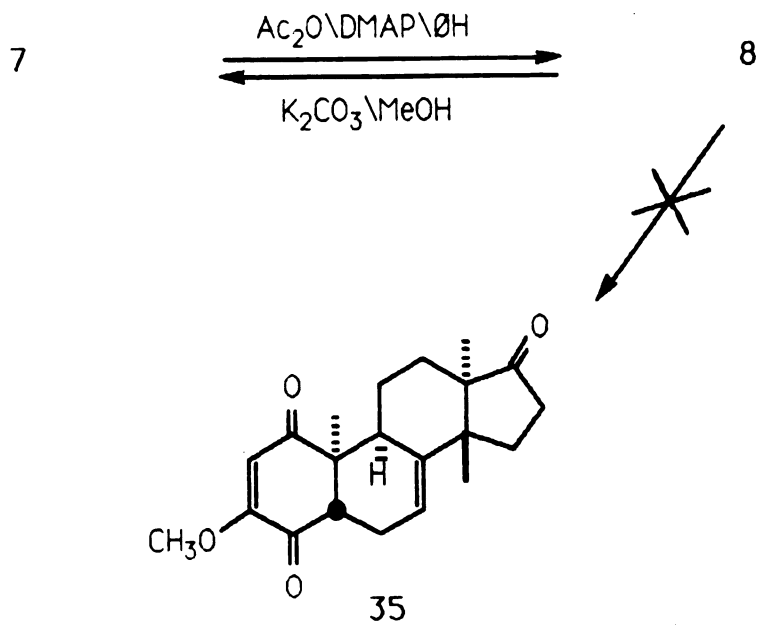
32 33

34

proved to be the same in both cases. The expected ketene intermediate **34** was identified by spectroscopic studies and by trapping experiments with cyclohexylamine. Thus, a photoequilibrium is established between the two tetracyclic dienones **32** and **33**, and the photostationary ratio of **32** and **33** varies from 6.5:1 to 5.7:1, depending on the reaction conditions. The naturally occurring C-10 β-methyl isomer **32** predominates. This result is not surprising since, in isomer **32**, the anti relationship of the C-10 methyl and C-9 proton allows the B-ring to adapt a stable chair conformation; whereas, the C-9, C-10 syn relationship in isomer **33** forces ring B into a less stable boat conformation.

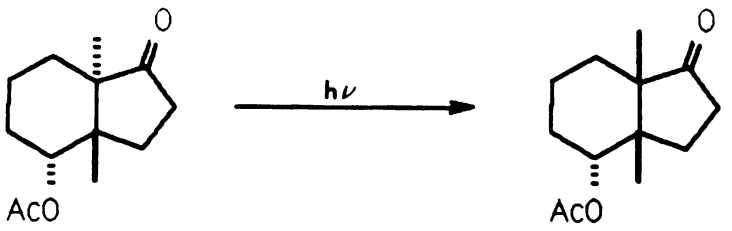
Reusch and Tou reported[41] that the C-4 carbonyl group of Diels-Alder adduct **7** was enolizable and they trapped it

as the acetate **8** by reaction with acetic anhydride. Mild base ($K_2CO_3$ in methanol) treatment of **8** gave back the starting triketone **7** instead of the AB trans-fused **35**, indicating that the AB cis configuration was more stable.




Enol acetate **8** has a 9,10-syn configuration analogous to the minor isomer **33** in the Quinkert study. We expected, therefore, that **8** would undergo photoisomerization to give the desired euphane-like configuration **28** as the major product. However, in practice, two concerns remained unanswered. First, the possible effect of the oxygen functionality at C-3 and C-4 on the course of the photoisomerization and, second, the presence of the C-17 carbonyl function.

Photochemical isomerization of keto-acetate **36** was investigated in this laboratory.[56] Iradiation of a solution of **36** in ether solution with a 400 watt mercury lamp using a pyrex filter causes isomerization to the cis-fused keto-acetate **37**. This Norish-type I cleavage-recombination



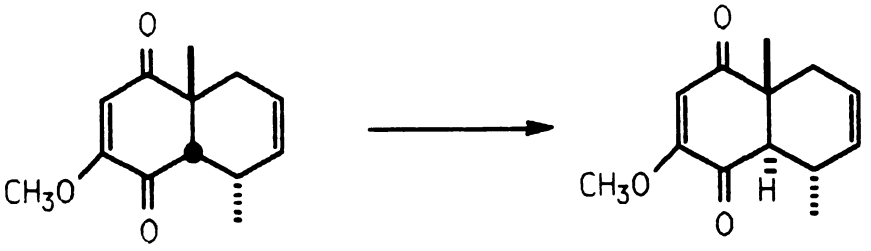

36 37

reaction requires higher energy light than the photoisomerization of enolacetate **8**. Thus, by using a saturated copper (II) sulfate filter to block wavelengths below 365 nm, this undesired epimerization at C-13 can be avoided.

Acting on the assumption that the substituents at C-3 and C-4 and $\Delta^{7(8)}$ double bond would not perturb the photochemical reaction seriously; a solution of enolacetate **8** in acetonitrile was irradiated under Quinkert's conditions. This photolysis generated a 5.5:1 mixture of photoenol acetate isomer **28** and starting material **8**, respectively.[9]

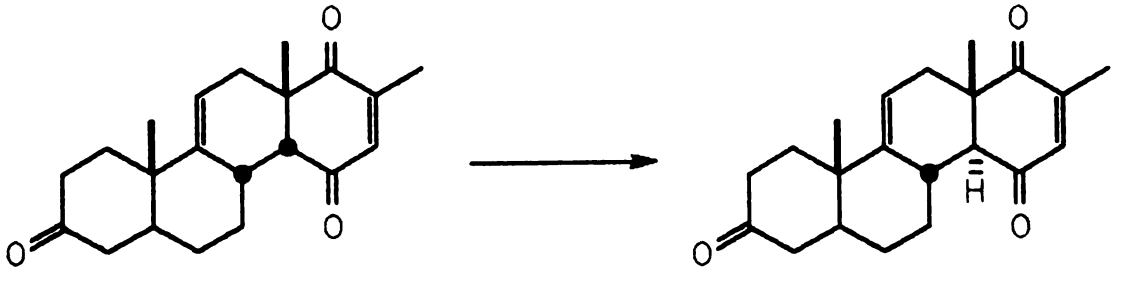
Many cis-fused bicyclic Diels-Alder adducts with quinones are known to be converted to the corresponding trans-fused isomers on mild base treatment. For example,

the cycloaddition adduct **38** from the reaction of quinone **24** with pypenylene even isomerized to the trans compound **39** on standing.[35]

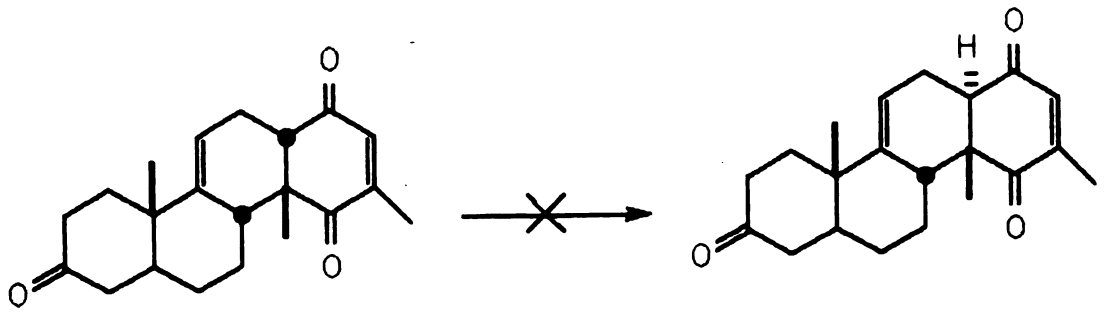



38 39

In more complex systems, isomerization proved to be dependent upon the stability of the product. Valenta, *et. al.*, reported[44a,57] that in the case of Diels-Alder adducts **40** and **41**, **41** was converted smoothly to its trans isomer **43** under various conditions. These observations suggest that

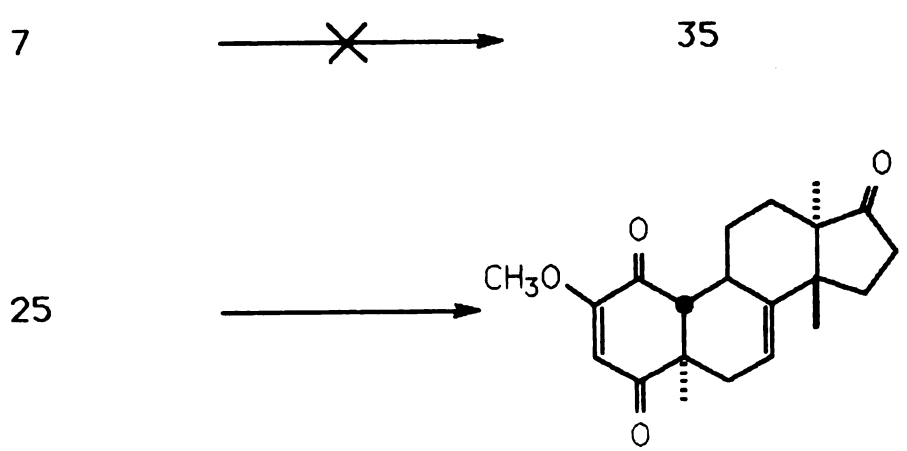



40 42



41 43

the anti-trans relationship at C-8, C-13 and C-14 in **42** is a particularly stable configuration, whereas the syn-cis relationship in **41** is more stable than the related syn-anti configuration of **43**. A similar observation was made for the regioisomeric Diels-Alder adducts **7** and **25**.[39] These results

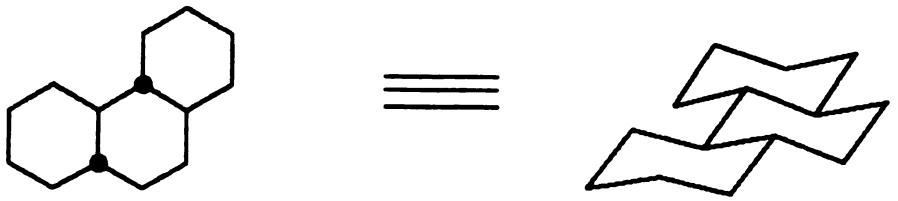


7 35

25

are in accord with the work of W. S. Johnson[58] on the relative stabilities of perhydrophenanthrene isomers. According to Johnson's analysis, the trans-anti-trans isomer has the lowest energy among the many stereoisomers of

perhydrophenanthrene since this arrangement allows all the B-ring bonds to assure equatorial orientation and all three rings to adopt chair conformations.

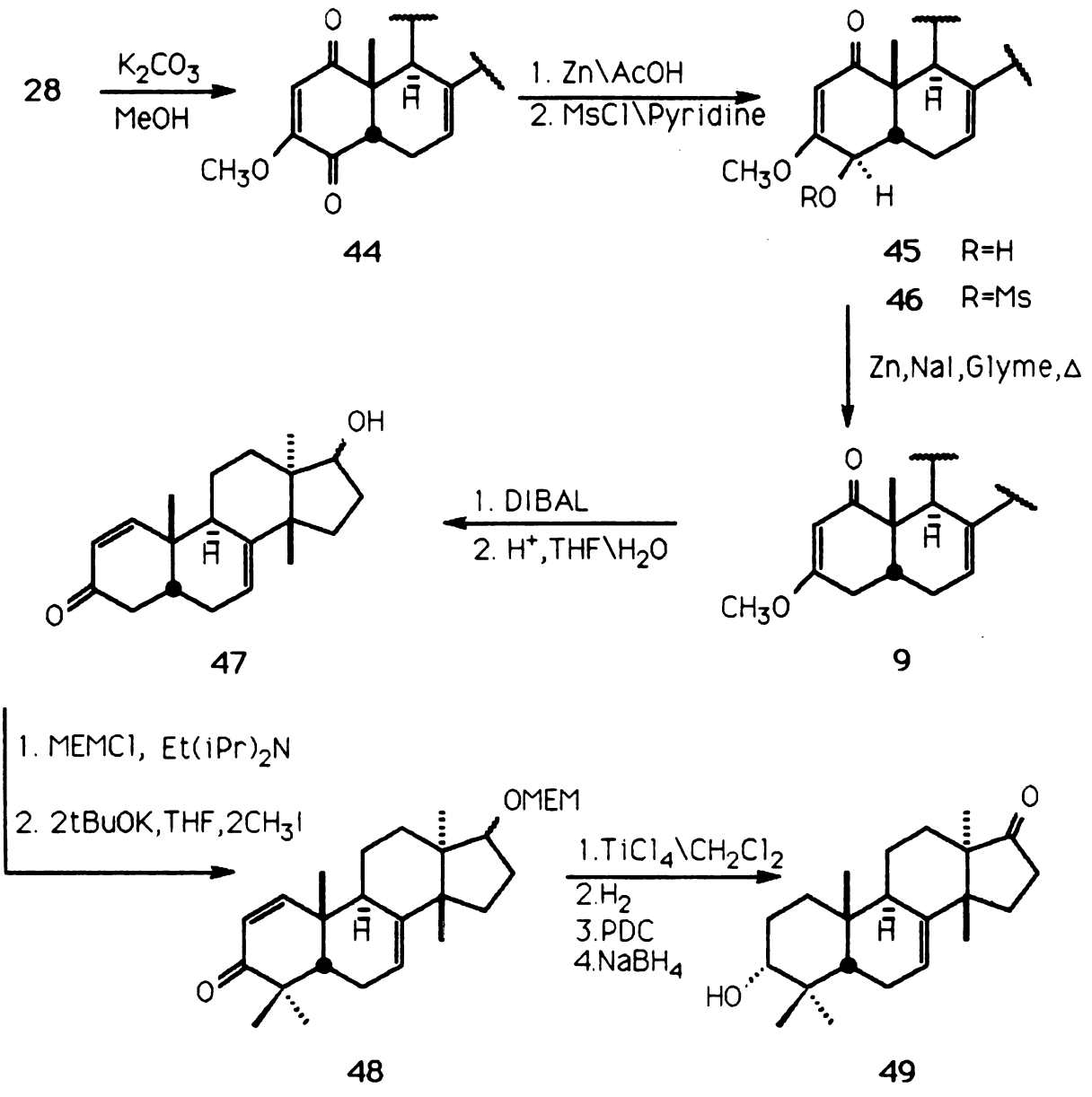


Trans-anti-trans
Phenanthrene

All previous results indicated that the tetracyclic enedione derived from **28** by base hydrolysis would have an AB-trans relationship since an anti-relationship at C-9 and C-10 exist in **28**.

A series of reactions, outlined in Scheme XI, was then carried out by Larry Kolaczkowski[9], under the assumption that the product from base-catalyzed solvolysis of **28** was the AB trans-fused endione **44**. The expected product was the tetracyclic intermediate **49**, a precursor to butyrospermol. However, the actual product **49** resisted all attempts to isomerize the $\Delta^{7(8)}$ double bond to the more stable $\Delta^{8(9)}$ location. Therefore, an X-ray crystallographic analysis was conducted, and this demonstrated that the AB-ring fusion in **49** was cis, as shown throughout Scheme XI.

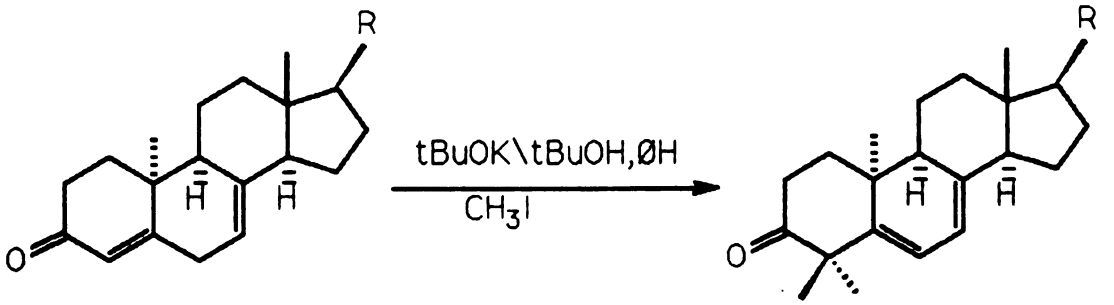
At this stage of our synthesis, modifications were sought to convert the AB-cis 5-epi-butyrospermol tetracyclic



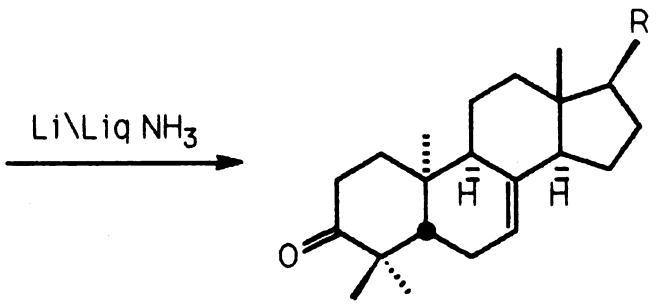

Scheme XI

**core to the desired AB-trans ring fusion. The most attractive of these modifications was based on the work of**

Pike, Summers and Klyne with lumistan-3-one derivatives.[59] These workers reported that dried methylation of lumista-4,7,22-triene-3-one **50**, followed by dissolving metal reduction of **51**, gave AB-trans fused 4,4-dimethyl-5β-lumista-7,22-diene-3-one **52** in excellent yield.

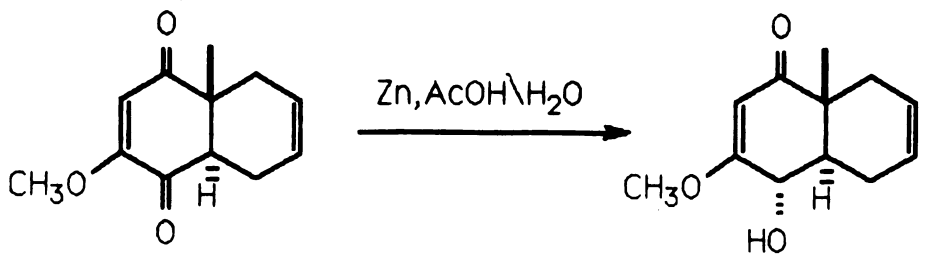



50 51




52

To effect transformation of **44** to a form suitable for the introduction of a double bond at C-4, we followed the sequence of Scheme XI to intermediate **48**. This procedure was patterned after one developed by Speziale, *et. al.*[60], for the preparation of a key CD synthone in the Woodard cholesterol synthesis.[44b] Thus, zinc dust reduction of **44**,



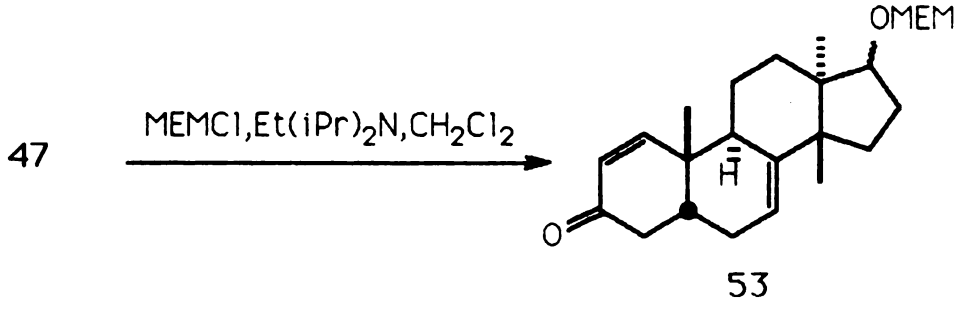

followed by mesylation and further reductive elimination, gave the methoxy enone 9.

Selective reduction of one carbonyl function among three carbonyl groups present in 44 was not a serious concern since the C-1 carbonyl is ester-like in character, due to donation of the electron density from the C-3 methoxy group; and the C-17 carbonyl function was known to be relatively unreactive due in part to severe steric hinderance.

The conversion of alcohol 53 to enone 47 was carried out by transforming the hydroxy function at C-4 to a good leaving group, in this case, mesylate, followed by hydride displacement and concurrent reduction of the remaining carbonyl functions. Several methods for the selective removal of mesylate in the presence of other sensitive functionality have been reported.[61a-c] One of the mildest, the method of Fujimoto and Tsatsuno[61c], involves treatment of mesylate with sodium iodide and zinc dust in refluxing glyme. Under these conditions, mesylate 46 was converted to enedione 9 in good yield. Subsequent reduction of endione 9 with diisobutylaluminum hydride (DIBAL) gave, after careful

acid hydrolysis, a mixture of epimeric 17-alcohols **47** (α and β) having the desired 1-en-3-one function in ring A. These epimers were separated initially to facilitate subsequent structural assignment; however, this is not a necessary operation in the synthesis.

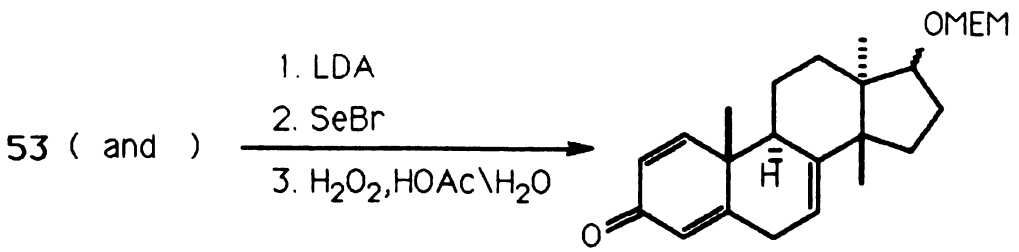
Protection of the C-17 alcohols prior to the introduction of a double bond at C-4 proved necessary. In fact, Kolaczkowski and Reusch reported[35] that the introduction of the geminal dimethyl substituent at C-4 to the compound **47**, without protecting the C-17 hydroxyl function, was troublesome. For this purpose, β-methoxyethoxymethyl chloride (MEMCl), a reagent developed by E. J.a Corey, *et. al.*[62], proved to be effective.




53

The MEM-ether derivatives **53** (α and β) are ideally suited for the introduction of a double bond at C-4 and subsequent gem-dimethylation. Both enolization and alkylation at C-2 is blocked by the $\Delta^{1(2)}$ double bond, and the reduced state of the C-17 carbonyl prevents enolization at the C-17 ketone. Thus, the $\Delta^{4(5)}$ double bond was introduced smoothly via selenylation[63] of the enolate

generated by LDA, followed by oxidation ($H_2O_2$, HOAc/$H_2O$), and then elimination of the selenoxide to give trienone **54** (85% yield).

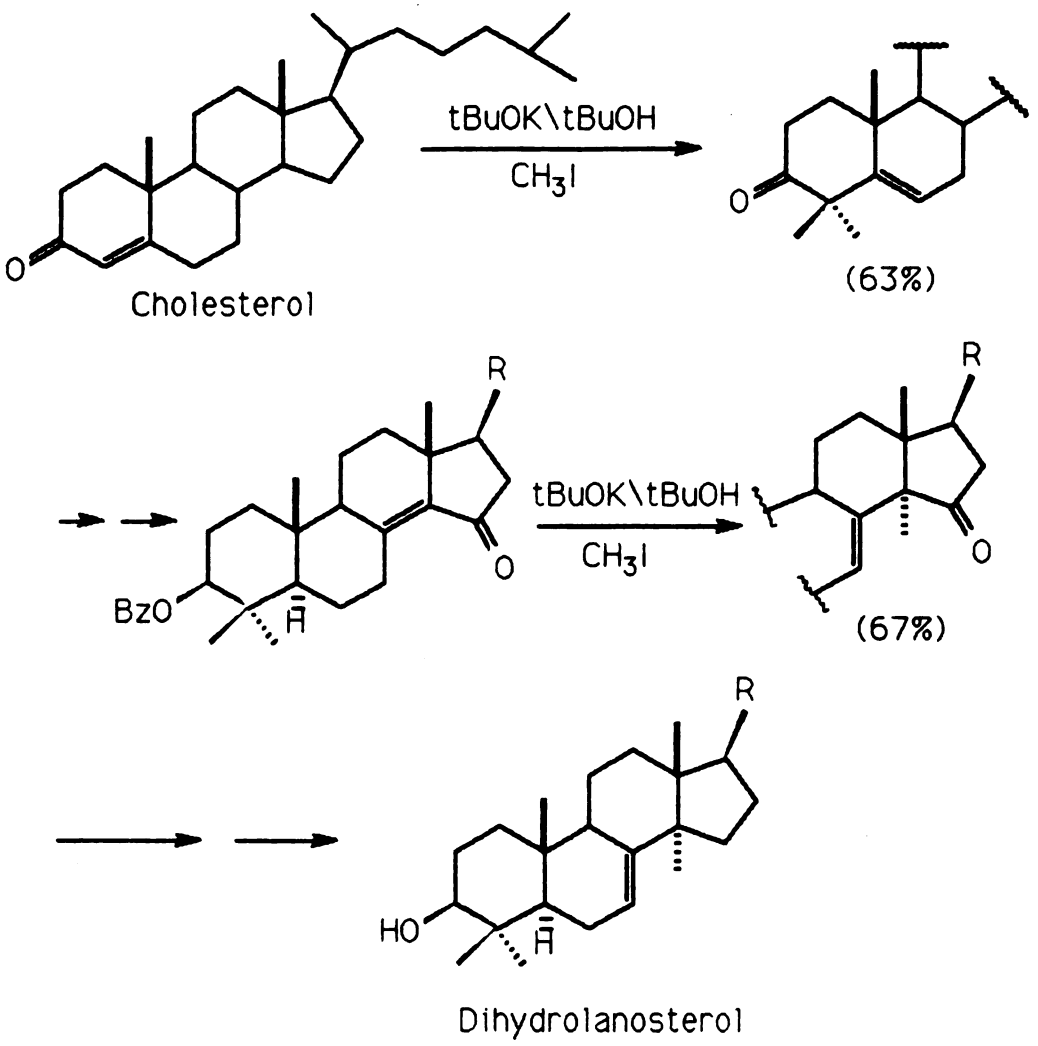



54

Our plan at this state was to introduce the gem-dimethyl moiety at C-4, generating a B-ring homoannular diene analogous to that of lumisterol.

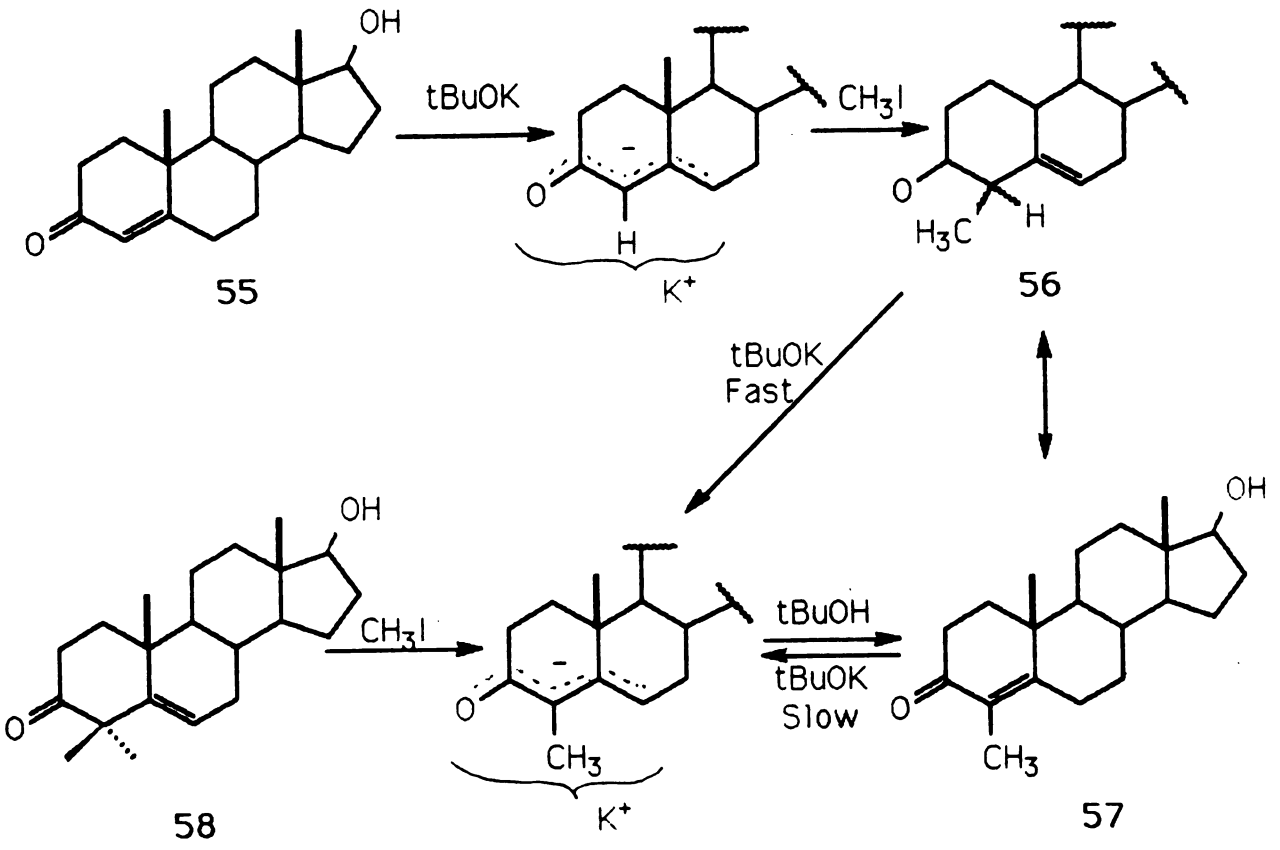
Alkylation of $\alpha,\beta$-unsaturated ketones with sodium or potassium salts of tertiary alcohols serving as the base normally gives the $\alpha,\alpha$-dialkyl-$\beta,\gamma$-unsaturated ketone as the major product.[64] Woodward and co-workers developed[6] this method on their first total synthesis of lanosterol (Scheme XII).

Ringold, *et. al.*, reported[64b] that alkylation of the $\Delta^4$-3-keto steroid **55**, even with a limited amount of base and alkyl halide, led to the 4,4-dimethyl-$\Delta^5$-3-one **58** as the major product, together with 4-monomethyl-$\Delta^4$-3-one **57** as a




Scheme XII

**minor product. This result can be explained by the following scheme (Scheme XIII).**

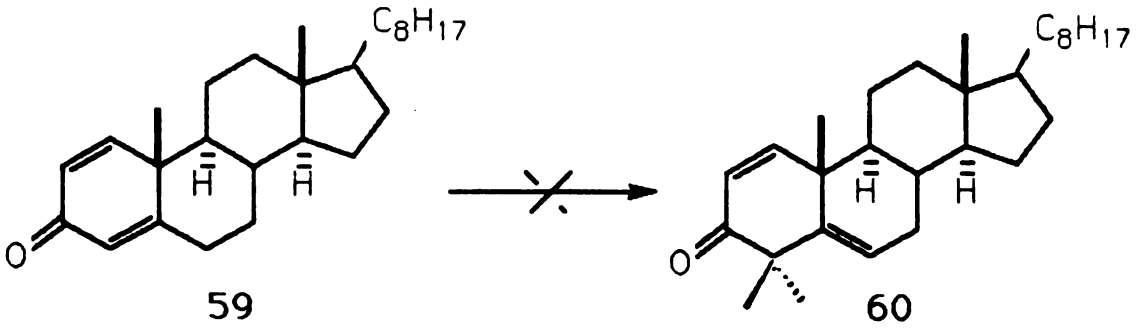



Scheme XIII

The thermodynamically favored dienolate anion undergoes kinetically controlled methylation at the α-position to give 4-monomethyl-β,γ-unsaturated ketone **56**. the α-proton in this compound is more acidic than the γ-proton in the starting material **55** since it is activated by both a carbonyl group and an ethylenic double bond. The resulting anion is again methylated at the α-position to give 4,4-dimethyl-$\Delta^{5(6)}$-3-one **58**. If further alkylation does not occur, compound **56**

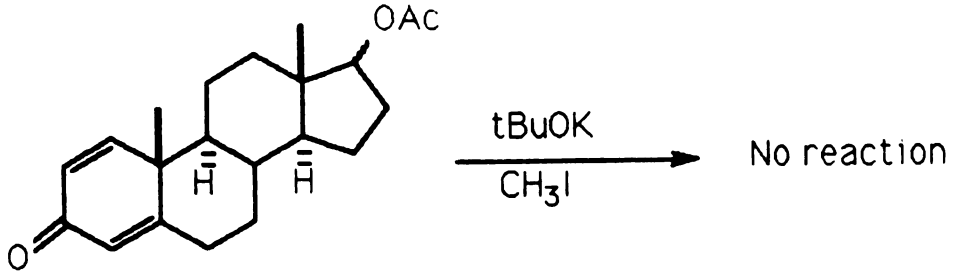
isomerizes to the thermodynamically more stable $\alpha,\beta$-unsaturated ketone **67**. Isolation of the dimethylated compound **68** as the major product indicates that the second alkylation step and/or tertiary carbanion formation proceeds more rapidly than the first alkylation step and/or secondary carbanion formation.

Methylation of cross-conjugated dienones in the steroidal system have also been studied. V. Petrov, *et. al.*, reported[65] that direct dimethylation of compound **59** failed to give any of the desired 4,4-dimethyl compound **60**.

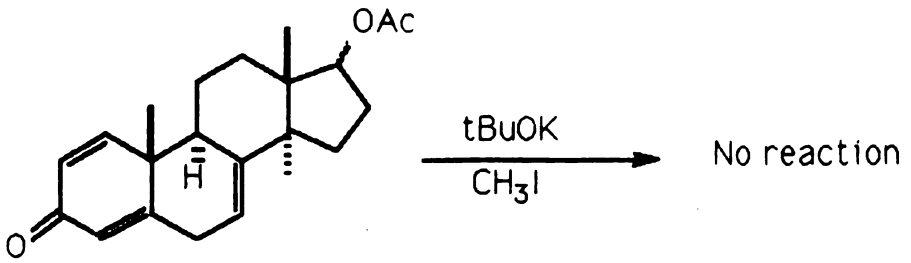



59 60

A similar lack of reactivity is reported for these same dienones in the deconjugation studies of Ringold and Molhotra.[64b] A remarkable resistance to gem-dimethylation at C-4 was also found for the cross-conjugated dienone **61** and **62** in this laboratory.[66] Therefore, we were concerned that

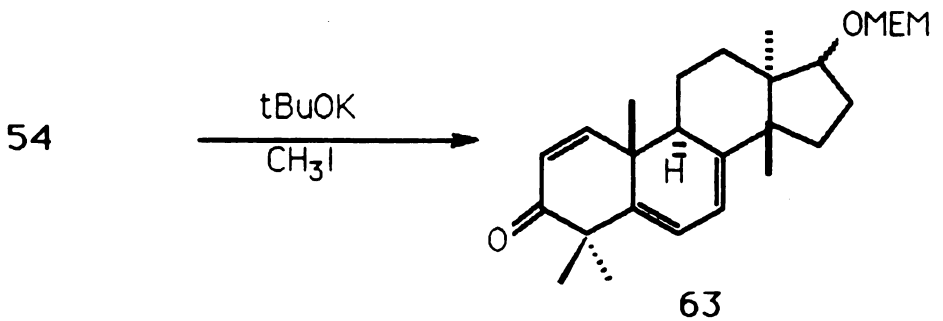



61




62

the $\Delta^{1(2)}$-double bond might expert a negative influence on the methylation reaction of **54**. Fortunately, in the event, a solution of trienone **54** is benzene was gem-dimethylated in over 90% yield by the classical procedure of Woodward, *et. al.*[6]

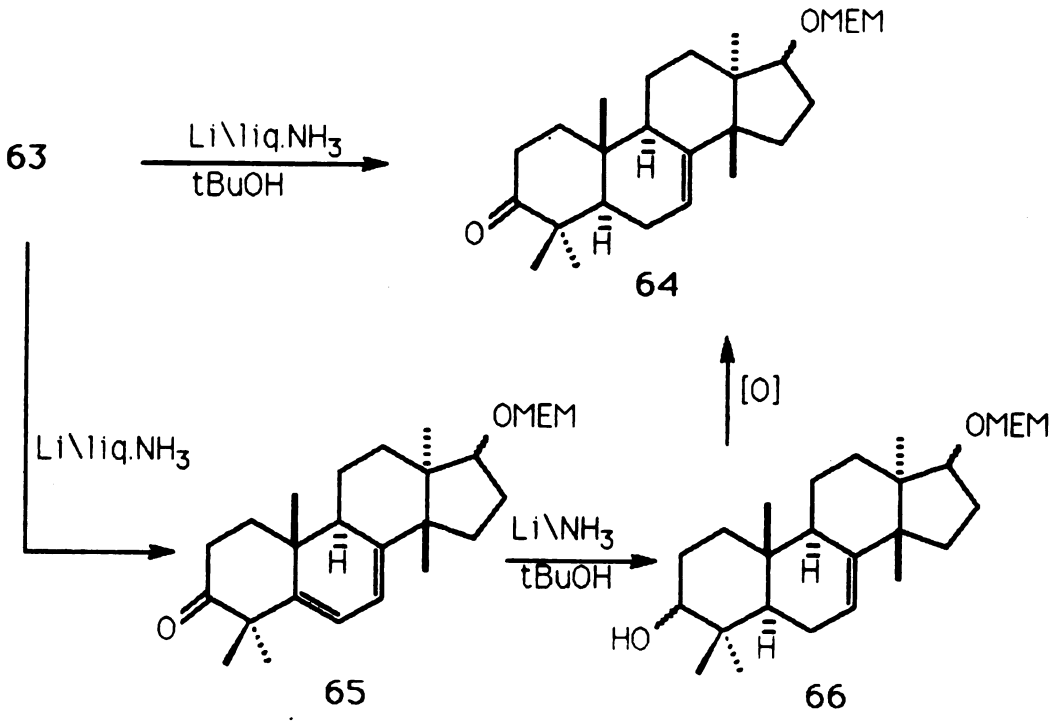



63

An examination of the Drieding molecular models of trienone **54** and cross-conjugated dienone **61** is helpful in explaining the outcome of this methylation. Drieding models show that a $\Delta^{1}$-double bond causes the dienolate derivated from a $\Delta^{1,4}$-diene-3-one **61** to twist about the C-4:C-5 bond by 30° to 35°. This reduces the effective charge delocalization available to this species. However, the addition of a double bond at C-7, not only resists this

twisting, thus neutralizing the adverse effect of the $\Delta^{1}$-double bond, but also extends the charge delocalization (*i.e.*, gives a trienolate).

Treatment of 4,4-dimethyltrienone **63** with 20 equivalents of lithium in liquid ammonia solution containing t-butyl alcohol (10 equivalents) yielded the AB trans-fused $\Delta^{7(8)}$-3-one **64** in excellent yield. Without the t-butyl

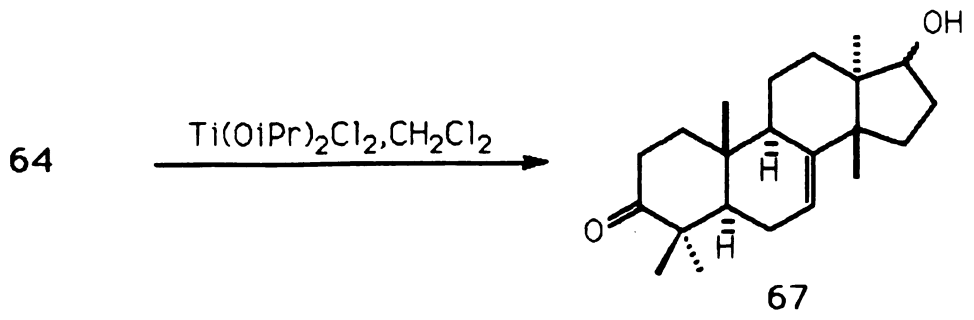



alcohol, this reduction stopped after reduction of the C-1 double bond to give homodiene **65**. The homodiene **65** was also converted to **64** by treatment with lithium in liquid ammonia, followed by oxidation of the resulting epimeric mixture of C-3 alcohols **66**.

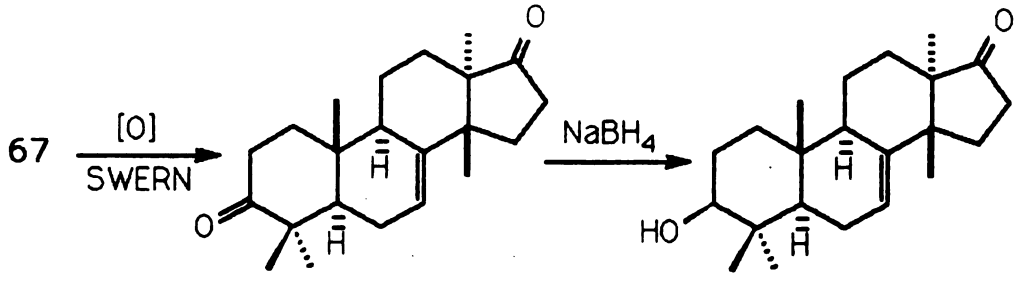
The structure of **64** was assigned from its chemical and spectral properties, and in part on the lumisterol analogy. The infrared spectrum of **64** had a strong carbonyl absorption at 1715 $cm^{-1}$. The 250 MHz $^1H$ NMR spectrum showed a quartet-like ($J$ = 3.3 Hz) signal at $\delta$ 5.22 for the vinyl proton at C-7. In addition, there were four sharp singlets at $\delta$ 0.84, 1.02, 1.05 and 1.15 (overlap) for the five methyl groups. The $^{13}C$ NMR spectrum displayed the expected 26 signals, including a saturated carbonyl peak at $\delta$ 216.45 and two olefinic signals at $\delta$ 145.33 and 117.73.

Removal of the C-17 MEM group in **64** by reaction with titanium tetrachloride ($TiCl_4$) in methylene chloride[62] caused an unexpected problem. Even at -78° for 1 minute, $TiCl_4$, not only cleaved the MEM ether, but also rearranged the ring system to give an unidentified product which showed signals in the aromatic region of the $^1H$ NMR.

It is well known[67] that $TiCl_4$ is a powerful Lewis acid and the acidity of this Lewis acid can be tempered by replacing chloride by alkoxy groups, such as isopropoxy. Realizing that $TiCl_4$ is too strong an acid to be used in our system, a series of modified $TiCl_4$ catalysts were tried to effect cleavage of the MEM ether without any undesired rearrangement. Finally, the MEM protecting group was cleaved cleanly with titanium diisopropyl dichloride ($Ti(O\text{-}iPr)_2Cl_2$) to give the C-17 alcohols **67** in 90% yield.




The last two steps of this synthesis of the tetracyclic core of butyrospermol were straight forward. Swern



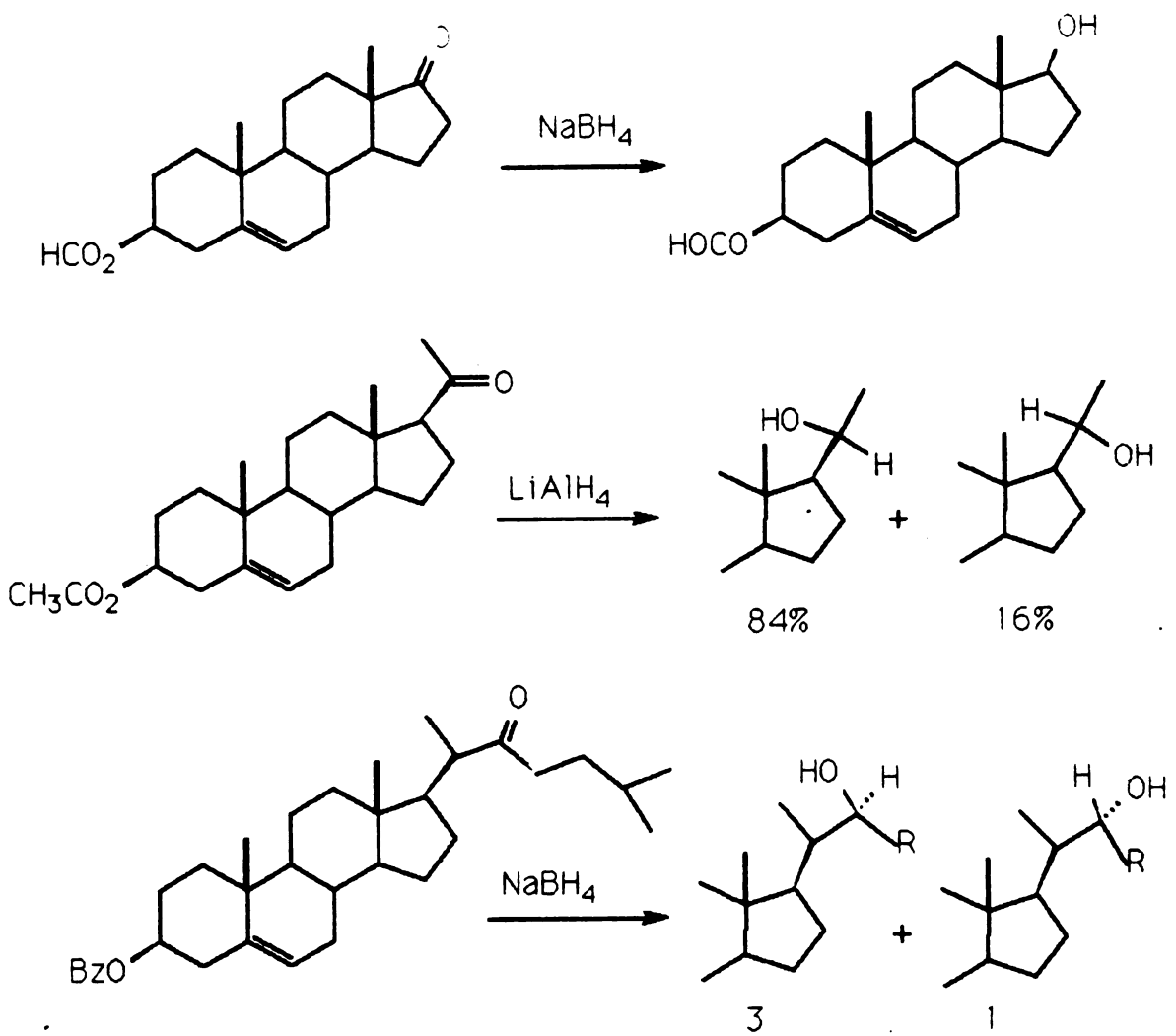

oxidation[68] of the epimeric alcohol mixture **67** gave diketone **68** (93%). Finally, taking advantage of the low reactivity of the C-17 carbonyl group, treatment of **68** with sodium borohydride ($NaBH_4$) gave selective reduction of the C-3 carbonyl function, yielding the equatorial alcohol **69** (91%).

With this compound in hand, we were able to achieve a final conformation of its AB trans-ring fusion. Comparison of chemical and spectral data of **69** with that of its C-5 epimer **49**, prepared and characterized by X-ray crystallography in an earlier study[9], provided unequivocal evidence for these assignments.

## II. Construction of the $C_8$ Side-chain.

With the butyrospermal tetracyclic core **69** in hand, our next task was to attach the $C_8$ side-chain stereoselectively.

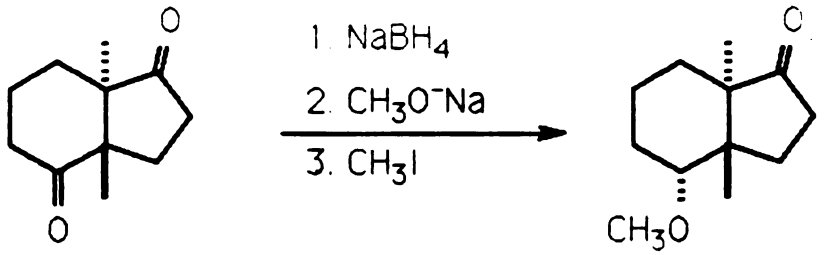
Many excellent stereoselective side-chain syntheses for steroids have been published[18,19,20], whereas for triterpenes, only the epoxide rearrangement/addition procedure described by Krief[29] has been known.




Scheme XIV

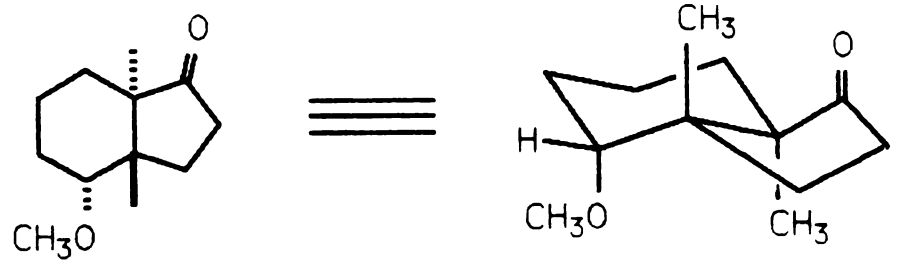
As illustrated in Scheme XIV, reactions of the 17-keto group in steroids can be highly stereoselective with the effect diminishing as one proceeds along the flexible side-chain to C-20 and C-22. Therefore, our task was to find an appropriate synthetic pathway to control the stereochemistry at C-20.

Compound **10**, derived from bicyclic ketone **1**, has been used as a model compound for construction of the side-chain for triterpenes in our laboratory. Examination of a




1 10

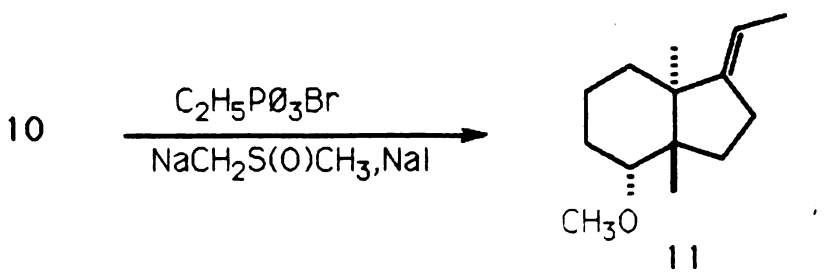
Drieding model of **10** indicates that its trans-configuration induces a puckering of the five-membered ring, analogous to the configuration of the butyrospermol tetracyclic core **69**.




10

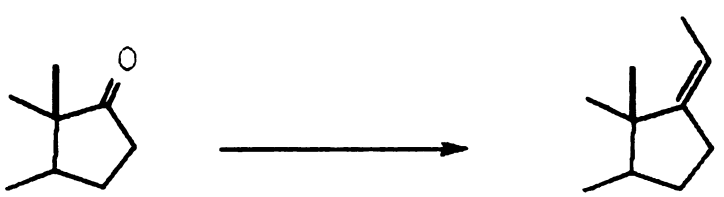
Gibson and Reusch reported[30] that the Wittig reaction of ketone **10** with ethylidene triphenyl phosphorane yielded

the synthetically useful olefin **11** in good yield. The configuration of the double bond of **11** was assigned on the

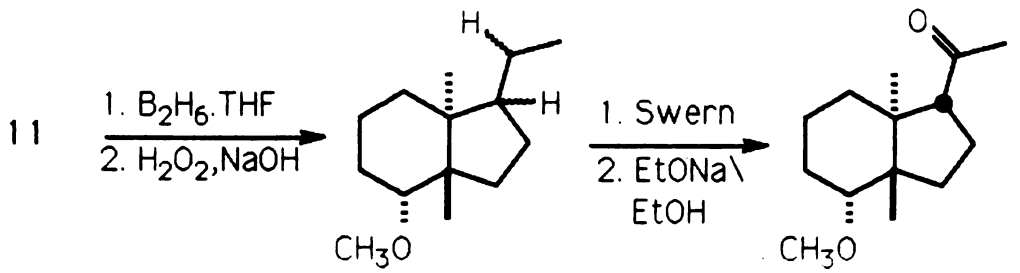



**11**

basis of its proton NMR spectrum compared to the known steroid analogs. It is interesting to note that the olefination of **10** to **11** gave the E-olefin in contrast to equivalent reactions with 17-keto steroids[69], where the Z-isomer dominates. For the 17-keto steroids, the least-hindered approach of nucleophilic reagent is from α-face[21] (opposite side to the C-13 β-methyl group), which leads to

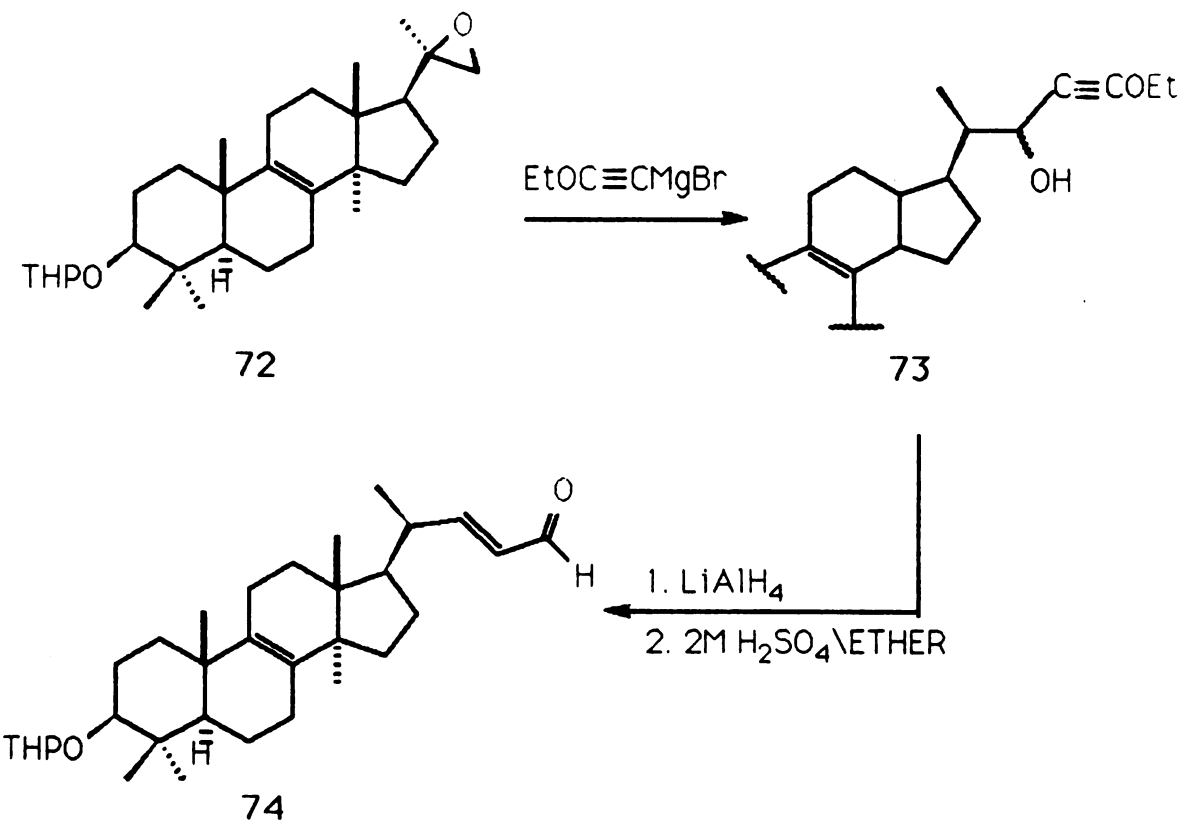



the Z-isomer. For compound **10**, molecular models reveal very little difference in the steric environment of both the α- and β-faces. However, the observed stereselectivity reflected a lesser hindrance of the β-face despite the similarities indicated by the molecular models.



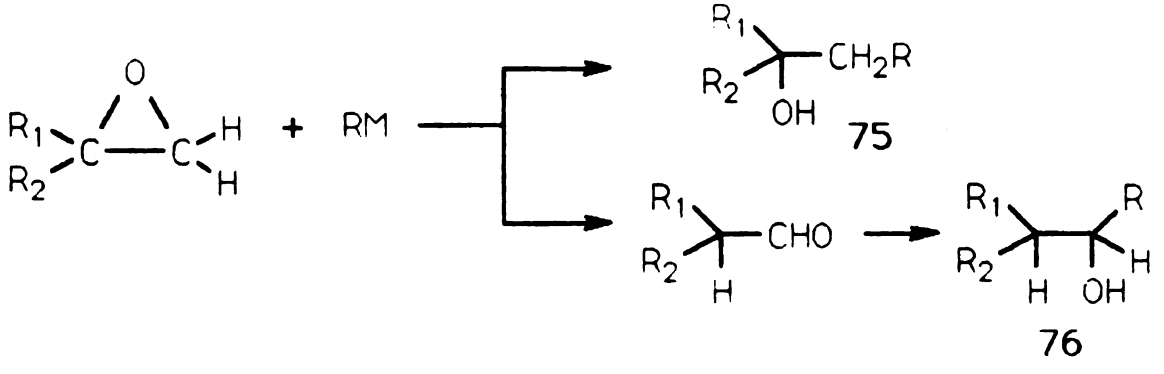

70 12

**Hydroboration of 11 with diborane ($B_2H_6$) yielded alcohol 70 as a mixture of isomers, and subsequent oxidation followed by epimerization with base gave a single isomer 12. Gibson and Reusch assigned[30] the α-configuration at C-17 on the basis of the proton NMR spectrum.**

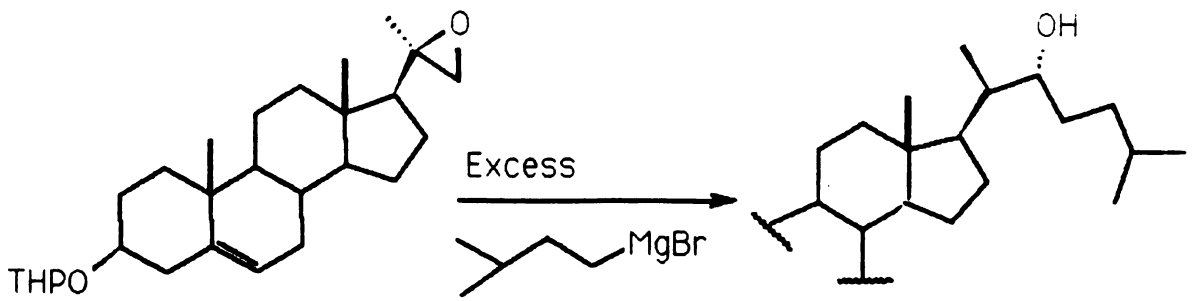


Recently, Krief, *et. al.*[29], reported the first stereoselective side-chain synthesis of unnatural 20-S isolanosterol. The key step of this synthesis is a novel stereospecific isomerization of the epoxide **72** to the corresponding alcohol **73**, using a technique developed by Koreeda in his 20-isocholesterol side-chain synthesis.[28]

It has been known[70,71,72] that epoxides react with organometallics to give two different types of alcohols, **75** and **76**, depending upon the nature of the reagents and the reaction conditions. A direct nucleophilic ring opening of the epoxide gives alcohol **75**. On the other hand, rearrangement of epoxides prior to organometallic attack leads to alchol **76**.




In Koreeda's 20-isocholesterol side-chain syntheis[28], the reaction of isoamyl magnesium bromide with the epoxide **13** produced a rearranged alcohol **77** with a 100% stereoselective hydride shift during the transformation.



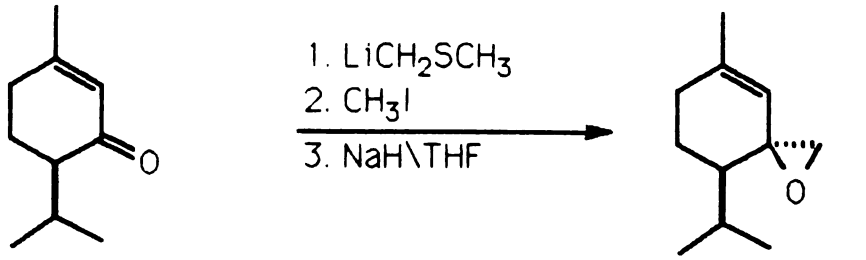

13 77

Similarly, Krief reported[29] that the epoxide **72** gives a 92:8 (20R:20S) mixture of alcohols based largely on an examination of the α,β-unsaturated aldehyde **74**.

These results suggest a solution for our side-chain synthesis with control of the configuration at C-20. Butyrospermol has the same C-20 configuration (R) as does lanosterol. However, the relative configuration at C-13, C-17 and C-20 in these two natural products are different: these are 13-R, 17-R and 20-R for lanosterol; 13-S, 17-S and 20-R for butyrospermol. Therefore, assuming that the C-14 methyl substituent in butyrospermol core **69** will not perturb the stereoselectivities of the side-chain significantly, the epoxide rearrangement/addition sequence described by Krief[29] should offer the control needed for the butyrospermol synthesis. Our application of this procedure was first exercised on the model ketone **12**.

There are many ways to form a one-carbon, extended epoxide from a carbonyl compound.[73] The most direct approach is Corey's dimethylsulfonium methylide[73f]; however, the

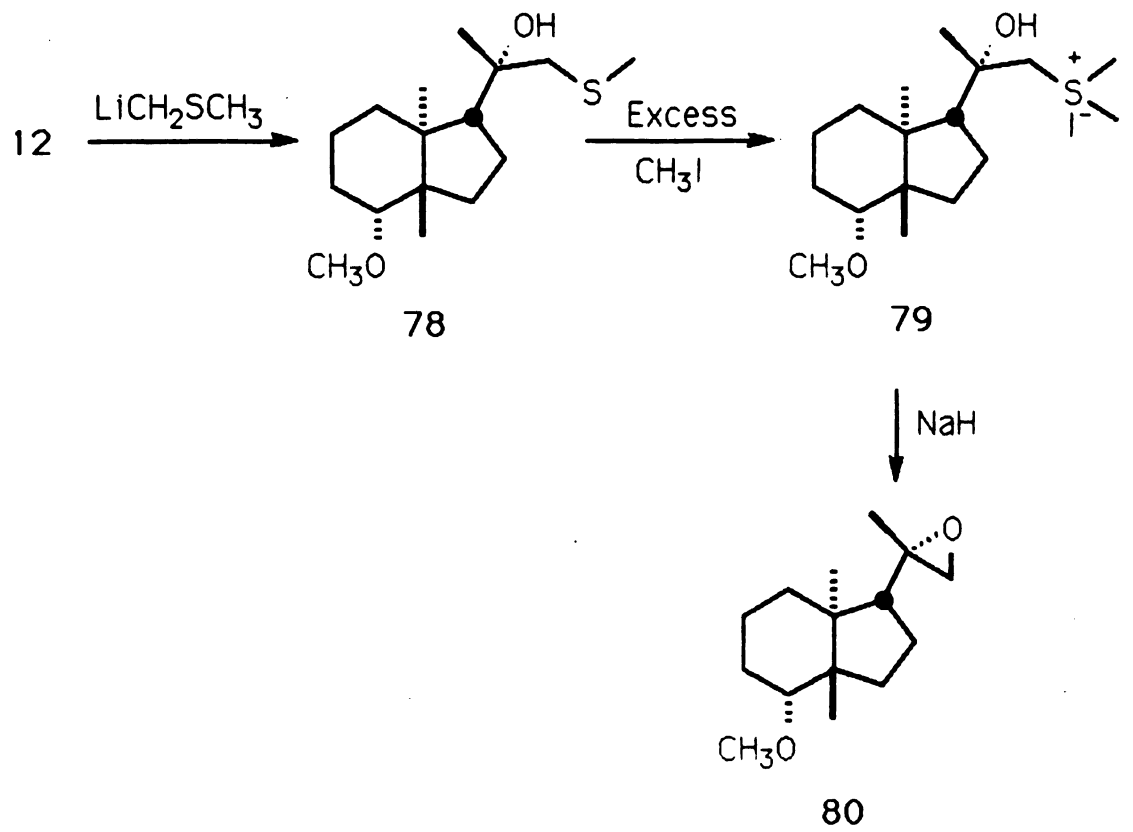
outcome of the stereoselectivity of the resulting epoxide is doubtful. Recently, Tanis, *et. al.*[74], described a convenient method to prepare spiroepoxides with high stereoselectivity using methylthiomethyl lithium.



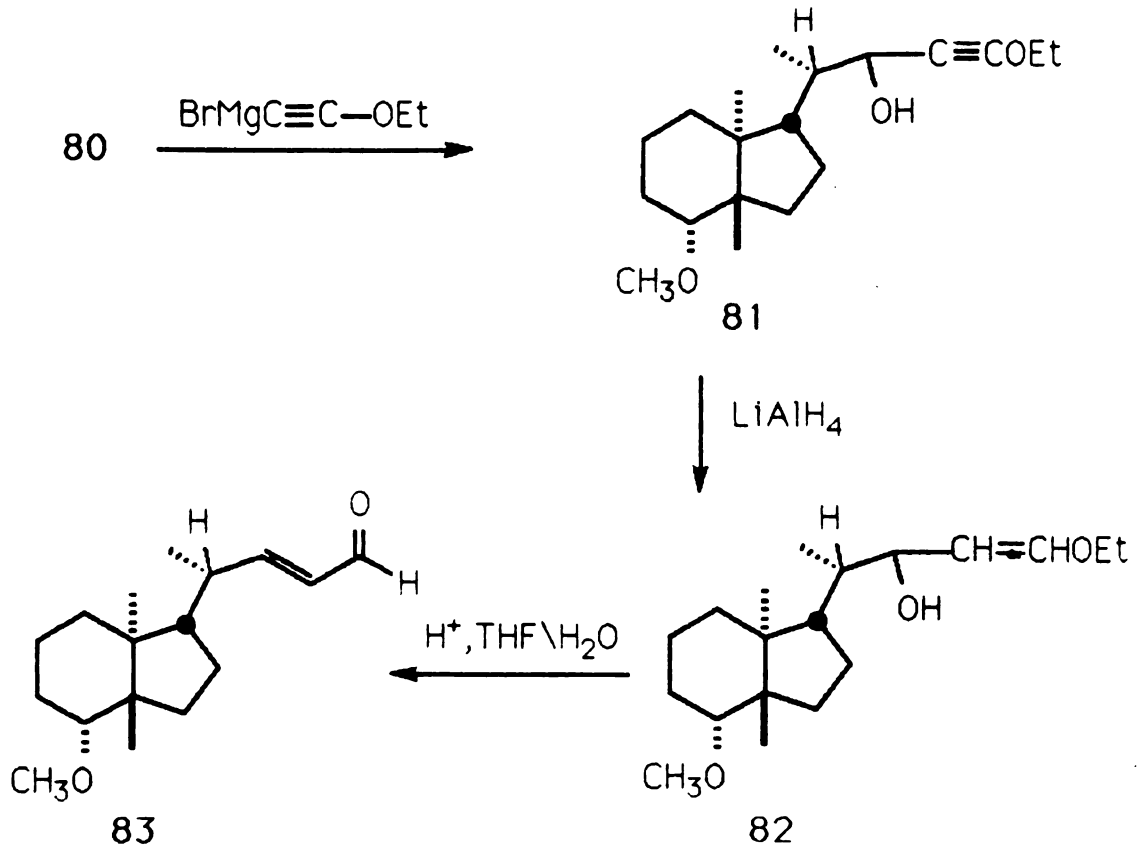

(90%, 15 : 1 )

Treatment of **12** with methylthiomethyl lithium gave alcohol **78** (98% yield, stereoselectivity 92:8 determined by integration of proton NMR). Treatment of **78** with neat methyl iodide provided sulfonium salt **79**, which was used without further purification. Ring closure of the hydroxy sulfonium salt **79** with sodium hydride in THF proceeded smoothly to give the desired epoxide **80** as a single isomer (determined by carbon NMR).

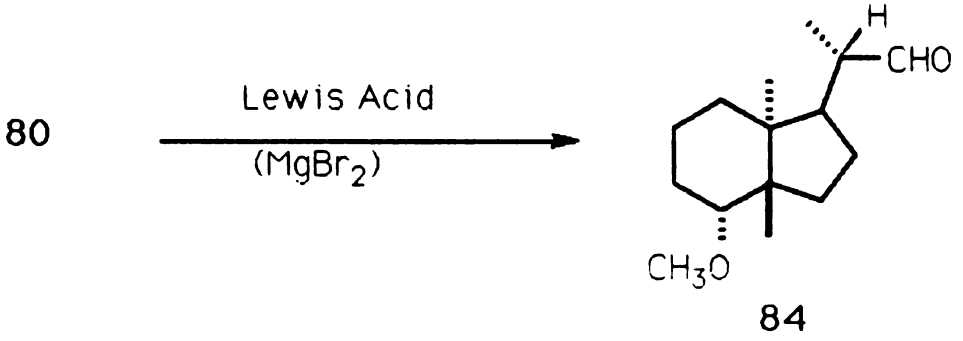
The configuration of the major product at C-12 (C-20 for tetracyclic analogs) in alcohol **78** was assigned in part by examining the molecular models of **78** and in part on Krief's work.[29] Molecular models show that the attack of a nucleophile from the least-hindered side (away from the C-9 methyl group) of the carbonyl group will give the desired C-12(S) thio alcohol (precursor of C-20(R) for the final triterpene).



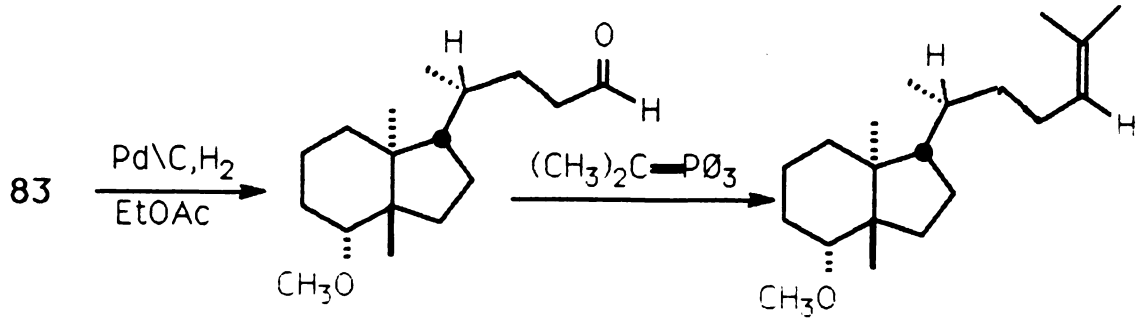

The desired alcohol **81** was obtained by reaction of ethoxyethynyl magnesium bromide with epoxide **80** under the conditions described by Krief[29] (ether:benzene:3:1, 20°, 1h). The carbon NMR spectrum of alcohol **81** shows 19 signals indicating that **81** was obtained largely as a single diastereomer. Thus, the Grignard reaction presumably proceeded via an initial $MgBr_2$-catalyzed, stereospecific isomerization of epoxide **80** into aldehyde **84**, followed by addition of the Grignard reagent. Reduction of the ynolether **81** by lithium aluminum hydride ($LiAlH_4$), followed by acidic hydrolysis of the resulting γ-hydroxy enolether **82**




**produced the α,β-unsaturated aldehyde 83 in 83% overall yield. Aldehyde 83 was then reduced by catalytic hydrogenation (palladium on charcoal). The Wittig reaction**



of the resulting saturated aldehyde **85** with isopropylidene triphenyl phosphorane gave the final product **86** in 88% yield.




85 86

The stereochemical outcome of this whole set of reactions was studied at this stage by comparing carbon-13 chemical shifts of **86** to the chemical shifts of equivalent natural products, reported by S. A. Knight.[75] The chemical shifts reported for euphenol (Figure 1) and the assignments proposed for **86** are shown in Figure 2. Based on these assignments, we assume that compound **86** has a configuration which is analogous to euphenol. However, a definitive assignment may have to wait until the real tetracyclic system is assembled.

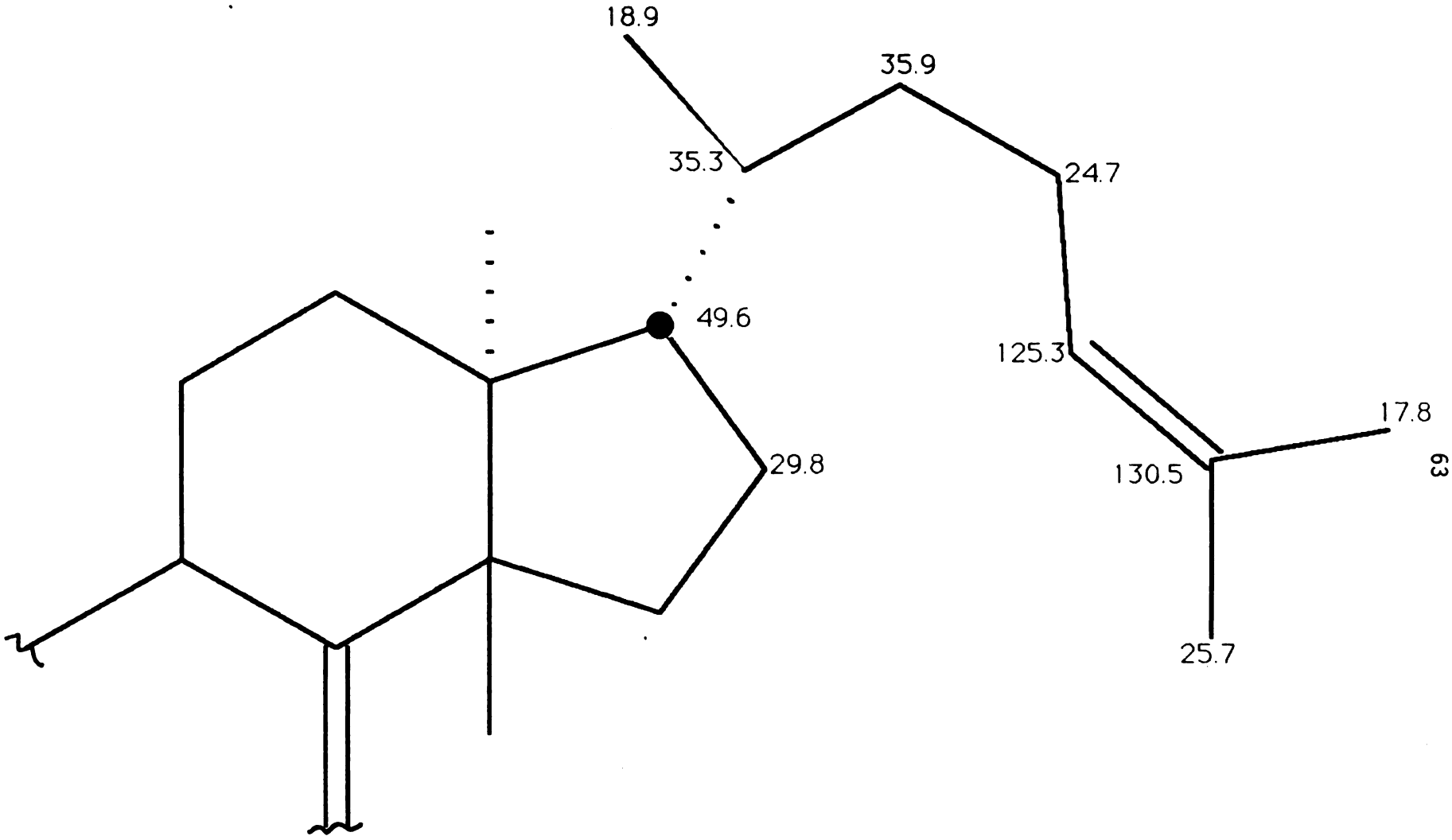



Figure 1

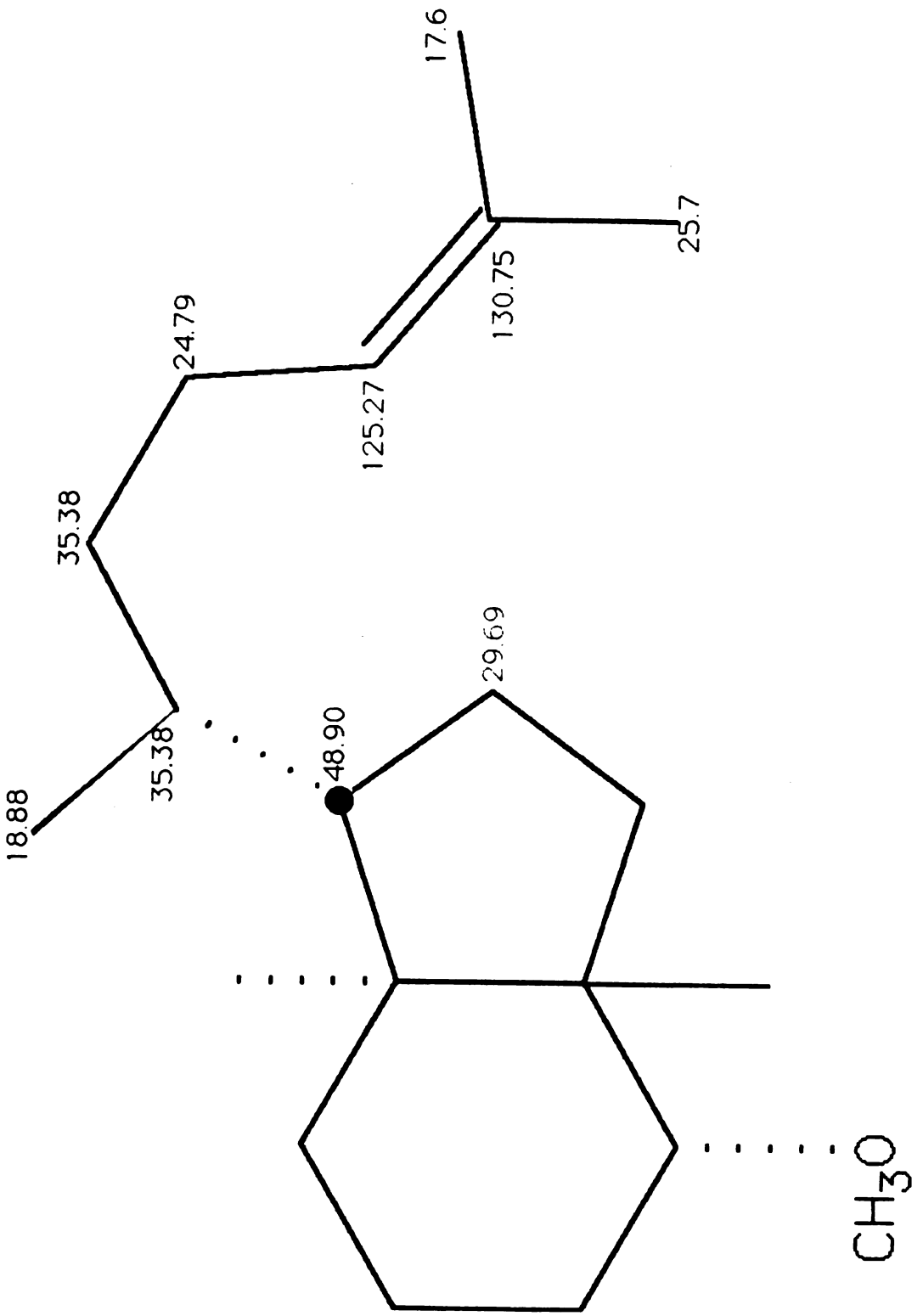



Figure 2

## EXPERIMENTAL

Except where otherwise indicated, all reactions were conducted under a dry argon or nitrogen atmosphere using solvents distilled from appropriate drying agents. Small-scale chromatographic separations were accomplished with the use of 2 mm silica plates (Merck F-254, 20 x 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 solution using either a Varian T-60 or a Bruker WM 250 spectrometer and are calibrated in parts per million ($\delta$) 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 ($\delta$) from TMS as internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Eagle Harbor, Michigan. High resolution mass spectra were performed by the Michigan State University Department of Biochemistry, Mass Spectroscopy Facility, East Lansing, Michigan.

**Trienone 54**

To a solution of diisoproylamine (0.28 mL, 2 mmol) in 5mL THF, cooled to -78°C in a dry ice-acetone bath, was added n-butyllithium (1.1 mL, 1.55 M in hexane, 1.70 mmol) over 2 minutes and the solution was stirred at -78°C for 30 minutes. A solution of enone 53 (610 mg, 1.57 mmol) in 5 mL of THF was added over 2 minutes and the resulting pale yellow solution was stirred at -78°C for 30 minutes. To this solution was added phenyl selenyl bromide (378 mg, 1.6 mmol) in 3 mL THF in one portion. Stirring was continued for an additional 2 h and the reaction mixture was slowly warmed to 0°C and then 20% acetic acid (15 mL) was added followed by addition of 30% hydrogen peroxide (6 mL). This mixture was stirred for 1 h at 0°C and warmed to room temperature in a period of 30 minutes. The reaction was quenched with 10 mL of water and extracted with ether (4 times). The combined organic layers were washed with water, brine and dried with anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil which was chromatographed

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J=3

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CMR

128

(silica-ether) to give 515 mg (85%) of trienone **54** as a yellow oil. Characteristic properties of **54** $\beta$ are:

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.78 (s, 3H), 1.20 (s, 3H), 1.21 (s, 3H), 1.3-2.4 (m, 8H), 2.65 (m, 1H), 3.05 (m, 2H), 3.40 (s, 3H), 3.56 (m, 2H), 3.70 (m, 3H), 4.62 (d, 1H, $J$=6.7Hz), 4.73 (d, 1H, $J$=6.7Hz), 5.37 (q, 1H, $J$=3.3Hz), 6.11 (t, 1H, $J$=1.8Hz), 6.27 (dd, 1H, $J$=1.8,10.1Hz), 7.0 (d, 1H, $J$=10.1Hz).

CMR ($CDCl_3$) 69.8 MHz: $\delta$ 185.74, 165.87, 154.81, 145.28, 128.16, 123.67, 116.52, 94.58, 83.89, 74.94, 71.54, 66.48, 58.72, 49.42, 46.23, 44.35, 42.36, 34.89, 33.10, 32.91, 27.37, 24.71, 19.49, 16.70.

IR ($CCl_4$): 3040, 2940, 2880, 2805, 1665, 1630, 1605, 1375 $cm^{-1}$.

Mass spectrum (70eV): $m/e$ (rel. intens.) 386 ($M^+$, 2), 371 (1), 310 (2), 265 (6), 159 (12), 89 (54), 59 (100).

Characteristic properties of **54** $\alpha$ are:

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.86 (s, 3H), 1.09 (d, 3H, $J$=1Hz), 1.18 (s, 3H), 1.5-2.0 (m, 7H), 2.25 (m, 1H), 2.65 (m, 1H), 3.05 (m, 2H), 3.40 (s, 3H), 3.57 (m, 2H), 3.70 (m, 2H), 4.0 (dd, 1H, $J$=6.4 and 9.0Hz), 4.71 (s, 2H), 5.35 (q, 1H, $J$=3.3Hz), 6.11 (t, 1H, $J$=1.8Hz), 6.27 (dd, 1H, $J$=1.8,10.1Hz), 7.0 (d, 1H, $J$=10.1Hz).

CMR ($CDCl_3$) 69.8 MHz: $\delta$ 185.45, 165.35, 154.47, 144.52, 128.05, 123.55, 116.57, 94.52, 84.65, 71.35, 66.30, 58.58,

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crude p

48.07, 43.83, 43.38, 42.05, 33.06, 32.86, 29.70, 27.56, 26.82, 20.67, 19.03, 16.56.

IR ($CCl_4$): 3030, 2960, 2890, 2830, 1675, 1640, 1615, 1480, 1460, 1300 $cm^{-1}$.

Mass spectrum (70eV): *m/e* (rel. intens.) 386 ($M^+$, 1), 280 (2), 265 (2), 225 (1), 259 (6), 89 (43), 59 (100).

**4,4-Dimethyltrienone 63**

A solution of trienone 54 (405 mg, 1.05 mmol) in 50 mL of dry benzene was prepared in a 100 mL three-necked round-bottomed flask equipped with an argon inlet, reflux condenser, magnetic stirrer and an oil heating bath. A freshly prepared solution of potassium t-butoxide in t-butanol (6.3 mmol) was then added dropwise, and the resulting dark brown solution was stirred and heated to 50°C. An excess of methyl iodide (2.980g, 21 mmole) was added 10 minutes later, and this mixture was maintained at 50°C for 3 h. The resulting bright-yellow solution was cooled, quenched with 10 mL of water, and then extracted with three 20 mL portions of ether. The combined ether extracts were washed with water, then brine and finally dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 417 mg (96%) of a dark brown oil. This crude product proved to be air and light sensitive and was,

therefore, used in the next step without further purification. Characteristic properties of **63** $\beta$ are:

PMR ($CDCl_4$) 250 MHz: $\delta$ 0.69 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.23 (s, 3H), 1.30 (s, 3H), 0.80~2.70 (m, 9H), 3.37 (s, 3H), 3.55 (m, 2H), 3.70 (m, 3H), 4.60 (d, 1H, $J$=6.7Hz), 4.71 (d, 1H, $J$=6.7Hz), 5.65 (dd, 1H, $J$=2.9,5.6Hz), 5.91 (d, 1H, $J$=4.2Hz), 5.96 (d, 1H, $J$=10.3Hz), 6.75 (d, 1H, $J$=10.3Hz).

CMR ($CDCl_3$) 69.8 MHz: $\delta$ 202.69, 153.83, 148.22, 144.69, 124.91, 119.33, 115.84, 94.79, 84.33, 71.76, 66.88, 85.92, 49.26, 47.79, 46.33, 44.35, 39.03, 34.18, 30.85, 30.28, 29.60, 27.08, 24.72, 21.80, 16.60, 15.12.

IR ($CCl_4$): 3050, 2980, 2950, 2890, 2840, 1690, 1670, 1485, 1380 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 414 ($M^+$, 1), 389 (1), 330 (27), 279 (54), 190 (53), 175 (34), 159 (20), 149 (23), 133 (34), 119 (33), 55 (58), 43 (100).

**47(a), 3-one 64**

To a 500 mL three-necked, round-bottomed flask equipped with an argon inlet adaptor, dry-ice condenser, and mechanical stirrer was added 200 mL of ammonia (freshly distilled from sodium) at -78°C. Lithium wire (171 mg, 24.6 mmole) and 100 mL of dry THF were then added, and the resulting dark blue solution was stirred at -78°C for 30 minutes. To this solution was added a solution of 4,4-dimethyl trienone **64** (510 mg, 1.231 mmol) in 50 mL of dry

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THF, followed by t-butyl alcohol (910 mg, 12.3 mmol). After stirring at -78°C for 5 h, the reaction was quenched by adding 1g of ammonium chloride, and the excess ammonia was evaporated into the hood under a stream of argon. The residue was treated with 50 mL of water, and this mixture was extracted by four 20 mL portions of ether. The combined organic layers were washed with ether, brine and dried over anhydrous sodium sulfate. Removal of the solvent yielded 504 mg (98%) of 4,4-dimethyl $\Delta^{7(8)}$, 3-one **64** as an off-white oil. Characteristic properties of **64** $\beta$ are:

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.84 (s, 3H), 1.02 (s, 3H), 1.05 (s, 3H), 1.15 (s, 6H, overlap), 0.80-2.40 (m, 15H), 2.76 (dt, 1H, $J$=5.5,14.5Hz), 3.39 (s, 3H), 3.55 (m, 2H), 3.70 (m, 3H), 4.62 (d, 1H, $J$=6.7Hz), 4.73 (d, 1H, $J$=6.7Hz), 5.22 (q, 1H, $J$=3.3Hz).

IR ($CCl_4$): 2960, 2940, 2880, 1710, 1450, 1380, 1370, 1260, 1035 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 418 ($M^+$, 4), 403 (1), 327 (10), 312 (5), 297 (26), 159 (5), 89 (100), 59 (89), 45 (13).

Characteristic properties of **64** $\alpha$ are:

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.93 (s, 3H), 1.01 (s, 6H, overlap), 1.05 (s, 3H), 1.11 (s, 3H), 0.80-2.45 (m, 15H), 2.75 (dt, 1H, $J$=5.5,14.5Hz), 3.40 (s, 3H), 3.58 (m, 2H), 3.70 (m, 2H), 4.22 (dd, 1H, $J$=6.4,9.0Hz), 4.71 (s, 2H), 5.30 (q, 1H, $J$=3.3Hz).

CMR ($CDCl_3$) 69.8 MHz: δ 216.45, 145.33, 117.73, 94.87, 85.35, 71.72, 66.59, 58.90, 52.29, 48.28, 47.73, 43.84, 38.37, 35.06, 34.77, 33.42, 31.00, 30.41, 28.07, 27.13, 24.47, 24.20, 21.48, 21.26, 17.27, 12.65.

IR ($CCl_4$): 2960, 2900, 2830, 1730, 1480, 1460, 1395, 1375, 1210, 1130, 1050 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 418 ($M^+$, 1), 403 (1), 312 (1), 297 (7), 271 (2), 213 (1), 159 (3), 89 (100), 59 (79), 45 (8).

**C-17 Alcohol 67**

This procedure will be illustrated for a single C-17 α-epimer **67**. A solution of 17α-MEM ether **64** (240 mg, 0.57 mmol) in 30 mL of dry methylene chloride was cooled to 0°C, and a freshly prepared solution of titanium dichloro-diisoproxide in methylene chloride (5.74 mmol) was added dropwise with stirring. The resulting pale yellow solution was warmed to room temperature and it slowly turned orange as the reaction proceeded. This solution was stirred for 12 h at room temperature; the starting material was no longer evident by TLC analysis (silica-ether). The reaction was then quenched by addition of 2 mL of concentrated ammonium hydroxide solution and then was diluted with 10 mL of water. The aqueous phase was extracted twice with methylene chloride, and the combined organic phases were washed with water until the aqueous phase was neutral. Removal of the

solvent from the dried extracts gave a yellow oil, which was chromatographed (silica-ether) to give 170.5 mg (90%) of the 17α-alcohol **67** as an off-white solid. Characteristic properties of **67** β are:

PMR ($CDCl_3$) 250 MHz: δ 0.81 (s, 3H), 1.03 (s, 3H), 1.05 (s, 3H), 1.12 (s, 3H), 1.17 (s, 3H), 0.8-2.40 (m, 15H), 2.76 (dt, 1H, $J$=5.5,14.5Hz), 3.78 (dd, 1H, $J$=1.7,7.4Hz), 5.32 (q, 1H, $J$=3.3Hz).

IR: 3600, 2960, 2860, 1700, 1445, 1380 $cm^{-1}$.

Mass spectrum (70eV): 330 ($M^+$, 19), 315 (100), 279 (40), 271 (6), 243 (12), 159 (13).

Characteristic properties of **67** α are:

PMR ($CDCl_3$) 250 MHz: δ 0.91 (s, 3H), 1.00 (s, 3H), 1.01 (s, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.26 (s, 3H), 1.74 (s, 3H), 0.80-2.45 (m, 16H), 2.76 (dt, 1H, $J$=5.5,14.5Hz), 4.09 (dd, 1H, $J$=6.6,9.0Hz), 5.30 (q, 1H, $J$=3.3Hz).

CMR ($CDCl_3$) 69.8 MHz: δ 216.68, 145.47, 117.77, 80.60, 52.37, 48.31, 47.82, 44.01, 38.43, 35.13, 34.83, 33.52, 30.67, 29.71, 27.10, 24.52, 24.25, 21.54, 20.41, 17.24, 12.71.

IR ($CCl_4$): 3640, 2970, 2940, 2880, 1740, 1465, 1390, 1275, 1120, 1045 $cm^{-1}$.

Mass spectrum (70eV) 330 (5), 315 (19), 297 (8), 243 (4), 149 (12), 145 (9), 119 (18), 105 (24), 57 (41), 43 (100).

**C3,17-Diketone 68**

A solution of oxaryl chloride (0.1 mL, 1.14 mmol) in 5 mL of methylene chloride was placed in a 25 mL pear-shaped flask equipped with an argon inlet, a magnetic stirred, and cooled by a dry-ice/acetone bath. Dimethyl sulfoxide (0.2 mL, 3.2 mmol) was added slowly to the stirred oxaryl chloride solution at -78°C, and after a 2 minute pause, a solution of alcohol **67** (230 mg, 0.7 mmol) in 2 mL of methylene chloride was added. Stirring was continued for an additional 15 minutes; triethylamine (1 mL, 7.1 mmol) was then added and the reaction mixture was slowly warmed to room temperature. After mixing with 10 mL of cold water, the organic phase was separated and the aqueous phase was extracted twice with ether. The combined organic phases were washed with water, brine and dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil which was chromatographed (silica-hexane:ether:3:1) to give 210 mg (91%) of the C3,17-diketone **68** as a white solid.

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.98 (s, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 1.07 (s, 3H), 1.13 (s, 3H), 0.80-2.40 (m, 14H), 2.50 (ddd, 1H, $J$=1.8,9.6,19.4Hz), 2.77 (dt, 1H, $J$=5.5,14.5Hz), 5.47 (q, 1H, $J$=3.5,6.6Hz).

CMR ($CDCl_3$) 68.7 MHz: $\delta$ 219.46, 216.19, 142.86, 119.17, 52.36, 48.52, 47.78, 46.17, 38.39, 35.19, 34.76, 34.21, 30.77, 29.65, 26.85, 24.56, 24.43, 24.19, 23.54, 21.58, 16.97, 12.66.

IR ($CCl_4$): 2985, 2970, 1750, 1720, 1470, 1395, 1380, 1375 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 328 ($M^+$, 5), 313 (10), 295 (3), 271 (4), 257 (4), 241 (4), 175 (5), 149 (37), 129 (48), 119 (23), 83 (37), 69 (30), 55 (82), 41 (100).

**C-3β-Alcohol 69**

A solution of C3,17-diketone **68** (210 mg, 0.66 mmol) in 15 mL of 95% aqueous ethanol was cooled to 0°C, and 6 mL of 0.1M sodium borohydride in 3N aqueous sodium hydroxide was added dropwise. This solution was stirred at 0°C, and the reaction progress was monitored by TLC (silica-ether). After 3 h, the soltuion was diluted with 20 mL of water and extracted three 20 mL portions of ether. The combined ether layers were washed with water, brine, and dried over anhydrous sodium sulfate. Removal of the solvent yielded 189 mg (91%) of the C-3β-alcohol **69** as an off-white solid.

PMR ($CDCl_3$) 250 MHz: δ 0.78 (s, 3H), 0.88 (s, 3H), 0.94 (s, 3H), 0.99 (s, 3H), 1.05 (s, 3H), 0.8-2.4 (m, 16H), 2.50 (ddd, 1H, *J*=1.8,9.6,19.4Hz), 3.26 (dd, 1H, *J*=4.4,10.8Hz), 5.44 (q, 1H, *J*=3.3Hz).

CMR ($CDCl_3$) 69.8 MHz: δ 220.09, 142.58, 119.20, 78.94, 50.63, 48.90, 46.12, 38.89, 37.08, 35.05, 34.24, 31.12, 30.69, 29.62, 27.54, 26.67, 24.43, 23.73, 23.47, 16.77, 14.70, 12.91.

IR ($CCl_4$): 3600, 2990, 1720, 1475, 1360 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 331 (7), 330 ($M^+$, 27), 297 (42), 285 (4), 271 (4), 190 (32), 175 (17), 163 (10), 149 (25), 133 (15), 119 (19), 84 (100), 57 (79), 43 (89).

**Compound 12**

To a cooled (-78°C) stirred solution of oxaryl chloride (1.22 mL, 13.95 mmol) in 30 mL dry methylene chloride was added (5 minutes) a solution of dimethyl sulfoxide (1.5 mL, 2.1 mmol) in 5 mL of methylene chloride. This mixture was stirred for 5 minutes, and a solution of alcohol **70** (1.05g, 4.65 mmol) was then added over a 10 minute period. Stirring was continued for an additional 20 minutes at -78°C, followed by addition of 10 mL of triethylamine. The reaction mixture was warmed to room temperature, diluted with 50 mL of water and the organic phase was separated. The aqueous layer was extracted with three 30 mL portions of ether, and the combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 980 mg of a yellow oil as a mixture of ketones epimeric at C-17. This epimeric mixture, in 30 mL of dry ethanol, was added to a freshly prepared solution of sodium ethoxide (15 mmol) in ethanol (15 mL of a 1 molar solution in ethanol). After stirring at room temperature for 3 h, the reaction mixture was quenched with

water and extracted with ether (five times). The combined ether extracts were washed and dried; and evaporation of the solvent, followed by flash chromatography (silica-hexane:ethylacetate:4:1), yielded 843 mg (80.3%) of the 17-α methyl ketone **12** as an off-white solid, m.p. 47-48°. PMR ($CDCl_3$) 250 MHz: δ 0.91 (s, 3H), 0.92 (d, 3H, J=1Hz), 0.8-2.0 (m, 9H), 2.08 (s, 3H), 2.22-2.38 (m, 1H), 2.75 (t, 1H, J=8.3Hz), 3.2 (m, 1H), 3.27 (s, 3H).

**Compound 78 and 79**

To a chilled (0°C) solution of n-butyllithium (1.85 mL of a 1.6M hexane solution, 2.96 mmol) in 2.6 mL of THF was added TMEDA (317 ul, 2.96 mmol). This mixture was warmed to room temperature and stirred for 30 minutes. The resulting pale yellow solution was cooled to 0°C and dimethylsulfide (220 ul, 3.0 mmol) was added. The resulting yellow solution was stirred for 3 h at room temperature, cooled to -78°C in a dry-ice/acetone bath, and then mixed with a pre-cooled (-78°C) solution of 17-α methyl ketone **12** (663 mg, 2.96 mmol) in 15 mL of THF. This mixture was warmed to room temperature and then diluted with 50 mL of ether and 10 mL of saturated aqueous ammonium chloride. The organic phase was separated, washed with water, brine and dried over anhydrous sodium sulfate. Removal of the solvent gave the crude adduct (698 mg, 99%) as a yellow oil which was used

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without further purification. The characteristic properties of this C-21 alcohol **78** are:

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.90 (s, 3H), 1.18 (s, 3H), 1.31 (s, 3H), 0.9-2.0 (m, 12H), 2.15 (s, 3H), 2.60 (s, 2H), 3.19 (m, 1H), 3.28 (s, 3H).

IR (neat): 3500, 2970, 2940, 2910, 1470, 1430, 1380, 1090 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 286 ($M^+$, 1), 269 (1), 225 (16), 193 (12), 175 (16), 149 (48), 123 (30), 71 (100), 43 (87).

A portion of this alcohol (238 mg, 1 mmol) was added to excess methyl iodide (5 mL, 35 mmol) in 10 mL of dry acetone, and the reaction mixture was refluxed overnight. Evaporation of the solvent gave a brown solid, which on trituration with ether, yielded a white solid (310 mg, 75%) identified as sulfonium salt **79**. Pure **79** displays the following properties: m.p. = 210 (Dec).

PMR ($d_6$-Acetone) 250 MHz: $\delta$ 0.90 (s, 3H), 1.19 (s, 3H), 1.56 (s, 3H), 0.90-2.0 (m, 12H), 3.19 (m, 1H), 3.21 (s, 3H), 3.24 (s, 3H), 3.28 (s, 3H), 3.79 (d, 1H, $J$=13Hz), 3.98 (d, 1H, $J$=13Hz).

Mass spectrum (70eV) *m/e* (rel. intens.) 255 (1), 225 (37), 207 (3), 193 (24), 175 (28), 149 (50), 142 (99), 127 (45), 109 (25), 71 (100).

**Compound 80**

To a suspension of the sulfonium salt 79 (414 mg, 1 mmol) in 20 mL of THF was added 30 mg (1.25 mmole) of sodium hydride in one portion. After this mixture was stirred at room temperature for 4 h, the starting material was no longer evident by TLC analysis (silica-hexane:ether:3:1), and the reaction was quenched with water and then extracted with ether (three times). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulfate. Removal of the solvent gave 230 mg of crude product, which on chromatography (silica-hexane:ether:3:1), yielded 215 mg (90%) of pure epoxide 80.

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.88 (s, 3H), 1.11 (s, 3H), 1.35 (s, 3H), 1.0-2.10 (m, 11H), 2.30 (d, 1H, $J$=5.25Hz), 2.49 (d, 1H, $J$=5.25Hz), 3.16 (m, 1H), 3.28 (s, 3H).

CMR ($CDCl_3$) 69.8 MHz: $\delta$ 85.00, 57.71, 56.24, 51.20, 49.89, 48.70, 44.83, 32.95, 28.95, 23.65, 23.13, 22.72, 20.05, 17.83, 17.60.

IR ($CCl_4$): 3050, 2990, 2975, 2800, 2830, 1475, 1450, 1390, 1350, 1270, 1190, 1100 $cm^{-1}$.

Mass spectrum (70eV) $m/e$ (rel. intens.) 238 ($M^+$, 1), 223 (1), 206 (3), 191 (3), 175 (5), 147 (18), 122 (37), 107 (37), 98 (30), 71 (82), 43 (100).

**Compound 81**

To a cooled (0°C) solution of epoxide 80 (215 mg, 0.90 mmol) in 20 mL of 3:1 (v/v) ether/benzene was added 3 mL of a 1M solution of ethoxy ethynyl magnesium bromide (3.0 mmol, freshly prepared by reacting ethyl magnesium bromide in ether with ethoxyacetylene in benzene). The light brown mixture was warmed to room temperature, and reaction progress was monitored by TLC analysis (silica-hexane:ether:3:1). After 2 h, the reaction was quenched with 5 mL of saturated aqueous ammonium chloride and extracted with ether (four times). The combined organic layers were washed with water, brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 247 mg (89%) of ynol ether 81 as a yellow oil.

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.89 (s, 3H), 1.0 (s, 3H), 1.01 (d, 3H, $J$=6.8Hz), 1.37 (t, 3H, $J$=7.0Hz), 0.9-2.0 (m, 13H), 3.16 (m, 1H), 3.28 (s, 3H), 4.2 (q, 2H, $J$=7.0Hz), 4.67 (d, 1H, $J$=2.3Hz).

CMR ($CDCl_3$) 69.8 MHz: $\delta$ 93.88, 85.35, 74.47, 63.97, 57.71, 48.83, 46.41, 43.69, 41.24, 39.52, 32.75, 29.26, 26.18, 23.77, 23.23, 17.77, 17.05, 14.37, 13.42.

IR ($CCl_4$): 3620, 2955, 2895, 2850, 1685, 1460, 1380, 1260, 1115 $cm^{-1}$.

**Compound 82 and 83**

To a chilled (0°C) suspension of lithium aluminum hydride (22.2 mg, 0.584 mmol) in 30 mL of ether was added (dropwise with stirring) a solution of ynol ether 81 (180 mg, 0.584 mmol) in 5 mL of ether. The reaction mixture was warmed to room temperature; and after stirring for 2 h, excess hydride was destroyed by addition of 2 mL of 3N NaOH solution and diluted with 10 mL of water. Extraction with ether followed by removal of solvent yielded 180 mg (99%) of vinyl ether 82, a colorless oil which was used without further purification. The characteristic properties of vinyl ether 82 are:

PMR ($CDCl_3$) 250 MHz: δ 0.88 (s, 3H), 0.88 (d, 3H, $J$=6.8Hz), 1.01 (s, 3H), 1.28 (t, 3H, $J$=7.0Hz), 0.9-2.0 (m, 13H), 3.16 (m, 1H), 3.28 (s, 3H), 3.74 (q, 1H, $J$=7.0Hz), 4.29 (dd, 1H, $J$=2.3,7.9Hz), 4.91 (dd, 1H, $J$=7.9,12.6Hz), 6.44 (d, 1H, $J$=12.6Hz).

CMR ($CDCl_3$) 69.8 MHz: δ 148.11, 105.94, 85.27, 71.42, 64.68, 57.65, 48.76, 46.65, 43.74, 40.80, 32.69, 29.21, 26.03, 23.20, 17.72, 16.95, 14.62, 12.33.

This product was dissolved in 20 mL of 5:1 (v/v) THF/water containing two drops of concentrated hydrochloric acid. The resulting solution was stirred at room temperature and reaction progress was monitored by TLC. After 3 h, the mixture was diluted with water and then extracted with ether. The combined ether extracts were

washed with saturated aqueous sodium bicarbonate, water, brine and dried over sodium sulfate. Evaporation of the solvent yielded a light yellow oil which was flash chromatographed (silica-hexane:ethylacetate:3:1) to give 130 mg (84.4%) of pure unsaturated aldehyde **83** as a white solid, m.p. = 51-53°.

PMR ($CDCl_3$) 250 MHz: δ 0.86 (s, 3H), 0.96 (s, 3H), 1.04 (d, 3H, $J$=6.9Hz), 1.0-2.0 (m, ?H), 2.48 (m, 1H), 3.16 (m, 1H), 3.28 (s, 3H), 6.06 (dd, 1H, $J$=7.9,15.7Hz), 6.70 (dd, 1H, $J$=9.6,15.7Hz), 9.49 (d, 1H, $J$=7.9Hz).

CMR ($CDCl_3$) 69.8 MHz: δ 194.26, 165.03, 130.57, 84.92, 57.56, 51.55, 48.53, 43.88, 39.94, 32.47, 28.91, 26.13, 23.32, 23.02, 17.42, 16.99.

IR ($CCl_4$): 3020, 2980, 2960, 2880, 2820, 2740, 1695, 1635, 1455, 1380, 1190, 1095 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 264 ($M^+$, 10), 249 (1), 232 (12), 214 (5), 149 (51), 139 (20), 122 (100), 107 (61), 93 (39), 71 (91), 55 (60), 41 (53).

**Compound 85 and 86**

The unsaturated aldehyde **83** (60 mg, 0.227 mmol) was reduced by hydrogen (1 atm.) in the presence of palladium on charcoal suspended in 20 mL of ethyl acetate. The resulting aldehyde **85** (60 mg, 100%) exhibits the following characteristic properties:

PMR ($CDCl_3$) 250 MHz: δ 0.84 (d, 3H, $J$=6.8Hz), 0.86 (s, 3H), 1.01 (s, 3H), 1.0-2.0 (m, 15H), 2.42 (m, 1H), 3.16 (m, 1H), 3.28 (s, 3H), 9.76 (t, 1H, $J$=1.9Hz).

CMR ($CDCl_3$) 69.8 MHz: δ 202.94, 85.22, 57.60, 50.76, 48.83, 43.82, 40.89, 34.37, 33.27, 29.07, 27.14, 26.83, 23.52, 23.04, 18.66, 17.70, 16.59.

IR ($CCl_4$): 2940, 2880, 2820, 1710, 1470, 1380, 1090 $cm^{-1}$.

Mass spectrum (70eV) *m/e* (rel. intens.) 266 ($M^+$, 3), 251 (2), 234 (10), 219 (3), 201 (3), 179 (5), 154 (30), 122 (100), 107 (36), 71 (38), 55 (18).

To a suspension of isopropyl triphenylphosphine iodide (994 mg, 2.3 mmol) in 30 mL of dry toluene was added 2.2 mL of a 1M solution of potassium t-amylate (2.2 mmol). Refluxing for 30 minutes gave a dark red solution, to which was added a solution of the reduced aldehyde **85** (60 mg, 0.227 mmol) in 2 mL of toluene. After this mixture was stirred for 16 h under reflux, the starting material was no longer evident by TLC analysis (silica-hexane:ethylacetate:4:1). The cooled reaction mixture was diluted with 20 mL of water and extracted (three times) with pentane:ether (4:1). The combined organic phases were washed with water, brine and dried over anhydrous magnesium sulfate. Evaporation of solvent followed by column chromatography yielded 58 mg (88%) of the product **86** as a colorless oil.

PMR ($CDCl_3$) 250 MHz: $\delta$ 0.84 (d, 3H, $J$=6.1Hz), 0.85 (s, 3H), 0.99 (s, 3H), 0.9-2.10 (m, 16H), 1.60 (s, 3H), 1.68 (s, 3H), 3.16 (m, 1H), 3.27 (s, 3H), 5.08 (t, 1H, $J$=7.0Hz).

CMR ($CDCl_3$) 69.8 MHz: $\delta$ 130.75, 125.27, 85.48, 57.71, 51.04, 48.90, 43.90, 35.87, 34.85, 33.40, 29.69, 29.24, 26.96, 25.70, 24.79, 23.66, 23.26, 18.88, 17.84, 16.64.

IR ($CCl_4$): 2920, 2885, 1470, 1380, 1095 $cm^{-1}$.

Mass spectrum (CI) $m/e$ (rel. intens.) 291 ($M^+$, 1), 273 (2), 251 (24), 233 (100), 215 (39), 203 (12), 175 (9).

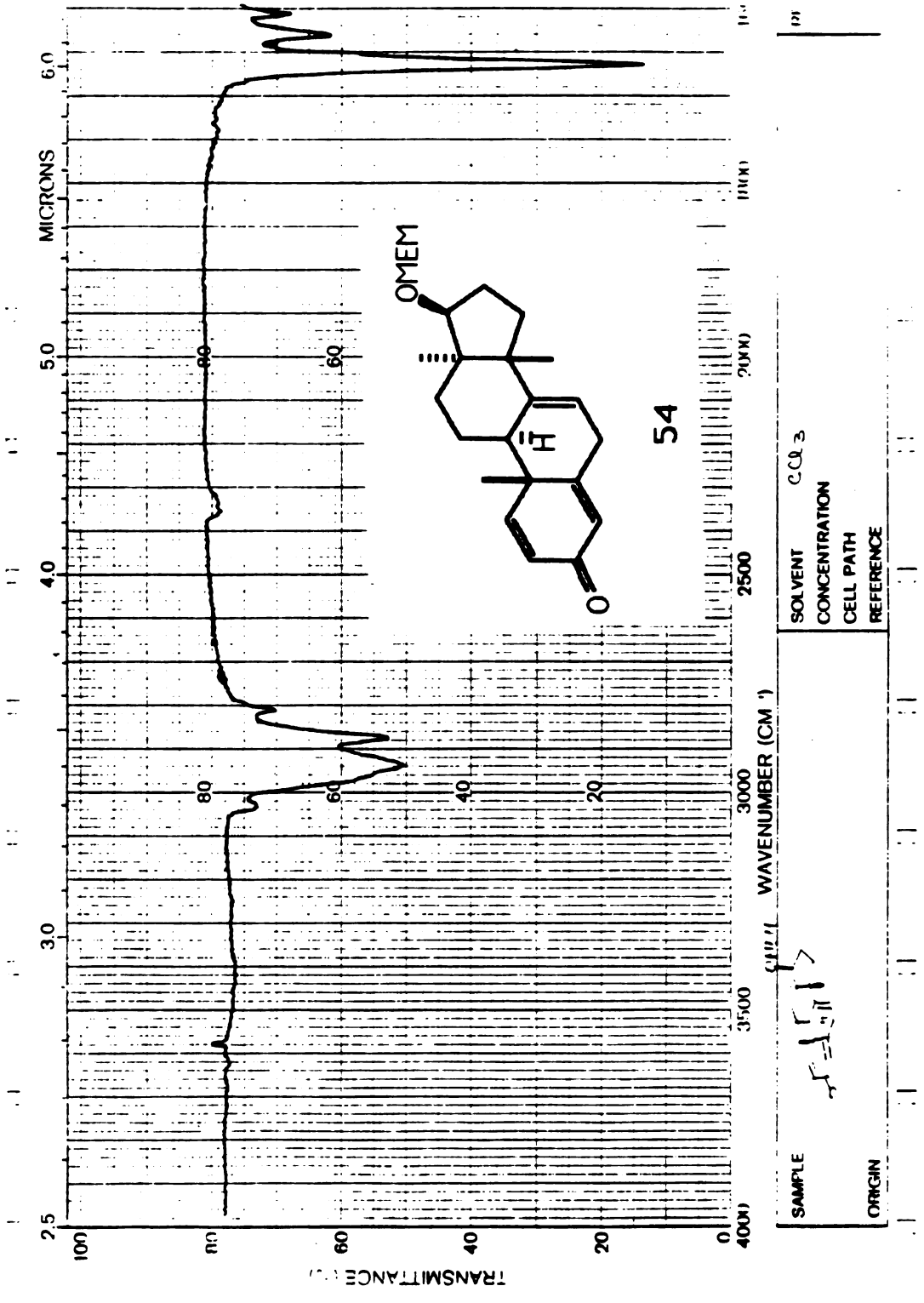
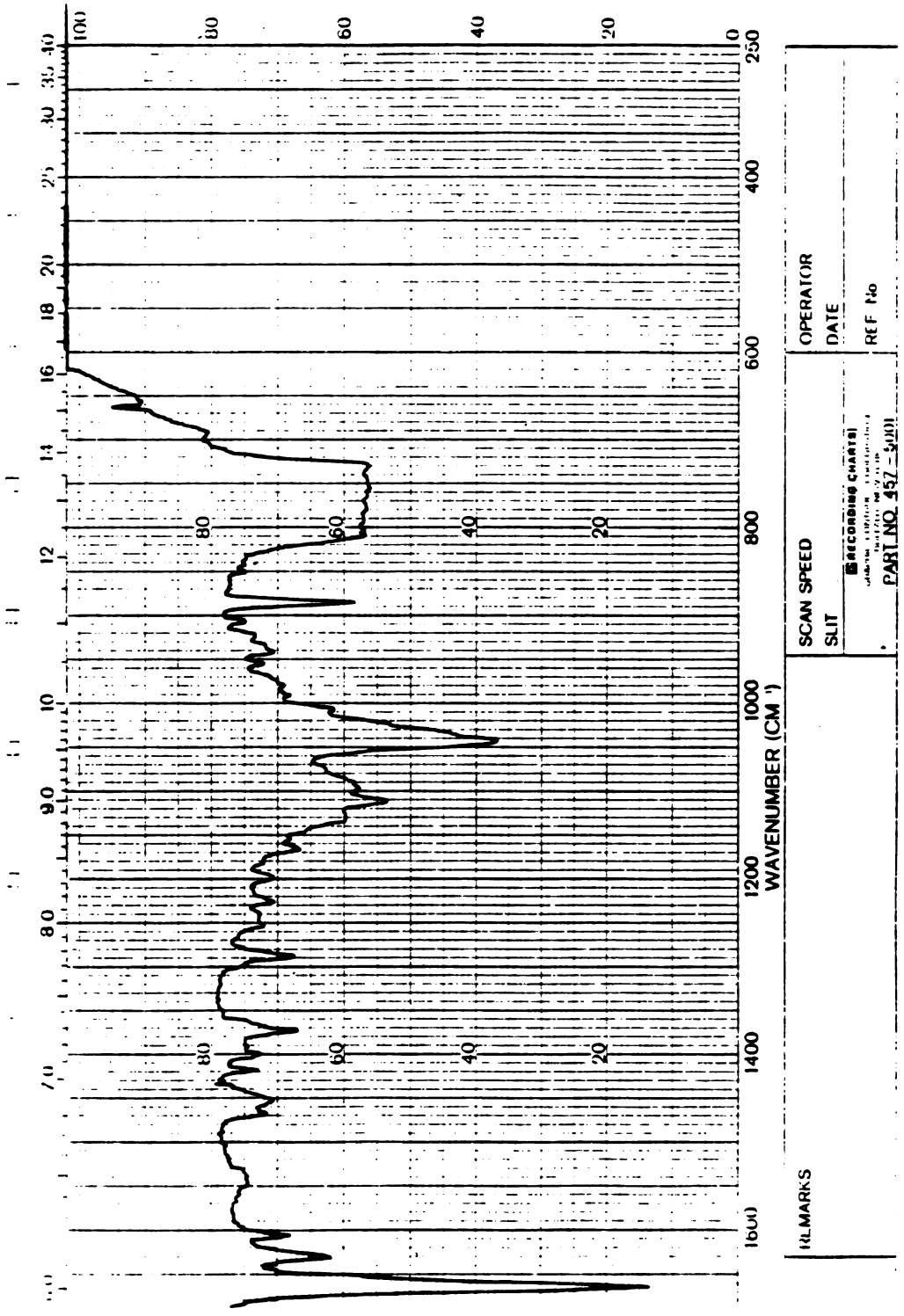



Figure 3 IR Spectrum of Compound 54(β)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PART NO 457-5001
REMARKS

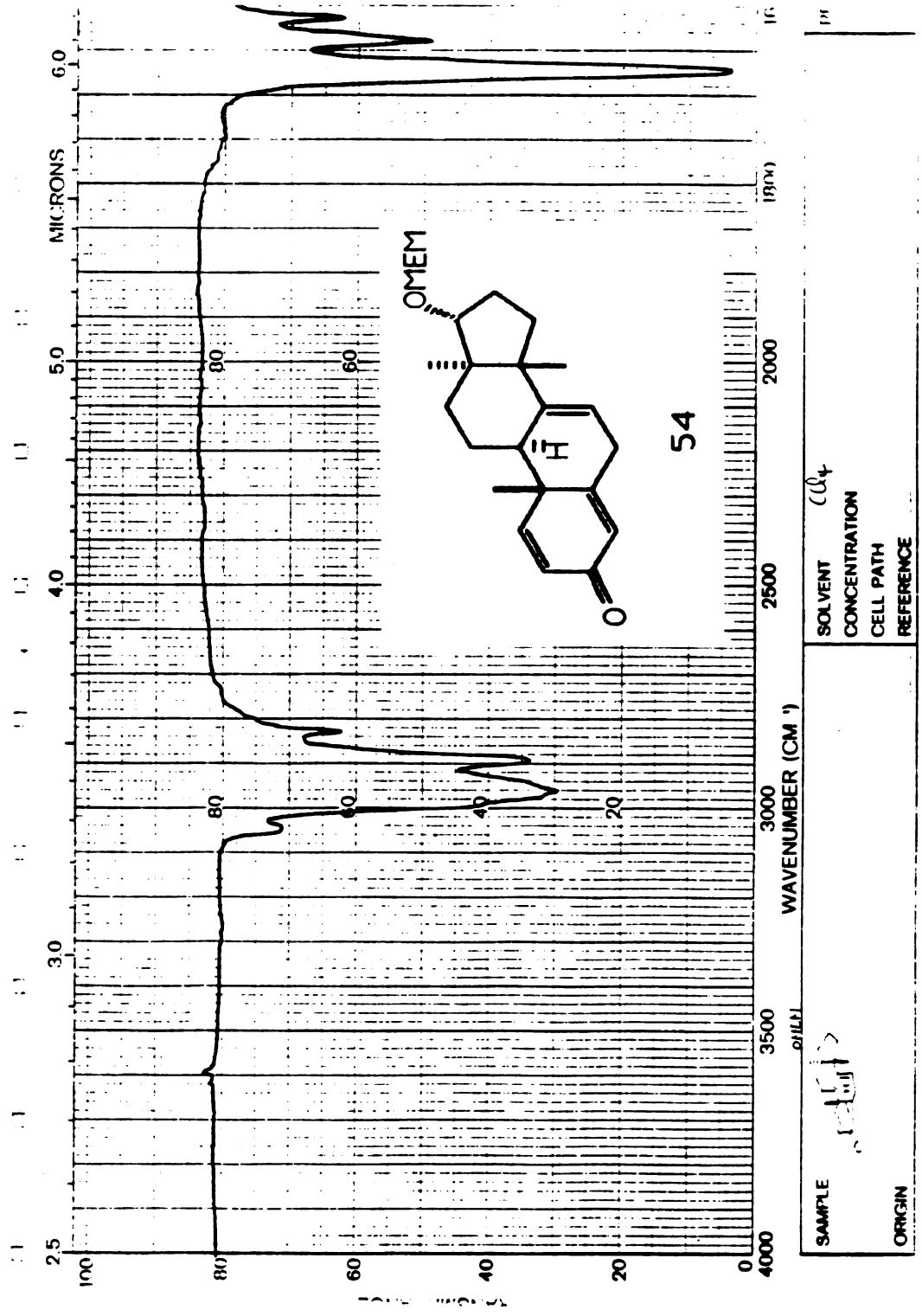
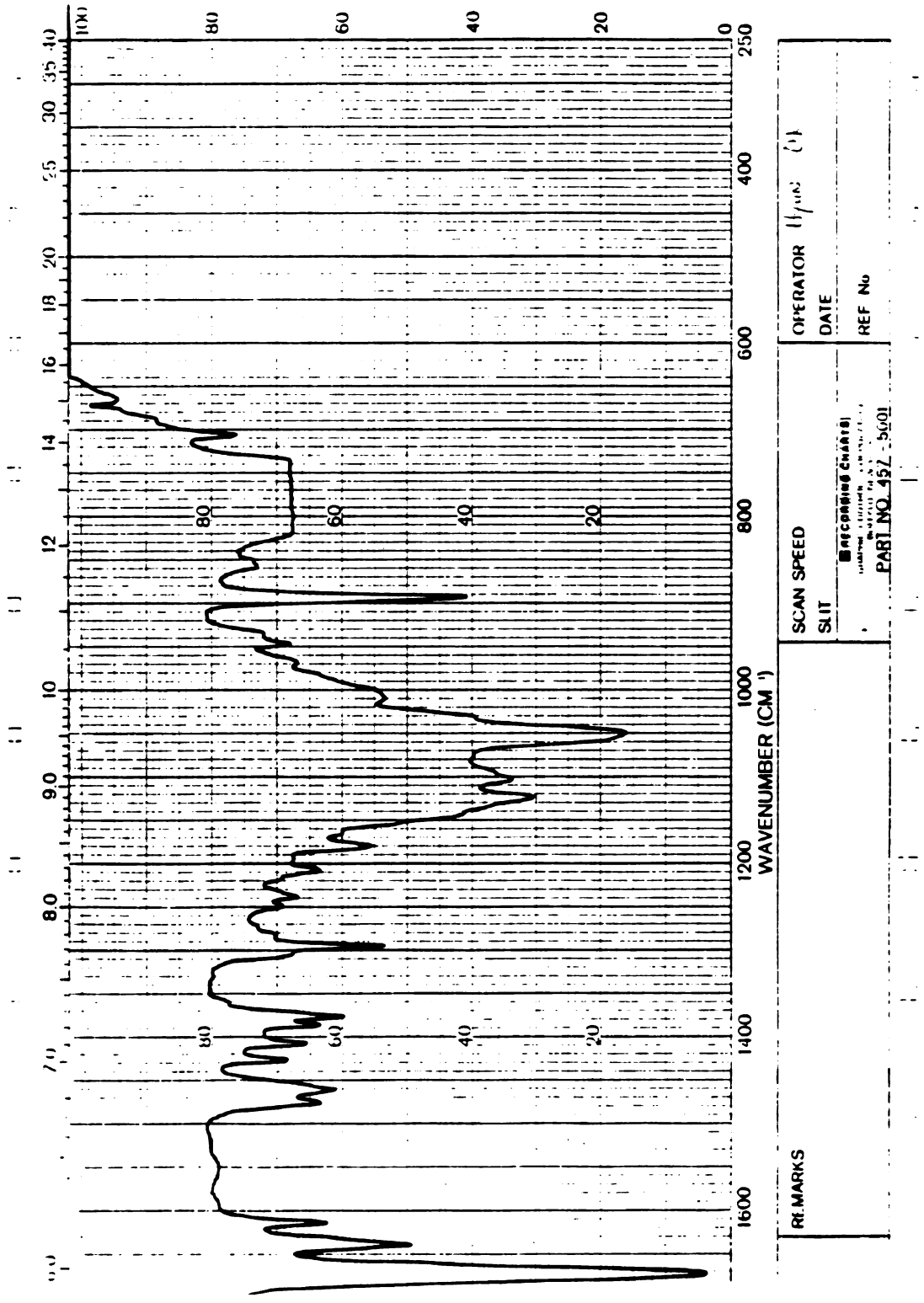



Figure 4 IR Spectrum of Compound 54(a)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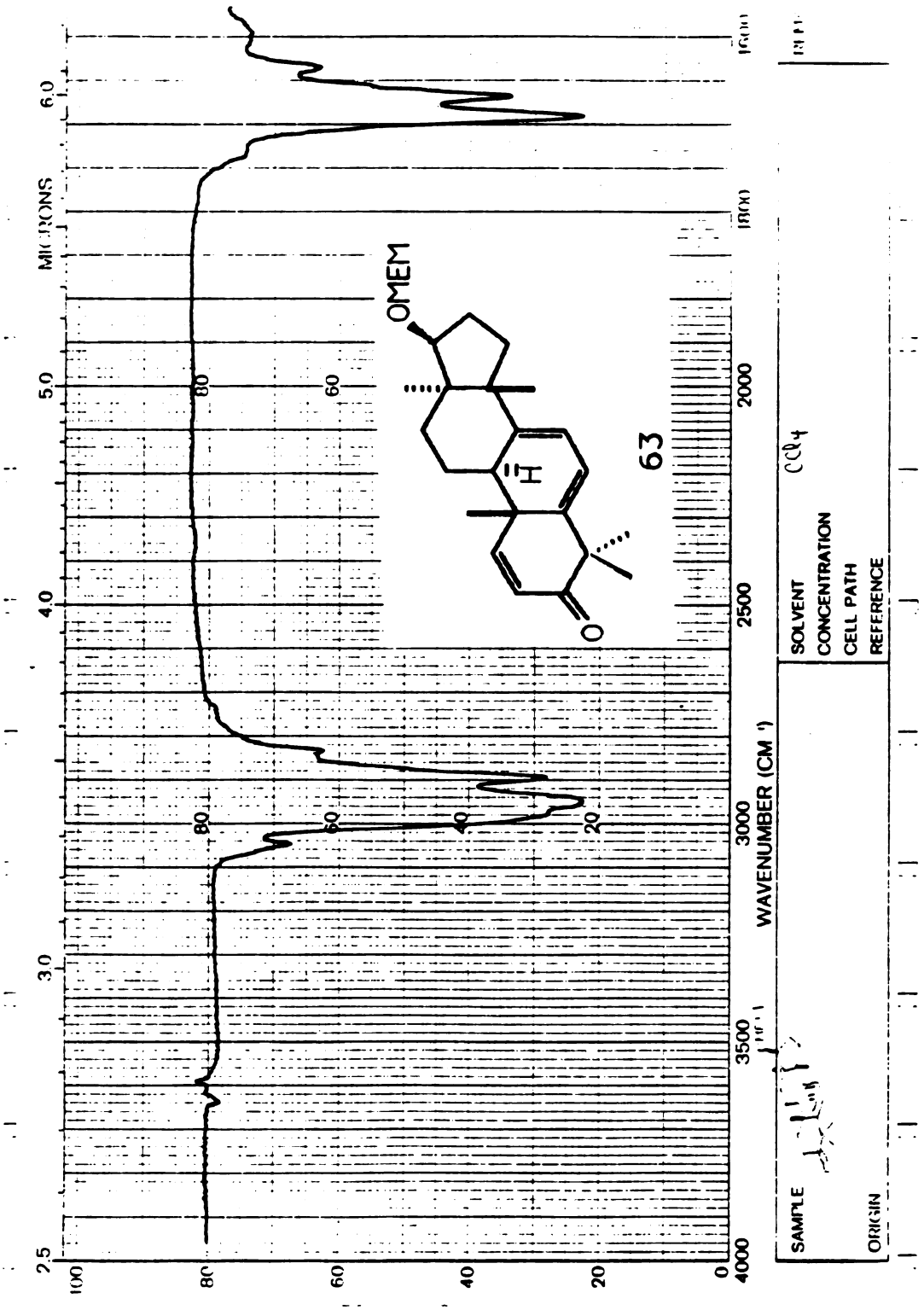
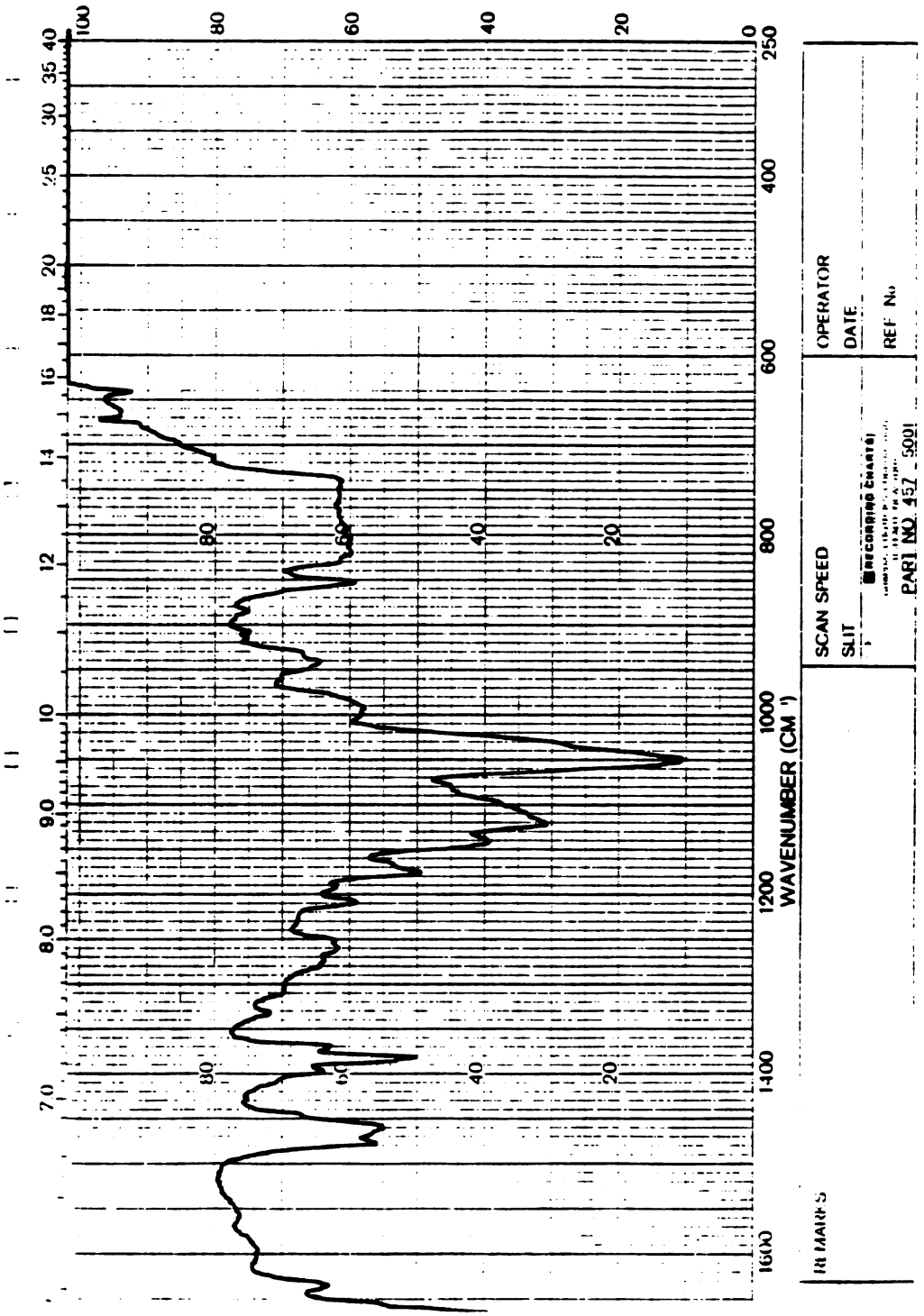



Figure 5 IR Spectrum of Compound 63(β)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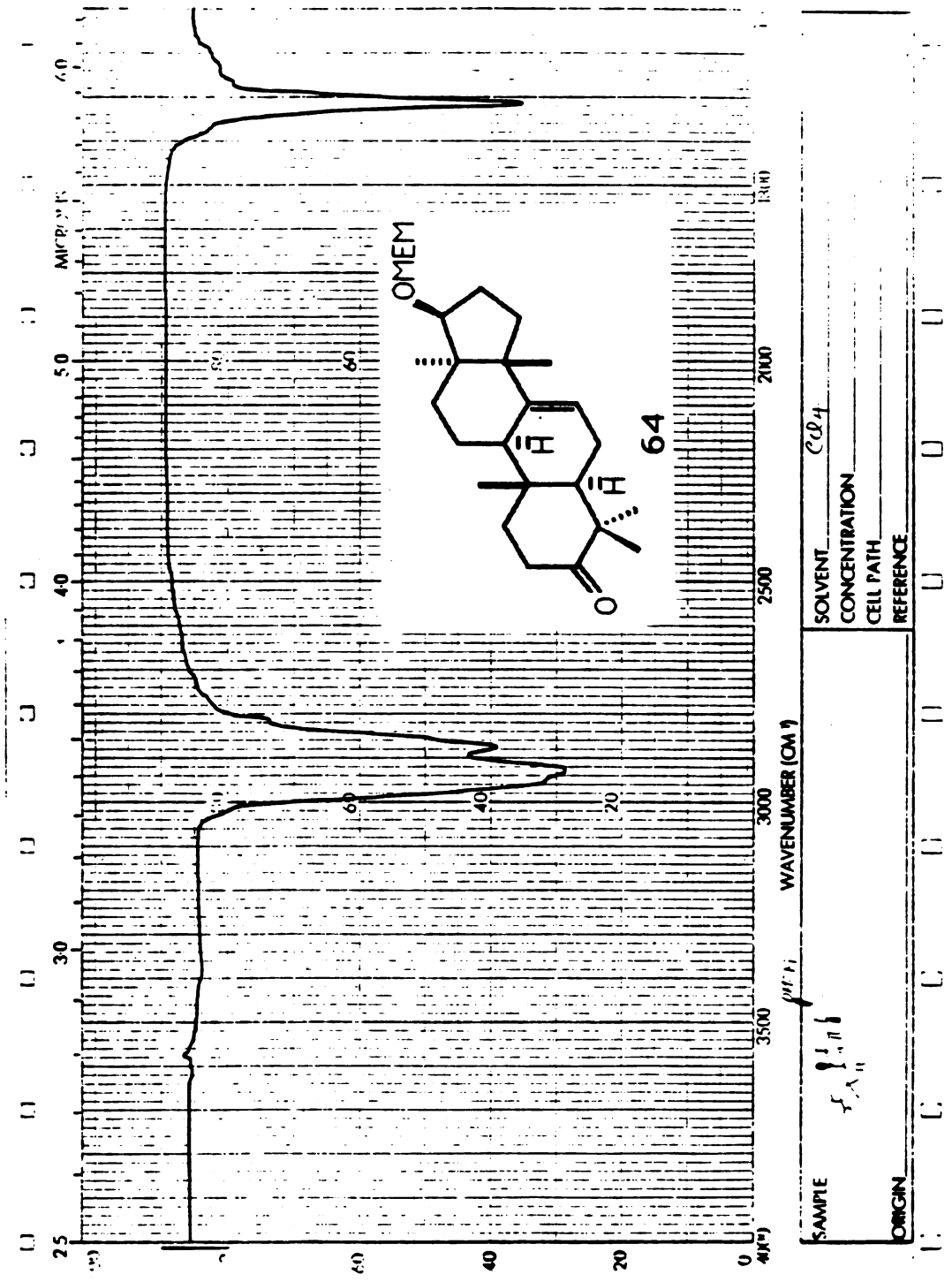
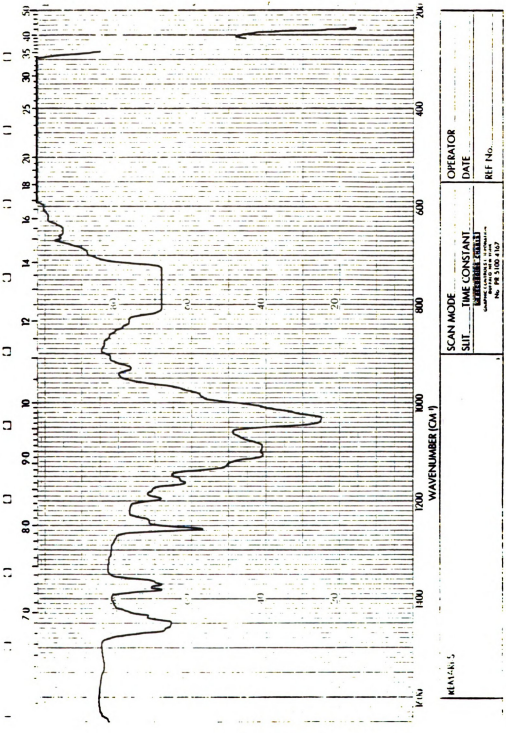



Figure 6 IR Spectrum of Compound 64(β)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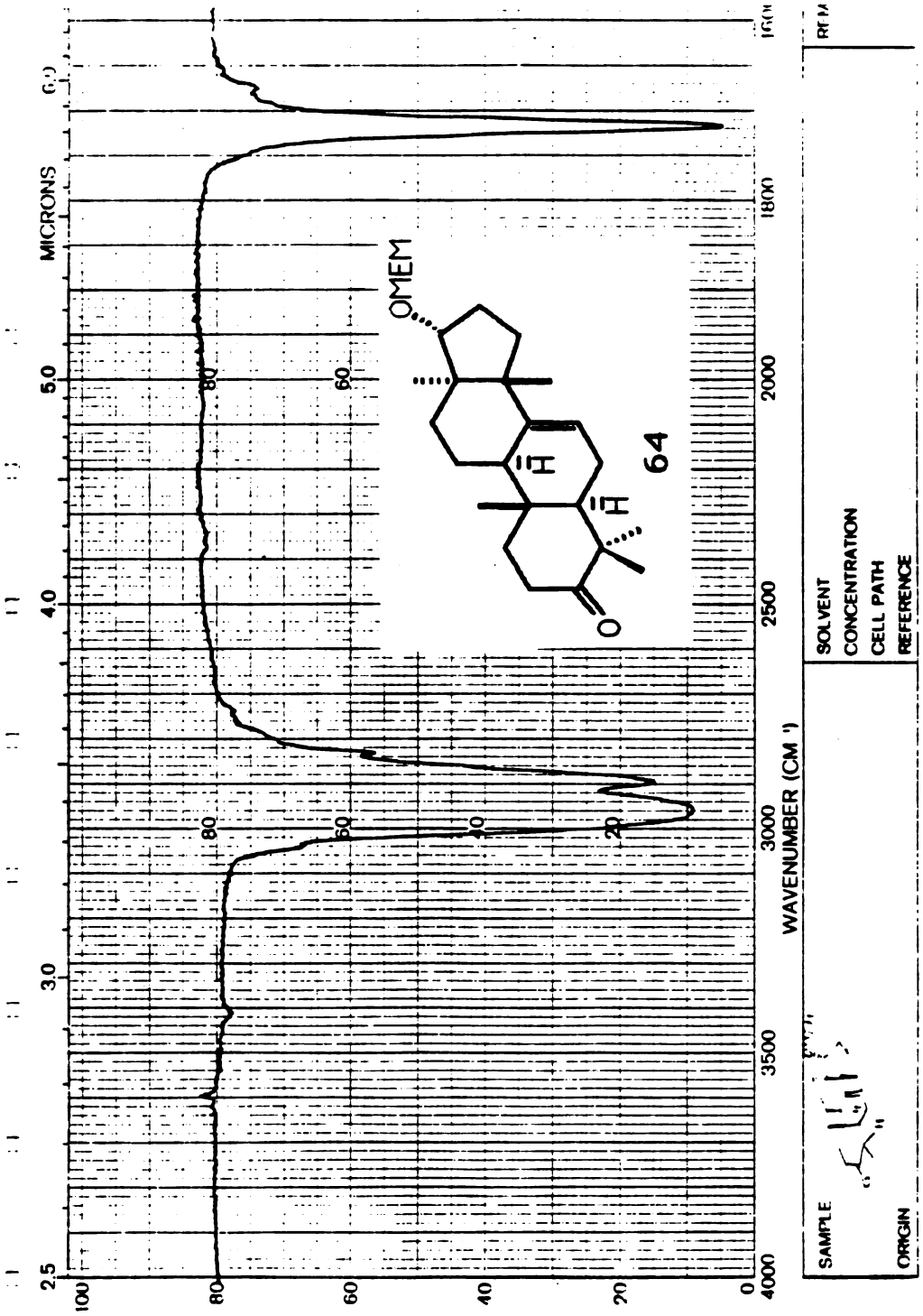
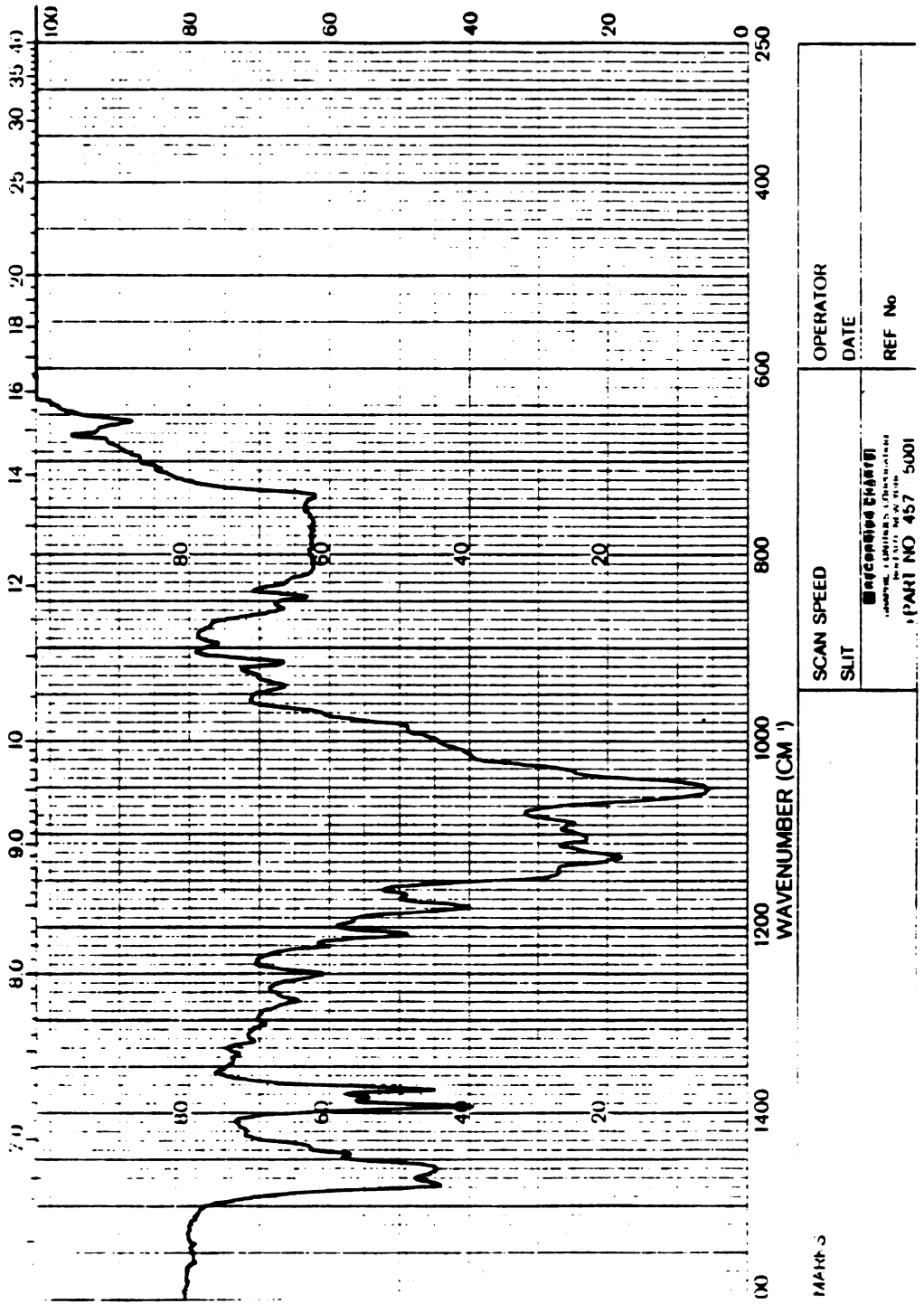



Figure 7 IR Spectrum of Compound 64(α)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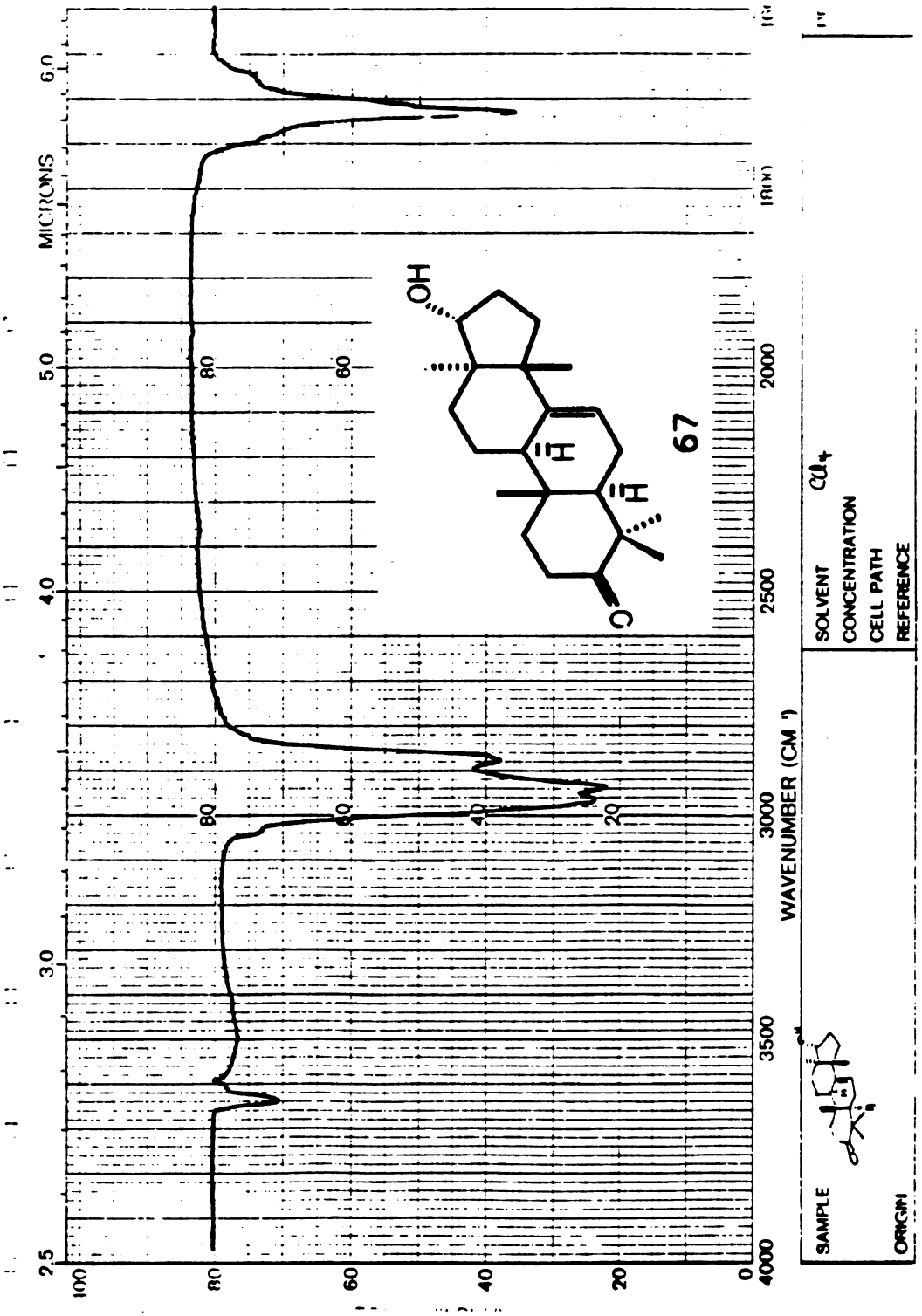
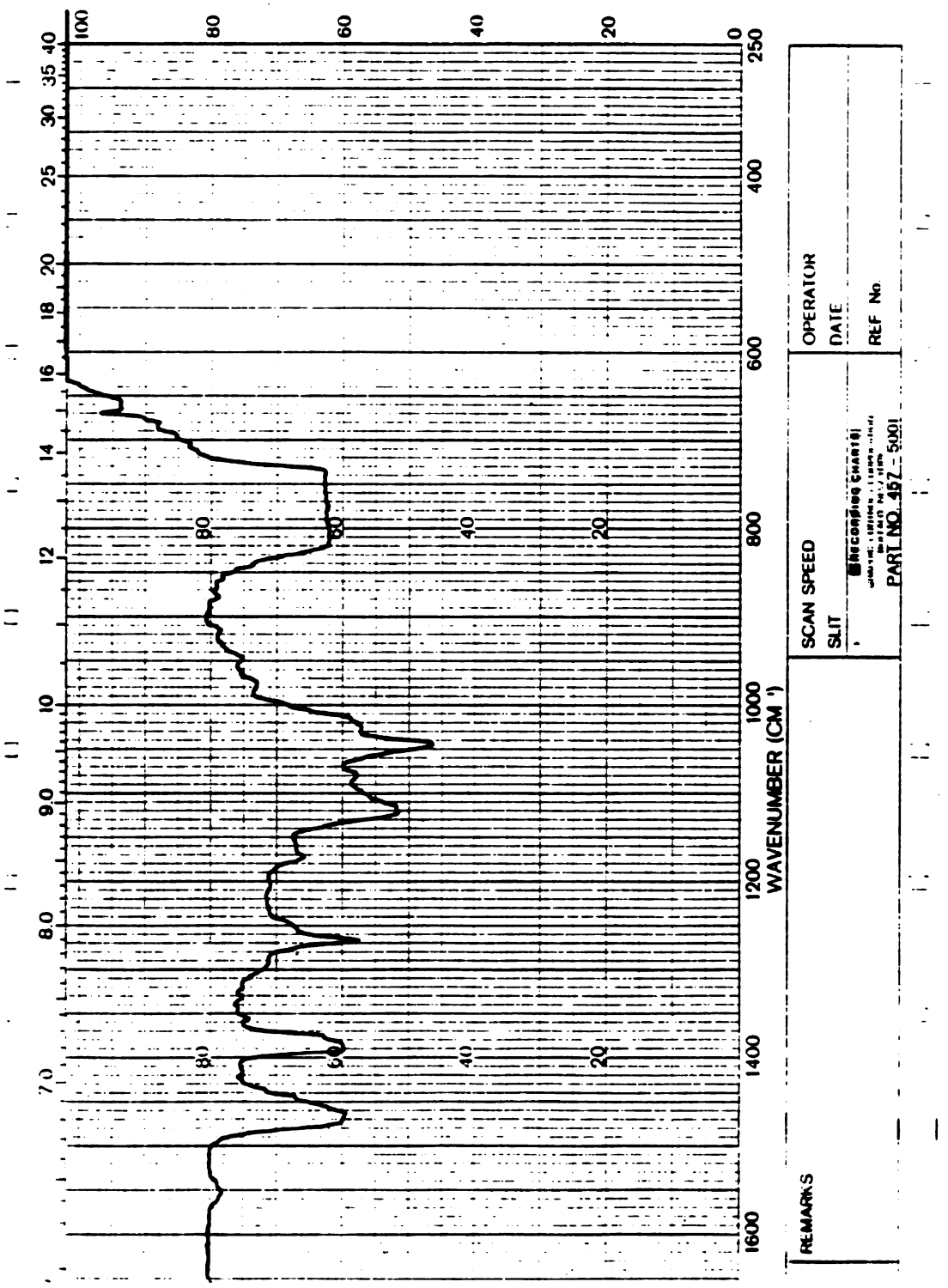



Figure 8 IR Spectrum of Compound 67(α)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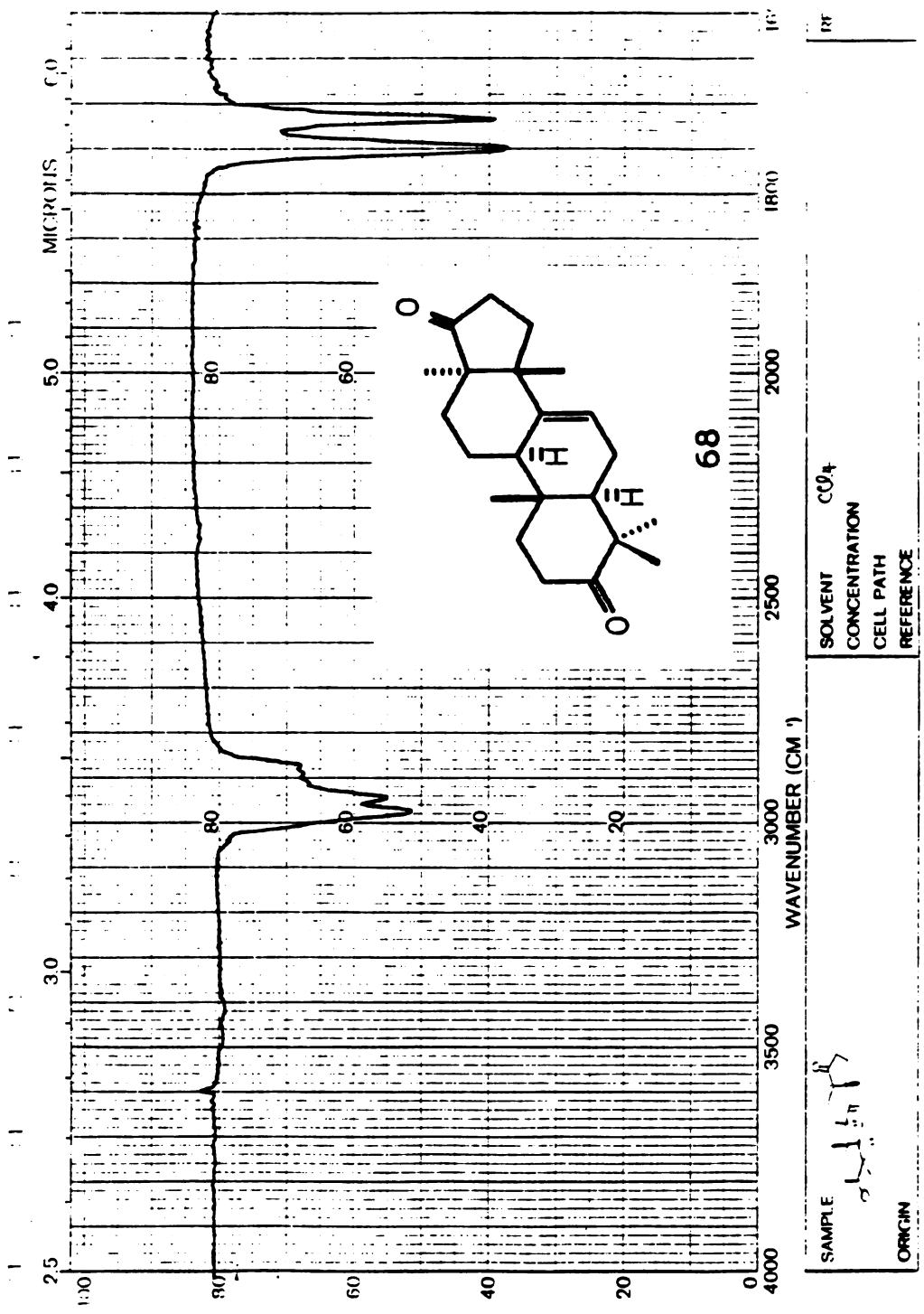
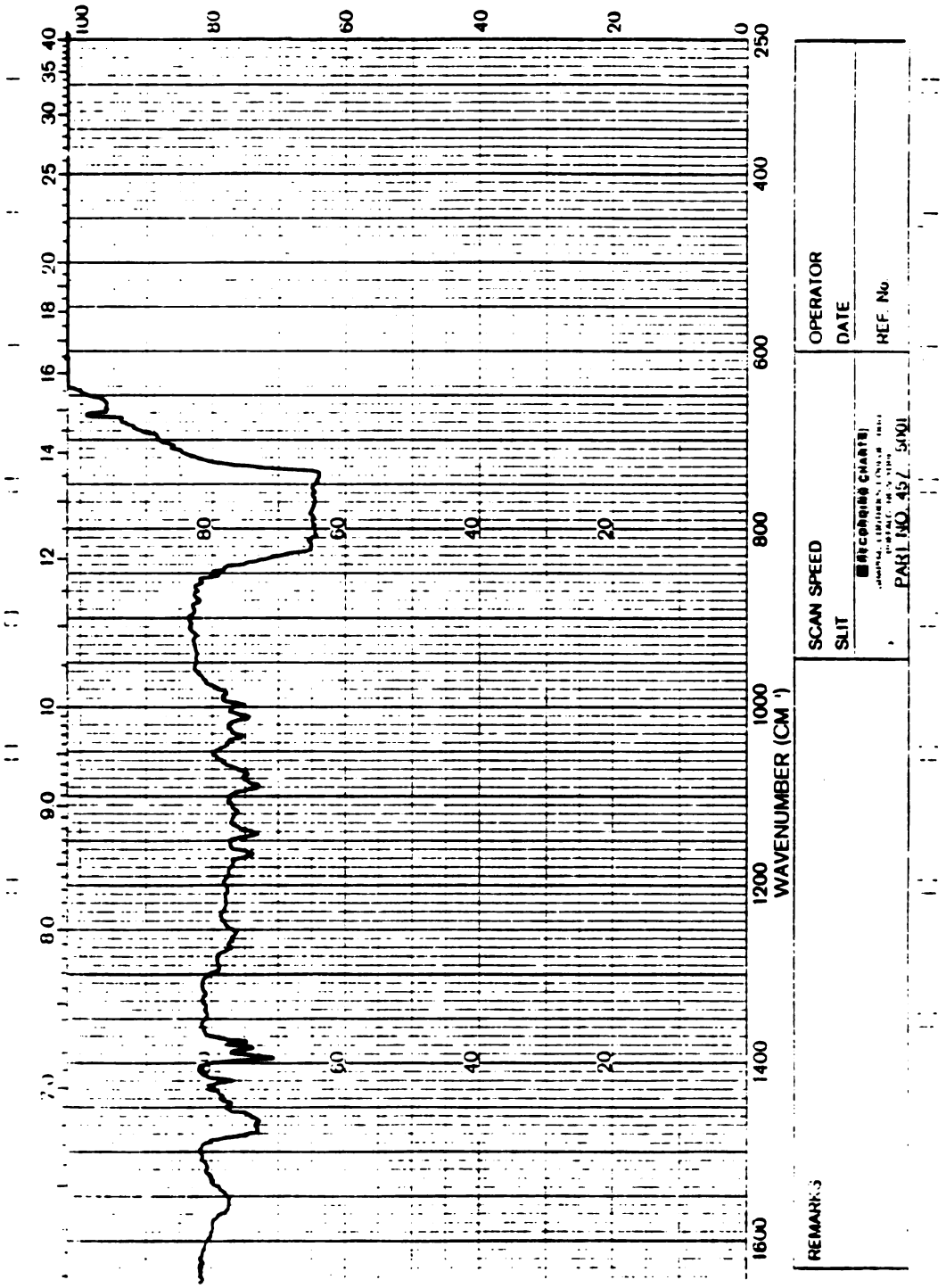



Figure 9 IR Spectrum of Compound 68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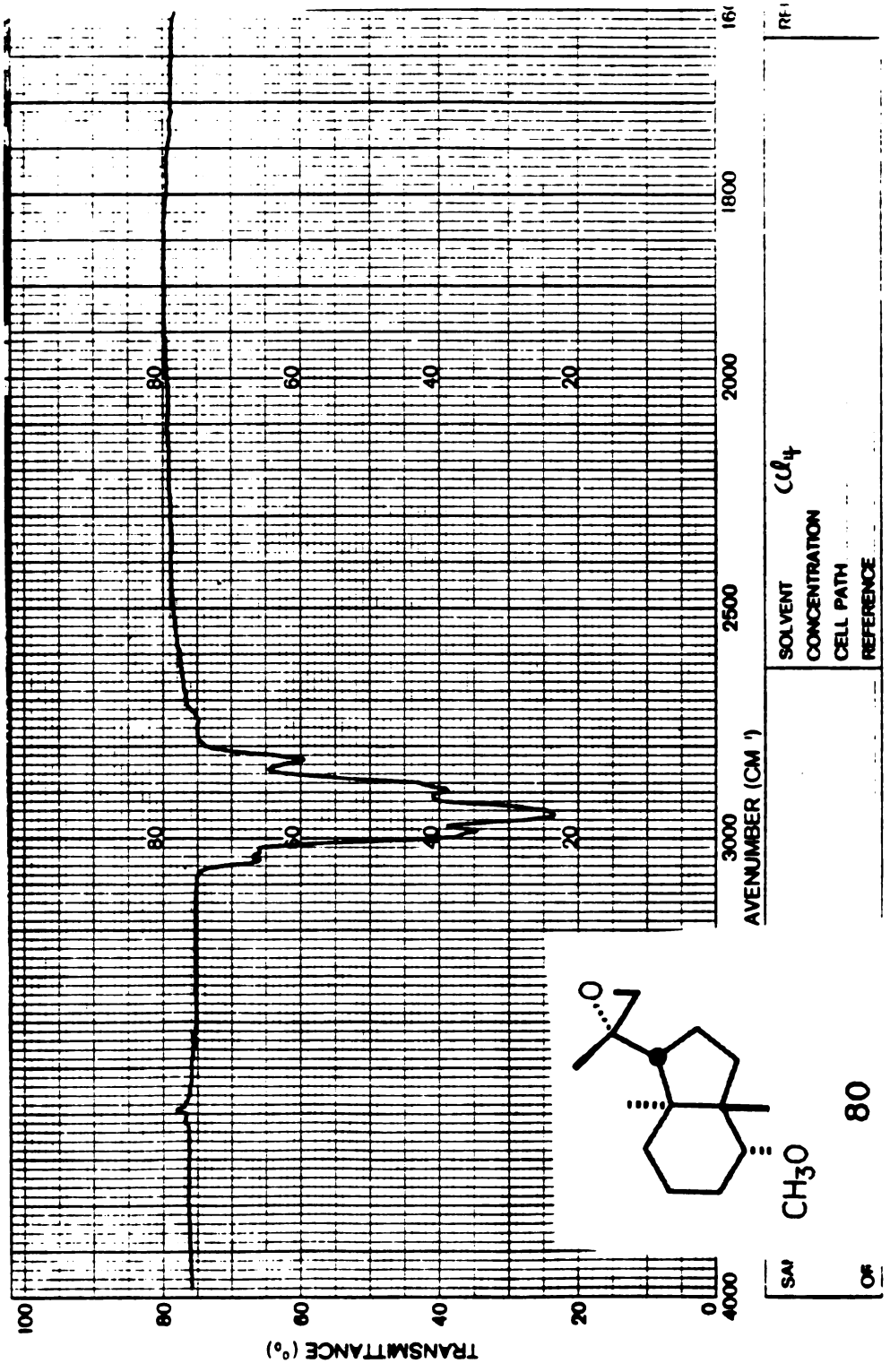
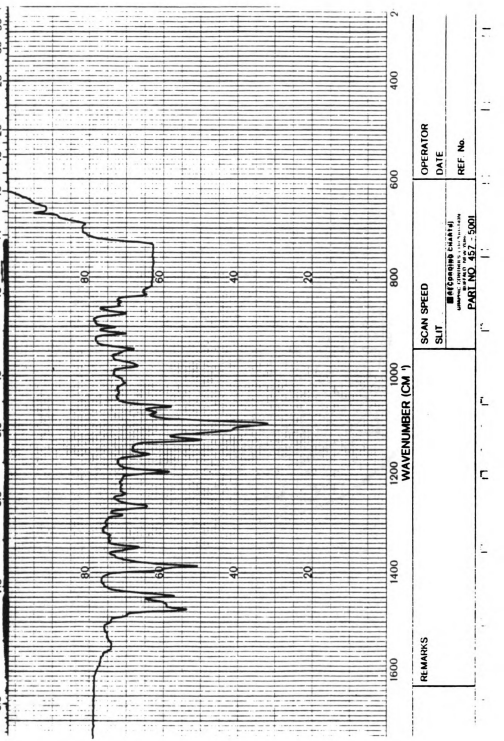



Figure 10 IR Spectrum of Compound **80**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SCAN SPEED
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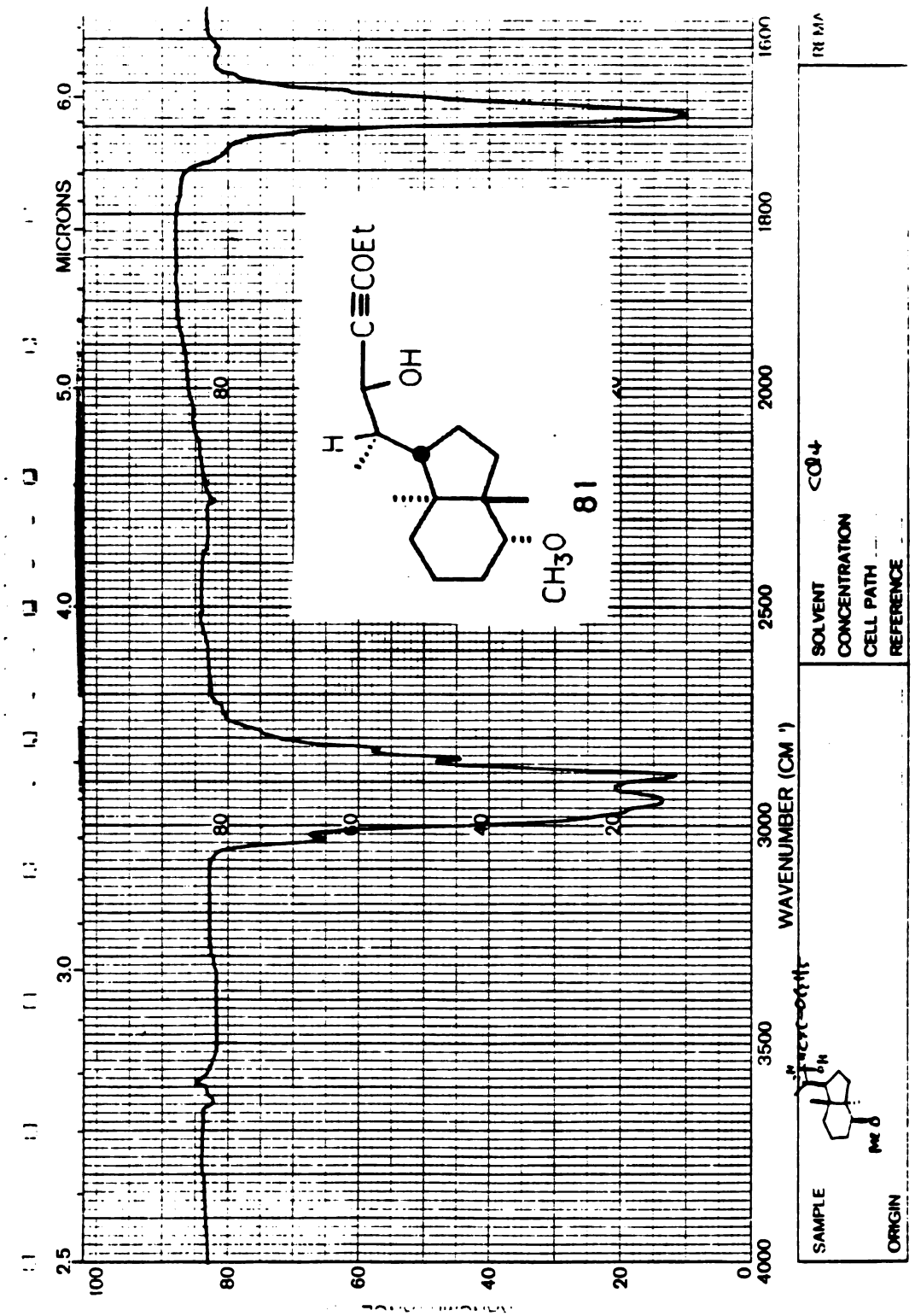
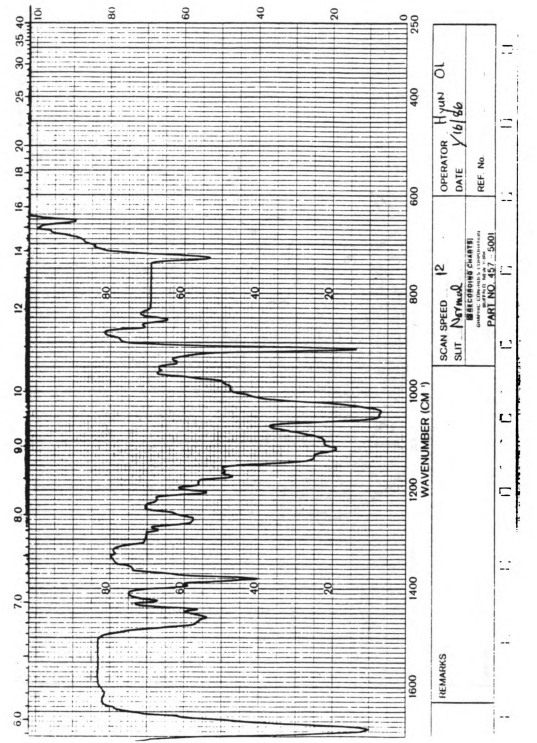



Figure 11 IR Spectrum of Compound 81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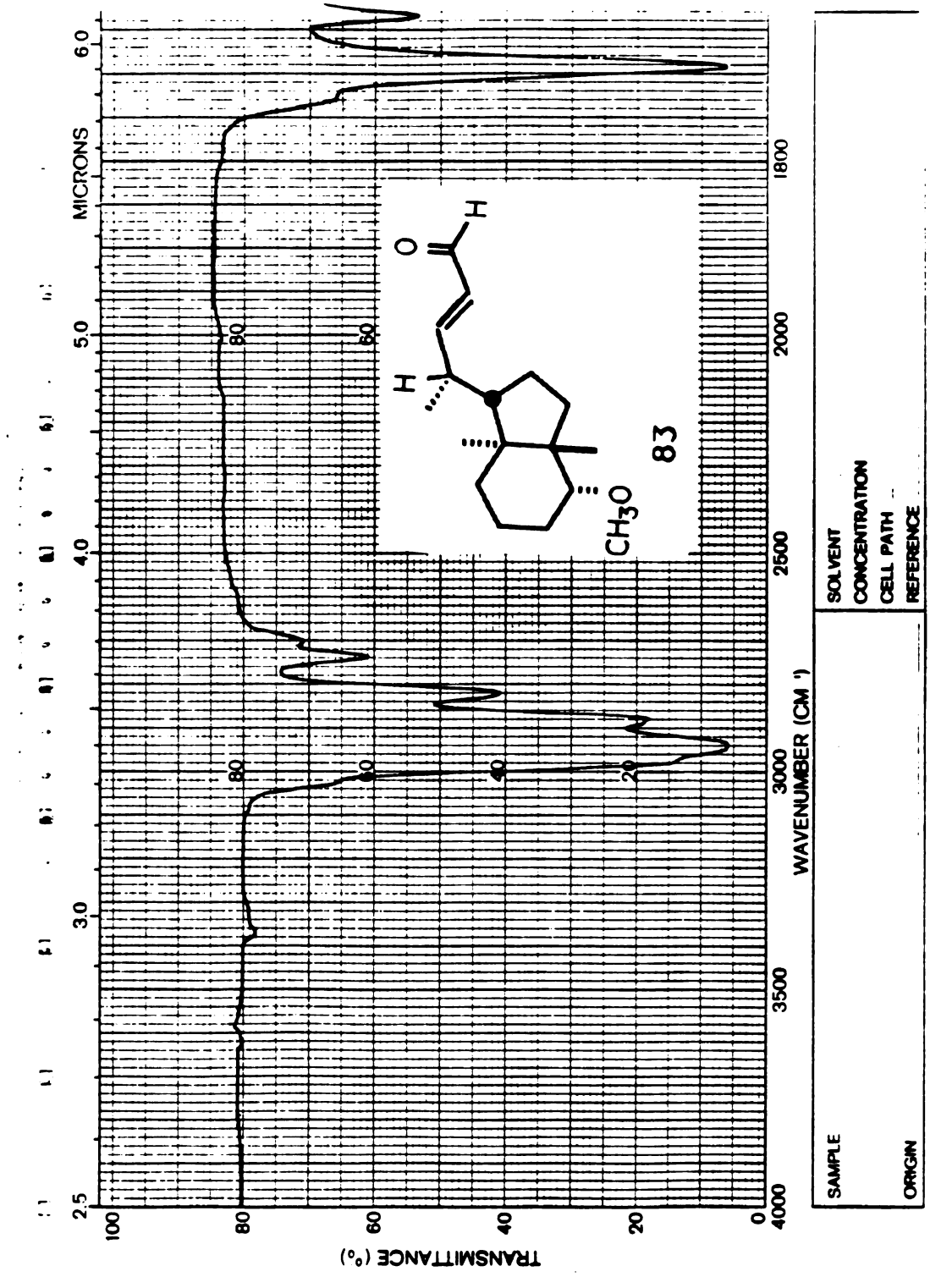
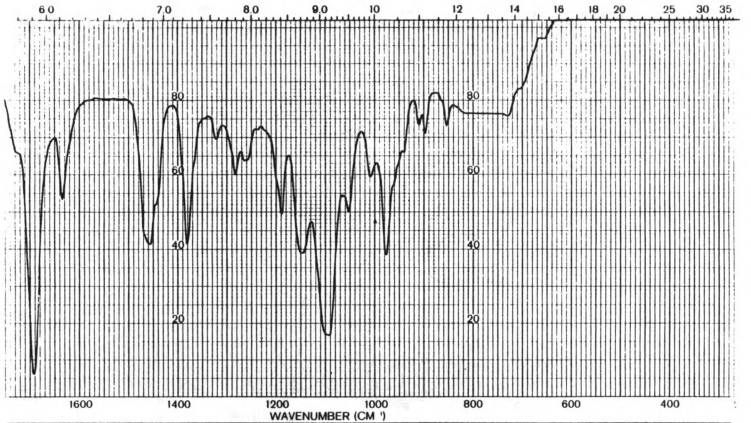



Figure 12 IR Spectrum of Compound 83




| REMARKS | SCAN SPEED | OPERATOR |
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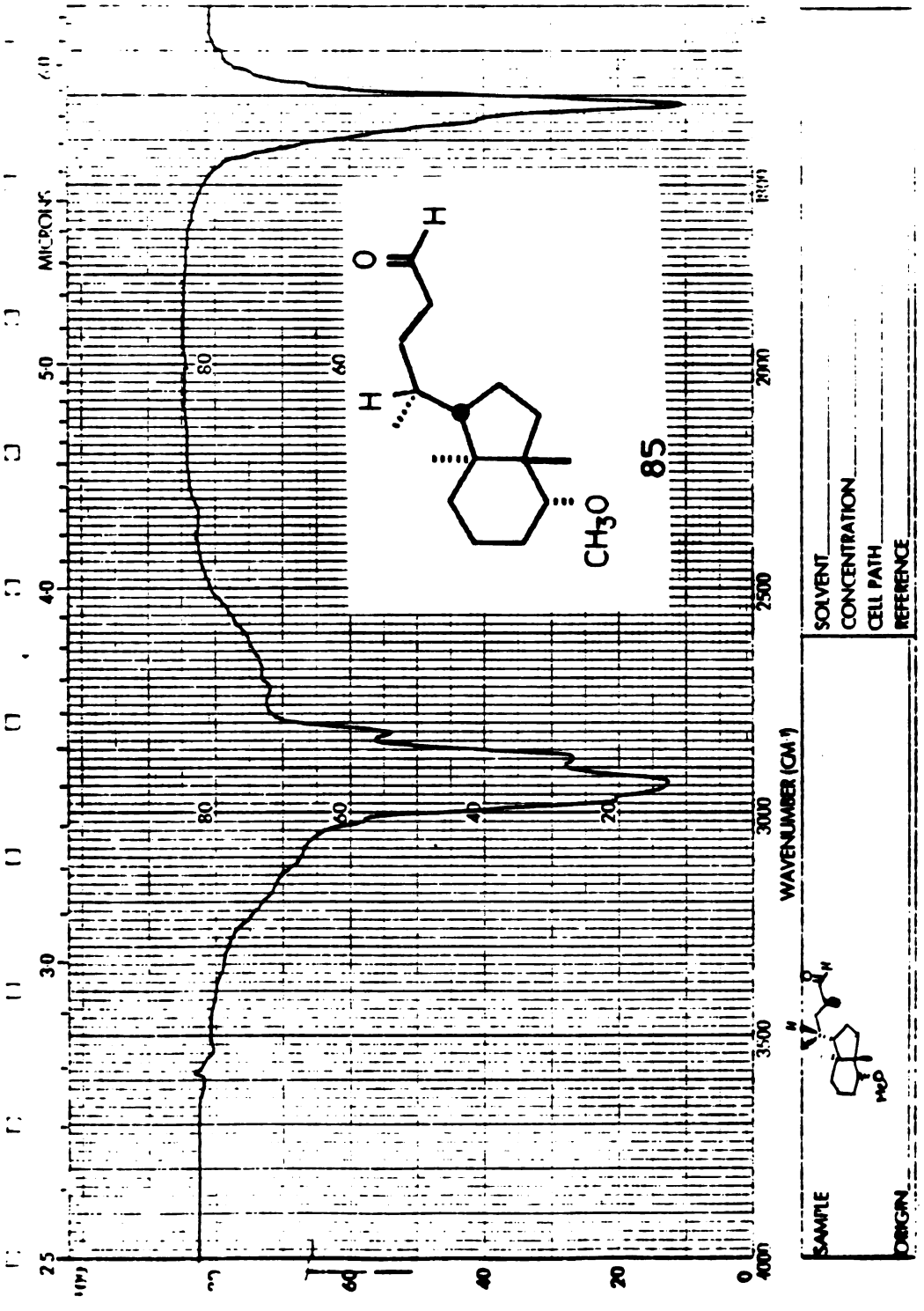
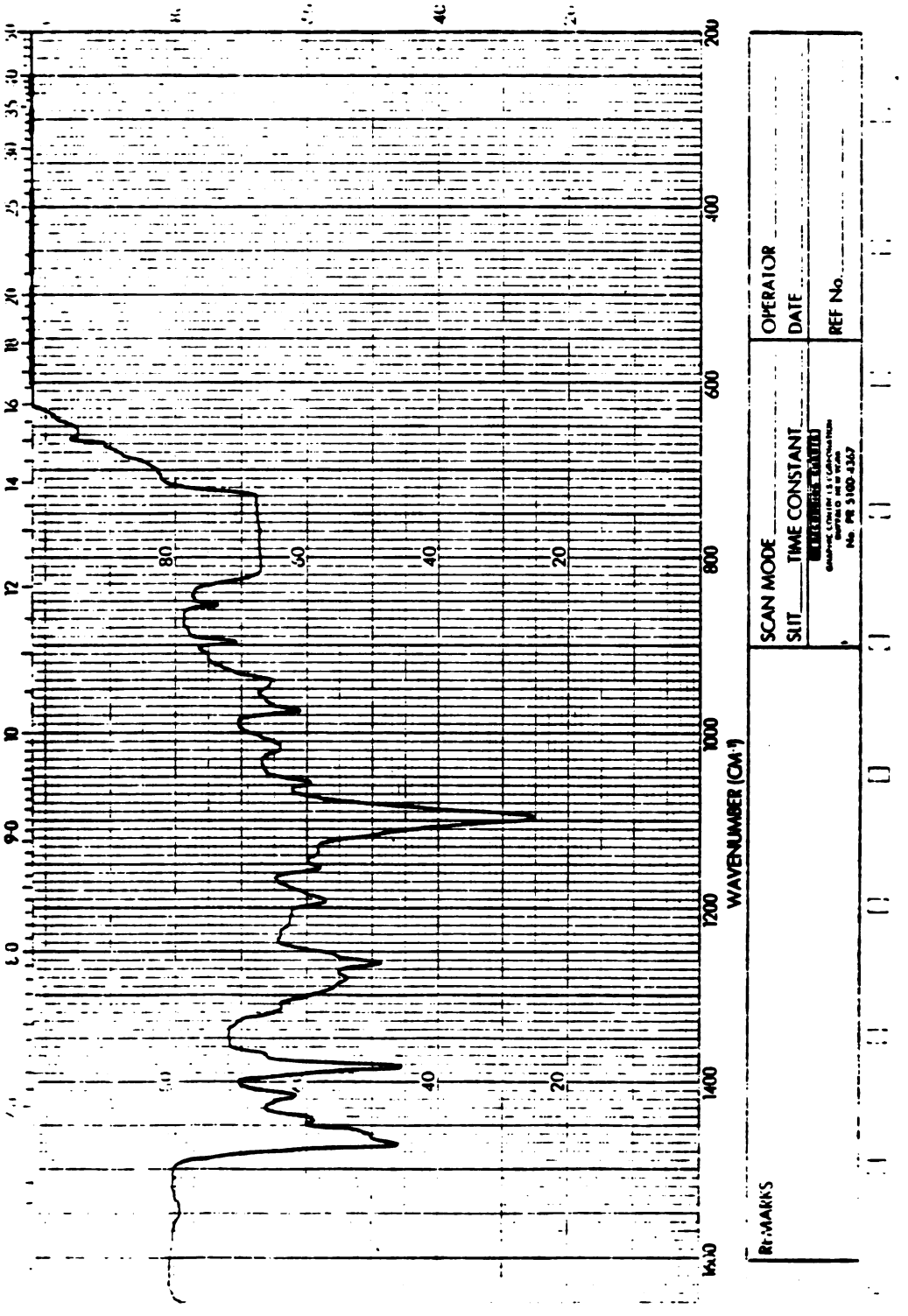



Figure 13 IR Spectrum of Compound 85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TIME CONSTANT
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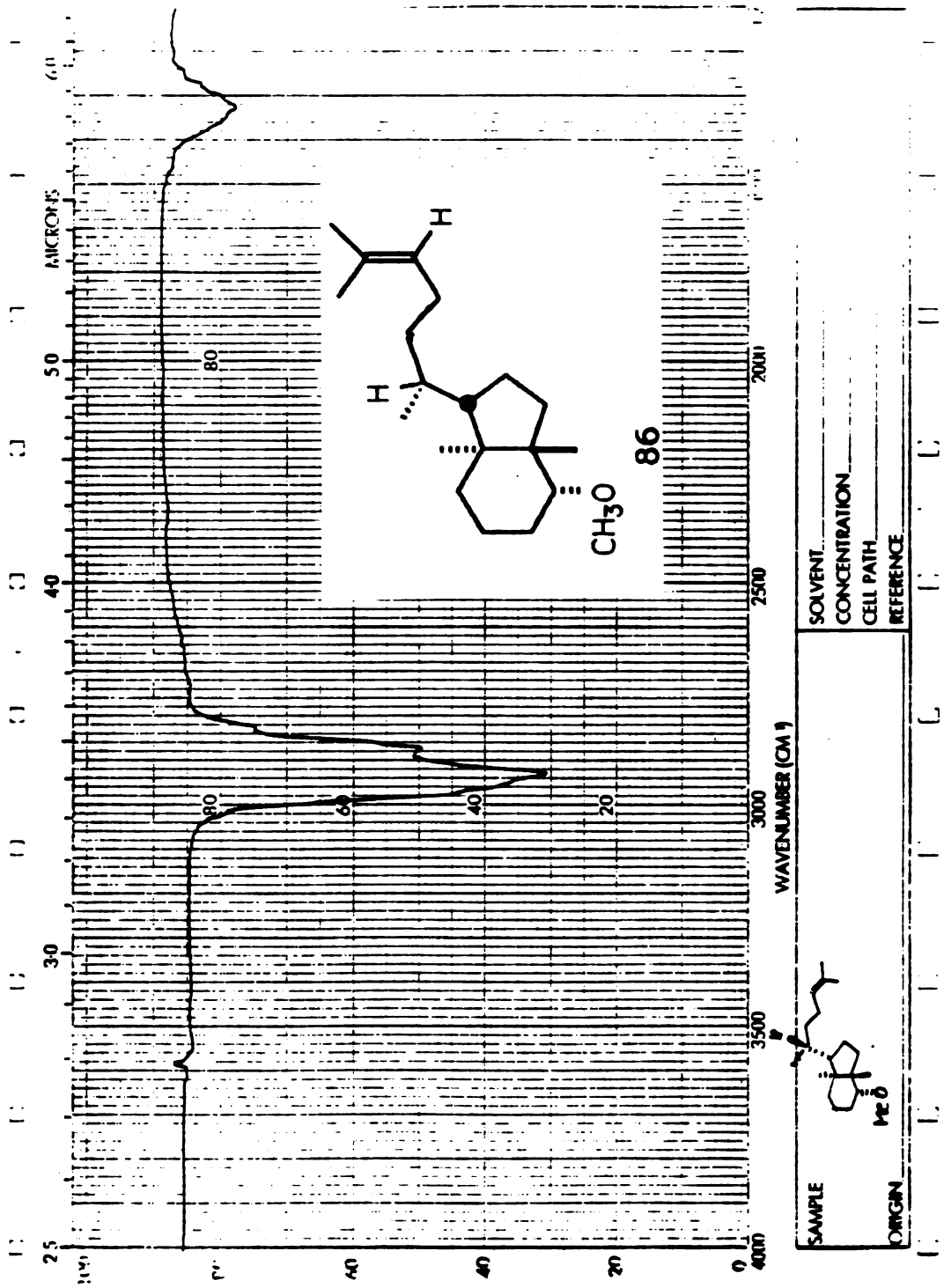
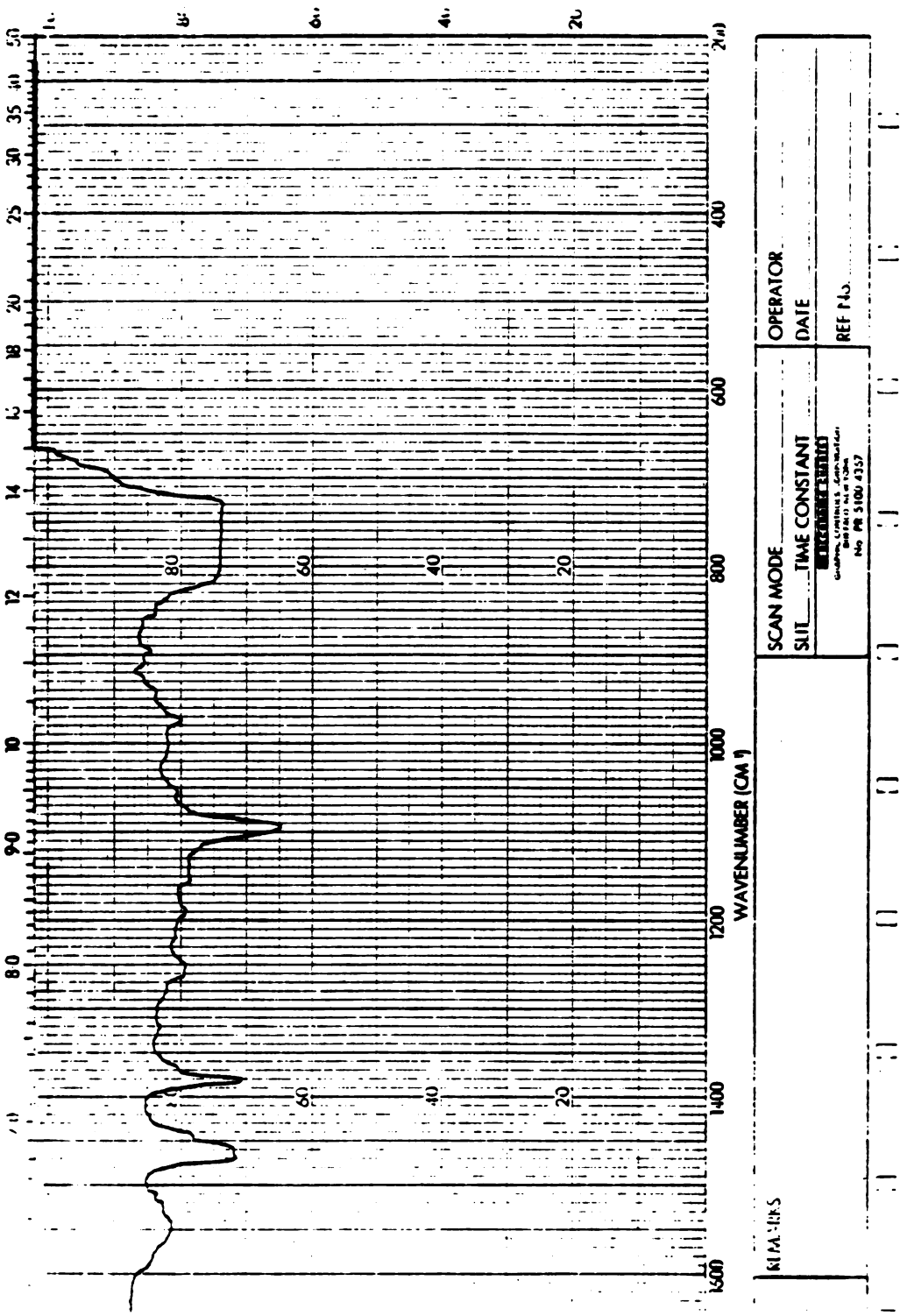



Figure 14 IR Spectrum of Compound 86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TIME CONSTANT
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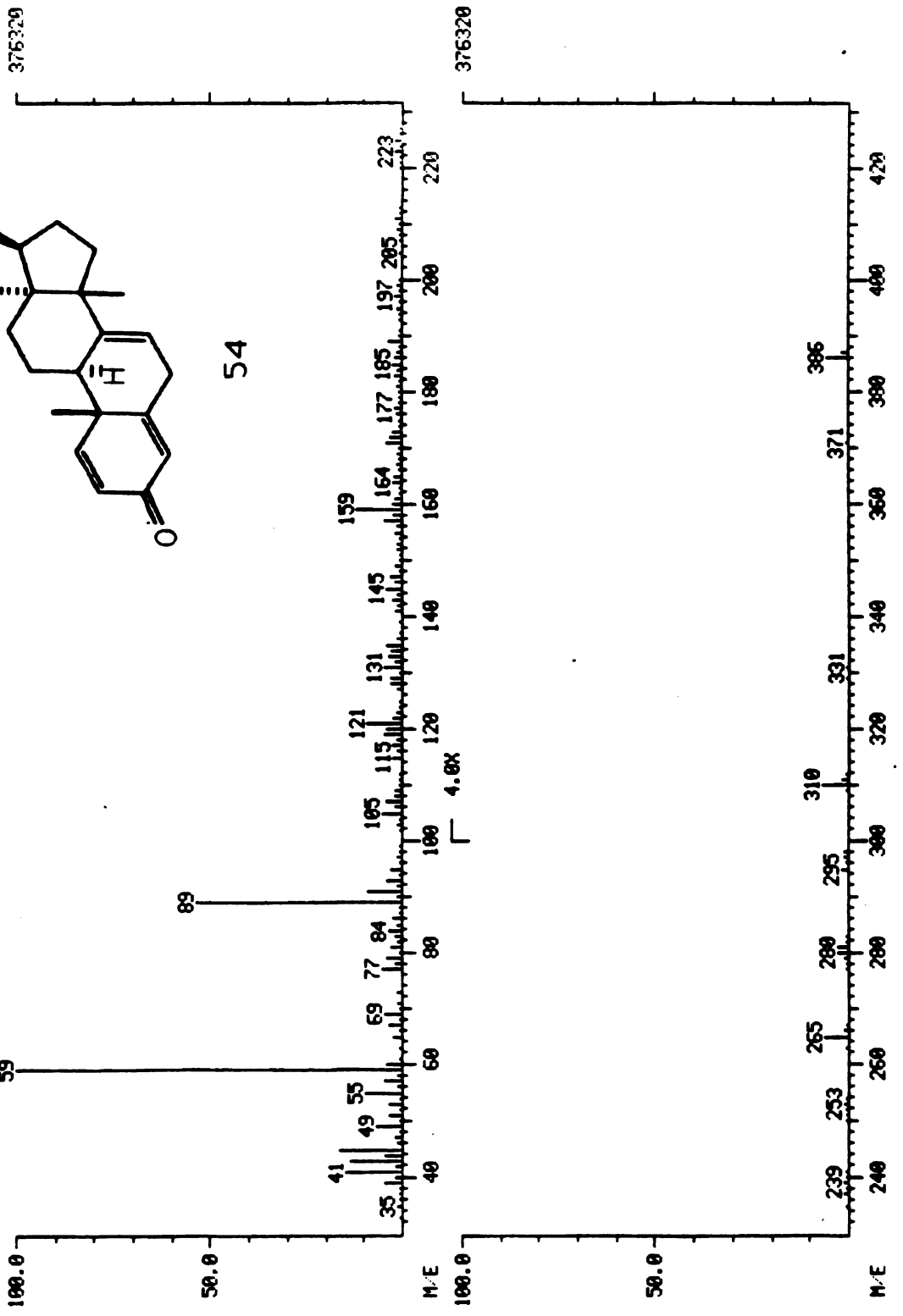



Figure 15 Mass Spectrum of Compound 54(β)


Figure 16 Mass Spectrum of Compound 54(a)

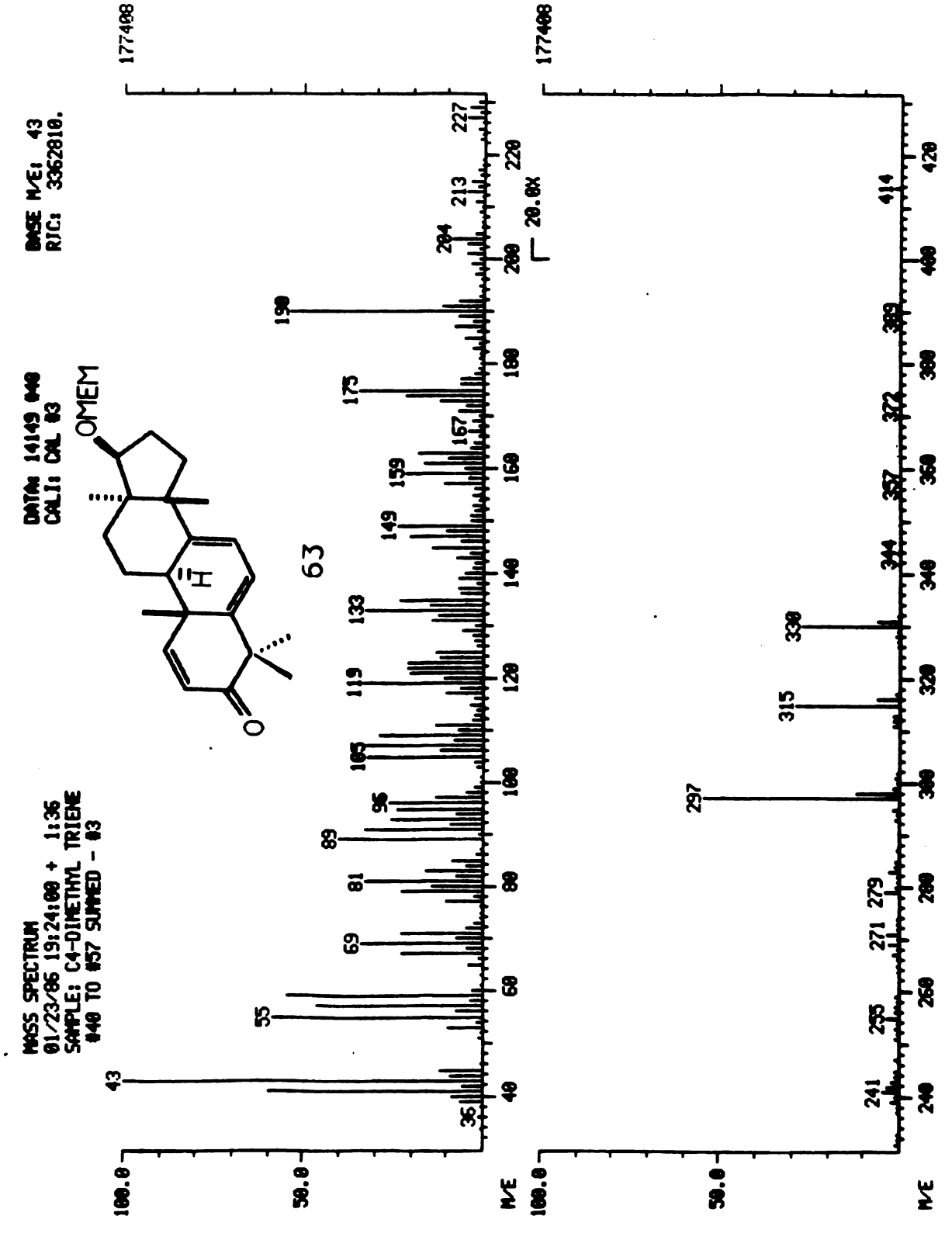



Figure 17 Mass Spectrum of Compound 63(β)

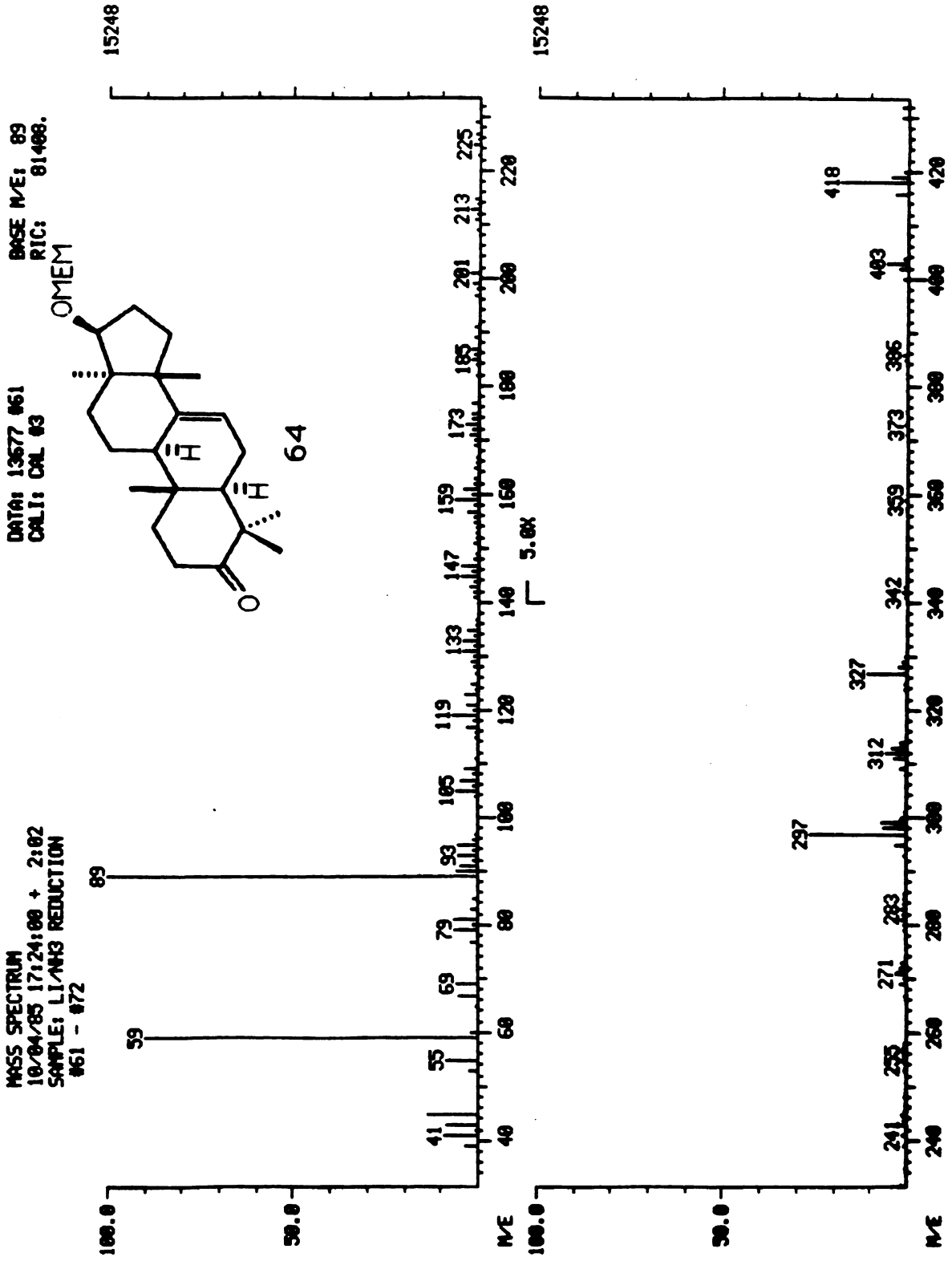



Figure 18 Mass Spectrum of Compound 64(β)

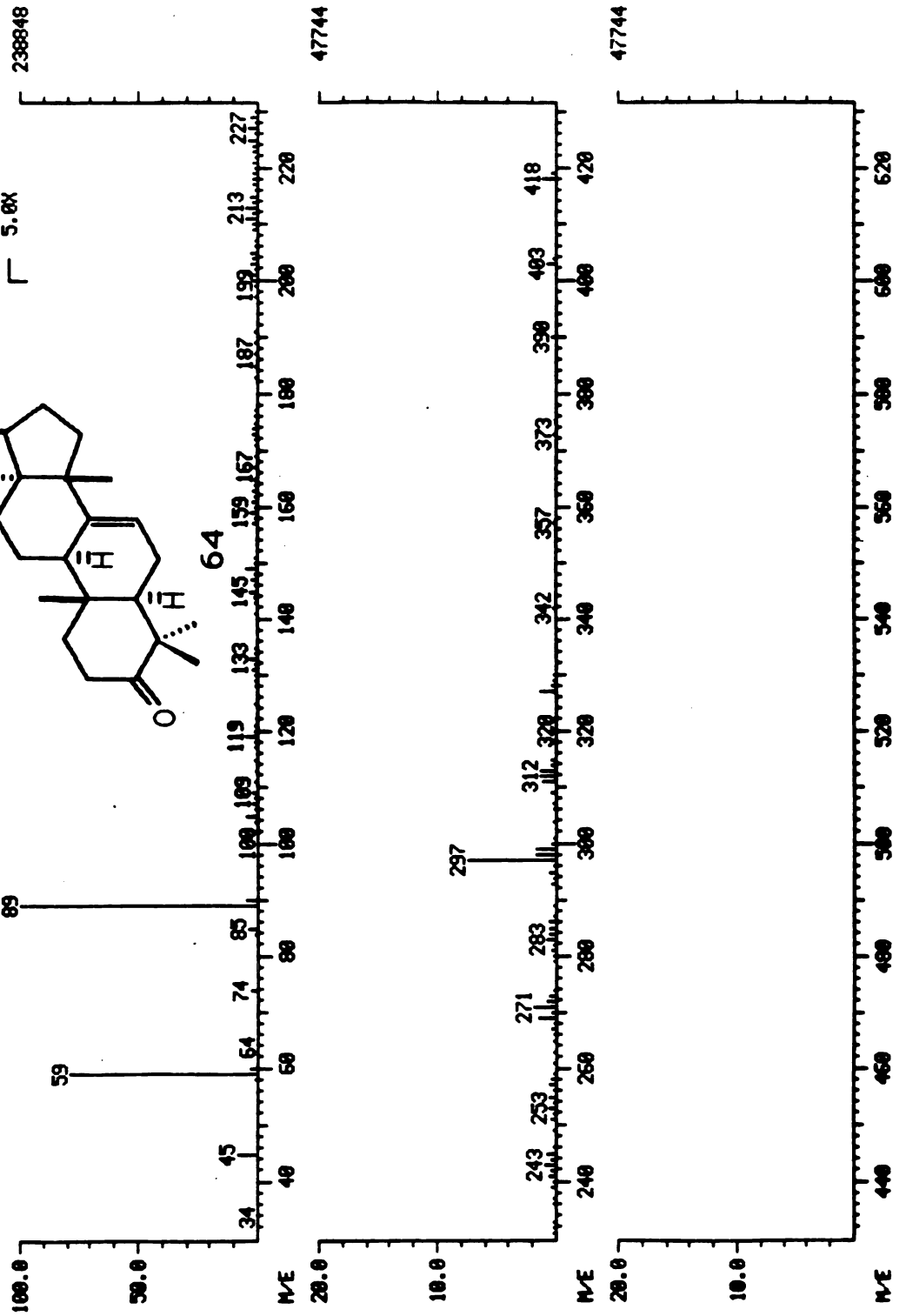



Figure 19 Mass Spectrum of Compound 64(α)

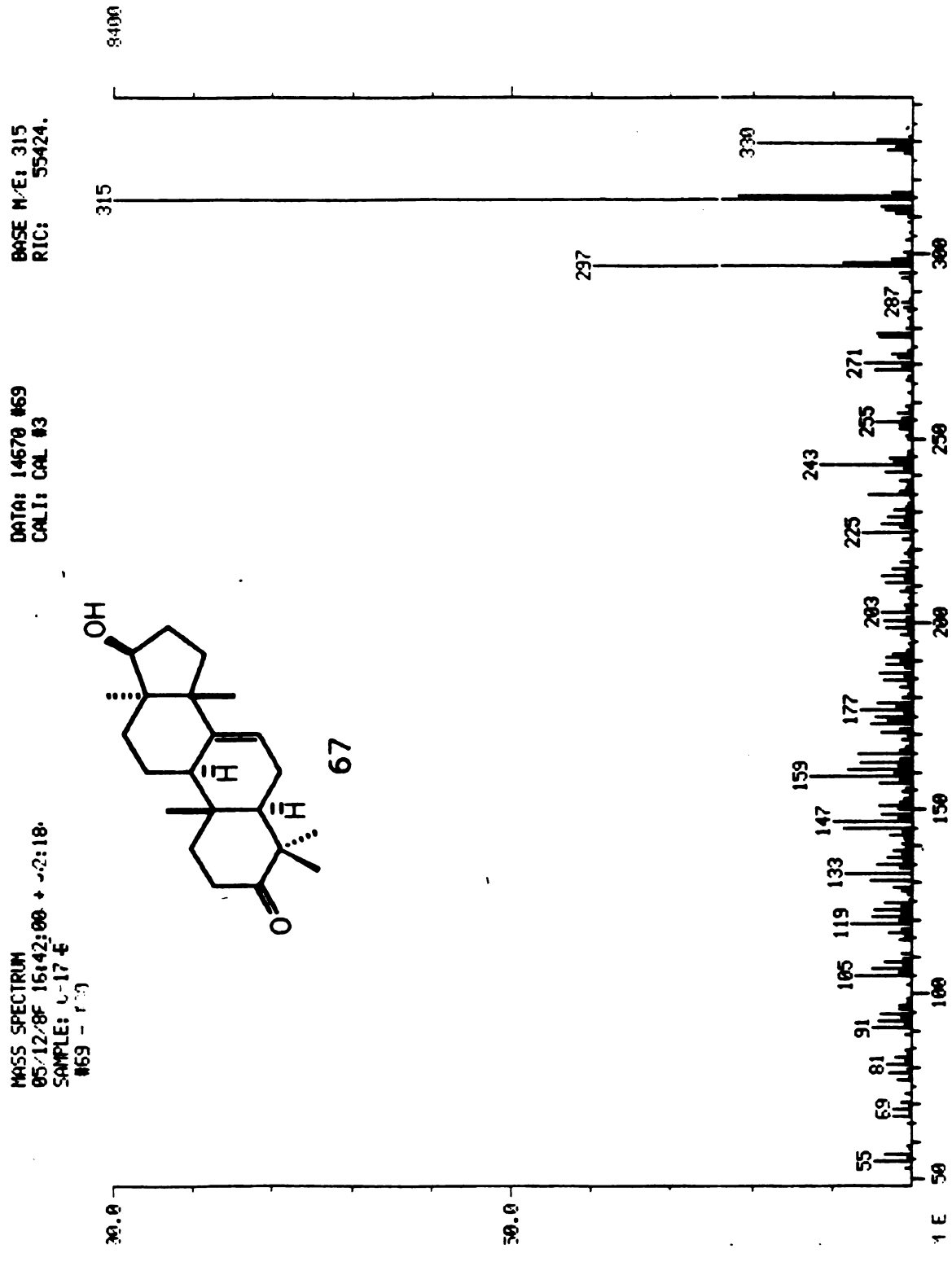



Figure 20 Mass Spectrum of Compound 67(β)

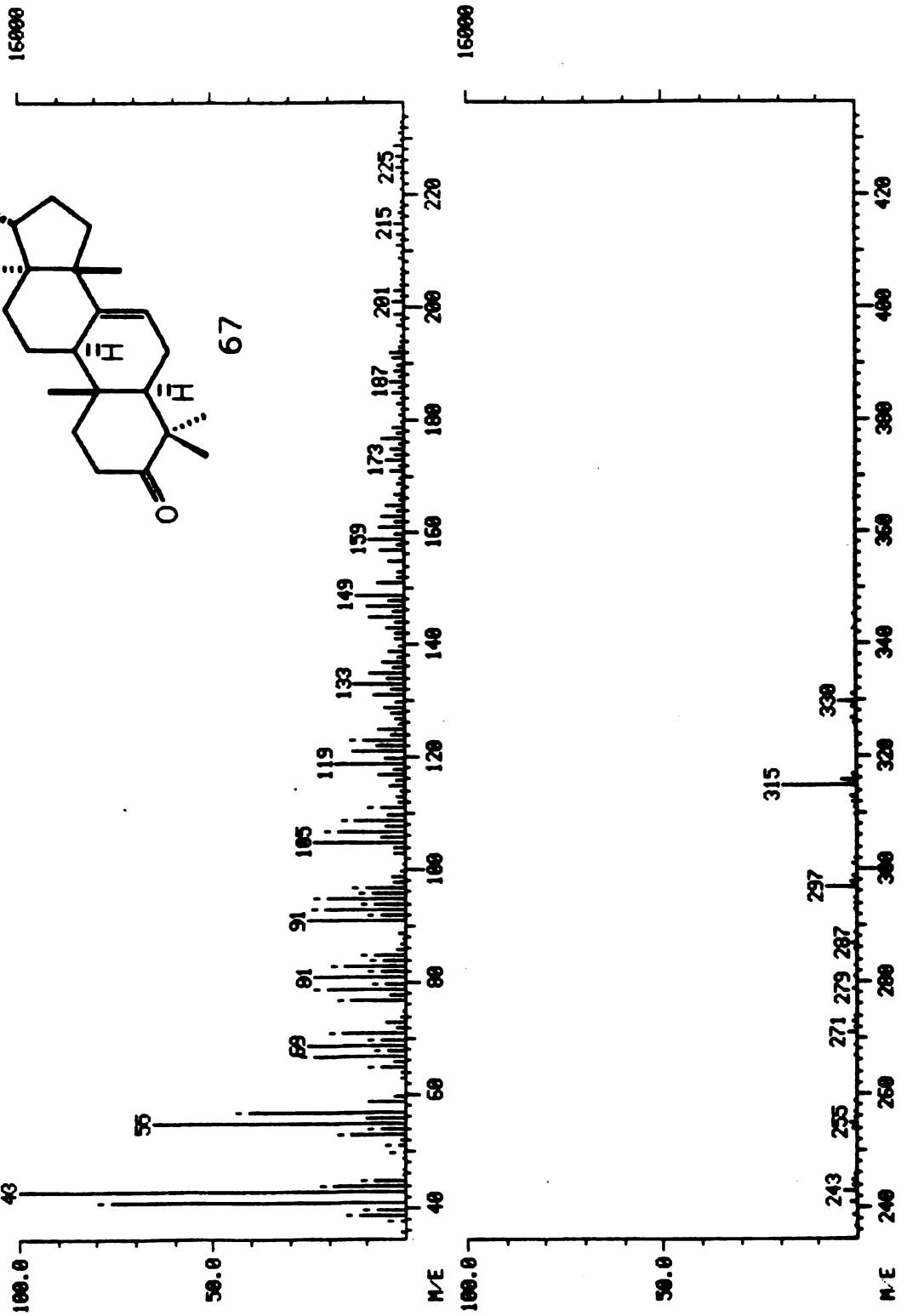



Figure 21 Mass Spectrum of Compound 67(α)

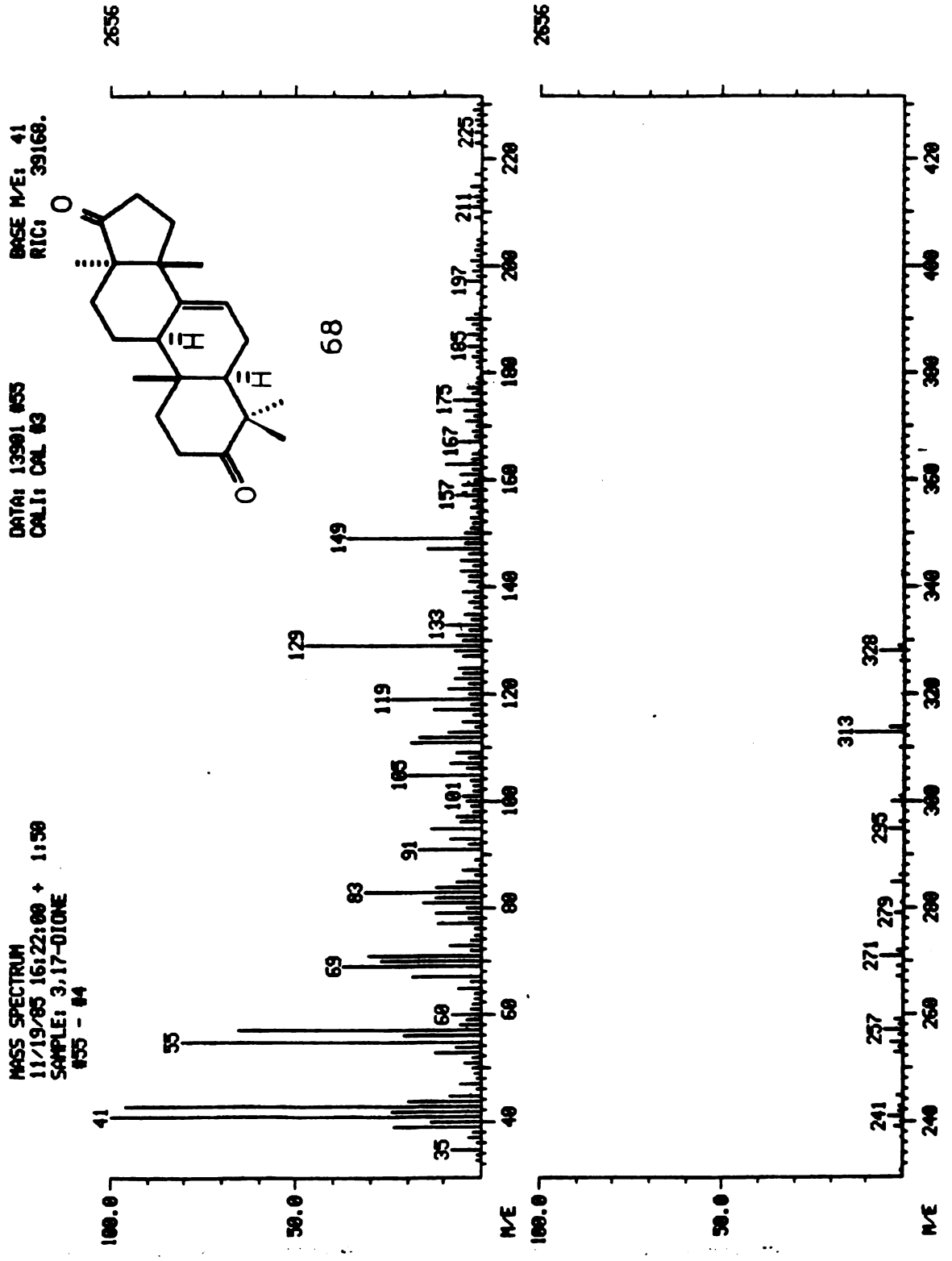



Figure 22 Mass Spectrum of Compound 68

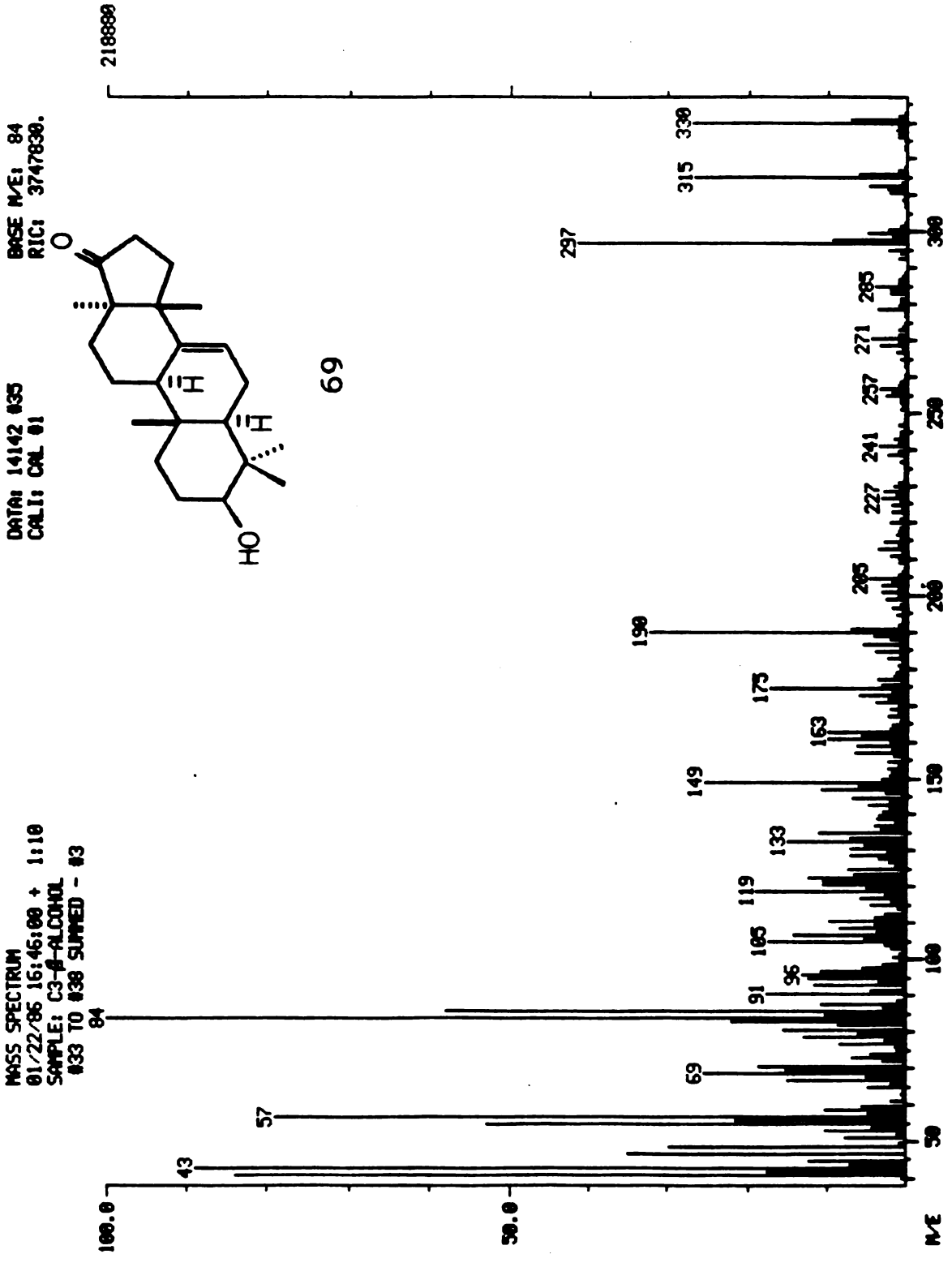



Figure 23 Mass Spectrum of Compound 69

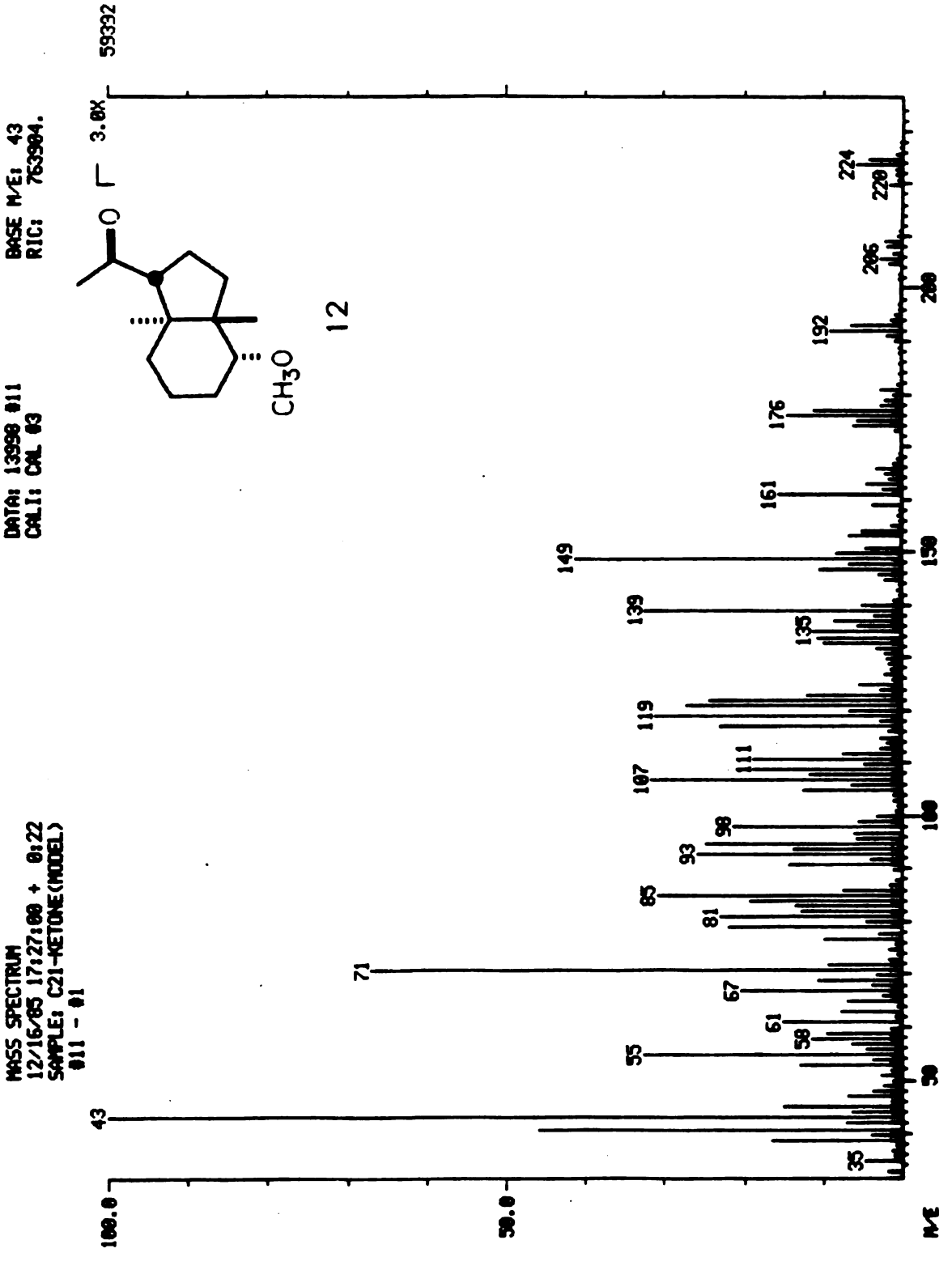



Figure 24 Mass Spectrum of Compound 12

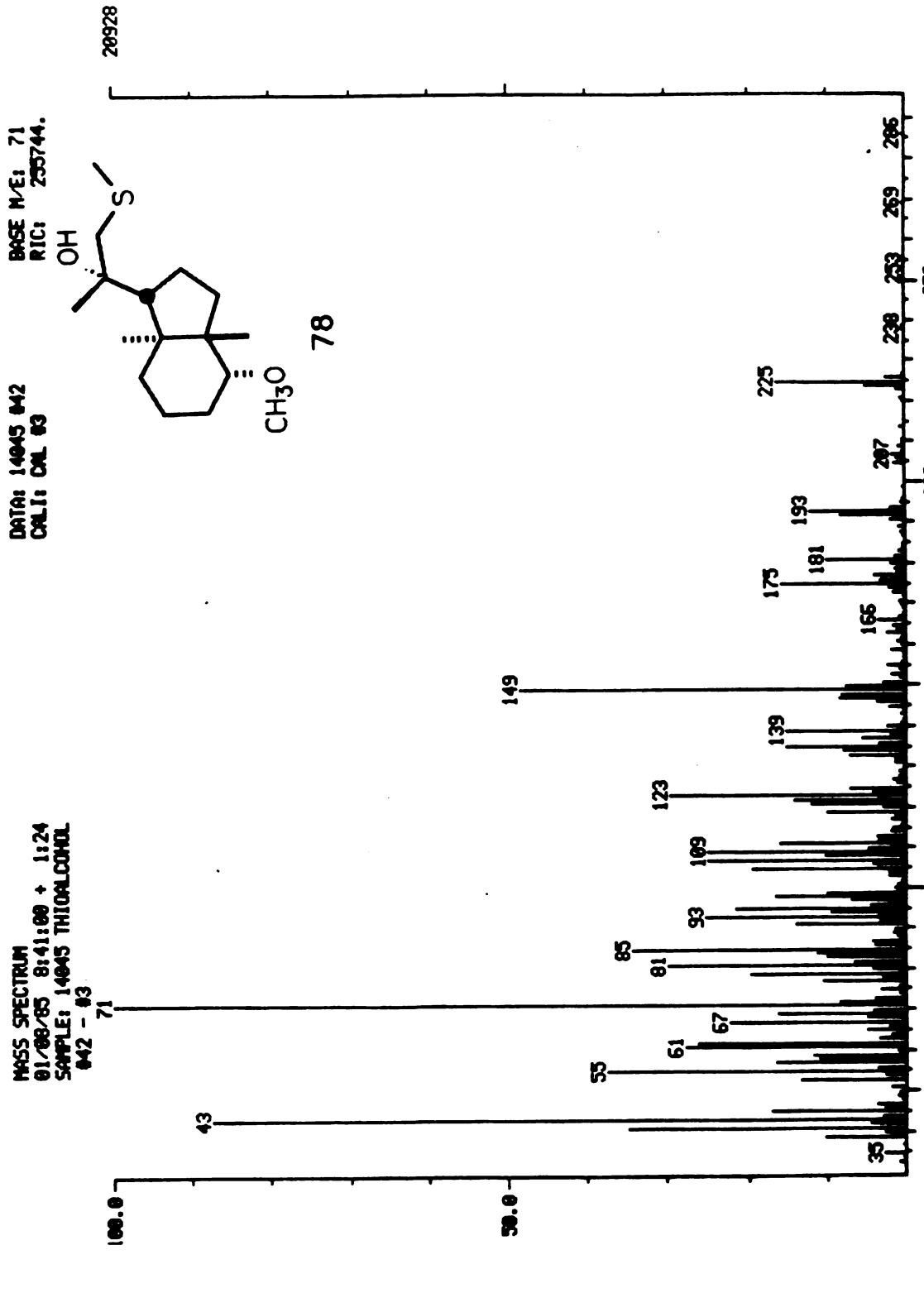



Figure 25 Mass Spectrum of Compound 78

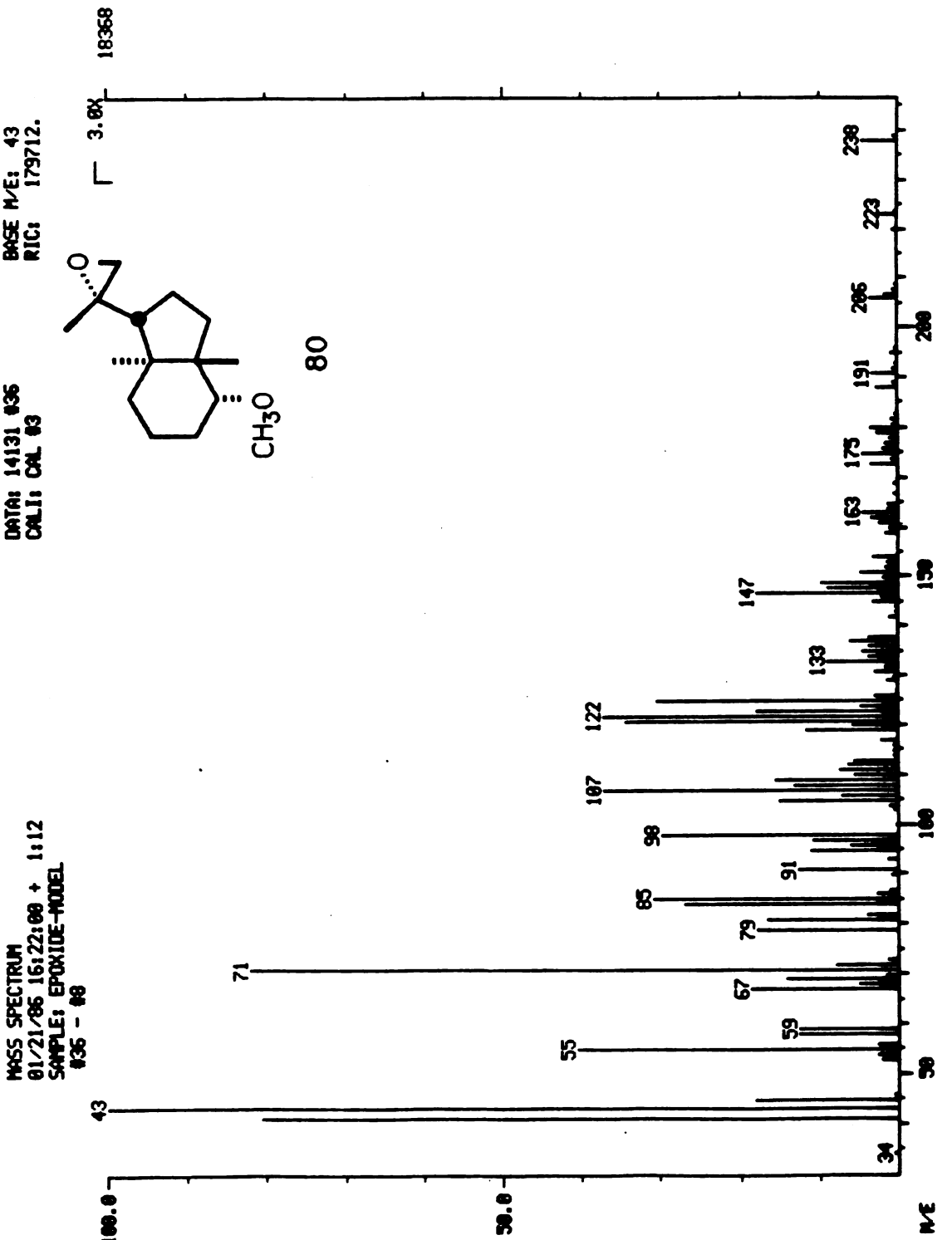



Figure 26 Mass Spectrum of Compound 80

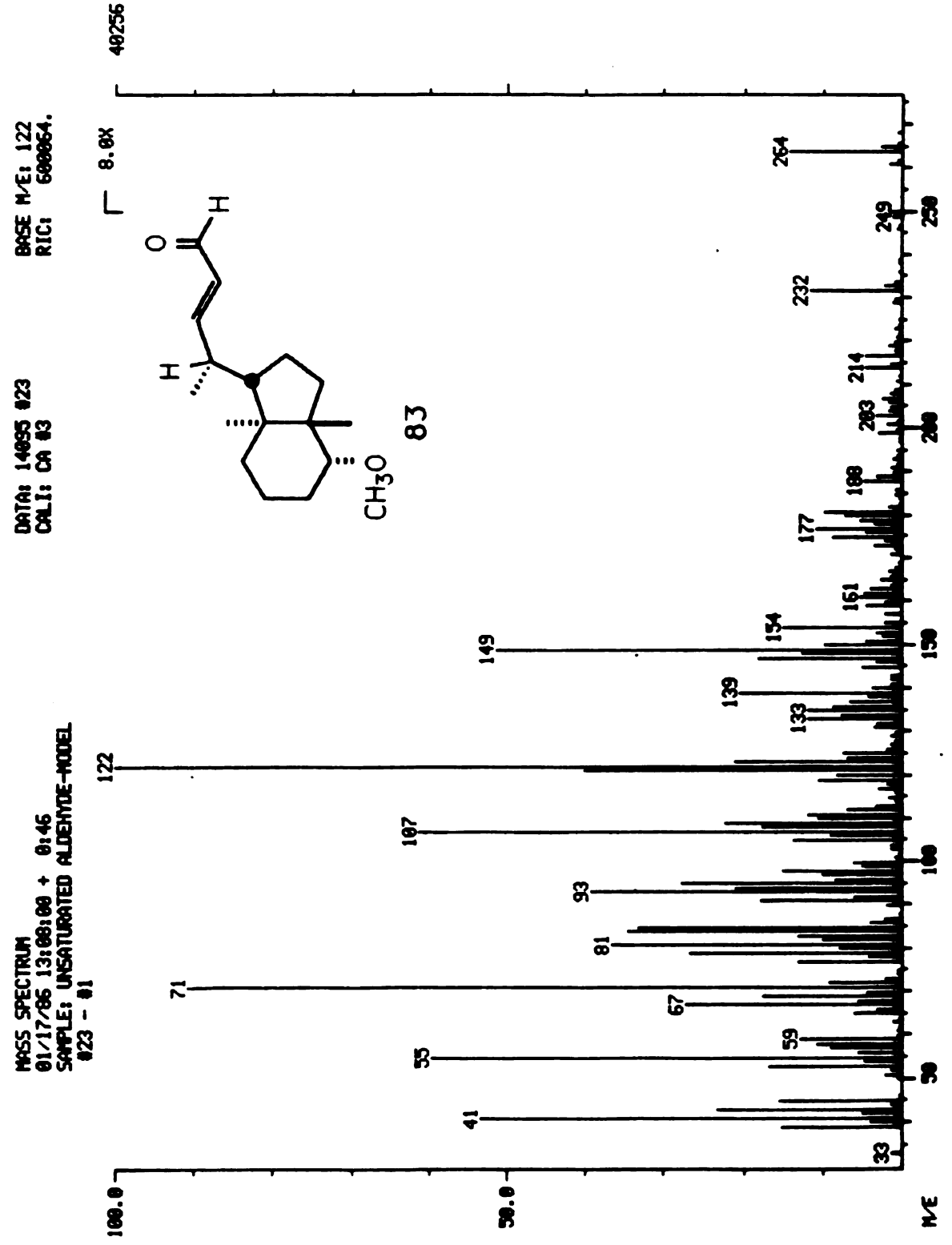



Figure 27 Mass Spectrum of Compound 83

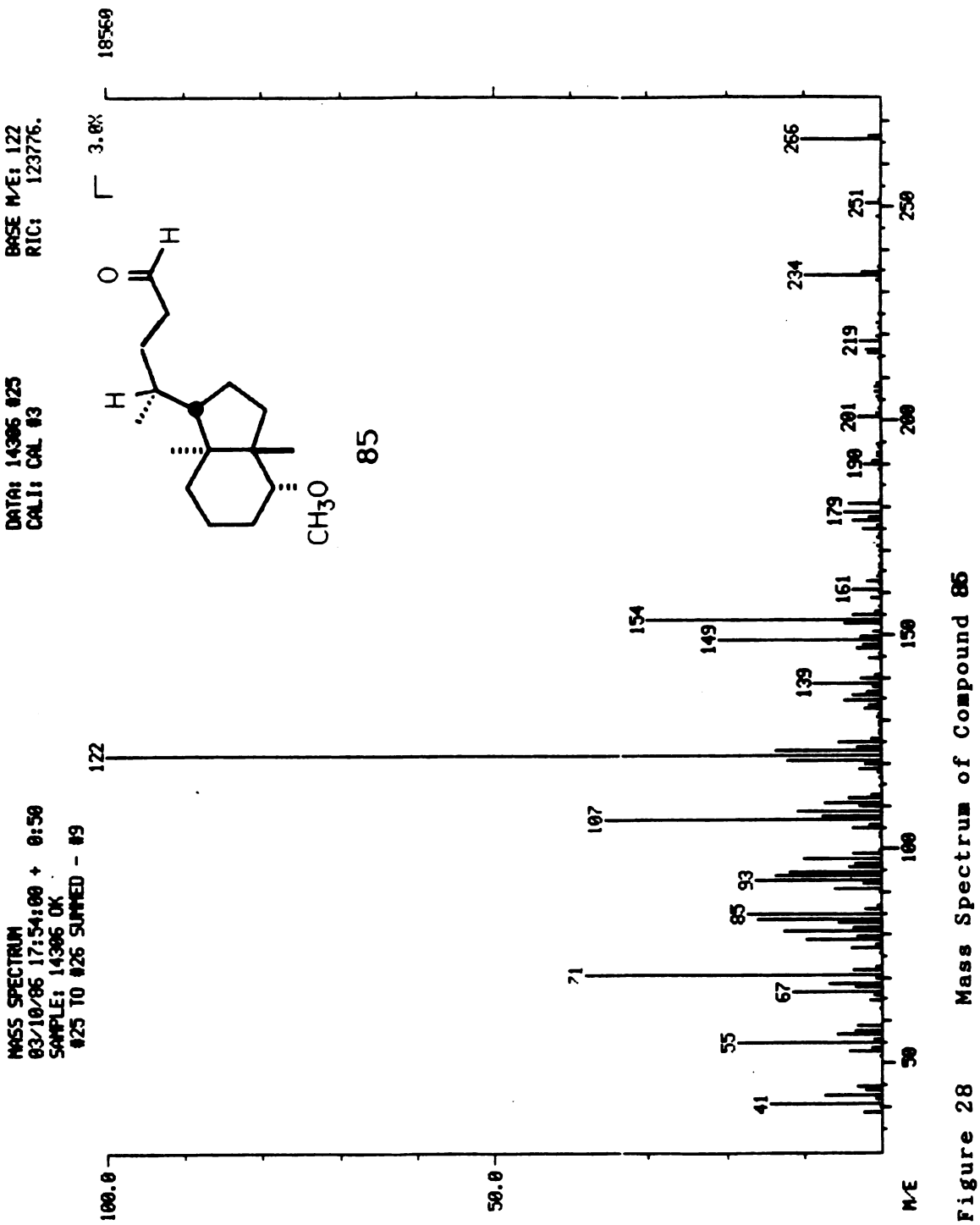



Figure 28 Mass Spectrum of Compound 85

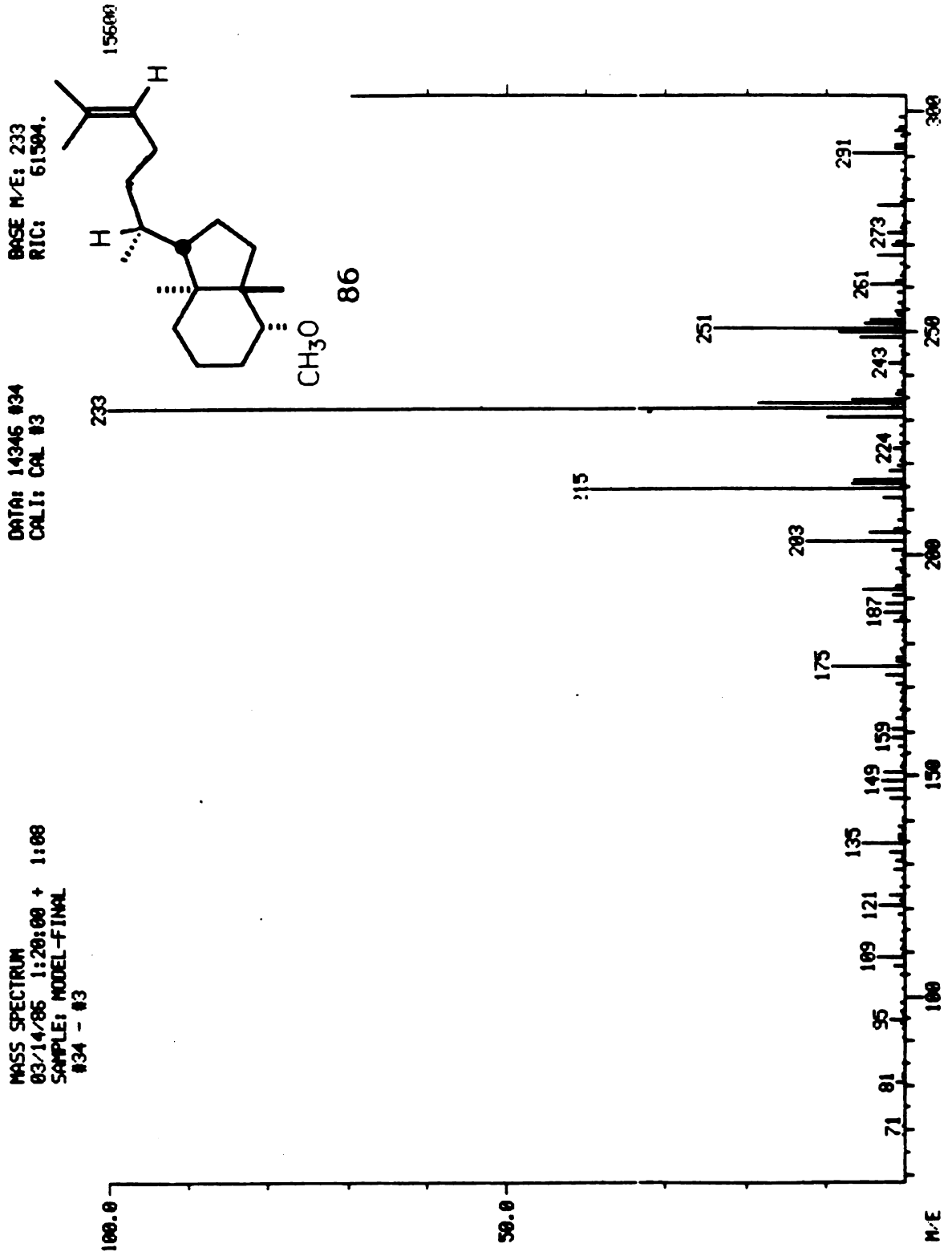



Figure 29 Mass Spectrum of Compound 86

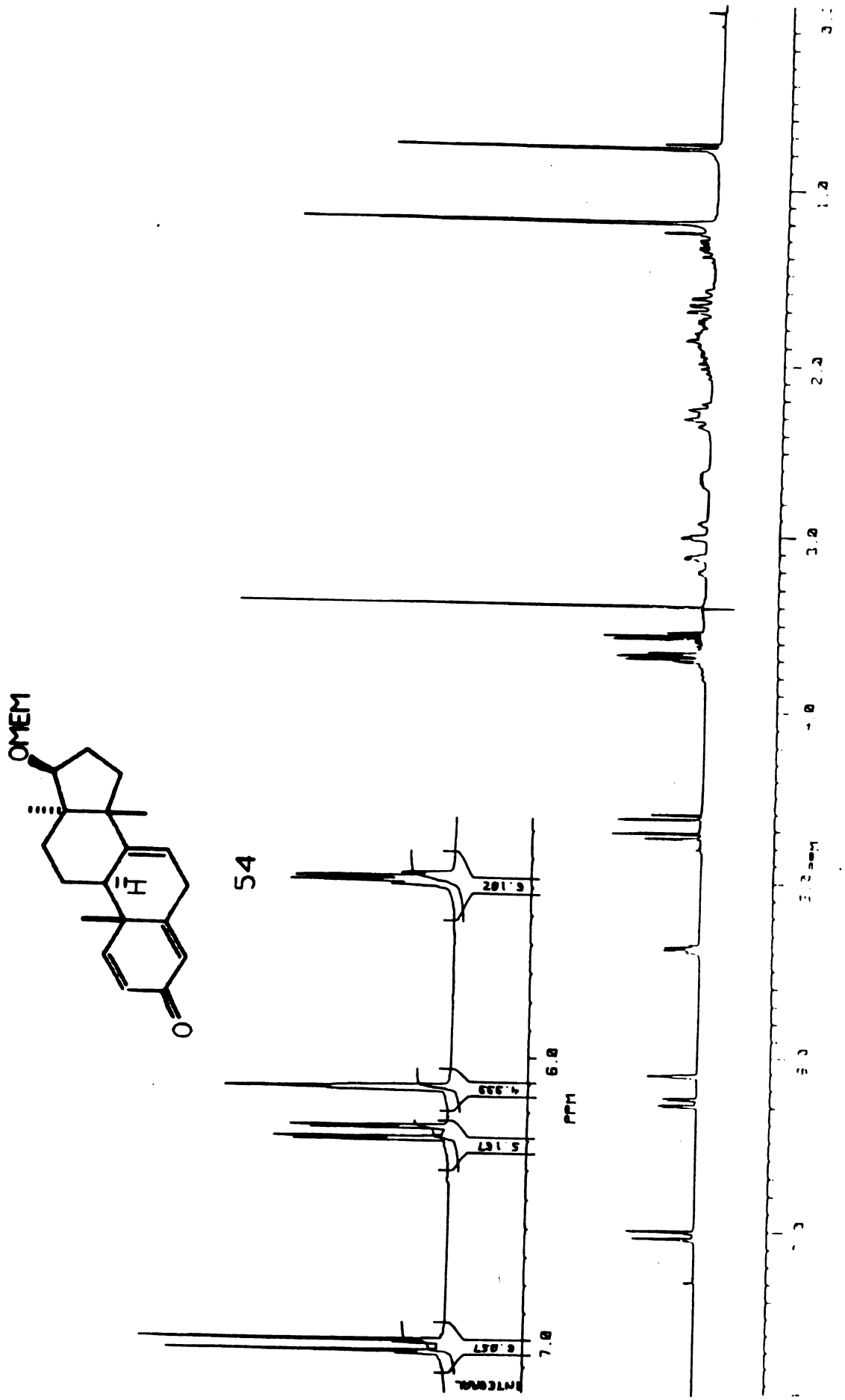



Figure 30 $^1H$ NMR Spectrum of Compound 54(β)

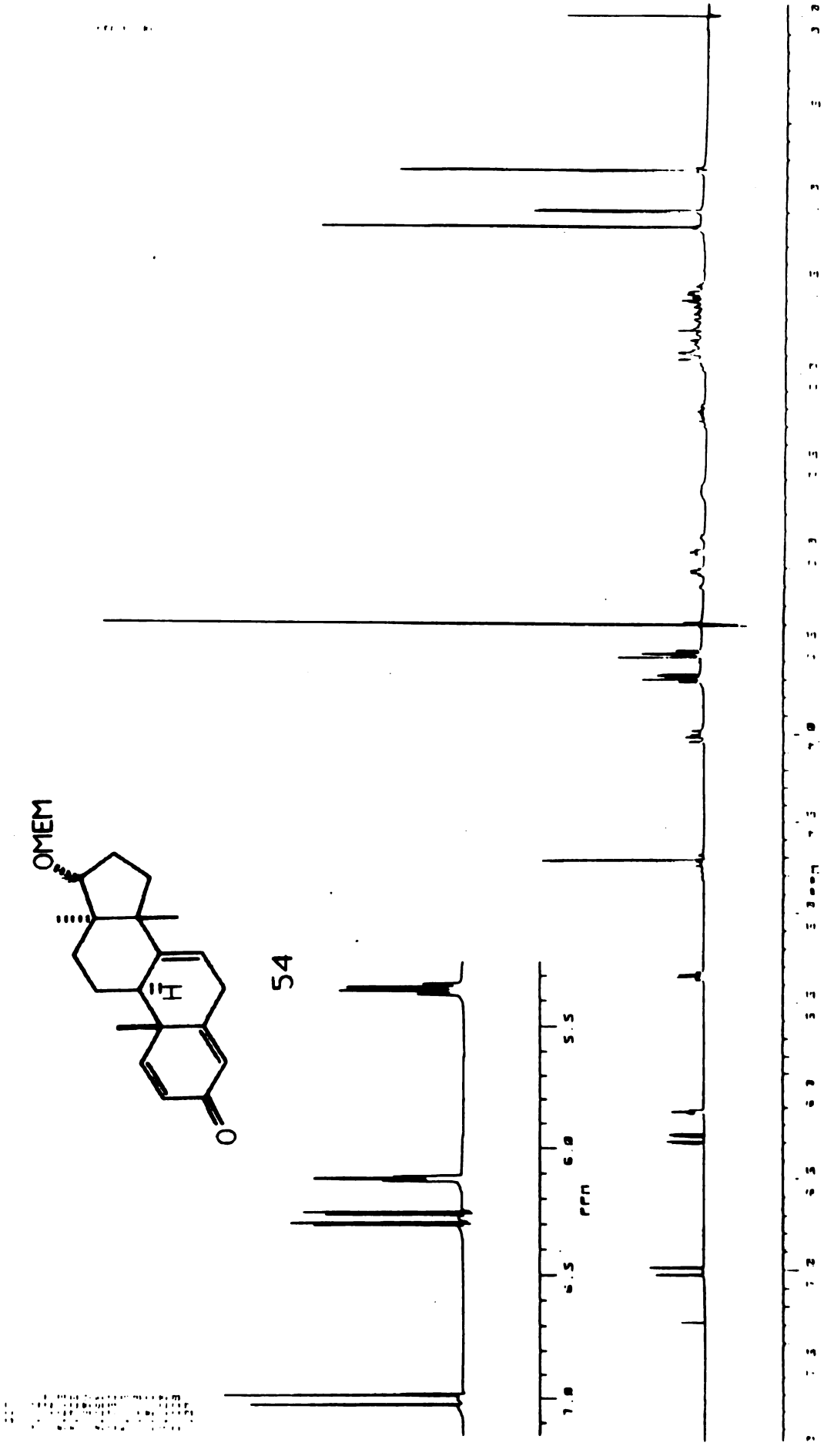



Figure 31 $^1$H NMR Spectrum of Compound 54(α)

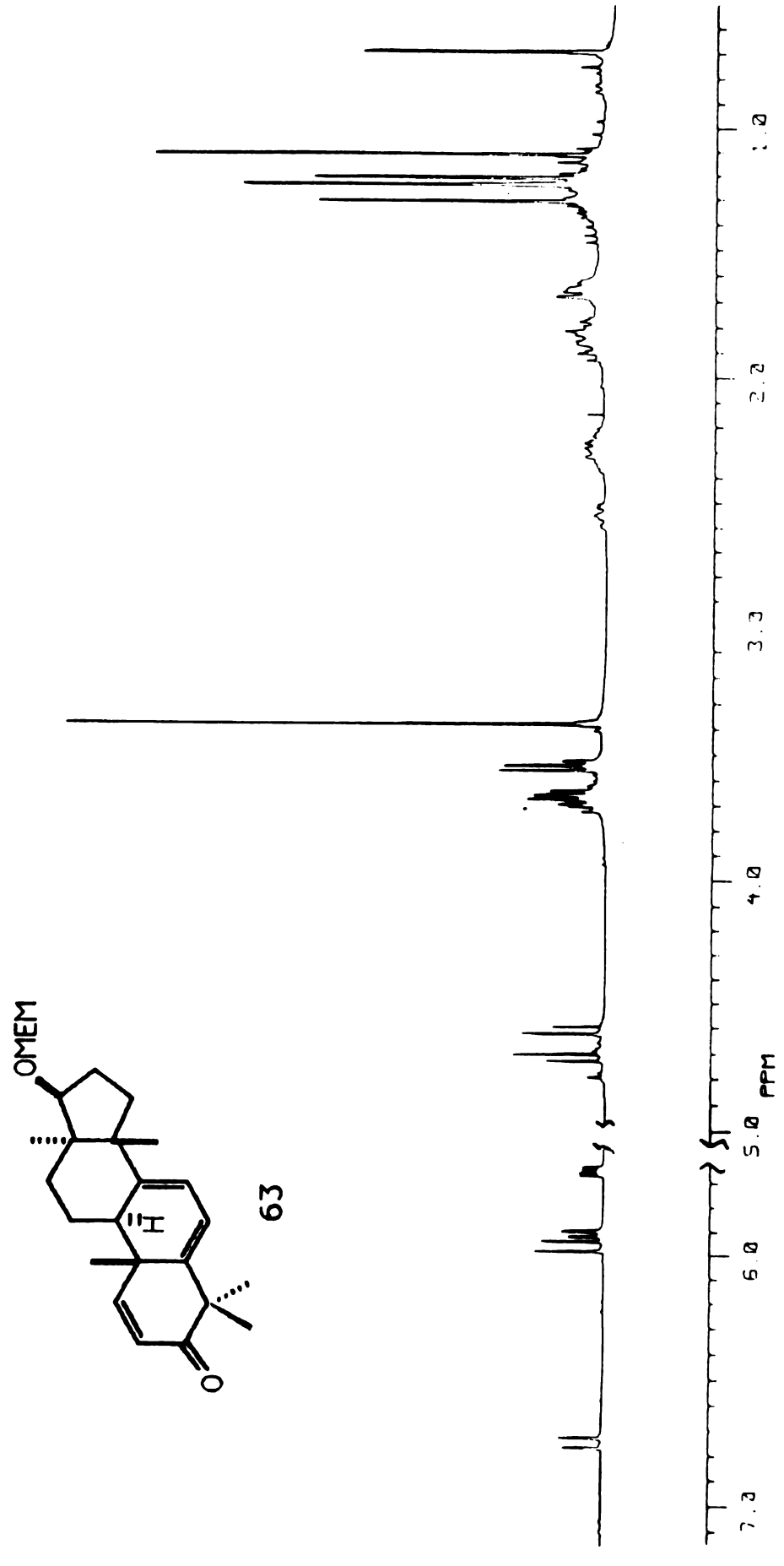



Figure 32 $^1$H NMR Spectrum of Compound 63(β)

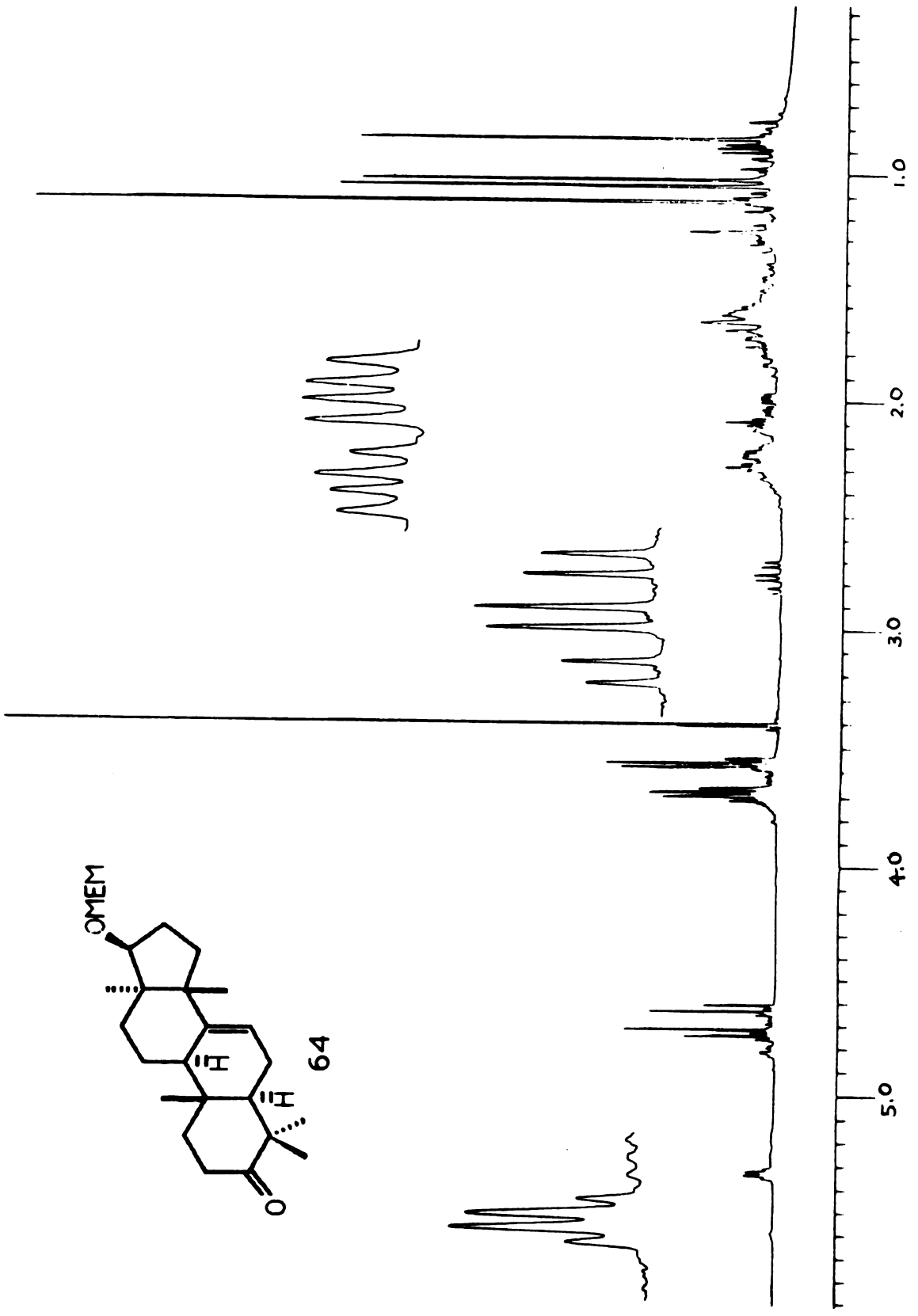



Figure 33 $^{1}H$ NMR Spectrum of Compound 64(β)

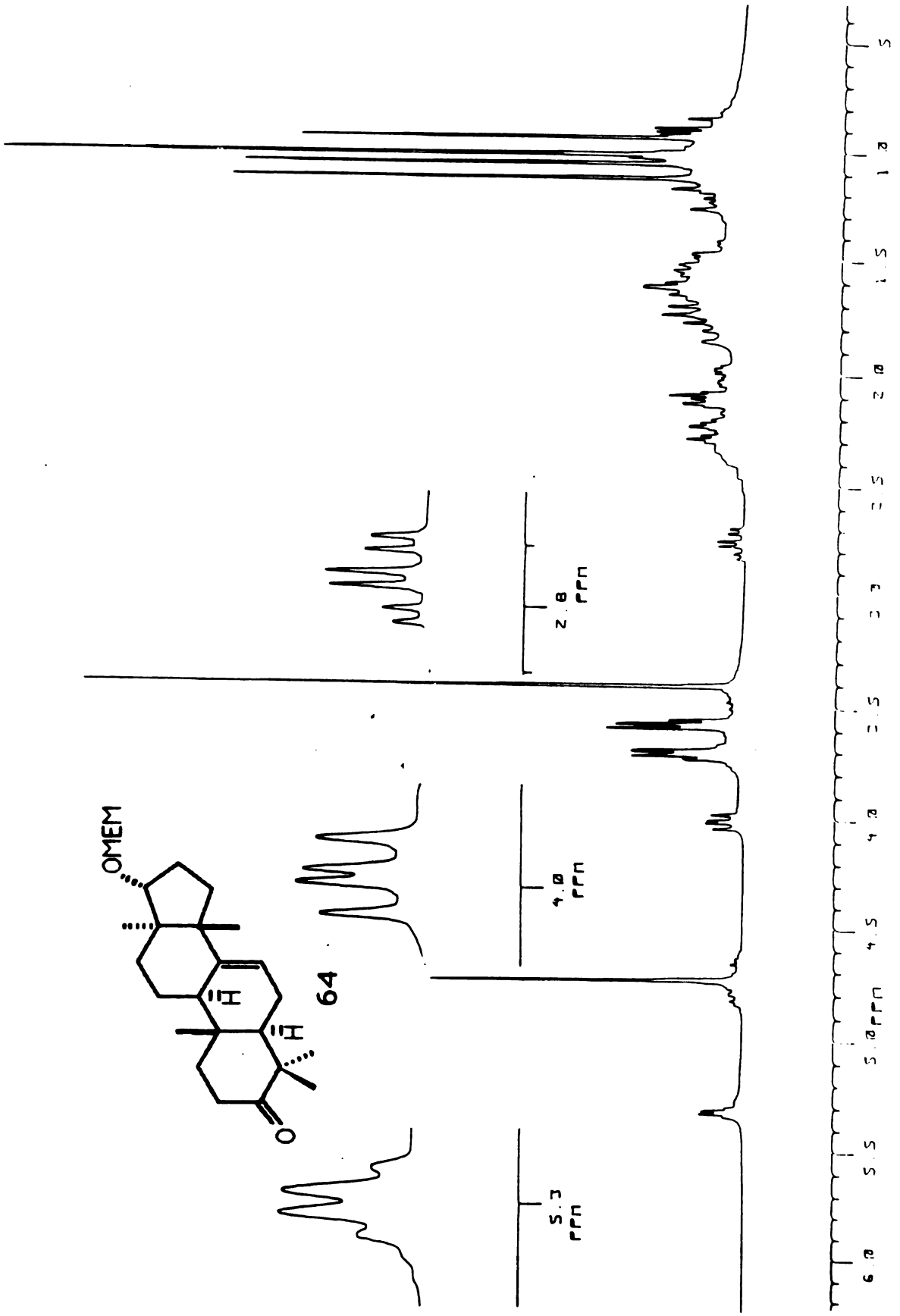



Figure 34 $^1$H NMR Spectrum of Compound 64(α)

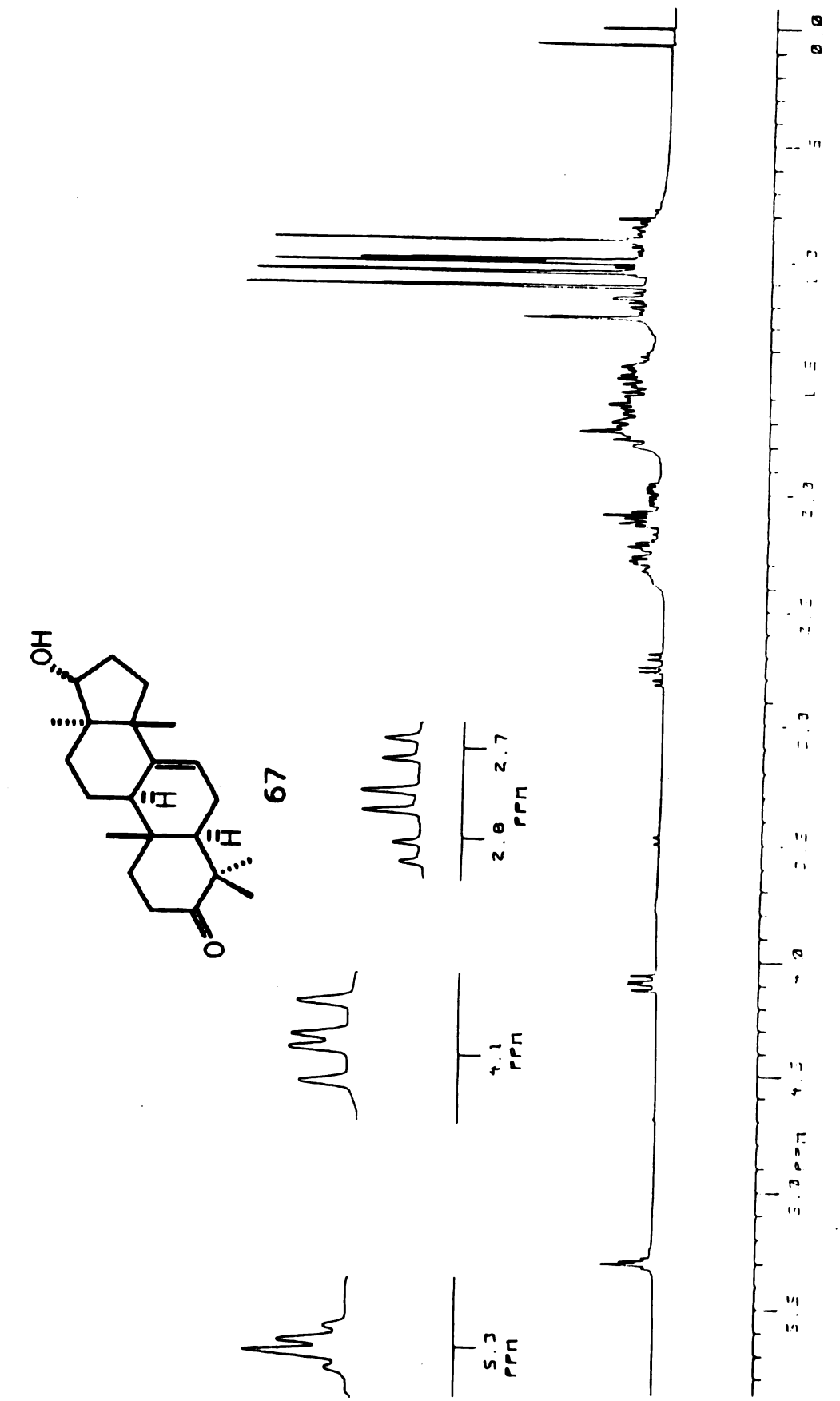



Figure 35 $^1$H NMR Spectrum of Compound 67(a)

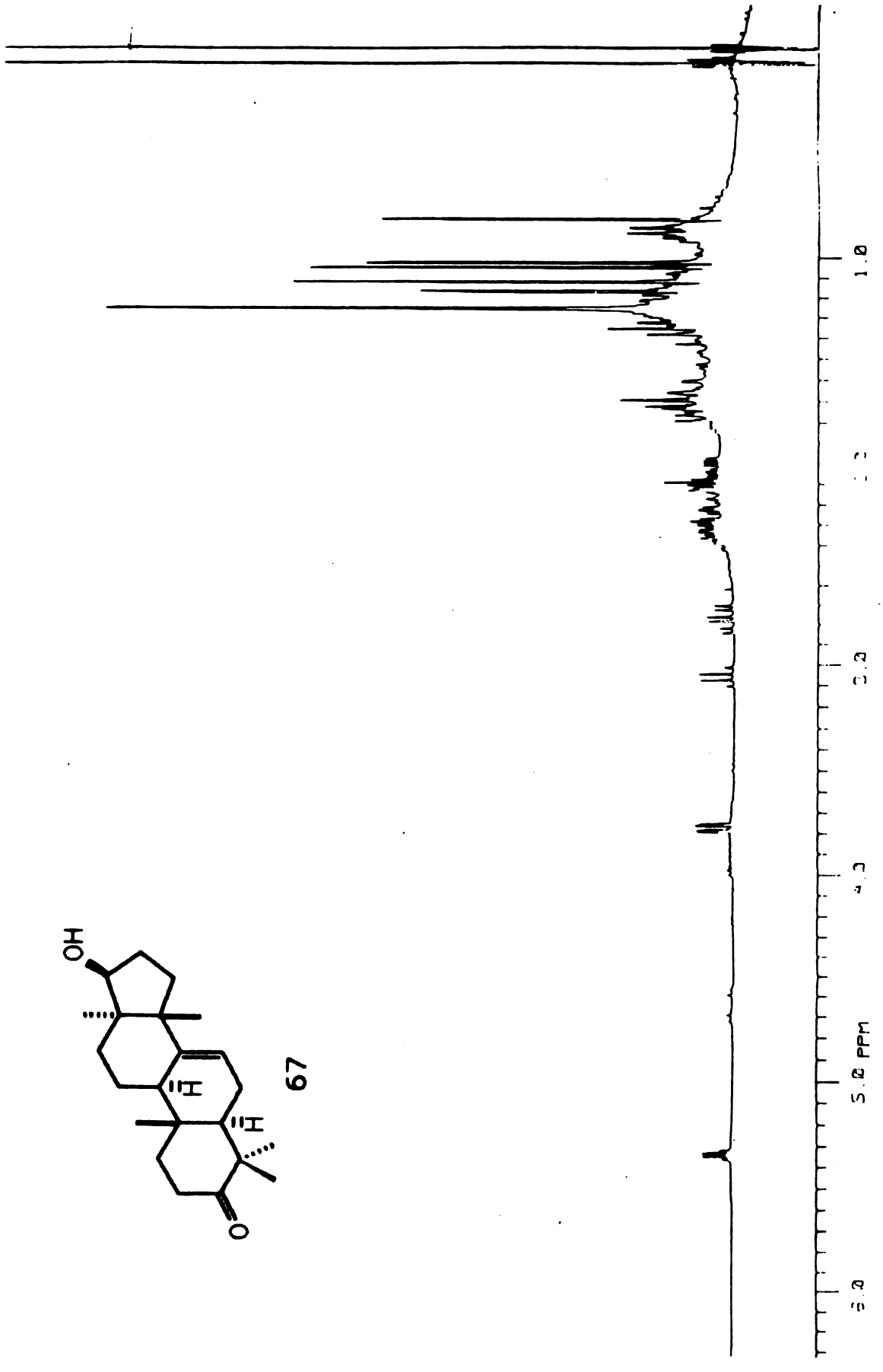



Figure 36 $^1$H NMR Spectrum of Compound 67(β)

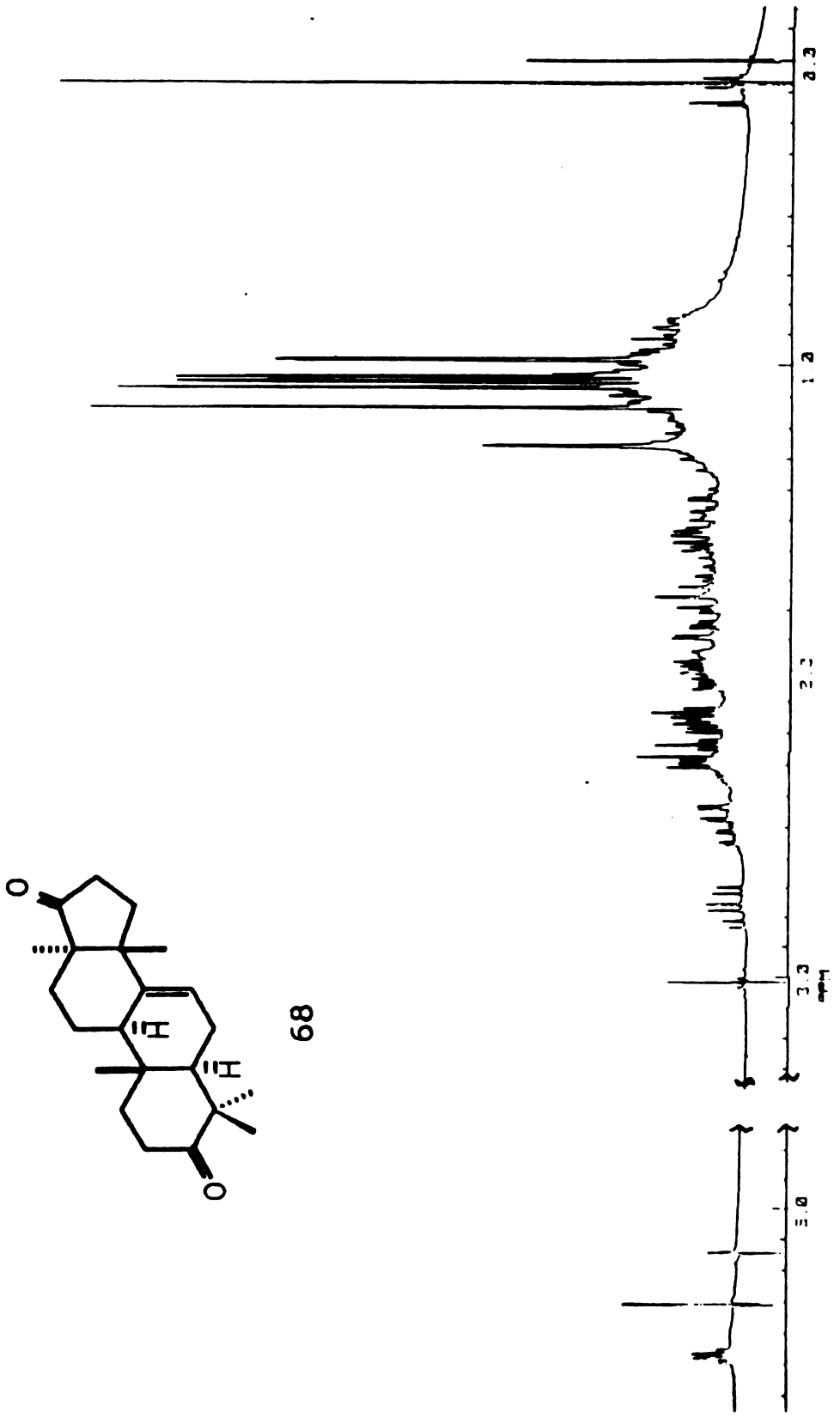



Figure 37 $^{1}H$ NMR Spectrum of Compound **68**

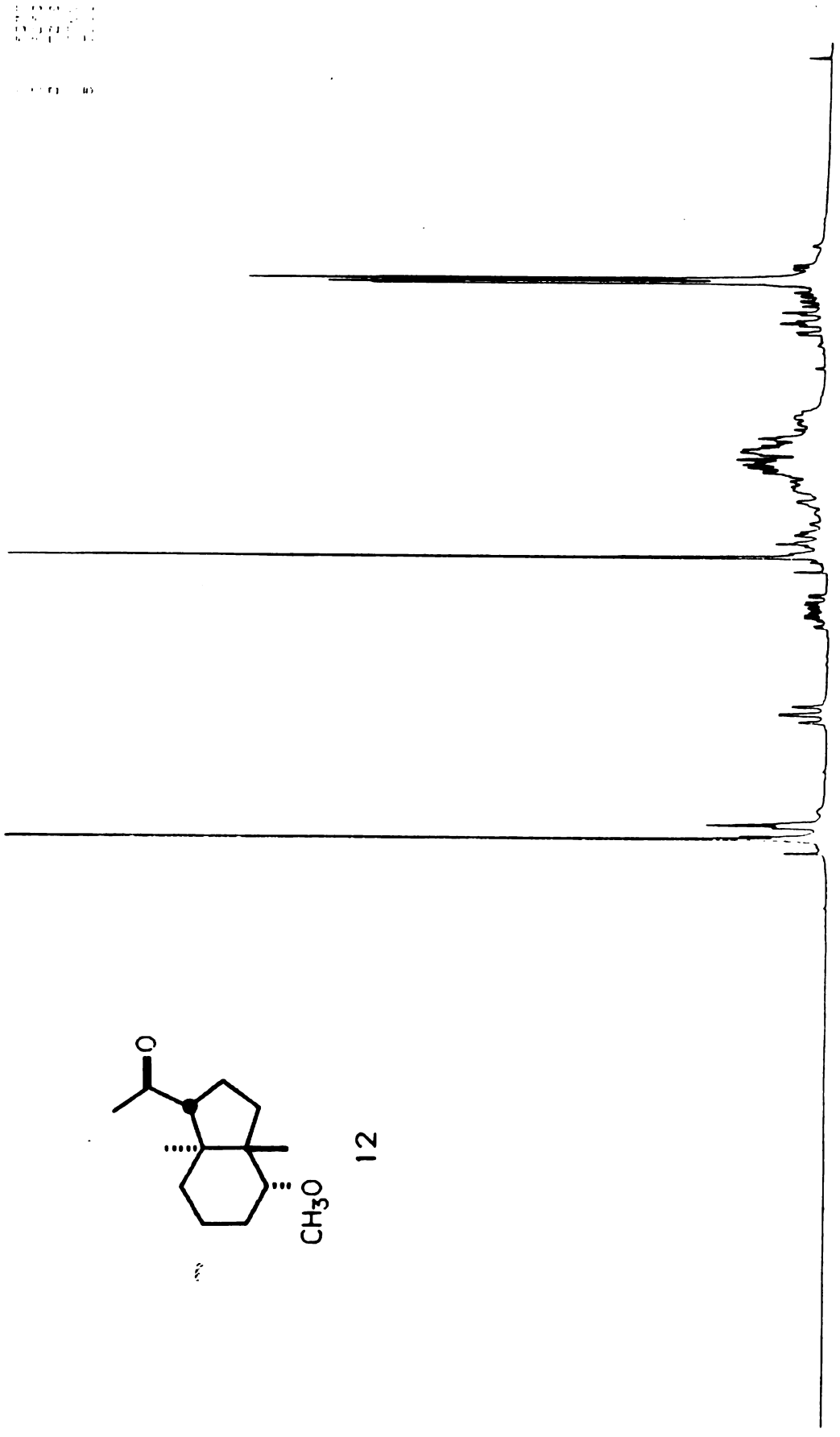



**Figure 38** $^{1}H$ NMR Spectrum of Compound 12

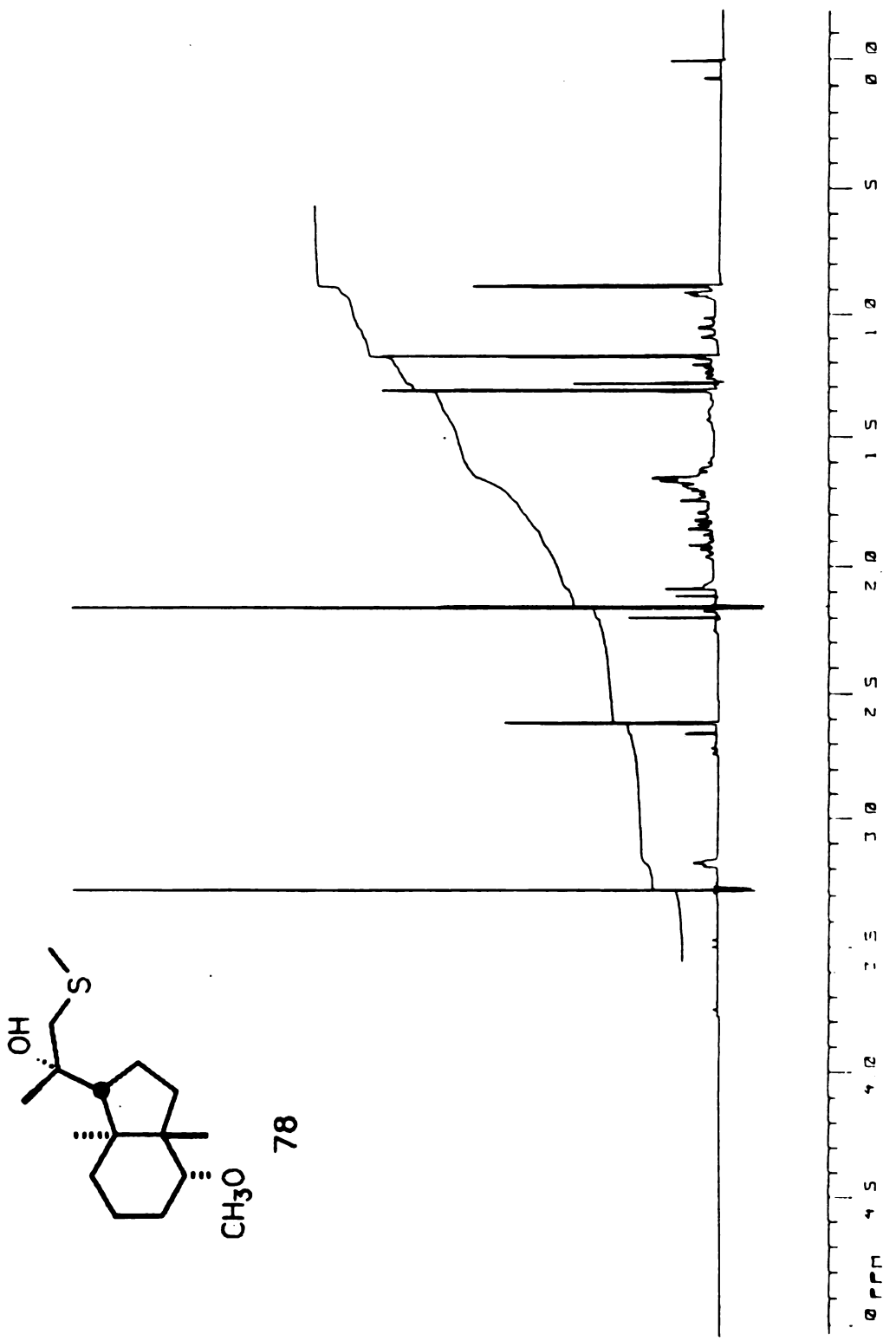



Figure 39 $^{1}H$ NMR Spectrum of Compound **78**

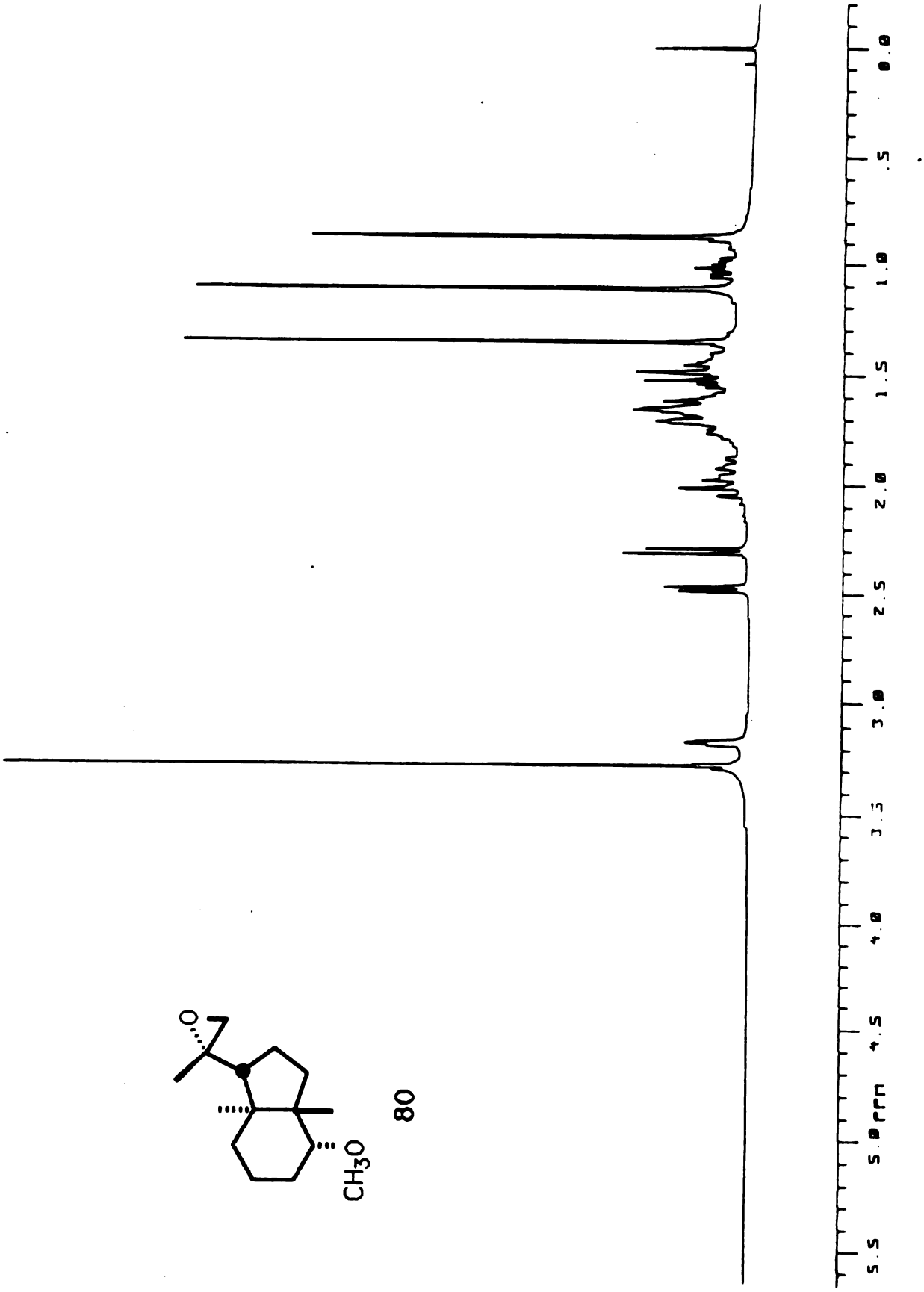



Figure 40 $^1$H NMR Spectrum of Compound **80**

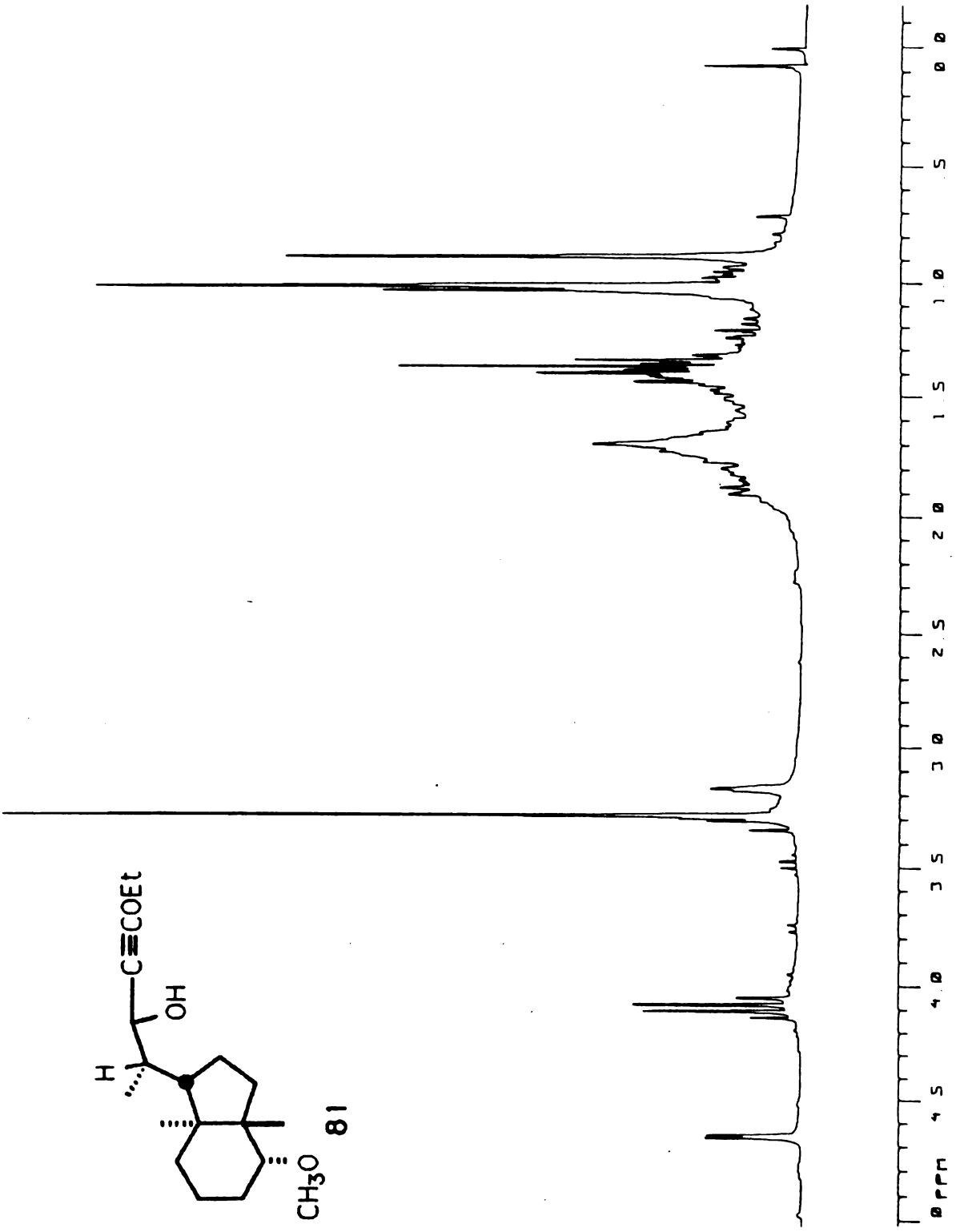



Figure 41 $^1$H NMR Spectrum of Compound 81

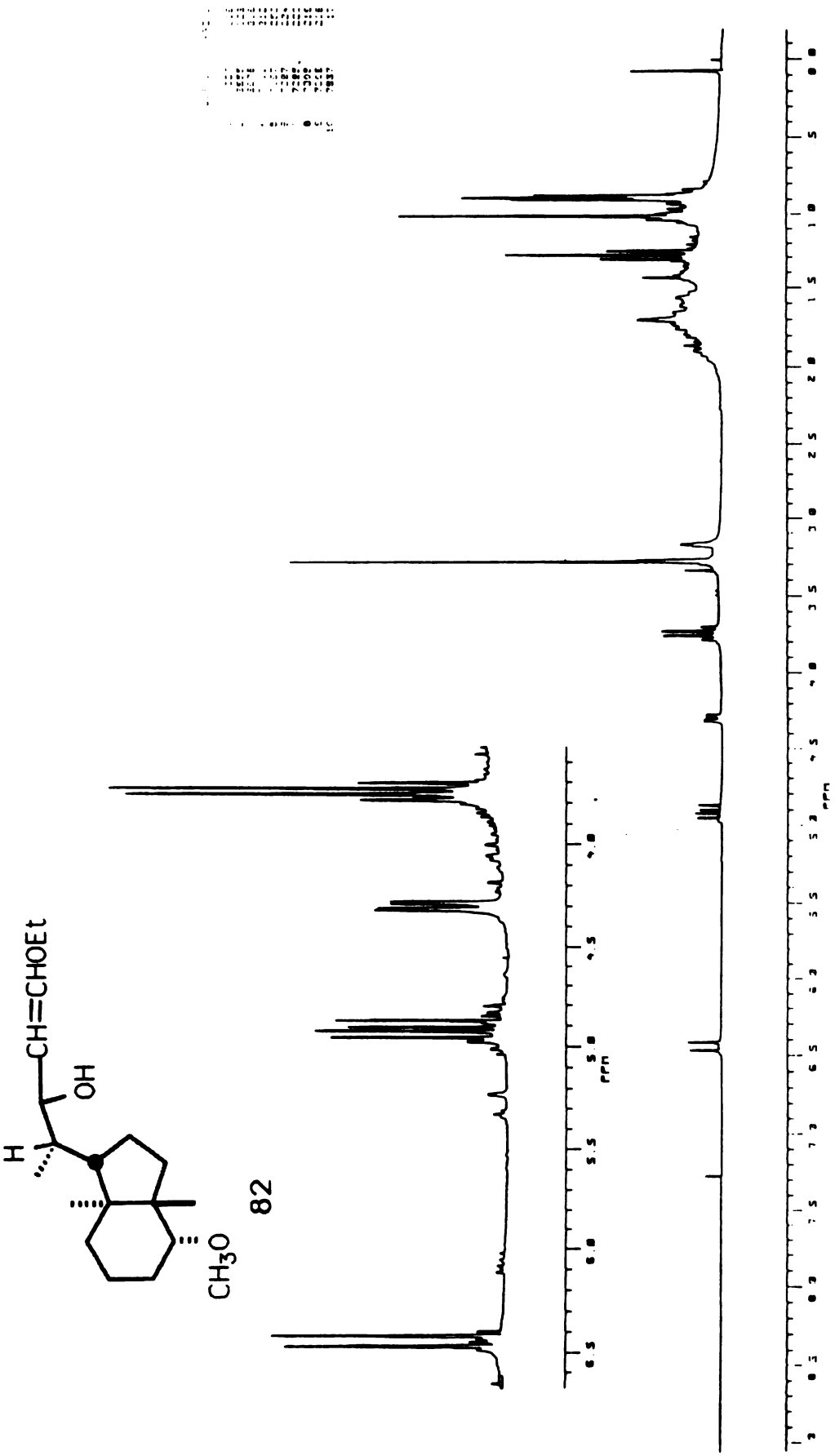



Figure 42 $^1$H NMR Spectrum of Compound 82

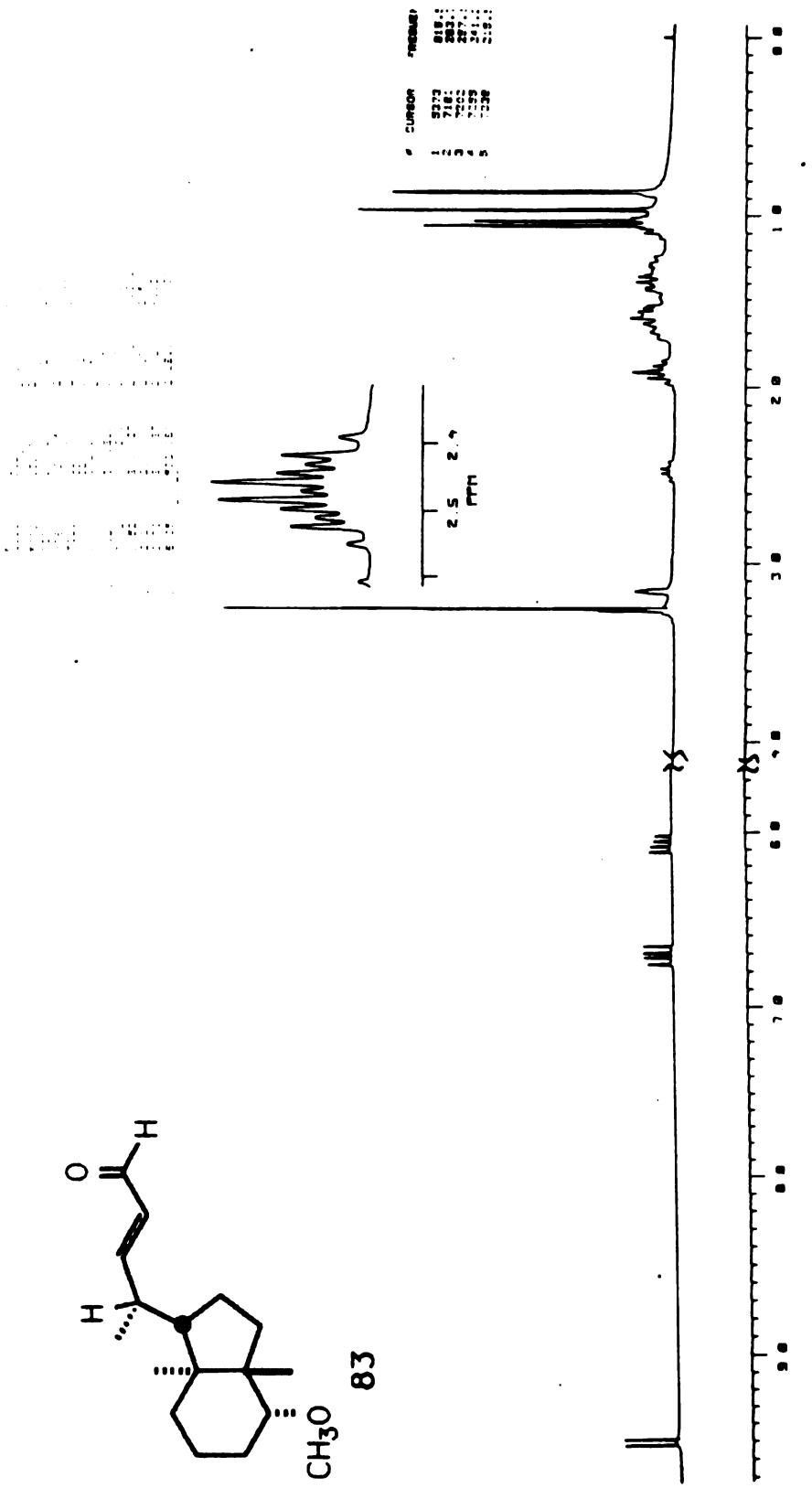



Figure 43 $^1H$ NMR Spectrum of Compound 83

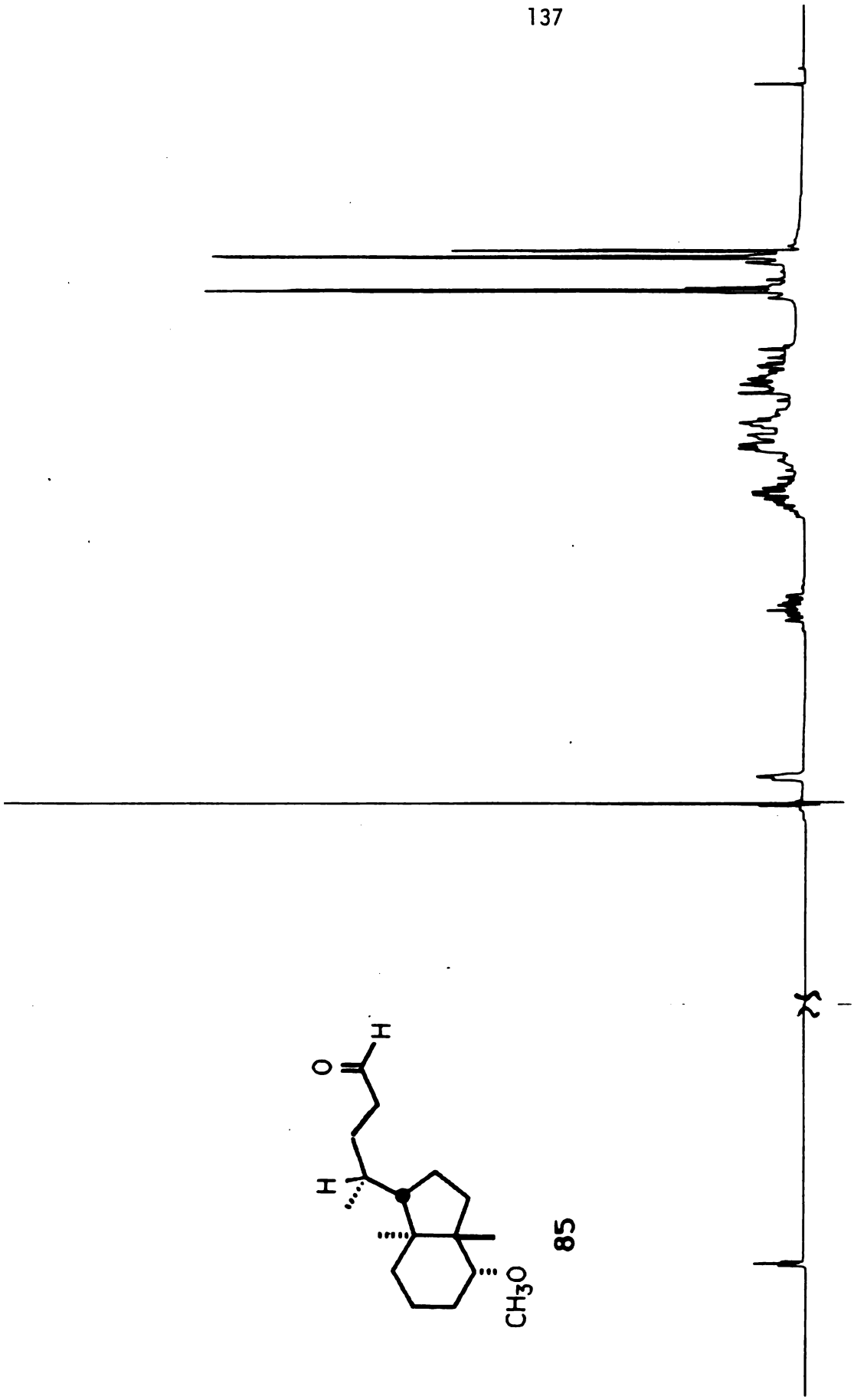



Figure 44 $^1$H NMR Spectrum of Compound **85**

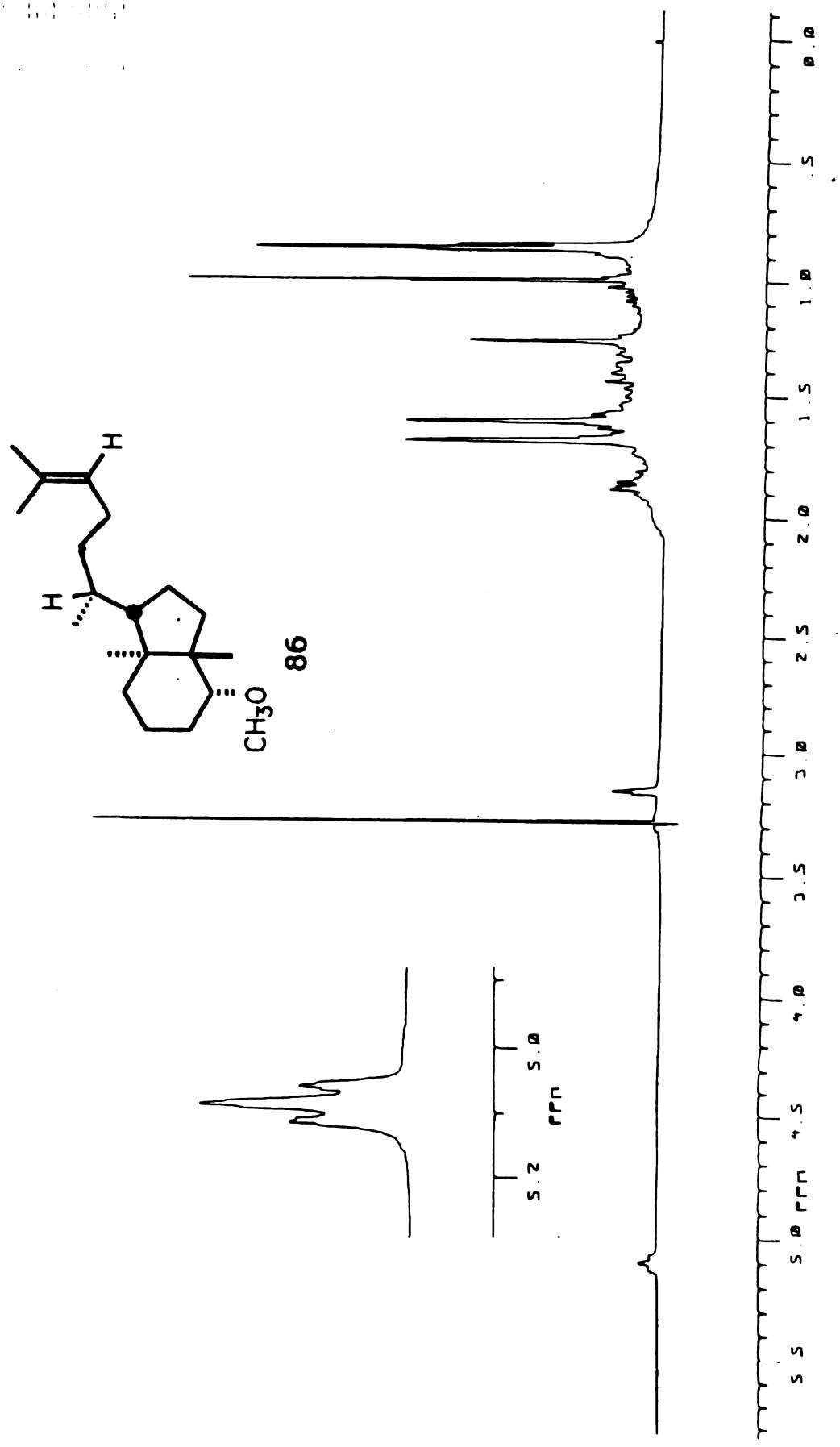
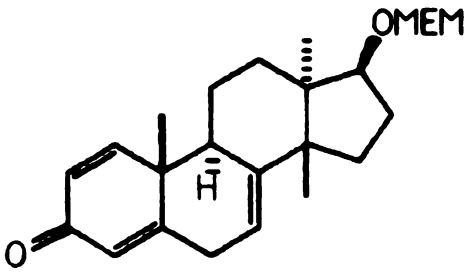



Figure 45 $^{1}H$ NMR Spectrum of Compound **86**




54

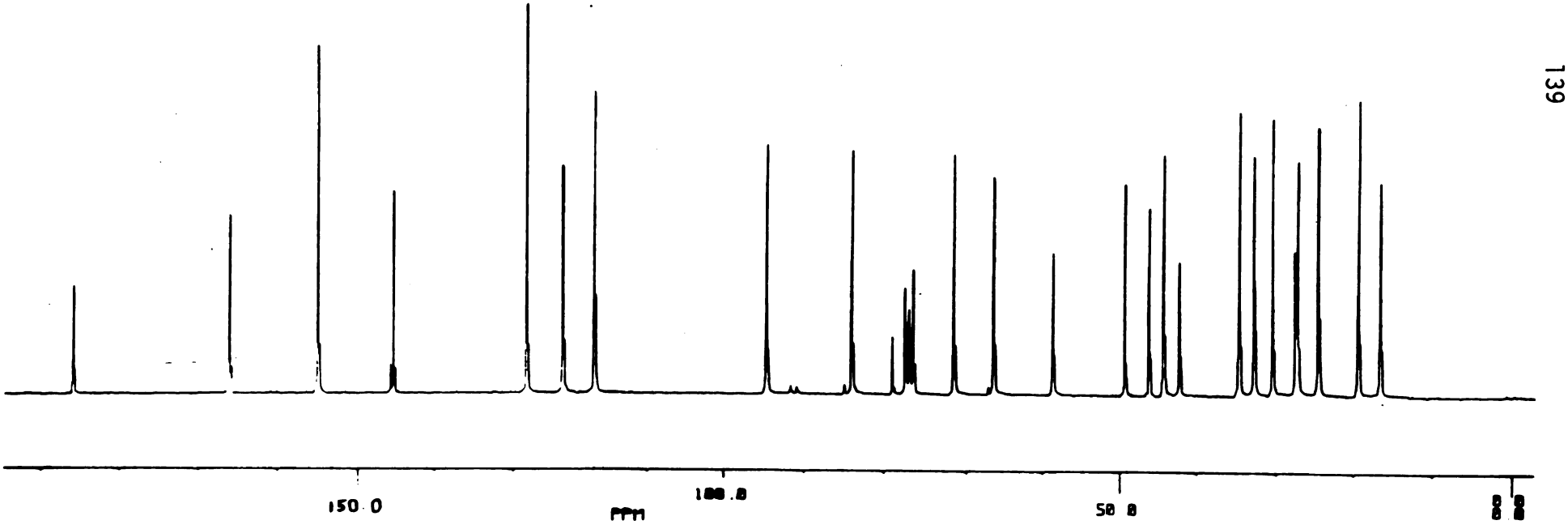
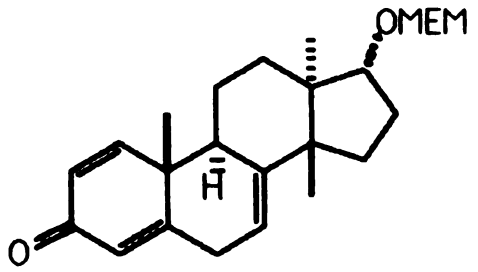



Figure 46 $^{13}C$ NMR Spectrum of Compound 54(β)




54



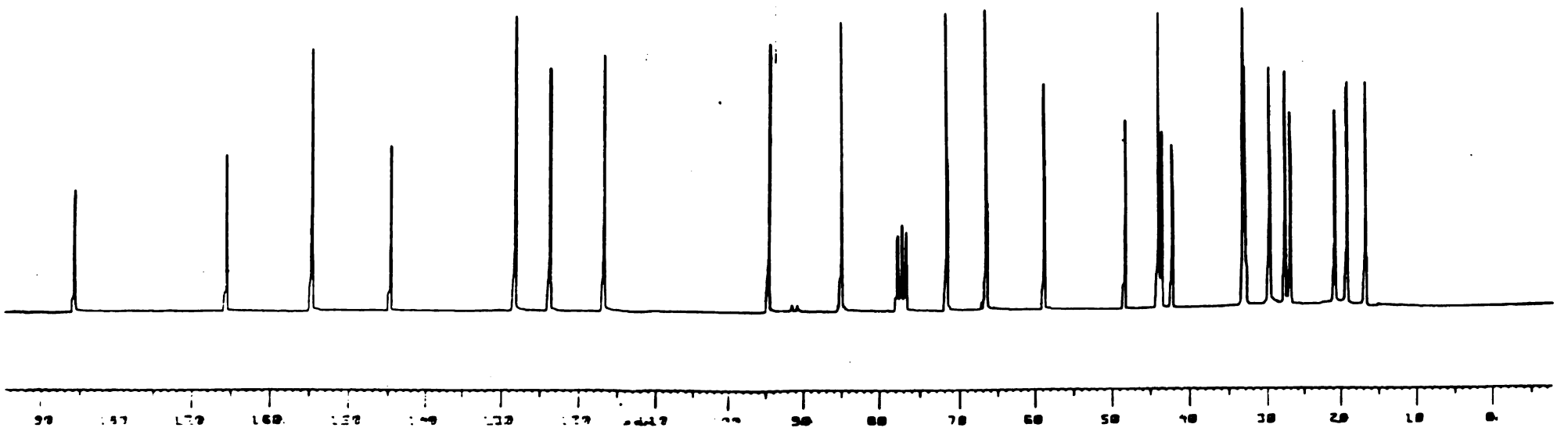
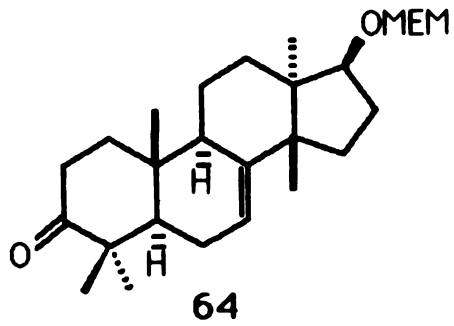


Figure 47 $^{13}C$ NMR Spectrum of Compound 54($\alpha$)




64



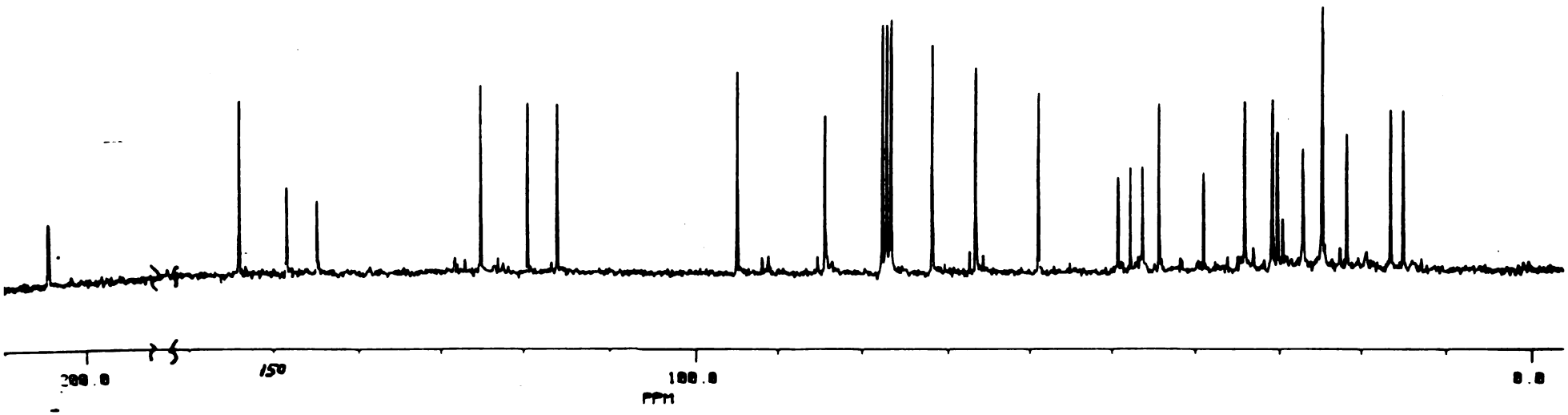



Figure 48 $^{13}C$ NMR Spectrum of Compound 64(β)

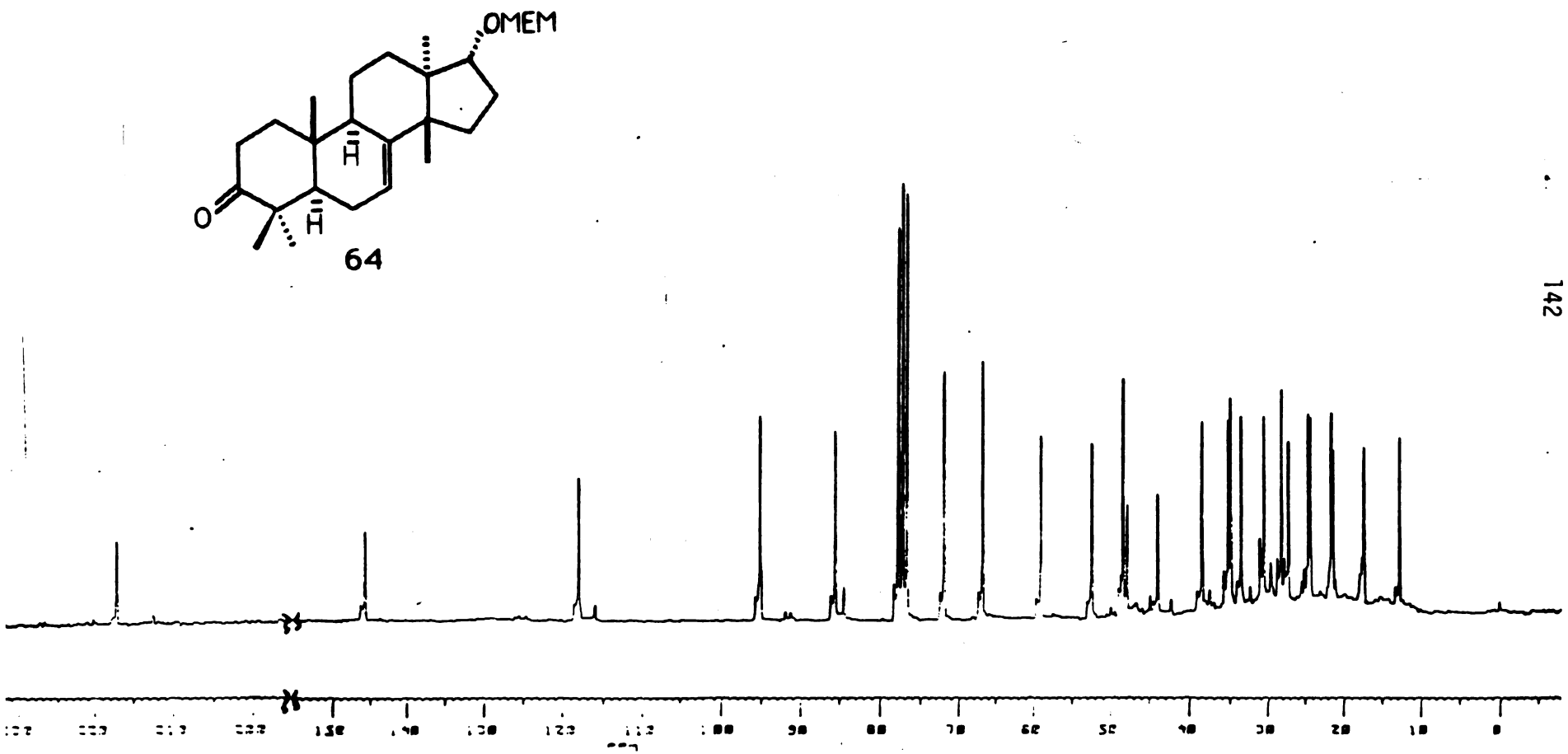
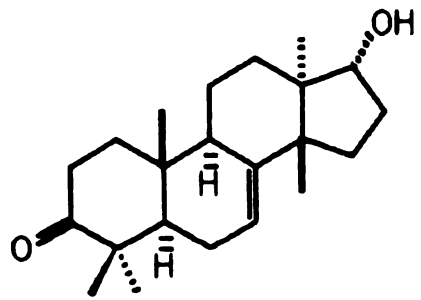



Figure 49 $^{13}C$ NMR Spectrum of Compound 64(α)

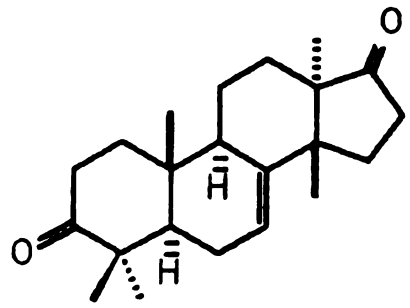



67





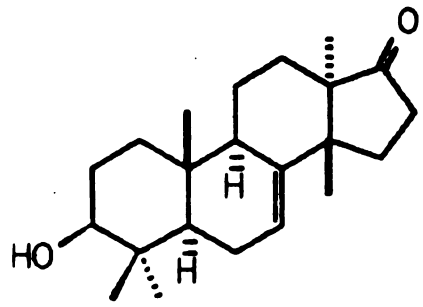
Figure 50 $^{13}C$ NMR Spectrum of Compound 67(α)




68



Figure 51 $^{13}C$ NMR Spectrum of Compound 68




69

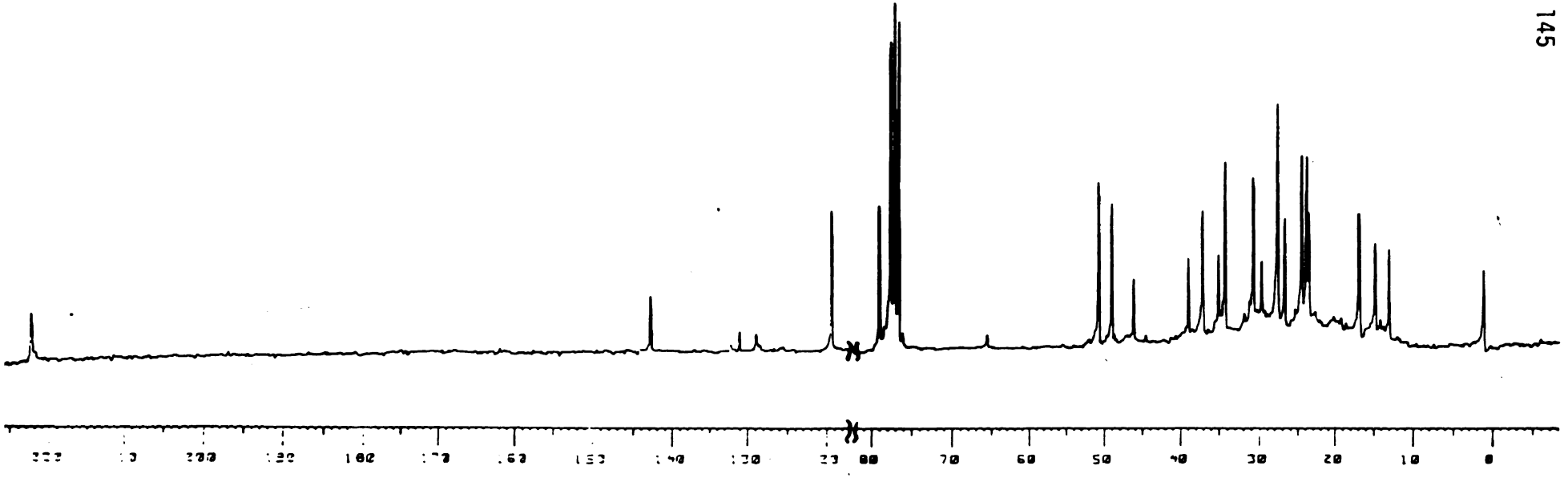




Figure 52 $^{13}C$ NMR Spectrum of Compound 69

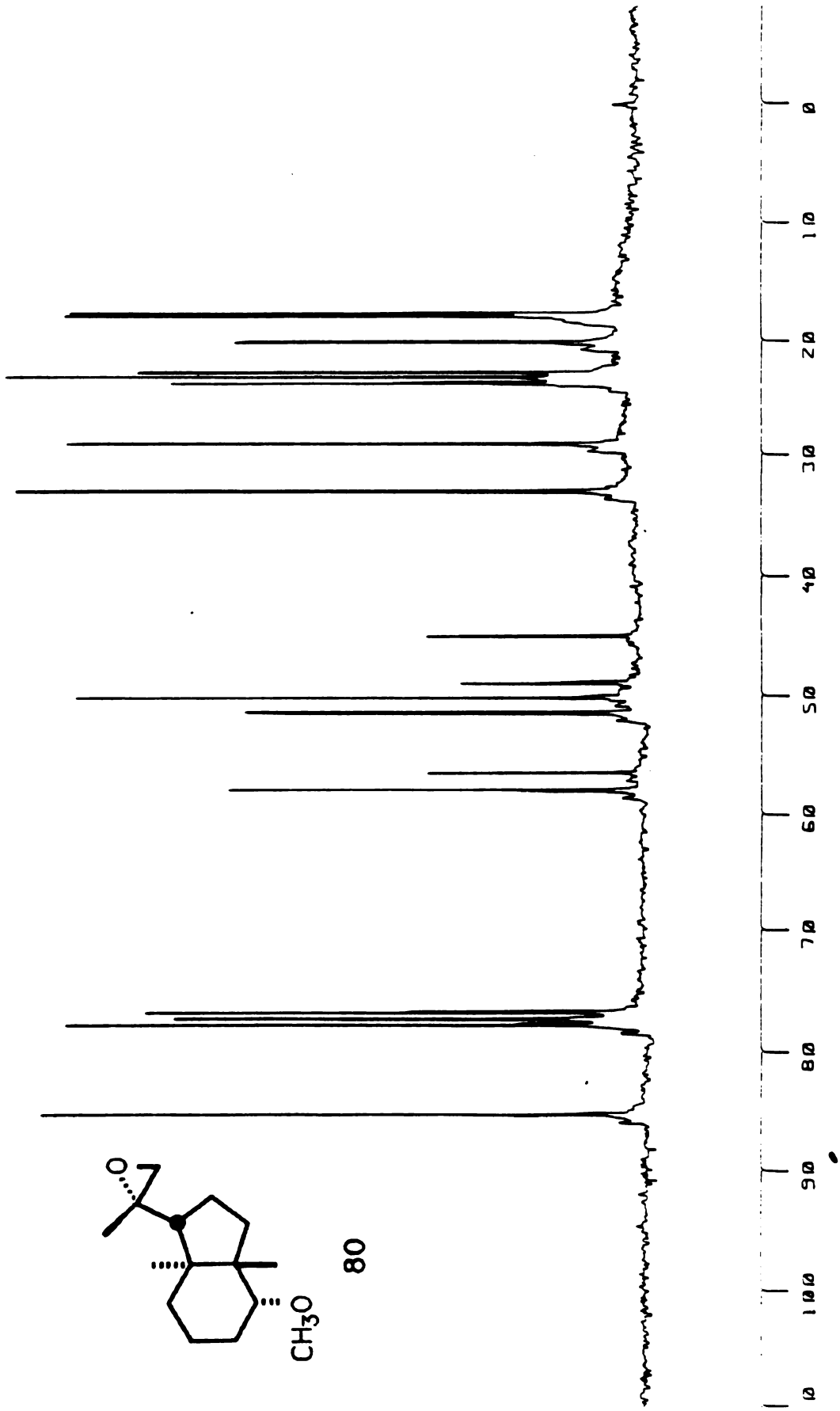



Figure 53 $^{13}C$ NMR Spectrum of Compound **80**

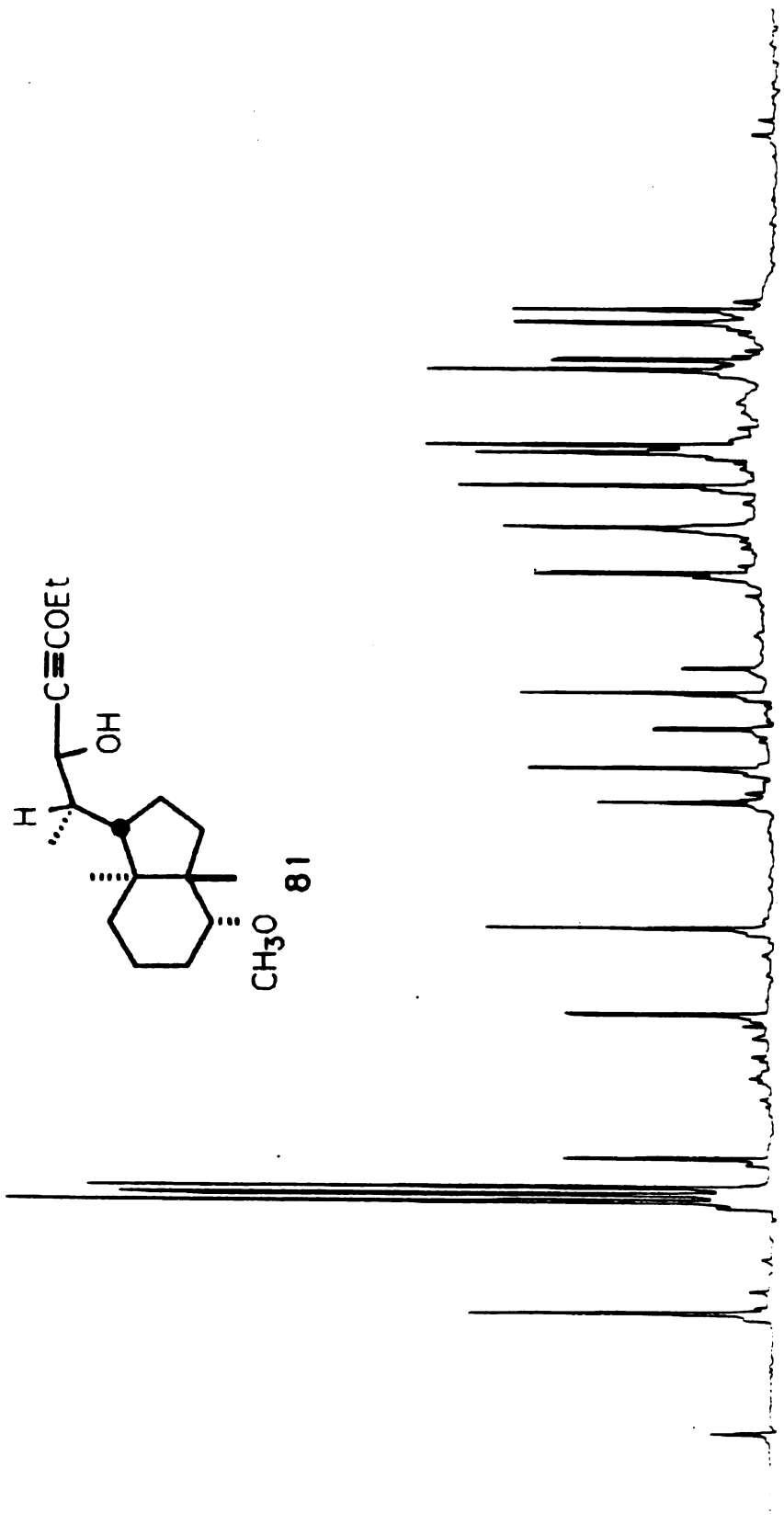



Figure 54 $^{13}C$ NMR Spectrum of Compound **81**

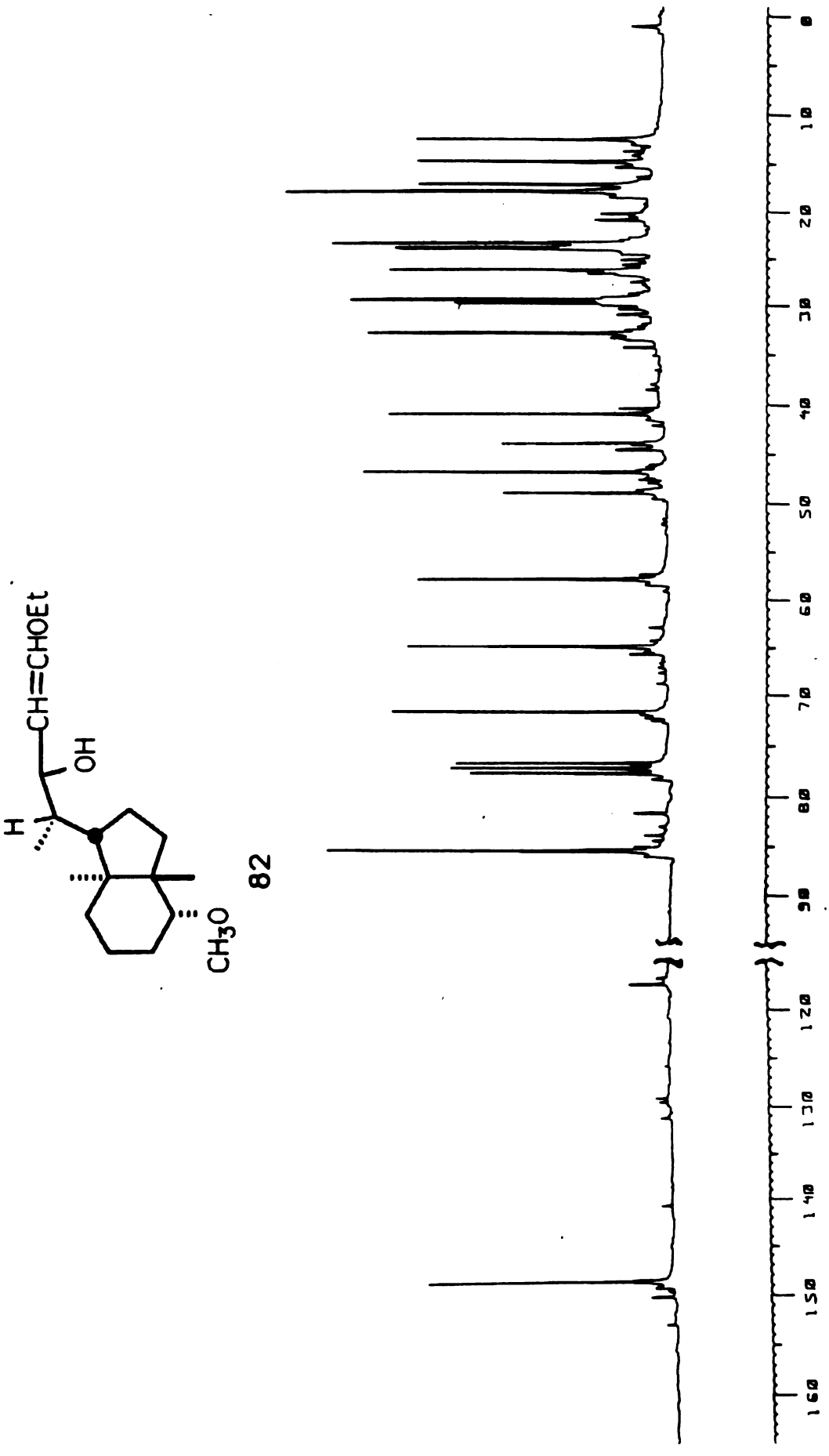



Figure 55 $^{13}C$ NMR Spectrum of Compound 82

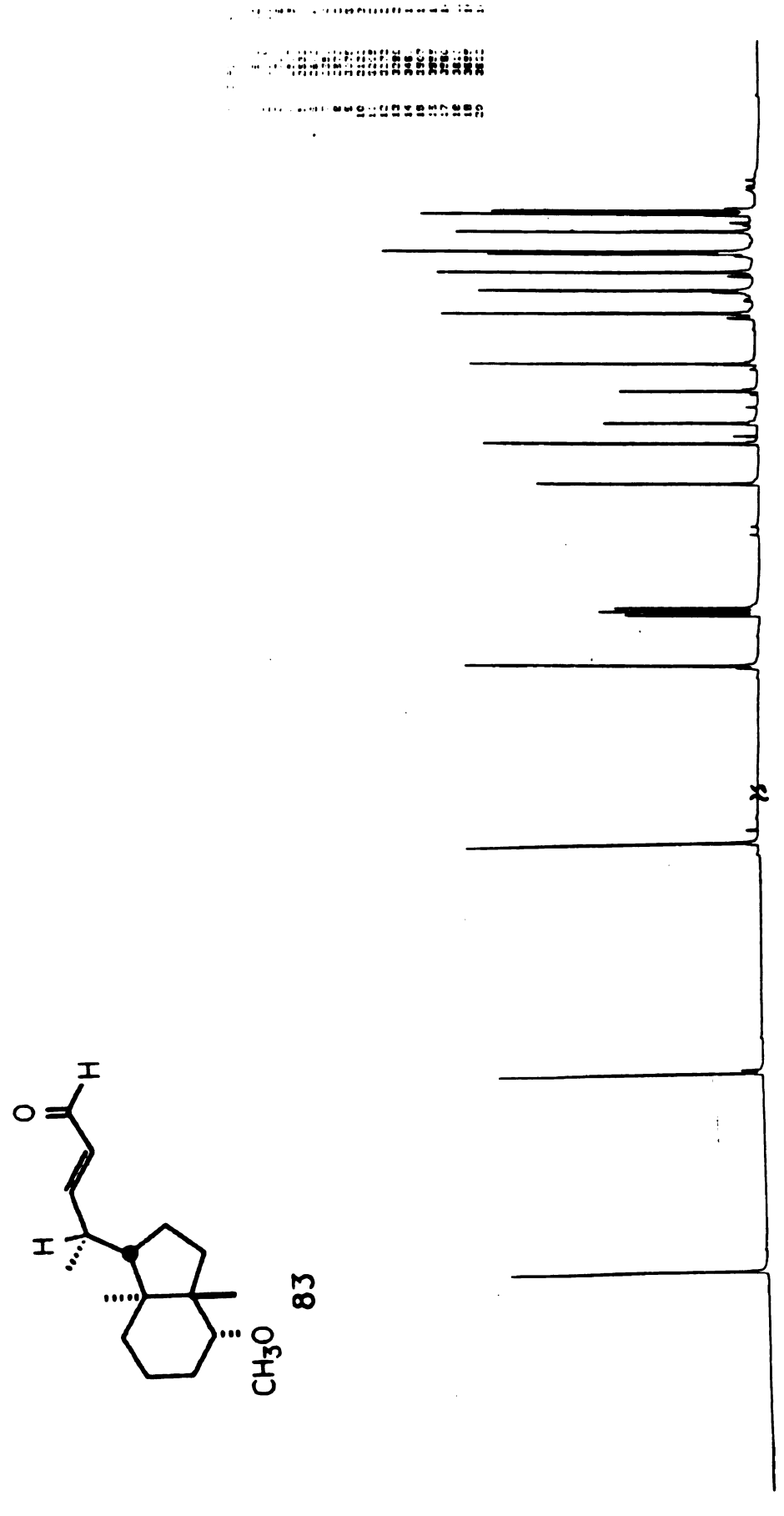



Figure 56 $^{13}C$ NMR Spectrum of Compound 83

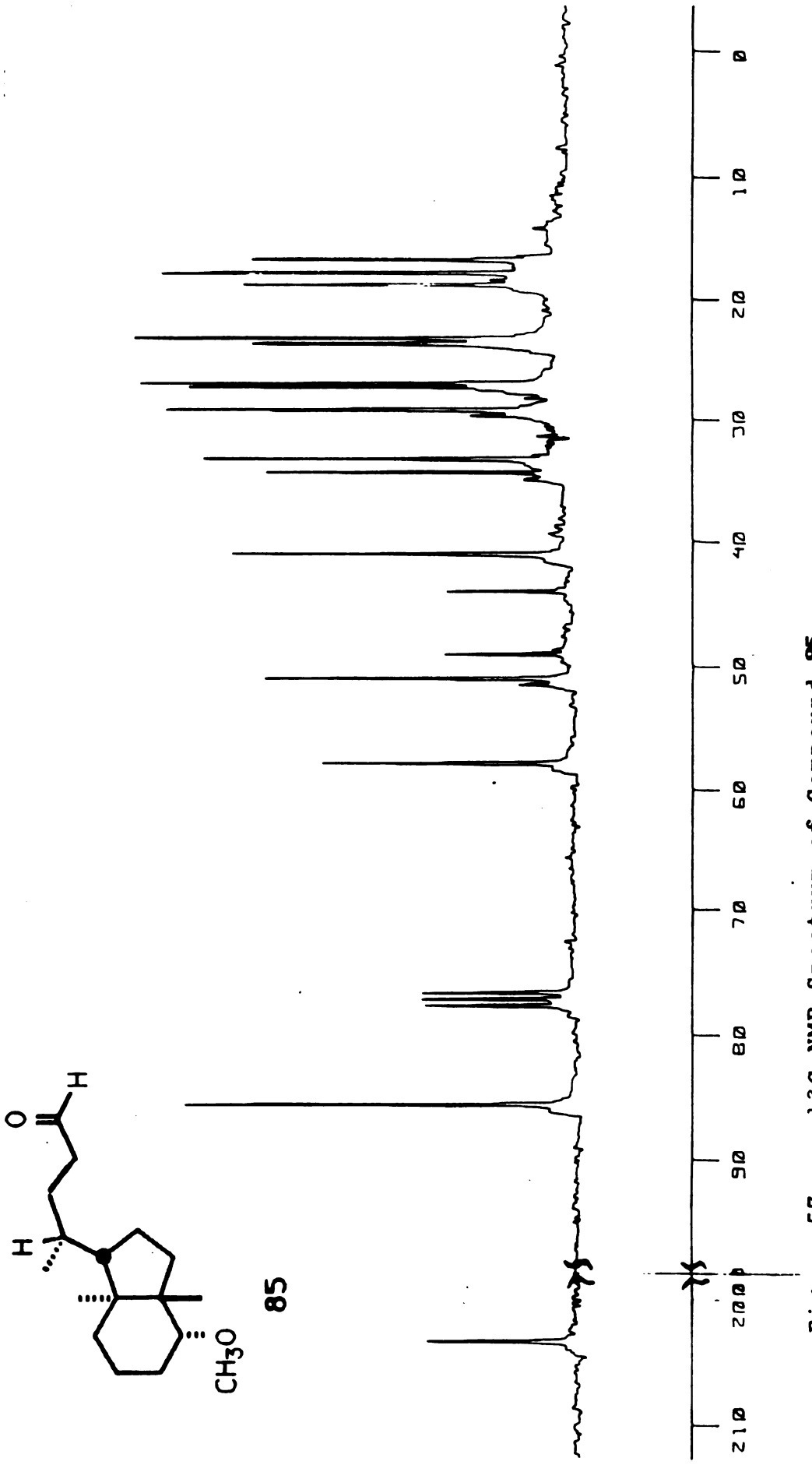



Figure 57 $^{13}C$ NMR Spectrum of Compound 85

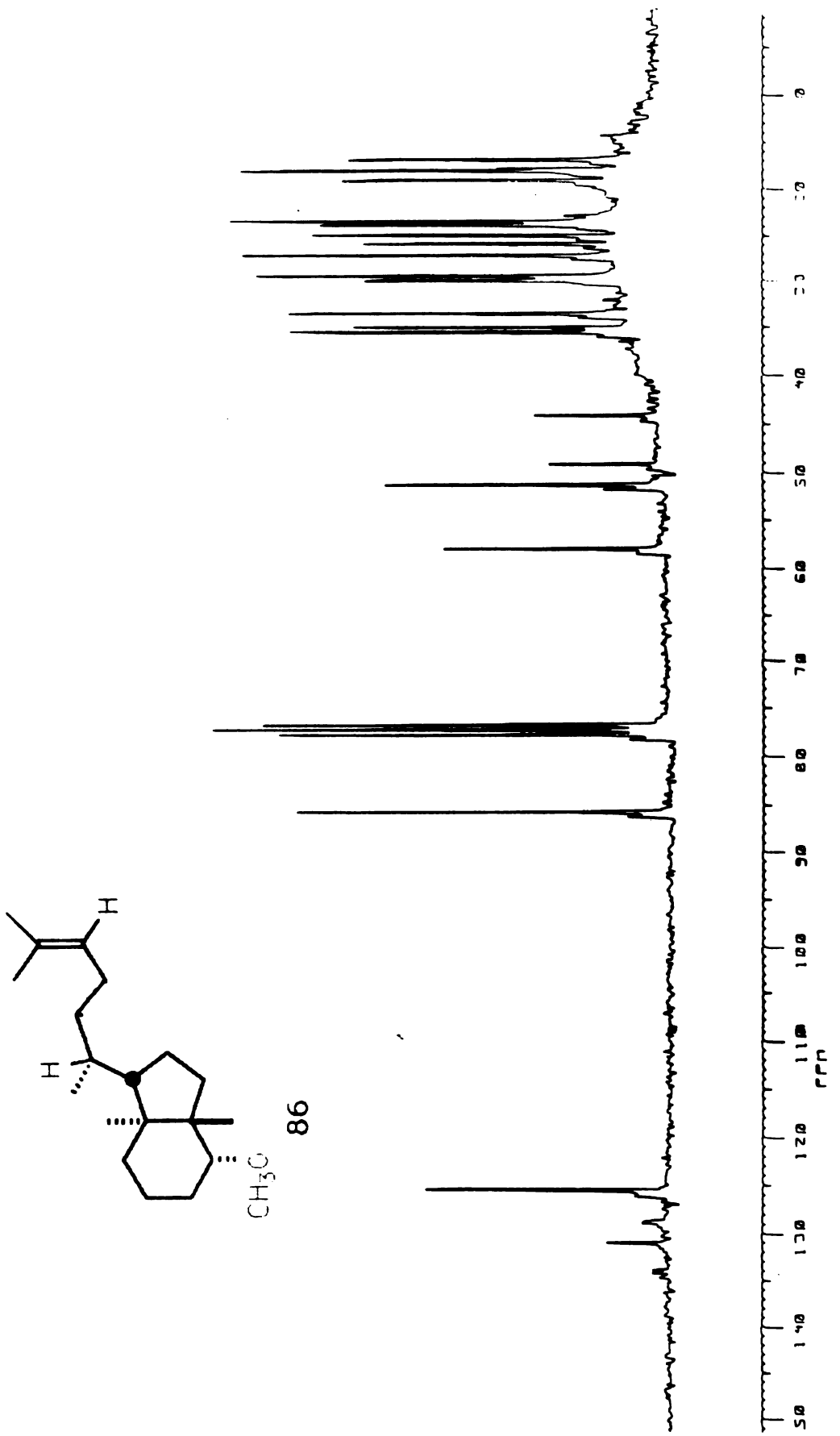



Figure 58 $^{13}C$ NMR Spectrum of Compound **86**

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