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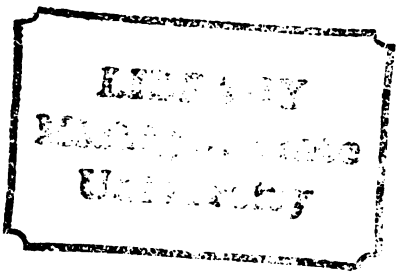

This is to certify that the

dissertation entitled

A MODEL FOR TETRACYCLIC TRITERPENE
SIDE CHAIN SYNTHESIS

presented by

Joseph Renato Gibson

has been accepted towards fulfillment
of the requirements for

Doctoral degree in Chemistry

William Reusch
Major professor

Date April 22, 1982

O-12771

A MODEL FOR TETRACYCLIC TRITERPENE SIDE CHAIN SYNTHESIS

By

Joseph Renato Gibson

A DISSERTATION

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1982

ABSTRACT

A MODEL FOR TETRACYCLIC TRITERPENE
SIDE CHAIN SYNTHESIS

By

Joseph R. Gibson

Although the hindered carbonyl function in trans-1,6-dimethyl-2-methoxybicyclo[4.3.0]nonan-7-one 3 resists nucleophilic addition and is prone to enolate formation, good yields of addition products from trimethylsilyl cyanide, methylenetriphenylphosphorane and crotyl magnesium bromide were obtained. Partial success in controlling the stereoselectivity of the latter reaction was achieved by lowering the temperature to -100°. Efforts to transform the methallyl adduct 4 to a C_8H_{17} terpenoid side chain failed because of a facile methyl shift in the course of dehydration of the tertiary alcohol. The nature of this rearrangement was demonstrated by conversion of the rearranged olefin 14 to the unsaturated ketone 17. All efforts to transform the trimethylsilyl cyanide adduct 18 failed to produce a useful product. Introduction of the terpenoid side chain

was eventually accomplished by conversion of 3 to the E-ethylidene derivative 20, from there to the 7β-acetyl intermediate 22, and finally to a mixture of side chain epimers 24 by a Wittig condensation followed by hydrogenation. The ratio of epimers in the mixture was found to be 2:1 by carbon-13 NMR and gas chromatography. Interesting stereochemical differences in reactions of 3 and its derivatives compared with the steroid analogs are noted.

For my parents, for their love and support even when they didn't really understand.

ACKNOWLEDGMENTS

The author wishes to express his deepest appreciation to Dr. William Reusch for his guidance and friendship. His suggestions were invaluable and he always seemed to be present when needed. He has contributed greatly to my professional development.

Thanks are extended to my colleagues for their friendship and humor; it made the going easier. Especially enjoyable were the lunch time round table discussions about life, chemistry, and whatever, that often extended into the afternoon.

Finally, the author would like to thank Michigan State University for financial support.

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INTRODUCTION

"Organic chemistry nowadays almost drives me mad. To me it appears like a primeval tropical forest full of the most remarkable things, a dreadful endless jungle into which one does not dare enter, for there seems no way out."

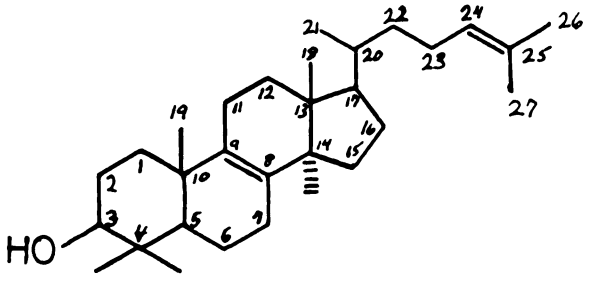
Friedrich Woehler
(1800-1882)

INTRODUCTION

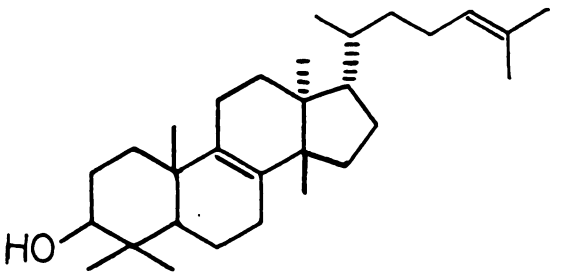
Tetracyclic triterpenes are primarily thirty carbon isoprenoid compounds found mainly in the plant kingdom, with a few (e.g. lanosterol) also occurring in animals (Figure 1). Tetracyclic triterpenes are sometimes called methylsteroids because of their strong structural resemblance to steroids. Like many of the steroids, some tetracyclic triterpenes possess a physiological activity. Cucurbitacins are present in many medicinal plants that are used as narcotics, purgatives, and emetics, and other cucurbitacins possess anti-tumor activity[1,2].

In nature, the tetracyclic triterpenes are formed by enzymatic cyclization of squalene 2,3-oxide followed by carbocation initiated rearrangements[3]. The product of the cyclization depends upon the conformation the enzyme imparts to the squalene chain. A chair-boat-chair-boat orientation leads to lanosterol, whereas a chair-chair-chair-boat conformer leads to euphol (1).

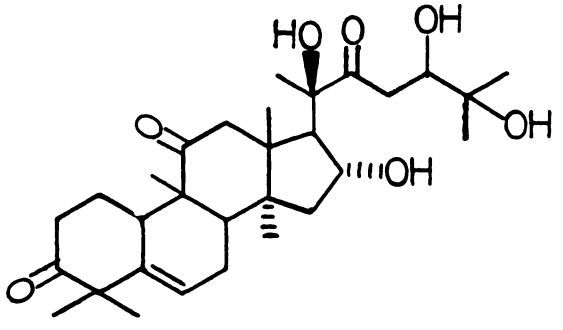
The main difference between steroids and lanostane tetracyclic triterpenes is the presence of three extra methyl groups, two at C-4 and one at C-14, in the latter. Despite this great similarity, very little work has been done on the total synthesis of tetracyclic triterpenes,



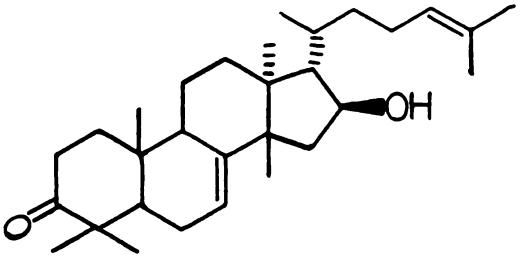
Lanosterol



Euphol



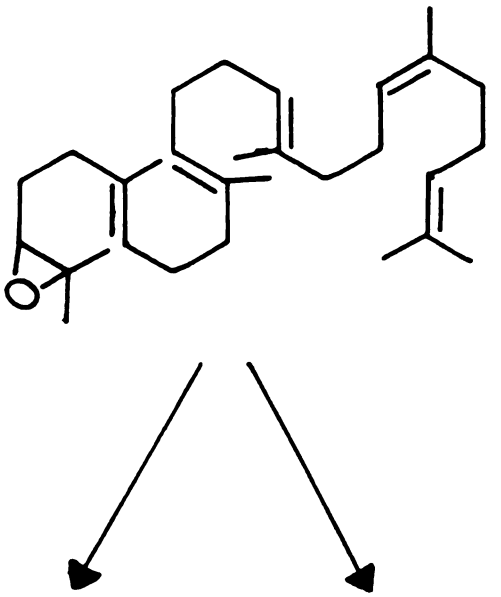
Cucurbitacin G



Kulinone

Figure 1. Representative triterpenes.

(1)

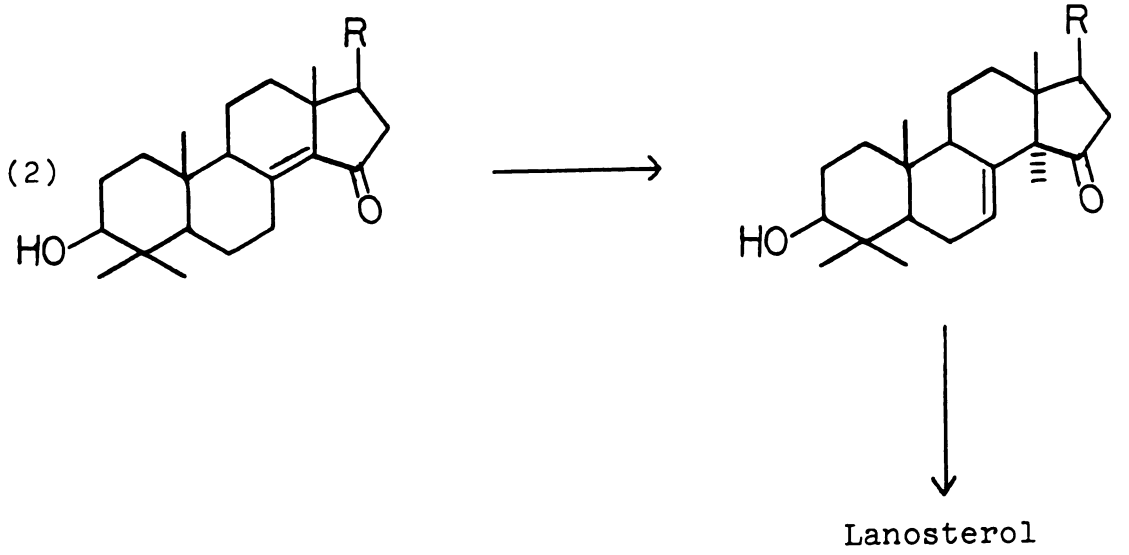


Lanosterol Euphol

especially when compared to the great mass of work on steroid total synthesis. To date, the successful total synthesis of a tetracyclic triterpene has been accomplished only twice. One approach, developed by R. B. Woodward's group at Harvard, prepared lanosterol by adding methyl groups to cholesterol; and the other, developed by van Tamelen, used a biogenetic type polyene cyclization.

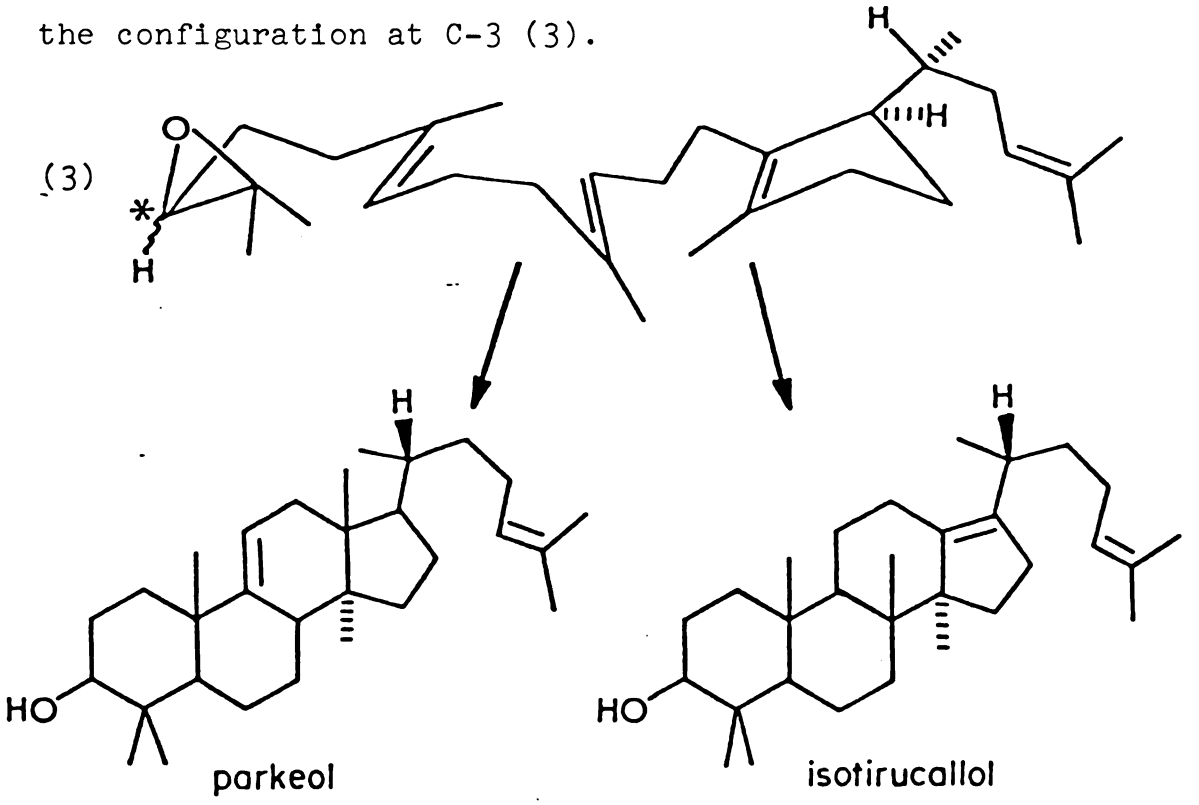
In the Woodward approach[4], an important step was the alkylation of a cholesterol derivative to introduce the 14 α-methyl group (2). This overall reaction scheme achieved lanosterol in approximately twenty steps and in a low overall yield.

(2)

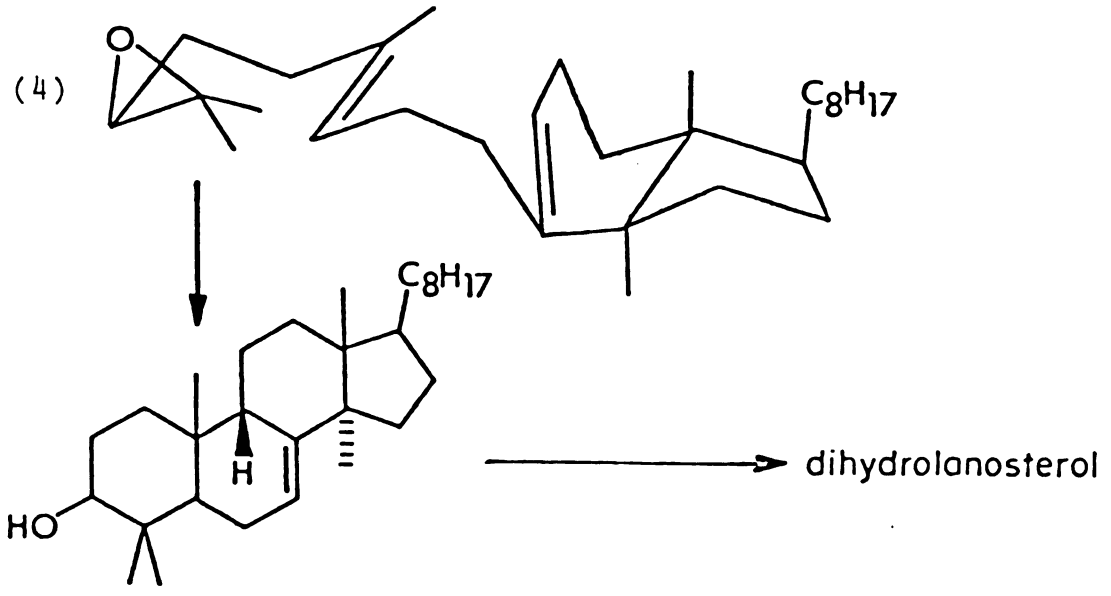


Lewis acid induced cyclization of a squalene like epoxide derivative was studied by van Tamelen et al.[5], and yielded either parkeol or isotirucallol depending on the configuration at C-3 (3).

(3)



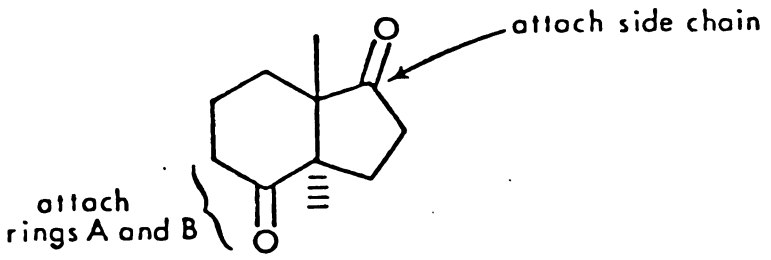
A similar cyclization using a polyene epoxide with a preformed C and D rings gave a dihydrolanosterol precursor[6] (4).



As can be seen from the above examples, only the lanostane skeleton has been successfully synthesized. There have been no reported syntheses of the euphane or cucurbitacin skeletons. It is unlikely that a polyene cyclization approach would be successful in generating the euphane skeleton because of its facile rearrangement to the iso system[2].

Several years ago the synthesis of the bicyclic diketone 1 was reported from this laboratory[7]. Inspection reveals that it should be ideally suited for elaboration to tetracyclic triterpenes. It incorporates the C and D rings, the C-13 and C-14 methyl groups in the required trans configuration, and functionality in both rings

that should allow construction of the desired structures.



1

Fortunately, the carbonyl group in the six membered ring is more reactive than the other[8]. This is important because it allows selective transformations to be carried out.

An important advantage of diketone 1 is that it can be used as a synthon for the lanostanes, euphanes, or cucurbitacins, depending on the position and configuration of the angular methyl group introduced with the A and B rings. Introduction of a 9 β-methyl group leads to the cucurbitacin skeleton, a C-10 α-methyl group leads to the euphanes, and a C-10 β-methyl group leads to the lanostanes.

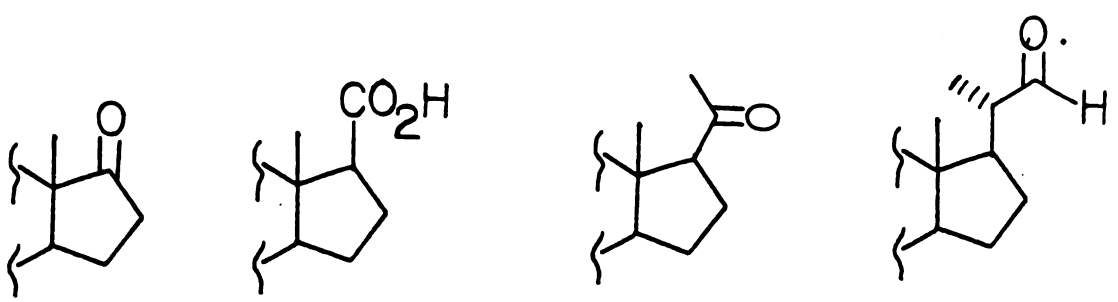
Many of the side chains found at C-17 in the tetracyclic triterpenes are very similar; the cucurbitacins are an exception. Therefore, a versatile general side chain synthesis would be applicable to most of the tetracyclic triterpenes. Before proceeding to this end, it was necessary to evaluate previous methods or approaches

that have been used in side chain synthesis.

In the past, a primary interest in steroid side chains focused on the synthesis of the two carbon side chains of the corticosteroids and pregnanes (Figure 2). This was due largely to their biological activity and also to a scarcity of knowledge about the more elaborate side chains present in other systems. This void was quickly filled by the discovery and characterization of cholesterol metabolites, marine sterols, insect hormones, brain sterols and many others (Figure 2). As a result, steroid side chain chemistry entered a new age, so to speak, in which attention was focused on the newly discovered side chains with eight or more carbons and away from the two carbon ones that had been in the limelight.

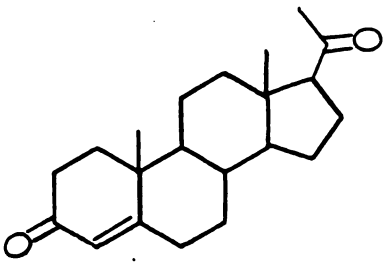
A large proportion of side chain syntheses use one of the following substrates due to their availability from naturally occurring compounds (5). A and B are products

(5)

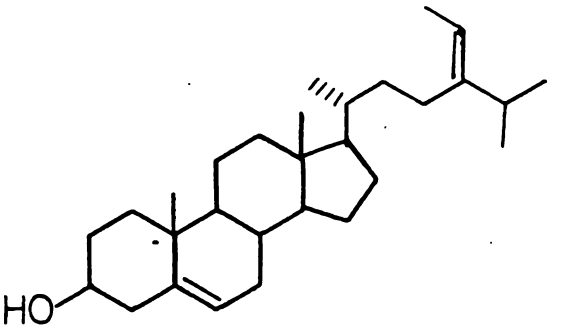


A B C D

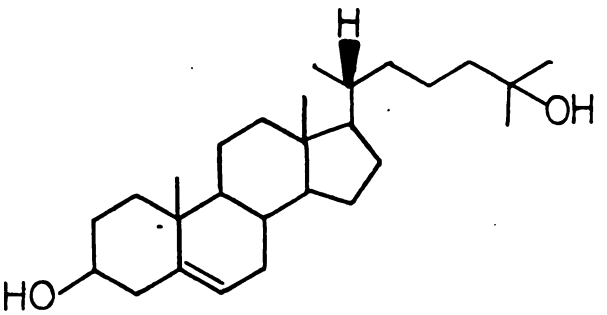
of a chromic acid oxidation of cholesterol[9], C is derived from plant sapogenins such as diosgenin[10], and D is the product of an ozonolysis of stigmasterol or ergosterol[11].



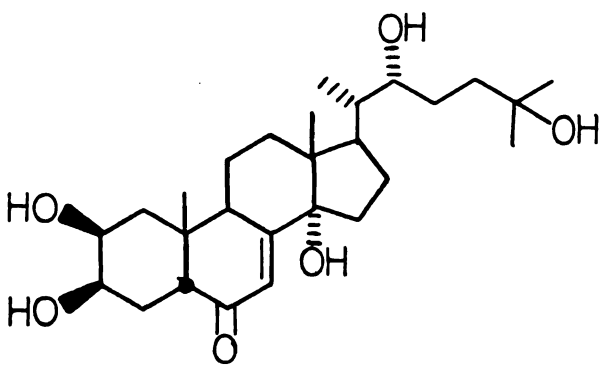
Progesterone



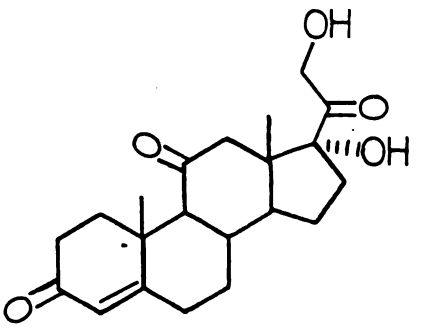
Fucsterol



25-Hydroxycholesterol



Ecoysone



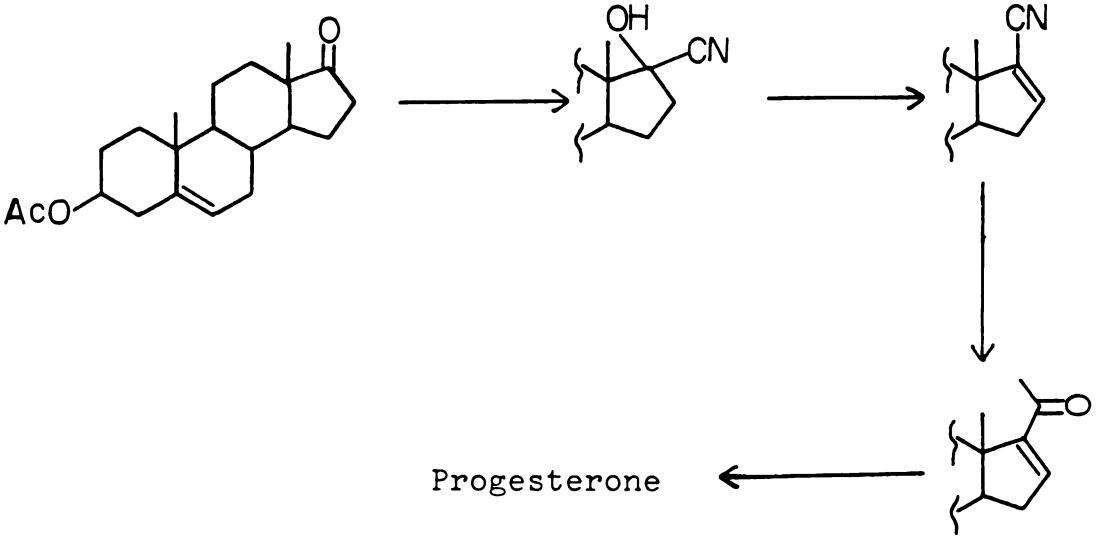
Cortisone

Figure 2. Representative side chains.

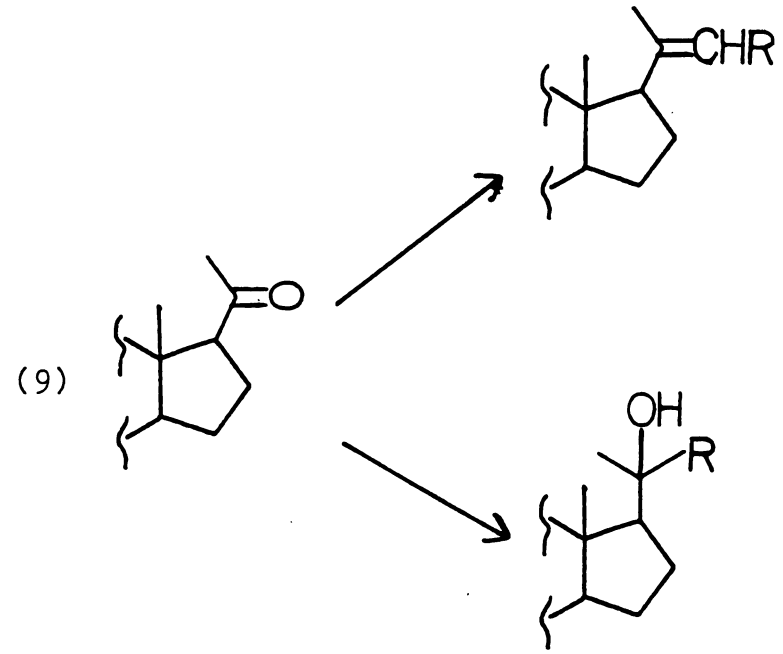
Starting in the late 1930's, A and B were used for the synthesis of the two carbon pregnane type side chain[12]. The common reactions at the C-17 carbonyl include addition of hydrogen cyanide[12], acetylenes[13], and Wittig reagents[14] (6), while the C-20 carboxylic acid is transformed through its acid chloride[12] or by direct addition of alkyl lithiums[15] (7).

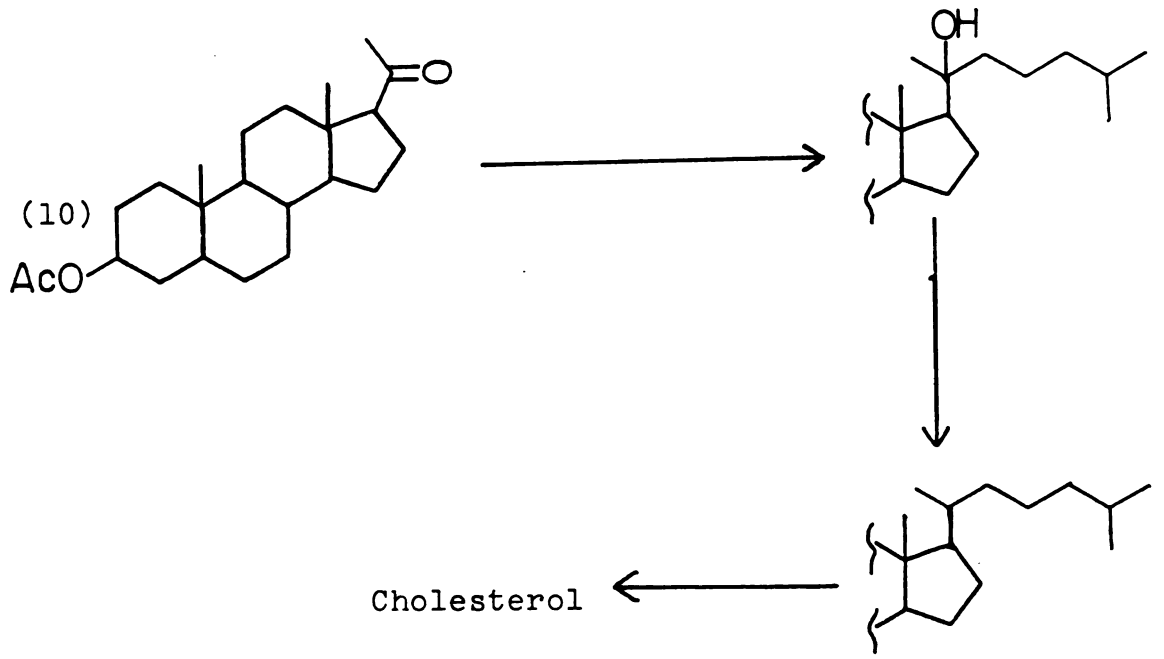
An example is the synthesis of progesterone from androstenolone by Butenandt[16] (8).

(8)



The main approaches that have been used to elaborate the pregnane side chain (substrate C) are the addition of Grignard or lithium[17,18] reagents and the addition of


(9)
O
CHR
OH
R


(10)
AcO
O
OH
Cholesterol

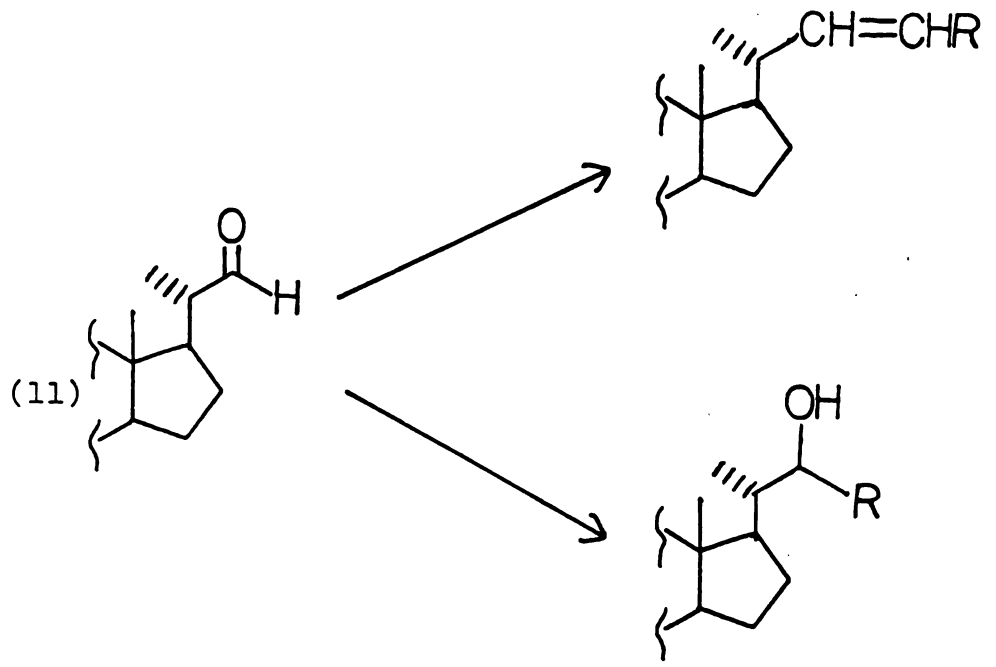
Wittig reagents[17,19] (9). Woodward's synthesis of cholesterol[20] made use of the addition of a Grignard reagent to a C-20 ketone (10).

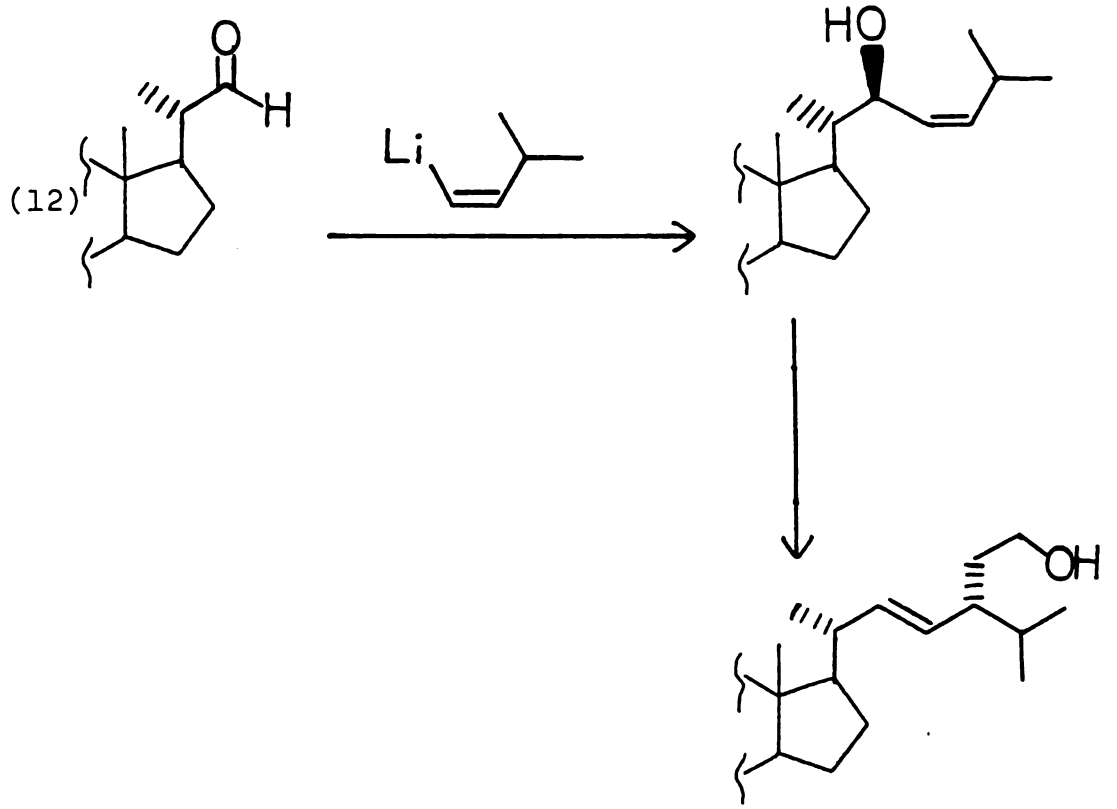
The C-22 aldehyde (substrate D) may be transformed in much the same way; namely, the addition of Wittig reagents[17,21] and Grignard or lithium reagents[17,22] (11).

The use of this approach can be seen in Djerassi's recent synthesis of the side chain of the plant sex hormone oogoniol[23] (12).

A crucial aspect of side chain synthesis, be it steroid or tetracyclic triterpene, is the control of stereochemistry, especially at C-17 and C-20. Unfortunately, all of the methods listed above fail to give good stereochemical control, particularly at C-20. The 1,2-addition to ketones and the reduction of olefins produces an epimeric mixture at C-20 which may be difficult to separate to obtain pure compounds. Even though substrate D has the configuration at C-17 and C-20 fixed, care must be taken to avoid epimerization at C-20, due to the neighboring aldehyde[17].

Recently, several groups have developed stereospecific syntheses of sterol side chains. The ene reaction[24], the oxy-Cope[25] and Claisen[26] rearrangements, nucleophilic attack at π-allylpalladium complexes[27], 1,4 addition of alkyl cyanocuprates[28], and nucleophilic displacement[29] have been used as the key stereodirecting processes. The key steps in each approach are shown in order in Figure 3.


CH=CHR
O
H
(11)
OH
R


O
H
(12)
Li
HO
OH

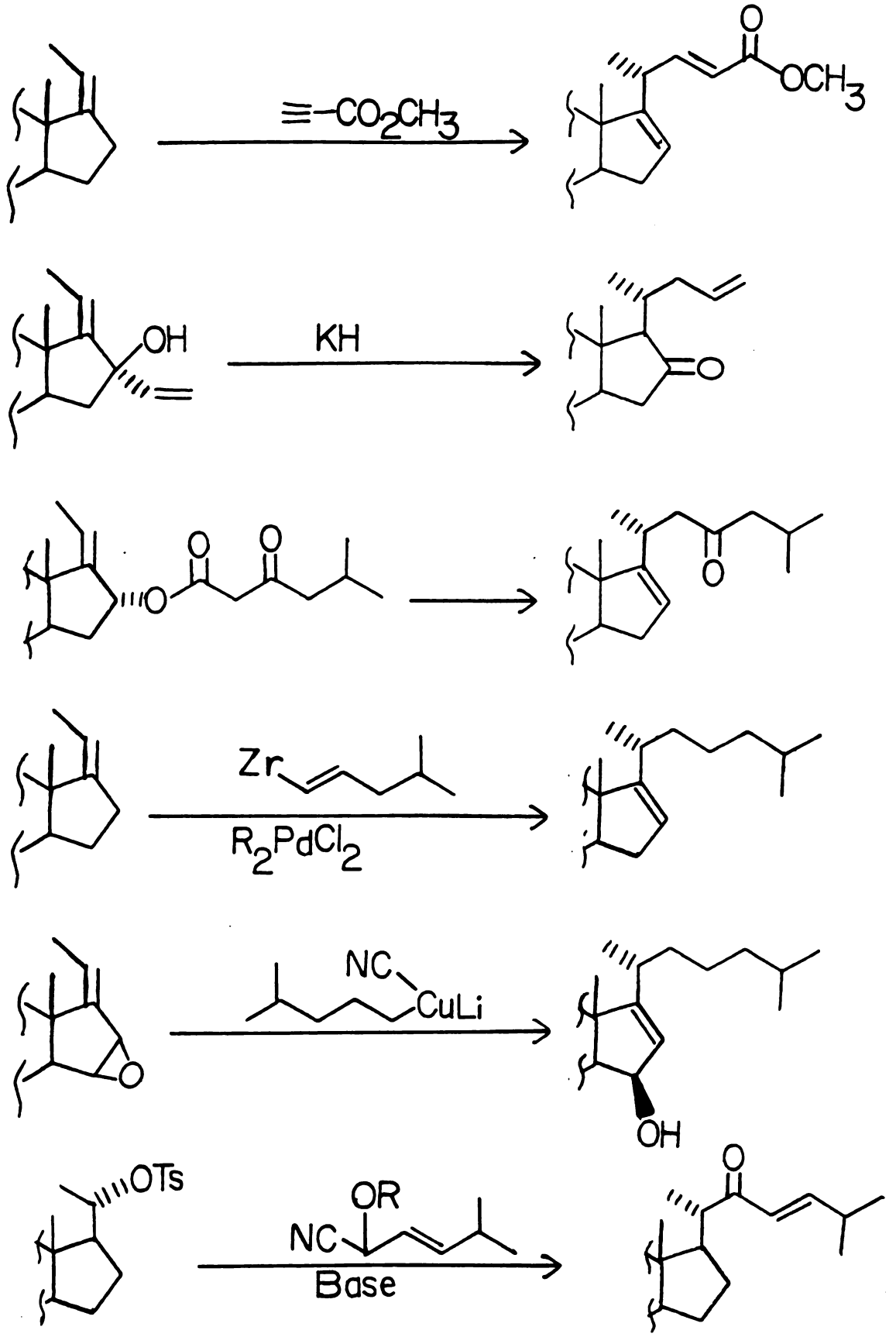


Figure 3. Stereospecific side chain syntheses.

Close scrutiny of the literature reveals little information concerning the synthesis of tetracyclic triterpene side chains that is comparable in any way to the body of work outlined above. In particular, there is reason to believe that the presence of a 14 α-methyl group will perturb the stereospecificity of many of these transformations to a significant degree. The work described in this dissertation was undertaken to explore the problem of stereospecific side chain synthesis on a model of the triterpene C, D ring moiety.

RESULTS AND DISCUSSION

"Without fantasy there is no science.
Without fact there is no art."

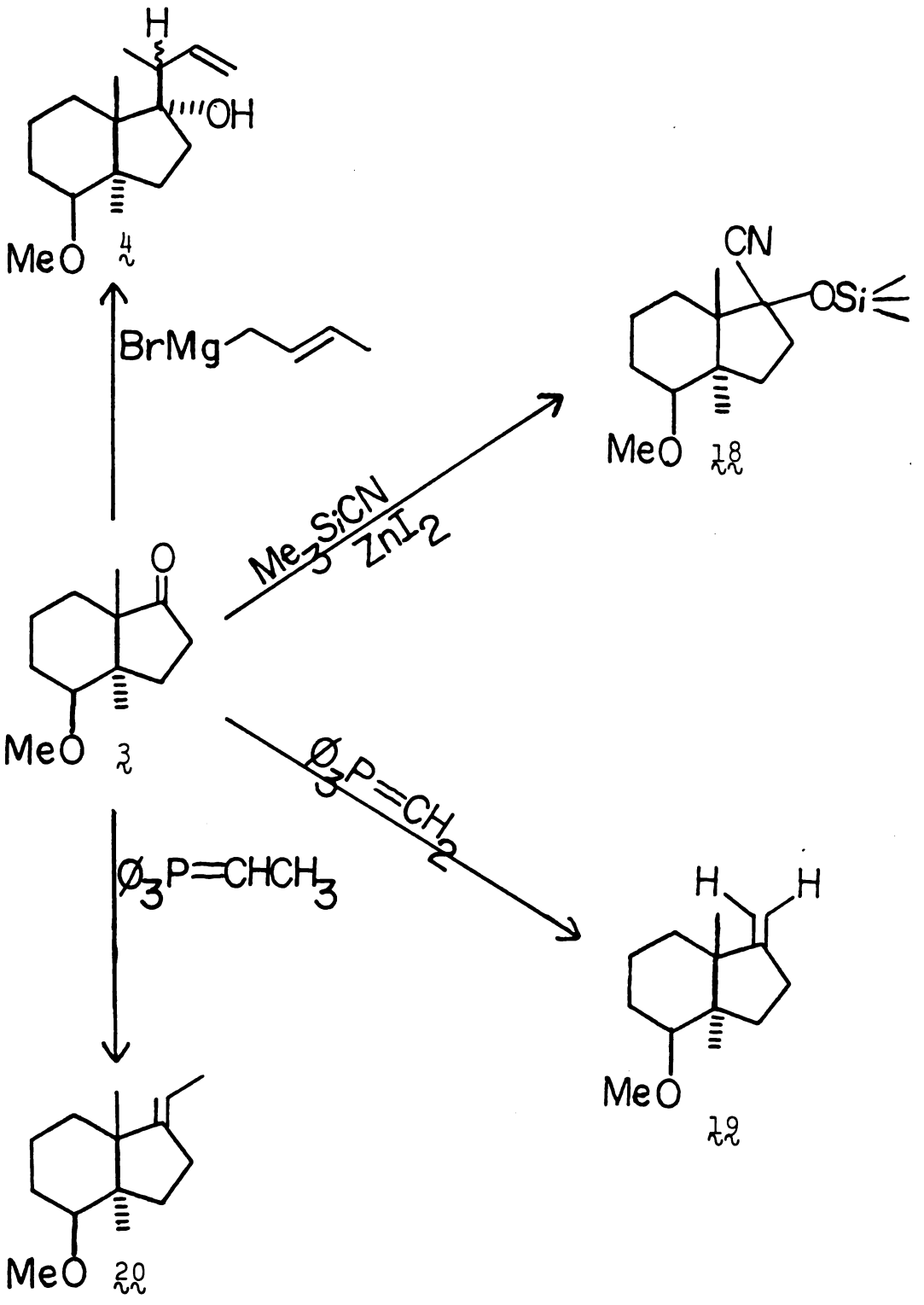
Nabokov

RESULTS AND DISCUSSION

In our studies on the synthesis of tetracyclic triterpene side chains, the methoxy ketone 3 has been used as a model compound. Unfortunately, the 5-membered carbonyl is relatively unreactive towards reagents that normally add to ketones. An initial study by J. Martin and J. Tou[8] showed that stabilized ylides, organometallic reagents, and enolate salts failed to add to 3. It was also determined that part of the problem with these nucleophilic addition reactions was due to a facile enolization of the ketone by strong bases. Since then, several reagents have been found to give adducts with ketone 3. They are shown in Scheme 1, and each will be discussed in the following pages.

Reaction of 3 with crotyl magnesium bromide in ether produces a high yield of 4. The success of this reaction is believed to be the result of a cyclic mechanism with the magnesium coordinating with the ketone oxygen[30]. There is the possibility of forming four stereoisomeric products since two new chiral centers are being introduced into the molecule.

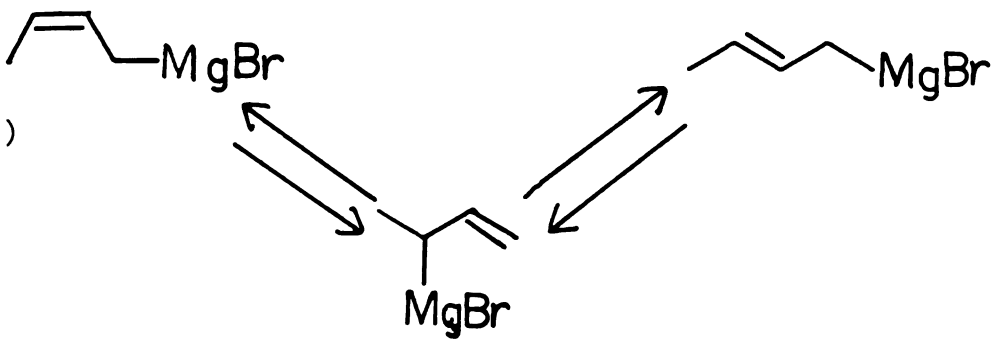
The equilibrium between cis and trans crotyl magnesium bromide is very rapid even at low temperatures[33] (13).



Scheme 1. Additions to 3.

Therefore, both the cis and trans crotyl Grignard reagents will form the six membered cyclic transition state which

(13)



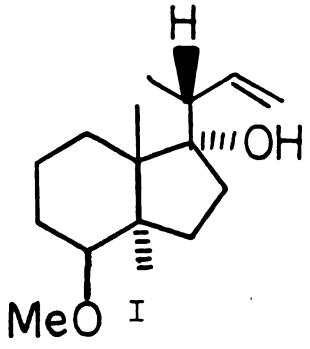
can be either in the boat or chair form. Also, the addition can take place from the α or β face of the molecule. Figure 4 shows the four possible stereoisomers and Table 1 shows the different transition states that can lead to their formation.

Table 1. Transition States That Lead to $\underset{\sim}{4}$.

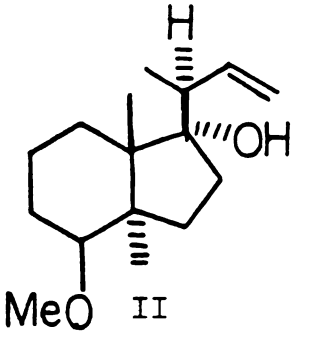
	β Attack	α Attack
Cis[a]	[b]Chair → I	Chair → IV
	Boat → II	Boat → III
Trans	Chair → II	Chair → III
	Boat → I	Boat → IV

[a]Refers to geometrical isomer of Grignard reagent.

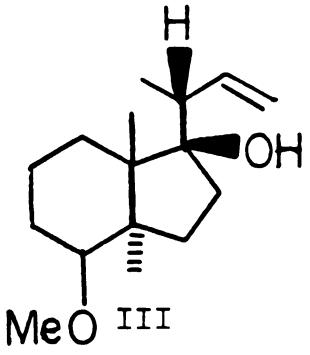
[b]Refers to boat or chair transition state.



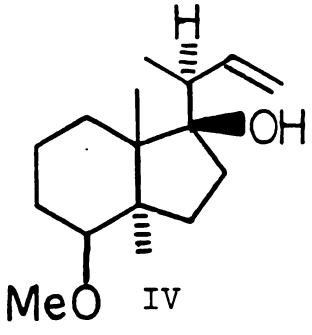
I



II



III



IV

Figure 4. Possible stereoisomers of $\underset{\sim}{4}$.

Examination of the proton and carbon-13 NMR spectra revealed that 4 was a mixture of only two isomers with a ratio of approximately 1:1. Hydroboration followed by dehydration yielded an olefinic product which was shown to still be a mixture. Therefore, 4 is epimeric at C-20 and the mixture must consist of either I and II or III and IV. On the basis of molecular models and the chemical shifts of the angular methyl groups, 4 appeared to consist of I and II. Because of the potential synthetic usefulness of this adduct, a study was undertaken to increase the stereoselectivity of the addition.

In the reaction of allylic organometallic reagents with simple aldehydes it is known that the stereoselectivity of the reaction does not vary much with the temperature or the solvent; but it increases as the steric hindrance of the aldehyde increases, and with the electronegativity of the metal: Mg < Zn < Cd[31]. Unfortunately, both dicrotylzinc and dicrotylcadmium failed to react with 3. This was also the case with Hiyama's[32] crotyl chromium reagent, but crotylaluminum sesquibromide did react to give adduct 4 or 13, depending on the conditions of the workup. When 4 was the product, it was formed in high yield as a 1:1 mixture of isomers; identical to the mixture obtained from crotylmagnesium bromide.

Partial success in improving the stereospecificity of

the reaction was achieved by lowering the temperature of the reaction. A value of about 2:1 (determined by proton NMR) in the isomer ratio was obtained at the lowest temperatures (Table 2). Since the equilibrium between the

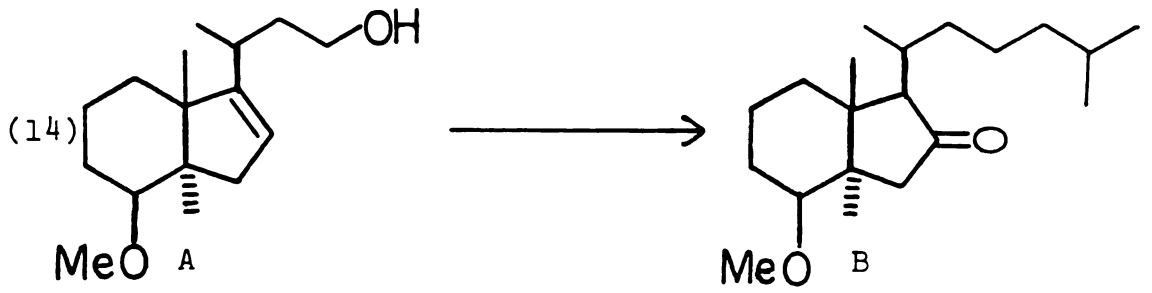
Table 2. Low Temperature Experiments.

Conditions	Ratio
Ether, 23°C	1:1
Ether, 0°C	1:1
Benzene, 23°C	1:1
Ether, -78°C	2:1
Ether, Toluene, -110°C	2:1

cis and trans crotyl Grignard reagents is very rapid[33], the change in stereoselectivity is presumed to reflect slight differences in the energies of the cyclic transition states.

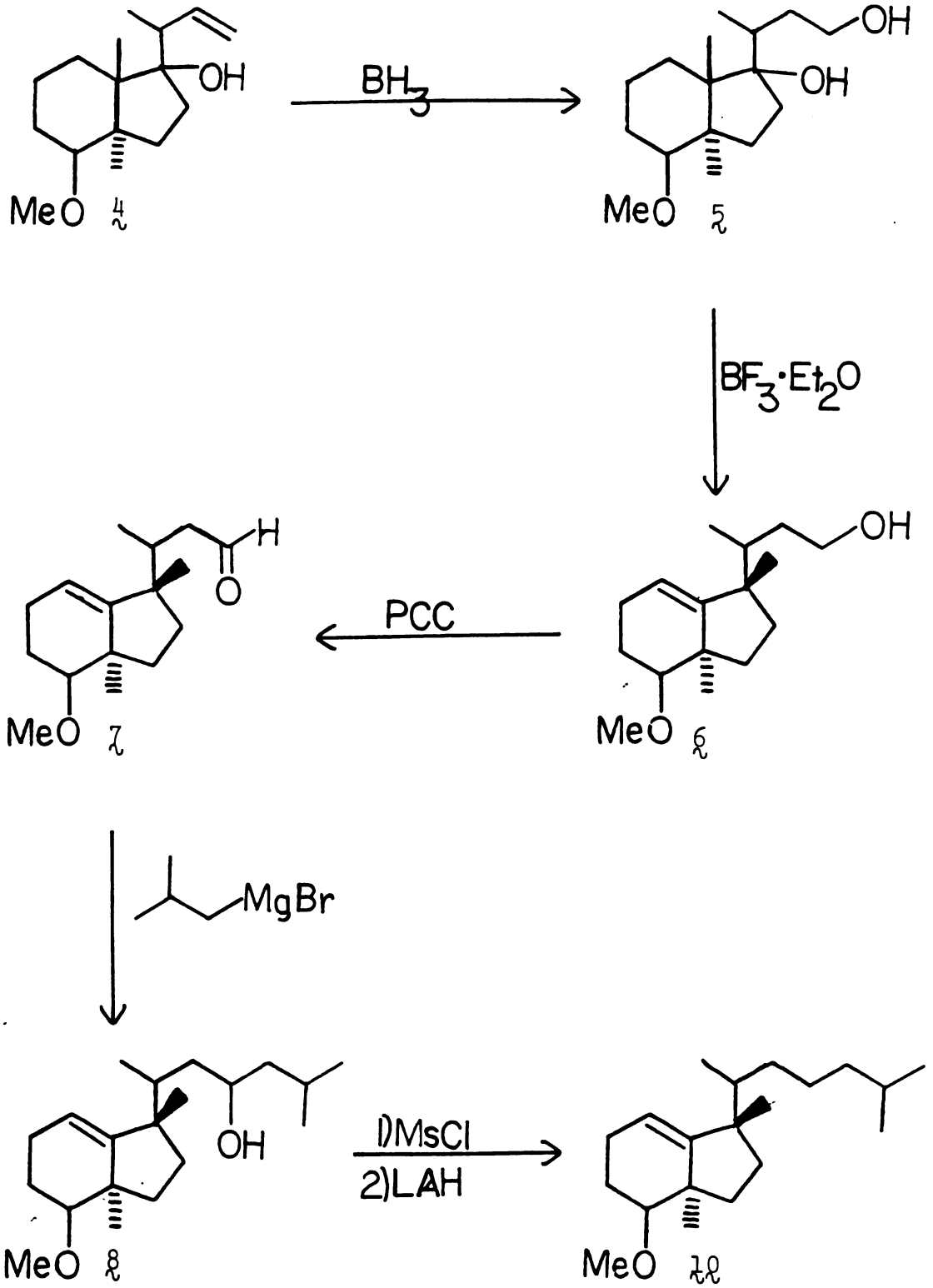
Hydroboration of $\underset{\sim}{4}$ yielded diol $\underset{\sim}{5}$ as a mixture of isomers which could be cleanly separated by recrystallization from ether. The crystalline diols were obtained in a 3:1 ratio with an overall yield of 75%. This indicated that the actual isomer ratio is a little better than that

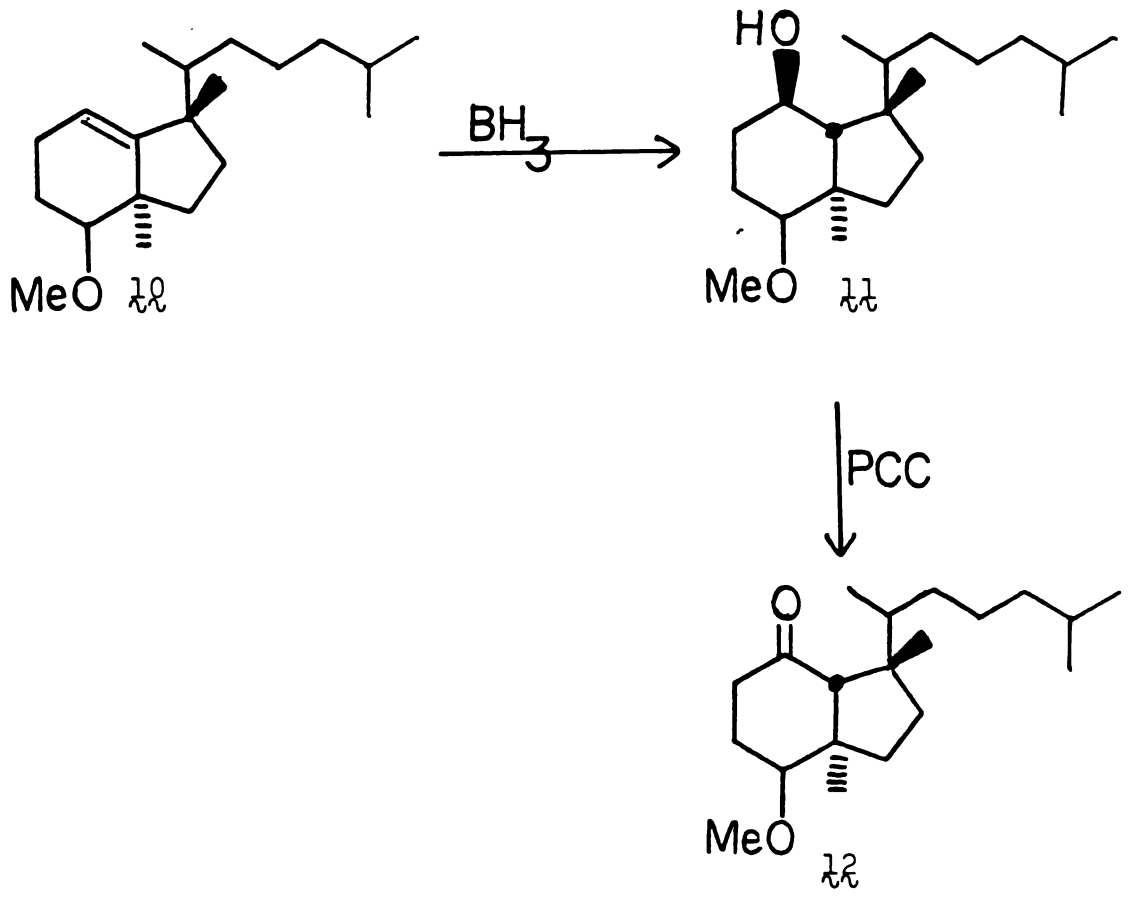
determined by proton NMR. Unfortunately, mild Lewis acid-catalyzed dehydration[34] of either epimer of 5 failed to give the desired olefin A (14). Instead, the rearranged



olefin 6 (Scheme 2) was obtained. This rearrangement was not discovered until ketone 12 was synthesized from 6, and its IR spectrum was examined. Carbonyl adsorption occurred at 1700 cm^{-1} and not at 1735-1750 cm^{-1}, as expected for a carbonyl group in a 5-membered ring, such as that in the desired compound B.

Ketone 12 was synthesized as shown in Scheme 2. Oxidation of alcohol 6 by pyridium chlorochromate[35] yielded the unstable aldehyde 7, which was immediately treated with isobutylmagnesium bromide to give the alcohol 8 as a mixture of isomers. The hydroxyl group in 8 was removed by lithium aluminum hydride reduction of the corresponding mesylate 9 to form the olefin 10. The hindered nature of the double bond in 10 was revealed by its inertness to hydrogenation under several different sets of conditions. Alcohol 11 was generated by hydroboration of olefin 10 in

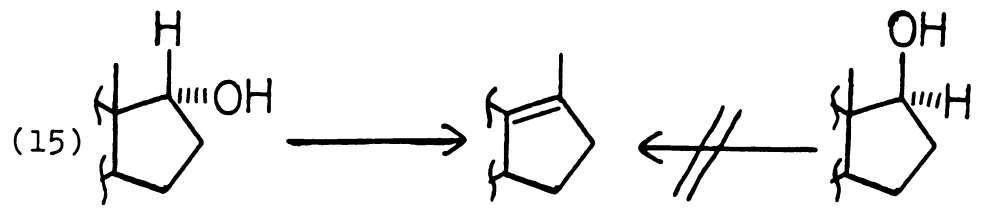

OH
BH3
OH
OH
MeO
4
MeO
5
BF3·Et2O
OH
H
O
PCC
MeO
7
MeO
6
MgBr
OH
1)MsCl
2)LAH
MeO
8
MeO
10



Scheme 2. Synthesis of ketone 12.

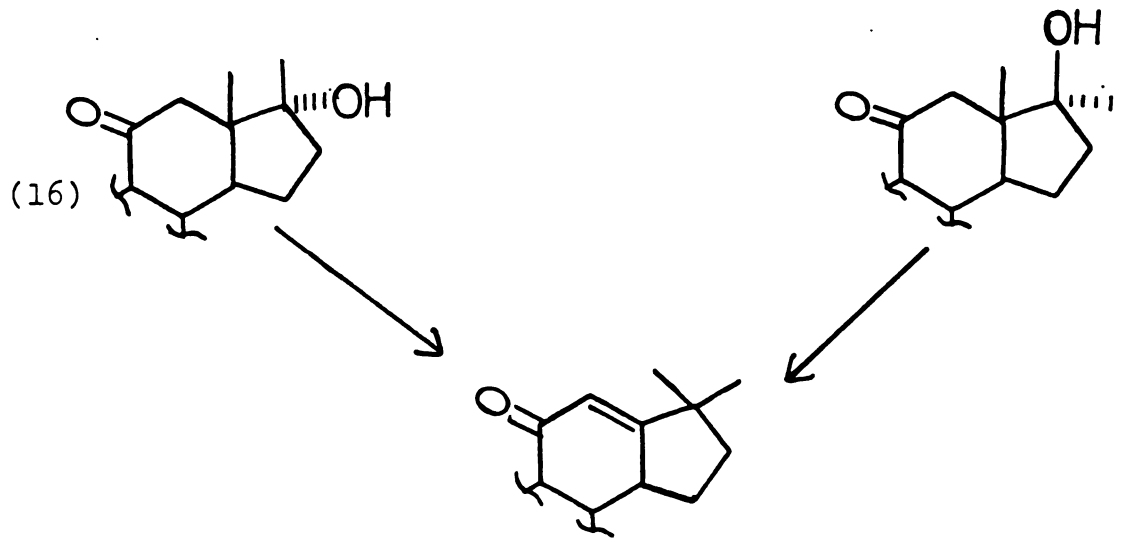
ether solution using diborane generated *in situ* from boron trifluoride etherate and lithium aluminum hydride[36]. Oxidation with pyridium chlorochromate[35] produced ketone 12, the IR spectrum of which provided conclusive evidence that a rearrangement had occurred.

There is precedent in the steroid field for rearrangements of this kind[37,38]. Steroids bearing a secondary C-17 hydroxyl group were found to give a 1,2-methyl shift only when the methyl and hydroxyl groups have a trans-diaxial orientation to each other (15).



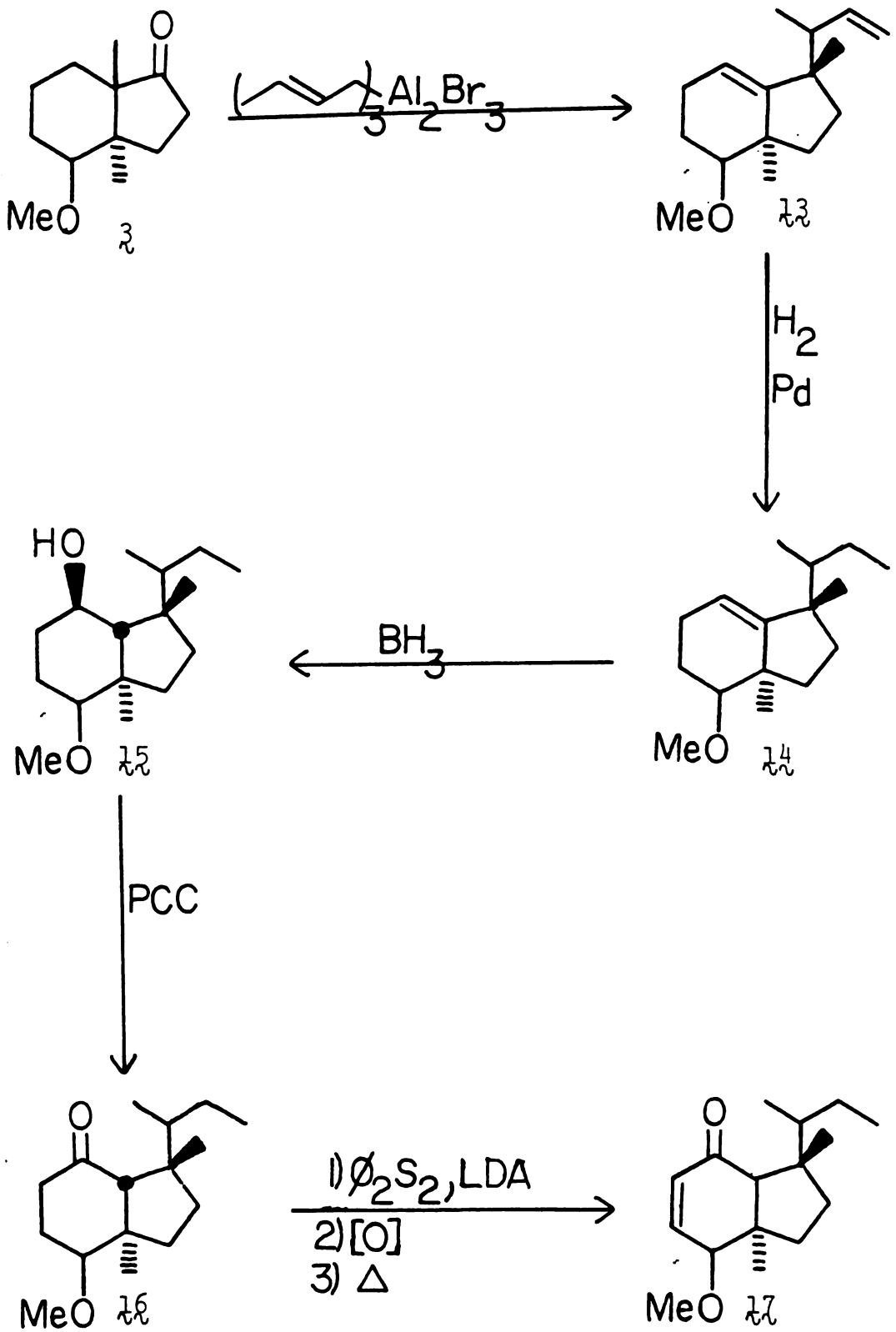
However, if the C-17 carbinol is tertiary the orientation of the methyl group to the hydroxyl group is not important (16). Thus, the geometrical selectivity appears to be counter-balanced by the greater stability of the tertiary carbocation.

As mentioned previously, reaction of 3 with crotylaluminum sesquibromide yielded either 4 or 13, depending upon the conditions used in the workup. Compound 13 was assumed to be formed via 4 by a dehydration-rearrangement induced by aluminum bromide. This was confirmed



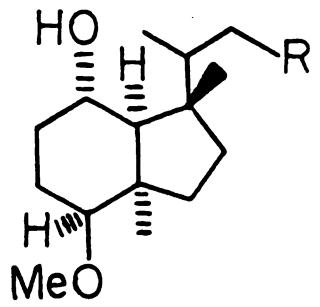
by treating a known sample of 4 with aluminum bromide in ether. Compound 13 was obtained quantitatively after stirring at room temperature for only two minutes. Conversion of the olefin to a carbonyl group was effected in order to further corroborate the rearrangement (Scheme 3).

Hydrogenation of 13 saturated only the side chain double bond, as the double bond in the ring is hindered and does not reduce. Hydroboration[36] of 14 then yielded alcohol 15 which was oxidized by pyridium chlorochromate[35] to ketone 16. Once again the IR spectrum of 16 showed a carbonyl absorbance at 1700 cm^{-1} revealing that the ketone was indeed in the six membered ring. Further evidence for the location of the carbonyl group in 16 was obtained by introduction of a double bond[39] to form the unsaturated ketone 17. If the rearrangement had not occurred, the ketone would be in the five membered ring and it would be impossible to introduce a conjugated double bond.

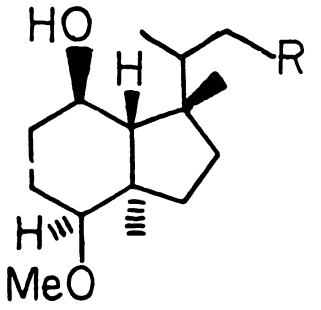


Scheme 3. Synthesis of unsaturated ketone 17.

The trans ring junction was assigned to alcohols 11 and 15 for several reasons. Examination of molecular models revealed that the α face of the double bond is severly hindered by the α side chain at C-17 and the α methyl group at C-14. As a result, cis addition of diborane should occur from the β face, giving the trans ring junction. Additional evidence for the trans ring junction can be obtained from the proton NMR of compounds 11 and 15. Examination of Dreiding models of the compounds with the cis (A) and trans (B) ring junction revealed that the coupling constants for the carbinol proton would be of no use



A



B

in predicting the correct structure, as they both have two diaxial and one axial equatorial coupling and would give the same splitting pattern. The diagnostically useful proton is the one attached to the carbon bearing the methoxy group. In A that proton should be axial, and the model suggests that a doublet of doublets with coupling constants of 12-13 Hz and 3-4 Hz should be observed. In the case

having a trans ring junction (B), the corresponding hydrogen is equatorial and a triplet with J = 3-5 Hz is predicted[40]. In fact, the proton NMR of 11 displays a signal for that hydrogen which is a triplet with J = 4.3 Hz, lending support to the trans ring junction.

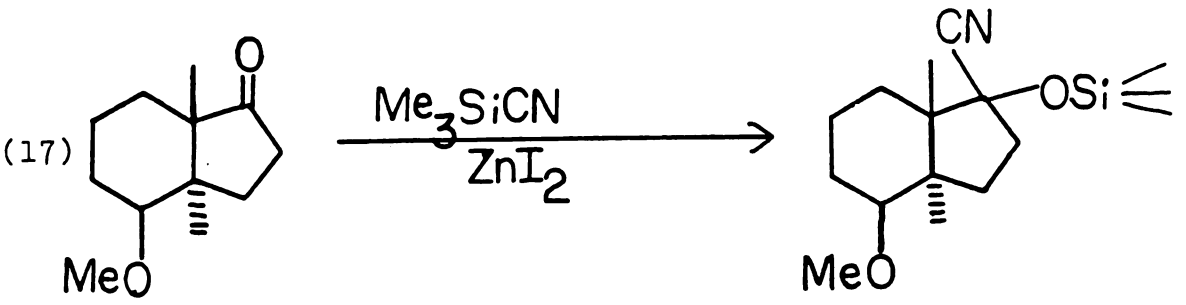
In the ketones, 12 and 16, the situation is a little more complex due to the possibility of epimerization at the ring junction. However, the proton NMR evidence still tends to indicate that the ring junction is trans.

Carbon-13 NMR also proved useful in assigning the configuration of the ring junction. For cyclohexane systems it is known that a carbon bearing a methoxy group undergoes a 4-6 ppm downfield shift when the methoxy group goes from axial to equatorial[41]. In compound 3, the methoxy group is known to be axial[8] and it has a chemical shift of 83.6 ppm. The carbon-13 NMR spectra of compounds 6, 8, 10, 11, 12, 14, 15 and 16 revealed that the chemical shift of the methoxy-bearing carbon was always in the range 82-84 ppm. Clearly, a downfield shift has not occurred and the conclusion is drawn that the ring junction is trans.

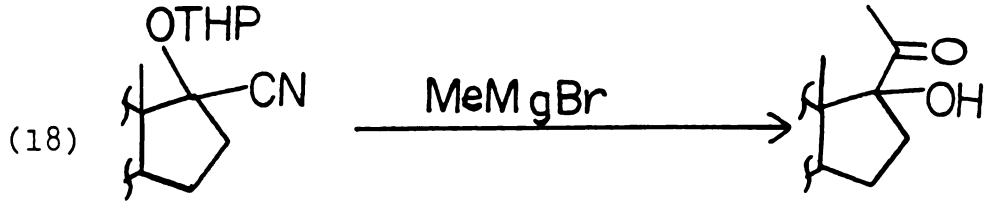
While the preceding NMR evidence is good, it is not compelling due to the possibility of non-chair conformations. These could arise from distortion introduced into the system by interaction of the C-14 methyl group with the α side chain at C-17.

Treatment of ketone 3 with trimethylsilyl cyanide[42]

and zinc iodide yielded the silyl cyanohydrin 18 in excellent yield (17) as a 1:1 mixture of isomers at C-17. It



is known that methylmagnesium bromide adds to protected cyanohydrins to form α hydroxy ketones in good yield (18).



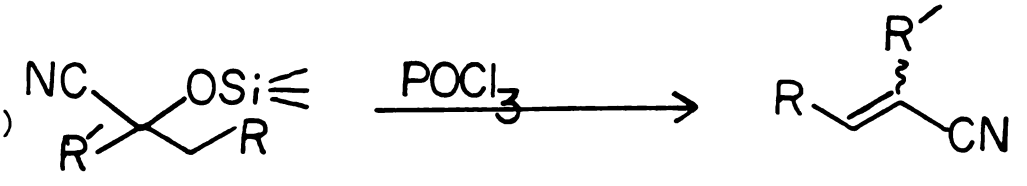
However, all attempts to apply this reaction to 18, using either methylmagnesium iodide or methyl lithium failed (Table 3). Either no reaction occurred or the reagent attacked the silicon atom, and the ketone 3 was regenerated by loss of cyanide ion.

Oda et al. have developed a method[43] for the dehydration of trimethylsiloxy nitriles to α, β-unsaturated nitriles (19). However, when this procedure was attempted

Table 3. Attempted Reactions of 18.

Conditions	Product
MeMgI, Et_2O, 23°C	18
MeMgI, Et_2O, 35°C	18
MeMgI, Benzene, 80°C	3 + 18
MeLi, Et_2O, 23°C	18
MeLi, THF, 23°C	3

on 18 no reaction occurred and starting material was recovered. In light of these failures, the rearrangement

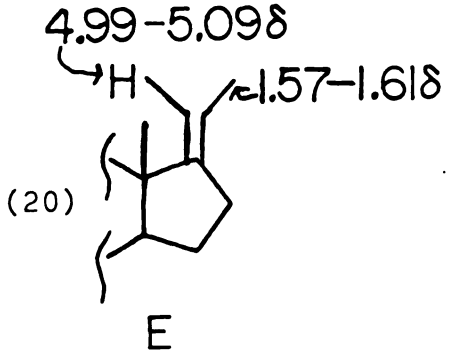
(19) 

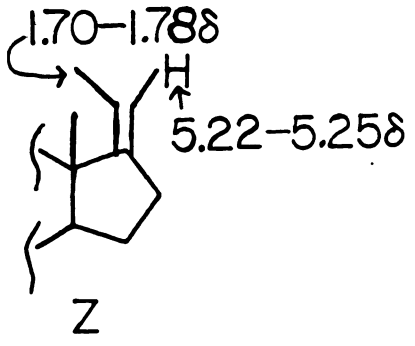
that occurred with 4, and the success of the Wittig reaction, further work in this area was postponed.

The Wittig reaction of ketone 3 with methylenetriphenylphosphorane, using the Corey modification[44], yielded olefin 19 in good yield. However, substitution of the ethylidene analog produced the synthetically more useful olefin 20 in only 35% yield. This lower yield is probably due to increased steric interactions caused by the presence

of an additional methyl substituent in the reagent that must add to the hindered ketone. Fortunately, the addition of ten equivalents of sodium iodide to the Wittig reagent solution increased the yield of 20 to 61%. It is not entirely clear why the sodium iodide improved the yield. It could complex with the carbonyl group to decrease enolization and thereby facilitate addition, or it could act by increasing the ionic strength of the medium.

The configuration about the double bond of 20 was assigned on the basis of its proton NMR spectrum. Steroid analogs in which the 17-ethylidene groups are known to have E and/or Z configurations have distinct and characteristic chemical shifts for the vinyl proton and the vinyl methyl group of this function[27,45] (20).

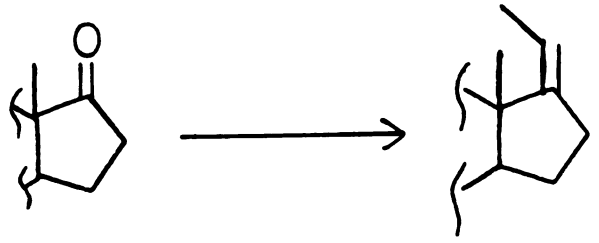




In 20, the chemical shift of the vinyl proton is 5.06 ppm and that of the vinyl methyl group is 1.61 ppm. These values agree very well with the configuration (E) in which the methyl group is anti to the ring system of the molecule, and do not match the corresponding signals for the

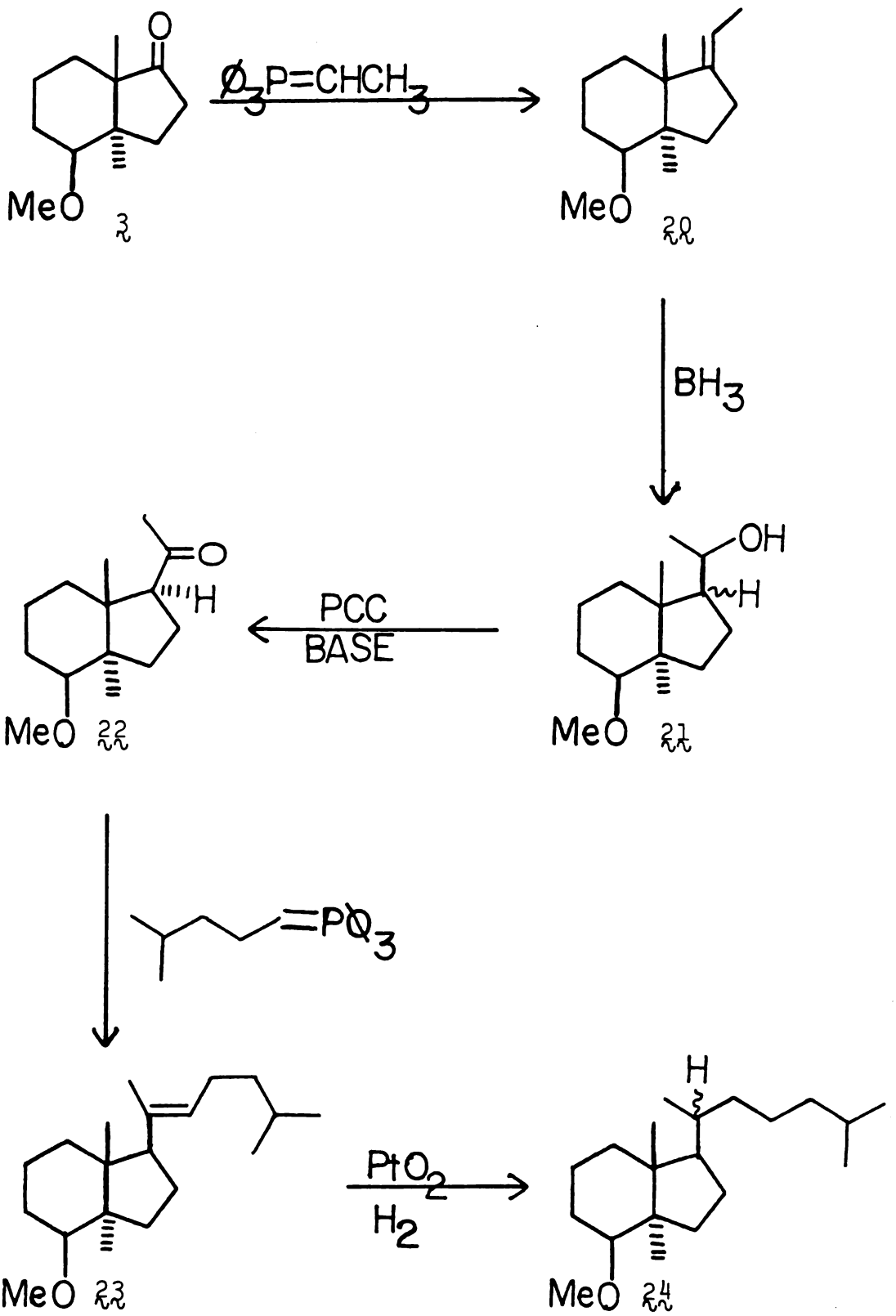
Z isomer.

It is interesting to note that the E configuration obtained in the conversion of 3 to 20 does not correspond to that obtained when the same Wittig reaction is performed on 17-keto steroids[46] (21). In the case of 17-keto steroids, it is proposed that the Z isomer arises

(21) 

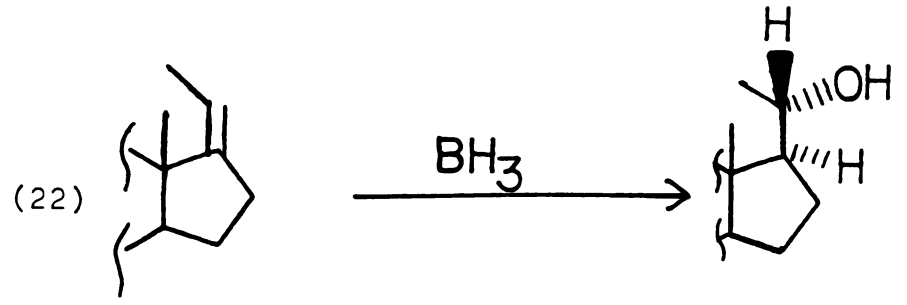
from ylide attack at the less hindered α face[12]. A molecular model of 3 reveals that there is very little difference in the steric environment of the α and β faces. It also suggests that attack from the α face would yield the Z isomer and attack at the β face would yield the E isomer. The observed stereoselective formation of 20 from 3 may reflect a lesser hindrance of the β face, despite the similarities indicated by the model.

Hydroboration of 20 with diborane (Scheme 4) yielded alcohol 21 as a mixture of isomers; probably from attack of diborane on both the α and β faces of the double bond. Steroids having a Z 17-ethylidene group react with diborane predominantly at the α face (22), yielding the 17 β-isomer, containing about 5% of the C-17 epimer[46]. An



Scheme 4. Synthesis of side chain.

attempt was made to improve the selectivity of the hydroboration by using 9-BBN. However, no reaction occurred



with 20 and the starting material was recovered. Again, this result contrasts with corresponding reactions of steroids, which are known to occur[29] with excellent stereoselectivity.

Oxidation of the mixture of alcohols 21 with pyridinium chlorochromate yielded a 1:1 mixture of ketones, which was epimerized with base to give a single isomer, 22. The β configuration was assigned to the pregnane side chain in 22 on the basis of steric hindrance estimates and the proton NMR spectrum. Since the mixture of ketones is epimeric at C-17, base-catalyzed epimerization interconverts the two possible configurations for the side chain: α and β. Molecular models indicate that the β-epimer should be the more stable, since the α epimer would be severely compressed due to interaction between the C-14 α methyl group and the C-17 α side chain. Therefore, epimerization should favor the more stable β side

chain. Coupling constants for the C-17 hydrogen atom can be predicted from a molecular model and the Karplus equation[40], and are known in steroid analogs. For the β side chain, the C-17 hydrogen is predicted to be a triplet with J = 8-10 Hz and for the α side chain, a doublet of doublets with J = 7-9 Hz and 4-5 Hz. The proton spectrum of the mixture of ketones had a triplet (J = 8.5 Hz) at 2.72 ppm and a doublet of doublets (J = 9.1 Hz, 4.4 Hz) at 2.55 ppm. The latter disappeared upon epimerization, leaving only the triplet. This confirms the β configuration assigned to the side chain in 22.

The remaining carbons of the terpenoid side chain were then introduced by a Wittig reaction, using a modification of McMorris' procedure[47]. Addition of isohexylphosphorane to ketone 22 produced olefin 23 in fair yield. The E configuration of this olefin was indicated by the chemical shift of the C-21 methyl signal at 1.6 ppm. This is within the range expected for the E isomer (1.6-1.65 ppm), whereas the range for the Z isomer is 1.68-1.71 ppm[48].

Hydrogenation of the double bond with platinum oxide in dioxane: acetic acid (50:1) produced 24 as a 2:1 mixture epimeric at C-20. The 2:1 isomer ratio was determined by carbon-13 NMR and confirmed by gas chromatography. Hydrogenation of the 20(22) double bond has been widely studied, but the results vary considerably[17]. The reaction seems to be extremely sensitive to both the substrate and the

reaction conditions; however, platinum oxide in dioxane: acetic acid is reported to give the best stereoselectivity.

Since 3 is racemic, the mixture 24 is actually composed of two pairs of enantiomers. Therefore, referring to the newly introduced chiral center at C-20 as R or S is improper, because in each pair of enantiomers C-20 will be both R and S. By using two chiral centers, C-20 plus one other, it should be possible to unambiguously designate all four of the isomers. For example, if C-17 is used as the reference site, then one enantiomeric pair of 24 would be R,R and S,S and the other would be S,R and R,S.

In order to use carbon-13 chemical shifts to determine the configurations of these isomers, it is important to have good reference standards[49] (Figure 5 and 6). In this instance, dihydrolanosterol and euphenol serve as excellent models. Using the system described above, natural dihydrolanosterol is R,R and its unknown enantiomer is S,S; euphenol is R,S and its enantiomer is S,R.

In an achiral solvent the carbon-13 NMR chemical shifts of the side chain carbon atoms of the R,R and S,S enantiomers in 24 should correlate with the corresponding signals in the spectrum of dihydrolanosterol. Similarly, the R,S and S,R enantiomers in 24 should correlate with the side chain signals in the euphenol spectrum. From the chemical shifts reported for these natural products (Figure 5 and 6), the assignments proposed for the diastereomers in 24 are

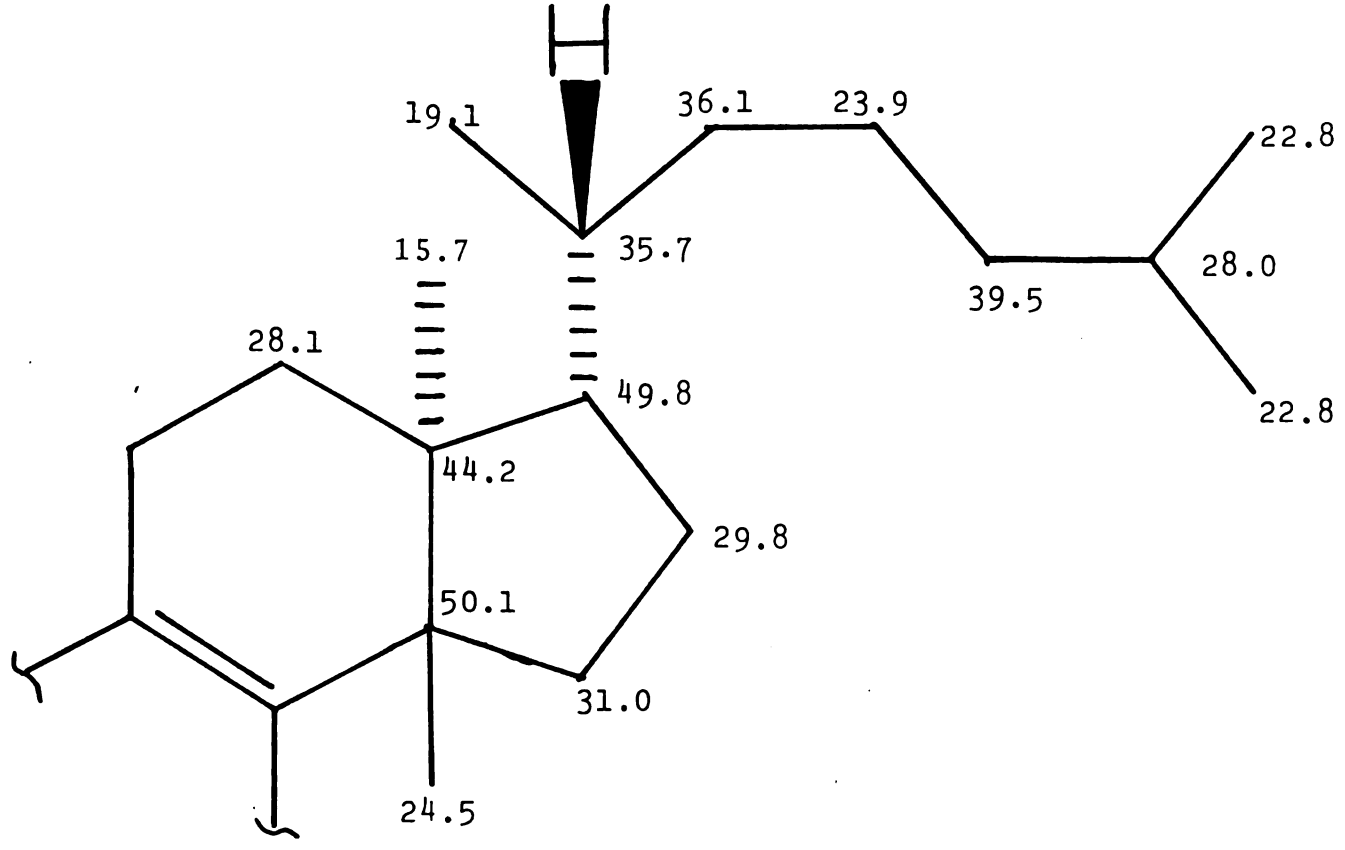


Figure 5. Euphenol ^{13}C chemical shifts.

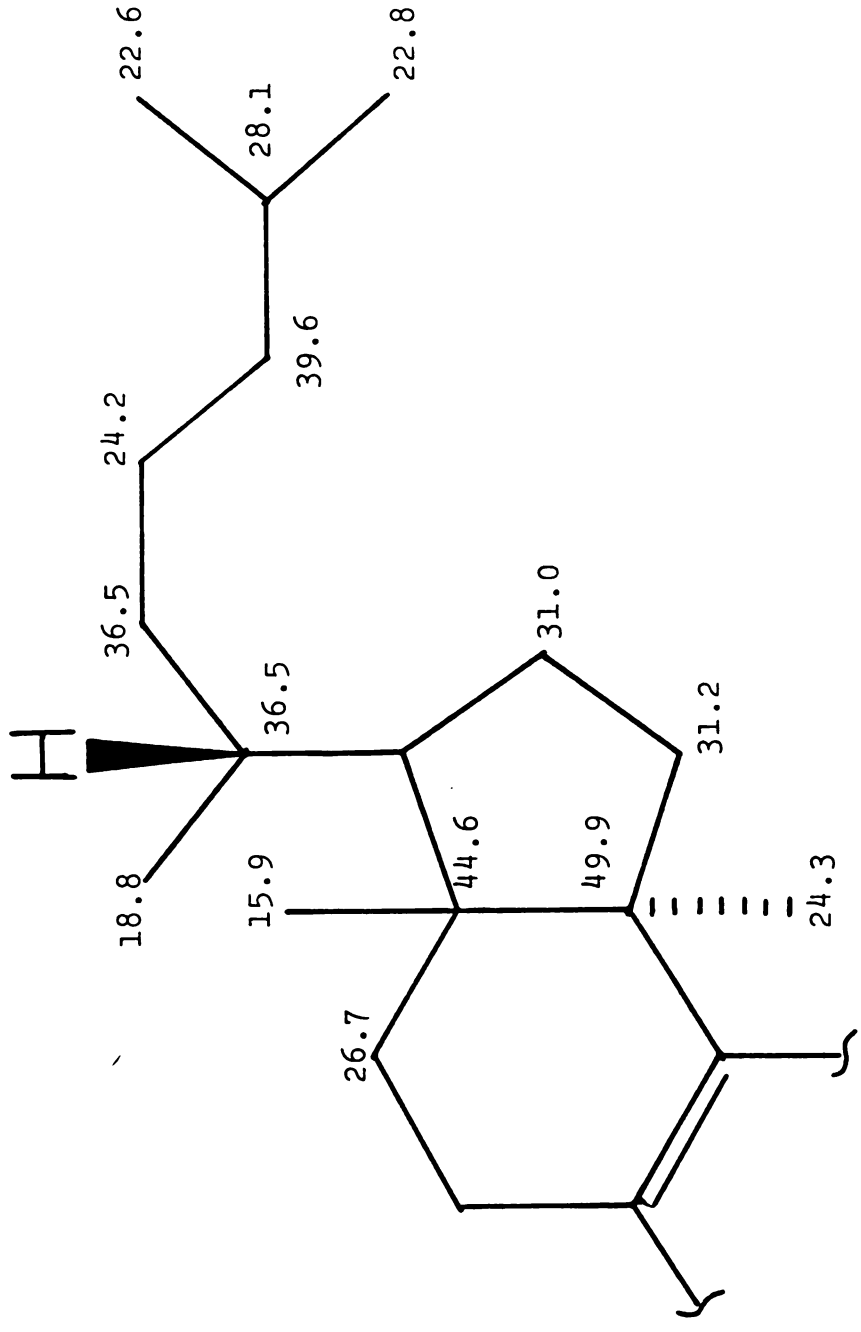


Figure 6. Dihydrolanosterol ^{13}C chemical shifts.

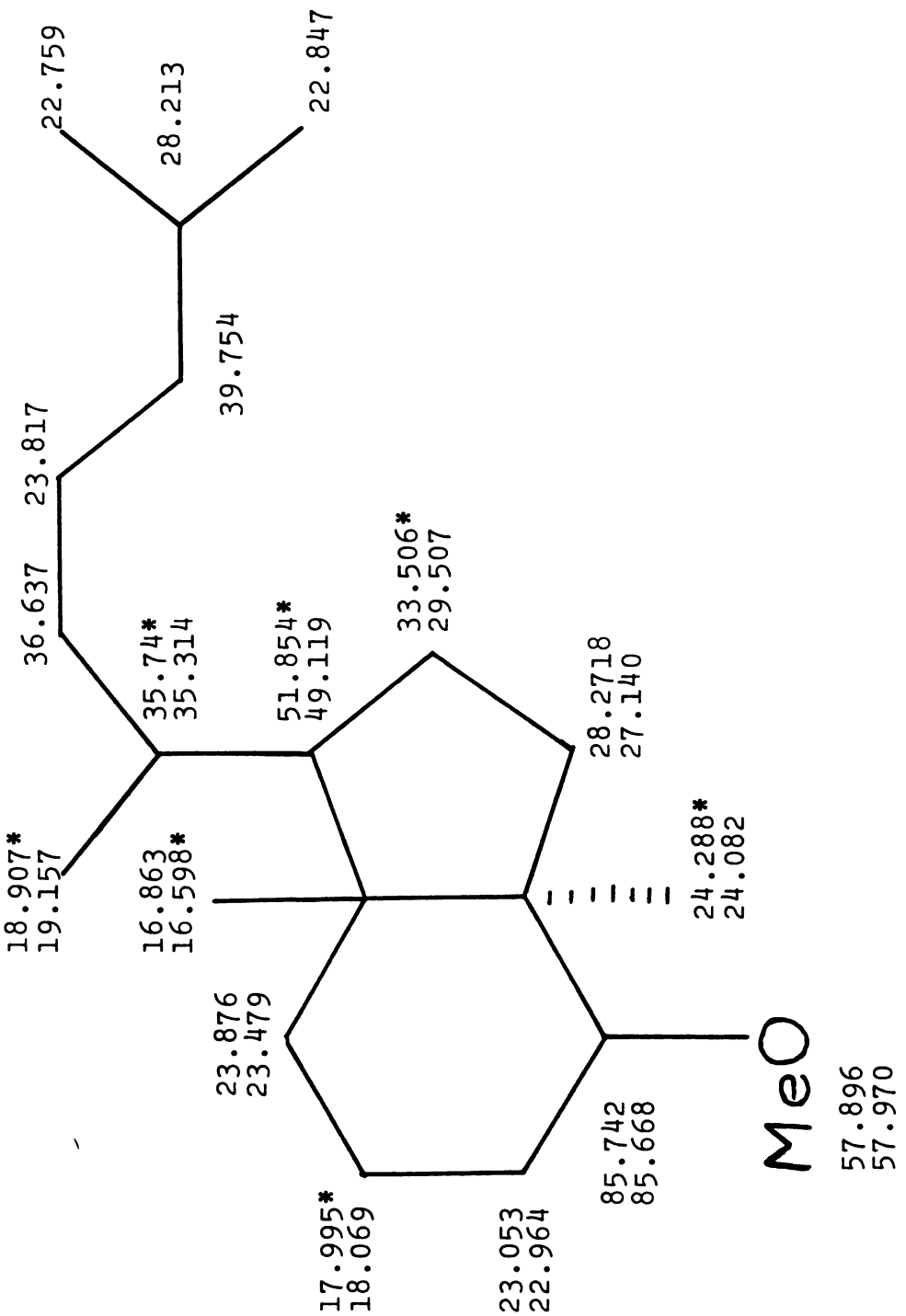


Figure 7. ^{13}C chemical shifts of 24.

shown in Figure 7. The starred numbers indicate the more intense peak of the pair, and presumably the more abundant isomer. Based on these assignments, the major isomer appeared to be 17R, 20R which is analogous to dihydrolanosterol. However, this assignment cannot be considered firm because in two instances, C-13 and C-18, the more intense peak was not the predicted one. In fact, a definitive assignment may have to wait until the entire tetracyclic triterpene is assembled.

Even though the promising crotyl adduct 4 could not be carried on to the terpenoid side chain, due to its facile rearrangement, the initial objective of this project was reached. The terpenoid side chain was introduced by conversion of 3 to the E-ethylidene derivative 20, from there to the 7 β-acetyl intermediate 22, and finally to a mixture of side chain epimers 24 by a Wittig condensation followed by hydrogenation. While the synthesis is straight forward, it would be desirable to increase the stereoselectivity of the hydrogenation.

EXPERIMENTAL

"The chemists are a strange class of mortals who seek their pleasures among soot and flame, poisons and poverty, yet among all these evils, I seem to live so sweetly that I may die if I would change places with the Persian King."

John Joachim Becher

General

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

Analysis by GLPC was conducted with a Varian 1200 gas chromatograph. Melting points were determined on a Hoover-Thomas apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were taken in deuterochloroform solutions with either a Varian T-60 or a Bruker 250 MHz spectrometer and are calibrated in parts per million downfield from tetramethylsilane as an internal standard. Carbon-13 NMR spectra were taken in deuterochloroform solutions on the Bruker 250 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained with a Finnigan 4000 GC/MS spectrometer.

6-Methyl-5-hydroxytricyclo[4.4.0.0]decan-9-one

A 2 liter three neck round bottom flask was dried, purged with dry nitrogen and fitted with a mechanical stirrer, a dry ice condenser and a dry ice acetone cooling bath. To this flask was added 1 liter of ammonia, 50 mL of dry THF and sufficient lithium metal to just maintain a blue solution. To this stirred solution at -78°C was added 3.5 g (0.5 mol) of lithium wire, followed over a 50 minute period by a solution of the Wieland-Miescher ketone (34.5 g, 0.194 mol) in THF (250 mL). The resulting blue solution was stirred at -78°C for 1.5 hours and then quenched by addition of anhydrous ammonium chloride (30 g). After evaporation of the ammonia with a warm water bath (50°C), water (200 mL) and ether (200 mL) was added. The water layer was extracted with ether (3 x 100 mL). The combined ether layers were washed with water (100 mL) and brine (100 mL) and these washes were then reextracted with ether (2 x 50 mL). The ether extracts were dried ($MgSO_4$) and the ether was removed under vacuum at room temperature to yield an oil which crystallized to yield 23.8 g (68%) of pure cyclopropanol.

trans-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione

A solution of potassium hydroxide (6.24 g, 0.111 mol) in 1:1 methanol-water (80 mL) was deoxygenated by bubbling

nitrogen through it for 15 minutes. The solution was then cooled to 0°C and the cyclopropanol (20 g, 0.111 mol) was added. After stirring for 5 hours at 0°C, the solution was allowed to warm to room temperature and the stirring was continued for 8 hours. The solution was filtered and the resulting solid was washed with water and dried to yield 14 g (70%) of hydrindandione 1: mp 166-167°C; MS, m/e 180(M^+).

trans-1,6-dimethyl-2-hydroxybicyclo[4.3.0]nonan-7-one 2

To a stirred solution of 1 (21.1 g, 0.117 mol) in ethanol (700 mL) at 0°C was added over a 15 minute period a solution of sodium borohydride (4.43 g, 0.117 mol) in 3N sodium hydroxide (100 mL). After stirring for 4 hours at 0°C, this mixture was neutralized with 3N hydrochloric acid and the ethanol was removed. Ether and water was added to the residue and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, brine, and then dried. Removal of the solvent yielded 18.5 g (87%) of the alcohol 2: mp 173-175°C; MS, m/e 182 (M^+).

trans-1,6-dimethyl-2-methoxybicyclo[4.3.0]nonan-7-one 3

A mixture of sodium hydride (1.6 g, 67 mmol) and dimethylsulfoxide (180 mL) was heated at 65°C for 1 hour. The resulting solution of dimsyl sodium was cooled to room temperature, the alcohol 2 (6.6 g, 36 mmol) was added and

stirring was continued for 1 hour. Following the addition of methyl iodide (7.72 g, 54 mmol), the solution was stirred overnight (14 hours), water was added and the resulting mixture was extracted with ether. The combined organic layers were washed with water, brine, and dried. Removal of the solvent yielded 7.9 g of an oil which was submitted to Kugelrohr distillation, yielding 5.1 g (72%) of methyl ether 3. The remaining oil contained mainly alcohol 2 which could be recycled. IR (CCl_4) 1740 cm^{-1}; MS, m/e 196 (M^+).

Homoallylic Alcohol 4

To magnesium (10 g, 0.417 mol) in ether (50 mL) was slowly added (6 hr) a solution of crotyl bromide (31.5 g, 0.233 mol) in ether (150 mL). The metallic gray solution was stirred for 1 hour, toluene (90 mL) was added, and the resulting solution was cooled to -78°C. A solution of the methoxy ketone 3 (7.4 g, 38 mmol) in ether (50 mL) was added over 45 minutes and this mixture was stirred for 5 hours at -78°C. After warming to room temperature, saturated ammonium chloride was added, and the mixture was filtered. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water, brine, and dried. Removal of solvent yielded 9.5 g (99%) of homoallylic alcohol 4: IR (CCl_4) 3605, 3550, 1625 cm^{-1}; MS, m/e 252 (M^+).

Isomeric diols 5

To a solution of 4 (8 g, 32 mmol) in THF (70 mL) at 0°C was added a solution of diborane in THF (32 mmol, 32 mL of a 1 M solution) over a period of 20 minutes. After stirring for 30 minutes at 0°C, the cooling bath was removed and the stirring continued for 1.5 hours at room temperature. Sufficient water was added to quench the excess diborane, and then 3N sodium hydroxide (12 mmol) and 30% hydrogen peroxide (120 mmol) was added. After stirring for 18 hours, the THF was removed and the residue was extracted with ether. The ether extracts were washed with water and brine, and dried. Removal of the solvent yielded a viscous oil which was recrystallized from ether to yield two isomeric diols 5; 1.6 g (19%) mp 142.5-144.5°C, 4.82 g (56%) mp 118-119°C; IR (CCl_4) 3600, 3375 (br) cm^{-1}; MS m/e 252 (M-18), 220 (M-50). See Appendix I.

Methoxy alcohol 6

A solution of diol 5 (2.6 g, 9.6 mmol) in benzene (40 mL) and THF (10 mL) was heated to 50°C (oil bath temperature) and boron trifluoride etherate (1.5 mL, 12 mmol) was added. After stirring for 35 minutes at 50°C, the solution was poured into ice-water, extracted with ether, and the combined ether extracts were then washed with brine and dried. Removal of the solvent followed by column chromatography (silica gel, 25% ethyl acetate/ hexane) of the crude product yielded 1.97 g (81%) of

olefin 6. An identical procedure was used for the other isomer and the yields were equivalent. IR (CCl_4) 3610, 3400 (br) cm^{-1}; ms, m/e 252 (M^+).

Aldehyde 7

To a suspension of pyridinium chlorochromate (0.5 g, 2.3 mmol) in methylene chloride (3 mL) was added a solution of alcohol 6 (0.39 g, 1.5 mmol) in methylene chloride (2 mL). After stirring for 1 hour the reaction mixture was diluted with ether and filtered through a short column of Florisil. Removal of the solvent yielded 0.333 (86%) of a clear oil which appeared pure by TLC and NMR. The aldehyde 7 is unstable and is always used immediately in the following reaction. IR (CCl_4) 1720 cm^{-1}; MS, m/e 250 (m^+).

Alcohol 8

A solution of sec-butyl bromide (0.5 mL, 4.6 mmol) in ether (5 mL) was slowly added to a suspension of magnesium turnings (0.131 g, 5.4 mmol) in ether (10 mL). The resulting metallic gray solution was stirred for 30 minutes, and then a solution of aldehyde 7 (0.333 g, 1.3 mmol) in ether (7 mL) was added over a 20 minute period. After stirring this reaction mixture for 30 minutes, water was added and the solution was extracted with ether. The ether extracts were washed, dried and evaporated to yield 0.348 g (85%) of 8 as a clear oil: IR (CCl_4) 3620, 3480 cm^{-1}; MS, m/e 258 (M-50).

Mesylate 9

To a cold (0°) solution of alcohol 8 (0.312 g, 1.01 mmol) in pyridine (5 mL) was added methane sulfonyl chloride (0.12 mL, 1.51 mmol). After stirring for 1 hour at 0°C, cold water was added and the resulting solution was extracted with ether. The ether extracts were washed with cold 5% hydrochloric acid, dilute sodium bicarbonate, water, brine and then dried. Removal of the solvent gave 0.37 g (95%) of mesylate 9.

Methoxy olefin 10

To a suspension of lithium aluminum hydride (0.208 g, 5.5 mmol) in THF (5 mL) was added a solution of mesylate 9 (0.39 g, 1.02 mmol) in THF (10 mL). After refluxing for 24 hours, aqueous sodium sulfate was added, the mixture was filtered, and the aqueous filtrate was extracted with ether. The ether extracts were washed and dried. Removal of the solvent, followed by column chromatography (silica gel, 15% ethyl acetate/hexane) of the crude oil yielded 0.2 g (67%) of olefin 10 plus 62 mg (20%) of alcohol 8: MS, m/e 292 (M^+).

Alcohol 11

To a cold (0°C) solution of olefin 10 (0.35 g, 1.2 mmol) in ether (25 mL) was added boron trifluoride etherate

(3 mL, 24 mmol), followed 10 minutes later by slow addition of a suspension of lithium aluminum hydride (0.455 g, 12 mmol). The stirring was continued for 4 hours at room temperature, and water was then added to quench the excess diborane. The aqueous layer was extracted with ether, and the residue remaining after removal of the solvent was dissolved in ethanol (20 mL). This solution was treated with 3N sodium hydroxide (3 mL) and 30% hydrogen peroxide (1 mL), stirred for 3 hours, and water was added. After extraction with ether, the ether extracts were washed with water, brine, and dried. Removal of the solvent yielded 0.315 g (85%) of alcohol **11**: IR (CCl_4) 3630 cm^{-1}; MS, m/e 278 (M-32).

Methoxy ketone **12**

To a suspension of pyridium chlorochromate (0.183 g, 0.84 mmol) in methylene chloride (3 mL) was added a solution of alcohol **11** (0.175 g, 0.56 mmol) in methylene chloride (2 mL). After stirring for 2 hours, the reaction mixture was diluted with ether and filtered through a short column of silica gel. Removal of the solvent yielded 0.156 g (90%) of **12** which appeared homogeneous by TLC and NMR: IR (CCl_4) 1695 cm^{-1}; MS, m/e 308 (M^+).

Diene **13**

To a suspension of aluminum powder (1.25 g, 46 mmol) in ether (10 mL) was added mercuric chloride (0.3 g) and

crotyl bromide (1 mL, 9.7 mmol). After stirring this mixture for 10 minutes, a solution of crotyl bromide (6 mL, 58 mmol) in ether (20 mL) was added over a 1.25 hour period. Following a 3 hour reaction period, a solution of ketone 3 (3 g, 15.3 mmol) in ether (20 mL) was added to the resulting dark gray solution of crotyl aluminum. After stirring for 5.5 hours, the reaction mixture was quenched with water, filtered to remove solids, and the organic layer was washed with water, brine, and dried. Removal of the solvent, followed by column chromatography (silica gel, 10% ethyl acetate/hexane) of the resulting oil yielded 2.82 g (79%) of 13 as an oil: IR (CCl_4) 1630 cm^{-1}; MS, m/e 234 (M^+). See Appendix I.

Monoolefin 14

A solution of diene 13 (0.533 g, 2.28 mmol) in absolute ethanol (50 mL) was mixed with 10% Pd on carbon (97 Mg), and shaken under hydrogen (40 psi) using a Parr apparatus. The solution was filtered and the solvent was removed to yield 0.5345 g (99%) of 14 as an oil: MS, m/e 236 (M^+). See Appendix I.

Alcohol 15

To a cold (0°C) solution of olefin 14 (0.23 g, 0.97 mmol) and boron trifluoride etherate (2.6 mL, 21.2 mmol) in ether (10 mL) was added a suspension of lithium aluminum hydride (0.4 g, 10.7 mmol) in ether (15 mL). After

stirring this mixture at room temperature for 4 hours, the reaction was quenched with water, filtered, and the organic layer was washed and dried. Removal of the solvent yielded 0.24 g (98%) of 15: IR (CCl_4) 3590 cm^{-1}.

Methoxy ketone 16

To a suspension of pyridium chlorochromate (0.45 g, 2.1 mmol) in methylene chloride (5 mL) was added a solution of alcohol 15 (0.24 g, 0.94 mmol) in methylene chloride (2 mL). After stirring for 3 hours, the reaction mixture was diluted with ether and filtered through a short column of silica gel. Removal of the solvent followed by column chromatography (silica gel, 10% ethyl acetate/hexane) of the residue yielded 0.141 g (60%) of ketone 16: IR (CCl_4) 1695 cm^{-1}; MS, m/e 252 (M^+). See Appendix I.

Methoxy enone 17

A solution of diisopropylamine (0.156 mL, 1.1 mmol) and butyl lithium (1.1 mmol) in THF (5 mL) was stirred at -78°C for 30 minutes. Ketone 16 (0.139 g, 0.55 mmol) was added and the stirring was continued for 1 hour at -78°C. After warming to 0°C, diphenyl disulfide (0.14 g, 0.64 mmol) was added, the reaction mixture was stirred at room temperature for 4 hours, and then poured into ether and 10% hydrochloric acid. The ether extracts were washed with saturated sodium bicarbonate and dried. After the

solvent was removed, the residue was dissolved in methanol (8 mL), cooled to 0°C, and sodium periodate (0.134 g, 0.63 mmol) dissolved in a minimum amount of water was added. The reaction mixture was stirred for 14 hours, filtered, and the solvent was removed. The residue was dissolved in ether and dried. Evaporation of the ether yielded a residue which was dissolved in xylene (10 mL), calcium carbonate (100 mg) was added, and the mixture was refluxed for 12 hours. After filtration, the xylene was evaporated and column chromatography (silica gel, 5% ethyl acetate/hexane) of the residue yielded 92 mg of an oil containing the methoxy enone 17 and the ketone 16. This was determined by NMR, MS, and IR: IR (CCl_4) 1695, 1670 cm^{-1}; MS, m/e 252 (M^+), 250 (M^+).

trans-1,6-dimethyl-7-cyano-7-trimethylsiloxy-2-methoxy-bicyclo[4.3.0]nonane 18

To a solution of methoxy ketone 3 (1.99 g, 10.2 mmol) in methylene chloride (50 mL) was added trimethylsilyl-cyanide (3.9 mL, 30.5 mmol) and zinc iodide (0.35 g). After refluxing for 48 hours, TLC showed the reaction was complete. The solution was filtered, the solvent was removed, and the resulting dark oil was subjected to column chromatography (silica gel, 10% ethyl acetate/hexane) to yield 2.8 g (93%) of silylcyanohydrin 18; mp 90-92°C. The proton NMR at 250 MHz clearly shows this product to be a roughly equimolar mixture of C-7 diasteromers: MS, m/e 295 (M^+). See Appendix I.

trans-1,6-dimethyl-7-methylene-2-methoxybicyclo[4.3.0]-nonane 19

A solution of dimsyl sodium was prepared by heating a suspension of sodium hydride (0.41 g, 17.1 mmol) in dimethyl sulfoxide (20 mL) at 65°C for 45 minutes. After cooling to room temperature, a solution of methyltriphenylphosphonium bromide (6.3 g, 17.6 mmol) in DMSO (10 mL) was added followed 45 minutes later, by the ketone 3 (0.574 g, 2.9 mmol) in DMSO (3 mL). The yellow orange solution was then heated at 60°C for 60 hours, cooled to room temperature, poured into water, and extracted with hexane. The hexane extracts were washed with water, the solvent was evaporated and the residue was dissolved in petroleum ether (30-60°C) and filtered through an alumina column to yield 0.4416 g (77%) of 19 as a clear oil: IR (CCl_4) 1650 cm^{-1}; MS, m/e 194 (M^+).

E-7-ethylidene-trans-1,6-dimethyl-2-methoxybicyclo[4.3.0] nonane 20

A solution of dimsyl sodium was prepared by heating a suspension of sodium hydride (0.612 g, 25.5 mmol) in DMSO (60 mL) at 65°C for 1 hour. After cooling to room temperature, ethyltriphenylphosphonium bromide (9.5 g, 25.5 mmol) was added and the resulting red solution was stirred for 45 minutes. Sodium iodide (7.6 g, 51 mmol) was added, followed by a solution of ketone 3 (1 g, 5.1 mmol) in DMSO (5 mls), and the resulting mixture was heated at 60°C

for 65 hours, cooled, poured into water and extracted with hexane. The hexane extracts were washed with water, brine, and dried. Evaporation of the solvent, followed by column chromatography (silica gel, hexane) yielded 0.6345 g (61%) of olefin 20 plus 0.25 g (25%) of ketone 3 as oils. The proton and carbon-13 NMR spectra show 20 to be solely one isomer: MS, m/e 208 (M^+). See Appendix I.

Alcohol 21

To a cold solution of olefin 20 (0.182 g, 0.88 mmol) in THF (10 mL) was added a solution of diborane (2 mmol) in THF. After stirring this mixture at room temperature for 3 hours, water was added to quench the excess diborane. Following addition of 3N sodium hydroxide (3 mmol) and 30% hydrogen peroxide (10 mmol), the reaction mixture was stirred for 2 hours, the solvent was removed and the aqueous residue was extracted with ether. The combined organic layers were washed with water, brine, and dried. Evaporation of the solvent yielded 0.186 g (93%) of 21 as a mixture of alcohols: IR (CCl_4) 3610, 3375 (br) cm^{-1}; MS, m/e 226 (M^+).

Methoxy ketone 22

To a suspension of pyridinium chlorochromate (0.355 g, 1.65 mmol) in methylene chloride (3 mL) was added a solution of the alcohol mixture 21 (0.186 g, 0.82 mmol) in

methylene chloride (2 mL). After stirring for 1.5 hours, this reaction mixture was diluted with ether and filtered through a short column of silica gel. Removal of the solvent yielded 164 mg of an oil identified by NMR as a mixture of ketones epimeric at C-17. This epimer mixture in ethanol (3 mL) was added to a solution of sodium ethoxide prepared by dissolving sodium (93 mg, 4 mmol) in ethanol (10 mL). After stirring for 3 hours, water was added, the solution was extracted with ether, and the combined organic layers were washed and dried. Evaporation of the solvent followed by column chromatography (silica gel, 20% ethyl acetate/hexane) of the residue yielded 0.122 g (65%) of 22: IR (CCl_4) 1705 cm^{-1}; MS, m/e 224 (M^+). See Appendix I.

Olefin 23

A solution of dimsyl sodium was prepared by heating a suspension of sodium hydride (0.084 g, 3.48 mmol) in DMSO (10 mL) at 65°C for 45 minutes. After cooling to room temperature, isohexyltriphenylphosphonium bromide (1.49 g, 3.48 mmol) was added followed, 30 minutes later, by a solution of ketone 22 (0.195 g, 0.87 mmol) in DMSO (3 mL). The red solution was then heated at 60°C for 18 hours, cooled, poured into water, and extracted with hexane. The hexane extracts were washed with water, brine, and dried. Evaporation of the solvent, followed by column chromatography (silica gel, hexane) yielded 0.1 g (40%)

of 23 as a volatile liquid: MS, m/e 292 (M^+). See Appendix I.

Methoxy alkane 24

A solution of olefin 23 (39 mg, 0.13 mmol) in 50:1 dioxane/acetic acid (2.5 mL) was mixed with platinum oxide (10 mg) and stirred for 4 hours under an atmosphere of hydrogen. More platinum oxide (10 mg) was added and the stirring continued for 5 hours under a hydrogen atmosphere. Filtration, and evaporation of the solvent yielded 35 mg (89%) of 24 as an oil. Gas chromatography and carbon-13 NMR shows it to be a 2:1 mixture of isomers: MS, m/e 294 (M^+). See Appendix I.

APPENDIX I

"All that is gold does not glitter; not all those that wander are lost."

J. R. R. Tolkien
The Fellowship of the Ring

Compound	Calculated	Found
5a	C, 71.10 H, 11.19	70.80 11.21
5b	C, 71.10 H, 11.19	71.14 11.17
14*	C, 81.29 H, 11.75	78.50 $\pm$ 0.4 11.29 $\pm$ 0.04
18	C, 65.03 H, 9.89	64.64 9.85
20	C, 80.71 H, 11.61	80.62 11.53
22	C, 74.95 H, 10.78	75.52 10.98
23	C, 82.13 H, 12.41	82.24 12.29

* The found value is an average of three determinations, due to sample volatility. However, the calculated and found C/H ratios are 6.918 and 6.926$\pm$0.045 respectively, well within experimental error.

APPENDIX

"....when you have excluded the impossible, whatever remains, however improbable, must be the truth."

Sherlock Holmes

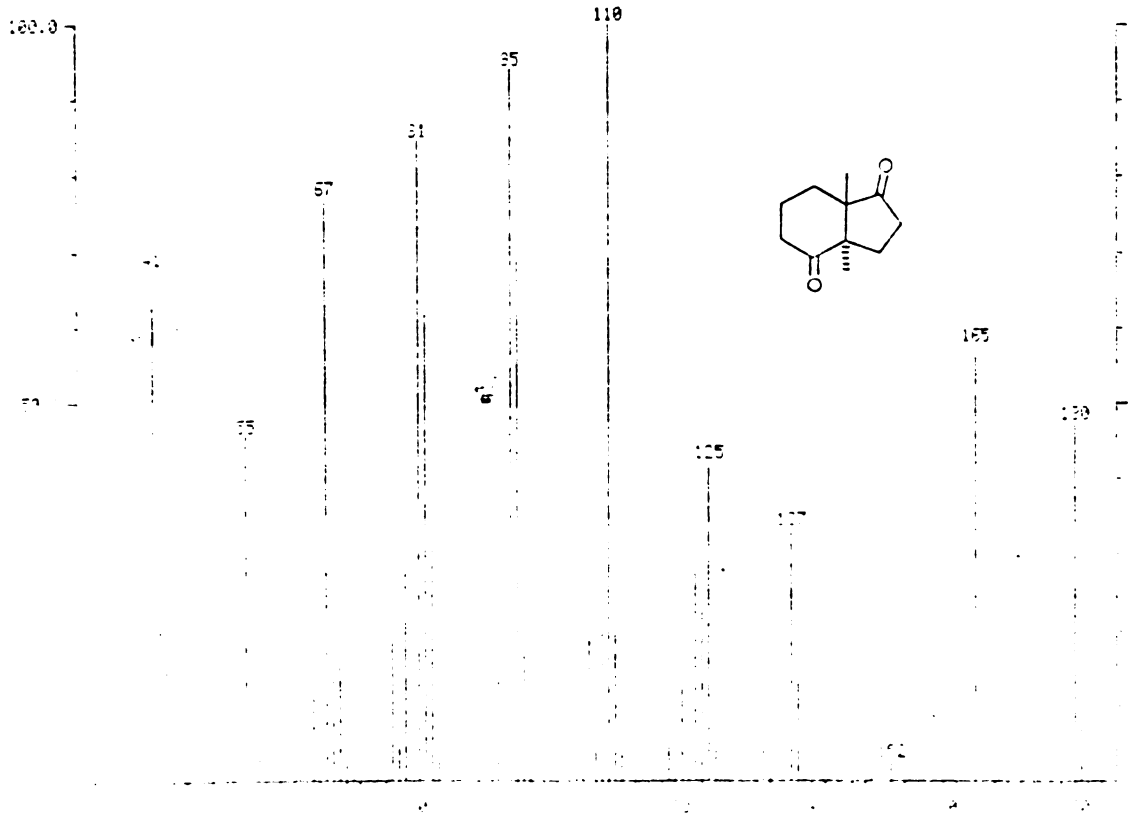


Figure 8. Mass spectrum of 1.

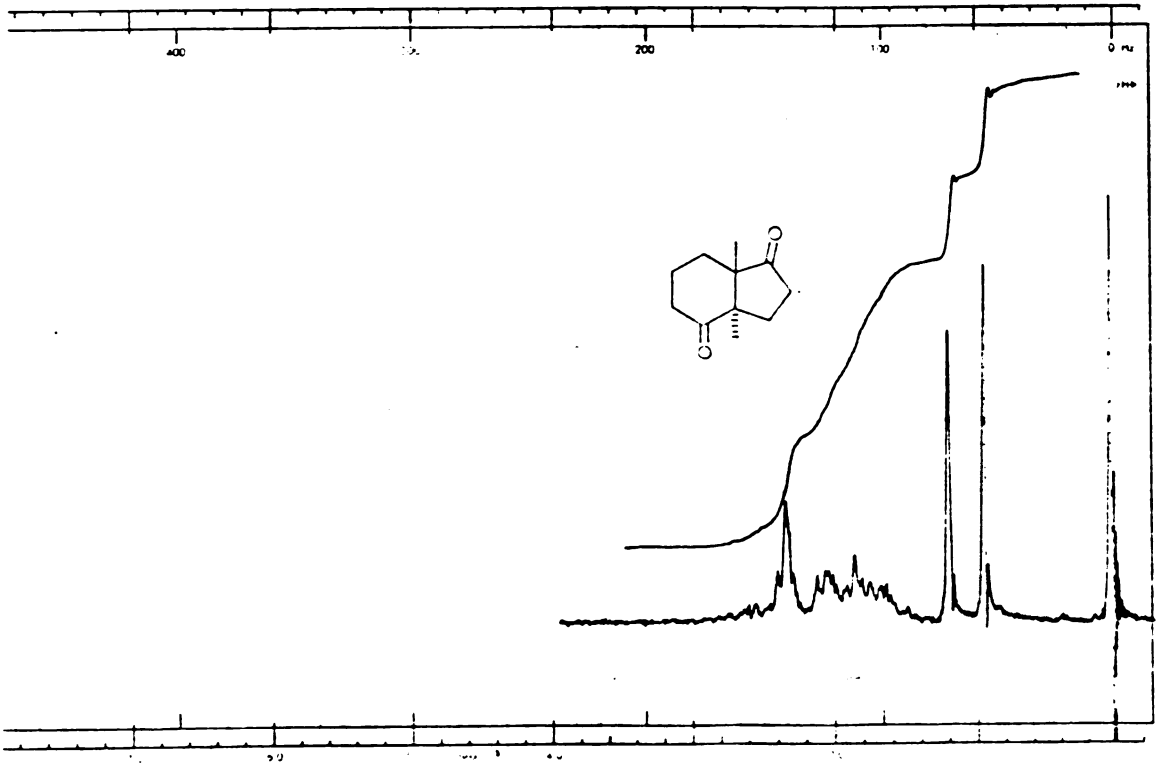


Figure 9. Proton NMR of 1.

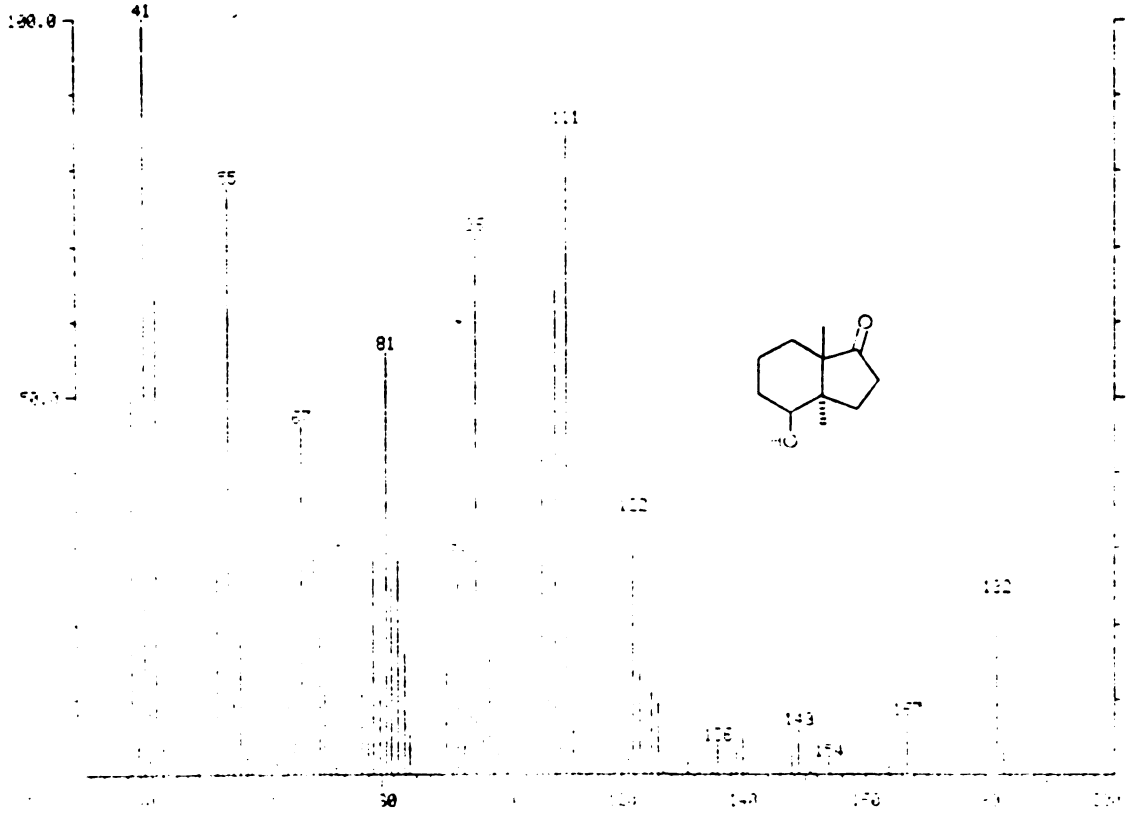


Figure 10. Mass spectrum of 2.

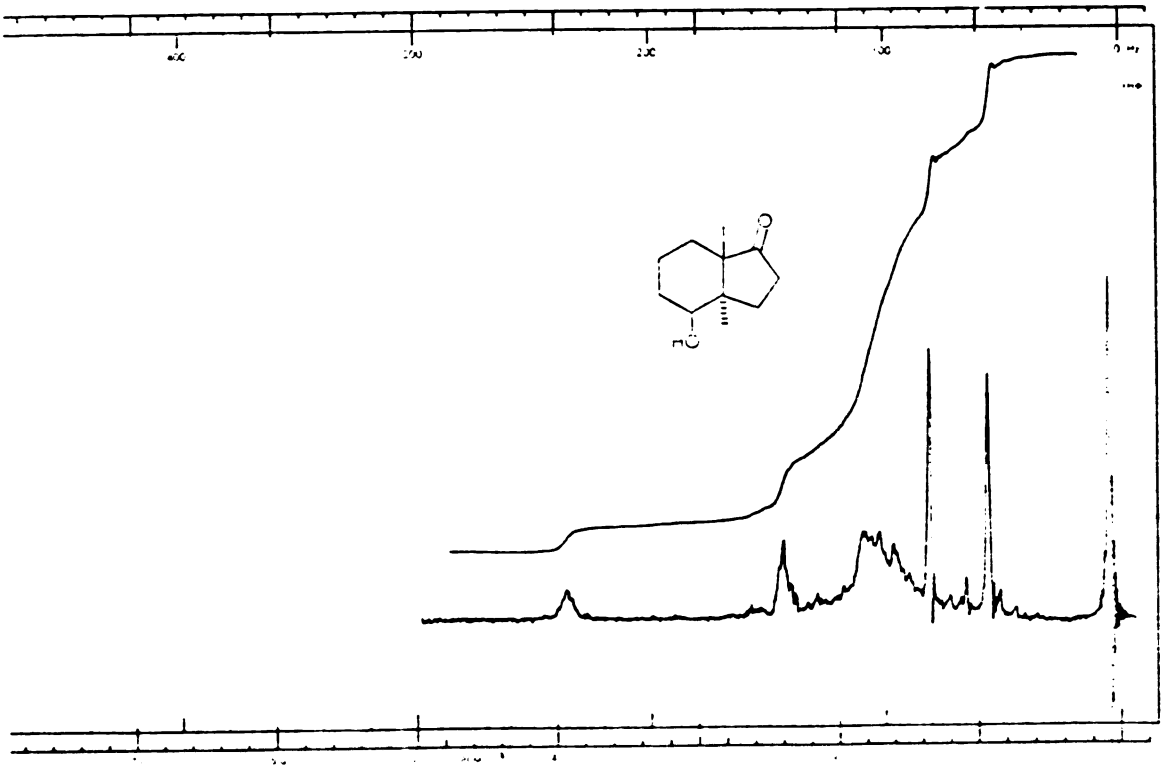


Figure 11. Proton NMR of 2.

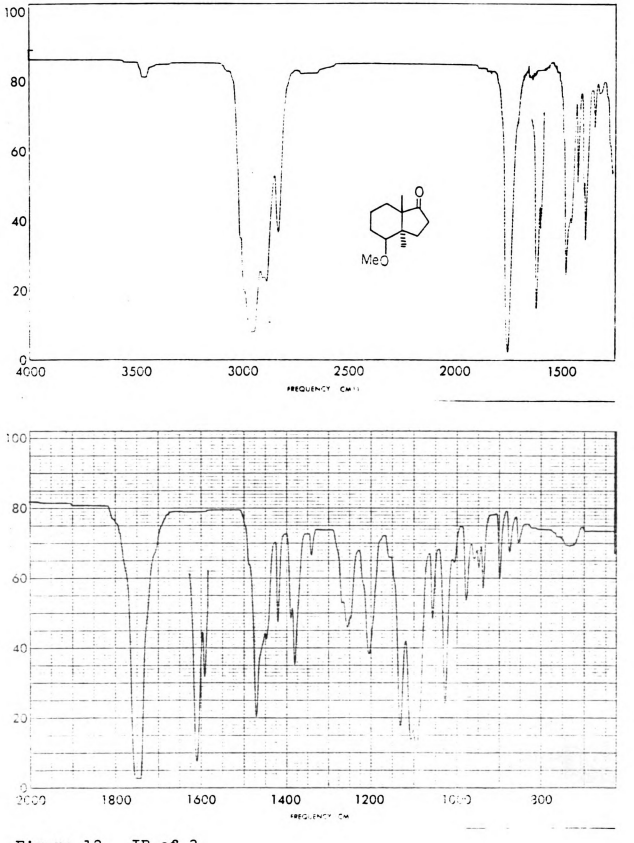


Figure 12. IR of 3.

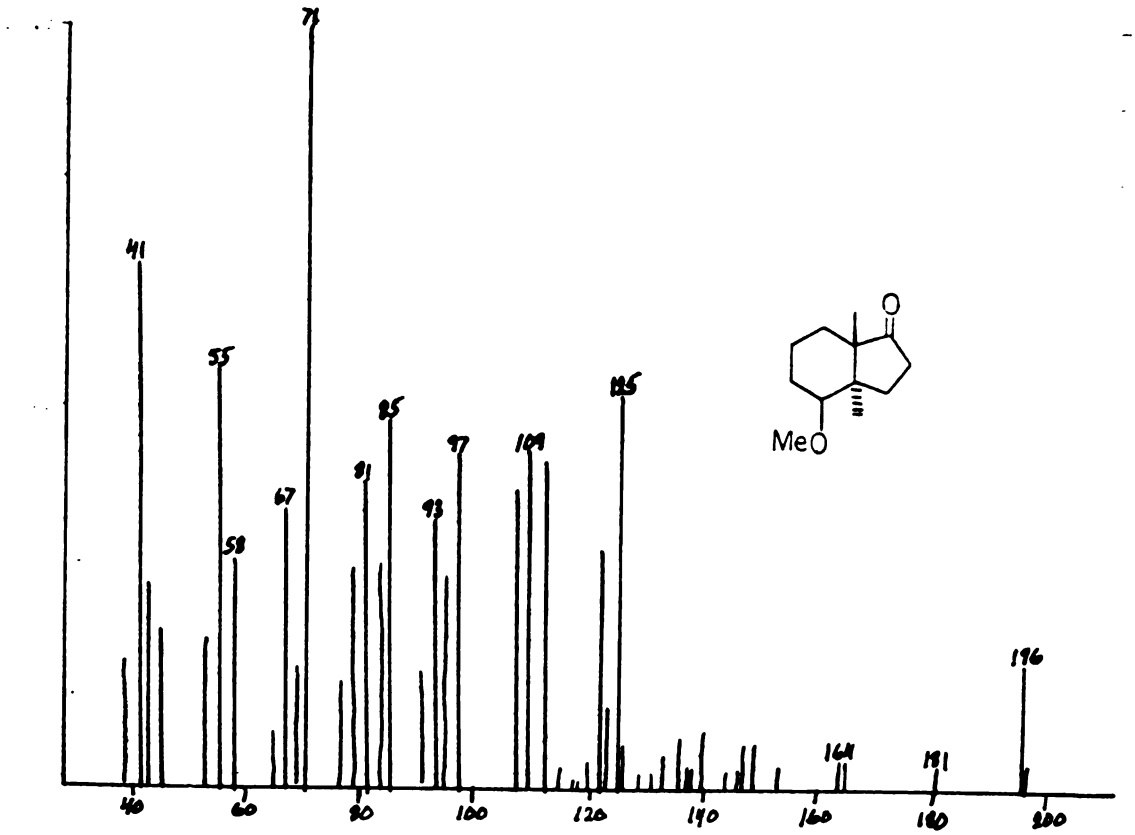


Figure 13. Mass spectrum of 3.

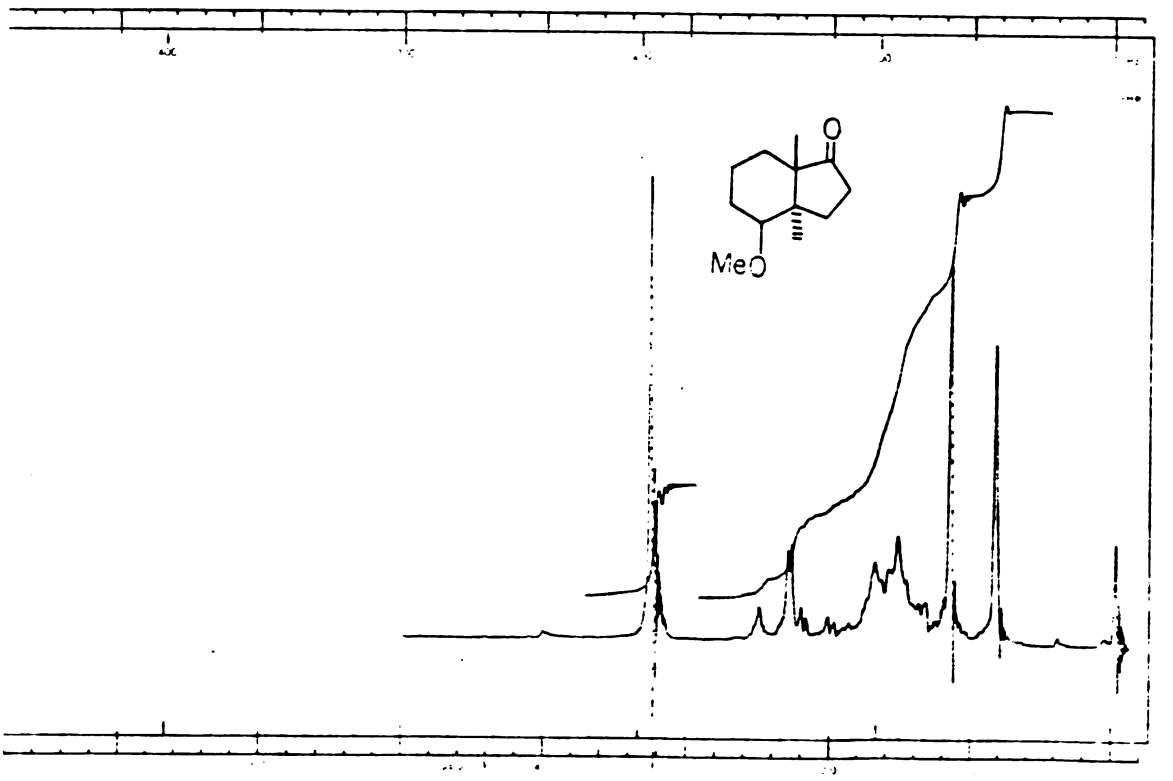


Figure 14. Proton NMR of 3.

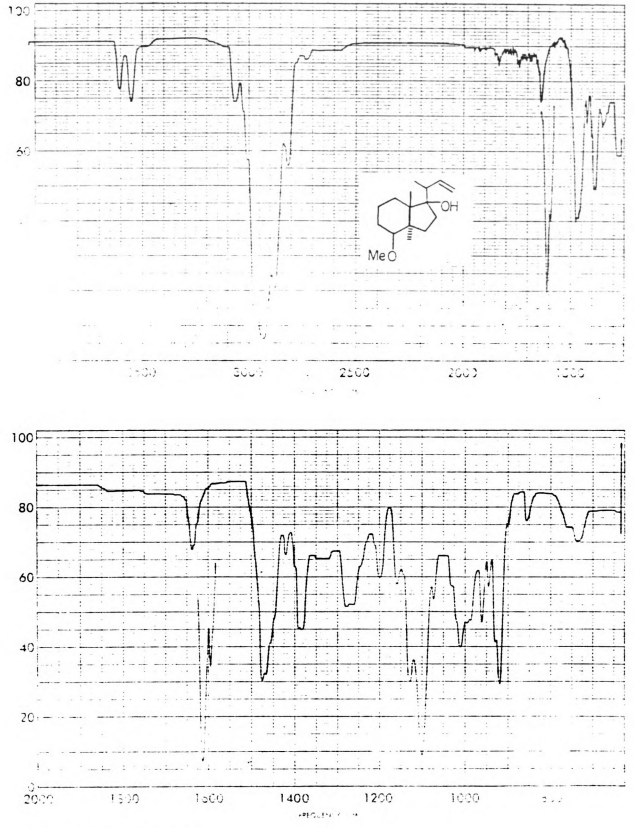


Figure 15. IR of $\frac{4}{\sim}$.

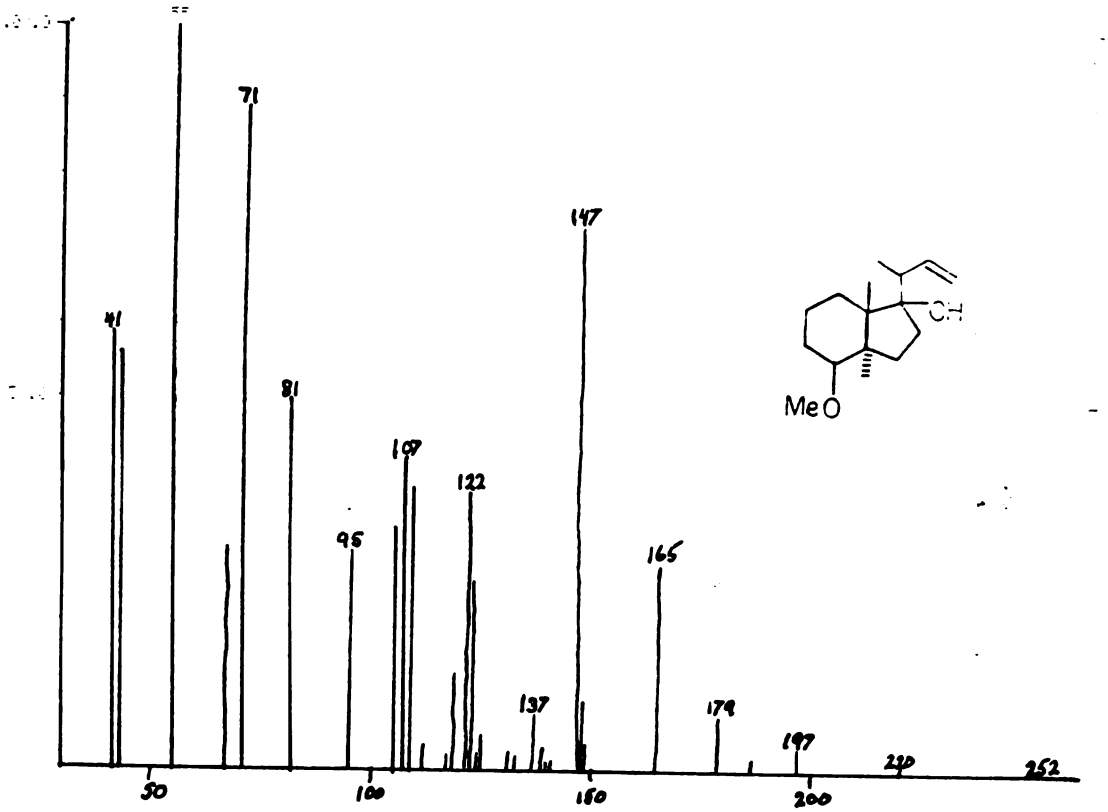


Figure 16. Mass spectrum of 4.

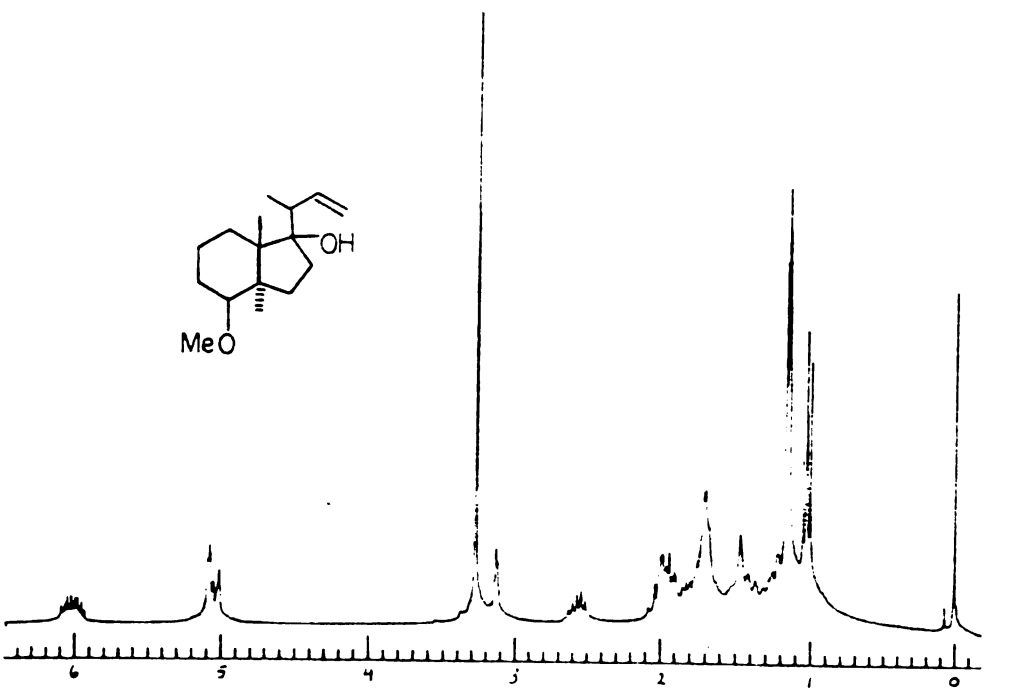
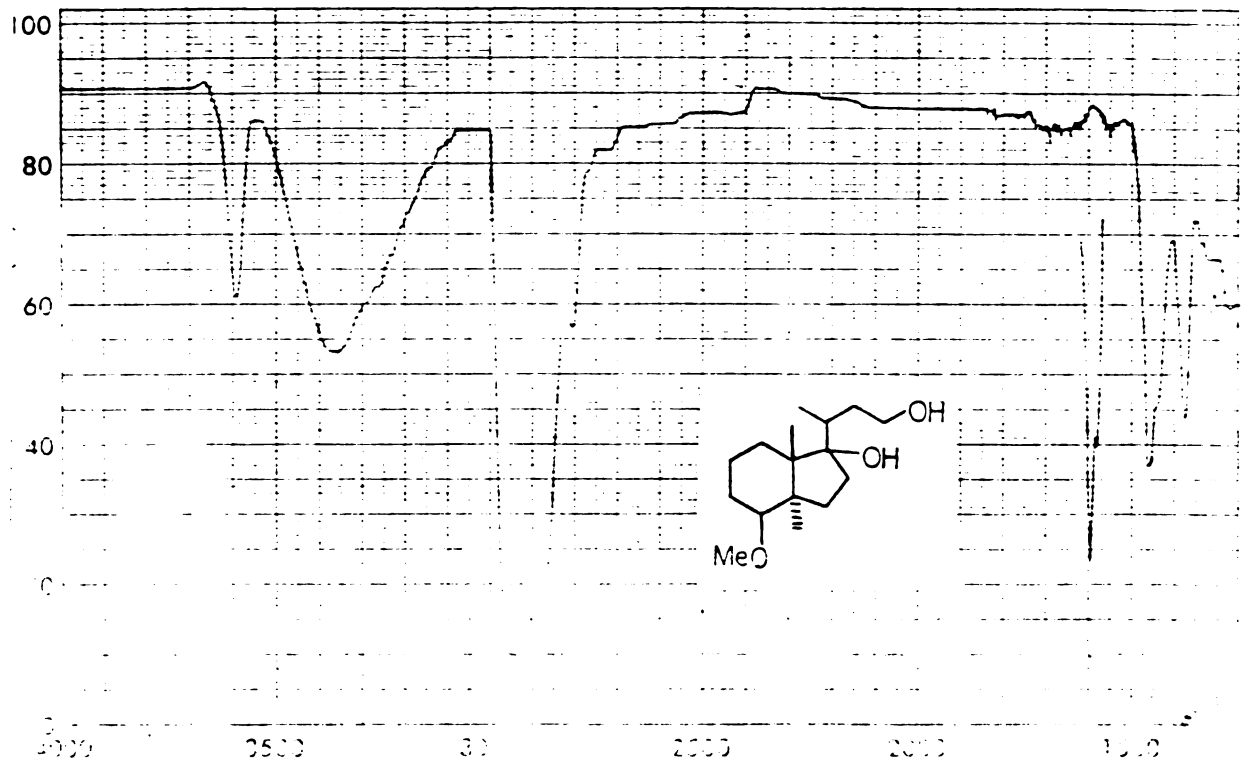


Figure 17. Proton NMR of 4.



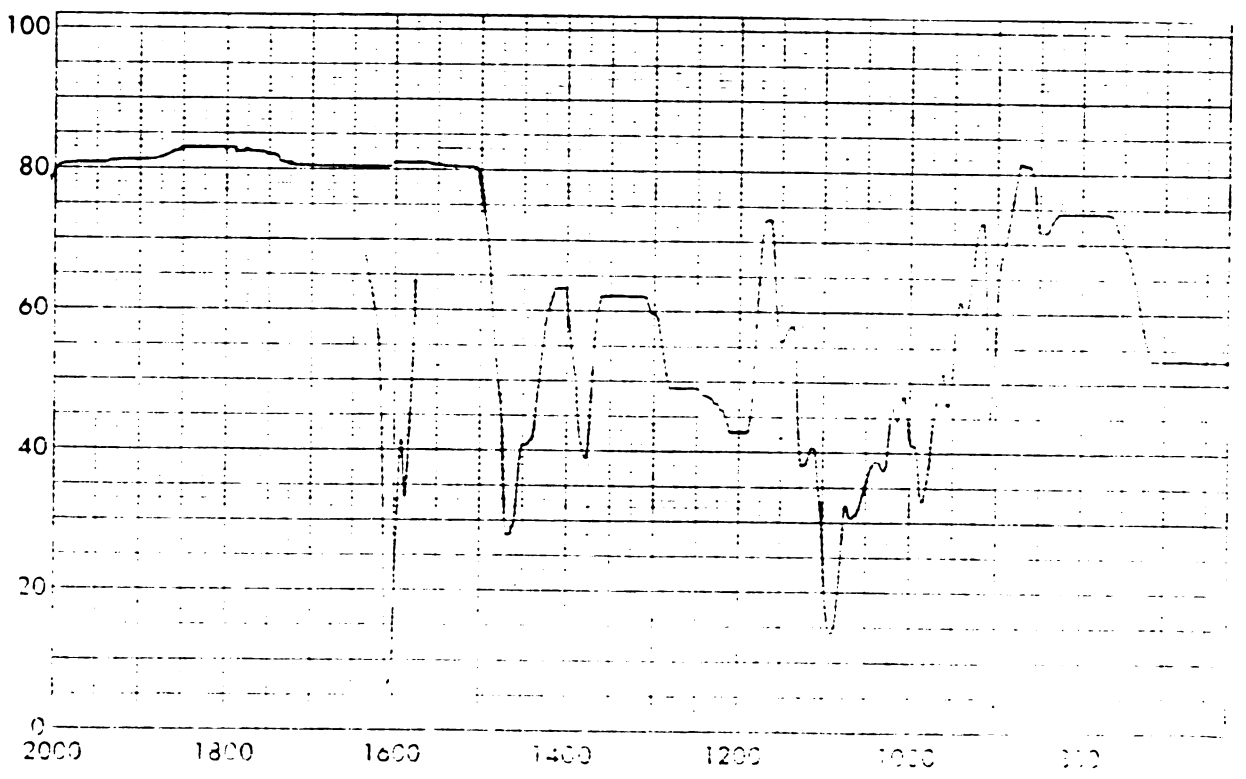


Figure 18. IR of 5a.

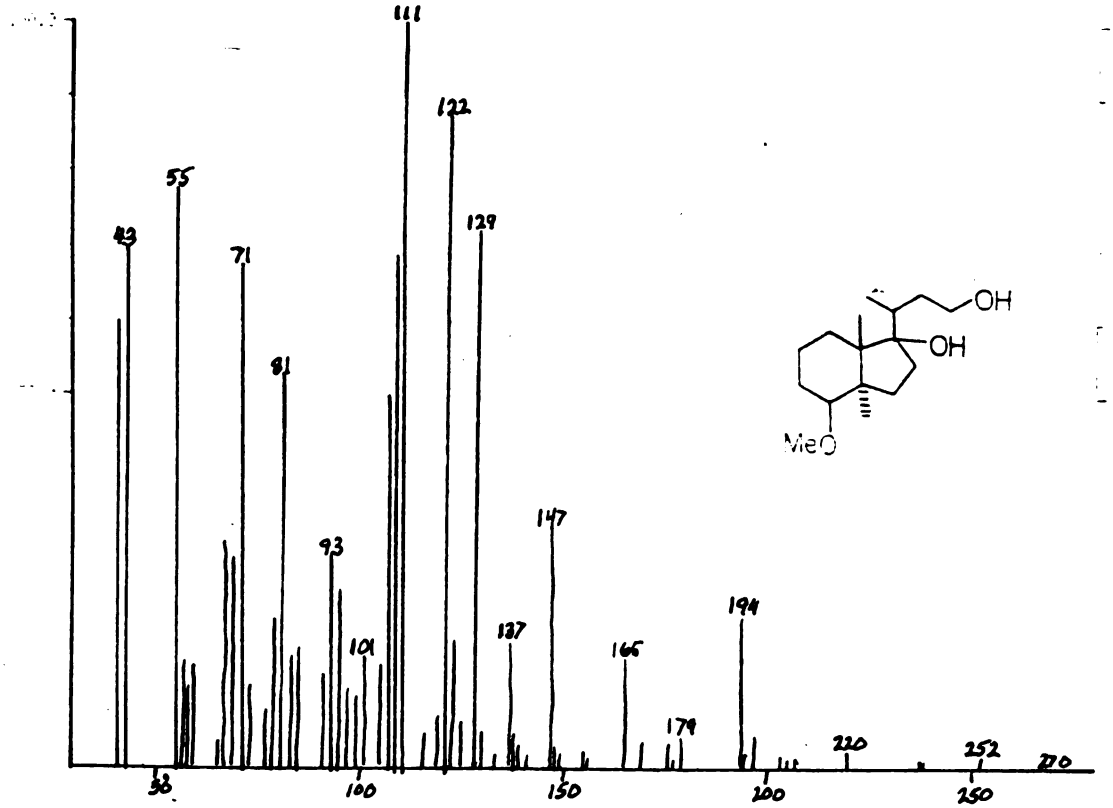


Figure 19. Mass spectrum of 5a.

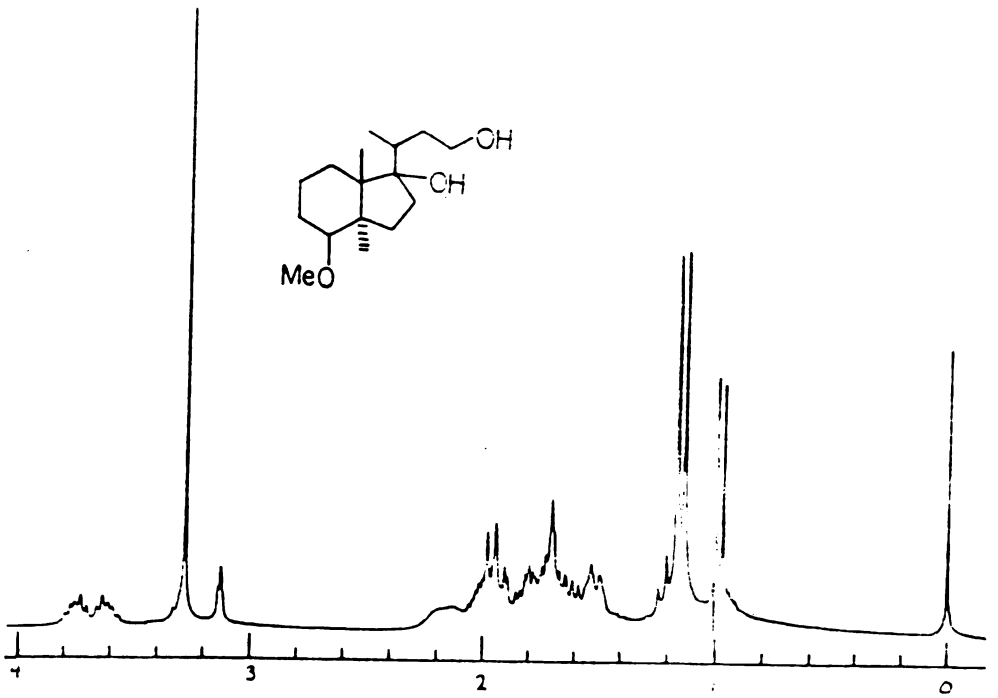


Figure 20. Proton NMR of 5a.

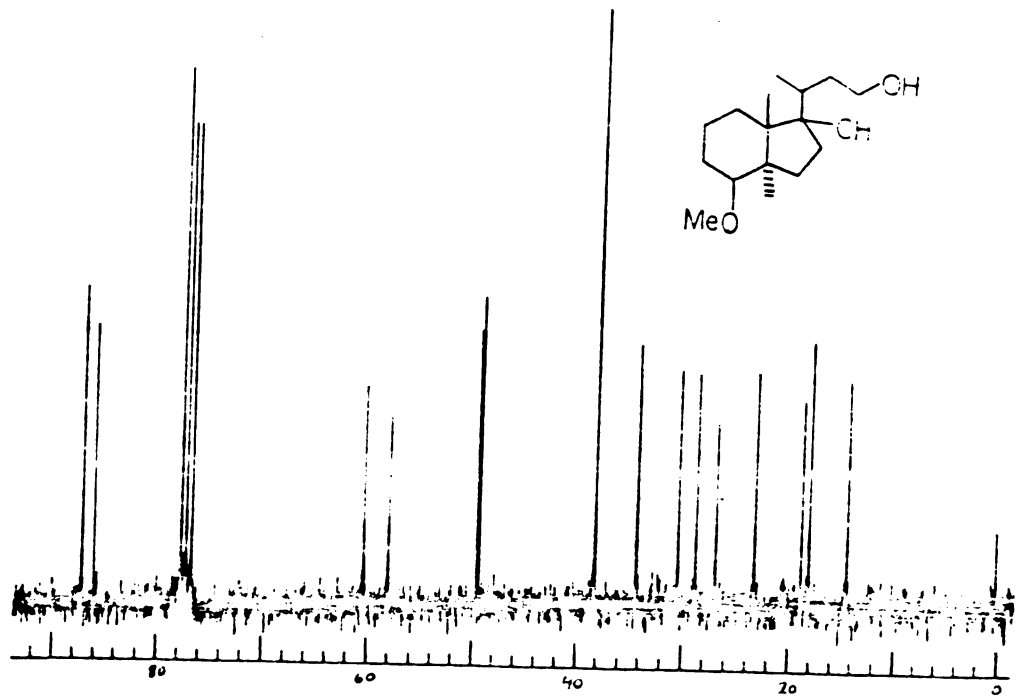


Figure 21. Carbon-13 NMR of 5a.

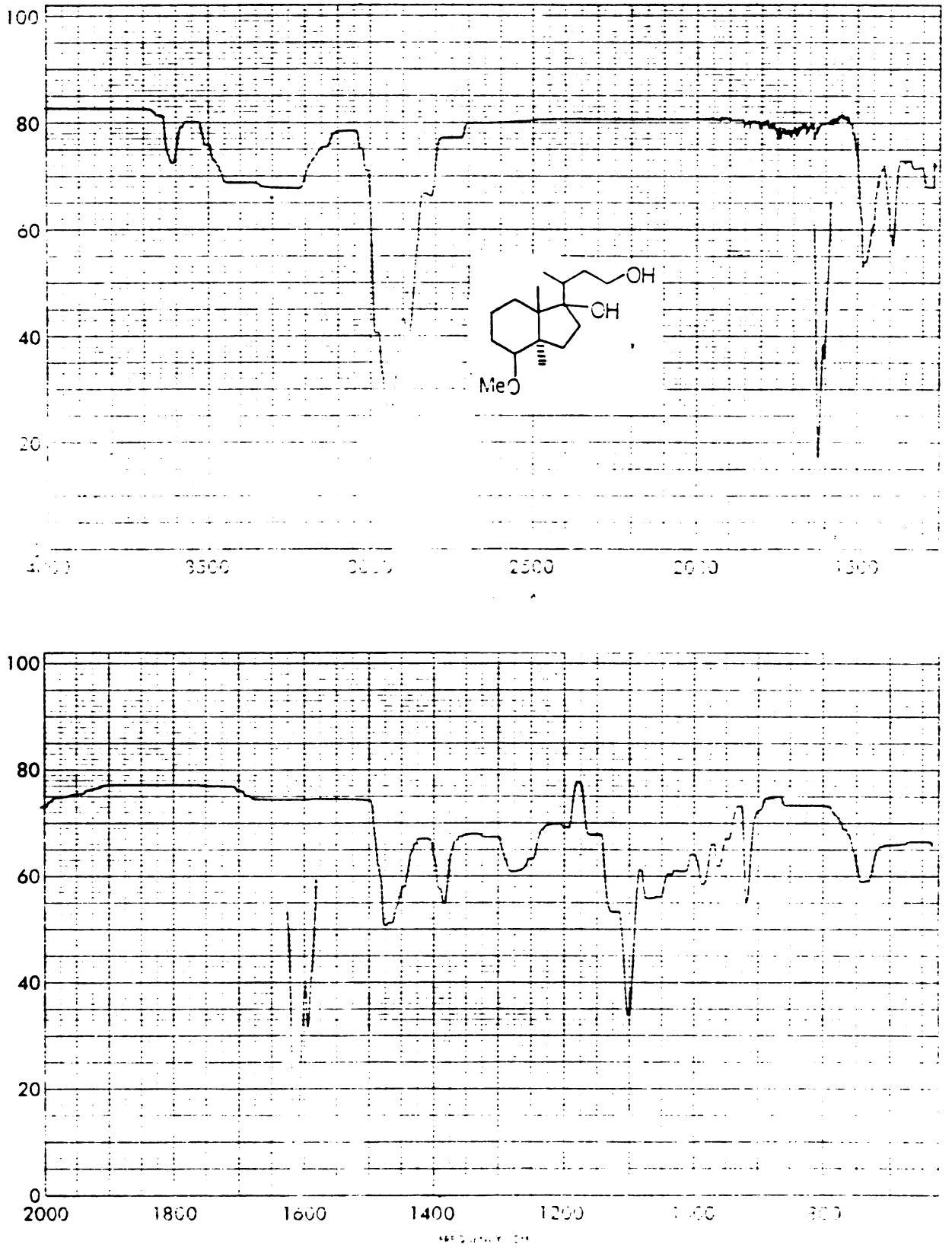


Figure 22. IR of 5b.

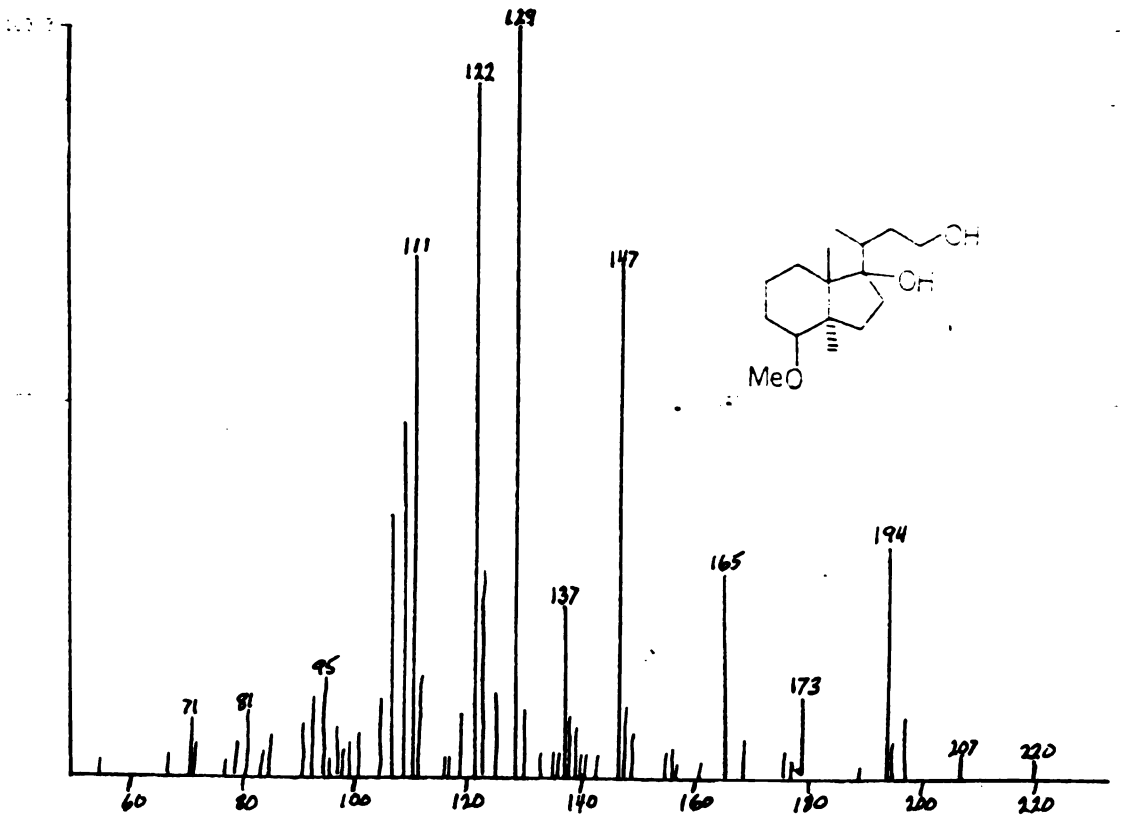


Figure 23. Mass spectrum of 5b.

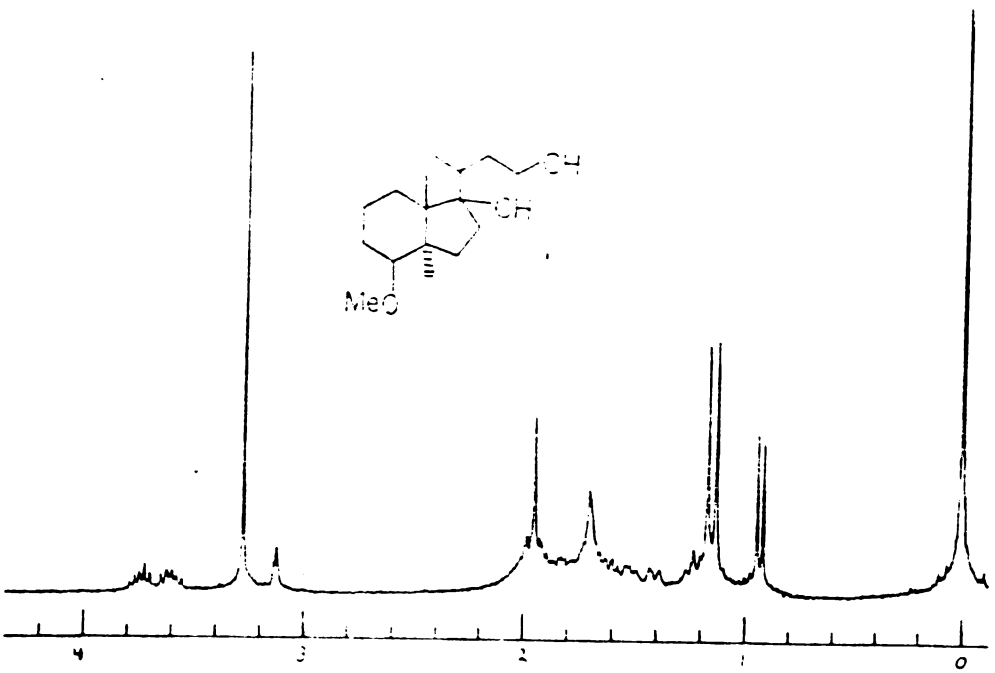


Figure 24. Proton NMR of 5b.

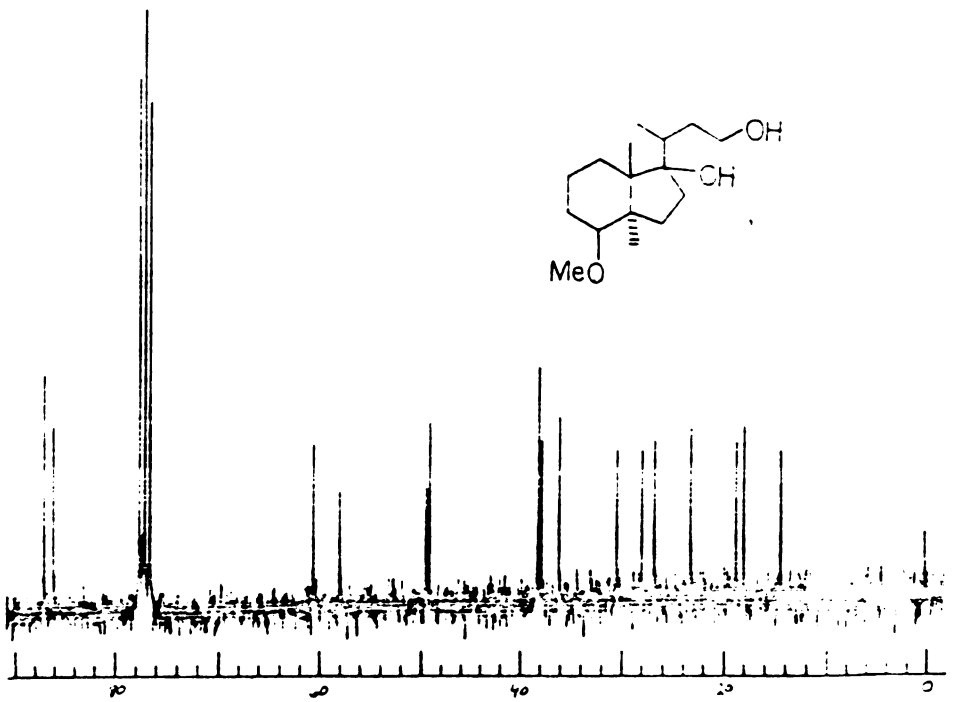
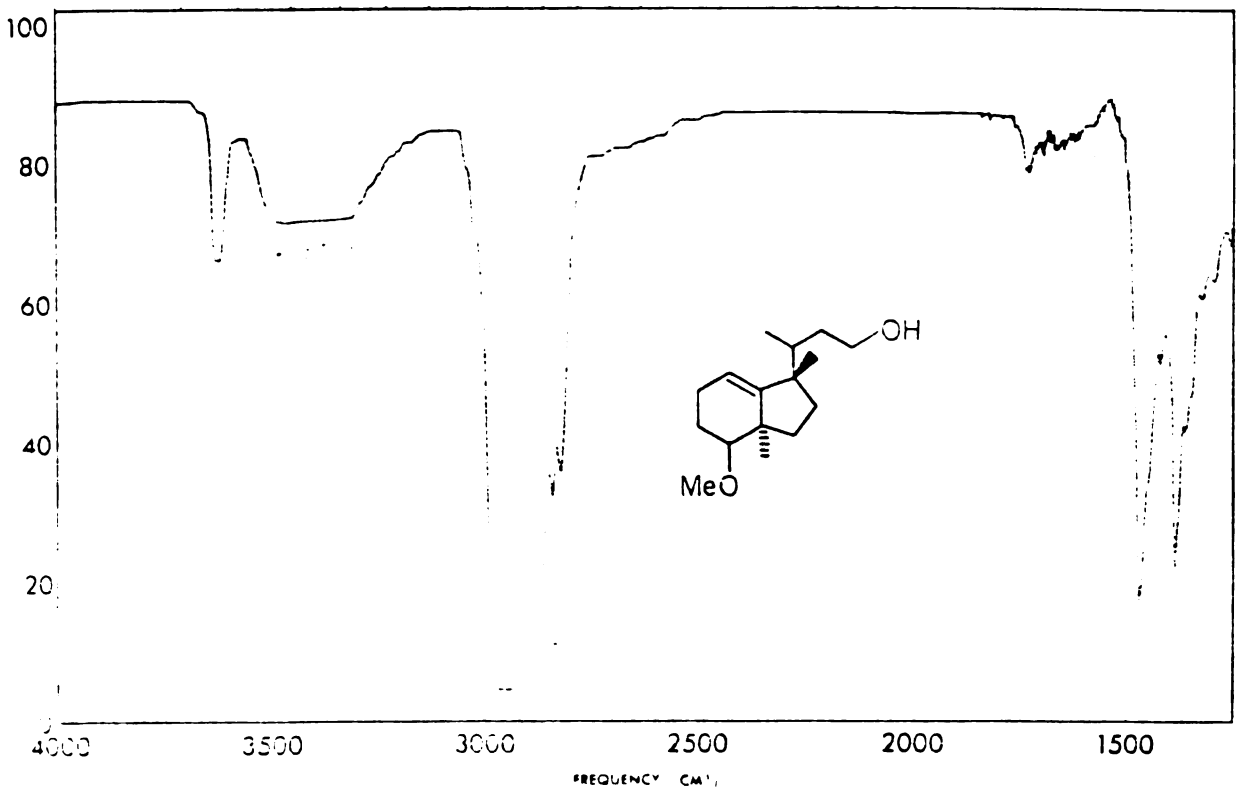


Figure 25. Carbon-13 NMR of 5b.



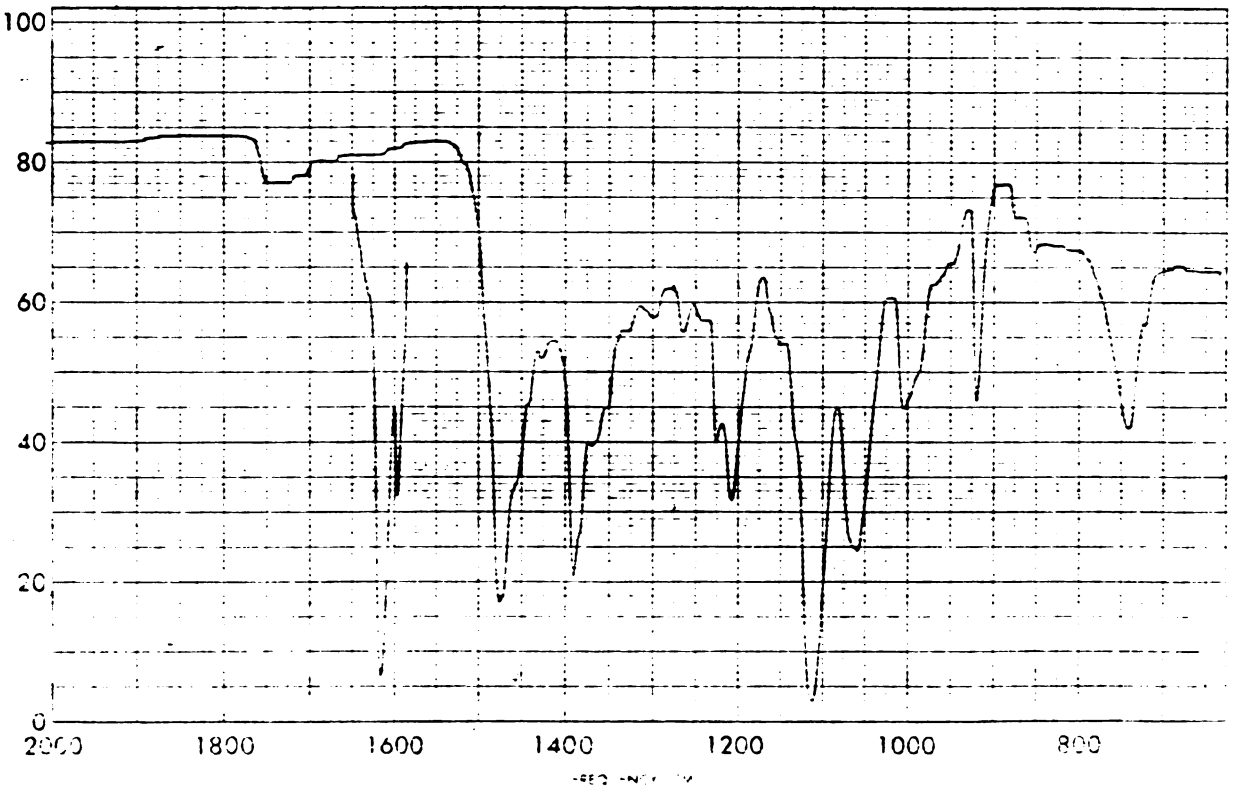


Figure 26. IR of 6.

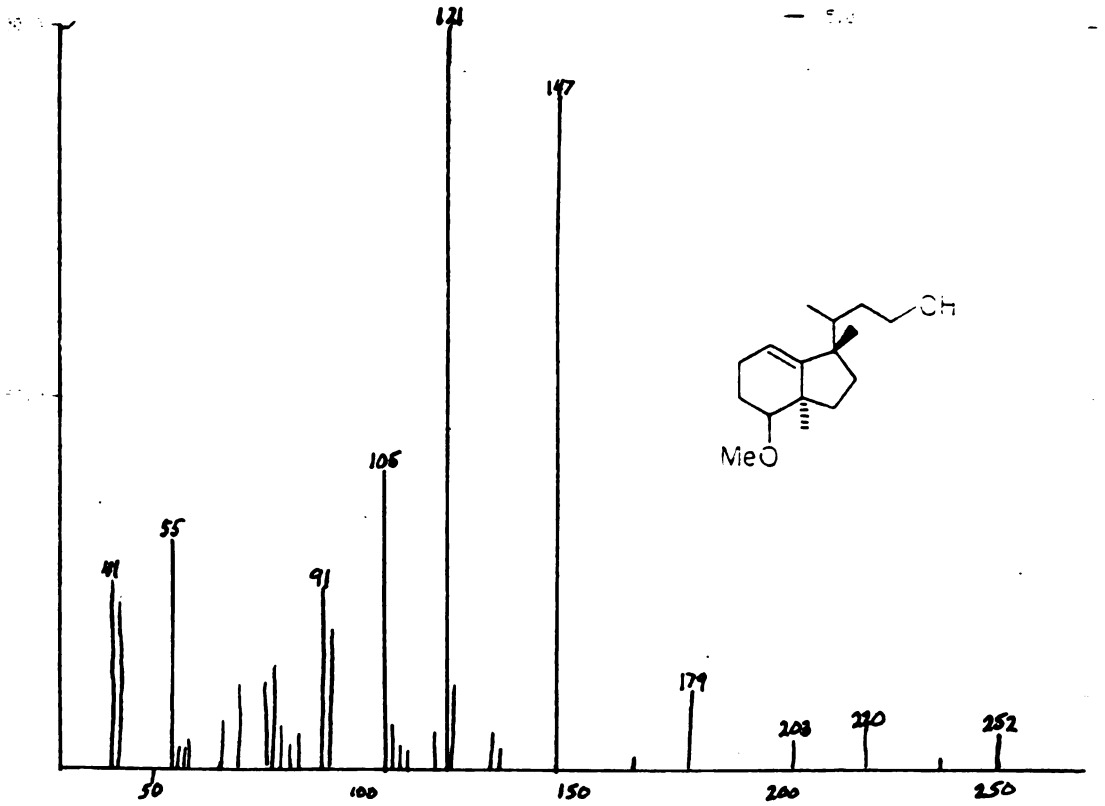


Figure 27. Mass spectrum of 6.

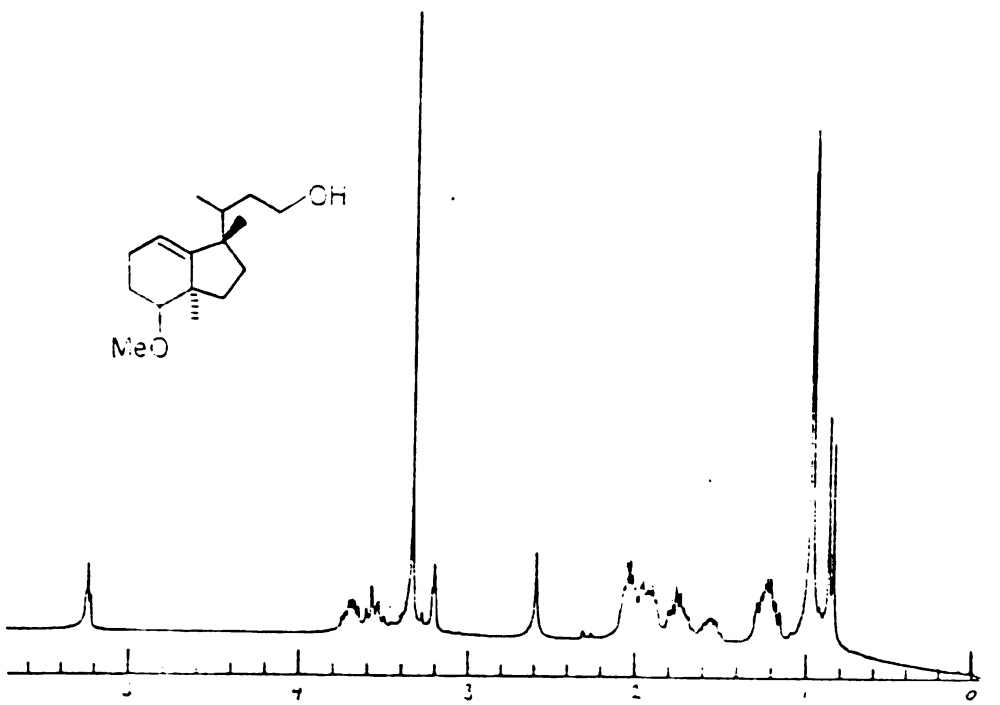


Figure 28. Proton NMR of 6.

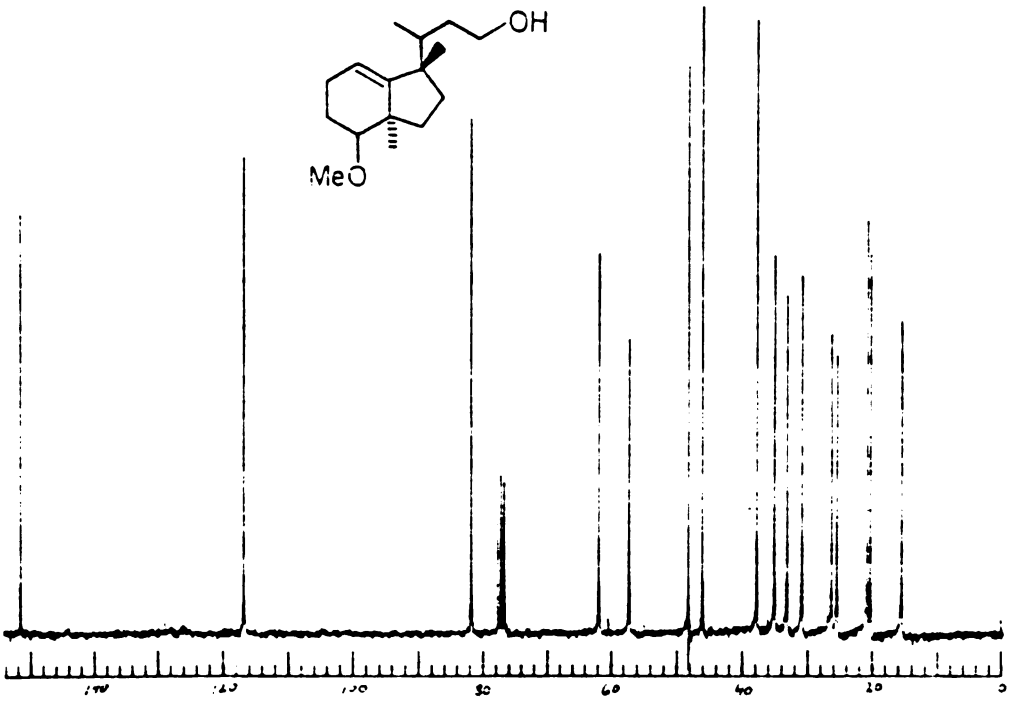


Figure 29. Carbon-13 NMR of 6.

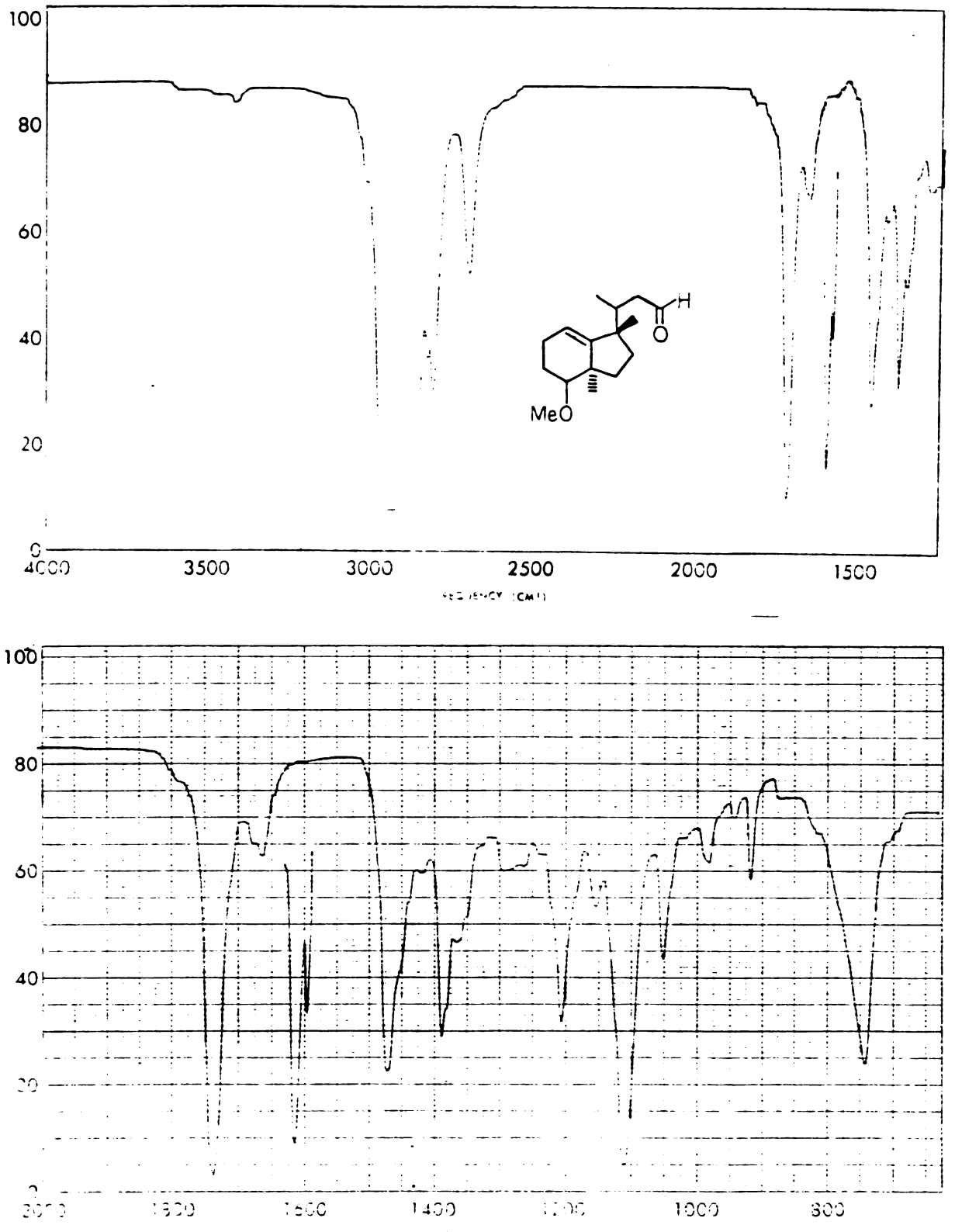


Figure 30. IR of 7.

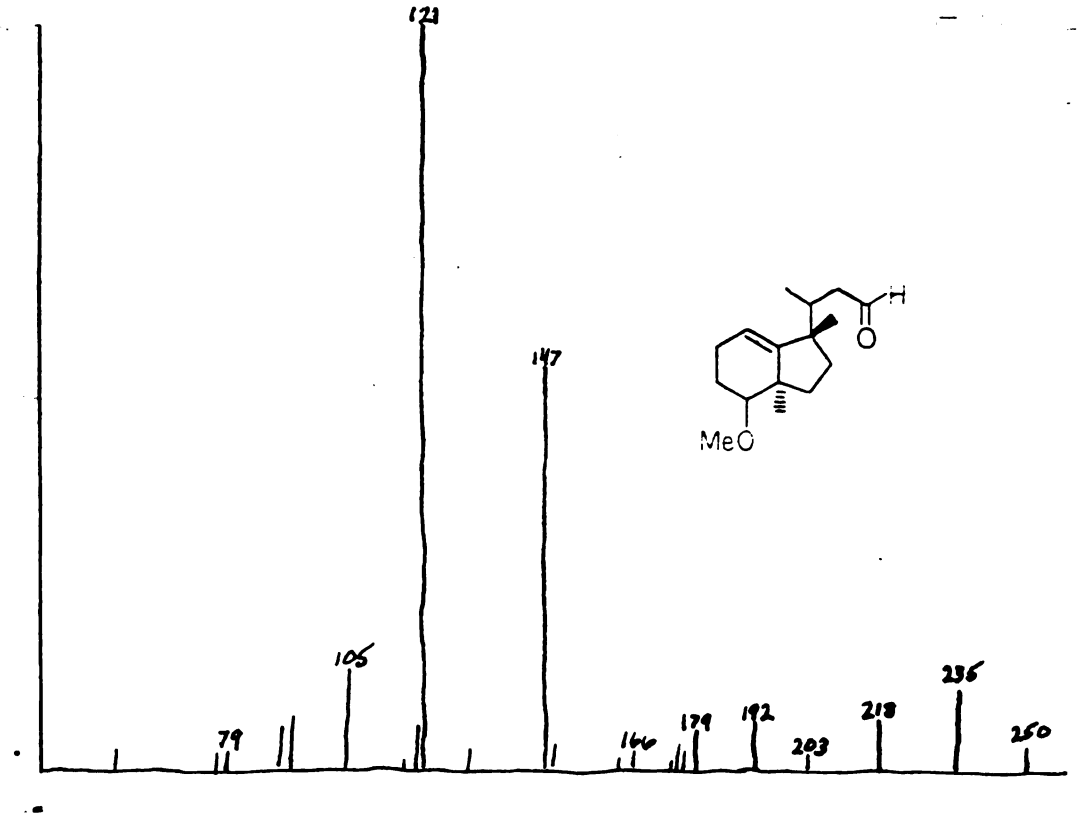


Figure 31. Mass spectrum of 7.

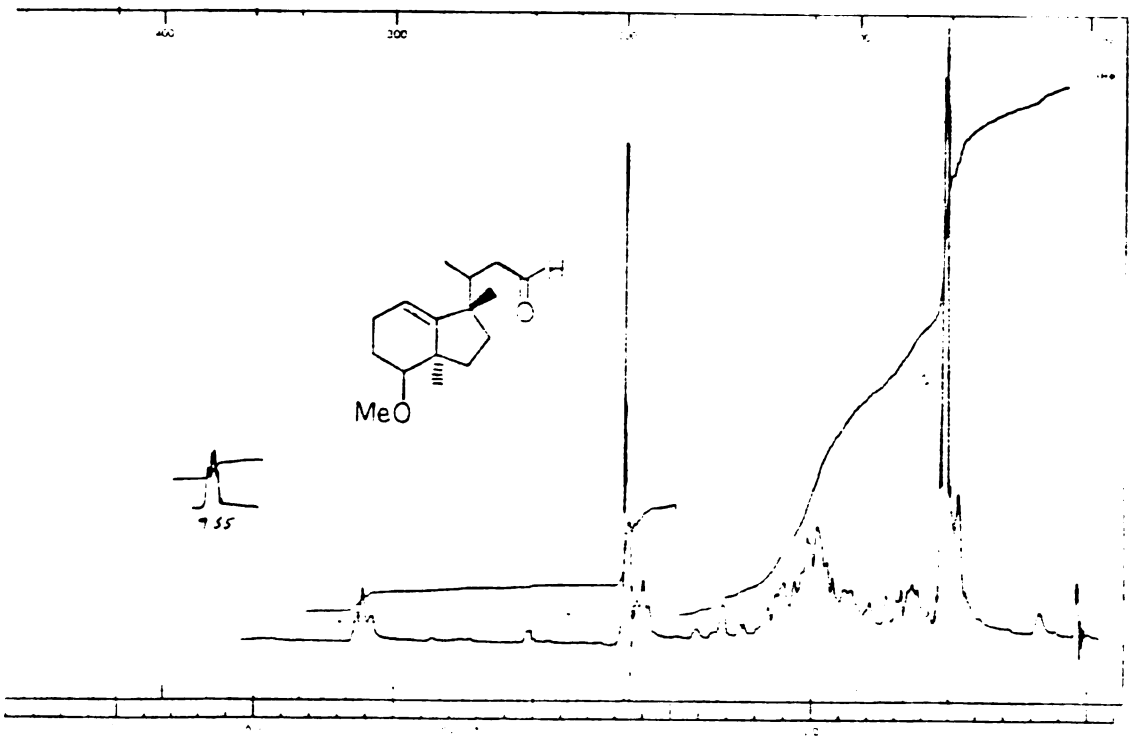
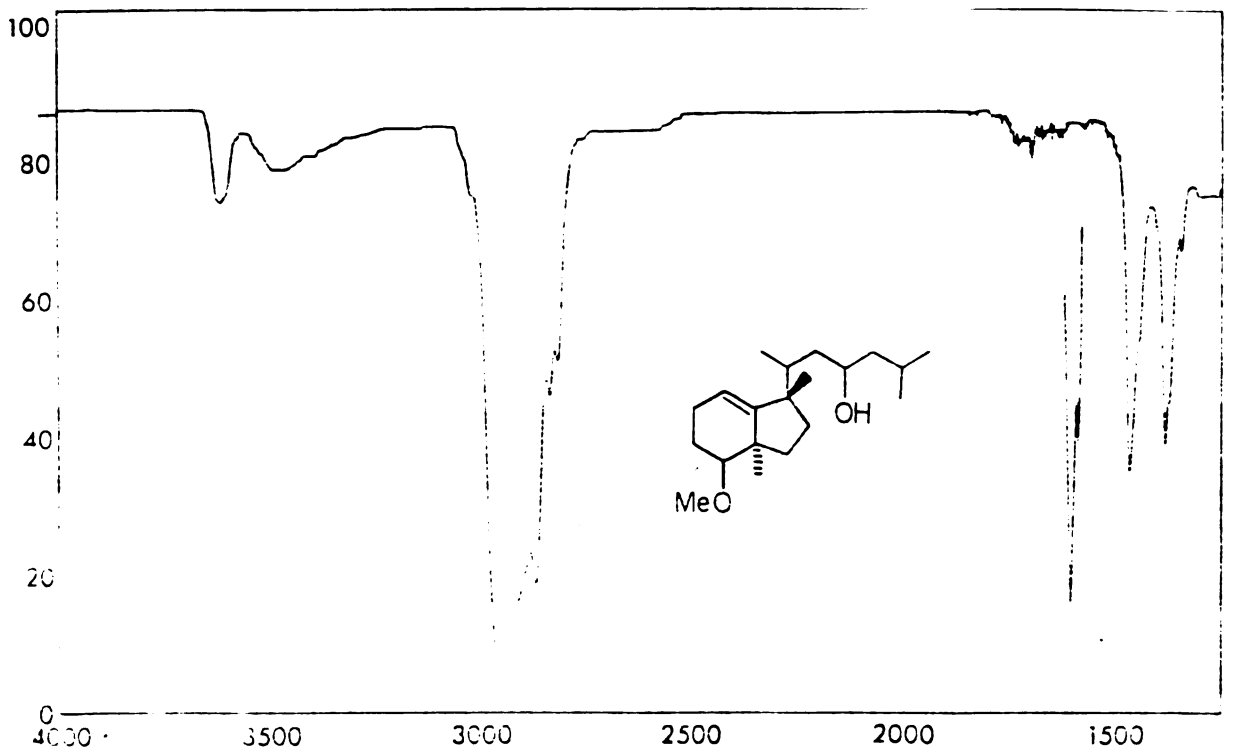


Figure 32. Proton NMR of 7.



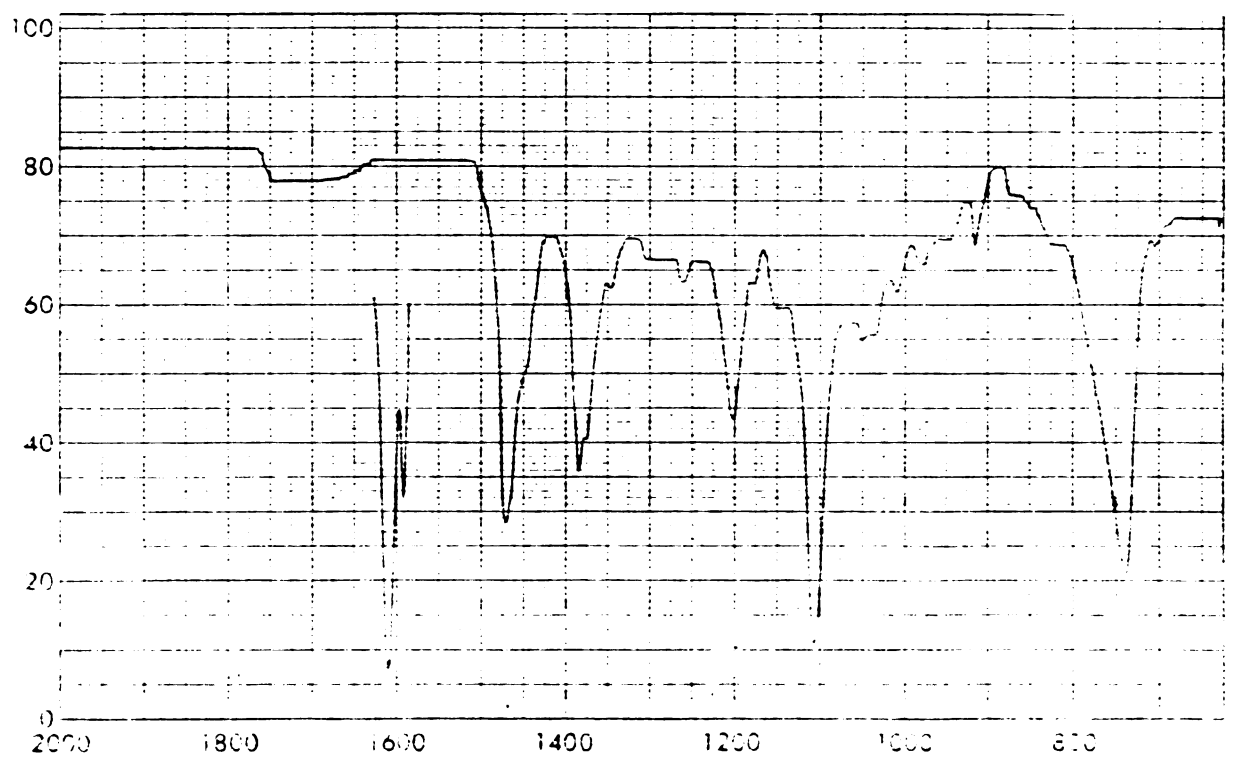


Figure 33. IR of 8.

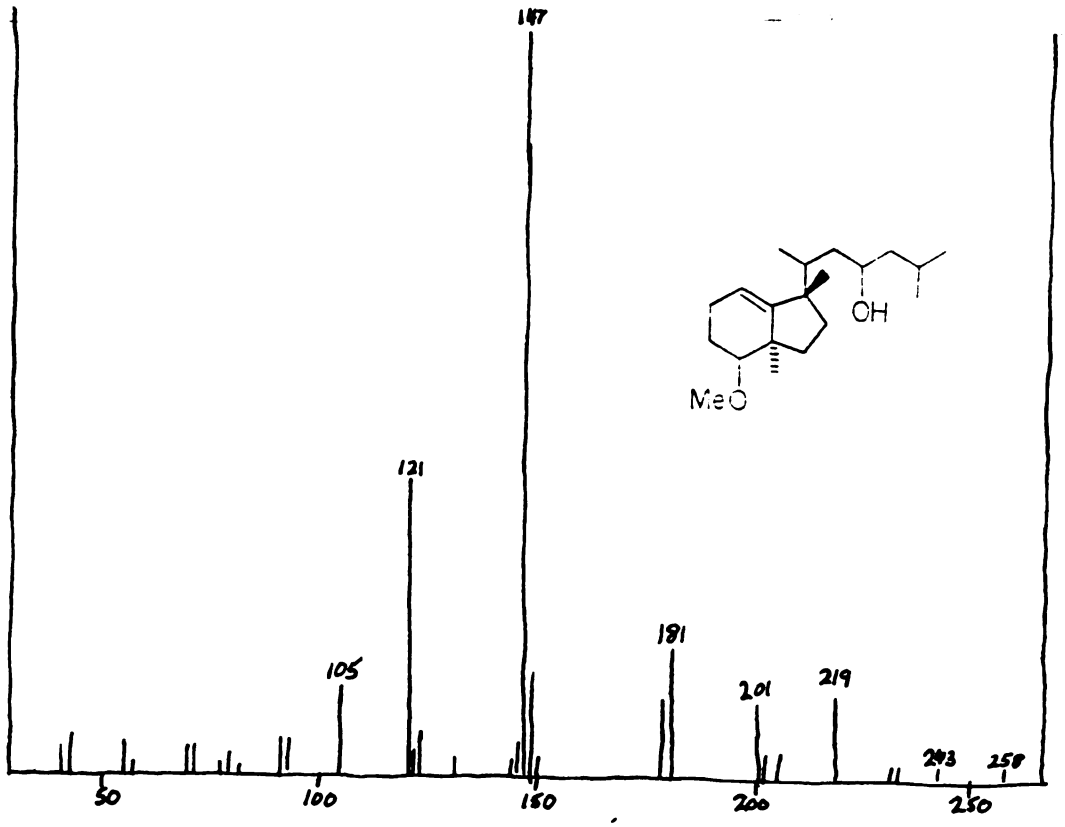


Figure 34. Mass spectrum of 8.

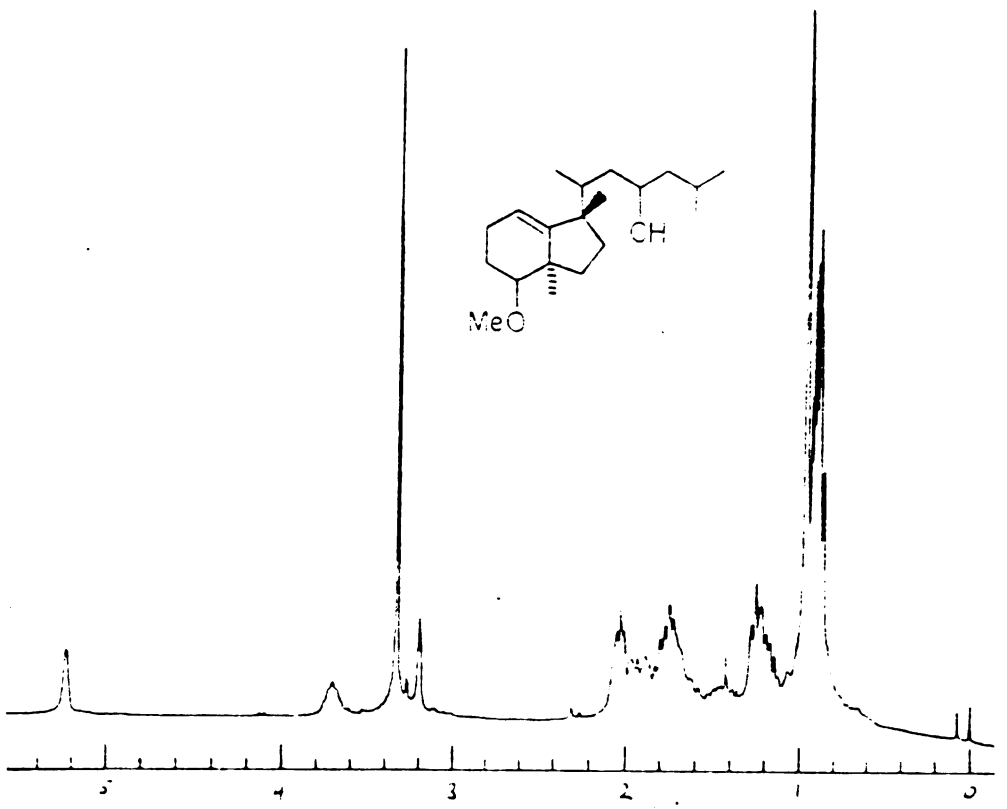


Figure 35. Proton NMR of 8.

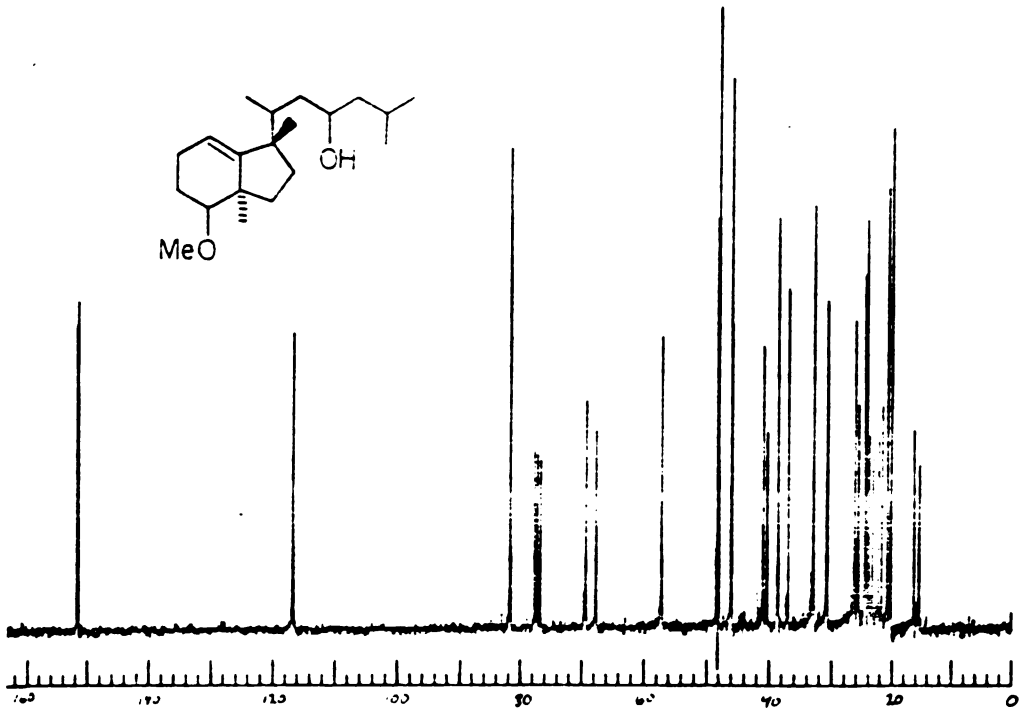


Figure 36. Carbon-13 NMR of 8.

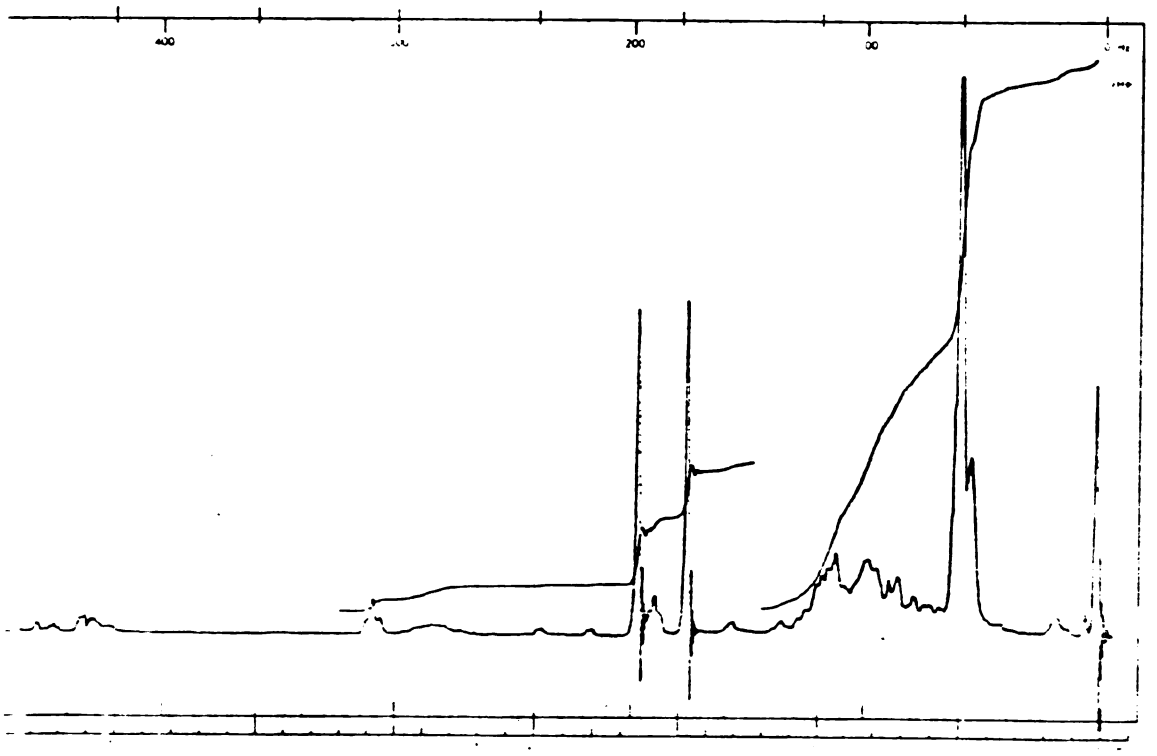


Figure 37. Proton NMR of 9.

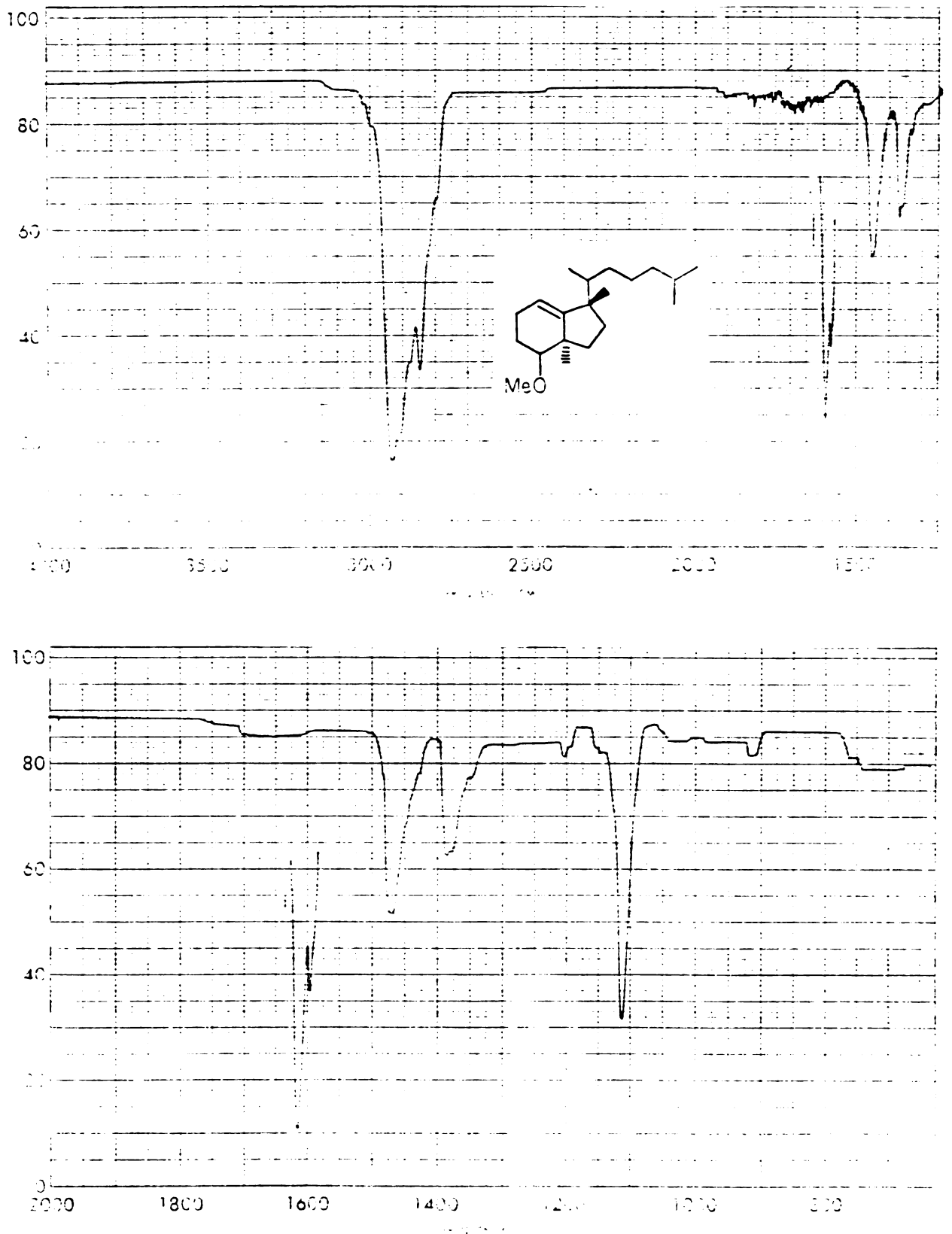


Figure 38. IR of 10.

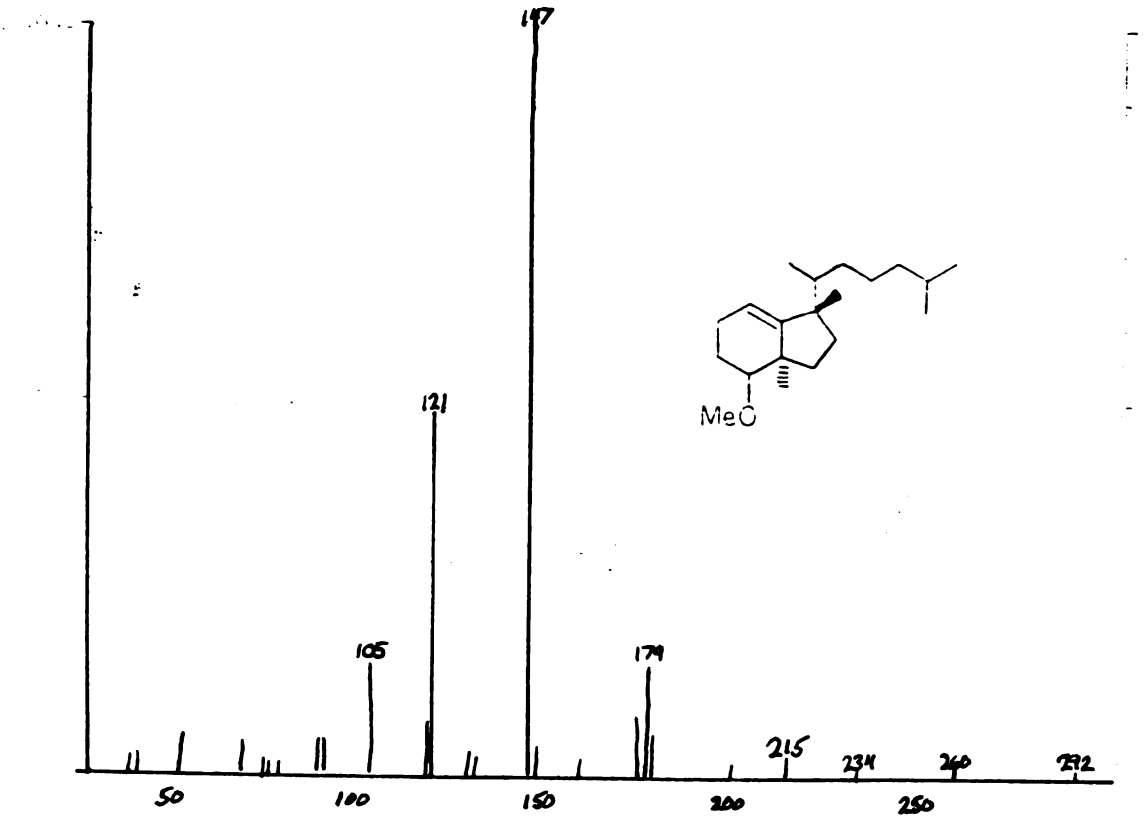


Figure 39. Mass spectrum of 10.

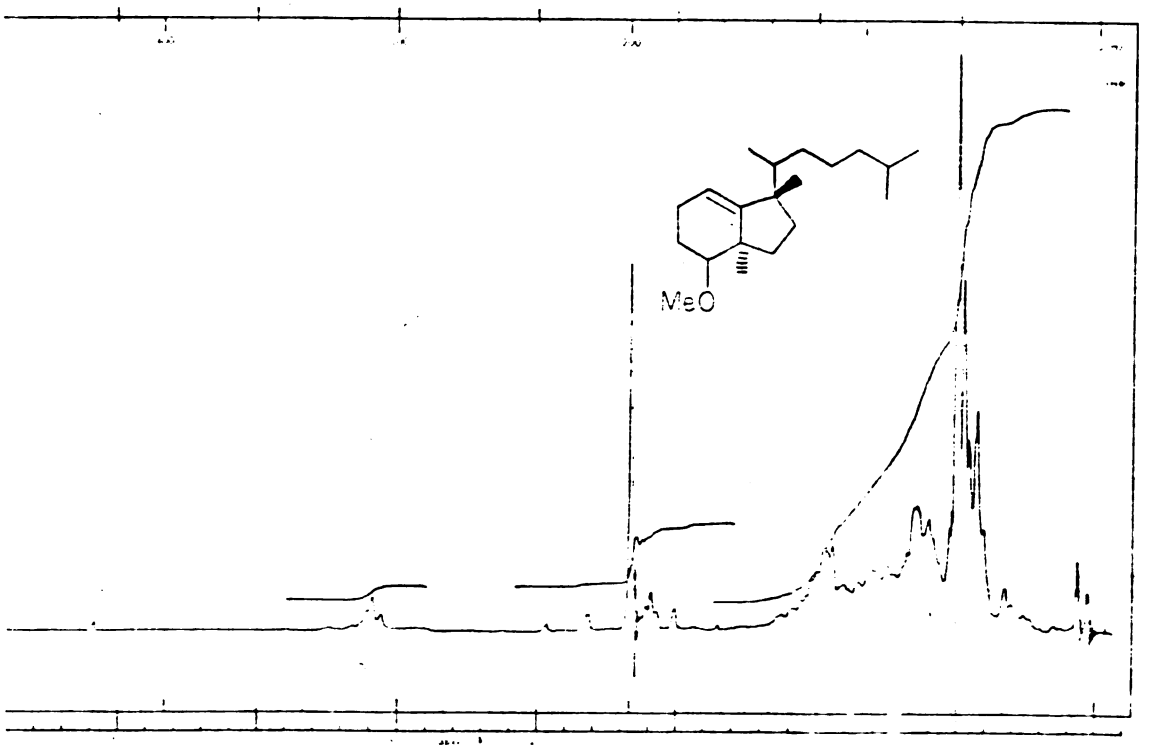


Figure 40. Proton NMR of 10.

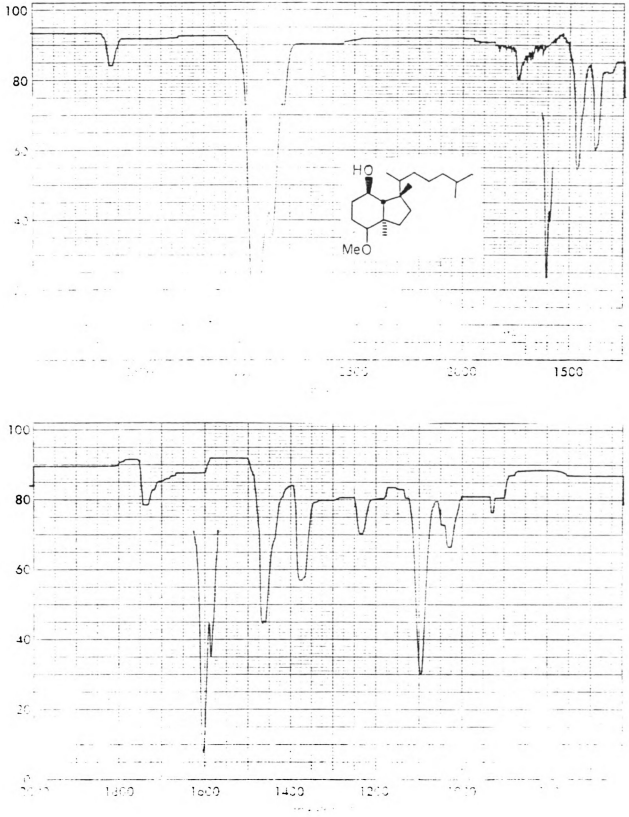


Figure 41. IR of 11.

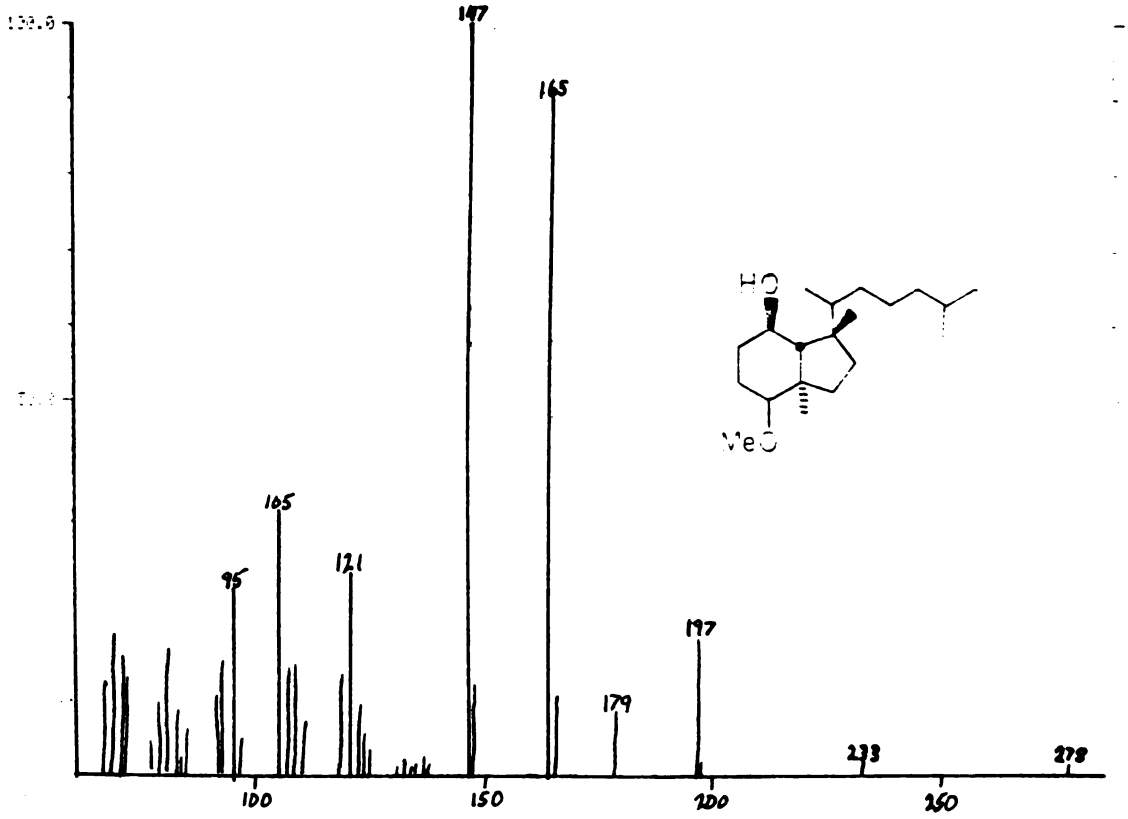


Figure 42. Mass spectrum of 11.

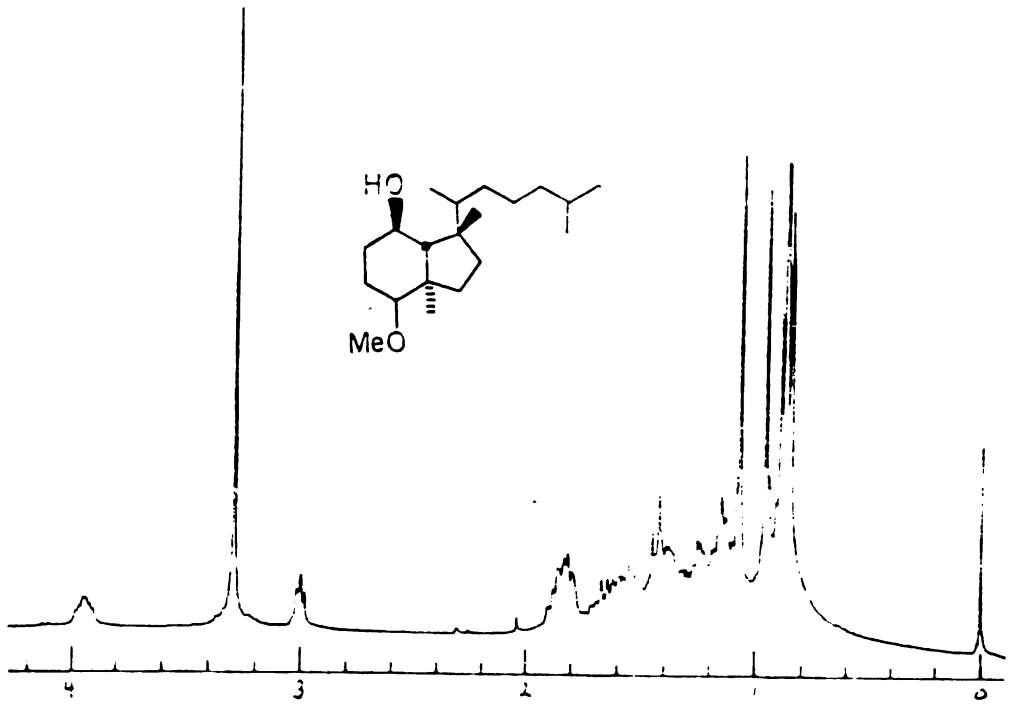


Figure 43. Proton NMR of 11.

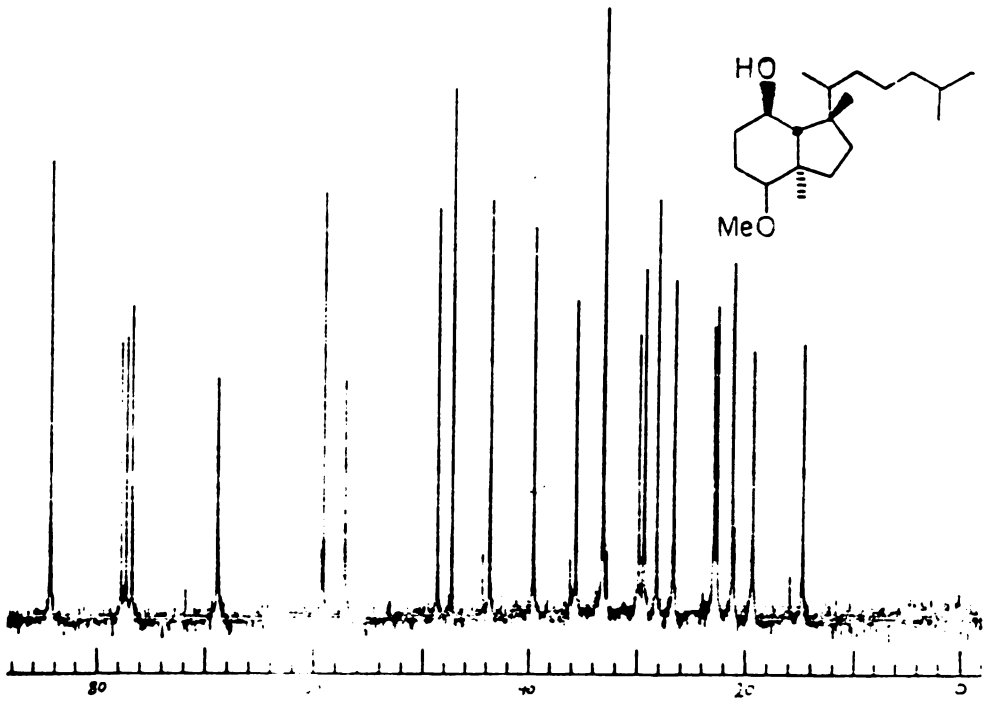


Figure 44. Carbon-13 NMR of 11.

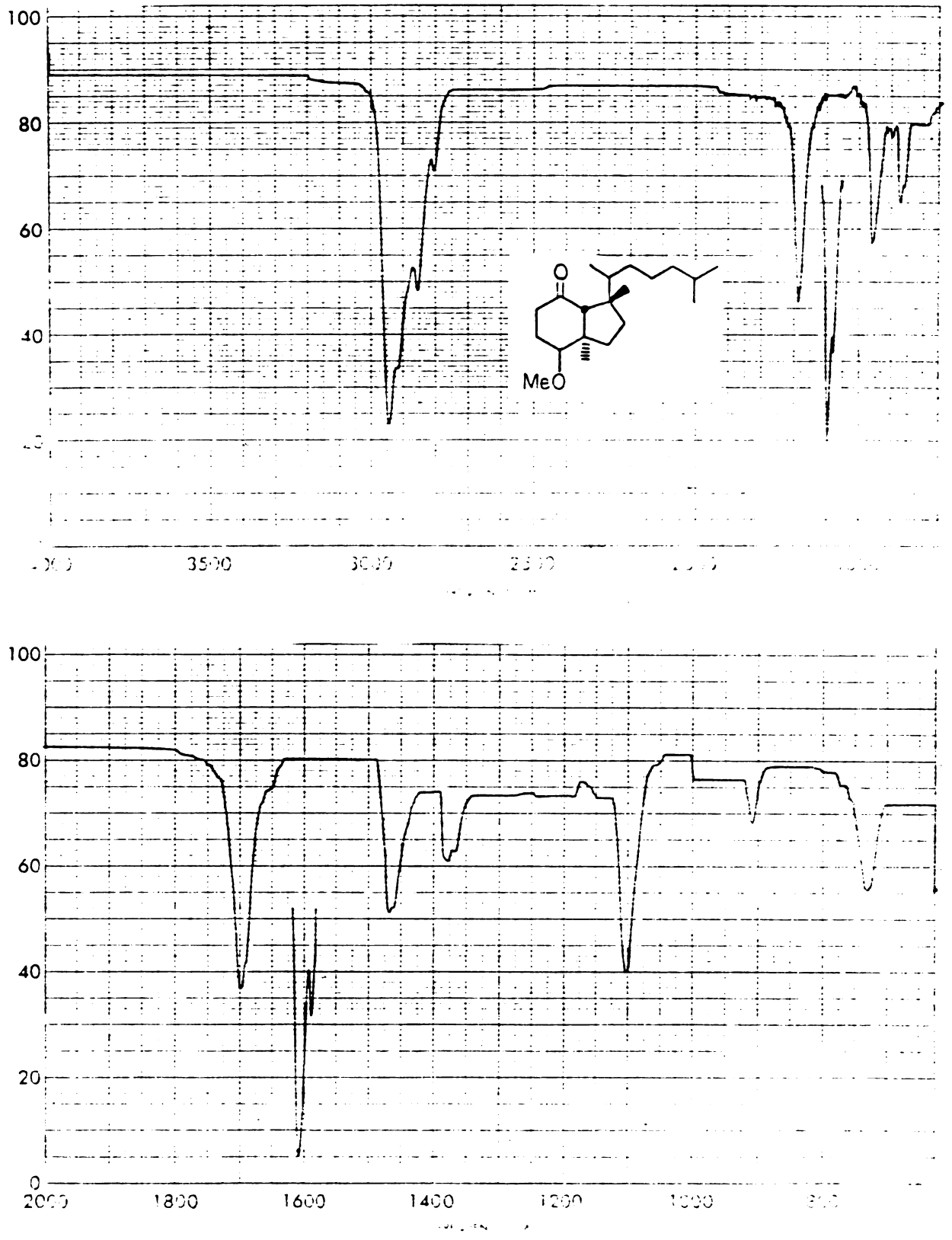


Figure 45. IR of 12.

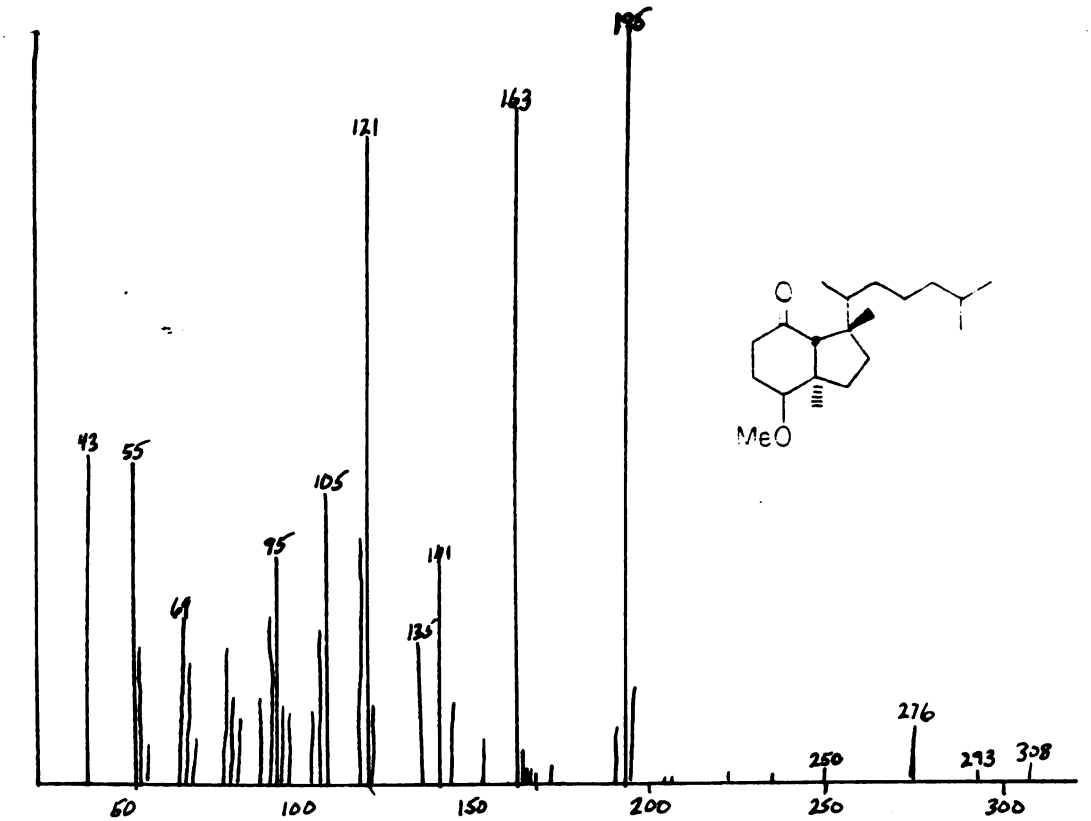


Figure 46. Mass spectrum of 12.

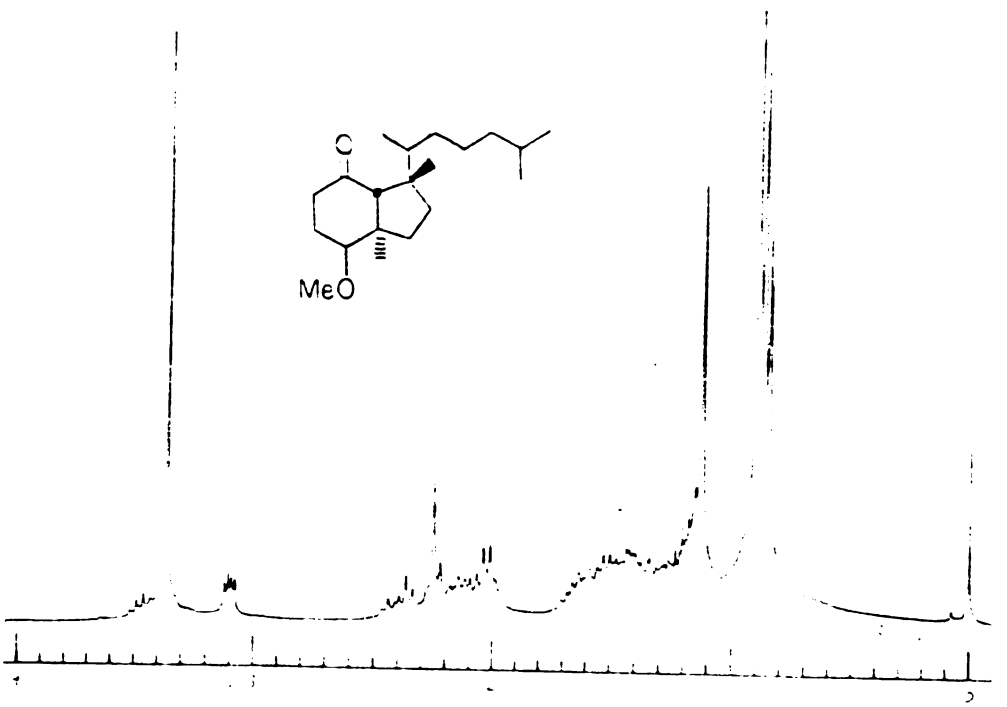


Figure 47. Proton NMR of 12.

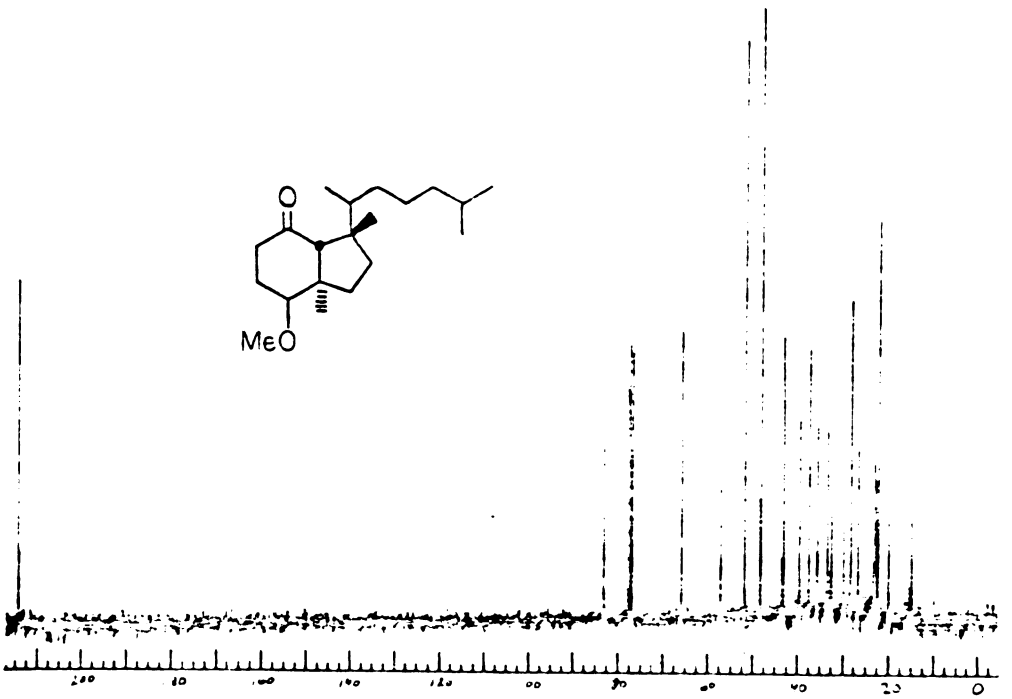
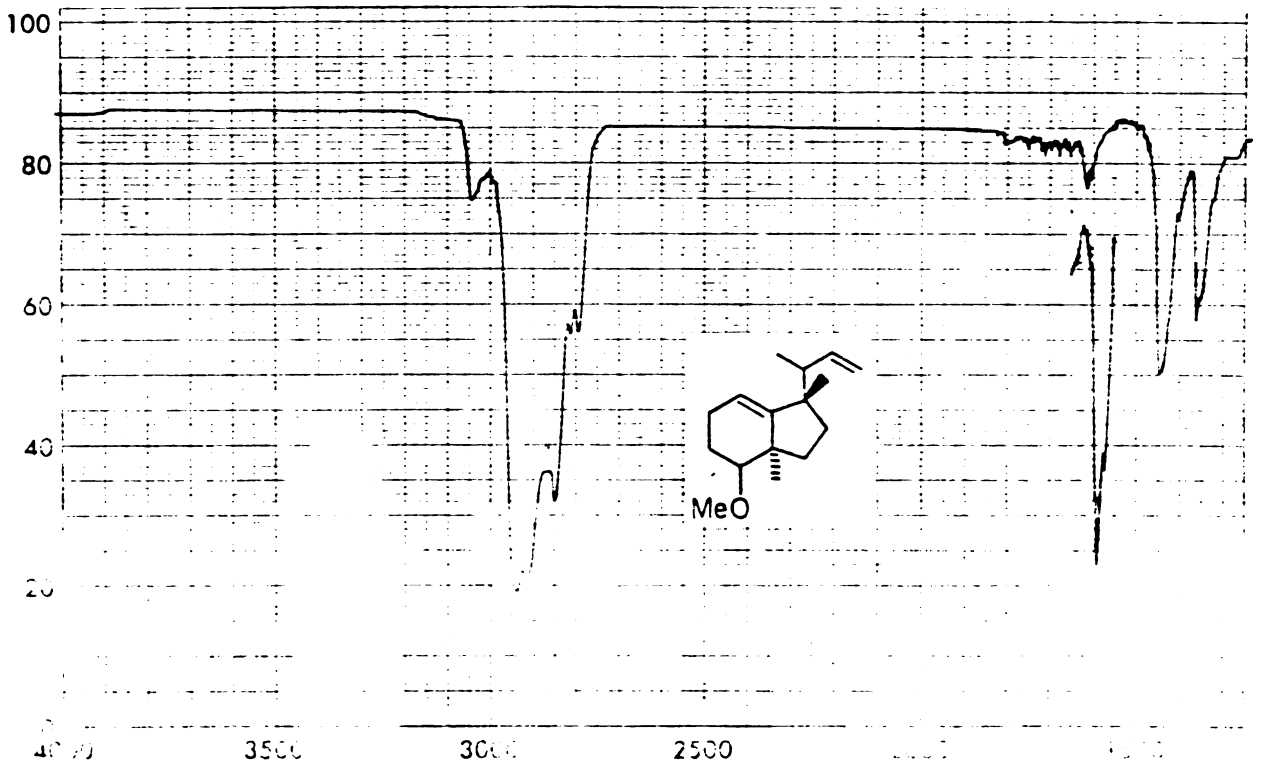


Figure 48. Carbon-13 NMR of 12.



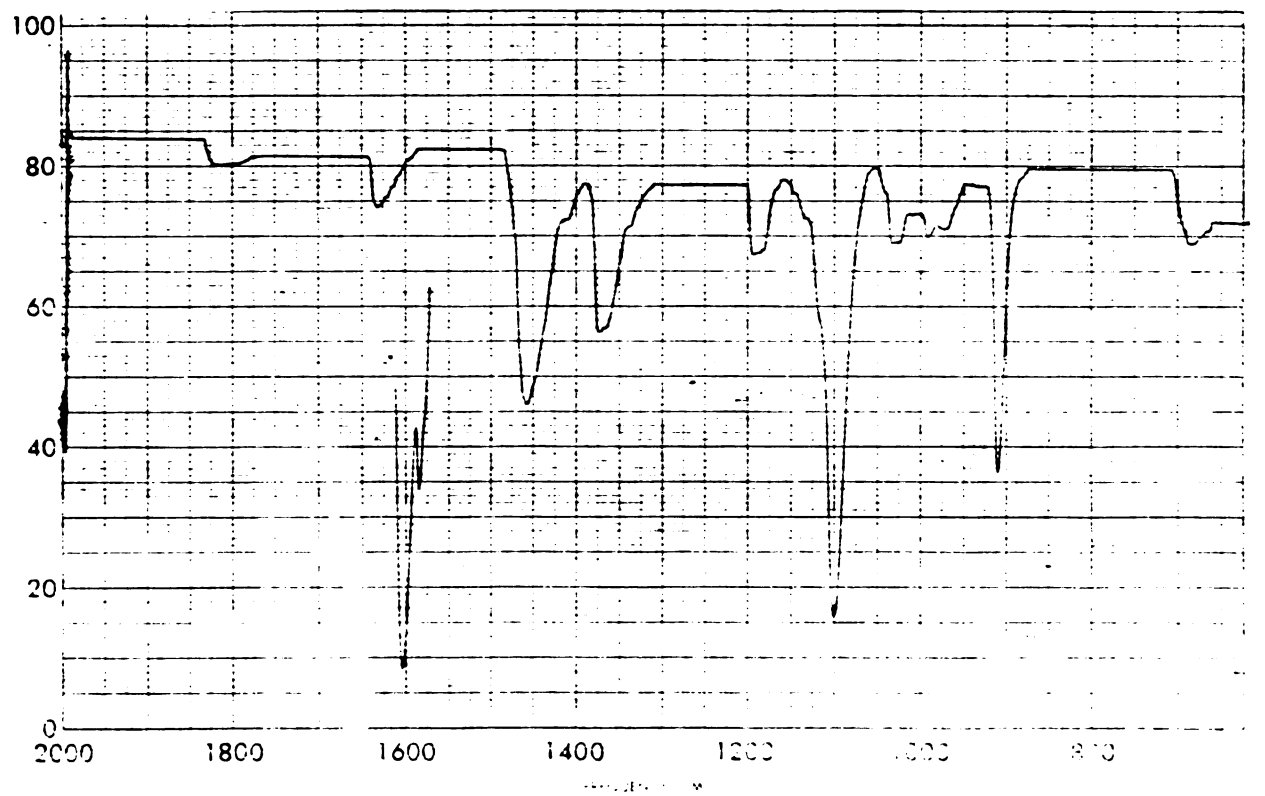


Figure 49. IR of 13.

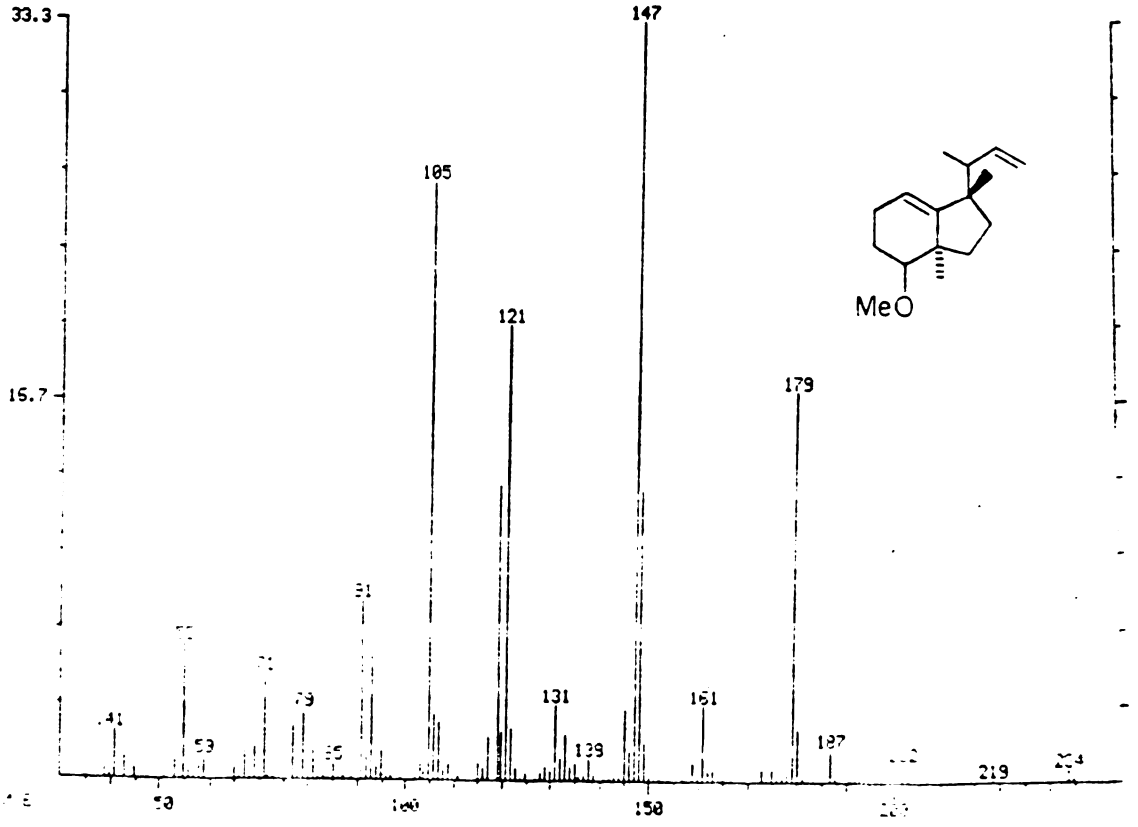


Figure 50. Mass spectrum of 13.

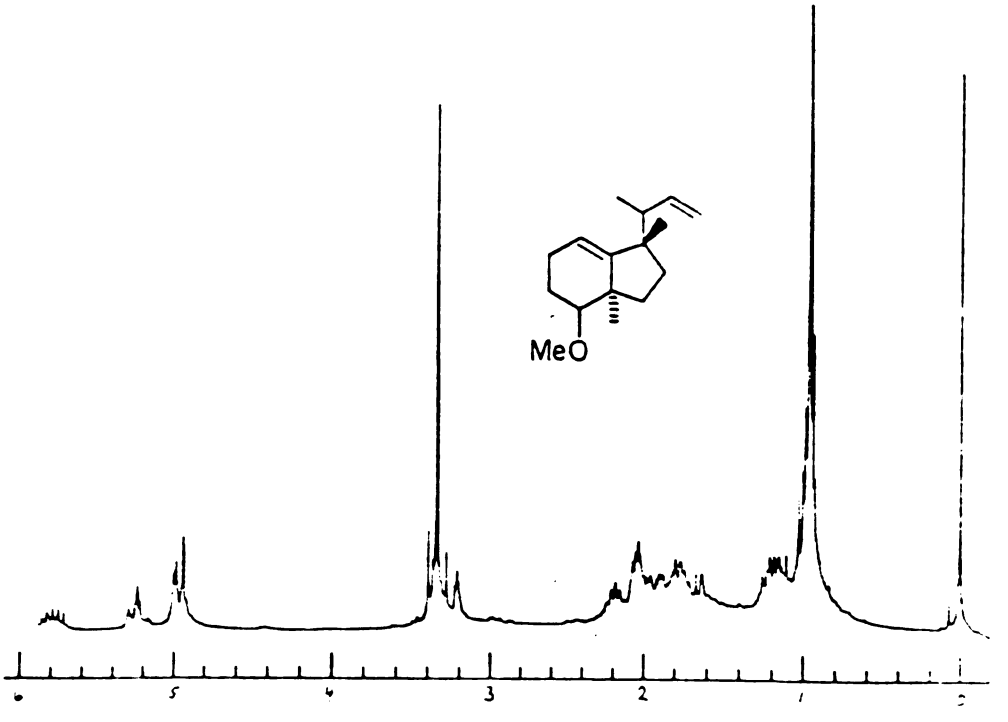


Figure 51. Proton NMR of 13.

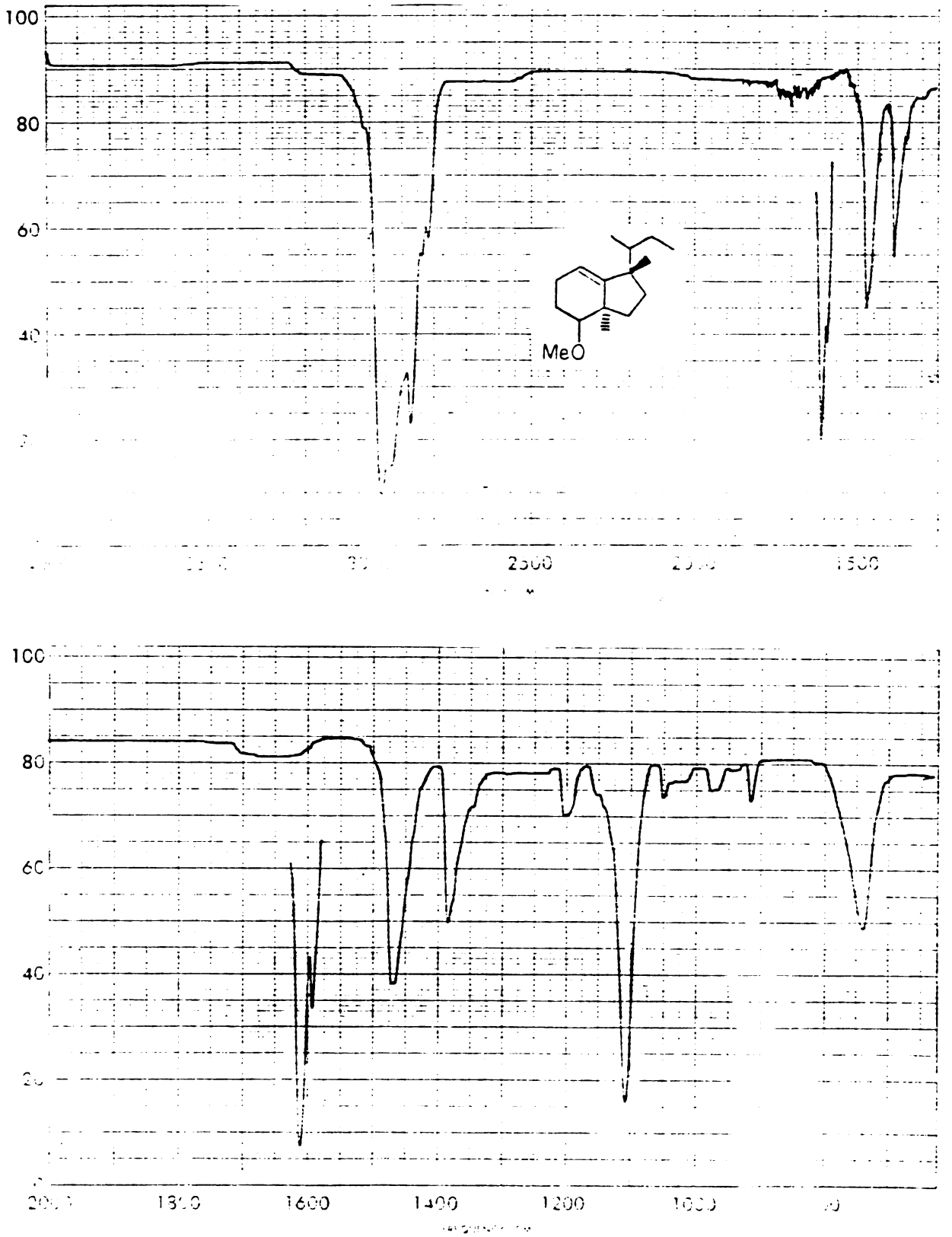


Figure 52. IR of 14.

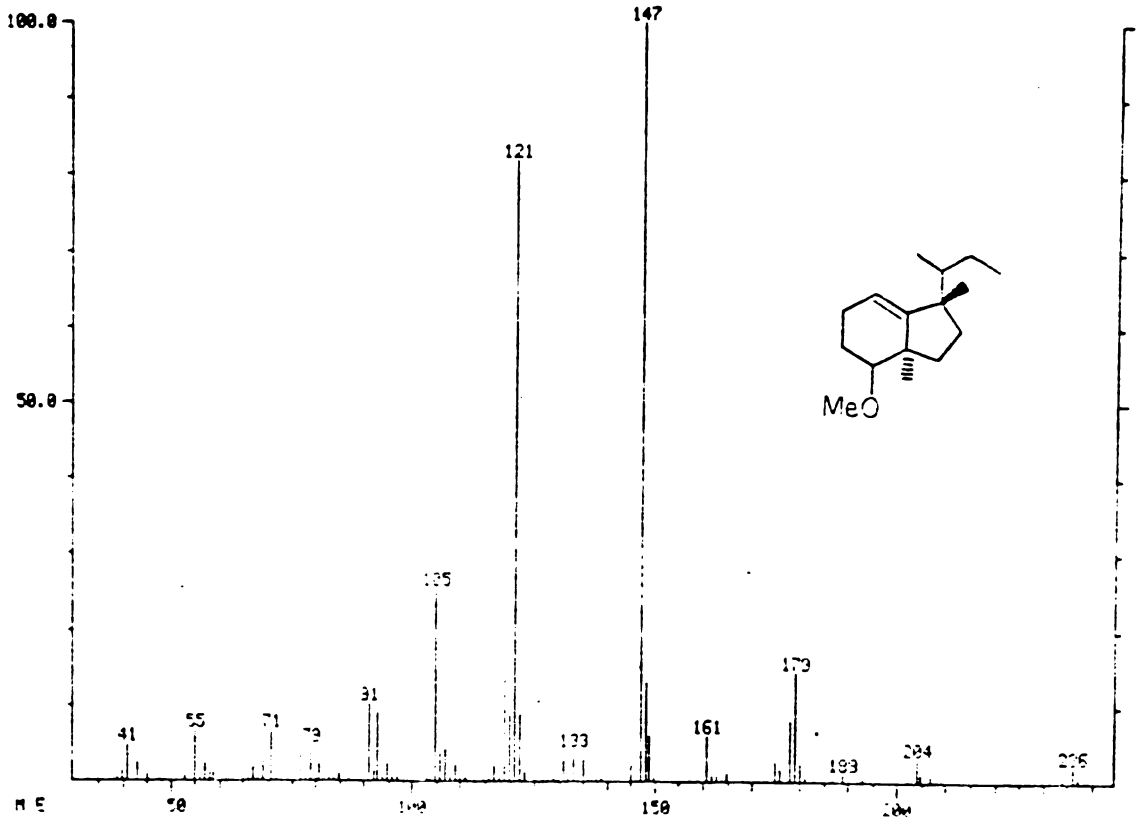


Figure 53. Mass spectrum of 14.

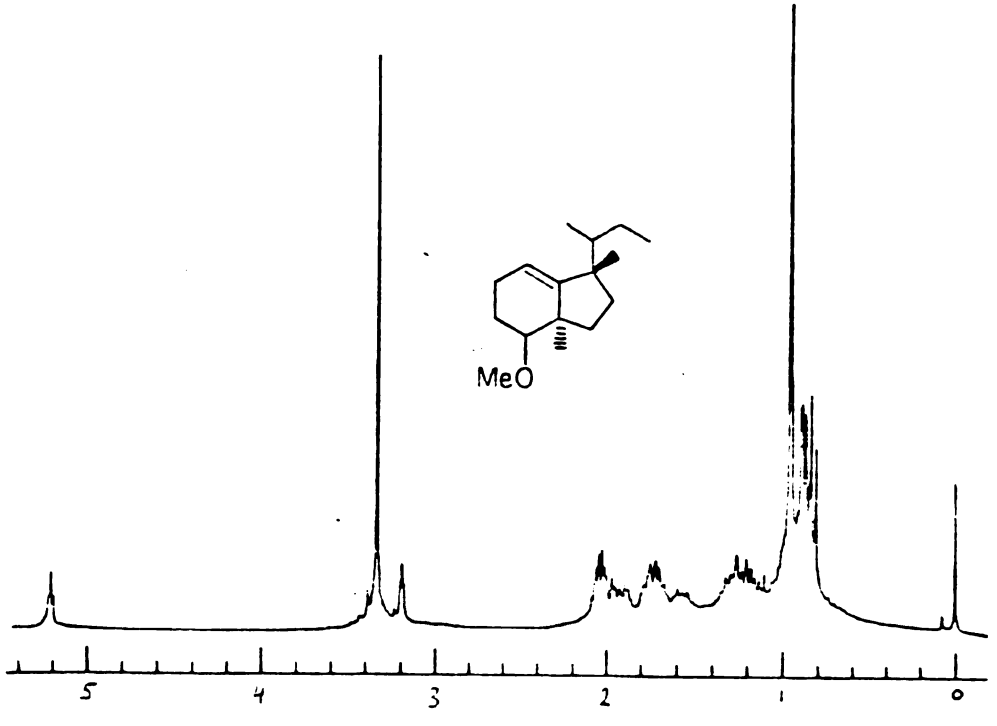


Figure 54. Proton NMR of 14.

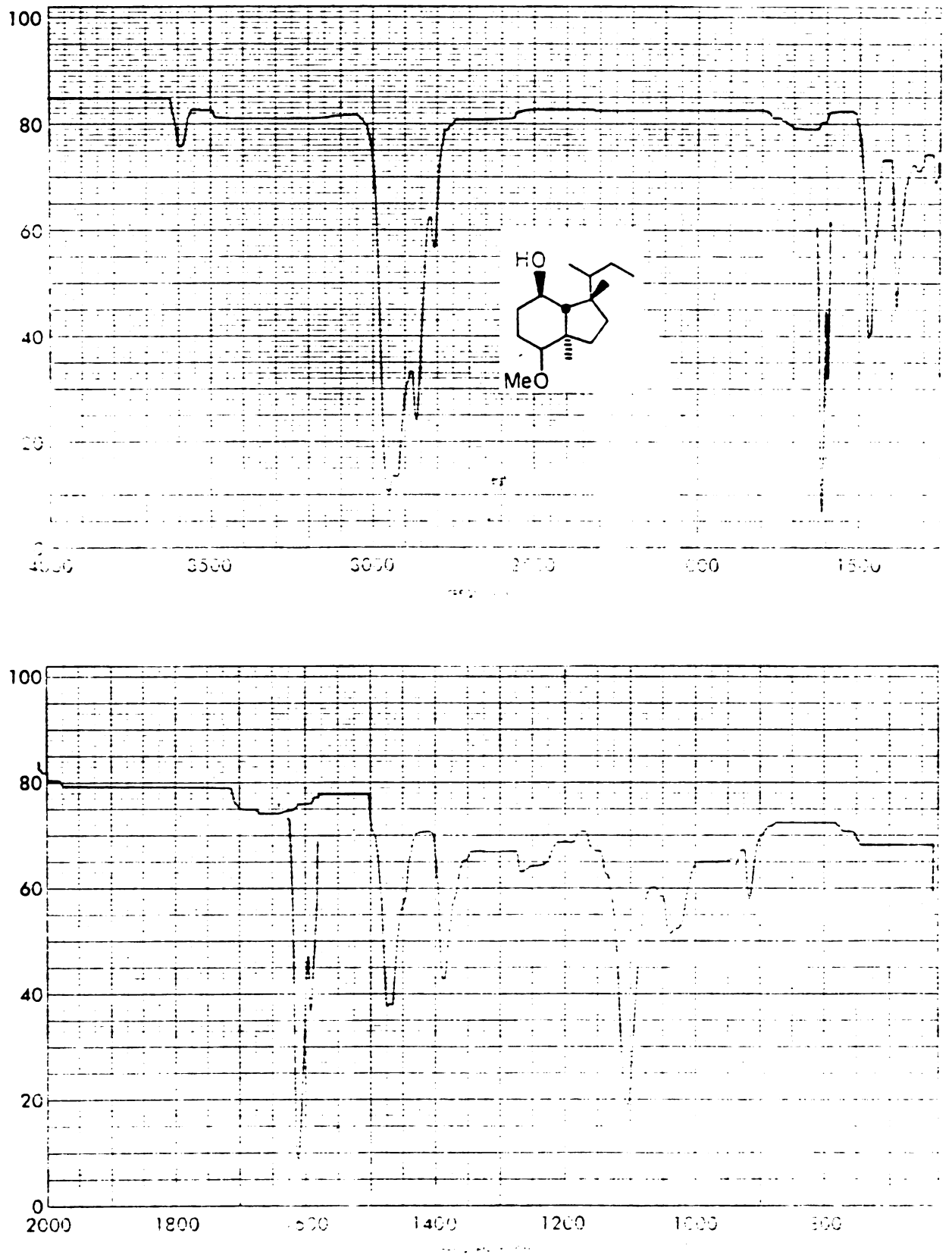


Figure 55. IR of 15.

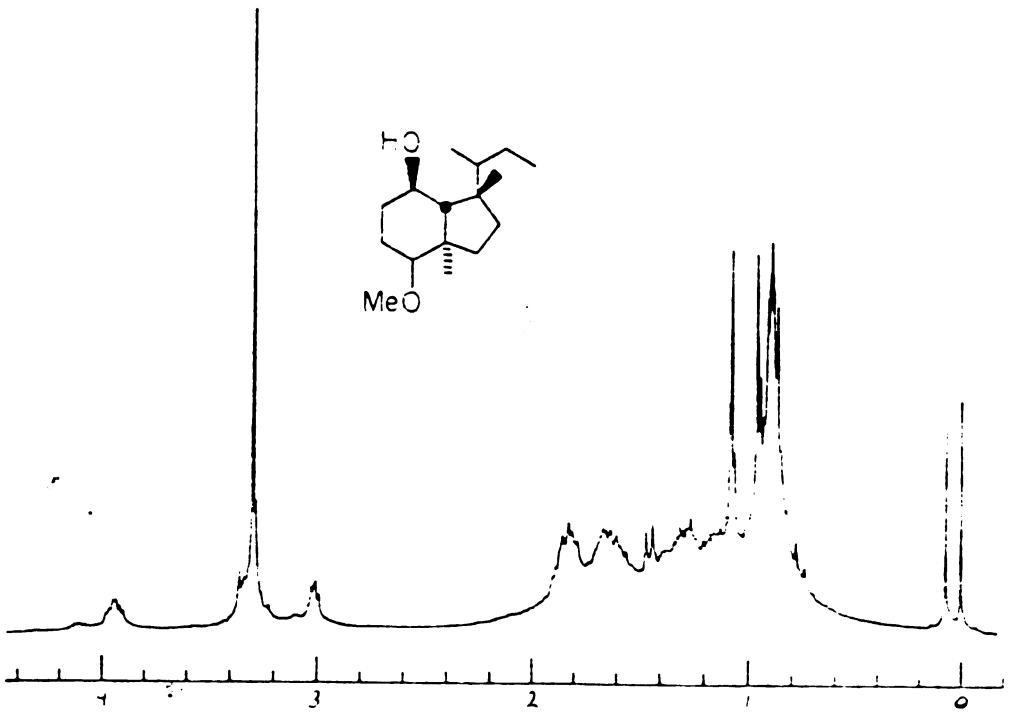
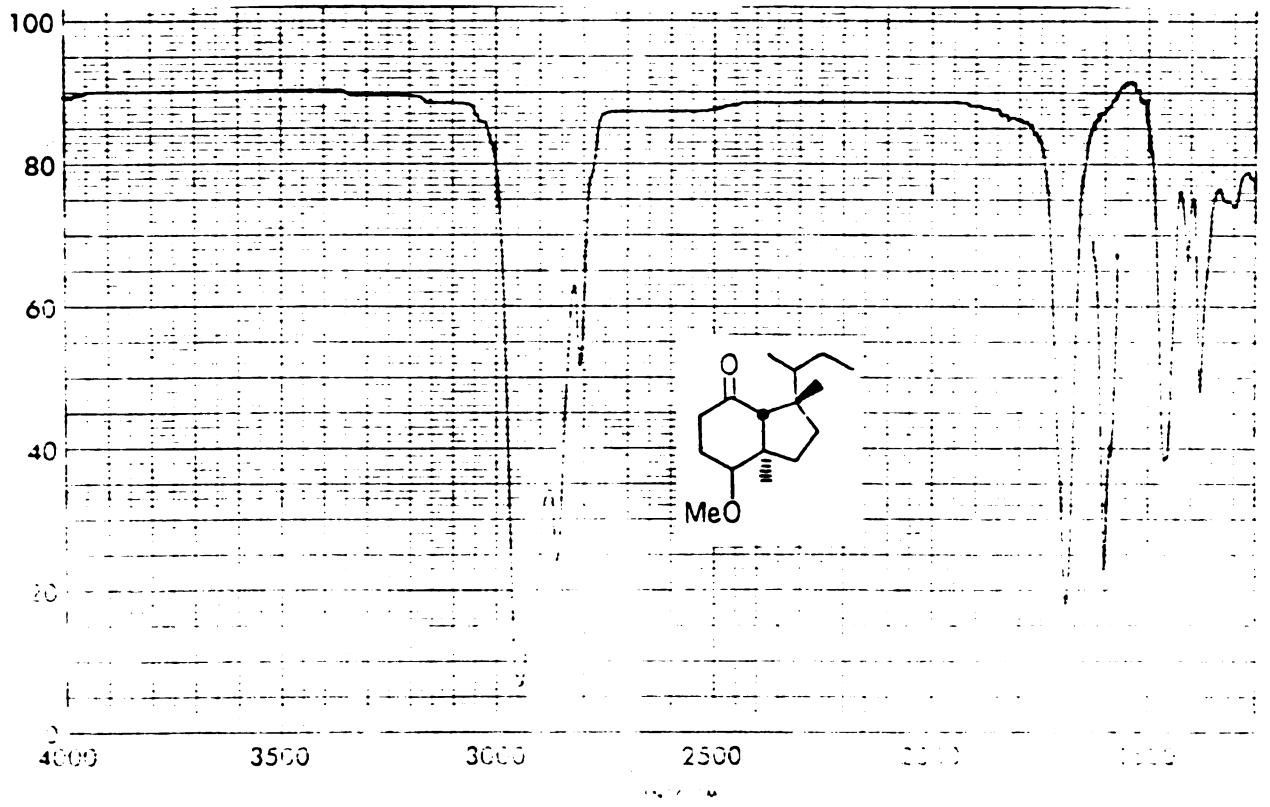


Figure 56. Proton NMR of 15.



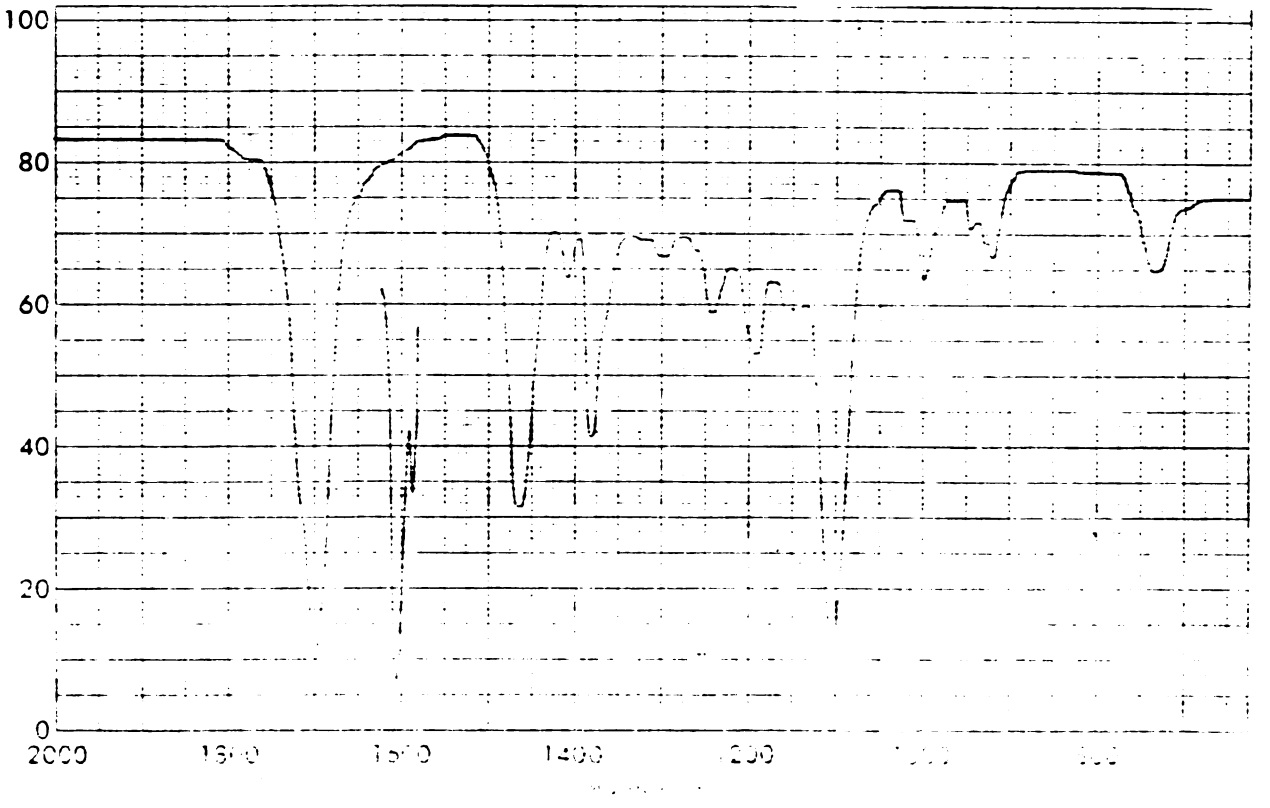


Figure 57. IR of 16.

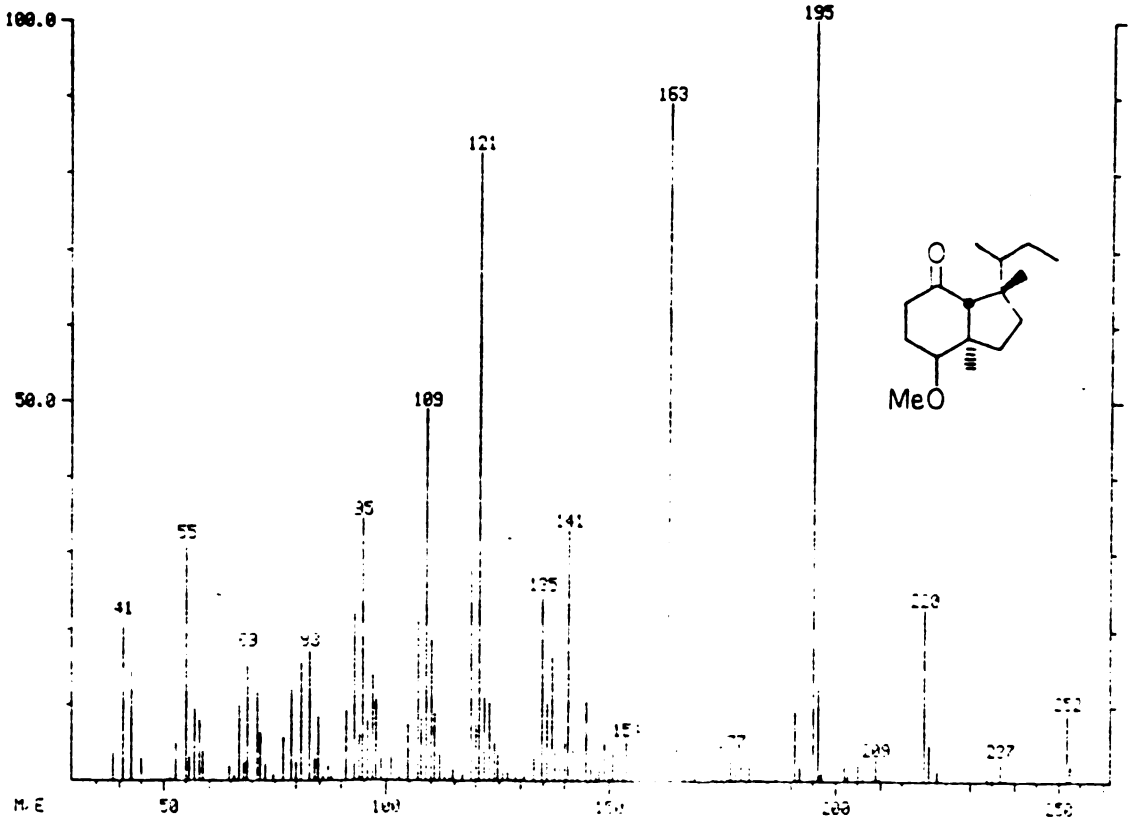


Figure 58. Mass spectrum of 16.

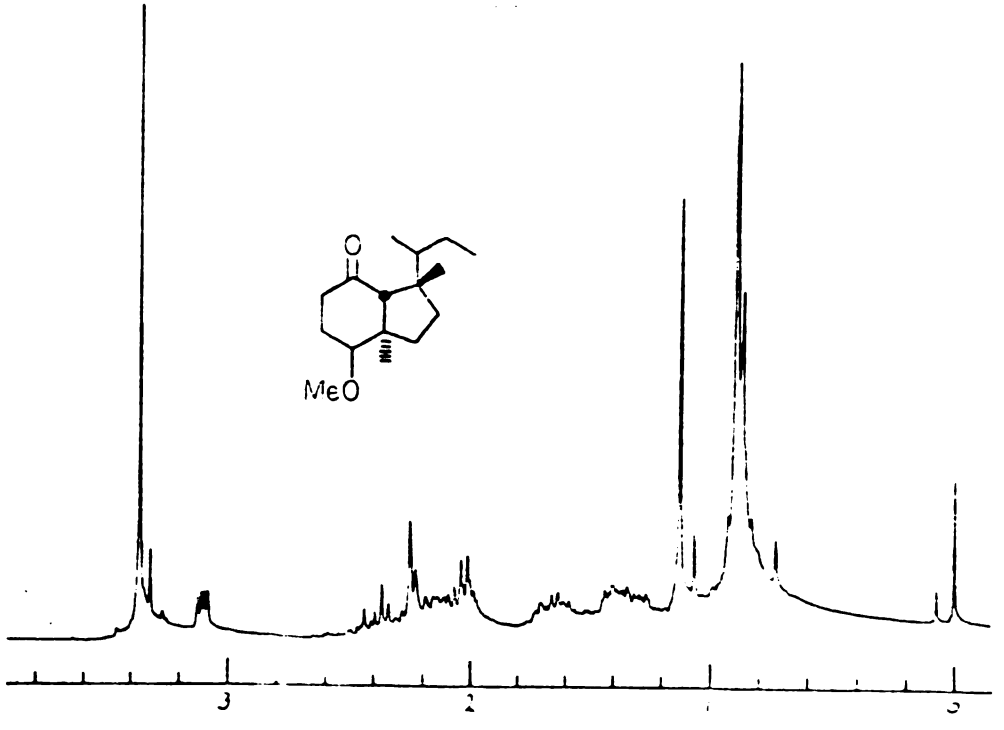
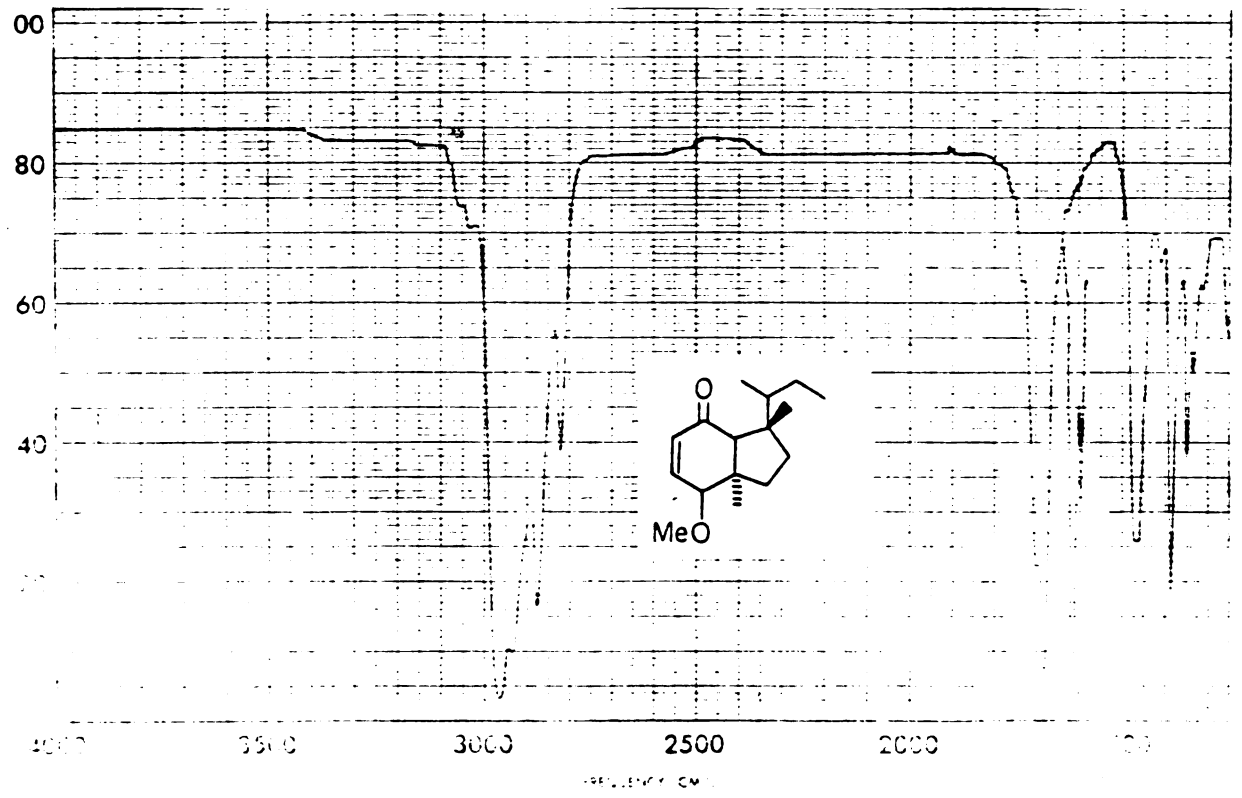


Figure 59. Proton NMR of 16.



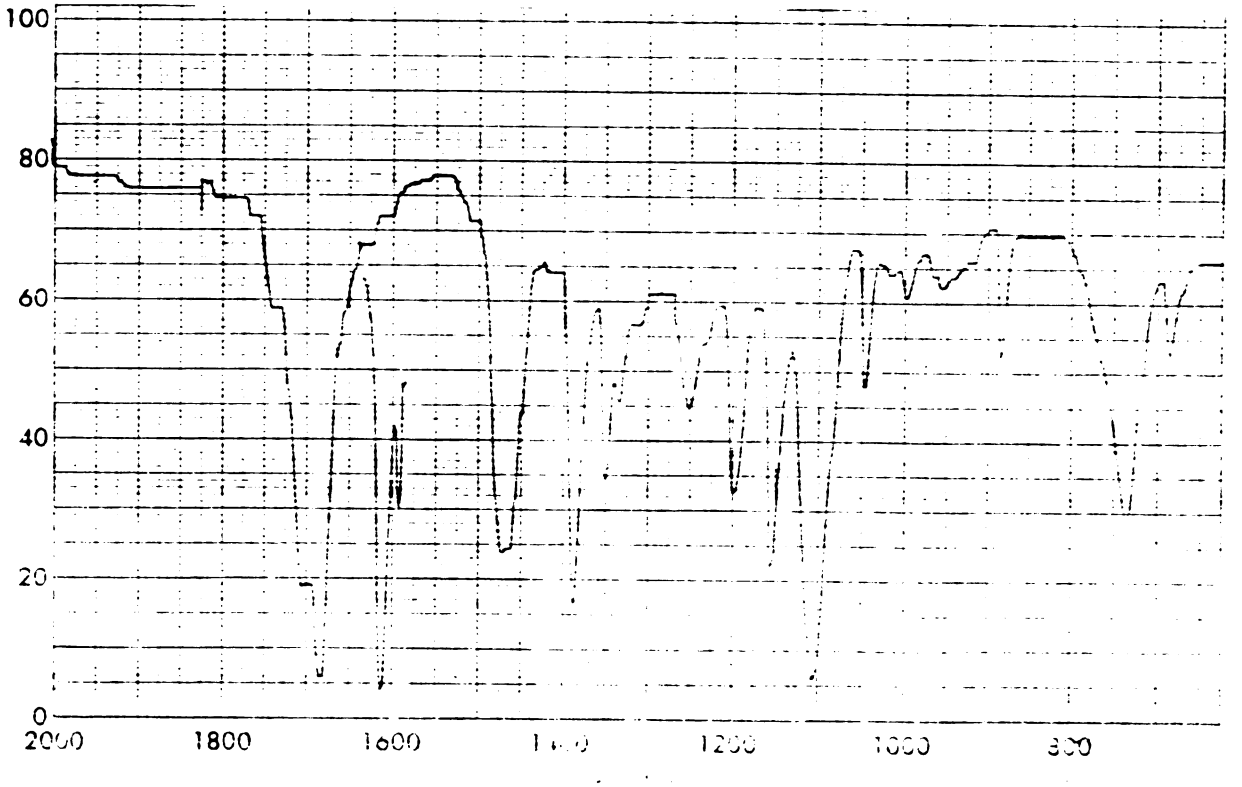


Figure 60. IR of 16 and 17.

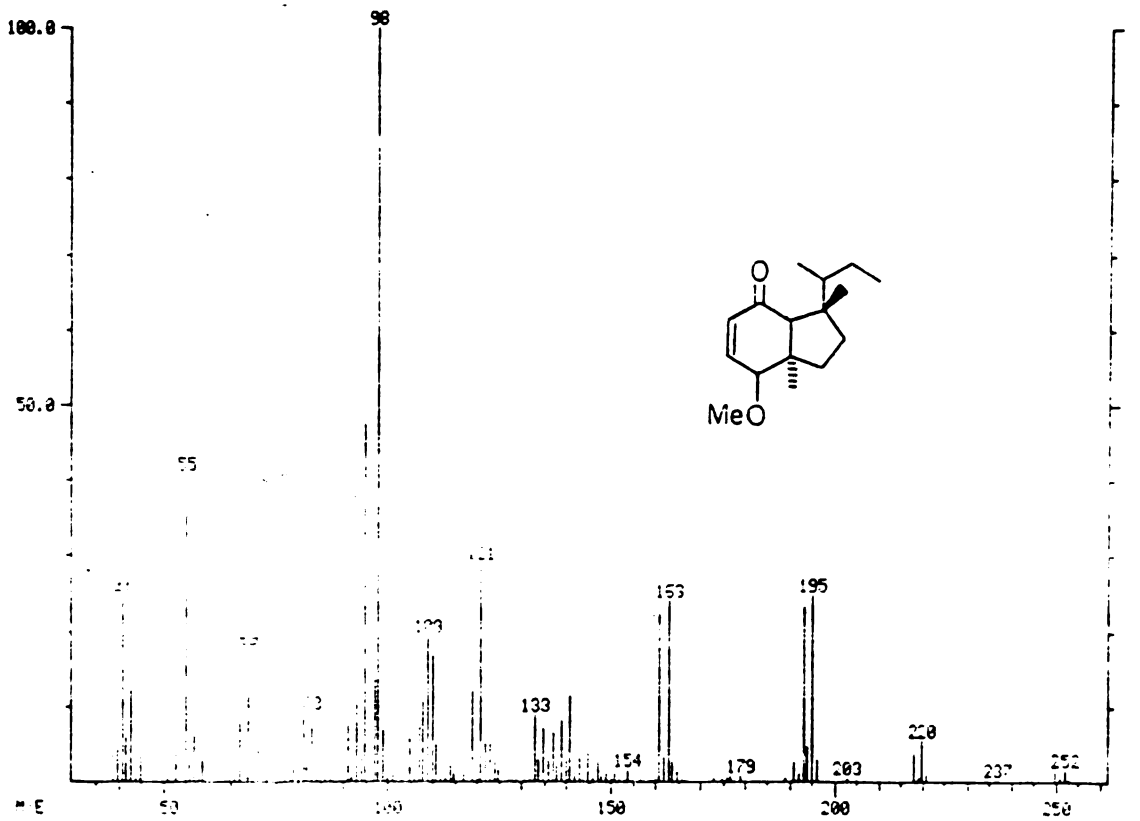


Figure 61. Mass spectrum of 16 and 17.

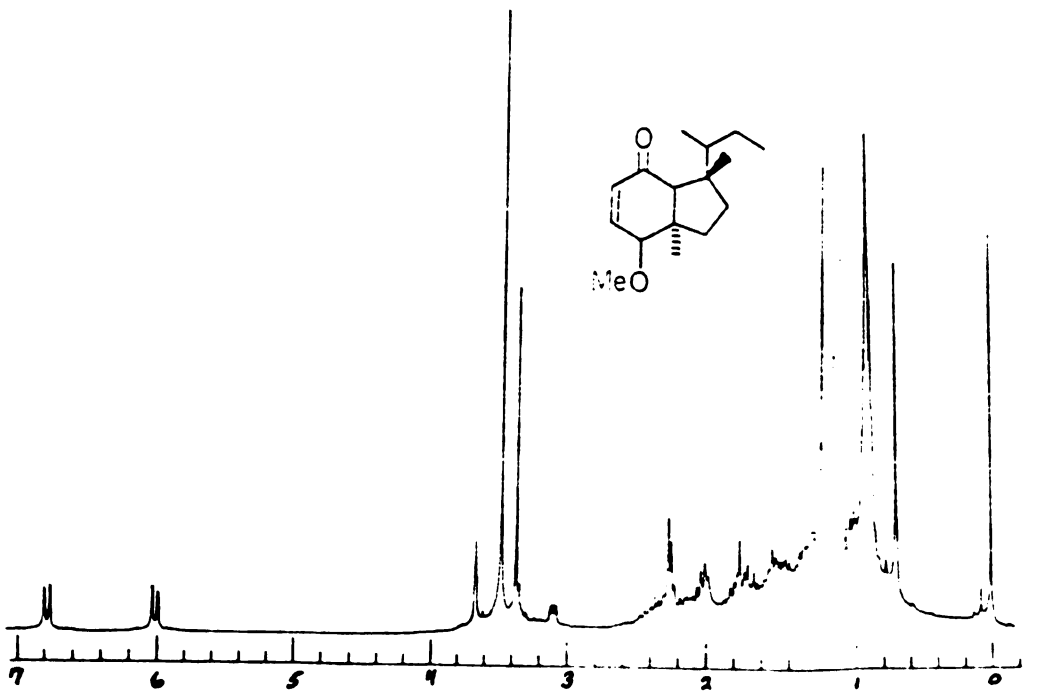


Figure 62. Proton NMR of 16 and 17.

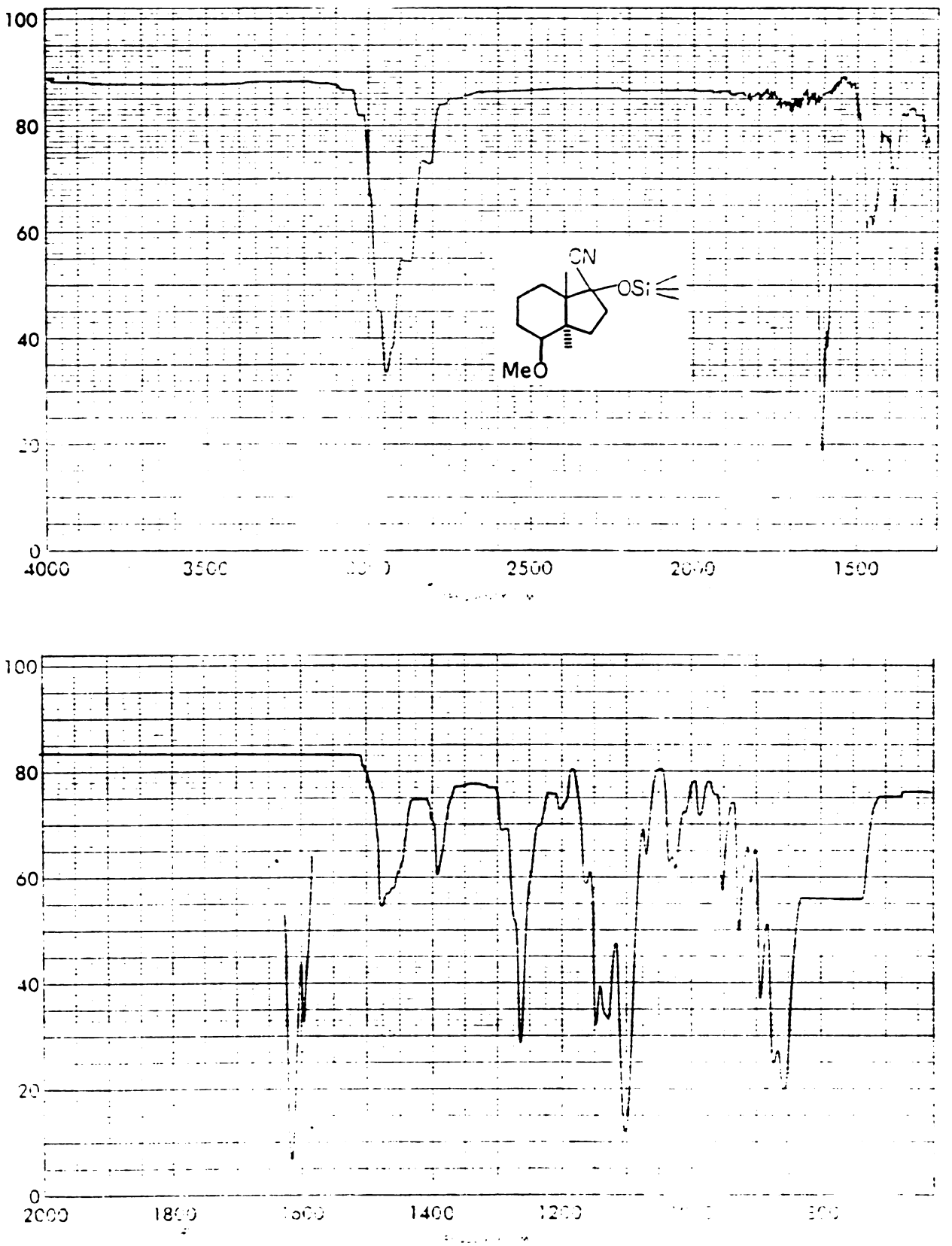


Figure 63. IR of 18.

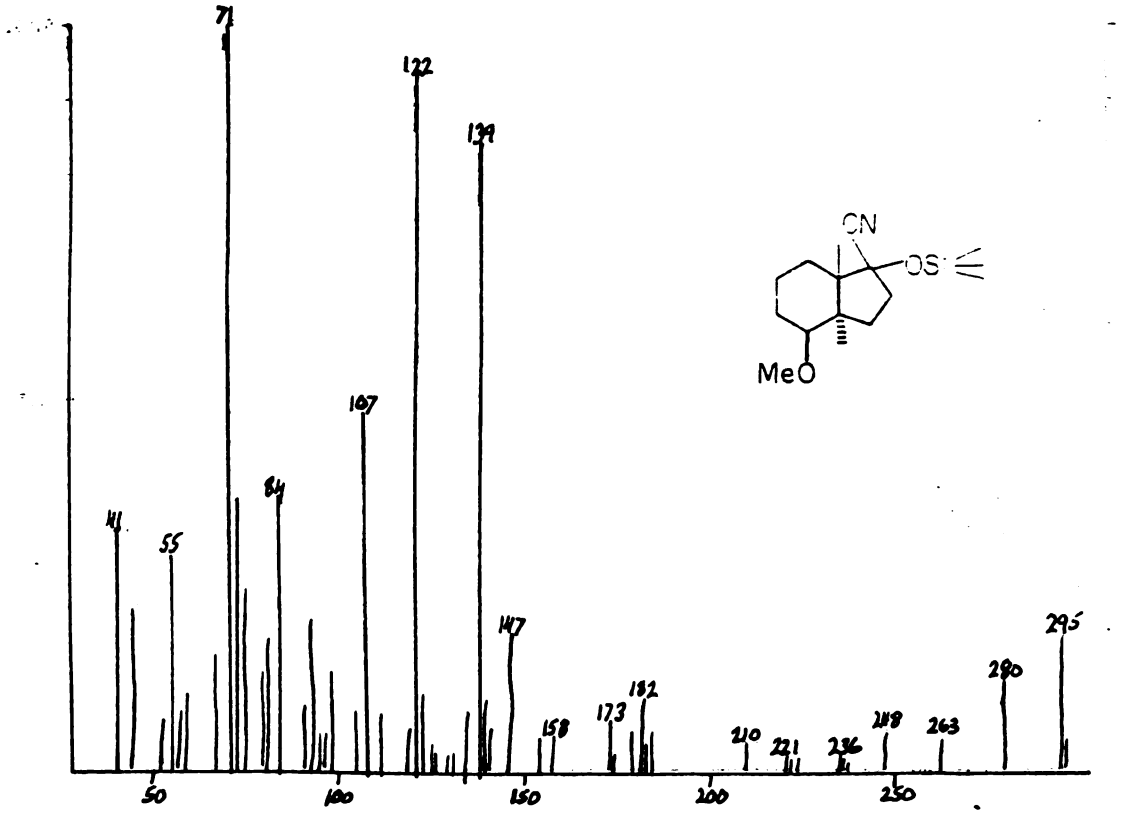


Figure 64. Mass spectrum of 18.

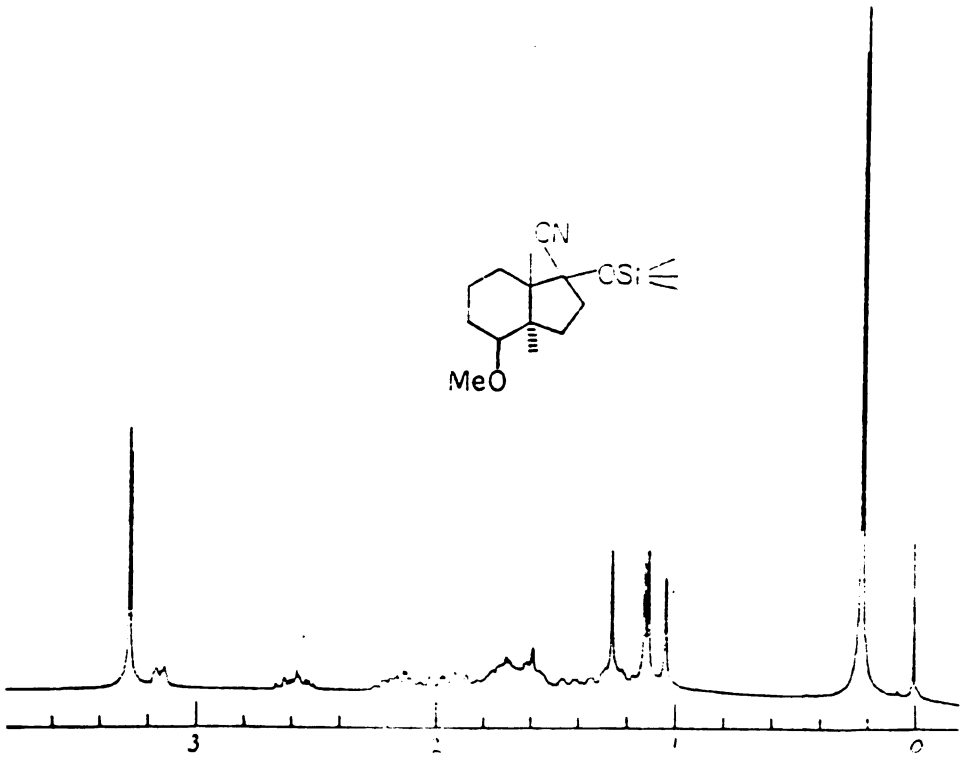


Figure 65. Proton NMR of 18.

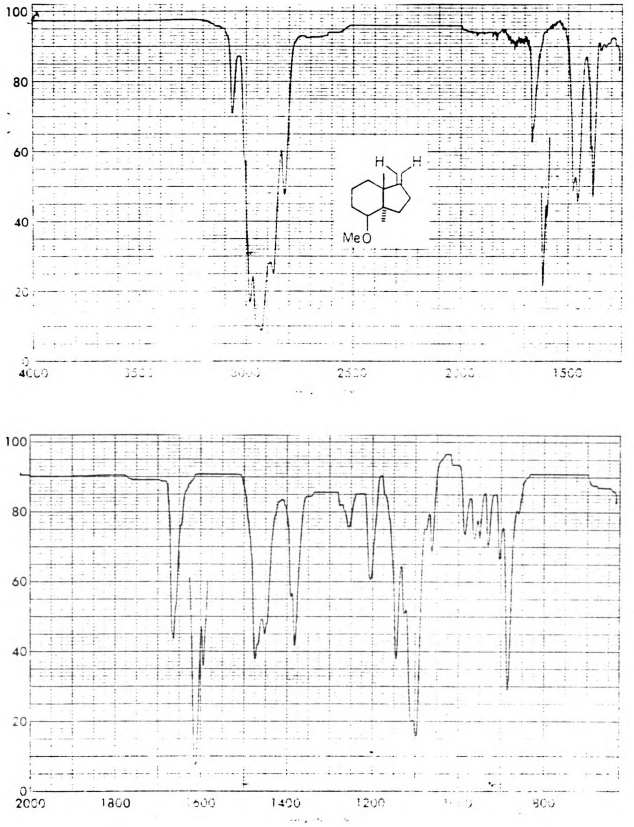


Figure 66. IR of 19.

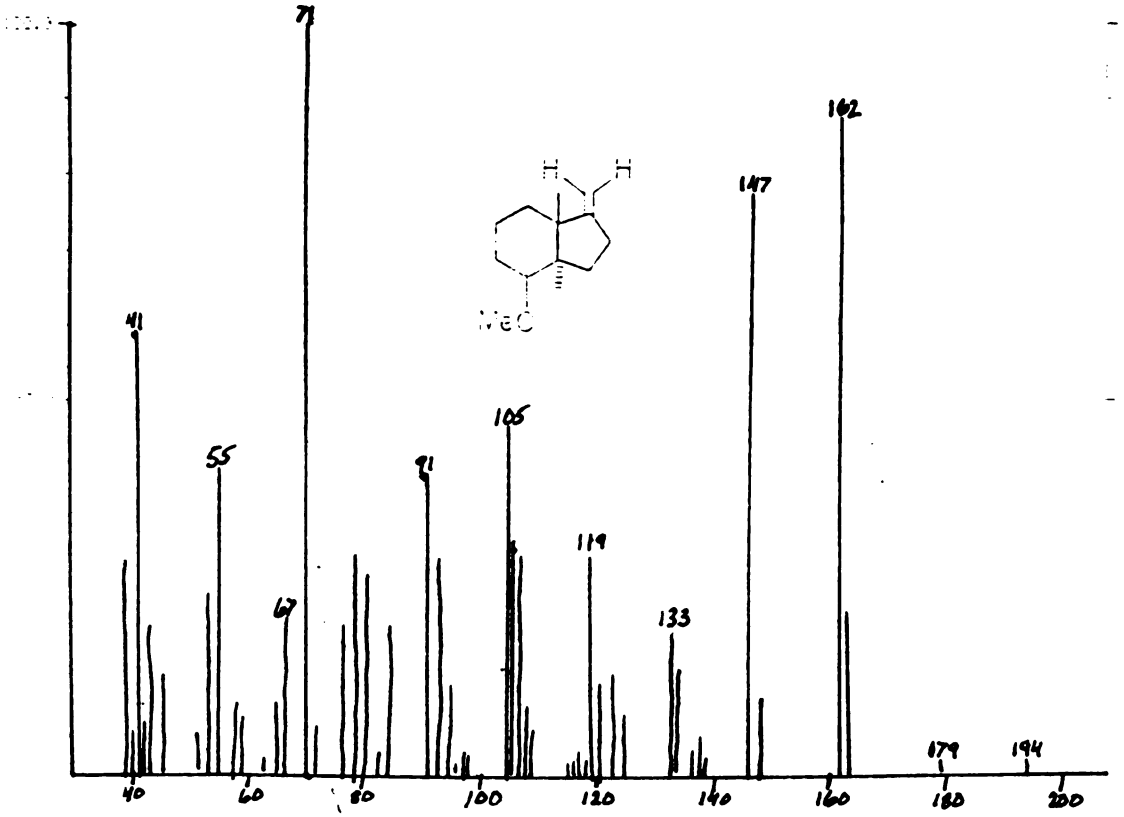


Figure 67. Mass spectrum of 19.

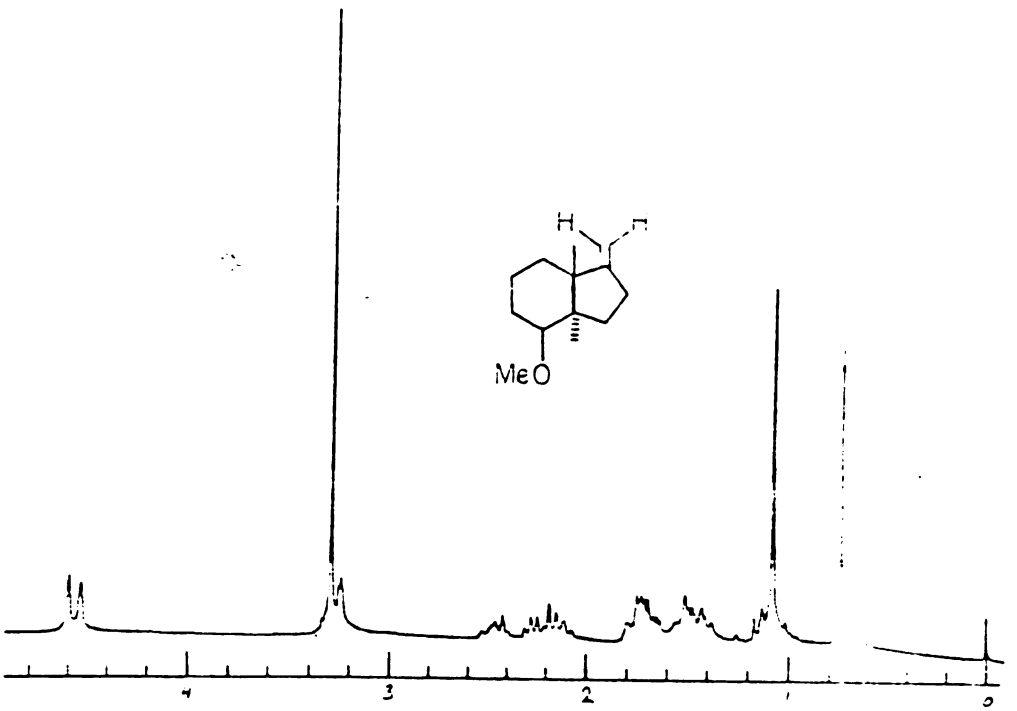


Figure 68. Proton NMR of 19.

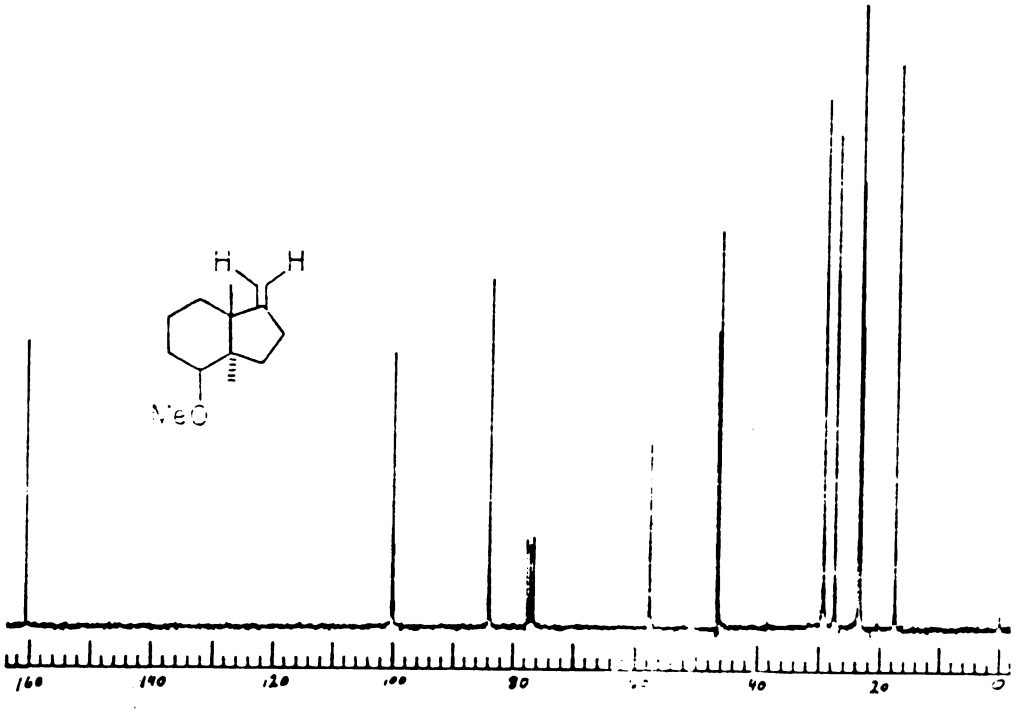
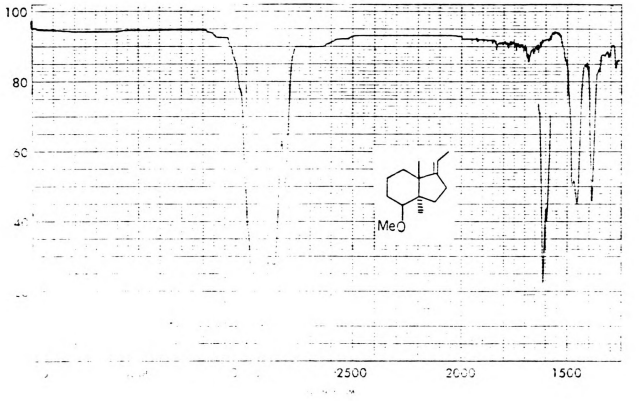


Figure 69. Carbon-13 NMR of 19.



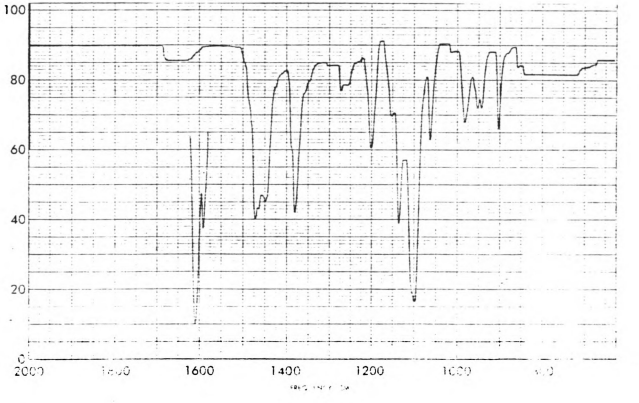


Figure 70. IR of 20.

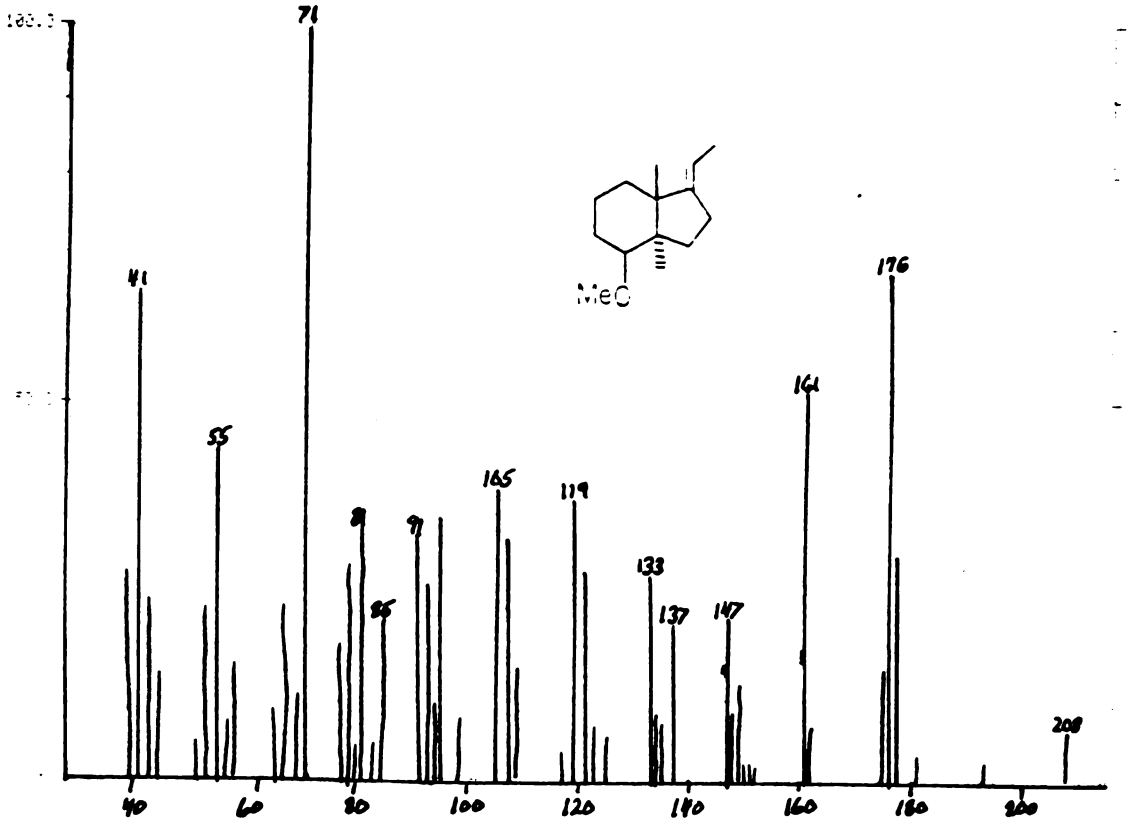


Figure 71. Mass spectrum of 20.

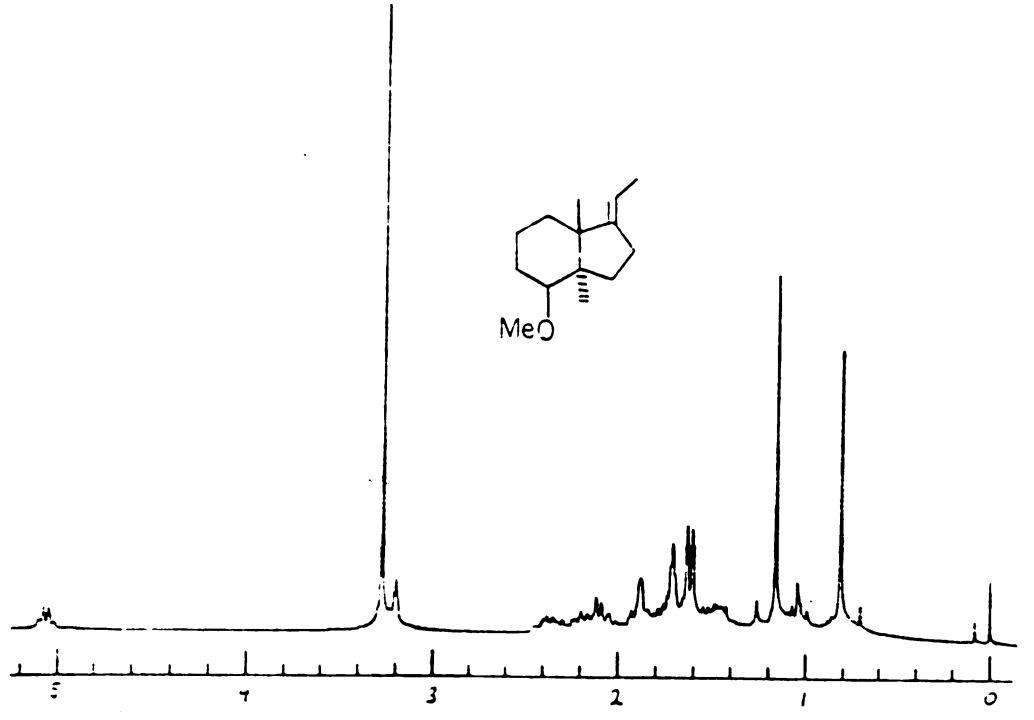


Figure 72. Proton NMR of 20.

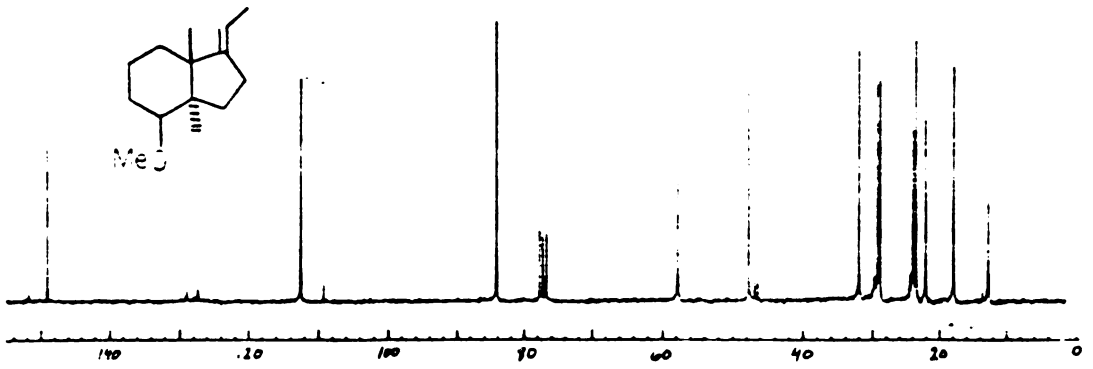


Figure 73. Carbon-13 NMR of 20.

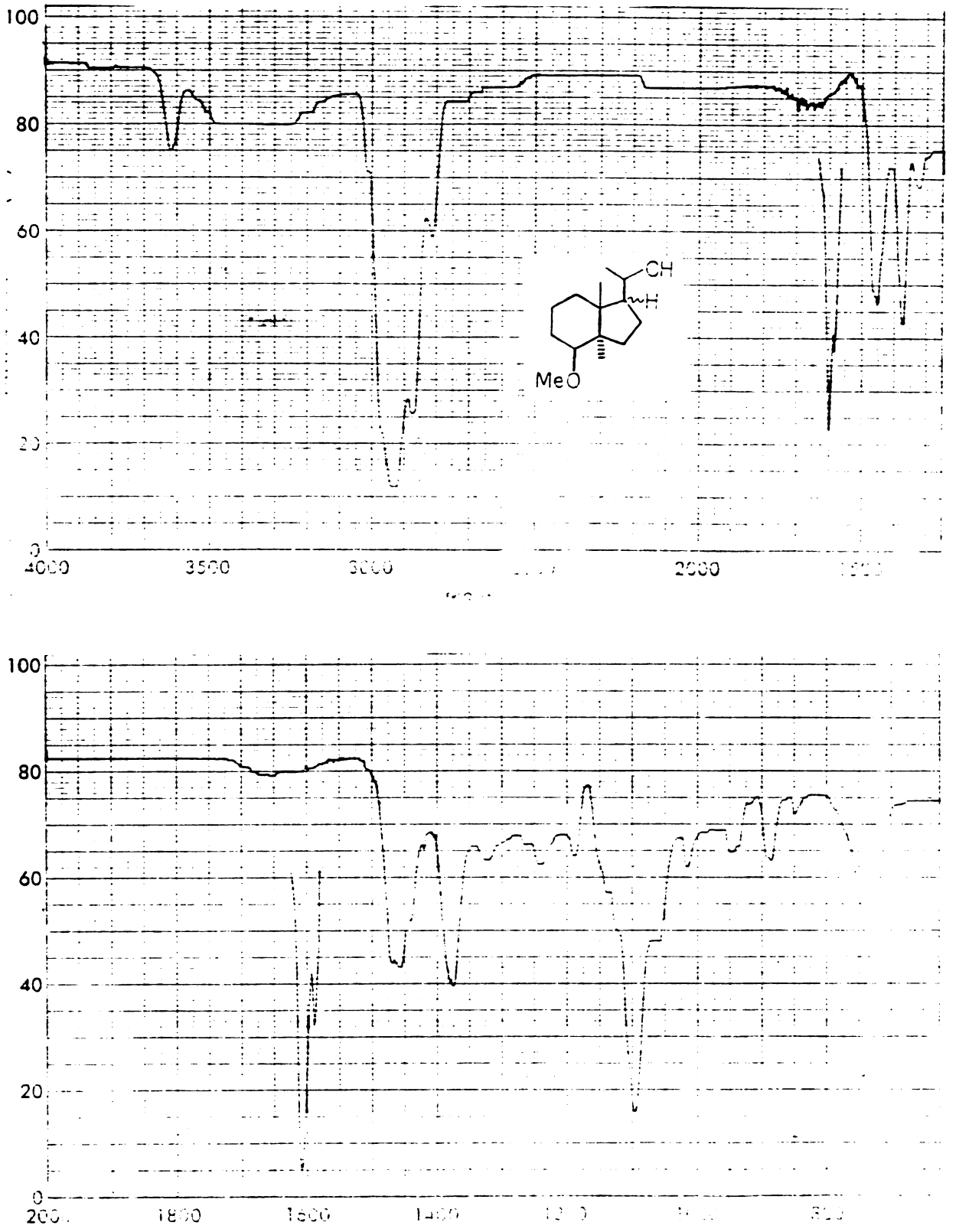


Figure 74. IR of 21.

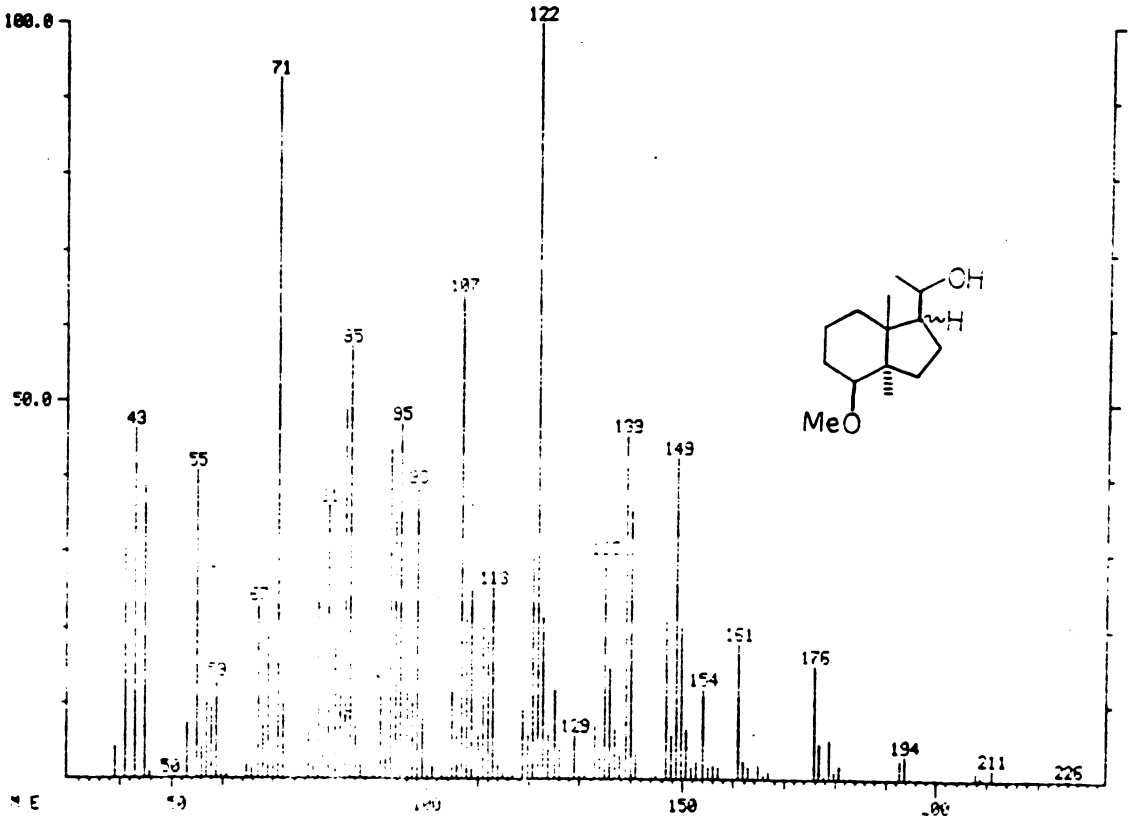


Figure 75. Mass spectrum of 21.

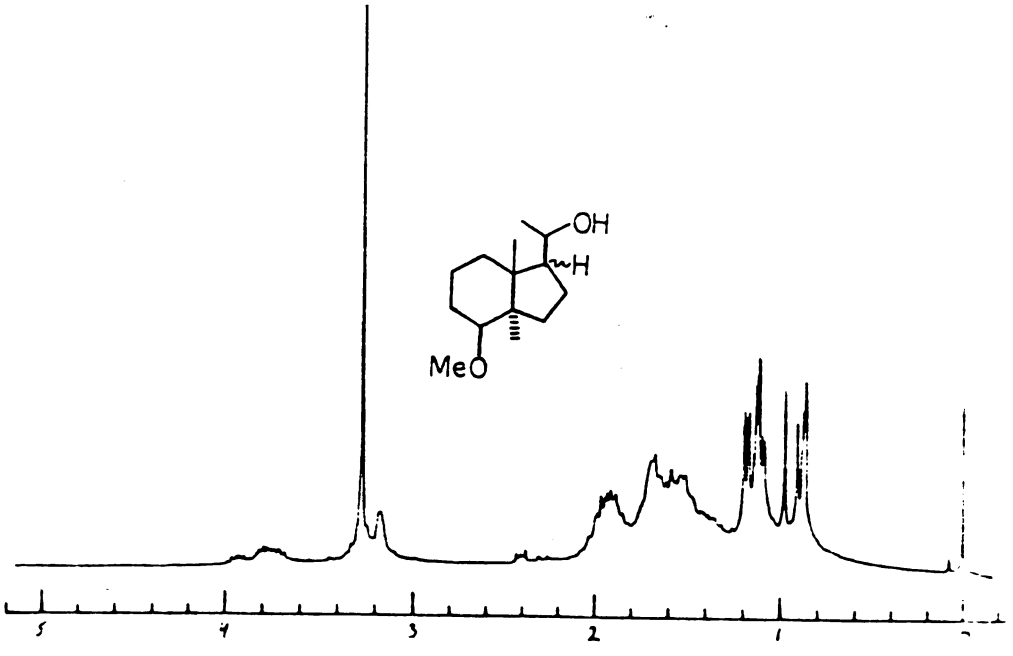


Figure 76. Proton NMR of 21.

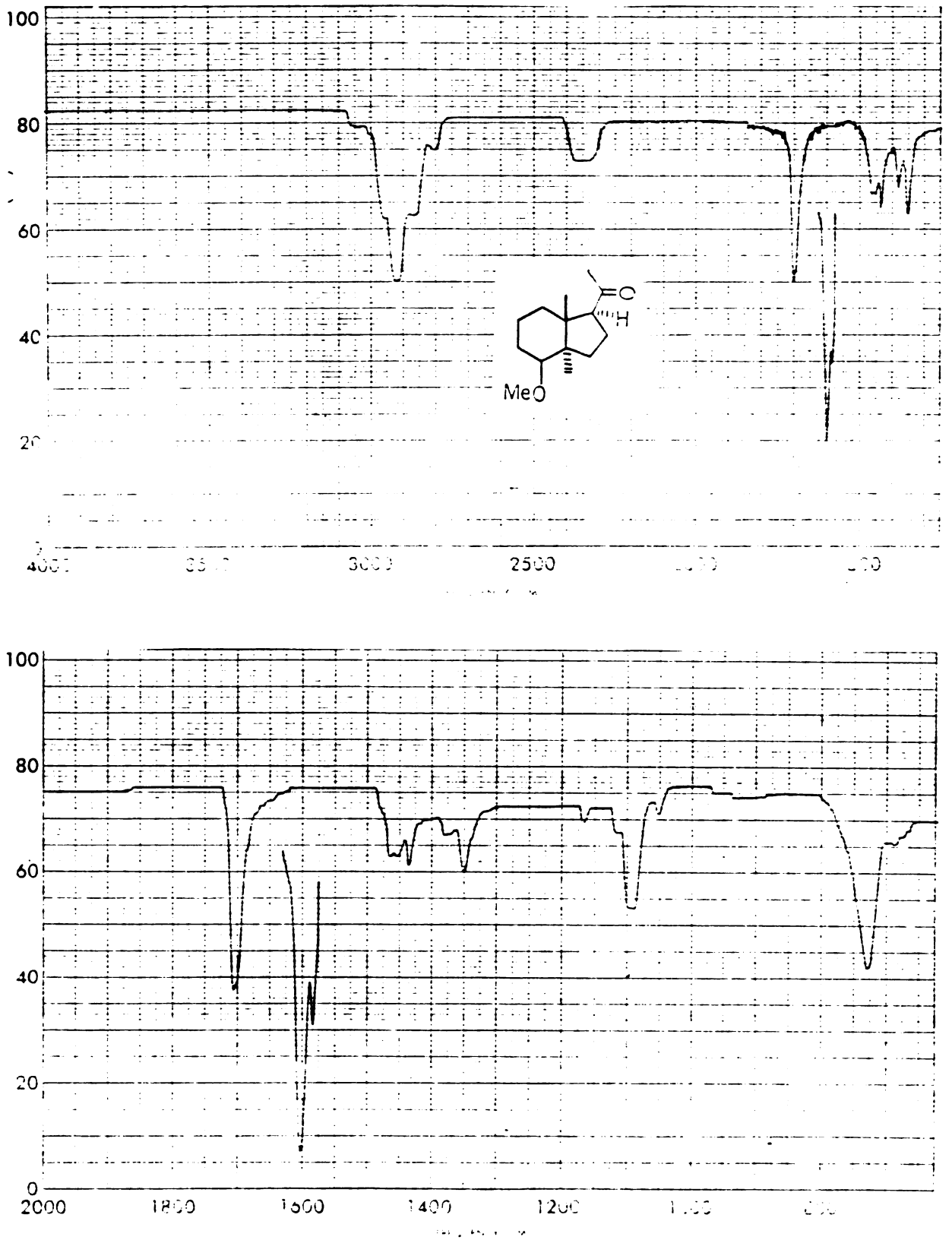


Figure 77. IR of 22.

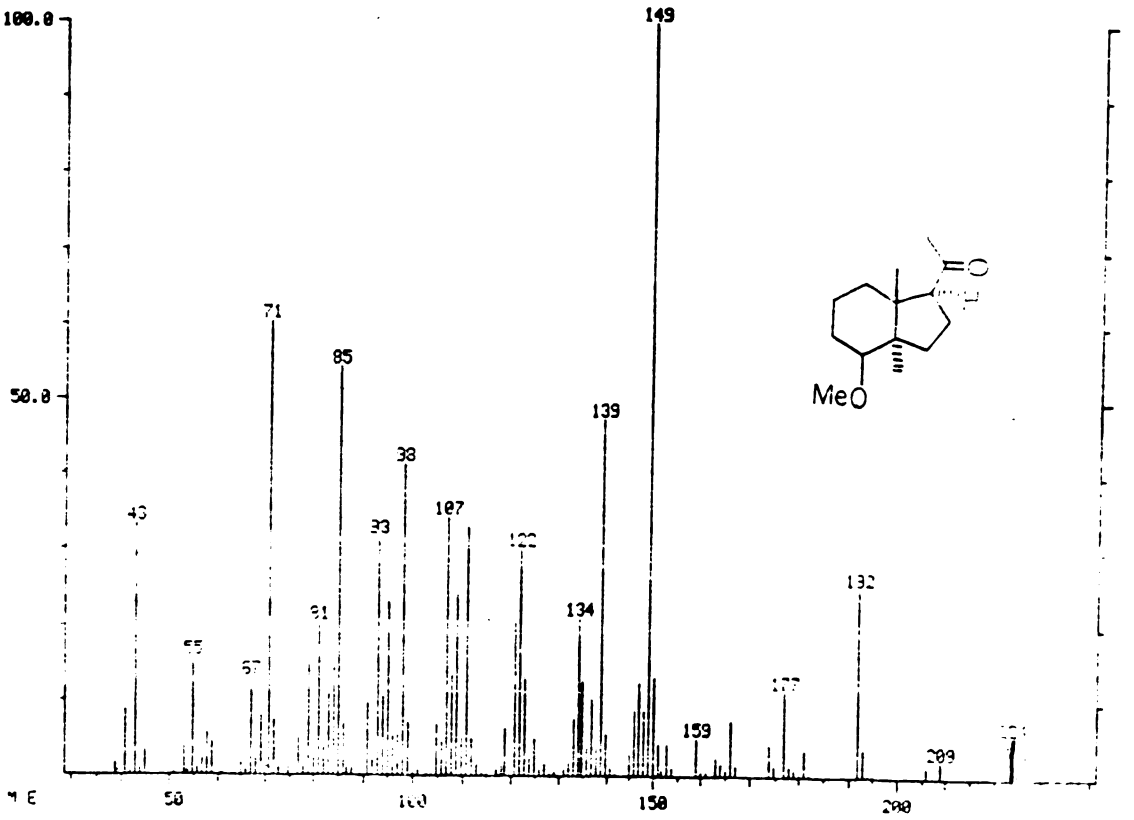


Figure 78. Mass spectrum of 22.

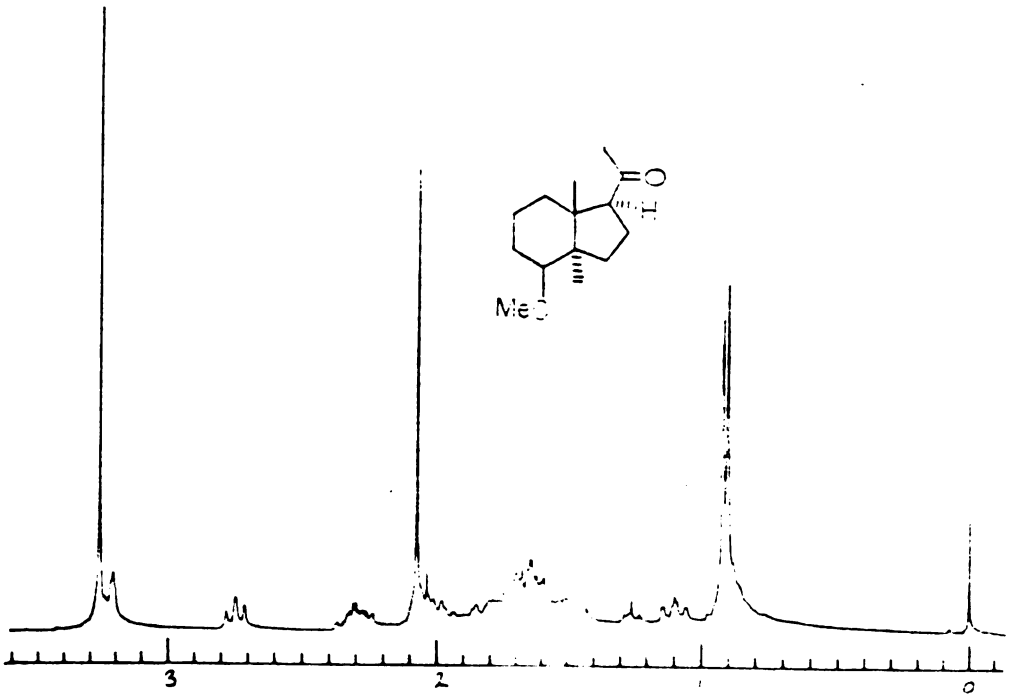


Figure 79. Proton NMR of 22.

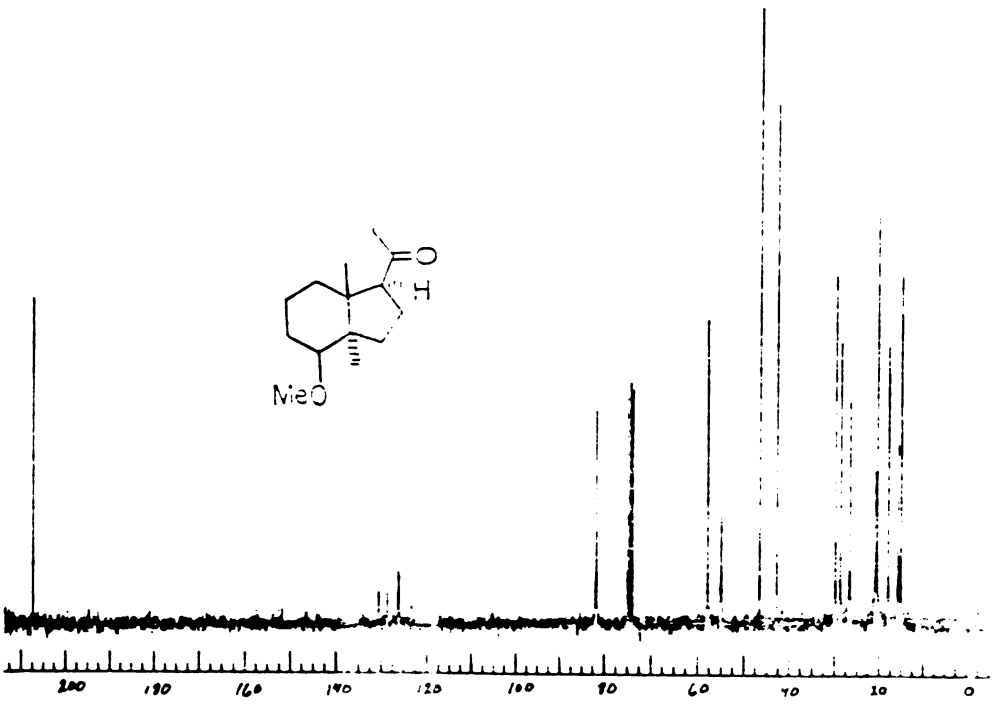


Figure 80. Carbon-13 NMR of 22.

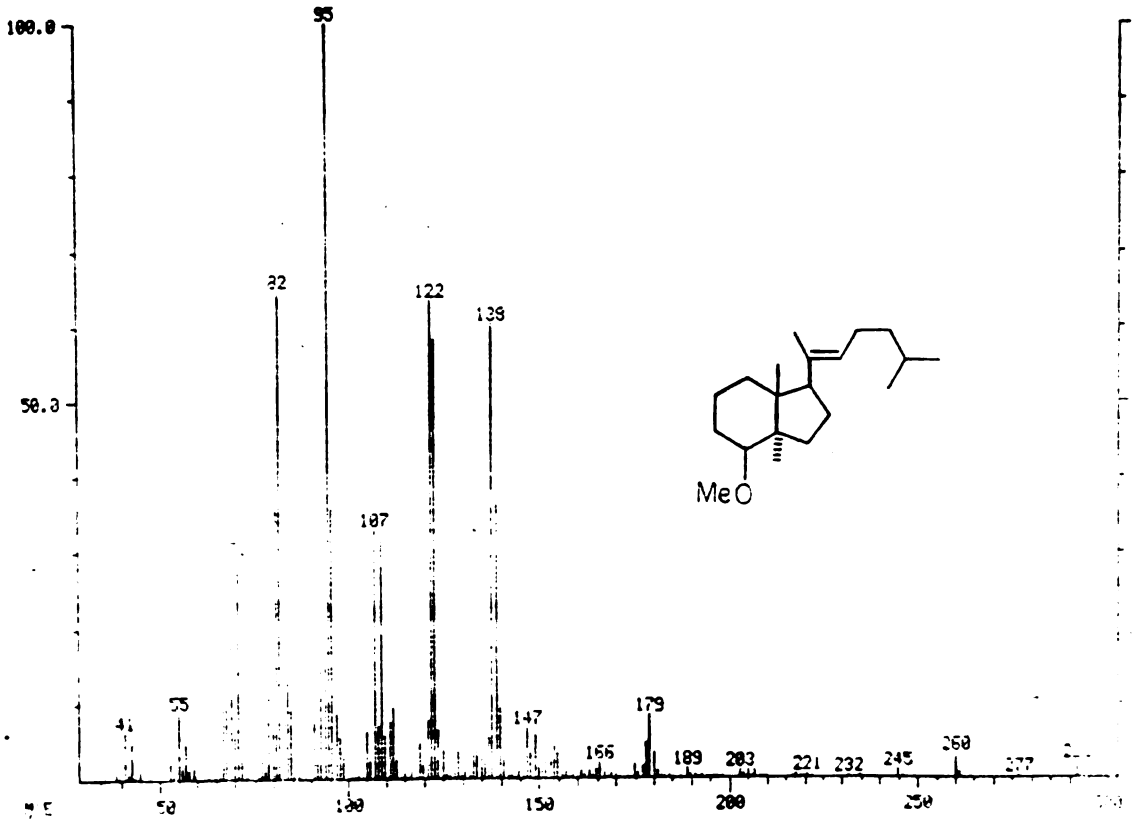


Figure 81. Mass spectrum of 23.

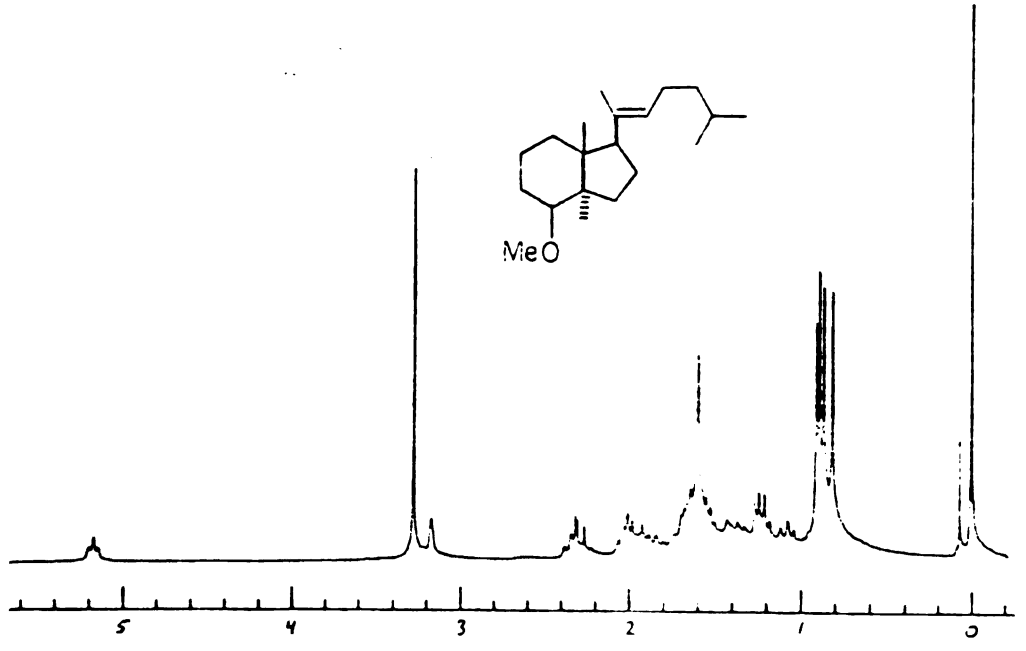


Figure 82. Proton NMR of 23.

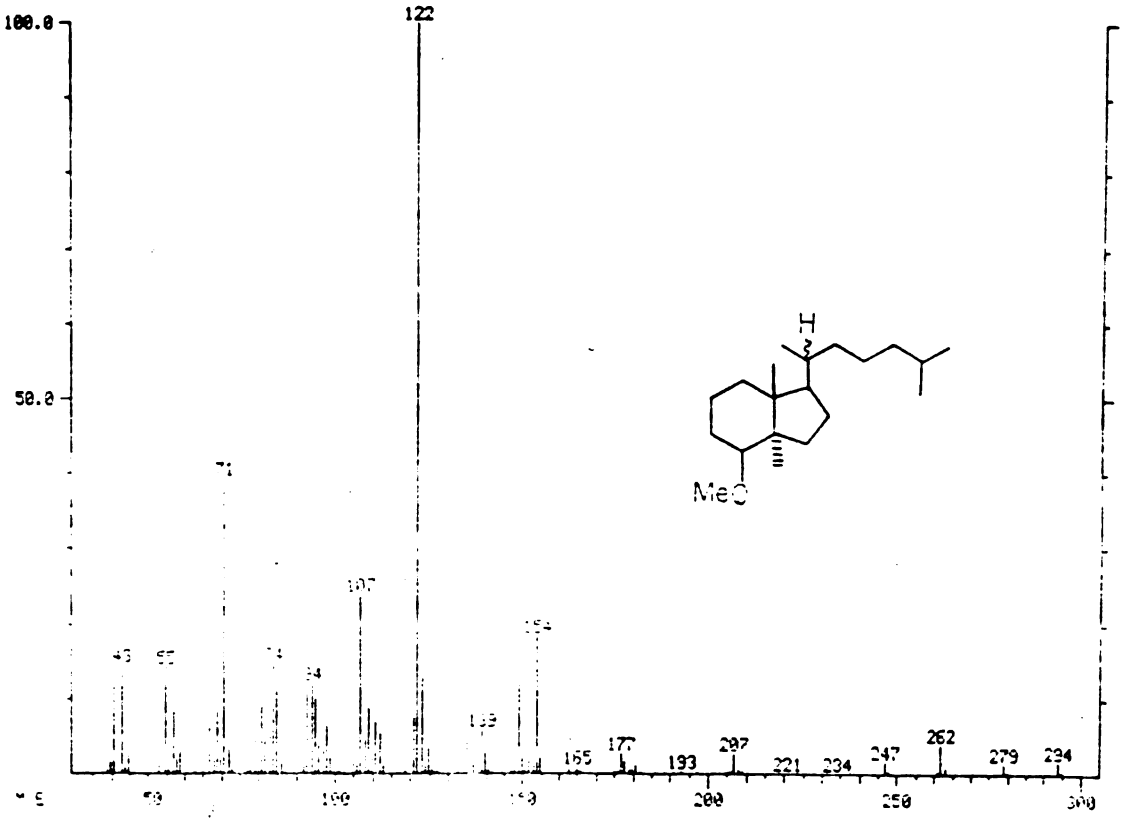


Figure 83. Mass spectrum of 24.

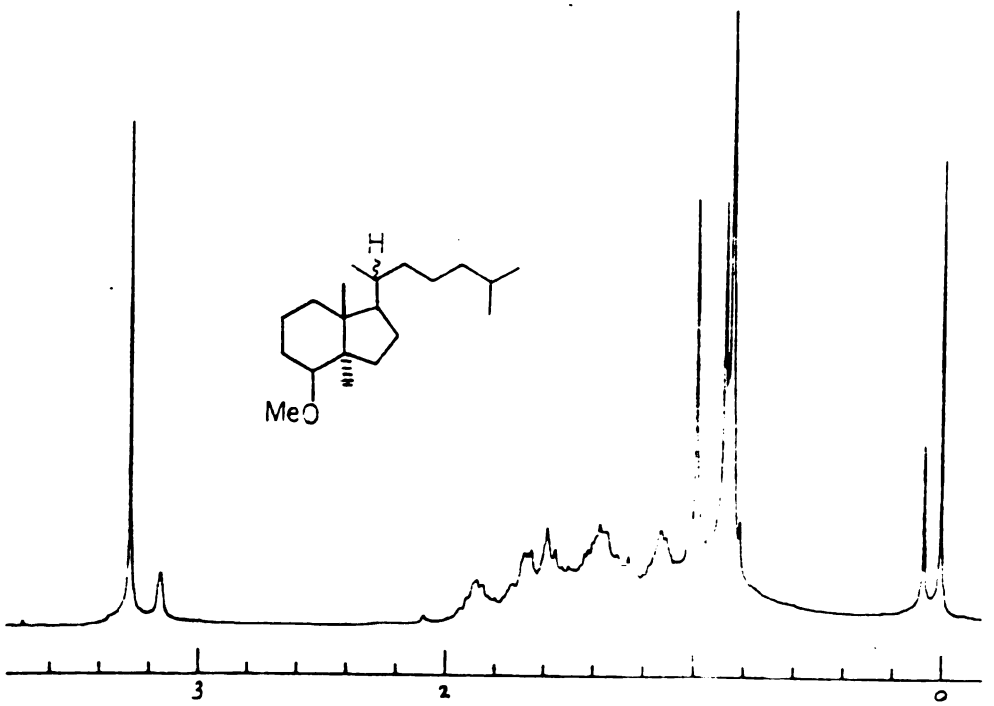


Figure 84. Proton NMR of 24.

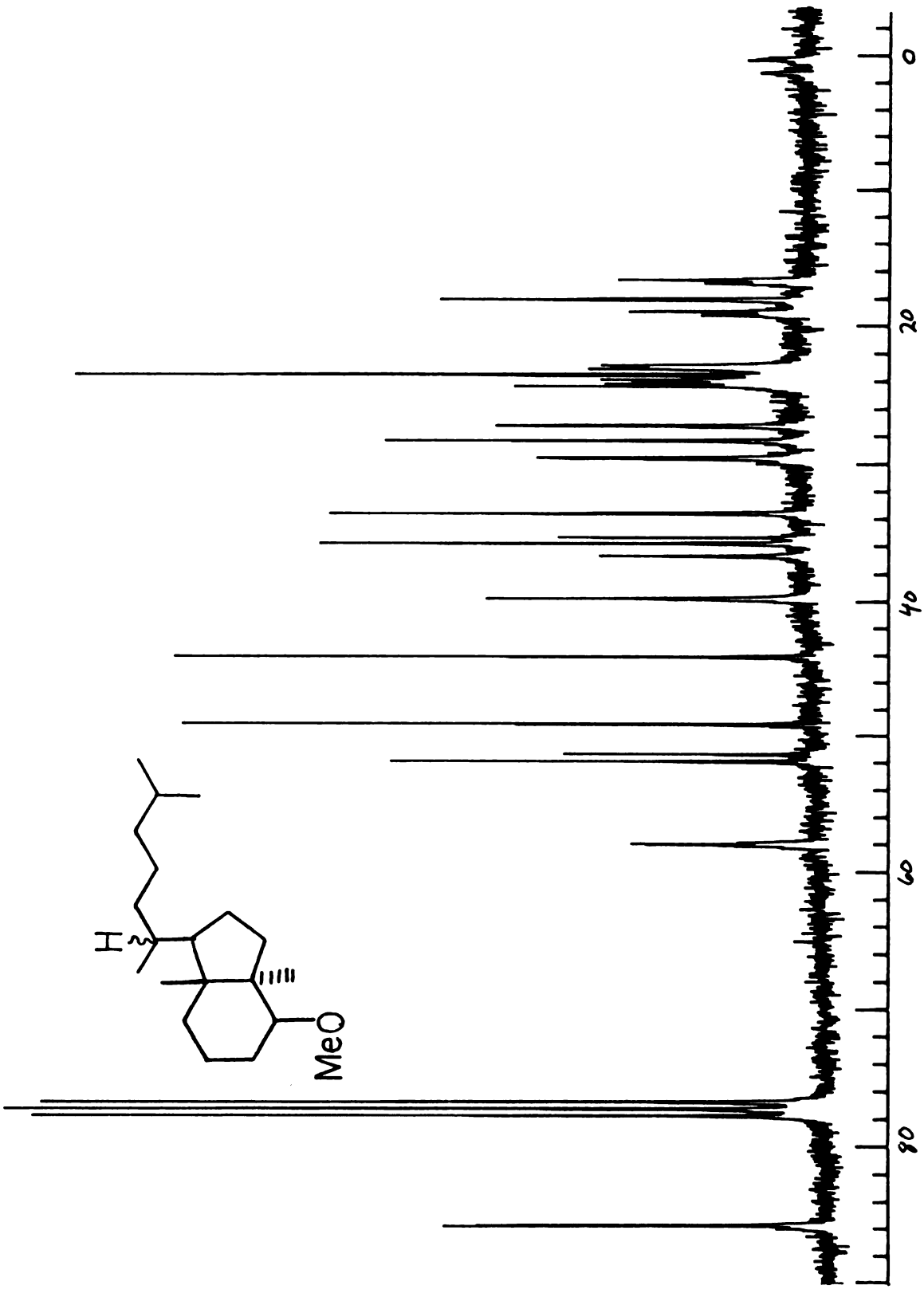


Figure 85. Carbon-13 NMR of 24.

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"A man would make but a very sorry chemist if he attended to that department of human knowledge alone."

M. Waldman to
Victor Frankenstein

Frankenstein, Mary Shelley

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