STUDIES TOWARD
THE TOTAL SYNTHESIS OF CUCURBITACINS

By

BALAN CHENERA

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ABSTRACT

STUDIES TOWARD THE TOTAL SYNTHESIS OF CUCURBITACINS

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BALAN CHENNRA

The studies directed toward the total synthesis of cucurbitacins, a group of roughly twenty tetracyclic triterpenes, are presented. This research has culminated in the construction of tetracyclic ring structures ideally suited for the cucurbitacin synthesis. A major effort has also been directed toward the preparation of several CD bicyclic synthons for tetracyclic triterpenes.

Thermal Diels Alder reaction of diene **4** and p-benzoquinone yielded the adduct **10** in over 75%. The chemistry of the adduct **10** was explored as a possible route toward the introduction of 11-oxo group and 9β-methyl group, which are unique for cucurbitacins. Brief acid treatment of **10** gave the A-aromatic derivatives **11** and **12** in 80:20 ratio. Prolonged treatment of **10** with acid isomerized it to a mixture of $\Delta^{9,11}$ and $\Delta^{8,9}$ isomers(**17** and **12**) in 80:20 ratio. The facile double bond migration is attributed to the stabilizing influence of C-1 oxygen functionality in **17**. The conversion of **17** to **16** followed by epoxidation and ring opening yielded the 11-oxo derivatives **26** and **27**, in which the 9β isomer, **27** was found to be the kinetically

favored product. The stable enol **30** was isolated when **26** and **27** was subjected to base treatment. The alkylation of **26** and **27** was also studied; however only O-alkylated derivatives **31,32,33** have been isolated. Several 14α-methyl estrane derivatives were prepared during the course of these studies. The Pd/C dehydrogenation of 11 gave **18** and **19**. Dehydrogenation of **13** with dichlorodicyano p-benzoquinone (DDQ) yielded **21** as the only product.

The reactions of enone **36** and **52** were studied in order to construct useful intermediates toward a possible intramolecular Diels Alder (IMDA) strategy to cucurbitacins. The spirolactones **51** and **59** were synthesized together with various other CD synthons.

The chemistry of trans dienes **62** and **63** was studied in an attempt to prepare highly functionalized analogues of diene **4**. A kinetic selectivity has been observed during the acid catalyzed isomerization of **4** to **63** and it proceeds through compound **62**. An efficient synthesis of dienedione **74** from **62** and the preparation of the bissilyl tetraene **75** has been discussed.

To my parents

ACKNOWLEDGEMENTS

I would like to thank Professor William H Reusch for his encouragement and guidance throught the course of my studies at MSU. I also wish to thank Dr. Steven P Tanis for several useful discussions.

My academic years were greatly enriched by my friends at MSU and elsewhere. I thank the entire Reusch group for providing a pleasant atmosphere in the laboratory. In particular, I would like to thank Larry Kolaczkowski for his friendship and for a copious supply of chemicals needed for part of my project.

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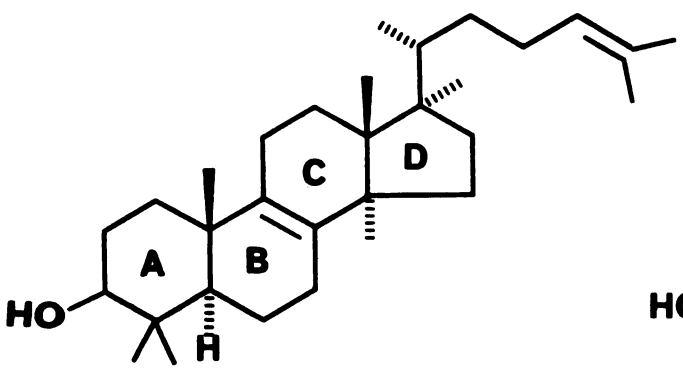
TABLE OF CONTENTS

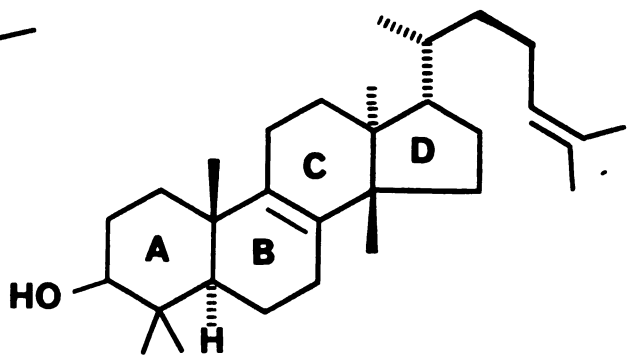
LIST OF FIGURES

INTRODUCTION

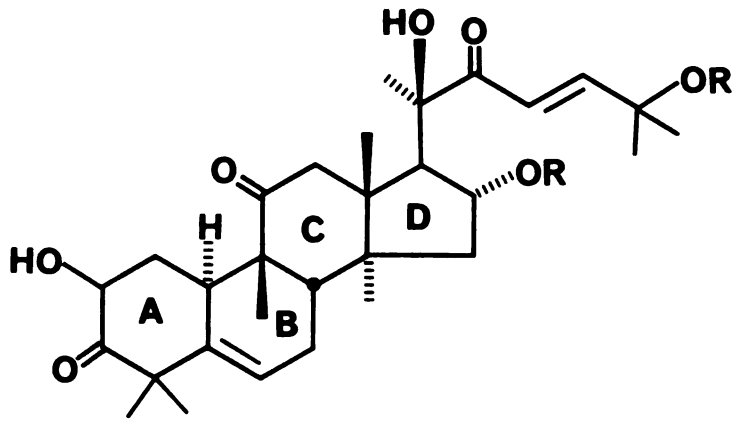
Total synthesis of steroidal natural products continues to provide a fruitful ground for testing new synthetic methods and strategies.[1] The challenge lies in devising efficient methods for assembling the tetracyclic structure including the establishment of correct stereochemistry and the introduction of desired functionality. Tetracyclic triterpenes [2,3] or 14α-methyl steroids as they are commonly known, have received remarkably little attention with respect to their total synthesis. This is surprising in view of the fact that tetracyclic triterpenes with several diverse structural features form the largest class of triterpenes. Especially important among these are lanostanes, euphanes and cucurbitacins[4], which are distributed widely among the plant kingdom. Representative structures are shown below.



LANOSTEROL



EUPHOL



$R^1 = R^2 = H$; CUCURBITACIN D

$R^1 = H$; $R^2 = Ac$; CUCURBITACIN B

Although most of these structures resemble steroids, the structural and chemical differences make their synthesis more challenging than that of most steroids. An X-ray crystallographic analysis of a bis(p-iodobenzoate) of datiscoside[5] (a cucurbitacin) confirms that this molecule has a 90 bend at the B/C ring junction, in contrast to the flat conformation of the steroids. The stereodrawings of a datiscoside derivative and a typical steroid illustrate this difference (fig 1). Because of this folding, the 14α-methyl group comes

very close to C-5 and C-10(3.43 and 3.23 Å respectively) making the α-side of the cucurbitacin system sterically hindered, in contrast again to steroids. In addition cucurbitacins are highly functionalized compared to most steroids.

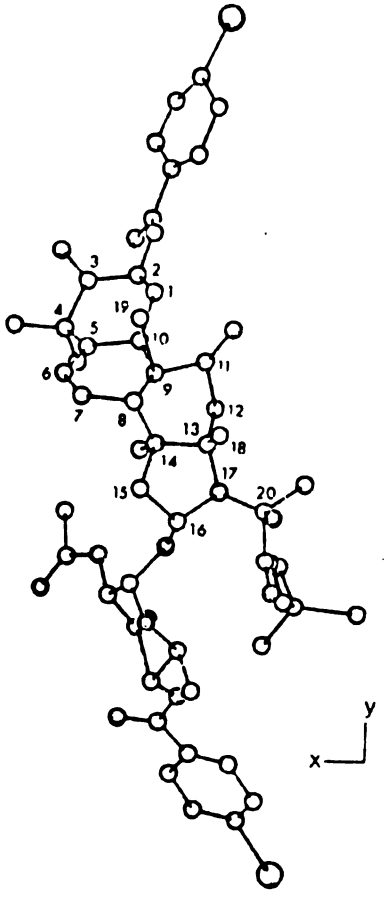


Fig 1a

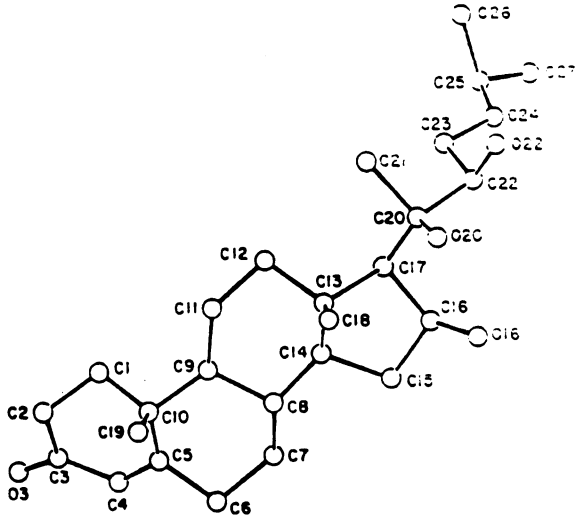


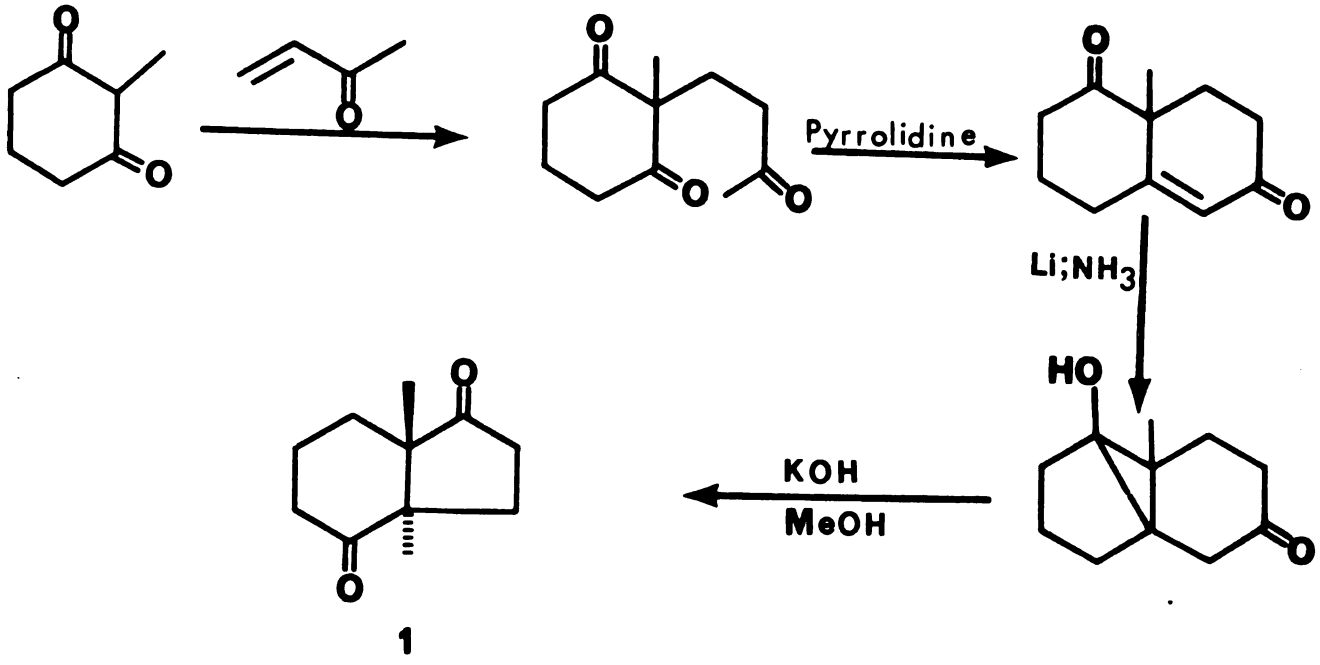
Fig 1b

Stereodrawings of 1a) a datiscoside derivative and
1b) a steroid.

One of the factors that make the tetracyclic triterpenes challenging targets for synthesis is the presence of a bis-angularly methylated CD ring moiety. Introduction of the 14α methyl group into the steroid system was acheived previously by the base catalyzed alkylation of 15-oxo steroid.[6] The lack of control of stereochemistry of alkylation and the difficulties in transposing 15-oxo function to the 17 position are the disadvantages of this approach. It was the discovery of a synthon, ideally suited for the construction of various tetracyclic triterpenes, that prompted our studies in this field. It should also be possible to effect the asymmetric synthesis of optically pure triterpenes, since the only chiral reagent employed in the proposed synthesis is trans-1,6-dimethylbicyclo(4,3,0)-nona-2,7-dione 1.[7] Efficient asymmetric synthesis of either antipode of Wieland-Miescher ketone has been acheived by using eiter (R) or (S) proline as a chiral catalyst during the Robinson annulation.[8] Intermediate 1 is derived from Wieland Miescher ketone as we have previosly reported.[9] Consequently it is in priciple available as either antipode or the racemic modification (Scheme 1).

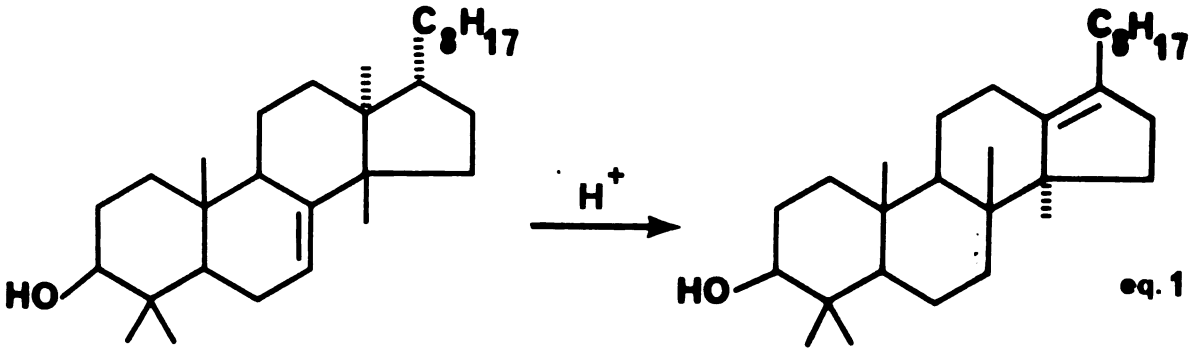
Two distinct approaches were studied previously for the construction of tetracyclic triterpenes. Woodward's lanosterol synthesis from cholesterol in over twentyfive steps involved the alkylation of a 15-oxo cholestane derivative as the key step towards the introduction of 14α- methyl group.[10] Van Tamelen's strategy on the other hand involved

a biomimetic polyene cyclization for the synthesis of parkeol and isotirucallol.[11] To date euphanes have noy been prepared by a total synthesis. The difficulty in preparing euphane skeleton by the polyene cyclization approach is attributed to the facile acid catalyzed rearrangement of this compound to the isoeuphane system as shown in equation 1.[12] Several research groups have studied the synthesis of cucurbitacins and a partial synthesis from lanosterol has been reported.[13]



1

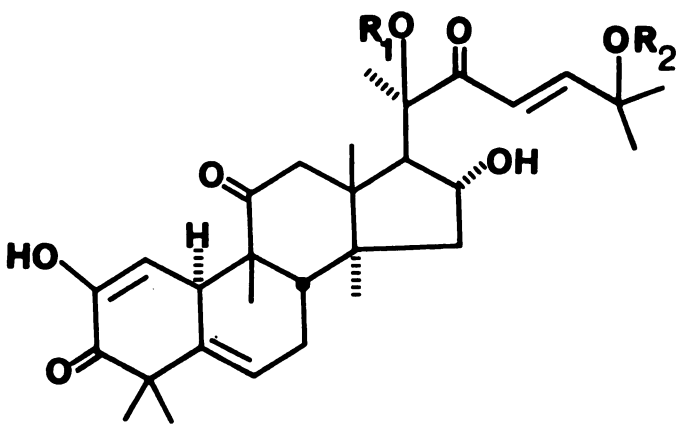
Scheme 1



eq. 1

Among the tetracyclic triterpenes cucurbitacins are probably the most complex. This complexity is mainly derived from the presence of a 9β- methyl group, 11-oxygen functionality and several other sensitive oxygen functionalities around the carbon skeleton. Many cucurbitacins possess interesting and useful biological properties. Cytotoxic and anti-tumor activity has been reported for cucurbitacins B, D,E and I among others,[14] and for related compounds datiscoside and datiscacin, isolated from the roots of Datisca glomerata Baill.[15] The latter compound showed significant activity in vivo against Walker 256 carcinosarcomas and P-388 lymphocytic mouse leukemia, and in vitro against human carcinoma of nasopharynx(KB). Lavie and coworkers note that the 2-methyl ether derivative of cucurbitacin E was one of the most effective anti-tumor agents studied by their group.[16] The cucurbitacins have also been shown

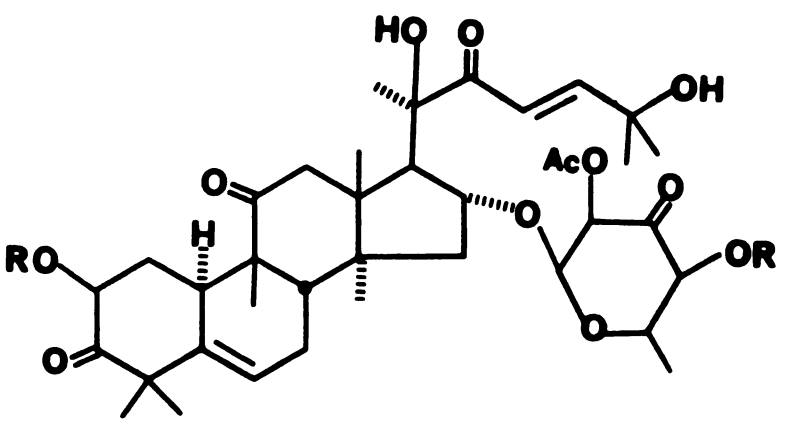
to be plant growth agents that behave as giberellin antagonists,[17] insect attractants (for the spotted cucumber beetle)[18] and insect feeding inhibitors (for a chrysomelidae leaf beetle).[19]



(a) R^1 = R^2 =H; CUCURBITACIN I(Elatericin B)

(b) R^1 =H, R^2 =Ac; CUCURBITACIN E(-Elaterin)

(c) R^1 =Ac; R^2 =H; Datiscacin.



DATISCOSIDE

Any total synthesis of a tetracyclic triterpene from the CD synthon 1, would require the stereoselective attachment of the A and B rings, so as to generate the complete tetracyclic skeleton. Several fundamentally different strategies may be used for fusing AB rings to an existing CD moiety. These are outlined below.

1. CD ⟶ BCD ⟶ ABCD

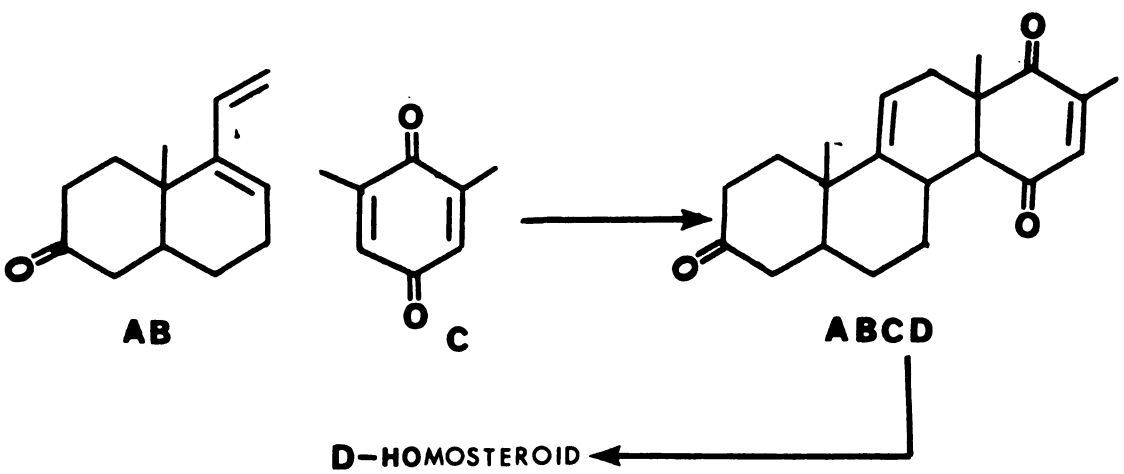
A wide variety of steroids have been prepared by Johnson and coworkers using this route starting from 5-methoxy-2-tetralone.[20]

2. CD + A ⟶ ACD ⟶ ABCD

Johnson's estrone methyl ether synthesis is an example of this approach.[21]

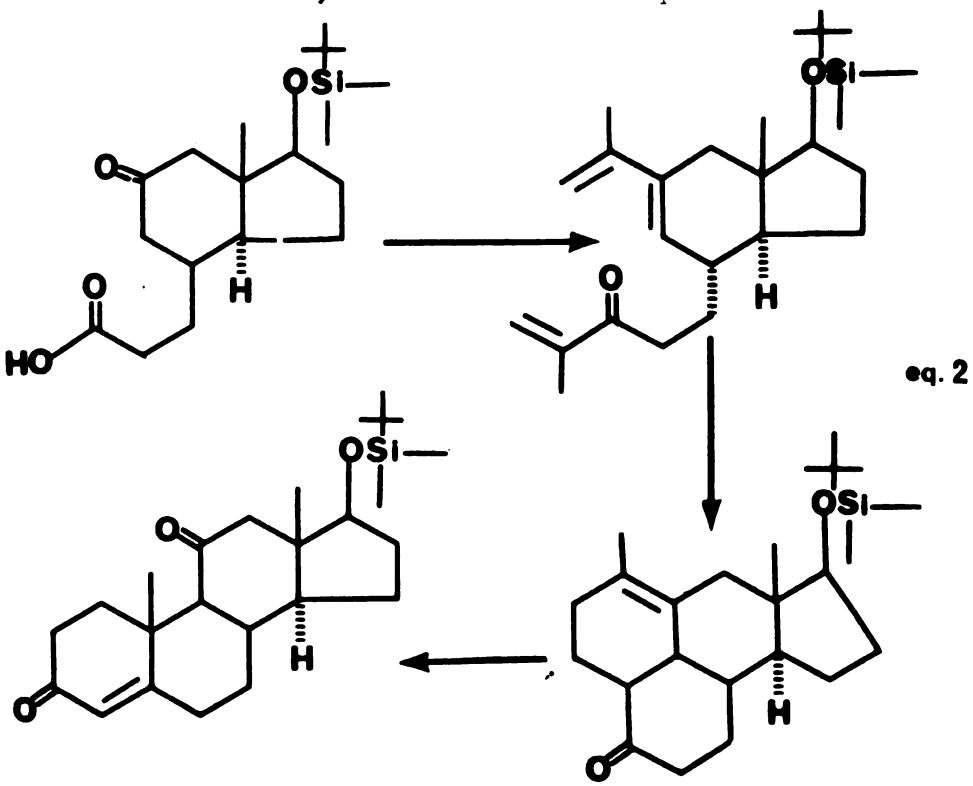
3. CD + A ⟶ ABCD

Scott Denmark has proposed an A + CD Diels Alder strategy for the construction of an 11-oxo steroid, and a key bicyclic synthon has been synthesised towards this end.[22] Valenta's synthesis of a D-homosteroid involves an AB + D ⟶ ABCD strategy for the construction of the tetracyclic system.[23]



Since the present study involves the construction of the cucurbitacin skeleton, it is appropriate to consider advances made in the synthesis of steroidal natural products bearing groups that are similar to those of the cucurbitacins. The introduction of an 11-oxo group and the establishment of the unusual 9β-methyl configuration are two such features.

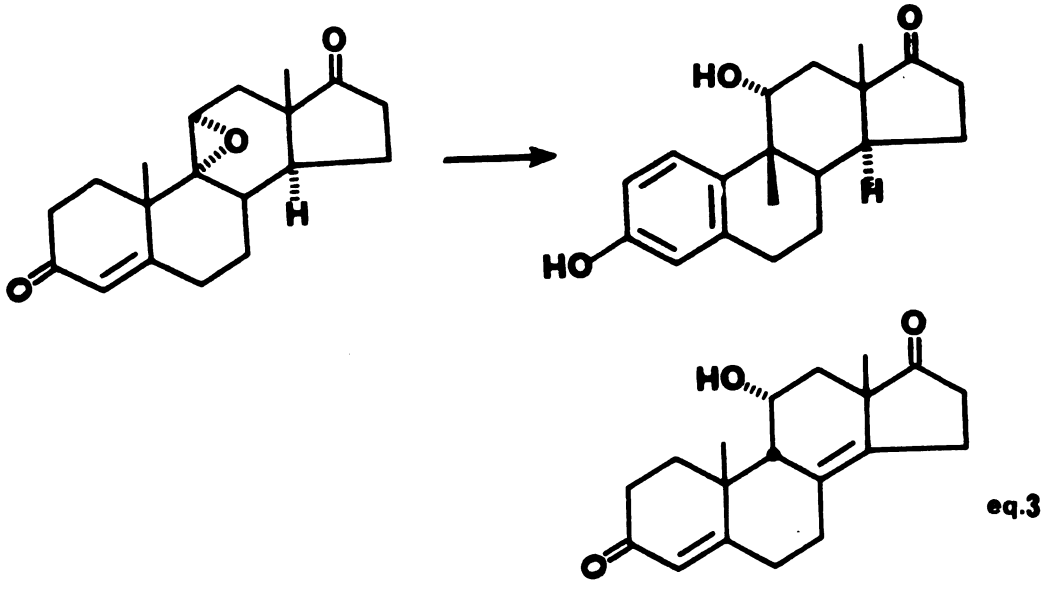
The introduction of an 11-oxo group has been acheived in many ways. Hydroboration-oxidation of $\Delta^{9,11}$ steroidal olefins routinely gives excellent yields of 11-oxo analogues and their alkylations have been studied as a means to introduce alkyl groups at C-9.[24] Epoxidation of a $\Delta^{9,11}$ double bond followed by acid catalyzed ring opening also gives 11-oxo steroids.[25] Recently Stork has reported an elegant synthesis of 11-oxo steroid by an intramolecular Diels Alder reaction, as described in equation 2.[26]



eq. 2

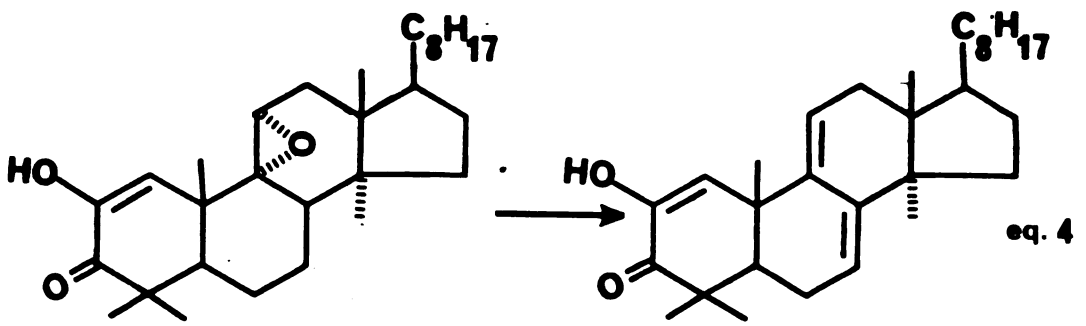
In order to introduce the 9β-methyl group and 11-hydroxy group simultaneously, several workers have explored the migration of 10β-methyl group to the 9β-position during the acid catalyzed cleavage of 9,11-epoxides.

Apsimon and coworkers studied the boron trifluoride catalyzed cleavage of some steroidal 9,11-epoxides.[27] In the case of 9α,11α-epoxy androst-4-ene-3,17-dione, cleavage with boron trifluoride yielded two major products. One of these was identified as the 3,11α-hydroxy-9β-methylestra-1,3,5(10) trien-17-one. The other proved to be 11α-hydroxy-9β-androst-4,8(14)-diene-3,17-dione (equation 3).



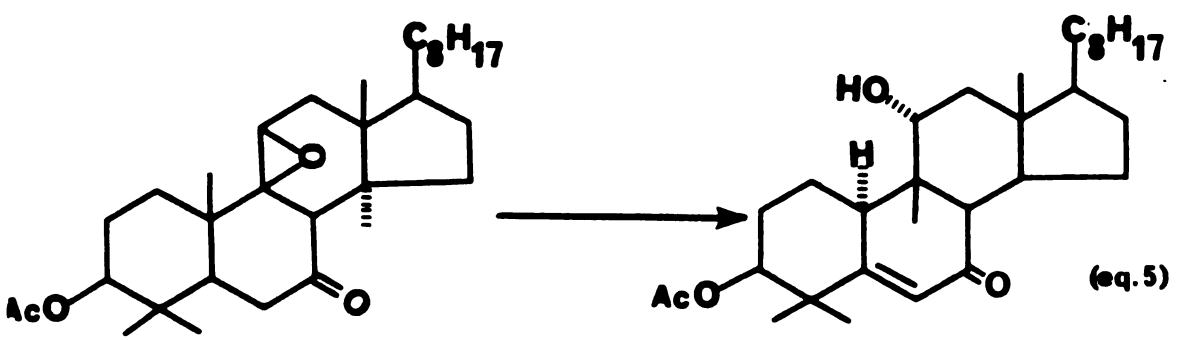
eq.3

Lavie and coworkers attempted a lanostane to cucurbitane transformation using Ourisson's strategy. However only elimination products were isolated.(equation 4).[28]



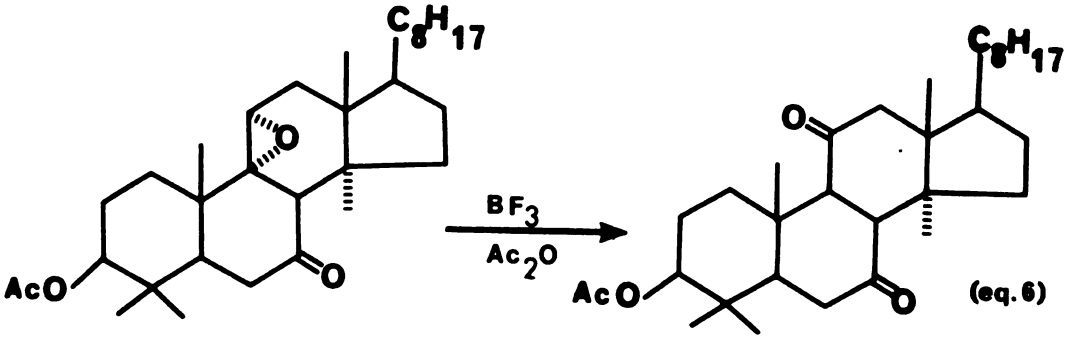
eq. 4

Edwards and Paryzek have reported extensive studies with tetracyclic triterpenes. One of these involved an efficient 10 → 9 methyl migration leading to compounds having the cucurbitacin skeleton.[13] When 3β-acetoxy-9β,11β-epoxylanostan-7-one was treated with boron trifluoride in acetic anhydride, the 9β-methyl isomer was isolated in moderate yield. (equation 5). The course of this rearrangement was found to be very sensitive to substrate configuration and reaction conditions. The corresponding 9α-11α-epoxide isomer reacted sluggishly to give 7,11-diketolanostane product.(equation 6).

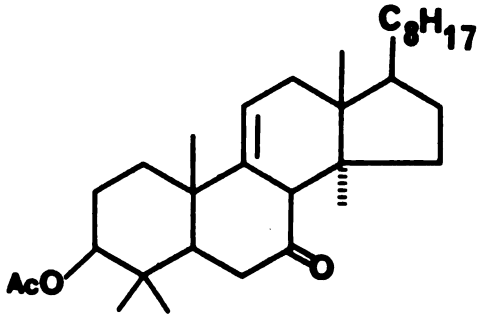


(eq.5)

Since the cucurbitacins possess no functionality at C-7, reductive removal of the 7-oxo group was attempted. This failed and the authors suggest that this difficulty is due to the steric hindrance by the 9β-methyl, 15-methylene and 14α-methyl groups. Unfortunately, the undesired 7-oxo function was necessary for β-epoxidation. Epoxidation of 3β-acetoxy lanost-9(11)-ene gave only the α-epoxide.[29] Preparation of the β-epoxide via the bromohydrin route failed to yield this product. Only the reaction of 3β-acetoxylanost-9(11)-ene-7-one with m-chloro perbenzoic acid gave substantial β-epoxidation.[30] (equation 7).

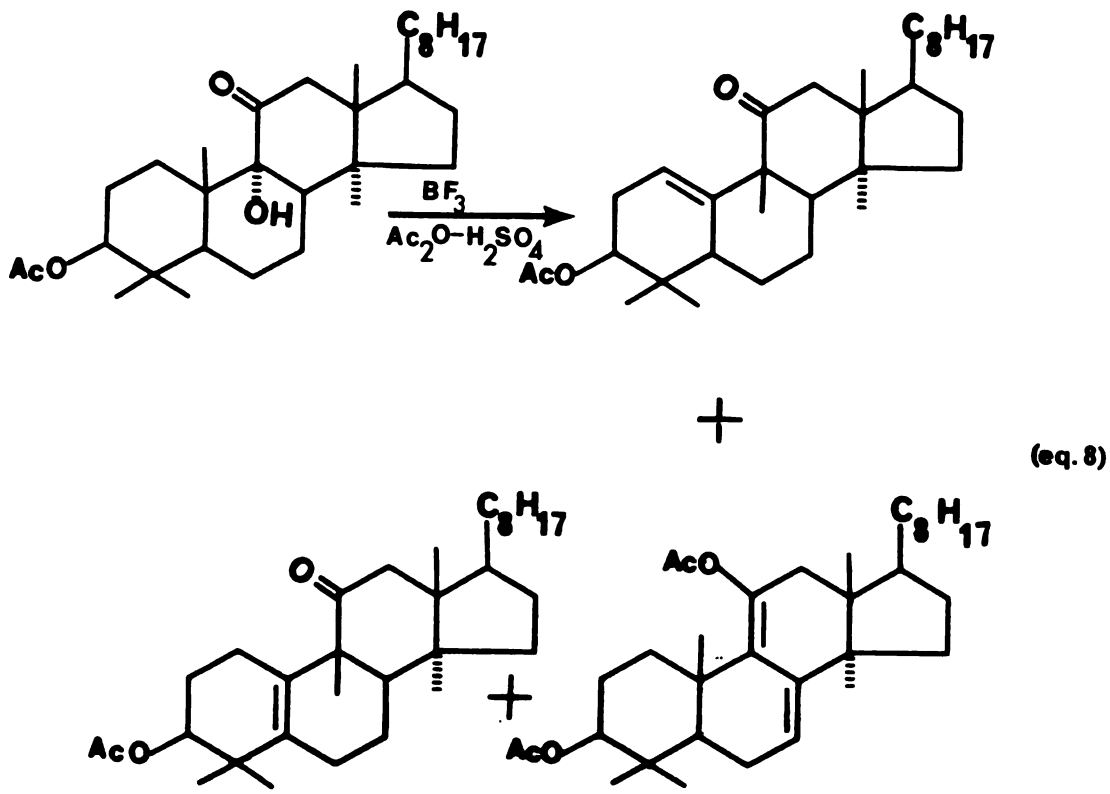


(eq. 6)



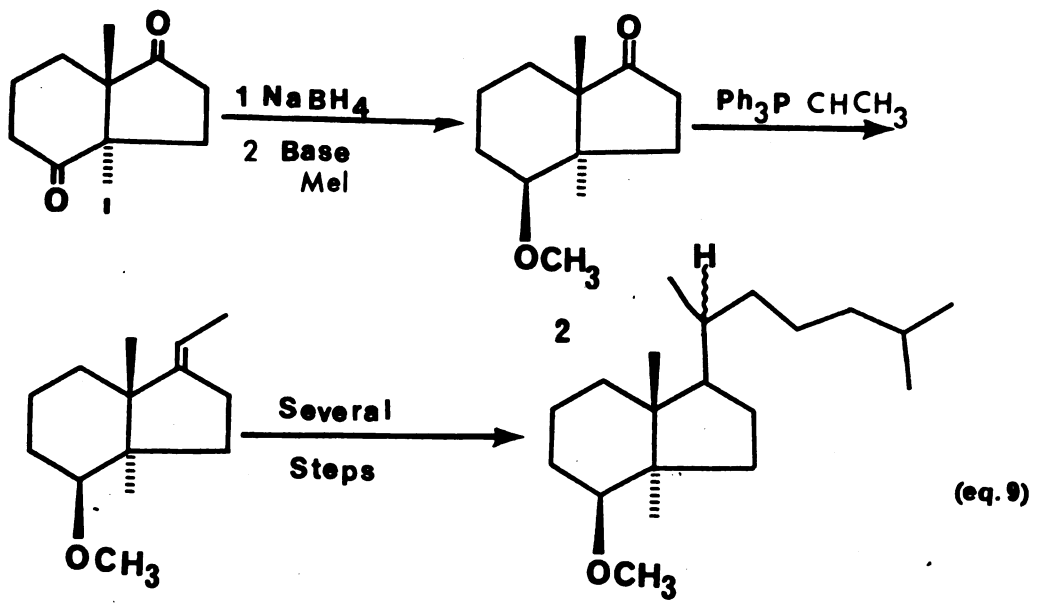
MCPBA → $\alpha+\beta$ Epoxides (eq. 7)

Very recently Edwards and Paryzek have reported another lanostane to cucurbitane transformation.[31] They applied a Westphalen type rearrangement to a 9 α-hydroxy-11-ketone[32] derived from lanosterol in order to induce the migration of C-10 methyl group to C-9. Three products were identified from this reaction. (equation 8). Although this work represents the first synthesis of a true cucurbitacin skeleton, the desired product is formed in poor yield. Improvements are needed for an efficient synthesis of cucurbitacins.



(eq. 8)

As a result of previous work in our laboratory, many transformation of bicyclic dione 1 have been studied and the synthesis of tetracyclic intermediates has been acheived. Because of the difference in reactivity of the two carbonyl functions it is possible to conduct many reactions at the more reactive site without protecting the other. The side chain construction has also been effected on a model compound 2 derived from the parent dione 1.[34] (equation 9).

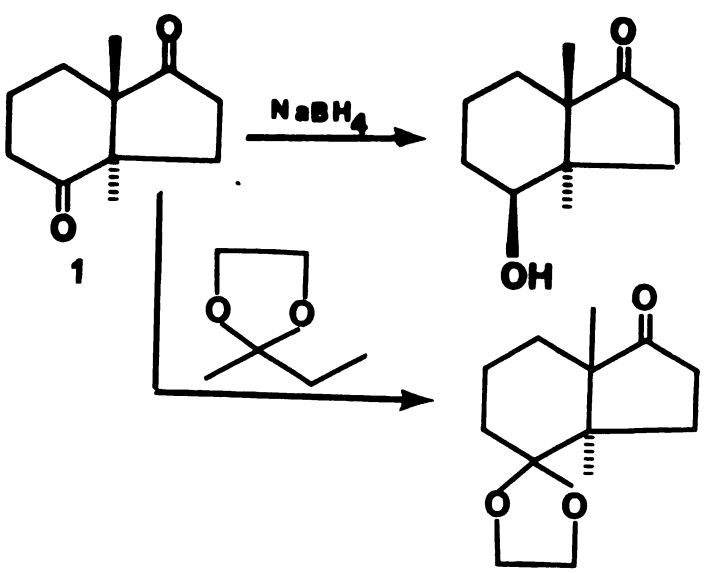


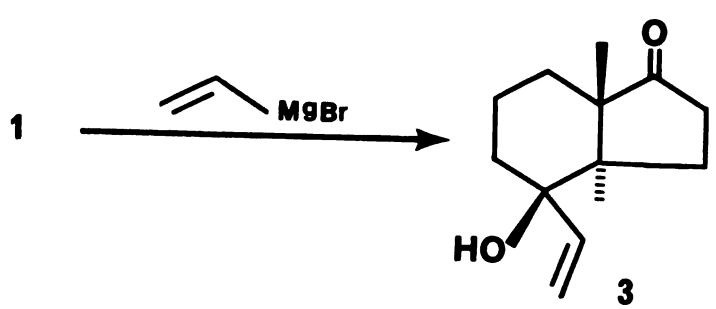
(eq. 9)

The first part of this dissertation discusses an efficient construction of a tetracyclic intermediate ideally suited for cucurbitacin synthesis. Several useful and novel transformations leading to 14α-methyl estrane derivatives will also be discussed. The second part describes the synthesis of a large class of functionalized bicyclic synthons for the construction of tetracyclic triterpenes, starting from trans-1,6-dimethylbicyclo(4,3,0)-nona-2,7-dione 1.

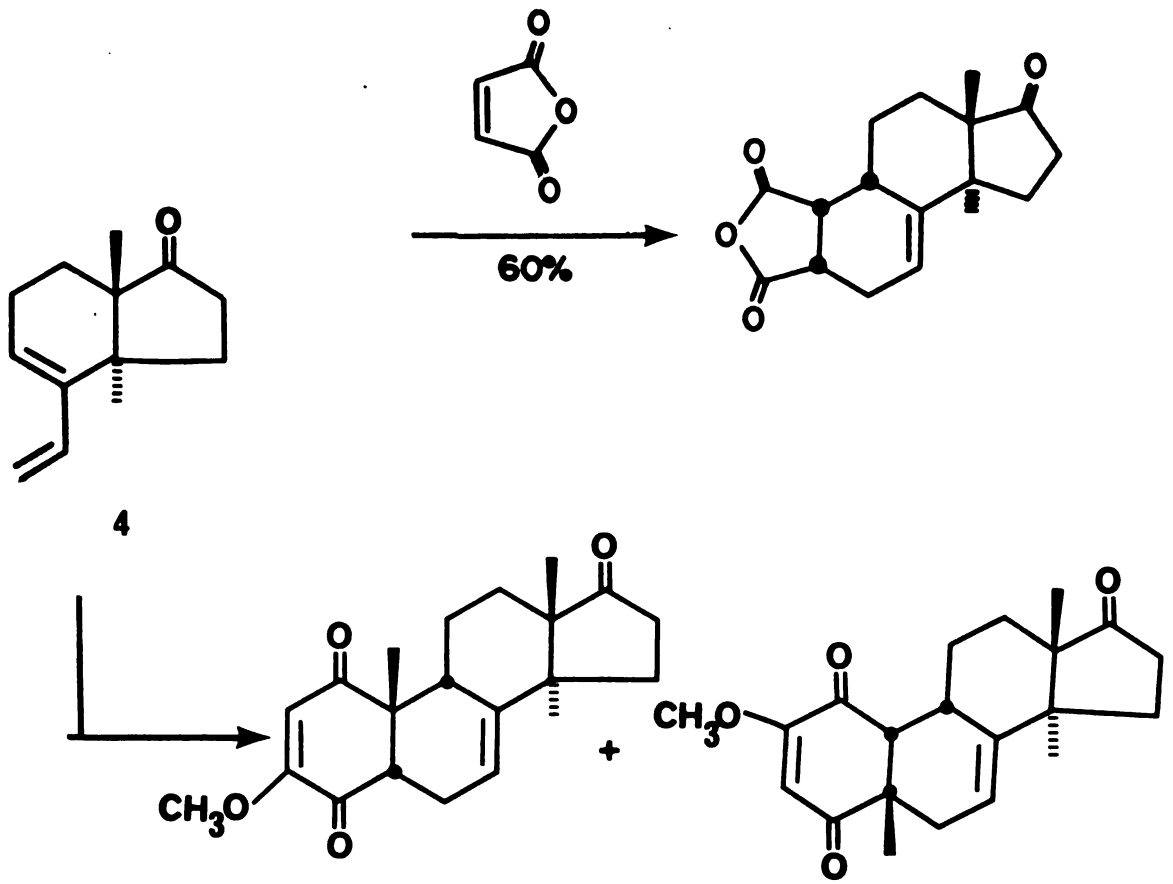
RESULTS AND DISCUSSION

As noted earlier, trans-1,6-dimethyl bicyclo(4,3,0)-nonane-2,7-dione, 1, undergoes nucleophilic reactions selectively at the six membered carbonyl function. For example, sodium borohydride reduction, ketalization, organolithium addition etc. proceed exclusively at this site. The difference in reactivity between five and six membered cyclic ketones was discussed by H.C.Brown almost three decades ago and is attributed to the I-strain effect[35, 36].

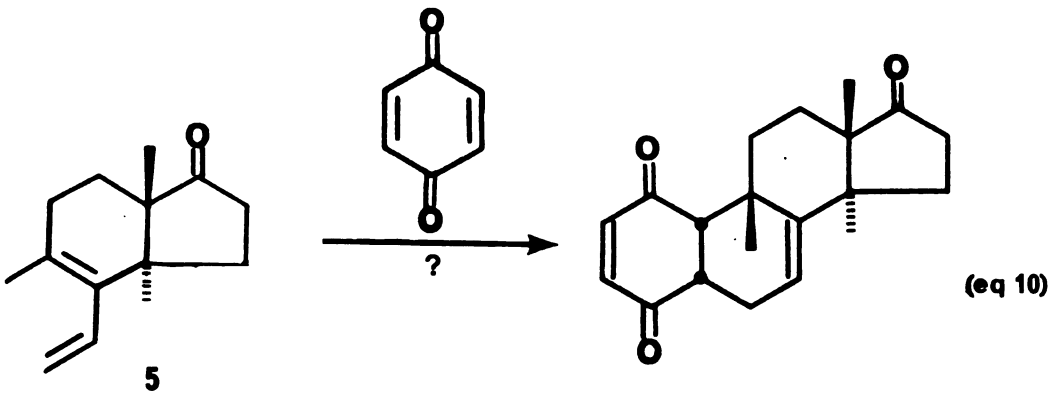




Upon treatment with boron trifluoride etherate in THF-benzene, vinyl carbinol 3 yields diene 4 which undergoes Diels-Alder reactions with various dienophiles. Both the thermal and Lewis-acid-catalyzed Diels-Alder reactions of diene 4 provide the α-endo adducts exclusively. The structures of some of these adducts have been confirmed by X-ray crystallography.



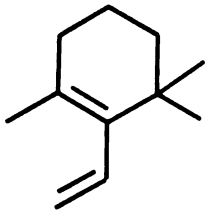
It was the remarkable α-endo selectivity observed in the Diels-Alder reactions of diene 4 that prompted us to investigate the use of the homologous diene 5 in a cucurbitacin total synthesis(eq. 10).



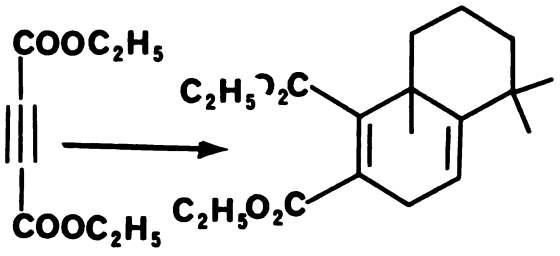
5

(eq 10)

We were concerned about the effect of the additional methyl group on the diene 5; it was expected to cause severe steric crowding as the diene becomes s-cis and nearly planar in the transition state. However many workers have observed a smooth thermal cycloaddition of diene 6 with acetylene dicarboxylic ester[37], thus providing ample precedent for the desired cyclo addition of diene 5. The work of Loperfido in this laboratory has shown that a (1,5) sigmatropic rearrangement of 6 to an isomeric diene having exocyclic double bonds is slow at 200° C. The Diels-Alder reaction, however, proceeded at ca. 110° C, providing no rearranged dienes (equation 11).

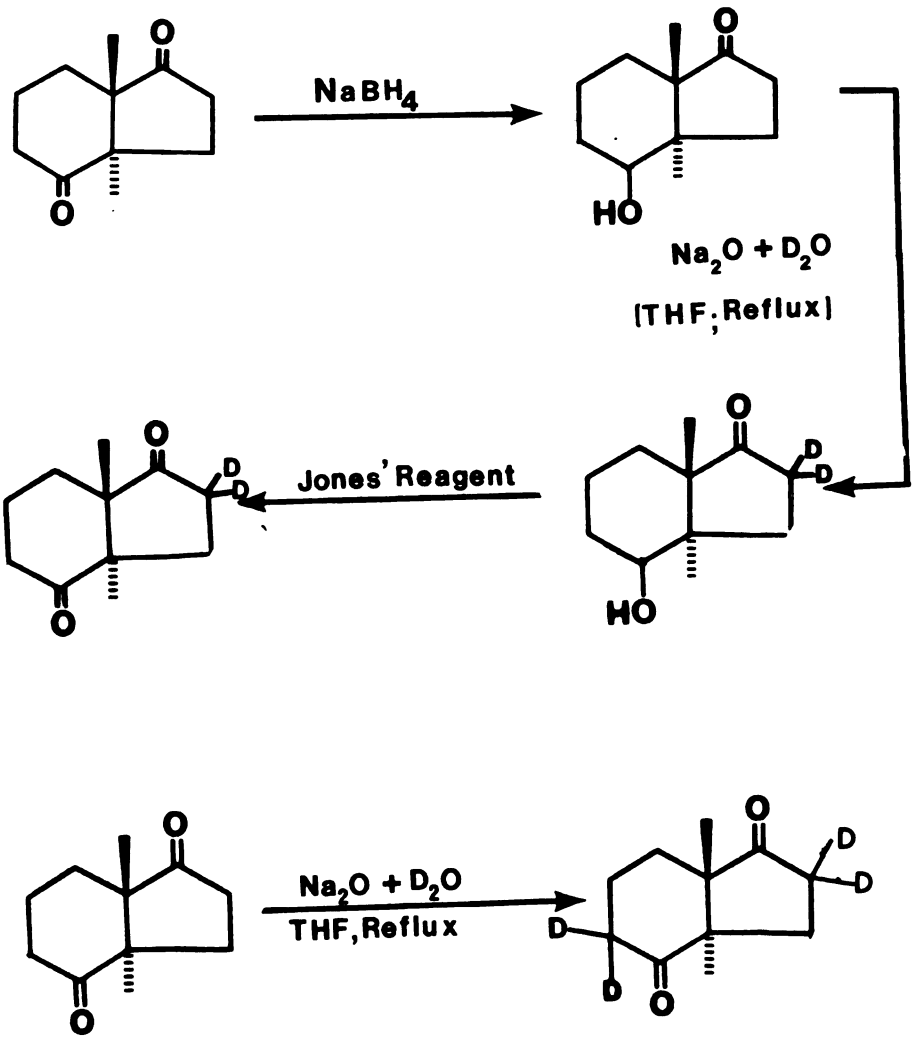


6



(eq 11)

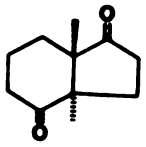
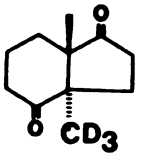
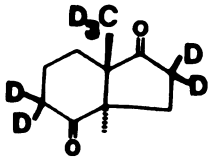
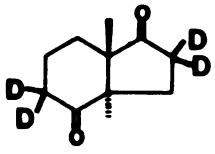
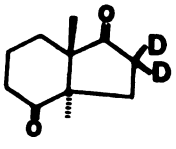
Previous studies in our laboratory have described the kinetic and thermodynamic trapping of enolates derived from dione 1. It has been observed that both kinetic and thermodynamic monoenolates are formed at the six-membered carbonyl site. In order to confirm this observation, a deuterium labelling study was undertaken. The incorporation of deuterium into the α-positions by base-catalyzed exchange (Na_2O, D_2O) was followed by mass spectroscopy. By analysing the mass spectra of several deuterated derivatives of 1, we discovered that the base peak ion (m/e 110 in 1) contained deuterium in the 3-position (steroid numbering) of the six-membered ring and not in the five-membered ring. The molecular ions and base peaks of the parent dione and its deuterated derivatives are summarized in Table 1. The trideutero (entry 2) and the heptadeutero (entry 3) derivatives were reported earlier[38]. The tetra and dideutero derivatives were synthesized in the following manner (Scheme 2).



Scheme 2

TABLE # 1

Mass spectral fragments for 1 and its deuterated derivatives.

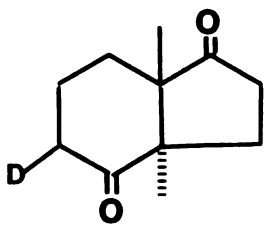
Entry #	Compound	M^+	base peak
1		180	110
2		183	113
3		187	115
4		184	112
5		182	110

Entries 2 and 3 showed that the angular methyl groups are both retained in the base peak, whereas entries 4 and 5 [illegible] indicated that the methylene group adjacent to the five-membered carbonyl function was lost in forming the base peak. With this information in hand, the extent and the location of deuterium incorporation was calculated from the mass spectra of aliquots removed at frequent intervals from the reaction mixture and is summarized in Table 2.

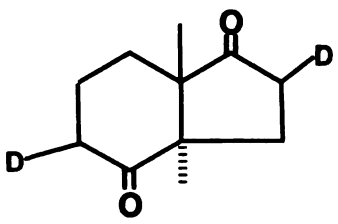
TABLE 2

Extent of deuterium incorporation at the α-positions of dione 1

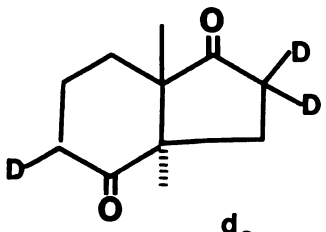
Time	% d_0	% d_1	% d_2	% d_3	% d_4
5 min	35.92	38.36	18.71	6.00	1.00
10 min	10.36	34.80	32.68	16.74	5.40
15 min	8.69	30.06	32.82	19.88	8.53
30 min	7.42	28.80	32.6	21.4	9.8



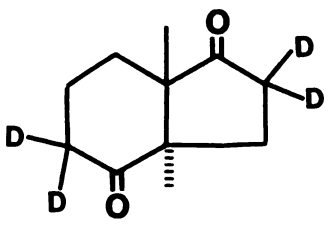
d_1



d_2



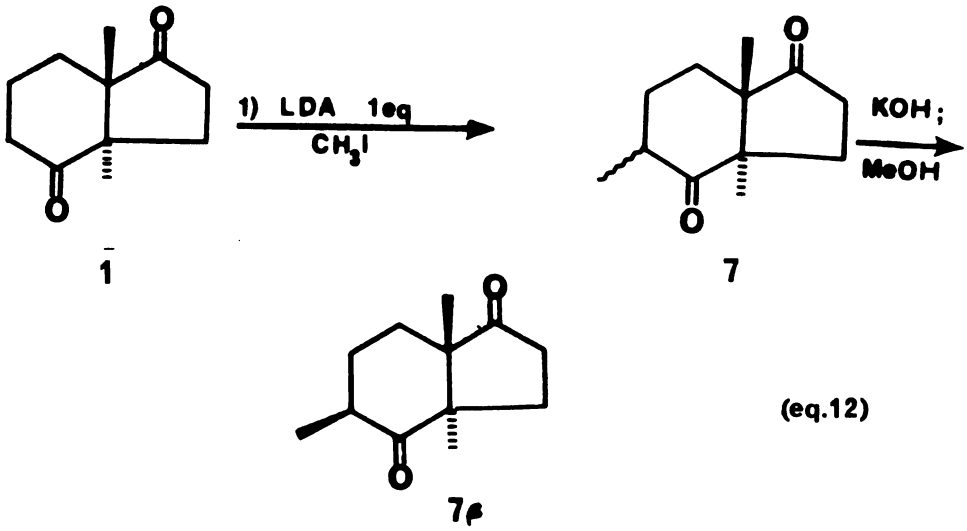
d_3



d_4

These results are in excellent agreement with trapping experiments carried out by Jacob Tou in our laboratory.

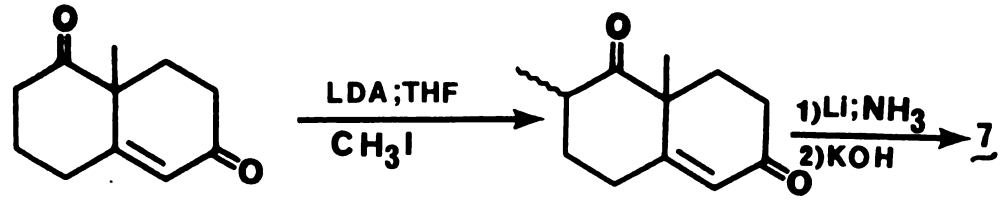
The parent dione 1 on treatment with one equivalent of lithium diisopropylamide (LDA) in THF-HMPA followed by alkylation with methyl iodide gave a mixture of monomethylated diastereomers 7. This mixture was then equilibrated to the thermodynamically more stable isomer 7β (equation 12) with KOH in methanol (54% yield).



1 7 7β

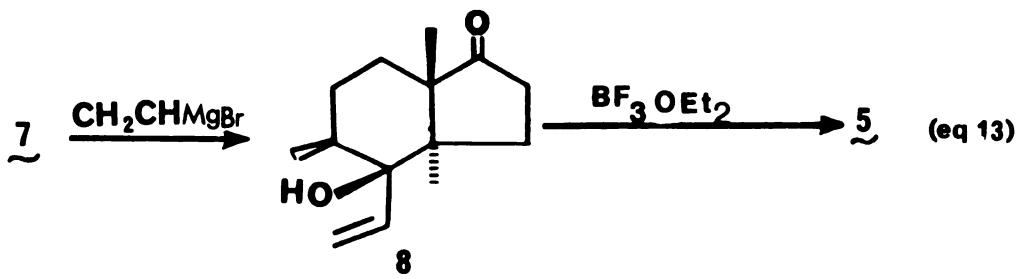
(eq.12)

An alternative synthesis of 7, starting from the mono-alkylated Wieland Miescher ketone[39] was explored according to scheme 3. However the overall yield (25%) was very poor due to the poor selectivity observed in the methylation of Wieland Miescher ketone.

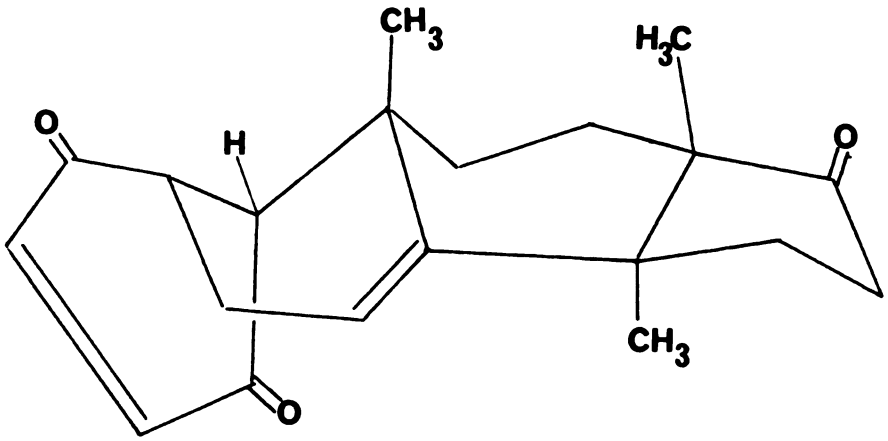


Scheme 3

Addition of vinyl magnesium bromide to compound 7 proceeded smoothly to give the adduct 8 in 98% yield. Dehydration of 8 by the action of boron trifluoride etherate in THF-benzene was found to be very sluggish. However on prolonged treatment with boron trifluoride in THF-toluene a mixture of cisoid and transoid isomers was obtained, which was sufficiently pure to use in studies of the Diels-Alder reaction. The yield of the required diene was not optimized because of the uncertainty involved in the key Diels-Alder reaction (equation 13).

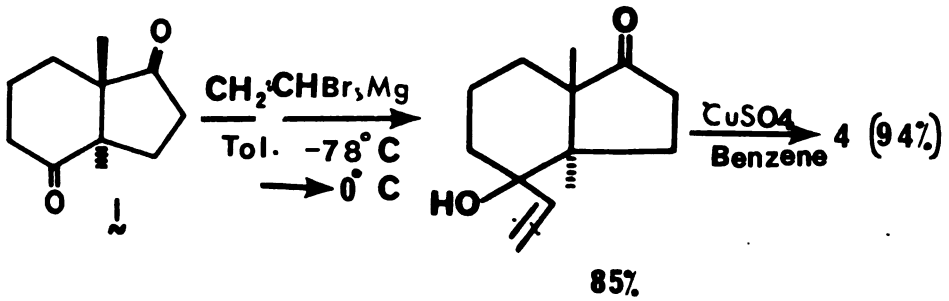


The diene derived from 8 was found to be unreactive towards p-benzoquinone and acetylene dicarboxylic ester under thermal and Lewis-acid-catalyzed conditions. This may be explained in part by steric crowding in the expected α-endo product 9. As a result of the placement of the double bond in ring B (C7-C8), the ring C of 9 is forced into a boat form. This results in severe steric crowding between 9β and the 13β-methyl groups (Figure 2).



Fig, 2. Crowding of the expected α-endo adduct between 5 and p-benzoquinone, as predicted by Dreiding molecular model.

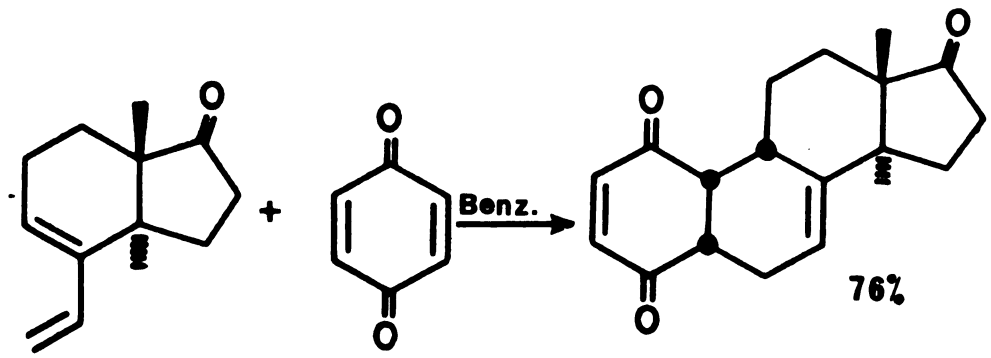
Since the diene 5 failed to yield any adducts, we abandoned that strategy and next explored the chemistry of the Diels Alder adduct derived from p-benzoquinone and diene 4. Our ultimate goal in this study was to introduce the 9β-methyl group into the tetracyclic skeleton. To this end an improved procedure for the synthesis of 4 was developed as shown in scheme 4.



Scheme 4

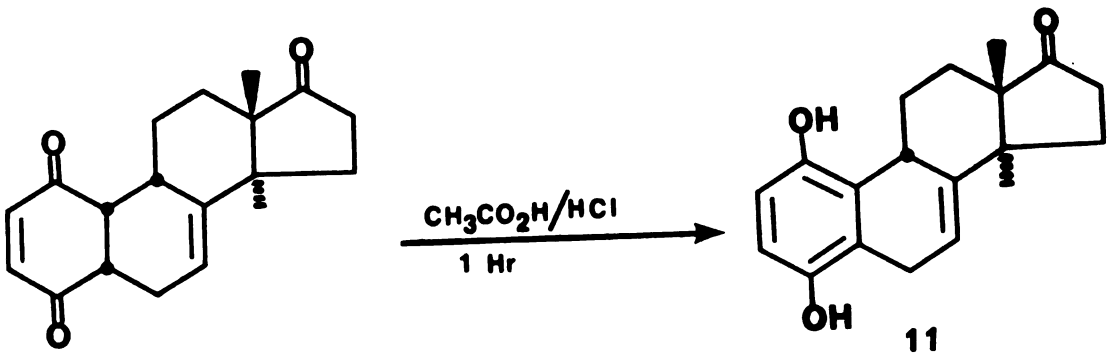
The poor to moderate yields from our previously reported preparation of vinyl carbinol 2 were attributed to extensive enolization of the carbonyl functions by the Grignard reagent in THF solution. By performing the reaction at low temperature in a hydrocarbon solvent with freshly prepared vinyl magnesium bromide, we obtained an excellent yield (80 to 85%) of 2. Next we observed that treatment of 2 with copper sulfate in hot benzene gave facile dehydration to 4 with no trace of the isomerized diene[40].

In an attemt to improve the yield of the quinone adduct 10, the Diels Alder was carried out with stannic chloride and boron trifluoride as catalysts. However the desired adduct was obtained only in moderate yield (45%). Isomerization of the diene 4 to an extent of 25% was also observed during the Lewis-acid-catalyzed reactions. Fortunately slow addition of diene 4 to a refluxing solution of benzoquinone in benzene provided the desired adduct in over 70% yield. In this case the thermal Diels Alder reaction gave better results than the Lewis-acid-catalyzed modification. Two isomers were actually obtained in the thermal Diels Alder reaction. The minor isomer was observed to rearrange slowly to the major isomer in solution. Therefore rigorous structural assignment of the minor isomer was not attempted. However the major isomer was tentatively assigned the α-endo configuration based on the known structures of related adducts from other quinone dienophiles.



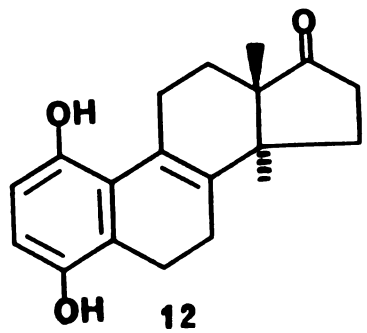
4 10

Brief acid treatment of 10 according to the procedure of Ansell and coworkers[41] gave the nonconjugated aromatic isomer 11 contaminated with a small amount of the conjugated isomer 12. (Equation 14).



11

+



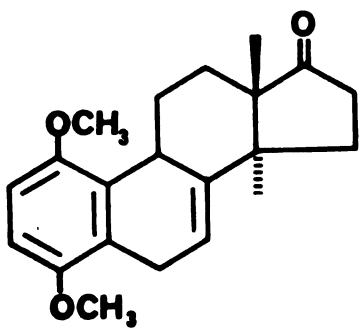
12

(eq.14)

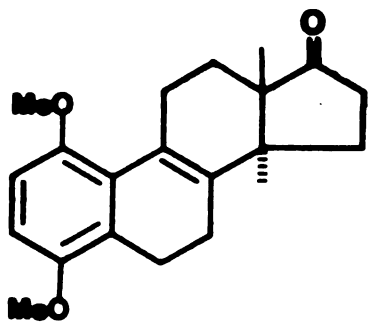
One notable feature observed for 11 is the large homoallylic coupling constant between the 6α and 6β hydrogens and the 9β hydrogen ($J_{6\alpha,9\beta}$ =5.5 Hz, $J_{6\beta,9\beta}$ =8.0 Hz). Large homoallylic coupling constants of this kind have been reported for 1,4-dihydronaphthalene systems of rigid conformation[42].

In compound 11, the large homoallylic coupling constants, together with other coupling constants ($J_{6\beta,7}$=5.2 Hz, $J_{6\alpha,6\beta}$ =22.6 Hz), serve to establish the assigned configuration.

The relative insolubility of 11 and 12 hindered their purification, so this mixture was converted in excellent yield (91%) to the dimethyl ether derivative 13. Chromatography of 13 on silica gel gave crystalline 13 with a small amount of 14.



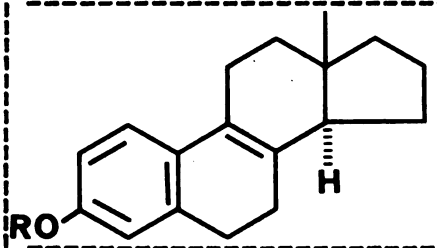
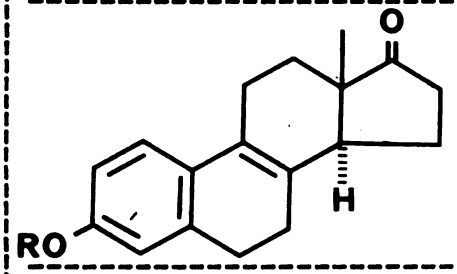
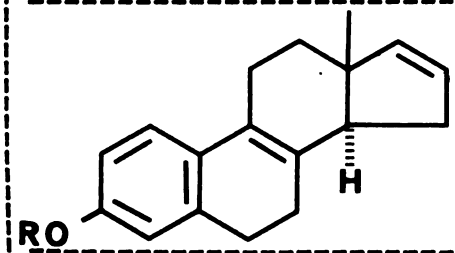
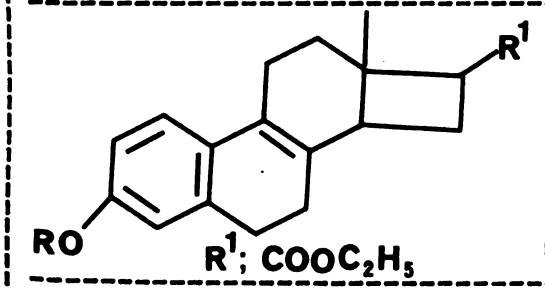
13



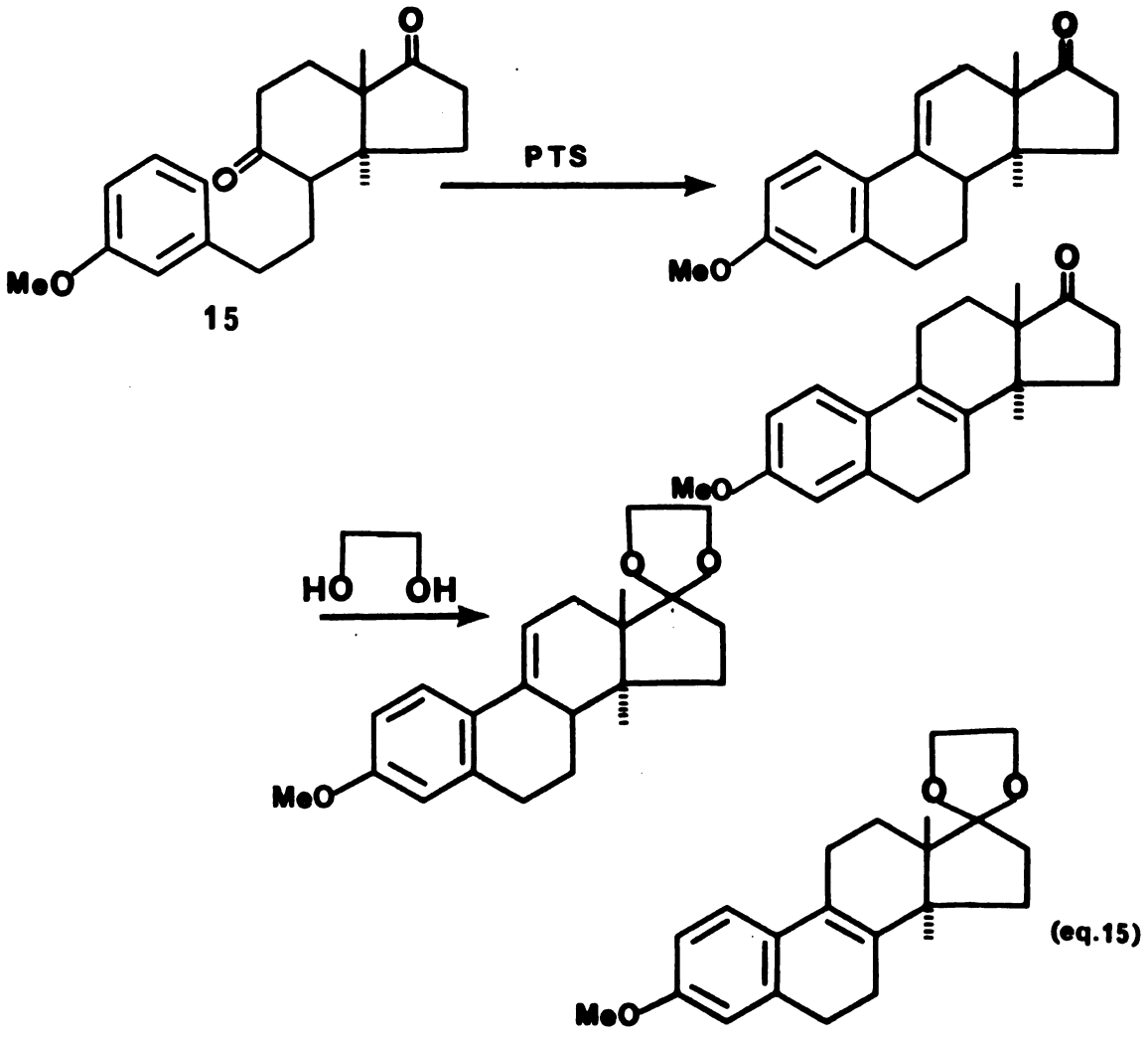
14

It is known that for steroidal analogs having an aromatic A ring, the $\Delta^{8,9}$ and $\Delta^{9,11}$ isomers may be equilibrated by acid treatment, and the equilibrium ratio depends upon structural changes in ring D. Hainaut and Bucourt have studied the effect of ring D puckering and angle strain on the equilibrium composition of $\Delta^{8,9}$and $\Delta^{9,11}$ isomers of estratetraenes and their results are summerized in table 3 [43].

TABLE 3. Equilibrium composition of $\Delta^{8,9}$ and $\Delta^{9,11}$ isomers of estratetraenes in acid.

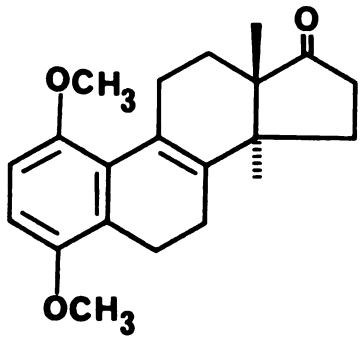
Compound	% $\Delta^{8,9}$ in acid	% $\Delta^{9,11}$ in acid
	40.	60
	36	64
	12	88
	2	98

Assuming no serious perturbation by the 14 α-methyl group we expect a 40:60 ratio of $\Delta^{8,9}$ and $\Delta^{9,11}$ isomers of 14. Indeed a recent report by Bull and others show that the equilibrium composition of $\Delta^{9,11}$ to $\Delta^{8,9}$ product isomers is 1:1 during the acid catalyzed cyclization of compound 15. He also found that on conversion of the ketone function at C-17 to a ketal this isomer ratio changed to 40:60 in favor of the $\Delta^{8,9}$ isomer (equation 15)[44].

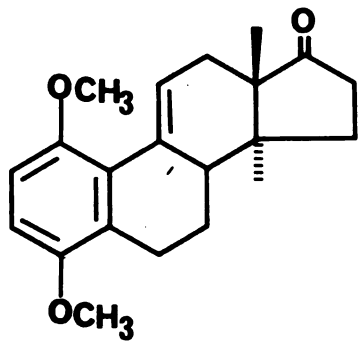


(eq.15)

Treatment of 13 and 14 with p-toluene sulfonic acid gave a 1:2 mixture of conjugated isomers 14 and 16 in quantitative yield. The angular methyl groups in 14 and 16 showed ^{1}H NMR signals that correspond closely to those reported from the 3-methoxy-14-methylestratetraen-17-ones by Bischofberger and Bull[44]. However the C-11 olefinic proton in 16 has shifted downfield due to its proximity to the C-1 methoxy group. The predominance of this isomer in the acid catalyzed equilibrium mixture is unexpected, when one considers long range conformational effects[43] and the crowding of the 1-methoxy substituent.

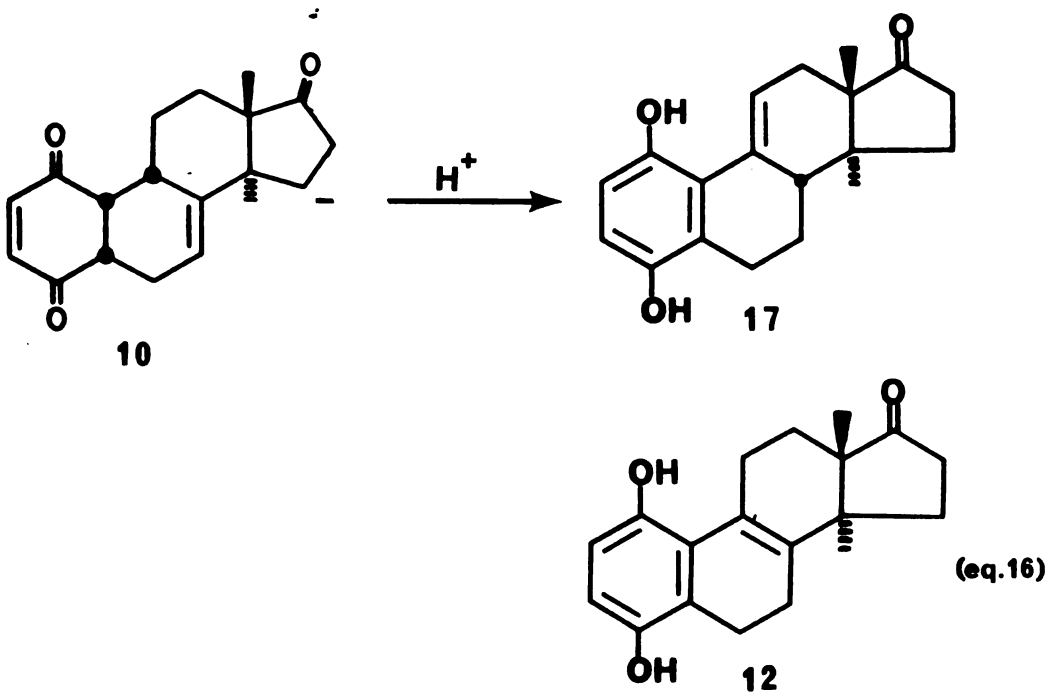


14



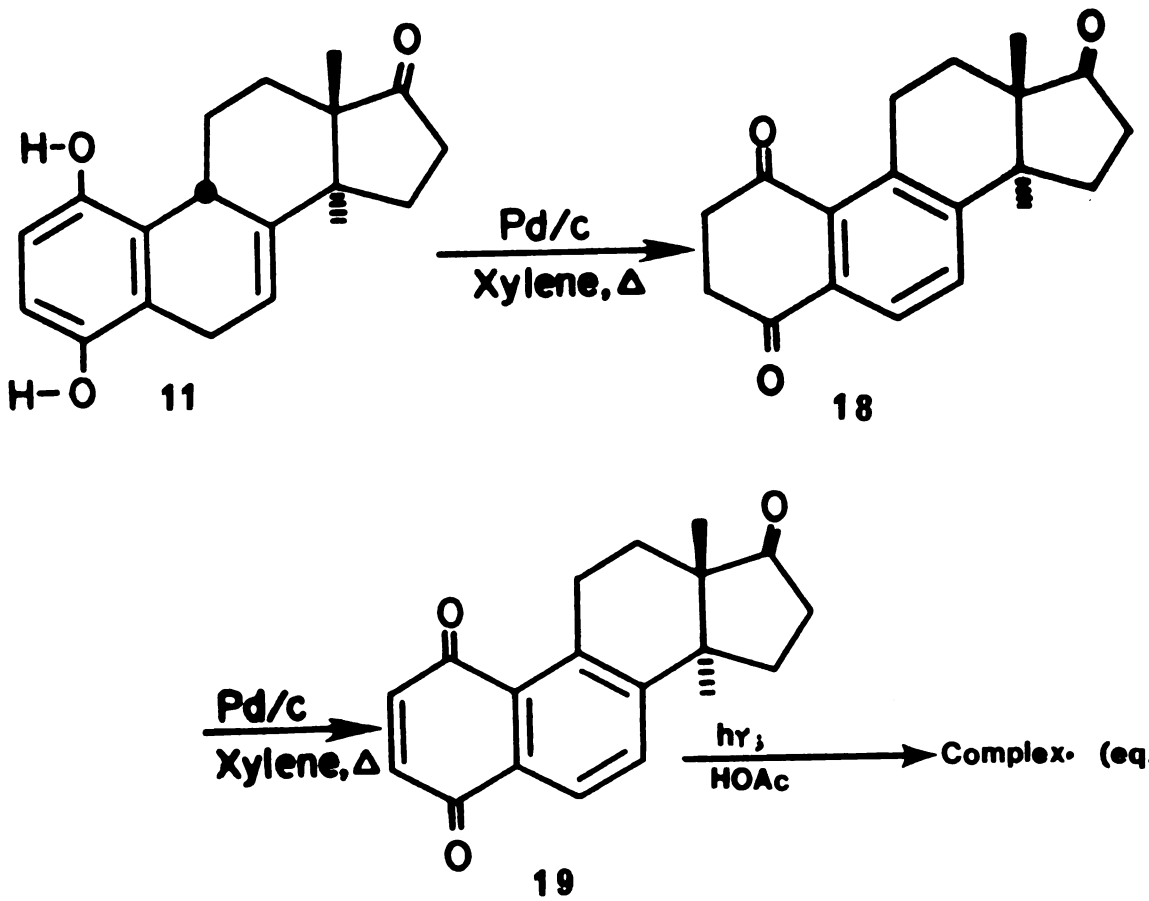
16

With regard to the possible conversion of these 14α-methyl estrane derivatives to cucurbitacins, it is clear that the 9(11) double bond in 16 might serve as a latent 11-keto function. However the petential utility of such an approach was diminished by the substantial amount of 14 that accompanied 16. We anticipated that this difficulty might be lessened in the hydroxyl series due to the smaller size of OH as compared to OMe, and were pleased to find that 11 (or even 10) was isomerized to the required 9,11-double bond isomer 17 in over 80% yield by acid treatment. This transformation can now be achieved by dissolving the initial adduct 10 in glacial acetic acid containing a small amount of concentrated hydrochloric acid, and allowing the solution to remain overnight at room temperature (equation 16).



With previous work in mind, it seems likely that the predominant formation of the $\Delta^{9,11}$ isomer in our studies is due to a stabilizing influence of the oxygen function at C-1. The close proximity of the C-1 hydroxyl group to C-11 was confirmed by the chemical shift of the vinyl proton at C-11 (δ 7.1 ppm). The C-11 hydrogen in the corresponding 14α-methyl estrane derivatives reported by Bull appeared at 6.2 ppm in the ^{1}H NMR .

Attempted dehydrogenation of 11 and its derivative led to some novel transformations. When 11 or a mixture of 11 and 12 was treated with a palladium catalyst (10% Pd-C), in refluxing xylene, 18 and 19 were isolated, their amount and ratio varying with the reaction conditions. If the weight ratio of catalyst to substrate was 0.3 or less the B-aromatic-1,4-diketone 18 was obtained in 50% yield. With larger amounts of catalyst (ratio ca 1.0) and a longer reaction time (24 hrs), the naphthaquinone derivative 19 was formed in almost quantitative yield. We explored the possibility of effecting a photochemical oxidation of 19 at C-11, following the procedure of Rommel and Wirz for 5-methyl-1,4-naphthaquinone [45]; however this reaction gave complex mixtures (equation 17).

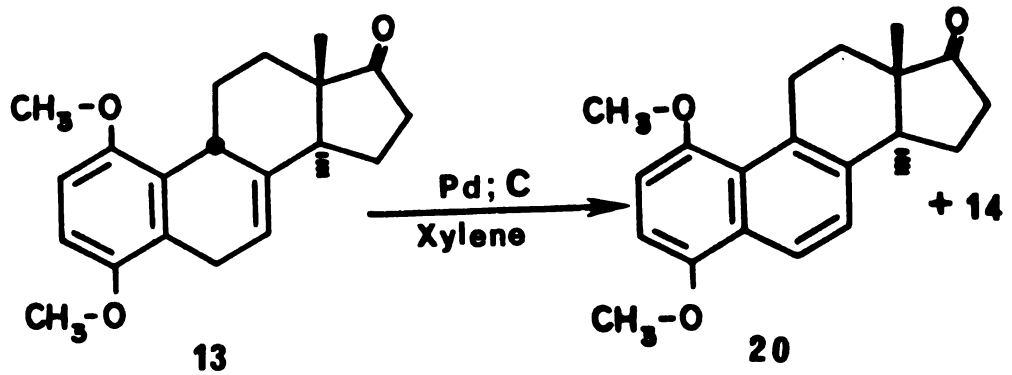


The formation of 18 in the palladium-charcoal dehydrogenation was unexpected. The keto-enol tautomerism of 1,4-dihydroxy naphthalenes has been studied by Bruce and others[46], and these workers have found that additional hydroxyl groups in the 5 and 8 positions of the 1,4-dihydroxynaphthalene system favored the 1,4-diketo form over the enol tautomer. The unexpected stabilization of the carbonyl tautomer in this case was attributed to intramolecular hydrogen bonding. However there

is no such stabilization in compound 18. We speculate that the peri interactions in 18 may be less than those in the naphthalene diol tautomer thus stabilizing 18. The four protons on C-2 and C-3 displayed as a singlet at δ 3.0ppm in excellent agreement with that of similar compounds.

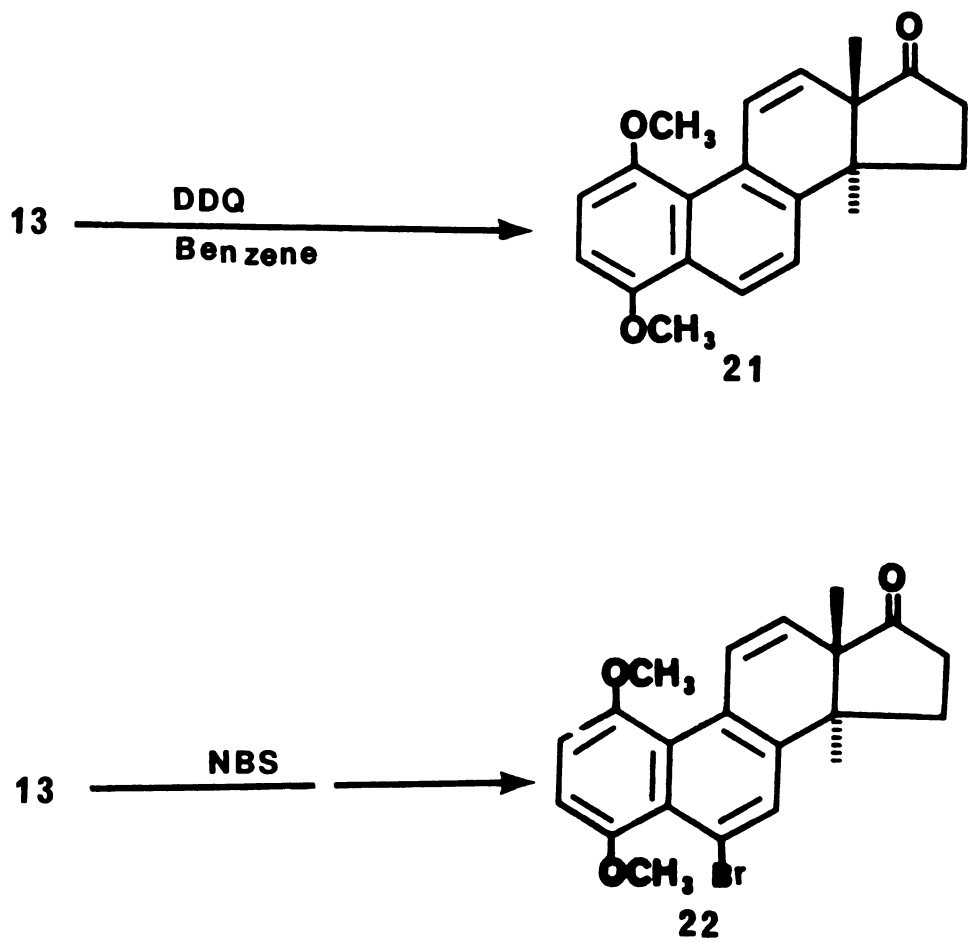
In an attempt to prepare AB aromatic 14α-methylestrane derivatives, similar dehydrogenations were effected with the dimethyl ether derivative 13. Treatment of 13 with Pd/C in refluxing xylene gave a mixture of $\Delta^{8,9}$ and the desired AB aromatic compound 20. Although the mass recovery was nearly quantitative, this reaction proved to be capricious, and the products were extremely difficult to separate. A clean high yield oxidation of 13 to 21 was acheived by treatment with dicyano dichloro parabenzoquinone, but the 11,12-double bond resisted all hydrogenation efforts. Finally, N-bromosuccinimide reacted with 13 to give 22, a bromo derivative of 21 (scheme 5).

Scheme 5

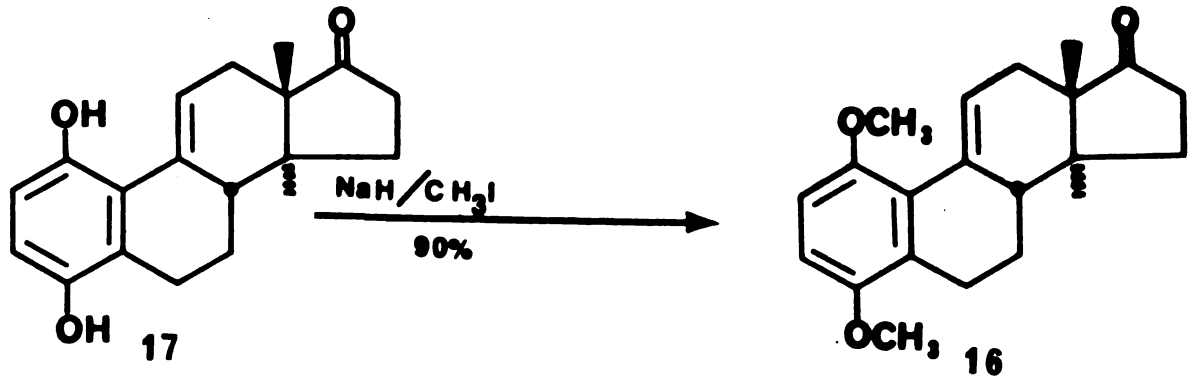


13 20

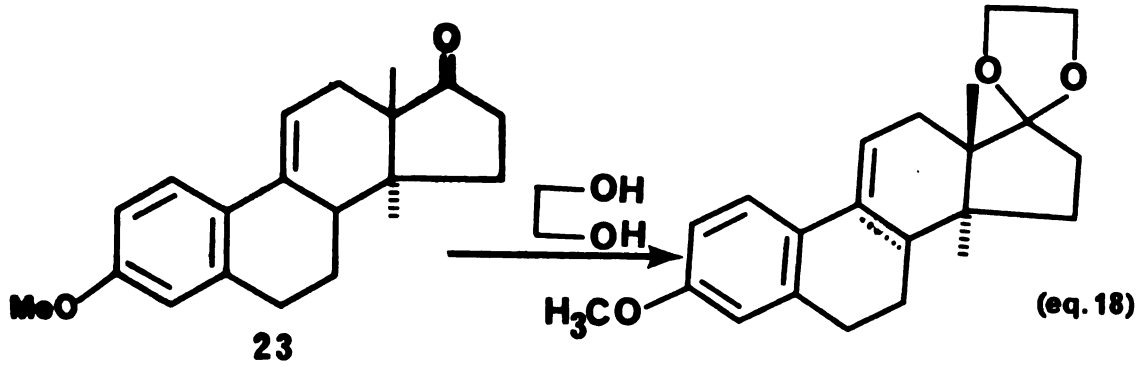
Scheme 5(cont)



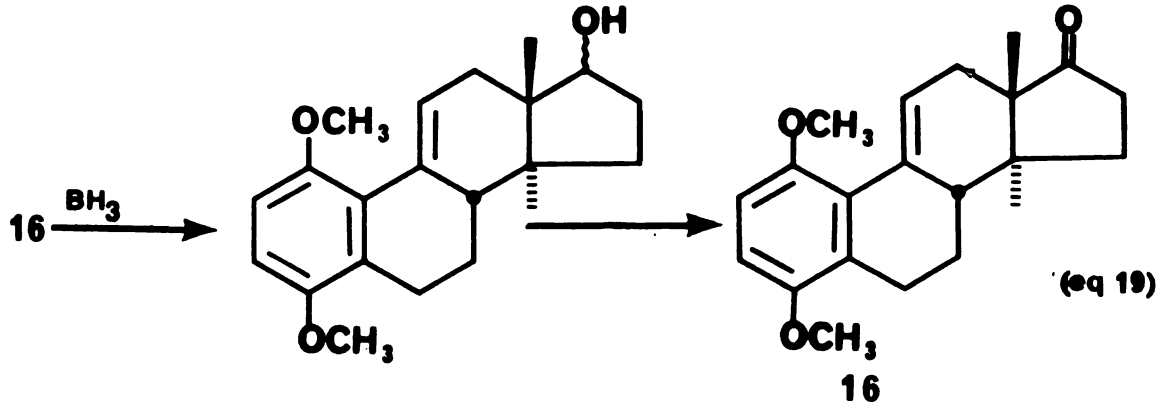
Since the facile preparation of compound 17 from dione 1, had been demonstrated, our attention was next turned to the transformation of this olefin into the 11-oxo derivative. Again, because 17 proved to be insoluble in most common organic solvents, it was converted in excellent yield (90%) to the bismethoxy derivative 16, by reaction with sodium hydride and methyl iodide.



The formation of 11α-alcohols of steroidal $\Delta^{9,11}$ olefins is well known[47]. As the stereochemistry at C-11 was not critical to our synthesis, a similar hydroboration was attempted on 16. The protection of ketone was not undertaken because this functional group is known to be very hindered and therefore unreactive. Also Bull et al[43] found that upon ketalization of compound 23, the $\Delta^{9,11}$ double bond shifted substantially to the $\Delta^{8,9}$ position. Furthermore, an extremely poor yield (40%) of the ketal was realized in their synthesis (equation 18).



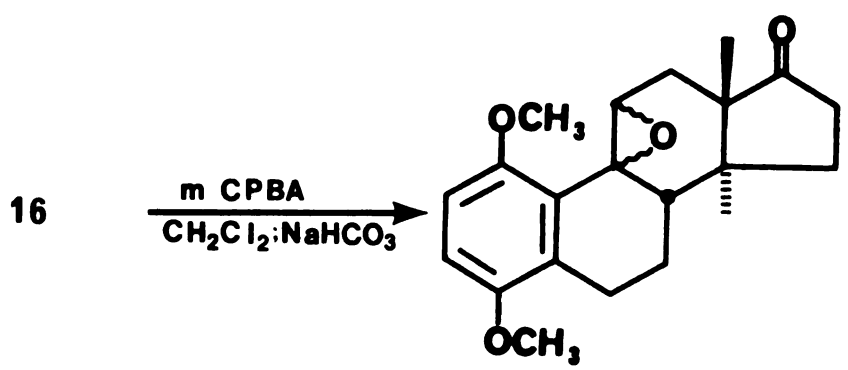
Hydroboration-oxidation of 16 surprisingly gave reduction of the C-17 carbonyl. High resolution NMR revealed it to be a mixture of α and β alcohols, which was readily oxidised to 16 with pyridinium chlorochromate[48] (equation 19).



(eq 19)

Since the introduction of an oxygen function at C-11 via hydroboration failed we next studied the rearrangement of epoxides derived from 16. Initial attempts to epoxidize 16 with unbuffered meta chloro perbenzoic acid gave rise to several rearranged products (mainly allylic alcohols and 11-ketones). However, epoxidation of 16 by the two phase dichloromethane/aqueous potassium carbonate procedure of Anderson and Veygeslu[49] afforded a crystalline, but extremely acid sensitive epoxide mixture. The ratio of these epoxides was determined by ^{1}H NMR, to be 70:30 favoring the β-epoxide. The two epoxides exhibited the following relevant resonances in ^{1}H NMR (250 MHz, $CDCl_3$). A doublet at δ 4.88 (J=5.8 Hz)

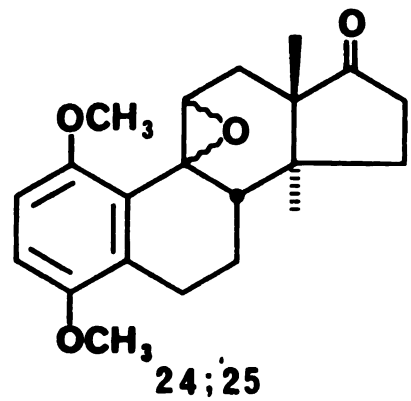
and a triplet at δ 5.05 (J=2.14 Hz) for 24 and 25 respectively. The coupling constants observed for these two compounds were in excellent agreement with that predicted from an inspection Dreiding models and an application of Kouplus equation. They were also similar in magnitude to that observed for somewhat related steroidal 9,11-epoxides[50]. However the large chemical shifts observed for 24 and 25 (4.88 and 5.05 respectively) might be attributed to the influence of C-1 methoxy group.



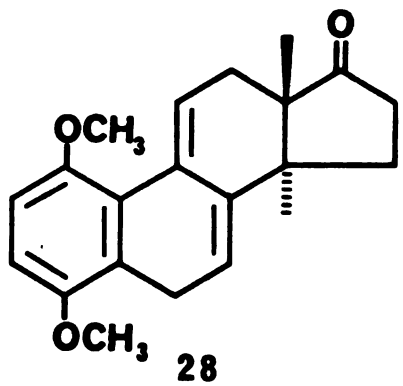
24 = 9α,11α

25 = 9β,11β

We then examined the rearrangement of epoxides 24 and 25. Lithium perchlorate was selected as our first Lewis acid because it cleanly catalyzes the rearrangement of certain cyclohexene epoxides[51] into the corresponding cyclohexanones. When the epoxides 24 and 25 were treated under reflux in dry benzene containing a small amount of lithium perchlorate, the products obtained included the expected 9αH and 9βH 11-ketones 26 and 27 together with a substantial amount of Δ^{6}, $\Delta^{9,11}$ diene 28 in 30 to 40% yield. (equation 20)



24;25



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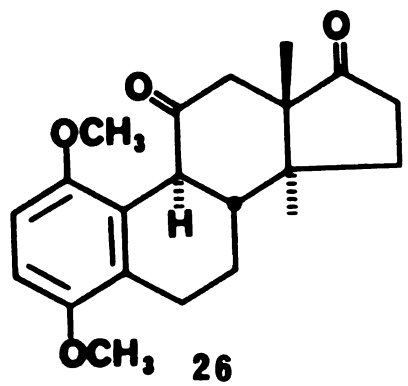
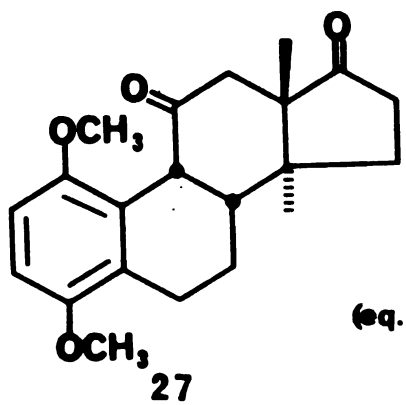


26

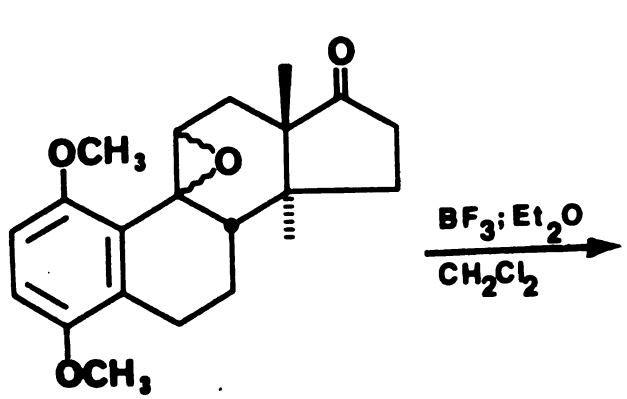
+



27

(eq. 20)

The more potent Lewis acid boron trifluoride etherate in methylene chloride as a catalyst for epoxide rearrangement proved to be too severe, providing diene 29 in poor yield (30%) as the only identifiable product (equation 21).

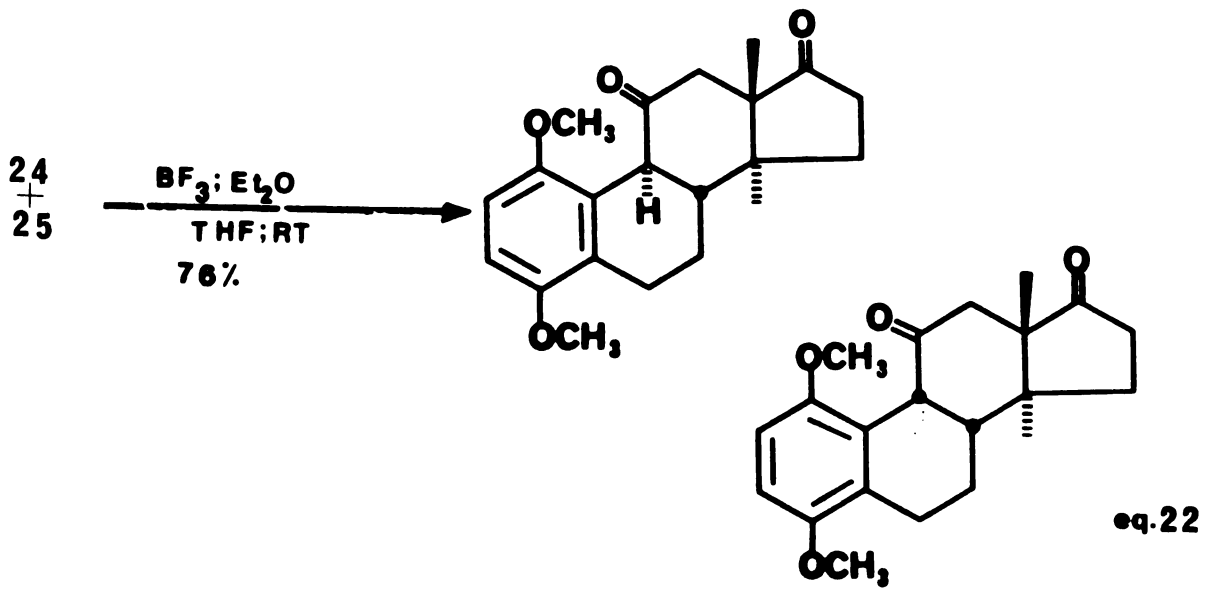


29

eq. 21

Fortunately, the conversion of epoxides 24 and 25 to the 11-keto isomers 26 and 27 was improved by conducting the rearrangement of these epoxides in tetrahydro furan solution containing boron trifluoride etherate as a catalyst. The milder reaction condition of the THF medium is presumably due to the relatively strong Lewis basicity of this solvent and the resulting decrease in the acidity of the complexed Lewis acid. Although addition of triethylamine has been suggested for the cleavage of sensitive epoxides, this proved to be of no advantage in this study. (equation 22).

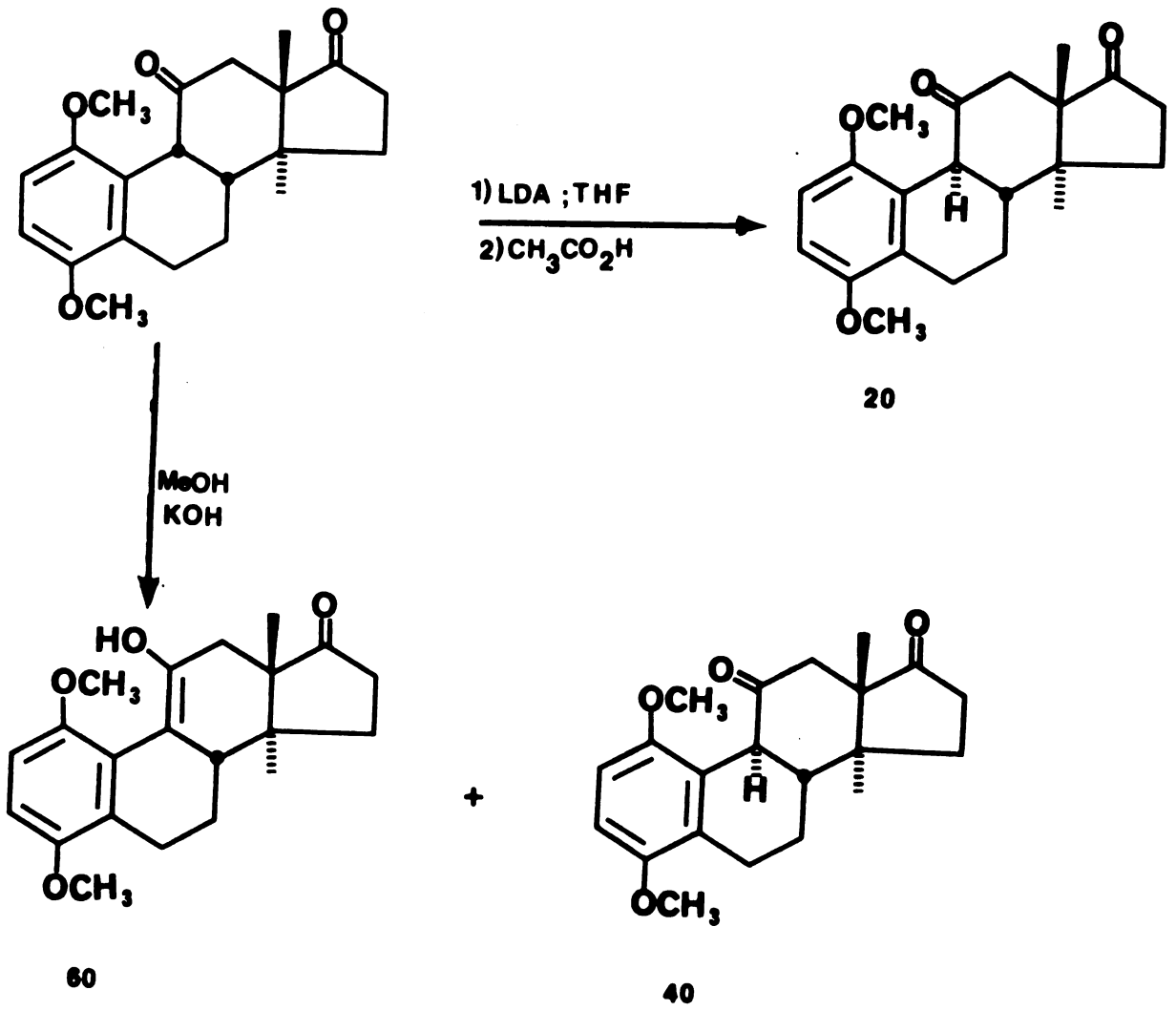
The stereochemical assignments at C-9 in 26 and 27 were based mainly on ^{1}H NMR evidence. The 10.4 Hz coupling constant between the 8 and 9-αhydrogens of 26 agreed with the assigned trans configuration. A similar coupling constant has been reported for the A-aromatic steroidal analogs. ($J_{9\alpha,8\beta}$=9.5 Hz for 11-oxo-9α-estradiol-3-benzyl ether[52].



eq.22

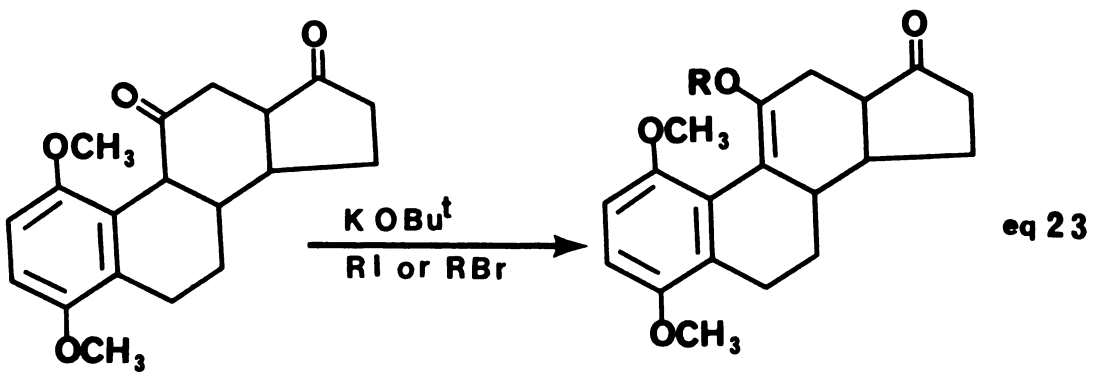
However one must now consider the abnormally large 8,9 hydrogen coupling (12.8 Hz) for the molecule assigned as the cis isomer 27. Clearly some kind of structural deformation is needed to explain this value. An inspection of molecular models suggest that a boat like conformation of ring B alleviating steric interaction between 14α-methyl group and ring A, causes a near eclipsing of the hydrogens at C-8 and C-9. The relatively low chemical shift observed for 14α-methyl group (1.5 ppm) of 26 might result from the deshielding effects of 11-keto and 17-keto functions, assuming that ring C adopts a chair conformation [53].

A study was then undertaken in order to determine the products derived under kinetic and equilibration conditions. Kinetic protonation of the enolate anion derived from 26 and 27 gave mixtures in which 27 (the cis epimer) predominated (75%) Protonation under equilibrating conditions (KOH/MeOH) yielded the trans isomer 26 and the enol 30 in the ratio 40:60. No observable amount of 27 was found in the crude product mixture. However upon purification on silica gel, 30 underwent slow isomerization to 27. The enol proton of 30 gave a ^{1}H NMR signal at δ 7.2 ppm and this disappeared on exchange with D_2O. The formation of the 9α-isomer under thermodynamic control indicates that the 14α-methyl group has a strong influence on this stereochemical outcome. In steroidal analogs bearing an 11-keto function, the 9β isomer is found to be more stable than the 9α isomer.[25] (scheme 6).



Scheme 6

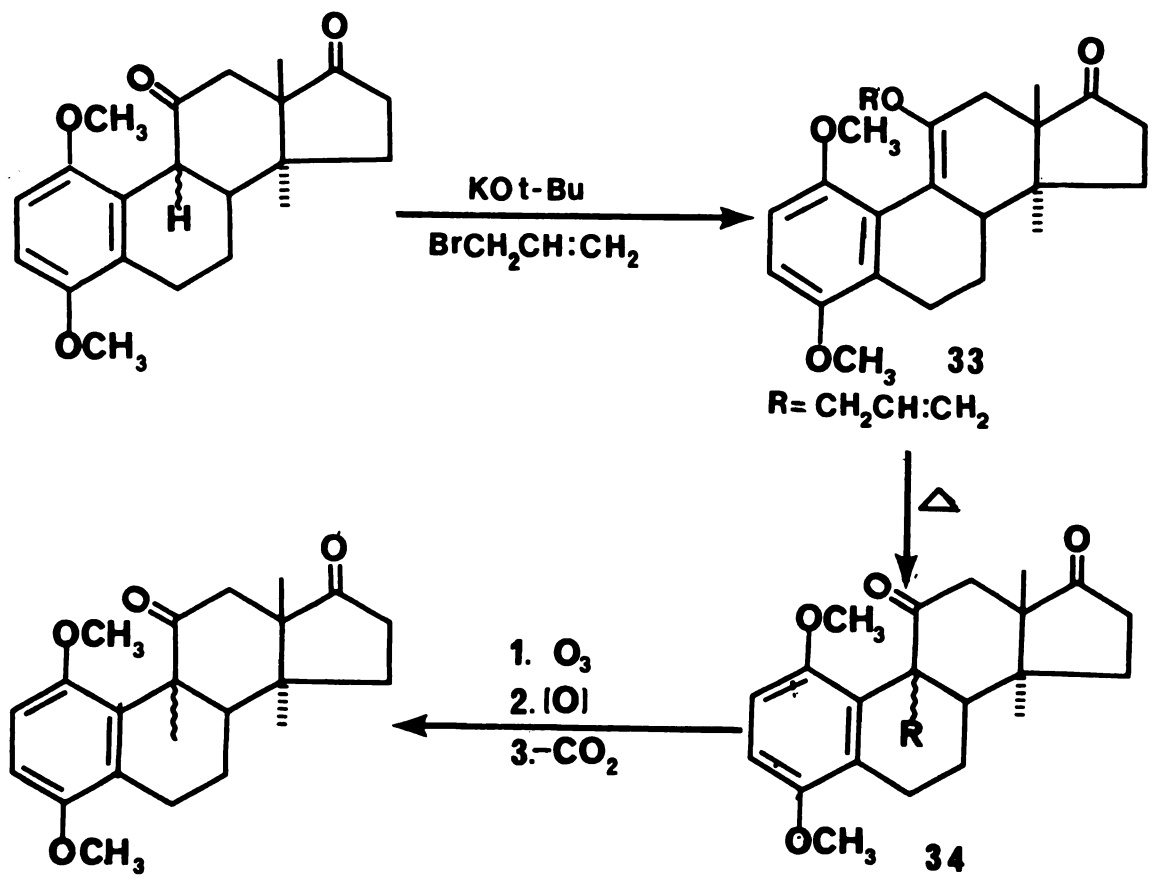
Alkylation of the 11-keto derivative was next studied as a means of introducing a 9β -methyl group. Unfortunately all attempts to introduce a methyl group by enolate alkylation failed. The only product isolated was the enol ether 31. Similar O- alkylations were observed with ethyl bromo acetate and allyl bromide giving 32 and 33 respectively (equation 23).



eq 23

31; R = CH_3
32; R = $CH_2CO_2C_2H_5$
33; R = CH_2CHCH_2

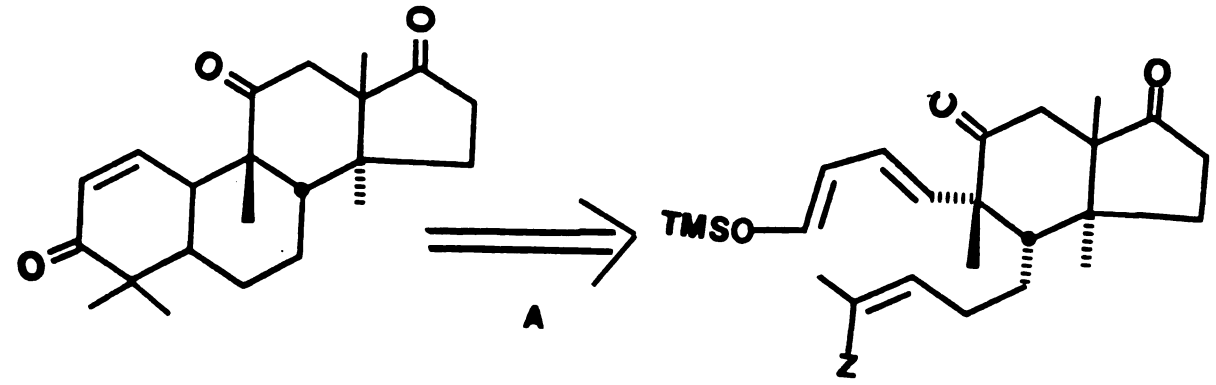
Attempted cyclopropanation of 31 with Zn/Cu couple and CH_2I_2[54] resulted in the complete recovery of starting material. In situ generation of silyl ether of 26 and 27 followed by trapping with chloromethyl phenylsulfide was unsuccessful[55]. A possible route for the introduction of the alkyl group at C-9 would involve a Claisen rearrangement of 33 to the C-alkyl derivative 34[56]. If this reaction proceeds stereospecifically as shown, an efficient conversion of allyl group to methyl group can be acheived by ozonolysis followed by oxidation and decarboxylation (scheme 7).



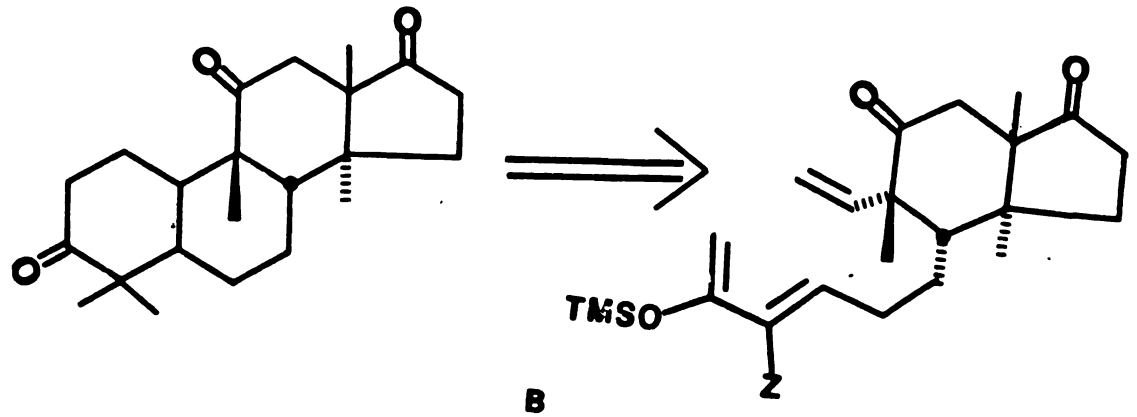
Scheme 7

PART B

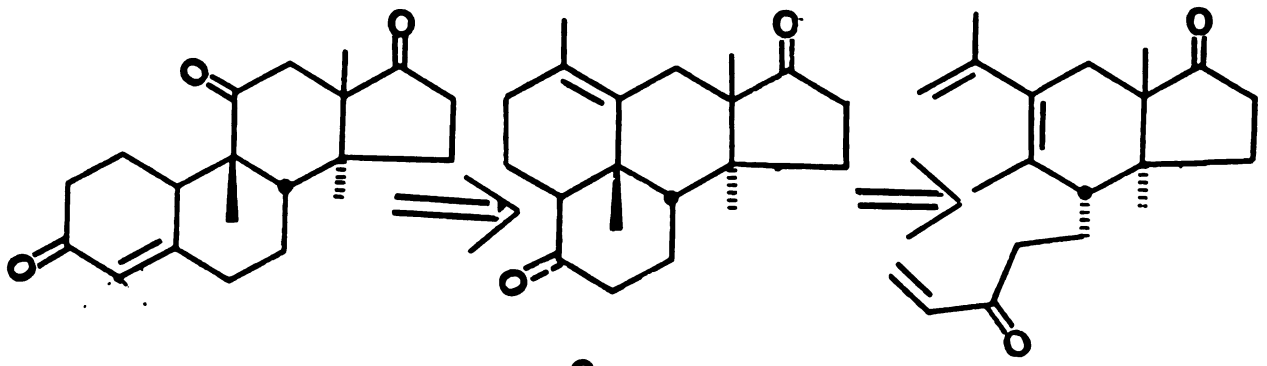
A general approach to cucurbitacins may be based on the application of the intramolecular Diels Alder reaction.[57] A retrosynthetic analysis starting from our C/D bicyclic intermediate suggests two similar strategies (A&B). A third strategy (C) is based on Stork's approach to the synthesis of 11-keto steroids.



A

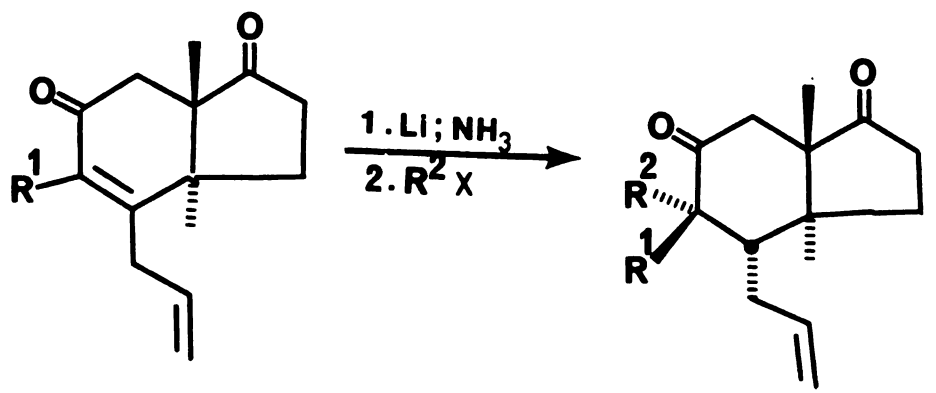


B



C

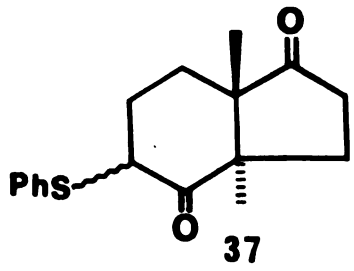
As can be seen in strategies A and B, very similar intermediates are involved in these strategies. Of paramount importance in these sequences is the control of stereochemistry at the potential C-9 site. If the reductive alkylation step (equation 24) proceeds with good stereoselectivity, the desired products may be readily obtained by adjusting the order of the alkylations.



(eq. 24)

The bicyclic intermediates needed for these reactions may be prepared from the readily available diketone 1.

The preparation of enone 36 from bicyclic dione 1 was reported previously by Jacob Tou[58]. However the sulfoxide and/or selenoxide elimination routes used gave only poor yield of the enone. The major problem encountered in these reactions was the difficulty in preparing the α-ketosulfide 37 or the α-ketoselenide 38.



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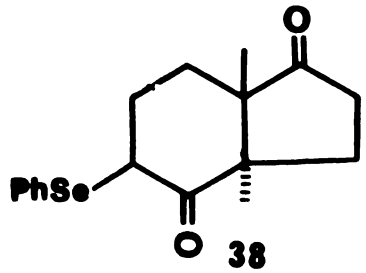

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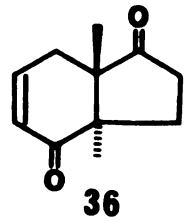
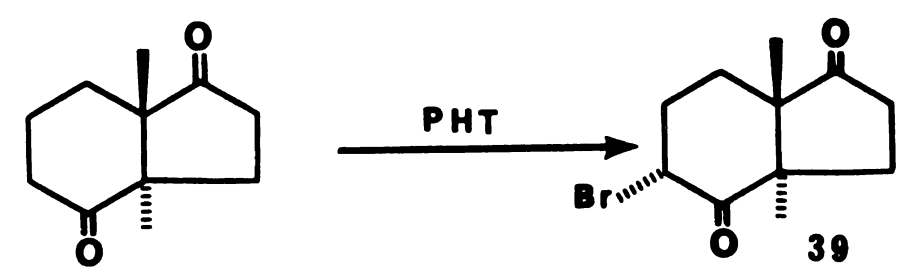


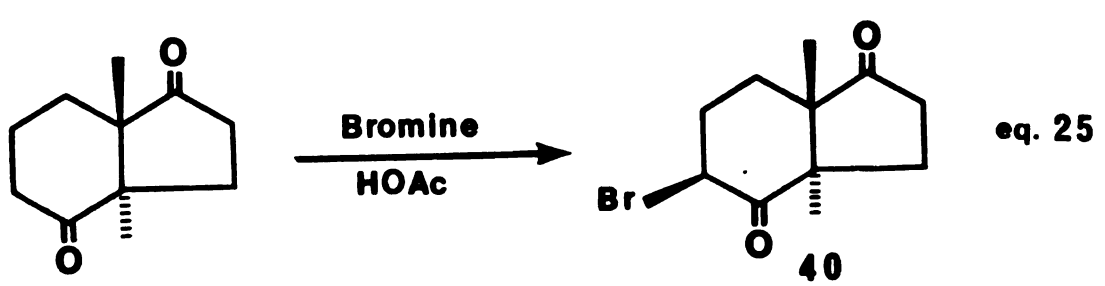
36

A careful examination of the reaction mixture derived from the sulfenylation of parent dione 1 by treatment with LDA followed by diphenylsulfide revealed the presence of a substantial amount of starting material (50%). This observation agrees with reports by Trost for the sulfenylation of other carbonyl compounds[59]. Because the acidity of the initially formed α-ketosulfides exceeds that of the starting material, unreacted enolates react faster with the product α-ketosulfide

than with diphenyl disulfide. Normally, two equivalents of base may be used and excellent yields of products are realized. However, since dione 1 forms a bisenolate on treatment with two equivalents of base, such an approach was considered unwise. More reactive reagents such as phenyl phenylthiosulfonate or phenyl selenylbromide gave no improvements in the yields of 37 or 38. Therefore an alternate synthesis of 36 was required.

Kinetically controlled bromination of 1 with 2-pyrrolidone hydrotribromide (PHT) was reported to give an excellent yield (84%) of 39[60]. By performing the bromination with bromine in glacial acetic acid at room temparature, the thermodynamically favored equatorial bromoketone 40 was isolated in over 90% as a white crystalline solid (equation 25)

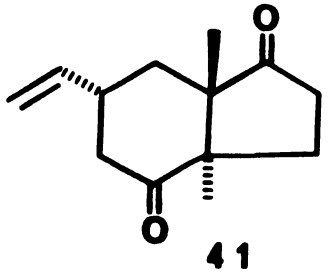




eq. 25

The dehydrobromination of 40 with $CaCO_3$ in dimethyl formamide[61] proceeded smoothly to give 36 in 86% yield. Since enone 36 proved to be readily available, we next examined some of its reactions to determine whether potentially useful intermediates for cucurbitacin synthesis may be prepared in this manner.

The addition of vinylmagnesium bromide to 36 provided only the 1,4 addition product 41. Reaction of 36 with one equivalent of allylmagnesium bromide gave 85-90% yield of the 1,2 adduct 42. The amount of allylmagnesium bromide in this case is critical because of the facile addition of allylic organometallic to the five membered carbonyl function of 36. A substantial amount of the bis adduct 43 was in fact isolated from the reaction of 36 with excess allylmagnesium bromide. The facile addition of allylic Grignard to the carbonyl functions can be rationalized by the six membered transition state as shown in scheme 8[62].



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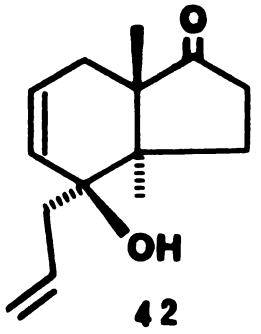
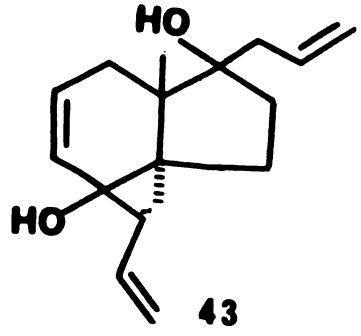


42



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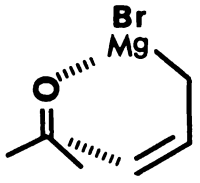
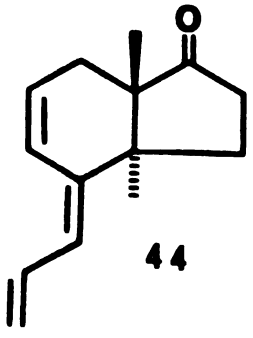
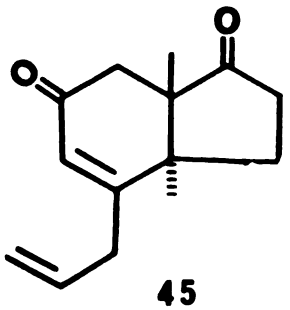


Scheme 8

Oxidation of 42 with PCC gave the triene 44 as the major component. Only a small amount of the expected product 45 was obtained with PCC (pyridinium chlorochromate).

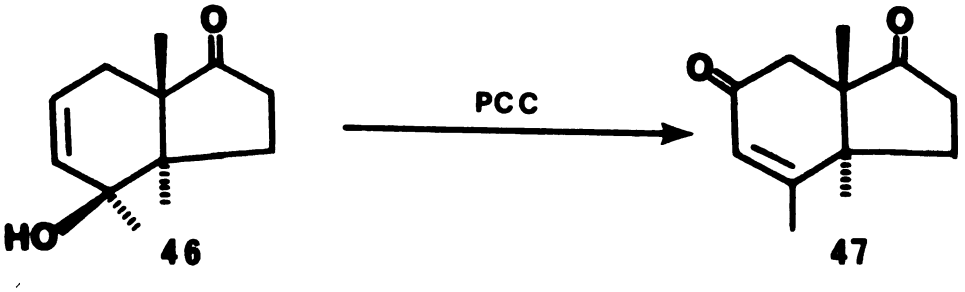


44



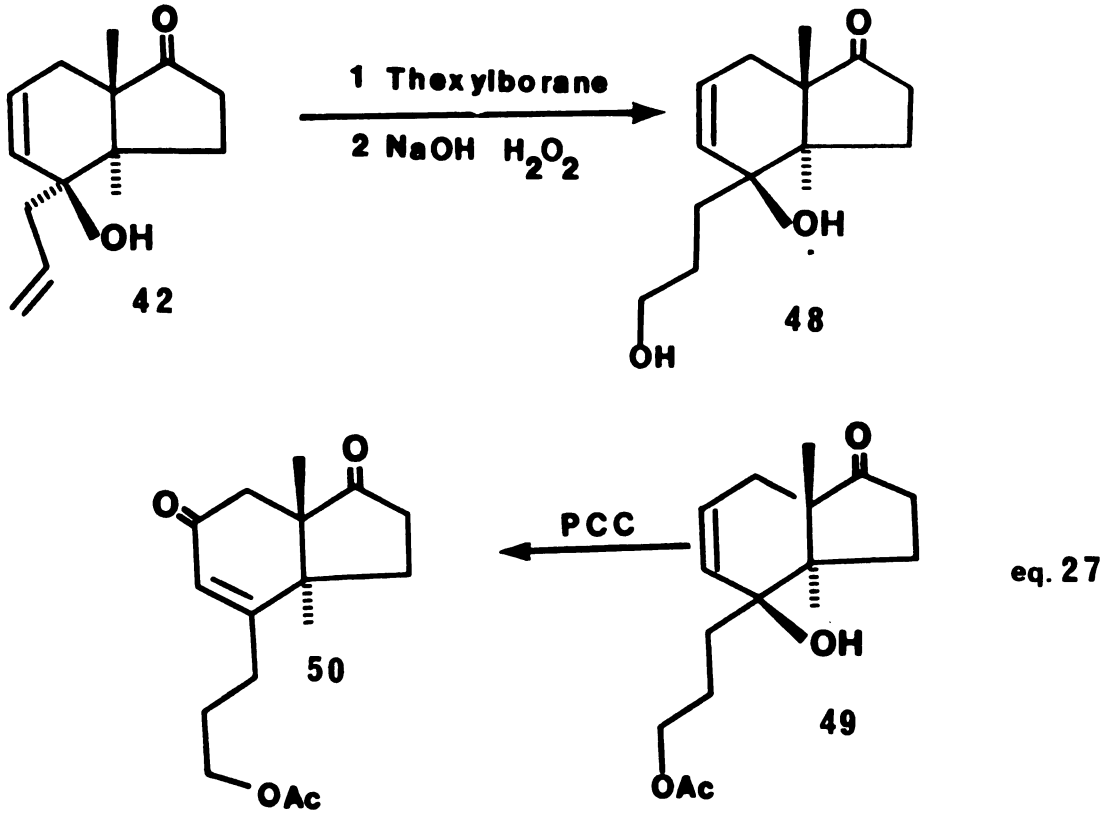
45

The dehydration of 42 with PCC can be explained by the action of slightly acidic reagent upon a sensitive allylic tertiary alcohol 42. However, a facile oxidative transposition of 46 to 47 by PCC (equation 26) suggested that such an approach could well be applied to 44 after functionalizing the terminal double bond.



46 **47** **eq. 26**

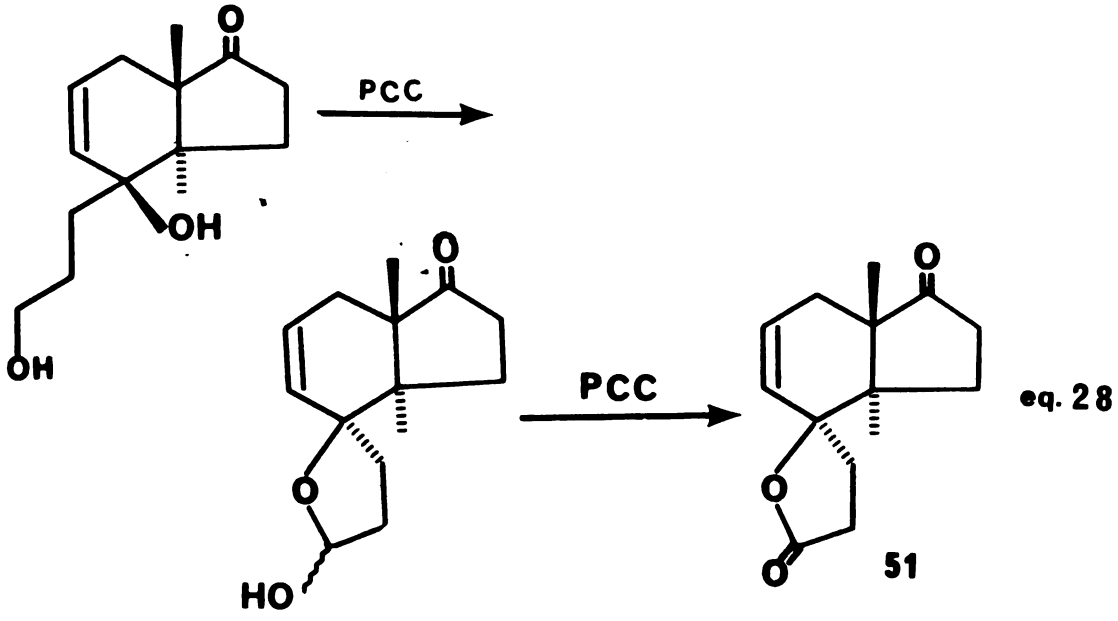
Thus on hydroboration with thexylborane followed by oxidation of the derived organoborane with alkaline hydrogen peroxide,[63] 42 gave the keto diol 48 in almost quantitative yield. The primary hydroxyl group of 48 was protected as the acetate with dimethylamino pyridine (DMAP) / acetic anhydride to give 49.[64] PCC oxidation of 49 yielded the transposed enone 50 in 90% yield. (equation 27).



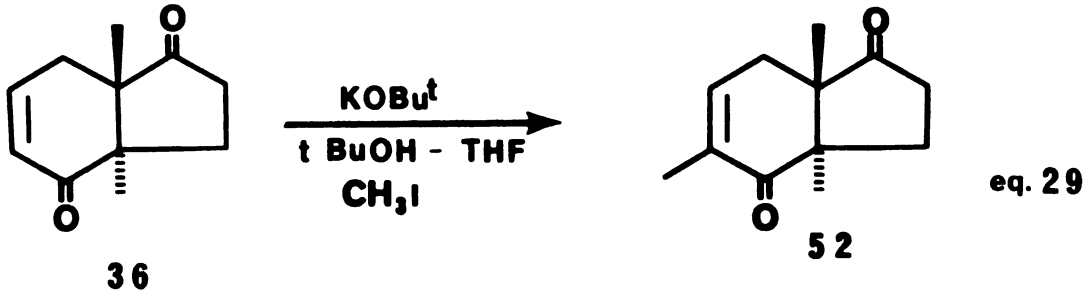
eq. 27

When the diol 48 was treated with PCC, the expected spirolactone 51 was obtained as the only product. The formation of 51 can be envisioned as proceeding through the lactol intermediate. (equation 28). Both 50 and 51 should serve as potential intermediates towards the proposed intramolecular Diels Alder (IMDA) strategy for cucurbitacins and the synthesis of several

other tetracyclic triterpenes.

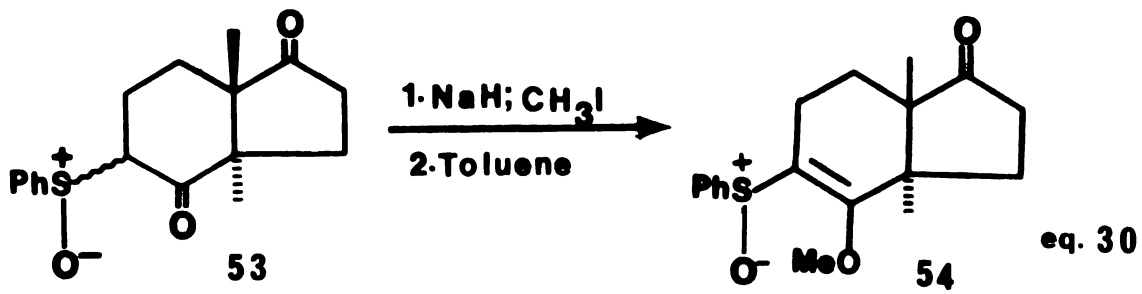


Next we explored the chemistry of the homologous enone 52. The enone 52 was prepared in over 80% yield from 36 by the alkylation of the potassium enolate (KOt-Bu) with methyl iodide. (equation 29).

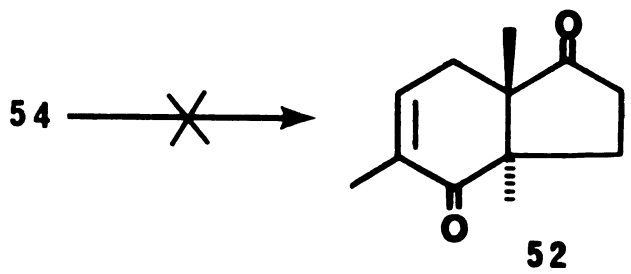


An alternate route to the enone 52 through the alkylation of sulfoxide 53 followed by thermolysis was complicated by the formation of considerable amount of the O-methylated derivative

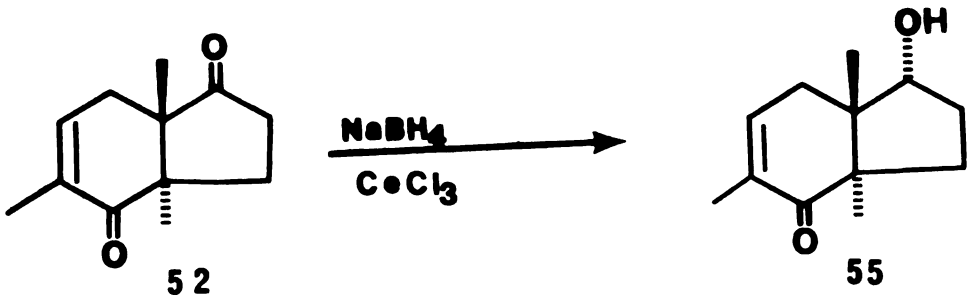
54. (equation 30).



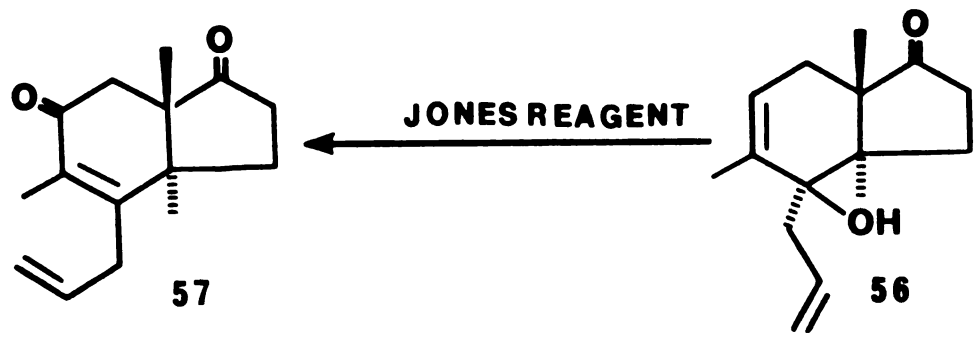
eq. 30



In contrast to the facile addition of allylmagnesium bromide to 36, 52 was found to yield several products by the attack of the organometallic on both carbonyl sites. Therefore a selective protection of the 8-keto group was required. During a related study, we discovered that the five membered ketone of 52 could be reduced with the $NaBH_4/CeCl_3$ reagent[65], in 81% yield, to give 55. The stereochemistry assigned for 55 is based on the ^1H NMR signal of C-17 hydrogen (dd, J=8 Hz, 2 Hz) Addition of allylmagnesium bromide to 55 followed by oxidation with PCC gave 56; no further oxidation was observed with this reagent. However 56 underwent smooth oxidative transposition

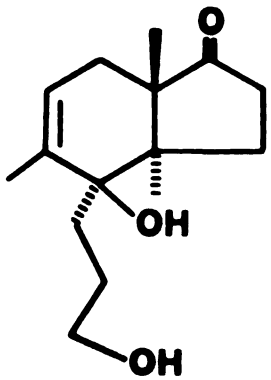


52 55

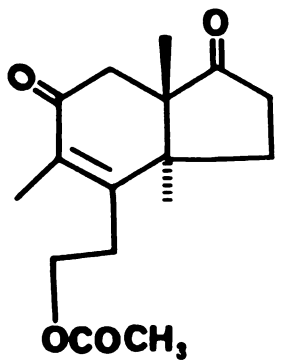


57 56

with Jones reagent[66] to give the expected enone 57 in 91% yield. The intermediate 56 was also converted into 58, 59 and 60 by the procedures applied to the parent system.



58



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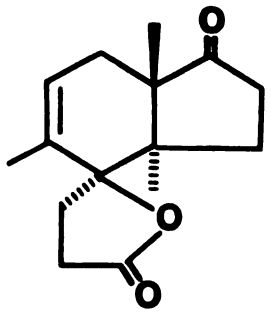
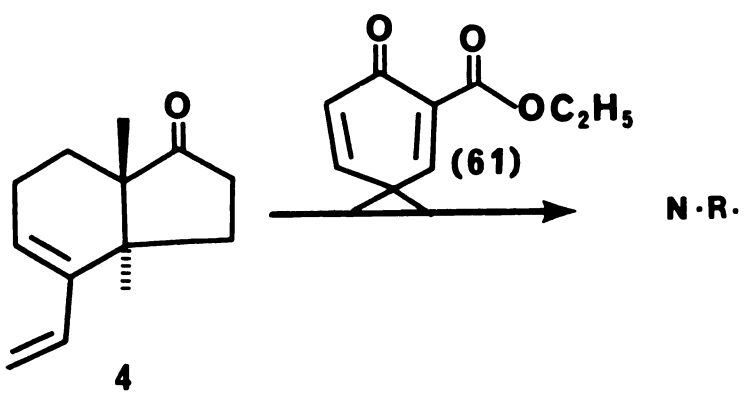
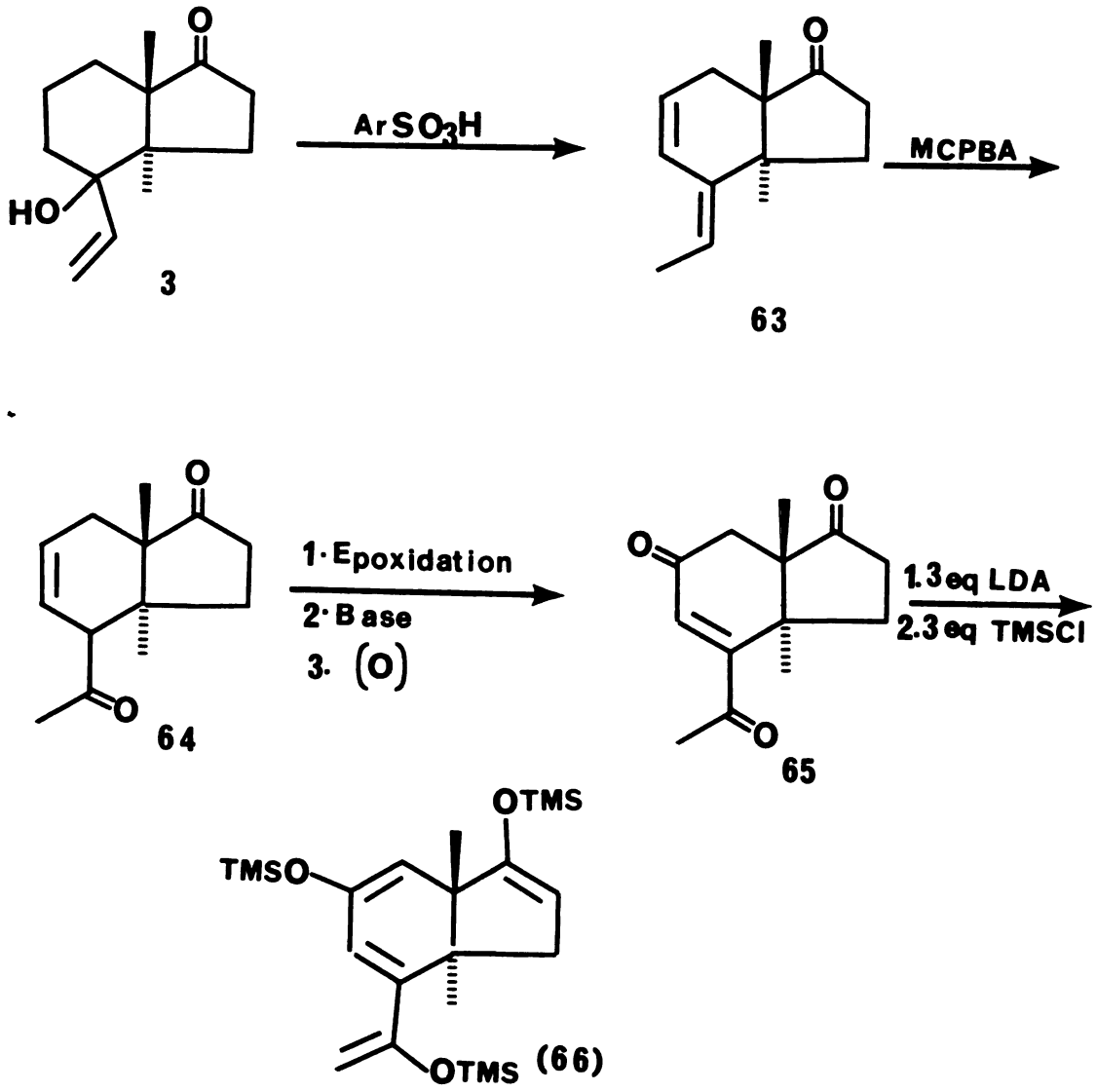


59

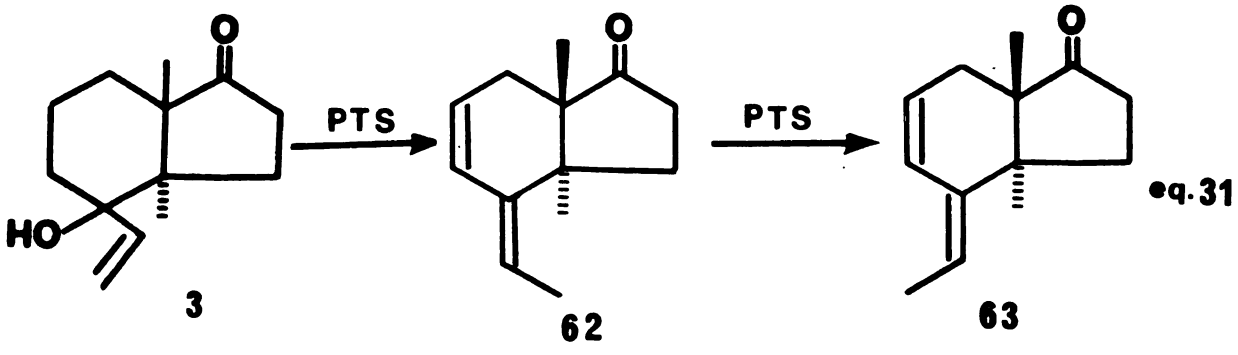
We also explored the possible construction of functionalized analogs of diene 4, which are expected to show enhanced reactivity towards electron deficient dienophiles. Although the addition of diene 4 to various quinone dienophiles proceeds efficiently, an attempted addition of this diene to the novel dienophile 61 failed. A facile addition of diene 4 or its analog to 61 should ease the ring-A modification greatly, including the introduction of geminal dimethyl group which in the past has caused considerable problems to our synthesis of tetracyclic triterpenes. We hoped that this sluggishness could be overcome by introducing a siloxy substituent at the diene moiety of 4. To this end we have prepared a triketone precursor 65 to the trisiloxy tetraene 66 as shown in scheme 9.




O
HO
3
ArSO3H
O
63
MCPBA
O
64
1·Epoxidation
2·Base
3. (O)
O
O
O
65
1.3eq LDA
2.3eq TMSCl
OTMS
TMSO
OTMS
(66)

Scheme 9

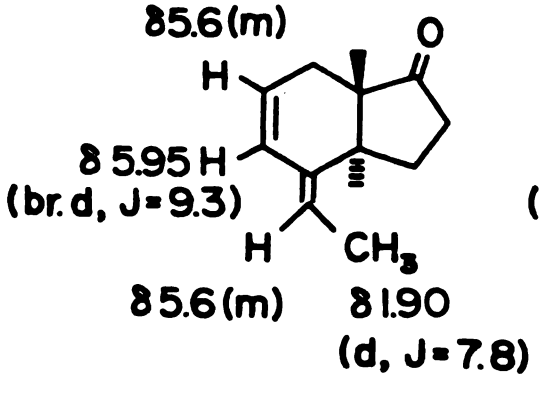
In the course of this study, we observed an interesting kinetic selectivity in the acid catalyzed rearrangement of 4. The preparation of the thermodynamically more stable isomer of the trans diene 63 from the vinyl carbinol 3 on treatment with either PTS or iodine has been reported . When the dehydration of 3 was carried out with PTS in refluxing toluene for 1 hour a mixture of trans dienes 62 and 63 were obtained in almost 1:1 ratio, as determined by high resolution NMR. However on prolonged treatment, this diene mixture underwent complete isomerization to the more stable isomer 63 (equation 31)

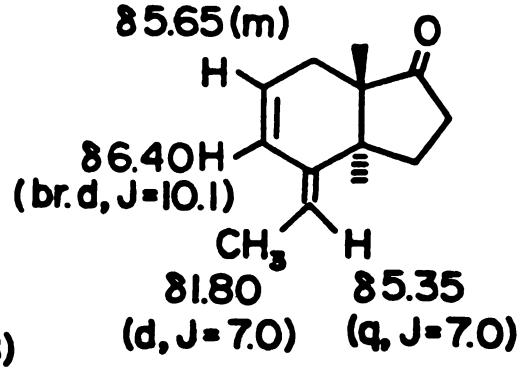


eq. 31

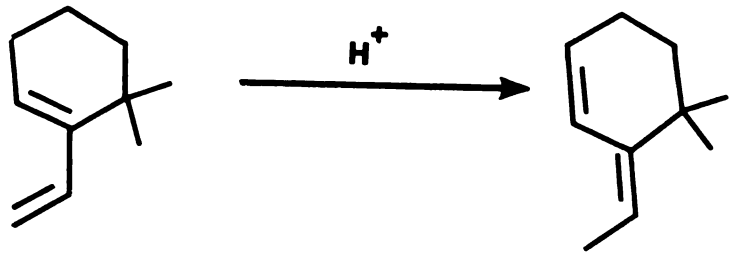
Since the formation of either 62 or 63 must proceed through the intermediate formation of diene 4, we studied the rearrangement of 4 under Bronsted acid condition. Treatment of 4 with 0.1 equivalent of p-toluenesulfonic acid in refluxing benzene for 1 hour gave the Z-isomer 63 in 85% yield. When the acid catalyzed isomerization of 4 was monitored by ^{1}H NMR, a

new set of signals appeared, reached a maximum after 20 minutes, at 75°C and then faded as the spectrum of 63 grew stronger. Careful treatment of 4 with p-toluenesulfonic acid in chloroform enabled us to isolate the intermediate 62 as a crystalline product to which the E-configuration was assigned on the basis of ^{1}H NMR. A nuclear Overhauser effect for the 1.8 methyl doublet and the 6.5 multiplet was observed for 63, but no equivalent signal effect was found for 62.[67] Some of the important ^{1}H NMR assignments for these compounds are shown in the accompanying formulas. The ^{13}C data also confirms the assigned configuration for 62 and 63. A $\Delta\delta$=6.61 has been observed for the C-3 carbons (steroid numbering) of 62 and 63.[68]

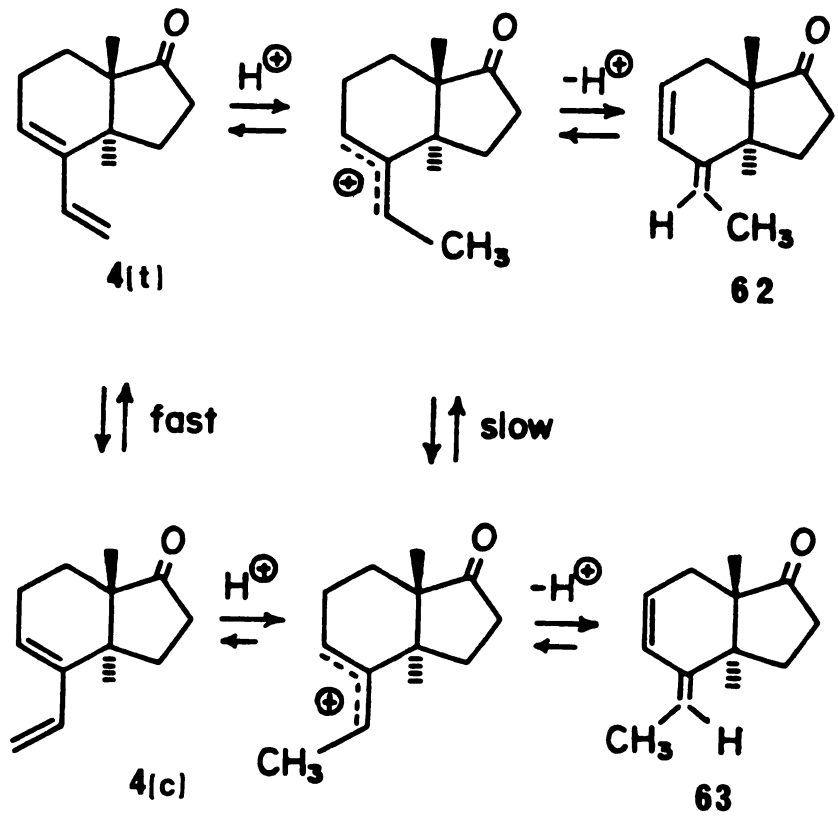




Since the corresponding isomerization of 6,6-dimethyl-1-vinylcyclohexene 67[69] to its trans isomer 68 did not exhibit the above phenomenon, the possibility that it reflected unexpected differences in conformer equilibria was considered. Scheme 10 illustrates a possible explanation for the rapid formation of the thermodynamically less stable diene 62 from 4. The barrier for conformational interconversion in simple dienes is low (6 K.cal/mole), and in the absence of steric hindrance effects, the s-trans conformer is more stable than the s-cis or s-skew conformers by approximately 2.1 kcal/mole.[70] Allylic carbocations on the other hand have conformational barriers in the 38-43 kcal/mole range and such intermediates exhibit strong structural integrity.[71] If protonation of 4 were to generate intermediate cation X(t) preferentially we would expect to obtain diene 62 provided deprotonation of X(t) is faster than its isomerization to X(c).



67 68



Scheme 10

It is known that the s-trans conformer of acyclic dienes generally has a larger molar absorptivity (ε) than the corresponding s-cis conformer.[72] From the examples cited in Table we see that the UV absorption of 4 is similar to that of 1-vinyl cyclohexene, indicating a similar s-trans: s-cis equilibrium for these compounds (s- trans predominates). Diene 67 on the other hand , appears to assume mainly the s-cis conformation.

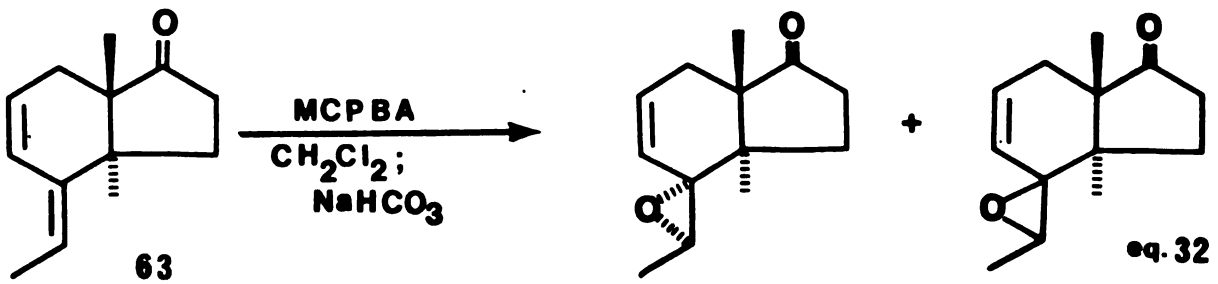
Because of the low barrier for conformational interconversion of the diene, such a preferential protonation requires that the activation energy for 4(t) ⟶ X(t) be lower than that for 4(c) X(c).[73] Since this does not appear to be true for the protonation of 67, we have looked for a unique conformational factoe in X that might reflect in properties of 4. Evidence for such a factor has been found in the UV absorption spectra of 4, 67, and related dienes.

Absorption Maxima and Molar Absorptivities of Some Conjugated Dienes

Compound	λ_{max}^{EtOH} (nm)	ε	Ref.
3-methylenecyclohexene	231 (hexane)	21,000	74
1-vinylcyclohexene	231	10,600	75
1,2-bismethylenecyclohexane	220	6,400	76
1,3-cycloheptadiene	246	7,500	77
4	235	11,900	This Work
67	237	6,600	This Work

The unexpected similarity of the molar absorptivity of 4 to that of 1-vinylcyclohexene rather than 67 may be attributed to structural distortion in 4 introduced by the trans-fused five-membered ring. Molecular models indicate that the six-membered ring in 4 is forced into a boat(or twist boat) conformation. This permits the s-trans diene conformation to experience less steric crowding than it does in 67. We suggest that this factor helps to lower the activation energy of the 4(t)⟶X(t) reaction relative to that for compound 67.

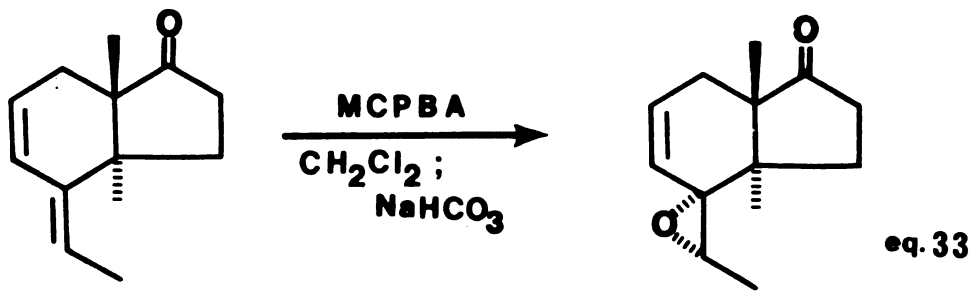
The transformation of diene 63 to the non-conjugated enone 64 has been achieved previously. However the isolation of the sensitive epoxides from 63 has not been reported. When the epoxidation of 63 was monitored by ^{1}H NMR two stereoisomeric epoxides were observed in almost 1:1 ratio. (equation 32)



eq. 32

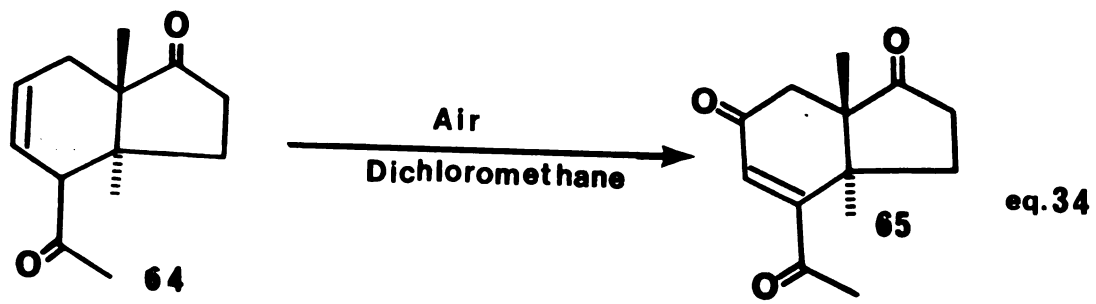
Recently, these two epoxides were separated in our laboratory[78] by chromatography on silica gel.

In contrast to the epoxidation of 63, 62 gave a single crystalline compound in quantitative yield (equation 33) on treatment with m-chloro perbenzoic acid.



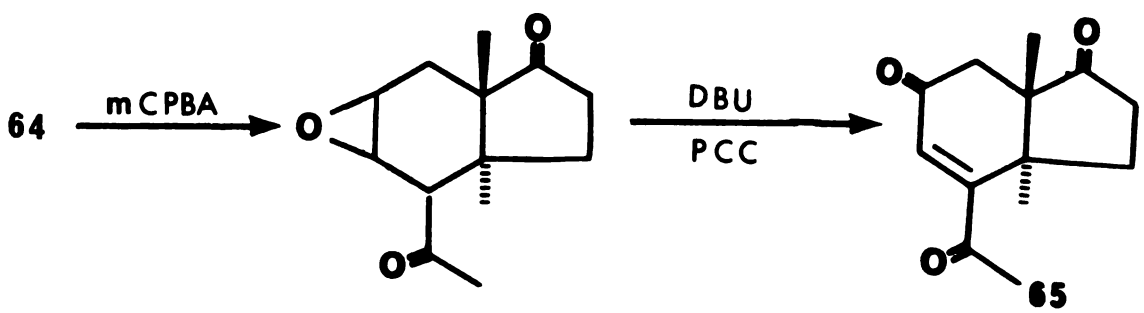
eq. 33

The non-conjugated enone 64 was found to be very sensitive towards exposure to air. For example 64 underwent smooth transformation to the triketone 65 (equation 34).

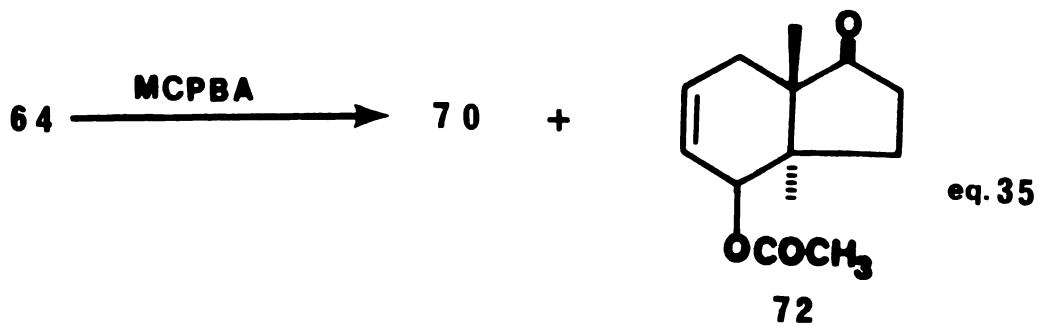


eq. 34

The preparation of the triketone 65 was achieved in moderate yield(50%) from 64 according to the scheme

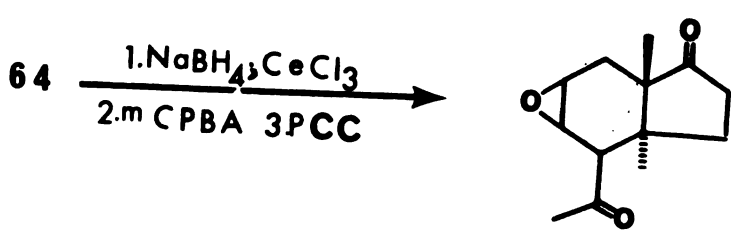


The epoxidation of 64 with m-chloro perbenzoic acid under a variety of condition yielded, besides the expected epoxide 70, a substantial amount of the Baeyer Villiger product 72. Thus only about 50% of the required epoxide was obtained by this route.(equation 35)

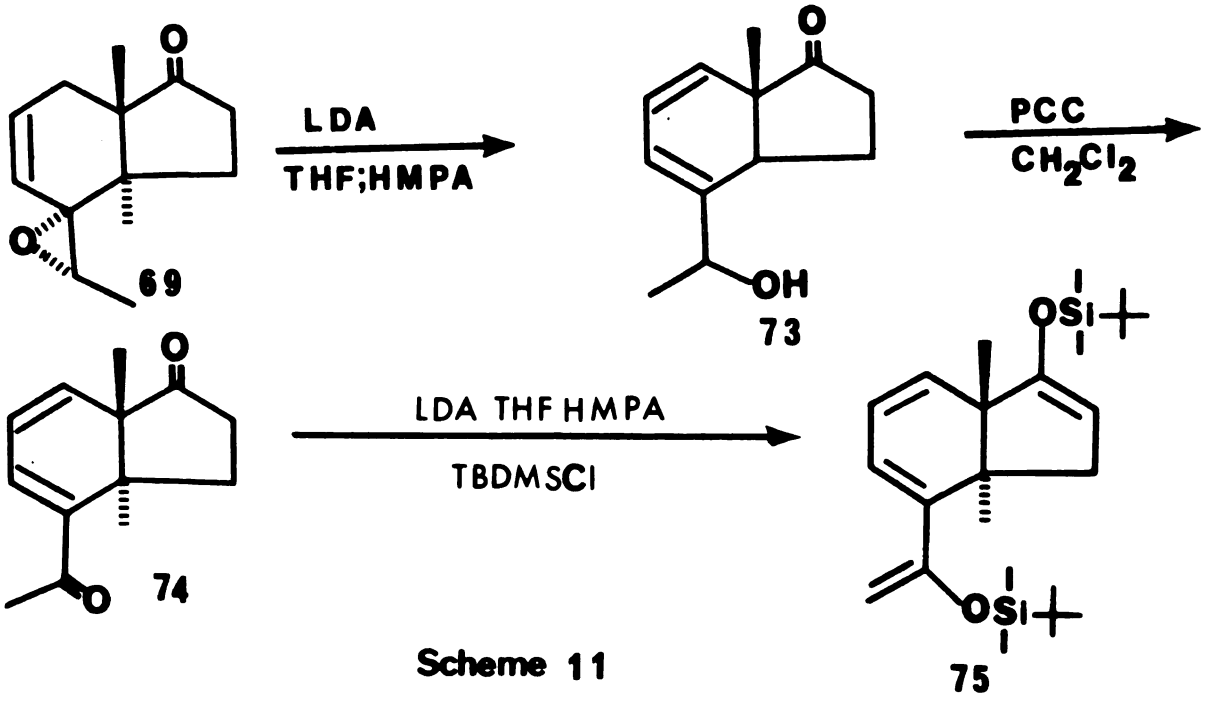


eq. 35

We thought the formation of 72 could be totally suppressed by first reducing the ketone functionalities in 64 followed by epoxidation and reoxidation as shown in equation 36 .Unfortunately the reduction of 64 with sodium borohydride/ ceric chloride was found to be capricious.



Since the isolation of an epoxide from 62 was easy we studied some of its reactions as a means to construct a functionalized analog of 4. Scheme 11 illustrates the transformation of 69 into the bis-silyl tetraene 75. The reaction sequences in scheme 11 might be very well applied to the epoxides derived from the thermodynamically more stable isomer of the trans diene 63 also.



Scheme 11

Treatment of 69 with 3 equivalent of lithium diisopropyl amide(LDA) in THF/HMPA isomerized it to the dienol 73 in 88% yield. Oxidation of 73 with pyridinium chlorochromate gave the dienone 74 in 87% yield. Upon treatment with excess LDA followed by trapping with tert-butyldimethylsilyl chloride 74 yielded the bissilyl ether 75 (60%).

The intermediate 75 may be considered as a valuable synthon for the construction of various tetracyclic triterpenes. A thorough study of the Diels Alder reactions between this reactive diene and various dienophiles should give fruitful results. A preliminary study involving 75 and p-benzoquinone has been partially successful. A rigorous structural elucidation for the adduct obtained was not completed. An efficient addition of 75 to the novel dienophile 61[79] should open new avenues for the total synthesis of tetracyclic triterpenes.

EXPERIMENTAL

General

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

Analysis by GLPC was conducted with A-90-P3 or 1200 Varian-Aerograph instruments. Flash chromatograhy was carried out on flash silica (37- 53 mesh) as suggested by Still et al. Melting points were determined on a Hoover-Thomas apparatus (capillary tube) and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra (^{1}H NMR) were taken in deuterochloroform or acetone -d_6 solutions with either a Varian T-60 or a Bruker 250 MHz spectrometer and are cali-

brated in most cases in parts per million (δ) downfield from tetramethyl silane as an internal standard. In some cases the chloroform peak (7.26) was used as a standard for ^{1}H NMR measurements. Ultraviolet spectra (UV) were recorded on a Unicam SP-800 spectrophotometer. Mass spectra (MS) were obtained with either a Hitachi RMU 6 mass spectrometer or a Finnigan 4,000 GC/MS spectrometer. Carbon magnetic resonance spectra (^{13}C NMR) were taken in deuterochloroform solutiom with a Bruker 250 spectrometer and are calibrated in parts per million (δ) downfield from tetramethyl silane as an internal standard.

Microanalysis were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Preparation of cisoid diene 4 by copper sulfate dehydration of the vinyl carbinol 3.

500 mg of alcohol 3 was refluxed in 100 ml of benzene with 800 mg of copper sulfate. Water was removed azeotropically. After two days of refluxing, the copper sulfate was removed by filtration. The filtrate was washed with ether and the combined organic solvents were evaporated under reduced pressure. The product was purified by Kugel rohr distillation. 402 mg (94% yield) of cis diene was obtained as a semi solid. UV (EtOH) λ_{max} 235nm ($\log \epsilon$ 4.08); IR 1750, 1665, 1625 cm^{-1}; ^1H NMR δ 0.9 (s, 3H), 1.0 (s, 3H), 1.1-2.6 (m, 8H), 4.7 (d, 1H, J=11 Hz), 5.05 (d, 1 H, J=17 Hz), 5.4 (t, 1H, J=3 Hz), 6.0 (dd, 1H, J=11 and 17 Hz); MS m/e (rel. abund.) 190 (79), 175 (38), 133 (100), 119.

Preparation of diketone 7.

To a solution of lithium diisopropyl amide, prepared by reacting 2.5 ml of diisopropyl amine (17.87 mmol) in 50 ml of THF with 7.3 ml of a 2.42 M n-butyl lithium in hexane, (17.67 mmol), was added at -78° C, 2.85 gms of dione 1 (15.83 mmol) in 100 ml of THF. It was allowed to stir at -78° C for 30 min, warmed to room temparature and then 30 ml of HMPA was added. It was then stirred at this temparature for an additional 30 min, cooled to 0° C followed by addition of 1.5 ml of methyl iodide. After 5 min the reaction mixture was quenched with water, extracted with ether, washed sequentially with sodium bicarbonate

and brine. The ether layer was dried over anhydrous magnesium sulfate and the solvent was evaporated to give a yellow crystalline material. This product was treated overnight with methanolic potassium hydroxide. The resulting solution was diluted with benzene, washed with water, brine and dried. Evaporation of solvents yielded a pale yellow solid weighing 2.66 g . It was first crystallised from ether and then from ethyl acetate-hexane to give 1.6 g (54%) of white crystalline solid 7. M.Pt 118-120°C; IR($CHCl_3$) 1710, 1740 cm^{-1} ^1H NMR($CDCl_3$) 0.9 (s, 3H), 1.1 (d, 3H, J=7 Hz), 1.2 (s,3H), 1.3-2.4 (complex, 9H). MS (70 ev) m/e (rel intensity) 194 (56.4), 179 (50.06), 165 (19.65), 152 (45.88), 137 (29.85), 124 (79.09), 109 (85.04), 96 (70.72), 82 (100), 67 (70.22), 55 (48.99).

Preparation of vinyl carbinol 8.

To 290 mg of dione 7 (1.5 mmol) in 10 ml of THF was added 4 ml of 1.1 M vinyl magnesium bromide in THF. The reaction mixture was stirred under nitrogen for two days, quenched with saturated ammonium chloride and processed as usual to give 330 mg (98%) of alcohol 8 as a white crystalline compound. M.Pt 135-137 C. IR (nujol); 3500, 1735 cm^{-1}. ^1H NMR ($CDCl_3$) 0.95 (s, 3H), 0.9 (d, 3H, J=7 Hz), 1.3 (s, 3H), 1.4-2.5 (complex, 10H), 5.0-6.2 (typical vinyl pattern, 3H). MS (70 eV) m/e (rel intensity) 222 (4.96), 207 (23.18), 204 (0.53), 126 (17.54), 111 (100), 97 (20.39), 84 (24.39).

Preparation of the Diels Alder adduct 10.

To a refluxing solution of 6.5 gms of p-benzoquinone in 200 ml of benzene was added 4.0 gms of diene 4 in 150 ml of benzene under argon, over a period of one hour. The reaction mixture was refluxed overnight, cooled and washed with 100 ml of 10% sodium bisulfite solution. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of solvents yielded an oil which on trituration with ether gave 4.66 gms (77.66%) of slight yellow crystalline solid. The solid was found to be a mixture of two products. The major isomer (80%) displayed the following properties. M.Pt. 170-173 C; IR 1740, 1690, 1600 cm^{-1}; ^{1}H NMR 1.05 (s, 3H), 1.20 (s, 3H), 1.4-2.8 (m, 11H), 3.2 (broad s, 2H), 5.20 (q, 1H, J=2.9 Hz), 6.53 (dd, 1H, J=1.2 and 10.3 Hz), 6.62 (d, 1H, J=10.3 Hz); ^{13}C NMR 219.2, 201.0, 198.9, 144.8, 141.0, 137.0, 115.6 ppm and eleven higher field signals; MS m/e (rel. abund.) 298 (14), 189 (27), 145 (25), 131 (27), 123 (100), 91 (65). The minor isomer displayed the following ^{1}H NMR 0.94 (3H, s), 0.99 (3H,s), 1.5-3.4 (13H, multiplet), 5.45 (1H, quartet, J=3.36 Hz), 6.65-6.7 (1H, dd, J=1.52 Hz and 10.4 Hz), 6.75-6.82 (1H, d, J=10.4 Hz).

Acid treatment of Diels Alder adduct; preparation of 11.

500 mg of the Diels Alder adduct 10 was dissolved in 2 ml of glacial acetic acid (hot) and to this was added two drops of conc. hydrochloric acid. It was then allowed to cool to room temparature. The white crystalline solid formed was suction

filtered, washed with water and dried to give 447 mg (90%) of a mixture of 7,8 and 8,9 double bond isomers in a ratio 80:20 as determined by proton NMR. M.Pt. 220-240 C; IR 3200-2400, 1725, 1600 cm^{-1}; The major isomer displayed the following ^1H NMR resonances. (CD_3COCD_3) 1.12 (s, 3H), 1.5-2.7 (m, 8H), 3.03 (ddd, 1H, J=2.5, 7.6 and 22.3 Hz), 3.3 (m, 1H), 3.43 (dt, 1H, J=5.2 and 22.3 Hz), 3.85 (2H), 5.85 (dt, 1H, J=5.2 and 2.5 Hz), 6.5 (s, 2H); MS m/e (rel. abund.) 298 (100), 283 (37), 265 (26).

Preparation of bismethoxy derivative 13

To 100 mg of the 1,4-dihydroxy derivative 11 in 8 ml of THF at 0 C was added 75 mg of 99% sodium hydride under an atmosphere of argon. After stirring for half hour, 0.5 ml of methyl iodide was added and the reaction mixture was allowed to warm up to room temparature. After stirring overnight at this temparature, it was quenched with water and extracted with ether. The ether layer was washed with water and then with brine, dried over anhydrous sulfate. Removal of the solvent gave 96 mg (91% yield), of colorless solid which was found to be a mixture of 13 and its 8,9 isomer in the ratio 80:20 as determined by high resolution NMR. An analytical sample of 13 obtained by HPLC (silica, methylene chloride) displayed the following properties. M.Pt. 124-128° C; IR 1730, 1600, 1475, 1250, 1075 cm^{-1}; ^1H NMR 1.05 (s, 3H), 1.26 (s, 3H),

1.4-3.0 (m, 8H), 3.13 (m, 2H), 3.5 (dt, 1H, J=5.5 and 22.6 Hz), 3.78 (s, 6H), 5.78 (dt, 1H, J=5.5 and 2.5 Hz), 6.7 (br s, 2H); MS m/e (rel. abund.) 326 (100), 311 (31), 293 (11).

Preparation of the bishydroxy derivative 17.

One gm of the Diels Alder adduct 10 was dissolved in 5 ml of hot glacial acetic acid and to this was added 5 drops of concentrated hydrochloric acid. The reaction mixture was allowed to remain at room temparature overnight. The colorless crystalline product formed was suction filtered, washed with water and dried to give 950 mg of a mixture of 17 and its 8,9 isomer in the ratio 80:20 as determined by NMR. (yield=95%) The major isomer displayed the following properties. M.Pt. 220-225 C (d); ^{1}H NMR 0.76 (s, 3H), 0.94 (s, 3H), 1.4-3.0 (m, 11H), 6.50 (d, 1H, J=8.5 Hz), 6.55 (d, 1H, J=8.5 Hz), 7.18 (dt, 1H, J=2.6 Hz); MS m/e (rel. abund.) 298 (100), 283 (26), 265 (24).

Preparation of the bismethoxy derivative 16.

500 mg of sodium hydride (60% in mineral oil) was washed three times with pentane under argon. To this was added a solution of 1.27 gm of the bishydroxy derivative 17 in 10 ml of THF. After stirring at room temparature for 30 min. the reaction mixture was cooled in an ice bath and 0.5 ml of methyl iodide was added. It was allowed to react overnight and then quenched with water. The reaction mixture was extracted with ether, washed with water and then with brine. It was dried

over anhydrous sodium sulfate and the solvent evaporated, to give 1.287 gm(100%) of a crude solid which was crystallized from ether. 1.037 gm (81%) of 16 was obtained as a colorless crystalline solid. The mother liquor (0.25 gm) was found to be mainly the required bismethoxy derivative on high resolution analysis. 16 displayed the following properties. M.Pt. 160-162 C; ^{1}H NMR 0.86 (s, 3H), 1.06 (s, 3H), 1.5-3.1 (m, 11H), 3.85 (s, 6H), 6.72 (d, 1H, J=9 Hz), 6.80 (d, 1H, J=9 Hz), 7.17 (brd, 1H, 6 Hz); MS m/e (rel. abund.) 326 (100), 311 (22), 293 (7), 269 (10).

Preparation of the B-aromatic 1,4-diketo derivative 18

900 mg of a mixture of the bishydroxy derivatives 11 and 12(ratio 80:20 respectively) was refluxed in 50 ml of xylene with 200 mg of Pd/C(10%) for 10 hours. The reaction mixture was cooled, the catalyst was removed by filtration and washed with ether. The combined solvents were evaporated under reduced pressure to give 900 mg of a crude product. Crystallization from ethanol gave 450 mg(50%) of pure 18 which displayed the following properties. M.Pt=138-141 C., IR($CHCl_3$) 1735,1685 cm^{-1}; ^{1}HNMR 0.8(s, 3H), 1.1(s, 3H), 1.8-2.8(m, 6H), 3.0(s, 4H), 3.4 (m, 2H), 7.52(d, 1H, J=8.0 Hz), 8.02(d, 1H, J=8.0 Hz); MS m/e (rel. abund.) 296(100), 281 (47), 239 (65).
Anal. Calculated, C=77.002%; H= 6.8%; Found, C=77.05%; H= 6.69%.

Preparation of the quinone derivative 19

1.4 gms of a mixture of dihydroxy derivatives 11 and 12 (ratio 80:20 respectively) was refluxed in 50 ml of xylene with 1.0 gm of Pd/C(10%) for 24 hours. The reaction mixture was cooled to room temperature, the catalyst was removed by filtration and washed with ether. The combined solvents were evaporated under reduced pressure to give 1.4 gm of a red orange solid 19 (100%). An analytical sample obtained by crystallization from ethanol displayed the following properties.
M.Pt= 202-205 C; IR ($CHCl_3$) 1740, 1660 cm^{-1}; ^1H NMR 0.8 (s,3H) 1.1 (s, 3H), 1.8-2.8 (m, 6H), 3.5 (m, 2H), 6.9 (s, 2H), 7.55(d, 1H, J=8.0 Hz), 8.10 (d, 1H, J=8.0 Hz); MS m/e (rel. abund.) 294 (100), 279 (21), 252 (74).
Anal. Calculated, C=77.52%; H= 6.16%; Found, C= 77.51%, H= 6.06%.

Preparation of 21

652 mg of the bismethoxy derivative 13 was refluxed in 10 ml of benzene with 2.2 gms of DDQ for 20 hours. The reaction mixture was cooled and poured into a short column of alumina. The product was eluted from the column with methylene chloride. Evaporation of the solvent followed by crystallization from ether gave 570 mg(87.5%) of 21 as a slight yellow solid. The characteristic properties of 21 are, M.Pt= 155-157 C; IR ($CHCl_3$) 1740, 1600 cm^{-1} ^1H NMR 1.0(s, 3H), 1.18(s, 3H), 2.1-2.8(m, 4H), 3.9(s, 3H), 4.0(s, 3H), 6.36(d, 1H, J=10.0 Hz), 6.66(d, 1H, J=8.5 Hz),

6.78 (d, 1H, J=8.5 Hz), 7.31 (d, 1H, J=8.5 Hz), 8.02 (d, 1H, J=10 Hz), 8.26 (d, 1H, J=8.5 Hz); MS m/e (rel. abund.) 322 (100), 307 (25), 265 (63). ^{13}C NMR 214.36, 151.55, 149.9, 142.02, 128.67, 128.55, 128.26, 126.85, 123.49, 122.61, 122.44, 106.68, 102.62, 56.04, 55.69, 53.1, 46.05, 35.23, 26.82, 24.35, 18.41. Analysis, Calculated, C= 78.23%, H= 6.88%; Found, C= 78.14%, H= 6.75%.

Preparation of the bismethoxy bromoderivative 22

100 mg of the bismethoxy derivative 13 was dissolved in 15 ml of carbon tetrachloride and to this was added 130 mg of N-bromo succinimide and a small amount(10 mg) of AIBN. The reaction mixture was refluxed for 3 hours under nitrogen. TLC analysis (silica, methylene chloride) showed the complete disappearance of the starting material. The product was however found to be non homogeneous on TLC. The precipitated succinimide was filtered off, and the filtrate was evaporated to give an oil which was chromatographed on silica gel. The bromo derivative was eluted with methylene chloride. Evaporation of the solvent gave pure 22 which displayed the following properties. IR($CHCl_3$) 1740, 1300 cm^{-1}; ^1H NMR 1.2(s, 3H), 1.4(s, 3H), 2.0-3.0(m, 4H), 3.9(s, 3H), 3.92(s, 3H), 6.6(AB quartet, 2H, J= 8 Hz), 7.15 (d, 1H, J=8.0 Hz), 7.85(d, 1H, J=8 Hz), 8.10(s, 1H). MS m/e (rel. abund.) 402 (100), 400 (81.15), 387 (24.59), 385 (27.46), 345 (77.46), 343 (68.03), 306 (45.49).

Preparation of epoxides 24, 25.

m-chloroperbenzoic acid (110 mg, 80-90%) was added in small portions with vigorous stirring to a two-phase mixture of 2.5 ml of sodium bicarbonate and a solution of 75 mg of the bismethoxy derivative 16, in 5 ml of methylene chloride. After stirring for 4 hours, 10 ml of 2% aqueous sodium sulfite was added and the mixture was stirred for an additional 15 min. The organic layer was diluted with ether, washed with 0.5 M sodium bicarbonate and then with water. A trace amount of pyridine was added during the extraction. The organic layer was dried over anhydrous potassium carbonate and the solvents were evaporated to give 87 mg of a crude product. Trituration with ether gave 74 mg of a colorless solid which was found to be a mixture of epoxides 24 and 25, by high resolution NMR. The epoxides exhibited the following properties. IR 1740, 1475, 1250 cm^{-1}; MS m/e (rel. abund.), 342 (3.86), 326 (2.08), 311 (1.68), 217 (1.57), 173 (4.19), 149 (4.59), 40 (100); ^1H NMR for the β-epoxide: 0.87 (s, 3H), 1.2 (s, 3H), 5.05 (t, 1H; J=2.4 Hz); ^1H NMR for the α-epoxide: 1.0 (s, 3H), 1.08 (s, 3H), 4.88 (d, 1H; J=5.8 Hz).

Preparation of 26 and 27.

To 194 mg of the mixture of epoxides dissolved in 10 ml of THF was added under an atmosphere of argon, 100 l of BF_3-OEt_2 at 0 C. The reaction mixture was allowed to warm up to room temparature and stirred overnight. It was then extracted with ether, washed with sodium bicarbonate solution

and with brine. It was then dried over anhydrous sodium sulfate and the solvent evaporated, to yield 208 mg of a crude product. Chromatography on silica gel gave 161 mg of 26 and 27 in the ratio of approximately 2:1. Analytical samples of 26 and 27 were obtained by fractional crystallization from ether/hexane. Compound 26 exhibited the following properties. M.Pt. 229-231 C IR 1710, 1735, 1275, 900 cm^{-1}; ^{1}H NMR 0.81 (3H, s), 4.22 (1H, d, J=8.85 Hz), 1.51 (3H,s), 1.6-2.9 (complex, 11H), 3.68 (3H, s), 3.78 (3H, s), 6.75 (2H, AB quartet, J=8.85 Hz). ^{13}C NMR ($CDCl_3$): 217.51, 209.26, 151.73, 150.50, 128.71, 123.10, 108.89, 107.99, 55.99 (two overlapping signals), 54.07, 45.23, 45.05, 44.51, 39.44, 34.45, 31.85, 22.64, 21.62, 20.73, 20.03. MS m/e (rel. abund.) 342 (41), 217 (47), 190 (74.9), 175 (40.8), 159 (25.4), 115 (40.6), 110 (21.33), 67 (57.09), 41 (100). Compound 27 exhibited the following properties. M.Pt. 175-176 C IR 1715, 1740, 1250, 880 cm^{-1}; ^{1}H NMR 1.0 (3H, s), 1.26 (3H, s), 1.4-3.0 (complex, 11H), 3.68 (3H, s), 3.76 (3H, s), 3.98 (1H, d, J=12.8 Hz), 6.7 (2H, s). ^{13}C NMR ($CDCl_3$) : 214.85, 206.52, 152.18, 151.49, 128.02, 122.87, 108.69, 108.51, 57.67, 55.74 (two overlapping signals), 49.18, 45.36, 43.74, 43.02, 34.59, 29.28, 24.54, 22.33, 18.22, 17.43. MS m/e (rel. abund.) 342 (51.45), 243 (6.93), 217 (64.01), 119 (100), 175 (49.14), 159 (36.31), 115 (50.27).

Kinetic protonation of anion derived from 26

Sodium hydride (30 mg, 60% dispersion in oil) was rinsed twice with dry pentane and to this was added 50 mg of ketone 26 in 5 ml of dry benzene. The reaction mixture was heated under reflux for 5 hrs. It was then cooled in ice and 0.1 ml of glacial acetic acid was added dropwise with rapid stirring. The solution was washed until neutral, dried over anhydrous sodium sulfate and the solvent was evaporated to give 50 mg of a crude solid which was found to be a mixture of 26 and 27 in the ratio of 20:80 as determined by ^{1}H NMR.

Preparation of enol 30.

A solution of 50 mg of ketone 26 in 5 ml of 5% methanolic potassium hydroxide was heated under reflux in a nitrogen atmosphere,for 8 hours. The excess methanol was evaporated, water was added and the product was extracted with methylene chloride. Evaporation of the washed, dried (Na_2SO_4) extract gave 50 mg of a yellow solid, which was found to be a mixture of 26 and the enol 30 in the ratio 40:60. The enol displayed the following ^{1}H NMR. 0.91 (s, 3H), 1.08 (s,3H), 3.76 (s, 3H), 3.85 (s, 3H), 6.78 (q, 2H; J=8.2 Hz), 6.92 (1H, s; disappeared on D_2O exchange).

Preparation of 31

30 mg of bismethoxy dione 27 was dissolved in 2 ml of THF and 1 ml of t-BuOH. To this was added 25 mg of potassium t-butoxide. After stirring for 10 min the reaction mixture was

cooled in an ice bath followed by treatment with 100 μl of methyl iodide. It was then warmed to room temparature and stirred for an additional 2 hours, quenched with water, extracted with ether, washed with brine and dried over sodium sulfate. Removal of solvent yielded 32 mg of an oil (100%) which was found to be pure 33 by NMR. Crystallization from ether gave 20 mg of colorless solid which displayed the following properties. M.Pt. =227-230 C; IR ($CHCl_3$) 1735, 1475, 1230, 1075 cm^{-1}. ^1H NMR ($CDCl_3$) 0.92 (s, 3H), 1.18 (s, 3H), 1.5-3.2 (m, 11H), 3.48 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 6.71 (s, 2H); MS m/e (rel. abund.), 356 (100), 341 (7.23), 309 (4.17), 283 (5.44), 267 (10.54), 215 (33.84).

Preparation of 32 and 33.

10 mg f the bismethoxy dione 27 gave on treatment with 10 mg of potassium tert-butoxide and 20 micro liters of ethyl bromoacetate, 32 as the only product. 32 displayed the following ^1H NMR ($CDCl_3$) 0.9(s, 3H), 1.15(s, 3H), 1.25 (t, 2H, J=14 Hz), 1.4- 3.2 (m, 11H), 3.75 (s, 3H), 3.78 (s, 3H), 4.15 (q, 1H, J=14 Hz), 4.1 (d, 1H, J=22 Hz), 4.25 (d, 1H, J= 22 Hz), 6.65 (d, 1H, J=12 Hz), 6.75 (d, 1H, J=12 Hz).

A sample of 33 prepared by treating 27 with potassium tert-butoxide followed by trapping with allyl bromide displayed the following ^1H NMR ($CDCl_3$) 0.9 (s, 3H), 1.15 (s, 3H), 1.4- 3.2 (m, 11H), 3.75 (s, 3H), 3.78 (s, 3H), 4.1- 4.3 (m, 2H), 5.0- 5.2 (m, 2H), 5.7- 5.9 (m, 1H), 5.7 (AB q, 2H, J=10 Hz).

Preparation of the α-bromo diketone 40.

To 287 mg of dione 1 in 8 ml of glacial acetic acid, was added at room temparature, 1.8 mmol of bromine was 5 ml of glacial acetic acid. The reaction mixture was stirred for 16 hours. The precipitated α-bromo ketone was filtered and dried to yield 310 mg of the product. An additional 80 mg was obtained from the mother liquor by extraction with benzene and evaporation of the solvent. (Total yield 94%). An analytical sample obtained by crystallization from ether exhibited the following properties. M.Pt. 210-212° C; IR 1740-1730; MS (rel. abund.) 260 (14.8), 258 (15.3), 245 (8.3), 243 (8.74), 179 (42.5), 152 (21.6), 151 (26.99), 109 (56.22), 95 (64.97), 82 (97.76), 67 (82.1), 55 (99.44), 41 (100); ^{1}H NMR 0.95 (s, 3H), 1.25 (w, 3H), 1.6-2.8 (complex, 8H), 5.0-5.2 (q, 1H, J=8.1 Hz).

Preparation of enone 36.

310 mg of α-bromo ketone 40 and 600 mg of anhydrous calcium carbonate in 8 ml of dimethyl acetamide was refluxed for 5 hours. GC analysis (SE 30, 190 C), showed the complete disappearance of the starting material. The reaction mixture was cooled to room temparature, decomposed with dilute hydrochloric acid and extracted with benzene. The organic layer was washed with water and with brine, and dried over anhydrous sodium sulfate. The evaporation of the solvent yielded 187 mg of a colorless solid which exhibited the following properties. M.Pt. 188-191° C;

IR ($CDCl_3$) : 3120, 2950, 1745, 1680, 1605 cm^{-1}; ^1H NMR : 1.1 (s, 3H), 1.2 (s, 3H), 1.4-2.7 (m, 6H), 5.7-6.1 (m, 1H), 6.5-6.9 (m, 1H); MS (70 eV) m/e (rel intensity) 178 (54), 163 (18), 150 (30), 123 (56), 68 (100).

Preparation of 42.

680 mg of the enone 36 was dissolved in 15 ml of THF. This was cooled to -78 C and to this was added 4 ml of 1M allyl magnesium bromide in THF. After the addition the reaction mixture was slowly warmed to room temparature and quenched with saturated ammonium chloride. It was extracted with ether ,washed with water and brine and dried. The solvent was evaporated to yield 784 mg (93%) of the allyl alcohol. An analytical sample obtained after chromatography (silica gel, ethyl acetate) exhibited the following properties. IR($CHCl_3$) 3500, 1740 cm^{-1}; ^{1}HNMR($CDCl_3$) .88(s, 3H), 1.2 (s, 3H), 1.5-2.6(m, 9H), 5.1-5.3 (m, 2H), 5.55-5.65 (m, 1H), 5.7-5.8(M, 1H), 5.9-6.1 (m, 1H). ^{13}C NMR 220, 134, 131, 127, 52, 47(two overlapping signals), 43, 33, 30, 26, 21.

Preparation of 41.

To 96 mg of enone 36 in 10 ml of THF was added 1 ml of a 1.4 M solution of vinyl magnesium bromide in THF. The reaction mixture was stirred under argon for 30 minutes and processed as usual to give 122 mg of a slight yellow oil. Trituration with ether gave 110 mg of colorless solid. M. Pt IR ($CHCl_3$) 1740, 1710, 800 cm^{-1} ; ^1H NMR ($CDCl_3$) 0.98 (s, 3H), 1.2 (s, 3H)

1.5- 2.9 (m, 9H), 5.0 (d, 1H, J=9 Hz), 5.1 (d, 1H, J=14 Hz) 5.85- 5.95 (ddd, 1H, J= 14, 9, 5 Hz); MS m/e (rel. abund.) 206 (74.95), 191 (58.14), 163 (19.25), 151 (46.9), 111(100).

Treatment of 42 with pyridinium chlorochromate.

100 mg of the alcohol 42 was subjected to oxidation with 120 mg of PCC in 5 ml of methylene chloride. The reaction mixture was stirred overnight at room temperature. It was filtered through a short column of silica and the solvent was removed under vacuum. Analysis of the crude product (100 mg) showed that the major component was the dehydrated product 44. Chromatography on silica gel (CH_2Cl_2) yielded 70 mg of pure 44 which displayed the following properties. ^{1}H NMR ($CDCl_3$) 1.1 (s, 3H), 1.2 (s, 3H), 1.7- 2.8 (m, 6H), 5.2- 7.2 (m, 6H). MS m/e (rel. abund.) 202 (78.42), 187 (100),145(46), 131 (49.54), 91 (42.63). A small amount of the transposed enone 45 was obtained from this reaction. 45 displayed the following ^{1}H NMR. 1.1 (s, 3H), 1.2 (s, 3H), 1.7-2.8 (m, 6H), 5.1-5.3 (m, 2H), 5.7- 5.9 (m, 2H). MS m/e (rel. abund.) 218 (55.73), 206 (38.11), 177 (57.38), 149 (59.82), 135 (76), 119 (63.17), 91 (83.66), 39 (100).

Note. Attempted oxidation of 42 with Jone's reagent gave mainly the triene 44 and several other unidentified products.

Preparation of compound 46.

To 150 mg of the enone 36 in 20 ml of ether was added at 0 C, under an atmosphere of nitrogen, 2 ml of a 1M solution of methyl lithium (low halide) in ether. A white precipitate was formed immediately. After 1 hr. the reaction mixture was quenched with saturated ammonium chloride and extracted with ether. The ether extract was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 140 mg (87%) of an oil which exhibited the following properties. ^{1}H NMR 0.85 (3H, s), 1.2 (3H, s), 1.28 (3H, s), 1.4-2.6 (7H, complex), 5.6-5.9 (2H ,m); MS m/e (rel. intensity) 176 (2), 133 (1.5), 119 (18.66), 111 (21.11), 105 (22.67), 91 (13.12), 84 (43.08), 77 (12.2), 69 (47.6), 55 (24.7), 43 (100).

Preparation of compound 47.

100 mg of the crude 46 was dissolved in 4 ml of methylene chloride and this was added 200 mg of pyridinium chlorochromate (PCC). The mixture was then stirred for 24 hours. It was then diluted with ether and filtered through a short column of florisil. Evaporation of the solvent yielded a colorless oil which displayed the following properties. IR : 1740, 1680, 1225 cm^{-1}; ^{1}H NMR : 1.10 (3H, s), 1.20 (3H, s), 2.0 (3H, s), 1.7-2.7 (6H, complex), 5.77 (1H, s); MS : m/e (rel. intensity) 192 (33.8), 150 (29.4), 136 (3.37), 123 (26.78), 108 (63.2), 93 (100).

Preparation of compound 48.

90 mg of the enone 42 was dissolved in 5 ml of THF and this was added to 0.6 mmol of thexyl borane (prepared from 2,3 dimethyl-2-butene and borane). It was stirred at 0 C for 3 hours, warmed up to room temparature and stirred overnight. The reaction mixture was quenched with 2 ml of 10% sodium hydroxide followed by the addition of 1 ml of 30% hydrogen peroxide. After stirring for an additional 5 hours, it was extracted with ether, washed with water and with brine, and the organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 100 mg of a crude product which was found to be pure 48 by ^{1}H NMR. The characteristic properties of 48 are as follows: IR 3300-3500, 1735 cm^{-1}; ^{1}H NMR 0.8 (s, 3H), 1.25 (s, 3H), 1.6-3.0 (complex, 12H), 3.6 (t, 2H, J=6 Hz), 5.6-5.7 (s, 2H).

Preparation of 49 and 50.

To 16 mg of the diol 48 in 1 ml of methylene chloride was added 140 micro liter of acetic anhydride, 100 micro liter of triethyl amine and a small crystal of DMAP. The mixture was stirred under argon for 3 hrs at room temparature. The reaction mixture was purified by chromatography (silica gel, ethyl acetate). Evaporation of the solvent gave 20 mg of the acetate which displayed the following properties. ^{1}H NMR : 0.85 (s, 3H), 1.15 (s, 3H), 2.1 (s, 3H), 1.3-2.6 (m, 11H), 4.1 (t, 2H; J=6 Hz), 5.6-5.7 (m, 1H), 5.7-5.8 (m, 1H).

Oxidation of the above product 49 with 25 mg of PCC in 2 ml of methylene chloride followed by the usual work up gave 22 mg of 50 as a colorless oil. Compound 50 exhibited the following characteristics : MS m/e (rel. intensity) 292 (3.0), 218 (19.71), 202 (55.04), 187 (86.93), 43 (100).

Preparation of the spirolactone 51.

25 mg of the diol 48 was dissolved in 1 ml of methylene chloride and was stirred under argon with 25 mg of PCC. TLC analysis (ethyl acetate, silica gel) showed completion of the reaction within 30 min. The reaction mixture was filtered through a short column of silica gel and the product eluted with methylene chloride. Evaporation of the solvent gave 22 mg (88%) of pure spirolactone which displayed the following properties : IR ($CDCl_3$) 1735, 1765, 1200, 1150, 1000 cm^{-1}; ^1H NMR 0.9 (s, 3H), 1.15 (s, 3H), 1.5-2.8 (complex, 10H), 5.6-5.75 (complex, 1H), 5.9-6.0 (m, 1H); MS m/e(rel. intensity) 234 (16.7), 216 (6.88), 201 (2.84), 124 (100), 119 (40.07), 96 (46.69).

Preparation of the compound 52.

To 177 mg of enone 36 in 10 ml of 1:1 mixture of THF and t-butanol, was added 225 mg of potassium t-butoxide. After 5 minutes at room temparature, it was cooled to 0 C, and 450 micro liters of methyl iodide was added. After 10 hours it was quenched with water, extracted with ether and washed with brine. The solvent was dried over anhydrous sodium sulfate

and evaporated to yield 184 mg (96%) of a white solid. An analytical sample obtained by crystallization from ether exhibited the following properties : M.Pt. 175-177 C; ^{1}H NMR ($CDCl_3$) 0.8 (3H, s), 0.95 (3H, s), 1.6 (3H, complex), 2.0-2.4 (6H, complex), 6.35 (1H, complex); MS m/e (rel. intensity) 192 (33.8), 177 (11.3), 164 (25.78), 137 (43.10), 121 (55.4), 82 (100).

Analysis : Calculated : 74.96% C; 8.38% H.

Observed : 74.85% C; 8.35% H.

Preparation of compound 55.

To 90 mg of enone in 5 ml of methanol was added 1.5 ml of 0.4M $CeCl_3.6H_2O$ in methanol, followed by addition of 20 mg of sodium borohydride. After stirring for 30 minutes it was quenched with 10% sodium hydroxide. It was extracted ether, washed with water and with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded an oily residue which was purified by HPLC (silica, ethyl acetate:hexane 2:1) to give 75 mg (83%) of alcohol 55. IR : 1675, 3450 cm^{-1}; ^{1}H NMR 0.8 (s, 3H), 1.3 (s, 3H), 1.8 (complex, 3H), 1.7-3.2 (complex, 7H), 4.0-4.2 (dd, 1H; J=8, 2.5 Hz), 6.6-6.8 (complex, 1H). MS m/e (rel. intensity) 194 (34.51), 179 (8.64), 176 (15.85), 150 (100), 135 (64.12), 121 (81.53), 107 (90.7).

Preparation of compound 56.

1.08 gm of the alcohol 55 was dissolved in 10 ml of THF.

To this was added at room temparature, under argon, 10 ml of allylmagnesium bromide in ether (1M solution). The reaction mixture was allowed to stir overnight. It was then quenched with saturated ammonium chloride and extracted with ether. The ether layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 1.065 gm (86%) of the adduct which exhibited the following ^{1}H NMR resonances : ^{1}H NMR ($CDCl_3$) 0.9 (s, 3H), 1.1 (s, 3H), 1.3-2.6 (m, 13H), 3.8-3.9 (dd, 1H; J=8, 2.5 Hz), 5.0-5.1 (m, 2H), 5.5-5.6 (m, 1H), 5.9-6.1 (m, 1H).

To 620 mg of the intermediate diol in 5 ml of methylene chloride was added 500 mg of PCC at room temparature. The reaction mixture was stirred overnight. It was then diluted with ether, filtered through a short column of silica and the solvents were evaporated, to give 550 mg (88%) of 56 as an oil. An analytical sample was obtained by HPLC.(silica, ethyl acetate). IR : 3500-3600, 1740, 1430, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.85 (s, 3H), 1.1 (s, 3H), 1.4-2.6 (m, 12H), 6.0-6.2 (m, 2H), 6.4-6.5 (m, 1H), 6.9-7.1 (m, 1H); MS m/e (rel. intensity) 234 (1.5), 216 (2.21), 193 (100), 175 (8.71), 133 (82.46);

Preparation of compound 58.

A solution of 0.5 mmol of thexyl borane was prepared by reacting 0.5 ml of a 1M solution of borane in THF with 0.5 ml of a 1M solution of 2,3-dimethyl-2-butene in THF at 0 C. To this was added 90 mg of alcohol 56 in 5 ml of THF. It was stirred

overnight under an argon atmosphere. The reaction mixture was quenched with 1 ml of 10% sodium hydroxide followed by the addition of 0.5 ml of 30% hydrogen peroxide. After stirring for an additional 2 hours the reaction mixture was extracted with ether, washed with water and with brine. The ether layer was dried with anhydrous sodium sulfate and the solvents were evaporated. The crude product was purified by chromatography (silica gel, ethyl acetate) to give 82 mg (85%) of 58. 58 diplayed the following ^{1}H NMR($CDCl_3$) 0.88 (s, 3H), 1.28 (s, 3H), 1.86-3.0 (m, 15H), 3.82 (bt, 2H, J=6 Hz), 5.4-5.6 (m, 1H).

Preparation of the acetate of 58., and oxidation to 60.

230 mg of the diol 58 was dissolved in 2 ml of CH_2Cl_2. To this was added 100 micr liters of Et_3N, 150 micro liters of acetic anhydride and 10 mg of DMAP. This was stirred for 2 hours at room temparature. The reaction mixture was purified by chromatography (silica gel, methylene chloride). 253 mg of a crude product was obtained which was found to be pure by NMR. ^{1}H NMR : 0.9 (s, 3H), 1.2 (s, 3H), 1.8 (m, 3H), 2.1 (s, 3H), 2.0-2.8 (m, 11H), 4.0-4.2 (broad triplet, 2H; J=6 Hz), 5.4-5.6 (m, 1H).

59 mg of the above acetate was dissolved in 1 ml of acetone. To this was added at 0 C, 100 micro liters of Jones reagent. The reaction mixture was stirred under nitrogen for 15 minutes and slowly warmed up to room temparature. It was stirred at

this temparature for an additional 4 hours. The excess oxidant was removed by dropwise addition of isopropanol until the solution turned colorless. It was extracted with ether, washed with water and with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 55 mg (91%) of the transposed enone 60. This compound exhibited the following properties : IR 1760-1740, 1670, 1225 cm^{-1}; ^1H NMR : 1.1 (s, 3H), 1.2 (s, 3H), 1.8 (s, 3H), 2.1 (s, 3H), 2.0-2.8 (complex, 10H), 4.2 (t, 2H; J=6 Hz); MS m/e (rel. intensity) 292 (5.0), 264 (5.0), 246 (2.3), 232 (29.6), 217 (18.2), 149 (22.3).

Preparation of the homologous spirolactone 59.

A small amount of the diol 58 on oxidation with PCC gave the spirolactone 59 as the only product. It displayed the following properties : IR : 1735, 1770, 1260, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) : 0.9 (s, 3H), 1.15 (s, 3H), 1.8 (broad s, 3H), 1.6-2.8 (m, 10H), 5.6-5.7 (m, 1H). MS m/e (rel. intensity) 248 (66.12), 206 (9.6), 138 (100).

Preparation of trans diene 63

100 mg of the vinyl carbinol and 10 mg of p-toluene sulfonic acid were refluxed in 5 ml of toluene for three hours. The reaction mixture was cooled and diluted with ether. It was washed with 10% sodium hydroxide solution, water and brine. The organic layer was dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure (Temp below 35C). An oil weighing 105 mg was obtained which was purified by kugel rohr distillation(60-65 C, 10 microns) to give 90 mg (95%). This product was found to be identical in all respects with that reported by Jacob Tou. M.Pt 67-71 C; ^{1}H NMR($CDCl_3$) 0.84(s, 3H), 0.92 (s, 3H), 1.8 (d, 3H, J=5.88 Hz) 1.9-2.6 (m, 6H), 5.35 (q, 1H, J=5.88 Hz), 5.6-5.7 (m, 1H), 6.3-6.45 (m, 1H).

Preparation of trans diene 62

50 mg of the cisoid diene 4 was refluxed in 5 ml of $CHCl_3$ with a small crystal of p-toluene sulfonic acid. The progress of the reaction was monitored by analysing the sample with high resolution NMR. After 30 minutes the reaction mixture was found to be mostly 62 contaminated with a small amount (10%) of 63. It was processed as usual and crystallized from eher- hexane to obtain pure 62. 62 displayed the following properties. M.Pt 88-90 C. ^{1}H NMR($CDCl_3$) 0.98(s,3H), 1.02 (s, 3H), 1.9(d, 3H, J=6Hz), 1.92-2.6 (m, 6H), 5.4-5.7 (m, 2H), 5.9-5.6 (m, 1H). MS m/e (rel. abund.)

Preparation of 65.

75 mg of the epoxide 70 was treated with 25 micro liters of DBU in 5 ml of dry benzene. The reaction mixture was stirred at room temperature for 36 hours. It was extracted with ether and washed with dilute hydrochloric acid, water and brine. Removal of the solvent gave a crude product which was subjected to HPLC separation (silica, ethyl acetate: hexane::25:75). 52 mg of the alcohol 65a was obtained as a yellow oil. This alcohol displayed the following properties. IR ($CHCl_3$) 3400, 1735, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) 1.0(s, 3H), 1.1 (s, 3H), 1.7- 2.7 (m, 7H), 2.4 (s, 3H), 4.6- 4.7 (dd, 1H, J=8, 3 Hz), 6.7 (d, 1H, J=3 Hz). MS m/e (rel. abund.) 222(100), 207(3), 189(3), 161 (19.27), 147 (24.72).

The above product was subjected to oxidation with PDC (50 mg, 5 ml methylene chloride, overnight). The reaction mixture was passed through a short silica column and the product was eluted with methylene chloride. Evaporation of the solvent followed by purification by flash chromatography (silica, methylene chloride) gave 38 mg of the enedione 65 which was found to be the same product obtained by the air oxidation of the non conjugated enone 64.
65 displayed the following properties. IR ($CDCl_3$) 1740, 1680, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) 1.1 (s, 3H), 1.3 (s, 3H), 2.4 (s, 3H), 2.2- 2.8 (m, 6H), 6.3 (s, 1H); MS m/e (rel. abund.) 220 (65.50), 205 (6.70), 192 (5.21), 178 (20.59),43 (100).

Preparation of 70 and 72

To 1.3 gm of the non conjugated enone 64 dissolved in 15 ml of methylene chloride was added with vigorous stirring 1.325 gm of an 80-90% MCPBA. The progress of the reaction followed by GC (SE 30, 180 C). Additional amounts of MCPBA was occasionally added inorder to complete the reaction. After stirring for 24 hours the reaction mixture was washed with 5% sodium sulfite, 10% sodium carbonate, water and brine, and dried over anhydrous sodium sulfate. Removal of the solvent yielded an oily residue which was chromatographed on silica gel (ethyl acetate:hexane 2:3). The initial fractions were combined and evaporated to give 206 mg of pure ester 72. 72 displayed the following properties. IR ($CHCl_3$) 1745 (s), 1230 cm^{-1}; ^1H NMR ($CDCl_3$) 0.9 (s, 3H), 1.1 (s, 3H), 2.15 (s, 3H), 1.7-2.6 (m, 6H), 5.4- 5.6 (m, 2H), 5.7- 5.9 (m, 1H). MS m/e (rel. abund.) 222(7.5), 180 (12.6), 147 (29.6), 105 (21.3), 43 (100).

The remaining fractions were combined and evaporated to give 505 mg of the required epoxide(39%), 70 which exhibited the following properties. IR ($CHCl_3$) 1740, 1710, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) 0.82 (s, 3H), 1.16 (s, 3H), 2.3 (s, 3H), 1.8- 2.6 (m, 6H), 3.28 (s, 1H), 3.34 (bs, 1H), 3.56 (d, 1H, J= 4 Hz); MS m/e (rel. abund.) 222 (7.64), 121 (14.68), 95 (17.30), 43 (100).

Preparation of the epoxide 69

To a two phase mixture of 950 mg of trans diene 62 in 120 ml of methylene chloride and 60 ml of .5 M sodium bicarbonate was added 1 gm of m-chloroperbenzoic acid (80-90%) in small portions. The mixture was stirred under nitrogen for 2 hours at room temperature. It was washed with 25 ml of 2% sodium sulfite. The organic layer was separated and washed with .5 M sodium bicarbonate. A few drops of pyridine were added and the extract was washed with distilled water and dried over anhydrous potassium carbonate. Evaporation of the solvent yielded an oily residue which on trituration with ether gave 930 mg(90%) of 69 as a colorless crystalline solid. It exhibited the following properties. M.Pt **80-81°C** IR($CDCl_3$) 3000, 1740, 1375, 1180 cm^{-1}. ^1H NMR($CDCl_3$) 1.0(s, 3H), 1.15(s, 3H), 1.45(d, 3H, J=6 Hz), 1.5-2.6(m, 6H), 2.9(q, 1H, J=6 Hz), 5.1-5.2(m, 1H), 5.9-6.0 (ddd, 1H, J=7.6, 5.5, 2 Hz). MS m/e (rel. abund.) 206 (5.29), 147 (15.02), 105 (12.96), 85 (100).

Preparation of 73

A solution of 3 mmols of LDA was prepared in 10 ml of THF using the conventional procedure. To this was added at -78 C 95 mg of the epoxide 69 in 2 ml of THF. The reaction mixture was stirred at this temperature for 30 minutes and then warmed to room temperature followed by the addition of 3ml of HMPA. It was allowed to stir overnight and was quenched with saturated ammonium chloride solution. The product was extracted into ether and the organic layer was washed sequentially with 5%

sodium hydroxide solution, water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by chromatography on silica gel(methylene chloride) gave 83 mg(88%) of dienol 73 as a slight yellow oil. It displayed the following properties. ^{1}H NMR($CDCl_3$) 1.0 (s, 3H), 1.05 (s, 3H), 1.4 (d, 3H, J=7 Hz), 4.4 (q, 1H, J=7 Hz), 5.9-6.2 (m, 3H), 1.6-2.6 (m, 5H). MS m/e (rel. abund.) 206 (19.35), 188 (8.44), 173 (4.5), 147 (39.0), 131 (100), 119 (84.1), 91 (43.92).

Oxidation of the dienol 73 to dienone 74

To 60 mg of the dienol 73 dissolved in 3 ml of methylene chloride was added 100 mg of pyridinium chlorochromate(PCC). It was stirred overnight under nitrogen. GC analysis (SE 30, 180 C) showed the complete disappearance of the starting material. The reaction mixture was filtered through a short column of silica gel and the product was eluted with methylene chloride. Evaporation of the solvent gave 52 mg(87%) of a slight yellow oil which exhibited the following properties. IR($CHCl_3$) 1735, 1660, 1250 cm^{-1}; ^{1}H NMR($CDCl_3$) 1.05 (s, 3H), 1.1 (s, 3H), 2.3 (s, 3H), 2.2-2.6 (m, 4H), 6.05-6.15 (dd, 1H, J=9.5, 5.0 Hz), 6.55 (d, 1H, J=9.5 Hz), 6.84 (d, 1H, J=5.7 Hz); MS m/e (rel. abund.) 204 (7.8), 189 (4.4), 161 (12.2), 147 (42.0), 133 (20.5) 119 (38.2), 105 (15.5), 91 (13.4), 77 (11.2), 43 (100).

Preparation of the bissilyl ether 75

260 mg of the dienone 74 in 10 ml of THF was added to a solution of 3.1 mmol of LDA in 10 ml of THF at 78 C. The reaction mixture was slowly warmed to 0 C followed by the addition of 2 ml of dry HMPA. It was stirred at this temperature for 10 minutes and a solution of 450 mg of tert-butyldimethyl silyl chloride in 3 ml of THF was added. After a reaction time of 30 minutes it was quenched with water, extracted with ether and washed with ice cold water. The solvents were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude material obtained was purified by bulb to bulb distillation to give 325 mg (59%) of 75 which was found to be pure by high resolution NMR. 75 exhibited the following properties. ^{1}H NMR ($CDCl_3$) 0.2 (s, 12H), 1.1 (s, 18H), 1.2 (s, 3H), 1.4 (s, 3H), 2.2- 2.4 (m, 2H), 4.4- 4.5 (m, 2H), 4.7- 4.8 (bs, 1H), 6.0- 6.6 (m, 3H). MS m/e (rel. abund.) 432 (8.87), 417 (8.67), 301 (11.92), 285 (9.12), 115 (34.4), 73 (100).

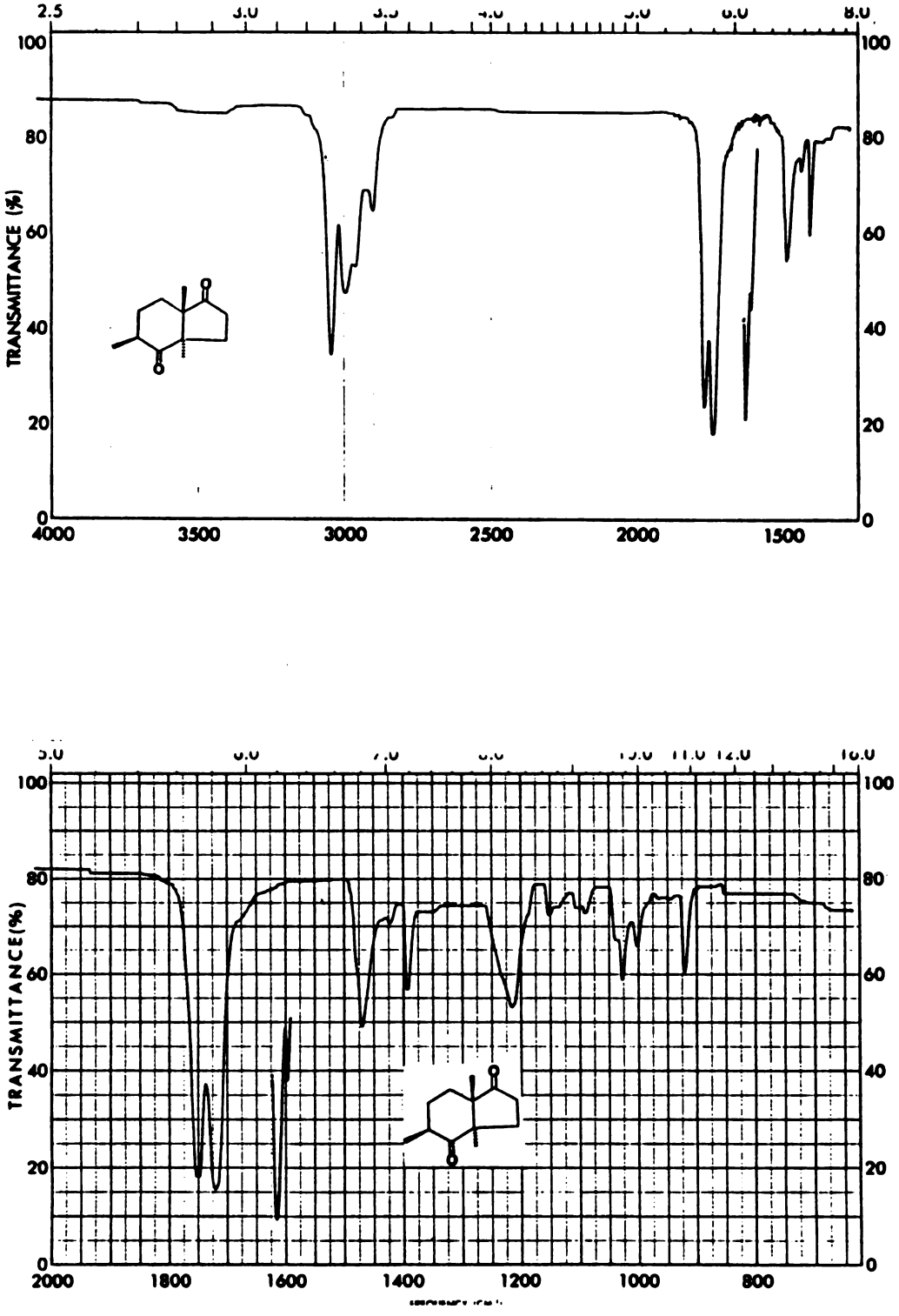


Figure 3. Infrared spectrum of 7

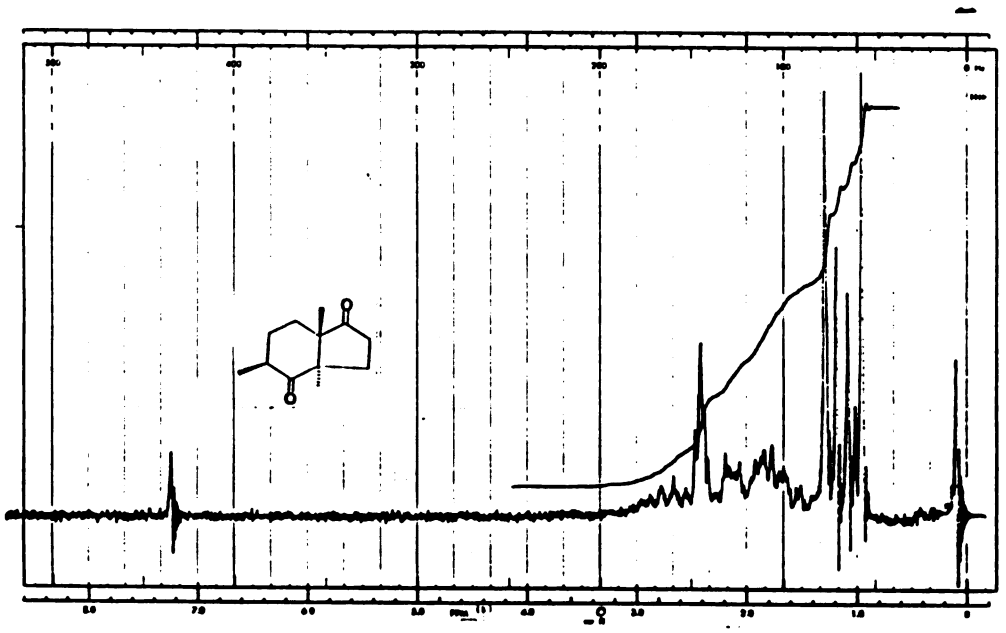


Figure 4. ^{1}H NMR spectrum of 7

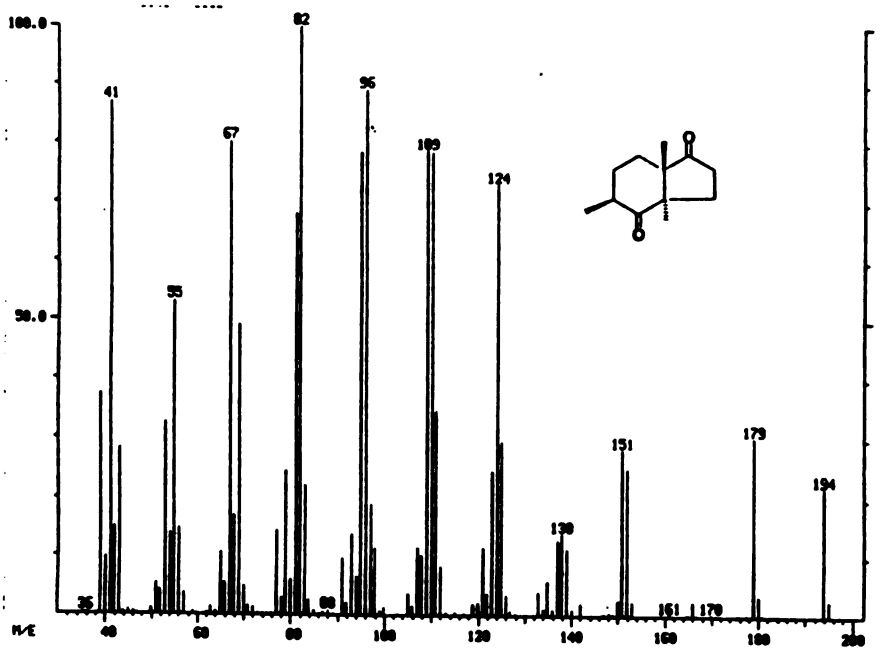


Figure 5. Mass spectrum of 7

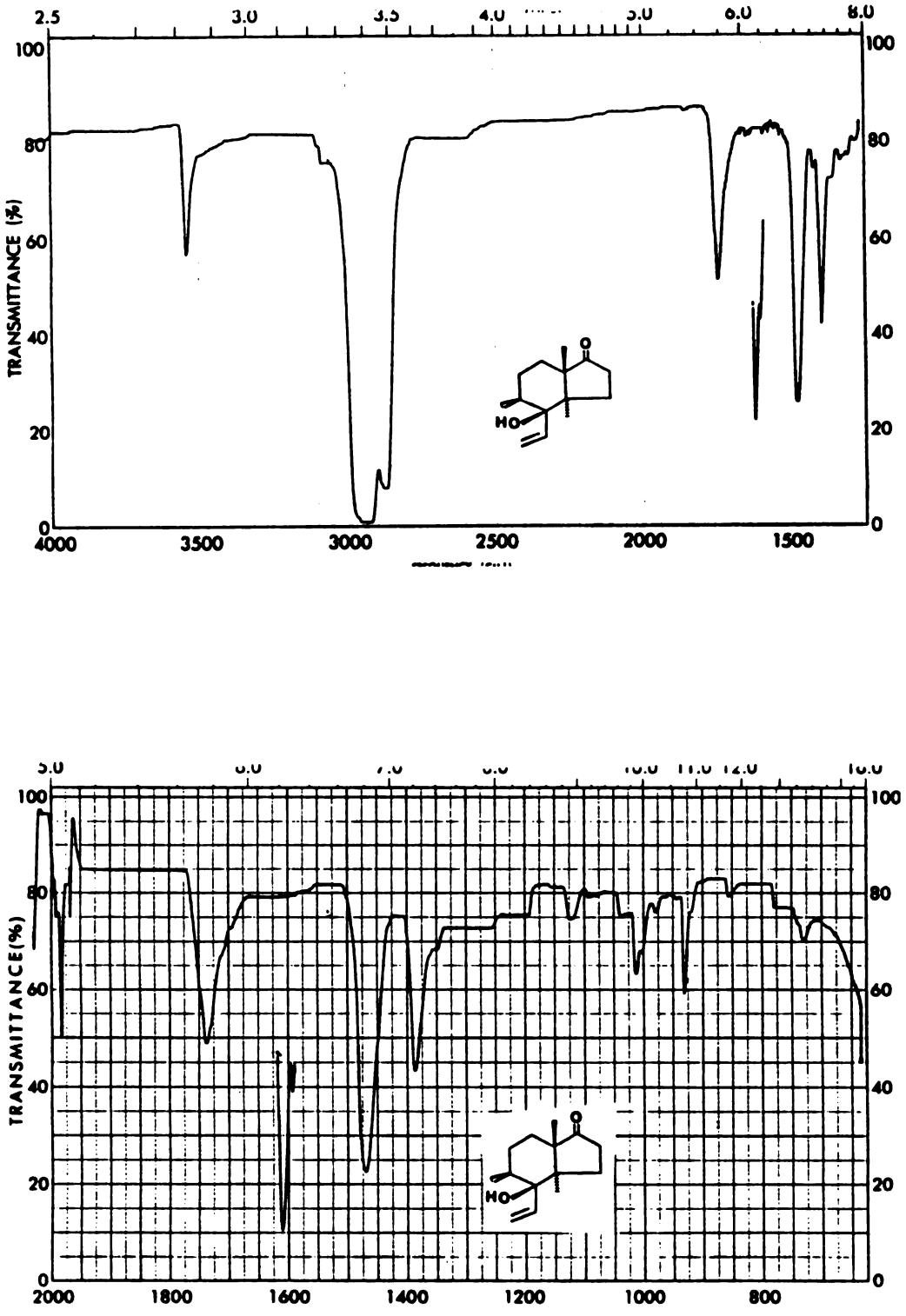


Figure 6. Infrared spectrum of 8

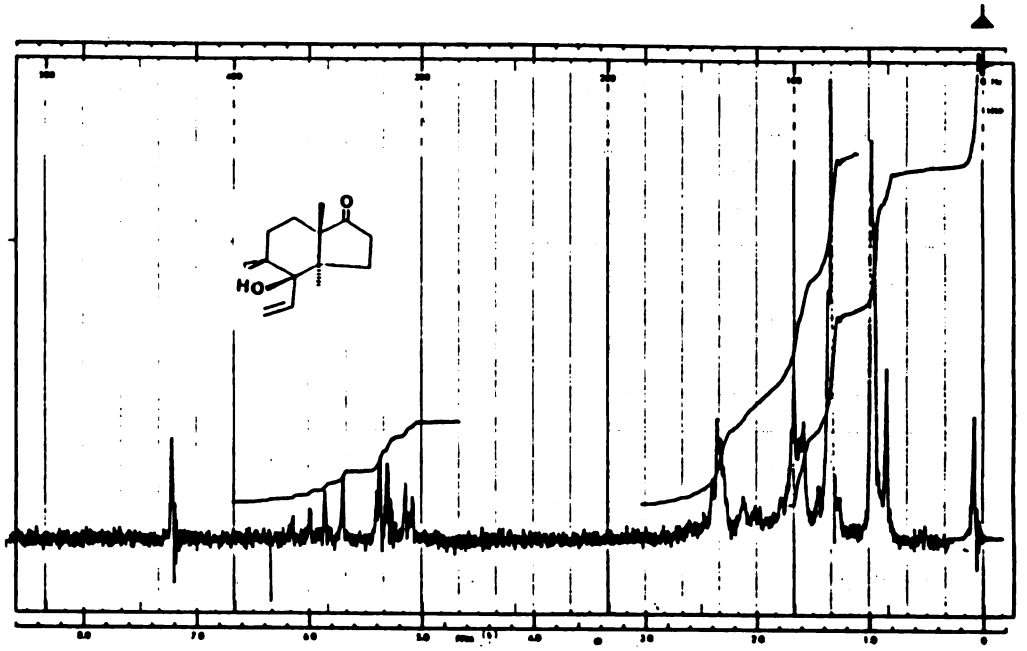


Figure 7. ^{1}H NMR spectrum of 8

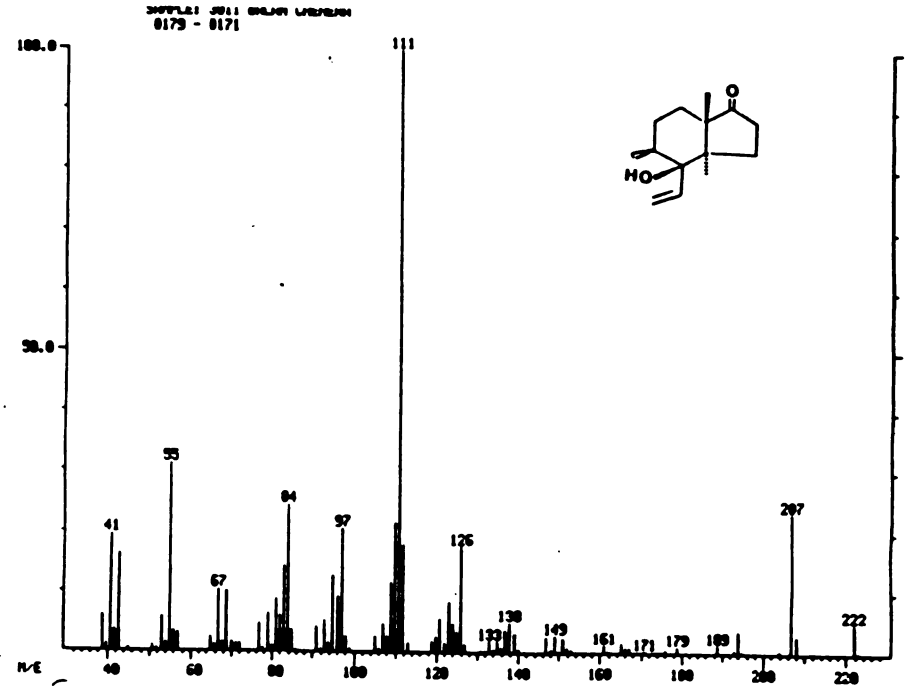


Figure 8. Mass spectrum of 8

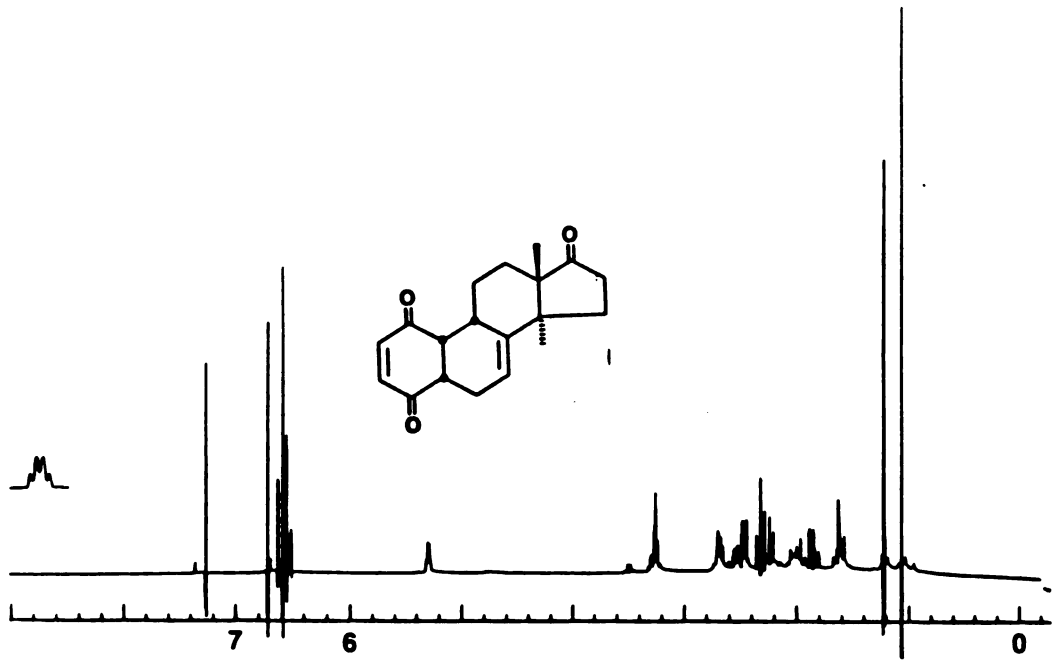


Figure 9. ^{1}H NMR spectrum of 10

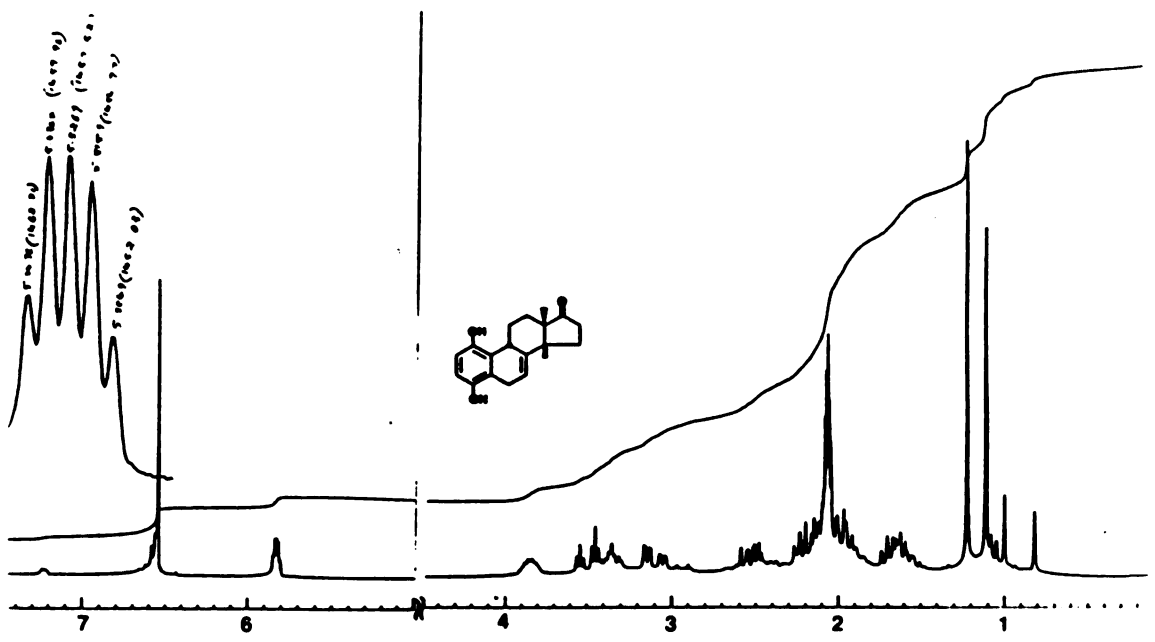


Figure 10. ^{1}HNMR spectrum of 11

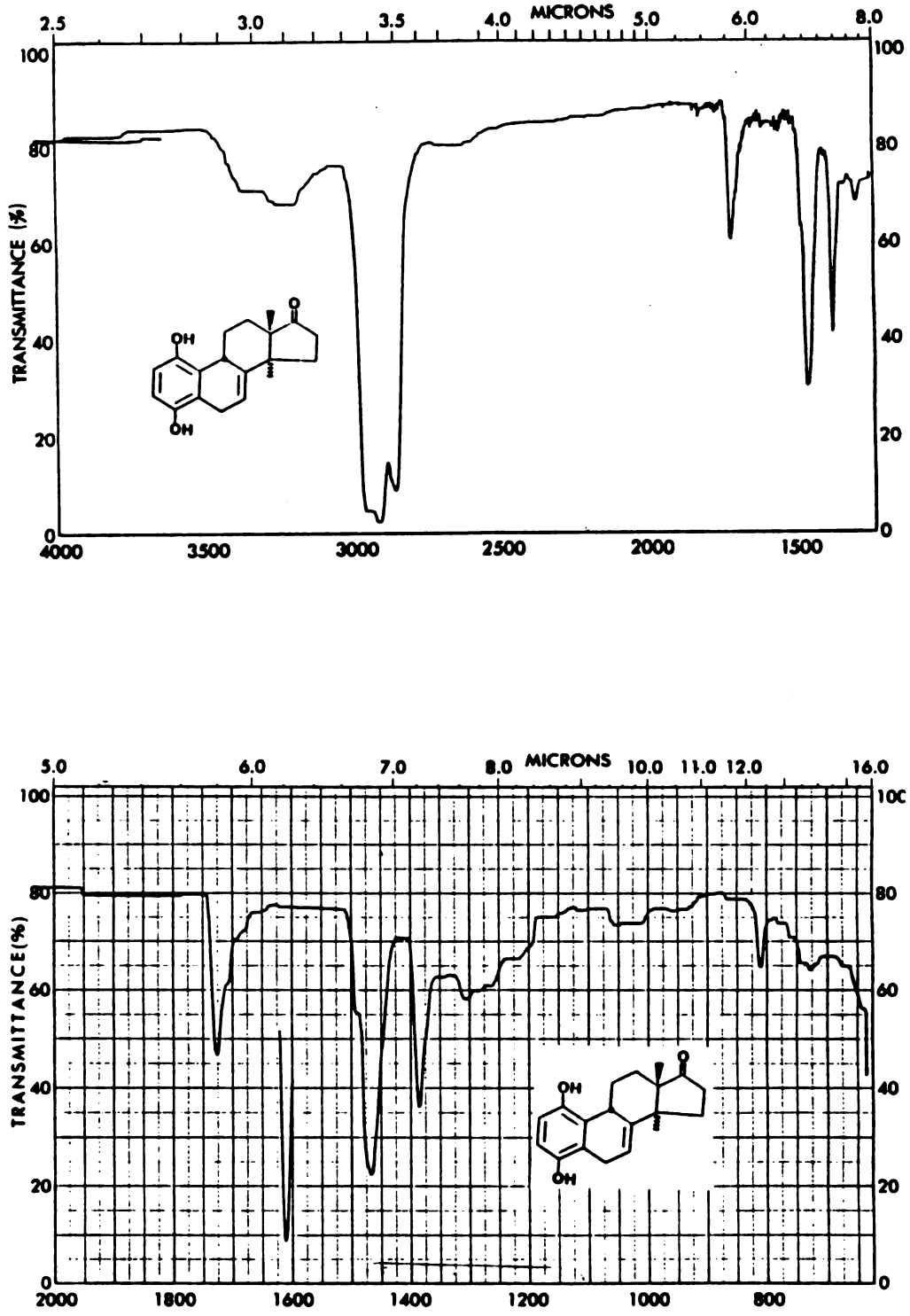


Figure 11. Infrared spectrum of 11

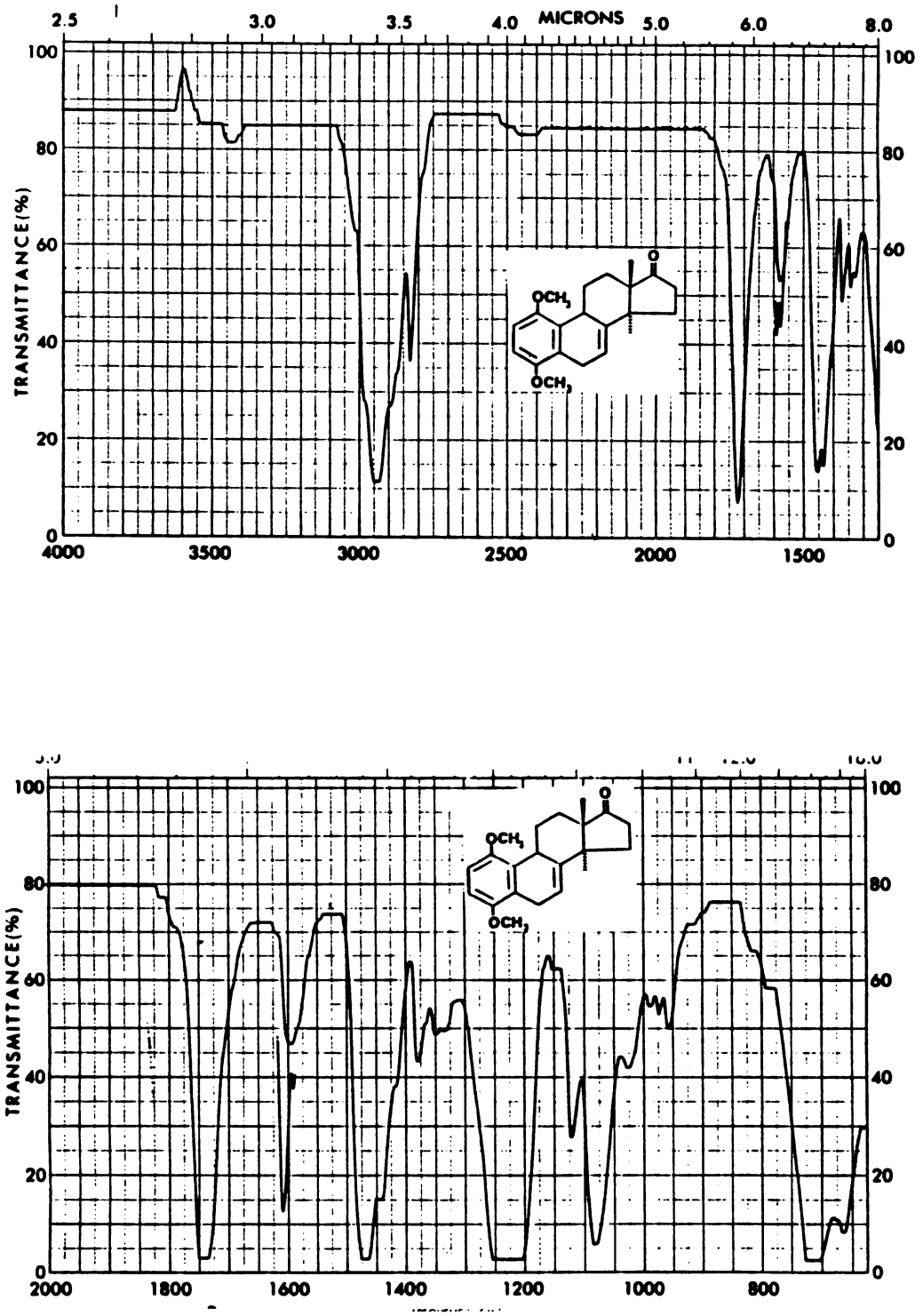


Figure 12. Infrared spectrum of 13

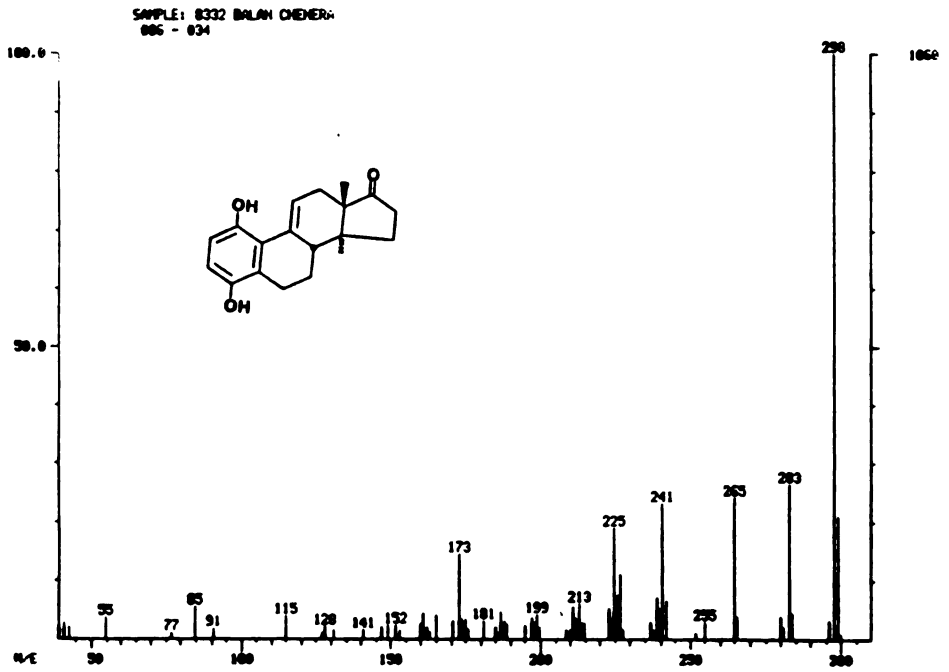


Figure 13. Mass spectrum of 17

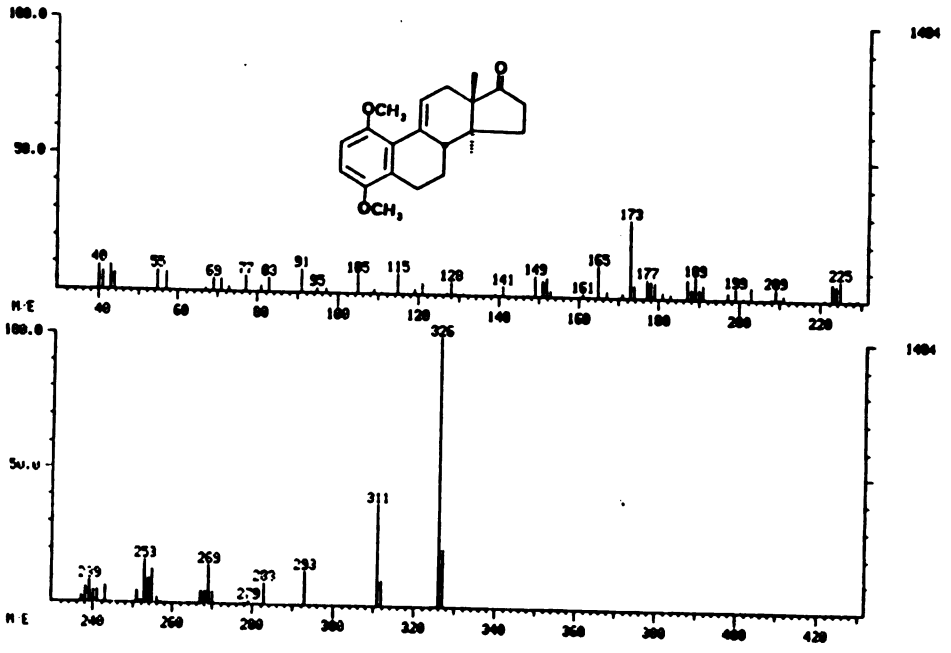


Figure 14. Mass spectrum of 16

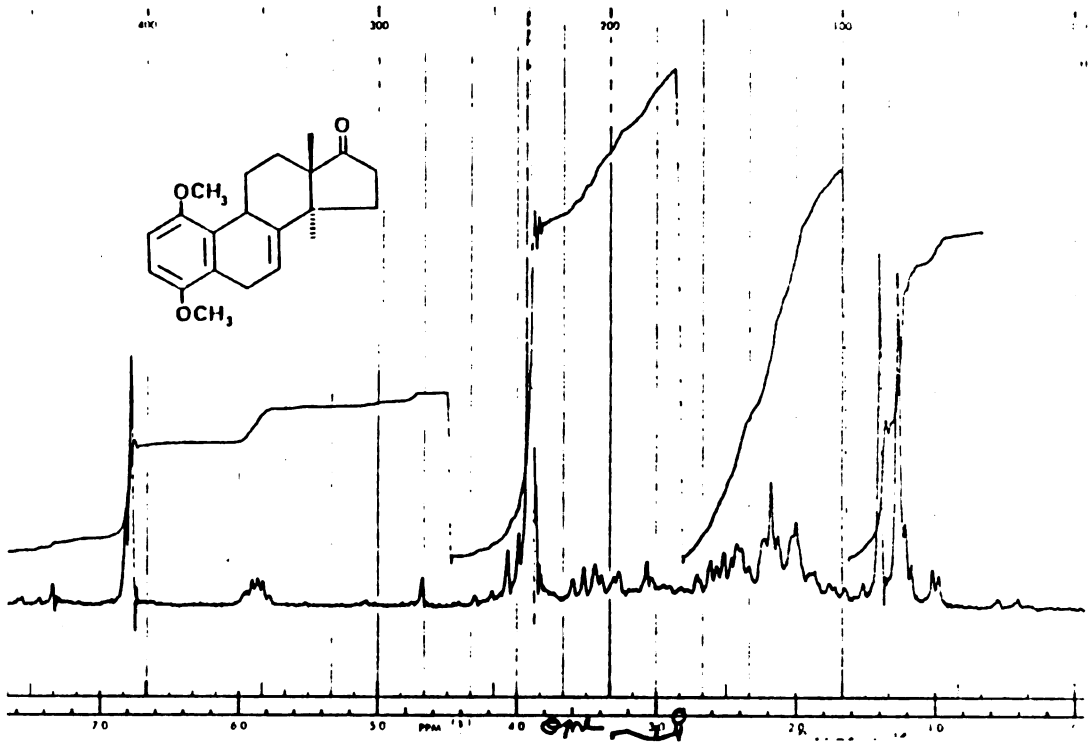


Figure 15. ^{1}H NMR spectrum of 13

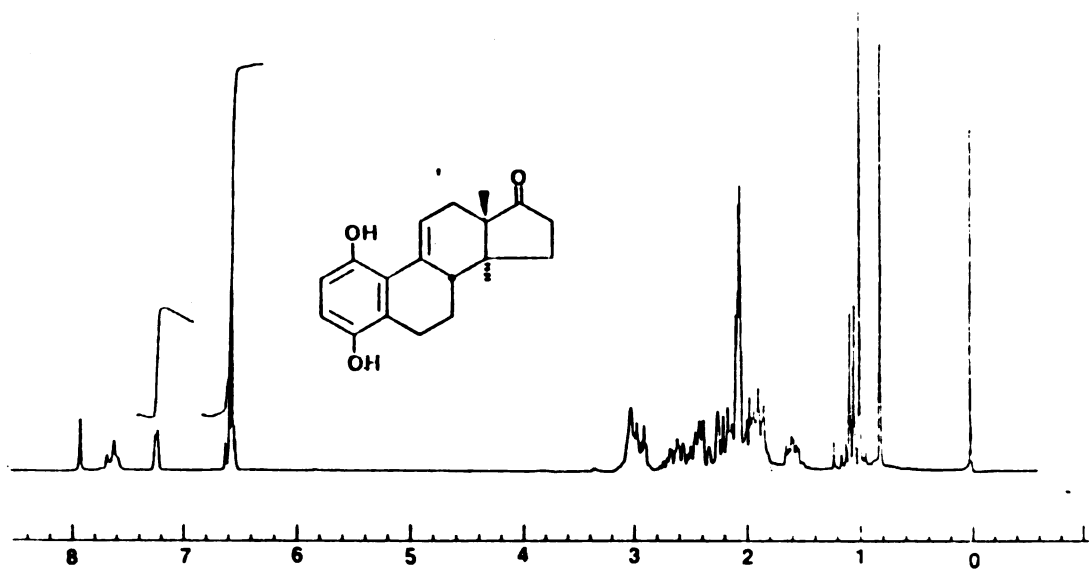


Figure 16. ^{1}H NMR spectrum of 17

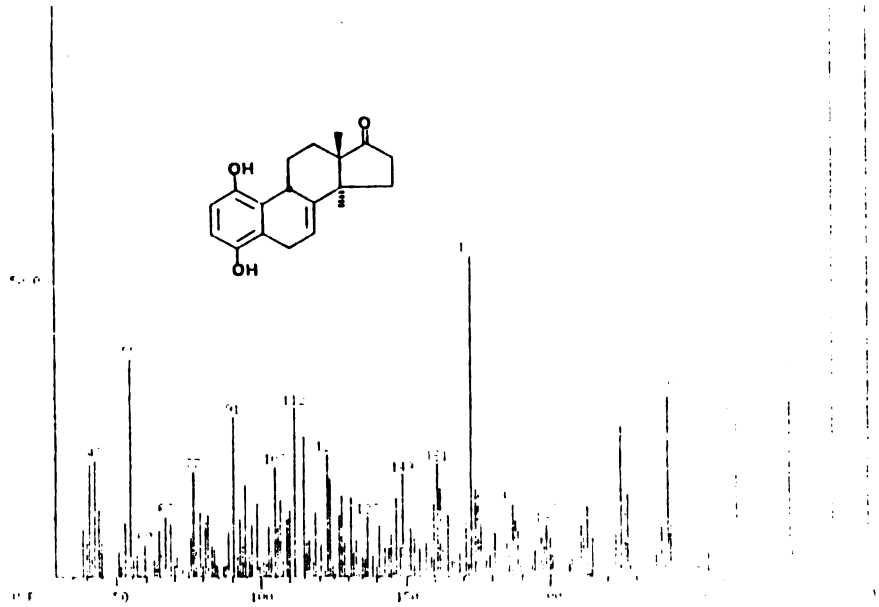


Figure 17. Mass spectrum of 11

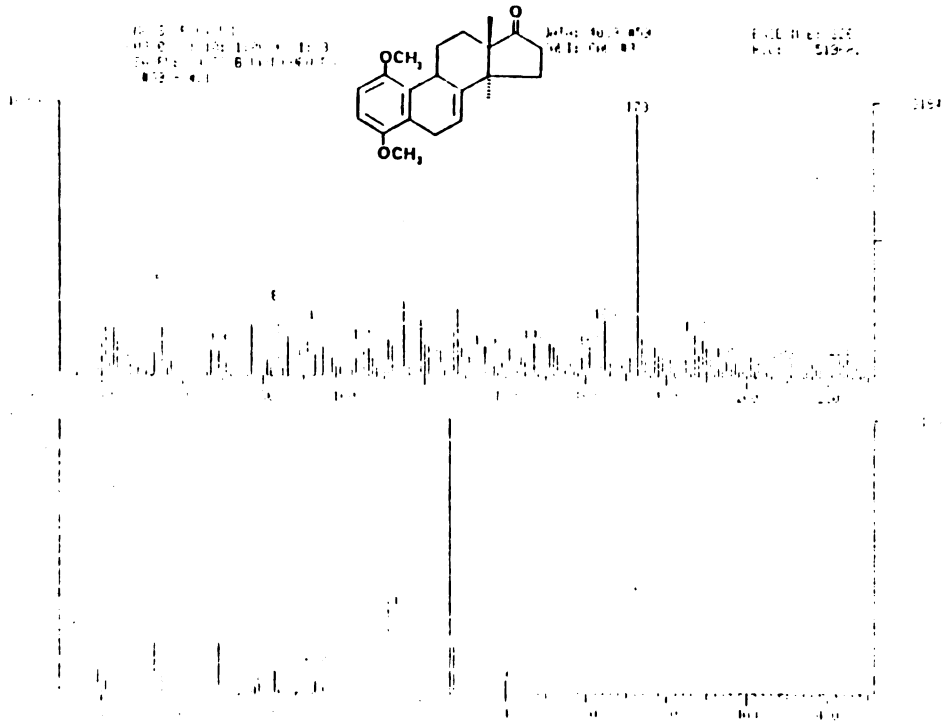


Figure 18. Mass spectrum of 13

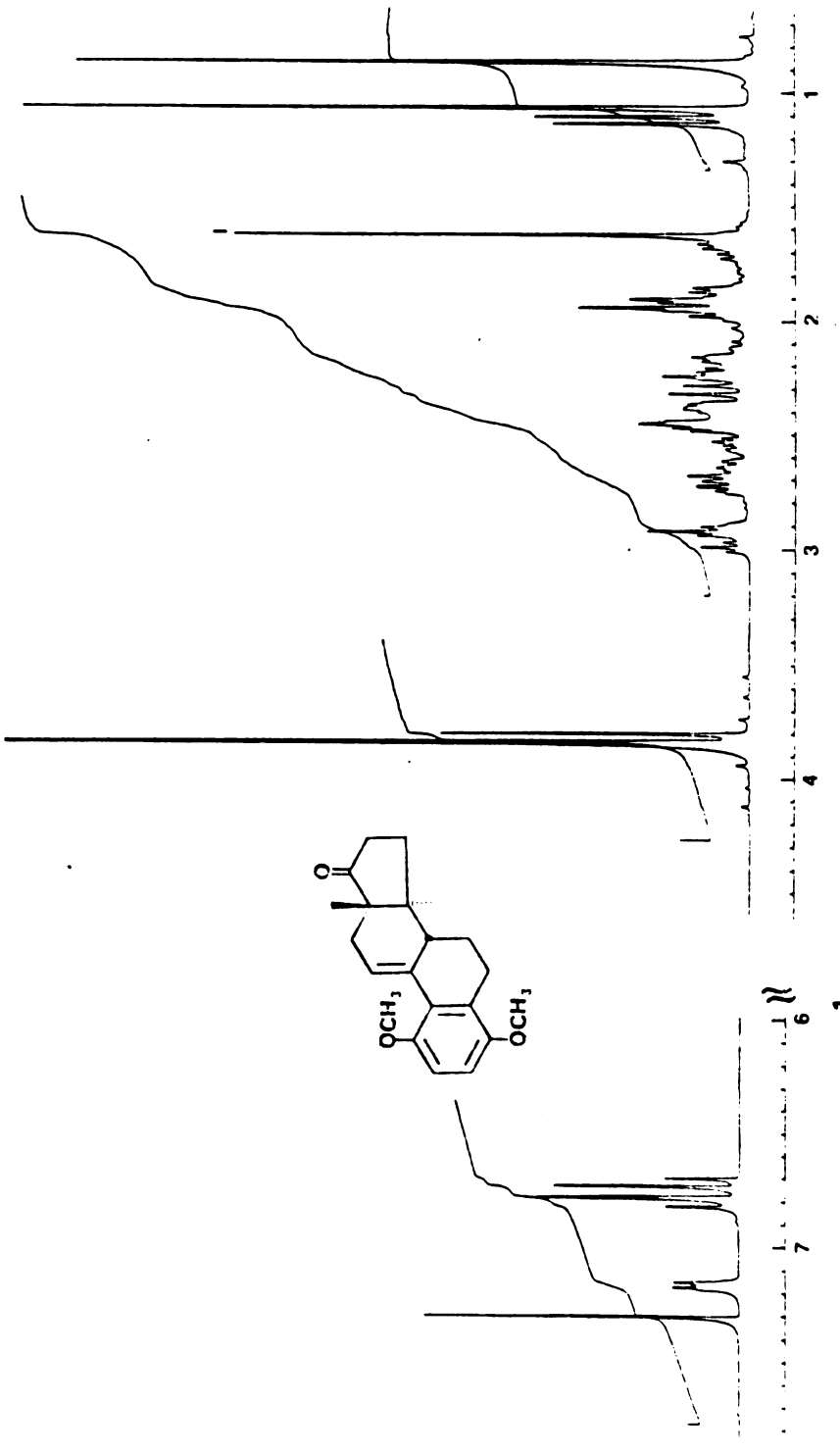


Figure 19. ^{1}H NMR spectrum of 16

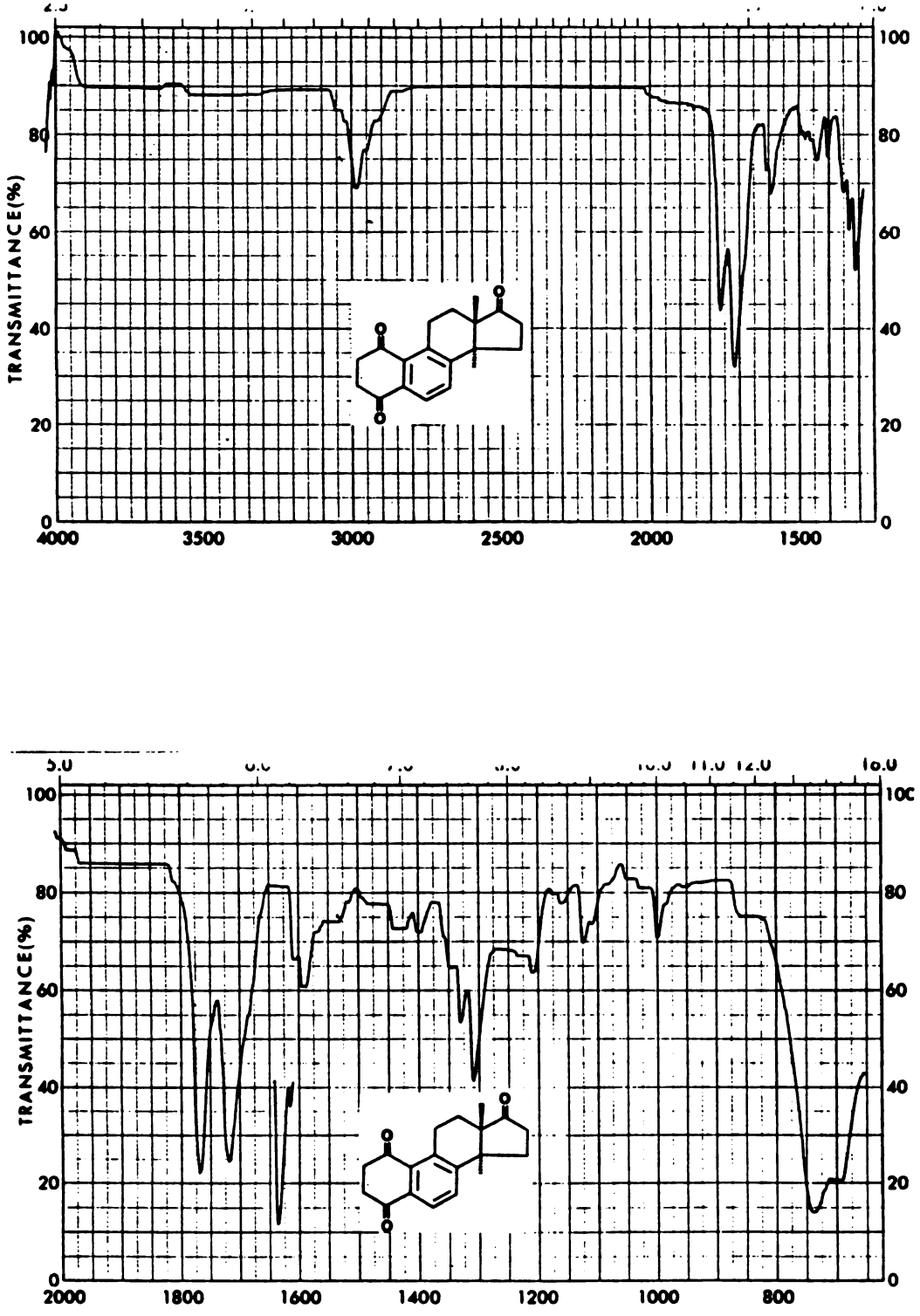


Figure 20. Infrared spectrum of 18

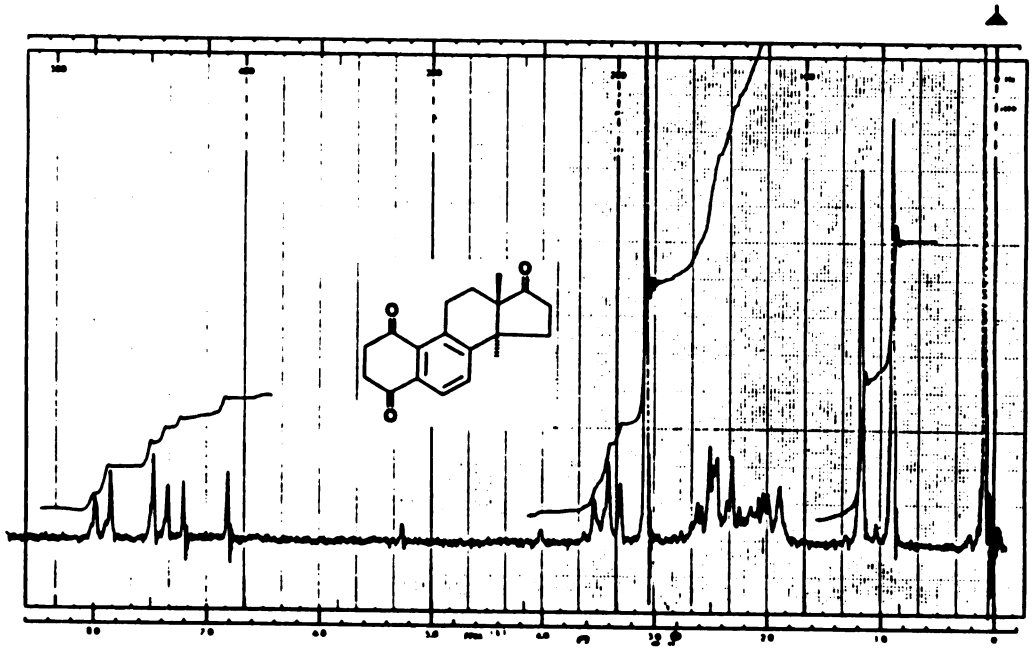


Figure 21. ^{1}H NMR spectrum of 18

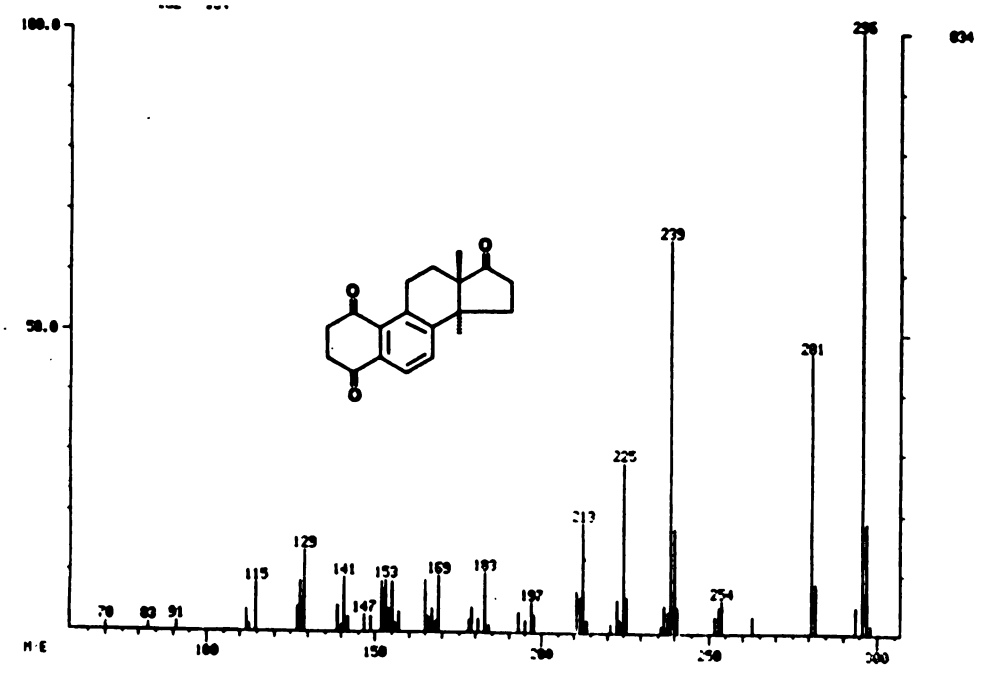


Figure 22. Mass spectrum of 18

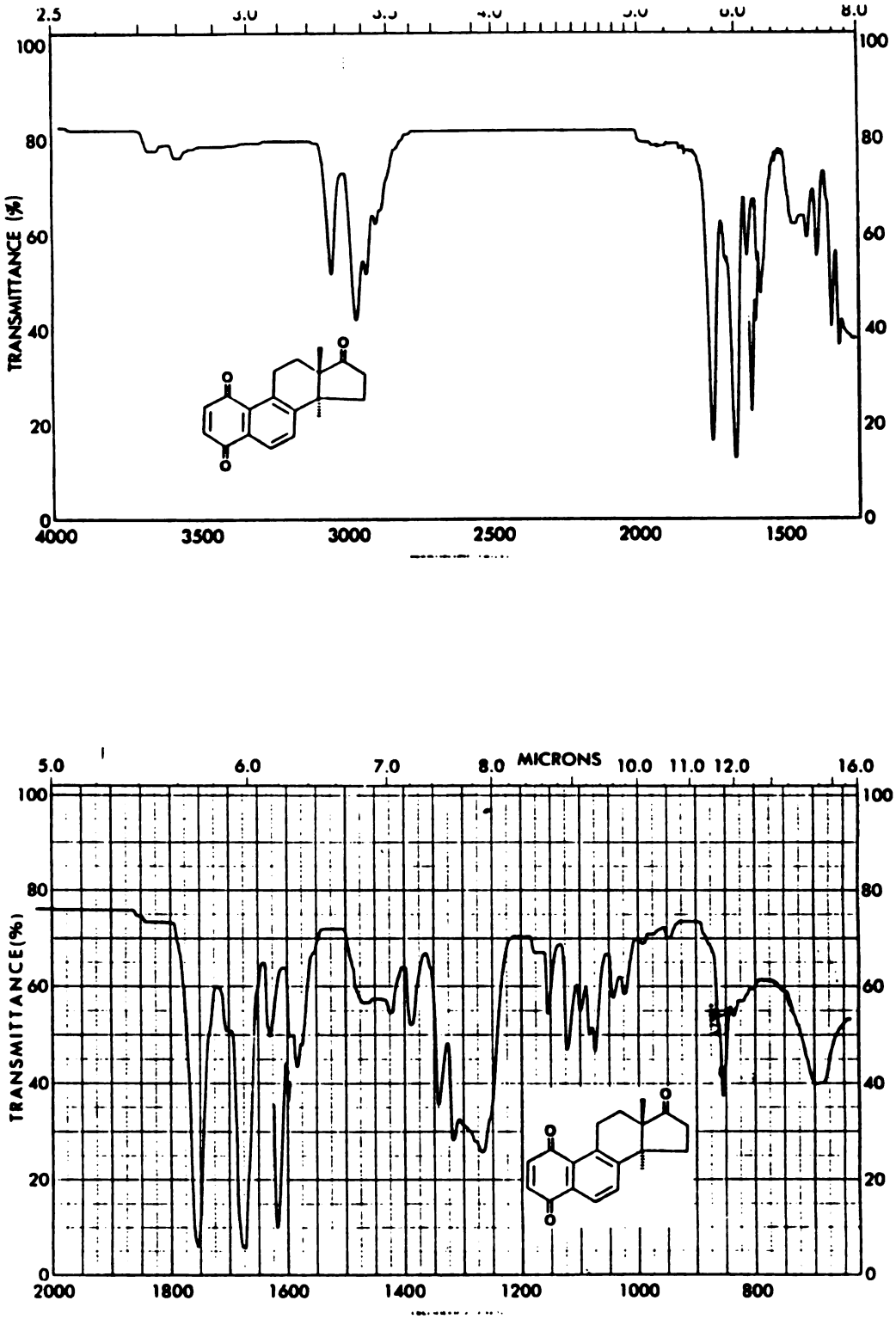


Figure 23. Infrared spectrum of 19

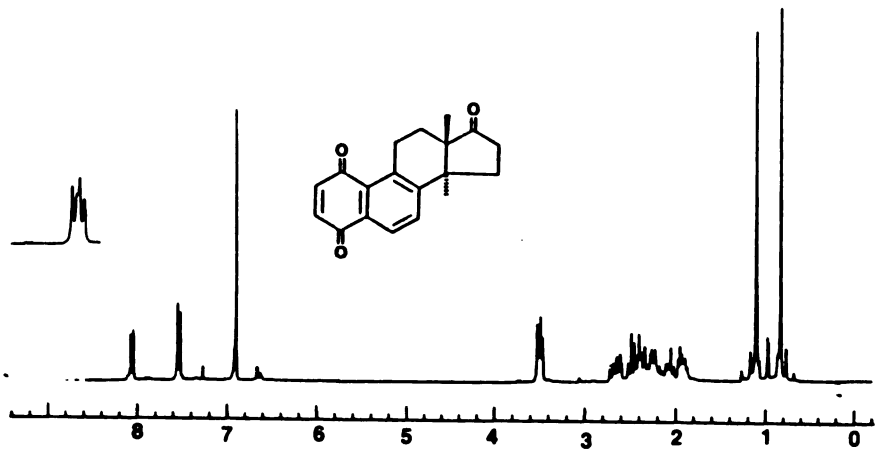


Figure 24. ^{1}H NMR spectrum of 19

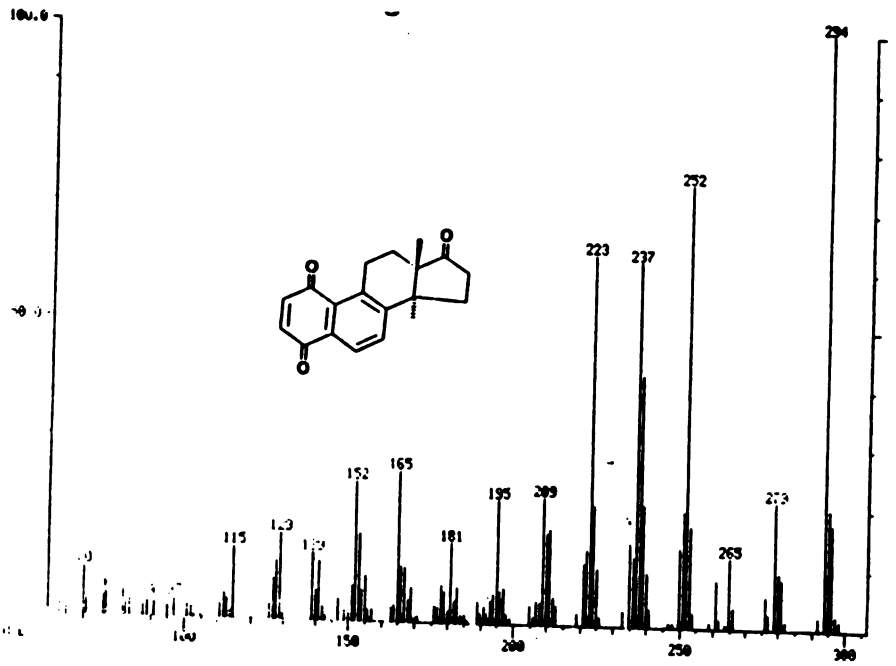


Figure 25. Mass spectrum of 19

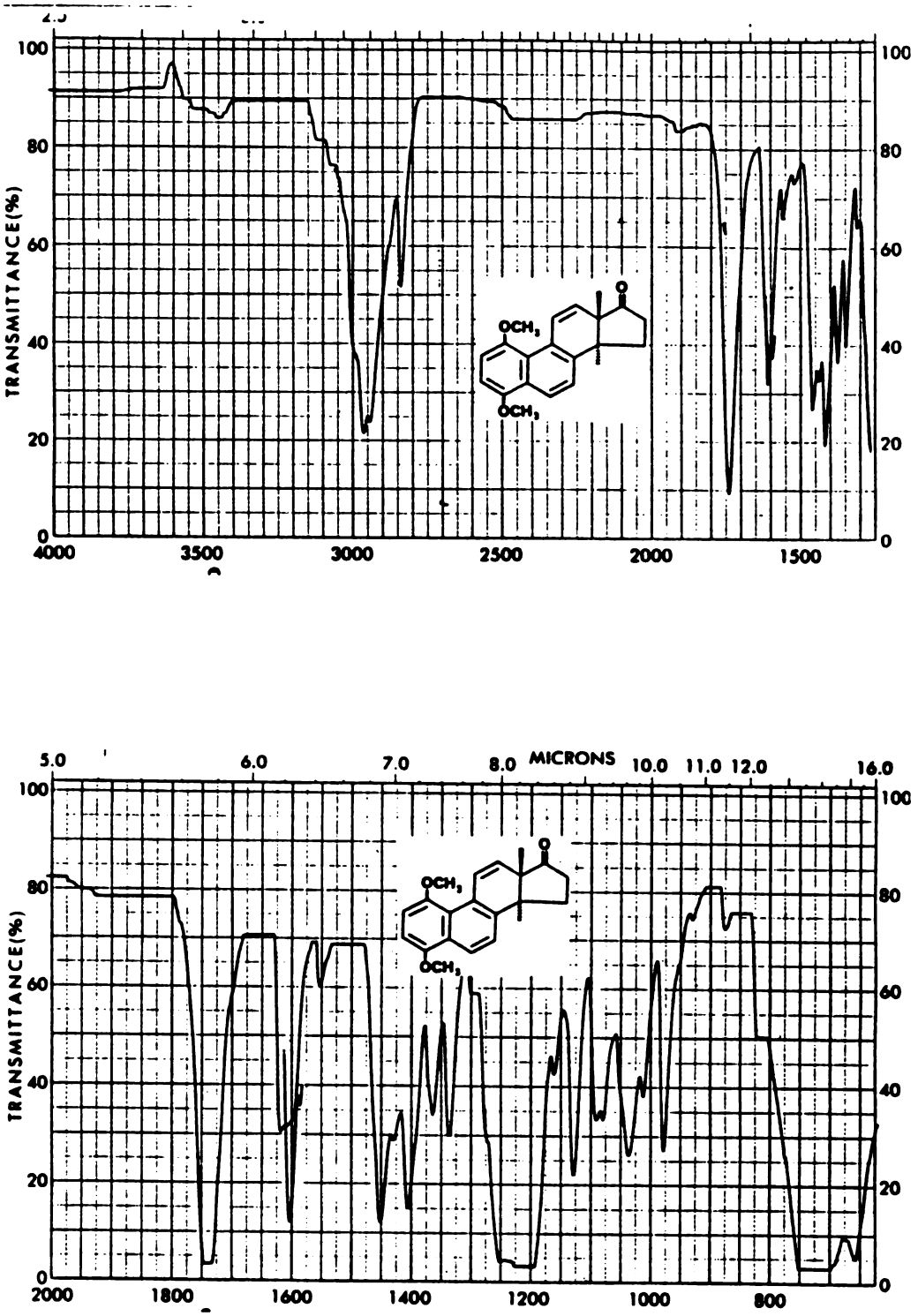


Figure 26. Infrared spectrum of 21

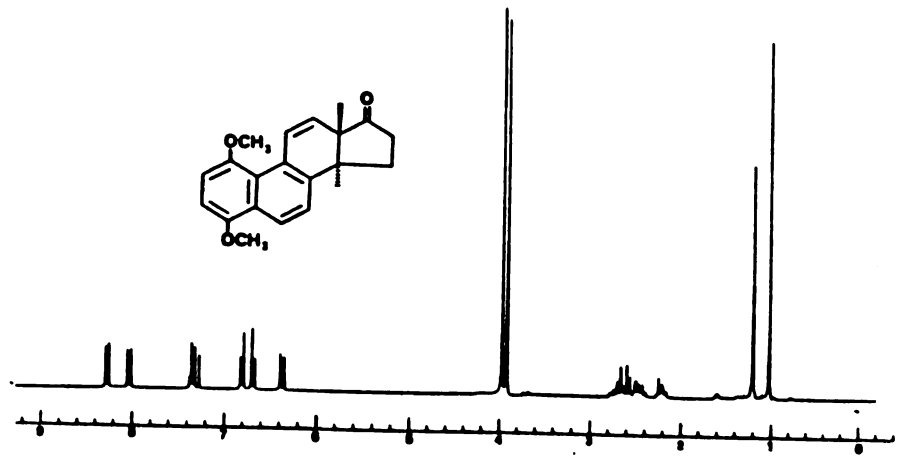


Figure 27. ^{1}H NMR spectrum of 21

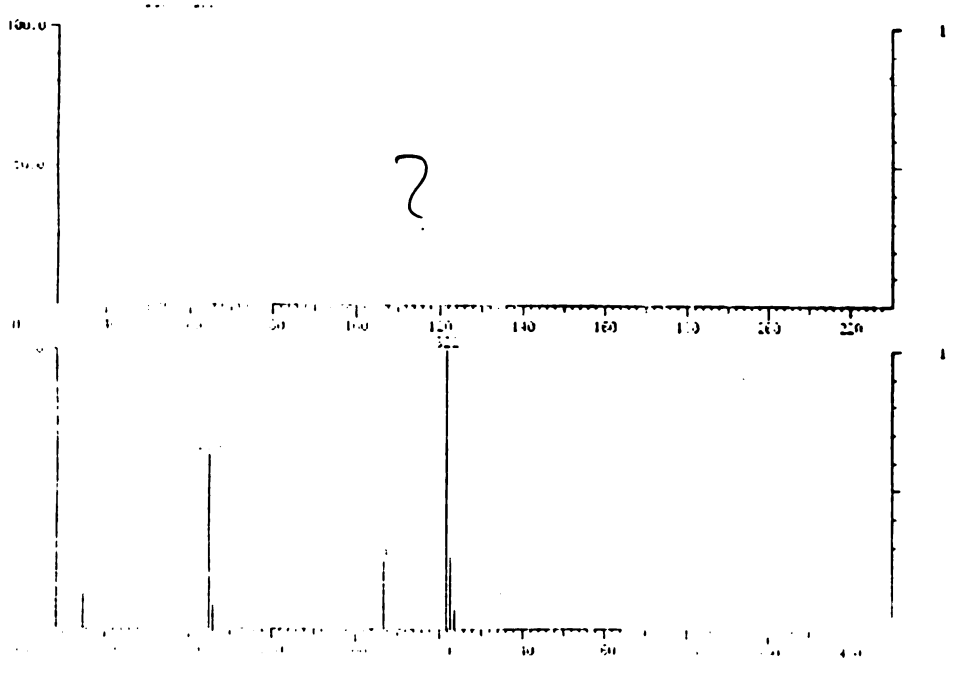


Figure 28. Mass spectrum of 21

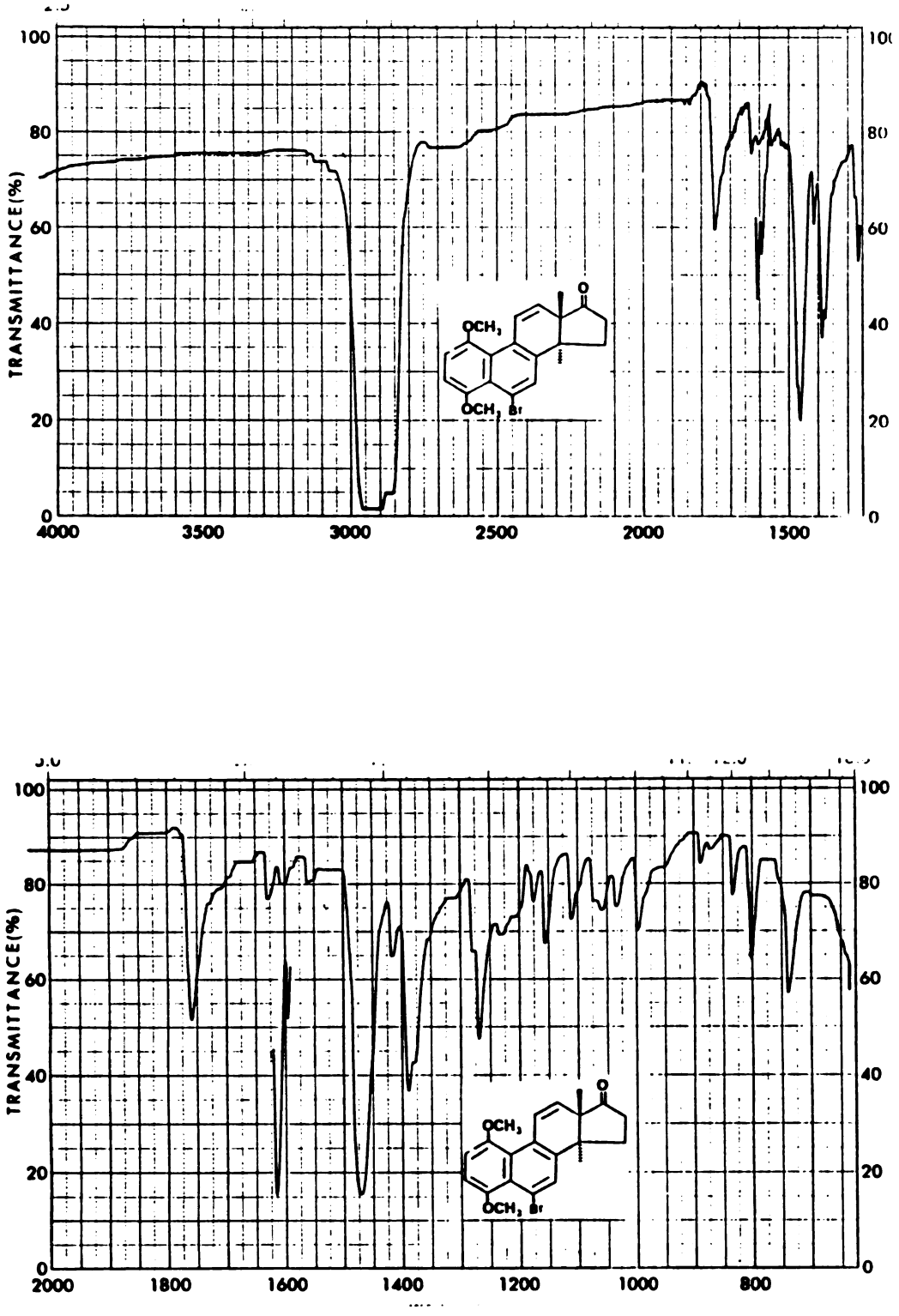


Figure 29. Infrared spectrum of 22

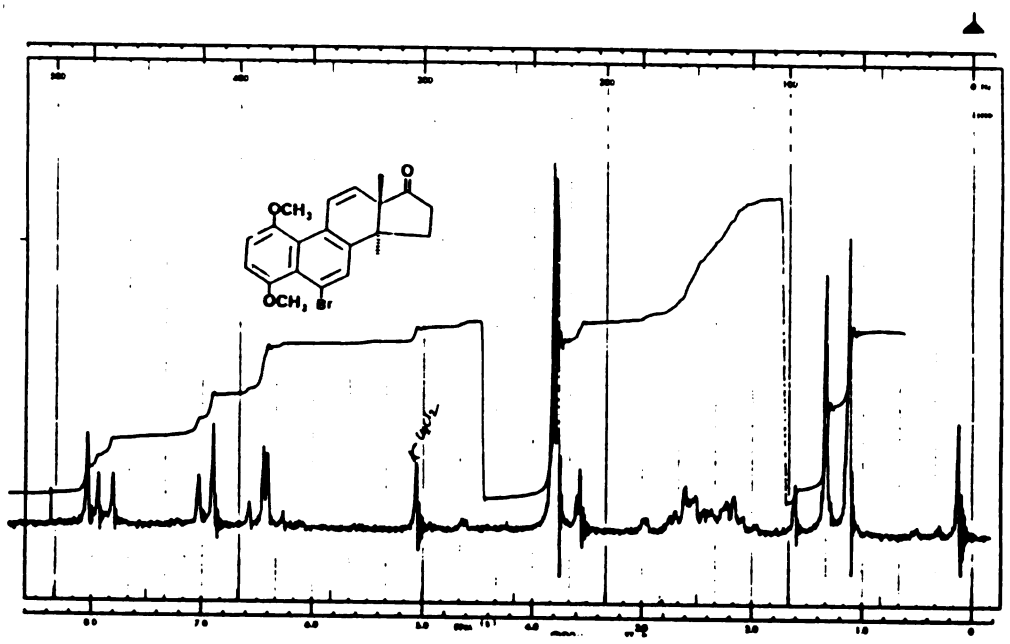


Figure 30. ^{1}H NMR spectrum of 22

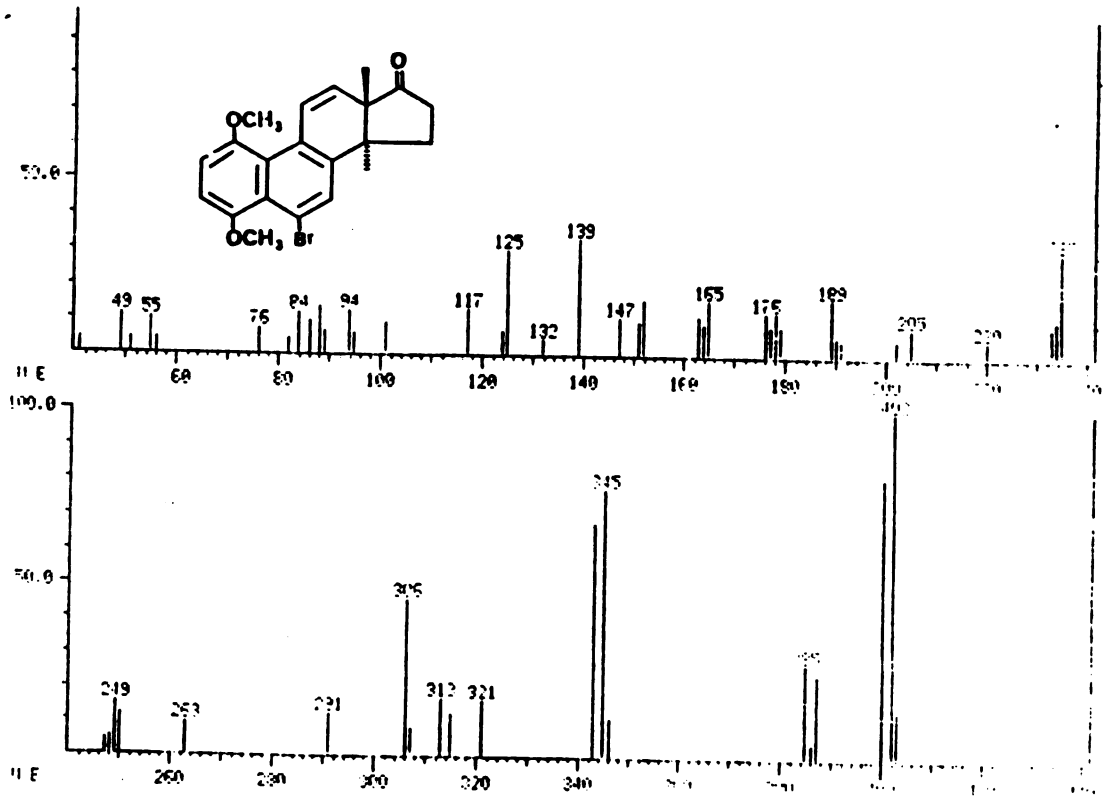


Figure 31. Mass spectrum of 22

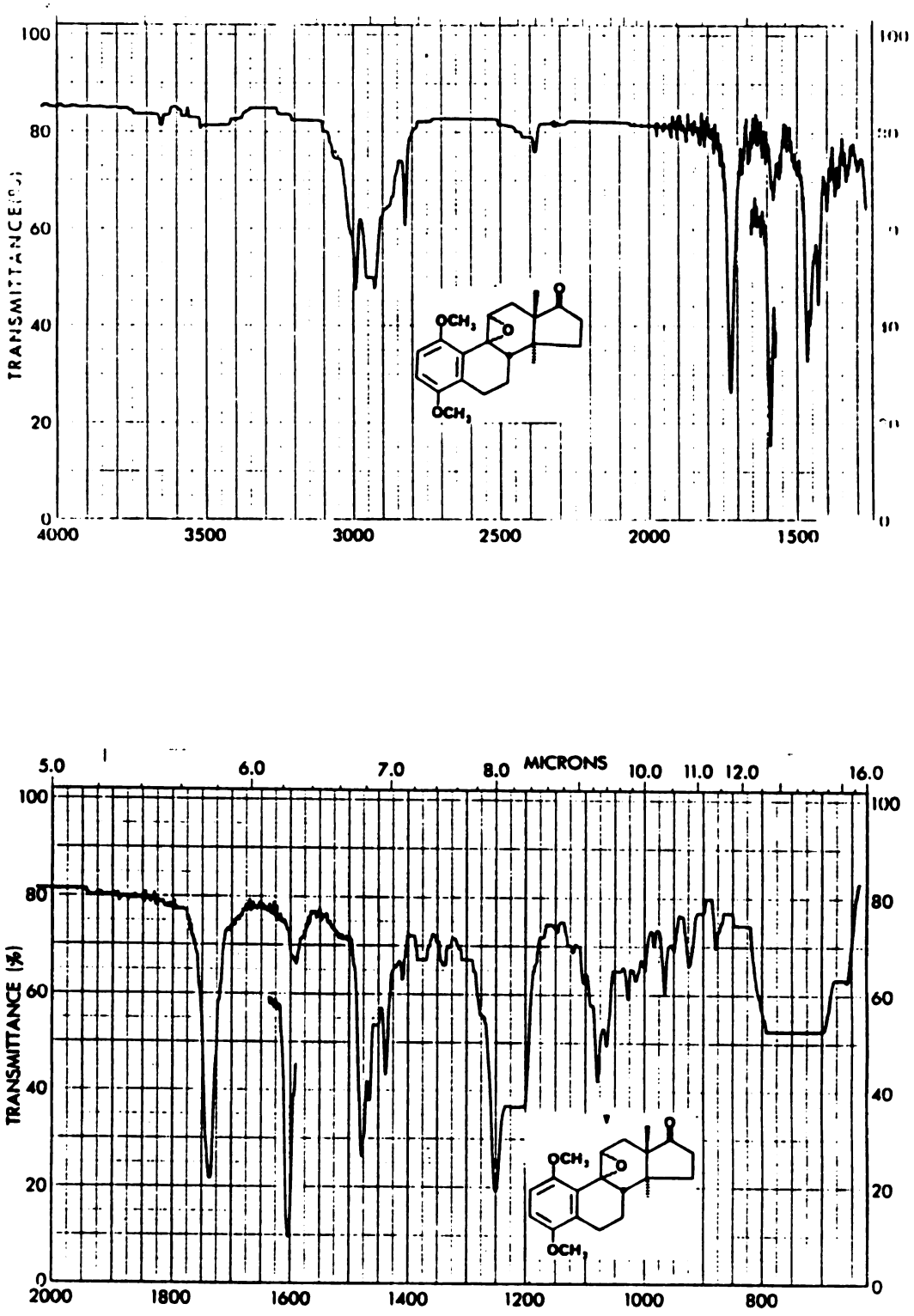


Figure 32. Infrared spectrum of 24 and 25

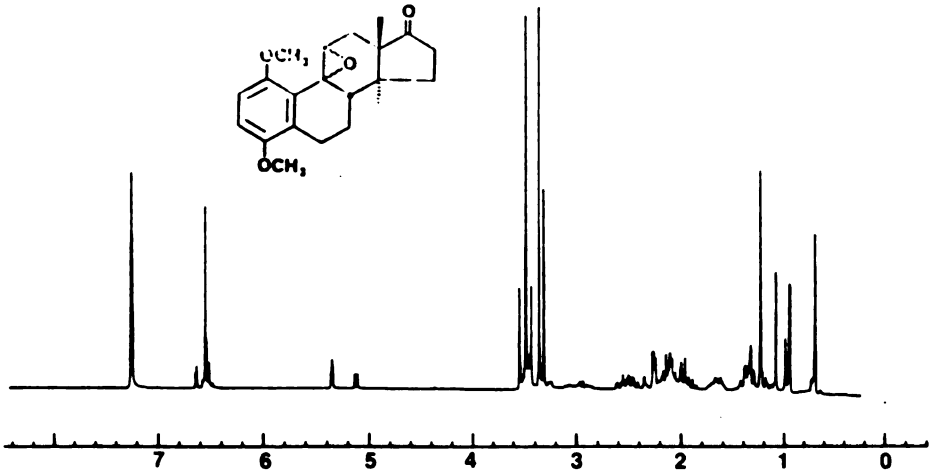


Figure 33. ^{1}H NMR spectrum of 24 and 25

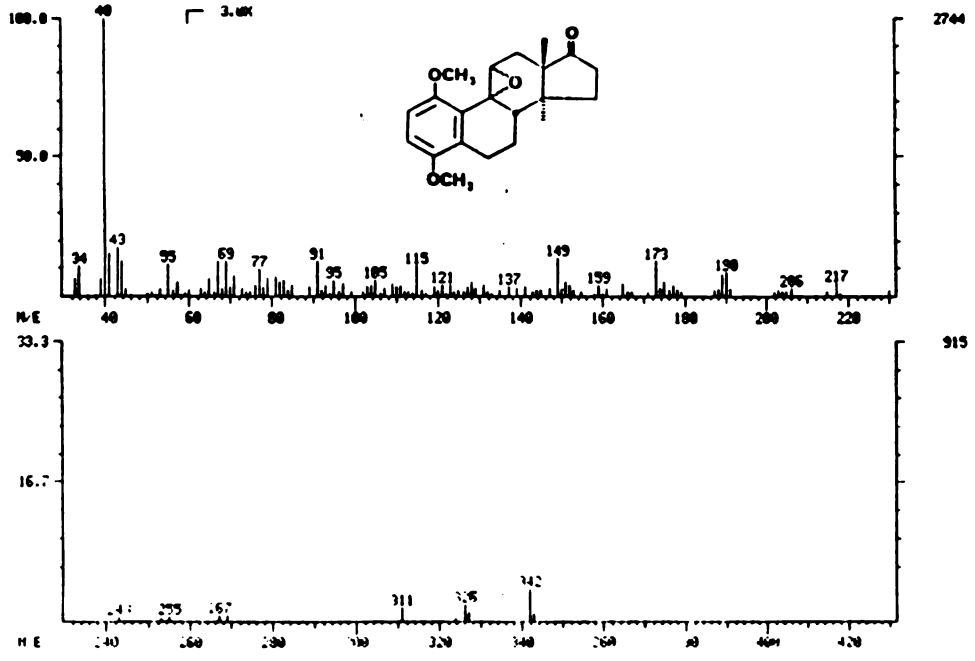


Figure 34. Mass spectrum of 24 and 25

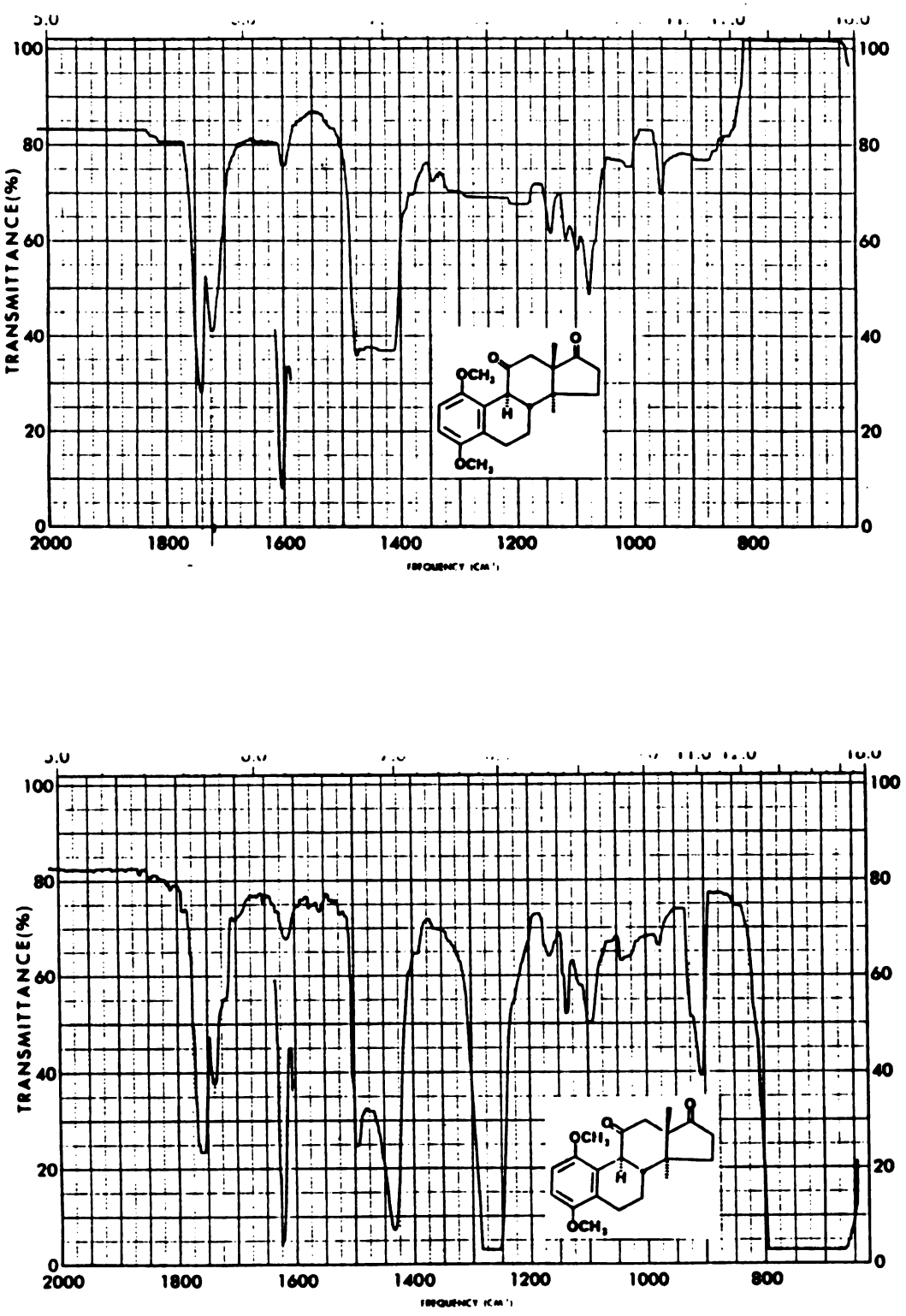


Figure 35. Infrared spectrum of 26

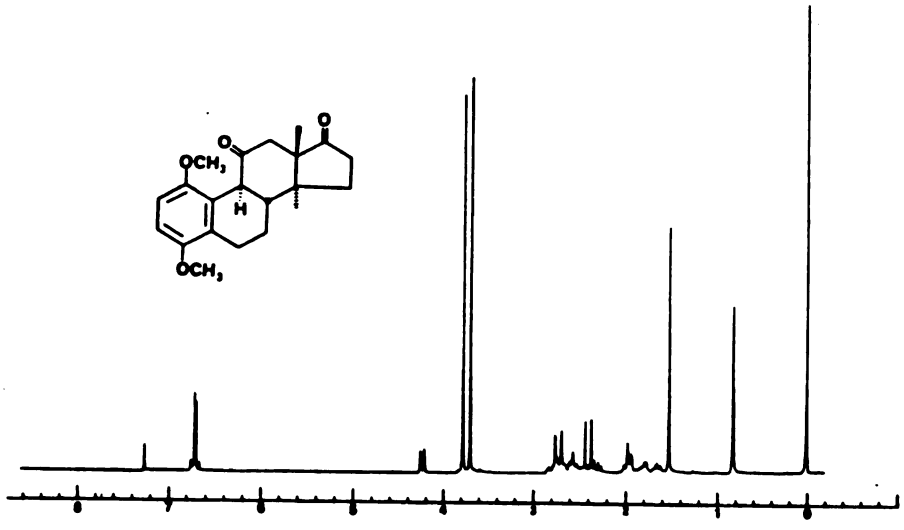


Figure 36. ^{1}H NMR spectrum of 26

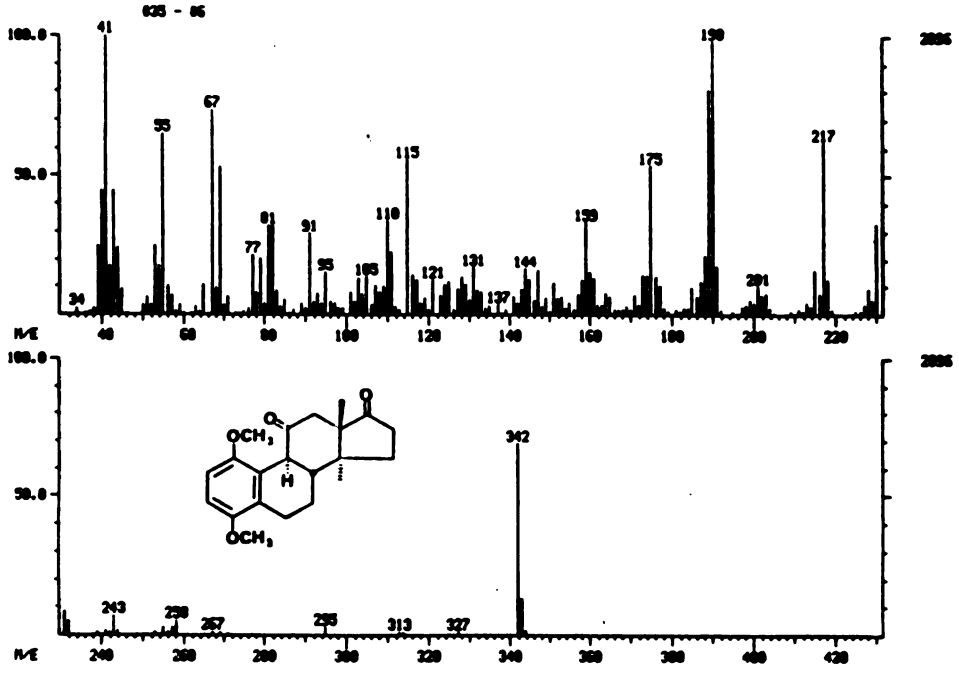


Figure 37. Mass spectrum of 26

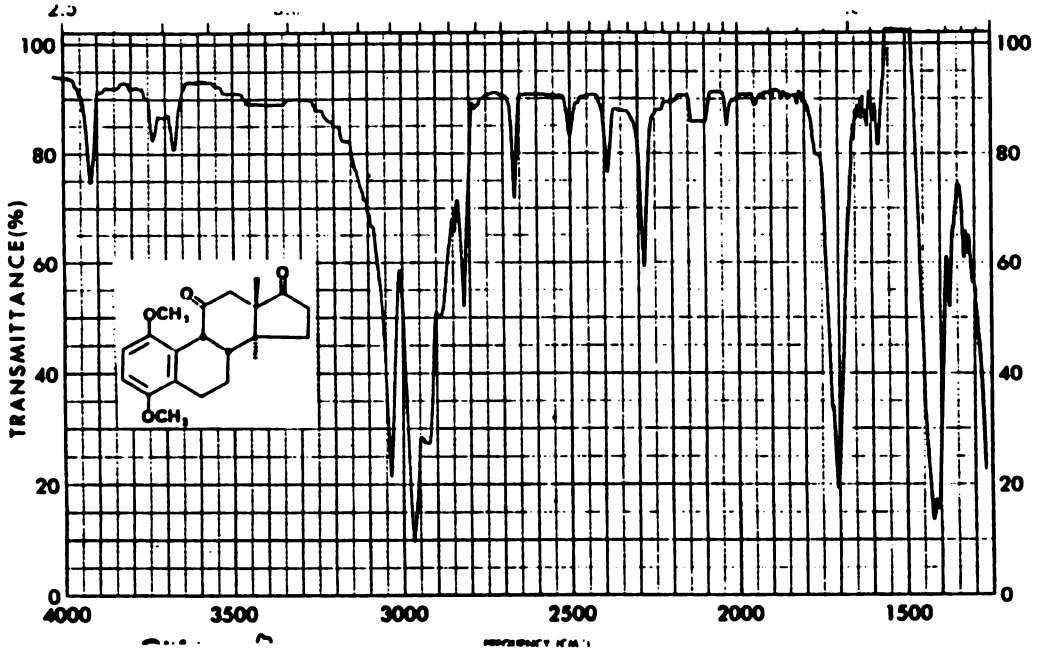


Figure 38. Infrared spectrum of 27

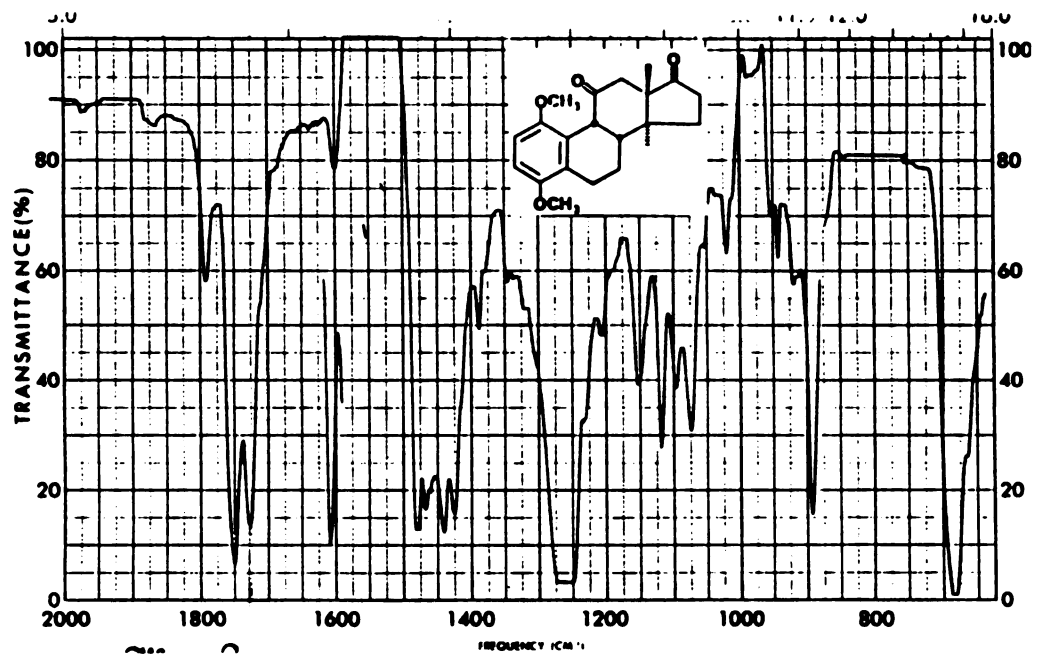


Figure 38. Infrared spectrum of 27

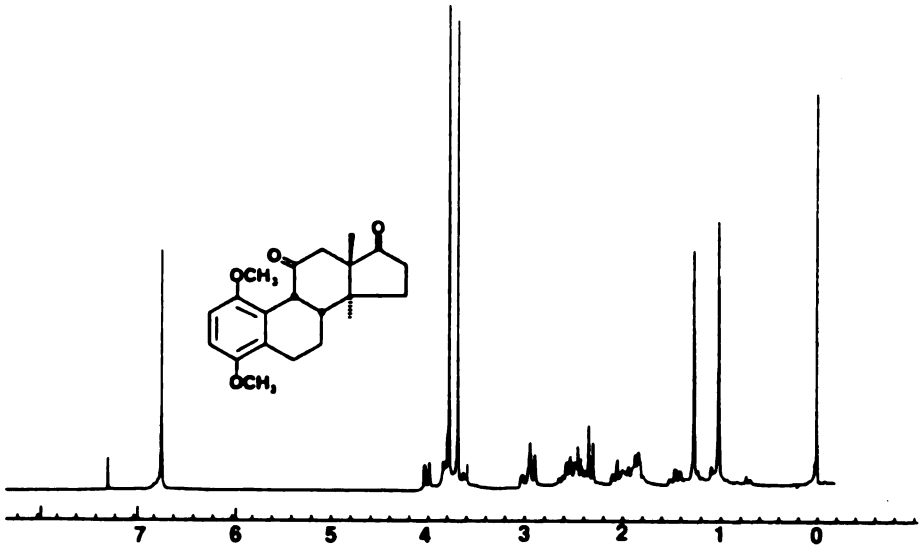


Figure 39. ^{1}H NMR spectrum of 27

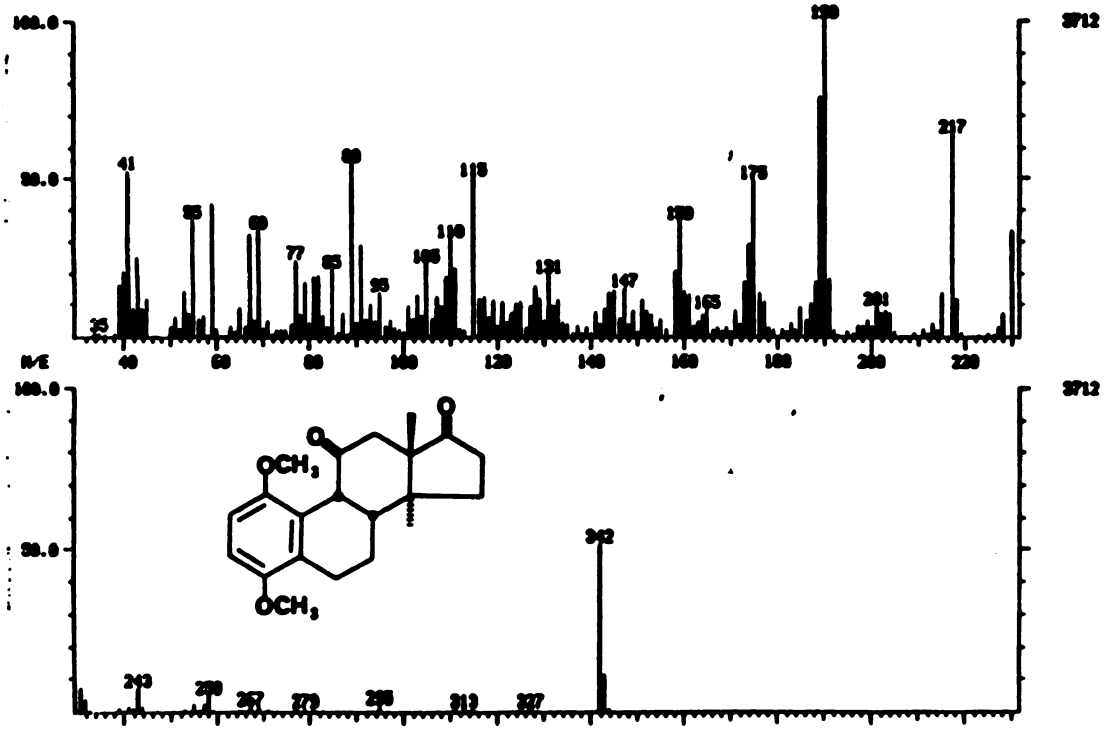


Figure 40. Mass spectrum of 27

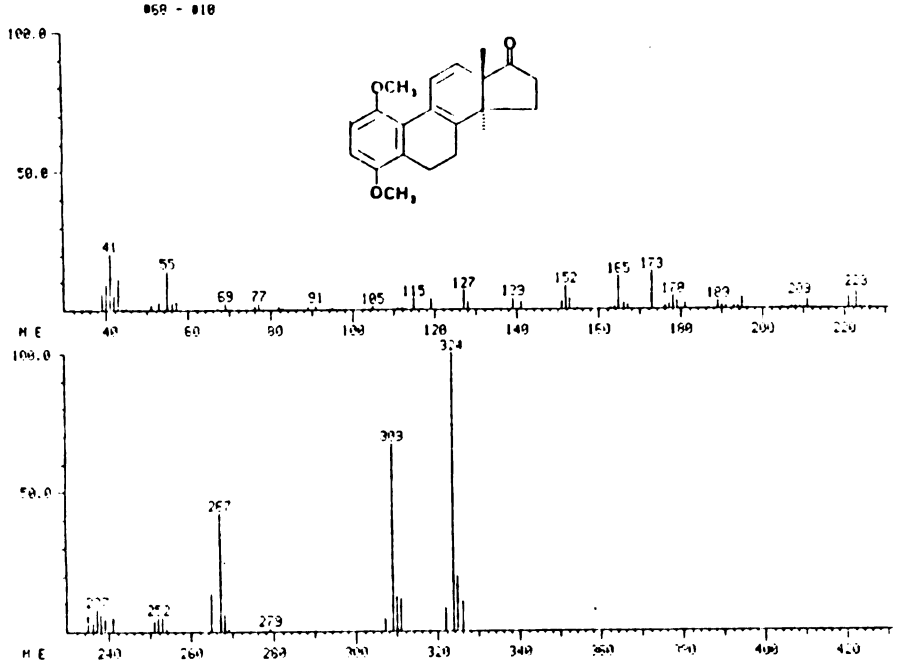


Figure 41. Mass spectrum of 29

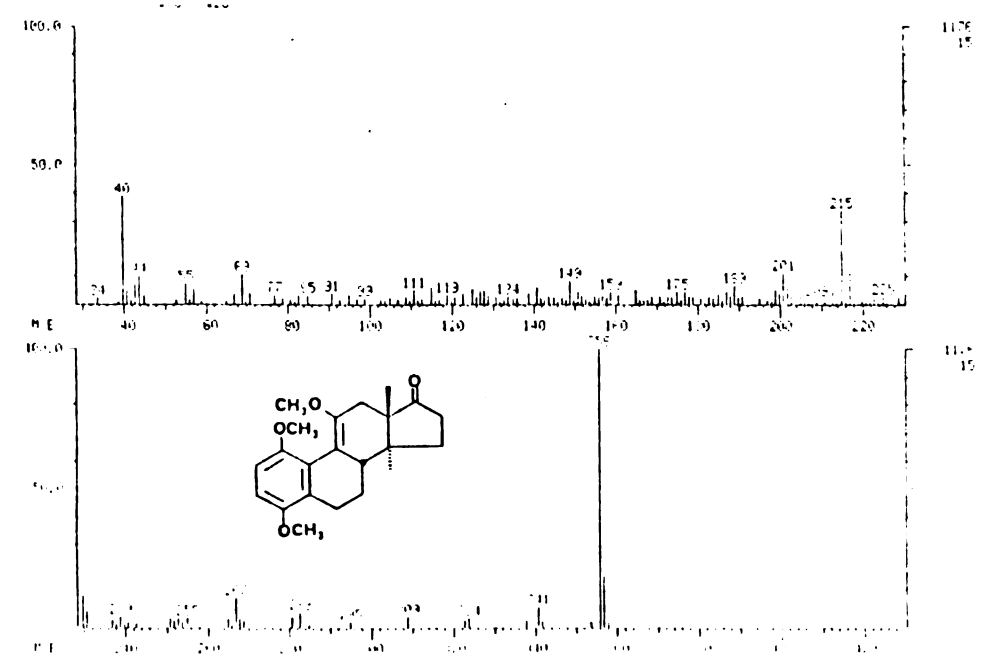


Figure 42. Mass spectrum of 31

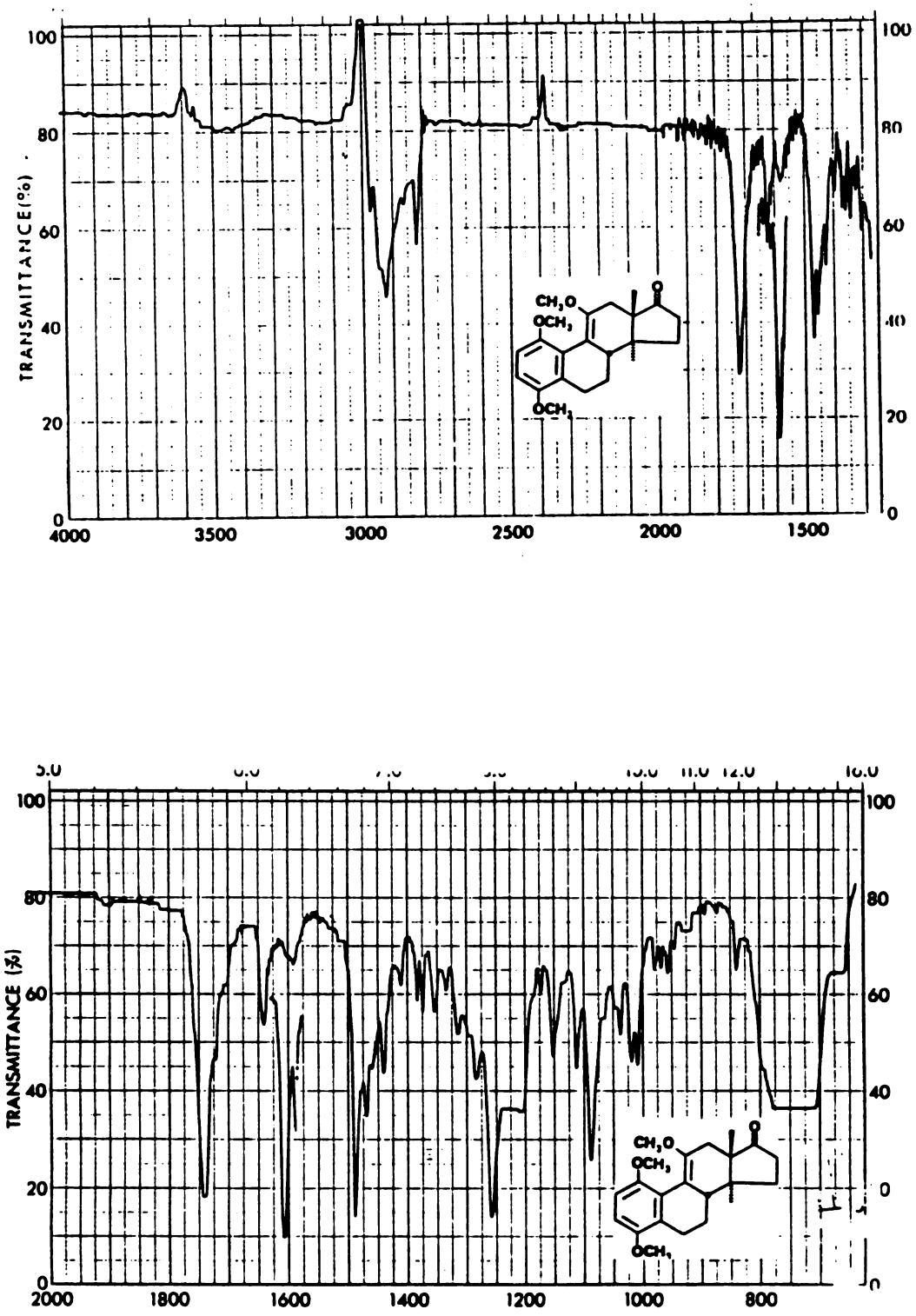


Figure 43. Infrared spectrum of 31

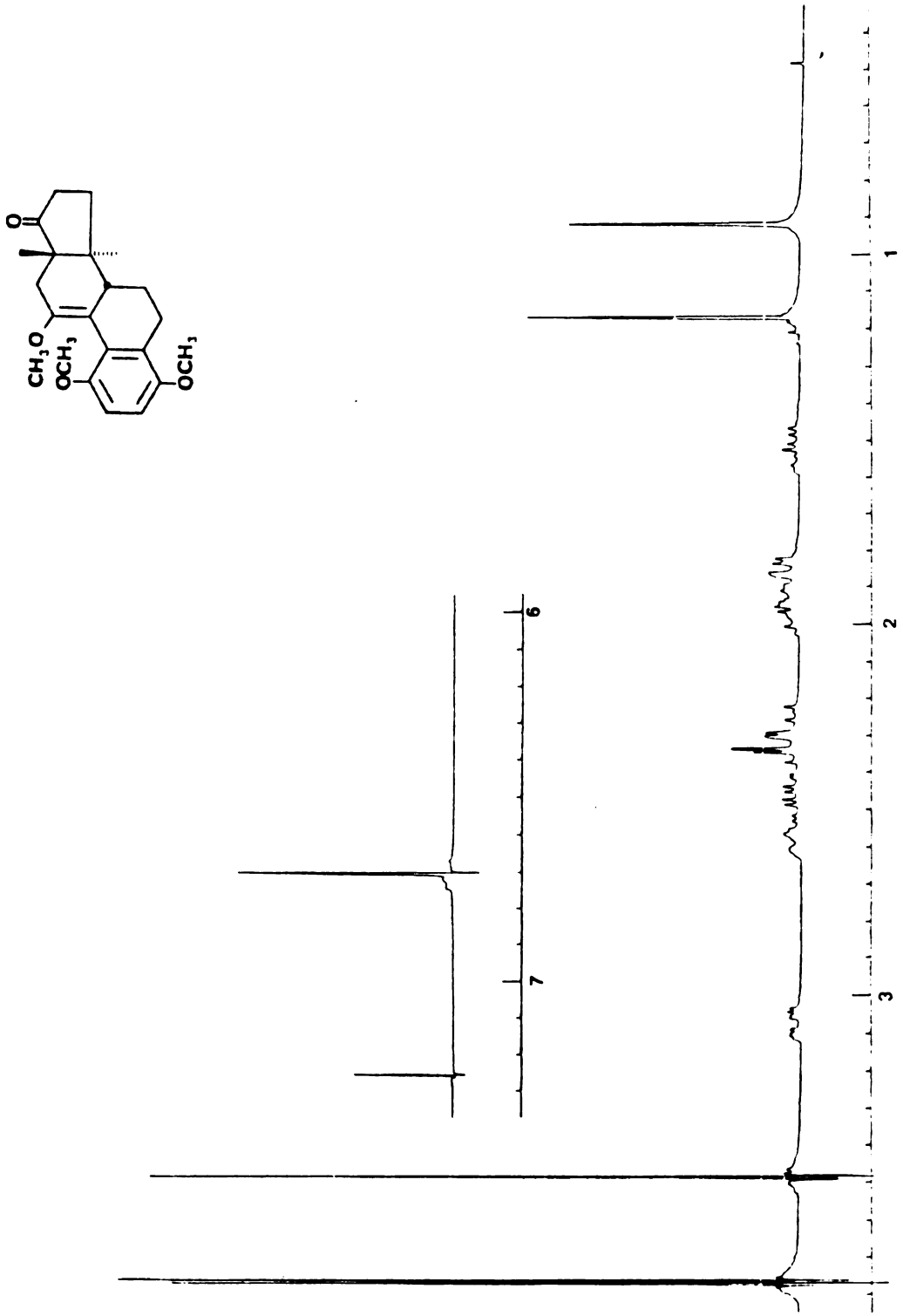


Figure 44. ^{1}H NMR spectrum of 31

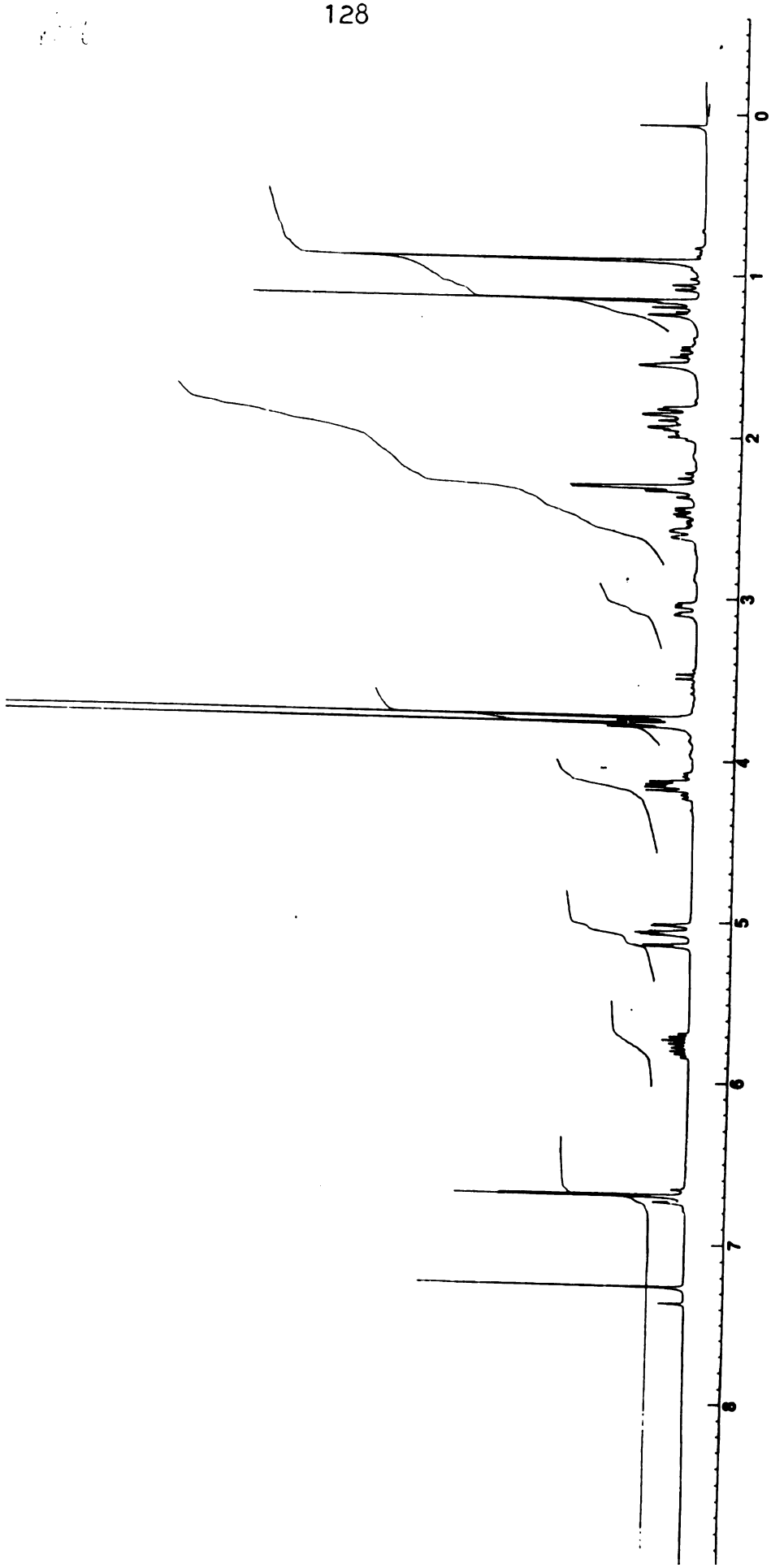
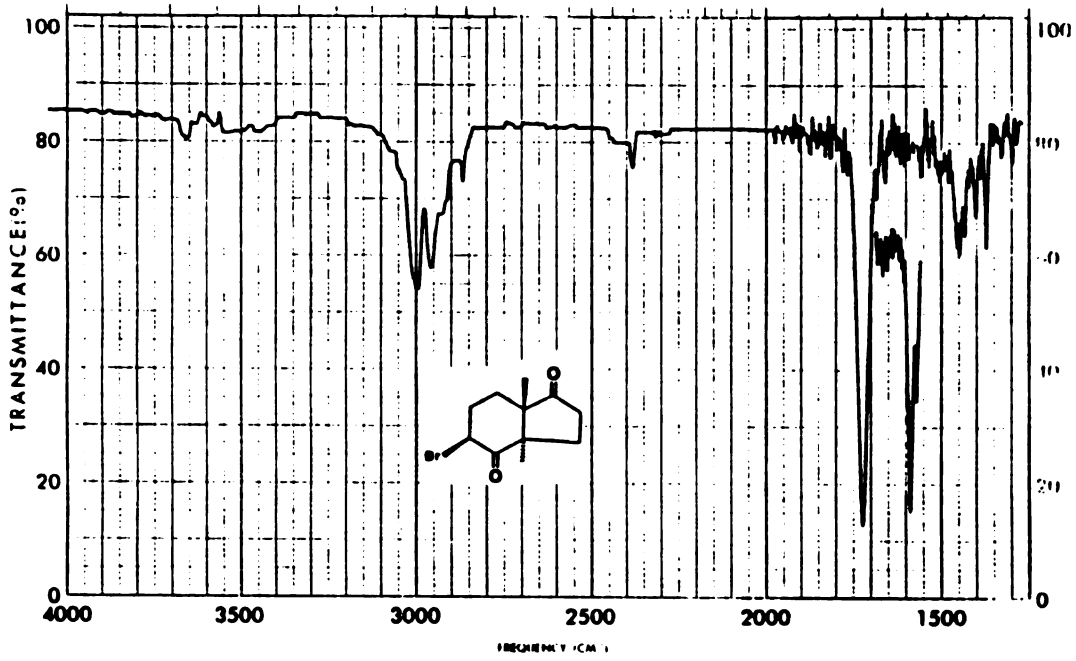


Figure 45. ^{1}H NMR spectrum of 33



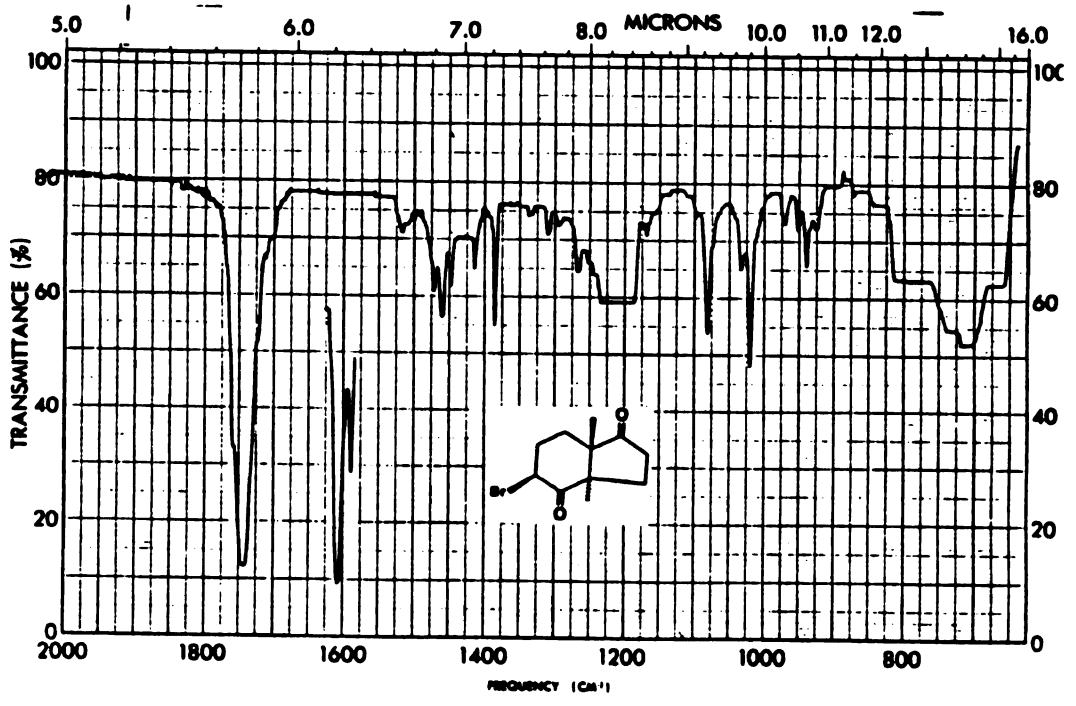


Figure 46. Infrared spectrum of 40

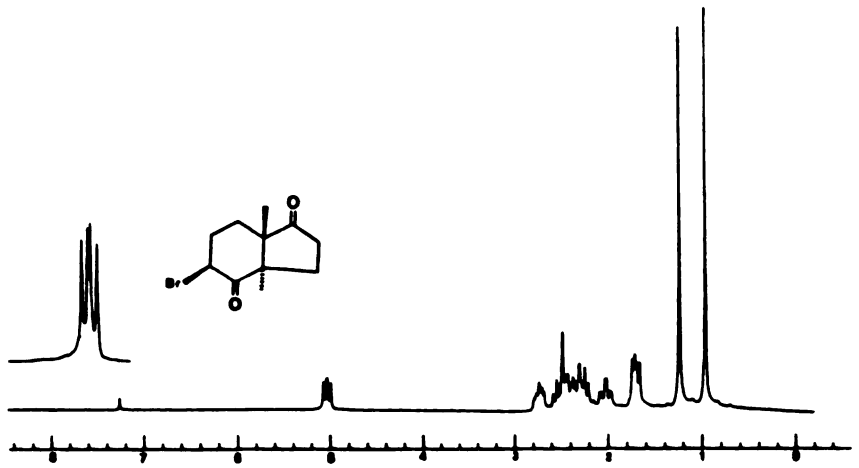


Figure 47. ^{1}H NMR spectrum of 40

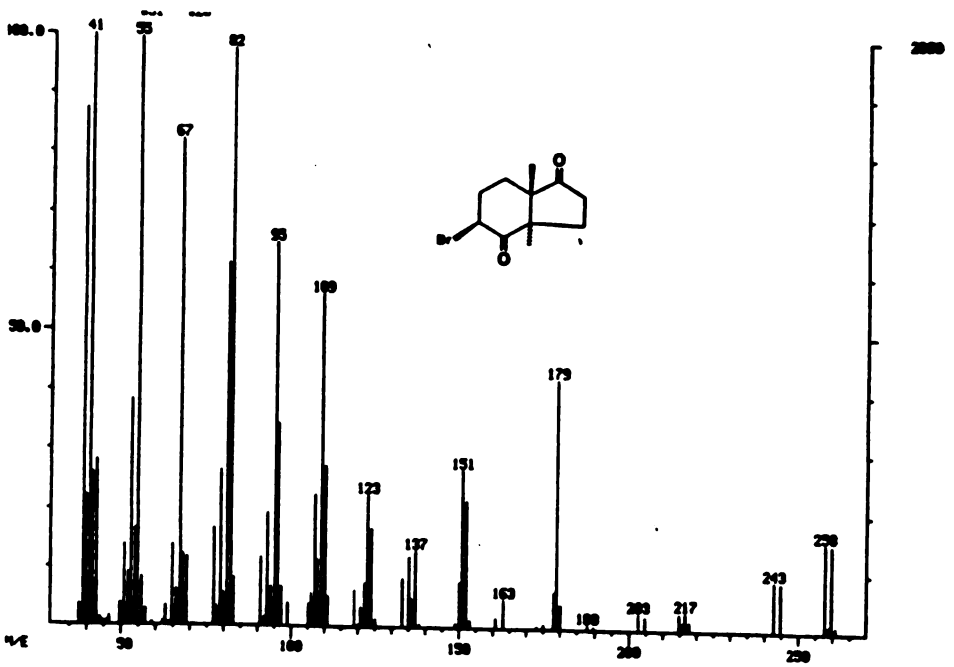


Figure 48. Mass spectrum of 40

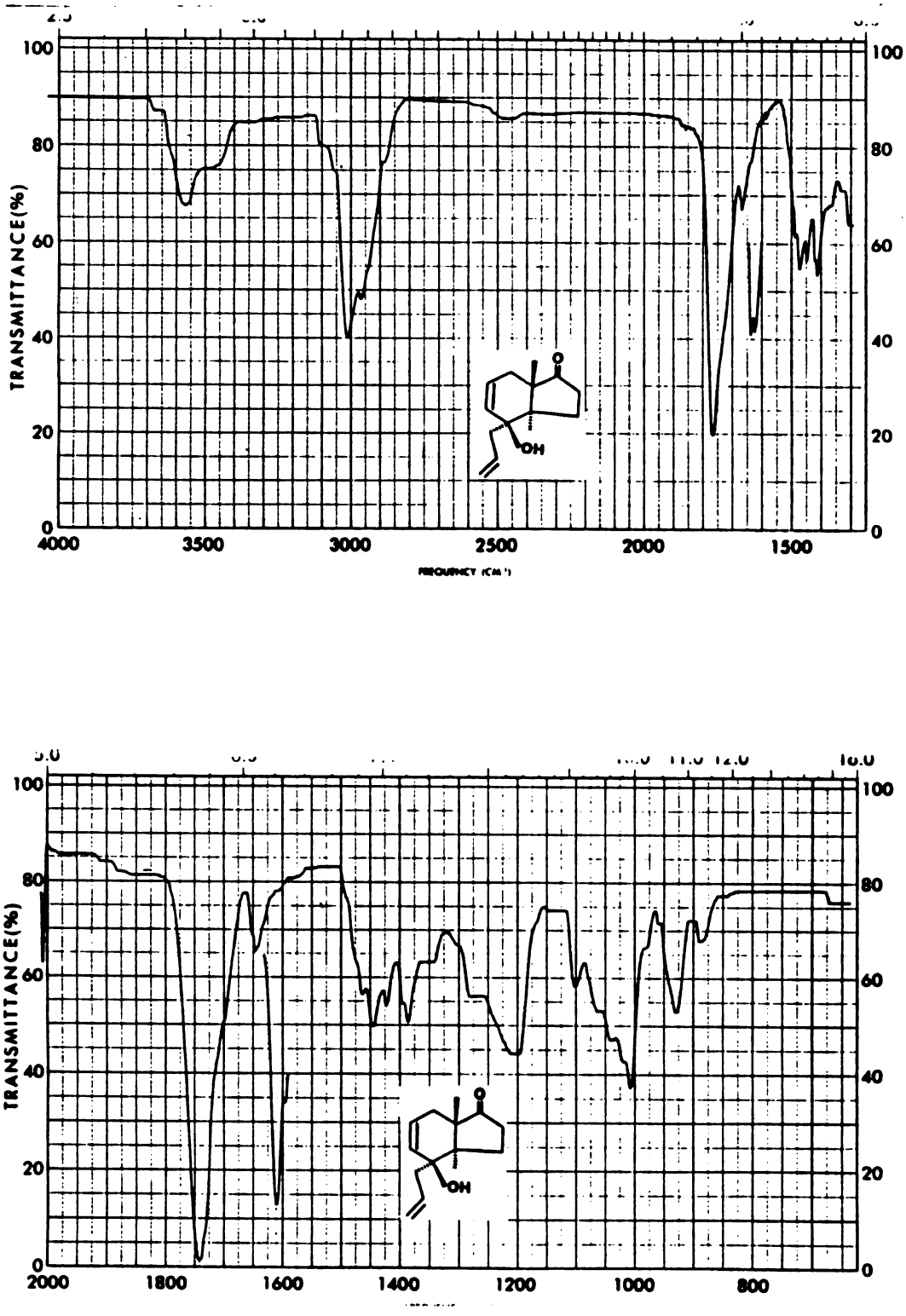


Figure 49. Infrared spectrum of 42

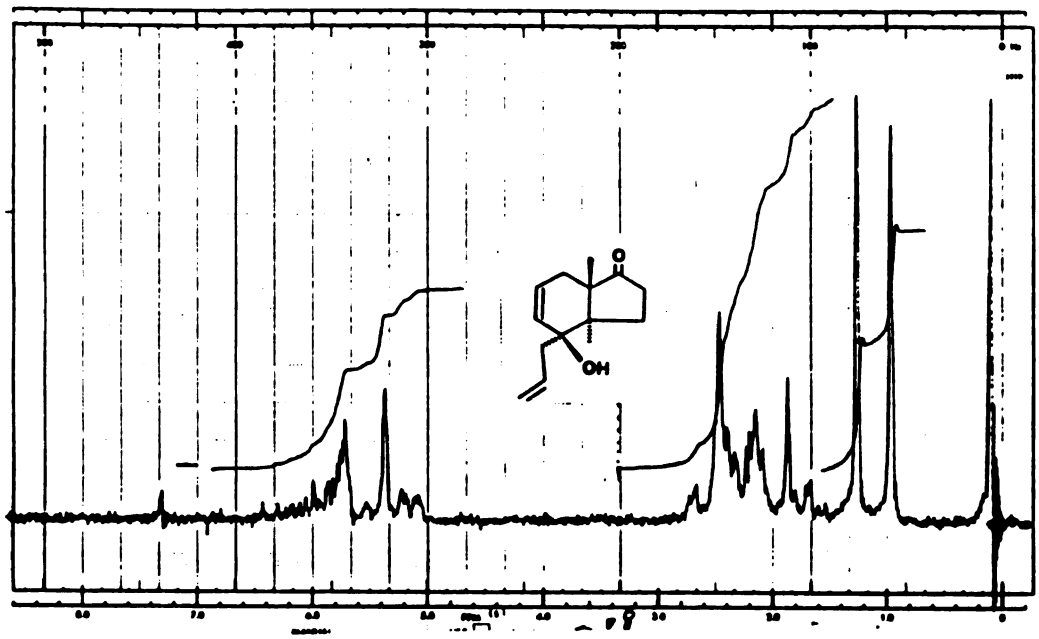


Figure 50. ^{1}H NMR spectrum of 42

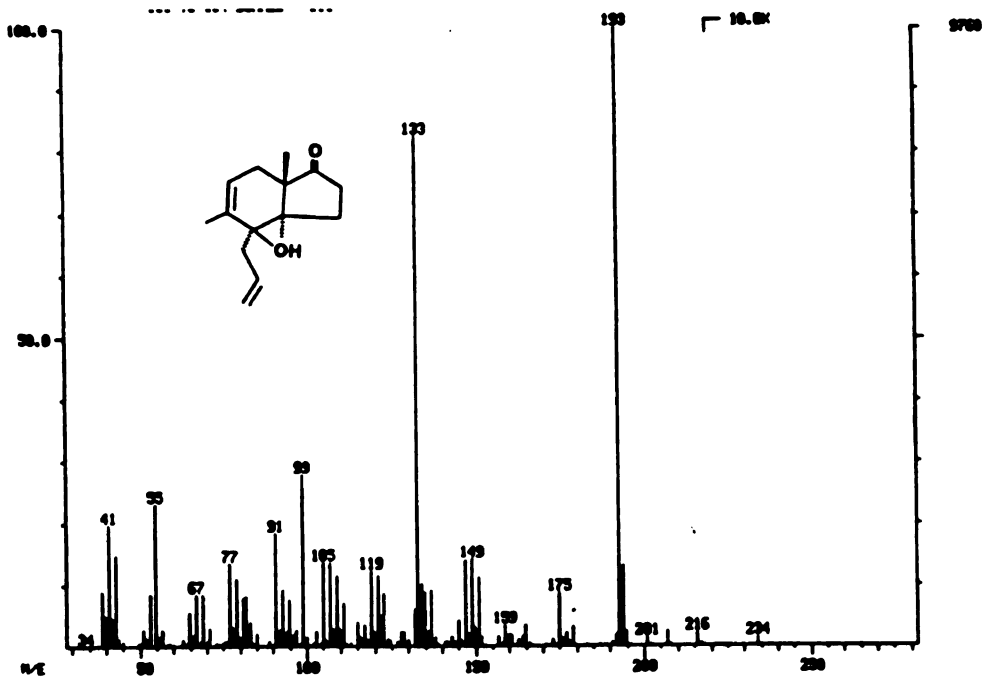


Figure 51. Mass spectrum of 56

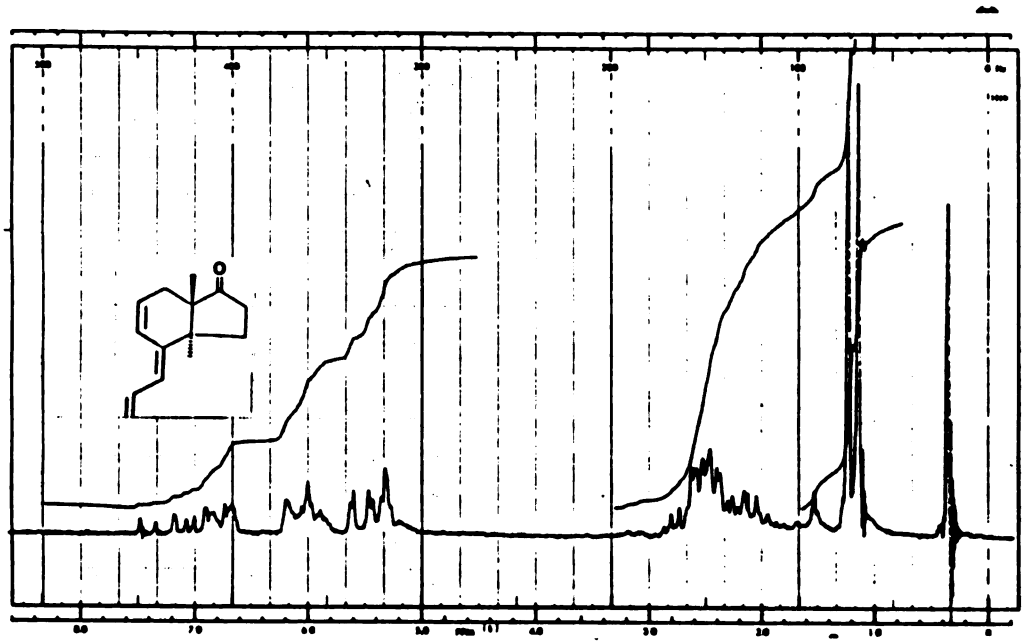


Figure 52. ^{1}H NMR spectrum of 44

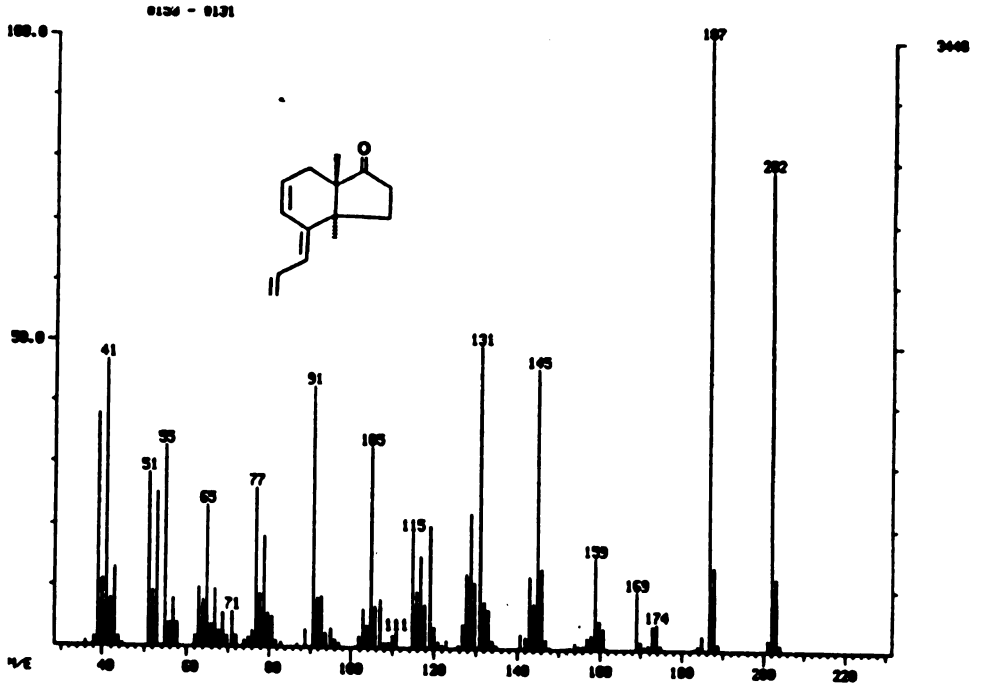


Figure 53. Mass spectrum of 44

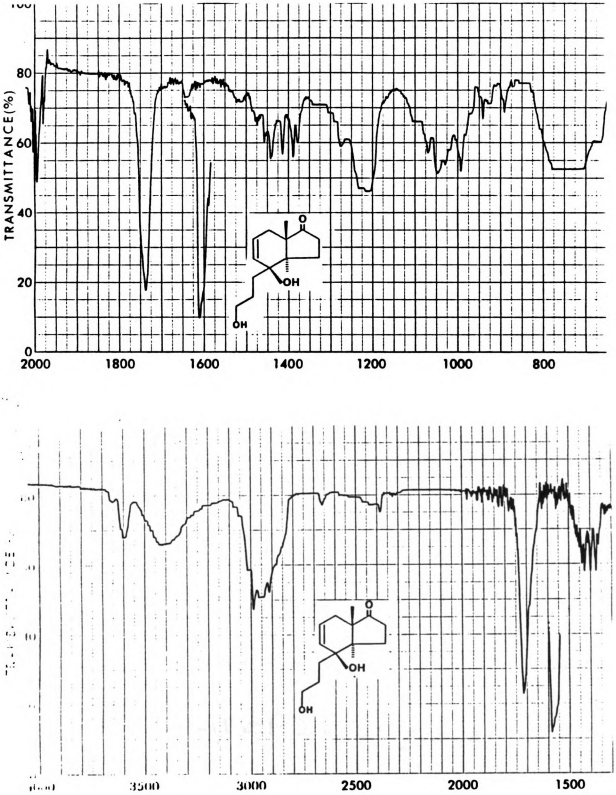


Figure 54. Infrared spectrum of 48

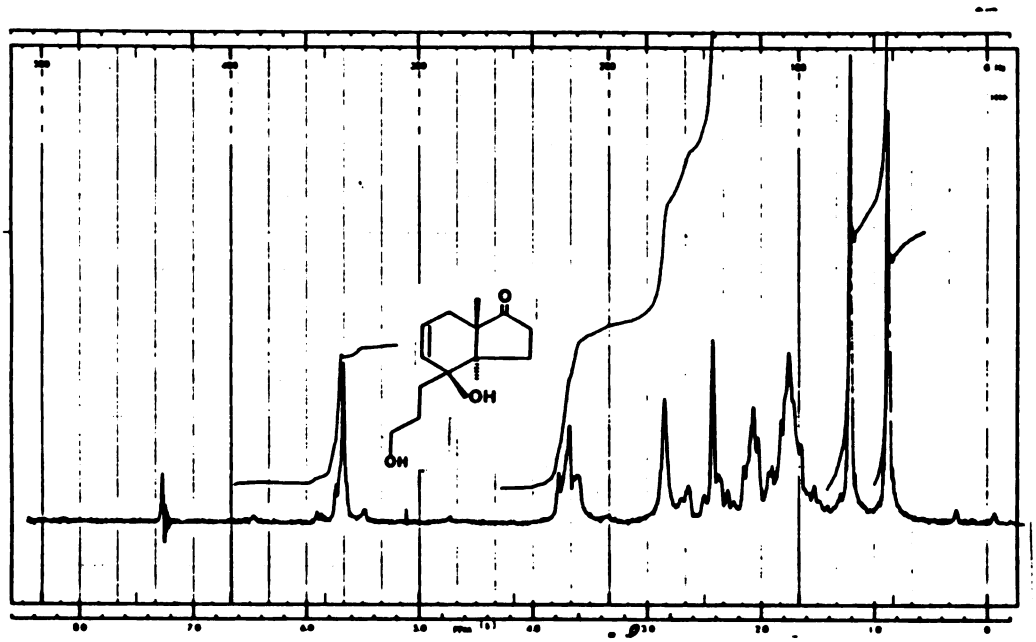


Figure 55. ^{1}H NMR spectrum of 48

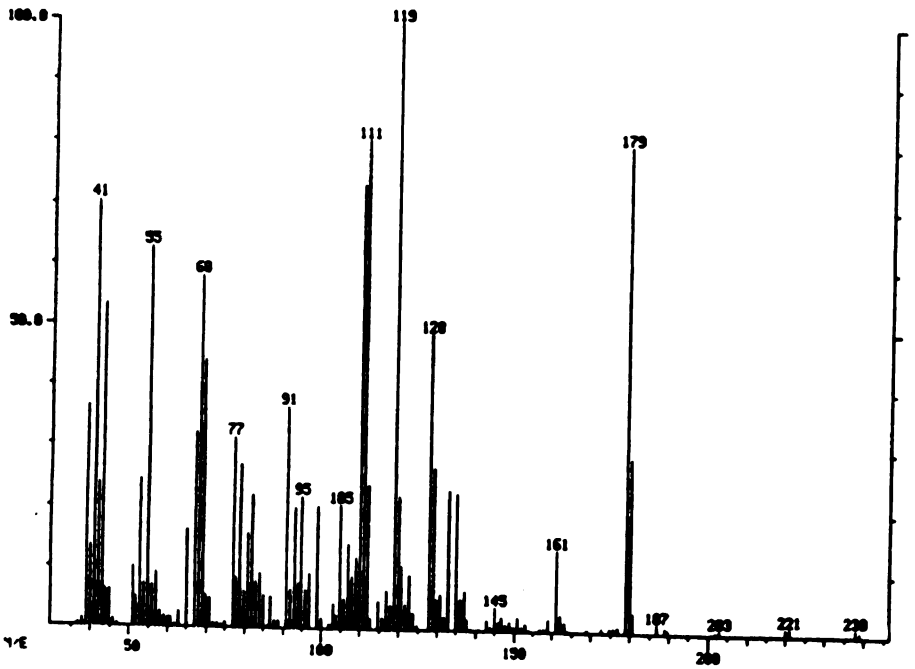
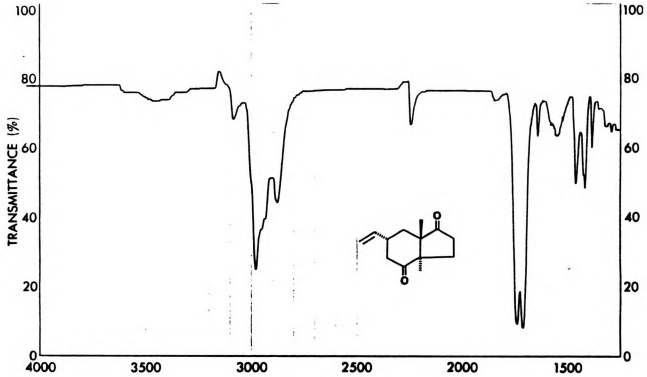


Figure 56. Mass spectrum of 48



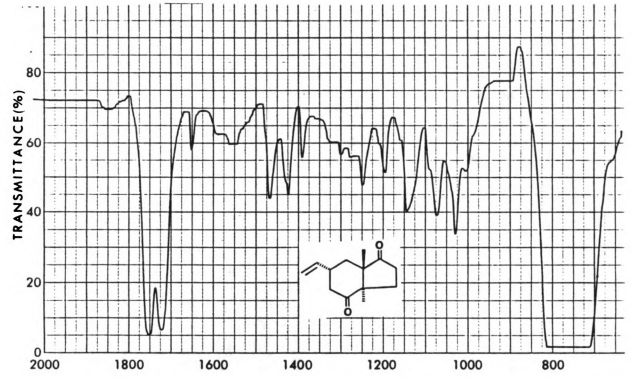


Figure 57. Infrared spectrum of 41

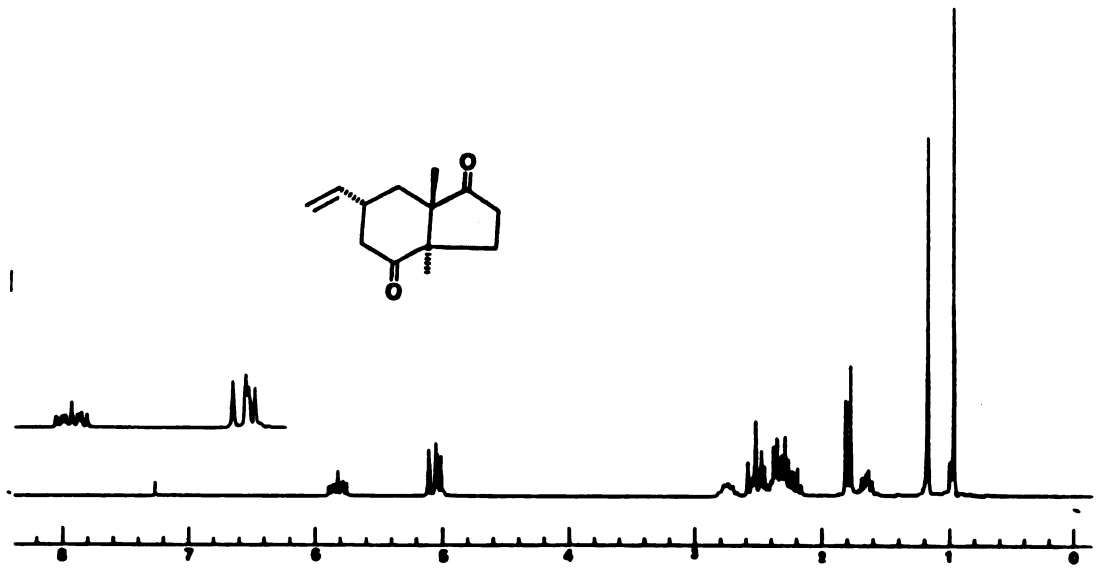


Figure 58. ^{1}H NMR spectrum of 41

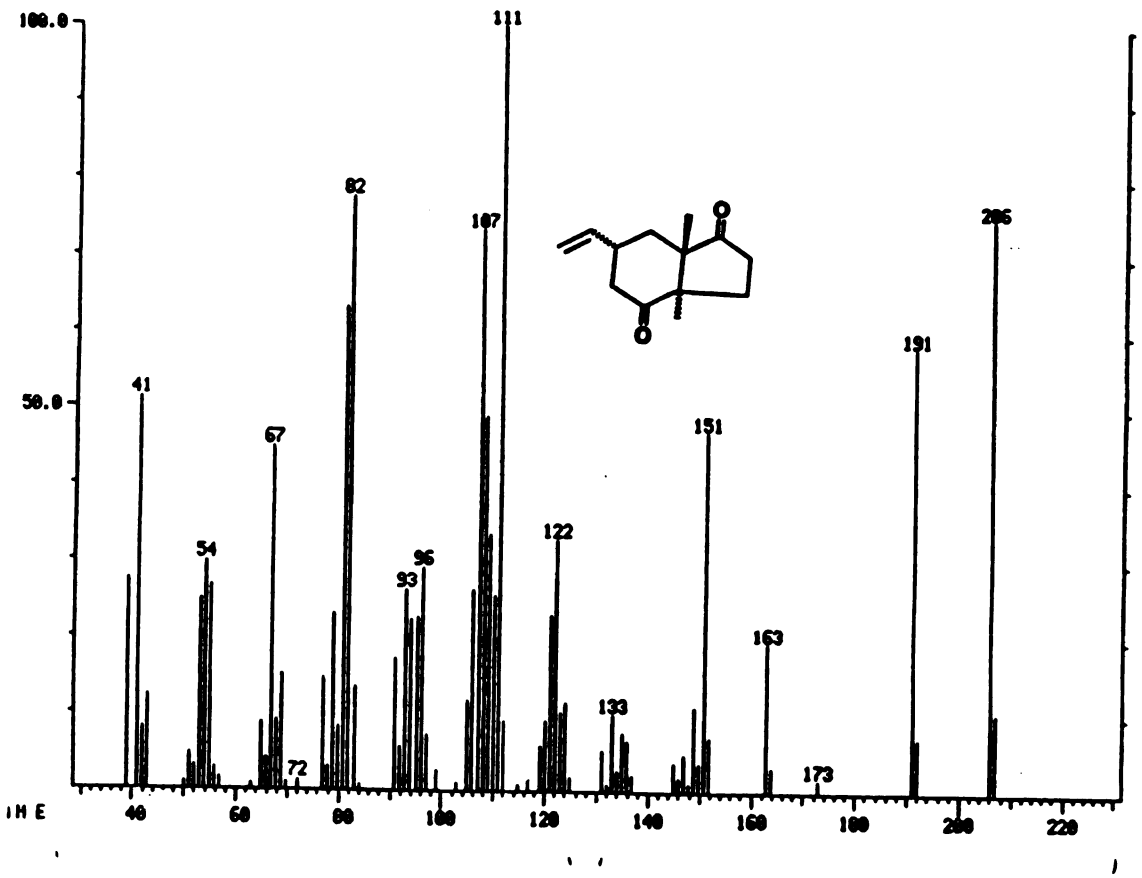


Figure 59. Mass spectrum of 41

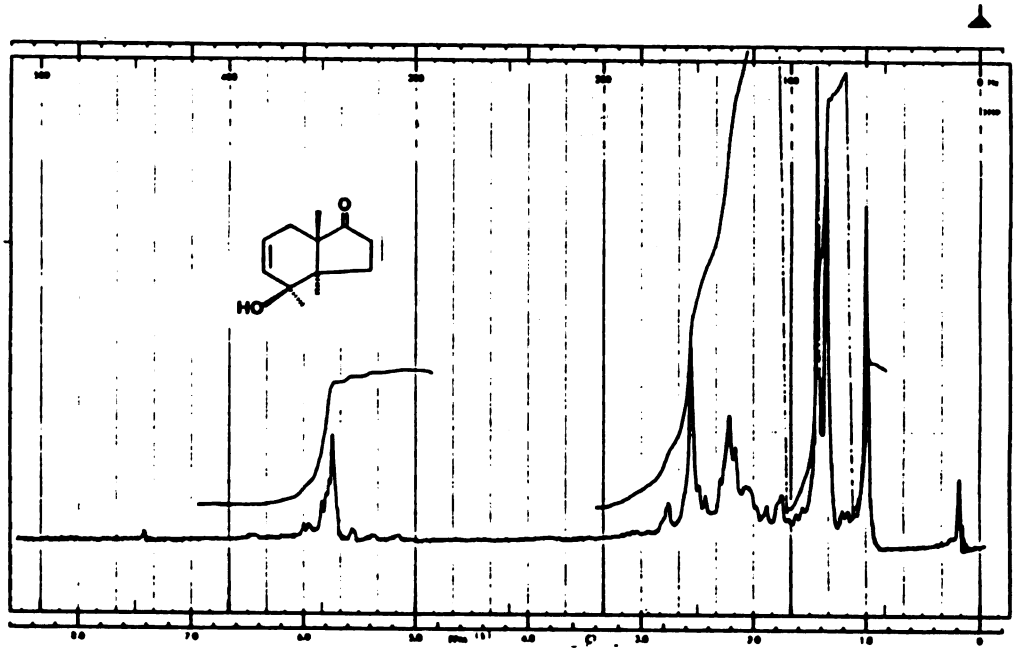


Figure 60. ^{1}H NMR spectrum of 46

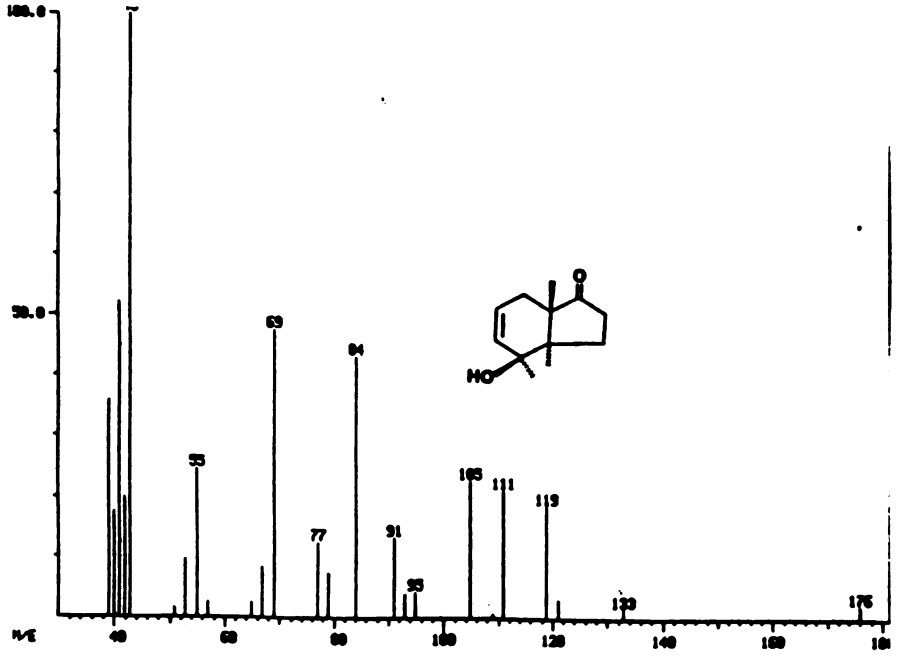


Figure 61. Mass spectrum of 46

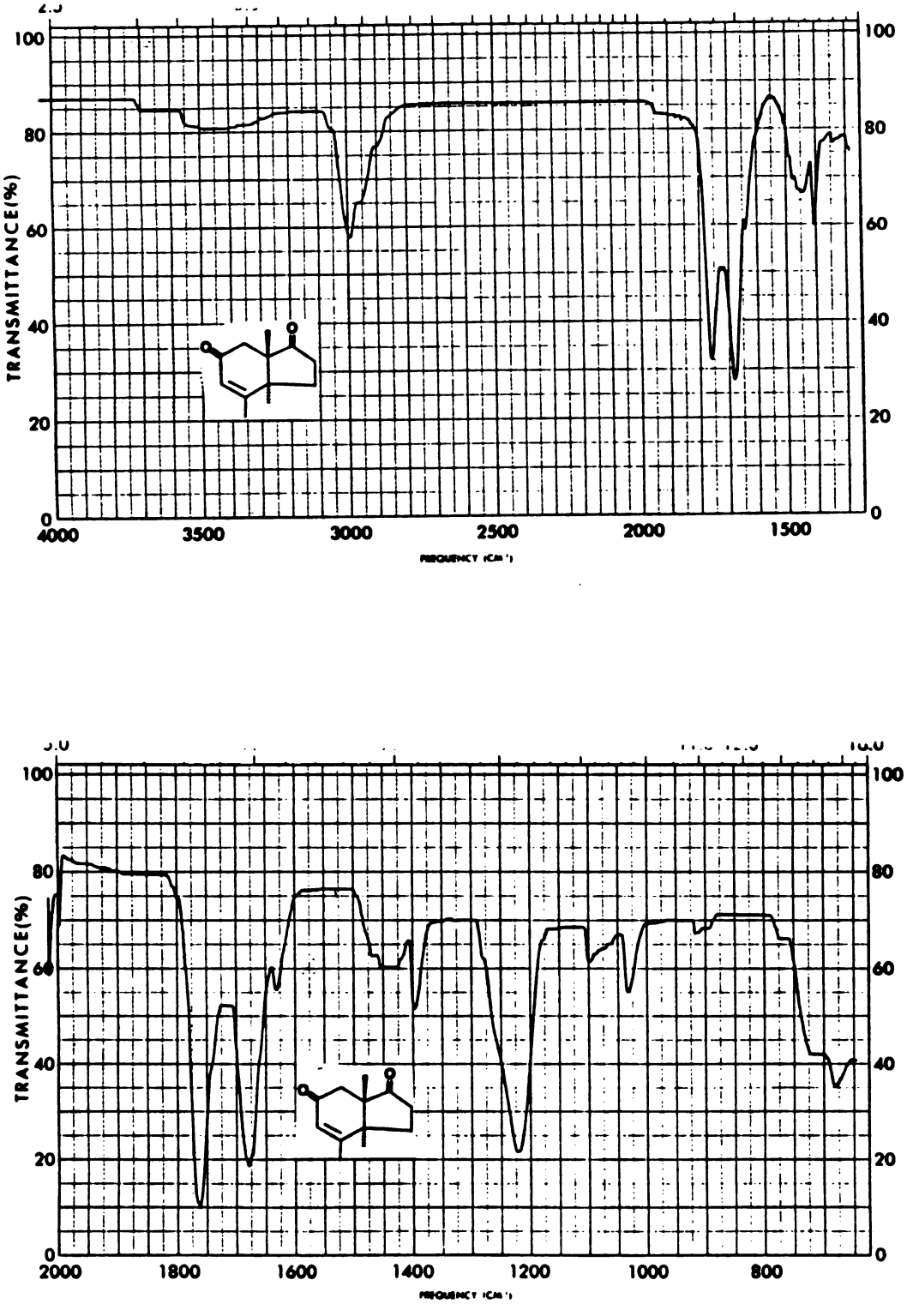


Figure 62. Infrared spectrum of 47

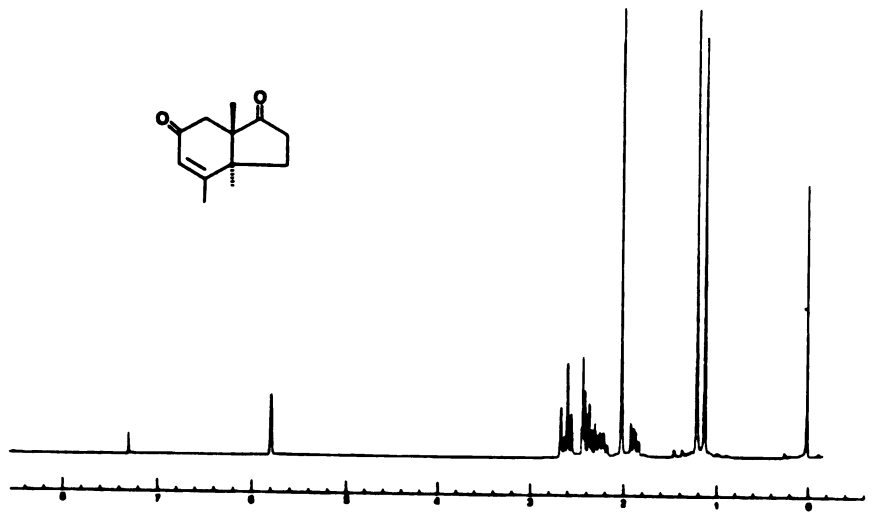


Figure 63. ^{1}H NMR spectrum of 47

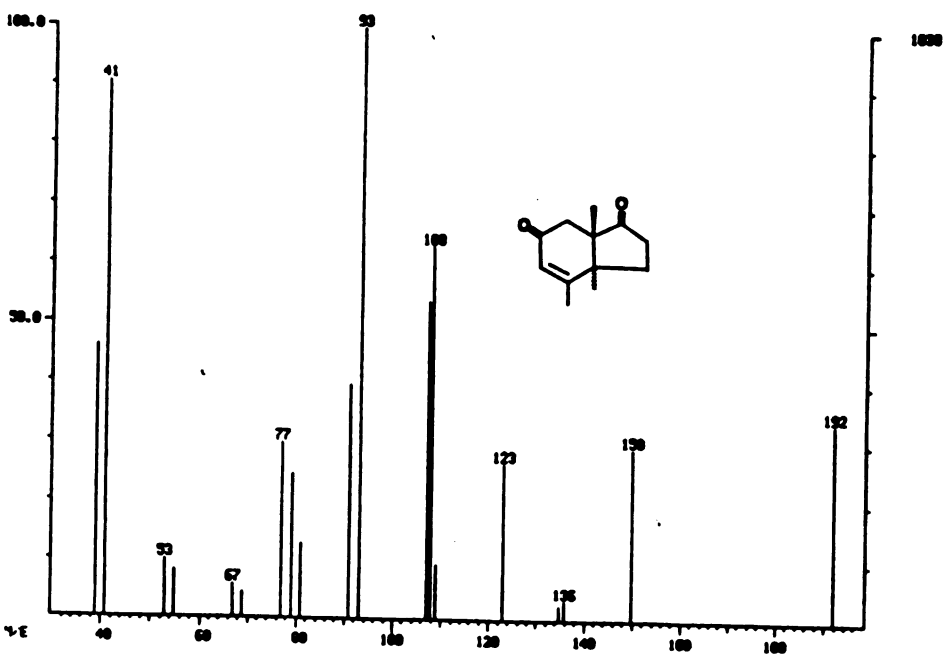


Figure 64. Mass spectrum of 47

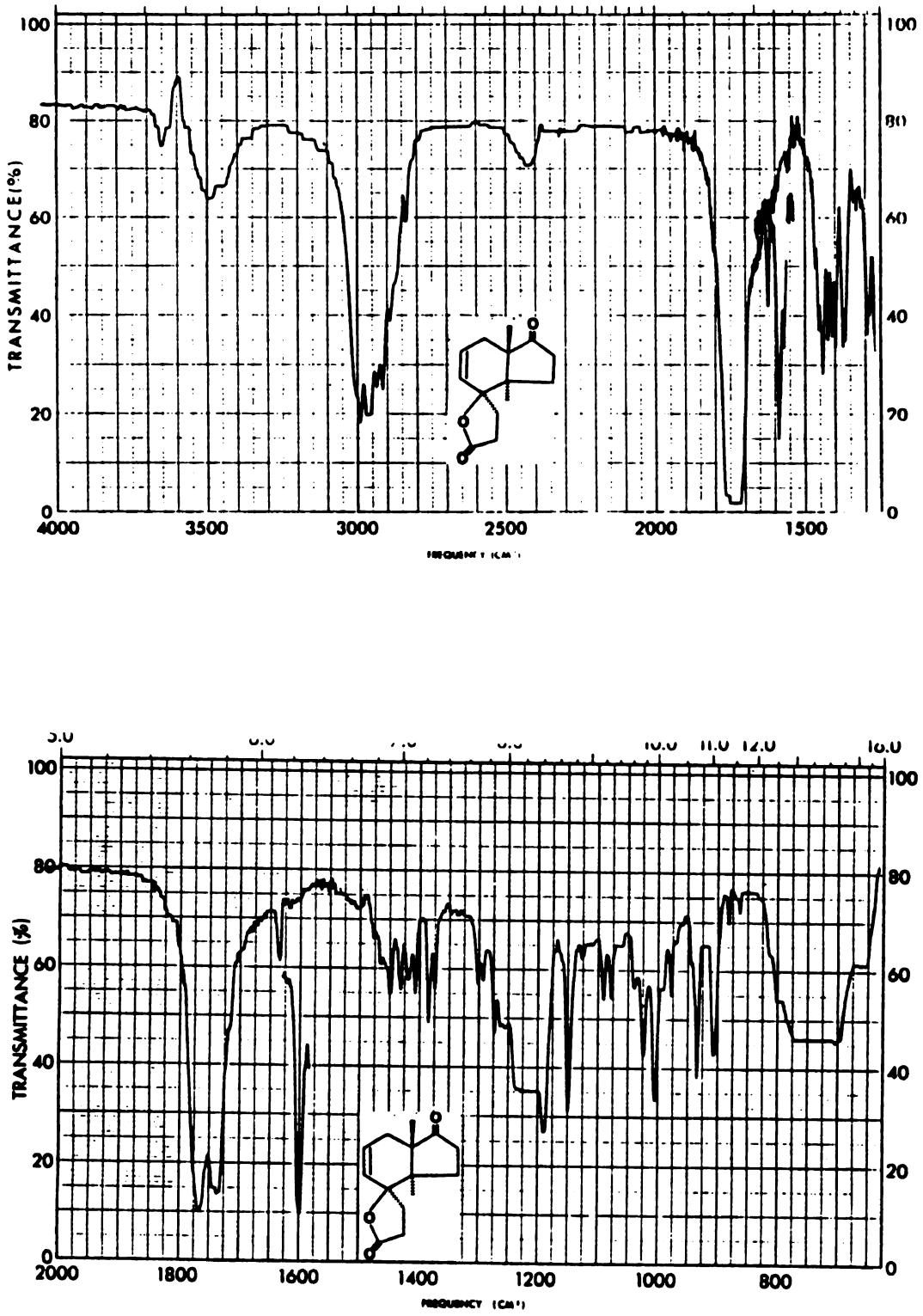


Figure 65. Infrared spectrum of 51

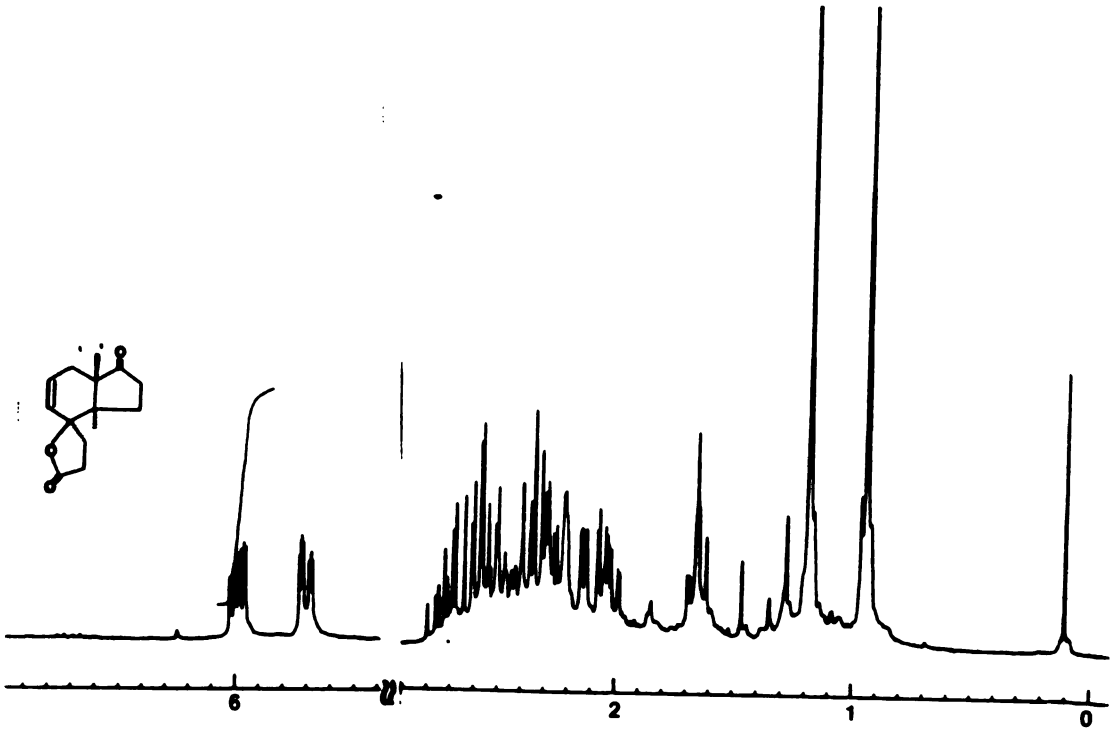


Figure 66. ^{1}H NMR spectrum of 51

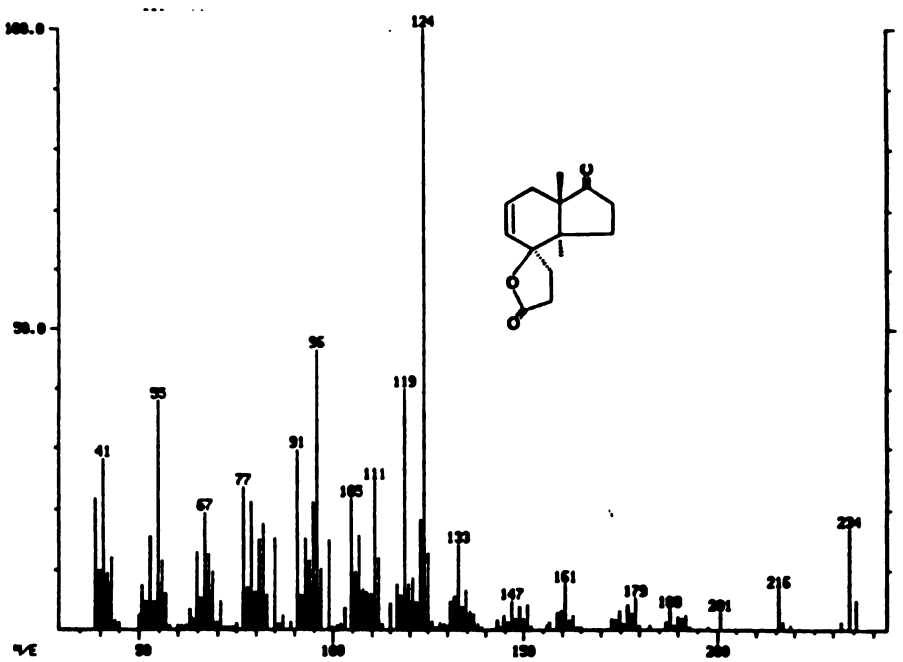


Figure 67. Mass spectrum of 51

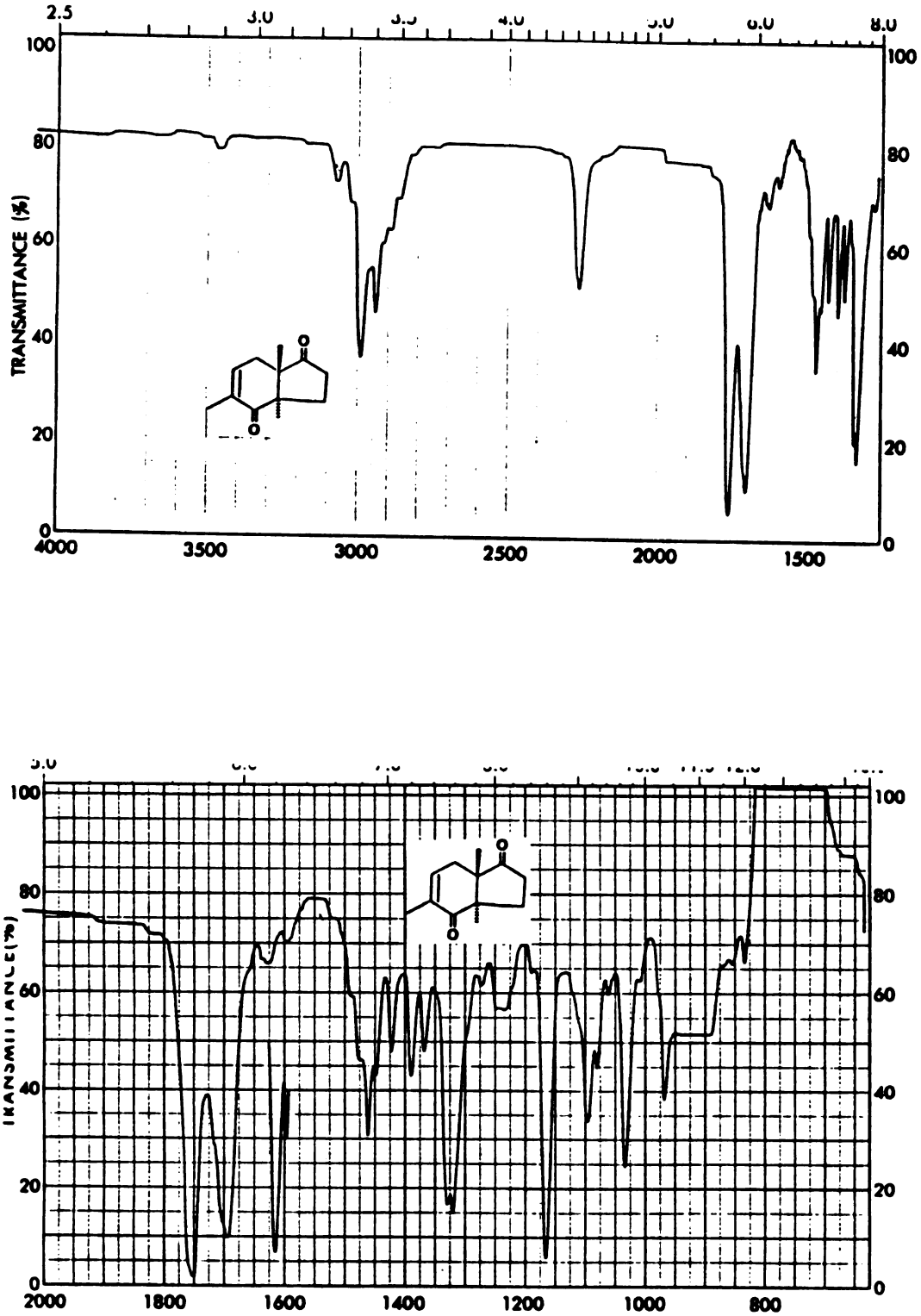


Figure 68. Infrared spectrum of 52

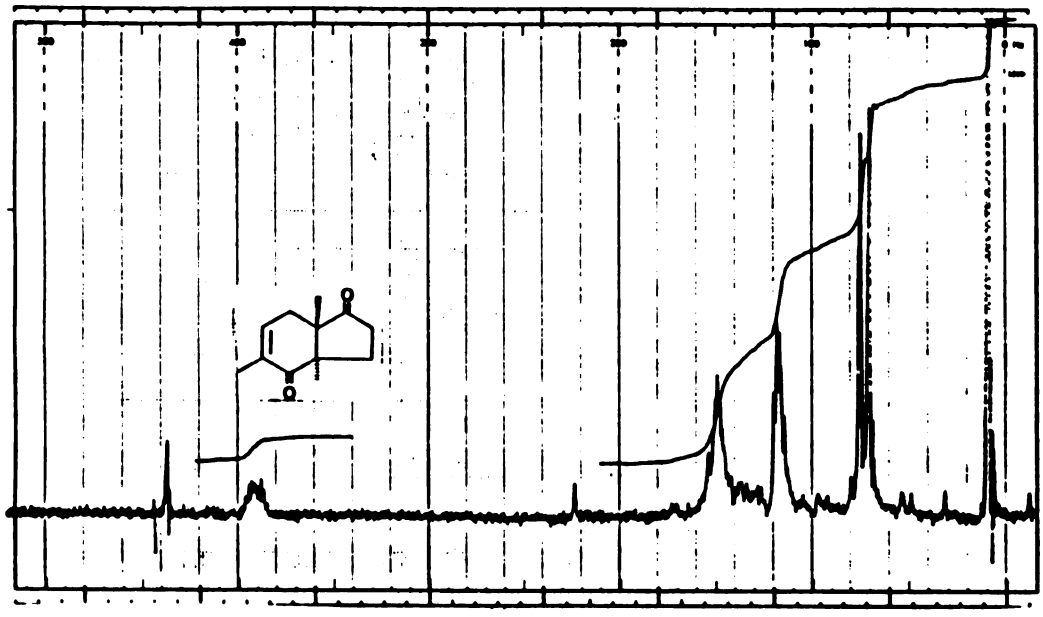


Figure 69. ^{1}H NMR spectrum of 52

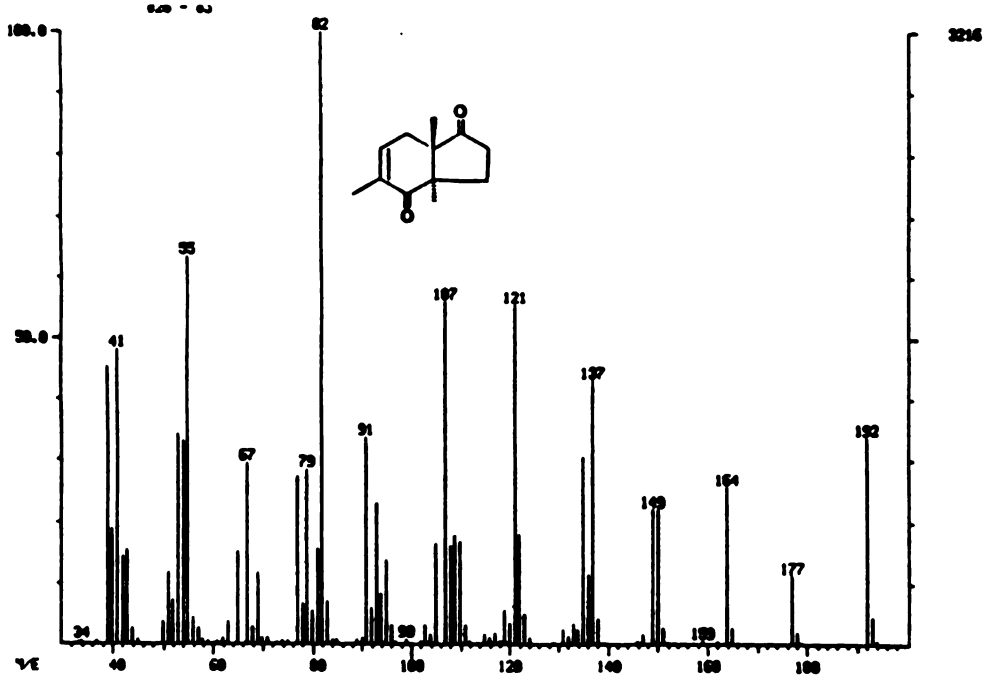


Figure 70. Mass spectrum of 52

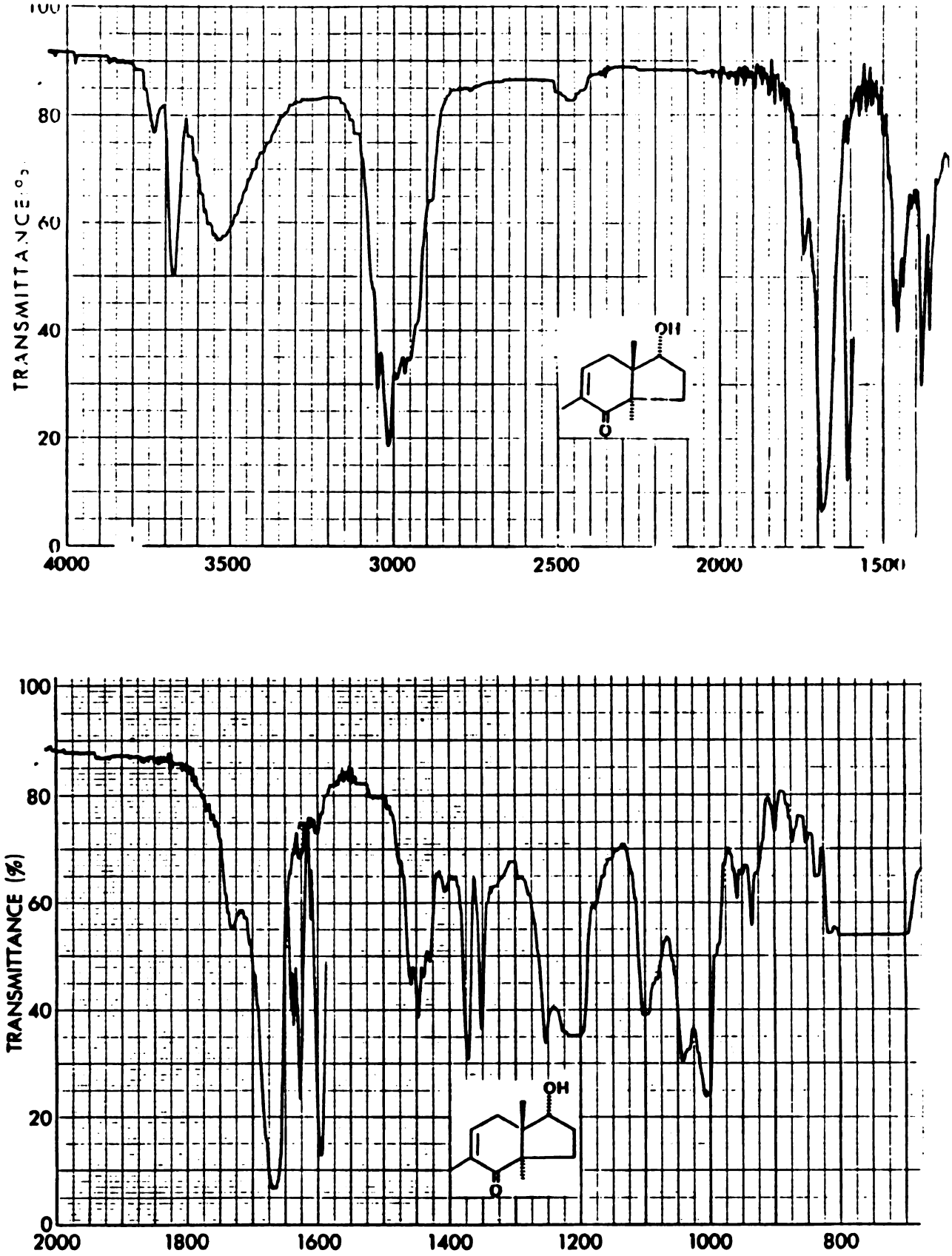


Figure 71. Infrared spectrum of 55

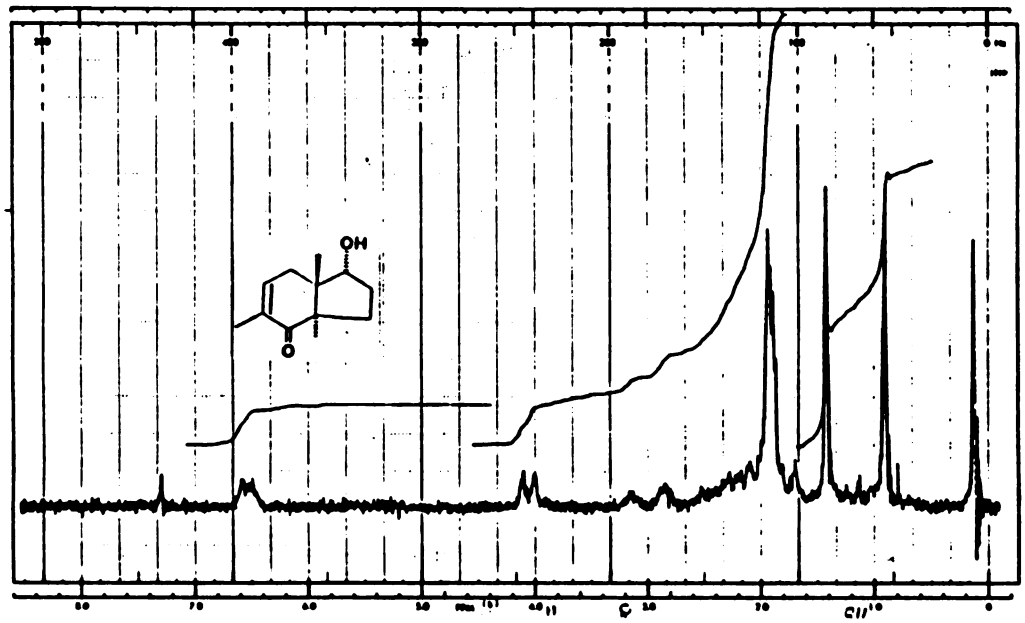


Figure 72. ^{1}H NMR spectrum of 55

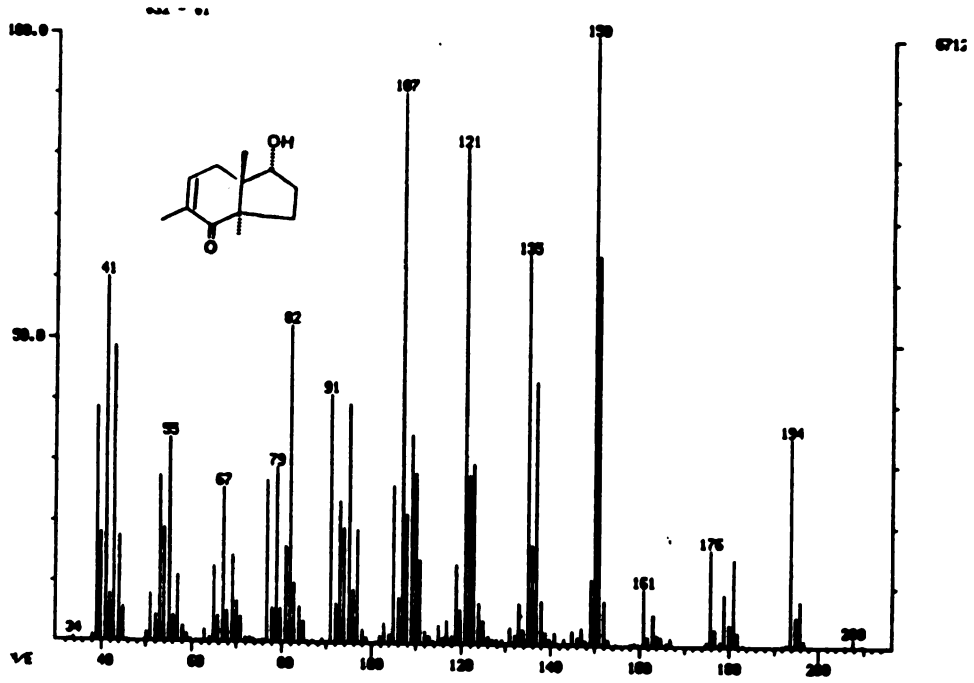


Figure 73. Mass spectrum of 55

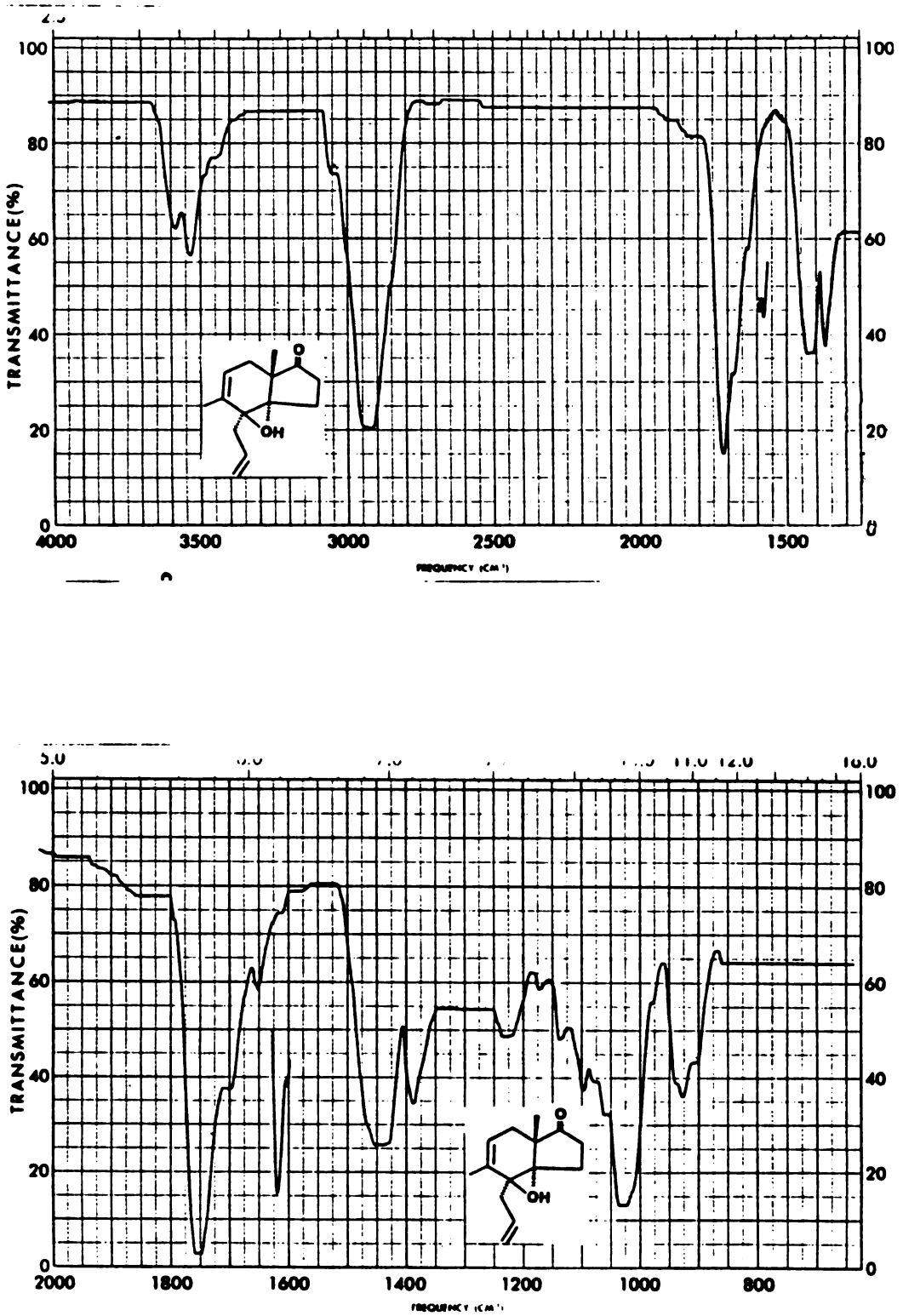


Figure 74. Infrared spectrum of 56

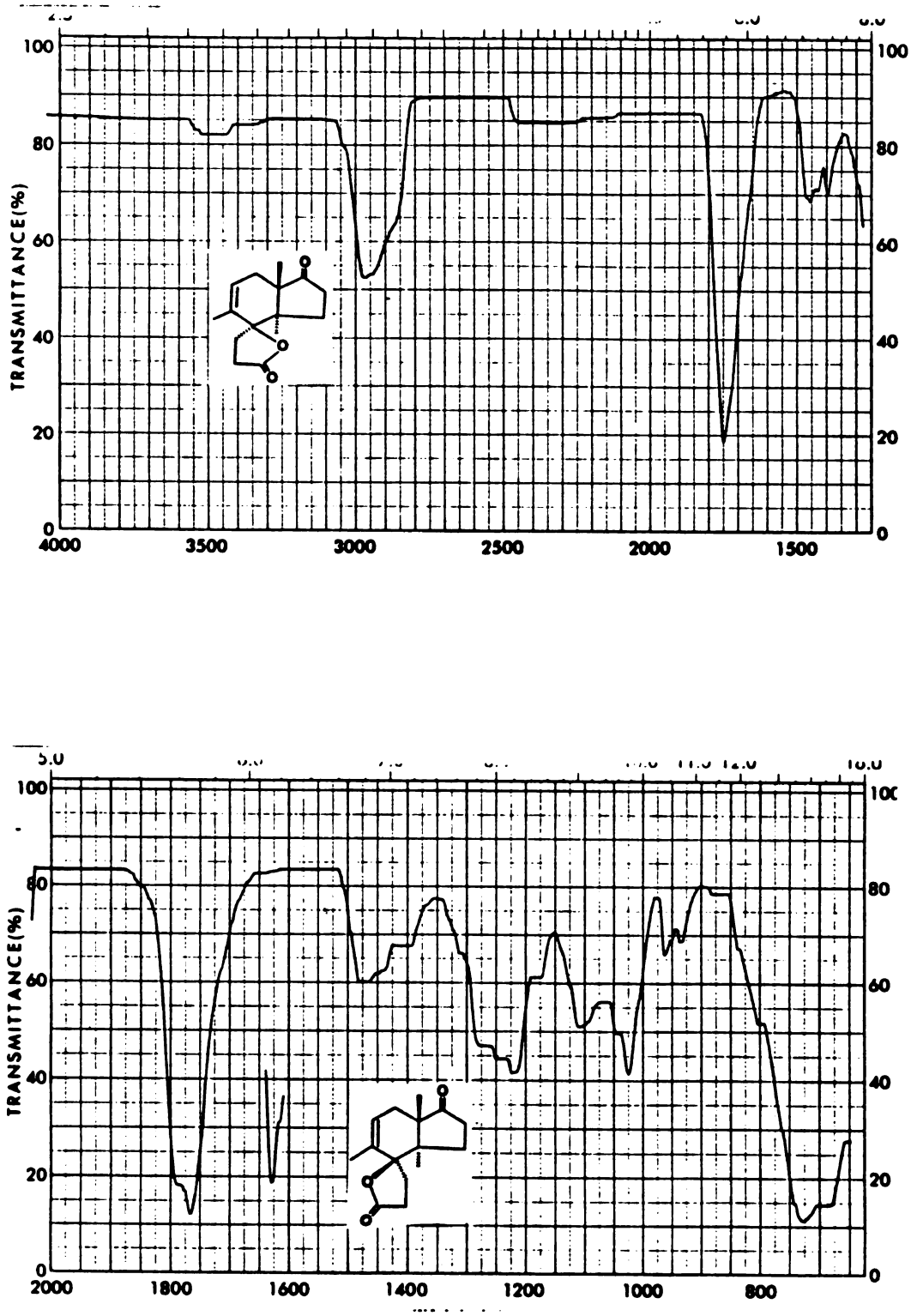


Figure 75. Infrared spectrum of 59

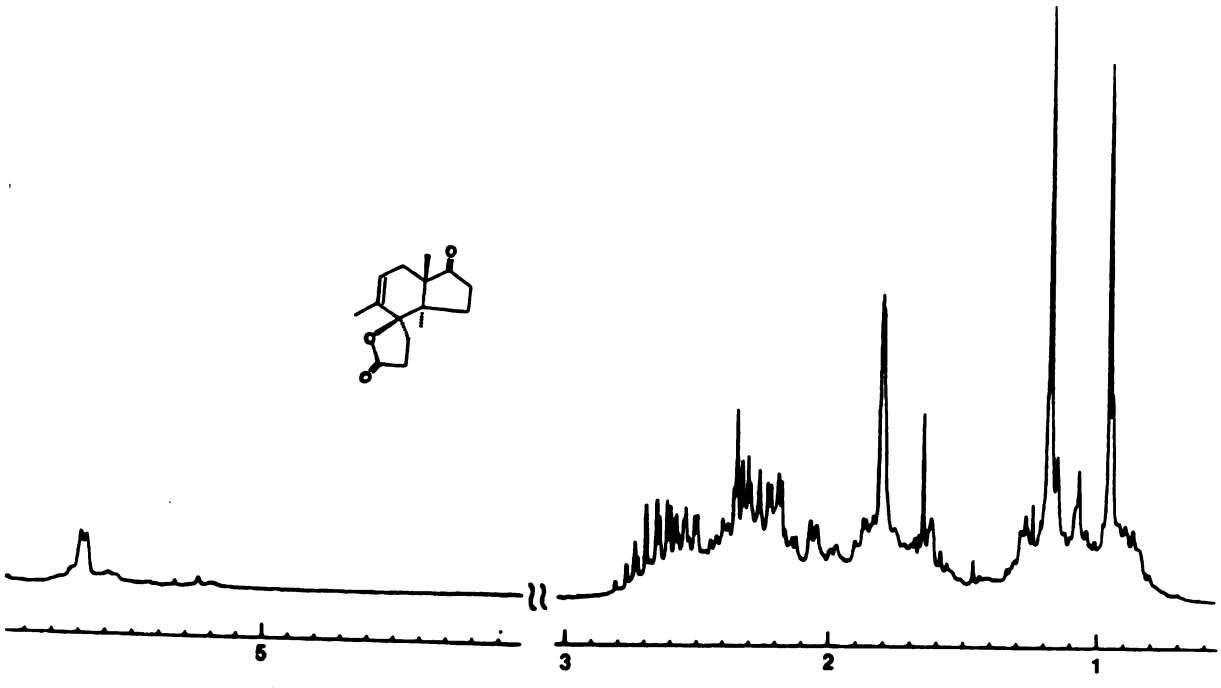


Figure 76. ^{1}H NMR spectrum of 59

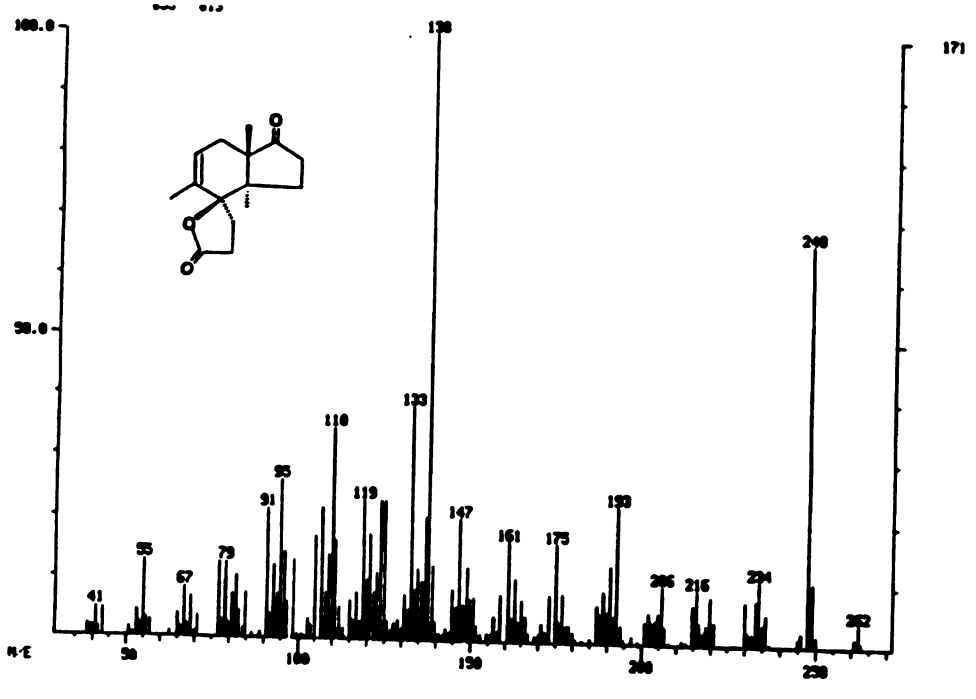


Figure 77. Mass spectrum of 59

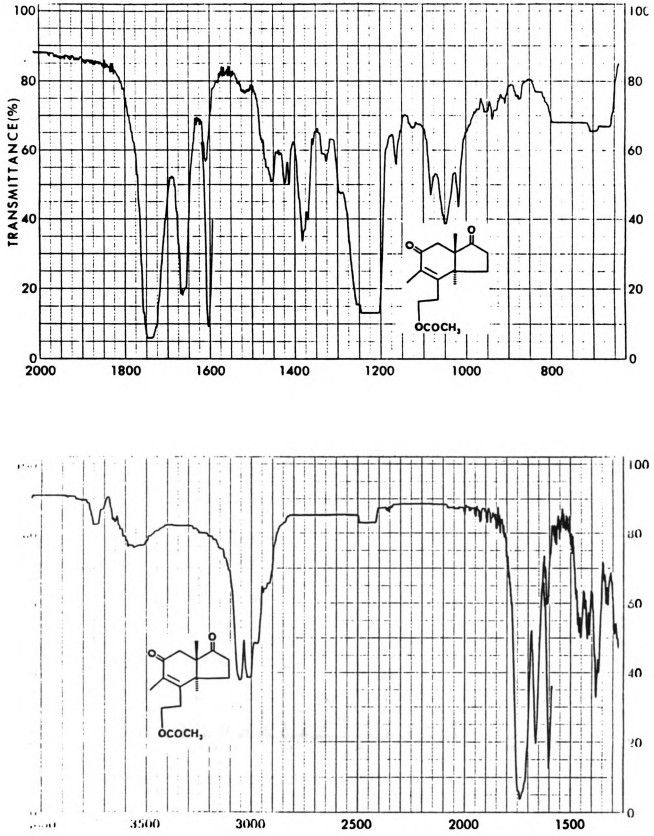


Figure 78. Infrared spectrum of 60

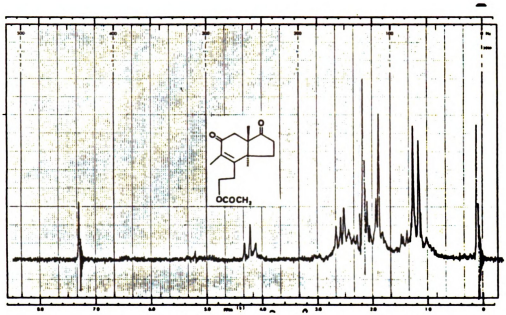


Figure 79. ^{1}H NMR spectrum of 60

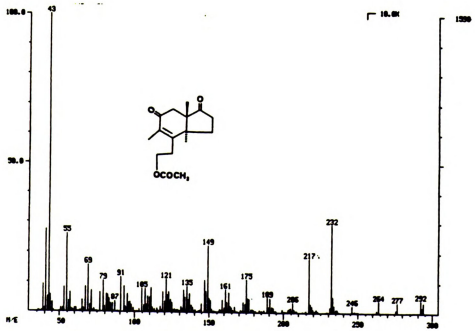


Figure 80. Mass spectrum of 60

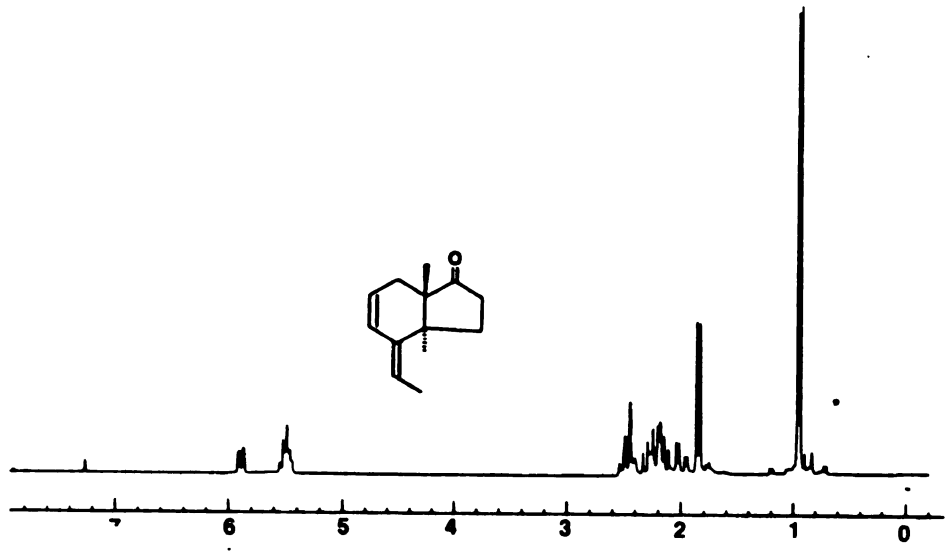


Figure 81. ^{1}H NMR spectrum of 62

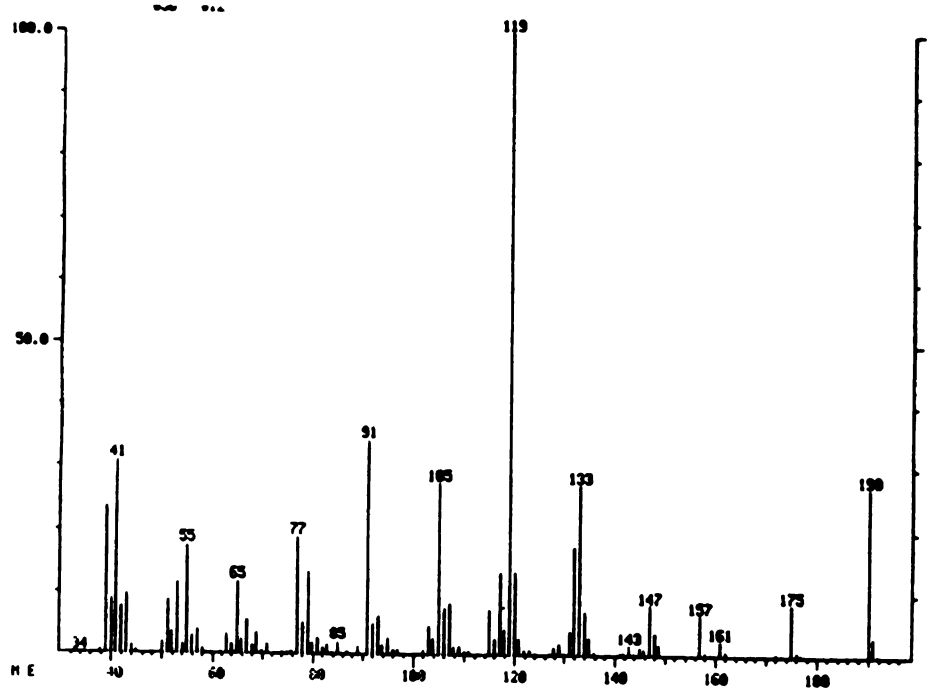


Figure 82. Mass spectrum of 62

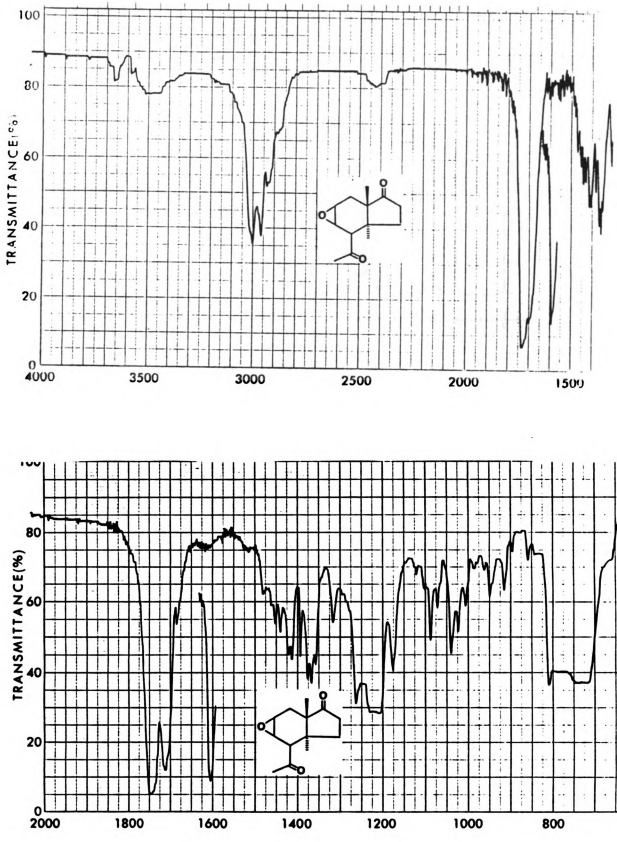


Figure 83. Infrared spectrum of 70

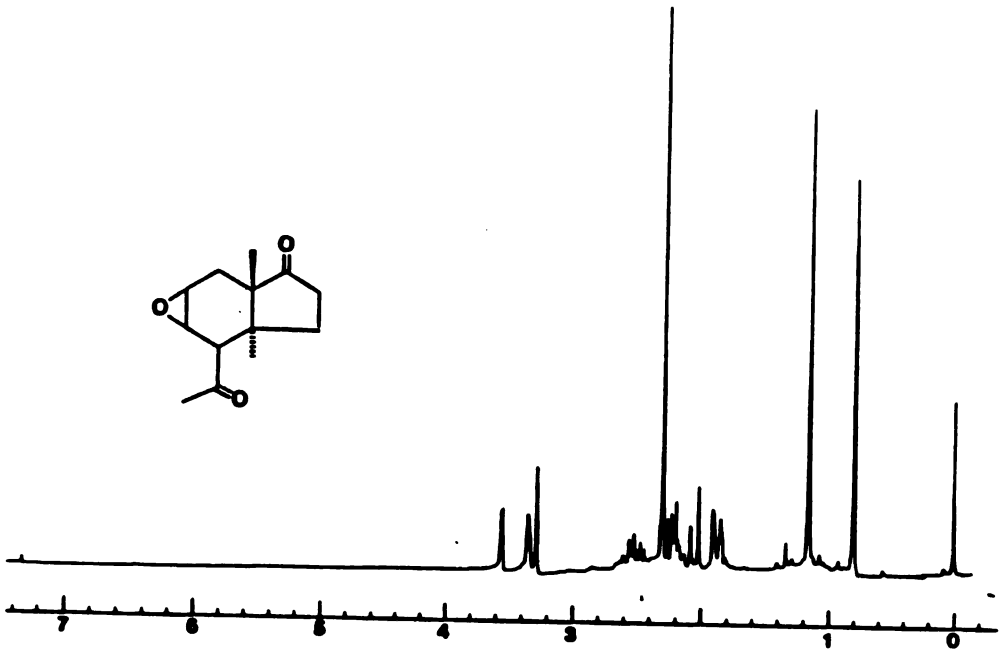


Figure 84. ^{1}H NMR spectrum of 70

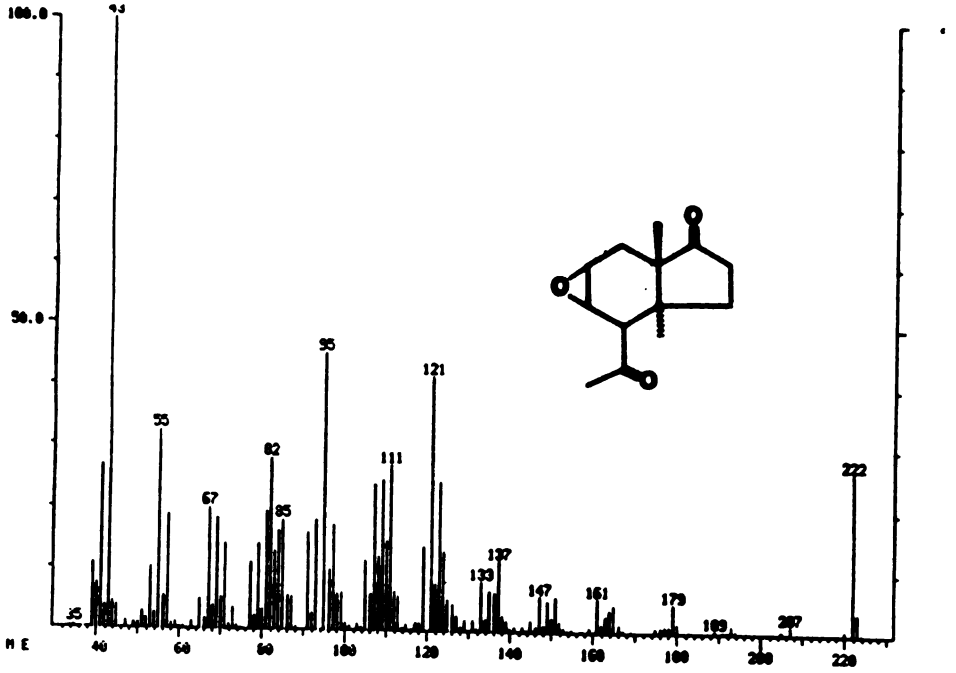


Figure 85. Mass spectrum of 70

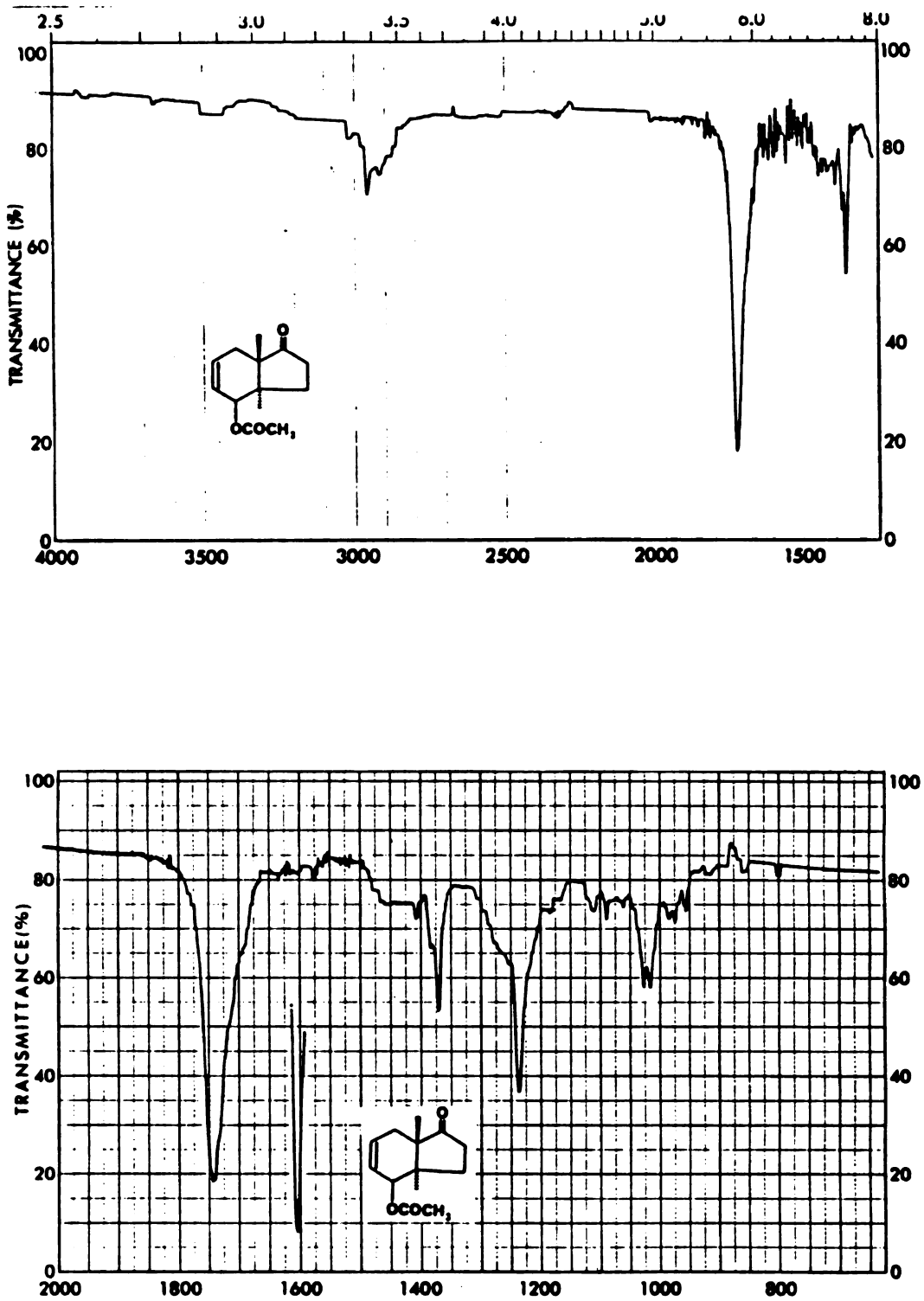


Figure 86. Infrared spectrum of 72

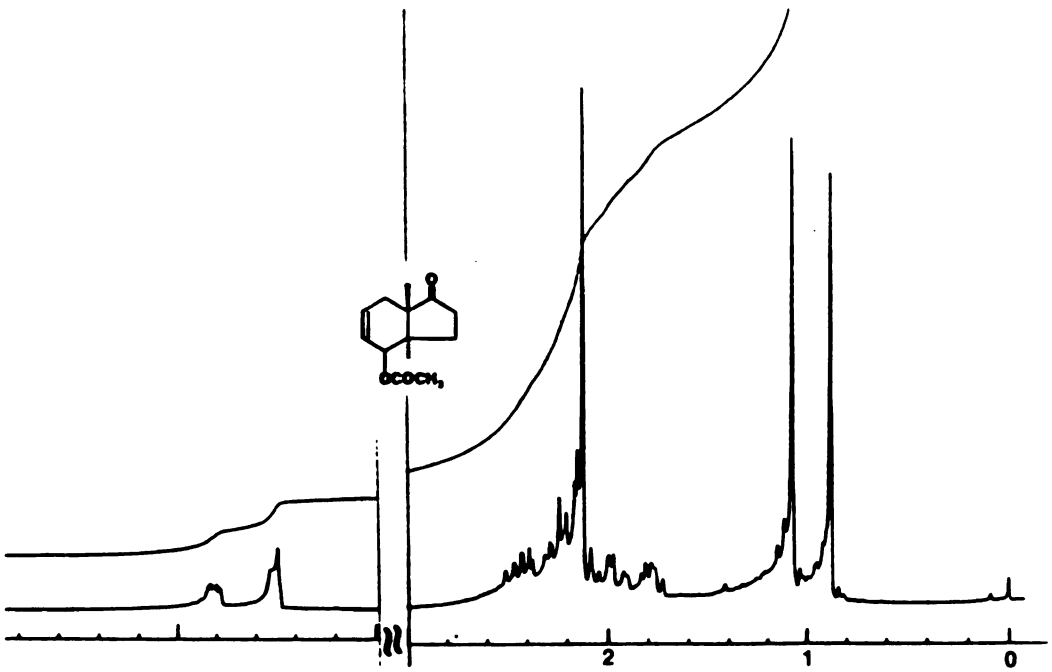


Figure 87. ^{1}H NMR spectrum of 72

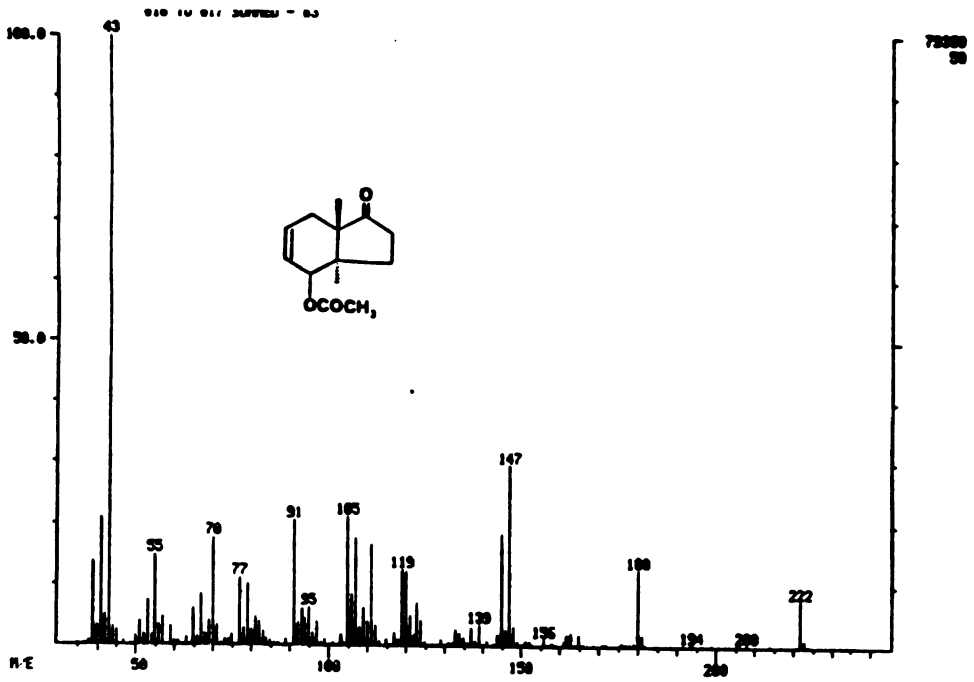
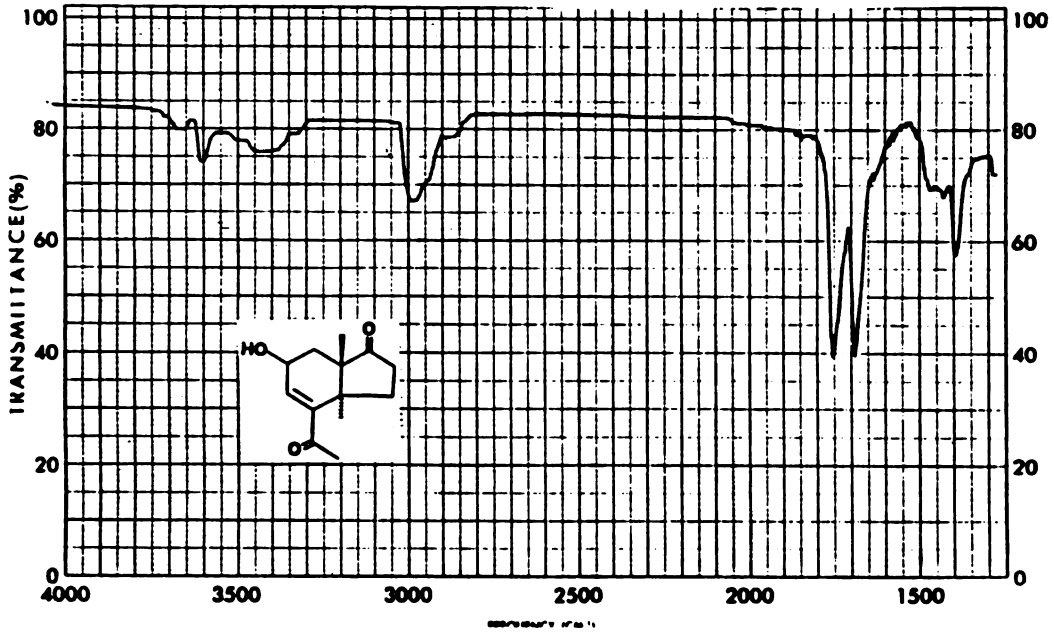


Figure 88. Mass spectrum of 72



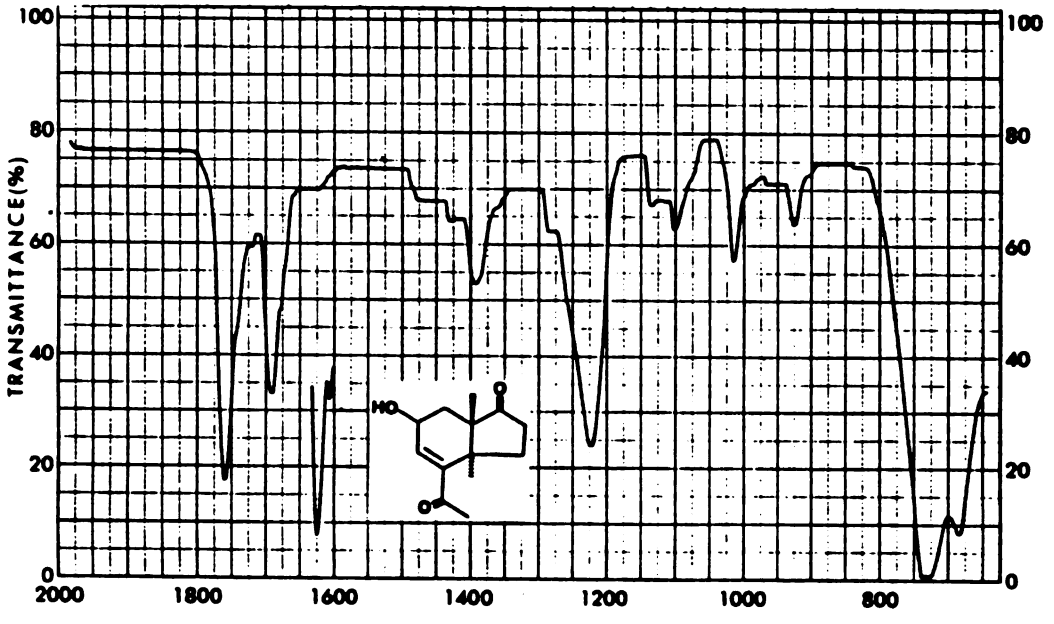


Figure 89. Infrared spectrum of 71

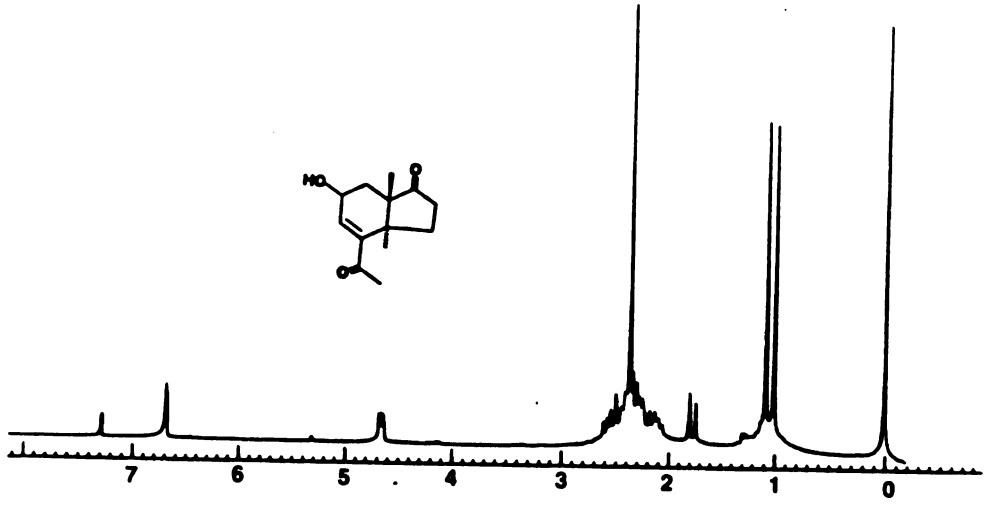


Figure 90. ^{1}H NMR spectrum of 71

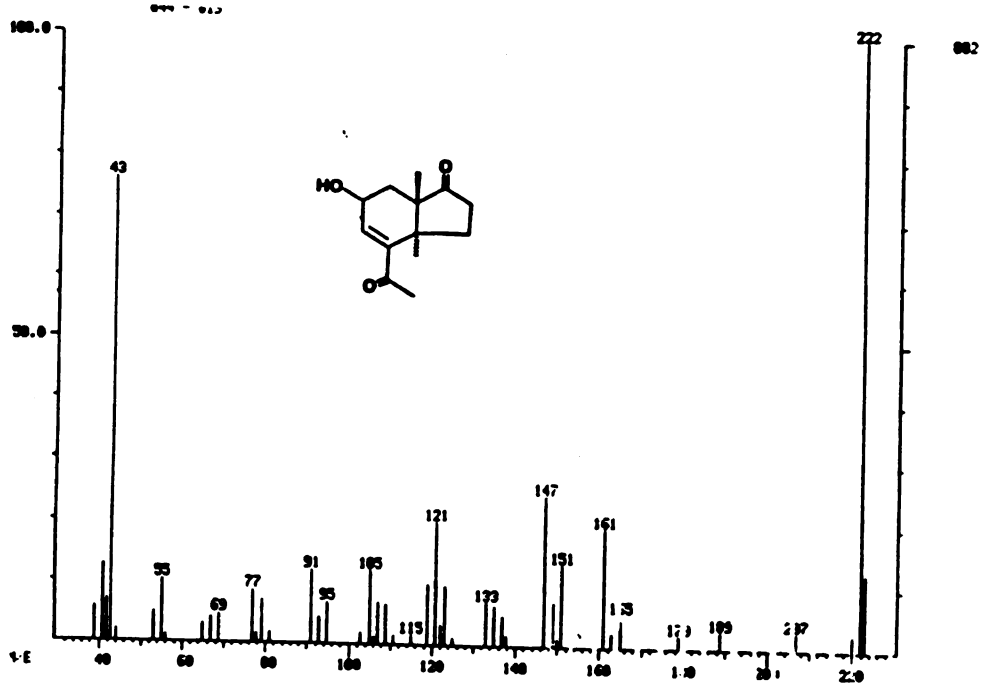
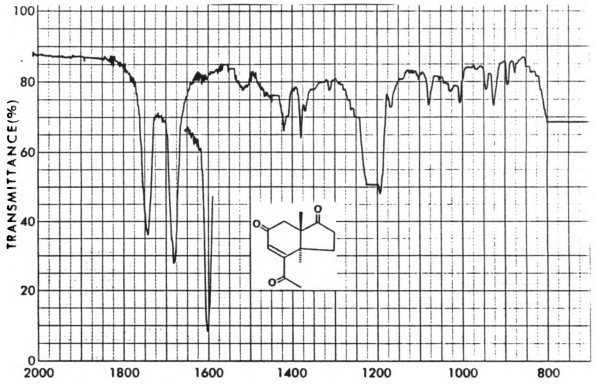


Figure 91. Mass spectrum of 71



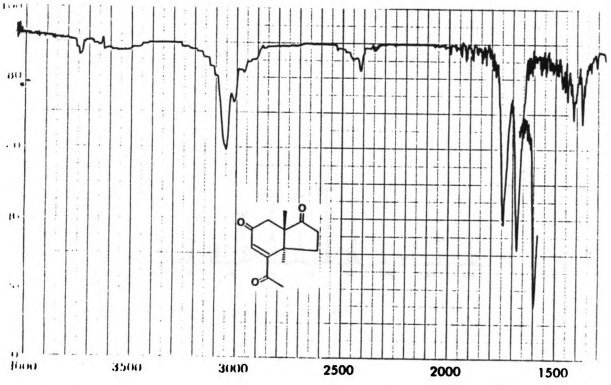


Figure 92. Infrared spectrum of 65

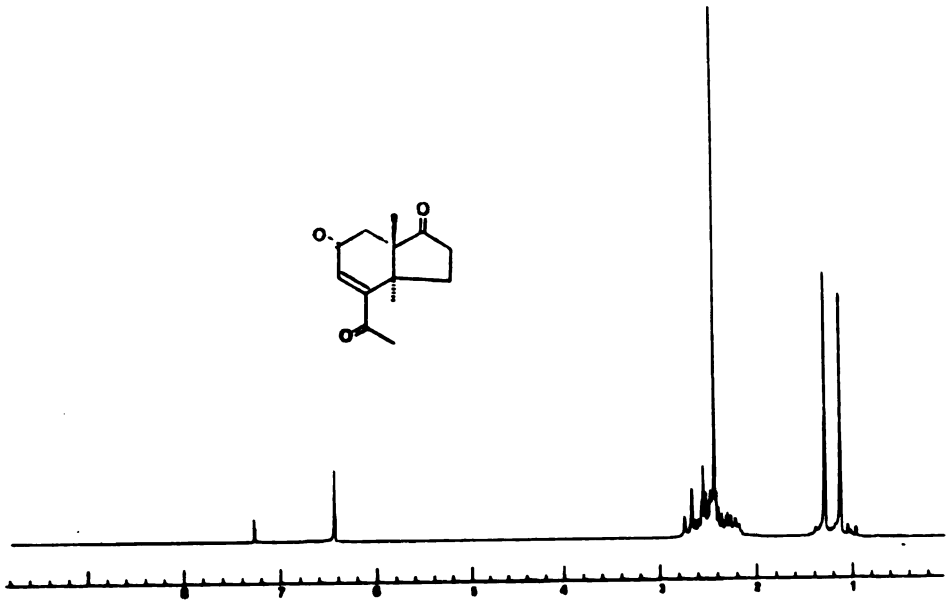


Figure 93. ^{1}H NMR spectrum of 65

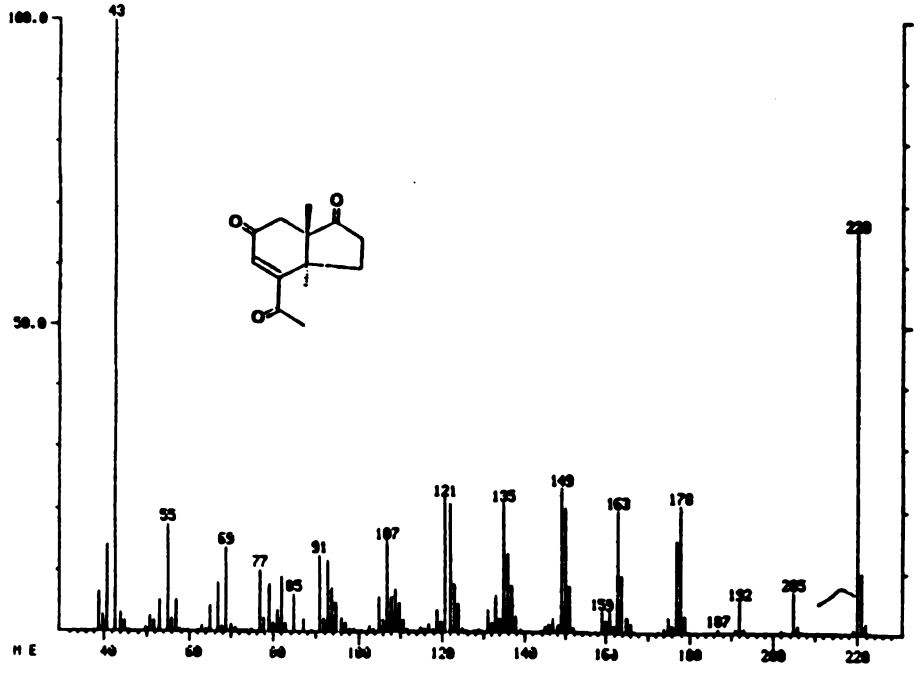


Figure 94. Mass spectrum of 65

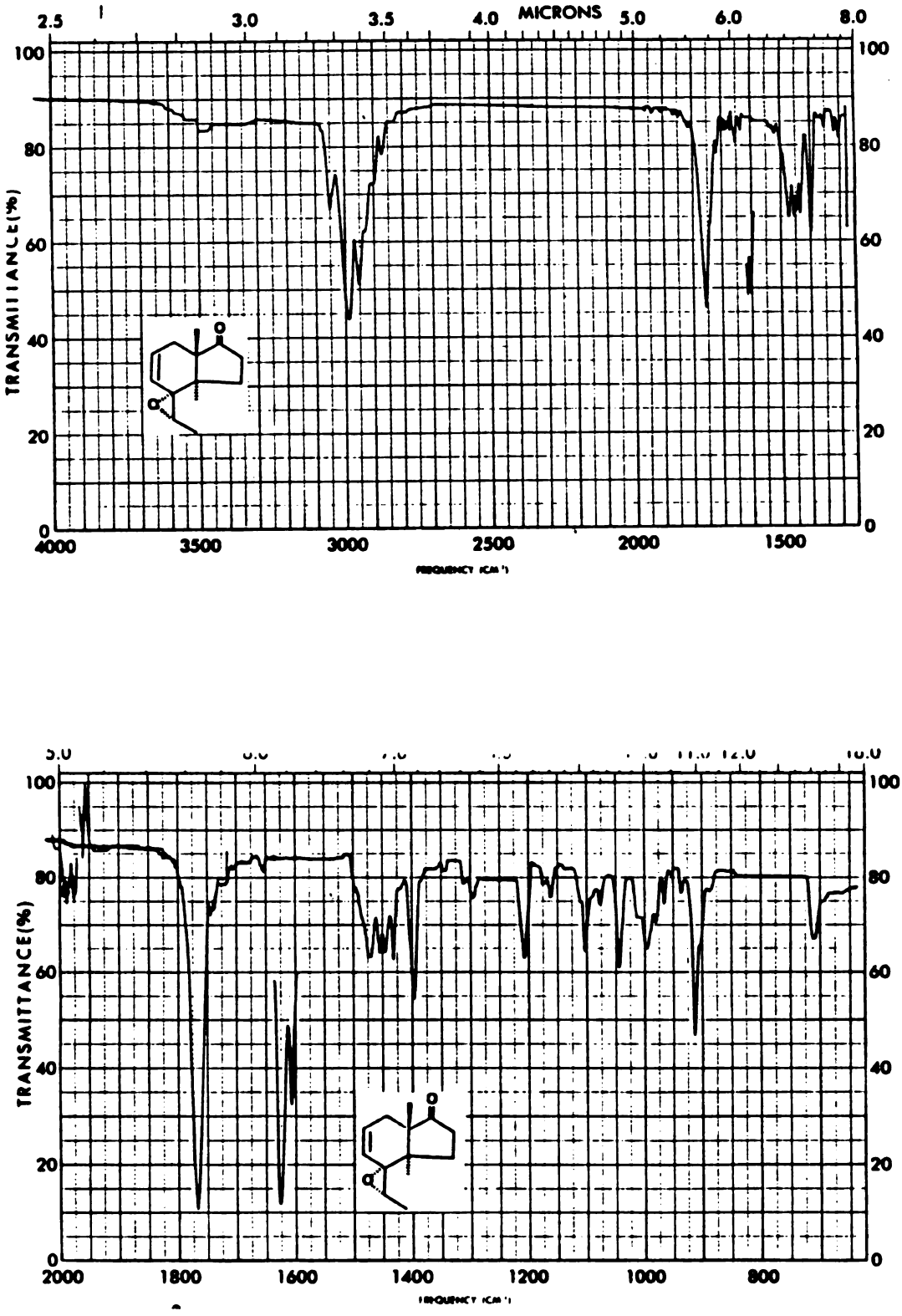


Figure 95. Infrared spectrum of 69

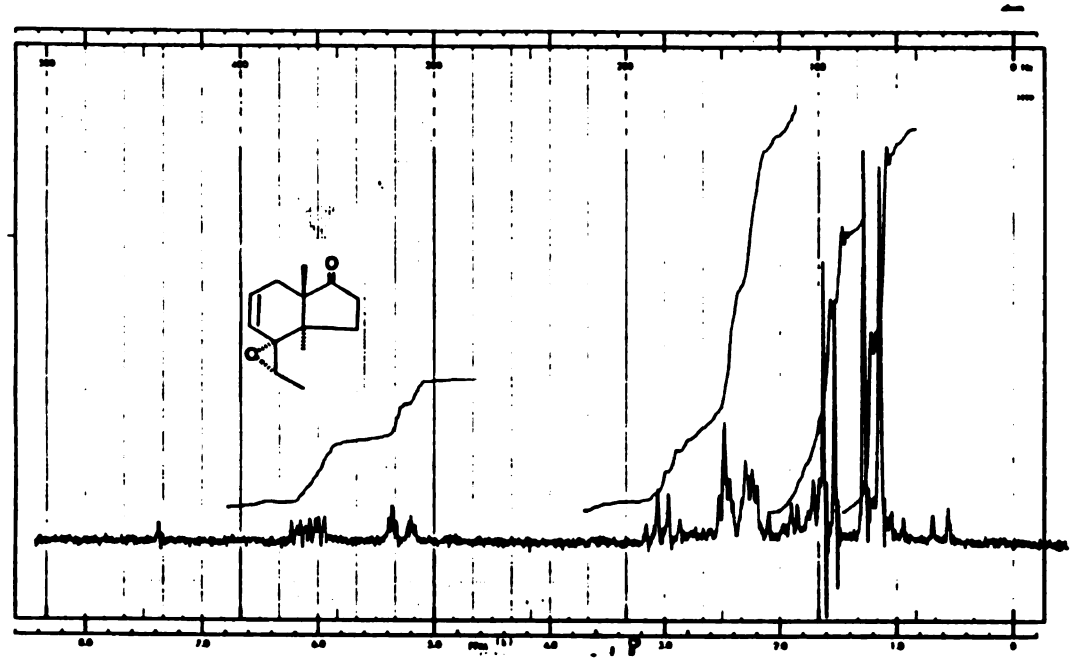


Figure 96. ^{1}H NMR spectrum of 69

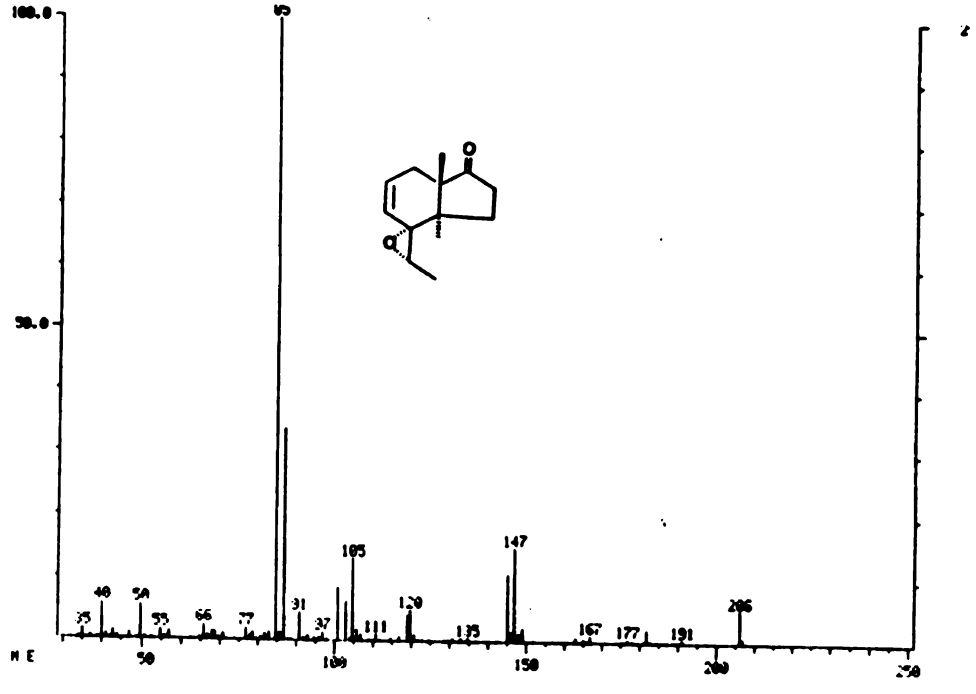


Figure 97. Mass spectrum of 69

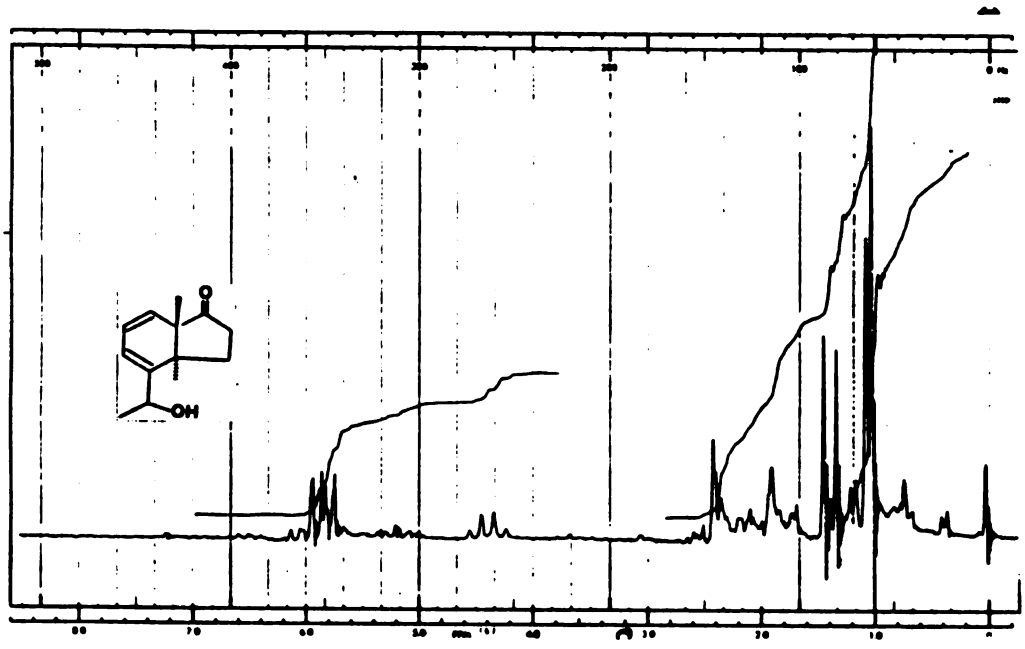


Figure 98. ^{1}H NMR spectrum of 73

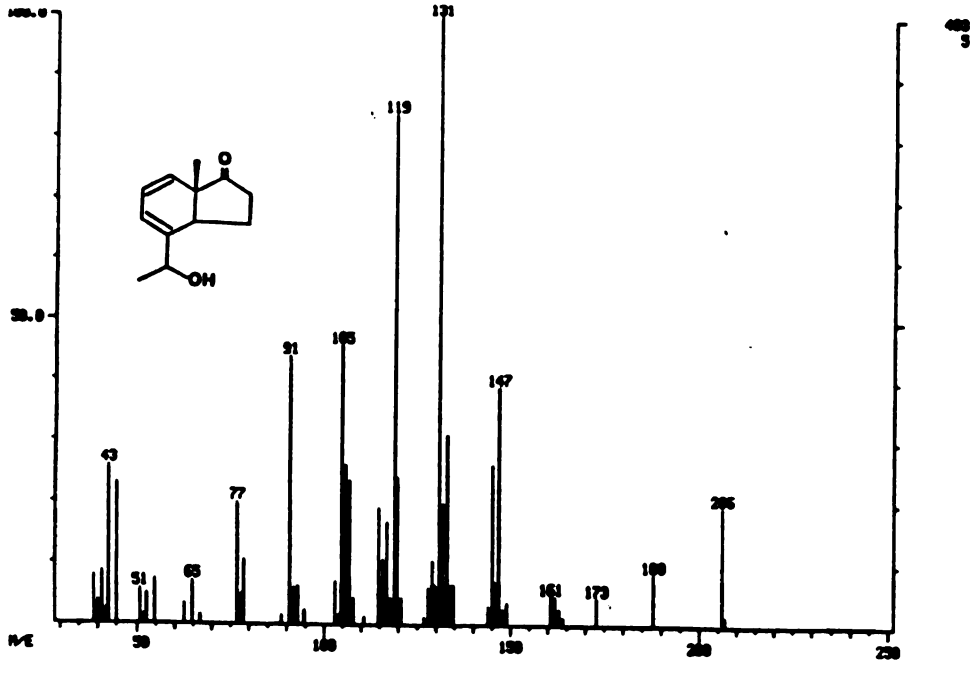


Figure 99. Mass spectrum of 73

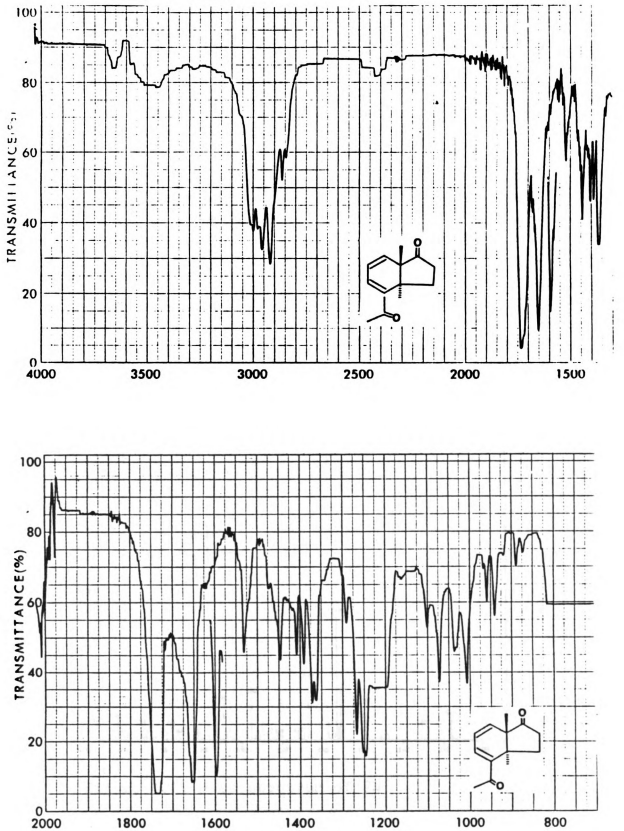


Figure 100. Infrared spectrum of 74

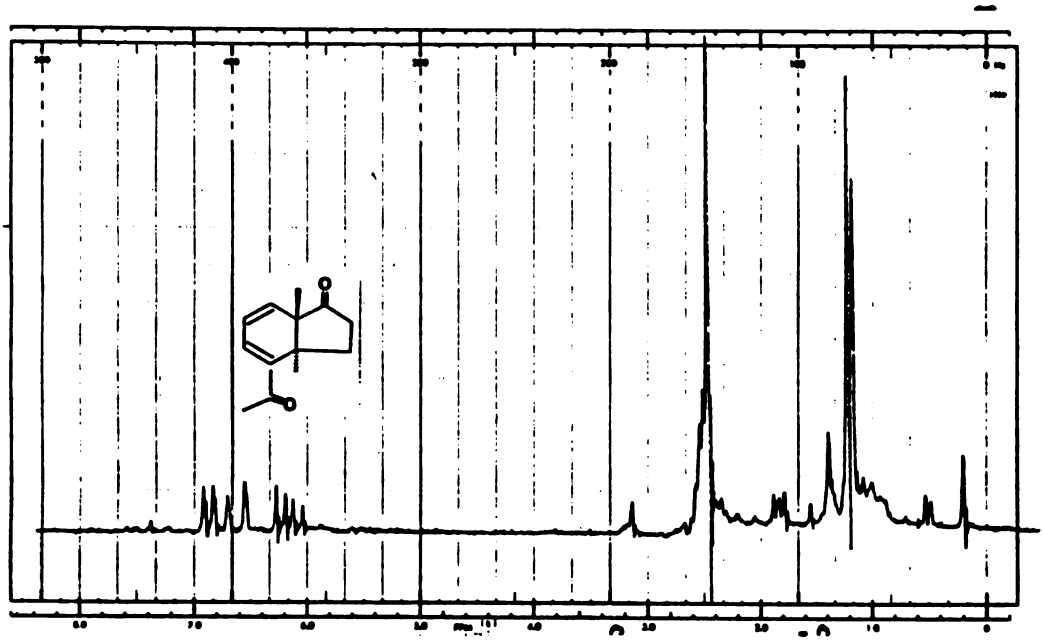


Figure 101. ^{1}H NMR spectrum of 74

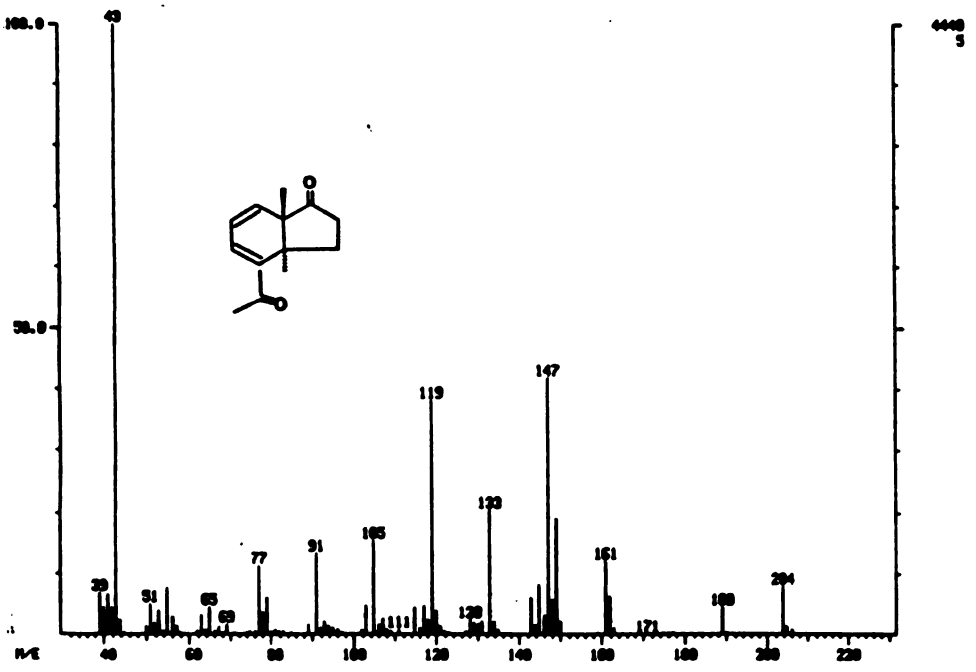


Figure 102. Mass spectrum of 74

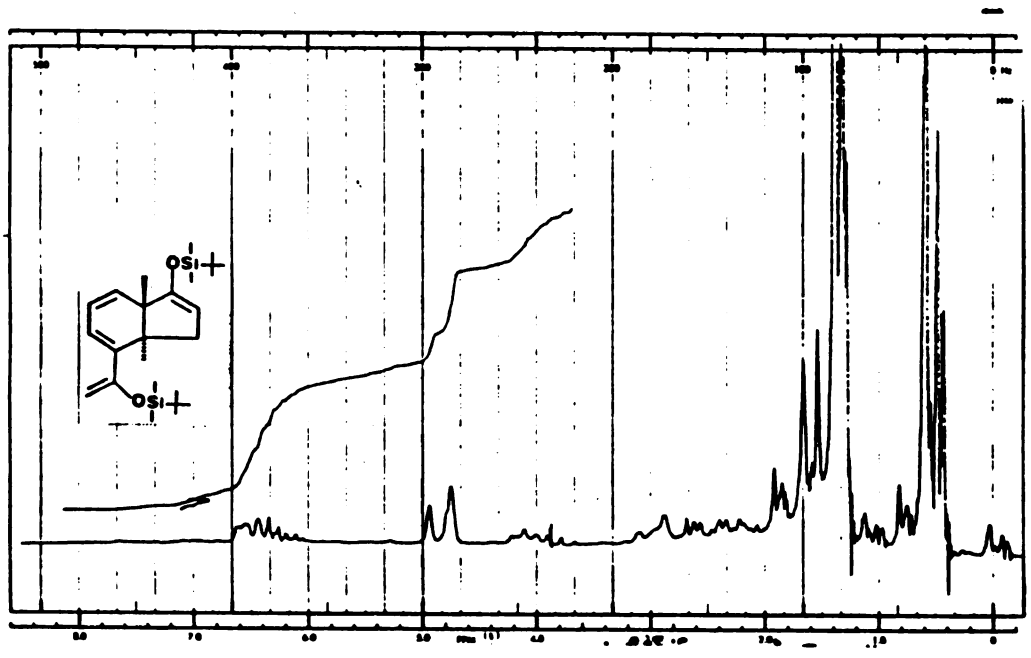


Figure 103. ^{1}H NMR spectrum of 75

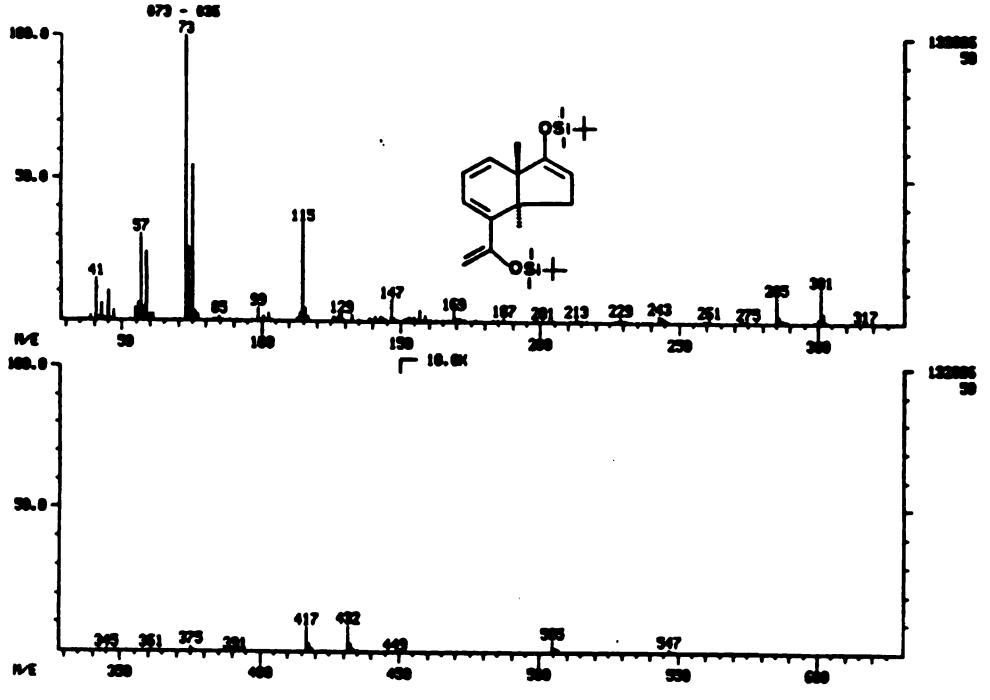


Figure 104. Mass spectrum of 75

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